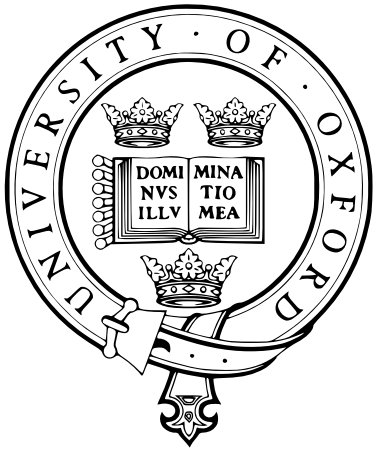
Enantioselective Desymmetrisation Towards the Synthesis of *Daphniphyllum* Alkaloids



A thesis submitted in partial fulfilment of the requirement

for the degree of Doctor of Philosophy (DPhil)

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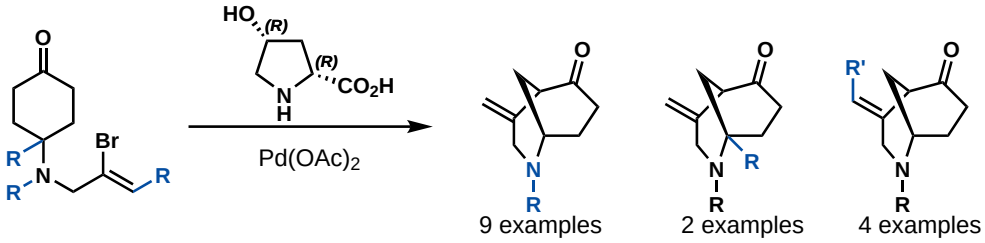
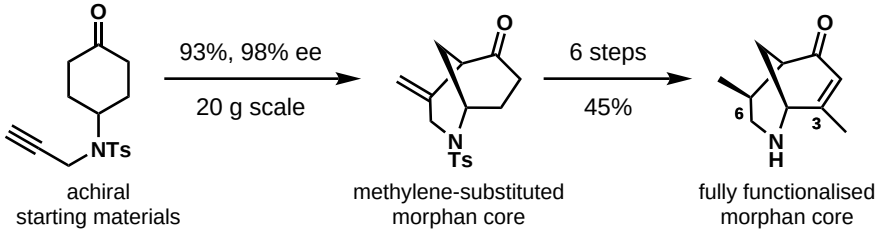
Abstract

Chapter One introduces the *Daphniphyllum* alkaloids and the Calyciphylline A-type alkaloid sub-family, including proposed biosyntheses and recently reported total syntheses. The morphan core is introduced, and methods for its synthesis are discussed, with a focus on enantioselective desymmetrising cyclisations.

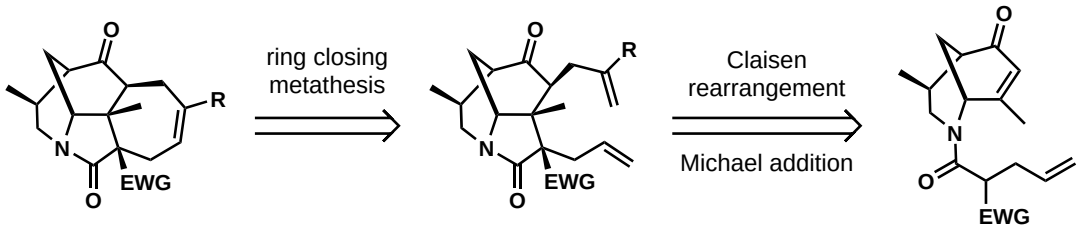
Chapter Two details the development of a Pd(II)/secondary amine co-catalysed desymmetrising cyclisation for the enantioselective synthesis of the morphan core. The method addresses several limitations of previous methods, and provides access to a broad range of products including trisubstituted alkenes.



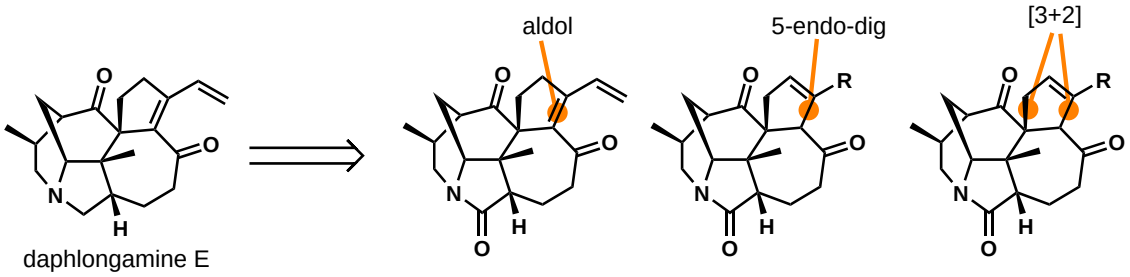
Chapter Three details the preparative synthesis of the morphan core via an enantioselective desymmetrisation reaction on up to 20 g scale. Functionalisation of the bicyclic core is discussed, including a diastereoselective hydrogenation to afford the desired stereochemical configuration.



Chapter Four describes the synthesis of the tetracyclic core common to many *Daphniphyllum* alkaloids. An intramolecular Michael addition reaction is used to form the five-membered lactam, while the seven-membered ring is constructed by ring closing metathesis.



Chapter Five details a range of synthetic strategies investigated in an attempt to construct the pentacyclic core of the Calyciphylline A-type alkaloids in an effort to achieve a total synthesis. Some of the key approaches investigated include an aldol condensation, a 5-*endo*-dig cyclisation, and a [3+2] cycloaddition.



Declaration

The work described in this thesis was carried out at the Chemistry Research Laboratory, University of Oxford, between October 2014 and April 2019, under the supervision of Professor Darren J. Dixon. All of the work is entirely my own unless stated otherwise, and has not been submitted previously for any other degree at this or any other university.

Samuel R Ellis

April 2019

Acknowledgements

Firstly, I am very grateful to Darren for his advice, guidance, and support. Over the last four years I have learnt so much from his infectious enthusiasm for organic chemistry.

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I'm very grateful to Alistair, Jamie, Matt, Pablo, Peter, and Yao, for having taken the time to proof-read and improve this thesis.

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This work was made possible by funding from the SBM CDT – a joint venture between the EPSRC and industrial collaborators– and Balliol College. This work would also not have been possible without the facilities and research support staff at the Chemistry Research Laboratory.

Special mentions go to Brook, Ed, Matt, Jack, Jai, Shreya, and Vaish, for those rare opportunities we find to meet up. Finally, I am extremely grateful to Mum, Dad, James, and Sarah, for their constant love and support.

Abbreviations

Abbreviation	Full Name
9-BBN	9-borabicyclo[3.3.1]nonane
Ac	acetyl
AIBN	azobisisobutyronitrile
aq.	aqueous
Ar	aryl
atm	atmospheres
BHT	butylated hydroxytoluene
Boc	*t*-butoxycarbonyl
bp	boiling point
BQ	1,4-benzoquinone
Bu	butyl
CAN	cerium ammonium nitrate
cat.	catalytic
CM	cross metathesis
cod	1,5-cyclooctadiene
conc.	concentrated
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
Cy	cyclohexyl
d	days
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	N,N'-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
DFT	density functional theory
DIAD	diisopropyl azodicarboxylate
DIPA	diisopropylamine
DMF	N,N-dimethylformamide
DMP	Dess–Martin periodinane
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
DNP	2,4-dinitrophenol

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Abbreviation	Full Name
dpm	dipivaloyl-methane
DPPA	diphenylphosphoryl azide
DPPF	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
DTBPF	1,1'-bis(di-*tert*-butylphosphino)ferrocene
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
equiv.	equivalents
ESI	electrospray ionisation
Et	ethyl
G-I / G-II	Grubbs catalyst $1^{st}/2^{nd}$ generation
h	hours
HAT	H-atom transfer
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
HMBC	heteronuclear multiple bond coupling
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HG-I / HG-II	Hoveyda–Grubbs catalyst $1^{st}/2^{nd}$ generation
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coupling
HWE	Horner–Hadwsworth–Emmons
i	iso
IBA	2-iodosobenzoic acid
IBX	2-iodoxybenzoic acid
IR	infrared spectroscopy
IUPAC	International Union of Pure and Applied Chemistry
KAPA	potassium-3-aminopropylamide
KHMDS	potassium bis(trimethylsilyl)amide
L	ligand
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
LUMO	lowest occupied molecular orbital
m	meta
mCPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
min	minutes

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Abbreviation	Full Name
MOM	methoxymethyl
mp	melting point
MPO	*N*-methoxypyridine *N*-oxide
n	normal (unbranched alkyl chain)
NaHMDS	sodium bis(trimethylsilyl)amide
NBS	*N*-bromosuccinimide
nbd	norbornadiene
NCS	*N*-chlorosuccinimide
NMP	*N*-methyl-3-pyrrolidone
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Ns	*p*-nitrobenzenesulfonyl
o	ortho
OXONE®	potassium peroxymonosulfate
p	para
PCC	pyridinium chlorochromate
Ph	phenyl
pin	pinacol
PP	pyrophosphate
Pr	propyl
pTSA	*para*-toluenesulfonic acid
py	pyridine
rac	racemic
RCM	ring closing metathesis
rt	room temperature
sat.	saturated
sec	secondary
t	tert
TBAC	tetrabutylammonium chloride
TBAI	tetrabutylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBD	1,5,7-triazabicyclodec-5-ene
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride

continued on next page

Abbreviation	Full Name
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMANO	trimethyl amine *N*-oxide
TMDS	1,1,3,3-tetramethyldisiloxane
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl
TS	transition state

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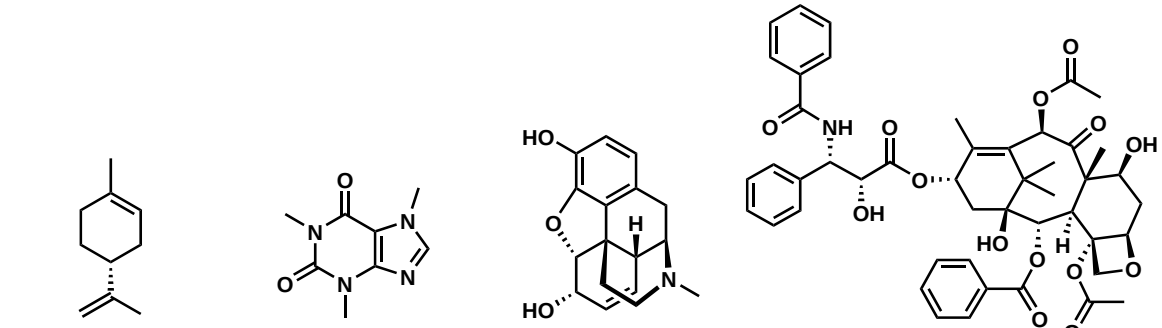
Chapter 1

Introduction

1.1 Why Total Synthesis?

All over the world, from sea sponges found in the depths of the oceans to cacti living in the high altitudes of the Andes, living organisms produce compounds essential to their survival. Often, these compounds serve as defence mechanisms to protect the organisms from predators. Caffeine, for example, the most consumed psychoactive drug in the world, acts as a pesticide, while the opiate painkiller morphine deters herbivores. From (+)-limonene, responsible for the aroma of oranges and lemons, to paclitaxel, one of the most successful anti-cancer drugs developed, natural product structures come in an array of shapes and sizes.

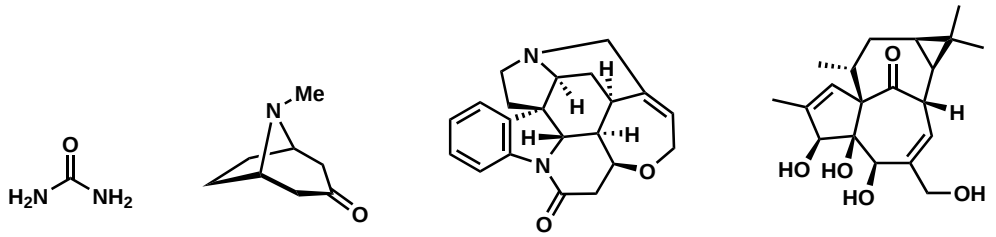


(+)-limonene (**1**) *Citrus sinensis* | caffeine (**2**) *Coffea arabica* | morphine (**3**) *Papaver somniferum* | paclitaxel (**4**) *Taxus brevifolia*

Figure 1.1: Examples of natural products.

For thousands of years, due to the effects that many natural products exhibit in humans, plants have been used or consumed to treat illness and disease. As a result they play a significant role within the drug discovery process; over 40% of all New Chemical Entities (NCEs) approved between 1981 and 2014 were natural products or their derivatives.[1]

The pursuit to construct – in a laboratory setting – compounds which are made with tremendous efficiency by living organisms began with Wöhler's synthesis of urea in 1828. Since then, the field has had many watershed moments, from Robinson's synthesis of tropinone,[2] to Woodward's synthesis of strychnine.[3] Modern synthetic targets, such as ingenol, are tackled in ever more efficient and elegant ways, pushing the boundaries of what is possible in synthesis.[4]



urea (**5**) 1828 | tropinone (**6**) 1917 | strychnine (**7**) 1954 | (+)-ingenol (**8**) 2013

Figure 1.2: Milestones in total synthesis.

Tackling the synthesis of natural products has thrust the field of organic chemistry forwards, leading to the discovery and development of new methods and transformations which are now applied routinely.[5–7] Beyond organic chemistry, the societal impacts from natural product synthesis can also be significant. The first total syntheses of paclitaxel in 1994 by Holton and Nicolaou represented a tremendous achievement in the field.[8–10] However, it was Holton's development of a semi-synthesis which made a significant ecological impact,[11] enabling the sustainable harvest of European yew tree needles, rather than the controversial harvest of Pacific yew bark which risked endangerment of the whole species.

1.2 The *Daphniphyllum* Alkaloids

1.2.1 Daphniphylline and the First *Daphniphyllum* Alkaloids

The *Daphniphyllum* alkaloids are a large family of natural products isolated from the *Daphniphyllum* genus (belonging to the family *Daphniphyllaceae*). The genus was first described by Dutch-German botanist Carl Ludwig von Blume in 1826,[12] and since then 34 different species have been identified, largely across tropical and sub-tropical Asia.[13]

The leaves and bark of *Daphniphyllum* plants have been used as herbal medicines for thousands of years, and therefore the potential biological activities of *Daphniphyllum* alkaloids are of broad interest. Hanessian and co-workers compiled a comprehensive list of biological activities known for the *Daphniphyllum* alkaloids as of 2017.[14] Many of the studies focussed on cytotoxicity against numerous cancer cell lines, such as P-388 (leukemia), MCF-7 (breast), BEL-7420 (liver), and L1210 (murine lymphoma). In addition, other properties such as insecticidal and pesticidal activities, inhibition of platelet aggregation, and anti-HIV activity have been demonstrated. The *Daphniphyllum* alkaloids are therefore a rich source of biologically active compounds, and as a result their synthesis is deserving of considerable attention and effort.

In 1909, Yagi reported the isolation of the first *Daphniphyllum* alkaloid, daphnimacrine ($C_{27}H_{41}O_4N$), from *D. macropodum*.[15] However, the spectral data acquired at that time did not allow for full elucidation of its molecular structure. It was not until 1966 that the structural complexity of the *Daphniphyllum* alkaloids became clear, following seminal work by Hirata, Irikawa, Sakabe, and Sakurai.[16–19] The authors isolated several alkaloids including daphniphylline (**9**) and yuzurimine (**10**)

from the leaves and bark of *D. macropodum* (Figure 1.3).[16] The structures of **9** and **10** were determined using single crystal X-ray diffraction studies, revealing novel and complex architectures.[17,18]

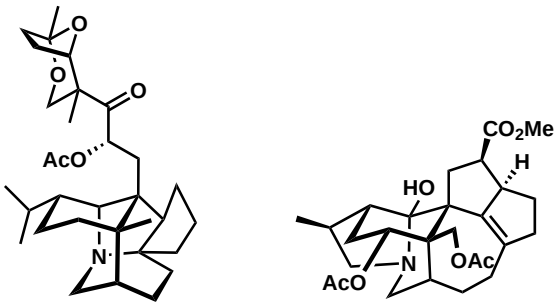


Figure 1.3: Daphniphylline and yuzurimine, the first *Daphniphyllum* alkaloids to be isolated and structurally assigned by X-ray crystallography.

In the years following, many other *Daphniphyllum* alkaloids were isolated and identified,[19–21] and to date this number has risen to over 320.[14,22] The structural diversity of these natural products is vast, with 35 distinct skeletal forms identified thus far (Figure 1.4). All are polycyclic, consisting of four or more fused or bridged ring systems, which are generally five-, six-, and seven-membered rings. Typically, the alkaloids exhibit three-dimensional structures rich in sp^3-sp^3 connectivity, frequently including one or more all-carbon quaternary stereocenters. Consequently, their construction presents a formidable challenge.

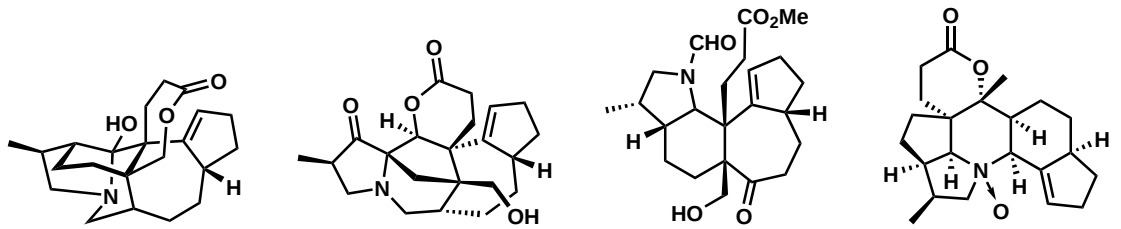
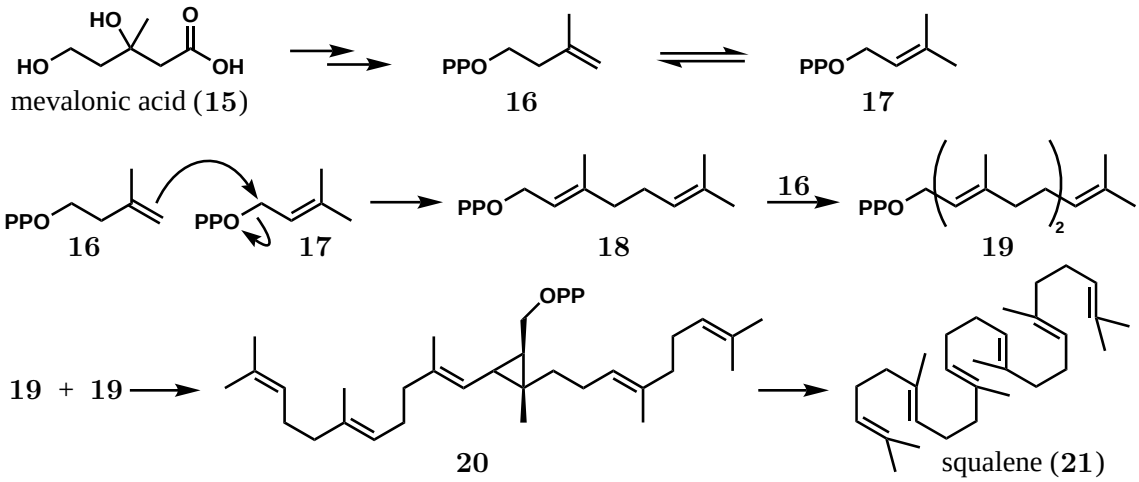


Figure 1.4: Selected *Daphniphyllum* alkaloids, demonstrating the structural diversity within the family.

1.2.2 Biosynthesis of Daphniphylline and Yuzurimine

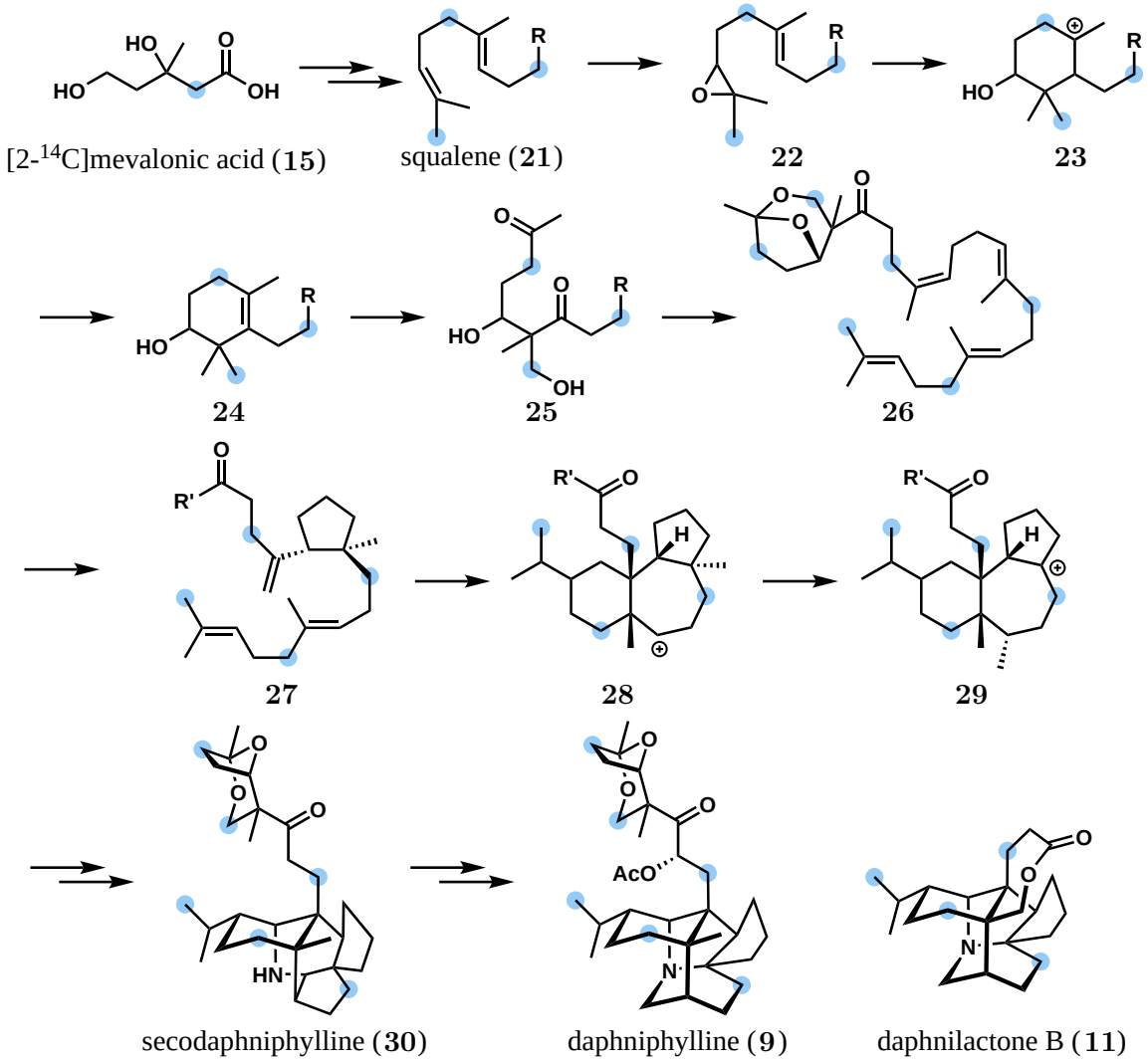
A significant proportion of natural products are terpenes or terpenoids, which originate from the mevalonate pathway (Scheme 1.1).[23] Under this process, mevalonic acid (**15**) undergoes double phosphorylation followed by decarboxylative elimination to afford isopentenyl pyrophosphate **16** and the isomeric form dimethyl allyl pyrophosphate **17**. Condensation of these five-carbon isoprene units in either a head-to-tail or head-to-head fashion results in the formation of an array of terpenes. The condensation of **16** with **17** yields geranyl pyrophosphate **18**, and condensation with another isoprene unit yields farnesyl pyrophosphate **19**. Reductive head-to-head coupling of two equivalents of **19** affords the triterpene squalene (**21**), a precursor to the steroids among many other terpenoids.



Scheme 1.1: Synthesis of squalene (**21**) from mevalonic acid (**15**). PP = pyrophosphate $(P_2O_7)^{4-}$.

Early investigations into the biosynthesis of daphniphylline (**9**) by Yamamura and co-workers revealed that the C_{30} alkaloids were likely formed from a squalene-type intermediate.[24–26] The authors fed *D. macropodum* with DL-[2-^{14}C]mevalonic acid and observed incorporation of ^{14}C into **9**. On this basis, the authors proposed a possible biosynthesis of daphniphylline from squalene (Scheme 1.2). Epoxida-

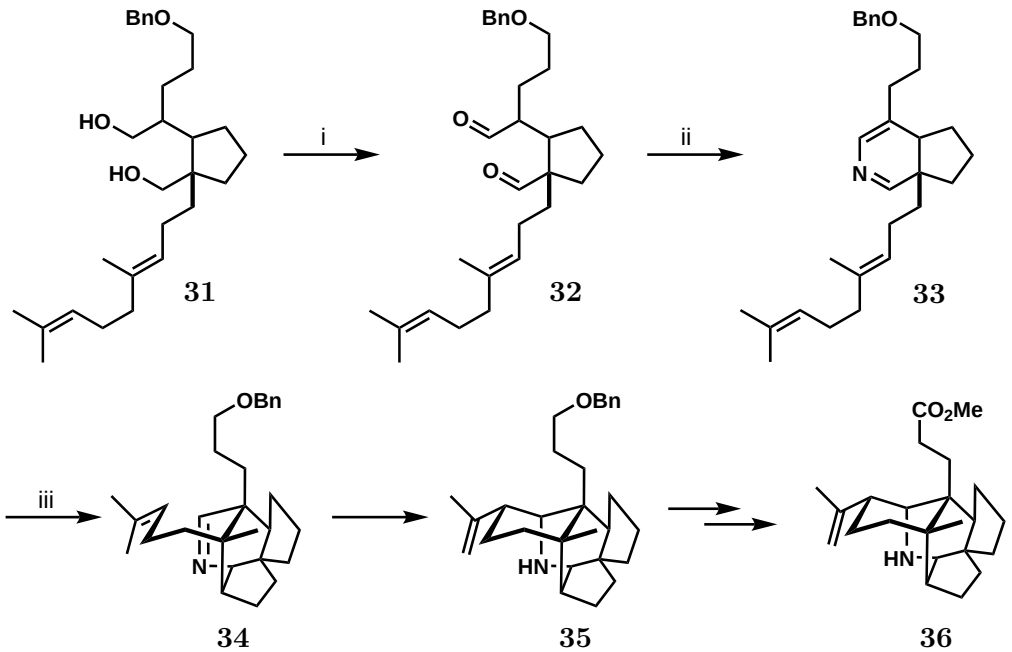
tion of squalene followed by six-membered ring formation would generate alkene **24**. Oxidative cleavage of **24** would produce diketone **25**, with subsequent acetalisation affording the bridged ketal **26**. Following formation of the five-, six-, and seven-membered rings to construct the tricyclic core **28**, a transannular methyl migration and amine incorporation would produce secodaphniphylline **30**. From this point the biosynthesis of other observed alkaloids such as daphniphylline (**9**) and daphnilactone B (**11**) could be postulated.



Scheme 1.2: Yamamura's proposed biosynthesis of secodaphniphylline **30** from squalene (**21**). ^{14}C labelled carbon atoms are designated by blue shading.

1.2.3 Heathcock's Biosynthesis Proposal

In 1988, Heathcock and co-workers carried out a biomimetic synthesis of methyl homosecodaphniphyllate **36** (Scheme 1.3).[27] Diol **31** was oxidised under Swern conditions to the dialdehyde **32**, which then underwent condensation with ammonia to form dihydropyridine **33**. Treatment of **33** with acetic acid led to an intramolecular [4+2] cycloaddition to generate **34** which, on heating, underwent an intramolecular aza-Prins reaction to afford the pentacycle **35**. This efficient cyclisation constructs four rings and five bonds in a single step, and the authors believed that a similar process may be an integral component to the biosynthesis of the *Daphniphyllum* alkaloids.

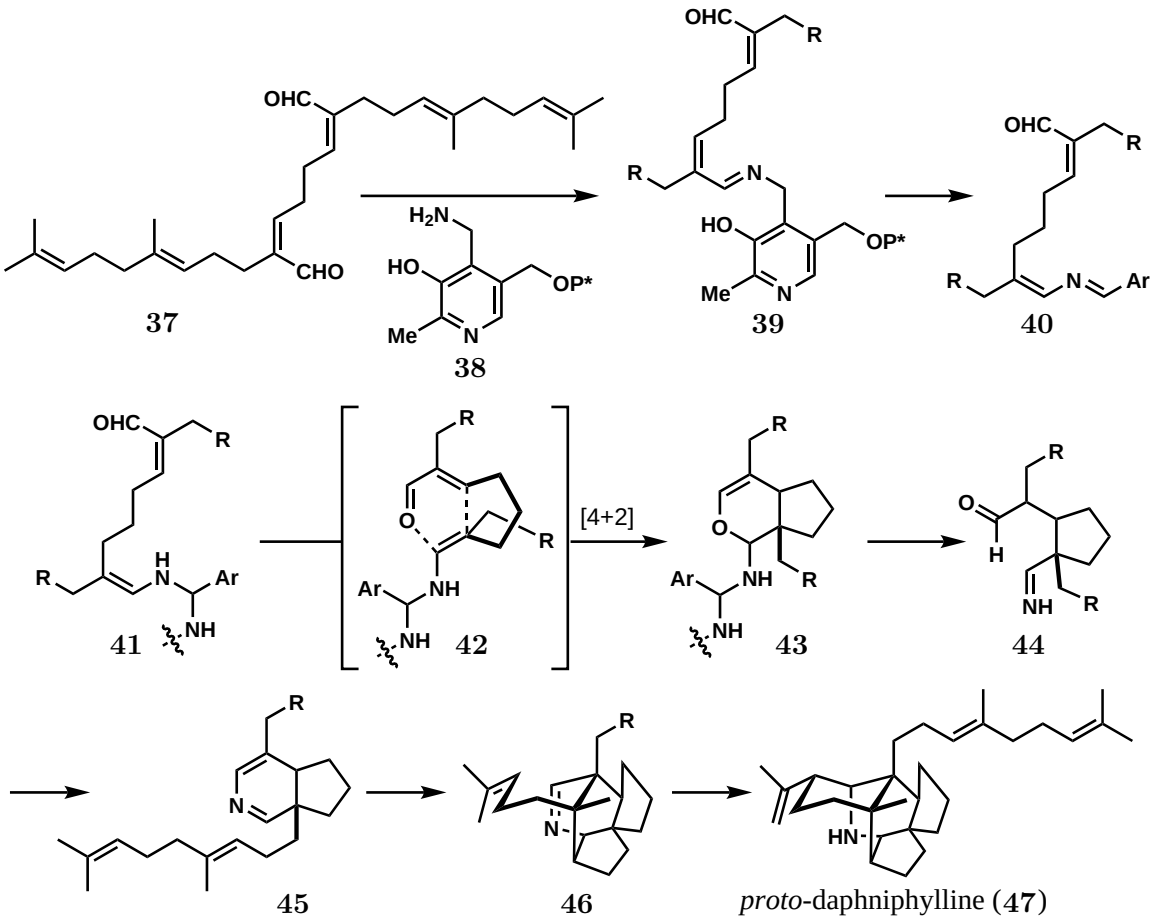


Reagents and conditions: (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (ii) NH_3, CH_2Cl_2; (iii) AcOH, 70 °C, 1.5 h, 77% from **31**.

Scheme 1.3: Heathcock's biomimetic synthesis of methyl homosecodaphniphyllate **36**.

Based on this tetracyclisation process, Heathcock and co-workers subsequently proposed a biosynthesis that would account for the formation of many of the observed *Daphniphyllum* alkaloids (Scheme 1.4).[28–30] The authors suggested that di-

aldehyde **37** could undergo condensation with an amine donor such as pyridoxamine **38** to afford imine **39**. Following isomerisation and addition of an amine residue, such as lysine, the authors proposed an intramolecular enal/enamine [4+2]-cycloaddition of **41** could take place to generate dihydropyran **43**. Following loss of the pyridoxamine group, a re-organisation could take place to yield dihydropyridine **45**. Analogous to the previous work, the authors proposed that an intramolecular [4+2] cycloaddition followed by an aza-Prins reaction would then complete the synthesis of pentacycle **47**, known as *proto*-daphniphylline. From this point, the biosynthesis of many of the known *Daphniphyllum* alkaloids could be achieved by further transformations of the isoprenyl side-chain, such as those proposed by Yamamura (see Scheme 1.2).



Scheme 1.4: Heathcock's proposed biosynthesis of *proto*-daphniphylline (**47**).

1.3 The Calyciphylline A-Type Alkaloids

The Calyciphylline A-type alkaloids are a *Daphniphyllum* alkaloid sub-family,[31] the members of which bear similarity to the parent compound calyciphylline A (**48**), which was isolated from *D. calycinum* in 2003 by Kobayashi (Figure 1.5).[32] To date, dozens of isolated *Daphniphyllum* alkaloids belong to this sub-family including daphenylline,[33] daphniyunnines A–E,[34] daphlongamines E–G,[35] daphnilongeranins A–C,[36] and the daphnipaxianines A–C.[37] In 2015, Yue and co-workers isolated 13 hydroxylated *Daphniphyllum* alkaloids from *D. himalense* including himalenines A–D,[38] and himalensines A and B.[39]

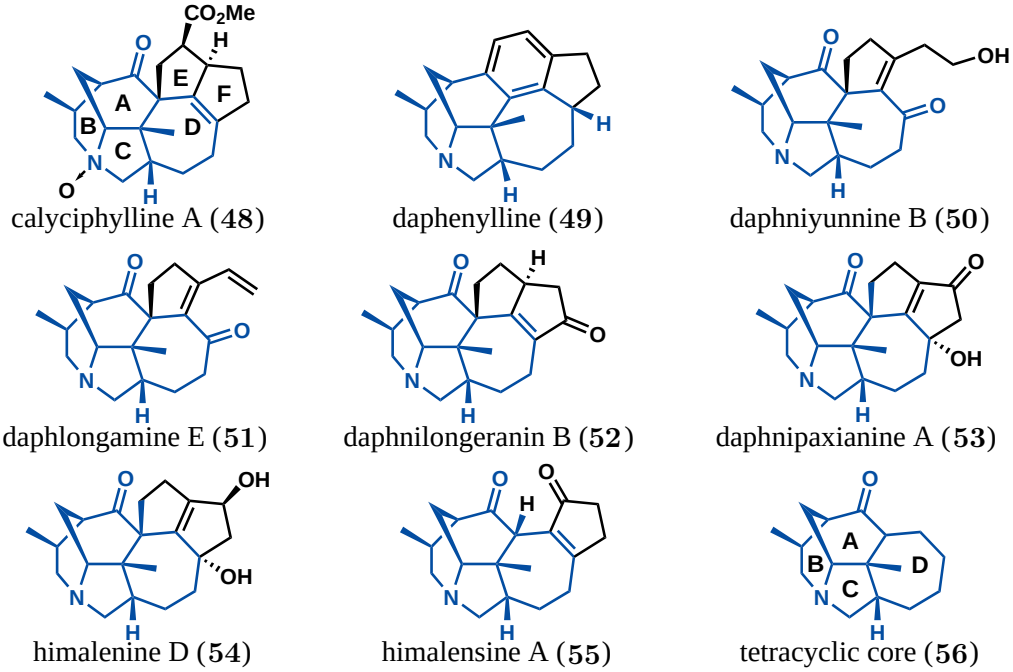
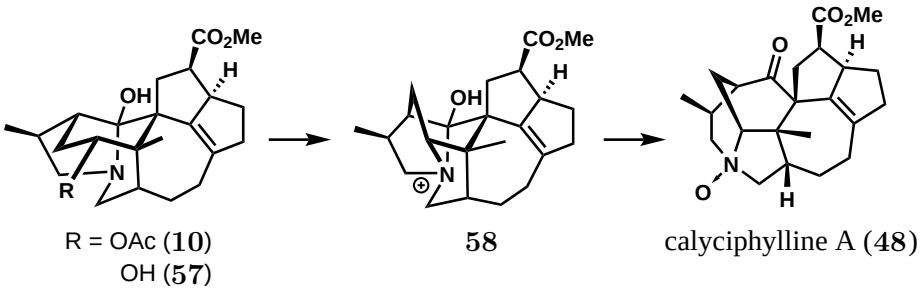


Figure 1.5: Selected examples of the Calyciphylline A-type alkaloids.

These compounds feature a common 6-6-5-7 (ABCD) tetracyclic core **56**, with additional rings fused to the seven membered ring. In most cases, this results in the presence of two adjacent all-carbon quaternary stereocenters; this contiguous all-carbon quaternary stereocenter motif is among one of the most challenging to install.[40]

While the biosynthesis of Calyciphylline A-type alkaloids is limited in study, formation of the framework is believed to arise from rearrangement of the yuzurimine (**10**) or macrodaphniphyllamine (**57**) cores. A semi-pinacol-type rearrangement via quaternary ammonium **58** would lead to C–N bond migration, yielding **48** and related natural products.[22,34]



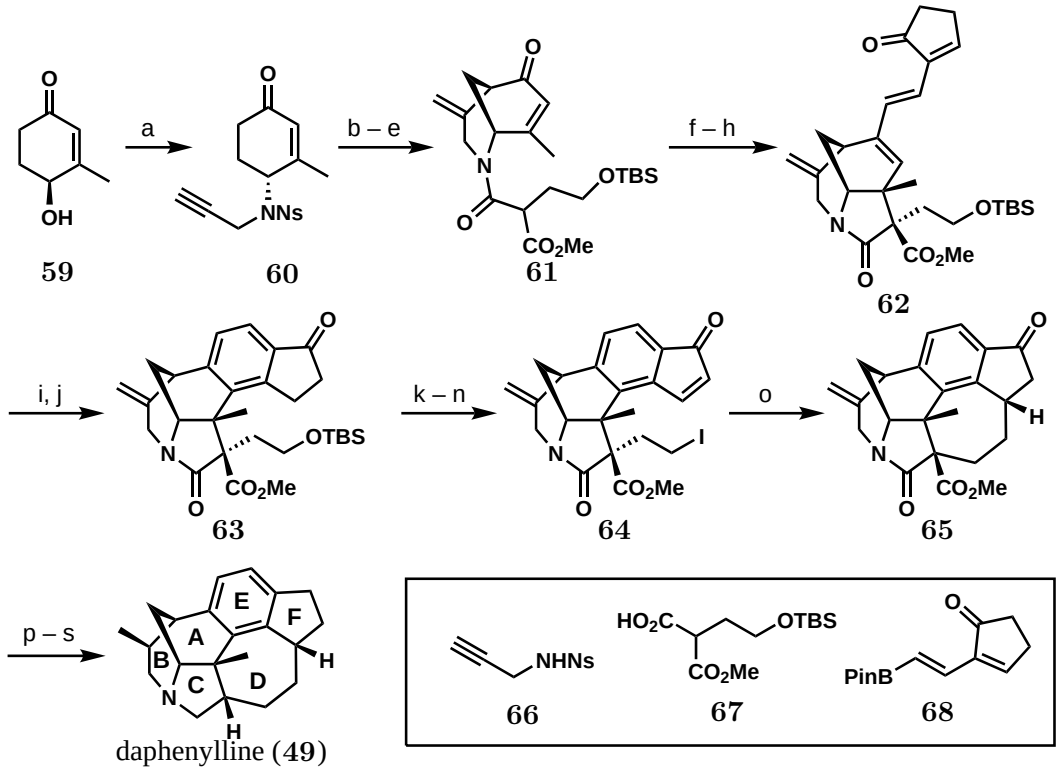
Scheme 1.5: Possible biosynthesis of calyciphylline A based on proposals by Kobayashi and Zhang.

1.3.1 Total Syntheses of Calyciphylline A-Type Alkaloids

Until recently, the total synthesis of the Calyciphylline A-type alkaloids was an unsolved challenge owing to their structural complexity. At the time this project commenced, Li and co-workers were the only group to have published a total synthesis.[41] Since 2016, however, the area has become highly active, with nine syntheses published at the time this thesis was prepared. An overview of these syntheses is presented in the following section for completeness, however, much of the work described in this thesis was carried out prior to these disclosures.

In 2013, Li and co-workers completed the first total synthesis of daphenylline (**49**; Scheme 1.6).[41] The authors commenced their synthesis with enantioenriched alcohol **59**, derived from the corresponding acetate by an enzyme-mediated kinetic resolution.[42] Following a Mitsunobu reaction with amine **66**, the B ring was constructed by a gold-catalysed 6-*exo*-*dig* cyclisation. Construction of C-ring was achieved by an intramolecular Michael addition reaction of amide **61**, which was followed by

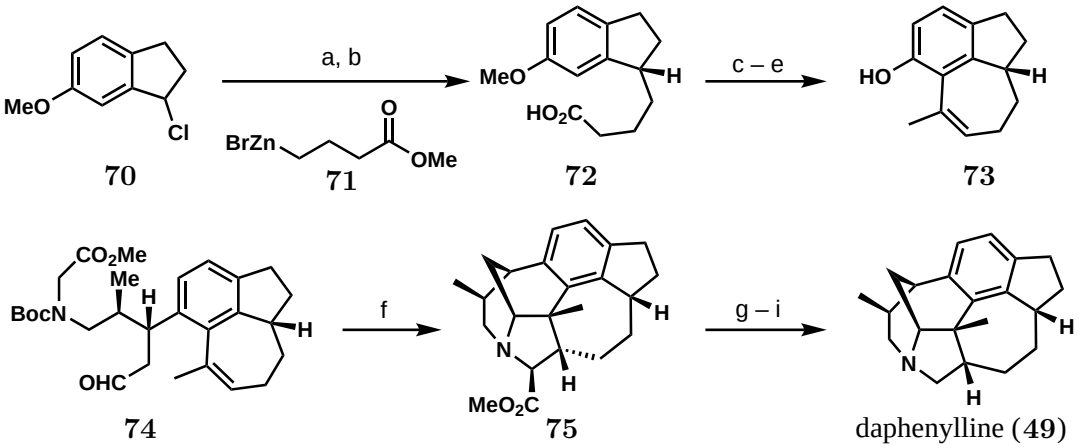
a Suzuki coupling with vinyl boronate **68** to afford triene **62**. Irradiation with a 500 W Hg lamp resulted in an isomerisation-6π-electrocyclisation cascade reaction taking place, and subsequent treatment with DBU under air led to formation of the aromatic pentacyclic core **63**. Formation of the D-ring was achieved by a radical cyclisation of iodide **64** to furnish the hexacyclic core **65**. The authors then carried out a diastereoselective hydrogenation using $[Ir(cod)(PCy_3)(Py)]PF_6$ (Crabtree's catalyst, **69**), followed by a Krapcho dealkoxycarbonylation and amide reduction to afford daphenylline in 19 steps from alcohol **59**.



Reagents and conditions: (a) **66**, PPh_3, DIAD, 0 °C, 86%; (b) TBSOTf, 2,6-lutidine, –78 °C; (c) $Au(PPh_3)Cl$, AgOTf, 70% (2 steps); (d) K_2CO_3, *p*-thiocresol; (e) **67**, HOBt, EDC · HCl, Et_3N, 72% (2 steps); (f) K_2CO_3, 100 °C, 86%; (g) KHMDS, $PhNTf_2$. –78 °C; (h) **68**, $Pd(PPh_3)_4$, K_2CO_3, 60 °C, 73% (2 steps); (i) Hg lamp, 500 W, 0 °C, 71%; (j) DBU, air, 60 °C, 67%; (k) TMSOTf, Et_3N, –78 °C; (l) $Pd(OAc)_2$, 81% (2 steps); (m) HF · py, 0 °C; (n) I_2, PPh_3, imidazole, 93% (2 steps); (o) $(TMS)_3SiH$, AIBN, 75 °C, 98%; (p) $[Ir(cod)(PCy_3)Py]PF_6$ (20 mol%; **69**), H_2 (1 bar); (q) $LiCl \cdot H_2O$, 160 °C, 86% (2 steps); (r) Pd/C, MeOH; (s) $LiAlH_4$, 40 °C, 66% (2 steps).

Scheme 1.6: Li's synthesis of daphenylline.

In 2016, Yoshima and Fukuyama disclosed a total synthesis of daphenylline, using an enantioselective Negishi coupling of chloride **70** and alkylzinc **71** to form **72**. The authors then constructed the seven-membered ring by an intramolecular Friedel–Crafts reaction to form the tricyclic core **73** (Scheme 1.7).[43] Later, irradiation of **74** led to *N*-Boc deprotection and formation of an azomethine ylide, which underwent cycloaddition with the nearby alkene to afford hexacycle **75**, constructing three rings in a single step.



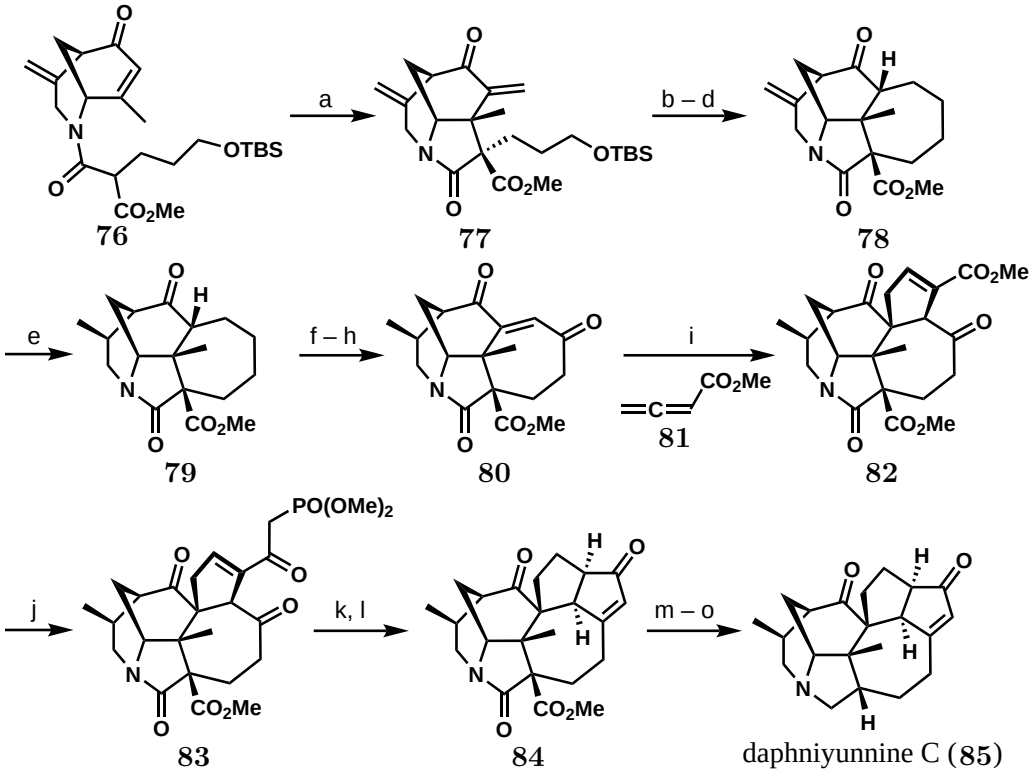
Reagents and conditions: (a) **71**, $NiBr_2 \cdot$ diglyme, (*S*)-*i*-Pr-Pybox, 0 °C; (b) NaOH, EtOH, 45% (2 steps); (c) TFAA, TFA, CH_2Cl_2, *then* aq. Na_2CO_3, 81%; (d) BBr_3, 0 °C, quant.; (e) MeMgBr, 0 °C, *then* $MgBr_2$, $TsOH \cdot H_2O$, 50 °C, 68%; (f) NaOAc, BHT, microwave, 200 °C, 53%; (g) NH_3, MeOH, 70 °C, 79%; (h) Burgess reagent, 94%; (i) $NaBH_4$, MeOH, reflux, 36%.

Scheme 1.7: Fukuyama's synthesis of daphenylline.

In 2017, Li demonstrated the total synthesis of daphniyunnine C[†] **85**, in which amide **76** (prepared in a similar manner to **61**) underwent an intramolecular Michael addition in the presence of formaldehyde to generate enone **77** (Scheme 1.8).[44] The seven-membered ring was constructed using Luche conjugate addition conditions (Zn, CuI), which the authors found superior to radical-based methods such as those employed in their earlier synthesis of daphenylline (Scheme 1.6). In addition, the authors developed an alternative method for the diastereoselective hydrogenation of the exocyclic alkene, employing $[Rh(cod)Cl]_2/PPh_3/AgBF_4$ as the catalyst sys-

[†]Daphniyunnine C has also been identified as longeracinphyllin A as a result of its isolation from several *Daphniphyllum* species by different groups.

tem. A phosphine-catalysed [3+2] cycloaddition of enedione **80** with allene **81** was developed to construct the E-ring, which was followed by an intramolecular Horner–Wadsworth–Emmons olefination to complete the hexacylic core **84**. Finally, a Krapcho dealkoxycarbonylation and amide reduction were carried out to complete the synthesis of daphniyunnine C.

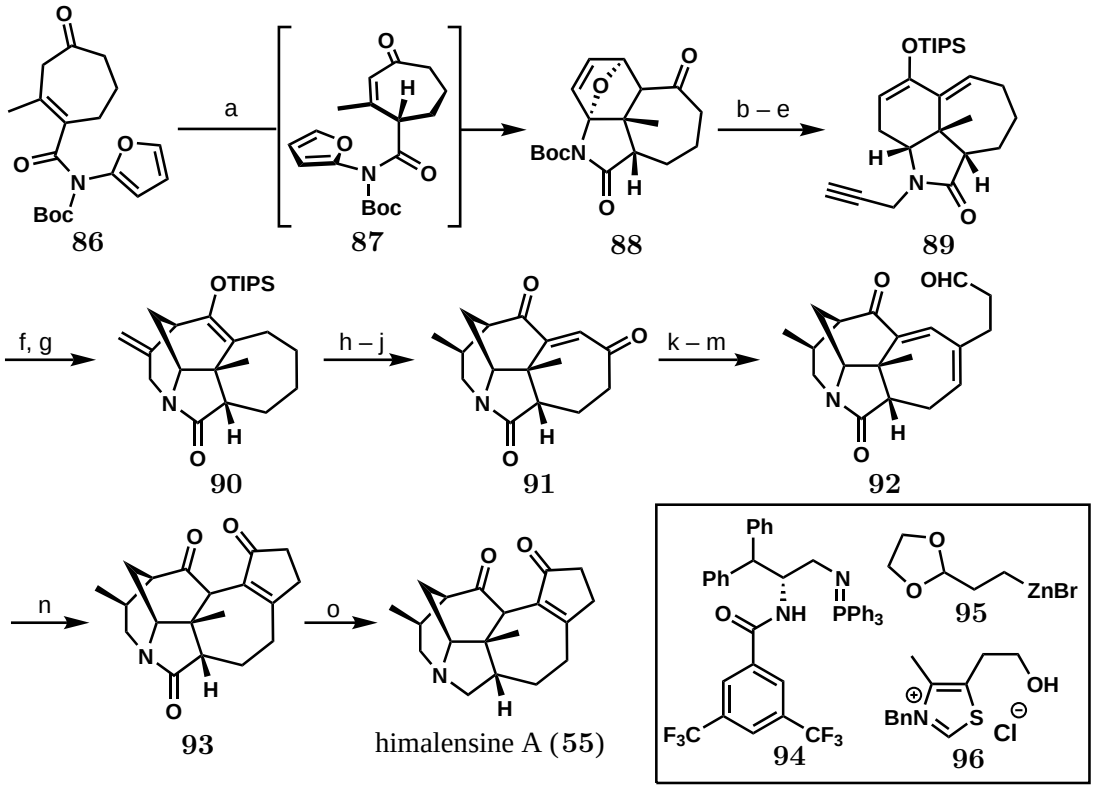


Reagents and conditions: (a) DBU, $(CH_2O)_n$; (b) $HF \cdot py$; (c) I_2, PPh_3, imidazole, 85% (2 steps); (d) Zn, CuI, 90%; (e) $[Rh(cod)Cl]_2$, PPh_3, $AgBF_4$, H_2, 98%; (f) KHMDS, PhSeBr; (g) *m*CPBA, 75% (2 steps); (h) DABCO, air, 91%; (i) **81**, DPPF, 45%; (j) $LiCH_2PO(OMe)_2$, 86%; (k) Pd/C, H_2; (l) TBD, 91% (2 steps); (m) LiCl, H_2O, 95%; (n) Lawesson's reagent *then* silica gel, air, 67%; (o) Raney Ni, 90%.

Scheme 1.8: Li's synthesis of daphniyunnine C.

Also in 2017, the Dixon group disclosed an enantioselective synthesis of himalensine A, which featured an asymmetric prototropic shift/intramolecular furan Diels–Alder cascade reaction as the key step (Scheme 1.9).[45] The use of bifunctional iminophosphorane organocatalyst **94** enabled the cascade reaction of **86** to construct the tricyclic core **88** with excellent diastereo- and enantioselectivity. Formation of the B ring was achieved by a Bu_3SnH-mediated radical cyclisation of alkyne **89**,

which was followed by a diastereoselective hydrogenation of the alkene using Crabtree's catalyst. Interestingly, the hydrogenation relied on a low pressure of H_2 to achieve high levels of diastereoselectivity. Later, a Stetter reaction catalysed by thiazolium salt **96** was used to install the cyclopentene ring. Finally, a one-step reduction of the amide was achieved using $[IrCl(CO)(PPh_3)_2]$ (Vaska's catalyst, **97**) with TMDS, which upon treatment with formic acid afforded himalensine A (**55**).

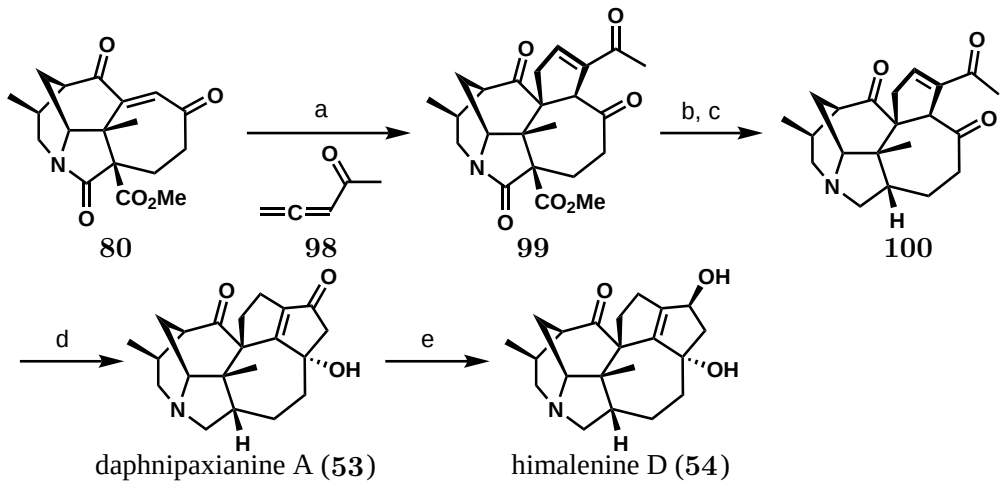


Reagents and conditions: (a) **94** (5 mol%), 60 °C, 86%, 92:8 dr, 90% ee; (b) TFA *then* $Pd(OH)_2$, H_2, 63%; (c) NaHMDS, propargyl bromide, 0 °C, 83%; (d) $LiAlH_4$, –10 °C, *then* MeOH, HCl (aq.), 95%; (e) TIPSOTf, 2,6-lutidine, 86%; (f) Bu_3SnH, AIBN, 90 °C, 80%; (g) CSA, 0 °C, 97%; (h) $[Ir(cod)(PCy_3)Py]PF_6$ (20 mol%), H_2/Ar (1:2), 92%, >20:1 dr; (i) NBS, 82%; (j) pyridine, PTSA, O_2, reflux, 65%; (k) NaHMDS *then* $PhNTF_2$, 58%; (l) $Pd_2(dba)_3$, DTBPF, NMP, *then* **95**, 96%; (m) HCl (aq.), 87%; (n) **96** (30 mol%), Et_3N, 60 °C, 75%; (o) $IrCl(CO)(PPh_3)_2$ (**97**) (10 mol%), TMDS, *then* formic acid, 60 °C, 67%. TMDS=(1,1,3,3-tetramethyldisiloxane), DTBPF=(1,1'-bis(di-tertbutylphosphino)ferrocene)

Scheme 1.9: Dixon's synthesis of himalensine A.

In 2018, the Li group elaborated on their previous work to achieve syntheses of daphnipaxianine A and himalenine D from enedione **80** (Scheme 1.10).[46] A similar phosphine-catalysed [3+2] cycloaddition between enone **80** and allenoate ester **98** was carried out to synthesise the pentacyclic core **99**, after which a Krapcho

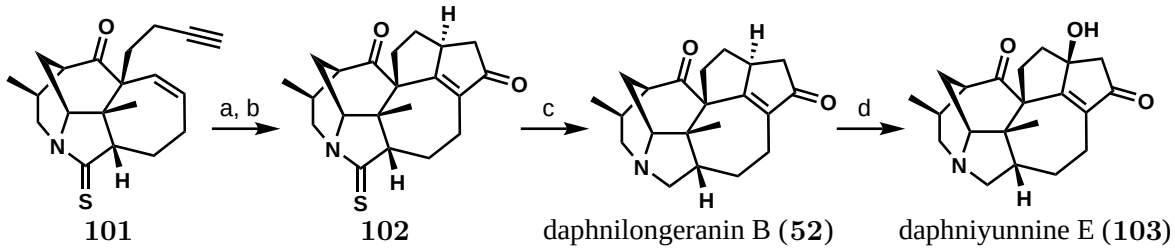
dealkoxycarbonylation and amide reduction using Vaska's catalyst afforded **100**. Treatment of **100** with DBU yielded daphnipaxianine A (**53**), and a subsequent Luche reduction afforded himalenine D (**54**).



Reagents and conditions: (a) **98**, DPPF, 52%; (b) LiCl, H_2O, 72%; (c) $IrCl(CO)(PPh_3)_2$, TMDS, $NaBH(OAc)_3$, 81%; (d) DBU, LiCl, 79%; (e) $NaBH_4$, $CeCl_3$, 72%.

Scheme 1.10: Li's synthesis of daphnipaxianine A and himalenine D.

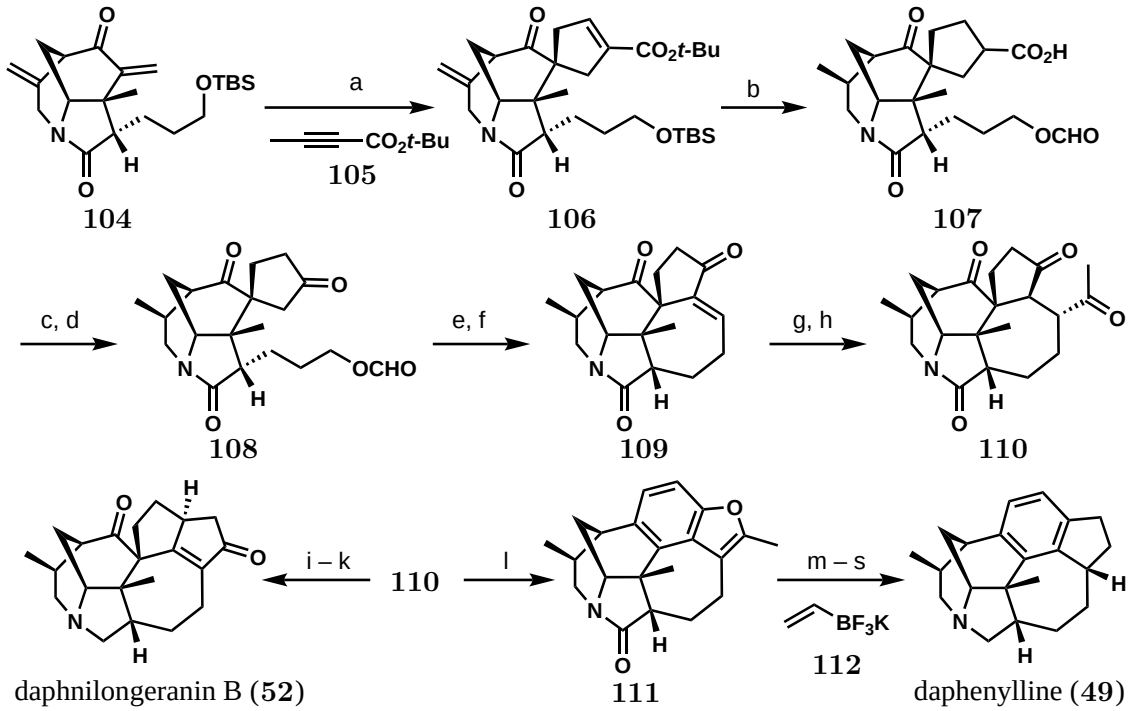
The Li group also developed an alternative approach to the construction of the E and F ring system; the authors used a Pauson–Khand reaction of eneyne **101** to form the hexacylic core **102** (Scheme 1.11).[47] A subsequent thioamide reduction afforded daphnilongeranin B (**52**), and daphniyunnine E (**103**) could then be accessed via hydroxylation by γ-deprotonation in the presence of O_2 and $P(OEt)_3$.



Reagents and conditions: (a) $Co_2(CO)_8$, MeCN; (b) K_2CO_3, TFE, 63% (2 steps); (c) Raney Ni, 81%; (d) *t*BuOK, O_2, $P(OEt)_3$, 61%.

Scheme 1.11: Li's synthesis of daphnilongeranin B and daphniyunnine E using an intramolecular Pauson–Khand reaction to generate the E and F ring system.

Also in 2018, the Zhai group developed a synthesis of daphnilongeranin B and daphenylline, starting from amide **104**.[48] The E ring was constructed via a similar phosphine-catalysed [3+2] cycloaddition reaction to that developed by Li and co-workers,[44,46] with spirocycle **106** formed in good yield (Scheme 1.12). The authors then constructed the seven membered ring by an intramolecular aldol condensation to afford enone **109**. Conjugate addition of nitroethane led to direct formation of the vinyl adduct (NO_2 was eliminated *in situ* under the reaction conditions), and a subsequent Wacker oxidation afforded the corresponding ketone **110**. From this point, the authors demonstrated that an intramolecular aldol reaction could be carried out to generate the F ring and deliver daphnilongeranin B (**52**). Alternatively, under dehydrating conditions a 1,2-migration took place to afford benzofuran **111**, which could be subsequently converted to daphenylline (**49**).



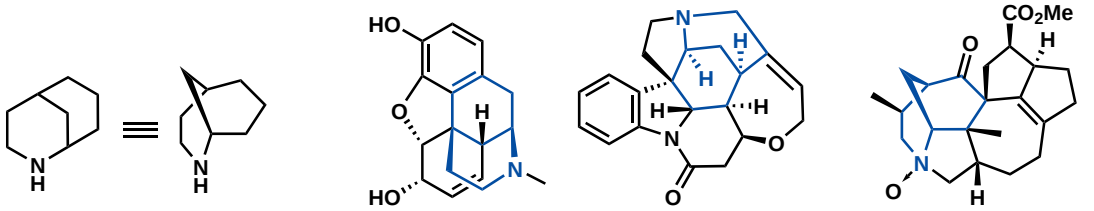
Reagents and conditions: (a) **105**, PBu_3, 83%; (b) $[Ir(cod)(PCy_3)Py]PF_6$ *then* HCO_2H, 91%; (c) DCC, *m*CPBA; (d) PCC, 79%; (e) K_2CO_3 *then* DMP; (f) PTSA, 71%; (g) $EtNO_2$, 81%; (h) $PdCl_2$, $CuCl_2$, 87%; (i) NaOH, 80%; (j) $LiAlH_4$; (k) DMP, 61% (2 steps); (l) PTSA, 85%; (m) PCC, quant.; (n) K_2CO_3 *then* Tf_2O; (o) **112**, $Pd(dppf)Cl_2$; (p) $PdCl_2$, $CuCl_2$, 80% (3 steps); (q) NaOH, 76%; (r) Pd/C, H_2, AcOH; (s) $LiAlH_4$, 58%.

Scheme 1.12: Zhai's divergent synthesis of daphnilongeranin B and daphenylline.

From the significant synthetic effort and continuous output over the past three years, it is clear that the Calyciphylline A-type alkaloids have provided broad inspiration to many natural product synthesis groups. The pace of discovery remains high, with several total syntheses published in early 2019.[49,50]

1.4 The Morphan Core

Central to the polycyclic skeleton of the Calyciphylline A-type alkaloids is the 2-azabicyclo[3.3.1]nonane unit, known as the morphan core (**113**). This bicyclic motif is found in over 300 natural products,[51] with some of the most well-known examples, such as morphine and strychnine, exhibiting potent biological activities (Figure 1.6).

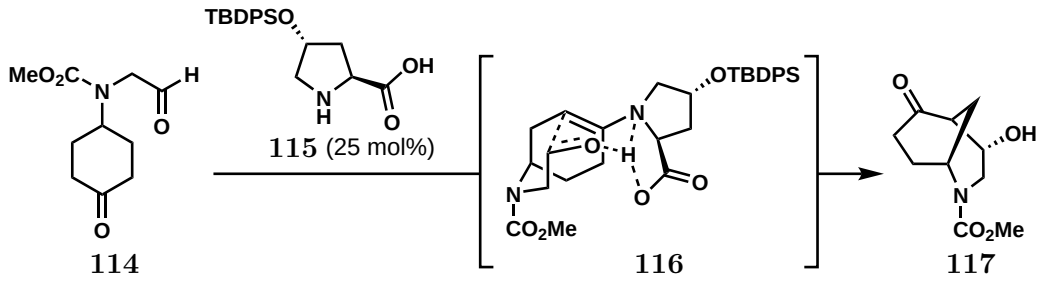


2-azabicyclo[3.3.1]nonane (**113**) morphine (**3**) strychnine (**7**) calyciphylline A (**48**)

Figure 1.6: The morphan core and selected natural products containing this moiety.

1.4.1 Catalytic Enantioselective Morphan Core Syntheses

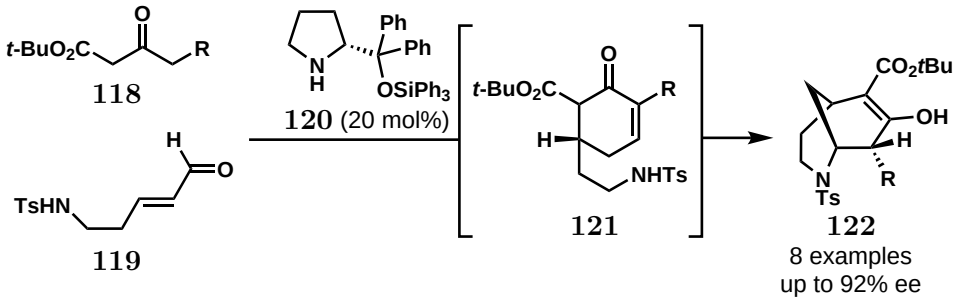
While many racemic methods to construct the morphan core have been developed,[51] enantioselective syntheses are less common. In 2009, Bonjoch and Diaba developed the first organocatalytic enantioselective synthesis of the morphan core. Using silyl-protected hydroxyproline catalyst **115**, the authors carried out an intramolecular aldol reaction to form the hydroxylated morphan core **117** in 70% ee (Scheme 1.13).[52]



Reagents and conditions: **115** (25 mol%), 100 °C, µW (300 W), 15 mins, 70%, 70% ee.

Scheme 1.13: Enantioselective desymmetrisation of aldehyde **114** by an organocatalysed intramolecular aldol reaction.

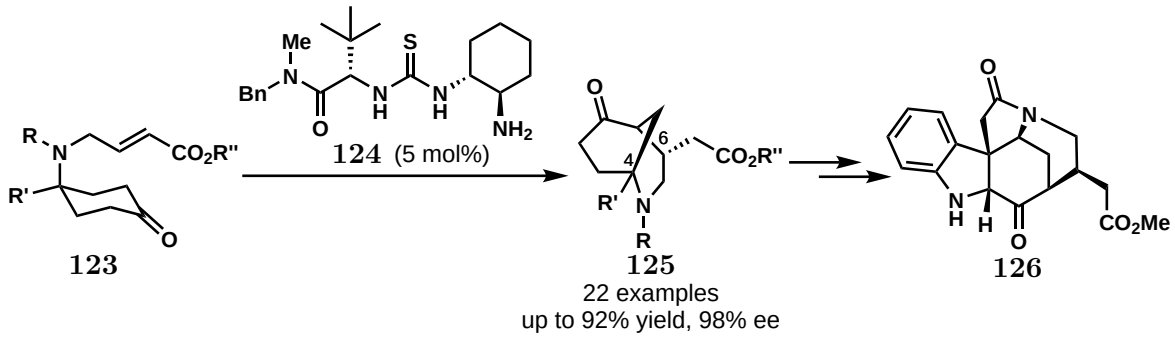
Bonjoch and co-workers later developed an organocatalysed cascade reaction of β-ketoesters (**118**) and enal **119** (Scheme 1.14).[53] This approach consisted of a Michael addition and Robinson annulation to afford **121**, which underwent a subsequent aza-Michael reaction to afford morphan core derivatives **122** with excellent enantioselectivity (up to 92% ee).



Reagents and conditions: **118** (2 equiv), **119** (1 equiv), **120** (20 mol%), LiOAc, H_2O, *then* $LiOH \cdot H_2O$, *then* *i*-PrOH, H_2O.

Scheme 1.14: Organocatalysed cascade reaction between β-keto esters (**118**) and enal **119** to form morphan core derivatives **122**.

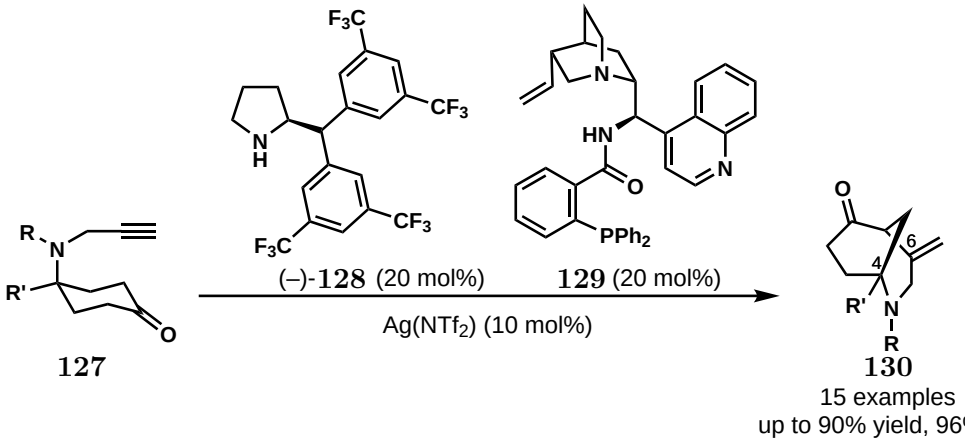
In 2015, the Dixon group developed a method for the enantioselective construction of the morphan core using bifunctional amine organocatalyst **124** to enable the intramolecular Michael addition of cyclohexanones to unsaturated esters (Scheme 1.15). The method provides access to ester derivatives of the morphan core in excellent yield and enantioselectivity,[54] and was subsequently applied to the synthesis of the pentacyclic core (**126**) of the *Strychnos* alkaloids.[55]



Reagents and conditions: **124** (5 mol%), $PhCO_2H$ (1.25 mol%), CH_2Cl_2, 45 °C, 36–120 h.

Scheme 1.15: Enantioselective desymmetrisation via an intramolecular Michael addition reaction and application to the synthesis of *Strychnos* alkaloids.

In 2017, the Dixon group demonstrated the silver(I) and amine co-catalysed desymmetrisation of 4-propargylamino cyclohexanones (Scheme 1.16).[56] This method delivered the methylene-substituted morphan core **130** with excellent yields and enantioselectivities, tolerating a range of *N*-substituents in addition to substrates bearing a fully substituted carbon at C-4. While the absolute stereochemical outcome of the reaction was determined by the chirality of **128**, the use of cinchonine-derived aminophosphine ligand **129** reinforced the enantioselectivity compared to achiral phosphine ligands. The pseudoenantiomeric cinchonidine-derived ligand, on the other hand, led to a mis-matched effect and a reduction in enantioselectivity.

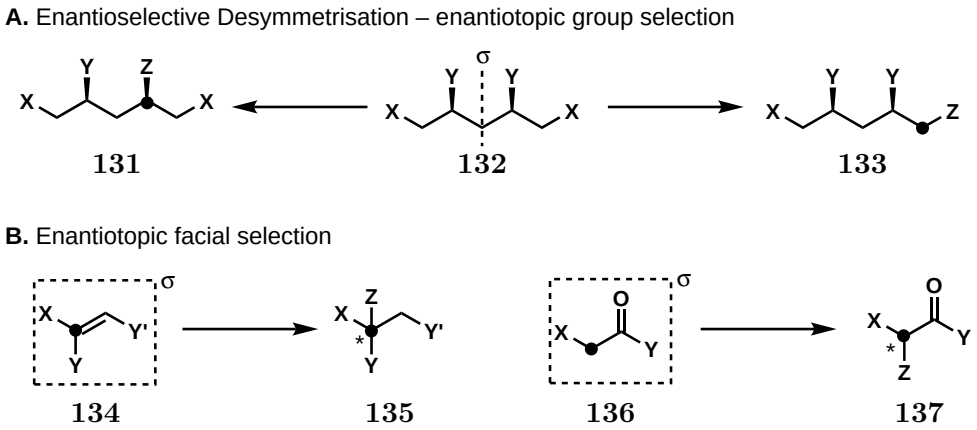


Reagents and conditions: (–)-**128** (20 mol%), **129** (20 mol%), $Ag(NTf_2)$ (10 mol%), 2,4-dinitrophenol (20 mol%), *i*-PrOH, 60 °C, 72 h.

Scheme 1.16: Enantioselective desymmetrisation of 4-propargylamino tethered cyclohexanones using co-operative Ag(I)/amine catalysis.

1.5 Desymmetrisation to Simplify Synthesis

Key to many of the approaches employed by the Bonjoch and Dixon groups towards the asymmetric synthesis of morphan core derivatives is the use of enantioselective desymmetrisation.[57,58] These reactions transform *achiral* or *meso* compounds into enantiomerically enriched chiral products. This requires the destruction of an improper symmetry element, which is often a mirror plane (σ), but can also be i, or S_n. Importantly, the site of reaction does not lie on the plane of the symmetry element being lost; this differentiates such reactions from, for example, enantiotopic facial differentiation reactions such as asymmetric hydrogenation.[58]

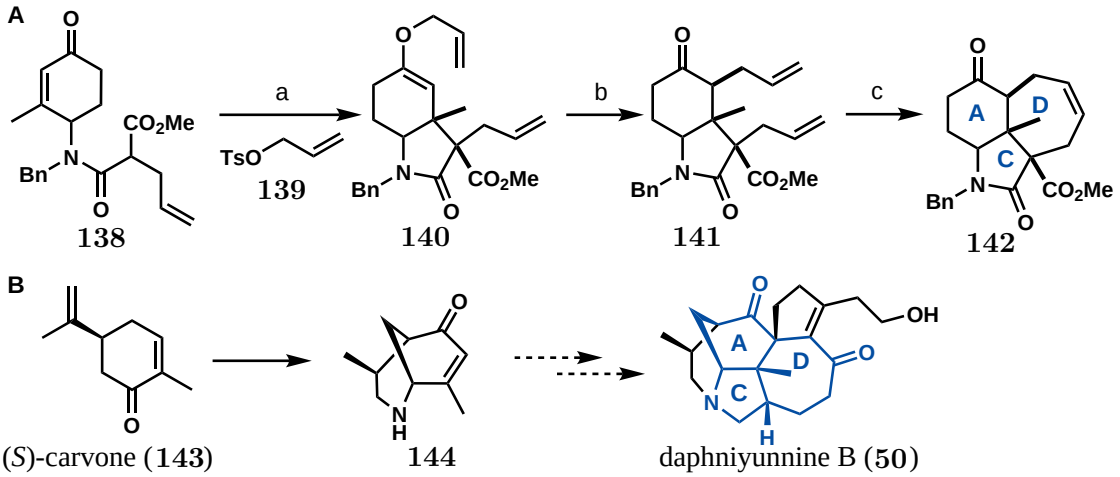


Scheme 1.17: A. Enantioselective desymmetrisation through the differentiation of enantiotopic groups, resulting in the destruction of a σ symmetry element. B. Enantiotopic facial differentiation of alkenes and carbonyls resulting in loss of σ symmetry element, not formally considered enantioselective desymmetrisation.

