To Piperidines and Beyond

A thesis submitted in partial fulfilment of the requirement

for the degree of Doctor of Philosophy

by

Cameron E. Taylor

New College

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The work described in this thesis was carried out in the Chemistry Research Laboratory, University of Oxford from October 2017 until December 2020, under the supervision of Professor Stephen G. Davies and Professor Angela J. Russell. All of the work is my own unless otherwise stated and has not been submitted for any other degree at this or any other university.

Cameron Taylor

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Abstract

This thesis describes the development of synthetic routes to investigate the relative and absolute stereochemistry of a number of piperidine alkaloids isolated from *Microcos Paniculata*. This thesis then goes on to explore an intramolecular Diels-Alder reaction, and explores its applicability to natural product synthesis.

Chapter 1 introduces the biological significance of piperidine alkaloids, followed by a brief review of noteworthy chemical syntheses of piperidine and (piperidine-containing) natural products.

Chapter 2 describes the isolation of Microcosamine A, and previous synthetic efforts towards the alkaloid. The chapter then describes the development and optimisation of a synthetic route to the alkaloid, culminating with independent verification of its relative and absolute configuration.

Chapter 3 describes the isolation, synthesis, and independent assessment of relative and absolute configuration of Microgrewiapines A─C, natural products from *Microcos Paniculata*.

Chapter 4 presents corrected ^{1}H NMR data for the originally isolated sample of the alkaloid microconine. The asymmetric synthesis of the two C(3) epimeric forms of this compound are presented which allow the unambiguous assignment of relative and absolute configuration.

Chapter 5 describes the exploration of an intramolecular Diels Alder reaction using substrates derived from the amine ring opening of benzene oxide. Initial experiments use *N*-substituted allyl amines, which perform a ring opening and spontaneous cycloaddition in 1 step to yield racemic tricycles. Later an enantiopure route is developed utilising ring opening with a chiral amine.

Chapter 6 contains full experimental procedures and characterisation data for all compounds synthesised in Chapters 2–5.

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Contents

Abbreviations

~	Approximately
(+)	Dextrorotatory
°	Degrees
<	Greater than
ν_{max}	Infrared absorption maximum
>	Less than
(−)	Levorotatory
ε	Molar absorption coefficient
μW	Microwave
δ	NMR Chemical shift
π*	Pi antibonding orbital
±	Racemic
$[\alpha]_D$	Specific Rotation
σ*	Sigma antibonding orbital
Å	Angstrom
Ac	Acetyl
app	Apparent
APCI	Atmospheric Pressure Chemical Ionisation
aq	Aqueous
Ar	Aryl
Ax	Axial
atm	Atmosphere
ATR	Attenuated total reflectance
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl

br	Broad
Bu	Butyl
Bus	*tert*-Butylsulfonyl
BT	Benzothiazolyl
c	Concentration
C	Celsius
Cbz	Carboxybenzyl
CD	Circular Dichroism
cm	Centimetre
CSA	Camphorsulfonic acid
CSO	Camphorsulfoxaziridine
D	Dextrorotatory relative to (+)-glyceraldehyde
d	Doublet
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DCC	*N*,*N*'-Dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
dec	Decomposed
deg	Degrees
DET	Diethyltartrate
DHQD	Dihydroquinidine
DIBAL-H	Diisobutylaluminium hydride
Dipp	2,6-Diisopropylphenyl
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMP	Dess–Martin periodinane

DMSO	Dimethyl sulfoxide
dr	Diastereomeric ratio
DTBMP	2,6-Di-tert-butylpyridine
E	Entgegen
ECD	Electronic Circular Dichroism
ee	Enantiomeric excess
ent	Enantiomer
epi	Epimer
eq	Equatorial
equiv.	Equivalent
er	Enantiomeric ratio
ESI	Electrospray ionisation
Et	Ethyl
FT	Fourier transform
g	Gaseous
g	Gram
h	Hour
HMBC	Heteronuclear Multiple Bond Correlation spectroscopy
HMDS	Bis(trimethylsilyl)amine
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
hν	light
HWE	Horner–Wadsworth–Emmons
Hz	Hertz
i	iso
IBX	2-Iodoxybenzoic acid
IR	Infrared

J	Coupling Constant
kJ	Kilojoule
L	Levorotatory relative to (+)-glyceraldehyde
L	Litre
LDA	Lithium diisopropylamide
lit.	Literature
μ	Micro
m	multiplet
m	meta
M	Molar
M^+	Molecular ion
m/z	Mass to charge ratio
m-CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
mg	Milligram
MHz	Megahertz
min	Minute
mL	Millilitre
mmol	Millimole
mol	Mole
MOM	Methoxymethyl
mp	Melting point
Ms	Methanesulfonyl
MS	Mass Spectrometry
MS	Molcular Sieves
MVK	Methyl vinyl ketone
N	Normality

NBS	N-Bromosuccinimide
nm	Nanometer
NMO	4-Methylmorpholine *N*-oxide
NMR	Nuclear Magnetic Resonance
Nu	Nucleophile
nOe	Nuclear Overhauser effect
NOESY	Nuclear Overhauser Effect Spectroscopy
o	ortho
p	para
p	pentet
PG	Protecting Group
pH	Potential of Hydrogen
Ph	Phenyl
PHAL	1,4-Phthalazinediyl diether
Piv	Pivaloyl
Pin	Pinacolato
PMB	para-Methoxybenzyl
PMP	para-Methoxyphenyl
ppm	parts per million
PPTS	Pyridinium *p*-toluenesulfonate
Pr	Propyl
PT	Phenyltetrazole
Py	Pyridine
quant	Quantitative
R	Rectus
R	Unspecified organic group
rac	Racemic

Ref	Reference
rt	Room temperature
S	Sinister
s	Second
s	Singlet
satd	Saturated
t	tertiary
t	triplet
TBAF	*tetra*-*N*-Butylammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TBHP	*tert*-Butylhydroperoxide
TBS	*tert*-Butyldimethylsilyl
^{t}Bu	*tert*-Butyl
temp/T	Temperature
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy
Tf	Trifluoromethanesulfonyl
TFE	2,2,2-Trifluoroethanol
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin Layer Chromatography
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
ToF	Time of Flight
TPAP	Tetrapropylammonium perruthenate
Ts	4-Toluenesulfonyl

TSP	Trimethylsilylpropanoic acid
UV	Ultraviolet
V	Volume
w	Weight
Z	Zusammen

Chapter 1 Introduction

1.1 Metabolites

Compounds found in living organisms can be split into two major groups: primary and secondary metabolites. Primary metabolites are those involved in, and produced by, primary metabolic processes. This includes glycolysis, the citric acid cycle, and photosynthesis. Primary metabolites comprise many sugars, amino acids, low molecular weight organic acids, fatty acids, and some proteins that are identical across most of life. Despite this overlap, there are huge differences in the specific pathways leading to these primary metabolites.[1–3]

Secondary metabolites originate from mutations to genes originally associated with primary metabolic pathways. These mutations are likely to lead to death, particularly in haploidic organisms. In diploidic, prokaryotic organisms the accumulation of recessive characters is possible, and mutations are not necessarily expressed immediately. This has allowed secondary metabolites to become numerous and widespread. The onset of secondary metabolism is linked to the developmental stage of the organism, closely tied to morphological and cytological changes.[1,4]

1.2 Secondary Metabolites in Plantae

Of course there is some overlap between primary and secondary metabolites, and many metabolites in plants are frequently referred to as both primary and secondary metabolites.[5] Plant hormones such as abscisic acid **1**, indoleacetic acid (auxin) **2**, ethylene, gibberellic acid **3**, and kinetin **4**, as well as compounds involved in plant cell wall structure such as cinnamic acid **5** and its polymeric derivative, lignin (Figure 1), have been referred to both as primary and secondary metabolites.

Further to this, compounds normally considered to be primary metabolites may accumulate in such large quantities that they behave like secondary metabolites. Historically, shikimic acid **6**[6,7]

and squalene **7**[8] were considered as secondary metabolites, before being shown to be important intermediates in the formation of primary metabolites (phenylalanine, tyrosine, tryptophan, and steroids) (Figure 1).

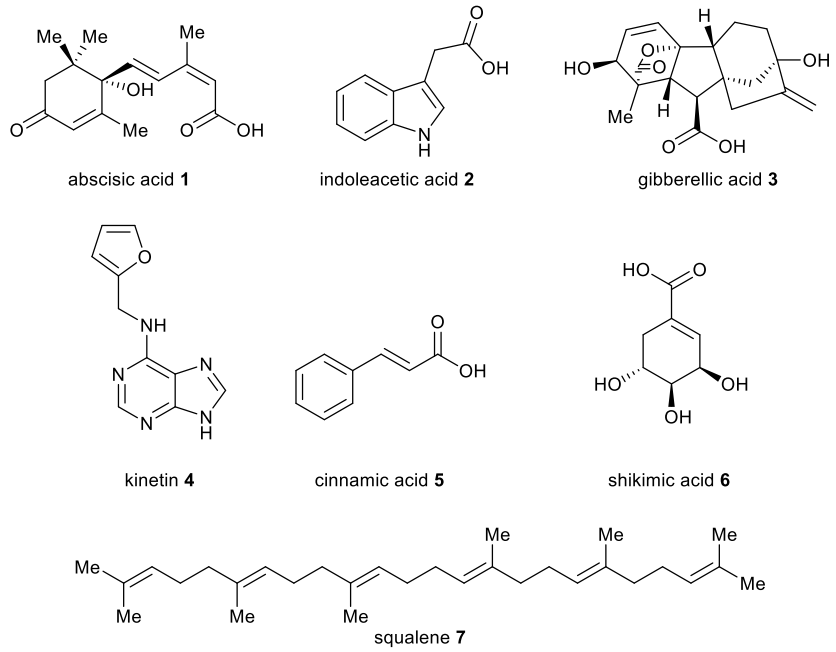


Figure 1: Selection of Primary metabolites in Plantae.

1.3 Natural Products as drugs

For virtually the whole of human history, natural products from plants and animals have been the sole source of medicines. The enormous structural variation associated with natural products continues to provide a source of inspiration that results in natural products continuing to enter clinical trials or to provide leads for compounds that have entered clinical trials, particularly as anticancer and antimicrobial agents.[9–11]

1.4 Alkaloids

Alkaloids, nitrogen-containing compounds produced by vascular plants, are some of the most chemically complex molecules found in Nature, and exhibit an appropriately diverse array of biological activities. The first of these to be discovered was morphine in 1805.[12] The seminal biosynthetic work done in the field was by Sir Robert Robinson in 1917.[13]

There are an astonishingly large list of plant alkaloids which are marketed drugs with no chemical modification at all,[2] and a cursory glance over this list shows the huge proportion which contain the piperidine motif (a subset within the alkaloids). Exemplar drugs are cytisine **8**, atropine **9**, hyoscine **10**, catuabine A **11** and ergotamine **12** (Figure 2).

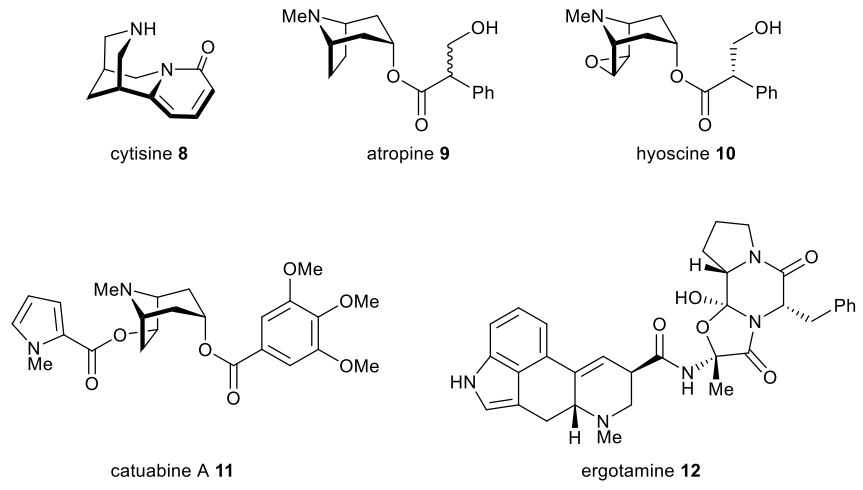


Figure 2: Exemplar piperidine Containing Drugs.

1.5 Piperidines

The piperidine group is named after the *Piper* genus, from which a large number of piperidines were isolated.[14] Piperidine alkaloids are characteristically found in plants, although some have been isolated from outside of the kingdom Plantae.[15,16] Piperidines are a so-called "privileged scaffold"[17,18] found in a large number of important pharmaceutical compounds.[19–21]

The piperidine motif exists also as a component of other natural products classes including; indolizidines (e.g., tashiroimine **13**), quinolizidines (e.g., myrtine **14**) and indoles (e.g., geissoschizine **15**) (Figure 3).

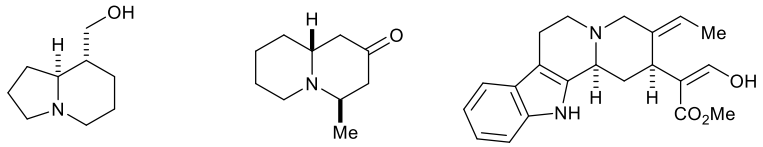


Figure 3: The structures of tashiroimine **13**, myrtine **14**, and geissoschizine **15**.

1.6 Syntheses of piperidines

It is of the upmost importance in any synthetic route to piperidines that the azacycle is constructed in a manner which enables the desired substitution pattern to be introduced diastereo- and enantioselectively.

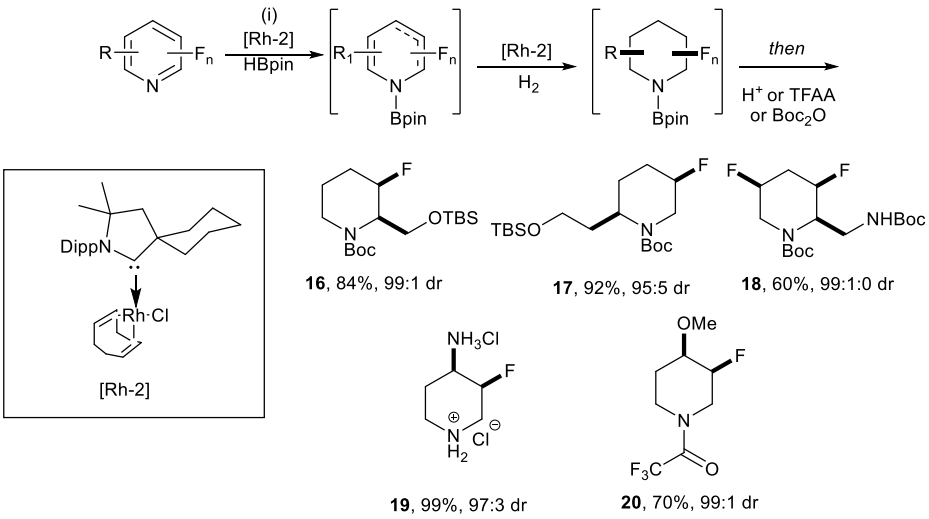
To this end, an enormous variety of different methods exist, and rightly the synthesis of piperidine skeletons has been reviewed extensively.[22–25] Exemplar routes include: reduction of pyridines, aza-Diels-Alder reactions, ring-expansions of pyrrolidines, and intramolecular reductive aminations. A representative example from each class is discussed in the following sections.

1.6.1 *Piperidines from the Reduction of Pyridines*

The reduction of pyridines to piperidines is a very powerful technique because pyridines with varying substitution patterns are readily available. The reaction can proceed through simultaneous

reduction of all the π-bonds, or sequential reduction forming the corresponding dihydro- and tetrahydropyridines, which allows the possibility for further functionalisation of the remaining double bond(s). Complete reduction of pyridines to piperidines via catalytic hydrogenation has the potential to create up to five stereocentres in a single transformation. In order to discriminate between the two faces of the piperidine ring, either a group containing a stereogenic centre must be attached to the pyridine, or a chiral catalyst must be used.

Recently the formation of all *cis*-(poly) fluorinated piperidines by a one-pot dearomatization–hydrogenation process in a highly diastereoselective fashion was shown by Glorius and co-workers[26] (Scheme 1). A variety of rhodium complexes were examined, from which the Rh–CAAC complex **[Rh-2]** was found to be superior. Upon complete reduction of the (poly)fluorinated pyridines, a trapping agent (H^+, TFAA, or Boc_2O) was added to prevent loss of the volatile fluorinated piperidine derivatives. The reaction works for a wide range of pyridines, some of which are shown below.

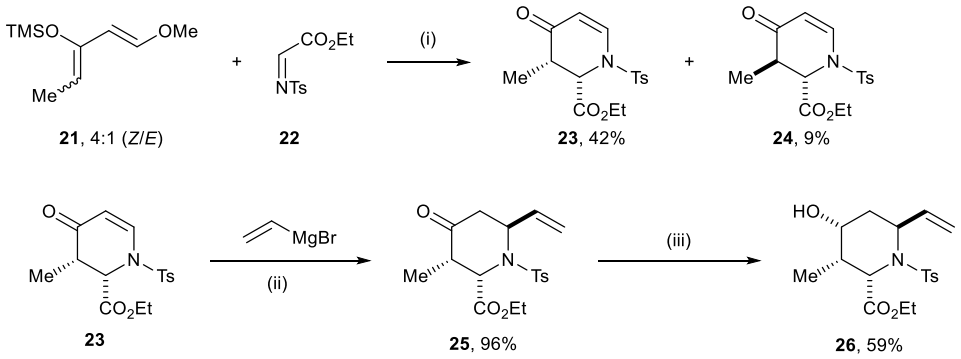


Scheme 1: *cis*-(poly) fluorinated piperidine syntheses by Glorius and co-workers.[26] *Reagents and Conditions*: (i) 4 Å MS, THF (1 M), H_2 (50 bar) 25–40 °C, 24 h.

1.6.2 *Piperidines from aza-Diels-Alder reactions*

The aza-Diels-Alder reaction is a powerful, general method for the preparation of piperidines, allowing the construction of complex systems with high regio-, diastereo,- and enantioselectivity.[27] The nitrogen atom present in the piperidine core may be introduced as part of an azadiene (diene) or as an imine (dienophile).

Heintzelman and Weinreb showed the impact of this method by the synthesis of the piperidine A-ring precursor to the alkaloid cylindrospermopsin (Scheme 2).[28] The known diene **21** reacted with the glyoxylate-derived *N*-tosylimine **22** to afford (after in situ acid hydrolysis) a mixture of enones **23** and **24**. The major *cis* product **23** is proposed to arise from the (*Z*)-diene via a transition state in which the carboxylate group of the imine **22** is *endo*. The major enone was found to undergo copper-promoted conjugate addition to yield vinyl ketone **25** as a single diastereomer in 96% yield. This was then reduced with L-selectride to form the desired piperidin-ol **26** in 59% yield (Scheme 2).

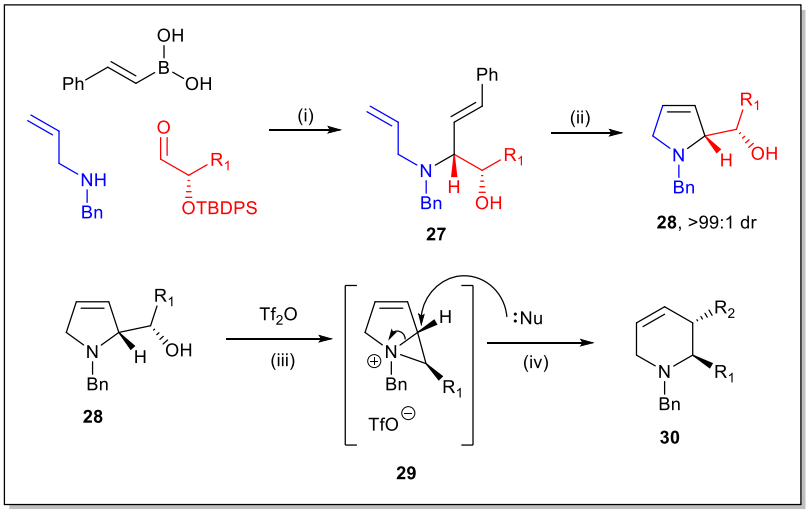


Scheme 2: Piperidines from aza-Diels-Alder reactions by Heintzelman and Weinreb.[28] *Reagents and conditions*: (i) PhMe, rt, 3 h, then 5% aq HCl, rt, 30 min; (ii) CuI/THF, $BF_3{\cdot}Et_2O$, −78 °C, 16 h; (iii) L-selectride, THF, −78 °C, 1.5 h.

1.6.3 *Piperidines from Ring-expansions*

Jarvis and Charette reported the asymmetric synthesis of 3-substituted piperidines via irreversible pyrrolinol ring-expansion.[29] The pyrrolinols **28** were synthesised via a Petasis-Mannich condensation from readily available chiral pool starting materials. Aziridinium ion **29** was prepared

by treatment with triflic anhydride and proton sponge at −15 °C, and subsequent treatment with a range of nucleophiles allowed a series of piperidines to be formed. Highly regioselective strain-promoted ring-expansion allows the introduction of a large variety of nucleophiles at the 3-position and tolerates substitution at the 2- and 6-position giving mono-, di-, or trisubstituted piperidines with high diastereocontrol (Table 1).



Reagents and conditions: (i) TBAF, EtOH, reflux, 16 h; (ii) Grubbs' 2nd gen. cat., CH_2Cl_2, 50 °C, 16 h; (iii) proton sponge, CH_2Cl_2, −15 °C, 1 h; (iv) **see table**.

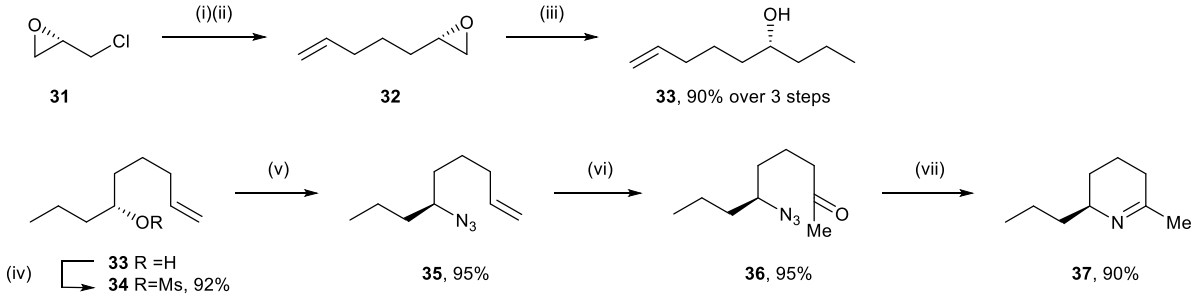
Nucleophile	R_1	R_2	Yield of 30 from Pyrrolinol 28 (%)
$NaCH(CO_2Me)_2$	H	$CH(CO_2Me)_2$	87
$NaCH(CO_2Me)_2$	Me	$CH(CO_2Me)_2$	71
$NaCH(CO_2Me)_2$	$CH(Me)_2$	$CH(CO_2Me)_2$	73
NH_2Ph	Me	NHPh	80
TBAF	Me	F	57

Table 1: Pyrrolinol ring-expansion by Jarvis and Charette.[29]

1.6.4 *Intramolecular reductive aminations*

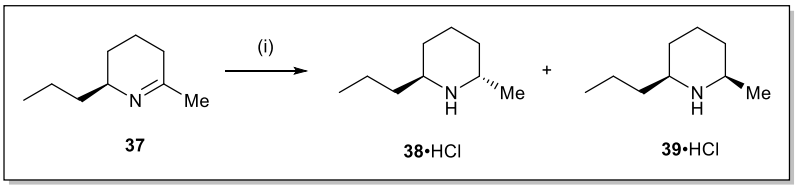
Intramolecular reductive aminations are particularly powerful methods to synthesise 2,6-disubstituted piperidines. Either 2,6-*cis* or 2,6-*trans* cyclisation can be afforded with high levels of diastereoselectivity.

Kavala et al.[30] have recently shown how effectively 2,6-*cis* or 2,6-*trans* cyclisation can be influenced with the synthesis of (+)-dihydropinidine·HCl **39** and (−)-epidihydropinidine·HCl **38**. First alkenol **33** was synthesised in 3 steps from (*S*)-epichlorohydrin **31**, via epoxide-opening with the requisite Grignard reagent, followed by epoxide reformation, then a second epoxide-opening with ethylmagnesium chloride which gave **33** in 90% yield over 3 steps. Alkenol **33** was then mesylated in 92% yield, and subsequently substituted for an azide in 95% yield. Regioselective Wacker-Tsuji oxidation of alkenylazide **35** ensued to give azidoketone **36**. In order to obtain the highest level of regioselectivity (desired ketone vs unwanted aldehyde), extensive reaction screening was performed. Azidoketone **36** subsequently underwent an intramolecular Staudinger aza-Wittig condensation to furnish cyclic imine **37** in 90% yield (Scheme 3).



Scheme 3: Imine synthesis by Kavala et al.[30] *Reagents and Conditions*: (i) C_4H_7MgBr, cat. CuI, THF, −78 °C, 1 h; (ii) NaOH, Et_2O, rt, 4 h; (iii) EtMgCl, cat. CuI, Et_2O, −78 °C, 2 h; (iv) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 2 h; (v) NaN_3, DMF, ultrasound, 50 °C, 3 h; (vi) O_2, cat. $PdCl_2$, NMP/H_2O, rt, 1 h; (vii) polymer-bound Ph_3P, Et_2O, sealed tube, reflux, 16 h.

This was subsequently subjected to the reaction screening to obtain both 2,6-*trans* and 2,6-*cis* arrangement of substituents on the piperidine ring (Table 2).



Reagents and conditions: (i) **see table**, −78 °C, 4 h.

$LiAlH_4$ (equiv.)	Me_3Al (equiv.)	Solvent	Ratio *cis*/*trans*
7	7	THF	20:80
7	7	THF	2:98
2	2	THF	40:60
2	7	THF	33:67
25	-	THF	86:14
25	-	Et_2O	57:43

Table 2: Imine Reduction by Kavala et al.[30]

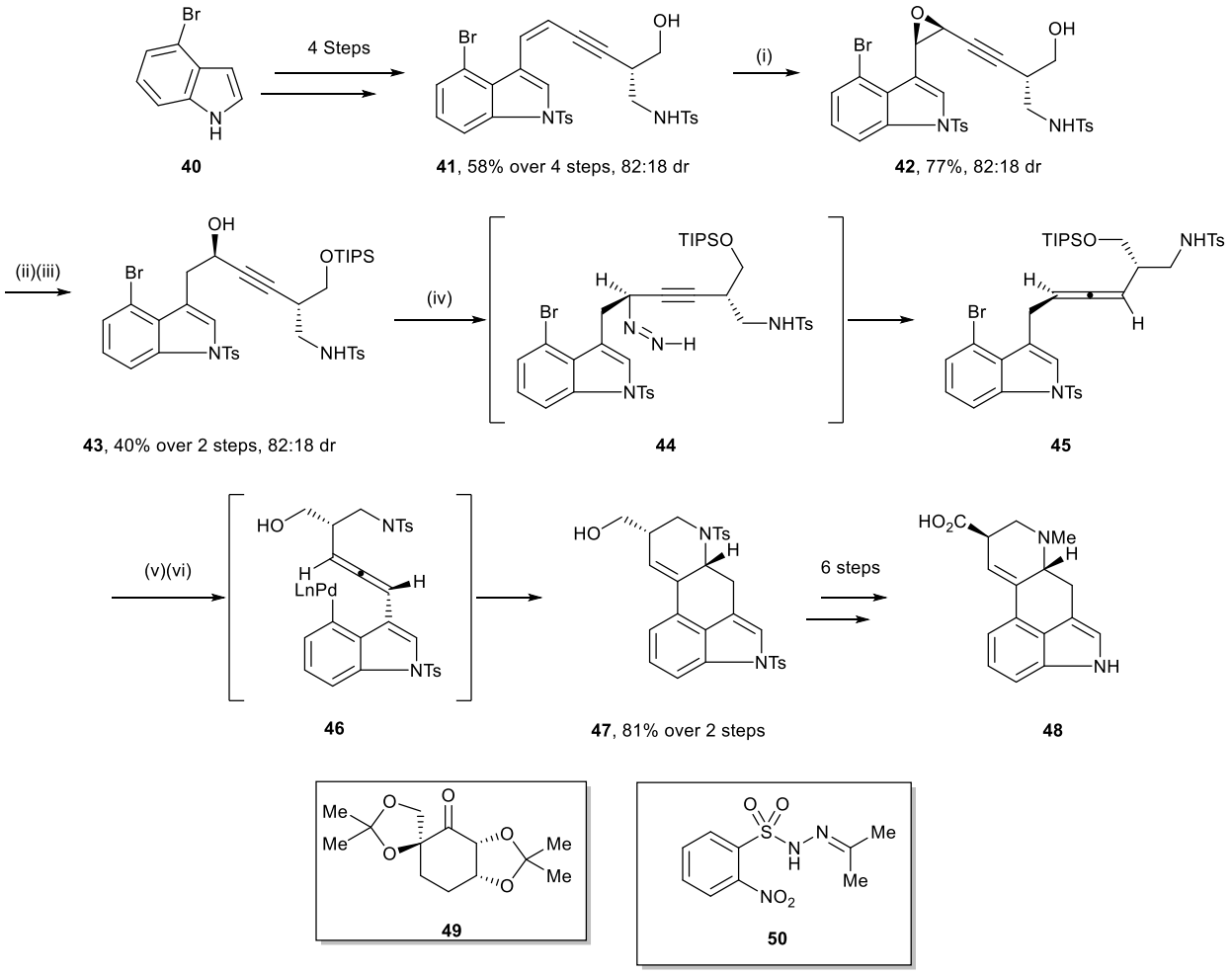
The origin of the selectivity of the imine reduction presumably arises from the steric bulk of the reducing agent *in situ*, with the Me_3Al forming a bulkier reducing species, and thus favouring pseudo-equatorial attack.

1.7 Syntheses of Piperidine-containing Motifs

1.7.1 *Lysergic Acid*

In 2011, Iwata et al.[31] published a formal synthesis of (+)-lysergic acid **48** featuring an amino-palladation cascade that established the C and D rings in a single step. Starting with enyne **41**, available in four steps from 4-bromoindole **40**, a Shi epoxidation (using catalyst **49**) afforded epoxide **42**, which was taken forward as a mixture of diastereomers. Silyl protection of the primary alcohol then followed. $Zn(OTf)_2$ mediated reductive oxirane opening yielded ynol **43**. A Movassaghi-modified Myers allenation, then stereoselective formation of **45** occurred presumably through the concerted Alder-Ene reaction of intermediate **44** which established the allene needed for the amino-palladation cascade.. With the allene in hand, TBAF deprotection of the primary alcohol and subsequent treatment with $Pd(PPh_3)_4$ and K_2CO_3, cyclization conditions previously

established by the authors, yielded tetracycle **47**. The amino-palladation precursor and the resulting product **47** intersected with a previously disclosed synthesis of (+)-lysergic acid (Scheme 4).[32]

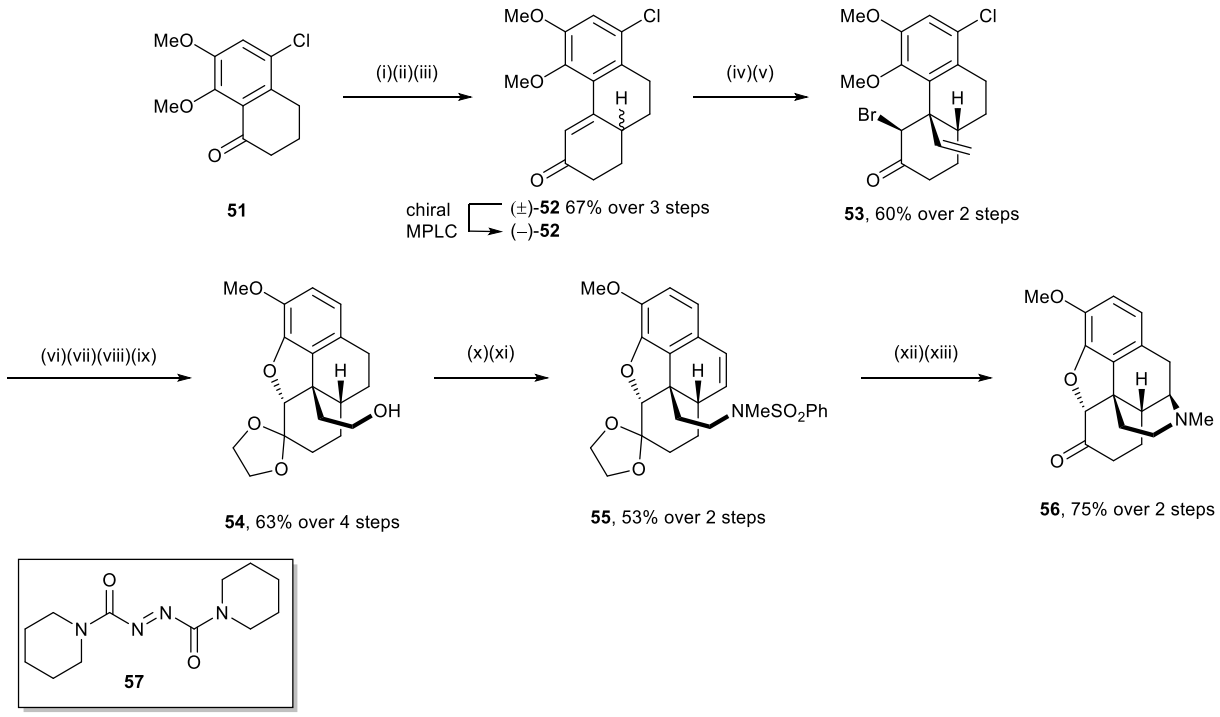


Scheme 4: Lysergic Acid Synthesis by Iwata et al.[31] *Reagents and Conditions*: (i) oxone, **49**, *n*-Bu_4NHSO_4; (ii) TIPSOTf, 2,6-lutidine; (iii) $Zn(OTf)_2$, $NaBH_3CN$; (iv) **50**, PPh_3, DEAD, then TFE/H_2O; (v) TBAF; (vi) $Pd(PPh_3)_4$, K_2CO_3.

1.7.2 *(−)-Hydrocodone*

Trauner and co-workers published a synthesis of (−)-hydrocodone in 1999.[33,34] Their work began with an aldol condensation of (±)-**51** with methyl formate. After a Robinson annulation using MVK, treatment with KOH cleaved the formate via a retro-Claisen reaction. Chiral resolution of racemic enone (±)-**52** gave (−)-**52**. Cuprate 1,4-addition was followed by trapping with TMSCl to give a transient silylenol ether. This species was reacted with NBS to give α-bromoketone (−)-**53**. Heating of (−)-**53** at 140 °C led to the closure of the E ring. Following ketalization, hydroboration

quenched with basic H_2O_2 installed a distal primary alcohol. Subsequent dechlorination with Raney nickel gave intermediate (−)-**54**. After amine installation via Mitsunobu reaction with protected methylamine, unsaturation was introduced via radical benzylic bromination and elimination. Dissolving metal reduction of **55** liberated the amine and allowed reductive closure of the D ring. Finally, ketal hydrolysis gave (−)-hydrocodone **56** (Scheme 5).



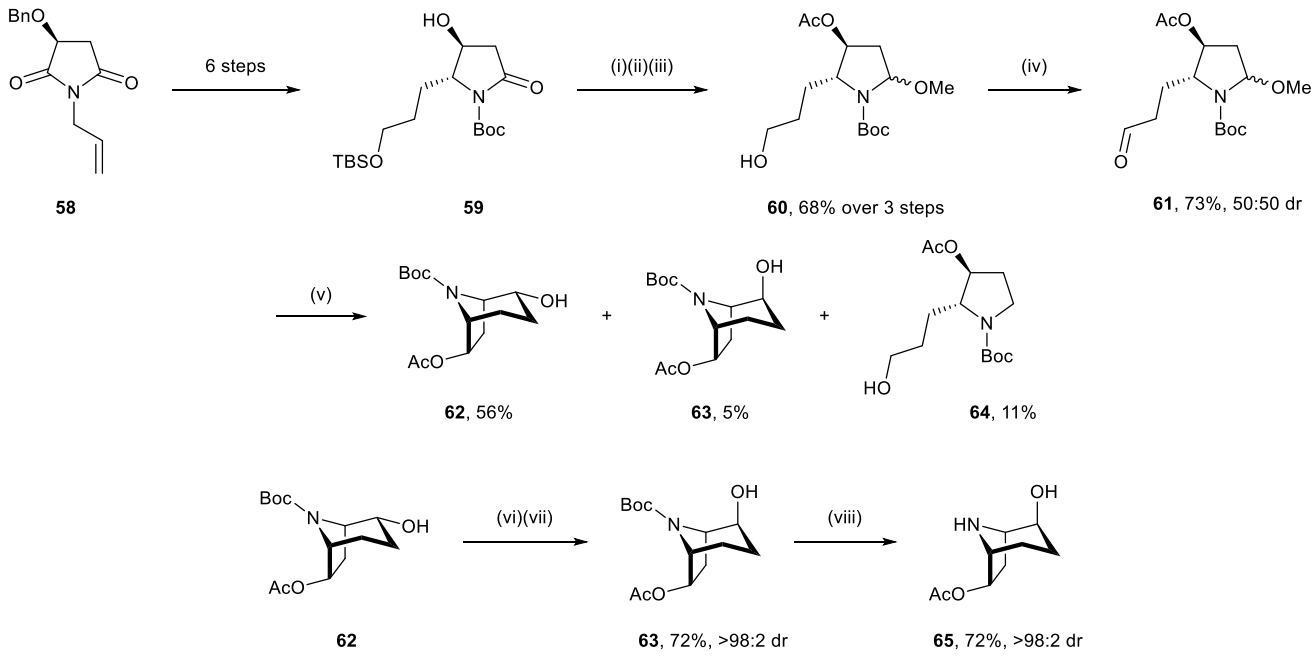
Scheme 5: Hydrocodone Synthesis by Trauner and co-workers.[33,34] *Reagents and Conditions*: (i) HCO_2Me, NaOMe; (ii) MVK, Et_3N, MeOH; (iii) KOH, dioxane, H_2O; (iv) $(CH_2{=}CH)_2CuMgCl$, then TMSCl; (v) NBS, THF; (vi) DMF, 140 °C; (vii) $(CH_2OH)_2$, TMSCl (viii) $BH_3{\cdot}SMe_2$, then H_2O_2, NaOH; (ix) Raney Ni; (x) $PhSO_2NHMe$, PBu_3, **57**; (xi) NBS, $(BzO)_2$, reflux; (xii) Li^0, NH_3 (l); (xiii) 3 N HCl.

1.7.3 *Hydroxytropanes*

Hydroxylated tropanes are a significant class of alkaloid, which comprise a number of members including calystegines.[35] An efficient and highly diastereoselective method for the construction of the hydroxylated tropane skeleton of (−)-Bao Gong Teng A has been described by Lin et al.[36]

Controlled partial reduction of the activated amide **59** with $NaBH_4$ in MeOH produced the hemiaminal as a diastereomeric mixture, which without separation, was treated with Ac_2O/py to yield the corresponding bis-acetate. Treatment of the crude labile bis-acetate with iodine gave

chemoselectively desilylated and transacetylated product *N*,*O*-acetal **60** in 68% yield over three steps. Dess–Martin oxidation of the diastereomeric mixture **60** provided the key precursor **61** as a 50:50 diastereomeric mixture in 73% yield. Radical cyclisation gave the undesired diastereomer **62** in 56% yield, this was converted to the desired diastereomer **63** via an oxidation/reduction process with DMP/L-selectride. Chemoselective *N*-Boc deprotection via the TMS ether resulted in (−)-Bao Gong Teng A **65** in 72% yield (Scheme 6).



Scheme 6: Bao Gong Teng A Synthesis by Lin et al.[36] *Reagents and conditions*: (i) $NaBH_4$, MeOH; (ii) Ac_2O, Py, CH_2Cl_2; (iii) MeOH, I_2; (iv) DMP, CH_2Cl_2; (v) $BF_3{\cdot}OEt_2$, SmI_2, *t*-BuOH/THF, −50 °C (vi) DMP, CH_2Cl_2; (vii) L- selectride, THF, −78 °C; (viii) TMSOTf, 2,6-lutidine, TBAF, THF.

1.8 Project Aim

This thesis describes the development of enantiopure synthetic routes to investigate the relative and absolute stereochemistry of a number of piperidine-containing natural products isolated from *Microcos Paniculata*. The synthetic route relies upon the conjugate addition of a secondary lithium amide to an α,β-unsaturated ester as a key stereo-defining step. This thesis then goes on to explore an intramolecular Diels-Alder reaction, and explores its applicability to natural product synthesis.

Chapter 2 Synthesis of Microcosamine A

2.1 Chapter Outline

This chapter describes the development of an asymmetric synthesis of the piperidine alkaloid microcosamine A **70** utilising a lithium amide conjugate addition as a key stereo-defining step (Figure 4). The relative and absolute configuration of the piperidine alkaloid is then verified on the basis of specific rotation values and ^{1}H and ^{13}C NMR spectroscopic comparisons, and the natural product will then be used as an advanced intermediate for the synthesis of other alkaloids isolated from *Microcos Paniculata.*

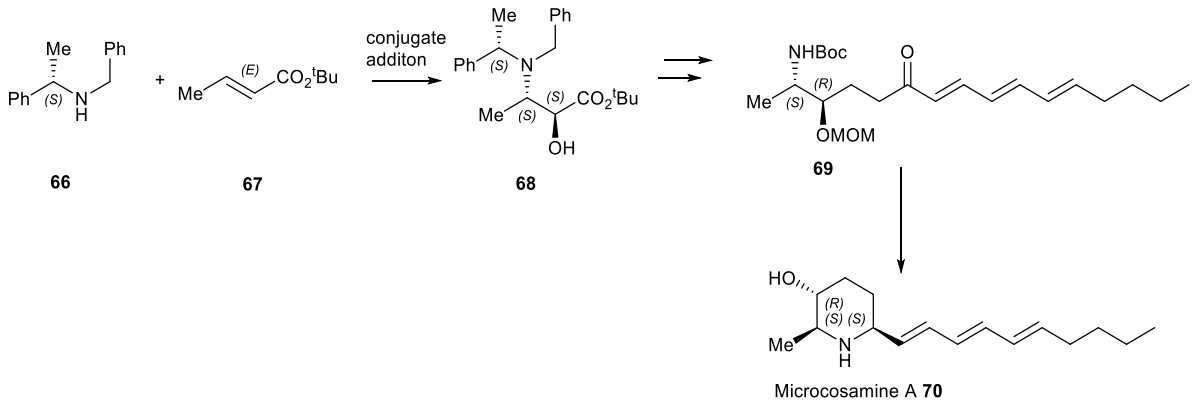


Figure 4: Synthetic route to microcosamine A **70**.

2.2 Microcos Paniculata

Microcos paniculata is a shrub indigenous to southern China that is ubiquitous in the local folk medicine for use in the treatment of a range of ailments and maladies, and as an ingredient (the dried leaves, called buzhaye) for herbal teas. Investigations into the phytochemical composition of various parts of the plant have identified a number of flavonoids, terpenoids, alkaloids, and other compounds.[37] Within the alkaloid class, several 2,6-disubsituted piperidin-3-ols and derivatives have been identified. These represent a relatively populous family, which are all 2,6-*cis* substituted.

The family can be split into 2 sub-categories illustrated in Figure 5.

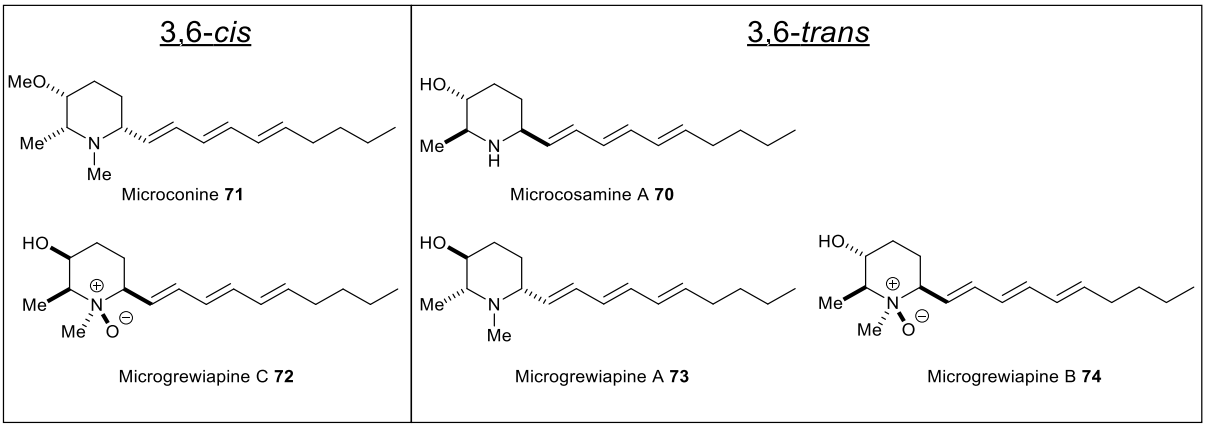


Figure 5: 2,6-disubsituted piperidine-3-ols from *Microcos Paniculata*.

The isolation of Microgrewiapines A-C in 2013 by Still et al.[38] provided the impetus and incentive for this project, with the confirmation of the structures for the 3 alkaloids Microgrewiapines A-C the initial aim of this study. However, as the project developed discrepancies and inconsistencies were founds in the literature for many of the alkaloids of the family (Figure 5). Thus, the studies into the synthesis and stereochemical assignment of each alkaloid are described in turn.

2.3 Isolation of Microcosamine A

In 2008, Feng et al. isolated microcosamine A from the leaves of *Microcos Paniculata*.[39] Analysis by standard techniques (IR, NMR etc.) led to the proposal of the gross structure of the alkaloid. Concerning stereochemistry, the diagnostically large ^{3}J coupling constant between C(2)*H* and C(3)*H* ($^{3}J_{2,3}$ = 10.0 Hz) suggested a diaxial relationship of the two protons in a chair conformation. An nOe enhancement between C(2)*H* and C(6)*H* also suggested that the two were axial, thus completing the relative configurational assignment: all three protons of the stereogenic centres were placed axially, thus all the substituents of the piperidine ring occupied equatorial sites, and the relative 2,3-*trans*-3,6-*trans*-configuration was assigned to the alkaloid (Figure 6).

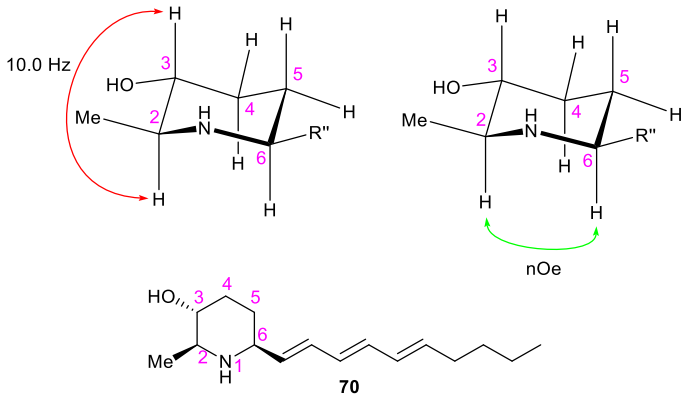


Figure 6: Evidence used by Feng et al.[39] to assign the relative configuration of Microcosamine A.

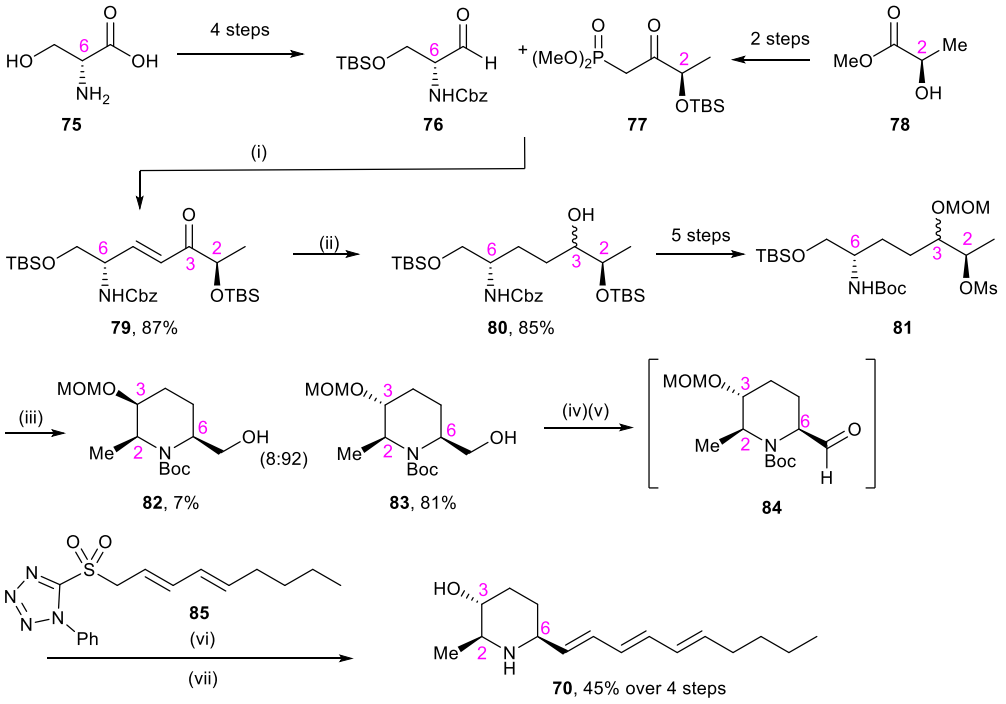
No attempt was made to assign an absolute configuration to the alkaloid, although a non-zero specific rotation value was recorded {$[\alpha]_D^{20}$ +4 (c = 1.0 MeOH)}.

Microcosamine A was later re-isolated in 2013 by Still et al.[40], and by Zhang et al.[41] in 2017. Both recorded specific rotation values {$[\alpha]_D^{25}$ +4 (c = 0.1 MeOH)}[40] and {$[\alpha]_D^{25}$ +3.45 (c = 0.05 MeOH)}[41] in agreement with that recorded by Feng et al.[39].

2.4 Microcosamine A Synthesis

Microcosamine A was first synthesised in 2016 by Reddy et al.[42–44] Starting from the unnatural amino acid D-serine **75** and the chiral pool building block methyl D-lactate **78**, which set the C(6) and C(2) stereogenic centres respectively. HWE coupling of **76** and **77** resulted in unsaturated ketone **79** in 87% yield (diastereoselectivity unknown). Luche reduction of this ketone proceeded with dr >9:1 in 85%. The mixture of diastereomers was carried through at this stage. After some protecting group manipulation, **81** was prepared in 5 steps ready for cyclisation. Basic cyclisation conditions using KO^{t}Bu allowed the formation of piperidine **83** in 81% yield; here the two diastereomers from the Luche reduction could be separated. The evidence for the configuration of the piperidin-ols **82** and **83** was nOe correlations alone. Silyl deprotection mediated by HF (aq), then IBX oxidation formed aldehyde **84**. Subsequent Julia-Kocienski olefination using KHMDS,

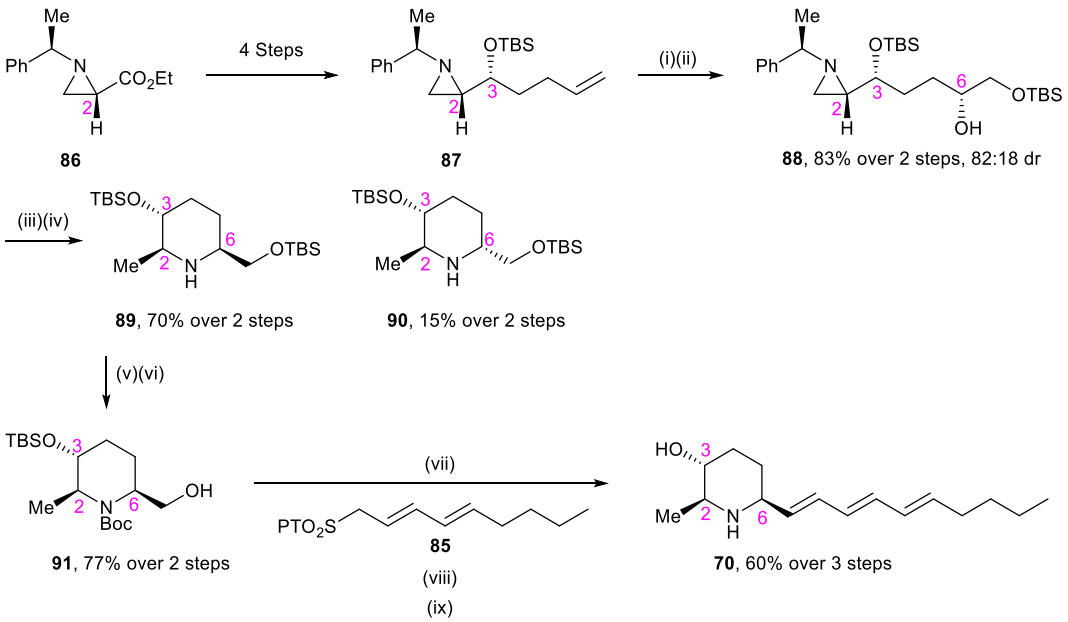
18-crown-6 in DME followed by *N*-Boc deprotection resulted in the first synthesis of Microcosamine A (13 steps from D-serine, 12% overall yield) (Scheme 7).



Scheme 7: Synthesis of Microcosamine A **70** by Reddy et al.[42–44] *Reagents and conditions*: (i) $Ba(OH)_2{\cdot}8H_2O$, THF:H_2O, 0 °C to rt, 4 h; (ii) $CeCl_3{\cdot}H_2O$, MeOH, $NaBH_4$, −78 °C, 1 h; (iii) KOtBu, THF, 0 °C to rt, 1 h; (iv) HF (aq), MeCN, 0 °C, 1 h; (v) IBX, DMSO, EtOAc, rt to 70 °C, 30 min; (vi) KHMDS, 18-crown-6, DME, −78 °C to rt, 12 h; (vii) 3 N HCl, MeOH, 12 h

This synthesis supported the gross structure, and the relative configuration, of microcosamine A. The identical sign and magnitude of the specific rotation value of the synthetic material of known absolute (2*S*,3*R*,6*S*)-configuration $\{[\alpha]_D^{20}$ + 5.6 (*c* = 1.00 MeOH)$\}$ compared to isolation value $\{[\alpha]_D^{20}$ + 4 (*c* = 1.0 MeOH)$\}$, indicted the absolute (2*S*,3*R*,6*S*)-configuration for the alkaloid itself.

In 2018 the second synthesis of microcosamine A was realised by Macha et al.[45] Starting from commercially available (2*S*)-aziridine-2-carboxylate **86**, the ester functionality was elaborated to terminal olefin **87** in 4 steps. Asymmetric dihydroxylation of the olefin was optimised to 92% yield and 82:18 dr, which upon terminal *O*-protection yielded **88** in 83% yield over the 2 steps. The identity of each diastereomer was not established at this point, and they were not separated at this stage either. Reductive ring closure obtained the major piperidine 2,6-*cis* diastereomer **89** in 70% yield for the two steps, again no rationalisation was given for the assignment of the relative configuration. *N*-Boc protection and then primary OTBS removal gave alcohol **91** in 77% over 2 steps. DMP oxidation, then subsequent Julia-Kocienski olefination and the removal of TBS and Boc groups gave microcosamine A **70**. The NMR data of **70** was reported to have full agreement with the natural product, and the specific rotation value obtained for the synthetic sample **70** $\{[\alpha]_D^{20}$ +5.6 (c = 1.00 MeOH)$\}$ provided further support for the assigned absolute (2*S*,3*R*,6*S*)-configuration of the natural product.



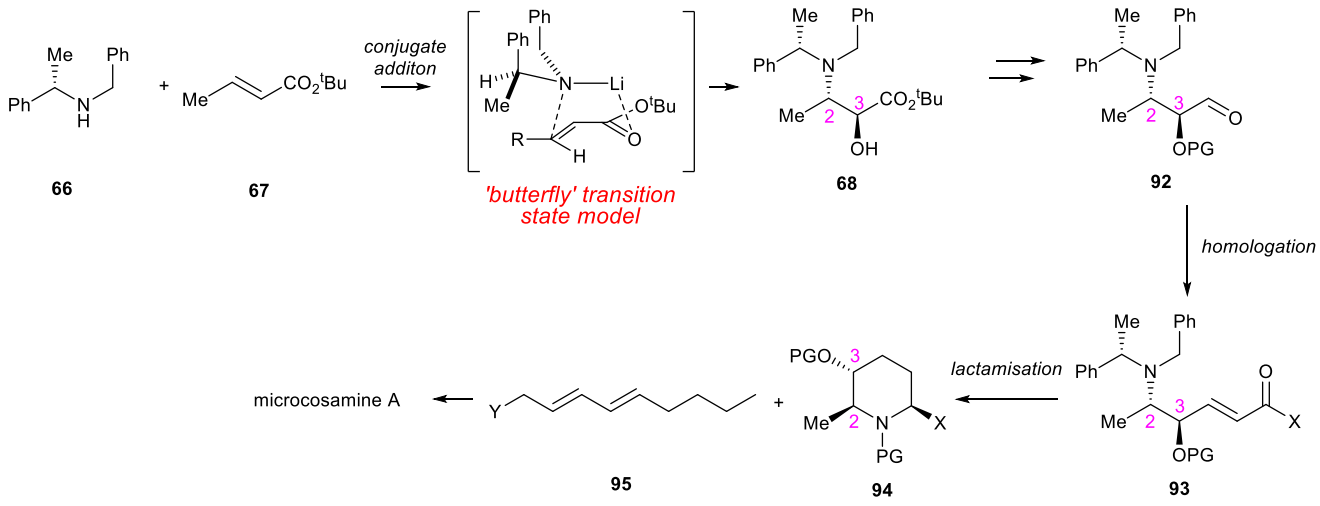
Scheme 8: Second synthesis of Microcosamine A **70**, by Macha et al.[45] *Reagents and Conditions*: (i) AD-mix-β, $(DHQD)_2PHAL$, $CH_3SO_2NH_2$ $NaHCO_3$, *t*BuOH:H_2O, 0 °C, 4 h; (ii) TBSCl, imidazole, CH_2Cl_2; (iii) MsCl, Et_3N, DMAP, CH_2Cl_2; (iv) 20% $Pd(OH)_2$, H_2, MeOH, rt, 12 h; (v) $NaHCO_3$, Boc_2O, MeOH, 0 °C to rt, 90%; (vi) 70% HF·Py, THF, rt; (vii) DMP, CH_2Cl_2, 0 °C to rt, 4 h; (viii) KHMDS, 18-crown-6, DME, −78 °C to rt, 12 h; (ix) 3 M HCl, MeOH, rt, 12 h.

2.5 Chapter Aim

The aim of this chapter is to establish an independent synthesis of microcosamine A, which can then be used to investigate the inconsistencies and errors in the data reported for range of natural products isolated from *Microcos Paniculata*.

2.6 Retrosynthetic Analysis

It was hypothesised that the stereochemistry at C(2) and C(3) could be set via a lithium amide conjugate addition to α,β-unsaturated ester **67** and trapping of the subsequent chiral enolate with a chiral electrophilic oxygen source (+)-camphorsulfonyloxaziridine [(+)-CSO]. Subsequent *O*-protection and ensuing chemoselective ester reduction would give aldehyde **92**. This could then be homologated to yield **93**, with functionality X (eg. X = CO_2Et, CH_2OH) which, after a stereoselective lactamisation, would allow the introduction of the tail fragment within **70** as was shown to be a successful strategy in the previous two syntheses (Scheme 9).

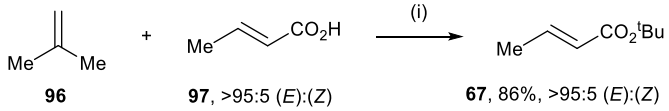


Scheme 9: Proposed Synthesis of microcosamine A.

2.7 Substrate Preparation

2.7.1 *Michael Acceptor*

To begin the synthesis, a 100 g scale synthesis of α,β-unsaturated *tert*-butyl ester **67** was developed, condensing isobutylene gas into an acidic mixture of commercially available crotonic acid (>95:5 (*E*):(*Z*)) and conc. aq H_2SO_4. Careful drying of this volatile ester gave α,β-unsaturated *tert*-butyl ester **67** in 86% yield (Scheme 10). Confirmation of the double bond geometry was based on diagnostic values of the ^{1}H NMR ^3J coupling constants between the C(2) and C(3) protons: ^3J = 15.5 Hz.

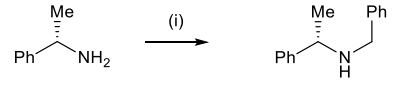


96 **97**, >95:5 (*E*):(*Z*) **67**, 86%, >95:5 (*E*):(*Z*)

Scheme 10: Synthesis of α,β-unsaturated *tert*-butyl ester **67**. *Reagents and Conditions*: (i) conc. aq H_2SO_4, rt, 48 h.

2.7.2 *Enantiopure Amine*

Enantiopure secondary amine (*S*)-**66** was prepared by formation of the corresponding imine (from enantiopure amine (*S*)-**98** (>99.0% ee) and benzaldehyde) followed by reduction with $NaBH_4$ which gave (*S*)-**66** in 78% yield and >99.0% ee.[46] (*S*)-**66** was determined to be >95:5 er from ^{1}H NMR spectroscopic analysis in the presence of the chiral solvating agent (*S*)-O-acetylmandelic acid, and comparison with an authentic racemic sample. However, given that primary amine **98** was deemed to be 99% ee and that no racemisation has previously been observed, it can be reasonably assumed that (*S*)-**66** has an enantiomeric excess of 99% (Scheme 11).

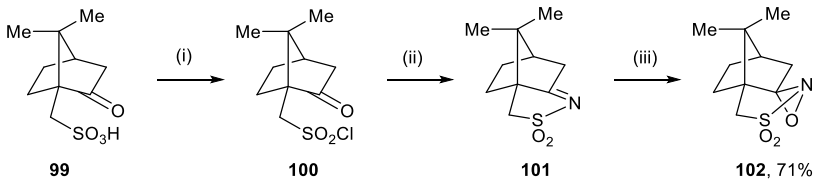


98, >99.0% ee **66**, 78%, >99.0% ee

Scheme 11: Syntheis of Enantiopure secondary amine (*S)*-**66**. *Reagents and conditions*: (i) Benzaldehyde, EtOH, reflux then $NaBH_4$, 0 °C to rt, 48 h.

2.7.3 *Chiral oxygen source*

(+)-CSO **102** was prepared from (+)-camphorsulfonic acid **99** according to a literature procedure.[47] Initial conversion to the corresponding sulfonyl chloride **100**, was followed by imine formation, subsequent dehydration, and finally oxidation with peracetic acid gave oxaziridine (+)-**102** in 71% yield from (+)-**99** and >95:5 dr (Scheme 12).

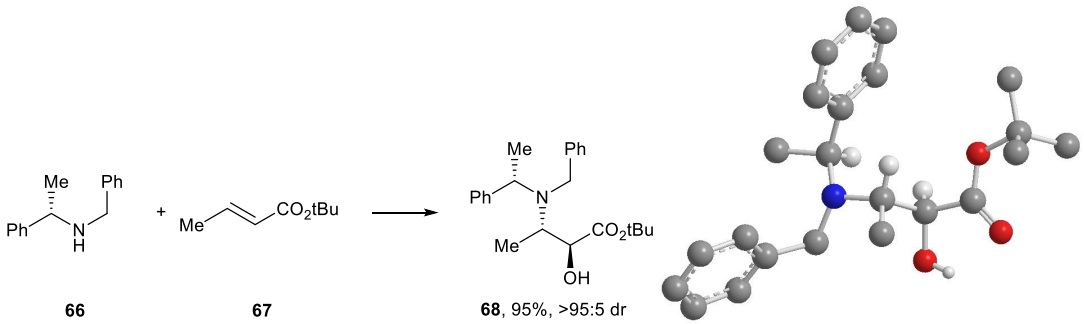


99 **100** **101** **102**, 71%

Scheme 12: Synthesis of (+)-CSO **102**. *Reagents and conditions*: (i) $SOCl_2$, $CHCl_3$, reflux, 12 h; (ii) conc. aq NH_4OH, 0 °C, 4 h then Amberlyst® 15 ion exchange resin, PhMe, reflux, 12 h; (iii) $MeCO_3H$, Aliquat, K_2CO_3, CH_2Cl_2, rt, 8 h.

2.8 Opening Synthetic Steps

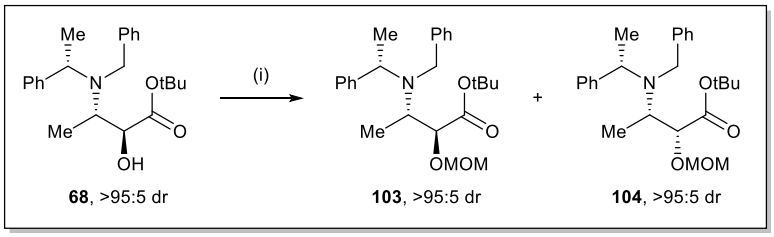
With the requisite starting materials in-hand, the synthetic route could begin. The lithium amide reagent was prepared in situ by treatment of amine (*S*)-**66** with ^nBuLi at −78 °C. Conjugate addition of the lithium amide to *tert*-butyl crotonate **67**, followed by in situ oxidative trapping of the resulting enolate with the enantiopure, electrophilic oxygen source (+)-CSO **102** gave α-hydroxy-β-amino ester **68** as a crystalline white solid in 95% yield and >95:5 dr (Figure 7). **68** has been previously prepared, and its stereochemistry has been established by conversion to a range of natural products[48–52]. The stereochemistry is also consistent with the well established transition-state model for the reaction. In this case, the relative configuration was confirmed by single crystal X-ray diffraction analysis, and the (2*S*,3*S*,α*S*)-configuration of **68** was thus, firmly established by reference to the known (*S*)-configuration of the α-methylbenzyl stereocentre.



66 **67** **68**, 95%, >95:5 dr

Figure 7: Synthesis of, and X-ray crystal structure of **68** (selected H atoms are omitted for clarity). *Reagents and conditions*: ^{n}BuLi, THF, –78 °C, 2 h then (+)-CSO, –78 °C to rt, 16 h.

Protection of the free hydroxyl was expected to proceed with ease using MOM as a suitably labile protecting group. However, initial protection attempts with 1.2 equiv. NaH in DMF and MOMCl resulted in only 60% conversion after 30 min. It was presumed that this observed lack of conversion originated from incomplete deprotonation of the alcohol. Chromatographic separation of the protected alcohol **103** from the free hydroxyl starting material **68** proved impossible due to the identical polarity of the β-amino esters **103** and **68**, and thus it was imperative that the conversion was increased because the free alcohol would not be compatible for the following DIBAL-H reduction. Re-subjection of the crude mixture resulted in epimerisation at the acidic α-position to give **104** (which is a known compound[53]). In order to circumvent this, conditions were trialled to improve the initial conversion. Solvent change to THF resulted in 45% conversion, and trituration of the NaH gave 35% conversion. Eventually it was found that stirring the NaH in THF solvent prior to the addition of the alcohol allowed isolation of the clean MOM protected product in 99% isolated yield (Table 3).

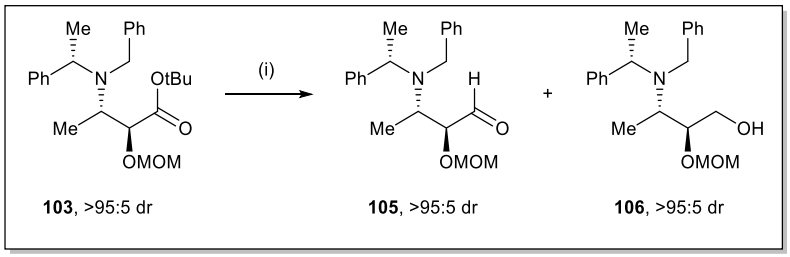


Reagents and conditions: (i) **see table**.

Base	MOMCl equiv.	Solvent	Base equiv.	Method of deprotonation	Time for deprotonation (min)	Crude ratio 68:103:104
NaH	1.2	DMF	1.2	Base added to solution of alcohol	30	60:40:0
NaH	1.2	DMF	1.2	Resubjection of crude mixture	30	20:40:40
NaH	1.8	DMF	1.5	Base added to solution of alcohol	30	55:45:0
NaH	1.8	DMF	1.5	Base added to solution of alcohol	90	54:46:0
NaH	1.2	THF	1.2	Base added to solution of alcohol	30	55:45:0
NaH	1.2	THF	1.2	Base triturated in solvent × 3	30	65:35:0
NaH	1.2	THF	1.2	Base stirred in solvent 30 min	30	0:100:0

Table 3: MOM protection.

DIBAL-H reduction of the *tert*-butyl ester was carried in CH_2Cl_2 at −78 °C. Initially the reaction was carried out under very dilute (0.015 M) conditions, which limited the practicality of reaction scale-up. However, the reaction was shown to tolerate almost tenfold increase in concentration to 0.1 M with little effect on the reaction. Use of DIBAL-H (CH_2Cl_2) resulted in some over-reduction to alcohol **106** (16%), however when using DIBAL-H (Toluene) the requisite aldehyde **105** was isolated in 95% yield with no alcohol formation observed (Table 4).



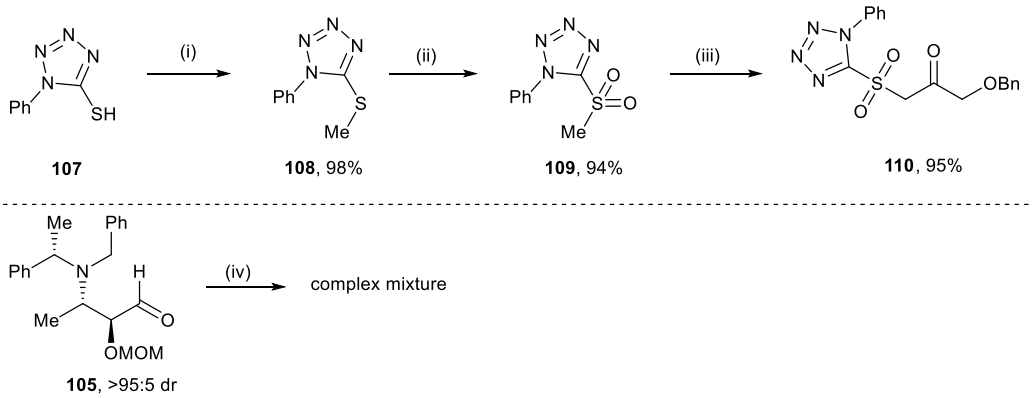
Reagents and conditions: DIBAL-H (1.0 M in **solvent**), CH_2Cl_2 (**n** M), −78 °C, 30 min.

DIBAL-H Solvent	Concentration	105:106
DCM	0.015	85:15
DCM	0.1	84:16
PhMe	0.1	100:0

Table 4: Ester Reduction.

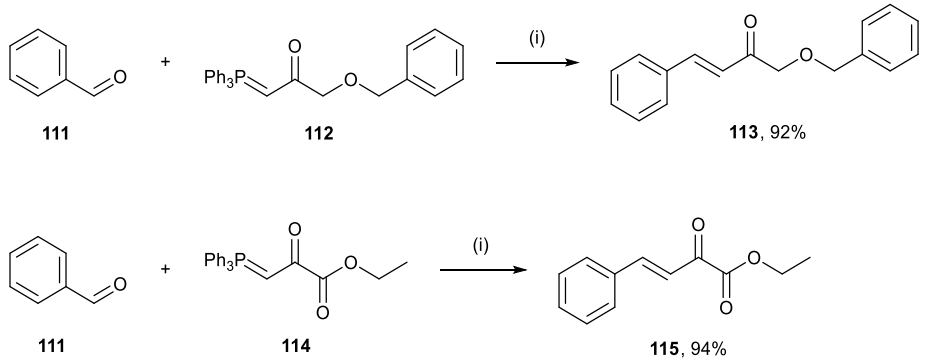
2.9 Homologation

In order to homologate aldehyde **105** and introduce the functionality X within **94** (Scheme 9), it was proposed that a Julia-Kocienski olefination of **105** could be a facile route to **93**. Sulfone **110** was synthesised from tetrazole **107**, however, reaction with aldehyde **105** in a variety of conditions gave a complex mixture of chromatographically inseparable material (Scheme 13).

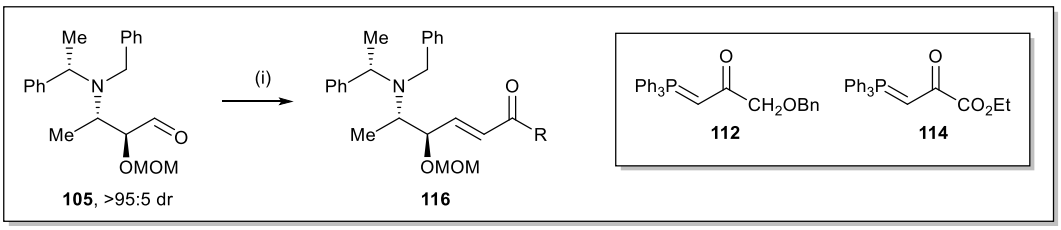


Scheme 13: Attempted Julia-Kocienski Olefination. *Reagents and Conditions*: (i) NaH, MeI, DMF, rt, 2 h; (ii) Ammonium molybdate tetrahydrate, H_2O_2, EtOH, rt, 12 h; (iii) LiHMDS, 2-(benzyloxy)acetyl chloride, THF, −78 °C to 0 °C, 1.5 h. (iv) **110**, various conditions.

Wittig reactions with pyruvate-derived ylid **114**, and OBn protected ylid **112** were attempted.[54–59] There are some literature examples of OBn ylid **112** being used,[57,60–62] however upon addition to aldehyde **105** no/little reactivity was observed, even under forcing conditions such as microwave and reflux in toluene (Table 5). Similarly for pyruvate derived ylid **114**, there are numerous examples of literature reactions,[23–25] however none or very little reactivity was observed between aldehyde **105** and ylid **114** (Table 5). Both ylids showed full conversion with benzaldehyde in trial reactions (Scheme 14).



Scheme 14: Witting reaction with Ylids **112** and **114**. *Reagents and conditions*: (i) CH_2Cl_2, reflux, 24 h.



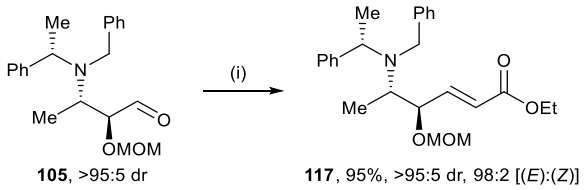
Reagents and conditions: **see table**.

Ylid	Ylid equiv.	Conditions	105:116
114	1.1	CH_2Cl_2 (0.2 M), rt, 12 h	100:0
114	1.1	CH_2Cl_2 (0.2 M), reflux, 12 h	100:0
114	1.1	Silica, 400 W, 5 min	100:0
114	1.5	PhMe (0.2 M), reflux, 12 h	90:10
114	2.5	EtOH (0.2 M), reflux, 12 h	100:0
114	2.5	DCE (0.2 M), reflux, 12 h	complex
114	6.0	THF (0.05 M), rt, 36 h	100:0
114	6.0	DCE (0.2 M), 60 °C, 3 d	100:0
114	6.0	CH_2Cl_2 (0.2 M), reflux, 3 d	100:0
114	6.0	CH_2Cl_2 (0.2 M), 0.50 equiv. $PhCO_2H$, reflux, 3 d	100:0
114	6.0	dioxane (0.2 M) 100 °C, μW, 3 h	100:0

114	5.8	^{n}BuLi, THF (0.02M), rt, 12 h	complex
112	0.8	CH_2Cl_2 (0.2 M) rt	100:0
112	1.1	CH_2Cl_2 (0.2 M) reflux, 12 h	10%
112	1.1	Silica, 400 W, 50 s	complex
112	1.1	H_2O (0.2 M), LiCl, reflux, 1 h	complex
112	2.5	DCE (0.2 M), reflux, 12 h	77:33
112	2.5	CH_2Cl_2 (0.2 M) reflux, 3 d	88:22
112	6.0	DCE (0.2 M), 60 °C, 3 d	65:35
112	6.0	CH_2Cl_2 (0.2 M), reflux, 3 d	complex

Table 5: Attempted olefination of aldehyde 105.

Utilising a classical Wittig ylid,[63] Ph_3PCHCO_2Et showed full conversion by ^{1}H NMR and (although slow, as monitored by TLC analysis) proceeded in excellent yield with good (*E*)-selectivity (^{3}J = 15.9 Hz) (Scheme 15).

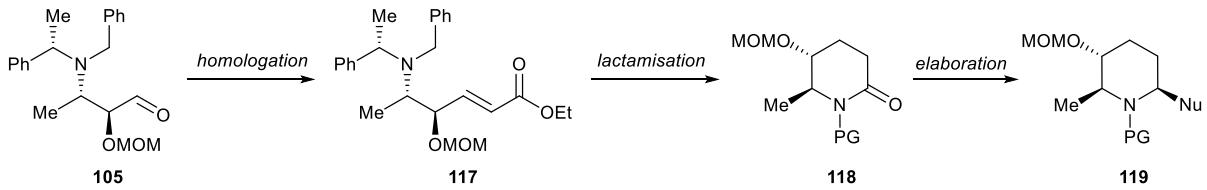


105, >95:5 dr

117, 95%, >95:5 dr, 98:2 [(*E*):(*Z*)]

Scheme 15: Wittig reaction to form α,β-unsaturated ester **117**. *Reagents and Conditions*: (i) Ph_3PCHCO_2Et, CH_2Cl_2, rt, 60 h.

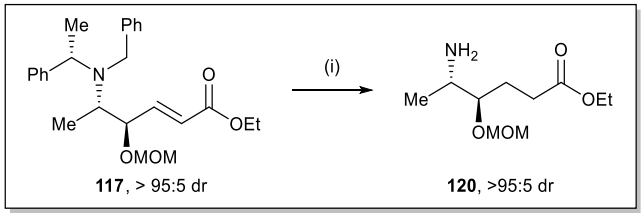
With this successful reaction in hand, a route change was proposed. Reductive lactamisation of ester **117** would be an efficient route to lactam **118**. This could then be elaborated diastereoselectively to introduce the unsaturated side chain (Scheme 16).[64–66]



Scheme 16: Proposed Synthesis of piperidine **119**.

2.10 Lactam Route

Initial hydrogenation/hydrogenolysis of **117** using Pearlman's catalyst at 0.4 M (MeOH) resulted in deprotected product **120** in 76% isolated yield. Dilution of the reaction conditions to 0.04 M was followed by an increase in the yield to 89%. The reaction was tolerant to a reduction of the hydrogen pressure from 5 bar to 1 bar, which enabled much simpler scale-up (Table 6).



Reagents and conditions: (i) $Pd(OH)_2/C$ (50% w/w), H_2 (**n** atm.), MeOH (**n** M), rt, 16 h.

Concentration (M)	H_2 pressure (atm.)	Yield of 120
0.4	5	76
0.04	5	89
0.04	1	87

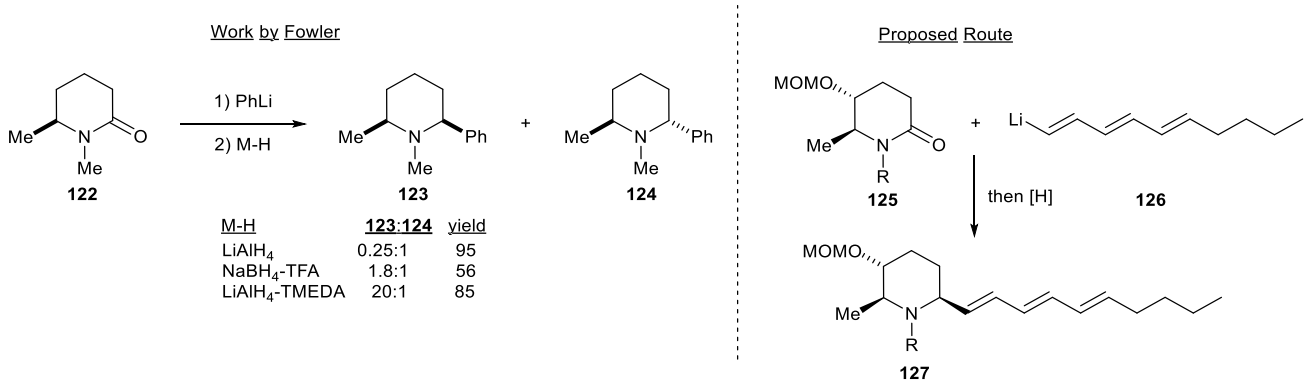
Table 6: Hydrogenation/Hydrogenolysis of 117.

Subsequent cyclisation of **120** was evoked upon treatment with KOH to return lactam **121** in quantitative yield (Scheme 17).

Scheme 17: Base-induced cyclisation of **120**. *Reagents and Conditions*: (i) KOH, EtOH, rt, 2.5 h.

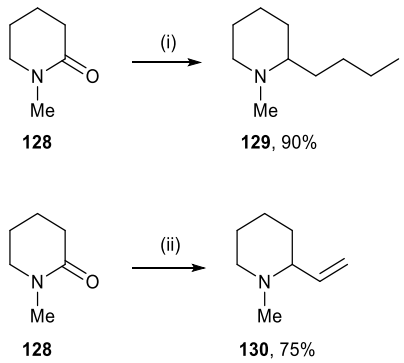
2.11 Nucleophilic Lactam addition

Diastereoselective addition of PhLi to *N*-Me,2-Me,δ-valerolactam **120** followed by reduction of the ensuing imine has been previously outlined by Fowler and co-workers,[67,68] and so the addition of the vinyl lithium **126** was planned to install the side-chain in the synthesis of microcosamine A in a highly diastereoselective manner (Scheme 18).



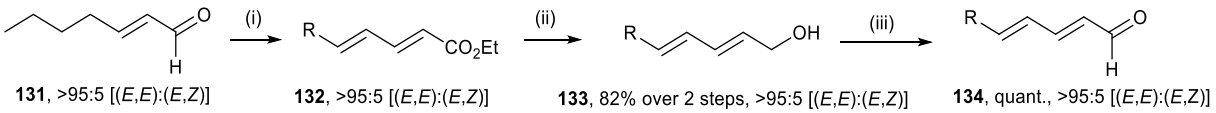
Scheme 18: PhLi additions by Fowler and co-workers,[68] and Proposed Route to Piperidine **127**.

Work by Fowler had used only PhLi as a nucleophile, so initially a model system investigation was set up to briefly investigate the use of other nucleophiles. Using *N*-methylpiperidin-2-one **128** as a model, both ^{n}BuLi and vinyl lithium added to the lactam to give the corresponding piperidines **129** and **130** after reduction (90% and 75% respectively (Scheme 19)), which was a good indication about the possible efficacy of the planned synthetic route (Scheme 18).



Scheme 19: Model synthesis of piperidines **129** and **130**. *Reagents and Conditions*: (i) ^{n}BuLi, 0 °C, 45 min, then $LiAlH_4$-TMEDA. (ii) vinylLi, rt, 45 min, then $LiAlH_4$-TMEDA.

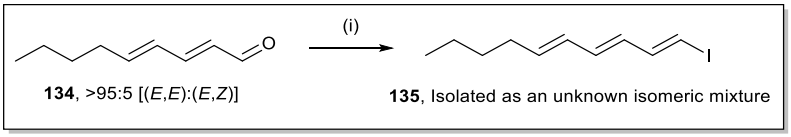
It was planned that the requisite vinyl lithium **126** (Scheme 18) would be synthesised via the corresponding vinyl iodide. Synthesis of the vinyl iodide **135** was initiated via an initial Wittig reaction from commercially available *trans*-2-heptenal (97%). This proceeded with good sterecocontrol to furnish **132** (89%) with ^{3}J = 15.4 Hz for the newly formed C=C, allowing the assignment of (*E*,*E*) configuration. Subsequent chemoselective reduction of the α,β-unsaturated ester with DIBAL-H (1.0 M in Toluene) occurred with excellent preservation of stereochemical integrity to give allylic alcohol **133** in 92% yield with ^{3}J = 15.3 Hz, 15.1 Hz, characteristic of the retained (*E*,*E*) configuration. Subsequent re-oxidation using a Swern reaction gave aldehyde **134** as a single product, isolated in 82% yield with $^{3}J_{2,3}$ = 15.3 Hz characteristic of the retained *E* configuration, with no evidence of C(4)/C(5) olefin isomerisation by ^{1}H and ^{13}C NMR analyses. The oxidation reaction was optimized by a change of oxidant to IBX, which improved the oxidation yield to quantitative (Scheme 20).



131, >95:5 [(*E*,*E*):(*E*,*Z*)] **132**, >95:5 [(*E*,*E*):(*E*,*Z*)] **133**, 82% over 2 steps, >95:5 [(*E*,*E*):(*E*,*Z*)] **134**, quant., >95:5 [(*E*,*E*):(*E*,*Z*)]

Scheme 20: Synthesis of aldehyde **134**. *Reagents and Conditions*: (i) Ph_3PCHCO_2Et, CH_2Cl_2, rt, 12 h; (ii) DIBAL-H, CH_2Cl_2 , −78 °C to 0 °C, 1 h; (iii) IBX, DMSO, rt, 12 h.

Now well-established, the Takai olefination has often be used to convert aldehydes into the corresponding vinyl iodide.[69,70] However, attempted use of this protocol on **134** failed, resulting in low conversion and inseparable mixtures of geometric isomers. Varying the reaction temperature, solvent, and reaction times could not adequately improve the results (Table 7).

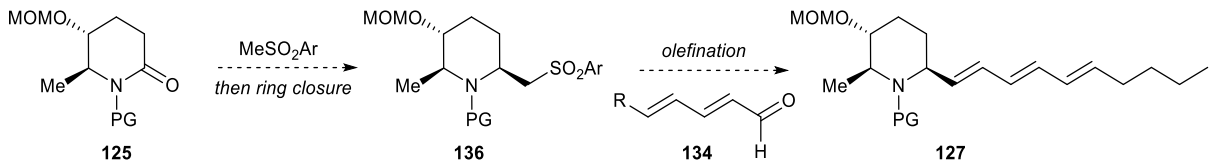


Reagents and conditions: CHI_3 (2.0 equiv.), $CrCl_2$ (9.5 equiv.), **see table**.

Solvent	Conditions	Conversion
THF	0 °C 30 min	0%
THF	0 °C to rt, 30 min	5%
THF	rt, 30 min	8%
THF	0 °C to rt, 4.5 h	45%
THF	60 °C , 4 h	30%
dioxane	0 °C to rt, 4.5 h	32%
dioxane	60 °C , 4 h	27%

Table 7: Takai Olefination.

With the requisite vinylic iodide **135** seemingly difficult to prepare, it was decided that modification of lactam **125** to an α-aryl sulfonyl would allow installation of the unsaturated alkyl chain via a Julia olefination (or suitable modifications) from aldehyde **134**, for which a robust synthesis has been developed (Scheme 20).

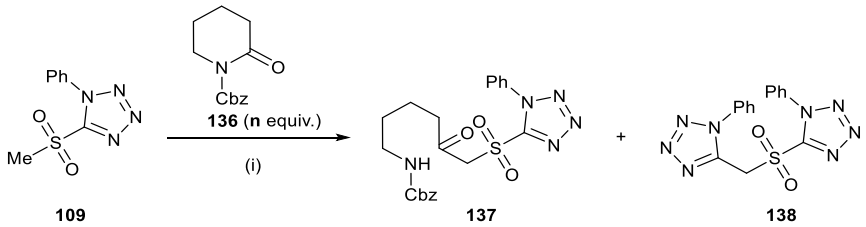


Scheme 21: Proposed Synthesis of piperidine **127**.

2.12 Model System

In order to probe the value of this newly proposed route, and optimise the steps, work began on a model system using *N*-Cbz protected δ-valerolactam **136**.

The lithium anion of $MeSO_2PT$ was trialled as a nucleophile which would facilitate a subsequent 1-step Julia-Kocienski reaction.[71] Initial probing resulted large amounts of the self-condensation side product **138** in 60% yield with no observed product. Increasing the base equivalent allowed some product formation in 10% isolated yield, and increasing the reaction temperature from 0 °C to rt further supressed self-condensation (**137** isolated in 40% yield). Further optimisation of the ring-opening eventually yielded the α-sulfonyl aminoketone **137** in 66% isolated yield (Table 8).

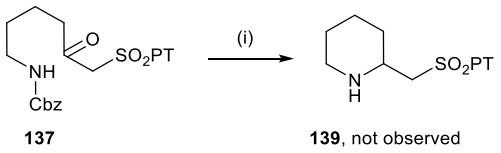


Reagents and Conditions: (i) LiHMDS (**n** equiv.), THF, −78 °C, 30 min, then **n** °C, 1 h.

Base equiv.	Lactam equiv.	Conditions	137 yield	138 yield
1.2	1.1	0 °C	-	60%
2.2	1.1	0 °C	10%	50%
2.2	1.1	rt	40%	33%
2.2	0.2	rt	5%	70%
2.2	5.0	rt	66%	5%

Table 8: Lactam Ring-Opening.

Disappointingly, hydrogenolysis/hydrogenation of **137** resulted in returned starting material despite various conditions being trialled.[72,73] A possible explanation is that the phenyl-tetrazole moiety sequestered the palladium catalyst. However use of $NaBH_3CN$ as the reducing agent also resulted in returned starting material (Scheme 22).[74]

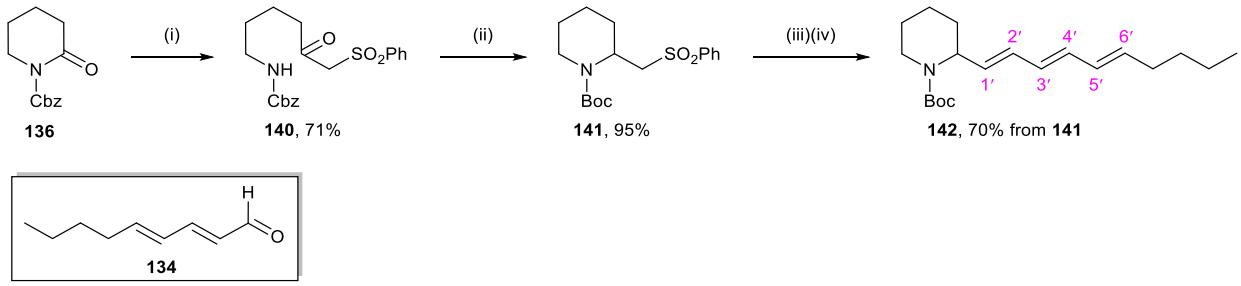


137 **139**, not observed

Scheme 22: Attempted ring closure of **137**. *Reagents and Conditions*: (i) $Pd(OH)_2/C$, H_2, MeOH, rt, 45 h; or $Pd(OH)_2/C$, H_2, EtOH:AcOH (2:100), rt, 6 h; or $NaBH_3CN$, TFA, 4 Å mol. sieves, CH_2Cl_2, rt, 24 h.

It was hoped that switching the tetrazole moiety to phenyl may facilitate the ring closure,[72] and so the lithium anion of commercially available $MeSO_2Ph$ was used. The ring opening of model Cbz protected δ-valerolactam **136** occurred with excellent regioselectivity in 71% yield. Pleasingly, the subsequent hydrogenolysis/hydrogenation ring-closure proceeded in 95%. In order to allow the following olefination, subsequent *N*-Boc protection was required. This was later streamlined into a one-pot procedure with the hydrogenolysis/hydrogenation ring-closure, resulting in piperidine **141** in 95% yield. The piperidine **141** was extremely rotameric in nature and the conformation adopted therein was not investigated due to the complicated NMR spectra of **141**.

In order to complete the model system, the two-step Julia olefination of **141** and aldehyde **134** was performed. This gave triene *E*,*E*,*E*-**142** with good sterecocontrol in 70% overall yield (>95:5 *E*,*E*,*E*:*Z*,*E*,*E*) (Scheme 23). Only two *J* values are observable by ^{1}H NMR spectroscopy analysis; $^{3}J_{1'2'}$ = 14.7 Hz and $^{3}J_{5'6'}$ = 14.4 Hz, but no evidence of olefin isomerisation was observed by ^{1}H and ^{13}C NMR analyses, and so the internal olefin is assumed to have (*E*)-configuration from the geometry of the parent aldehyde **134**.

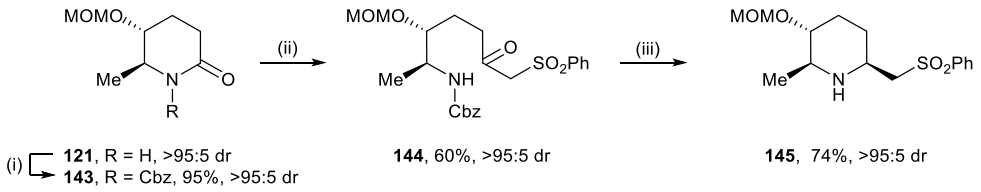


Scheme 23: Synthesis of piperidine **142**. *Reagents and Conditions*: (i) $MeSO_2Ph$, ^{n}BuLi, THF, −78 °C, 1 h; (ii) $Pd(OH)_2/C$, Boc_2O, H_2, MeOH, rt, 72 h (iii) ^{n}BuLi, then **134**, THF, −78 °C then BzCl, −78 °C to rt, 30 min; (vi) Na(Hg), THF:MeOH, rt, 2.5 h.

2.13 Installation of C(6) sulfone

Having successfully ring opened model lactam **136**, followed by ring closure and subsequent installation of the unsaturated chain (Scheme 23), the optimised procedures were applied to Cbz-protected lactam **143** for the synthesis of microcosamine A.

Ring opening with the lithium anion of commercially available $MeSO_2Ph$ proceeded with excellent regioselectivity, as expected from the model system work, in 60% yield (Scheme 24).



Scheme 24: Piperidine **145** synthesis. *Reagents and Conditions*: (i) ^{n}BuLi, CbzCl, THF, −78 °C, 4 h; (ii) $MeSO_2Ph$, ^{n}BuLi, THF, −78 °C, 1 h; (iii) $Pd(OH)_2/C$, H_2 (1 atm.), MeOH, rt, 72 h.

Ring-closure via hydrogenation/hydrogenolysis proceeded in 74% yield (Scheme 24). The 2,6-*cis*-configuration of **145** was verified by analysis of the ^{3}J coupling constants in the ^{1}H NMR spectrum, assuming that a chair conformation would be adopted in solution. Crucially a large ^{3}J coupling constant was noted between C(2)*H* and C(3)*H* $^{3}J_{2,3}$ = 9.0 Hz, indicative of an axial-axial relationship between these two protons and hence with an axial placement of both. A significant, reciprocal nOe correlation was also noted between C(2)*H* and C(6)*H*, which thus indicated the axial placement of the latter when considering the axial placement of the former, thus completing the relative 2,3-*trans*-3,6-*trans*-configurational assignment of the three stereogenic centres at carbon.

This conformation is supported by molecular modelling with Gaussian16 which suggests an energy minima with a C(3)*H*-*C*(3)-*C*(2)-C(2)*H* dihedral angle θ = 172.9 ° consistent with the observed large ^{3}J coupling. The ring-flipped conformer, with all substituents axial was calculated to be 23.6 kJmol^{-1} higher in energy with a C(3)*H*-*C*(3)-*C*(2)-C(2)*H* dihedral angle θ = 68.5 ° (Figure 5).

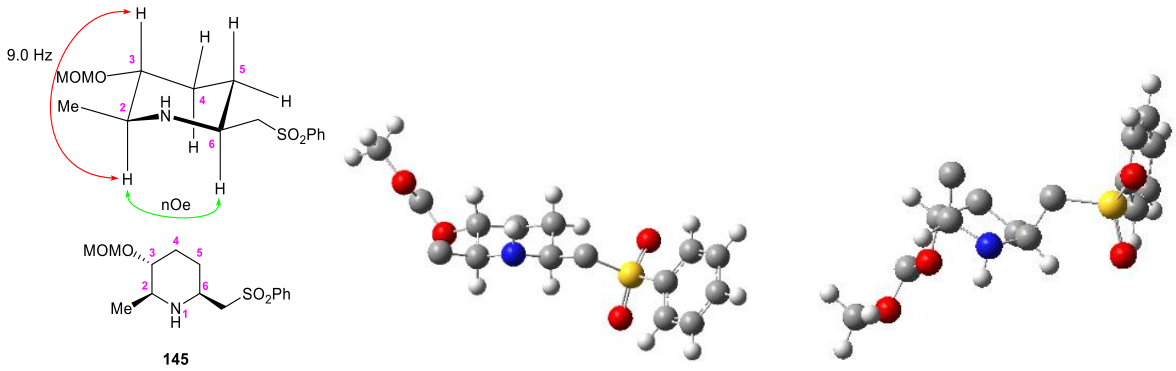
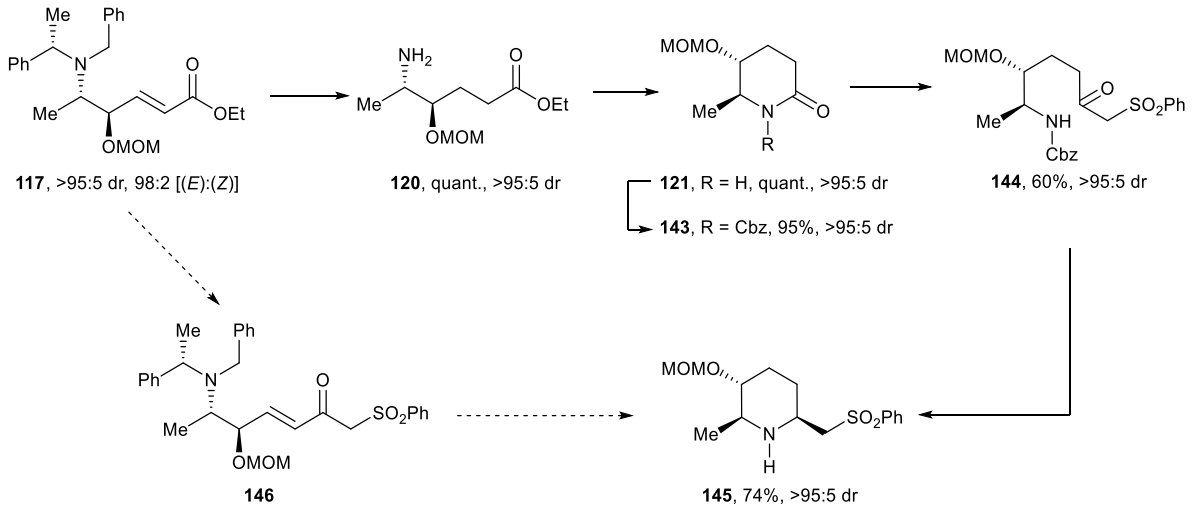


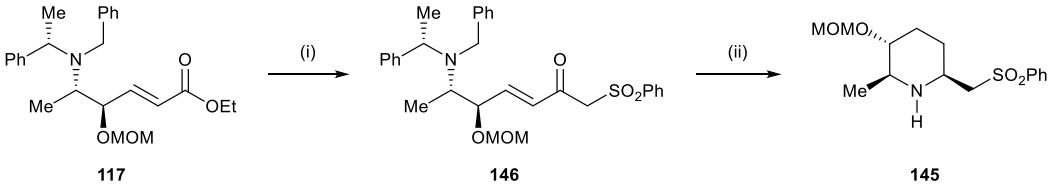
Figure 2. ^{1}H NMR ^{3}J coupling constants (red arrows) and reciprocal nOe enhancements (green arrows) observed for **145**, along with energy minimised structures of ring-flipped conformers (selected H atoms are omitted for clarity).

With *N*-H piperidine **145** in hand, it was proposed that the step count of this route could be reduced by addition of the $MeSO_2Ph$ to acyclic unsaturated ester **117,** which could then be cyclised and deprotected under hydrogenation/hydrogenolysis conditions to yield **147** (Scheme 25).



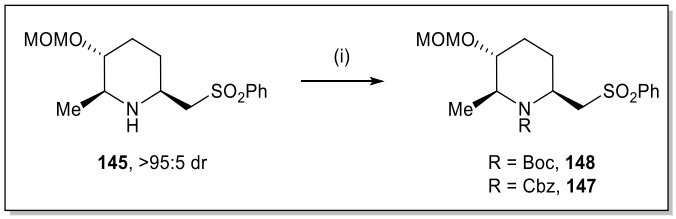
Scheme 25: Current synthetic route to piperidine **145**, and proposed new route.

Addition of the lithium anion of $MeSO_2Ph$ directly to acyclic ester **117** using the previously employed conditions occurred in 95% yield. The subsequent ring-closure via hydrogenation/hydrogenolysis proceeded in a pleasing 85% yield (Scheme 26).



Scheme 26: Streamlined Piperidine **145** Synthesis. *Reagents and conditions*: (i) $MeSO_2Ph$, ^nBuLi, THF, −78 °C, 1 h; (ii) $Pd(OH)_2/C$, H_2, MeOH, rt, 5 days.

Subsequent *N*-Boc protection as used in the model system (Scheme 23) could not be realised as 2,3,6-substituted piperidine **145** proved unreactive towards Boc_2O despite a variety of forcing conditions (heating, nucleophilic catalyst, large reagent excesses), and also no reaction was observed with BocON (2-(Boc-oxyimino)-2-phenylacetonitrile). Instead, *N*-Cbz protection under Schotten-Baumann conditions resulted in **147** in 72% yield (Table 9).



Reagents and Conditions: (i) **see table**.

Reagent (equiv.)	Base (equiv.)	Solvent	Conditions	Conversion
Boc_2O (1.6)	$NaHCO_3$ (3.0)	THF:H_2O	rt, 33 h	-
Boc_2O (1.2)	$NaHCO_3$ (3.0)	MeOH	rt, 33 h	-
Boc_2O (1.6)	$NaHCO_3$ (3.0)	THF	rt, 70 h	-
Boc_2O (10), cat.DMAP	Et_3N (1.5)	CH_2Cl_2	rt, 12 h	-
Boc_2O (10), cat.DMAP	Et_3N (1.5)	CH_2Cl_2	40 °C, 12h	-
BocON (1.2)	Et_3N (1.5)	THF	rt, 16 h	-
Boc_2O (1.1)	Hünig's (1.1)	CH_2Cl_2	50 °C, 36 h	-
CbzCl (5.0)	Na_2CO_3 (15)	CH_2Cl_2	rt, 2 h	95%

Table 9: Piperidine *N*-Protection.

Within **147** the ^{3}J coupling constant noted between C(2)*H* and C(3)*H* $^{3}J_{2,3}$ ~ 1.0 Hz, consistent with a near 90 ° angle between C(2)*H* and C(3)*H*. It is postulated that *N*-Cbz protection forces the ring into a distorted chair, placing the substituents in semi-axial positions. This distorted conformation is largely supported by molecular modelling with Gaussian16, although this suggests an energy minima with a C(3)*H*-*C*(3)-*C*(2)-C(2)*H* dihedral angle θ = 69.2 °.

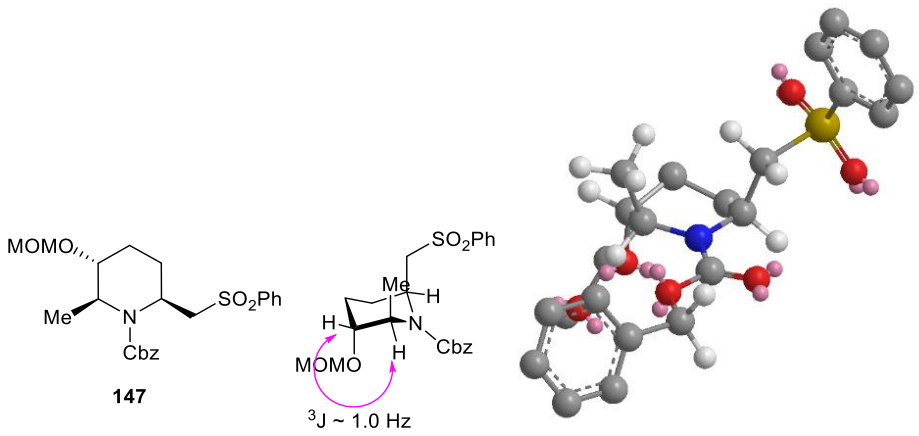
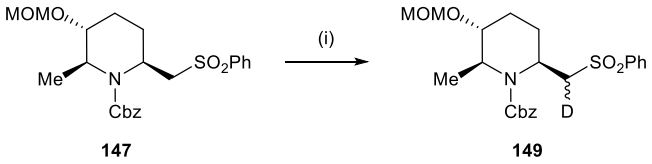


Figure 8: Observed ^{3}J coupling and energy minimised structure of **147** (selected H atoms are omitted for clarity).

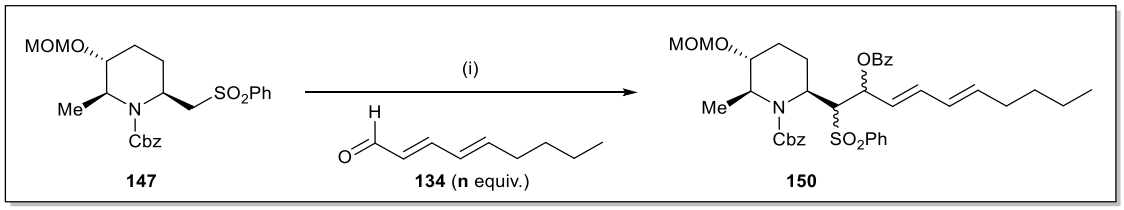
2.14 Julia Olefination

With a good route to *N*-Cbz protected piperidine **147** in-hand, the 2-step Julia olefination to install the unsaturated side chain was attempted. Using ^{n}BuLi to deprotonate sulfone **147**, no addition was observed to aldehyde **134**. Failure to deprotonate was deemed unlikely, and quenching of the presumed lithium anion with D_2O resulted in full conversion to the deuterium-incorporated sulfone (Scheme 27). Analysis of the crude reaction mixture was conducted using HRMS where the ratio of molecular ions $[M(D)+H]^{+}$and $[M(H)+H]^{+}$ was be used to quantify deuterium incorporation as 95%. Despite heating the reaction and use of additives to encourage the addition, no reaction was observed with the sulfone (Table 10).



147 149

Scheme 27: Deuteration Experiment. *Reagents and conditions*: (i) ^{n}BuLi (1.0 equiv.), −78 °C, THF, 20 min, then D_2O.



147 134 (**n** equiv.) 150

Reagents and conditions: (i) ^{n}BuLi (**n** equiv.), −78 °C, **solvent**, 20 min, then 0.2 M aldehyde, **conditions**, then BzCl 2.0 equiv.

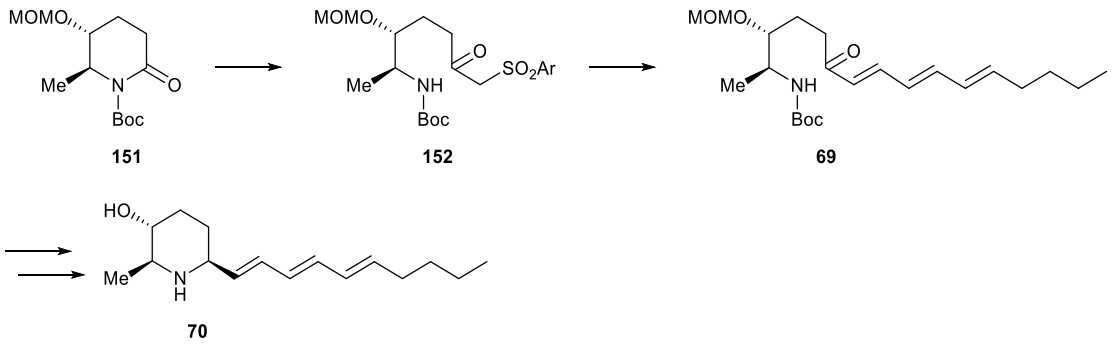
Ald equiv.	Base equiv.	Conditions	Solvent	Conversion
1.2	1.2	−78 °C, 1 h	THF	<5%
1.5	1.0	−78 °C, 3 h	THF	<5%
1.5	1.0	0 °C, 1 h	THF	<5%
1.5	1.0	rt, 16 h	THF	<5%
1.5	1.0	rt, 16 h	DME	<5%
1.2	1.2	rt, 5 h	THF*DIBAL-OMe additive*	<5%

Table 10: Sulfone Addition.

It is plausible that the distorted conformation adopted by the *N*-Cbz piperidine (Figure 8) hinders the approach of the aldehyde.

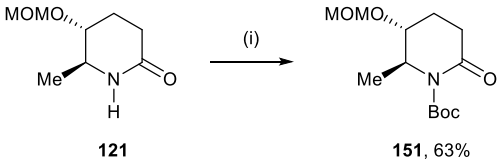
2.15 Route Change

Owing to the lack of addition observed during the attempted Julia olefination (Table 10), it was proposed that the olefination could take place prior to a final ring closure on the acyclic system (Scheme 28). This route would require a change from the *N*-Cbz protecting group (as removal via hydrogenolysis would hydrogenate the newly installed olefins), and so it was decided acid labile Boc would be suitable.



Scheme 28: Proposed Olefination prior to final ring closure.

The requisite *N*-Boc lactam **151** was made by protection of lactam **121** with Boc_2O and cat. DMAP in 63% yield (Scheme 29).



Scheme 29: *N*-Boc protection of lactam **121**. *Reagents and Conditions*: (i) Boc_2O, cat. DMAP, THF, rt, 16 h.

The Boc addition induced a conformational change from diequatorial to diaxial. The observed ^3J coupling between C(2)*H* and C(3)*H* is 2.8 Hz, consistent with axial substituents (and thus equatorial protons). This conformation is supported by molecular modelling with Gaussian16 which suggests an energy minima with a C(3)*H*-*C*(3)-*C*(2)-C(2)*H* dihedral angle $\theta = 69.1°$ consistent with the observed low ^3J coupling. The ring-flipped conformer was calculated to be 29.1 $kJmol^{-1}$ higher in energy with a C(3)*H*-*C*(3)-*C*(2)-C(2)*H* dihedral angle $\theta = 167°$ (Figure 9).

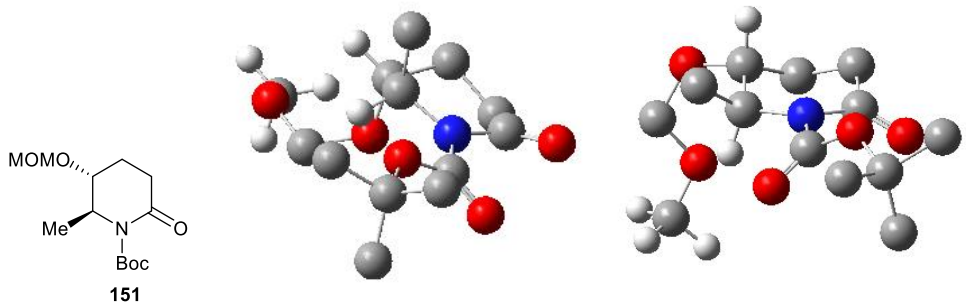
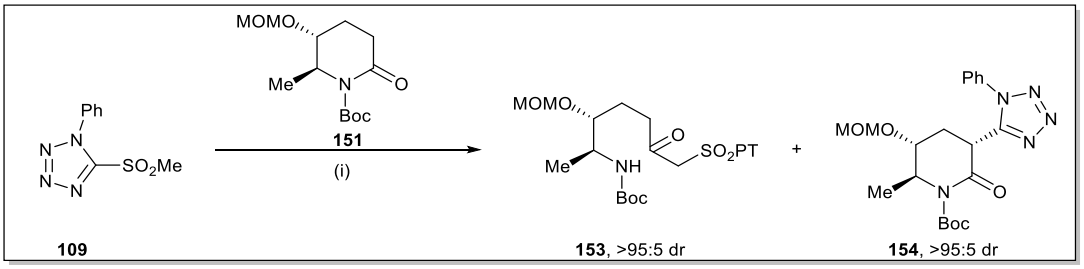


Figure 9: Energy minimised structure of **151** (selected H atoms are omitted for clarity).

With lactam **151** in hand, work began with ring opening of lactam **151** using the lithium anion of $MeSO_2PT$, as had previously worked on model lactam **136**. Initial experiments using conditions that had worked previously with the *N*-Cbz protected model lactam (Table 8) proved fairly unreactive with the *N*-Boc protected substituted lactam, resulting in large amounts of enolate addition to the tetrazole. However the previous problem of $MeSO_2PT$ self-condensation was not observed. Enolate addition to the tetrazole was increased by increasing the equivalents of lactam. Switching base from LiHMDS to ^{n}BuLi gave **153** in 22% yield (Table 11).



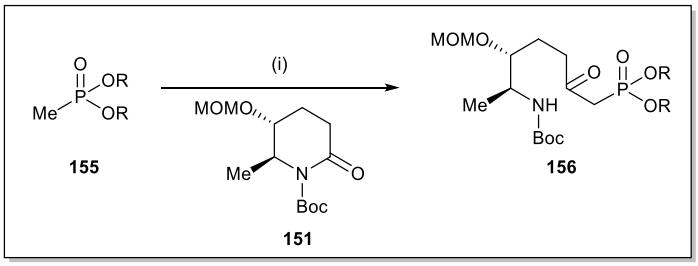
Reagents and Conditions: (i) **base**, −78 °C, THF, then lactam (**n** equiv.), **conditions**.

base (equiv.)	lactam equiv.	conditions	crude ratio 151:153:154
LiHMDS (2.00)	3.00	−78 °C 30 min, rt 1 h	34:22:44
LiHMDS (2.20)	5.50	−78 °C 30 min, rt 1 h	14:16:70
LiHMDS (3.00)	3.00	−78 °C 30 min, rt 1 h	65:20:15
LiHMDS (3.00)	3.00	−78 °C 4.5 h	100:0:0
^{n}BuLi (3.00)	3.00	−78 °C 4 h	complex
^{n}BuLi (1.00)	0.20	−78 °C 4 h	complex
^{n}BuLi (1.00)	0.20	−78 °C 30 min, rt 1.5 h	complex
^{n}BuLi (1.00)	0.50	−78 °C 1.5 h	85:15:0
^{n}BuLi (1.00)	0.50	−78 °C 30 min, rt 2.5 h	88:22:0

Table 11: Lactam ring opening with sulfone 109.

Again, it was postulated that the poor ring-opening yield was because of axial substituents blocking the approach of the nucleophile.

In parallel to these experiments, the lithium anion of diethyl methyl phosphonate was also being trialled as a nucleophile for the lactam ring opening, this would enable a Horner-Wadsworth-Emmons reaction to install the aliphatic chain. Reactions with the phosphate were found to be difficult to reproduce, and initial yields were generally low. Switching from diethyl methyl phosphonate to dimethyl methyl phosphonate increased the yield of the addition to 35%, presumably since the smaller nucleophile was better able to access the π* of the carbonyl. However despite some modest improvements the yield for the addition was still low, and although use of the lactam in excess did result in an acceptable yield of 48%, recovery of the excess lactam was low yielding (10%) (Table 12) and so an alternate strategy was devised.



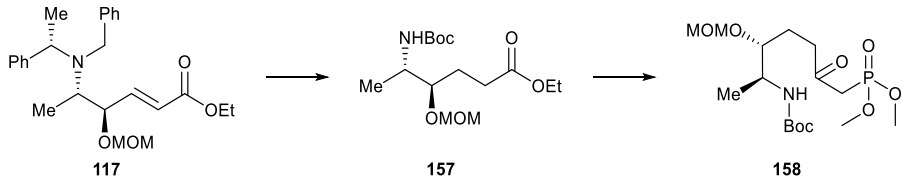
Reagents and Conditions: (i) ^{n}BuLi (**n** equiv.), −78 °C, THF, 30 min, then lactam **151** (1.0 equiv.), **conditions**.

R	Phosphonate equiv.	^{n}BuLi equiv.	conditions	crude ratio 151:156	Yield 151 recovered	Yield product
Et	1.5	1.6	−78 °C, 3 h	91:9	45%	<5%
Et	1.5	1.6	−0 °C, 3 h	88:12	42%	10%
Et	1.5	1.6	rt, 1 h	72:28	35%	15%
Et	1.5	1.6	rt, 2 h	71:29	34%	15%
Me	1.5	1.6	rt, 1 h	55:45	27%	35%
Me	0.5	0.75	rt, 1 h	24:76	10%	48%
Me	3.0	2.5	rt, 1 h	complex	11%	<5%

Table 12: Lactam opening with Phosphonate.

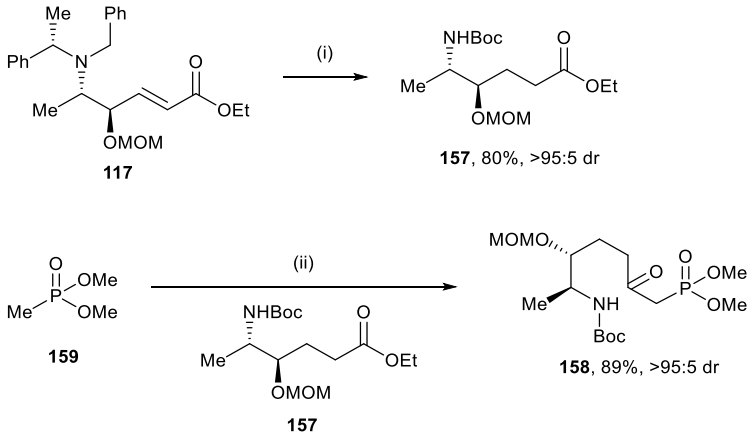
2.16 Acyclic Route

It seemed the approach of the nucleophile was hindered in the lactam system. Given the lack of reactivity observed, a new route was planned. Instead of ring closure followed by ring opening, a tandem hydrogenation/hydrogenolysis of **117** with in situ *N*-Boc protection was planned. Methyl dimethyl phosphonate addition to acyclic ester **157** was envisaged to occur much easier than addition to the lactam (Scheme 30).



Scheme 30: Proposed Acyclic Route to desired keto phosphonate **158**.

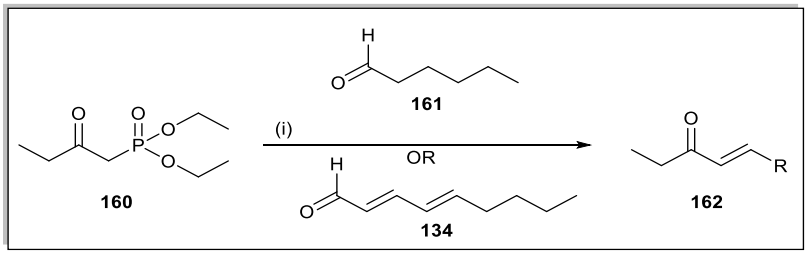
Initial hydrogenation/hydrogenolysis with in situ *N*-Boc protection worked well resulting in *N*-Boc protected acyclic ester **157** in 80% yield. Pleasingly, phosphonate addition to this acyclic ester worked extremely smoothly to give full conversion. However, separation of the excess dimethyl methyl phosphonate from the phosphonate product **158** proved difficult. Reducing the phosphonate excess to 2.00 equiv. resulted in a reduction to 65% conversion, and so different separation methods were attempted. Washing could not separate the phosphonates, and in a basic wash both phosphonates would remain together. Eventually the solution was found to be extremely slow gradient column chromatography (eluent 30–40 °C petrol/Et_2O, 1:1) increased to (eluent 30–40 °C petrol /Acetone, 7:3), allowing isolation of clean keto phosphonate **158** in 89% yield (Scheme 31).



Scheme 31: Keto phosphonate **158** preparation. *Reagents and Conditions*: (i) $Pd(OH)_2/C$, H_2 (5 atm), Boc_2O, EtOAc, rt, 12 h; (ii) ^nBuLi, THF, −78 °C to 0 °C, 1 h.

2.17 Model Horner-Wadsworth-Emmons

With ketophosphonate **158** in hand, a model system was set up in order to optimise the Horner-Wadsworth-Emmons olefination conditions. Initially using hexanal as a model aldehyde, bases for the reaction were trialled using model ketophosphonate **160**. It was surprising to observe that NaH was the only base with which appreciable conversion was observed. Both organometallic reagents (MeMgBr and ^{n}BuLi) were titrated before use (against I_2[75] and diphenylacetic acid[76] respectively). Subsequently using desired aldehyde **134**, the same trend was observed, with NaH deprotonation resulting in 89% conversion and 91:9 dr (Table 13).



Reagents and Conditions: (i) **Base** (1.00 equiv.), **Aldehyde** (1.5 equiv.), THF, **conditions**.

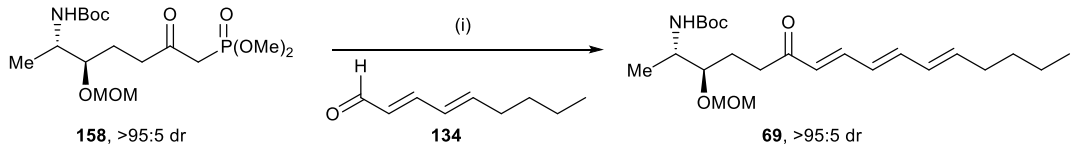
base	aldehyde	conditions	conversion	dr
MeMgBr	**161**	rt, 15 min, then reflux 2.5 h	22%	>95:5
^{n}BuLi	**161**	−78 °C, 30 min then rt, 12 h	14%	>95:5
NaH	**161**	rt, 15 min then rt, 2.5 h	86%	89:11
NaH	**161**	rt, 15 min then reflux, 2.5 h	84%	91:9
^{n}BuLi	**134**	−78 °C, 30 min then rt, 12 h	23%	89:11
MeMgBr	**134**	rt, 15 min, then reflux 2.5 h	0%	>95:5
NaH	**134**	rt, 15 min then rt, 2.5 h	85%	90:10
NaH	**134**	rt, 15 min then reflux, 2.5 h	89%	91:9

Table 13: Model HWE Reactions.

2.18 Horner-Wadsworth-Emmons Reaction

Having screened the base and reaction temperature required for the Horner-Wadsworth-Emmons, the conditions could be applied to the real substrate. Using 1.5 equiv. of aldehyde **134** (which had been synthesised previously (Scheme 20)), the reaction proceeded to full conversion. However the reaction proved very difficult to reliably repeat. Switching to a 1:1 ratio of phosphonate and aldehyde was trialled, however this proved to be less reliable and reduced the conversion to 83%.

As well as being a very unreliable reaction, isolating the α,β;γ,δ;ε,ζ-unsaturated ketone **69** proved extremely troublesome, resulting in very low yields. The major impurity was the excess aldehyde, but reaction stoichiometry of 1:1 was shown to result in only 83% conversion. It was postulated that the unsaturated ketone was unstable to silica FC conditions, and so alumina was trialled as the stationary phase. However, this offered no improvement to the isolated yield. It was found that the excess aldehyde could be removed using an optimised sodium bisulfite/Et_2O wash,[77] leaving the crude product in (88% mass return) without need for further purification (**Table 14**).



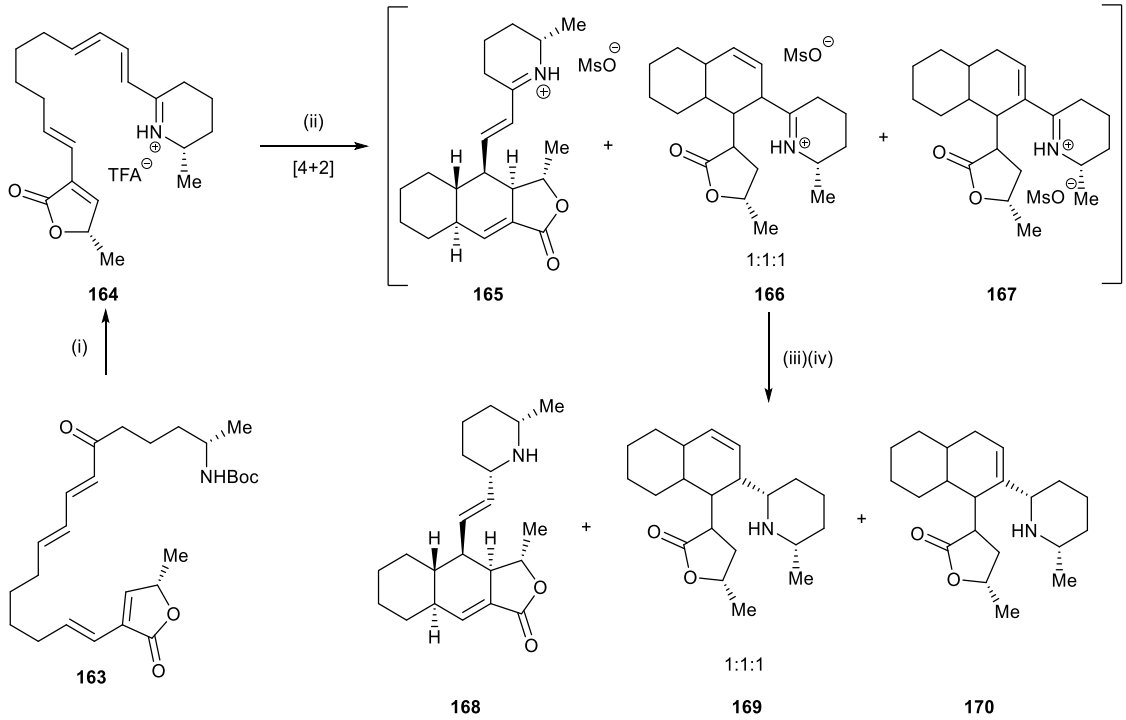
Reagents and Conditions: (i) NaH (1.0 equiv.), THF, rt 2 h, then reflux 12 h.

Aldehyde equiv.	conversion	Purification Method	Isolated yield (~90% purity)
1.5	100%	silica FC	24%
1.0	83%	silica FC	15%
1.5	100%	alumina FC	22%
1.5	100%	add 10% $NaHSO_3$, wash × 1 with Et_2O	55%
1.5	100%	Stir 10 min in 2:5 (DMF:sat aq. $NaHSO_3$). Add H_2O, extract Et_2O, wash 3 × H_2O.	88%

Table 14: HWE reaction.

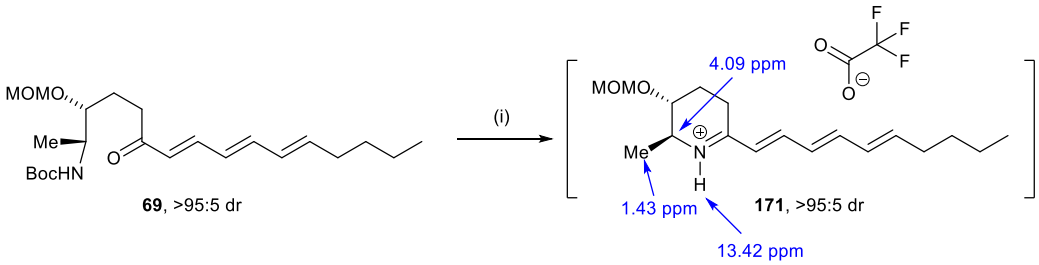
2.19 Piperidine Formation

Having established a route to unsaturated ketone **69**, the stage was set for ring closure. There are many literature examples of intramolecular TFA induced ring closures of *N*-Boc ketones to form piperidine iminium species. However, despite this well-established process, there is just one example using an unsaturated ketone.[78] In this example by Larson et al., α,β;γ,δ-unsaturated ketone **163** was cyclised with TFA to the corresponding α,β;γ,δ-unsaturated iminium **164**, before a [4 + 2] cycloaddition. The resulting iminium ions **165**, **166**, and **167** were then reduced with $NaCNBH_3$, before Boc_2O protection of the nitrogen resulting in the protected piperidines **168**, **169**, and **170**. The 2,6-*cis* iminium reduction was verified X-Ray analyses of subsequent piperidine derivatives (**168**-**170**).



Scheme 32: TFA induced Ring-closure by Larson et al.[78] *Reagents and Conditions*: (i) TFA, CH_2Cl_2, 0 °C 15 min, rt, 15 min; (ii) MsOH, $CDCl_3$, 55 °C, 5−7 day; (iii) $NaCNBH_3$, EtOH, 0 °C to rt; (iv) Boc_2O, Et_3N.

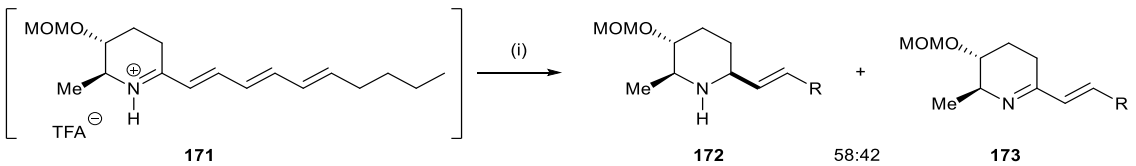
Initially following the work by Larson et al.,[78] ring closure of **69** with TFA resulted in *N*-deprotection, and iminium formation as expected. However, there was some evidence of olefin degradation in the ^{1}H and ^{13}C NMR spectra. The reaction time and temperature was reduced to 0 °C and 10 min, which gave a cleaner iminium ion product by NMR analysis. The triflouroacetate iminium ion **171**, a remarkably stable purple solid, was partially characterised by proton NMR spectroscopy.



Scheme 33: Iminium formation. *Reagents and Conditions*: (i) TFA/CH_2Cl_2 (1:2), 0 °C, 10 min.

2.20 Iminium Reduction

Reduction of the unsaturated trifluoroacetate iminium ion **171** was attempted with sodium cyanoborohydride. Using very mild conditions to avoid conjugate reduction, the iminium ion proved very resistant to reduction, and low conversion was observed (58%). However, this was accepted at this stage as it was hoped that recovered imine **173** could be resubjected to reduction (Scheme 34).



Scheme 34: Iminium Reduction. *Reagents and Conditions*: (i) $NaCNBH_3$ (9.0 equiv.), CH_2Cl_2/EtOH, 30 s, 0 °C.

However, the resultant mixture of imine **173** and amine **172** were inseparable by silica flash column chromatography. This led to the consideration of other purification methods. Because of the difference in basicity between the amine (pKa ~ 11) and imine (pKa ~0), recrystallization of the

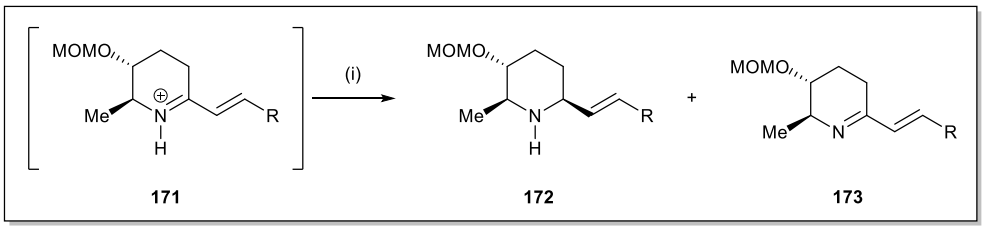
HCl salt was attempted. However, no appreciable separation was observed. It was also hoped that the amine may be suitably more polar than the imine and so could be triturated out. However using a range of solvent systems, little separation was observed.

It was also proposed that a citric acid wash could separate the two protonated species, as in the first step of the synthesis (lithium amide addition) citric acid was used to separate the citrate salts of the secondary and tertiary amines on the basis of the water solubility of the citrate ions. Addition of 10% aq citric acid to the mixture of imine and amine discovered that indeed the amine was water soluble and the imine was largely not. This was using the initial conditions of Et_2O and 10% aq citric acid. However, the separation failed to remove >50% of the imine, and the use of different organic solvents (CH_2Cl_2, $CHCl_3$, CHl_3:iPrOH (3:1)) could not improve this.

Use of other acids (1 M hydrochloric, 2 M acetic, and 1 M sat aq NH_4Cl) with Et_2O did not result in any separation of imine from amine.

2.21 Reduction Additives

In order to improve conversion, more forcing reduction conditions were trialled. Raising the temperature did increase conversion, but also introduced new impurities. However, longer reduction times did result in higher conversion. The optimal conditions were 30 min and 0 °C, as conversion >90% could not be obtained through time increase alone as reaction times longer than 30 min lead to new unidentified impurities (Table 15).

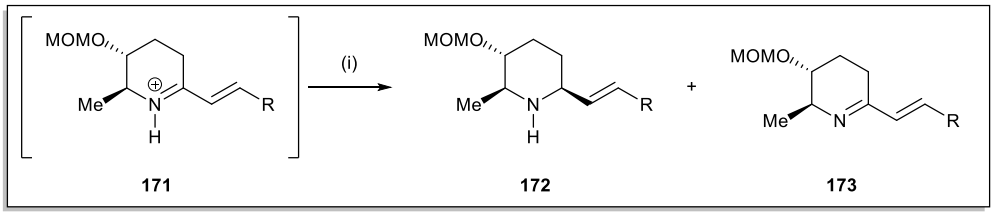


Reagents and Conditions: (i) $NaCNBH_3$ (9.0 equiv.), CH_2Cl_2/EtOH, **conditions**.

Conditions	Conversion %
30 s 0 °C	58
4 min 0 °C	63
10 min 0 °C	74
10 min rt	82 *(with new impurities)*
10 min 0 °C, 10 min rt	86
30 min 0 °C	90
60 min 0 °C	90 *(with new impurities)*

Table 15: Iminium Reduction Conditions.

Further forcing conditions were trialled, and initial reaction with sodium borohydride did result in higher conversion, but also some inseperable impurities by ^{1}H NMR. It was clear than an additive would be required to achieve 100% conversion. Looking to avoid the use of TFA as a promotor (given the degradation observed in longer reaction times for iminium formation), addition of HCl as a promotor resulted in increased conversion, however increasing reaction time or amount of acid could not achieve complete conversion. Eventually it was found that adding an extra portion of both $NaCNBH_3$ and HCl midway through the reduction could achieve >99% conversion (Table 16).



171 172 173

Reagents and Conditions: (i) $NaCNBH_3$ (9.0 equiv.), CH_2Cl_2/EtOH (1:2), **conditions**.

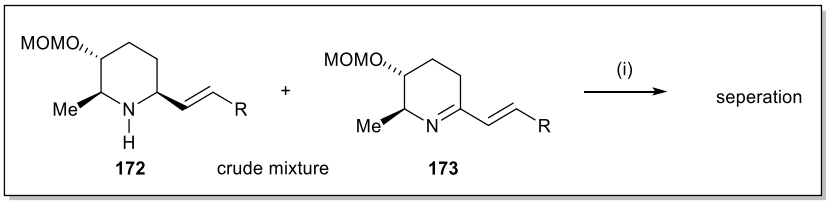
Conditions	Conversion (%)
0.4 M MeOH, 1.5 equiv. $NaBH_4$, rt, 1 h	96*cont. some impurities
1% acetic acid, 30 min, 0 °C	90
3% HCl, 30 min, 0 °C	95
4% HCl, 30 min, 0 °C	97
3% HCl, 1 h 0 °C	95
4% HCl, 15 min 0 °C, 15 min rt	98
4% HCl, 15 min 0 °C then 50% extra $NaCNBH_3$, 45% extra acid 15 min 0 °C	100

Table 16: Iminium Reduction Additives.

2.22 Purification

Despite the full conversion from the reaction, in the following chromatography a very poor mass return was observed (48%) giving impure product, which proved extremely troublesome at this late stage of the synthesis. Despite trying a variety of solvent systems including both classic basic additives NH_4OH and NEt_3, the mass return could not be improved above 55%. Use of silver nitrate doped silica gel did not improve mass return either.[79,80] Use of basic alumina did marginally improve the mass return to 62%, although this was still deemed sub-optimal (

Table 17).



Reagents and Conditions: (i) **see table**.

Stationary Phase	Mobile Phase	Mass Return (%)
Silica	95:3 EA:MeOH	48
Silica	1:1 CH_2Cl_2:EA→10:1 EA:MeOH	47
Silica*	1:1 CH_2Cl_2:EA→10:1 EA:MeOH	52
Silica	3:1 CH_2Cl_2:EA 1% (NH_4OH)	51
Silica	3:1 CH_2Cl_2:EA 2% (NH_4OH)	55
Silica	5:1 CH_2Cl_2:EA 2% (NEt_3)	54
Silica	10:1 CH_2Cl_2:EA 5% (NEt_3)	54
$AgNO_3$ doped Silica	1:1 Petrol:EA→1:2 Petrol:EtOAc	49
$AgNO_3$ doped Silica	3:1 CH_2Cl_2:EA 1% (NH_4OH)	45
Neutral Alumina	1:1 Petrol:EA→1:2 Petrol:EtOAc	61
Basic Alumina	1:1 Petrol:EA→1:2 Petrol:EtOAc	62
Basic Alumina	3:1 CH_2Cl_2:EA 1% (NH_4OH)	62

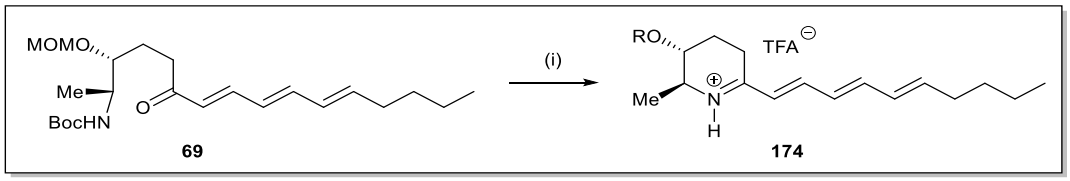
**silica prewashed with 1:1:0.1 CH_2Cl_2:EA:Et_3N*

Table 17: Piperidine Purification.