Enantioselective desymmetrisation is a powerful technique to rapidly generate molecular complexity, and as a result it has seen many applications to natural product synthesis.[59] These transformations can be achieved in many different ways, including through the use of transition metals, organocatalysts, and enzymes, and has been applied to a broad range of substrates, from diols and ketones to aziridines and dienes.[58,60–62]

1.6 Previous Work Within the Dixon Group

The Dixon group have focussed synthetic efforts in recent years on the Calyciphylline A-type alkaloids, with daphniyunnine B (**50**) a primary target. In 2011, the group developed an efficient three-step procedure to form **142**, the 6-5-7 (ACD) tricyclic core of daphniyunnine B (Scheme 1.18).[63] This involved an intramolecular Michael addition reaction of amide **138** to form the C ring, with a tandem enolate allylation to afford enol ether **140**. Following a thermal Claisen rearrangement, ketone **141** underwent ring closing metathesis to afford the tricyclic core **142**.



Reagents and conditions: (a) KHMDS *then* **139**, 18-crown-6, 78% (b) mesitylene, reflux, 63% (c) Grubbs I (5 mol%), CH_2Cl_2, reflux, 98% **142**.

Scheme 1.18: A. Synthesis of ACD tricyclic core **142** using an intramolecular Michael addition reaction, Claisen rearrangement, and ring closing metathesis. B. Application towards synthesis of daphniyunnine B via bicyclic core **144**, synthesised from (*S*)-carvone.

In efforts to extend this work to a total synthesis of daphniyunnine B, a synthesis of the AB core **144** was developed from (*S*)-carvone in 16 steps.[64] Unfortunately, the large number of steps was prohibitive, and despite extensive efforts a synthesis of daphniyunnine B could not be realised. It was clear that a more efficient method to access the bicyclic core **144** was required to achieve a total synthesis.

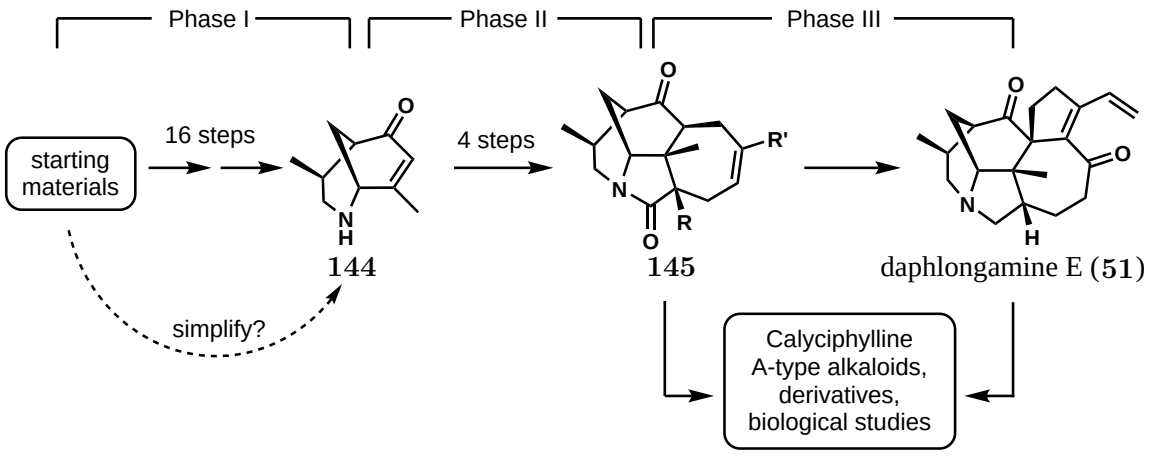
1.7 Thesis Aims

The core aim of this work was to develop an enantioselective total synthesis of daphlonagmine E (**51**), which was chosen as the latent alkene functionality could provide a synthetic handle for further functionalisations towards other members of the Calyciphylline A-type alkaloids or derivatives. The synthesis was separated into three phases (Scheme 1.19):

Phase I was to develop a scalable enantioselective synthesis of the functionalised bicyclic core **144**. By applying new catalytic methods, the aim was to simplify the synthesis to ensure a more efficient and scalable route to **144** than was previously developed.

Phase II was to apply the Michael addition, Claisen rearrangement, and ring closing metathesis reaction sequence to construct the tetracyclic ABCD core **145**, with appropriate substituents chosen to facilitate further functionalisation.

Phase III aimed to complete the total synthesis of daphlongamine E. If successful, the strategy would be broadened to pursue the synthesis of other members of the Calyciphylline A-type alkaloids.

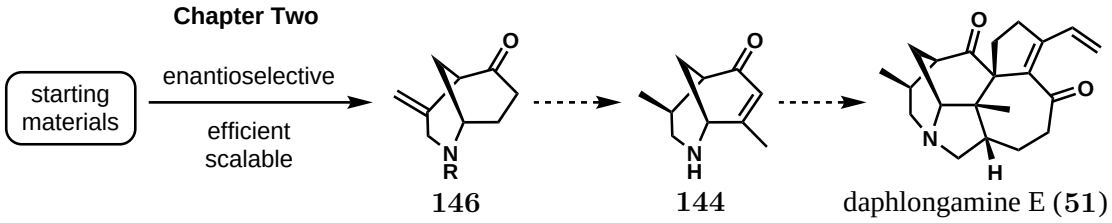


Scheme 1.19: Overview of the three-phase approach towards the synthesis of daphlongamine E and other Calyciphylline A-type alkaloids.

Chapter 2

Enantioselective Synthesis of the Morphan Core

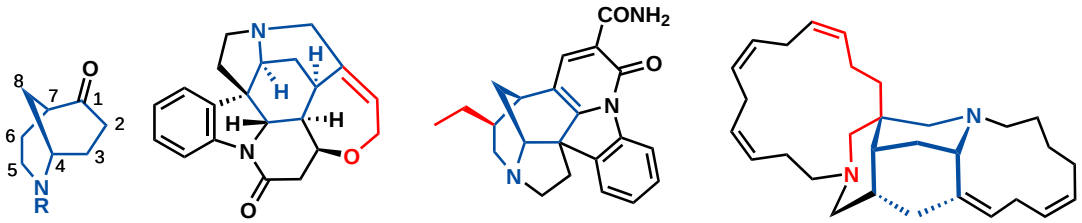
The first phase of the synthesis aimed to develop a scalable method to prepare the functionalised AB core **144** of daphlongamine E (**51**, Scheme 2.1). Key to an efficient synthesis would be rapid formation of the bicyclic core **146** from simple starting materials. While several methods have been reported for the enantioselective synthesis of **146** or similar compounds, these are limited in scope, with products relevant to specific natural product families. This chapter will discuss those limitations and describe the development of an alternative method to construct the morphan core, with a focus on accessing a broader range of natural product scaffolds.



Scheme 2.1: Overview of Chapter Two.

2.1 Context and Limitations of Current Methods

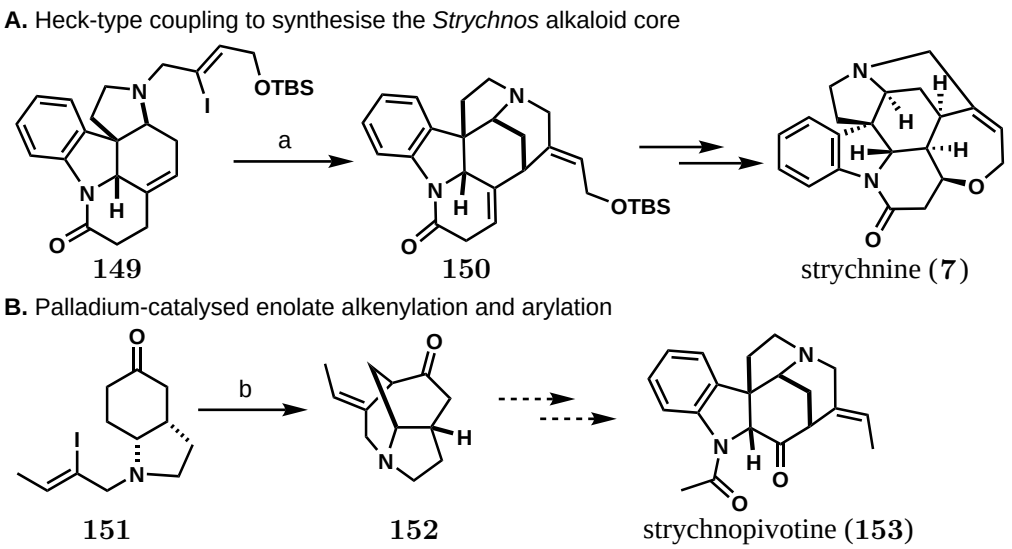
The morphan core (**113**) is found in over 300 natural products, and in many cases this bicyclic motif is highly substituted.[51] In particular, the C-6 position (Figure 2.1) is typically substituted with alkyl, alkenyl, or heteroatom-containing groups. As a result, the ability to readily modify this position is of strategic importance, and a cyclisation method which tolerates a range of functionality at C-6 could be broadly applicable to many natural product scaffolds. Current methods developed for the enantioselective synthesis of the morphan core tolerate various amine and C-4 substituents. However, the C-6 position is limited to $-OH$, $-CO_2R$, or $=CH_2$.[52,54,56]



113 strychnine (**7**) leuconicine A (**147**) madangamine A (**148**)

Figure 2.1: Selected natural products containing the morphan core (highlighted in blue) with key points of variation at C-6 (highlighted in red).

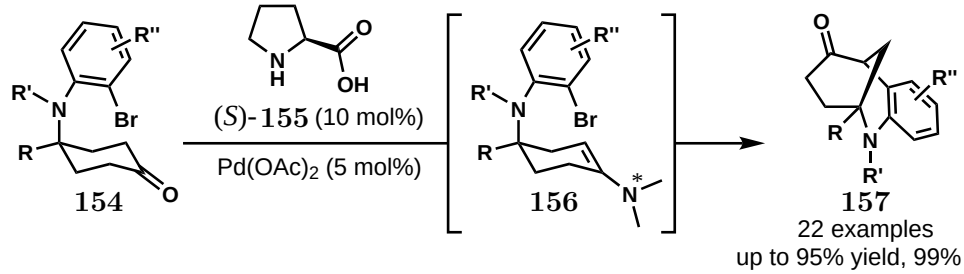
Compared to enantioselective methods, racemic cyclisation procedures often tolerate more diverse substrates. For example, Rawal's Heck coupling of iodide **149** to construct the hexacyclic core **150** of the *Strychnos* alkaloids features a pendant protected alcohol (Scheme 2.2 A).[65] Bonjoch and Solé developed a palladium-catalysed enolate alkenylation to generate trialkyl-substituted alkenes **152**,[66,67] and applied the method towards a synthesis of strychnopivotine (**153**; Scheme 2.2 B).[68] A key advantage of such palladium-catalysed methods is retention of the alkene geometry during product formation.



Reagents and conditions: (a) $Pd(OAc)_2$, Bu_4NCl, DMF, K_2CO_3, 70 °C, 3 h, 74%; (b) $Pd(PPh_3)_4$, PhOK, 56%; (c) $Pd(PPh_3)_4$, PhOK, THF, reflux, 52%.

Scheme 2.2: Synthesis of structures containing the morphan core by A. Rawal and B. Bonjoch, *en route* to the total syntheses of strychnine and strychnopivotine respectively.

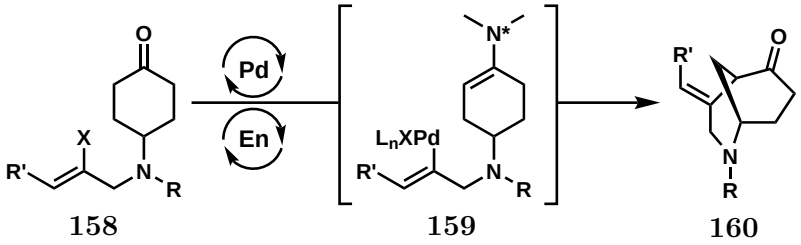
In 2016, Jia and co-workers reported the first example of an asymmetric synthesis of the benzazocine core, an arylated derivative of the morphan core (Scheme 2.3).[69] The authors employed a co-operative palladium(II)/amine catalyst system to carry out an intramolecular Heck-type cyclisation of aryl bromides **154**. Using L-proline (**155**) resulted in formation of chiral enamine complex **156** which enabled the synthesis of a range of benzazocine derivatives **157** with excellent yields and enantioselectivities (up to 99% ee). Prior attempts to develop a similar method using chiral phosphine ligands by Bonjoch and co-workers had been unsuccessful.[70]



Reagents and conditions: (a) L-proline (10 mol%), $Pd(OAc)_2$ (5 mol%), PPh_3 (12 mol%), K_3PO_4 (1.5 equiv), AcOH (1.5 equiv), MeOH, 85 °C, 24 h.

Scheme 2.3: Enantioselective construction of benzazocine core derivatives **157** by Jia, using a co-operative palladium(II)/amine catalyst system.

At the outset of this project there were no examples of a highly enantioselective synthesis of trisubstituted alkene derivatives of the morphan core **160** (Scheme 2.4).† Inspired by the broad substrate tolerance of racemic methods and recent work by the Jia group, an alternative method was proposed in order to desymmetrise substituted 4-*N*-(2-bromoallyl)cyclohexanones **158**. By combining palladium catalysis for C−Br bond insertion and chiral enamine catalysis for activation of the ketone, a co-catalytic approach was envisaged to enable the synthesis of enantioenriched morphan core derivatives **160**. If successful, such an approach could allow access to a range of natural product scaffolds to target the *Daphniphyllum* and *Strychnos* alkaloids, in addition to the opioids, the akuammilines, and many others.



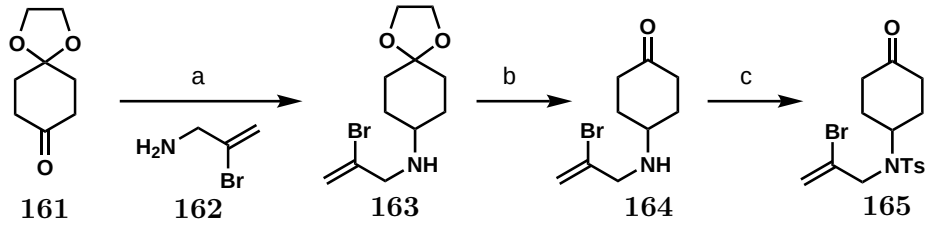
Scheme 2.4: Proposed strategy to access a range of morphan core derivatives **160** via desymmetrisation of vinyl bromides **158** using Pd(II)/amine co-catalysis.

†In the course of this work, the Jia group disclosed a similar transformation resulting in the synthesis of di- and tri-substituted morphan core derivatives with low enantioselectivities (up to 50% ee).[71]

2.2 Reaction Development

2.2.1 Synthesis of Starting Materials

In order to probe the feasibility of this transformation, vinyl bromide **165** was selected as a model substrate; the absolute configuration of both enantiomers of the *N*-Ts-protected cyclised product (**166**) had previously been confirmed by single crystal X-ray diffraction studies, which would enable rapid and unambiguous determination of the stereochemical configuration of the resulting product.[56] Vinyl bromide **165** was synthesised from readily available ketone **161** by reductive amination with **162**, followed by *N*-Ts protection of the secondary amine and deprotection of the acetal in excellent overall yield (85% over three steps; Scheme 2.5).



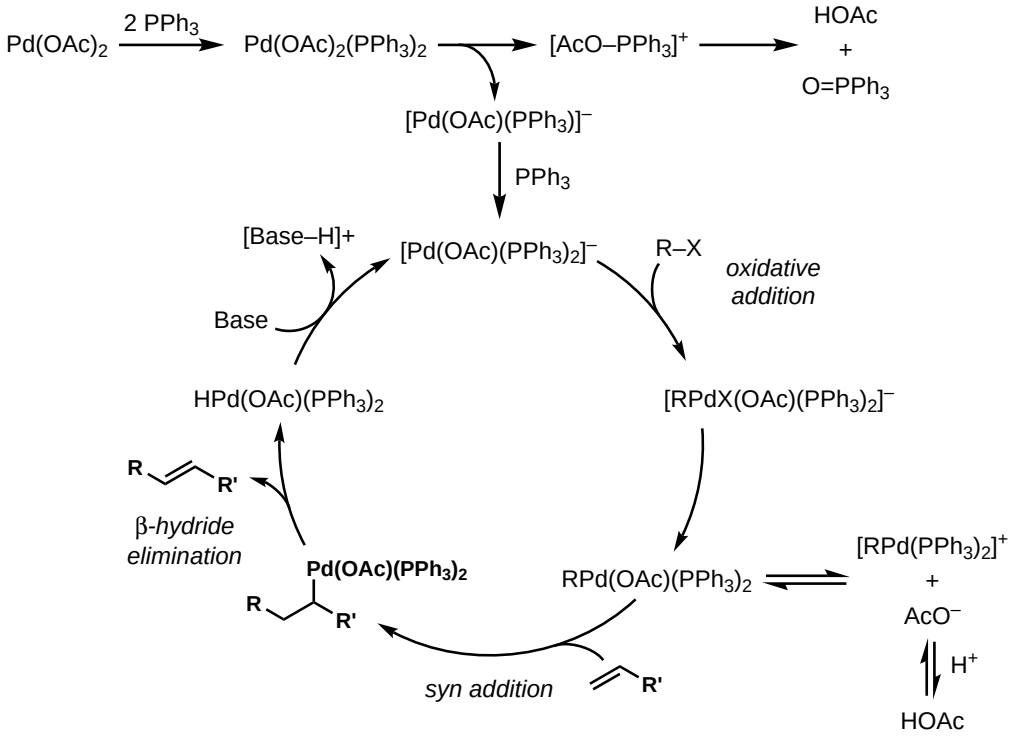
Reagents and conditions: (a) **162**, $NaBH(OAc)_3$, DCE, RT, 24 h, 95%; (b) HCl (3 M, aq.), THF, RT, 24 h, 97%; (c) TsCl, Et_3N, DMAP, CH_2Cl_2, RT, 72 h, 86%. Reactions carried out by Nikita Chekshin.

Scheme 2.5: Synthesis of *N*-Ts protected vinyl bromide **165** from ketone **161**.

2.2.2 Initial Catalyst System and Choice of Base

A common catalyst/ligand manifold for Heck-type cyclisations employs Pd(II) catalysts such as $Pd(OAc)_2$ and triarylphosphine ligands such as PPh_3.[72–74] In general, the activation of $Pd(OAc)_2$ begins with the addition of two equivalents of PPh_3 to generate $Pd(OAc)_2(PPh_3)_2$ (Scheme 2.6). This is followed by loss of the phosphonium salt $[AcO{-}PPh_3]^+$, which is then hydrolysed to form $Ph_3P{=}O$. The resulting

anionic complex $[Pd(OAc)(PPh_3)]^-$ undergoes further addition of PPh_3 to form the reactive species for oxidative addition, $[Pd(OAc)(PPh_3)_2]^-$. From this stage, oxidative addition, *syn*-addition of the olefin, and β-hydride elimination take place to generate the product. Following this, the Pd-hydride species $HPd(OAc)(PPh_3)_2$ is recycled to the anionic complex $[Pd(OAc)(PPh_3)_2]^-$.

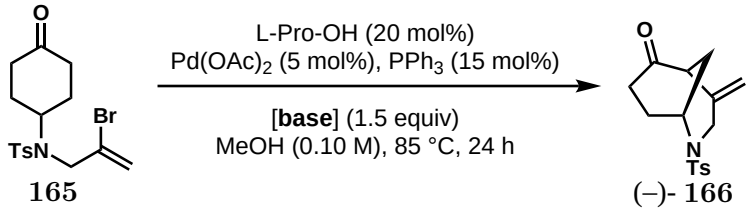


Scheme 2.6: General catalytic cycle for Heck-type reactions catalysed by Pd(0), including the activation of Pd(II) complexes with triarylphosphine ligands.

While a base is required to recycle the Pd(II) hydride species $HPd(OAc)(PPh_3)_2$ back to the active Pd(0) catalyst complex $[Pd(OAc)(PPh_3)_2]^-$ following β-hydride elimination, several of the other steps are affected by base in subtle ways. For example, the presence of base can slow oxidative addition by stabilising the anionic complex $[Pd(OAc)(PPh_3)_2]^-$. However, following oxidative addition, neutralisation of protons by the base can help maintain a high concentration of the reactive $[RPd(OAc)(PPh_3)_2]$ species, in turn accelerating the rate of reaction with the olefin. Consequently, the choice of base can have a significant impact on the reaction outcome due to its involvement at several different stages during the process.

Reaction development began using $Pd(OAc)_2$ and PPh_3, a common system for similar transformations, and L-proline as the organocatalyst inspired by the work of Jia and co-workers.[69] In the absence of base, or with AcOH, ketal formation of **165** occurred, thus preventing cyclisation taking place (Table 2.1, Entries 1 and 2). Using Cs_2CO_3, NaOAc, and K_3PO_4 resulted in formation of the cyclised product (–)-**166** in low yields and promising levels of enantioselectivity (up to 68% ee; Entries 4–7). With either K_2HPO_4 or KOAc, the yield was improved (up to 28%) and high levels of enantioselectivity (up to 82% ee) were observed (Entries 8 and 9). Further improvements were obtained at a lower reaction concentration; (–)-**166** was afforded in 40% yield and 86% ee at a concentration of 0.05 M (Entry 11).

Table 2.1: Initial optimisation of reaction parameters.



165 (–)- **166**

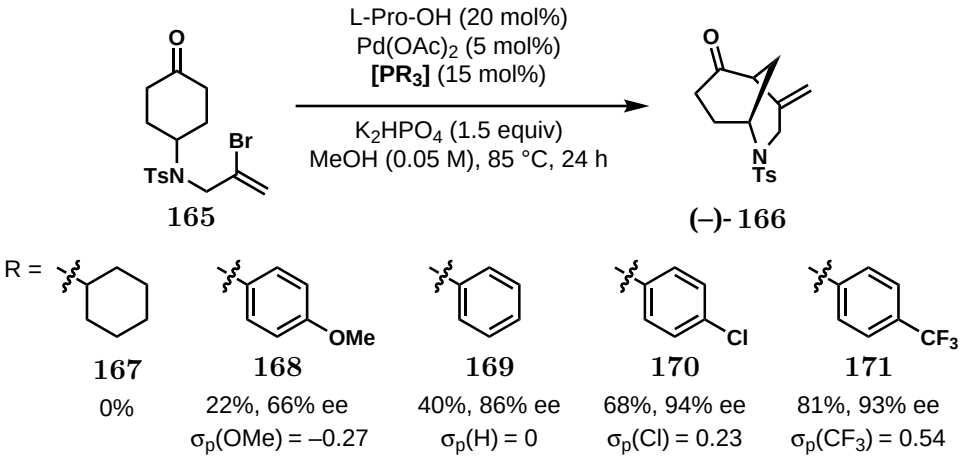
Entry	Base	Changes	Yield (%)	ee (%)
1	None	-	0	n/a
2	None	AcOH (1.5 equiv)	0	n/a
3	K_2CO_3	-	0	n/a
4	Cs_2CO_3	-	16	29
5	NaOAc	-	15	68
6	K_3PO_4	-	17	42
7	K_3PO_4	AcOH (1.5 equiv)	27	75
8	KOAc	-	28	82
9	K_2HPO_4	-	27	82
10	K_2HPO_4	0.20 M	16	86
11	**K_2HPO_4**	**0.05 M**	**40**	**86**

Reagents and conditions: Reactions were carried out on 0.10 mmol scale in sealed 12 mL screw-cap tubes. Reactions were degassed using pump-fill cycles and were sealed under Ar. Yields were determined by ^{1}H NMR analysis of crude reaction mixtures and were calculated relative to an internal standard (mesitylene).

[†]Preliminary studies showed that $Pd(OAc)_2$ was superior to other Pd(II) or Pd(0) catalysts tested. Additionally, these studies found that MeOH offered superior results compared to several other solvents.[75]

2.2.3 Phosphine Ligand Optimisation

At this stage, the effect of the phosphine ligand was investigated (Scheme 2.7). Trialkylphosphines such as PCy_3 (**167**) were found to be ineffective as no reaction took place, while triarylphosphines with *para*-electron donating groups (such as –OMe, **168**) resulted in a lower yield (22%) and enantioselectivity (66% ee) of (–)-**166** compared to using PPh_3. On the other hand, triarylphosphines with *para*-electron withdrawing groups offered a significant improvement; (–)-**166** was obtained in good yield (81%) and excellent enantioselectivity (93% ee) using *para*-trifluoromethyl-susbtituted triarylphosphine **171**.



Scheme 2.7: Optimisation of phosphine ligand. Hammett constants (σ_p) given for *para*-substituents.[76]

In general, the presence of electron-donating groups on phosphine ligands improves the rate of oxidative addition, while the presence of electron-withdrawing groups improves the rate of elimination. In addition, the conversion of $Pd(OAc)_2$ to Pd^0 by *para*-substituted triarylphosphines is faster with electron-withdrawing groups.[72] A possible explanation for the observed ligand effect is that differences in the rates of oxidative addition or β-hydride elimination could lead to changes in the distribution between the productive reaction pathway (i.e. product formation) and non-productive pathways (such as decomposition of the intermediate Pd complex).

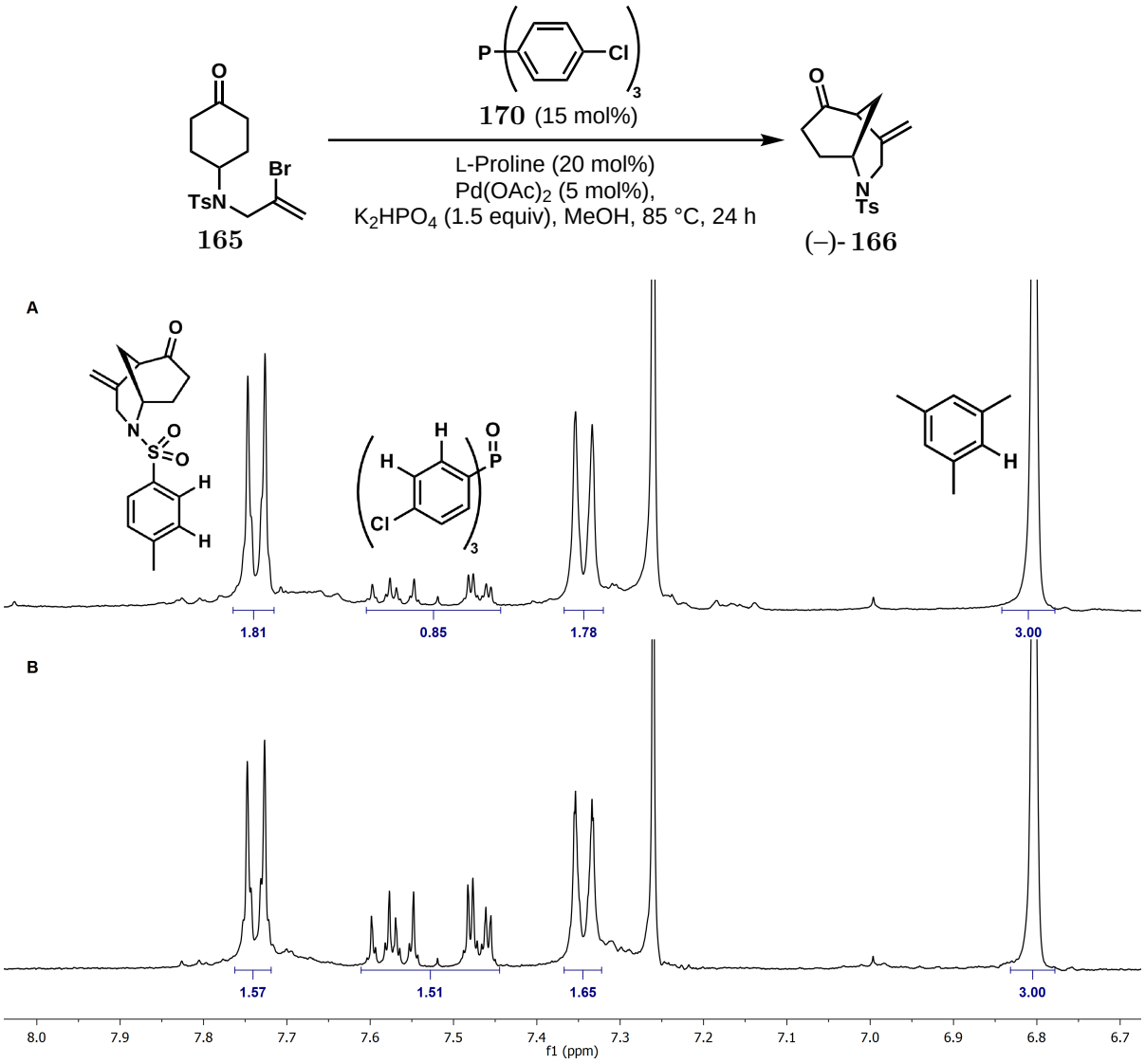
Furthermore, the increase in enantioselectivity with electron-deficient phosphine ligands could indicate improved coordination between the organocatalyst carboxylate moiety and the palladium complex as a result of the reduced electron density at Pd.

2.2.4 Reproducibility

Although the use of *para*-substituted triarylphosphines bearing electron-withdrawing groups improved the yield and enantioselectivity greatly, this led to poorer reproducibility. Repeated reactions fell broadly into two categories: those in which (–)-**166** was formed in excellent yield and enantioselectivity (>90% ee), and those with poor conversion and enantioselectivity (ca. 70% ee). Inspection of crude reaction mixtures by ^{1}H NMR showed a correlation between the amount of triarylphosphine oxide observed and the reaction outcome. For example, in reactions that employed **170** as the phosphine ligand, when the product was formed in high yield and enantioselectivity the crude reaction mixtures contained approximately 7 mol% phosphine oxide (**172**) on average (Scheme 2.8). By contrast, reactions which were unsuccessful contained 13 mol% phosphine oxide on average.

In general, the complete formation of Pd^0 from $Pd(OAc)_2$ requires three equivalents of PAr_3 and generates one equivalent of $Ar_3P{=}O$ (Scheme 2.6). Therefore, the presence of more than 5 mol% of phosphine oxide **172** in the ^{1}H NMR spectra of crude reaction mixtures is indicative of over-oxidation of the phosphine ligand **170**. Repeating the reaction with more careful and rigorous exclusion of oxygen led to restored reactivity and good reproducibility. This was achieved by degassing the reaction vessel prior to and following addition of solid reagents and solvent, using a combination of high-vacuum[†] and Ar (see Experimental Section, pp. 120 for details).

[†]High-vacuum refers to <1 mbar, low-vacuum refers to ca. 10–20 mbar.



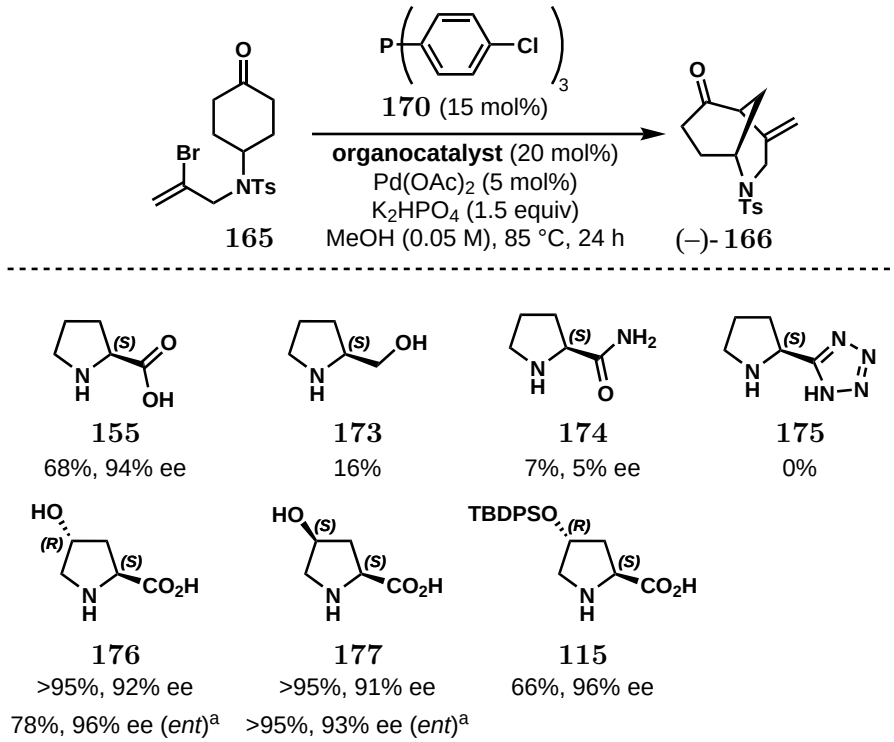
Scheme 2.8: Comparison of ^{1}H NMR spectra of crude reaction mixtures in which A: the reaction proceeds well with high yield and enantioselectivity and 7 mol% of phosphine oxide **172** is observed, and B: the reaction is incomplete with poorer enantioselectivity, and approximately 13 mol% **172** is observed.

2.2.5 Organocatalyst

At this stage, the *N*-Ts-protected bicycle (–)-**166** could be formed in high yields (up to 81%) and enantioselectivities (up to 94% ee) by employing L-proline as the organocatalyst in combination with *para*-chloro- or *para*-trifluoromethyl-substituted triarylphosphine ligands **170** or **171** respectively. By varying the organocatalyst, it was envisaged that an improvement in the yield of (–)-**166** could be achieved. In general, the organocatalysts investigated were five-membered cyclic secondary amines.

Other organocatalyst classes such as acyclic amino acids (e.g. L-*tert*-leucine) or cinchona alkaloid derivatives (e.g. 9-aminocinchonine) did not result in product formation.

In the presence of phosphine ligand **170**, prolinol (**173**) and prolinamide (**174**) performed poorly, affording the product in 16% and 7% yield respectively (Scheme 2.9). Furthermore, enantioselectivity with **174** was poor (5% ee). Proline tetrazole catalyst **175** was also investigated. Tetrazoles are often employed as carboxylic acid bioisosteres due to the similar pKa values of both groups. Surprisingly, however, no reaction took place when **175** was used as the organocatalyst.

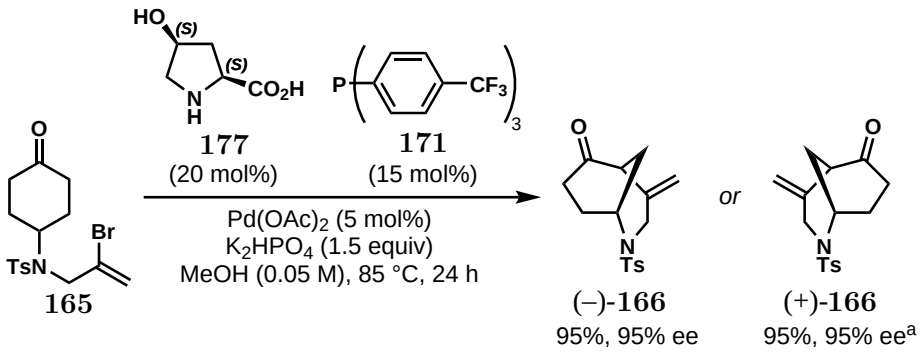


Scheme 2.9: Optimisation of organocatalyst. [a]The enantiomeric organocatalyst was used to produce (+)-**166**.

Given the apparent importance of the carboxylate moiety, additional organocatalysts containing carboxylic acids were investigated. Employing (2*S*,4*R*)-4-hydroxyproline **176** led to a drastic improvement in the outcome of the reaction; (–)-**166** was formed in excellent yield (>95%) and enantioselectivity (92% ee). Additionally, use

of the enantiomeric catalyst enabled formation of (+)-**166** in 96% ee.† Interestingly, the use of the C-4 epimeric catalyst **177** had no significant impact on enantioselectivity compared with **166**. This suggests that the 4-hydroxyl group has minimal effect on enantioselectivity, likely due to its remote location. The silyl-protected 4-hydroxyproline catalyst **115** also led to formation of (–)-**166** with excellent enantioselectivity (96% ee), albeit in lower yields (66%).

The combination of (2*S*,4*S*)-4-hydroxyproline **177** as the organocatalyst and *para*-trifluoromethyl-substituted triarylphosphine **171** as the ligand led to further improvement in both yield and enantioselectivity; either enantiomer of **166** could be prepared in excellent yield (>95%) and enantioselectivity (95% ee) by employing **177** or *ent*-**177** (Scheme 2.10).



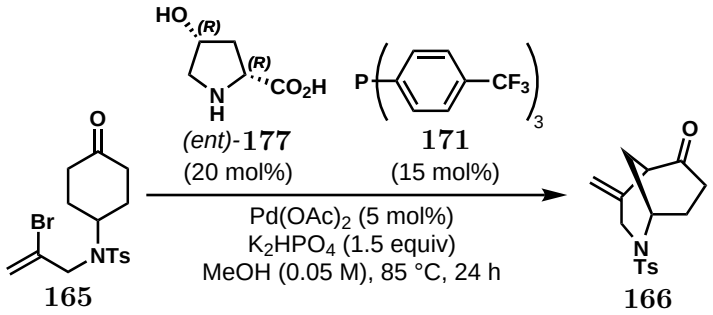
Scheme 2.10: Optimised conditions for the synthesis of **166** in excellent yield and enantioselectivity. [a]The enantiomeric organocatalyst *ent*-**177** was used to produce (+)-**166**.

†The reduced yield obtained using *ent*-**176** is believed to be caused by an impure batch of commercial catalyst. Given the evidence that the other three catalysts in the series behave nearly identically, this is the most likely explanation, although further investigation would be required.

2.3 Control Studies†

At this stage, several control studies were carried out to ascertain the importance of each reaction component (Table 2.2). In the absence of $Pd(OAc)_2$ (Entry 1) or organocatalyst (Entry 2), no reaction took place, and with no phosphine ligand there was minimal reactivity (9% yield, Entry 3). Using an achiral organocatalyst (pyrrolidine) led to formation of racemic product in 23% yield. Additionally, earlier studies demonstrated that no reaction took place in the absence of base (see Section 2.2.2). Together, these results demonstrated that each reaction component was vital, and that minimal background reaction takes place in the absence of any single component.

Table 2.2: Control studies to determine the importance of each reaction component.



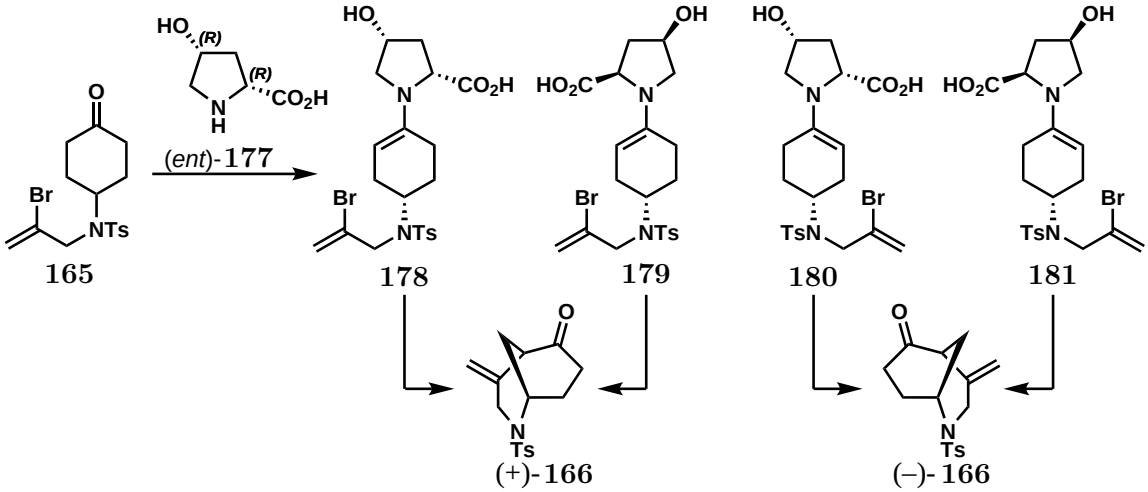
165 **166**

Entry	Change from Standard Conditions	Yield (%)
1	No $Pd(OAc)_2$	0
2	No **177**	0
3	No **171**	9
4	pyrrolidine instead of **177**	23 (rac)

†The work described in this section was carried out by a Part II student, Jack Hayward Cooke, under my supervision, and is included here for completeness.

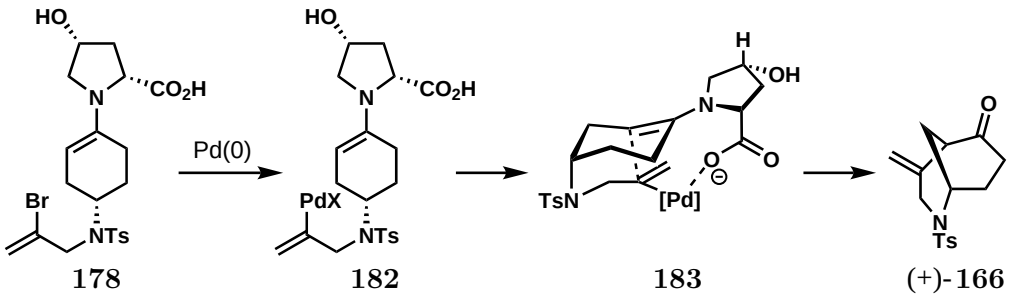
2.4 Mechanistic Proposal

Enamine formation between (2*R*,4*R*)-4-hydroxyproline and the substrate **165** will be rapid and reversible; the rotameric and diastereomeric forms (**178**–**181**) will be accessible and in equilibrium (Scheme 2.11). From single crystal X-ray diffraction studies, it is known that *ent*-**177** affords (+)-**166**, which must therefore arise from the rotamers **178** or **179** – the other possibilities would lead to formation of (–)-**166**.



Scheme 2.11: Possible enamine diastereomers and rotamers formed during the reaction between ketone **165** and (*ent*)-**177**.

Organocatalyst optimisation studies signified the importance of the carboxylate moiety; employing catalysts with blocking groups was not effective, and catalysts featuring other polar groups such as amides or tetrazoles were inferior to a carboxylic acid. This enhanced reactivity is likely the result of coordination or otherwise association of the carboxylate moiety of the organocatalyst with the palladium(II) complex resulting from oxidative insertion of Pd(0) into the C–Br bond. Our assumption is that the following step is enantiodetermining, which could be either carbopalladation or enamine metallation (with subsequent reductive elimination to result in C–C bond formation.) Thus the high enantioselectivity is a result of preferential coordinated delivery of the C–Pd bond to the bottom face of **178** (Scheme 2.12).



Scheme 2.12: Proposed coordinated delivery of the Pd−C bond.

2.5 Scope†

With conditions established to synthesise the model system **166** in excellent yield (95%) and enantioselectivity (95% ee), the scope of the reaction was next investigated. These studies were focussed on introducing variation in three key ways: substituents on nitrogen, fully functionalised carbon centers, and trisusbtituted alkenes.

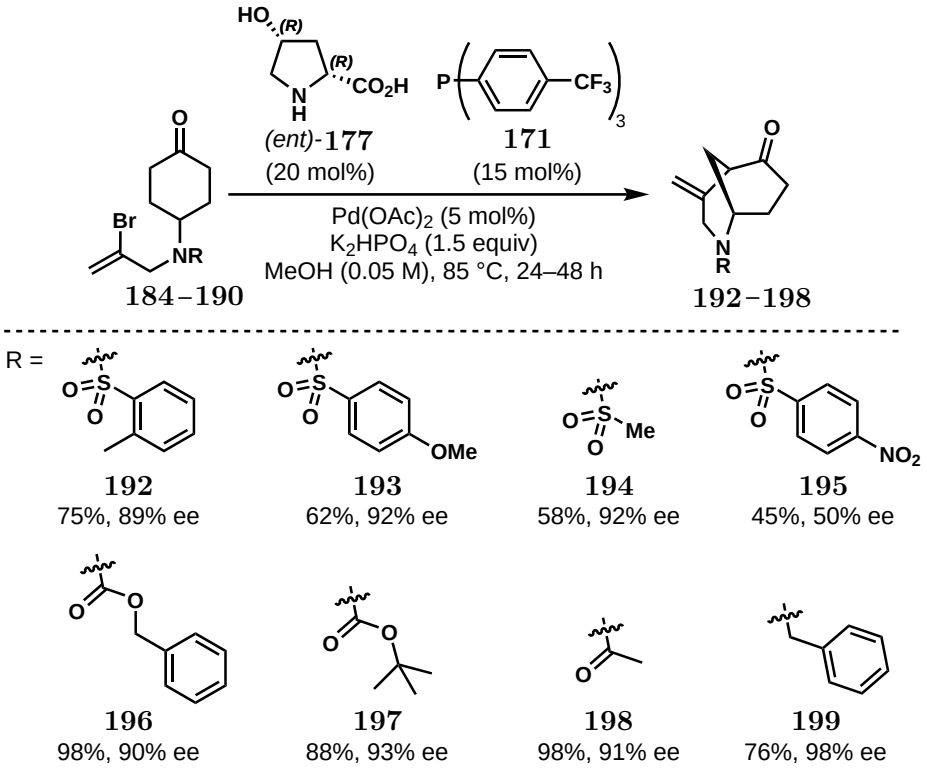
2.5.1 Variation at Nitrogen

The ability of the reaction to tolerate a range of substituents on nitrogen was considered important in order to access highly functionalised morphan core derivatives. Amine substituents could serve as protecting groups or as additional functionality which may be useful for further transformations.

The preparation of *N*-substituted starting materials **184** – **190** was carried out from secondary amine **164** using standard procedures (see Experimental section for details). The *N*-*o*Ts-, *N*-Mbs- and *N*-Ms-protected protected bicycles (**192**, **193** and **194** respectively) were formed in good yields and with excellent enantioselectivities (up to 92% ee) (Scheme 2.13). These results demonstrate good tolerance for commonly employed sulfonamides. By contrast, the *N*-Ns-protected bicycle **195** was formed in only moderate yield (45%) and enantioselectivity (50% ee). The

†The work described in this section was carried out by a Part II student, Jack Hayward Cooke, under my supervision, and is included here for completeness.

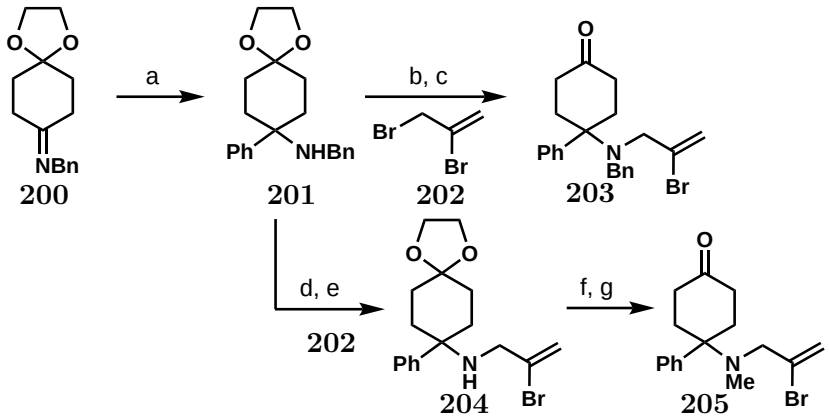
poor results obtained when using sulfonamides with strongly electron-withdrawing groups suggests the possibility of an interaction between the sulfonamide moiety and the catalyst-ligand complex. The *N*-Cbz-, *N*-Boc-, and *N*-Ac-substituted bicycles (**196**–**198**) were formed in excellent yields (up to 98%) and enantioselectivities (up to 93% ee), demonstrating good tolerance for amide substrates. Furhtermore, the *N*-Bn derivative was formed in high yield (76%) and excellent enantioselectivity (98% ee) demonstrating good reactivity in the absence of substituents containing Lewis basic heteroatoms, expanding the potential applications for this reaction.



Scheme 2.13: Scope of reaction for substrates bearing various amine substituents.

2.5.2 Fully Substituted Carbon at C-4

The cyclisation of achiral substrates possessing a fully substituted carbon at C-4 would generate products with α-tertiary amines. The introduction of a phenyl substituent at C-4 was achieved by addition of phenyl lithium into imine **200** to afford amine **201** (Scheme 2.14). Alkylation of **201** with 2,3-dibromopropene followed by hydrolysis of the ketal afforded *N*-Bn substrate **203**. Alternatively, deprotection of the benzyl group followed by alkylation with 2,3-dibromopropene afforded amine **204**, which could undergo methylation of the amine and ketal deprotection to yield *N*-Me substrate **205**.

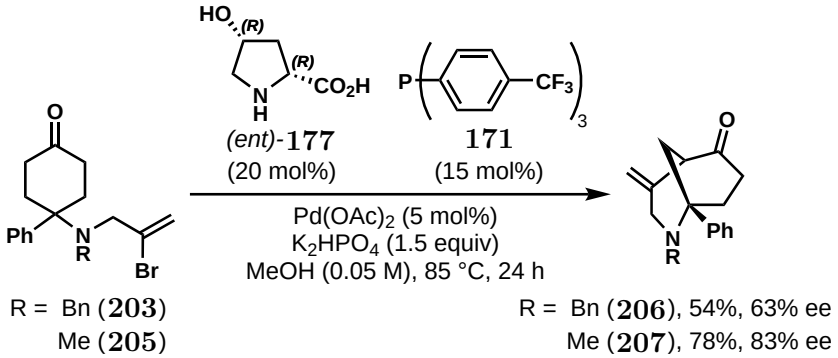


Reagents and conditions: (a) PhLi (2 equiv), $BF_3 \cdot OEt_2$ (2 equiv), THF, –78 °C to RT, 3 h, 67%; (b) **202** (4 equiv), K_2CO_3 (4 equiv), MeCN, 60 °C, 16 h, 57%; (c) HCl (3 M), THF, RT, 2 d, 68%; (d) Pd/C (10 mol%), H_2 (1 bar), MeOH/AcOH (20:1), RT, 24 h, 92%; (e) **202** (1 equiv), K_2CO_3 (2 equiv), MeCN, 60 °C, 16 h, 70%; (f) $(CH_2O)_n$ (8 equiv), AcOH (8 equiv), $NaBH_3CN$ (2 equiv), MeOH, RT, 2 h, 60%; (g) HCl (3 M), THF, RT, 2 d, 88%.

Scheme 2.14: Synthesis of substrate for cyclisation bearing fully substituted carbon at C-4.

Both **203** and **205** underwent cyclisation on subjection to the standard reaction conditions. The *N*-Bn substituted cyclised product was formed in lower yield (54%) and enantioselectivity (63% ee) compared to the corresponding α-secondary amine **199** (76%, 98% ee). This suggests that the presence of additional substituents at the α-positon hinders reactivity in this case. Pleasingly, the *N*-Me substituted

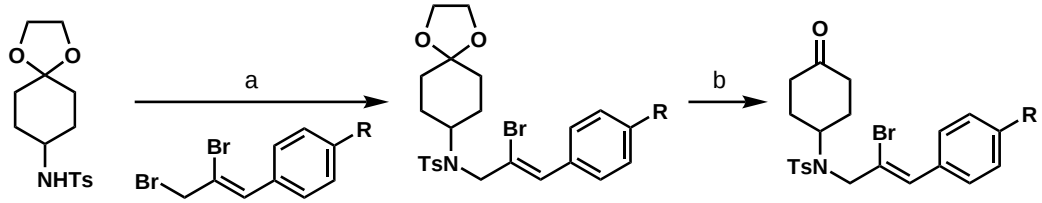
bicycle **207** was formed in high yield (78%) and excellent enantioselectivity (95% ee), demonstrating the tolerance of these reaction conditions to amine functionality in the substrate.



Scheme 2.15: Synthesis of bicyclic product **207**, containing a fully substituted stereogenic carbon center.

2.5.3 Trisubstituted Alkenes

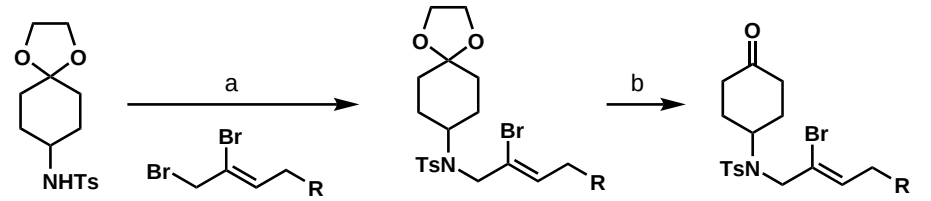
The ability to form trisubstituted alkene products via this reaction was of particular importance due to the potential application to a wide variety of natural product scaffolds. Formation of trisubstituted styrenyl bromide substrates **213** and **214** was achieved by substitution of bromides **209** and **210** with amine **208**, followed by ketal hydrolysis (Scheme 2.16).



Reagents and conditions: (a) **209** or **210**, K_2CO_3, MeCN, 80 °C, 16 h, 74% (R=H); 55% (R=OMe); (b) HCl (3 M, aq.), THF, RT, 3 d, 80% (R=H); 99% (R=OMe).

Scheme 2.16: Synthesis of trisubstituted alkene substrates **213** and **214**.

Trialkylsubstituted vinyl bromides **219** and **220** were prepared analogously by alkylation of amine **208** with bromides **215** and **216** (Scheme 2.17).



Reagents and conditions: (a) **215** or **221**, K_2CO_3, MeCN, 80 °C, 16 h, 59% (R=CH_2CH_3); 46% (R=OTBS); (b) HCl (3 M, aq.), THF, RT, 3 d, 89% (R=CH_2CH_3); 70% (R=OTBS).

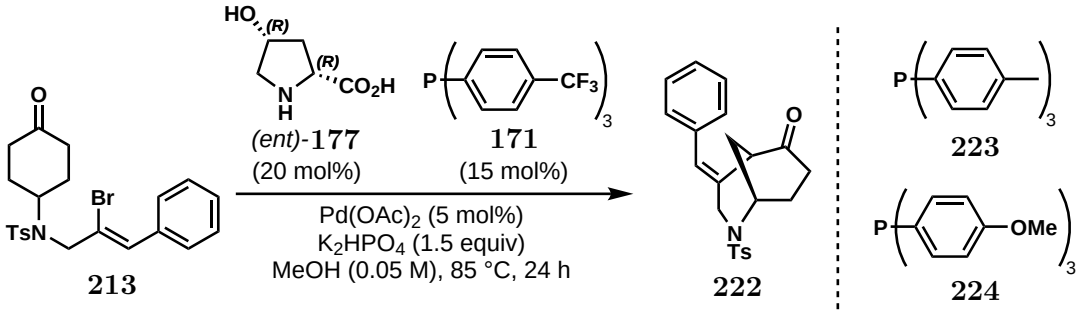
Scheme 2.17: Synthesis of trisubstituted alkene substrates **219** and **220**.

Under the optimised cyclisation conditions employed thus far, the cyclisation of phenyl-substituted alkene **213** took place in low yield (22%, Table 2.3, Entry 1). Despite the low yield, formation of the product was promising and demonstrated the capability of this catalyst system to afford trisubstituted alkene products. Increasing the temperature led to an improvement in yield (up to 80%) and moderate enantioselectivity (up to 50% ee), although increasing reaction time offered no further improvement (Entries 2 and 3). Doubling the loading of the palladium catalyst, organocatalyst and phosphine ligand improved the yield and enantioselectivity (Entry 4), and combining this with higher temperatures (100 °C) led to formation of **222** in good yield (82%) and with moderate enantioselectivity (60% ee). Furthermore, increasing the amount of K_2HPO_4 used from 1.5 to 3.0 equivalents afforded **222** in quantitative yield but again offered no improvement in enantioselectivity (60% ee, Entry 6).

Interestingly, carrying out the reaction using PPh_3 instead of **171** led to a significant improvement in enantioselectivity; **222** was formed in 88% ee (Entry 7). As a result, triarylphosphines bearing *para*-electron-donating groups were investigated. Using *para*-tolyl-susbtituted triaryl phosphine **223** led to formation of **222** in good yield (78%) and very high enantioselectivity (88% ee); similar results were observed using **223** at 100 °C with the standard catalyst, ligand, and base loadings (Entry 9).

Finally, using $P(PMP)_3$ (**224**) as the phosphine ligand at 100 °C afforded **222** in excellent yield (89%) and enantioselectivity (91% ee, Entry 10).

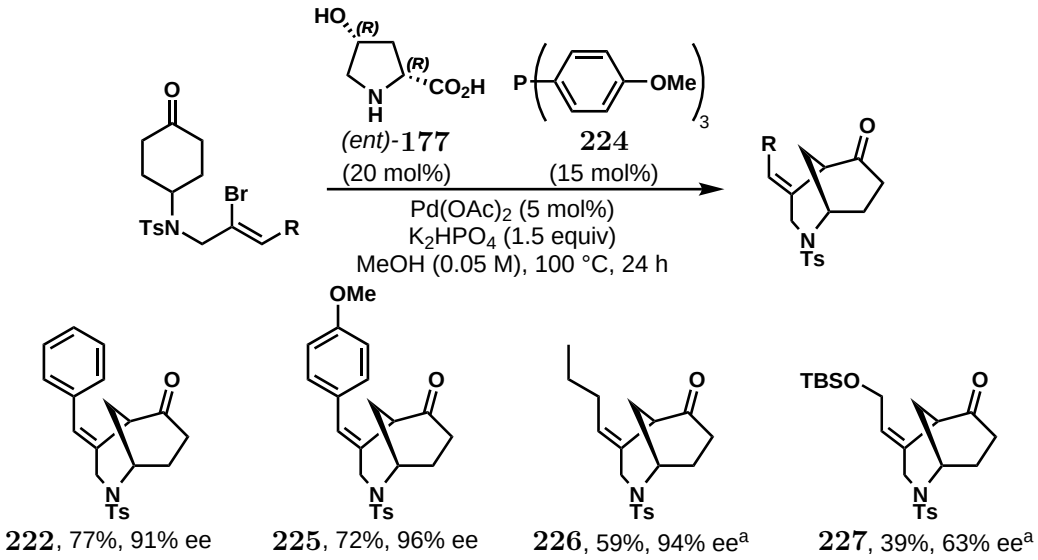
Table 2.3: Modifying reaction conditions for trisubstituted alkene substrates.



Entry	Change from Standard Conditions	Yield (%)	ee (%)
1	None	22	nd
2	95 °C	80	50
3	95 °C, 37 h	80	50
4	Catalyst and ligand loadings doubled[a]	40	60
5	100 °C, Catalyst and ligand loadings doubled[a]	82	60
6	100 °C, Catalyst, ligand, and base loadings doubled[a,b]	99	60
7	As in Entry 6, substituting PPh_3 (30 mol%) for **171**	78	88
8	As in Entry 6, substituting **223** (30 mol%) for **171**	78	90
9	100 °C, substituting **223** for **171**	68	88
10	**100 °C, substituting 224 for 171**	**89**	**91**

[a]$Pd(OAc)_2$ (10 mol%), **171** (30 mol%), **177** (40 mol%); [b] K_2HPO_4 (3 equivs). Yields were determined by ^1H NMR analysis of crude reaction mixtures relative to an internal standard (mesitylene).

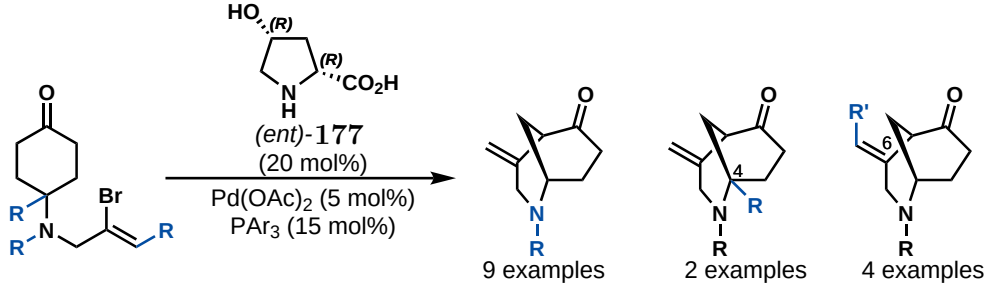
Under these modified conditions the synthesis of several trisubstituted alkene products was possible (Scheme 2.18). Aryl-substituted cyclised products **222** and **225** were formed in good yield (72 and 77% respectively) and excellent levels of enantioselectivity (91 and 96% respectively). Alkyl substituted products could also be formed, with **226** being formed in moderate yield (54%) and with similarly high levels of enantioselectivity (94% ee). Products containing heteroatoms, such as **227**, could also be formed, albeit with lower yield and enantioselectivity.



Scheme 2.18: Scope of reaction for the synthesis of trisubstituted alkene products. [a]Carried out using PPh_3 instead of **224**.

2.6 Conclusions and Future Work

In this chapter, the development of a novel and highly enantioselective method for the synthesis of morphan core derivatives has been developed. This co-catalytic process employs $Pd(OAc)_2$ and 4-hydroxyproline, both of which are commercially available and affordable components. A wide scope has been demonstrated, showing tolerance for a range of substituents on nitrogen, in addition to C-4 which allows for the synthesis of α-tertiary amines, and at C-6 which affords trisubstituted alkene derivatives. As a result, this method shows promise for accessing a broader range of natural product scaffolds than was previously possible.

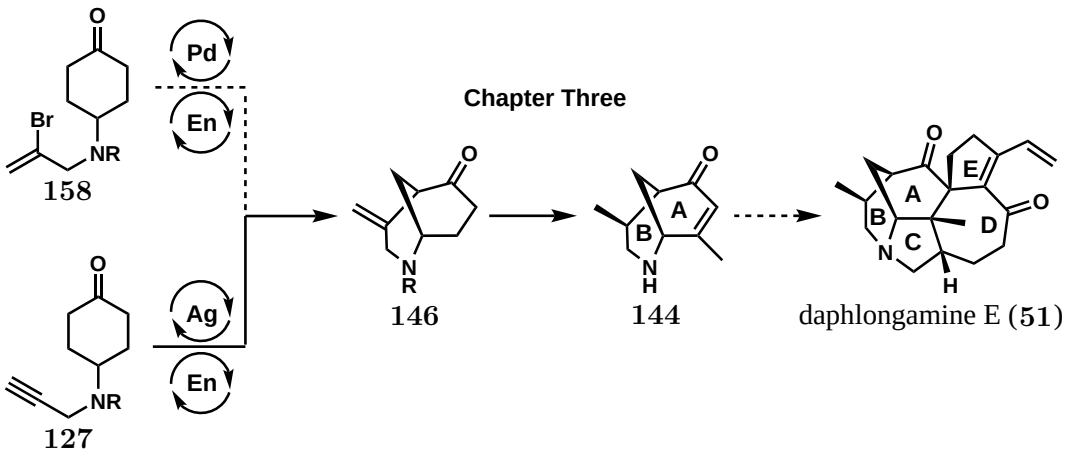


Scheme 2.19: Summary of highly enantioselective co-catalytic method developed to access morphan core derivatives.

Chapter 3

Functionalisation of the Morphan Core

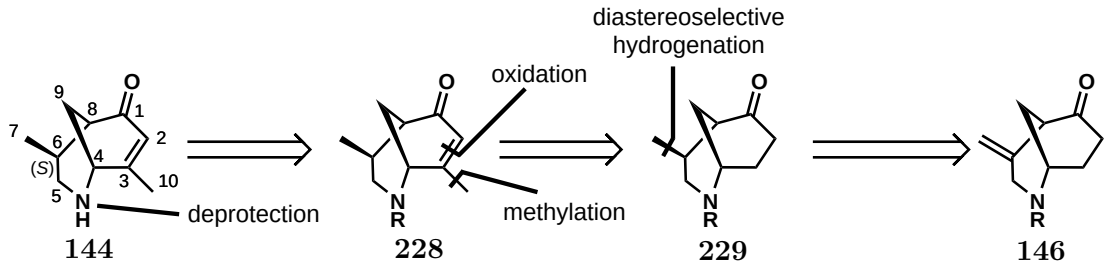
In the previous chapter, a new enantioselective method to construct the methylene-substituted morphan core was developed using a co-operative Pd(II)/amine catalyst system. The preparative scale synthesis of the bicyclic core was investigated in parallel, applying the Ag(I)/amine co-catalysed desymmetrisation of alkynes previously disclosed by the Dixon group.[56] This chapter will describe optimisation of the Ag(I)/amine co-catalysed desymmetrisation to enable a large scale synthesis of bicycle **146**, and the subsequent transformations required to provide the fully functionalised AB core **144** (Scheme 3.1).



Scheme 3.1: Overview of Chapter Three.

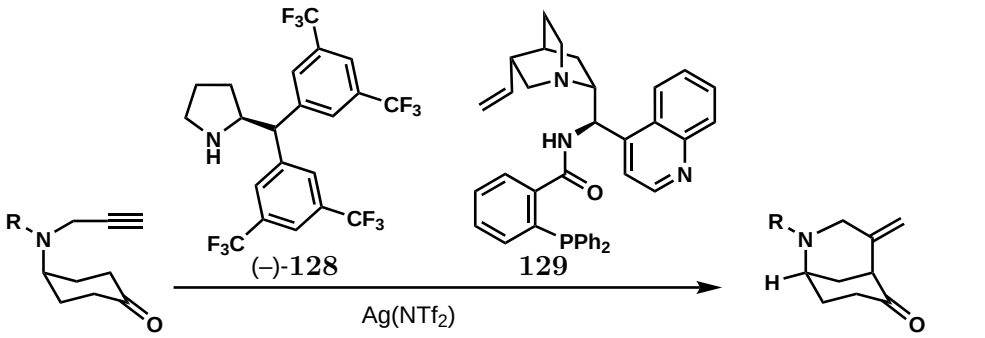
3.1 Synthetic Strategy

Functionalisation of the bicyclic core **144** would involve several transformations (Scheme 3.2): (i) diastereoselective hydrogenation of the exocyclic alkene to form the *6S* diastereomer, (ii) installation of the methyl group at C-3, (iii) formation of the C-2/C-3 enone to facilitate an intramolecular Michael addition at a later stage, and (iv) deprotection to reveal the secondary amine. The order of transformations would be largely dictated by chemoselectivity concerns; in particular, hydrogenation of the methylene group would be required before introduction of the enone.



Scheme 3.2: Strategy to access the functionalised AB core **144** from the methylene-substituted morphan core **146**.

A suitable protecting group was required such that the desymmetrisation reaction would take place in high yield and enantioselectivity. Furthermore, the protecting group must tolerate the subsequent transformations well and be readily deprotected at a suitable stage in the synthesis. As the *N*-Ts protected substrate **230** performed better than all others tested under the cyclisation conditions, it was considered as a potential candidate (Scheme 3.3). However, deprotection was anticipated to be challenging due to the harsh conditions often employed for the removal of *N*-Ts groups.[77] Other protecting groups such as *N*-Boc and *N*-Ns were considered as both are more readily deprotected. However, despite high levels of enantioselectivity during the cyclisation reaction, the respective products were afforded in low yields and were therefore deemed unsuitable.



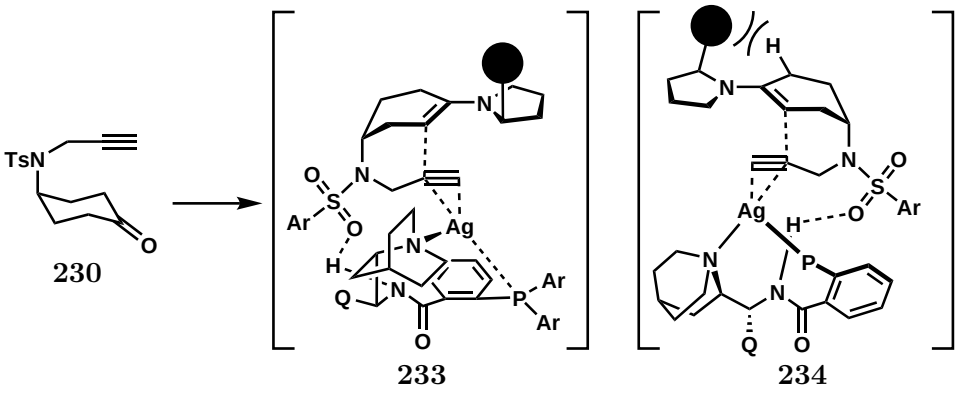
R = Ts (**230**)
Boc (**231**)
Ns (**232**)

R = Ts (**166**) 99%, 95% ee
Boc (**197**) 38%, 90% ee
Ns (**195**) 40%, 93% ee

Reagents and conditions: (–)-**128** (20 mol%), **129** (20 mol%), $Ag(NTf_2)$ (10 mol%), 2,4-dinitrophenol (20 mol%), *i*-PrOH, 60 °C, 72 h.

Scheme 3.3: Examples of *N*-protecting groups tolerated during the enantioselective desymmetrisation reaction.

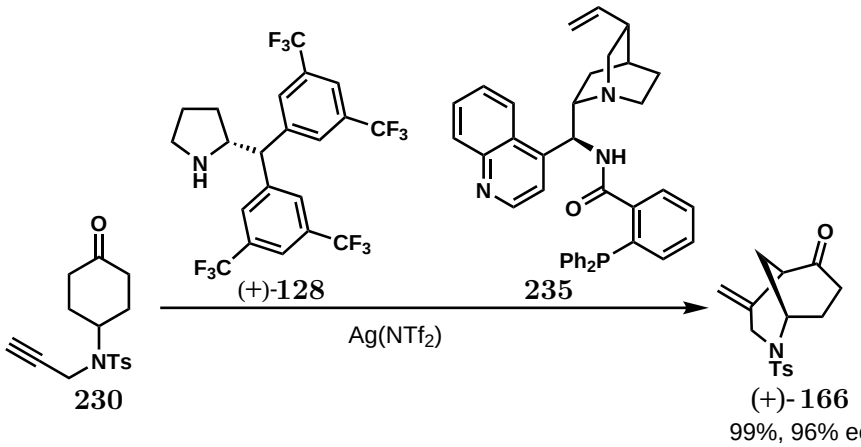
In order to understand the origins of enantioselectivity, Dixon, Paton and co-workers carried out computational studies. Computed transition structures demonstrated that the *s-cis* enamine **233** was 2.8 kcal mol^{-1} lower in energy than the *s-trans* rotamer **234**.[56] This was due to increased steric hindrance between the organocatalyst diaryl moiety and the substrate sp^3 center in the latter case compared to the sp^2 center. In addition, a secondary hydrogen-bonding interaction between the aminophosphine ligand (N–H) and the sulfonamide (S=O) was observed – this interaction would be more favoured by electron-rich sulfonamides, hence the reduced reactivity observed in the case of electron-deficient sulfonamides such as Ns.



Scheme 3.4: Computed transition structures for the Ag(I)/amine co-catalysed desymmetrisation of **230**; Q = quinolin-4-yl

3.2 Enantioselective Desymmetrisation on Scale

To produce significant quantities of enantiopure material, the enantioselective desymmetrisation reaction required optimisation to ensure scalability. Under the reported conditions,[56] both enantiomers of the *N*-Ts-protected bicycle **166** were accessible in excellent yield and enantioselectivity. Formation of (+)-**166**, which has the same stereochemical configuration as the AB core in the Calyciphylline A-type alkaloids, employs the pyrrolidinyl organocatalyst (+)-**128** and the cinchonine-derived aminophosphine ligand **235** (Scheme 3.5).



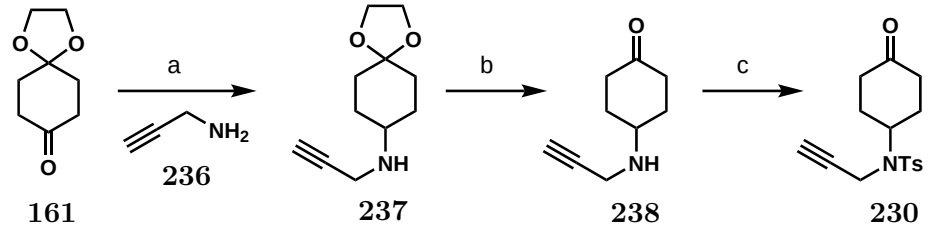
Reagents and conditions: (+)-**128** (20 mol%), **235** (20 mol%), $Ag(NTf_2)$ (10 mol%), 2,4-dinitrophenol (20 mol%), *i*-PrOH, 60 °C, 72 h, 99%, 96% ee.

Scheme 3.5: Enantioselective desymmetrisation of *N*-Ts protected alkyne **230** to afford (+)-**166**.

The high molecular weight of amine (+)-**128** and phosphine **235** meant that at 20 mol% the two components combined represented more than 36% of the reaction mass balance. Reducing the catalyst and ligand loadings would therefore be key issues to address in order to improve efficiency and practicality on scale. In addition, the reactions were carried out in sealed tubes which is well-suited to parallel screening but is prohibitive for larger scales. Before undertaking the development of a preparative scale desymmetrisation reaction, it was first necessary to synthesise alkyne **230**, organocatalyst (+)-**128**, and phosphine ligand **235** on multi-gram scale.

3.2.1 Synthesis of Starting Material

The synthesis of *N*-Ts-protected 4-propargylamino cyclohexanone was achieved in three steps from commercially available mono-protected diketone **161**. Reductive amination of ketone **161** with propargylamine using $NaBH(OAc)_3$ afforded amine **237**. Following acetal hydrolysis, the secondary amine was protected to afford alkyne **230** (Scheme 3.6). Importantly, the synthesis could be carried out on >50 g scale and purification was only required after the final step, providing significant quantities of **230** to begin working on the synthetic route.

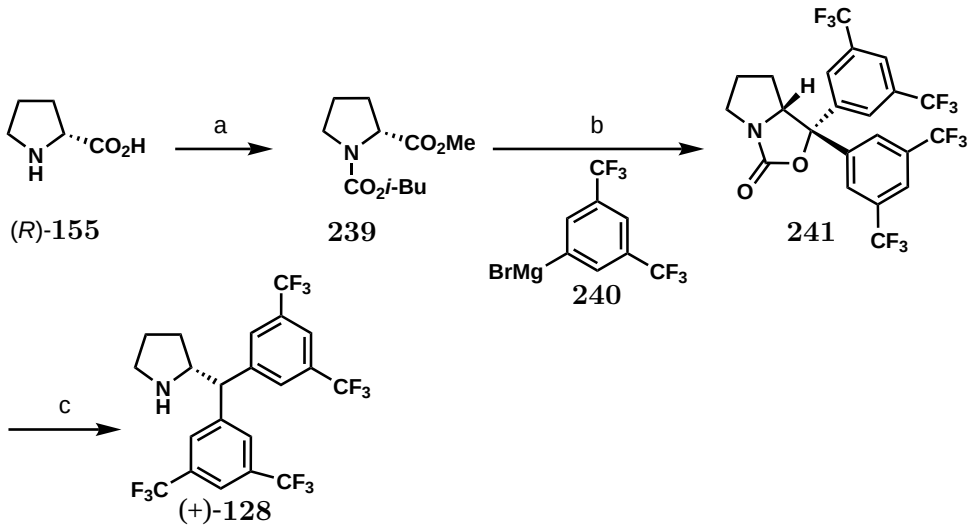


Reagents and conditions: (a) **236**, $NaBH(OAc)_3$, 1,2-dichloroethane, 0 °C then RT, 19 h; (b) 3 M HCl, THF, RT, 24 h; (c) TsCl, Et_3N, DMAP (10 mol%), CH_2Cl_2, RT, 24 h, 73% (3 steps).

Scheme 3.6: Synthesis of desymmetrisation substrate, alkyne **230**, from ketone **161**.