With the failure of adequate chromatography, the crude product piperidine at ~80% purity by ^1H NMR pre-chromatography, was taken forward without purification.

2.23 MOM Deprotection

The concluding step of the synthesis was MOM deprotection. As the strong acid TFA was used for the iminium formation step (Scheme 33), it was proposed that MOM deprotection could be also performed in 1 step. Unfortunately MOM deprotection was not possible at 0 °C, and although increasing the reaction temperature to rt did induce deprotection after 6 h, it also induced significant degradation of the product (<50% pure by ^{1}H NMR spectroscopy) (Table 18).



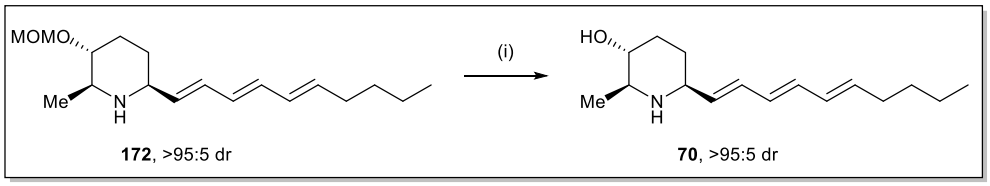
69 174

Reagents and Conditions: (i) TFA, CH_2Cl_2, 0 °C, 10 min.

Conditions	Outcome
6 h 0 °C	zero conversion
15 min 0 °C, then 15 min rt	zero conversion
10 min 0 °C, then 30 min rt	zero conversion
10 min 0 °C, then 2 h rt	zero conversion
10 min 0 °C, then 4 h rt	MOM partially deprotected but complex mixture
10 min 0 °C, then 6 h rt	MOM deprotected but complex mixture

Table 18: Attempted MOM deprotection/Iminium Formation.

Deprotection was then attempted from piperidine **172** in a separate step. It was anticipated that the triene motif would be sensitive to strong acid, and so mild conditions were initially trialled. However, use of DOWEX-50W-X2 (H^+ form) returned starting protected alcohol,[81] and TMSBr returned starting protected alcohol with degraded olefin integrity visible by ^{1}H NMR. More forcing conditions resulted in starting material degradation and complex mixtures. Use of ~1.25 M HCl/MeOH initially resulted in returned starting material, but after 15 h deprotected alcohol **70** was formed in 70% purity. Reducing the temperature of the reduction could not improve the product purity (Table 19).



172, >95:5 dr **70**, >95:5 dr

Reagents and Conditions: (i) **see table**.

Conditions	Outcome
DOWEX-50W-X2 (H^+ form) CH_2Cl_2, rt, 1 h	returned **172**
TMSBr, CH_2Cl_2, −30 °C, 30 min	returned **172** *E*:*Z* ~80:20
TMSOTf, 2,2′-bipyridyl, CH_2Cl_2, 0 °C, 2 h	degraded **172**
TFA, 20% CH_2Cl_2, rt, 15 h	complex mixture
TFA, 50% CH_2Cl_2, rt, 1 h	complex mixture
~1.25 M HCl/MeOH, rt, 3 h	returned **172**
~1.25 M HCl/MeOH, rt, 15 h	product 70% purity, 95% mass return
~1.25 M HCl/MeOH, 0 °C, 15 h	10% conversion

Table 19: MOM Deprotection.

2.24 Microcosamine A Purification

The resulting product at ~70% purity by NMR analysis required further purification. Because of previous problems with column chromatography, trituration was attempted initially, however this made no difference to product purity at a variety of temperatures.

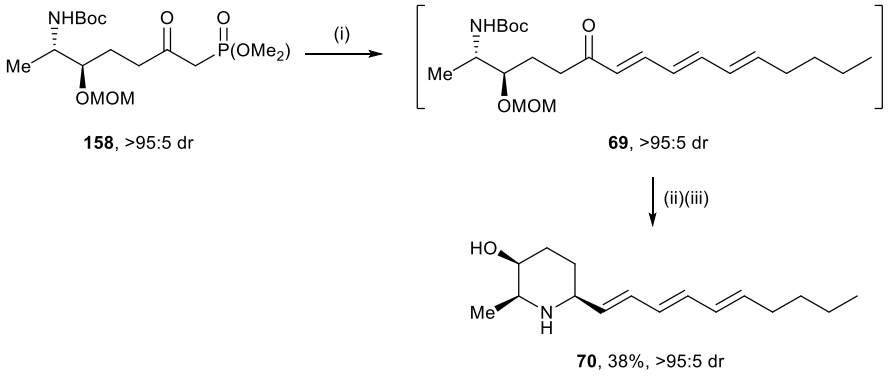
Chromatography was needed. Use of a silica stationary phase, utilising the best conditions from the previous step $CHCl_3$/MeOH (2.5% NH_4OH) gave a mass return of 80%. Use of other stationary phases/mobile phases could not improve this mass return higher (Table 20).

Stationary Phase	Mobile Phase	Mass Return (%)
Silica	$CHCl_3$/MeOH	65
Silica	$CHCl_3$/MeOH (2.5% NH_4OH)	80
Silica	$CHCl_3$/MeOH 2% (NEt_3)	75
Prep TLC	$CHCl_3$/MeOH (2.5% NH_4OH)	50
$AgNO_3$ doped Silica	$CHCl_3$/MeOH	65
$AgNO_3$ doped Silica	$CHCl_3$/MeOH (2.5% NH4OH)	70
Neutral Alumina	$CHCl_3$/MeOH	55
Basic Alumina	$CHCl_3$/MeOH	56
Basic Alumina	$CHCl_3$/MeOH (2.5% NH_4OH)	75

Table 20: Microcosamine A purification.

After column chromatography, the product was at ~90% purity by ^{1}H NMR analysis. It was found that pure microcosamine A could be isolated by acid/base wash. Thus dissolving the amine in 6 M HCl, and washing with Et_2O, one could then be certain of recovering the free base by adjusting the aqueous to >pH 14 with 2 M NaOH, before extraction with Et_2O.

This resulted in isolation of microcosamine A in 38% yield from phosphonate **158** (Scheme 35).



Scheme 35: Synthesis of microcosamine A **70**. *Reagents and Conditions*: (i) NaH, (*E*,*E*)-2,4-nonadienal, THF, 0 °C, 1 h, then 72 °C, 12 h; (ii) TFA, CH_2Cl_2, 0 °C, 10 min; (iii) $NaBH_3CN$, conc. aq. HCl, CH_2Cl_2, EtOH, 0 °C, 30 min.

2.25 Microcosamine A Data Analysis

2.25.1 *Relative Configuration*

The relative configuration of the natural product was independently verified by analysis of the ^{3}J coupling constants in the ^{1}H NMR spectrum, assuming that a chair conformation would be adopted in solution. Crucially a large ^{3}J coupling constant was noted between C(2)*H* and C(3)*H* $^{3}J_{2,3}$ = 8.8 Hz, indicative of an axial-axial relationship between these two protons and hence with an axial placement of both. A significant, reciprocal nOe correlation was also noted between C(2)*H* and C(6)*H*, which thus suggested the axial placement of the latter when considering the axial placement of the former, thus completing the relative 2,3-*trans*-3,6-*trans*-configurational assignment of the three stereogenic centres at carbon (Figure 10).

The implication of this stereochemical assignment for the stereochemical course of the intramolecular reductive amination (i.e., preferential formation of the relative 2,6-*cis*-configuration) is thus consistent with that observed in the closely related synthesis of microconine,[53] as well as with many other reports concerning intramolecular reductive aminations of δ-amino ketones,[78,82,83] all of which have a predilection for formation of the corresponding 2,6-*cis*-configuration within the corresponding product.

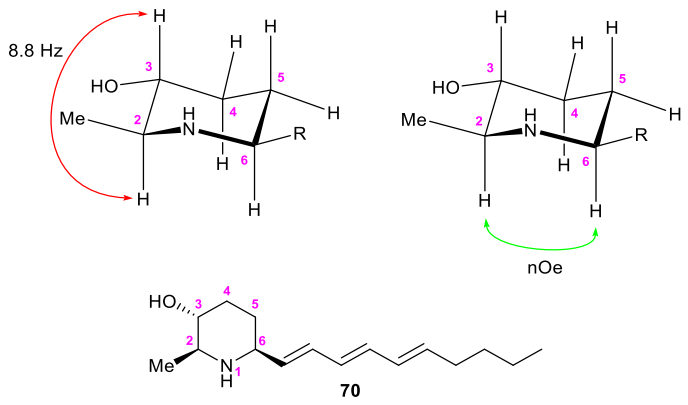


Figure 10: ^{1}H NMR ^{3}J coupling constants (red arrows) and reciprocal nOe enhancements (green arrows) observed for **70**.

2.25.2 *Comparison of Relative Configuration with Natural Product*

With the relative configuration within **70** independently established by analysis and interpretation of the spectroscopic data, comparison with the reported spectroscopic data for the sample of microcosamine A from nature was undertaken (Figure 11).[39] Excellent agreement was noted between the data set for the natural product and the corresponding synthetic sample **70**. It is therefore unequivocal that natural microcosamine A possesses the relative 2,3-*trans*-3,6-*trans*-configuration.

Microcosamine A	70	$\Delta\delta_C$
13.9	14.1	+0.2
19.0	19.1	+0.1
22.2	22.4	+0.2
31.4	31.6	+0.2
32.0	32.2	+0.2
32.5	32.6	+0.1
33.9	34.1	+0.2
58.4	58.6	+0.2
58.6	58.8	+0.2
73.6	73.8	+0.2
129.9	130.1	+0.2
130.1	130.3	+0.2
130.4	130.6	+0.2
132.9	133.1	+0.2
135.2	135.3	+0.1
135.6	135.8	+0.2

Microcosamine A	70
0.86 (3H, t, 6.8)	0.89 (3H, t, 7.2)
1.17 (3H, d, 6.4)	1.20 (3H, d, 6.2)
1.31 (6H, m)[a]	1.34 (6H, m)
1.71 (1H, m)	1.73 (1H, m)
2.06 (3H, m)[b]	2.07 (3H, m)
2.50 (1H, dq, 10.0, 6.4)	2.53 (1H, dq, 8.8, 6.2)
3.15 (2H, m)[c]	3.17 (2H, m)
5.57 (1H, dd, 15.2, 7.2)	5.60 (1H, dd, 15.2, 7.0)
5.67 (1H, dt, 15.2, 7.2)	5.69 (1H, dt, 15.1, 7.0)
6.10 (4H, m)[d]	6.11 (4H, m)

Figure 11: ^{1}H and ^{13}C NMR data of microcosamine A (Ref [39]) and synthetic sample **70**. Reference frequencies employed for the natural product are unknown. Reference frequencies employed for **70** are: $CHCl_3$, δ_H = 7.26; $CDCl_3$, δ_C = 77.16 (Refs [84] and [85]). Midpoints of all multiplets are quoted. [$\Delta\delta_C = \delta_C$ (natural) − δ_C (synthetic)].[a]The ^{1}H NMR data for the natural product includes resonances at 1.24–1.37 (2H, m), 1.34 (1H, m) and 1.36 (1H, m); the mid-point of these has been quoted here for purposes of comparison.[b]The ^{1}H NMR data for the natural product includes resonances at 2.04 (1H, m) and 2.07 (2H, q, 7.2); the mid-point of these has been quoted here for purposes of comparison.[c]The ^{1}H NMR data for the natural product includes resonances at 3.13 (1H, m) and 3.16 (1H, m); the mid-point of these has been quoted here for purposes of comparison.[d]The ^{1}H NMR data for the natural product includes resonances at 6.04 (1H, m), 6.13 (1H, m), 6.14 (1H, m) and 6.15(1H, m); the mid-point of these has been quoted here for purposes of comparison.

2.25.3 *Absolute Configuration*

With the question of the relative configuration within the alkaloid unambiguously resolved, the question turned to the absolute configurational assignment of microcosamine A. From the known

absolute configuration of α-hydroxy-β-amino ester **70**, and the fact that the relative configurations within **70** had been unambiguously assigned, it followed that the absolute (2*S*,3*R*,6*S*)-configuration could be assigned to the three stereogenic centres of the piperidine ring within **70**.

It was ensured that the specific rotation value for **70** was measured under analogous conditions (temperature and concentration, as well as solvent) to that of the samples of the microcosamine A derived from nature, in order that a valid comparison could be made. With this data in hand, it was found that the sign and magnitude of the specific rotation values observed for **70** were in good agreement with the value reported for the corresponding sample of the alkaloid isolated from nature. Microcosamine A was reported to have $\{[\alpha]_D^{20}$ +4 (c = 1.0 MeOH)$\}$[86] and $\{[\alpha]_D^{20}$ +4.5 (c = 1.0 MeOH)$\}$ was obtained for (2*S*,3*R*,6*S*)-**70**. This data is therefore consistent with microcosamine A possessing the absolute (2*S*,3*R*,6*S*)-configuration.

The specific rotation of natural products has been shown to vary greatly with even trace amounts of acid present.[70] The specific rotation of microcosamine A was measured whilst doping the sample with TFA in order to investigate if the protonated natural product had a greatly different specific rotation (Figure 12). Whilst the recorded value does change from +4.2 to +13.3, there was crucially no change of sign.

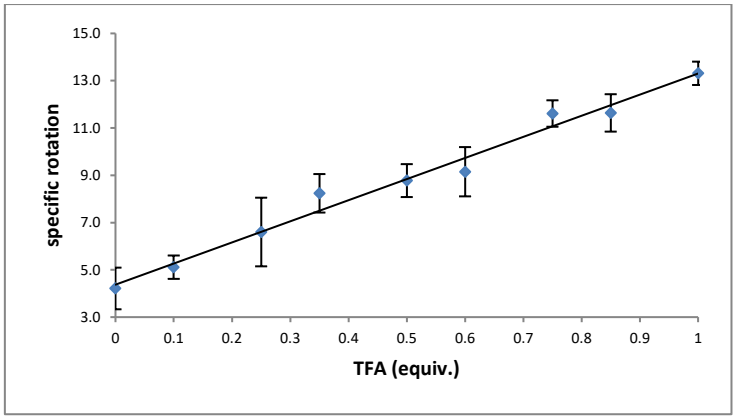


Figure 12: Effect of acid on the specific rotation of **70** (average ± standard deviation plotted, n=3).

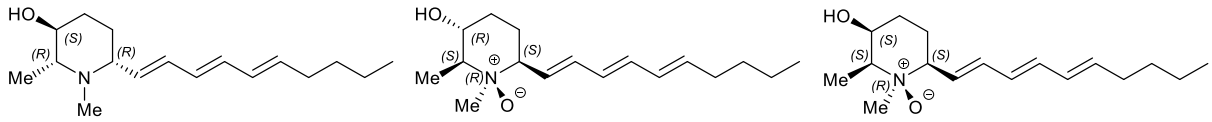
2.26 Conclusion

In conclusion, an independent asymmetric synthesis of the alkaloid microcosamine A, has been established. The key stereodefining steps in the synthesis were the conjugate addition of enantiopure lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to *tert*-butyl crotonate with in situ enolate oxidation, and an intramolecular reductive amination of a δ-amino ketone; both of these transformations proceed with a well-established (and predictable) sense of diastereocontrol to facilitate construction of the targets. Interrogation of the synthetic sample of the alkaloid using ^{1}H NMR ^{3}J coupling constant analysis and NOESY analyses independently established the relative configuration, which was entirely consistent with the expected diastereoselectivity of the synthetic process. Comparison of specific rotation data for microcosamine A is consistent with the alkaloid possessing the absolute (2*S*,3*R*,6*S*)- configuration previously assigned.

Chapter 3 Synthesis of Microgrewiapines A-C

3.1 Chapter Outline

This chapter describes the elaboration of the synthetic piperidine natural product microcosamine A to two other alkaloids isolated from *Microcos Paniculata*, microgrewiapines A and B, and also the development of a synthesis of a C(3) epimeric series to enable access to microgrewiapine C (Figure 13).



Microgrewiapine A **73** Microgrewiapine B **74** Microgrewiapine C **72**

Figure 13: Structures of Microgrewiapines A-C.

3.2 Microgrewiapine A-C Isolation

In 2013, four piperidine alkaloids were isolated from the same plant in the same study. Still et al.[38] isolated microcosamine A, and microgrewiapines A−C, from the stem bark, branches, and leaves of *Microcos Paniculata*. The characterisation of microcosamine A was discussed in Chapter 2. The characterisation of each of microgrewiapine A−C are discussed in turn below.

3.3 Microgrewiapine A

Analysis by standard techniques led to the proposal of the gross structure of microgrewiapine A. Concerning stereochemistry, the diagnostically large ^3J coupling constant between C(2)*H* and C(3)*H* ($^3J_{2,3}$ = 8.9 Hz) suggested a diaxial relationship of the two protons in a chair conformation. An nOe enhancement between C(2)*H* and C(6)*H* also suggested that the two were axial, thus completing the relative configurational assignment: all three protons of the stereogenic centres were placed axially, thus all the substituents of the piperidine ring occupied equatorial sites, and

the relative 2,3-*trans*-3,6-*trans*-configuration was assigned to the alkaloid **73** (Figure 14). This is similar to the analysis for microcosamine A.

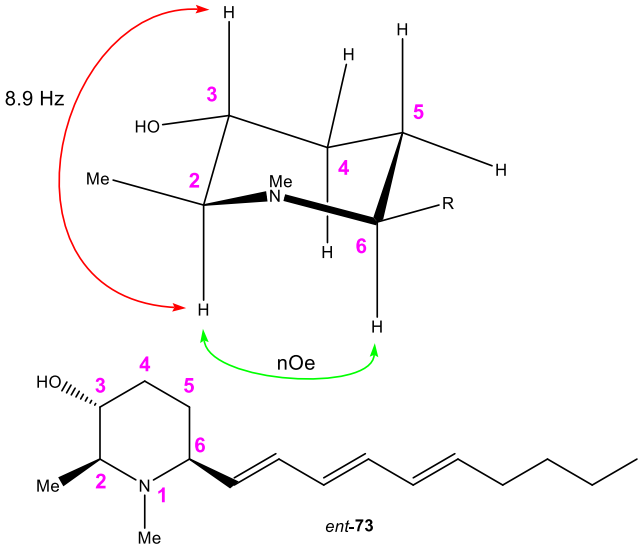


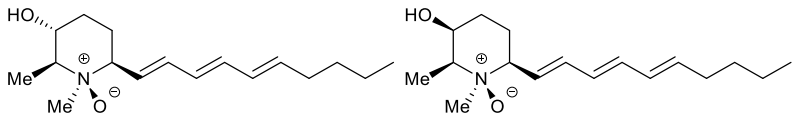
Figure 14: ^{1}H NMR ^{3}J coupling constants (red arrows, φ ≈ 180 °; blue arrows, φ ≈ 60 °) and reciprocal nOe enhancements (green arrows) observed for microgrewiapine A by Still et al.[38]

A non-zero specific rotation value was recorded {$[\alpha]_D^{25}$ +15.4 (c = 0.1 MeOH)}. The absolute configuration of the secondary alcohol was assigned as *R* on the basis of Mosher ester analysis.[1]

Microgrewiapine A was also reportedly isolated in 2017 by Meena et al.,[87] however no supporting data is presented.[88]

3.4 Microgrewiapine B and C

Also isolated from the same plant in the same study,[38] were the two *N*-oxide containing piperidines microgrewiapine B and C.



Microgrewiapine B **74** Microgrewiapine C **72**

Figure 15: Microgrewiapine B and C.

The gross structure of Microgrewiapine B was assigned by analogy to microgrewiapine A, with the *N*-oxide moiety identified by the significant downfield shifts of the protons on the piperidine ring in the ^{1}H NMR spectra. Concerning stereochemistry, the diagnostically large ^{3}J coupling constant between C(2)*H* and C(3)*H* ($^{3}J_{2,3}$ = 10.7 Hz) suggested a diaxial relationship of the two protons in a chair conformation. An nOe enhancement between C(2)*H* and C(6)*H* also suggested that the two were axial, thus completing the relative configurational assignment: all three protons of the stereogenic centres were placed axially, thus all the substituents of the piperidine ring occupied equatorial sites, and the relative 2,3-*trans*-3,6-*trans*-configuration was assigned to the alkaloid. The relative configuration at *N* was assigned by nOe analysis, with no interaction observed between *N*Me-C(3)H, and strong interaction between *N*Me-C(2)H-C(6)H (Figure 16). The absolute (1*R*,2*S*,3*R*,6*S*)-configuration of microgrewiapine B was thence assigned by analogy to that established for microgrewiapine A.

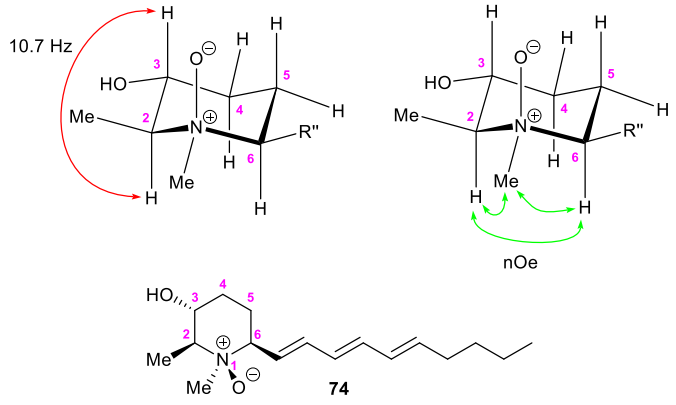


Figure 16: ^{1}H NMR ^{3}J coupling constants (red arrows) and reciprocal nOe enhancements (green arrows) observed for microgrewiapine B by Still et al.[38]

The gross structure of microgrewiapine C was not elaborated upon by the authors. There were strong nOe correlations between C(2)*H*, C(3)*H*, and C(6)*H*. On this basis the C(3) stereocentre was proposed as (*S*). The relative configuration of the nitrogen atom was assigned as (*R*) by the nOe interactions observed between the *N*Me group and C(3)*H* (Figure 17). The absolute (1*R*,2*S*,3*S*,6*S*)-configuration of microgrewiapine C was thence assigned by analogy to that established for microgrewiapine A.

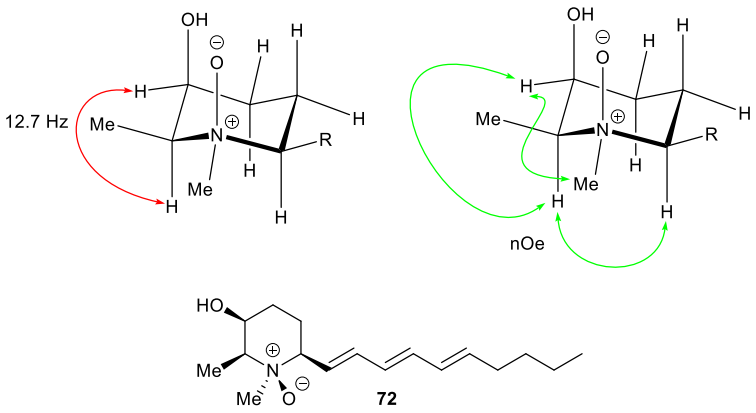
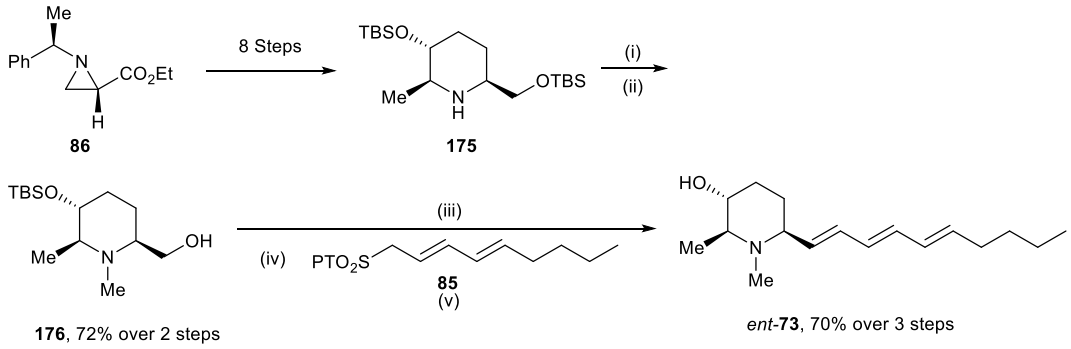


Figure 17: ^{1}H NMR ^{3}J coupling constants (red arrows) and reciprocal nOe enhancements (green arrows) observed for microgrewiapine C by Still et al.[38]

3.5 Microgrewiapine A Synthesis by Macha and Ha

In 2018 the first synthesis of Microgrewiapine A was reported by Macha and Ha, building on their synthesis of microcosamine A.[45]

N-Methylation of **175** (an advanced intermediate from their synthesis of microcosamine A) via a reductive amination using aqueous formaldehyde, then primary *O*-silyl deprotection mediated by 70% HF·py gave primary alcohol **176** (72% over 2 steps). Swern oxidation of the corresponding alcohol, and subsequent Julia-Kocienski olefination followed by silyl deprotection provided microgrewiapine A (13 steps from (2*S*)-aziridine-2-carboxylate **86**, 23% overall yield) (Scheme 36).



Scheme 36: Synthesis of microgrewiapine A by Macha and Ha.[45] *Reagents and Conditions*: (i) 37% HCHO, AcOH, $NaCNBH_3$, rt, 1 h; (ii) 70% HF·Py, THF, rt, 12 h; (iii) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 2 h; (iv) KHMDS, 18-crown-6, DME, rt, 12 h; (v) TBAF, THF, rt, 1 h.

Macha and Ha[45] reported that the NMR data were in full agreement with the isolated sample, which is clear from analysis of the ^{13}C spectra (Table 21).

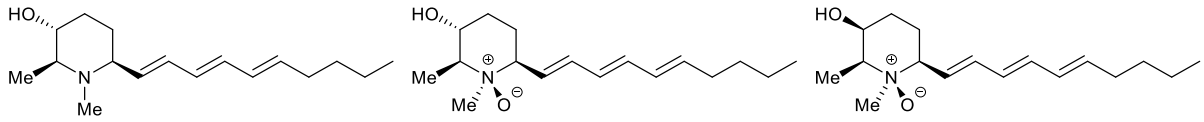
Still et al.[38] (Natural)	Macha and Ha[45] (Synthetic)	$\Delta\delta_C$
14.1	14.0	+0.1
16.4	16.3	+0.1
22.0	22.3	−0.3
31.3	31.2	+0.1
31.4	31.5	−0.1
32.5	32.6	−0.1
33.5	33.5	0
40.4	40.3	+0.1
66.1	66.1	0
67.6	67.6	0
72.6	72.6	0
131.4	131.1	+0.3
131.4	131.1	+0.3
131.4	131.1	+0.3
131.4	131.1	+0.3
135.7	135.8	−0.1
136.7	136.5	+0.2

Table 21: ^{13}C NMR data of natural microgrewiapine A (Ref [38]) and synthetic sample (Ref [45]). Reference frequency employed for the natural product is unknown. Reference frequency employed for synthetic is $CDCl_3$, δ_C = 77.0 [$\Delta\delta_C = \delta_C$ (natural) − δ_C (synthetic)].

The authors noted that the measured specific rotation for the (2*S*,3*R*,6*S*)-sample **73** did not match that recorded for the natural sample. The synthetic (2*S*,3*R*,6*S*)-sample **73** value recorded was {$[\alpha]_D^{20}$ −16.0 (c = 0.8 MeOH)}, which was deemed opposite to the isolation sample {$[\alpha]_D^{25}$ +15.4 (c = 0.1 MeOH)}, whilst the value recorded for enantiomeric (2*R*,3*S*,6*R*)-stereoisomer of microgrewiapine A {$[\alpha]_D^{20}$ +15.8 (c = 1.05 MeOH)} suggested that the assigned absolute (2*S*,3*R*,6*S*)-configuration of the natural product should be revised to the absolute (2*R*,3*S*,6*R*)-configuration. It is worth noting however, that the values recorded for the synthetic samples are measured under conditions quite different from those recorded for the isolated sample, namely different concentration and temperature.

3.6 Chapter Aim

The aim of this chapter is to utilise the optimised synthetic route to microcosamine A in order to synthesise microgrewiapines A and B, and also to develop a synthesis of the C(3) epimeric series in order to synthesise microgrewiapine C. This will help elucidate and confirm the structures of the natural products.



Microgrewiapine A *ent*-**73** Microgrewiapine B **74** Microgrewiapine C **72**

Figure 18: Target compounds microgrewiapines A-C.

3.7 Microgrewiapine A Synthesis

Reductive *N*-methylation of synthetic microcosamine A **70** was achieved upon treatment with formalin and $NaBH_3CN$. TLC and NMR analysis revealed clean conversion to microgrewiapine A. However, purification was (as observed with microcosamine A) low yielding. Previously it was found that $CHCl_3$/MeOH was the best chromatography eluent for these systems, and so a variety of basic additives were trialled, with $CHCl_3$/MeOH (2.5% NH_4OH) proving to be the best conditions (Table 22).

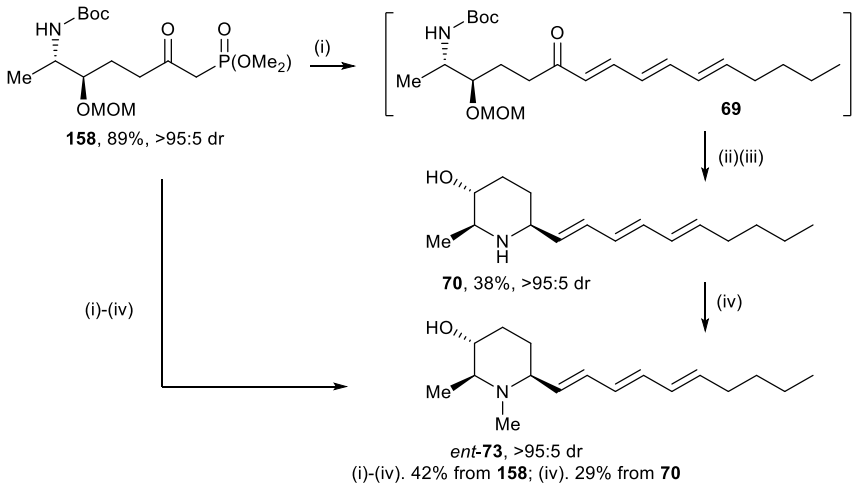
Stationary Phase	Mobile Phase	Isolated Yield (%)
Silica	$CHCl_3$/MeOH	20%
Silica	$CHCl_3$/MeOH (2.5% NH_4OH)	45%
Silica	$CHCl_3$/MeOH 2% (NEt_3)	40%
Prep TLC	$CHCl_3$/MeOH (2.5% NH_4OH)	35%

Table 22: Purification of microgrewiapine A.

After column chromatography, the product was at ~90% purity by ^1H NMR analysis. It was found that pure (>95%) microgrewiapine A could be isolated after the column chromatography by an acid/base wash, just as for microcosamine A. Dissolving the amine in 6 M HCl, and washing with Et_2O removed non-basic impurities. One could then be certain of recovering the free base by

adjusting the aqueous to >pH 14 with 2 M NaOH, before extraction with Et_2O. This gave synthetic microgrewiapine A *ent*-**73** in 29% isolated yield.

A superior yield of *ent*-**73** was achieved if **70** was subjected directly (i.e., without purification) to the reductive amination conditions; thus *ent*-**73** was isolated in 42% yield from **158** after chromatography (Scheme 37).



Scheme 37: Synthesis of microgrewiapine A. *Reagents and Conditions*: (i) NaH, (*E*,*E*)-2,4-nonadienal, THF, 0 °C, 1 h, then 72 °C, 12 h; (ii) TFA, CH_2Cl_2, 0 °C, 10 min; (iii) $NaBH_3CN$, conc. aq. HCl, CH_2Cl_2, EtOH, 0 °C, 30 min; (iv) formalin, $NaBH_3CN$, MeCN, rt, 16 h.

3.8 Microgrewiapine A Data Analysis

3.8.1 *Relative Configuration*

The relative configuration of *ent*-**73** was verified by analysis of the ^{3}J coupling constants in the ^{1}H NMR spectrum, assuming that a chair conformation would be adopted in solution. Crucially, a large ^{3}J coupling constant was noted between C(2)*H* and C(3)*H* within *ent*-**73** ($^{3}J_{2,3}$ = 8.9 Hz), indicative of an axial-axial relationship between these two protons and hence with an axial placement of both. A significant, reciprocal nOe correlation was also noted between C(2)*H* and C(6)*H*, which thus established the axial placement of the latter when considering the axial placement of the former, thus completing the relative 2,3-*trans*-3,6-*trans*-configurational assignment of the three stereogenic centres at carbon for *ent*-**73**. It was possible to resolve additional ^{3}J coupling constants that provided further support for the assigned relative configurations ($^{3}J_{3,4ax}$ = 7.4 Hz, $^{3}J_{3,4eq}$ = 4.6 Hz, $^{3}J_{5ax,6}$ = 11.2 Hz, $^{3}J_{5eq,6}$ = 3.0 Hz) (Figure 19). The implication of this stereochemical assignment for the reaction is that no epimerisation at C(6) was observed during the *N*-methylation.

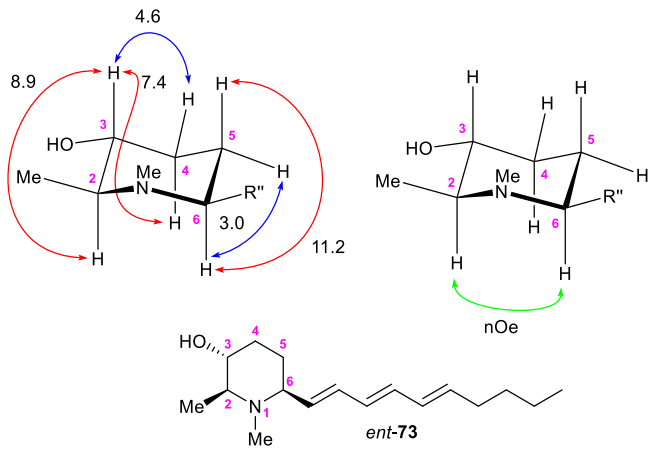


Figure 19:^{1}H NMR ^{3}J coupling constants (Hz) (red arrows, φ ≈ 180 °; blue arrows, φ ≈ 60 °) and reciprocal nOe enhancements (green arrows) observed for *ent*-**73**.

3.8.2 *Comparison of Relative Configuration with Natural Product*

With the relative configuration within microgrewiapine A independently established by analysis and interpretation of the spectroscopic data, comparison with the reported spectroscopic data for the sample of the alkaloid isolated from nature in the isolation study of Kinghorn et al.[38] was undertaken. Prior to comparing these data sets, the reported ^{1}H and ^{13}C NMR spectroscopic data for microgrewiapine A was validated by analysis of the copies of the original ^{1}H and ^{13}C NMR spectra supplied by Kinghorn et al. as supporting information. Some transcription errors were noted in the ^{1}H, and thus the data for the natural product was corrected. In the event then, excellent agreement was noted between the corrected data set for microgrewiapine A and *ent*-**73** (Table 23). It is therefore unequivocal that microcosamine A, and now microgrewiapine A, both possess the relative 2,3-*trans*-3,6-*trans*-configuration of the three common stereogenic centres (at carbon) around the piperidine ring.

Microgrewiapine A	*ent*-**73**	$\Delta\delta_C$	**Microgrewiapine A**	*ent*-**73**
14.1	14.0	−0.1	0.89 (3H, t, 7.2)	0.88 (3H, t, 7.2)
16.4	16.4	0	1.26 (3H, d, 6.1)	1.26 (3H, d, 6.1)
22.3	22.3	0	1.34 (5H, m)	1.35 (5H, m)
31.3	31.3	0	1.49 (1H, app qd, 10.1, 3.0)*	1.49 (1H, tdd, 13.3, 11.2, 3.5)
31.6	31.6	0	1.63 (1H, m)	1.64 (1H, ddt, 13.3, 4.0, 3.1)
32.6	32.6	0	1.83 (1H, dq, 8.9, 6.1)	1.82 (1H, dq, 8.9, 6.1)
33.5	33.5	0	2.03 (1H, m)	2.02 (1H, ddt, 11.7, 4.7, 3.3)
40.4	40.4	0	2.09 (2H, app q, 7.2)*	2.09 (2H, qd, 7.2, 1.4)
66.2	66.2	0	2.21 (3H, s)	2.21 (3H, s)
67.6	67.6	0	2.48 (1H, ddd, 11.2, 8.7, 3.0)	2.47 (1H, ddd, 11.2, 8.9, 3.0)
72.6	72.6	0	3.27 (1H, ddd, 10.8, 8.9, 4.5)	3.26 (1H, ddt, 8.9, 7.4, 4.6)
130.1	130.1	0	5.53 (1H, dd, 14.6, 8.8)*	5.52 (1H, dd, 14.6, 8.9)*
130.3	130.3	0	5.71 (1H, dt, 14.5, 7.4)*	5.69 (1H, dt, 14.3, 7.2)*
131.6	131.6	0	6.10 (4H, m)	6.10 (4H, m)
132.7	132.7	0		
135.8	135.7	−0.1		
136.7	136.7	0		

Table 23: ^{1}H and ^{13}C NMR data of natural microgrewiapine A[38] and synthetic sample *ent*-**73**. Reference frequencies employed for the natural product are unknown. Reference frequencies employed for *ent*-**73** are: $CHCl_3$, δ_H = 7.26; $CDCl_3$, δ_C = 77.16[85]. Midpoints of all multiplets are quoted. [$\Delta\delta_C = \delta_C$ (natural) − δ_C (synthetic)]. *These ^{1}H NMR data of microgrewiapine A are corrected here (compared to those reported in Ref [38]) following re-analysis of the copies of the NMR spectra of the natural product.

3.8.3 *Absolute Configuration*

With the question of the relative configuration within microgrewiapine A unambiguously resolved, the question turned to the absolute configurational assignment of microgrewiapine A.

From the known absolute configuration of α-hydroxy-β-amino ester **68**, and the fact that the relative configurations within *ent*-**73** had all been unambiguously assigned, it followed that the absolute (2*S*,3*R*,6*S*)-configurations could be assigned to the three common stereogenic centres of the piperidine ring within *ent*-**73**.

Given the importance of the specific rotation for the determination of the absolute configuration of microgrewiapine A, further investigations were carried out regarding the specific rotation.

Owing to different concentrations and temperatures used in the isolation and synthetic studies on microgrewiapine A, the specific rotation value for the prepared synthetic sample *ent*-**73** was measured at a range of temperature and concentration values (Figure 20).

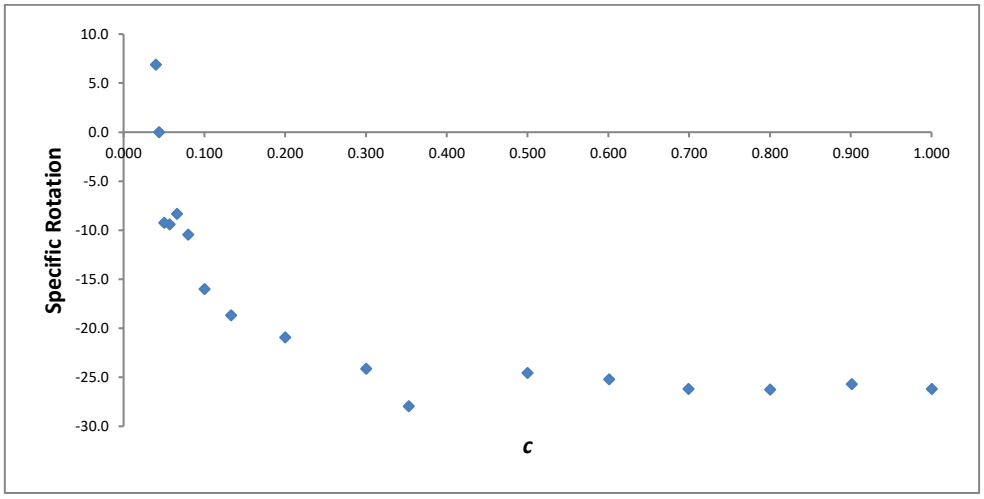


Figure 20: Concentration dependence of the specific rotation of *ent*-**73** (measurements taken at 25 °C). (average ± standard deviation plotted, n=3).

It is clear that at low concentrations the specific rotation is no longer a reliable measurement likely due to the larger impact of errors and inaccuracies. The isolation measurement was taken with c = 0.1.[38]

The investigations into the specific rotation of microgrewiapine A were continued by measuring the effect that trace acid had on the measurement. By adding increasing equivalents of TFA to the synthetic sample, although the magnitude of the rotation does change with acid, the change is not significant in this case *ent*-**73** (free base) $\{[\alpha]_D^{25}$ −26.2 (*c* = 0.8 MeOH)}, *ent*-**73**·0.1 TFA $\{[\alpha]_D^{25}$ −24.3 (*c* = 0.8 MeOH)}, *ent*-**73**·1.0 TFA $\{[\alpha]_D^{25}$ −12.3 (*c* = 0.8 MeOH)} (Figure 21).

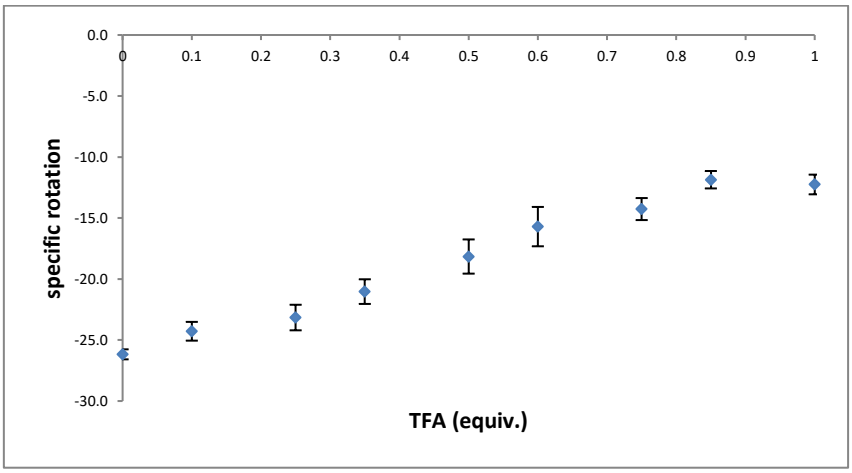


Figure 21: Acid dependence of the specific rotation of *ent*-**73** (measurements taken at 25 °C). (average ± standard deviation plotted, n=3).

Given the observed variation of the specific rotation of *ent*-**73** on concentration, values should only be compared when they have been recorded under identical conditions of concentration (as well as solvent).

The observed specific rotation value for (2*S*,3*R*,6*S*)-*ent*-**73** $\{[\alpha]_D^{25}$ −16.0 (*c* = 0.1 MeOH)} was in essence identical in magnitude but of opposite sign to the value reported for microgrewiapine A $\{[\alpha]_D^{25}$ +15.4 (*c* = 0.1 MeOH)}.[3] Based on this alone, it is therefore tempting to assign the absolute (2*R*,3*S*,6*R*)-configuration for microgrewiapine A. It is significant, however, that the outcome of the Mosher's analysis conducted on the natural product concludes the absolute (2*S*,3*R*,6*S*)-configuration. The implication of this is clear: conflicting data are presented in the isolation study of microgrewiapine A, with either the Mosher's analysis[3] or the sign of the specific rotation value $\{[\alpha]_D^{25}$ +15.4 (*c* = 0.1 MeOH)}[3] being erroneous. In the latter case, this may be due to a simple

typographical error (similar to those found within the associated ^{1}H and ^{13}C NMR data for the natural product), and as such it seems unwise to take the sign of the specific rotation value reported for the natural product at face value. To unambiguously assign an absolute configuration to microgrewiapine A it is necessary to re-isolate the natural product.

3.8.4 *Circular Dichroism*

To provide data to further support the absolute configuration of re-isolated natural product, a CD spectra of the synthetic sample was measured.

Circular dichroism has recently shown to be an effective and reliable method for the assignment of absolute configuration.[89–91] Measured as a function of wavelength, the readout is the difference in absorbance of left-handed circularly polarized light and right-handed circularly polarized light. CD has led to a series of structural reassignments.[92–101] However, despite recent advances in direct assignment of absolute configuration using CD approaches, CD has not been widely embraced by the synthetic community.

The whole range of wavelengths available on the spectrometer were scanned to determine the optimal wavelength. Presumably of the triene moiety within the molecule, some absorption in the UV range was observed, corresponding to electronic transitions.

In order to validate the ECD spectra, synthesis of the enantiomer was completed starting from enantiopure (*R*) secondary amine and (−)-CSO. CD spectra of the 2 enantiomers were then measured (Figure 22). Although no Cotton effect[102] was observed at the wavelengths available on the spectrometer, it is hoped that this addition piece of supporting information may help elucidate the true absolute configuration of microgrewiapine A when it is reisolated, and hoped that the natural sample may be measured over a greater range of wavelengths to observe a Cotton effect.

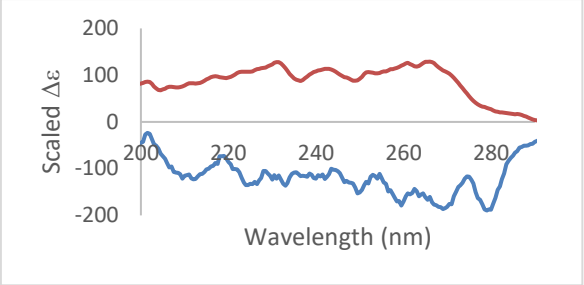
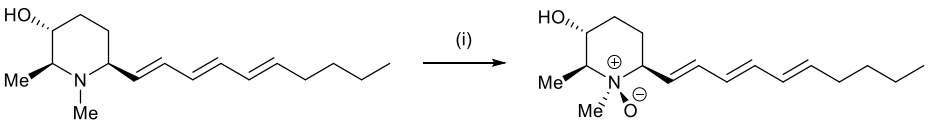


Figure 22: ECD spectra of microgrewiapine A. Red = *S*,*R*,*S* Blue = *R*,*S*,*R*.

It is therefore proposed that it is not currently possible to unambiguously assign the absolute configuration of microgrewiapine A. In order to resolve this issue, it is necessary to verify the sign of the specific rotation of the natural product (as well as re-evaluate its absolute configurational assignment by application of the Mosher's ester analysis), which requires its re-extraction and re-isolation from the natural source.

3.9 Microgrewiapine B Synthesis

With microgrewiapine A in hand, synthesis began on *N*-oxide formation. It was expected that oxidation of *ent*-**73** would result in a mixture of diastereomers. However straightforward oxidation of *ent*-**73** with 1.0 equiv. *m*-CPBA for 30 s gave synthetic microgrewiapine B **74** in 76% isolated yield as a single diastereomer (Scheme 38). No diastereomer formation was observed, suggesting the conformation at Nitrogen was locked with the methyl in a pseudo-equatorial position.



ent-**73**, >95:5 dr **74**, >95:5 dr

Scheme 38: Synthesis of Microgrewiapine B. *Reagents and conditions*: (i) *m*-CPBA, $CHCl_3$, rt, 30 s.

3.10 Microgrewiapine B Data Analysis

3.10.1 *Relative Configuration*

The relative configuration within **74** was first independently verified by analysis of the ^3J coupling constants in the ^{1}H NMR spectrum, assuming that a chair conformation would be adopted in solution. Crucially, a large ^3J coupling constant was noted between C(2)*H* and C(3)*H* ($^3J_{2,3}$ = 9.5 Hz), indicative of an axial-axial relationship between these two protons and hence with an axial placement of both. A significant, reciprocal nOe correlation was also noted between C(2)*H* and C(6)*H*, which thus engendered the axial placement of the latter when considering the axial placement of the former, thus completing the relative 2,3-*trans*-3,6-*trans*-configurational assignment of the three stereogenic centres at carbon. It was also possible to resolve additional ^3J coupling constants that provided further support for the assigned relative configurations ($^3J_{3,4ax}$ = 11.1 Hz, $^3J_{3,4eq}$ = 4.8 Hz, $^3J_{5ax,6}$ = 12.0 Hz, $^3J_{5eq,6}$ = 2.8 Hz) (Figure 23). Meanwhile, the relative configuration of the stereogenic centre at nitrogen within **74** was assigned on the basis of reciprocal nOe interactions between the N*Me* group and both C(2)*H* and C(6)*H*; it followed that

the N*Me* group should be placed *cis* to both C(2)*H* and C(6)*H*, i.e., in an equatorial position (Figure 23).

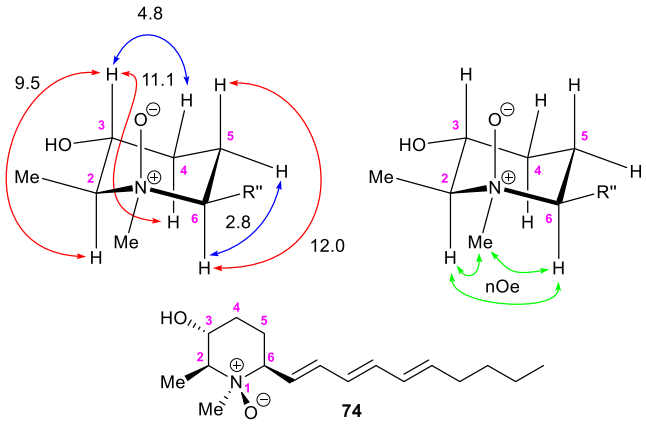


Figure 23: ^{1}H NMR ^{3}J coupling constants (Hz) (red arrows, φ ≈ 180 º; blue arrows, φ ≈ 60 º) and reciprocal nOe enhancements (green arrows) observed for **74**.

3.10.2 *Comparison of Relative Configuration with Natural Product*

Reanalysis of copies of the NMR spectra provided for the natural sample led to two corrections in the ^{1}H NMR spectrum at 5.74 ppm and 5.94 ppm. Several peaks were unresolved in the isolation paper, however the quality of the NMR spectra provided was not sufficient to resolve them by re-analysis. In the event then, very good agreement was noted between the natural product and synthetic sample **74** in both the ^{13}C and ^{1}H NMR spectra.

Prior to comparing these data sets, the reported ^{1}H and ^{13}C NMR spectroscopic data for microgrewiapine A was validated by analysis of the copies of the original ^{1}H and ^{13}C NMR spectra supplied by Kinghorn et al. as supporting information. Some transcription errors were noted in the ^{1}H NMR spectroscopic data, and thus the data for the natural product was corrected. In the event then, excellent agreement was noted between the corrected data set for microgrewiapine B and **74** (Table 24). It is therefore unequivocal that microgrewiapine A and microgrewiapine B both

possess the relative 2,3-*trans*-3,6-*trans*-configuration of the three common stereogenic centres (at carbon) around the piperidine ring.

Microgrewiapine B	74	$\Delta\delta_C$	Microgrewiapine B	74
10.7	10.5	+0.2	0.89 (3H, t, 7.0)	0.89 (3H, t, 7.2)
14.3	14.1	+0.2	1.34 (4H, m)	1.34 (4H, m)
22.6	22.4	+0.2	1.46 (1H, m)	1.46 (1H, m)
26.6	26.4	+0.2	1.57 (3H, d, 6.0)	1.57 (3H, d, 6.2)
31.7	31.5	+0.2	1.62 (1H, m)	1.61 (1H, m)
32.9	32.6	+0.3	2.11 (3H, m)[a]	2.12 (3H, m)
33.0	32.9	+0.1	2.33 (1H, m)	2.39 (1H, qd, 14.1, 3.9)
55.1	55.1	0	2.86 (1H, dq, 10.7, 6.1)	2.81 (1H, qd, 9.5, 6.2)
67.5	67.6	−0.1	2.95 (3H, s)	2.93 (3H, s)
76.5	76.0	+0.5	3.44 (1H, m)	3.40 (1H, ddd, 12.0, 9.0, 2.8)
78.9	78.6	+0.3	3.90 (1H, ddd, 11.2, 10.5, 4.8)	3.97 (1H, ddd, 11.0, 9.5, 4.7)
128.0	128.1	−0.1	5.74 (1H, dt, 14.2, 7.2)*	5.75 (1H, dt, 14.7, 7.1)
129.3	129.2	+0.1	5.94 (1H, dd, 15.3, 8.9)*	6.01 (1H, dd, 15.6, 9.0)
130.3	130.1	+0.2	6.16 (4H, m)	6.15 (4H, m)
135.4	135.0	+0.4		
136.2	135.6	+0.6		
137.7	137.2	+0.5		

Table 24: ^{1}H and ^{13}C NMR data of microgrewiapine B (Ref [38]) and synthetic sample **74**. Reference frequencies employed for the natural product are unknown. Reference frequencies employed for **74** are: $CHCl_3$, δ_H = 7.26; $CDCl_3$, δ_C = 77.16 (Refs [85] and [84]). Midpoints of all multiplets are quoted. [$\Delta\delta_C$ = δ_C (natural) − δ_C (synthetic)]. [a]The ^{1}H NMR data for the natural product includes resonances at 2.09 (2H, dt) and 2.13 (1H, m); the mid-point of these has been quoted here for purposes of comparison. *These ^{1}H NMR data of microgrewiapine B are corrected here (compared to those reported in Ref 3) following re-analysis of the copies of the NMR spectra of the natural product.

3.10.3 *Absolute Configuration*

With the question of the relative configuration within microgrewiapine B unambiguously resolved, the question turned to its absolute configurational assignments. From the known absolute configuration of α-hydroxy-β-amino ester **68**, and the fact that the relative configurations within **74** had all been unambiguously assigned, it followed that the absolute (2*S*,3*S*,6*S*)-configurations could be assigned to the three common stereogenic centres of the piperidine rings within **74**; by extension, from the assigned relative configuration, the absolute (1*R*)-configuration can be assigned to the stereogenic centre at the nitrogen atom within **74**.

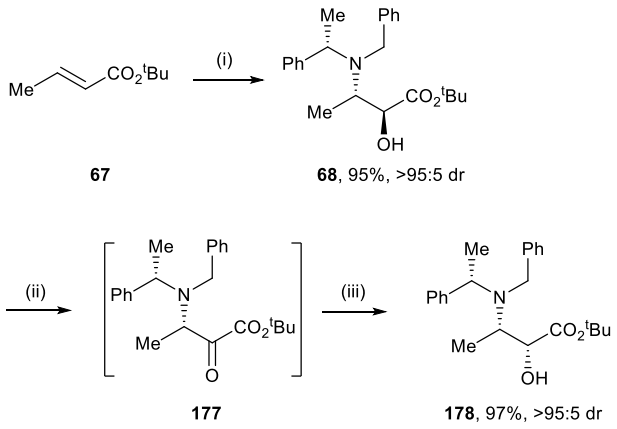
The specific rotation value for **74** was acquired under analogous conditions (temperature and concentration, as well as solvent) to that of the derived from nature, in order that a valid

comparison could be made. It was found that the sign and magnitude of the specific rotation values observed was in good agreement with the value reported for the corresponding sample: microgrewiapine B was reported to have {$[\alpha]_D^{25}$ +4.0 (*c* = 0.1 MeOH)}[3] and {$[\alpha]_D^{25}$ +3.9 (*c* = 0.1 MeOH)} was obtained for (1*R*,2*S*,3*R*,6*S*)-**74**. This is therefore consistent with microgrewiapine B possessing the absolute (1*R*,2*S*,3*R*,6*S*)-configuration, and thus being a member of the same enantiomeric series, i.e., same absolute (2*S*,3*R*,6*S*)-configurations of the three common stereogenic centres (at carbon) as microcosamine A. Microgrewiapine B has not previously been prepared, and therefore the data contained herein constitute the first synthesis and absolute configuration assignment for this alkaloid.

3.11 Microgrewiapine C Synthesis

The remaining family member to be synthesised was the C(3) epimer of microgrewiapine B, microgrewiapine C. In order to access the C(3) epimer, a diastereoselective oxidation/reduction procedure was performed on **68**. The synthetic aim was to isolate and fully characterise the plausible epimeric *N*H and *N*Me piperidine natural products.

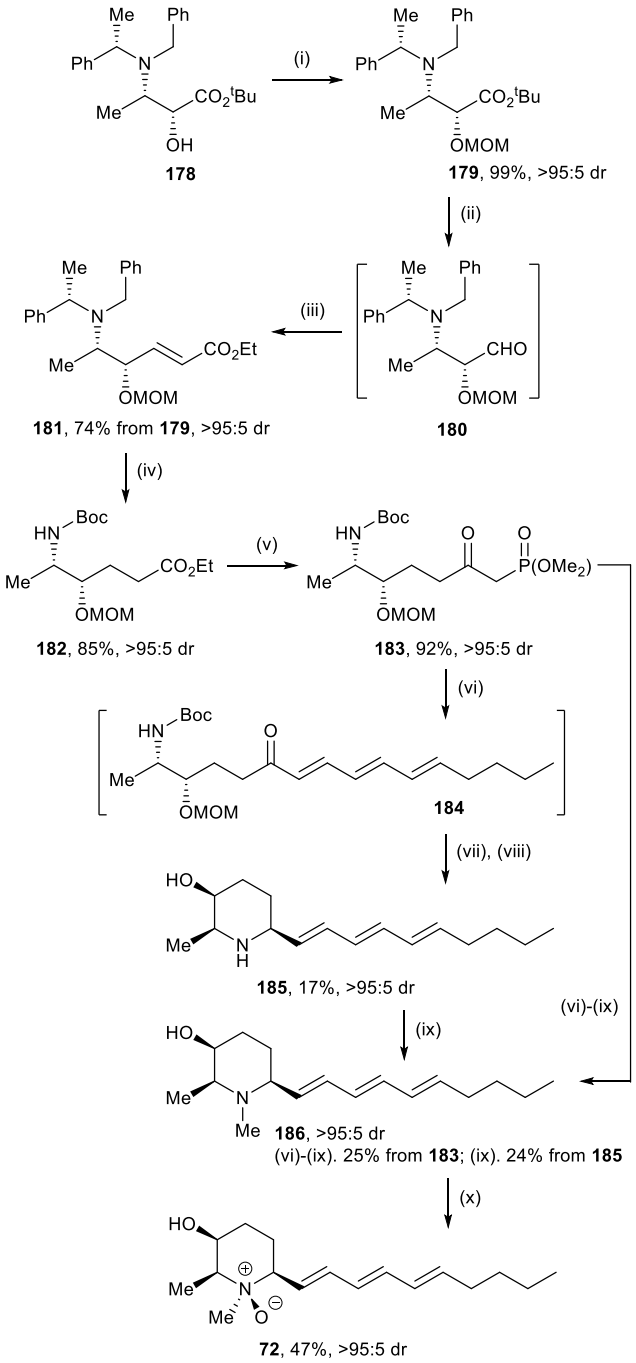
Oxidation of **68** under Swern conditions gave complete conversion to ketone **177**, with subsequent reduction upon addition of $NaBH_4$ in MeOH at −20 °C proceeding to give the corresponding *syn*-α-hydroxy-β-amino ester **178** in 97% yield from **68**, and in >95:5 dr[48,50] (Scheme 39).



Scheme 39: Epimerisation of **68**. *Reagents and conditions:* (i) Lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide, THF, −78 °C, 2 h, then (+)-CSO, −78 °C to rt, 12 h; (ii) DMSO, $(ClCO)_2$, Et_3N, CH_2Cl_2, −78 °C to rt, 1 h; (iii) $NaBH_4$, MeOH, −20 °C, 2 h.

Following the epimerisation, a sequence of transformations analogous to that of the epimeric series was applied. The known *anti*-α-hydroxy-β-amino ester **178**[48,50] was treated with NaH then MOMCl to give the α-methoxymethyloxy-β-amino ester **179** in 99% yield. Treatment of **179** with DIBAL-H gave the intermediate aldehyde **180**, and addition of $Ph_3P{=}CHCO_2Et$ provided **181** in 74% isolated yield from **179** as a single diastereoisomer. Treatment of **181** with $Pd(OH)_2/C$ in the presence of H_2 and Boc_2O in EtOAc gave **182** in 85% yield, and addition of the lithium anion of $MeP(O)(OMe)_2$ to **182** gave β-keto phosphonate **183** in 92% yield. Olefination of *(E,E)*-2,4-nonadienal using β-keto phosphonate **183** gave the conjugated triene **184**, which upon sequential

treatment with TFA and $NaBH_3CN$ gave piperidine **185** in 17% yield from **183** after chromatography. Subsequent reductive *N*-methylation omitting purification of **185** resulted in formation of **186** in 25% yield from **183** after chromatography. Finally, treatment of **186** with *m*-CPBA for 30 s gave synthetic microgrewiapine C **72** in 47% isolated yield (Scheme 40).



Scheme 40: Synthesis of microgrewiapine C. *Reagents and Conditions*: (i) NaH, MOMCl, THF, 0 °C to rt, 12 h; (ii) DIBAL-H, CH_2Cl_2, −78 °C, 30 min; (iii) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, rt, 60 h; (iv) H_2, $Pd(OH)_2/C$, Boc_2O, EtOAc, rt, 16 h; (v) ^{n}BuLi, $MeP(O)(OMe)_2$, THF, −78 °C to 0 °C, 90 min; (vi) NaH, (*E*,*E*)-2,4-nonadienal, THF, 0 °C, 1 h, then 72 °C,

12 h; (vii) TFA, CH_2Cl_2, 0 °C, 10 min; (viii) $NaBH_3CN$, conc. aq. HCl, CH_2Cl_2, EtOH, 0 °C, 30 min; (ix) formalin, $NaBH_3CN$, MeCN, rt, 16 h; (x) *m*-CPBA, $CHCl_3$, 30 s.

3.12 Microgrewiapine C Data Analysis

3.12.1 *Relative Configuration*

The relative configurations within **185**, **186**, and **72** were investigated and verified by analysis of the ^3J coupling constants in the ^{1}H NMR spectrum, assuming that a chair conformation would be adopted in solution. The large value of the coupling constant between C(6)*H* and one of the diastereotopic C(5) methylene protons ($^3J_{5,6}$ = 11.6 Hz) within **185**, **186**, and **72** was consistent with an axial placement of C(6)*H*. In contrast to the epimeric series, the much smaller values of the coupling constant between C(3)*H* and both of the diastereotopic C(4) methylene protons ($^3J_{3,4}$ < 5 Hz) within **185**, **186**, and **72** indicated an equatorial placement of C(3)*H*. It followed that the small value of the coupling constant between C(2)*H* and C(3)*H* ($^3J_{2,3}$ < 5 Hz) was not diagnostic, as it would be consistent with either an axial or equatorial placement of C(2)*H*. However, a reciprocal nOe enhancement was observed between the C(2)-proton and the C(6)-proton, which enabled axial placements of the C(2) protons to be inferred. It is also of note that a reciprocal nOe enhancement was observed between C(2)*H* and C(3)*H* within **185**, **186**, and **72**; such an enhancement was absent for **70**, *epi*-**73** and **74**. Thus, the relative 2,3-*cis*-3,6-*cis*-configurational assignment of the three stereogenic centres of **185**, **186**, and **72** was complete (Figure 24). The stereochemical assignment of **185**, **186**, and **72** is consistent with the relative configurations of the C(2) and C(3) stereogenic centres imported from the α-hydroxy-β-amino ester starting material **178**[48,50] and in accord with the expectation that the intramolecular reductive aminations would again proceed with formation of the corresponding 2,6-*cis*-configuration.

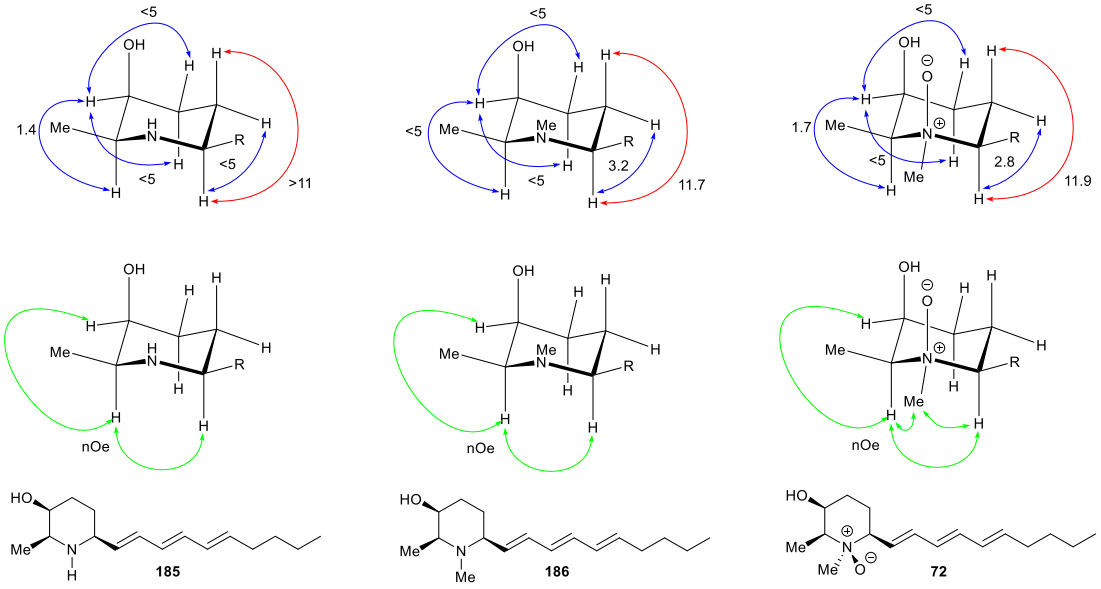


Figure 24: ^{1}H NMR ^{3}J coupling constants (Hz) (red arrows, φ ≈ 180 °; blue arrows, φ ≈ 60 °) and reciprocal nOe enhancements (green arrows) observed for **185**, **186**, and **72**.

3.12.2 *Comparison of Relative Configuration with Natural Product*

With the relative configuration within all of **185**, **186**, and **72** established by analysis and interpretation of their spectroscopic data, comparison with the reported spectroscopic data for **72** isolated from nature was undertaken. Prior to comparing this data set, the reported ^{1}H and ^{13}C NMR spectroscopic data for microgrewiapine C was validated by analysis of the copies of the original ^{1}H and ^{13}C NMR spectra supplied by Kinghorn et al. as supporting information.[38] Unfortunately, some transcription errors were noted, and thus the data for the natural product was corrected. In the event then, excellent agreement was noted between the corrected data set for the natural microgrewiapine C and **72** (Table 25). It is therefore unequivocal that microgrewiapine C possesses the relative 2,3-*cis*-3,6-*cis*-configuration of the three common stereogenic centres (at carbon) around the piperidine ring. The relative configuration at the nitrogen atom within microgrewiapine C has also been confirmed by this analysis.

Microgrewiapine C	72	$\Delta\delta_C$	Microgrewiapine C	72
13.7*	13.4	+0.3	0.89 (3H, t, 7.1)	0.89 (3H, t, 7.2)
14.3*	14.1	+0.2	1.32 (4H, m)	1.32 (4H, m)
22.6*	22.4	+0.2	1.56 (1H, m)	1.56 (1H, m)
24.0*	23.8	+0.2	1.57 (1H, m)	1.60 (1H, m)
31.7*	31.5	+0.2	1.66 (3H, d, 6.5)	1.67 (3H, d, 6.5)
32.1	32.0	+0.1	2.01 (1H, m)	2.03 (1H, ddd, 13.7, 6.5, 3.4)
32.9*	32.6	+0.3	2.09 (2H, dt, 7.0, 6.2)	2.11 (2H, app q, 6.8)
54.1	54.0	+0.1	2.67 (1H, m)*	2.70 (1H, m)
68.7*	68.4	+0.3	2.86 (3H, s)	2.85 (3H, s)
71.1	71.0	+0.1	3.05 (1H, dq, 12.7, 6.5)	3.00 (1H, dq, 6.5, 1.7)
79.5	79.3	+0.2	3.53 (1H, ddd, 11.4, 9.4, 1.9)	3.46 (1H, ddd, 11.9, 9.0, 2.8)
127.9	127.9	0	3.82 (1H, m)*	3.83 (1H, m)
129.2*	129.0	+0.2	5.72 (1H, dd, 15.2, 9.0)	5.76 (1H, dt, 14.7, 7.1)
130.3*	130.0	+0.3	5.98 (1H, dt, 15.1, 7.0)	6.03 (1H, dd,15.6, 9.0)
135.5*	135.1	+0.4	6.11 (4H, m)	6.11 (4H, m)
136.1*	135.6	+0.5		
137.7*	137.4	+0.3		

Table 25: ^{1}H and ^{13}C NMR data of microgrewiapine C (Ref [38]) and synthetic sample **72**. Reference frequencies employed for the natural product are unknown. Reference frequencies employed for **72** are: $CHCl_3$, δ_H = 7.26; $CDCl_3$, δ_C = 77.16 (Refs [85] and [84]). Midpoints of all multiplets are quoted. [$\Delta\delta_C$ = δ_C (natural) − δ_C (synthetic)]. *These $^{1}H/^{13}C$ NMR data of microgrewiapine C are corrected here (compared to those reported in Ref [38]) following re-analysis of the copies of the NMR spectra of the natural product.

3.12.3 *Absolute Configuration*

With the question of the relative configuration within microgrewiapine C unambiguously resolved, the question turned to its absolute configurational assignments. From the known absolute configuration of α-hydroxy-β-amino ester **68**, and the fact that the relative configurations within **185**, **186**, and **72** had all been unambiguously assigned, it followed that the absolute (2*S*,3*S*,6*S*)-configurations could be assigned to the three common stereogenic centres of the piperidine rings within **185**, **186**, and **72**; by extension, from the assigned relative configuration, the absolute (1*R*)-configuration can be assigned to the stereogenic centre at the nitrogen atom within **72**.

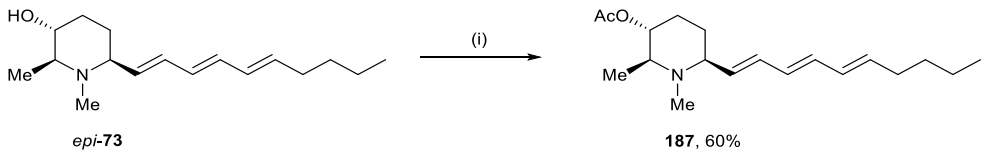
The specific rotation value for **72** was acquired under analogous conditions (temperature and concentration, as well as solvent) to that of the derived from nature, in order that a valid comparison could be made. It was found that the sign and magnitude of the specific rotation values observed was in good agreement with the value reported for the corresponding sample:

microgrewiapine C was reported to have $\{[\alpha]_D^{25}$ +77.8 (c = 0.1 MeOH)$\}$[3] and $\{[\alpha]_D^{25}$ +77.1 (c = 0.1 MeOH)$\}$ was obtained for (1*R*,2*S*,3*S*,6*S*)-**72**. This is therefore consistent with microgrewiapine C possessing the absolute (1*R*,2*S*,3*S*,6*S*)-configuration, and thus being a C(3) epimeric member of the same enantiomeric series, i.e., same absolute (1*R*,2*S*,6*S*)-configurations of the three common stereogenic centres as microgrewiapine B. Microgrewiapine C has not previously been prepared, and therefore the data contained herein constitute the first synthesis and absolute configuration assignment for this alkaloid.

3.13 Microgrewiapine A Acetate

Given the confusion surrounding the absolute configuration of microgrewiapine A, and the disagreement of data reported for the natural product, it seemed prudent to explore the relative and absolute configuration of the semi-synthetic microgrewiapine A acetate.

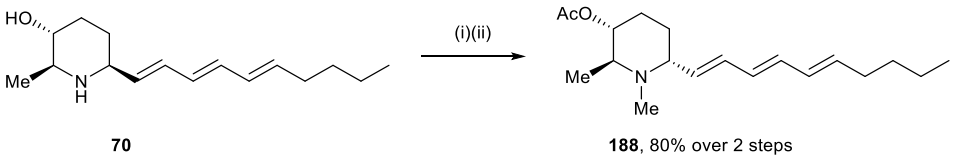
Using 5 mg of natural microgrewiapine A, Still et al.[38] synthesised the partially synthetic acetate for testing for nAChR inhibition (Scheme 41). Although the authors do provide an experimental procedure, only partial characterisation data for the acetate is provided, with no structural validation given.



epi-**73** **187**, 60%

Scheme 41: Synthesis of microgrewiapine A acetate by Still et al.[38]. *Reagents and Conditions*: Ac_2O, Et_3N, cat. DMAP, CH_2Cl_2, rt, 3 h.

Returning to the first synthesis of Microgrewiapine A, by Macha and Ha[45] it was reported by the authors that reductive *N*-methylation of microcosamine A, followed by acetylation with Ac_2O and Et_3N furnished 6-*epi*-microgrewiapine A 3-acetate **188** as a single isomer (Scheme 42). The authors provide no evidence for this apparent epimerisation.

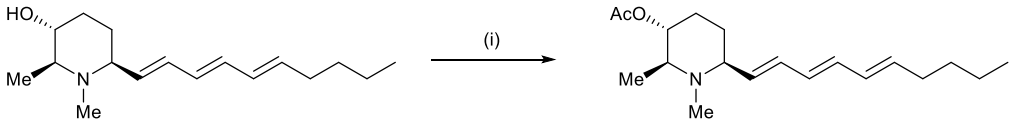


70 **188**, 80% over 2 steps

Scheme 42: Apparent C(6) epimerisation observed by Macha and Ha[45]. *Reagents and Conditions*: (i) 37% HCHO. AcOH, $NaCNBH_3$, rt, 1 h; (ii) Ac_2O, Et_3N, CH_2Cl_2.

3.14 Microgrewiapine A Acetate Synthesis

Largely following the experimental procedure outlined by Still et al[38], microgrewiapine A was transformed to the *O*-Acetate. However the purification method described "*The crude product was chromatographed over silica gel (CHCl₃/MeOH/AcOH, 10:1:0.1)*" was altered to using $CHCl_3$/(Ammonia, ca. 7 N solution in MeOH) 10:0.05 as the eluent in order to exclude the possibility of forming a partial acetic acid salt. This resulted in isolation of **187** in 57%.



epi-**73** **187**, 57%, >95:5 dr

Scheme 43: Synthesis of Microgrewiapine A Acetate. *Reagents and Conditions*: Ac_2O, Et_3N, cat. DMAP, CH_2Cl_2, 0 °C.

3.15 Microgrewiapine A Acetate Data analysis

3.15.1 *Relative Configuration*

The relative configuration of **187** was corroborated by analysis of the ^{3}J coupling constants in the ^{1}H NMR spectrum, assuming that a chair conformation would be adopted in solution. Crucially a large ^{3}J coupling constant was noted between C(2)*H* and C(3)*H* within **187** ($^{3}J_{2,3}$ = 9.5 Hz), indicative of an axial-axial relationship between these two protons and hence with an axial placement of both. A significant, reciprocal nOe correlation was also noted between C(2)*H* and C(6)*H*, which thus engendered the axial placement of the latter when considering the axial placement of the former, thus completing the relative 2,3-*trans*-3,6-*trans*-configurational assignment of the three stereogenic centres at carbon for **187**. It was possible to resolve additional ^{3}J coupling constants that provided further support for the assigned relative configurations ($^{3}J_{3,4ax}$ = 11.1 Hz, $^{3}J_{3,4eq}$ = 4.6 Hz, $^{3}J_{5ax,6}$ = 11.4 Hz, $^{3}J_{5eq,6}$ = 3.0 Hz) (Figure 25). The implication of this stereochemical assignment for the reaction is that no epimerisation at C(6) was observed.

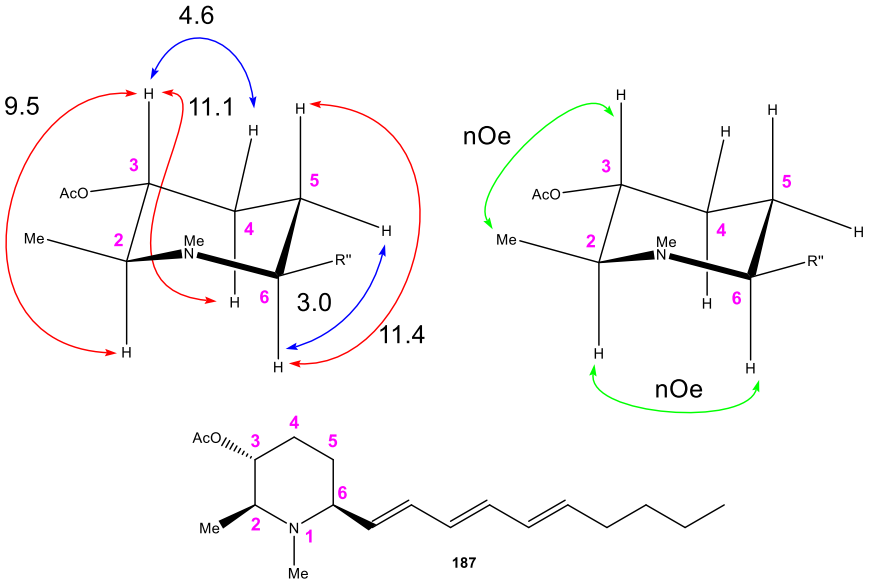


Figure 25:^{1}H NMR ^{3}J coupling constants (Hz) (red arrows, φ ≈ 180 °; blue arrows, φ ≈ 60 °) and reciprocal nOe enhancements (green arrows) observed for **187**.

3.15.2 *Comparison of Relative Configuration with Partially Synthetic Product*

With the relative configuration within microgrewiapine A acetate **187** established by analysis and interpretation of their spectroscopic data, comparison with the reported spectroscopic data for the sample of the alkaloid isolated from nature in the isolation study of Kinghorn et al.[38] was undertaken. It was not possible to validate the reported ^{1}H and ^{13}C NMR spectroscopic data for microgrewiapine A Acetate because the original ^{1}H and ^{13}C NMR spectra was not supplied by Kinghorn et al. either as supporting information or in the original PhD thesis. Unfortunately, many data points were missing. Despite these shortcomings, reasonable agreement ($\Delta\delta_C$) was noted between the available data set for microgrewiapine A acetate and **187** (Table 26).

Microgrewiapine A Acetate	187	$\Delta\delta_C$
14.7	14.1	0.6
*	16.5	N/A
21.8	21.4	0.4
22.4	22.3	0.1
*	29.9	N/A
*	30.9	N/A
31.4	31.6	-0.2
32.3	32.6	-0.3
*	40.3	N/A
*	62.9	N/A
67.2	67.4	-0.2
75.1	74.8	0.3
*	130.0	N/A
*	130.3	N/A
*	131.7	N/A
*	132.8	N/A
*	135.8	N/A
136.7	136.4	0.3
170.7	170.4	0.3

Microgrewiapine A Acetate	187
0.87 (3H, t, 7.0)	0.89 (3H, t, 7.2)
1.11 (3H, d, 5.8)	1.11 (3H, d, 6.2)
1.33 (6H, m)[a]	1.33 (6H, m)
1.55 (1H, ddd, 13.2, 3.3, 2.0)	1.53 (1H, tdd, 13.6, 11.4, 3.7)
1.69 (1H, m)	1.64 (1H, ddd, 13.6, 7.4, 3.0)
2.05 (3H, s)	2.05 (3H, s)
*	2.06 (1H, m)
2.12 (1H, m)	2.10 (2H, m)
2.21 (3H, s)	2.21 (3H, s)
2.54 (1H, ddd, 11.2, 8.6, 3.4)	2.50 (1H, ddd, 11.4, 8.7, 3.0)
4.48 (1H, ddd, 10.6, 7.3, 2.6)	4.49 (1H, ddd, 11.1, 9.5, 4.6)
5.55 (1H, dt, 14.4, 8.8)[b]	5.52 (1H, dd, 14.6, 8.7)
5.72 (1H, dd, 7.1, 7.0)[b]	5.70 (1H, dt, 14.5, 7.1)
6.11 (4H, m)	6.10 (4H, m)

Table 26: ^{1}H and ^{13}C NMR data of microgrewiapine A acetate (Ref [38]) and synthetic sample **187**. Reference frequencies employed for the natural product are unknown. Reference frequencies employed for **187** are: $CHCl_3$, δ_H = 7.26; $CDCl_3$, δ_C = 77.16 (Refs [85] and [84]). Midpoints of all multiplets are quoted. [$\Delta\delta_C = \delta_C$ (natural) − δ_C (synthetic)]. [a]The ^{1}H NMR data for the natural product includes resonances at 1.30 (1H, m), 1.31–1.42 (1H, m), 1.31–1.42 (2H, m), and 1.35 (1H, m); the mid-point of these has been quoted here for purposes of comparison. [b]The ^{1}H NMR multiplicity and scalar coupling for the natural product is presumed to be incorrect by comparison to microcosamine A and microgrewiapine A. *These data points are missing from the NMR spectra reported.

3.15.3 *Comparison of Absolute Configuration with Partially Synthetic Product*

Having likely synthesised the same compound, it was now meaningful to compare the specific rotation values of the two compounds.

The optical rotation for the synthetic sample from isolated microgrewiapine A $\{[\alpha]_D^{25}$ +19.5 (c = 1.0 MeOH)$\}$, and that the synthetic sample **187** prepared herein $\{[\alpha]_D^{25}$ −23.2 (c = 1.0 MeOH)$\}$again imply opposite absolute configuration, but there is still the need to reisolate the natural product to exclude the possibility of cut and paste sign error in isolation paper.

3.15.4 *Comparison of Relative Configuration with Synthetic Epimeric compound*

Comparison with the data for the reported C(6) epimeric compound **188** reported by Macha and Ha[45] was undertaken. Prior to comparing these data sets, the reported ^{1}H and ^{13}C NMR spectroscopic data for microgrewiapine A Acetate were validated by analysis of the copies of the original ^{1}H and ^{13}C NMR spectra supplied by Macha and Ha as supporting information. It was noted that there were 2 peaks missing in the reported data, and also that 2 peaks were reported as multiplets when clear multiplicity was visible. In the event then, excellent agreement was noted between the data set for microgrewiapine A Acetate **187** and **188** (Table 27). It is therefore clear that Macha and Ha had misreported the epimerisation of **188**, and that **188** has the relative 2,3-*cis*-3,6-*cis*-configuration of the three stereogenic centres (at carbon) around the piperidine ring.

Macha and Ha 188	187	$\Delta\delta_C$	Macha and Ha 188	187
13.9	14.1	-0.2	0.89 (3H, t, 7.1)	0.89 (3H, t, 7.2)
16.3	16.5	-0.2	1.12 (3H, d, 6.1)	1.11 (3H, d, 6.2)
21.2	21.4	-0.2	1.32 (6H, m)	1.33 (6H, m)
22.1	22.3	-0.2	1.60 (3H, m)*	1.53 (1H, tdd, 13.6, 11.4, 3.7)
29.7	29.9	-0.2		1.64 (1H, ddd, 13.6, 7.4, 3.0)
30.7	30.9	-0.2	2.05 (3H, s)	2.05 (3H, s)
31.4	31.6	-0.2		2.06 (1H, m)
32.4	32.6	-0.2	2.10 (1H, m)	2.10 (2H, m)
40.1	40.3	-0.2	2.22 (3H, s)	2.21 (3H, s)
62.7	62.9	-0.2	2.50 (1H, m)*	2.50 (1H, ddd, 11.4, 8.7, 3.0)
67.2	67.4	-0.2	4.49 (1H, dt, 10.9, 4.6)	4.49 (1H, ddd, 11.1, 9.5, 4.6)
74.6	74.8	-0.2	5.52 (1H, dd, 14.4, 8.7)	5.52 (1H, dd, 14.6, 8.7)
129.8	130.0	-0.2	5.70 (1H, dt, 14.4, 7.0)	5.70 (1H, dt, 14.5, 7.1)
130.1	130.3	-0.2	6.13 (4H, m)	6.10 (4H, m)
131.4	131.7	-0.3		
132.6	132.8	-0.2		
135.6	135.8	-0.2		
136.3	136.4	-0.1		
170.2	170.4	-0.2		

Table 27: ^{1}H and ^{13}C NMR data of **188** (Ref [45]) and synthetic sample **187**. Reference frequencies employed for **188** are: $CHCl_3$, δ_H = 7.26; $CDCl_3$, δ_C = 77.00. Reference frequencies employed for **187** are: $CHCl_3$, δ_H = 7.26; $CDCl_3$, δ_C = 77.16 (Refs [85] and [84]). Midpoints of all multiplets are quoted. [$\Delta\delta_C$ = δ_C (Ref [45]) − δ_C (synthetic)].

3.15.5 *Comparison of Absolute Configuration with Synthetic Epimeric compound*

The optical rotation for their synthetic sample **188** from **70** was {$[\alpha]_D^{20}$ −76.8 (*c* = 1.0 $CHCl_3$)},[45] and that of synthetic sample **187** {$[\alpha]_D^{20}$ −64.8 (*c* = 1.0 $CHCl_3$)}. The matches suggest an error in the synthetic paper, and unfortunately adds more confusion to the data surrounding the absolute configuration of these alkaloids.

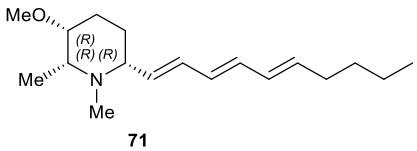
3.16 Conclusion

Independent syntheses of microgrewiapines A-C have been completed, and also that of microgrewiapine A acetate. Interrogation of the synthetic sample of the alkaloids (are derivative) using ^{1}H NMR ^3J coupling constant analysis and NOESY analyses independently established the relative configuration, which was entirely consistent with the expected diastereoselectivity of the synthetic process. Comparison of specific rotation data for microgrewiapine B and C is consistent with both of the alkaloids possessing the absolute (1*R*,2*S*,3*R*,6*S*)- and (1*R*,2*S*,3*S*,6*S*)-configurations previously assigned to them. This represents the first time that these alkaloids has succumbed to total synthesis. Thus, it is established that microcosamine A and microgrewiapine B and C are members of the same enantiomeric series. For microgrewiapine A, however, it becomes evident that the data reported in the isolation study is in conflict regarding its absolute configuration assignment: a Mosher's analysis concludes a (2*S*,3*R*,6*S*)-configuration, but comparison of the specific rotation value with the synthetic sample suggests a (2*R*,3*S*,6*R*)-configuration. Owing to these conflicting data, it is promulgated that it is imprudent to suggest the absolute configuration of this natural product at this time, with re-isolation of microgrewiapine A from the natural source being required to effect unambiguous resolution of this problem.

Chapter 4 Microconine Synthesis, Stereochemistry, and Spectroscopic Data

4.1 Chapter Outline

Previously reported spectroscopic data for the piperidine alkaloid microconine (Figure 26) are in discord with its configurational assignment. This chapter includes the re-analysis of the original ^{1}H NMR spectrum obtained for the natural product alongside an independent asymmetric synthesis of two epimeric forms, which confirm the relative configuration of the natural product beyond doubt. The specific rotation value (including its sign) of the sample is found to be highly sensitive to the temperature and concentration of the sample, and on balance of evidence the absolute configuration of the alkaloid is also assigned. This work embellishes upon the optimised synthetic route to microcosamine A and microgrewiapines A-C (Chapter 2 and 3).



71

Figure 26: Structure of microconine **71**.

4.2 Isolation of Microconine

The isolation of *N*-methyl-2-methyl-3-methoxy-6-(deca-l',3',5'-trienyl)piperidine from the stem bark of *Microcos paniculata* was reported by Kumar and co-workers in 2000.[103] The same alkaloid *may* have been isolated in two further studies, and thus (in one case) may also have been named micropiperidine A, however the scarcity of, and inconsistencies within, the provided characterisation data add additional complications to the situation. As such, this data is not explored in any further detail. Although the alkaloid was not given a trivial name in the isolation study it has been sporadically dubbed microconine in the secondary literature, and this name is

promulgated herein. Spectroscopic (IR, NMR) and mass spectrometric evidence allowed the gross structure of microconine to be assigned; the identity of the side chain [including the (*E*)-configurations of the olefins] was established by comparison to the corresponding signals in the ^{1}H and ^{13}C NMR spectra for another related alkaloid, micropine. The relative 2,3-*cis*-3,6-*cis*-configuration was assigned from various nOe correlations present in the NOESY spectrum of the alkaloid: it was reported that C(2)*H,* C(3)*H*, and C(6)*H* were all correlated in the NOESY spectrum and it was therefore proposed that they were all *cis* to one another (Figure 27). However, the accompanying ^{1}H NMR characterisation data provided by Kumar and co-workers for microconine includes the descriptors 2eq-CH_3, H-2ax, H-3ax and H-6ax,[103] implying that C(2)*Me* occupies an equatorial site whilst C(2)*H,* C(3)*H* and C(6)*H* all occupy axial sites. This is in direct contradiction of the 2,3-*cis*-3,6-*cis*-configuration was assigned from various nOe correlations. The all axial placement of the C(2)*H,* C(3)*H* and C(6)*H* protons appears to be supported from the accompanying scalar coupling constants; $^{3}J_{2,3}$ = 9.1 Hz, $^{3}J_{3,4}$ = 10.7 Hz, $^{3}J_{3,4'}$ = 4.8 Hz, $^{3}J_{5,6}$ = 11.4 Hz, and $^{3}J_{5,6'}$ = 3.2 Hz. In each case, the large (>9 Hz) coupling constants between the various protons suggests the dihedral angles may be close to 180° and therefore indicate axial-axial relationships and, hence, the relative 2,3-*cis*-3,6-*cis*-configuration (Figure 27).

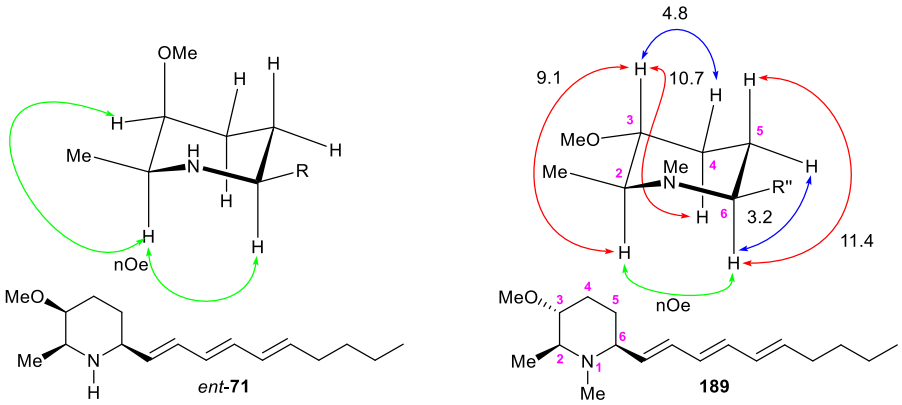
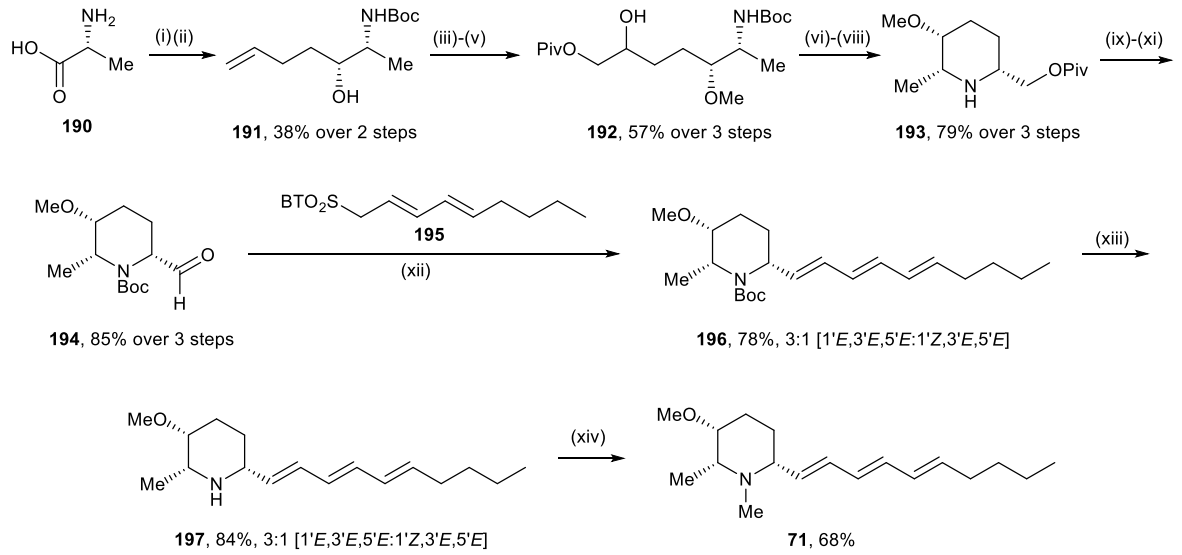


Figure 27: Seemingly conflicting ^{1}H NMR ^{3}J coupling constants (Hz) (red arrows, φ ≈ 180 °; blue arrows, φ ≈ 60 °) and reciprocal nOe enhancements (green arrows) observed by Bandara et al.[103] for micropine.

No attempt was made to assign an absolute configuration to microconine, although a non-zero specific rotation value was recorded {$[\alpha]_D^{25}$+29.2 (*c* = unknown, $CHCl_3$)}.[103]

4.3 Synthesis of Microconine

In 2006 Nakatani et al. set out to synthesise microconine.[104] The reasoning for the undertaking was that "*the relative configuration of (microconine) has been elucidated by NMR spectroscopic analysis, its absolute configuration remained unclear*". The synthetic sequence began from L-alanine, which was converted to alcohol **191** over 2 steps in 38% yield. *O*-methylation of **191**, followed by dihydroxylation of the terminal olefin, and then selective pivaloyl protection of the resulting primary alcohol gave **192** in 57% over the three steps. Oxidation of the secondary alcohol to ketone then reductive cyclisation gave piperidine **193** (79% over 3 steps). *N*-Boc protection, then conversion to aldehyde **194** set the stage for a modified Julia olefination to install the unsaturated side chain. The authors noted that use of *N*-Me rendered the compound particularly unstable during purification. Following some optimisation, the olefination occurred in 78% yield (3:1 (*E*:*Z*)). The synthesis was completed by Boc removal, then *N*-methylation and separation of the unwanted *Z* olefin. This gave **71** in 14 steps from L-alanine in 6% overall yield (Scheme 44).



Scheme 44: Synthesis of **71** by Nakatani et al.[104] *Reagents and Conditions*: (i) $LiAlH_4$, THF then Boc_2O, rt, 12 h; (ii) Swern oxidation, then $H_2C{=}CH(CH_2)_2MgBr$, rt, 12 h; (iii) NaH, MeI, THF, rt, 12 h; (iv) OsO_4, NMO, THF-acetone, rt, 2 h; (v) Piv-Cl, Py, 0 °C, 21 h; (vi) PDC, 4Å MS, CH_2Cl_2, rt, 12 h; (vii) TFA, CH_2Cl_2, then $NaHCO_3$, rt, 1 h; (viii) Pd/C, H_2, MeOH, rt, 12 h; (ix) Boc_2O, Hünig's base, CH_2Cl_2, 50 °C, 36 h; (x) DIBAL-H, CH_2Cl_2, −78 °C, 2 h; (xi) Swern oxidation; (xii) KHMDS, 18-crown-6, −78 °C, 2 h; (xiii) TMSOTf, 2,6-lutidine, CH_2Cl_2, rt, 2 h; (xiv) $NaBH_3CN$, HCHO, CH_3CN, rt, 2.5 h.

It was stated that the NMR data for the synthetic sample were *"identical"* to those reported for the natural product but in fact comparison of the ^{1}H NMR data for the synthetic material (no accompanying ^{13}C NMR data were reported) with the corresponding data reported for the natural product reveals discrepancies: even though the peak positions are in good accord (typically within 0.05 ppm) the peak multiplicities and associated ^{3}J coupling constants differ significantly, particularly those associated with the key protons attached to the stereogenic centres of the piperidine ring (Table 28).

Natural Microconine by Kumar	Synthetic Sample by Kitahara
0.88 (3H, t, 7.0)	0.88 (3H, t, 7.5)
1.21 (3H, d, 7.1)	1.19 (3H, d, 6.5)
1.35 (6H, m)	1.33 (6H, m)
1.81 (1H, ddd, 9.7, 3.2, 3.2)	1.77 (1H, ddt, 11.5, 4.5, 15.0)
2.05 (1H, m)	-
2.09 (2H, dt, 7.1, 7.0)	2.08 (4H, m)
2.10 (1H, dq, 9.1, 7.1)	-
2.15 (3H, s)	2.14 (3H, s)
2.47 (1H, ddd, 11.4, 8.4, 3.2)	2.44 (1H, dt, 11.0, 2.5)
3.14 (1H, ddd, 10.7, 9.1, 4.8)	3.13 (1H, br s)
3.33 (3H, s)	3.32 (3H, s)
5.70 (1H, dt, 15.5, 7.2)	5.67 (2H, m)
5.75 (1H, dd, 15.8, 8.4)	
6.13 (4H, m)	6.10 (4H, m)

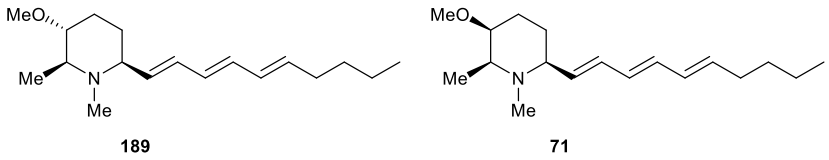
Table 28: ^{1}H NMR data reported for natural microconine (Kumar, Ref [103]) and the synthetic sample of **71** (Kitahara, Ref [104]). Midpoints of all multiplets are quoted. Assignments are stated as in Ref [103].

The specific rotation of the synthetic compound **71** $\{[\alpha]_D^{15}$ +37.5 (c = 1.0 $CHCl_3$)$\}$ broadly matched with that reported for the natural product $\{[\alpha]_D^{15}$ +29.2 (c unknown $CHCl_3$)$\}$. However, the two measurements are taken at quite different temperatures.

4.4 Chapter Aim

It is clear there is a need to investigate the discrepancies in these data sets by independent synthesis and analysis. The aim of this chapter is to utilise the optimised synthetic route to microgrewiapines B and C in order to synthesise the 2,3-*trans*-3,6-*trans*-(2*S*,3*R*,6*S*)- and 2,3-*cis*-3,6-*cis*-(2*S*,3*S*,6*S*)-

stereoisomers **189** and *ent*-**71** [epimeric at C(3)] of *N*-methyl-2-methyl-3-methoxy-6-(deca-l',3',5'-trienyl)piperidine. It is hoped that this will unambiguously establish the congruency of the ^{1}H and ^{13}C NMR data of one of the stereoisomers with the natural product and, by comparison of specific rotation data, the absolute configuration for microconine can be inferred.

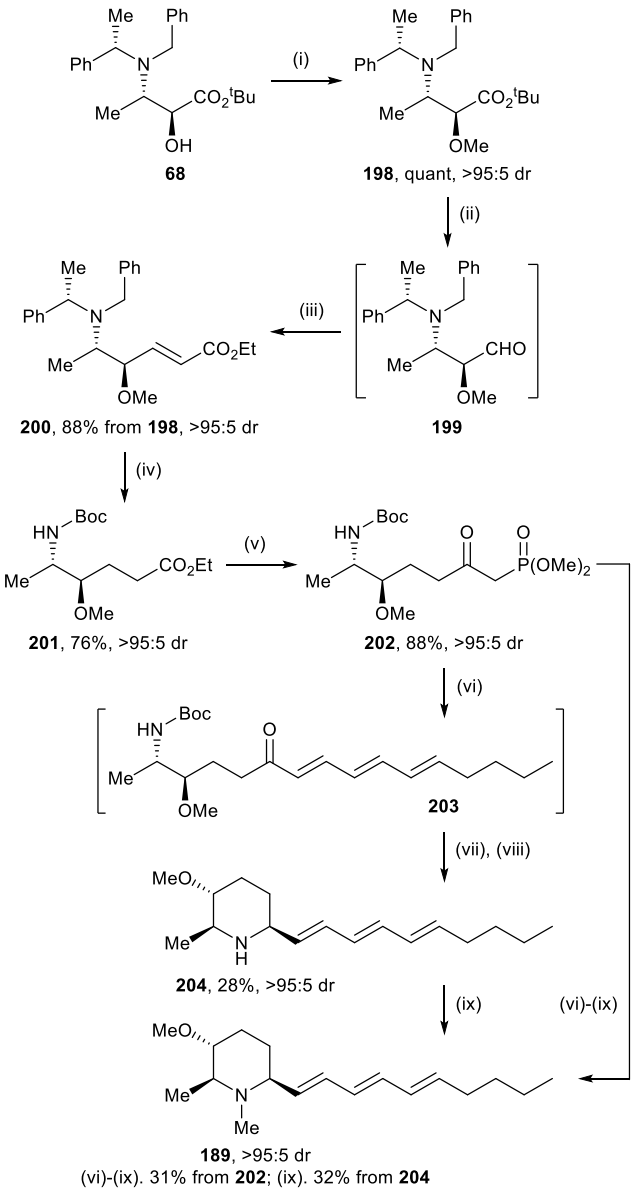


Scheme 45: Synthetic targets; 2,3-*trans*-3,6-*trans*-*(2S,3R,6S)*- and 2,3-*cis*-3,6-*cis*-*(2S,3S,6S)*-stereoisomers **189** and *ent*-**71** [epimeric at C(3)] of *N*-methyl-2-methyl-3-methoxy-6-(deca-l',3',5'-trienyl)piperidine.

4.5 Synthesis of 2,3-*trans*-3,6-*trans*-(2*S*,3*R*,6*S*) microconine

Following an analogous synthetic route to that of microgrewiapine A, treatment of **68** with NaH then MeI gave α-methoxy-β-amino ester **198** in quantitative yield, which was to be followed by reduction to give the aldehyde and chain elongation through Wittig reaction. In this case, treatment of **198** with DIBAL-H cleanly gave the intermediate aldehyde **199** directly, and **199** was immediately treated with the ylide $Ph_3P{=}CHCO_2Et$ to give the corresponding olefin **200** as a single geometric isomer (>95:5 dr [(*E*):(*Z*) ratio]), which was isolated in 88% yield from **198** after chromatography. Confirmation of the double bond geometry was based on diagnostic values of the ^{1}H NMR ^{3}J coupling constants between the C(2) and C(3) protons:^{3}J = 15.9 Hz . Exposure of **200** to $Pd(OH)_2/C$ in the presence of H_2 and Boc_2O in EtOAc gave **201** in 76% yield, in which hydrogenation of the double bond, hydrogenolytic removal of both the *N*-benzyl and *N*-α-methylbenzyl groups, and in situ *N*-Boc protection had occurred. Addition of the lithium anion of $MeP(O)(OMe)_2$ to **201** gave the corresponding β-keto phosphonate **202** in 88% yield. Olefination of (*E,E*)-2,4-nonadienal using β-keto phosphonate **202** gave the conjugated triene **203**, which was not isolated but immediately subjected to the sequential actions of TFA (to effect cleavage of the *N*-Boc group) and then $NaBH_3CN$ (to effect intramolecular reductive amination) to give

piperidine **204**. This proved to be a rather sensitive compound and was isolated in 28% yield from **202** after chromatography. Reductive *N*-methylation of **204** upon treatment with formalin and $NaBH_3CN$ gave **189** in 32% isolated yield; however, in order to circumvent the problems associated with isolation of **204**, it was treated with formalin and $NaBH_3CN$ (i.e., omitting purification) to give **189** in 31% yield from **202** after chromatography (Scheme 46).



Scheme 46: Synthesis of **189**. *Reagents and Conditions*: (i) NaH, MeI, THF, 0 °C to rt, 12 h; (ii) DIBAL-H, CH_2Cl_2, −78 °C, 30 min; (iii) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, rt, 60 h; (iv) H_2, $Pd(OH)_2/C$, Boc_2O, EtOAc, rt, 16 h; (v) ^{n}BuLi, $MeP(O)(OMe)_2$, THF, −78 °C to 0 °C, 90 min; (vi) NaH, (*E*,*E*)-2,4-nonadienal, THF, 0 °C, 1 h, then 72 °C, 12 h; (vii) TFA, CH_2Cl_2, 0 °C, 10 min; (viii) $NaBH_3CN$, conc. aq. HCl, CH_2Cl_2, EtOH, 0 °C, 30 min; (ix) formalin, $NaBH_3CN$, MeCN, rt, 16 h.

4.5.1 *Relative Configuration*

The relative configuration of **189** was established by analysis of the ^{3}J coupling constants in the ^{1}H NMR spectrum, assuming that a chair conformation would be adopted in solution. The large value of the coupling constant between C(6)*H* and one of the diastereotopic C(5) methylene protons ($^{3}J_{5,6}$ = 11.6 Hz) was consistent with the presence of an axial-axial relationship and hence an axial placement of C(6)*H*. Similarly, the large value of the coupling constant between C(3)*H* and one of the diastereotopic C(4) methylene protons ($^{3}J_{3,4}$ = 11.0 Hz) was also consistent with the presence of an axial-axial relationship and hence an axial placement of C(3)*H*. A large coupling constant was also noted between C(2)*H* and C(3)*H* ($^{3}J_{2,3}$ = 9.1 Hz), again indicative of an axial-axial relationship between these two protons and hence with an axial placement of C(2)*H,* thus completing the relative 2,3-*trans*-3,6-*trans*-configurational assignment of the three stereogenic centres of **189** (Figure 28). A ^{1}H NMR nOe analysis was also conducted and provided further support for this relative configurational assignment: a reciprocal enhancement was noted between C(2)*H* and C(6)*H,* but no enhancement was noted between C(2)*H* and C(3)*H* (Figure 28). This stereochemical assignment for **189** is consistent with the relative configurations of the C(2) and C(3) stereogenic centres within the α-hydroxy-β-amino ester starting material **68**,[48,50] and in accord with the expectation that the intramolecular reductive amination would proceed with formation of the corresponding 2,6-*cis*-configuration.[82,83] An analogous configurational analysis applied to **204** was able to assign the relative configurations of the C(2) and C(3) stereogenic centres due to the large coupling constant between C(2)*H* and C(3)*H* ($^{3}J_{2,3}$ = 8.9 Hz), again indicative of an axial-axial relationship between the two protons. However, no diagnostic values for the ^{3}J coupling constants associated with C(6)*H* could be discerned from the spectrum. The relative configuration within **204** was therefore assigned by reference to the relative configuration established for **189**. Given the known relative configurations of α-hydroxy-β-amino ester **68** and piperidine **189**, the relative configurations within all the other synthetic intermediates **198–203** were thus also confidently assigned.

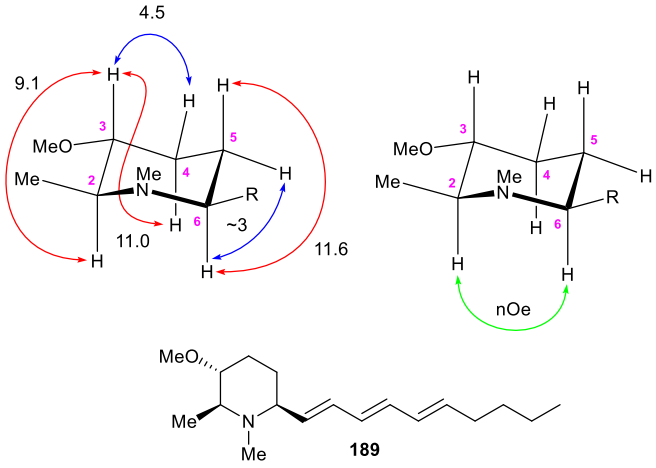
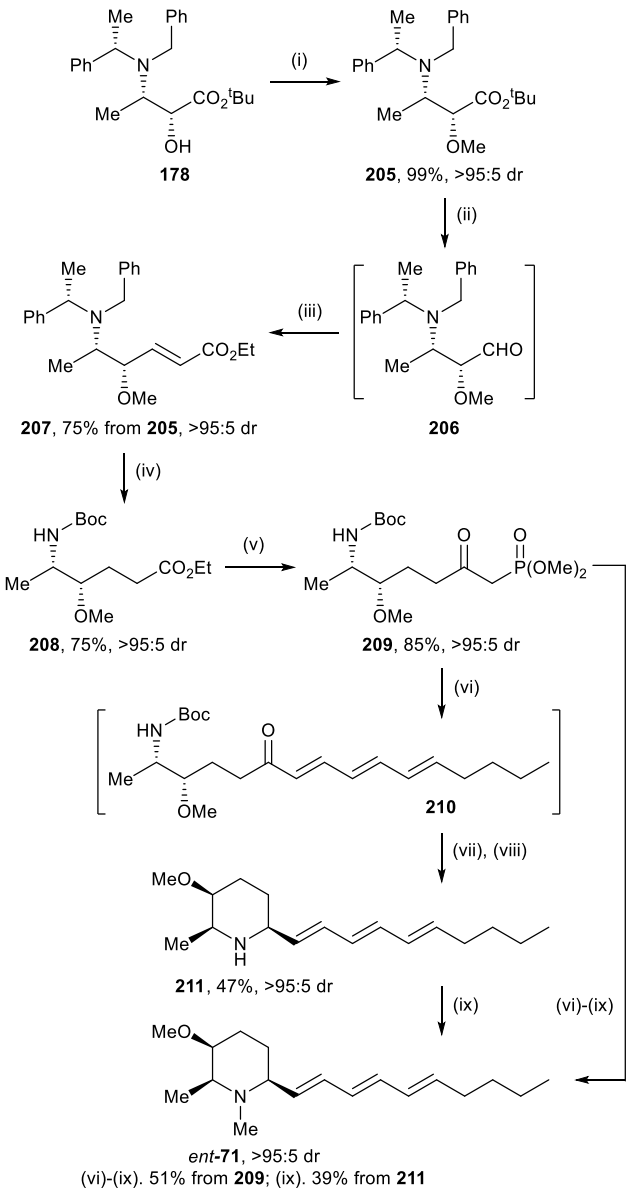


Figure 28: ^{1}H NMR ^{3}J coupling constants (red arrows, φ ≈ 180 °; blue arrows, φ ≈ 60 °) and reciprocal nOe enhancements (green arrows) observed for **189**.

4.6 Synthesis of 2,3-*cis*-3,6-*cis*-(2*S*,3*S*,6*S*) *ent*-71

In order to access the alternative C(3)-epimer *ent*-**71**, an analogous sequence of transformations was applied to α-hydroxy-β-amino ester **178**. *O*-Methylation of **178** with NaH and MeI gave α-methoxy-β-amino ester **205** in 99% yield. Treatment of **205** with DIBAL-H gave the intermediate aldehyde **206**, and addition of $Ph_3P{=}CHCO_2Et$ provided **207** in 75% isolated yield from **205** as a single diastereoisomer. Treatment of **207** with $Pd(OH)_2/C$ in the presence of H_2 and Boc_2O in EtOAc gave **208** in 75% yield, and addition of the lithium anion of $MeP(O)(OMe)_2$ to **208** gave β-keto phosphonate **209** in 85% yield. Olefination of (*E*,*E*)-2,4-nonadienal using β-keto phosphonate **209** gave the conjugated triene **210**, which upon sequential treatment with TFA and $NaBH_3CN$ gave piperidine **211** in 47% yield from **209** after chromatography. Subsequent reductive *N*-methylation of **211** gave *ent*-**71** in 39% isolated yield; omitting purification of **211** resulted in formation of *ent*-**71** in an improved 51% yield from **209** after chromatography (Scheme 47).



Scheme 47: Synthesis of *ent*-**71**. *Reagents and Conditions*: (i) NaH, MeI, THF, 0 °C to rt, 12 h; (ii) DIBAL-H, CH_2Cl_2, −78 °C, 30 min; (iii) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, rt, 60 h; (iv) H_2, $Pd(OH)_2/C$, Boc_2O, EtOAc, rt, 16 h; (v) ^nBuLi, $MeP(O)(OMe)_2$, THF, −78 °C to 0 °C, 90 min; (vi) NaH, (*E*,*E*)-2,4-nonadienal, THF, 0 °C, 1 h, then 72 °C, 12 h; (vii) TFA, CH_2Cl_2, 0 °C, 10 min; (viii) $NaBH_3CN$, conc. aq. HCl, CH_2Cl_2, EtOH, 0 °C, 30 min; (ix) formalin, $NaBH_3CN$, MeCN, rt, 16 h.

4.6.1 *Relative Configuration*

The relative configuration of *ent*-**71** was investigated by analysis of the ^3J coupling constants in the ^{1}H NMR spectrum, assuming that a chair conformation would be adopted in solution. As with **189**, the large value of the coupling constant between C(6)*H* and one of the diastereotopic C(5) methylene protons ($^3J_{5,6}$ = 11.6 Hz) within *ent*-**71** was consistent with an axial placement of C(6)*H*. In contrast to **189**, however, the much smaller values of the coupling constant between C(3)*H* and

both of the diastereotopic C(4) methylene protons ($^3J_{3,4}$ < 5 Hz) within *ent*-**71** indicated an equatorial placement of C(3)*H*. It followed that the small value of the coupling constant between C(2)*H* and C(3)*H* ($^3J_{2,3}$ < 5 Hz) was not diagnostic, as it would be consistent with either an axial or equatorial placement of C(2)*H*. However, a reciprocal nOe enhancement was observed between the C(2)-proton and the C(6)-proton, which enabled an axial placement of the C(2) proton to be inferred. It is also of note that a reciprocal nOe enhancement was observed between C(2)*H* and C(3)*H* within *ent*-**71**; such an enhancement was absent for **189**. Thus, the relative 2,3-*cis*-3,6-*cis*-configurational assignment of the three stereogenic centres of *ent*-**71** was complete (Figure 29). The stereochemical assignment of *ent*-**71** is consistent with the relative configurations of the C(2) and C(3) stereogenic centres imported from the α-hydroxy-β-amino ester starting material **178**,[48,50] and in accord with the expectation that the intramolecular reductive amination would proceed with formation of the corresponding 2,6-*cis*-configuration.[82,83] No diagnostic ^3J coupling constant data could be extracted from the ^{1}H NMR spectrum of **211** and therefore its relative configuration was assigned by reference to the relative configuration established for *ent*-**71**. Applying the same logic as previously, given the known relative configurations of α-hydroxy-β-amino ester **68** and piperidine *ent*-**71**, the relative configurations within all the other synthetic intermediates **205**–**210** were thus also confidently assigned.

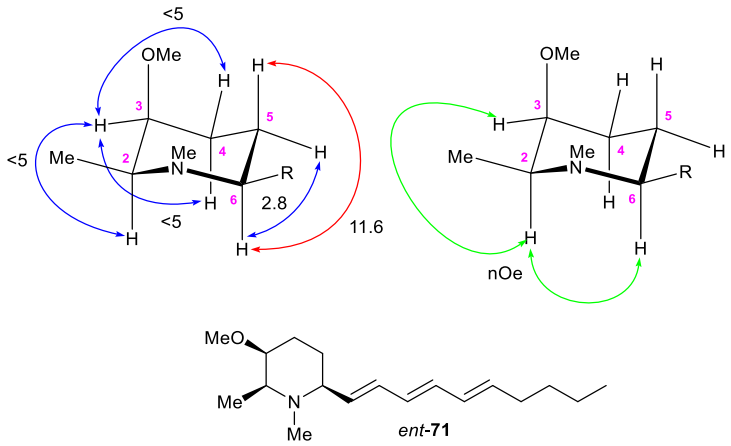
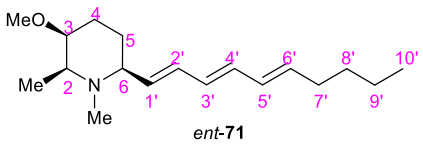


Figure 29:^{1}H NMR ^3J coupling constants (Hz) (red arrows, φ ≈ 180 °; blue arrows, φ ≈ 60 °) and nOe enhancements (green arrows) observed for *ent*-**71**.

4.7 Assignment of the Relative Configuration of Microconine

With authentic samples of the C(3)-epimers *ent*-**71** and **189** in hand, attention turned towards comparison of their NMR data with those of the natural product. A copy of the ^{1}H NMR spectrum recorded for the sample of the alkaloid isolated from the natural source was provided by Professor Kumar. When the spectrum was examined it became apparent that the raw ^{1}H NMR data for the alkaloid were different to those reported in the original isolation study, and in particular many of the protons appeared as complex multiplets with unresolvable fine structure. The ^{1}H NMR data for the natural product was therefore first validated (Table 29). Comparison of the validated ^{1}H NMR spectroscopic data for microconine with those of synthetic sample *ent*-**71** showed good agreement of peak position (and significant differences with those of **189**), therefore supporting the original relative configurational assignment. The reciprocal nOe enhancements noted by Kumar et al. linking the C(2), C(3) and C(6) protons (the sole basis for the configurational assignment) were also present for *ent*-**71** (Figure 29), with no such correlation between the C(2) and C(3) protons within **189** (Figure 28). The corrected ^{1}H NMR spectroscopic data for the natural sample of microconine do not enable the relative configuration to be assigned from ^{3}J coupling constant data but the improved resolution of the ^{1}H NMR spectrum of *ent*-**71** enabled these data to be extracted (Figure 29), and so provides further independent evidence to substantiate the configurational assignment of the natural product. Despite a copy of the ^{13}C NMR spectrum recorded for microconine being unavailable, comparison of the reported data with those of *ent*-**71** provided further support for their congruity. Excellent agreement was noted between the two data sets, with $-0.4 < \Delta\delta C < -0.2$ ppm in all instances (Table 30). These data suggest that there may be a small difference (of ~0.3 ppm) between the reference frequency of the natural sample and the synthetic sample *ent*-**71** (for which the resonance due to $CDCl_3$ was referenced to 77.16 ppm)[84,85] but clearly in the absence of a copy of the ^{13}C NMR spectrum of the natural product it is impossible to establish the reference frequency employed. The ^{13}C NMR data of **189**, meanwhile,

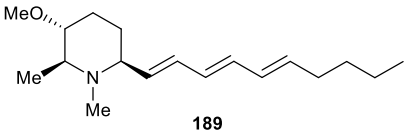
showed significant differences to that of microconine (Table 30). In summary, therefore, it is unequivocal from the data presented herein that natural microconine possesses the relative 2,3-*cis*-3,6-*cis*-configuration, in accordance with the initial assignment made by Kumar et al. upon isolation of the alkaloid. These data also suggest that the ^{1}H NMR ^{3}J coupling constant data reported by Kitahara et al. are erroneous; the differences in the characterisation data for microconine and their synthetic sample remain unexplained.



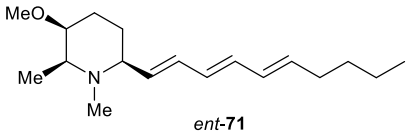
ent-**71**

Assignment	Microconine	*ent*-**71**
C(10')H$_3$	0.88 (3H, t, 7.0)	0.88 (3H, t, 7.1)
C(2)Me	1.21 (3H, d, 6.4)	1.19 (3H, d, 6.5)
C(4)H$_A$, C(5)H$_A$, C(8')H$_2$, C(9')H$_2$	1.35 (6H, m)	1.33 (6H, m)
C(5)H$_B$	1.81 (1H, m)	1.78 (1H, td, 14.7, 11.6, 4.2)
C(2)H, C(4)H$_B$	2.10 (4H, m)	2.05 (2H, m)
C(7')H$_2$		2.08 (2H, app q, 6.6)
N*Me*	2.15 (3H, s)	2.13 (3H, s)
C(6)H	2.47 (1H, m)	2.44 (1H, ddd 11.6, 8.6, 2.8)
C(3)H	3.14 (1H, m)	3.13 (1H, m)
O*Me*	3.33 (3H, s)	3.32 (3H, s)
C(1')H, C(6')H	5.70 (2H, m)	5.67 (2H, m)
C(2')H, C(3')H, C(4')H, C(5')H	6.13 (4H, m)	6.09 (4H, m)

Table 29: ^{1}H NMR (500 MHz, $CDCl_3$) Comparison of ^{1}H NMR chemical shifts for microconine with those of *ent*-**71**. Midpoints of all multiplets are quoted. Assignments are as determined in this study.



189



ent-**71**

189		**Microconine**	*ent*-**71**	
14.1	(−0.2)	14.3	14.1	(−0.2)
16.4	(−2.0)	18.4	18.2	(−0.2)
22.3	(−0.3)	22.6	22.3	(−0.3)
28.8	(+2.2)	26.6	26.4	(−0.2)
31.2	(+2.9)	28.3	28.3	0
31.6	(−0.2)	31.8	31.6	(−0.2)
32.6	(−0.3)	32.9	32.6	(−0.3)
40.5	(−0.4)	40.9	40.8	(−0.1)
56.8	(−0.5)	57.3	57.1	(−0.2)
64.5	(+1.9)	62.6	62.4	(−0.2)
67.6	(−1.2)	68.8	68.6	(−0.2)
81.6	(+2.0)	79.6	79.4	(−0.2)
130.1	(−0.5)	130.6	130.4	(−0.2)
130.3	(−0.4)	130.7	130.5	(−0.2)
131.5	(+0.4)	131.1	130.8	(−0.3)
132.6	(+0.1)	132.5	132.1	(−0.4)
135.7	(+0.1)	135.6	135.3	(−0.3)
136.9	(−0.9)	137.8	137.8	0

Table 30: ^{13}C NMR (125 MHz, $CDCl_3$). Comparison of ^{13}C NMR chemical shifts (by ordinal number) for microconine with those of **189** and *ent*-**71**.

4.8 Assignment of the Absolute Configuration of Microconine

With the relative configurational assignment of microconine secured unambiguously, attention turned to its absolute configurational assignment. Given the known relative configurations within *ent*-**71**, it followed that the absolute configuration could be assigned to **178** and *ent*-**71** from the known absolute configuration of the α-hydroxy-β-amino ester precursor **68**.

In order to justify a comparison of the specific rotation of microconine with synthetic *ent*-**71** (which has been shown to possess the same relative configuration as the natural product microconine), the effect (if any) of concentration on the specific rotation value of *ent*-**71** was measured.

At 22 ºC, the specific rotation value of *ent*-**71** was found to display significant dependence on the concentration of the sample, with *both magnitude and sign* being affected in this instance; $\{[\alpha]_D^{22}$ −29.0 (c = 1.0 $CHCl_3$)}, $\{[\alpha]_D^{22}$ −26.8 (c = 0.5 $CHCl_3$)}, $\{[\alpha]_D^{22}$ −20.9 (c = 0.1 $CHCl_3$)}, $\{[\alpha]_D^{22}$ −10.2 (c = 0.08 $CHCl_3$)}, $\{[\alpha]_D^{22}$ −8.6 (c = 0.06 $CHCl_3$)}, $\{[\alpha]_D^{22}$ +7.2 (c = 0.04 $CHCl_3$)}

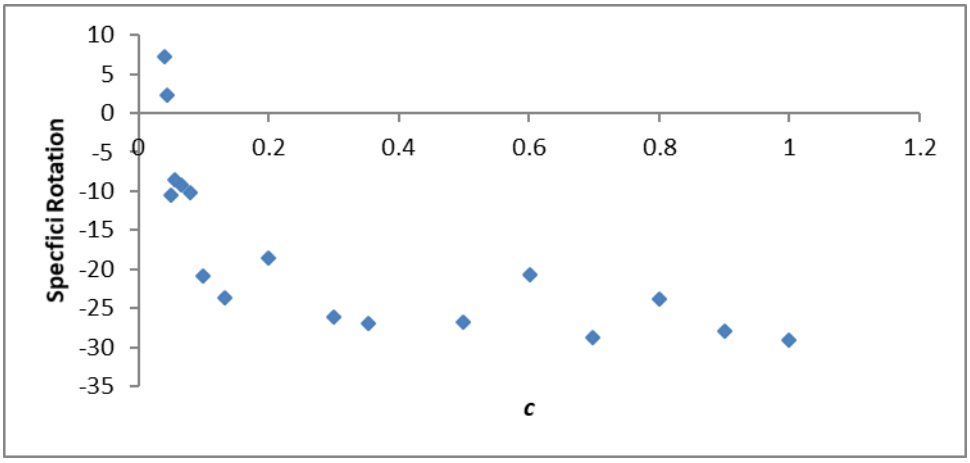


Figure 30: The measured effect of concentration on the specific rotation value of *ent*-**71** (measurements taken at 22 °C). (average ± standard deviation plotted, n=3).

It was also postulated that the specific rotation of microconine may exhibit some temperature-dependence.

In fact, the magnitude of the specific rotation value of *ent*-**71** [having known absolute (2*S*,3*S*,6*S*)-configuration] was found to be highly dependent on the temperature of the sample; {$[\alpha]_D^{15}$ −43.2 (*c* = 1.0 $CHCl_3$)}, {$[\alpha]_D^{22}$ −29.0 (*c* = 1.0 $CHCl_3$)}, {$[\alpha]_D^{24}$ −26.0 (*c* = 1.0 $CHCl_3$)}, {$[\alpha]_D^{25}$ −30.5 (*c* = 1.0 $CHCl_3$)} (Figure 31).

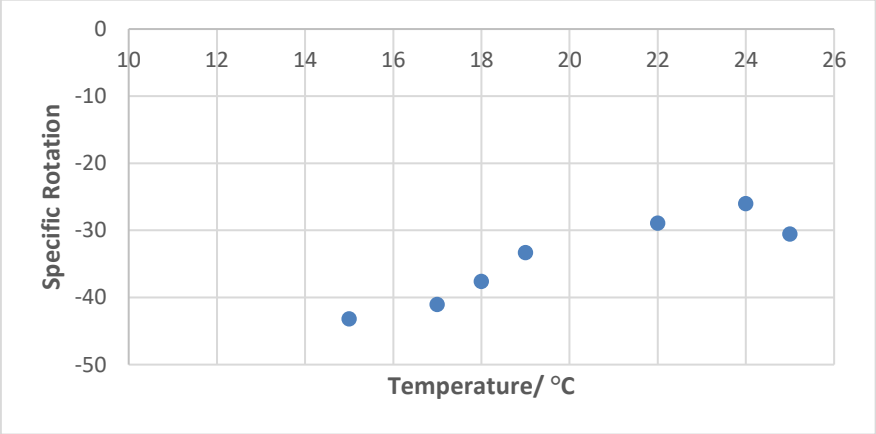


Figure 31: The measured effect of temperature on the specific rotation value of *ent*-**71** (measurements taken at *c* = 1.0). (average ± standard deviation plotted, n=3).

Given the observed variation of the specific rotation of *ent*-**71** on temperature and concentration, comparison of specific rotation values for this alkaloid *should be done with caution,* especially if they are being used to assign absolute configuration. Thus values should only be compared when they have been recorded under identical conditions of temperature and concentration (as well as solvent). As the concentration at which the value was recorded for the natural product was not reported, this is unfortunately rendered impossible in this instance. At 22 °C (the temperature at which the value of the natural product was obtained) and at *c* = 1.0, the specific rotation value of *ent*-**71** is essentially identical in magnitude but of opposite sign; {$[\alpha]_D^{22}$ −29.0 (*c* = 1.0 $CHCl_3$)} to that recorded for the natural product {$[\alpha]_D^{22}$ +29.2 (*c* = unknown $CHCl_3$)}.[103]

4.9 Conclusion

An independent asymmetric synthesis of the alkaloid microconine, has been established. Interrogation of the synthetic sample of the alkaloid using ^{1}H NMR ^{3}J coupling constant analysis and NOESY analyses independently established the relative configuration, which was entirely consistent with the expected diastereoselectivity of the synthetic process. Re-interpretation of the NMR data for the natural sample, allowed the relative configuration of the alkaloid to be assigned. The balance of evidence therefore suggests that the alkaloid should be assigned the absolute (2*R*,3*R*,6*R*)-configuration. In conclusion, an independent asymmetric synthesis of the 2,3-*trans*-3,6-*trans*-(2S,3R,6S)- and 2,3-*cis*-3,6-*cis*-(2S,3S,6S)-stereoisomers [epimeric at C(3)] of the alkaloid microconine [*N*-methyl-2-methyl-3-methoxy-6-(deca-l',3',5'-trienyl)piperidine] has been developed. Correction of the originally reported ^{1}H NMR data for the alkaloid reveals excellent correlation with the corresponding data for the 2,3-*cis*-3,6-*cis*-stereoisomer, thus unambiguously establishing its relative configuration. The superior resolution of the ^{1}H NMR spectrum acquired for the synthetic sample also yields ^{3}J coupling constant data which are also consistent with the assigned relative configuration (with the piperidine ring adopting a chair conformation), and so provide support for the nOe data originally used for assignment of the relative configuration. Comparison of specific rotation data for the synthetic sample of the 2,3-*cis*-3,6-*cis*-(2*S*,3*S*,6*S*)-stereoisomer with that of the natural product suggests that microconine possesses the absolute (2*R*,3*R*,6*R*)-configuration.

4.10 Chapters 2–4 Conclusion

In conclusion, an independent asymmetric synthesis of the alkaloids; microcosamine A, microgrewiapines A-C, and microconine has been realised. In the case of microgrewiapines B and C, this work represents the first synthesis of the natural products (Figure 32).

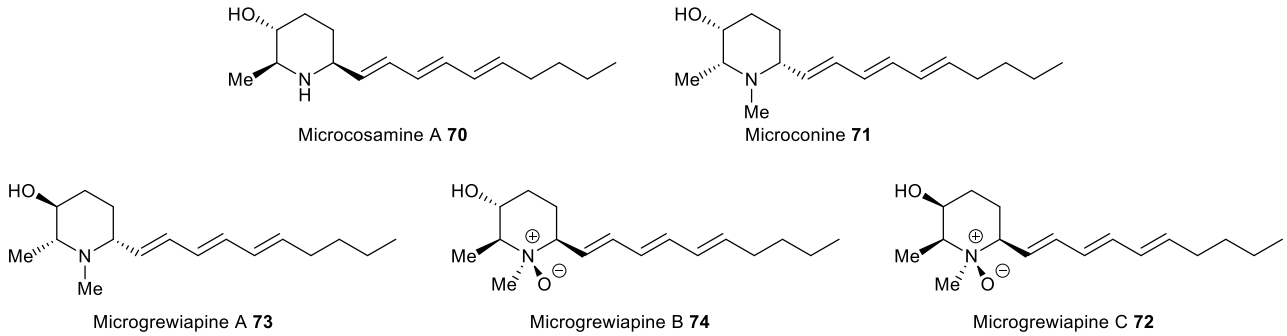


Figure 32: Natural Products synthesised in this work.

The work has independently established the relative configuration of all 5 alkaloids. The absolute configuration of the alkaloids has also been confirmed, however microgrewiapine A remains unsubstantiated. These findings raise deep questions about the biosynthetic origins of the family, as (for example) microgrewiapine C and microconine are apparently members of the opposite enantiomeric series.

Future work will involve application of the established synthetic route to further alkaloids from *Microcos Paniculata*. Microcosamine B[39] and C[41], which have been assigned opposite configurations are of particular interest.

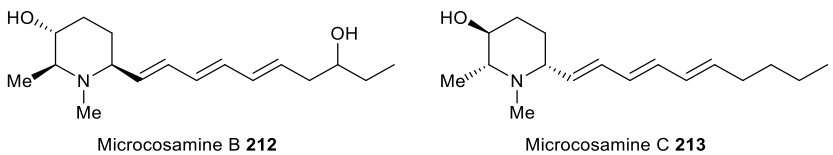


Figure 33: Further piperidine natural products isolated from *Microcos Paniculata*.

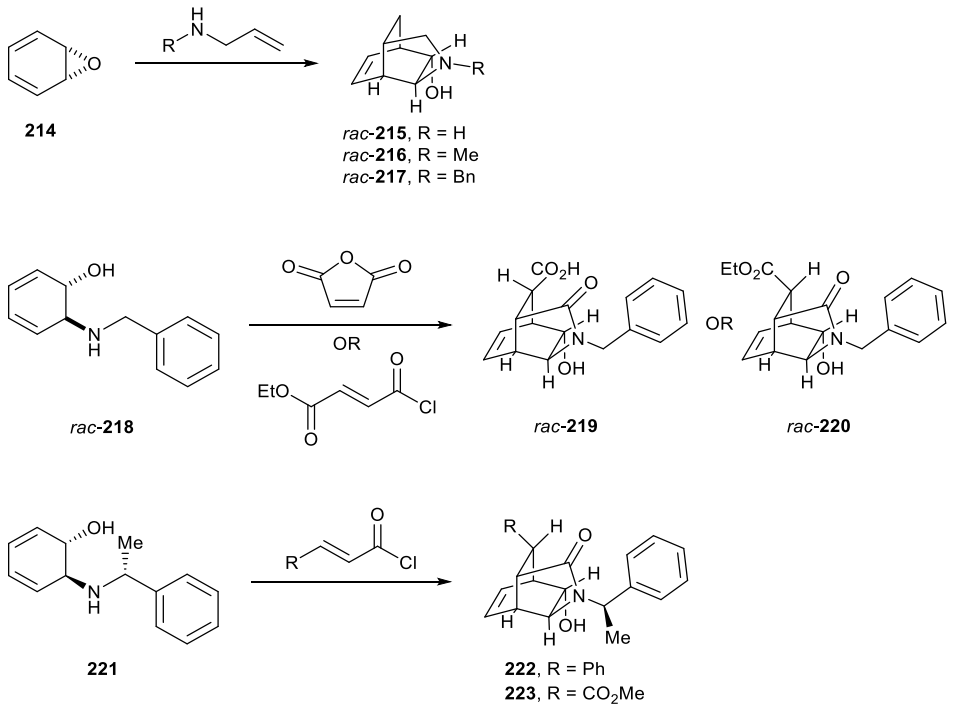
Further to this, an independent asymmetric synthesis of the semi synthetic piperidine-microgrewiapine A Acetate, was realised. In addition, a number of quasi-natural products (3-*epi*-

microcosamine A, 3-*epi*-microgrewiapine A, 3-*epi*-microconine, *N*-demethyl microconine, and *N*-demethyl-3-*epi*-microconine) have been synthesised, isolated, and fully characterised.

Chapter 5 Development of a Diels-Alder Reaction

5.1 Chapter Outline

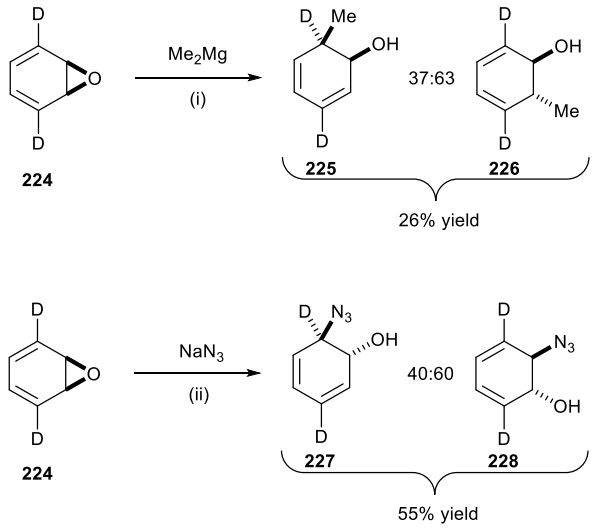
This chapter describes the exploration of an intramolecular Diels-Alder reaction using substrates derived from the ring opening of benzene oxide. Initial experiments used *N*-substituted allyl amines, which performed a ring opening and spontaneous cycloaddition in 1 step. Later work focussed on epoxide opening with benzylamine, isolating the ring opened product, then adding the allyl motif required for the cycloaddition in a separate step. This allowed the development of an enantiopure route utilising a ring opening with a chiral amine (Scheme 48).



Scheme 48: Overview of Syntheses Explored in this Chapter.

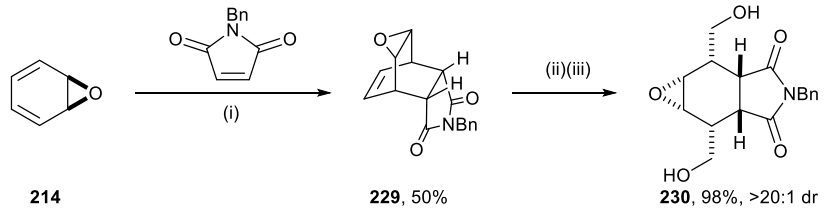
5.2 Synthetic Utility of Benzene Oxide

Benzene oxide **214** is an under-utilized building block in organic synthesis. The ring-opening, for example, has been surprisingly little investigated; the few studies that do exist show that for a variety of carbon, nitrogen, oxygen, and sulphur nucleophiles; both *cis* and *trans* 1,6 additions, as well as the expected *trans* 1,2 additions are observed (Scheme 49).[105–108]



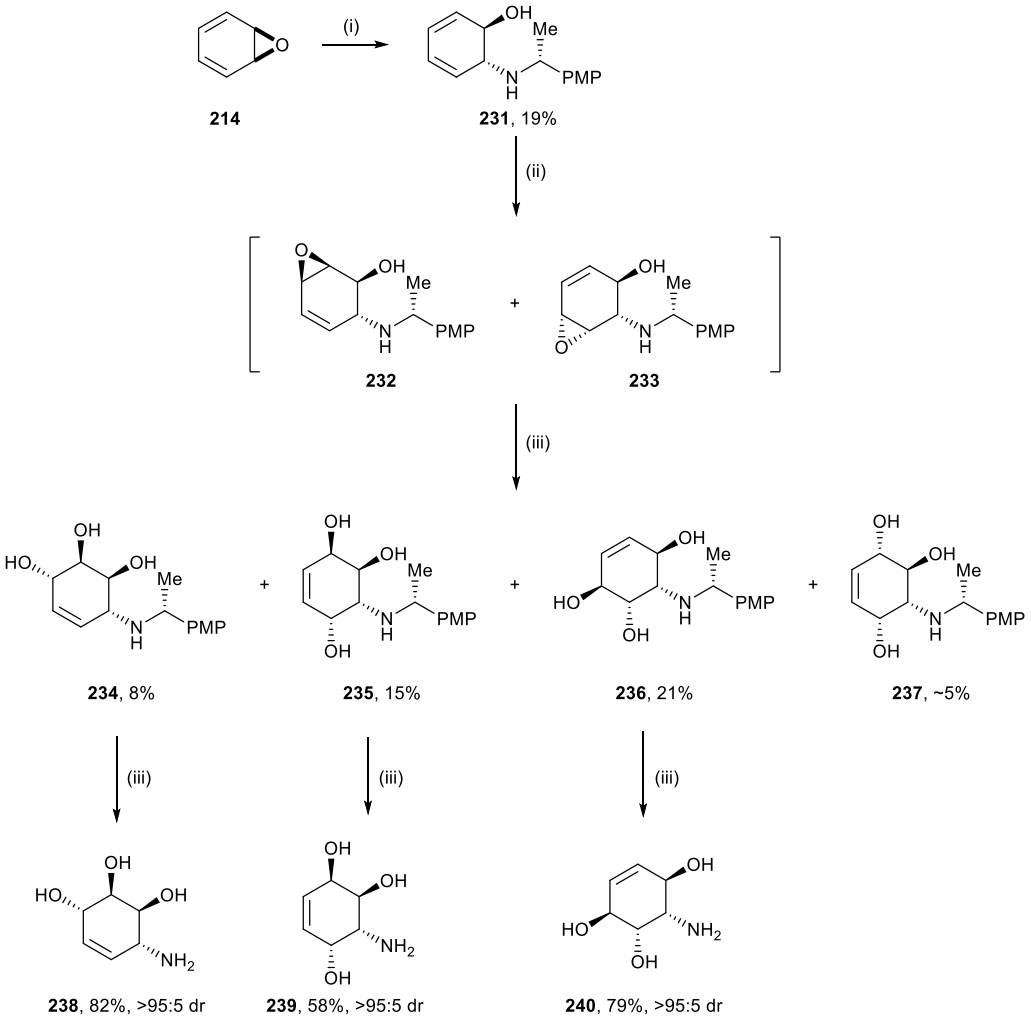
Scheme 49: Exemplar ring openings of benzene oxide.[105–108] *Reagents and conditions*: (i) Et_2O, 0 °C, 1 h; (ii) H_2O, rt, 3 h.