3.2.2 Synthesis of Pyrrolidinyl-Catalyst (+)-128

The synthesis of amine organocatalyst (+)-**128** commenced with the esterification of D-proline with isobutyl chloroformate to provide ester **239** (Scheme 3.7).[78] Addition of two equivalents of aryl Grignard **240**, formed *in situ* from the corresponding aryl bromide and magnesium, afforded bicycle **241**. Finally, hydrogenolysis of **241** afforded organocatalyst (+)-**128** in good overall yield (42%, 3 steps).[56]

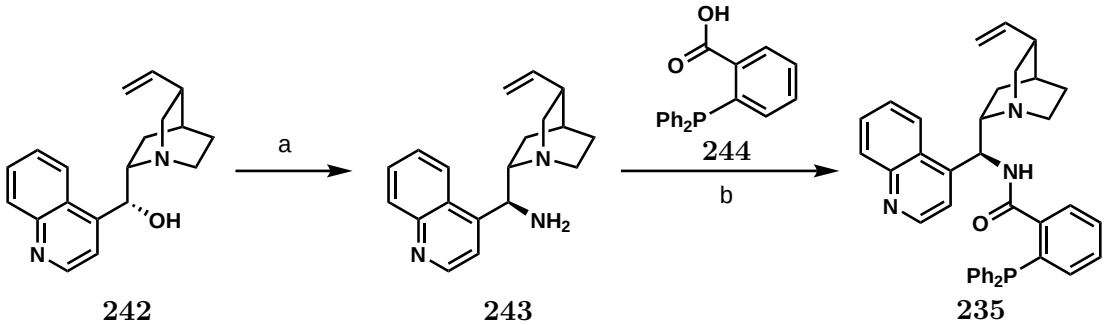


Reagents and conditions: (a) isobutylchloroformate (2.2 equiv), K_2CO_3 (1.0 equiv), MeOH, RT, 12 h, 86%; (b) **240** (2.0 equiv), THF, reflux, 3 h, 56%; (c) Pd/C (10 mol%), H_2 (1 bar), EtOH/Et_3N (18:1), RT, 16 h, 87%.

Scheme 3.7: Synthesis of organocatalyst (+)-**128** from D-proline.

3.2.3 Synthesis of Aminophosphine Ligand 235

Cinchona alkaloid-derived aminophosphine ligand **235** was prepared according to literature procedures from cinchonidine **242** (Scheme 3.8).[79,80] A Mitsunobu–Staudinger reaction sequence converted the alcohol to the corresponding amine **243**. Following this, an amide coupling reaction with 2-(diphenylphosphino)benzoic acid (**244**) afforded **235** in good yield.



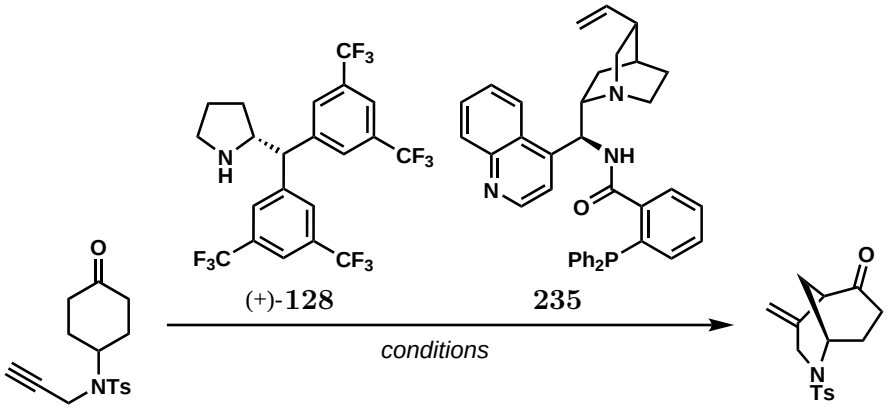
Reagents and conditions: (a) DIAD, DPPA, PPh_3, THF, RT, 4 h *then* PPh_3, H_2O, 45 °C, 14 h, 80%; (b) **244**, EDC · HCl, DMAP (10 mol%), CH_2Cl_2, RT, 48 h, 69%.

Scheme 3.8: Synthesis of aminophosphine ligand **235** from cinchonidine.

3.2.4 Reduction of Catalyst and Ligand Loadings

Repeating the reported literature reaction conditions (Table 3.1, Entry 1) led to formation of (+)-**166** in quantitative yield with excellent enantioselectivity (98% ee); reducing the reaction time to 48 h gave similar results (Entry 2). Importantly, after halving all component loadings the reaction behaved similarly well at both 72 and 48 h (Entries 3 and 4 respectively). At shorter reaction times (24 h, Entry 5) or with a further reduction in component loadings for 72 h (Entry 6) the yield of (+)-**166** was reduced, although excellent levels of enantioselectivity were maintained in both cases. The latter results suggest that although the component loadings could be reduced significantly, longer reaction times would likely be required to achieve full conversion, and for practicality this was not investigated further.

Table 3.1: Optimisation of the enantioselective synthesis of (+)-**166**.



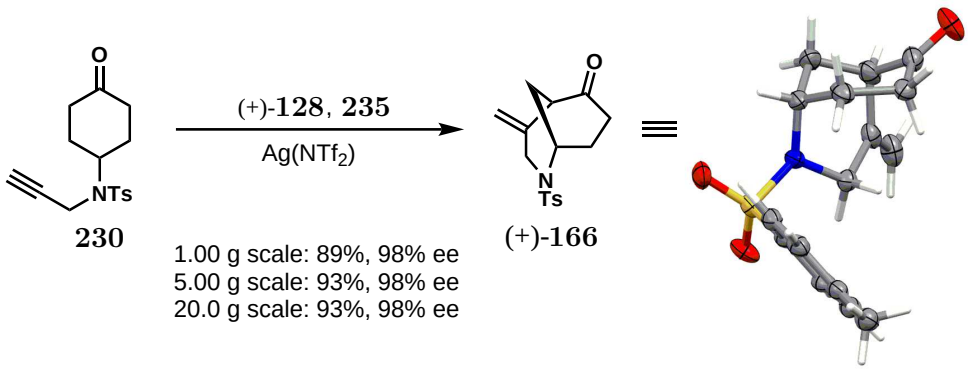
230 **(+)-166**

Entry	(+)-**128** (mol%)	**235** (mol%)	$Ag(NTf_2)$ (mol%)	2,4-DNP (mol%)	Time (h)	Yield (%)	ee (%)
1	20	20	10	20	72	quant.	97.5
2	20	20	10	20	48	quant.	97.9
3	10	10	5	10	72	quant.	97.6
4	**10**	**10**	**5**	**10**	**48**	**quant.**	**98.1**
5	10	10	5	10	24	76	97.5
6	5	5	2.5	5	72	67	97.2

[a] *Reagents and conditions*: **230** (0.20 mmol), (+)-**128**, **235**, $Ag(NTf_2)$, 2,4-dinitrophenol, *i*-PrOH (0.20 M), 60 °C. Reactions carried out in 15 mL sealed tubes.

3.2.5 Desymmetrisation Scale-up

Having determined a lower limit for reaction time and component loadings, the scalability of the reaction was investigated (Scheme 3.9). Firstly, the reaction was repeated in a round-bottomed flask fitted with a reflux condenser under 1 atmosphere of N_2 (balloon). Pleasingly, the product was formed in similar yield and enantioselectivity compared to reactions carried out in sealed tubes. On a range of scales from 305 mg (1.00 mmol) to 20 g (65 mmol) the reaction performed exceptionally well, suffering only a minor reduction in yield. Recrystallisation from methanol enriched the scalemic mixture to >99% ee (>99.5 : 0.5 er), enabling the synthesis of enantiopure (+)-**166** on decagram scale. At this stage it was also possible to obtain a crystal of (+)-**166** suitable for single crystal X-ray diffraction analysis, which enabled confirmation of the absolute and relative stereochemical configuration.

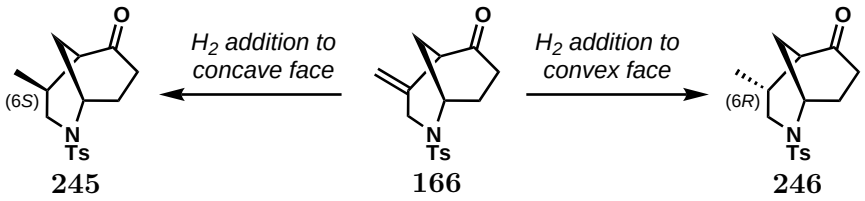


Reagents and conditions: (+)-**128** (10 mol%), **235** (10 mol%), $Ag(NTf_2)$ (5 mol%), 2,4-dinitrophenol (10 mol%), *i*-PrOH, 60 °C, 48 h.

Scheme 3.9: Scalable enantioselective desymmetrisation of *N*-Ts protected alkyne **230** with reduced catalyst and ligand loadings. Structure obtained by single crystal X-ray diffraction analysis.

3.3 Diastereoselective Hydrogenation

The first step required to functionalise the methylene-substituted bicyclic core **166** was hydrogenation of the exocyclic alkene. In order to ensure the 6*S* stereochemical configration, addition of H_2 must take place on the concave face (Scheme 3.10).



Scheme 3.10: Addition of H_2 to the concave and convex faces of **166** affording **245** and **246** respectively.

3.3.1 Alkene Hydrogenation

Hydrogenation of alkenes using heterogeneous catalysts such as Pd/C typically results in addition of H_2 to the most accessible face of the alkene. From structures obtained by single crystal X-ray diffraction studies of *N*-Ts-protected bicycle (+)-**166** (Scheme 3.9), the piperidine ring can be observed in both chair-like and boat-like conformations (Figure 3.1).

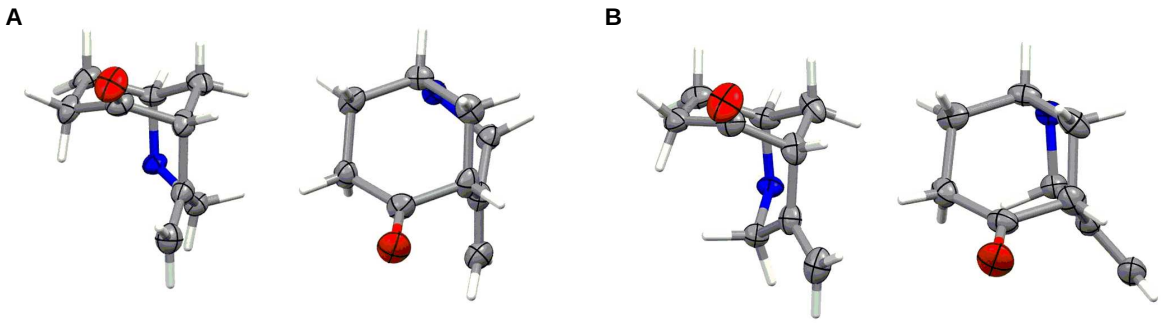
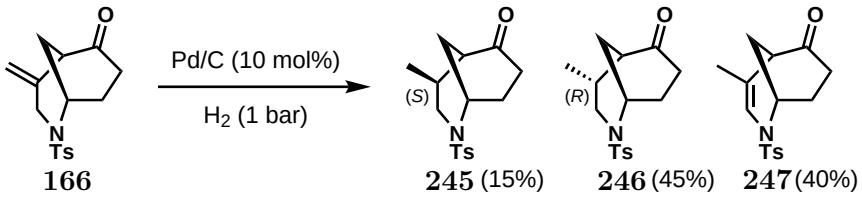


Figure 3.1: Comparison of two possible conformations of **166** as observed by single-crystal X-ray diffraction studies viewed from the 'carbonyl-end' and 'top-down'. (A) piperidine ring in boat-like conformation, and (B) piperidine ring in chair-like conformation. Ellipsoids drawn at 50% probability, hydrogens drawn as fixed-size spheres of radius 0.10 Å, Ts group removed for clarity.

In the boat-like conformation (Figure 3.1 A) the alkene is positioned in such a way that the convex face appears more accessible. However, in the chair-like conformation (Figure 3.1 B) neither the convex or concave face looks significantly more accessible than the other. Consequently, hydrogenation of the alkene was expected to favour addition of H_2 to the convex face, but with relatively low diastereoselectivity.

Indeed, hydrogenation of **166** with Pd/C (10 mol%) results in the formation of a 3:1 mixture of diastereomers favouring the undesired (6*R*) diastereomer **246** (Scheme 3.11). Additionally, partial isomerisation of **166** to the internal alkene **247** took place.



166 **245** (15%) **246** (45%) **247** (40%)

Reagents and conditions: Pd/C (10 mol%), H_2 (1 bar), EtOAc, RT, 5 h.

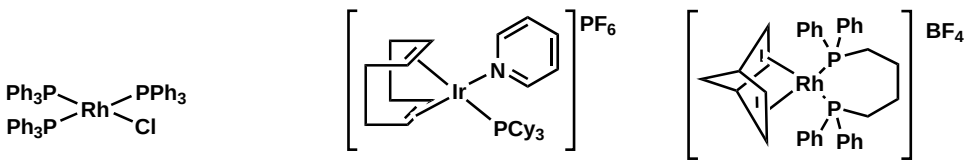
Scheme 3.11: Hydrogenation of **166** using Pd/C. Yields were determined by component analysis of ^{1}H NMR spectra of crude reaction mixtures.

3.3.2 Directed Hydrogenation Methods

The use of certain catalysts in the presence of functional groups which are capable of binding to the catalyst can result in addition of H_2 to a particular face – this is commonly termed substrate-directed hydrogenation, and can be used to override inherent steric effects.[81,82] Effective directing groups typically contain Lewis basic heteroatoms which are capable of chelating metal complexes; often these take the form of carbonyl groups, alcohols, or alkoxides. Catalysts are typically low valent cationic metal complexes which feature coordinating diene ligands such as cyclooctadiene or norbornadiene; these olefins are reduced upon treatment with H_2 to expose

one or more vacant metal coordination sites. Reactions are usually carried out in non-coordinating solvents such as CH_2Cl_2 to maintain these vacant sites, allowing the alkene and directing group to coordinate.

The first example of functional group directed hydrogenation of alkenes was reported by Thompson in 1974.[83] Using Wilkinson's catalyst ($Rh(PPh_3)_3Cl$, **248**, Scheme 3.12), an adjacent potassium alkoxide group was used to achieve diastereoselective alkene hydrogenation.[83] Crabtree's catalyst ($[Ir(cod)(PCy_3)(py)]PF_6$, **69**)[84,85] is commonly used as a directing catalyst, first demonstrated by Crabtree and Stork using alcohol functionality as a directing group.[86,87] It has also been used by the Dixon,[45] Li,[41] Qui,[88] and Zhai[46] groups in the total syntheses of Calyciphylline A-type alkaloids (see Section 1.3.1). Alternatively, cationic rhodium catalysts such as $[Rh(nbd)(dbbp)]ClO_4]$ (**249**) and $[Rh(diphosphine)_2]BF_4$ complexes have also been used.[44,48,89,90]



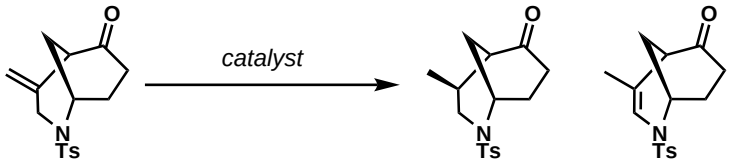
Wilkinson's catalyst (**248**) Crabtree's catalyst (**69**) **249**

Scheme 3.12: Selected examples of catalysts employed in the directed hydrogenation of alkenes.

3.3.3 Catalyst Identification for Directed Hydrogenation

In order to identify conditions to achieve diastereoselective hydrogenation, *N*-Ts protected bicycle **166** was subjected to several different homogeneous catalysts in the presence of H_2 (Table 3.2). Compared to the use of Pd/C (Entry 1), both $Rh(PPh_3)_3Cl$ (**248**) and $[Rh(nbd)(dppb)]ClO_4$ (**249**) led to no improvement in diastereoselectivity (Entries 2–4). Crabtree's catalyst (**69**), however, led to good diastereoselectivity (15:1 dr), albeit with considerable isomerisation (Entry 4).

Table 3.2: Preliminary screen of catalysts for the directed hydrogenation of **166**.

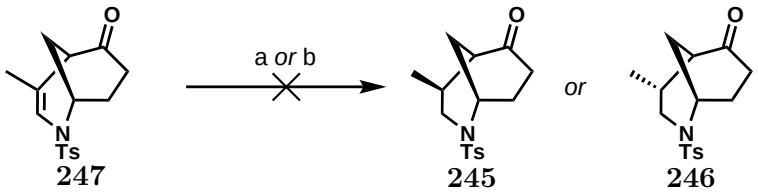


166 **245** **247**

Entry	Catalyst	**245** (%)	**247** (%)	dr
1[a]	Pd/C (10 mol%)	15	40	1:3
2	$Rh(PPh_3)_3Cl$ (**248**), 5 mol%	38	14	1:2.25
3	$[Rh(dppb)(nbd)]ClO_4$ (**249**), 5 mol%	20	2	1:2.50
4	$[Rh(dppb)(nbd)]ClO_4$ (**249**), 10 mol%	14	<1	1:5.22
5	$[Ir(cod)(PPh_3)py]PF_6$ (**69**), 20 mol%	40	60	15:1

Reagents and conditions: *Catalyst*, H_2 (1 bar), CH_2Cl_2, RT, 5–16 h. [a]EtOAc used as solvent. Yields were determined by analysis of ^{1}H NMR spectra of crude reaction mixtures; dr is the ratio of **245**:**246**.

Isolation of enamide **247** and attempted hydrogenation using either Pd/C or Crabtree's catalyst under a H_2 atmosphere led to no desirable reaction taking place (Scheme 3.13). With **247** being inert under these conditions, avoiding isomerisation would be essential in order to improve the efficiency of this transformation.

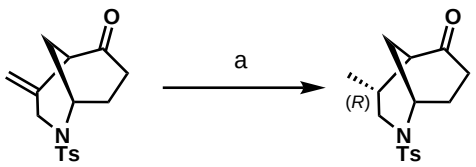


247 **245** **246**

Reagents and conditions: (a) Pd/C (10 mol%), H_2 (1 bar), EtOAc, RT, 16 h, NR; (b) $[Ir(cod)(PCy_3)Py]PF_6$ (20 mol%), H_2 (1 bar), CH_2Cl_2, RT, 16 h, NR.

Scheme 3.13: Attempted hydrogenation of enamide **247**.

The diastereomeric product **246** could be formed using Shenvi's HAT catalyst system ($Mn(dpm)_3$)[91] in moderate yield (68%) with excellent diastereoselectivity (>20:1; Scheme 3.14).



166 **246**

Reagents and conditions: (a) $Mn(dpm)_3$ (10 mol%), $PhSiH_3$ (1.0 equiv), TBHP (1.5 equiv), IPA, RT, 16 h, 68% yield, >20:1 dr. dpm = dipivaloyl-methane, TBHP = *tert*-butyl hydroperoxide.

Scheme 3.14: Application of Shenvi's catalyst to the hydrogenation of **166** to afford the diastereomeric product **246**.

Importantly, the absolute and relative stereochemical configuration of **245** was determined by single crystal X-ray diffraction analysis (Figure 3.2). These studies confirmed the desired (6*S*) configuration in **245** and validated this substrate-directed hydrogenation approach.

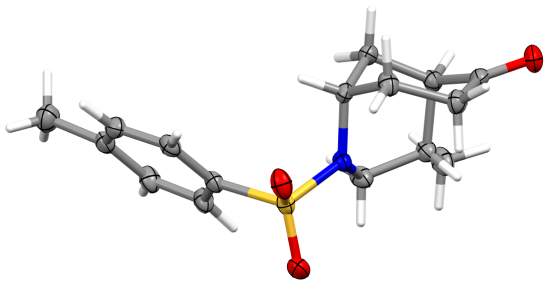


Figure 3.2: Structure of directed hydrogenation product **245** determined by single crystal X-ray diffraction studies, providing confirmation of absolute and relative stereochemical configuration.

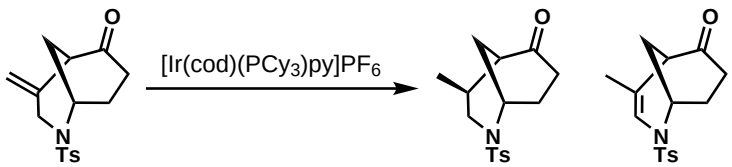
3.3.4 Optimisation of Directed Hydrogenation

Given the promising diastereoselectivity obtained with Crabtree's catalyst, a more detailed investigation into the effects of the reaction parameters was carried out, with a focus on maintaining the high diastereoselectivity and reducing isomerisation (Table 3.3). Encouragingly, reducing the catalyst loading from 20 mol% to 5 mol% had minimal impact on both yield and diastereoselectivity (Entry 2). Increasing the pressure of H_2 to 5 bar and 9 bar (Entries 3 and 4 respectively) led to considerable improvement in diastereoselectivity, with **245** formed in >20:1 dr at the higher pres-

sures. Additionally, the use of higher H_2 pressure suppressed isomerisation, leading to improved yields of hydrogenation product. These results differ greatly from work carried out by the Dixon group towards the synthesis of himalensine A, whereby a lower pressure of H_2 was neccessary to achieve high levels of diastereocontrol,[45] a problem that the Qui group also observed.[88]

Other reaction conditions investigated in an attempt to reduce isomerisation further were less successful. Either increasing the temperature to 40 °C (Entry 5) or cooling to 0 °C (Entry 6) had a negative impact, with isomerisation being considerably more favourable at higher temperatures and no reaction occurring at lower temperatures. Higher concentrations offered no improvement (Entry 7), while lower concentrations resulted in a slight decrease in yield due to an increase in isomerisation taking place (Entry 8). Studies into reaction duration revealed that the reaction was complete after 30 mins (Entry 9).

Table 3.3: Effect of catalyst loading and H_2 pressure on the directed hydrogenation of **166** using Crabtree's catalyst.



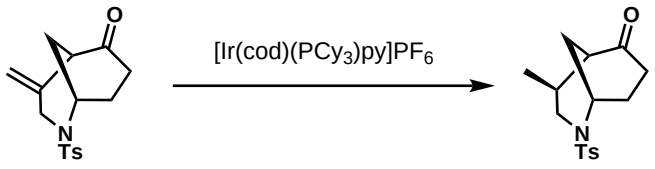
166 **245** **247**

Entry	Loading (mol%)	Pressure (bar)	Conc. (mg mL^{-1})	Temp. (°C)	**245** (%)	**247** (%)	dr (**245**:**246**)
1	20	1	20	RT	40	60	15:1
2	5	1	20	RT	50	50	15:1
3	5	5	20	RT	60	40	>20:1
4	**5**	**9**	**20**	**RT**	**86**	**14**	**>20:1**
5	5	5	20	40	20	80	nd
6	5	5	20	0	0	0	n/a
7	5	9	30	RT	86	14	>20:1
8	5	9	10	RT	79	21	>20:1
9[a]	5	9	20	RT	83	17	>20:1

Reagents and conditions: $[Ir(cod)(PCy_3)py]PF_6$, H_2, CH_2Cl_2, RT, 4 h; [a]Reaction time 30 mins.

At this stage, a further reduction in catalyst loading was desired to increase scalability (Table 3.4). Although initial attempts to reduce the loading below 5 mol% led to poor diastereoselectivity (Entry 2), results obtained with different batches of starting material were variable, with some batches tolerating a lower 'minimal catalyst loading' than others. This was traced to contaminated starting material which contained minor amounts (<5% by ^{1}H NMR) of phosphine impurities – either PPh_3 or **235** – which were used in the previous step as ligands for the racemic or enantioselective cyclisation respectively. Re-purification of **166** to remove traces of phosphine enabled a reduction in catalyst loading to as low as 2 mol%, whilst maintaining the high yields and diastereoselectivity previously observed (Entry 3). The deliberate addition of PPh_3 (5 mol%) led to a drastic reduction in both reactivity (25% yield) and diastereoselectivity (3:2 dr, Entry 4), confirming the negative impact that minor traces of phosphine impurities had on the reaction, likely due to the formation of an alternative ligated metal complex.

Table 3.4: Effect of trace phosphine impurities on the diastereoselective hydrogenation of **245**.



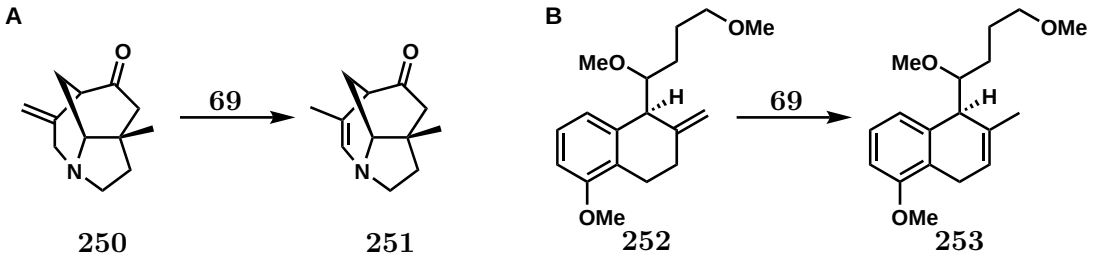
166 **245**

Entry	Description and Changes to Conditions	**245** (%)	dr
1	None	83	>20:1
2	**69** (2.5 mol%)	86	4:1
3	**166** free from PPh_3, **69** (2 mol%)	81	>20:1
4	**166** free from PPh_3, **69** (5 mol%), PPh_3 (5 mol%)	25	3:2

Reagents and conditions: $[Ir(cod)(PCy_3)py]PF_6$ (5 mol% unless stated otherwise), H_2 (9 bar), CH_2Cl_2 (20 mg mL^{-1}), RT, 30 mins.

3.3.5 Origins of Isomerisation

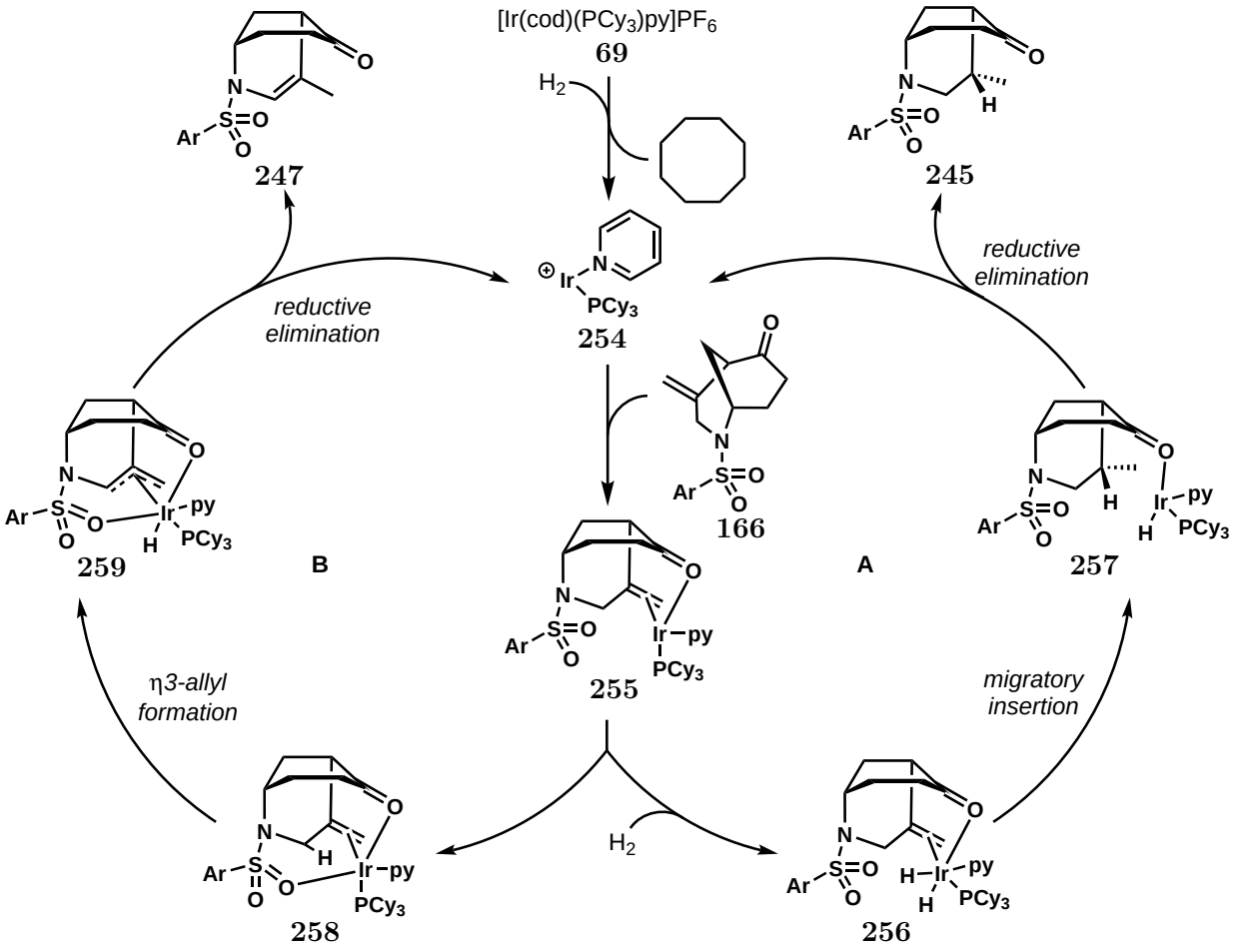
Crabtree's catalyst is often used as an alkene isomerisation catalyst. Typically it is activated with H_2 to release cyclooctane, before the isomerisation reaction is carried out under an inert (non-H_2) atmosphere.[92] The unintended isomerisation of alkenes by Crabtree's catalyst during attempted hydrogenation reactions has been noted by several authors including Bonjoch[89] and Guillou (Scheme 3.15).[93]



Scheme 3.15: Isomerisation of exocyclic alkenes by Crabtree's catalyst observed by (A) Bonjoch[89] and (B) Guillou.[93]

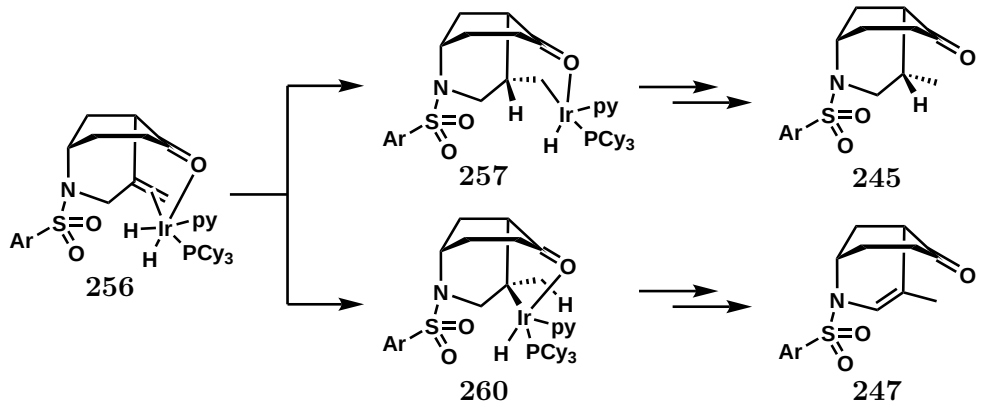
In the case of **166**, both the ketone and sulfonamide contain Lewis basic heteroatoms which could be capable of coordinating to the iridium complex. Consequently, one possible explanation for the mixture of hydrogenation and isomerisation products involves the competitive binding of an additional group, preventing addition of H_2. Following activation of Crabtree's catalyst and co-ordination of the substrate to afford intermediate **255**, addition of H_2 to iridum would result in the formation of the dihydride species **256**. Subsequently, undergo migratory insertion followed by reductive elimination would afford the desired hydrogenated product **245**. Alternatively, co-ordination of both the ketone and sulfonamide to iridium would result in the formation of complex **258**, which would prevent addition of H_2 to the iridium center. Consequently, formation of the η_1-3-allyl complex **259** would likely occur, followed by reductive elimination to yield the internal alkene **247**. Higher pressures of H_2 may therefore improve product formation by out-competing

the additional binding group.



Scheme 3.16: Possible competing catalytic cycles resulting in (A) hydrogenation or (B) isomerisation of the exocyclic alkene in **245**. Ar = *p*-tolyl.

Alternatively, it is possible that, following addition of H_2 to form the dihydride species **256**, regioselectivity of the migratory insertion step could dictate the product distribution (Scheme 3.17). Formation of the intermediate **257** would lead to the hydrogenation product **245**, while formation of the regioisomer **260** would likely result in elimination to afford the internal alkene **247**.

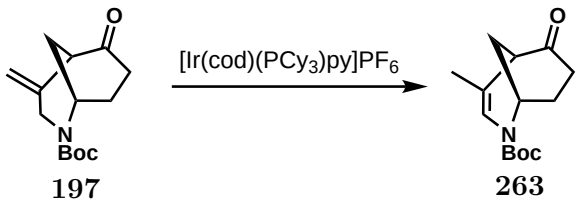


Scheme 3.17: Regioselectivity in the migratory insertion step may lead to formation of either the hydrogenated or isomerised products.

3.3.6 Effect of Protecting Group on Hydrogenation

In order to investigate the extent of this secondary interaction, *N*-Boc- and *N*-Ns-protected bicycles (**197** and **195** respectively) were subjected to the optimised hydrogenation conditions. The different electronic properties of the two groups would be expected to result in a change in reactivity if such groups were indeed interacting with the catalyst, whether by coordination to the iridium complex, or by altering the regioselectivity of migratory insertion.

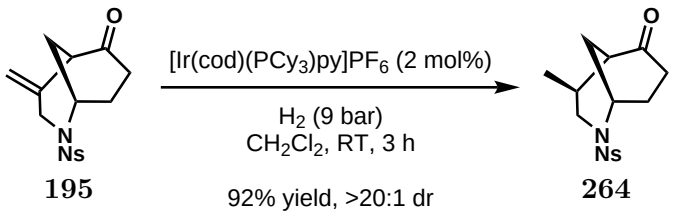
Interestingly, attempting hydrogenation of the *N*-Boc protected bicycle **197** resulted in complete isomerisation taking place to afford enamide **263** in 70% yield (Scheme 3.18).



Reagents and conditions: (a) **69** (2 mol%), H_2 (9 bar), CH_2Cl_2, RT, 3 h, 70%.

Scheme 3.18: Hydrogenation of *N*-Boc protected bicycle **197** using Crabtree's catalyst.

By contrast, the *N*-Ns protected bicycle **195** performed well under the same conditions (Scheme 3.19). The hydrogenated product **264** was afforded in 92% yield with excellent diastereoselectivity (>20:1 dr).



Reagents and conditions: **69** (2 mol%), H_2 (9 bar), CH_2Cl_2, RT, 3 h, 92%.

Scheme 3.19: Diastereoselective hydrogenation of *N*-Ns protected bicycle **195** using Crabtree's catalyst.

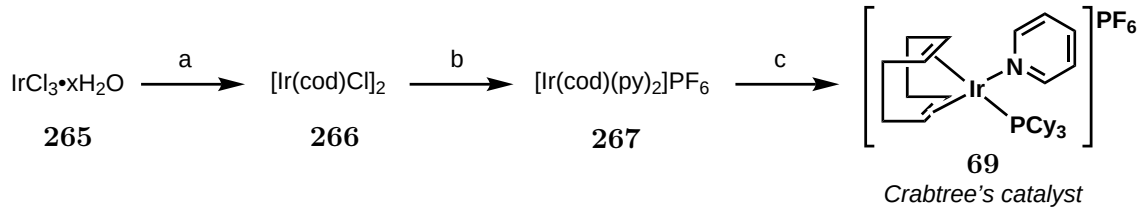
Given the superior behaviour of the *N*-Ns-protected bicycle **195** under the directed hydrogenation conditions and the milder conditions often employed for the removal of *N*-Ns groups,[77] it was considered as an alternative protecting group to *N*-Ts. However, at this point the enantioselective synthesis of **195** was only possible in low yields (20%) with good enantioselectivity (80%). Subsequent optimisation improved both yield (43%) and enantioselectivity (93%), however, despite exhaustive efforts no significant improvement in yield could be achieved. As a result, the *N*-Ns-protected alkyne was deemed not suitable for use in the synthesis.

3.4 Preparative-Scale Directed Hydrogenation

In order to carry out the directed hydrogenation on large scales, significant quantities of Crabtree's catalyst were required. Crabtree's catalyst was synthesised in three steps from $IrCl_3 \cdot xH_2O$[†] (Scheme 3.20). Firstly, following Herde's procedure, $IrCl_3 \cdot xH_2O$ was reduced with 1,5-cyclooctadiene to form the dimeric species $[Ir(cod)Cl]_2$.[94] Next, using Stork's modification of Crabtree's procedure,[85,87] treat-

[†]The use of the hydrate is important – anhydrous $IrCl_3$ is considerably less soluble than the hydrate and as a result the first step is not effective.

ment of $[Ir(cod)Cl]_2$ with pyridine and KPF_6 led to the formation of the cationic complex $[Ir(cod)(py)_2]PF_6$, which underwent ligand exchange when treated with PCy_3 to give Crabtree's catalyst in good overall yield (56%, 3 steps). The synthesis could be carried out on gram scale and was not found to be overly sensitive to air or moisture, although precautions were taken where possible (see Experimental Section, pp. 179 for details).



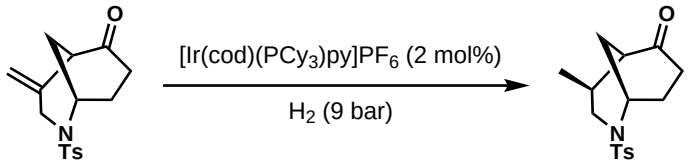
265 **266** **267** **69**

Crabtree's catalyst

Reagents and conditions: (a) 1,5-cyclooctadiene, EtOH, H_2O, reflux, N_2 stream, 16 h, 76%; (b) KPF_6, pyridine, EtOH, acetone, RT, 45 mins, 76%; (c) PCy_3, CH_2Cl_2, RT, 15 mins, 97%.

Scheme 3.20: Synthesis of Crabtree's catalyst from $IrCl_3 \cdot xH_2O$.

The directed hydrogenation of **166** scaled well, with high yields and excellent diastereoselectivity maintained on scales ranging from 61 mg (0.20 mmol) up to 3.05 g (10.0 mmol). Reaction scale was limited by a combination of the reaction vessel size (internal volume 500 mL) and optimal concentration (20 mg mL^{-1}), with a maximum solvent volume of 300 mL being optimal. On larger scales reactivity was poorer, which is likely a consequence of the greater solvent volume reducing the vessel headspace, in turn reducing the volume of H_2 present.



166 **245**

Reagents and conditions: (a) $[Ir(cod)(PCy_3)py]PF_6$ (2 mol%), H_2 (9 bar), CH_2Cl_2, RT, 30 mins, **245**: 80%, >20:1 dr, **247**: 10%.

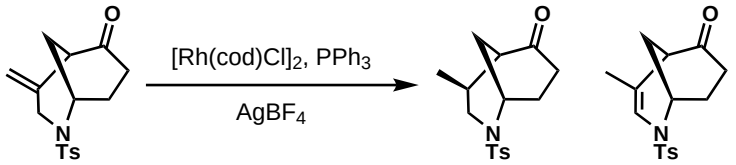
Scheme 3.21: 3 g scale directed hydrogenation of **166** to form **245** with excellent diastereoselectivity using low catalyst loadings.

3.4.1 Cationic Rhodium Catalysts

Following the disclosure by Li and co-workers on the use of cationic Rh-diphosphine complexes, (generated *in situ* from $[Rh(cod)Cl]_2$, phosphine ligands such as PPh_3, and $AgBF_4$)[44,48,90] the use of such catalysts was also investigated

Under the reported conditions,[44] hydrogenation of **166** took place to afford **245** in good yield (75%) with excellent diastereoselectivity (>20:1 dr), albeit with partial isomerisation (24%) taking place (Entry 1, Table 3.5). Following a reduction in catalyst loading, the product was formed in similar yield and diastereoselectivity (Entry 2). Increasing the concentration (Entry 3) or pressure of H_2 (Entry 4), however, led to a reduction in both yield and diastereoselectivity; the product was formed in 5:1 dr in both cases.

Table 3.5: Diastereoselective hydrogenation using cationic rhodium complexes as developed by Li and co-workers.



166 **245** **247**

Entry	$[Rh(cod)Cl]_2$ (mol%)	PPh_3 (mol%)	$AgBF_4$ (mol%)	**245**	**247**	dr
1	5	10	15	74	24	>20:1
2	2.5	5	7.5	69	20	>20:1
3[a]	5	10	15	52	19	5:1
4[b]	5	10	15	53	2	5:1
5[c]	–	–	–	86	14	>20:1

Reagents and conditions: $[Rh(cod)Cl]_2$, PPh_3, $AgBF_4$, CH_2Cl_2 (0.015 M), H_2 (1 bar), RT, 18 h; Yields and drs determined by component analysis of ^{1}HNMR spectra of crude reaction mixtures. [a]Concentration of 0.050 M used; [b]9 bar H_2; [c]Crabtree's catalyst (5 mol%), CH_2Cl_2 (0.065 M), H_2 (9 bar).

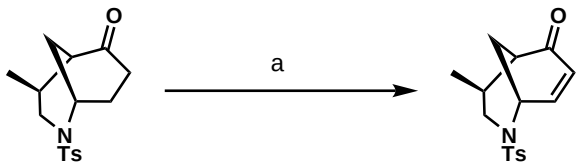
Compared to the use of Crabtree's catalyst under similar conditions (Entry 5), the use of $[Rh(cod)Cl]_2/PPh_3/AgBF_4$ offered no improvement. While the use of alternative phosphine ligands and Ag salts was investigated, these offered no improve-

ment in reactivity. Furthermore, attempts to increase the scale using the cationic Rh system were unsuccessful, and therefore the complex was not deemed to be a suitable alternative to Crabtree's catalyst.

3.5 Synthesis of β-Methyl Enone

3.5.1 Oxidation to Enone

Installation of the methyl group at C-3 was planned via conjugate addition, and therefore required the oxidation of ketone **245** to the corresponding enone **268**. This could be achieved using IBX (Nicolaou reaction)[95–97] which resulted in good yields of enone **268** (up to 90%), particularly when carried out in EtOAc instead of the more standard solvent DMSO (Scheme 3.22).† However, the use of stoichiometric IBX at an early stage in the synthesis was not practical, thus alternative methods were sought.



245 **268**

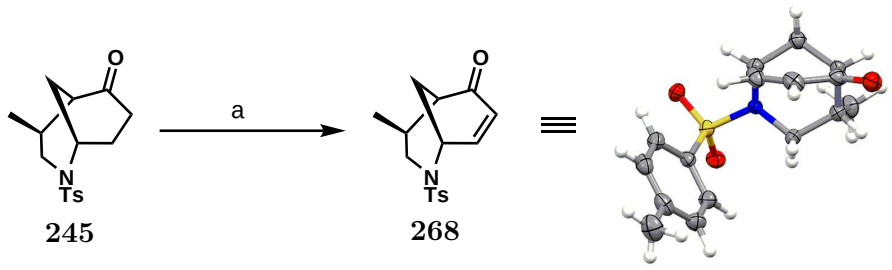
Reagents and conditions: (a) IBX (1.5 equiv), EtOAc, 100 °C, sealed tube, 16 h, 90%.

Scheme 3.22: Synthesis of enone **268** via oxidation of ketone **245** using IBX.

Catalytic methods for the oxidation of ketones to enones frequently involve oxidation of the corresponding enolsilanes and employ palladium catalysts.[98] This was first demonstrated by Saegusa and Ito, and required the use of high loadings of $Pd(OAc)_2$ (50 mol%) and employed *p*-benzoquinone as the reoxidant for Pd(0).[99]

†The use of EtOAc can improve purification as IBX, IBA and other by-products are less soluble in EtOAc at room temperature than DMSO. Thus, cooling then filtering through Celite® frequently affords product of sufficient purity.[96]

Later developments enabled reduced catalyst loadings by employing alternative reoxidants, such as O_2 by Larock,[100] and Oxone® by Lebel.[101] Recently, Stahl developed a chemoselective synthesis of cyclic enones from cyclohexanones, without promoting dehydrogenation to the corresponding phenols.[102,103] The authors identified that the use of DMSO as a ligand (rather than a solvent) led to a highly active Pd(II) catalyst system for the oxidation of ketones to cyclic enones. Employing the Stahl conditions ($Pd(TFA)_2(DMSO)_2$ in AcOH under an O_2 atmosphere) resulted in clean formation of **268** in very good yield (89%) using low catalyst loadings (Scheme 3.23). At this stage, given the highly crystalline nature of enone **268**, a suitable crystal was obtained for single crystal X-ray diffraction analysis, providing structural confirmation.



245 **268**

Reagents and conditions: (a) $Pd(TFA)_2$ (3 mol%), DMSO (6 mol%), AcOH, O_2 (1 bar), 80 °C, 16 h, 89%.

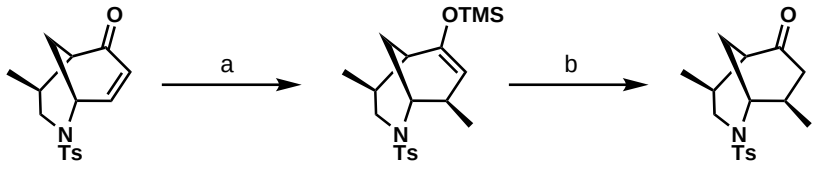
Scheme 3.23: Synthesis of enone **268** via oxidation of ketone **245** using catalytic $Pd(TFA)_2(DMSO)_2$.

3.5.2 Conjugate Methyl Addition

Introduction of the methyl group was achieved by conjugate addition using the organocuprate reagent $Me_2CuLi \cdot LiI$ (generated *in situ* from MeLi and CuI)[104,105] in the presence of TMSCl to afford β-methyl enolsilane **269** (Scheme 3.24). The enolsilane could be isolated cleanly by maintaining a low temperature during the

[†]The authors observed a negligible impact of the ratio of DMSO to Pd on the initial rate of ketone oxidation, while higher amounts of DMSO led to significant suppression of further oxidation/dehydrogenation to the corresponding phenol.

workup procedure. Alternatively, quenching with 1 M HCl led to hydrolysis of the enolsilane to afford β-methyl ketone **270**. Both enolsilane **269** and ketone **270** were obtained as single diastereomers, with the methyl group believed to occupy the axial position as a consequence of addition to the less hindered convex face.



268 **269** **270**

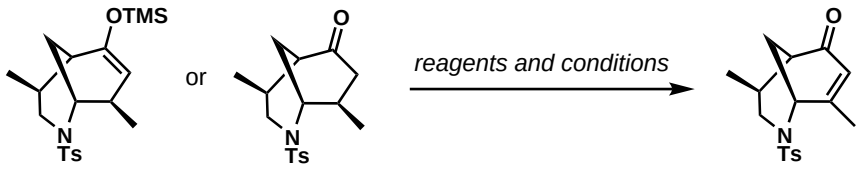
Reagents and conditions: MeLi (2.2 equivs), CuI (1.2 equivs), THF, –78 °C, 15 mins *then* **268**, Et_3N, TMSCl, –78 °C, 30 mins, quant.; (b) HCl (1 M, aq.) at 0 °C, quant.

Scheme 3.24: Introduction of β-methyl group via conjugate addition using $Me_2CuLi \cdot LiI$.

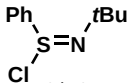
3.5.3 Oxidation to β-Methyl Enone

The oxidation of β-methyl enolsilane **269** or β-methyl ketone **270** proved much more challenging than the oxidation of ketone **245**. Conditions which performed well in the first oxidation were significantly poorer in the second (Table 3.6). Under the Stahl conditions, ketone **270** did not undergo oxidation to enone **271** (Entry 1), while enolsilane **269** was hydrolysed to ketone **270** under the acidic reaction conditions (Entry 2). Treatment of ketone **270** with IBX, or enolsilane **269** with IBX, with or without the additive *para*-methyoxypyridine-*N*-oxide (MPO),[106] led to formation of enone **271** in very low yields (Entries 3–5). Low yields were also obtained using $Pd(OAc)_2$ under Saegusa–Ito conditions with *p*-benzoquinone,[99] Larock conditions with O_2,[100] or Lebel conditions with Oxone®,[101] and meaningful yields could only be obtained with stoichiometric quantities of Pd catalyst (Entries 6–9). The use of *N*-*tert*-butyl phenylsulfinimidoyl chloride (Mukaiyama's reagent, **272**)[107] was also unsuccessful (Entry 10), as were attempts at carrying out a one-pot conjugate addition-oxidation from enone **268** as described by Matsuo and Kerr.[108,109]

Table 3.6: Unsuccessful attempts at formation of β-methyl enone **271** from ketone **270** or enolsilane **269**.

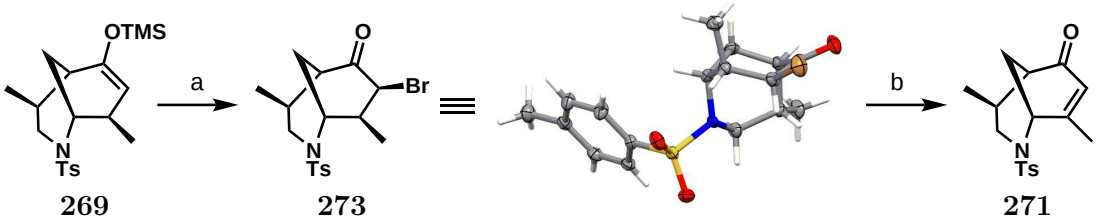


269 **270** **271**

Entry	Starting Material	Reagents and Conditions	Yield[a]
1	**270**	$Pd(TFA)_2(DMSO)_2$ (5 mol%), O_2, AcOH, 80 °C	0%
2	**269**	$Pd(TFA)_2(DMSO)_2$ (5 mol%), O_2, AcOH, 80 °C	0%
3	**270**	IBX, EtOAc, 100 °C	10–20%
4	**269**	IBX, EtOAc, 100 °C	10–20%
5	**269**	IBX, MPO, EtOAc, 100 °C	10–20%
6	**269**	$Pd(OAc)_2$ (20 mol%), *p*-benzoquinone	10–20%
7	**269**	$Pd(OAc)_2$ (20 mol%), O_2	10–20%
8	**269**	$Pd(OAc)_2$ (20 mol%), Oxone	10–20%
9	**269**	$Pd(OAc)_2$ (100 mol%), O_2	40%
10	**270**	 **272**	0%

[a] Yields determined by component analysis of ^{1}HNMR spectra of crude reaction mixtures.

To circumvent this issue, enolsilane **269** was brominated at the α-position using *N*-bromosuccinimide (NBS)[110] to form bromide **273** as a single diastereomer (Scheme 3.25). Dehydrobromination of **273** was smoothly effected using Li_2CO_3 and LiBr to form β-methyl enone **271** in excellent yield. Importantly, the methyl conjugate addition, α-bromination, and elimination reactions did not require purification and were readily scalable to over 10 g. The one-pot conjugate addition-bromination of enone **268** using either NBS or Br_2 as brominating agents was investigated, however this method resulted in impurities or decomposition and was not pursued further, given the efficiency and scalability of the two-step method.

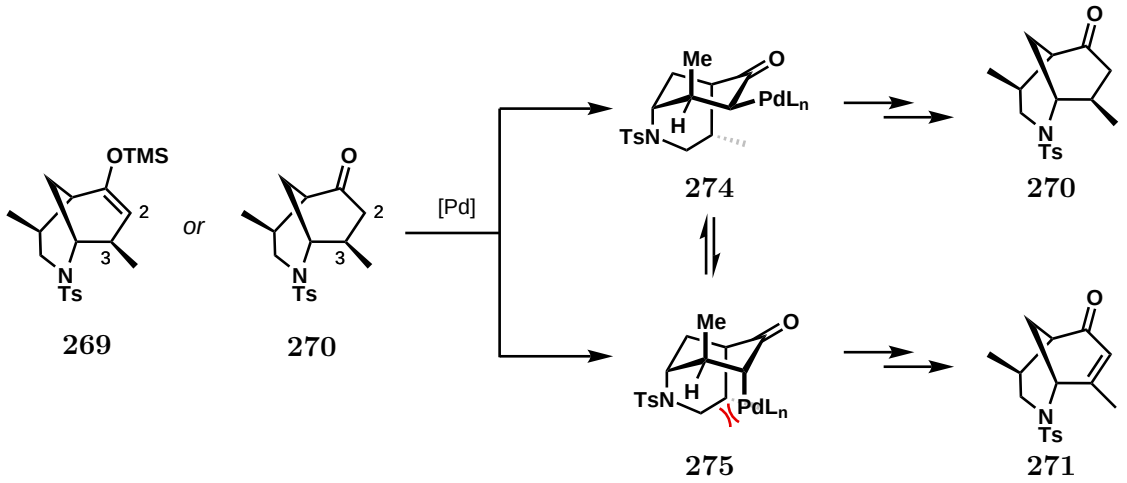


Reagents and conditions: (a) NBS (1.2 equivs), $NaHCO_3$ (1.2 equivs), THF, –78 °C, 30 mins; (b) Li_2CO_3 (2.5 equiv), LiBr (1.5 equiv), DMF, 120 °C, 3 h, 73% (3 steps from **268**).

Scheme 3.25: Synthesis of β-methyl enone **271** by bromination-elimination of **269**.

3.5.4 Cause of Problematic Re-Oxidation

A structure obtained by single crystal X-ray diffraction studies of bromide **273** confirmed several key structural points: Firstly, the methyl group at C-3 occupies the axial position, as was predicted based on transition state models, and therefore the proton at C-3 is equatorial. Secondly, the C-2 position is hindered by diaxial interactions with the C–N and C–C bonds of the piperidine ring system, and therefore substituents will preferentially sit in the equatorial position. In the case of palladium-catalysed oxidation methods, elimination takes place via β-hydride elimination, which requires the adjacent Pd–C and C–H bonds be aligned in a *syn*-coplanar arrangement. As a consequence of these combined factors, following palladation of enolsilane **269** or ketone **270**, Pd will preferentially occupy the equatorial position at C-2 (**274**), which restricts its ability to undergo β-hydride elimination. Instead, this results in protonolysis, leading to ketone **270** (Scheme 3.26).



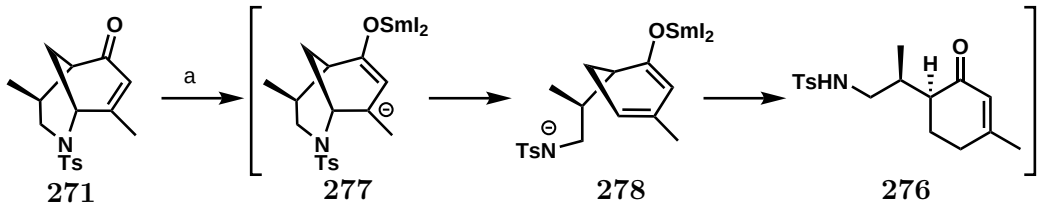
Scheme 3.26: Steric hindrance between the methyl group at C-3 and the piperidine ring, preventing β-hydride elimination for the formation of enone **271**.

3.6 Deprotection of *N*-Ts Group

The final step remaining to complete the synthesis of the fully functionalised AB core was removal of the *N*-Ts group. A wide variety of methods have been described for the cleavage of *N*-Ts groups which typically involve harsh conditions using strong acids such as HBr or HF, or strong reductants such as Na in naphthalene or Li in ammonia.[77] Encouragingly, there have been several examples in which *N*-Ts groups were cleaved in the presence of enones, including the use of Na(Hg) by Somfai,[111] and Li/NH_3 by Langlois.[112]

Treating sulfonamide **271** with HF · Py,[113] TMSI,[114] Na/IPA,[115] or Na(Hg)[111] led to no reaction taking place, whilst treatment with HBr/AcOH,[115] Mg/MeOH, SmI_2[116] or Na/naphthalene led to a complex mixture of often unidentifiable products owing to incompatibility with the enone functional group. When subjecting **271** to SmI_2 at low temperatures for very short reaction times, it was possible to tentatively identify a major undesired reaction product as enone **276** (Scheme 3.27). This was proposed to arise as a result of the SmI_2-mediated conjugate reduction of the enone

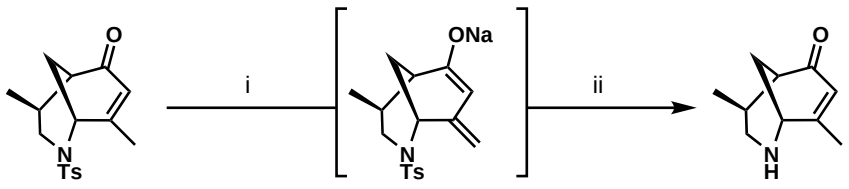
to form enolate **277**,[117] followed by cleavage of the C–N bond, likely driven by relief of strain and generation of a stable anion.



Reagents and conditions: (a) SmI_2, THF, –78 °C, 5 min.

Scheme 3.27: Proposed mechanism for C–N bond cleavage resulting in ring opening on treatment of enone **271** with SmI_2.

In order to prevent this undesired side-reaction, enone **271** was treated with NaHMDS, generating the extended enolate **279**. This protects the enone from conjugate reduction by temporarily raising the energy of the LUMO. Treatment of the enolate **279** *in situ* with Na/naphthalene led to clean deprotection of the *N*-Ts group to form the AB core **144** in very good yield (83%). This represents a rare example of *N*-Ts deprotection in the presence of enones.[77]

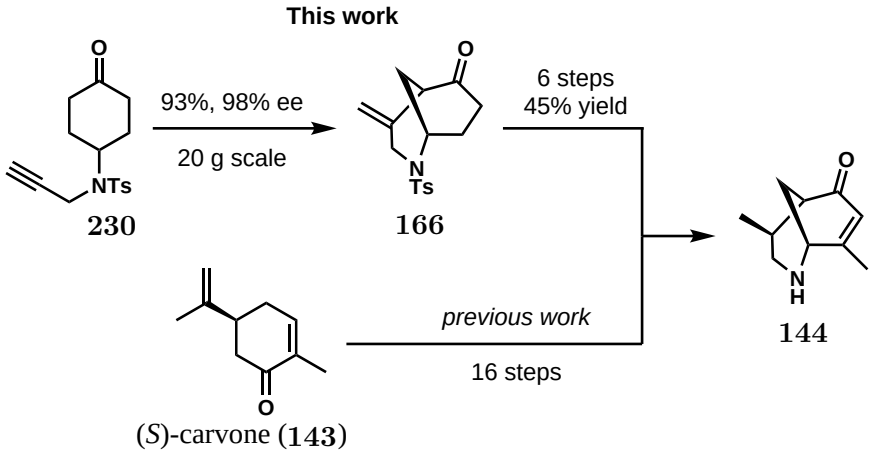


Reagents and conditions: (i) NaHMDS, THF, –78 °C, 30 mins *then* (ii) Na-naphthalenide (1 M in THF), –78 °C, 30 mins, 83%.

Scheme 3.28: Deprotection of the *N*-Ts group of **271** via formation of an extended enolate and subsequent reduction.

3.7 Summary

This chapter has described the synthesis of the functionalised morphan core by applying a scalable Ag(I)/amine co-catalysed enantioselective desymmetrisation of 4-propargylamino cyclohexanones. The resulting bicycle (**166**) underwent a substrate-directed hydrogenation reaction to achieve the desired (6*S*) configuration. In addition, the β-methyl group was installed by conjugate addition, and a challenging *N*-Ts deprotection was carried out to reveal the free amine **144** (Scheme 3.29).



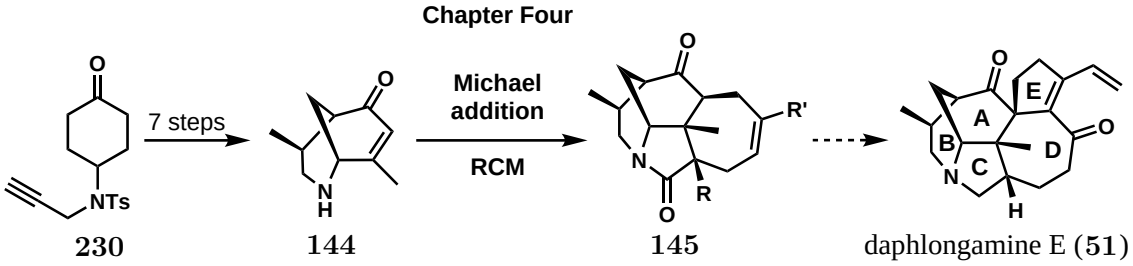
Scheme 3.29: Synthesis of fully functionalised morphan core **144** from achiral alkyne **230**.

The developed route requires relatively few purification stages (four out of seven steps) and allows for the gram-scale synthesis of the AB core **144** from achiral starting materials. This intercepts the previous work carried out in the Dixon group during attempts to synthesise daphniyunnine B, which required 16 steps to form **144** from chiral starting materials. The work presented therefore represents a significant improvement in efficiency and provides sufficient material to continue to the next phase of the synthesis.

Chapter 4

Synthesis of the Tetracyclic Core

The previous chapter discussed the development of a gram-scale synthesis of the AB core **144**, completing the first phase of the synthesis. This chapter describes the second phase, which aimed to construct the tetracyclic ABCD core **145** (Scheme 4.1). Broadly, this would be based on the intramolecular Michael addition and ring closing metathesis strategy developed by the Dixon group to synthesise the ACD tricyclic core of the Calyciphylline A-type alkaloids (See Section 1.6).[63]

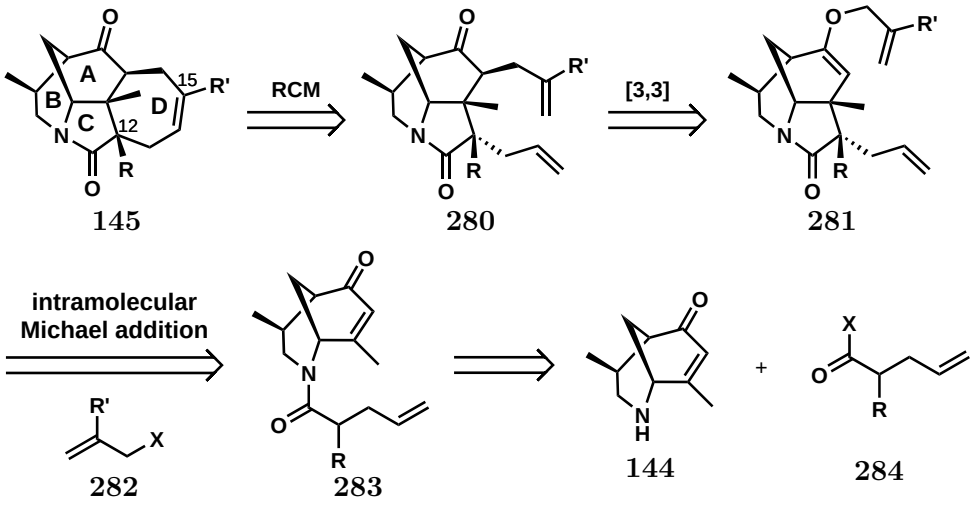


Scheme 4.1: Overview of Chapter Four.

4.1 Retrosynthetic Analysis

The synthesis of the ABCD core **145** from **144** would require four transformations (Scheme 4.2). The seven-membered ring would be constructed by ring closing metathesis of diene **280**, which would in turn be formed by a Claisen rearrangement of enol ether **281**. Formation of the C-ring by an intramolecular Michael addition could be accompanied by allylation of the enolate *in situ*, enabling the synthesis of **281** from amide **283** in a single step. Amide **283** would be formed by coupling or

acylating amine **144** with an appropriate partner (**284**). Using this strategy, both the C-12 and C-15 positions of **145** could be readily varied by changing the coupling partner (**284**) and electrophile (**282**) respectively. As a result, this approach provides opportunity to diversify the synthesis and prepare analogues of the tetracyclic core.

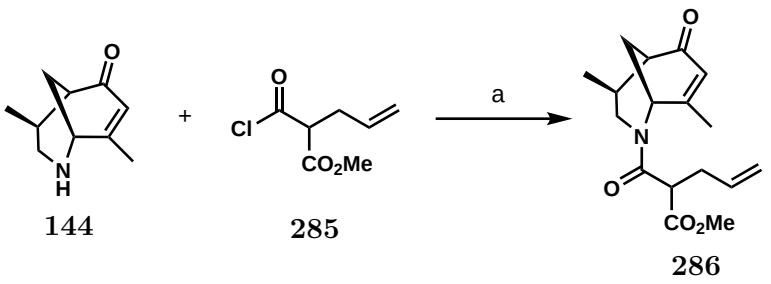


Scheme 4.2: Retrosynthetic analysis of tetracyclic core **145** using an intramolecular Michael addition and ring closing metathesis as key disconnections.

4.2 Amide Coupling

To facilitate the intramolecular Michael addition reaction, an electron-withdrawing group (such as $-CO_2Me$ or $-C{\equiv}N$) was desired to increase acidity of the α-amide position through stabilisation of the enolate. In addition, such groups would need to be readily removable at an appropriate stage in the synthesis, for example by a Krapcho dealkoxycarbonylation (for $-CO_2Me$) or an analogous hydrolytic decyanation reaction (for $-C{\equiv}N$).

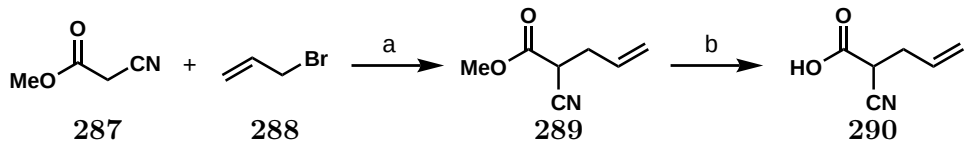
Formation of the α-amino ester **286** was achieved by acylation of the bicyclic core **144** with acid chloride **285**, affording **286** in 70% yield as a mixture of rotameric diastereomers (Scheme 4.3).



Reagents and conditions: (a) NEt_3, CH_2Cl_2, 0 °C, 3 h, 70%.

Scheme 4.3: Synthesis of amide **286** by acylation of amine **144**.

In order to install a nitrile group at C-12, the α-nitrile-substituted acid **290** was prepared by allylation of methyl cyanoacetate with allyl bromide followed by hydrolysis of the methyl ester (Scheme 4.4).[118,119] Low yields of the allylated product **289** are a consequence of the statistical nature of the reaction, which produces a significant quantity of the diallylated product. Alternative methods for allylic alkylation using iridium[120] or palladium[121] catalysis also led to the double allylation product predominating. While deallylation of the diallylated product can be achieved,[122] this was relatively costly and not deemed viable on large scales.

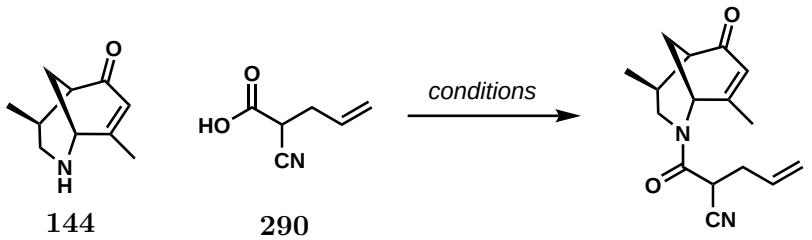


Reagents and conditions: (a) **287** (1.1 equiv), NaH (1.05 equiv), THF *then* **288** (1.0 equiv), RT, 19 h, 19%; (b) KOH, MeOH, RT, 1 d, 71%.

Scheme 4.4: Synthesis of acid coupling partner **290** by allylation of methyl cyanoacetate.

Coupling of amine **144** and acid **290** could be achieved using either HATU (Table 4.1, Entry 1) or EDC · HCl (Entry 2) in very good yield. The use of EDC · HCl without base delivered the product in excellent yield (92% Entry 3), which was maintained when carrying out the reaction on gram-scale (88%, Entry 4). As in the case of amide **286**, amide **292** was formed as a mixture of rotameric diastereomers.

Table 4.1: Coupling of amine **144** with acid **290**.

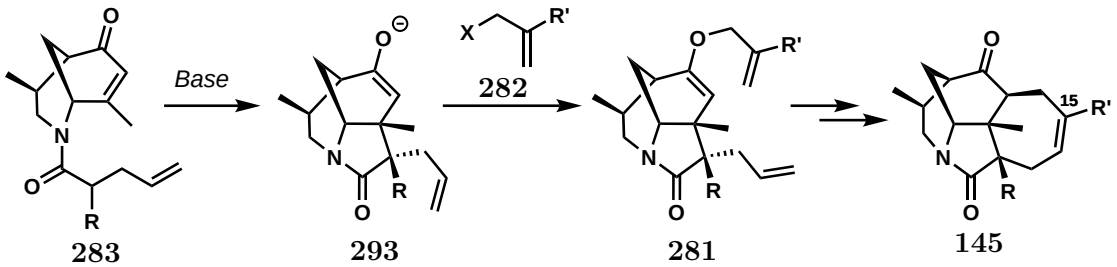


Entry	Conditions	Yield
1	HATU, DIPEA, DMF, RT, 2 h	82%
2	EDC · HCl, NEt_3, CH_2Cl_2, RT, 24 h	71%
3	EDC · HCl, CH_2Cl_2, RT, 2 h	92% (88%)[a]

[a] 1 g scale.

4.3 C-Ring Formation

Formation of the five-membered lactam would be achieved by an intramolecular Michael addition reaction (Scheme 4.5). The resulting enolate (**293**) provides the opportunity to install further functionality by treatment *in situ* with an electrophile (**282**) to afford the enol ether **281**. By carefully selecting an appropriate electrophile, various functionalities could be installed at the C-15 position in the tetracyclic core **145**, enabling access to a range of late-stage tetracyclic intermediates.

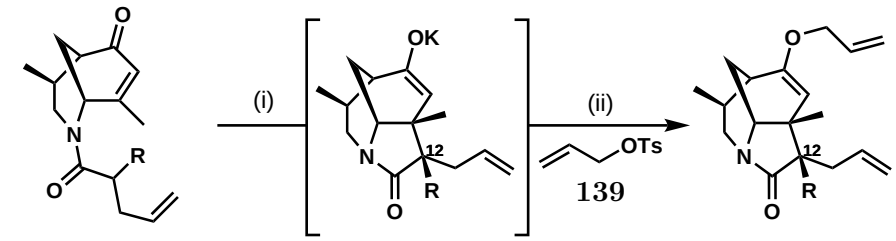


Scheme 4.5: Planned synthesis of the tricylic core **281** by an intramolecular Michael addition and tandem enolate allylation.

Using electrophiles in which R'=H would provide the olefinic product, while R'=OR" would lead to the formation of an enol ether. The latter case confers greater synthetic utility, as the resulting enol ether could be unmasked at an appropriate stage to provide a ketone.

4.3.1 Allylic Electrophiles

On treatment with KHMDS, amides **286** and **292** underwent the desired intramolecular Michael addition reaction (Scheme 4.6). Subsequent addition of a solution of 18-crown-6 and allyl tosylate (**139**) resulted in allylation of the enolate to afford tricycles **296** and **297** respectively in good yields (up to 70%) and high levels of diastereoselectivity.



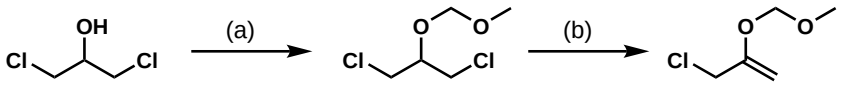
R = CO_2Me (**286**) CN (**292**) R = CO_2Me (**294**) CN (**295**) R = CO_2Me (**296**) CN (**297**)

Reagents and conditions: (i) KHMDS (1.2 equiv), THF, RT, 15 mins; (ii) 18-crown-6 (0.25 equiv), **139** (1.2 equiv), RT, 16 h, 65%, 15:1 dr at C-12 for **296**; RT, 2 h, 70%, >20:1 dr at C-12 for **297**.

Scheme 4.6: Synthesis of the ABC tricyclic cores **296** and **297** by an intramolecular Michael addition and tandem enolate allylation.

4.3.2 Enol Ether Electrophiles

In order to introduce a ketone on the seven-membered ring, an enol ether would first be installed, and could remain in the protected form until the carbonyl functionality is required. Chloride **300** was chosen as an ideal electrophilic carbonyl equivalent, and could be prepared in two steps from 1,3-dichloro-2-propanol (**298**; Scheme 4.7).[123,124] Protection of alcohol **298** as the methoxymethyl ether **299**, followed by chloride elimination, afforded **300** in good yield in a scalable manner.

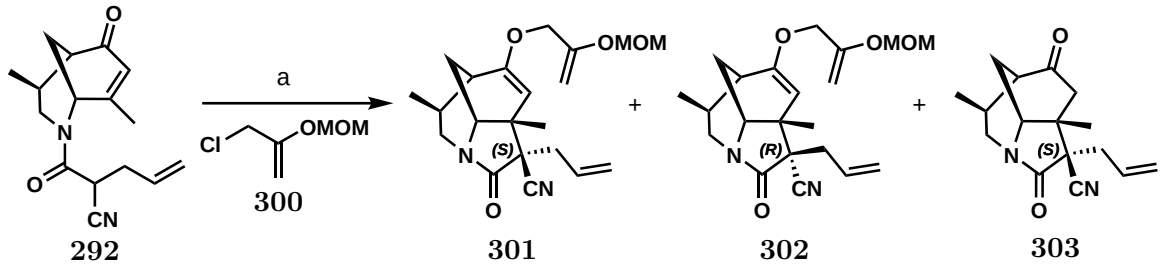


298 **299** **300**

Reagents and conditions: (a) $(MeO)_2CH_2$, P_2O_5, CH_2Cl_2, RT, 16 h, 84%; (b) KO*t*Bu, THF, –10 °C to RT, 16 h, 77%.

Scheme 4.7: Synthesis of chloride **300** from 1,3-dichloro-2-propanol.

Attempting the intramolecular Michael addition of **292** in the presence of chloride **300** led to formation of the tricyclic product (**301**) in moderate yield (41%) with good diastereoselectivity (9:1 dr, Scheme 4.8).[†] In addition, ketone **303** was also observed in substantial quantities (20%) indicating that the *O*-allylation stage of the reaction was incomplete.



292 **300** **301** **302** **303**

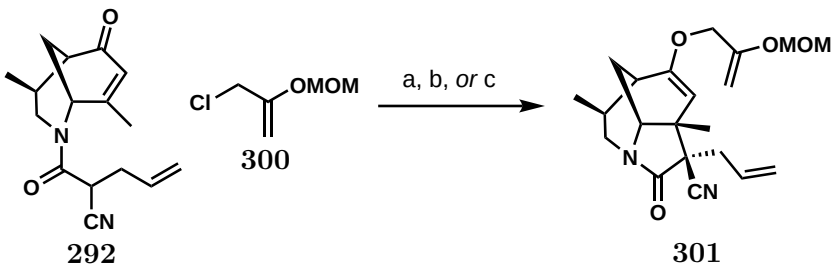
Reagents and conditions: KHMDS (1.2 equiv), THF, 0 °C *then* RT, 15 mins *then* 18-crown-6 (0.25 equiv), **300** (1.2 equiv), RT, 16 h, 41% **301**, 9:1 dr, 20% **303**.

Scheme 4.8: Initial attempt at Michael addition using electrophilic enol ether **300**.

In an attempt to improve the yield of the *O*-allylation step, the reaction was carried out at higher temperatures (Table 4.2). On warming the reaction to 65 °C, ketone **303** was fully consumed after 1 h. However, the product **301** was formed as a 3:1 mixture of diastereomers. Longer reaction times (3 and 16 h) led to a similar outcome and no further change in diastereoselectivity.

[†]The stereochemical configuration of **301** and **302** was initially assigned by analogy with previous similar work in the Dixon group. The relative configuration was later determined by nOe studies (see p. 79.)

Table 4.2: Attempts to improve Michael addition and enolate allylation yields by heating.



(a) 1 h, 2.6:1 dr
(b) 3 h, 3.2:1 dr
(c) 16 h, 2.8:1 dr

Reagents and conditions: KHMDS (1.2 equiv), THF, 0 °C *then* RT, 15 mins *then* 18-crown-6 (0.25 equiv), **300** (1.2 equiv), 65 °C for (a) 1 h; (b) 3 h; (c) 16 h; dr determined by ^{1}H NMR analysis of crude reaction mixtures.