As far as the synthetic utility of benzene oxide, little has been explored. In 2018 work by Matías et al. produced meso bicyclic systems such as **230** bearing six continuous stereocentres in 2 steps from benzene oxide.[109] Initial cycloaddition of benzene oxide with *N*-benzylmaleimide produced **229**, and subsequent ozonolysis of the Diels−Alder adducts resulted in **230** (isolated as a diol following reductive workup with $NaBH_4$) (Scheme 50).



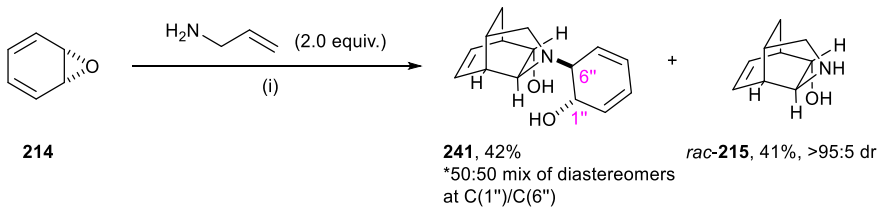
Scheme 50: Bicycle synthesis by Matías et al.[109] *Reagents and Conditions*: (i) Et_2O, rt, 24 h; (ii) O_3, − 78 °C, MeOH:CH_2Cl_2 (2:1); (iii) $NaBH_4$, 0 °C, 1 h, MeOH:CH_2Cl_2 (2:1).

Work from Davies et al.[110] has recently probed the synthetic use of benzene oxide, producing a method to enable the synthesis of enantiopure conduramines in three steps from benzene oxide. Initial epoxide opening with α-methyl-*p*-methoxybenzylamine gave **231** in 19% yield. Epoxidation with *m*-CPBA gave a mixture of two epoxides **232** and **233**, which upon 1,2 and 1,6 water opening, gave protected conduramines **234**-**236**. Deprotection with Et_3SiH and TFA gave conduramines **238**, **239**, and **240** in 82, 58, and 79% respectively (Scheme 51).



Scheme 51: Conduramine syntheses by Davies et al.[110] *Reagents and Conditions*: (i) (*R*)-α-Methyl-*p*-methoxybenzylamine, MeOH, 66 °C, 72 h; (ii) HBF_4 (40% aq), *m*-CPBA, CH_2Cl_2, 21 h; (iii) Et_3SiH, TFA, 50 °C, 18 h.

It was noted during experimentation for the conduramine project that treatment of benzene oxide **214** with allyl amine spontaneously resulted in the 2 tricyclic structures **241** and *rac*-**215** in 42% and 41% yield respectively, with no non-cyclised product observed (Scheme 52).



214

241, 42%
*50:50 mix of diastereomers at C(1")/C(6")

rac-**215**, 41%, >95:5 dr

Scheme 52: Serendipitous Diels Alder reaction. *Reagents and Conditions*: (i) MeOH, 65 °C, 48 h.

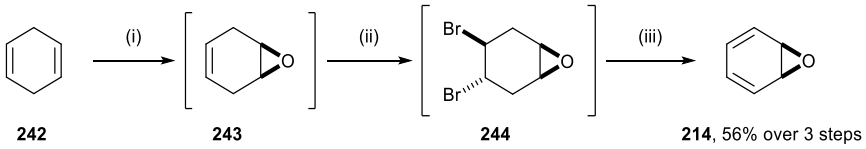
5.3 Chapter Aim

The aim of this chapter is to investigate the applicability of the afore mentioned tricycle-forming Diels-Alder reaction (Scheme 52) to natural product-like scaffolds. This will involve optimising the reaction to favour formation of the secondary amine *rac*-**215**, expanding the scope of the reaction, and also the development of an enantiopure route.

5.4 Synthesis of Benzene Oxide

Improving upon previous literature protocols,[109,111] benzene oxide **214** was synthesised in 3 steps from cyclohexa-1,4-diene **242** (56% overall yield). Treatment of cyclohexa-1,4-diene **242** with AcOOH in CH_2Cl_2, followed by dilution with $CHCl_3$ and addition of Br_2 delivered dibromide **244**. Treatment of **244** with DBU in Et_2O gave benzene oxide **214** in 56% yield (10 g scale); this was generated, isolated, and immediately used, as required (Scheme 53).

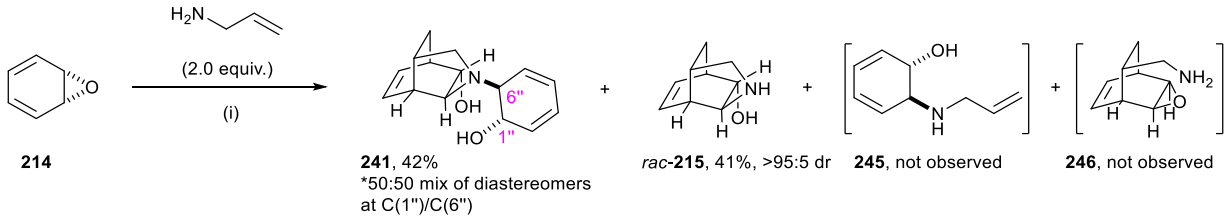
The troublesome final purification (2 × distillation) previously reported,[111] was significantly improved by modification of the work up procedure from Matías et al.,[109] which involves a basic wash with sat aq $NaHCO_3$ then simple evaporation. This gave benzene oxide of sufficient purity (>95% by ^{1}H NMR) to use.



Scheme 53: Benzene oxide synthesis. *Reagents and conditions*: (i) AcOOH, Na_2CO_3, CH_2Cl_2, 0 °C to rt, 18 h, (ii) CH_2Cl_2:$CHCl_3$ (1:1 v/v), Br_2, –78 °C, 30 min (iii) DBU, Et_2O, rt, 24 h.

5.5 Allyl Amine Addition

The initial investigation began with repetition of the previously reported reaction (Scheme 52). Addition of 2 equiv. allyl amine to benzene oxide resulted in a 1:1 ratio of tertiary amine **241** and secondary amine *rac*-**215** (Scheme 54). Neither plausible intermediates **246** (from an initial Diels-Alder but no epoxide opening) or **245** (from and initial epoxide opening but no Diels-Alder) were observed. **241** was isolated in 42% yield, and *rac*-**215** in 41%.

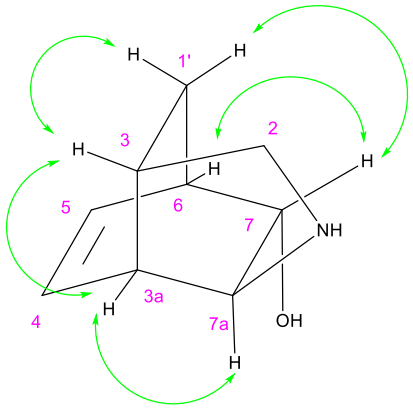


214 | **241**, 42% *50:50 mix of diastereomers at C(1")/C(6") | *rac*-**215**, 41%, >95:5 dr | **245**, not observed | **246**, not observed

Scheme 54: Allyl amine cycloaddition. *Reagents and Conditions*: (i) MeOH, 65 °C, 48 h.

5.5.1 *rac-215 Structural and Stereochemical Assignment*

The 3,6-methanoindan-7-ol structure of *rac*-**215** was proposed on the basis of standard ^{1}H and ^{13}C NMR techniques. COSY and HMBC correlations were noted between C(2)*H* through to C(7a)*H*. The *trans* epoxide opening was shown by the absence of any nOe correlation between C(7)*H* and C(7a)*H*, suggesting that the protons were on opposite faces. Further nOe correlations between C(7)*H* and C(1′)*H*, provided evidence that the cycloaddition occurred on the same face as the nitrogen (Figure 34).



rac-**215**

Figure 34: Selected reciprocal nOe enhancements (green arrows) observed for *rac*-**215**.

5.5.2 ***Reaction Optimisation***

The formation of unwanted tertiary amine **241** (a mixture of two inseparable diastereomers) was likely occurring from a second epoxide opening from the secondary amine (and desired product) *rac*-**215** which was postulated to be more nucleophilic than the starting primary amine, this proposal was supported by evidence that treatment of *rac*-**215** with benzene oxide led to complete formation of **241**. In order to reduce formation of tertiary amine **241** it was proposed that altering the concentration would affect the product distribution (Figure 35). Increasing the concentration to 2 M led to a large increase in the formation of tertiary amine **241**, and correspondingly, reduction of the reaction concentration did supress formation of the tertiary amine **241**. However at lower concentrations the formation of phenol became significant, reducing the yield of product *rac*-**215**. A concentration of c=1.0 was taken as the concentration for further optimisation as phenol production was low (10%), whilst tertiary amine was (45%). In all cases full conversion from benzene oxide was observed.

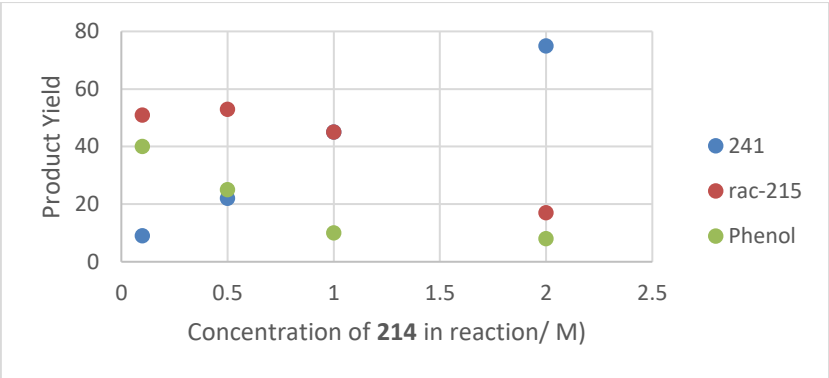


Figure 35: Product distribution observed in a series of experiments carried out with varying concentrations of **214**.

In order to outcompete the secondary amine and further favour product formation, the equivalents of allyl amine were increased (Figure 36). It was found that increasing the amine equivalents consistently resulted in increased product formation, and that at 10 equiv. amine the product could be isolated in 90% yield.

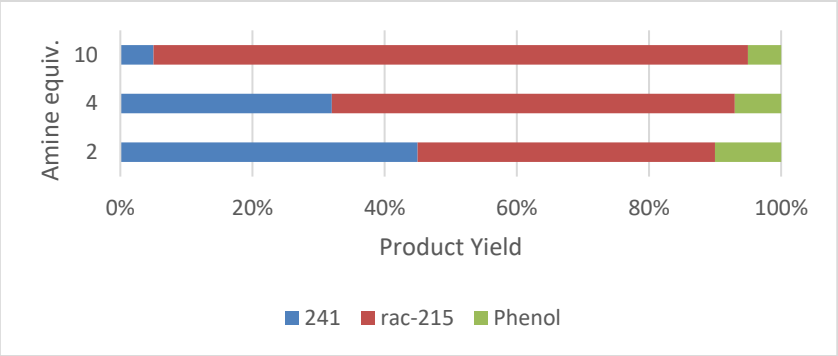


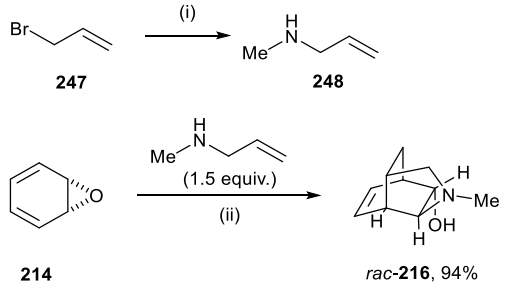
Figure 36: Effect of amine equiv. on product distribution at c = 1.0 M.

Henceforth these optimised conditions (10.0 equiv. amine, 1 M MeOH) were used for primary amine additions to benzene oxide **214**.

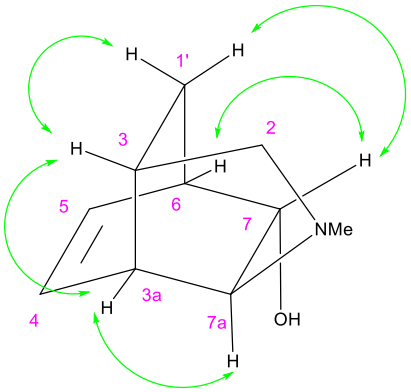
5.6 Secondary Amines as Nucleophiles

The formation of five-membered rings using *N*-substituted allyl amines was then investigated. It was found that the amine equivalent could be reduced to 1.5 equiv. which greatly improved the ease of purification. Addition of *N*-Methyl allyl amine **248** to benzene oxide **214** gave tricycle *rac*-**216** in 94% (Scheme 55).

The 3,6-methanoindan-7-ol structure of *rac*-**216** was proposed on the basis of standard ^{1}H and ^{13}C NMR techniques. COSY and HMBC correlations were noted between C(2)*H* through to C(7a)*H*. The *trans* epoxide opening was shown by the absence of any nOe correlation between C(7)*H* and C(7a)*H*, suggesting that the protons were on opposite faces. Further nOe correlations between C(7)*H* and C(1′)*H*, provided evidence that the cycloaddition occurred on the same face as the nitrogen (Figure 37). In essence, the compound showed the same nOe correlations as the *N*H compound *rac*-**215**, with very similar ^{1}H and ^{13}C NMR spectra.



Scheme 55: Diels Alder reaction with *N*-methyl allylamine. *Reagents and Conditions*: (i) Methyl amine, EtOH, rt, 12 h; (ii) MeOH, 65 °C, 48 h



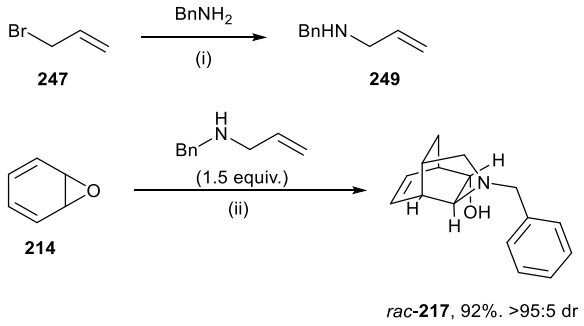
rac-**216**

Figure 37: Selected reciprocal nOe enhancements (green arrows) observed for *rac*-**216**.

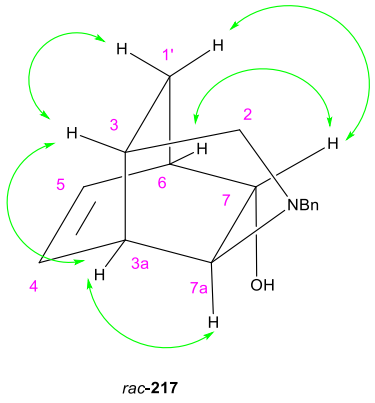
Seemingly the steric bulk of tertiary amine *rac*-**216** outweighs the possible increased nucleophilicity, and/or the initial addition occurs at a much faster rate (than that of the allyl amine).

In order to further probe the scope of the reaction, the significantly bulkier secondary amine *N*-Bn allyl amine **249** (synthesised from allyl bromide in 72% yield) was also trialled, resulting in full conversion and hexahydro-3,6-methanoindol-7-ol *rac*-**217** isolated in 92% (Scheme 56).

The 3,6-methanoindan-7-ol structure of *rac*-**217** was proposed on the basis of standard ^{1}H and ^{13}C NMR techniques. COSY and HMBC correlations were noted between C(2)*H* through to C(7a)*H*. The *trans* epoxide opening was shown by the absence of any nOe correlation between C(7)*H* and C(7a)*H*, suggesting that the protons were on opposite faces. Further nOe correlations between C(7)*H* and C(1′)*H*, provided evidence that the cycloaddition occurred on the same face as the nitrogen (Figure 38). In essence, the compound showed the same nOe correlations as the *N*H and *N*Me compounds *rac*-**215** and *rac*-**216**, with very similar ^{1}H and ^{13}C NMR spectra.



Scheme 56: Diels Alder reaction with *N*-benzyl allylamine. *Reagents and Conditions*: (i) KI, DMSO, rt, 18 h (ii) MeOH, 65 °C, 48 h.

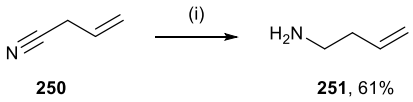


rac-**217**

Figure 38: Selected reciprocal nOe enhancements (green arrows) observed for *rac*-**217**.

5.7 Six Membered Ring Synthesis

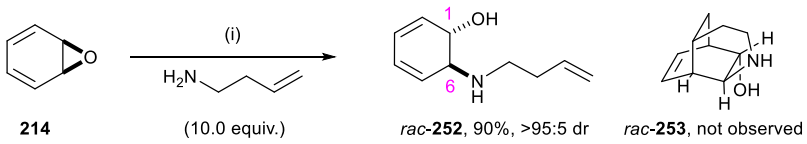
It was hoped that the procedure could be applied for the formation of a 6-membered ring using homoallyl amine **251**. Homoallyl amine **251** was synthesised 61% via reduction of the corresponding nitrile **250** (Scheme 57).



Scheme 57: Homoallyl amine synthesis. *Reagents and conditions:* (i) $LiAlH_4$, Et_2O, rt, 18 h.

When the optimised primary amine conditions were used, the desired Diels Alder product *rac*-**253** was not observed, with ring-opened product *rac*-**252** isolated in 90% yield (Scheme 58). The relative configuration of *rac*-**252** was supported by analysis of the ^3J coupling constants in the ^{1}H NMR spectrum of the cyclohexa-2,4-diene. A large ^3J coupling constant was noted between C(1)*H* and C(6)*H* within *rac*-**252** ($^3J_{1,6}$ = 11.7 Hz), indicative of a pseudo axial-axial relationship between these two protons and hence with transdiaxial epoxide opening.

In an attempt to force the cycloaddition, the ring opened product *rac*-**252** was heated in a variety of further solvents (dichloromethane, benzene, toluene) but no cycloaddition (or further transformation) was observed.

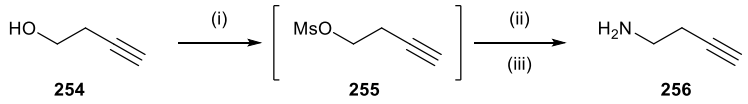


Scheme 58: Ring-opening with **251**. *Reagents and conditions:* (i) MeOH, 65 °C, 48 h.

5.8 Attempts to activate Dienophile Moiety

5.8.1 *Alkyne*

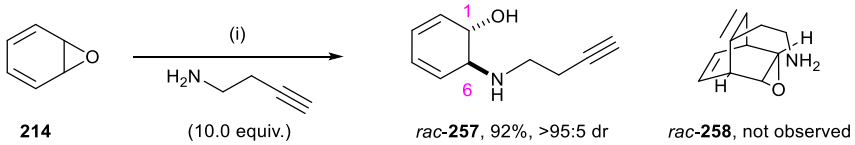
In an attempt to activate the dienophile, it was planned to exchange the terminal olefin for an alkyne.[112] The requisite but-3-yne-1-amine **256** was synthesised relatively easily in 3 steps from 3-butyn-1-ol **254** via mesylation, an azide S_N2, then a Staudinger reaction (45% over 3 steps) (Scheme 59).



Scheme 59: Synthesis of alkyne **256**. *Reagents and conditions:* (i) MsCl, Et_3N, Et_2O, 0 °C, 4 h; (ii) NaN_3, DMF, 70 °C, 4 h; (iii) PPh_3, H_2O, Et_2O, rt, 12 h.

When the optimised conditions for hexahydroindol-7-ol *rac*-**215** were used, no cycloaddition was observed. Instead, epoxide opened alkyne *rac*-**257** was isolated in 92% yield (Scheme 60). The relative configuration of *rac*-**257** was supported by analysis of the ^3J coupling constants in the ^{1}H NMR spectrum of the cyclohexa-2,4-diene. A large ^3J coupling constant was noted between C(1)*H* and C(6)*H* within *rac*-**257** ($^3J_{1,6}$ = 11.7 Hz), indicative of a pseudo axial-axial relationship between these two protons and hence with transdiaxial epoxide opening.

In an attempt to force the cycloaddition, the ring opened product was heated in a variety of further solvents (dichloromethane, benzene, toluene) but no cycloaddition (or further transformation) was observed (Scheme 60).

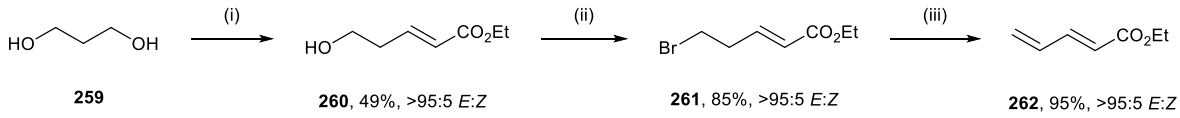


Scheme 60: Ring-opening with **256**. *Reagents and conditions:* (i) MeOH, 65 °C, 48 h.

5.8.2 *Introduction of EWG*

It was postulated that the increased conformational flexibility of the homo system increased the $\Delta S^{\ddagger}$ of the reaction, and/or the geometric constraints result in poorer overlap thus resulting in an increase in $\Delta H^{\ddagger}$. In order to facilitate the reaction, the LUMO of the dienophile was lowered by placing an electron withdrawing group on the olefin in order to make $\Delta H^{\ddagger}$ more favourable.

The synthesis of the requisite amine began with a standard oxidation/olefination of propane-1,3-diol to give unsaturated ester **260** in 49% yield. Confirmation of the double bond geometry was based on diagnostic values of the ^{1}H NMR ^{3}J coupling constants between the C(2) and C(3) protons: ^{3}J = 15.7 Hz. The alcohol was simply activated and substituted by bromide to give **261** in 85% yield with no observed olefin degradation (^{3}J = 15.7 Hz, >95:5 *E*:*Z*). Attempts to substitute the bromide with methylamine resulted in elimination to the known conjugated ester **262** in 95% isolated yield. The less basic nucleophilic nitrogen source, potassium phthalimide, was also trialled, however the elimination product was again obtained as the major product in 89% isolated yield (Scheme 61).

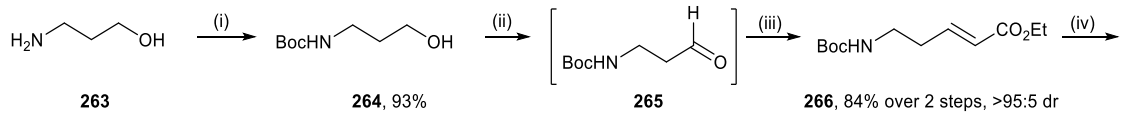


259 **260**, 49%, >95:5 *E*:*Z* **261**, 85%, >95:5 *E*:*Z* **262**, 95%, >95:5 *E*:*Z*

Scheme 61: Failed formation of ethyl ester activated substrate. *Reagents and Conditions*: (i) Activated MnO_2, $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, rt, 16 h; (ii) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 15 min; (iii) $MeNH_2$, THF, rt, 3 h or potassium phthalimide, THF, rt, 3 h.

In order to circumvent the observed elimination during substitution, the synthetic route was altered to start from 3-aminopropanol **263**, which has the nitrogen already installed. Initial *N*-Boc protection with Boc_2O and Et_3N gave **264** in 93% yield. Swern oxidation and concomitant olefination via a Wittig reaction gave unsaturated ester **266** in 86% yield. Confirmation of the double bond geometry was based on diagnostic values of the ^{1}H NMR ^{3}J coupling constants

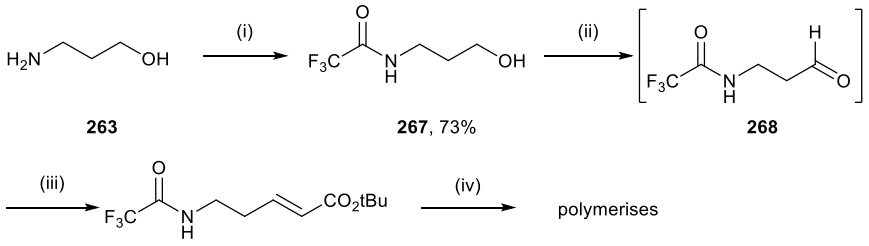
between the C(2) and C(3) protons: ^{3}J = 15.7 Hz. Unfortunately, deprotection of the nitrogen resulted in both a complex mixture and mass loss, consistent with polymerisation (Scheme 62).



263 **264**, 93% **265** **266**, 84% over 2 steps, >95:5 dr

Scheme 62: Failed synthesis of ethyl ester activated olefin. *Reagents and conditions:* (i) Boc_2O, Et_3N, CH_2Cl_2 rt, 20 min; (ii) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, –78 °C to rt, 30 min; (iii) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, rt, 16 h; (iv) TFA, CH_2Cl_2, 0 °C to rt, 1 h.

In an attempt to circumvent the polymerisation, it was proposed to replace the ethyl ester with the more sterically hindered *tert*-butyl ester. To avoid possible complications regarding the selective removal of the *N*-Boc in the presence of an *O*-^{t}Bu, the nitrogen protecting group was switched to trifluoroacetate. Protection of **263** with ethyl trifluoroacetate in MeOH gave **267** in 73% yield. Swern oxidation and concomitant olefination via a Wittig reaction gave unsaturated ester **269** in 75% yield over 2 steps. Confirmation of the double bond geometry was based on diagnostic values of the ^{1}H NMR ^{3}J coupling constants between the C(2) and C(3) protons:^{3}J = 15.7 Hz. Unfortunately, deprotection of the nitrogen again resulted in polymerisation (Scheme 63).



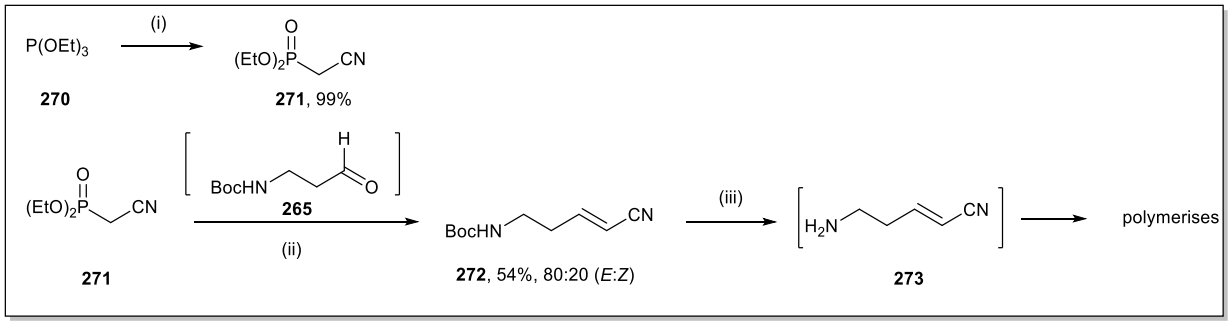
263 **267**, 73% **268**

269, 75% over 2 steps, >95:5 dr

Scheme 63: Failed synthesis of *tert*-butyl ester activated olefin. *Reagents and conditions:* (i) Ethyl trifluroacetate, MeOH, 0 °C, 2 h (ii) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, –78 °C to rt, 30 min; (iii) $Ph_3P{=}CHCO_2tBu$, CH_2Cl_2, rt, 16 h; (iv) K_2CO_3, MeOH:H_2O (12:1), 70 °C, 2 h.

As a further attempt to avoid polymerisation, it was proposed that a nitrile could be a suitable electron withdrawing group which would be less prone to polymerisation than the ester. Phosphonate **271** was synthesised via an Arbusov reaction in 99% yield from triethyl phosphite, which allowed vinyl nitrile **272** to be formed via a HWE from aldehyde **265** (previously synthesised in Scheme 62). The reaction was poorly selective (53:47 *E*:*Z*), and this ratio proved to be

independent of reaction temperature (Table 31). The olefin isomers were not separable by silica chromatography, but $AgNO_3$ doped silica (created by dissolving $AgNO_3$ in methanol and adding the solution to silica followed by evaporation and drying)[79,80] allowed partial separation of the isomers to 80:20 (*E*:*Z*). Deprotection resulted in unstable amine **273**, which was found to polymerise within <10 min.



Reagents and conditions: (i) chloroacetonitrile, 150 °C, 3.5 h; (ii) NaH, THF, **n** °C, 3 h; (iii) TFA, CH_2Cl_2, 20 min, rt.

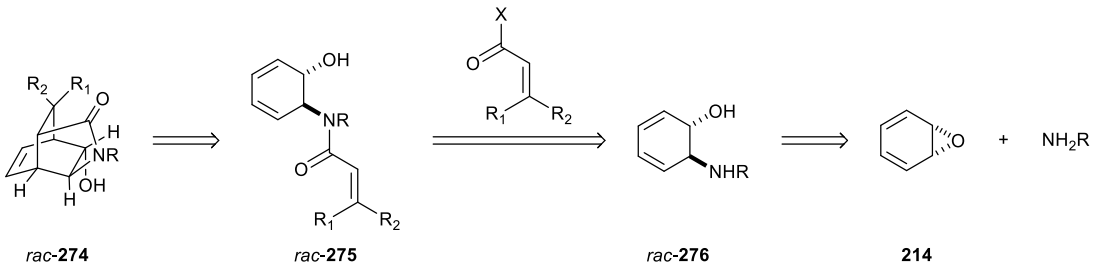
Temperature (°C)	*E*:*Z*	Conversion (%)	yield
0	53:47	10	<5%, 80:20 (*E*:*Z*)
25	53:47	100	53%, 80:20 (*E*:*Z*)
70	54:46	100	54%, 80:20 (*E*:*Z*)

Table 31: Nitrile synthesis via HWE.

As such, this approach to 6-ring synthesis was abandoned and focus returned to the 5-membered ring system.

5.9 Substituted Allyl Motif

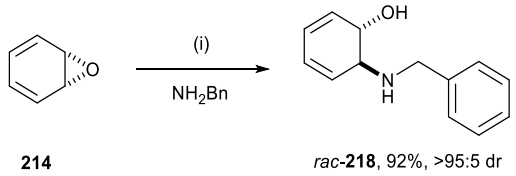
Attention now turned to the introduction of carbonyl derivatives at C(1′) which would act as synthetic handles for the future modification of such structures. Given the polymerisation issues observed with amino-unsaturated esters earlier in this work, a new synthetic route was proposed for their introduction. It was proposed that a substituted allyl motif could be introduced via a carbonyl derivative, to the secondary amine *rac*-**276** obtained via ring opening of benzene oxide with a primary amine. Once formed, this motif *rac*-**275** would allow intramolecular cycloaddition to product *rac*-**274** (Scheme 64).



Scheme 64: Proposed Retrosynthesis of substituted motif *rac*-**274**.

Initial epoxide opening with *N*-Bn amine worked well, resulting in ring opened product *rac*-**218** in 92% (Scheme 65).[110]

The relative configuration of the known compound *rac*-**275** was supported by analysis of the ^{3}J coupling constants in the ^{1}H NMR spectrum of the cyclohexa-2,4-diene. A large ^{3}J coupling constant was noted between C(1)*H* and C(2)*H* within *rac*-**275** ($^{3}J_{1,2}$ = 11.4 Hz), indicative of a pseudo axial-axial relationship between these two protons and hence with transdiaxial epoxide opening. This scalar coupling data was consistent with that observed previously for the transdiaxial epoxide openings.

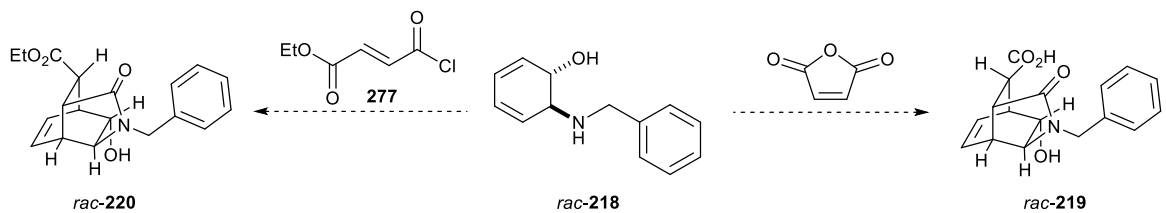


214 *rac*-**218**, 92%, >95:5 dr

Scheme 65: Epoxide opening with benzyl amine. *Reagents and Conditions*: (i) MeOH, 65 °C, 48 h.

5.10 Dienophile Addition and Subsequent Cycloaddition

Two different electrophilic groups were chosen to incorporate the dienophile: the acid chloride derived from mono ethyl fumaric acid **277**, and maleic anhydride (Scheme 66). It was hoped that use of these pseudo isomeric carbonyls would result in pseudo epimeric compounds *rac*-**220** and *rac*-**219**. This would be good evidence that the reaction occurs via a cycloaddition, as formation of a single diastereomer could only occur through a stereospecific pathway.



rac-**220** *rac*-**218** *rac*-**219**

Scheme 66: Proposed synthesis of lactams *rac*-**220** and *rac*-**219**.

Addition of maleic anhydride occurred to give *rac*-**219** as a single product in 85% isolated yield. Likewise, addition of acid chloride **227** gave *rac*-**220** as a single product in 98% yield (Scheme 67). The structures of both compounds were validated by ^{1}H and ^{13}C NMR analyses.

Regioselectivity - Addition of the electrophilic groups could occur onto either the oxygen or nitrogen in *rac*-**218** which would result in either the corresponding γ-lactam or γ-lactones. Evidence for the regioselective formation of the γ-lactam is as follows: The HMBC of both compounds showed connectivity between the NC*H*$_2$Ph protons and *C*(2), HMBC connectivity between the C(7a)H and *C*(2) and reciprocal nOe enhancement between NC*H*$_2$Ph and C(7a)*H*. Hence all 3 groups attached to the nitrogen show connectivity to each other; The IR stretches for γ-lactams and γ-lactones are known to be significantly different. The recorded IR stretches for *rac*-**220** and *rac*-**219** were 1721 cm^{-1} and 1718 cm^{-1}, which is consistent with that expected for γ-lactams. Hence the data recorded for *rac*-**220** and *rac*-**219** is consistent with the formation of a γ-lactam, and not of a γ-lactone.

Stereospecificity - Within compound *rac*-**220**, a significant, reciprocal nOe correlation was noted between C(1′)*H* and C(7)*H*. Within compound *rac*-**219**, no such nOe correlation was observed (Figure 39). The same nOe enhancements were present as in the previously synthesised compound *rac*-**215** (in which the allyl group is known to be on the nitrogen).

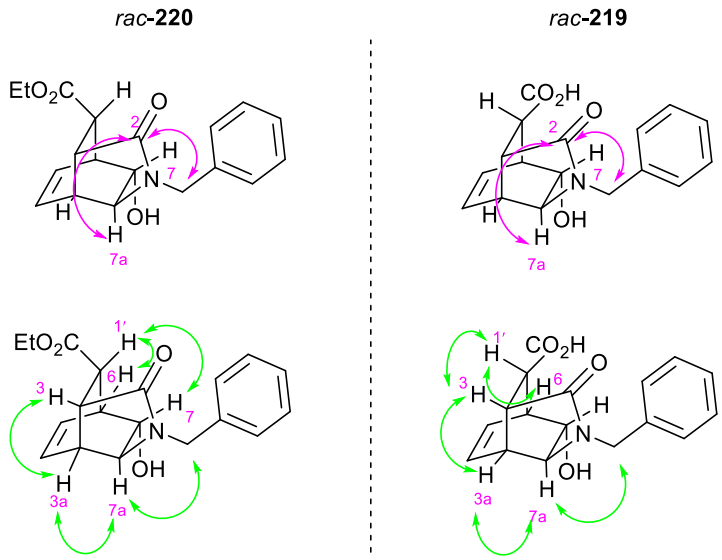
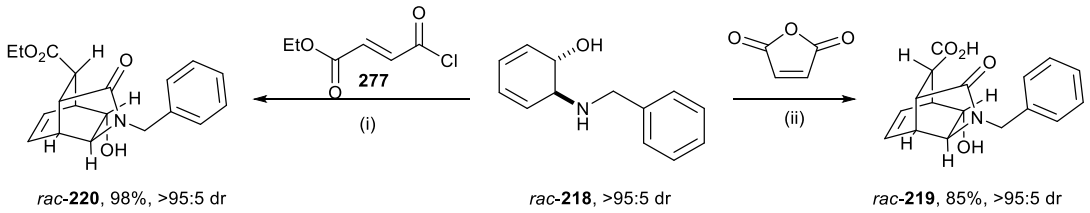


Figure 39: Selected HMBC correlations (magenta arrows) and reciprocal nOe enhancements (green arrows) observed for *rac*-**220** and *rac*-**219**.

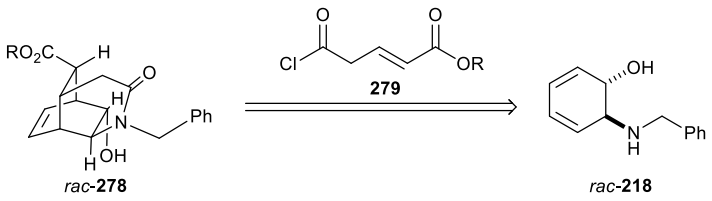


Scheme 67: Addition of dienophiles. *Reagents and Conditions*: (i) Et_3N, CH_2Cl_2, rt, 15 min; (ii) CH_2Cl_2, rt, 15 min.

The observed exo product *rac*-**219** is further evidence that the cycloaddition occurs *after* the ring opening of the anhydride.

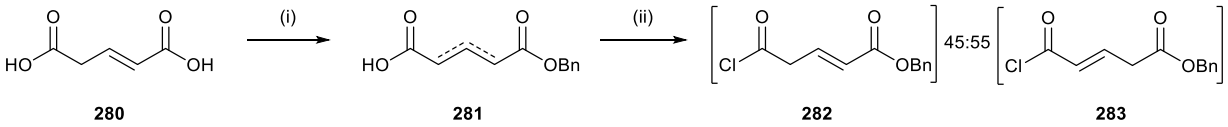
5.11 Application to 6 membered ring synthesis

The possibility of using this methodology to form a 6 membered ring *rac*-**278** using a homoallyl motif was then explored (Scheme 68).



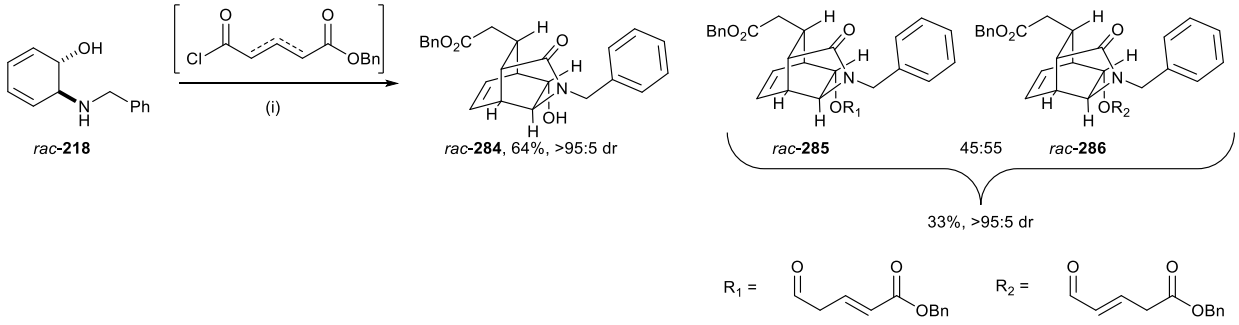
Scheme 68: Proposed Retrosynthesis of lactam *rac*-**278**.

In the event, acid chloride **279** proved quite challenging to synthesise. The highest yielding synthesis involved a poorly selective mono benzylation of commercially available glutaconic acid **280** to a mixture of inseparable mono-esters **281**, followed by conversion of the mixture to the corresponding acid chlorides with $SOCl_2$. The acid chloride was used as the 45:55 mix of stereoisomers **282** and **283** as a proof of concept (Scheme 69).



Scheme 69: Synthesis of acid chlorides **282** and **283**. *Reagents and Conditions*: (i) Dicyclohexylamine, BnBr, DMF, 80 °C; (ii) $SOCl_2$, 50 °C, 20 min.

It was hoped that reaction with ring opened product *rac*-**218** in the conditions used previously would give a 45:55 mix of 5 and 6 membered rings. Reaction with 1.5 equiv. acid chloride and 3.0 equiv. NEt_3 resulted in the expected 5 membered ring *rac*-**284** in 64% yield, but also the ester of *rac*-**284** (as a 45:55 mixture of *rac*-**285** and *rac*-**286**) in 33% yield. No 6 ring formation was observed (Scheme 70).



Scheme 70: Synthesis of lactams *rac*-**284**. *Reagents and Conditions*: (i) Et_3N, CH_2Cl_2, rt, 15 min.

A possible explanation for this observation is that the acylation goes to full conversion using up 1 equivalent of the acid chloride. The 6 ring is presumably slow to form, and so the intermediate unsaturated ester has the chance to isomerise under the reaction conditions to the unsaturated amide and this is subsequently trapped out by the cycloaddition to the 5 ring. The remaining 0.5 equivalent of acid chloride is then picked up by the hydroxyl. In effect the reaction seemingly operates a isomerisation of the acid chloride mixture, forming the 5-membered ring exclusively.

The structures of compounds *rac*-**284**, *rac*-**285**, and *rac*-**286** were validated by ^{1}H and ^{13}C NMR analyses.

Regioselectivity – As before, addition of the electrophilic acid chloride could occur onto either the oxygen or nitrogen in *rac*-**218** which would result in either the corresponding γ-lactam or γ-lactones. Evidence for the regioselective formation of the γ-lactam is as follows: The HMBC of both compounds showed connectivity between the NC*H*$_2$Ph protons and *C*(2), HMBC connectivity between the C(7a)H and *C*(2) and reciprocal nOe enhancement between NC*H*$_2$Ph and C(7a)*H*. Hence all 3 groups attached to the nitrogen show connectivity to each other; The IR

stretches for γ-lactams and γ-lactones are known to be significantly different. The recorded IR stretches were 1722 cm^{-1} and 1710 cm^{-1}, which is consistent with that expected for γ-lactams. Hence the data recorded for *rac*-**284**-**285** is consistent with the formation of a γ-lactam, and not of a γ-lactone.

Five Ring Evidence - The ester *C*(O) showed HMBC connectivity to the CH_2 at C(1′), and no connectivity was observed between CH_2 at C(1′) and *C*(2).

Stereospecificity - Significant, reciprocal nOe correlations were noted between C(1′)*H* and C(7)*H* (Figure 40). The same nOe enhancements were present as in the previously synthesised compound *rac*-**215** (in which the allyl group is known to be on the nitrogen).

Location of R group - In *rac*-**285** and *rac*-**286**, there was HMBC connectivity between C(7)*H* and C(1″).

Six ring formation via this method was not investigated further.

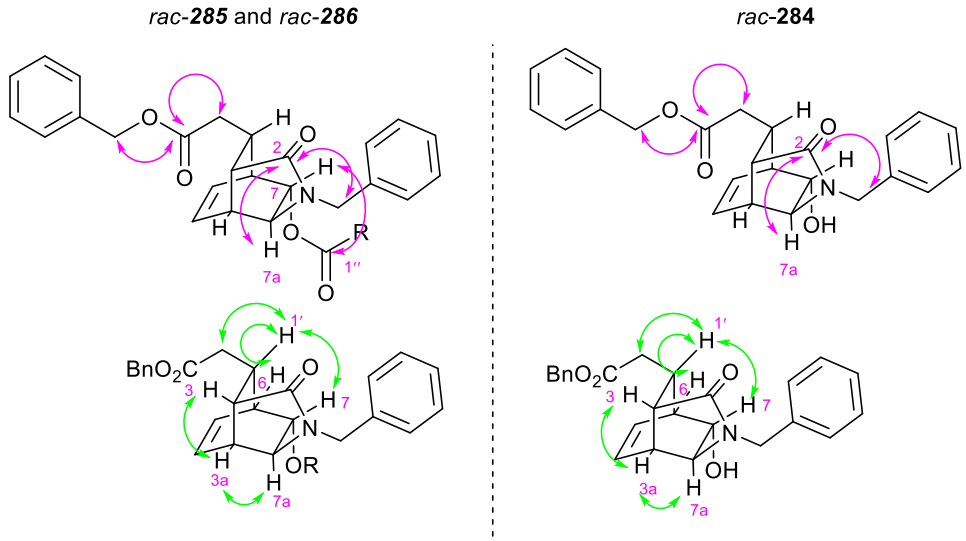
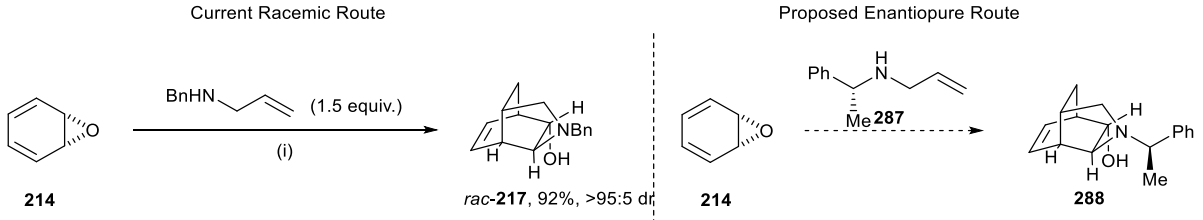


Figure 40: Selected HMBC correlations (magenta arrows) and reciprocal nOe enhancements (green arrows) observed for *rac*-**284**, *rac*-**285**, and *rac*-**286**.

5.12 Enantiopure Route

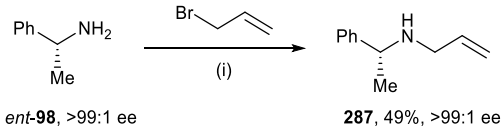
In order to increase the applicability of the reaction to natural product synthesis, it was hoped that the use of enantiopure amines, in analogous reactions to those explored, would allow access non-racemic tricycles (Scheme 71).



Scheme 71: Proposed Enantiopure Route using previous racemic conditions. *Reagents and conditions*: (i) MeOH, 65 °C, 48 h.

5.12.1 *Amine Addition*

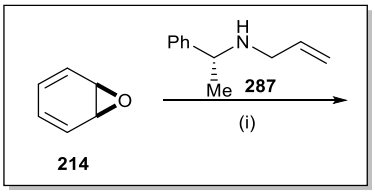
Enantiopure allyl amine (*R*)-*N*-(α-methylbenzyl)allylamine **287** was the chiral amine of choice. This was simply synthesised from (*R*)-*N*-(α-methylbenzyl)amine in 49% yield (Scheme 72).



Scheme 72: Synthesis of (*R*)-*N*-Allyl-*N*-(α-methylbenzyl)amine. *Reagents and conditions*: (i) ^{n}BuLi, THF, 0 °C, 2 h.

Addition of **287** to benzene oxide **214** in the same conditions that had worked with *N*-Bn allyl amine, resulted with no ring opening observed. Increasing to 10 equiv. amine still gave zero conversion (Table 32).

The ring opening of benzene oxide by amine nucleophiles has been optimised in previous work,[111] however there were a few remaining possible modifications that could be made. The first was addition of ½ equiv. phenol as a possible acid catalyst. Further to this, a range of Lewis acid catalysts have previously been trialled, but missing from the list was Ytterbium(III) trifluoromethanesulfonate. The third modification tried was deprotonation of the amine with NaH, prior to addition to the epoxide. In no case was any addition observed (Table 32), which indicates the addition is sensitive to sterics.



Reagents and conditions: (i) MeOH (1.0 M), 65 °C, **conditions**.

Amine Equiv.	Modification	Conversion
2.0	-	0
10	-	0
2.0	0.5 equiv. phenol	0
2.0	$Yb(OTf)_3$	0
2.0	NaH deprotonation	0

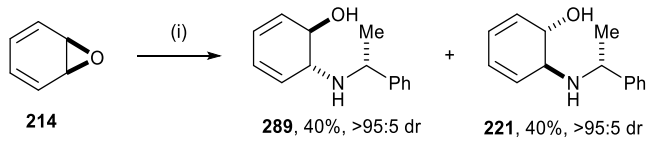
Table 32: Epoxide opening with (*R*)-*N*-Allyl-*N*-(α-methylbenzyl)amine.

Given the lack of reactivity observed, it was postulated that the α-methyl was simply too bulky to allow addition to the epoxide (given the ease of addition of *N*Bn allyl amine (Scheme 56)).[113,114]

5.13 Ring opening with (*R*)-*N*-(α-methylbenzyl)amine

One-pot ring-opening/cycloaddition was not investigated further, instead it was proposed to utilise the reaction explored for the addition of the motif in a second step as shown previously (Scheme 67). The substituted allyl motif would be introduced via an a carbonyl derivative, to the secondary amine obtained via ring opening of benzene oxide with a enantiopure primary amine. Once formed, this motif would allow intramolecular cycloaddition.

Initial addition of primary chiral amine (*R*)-*N*-(α-methylbenzyl)amine proceed to 95% conversion, and an isolated yield of 40% of both diastereomers **289** and **221** (Scheme 73).



214 **289**, 40%, >95:5 dr **221**, 40%, >95:5 dr

Scheme 73: *Reagents and conditions:* (i) MeOH, 65 °C, 48 h.

The diastereomers were assigned by analogy to those characterised by Da Silva Pinto et al.[110] through comparison of the compound's polarity and ^{1}H NMR spectra: In the pair of diastereomers characterised by Da Silva Pinto et al.,[110] there is a large difference in the magnitude of the scalar coupling between C(1)H and C(2)H in **231** and **290**. This is accompanied by a consistent pattern in the peak position of key protons (C(2)*H*, C(α)*Me* and C(α)*H*). The most polar compound correlates with the lower magnitude of scalar coupling; In the pair observed here, there is again a large difference in the magnitude of the scalar coupling between C(1)*H* and C(2)*H* in **289** and **221**. This is again accompanied by a consistent pattern in the peak position of key protons (C(2)*H*, C(α)*Me* and C(α)*H*). Further to this, the most polar compound also correlates with the lower magnitude of scalar coupling. On the basis of this evidence, the 2 diastereomers were assigned (Figure 41).

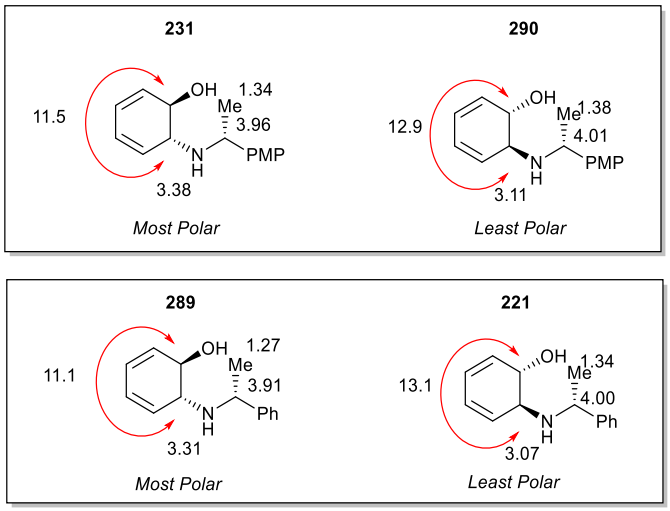
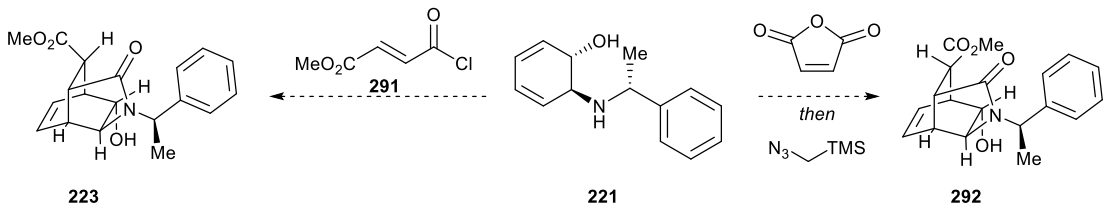


Figure 41: Comparison of (*R*)-*N*-(α-methylaryl)amine opened products. Red arrows show scalar coupling (Hz). Proton shifts are shown in ppm.

5.14 Dienophile Addition and Cycloaddition

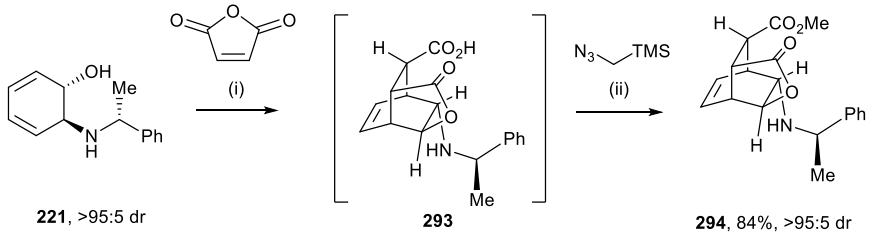
The strategy used for racemic substrate **218** (Scheme 67) was utilised. It was proposed that addition of maleic anhydride then direct conversion of the resultant acid to the mono methyl ester would give the C(1′)H epimer of the product obtained from the addition of the acid chloride derived from mono methyl fumaric acid **291** (Scheme 74).



Scheme 74: Proposed syntheses of epimers **223** and **292**.

5.14.1 *Maleic Anhydride Addition*

Under the conditions previously used on the racemic series (Scheme 67) (CH_2Cl_2, rt), no conversion was observed after 24 h. Addition was complete for the racemic series after 15 min. In order to drive the reaction, the mixture was heated to 40 °C, and stirred for 4 days. This gave **293** as the sole product, which was not isolated but converted directly to the methyl ester with TMS diazomethane to give methyl ester lactone **294** in 84% over the two steps (Scheme 75).



221, >95:5 dr **293** **294**, 84%, >95:5 dr

Scheme 75: Maleic Anhydride addition. *Reagents and conditions:* (i) CH_2Cl_2, 40 °C, 4 days; (ii) Benzene/MeOH (10:1), rt, 2.5 h.

The structure of **294** was validated by ^{1}H and ^{13}C NMR analyses.

Regioselectivity - Addition of the maleic anhydride could occur onto either the oxygen or nitrogen in **221** which would result in either the corresponding γ-lactam or γ-lactones. Evidence for the regioselective formation of the γ-lactone is as follows: The shift of C(7a)*H* was much higher than that observed for the lactams. This proton showed HMBC connectivity with *C*(2). There was no connectivity between the C(α)*H* and the *C*(2), but HMBC connectivity was observed between C(α)*H* and C(7)*H*. nOe correlation was also noted between C(α)*H* and C(6)*H* and C(7)*H*, with no correlation between C(α)*H* and C(7a)*H*. The recorded IR stretch for the **294** was 1762 cm^{-1}, significantly higher that that of the γ-lactams. Hence the data recorded for **294** is consistent with the formation of a γ-lactone, and not of a γ-lactam.

Stereospecificity - Within compound **294**, no reciprocal nOe correlation was noted between C(1′)*H* and C(7)*H* (Figure 42). The same nOe enhancements were present as in the previously synthesised compound *rac*-**215**.

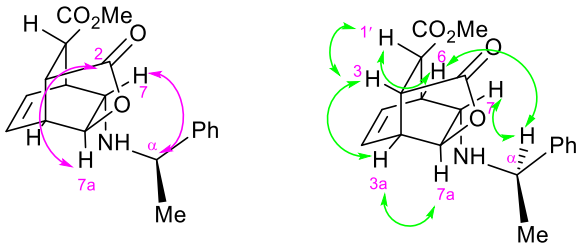
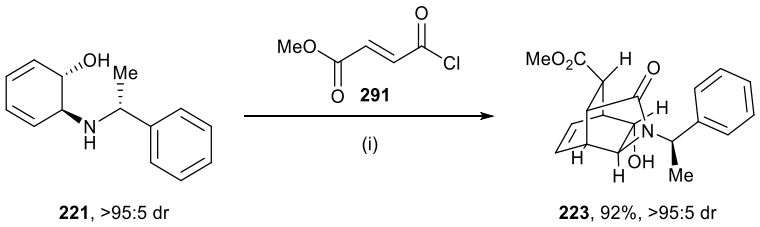


Figure 42: Selected HMBC correlations (magenta arrows) and reciprocal nOe enhancements (green arrows) observed for **294**.

The result of the observed lactone formation is that heating the reaction with the αMe group leads to a complete switch in product selectivity from the γ-lactam to the γ-lactone. The implication of this is that one of (or both) of the steps (acylation and cycloaddition) is reversible under the reaction conditions.

5.14.2 *Fumarate Derived Acid Chloride*

The reactivity of the acid chloride derived from mono methyl fumaric acid **291** was then explored. Again, reaction monitoring showed the reaction to be slower than the racemic analogue, however after 1 h at rt the reaction did reach full conversion to give lactam **223** as a single product in 92% (Scheme 76).



Scheme 76: Synthesis of lactam **223**. *Reagents and Conditions*: (i) Et_3N, CH_2Cl_2, rt, 1 h.

The structure of **223** was validated by ^{1}H and ^{13}C NMR analyses.

Regioselectivity - Addition of the acid chloride could occur onto either the oxygen or nitrogen in **221** which would result in either the corresponding γ-lactam or γ-lactones. Evidence for the regioselective formation of the γ-lactam is as follows: The HMBC showed connectivity between C(α)*H* proton and *C*(2), HMBC connectivity between the C(7a)*H* and *C*(2), and reciprocal nOe

enhancement between C(α)H and C(7a)*H*. Hence all 3 groups attached to the nitrogen show connectivity to each other. The recorded IR stretch for **223** was 1722 cm^{-1} which is consistent with that expected for a γ-lactam. Hence the data recorded for **223** is consistent with the formation of a γ-lactam, and not of a γ-lactone.

Stereospecificity - Within compound **223**, a significant, reciprocal nOe correlation was noted between C(1′)*H* and C(7)*H*. The same nOe enhancements were present as in the previously synthesised compound *rac*-**215** (Figure 43).

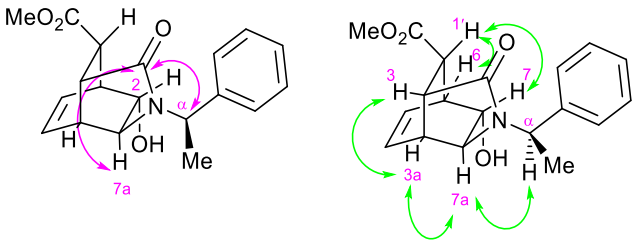


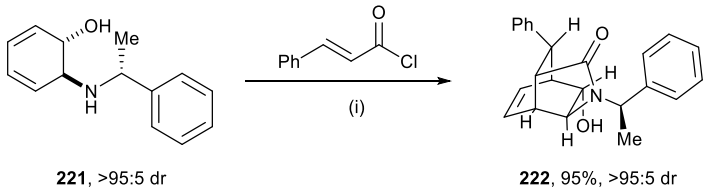
Figure 43: Selected HMBC correlations (magenta arrows) and reciprocal nOe enhancements (green arrows) observed for **215**.

5.14.3 *Cinnamoyl Chloride*

In order to expand the scope of the reaction away from activated olefins, (*E*)-cinnamoyl chloride was trialled. Addition gave lactam **222** as a single product in 95% (Scheme 77). The structure of compound **222** was validated by ^{1}H and ^{13}C NMR analyses.

Regioselectivity - Evidence for the regioselective formation of the γ-lactam is as follows: The HMBC showed connectivity between C(α)*H* proton and *C*(2), HMBC connectivity between the C(7a)*H* and *C*(2), and reciprocal nOe enhancement between C(α)H and C(7a)*H*. Hence all 3 groups attached to the nitrogen show connectivity to each other. The recorded IR stretch for **222** was 1719 cm^{-1} which is consistent with that expected for a γ-lactam. Hence the data recorded for **222** is consistent with the formation of a γ-lactam, and not of a γ-lactone.

Stereospecificity - Within compound **222**, a significant, reciprocal nOe correlation was noted between C(1′)*H* and C(7)*H*. The same nOe enhancements were present as in the previously synthesised compound *rac*-**215** (Figure 44).



221, >95:5 dr **222**, 95%, >95:5 dr

Scheme 77: Addition of cinnamoyl chloride. *Reagents and Conditions*: (i) Et_3N, CH_2Cl_2, rt, 1 h.

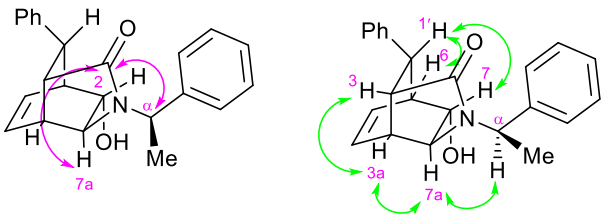


Figure 44: Selected HMBC correlations (magenta arrows) and reciprocal nOe enhancements (green arrows) observed for **222**.

5.15 Conclusion and Future Work

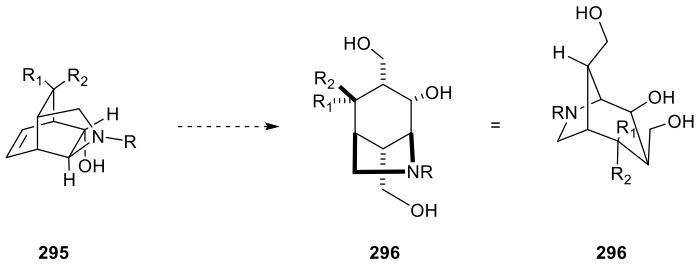
The initially discovered Diels-Alder reaction has been optimised to reliably give 3,6-methanoindan-7-ols from both primary and secondary allyl amines. The reaction has been expanded to allow a further stereogenic centre to be set at C(1′) with >95:5 dr, which would allow further manipulation and modification of the resulting motif.

An enantiopure series has been explored, and the reaction has been discovered to give both the γ-lactam and γ-lactone.

Significant attempts had been made to allow 4,7-methanoquinolin-8-ol formation, but none could be realised.

Future Work will involve further investigations into controlling the γ-lactam/γ-lactone selectivity, and will no doubt include probing of the reaction mechanism and possible reversibility therein.

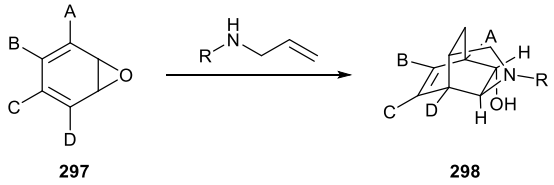
Hydroxylated tropanes are a significant class of alkaloid, which comprise a number of members,[35] and ozonolysis of the olefin within **295** which would lead to the pseudo-hydroxytropane structure **296** (Scheme 78).



295 **296** **296**

Scheme 78: Proposed ozonolysis to pseudo-hydroxytropane **296**.

Further extension of this work would involve the synthesis of substituted benzene oxides **297** which will allow the formation of (poly)-substituted products (Scheme 79).



297 **298**

Scheme 79: Proposed utility of substituted benzene oxide **297**.

Chapter 6 Experimental

6.1 Experimental for Chapter 2

(*S*)-*N*-Benzyl-*N*-(α-methylbenzyl)amine 66

Benzaldehyde (83.8 mL, 826 mmol) was added to a stirred solution of (S)-α-methylbenzylamine (100 mL, 786 mmol) in EtOH (500 mL). The resultant mixture was stirred at rt for 2 h before being cooled to 0 °C. $NaBH_4$ (29.7 g, 786 mmol) was then added and the resultant suspension was stirred at rt for 48 h. The resultant mixture was concentrated in vacuo and the residue was partitioned between 10% aq citric acid solution and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2, and the combined aqueous extracts were neutralised with 2.0 M aq NaOH, extracted with CH_2Cl_2, washed with brine, then dried and concentrated in vacuo to give **66** as a yellow oil (128 g, 78%, >95:5 dr); $[\alpha]_D^{25}$ −42.6 (c 1.0 in $CHCl_3$); {lit.[115] $[\alpha]_D^{25}$ −52.1 (c 1.50 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.42 (3H, d, *J* 6.6, C(α)Me), 1.63 (1H, br s, N*H*), 3.65 (1H, d, *J* 13.2, NC$H_A$$H_B$Ph), 3.72 (1H, d, *J* 13.2, NCH$_A$$H_B$Ph), 3.88 (1H, q, *J* 6.6, C(α)*H*), 7.26-7.43 (10H, m, *Ph*).

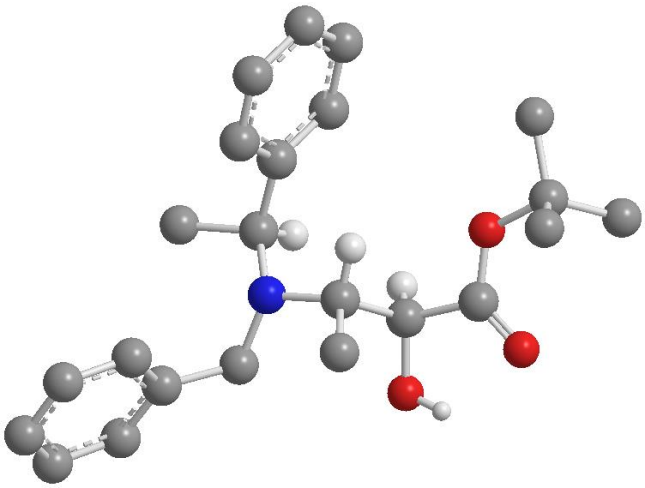
tert-Butyl crotonate 67

Condensed isobutylene (550 mL, 5.8 mol) at –78 °C was added to a stirred solution of crotonic acid (50 g, 0.58 mol) and conc aq H_2SO_4 (5 mL) in CH_2Cl_2 (500 mL) at 0 °C, and the resultant mixture was stirred at 0 °C for 1 h, then allowed to warm to rt and stirred at rt for 48 h. 2 M aq NaOH solution was then added until pH >7 was achieved. The resultant mixture was then extracted with CH_2Cl_2 (2 × 300 mL), and the combined organics were washed with brine (500 mL), then dried ($MgSO_4$) and concentrated in vacuo to give **67** as a pale yellow oil (70.8 g, 86%, >95:5 dr [(*E*):(*Z*) ratio]); δ_H (400 MHz, $CDCl_3$) 1.47 (9H, s, C*Me*$_3$), 1.84 (3H, dd, *J* 6.9, 1.7, C(4)*H*$_3$), 5.76 (1H, dq, *J* 15.5, 1.7, C(2)*H*), 6.86 (1H, dq, *J* 15.5, 6.9, C(3)*H*).[115]

***tert*-Butyl (2*S*,3*S*,α*S*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]butanoate 68**

^{n}BuLi (2.5 M in hexanes, 43.6 mL, 109 mmol) was added dropwise to a stirred solution of (*S*)-**66** (23.8 g, 113 mmol, >98% de) in THF (390 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of **67** (10.0 g, 70.4 mmol) in THF (200 mL) was then added via cannula and the resultant mixture was stirred at −78 °C for 2 h. (+)-CSO (25.9 g, 113 mmol) was then added and the resultant mixture was allowed to warm to rt over 16 h. Satd aq NH_4Cl (60 mL) was added and the resultant mixture was concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (1 L) and 10% aq citric acid (1 L), the aqueous layer was extracted with CH_2Cl_2 (3 × 500 mL), and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (1 L) and brine (1 L), then dried ($MgSO_4$) and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **68** as a white solid (24.7 g, 95%, >95:5 dr); mp 83-84 °C; {lit.[116] mp 87-88 °C}; $[\alpha]_D^{25}$ +21.2 (*c* 1.0 in $CHCl_3$); {lit.[52] $[\alpha]_D^{25}$ +34.7 (*c* 1.05 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.07 (3H, d, *J* 7.0, C(4)H_3), 1.31 (3H, d, *J* 6.9, C(α)*Me*), 1.36 (9H, s, CMe_3), 2.90 (1H, br s, O*H*), 3.25 (1H, qd, *J* 7.0, 2.6, C(3)*H*), 3.87 (1H, d, *J* 14.8, NCH_AH_BPh), 3.95–4.05 (3H, m, C(2)*H*, C(α)*H*, NCH_AH_BPh)), 7.17–7.52 (10H, m, *Ph*).