The two diastereomeric products were readily separable, enabling confirmation of the relative stereochemical configuration by nOe studies (Figure 4.1). The desired (12-*S*) diastereomer **301** displays nOe correlations between the allyl chain (C-13–15) and the enol C-2, while the correlation with C-4 is absent. Conversely, the undesired (12-*R*) diastereomer **302** shows correlation between the allyl group (C-13–15) with C-4 and not with enol C-2.

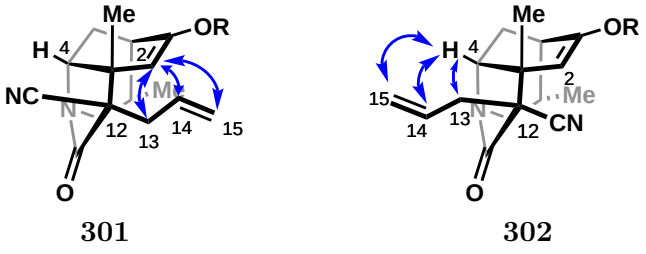
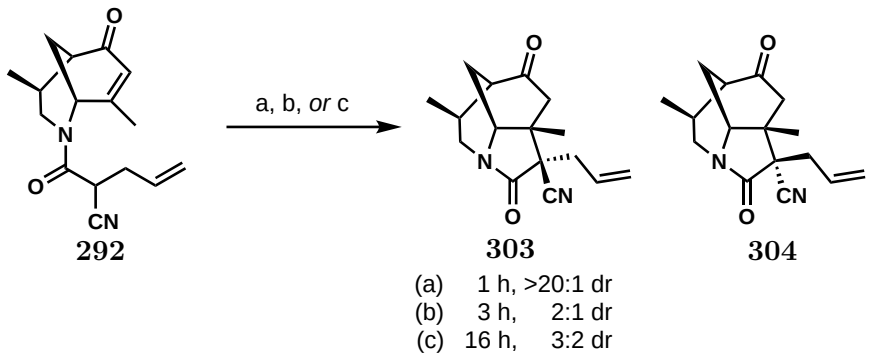


Figure 4.1: Observed nOe correlations in **301** and **302**. Arrows indicate nOe between proton environments. R = $CH_2C(CH_2)OMOM$. Protons have been omitted for clarity.

4.3.3 Understanding Origins of Diastereocontrol

To better understand the reaction, the initial Michael addition was considered independently of the subsequent *O*-allylation step. Amide **292** was treated with KHMDS at 0 °C then warmed to room temperature and held at that temperature until the

reaction was complete (Scheme 4.9). Interestingly, the Michael adduct **303** was formed in quantitative yield as a single diastereomer. Repeating the reaction at 65 °C for 1 h led to the formation of **303** and the diastereomer **304** in 2:1 dr, and extending the reaction time to 2.5 h led to a 2:3 dr. These results suggest that the Michael addition takes place with high kinetic diastereoselectivity for **303**, but becomes reversible at higher temperatures, showing little preference for either epimer.



Reagents and conditions: (a) KHMDS, THF, RT, 15 mins, >20:1 dr; (b) KHMDS, THF, 65 °C, 60 mins, 2:1 dr; (c) KHMDS, THF, 65 °C, 150 mins, 2:3 dr. dr calculated by ^{1}H NMR analysis of crude reaction mixtures.

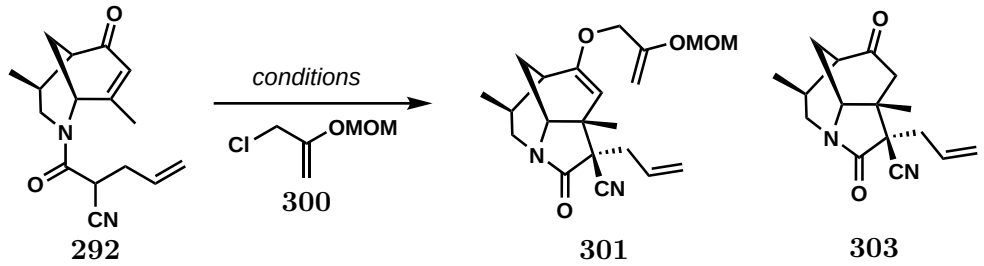
Scheme 4.9: Investigating effect of temperature on diastereoselectivity of intramolecular Michael addition of amide **292**.

4.3.4 Optimisation of Intramolecular Michael Addition

In order to improve the reaction yield, the effect of increasing the loading of each component was investigated individually (Table 4.3). The use of more base (Entry 2) and more 18-crown-6 (Entry 4) gave the largest improvements in conversion. Increasing the amount of chloride **300** had no overall benefit (Entry 3), while a lower concentration reduced reactivity (Entry 5). The use of TBAI (Bu_4NI) as an additive also led to an improvement in conversion (Entry 6). Importantly, in all cases **301** and **303** were formed as single diastereomers.

In addition, the purity of reagents was of considerable importance, and changes in the product distribution were indicative of any problematic reagents. For example, 18-crown-6 was recrystallised from acetonitrile and then azeotroped with toluene, and stored as a stock solution in dry toluene, while TBAI was recrystallised from toluene.[125] Poor quality of either reagent led to incomplete *O*-allylation as indicated by isolation of the Michael adduct **303**. In addition to using dry THF, the solvent was degassed immediately prior to use – without this precaution the enolate would on occasion undergo oxidation.

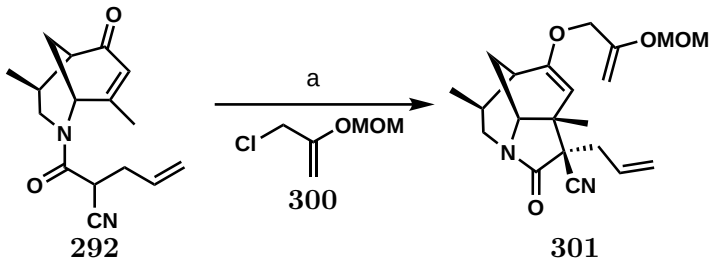
Table 4.3: Optimisation of Michael addition reaction. Note that in all cases, **301** was formed in >20:1 dr.



entry	KHMDS (equiv.)	**300** (equiv.)	18-crown-6 (equiv.)	conc. (M)	additive (equiv.)	**301** (%)	**303** (%)
1	1.2	1.5	0.5	0.20	–	63	37
2	**1.5**	1.5	0.5	0.20	–	75	25
3	1.2	**2.0**	0.5	0.20	–	59	41
4	1.2	1.5	**1.0**	0.20	–	74	26
5	1.2	1.5	0.5	**0.10**	–	56	44
6	1.2	1.5	0.5	0.20	**Bu_4NI (0.25)**	75	25

Reagents and conditions: **292**, THF, KHMDS, 0 °C, 10 mins *then* RT, 20 mins *then* **300**, 18-crown-6, *additive*, RT, 16 h. Percentages of **301** and **303** were determined by ^{1}H NMR analysis of crude reaction mixtures.

By combining the increase in the equivalents of base employed, using TBAI as an additive, and increasing the reaction concentration further to 0.35 M, the formation of **301** could be acheived in 73% yield (Scheme 4.10). Increasing the reaction concentration further was not possible, as this led to precipitation of the enolate and prevented effective stirring.

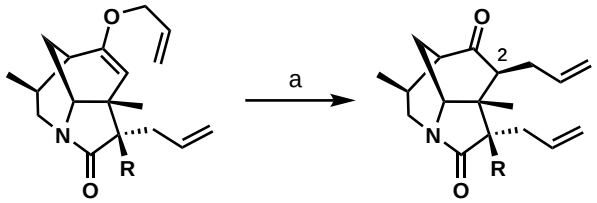


Reagents and conditions: KHMDS, THF (0.35 M), 0 °C *then* RT, 15 mins *then* 18-crown-6, **300**, TBAI, RT, 16 h, 73% yield, >20:1 dr.

Scheme 4.10: Optimised conditions for the intramolecular Michael addition of **292**.

4.4 Claisen Rearrangement

In order to produce substrates for ring closing metathesis, a [3,3]-sigmatropic shift was required to migrate the allyl or enol groups to C-2. The rearrangement of allyl enol ethers **296** and **297** could be achieved by heating in mesitylene to 185 °C for 2–3 h, affording the corresponding ketones **305** and **306** in very good yields (Scheme 4.11).



R = CO_2Me (**296**) CN (**297**)

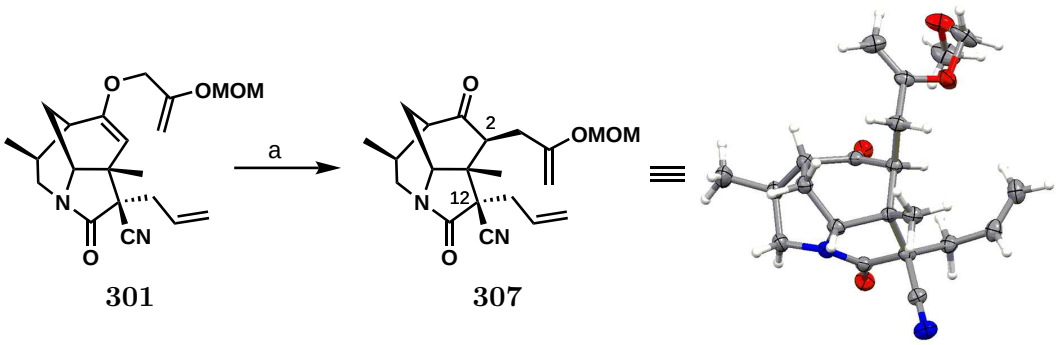
R = CO_2Me (**305**) CN (**306**)

Reagents and conditions: (a) mesitylene, 185 °C, 3 h, quant. for **305**; 2 h, 79% for **306**.

Scheme 4.11: Claisen rearrangement of allyl enol ethers **296** and **297**.

The Claisen rearrangement of dienol ether **301** could be achieved in a similar manner to afford ketone **307** in up to 80% yield (Scheme 4.12). In addition, the rearrangement could be carried out on up to 3 g scale, allowing significant throughput of material at a late stage in the synthesis. Furthermore, the relative stereochemical configuration of **307** was confirmed by single crystal X-ray diffraction studies. Importantly, this confirmed the stereochemical configuration at C-12 was *S* as predicted by nOe studies. In addition, these studies determined that the C-2 position

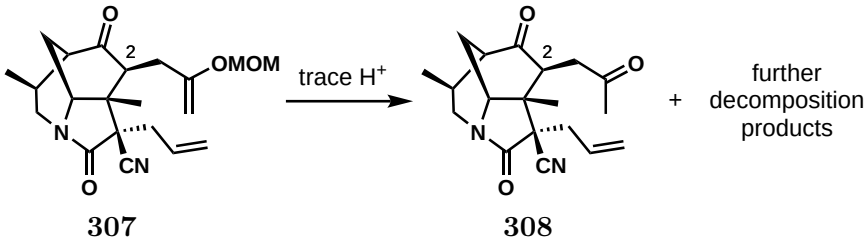
was *S*, with the enol ether occupying a pseudo-axial position due to the boat-like conformation of the cyclohexanone ring. While this is not the stereochemical configuration at C-2 which is required for the Calyciphylline A-type alkaloids, it was anticipated that this position would be readily epimerised due to its location α to a carbonyl group.



Reagents and conditions: (a) mesitylene, 185 °C, 8 h, 80%.

Scheme 4.12: Claisen rearrangement of **301** and X-ray structure confirming absolute stereochemical configuration at C-2 and C-12.

In comparison to the allyl products **305** and **306**, the enol ether **307** was found to be highly unstable and readily decomposed when exposed to air for several hours or in solution. Decomposition led to a mixture of by-products, one of which was identified as the diketone **308** arising from hydrolysis of the enol ether (Scheme 4.13). Furthermore, **307** was found to be highly acid sensitive, thus as a preventative measure, all glassware used at this stage was base-washed before use.



Scheme 4.13: Acid-mediated decomposition of Claisen rearrangement product **307** to form ketone **308** and other decomposition products.

An investigation into alternative conditions to effect the [3,3]-sigmatropic shift did not identify any improvements. For example, no product formation occurred at lower temperatures (160 °C). Furthermore, while gold catalysts are often used to effect sigmatropic shifts, in this case decomposition or side-reactions were prevalent.

4.5 D-Ring Formation

Formation of the seven-membered ring was planned via ring closing metathesis. Ruthenium complexes such as the Grubbs-I (**309**)[126,127] Grubbs-II (**310**)[128], Hoveyda–Grubbs-I (**311**),[129] and Hoveyda–Grubbs-II (**312**)[130] catalysts are some of the most commonly employed to facilitate cross- and ring closing metathesis. The use of *N*-heterocyclic carbene ligands in **310** and **312** typically increases the catalyst lifetime, while the chelating alkoxide present in **311** and **312** increases catalyst activity and recyclability.

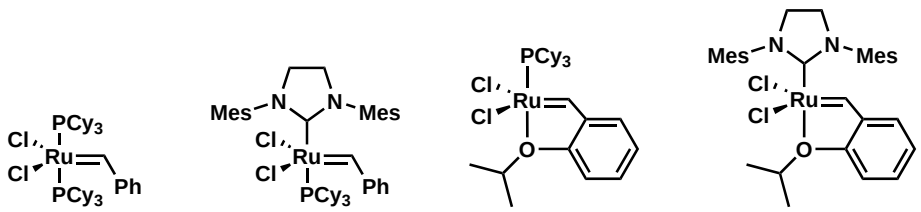
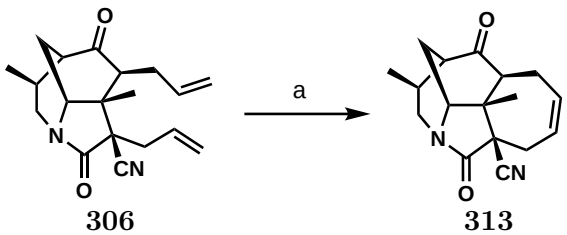


Figure 4.2: Commonly used Ruthenium-based metathesis catalysts.

Synthesis of the ABCD core **313** could be achieved using Grubbs II (**310**) in refluxing CH_2Cl_2, affording tetracycle **313** in 70% yield.



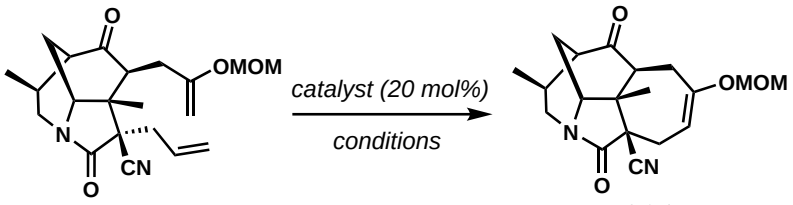
Reagents and conditions: (a) Hoveyda–Grubbs II (**312**, 10 mol%), CH_2Cl_2, 50 °C, 1 h, 70%.

Scheme 4.14: Ring closing metathesis to afford the tetracyclic core **313**.

Enol ether ring closing metathesis is often a more challenging transformation than alkenyl metathesis. The Grubbs and Rainer groups, among others, have demonstrated that the imidazolidine catalyst **310** facilitates enol ether RCM whereas **309** does not,[131,132] and the Ley group demonstrated an example of an enol ether RCM catalysed by **310** to form a seven-membered ring during the synthesis of the Thapsigargins.[133] The use of chelating alkoxide catalysts such as **312** have also been demonstrated, and often promote RCM better than **310**.[134] The groups of Schrock and Hoveyda have developed several Mo-alkylidene catalysts which facilitate enol ether RCM, and are typically more effective than the Ru-based catalysts, with the latter requiring higher temperatures.[135] However, the Mo-alkylidene catalysts are much more sensitive to air and moisture and frequently require glovebox conditions.

Initial attempts at effecting the ring closing metathesis of enol ether **307** using **310** or **312** in CH_2Cl_2 at 40 °C led to no reaction taking place (Entries 1 and 2, Table 4.4), suggesting more forcing conditions were required. The use of **312** in toluene at higher temperatures (90 °C) led to product formation (Entry 3), which could be slightly improved using higher temperatures (110 °C, Entry 4).

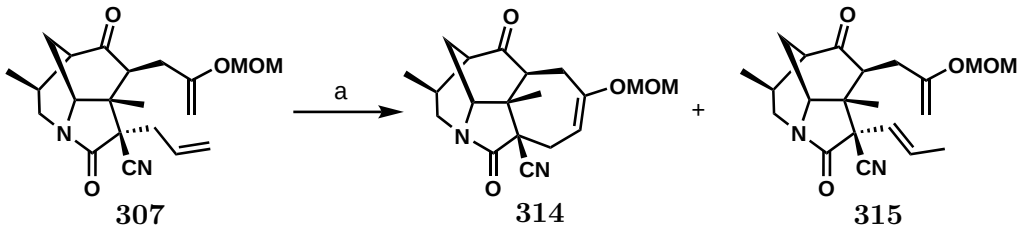
Table 4.4: Preliminary catalyst screen for the ring closing metathesis of **307**.



307 **314**

entry	catalyst	conditions	yield (%)
1	**310**	CH_2Cl_2, 40 °C, 16 h	NR
2	**312**	CH_2Cl_2, 40 °C, 16 h	NR
3	**312**	toluene, 90 °C, 16 h	75
4	**312**	toluene, 110 °C, 16 h	90

At this stage, a reduction in catalyst loading was desirable prior to scale-up. However, as the loading of **312** was reduced, the yield of **314** decreased. In addition to the formation of **314**, a major side-product was also formed which was tentatively identified as **315**, arising from isomerisation of the terminal alkene in the starting material to the internal alkene.†



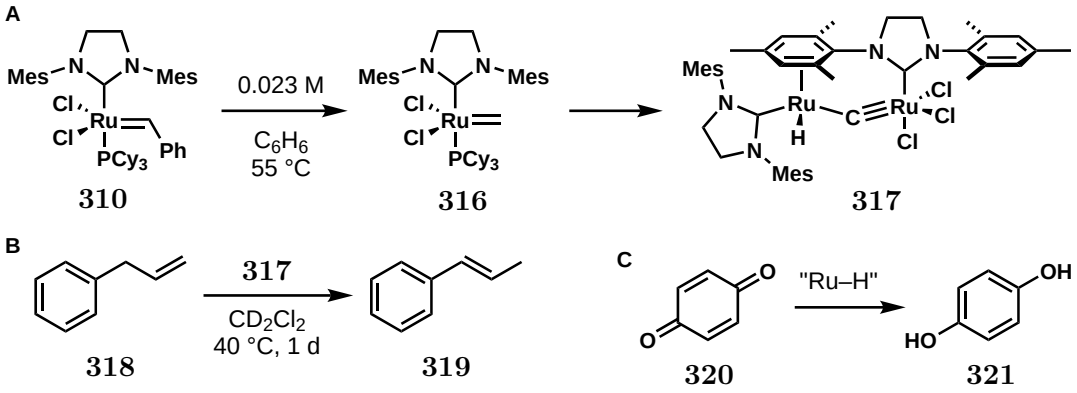
307 **314** **315**

Reagents and conditions: (a) Hoveyda–Grubbs II (**312**, 5 mol%), toluene, 110 °C, 16 h, 39% (**314**). Yield determined by component analysis of ^{1}H NMR spectra following flash column chromatography.

Scheme 4.15: Attempted reduction in catalyst loading led to partial isomerisation of starting material.

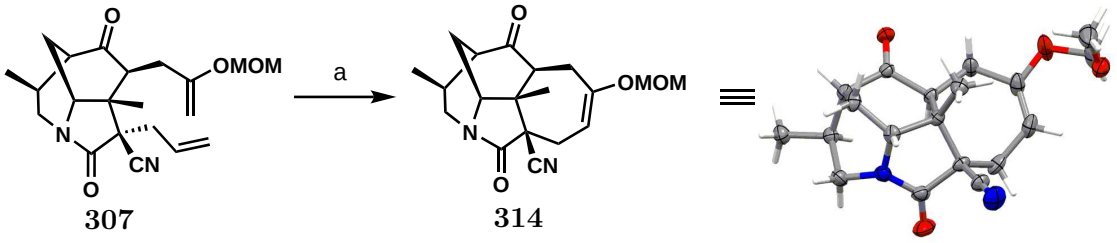
The isomerisation of alkenes under ring closing metathesis conditions is a known problem, and is observed with both Mo- and Ru-based catalysts.[136] While investigating the stability of methylidene complex **316**, an intermediate in the RCM catalytic cycle, Grubbs and co-workers identified the formation of dinuclear ruthenium-hydride complex **317**.[137] The formation of **317** occurred when catalyst **310** was subjected to high temperatures in dilute solutions over a long period of time (Scheme 4.16 A). Furthermore, the authors demonstrated that **317** catalysed the isomerisation of allylbenzene under standard metathesis conditions (Scheme 4.16 B). The authors found that addition of hydride acceptors such as *p*-benzoquinone suppresses isomerisation during metathesis,[138] with quinones known to undergo reduction to the corresponding hydroquinones in the presence of Ru-hydride complexes.[139]

†The starting material (**307**), product (**314**), and side-product (**315**) could not be fully separated despite extensive efforts.



Scheme 4.16: A. Decomposition of Ru-based metathesis catalyst **310** to form dinuclear species **317**; B. Demonstration of isomerisation catalysed by **317**; C. Reduction of *para*-benzoquinone to the corresponding hydroquinone by Ru-hydride complexes.

Pleasingly, ring closing metathesis of enol ether **307** with HG-II (5 mol%) in the presence of *p*-benzoquinone (10 mol%) proceeded cleanly to form the tetracycle **314** in good yield, without isomerisation being observed (Scheme 4.17). In addition, single crystal X-ray diffraction studies confirmed the stereochemical configuration of **314**.

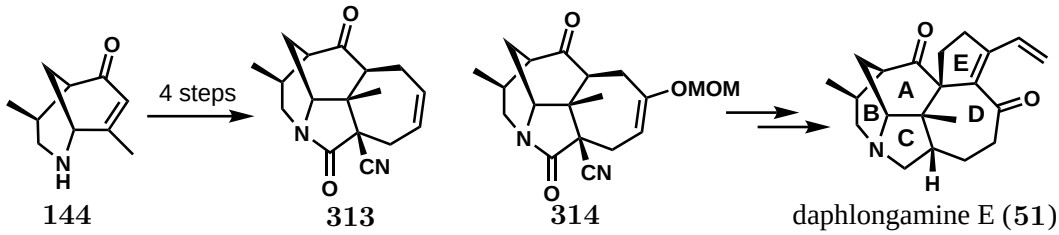


Reagents and conditions: (a) Hoveyda–Grubbs II (**312**, 5 mol%), *p*-benzoquinone (10 mol%), toluene (0.01 M), 110 °C, 4 h, 89%.

Scheme 4.17: Ring closing metathesis of **307** in the presence of *p*-benzoquinone to suppress isomerisation.

4.6 Summary

This chapter has described the synthesis of several tetracyclic cores relevant to the Calyciphylline A-type alkaloids. By employing an intramolecular Michael addition, Claisen rearrangement, and ring closing metathesis strategy, such cores can be obtained in just four steps from the functionalised morphan core **144** (Scheme 4.18). These offer the potential to tackle formation of the remaining E ring system in a multitude of different ways, in addition to the possibility of intercepting total syntheses developed by the Dixon, Li, and Zhai groups.



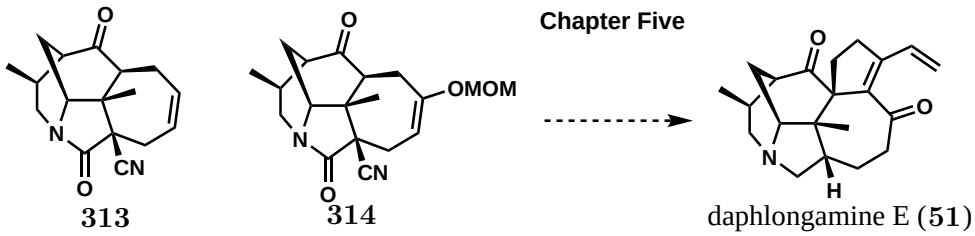
144 **313** **314** daphlongamine E (**51**)

Scheme 4.18: Synthesis of tetracyclic cores **313** and **314** achieved in four steps from bicyclic core **144**.

Chapter 5

Endgame

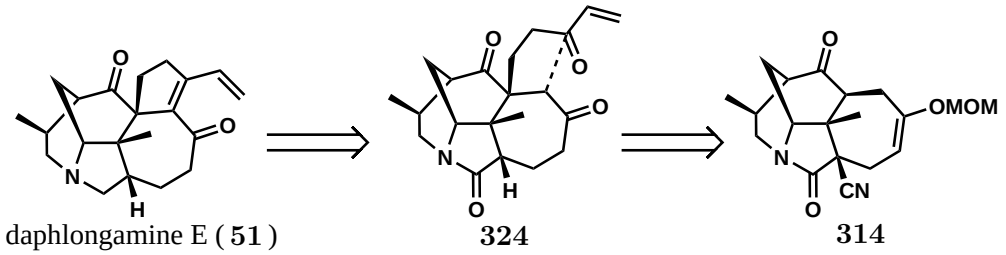
The previous chapter described the synthesis of tetracyclic cores **313**, and **314**. The aim of the next and final phase of the synthesis was to install the E ring in order to complete a total synthesis of daphlongamine E or other Calyciphylline A-type alkaloids (Scheme 5.1). Many different annulation strategies were considered, and those which were explored in detail are described in this chapter. Most strategies which were considered commenced from tetracycle **314**, as the enol ether could be hydrolysed at an appropriate stage to reveal a ketone – useful for a variety of ring forming methods – but remain protected until that point.



Scheme 5.1: Overview of Chapter Five.

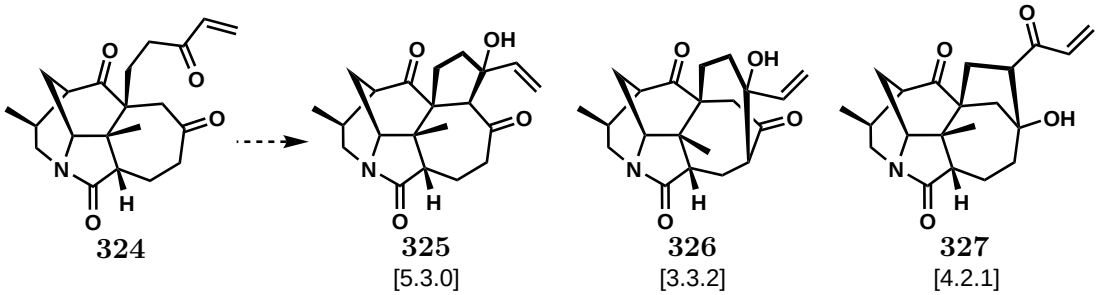
5.1 Aldol Condensation

The primary strategy considered to form the five-membered ring was an intramolecular aldol condensation of **324** (Scheme 5.2).



Scheme 5.2: Proposed synthesis of daphlongamine E by an intramolecular aldol reaction to construct the E ring.

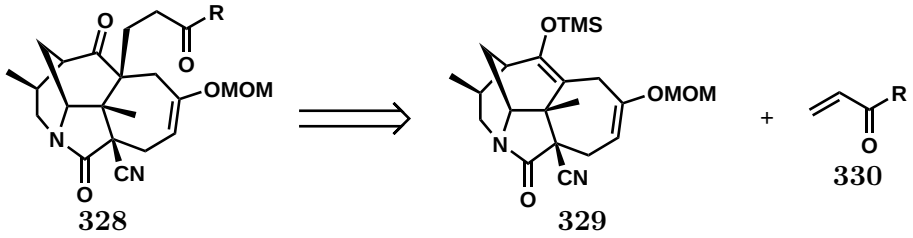
The aldol substrate **324** has three enolisable positions of similar reactivity, thus it was anticipated that reversible conditions would be required to achieve selectivity for the desired product. Upon enolisation, cyclisation to form the pentacyclic alcohols **325**, **326**, and **327** could be expected (Scheme 5.3). Of these, the [5.3.0]- and [3.3.2]-ring systems (**325** and **326** respectively) could undergo elimination to afford the corresponding aldol condensation products. On the other hand, the [4.2.1] ring system **327** would be unlikely to undergo elimination as this would result in the formation of a bridgehead alkene – in violation of Bredt's rule. Under reversible conditions, formation of the desired fused [5.3.0] ring system was believed to be more favourable than the bridged [3.3.2] ring system.



Scheme 5.3: Possible pentacyclic alcohols expected to arise from treatment of **324** under acid- or base-mediated aldol conditions.

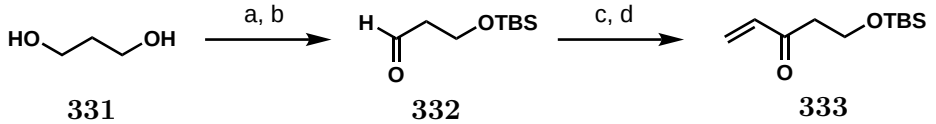
5.1.1 Mukaiyama–Michael Approach

An ideal synthesis of aldol substrates from the ABCD core would introduce the five-carbon side-chain in as few steps as possible. For this transformation, a Mukaiyama–Michael reaction was considered,[140] which would involve alkylation of enolsilane **329** with a suitable Michael acceptor in the presence of a Lewis acid (Scheme 5.4). While this approach would introduce all requisite carbon atoms and functionality in a single step, it was anticipated to be challenging owing to the formation of a highly congested quaternary center.



Scheme 5.4: Mukaiyama–Michael approach to the synthesis of aldol substrates **328**.

Divinyl ketone (**330**, R = CH=CH_2) was not considered a suitable Michael acceptor due to its high reactivity and propensity to polymerise.[141] Instead, enone **333** which contains a pendant silyl-protected alcohol was considered a suitable alternative. Deprotection to reveal the alcohol at a later stage would enable access to hydroxylated natural products such as daphniyunnine B, while elimination would provide olefinic products such as the target daphlongamine E. Enone **333** was prepared in four steps from propane-1,3-diol in good overall yield (Scheme 5.5).

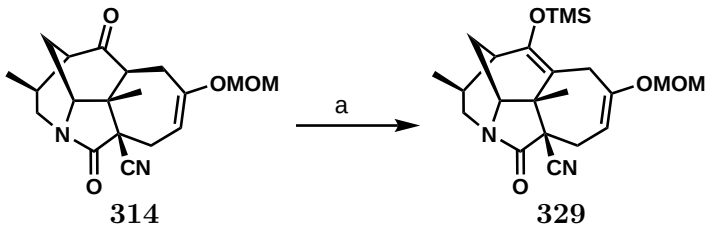


331 **332** **333**

Reagents and conditions: (a) TBSCl, Et_3N, THF, RT, 45 mins, 87%; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 2 h, –78 °C, 98%; (c) vinyl magnesium bromide, THF, –78 °C, 1 h; (d) IBX, EtOAc, reflux, 4 h, 76% (2 steps).

Scheme 5.5: Synthesis of Michael acceptor enone **333**.

Formation of the tetracyclic enolsilane **329** was achieved in excellent yield by treatment of the ABCD core **314** with NaHMDS followed by TMSOTf (Scheme 5.6).

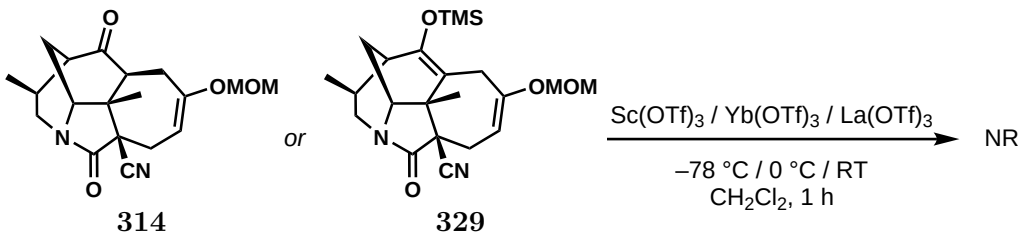


314 **329**

Reagents and conditions: (a) NaHMDS, TMSOTf, CH_2Cl_2, RT, 16h, 98%.

Scheme 5.6: Synthesis of enolsilane **329**.

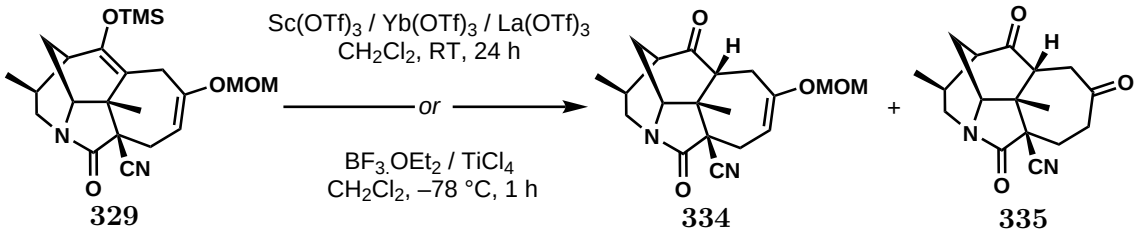
Firstly, control reactions were carried out in which ketone **314** and enolsilane **329** were treated with a range of Lewis acids to examine their reactivity in the absence of Michael acceptors. In the presence of Lewis acids such as $Sc(OTf)_3$, $Yb(OTf)_3$, and $La(OTf)_3$, minimal reactivity was observed at low temperatures (–78 or 0 °C) or at room temperature for short reaction times (Scheme 5.7).



314 **329**

Scheme 5.7: Control reactions of tetracycles **314** and **329** with weak Lewis acids.

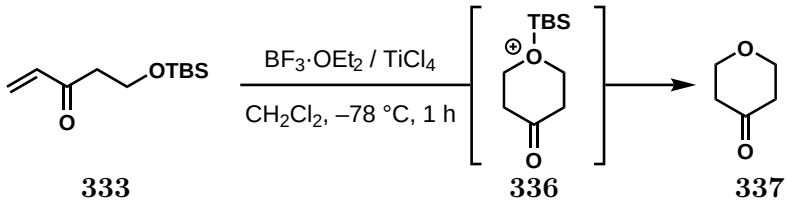
Enolsilane **329** was hydrolysed to ketone **334** when subjected to $Sc(OTf)_3$, $Yb(OTf)_3$ or $La(OTf)_3$ for longer times (24 h) at room temperature, or when treated with stronger Lewis acids such as $BF_3 \cdot OEt_2$ or $TiCl_4$ at low temperatures (Scheme 5.8). In addition, the diketone **335** was also tentatively observed by ^1H NMR and LCMS, resulting from hydrolysis of the methoxymethyl enol ether. These control reactions established that the tetracyclic enolsilane **329** was very susceptible to hydrolysis.



Scheme 5.8: Additional control reactions of enolsilane **329**.

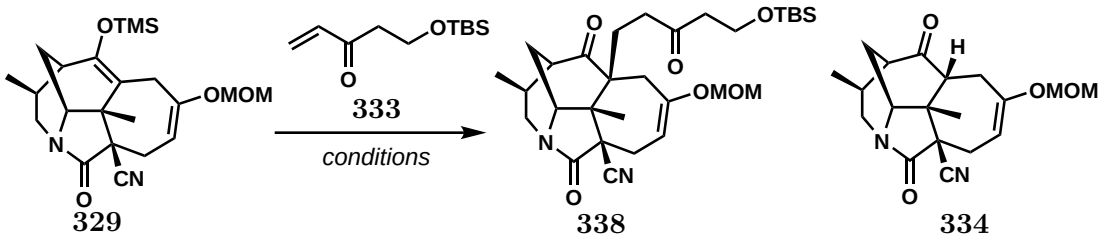
In an attempt to effect the Mukaiyama–Michael reaction between enolsilane **329** and enone **333**, a variety of Lewis acids were investigated (Table 5.1). However, in all cases no product formation was observed. In many cases, reactions at –78 °C afforded the ketone **334**, arising from hydrolysis of the enolsilane (Entries 1–5). Using $ZnCl_2$ or $Sc(OTf)_2$ at temperatures ranging from –78 °C to room temperature resulted in the formation of a mixture of starting material **329** and ketone **334** (Entries 6–9), with **334** predominating at the higher temperatures. In addition, attempts using DBU or MeLi instead of Lewis acids were also unsuccessful (Entries 10 and 11).

Given the lack of product formation when using enone **333**, additional control reactions were carried out. Treatment of **333** with $BF_3 \cdot OEt_2$ or $TiCl_4$ at –78 °C led to full conversion to tetrahydropyranone **337**, likely via Lewis acid-mpromoted cyclisation to **336** followed by desilylation (Scheme 5.9). The NMR shifts corresponding to tetrahydropyranone **337** could be observed in the ^{1}H NMR spectra of the crude reaction mixtures obtained previously (Table 5.1).



Scheme 5.9: Decomposition of enone **333** to tetrahydropyranone **337** on treatment with $BF_3 \cdot OEt_2$ or $TiCl_4$ at low temperatures.

Table 5.1: Attempted Mukaiyama–Michael reaction between enolsilane **329** and enone **333** using a range of Lewis acids or bases.

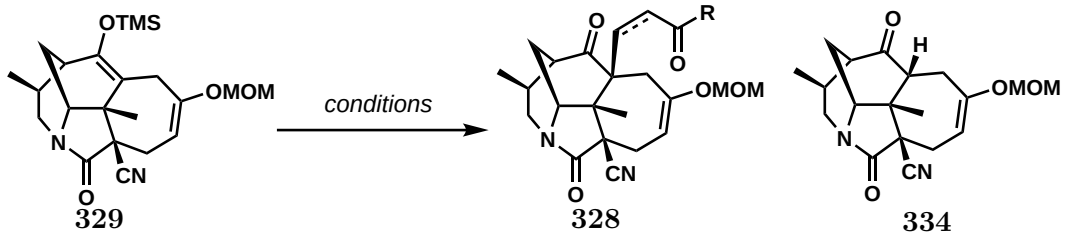


Entry	Lewis Acid or Base	Temperature (°C)	Outcome
1	$BF_3 \cdot OEt_2$	–78	**334**
2	$BF_3 \cdot THF$	–78	**334**
3	$TiCl_4$	–78	**334**
4	$MgBr_2$	–78	**334**
5	TMSOTf	–78	**334**
6	$ZnCl_2$	–78	**329** and **334**
7	$Sc(OTf)_3$	–78	**329** and **334**
8	$Sc(OTf)_3$	0	**329** and **334**
9	$Sc(OTf)_3$	RT	**329** and **334**
10	DBU	–78	**334**
11	MeLi	–78	**334**

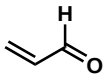
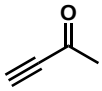
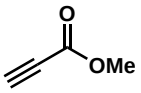
Reagents and conditions: **329** (0.10 mmol), **333** (5 equiv), CH_2Cl_2, *then* Lewis acid or Base, –78 °C (unless specified otherwise), 1 h.

As enone **333** was therefore not a suitable Michael acceptor, investigations continued with alternative electrophiles covering a broad range of reactivity, from unsaturated aldehydes to unsaturated esters. Unfortunately, in all cases no product formation was detected, and the results obtained bore similarity to the observations made using enone **333** (Table 5.2). At this stage, the lack of product formation was considered most likely to be a result of steric hindrance, and consequently hydrolysis of the enolsilane was believed to out-compete alkylation. As a result, it was clear that such a strategy was not well-suited to the formation of this challenging quaternary center, and alternative routes were sought.

Table 5.2: Attempted Mukaiyama–Michael reaction of enolsilane **329** with other Michael acceptors.



329 **328** **334**

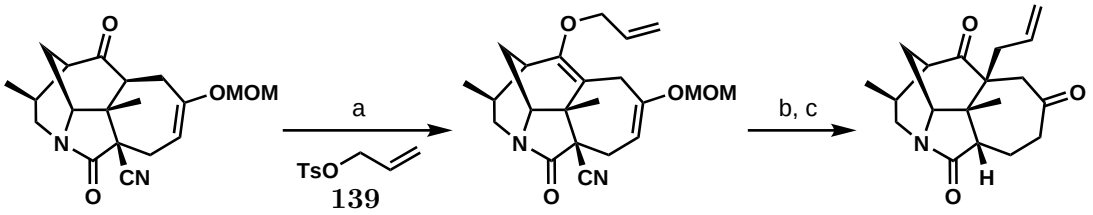
Entry	Michael Acceptor	Lewis Acid or Base	Temperature (°C)	Outcome
1	 **339**	$BF_3 \cdot OEt_2$	–78	**334**
2		$TiCl_4$	–78	**334**
3		$BF_3 \cdot OEt_2$	–78	**334**
4	 **340**	$TiCl_4$	–78	**334**
5		$Sc(OTf)_3$	–78	**329** and **334**
6		H_2O-THF	0	**329** and **334**
7		I_2	–78	**334**
8		$BF_3 \cdot OEt_2$	–78	**334**
9		$TiCl_4$	–78	**334**
10		$Sc(OTf)_3$	–78	**329** and **334**
11	**341**	$Sc(OTf)_3$	0	**329** and **334**
12		$Sc(OTf)_3$	RT	**329** and **334**
13	 **342**	$BF_3 \cdot OEt_2$	–78	**334**

Reagents and conditions: **329** (0.10 mmol), Michael acceptor (5 equiv), CH_2Cl_2, *then* Lewis acid or Base, –78 °C (unless specified otherwise), 1 h.

5.1.2 Sigmatropic Shift to Access Quaternary Center

Given the problematic formation of the quaternary center via a Mukaiyama–Michael-type reaction, an alternative approach was required. Treatment of ketone **314** with KHMDS followed by allyl tosylate led to the formation of allyl enol ether **343** (Scheme 5.10). Attempts at direct C-allylation using Tsuji–Trost-type methods were unsuccessful, likely due to steric hindrance.[142,143] On heating, **343** underwent a thermal [3,3]-sigmatropic (Claisen) rearrangement, which was followed by treatment with LiOH to effect hydrolytic decyanation of the nitrile group and hydrolysis of the

methoxymethyl enol ether to deliver diketone **344**.



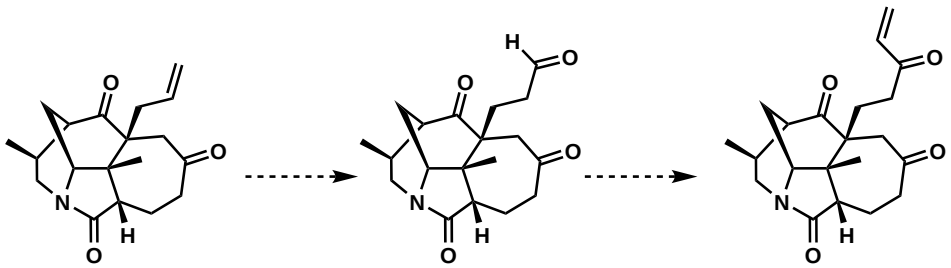
314 **343** **344**

Reagents and conditions: (a) KHMDS, THF, RT, 15 mins *then* **139**, 18-crown-6, RT, 80 mins, 79%; (b) mesitylene, 185 °C, 2 h, 93%; (c) LiOH (2 M), THF, MeOH, 100 °C, 16 h *then* HCl (6 M), RT, 30 mins, 59%;

Scheme 5.10: Addition of allyl group via Claisen rearrangement and subsequent removal of nitrile and enol ether.

5.1.3 Synthesis of Aldol Substrate

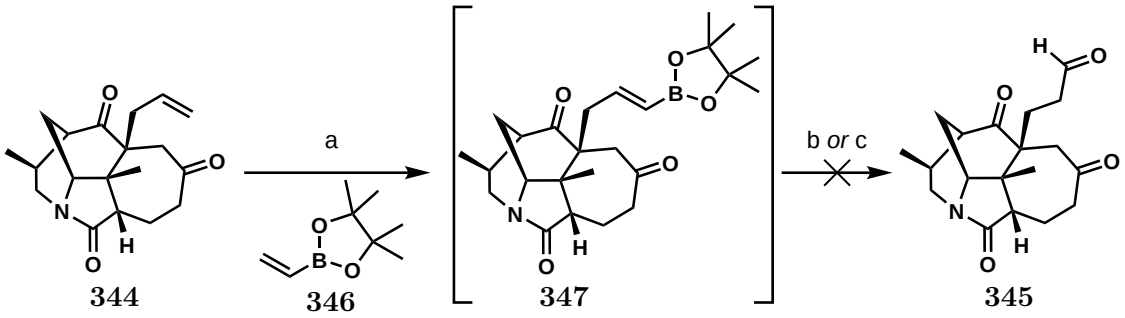
Having achieved formation of the final challenging all-carbon quaternary center, attention was turned to converting **344** into a precursor for ring closure. It was envisaged that oxidation of the allyl group to aldehyde **345** followed by addition of vinyl magnesium bromide and re-oxidation would afford enone **324** (Scheme 5.11).



344 **345** **324**

Scheme 5.11: Proposed route to aldol substrate **324** from allylated tetracycle **344**.

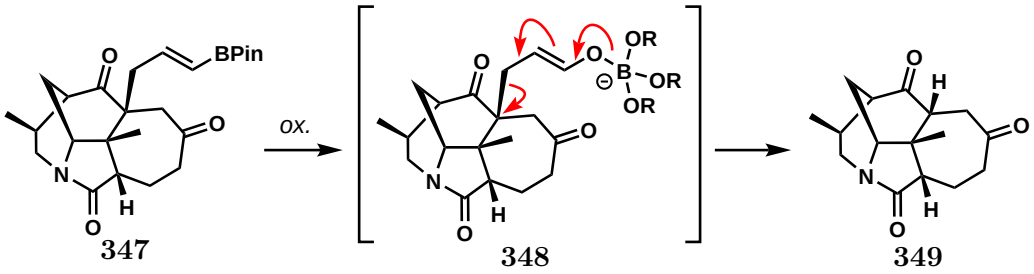
One effective method to access aldehydes from terminal alkenes is via cross metathesis with vinyl boronate esters[144,145] followed by oxidation.[146–148] Using Grubbs II, **344** underwent cross metathesis with vinylboronic acid pinacol ester (**346**). However, attempts to oxidise **347** using trimethylamine *N*-oxide (TMANO)[146,147] or $NaBO_3$[148] were unsuccessful (Scheme 5.12).



Reagents and conditions: (a) Grubbs II (5 mol%), CuI (10 mol%), **346**, CH_2Cl_2, 40 °C; (b) trimethylamine *N*-oxide (TMANO); (c) $NaBO_3$.

Scheme 5.12: Cross metathesis of allyl-substituted tetracycle **344** to afford vinyl boronate **347**.

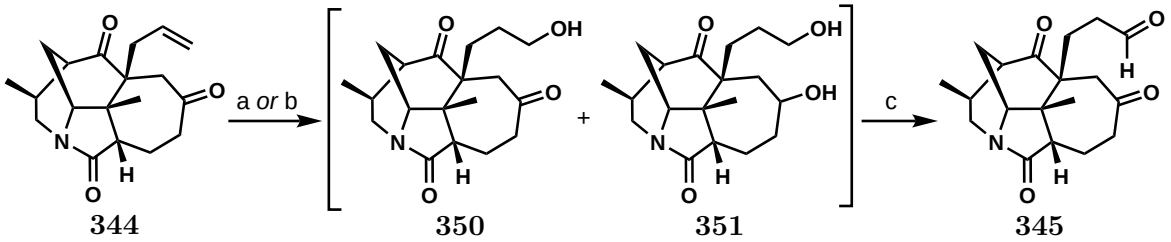
In both cases, attempting to oxidise the intermediate vinyl boronate **347** led to formation of the tetracycle **349** instead (Scheme 5.13). This disappointing result could be explained by a retro-Michael-type event taking place following formation of the trialkyl borate species **348**. Such a transformation would release strain caused by steric hindrance at the quaternary carbon center and form a stabilised anion.



Scheme 5.13: Proposed mechanism to account for formation of ketone **349** during attempted oxidation of vinyl boronate **347**.

In order to avoid the potential for E1cB or retro-Michael-type events, alternative methods were sought which did not involve enol or enolate intermediates. One such method considered was hydroboration-oxidation of the allyl group to afford the corresponding alcohol. While treatment of **344** with several different borane reagents led to hydroboration taking place, this was accompanied by reduction (determined by LCMS) believed to be of the cycloheptanone ketone to form **351** (Scheme 5.14). Despite investigating a range of boranes and reaction conditions, alcohol **350** could

not be formed selectively. Although the two products were not separable, the mixture of **350** and **351** could be re-oxidised using DMP to produce aldehyde **345**. However, the overall yield was poor (ca. 25% over two steps), and a more efficient route to aldehyde **345** was desired.

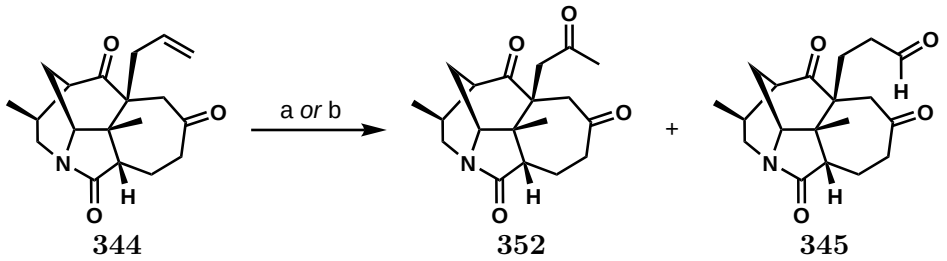


344 **350** **351** **345**

Reagents and conditions: (a) $HBCy_2$, *then* H_2O_2, NaOH; (b) BH_3, *then* H_2O_2, NaOH; (c) DMP, EtOAc, <25% (2 steps, approximate yield determined by component analysis of ^{1}H NMR of **345** contaminated with intermediate alcohols **350** and **351**.

Scheme 5.14: Hydroboration and oxdiation of allyl group in **344** to form aldehyde **345**.

The Wacker oxidation of terminal alkenes generally affords the corresponding methyl ketone,[149] although in some cases substrate control can lead to mixtures of ketone and aldehyde products.[150] The selective terminal oxidation of allyl groups to aldehydes can be achieved using the reverse- or nitrite-Wacker reaction developed by Grubbs and co-workers.[151,152] Under the standard Wacker conditions, **344** was converted into a mixture of ketone **352** and aldehyde **345** in a 1.2:1 ratio, suggesting that steric hindrance of the nearby quaternary center led to moderate substrate control (Scheme 5.15). Subjecting **344** to the nitrite-Wacker conditions on small scale led to excellent selectivity for the formation of aldehyde **345**. However, results were variable and both yield and selectivity were highly sensitive to changes in reaction conditions, reagent loadings, and scale.

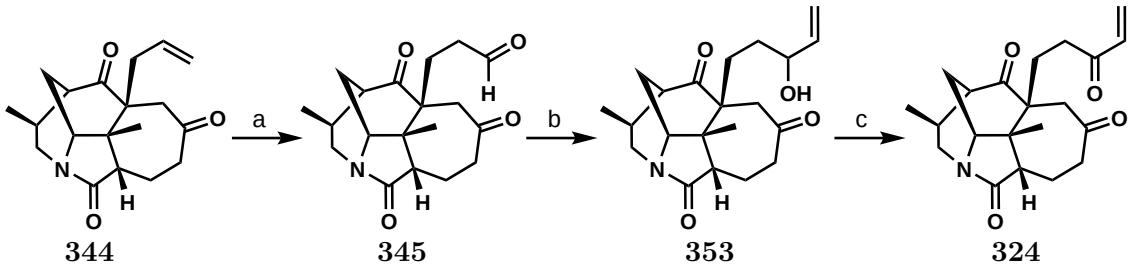


344 **352** **345**

Reagents and conditions: (a) $PdCl_2$ (20 mol%), CuCl (100 mol%), DMF/H_2O (7:1), O_2, RT, 16 h, **352**:**345** ratio 1.2:1; (b) $Pd(PhCN)_2Cl_2$ (20 mol%), $CuCl_2$ (20 mol%), $AgNO_2$ (10 mol%), *t*-BuOH/$MeNO_2$ (15:1), O_2, RT, 4 h; **352**:**345** ratio 1:>20.

Scheme 5.15: Standard Wacker and nitrite-Wacker oxidations of allyl **344** to favour formation of ketone **352** and aldehyde **345** respectively.

In order to validate the aldol route, a telescoped synthesis of the aldol substrate **324** was carried out on small scale from allylated tetracycle **344** (3.3 mg, 0.0105 mmol): Following the nitrite-Wacker oxidation to afford aldehyde **345**, addition of vinyl magnesium bromide was carried out to afford alcohol **353** as a mixture of diastereomers (Scheme 5.16). Finally, oxidation of **353** with Dess–Martin periodinane afforded enone **324** (1.0 mg, 0.0027 mmol, ca. 26% over 3 steps), which was sufficient to test the desired aldol reaction under several conditions.



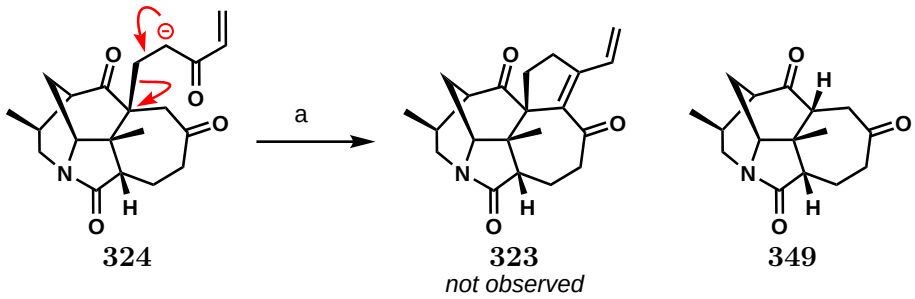
344 **345** **353** **324**

Reagents and conditions: (a) $Pd(PhCN)_2Cl_2$ (20 mol%), $CuCl_2$ (20 mol%), $AgNO_2$ (10 mol%), *t*-BuOH/$MeNO_2$ (15:1), O_2, RT, 4 h; (b) vinyl magnesium bromide, THF, –78 °C to RT, 16 h; (c) DMP, $NaHCO_3$, CH_2Cl_2, RT, 6 h, ca. 26% over 3 steps from **344**.

Scheme 5.16: Conversion of aldehyde **345** to aldol substrate **324** on small scale.

5.1.4 Attemped Aldol Condensation

Subjection of **324** to base-mediated aldol conditions (KO*t*-Bu/*t*-BuOH) resulted in rapid and complete consumption of starting material. However, ring formation did not take place, and tetracycle **349** was obtained instead (Scheme 5.17). The formation of **349** likely arises by an E1cB reaction taking place under the reversible conditions employed. Alternative acid- or base-mediated conditions led to the same outcome. This bears similarity to observations made previously (see Section 5.1.3), with the E1cB process resulting in a large reduction in steric hindrance and relief of compression.



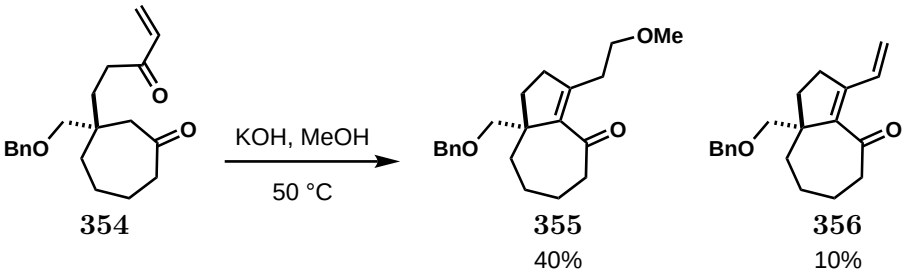
Reagents and conditions: (a) KO*t*-Bu, *t*-BuOH, RT, 15 mins.

Scheme 5.17: Attempted aldol reaction of **324**, resulting in an E1cB elimination to afford tetracycle **349**.

5.1.5 Summary of Aldol Route

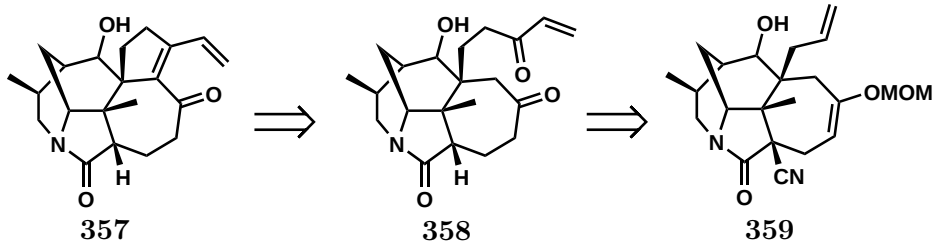
Very recently, Wang, Xu, and co-workers disclosed a synthesis of the tetracyclic core of Logeracemin A.[153] The authors utilised an intramolecular aldol condensation to form the 7,5-fused ring system of the Calyciphylline A-type alkaloids (Scheme 5.18).

This example indicates the feasibility of the aldol reaction to construct the 7,5-fused ring system. Clearly the additional steric hindrance and electron-withdrawing groups greatly increases the propensity for an E1cB reaction. A potential solution to this problem may be attempting the aldol reaction with the cyclohexanone ketone



Scheme 5.18: Intramolecular aldol reaction disclosed by Wang and Xu to form the 7,5-bicyclic ring structure.

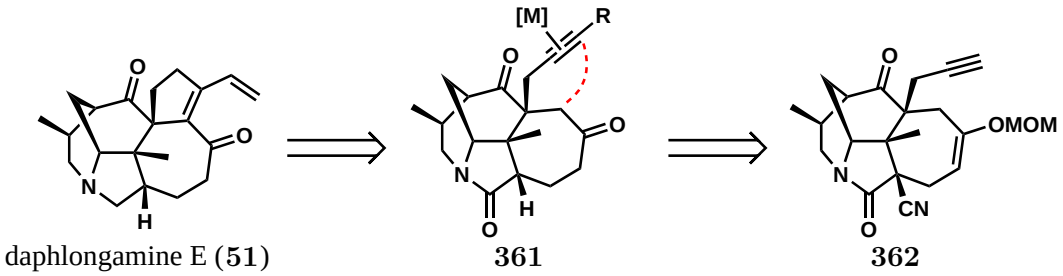
reduced to the alcohol (**358**), or a protected equivalent. This may enable the desired aldol process to take place without an E1cB or retro-Michael-type event occuring, although chemoselectivity would be a key issue to tackle and would require careful synthetic planning (Scheme 5.19).



Scheme 5.19: Reduction of the cyclohexanone ketone may prevent E1cB/retro-Michael-type reactions and enable cyclopentene formation via an aldol condensation of **353**.

5.2 5-*Endo-Dig* Cyclisation

Having determined that the desired aldol reaction was not suitable for formation of the E ring, alternative methods for ring closure were sought. Many examples of 5-*endo-dig* cyclisations between ketones and alkynes have been demonstrated, typically mediated by bases or transition metal catalysts.[154–157] Although examples are often limited to 1,3-dicarbonyls, the Toste group demonstrated a gold-catalysed 5-*endo-dig* cyclisation of enolsilanes onto alkynes.[158] On this basis, it was envisoned that a 5-*endo-dig* cyclisation of alkyne **361** would be a feasible method to install the cyclopentene ring (Scheme 5.20). Additionally, a range of groups could be installed onto the terminus of alkyne **362**, potentially affording access to various substituted cyclopentenes and, in turn, a range of Calyciphylline A-type alkaloids.

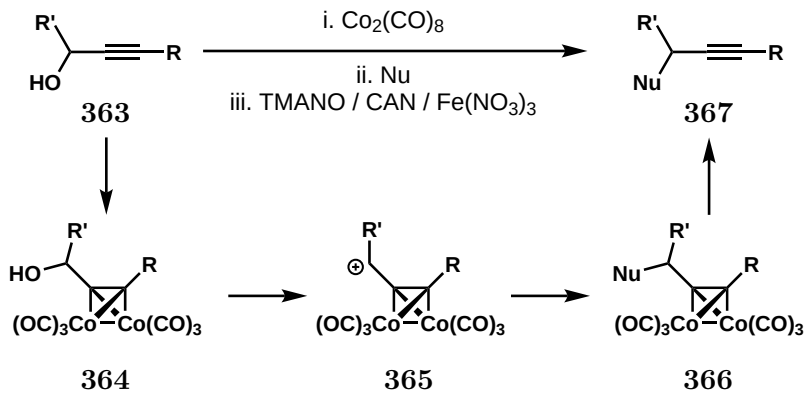


daphlongamine E (**51**) **361** **362**

Scheme 5.20: Proposed 5-*endo-dig* cyclisation of **361** to access the pentacyclic core.

5.2.1 Nicholas Reaction

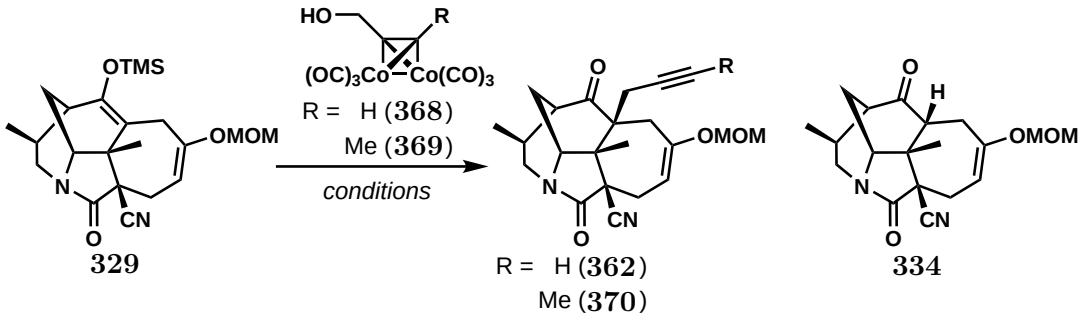
The Nicholas reaction involves the formation of α-(alkynyl)dicobalt hexacarbonyl carbonium ions (**365**) from propargylic alcohols (**363**, Scheme 5.21).[159] These complexes can undergo nucleophilic addition, for example using enolsilanes and Lewis acids as demonstrated by Schreiber and co-workers,[160] to afford substituted propargylic compounds **367**.



Scheme 5.21: Nicholas reaction for nucleophilic substitution of propargylic alcohols. CAN = cerium ammonium nitrate, TMANO = trimethylamine *N*-oxide.

In order to test the Nicholas reaction, several propargylic alcohols were converted into the corresponding Co complexes (**368** and **369**). Unfortunately, testing enolsilane **329** with these complexes under both Au(I) and Lewis acid catalysis led only to hydrolysis of the enolsilane (Table 5.3). No bond formation was observed, and this was again considered a result of steric hindrance in attempting to form the challenging quaternary center.

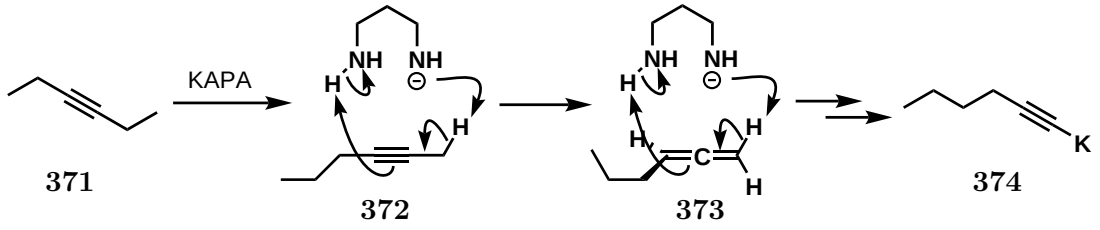
Table 5.3: Unsuccessful attempts at carrying out Nicholas reaction with enolsilane **329** and Co complexes **368** and **369**.



Entry	Conditions	Outcome
1	$AuCl_3$, **368** or **369**, CH_2Cl_2, RT	**334**
2	$NaAuCl_4$, **368** or **369**, CH_2Cl_2, RT	**334**
3	**368** or **369**, CH_2Cl_2, –78 °C, *then* $BF_3 \cdot OEt_2$, –78 °C	**334**

5.2.2 Zipper Reaction

The alkyne zipper reaction is a contrathermodynamic process which converts an internal alkyne to the terminal alkyne, and was first discovered by Brown in 1975 (Scheme 5.22).[161] These reactions are typically carried out using strong potassium amide bases, such as potassium 3-aminopropylamide (KAPA), formed from KH and 1,3-diaminopropane.[162] The process involves a series of isomerisations, ultimately leading to the formation of the potassium acetylide salt (**374**) as the lowest energy intermediate, affording the terminal alkyne on protonation.

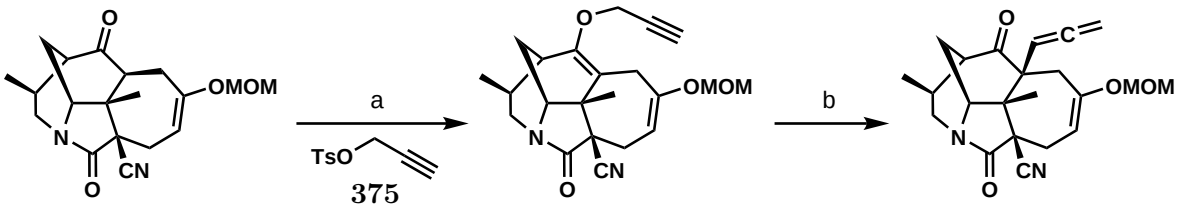


Reagents and conditions: KH and 1,3-diaminopropane (KAPA), 0 °C.

Scheme 5.22: General overview of the alkyne zipper reaction to convert internal alkynes (**371**) to potassium acetylide salts (**374**) and terminal alkynes.

Intermediate steps in the zipper reaction involve the formation of allenes, and several examples in the literature have demonstrated the synthesis of terminal alkynes from allenes under such conditions.[163] As such, it was anticipated that formation of a propargylic quaternary center could be achieved by a zipper reaction of the corresponding allene.

Treatment of ketone **314** with KHMDS followed by propargyl tosylate afforded the propargyl enol ether **376** in good yield (73%); using propargyl bromide instead of **375** led to reduced yields (61%). On heating, **376** underwent a propargyl Claisen rearrangement[164] to afford allene **377** (Scheme 5.23). Transition metal catalysts such as Au(I) and Pd(II) complexes are also often used to effect propargyl Claisen rearrangements,[165,166] however these did not offer improvement over the thermal

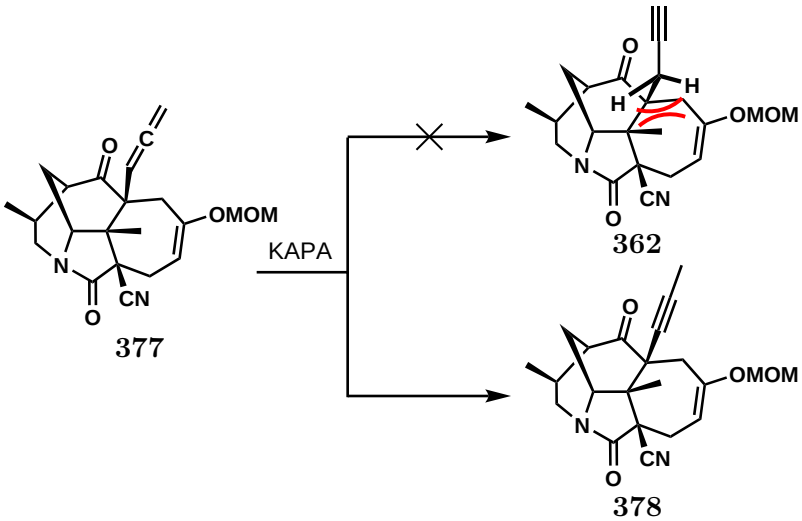


Reagents and conditions: (a) KHMDS, THF, RT, 15 mins, *then* **375**, 18-crown-6, RT, 2 h, 73%; (b) toluene, 150 °C, 15 h, 75%.

Scheme 5.23: Installation of allene and formation of quaternary stereocenter via a propargyl Claisen rearrangement.

rearrangement, and in some cases led to decomposition.

Unfortunately, treatment of allene **377** with KAPA (KH, 1,3-diaminopropane) resulted in rapid conversion to the internal alkyne **378**, not the desired and expected terminal alkyne **362** (Scheme 5.24). This appeared likely to be a consequence of steric hindrance due to diaxial interactions with the adjacent methyl group. The distal protons on allene **377** and alkyne **362** would likely clash with the methyl group, while such an interaction isn't present with alkyne **378**.



Reagents and conditions: (a) KH, 1,3-diaminopropane, 0 °C, 1 h.

Scheme 5.24: Attempted zipper reaction of allene **377**, resulting in formation of internal alkyne **378**. Possible steric clash in alkyne **362** indicated in red.

5.2.3 Computational Investigations into Zipper Reaction

In order to further investigate these results, the structures of **379**, **380**, and **381** were optimised using density functional theory (DFT) to assess possible reasons for the experimental result.[†] Energy minimised structures show that internal alkyne **381** is approximately 8.7 kcal mol^{-1} lower in energy than either the allene **379** or terminal alkyne **380**. In addition, the distances between the protons at C-17, C-10, and C-5 were measured. In both allene and propargyl cases, the distances were approximately 2.0 Å, which increased to approximately 2.5 Å in the case of the internal alkyne **381**. This suggests that one of the likely reasons for the energy difference is reduction in steric hindrance.

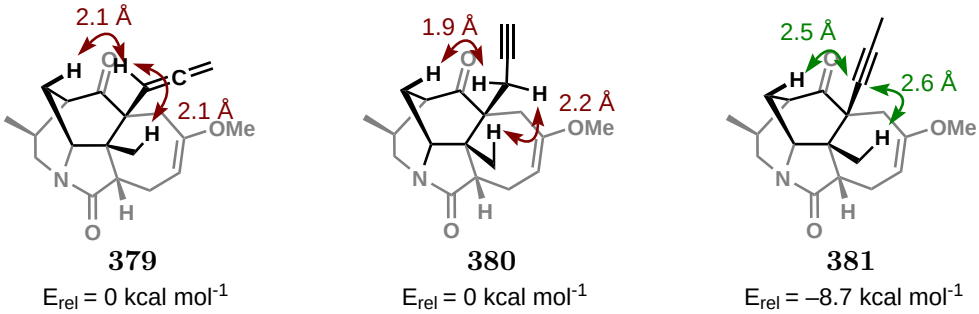


Figure 5.1: Relative energies of allene **379** and alkynes **380** and **381**, and distances between protons at C5, C10, and C17. Structures optimised and energies calculated at the ωb97xd/6-311+G** level of theory.

To gain a deeper understanding, the structures and energies of reaction intermediates were also calculated. This was first carried out on a simpler system: the zipper reaction of *tert*-butyl allene **382**. Structures of the protonated and metallated

[†]Conformational analysis was first carried out to investigate ring conformations and enol geometry. Both the cyclohexanone and piperidine rings preferentially occupy boat-like conformations, with the chair form converging to the boat form in many cases. The major conformations of the seven-membered ring are chair- and boat-like, with the former preferred in many cases. The syn-periplanar enol ether was found to be lower in energy than the anti-periplanar form, in line with studies by Sanders and co-workers.[167] Consequently, these parameters were used in determining structures and energies of the allenyl- and alkynyl-substituted tetracycles. To reduce computational time and cost, the nitrile group was replaced with H and the methoxy methyl enol ether was replace with a methyl ether. Comparison of structures with and without these changes revealed minimal differences on the conformation, and was considered a worthwhile trade-off.

species of the allene, alkynes, and 1,3-diaminopropane were optimised and energy levels were calculated at the ωb97xd/6-311+G** level of theory (Figure 5.2). Of the protonated species, the internal alkyne was lower in energy by 1.5 kcal mol^{-1} compared to the allene, while the terminal alkyne was 2.1 kcal mol^{-1} higher in energy, the overall trend being as expected. Of the metallated species, however, the potassium acetylide is approximately 2.1 kcal mol^{-1} lower in energy than all other species. As a result, this would be the preferential form under equilibrating conditions, and is the reason that, upon quenching, the terminal alkyne is formed as the major product.

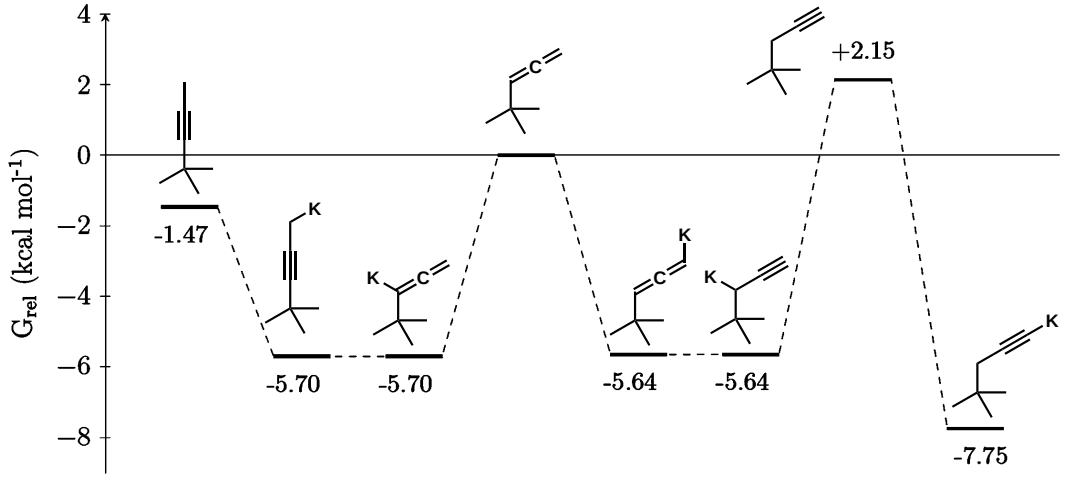


Figure 5.2: Relative energies of intermediates during the zipper reaction of *tert*-butyl allene.

A similar series of preliminary calculations were carried out on the model tetracyclic system, which has added complexities due to the diastereotopic nature meaning there are additional structures to consider (Figure 5.3). As discussed above, the internal alkyne is considerably lower in energy than the terminal alkyne or allene. In the case of the metallated species, the presence of Lewis basic groups such as the ketone and enol ether appear to afford additional stabilisation by complexation. However, this preliminary computational treatment requires significant refinement to account for additional variables, such as the effect of the diaminopropane as both a solvent and a ligand for potassium.

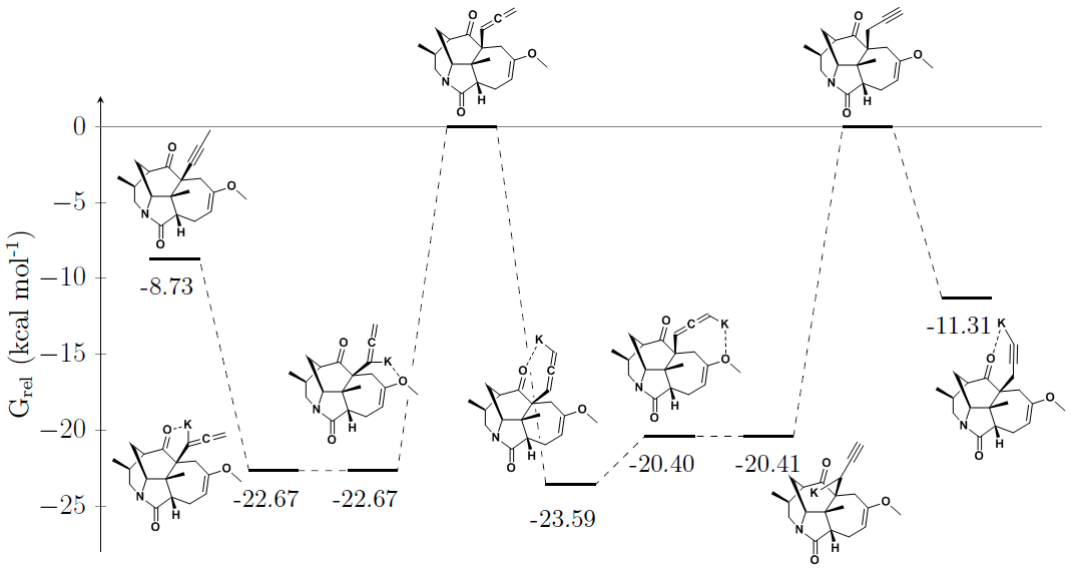
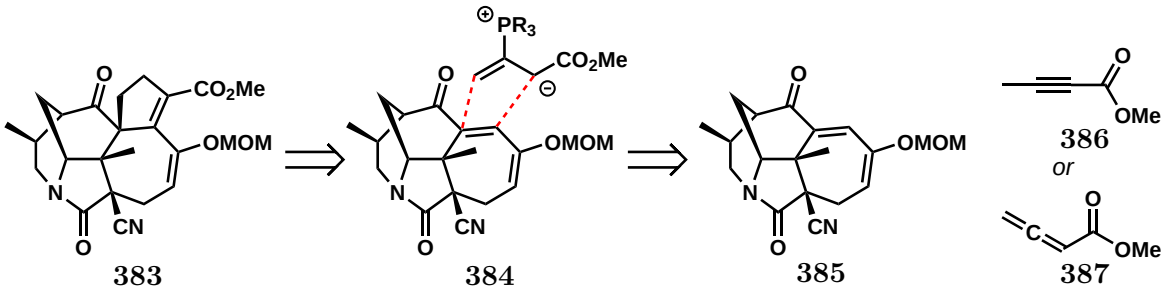


Figure 5.3: Relative energies of intermediates formed during the zipper reaction on the tetracyclic core.

Further studies and refinement are required to fully understand and explain these observations, however from this preliminary work it is clear that diaxial steric hindrance causes a significant increase in energy, which is minimised on forming the undesired internal alkyne.

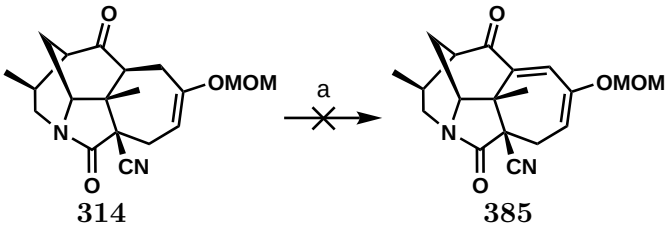
5.3 Phosphine-Catalysed [3+2] Cycloaddition

Another strategy envisioned to append the E ring was a phosphine-catalysed [3+2] cycloaddition of enone **385** with either alkynoate or allenoate esters (Scheme 5.25). Lu and co-workers demonstrated this transformation in 1995 using phosphine catalysts such as PPh_3 and PBu_3,[168] and it has since been applied by other groups.[169,170] Indeed, subsequent to this work being carried out, the Li and Zhai groups both employed this strategy to synthesise the E ring of several Calyciphylline A-type alkaloids.[44,46,48]



Scheme 5.25: Retrosynthetic analysis employing a phosphine-catalysed [3+2] cycloaddition of enone **385** with alkynoate or allenoate esters.

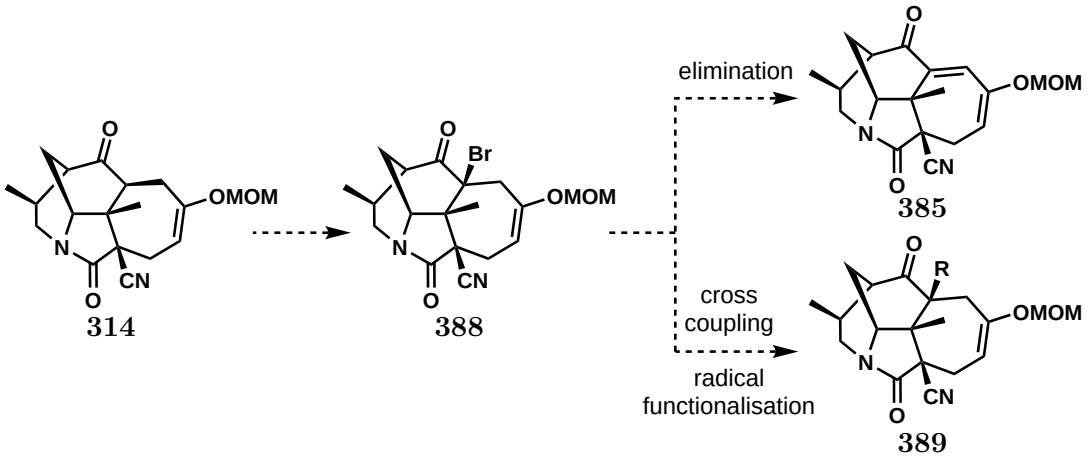
Initial attempts to prepare enone **385** by oxidation of ketone **314** using IBX were unsuccessful (Scheme 5.26). Chemoselectivity was considered an issue, as IBX can be used to oxidise enol ethers in addition to enolisable ketones.[95,96] However, no reaction took place at either position using IBX at 100 °C after 16 h. One likely explanation for the lack of reactivity was steric hindrance at the tertiary center.



Reagents and conditions: (a) IBX (1.2 equivs), EtOAc, 100 °C, 16 h.

Scheme 5.26: Attempted oxidation of tetracycle **314** with IBX.

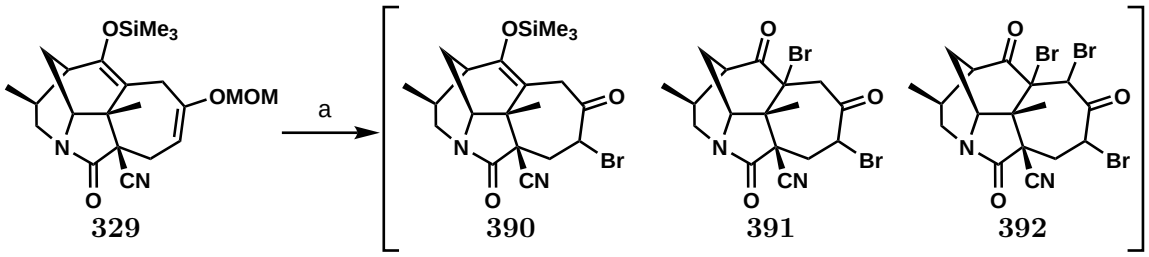
An alternative method considered was bromination to form the corresponding α-bromoketone **388** (Scheme 5.27). Bromide **388** could then undergo elimination to afford the desired enone **385**. Alternatively, the bromide could be employed in a variety of other ways such as cross coupling reactions or radical functionalisations to modify the α-ketone position (**389**).



Scheme 5.27: Strategy for formation of bromide **388** to enable synthesis of enone **385** or installation of additional functionality.

5.3.1 Synthesis of Enone Starting Material

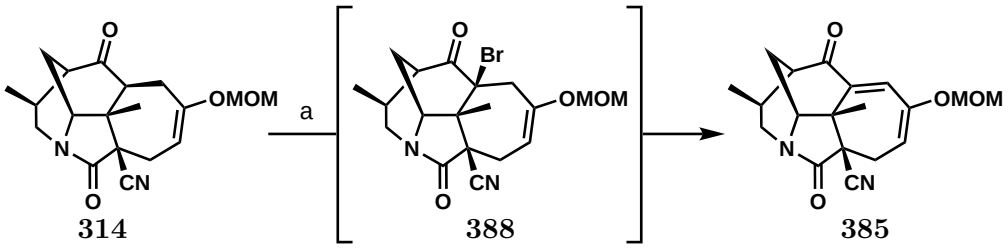
α-Bromination was first attempted by treating enolsilane **329** with NBS (Scheme 5.28). The enolsilane was expected to be more reactive than the methoxymethyl enol ether, however the lack of chemoselectivity led to formation of complex mixtures of mono-, di-, and tri-bromination products as evidenced by LCMS. These were believed to be **390**, **391**, and **392**, though separation and isolation of the products could not be achieved.



Reagents and conditions: (a) NBS (1.25 equiv), 0 °C, 30 mins;

Scheme 5.28: Attempted bromination of enolsilane **329** resulting in formation of complex mixture of poly-brominated products.

In order to tackle the chemoselectivity issues, it was anticipated that the enolate of ketone **314** would be more reactive than the methoxymethyl enol ether, which would give rise to improved chemoselectivity. Treatment of **314** with KHMDS followed by addition of 18-crown-6 and NBS at low temperatures resulted in α-bromination, however this was rapidly followed by elimination *in situ* to afford enone **385** in 42% yield. Similar transformations have been observed previously,[171,172] and while further attempts to improve the yield were not investigated, one worthwhile consideration would be to increase the amount of base used.



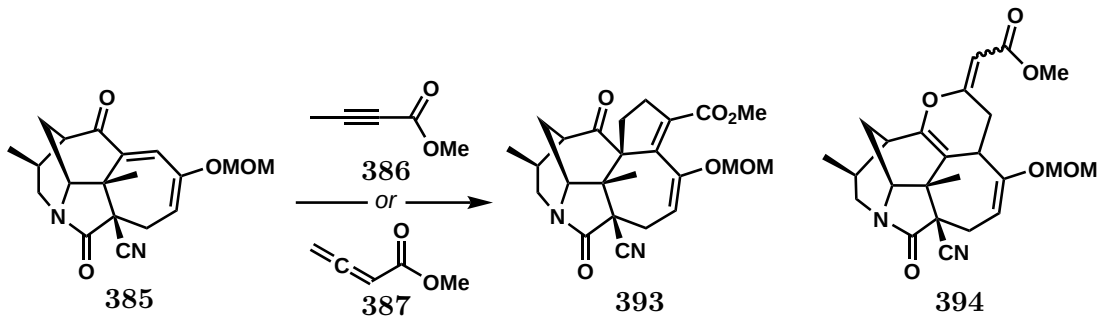
Reagents and conditions: (a) KHMDS (1.25 equiv), 0 °C, 15 mins, *then* NBS (1.25 equiv), 18-crown-6 (0.25 equiv), 0 °C, 30 mins, 42%.

Scheme 5.29: One-pot bromination-elimination of tetracycle **314** resulting in direct formation of enone **385**.

5.3.2 Attempted [3+2] Cycloaddition

On attempting the [3+2] cycloaddition, no reaction was observed when enone **385** and methyl butynoate (**386**) were treated with catalytic PPh_3 (Table 5.4, Entry 1). However, using PBu_3 with either methyl butynoate (**386**) or methyl butadienoate (**387**) led to a [4+2] cycloaddition taking place to afford pentacycle **394** (Entries 2 and 3). In both cases, the [3+2] product (**393**) could not be detected. Additionally, a Danheiser-type cycloaddition of allyl silanes under Lewis acid catalysis was attempted, though this too was unsuccessful.[173]

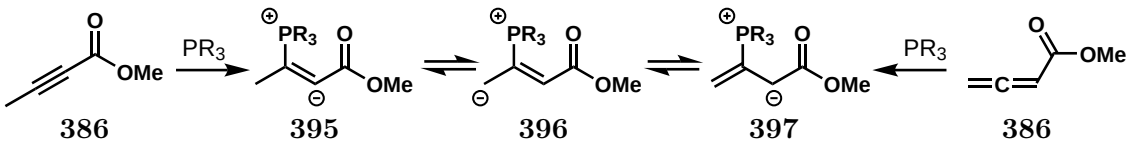
Table 5.4: Attempted [3+2] cycloaddition of **385**.



Entry	Conditions	Outcome
1	PPh_3 (25 mol%), **386**	NR
2	PBu_3 (25 mol%), **386**	**394** (40%)
3	PBu_3 (25 mol%), **387**	**394** (30%)

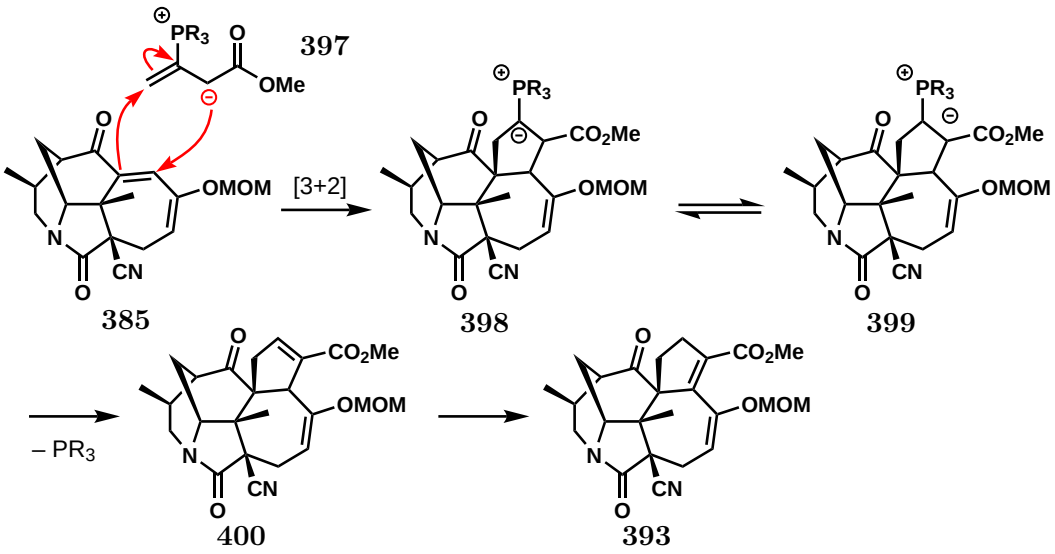
Reagents and conditions: **385**, **386** or **387** (3 equiv), phosphine, toluene, 85 °C, 2 h.

The treatment of alkynoates or allenoates, such as **386** or **387**, with phosphine catalysts leads to the formation of ylids **395**–**397**, which can interconvert through a series of proton transfers and isomerisations (Scheme 5.30).[168]



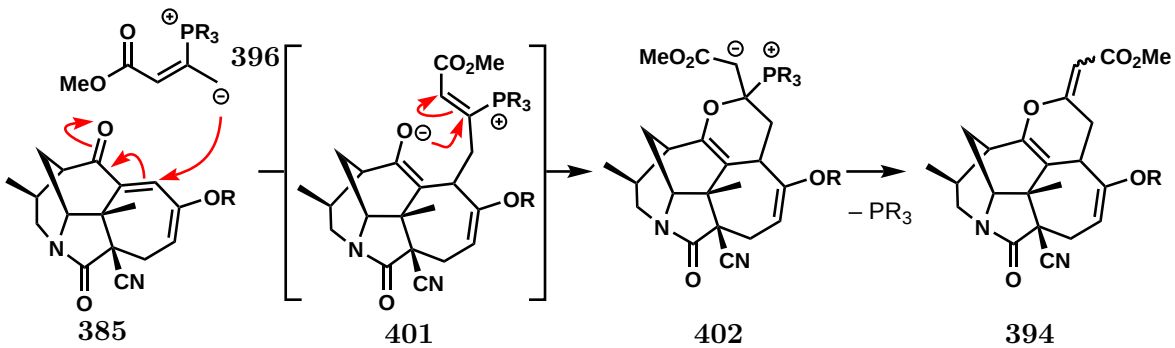
Scheme 5.30: Reaction of alkynoate **386** and allenoate **387** with phosphine catalysts.

The desired reaction would involve a [3+2] cycloaddition between enone **385** and **397** to form ylid **398**. Following a proton transfer, elimination of the phosphine catalyst would afford **400**, which could be expected to readily isomerise to **393**.



Scheme 5.31: Desired [3+2] cycloaddition between enone **385** and ylid **397** leading to pentacycle **393**.

The formation of the tetrahydropyran ring in **394** must instead be formed by the reaction between enone **385** and **396**. Following addition of **396**, an oxy-Michael reaction must take place to generate **402** which, following elimination, would afford the pentacycle **394**. Further investigations would be required to ascertain whether the nature of the process is a concerted [4+2] cycloaddition or a stepwise process.

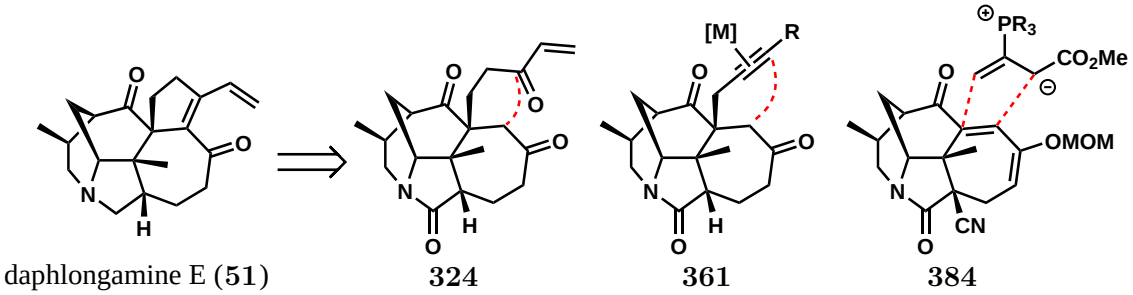


Scheme 5.32: Formation of pentacycle **394** resulting from reaction between enone **385** and **396**. R=CH_2OCH_3 (–MOM).

The Li group were recently successful in their application of a [3+2] cycloaddition to synthesise the E ring of several Calyciphylline A-type alkaloids.[44,46] The authors reported formation of a [4+2] adduct which could be minimised by using diphosphines such as 1,1'-bis(diphenylphosphino)ferrocene (DPPF). In addition, the authors reported that electron-deficient olefins were necessary for the desired [3+2] cycloaddition. Due to the absence of any [3+2] cycloaddition product being observed this route was not considered viable. However, the observations made by the Li group suggest that hydrolysis of the methoxymethyl enol ether and selection of an alternative phosphine catalyst may provide access to the [3+2] cycloadduct.

5.4 Summary of Chapter Five

This chapter has described a broad range of tactics investigated in an effort to append the E ring in order to achieve a total synthesis of daphlongamine E or other Calyciphylline A-type alkaloids (Scheme 5.33). Many annulation methods or substrate syntheses were unsuccessful due to retro-Michael or E1cB type side-reactions taking place. This was believed to be caused by severe steric hindrance about the contiguous all-carbon quaternary stereocenter motif. Consequently, these processes must be taken into account in future work on the Calyciphylline A-type alkaloid family.



Scheme 5.33: Summary of key approaches to E ring formation discussed in Chapter Five.

5.5 Thesis Summary

This thesis set out to develop an enantioselective total synthesis of daphlongamine E. The work carried out on the journey has led to several significant achievements:

In Chapter Two, the development of a new catalytic enantioselective method for the synthesis of morphan core derivatives was described. This method tolerates substrates with broad structural differences including tertiary alkenes and fully substituted carbon centers, affording complex cyclised products with excellent levels of enantioselectivity.

In Chapters Three and Four, the synthesis of several tetracyclic cores of the Calyciphylline A-type alkaloids was described. To achieve this required optimising a Ag/amine co-catalysed desymmetrisation reaction to be carried out on decagram scale, followed by several key functional transformations and ring forming reactions. This developed route provides a more efficient route to the tetracyclic core than had previously been developed by the Dixon group.

Finally, in Chapter Five, some approaches towards completion of the synthesis were discussed. Although many approaches were hampered by severe steric hindrance, identification of by-products led to a greater understanding of the nature of the Calyciphylline A-type alkaloids, and the challenges in constructing all-carbon quaternary stereocenters.

Chapter 6

Experimental Details

6.1 General Experimental Details

General Techniques: Reactions were carried out under a nitrogen atmosphere unless stated otherwise. Glassware was oven-dried and cooled under vacuum then purged with nitrogen before use. Room temperature refers to 22 ± 2 °C. Inert atmosphere techniques, such as Schlenk technqiue, were used for the handling of air/moisture sensitive reagents. Reactions carried out at 0 °C were cooled using an ice bath, those at –10 °C were cooled using a mixture of ice and NaCl, and those at –78 °C were carried out using a solid CO_2/acetone bath. Reactions carried out at high temperatures were heated using an oil bath or, preferably, using DrySyn® heating blocks. Reaction temperatures refer to external temperatures, for example of a heating block or oil bath, not of internal reaction temperatures unless stated otherwise.

Nomenclature and Numbering: Compounds are named following IUPAC nomenclature as generated by ACD LABS or ChemDraw. Carbon atoms are numbered in a systematic way where possible to ease comparison between related compounds in a synthetic sequence, not necessarily in accordance with IUPAC conventions.

Solvents and Reagents: Ether refers to diethyl ether; petrol refers to the fraction of petroleum ether that boils between 30 and 40 °C. Where solvent dryness was important, CH_2Cl_2, ether, methanol, THF, and toluene were either obtained from dry solvent bottles with septa (Aldrich), an MBRAUN-SPS solvent purification system in which solvent is passed through an activated alumina column under nitrogen, or by standing over 3 Å molecular sieves under an atmosphere of nitrogen. Reagents were used as obtained without further purification unless stated otherwise.

Chromatography: Thin layer chromatography (TLC) was carried out using Merck aluminium backed DC60 F254 plates (particle size 0.2 mm). TLC sheets were visualised by UV light, then developed by staining with potassium permanganate, anisaldehyde, cerium ammonium molybdate, vanillin, or iodine on silica. Purification by flash column chromatography[174] was carried out using Merck silicagel 60 F254 (particle size 43–60 μm). On larger scales, dry column vacuum chromatography was occasionally used to reduce silica and solvent volume.[175,176] HPLC separation of racemic and enantioenriched compounds was carried out using an Agilent Technologies 1200 series HPLC.

Characterisation: Proton (^{1}H) and carbon (^{13}C) spectra were recorded on Bruker AVG400 (400/101 MHz), Bruker AVH400 (400/101 MHz), Bruker AVF400 (400/101 MHz), Bruker AVB500 (500/126 MHz), Bruker AVC500 (500/126 MHz), and Bruker DPX200 (200 MHz) NMR spectrometers. Spectra are referenced to the residual solvent peak ($CHCl_3$: δ_H 7.26, δ_C 77.16 ppm; C_6D_5H: δ_H 7.15, δ_C 128.06 ppm). Chemical shifts (δ) are given in parts per million (ppm, $\pm$ 0.01) and coupling constants are given in Hertz (Hz, $\pm$ 0.5). The following convention is used to report chemical shifts: δ (multiplicity, coupling constant(s), number of protons, assignment), with chemical shifts reported in descending order. Peak assignments were made based

on chemical shifts, integrations, coupling constants, and two dimensional techniques such as COSY and HSQC. Where necessary, additional experiments such as HMBC, nOe, and NOESY were also used. Peak multiplicities are described as singlet (s), doublet (d), triplet (t), quartet (q), pentet (p), a combination e.g. doublet of doublets (dd), or as a multiplet (m) over a peak range. Additionally, peaks may be described as broad (br), or apparent (app.)

Infrared spectra were recorded using a Bruker Tensor 27 FT-IR spectrometer. Selected diagnostic absorption maxima ($\tilde{\nu}_{\max}$) are reported in wavenumbers (cm^{-1}). Low-resolution mass spectra were acquired using a Micromass LCT Premier spectrometer (ESI). High resolution mass spectra were recorded by Chemistry Research Laboratory staff using a Bruker Daltronics MicroTOF spectrometer (ESI). Mass to charge ratios (m/z) are reported in Daltons. Melting points were recorded using a Leica Galen III hot-stage microscope apparatus and are reported uncorrected in degrees Celcius (°C). Optical rotations were recorded using a Perkin Elmer 241 optical activity polarimeter at 25 °C. Specific rotations ($[\boldsymbol{\alpha}]_D^{25}$) are reported in 10^{-1} deg cm^2 g^{-1}, with concentrations (c) in g/100 mL. D refers to the D-line of sodium (589.44 nm).

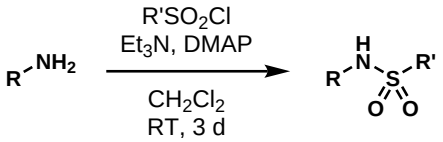
X-Ray Crystallography: Single crystal X-ray diffraction data were collected using an Enraf–Nonius KCCD diffractometer or an Oxford Diffraction SuperNova diffractometer at 150 K. Crystal structures were solved with SIR92 and refined with CRYSTALS by Dr Heyao Shi (University of Oxford) with assistance and guidance from Dr Amber L. Thompson and Dr Kirsten E. Christensen (University of Oxford Chemical Crystallography department).

Synthesis of Known Compounds: The synthesis of compounds previously reported in the literature are labelled as such. References are given for experimental

procedures and data. Details of experimental procedures are provided where relevant, however ^{1}H and ^{13}C NMR data is only included where relevant, such as prior to the formation of a novel compound.

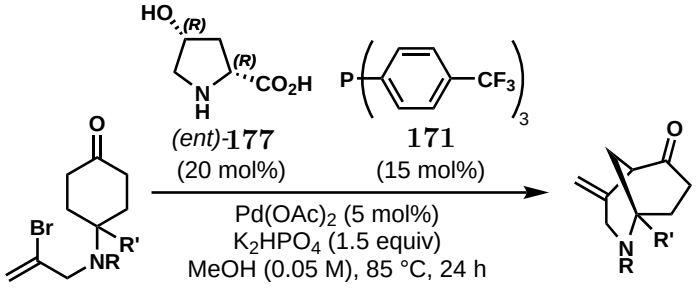
6.2 Compounds Synthesised in Chapter 2

6.2.1 General Procedure A: Sulfonamide Protection



To a solution of amine (1.00 equiv) in CH_2Cl_2 (0.20 M) at 0 °C was added Et_3N (1.75 equiv) dropwise. After addition of Et_3N was complete, DMAP (0.20 equiv) was added, followed by sulfonyl chloride (1.75 equiv). The reaction mixture was stirred at RT for 3 d until complete, then carefully acidified with aqueous 1 M HCl. The phases were separated and the aqueous layer was extracted with CH_2Cl_2, then the combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude residue was purified by flash column chromatography.

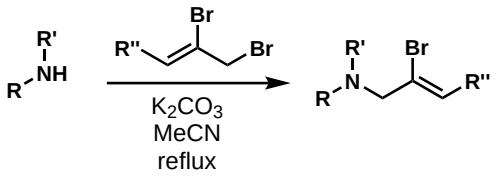
6.2.2 General Procedure B: Pd(II)/Amine Co-Catalysed Cyclisation



In the following procedure, degassing refers to three cycles of high vacuum followed by backfilling with Ar. An oven-dried 15 mL screw-capped tube, with a cap and PTFE septum loosely attached, was cooled under vacuum then degassed. The vessel was then charged with substrate (0.10 mmol if solid, otherwise the substrate

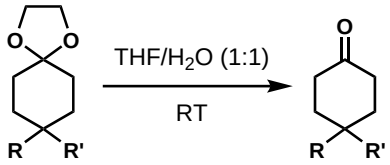
was added later as a solution in MeOH), $Pd(OAc)_2$ (1.1 mg, 0.0050 mmol, 5 mol%), tris(4-trifluoromethylphenyl)phosphine (7.0 mg, 0.015 mmol, 15 mol%), (2*R*,4*R*)-4-hydroxypyrrolidine-2-carboxylic acid (2.6 mg, 0.020 mmol, 20 mol%) and K_2HPO_4 (26 mg, 0.15 mmol), then the vessel was degassed. For solid substrates, dry, degassed MeOH (2 mL) was then added. Substrates which were oils were added at this stage as a solution in MeOH (1 mL) followed by rinsing with MeOH (1 mL). While stirring, the solution was degassed again, being careful to avoid bumping or excessive solvent evaporation, then the tube was sealed under a stream of Ar. The sealed tube was then transferred to a heating block pre-heated to 85 °C and stirred at that temperature for 24 h. After heating for 24 h the tube was removed from the heating block and allowed to cool to RT, before diluting with CH_2Cl_2 (2 mL). The suspension was then filtered through a plug of Celite® (1 cm) and silica (1 cm), eluting with additional CH_2Cl_2 (5 mL), then the filtrate was concentrated under vacuum. NMR yields and conversions were obtained by dissolving the crude reaction mixture in $CDCl_3$ before adding the appropriate volume of internal standard (mesitylene, 14 µL, 0.10 mmol) and transferring a small volume to an NMR tube, diluting with additional $CDCl_3$. Purification by flash column chromatography yielded the cyclised product. Enantiomeric excess was measured using HPLC with a chiral stationary phase and a hexane/isopropanol mobile phase as specified for each compound.

6.2.3 General Procedure C: Alkylation of Amines



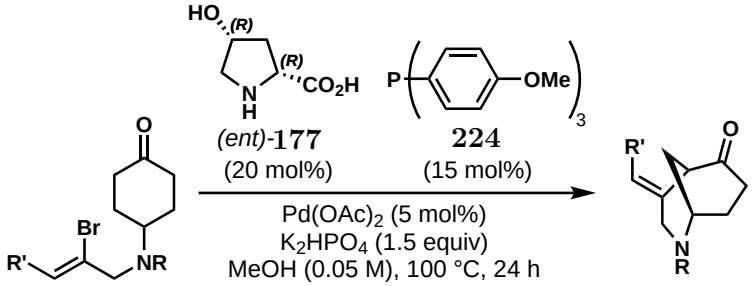
To a solution of amine (1.0 equiv) in MeCN (0.20 M) was added K_2CO_3 (2 equiv) followed by bromide (1 equiv) dropwise. The mixture was heated to reflux and stirred overnight. On completion the reaction was cooled to RT then filtered through Celite®, washing with EtOAc, then the filtrate was concentrated and purified by flash column chromatography.

6.2.4 General Procedure D: Ketal Hydrolysis



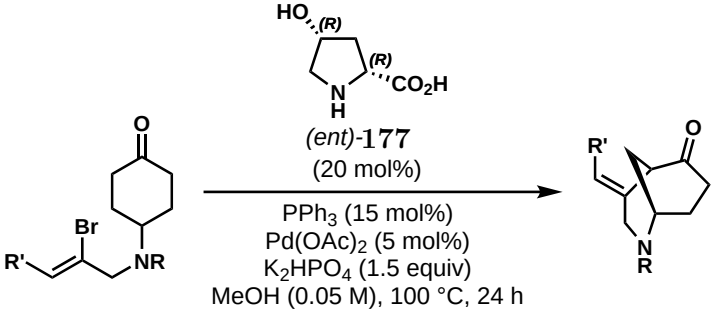
To a stirring solution of ketal (1 equiv) in THF (0.20 M) was added dropwise aq. 3 M HCl (0.2 M wrt ketal). The reaction mixture was stirred at RT until completion (typically 48 h, followed by TLC), then was basified with aq. 3 M NaOH to pH 12 and extracted with EtOAc. The combined organic layers were washed with water and brine to remove the ethylene glycol generated in the reaction, then dried with Na_2SO_4, filtered, and concentrated under vacuum. The crude residue was purified by flash column chromatography.

6.2.5 General Procedure E: Pd(II)/Amine Co-Catalysed Cyclisation for Trisubstituted Alkene Substrates



Carried out according to General Procedure B, except that the vessel was charged with tris(4-methoxyphenyl)phosphine (5.3 mg, 0.015 mmol, 15 mol%) instead of tris(4-trifluoromethylphenyl)phosphine, and the reaction was carried out at 100 °C instead of 85 °C. The rest of the procedure remains as described in General Procedure B.

6.2.6 General Procedure F: Pd(II)/Amine Co-Catalysed Cyclisation for Trisubstituted Alkene Substrates



Carried out according to General Procedure B, except that the vessel was charged with triphenylphosphine (3.9 mg, 0.015 mmol, 15 mol%) instead of tris(4--trifluoromethylphenyl)phosphine, and the reaction was carried out at 100 °C instead of 85 °C. The rest of the procedure remains as described in General Procedure B.

6.2.7 Synthesis of Ketone 164

2-bromoprop-2-en-1-amine (162)

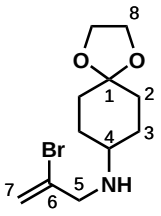


Prepared according to a literature procedure.[177] A 2-neck round bottomed flask was charged with hexamethylenetetramine (9.78 g, 69.8 mmol) and $CHCl_3$ (120 mL), then was fitted with a vertical condenser in one neck and a septum in the other. The solution was stirred and heated to reflux, then 2,3-dibromopropene (7.75 mL, 80%, 63.4 mmol) was added dropwise over 1 h using a syringe pump through the septum. After the addition was complete, the mixture was left stirring under reflux for a further 3 h, before cooling to RT and allowing to stand overnight. The mixture was then cooled to 0 °C and the precipitate was collected by suction filtration. After air-drying, the crude yellow 2-bromoallylhexaminium bromide (20.5 g, 60.3 mmol) was placed in an Erlenmeyer flask, dissolved in a mixture of water (40 mL), EtOH (20 mL), and 12 M HCl (48 mL), and left to stand at RT for 5 d. The white precipitate (NH_4Cl) was removed by filtration, and the filtrate was concentrated under vacuum and filtered again to remove additional NH_4Cl precipitate. The filtrate was evaporated to dryness and the resultant amine-HCl salt re-dissolved in aqueous 3 M NaOH (50 mL). The heavy red-brown oil was separated, then the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined oil and organic extracts were dried over Na_2SO_4, filtered, and concentrated. The resulting oil was purified by vacuum distillation (180 mbar, 65 – 67 °C) to afford amine **162** as a colourless liquid (4.89 g, 36.0 mmol, 57%). Data is in agreement with literature values.[178]

BP: 65 – 67 °C at 180 mbar (lit. 65 – 68 °C at 180 mbar); **IR** (thin film) $\tilde{\nu}_{max}{}^{-1}$

3270 (N–H), 1655 (C=C); ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 5.78 (dt, J = 2.0, 1.0 Hz, 1H, H-3a), 5.47 (dt, J = 2.0, 1.0 Hz, 1H, H-3b), 3.52 – 3.42 (m, 2H, H-1);

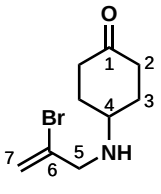
4-((2-bromoallyl)amino)cyclohexan-1-one (163)



To a solution of amine **162** (4.90 g, 36.0 mmol) in DCE (100 mL) was added 1,4-cyclohexanedione monoethylene acetal **161** (5.62 g, 36.0 mmol). The mixture was then cooled to 0 °C (ice bath) and $NaBH(OAc)_3$ (10.7 g, 50.4 mmol) was added slowly. The ice bath was removed and the mixture left stirring at RT for 24 h, before quenching with aq. 1 M KOH (100 mL). The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were then dried over Na_2SO_4, filtered, and concentrated under vacuum. Purification by flash column chromatography (1:4 acetone/pentane) afforded amine **163** (9.42 g, 34.1 mmol, 95%) as yellow oil.

IR (thin film) $\tilde{\nu}_{max}^{-1}$ 2935 (C−H), 2880 (C−H), 1626 (C=C), 1446, 1377, 1279, 1240, 1178 (C−N), 1104 (C−O); ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 5.79 (q, J = 1.5 Hz, 1H, H-7a), 5.54 (dd, J = 1.5, 1.0 Hz, 1H, H-7b), 3.92 (s, 4H, H-8), 3.46 (t, J = 1.0 Hz, 2H, H-5), 2.56 (tt, J = 9.5, 3.5 Hz, 1H, H-4), 1.88 – 1.71 (m, 4H, H-3, H-2), 1.61 – 1.32 (m, 4H, H-3, H-2); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 134.2 (C-6), 117.4 (C-7), 108.7 (C-1), 64.4 (C-8), 64.4 (C-8), 54.9 (C-5), 52.8 (C-4), 32.8 (C-3, C-2), 30.1 (C-3, C-2); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{11}H_{19}O_2N^{79}Br)^+$ requires 276.0594, found 276.0595.

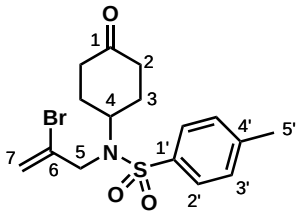
4-((2-bromoallyl)amino)cyclohexan-1-one (164)



To a solution of acetal **163** (6.39 g, 23.2 mmol) in THF (63 mL) was added aqueous 3 M HCl (63 mL), then the mixture was stirred at RT for 48 h until completion. The solution was then basified with aqueous 3 M NaOH to pH 12 and extracted with EtOAc (3 × 70 mL). The combined organic layers were washed with brine (100 mL) to remove ethylene glycol (which was confirmed by TLC), then dried over Na_2SO_4 and concentrated under vacuum. Purification by flash column chromatography (2:1 EtOAc/pentane) afforded ketone **164** (5.23 g, 22.5 mmol, 97% yield) as a yellow oil. **IR** (thin film) $\tilde{\nu}_{max}{}^{-1}$ 2933 (C−H), 2864 (C−H), 1712 (C=O), 1629 (C=C), 1446, 1424, 1329, 1233, 1172, 1118, 896, 842, 745, 678 (C–Br); ^{1}**H-NMR** (500 MHz, $CDCl_3$): δ_H 5.80 (dd, J = 2.0, 1.0 Hz, 1H, H-7a), 5.58 (d, J = 2.0 Hz, 1H, H-7b), 3.52 – 3.48 (m, 2H, H-5), 3.03 – 2.94 (m, 1H, H-4), 2.51 (dtd, J = 15.0, 6.0, 1.5 Hz, 2H, H-2a), 2.34 – 2.24 (m, 2H, H-2b), 2.07 – 1.97 (m, 2H, H-3a), 1.71 (dddd, J = 13.5, 9.5, 8.0, 5.0 Hz, 2H, H-3b); ^{13}**C-NMR** (126 MHz, $CDCl_3$): δ_C 211.2 (C-1), 133.8 (C-6), 117.9 (C-7), 54.8 (C-5), 50.8 (C-4), 38.2 (C-2), 31.7 (C-3); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_9H_{15}ON^{79}Br)^+$ requires 232.0332, found 232.0334.

6.2.8 Synthesis of Substrates: Variation at Nitrogen

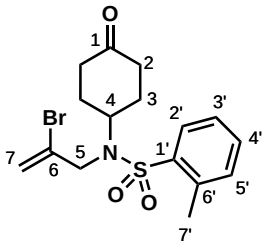
***N*-(2-bromoallyl)-4-methyl-*N*-(4-oxocyclohexyl)benzenesulfonamide (165)**



Prepared according to General Procedure A using amine **164** (2.80 g, 6.51 mmol) in CH_2Cl_2 (32 mL), Et_3N (1.59 mL, 11.4 mmol), DMAP (159 mg, 1.30 mmol), and a solution of *p*-toluenesulfonyl chloride (2.17 g, 11.4 mmol) in CH_2Cl_2 (5 mL). Purification by flash column chromatography (1:2 EtOAc/pentane) afforded **165** as a white solid (2.16 g, 5.59 mmol, 86% yield).

MP: 113–116 °C; **IR** (thin film) $\tilde{\nu}_{max}$$^{-1}$ 2980 (C−H), 1715 (C=O), 1642 (C=C), 1341 (SO_2), 1156 (SO_2), 1042 (C−N); ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 7.79–7.71 (m, 2H, H-2'), 7.36–7.29 (m, 2H, H-3'), 5.99 (dt, J = 2.0, 1.5 Hz, 1H, H-7a), 5.63 (dt, J = 2.0, 1.5 Hz, 1H, H-7b), 4.19 (tt, J = 12.0, 4.0 Hz, 1H, H-4), 4.01 (t, J = 1.5 Hz, 2H, H-5), 2.43 (s, 3H, H-5'), 2.40–2.30 (m, 4H, H-2), 1.96–1.75 (m, 4H, H-3); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 208.4 (C-1), 144.0 (C-4'), 137.6 (C-1'), 130.1 (C-3'), 129.9 (C-6), 127.2 (C-2'), 118.8 (C-7), 56.2 (C-4), 51.4 (C-5), 40.0 (C-2), 30.0 (C-3), 21.7 (C-5'); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ $(C_{16}H_{20}O_3N^{79}Br^{23}Na^{32}S)^+$ requires 408.0240, found 408.0239.

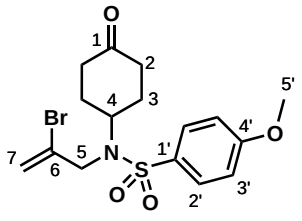
N-(2-bromoallyl)-2-methyl-*N*-(4-oxocyclohexyl)benzenesulfonamide (184)



Prepared according to General Procedure A using amine **164** (348 mg, 1.50 mmol) in CH_2Cl_2 (7.5 mL), Et_3N (0.37 mL, 2.7 mmol), DMAP (36 mg, 0.29 mmol), and a solution of *o*-toluenesulfonyl chloride (0.38 mL, 2.6 mmol) in CH_2Cl_2 (1 mL). Purification by flash column chromatography (1:3 EtOAc/pentane) afforded **184** as a grey oil (174 mg, 0.450 mmol, 30% yield).

IR (thin film) $\tilde{\nu}_{max}^{-1}$ 2954 (C−H), 1715 (C=O), 1642 (C=C), 1461, 1320 (SO_2), 1155 (SO_2); ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 8.00 (dd, J = 7.5, 1.5 Hz, 1H, H-2'), 7.48 (td, J = 7.5, 1.5 Hz, 1H, H-4'), 7.36 – 7.30 (m, 2H, H-3', H-5'), 5.93 (dd, J = 2.5, 1.5 Hz, 1H, H-7a), 5.54 (dt, J = 2.5, 1.5 Hz, 1H, H-7b), 4.18 (tt J = 12.0, 3.5 Hz, 1H, H-4), 4.11 (t, J = 1.5 Hz, 2H, H-5), 2.65 (s, 3H, H-7'), 2.41 – 2.34 (m, 4H, H-2), 2.12 – 2.02 (m, 2H, H-3), 2.00 – 1.87 (m, 2H, H-3); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 208.3 (C-1), 138.1 (C-1') 137.8 (C-2'), 133.3 (C-4'), 133.0 (C-3'), 130.4 (C-6'), 129.7 (C-6), 126.5 (C-5'), 119.4 (C-7), 55.9 (C-4), 51.8 (C-5), 40.1 (C-2), 30.2 (C-3), 20.8 (C-7'); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{16}H_{21}O_3N^{79}Br^{32}S)^+$ requires 386.0420, found 386.0421.

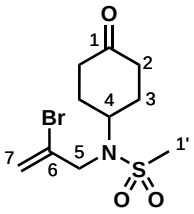
N-(2-bromoallyl)-4-methoxy-*N*-(4-oxocyclohexyl)benzenesulfonamide (185)



Prepared according to General Procedure A using amine **164** (348 mg, 1.50 mmol) in CH_2Cl_2 (7.5 mL), Et_3N (0.37 mL, 2.7 mmol), DMAP (36 mg, 0.29 mmol), and a solution of 4-methoxybenzenesulfonyl chloride (541 mg, 2.62 mmol) in CH_2Cl_2 (1 mL). Purification by flash column chromatography (2:3 EtOAc/pentane) afforded **185** (211 mg, 0.524 mmol, 35%) as a white solid.

MP: 106–108 °C; **IR** (thin film) $\tilde{\nu}_{max}{}^{-1}$ 2945 (C−H), 1709 (C=O), 1595 (C=C), 1497, 1341 (SO_2), 1304, 1259, 1151 (SO_2), 1094, 1032; ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 7.79 (d, J = 9.0 Hz, 2H, H-2'), 6.98 (d, J = 9.0 Hz, 2H, H-3'), 5.99 (s, 1H, H-7a), 5.63 (s, 1H, H-7b), 4.18 (tt, J = 11.5, 4.0 Hz, 1H, H-4), 4.00 (s, 2H, H-5), 3.88 (s, 3H, H-5'), 2.45 – 2.30 (m, 4H, H-2), 1.97 – 1.75 (m, 4H, H-3); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 208.5 (C-1), 163.2 (C-4'), 132.2 (C-1'), 130.0 (C-6), 129.4 (C-2'), 118.8 (C-7), 114.6 (C-3'), 56.2 (C-4), 55.8 (C-5'), 51.4 (C-5), 40.1 (C-2), 30.0 (C-3). **HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{16}H_{21}O_4N^{79}Br^{32}S)^+$ requires 402.0370, found 402.0370.

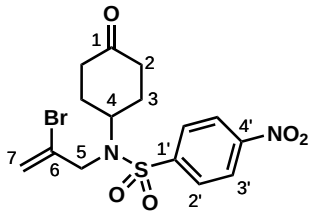
N-(2-bromoallyl)-*N*-(4-oxocyclohexyl)methanesulfonamide (186)



Prepared according to General Procedure A using amine **164** (348 mg, 1.50 mmol) in CH_2Cl_2 (7.5 mL), Et_3N (0.37 mL, 2.7 mmol), DMAP (36 mg, 0.29 mmol), and methanesulfonyl chloride (0.21 mL, 2.71 mmol). Purification by flash column chromatography (1:3 EtOAc/pentane then EtOAc) afforded **186** (171 mg, 0.551 mmol, 37% yield) as an orange solid.

MP: 68–70 °C; **IR** (thin film) $\tilde{\nu}_{max}^{-1}$ 2981 (C−H), 1710 (C=O), 1328 (SO_2), 1142 (SO_2), 1105, 1037; ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 6.01 (dt, J = 2.0, 1.5 Hz, 1H, H-7a), 5.70 (dt, J = 2.0, 1.5 Hz, 1H, H-7b), 4.20 (tt, J = 12.0, 4.0 Hz, 1H, H-4), 4.07 (t, J = 1.5 Hz, 2H, H-5), 3.01 (s, 3H, H-1'), 2.51 – 2.43 (m, 4H, H-2), 2.26 – 2.17 (m, 2H, H-3a), 2.12 – 1.97 (m, 2H, H-3b); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 208.3 (C-1), 129.7 (C-6), 120.3 (C-7), 56.6 (C-4), 52.1 (C-5), 42.0 (C-1'), 40.1 (C-2), 30.6 (C-3).

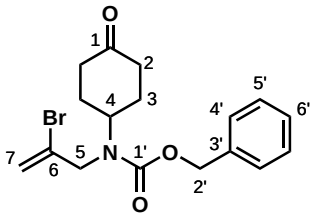
N-(2-bromoallyl)-4-nitro-*N*-(4-oxocyclohexyl)benzenesulfonamide (187)



Prepared according to General Procedure A using amine **164** (348 mg, 1.50 mmol) in CH_2Cl_2 (7.5 mL), Et_3N (0.37 mL, 2.7 mmol), DMAP (36 mg, 0.29 mmol), and a solution of 4-nitrobenzenesulfonyl chloride (582 mg, 2.63 mmol) in CH_2Cl_2 (1 mL). Purification by flash column chromatography (1:3 EtOAc/pentane then EtOAc) afforded **187** (233 mg, 0.558 mmol, 37% yield) as a yellow solid.

MP: 144–146 °C; **IR** (thin film) $\tilde{\nu}_{max}^{-1}$ 3098 (C−H), 2965 (C−H), 2874 (C−H), 1708 (C=O), 1523 (NO_2), 1348 (SO_2), 1166 (SO_2), 1088, 1044; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H 8.41 – 8.36 (m, 2H, H-3'), 8.09 – 8.04 (m, 2H, H-2'), 5.97 (dt, J = 2.5, 1.5 Hz, 1H, H-7a), 5.66 (dt, J = 2.5, 1.5 Hz, 1H, H-7b), 4.25 (tt, J = 11.5, 4.5 Hz, 1H, H-4), 4.11 (t, J = 1.5 Hz, 2H, H-5), 2.46 – 2.39 (m, 4H, H-2), 2.06 – 1.88 (m, 4H, H-3); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ_C 207.6 (C-1), 150.3 (C-4'), 146.5 (C-1'), 129.0 (C-6), 128.6 (C-2'), 124.7 (C-3'), 120.4 (C-7), 57.0 (C-4), 52.1 (C-5), 40.0 (C-2), 30.3 (C-3).

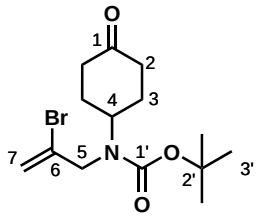
benzyl (2-bromoallyl)(4-oxocyclohexyl)carbamate (188)



To a solution of amine **164** (348 mg, 1.5 mmol) in acetonitrile (15 mL) was added a saturated aqueous solution of K_2CO_3 (15 mL) followed by benzyl chloroformate (0.43 mL, 3.0 mmol) dropwise. The resulting solution was stirred at RT overnight and, upon completion, diluted with EtOAc. The aqueous phase was extracted with EtOAc (3 × 15 mL) then the combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. Purification by flash column chromatography (3:7 EtOAc/pentane) afforded **188** (499 mg, 1.36 mmol, 91% yield) as a pale yellow oil.

IR (thin film) $\tilde{\nu}_{max}{}^{-1}$ 2955 (C−H), 1695, 1410, 1220, 1125; ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 7.42 – 7.29 (m, 5H, Ar), 5.70 (br.s, 1H, H-7a), 5.56 (br.s, 1H, H-7b), 5.17 (br.s, 2H, H-2'), 4.43 (br.s, 1H, H-4), 4.06 (br.s, 2H, H-5), 2.54 – 2.36 (m, 4H, H-2), 2.16 – 2.07 (m, 2H, H-3a), 2.03 – 1.88 (m, 2H, H-3b); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 209.2 (C-1), 155.7 (C-1'), 136.4 (C-3'), 130.2 (C-6'), 128.6 (C-5'), 128.3 (C-6), 128.1 (C-4'), 116.7 (C-7), 67.7 (C-2'), 54.6 (C-4), 51.5 (C-5), 40.0 (C-2), 29.8 (C-3); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{17}H_{21}O_3N^{79}Br)^+$ requires 366.0699, found 366.0701

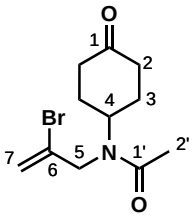
***tert*-butyl (2-bromoallyl)(4-oxocyclohexyl)carbamate (189)**



To a solution of amine **164** (348 mg, 1.50 mmol) in dry THF (1.5 mL) at 0 °C was added di-*tert*-butyldicarbonate (348 mg, 1.62 mmol) portionwise. The mixture was allowed to warm to RT overnight, and upon completion was quenched with H_2O and diluted with CH_2Cl_2. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. Purification by flash column chromatography (1:3 EtOAc/pentane) afforded **189** (397 mg, 1.19 mmol, 79% yield) as a white solid.

MP: 76–78 °C **IR** (thin film) $\tilde{\nu}_{max}{}^{-1}$ 2975 (C−H), 2938 (C−H), 1716 (C=O), 1680 (C=O), 1365, 1236; ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 5.72 (br s, 1H, H-7a), 5.56 (q, J = 1.5 Hz, 1H, H-7b), 4.46 (br s, 1H, H-4), 3.96 (br s, 2H, H-5), 2.52 – 2.38 (m, 4H, H-2), 2.15 – 2.05 (m, 2H, H-3a), 2.01 – 1.79 (m, 2H, H-3b), 1.47 (s, 9H, H-3'); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 209.5 (C-1), 155.0 (C-1'), 131.0 (C-6), 115.7 (C-7), 80.9 (C-2'), 53.4 (C-4), 51.5 (C-5), 40.0 (C-2), 29.7 (C-3), 28.3 (C-3'); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ $(C_{14}H_{22}O_3N^{79}Br^{23}Na)^+$ requires 354.0675, found 354.0676.

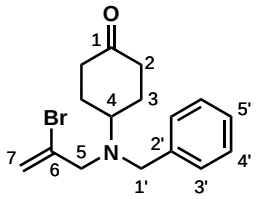
N-(2-bromoallyl)-*N*-(4-oxocyclohexyl)acetamide (190)



To a solution of amine **164** (348 mg, 1.5 mmol) in CH_2Cl_2 (7.5 mL) at 0 °C was added Et_3N (0.26 mL, 1.88 mmol) dropwise, followed by acetyl chloride (0.14 mL, 1.88 mmol). The resulting mixture was stirred at 0 °C for 2 h until complete, then was acidified with aqueous 1 M HCl. The layers were separated then the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, then filtered and concentrated. Purification by flash column chromatography (1:2 EtOAc/pentane) afforded **190** (336 mg, 1.23 mmol, 82% yield) as a pale orange solid.

MP: 72–74 °C; **IR** (thin film) $\tilde{\nu}_{max}^{-1}$ 2967 (C−H), 2873 (C−H), 1740 (C=O), 1631 (C=C), 1412, 1225, 1059; ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 5.82 (dt, J = 2.5, 2.0 Hz, 1H, H-7a), 5.69 (dt, J = 2.5, 2.0 Hz, 1H, H-7b), 4.87 (tt, 12.0, 4.0 Hz, 1H, H-4), 4.03 (t, 2.0 Hz, 2H, H-5), 2.56 – 2.38 (m, 4H, H-2), 2.14 (s, 3H, H-2'), 2.10 – 2.01 (m, 2H, H-3a), 1.91 – 1.78 (m, 2H, H-3b); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 209.4 (C-1), 171.5 (C-1'), 129.8 (C-6), 117.3 (C-7), 52.5 (C-5), 51.8 (C-4), 40.0 (C-2), 29.4 (C-3), 22.2 (C-2'); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{11}H_{17}O_2N^{79}Br)^+$ requires 274.0437, found 274.0439.

4-benzyl(2-bromoallyl)amino)cyclohexan-1-one (191)

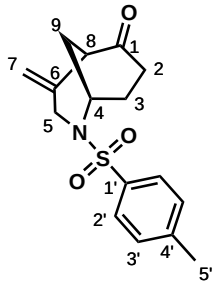


Compound **191** was prepared and provided by Nikita Chekshin.[75]

MP: 40–42 °C; **IR** (thin film) $\tilde{\nu}_{max}$$^{-1}$ 2933 (C-H), 2797 (C-H), 1715 (C=O), 1626 (C=C), 1493, 1447, 1325, 1262; ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 7.43–7.37 (m, 2H, H-3'), 7.36–7.30 (m, 2H, H-4'), 7.29–7.23 (m, 1H, H-5'), 5.96 (q, J = 1.5 Hz, 1H, H-7a), 5.57 (q, J = 1.5 Hz, 1H, H-7b), 3.71 (s, 2H, H-1'), 3.34 (t, J = 1.0 Hz, 2H, H-5), 3.06 (tt, J = 11.5, 3.5 Hz, 1H, H-4), 2.46–2.38 (m, 2H, H-2a), 2.36–2.25 (m, 2H, H-2b), 2.19–2.10 (m, 2H, H-3a), 1.82–1.69 (m, 2H, H-3b); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 210.9 (C-1), 139.7 (C-2'), 133.2 (C-6), 128.5 (C-3', C-4'), 127.2 (C-5'), 118.0 (C-7), 58.4 (C-5), 56.2 (C-4), 54.2 (C-1'), 40.2 (C-2), 27.7 (C-3) **HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{16}H_{21}ON^{79}Br)^+$ requires 322.0801, found 322.0802.

6.2.9 Cyclised Products: Variation at Nitrogen

(1*S*,5*R*)-2-(4-methylbenzene-1-sulfonyl)-4-methylidene-2-azabicyclo[3.3.1] nonan-6-one (+)-166

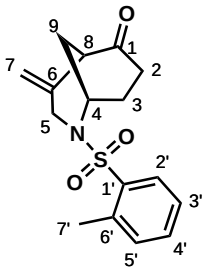


Prepared according to General Procedure B using **165** (40.2 mg, 0.10 mmol). Purification by flash column chromatography (40% EtOAc/pentane) afforded (+)-**166** (29 mg, 0.095 mmol, 95% yield, 95% ee) as a white solid. The enantiomeric form (–)-**166** was prepared in the same manner, using (2*R*,4*R*)-4-hydroxyproline to afford (–)-**166** (29 mg, 0.095 mmol, 95% yield, 95% ee) as a white solid. Data is in agreement with literature values.[56]

MP: 92–94 °C (>99% ee (+)-**166**), 140–142 °C (racemic, lit. 136–138 °C)[56]; **IR** (thin film) $\tilde{\nu}_{\text{max}}{}^{-1}$ 2925 (C–H), 1714 (C=O), 1344 (SO_2), 1161 (SO_2), 1096 (C–N); ^{1}**H-NMR** (500 MHz, $CDCl_3$): δ_H 7.75 (d, J = 8.0 Hz, 2H, H-2'), 7.36 (d, J = 8.0 Hz, 2H, H-3'), 5.13 (t, J = 1.5 Hz, 1H, H-7a), 5.04 (t, J = 1.5 Hz, 1H, H-7b), 4.19 (d, J = 14.0 Hz, 1H, H-5a), 4.12 (p, J = 3.0 Hz, 1H, H-4), 3.77 (dq, J = 14.0, 1.5 Hz, 1H, H-5b), 3.25 (br.s, 1H, H-8), 2.83 (ddd, J = 15.5, 13.0, 7.5 Hz, 1H, H-2a), 2.46 (s, 3H, H-5'), 2.43–2.34 (m, 1H, H-3a), 2.34–2.25 (m, 1H, H-2b), 1.99 (dq, J = 14.0, 3.0 Hz, 1H, H-9a), 1.94–1.82 (m, 2H, H-9b, H-3b); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 208.3 (C-1), 143.9 (C-6), 138.2 (C-1'), 134.8 (C-4'), 130.0 (C-3'), 127.4 (C-2'), 115.2 (C-7), 50.2 (C-8), 48.0 (C-4), 47.2 (C-5), 34.8 (C-2), 32.5 (C-3), 30.5 (C-9),

21.7 (C-5'); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{16}H_{20}O_3N^{32}S)^+$ requires 306.1158, found 306.1159; $[\alpha]_D^{25}$ = +94.6 (c 1.0, $CHCl_3$, >99% ee); **HPLC**: (Chiralpak AD-H, hexane/isopropanol 90:10, 1.0 mL min^{-1}, λ=240 nm) t_R = 24.5 min (major), 29.3 min (minor).

(1*S*,5*R*)-4-methylene-2-(*o*-tolylsulfonyl)-2-azabicyclo[3.3.1]nonan--6-one (+)-192



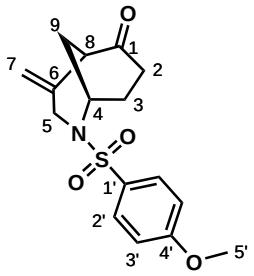
Prepared according to General Procedure B using **184** (38.6 mg, 0.1 mmol). Purification by flash column chromatography (3:7 EtOAc/pentane) afforded (+)-**192** (28.0 mg, 75% yield, 89% ee) as a white solid. The spectroscopic data match those reported in the literature.[56]

^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 7.99 – 7.95 (m, 1H, H-2'), 7.48 (td, J = 7.5, 1.5 Hz, 1H, H-4'), 7.34 (app.t, J = 7.5 Hz, 2H, H-3', H-5'), 5.03 (s, 1H, H-7a), 5.02 (s, 1H, H-7b), 4.22 (p, J = 3.5 Hz, 1H, H-4), 4.14 (dt, J = 14.5, 1.5 Hz, 1H, H-5a), 3.96 (dt, J = 14.5, 1.2 Hz, 1H, H-5b), 3.31 (d, J = 3.0 Hz, 1H, H-8), 2.72 (ddd, J = 17.0, 12.5, 8.0 Hz, 1H, H-2a), 2.63 (s, 3H, H-7'), 2.45 – 2.30 (m, 2H, H-2b, H-3a), 2.17 (dq, J = 13.5, 3.5 Hz, 1H, H-9a), 2.07 – 2.01 (m, 1H, H-9b), 1.94 (dddd, J = 14.5, 12.0, 7.0, 3.5 Hz, 1H, H-3b); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 208.1 (C-1), 137.9 (C), 137.8 (C), 136.9 (C), 133.2 (C-4'), 133.0 (C-5'), 130.2 (C-2'), 126.4 (C-3'), 115.1 (C-7), 51.8 (C-8), 46.9 (C-4,5), 36.1 (C-2), 32.1 (C-9), 31.5 (C-3), 20.5 (C-7'); $[\alpha]_D^{25}$ = +38.3 (c 1.0, $CHCl_3$, 89% ee); **HPLC**: (Chiralpak AD-H, hexane/isopropanol

90:10, 1.0 mL min^{-1}, λ= 220 nm) t_R = 16.3 (major), 18.4 (minor).

(1*S*,5*R*)-2-((4-methoxyphenyl)sulfonyl)-4-methylene-2-

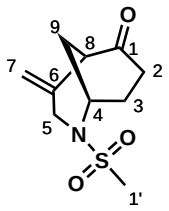
-azabicyclo[3.3.1]nonan-6-one (+)-193



Prepared according to General Procedure B using **185** (40.2 mg, 0.10 mmol). Purification by flash column chromatography (3:7 EtOAc/pentane) afforded (+)-**193** (20.0 mg, 62% yield, 92% ee) as a white solid. The spectroscopic data match those reported in the literature.[56]

IR (thin film) $\tilde{\nu}_{max}$$^{-1}$ 1709 (C=O), 1264, 1155, 1095, 926; ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 7.81 – 7.75 (m, 2H, H-2'), 7.03 – 6.97 (m, 2H, H-3'), 5.10 (d, J = 1.5 Hz, 1H, H-7a), 5.02 (dt, J = 1.5, 1.0 Hz, 1H, H-7b), 4.15 (d, J = 14.5 Hz, 1H, H-5a), 4.09 (t, J = 3.5 Hz, 1H, H-4), 3.88 (s, 3H, H-5'), 3.79 – 3.72 (m, 1H, H-5b), 3.23 (s, 1H, H-8), 2.80 (ddd, J = 16.0, 13.0, 7.5 Hz, 1H, H-2a), 2.42 – 2.32 (m, 1H, H-3a), 2.31 – 2.23 (m, 1H, H-2b), 1.98 (dq, J = 14.0, 3.5 Hz, 1H, H-9a), 1.92 – 1.84 (m, 2H, H-3b, H-9b); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 208.4 (C-1), 163.2 (C-4'), 138.3 (C-6), 129.6 (C-2'), 129.6 (C-1'), 115.2 (C-7), 114.6 (C-3'), 55.8 (C-5'), 50.3 (C-8), 47.9 (C-4), 47.3 (C-5), 34.9 (C-2), 32.5 (C-3), 30.6 (C-9); $[\boldsymbol{\alpha}]_D^{25}$ = +108.4 (c 1.0, $CHCl_3$, 92% ee); **HPLC**: (Chiralpak AD-H, hexane/isopropanol 90:10, 1.0 mL min^{-1}, λ= 240 nm) t_R = 36.3 (major), 38.4 (minor).

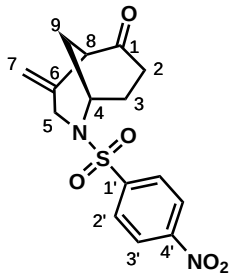
(1*S*,5*R*)-4-methylene-2-(methylsulfonyl)-2-azabicyclo[3.3.1]nonan--6-one (+)-194



Prepared according to General Procedure B using **186** (30.1 mg, 0.1 mmol). Purification by flash column chromatography (1:1 EtOAc/pentane) afforded (+)-**194** (13.3 mg, 58% yield, 92% ee) as an orange oil. The spectroscopic data match those reported in the literature.[56]

^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 5.14 (d, J = 1.5 Hz, 1H, H-7a), 5.09 (q, J = 1.5 Hz, 1H, H-7b), 4.21 – 4.12 (m, 2H, H-5a, H-4), 4.03 – 3.96 (m, 1H, H-5b), 3.36 (s, 1H, H-8), 2.90 (s, 3H, H-1'), 2.82 (ddd, J = 16.0, 13.5, 7.5 Hz, 1H, H-2a), 2.43 – 2.26 (m, 3H, H-2b, H-3a, H-9a), 2.07 (dt, J = 13.5, 3.0 Hz, 1H, H-9b), 1.94 (dddd, J = 14.5, 13.0, 6.5, 3.0 Hz, 1H, H-3b); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 207.9 (C-1), 138.0 (C-6), 115.4 (C-7), 50.6 (C-8), 48.0 (C-4), 47.1 (C-5), 36.7 (C-1'), 35.0 (C-2), 32.4 (C-3), 31.2 (C-9); $[\boldsymbol{\alpha}]_D^{25}$ = +108.3 (c 1.0, $CHCl_3$, 92% ee); **HPLC**: (Chiralpak AD-H, hexane/isopropanol 90:10, 1.0 mL min^{-1}, λ= 210 nm) t_R = 18.8 (minor), 21.2 (major).

(1*S*,5*R*)-4-methylene-2-((4-nitrophenyl)sulfonyl)-2-azabicyclo[3.3.1]--nonan-6-one (195)

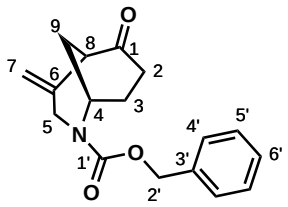


Prepared according to General Procedure B using **187** (41.7 mg, 0.10 mmol). Purification by flash column chromatography (3:7 EtOAc/pentane) afforded **195** (15.1 mg, 45% yield, 50% ee) as a white solid. The spectroscopic data match those reported in the literature.[56]

MP: 208–210 °C (>99% ee), 176–178 °C (rac); **IR** (thin film) $\tilde{\nu}_{\max}{}^{-1}$ 2932 (C−H), 1715 (C=O), 1529 (NO_2), 1351 (NO_2), 1164 (SO_2), 1095; ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 8.39 – 8.44 (m, 2H, H-3'), 8.01 – 8.08 (m, 2H, H-2'), 5.15 (d, J = 1.5 Hz, 1H, H-7a), 5.07 (d, J = 1.5 Hz, 1H, H-7b), 4.24 (d, J = 14.0 Hz, 1H, H-5a), 4.13 (t, J = 3.5 Hz, 1H, H-4), 3.80 – 3.88 (m, 1H, H-5b), 3.27 (br.s, 1H, H-8), 2.78 (ddd, J = 16.0, 13.0, 8.0 Hz, 1H, H-3a), 2.28 – 2.48 (m, 2H, H-2a,H-3b), 1.87 – 1.99 (m, 3H, H-2b, H-9); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 207.5 (C-1), 150.4 (C-6), 143.9 (C-1'), 137.2 (C-4'), 128.6 (C-2'), 124.7 (C-3'), 116.0 (C-7), 50.2 (C-4), 48.5 (C-8), 47.4 (C-5), 34.8 (C-3), 32.4 (C-2), 30.8 (C-9); **HRMS** (ES-) exact mass calculated for $[M-H]^-$ ($C_{15}H_{15}N_2O_5\,{}^{32}S^-$) requires 335.0707, found 335.0712; **HPLC**: (Chiralpak IA, hexane/isopropanol 70:30, 1.0 mL min^{-1}, λ=240 nm) t_R = 15.7 min (major), 18.7 min (minor).

(1*S*,5*R*)-phenyl 4-methylene-6-oxo-2-azabicyclo[3.3.1]nonane-

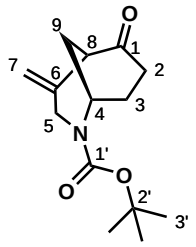
-2-carboxylate (+)-196



Prepared according to General Procedure B using **188** (36.6 mg, 0.1 mmol). Purification by flash column chromatography (3:7 EtOAc/pentane) afforded **196** (28.4 mg, 99% yield, 90% ee) as a yellow oil. The spectroscopic data match those reported in the literature.[56]

^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H (exhibits rotameric behaviour, data reported as observed at RT) 7.43 – 7.28 (m, 5H, H-Ar), 5.27 – 4.99 (m, 4H, H-7, H-2'), 4.49 – 4.29 (m, 2H, H-4, H-5a), 4.14 (ddt, J = 15.5, 12.0, 2.0 Hz, 1H, H-5b), 3.35 (br.s, 1H, H-8), 2.65 (dddd, J = 15.5, 13.0, 10.5, 7.5 Hz, 1H, H-2a), 2.48 – 2.19 (m, 3H, H-2b, H-3a, H-9a), 2.03 (ddt, J = 19.5, 13.5, 3.0 Hz, 1H, H-9b), 1.81 (tddd, J = 13.5, 10.5, 5.5, 3.0 Hz, 1H, H-3b); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 208.8 (C-1), 208.6 (C-1), 155.8 (C-1'), 155.5 (C-1'), 139.3 (C-6), 139.2 (C-6), 132.7 (C-3'), 132.6 (C-3'), 128.7 (C-Ar), 128.3 (C-Ar), 128.2 (C-Ar), 128.1 (C-Ar), 114.4 (C-7), 114.2 (C-7), 67.5 (C-2'), 67.4 (C-2'), 51.2 (C-8), 50.9 (C-8), 46.4 (C-4), 46.3 (C-4), 46.1 (C-5), 46.0 (C-5), 35.2 (C-2), 34.9 (C-2), 31.5 (C-3/9), 31.2 (C-3/9), 31.0 (C-3/9), 30.5 (C-3/9); $[\alpha]_D^{25}$ = +138.7 (c 1.0, $CHCl_3$, 90% ee); **HPLC**: (Chiralpak AD-H, hexane/isopropanol 90:10, 1.0 mL min^{-1}, λ= 210 nm) t_R = 11.6 (major), 12.5 (minor).

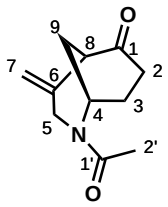
(1*S*,5*R*)-*tert*-butyl 4-methylene-6-oxo-2-azabicyclo[3.3.1]nonane--2-carboxylate (+)-197



Prepared according to General Procedure B using **189** (33.2 mg, 0.1 mmol). Purification by flash column chromatography (1:3 EtOAc/pentane) afforded **197** (22.1 mg, 88% yield, 93% ee) as a white solid. The spectroscopic data match those reported in the literature.[56]

MP: 68–72 °C; **IR** (thin film) $\tilde{\nu}_{max}$$^{-1}$ 2974 (C–H), 1717 (C=O), 1686 (C=O), 1390, 1164, 1051; ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H (exhibits rotameric behaviour, data reported as observed at RT) 4.90 – 5.11 (m, 2H, H-7), 4.12 – 4.40 (m, 2H, H-5a, H-4), 3.84 – 4.09 (m, 1H, H-5b), 3.29 (s, 1H, H-8), 2.62 (dddd, J = 18.5, 15.5, 13.5, 7.5, 1H, H-2a), 2.15 – 2.40 (m, 3H, H-2b, H-9), 1.97 (tt, J = 13.5, 3.0 Hz, 1H, H-3a), 1.75 (tdt, J = 13.5, 6.0, 3.0 Hz, 1H, H-3b), 1.45 (s, 9H, H-3'); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C (rotameric); 209.1 (C-1), 208.9 (C-1), 155.1 (C-1'), 154.9 (C-1'), 139.7 (C-6), 139.6 (C-6), 114.1 (C-7), 113.8 (C-7), 80.2 (C-2'), 51.3 (C-8), 50.8 (C-8), 46.3 (C-5), 46.3 (C-4), 45.5 (C-4), 45.3 (C-5), 35.3 (C-2), 34.9 (C-2), 31.4 (C-3), 31.1 (C-9), 30.6 (C-3), 28.5 (C-3'); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ $(C_{14}H_{21}O_3N^{23}Na)^+$ requires 274.1414, found 274.1415; $[\boldsymbol{\alpha}]_D^{25}$ = +128.8 (c 1.0, $CHCl_3$, 93% ee); **HPLC**: (Chiralpak AD-H, hexane/isopropanol 98:2, 1.0 mL min^{-1}, λ= 220 nm) t_R = 10.9 (major), 14.2 (minor).

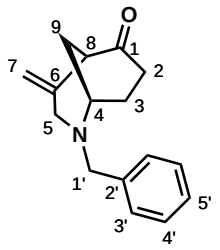
(1*S*,5*R*)-2-acetyl-4-methylene-2-azabicyclo[3.3.1]nonan-6-one (+)-198



Prepared according to General Procedure B using **190** (27.4 mg, 0.1 mmol). Purification by flash column chromatography (EtOAc) afforded **198** (18.9 mg, 98% yield, 91% ee) as a yellow oil. The spectroscopic data match those reported in the literature.[56] The product is observed as a rotameric mixture (approximately 3:2 ratio), and those peaks are referred to as maj and min respectively.

IR (thin film) $\tilde{\nu}_{max}^{-1}$ 1707, 1607, 1413, 1171; ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 5.04 (s, 2H, H-7_{maj}, H-7_{min}), 5.00 (s, 1H, H-7_{maj}), 4.96 (s, 1H, H-7_{min}), 4.57 (s, 1H, H-4_{maj}), 4.35 (d, J = 17.5 Hz, 1H, H-5_{min}), 4.30 (d, J = 17.7 Hz, 1H, H-5_{min}), 4.16 (s, 2H, H-5_{maj}), 4.13 (br.s, 1H, H-4_{min}), 3.31 (s, 2H, H-2_{maj}, H-8_{min}), 2.66 – 2.45 (m, 2H, H-2_{maj}, H-2_{min}), 2.42 – 2.29 (m, 2H), 2.28 – 2.16 (m, 3H), 2.13 (s, 3H, H-2'$_{min}$), 2.10 (s, 3H, H-2'$_{maj}$), 2.10 – 2.04 (m, 2H), 2.04 – 1.92 (m, 2H), 1.82 – 1.68 (m, 2H); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 208.8 (C-1_{maj}), 207.8 (C-1_{min}), 170.4 (C-1'$_{maj}$), 170.3 (C-1'$_{min}$), 139.3 (C-6_{maj}), 138.1(C-6_{min}), 114.8 (C-7_{maj}), 114.6 (C-7_{min}), 51.7 (C-8_{min}), 50.9 (C-8_{maj}), 48.4 (C-5_{maj}), 47.5 (C-4_{min}), 45.0 (C-5_{min}, C-4_{maj}), 35.5 (C-2_{min}), 35.1 (C-2_{maj}), 32.3 (C-3/9_{min}), 32.0 (C-3/9_{min}), 30.7 (C-3/9_{maj}), 30.0 (C-3/9_{maj}), 22.7 (C-2'$_{maj}$), 21.6 (C-2'$_{min}$); $[\boldsymbol{\alpha}]_D^{25}$ = +264.0 (c 1.0, $CHCl_3$, 74% ee); **HPLC**: (Chiralpak AS-H, hexane/isopropanol 70:30, 1.0 mL min^{-1}, λ= 210 nm) t_R = 27.2 (minor), 44.7 (major).

(1*S*,5*R*)-2-benzyl-4-methylene-2-azabicyclo[3.3.1]nonan-6-one (–)-199

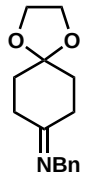


Prepared according to General Procedure B using **191** (32.2 mg, 0.10 mmol). Purification by flash column chromatography (1:3 EtOAc/pentane) afforded **199** (18.3 mg, 76% yield, 98% ee) as a white solid.

MP: 48–50 °C; **IR** (thin film) $\tilde{\nu}_{max}$$^{-1}$ 2926 (C-H), 1719 (C=O), 1669, 1323, 1176, 1132, 703; ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 7.38 – 7.30 (m, 4H, H-3', H-4'), 7.29 – 7.23 (m, 1H, H-5'), 4.95 – 4.91 (m, 1H, H-7a), 4.88 – 4.83 (m, 1H, H-7b), 3.82 – 3.69 (m, 2H, H-1'), 3.36 (s, 2H, H-5), 3.26 (s, 1H, H-8), 3.10 (s, 1H, H-4), 2.67 – 2.55 (m, 1H, H-2a), 2.52 – 2.42 (m, 1H, H-2b), 2.36 – 2.22 (m, 2H, H-3a, H-9a), 1.99 (dt, J = 13.0, 3.0 Hz, 1H, H-3b), 1.81 – 1.68 (m, 1H, H-9b); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 210.7 (C-1), 141.0 (C-6), 138.9 (C-2'), 128.8 (C-Ar), 128.5 (C-Ar), 127.3 (C-5'), 112.6 (C-7), 60.0 (C-1'), 53.9 (C-5), 53.7 (C-8), 50.2 (C-4), 38.1 (C-2), 32.9 (C-3), 25.7 (C-9); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{16}H_{20}ON)^+$ requires 242.1539, found 242.1541; $[\boldsymbol{\alpha}]_D^{25}$ = -16.3 (c 0.37, $CHCl_3$, 98% ee); **HPLC**: (Chiralpak AD-H, hexane/isopropanol 98:02, λ= 210 nm) t_R = 9.0 (major), 10.8 (minor).