X-ray crystal structure determination for 68



Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **68** [$C_{23}H_{31}NO_3$]: M = 369.50, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 21.2549(3) Å, b = 17.2838(2) Å, c = 5.91513(9) Å, V = 2173.02(5) Å^3, Z = 4, μ= 0.584 mm^{-1}, colourless block, crystal dimensions = 0.14 × 0.17 × 0.18 mm^3. A total of 4548 unique reflections were measured for $4 < \theta < 76$ and 3805 reflections were used in the refinement. The final parameters were wR_2 = 0.173 and R_1 = 0.054 [I>–3.0σ(I)], with Flack enantiopole = +0.1(4).[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

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[1]Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.
[2] Flack, H. D.; Bernardinelli, G. *Acta. Crystallogr., Sect. A* **1999**, *55*, 908.

(2*S*,3*R*,6*S*,1′*E*,3′*E*,5′*E*)-2-Methyl-6-(deca-1′,3′,5′-trienyl)piperidin-3-ol [Microcosamine A] 70

Step 1: NaH (60% dispersion in mineral oil, 19 mg, 0.48 mmol) was stirred in THF (0.82 mL) for 5 min. The resultant suspension was then cooled to 0 °C, a solution of **158** (175 mg, 0.440 mmol) in THF (2.16 mL) was added, and the resultant solution was stirred at rt for 15 min. A solution of (*E*,*E*)-2,4-nonadienal (89 mg, 0.64 mmol) in THF (1.36 mL) was then added, and the resultant solution was stirred at rt for 1 h. The resultant solution was then heated to 72 ºC, and stirred at 72 ºC for 12 h. The resultant solution was allowed to cool to rt, then poured into a mixture of satd aq brine (9 mL) and H_2O (9 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL), then the combined organics were dried ($MgSO_4$) and concentrated in vacuo. The residue was dissolved in DMF (1.0 mL), and satd aq $NaHSO_3$ (3.0 mL) was added. The resultant suspension was stirred at rt for 10 min, then diluted with H_2O (3 mL). The aqueous layer was extracted with Et_2O (3 mL), and the combined organics were washed with H_2O (2 × 3 mL, then 1 mL), then dried (Na_2SO_4) and concentrated in vacuo.

Step 2: The residue from the previous step was dissolved in CH_2Cl_2 (12.5 mL) and the resultant solution was cooled to 0 ºC. TFA (6.4 mL) was added dropwise, and the resultant solution was stirred at 0 ºC for 10 min. The resultant solution was then concentrated in vacuo.

Step 3: The residue from the previous step was dissolved in CH_2Cl_2 (16.0 mL); the resultant solution was conc. aq HCl (2.4 mL) were then simultaneously added to a stirred suspension of $NaBH_3CN$ (324 mg, 5.16 mmol) in EtOH (32 mL) at 0 ºC. The resultant suspension was stirred at 0 ºC for 15 min, then further portions of $NaBH_3CN$ (161 mg, 2.56 mmol) and conc. aq HCl (1.1 mL) were added sequentially. The resultant suspension was stirred at 0 ºC for 15 min, then H_2O (10 mL) was added. The resultant mixture was poured into a mixture of satd aq $NaHCO_3$ (160 mL) and H_2O (160 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL), then the combined organics were dried (Na_2SO_4) and concentrated in vacuo. The residue was then dissolved in 1.25 M methanolic HCl (3.0 mL) at rt, and the resultant solution was stirred at rt for 12 h. The resultant solution was then poured into 1 M aq KOH (6.5 mL), the aqueous layer was

extracted with $CHCl_3$/^{i}PrOH (v:v, 3:1, 4 × 6.5 mL), then the combined organics were dried (Na_2SO_4) and concentrated in vacuo. Purification via flash column chromatography (eluent $CHCl_3$/35% aq NH_4OH, 97:3, increased to $CHCl_3$/MeOH/35% aq NH_4OH, 190:10:5) gave a yellow oil (R_f = 0.51 in $CHCl_3$/MeOH/35% aq NH_4OH, 190:10:5). This was dissolved in 6 M aq HCl (2.0 mL) and the resultant solution was washed with Et_2O (3 × 2 mL), then basified by the addition of 2 M aq NaOH until pH >14 was achieved. The resultant solution was extracted with Et_2O (3 × 3 mL), then the combined organics were dried (Na_2SO_4) and concentrated in vacuo to give **70** as a white solid (42 mg, 38%, >95:5 dr); mp 115–117 °C; $[\alpha]_D^{25}$ +2.8 (*c* 0.1 in MeOH); $[\alpha]_D^{25}$ +3.9 (*c* 0.5 in MeOH); $[\alpha]_D^{25}$ +4.2 (*c* 1.0 in MeOH); $[\alpha]_D^{20}$ +4.5 (*c* 1.0 in MeOH); ν_{max} 3659, 3268, 2981, 2929, 1674; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.2, C(10′)H_3), 1.20 (3H, d, *J* 6.2, C(2)*Me*), 1.26–1.41 (6H, m, C(4)H_A, C(5)H_A, C(8′)H_2, C(9′)H_2), 1.71–1.75 (1H, m, C(5)H_B), 2.00–2.13 (3H, m, C(4)H_B, C(7′)H_2), 2.53 (1H, dq, *J* 8.8, 6.2, C(2)*H*), 3.11–3.22 (2H, m, C(3)*H*, C(6)*H*), 5.60 (1H, dd, *J* 15.2, 7.0, C(1′)*H*), 5.69 (1H, dt, *J* 15.1, 7.0, C(6′)*H*), 5.99–6.22 (4H, m, C(2′)*H*–C(5′)*H*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(10′)), 19.1 (C(2)*Me*), 22.4 (*C*(9′)), 31.6 (*C*(8′)), 32.2 (*C*(5)), 32.6 (*C*(7′)), 34.1 (*C*(4)), 58.6 (*C*(2)), 58.8 (*C*(6)), 73.8 (*C*(3)), 130.1, 130.3, 130.6, 133.1 (*C*(2′-5′)), 135.3 (*C*(1′)), 135.8 (*C*(6′)); *m*/*z* (ESI$^+$) 250 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{28}NO^+$ ([M+H]$^+$) requires 250.2165; found 250.2165.

(+)-Camphorsulfonyloxaziridine [(+)-CSO] 102

$SOCl_2$ (252 mL, 3.44 mol) was added dropwise to a stirred solution of (+)-CSA (200 g, 864 mmol) in $CHCl_3$ (750 mL) and the resultant mixture was heated at reflux for 12 h, then allowed to cool to rt and concentrated in vacuo. The residue was dissolved in $CHCl_3$ (250 mL) and the resultant solution was added dropwise to a stirred solution of conc aq NH_4OH (2.0 L) at 0 °C. The resultant mixture was stirred for 4 h then the aqueous layer was extracted with CH_2Cl_2 (2 × 1.0 L) and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was dissolved in PhMe (500 mL) and Amberlyst® 15 ion exchange resin (12 g) was added to the resultant solution. A Dean-Stark apparatus was fitted to the reaction flask and the reaction mixture was heated at reflux for 4 h before being allowed to cool to rt. The mixture was then filtered

through Celite (eluent CH_2Cl_2) and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (1.5 L) and Aliquat 336 (17.0 g, 42.1 mmol) was added. 2.0 M aq K_2CO_3 (713 mL, 1.43 mol) was added dropwise at 0 °C, maintaining the reaction temperature below 5 °C. $MeCO_3H$ (36% in AcOH, 276 mL, 1.31 mol) was then added dropwise, maintaining the reaction temperature below 5 °C and the resultant mixture was allowed to warm to rt over 8 h. Satd aq Na_2SO_3 (80 mL) and 1.0 M aq NaOH (800 mL) were added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 800 mL) and the combined organic layers were washed with H_2O (200 mL) and satd aq $NaHCO_3$ (400 mL), then dried ($MgSO_4$) and concentrated in vacuo to give **102** as a white solid (141 g, 71 %, >95:5 dr); mp 169–171 °C; {lit.[47] mp 165–167 °C};$[\alpha]_D^{25}$ +40.4 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.03 (3H, s, *Me*$_A$), 1.18 (3H, s, *Me*$_B$), 1.45–1.54 (1H, m, C*H*), 1.78 (1H, d, *J* 15.5, C*H*$_A$H$_B$), 1.89–2.15 (4H, m, 2 × C*H*$_2$), 2.63–2.68 (1H, m, CH$_A$*H*$_B$), 3.10 (1H, d, *J* 14.0, C*H*$_A$H$_B$SO$_2$), 3.27 (1H, d, *J* 14.0, CH$_A$*H*$_B$SO$_2$)

tert-Butyl (2*S*,3*S*,α*S*)-2-methoxymethyeneoxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]butanoate 103

NaH (60% dispersion in mineral oil, 1.24 g, 32.5 mmol) was stirred in THF (35 mL) for 30 min. The resultant suspension was then cooled to 0 °C, a solution of **68** (10.0 g, 27.1 mmol) in THF (100 mL) was added, and the resultant solution was stirred at 0 °C for 30 min. MOMCl (2.45 mL, 32.5 mmol) was then added and the resultant solution was allowed to warm to rt over 12 h. H_2O (100 mL) was then added and the aqueous layer was extracted with Et_2O (2 × 100 mL). The combined organics were washed with brine (50 mL), then dried ($MgSO_4$) and concentrated in vacuo to give **103** as a yellow oil (11.2 g, 99%, >95:5 dr); $[\alpha]_D^{25}$ −3.0 (*c* 1.0 in $CHCl_3$); ν_{max} 2977 (C−H), 1740 (C=O); δ_H (400 MHz, $CDCl_3$) 1.12 (3H, d, *J* 7.0, C(4)*H*$_3$), 1.29 (3H, d, *J* 6.9, C(α)*Me*), 1.35 (9H, s, C*Me*$_3$), 3.29 (1H, qd, *J* 7.0, 3.9, C(3)*H*), 3.35 (3H, s, OCH$_2$O*Me*), 3.87 (1H, d, *J* 15.0, NC*H*$_A$H$_B$Ph), 3.96 (1H, d, *J* 3.9 (C(2)*H*), 3.99 (1H, d, *J* 6.9, C(α)*H*), 4.04 (1H, d, *J* 15.0, NCH$_A$*H*$_B$Ph), 4.60 (2H, s, OC*H*$_2$OMe), 7.16–7.48 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.9 (C(4)),

17.9 (C(α)*Me*), 28.1 (C*Me*$_3$), 50.7 (N*C*H$_2$Ph), 54.6 (C(3)), 56.7 (OCH$_2$O*Me*), 59.3 (*C*(α)), 80.3 (C(2)), 81.0 (*C*Me$_3$), 97.0 (O*C*H$_2$OMe), 126.6, 126.8 (*p-Ph*), 127.9, 128.2, 128.2, 128.4 (*o,m-Ph*), 142.5, 144.5 (*i-Ph*), 171.3 (*C*(1)); *m/z* (ESI$^+$) 414 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{36}NO_4^+$ ([M+H]$^+$) requires 414.2638; found 414.2648.

(4*S*,5*S*,α*S*)-*O*-Methoxymethyl -3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]butanal 105

DIBAL-H (1.0 M in PhMe, 51 mL, 51 mmol) was added to a stirred solution of **103** (7.05 g, 17.1 mmol) in CH_2Cl_2 (170 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 30 min. MeOH (100 mL) was then added, and the resultant solution was allowed to warm to rt before satd aq Rochelle salt (100 mL) and CH_2Cl_2 (100 mL) were added sequentially. The resultant mixture was stirred at rt for 16 h. The aqueous layer was then extracted with CH_2Cl_2 (3 × 100 mL) and the combined organics were washed with brine (75 mL), then dried ($MgSO_4$) and concentrated in vacuo to give **105** as a yellow oil (5.54 g, >95:5 dr); $[\alpha]_D^{25}$ −34.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2972 (C−H), 1731 (C=O); δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, *J* 6.7, C(4)*H*$_3$), 1.38 (3H, d, *J* 7.0, C(α)*Me*), 3.23–3.32 (1H, m, C(3)*H*), 3.30 (3H, s, OCH$_2$O*Me*), 3.61 (1H, dd, *J* 8.6, 4.3, C(2)*H*), 3.76–3.86 (2H, m, NC*H*$_2$Ph), 3.88 (1H, q, *J* 7.0, C(α)*H*), 4.50 (1H, d, *J* 6.7, OC*H*$_A$H$_B$OMe), 4.55 (1H, d, *J* 6.7, OCH$_A$*H*$_B$OMe), 7.18–7.40 (10H, m, *Ph*), 8.65 (1H, d, *J* 4.3, C(1)*H*); δ_C (101 MHz, $CDCl_3$) 13.6 (C(α)*Me*), 14.5 (*C*(4)), 51.0 (N*C*H$_2$Ph), 51.1 (*C*(3)), 56.2 (O*C*H$_3$), 56.4 (*C*(α)), 84.3 (*C*(2)), 96.6 (O*C*H$_2$), 127.2, 127.3, 128.2, 128.4, 128.5, 129.2 (*o*, *m*, *p* – Ar), 140.2 (*i*-Ph), 143.3 (*i*-Ph), 200.9 (*C*(1)); m/z (ESI$^+$) 342 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{28}NO_3^+$ ([M+H]$^+$) requires 342.2064; found 342.2065.

5-(Methylthio)-1-phenyl-tetrazole 108

NaH (60% dispersion in mineral oil, 1.04 g, 26.0 mmol) was added portionwise to a solution of 1-phenyl-1*H*-tetrazole-5-thiol (4.63 g, 26.0 mmol) in DMF (130 mL) at 0 °C and the resultant mixture was stirred for 20 min at 0 °C. MeI (1.62 ml, 26.0 mmol) was added and the resultant

mixture was allowed to warm to rt over 2 h. Satd aq NH_4Cl was added, and the resultant solution diluted with EtOAc. The aqueous was then extracted with (3 × EtOAc), and the combined organic layers were washed with (4 × H_2O), then brine, then dried ($MgSO_4$) and concentrated in vacuo. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:1) gave **108** as a white solid (4.99 g, 98%); mp 79-81 °C; {lit.[116] mp 79-80 °C}; δ_H (400 MHz, $CDCl_3$) 2.84 (3H, s, S*Me*), 7.47 – 7.61 (5H, m, *Ph*).

5-(Methylsulfonyl)-1-phenyl-tetrazole 109

Ammonium molybdate tetrahydrate (16.2 g, 13.0 mmol), then hydrogen peroxide solution (30% (w/w) in H_2O) (12.0 mL, 117 mmol) were added sequentially to a solution of methyl sulfide **108** (5.00 g, 26.0 mmol) in EtOH (130 mL) at 0 °C. The resultant mixture was stirred at rt for 12 h, before being cooled to −10 °C. Sat aq $Na_2SO_3$was then added. The crude mixture was then diluted with EtOAc, washed with (3 × EtOAc), brine, then dried ($MgSO_4$) and concentrated in vacuo to give **109** as a white solid (5.46 g, 94%); mp 80-81 °C; {lit.[117] mp 83-84 °C}; δ_H (400 MHz, $CDCl_3$) 3.64 (3H, s, SO_2*Me*), 7.55–7.75 (5H, m, *Ph*).

1-(Benzyloxy)-3-((1-phenyl-1H-tetrazol-5-yl)sulfonyl)propan-2-one 110

A solution of **109** (128 mg, 0.57 mmol) in THF (2.85 ml) was cooled to −78 °C, and LiHMDS (1.0 M in THF) (1.25 mL, 1.25 mmol) was added. Immediately afterwards a solution of 2-(benzyloxy)acetyl chloride (0.10 mL, 0.63 mmol) in THF (0.3 mL) was added. The mixture was stirred at −78 °C for 30 min, then warmed to 0 °C over 1 h, and stirred at 0 °C for 30 min. Sat aq NH_4Cl (10 mL) was then added, and the aqueous extracted with EtOAc (30 mL). The combined organics were then washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Purification via flash column chromatography (eluent EtOAc) gave **110** as a pale yellow oil (200 mg, 94%, >90% purity); ν_{max} (film) 3467 (O−H), 2926 (C−H), 2887 (C−H), 1678 (C=O); δ_H(400 MHz, $CDCl_3$) 3.99 (2H, s, CH_2Ph), 4.59 (2H, s, C(OH)CH_2), 5.52 (1H, br s, O*H*), 6.54 (1H, br s, C*H*), 7.28–7.78

(10H, m); δ_C (101 MHz, $CDCl_3$) 69.5 (*C*H_2Ph), 73.7 (C(OH)*C*H_2), 100.3 (*C*H), 125.1, 128.1, 128.3, 128.4, 128.8, 129.4 (*o*,*m*,*p*-Ph), 129.9 (*i*-Ph), 136.9 (*i*-Ph), 152.7 (SO_2CN_2), 172.5 (*C*(OH)); m/z (ESI^+) 395 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{17}H_{16}NaN_4O_4S^+$ ($[M+Na]^+$) requires 395.07845; found 395.07808.

1-(Benzyloxy)-3-triphenylphosphoranylidene-2-propanone 112

^{n}BuLi (2.5 M in hexanes, 5.00 mL, 12.5 mmol) was added to a suspension of methyltriphenylphosphonium bromide (4.47 g, 12.5 mmol) in THF (85 mL) at 0 °C and stirred for 30 min. At 0 °C, a solution of benzyloxyacetyl chloride (0.90 mL, 5.70 mmol) was added dropwise, and the mixture stirred at 0 °C for 40 min. The reaction was warmed to rt and concentrated in vacuo. The crude mixture was then stirred in EtOAc (180 mL) for 20 min, before being filtered. The filtrate was the n washed with H_2O, and dried ($MgSO_4$). The solution was then concentrated to ~90 mL, and left at −18 °C overnight. The solution was decanted from the crystals, and the yellow crystals were dried *in vacuo* to give **112** as a yellow solid (2.05 g, 85%); mp 120-122 °C; {lit.[59] mp 128-130 °C}; δ_H (400 MHz, $CDCl_3$) 4.03 (2H, s, C*H*$_2$OBn), 4.24 (1H, d, *J* 25.4, C(2)*H*), 4.68 (2H, s, OC*H*$_2$Ph), 7.27–7.70 (15H, m, Ph-*H*).

2-Ethoxycarbonyl-2-oxoethylidenetriphenylphosphorane 114

A solution of Ethyl bromopyruvate (19.3 mL, 154 mmol) in dry PhMe (60 mL) was added dropwise to a stirred solution of Ph_3P (40.3 g, 154 mmol) in dry PhMe (510 mL) at 0 °C. The resultant solution was allowed to warm to rt, then stirred at rt for 36 h. The supernatant was decanted, and the yellow crystals were triturated with dry Et_2O. The solid was dried in vacuo and then dissolved in MeOH (180 mL). The solution was cooled to 0 °C, and basified to pH 10 by gradual addition of iced 1.0 M aq Na_2CO_3. The basic mixture was diluted with ice water (1.2 L), and stirred for 1 h at 0 °C. The precipitate was collected, washed with cold water, then recrystallized from hot EtOH/cold H_2O to give **114** as a white solid (50.4 g, 87%); mp 179-180 °C;

{lit.[118] mp 182-183 °C}; δ_H (400 MHz, $CDCl_3$) 1.35 (3H, t, *J* 7.1, OCH_2CH_3), 4.26 (2H, q, *J* 7.1, OCH_2), 4.83 (1H, d, *J* 23.3, C(3)*H*), 7.43–7.72 (15H, m); δ_P (162 MHz, $CDCl_3$) 17.0.

(*E*)-1-(Benzyloxy)-4-phenylbut-3-en-2-one 113

112 (636 mg, 1.5 mmol) was added to a stirred solution of benzaldehyde (106 mg, 1.00 mmol) in CH_2Cl_2 (5.0 mL) at rt, and the resultant solution was refluxed for 24 h before being concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 3:1) gave **113** as a yellow oil (231 mg, 92%, >95:5 dr [(*E*):(*Z*) ratio]);[119] δ_H (400 MHz, $CDCl_3$) 4.32 (2H, s, OCH_2Ph), 4.67 (2H, s, $OCH_2C(O)$), 6.97 (1H, d, *J* 16.1, C(2)*H*), 7.32–7.61 (10H, m, *Ph*), 7.70 (1H, d, *J* 16.1, C(3)*H*).

(*E*)-Ethyl 2-oxo-4-phenylbut-3-enoate 115

114 (564 mg, 1.5 mmol) was added to a stirred solution of benzaldehyde (106 mg, 1.00 mmol) in CH_2Cl_2 (5.0 mL) at rt, and the resultant solution was refluxed for 24 h before being concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 3:1) gave **115** as a yellow oil (194 mg, 94%, >95:5 dr [(*E*):(*Z*) ratio]);[120] δ_H (400 MHz, $CDCl_3$) 1.40 (3H, t, *J* 7.2, CH_3), 4.39 (2H, q, *J* 7.2, CH_2CH_3), 7.31 (1H, d, *J* 16.1, C(3)*H*), 7.41-7.45 (3H, m, Ar*H*), 7.63-7.69 (2H, m, Ar*H*), 7.79 (1H, d, *J* 16.1, C(4)*H*.

1'-*O*-Benzyl-methyl(4*R*,5*S*,*E*)-5-(*N*-benzyl-*N*-(α-methylbenzyl)amino)-*O*-methoxymethyl)hex-2-enoate 116

112 (3.31 g, 7.82 mmol) was added to a stirred solution of **105** (0.40 g, 1.3 mmol) in DCE (6.5 mL) at rt, and the resultant solution was refluxed for 60 h before being concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 3:1) gave **116** as a yellow oil (190 mg, 30%, >95:5 dr [(*E*):(*Z*) ratio]); $[\alpha]_D^{25}$ −0.9 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3030 (C−H), 2968 (C−H), 1682 (C=O); δ_H (400 MHz, $CDCl_3$) 1.24 (3H, d, *J* 6.7, C(6)H_3), 1.34 (3H, d,

J 6.9, C(α)*Me*), 2.94 (1H, p, *J* 6.7, C(5)*H*), 3.29 (3H, s, CH_2OMe), 3.84 (2H, d, *J* 2.7, NCH_2Ph), 3.90 (1H, q, *J* 6.9, C(α)*H*), 3.97 (1H, td, *J* 7.1, 1.1, C(4)*H*), 4.10 (2H, d, *J* 3.2, CH_2OBn), 4.41 (1H, d, *J* 6.9, OCH_AH_B), 4.46 (1H, d, *J* 6.9, OCH_AH_B), 4.60 (2H, s, OCH_2Ph), 6.09 (1H, dd, *J* 16.1, 1.1, C(2)*H*), 6.42 (1H, dd, *J* 16.1, 7.1, C(3)*H*), 7.19 – 7.40 (15H, m, *Ar*); δ_C (101 MHz, $CDCl_3$) 14.3 (C(6)), 14.6 (C(α)*Me*), 51.0 (NCH_2Ph), 55.2 (C(5)), 56.2 (O*Me*), 56.8 (C(α)), 73.4 (OCH_2Ph), 73.9 (CH_2OBn), 79.3 (C(4)), 95.1 (OCH_2), 126.5 (C(2)), 126.9, 127.1, 128.1, 128.2, 128.4, 128.5, 128.5, 128.7, 128.8 (*o*, *m*, *p*-Ar), 137.4 (*i*-Ph), 140.8 (*i*-Ph), 143.8 (*i*-Ph), 147.0 (C(3)), 196.4 (C(1)); m/z (ESI^+) 488 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{31}H_{38}NO_4^+$ ($[M+H]^+$) requires 488.27954; found 488.27963.

Ethyl (4*R*,5*S*,α*S*,*E*)-4-methoxymethyleneoxy-5-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-2-enoate 117

$Ph_3P{=}CHCO_2Et$ (5.05 g, 14.5 mmol) was added to a stirred solution of **105** (4.50 g, 13.2 mmol) in CH_2Cl_2 (65 mL) at rt, and the resultant solution was stirred at rt for 60 h before being concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 3:1) gave **117** as a yellow oil (5.15 g, 90% from **103**, >95:5 dr [(*E*):(*Z*) ratio]); $[\alpha]_D^{25}$ −75.4 (*c* 1.0 in $CHCl_3$); ν_{max} 2981, 2888, 1719; δ_H (400 MHz, $CDCl_3$) 1.23 (3H, d, *J* 6.8, C(6)H_3), 1.32 (3H, t, *J* 7.2, OCH_2CH_3), 1.35 (3H, d, *J* 6.9, C(α)*Me*), 2.93 (1H, app quintet, *J* 6.8, C(5)*H*), 3.31 (3H, s, OCH_2OMe), 3.87 (2H, app s, NCH_2Ph), 3.93 (1H, q, *J* 6.9, C(α)*H*), 3.99 (1H, app td, *J* 7.0, 1.2, C(4)*H*), 4.21 (2H, q, *J* 7.2, OCH_2CH_3), 4.44 (1H, d, *J* 6.8, OCH_AH_BOMe), 4.51 (1H, d, *J* 6.8, OCH_AH_BOMe), 5.71 (1H, dd, *J* 15.9, 1.1, C(2)*H*), 6.54 (1H, dd, *J* 15.9, 7.0, C(3)*H*), 7.15–7.48 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(6)), 14.5 (C(α)*Me*), 15.0 (OCH_2CH_3), 51.0 (NCH_2Ph), 55.4 (*C*(5)), 56.2 (OCH_2OMe), 57.0 (*C*(α)), 60.4 (OCH_2CH_3), 79.2 (C(4)), 95.2 (OCH_2OMe), 122.3 (*C*(2)), 126.9, 127.0 (*p-Ph*), 128.1, 128.2, 128.4, 128.8 (*o,m-Ph*), 141.1, 143.9 (*i-Ph*), 147.8 (*C*(3)), 166.2 (*C*(1)); *m/z* (ESI^+) 412 ($[M+H]^+$, 100%), HRMS (ESI^+) $C_{25}H_{34}NO_4^+$ ($[M+H]^+$) requires 412.2482; found 412.2464.

Ethyl(4*R*,5*S*)-5-amino-*O*-methoxymethyl hexanoate 120

$Pd(OH)_2/C$ (50% w/w of **117**, 0.50 g) was added to a stirred solution of **117** (1.00 g, 2.43 mmol) in degassed MeOH (6.1 mL) and the resultant black suspension was stirred at rt under a hydrogen atmosphere (5 atm) for 16 h. After depressurisation, the reaction mixture was filtered through a plug of Celite (eluent CH_2Cl_2) and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 3:1, increased to 2:1) gave **120** as a yellow oil (404 mg, 76%, >95:5 dr); $[\alpha]_D^{25}$ −2.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3452 (N−H), 2980 (C−H), 1683 (C=O); δ_H (500 MHz, $CDCl_3$) 1.26 (3H, t, *J* 7.1, OCH_2CH_3), 1.38 (3H, d, *J* 6.7, C(6)H_3), 1.78 – 1.96 (2H, m, C(3)H_2), 2.29 – 2.56 (2H, m, C(2)H_2), 3.44 (3H, s, OCH_3), 3.47 – 3.58 (1H, m, C(5)H_2), 3.87 (1H, ddd, *J* 9.4, 4.0, 2.2, C(4)H_2), 4.13 (2H, q, *J* 7.1, OCH_2CH_3), 4.68 (1H, dd, *J* 6.8, 1.3, OCH_AH_B), 4.73 (1H, d, *J* 6.8, OCH_AH_B); δ_C (126 MHz, $CDCl_3$) 12.9 (C(6)), 14.4 (OCH_2CH_3), 26.9 (C(3)), 30.5 (C(2)), 50.4 (C(5)), 56.2 (OCH_3), 60.8 (OCH_2CH_3), 80.4 (C(4)), 98.1 (OCH_2), 173.0 (C(1)); m/z (ESI^+) 486 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{10}H_{22}NO_4^+$ ($[M+H]^+$) requires 220.15433; found 220.15424.

(5*R*,6*S*)-*N*-5-*O*-Methoxymethyl-6-methylpiperidin-2-one 121

KOH (169 mg, 3.03 mmol) was added to a solution of **120** (600 mg, 2.75 mmol) in EtOH (70 mL) and the resultant was stirred at rt for 2.5 h. The reaction mixture was then concentrated in vacuo. The resultant residue was dissolved in $CHCl_3$ (20 mL) and then washed with water, brine and then dried ($MgSO_4$) and concentrated in vacuo to give **121** as a colourless oil (475 mg, quant., >95:5 dr); $[\alpha]_D^{25}$ −30.2 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3408 (N−H), 2980 (C−H), 1654 (C=O); δ_H (500 MHz, $CDCl_3$) 1.24 (3H, d, *J* 6.4, C(7)H_3), 1.85 (1H, dtd, *J* 14.1, 8.0, 6.2, C(4)H_A), 2.07 (1H, dddd, *J* 13.3, 6.9, 6.3, 3.1, C(4)H_B), 2.34 (1H, ddd, *J* 17.9, 8.1, 6.3, C(3)H_A), 2.52 (1H, dt, *J* 17.9, 6.5, C(3)H_B), 3.39 (3H, s, C(9)H_3), 3.47–3.57 (2H, m, C(5)*H*, C(6)*H*), 4.67 (1H, d, *J* 7.0, OCH_AH_B), 4.74 (1H, d, *J* 7.0, CH_AH_B), 6.02 (1H, s, N*H*); δ_C (126 MHz, $CDCl_3$) 20.9 (C(7)), 24.4 (C(4)), 28.2 (C(3)), 53.0

(C(6)), 55.8 (O*Me*), 74.8 (C(5)), 95.4 (O*C*H$_2$), 171.5 (C(2)); m/z (ESI$^+$) 174 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_8H_{16}NO_3^+$ ([M+H]$^+$) requires 174.1125; found 174.1125.

2-Butyl-1-methylpiperidine 129

^{n}BuLi (2.5 M in hexanes, 1.06 mL, 2.64 mmol) was added dropwise to a stirred solution of *N*-Methyl-2-piperidone (0.10 mL, 0.88 mmol) in Et$_2$O (4.40 mL) at 0 °C. The reaction was stirred at rt for 45 min, then cooled to 0 °C. LiAlH$_4$-TMEDA (2.4 M in THF, 1.10 mL, 2.64 mmol) was added dropwise, the reaction was then allowed to rt, and stirred for 2 h at rt. 20% aq NaOH solution (2 mL) was then added, and the mixture was then filtered and washed with CH_2Cl_2, then dried (Na_2SO_4). Concentration in vacuo, then purification via flash column chromatography (eluent 30–40 °C petrol/Et$_2$O, 3:1, increased to 2:1) gave **129** as a clear oil (123 mg, 90%);[121] δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.0, CH_2CH_3), 1.16–1.74 (12H, m, C(3)H_2, C(4)H_2, C(5)H_2, $CH_2CH_2CH_2CH_3$), 1.76–1.84 (1H, m, C(6)H_AH_B), 2.00–2.09 (1H, m, C(1)*H*), 2.24 (3H, s, N*Me*), 2.83 (1H, dtd, *J* 11.5, 3.6, 1.5, C(6)H$_A$*H*$_B$).

***N*-Methyl-2-vinylpiperidine 130**

A solution of vinyl lithium was prepared via: ^{t}BuLi (1.7 M in pentane, 3.11 mL, 5.28 mmol) was added dropwise to a cooled (−78 °C) solution of vinyl bromide (1 M in THF, 2.64 mL, 2.64 mmol). The yellow solution was stirred for 30 min at −78 °C, then warmed to 0 °C. A solution of Methyl-2-piperidone (0.10 mL, 0.88 mmol) in Et$_2$O (4.40 mL) was added dropwise and the reaction stirred at rt for 45 min. LiAlH$_4$-TMEDA (2.4 M in THF, 1.1 mL, 2.64 mmol) was added dropwise at 0 °C and the reaction was then allowed to rt, and stirred for 2 h at rt. 20% aq NaOH solution (2 mL) was then added, and the mixture was then filtered and washed with CH_2Cl_2, then dried (Na_2SO_4). Concentration in vacuo then purification via flash column chromatography (eluent 30–40 °C petrol/Et$_2$O, 3:1, increased to 2:1) gave **130** as a clear oil (83 mg, 75%;[122] δ_H (400 MHz, $CDCl_3$) 1.00–2.10 (6H, m, C(3)H_2, C(4)H_2, C(5)H_2), 2.19 (3H, s, N*Me*), 2.27–2.32 (1H, m,

C(6)H_AH_B), 2.84–2.90 (1H, m, C(6)H$_A$$H_B$), 3.27 (1H, ddd, *J* 8.7, 4.4, 1.3, C(2)*H*), 5.02 (1H, dd, *J* 10.2, 1.9, CHCH_EH$_Z$), 5.13 (1H, ddd, *J* 17.1, 1.9, 0.7, CHCH$_E$$H_Z$), 5.73 (1H, ddd, *J* 17.1, 10.2, 8.7, C*H*CH$_2$).

Ethyl (2*E*,4*E*)-nona-2,4-dienoate 132

(*E*)-2-Heptenal **131** (1.60 mL, 12.3 mmol, >95:5 dr [(*E*):(*Z*) ratio]) was added to a stirred solution of Ph_3P=CHCO$_2$Et (4.70 g, 13.5 mmol) in CH_2Cl_2 (60 mL) at rt, and the resultant solution was stirred at rt for 12 h. The reaction mixture was then concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 95:5) gave **132** as a yellow oil (1.96 g, 89%, >95:5 dr [(2*E*,4*E*):(2*Z*,4*E*) ratio]); δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.1, C(9)H_3), 1.29 (3H, t, *J* 7.2, OCH$_2$CH_3), 1.31–1.36 (2H, m, C(8)H_2), 1.36–1.46 (2H, m, C(7)H_2), 2.17 (2H, q, *J* 7.0, C(6)H_2), 4.19 (2H, q, *J* 7.1, OCH_2CH$_3$), 5.78 (1H, d, *J* 15.4, C(2)*H*), 6.06–6.21 (2H, m, C(4)*H*, C(5)*H*), 7.20–7.30 (1H, m, C(3)*H*).

(2*E*,4*E*)-Nona-2,4-dien-1-ol 133

DIBAL-H (1.0 M in PhMe, 19.9 mL, 19.9 mmol) was added to a stirred solution of **132** (1.45 g, 7.97 mmol) in CH_2Cl_2 (50 mL) at −78 ºC and the resultant solution was stirred at −78 ºC for 15 min. The resultant solution was allowed to warm to 0 ºC, and stirred at 0 ºC for 1 h. Satd aq Rochelle salt (45 mL) was then added and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organics were washed with brine (100 mL), then dried (Na_2SO_4) and concentrated in vacuo to give **133** as a colourless oil (1.02 g, 92%, >95:5 dr [(2*E*,4*E*):(2*Z*,4*E*) ratio]); ν_{max} 3322, 3019, 2925; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.1, C(9)H_3), 1.26–1.41 (5H, m, (C(7)H_2, C(8)H_2, O*H*)), 2.05–2.12 (2H, m, C(6)H_2), 4.16 (2H, t, *J* 5.6, C(1)H_2), 5.66–5.77 (2H, m, C(2)*H*, C(5)*H*), 5.99–6.10 (1H, ddt, 15.1, 10.4, 1.5 C(4)*H*), 6.22 (1H, ddt, *J* 15.3, 10.4, 1.5 C(3)*H*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(9)), 22.4 (*C*(8)), 31.5 (*C*(7)), 32.4 (*C*(6)), 63.7 (*C*(1)), 129.4 (*C*(4), *C*(5)), 132.3 (*C*(3)), 136.0 (*C*(2)).

(2*E*,4*E*)-Nona-2,4-dienal 134

IBX (652 mg, 2.33 mmol) was added to a stirred solution of **133** (250 mg, 1.79 mmol) in DMSO (2 mL) at rt. The resultant solution was then stirred at rt for 12 h, then diluted with Et_2O (20 mL), washed sequentially with H_2O (5 × 2 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated in vacuo to give **134** as a colourless oil (140 mg, quant); δ_H (400 MHz, $CDCl_3$) 0.92 (3H, t, *J* 7.2, C(9)*H*$_3$), 1.28–1.42 (2H, m, C(8)*H*$_2$), 1.40–1.49 (2H, m, C(7)*H*$_2$), 2.15–2.29 (2H, m, C(6)*H*$_2$), 6.07 (1H, dd, *J* 15.3, 8.0, C(2)*H*), 6.19–6.38 (2H, m, C(4)*H*, C(5)*H*), 7.08 (1H, dd, *J* 15.3, 9.8, C(3)*H*), 9.53 (1H, d, *J* 8.0, C(1)*H*).

(1*E*,3*E*,5*E*)-1-Iododeca-1,3,5-triene 135

A solution of aldehyde **134** (108 mg, 0.79 mmol) and iodoform (1.40 g, 3.56 mmol) in degassed THF (4.6 mL) was added to a solution of flame-dried chromium(II) chloride (970 mg, 7.89 mmol) in degassed THF (2.62 mL) at 0 °C. The reaction mixture was warmed to rt and stirred for 4.5 h. The reaction was then filtered through Celite (Et_2O eluent), washed with water, then satd aq $Na_2S_2O_3$. The combined organic phases were then concentrated in vacuo, then separated between petrol and H_2O. The organic phase was then washed with brine, and dried (Na_2SO_4) and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/acetone, 400:1) gave **135** as a yellow oil (40 mg, 15%, inseparable mixture of isomers); ν_{max} (film) 3019 (C−H), 2924 (C−H), 2360 (C=C); δ_H(400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.2, C*H*$_3$), 1.36 (4H, m, C(8)*H*$_2$, C(9)*H*$_2$), 2.05–2.15 (2H, m, C(7)*H*$_2$), 6.12–6.30 (3H, m, C(1)*H*, C(2)*H,* C(5)*H*), 6.44 (1H, dd, *J* 14.9, 10.3, C(3)*H*), 6.72 (1H, dd, *J* 10.3, 7.5 C(4)*H*), 6.97–7.06 (1H, m, C(5)*H*); δ_C (101 MHz, $CDCl_3$) 14.1 (*C*H$_3$), 22.4 (*C*(9)), 31.3 (*C*(8)), 32.8 (*C*(7)), 81.3 (*C*(1)), 130.2 (*C*(2) or *C*(5)), 130.3 (*C*(2) or *C*(5)), 137.6 (*C*(4)), 138.6 (*C*(2), 145.6 (*C*(6).

***N*-Carboxybenzyl-piperidin-2-one 136**

^{n}BuLi (2.5 M in hexanes, 12.8 mL, 32.0 mmol) was added dropwise to a stirred solution of δ-valerolactam (3.00 mL, 32.0 mmol) in THF (160 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of benzyl chloroformate (4.51 mL, 32.0 mmol) in THF (32 mL) was then added dropwise and the resultant mixture was stirred at −78 °C for 4 h. Sat aq NH_4Cl (13 mL) was then added and the resultant mixture allowed to warm to rt. The aqueous layer was extracted with Et_2O (3 × 20 mL), then washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:3) gave **136** as a colourless oil (7.46 g, quant.);[123] δ_H (400 MHz, $CDCl_3$) 1.81–1.86 (4H, m, C(4)H_2, C(5)H_2), 2.50–2.58 (2H, m, C(3)H_2), 3.70–3.78 (2H, m, C(6)H_2), 5.28 (2H, s, OCH_2Ph), 7.28–7.46 (5H, m, *Ph*).

***N*-Cbz-1-(1-Phenyl-1*H*-tetrazole-5-sulfonyl)heptan-2-one 137**

LiHMDS (0.95 M in THF, 1.55 mL, 1.47 mmol) was added dropwise to a stirred solution of $MeSO_2PT$ (150 mg, 0.67 mmol) in THF (3.4 mL) at −78 °C then immediately a solution of lactam **136** (781 mg, 3.35 mmol) in THF (1.68 mL) was added dropwise, and the resulting mixture stirred at −78 °C for 30 min, then at rt for 1 h. Sat aq NH_4Cl (3 mL) was added, and the aqueous layer was extracted with EtOAc, then washed with brine and dried ($MgSO_4$). Concentration in vacuo, then purification via flash column chromatography (eluent $CHCl_3$/MeOH, 100:2) gave **137** as a pale yellow oil (200 mg, 66%); ν_{max} (film) 3328 (N−H), 2997 (C−H), 2361 (C−H), 1728 (C=O), 1688 (C=O); δ_H (400 MHz, $CDCl_3$) 1.41–1.68 (4H, m, C(4)H_2, C(5)H_2), 2.67 (2H, t, *J* 7.1, C(3)H_2), 3.18 (2H, q, *J* 6.6, C(6)H_2), 4.70 (2H, s, C(1)H_2), 5.09 (2H, s, CO_2CH_2Ph), 7.28–7.38 (5H, m, $NHCO_2CH_2$*Ph*), 7.56–7.68 (5H, m, SO_2CN*Ph*); δ_C (126 MHz, $CDCl_3$) 20.0 (*C*(4)), 29.0 (*C*(5)), 40.4 (*C*(6)), 43.7 (*C*(3)), 64.8 (*C*(1)), 66.8 (CO_2CH_2Ph), 125.6 (*Ar*), 128.3 (*Ph*), 128.3 (*i*-Ph), 128.7 (*Ph*), 129.8 (*Ph*), 131.7 (*Ph*), 133.0 (*Ph*), 136.73 (*o*-Ph), 153.5 (SO_2CN_2), 156.6 (CO_2Bn), 196.4 (*C*(O));

m/z (ESI$^+$) 568 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{24}N_5O_5S^+$ ([M+H]$^+$) requires 458.14927; found 458.14926.

1-Phenyl-5-(((1-phenyl-1H-tetrazol-5-yl)methyl)sulfonyl)-1H-tetrazole 138

LiHMDS (0.95 M in THF, 2.06 mL, 1.96 mmol) was added dropwise to a stirred solution of $MeSO_2PT$ (200 mg, 0.89 mmol) in THF (4.45 mL) at −78 °C then a solution of lactam **136** (228 mg, 0.98 mmol) in THF (0.50 mL) was added dropwise, and the resulting mixture stirred at −78 °C for 30 min, then at rt for 1 h. Sat aq NH_4Cl (3 mL) was added and the aqueous layer was extracted with EtOAc, then washed with brine and dried ($MgSO_4$). Concentration in vacuo, then purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 1:1) gave **138** as a white solid (54 mg, 33%); mp 141–144 °C; ν_{max} (film) 2981 (C−H), 1591 (N=N); δ_H (400 MHz, $CDCl_3$) 5.66 (2H, s, CH_2), 7.37–7.46 (4H, m, *Ph*), 7.47–7.54 (4H, m, *Ph*), 7.68–7.73 (2H, m, *Ph*); δ_C (101 MHz, $CDCl_3$) 75.6 (*C*H_2), 121.7, 128.9, 129.0, 129.1, 129.5, 129.7 (*o*,*m*,*p*-Ph), 134.1 (*i*-Ph), 138.9 (*i*-Ph), 150.5 (CH_2CN_2), 153.8 (SO_2CN_2); m/z (ESI$^+$) $C_{15}H_{13}N_8O_2S$ ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{15}H_{13}N_8O_2S^+$ ([M+H]$^+$) requires 369.08767; found 369.08701.

***N*-Cbz-1-(Phenylsulfonyl)heptan-2-one 140**

^{n}BuLi (2.5 M in hexanes, 2.27 mL, 5.68 mmol) was added dropwise to a stirred solution of $MeSO_2Ph$ (885 mg, 5.68 mmol) in THF (16 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 20 min. A solution of lactam **136** (600 mg, 2.58 mmol) in THF (16 mL) was added dropwise, and the resulting mixture stirred at −78 °C for 1 h. Sat aq NH_4Cl (3 mL) was added, and the aqueous layer was extracted with CH_2Cl_2, then washed with brine and dried (Na_2SO_4). Concentration in vacuo, then purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:4) gave **140** as a white solid (708 mg, 71%); mp 85-87 °C; {lit.[124] mp 83 °C}; δ_H (500 MHz, $CDCl_3$) 1.50 (2H, p, *J* 6.7, $NHCH_2CH_2$), 1.58–1.64 (2H, m, $COCH_2CH_2$), 2.74 (2H, t, *J* 7.0, $COCH_2$), 3.19 (2H, q, *J* 6.7, $NHCH_2$), 4.13 (2H, s, SO_2CH_2), 5.09 (2H, s, OCH_2Ph), 7.28–

7.35 (1H, m, *Ph*), 7.36 (4H, d, *J* 4.0, *Ph*), 7.54–7.61 (2H, m, *Ph*), 7.65–7.72 (1H, m, *Ph*), 7.88 (2H, d, *J* 7.1, *Ph*).

_N_-Boc-1-((Phenylsulfonyl)methyl)piperidine 141

$Pd(OH)_2/C$ (1.00 g) was added to a solution of **140** (2.00 g, 5.14 mmol) and Boc_2O (2.24 g, 10.28 mmol) in degassed MeOH (130 mL) and the resultant black suspension stirred under a hydrogen atmosphere (1 atm) for 72 h. After depressurisation, the reaction mixture was filtered through a plug of Celite (eluent MeOH), and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 2:1) gave **141** as a white solid (1.65 g, 4.88 mmol, 95%);[125] δ_H (400 MHz, $CDCl_3$) 1.41 (9H, s, CO_2tBu), 1.44–1.74 (5H, m, C(2)H_2, C(3)H_AH_B, C(4)H_2), 1.88 (1H, d, *J* 13.2, C(3)H_AH_B), 2.55 (1H, br s, C$H_AH_BSO_2$Ph), 3.17–3.42 (2H, m, C(5)H_2), 3.90 (1H, d, *J* 12.3, C$H_AH_BSO_2$Ph), 4.78 (1H, td, *J* 7.1, 6.7, 3.2, C(1)*H*), 7.47–7.60 (2H, m, *m*-Ph), 7.64 (1H, tt, *J* 7.3, 1.2, *p*-Ph), 7.82–8.03 (2H, m, *o*-Ph).

_N_-Boc-2-((1'*E*,3'*E*,5'*E*)-Deca-1,3,5-trien-1-yl)piperidine 142

Step 1: ^{n}BuLi (2.5 M in hexanes, 0.57 mL, 1.43 mmol) was added dropwise to a stirred solution of sulfone **141** (403 mg, 1.19 mmol) in THF (2.64 mL) at −78 °C, and the resultant yellow solution was stirred at −78 °C for 30 min. Freshly prepared aldehyde **134** (197 mg, 1.43 mmol) was added as a solution in THF (4.76 mL), and the resultant stirred at −78 °C for 1 h. Benzoyl chloride (0.28 mL, 2.38 mmol) was added, and the mixture allowed to rt over 30 min. Sat aq NH_4Cl (1 mL) was added, and the aqueous layer was extracted with EtOAc, then washed with brine and dried ($MgSO_4$). Concentration in vacuo, then purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 9:0 to 9:1) gave a mixture of diastereomers (550 mg, 80%); δ_H (500 MHz, $CDCl_3$) 0.87 (3H, t, *J* 7.1, CH_3), 1.26 – 1.38 (4H, m, C(8')H_2, C(9')H_2), 1.41 (1H, dt, *J* 12.3, C(6)H_AH_B)1.44 – 1.53 (2H, m, C(5)H_2), 1.50 (9H, s, CMe_3), 1.54 – 1.66 (2H, m, C(4)H_2), 1.78 (1H, ddt, *J* 13.9, 9.7, 4.5, C(3)H_AH_B), 1.99 – 2.13 (1H, m, C(3)H_AH_B), 2.06 (2H, app q, *J* 7.1, C(7')H_2),

3.64 (1H, d, *J* 12.3, C(6)H_AH_B), 4.03 (1H, app d, *J* 10.7, C(1')*H*), 5.09 (1H, dt, *J* 8.6, 3.9, C(2)*H*), 5.73 (1H, dt, *J* 15.2, 7.0, C(6')*H*), 5.79 (1H, dd, *J* 15.2, 7.0, C(3')*H*), 6.00 (1H, dd, *J* 15.2, 10.4, C(5')*H*), 6.21 (1H, dd, *J* 15.3, 10.4, C(4')*H*), 6.27 (1H, d, *J* 7.0, C(2')*H*), 7.35 –7.89 (10H, m, *Ph*); δ_C (126 MHz, $CDCl_3$) 14.0 (*C*H_3), 19.7 (*C*(4)), 22.3 (*C*(9')), 24.9 (*C*(5)), 27.3 (*C*(3)), 28.5 (C*Me*$_3$), 31.2 (*C*(8')), 32.4 (*C*(7')), 39.2 (*C*(6)), 50.0 (*C*(2)), 65.4 (*C*(1')), 71.6 (*C*(2')), 80.2 (*C*Me_3), 124.9 (*C*(3')), 128.7 (*C*(5')), 128.5, 128.5, 129.0, 129.7, 129.9, 130.2 (*o*,*m*,*p* – Ph), 133.3 (*i*-Ph), 133.4 (*i*-Ph), 135.1 (*C*(4')), 138.2 (*C*(6')), 154.5 (*C*$O_2{}^tBu$), 165.3 (*C*O_2Ph); ν_{max} (film) 2999 (C−H), 2930 (C−H), 1727 (C=O), 1693 (C=O);m/z (ESI$^+$) 604 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{33}H_{43}NaNO_6S^+$ ([M+H]$^+$) requires 604.2703; found 604.2709.

Step 2: 3.4% Na(Hg) was prepared via the slow addition of sodium (28 mg, 1.22 mmol) to mercury (830 mg, 4.15 mmol) at rt. The resulting metallic grey thick paste was left to stir at rt for 10 min. The mixture from the previous step (222 mg, 0.38 mmol) was added at rt as a solution in THF:MeOH (3:1)(1.52 mL) and the resultant solution stirred at rt for 20 min. At this point an extra 1 mL of THF:MeOH (3:1) was added and the reaction stirred for a further 2 h. The reaction was then diluted with EtOAc, and filtered through Celite, before being concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 10:0.5) gave **142** as a colourless oil as an inseparable mixture of stereoisomers (105 mg, 87%, 13:87 [*Z,E,E*:*E,E,E*], >90% purity); ν_{max} (film) 2930 (C−H), 2858 (C−H), 1694 (C=O); δ_H (400 MHz, $CDCl_3$) 0.85–0.93 (3H, m, *Me*), 1.22–1.41 (4H, m, C(8')H_2, C(9')H_2), 1.45 (9H, s, C*Me*$_3$), 1.52–1.65 (4H, m, C(4)H_2, C(5)H_2), 1.66–1.76 (2H, m, C(3)H_2), 2.10 (2H, q, *J* 7.0, C(7')H_2), 2.81 (1H, td, *J* 12.9, 2.8, C(6)H_AH_B), 3.94 (1H, app d, *J* 12.9, C(6)H_AH_B), 4.84 (1H, br s, C(2)*H*), 5.61 (1H, dd, *J* 14.7, 4.9, C(1')*H*), 5.70 (1H, dt, *J* 14.4, 7.1, C(6')*H*), 5.98–6.12 (2H, m, C(2')*H*, C(5')*H*), 6.09–6.17 (2H, m, C(3')*H*, C(4')*H*); δ_C (101 MHz, $CDCl_3$) 14.1 (Me), 19.8 (*C*(4)), 22.4 (*C*(9')), 25.7 (*C*(5)), 28.6 (C*Me*$_3$), 29.6 (*C*(3)), 31.6 (*C*(8')), 32.6 (*C*(7')), 40.0 (*C*(6)), 52.0 (*C*(2)), 79.5 (*C*Me_3), 130.1 (*C*(3')), 130.4

(*C*(5′)), 131.5 (*C*(2′)), 131.8 (*C*(1′)), 132.7 (*C*(4′)), 135.7 (*C*(6′)), 164.2 (*C*(O)); m/z (ESI$^+$) 342 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{33}NaNO_2$ ([M+Na]$^+$) requires 342.2404; found 342.2401.

(5*R*,6*S*)-*N*(1)-Carboxybenzyl-5-*O*-methoxymethyl-6-methylpiperidin-2-one 143

^{n}BuLi (2.5 M in hexanes, 0.24 mL, 0.60 mmol) was added dropwise to a stirred solution of **121** (104 mg, 0.60 mmol) in THF (2.40 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of benzyl chloroformate (0.09 mL, 0.60 mmol) in THF (0.60 mL) was then added dropwise and the resultant mixture was stirred at −78 °C for 4 h. Sat aq NH_4Cl (1 mL) was added and the resultant mixture allowed to warm to rt. The aqueous layer was extracted with Et_2O, then washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 1:1) gave **143** as a colourless oil (175 mg, 95%, >95:5 dr); $[\alpha]_D^{25}$ +15.4 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2981 (C−H), 1770 (ester C=O), 1713 (amide C=O); δ_H (400 MHz, $CDCl_3$) 1.26 (3H, d, *J* 6.8, NCHCH_3), 1.95–2.03 (1H, m, C(4)H_A), 2.03–2.13 (1H, m, C(4)H_B), 2.48 (1H, ddd, *J* 17.7, 7.1, 2.7, C(3)H_A), 2.76 (1H, ddd, *J* 17.7, 11.2, 8.0, C(3)H_B), 3.31 (3H, s, OCH_3), 3.81 (1H, q, *J* 3.0, C(6)*H*), 4.52 (1H, qdd, *J* 6.8, 2.7, 1.6, C(5)*H*), 4.68 (1H, d, *J* 7.1, OCH_A), 4.70 (1H, d, *J* 7.1, OCH_B), 5.29 (2H, s, CO_2CH_2Ph), 7.28–7.46 (5H, m, *Ph*); δ_C (101 MHz, $CDCl_3$) 19.6 (NCH*C*H_3), 22.3 (C(4)), 30.0 (C(3)), 55.8 (O*C*H_3), 56.4 (C(5)), 68.6 (CO_2CH_2Ph), 72.8 (C(6)), 95.1 (O*C*H_2), 128.1, 128.4, 128.7 (*o*, *m*, *p*-Ph), 154.5 (*C*O_2Bn), 170.9 (C(2)); m/z (ESI$^+$) 308 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{21}NNaO_5^+$ ([M+Na]$^+$) requires 330.1342; found 330.1312.

(5*R*,6*S*)-*N*-Cbz-*O*-(methoxymethyl)-1-(phenylsulfonyl)heptan-2-one 144

^{n}BuLi (2.5 M in hexanes, 1.19 mL, 2.97 mmol) was added dropwise to a stirred solution of $MeSO_2Ph$ (463 mg, 2.97 mmol) in THF (8.4 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 20 min. A solution of lactam **143** (415 mg, 1.35 mmol) in THF (8.4 mL) was added dropwise, and the resulting mixture stirred at −78 °C for 1 h. Sat aq NH_4Cl (1 mL) was added and

the resultant mixture allowed to warm to rt. The aqueous layer was extracted with Et_2O, then washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:2 to 1:4) gave **144** as a yellow oil (374 mg, 60%, >95:5 dr); $[\alpha]_D^{25}$ −7.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3348 (N−H), 2963 (C−H), 2835 (C−H), 1717 (C=O); δ_H (600 MHz, $CDCl_3$) 1.12 (3H, d, *J* 6.8, NCHCH_3), 1.75 (2H, dq, *J* 12.7, 6.8, 5.6, C(O)CH_2CH_2), 2.77–2.87 (2H, m, C(O)CH_2), 3.38 (3H, s, OCH_3), 3.46–3.49 (1H, m, NCHC*H*), 3.77 (1H, br s, NC*H*), 4.16 (2H, s, CH_2SO_2Ph), 4.58 (1H, d, *J* 6.9, OCH_ACH_B), 4.63 (1H, d, *J* 6.9, OCH_ACH_B), 5.05–5.13 (2H, m, CO_2CH_2Ph), 5.48 (1H, d, *J* 9.1, N*H*), 7.28–7.37 (5H, m, SO_2*Ph*), 7.58–7.89 (5H, m, CO_2CH_2*Ph*); δ_C (151 MHz, $CDCl_3$) 15.0 (NCH*C*H_3), 25.8 (C(O)CH_2*C*H_2), 40.8 (C(O)*C*H_2), 49.3 (N*C*H), 56.1 (O*C*H_3), 66.7 (CO_2*C*H_2Ph), 67.0 (*C*H_2SO_2Ph), 82.0 (NCH*C*H), 97.8 (O*C*H_2), 128.2, 128.2, 128.6 (*o*, *m*, *p*-SO_2*Ph*), 128.4, 129.5, 134.5 (*o*, *m*, *p*-CO_2CH_2*Ph*) 136.8 (*i*-SO_2*Ph*), 138.9 (*i*-CO_2CH_2*Ph*), 156.0 (*C*O_2Bn), 197.8 (*C*(O)); m/z (ESI$^+$) 486 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{29}NO_7{}^{32}S^{23}Na^+$ ([M+Na]$^+$) requires 486.1557; found 486.1554.

(2*S*,3*R*,6*S*)-*O*-Methoxymethyl-2-methyl-6-((phenylsulfonyl)methyl)piperidine 145

$Pd(OH)_2$/C (175 mg) was added to a solution of **144** (350 mg, 0.76 mmol) in degassed MeOH (19 mL) and the resultant black suspension stirred under a hydrogen atmosphere (1 atm) for 50 h. After depressurisation, the reaction mixture was filtered through a plug of Celite (eluent MeOH), and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 2:3) gave **145** as a yellow oil (174 mg, 74%, >95:5 dr); $[\alpha]_D^{25}$ −5.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3285 (N−H), 2928 (C−H); δ_H (400 MHz, $CDCl_3$) 1.16 (3H, d, *J* 6.1, CHCH_3), 1.27–1.37 (2H, m, C(5)H_AH$_B$, C(4)H_AH$_B$), 1.61 (1H, dt, *J* 8.8, 2.9, C(5)H$_A$$H_B$), 2.13 (1H, ddd, *J* 9.1, 6.8, 3.7, C(4)H$_A$$H_B$), 2.61 (1H, dq, *J* 9.0, 6.1, C(2)*H*), 3.00–3.27 (4H, m, C(6)*H*, C(3)*H*, CH_2SO_2Ph), 3.35 (3H, s, OCH_3), 4.59 (1H, d, *J* 6.8, OCH_ACH_B), 4.70 (1H, d, *J* 6.8, OCH_ACH_B), 7.57 (2H, t, *J* 7.7, *Ph*), 7.66 (1H, t, *J* 7.4, *Ph*), 7.91 (1H, d, *J* 7.1, *Ph*); δ_C (101 MHz, $CDCl_3$) 19.3 (CH*C*H_3), 31.0 (*C*(4)), 31.9 (*C*(5)), 50.9 (*C*(6)), 55.6 (O*C*H_3), 56.7 (*C*(2)), 61.8 (*C*H_2SO_2Ph), 78.7 (*C*(3)), 95.6 (O*C*H_2),

127.9, 129.6, 134.0 (o,m,p–*Ph*) 139.8 (i-Ph); m/z (ESI$^+$) 314 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{15}H_{24}NO_4{}^{32}S^+$ ([M+H]$^+$) requires 314.1421; found 314.1420.

1'-(Phenylsulfonyl)-(5*R*,6*S*,α*S*)-*N*-Cbz-*O*-(methoxymethyl)-hex-2-enoate 146

^{n}BuLi (2.5 M in hexanes, 0.45 mL, 0.68 mmol) was added dropwise to a stirred solution of $MeSO_2Ph$ (106 mg, 0.45 mmol) in THF (1.94 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 20 min. A solution of ester **117** (186 mg, 0.45 mmol) in THF (2.81 mL) was added dropwise, and the resulting mixture stirred at −78 °C for 1.5 h, then warmed to rt and stirred for a further 1 h. Sat aq NH_4Cl (1 mL) was added and the resultant mixture allowed to warm to rt. The aqueous layer was extracted with CH_2Cl_2, then washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave **146** as a yellow oil (180 mg, 77%, >95:5 dr); $[\alpha]_D^{25}$ −1.25 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3026 (C−H), 2973 (C−H), 1679 (C=O); δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, *J* 6.7, C(6)*H*$_3$), 1.36 (3H, d, *J* 6.9, (α)*Me*), 3.00 (1H, dd, *J* 7.8, 6.7, C(5)*H*), 3.32 (3H, s, O*Me*), 3.82 (1H, d, *J* 14.1, NC*H*$_A$CH$_B$), 3.88 (1H, d, *J* 14.1, NCH$_A$C*H*$_B$), 3.92 (1H, q, *J* 6.9, C(α)*H*), 3.99 (1H, ddd, *J* 7.8, 6.4, 1.2, C(4)*H*), 4.06 (1H, d, *J* 13.6, PhSO$_2$C*H*$_A$CH$_B$), 4.11 (1H, d, *J* 13.6, PhSO$_2$CH$_A$C*H*$_B$), 4.43 (1H, d, *J* 6.9, OC*H*$_A$CH$_B$), 4.46 (1H, d, *J* 6.9, OC*H*$_A$CH$_B$), 6.08 (1H, dd, *J* 16.0, 1.2, C(2)*H*), 6.40 (1H, dd, *J* 16.0, 6.4, C(3)*H*); δ_C (101 MHz, $CDCl_3$) 14.4 (*C*(6)), 14.4 ((α)*Me*), 50.4 (N*C*H$_2$), 55.1 (*C*(5)), 55.8 (O*Me*), 56.4 (*C*(α)), 64.2 (*C*H$_2$SO$_2$Ph), 78.6 (*C*(4)), 95.4 (O*C*H$_2$), 126.9-134.3 (*Ar*), 129.2 (*C*(2)), 150.7 (*C*(3)), 182.7 (*C*(1)); m/z (ESI$^+$) 522 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{36}NO_5S^+$ ([M+H]$^+$) requires 522.23087; found 522.23065.

(2*S*,3*R*,6*S*)-*N*-Cbz-*O*-Methoxymethyl-2-methyl-6-((phenylsulfonyl)methyl)piperidine 147

1 M aq Na_2CO_3 (5.27 mL) was added to a vigorously stirred solution of piperidine **145** (110 mg, 0.35 mmol) in CH_2Cl_2 (3.50 mL) at rt, and the resultant suspension cooled to 0 °C. Benzyl Chloroformate (0.25 mL, 1.76 mmol) was added, and the resultant warmed to rt and stirred at rt for 2 h. The aqueous layer was extracted with CH_2Cl_2, then washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 1:1 to 2:8) gave **147** as a pale yellow oil (112 mg, 72%, >95:5 dr); $[\alpha]_D^{25}$ +2.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2981 (C−H), 2888 (C−H), 1694 (C=O); δ_H (400 MHz, $CDCl_3$) 1.09 (3H, d, *J* 7.8, NCHCH_3), 1.74 (1H, dq, *J* 14.6, 3.6, C(4)H_{eq}), 1.83 (1H, tt, *J* 13.4, 3.2, C(4)H_{ax}), 2.00 (1H, app dd, *J* 14.3, 2.7, C(5)H_{eq}), 2.15 (1H, ddt, *J* 13.5, 10.3, 5.0, C(5)H_{ax}), 3.19 (1H, app d, *J* 13.6), 3.31 (3H, s, OCH_3), 3.42 (1H, dd, *J* 13.7, 10.8, $CH_ACH_BSO_2Ph$), 3.61 (1H, br s, C(3)*H*), 4.37 (1H, app q, *J* 6.8, C(2)*H*), 4.59 – 4.70 (1H, m, C(6)*H*), 4.63 (2H, s, CO_2CH_2Ph), 4.98 (1H, d, *J* 12.5, OCH_ACH_B), 5.04 (1H, d, *J* 12.5, OCH_ACH_B), 7.26 – 7.38 (5H, m, CO_2CH_2Ph), 7.51 (2H, br s, SO_2Ph), 7.58 – 7.67 (1H, m, SO_2Ph), 7.85 (2H, br s, SO_2Ph); δ_C (126 MHz, $CDCl_3$) 19.1 (*C*(4)), 19.8 (NCH*C*H_3), 20.5 (*C*(5)), 45.5 (*C*(6)), 50.9 (*C*(2)), 55.6 (O*C*H_3), 59.3 (*C*H_2SO_2Ph), 67.4 (O*C*H_2), 72.6 (*C*(3)), 95.0 (CO_2CH_2), 128.1 (*p*-SO_2Ph), 128.2 (*o*-*Ph*), 128.6 (*m*-*Ph*), 129.4 (*o*-SO_2Ph), 134.0 (*m*-SO_2Ph), 136.6 (*p*-*Ph*), 139.3 (*i*-*Ph*), 139.4 (*i*-*Ph*), 155.5 (CO_2Ph); m/z (ESI^+) 448 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{23}H_{29}NO_6S^+$ ($[M+H]^+$) requires 448.1788; found 448.1786.

(5R,6S)-*N*-Boc-5-*O*-Methoxymethyl-6-methylpiperidin-2-one 151

A solution of Boc_2O (1.79 g, 8.22 mmol) in THF (6.3 mL) and DMAP (334 mg, 2.74 mmol) were added to a solution of lactam **121** (948 mg, 5.48 mmol) in THF (15.7 mL), and the resultant solution stirred at rt for 16 h. The reaction was concentrated in vacuo, and purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:1) gave **151** as a colourless oil (944 mg, 63%, >95:5 dr); $[\alpha]_D^{25}$ −13.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2975 (C−H), 1765 (ester C=O), 1710

(amide C=O); δ_H (400 MHz, $CDCl_3$) 1.25 (3H, d, *J* 6.8, C(6)*Me*), 1.53 (9H, s, $C(Me)_3$), 1.91 – 2.00 (1H, m, C(4)*H*), 2.06 (1H, dddd, *J* 14.0, 11.1, 7.1, 2.8, C(4)*H*), 2.44 (1H, ddd, *J* 17.8, 7.1, 2.8, C(3)*H*), 2.71 (1H, ddd, *J* 17.8, 11.1, 7.9, C(3)*H*), 3.38 (2H, s, O*Me*), 3.78 (1H, dt, *J* 4.0, 2.8, C(5)*H*), 4.42 (1H, qdd, *J* 6.8, 2.8, 1.6, C(6)*H*), 4.70 (1H, d, *J* 7.1, OCH_ACH_B), 4.73 (1H, d, *J* 7.1, OCH_ACH_B); δ_C (101 MHz, $CDCl_3$) 19.8 ((C(6)*Me*), 22.3 (C(4)), 28.2 ($C(Me)_3$), 29.9 (C(3)), 55.8 (C(6)), 55.9 (O*Me*), 73.2 (C(5)), 83.0 (*C*$(Me)_3$), 95.2 (O*C*H_2OMe), 138.0 (*C*O_2tBu)170.9 (C(O)); m/z (ESI^+) 296 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{13}H_{23}NO_5Na^+$ ($[M+Na]^+$) requires 296.1469; found 296.1469.

(5*R*,6*S*)-*N*-Boc-*O*-(Methoxymethyl)-1-(phenylsulfonyl)heptan-2-one 153

^{n}BuLi (2.5 M in hexanes, 0.46 mL, 1.14 mmol) was added dropwise to a stirred solution of $MeSO_2PT$ (264 mg, 1.14 mmol) in THF (2.95 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 20 min. A solution of lactam **151** (155 mg, 0.57 mmol) in THF (0.63 mL) was added dropwise, and the resulting mixture stirred at −78 °C for 30 min, then warmed to rt and stirred at rt for 2.5 h. Sat aq NH_4Cl (1 mL) was added, and the aqueous layer was extracted with CH_2Cl_2, then washed with brine and dried (Na_2SO_4). Concentration in vacuo, then purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 1:1) gave **153** as a yellow oil (63 mg, 22%, >95:5 dr); $[\alpha]_D^{25}$ +11.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3401 (N−H), 3001 (C−H), 2985 (C-H), 1690 (C=O) , 1705 (C=O); δ_H (400 MHz, $CDCl_3$) 1.09 (3H, d, *J* 6.8, NCH*Me*), 1.43 (9H, s, C*Me*$_3$), 1.77 (2H, q, *J* 6.5, C(4)H_2), 2.74 (2H, td, *J* 7.1, 2.7, C(3)H_2), 3.37 (3H, s, O*Me*), 3.44 (1H, td, *J* 6.5, 3.6, C(5)*H*), 3.67 (1H, br s, C(6)*H*), 4.55 (1H, d, *J* 6.9, OCH_AH_B), 4.59 (1H, d, *J* 6.9, OCH_AH_B), 4.77 (2H, s, (C(1)H_2), 5.02 (1H, br s, N*H*), 7.53 – 7.72 (5H, m, *Ph*); δ_C (101 MHz, $CDCl_3$) 15.3 (NCH*Me*), 25.4 (C(4)), 28.5 (C*Me*$_3$), 40.5 (C(3)), 48.5 (C(2)), 56.0 (O*Me*), 64.9 (C(1)), 79.4 (*C*Me_3), 81.5 (C(3)), 97.5 (O*C*H_2), 125.7, 129.7, 131.7 (*o,m,p-Ph*), 151.6 (*i-Ph*), 153.6 (SO_2CN_2), 155.5 (*C*O_2tBu), 196.6 (C(O)); m/z (ESI^+) 498 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{21}H_{32}N_5O_7{}^{32}S^+$ ($[M+H]^+$) requires 498.20170; found 498.20105.