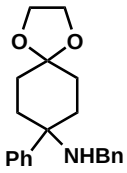
6.2.10 Synthesis of Substrates: Fully-Substituted Carbon

N-benzyl-1,4-dioxaspiro[4.5]decan-8-imine (200)



Prepared according to a literature procedure.[179] To a solution of 1,4-cyclohexanedione monoethylene acetal **161** (3.12 g, 20.0 mmol) in CH_2Cl_2 (62.5 mL) was added benzylamine (2.62 mL, 24.0 mmol) and 4 Å molecular sieves (10 g). The mixture was stirred at RT overnight until complete, then filtered through Celite® and concentrated under vacuum. The crude imine **200** was sufficiently pure to be used without further purification. The spectroscopic data match those reported in the literature.[179]

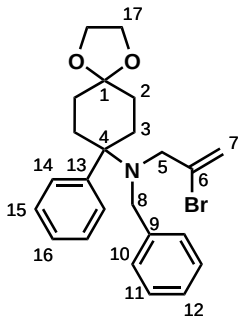
N-benzyl-8-phenyl-1,4-dioxaspiro[4.5]decan-8-amine (201)



Prepared according to a literature procedure.[56] Boron trifluoride diethyl ether complex (2.48 mL, 20.0 mmol) was added dropwise to a solution of imine **200** (2.45 g, 10.0 mmol), in dry THF (100 mL) at –78 °C, then the mixture was stirred at that temperature for 45 mins. A solution of phenyl lithium (10.5 mL, 1.9 M in Bu_2O, 20.0 mmol) was added dropwise to the imine solution, then the reaction mixture was stirred at –78 °C for a further 45 mins. The reaction was then warmed to RT

and stirred for a further 2 – 3 h until complete. The reaction was quenched with a 20% aqueous NaOH solution and diluted with Et_2O, then the phases were separated and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Purification by flash column chromatography (1:19 EtOAc/pentane then 3:17) afforded amine **201** (2.16 g, 13.4 mmol, 67% yield) as a white solid. The spectroscopic data match those reported in the literature.[56]

N-Benzyl-*N*-(2-bromoallyl)-8-phenyl-1,4-dioxaspiro[4.5]decan--8-amine (403)

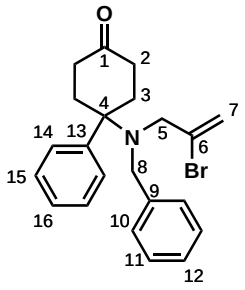


Prepared according to a literature procedure.[56] To a stirring solution of amine **201** (383 mg, 1.18 mmol) in MeCN (5.9 mL) was added K_2CO_3 (651 mg, 4.72 mmol) and dropwise 2,3-dibromopropene, 80% (0.58 mL, 80%, 4.72 mmol). The mixture was heated to reflux and stirred overnight, before allowing to cool to RT and filtering through Celite®, washing with EtOAc. The filtrate was concentrated under vacuum and the crude residue was purified by flash column chromatography (1:9 EtOAc/pentane) to afford **403** (297 mg, 57%) as an amorphous solid.

IR (thin film) $\tilde{\nu}_{max}^{-1}$ 2957 (C-H), 2880 (C-H), 1601, 1494, 1447, 1375, 1272, 1096, 1034; ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 7.52 – 7.45 (m, 2H, H-Ar), 7.44 – 7.36 (m, 2H, H-Ar), 7.36 – 7.14 (m, 6H, H-Ar), 5.78 – 5.75 (m, 1H, H-7a), 5.27 – 5.25 (m,

1H, H-7b), 4.00 – 3.85 (m, 4H, H-17), 3.55 (s, 2H, H-8), 3.29 (s, 2H, H-5), 2.39 – 2.31 (m, 2H, H-3a), 2.21 – 2.10 (m, 2H, H-3b), 1.81 – 1.73 (m, 2H, H-2a), 1.55 – 1.45 (m, 2H, H-2b); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ_C 141.2 (C-Ar), 134.6 (C-6), 128.9 (C-Ar), 128.3 (C-Ar), 128.1 (C-Ar), 127.8 (C-Ar), 127.0 (C-Ar), 126.7 (C-Ar), 126.0 (C-Ar), 117.3 (C-7), 108.7 (C-4), 105.7 (C-1), 64.4 (C-17), 58.9 (C-5), 54.8 (C-8), 31.9 (C-2), 31.4 (C-3); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{24}H_{29}O_2N^{79}Br)^+$ requires 442.1376, found 442.1369.

4-(benzyl(2-bromoallyl)amino)-4-phenylcyclohexan-1-one (203)

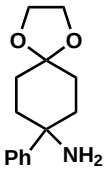


Prepared according to a literature procedure.[56] To a stirring solution of ketal **403** (170 mg, 0.38 mmol) in THF (1.9 mL) was added dropwise 3 M HCl (aq., 1.9 mL). The reaction mixture was stirred at RT until completion (48 h, followed by TLC), then basified with 3 M NaOH (aq.) to pH 12 and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL) to remove the ethylene glycol generated in the reaction, then dried with Na_2SO_4, filtered, and evaporated. The crude residue was purified by flash column chromatography (1:4 EtOAc/pentane) to afford the title compound (103 mg, 0.26 mmol, 68% yield) as an amorphous solid.

IR (thin film) $\tilde{\nu}_{max}^{-1}$ 2957 (C-H), 2361, 2341, 1716 (C=O), 1452, 1097; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H 7.58 – 7.53 (m, 2H, H-Ar), 7.50 – 7.44 (m, 2H, H-Ar), 7.39 – 7.34 (m, 1H, H-Ar), 7.31 – 7.16 (m, 5H, H-Ar), 5.73 (q, J = 1.0 Hz, 1H, H-7a),

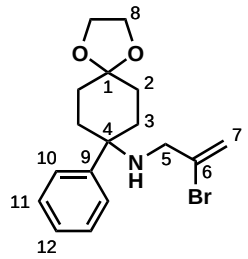
5.33 (q, J = 1.0 Hz, 1H, H-7b), 3.61 (s, 2H, H-8), 3.33 (s, 2H, H-5), 2.56 – 2.46 (m, 4H, H-2a, H-3a), 2.44 – 2.32 (m, 2H, H-3b), 2.26 – 2.16 (m, 2H, H-2b); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 211.2 (C-1), 140.9 (C-Ar), 140.0 (C-Ar), 134.0 (C-6), 128.8 (C-Ar × 2), 128.3 (C-Ar), 127.7 (C-Ar), 127.4 (C-Ar), 127.0 (C-Ar), 118.2 (C-7), 62.8 (C-4), 59.2 (C-5), 54.7 (C-8), 38.1 (C-2), 33.5 (C-3); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{22}H_{25}ON^{79}Br)^+$ requires 398.1114, found 398.1115.

8-phenyl-1,4-dioxaspiro[4.5]decan-8-amine (404)



Prepared according to a literature procedure.[56] To a solution of amine **201** (1.62 g, 5.0 mmol) in a mixture of MeOH (52 mL) and AcOH (2.52 mL) under N_2 was added palladium on carbon (248 mg, 0.5 mmol, 10 wt. % loading) portionwise. H_2 was bubbled through the solution for 2 mins, then the mixture was stirred under a H_2 atmosphere (balloon, two skins) for 24 h. Upon completion, the reaction mixture was filtered through Celite® and washed with EtOAc. The filtrate was then washed with aqueous 3 M NaOH, then the phases were separated and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to afford amine **404** (1.08 g, 4.63 mmol, 93% yield) as a pale yellow oil which was sufficiently pure to be used without further purification. The spectroscopic data match those reported in the literature.[56]

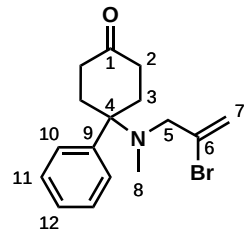
N-(2-bromoallyl)-8-phenyl-1,4-dioxaspiro[4.5]decan-8-amine (204)



To a solution of amine **404** (1.07 g, 4.60 mmol) in MeCN (23 mL) was added K_2CO_3 (1.27 g, 9.19 mmol) followed by 2,3-dibromopropene **202** (0.56 mL, 4.6 mmol, 80% technical grade) dropwise. The mixture was heated to reflux and stirred overnight. On completion the reaction was cooled to RT then filtered through Celite®, washing with EtOAc, then the filtrate was concentrated. Purification by flash column chromatography (1:9 to 1:4 EtOAc/pentane) afforded **204** (1.13 g, 70% yield) as a pale orange solid.

MP: 40–42 °C; **IR** (thin film) $\tilde{\nu}_{max}^{-1}$ 2934 (C−H), 1606 (C=C), 1510, 1335, 1249, 1154, 1091, 1032; ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 7.46 – 7.40 (m, 2H, H-11), 7.37 – 7.30 (m, 2H, H-10), 7.25 – 7.20 (m, 1H, H-12), 5.85 (q, J = 1.5 Hz, 1H, H-7a), 5.45 (d, J = 1.5 Hz, 1H, H-7b), 4.00 – 3.91 (m, 4H, H-8), 3.04 (s, 2H, H-5), 2.16 – 1.89 (m, 6H, H-2, H-3a), 1.68 – 1.60 (m, 2H, H-3b); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 145.9 (C-9), 133.5 (C-6), 128.4 (C-10), 126.7 (C-12), 126.0 (C-11), 116.6 (C-7), 108.7 (C-1), 64.3 (C-8), 56.7 (C-4), 51.3 (C-5), 33.7 (C-2), 30.9 (C-3).

4-((2-bromoallyl)(methyl)amino)-4-phenylcyclohexan-1-one (205)



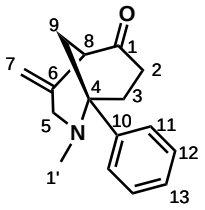
Prepared following a literature procedure.[180] To a solution of amine **204** (352 mg, 1.0 mmol) in MeOH (6.6 mL) was added formaldehyde (0.6 mL, 8 mmol, 37% aq. solution) dropwise, then AcOH (0.5 mL, 8 mmol) dropwise, and finally $NaBH_3CN$ (126 mg, 2 mmol) portionwise. The mixture was stirred at RT for 2 hours until complete, before quenching with saturated aqueous $NaHCO_3$ solution. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), then the combined organic layers were dried over Na_2SO_4, filtered and concentrated. Purification by flash column chromatography (1:9 EtOAc/pentane) afforded **405**, the ketal of **205** (220 mg, 60% yield) as a pale yellow oil. The ketal **405** was then dissolved in a 1:1 mixture of THF (3 mL) and aqueous 3 M HCl (3 mL) and stirred at RT until complete (48 h, monitored by TLC). The solution was then basified with aqueous 3 M NaOH to pH 12 and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (30 mL) then dried over Na_2SO_4 and concentrated under vacuum. Purification by flash column chromatography (1:9 EtOAc/pentane) afforded **205** (170 mg, 88% yield) as a white solid.

MP: 85 – 87 °C; **IR** (thin film) $\tilde{\nu}_{max}$$^{-1}$ 2959 (C−H), 2904 (C−H), 2879 (C−H), 2846 (C−H), 2816 (C−H), 2788 (C−H), 1713 (C=O); ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 7.43 – 7.35 (m, 4H, Ar-H), 7.34 (m, 1H, Ar-H), 5.81 (m, 1H, H-7a), 5.53 (m, 1H, H-7b), 3.12 (s, 2H, H-5), 2.85 (ddd, J = 16.0, 11.5, 5.5 Hz, 2H, H-2a), 2.77 – 2.68

(m, 2H, H-3a), 2.35 – 2.26 (m, 2H, H-2b), 2.18 – 2.08 (m, 2H, H-3b), 2.14 (s, 3H, H-8); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 211.7 (C-1), 139.3 (C-9), 133.4 (C-6), 128.4 (C-Ar), 127.4 (C-Ar), 126.6 (C-Ar), 118.0 (C-7), 59.6 (C-4), 59.4 (C-5), 37.3 (C-2), 34.3 (C-8), 33.5 (C-3).

6.2.11 Cyclised Products: Fully Substituted Carbon

(1*S*,5*R*)-2-methyl-4-methylene-1-phenyl-2-azabicyclo[3.3.1]nonan--6-one (+)-207

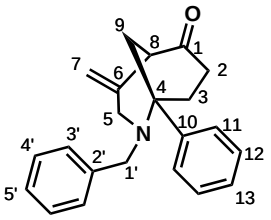


Prepared according to General Procedure B using **205** (32.2 mg, 0.1 mmol). Purification by flash column chromatography (1:4 EtOAc/pentane) afforded **207** (18.9 mg, 79% yield, 95% ee) as a pink oil.

IR (thin film) $\tilde{\nu}_{max}^{-1}$ 2938 (C−H), 2782 (C−H), 1708 (C=O), 1065, 1024; ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 7.52 – 7.47 (m, 2H, H-12), 7.36 – 7.30 (m, 2H, H-11), 7.27 – 7.21 (m, 1H, H-13), 4.99 (s, 1H, H-7a), 4.97 (s, 1H, H-7b), 3.76 – 3.63 (m, 2H, H-5), 3.31 (t, J = 3.0 Hz, 1H, H-8), 2.71 – 2.61 (m, 3H, H-2, H-3a), 2.42 – 2.30 (m, 2H, H-9a, H-3b), 2.16 – 2.13 (m, 1H, H-9b), 2.11 (s, 3H, H-1'); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 210.1 (C-1), 146.5 (C-10), 141.1 (C-6), 128.4 (C-11), 127.0 (C-13), 126.5 (C-12), 111.9 (C-7), 57.1 (C-5), 57.0 (C-4), 55.0 (C-8), 42.2 (C-9), 38.8 (C-1'), 38.4 (C-2), 29.0 (C-3); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{16}H_{20}ON)^+$ requires 242.1539, found 242.1540; $[\alpha]_D^{25}$ = +40.2 (c 1.0, $CHCl_3$, 95% ee); **HPLC**: (Chiralpak OJ, hexane/isopropanol 98:2, 1.0 mL min^{-1}, λ= 210 nm) t_R

= 17.7 (major), 21.9 (minor).

(1*S*,5*R*)-2-benzyl-4-methylene-1-phenyl-2-azabicyclo[3.3.1]nonan-6-one (+)-206

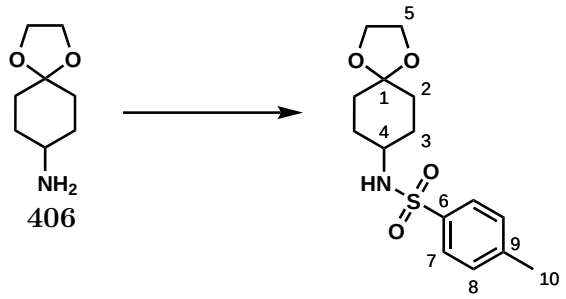


Prepared according to General Procedure B using **203** (39.8 mg, 0.1 mmol). Purification by flash column chromatography (1:9 EtOAc/pentane) afforded **206** (21.5 mg, 54%, 63% ee) as a white solid.

MP: 40–42 °C; **IR** (thin film) $\tilde{\nu}_{max}^{-1}$ 2938 (C-H), 2361, 2341, 1711, 1494, 1446, 1137, 910; ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 7.67 – 7.62 (m, 2H, H-Ar), 7.40 – 7.34 (m, 2H, H-Ar), 7.33 – 7.15 (m, 6H, H-Ar), 4.97 (s, 1H, H-7a), 4.83 (s, 1H, H-7b), 3.66 – 3.58 (m, 2H, H-1'), 3.61 (d, J = 13.5, 1H, H-5a), 3.36 – 3.32 (m, 1H, H-8), 2.76 – 2.62 (m, 3H, H-2, H-3a), 2.56 – 2.46 (m, 2H, H-9a, H-3b), 2.21 (dd, 1H, J = 13.5, 3.0 Hz, H-9b); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 210.0 (C-1), 146.7 (C-Ar), 140.9 (C-Ar), 139.5 (C-6), 128.52 (C-Ar), 128.43 (C-Ar), 128.37 (C-Ar), 126.6 (C-Ar), 112.3 (C-7), 57.7 (C-4), 55.7 (C-5), 54.8 (C-8), 53.1 (C-1'), 41.4 (C-9), 38.3 (C-2), 31.4 (C-3); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{22}H_{24}ON)^+$ requires 318.1852, found 318.1852; $[\boldsymbol{\alpha}]_D^{25}$ = +162.5 (c 0.04, $CHCl_3$, 63% ee); **HPLC**: (Chiralpak AD-H, hexane/isopropanol 98:2, 1.0 mL/min, λ= 210 nm) t_R = 9.8 (minor), 14.9 (major).

6.2.12 Synthesis of Trisusbtituted Alkene Substrates

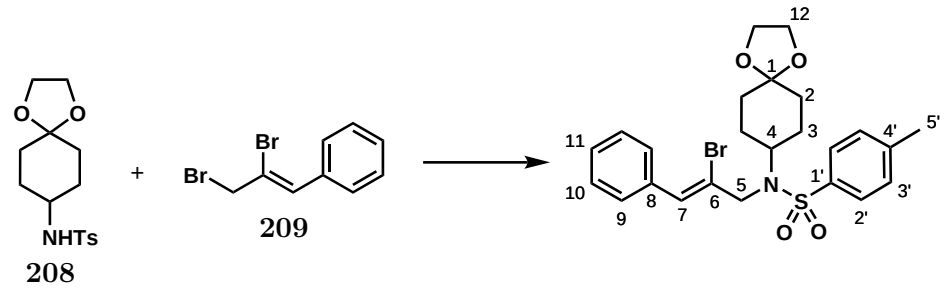
4-methyl-*N*-(1,4-dioxaspiro[4.5]decan-8-yl)benzenesulfonamide (208)



Prepared according to General Procedure A using 1,4-dioxaspiro[4.5]decan-8-amine (**406**, prepared according to literature procedures)[54,181] (5.5 g, 35 mmol), Et_3N (9.74 mL, 70 mmol), DMAP (488 mg, 4 mmol), and 4-toluenesulfonyl chloride (11.46 g, 60 mmol) in CH_2Cl_2 (175 mL) for 4 d. Purification by flash column chromatography (2:3 EtOAc/pentane then EtOAc) afforded **208** (9.89 g, 88% yield) as a pale yellow solid.

MP: 190–192 °C; ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 7.78 – 7.73 (m, 2H, H-7), 7.31 – 7.26 (m, 2H, H-8), 3.87 (s, 4H, H-5), 3.26 – 3.14 (m, 1H, H-4), 2.41 (s, 3H, H-10), 1.80 – 1.71 (m, 2H, H-3), 1.71 – 1.58 (m, 2H, H-2), 1.56 – 1.43 (m, 4H, H-2, H-3); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 143.4 (C-9), 138.3 (C-6), 129.8 (C-8), 127.0 (C-7), 107.6 (C-1), 64.44 (C-5), 64.35 (C-5), 51.1 (C-4), 32.8 (C-2), 30.7 (C-3), 21.6 (C-10); **IR** (thin film) $\tilde{\nu}_{max}^{-1}$ 3246 (N–H), 2934 (C–H), 1443, 1317 (SO_2), 1160 (SO_2), 1090, 1028, 928, 817, 669; **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ $(C_{15}H_{21}O_4N^{23}Na^{32}S)^+$ requires 334.1084, found 334.1083.

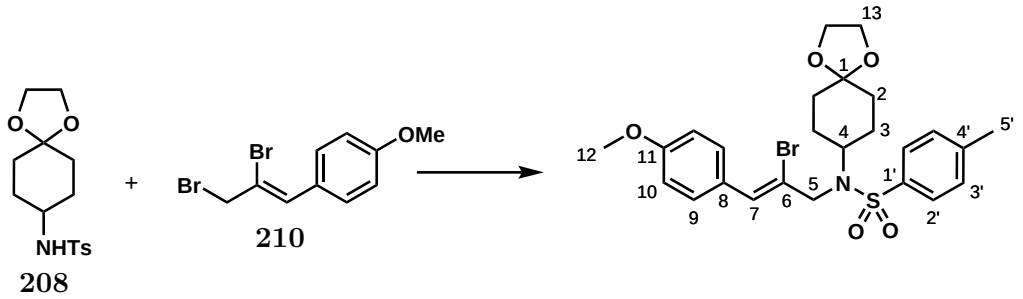
(*Z*)-*N*-(2-bromo-3-phenylallyl)-4-methyl-*N*-(1,4-dioxaspiro[4.5]decan--8-yl)benzenesulfonamide (211)



Prepared according to General Procedure C using amine **208** (373 mg, 1.2 mmol) and bromide[182] **209** (332 mg, 1.2 mmol). Purification by flash column chromatography (1:9 EtOAc/pentane then 1:3) afforded **211** (451 mg, 74% yield) as a white solid.

MP: 121–123 °C; **IR** (thin film) $\tilde{\nu}_{max}$$^{-1}$ 2944 (C−H), 1331 (SO_2), 1152 (SO_2), 1091, 1035; ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 7.77 – 7.72 (m, 2H, H-2'), 7.75 – 7.49 (m, 2H, H-10), 7.37 – 7.31 (m, 2H, H-9), 7.31 – 7.26 (m, 3H, H-3', H-11), 7.08 (s, 1H, H-7), 4.22 (d, J = 1.5 Hz, 2H, H-5), 3.93 – 3.84 (m, 5H, H-12, H-4), 2.41 (s, 3H, H-5'), 1.82 – 1.68 (m, 4H, H-2a, H-3a), 1.68 – 1.53 (m, 4H, H-2b, H-3b); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 143.5 (C-4'), 138.2 (C-8), 135.4 (C-6), 129.9 (C-3'), 129.3 (C-7), 129.1 (C-10), 128.2 (C-9), 128.1 (C-11), 127.3 (C-2'), 123.1 (C-1'), 107.3 (C-1), 64.5 (C-12), 57.2 (C-4), 52.6 (C-5), 34.3 (C-2), 28.1 (C-3), 21.6 (C-5'); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ $(C_{24}H_{28}O_4N^{79}Br^{23}Na^{32}S)^+$ requires 528.0815, found 528.0815.

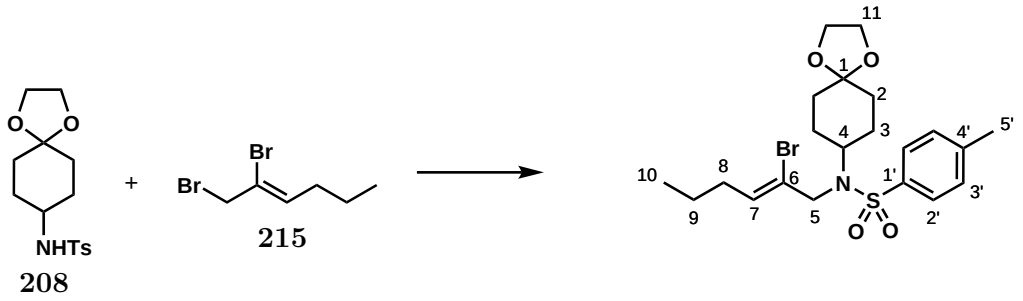
(*Z*)-*N*-(2-bromo-3-(4-methoxyphenyl)allyl)-4-methyl-*N*-(1,4-dioxaspiro[4.5]decan-8-yl)benzenesulfonamide (212)



Prepared according to General Procedure C using amine **208** (622 mg, 2 mmol) and bromide[183] **210** (612 mg, 2 mmol). Purification by flash column chromatography (3:7 EtOAc/pentane) afforded **212** (587 mg, 55% yield) as a white solid.

MP: 146–148 °C; **IR** (thin film) $\tilde{\nu}_{max}$$^{-1}$ 2947 (C-H), 1606, 1510, 1334, 1250, 1154, 1090, 1032; ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 7.76 – 7.71 (m, 2H, H-2'), 7.53 (m, 2H, H-9), 7.29 – 7.25 (m, 2H, H-3'), 7.00 (s, 1H, H-7), 6.90 – 6.85 (m, 2H, H-10), 4.20 (d, J = 1.5 Hz, 2H, H-5), 3.93 – 3.83 (m, 5H, H-13, H-4), 3.82 (s, 3H, H-12), 2.41 (s, 3H, H-5'), 1.83 – 1.68 (m, 4H, H-2a, H-3a), 1.68 – 1.52 (m, 4H, H-2b, H-3b); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 159.5 (C-11), 143.5 (C-4'), 138.3 (C-6), 130.5 (C-9), 129.8 (C-3'), 128.9 (C-7), 127.3 (C-2'), 121.1 (C-1'), 114.0 (C-8), 113.6 (C-10), 107.4 (C-1), 64.5 (C-13), 57.2 (C-4), 55.4 (C-12), 52.8 (C-5), 34.3 (C-2), 28.2 (C-3), 21.7 (C-5'); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ $(C_{25}H_{30}O_5N^{79}Br^{23}Na^{32}S)^+$ requires 558.0920, found 558.0918.

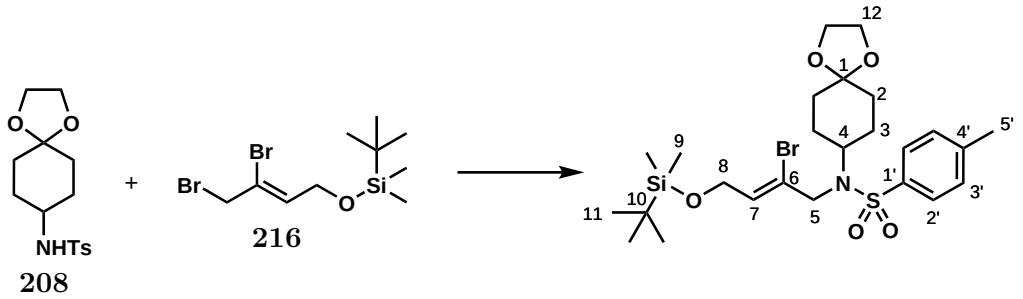
(*Z*)-*N*-(2-bromohex-2-en-1-yl)-4-methyl-*N*-(1,4-dioxaspiro[4.5]decan-8--yl)benzenesulfonamide (217)



Prepared according to General Procedure C using amine **208** (351 mg, 1.13 mmol) and bromide **215** (273 mg, 1.13 mmol). Purification by flash column chromatography (1:4 EtOAc/pentane) afforded **217** (314 mg, 59% yield) as a white solid.

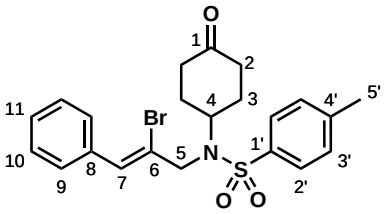
MP: 68–70 °C; **IR** (thin film) $\tilde{\nu}_{\text{max}}{}^{-1}$ 2957 (C-H), 2873 (C-H), 1336, 1155, 1091, 1035; ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_{H} 7.70 (d, J = 8.0 Hz, 2H, H-2'), 7.27 (d, J = 8.0 Hz, 2H, H-3'), 6.06 – 5.99 (m, 1H, H-7), 4.04 (s, 2H, H-5), 3.91 – 3.83 (m, 4H, H-11), 3.77 (tt, J = 12.5, 4.0 Hz, 1H, H-4), 2.41 (s, 3H, H-5'), 2.13 (q, J = 7.0 Hz, 2H, H-8), 1.77 – 1.62 (m, 4H, H-2a, H-3a), 1.60 – 1.48 (m, 4H, H-2b, H-3b), 1.40 (h, J = 7.5 Hz, 2H, H-9), 0.91 (t, J = 7.5 Hz, 3H, H-10); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_{C} 143.4 (C-4'), 138.3 (C-6), 131.2 (C-7), 129.7 (C-3'), 127.2 (C-2'), 123.9 (C-1'), 107.4 (C-1), 64.4 (C-11), 57.1 (C-4), 51.5 (C-5), 34.3 (C-2), 33.2 (C-8), 28.0 (C-3), 21.62 (C-9), 21.55 (C-5'), 13.9 (C-10); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{21}H_{31}O_4N^{79}Br^{32}S)^+$ requires 472.1152, found 472.1149.

(*Z*)-*N*-(2-bromo-4-((tert-butyldimethylsilyl)oxy)but-2-en-1-yl)-4-methyl-*N*-(1,4- dioxaspiro[4.5]decan-8-yl)benzenesulfonamide (218)



Prepared according to General Procedure C using amine **208** (177 mg, 0.57 mmol) and bromide **407** (195 mg, 0.57 mmol). Purification by flash column chromatography (3:7 Et_2O/pentane) afforded **218** (157 mg, 46% yield) as a white solid. **MP**: 78–80 °C; **IR** (thin film) $\tilde{\nu}_{max}$$^{-1}$ 2360 (C-H), 2341 (C-H), 1636, 1339, 1255, 1156, 1105, 1092; ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 7.71 (d, J = 8.5 Hz, 2H, H-2'), 7.28 (d, J = 8.5 Hz, 2H, H-3'), 6.22 (tt, J = 5.0, 1.5 Hz, 1H, H-7), 4.28 (d, J = 5.0 Hz, 2H, H-8), 4.04 (d, J = 1.5 Hz, 2H, H-5), 3.91 – 3.87 (m, 4H, H-12), 3.82 – 3.72 (m, 1H, H-4), 2.42 (s, 3H, H-5'), 1.75 – 1.65 (m, 4H, H-2a, H-3a), 1.63 – 1.49 (m, 4H, H-2b, H-3b), 0.90 (s, 9H, H-11), 0.08 (s, 6H, H-9); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 143.5 (C-4'), 134.5 (C-6), 131.6 (C-7), 129.8 (C-3'), 127.3 (C-2'), 122.7 (C-1'), 107.4 (C-1), 64.5 (C-12), 63.4 (C-8), 57.1 (C-4), 51.2 (C-5), 34.3 (C-2), 28.1 (C-3), 26.0 (C-11), 21.7 (C-5'), 18.4 (C-10), -5.1 (C-9); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{25}H_{41}O_5N^{79}Br^{32}S^{28}Si)^+$ requires 574.1664, found 574.1652.

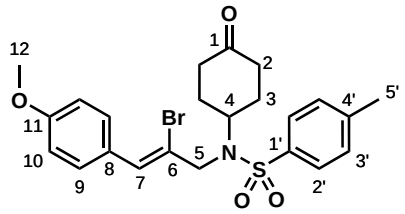
(*Z*)-*N*-(2-bromo-3-phenylallyl)-4-methyl-*N*-(4-oxocyclohexyl) benzenesulfonamide (213)



Prepared according to General Procedure D using **211** (450 mg, 0.88 mmol). Purification by flash column chromatography (2:3 Et_2O/ pentane) afforded **213** (326 mg, 80% yield) as a white solid.

MP: 114–116 °C; **IR** (thin film) $\tilde{\nu}_{max}$$^{-1}$ 2980 (C−H), 1708 (C=O), 1324 (SO_2), 1161 (SO_2), 1089, 1048; ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 7.80 – 7.75 (m, 2H, H-2'), 7.54 – 7.50 (m, 2H, H-10), 7.38 – 7.28 (m, 5H, H-3', H-9, H-11), 7.07 (s, 1H, H-7), 4.30 (tt, J = 11.8, 3.8 Hz, 1H, H-4), 4.23 (d, J = 1.4 Hz, 2H, H-5), 2.43 (s, 3H, H-5'), 2.48 – 2.35 (m, 4H, H-2), 2.12 – 1.86 (m, 4H, H-3); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 208.5 (C-1), 144.0 (C-4'), 135.0 (C-6), 130.1 (C-3'), 130.0 (C-7), 129.1 (C-10), 128.5 (C-8), 128.3 (C-9), 128.0 (C-11), 127.3 (C-2'), 123.0 (C-1') 56.5 (C-4), 53.3 (C-5), 40.2 (C-2), 30.3 (C-3), 21.7 (C-5'); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{22}H_{25}O_3N^{79}Br^{32}S)^+$ requires 462.0733, found 462.0734.

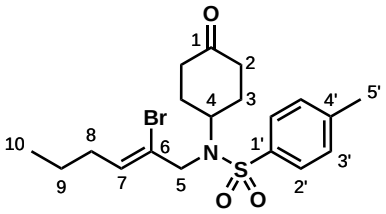
(*Z*)-*N*-(2-bromo-3-(4-methoxyphenyl)allyl)-4-methyl-*N*-(4-oxocyclohexyl)benzenesulfonamide (214)



Prepared according to General Procedure D using **212** (536 mg, 1 mmol). Purification by flash column chromatography (3:7 EtOAc/pentane) afforded **214** (487 mg, 99% yield) as a white solid.

MP: 135–137 °C; **IR** (thin film) $\tilde{\nu}_{\text{max}}^{-1}$ 2947 (C−H), 1712 (C=O), 1510, 1253, 1240, 1161, 1152, 1021; ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_{H} 7.76 (d, J = 8.5 Hz, 2H, H-2'), 7.52 (d, J = 8.5 Hz, 2H, H-9), 7.30 (d, J = 8.0 Hz, 2H, H-3'), 6.99 (s, 1H, H-7), 6.88 (d, J = 9.0 Hz, 2H, H-10), 4.28 (tt, J = 11.5, 4.0 Hz, H-4), 4.22 (d, J = 1.0 Hz, 2H, H-5), 3.82 (s, 3H, H-12), 2.43 (s, 3H, H-5'), 2.45 – 2.35 (m, 4H, H-2), 2.05 – 1.87 (m, 4H, H-3); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_{C} 208.6 (C-1), 159.7 (C-6), 130.6 (C-9), 130.0 (C-3'), 129.6 (C-7), 127.3 (C-2'), 113.7 (C-10), 56.5 (C-4), 55.5 (C-5), 53.5 (C-12), 40.2 (C-2), 30.3 (C-3), 21.7 (C-5'); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ $(C_{23}H_{26}O_4N^{79}Br^{23}Na^{32}S)^+$ requires 514.0658, found 514.0660.

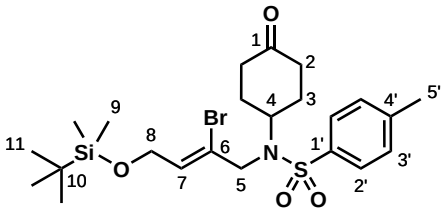
(*Z*)-*N*-(2-bromohex-2-en-1-yl)-4-methyl-*N*-(4-oxocyclohexyl) benzenesulfonamide (219)



Prepared according to General Procedure D using **217** (260 mg, 0.55 mmol). Purification by flash column chromatography (1:4 EtOAc/pentane) afforded **219** (210 mg, 89% yield) as a white solid.

MP: 79–81 °C; **IR** (thin film) $\tilde{\nu}_{max}^{-1}$ 2958 (C-H), 1717 (C=O), 1340, 1158, 1090, 1045; ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 7.76 – 7.71 (m, 2H, H-2'), 7.33 – 7.29 (m, 2H, H-3'), 6.03 (tt, J = 7.0, 1.5 Hz, 1H, H-7), 4.19 (tt, J = 11.5, 4.5 Hz, 1H, H-4), 4.08 – 4.05 (m, 2H, H-5), 2.43 (s, 3H, H-5'), 2.40 – 2.34 (m, 4H, H-2), 2.18 – 2.10 (m, 2H, H-8), 1.98 – 1.81 (m, 4H, H-3), 1.40 (h, J = 7.5 Hz, 2H, H-9), 0.91 (t, J = 7.5 Hz, 3H, H-10); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 208.6 (C-1), 143.8 (C-4'), 138.0 (C-6), 132.1 (C-7), 130.0 (C-3'), 127.3 (C-2'), 123.6 (C-1'), 56.3 (C-4), 52.1 (C-5), 40.2 (C-2), 33.2 (C-8), 30.2 (C-3), 21.7 (C-5'), 21.6 (C-9), 13.9 (C-10); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{19}H_{27}O_3N^{79}Br^{32}S)^+$ requires 428.0890, found 428.0888.

(*Z*)-*N*-(2-bromo-4-((tert-butyldimethylsilyl)oxy)but-2-en-1-yl)-4-methyl-*N*-(4- oxocyclohexyl)benzenesulfonamide (220)

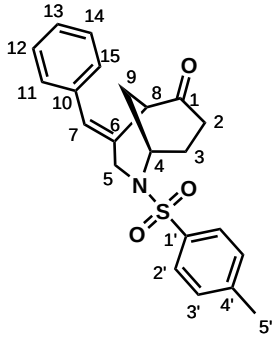


Prepared according to General Procedure D using **218** (133 mg, 0.23 mmol). Hydrolysis of the ketal yielded a mixture of **220** and the desilylated alcohol **408**, which was dissolved in dimethylformamide (2.3 mL), before tert-butyldimethylsilyl chloride (70.0 mg, 0.46 mmol) was added portionwise, followed by imidazole (31.0 mg, 0.46 mmol). The reaction mixture was stirred at RT for 2 h, then carefully quenched with 10% Na_2CO_3 (aq, 2 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3x10 mL). The combined organic layers were washed with sat. NH_4Cl (aq, 20 mL) and H_2O (20 mL), then dried with Na_2SO_4, filtered, and concentrated under vacuum. Purification by flash column chromatography (1:4 EtOAc/pentane) afforded **220** (86 mg, 70% yield, 2 steps) as a white solid.

MP: 73–75 °C; **IR** (thin film) $\tilde{\nu}_{max}^{-1}$ 2160, 2033, 1061, 962; ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 7.76 – 7.71 (m, 2H, H-2'), 7.34 – 7.29 (m, 2H, H-3'), 6.22 (tt, J = 5.5, 1.5 Hz, 1H, H-7), 4.27 (dt, J = 5.5, 1.5 Hz, 2H, H-8), 4.23 – 4.13 (m, 1H, H-4), 4.08 – 4.05 (m, 2H, H-5), 2.43 (s, 3H, H-5'), 2.41 – 2.33 (m, 4H, H-2), 1.99 – 1.79 (m, 4H, H-3), 0.89 (s, 9H, H-11), 0.07 (s, 6H, H-9); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 208.4 (C-1), 143.9 (C-4'), 137.8 (C-1'), 132.4 (C-7), 130.0 (C-3'), 127.3 (C-2'), 122.4 (C-6), 63.2 (C-8), 56.3 (C-4), 51.8 (C-5), 40.2 (C-2), 30.1 (C-3), 26.0 (C-11), 21.7 (C-5'), 18.4 (C-10), -5.1 (C-9); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{23}H_{37}O_4N^{79}Br^{32}S^{28}Si)^+$ requires 530.1390, found 530.1390.

6.2.13 Cyclised Products: Trisubstituted Alkenes

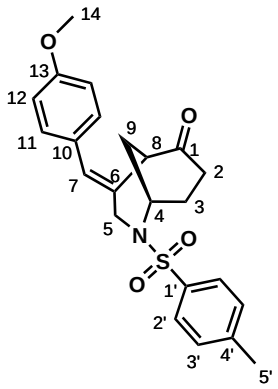
(1*S*,5*R*)-4-((*E*)-benzylidene)-2-tosyl-2-azabicyclo[3.3.1]nonan--6-one (–)-222



Prepared according to General Procedure E using **213** (46.2 mg, 0.1 mmol). Purification by flash column chromatography (1:4 EtOAc/pentane) afforded **222** (29.2 mg, 77% yield, 90% ee) as a white solid.

MP: 100–102 °C; **IR** (thin film) $\tilde{\nu}_{\max}{}^{-1}$ 2951 (C–H), 1710 (C=O), 1333 (SO_2), 1156 (SO_2), 1093, 1033; ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 7.79 – 7.75 (m, 2H, H-2'), 7.40 – 7.32 (m, 6H, Ar-H), 7.29 – 7.23 (m, 1H, Ar-H), 6.59 (s, 1H, H-7), 4.26 – 4.14 (m, 2H, H-5), 4.24 (t, J = 3.0 Hz, 1H, H-4), 3.74 (s, 1H, H-8), 2.78 – 2.66 (m, 1H, H-2a), 2.45 (s, 3H, H-5'), 2.44 – 2.36 (m, 1H, H-2b), 2.35 – 2.26 (m, 1H, H-3a), 2.03 – 1.85 (m, 3H, H-3b, H-9); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 208.5 (C-1), 143.9 (C-4'), 135.9 (C-1'), 135.0, 132.7, 132.6, 130.2, 130.1 (C-7), 129.9, 129.2, 128.6, 127.9, 127.5 (C-2'), 49.3 (C-5), 47.8 (C-4), 47.1 (C-8), 37.0 (C-2), 32.4, 31.8 (C-9), 31.1 (C-3), 21.7 (C-5'); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ $(C_{22}H_{23}O_3N^{23}Na^{32}S)^+$ requires 404.1291, found 404.1289; $[\boldsymbol{\alpha}]_D^{25}$ = -181.7 (c 1.0, $CDCl_3$, 90% ee); **HPLC**: (Chiralpak IA, hexane/isopropanol 80:20, 1.0 mL min^{-1}, λ= 210 nm) t_R = 18.7 (minor), 24.0 (major).

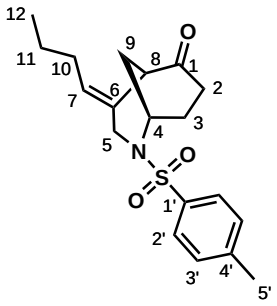
(1*S*,5*R*)-4-((E)-4-methoxybenzylidene)-2-tosyl-2-azabicyclo[3.3.1]nonan--6-one (−)-225



Prepared according to General Procedure E using **214** (49.2 mg, 0.1 mmol). Purification by flash column chromatography (1:4 EtOAc/pentane) afforded **225** (29.6 mg, 72% yield, 96% ee) as a white solid.

MP: 161–163 °C; **IR** (thin film) $\tilde{\nu}_{max}^{-1}$ 2921 (C−H), 1704 (C=O), 1608, 1515, 1459, 1316, 1303, 1252, 1147, 1097, 1033; ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 7.81 – 7.74 (m, 2H, H-2'), 7.38 – 7.32 (m, 4H, H-11, H-3'), 6.91 – 6.85 (m, 2H, H-12), 6.52 (s, 1H, H-9), 4.25 – 4.19 (m, 1H, H-5a), 4.23 – 4.19 (m, 1H, H-4), 4.16 – 4.09 (m, 1H, H-5b), 3.80 (s, 3H, H-14), 3.73 (s, 1H, H-8), 2.80 – 2.69 (m, 1H, H-2a), 2.44 (s, 3H, H-5'), 2.42 – 2.27 (m, 2H, H-2b, H-3a), 2.02 – 1.85 (m, 3H, H-3b, H-9); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 208.8 (C-1), 159.3, 143.9, 135.8, 130.7, 130.0, 129.9 (C-9), 127.5 (C-2'), 114.0 (C-12), 55.4 (C-14), 49.4 (C-5), 47.8 (C-4), 47.3 (C-8), 36.9 (C-2), 32.4 (C-9), 32.1 (C-3), 21.7 (C-5'); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ $(C_{23}H_{25}O_4N^{23}Na^{32}S)^+$ requires 434.1397, found 434.1395; $[\boldsymbol{\alpha}]_D^{25}$ = -196.8 (c 1.0, $CHCl_3$, 96% ee); **HPLC**: (Chiralpak IA, hexane/isopropanol 80:20, 1.0 mL min^{-1}, λ= 210 nm) t_R = 26.5 (minor), 28.3 (major).

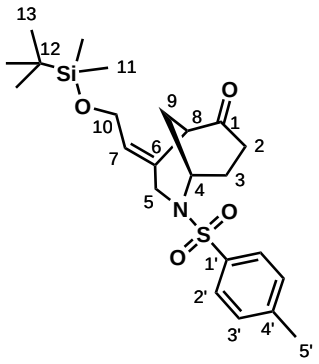
(1*S*,5*R*,*E*)-4-butylidene-2-tosyl-2-azabicyclo[3.3.1]nonan-6-one (–)-226



Prepared according to General Procedure F using **219** (42.8 mg, 0.1 mmol). Purification by flash column chromatography (Et_2O/pentane 3:7 then 3:2) afforded **226** (20.3 mg, 59%, 94% ee) as a white solid.

MP: 102–104 °C; **IR** (thin film) $\tilde{\nu}_{max}^{-1}$ 2959 (C-H), 2927 (C-H), 1712 (C=O), 1455, 1339, 1161, 1095, 932; ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 7.72 (d, J = 8.5 Hz, 2H, H-2'), 7.33 (d, J = 8.5 Hz, 2H, H-3'), 5.55 (tt, J = 8.0, 2.0 Hz, 1H, H-7), 4.10 (d, J = 13.5, 1H, H-5a), 4.03 – 3.98 (m, 1H, H-4), 3.65 – 3.58 (m, 1H, H-5b), 3.35 (s, 1H, H-8), 2.94 (ddd, J = 15.0, 13.5, 7.0 Hz, 1H, H-2a), 2.43 (s, 3H, H-5'), 2.43 – 2.36 (m, 1H, H-3a), 2.23 – 2.15 (m, 1H, H-2b), 2.02 – 1.90 (m, 3H, H-10, H-5a), 1.87 – 1.77 (m, 2H, H-3b, H-5b), 1.35 – 1.23 (m, 2H, H-11), 0.84 (t, J = 7.5 Hz, 3H, H-12); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 208.9 (C-1), 143.8 (C-4'), 134.5 (C-1'), 132.4 (C-7), 130.0 (C-3'), 128.6 (C-6), 127.6 (C-2'), 48.8 (C-4), 48.2 (C-5), 47.0 (C-8), 34.6 (C-2), 33.9 (C-3), 30.7 (C-9), 29.4 (C-10), 22.2 (C-11), 21.7 (C-5'), 13.8 (C-12); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{19}H_{26}O_3N^{32}S)^+$ requires 348.1628, found 348.1627; **HPLC**: (Chiralcel OD, hexane/isopropanol 90:10, 1.0 mL/min, λ= 210nm) t_R = 10.0 (minor), 11.9 (major). $[\boldsymbol{\alpha}]_D^{25}$ = -15.6 (c 1.0, $CHCl_3$, 94% ee).

(1*S*,5*R*,*E*)-4-(2-((tert-butyldimethylsilyl)oxy)ethylidene)-2-tosyl-2--azabicyclo[3.3.1]nonan-6-one (–)-227



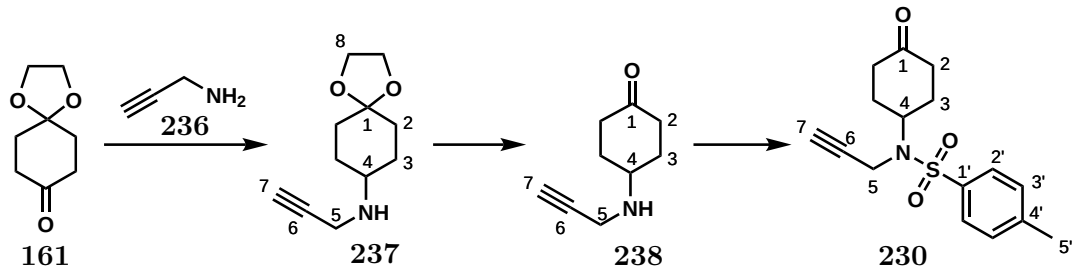
Prepared according to General Procedure F using **220** (53.1 mg, 0.1 mmol). Purification by flash column chromatography (2:3 Et_2O/pentane then 3:2) afforded a mixture of products containing **227** in 77% purity (22.3 mg, 50% yield of mixture, 39% yield of title compound, 63% ee) as an amorphous solid.

IR (thin film) $\tilde{\nu}_{max}^{-1}$ 2360 (C-H), 2341 (C-H), 1260, 1091, 798, 669; ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 7.75 – 7.70 (m, 2H, H-2'), 7.37 – 7.32 (m, 2H, H-3'), 5.71 – 5.65 (m, 1H, H-7), 4.26 – 4.19 (m, 1H, H-10a), 4.13 (d, J = 13.5 Hz, 1H, H-5a), 4.05 – 3.96 (m, 2H, H-4, H-10b), 3.63 (d, J = 13.5 Hz, 1H, H-5b), 3.29 (s, 1H, H-8), 2.87 (ddd, J = 15.0, 13.5, 7.0 Hz, 1H, H-2a), 2.48 – 2.39 (m, 1H, H-3a), 2.45 (s, 3H, H-5'), 2.26 – 2.18 (m, 1H, H-2b), 2.03 – 1.96 (m, 1H, H-9a), 1.88 – 1.84 (m, 1H, H-9b), 1.84 – 1.80 (m, 1H, H-3b), 0.87 (s, 9H, H-13), 0.04 (d, J = 2.5 Hz, 6H, H-11); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 207.9 (C-1), 144.0 (C-4'), 134.4 (C-1'), 131.9 (C-7), 130.1 (C-3'), 129.2 (C-6), 127.6 (C-2'), 59.0 (C-10), 48.7 (C-4), 47.8 (C-5), 47.2 (C-8), 34.6 (C-2), 33.6 (C-3), 30.3 (C-9), 26.0 (C-13), 21.7 (C-5'), 18.4 (C-12), -5.1 (2xC-11); **HPLC**: (Chiralpak AS-H, hexane/isopropanol 90:10, 1.0 mL/min, λ= 210nm) t_R = 13.0 (major), 15.0 (minor); $[\alpha]_D^{25}$ = +3.1 (c 1.0, $CHCl_3$, 63% ee).

6.3 Compounds Synthesised in Chapter 3

6.3.1 Synthesis of *N*-Ts-4-propargylamino cyclohexanone 230

Sulfonamide **230** was prepared in three steps from ketone **161** following literature procedures.[56]



***N*-(prop-2-yn-1-yl)-1,4-dioxaspiro[4.5]decan-8-amine (237)**

To a solution of 1,4-cyclohexanedione monoethylene acetal **161** (5.00 g, 32.0 mmol) in 1,2-dichloroethane (100 mL) at RT was added propargyl amine (2.11 mL, 32.9 mmol). The resulting solution was stirred at RT for 5 mins before cooling to 0 °C. $NaBH(OAc)_3$ (9.50 g, 44.8 mmol) was added portionwise (caution: exothermic), and the resulting suspension was stirred at RT for 20 h. The reaction was quenched with KOH (1 M, 100 mL), then the layers were separated and the aq. layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford amine **237** (6.14 g, assumed quant. for next step) as a yellow-white solid, which did not require further purification. Data are in agreement with those reported in the literature.[56]

MP: 58–60 °C (lit. 49–50 °C)[56]; **IR** (thin film) $\tilde{\nu}_{max}{}^{-1}$ 3500 (N–H, weak, broad), 3289 (C≡C–H), 2935 (C–H), 2881 (C–H), 1148 (C–O), 1102 (C–N), 1034 (C–O); ^{1}**H-NMR** (500 MHz, $CDCl_3$): δ_H 3.93 (s, 4H, H-8), 3.45 (d, J = 2.5 Hz, 2H, H-5),

2.78 (tt, J = 10.0, 4.0 Hz, 1H, H-4), 2.20 (t, J = 2.5 Hz, 1H, H-7), 1.88–1.82 (m, 2H, H-3a), 1.81–1.75 (m, 2H, H-2a), 1.61–1.55 (m, 2H, H-2b), 1.49–1.40 (m, 2H, H-3b); **^{13}C-NMR** (126 MHz, $CDCl_3$): δ_C 108.8 (C-1), 82.5 (C-6), 71.3 (C-7), 64.4 (C-8), 53.4 (C-4), 35.7 (C-5), 32.9 (C-2), 29.9 (C-3); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{11}H_{18}O_2N)^+$ requires 196.1332, found 196.1331.

4-[(prop-2-yn-1-yl)amino]cyclohexan-1-one (238)

To a solution of crude acetal **237** (6.14 g, theoretical 32.0 mmol) in THF (80 mL) was added HCl (aq., 3 M, 80 mL). The resulting solution was stirred at RT for 1 d until complete (confirmed by NMR analysis as the starting material and product have very similar R_f values). The reaction was basified with KOH (3 M), then the layers were separated and the aq. layer was extracted with $CHCl_3$/IPA (5:1) (3 × 500 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford amine **238** as a brown oil, which was used without further purification. Data are in agreement with those reported in the literature.[56]

IR (thin film) $\tilde{\nu}_{max}^{-1}$ 3500 (N–H weak, broad), 3285 (C≡C–H), 2934 (C–H), 2867 (C–H), 1709 (C=O), 1119 (C–N); **^{1}H-NMR** (500 MHz, $CDCl_3$): δ_H 3.49 (d, J = 2.5 Hz, 2H, H-5), 3.22 (tt, J = 8.0, 3.5 Hz, 1H, H-4), 2.50 (dt, J = 15.0, 6.0 Hz, 2H, H-2a), 2.32 (ddd, J = 15.0, 10.0, 5.5 Hz, 2H, H-2b), 2.24 (t, J = 2.5 Hz, 1H, H-7), 2.12–2.00 (m, 2H, H-3a), 1.78–1.64 (m, 2H, H-3b), 1.43 (s, 1H, N–H); **^{13}C-NMR** (126 MHz, $CDCl_3$): δ_C 211.3 (C-1), 81.9 (C-6), 71.7 (C-7), 51.6 (C-4), 38.3 (C-2), 35.7 (C-5), 31.5 (C-3); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_9H_{14}ON)^+$ requires 152.1070, found 152.1071.

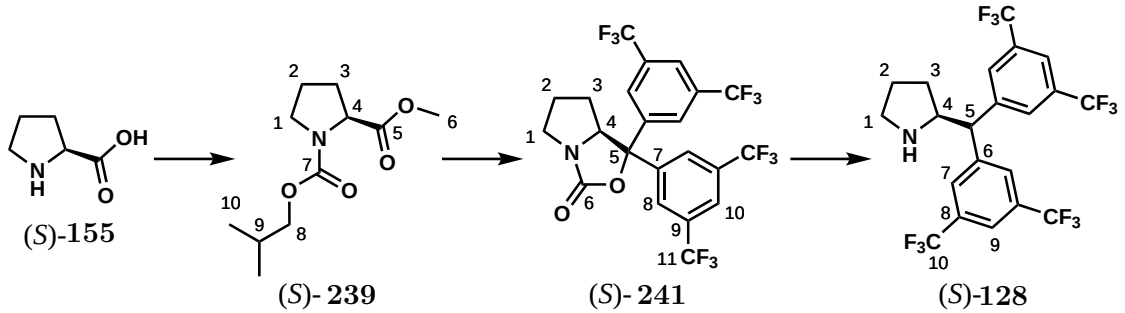
4-methyl-*N*-(4-oxocyclohexyl)-*N*-(prop-2-yn-1-yl)-benzene--1-sulfonamide (230)

To a solution of crude amine **238** (theoretical 32.0 mmol) in CH_2Cl_2 (100 mL) was added triethylamine (5.26 mL, 37.7 mmol) followed by *p*-toluenesulfonyl chloride (7.19 g, 37.7 mmol) and DMAP (384 mg, 3.14 mmol). The reaction was stirred at RT for 1 d until complete. The reaction mixture was diluted with CH_2Cl_2 (100 mL) then washed with HCl (1 M, 100 mL), followed by water (100 mL), and finally brine (100 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude protected amine as a brown solid. Purification by flash column chromatography (30% EtOAc in petrol) afforded tosylated propargyl amine **230** (7.17 g, 23.5 mmol, 73% over three steps from **161**, 32.0 mmol) as a white solid. Data are in agreement with those reported in the literature.[56]

MP: 126–129 °C (lit.[56] 126–127 °C); **IR** (thin film) $\tilde{\nu}_{max}{}^{-1}$ 3271 (C≡C–H), 2955 (C–H), 1716 (C=O), 1328 (SO_2), 1158 (SO_2), 1045 (C–N); ^{1}**H-NMR** (500 MHz, $CDCl_3$): δ_H 7.81 (d, J = 8.0 Hz, 2H, H-2'), 7.31 (d, J = 8.0 Hz, 2H, H-3'), 4.21 (tt, J = 11.5, 4.5 Hz, 1H, H-4), 4.12 (d, J = 2.5 Hz, 2H, H-5), 2.44 (s, 3H, H-5'), 2.42–2.38 (m, 4H, H-2), 2.18 (t, J = 2.5 Hz, 1H, H-7), 2.10–1.96 (m, 4H, H-3); ^{13}**C-NMR** (126 MHz, $CDCl_3$): δ_C 208.7 (C-1), 143.8 (C-1'), 137.6 (C-4'), 129.8 (C-3'), 127.4 (C-2'), 79.8 (C-6), 73.2 (C-7), 55.8 (C-4), 40.1 (C-2), 32.7 (C-5), 30.2 (C-3), 21.7 (C-5'); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ $(C_{16}H_{19}O_3N^{23}Na^{32}S)^+$ requires 328.0978, found 328.0980.

6.3.2 Synthesis of pyrrolidinyl catalysts (*S*)-128 and (*R*)-128

The syntheses of (*S*)-**128** and (*R*)-**128** were carried out according to literature procedures.[56,184,185]



2-methyl 1-(2-methylpropyl) (2*S*)-pyrrolidine-1,2-dicarboxylate ((*S*)-239)

Prepared according to a literature procedure.[56,78] To a solution of L-proline (5.00 g, 43.0 mmol) in MeOH (100 mL) at 0 °C was added K_2CO_3 (5.90 g, 43 mmol) carefully. Isobutyl chloroformate (12.3 mL, 94.6 mmol) was then added dropwise (over 20 minutes). The resulting solution was stirred at 0 °C for 10 h, then at RT for an additional 12 h. Over the course of the reaction, the solution turned milky white. The reaction was concentrated *in vacuo* to remove MeOH, and the resulting white solid was re-dissolved in $CHCl_3$ (50 mL) and water (50 mL). The layers were separated and the aq. layer was extracted with $CHCl_3$ (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford a colourless oil. Purification by flash column chromatography (10% EtOAc in Petrol) afforded **239** (5.59 g, 24.4 mmol, 57%) as a colourless oil. Data are in agreement with literature values.[56,78] ^{1}H NMR data is poorly resolved due to rotameric behaviour and is reported as observed at RT.

^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 4.19–4.37 (m, 1H, H-4), 3.77–3.90 (m, 1H, H-8), 3.70–3.77 (m, 1H, H-8), 3.62–3.70 (m, 3H, H-6), 3.34–3.61 (m, 2H, H-1), 2.05–2.27

(m, 1H, H-9), 1.74–2.02 (m, 4H, H-2,3), 0.75–0.94 (m, 6H, H-10); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 173.4 (C-5), 173.2 (C-5), 155.2 (C-7), 154.6 (C-7), 71.4 (C-8), 59.0 (C-4), 58.7 (C-4), 52.2 (C-6), 52.1 (C-6), 46.8 (C-1), 46.3 (C-1), 31.0 (C-3), 29.9 (C-3), 28.0 (C-9), 28.0 (C-9), 24.3 (C-2), 23.6 (C-2), 19.0 (C-10), 18.9 (C-10); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{11}H_{20}O_2N)^+$ requires 230.1387, found 230.1388

2-methyl 1-(2-methylpropyl) (2*S*)-pyrrolidine-1,2-dicarboxylate ((*R*)-239)

(*R*)-**239** was prepared in the same manner as (*S*)-**239** using D-proline (10.2 g, 88.6 mmol), K_2CO_3 (12.2 g, 88.6 mmol), and isobutyl chloroformate (25.3 mL, 195 mmol). Purification by flash column chromatography (10% EtOAc in Petrol) afforded (*R*)-**239** as a colourless oil (17.5 g, 76.3 mmol, 86% yield). Experimental data matched that of (*S*)-**239** and literature values.

(7a*S*)-1,1-bis[3,5-bis(trifluoromethyl)phenyl]tetrahydro- 1*H*,3*H*-
-pyrrolo[1,2-*c*] [1,3]oxazol-3-one ((*S*)-241)

Prepared according to a literature procedure.[56] Mg (1.16 g, 47.8 mmol) was suspended in THF (50 mL), and 3,5-bis(trifluoromethyl)bromobenzene (8.20 mL, 47.8 mmol) was added slowly to maintain a gentle reflux. The resulting solution was stirred for 1 h, allowing to cool gradually. THF (100 mL) was added, followed by a solution of (*S*)-**239** (5.47 g, 23.9 mmol) in THF (50 mL). The resulting solution was heated to reflux for 3 h, then allowed to cool to RT. The reaction was quenched with sat. aq. NH_4Cl soln. (150 mL), then the layers were separated and the aq. layer was extracted with EtOAc (3 × 150 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford a brown solid (2.45 g). Purification by flash column chromatography (2:1, CH_2Cl_2:petrol) afforded (*S*)-**241** (7.30 g, 13.2

mmol, 55%) as a white solid. Data is in agreement with literature values.[56]

IR (thin film) $\tilde{\nu}_{max}^{-1}$ 2360 (C–H), 2341 (C–H), 1761 (C=O), 1279, 1179, 1131; ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 7.98 (s, 2H, H-8), 7.91 (s, 1H, H-10), 7.88 (s, 1H, H-10), 7.87 (s, 2H, H-8), 4.57 (dd, J = 11.0, 5.0 Hz, 1H, H-4), 3.80 (dt, J = 11.5, 8.5 Hz, 1H, H-1a), 3.34 (ddd, J = 11.5, 10.0, 3.5 Hz, 1H, 1b), 2.18–2.08 (m, 1H, H-2a), 1.99 (dddt, J = 13.0, 11.0, 10.0, 7.5 Hz, 1H, H-2b), 1.80 (dddd, J = 12.0, 7.0, 5.0, 1.5 Hz, 1H, H-3a), 1.14–1.00 (m, 1H, H-3b); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 158.9 (C-6), 144.7 (C-7), 141.7 (C-7), 132.9 (q, J = 34.0 Hz, C-9), 132.8 (q, J = 34.0 Hz, C-9), 126.0 (d, J = 4.0 Hz, C-8), 125.6 (d, J = 4.0 Hz, C-8), 123.6–123.3 (m, C-10), 122.9 (q, J = 273.0 Hz, C-11), 123.1–122.8 (m, C-10), 122.9 (q, J = 273.0 Hz, C-11), 83.6 (C-5), 69.1 (C-4), 46.5 (C-1), 29.3 (C-3), 24.7 (C-2); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{22}H_{14}O_2NF_{12})^+$ requires 552.0827, found 552.0830.

(7a*R*)-1,1-bis[3,5-bis(trifluoromethyl)phenyl]tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*][1,3]oxazol-3-one ((*R*)-241)

(*R*)-**241** was prepared in the same manner as (*S*)-**241** using (*R*)-**239** (17.5 g, 76.3 mmol), Mg (3.80 g, 156 mmol), and 3,5-bis(trifluoromethyl)bromobenzene (27.0 mL, 156 mmol) in THF (100 mL for Grignard formation and 350 mL for alkylation). Purification by flash column chromatography (2:1 CH_2Cl_2/pentane) afforded (*R*)-**241** (23.7 g, 43.0 mmol, 56%) as a colourless oil. Experimental data matched that of (*S*)-**241** and literature values. **MP**: 182–186 °C.

(2*S*)-2-bis[3,5-bis(trifluoromethyl)phenyl]methylpyrrolidine (*S*)-128

To a solution of carbamate (*S*)-**241** (7.30 g, 13.2 mmol) in MeOH (500 mL) was added $Pd(OH)_2$ (500 mg). While stirring vigorously the vessel was evacuated and

filled with N_2 five times, then evacuated and filled with H_2 ten times using a balloon with four balloon skins. The mixture was stirred vigorously at RT for 2 d. Upon completion the flask was evacuated and filled with N_2, then the slurry was filtered through a pad of celite, washed with MeOH and EtOAc, and the resulting solution was concentrated to a pale yellow oil. Purification by flash column chromatography (20% EtOAc in petrol) afforded (*S*)-**128** which, after drying under vacuum for >1 d, ultimately crystallised as a white powder (5.40 g, 10.6 mmol, 80%). Data is in agreement with literature values.[56]

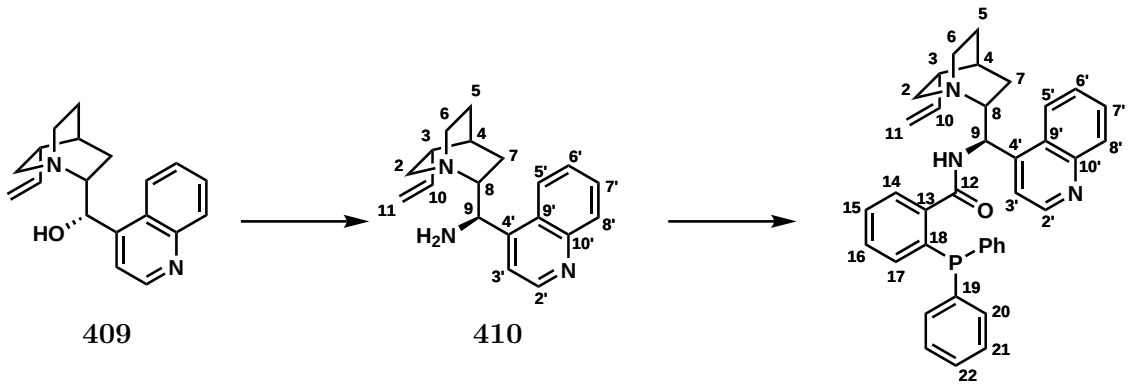
MP: 33–35 °C (lit. 32–34 °C)[56]; **IR** (thin film) $\tilde{\nu}_{max}{}^{-1}$ 2361 (C−H), 2341 (C−H), 1278, 1171, 1130; ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 7.81 (s, 2H, H-7), 7.78 (s, 2H, H-7), 7.73 (s, 2H, H-9), 4.04 (d, J = 9.0 Hz, 1H, H-5), 3.91 (td, J = 9.0, 8.5, 6.5 Hz, 1H, H-4), 3.04–2.90 (m, 2H, H-1), 1.90–1.67 (m, 4H, H-2, H-3a, NH), 1.42–1.31 (m, 1H, H-3b); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 144.5 (C-6), 132.4 (q, J = 33.0 Hz, C-8), 132.3 (q, J = 33.0 Hz, C-8), 128.8–128.5 (m, C-7), 128.5-128.2 (m, C-7), 123.3 (q, J = 273.0 Hz, C-10), 123.3 (q, J = 273.0 Hz, C-10), 121.7 – 121.2 (m, C-9), 61.9 C-(5), 58.0 (C-4), 46.8 (C-1), 31.0 (C-3), 25.5 (C-2); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{21}H_{16}NF_{12})^+$ requires 510.1086, found 510.1080.

(2*R*)-2-bis[3,5-bis(trifluoromethyl)phenyl]methylpyrrolidine (*R*)-128

Prepared according to a literature procedure.[56] (*R*)-**241** (14 g, 25 mmol) was dissolved in EtOH (450 mL) and Et_3N (25 mL) under an atmosphere of N_2. Pd/C (2.7 g, 10 mol%, 10 wt. %) was added, then while stirring vigorously the flask was evacuated and back-filled with N_2 three times, before evacuating and backfilling with H_2 three times. The reaction was heated to 40 °C and stirred under an atmosphere of H_2 for 16 h. After the reaction was complete, the flask was evacuated and back-

filled with N_2 three times, then the slurry was filtered through celite, washing with CH_2Cl_2. The filtrate was concentrated and purified by flash column chromatography (25% EtOAc/pentane) to afford (*R*)-**128** (18.9 g, 37.1 mmol, 87%) as a white solid. Experimental data matched that of (*S*)-**128** and literature values. **MP**: 38–40 °C.

6.3.3 Synthesis of aminophosphine ligand 129



9-amino(9-deoxy)-*epi*-cinchonine (410)

Prepared according to literature procedures.[56,79] To a suspension of cinchonine (5.89 g, 20.0 mmol) and PPh_3 (6.30 g, 24.0 mmol) in THF (100 mL) at 0 °C was added DIAD (4.70 mL, 24.0 mmol). The resulting (heterogenous) solution was stirred for 5 minutes at 0 °C, then DPPA (5.20 mL, 24.0 mmol) was added dropwise over 20 minutes. The solution was stirred at 0 °C for 20 minutes, then the ice bath was removed and stirring was continued for 4 h at rt. The solution was then heated to 45 °C for 2 h, before cooling to RT and adding a second portion of PPh_3 (6.30 g, 24.0 mmol) and heating to 45 °C for a further 2 h. Water (4.0 mL) was then added, and stirring was continued at 45 °C for 14 h. Methanol was removed *in vacuo*, then the resulting solid was dissolved in CH_2Cl_2 (80 mL) and stirred until

homogeneous. HCl (80 mL, aq. 1 M) was added and the resulting biphasic mixture was stirred vigorously for 10 mins. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL). The aqueous layer was then basified with sat. aq. NH_4OH solution, then extracted with CH_2Cl_2 (4 × 100 mL). These organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography (50:50:0.7 EtOAc:MeOH:NH_4OH) afforded **410** (3.24 g, 11.1 mmol, 56%). Data is in agreement with literature values.[56,79]

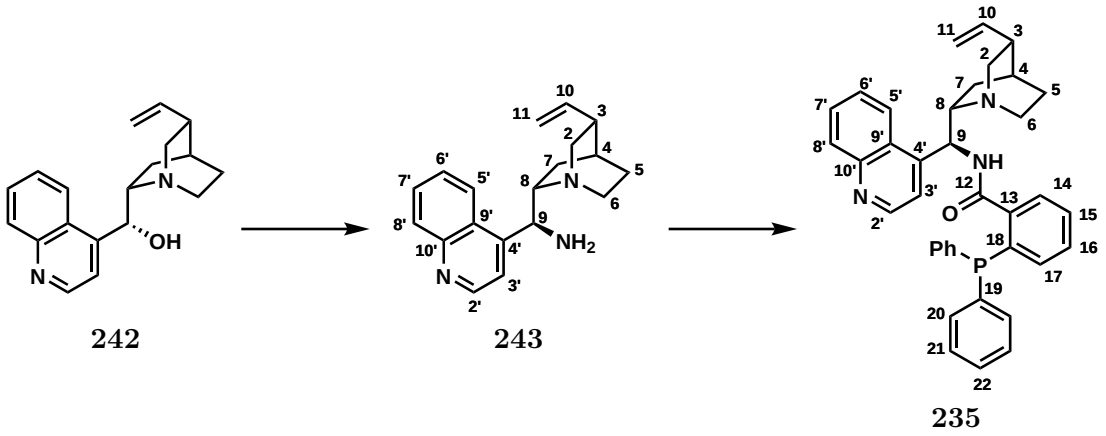
N-[(8ξ,9*R*)-cinchonan-9-yl]-2-(diphenylphosphanyl)benzamide (129)

Prepared according to literature procedures.[56,80] To a solution of **410** (3.24 g, 11.1 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added EDC·HCl (2.24 g, 11.7 mmol), DMAP (143 mg, 1.17 mmol) and 2-(diphenylphosphino)benzoic acid (3.58 g, 11.7 mmol). The resulting solution was allowed to warm to RT and stirred for 48 h. The reaction was concentrated *in vacuo* then diluted with EtOAc and washed with water, followed by 10% $NaHCO_3$ aq. soln. and finally brine. The organic layer was then dried over Na_2SO_4 and concentrated *in vacuo*. The orange crude oil was purified by flash column chromatography (5:5:1 CH_2Cl_2:EtOAc:MeOH) to give **129** (3.10 g, 5.33 mmol, 48%) as a yellow oil, which crystallised following azeotropic removal of solvent as a white solid. Data matches literature values.[80]

MP: 100-104 °C (lit.[80] 99-101 °C); **IR** (thin film) $\tilde{\nu}_{max}^{-1}$ 3317 (N–H), 3052, 2939 (C–H), 2870 (C–H), 1654 (C=C, C=O), 1508, 1482, 1456, 1434, 1308; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H 8.74 (d, J = 4.5 Hz, 1H), 8.36 (dd, J = 8.5, 1.5 Hz, 1H), 8.10 (dd, J = 8.5, 1.5 Hz, 1H), 7.63–7.72 (m, 2H), 7.37 (td, J = 7.65, 1.3 Hz, 1H), 7.26–7.34 (m, 12H), 7.20 (td, J = 7.6, 1.7 Hz, 2H), 6.92 (ddd, J = 7.5, 4.0, 1.0 Hz, 1H), 5.88 (ddd, J = 17.0, 10.5, 6.5 Hz, 1H), 5.34 (s, 1H), 5.05–5.18 (m, 2H), 2.64–

2.88 (m, 5H), 2.18–2.28 (m, 1H), 1.49 (tq, J = 9.5, 3.1 Hz, 1H), 1.40 (dddd, J = 13.0, 10.0, 7.6, 2.2 Hz, 1H), 1.26 (ddt, J = 13.0, 8.3, 2.2 Hz, 1H), 1.21–1.16 (m, 1H) 0.80–0.89 (m, 1H); ^{31}**P-NMR** (162 MHz, $CDCl_3$): δ_P 10.7; **HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{38}H_{37}ON_3P)^+$ requires 582.2669, found 582.2665.

6.3.4 Synthesis of aminophosphine ligand 235



9-amino(9-deoxy)-*epi*-cinchonidine (243)

Prepared according to literature procedures.[56,79] To a cloudy white suspension of cinchonidine (25.0 g, 84.9 mmol) and PPh_3 (27.0 g, 102 mmol) in THF (400 mL) at 0 °C was added DIAD (20 mL, 102 mmol) dropwise, after which the reaction became a clear yellow solution. After stirring for 5 mins at 0 °C, DPPA (22 mL, 102 mmol) was added dropwise, and the resulting solution was stirred for a further 20 mins at 0 °C, before removing the ice bath and stirring at RT for 4 h. The reaction was then heated to 45 °C for 2 h. After cooling to RT, PPh_3 (27.0 g, 102 mmol) was added, and the reaction was heated again to 45 °C for 2 h. Water (20 mL) was added, and heating was continued at 45 °C for 14 h. The reaction was cooled to RT and concentrated *in vacuo*. The resulting oil was dissolved in CH_2Cl_2 (250 mL),

stirring until homogeneous, before HCl (2 M, 250 mL) was added. After stirring vigorously for 10 mins, the layers were separated and the aq. layer was extracted with CH_2Cl_2 (2 × 200 mL). The aq. layer was then basified with NH_3 soln. and extracted with CH_2Cl_2 (4 × 250 mL). These combined extracts were dried over Na_2SO_4 and concentrated *in vacuo* to afford **243** (23.7 g, 81.0 mmol, 95%) as an orange oil which was used without further purification. Data is in agreement with literature values.[56,79]

N-[(8α,9*S*)-cinchonan-9-yl]-2-(diphenylphosphanyl)benzamide (235)

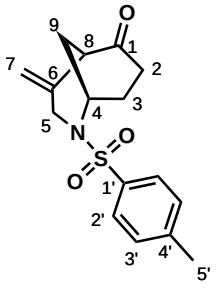
Prepared according to literature procedures.[56,79] To a solution of **243** (9.09 g, 31.1 mmol) in CH_2Cl_2 (300 mL) at 0 °C was added EDC·HCl (6.26 g, 32.7 mmol), DMAP (380 mg, 3.11 mmol), and 2-(diphenylphosphino)benzoic acid (10.0 g, 32.7 mmol). The resulting solution was allowed to warm to RT and was stirred for 26 h. Upon completion, CH_2Cl_2 was removed *in vacuo* then the resulting oil was dissolved in EtOAc (300 mL). The solution was washed with water (300 mL), followed by sat. aq. $NaHCO_3$ soln. (300 mL), followed by brine (300 mL). The organic layer was then dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude as an off-white foam. Purification by flash column chromatography (5:5:1 CH_2Cl_2, EtOAc, MeOH) afforded **235** (15.6 g, 26.8 mmol, 86%) as a white foam. Data is in agreement with literature values.[186]

MP: 104–108 °C (lit.[186] 98–100 °C); **IR** (thin film) $\tilde{\nu}_{max}^{-1}$ 3318 (N−H), 3052, 2943 (C−H), 1654 (C=O, C=C), 1508, 1482, 1456, 1434, 1321; ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 8.78 (d, J = 4.5 Hz, 1H), 8.40 (dd, J = 8.5, 1.5 Hz, 1H), 8.11 (dd, J = 8.5, 1.5 Hz, 1H), 7.70 (ddd, J = 8.5, 7.0, 1.5 Hz, 1H), 7.67 – 7.62 (m, 1H), 7.59 (ddd, J = 8.5, 7.0, 1.5 Hz, 1H), 7.39 – 7.34 (m, 2H), 7.34 – 7.22 (m, 10H), 7.21 –

7.14 (m, 2H), 6.92 (ddd, J = 7.5, 4.0, 1.5 Hz, 1H), 5.64 (ddd, J = 17.0, 10.5, 7.5 Hz, 1H, H-10), 5.40 (s, 1H), 4.97 – 4.88 (m, 2H, H-11), 3.07 (dd, J = 14.0, 10.0 Hz, 2H, H-2a), 2.90 (s, 1H) 2.57 (td, J = 14.5, 12.5, 5.5 Hz, 1H), 2.48 (d, J = 14.0 Hz, 1H, H-2b), 2.22 (s, 1H, H-3), 1.32–1.25 (m, 1H), 1.67 – 1.47 (m, 3H, H-4), 0.96 – 0.85 (m, 1H); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{38}H_{37}ON_3P)^+$ requires 582.2669, found 582.2662

6.3.5 Ag/Amine Co-Catalysed Synthesis of 166

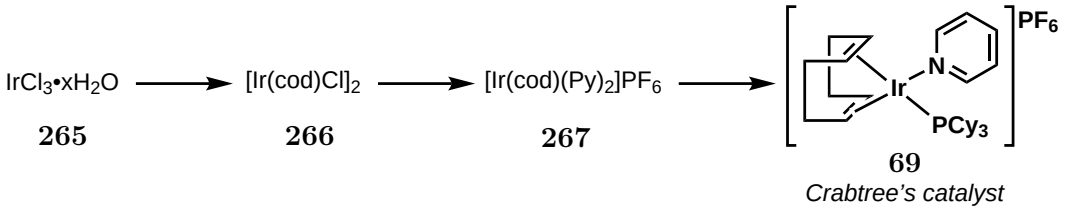
(1*S*,5*R*)-2-(4-methylbenzene-1-sulfonyl)-4-methylidene-2-azabicyclo[3.3.1] nonan-6-one (+)-166



To a flask containing *N*-Tosyl protected alkyne **230** (20.0 g, 65.5 mmol), $Ag(NTf_2)$ (1.26 g, 3.25 mmol), (+)-**128** (3.31 g, 6.50 mmol), **235** (3.78 g, 6.50 mmol), and 2,4-dinitrophenol (1.19 g, 6.46 mmol) was added isopropanol (325 mL). The flask was purged with N_2, then a reflux condenser was affixed. The resulting mixture was stirred under N_2 at RT for 5 mins, before heating to 60 °C and stirring for 48 h. Upon completion, the reaction mixture was cooled to RT and concentrated *in vacuo*. Purification by flash column chromatography afforded (+)-**166** as a white solid (18.4 g, 60.3 mmol, 93% yield, 98% ee). Trituration with Et_2O or recrystallization from MeOH was carried out to achieve enantiopurity (>99.5 : 0.5 er, >99% ee). Data are in agreement with those reported in the literature.[56]Preparation of the racemate (±)-**166** was carried out according to a literature procedure[56] using *N*-Tosyl protected alkyne **230** (19.4 g, 63.6 mmol), $Cu(OTf)_2$ (1.15 g, 3.18 mmol), PPh_3 (3.34 g, 12.7 mmol), and pyrrolidine (1.06 mL, 12.7 mmol) in THF (250 mL). Purification by flash column chromatography (20–33% EtOAc in petrol) afforded (±)-**166** (14.0 g, 45.9 mmol, 72%) as a white solid. For data, see p. 136.

6.3.6 Crabtree's Catalyst Synthesis

Crabtree's catalyst was synthesised in two steps from $[Ir(cod)Cl]_2$ according to the procedure published by Stork.[87] $[Ir(cod)Cl]_2$ could be purchased, or synthesised from $IrCl_3 \cdot H_2O$.[94]



Di-μ-chloro-bis(1,5-cyclooctadiene)diiridium(I) (266)

Prepared using a modification of literature procedures.[94] A three-neck flask was equipped with (i) a N_2 inlet and (ii) a reflux condenser with a septum in the top. Under a gentle stream of N_2, $IrCl_3 \cdot xH_2O$† (200 mg, 0.568 mmol), EtOH (3.4 mL), and H_2O (1.7 mL) were added, followed by 1,5-cyclooctadiene (0.60 mL). The third neck was connected to an oil bubbler, and the flow rate maintained at approximately 1 bubble per second. The dark red solution was heated to reflux and kept at that temperature for 16 h. Over time, the solution becomes lighter in colour, with a brick-red precipitate forming. The reaction must be monitored carefully. The flow of N_2 is neccessary to remove acetaldehyde formed by the oxidation of EtOH during the course of the reaction – a sealed system is not effective. However, a high flow rate will lead to a high rate of solvent evaporation which should be avoided. Upon completion, the reaction was cooled to RT and filtered. The brick red precipitate was washed with ice-cold MeOH then dried under vacuum to afford **266** (145 mg, 0.216 mmol, 76%). Experimental data agrees with literature data.[94]

†Use of the hydrate is important. The anhydrous form is insoluble and results in no reaction taking place. The exact stoichiometry of the purchased hydrate is unknown.

(η^4-1,5-cyclooctadiene)bis(pyridine)iridium(I) hexafluorophosphate (267)

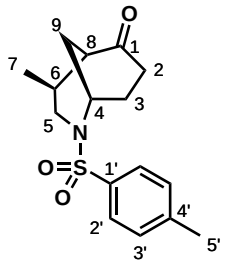
Prepared using a modification of literature procedures.[87] Pyridine (1.4 mL), acetone (9.2 mL), EtOH (4.8 mL), and H_2O (1.0 mL) were combined in a Schlenk flask and degassed by evacuating and backfilling with Ar three times. The solvent mixture was transferred to a flask containing **266** (660 mg, 0.984 mmol) and KPF_6 under N_2. The starting material (red powder) is observed to gradually dissolve over the course of the reaction. The mixture was stirred for 45 mins then was concentrated using a N_2 stream. The yellow residue was filtered, washed with H_2O, then dried under vacuum to afford **267** (948 mg, 1.50 mmol, 76%) as a fine yellow powder. Experimental data agrees with literature data.[85]

(η^4-1,5-Cyclooctadiene)(pyridine)(tricyclohexylphosphine)iridium(I) hexafluorophosphate (69)

Prepared using a modification of literature procedures.[87] To a solution of **267** (700 mg, 1.11 mmol) in CH_2Cl_2 (5 mL) at RT was added PCy_3 (345 mg, 1.22 mmol). The yellow solution becomes orange immediately as PCy_3 is added. After 15 mins, the solution was concentrated using a N_2 stream to remove most of the CH_2Cl_2 (approximately 1–2 mL is left), causing some precipitation of **69**. Et_2O was added, causing further precipitation, and the suspension was cooled to 0 °C and stirred at that temperature for 30 mins. The suspension was filtered, washing with Et_2O, and the orange solid was dried under vacuum to afford **69** (871 mg, 1.08 mmol, 97%). Experimental data agrees with literature data.[85]

6.3.7 Hydrogenation of *N*-Ts-Protected Bicycle 166

(1*S*,5*R*)-4-methyl-2-(4-methylbenzene-1-sulfonyl)-2-azabicyclo[3.3.1]--nonan-6-one (+)-245

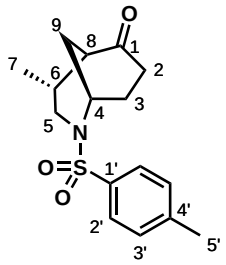


A pressurisable steel vessel (internal volume of 500 mL) was charged with alkene **166** (3.05 g, 10 mmol) and Crabtree's catalyst (160 mg, 0.20 mmol, 2 mol%), followed by CH_2Cl_2 (150 mL, 0.066 M). The vessel was sealed and, while stirring vigorously, filled with H_2 to a pressure of 9 bar. The reaction was stirred for 30 mins, then the pressure was released slowly (to prevent rapid evaporation of CH_2Cl_2). The solution was concentrated *in vacuo* to afford the crude as a dark orange oil. Three batches of crude reaction mixtures were combined and purified by flash column chromatography (20%–33% EtOAc in petrol) to afford **245** (7.93 g, 25.8 mmol, 85% yield from 9.15 g, 30.5 mmol of alkene **166**) as a white solid.

MP: 86–88 °C (>99% ee), 98-100 °C (rac); **IR** (thin film) $\tilde{\nu}_{max}^{-1}$ 2961 (C–H), 2928 (C–H), 1707 (C=O), 1331 (SO_2), 1162 (SO_2), 1093 (C–N); ^{1}**H-NMR** (500 MHz, $CDCl_3$): δ_H 7.68 (d, J = 8.0 Hz, 2H, H-2'), 7.32 (d, J = 8.0 Hz, 2H, H-3'), 4.21–4.12 (m, 1H, H-4), 3.26 (dd, J = 12.5, 5.0 Hz, 1H, H-5a), 3.00 (dd, J = 12.5, 6.0 Hz, 1H, H-5b), 2.59 (dt, J = 17.0, 8.0 Hz, 1H, H-2a), 2.43 (s, 3H, H-5'), 2.34 (ddd, J = 17.0, 7.5, 5.5 Hz, 1H, H-2b), 2.23 (d, J = 3.0 Hz, 1H, H-8), 2.16–2.08 (m, 2H, H-6,H-9a), 1.97–1.87 (m, 2H, H-3), 1.75 (dt, J = 14.0, 3.0 Hz, 1H, H-9b), 1.08 (d, J = 7.0 Hz, 3H, H-7); ^{13}**C-NMR** (126 MHz, $CDCl_3$): δ_C 213.4 (C-1), 143.6 (C-1'), 135.7 (C-4'),

129.8 (C-3'), 127.2 (C-2'), 48.1 (C-8), 47.2 (C-4), 45.4 (C-5), 35.6 (C-2), 31.9 (C-6), 28.1 (C-3), 26.0 (C-9), 21.6 (C-5'), 18.5 (C-7); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{16}H_{22}O_3N^{32}S)^+$ requires 308.1315, found 308.1316; $[\boldsymbol{\alpha}]_D^{25} = +78.9$ (c 1.0, $CHCl_3$, >99% ee).

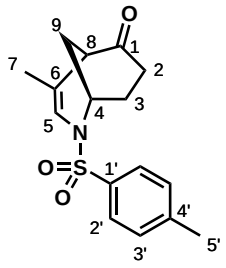
(1*S*,5*R*)-4-methyl-2-tosyl-2-azabicyclo[3.3.1]nonan-6-one (246)



To a solution of alkene **166** (31 mg, 0.10 mmol) in *i*-PrOH (0.20 mL) at RT under Ar was added $PhSiH_2$ (12 µL, 0.10 mmol) and *tert*-butyl hydroperoxide (12 µL, 0.15 mmol) followed by $Mn(dpm)_3$ (6 mg, 0.01 mmol). The reaction was stirred at RT for 16 h until complete, before concentrating under vacuum. Purification by flash column chromatography (20% to 40% EtOAc/pentane) afforded **246** (21 mg, 0.068 mmols, 68%, >20:1 dr) as a white solid.

MP: 88 – 91 °C; **IR** (thin film) $\tilde{\nu}_{max}^{-1}$ 2930 (C–H), 1703 (C=O), 1339 (SO_2), 1190, 1177 (SO_2), 1096 (C–N); ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 7.72 (dq, J = 8.5, 2.0 Hz, 2H, 2'), 7.35 – 7.29 (m, 2H, 3'), 4.34 – 4.28 (m, 1H, 4), 4.18 (s, 1H), 3.84 (dd, J = 13.5, 6.0 Hz, 1H, 5a), 2.87 – 2.78 (m, 1H, 5b), 2.49 – 2.43 (m, 5H, 2a, 8, 5'), 2.12 (ddd, J = 18.5, 11.0, 8.5 Hz, 1H, 2b), 2.05 – 1.86 (m, 5H, 3, 6, 9), 0.86 (d, J = 7.0 Hz, 2H, 7); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 211.1 (C-1), 143.6 (C-1'), 137.4 (C-4'), 130.0 (C-3'), 127.1 (C-2'), 49.0 (C-8), 47.4 (C-5), 46.1 (C-4), 39.3 (C-2), 32.9 (C-6), 32.8 (C-3), 28.7 (C-9), 21.7 (C-5'), 16.9 (C-7).

(1*S*,5*R*)-4-methyl-2-(4-methylbenzene-1-sulfonyl)-2-azabicyclo[3.3.1]non--3-en-6-one (247)

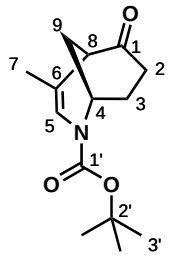


Enamide **247** was isolated as a side-product in the hydrogenation of **166**. Typically, **247** was isolated in 10–15% yield under the optimal hydrogenation conditions using Crabtree's catalyst.

MP: 120–122 °C (racemic); **IR** (thin film) $\tilde{\nu}_{max}^{-1}$ 2959 (C−H), 2933 (C−H), 1709 (C=O), 1341 (SO_2), 1162 (SO_2), 1094 (C−N); ^{1}**H-NMR** (500 MHz, $CDCl_3$): δ_H 7.69 (d, J = 8.0 Hz, 2H, H-2'), 7.31 (d, J = 8.0 Hz, 2H, H-3'), 6.82 (d, J = 1.5 Hz, 1H, H-5), 4.11–4.15 (m, 1H, H-4), 2.70–2.75 (m, 1H, H-8), 2.57 (ddd, J = 15.5, 13.5, 7.5 Hz, 1H, H-2a), 2.41 (s, 3H, H-5'), 2.37 (dddd, J = 14.0, 7.5, 3.5, 1.5 Hz, 1H, H-3a), 2.15 (dd, J = 15.7, 6.0 Hz, 1H, H-2b), 1.85—1.92 (m, 1H, H-3b), 1.83 (dt, J = 13.0, 2.5, 2.5 Hz, 1H, H-9a), 1.65 (d, 3H, J = 1.5 Hz, H-7), 1.27–1.34 (m, 1H, H-9b); ^{13}**C-NMR** (126 MHz, $CDCl_3$): δ_C 208.3 (C-1), 144.0 (C-1'), 135.9 (C-4'), 130.0 (C-3'), 126.9 (C-2'), 122.9 (C-5), 113.7 (C-6), 49.8 (C-8), 47.7 (C-4), 34.6 (C-3), 33.7 (C-2), 27.8 (C-9), 21.7 (C-5'), 19.5 (C-7); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{16}H_{20}O_2N^{32}S)^+$ requires 306.1158, found 306.1159.

6.3.8 Hydrogenation of *N*-Boc- and *N*-Ns-Protected Bicycles 197 and 195

(1*S*,5*R*)-*tert*-butyl 4-methyl-6-oxo-2-azabicyclo[3.3.1]non-7-ene--2-carboxylate (263)

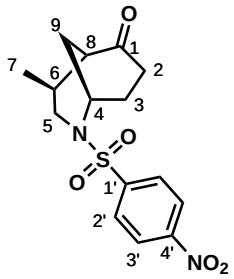


Enamide **263** was isolated during the attempted hydrogenation of *N*-Boc--protected bicycle **197**. Alkene **197** (50 mg, 0.20 mmol) and Crabtree's catalyst (8 mg, 0.01 mmol, 5 mol%) were dissolved in CH_2Cl_2 (2.5 mL) in a 12 mL vial and placed into the centre of a pressurisable vessel. While stirring vigorously, the vessel was filled with H_2 to a pressure of 9 bar. The reaction was stirred for 1 h then the pressure was released (slowly, to avoid rapid evaporation of CH_2Cl_2). The solution was concentrated *in vacuo* and the crude residue purified by flash column chromatography (1:1 petrol/Et_2O) to afford alkene **263** (34 mg, 0.14 mmol, 70%) as a colourless oil.

^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H (1:1 mixture of rotamers) 6.99 (s, 0.5H, H-5), 6.81 (s, 0.5H, H-5), 4.44 (s, 0.5H, H-4), 4.29 (s, 0.5H, H-4), 2.78–2.84 (m, 1H, H-8), 2.56 (tt, J = 14.5, 7.0, 1H, H-2a), 2.20–2.36 (m, 1H, H-3a), 2.15 (dt, J = 16.0, 4.5, 1H, H-2b), 2.02 (tt, J = 12.0, 2.5, 1H, H-9a), 1.70–1.97 (m, 2H, H-3b,9b), 1.64 (s, 3H, H-7), 1.50 (s, 9H, H-3'); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 209.7 (C-1), 209.5 (C-1), 152.3 (C-1'), 151.7 (C-1'), 123.6 (C-5), 123.4 (C-5), 111.7 (C-6), 110.8 (C-6),

81.4 (C-2'), 81.2 (C-2'), 50.4 (C-8), 50.2 (C-8), 45.7 (C-4), 44.8 (C-4), 33.9 (C-2), 33.8 (C-2), 33.6 (C-3), 33.0 (C-3), 29.5 (C-9), 29.3 (C-9), 28.4 (C-3'), 19.5 (C-7), 19.5 (C-7); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ $(C_{14}H_{23}O_3N^{23}Na)^+$ requires 276.1570, found 276.1572.

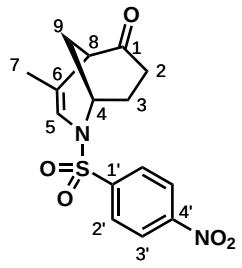
(1*S*,5*R*)-4-methyl-2-(4-nitrobenzene-1-sulfonyl)-2-azabicyclo[3.3.1]nonan-6-one (264)



A pressurisable vessel (internal volume of 500 mL) was charged with *N*-Nosyl-protected alkene **195** (498 mg, 1.48 mmol) and Crabtree's catalyst (24 mg, 0.03 mmol, 2 mol%), followed by CH_2Cl_2 (60 mL). The vessel was sealed and, while stirring vigorously, filled with hydrogen gas to 9 bar. The reaction was stirred for 3 h, then the pressure was released slowly. The solution was concentrated *in vacuo* to afford a yellow solid, which was purified by flash column chromatography (25% to 33% EtOAc in petrol) to afford **264** (460 mg, 1.36 mmol, 92%) as a white solid. **MP**: 155–158 °C (racemic); **IR** (thin film) $\tilde{\nu}_{max}{}^{-1}$ 2929 (C-H), 1707 (C=O), 1529 (NO_2), 1349 (NO_2), 1309 (SO_2), 1166 (SO_2); ^{1}**H-NMR** (500 MHz, $CDCl_3$): δ_H 8.36–8.41 (m, 2H, H-3'), 7.97–8.02 (m, 2H, H-2'), 4.24 (td, J = 5.0, 2.0 Hz, 1H, H-4), 3.31 (dd, J = 12.5, 5.0 Hz, 1H, H-5a), 3.11 (dd, J = 12.5, 5.0 Hz, 1H, H-5b), 2.57 (dt, J = 17.0, 8.0 Hz, 1H, H-2a), 2.36–2.44 (m, 1H, H-2b), 2.29 (q, J = 3.0 Hz, 1H, H-8), 2.15–2.20 (m, 1H, H-6), 2.13 (q, J = 3.0 Hz, 1H, H-9a), 1.96–2.06 (m, 1H, H-3a), 1.86–1.94 (m, 1H, H-3b), 1.81 (dt, J = 14.0, 3.0 Hz, 1H, H-9b), 1.09 (d, J =

7.0 Hz, 3H, H-7); ^{13}**C-NMR** (126 MHz, $CDCl_3$): δ_C 212.7 (C-1), 150.2 (C-1'), 145.0 (C-4'), 128.5 (C-2'), 124.7 (C-3'), 47.9 (C-8), 47.8 (C-4), 45.7 (C-5), 35.7 (C-2), 32.0 (C-6), 28.1 (C-3), 25.9 (C-9), 18.4 (C-7); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{15}H_{18}O_5N_2$ $^{23}Na^{32}S)^+$ requires 361.0829, found 361.0829

(1*S*,5*R*)-4-methyl-2-((4-nitrophenyl)sulfonyl)-2-azabicyclo[3.3.1]non--3-en-6-one (411)

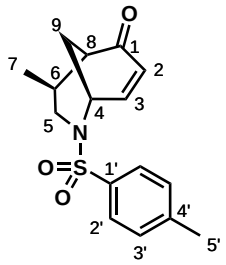


Enamide **411** was isolated as a side-product during hydrogenation of **195** in <10% yield.

IR (thin film) $\tilde{\nu}_{max}^{-1}$ 2942 (C−H), 1771, 1716, 1532 ((NO_2)), 1368 (NO_2), 1349 (SO_2), 1280, 1165 (SO_2), 1135; ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 8.41–8.35 (m, 2H, H-3'), 8.04–7.97 (m, 2H, H-2'), 6.82 (d, J = 1.5 Hz, 1H, H-5), 4.17 (t, J = 3.0 Hz, 1H, H-4), 2.76 (d, J = 2.5 Hz, 1H, H-8), 2.59 (ddd, J = 15.5, 13.5, 7.5 Hz, 1H, H-2a), 2.40 (dddd, J = 13.5, 7.5, 3.0, 1.3 Hz, 1H, H-3a), 2.21 (dd, J = 15.5, 6.0 Hz, 1H, H-2b), 1.96 (ddd, J = 13.5, 6.0, 3.0 Hz, 1H, H-3b), 1.90 (dt, J = 13.0, 2.5 Hz, 1H, H-9a), 1.68 (d, J = 1.5 Hz, 3H, H-7), 1.33 (dq, J = 13.0, 3.5 Hz, 1H, H-9b); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 207.3 (C-1), 150.3 (C-1'), 144.4 (C-4'), 128.1 (C-2'), 124.8 (C-3'), 121.9 (C-5), 115.8 (C-6), 49.6 (C-8), 48.3 (C-4), 34.5 (C-3), 33.6 (C-2), 27.9 (C-9), 19.6 (C-7).

6.3.9 Synthesis of Functionalised AB Core 144

(1*S*,5*R*)-4-methyl-2-(4-methylbenzene-1-sulfonyl)-2-azabicyclo[3.3.1]non--7-en-6-one (+)-268

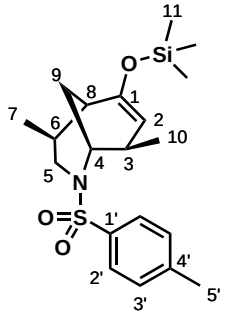


Prepared using the Stahl method.[102] To a solution of ketone **245** (6.14 g, 20 mmol) and $Pd(TFA)_2$ (200 mg, 0.06 mmol, 3 mol%) in AcOH (60 mL) was added DMSO (0.09 mL, 1.2 mmol, 6 mol%). A reflux condenser was attached, then the system was flushed with O_2, and an O_2 ballon was inserted through a septum in the top of the reflux condenser. The reaction was heated to 80 °C for 13 h (during heating the solution turned dark brown). After completion, the reaction was cooled to RT and concentrated *in vacuo*. Purification by flash column chromatography (30% EtOAc in petrol) afforded enone **268** (5.41 g, 17.7 mmol, 89%) as a white solid.

MP: 124–126 °C (rac), 115–118 °C (>99% ee); **IR** (thin film) $\tilde{\nu}_{max}^{-1}$ 2967 (C−H), 2927 (C−H), 2873 (C−H), 1678 (C=O), 1342 (SO_2), 1163 (SO_2), 1091 (C−N); ^{1}**H-NMR** (500 MHz, $CDCl_3$): δ_H 7.71–7.63 (m, 2H, H-2'), 7.33–7.25 (m, 2H, H-3'), 6.30 (ddd, J = 10.0, 6.0, 1.5 Hz, 1H, H-3), 6.06 (dd, J = 10.1, 1.0 Hz, 1H, H-2), 4.63 (dt, J = 6.0, 3.0 Hz, 1H, H-4), 3.45–3.37 (d, J = 12.5 Hz, 1H, H-5a), 3.01 (dd, J = 12.5, 4.0 Hz, 1H, H-5b), 2.42 (s, 3H, H-5'), 2.39–2.32 (m, 1H, H-8), 2.26 (dtd, J = 13.5, 3.0, 2.0 Hz, 1H, H-9a), 2.06–1.96 (m, 2H, H-6, H-9b), 1.17 (d, J = 7.0 Hz, 3H, H-7); ^{13}**C-NMR** (126 MHz, $CDCl_3$): δ_C 201.3 (C-1), 143.9 (C-1'), 140.7 (C-3),

136.6 (C-4'), 132.9 (C-2), 130.0 (C-3'), 127.2 (C-2'), 47.1 (C-4), 46.6 (C-8), 43.8 (C-5), 31.3 (C-6), 27.7 (C-9), 21.7 (C-5'), 17.5 (C-7); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{16}H_{20}O_2N^{32}S)^+$ requires 306.1158, found 306.1159; $[\boldsymbol{\alpha}]_D^{25}$ = +382.04 (c 1.0, $CHCl_3$); **HPLC**: (Chiralpak AD-H, hexane/isopropanol 75:25, 1.0 mL min^{-1}, λ=240 nm) t_R = 10.0 min (minor), 15.8 min (major).

(1*S*,5*R*)-4,8-dimethyl-2-(4-methylbenzene-1-sulfonyl)-6-
-[(trimethylsilyl)oxy]-2-azabicyclo[3.3.1]non-6-ene (269)

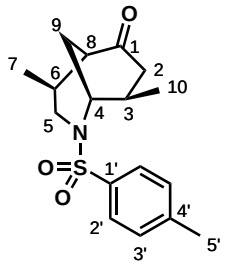


To a slurry of CuI (210 mg, 1.10 mmol) in dry THF (5 mL) at 0 °C was added MeLi (1.6 M in Et_2O, 1.31 mL, 2.10 mmol) slowly. (Note: the off-white slurry turns to a dark yellow suspension on addition of MeLi. The colour darkens slightly as addition continues. Throughout the course of addition the suspension becomes a yellow solution, before becoming colourless after addition is complete, indicating complete formation of $Me_2CuLi \cdot LiI$). The resulting solution was stirred at 0 °C for 15 mins, before cooling to –78 °C. To the solution of $Me_2CuLi \cdot LiI$ at –78 °C was added a solution of enone **268** (305 mg, 1 mmol) in THF (5 mL) slowly, followed by addition of Et_3N (0.56 mL, 4.0 mmol) then TMSCl (0.38 mL, 3.0 mmol). (Note: The solution becomes yellow on addition of enone **268**, and darkens on addition of TMSCl). After 30 mins, (completion of reaction checked by TLC; reaction is typically complete within a few minutes but is left for 30 mins on larger scales) the

reaction was diluted with Et_2O (40 mL, to a total volume 50 mL) and transferred to a separation funnel. The solution, while still cold, was washed with sat. aq. NH_4Cl soln. (4 × 25 mL) until the aq. phase was no longer blue. (note: TLC typically indicates that no back-extraction of the aq. layer is required, and that TMS enol ether **269** is stable to sat. aq. NH_4Cl soln. during washing.) The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to afford silyl enol ether **269** (391 mg, 1.00 mmol, quant.) as a white-yellow solid which was used without further purification.

MP: 54–56 °C (racemic), 74–77 °C (>99% ee); **IR** (thin film) $\tilde{\nu}_{max}^{-1}$ 3016 (C−H), 2957 (C−H), 1661 (C=C), 1332 (SO_2), 1252 (Si−C), 1194 (C−O), 1166 (SO_2), 1099 (C−N), 1011 (Si−O); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H 7.76 (d, J = 8.0 Hz, 2H, H-2'), 6.83 (d, J = 8.0 Hz, 2H, H-3'), 4.54 (d, J = 4.0 Hz, 1H, H-2), 4.01 (d, J = 3.5 Hz, 1H, H-4), 3.46 (d, J = 12.0, 1H, H-5a), 3.28 (dd, J = 12.5, 3.5 Hz, 1H, H-5b), 1.95 (qd, J = 7.5, 4.0 Hz, 1H, H-3), 1.90 (s, 3H, H-5'), 1.77–1.84 (m, 3H, H-6, H-8, H-9a), 1.36 (ddd, J = 13.5, 5.0, 3.5 Hz, 3H, H-9b), 0.97 (d, J = 7.0 Hz, 3H, H-7), 0.78 (d, J = 7.0 Hz, 3H, H-10), 0.06 (s, 9H, H-11); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ_C 152.9 (C-1), 142.5 (C-1'), 139.5 (C-4'), 129.7 (C-3'), 127.4 (C-2'), 108.2 (C-2), 53.3 (C-4), 44.5 (C-5), 39.4 (C-8), 33.7 (C-3), 29.9 (C-6), 22.4 (C-9), 21.3 (C-10), 21.2 (C-5'), 17.1 (C-7), 0.3 (C-11); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{20}H_{32}O_3N^{32}S^{28}Si)^+$ requires 394.1867, found 394.1864.

(1*S*,5*R*)-4,8-dimethyl-2-(4-methylbenzene-1-sulfonyl)-2-azabicyclo[3.3.1]--nonan-6-one (270)

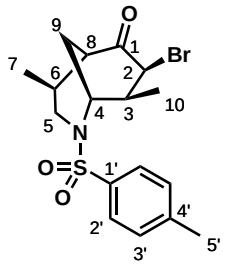


Ketone **270** was prepared from silyl enol ether **269** *in situ*. After formation of **269** was complete (by TLC), the reaction was warmed to RT and HCl (2 M) was added. The solution was stirred until formation of methyl ketone **270** was complete (confirmed by TLC). The reaction was then diluted with Et_2O and washed with sat. aq. NH_4Cl soln. until the aq. phase was no longer blue. The organic layer was dried of $MgSO_4$ and concentrated *in vacuo* to afford ketone **270**.

IR (thin film) $\tilde{\nu}_{max}^{-1}$ 2960 (C−H), 2925 (C−H), 1708 (C=O), 1330 (SO_2), 1155 (SO_2), 1092 (C−N); ^{1}**H-NMR** (400 MHz, C_6D_6): δ_H 7.66 (d, J = 8.0 Hz, 2H, H-2'), 6.83–6.87 (m, 2H, H-3'), 3.84 (tt, J = 3.0, 1.5 Hz, 1H, H-4), 3.06 (dd, J = 13.0, 4.0 Hz, 1H, H-5a), 2.84 (dd, J = 13.0, 4.0 Hz, 1H, H-5b), 2.18 (dd, J = 16.0, 7.0 Hz, 1H, H-2a), 1.89–2.01 (m, 1H, H-6), 1.94 (s, 3H, H-5'), 1.80 (q, J = 3.0 Hz, H-8), 1.64–1.79 (m, 1H, H-3), 1.59 (ddt, J = 13.5, 3.0, 1.5 Hz, 1H, H-9a), 1.53 (dd, J = 16.0, 8.0 Hz, 1H, H-2b), 1.26 (dt, J = 14.0, 3.0 Hz, 1H, H-9b), 0.80 (d, J = 7.0 Hz, 3H, H-7), 0.65 (d, J = 7.0 Hz, 3H, H-10); ^{13}**C-NMR** (101 MHz, C_6D_6): δ_C 212.2 (C-1), 143.0 (C-1'), 138.1 (C-4'), 129.8 (C-3'), 127.5 (C-2'), 54.2 (C-4), 46.7 (C-8), 44.9 (C-5), 44.7 (C-2), 32.4 (C-6), 31.9 (C-3), 21.8 (C-9), 21.4 (C-10), 21.2 (C-5'), 17.4 (C-7); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{17}H_{24}O_3N^{32}S)^+$ requires 322.1471, found 322.1474

(1*S*,5*R*)-7-bromo-4,8-dimethyl-2-(4-methylbenzene-1-sulfonyl)-

-2-azabicyclo[3.3.1]nonan-6-one (+)-273



To a solution of crude silyl enol ether **269** (16.7 mmol) in dry THF (150 mL) at –78 °C was added $NaHCO_3$ (2.94 g, 20.0 mmol) followed by *N*-bromosuccinimide (3.27 g, 20.0 mmol). The resulting suspension was stirred at –78 °C for 30 minutes (completion of reaction checked by TLC, typically complete within a few minutes but left for 30 mins on large scale). The reaction was then diluted with ether (200 mL) and washed with sat. aq. $NaHCO_3$ soln. (300 mL). The aq. layer was extracted with ether (3 × 150 mL), then the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford bromide **273** (6.42 g, 16.1 mmol, 96% yield over two steps) as a yellow-white solid which was used immediately without further purification.[†]

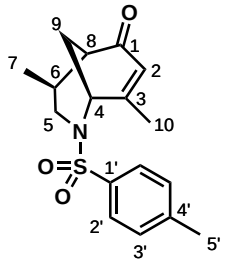
MP: 160–162 °C (racemic); **IR** (thin film) $\tilde{\nu}_{max}{}^{-1}$ 3018 (C–H), 2925 (C–H), 1721 (C=O), 1345 (SO_2), 1165 (SO_2), 1099 (C–N); ^{1}**H-NMR** (400 MHz, C_6D_6): δ_H 7.63 (d, J = 8.0, 2H, H-2'), 6.79 (d, J = 8.0, 1H, H-3'), 4.85 (d, J = 6.0, 1H, H-2), 3.63–3.71 (m, 1H, H-4), 3.08 (dd, J = 12.5, 5.5, 1H, H-5a), 2.66–2.76 (m, 1H, H-3), 2.45 (dd, J = 12.5, 8.0, 1H, H-5b), 1.92–1.97 (m, 1H, H-6), 1.89 (s, 3H, H-5'), 1.59 (dt, J = 14.5, 3.0, 1H, H-9a), 1.43 (ddd, J = 12.0, 7.0, 2.0, 1H, H-8), 1.14–1.23 (m, 1H, H-9b), 0.87 (d, J = 7.1, 3H, H-7), 0.43 (d, J = 6.8, 3H, H-10); ^{13}**C-NMR**

[†]Decomposition occurs quickly in solution. Stereochemistry at C-2 and C-3 was determined by X-ray crystallography.

(101 MHz, C_6D_6): δ_C 201.7 (C-1), 143.3 (C-1'), 136.3 (C-4'), 129.8 (C-3'), 127.7 (C-2'), 56.3 (C-2), 55.0 (C-4), 47.6 (C-6), 45.6 (C-5), 42.0 (C-3), 31.6 (C-8), 22.0 (C-9), 21.1 (C-5'), 18.6 (C-10), 16.9 (C-7); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ $(C_{17}H_{22}O_2N^{79}Br^{32}S^{23}Na)^+$ requires 422.0396, found 422.0395; $[\boldsymbol{\alpha}]_D^{25}$ = +35.93 (c 1.0, $CHCl_3$).

(1*S*,5*R*)-4,8-dimethyl-2-(4-methylbenzene-1-sulfonyl)-2-azabicyclo-

-[3.3.1]non-7-en-6-one (+)-271

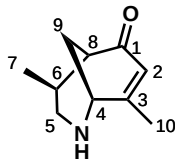


A solution of crude bromide **273** (6.69 g, 16.8 theoretical mmol), Li_2CO_3 (3.10 g, 41.9 mmol), and LiBr (2.18 g, 25.14 mmol) in DMF (70 mL) was heated to reflux (125 °C) for 3 h. The reaction was cooled to RT and diluted with EtOAc (180 mL), then washed with HCl (2 M, 2 × 150 mL) followed by brine (4 × 200 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give the crude as a brown solid (4.80 g, 90% crude yield). Purification by flash column chromatography (25% EtOAc in petrol) afford β-methyl enone **271** as a white solid, however it could be used in the following step without purification.

MP: 108–110 °C (racemic), 91–93 °C (>99% ee); **IR** (thin film) $\tilde{\nu}_{max}^{-1}$ 2923 (C−H), 1669 (C=O), 1329 (SO_2), 1160 (SO_2), 1094 (C−N); ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 7.72 (d, J = 8.0 Hz, 2H, H-2'), 7.29 (d, J = 8.0 Hz, 2H, H-3'), 5.98–6.03 (m, 1H, H-2), 4.51 (t, J = 3.0, 3.5 Hz, 1H, H-4), 3.31 (d, J = 14.0 Hz, 1H, 5a), 3.21 (dd, J = 14.0 Hz, 4.0, 1H, H-5b), 2.41 (s, 3H, H-5'), 2.27 (q, J = 3.0 Hz, 1H, H-8), 2.13 (dt,

J = 13.5, 3.0 Hz, 1H, H-9a), 1.96 (dt, J = 13.5, 3.5 Hz, 1H, H-9b), 1.87–1.91 (m, 1H, H-6), 1.87 (d, J = 1.5 Hz, 3H, H-10), 0.88 (d, J = 7.0 Hz, 3H, H-7); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 201.4 (C-1), 154.8 (C-3), 143.6 (C-1'), 137.7 (C-4'), 129.8 (C-3'), 129.4 (C-2), 127.2 (C-2'), 51.5 (C-4), 45.6 (C-8), 43.8 (C-5), 31.4 (C-6), 27.1 (C-9), 22.1 (C-10), 21.6 (C-5'), 17.6 (C-7); $[\boldsymbol{\alpha}]_D^{25}$ = +385.86 (c 1.0, $CHCl_3$);

(1*S*,5*R*)-4,8-dimethyl-2-azabicyclo[3.3.1]non-7-en-6-one (144)



To a solution of crude β-methyl enone **271** (638 mg, 2.0 theoretical mmol) in dry THF (20 mL) at 0 °C was added NaHMDS (4.20 mL, 1.0 M, 4.20 mmol) slowly. The resulting orange solution was stirred at 0 °C for 30 mins, over which time it became a dark red-brown colour. Freshly prepared sodium naphthalene solution[†] (8.00 mL, 1.0 M, 8.0 mmol) was added slowly, with the blue-black colour dissipating during addition until approx. 3 equivalents had been added, after which the solution remained black for some time. The solution was stirred at 0 °C for 30 mins (after this time, the colour of the solution lightened but remained brown) before diluting with Et_2O (30 mL) and quenching with water (20 mL). The layers were separated and the aq. layer was extracted with CH_2Cl_2/IPA (9:1) (5 × 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude as a brown solid. Purification by flash column chromatography (EtOAc then 33% MeOH in EtOAc) afforded amine **144** (273 mg, 1.65 mmol, 83%) as a dark orange oil.

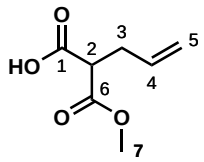
[†]Sodium naphthalene solution was prepared by sonicating an equimolar mixture of Na and naphthalene in dry THF (1 M) for 30–60 mins.

IR (thin film) $\tilde{\nu}_{max}{}^{-1}$ 3316 (N−H), 2959 (C−H), 2919 (C−H), 1661 (C=O); ^{1}**H-NMR** (400 MHz, C_6D_6): δ_H 6.02 (s, 1H, H-2), 2.81–2.86 (m, 1H, H-4), 2.77 (dd, J = 12.5, 4.5 Hz, 1H, H-5a), 2.19–2.23 (m, 1H, H-8), 2.15–2.19 (m, 1H, H-5b), 1.91 (app.dt, J = 12.5, 3.0, 1H, H-9a), 1.69–1.78 (m, 1H, H-6), 1.54–1.67 (br.s, 1H, NH), 1.46–1.54 (m, 1H, H-9b), 1.38 (d, J = 1.5 Hz, 3H, H-10), 1.03 (d, J = 7.0 Hz, 3H, H-7); ^{13}**C-NMR** (101 MHz, C_6D_6): δ_C 201.1 (C-1), 154.9 (C-3), 127.8 (C-2), 52.3 (C-4), 47.0 (C-8), 43.3 (C-5), 31.3 (C-6), 28.2 (C-9), 21.5 (C-10), 17.4 (C-7); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{10}H_{16}ON)^+$ requires 166.1226, found 166.1227.

6.4 Compounds Synthesised in Chapter 4

6.4.1 Synthesis of Acid Coupling Partners 285 and 290

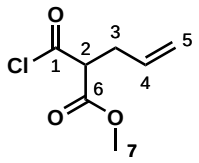
2-allyl-3-methoxy-3-oxopropanoic acid (412)



Prepared according to a literature procedure.[63] A solution of dimethyl allyl malonate (4.34 g, 25.2 mmol) in MeOH (4 mL) was cooled to 0 °C, and a solution of KOH (1.69 g, 30.2 mmol) in MeOH (10 mL) was added dropwise. The ice bath was removed and the reaction was stirred at RT for 16 h, before diluting with water (20 mL) and extracting with Et_2O (20 mL). The aqueous layer was acidified to pH 1-2 with HCl (6 M), then was extracted with CH_2Cl_2 (6 × 25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford acid **412** as a colourless oil (3.98 g, 25.2 mmol, quant.), which was used without further purification. Data is in agreement with literature values.[119]

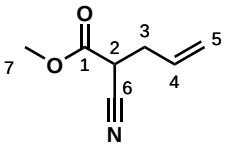
^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 10.47 (s, 1H), 5.86–5.71 (m, 1H), 5.20–5.04 (m, 2H), 3.76 (d, J = 2.0 Hz, 3H), 3.50 (td, J = 7.5, 2.0 Hz, 1H), 2.74–2.59 (m, 2H).

ethyl 2-(chlorocarbonyl)pent-4-enoate (285)



Prepared according to a literature procedure.[63] To a soluton of **412** (1.03 g, 6.53 mmol) in pentane (30 mL) was added oxalyl chloride (1.12 mL, 13.1 mmol) dropwise, followed by catalytic DMF (50 µL). The reaction was stirred at RT for 3 h, then the pentane layer was decanted off into a separate flask and concentrated *in vacuo*, to afford acid chloride **285** as a brown oil which was used immediately without further purification as the product is highly unstable.

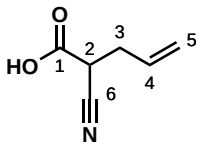
methyl 2-cyanopent-4-enoate (289)



Prepared following a literature procedure.[118] To a grey suspension of NaH (5.21 g, 60% dispersion in mineral oil, 130 mol) in dry THF under N_2 was added methyl 2-cyanoacetate (12.0 mL, 136 mol) dropwise (caution: exothermic, H_2 release). After 15 mins the white suspension was cooled to 0 °C, and allyl bromide (10.7 mL, 124 mol) was added dropwise with vigorous stirring. After completion of addition, the ice bath was removed and the reaction was left to stir at RT for 19 h. The reaction was quenched with water (200 mL), the layers were separated and the aq. layer was extracted with Et_2O (3 × 200 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford **289** (3.30 g, 23.7 mmol, 19%) as a

clear liquid, used without further purification. Data agrees with literature values.[120] ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 5.82 (ddt, J = 17.0, 10.0, 7.0, 1H), 5.21–5.30 (m, 2H), 3.82 (s, 3H), 3.58 (dd, J = 7.5, 6.0, 1H), 2.64–2.72 (m, 2H).

2-cyanopent-4-enoic acid (290)



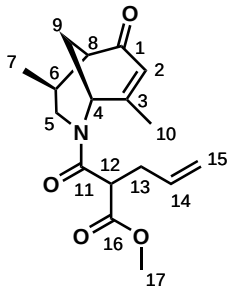
Prepared following a literature procedure.[119] To a solution of KOH (1.59 g, 28.4 mmol; finely ground) in MeOH (24 mL) was added ester **289** (3.30 g, 23.7 mmol). The resulting solution was stirred at RT under N_2 for 1 d. The reaction was diluted with EtOAc and acidified with HCl (1 M). The layers were separated and the aq. layer was extracted with EtOAc (5 × 50 mL) (note: the pH of the aq. layer should be checked after each extraction and re-acidified if necessary). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford **290** (2.35 g, 16.9 mmol, 71% yield) as a viscous orange oil, used without further purification. Data was in agreement with literature values.[119]

IR (thin film) $\tilde{\nu}_{max}^{-1}$ 3086 (br, O–H), 1733 (C=O), 1645 (C=C), 1991; ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 9.74 (s, 1H, CO_2H), 5.77 (ddt, J = 17.0, 10.0, 7.0, 1H, H-4), 5.13–5.33 (m, 2H, H-5), 3.61 (dd, J = 7.5, 6.0, 1H, H-2), 2.57–2.73 (m, 2H, H-3); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 170.9 (C-1), 131.0 (C-4), 120.7 (C-5), 115.5 (C-6), 37.7 (C-2), 33.8 (C-3).

6.4.2 Amide Coupling Reactions

methyl 2-(4,8-dimethyl-6-oxo-2-azabicyclo[3.3.1]non-7-ene-

-2-carbonyl)pent-4-enoate (286)



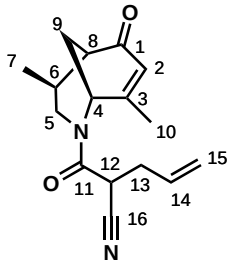
To a solution of amine **144** (245 mg, 1.48 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added triethylamine (0.33 mL, 2.4 mmol) followed by dropwise addition of a solution of acid chloride **285** (419 mg, 2.37 mmol) in CH_2Cl_2 (1 mL). The resulting solution was stirred at 0 °C for 3 h until complete by TLC. The reaction mixture was concentrated then partitioned between Et_2O (20 mL) and H_2O (20 mL), the layers were separated and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford an orange oil. Purification by flash column chromatography (40% EtOAc/pentane) afforded the coupled product **286** (317 mg, 1.04 mmol, 70%) as an orange oil as a mixture of rotameric diasteromers.

IR (thin film) $\tilde{\nu}_{max}{}^{-1}$ 2922 (C−H), 1710 (C=O), 1645 (C=C), 1199 (C−O); ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 6.08–6.04 (m, 1H, H-2), 5.88–5.63 (m, 1H, H-14), 5.38 (d, J = 3.2 Hz, 1H, H-4), 5.22–4.99 (m, 2H, H-15), 3.72 (s, 2H, H-17), 3.67 (s, 1H, H-17), 3.63 (t, J = 7.3 Hz, 1H, H-12), 3.53 (d, J = 13.6 Hz, 1H, H-5a), 3.43–3.30 (m, 1H, H-5b), 2.76–2.70 (m, 1H, H-13a), 2.66 (dd, J = 8.2, 7.0 Hz, 1H, H-13b), 2.42–2.32 (m, 1H, H-8), 2.21–2.09 (m, 1H, H-9a), 2.06–1.95 (m, 2H, H-6, 9b), 1.93

(d, J = 1.5 Hz, 1H, H-10), 1.89 (d, J = 1.5 Hz, 2H, H-10), 1.17 (d, J = 6.5 Hz, 1H, H-7), 1.14 (d, J = 6.5 Hz, 2H, H-7); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ_C 201.6 (C-1), 201.5 (C-1), 169.9 (C-16), 169.8 (C-16), 168.5 (C-11), 156.3 (C-3), 155.9 (C-3), 134.8 (C-14), 134.5 (C-14), 129.5 (C-2), 129.3 (C-2), 117.7 (C-15), 117.6 (C-15), 52.6 (C-17), 52.6 (C-17), 49.2 (C-12), 49.0 (C-12), 47.8 (C-4), 47.7 (C-4), 46.2 (C-8), 46.1 (C-8), 45.0 (C-5), 44.8 (C-5), 33.7 (C-13), 33.3 (C-13), 31.6 (C-6), 31.3 (C-6), 26.4 (C-9), 26.4 (C-9), 22.1 (C-10), 22.1 (C-10), 17.6 (C-7), 17.4 (C-7); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{17}H_{24}O_4N)^+$ requires 306.1700, found 306.1699.

2-(4,8-dimethyl-6-oxo-2-azabicyclo[3.3.1]non-7-ene-2-carbonyl)-

-pent-4-enenitrile (292)

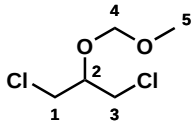


To a solution of amine **144** (977 mg, 5.91 mmol), acid **290** (1.04 g, 8.28 mmol), and DMAP (181 mg, 1.48 mmol) in CH_2Cl_2 (30 mL) at RT was added EDC · HCl (1.70 g, 8.87 mmol). The solution was stirred at RT for 2 h. The reaction was quenched with water (30 mL), the layers were separated, and the aqueous layer extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (40% EtOAc/pentane) afforded amide **292** (1.41 g, 5.19 mmol, 88%) as a white solid containing a 1:1 mixture of diastereomers exhibiting rotameric behaviour in NMR. **MP**: 107–110 °C (1:1 mixture of diasteromers); **IR** (thin film) $\tilde{\nu}_{max}^{-1}$ 2980 (C−H),

2929 (C−H), 1658 (C=O), 1428; ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H (1:1 mixture of diastereomers; rotameric) 6.05–6.15 (m, 1H, H-2), 5.81 (app.dddt, J = 24.0, 17.0, 10.0, 7.0, 7.0, 1H, H-14), 5.26–5.32 (m, 1H, H-4), 5.14–5.25 (m, 2H, H-15), 3.62 (ddd, J = 8.0, 7.0, 1.5, 1H, H-12), 3.30–3.59 (m, 2H, H-5), 2.57–2.77 (m, 2H, H-13), 2.39 (q, J = 3.0, 1H, H-8), 1.99–2.25 (m, 2H, H-9), 2.03–2.10 (m, 1H, H-6), 1.94 (d, J = 1.5, 1H, H-10), 1.89 (d, J = 1.5, 2H, H-10), 1.26 (d, J = 7.0, 2H, H-7), 1.18 (d, J=7.1, 1H, 7); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 201.0 (C-1), 200.8 (C-1), 164.6 (C-11), 164.3 (C-11), 155.4 (C-3), 155.2 (C-3), 132.4 (C-14), 132.2 (C-14), 129.8 (C-2), 119.8 (C-15), 119.7 (C-15), 116.8 (C-16), 116.3 (C-16), 48.6 (C-4), 48.5 (C-4), 45.9 (C-8), 45.8 (C-8), 45.5 (C-5), 45.2 (C-5), 35.2 (C-12), 35.1 (C-12), 34.0 (C-13), 33.6 (C-13), 31.7 (C-6), 31.2 (C-6), 26.4 (C-9), 26.3 (C-9), 22.2 (C-10), 22.1 (C-10), 17.7 (C-7), 17.7 (C-7); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{16}H_{21}O_2N_2)^+$ requires 273.1598, found 273.1599.

6.4.3 Synthesis of Electrophiles for Michael Addition

1,3-dichloro-2-(methoxymethoxy)propane (299)

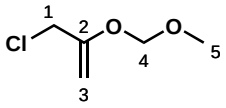


Prepared according to a literature procedure.[187] To a solution of 1,3-dichloro-2-propanol (37 mL, 390 mmol) in CH_2Cl_2 (80 mL) was added dimethoxymethane (80 mL). While stirring vigorously, P_2O_5 (33 g) was added portionwise. The resulting white suspension gradually forms a gum. The reaction was left to stir at RT overnight. The supernatant solution was decanted and washed with water, followed by sat. aq. $NaHCO_3$, followed by water again. The organic layer was dried over

Na_2SO_4 and concentrated *in vacuo* to afford **299** as an orange liquid (56.1 g, 326 mmol, 84% yield) which was used without further purification. Data agrees with literature values.[187]

^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 4.74 (s, 2H, H-4) 3.94 – 4.01 (m, 1H, H-2), 3.72 (d, J = 5.0, 4H, H-1,3), 3.42 (s, 3H, H-5).

3-chloro-2-(methoxymethoxy)prop-1-ene (300)

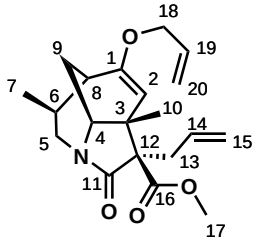


Prepared according to literature procedure.[124] To a solution of dichloride **299** (6.00 g, 34.9 mmol) in THF (60 mL) at –10 °C was added a solution of KO*t*Bu (4.11 g, 36.6 mmol) in THF (40 mL) via cannula. The reaction was allowed to warm to RT overnight, and was then partitioned between water (50 mL) and Et_2O (300 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to afford a pale yellow liquid. Purification by vacuum distillation (45 mbar) through an 8 inch Vigreux column at 45 °C afforded **300** as a colourless liquid (3.68 g, 27.0 mmol 77% yield). Data agrees with literature values.[124]

^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 5.01 (s, 2H, H-4), 4.41 (s, 2H, H-3), 3.99 (s, 2H, H-1), 3.44 (s, 3H, H-5).

6.4.4 Synthesis of Tricyclic Cores 296 297 and 301

methyl 3-allyl-5-(allyloxy)-3a,8-dimethyl-2-oxo-2,3,3a,6,7,7a-
-hexahydro-6,1-ethanoindole-3-carboxylate (296)

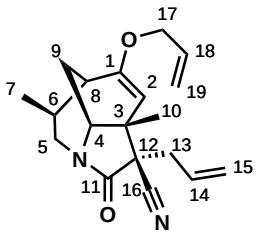


To a solution of ester **286** (147 mg, 0.481 mmol) in dry degassed THF (2 mL) at 0 °C was added KHMDS (1.4 mL, 0.72 mmol, 0.50 M in toluene). The ice bath was removed and the reaction was stirred at room temperature for 15 mins. A solution of allyl tosylate (153 mg, 0.722 mmol) and 18-crown-6 (63 mg, 0.241) in dry degassed THF (0.25 mL) was added, then the resulting solution was stirred at room temperature for 16 h. The reaction was quenched with H_2O (10 mL) and extracted with EtOAc (4 × 10 mL), then the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (40% EtOAc/pentane) afforded enol ether (**296**) as an orange oil (108 mg, 0.313 mmol, 65% yield).

IR (thin film) $\tilde{\nu}_{max}^{-1}$ 2949 (C−H), 2872 (C−H), 1754 (C=O), 1698 (C=O), 1651 (C=C), 1159 (C−O); ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 5.96–5.87 (m, 1H, H-19), 5.87–5.77 (m, 1H, H-14), 5.29–5.16 (m, 2H, H-20), 5.15–5.04 (m, 2H, H-15), 4.16–4.02 (m, 3H, H-5a, 18), 3.87 (d, J = 1.2 Hz, 1H, H-2), 3.74 (s, 3H, H-17), 3.71–3.67 (m, 1H, H-4), 2.79 (ddt, J = 13.5, 7.5, 1.5 Hz, 1H, H-13a), 2.45 (ddt, J = 13.5, 7.0, 1.5 Hz, 1H, H-13b), 2.35 (dd, J = 13.5, 10.5 Hz, 1H, H-5b), 2.17–2.05 (m, 1H, H-6), 1.96 (ddd, J = 13.5, 5.5, 2.5 Hz, 1H, H-9a), 1.91 (ddd, J = 4.5, 2.5, 1.0 Hz, 1H,

H-8), 1.62 (ddt, J = 13.5, 3.5, 1.0 Hz, 1H, H-9b), 1.21 (s, 3H, H-10), 0.94 (d, J = 7.0 Hz, 3H, H-7); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ_C 173.0 (C-16), 170.8 (C-11), 159.5 (C-1), 133.3 (C-14), 133.2 (C-19), 118.6 (C-15), 117.4 (C-20), 96.8 (C-2), 67.9 (C-18), 62.0 (C-12), 55.9 (C-4), 51.7 (C-17), 48.8 (C-3), 41.5 (C-5), 37.4 (C-8), 35.0 (C-13), 32.0 (C-6), 20.2 (C-9), 19.5 (C-7), 17.4 (C-10); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{20}H_{28}O_4N)^+$ requires 346.2018, found 346.2010; $[\boldsymbol{\alpha}]_D^{25}$ = -56.3 (c 1.0, $CHCl_3$, >99% ee).

3-allyl-5-(allyloxy)-3a,8-dimethyl-2-oxo-2,3,3a,6,7,7a-hexahydro-1,6--ethanoindole-3-carbonitrile (297)

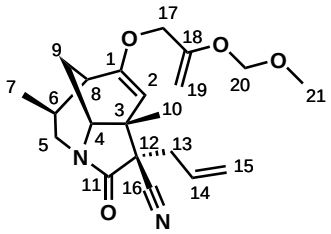


To a solution of **292** (54 mg, 0.20 mmol) in dry degassed THF (0.60 mL) at 0 °C was added KHMDS (0.60 mL, 0.30 mmol; 0.50 M in toluene). The ice bath was removed and the reaction was stirred at RT for 15 mins, before a solution of allyl tosylate (63 mg, 0.30 mmol) and 18-crown-6 (26 mg, 0.10 mmol) in THF (0.20 mL). The reaction was stirred at RT for 2 h, until complete by TLC. The reaction was quenched with H_2O (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (20% EtOAc/pentane) to afford **297** (45 mg, 0.14 mmol, 70%).

IR (thin film) $\tilde{\nu}_{max}^{-1}$ 2293 (C−H), 1710 (C=O), 1645 (C=C), 1199 (C−O); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H 6.08 (dddd, J = 17.0, 10.0, 9.0, 5.5 Hz, 1H, H-14), 5.88 (ddt,

J = 17.5, 10.5, 5.5 Hz, 1H, H-18), 5.34–5.17 (m, 4H, H-19, 15), 4.23 (ddt, J = 12.5, 5.5, 1.5 Hz, 1H, H-17a), 4.15 (ddt, J = 12.5, 5.5, 1.5 Hz, 1H, H-17b), 4.06 (d, J = 1.5 Hz, 1H, H-2), 4.00 (dd, J = 14.0, 8.0 Hz, 1H, H-5a), 3.86 (dq, J = 5.5, 1.0 Hz, 1H, H-4), 2.76 (ddt, J = 15.0, 5.5, 1.8 Hz, 1H, H-13a), 2.39 (s, 1H, H-5b), 2.39–2.32 (m, 1H, H-13b), 2.10–1.97 (m, 2H, H-6, 9a), 1.96 (dp, J = 3.5, 1.0 Hz, 1H, H-8), 1.67 (ddt, J = 14.0, 4.0, 1.0 Hz, 1H, H-9b), 1.33 (s, 3H, H-10), 0.97 (d, J = 7.0 Hz, 3H, H-7); **^{13}C-NMR** (101 MHz, $CDCl_3$): δ_C 169.5 (C-11), 160.9 (C-1), 133.0 (C-18), 132.5 (C-14), 119.4 (C-19), 117.7 (C-15), 117.4 (C-16), 92.0 (C-2), 68.0 (C-17), 57.2 (C-4), 51.6 (C-12), 50.6 (C-3), 41.7 (C-5), 37.5 (C-8), 34.7 (C-13), 31.7 (C-6), 19.9 (C-10), 19.6 (C-9), 19.4 (C-7); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{19}H_{25}O_2N_2)^+$ requires 313.1911, found 313.1909.

3-allyl-5-((2-(methoxymethoxy)allyl)oxy)-3a,8-dimethyl-2-oxo--2,3,3a,6,7,7a-hexahydro-1,6-ethanoindole-3-carbonitrile (301)

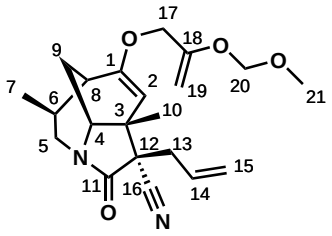


To a solution of amide **292** (966 mg, 3.55 mmol) in dry degassed THF (9 mL) at 0 °C was added KHMDS (10.6 mL, 0.50 M in THF, 5.33 mmol) slowly. The ice bath was then removed and the resulting solution was stirred for 15 mins at RT, over which time the solution became a dark orange colour and viscous. A solution of chloride **300** (729 mg, 5.33 mmol) in dry degassed THF (5 mL) was added, followed by 18-crown-6 (470 mg, 1.78 mmol) and tetra-*n*-butylammonium iodide (206 mg, 0.558 mmol). The resulting solution was stirred at room temperature for 16 h, until

complete as indicated by TLC. The reaction was quenched with H_2O (25 mL) then extracted with EtOAc (4 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude as an orange oil. Purification by flash column chromatography (20% EtOAc/PE) afforded O–alkylation product **301** (1014 mg, 2.72 mmol, 77% yield) as a white solid.

MP: 105–107 °C (rac), 130–132 °C (>99% ee); **IR** (thin film) $\tilde{\nu}_{max}^{-1}$ 3396, 2920 (C−H), 1711 (C=O), 1647 (C=C), 1154 (C−O); ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 6.06 (dddd, J = 17.0, 10.0, 9.0, 5.5, 1H, H-14), 5.19–5.31 (m, 2H, H-15), 4.92–5.00 (m, 2H, H-19), 4.38 (d, J = 2.5, 1H, H-20a), 4.27 (d, J = 2.5, 1H, H-20b), 4.16 (d, J = 12.5, 1H, H-17a), 4.10 (d, J = 1.5, 1H, H-2), 4.06 (d, J = 12.5, 1H, H-17b), 3.98 (dd, J = 14.0, 8.0, 1H, H-5a), 3.82–3.88 (m, 1H, H-4), 3.40 (s, 3H, H-21), 2.74 (ddt, J = 14.5, 5.5, 2.0, 1H, H-13), 2.31–2.45 (m, 2H, H-5b, H-13), 1.95–2.10 (m, 2H, H-6, H-8, H-9a), 1.62–1.70 (m, 1H, H-9b), 1.32 (s, 3H, H-10), 0.96 (d, J = 7.0, 3H, H-7); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 169.3 (C-11), 160.7 (C-1), 155.3 (C-18), 132.5 (C-14), 119.4 (C-15), 117.4 (C-16), 93.9 (C-19), 92.3 (C-2), 87.7 (C-20), 67.2 (C-17), 57.1 (C-4), 56.3 (C-21), 51.5 (C-12), 50.5 (C-3), 41.7 (C-5), 37.4 (C-8), 34.6 (C-13), 31.6 (C-6), 19.8 (C-10), 19.6 (C-9), 19.3 (C-7); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ $(C_{21}H_{28}O_4N_2\,^{23}Na)^+$ requires 395.1941, found 395.1942; $[\boldsymbol{\alpha}]_D^{25}$ = -87.9 (c 1.0, $CHCl_3$, >99% ee).

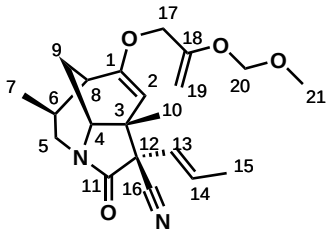
3-allyl-5-((2-(methoxymethoxy)allyl)oxy)-3a,8-dimethyl-2-oxo--2,3,3a,6,7,7a-hexahydro-6,1-ethanoindole-3-carbonitrile (302)



Tricycle **302** was isolated as a side-product during the formation of **301**.

IR (thin film) $\tilde{\nu}_{\max}{}^{-1}$ 2954 (C−H), 1707 (C=O), 1652, 1191, 1154, 1042; ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 5.91 (ddt, J = 17.0, 10.0, 7.0 Hz, 1H, H-14), 5.23 (dq, J = 8.5, 1.5 Hz, 1H, H-15a), 5.20 (q, J = 1.5 Hz, 1H, H-15b), 4.96 (d, J = 1.5 Hz, 2H, H-20), 4.48 (d, J = 1.5 Hz, 1H, H-2), 4.36 (d, J = 2.5 Hz, 1H, H-19a), 4.31 (d, J = 2.5 Hz, 1H, H-19b), 4.16 (d, J = 12.0 Hz, 1H, H-17a), 4.12 (d, J = 12.0 Hz, 1H, H-17b), 3.95 (dd, J = 13.5, 8.0 Hz, 1H, H-5a), 3.79–3.73 (m, 1H, H-4), 3.39 (s, 3H, H-21), 2.53 (dq, J = 7.5, 1.0 Hz, 2H, H-13), 2.34 (dd, J = 13.5, 10.5 Hz, 1H, H-5b), 2.16–2.04 (m, 1H, H-6), 2.02–1.93 (m, 2H, H-8, H-9a), 1.64 (ddt, J = 14.5, 4.5, 1.0 Hz, 1H, H-9b), 1.19 (s, 3H, H-10), 0.93 (d, J = 7.0 Hz, 3H, H-7); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 170.7 (C-11), 160.2 (C-1), 155.2 (C-18), 131.3 (C-14), 120.1 (C-15), 117.6 (C-16), 96.7 (C-2), 93.7 (C-20), 87.9 (C-19), 67.7 (C-17), 56.4 (C-4), 56.2 (C-21), 55.9 (C-12), 48.6 (C-3), 41.7 (C-5), 37.0 (C-8), 35.1 (C-13), 31.4 (C-6), 20.0 (C-9), 19.3 (C-7), 17.4 (C-10).

5-((2-(methoxymethoxy)allyl)oxy)-3a,8-dimethyl-2-oxo-3-((*E*)-prop-1--en-1-yl)-2,3,3a,6,7,7a-hexahydro-6,1-ethanoindole-3-carbonitrile (413)

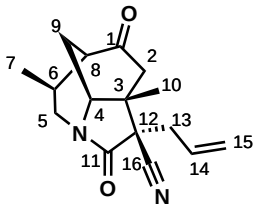


Tricycle **413** was, on one occasion, observed and isolated as a side-product during the formation of **301**.

^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 6.05–6.19 (m, 1H, H-14), 5.43 (dq, J = 15.5, 1.5, 1H, H-13), 4.99 (t, J = 1.5, 2H, H-19), 4.50 (s, 1H, H-2), 4.37–4.40 (m, 1H, H-20a), 4.31–4.36 (m, 1H, H-20b), 4.19 (dd, J = 12.0, 1.5, 1H, H-17a), 4.14 (dd, J = 12.0, 1.5, 1H, H-17b), 4.00 (ddd, J = 13.5, 8.0, 2.0, 1H, H-5a), 3.73 (d, J = 5.5, 1H, H-4), 3.41 (d, J = 1.5, 3H, H-21), 2.38 (dd, J = 13.5, 10.5, 1H, H-5b), 2.05–2.20 (m, 1H, H-6), 1.94–2.04 (m, 2H, H-8, H-9a), 1.78 (dt, J = 6.5, 1.5, 3H, H-15), 1.66 (dd, J = 14.5, 3.5, 1H, H-9b), 1.13 (s, 3H, H-10), 0.96 (d, J = 7.0, 3H, H-7); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 170.3 (C-11) 160.6 (C-1), 155.3 (C-18), 132.5 (C-14), 120.0 (C-13), 116.6 (C-16), 96.5 (C-2), 93.8 (C-19), 88.1 (C-20), 67.9 (C-17), 59.7 (C-12), 56.6 (C-4), 56.3 (C-21), 49.9 (C-3), 41.8 (C-5), 37.1 (C-8), 31.5 (C-6), 19.9 (C-9), 19.3 (C-7), 18.1 (C-15), 17.9 (C-10); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ $(C_{21}H_{28}O_4N_2\,^{23}Na)^+$ requires 395.1941, found 395.1939.

3-allyl-3a,8-dimethyl-2,5-dioxooctahydro-6,1-ethanoindole-

-3-carbonitrile (303)

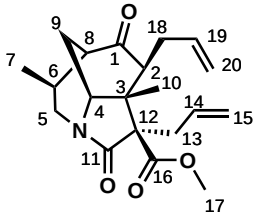


Tricycle **303** was isolated as a side-product during the formation of **301** in cases where *O*-alkylation was incomplete.

MP: 146–150 °C (racemic); **IR** (thin film) $\tilde{\nu}_{\mathrm{max}}{}^{-1}$ 2961 (C–H), 2927 (C–H), 1716 (C=O), 1668 (N–C=O); ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_{H} 6.04–5.86 (m, 1H, H-14), 5.35–5.19 (m, 2H, H-15), 4.02–3.94 (m, 1H, H-5a), 3.92 (d, J = 5.0 Hz, 1H, H-4), 2.95–2.88 (m, 1H, H-6), 2.82 (dtd, J = 15.0, 3.5, 2.0 Hz, 1H, H-13a), 2.49 (dq, J = 15.0, 1.0 Hz, 1H, H-2a), 2.42–2.26 (m, 3H, H-2b, H-5b, H-13b), 2.18–2.12 (m, 2H, H-9), 2.00–1.96 (m, 1H, H-8), 1.45 (d, J = 1.0 Hz, 3H, H-10), 1.01 (dd, J = 7.0, 1.0 Hz, 3H, H-7); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_{C} 211.2 (C-1), 166.9 (C-11), 131.1 (C-14), 120.4 (C-15), 117.1 (C-16), 59.3 (C-4), 51.0 (C-12), 50.1 (C-3), 45.9 (C-8), 44.2 (C-2), 41.4 (C-5), 36.2 (C-6), 34.5 (C-13), 22.0 (C-10), 19.4 (C-9), 17.8 (C-7); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{16}H_{20}O_2N_2$ $^{23}Na)^+$ requires 295.1417, found 295.1419.

6.4.5 Claisen Rearrangements

methyl 3,4-diallyl-3a,8-dimethyl-2,5-dioxooctahydro-6,1-ethanoindole--3-carboxylate (305)

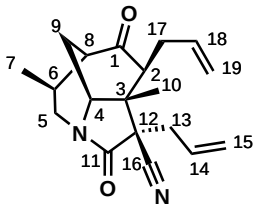


A solution of enol ether **296** (25 mg, 0.072 mmol) in dry degassed mesitylene (5.4 mL, 0.015 M) was heated to 185 °C for 3 h. The reaction was then cooled to RT and diluted with pentane (2 mL) and loaded directly onto a silica gel column for purification by flash column chromatography. After eluting with pentane to remove mesitylene, the product was eluted with 50% EtOAc/pentane to afford ketone **305** (25 mg, 0.072 mmol, quant.).

IR (thin film) $\tilde{\nu}_{\text{max}}^{-1}$ 2953 (C−H), 1754 (C=O), 1700 (C=O); ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 5.78 (dddd, J = 17.0, 10.0, 7.5, 7.0 Hz, 1H), 5.63 – 5.58 (m, 1H), 5.57 – 5.52 (m, 1H), 5.16 – 5.05 (m, 3H), 5.02 – 4.92 (m, 2H), 4.12 (dd, J = 13.5, 8.0 Hz, 1H, H-5a), 3.75 (s, 3H, H-17), 3.72 (d, J = 1.0 Hz, 1H, H-4), 2.79 (ddt, J = 13.5, 7.5, 1.5 Hz, 1H), 2.75 – 2.66 (m, 1H, H-6), 2.48 (dd, J = 11.0, 4.0 Hz, 1H), 2.46 – 2.41 (m, 1H), 2.41 – 2.33 (m, 2H), 2.33 – 2.24 (m, 2H), 2.20 – 2.15 (m, 1H), 1.20 (s, 3H, H-10), 1.00 (d, J = 7.0 Hz, 3H, H-7); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 211.3 (C-1), 171.4, 170.5, 136.0, 132.5, 119.2, 116.7, 63.7, 58.0, 53.4, 52.8, 52.3, 46.9, 41.2, 35.6, 35.2, 31.9, 20.7, 18.6 (C-7), 13.9 (C-10). $[\boldsymbol{\alpha}]_D^{25}$ = +63.5 (c 1.0, $CHCl_3$, >99% ee); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{20}H_{28}O_4N)^+$ requires 346.2013, found 346.2011.

3,4-diallyl-3a,8-dimethyl-2,5-dioxooctahydro-6,1-ethanoindole-

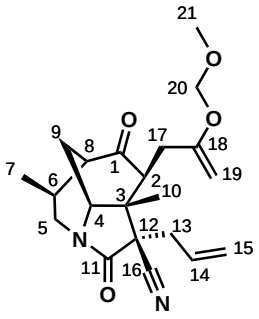
-3-carbonitrile (306)



A solution of **297** (43 mg, 0.14 mmol) in dry degassed mesitylene (9 mL) was heated to 185 °C for 2 h. The reaction mixture was loaded directly onto a column and eluted with pentane to remove mesitylene followed by 40% EtOAc/pentane, to afford **306** (34 mg, 0.11 mmol, 79%) as a colourless oil.

IR (thin film) $\tilde{\nu}_{max}$$^{-1}$ 2924 (C−H), 1715 (C=O); ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 5.97 (dddd, J = 17.0, 10.0, 9.0, 5.5 Hz, 1H, H-14), 5.68–5.54 (m, 1H, H-18), 5.33–5.23 (m, 2H, H-15), 5.00 (ddq, J = 14.0, 4.5, 1.5 Hz, 2H, H-19), 4.03 (dd, J = 14.0, 8.5 Hz, 1H, H-5a), 3.94–3.87 (m, 1H, H-4), 2.85 (ddt, J = 15.5, 5.5, 2.0 Hz, 1H, H-13a), 2.80–2.70 (m, 1H, H-6), 2.51–2.30 (m, 5H, H-13b, 2, 5b, 17), 2.19 (t, J = 3.0 Hz, 2H, H-9), 2.09–2.04 (m, 1H, H-8), 1.38 (s, 3H, H-10), 1.02 (d, J = 7.0 Hz, 3H, H-7); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 211.1 (C-1), 167.6 (C-11), 135.2 (C-18), 131.4 (C-14), 120.4 (C-15), 117.4 (C-19), 117.1 (C-16), 59.7 (C-4), 53.9 (C-12), 53.3 (C-3), 49.8 (C-2), 45.8 (C-8), 41.4 (C-5), 35.3 (C-6), 34.1 (C-13), 32.8 (C-17), 19.8 (C-9), 18.1 (C-7), 17.0 (C-10); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{19}H_{25}O_2N_2)^+$ requires 313.1911, found 313.1910;

3-allyl-4-(2-(methoxymethoxy)allyl)-3a,8-dimethyl-2,5-dioxooctahydro--6,1-ethanoindole-3-carbonitrile (307)

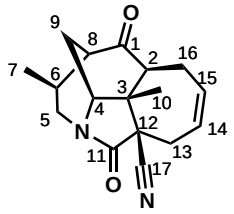


A solution of *O*-alkylation product **301** (986 mg, 2.65 mmol) in mesitylene (140 mL, 0.018 M) was heated to 185 °C for 8 h. After cooling to rt, the solution was poured directly onto a silica column, which was flushed with petrol until mesitylene no longer eluted. Elution with 2:1 Et_2O/petrol afforded *C*-alkylated product **307** (792 mg, 2.13 mmol, 80%) as a white solid.

MP: 102–104 °C; **IR** (thin film) $\tilde{\nu}_{max}^{-1}$ 2922 (C−H), 2860 (C−H), 2358, 2113, 1715 (C=O), 1020 (C−O); ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 5.98 (dddd, J = 17.0, 10.0, 9.5, 5.5, 1H, H-14), 5.25–5.36 (m, 2H, H-15), 4.86 (s, 2H, H-20), 4.14 (d, J = 2.5, 1H, H-19), 4.03 (dd, J = 14.0, 8.5, 1H, H-5), 3.96 (d, J = 2.5, 1H, H-19), 3.88–3.91 (m, 1H, H-4), 3.41 (s, 3H, H-21), 2.78–2.92 (m, 3H, H-2,13,6), 2.55 (dd, J = 15.0, 9.5, 1H, H-13), 2.34–2.43 (m, 3H, H-5, 17), 2.20 (t, J = 3.0, 2H, H-9), 2.12–2.15 (m, 1H, H-8), 1.39 (s, 3H, H-10), 1.03 (d, J = 7.0, 3H, H-7); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 210.9 (C-1) 167.5 (C-11), 157.1 (C-8'), 131.4 (C-14), 120.5 (C-15), 117.2 (C-16), 94.1 (C-20), 87.1 (C-19), 59.8 (C-4), 56.6 (C-21), 53.8 (C-12), 52.9 (C-3), 47.9 (C-6), 45.4 (C-8), 41.4 (C-5), 35.5 (C-2), 34.9 (C-17), 34.1 (C-13), 19.9 (C-9), 18.0 (C-7), 17.3 (C-10); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ $(C_{21}H_{28}O_4N_2\ ^{23}Na)^+$ requires 395.1941, found 395.1940; $[\boldsymbol{\alpha}]_D^{25}$ = -30.5 (c 1.0, $CHCl_3$, >99% ee).

6.4.6 Tetracyclic Cores 313 and 314

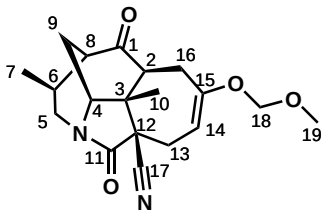
3,11a-dimethyl-6,12-dioxo-1,3,4,7,10,11,11a,11b-octahydro-2*H*-
-2,11-methanocyclohepta[*a*]indolizine-6a(6*H*)-carbonitrile (313)



A solution of **306** (34 mg, 0.11 mmol) and Hoveyda–Grubbs II (**312**, 6.8 mg, 0.011 mmol) in CH_2Cl_2 (1 mL) in a sealed 12 mL tube was heated to 50 °C for 1 h. After completion, the reaction was cooled to RT and concentrated *in vacuo*, then the crude residue was purified by flash column chromatography (20% EtOAc/pentane) to afford tetracycle **313** (22 mg, 0.077 mmol, 70%).