(2*R*,3*R*,6*S*)-*N*-Boc-3-(1-Phenyl-1H-tetrazol-5-yl)-5-*O*-methoxymethyl-6-methylpiperidin-2-one 154

$[\alpha]_D^{25}$ +48.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3002 (C−H), 2978 (C−H), 1717 (C=O), 1764 (C=O); δ_H (400 MHz, $CDCl_3$) 1.39 (3H, d, *J* 6.8, C(6)*Me*), 1.51 (9H, s, C*Me*$_3$), 2.21 – 2.28 (1H, m, C(4)H_{ax}), 2.85 (1H, ddd, *J* 14.5, 12.4, 2.3, C(4)H_{eq}), 3.27 (3H, s, O*Me*), 3.90 (1H, app q, *J* 2.5, C(5)*H*), 4.31 (1H, dd, *J* 12.4, 6.9, C(3)*H*), 4.48 (1H, dtdd, *J* 8.6, 6.8, 4.4, 2.3, C(6)*H*), 4.68 (1H, d, *J* 7.3, OCH_ACH$_B$), 4.70 (1H, d, *J* 7.3, OCH$_A$CH_B), 7.53 – 7.68 (5H, m, *Ph*); δ_C (101 MHz, $CDCl_3$) 19.8 ((C(6)*Me*), 28.1 (C(*Me*)$_3$), 28.9 (C(4)), 36.5 (C(3)), 56.0 (O*Me*), 56.5 (C(6)), 72.8 (C(5)), 83.9 (*C*(Me)$_3$), 95.7 (O*C*H$_2$OMe), 126.0, 130.0, 130.8 (*o*,*m*,*p*-*Ph*), 152.2 (C(3)*C*N$_2$), 167.4 (*i*-*Ph*), 170.6 (*C*O$_2$tBu), 220.4 (*C*(O); m/z (ESI$^+$) 440 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{27}N_5O_5Na^+$ ([M+Na]$^+$) requires 440.1904; found 440.1900.

Ethyl (4*R*,5*S*)-4 *O*-methoxymethyl-5-(*N*-*tert*-butoxycarbonylamino)hexanoate 157

Pd(OH)$_2$/C (50% w/w of **117**, 1.10 g) was added to a stirred solution of **117** (2.20 g, 5.34 mmol) and Boc$_2$O (3.49 g, 16.0 mmol) in degassed EtOAc (18 mL) and the resultant black suspension was stirred at rt under a hydrogen atmosphere (5 atm) for 16 h. After depressurisation, the reaction mixture was filtered through a plug of Celite (eluent CH_2Cl_2) and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et$_2$O, 3:1, increased to 2:1) gave **157** as a yellow oil (1.36 g, 80%, >95:5 dr); $[\alpha]_D^{25}$ −7.0 (*c* 1.0 in $CHCl_3$); ν_{max} 3369, 2978, 1744, 1713; δ_H (400 MHz, $CDCl_3$) 1.10 (3H, d, *J* 6.8, C(6)H_3), 1.25 (3H, t, *J* 7.1, OCH$_2$CH_3), 1.43 (9H, s, C*Me*$_3$), 1.71–1.88 (2H, m, C(3)H_2), 2.30–2.49 (2H, m, C(2)H_2), 3.41 (3H, s, OCH$_2$OCH_3), 3.53 (1H, ddd, *J* 8.1, 4.9, 2.9, C(4)*H*), 3.72 (1H, m, C(5)*H*), 4.13 (2H, q, *J* 7.1, OCH_2CH$_3$), 4.62 (1H, d, *J* 7.0, OCH_AH$_B$OMe), 4.68 (1H, d, *J* 7.0, OCH$_A$$H_B$OMe), 5.16 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 14.4 (OCH$_2$*C*H$_3$), 15.0 (*C*(6)), 27.3 (*C*(3)), 28.6 (C*Me*$_3$), 30.8 (*C*(2)), 48.7 (*C*(5)), 56.0 (OCH$_2$O*Me*), 60.6 (O*C*H$_2$CH$_3$), 79.2 (*C*Me$_3$), 81.9 (*C*(4)), 97.5 (O*C*H$_2$OMe), 155.5 (N*C*O), 173.4 (*C*(1)); *m*/*z*

(ESI$^+$) 342 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{15}H_{29}NNaO_6^+$ ([M+Na]$^+$) requires 342.1887; found 342.1889.

(5*R*,6*S*)-1-(Dimethoxyphosphoryl)-5-methoxymethyleneoxy-6-(N-tert-butoxycarbonylamino)heptan-2-one 158

^{n}BuLi (2.5 M in hexanes, 3.98 mL, 9.95 mmol) was added dropwise to a stirred solution of dimethyl methyl phosphonate (1.08 mL, 9.95 mmol) in THF (28 mL) at −78 °C. The resultant solution was stirred at −78 °C for 30 min, then a solution of **157** (1.15 g, 3.97 mmol) in THF (5.8 mL) was added dropwise. The resultant solution was stirred at −78 °C for 30 min, before being allowed to warm to 0 °C over 1 h. Satd aq NH_4Cl (2 mL) was then added, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organics were dried ($MgSO_4$) and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:1, increased to 30–40 °C petrol/acetone, 7:3) gave **158** as a yellow oil (1.28 g, 88%, >95:5 dr); $[\alpha]_D^{25}$ −8.8 (*c* 1.0 in $CHCl_3$); ν_{max} 3320, 2978, 1709, 1251; δH (500 MHz, $CDCl_3$) 1.07 (3H, d, *J* 6.8, C(7)H_3), 1.42 (9H, s, C*Me*$_3$), 1.69–1.82 (2H, m, C(4)H_2), 2.56–2.75 (2H, m, C(3)H_2), 3.10 (2H, d, *J* 22.7, C(1)H_2), 3.40 (3H, s, OCH_2OMe), 3.50 (1H, ddd, *J* 8.3, 5.4, 3.2, C(5)*H*), 3.65–3.74 (1H, m, C(6)*H*), 3.78 (3H, d, *J* 11.2, PO*Me*), 3.79 (3H, d, *J* 11.2, PO*Me*), 4.62 (1H, d, *J* 6.9, OCH_AH_BOMe), 4.65 (1H, d, *J* 6.9, OCH_AH_BOMe), 5.13 (1H, br s, N*H*); δC (125 MHz, $CDCl_3$) 15.0 (*C*(7)), 25.7 (*C*(4)), 28.6 (C*Me*$_3$), 40.5 (*C*(3)), 41.5 (d, J_{CP} 128.4, *C*(1)), 53.2 (d, *J* 6.6, PO*Me*), 53.2 (d, *J* 6.6, PO*Me*), 56.0 (OCH_2OMe), 79.3 (*C*Me$_3$), 81.6 (*C*(5)), 97.5 (OCH_2OMe), 155.5 (N*C*O), 201.4 (d, J 6.3, *C*(2)); m/z (ESI+) 390 ([M+Na]$^+$, 100%); HRMS (ESI+) $C_{15}H_{30}NNaO_7P$+ ([M+Na]$^+$) requires 390.1652; found 390.1654.

(*E*)-Dec-4-en-3-one 162

NaH (60% dispersion in mineral oil, 102 mg, 2.55 mmol) was stirred in THF (20 mL) at rt for 30 min. The suspension was then cooled to 0 °C, and a solution of diethyl (2-oxobutyl) phosphonate (530 mg, 2.55 mmol) in THF (3.0 mL) was added. The resultant was stirred at rt for 15 min, then a solution of hexanal (382 mg, 3.82 mmol) in THF (3.0 mL) was added. The mix was then refluxed for 2.5 h. The reaction was quenched by the addition of sat aq NH_4Cl (1.00 mL). The aqueous layer was then extracted with Et_2O (3 × 20 mL) and the combined organics were washed with brine, then dried ($MgSO_4$), and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **162** as a yellow oil (325 mg, 83%, >91:9 dr);[126] δ_H (400 MHz, $CDCl_3$) 0.89 (1H, t, *J* 7.0, C(10)H_3), 1.09 (1H, t, *J* 7.4, C(1)H_3), 1.24 – 1.36 (4H, m, C(8)H_2, C(9)H_2, 1.41 – 1.51 (2H, m, C(7)H_2), 2.20 (2H, qd, *J* 7.0, 1.6, C(6)H_2), 2.56 (1H, q, *J* 7.4, C(2)H_2), 6.09 (1H, dt, *J* 15.9, 1.6, C(4)*H*), 6.83 (1H, dt, *J* 15.9, 7.0, C(5)*H*).

6.2 Experimental for Chapter 3

(1*R*,2*S*,3*S*,6*S*,*E*,*E*,*E*)-*N*-Methyl-2-Methyl-6-(deca-1′,3′,5′-trienyl)piperidin-3-ol–1 oxide [microgrewiapine C] 72

*m*CPBA (33%) (17 mg, 0.08 mmol) was added to a solution of **186** (20 mg, 0.08 mmol) in $CHCl_3$ (washed through basic alumina) (0.80 mL). After 30 s, Et_3N (0.07 mL, 0.46 mmol) was added and the reaction mix concentrated in vacuo. The residue was then dissolved in CH_2Cl_2 and the organic washed with sat aq $NaHCO_3$. The organic layers were then concentrated *in vacuo*, and filtered through basic alumina (eluent $CHCl_3$, then 3:1 ($CHCl_3$:MeOH). The combined fractions were then further purified *via* flash column chromatography (eluent $CHCl_3$/MeOH/Et_3N 14:1:0.1) to give **72** as a white solid (10 mg, 47%, >95:5 dr); mp 135–136 °C; $[\alpha]_D^{25}$ +77.1 (*c* 1.0 in MeOH); ν_{max} (film) 3377 (O−H), 2956 (C-H) ,2926 (C-H) ,1672 (C-N); δ_H (500 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.2, C(10′)H_3), 1.24 – 1.39 (4H, m, C(8′)H_2, C(9′)H_2), 1.52 – 1.60 (1H, m, C(5)H_{eq}), 1.57 – 1.63 (1H, m, C(4)H_{eq}), 1.67 (3H, d, *J* 6.5, C(2)*Me*), 2.03 (1H, ddd, *J* 13.7, 6.5, 3.4, C(4)H_{ax}), 2.11 (2H, app q, *J* 6.8, C(7′)H_2), 2.65 – 2.75 (1H, m, C(5)H_{ax}), 2.85 (3H, s, N*Me*), 3.00 (1H, qd, *J* 6.5, 1.7, C(2)*H*), 3.46 (1H, ddd, *J* 11.9, 9.0, 2.8, C(6)*H*), 3.81 – 3.85 (1H, m, C(3)*H*), 5.76 (1H, dt, *J* 14.7, 7.1, C(6′)*H*), 6.03 (1H, dd, *J* 15.6, 9.0, C(1′)*H*), 6.09 – 6.25 (4H, m, C(2′)-C(5′)*H*); δ_C (126 MHz, $CDCl_3$) 13.4 (C(2)*Me*), 14.1 (*C*(10)), 22.4 (*C*(9′)), 23.8 (*C*(5)), 31.5 (*C*(8′)), 32.0 (*C*(4)), 32.6 (*C*(7′)), 54.0 (N*Me*), 68.4 (*C*(2)), 71.0 (*C*(3)), 79.3 (*C*(6)), 127.9 (*C*(1′)), 129.0 (*C*(2′)), 130.0 (*C*(4′)), 135.1 (*C*(5′)), 135.6 (*C*(3′)), 137.4 (*C*(6′)); m/z (ESI$^+$) 280 ([M+H]$^+$, 100%), HRMS (ESI$^+$) $C_{17}H_{30}O_2N^+$ ([M+H]$^+$) requires 280.2271; found 280.2270.

(2*S*,3*R*,6*S*,1′*E*,3′*E*,5′*E*)-N-Methyl-2-Methyl-6-(deca-1′,3′,5′-trienyl)piperidin-3-ol [Microgrewiapine A] ***ent*-73**

Step 1: NaH (60% dispersion in mineral oil, 13.0 mg, 0.325 mmol) was stirred in THF (0.57 mL) at rt for 5 min. The resultant suspension was then cooled to 0 °C, a solution of **158** (123 mg, 0.310 mmol) in THF (1.51 mL) was added, and the resultant solution was stirred at rt for 15 min. A solution of (*E*,*E*)-2,4- nonadienal (62 mg, 0.46 mmol) in THF (0.95 mL) was then added, and the resultant suspension was stirred at rt for 1 h. The resultant solution was then heated to 72 ºC, and stirred at 72 ºC for 12 h. The resultant solution was allowed to cool to rt, then poured into a mixture of satd aq brine (6 mL) and H_2O (6 mL). The aqueous layer was extracted with EtOAc (3 × 7 mL), then the combined organics were dried ($MgSO_4$) and concentrated in vacuo. The residue was dissolved in DMF (0.7 mL), and satd aq $NaHSO_3$ (2.0 mL) was added. The resultant suspension was stirred at rt for 10 min, then diluted with H_2O (2 mL). The resultant solution was extracted with Et_2O (2 × 3 mL), and the combined organics were washed with H_2O (2 × 2 mL, then 1 mL), then dried (Na_2SO_4) and concentrated in vacuo.

Step 2: The residue from the previous step was dissolved in CH_2Cl_2 (8.8 mL) and the resultant solution was cooled to 0 ºC. TFA (4.5 mL) was added dropwise, and the resultant solution was stirred at 0 ºC for 10 min. The resultant solution was then concentrated in vacuo.

Step 3: The residue from the previous step was dissolved in CH_2Cl_2 (11.0 mL); the resultant solution and conc aq HCl (1.7 mL) were then simultaneously added to a stirred suspension of $NaBH_3CN$ (227 mg, 3.61 mmol) in EtOH (22 mL) at 0 ºC. The resultant suspension was stirred at 0 ºC for 15 min, then further portions of $NaBH_3CN$ (113 mg, 1.80 mmol) and conc aq HCl (0.80 mL) were added sequentially. The resultant suspension was stirred at 0 ºC for 15 min, then H_2O (10 mL) was added. The resultant mixture was poured into a mixture of satd aq $NaHCO_3$ (110 mL) and H_2O (110 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 90 mL), then the

combined organics were dried (Na_2SO_4) and concentrated in vacuo. The residue was then dissolved in 1.25 M methanolic HCl (2.0 mL) at rt, and the resultant solution was stirred at rt for 12 h. The resultant solution was then poured into 1 M aq KOH (4.6 mL), the aqueous layer was extracted with $CHCl_3$/ iPrOH (v:v, 3:1, 4 × 4.6 mL), then the combined organics were dried (Na_2SO4) and concentrated in vacuo. Step 4: The residue from the previous step was dissolved in MeCN (12.0 mL), and 35% aq HCHO (0.50 mL, 4.47 mmol) was added. The resultant solution was cooled to 0 ºC and $NaBH_3CN$ (46 mg, 0.73 mmol) was added. The resultant solution was allowed to warm to rt, and then stirred at rt for 16 h. The resultant solution was poured into 1 M aq NaOH (15 mL) and then extracted with CHCl3 (3 × 10 mL). The combined organics were washed with brine (20 mL), then dried (Na_2SO_4) and concentrated in vacuo. Purification via flash column chromatography (eluent $CHCl_3$/MeOH/35% aq NH_4OH, 200:3:1, increased to $CHCl_3$/MeOH/35% aq NH_4OH 90:10:1) gave a yellow oil (Rf = 0.21 in $CHCl_3$/MeOH/35% aq NH_4OH 90:10:1). This was dissolved in 6 M aq HCl (2.0 mL) and the resultant solution was washed with Et_2O (3 × 2 mL), then basified by the addition of 2 M aq NaOH until pH >14 was achieved. The resultant solution was washed with Et_2O (3 × 3 mL), then the combined organics were dried (Na_2SO_4) and concentrated in vacuo to give *ent*-**73** as an off-white solid (34 mg, 42% from **158**, >95:5 dr); mp 125–126 °C; $[\alpha]_D^{25}$ −9.3 (c 0.05 in MeOH); $[\alpha]_D^{25}$ −16.0 (c 0.1 in MeOH); $[\alpha]_D^{25}$ −24.6 (c 0.5 in MeOH); $[\alpha]_D^{25}$ −26.2 (c 1.0 in MeOH); ν_{max} 3658, 2980, 2925; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.1, C(10′)H_3), 1.26 (3H, d, *J* 6.1, C(2)Me), 1.29–1.41 (5H, m, C(4)H_A, C(8′)H_2, C(9′)H_2), 1.49 (1H, tdd, *J* 13.3, 11.2, 3.5, C(5)H_A), 1.64 (1H, ddt, *J* 13.3, 4.0, 3.1, C(5)H_B), 1.82 (1H, dq, *J* 8.9, 6.1, C(2)H), 2.02 (1H, ddt, *J* 11.7, 4.7, 3.3, C(4)H_B), 2.09 (2H, qd, *J* 7.2, 1.4, C(7′)H_2), 2.21 (3H, s, NMe), 2.47 (1H, ddd, *J* 11.2, 8.9, 3.0, C(6)H), 3.26 (1H, ddt, *J* 8.9, 7.4, 4.6, C(3)H), 5.52 (1H, dd, *J* 14.6, 8.9, C(1′)H), 5.69 (1H, dt, *J* 14.3, 7.2, C(6′)H), 6.00–6.19 (4H, m, C(2′)H–C(5′)H); δ_C (100 MHz, CDCl3) 14.0 (C(10′)), 16.4 (C(2)Me), 22.3 (C(9′)), 31.3 (C(5)), 31.6 (C(8′)), 32.6 (C(7′)), 33.5 (C(4)), 40.4 (NMe), 66.2 (C(2)), 67.6 (C(6)), 72.6 (C(3)), 130.1, 130.3, 131.6, 132.7

(C(2)′–C(5′)), 135.7 (C(6′)), 136.7 (C(1′)); m/z (ESI$^+$) 264 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{17}H_{30}NO^+$ ([M+H]$^+$) requires 264.2322; found 264.2323.

(1*R*,2*S*,3*R*,6*S*,1′*E*,3′*E*,5′*E*)-N-Methyl-2-Methyl-6-(deca-1′,3′,5′-trienyl)piperidin-3-ol-N-oxide [Microgrewiapine B] 74

m-CPBA (33% by wt, 34 mg, 0.15 mmol) was added to a stirred solution of *ent*-**73** (40 mg, 0.15 mmol) in $CHCl_3$ (1.6 mL)[3] at rt, and the resultant solution was stirred at rt for 30 s. Et_3N (0.13 mL, 0.92 mmol) was then added and the resultant solution was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (5 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (5 mL), then concentrated in vacuo. Purification via flash column chromatography on activated basic alumina (eluent $CHCl_3$, then $CHCl_3$/MeOH, 3:1) gave **74** as a white solid (32 mg, 76%, >95:5 dr); mp 128–129 °C; $[\alpha]_D^{25}$ +3.9 (c 0.1 in MeOH); $[\alpha]_D^{25}$ +5.3 (c 0.5 in MeOH); $[\alpha]_D^{25}$ +6.7 (c 1.0 in MeOH); ν_{max} 3337, 2957, 2926, 1635; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.2, C(10′)H_3), 1.26–1.41 (4H, m, C(8′)H_2, C(9′)H_2), 1.41–1.51 (1H, m, C(4)H_A), 1.57 (3H, d, *J* 6.2, C(2)Me), 1.59–1.62 (1H, m, C(5)H_A), 2.08–2.15 (3H, m, C(4)H_B, C(7′)H_2), 2.39 (1H, qd, *J* 14.1, 3.9, C(5)H_A), 2.81 (1H, dq, *J* 9.5, 6.2, C(2)H), 2.93 (3H, s, NMe), 3.40 (1H, ddd, *J* 12.0, 9.0, 2.8, C(6)H), 3.97 (1H, ddd, *J* 11.0, 9.5, 4.7, C(3)H), 5.75 (1H, dt, *J* 14.7, 7.1, C(6′)H), 6.01 (1H, dd, *J* 15.6, 9.0, C(1′)H), 6.05–6.25 (4H, m, C(2′)H–C(5′)H); δ_C (125 MHz, CDCl3) 10.5 (C(2)Me), 14.1 (C(10′)), 22.4 (C(9′)), 26.4 (C(5)), 31.5 (C(8′)), 32.6 (C(4)), 32.9 (C(7′)), 55.1 (NMe), 67.6 (C(3)), 76.0 (C(2)), 78.6 (C(6)), 128.1 (C(1′)), 129.2 (C(2′)), 130.1, 135.0, 135.6 (C(3′)–C(5′)), 137.2 (C(6′)); m/z (ESI+) 280 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{17}H_{30}O_2N^+$ ([M+H]$^+$) requires 280.2271; found 280.2272.

[3] The chloroform used as the reaction solvent in the preparation of **74** was first neutralised by passage through a column of activated basic Brockman I alumina.

***tert*-Butyl (2*R*,3*S*,α*S*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]butanoate 178**

Step 1: DMSO (0.77 mL, 11 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (0.46 mL, 5.4 mmol) in CH_2Cl_2 (11.0 mL) at−78 °C and the resultant mixture was stirred at −78 °C for 20 min. A solution of **68** (1.00 g, 2.71 mmol, >95:5 dr) in CH_2Cl_2 (5.0 mL) was added and the resultant mixture was stirred at −78 °C for 30 min. Et_3N (2.26 mL, 16.3 mmol) was added then the reaction mixture was allowed to warm to rt and stirred at rt for 30 min H_2O (25 mL) was then added, the reaction mixture extracted with CH_2Cl_2 (50 mL), and the combined organics were dried ($MgSO_4$) and concentrated in vacuo to give **177**.

Step 2: $NaBH_4$ (108 mg, 2.85 mmol) was added to a stirred solution of the residue of **177** from the previous step in MeOH (10.0 mL) at −20 °C and the resultant mixture was stirred at −20 °C for 2 h, then allowed to warm to rt and concentrated in vacuo. The reaction mixture was then partitioned between CH_2Cl_2 (40 mL) and H_2O (30 mL), and the aqueous layer was extracted with CH_2Cl_2 (150 mL). The combined organics were dried ($MgSO_4$) and concentrated in vacuo to give **178** as a pale yellow oil (980 mg, 97%, >95:5 dr); $[\alpha]_D^{25}$ +65.8 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.15 (3H, d, *J* 6.7, C(4)H_3), 1.40 (9H, s, CMe_3), 1.45 (3H, d, *J* 7.0, C(α)*Me*), 3.05 (1H, dq, *J* 8.6, 6.7, C(3)*H*), 3.62–3.73 (2H, m, C(2)*H*, NCH_AH_BPh), 3.79 (1H, d, *J* 13.6, NCH_AH_BPh), 4.04 (1H, q, *J* 7.0, C(α)*H*), 7.16–7.39 (10H, m, *Ph*).

tert-Butyl (*R*,*S*,*S*)-*O*-methoxymethyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]butanoate 179

NaH (60% dispersion in mineral oil, 116 mg, 1.60 mmol) was stirred in THF (10.1 mL) for 30 min. The resultant suspension was then cooled to 0 °C, a solution of **178** (890 mg, 2.41 mmol) in THF (2.0 mL) was added, and the resultant solution was stirred at 0 °C for 30 min. MOMCl (0.22 mL, 2.9 mmol) was then added and the resultant solution was allowed to warm to rt over 12 h. H_2O (12 mL) was then added and the aqueous layer was extracted with Et_2O (3 × 10 mL). The

combined organics were washed with brine (10 mL), then dried ($MgSO_4$) and concentrated in vacuo to give **179** as a yellow oil (981 mg, 99%, >95:5 dr); $[\alpha]_D^{25}$ −9.7(*c* 1.0 in $CHCl_3$); ν_{max} (film) 2974 (C−H), 2931 (C−H), 1737 (C=O); δ_H (400 MHz, $CDCl_3$) 1.14 (3H, d, *J* 7.0, C(4)H_3), 1.31 (3H, d, *J* 6.9, C(α)*Me*), 1.43 (9H, s, CMe_3), 3.26 (3H, s, O*Me*), 3.25 – 3.39 (1H, m, C(3)*H*), 3.78 (1H, d, *J* 14.7, NC$H_A$$H_B$Ph), 3.83 (1H, d, *J* 5.9, C(2)*H*), 3.94 (1H, d, *J* 14.7, NCH$_A$$H_B$Ph), 4.15 (1H, q, *J* 6.9, C(α)*H*), 4.41 (1H, d, *J* 6.8, OCH_ACH$_B$), 4.53 (1H, d, *J* 6.8, OCH$_A$CH_B), 7.16 – 7.49 (10H, m, *Ph*); δ_C (101 MHz, $CDCl_3$) 14.1 (*C*(4)), 17.6 (C(α)*Me*), 28.1 (CMe_3), 50.6 (N*C*H$_2$), 55.6 (*C*(3)), 56.2 (O*Me*), 59.2 (*C*(α)), 81.5 (*C*(3)), 96.6 (O*C*H$_2$), 126.6, 126.7, 128.0, 128.1, 128.1, 128.6 (*o,m,p-Ph*), 142.3 (*i-Ph*), 145.0 (*i-Ph*), 171.2 (*C*(1)); m/z (ESI$^+$) 436 ([M+Na]$^+$, 100%), HRMS (ESI$^+$) $C_{25}H_{35}O_4N^{23}Na^+$ ([M+Na]$^+$) requires 436.2458; found 436.2464

(*R,S,S*)-*O*-methoxymethyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]butanal 180

Ethyl(*S,S,E*)-5-(*N*-benzyl-*N*-(α-methylbenzyl)amino)-*O*-methoxymethyl)hex-2-enoate 181

Step 1: DIBAL-H (1.0 M in PhMe, 45 mL, 45 mmol) was added to a stirred solution of **179** (6.27 g, 15.2 mmol) in CH_2Cl_2 (150 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 30 min. MeOH (90 mL) was then added, and the resultant solution was allowed to warm to rt before satd aq Rochelle salt (90 mL) and CH_2Cl_2 (90 mL) were added sequentially. The resultant mixture was stirred at rt for 16 h. The aqueous layer was then extracted with CH_2Cl_2 (3 × 90 mL) and the combined organics were washed with brine (50 mL), then dried ($MgSO_4$) and concentrated in vacuo to give **180** as a pale yellow oil (4.73 g, 91%, >95:5 dr); $[\alpha]_D^{25}$ −91.4 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2969 (C−H), 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 1.34 (3H, d, *J* 6.9, C(4)H_3), 1.38 (3H, d, *J* 7.0, C(α)*Me*), 3.36 (3H, s, OCH_3), 3.51 (1H, qd, *J* 6.9, 4.0, C(3)*H*), 3.65 (1H, d, *J* 13.6, NC$H_A$$H_B$Ph), 3.81 (1H, dd, *J* 4.0, 0.7, C(2)*H*), 4.00 (1H, q, *J* 7.0, C(α)*H*), 4.22 (1H, d, *J* 13.6, NCH$_A$$H_B$Ph), 4.59 (1H, d, *J* 6.9, OCH_ACH$_B$), 4.64 (1H, d, *J* 6.9, OCH$_A$CH_B), 7.19 – 7.40 (10H, m,

Ar), 8.86 (1H, d, *J* 13.6, C(1)*H*); δ_C (101 MHz, $CDCl_3$) 12.8 (C(α)*Me*), 14.3 (*C*(4)), 51.6 (*C*(3)), 51.7 (N*C*H_2Ph), 56.1 (O*C*H_3), 56.4 (*C*(α)), 87.2 (*C*(2)), 97.0 (O*C*H_2), 127.0, 128.1, 128.4, 128.4, 128.4, 129.2 (*o*, *m*, *p* – Ar), 141.1 (*i*-Ph), 143.8 (*i*-Ph), 201.7 (*C*(1)); m/z (ESI^+) 342 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{21}H_{28}NO_3^+$ ($[M+H]^+$) requires 342.2064; found 342.2065

Step 2: $Ph_3P{=}CHCO_2Et$ (7.41 g, 21.3 mmol) was added to a stirred solution of **180** (4.84 g, 14.2 mmol) in CH_2Cl_2 (37 mL) at rt, and the resultant solution was stirred at rt for 60 h before being concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1 increased to 7:3) gave **181** as a yellow oil (5.20 g, 81% from **179**, >95:5 dr); $[\alpha]_D^{25}$ −65.4 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2990 (C−H), 2886 (C−H), 1723 (C=O); δ_H (400 MHz, $CDCl_3$) 1.12 (3H, d, *J* 7.0, C(6)H_3), 1.22 (3H, t, *J* 7.1, OCH_2CH_3), 1.28 (3H, d, *J* 6.7, C(α)*Me*), 3.01 (1H, qd, *J* 7.0, 4.5, C(5)*H*), 3.11 (3H, s, O*Me*), 3.68 (1H, d, *J* 14.3, NCH_ACH_B), 3.85 (1H, ddd, *J* 6.1, 4.5, 1.4, C(4)*H*), 3.93 (1H, d, *J* 14.3, NCH_ACH_B), 3.96 (1H, q, *J* 6.7, C(α)*H*), 4.11 (2H, qd, *J* 7.1, 1.1, OCH_2CH_3), 4.27 (1H, d, *J* 6.6, OCH_AH_B), 4.35 (1H, d, *J* 6.6, OCH_AH_B), 5.82 (1H, dd, *J* 15.8, 1.3, C(2)*H*), 6.79 (1H, dd, *J* 15.8, 6.1, C(3)*H*), 7.09 – 7.44 (10H, m, *Ph*); δ_C (101 MHz, $CDCl_3$) 13.5 (*C*(6)), 13.7 (C(α)*Me*), 14.4 (OCH_2CH_3), 51.5 (N*C*H_2Ph), 54.8 (*C*(5)), 55.7 (O*Me*), 56.7 (C(α)), 60.4 (O*C*H_2CH_3), 80.2 (C(4)), 94.9 (O*C*H_2), 122.6 (*C*(2)), 126.7, 126.9, 128.0, 128.2, 128.4, 128.7 (*o*, *m*, *p*-Ar), 141.5 (*i*-Ph), 144.3 (*i*-Ph), 146.7 (*C*(3)), 166.2 (*C*(1)); m/z (ESI^+) 434 ($[M+Na]^+$, 100%), HRMS (ESI^+) $C_{25}H_{33}O_4N^{23}Na^+$ ($[M+Na]^+$) requires 434.2302; found 434.2237.

Ethyl(4*S*,5*S*)-5-(*N*-Boc-amino)-*O*-methoxymethyl hexanoate 182

$Pd(OH)_2/C$ (50% w/w of **181**, 2.25 g) was added to a stirred solution of **181** (4.50 g, 10.9 mmol) and Boc_2O (7.96 g, 36.5 mmol) in degassed EtOAc (42 mL) and the resultant black suspension was stirred at rt under a hydrogen atmosphere (5 atm) for 16 h. After depressurisation, the reaction mixture was filtered through a plug of Celite (eluent CH_2Cl_2) and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 3:1 increased to 2:1)

gave **182** as a yellow oil (2.96 g, 85%, >95:5 dr); $[\alpha]_D^{25}$ −15.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3402 (N−H), 2967 (C−H), 1738 (C=O) 1711 (C=O); δ_H (500 MHz, $CDCl_3$) 1.15 (3H, d, *J* 6.8, C(6)H_3), 1.23 (3H, t, *J* 7.1, OCH_2CH_3), 1.42 (9H, s, CMe_3), 1.73 – 1.87 (2H, m, C(3)H_2), 2.29 – 2.46 (2H, m, C(2)H_2), 3.38 (3H, s, OCH_3), 3.47 (1H, td, *J* 6.6, 2.9, C(4)*H*), 3.71 – 3.82 (1H, m, C(5)*H*), 4.11 (2H, q, *J* 7.1, OCH_2CH_3), 4.62 (1H, d, *J* 6.9, OCH_AH_B), 4.66 (1H, d, *J* 6.9, OCH_AH_B), 4.71 (1H, br d, *J* 6.0, NBoc*H*); δ_C (126 MHz, $CDCl_3$) 14.3 (OCH_2CH_3), 18.1 (C(6)), 26.6 (C(3)), 28.5 (CMe_3), 30.4 (C(2)), 48.3 (C(5)), 56.1 (OCH_3), 60.5 (OCH_2CH_3), 79.3 (*C*Me$_3$), 80.0 (C(4)), 96.8 (OCH_2), 155.7 (*C*O_2^{t}Bu), 173.4 (C(1)); m/z (ESI$^+$) 342 ([M+Na]$^+$, 100%), HRMS (ESI$^+$) $C_{15}H_{29}NO_6Na^+$ ([M+Na]$^+$) requires 342.1887; found 342.1888.

(5*S*,5*S*)-*N*-Boc-*O*-(methoxymethyl)-1-(dimethoxyphosphoryl)heptan-2-one 183

^{n}BuLi (2.5 M in hexanes, 3.31 mL, 8.28 mmol) was added dropwise to a stirred solution of dimethyl methylphosphonate (0.89 mL, 8.28 mmol) in THF (24 mL) at −78 °C. The resultant solution was stirred at −78 °C for 30 min, then a solution of **182** (1.06 g, 3.31 mmol) in THF (4.88 mL) was added dropwise. The resultant solution was stirred at −78 °C for 30 min, before being allowed to warm to 0 °C over 1 h. Satd aq NH_4Cl (1 mL) was then added, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organics were dried ($MgSO_4$) and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:1, increased to 30–40 °C petrol/acetone, 7:3) gave **183** as a clear oil (1.21 g, 92%, >95:5 dr); $[\alpha]_D^{25}$ −21.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3309(N−H), 2973 (C−H), 1715 (C=O), 1265 (P=O); δ_H (400 MHz, $CDCl_3$) 1.15 (3H, d, *J* 6.8, C(7)H_3), 1.43 (9H, s, CMe_3), 1.70 – 1.86 (2H, m, C(4)H_2), 2.71 (2H, app q, *J* 7.4, C(3)H_2), 3.08 (1H, d, *J* 22.5, C(1)H_A), 3.11 (1H, d, *J* 22.5, C(1)H_B), 3.39 (3H, s, O*Me*), 3.45 (1H, td, *J* 6.6, 2.9, C(5)*H*), 3.70 – 3.81 (1H, m, C(6)*H*), 3.78 (3H, d, *J* 11.2, PO*Me*), 3.79 (3H, d, *J* 11.2, PO*Me*), 4.61 (1H, d, *J* 6.8, OCH_AH_B), 4.67 (1H, d, *J* 6.8, OCH_AH_B), 4.65 – 4.72 (1H, s, N*H*); δ_C (101 MHz, $CDCl_3$) 18.1 (C(*7*)), 24.9 (C(*4*)), 28.5 (CMe_3), 40.2 (C(*3*)), 41.4 (d, *J* 128.4, C(*1*))), 48.1 (C(*6*)), 53.1 (d, *J* 6.6, P(O*Me*), 53.1 (d, *J* 6.6, P(O*Me*), 56.0 (O*Me*), 79.3 (*C*Me$_3$), 79.8 (C(*5*)), 96.7

(O*C*H$_2$), 155.7 (*C*O$_2$^{t}Bu), 201.5 (d, *J* 6.4,*C*(2)); m/z (ESI$^+$) 420 ([M+Na]$^+$, 100%), HRMS (ESI$^+$) $C_{16}H_{32}NO_8PNa^+$ ([M+Na]$^+$) requires 420.1758; found 420.1759.

(2*S*,3*S*,6*S*,*E*,*E*,*E*)-2-Methyl-6-(deca-1′,3′,5′-trienyl)piperidin-3-ol [3-epi-microcosamine A] 185

Step 1: NaH (60% dispersion in mineral oil, 14.0 mg, 0.362 mmol) was stirred in THF (0.66 mL) for 5 min, then cooled to 0 °C. A solution of **183** (139 mg, 0.349 mmol) in THF (1.36 mL) was added, and the resultant yellow solution allowed to stir at rt for 15 min. A solution of (*E*,*E*)-2,4-nonadienal (71 mg, 0.52 mmol) in THF (1.11 mL) was added and the reaction stirred at rt for 1 h. The mixture was then heated to 72 ºC and stirred overnight. The reaction was then cooled to rt, and poured into a mixture of sat aq brine (7 mL) and H_2O (7 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL), then the combined organics were dried ($MgSO_4$) and concentrated in vacuo. The residue was dissolved in DMF (3.0 mL), and satd aq $NaHSO_3$ (6.0 mL) was added. The resultant suspension was stirred at rt for 10 min, then diluted with H_2O (6 mL). The aqueous layer was extracted with Et_2O (6 mL), and the combined organics were washed with H_2O (2 × 4 mL, then 1 mL), then dried (Na_2SO_4) and concentrated in vacuo.

Step 2: The residue from the previous step was dissolved in CH_2Cl_2 (11.3 mL) and the resultant solution was cooled to 0 ºC. TFA (6.0 mL) was added dropwise, and the resultant mixture was stirred at 0 ºC for 10 min. The resultant maroon solution was then concentrated in vacuo.

Step 3: The residue from the previous step was dissolved in CH_2Cl_2 (15 mL); the resultant solution and conc aq HCl (2.4 mL) were then simultaneously added to a stirred suspension of $NaBH_3CN$ (302 mg, 4.79 mmol) in EtOH (30 mL) at 0 ºC. The resultant suspension was stirred at 0 ºC for 15 min, then further portions of $NaBH_3CN$ (145 mg, 2.30 mmol) and conc aq HCl (1.5 mL) were added sequentially. The resultant suspension was stirred at 0 ºC for 15 min, then H_2O (10 mL) was added. The resultant mixture was poured into a mixture of satd aq $NaHCO_3$ (150

mL) and H_2O (150 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL), then the combined organics were dried (Na_2SO_4) and concentrated in vacuo.

Step 4: The residue from the previous step was then dissolved in a methanolic solution of HCl (1.25 M, 3.2 mL) and stirred at rt overnight. The mixture was then poured into 1 M aq KOH (6 mL). The aqueous layer was extracted with $CHCl_3$/^{i}PrOH (3:1) (4 × 6 mL), then the combined organics were dried (Na_2SO_4) and concentrated in vacuo. Purification via flash column chromatography (eluent $CHCl_3$/(Ammonia, ca. 7 N solution in MeOH) 99:1) gave a yellow oil. This was dissolved in 6 M aq HCl (2.0 mL) and washed with Et_2O (3 × 2 mL). The aqueous layer was then basified by the addition of 2 M aq NaOH, and washed with Et_2O (3 × 3 mL). The combined organics were then dried (Na_2SO_4), and concentrated in vacuo to give **185** as a white solid (15 mg, 17%, >95:5 dr); $[\alpha]_D^{25}$ +6.2 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3352 (O−H), 3349 (N-H), 2956 (C-H), 2926 (C-H); δ_H (500 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.2, C(10)H_3), 1.11 (3H, d, *J* 6.5, C(2)*Me*), 1.27 – 1.40 (4H, m, C(8′)H_2, C(9′)H_2), 1.45 – 1.57 (2H, m, C(4)H_A, C(5)H_A), 1.90 – 1.95 (1H, m, C(4)H_B), 2.00 – 2.06 (1H, m, C(5)H_B), 2.09 (2H, app q, *J* 8.8, 7.0, C(7′)H_2), 2.81 (1H, qd, *J* 6.5, 1.4, C(2)*H*), 3.19 (1H, q, *J* 7.2, C(6)*H*), 3.53 – 3.56 (1H, m, C(3)*H*), 5.61 (1H, dd, *J* 15.3, 7.2, C(1′)*H*), 5.70 (1H, dt, *J* 14.6, 7.0, C(6′)*H*), 6.01 – 6.21 (4H, m, C(2′)*H*, C(3′)*H*, C(4′)*H*, C(5′)*H*); δ_C (126 MHz, $CDCl_3$) 14.1 (*C*(10)), 18.8 (C(2)*Me*), 22.4 (*C*(9′)), 26.6 (*C*(5)), 31.6 (*C*(8′)), 32.0 (*C*(4)), 32.6 (*C*(7′)), 55.7 (*C*(2)), 59.6 (*C*(6)), 67.6 (*C*(3)), 130.0 (*C*(2′)), 130.3, 130.4 (*C*(3′-4′)), 133.1 (*C*(5′)), 135.6 (*C*(1′)), 135.8 (*C*(6′)); m/z (ESI^+) 250 ($[M+H]^+$, 100%), HRMS (ESI^+) $C_{16}H_{28}NO^+$ ($[M+H]^+$) requires 250.2165; found 250.2167.

(2*S*,3*S*,6*S*,*E*,*E*,*E*)- *N*-Methyl-2-Methyl-6-(deca-1′,3′,5′-trienyl)piperidin-3-ol 186

Step 1: NaH (60% dispersion in mineral oil, 11.1 mg, 0.278 mmol) was stirred in THF (0.52 mL) for 5 min, then cooled to 0 °C. A solution of **183** (110 mg, 0.277 mmol) in THF (1.08 mL) was added, and the resultant yellow solution allowed to stir at rt for 15 min. A solution of (*E*,*E*)-2,4-nonadienal (56 mg, 0.41 mmol) in THF (0.88 mL) was added and the reaction stirred at rt for 1 h. The mixture was then heated to 72 ºC and stirred overnight. The reaction was then cooled to rt, and poured into a mixture of sat aq brine (5 mL) and H_2O (5 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL), then the combined organics were dried ($MgSO_4$) and concentrated in vacuo. The residue was dissolved in DMF (2 mL), and satd aq $NaHSO_3$ (5 mL) was added. The resultant suspension was stirred at rt for 10 min, then diluted with H_2O (5 mL). The aqueous layer was extracted with Et_2O (5 mL), and the combined organics were washed with H_2O (2 × 3 mL, then 1 mL), then dried (Na_2SO_4) and concentrated in vacuo.

Step 2: The residue from the previous step was dissolved in CH_2Cl_2 (9.0 mL) and the resultant solution was cooled to 0 ºC. TFA (4.8 mL) was added dropwise, and the resultant mixture was stirred at 0 ºC for 10 min. The resultant maroon solution was then concentrated in vacuo.

Step 3: The residue from the previous step was dissolved in CH_2Cl_2 (11.5 mL); the resultant solution and conc aq HCl (1.9 mL) were then simultaneously added to a stirred suspension of $NaBH_3CN$ (240 mg, 3.81 mmol) in EtOH (24 mL) at 0 ºC. The resultant suspension was stirred at 0 ºC for 15 min, then further portions of $NaBH_3CN$ (115 mg, 1.83 mmol) and conc aq HCl (1.2 mL) were added sequentially. The resultant suspension was stirred at 0 ºC for 15 min, then H_2O (10 mL) was added. The resultant mixture was poured into a mixture of satd aq $NaHCO_3$ (120 mL) and H_2O (120 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL), then the combined organics were dried (Na_2SO_4) and concentrated in vacuo.

Step 4: The residue from the previous step was then dissolved in a methanolic solution of HCl (1.25 M, 2.6 mL) and stirred at rt overnight. The mixture was then poured into 1 M aq KOH (5 mL). The aqueous layer was extracted with $CHCl_3$/^{i}PrOH (3:1) (4 × 5 mL), then the combined organics were dried (Na_2SO_4) and concentrated in vacuo.

Step 5: The residue from the previous step was dissolved in MeCN (13 mL), and 35% aq HCHO (0.54 mL, 4.83 mmol) was added. The resultant orange solution was cooled to 0 °C and $NaBH_3CN$ (51 mg, 0.81 mmol) was added. The resultant solution was allowed to rt, and then stirred at rt for 16 h. The resultant solution was poured into 1 M aq NaOH (15 mL) and then extracted with $CHCl_3$ (3 × 15 mL). The combined organics were washed with brine (20 mL), then dried (Na_2SO_4) and concentrated in vacuo. Purification *via* flash column chromatography (eluent $CHCl_3$/(Ammonia, ca. 7 N solution in MeOH) 98:2 gave a yellow oil. This was dissolved in 6 M aq HCl (2.0 mL) and washed with Et_2O (3 × 2 mL). The aqueous layer was then basified by the addition of 2 M aq NaOH, and washed with Et_2O (3 × 3 mL). The combined organics were then dried (Na_2SO_4), and concentrated in vacuo to give **186** as a yellow solid (18 mg, 25%, >95:5 dr); $[\alpha]_D^{25}$ −15.2 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3650 (O−H), 3024 (C-H), 2925 (C-H); δ_H (500 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.2, C(10)H_3), 1.19 (3H, d, *J* 6.5, C(2)*Me*), 1.26 – 1.39 (4H, m, C(8′)H_2, C(9′)H_2), 1.42 – 1.46 (1H, m, C(5)H_A), 1.53 (1H, dddd, *J* 13.4, 4.7, 2.5, C(4)H_{ax}), 1.69 – 1.78 (1H, m, C(5)H_B), 1.82 – 1.88 (1H, m, C(4)H_{eq}), 2.07 – 2.12 (2H, m, C(7′)H_2), 2.12 – 2.16 (1H, m, C(2)*H*), 2.14 (3H, s, N*Me*), 2.49 (1H, ddd, *J* 11.7, 8.8, 3.2, C(6)*H*), 3.52 – 3.61 (1H, m, C(3)*H*), 5.54 (1H, dd, *J* 14.2, 8.8, C(1′)*H*), 5.70 (1H, dt, *J* 14.5, 7.1, C(6′)*H*), 6.01 – 6.17 (4H, m, C(2′)*H*, C(3′)*H*, C(4′)*H*, C(5′)*H*); δ_C (126 MHz, $CDCl_3$) 14.1 (*C*(10)), 18.4 (C(2)*Me*), 22.4 (*C*(9′)), 28.1 (*C*(5)), 31.5 (*C*(8′)), 31.6 (*C*(4)), 32.6 (*C*(7′)), 40.0 (N*Me*), 62.5 (*C*(2)), 68.4 (*C*(6)), 70.4 (*C*(3)), 130.1 (*C*(2′)), 130.3, 131.2 (*C*(3′-4′)), 132.6, (*C*(5′)) 135.7 (*C*(6′)), 136.8 (*C*(1′)); m/z (ESI$^+$) 264 ([M+H]$^+$, 100%), HRMS (ESI$^+$) $C_{17}H_{29}NO^+$ ([M+H]$^+$) requires 264.2322; found 264.2322.

(2*S*,3*R*,6*S*,*E*,*E*,*E*)-*N*-Methyl-2-Methyl-6-(deca-1′,3′,5′-trienyl)piperidin-3-Acetate 187

A catalytic amount of N,N-dimethylaminopyridine was added to a solution of *epi*-**73** (15 mg, 0.057 mmol) in CH_2Cl_2 (1.5 mL). The reaction was cooled to 0 °C. NEt_3 (15.9 μL, 0.114 mmol) and Ac_2O (16.2 μL, 0.171 mmol) were added and the reaction was warmed to room temperature and stirred for 3 h. The reaction was quenched with satd aq $NaHCO_3$ (2 mL) at 0 °C. The aqueous layer was extracted with EtOAc (3 × 5 mL), then the combined organics were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified via preparative thin layer chromatography (eluent $CHCl_3$/(Ammonia, ca. 7 N solution in MeOH), 10:0.05) to give a yellow oil (Rf = 0.79). This was dissolved in 6 M aq HCl (2.0 mL) and the resultant solution was washed with Et_2O (3 × 2 mL), then basified by the addition of 2 M aq NaOH until pH >14 was achieved. The resultant solution was extracted with Et_2O (3 × 3 mL), then the combined organics were dried (Na_2SO_4) and concentrated in vacuo to give **187** as an amorphous white solid (10 mg, 57%, >95:5 dr); $[\alpha]_D^{20}$ −23.2 (*c* 1.0 in MeOH) $[\alpha]_D^{20}$ −64.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film), 2975, 2934, 1745; δ_H (600 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.2, C(10′)H_3), 1.11 (3H, d, *J* 6.2, C(2)*Me*), 1.26 – 1.39 (6H, m, C(4)H_2, C(8′)H_2, C(9′)H_2), 1.53 (1H, tdd, *J* 13.6, 11.4, 3.7, C(5)H_{ax}), 1.64 (1H, ddd, *J* 13.6, 7.4, 3.0, C(5)H_{eq}), 2.05 (3H, s, OCO*Me*), 2.05 – 2.07 (1H, m, C(2)*H*), 2.07 – 2.13 (2H, m, C(7′)H_2), 2.21 (3H, s, N*Me*), 2.50 (1H, ddd, *J* 11.4, 8.7, 3.0, C(6)*H*), 4.49 (1H, ddd, *J* 11.1, 9.5, 4.6, C(3)*H*), 5.52 (1H, dd, *J* 14.6, 8.7, C(1′)*H*), 5.70 (1H, dt, *J* 14.5, 7.1, C(6′)*H*), 6.01 – 6.18 (4H, m, C(2′)-C(5′)*H*); δ_C (151 MHz, $CDCl_3$) 14.1 (*C*(10)), 16.5 (C(2)*Me*), 21.4 (OCO*Me*), 22.3 (*C*(9′)), 29.9 (*C*(4)), 30.9 (*C*(5)), 31.6 (*C*(8′)), 32.6 (*C*(7′)), 40.3 (N*Me*), 62.9 (*C*(2)), 67.4 (*C*(6)), 74.8 (*C*(3)), 130.0 (*C*(2′)), 130.3, 131.7 (*C*(3′-4′)), 132.8 (*C*(5′)), 135.8 (*C*(6′)), 136.4 (*C*(1′)), 170.4 (O*C*OMe); m/z (ESI^+) 328 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{19}H_{31}O_2N^+$ ($[M+Na]^+$) requires 328.2247; found 328.2248.

6.3 Experimental for Chapter 4

(2*S*,3*R*,6*S*,*E*,*E*,*E*)-*N*-Methyl-2-methyl-3-methoxy-6-(deca-1′,3′,5′-trienyl)piperidine 189

Step 1: NaH (60% dispersion in mineral oil, 34 mg, 0.85 mmol) was stirred in THF (1.5 mL) for 30 min. The resultant suspension was then cooled to 0 °C, a solution of **202** (296 mg, 0.812 mmol) in THF (3.95 mL) was added, and the resultant yellow solution was stirred at rt for 15 min. A solution of (*E*,*E*)-2,4-nonadienal (163 mg, 1.21 mmol) in THF (2.5 mL) was then added, and the resultant solution was stirred at rt for 1 h. The resultant solution was then heated to 72 ºC, and stirred at 72 ºC for 12 h. The resultant solution was allowed to cool to rt, then poured into a mixture of satd aq brine (16 mL) and H_2O (16 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL), and the combined organics were dried ($MgSO_4$) and concentrated in vacuo. The residue was dissolved in DMF (2.0 mL), and satd aq $NaHSO_3$ (6.0 mL) was added. The resultant cream suspension was stirred at rt for 10 min, then diluted with H_2O (6 mL). The aqueous layer was extracted with Et_2O (6 mL), and the combined organics were washed three times with H_2O (5 mL, then 3 mL, then 1 mL), dried (Na_2SO_4) and concentrated in vacuo.

Step 2: The residue from the previous step was dissolved in CH_2Cl_2 (15.5 mL) and the resultant solution was cooled to 0 ºC. TFA (7.5 mL) was added dropwise, and the resultant mixture was stirred at 0 ºC for 10 min. The resultant maroon solution was then concentrated in vacuo.

Step 3: The residue from the previous step was dissolved in CH_2Cl_2 (20.5 mL); the resultant solution and conc aq HCl (3.0 mL) were then simultaneously added to a stirred suspension of $NaBH_3CN$ (400 mg, 6.34 mmol) in EtOH (41 mL) at 0 ºC. The resultant suspension was stirred at 0 ºC for 15 min, then further portions of $NaBH_3CN$ (200 mg, 3.17 mmol) and conc aq HCl (1.5 mL) were added sequentially. The resultant suspension was stirred at 0 ºC for 15 min, then H_2O (10 mL) was added. The resultant mixture was poured into a mixture of satd aq $NaHCO_3$ (200

mL) and H_2O (200 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL), and the combined organics were dried (Na_2SO_4), and concentrated in vacuo.

Step 4: The residue from the previous step was dissolved in MeCN (30.0 mL), and 35% aq HCHO (1.50 mL, 13.4 mmol) was added. The resultant orange solution was cooled to 0 ºC and $NaBH_3CN$ (120 mg, 1.90 mmol) was added. The resultant solution was allowed to rt, and then stirred at rt for 16 h. The resultant solution was poured into 1 M aq NaOH (30 mL) and then extracted with $CHCl_3$ (3 × 30 mL). The combined organics were washed with brine (20 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue was purified via preparative thin layer chromatography (eluent $CHCl_3$/MeOH/Et_3N, 230:5:2 to give a yellow solid (R_f = 0.46). This was dissolved in 6 M aq HCl (2.0 mL) and the resultant solution was washed with Et_2O (3 × 2 mL), then basified by the addition of 2 M aq NaOH until pH >14 was achieved. The resultant solution was extracted with Et_2O (3 × 3 mL), and the combined organics were dried (Na_2SO_4) and concentrated in vacuo to give **189** as a beige solid (70 mg, 31%, >95:5 dr); mp 62–64 °C; $[\alpha]_D^{25}$ −4.9 (*c* 1.0 in $CHCl_3$); ν_{max} 2987, 2928; δ_H (500 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.1, C(10′)H_3), 1.18–1.27 (1H, m, C(4)H_A), 1.23 (3H, d, *J* 6.1, C(2)*Me*), 1.28–1.40 (4H, m, C(8′)H_2, C(9′)H_2), 1.40–1.47 (1H, m, C(5)H_A), 1.66 (1H, app dq, *J* 13.5, 3.4, C(5)H_B), 1.87 (1H, dq, *J* 9.1, 6.1, C(2)*H*), 2.09 (2H, q, *J* 7.1, C(7′)H_2), 2.15–2.23 (1H, m, C(4)H_B), 2.20 (3H, s, N*Me*), 2.46 (1H, ddd, *J* 11.6, 8.8, 2.8, C(6)*H*), 2.79 (1H, ddd, *J* 11.0, 9.1, 4.5, C(3)*H*), 3.36 (3H, s, O*Me*), 5.52 (1H, dd, *J* 14.6, 8.8, C(1′)*H*), 5.69 (1H, dt, *J* 14.4, 7.1, C(6′)*H*), 6.00–6.19 (4H, m, C(2′)–C(5′)*H*); δ_C (125 MHz, $CDCl_3$) 14.1 (*C*(10)), 16.4 (C(2)*Me*), 22.3 (*C*(9′)), 28.8 (*C*(4)), 31.2 (*C*(5)), 31.6 (*C*(8′)), 32.6 (*C*(7′)), 40.5 (N*Me*), 56.8 (O*Me*), 64.5 (*C*(2)), 67.6 (*C*(6)), 81.6 (*C*(3)), 130.1, 130.3, 131.5, 132.6 (*C*(2′)–C(5′)), 135.7 (*C*(6′)), 136.9 (*C*(1′)); *m*/*z* (ESI$^+$) 278 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{32}NO^+$ ([M+H]$^+$) requires 278.2478; found 278.2478.

***tert*-Butyl (2*S*,3*S*,α*S*)-2-methoxy-3-[N-benzyl-N-(amethylbenzyl)amino]butanoate 198**

NaH (60% dispersion in mineral oil, 64 mg, 1.6 mmol) was stirred in THF (5.4 mL) for 30 min. The resultant suspension was then cooled to 0 °C, a solution of **68** (500 mg, 1.36 mmol) in THF (1.4 mL) was added, and the resultant solution was stirred at 0 °C for 30 min. MeI (0.10 mL, 1.6 mmol) was then added and the resultant solution was allowed to warm to rt over 12 h. H_2O (7 mL) was then added and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organics were washed with brine (10 mL), dried ($MgSO_4$) and concentrated in vacuo to give **198** as a yellow oil (519 mg, quant, >95:5 dr); $[\alpha]_D^{25}$ −161 (*c* 1.0 in $CHCl_3$); ν_{max} 2980, 2888, 1740; δ_H (400 MHz, $CDCl_3$) 1.09 (3H, d, *J* 7.0, C(4)H_3), 1.32 (3H, d, *J* 6.9, C(α)*Me*), 1.36 (9H, s, CMe_3), 3.26 (1H, qd, *J* 7.0, 3.4, C(3)*H*), 3.30 (3H, s, O*Me*), 3.55 (1H, d, *J* 3.4, C(2)*H*), 3.88 (1H, d, *J* 14.9, NC$H_A$$H_B$Ph), 3.95–4.04 (2H, m, C(α)*H*, NC$H_A$$H_B$Ph), 7.17–7.46 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.7 (*C*(4)), 17.5 (C(α)*Me*), 28.2 (CMe_3), 50.7 (N*C*H_2), 54.3 (*C*(3)), 58.2 (O*Me*), 58.8 (*C*(α)), 81.0 (*C*Me_3), 85.0 (*C*(2)), 126.5, 126.7 (*p-Ph*), 127.9, 128.1, 128.2, 128.4 (*o*,*m-Ph*), 142.7, 144.6 (*i-Ph*), 171.2 (*C*(1)); *m*/*z* (ESI$^+$) 384 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{34}NO_3^+$ ([M+H]$^+$) requires 384.2533; found 384.2537.

Ethyl (4*R*,5*S*,α*S*,*E*)-4-methoxy-5-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-2-enoate 200

Step 1: DIBAL-H (1.0 M in PhMe, 24.2 mL, 24.2 mmol) was added to a stirred solution of **198** (3.10 g, 8.09 mmol) in CH_2Cl_2 (82 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 30 min. MeOH (50 mL) was then added, and the resultant solution was allowed to warm to rt before satd aq Rochelle salt (50 mL) and CH_2Cl_2 (50 mL) were added sequentially. The resultant mixture was stirred at rt for 16 h. The aqueous layer was then extracted with CH_2Cl_2 (3 × 50 mL) and the combined organics were washed with brine (40 mL), dried ($MgSO_4$) and concentrated in vacuo to give **199** as a yellow oil (2.52 g, 99%, >95:5 dr); δ_H (400 MHz, $CDCl_3$) 1.24 (3H, d, *J* 6.3, C(4)H_3), 1.38 (3H, d, *J* 6.9, C(α)*Me*), 3.13–3.23 (2H, m, C(2)*H*, C(3)*H*), 3.25 (3H,

s, O*Me*), 3.79 (2H, app br s, NCH_2), 3.86 (1H, q, *J* 6.9, C(α)*H*), 7.17–7.38 (10H, m, *Ph*), 8.54 (1H, d, *J* 4.3, C(1)*H*).

Step 2: $Ph_3P{=}CHCO_2Et$ (2.78 g, 7.99 mmol) was added to a stirred solution of **199** (2.26 g, 7.27 mmol) in CH_2Cl_2 (37 mL) at rt, and the resultant solution was stirred at rt for 60 h before being concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 14:1) gave **200** as a yellow oil (2.44g, 88%, >95:5 dr); $[\alpha]_D^{25}$ −70.5 (*c* 1.0 in $CHCl_3$); ν_{max} 2981, 2825, 1718; δ_H (400 MHz, $CDCl_3$) 1.16 (3H, d, *J* 6.8, C(6)H_3), 1.32 (3H, t, *J* 7.1, OCH_2CH_3), 1.33 (3H, d, *J* 6.9, C(α)*Me*), 2.88 (1H, qd, *J* 6.8, 5.5, C(5)*H*), 3.18 (3H, s, O*Me*), 3.51 (1H, ddd, *J* 6.5, 5.5, 1.3, C(4)*H*), 3.83–3.96 (3H, m, NCH_2, C(α)*H*), 4.21 (2H, q, *J* 7.1, OCH_2CH_3), 5.71 (1H, dd, *J* 15.9, 1.3, C(2)*H*), 6.52 (1H, dd, *J* 15.9, 6.5, C(3)*H*), 7.15–7.45 (10H, m, *Ph*); δ_C (101 MHz, $CDCl_3$) 13.4 (*C*(6)), 14.5 (OCH_2CH_3), 15.4 (C(α)*Me*), 50.9 (NCH_2), 55.1 (*C*(5)), 57.2 (C(α)*H*), 57.5 (O*Me*), 60.4 (OCH_2CH_3), 84.8 (*C*(4)), 121.8 (*C*(2)), 126.8, 126.9 (*p-Ph*), 128.1, 128.4, 128.7 (*o*,*m-Ph*), 141.6, 144.1 (*i-Ph*), 147.8 (*C*(3)), 166.4 (*C*(1)); *m*/*z* (ESI^+) 382 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{24}H_{32}NO_3^+$ ($[M+H]^+$) requires 382.2377; found 382.2381.

Ethyl (4*R*,5*S*)-4-methoxy-5-(*N*-*tert*-butoxycarbonylamino)hexanoate 201

$Pd(OH)_2/C$ (50% w/w of **200**, 830 mg) was added to a stirred solution of **200** (1.66 g, 4.36 mmol) and Boc_2O (2.87 g, 13.2 mmol) in degassed EtOAc (15 mL) and the resultant black suspension was stirred at rt under a hydrogen atmosphere (5 atm) for 16 h. After depressurisation, the reaction mixture was filtered through a plug of Celite (eluent CH_2Cl_2) and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1) gave **201** as a yellow oil (1.03 g, 76%, >95:5 dr); $[\alpha]_D^{25}$ −1.9 (*c* 1.0 in $CHCl_3$); ν_{max} 3658, 2980, 1740, 1711; δ_H (400 MHz, $CDCl_3$) 1.09 (3H, d, *J* 6.8, C(6)H_3), 1.26 (3H, t, *J* 7.1, OCH_2CH_3), 1.44 (9H, s, CMe_3), 1.72 (1H, dddd, *J* 14.0, 8.9, 6.8, 5.4, C(3)H_A), 1.82 (1H, dddd, *J* 14.0, 8.6, 7.7, 6.3, C(3)H_B), 2.36 (1H, ddd, *J* 15.4, 7.7, 6.8, C(2)H_A), 2.42 (1H, ddd, *J* 15.4, 8.9, 6.3, C(2)H_B), 3.18 (1H, dt, *J* 8.3, 4.9,

C(4)*H*), 3.39 (3H, s, OCH_3), 3.76 (1H, br s, C(5)*H*), 4.13 (2H, q, *J* 7.1, OCH_2CH$_3$), 4.64 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 14.4 (OCH$_2$*C*H$_3$), 15.4 (*C*(6)), 25.7 (*C*(3)), 28.6 (C*Me*$_3$), 30.6 (*C*(2)), 48.1 (*C*(5)), 58.6 (O*C*H$_3$), 60.6 (O*C*H$_2$CH$_3$), 79.3 (*C*Me$_3$), 82.8 (*C*(4)), 155.5 (N*C*O), 173.5 (*C*(1)); *m*/*z* (ESI$^+$) 312 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{27}NNaO_5^+$ ([M+Na]$^+$) requires 312.1781; found 312.1780.

(4*R*,5*S*)-1-(Dimethoxyphosphoryl)-5-methoxy-6-(*N*-*tert*-butoxycarbonylamino)heptan-2-one 202

^{n}BuLi (2.5 M in hexanes, 3.97 mL, 9.95 mmol) was added dropwise at −78 °C to a solution of dimethyl methyl phosphonate (1.08 mL, 9.95 mmol) in THF (28 mL). The resultant green solution was stirred at −78 °C for 30 min, then a solution of **201** (1.15 g, 3.97 mmol) in THF (5.8 mL) was added dropwise. The resultant yellow solution was stirred at −78 °C for 30 min, before being allowed to warm to 0 °C over 1 h. Satd aq NH_4Cl (2 mL) was then added, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organics were dried ($MgSO_4$) and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:1, increased to 30–40 °C petrol/acetone, 7:3) gave **202** as a yellow oil (1.28 g, 88%, >95:5 dr); $[\alpha]_D^{25}$ −8.8 (*c* 1.0 in $CHCl_3$); ν_{max} 3320, 2978, 1709, 1251; δ_H (500 MHz, $CDCl_3$) 1.07 (3H, d, *J* 6.8, C(7)H_3), 1.42 (9H, s, C*Me*$_3$), 1.64–1.81 (2H, m, C(4)H_2), 2.69 (2H, td, *J* 7.4, 2.8, C(3)H_2), 3.09 (1H, d, *J* 22.6, C(1)H_A), 3.10 (1H, d, *J* 22.7, C(1)H_B), 3.10–3.16 (1H, m, C(5)*H*), 3.36 (3H, s, C(5)O*Me*), 3.64–3.77 (1H, m, C(6)*H*), 3.77 (3H, d, *J* 11.2, PO*Me*), 3.77 (3H, d, *J* 11.3, PO*Me*), 4.63 (1H, s, N*H*); δ_C (125 MHz, $CDCl_3$) 15.6 (*C*(6)), 23.9 (*C*(3)), 28.5 (C*Me*$_3$), 40.2 (*C*(2)), 41.4 (d, *J* 128.4, *C*(1)), 53.2 (d, *J* 6.6, PO*Me*), 53.2 (d, *J* 6.6, PO*Me*), 58.3 (C(3)O*Me*), 79.3 (*C*Me$_3$), 82.5 (*C*(4)), 155.5 (N*C*O), 201.5 (d, *J* 6.4, *C*(2)); *m*/*z* (ESI$^+$) 390 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{15}H_{30}NNaO_7P^+$ ([M+Na]$^+$) requires 390.1652; found 390.1654.

(2*S*,3*R*,6*S*,*E*,*E*,*E*)-2-Methyl-3-methoxy-6-(deca-1′,3′,5′-trienyl)piperidine 204

Step 1: NaH (60% dispersion in mineral oil, 23 mg, 0.58 mmol) was stirred in THF (1.0 mL) for 30 min. The resultant suspension was then cooled to 0 °C, a solution of **202** (200 mg, 0.55 mmol) in THF (2.67 mL) was added, and the resultant yellow solution was stirred at rt for 15 min. A solution of (*E*,*E*)-2,4-nonadienal (110 mg, 0.797 mmol) in THF (1.7 mL) was then added, and the resultant solution was stirred at rt for 1 h. The resultant solution was then heated to 72 °C, and stirred at 72 °C for 12 h. The resultant solution was allowed to cool to rt, then poured into a mixture of satd aq brine (11 mL) and H_2O (11 mL). The aqueous layer was extracted with EtOAc (3 × 15 mL), and the combined organics were dried ($MgSO_4$) and concentrated in vacuo. The residue was dissolved in DMF (1.5 mL), and satd aq $NaHSO_3$ (4.0 mL) was added. The resultant cream suspension was stirred at rt for 10 min, then diluted with H_2O (4 mL). The aqueous layer was extracted with Et_2O (4 mL), and the combined organics were washed three times with H_2O (4 mL, then 2 mL, then 1 mL), dried (Na_2SO_4) and concentrated in vacuo.

Step 2: The residue from the previous step was dissolved in CH_2Cl_2 (10.4 mL) and the resultant solution was cooled to 0 °C. TFA (5.0 mL) was added dropwise, and the resultant mixture was stirred at 0 °C for 10 min. The resultant maroon solution was then concentrated in vacuo.