IR (thin film) $\tilde{\nu}_{max}^{-1}$ 2924 (C−H), 1699 (C=O); ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 5.70 (ddt, J = 11.0, 5.0, 2.5 Hz, 1H, H-15), 5.61 (ddddd, J = 11.0, 8.5, 4.5, 2.5, 1.5 Hz, 1H, H-14), 4.08 (dd, J = 13.5, 7.0 Hz, 1H, H-5a), 3.85 (d, J = 4.0 Hz, 1H, H-4), 3.08 (dddt, J = 16.5, 4.5, 3.5, 2.5 Hz, 1H, H-13a), 2.95 (dd, J = 11.5, 4.5 Hz, 1H, H-2), 2.74 (dd, J = 14.0, 11.5 Hz, 1H, H-5b), 2.70–2.62 (m, 2H, H-13b, H-16a), 2.42–2.23 (m, 3H, H-8, H-9a, H-16b), 2.14–2.01 (m, 1H, H-6), 1.93–1.85 (m, 1H, H-9b), 1.40 (s, 3H, H-10), 1.03 (d, J = 6.9 Hz, 3H, H-7); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 209.6 (C-1), 171.4 (C-11), 131.8 (C-15), 121.2 (C-14), 117.3 (C-17), 58.0 (C-4), 55.4 (C-12), 52.5 (C-3), 49.4 (C-8), 42.9 (C-2), 42.4 (C-5), 32.2 (C-6), 30.1 (C-13), 27.1 (C-16), 21.6 (C-9), 19.8 (C-7), 15.5 (C-10); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{17}H_{21}O_2N_2)^+$ requires 285.1598, found 285.1599; $[\boldsymbol{\alpha}]_D^{25}$ = +86.16 (c 1.0, $CHCl_3$).

9-(methoxymethoxy)-3,11a-dimethyl-6,12-dioxo-1,3,4,7,10,11,11a,11b-
-octahydro-2*H*-2,11-methanocyclohepta[*a*]indolizine-
-6a(6*H*)-carbonitrile (314)



A solution of **307** (74 mg, 0.20 mmol) in toluene (20 mL, 0.01 M) was degassed (3 × vacuum-Ar cycles) followed by addition of Hoveyda–Grubbs II catalyst (6.3 mg, 0.01 mmol, 5 mol%) and *p*-benzoquinone (2.2 mg, 0.02 mmol, 10 mol%). The solution was transferred to an oil bath pre-heated to 110 °C and stirred for 4 h. After cooling to RT, the reaction solution was purified directed by flash column chromatography (silica packed with pentane, eluted first with pentane to remove toluene, followed by 2:1 Et_2O/pentane) to afford ABCD core **314** (61 mg, 0.177 mmol, 89%).

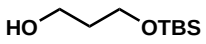
MP: 62–164 °C; **IR** (thin film) $\tilde{\nu}_{max}^{-1}$ 2920 (C−H), 1712 (C=O); ^{1}**H-NMR** (400 MHz, C_6D_6): δ_H 4.72 (ddd, J = 9.5, 5.5, 2.0, 1H, H-14), 4.61 (d, J = 6.5, 1H, H-18), 4.55 (d, J = 6.5, 1H, H-18), 3.69 (dd, J = 13.5, 7.0, 1H, H-5), 3.13 (d, J = 4.5, 1H, H-4), 3.11 (s, 3H, H-19), 2.86 (dtd, J = 16.5, 3.5, 1.5, 1H, H-13), 2.69 (dt, J = 13.0, 2.0, 1H, H-16), 2.59 (dd, J = 16.5, 9.5, 1H, H-13), 2.43 (s, 1H, H-2), 2.34–2.49 (m, 1H, H-16), 1.89–1.95 (m, 1H, H-5), 1.86–1.89 (m, 1H, H-8), 1.27–1.36 (m, 1H, H-9), 1.23 (dtd, J = 13.0, 6.5, 1.6, 1H, H-6), 1.07 (s, 3H, H-10), 1.00 (ddd, J = 15.0, 3.0, 1.5, 1H, H-9), 0.36 (d, J = 6.9, 3H, H-7); ^{13}**C-NMR** (101 MHz, C_6D_6): δ_C 207.5 (C-1), 171.0 (C-11), 156.2 (C-15), 117.5 (C-17), 93.8 (C-18), 92.9 (C-14), 57.5 (C-4), 55.8 (C-19), 54.7 (C-12), 52.8 (C-3), 49.4 (C-8), 41.9 (C-5), 40.8 (C-2),

31.6 (C-6), 29.9 (C-16), 27.9 (C-13), 21.2 (C-9), 19.4 (C-7), 15.1 (C-10); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ $(C_{19}H_{24}O_4N_2\ ^{23}Na)^+$ requires 367.14628, found 367.1629.

6.5 Compounds Synthesised in Chapter 5

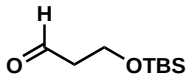
6.5.1 Synthesis of Michael Acceptor 333

3-((*tert*-butyldimethylsilyl)oxy)propan-1-ol (415)



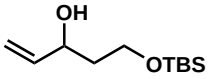
Prepared according to a literature procedure.[188] To a vigorously stirring suspension of NaH (60% suspension in mineral oil; 2.10 g, 52.5 mmols) in dry THF (100 mL) was added propanediol (3.77 mL, 52.6 mmol) dropwise. The suspension was stirred at RT for 45 mins, before TBSCl (7.90 g, 52.4 mmol) was added portionwise. The suspension was stirred at RT for a further 45 mins, over which time it gradually became white and viscous. Upon completion, the reaction was quenched slowly with Na_2CO_3 (10 mL; 10% aq. solution), which caused the solution to become clear and biphasic. The layers were separated and the aq. layer was extracted with Et_2O (3 $\times$ 20 mL). The combined organic layers were washed with brine then dried over $MgSO_4$ then concentrated under vacuum to afford the crude mono-protected alcohol **414** (8.68 g, 45.7 mmol, 87%) as a colourless oil which did not require further purification. Data was consistent with literature values.[189]

3-((*tert*-butyldimethylsilyl)oxy)propanal (332)



Oxidation of **415** was achieved using the Swern method according to a literature procedure.[189] To a solution of oxalyl chloride (5.09 mL, 59.4 mmol) in CH_2Cl_2 (200 mL) at –78 °C under argon was added a solution of DMSO (7.14 mL, 100.5 mmol) in CH_2Cl_2 (7 mL) dropwise. The solution was then stirred for a further 10 mins at –78 °C, before a solution of alcohol **414** (8.68 g, 45.7 mmol) in CH_2Cl_2 (50 mL) was slowly added. The resulting solution was stirred for 15 mins at –78 °C, then Et_3N (31.8 mL, 228.5 mmol) was added dropwise and the resulting solution was stirred for a further 2 h at –78 °C. Upon completion, the reaction was warmed to 0 °C and quenched by slow addition of H_2O (200 mL). The layers were separated and the aq. layer was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were dried over Na_2SO_4 then concentrated under vacuum to afford aldehyde **332** (8.40 g, 44.7 mmols, 98%) which was used immediately without further purification. Data was consistent with literature values.[189]

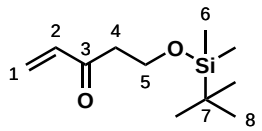
5-((*tert*-butyldimethylsilyl)oxy)pent-1-en-3-ol (416)



Prepared according to a literature procedure.[190] To a solution of aldehyde **332** (8.40 g, 44.7 mmol) in THF (250 mL) at –78 °C was added vinyl magnesium bromide (1.0 M, 50 mL, 50 mmol) slowly. The resulting solution was stirred at –78 °C, before warming to RT. Upon completion, the reaction was quenched with a sat. aq. solution

of NH_4Cl (200 mL) and stirred vigorously for 30 mins. The layers were separated then the organic layer was washed with H_2O (2 × 200 mL) followed by brine (200 mL), before drying over Na_2SO_4 and concentrating under vacuum to afford alcohol **416** (5.88 g) as an amber oil which was used crude in the subsequent step. Data was consistent with literature values.[190]

5-((*tert*-butyldimethylsilyl)oxy)pent-1-en-3-one (333)

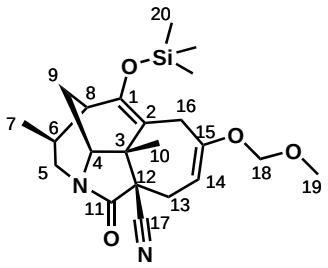


A suspension of IBX (672 mg, 2.40 mmol), alcohol **416** (432 mg, 2.00 mmol) in EtOAc (20 mL) was heated to reflux for 4 h. Upon completion, the solution was cooled to 0 °C before filtering through a plug of celite, washing with EtOAc. The filtrate was then concentrated under vacuum. Purification by flash column chromatography (20% Et_2O/pentane) afforded the enone **333** (325 mg, 1.52 mmol, 76% from crude **416**)as a colourless oil.

IR (thin film) $\tilde{\nu}_{max}{}^{-1}$ 2391 (C−H), 1711 (C=O), 1377, 1253, 1106 (C−O); ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 6.37 (dd, J = 17.5, 10.5 Hz, 1H, H-2), 6.23 (dd, J = 17.5, 1.0 Hz, 1H, H-1a), 5.86 (dd, J = 10.5, 1.0 Hz, 1H, H-1b), 3.93 (t, J = 6.5 Hz, 2H, H-5), 2.81 (t, J = 6.5 Hz, 2H, H-4), 0.87 (s, 9H, H-8), 0.04 (s, 7H, H-6); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 199.9 (C-3), 137.2 (C-2), 128.7 (C-1), 59.1 (C-4), 42.6 (C-5), 26.0 (C-8), 18.4 (C-7), -5.3 (C-6); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ $(C_{11}H_{22}O_2{}^{23}Na{}^{32}Si)^+$ requires 237.1281, found 237.1284.

6.5.2 Attempted Mukaiyama–Michael Reaction

9-(methoxymethoxy)-3,11a-dimethyl-6-oxo-12-((trimethylsilyl)oxy)--1,2,3,4,7,10,11a,11b-octahydro-2,11-(metheno)cyclohepta[*a*]indolizine--6a(6*H*)-carbonitrile (329)

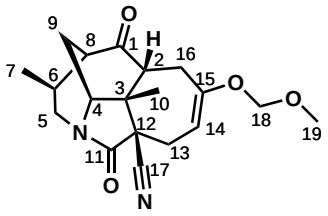


To a solution of tetracycle **314** (17 mg, 0.049 mmol) in dry THF (0.50 mL) at –78 °C was added LiHMDS (0.06 mL, 0.06 mmol) dropwise. The solution was stirred at –78 °C for 10 mins then TMSCl (16 µL, 0.12 mmol) was added. The solution was warmed to 0 °C and stirred until complete, before quenching with cold sat. aq. $NaHCO_3$ (5 mL) and diluting with Et_2O. The layers were separated and the aq. layer was extracted with Et_2O (3 × 5 mL), then the combined organic layers were combined and dried over Na_2SO_4 and concentrated under vacuum to afford enolsilane **329** (18 mg, 0.048 mmol, 98%) as a colourless oil which was used immediately without purification. Some limited data are provided below, however the instability of **329** prevented full data being obtained.

^{1}**H-NMR** (400 MHz, C_6D_6): δ_H 4.77 (t, J = 7.5 Hz, 1H, H-14), 4.63 (d, J = 6.0 Hz, 1H, H-18a), 4.58 (d, J = 6.0 Hz, 1H, H-18b), 3.95 (dd, J = 18.5, 12.5 Hz, 1H, H-5a), 3.37 (dt, J = 5.0, 1.0 Hz, 1H, H-4), 3.32 (d, J = 17.5 Hz, 1H, H-16a), 3.13 (s, 3H, H-19), 2.68 (dd, J = 7.5, 1.0 Hz, 2H, H-13a), 2.55 (dd, J = 17.5, 1.5 Hz, 1H, H-16b), 1.89 – 1.77 (m, 2H, H-5b, 13b), 1.45 (s, 1H, H-6), 1.38 (s, 1H, H-8), 1.30 (s, 3H, H-10), 1.22 (ddd, J = 14.0, 5.0, 2.5 Hz, 1H, H-9a), 1.03 (ddt, J = 14.0, 4.0, 1.0

Hz, 1H, H-9b), 0.46 (d, J = 7.0 Hz, 4H, H-7), 0.04 (s, 9H, H-20); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ $(C_{22}H_{32}O_4N^{28}_2Si^{23}Na)^+$ requires 439.2024, found 439.2023.

9-(methoxymethoxy)-3,11a-dimethyl-6,12-dioxo-1,3,4,7,10,11,11a,11b--octahydro-2H-2,11-methanocyclohepta[*a*]indolizine--6a(6*H*)-carbonitrile (334)



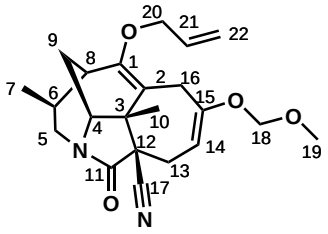
Ketone **334** was recovered during attempted *O*-alkylations of ketone **314**. Treatment of **314** with one equivalent of LiHMDS, NaHMDS, or KHMDS results in quantitative conversion to **334**. NMR data are provided in both $CDCl_3$ and C_6D_6 for reference.

IR (thin film) $\tilde{\nu}_{max}^{-1}$ 2957 (C−H), 1710 (C=O); ^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 4.96 (d, J = 6.0 Hz, 1H, H-18b), 4.87 (d, J = 6.0 Hz, 1H, H-18a), 4.82 (dd, J = 8.5, 6.0 Hz, 1H, H-14), 4.01 (dd, J = 14.0, 9.0 Hz, 1H, H-5a), 3.95–3.91 (m, 1H, H-4), 3.46 (s, 3H, H-19), 2.97-2.85 (m, 1H, H-6), 2.67–2.53 (m, 4H, H-2, H-13, H-16), 2.46 (dd, J = 14.5, 3.0 Hz, 1H, H-13/H-16), 2.30 (dd, J = 14.0, 9.5 Hz, 1H, H-5b), 2.15 (t, J = 3.0 Hz, 2H, H-9), 1.98 (dt, J = 4.0, 2.0 Hz, 1H, H-8), 1.61 (s, 3H, H-10), 1.03 (d, J = 7.0 Hz, 3H, H-7); ^{13}**C-NMR** (101 MHz, $CDCl_3$): δ_C 209.1 (C-1), 165.0 (C-11), 156.4 (C-15), 117.5 (C-17), 93.2 (C-18), 92.4 (C-14), 59.5 (C-4), 55.5 (C-19), 51.9 (C-12), 49.0 (C-2), 48.5 (C-3), 45.3 (C-8), 39.9 (C-5), 35.3 (C-6), 25.9 (C-16), 25.5 (C-13), 20.3 (C-10), 17.3 (C-9), 16.8 (C-7); ^{1}**H-NMR** (500 MHz, C_6D_6): δ_H

4.85 (dd, J = 9.0, 5.5 Hz, 1H, H-14), 4.83 (d, J = 6.0 Hz, 2H, H-18a), 4.74 (d, J = 6.0 Hz, 1H, H-18b), 3.80 (dd, J = 13.5, 9.0 Hz, 1H, H-5a), 3.34 (s, 3H, H-19), 3.25 (d, J = 6.0 Hz, 1H, H-4), 2.80–2.69 (m, 1H, H-6), 2.67 (dd, J = 15.5, 9.0 Hz, 1H, H-13b), 2.50–2.41 (m, 1H, H-16b), 2.37 (dd, J = 15.5, 5.5 Hz, 1H, H-13a), 1.98 (dd, J = 15.5, 4.0 Hz, 1H, H-16a), 1.58 (t, J = 6.0, 4.0 Hz, 1H, H-2), 1.51 (dd, J = 13.5, 9.5 Hz, 1H, H-5a), 1.24 (dd, J = 5.0, 1.0 Hz, 1H, H-8), 1.15 (ddd, J = 15.0, 6.0, 1.5 Hz, 1H, H-9b), 1.08 (d, J = 4.5 Hz, 1H, H-9a), 1.05 (s, 3H, H-10), 0.41 (d, J = 7.0 Hz, 3H, H-7); ^{13}**C-NMR** (126 MHz, C_6D_6): δ_C 209.1 (C-1), 165.9 (C-11), 157.6 (C-15), 119.0 (C-17), 94.4 (C-18), 93.7 (C-14), 60.1 (C-4), 56.1 (C-19), 52.5 (C-3), 50.1 (C-12), 49.0 (C-2), 46.1 (C-8), 40.4 (C-5), 36.0 (C-6), 27.1 (C-16), 26.9 (C-13), 20.8 (C-10), 17.8 (C-9), 17.3 (C-7); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ $(C_{19}H_{24}O_4N_2\,^{23}Na)^+$ requires 367.1628, found 367.1628.

6.5.3 Allylation of Tetracycle 314

12-(allyloxy)-9-(methoxymethoxy)-3,11a-dimethyl-6-oxo--1,2,3,4,7,10,11a,11b-octahydro-2,11-(metheno)cyclohepta[*a*]indolizine--6a(6*H*)-carbonitrile (343)

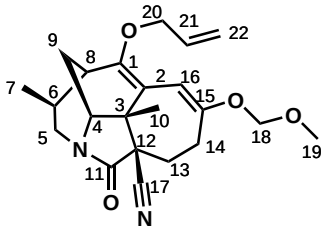


To a solution of tetracycle **314** (47 mg, 0.14 mmol) in THF (2.5 mL) at 0 °C was added KHMDS (0.32 mL, 0.16 mmol; 0.50 M in toluene). The ice bath was removed and the solution was stirred at RT for 15 mins. A solution of allyl tosylate (43 mg, 0.21 mmol) and 18-crown-6 (11 mg, 0.041 mmol) in THF (0.2 mL) was added slowly, and the resulting solution was stirred at RT for 80 mins, until completion. The reaction was quenched with water (5 mL) and then diluted with EtOAc (5 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 5 mL), then the combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. Purification by flash column chromatography (25% EtOAc/pentane) afforded propargyl enol ether **343** (40 mg, 0.11 mmol, 79%).

IR (thin film) $\tilde{\nu}_{max}^{-1}$ 2953 (C−H), 1707 (C=O), 1175 (C−O); ^{1}**H-NMR** (500 MHz, $CDCl_3$): δ_H 5.90 (ddt, J = 17.2, 10.5, 5.0 Hz, 1H, H-21), 5.35 (dq, J = 17.3, 1.7 Hz, 1H, H-22a), 5.20 (dq, J = 10.5, 1.5 Hz, 1H, H-22b), 4.91 (d, J = 6.0 Hz, 1H, H-18a), 4.85 (d, J = 6.0 Hz, 1H, H-18b), 4.80 (dd, J = 8.1, 6.5 Hz, 1H, H-14), 4.28–4.16 (m, 2H, H-20), 4.00 (dd, J = 13.7, 8.0 Hz, 1H, H-5a), 3.77 (dt, J = 5.0, 1.1 Hz, 1H, H-4), 3.49 (d, J = 17.5 Hz, 1H, H-16a), 3.40 (s, 3H, H-19), 2.69–2.63

(m, 2H, H-13a, 16b), 2.56 (dd, J = 15.7, 8.0 Hz, 1H, H-13b), 2.45 (dd, J = 13.7, 10.5 Hz, 1H, H-5b), 2.19 (d, J = 3.3 Hz, 1H, H-8), 2.07–1.97 (m, 2H, H-6, 9a), 1.65 (s, 1H), 1.61 (ddt, J = 14.0, 4.0, 1.0 Hz, 1H, H-9b), 1.46 (s, 3H, H-10), 0.98 (d, J = 6.9 Hz, 3H, H-7); **^{13}C-NMR** (126 MHz, $CDCl_3$): δ_C 169.0 (C-11), 157.5 (C-15), 153.8 (C-1), 133.8 (C-21), 118.4 (C-17), 117.0 (C-22), 110.3 (C-2), 93.8 (C-18), 92.3 (C-14), 68.6 (C-20), 58.2 (C-4), 56.4 (C-19), 52.2 (C-3), 50.5 (C-12), 41.2 (C-5), 33.7 (C-8), 31.3 (C-6), 29.7 (C-16), 28.0 (C-13), 19.8 (C-9), 18.7 (C-10, C-7); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ $(C_{22}H_{28}O_4N_2\,^{23}Na)^+$ requires 407.1941, found 407.1935.

12-(allyloxy)-9-(methoxymethoxy)-3,11a-dimethyl-6-oxo-
-1,2,3,4,7,8,11a,11b-octahydro-2,11-(metheno)cyclohepta[*a*]indolizine-
-6a(6*H*)-carbonitrile (417)

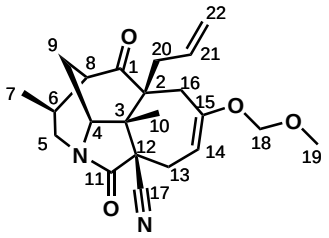


417 was occasionally observed, arising from isomerisation of the methoxymethyl enol ether into conjugation.

^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 5.91 (ddt, J = 17.2, 10.4, 5.2 Hz, 1H, H-21), 5.56 (d, J = 2.4 Hz, 1H, H-16), 5.30 (dq, J = 17.1, 1.7 Hz, 2H, H-22a), 5.19 (dq, J = 10.4, 1.4 Hz, 1H, H-22b), 4.97 (d, J = 6.3 Hz, 1H, H-18a), 4.89 (d, J = 6.4 Hz, 1H, H-18b), 4.47 (ddt, J = 13.0, 5.0, 1.6 Hz, 1H, H-20a), 4.18 (ddt, J = 13.0, 5.4, 1.5 Hz, 1H, H-20b), 4.01 (dd, J = 13.7, 8.0 Hz, 1H, H-5a), 3.83 (dt, J = 5.3, 1.2 Hz, 1H, H-4), 3.40 (s, 3H, H-19), 2.61 (ddd, J = 18.5, 12.5, 2.5 Hz, 1H, H-14a), 2.48–2.31

(m, 3H, H-13a, 14b, 5b), 2.14 (p, J = 1.9 Hz, 1H, H-8), 2.12–2.05 (m, 2H, H-13b, 6), 2.01 (ddd, J = 14.0, 5.2, 2.3 Hz, 1H, H-9a), 1.62–1.58 (m, 1H, H-9b), 1.46 (s, 3H, H-10), 0.98 (d, J = 6.9 Hz, 3H, H-7); **^{13}C-NMR** (126 MHz, $CDCl_3$): δ_C 169.7 (C-11), 157.5 (C-1), 156.1 (C-15), 134.2 (C-21), 118.1 (C-17), 117.1 (C-22), 110.9 (C-2), 99.6 (C-16), 93.9 (C-18), 72.5 (C-20), 58.2 (C-4), 56.1 (C-19), 53.4 (C-3), 50.3 (C-12), 41.8 (C-5), 36.8 (C-8), 32.5 (C-6), 31.7 (C-13), 28.1 (C-14), 20.4 (C-10), 19.6 (C-9), 19.1 (C-7).

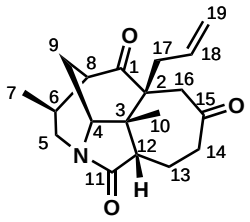
11-allyl-9-(methoxymethoxy)-3,11a-dimethyl-6,12-dioxo-
-1,3,4,7,10,11,11a,11b-octahydro-2*H*-2,11-methanocyclohepta[*a*]-
-indolizine-6a(6*H*)-carbonitrile (418)



To a flask containing enol ether **314** (55 mg, 0.14 mmol) under Ar was added dry degassed mesitylene (10 mL, 0.015 M). The solution was sparged with Ar, then a reflux condenser was affixed, with a balloon of Ar inserted through the top septum. The solution was heated to 185 °C and stirred for 2 h. On completion, the solution was cooled to RT, diluted with pentane (5 mL) and loaded directly onto a silica gel column, packed with pentane. After flushing with pentane to remove mesitylene the product was eluted with 40% EtOAc/pentane to afford **418** (49 mg, 0.13 mmol, 93%) as a colourless oil. Due to broad ^{1}H NMR shifts, characterisation of **418** was not possible. **418** was treated with LiOH in THF/MeOH/H_2O at 100 °C for 16 h to effect enol ether hydrolysis and nitrile dealkoxycarbonylation, affording **344** to

aid with identification and characterisation.

11-allyl-3,11a-dimethyldecahydro-2*H*-2,11-methanocyclohepta[*a*]-
-indolizine-6,9,12-trione (344)

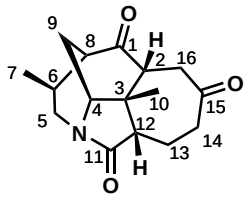


To a solution of **418** (33 mg, 0.086 mmol) in THF (3.4 mL) in a thick-walled tube (microwave vial) was added a solution of LiOH (163 mg, 6.80 mmol) in H_2O (3.4 mL) and MeOH (1.7 mL). The solution was sparged with Ar for 1 min then was sealed and placed in an oil bath pre-heated to 100 °C, and was stirred at that temperature for 16 h. The reaction was then cooled to RT and HCl (aq. 6 M, 4 mL) was added, and the resulting solution was stirred at RT for 30 mins. The solution was then neutralised with KOH (aq. 3 M), before extracting with EtOAc (5 x 20 mL). The combined organic layers were combined and dried over $MgSO_4$ and concentrated under vacuum. Purification by flash column chromatography (100% EtOAc) afforded ketone **344** (16 mg, 0.051 mmol, 59%) as a white solid.

^{1}**H-NMR** (400 MHz, $CDCl_3$): δ_H 5.44 (ddt, J = 17.1, 10.0, 7.2 Hz, 1H, H-18), 5.20–5.07 (m, 2H, H-19), 4.05 (dd, J = 13.7, 9.1 Hz, 1H, H-5a), 3.57 (d, J = 5.6 Hz, 1H, H-4), 3.16–3.09 (m, 1H, H-6), 3.05 (dd, J = 12.6, 1.7 Hz, 1H, H-16a), 2.69 (td, J = 8.7, 1.1 Hz, 1H, H-12h), 2.64–2.49 (m, 4H, H-14a, 9a, 17), 2.47–2.33 (m, 2H, H-13a, 14b), 2.29 (d, J = 12.7 Hz, 1H, H-16b), 2.21 (ddd, J = 13.7, 9.1, 1.2 Hz, 1H, H-5b), 2.15–2.10 (m, 1H, H-13b), 2.08 (ddd, J = 15.3, 5.7, 1.0 Hz, 1H, H-9b), 1.93 (dd, J = 5.2, 1.2 Hz, 1H, H-8), 1.32 (s, 3H, H-10), 1.02 (d, J = 6.9 Hz, 3H, H-7);

^{13}**C-NMR** (126 MHz, $CDCl_3$): δ_C 213.6 (C-15), 211.7 (C-1), 173.7 (C-11), 132.4 (C-18), 120.5 (C-19), 62.5 (C-4), 55.7 (C-3), 53.1 (C-2), 52.8 (C-12), 45.2 (C-8), 43.5 (C-16), 40.3 (C-5), 38.8, 38.0, 37.8 (C-6), 22.1 (C-10), 20.9 (C-13), 19.1 (C-9), 17.6 (C-7); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ $(C_{19}H_{25}O_3N^{23}Na)^+$ requires 338.1727, found 338.1727.

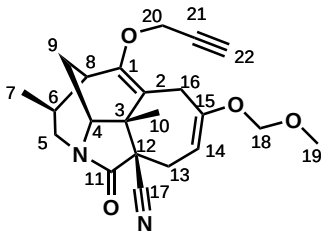
3,11a-dimethyldecahydro-2*H*-2,11-methanocyclohepta[*a*]indolizine-6,9,12-trione (349)



349 was formed as a by-product in several reactions. **IR** (thin film) $\tilde{\nu}_{max}^{-1}$ 2957 (C−H), 2853 (C−H), 1699 (C=O), 1457; ^{1}**H-NMR** (500 MHz, $CDCl_3$): δ_H 4.09 (dd, J = 13.5, 9.0 Hz, 1H, H-5a), 3.80–3.75 (m, 1H, H-4), 2.99 (H, H-J = 7.5 Hz, 1H, H-6), 2.72 (t, J = 4.5 Hz, 1H, H-2), 2.63–2.56 (m, 3H, H-8, H-16), 2.55 (dd, J = 13.0, 2.0 Hz, 1H, H-14a), 2.44 (dd, J = 18.0, 6.5 Hz, 1H, H-14b), 2.27 (ddd, J = 13.5, 9.5, 1.0 Hz, 1H, H-5b), 2.20–2.15 (m, 3H, H-9a, H-13), 1.99 (t, J = 2.5 Hz, 1H, H-12), 1.81 (dddd, J = 16.0, 13.0, 3.1, 1.6 Hz, 1H, H-9b), 1.47 (s, 3H, H-10), 1.03 (d, J = 7.0 Hz, 3H, H-7); ^{13}**C-NMR** (126 MHz, $CDCl_3$): δ_C 212.6 (C-1), 211.5 (C-15), 173.0 (C-11), 61.4 (C-4), 51.8 (C-2), 50.8 (C-8), 50.6 (C-3), 46.2 (C-12), 40.7 (C-5), 39.1 (C-14), 37.7 (C-16), 36.6 (C-6), 24.3 (C-10), 19.6 (C-13), 18.7 (C-9), 17.8 (C-7).

6.5.4 Zipper Route

9-(methoxymethoxy)-3,11a-dimethyl-6-oxo-12-(prop-2-yn-1-yloxy)--1,2,3,4,7,10,11a,11b-octahydro-2,11-(metheno)cyclohepta[*a*]indolizine--6a(6*H*)-carbonitrile (376)

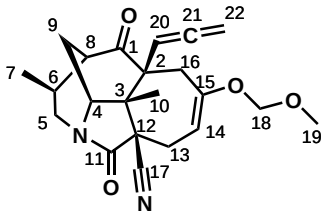


To a solution of tetracycle **314** (47 mg, 0.14 mmol) in dry degassed THF (2 mL) at 0 °C was added KHMDS (0.34 mL, 0.17 mmol; 0.50 M in toluene). The ice bath was removed and the solution was stirred at RT for 15 mins. A solution of propargyl tosylate (43 mg, 0.20 mmol) and 18-crown-6 (9.0 mg, 0.034 mmol) in THF (0.2 mL) was added slowly, and the resulting solution was stirred at RT for 2 h until completion. The reaction was quenched with H_2O and diluted with EtOAc, the layers were separated, then the aqueous phase was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated. Purification by column chromatography (40% EtOAc/pentane) afforded **376** (38 mg, 0.10 mmol, 73%).

^{1}**H-NMR** (500 MHz, C_6D_6): δ_H 4.81 (dd, J = 8.0, 6.5 Hz, 1H, H-14), 4.66 (d, J = 6.0 Hz, 1H, H-18b), 4.59 (d, J = 6.0 Hz, 1H, H-18a), 3.94–3.87 (m, 1H, H-5b), 3.86 (d, J = 2.5 Hz, 2H, H-20), 3.61 (d, J = 17.5 Hz, 1H, H-16b), 3.34 (d, J = 5.0 Hz, 1H, H-4), 3.14 (s, 3H, H-19), 2.71 (dd, J = 15.5, 8.0 Hz, 1H, H-13b), 2.67 (dd, J = 15.5, 7.0 Hz, 2H, H-13a), 2.62 (d, J = 17.5 Hz, 1H, H-16a), 1.93 (t, J = 2.5 Hz, 1H, H-22), 1.84–1.77 (m, 1H, H-5a), 1.75–1.69 (m, 1H, H-6), 1.66–1.64 (m, 1H, H-8),

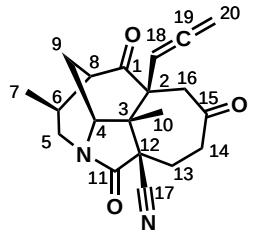
1.28 (s, 3H, H-10), 1.23 (ddd, J = 14.0, 5.0, 2.5 Hz, 2H, H-9b), 0.99 (dd, J = 14.0, 4.0 Hz, 2H, H-9a), 0.37 (d, J = 6.5 Hz, 3H, H-7); **^{13}C-NMR** (126 MHz, C_6D_6): δ_C 168.8 (C-11), 157.2 (C-15), 152.7 (C-1), 118.7 (C-17), 113.6 (C-2), 93.9 (C-18), 93.0 (C-14), 79.1 (C-21), 75.5 (C-22), 57.9 (C-4), 55.9 (C-19), 55.3 (C-20), 52.1 (C-3), 50.7 (C-12), 40.8 (C-5), 33.7 (C-8), 31.2 (C-6), 30.2 (C-16), 28.5 (C-13), 19.6 (C-9), 18.6 (C-10), 18.3 (C-7);

9-(methoxymethoxy)-3,11a-dimethyl-6,12-dioxo-11-(propa-1,2-dien-1-yl)-1,3,4,7,10,11,11a,11b-octahydro-2*H*-2,11-methanocyclohepta[*a*]indolizine-6a(6*H*)-carbonitrile (377)



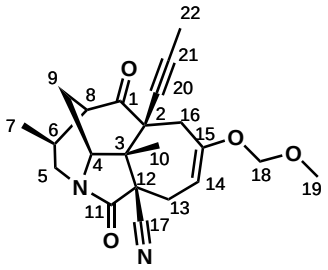
A solution of propargyl enol ether **376** (54.0 mg, 0.141 mmol) in dry degassed toluene (9.4 mL) in a sealed thick-walled tube was heated to 150 °C for 15 h. Upon completion, the reaction was cooled to RT then diluted with pentane (5 mL) and loaded directly onto a pentane-packed column. After flushing with pentane to remove toluene the product was eluted with 2:1 Et_2O/pentane to afford **377** (40.3 mg, 0.106 mmol, 75%). Due to broad ^{1}H NMR shifts, characterisation of **377** was not possible. **377** was treated with TFA/CH_2Cl_2 (1:1) at RT for 5 mins to hydrolyse the enol ether and afford **419** to aid with identification and characterisation.

3,11a-dimethyl-6,9,12-trioxo-11-(propa-1,2-dien-1-yl)decahydro-2*H*-2,11-methanocyclohepta[*a*]indolizine-6a(6*H*)-carbonitrile (419)



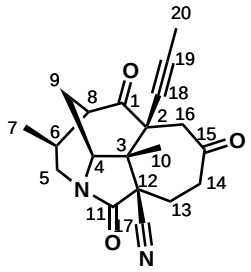
^{1}**H-NMR** (500 MHz, C_6D_6): δ_H 5.33 (t, J = 6.8 Hz, 1H, H-18), 4.42 (dd, J = 11.6, 6.8 Hz, 1H, H-20b), 4.28 (dd, J = 11.6, 6.8 Hz, 1H, H-20a), 3.81 (dd, J = 13.7, 9.1 Hz, 1H, H-5b), 3.25 (d, J = 13.3 Hz, 1H, H-16b), 3.22 (d, J = 6.0 Hz, 1H, H-4), 2.92 (dtdd, J = 10.3, 8.8, 7.6, 6.2 Hz, 1H, H-6), 2.43–2.34 (m, 1H, H-14b), 2.24 (d, J = 13.5 Hz, 1H, H-16a), 2.22–2.13 (m, 1H, H-13b), 1.99–1.90 (m, 2H, H-13a, 14a), 1.78 (ddd, J = 15.0, 5.0, 1.3 Hz, 1H, H-9b), 1.68 (dd, J = 4.9, 1.1 Hz, 1H, H-8), 1.47 (dd, J = 13.7, 9.3 Hz, 1H, H-5a), 1.12 (s, 2H, H-10), 1.11–1.06 (m, 1H, H-9a), 0.38 (d, J = 6.9 Hz, 3H, H-7); ^{13}**C-NMR** (126 MHz, C_6D_6): δ_C 208.1 (C-15), 207.5 (C-1), 205.2 (C-19), 166.5 (C-11), 119.6 (C-17), 93.9 (C-18), 78.9 (C-20), 61.0 (C-4), 56.4 (C-3), 55.3 (C-2), 53.4 (C-12), 47.7 (C-16), 45.3 (C-8), 40.7 (C-5), 37.2 (C-13), 36.7 (C-6), 28.2 (C-14), 19.4 (C-10), 17.6 (C-9), 17.1 (C-7).

9-(methoxymethoxy)-3,11a-dimethyl-6,12-dioxo-11-(prop-1-yn-1-yl)--1,3,4,7,10,11,11a,11b-octahydro-2*H*-2,11-methanocyclohepta[*a*]indolizine-6a(6*H*)-carbonitrile (378)



A 0.25 M solution of "KAPA" was prepared by dissolving KH (19 mg, 0.47 mmol) in 1,3-diaminopropane (1.9 mL). To a solution of allene **377** (15 mg, 0.039 mmol) in THF (0.5 mL) at 0 °C was added KAPA (0.63 mL, 0.16 mmol, 0.25 M solution). The resulting solution was stirred at 0 °C for 15 mins until complete. The reaction was quenched with H_2O (5 mL) then diluted with EtOAc (5 mL). The layers were separated then the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ then concentrated under vacuum. Purification by flash column chromatography (40% EtOAc/pentane) afforded **378** (7.8 mg, 0.021 mmol, 45%). Due to broad ^{1}H NMR shifts, characterisation of **378** was not possible. **378** was treated with TFA/CH_2Cl_2 (1:1) at RT for 5 mins to hydrolyse the enol ether and afford **420** to aid with identification and characterisation.

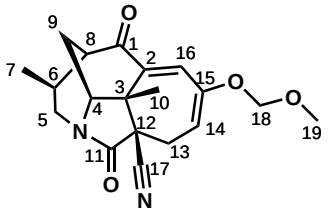
3,11a-dimethyl-6,9,12-trioxo-11-(prop-1-yn-1-yl)decahydro-2H-2,11--methanocyclohepta[a]indolizine-6a(6H)-carbonitrile (420)



IR (thin film) $\tilde{\nu}_{max}$$^{-1}$ 2958 (C−H), 2924 (C−H), 2231 (C≡C), 1719 ((C=O), 1429; ^{1}**H-NMR** (500 MHz, C_6D_6): δ_H 3.78 (dd, J = 13.7, 8.9 Hz, 1H, H-5b), 3.28 (d, J = 5.8 Hz, 1H, H-4), 3.22 (d, J = 14.7 Hz, 1H, H-16b), 2.88–2.79 (m, 1H, H-6), 2.66 (ddd, J = 15.1, 5.0, 1.3 Hz, 1H, H-9b), 2.45 (d, J = 14.7 Hz, 1H, H-16a), 2.38–2.24 (m, 4H, H-14), 2.23–2.15 (m, 2H, H-13b), 1.85–1.82 (m, 1H, H-8), 1.73–1.67 (m, 1H, H-13a), 1.51 (s, 3H, H-10), 1.50–1.44 (m, 2H, H-5a), 1.21 (s, 3H, H-20), 1.20–1.15 (m, 2H, H-9a), 0.34 (d, J = 7.0 Hz, 3H, H-7); ^{13}**C-NMR** (126 MHz, C_6D_6): δ_C 206.3 (C-15), 205.4 (C-1), 166.1 (C-11), 118.9 (C-17), 84.3 (C-19), 78.7 (C-18), 61.1 (C-4), 55.4 (C-3), 53.0 (C-2), 52.8 (C-12), 47.5 (C-16), 44.3 (C-8), 40.8 (C-5), 37.2 (C-14), 36.1 (C-6), 26.7 (C-13), 20.0 (C-10), 18.9 (C-9), 16.8 (C-7), 3.2 (C-20); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ $(C_{20}H_{23}O_3N_2)^+$ requires 339.1703, found 339.1704; **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ $(C_{20}H_{22}O_3N_2\,^{23}Na)^+$ requires 361.1523, found 361.1522.

6.5.5 [3+2] Cycloaddition Route

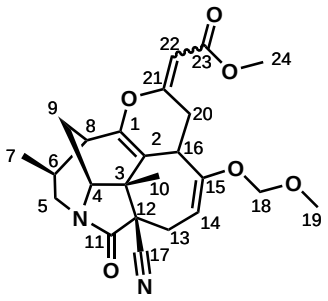
9-(methoxymethoxy)-3,11a-dimethyl-6,12-dioxo-1,3,4,7,11a,11b-hexahydro-2H-2,11-methanocyclohepta[a]indolizine-6a(6H)-carbonitrile (385)



To a solution of **314** (30 mg, 0.087 mmol) in dry degassed THF (1 mL) at RT was added KHMDS (0.50 M; 0.21 mL, 0.105 mmol). The solution was stirred for 10 mins, before NBS (19 mg, 0.11 mmol) was added by removing the septum and replacing following addition. The reaction was stirred at RT for 30 mins until complete, before diluting with sat. aq. solution of $NaHCO_3$ (5 mL) and extracting with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. Purification by flash column chromatography (40% EtOAc/pentane) afforded enone **385** (15 mg, 0.044 mmol, 51%) as a colourless oil. **IR** (thin film) $\tilde{\nu}_{max}^{-1}$ 2960 (C−H), 2924 (C−H), 1721 (C=C), 1287, 1156, 1072; ^{1}**H-NMR** (500 MHz, C_6D_6): δ_H 7.34 (q, J = 1.0 Hz, 1H, H-16), 5.23 (ddd, J = 8.5, 5.5, 1.0 Hz, 1H, H-14), 4.51 (d, J = 6.5 Hz, 1H, H-18a), 4.46 (d, J = 6.5 Hz, 1H, H-18b), 3.81 (dd, J = 13.5, 8.0 Hz, 1H, H-5a), 3.12 (dd, J = 6.0, 1.0 Hz, 1H, H-4), 3.04 (s, 2H, H-19), 2.57 (dd, J = 15.0, 8.5 Hz, 1H, H-13a), 2.41 (ddd, J = 15.0, 5.5, 1.0 Hz, 1H, H-13b), 2.19–2.07 (m, 1H, H-6), 1.86 (ddt, J = 3.5, 2.0, 1.0 Hz, 1H, H-8), 1.73 (dd, J = 13.5, 10.5 Hz, 1H, H-5b), 1.40 (s, 3H, H-10), 1.23 (ddd, J = 15.0, 6.0, 2.0 Hz, 1H, H-9a), 1.12 (dd, J = 15.0, 4.0 Hz, 1H, H-9b), 0.48 (d, J = 7.0 Hz, 3H, H-7); ^{13}**C-NMR** (126 MHz, C_6D_6): δ_C 198.1 (C-1), 167.6 (C-11),

155.0 (C-15), 141.4 (C-2), 140.4 (C-16), 117.3 (C-17), 104.5 (C-14), 94.1 (C-18), 62.4 (C-12), 57.0 (C-4), 55.8 (C-19), 52.3 (C-3), 45.6 (C-8), 41.4 (C-5), 38.0 (C-6), 30.9 (C-13), 19.3 (C-7), 18.8 (C-10), 17.1 (C-9);

methyl (E)-2-(10a-cyano-8-(methoxymethoxy)-2a1,11-dimethyl-1-oxo--2a,2a1,3,4,7,7a,10,10a-octahydro-5-oxa-2-aza-4,2-ethanonaphtho--[2,1,8-cde]azulen-6(1H)-ylidene)acetate (394)



To a solution of enone **385** (4.0 mg, 0.012 mmol) and ester **386** (3.2 mg, 0.033 mmol) in dry degassed toluene (0.25 mL) in a screw cap tube was added PBu_3 (1 *micro*L, 0.003 mmol). The tube was sealed under a flow of Ar and then heated to 85 °C for 2 h. Upon completion, the solution was concentrated under vacuum. Purification by flash column chromatography (20 to 40% EtOAc/pentane) afforded pentacycle **394** (2 mg, 0.005 mmol, ca. 40%).

IR (thin film) $\tilde{\nu}_{max}{}^{-1}$ 2960 (C−H), 1725 (C=O), 1463, 1261, 1122; ^{1}**H-NMR** (500 MHz, C_6D_6): δ_H 5.75 (d, J = 2.0 Hz, 1H, H-22), 4.63 (td, J = 8.0, 2.0 Hz, 1H, H-14), 4.53 (d, J = 6.0 Hz, 1H, H-18a), 4.45 (dd, J = 16.5, 3.5 Hz, 1H, H-20a), 4.35 (d, J = 6.0 Hz, 2H, H-18b), 4.35 – 4.25 (m, 4H), 3.87 (dd, J = 13.0, 7.5 Hz, 1H, H-5a), 3.43 (s, 3H, H-24), 3.25 (d, J = 5.0 Hz, 2H, H-4), 3.06 (s, 3H, H-19), 3.00 (d, J = 14.0 Hz, 1H, H-16), 2.72 (dd, J = 16.0, 8.0 Hz, 1H, H-13a), 2.49 (dd, J = 16.0, 8.0 Hz, 1H, H-13b), 2.27 – 2.16 (m, 1H, H-20b), 2.09 (t, J = 7.5 Hz, 2H), 1.81

– 1.69 (m, 2H, H-5b, H-6), 1.45 – 1.41 (m, 1H, H-8), 1.20 (s, 3H, H-10), 1.15 – 1.07 (m, 1H, H-9a), 1.01 – 0.96 (m, 1H, H-9b), 0.43 (d, J = 6.5 Hz, 3H, H-7); **^{13}C-NMR** (126 MHz, C_6D_6): δ_C 169.6 (C-1), 168.6 (C-21), 167.6 (C-11), 167.4 (C-23), 153.8 (C-15), 151.6 (C-2), 109.3 (C-17), 97.4 (C-22), 93.9 (C-18), 93.5 (C-14), 58.1 (C-4), 56.2 (C-19), 51.4 (C-12), 50.8 (C-24), 49.3 (C-3), 40.8 (C-5), 36.5 (C-8), 33.6 (C-16), 31.4 (C-6), 29.9 (C-13), 26.4 (C-20), 20.0 (C-10), 18.7 (C-7), 18.5 (C-9).

6.6 Single Crystal X-Ray Diffraction Data

6.6.1 Single crystal X-ray structure of (+)-166

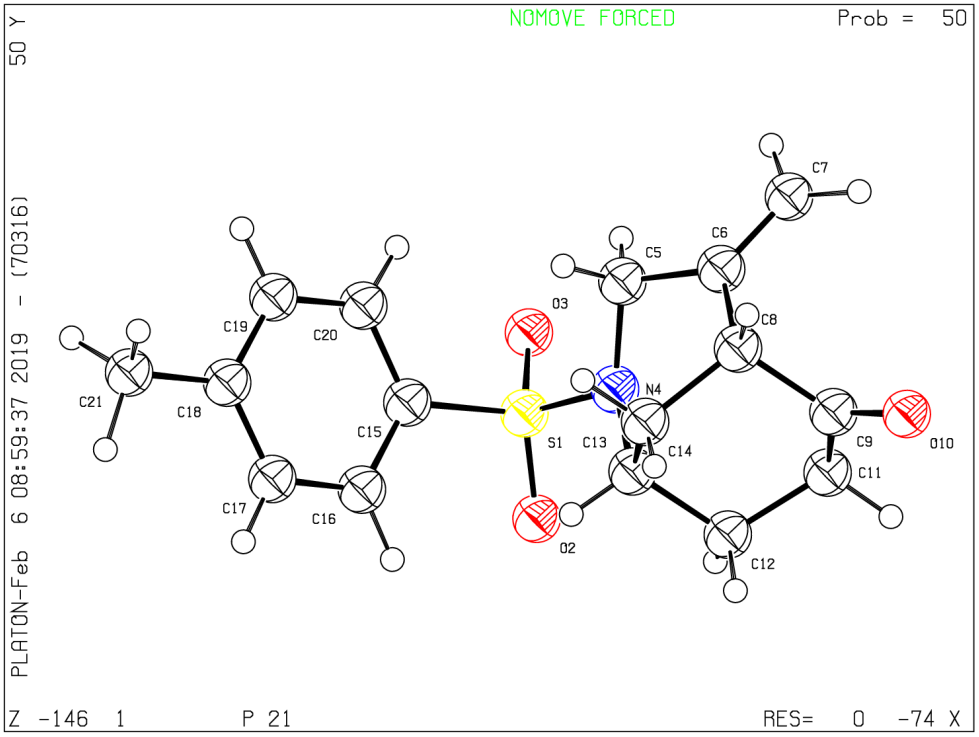


Figure 6.1: Ellipsoid plot for (+)-**166**.

Table 6.1: Experimental details for (+)-**166**

Crystal Data	
Chemical formula	$C_{16}H_{19}NO_3S$
M_r	305.40
Crystal system, space group	Monoclinic, $P2_1$
Temperature (K)	150
a, b, c (Å)	8.9552 (1), 7.8267 (1), 21.2948 (3)
β (°)	90.8045 (5)
V (Å^3)	1492.40 (2)
Z	4
Radiation type	Mo $K\alpha$
μ (mm^{-1})	0.23
Crystal size (mm)	0.12 x 0.20 x 0.30
Data collection	
Diffractometer	Nonius KappaCCD
Absorption correction	Multi-scan *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997)

T_{min}, T_{max}	1.00, 1.00
No. of measured, independent and observed [$I > 2.0\sigma(I)$] reflections	6799, 6799, 5920
R_{int}	0.000
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.649
Refinement	
R[$F^2 > 2\sigma(F^2)$], wR(F^2), S	0.034, 0.081, 0.36
No. of reflections	6799
No. of parameters	380
No. of restraints	1
H-atom treatment	H-atom parameters constrained
$\Delta_{\rho max}$, $\Delta_{\rho min}$ (e Å^{-3})	0.25, -0.26
Absolute structure	Flack (1983), 3157 Friedel-pairs
Absolute structure parameter	0.04 (6)

Table 6.2: Selected Geomtric Parameters for (+)-**166**

Atoms	**Parameters** (Å *or* °)	**Atoms**	**Parameters** (Å *or* °)
S1—O2	1.4357 (17)	C9—C11	1.514 (3)
S1—O3	1.4346 (18)	C11—C12	1.528 (3)
S1—N4	1.6372 (18)	C12—C13	1.526 (3)
S1—C15	1.757 (2)	C13—C14	1.524 (3)
N4—C5	1.482 (3)	C15—C16	1.392 (3)
N4—C13	1.500 (3)	C15—C20	1.395 (3)
C5—C6	1.509 (3)	C16—C17	1.396 (4)
C6—C7	1.321 (4)	C17—C18	1.394 (4)
C6—C8	1.530 (3)	C18—C19	1.384 (4)
C8—C9	1.517 (3)	C18—C21	1.513 (4)
C8—C14	1.538 (3)	C19—C20	1.393 (4)
C9—O10	1.218 (3)		
O2—S1—O3	120.07 (11)	O10—C9—C11	124.3 (2)
O2—S1—N4	106.92 (10)	C9—C11—C12	111.8 (2)
O3—S1—N4	106.67 (10)	C11—C12—C13	112.87 (18)
O2—S1—C15	108.09 (11)	C12—C13—N4	110.24 (18)
O3—S1—C15	108.32 (11)	C12—C13—C14	110.42 (19)
N4—S1—C15	105.94 (10)	N4—C13—C14	109.55 (18)
S1—N4—C5	116.17 (14)	C8—C14—C13	108.76 (19)
S1—N4—C13	115.63 (14)	S1—C15—C16	120.03 (18)
C5—N4—C13	116.26 (17)	S1—C15—C20	119.63 (18)
N4—C5—C6	108.72 (18)	C16—C15—C20	120.2 (2)
C5—C6—C7	121.9 (2)	C15—C16—C17	119.4 (2)
C5—C6—C8	115.1 (2)	C16—C17—C18	121.0 (2)
C7—C6—C8	123.0 (2)	C17—C18—C19	118.6 (2)
C6—C8—C9	110.2 (2)	C17—C18—C21	120.4 (3)
C6—C8—C14	108.92 (19)	C19—C18—C21	120.9 (3)
C9—C8—C14	107.9 (2)	C18—C19—C20	121.5 (2)
C8—C9—O10	121.8 (2)	C15—C20—C19	119.2 (2)
C8—C9—C11	113.89 (19)		

6.6.2 Single crystal X-ray structure of (+)-245

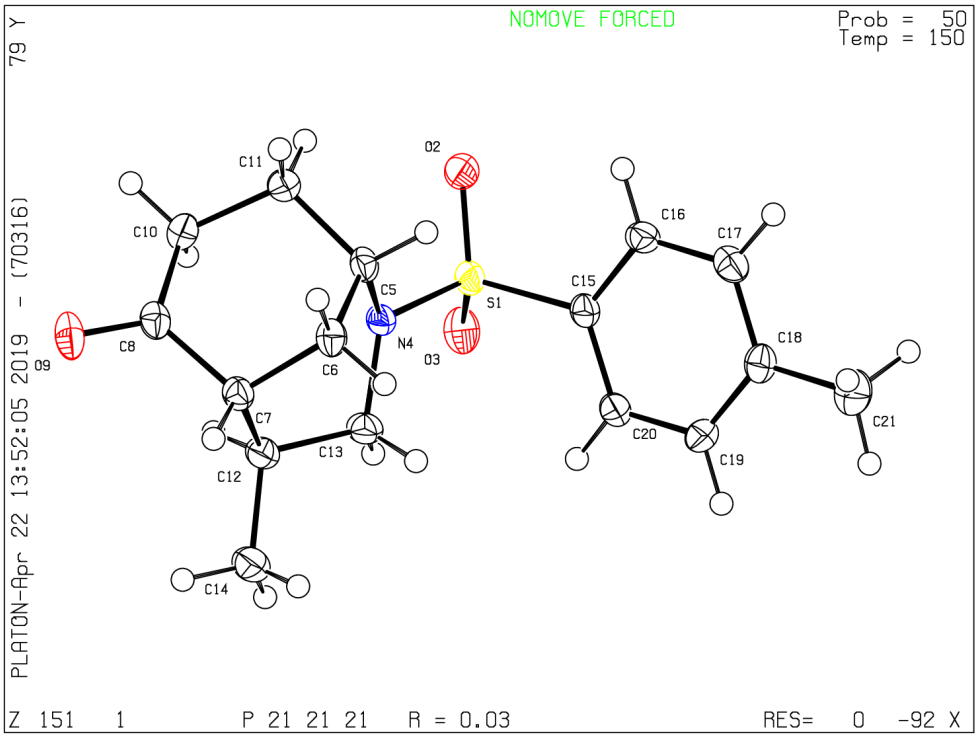


Figure 6.2: Ellipsoid plot for (+)-**245**.

Table 6.3: Experimental details for (+)-**245**

Crystal Data	
Chemical formula	$C_{16}H_{21}NO_3S$
M_r	307.41
Crystal system, space group	Orthorhombic, P212121
Temperature (K)	150
a, *b*, *c* (Å)	8.4462 (1), 11.7156 (2), 15.1836 (2)
V (Å^3)	1502.45 (4)
Z	4
Radiation type	Cu Kα
μ(mm^{-1})	2
Crystal size (mm)	0.32 × 0.32 × 0.32
Data collection	
Diffractometer	Nonius KappaCCD
Absorption correction	Multi-scan *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997)
T_{min}, T_{max}	0.49, 0.53
No. of measured, independent and observed [I >2.0σ(I)] reflections	21950, 3110, 3076
R_{int}	0.044
(sin θ/λ)$_{max}$ (Å^{-1})	0.630

Refinement	
R[$F^2 > 2\sigma(F^2)$], wR(F^2), S	0.027, 0.067, 0.93
No. of reflections	3099
No. of parameters	191
No. of restraints	H-atom parameters constrained
H-atom treatment	0.18, -0.29
$\Delta_{\rho max}$, $\Delta_{\rho min}$ (e Å^{-3})	Flack (1983), 1308 Friedel-pairs
Absolute structure	0.013 (13)
Absolute structure parameter	

Table 6.4: Selected Geomtric Parameters for (+)-**245**

Atoms	**Parameters** (Å *or* °)	**Atoms**	**Parameters** (Å *or* °)
S1—O2	1.4349 (11)	C8—C10	1.503 (2)
S1—O3	1.4332 (12)	C10—C11	1.536 (2)
S1—N4	1.6340 (11)	C12—C13	1.5076 (19)
S1—C15	1.7697 (15)	C12—C14	1.515 (2)
N4—C5	1.4953 (17)	C15—C16	1.388 (2)
N4—C13	1.4729 (17)	C15—C20	1.3906 (19)
C5—C6	1.517 (2)	C16—C17	1.382 (2)
C5—C11	1.5284 (19)	C17—C18	1.389 (2)
C6—C7	1.5383 (19)	C18—C19	1.394 (2)
C7—C8	1.5153 (19)	C18—C21	1.511 (2)
C7—C12	1.5599 (19)	C19—C20	1.385 (2)
C8—O9	1.2196 (18)		
O2—S1—O3	119.65 (7)	O9—C8—C10	121.99 (14)
O2—S1—N4	106.27 (6)	C8—C10—C11	114.02 (13)
O3—S1—N4	107.04 (6)	C10—C11—C5	111.81 (12)
O2—S1—C15	107.76 (7)	C7—C12—C13	111.92 (11)
O3—S1—C15	108.05 (7)	C7—C12—C14	112.53 (12)
N4—S1—C15	107.52 (6)	C13—C12—C14	110.44 (12)
S1—N4—C5	116.58 (9)	C12—C13—N4	111.06 (11)
S1—N4—C13	117.53 (9)	S1—C15—C16	119.70 (11)
C5—N4—C13	116.47 (11)	S1—C15—C20	119.49 (11)
N4—C5—C6	109.09 (11)	C16—C15—C20	120.79 (14)
N4—C5—C11	109.90 (11)	C15—C16—C17	119.05 (14)
C6—C5—C11	109.71 (12)	C16—C17—C18	121.30 (14)
C5—C6—C7	109.30 (12)	C17—C18—C19	118.66 (14)
C6—C7—C8	110.29 (11)	C17—C18—C21	120.58 (14)
C6—C7—C12	109.77 (11)	C19—C18—C21	120.74 (14)
C8—C7—C12	108.23 (11)	C18—C19—C20	120.85 (14)
C7—C8—O9	121.36 (14)	C15—C20—C19	119.19 (14)
C7—C8—C10	116.55 (12)		

6.6.3 Single crystal X-ray structure of 268

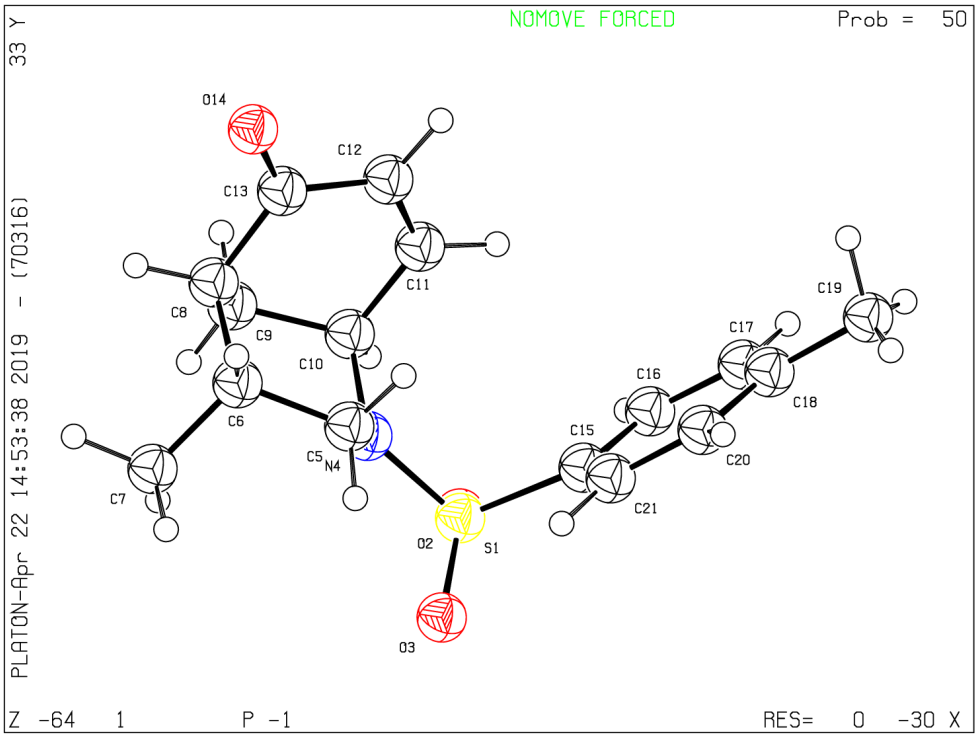


Figure 6.3: Ellipsoid plot for (+)-**268**.

Table 6.5: Experimental details for (+)-**268**

Crystal Data	
Chemical formula	$C_{16}H_{19}NO_3S$
M_r	305.4
Crystal system, space group	Triclinic, P1
Temperature (K)	150
a, b, c (Å)	6.8018 (2), 10.2652 (3), 21.6269 (8)
α, β, γ (°)	90.0270 (13), 89.9139 (13), 91.2601 (14)
V (Å^3)	1509.66 (6)
Z	4
Radiation type	Mo Kα
μ(mm^{-1})	0.22
Crystal size (mm)	0.15 × 0.20 × 0.50
Data collection	
Diffractometer	Nonius KappaCCD
Absorption correction	Multi-scan *DENZO/SCALEPACK* (Otwinowski & Minor, 1997)
T_{min}, T_{max}	1.00, 1.00
No. of measured, independent and observed [I >2.0σ(I)] reflections	11234, 6753, 3878
R_{int}	0.055
(sin θ/λ)$_{max}$ (Å^{-1})	0.648

Refinement	
R[$F^2 > 2\sigma(F^2)$], wR(F^2), S	0.055, 0.135, 0.90
No. of reflections	6753
No. of parameters	379
H-atom treatment	H-atom parameters constrained
$\Delta_{\rho max}$, $\Delta_{\rho min}$ (e Å^{-3})	0.82, -0.87

Table 6.6: Selected Geomtric Parameters for (+)-**268**

Atoms	**Parameters** (Å *or* °)	**Atoms**	**Parameters** (Å *or* °)
S1—O2	1.4346 (19)	C10—C11	1.491 (4)
S1—O3	1.4296 (19)	C11—C12	1.341 (4)
S1—N4	1.633 (2)	C12—C13	1.480 (4)
S1—C15	1.760 (3)	C13—O14	1.223 (3)
N4—C5	1.480 (3)	C15—C16	1.389 (4)
N4—C10	1.494 (3)	C15—C21	1.393 (4)
C5—C6	1.527 (4)	C16—C17	1.389 (4)
C6—C7	1.519 (4)	C17—C18	1.381 (4)
C6—C8	1.549 (4)	C18—C19	1.508 (4)
C8—C9	1.530 (4)	C18—C20	1.393 (4)
C8—C13	1.501 (4)	C20—C21	1.383 (4)
C9—C10	1.522 (4)		
O2—S1—O3	120.01 (12)	C9—C10—C11	111.0 (2)
O2—S1—N4	106.68 (11)	N4—C10—C11	111.6 (2)
O3—S1—N4	106.56 (11)	C10—C11—C12	122.0 (3)
O2—S1—C15	108.11 (12)	C11—C12—C13	121.1 (3)
O3—S1—C15	107.61 (12)	C8—C13—C12	116.9 (2)
N4—S1—C15	107.25 (12)	C8—C13—O14	122.1 (3)
S1—N4—C5	117.94 (17)	C12—C13—O14	121.0 (3)
S1—N4—C10	118.91 (17)	S1—C15—C16	120.5 (2)
C5—N4—C10	113.8 (2)	S1—C15—C21	119.4 (2)
N4—C5—C6	110.8 (2)	C16—C15—C21	120.0 (3)
C5—C6—C7	111.7 (2)	C15—C16—C17	119.5 (3)
C5—C6—C8	111.2 (2)	C16—C17—C18	121.2 (3)
C7—C6—C8	112.3 (2)	C17—C18—C19	120.7 (3)
C6—C8—C9	110.4 (2)	C17—C18—C20	118.6 (3)
C6—C8—C13	110.0 (2)	C19—C18—C20	120.7 (3)
C9—C8—C13	110.8 (2)	C18—C20—C21	121.1 (3)
C8—C9—C10	107.2 (2)	C15—C21—C20	119.5 (3)
C9—C10—N4	106.9 (2)		

6.6.4 Single crystal X-ray structure of 273

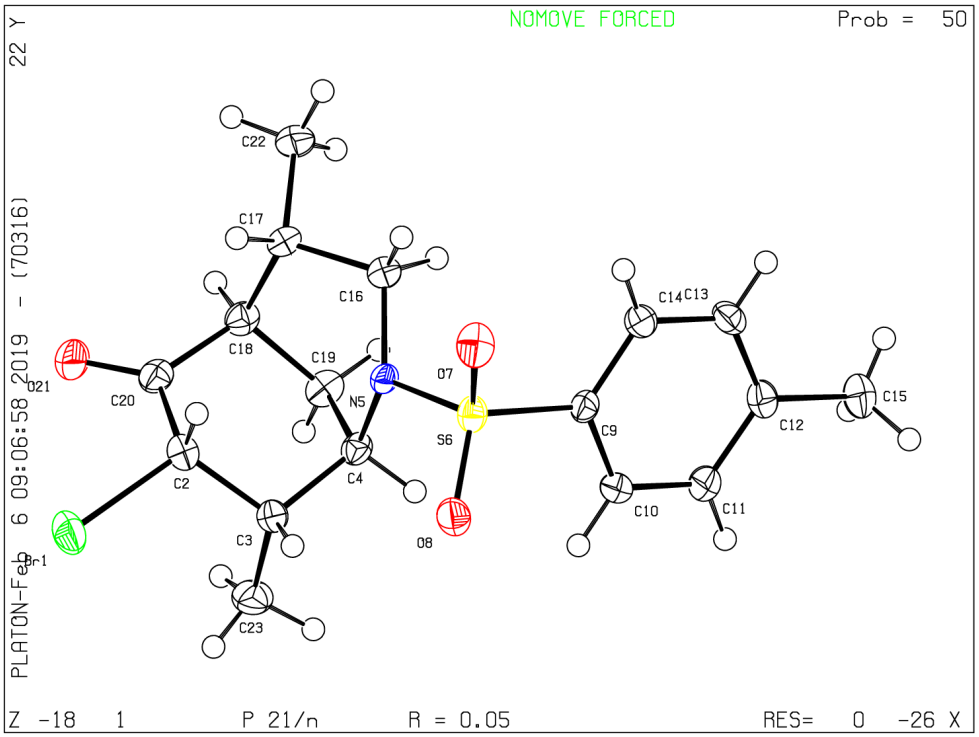


Figure 6.4: Ellipsoid plot for (+)-**273**.

Table 6.7: Experimental details for (+)-**273**

Crystal Data	
Chemical formula	$C_{17}H_{22}BrNO_3S$
M_r	400.34
Crystal system, space group	Monoclinic, P21/n
Temperature (K)	150
α, β, γ (Å)	10.1221 (2), 13.5269 (3), 12.3068 (3)
β (°)	93.4712 (8)
V (Å^3)	1681.96 (4)
Z	4
Radiation type	Mo Kα
μ(mm^{-1})	2.58
Crystal size (mm)	0.15 × 0.20 × 0.30
Data collection	
Diffractometer	Nonius KappaCCD
Absorption correction	Multi-scan *DENZO/SCALEPACK* (Otwinowski & Minor, 1997)
T_{min}, T_{max}	1.00, 1.00
No. of measured, independent and observed [I >2.0σ(I)] reflections	7100, 3826, 3398
R_{int}	0.019
(sin θ/λ)$_{max}$ (Å^{-1})	0.649

Refinement

R[$F^2 > 2\sigma(F^2)$], wR(F^2), S	0.047, 0.096, 0.69
No. of reflections	3826
No. of parameters	274
H-atom treatment	Only H-atom coordinates refined
$\Delta_{\rho max}$, $\Delta_{\rho min}$ (e Å^{-3})	3.14, -0.79

Table 6.8: Selected Geomtric Parameters for (+)-**273**

Atoms	**Parameters** (Å *or* °)	**Atoms**	**Parameters** (Å *or* °)
Br1—C2	1.948 (3)	C9—C14	1.385 (4)
C2—C3	1.531 (4)	C10—C11	1.383 (4)
C2—C20	1.526 (4)	C11—C12	1.390 (4)
C3—C4	1.536 (4)	C12—C13	1.395 (5)
C3—C23	1.528 (4)	C12—C15	1.505 (4)
C4—N5	1.497 (4)	C13—C14	1.388 (4)
C4—C19	1.535 (4)	C16—C17	1.520 (4)
N5—S6	1.637 (2)	C17—C18	1.568 (4)
N5—C16	1.482 (4)	C17—C22	1.530 (4)
S6—O7	1.430 (2)	C18—C19	1.525 (4)
S6—O8	1.442 (2)	C18—C20	1.513 (4)
S6—C9	1.758 (3)	C20—O21	1.209 (4)
C9—C10	1.392 (4)		
Br1—C2—C3	111.5 (2)	C10—C9—C14	120.3 (3)
Br1—C2—C20	110.8 (2)	C9—C10—C11	119.6 (3)
C3—C2—C20	114.4 (3)	C10—C11—C12	121.2 (3)
C2—C3—C4	108.8 (2)	C11—C12—C13	118.3 (3)
C2—C3—C23	114.9 (3)	C11—C12—C15	120.6 (3)
C4—C3—C23	111.0 (3)	C13—C12—C15	121.1 (3)
C3—C4—N5	110.2 (2)	C12—C13—C14	121.4 (3)
C3—C4—C19	110.3 (3)	C13—C14—C9	119.3 (3)
N5—C4—C19	108.5 (2)	N5—C16—C17	110.7 (2)
C4—N5—S6	116.69 (19)	C16—C17—C18	111.8 (2)
C4—N5—C16	116.5 (2)	C16—C17—C22	108.7 (3)
S6—N5—C16	115.52 (19)	C18—C17—C22	109.7 (3)
N5—S6—O7	107.39 (14)	C17—C18—C19	108.9 (2)
N5—S6—O8	105.76 (13)	C17—C18—C20	112.4 (3)
O7—S6—O8	119.64 (15)	C19—C18—C20	110.4 (3)
N5—S6—C9	108.03 (13)	C4—C19—C18	108.8 (2)
O7—S6—C9	107.96 (14)	C2—C20—C18	115.2 (3)
O8—S6—C9	107.58 (14)	C2—C20—O21	123.0 (3)
S6—C9—C10	118.6 (2)	C18—C20—O21	121.8 (3)
S6—C9—C14	121.1 (2)		

6.6.5 Single crystal X-ray structure of 314

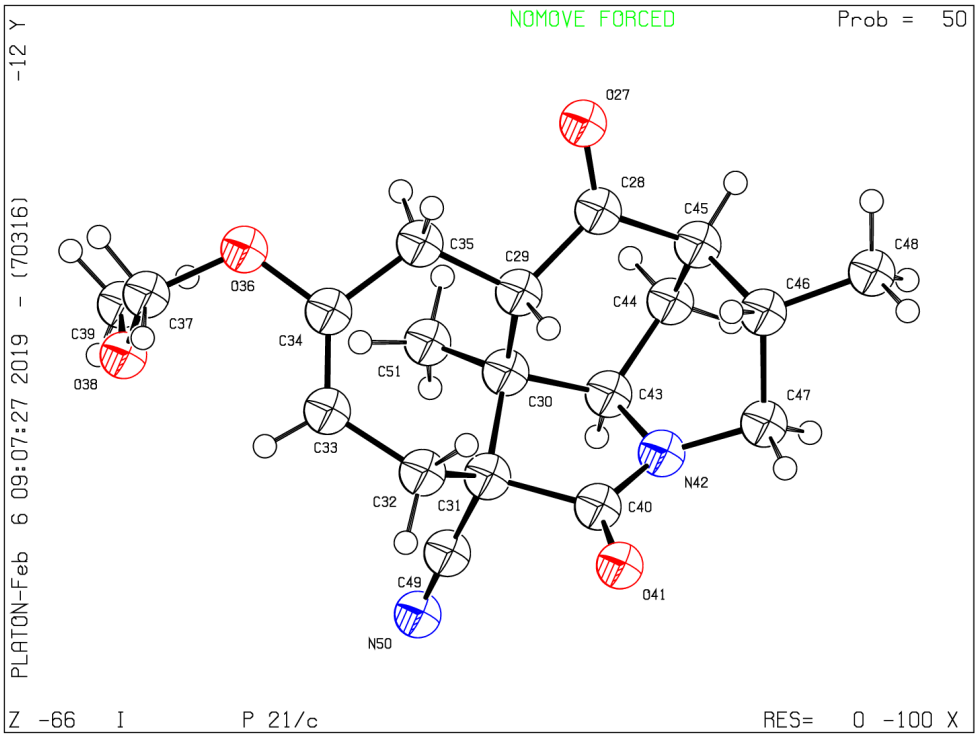


Figure 6.5: Ellipsoid plot for (+)-**314**.

Table 6.9: Experimental details for (+)-**314**

Crystal Data	
Chemical formula	$C_{19}H_{24}N_2O_4$
M_r	351.91
Crystal system, space group	Monoclinic, P21/c
Temperature (K)	150
a, b, c (Å)	8.5157 (1), 24.3538 (4), 16.6879 (3)
β (°)	91.4921 (16)
V (Å^3)	3459.72 (6)
Z	8
Radiation type	Cu Kα
μ (mm^{-1})	0.8
Crystal size (mm)	0.12 × 0.20 × 0.32
Data collection	
Diffractometer	Oxford Diffraction SuperNova
Absorption correction	Multi-scan CrysAlis PRO (Agilent, 2011)
T_{min}, T_{max}	0.88, 1.00
No. of measured, independent and observed [I >2.0σ(I)] reflections	54114, 7228, 6543
R_{int}	0.032
(sin θ/λ)$_{max}$ (Å^{-1})	0.63

Refinement	
R[$F^2 > 2\sigma(F^2)$], wR(F^2), S	0.067, 0.204, 0.99
No. of reflections	7228
No. of parameters	460
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta_{\rho max}$, $\Delta_{\rho min}$ (e Å^{-3})	0.68, -1.21

Table 6.10: Selected Geomtric Parameters for (+)-**314**

Atoms	**Parameters** (Å *or* °)	**Atoms**	**Parameters** (Å *or* °)
O1—C2	1.213 (3)	N10—C15	1.460 (3)
C2—C3	1.530 (3)	C11—C12	1.512 (3)
C2—C13	1.519 (3)	C12—C13	1.528 (3)
C3—C4	1.557 (3)	C13—C14	1.568 (3)
C3—C20	1.530 (3)	C14—C15	1.538 (3)
C4—C5	1.572 (3)	C14—C16	1.527 (3)
C4—C11	1.542 (3)	C17—C18	1.498 (4)
C4—C25	1.528 (3)	C18—C19	1.324 (4)
C5—C6	1.470 (3)	C19—C20	1.511 (3)
C5—C8	1.560 (3)	C19—O21	1.384 (3)
C5—C17	1.553 (3)	O21—C22	1.424 (3)
C6—N7	1.141 (3)	C22—O23	1.383 (4)
C8—O9	1.214 (3)	O23—C24	1.430 (4)
C8—N10	1.344 (3)	O26—C27	1.375 (3)
N10—C11	1.466 (3)		
O1—C2—C3	120.82 (19)	C11—N10—C15	118.81 (18)
O1—C2—C13	121.69 (19)	C4—C11—N10	102.40 (16)
C3—C2—C13	117.44 (17)	C4—C11—C12	115.72 (18)
C2—C3—C4	114.85 (16)	N10—C11—C12	110.47 (18)
C2—C3—C20	110.07 (17)	C11—C12—C13	108.36 (17)
C4—C3—C20	114.45 (17)	C12—C13—C2	106.19 (17)
C3—C4—C5	105.83 (15)	C12—C13—C14	111.36 (17)
C3—C4—C11	110.06 (16)	C2—C13—C14	113.25 (17)
C5—C4—C11	100.09 (16)	C13—C14—C15	111.55 (18)
C3—C4—C25	113.73 (17)	C13—C14—C16	111.53 (18)
C5—C4—C25	116.29 (17)	C15—C14—C16	110.21 (18)
C11—C4—C25	109.93 (17)	C14—C15—N10	109.22 (17)
C4—C5—C6	111.55 (17)	C5—C17—C18	114.69 (19)
C4—C5—C8	101.55 (16)	C17—C18—C19	122.3 (2)
C6—C5—C8	108.72 (18)	C18—C19—C20	127.7 (2)
C4—C5—C17	116.01 (17)	C18—C19—O21	125.8 (2)
C6—C5—C17	110.26 (18)	C20—C19—O21	106.5 (2)
C8—C5—C17	108.15 (18)	C3—C20—C19	117.57 (18)
C5—C6—N7	178.6 (3)	C19—O21—C22	118.6 (2)
C5—C8—O9	124.9 (2)	O21—C22—O23	112.7 (2)
C5—C8—N10	107.59 (18)	C22—O23—C24	115.7 (3)
O9—C8—N10	127.5 (2)	C27—O26—C48	118.2 (2)
C8—N10—C11	112.61 (18)	O26—C27—C28	125.3 (2)

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