Step 3: The residue from the previous step was dissolved in CH_2Cl_2 (13.6 mL); the resultant solution and conc aq HCl (2.0 mL) were then simultaneously added to a stirred suspension of $NaBH_3CN$ (268 mg, 4.25 mmol) in EtOH (28 mL) at 0 °C. The resultant suspension was stirred at 0 °C for 15 min, then further portions of $NaBH_3CN$ (134 mg, 2.13 mmol) and conc aq HCl (1.0 mL) were added sequentially. The resultant suspension was stirred at 0 °C for 15 min, then H_2O (10 mL) was added. The resultant mixture was poured into a mixture of satd aq $NaHCO_3$ (140 mL) and H_2O (140 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL), and the combined organics were dried (Na_2SO_4), and concentrated in vacuo. The residue was purified via

preparative thin layer chromatography (eluent CH_2Cl_2/EtOAc/Et_3N, 24:12:1) to give a yellow solid (R_f = 0.52). This was dissolved in 6 M aq HCl (2.0 mL) and the resultant solution was washed with Et_2O (3 × 2 mL), then basified by the addition of 2 M aq NaOH until pH >14 was achieved. The resultant solution was extracted with Et_2O (3 × 3 mL), and the combined organics were dried (Na_2SO_4) and concentrated in vacuo to give **204** as a white solid (41 mg, 28%, >95:5 dr); mp 128–129 °C; $[\alpha]_D^{25}$ −13.9 (*c* 1.0 in $CHCl_3$); ν_{max} 3386, 2975, 2918, 1665; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.2, C(10′)H_3), 1.17 (3H, d, *J* 6.1, C(2)*Me*), 1.23–1.41 (6H, m, C(4)H_A, C(5)H_A, C(8′)H_2, C(9′)H_2), 1.73–1.79 (1H, m, C(5)H_B), 2.09 (2H, q, *J* 7.1, C(7′)H_2), 2.18–2.24 (1H, m, C(4)H_B), 2.58 (1H, dq, *J* 8.9, 6.1, C(2)*H*), 2.71 (1H, ddd, *J* 10.2, 8.9, 4.3, C(3)*H*), 2.93–3.06 (1H, m, N*H*), 3.13–3.22 (1H, m, C(6)*H*), 3.37 (3H, s, O*Me*), 5.60 (1H, dd, *J* 15.2, 7.1, C(1′)*H*), 5.69 (1H, dt, *J* 14.6, 7.0, C(6′)*H*), 6.00–6.21 (4H, m, C(2′)*H*–C(5′)*H*); δ_C NMR (125 MHz, $CDCl_3$) 14.1 (*C*(10)), 19.4 (C(2)*Me*), 22.4 (*C*(9′)), 29.6 (*C*(4)), 31.6 (*C*(8′)), 32.0 (*C*(7′)), 32.6 (*C*(5)), 56.9, (*C*(2)) 57.1 (*C*(6)), 58.8 (O*Me*), 82.7 (*C*(3)), 130.1, 130.3, 130.5, 133.0 (*C*(2′)–C(5′)), 135.5 (*C*(1′)), 135.7 (*C*(6′)); *m*/*z* (ESI$^+$) 264 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{17}H_{30}NO^+$ ([M+H]$^+$) requires 264.2322; found 264.2324.

tert-Butyl (2*R*,3*S*,α*S*)-2-methoxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]butanoate 205

NaH (60% dispersion in mineral oil, 584 mg, 14.6 mmol) was stirred in THF (50 mL) for 30 min. The resultant suspension was then cooled to 0 °C, a solution of **178** (4.50 g, 12.2 mmol) in THF (11 mL) was added, and the resultant solution was stirred at 0 °C for 30 min. MeI (0.90 mL, 15 mmol) was then added and the resultant solution was allowed to warm to rt over 12 h. H_2O (60 mL) was then added and the aqueous layer was extracted with Et_2O (3 × 60 mL). The combined organics were washed with brine (50 mL), dried ($MgSO_4$) and concentrated in vacuo to give **205** as a yellow oil (4.67 g, 99%, >95:5 dr); $[\alpha]_D^{25}$ +1.1 (*c* 1.1 in $CHCl_3$); ν_{max} 2978, 2888, 1741; δ_H (400 MHz, $CDCl_3$) 1.08 (3H, d, *J* 7.0, C(4)H_3), 1.30 (3H, d, *J* 6.9, C(α)*Me*), 1.43 (9H, s, C*Me*$_3$), 3.19 (3H, s, O*Me*), 3.22–3.32 (1H, m, C(3)*H*), 3.48 (1H, d, *J* 6.4, C(2)*H*), 3.80 (1H, d, *J* 15.0, NCH_AH_BPh), 3.91 (1H, d, *J* 15.0, NCH$_A$$H_B$Ph), 4.16 (1H, q, *J* 6.9, C(α)*H*), 7.14–7.49 (10H, m, *Ph*); δ_C (100 MHz,

$CDCl_3$) 14.4 (*C*(4)), 18.4 (C(α)*Me*), 28.2 (C*Me*$_3$), 50.5 (N*C*H$_2$), 55.6 (*C*(3)), 57.8 (O*Me*), 59.4 (*C*(α)), 81.4 (*C*Me$_3$), 86.1 (*C*(2)), 126.5, 126.6 (*p-Ph*), 128.0, 128.1, 128.5 (*o*,*m-Ph*), 142.6, 145.3 (*i-Ph*), 171.5 (*C*(1)); *m*/*z* (ESI$^+$) 384 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{34}NO_3^+$ ([M+H]$^+$) requires 384.2533; found 384.2536.

Ethyl (4*S*,5*S*,α*S*,*E*)-4-methoxy-5-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-2-enoate 207

Step 1: DIBAL-H (1.0 M in PhMe, 36.4 mL, 36.4 mmol) was added to a stirred solution of **205** (4.65 g, 12.1 mmol) in CH_2Cl_2 (120 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 30 min. MeOH (70 mL) was then added, and the resultant solution was allowed to warm to rt before satd aq Rochelle salt (70 mL) and CH_2Cl_2 (70 mL) were added sequentially. The resultant mixture was stirred at rt for 16 h. The aqueous layer was then extracted with CH_2Cl_2 (3 × 60 mL) and the combined organics were washed with brine (50 mL), dried ($MgSO_4$) and concentrated in vacuo to give **206** as a yellow oil (3.72 g, 99%, >95:5 dr); δ_H (400 MHz, $CDCl_3$) 1.20 (3H, d, *J* 6.8, C(4)*H*$_3$), 1.28 (3H, d, *J* 6.9, C(α)*Me*), 3.26 (3H, s, O*Me*), 3.28 (1H, dd, *J* 4.3, 1.0, C(2)*H*), 3.30 – 3.42 (1H, m, C(3)*H*), 3.57 (1H, d, *J* 13.7, NC*H*$_A$H$_B$Ph), 3.93 (1H, q, *J* 6.9, C(α)*H*), 4.08 (1H, d, *J* 13.7, NCH$_A$*H*$_B$Ph), 7.05–7.38 (10H, m, *Ph*), 8.89 (1H, d, *J* 1.0, C(1)*H*).

Step 2: $Ph_3P{=}CHCO_2Et$ (6.40 g, 18.4 mmol) was added to a stirred solution of **206** (3.81 g, 12.3 mmol) in CH_2Cl_2 (60 mL) at rt, and the resultant solution was stirred at rt for 60 h before being concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **207** as a yellow oil (3.51 g, 75%, >95:5 dr); $[\alpha]_D^{25}$ −189 (*c* 1.0 in $CHCl_3$); ν_{max} 2980, 2889, 1718; δ_H (400 MHz, $CDCl_3$) 1.10 (3H, d, *J* 7.0, C(6)*H*$_3$), 1.28 (3H, t, *J* 7.0, OCH$_2$C*H*$_3$), 1.32 (3H, d, *J* 7.0, C(α)*Me*), 2.99–3.07 (1H, m, C(5)*H*), 3.08 (3H, s, O*Me*), 3.38–3.43 (1H, m, C(4)*H*), 3.76 (1H, d, *J* 14.3, NC*H*$_A$H$_B$Ph), 3.95 (1H, d, *J* 14.3, NCH$_A$*H*$_B$Ph), 4.05 (2H, q, *J* 7.0, OC*H*$_2$CH$_3$), 4.18 (1H, q, *J* 7.0, C(α)*H*), 5.86 (1H, d, *J* 15.8, C(2)*H*), 6.78 (1H, dd, *J* 15.8, 6.3, C(3)*H*), 7.15–7.49 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.0 (*C*(6)), 14.4 (OCH$_2$*C*H$_3$), 14.9 (C(α)*Me*),

51.3 (N*C*H$_2$), 55.0 (*C*(5)), 57.4 (O*Me*), 57.4 (*C*(α)), 60.4 (O*C*H$_2$CH$_3$), 85.4 (*C*(4)), 122.5 (*C*(2)), 126.7, 126.8 (*p-Ph*), 128.0, 128.2, 128.3, 128.6 (*o*,*m-Ph*), 141.9, 144.7 (*i-Ph*), 147.1 (*C*(3)), 166.3 (*C*(1)); *m*/*z* (ESI$^+$) 382 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{32}NO_3^+$ ([M+H]$^+$) requires 382.2377; found 382.2378.

Ethyl (4*S*,5*S*)-4-methoxy-5-(*N*-*tert*-butoxycarbonylamino)hexanoate 208

Pd(OH)$_2$/C (50% w/w of **207**, 1.61 g) was added to a stirred solution of **207** (3.21 g, 8.43 mmol) and Boc$_2$O (5.52 g, 25.3 mmol) in degassed EtOAc (28 mL) and the resultant black suspension was stirred at rt under a hydrogen atmosphere (5 atm) for 16 h. After depressurisation, the reaction mixture was filtered through a plug of Celite (eluent CH_2Cl_2) and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et$_2$O, 5:1, increased to 30–40 °C petrol/Et$_2$O, 2:1) gave **208** as a yellow oil (1.83 g, 75%, >95:5 dr); $[\alpha]_D^{25}$ −2.1 (*c* 1.0 in $CHCl_3$); ν_{max} 3658, 2980, 1734, 1711; δ_H (500 MHz, $CDCl_3$) 1.15 (3H, d, *J* 6.8, C(6)*H*$_3$), 1.25 (3H, t, *J* 7.1, OCH$_2$C*H*$_3$), 1.44 (9H, s, C*Me*$_3$), 1.66–1.77 (1H, m, C(3)*H*$_A$), 1.82 (1H, dq, *J* 14.8, 7.5, C(3)*H*$_B$), 2.35–2.41 (2H, m, C(2)*H*$_2$), 3.11–3.14 (1H, m, C(4)*H*), 3.41 (3H, s, O*Me*), 3.79 (1H, br s, C(5)*H*), 4.13 (2H, q, *J* 7.1, OC*H*$_2$CH$_3$), 4.64 (1H, br s, N*H*); δ_C (125 MHz, $CDCl_3$) 14.4 (OCH$_2$*C*H$_3$), 17.8 (*C*(6)), 25.8 (*C*(3)), 28.5 (C*Me*$_3$), 30.6 (*C*(2)), 47.8 (*C*(5)), 58.9 (O*Me*), 60.5 (O*C*H$_2$CH$_3$), 79.3 (*C*Me$_3$), 82.7 (*C*(4)), 155.7 (N*C*O), 173.6 (*C*(1)); *m*/*z* (ESI$^+$) 312 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{27}NNaO_5^+$ ([M+Na]$^+$) requires 312.1781; found 312.1780.

(4*S*,5*S*)-1-(Dimethoxyphosphoryl)-5-methoxy-6-(*N*-*tert*-butoxycarbonylamino)heptan-2-one 209

^{n}BuLi (2.5 M in hexanes, 0.64 mL, 1.60 mmol) was added dropwise at −78 °C to a solution of dimethyl methyl phosphonate (0.17 mL, 1.6 mmol) in THF (4.6 mL). The resultant green solution was stirred at −78 °C for 30 min, then a solution of **208** (185 mg, 0.644 mmol) in THF (0.93 mL) was added dropwise. The resultant yellow solution was stirred at −78 °C for 30 min, before being

allowed to warm to 0 °C over 1 h. Satd aq NH_4Cl (0.4 mL) was then added, and the aqueous was extracted with EtOAc (3 × 3 mL). The combined organics were dried ($MgSO_4$) and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:1, increased to 30–40 °C petrol/acetone, 7:3) gave **209** as a colourless oil (200 mg, 85%, >95:5 dr); $[\alpha]_D^{25}$ −3.2 (*c* 1.0 in $CHCl_3$); ν_{max} 3658, 2980, 1709, 1252; δ_H (400 MHz, $CDCl_3$) 1.11 (3H, d, *J* 6.8, C(7)H_3), 1.40 (9H, s, CMe_3), 1.58–1.70 (1H, m, C(4)H_A), 1.72–1.83 (1H, m, C(4)H_B), 2.60–2.79 (2H, m, C(3)H_2), 2.98–3.17 (3H, m, C(1)H_2, C(5)*H*), 3.36 (3H, s, C(3)O*Me*), 3.73–3.80 (1H, m, C(6)*H*), 3.79 (3H, d, *J* 11.2, PO*Me*), 3.79 (3H, d, *J* 11.2, PO*Me*), 4.62 (1H, br d, *J* 8.9, N*H*); δ_C (100 MHz, $CDCl_3$) 17.6 (*C*(*7*)), 24.1 (*C*(4)), 28.5 (CMe_3), 40.4 (*C*(3)), 41.3 (d, *J* 128.4, *C*(1)), 47.5 (*C*(6)), 53.1 (d, *J* 6.5, PO*Me*), 53.2 (d, *J* 6.5, PO*Me*), 58.5 (C(3)O*Me*), 79.3 (*C*Me$_3$), 82.4 (*C*(*5*)), 155.7 (N*C*O), 201.6 (d, *J* 6.3, *C*(2)); *m*/*z* (ESI$^+$) 390 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{15}H_{30}NNaO_7P^+$ ([M+Na]$^+$) requires 390.1652; found 390.1645.

(2*S*,3*S*,6*S*,*E*,*E*,*E*)-2-Methyl-3-methoxy-6-(deca-1′,3′,5′-trienyl)piperidine 211

Step 1: NaH (60% dispersion in mineral oil, 7.0 mg, 0.18 mmol) was stirred in THF (0.29 mL) for 30 min. The resultant suspension was then cooled to 0 °C, a solution of **209** (58 mg, 0.16 mmol) in THF (0.77 mL) was added, and the resultant yellow solution was stirred at rt for 15 min. A solution of (*E*,*E*)-2,4-nonadienal (32 mg, 0.24 mmol) in THF (0.49 mL) was then added, and the resultant solution was stirred at rt for 1 h. The resultant solution was then heated to 72 ºC, and stirred at 72 ºC for 12 h. The resultant solution was allowed to cool to rt, then poured into a mixture of satd aq brine (4 mL) and H_2O (4 mL). The aqueous layer was extracted with EtOAc (3 × 8 mL), and the combined organics were dried ($MgSO_4$) and concentrated in vacuo. The residue was dissolved in DMF (0.5 mL), and satd aq $NaHSO_3$ (2.0 mL) was added. The resultant cream suspension was stirred at rt for 10 min, then diluted with H_2O (2 mL). The aqueous layer was extracted with Et_2O (2 mL), and the combined organics were washed three times with H_2O (2 × 2 mL, then 1 mL), dried (Na_2SO_4) and concentrated in vacuo.

Step 2: The residue from the previous step was dissolved in CH_2Cl_2 (1.5 mL) and the resultant solution was cooled to 0 ºC. TFA (3.1 mL) was added dropwise, and the resultant mixture was stirred at 0 ºC for 10 min. The resultant maroon solution was then concentrated in vacuo.

Step 3: The residue from the previous step was dissolved in CH_2Cl_2 (4.0 mL); the resultant solution and conc aq HCl (0.6 mL) were then simultaneously added to a stirred suspension of $NaBH_3CN$ (80 mg, 1.27 mmol) in EtOH (8.3 mL) at 0 ºC. The resultant suspension was stirred at 0 ºC for 15 min, then further portions of $NaBH_3CN$ (40 mg, 0.63 mmol) and conc aq HCl (0.27 mL) were added sequentially. The resultant suspension was stirred at 0 ºC for 15 min, then H_2O (10 mL) was added. The resultant mixture was poured into a mixture of satd aq $NaHCO_3$ (40 mL) and H_2O (40 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 75 mL), and the combined organics were dried (Na_2SO_4), and concentrated in vacuo. The residue was purified via preparative thin layer chromatography (eluent CH_2Cl_2/EtOAc/Et_3N, 24:12:1) to give a yellow solid (R_f = 0.32). This was dissolved in 6 M aq HCl (2.0 mL) and the resultant solution was washed with Et_2O (3 × 2 mL), then basified by the addition of 2 M aq NaOH until pH >14 was achieved. The resultant solution was extracted with Et_2O (3 × 3 mL), and the combined organics were dried (Na_2SO_4) and concentrated in vacuo to give **211** as a yellow solid (19 mg, 47%, >95:5 dr); mp 115–118 °C; $[\alpha]_D^{25}$ +7.3 (*c* 1.0 in $CHCl_3$); ν_{max} 3658, 2981, 2888; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.1, C(10′)H_3), 1.13 (3H, d, *J* 6.6, C(2)*Me*), 1.27–1.42 (5H, m, C(4)H_A, C(8′)H_2, C(9′)H_2), 1.42–1.53 (2H, m, C(5)H_2), 2.08 (2H, app q, *J* 6.7, C(7′)H_2), 2.15 (1H, dt, *J* 10.5, 3.1, C(4)H_B), 2.79 (1H, qd, *J* 6.6, 1.8, C(2)*H*), 3.04–3.08 (1H, m, C(3)*H*), 3.16–3.23 (1H, m, C(6)*H*), 3.34 (3H, s, O*Me*), 5.63–5.72 (2H, m, C(1′)*H*, C(6′)*H*), 5.99–6.20 (4H, m, C(2′)*H*–C(5′)*H*); δ_C (125 MHz, $CDCl_3$) 14.1 (*C*(10)), 18.9 (C(2)*Me*), 22.4 (*C*(9′)), 26.6 (*C*(5)), 27.1 (*C*(4)), 31.6 (*C*(8′)), 32.6 (*C*(7′)), 55.3 (*C*(2)), 57.0 (O*Me*), 58.9 (*C*(6)), 76.6 (*C*(3)), 129.8, 130.5, 132.6 (*C*(2′)–C(5′)), 135.3 (*C*(1′), 136.2, *C*(6′)); *m*/*z* (ESI$^+$) 264 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{17}H_{30}NO^+$ ([M+H]$^+$) requires 264.2323; found 264.2322.

(2*S*,3*S*,6*S*,*E*,*E*,*E*)-*N*-Methyl-2-methyl-3-methoxy-6-(deca-1′,3′,5′-trienyl)piperidine *ent*-**71**

Step 1: NaH (60% dispersion in mineral oil, 8.0 mg, 0.20 mmol) was stirred in THF (0.34 mL) for 30 min. The resultant suspension was then cooled to 0 °C, a solution of **209** (68 mg, 0.19 mmol) in THF (0.90 mL) was added, and the resultant yellow solution was stirred at rt for 15 min. A solution of (*E*,*E*)-2,4-nonadienal (37 mg, 0.28 mmol) in THF (0.57 mL) was then added, and the resultant solution was stirred at rt for 1 h. The resultant solution was then heated to 72 ºC, and stirred at 72 ºC for 12 h. The resultant solution was allowed to cool to rt, then poured into a mixture of satd aq brine (4 mL) and H_2O (4 mL). The aqueous layer was extracted with EtOAc (3 × 8 mL), and the combined organics were dried ($MgSO_4$) and concentrated in vacuo. The residue was dissolved in DMF (0.5 mL), and satd aq $NaHSO_3$ (2 mL) was added. The resultant cream suspension was stirred at rt for 10 min, then diluted with H_2O (2 mL). The aqueous layer was extracted with Et_2O (2 mL), and the combined organics were washed three times with H_2O (2 × 2mL, then 1 mL), dried (Na_2SO_4) and concentrated in vacuo.

Step 2: The residue from the previous step was dissolved in CH_2Cl_2 (4.7 mL) and the resultant solution was cooled to 0 ºC. TFA (3.1 mL) was added dropwise, and the resultant mixture was stirred at 0 ºC for 10 min. The resultant maroon solution was then concentrated in vacuo.

Step 3: The residue from the previous step was dissolved in CH_2Cl_2 (4.0 mL); the resultant solution and conc aq HCl (0.7 mL) were then simultaneously added to a stirred suspension of $NaBH_3CN$ (94 mg, 1.49 mmol) in EtOH (9.7 mL) at 0 ºC. The resultant suspension was stirred at 0 ºC for 15 min, then further portions of $NaBH_3CN$ (47 mg, 0.75 mmol) and conc aq HCl (0.32 mL) were added sequentially. The resultant suspension was stirred at 0 ºC for 15 min, then H_2O (10 mL) was added. The resultant mixture was poured into a mixture of satd aq $NaHCO_3$ (50 mL) and H_2O (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organics were dried (Na_2SO_4), and concentrated in vacuo.

Step 4: The residue from the previous step was dissolved in MeCN (6.0 mL), and 35% aq HCHO (0.34 mL, 3.04 mmol) was added. The resultant orange solution was cooled to 0 ºC and $NaBH_3CN$ (34 mg, 0.54 mmol) was added. The resultant solution was allowed to rt, and then stirred at rt for 16 h. The resultant solution was poured into 1 M aq NaOH (5 mL) and then extracted with $CHCl_3$ (3 × 10 mL). The combined organics were washed with brine (20 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue was purified via preparative thin layer chromatography (eluent $CHCl_3$/MeOH/Et_3N, 230:5:2 to give a yellow solid (R_f = 0.72). This was dissolved in 6 M aq HCl (2.0 mL) and the resultant solution was washed with Et_2O (3 × 2 mL), then basified by the addition of 2 M aq NaOH until pH >14 was achieved. The resultant solution was extracted with Et_2O (3 × 3 mL), and the combined organics were dried (Na_2SO_4) and concentrated in vacuo to give *ent*-**71** as a yellow solid (27 mg, 51%, >95:5 dr); mp 57–59 °C; $[\alpha]_D^{25}$ −47.3 (*c* 1.0 in $CHCl_3$); ν_{max} 2976, 2924; δ_H (500 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.1, C(10')H_3), 1.19 (3H, d, *J* 6.5, C(2)*Me*), 1.24–1.41 (6H, m, C(4)H_A, C(5)H_A, C(8')H_2, C(9')H_2), 1.78 (1H, tdd, *J* 14.7, 11.6, 4.2, C(5)H_B), 1.99–2.11 (2H, m, C(2)*H*, C(4)H_B), 2.08 (2H, q, *J* 6.6, C(7')H_2), 2.13 (3H, s, N*Me*), 2.44 (1H, ddd, *J* 11.6, 8.6, 2.8, C(6)*H*), 3.13 (1H, br s, C(3)*H*), 3.32 (3H, s, O*Me*), 5.66 (1H, dd, *J* 14.6, 8.6, C(1')*H*), 5.67 (1H, dt, *J* 14.3, 7.0, C(6')*H*), 6.00–6.17 (4H, m, C(2')*H*–C(5')*H*); δ_C (125 MHz, $CDCl_3$) 14.1 (*C*(10')), 18.2 (*C*(2)*Me*), 22.3 (*C*(9')), 26.4 (*C*(4)), 28.3 (*C*(5)), 31.6 (*C*(7')), 32.6 (*C*(8')), 40.8 (N*Me*), 57.1 (O*Me*), 62.4 (*C*(2)), 68.6 (*C*(6)), 79.4 (*C*(3)), 130.4, 130.5, 130.8, 132.1 (*C*(2')–*C*(5')), 135.3 (*C*(6')), 137.8 (*C*(1')); *m*/*z* (ESI^+) 278 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{18}H_{32}NO^+$ ($[M+H]^+$) requires 278.2478; found 278.2481.

6.4 Experimental for Chapter 5

1,2-Epoxy-3,4-dibromocyclohexane 244

Benzene Oxide 214

Step 1: Peracetic acid (39% in AcOH, 22 mL, 130 mmol) was added dropwise to a mechanically stirred suspension of 1,4-cyclohexadiene **242** (11.8 mL, 125 mmol) and Na_2CO_3 (17.5 g, 165 mmol) in CH_2Cl_2 (175 mL) at 0 °C and the resultant suspension was stirred at 0 °C for 18 h. H_2O (100 mL) was added and the aqueous layer was extracted with $CHCl_3$ (3 × 60 mL). The combined organic extracts were washed with satd aq Na_2SO_3 (~100 mL) until starch-iodide paper indicated that no peroxide was present, then dried (Na_2SO_4).

Step 2: A solution of Br_2 (6.4 mL) in $CH_2Cl_2/CHCl_3$ (1:1, v/v, 22 mL) was added dropwise to the resulting solution from step 1 at –78 °C. The resultant solution was stirred at –78 °C for 30 min, then allowed to warm to rt. Satd aq $Na_2S_2O_3$ (200 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 75 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give **244** as a crude white solid; δ_H (400 MHz, $CDCl_3$) 2.45 (1H, ddd, *J* 16.0, 6.7, 3.4, C(3)H_A), 2.65 (1H, dd, *J* 16.5, 6.3, C(6)H_A), 2.89 (1H, ddd, *J* 16.5, 6.4, 3.6, C(6)H_B), 2.99 (1H, ddt, *J* 16.0, 4.5, 1.1, C(3)H_B), 3.21 – 3.26 (2H, m, C(1)*H,* C(2)*H*), 4.16 – 4.22 (1H, m, C(5)*H*), 4.30 (1H, ddd, *J* 7.7, 6.7, 4.6, C(4)*H*).

Step 3: DBU (54 mL, 380 mmol) was added dropwise to a solution of the residue from the previous step in Et_2O (351 mL) at 0 °C and the resultant solution was stirred at rt for 24 h. The solution was then washed with sat aq $NaHCO_3$ (2 × 150 mL). The organic layer was then washed with brine (100 mL), and dried (Na_2SO_4). The solvent was removed at rt under a stream of N_2 to give **214** as an orange liquid (6.60 g, 56%);[111] δ_H (400 MHz, MeOD) 5.20 (1H, dt, *J* 4.9, 0.8, C(1)*H*), 5.84 – 5.88 (1H, m, C(2)*H*), 6.22 (1H, ddt, *J* 4.7, 2.8, 0.8, C(3)*H*)

(±)-2,3,3a,6,7,7a-Hexahydro-1H-3,6-methanoindol-7-ol *rac*-**215**

Allyl amine (0.56 mL, 3.7 mmol) was added to a solution of benzene oxide (35 mg, 0.37 mmol) in MeOH (0.35 mL) and the resultant solution was heated at 65 °C for 48 h. The orange solution was then concentrated in vacuo. Purification via flash column chromatography (eluent Chloroform/MeOH/NH_4OH, 9:1:0.1) gave *rac*-**215** as a yellow oil (49 mg, 90%, >95:5 dr); ν_{max} (film) 3658 (N-H), 2935 (C-H), 2895 (C-H); δ_H (400 MHz, MeOD) 1.20 (1H, ddd, *J* 13.3, 3.1, 1.5, C(1′)H_AH_B), 1.57 (1H, dddd, *J* 13.3, 10.4, 2.7, 0.7, C(1′)H_AH_B), 1.96 – 2.04 (1H, m, C(3)*H*), 2.68 (1H, tddd, *J* 5.3, 4.0, 2.7, 1.5, C(6)*H*), 2.78 (1H, d, *J* 10.7, C(2)H_AH_B), 2.80 – 2.85 (1H, m, C(3a)*H*), 2.89 (1H, dt, *J* 4.8, 1.1, C(7a)*H*), 3.09 (1H, dd, *J* 10.7, 5.1, C(2)H_AH_B), 3.61 (1H, d, *J* 3.8, C(7)*H*), 6.18 (1H, ddd, *J* 8.2, 6.4, 1.5, C(4)*H*), 6.26 (1H, ddt, *J* 7.3, 6.4, 1.1, C(5)*H*); δ_C (101 MHz, MeOD) 32.3 (C(1′)), 33.6 (C(3)), 35.6 (C(6)), 41.3 (C(3a)), 52.8 (C(2)), 64.5 (C(7a)), 78.2 (C(7)), 127.4 (C(4)), 133.6 (C(5)); m/z (ESI^+) 152 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_9H_{14}ON^+$ ($[M+H]^+$) requires 152.1070; found 152.1069.

(±) N-*Me*, 2,3,3a,6,7,7a-Hexahydro-3,6-methanoindol-7-ol *rac*-**216**

248 (77 μL, 0.80 mmol) was added to a solution of benzene oxide (50 mg, 0.53 mmol) in MeOH (0.50 mL) and the resultant solution was heated at 65 °C for 48 h. The orange solution was then concentrated in vacuo. Purification via flash column chromatography (eluent $CHCl_3$/MeOH/NH_4OH, 9:1:0.1) gave *rac*-**215** as a yellow oil (82 mg, 94%, >95:5 dr); ν_{max} (film) 3434 (O-H), 2933 (C-H), 2897 (C-H); δ_H (400 MHz, MeOD) 1.19 (1H, ddd, *J* 13.2, 3.1, 1.7, C(1′)H_AH_B), 1.50 (1H, ddd, *J* 13.2, 10.4, 2.6, C(1′)H_AH_B), 1.92 – 2.04 (1H, m, C(3)*H*), 2.49 – 2.52 (1H, m, C(7a)*H*), 2.53 (3H, s, N*Me*), 2.57 (1H, d, *J* 10.0, C(2)H_AH_B), 2.65 (1H, dddd, *J* 8.6, 5.4, 2.6, 1.7, C(6)*H*), 2.81 (1H, dd, *J* 10.0, 5.3, C(2)H_AH_B), 2.91 (1H, ddd, *J* 6.4, 5.2, 2.6, C(3a)*H*), 3.77 (1H, d, *J* 3.9, C(7)*H*), 6.16 (1H, ddd, *J* 8.2, 6.4, 1.5, C(4)*H*),), 6.20 – 6.25 (1H, m, C(5)*H*); δ_C (101 MHz, MeOD) 33.9 (C(1′)), 35.5 (C(3)), 36.7 (C(6)), 40.3 (C(3a)), 42.6 (NMe), 63.9 (C(2)), 73.2 (C(7a)),

74.4 (C(7)), 128.6 (C(4)), 134.3 (C(5)); m/z (ESI^+) 166 ($[M+H]^+$, 100%) HRMS (ESI^+) $C_{10}H_{16}ON^+$ ($[M+H]^+$) requires 166.1226; found 166.1225

(±) *N*-Bn, 2,3,3a,6,7,7a-Hexahydro-3,6-methanoindol-7-ol *rac*-**217**

249 (109 mg, 0.742 mmol) was added to a solution of benzene oxide (35 mg, 0.37 mmol) in MeOH (0.35 mL), and the resultant solution was heated at 65 °C for 48 h. The orange solution was then concentrated in vacuo. Purification via flash column chromatography (eluent Chloroform/ Ammonia, ca. 7 N solution in MeOH, 200:1) gave *rac*-**217** as a yellow oil (82 mg, 92%, >95:5 dr); ν_{max} (film) 3439 (O-H, 2994 (C-H), 2935 (C-H); δ_H (400 MHz, MeOD) 1.25 (1H, ddd, *J* 13.0, 3.1, 1.9, C(1′)H_A), 1.50 (1H, ddd, *J* 13.0, 10.4, 2.6, C(1′)H_B), 1.94 (1H, dddd, *J* 10.3, 5.0, 3.6, 1.7, C(3)*H*), 2.57 (1H, d, *J* 9.4, C(2)H_A), 2.61 – 2.66 (2H, m, C(6)*H*, C(7a)*H*), 2.79 (1H, dd, *J* 9.5, 4.8, C(2)H_B), 2.79 – 2.88 (1H, m, C(3a)*H*), 3.83 (1H, dd, *J* 4.0, 0.8, C(7)*H*), 3.84 (1H, d, *J* 13.4, NCH_APh), 3.89 (1H, d, *J* 13.4, NCH_BPh), 6.12 – 6.22 (2H, m, C(4)*H*, C(5)*H*), 7.19 – 7.39 (5H, m, *Ph*); δ_C (101 MHz, MeOD) 32.9 (C(1′)), 34.7 (C(3)), 36.2 (C(6)), 39.9 (C(3a)), 60.0 (N*C*H_2Ph), 61.4 (C(2)), 70.1 (C(7a)), 75.5 (C(7)), 127.3 (*o-Ph*), 128.6 (C(4)), 128.8 (*p-Ph*), 129.3 (*m-Ph*), 133.2 (C(5)), 140.2 (*i-Ph*); m/z (ESI^+) 242 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{16}H_{20}ON^+$ ($[M+H]^+$) requires 242.1540; found 242.1541.

(±) (1*R*,2*R*)-2-*N*-(Benzylamino)cyclohexa-3,5-dien-1-ol *rac*-**218**

Benzylamine (0.58 mL, 5.3 mmol) was added to a solution of **214** (50 mg, 0.53 mmol) in MeOH (0.50 mL) at rt and the resultant solution was stirred at 66 °C for 48 h, then concentrated in vacuo. Purification via column chromatography (eluent $CHCl_3$/ MeOH 100:3) gave *rac*-**218** as a brown solid (92 mg, 86%, >95:5 dr);[111] mp 54.5–55.5 °C; δ_H (400 MHz, MeOD) 3.49 (1H, dddd, *J* 11.4, 2.6, 1.8, 0.8, C(2)*H*), 3.77 (1H, d, *J* 13.0, NCH_APh, 3.90 (1H, d, *J* 13.0, NCH_BPh), 4.37 (1H, ddd, *J* 11.4, 2.8, 2.0, C(1)*H*), 5.83 – 6.00 (4H, m, C(3)*H,* C(4)*H,* C(5)*H,* C(6)*H*), 7.22 – 7.38 (5H, m, *Ph*).

(±) 7-Hydroxy-2-oxo-(*N*-benzyl)-2,3,3a,6,7,7a-hexahydro-1H-3,6-methanoindole-8-carboxylic acid *rac*-**219**

Maleic anhydride (18 mg, 0.18 mmol) was added to a solution of *rac*-**218** (30 mg, 0.15 mmol) in CH_2Cl_2 (0.75 mL) and stirred at rt for 5 min. The reaction was then concentrated in vacuo and purification via recrystallization (hexane:CH_2Cl_2) gave *rac*-**219** as a clear oil (38 mg, 85%, >95:5 dr); ν_{max} (film) 2999 (O-H), 2975 (C-H), 2912 (C-H), 1718 (C=O); δ_H (500 MHz, CD_2Cl_2) 2.57 – 2.61 (2H, m, C(3)*H*, C(1′)*H*), 3.08 (1H, dd, *J* 4.6, 1.1, C(7a)*H*), 3.19 (1H, ddt, *J* 6.7, 2.6, 1.4, C(6)*H*), 3.43 (1H, dddd, *J* 6.0, 4.7, 2.8, 1.1, C(3a)*H*), 4.08 (1H, d, *J* 15.0, NCH_APh), 4.39 (1H, d, *J* 3.8, C(7)*H*), 4.84 (1H, d, *J* 15.0, NCH_BPh), 6.17 (1H, ddd, *J* 8.1, 6.5, 1.4, C(4)*H*), 6.49 (1H, tt, *J* 6.6, 1.1, C(5)*H*), 7.24 – 7.37 (5H, m, *Ph*); δ_C (126 MHz, CD_2Cl_2) 40.5 (C(6)), 41.8 (C(3a)), 41.8 (C(1′)), 45.9 (C(3)), 64.2 (C(7a)), 67.5 (C(7)), 128.0 (C(4)), 128.2 (*p-Ph*), 128.6 (*m-Ph*), 129.1 (*o-Ph*), 135.8 (C(5)), 136.2 (*i-Ph*), 174.8 (CO_2H), 177.6 (C(2)) ; m/z (ESI$^+$) 298 ([M−H]$^-$, 100%); HRMS (ESI$^+$) $C_{17}H_{16}O_4N^-$ ([M−H]$^-$, requires 298.1084; found 298.1083.

(±) Ethyl 7-hydroxy-2-oxo-(*N*-benzyl)-2,3,3a,6,7,7a-hexahydro-1H-3,6-methanoindole-8-carboxylate *rac*-**220**

277 (55 mg, 0.34 mmol) was added to a solution of *rac*-**218** (45 mg, 0.22 mmol) and NEt_3 (92 µL, 0.66 mmol) in CH_2Cl_2 (0.75 mL) at rt and stirred for 15 min. The mixture was then concentrated in vacuo, and then portioned between a mixture of H_2O (5 mL) and sat aq $NaHCO_3$ (5 mL) and CH_2Cl_2 (10 mL). The aqueous layer was then extracted with CH_2Cl_2 (2 × 10 mL) then the combined organics were dried (Na_2SO_4) and concentrated in vacuo. Purification via flash column chromatography (eluent Chloroform/MeOH 100:0 increased to 100:1) gave *rac*-**220** as a clear oil (71 mg, 98%, >95:5 dr); ν_{max} (film) 3067 (O-H), 2948 (C-H), 2899 (C-H), 1751 (C=O), 1721 (C=O); δ_H (500 MHz, MeOD) 1.24 (3H, t, *J* 7.1, OCH_2CH_3), 2.75 (1H, dt, *J* 4.6, 1.5, C(3)*H*), 2.78 (1H, dd, *J* 3.2, 1.8, C(1′)*H*), 3.00 (1H, dt, *J* 4.6, 1.3, C(7a)*H*), 3.30 (2H, tdd, *J* 6.2, 3.9, 2.4, C(3a)*H*),

3.42 (1H, tdd, *J* 5.3, 3.2, 1.5, C(6)*H*), 3.74 (1H, d, *J* 3.8, C(7)*H*), 4.07 – 4.15 (3H, m, OCH_2CH$_3$, NCH_APh), 4.82 (1H, d, *J* 15.1, NCH_BPh), 6.14 – 6.24 (2H, m, C(4)*H*, C(5)*H*), 7.26 – 7.40 (5H, m, *Ph*); δ_C (126 MHz, MeOD) 14.5 (OCH$_2$*C*H$_3$), 40.0 (C(3a)), 42.3 (C(6)), 43.6 (C(3)), 45.7 (C(1′)), 46.2 (N*C*H$_2$Ph), 62.3 (O*C*H$_2$CH$_3$), 64.7 (C(7a)), 71.7 (C(7)), 128.8 (*p-Ph*), 129.1 (C(4)), 129.2 (*m-Ph*), 129.9 (*o-Ph*), 132.7 (C(5)), 137.7 (*i-Ph*), 172.8 (*C*O$_2$Et), 179.8 (C(2)); m/z (ESI$^+$) 328 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{22}O_4N^+$ ([M+H]$^+$) requires 328.1543; found 328.1544.

8-Phenyl, 7-hydroxy-2-oxo-1-(*N*-(α-methylbenzyl)amino)-2,3,3a,6,7,7a-hexahydro-1H-3,6-methanoindole 222

Cinnamoyl chloride (12 mg, 0.07 mmol) was added to a solution of **221** (10 mg, 0.05 mmol) and trimethylamine (20 μL, 0.14 mmol) in CH_2Cl_2 (0.40 mL) at rt and stirred for 1 h. The mixture was then concentrated in vacuo, and then portioned between a mixture of H_2O (5 mL) and sat aq $NaHCO_3$ (5 mL) and CH_2Cl_2 (10 mL). The aqueous layer was then extracted with CH_2Cl_2 (2 × 10 mL) then the combined organics were dried (Na_2SO_4) and concentrated in vacuo. Purification via flash column chromatography (eluent Chloroform/MeOH 100:0 increased to 100:1) gave **222** as a clear oil (15 mg, 95%, >95:5 dr); $[\alpha]_D^{25}$ +38.4 (*c* 1.0 in CH_2Cl_2); ν_{max} (film) 3350 (O-H), 2975 (C-H), 2904 (C-H), 1719 (C=O); δ_H (400 MHz, CD_2Cl_2) 1.67 (3H, d, *J* 7.2, C(α)*Me*), 2.48 (1H, dt, *J* 4.0, 2.0, C(3)*H*), 2.90 (1H, dt, *J* 4.6, 1.3, C(7a)*H*), 3.19 (1H, dtt, *J* 6.7, 4.5, 1.2, C(3a)*H*), 3.21 – 3.26 (2H, m, C(6)*H*, C(1′)*H*), 3.94 (1H, d, *J* 3.8, C(7)*H*), 5.43 (1H, q, *J* 7.3, C(α)*H*), 6.07 – 6.12 (1H, m C(5)*H*), 6.34 (1H, ddd, *J* 8.1, 6.6, 1.4, C(4)*H*), 7.08 – 7.41 (10H, m, *Ph*, C(1′)*Ph*); δ_C (126 MHz, CD_2Cl_2) 18.1 (C(α)*Me*), 40.6 (C(3a)), 45.9 (C(1′)), 46.9 (C(6)), 48.0 (C(3)), 49.5 (*C*(α)), 61.6 (C(7a)), 74.7 (C(7)), 126.8 (*p-Ph*)), 127.3 (*o-Ph*), 127.9 (C(1′)(*p-Ph*)), 128.5 (*m-Ph*), 128.6 (C(1′)(*o-Ph*)), 129.0 (C(1′)(*m-Ph*)), 130.5 (C(5)), 131.6 (C(4)), 141.7 (*i-Ph*), 143.4 (C(1′)(*i-Ph*)), 177.9 (C(2)); m/z (ESI$^+$) 368 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{23}O_2NNa^+$ ([M+Na]$^+$) requires 368.1621; found 368.1625.

Methyl 7-hydroxy-2-oxo-1-(*N*-(α-methylbenzyl)amino)-2,3,3a,6,7,7a-hexahydro-1H-3,6-methanoindole-8-carboxylate 223

291 (31 mg, 0.21 mmol) was added to a solution of **221** (30 mg, 0.14 mmol) and trimethylamine (58 μL, 0.42 mmol) in CH_2Cl_2 (0.47 mL) at rt and stirred for 1 h. The mixture was then concentrated in vacuo, and then portioned between a mixture of H_2O (5 mL) and sat aq $NaHCO_3$ (5 mL) and CH_2Cl_2 (10 mL). The aqueous layer was then extracted with CH_2Cl_2 (2 × 10 mL) then the combined organics were dried (Na_2SO_4) and concentrated in vacuo. Purification via flash column chromatography (eluent Chloroform/MeOH 100:0 increased to 100:1) gave **223** as a clear oil (63 mg, 92%, >95:5 dr); $[\alpha]_D^{25}$ −45.9 (*c* 1.0 in MeOH); ν_{max} (film) 3259 (O-H), 2968 (C-H), 2915 (C-H), 1752 (C=O), 1722 (C=O);δ_H (400 MHz, MeOD) 1.61 (3H, d, *J* 7.2, C(α)*Me*), 2.59 (1H, dd, *J* 3.1, 1.8, C(1′)*H*), 2.67 (1H, dt, *J* 4.4, 1.6, C(3)*H*), 3.03 (1H, dt, *J* 4.0, 0.8, C(7)*H*), 3.15 – 3.20 (1H, m, C(6)*H*), 3.27 (1H, tt, *J* 4.6, 1.4, C(7a)*H*), 3.29 – 3.30 (1H, m, C(3a)*H*), 3.63 (3H, s, CO_2*Me*), 5.31 (1H, q, *J* 7.2, C(α)*H*), 6.09 – 6.18 (1H, m, C(5)*H*), 6.14 – 6.23 (1H, m, C(4)*H*), 7.28 – 7.45 (5H, m, *Ph*); δ_C (101 MHz, MeOD) 17.3 (C(α)*Me*), 40.8 (C(3a)), 42.3 (C(6)), 44.2 (C(3)), 45.4 (C(1′)), 51.7 (*C*(α)), 52.7 (CO_2*Me*), 62.2 (C(7a)), 72.5 (C(7)), 128.7 (*o-Ph*), 129.1 (C(4), (*p-Ph*)), 129.8 (*m-Ph*), 132.8 (C(5)), 141.6 (*i-Ph*), 173.4 (*C*O_2Me), 179.3 (C(2)); m/z (ESI$^+$) 350 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{21}O_4NNa^+$ ([M+Na]$^+$) requires 350.1363; found 350.1362.

1-((1″*S*,6″*S*)-6″-Hydroxycyclohexa-2″,4″-dien-1″-yl)-2,3,3a,6,7,7a-hexahydro-1H-3,6-methanoindol-7-ol and (±) 1-((1″*R*,6″*R*)-6″-Hydroxycyclohexa-2″,4″-dien-1″-yl)-2,3,3a,6,7,7a-hexahydro-1H-3,6-methanoindol-7-ol 241

Allyl amine (0.11 mL, 0.74 mmol) was added to a solution of benzene oxide (35 mg, 0.37 mmol) in MeOH (0.35 mL) and the resultant solution was heated at 65 °C for 48 h. The orange solution was then concentrated in vacuo. Purification via flash column chromatography (eluent Chloroform/MeOH/NH_4OH, 9:1:0.1) gave **241** as an inseparable mixture of diastereomers

(38 mg, 42%, >95:5 dr); ν_{max} (film) 3305 (O-H), 2942 (C-H), 2899 (C-H); δ_H (400 MHz, MeOD) 1.30 (2H, ddt, *J* 12.9, 10.1, 2.5, C(1′)H_A), 1.46 – 1.55 (2H, m, C(1′)H_B), 1.95 (2H, dddq, *J* 9.7, 5.6, 3.7, 1.9, C(3)*H*), 2.57 (1H, d, *J* 8.8, C(2)H_A), 2.63 (2H, ddtt, *J* 8.3, 4.0, 2.9, 1.5, C(6)*H*), 2.72 – 2.78 (2H, m, C(3a)*H*), 2.78 – 2.79 (3H, m, C(2)H_A, C(7a)*H*), 2.86 – 2.96 (2H, m, 2 × C(2)H_B), 3.56 (2H, ddd, *J* 9.0, 3.5, 2.2, C(6″)*H*), 3.74 (2H, d, *J* 4.2, C(7)*H*), 4.49 (2H, ddd, *J* 8.9, 3.3, 1.4, C(1″)*H*), 5.86 – 6.02 (4H, m, C(2″)*H*, C(5″)*H*), 6.10 (4H, dddt, *J* 16.7, 9.8, 4.9, 1.8, C(3″)*H*, C(4″)*H*), 6.17 (4H, tt, *J* 3.5, 1.5, C(4)*H*, C(5)*H*); δ_C (101 MHz, MeOD) 30.6, 31.2 (C(1′)), 34.9, 34.9 (C(3)), 35.9 (C(6)), 41.0 (C(3a)), 55.8, 57.5 (C(2)), 64.8 (C(7a)), 64.9 (C(6″)), 70.1 (C(1″)), 78.1 (C(7)), 124.2, 124.5 (C(2″)), 126.1, 127.1 (C(3″)), (C(4″)), 128.7, 128.9 (C(5)), 130.0 (C(5″)), 132.7, 132.9 (C(4)); m/z (ESI$^+$) 268 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{15}H_{19}O_2NNa^+$ ([M+Na]$^+$) requires 268.1308; found 268.1307.

_N_-Methyl allyl amine 248

To a solution of $MeNH_2$ in EtOH (33 wt. %, 1.00 g, 10.6 mmol) was added a solution of allyl bromide (0.31 mL, 3.55 mmol) in EtOH (2.00 mL) slowly over 10 minute at 0 °C and then stirred at rt for 12 h. The reaction was the concentrated in vacuo and the residue was washed with Et_2O (4 × 2 mL). The residue was then dissolved in 1 M aq NaOH and extracted with Et_2O (3 × 2 mL). The combined organics were then dried ($MgSO_4$) and concentrated in vacuo to yield **248** as a colourless oil (136 mg, 54%);[127] δ_H (400 MHz, MeOD) 2.34 (3H, s, N*Me*), 3.17 (2H, dt, *J* 6.1, 1.5, C(1)H_2), 5.13 (1H, dq, *J* 10.3, 1.4, C(3)H_Z), 5.20 (1H, dq, J 16.8, 1.7, C(3)H_E), 5.89 (1H, ddt, *J* 16.8, 10.3, 6.2, C(2)*H*); δ_C (101 MHz, MeOD) 35.4 (N*Me*), 54.9 (C(1)), 117.2 (C(3)), 137.0 (C(2)).

_N_-Benzyl allyl amine 249

To a suspension of benzyl amine (2.74 mL, 25.1 mmol) and KI (21 mg, 0.13 mmol) in DMSO (15 mL) was added Allyl bromide (1.10 mL, 12.7 mmol) at 0 °C. The mixture was then stirred at rt for 18 h. The mixture was then poured into sat aq $NaHCO_3$ (30 mL) and extracted with Et_2O (5 × 15 mL). The combined organics were then washed with brine, and dried ($MgSO_4$), then concentrated in vacuo. Purification via flash column chromatography (eluent CH_2Cl_2/(Ammonia, ca. 7 N solution in MeOH) 100:5) gave **249** as a yellow oil (54 mg, 72%);[128] δ_H (400 MHz, $CDCl_3$) 3.22 (2H, dt, *J* 6.0, 1.5, C(1)H_2), 3.74 (2H, s, NCH_2Ph), 5.05 (1H, ddt, *J* 10.2, 1.8, 1.3, C(3)H_Z), 5.14 (1H, dq, *J* 17.2, 1.7, C(3)H_E), 5.88 (1H, ddt, *J* 17.2, 10.2, 5.9, C(2)*H*), 7.16 – 7.28 (5H, m, *Ph*).

Homo allyl amine 251

A solution of allyl cyanide (1.00 mL, 12.4 mmol) in Et_2O (12.4 mL) was cooled to 0 °C and $LiAlH_4$ (1.0 M in Et_2O, 31 mL, 31 mmol) was added. The mixture was brought to rt and stirred overnight. The reaction was then cooled to 0 °C, and Et_2O (6 mL) was added, followed by H_2O (6 mL), and 10% aq NaOH (6 mL). $MgSO_4$ (12 g) was then added, and the mixture stirred for 30 min. The reaction was then filtered through a plug of Celite (eluent Et_2O) and concentrated in vacuo. The crude mixture was purified by distillation (atmospheric pressure, 76 °C) to give **251** as a pale orange liquid (592 mg, 61%);[129] δ_H (400 MHz, MeOD) 2.21 (2H, qt, *J* 6.9, 1.4, C(2)H_2), 2.68 (2H, t, *J* 6.9, C(1)H_2), 5.01 – 5.14 (2H, m, C(4)H_2), 5.81 (1H, ddt, *J* 17.2, 10.2, 6.9, C(4)H_2); δ_C (101 MHz, MeOD) 38.3 (*C*(2)), 41.9 (*C*(1)), 117.1 (*C*(4)), 137.3 (*C*(3)).

(±) (1*R*,6*R*)-6-(But-3′-en-1-ylamino)cyclohexa-2,4-dien-1-ol *rac*-252

But-3-en-1-amine (0.34 mL, 3.7 mmol) was added to a solution of benzene oxide (35 mg, 0.37 mmol) in MeOH (0.35 mL) and the resultant solution was heated at 65 °C for 48 h. The orange solution was then concentrated in vacuo. Purification via flash column chromatography (eluent $CHCl_3$/MeOH/NEt_3, 9:1:0.05 increased to 1:1:0.05) gave *rac*-**215** as a yellow oil (55 mg,

90%, >95:5 dr); ν_{max} (film) 3647 (O-H), 2970 (C-H), 2891 (C-H); δ_H (400 MHz, MeOD) 2.30 (2H, dddd, *J* 8.4, 7.1, 6.2, 1.4, C(2′)H_2), 2.67 (1H, dt, *J* 11.4, 7.1, C(1′)H_AH_B), 2.82 (1H, dt, *J* 11.4, 7.4, 6.7, C(1′)H_AH_B), 3.46 (1H, dt, *J* 11.7, 2.7, C(6)*H*), 4.32 (1H, ddd, *J* 11.7, 2.7, 2.0, C(1)*H*), 5.06 (1H, ddt, *J* 10.2, 2.2, 1.6, C(4′)H_{cis}), 5.12 (1H, dq, *J* 17.1, 1.6, C(4′)H_{trans}), 5.77 – 5.94 (3H, m, C(3′)*H*, C(2)*H,* C(3)*H,* C(4)*H*), 5.97 (1H, dddd, *J* 9.4, 5.1, 2.7, 1.3*,* C(5)*H*); δ_C (101 MHz, MeOD) 34.1 (C(2′)), 45.6 (C(1′)), 61.4 (C(6)), 70.6 (C(1)), 116.6 (C(4′)), 124.2 (C(4)), 124.9 (C(5)), 128.1 (C(3)), 131.5 (C(2)), 136.3 (C(3′)); m/z (ESI$^+$) 166 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{10}H_{16}ON^+$ ([M+H]$^+$) requires 166.1226; found 166.1224

But-3-yne-1-amine 256

Step 1: MsCl (4.60 mL, 59.5 mmol) was added dropwise to a stirred solution of butyl-1-yne-3-ol (3.00 mL, 39.6 mmol) and Et_3N (8.30 mL, 59.5 mmol) in Et_2O (100 mL) at 0 °C. After 4 h, the precipitate was filtered, and washed with brine (20 mL). The organic layer was separated, dried (Na_2SO_4) and concentrated in vacuo.

Step 2: The residue from the previous step was dissolved in DMF (30 mL), and NaN_3 (6.25 g, 96.0 mmol) was added. The mixture was heated to 70 °C and stirred for 4 h. The reaction mixture was then poured onto ice (25 g) and extracted with ethyl ether (3 × 30 mL). The solution was then dried (Na_2SO_4) and then cooled to 0 °C. PPh_3 (8.06 g, 30.7 mmol) was then added followed by H_2O (5.0 mL). The reaction was then allowed to warm to rt, and stirred for 12 h. The reaction mixture was then poured into 10% aq HCl (30 mL) and stirred for 10 min. The aqueous layer was then washed with CH_2Cl_2 (3 × 30 mL), and the aqueous layer was concentrated in vacuo. The residue was then dissolved in 6 M aq NaOH, and extracted with CH_2Cl_2 (3 × 30 mL), dried (Na_2SO_4), and concentrated in vacuo to give **256** as a light yellow oil (1.23 g, 45%);[130] δ_H (400 MHz, MeOD) 2.30 – 2.35 (3H, m, C(2)H_2, C(4)*H*), 2.73 – 2.78 (2H, m, C(1)H_2); δ_C (101 MHz, MeOD) 23.1 (*C*(2)), 41.6 (*C*(1)), 71.0 (*C*(4)), 82.9 (*C*(3)).

(±) (1*R*,6*R*)-6-(But-3′-yn-1-ylamino) cyclohexa-2,4-dien-1-ol *rac*-**257**

But-3-yn-1-amine (0.30 mL, 3.70 mmol) was added to a solution of benzene oxide (35 mg, 0.37 mmol) in MeOH (0.35 mL) and the resultant solution was heated at 65 °C for 48 h. The orange solution was then concentrated in vacuo. Purification via flash column chromatography (eluent Chloroform/MeOH/NEt_3, 83:17:2 increased to 50:50:2) gave *rac*-**257** as a yellow oil (55 mg, 92%, >95:5 dr); ν_{max} (film) 3649 (O-H), 2985 (C-H), 2894 (C-H), 2126 (C≡C); δ_H (400 MHz, MeOD) 2.34 (1H, t, *J* 2.7, C(4′)*H*), 2.38 – 2.45 (2H, m, C(2′)*H*), 2.77 (1H, dt, *J* 11.6, 6.9, C(1′)H_A), 2.89 (1H, dt, *J* 11.6, 6.7, C(1′)H_B), 3.47 (1H, ddd, *J* 11.7, 3.1, 2.4, C(6)*H*), 4.31 (1H, dt, *J* 11.7, 3.0, C(1)*H*), 5.82 – 5.94 (3H, m, C(2)*H*, C(4)*H*, C(5)*H*), 5.97 (1H, dddd, *J* 9.5, 5.0, 2.4, 1.0, C(3)*H*); δ_C (101 MHz, MeOD) 19.9 (C(2′)), 45.7 (C(1′)), 61.7 (C(1)), 71.2 (C(6)), 71.4 (C(4′)), 82.5 (C(3′)), 124.8 (C(4)), 125.6 (C(3)), 128.9 (C(5)), 132.1 (C(2)); m/z (ESI^+) 164 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{10}H_{14}ON^+$ ($[M+H]^+$) requires 164.1070; found 164.1069

Ethyl (*E*)-5-hydroxypent-2-enoate 260

Propane-1,3-diol (0.70 mL, 9.5 mmol) was dissolved in CH_2Cl_2 (250 mL), and $Ph_3P{=}CHCO_2Et$ (7.95 g, 22.8 mmol) and activated MnO_2 (16.5 g, 190 mmol) were added at rt. The reaction was then stirred for 24 h, before being filtered through a plug of Celite (eluent CH_2Cl_2) and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 2:1) gave **260** as a yellow oil (670 mg, 49%, >95:5 dr);[131] δ_H (400 MHz, MeOD) 1.27 (3H, t, *J* 7.2, OCH_2CH_3), 2.43 (2H, qd, *J* 6.4, 1.6, C(4)H_2), 3.67 (2H, t, *J* 6.3, C(5)H_2), 4.17 (2H, q, *J* 7.1, OCH_2CH_3), 5.91 (1H, dt, *J* 15.7, 1.5, C(2)*H*), 6.99 (1H, dt, *J* 15.7, 7.1, C(3)*H*); δ_C (101 MHz, MeOD) 14.5 (OCH_2CH_3), 36.4 (C(4)), 61.3 (OCH_2CH_3), 61.3 (C(5)), 123.9 (C(2)), 147.6 (C(3)), 168.1 (C(1)).

Ethyl (*E*)-5-bromopent-2-enoate 261

CBr_4 (1.87 g, 5.63 mmol) was added to a solution of **260** (540 mg, 3.75 mmol) in CH_2Cl_2 (7.5 mL). The solution was cooled to 0 °C, and a solution of PPh_3 (1.28 g, 4.88 mmol) in CH_2Cl_2 (7.0 mL) was added dropwise. After 15 min, the reaction was concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **261** as a yellow oil (660 mg, 85%, >95:5 dr);[132] δ_H (400 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.1, OCH_2CH_3), 2.78 (2H, qd, *J* 6.8, 1.6, C(4)H_2), 3.45 (2H, t, *J* 6.8, C(5)H_2), 4.20 (2H, q, *J* 7.1, OCH_2CH_3), 5.91 (1H, dt, *J* 15.7, 1.5, C(2)*H*), 6.89 (1H, dt, *J* 15.7, 6.9, C(3)*H*).

Ethyl pentadienoate 262

$MeNH_2$ (2 M in THF, 1.20 mL, 3.40 mmol) was added to a solution of bromide **261** (50 mg, 0.24 mmol) in THF (0.48 mL), and the resultant solution was stirred for 3 h at rt. The mixture as then poured into 2 M aq NaOH (2.0 mL), and extracted with Et_2O (3 x 5 mL), washed with brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo to give **262** as a colourless oil (29 mg, 95%);[133] δ_H (400 MHz, $CDCl_3$) 1.30 (3H, t, *J* 7.2, OCH_2CH_3), 4.21 (2H, q, *J* 7.1, OCH_2CH_3), 5.48 (1H, ddt, *J* 10.0, 1.4, 0.7, C(5)H_Z), 5.60 (1H, ddt, *J* 17.0, 1.5, 0.8, C(5)H_E), 5.91 (1H, dq, *J* 15.5, 0.7, C(2)*H*), 6.45 (1H, dddd, *J* 17.0, 10.9, 10.0, 0.7, C(4)*H*), 7.26 (1H, ddt, *J* 15.4, 11.0, 0.8, C(3)*H*).

3-*N*-Boc-Propan-1-ol 264

A solution of 3-amino-propan-1-ol (1.00 g, 13.0 mmol) and Et_3N (2.17 mL, 15.6 mmol) in CH_2Cl_2 (10.0 mL) was cooled to 0 °C, and Boc_2O (2.83 g, 13.0 mmol) was added. The reaction was allowed to warm to rt, before the organics were washed with 0.1 M aq HCl (3 × 5 mL), then H_2O (10 mL), then brine, dried (Mg_2SO_4), and concentrated in vacuo to give **264** as a colourless oil (2.12 g, 93%);[134] δ_H (400 MHz, $CDCl_3$) 1.45 (9H, s, CMe_3), 1.66 (2H, p, *J* 5.9, C(2)H_2), 3.04 (1H, br s, O*H*), 3.29 (2H, q, *J* 6.3, C(3)H_2), 3.66 (2H, q, *J* 6.0, C(1)H_2), 4.74 (1H, br s, N*H*).

(*E*)-Ethyl 5-*N*-Boc-pent-2-enoate 266

Step 1: DMSO (0.81 mL, 11 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (0.48 mL, 5.7 mmol) in CH_2Cl_2 (3.8 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 10 min. A solution of **264** (0.50 g, 2.9 mmol) in CH_2Cl_2 (3.8 mL) was added and the resultant mixture was stirred at −78 °C for 30 min. Et_3N (2.38 mL, 17.1 mmol) was added then the reaction mixture was allowed to warm to rt and stirred at rt for 30 min. H_2O (25 mL) was then added and the reaction mixture extracted with CH_2Cl_2 (50 mL). The combined organics were then dried ($MgSO_4$) and concentrated in vacuo.

Step 2: The residue from the previous step was dissolved in CH_2Cl_2 (14 mL) and $Ph_3P{=}CHCO_2Et$ (1.49 g, 4.29 mmol) was added at rt and the resultant mixture was stirred overnight at rt. The reaction mixture was then concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 9:1) gave **266** as a yellow oil (598 mg, 86%, >95:5 [*E*:*Z*]);[135] δ_H (400 MHz, $CDCl_3$) 1.28 (3H, t, *J* 7.1, OCH_2CH_3), 1.44 (9H, s, CMe_3), 2.40 (2H, qd, *J* 6.8, 1.6, C(4)H_2), 3.26 (2H, t, *J* 6.8, C(5)H_2), 4.19 (2H, q, *J* 7.1, OCH_2CH_3), 4.58 (1H, br s, N*H*), 5.87 (1H, dt, *J* 15.7, 1.5, C(2)*H*), 6.89 (1H, dt, *J* 15.7, 7.1, C(3)*H*).

3-*N*-Trifluroacetate-propan-1-ol 267

A solution of 3-amino-propan-1-ol (500 mg, 6.67 mmol) in MeOH (33 mL) was cooled to 0 °C, and ethyl trifluroacetate (0.79 mL, 6.7 mmol) was added. The reaction was stirred at 0 °C for 2 h, then concentrated in vacuo to give **267** as a colourless oil (833 mg, 73%);[136] δ_H (400 MHz, $CDCl_3$) 1.78 – 1.88 (3H, m, C(2)H_2, O*H*), 3.51 – 3.59 (2H, m, C(3)H_2), 3.79 – 3.85 (2H, m, C(1)H_2), 7.16 (1H, br s, N*H*).

(*E*)-*tert*-Butyl 5-*N*-trifluroacetate-pent-2-enoate 269

Step 1: DMSO (1.38 mL, 18.7 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (0.79 mL, 9.4 mmol) in CH_2Cl_2 (6.2 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 10 min. A solution of **267** (800 mg, 4.68 mmol) in CH_2Cl_2 (6.2 mL) was added and the resultant mixture was stirred at −78 °C for 30 min. Et_3N (3.89 mL, 28.0 mmol) was added then the reaction mixture was allowed to warm to rt and stirred at rt for 30 min. H_2O (30 mL) was then added and the reaction mixture extracted with CH_2Cl_2 (50 mL). The combined organics were then dried ($MgSO_4$) and concentrated in vacuo.

Step 2: The residue from the previous step was dissolved in CH_2Cl_2 (23 mL) and $Ph_3P{=}CHCO_2{}^tBu$ (2.44 g, 7.02 mmol) was added at rt and the resultant mixture was stirred overnight. The reaction mixture was then concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 9:1) gave **269** as a yellow oil (937 mg, 75%, >95:5 [*E*:*Z*]);[136] ν_{max} (film) 3328 (N-H), 2985 (C-H), 2894 (C-H), 1723 (C=O), 1716 (C=O); δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, C*Me*$_3$), 2.48 (2H, qd, *J* 6.9, 1.5, C(4)*H*$_2$), 3.45 – 3.55 (2H, m, C(5)*H*$_2$), 5.83 (1H, dt, *J* 15.6, 1.5, C(3)*H*), 6.48 (1H, s), 6.75 (1H, dt, *J* 15.6, 7.1, C(2)*H*).

Diethyl (cyanomethyl)phosphonate 271

Triethyl phosphite (6.19 mL, 40.0 mmol) and chloroacetonitrile (2.53 mL, 40.0 mmol) were heated to 150 °C and stirred at this temperature for 3.5 h. The reaction was then concentrated in vacuo to yield **271** as a pale yellow oil (7.00 g, 99%);[137] δ_H (400 MHz, $CDCl_3$) 1.37 – 1.42 (6H, m, OCH_2CH_3), 2.81 – 2.91 (2H, d, *J* 21.1, CH_2), 4.18 – 4.32 (4H, m, OCH_2CH_3).

***N*-Boc-(4-cyanobut-3-en-1-yl) 272**

A solution of phophonate **271** (607 mg, 3.43 mmol) in THF (5.7 mL) was cooled to 0 °C. NaH (60% dispersion in mineral oil, 172 mg, 4.29 mmol) was then added portionwise, and the mixture

was stirred for 10 min. A solution of aldehyde **265** (500 mg, 2.86 mmol) in THF (1.40 mL) was added, and then the reaction warmed to 70 °C and stirred for 3 h. The reaction was then cooled to rt, and poured into H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), then the combined organics were dried ($MgSO_4$) and concentrated in vacuo. Purification via flash column chromatography ($AgNO_3$ doped silica) (eluent $CHCl_3$/(Ammonia, ca. 7 N solution in MeOH) 100:1) gave **272** as a yellow oil (363 mg, 54%, 80:20 [*E*:*Z*]);[138] δ_H (500 MHz, $CDCl_3$) 1.43 (9H, s, C*Me*$_3$), 2.39 – 2.47 (2H, m, C(2)*H*$_2$), 3.22 – 3.33 (2H, m, C(3)*H*$_2$), 4.62 (1H, br s, N*H*), 5.40 (1H, dt, *J* 16.3, 1.6, C(4)*H*), 6.67 (1H, dt, *J* 16.3, 7.2, C(3)*H*); δ_C (126 MHz, $CDCl_3$) 28.5 (C*Me*$_3$), 34.2 (*C*(2)), 38.9 (*C*(1)), 79.8 (*C*Me$_3$), 102.0 (*C*(4)), 117.2 (*C*N), 152.5 (*C*(3)), 156.0 (*C*(O)).

(*E*)-5-Aminopent-2-enenitrile 273

N-Boc nitrile **272** (70 mg, 0.36 mmol) was dissolved in TFA:CH_2Cl_2 (1:1, 1.80 mL), and stirred at rt for 20 min. This was dissolved in 6 M aq HCl (2.0 mL) and the resultant solution was washed with CH_2Cl_2 (2 × 2.0 mL), then basified by the addition of 2 M aq NaOH until pH >14 was achieved. The resultant solution was extracted with CH_2Cl_2 (3 × 3 mL), then the combined organics were dried (Na_2SO_4) and concentrated in vacuo to give **272** as a colourless oil which was found to polymerise rapidly; δ_H (400 MHz, $CDCl_3$) 2.31 (2H, qd, *J* 6.8, 1.6, C(4)*H*$_2$), 2.82 (2H, t, *J* 6.6, C(5)*H*$_2$), 5.35 (1H, dt, *J* 16.5, 1.6, C(2)*H*), 6.65 (1H, dt, *J* 16.5, 7.2, C(3)*H*).

Mixture 1- and 5-Benzyl glutaconates 281

A solution of glutaconic acid (108 mg, 0.83 mmol) in DMF (0.12 ml) was heated at 80 °C and stirred vigorously during the addition of dicyclohexylamine (0.16 ml, 0.83 mmol) and a single portion of benzyl bromide (0.10 ml, 0.83 mmol). The resulting solid mass was cooled, triturated with EtOAc, filtered and washed several times with EtOAc. The combined filtrates were washed with H_2O (4 ×10 mL), concentrated in vacuo, and the residue was dissolved in Et_2O and extracted with sat aq $NaHCO_3$ (3 × 10 mL). The extracts were combined, acidified with 6 M aq HCl and

washed with Et_2O (3 × 10 mL). The combined organic were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* yielding **281** as a clear oil (100 mg, 55%, >95:5 dr, 1:5 = 1:1.2); [139] 5-benzyl glutaconate δ_H (400 MHz, $CDCl_3$) 3.30 (2H, dd, *J* 7.1, 1.6, C(4)H_2), 5.20 (2H, s, OCH_2Ph), 6.02 (1H, dt, *J* 15.7, 1.5, C(2)*H*), 7.05 (1H, dt, *J* 15.7, 7.1, C(3)*H*), 7.31 – 7.39 (5H, m, *Ph*) 1-benzyl glutaconate δ_H (400 MHz, $CDCl_3$) 3.33 (2H, dd, *J* 7.2, 1.6, C(4)H_2), 5.17 (2H, s, OCH_2Ph), 5.95 (1H, dt, *J* 15.7, 1.6, C(2)*H*), 7.15 (1H, dt, *J* 15.7, 7.1, C(3)*H*), 7.31 – 7.39 (5H, m, *Ph*).

(±) 7-((*E*)-Pent-2-enedioate) -hydroxy-2-oxo-(-*N*-benzyl)-2,3,3a,6,7,7a-hexahydro-1H-3,6-methanoindole-8-methylene benzyl ester *rac*-**284**

281 (100 mg, 0.45 mmol) was heated with $SOCl_2$ (0.04 mL, 0.55 mmol) at 50 °C under a drying tube ($CaCl_2$) for 20 min. The mixture was then concentrated in vacuo, and added to a solution of *rac*-**218** (60 mg, 0.30 mmol) and trimethylamine (0.13 mL, 0.90 mmol) in CH_2Cl_2 (1.00 mL) at rt and stirred for 15 min. The mixture was then concentrated in vacuo, and then portioned between a mixture of H_2O (5 mL) and sat aq $NaHCO_3$ (5 mL) and CH_2Cl_2 (10 mL). The aqueous layer was then extracted with CH_2Cl_2 (2 × 10 mL) then the combined organics were dried (Na_2SO_4) and concentrated in vacuo. Purification via flash column chromatography (eluent Chloroform/MeOH 10:0.5) gave an inseparable 1.2:1 mix of *rac*-**285** and *rac*-**286** (54 mg, 33%, >95:5 dr); ν_{max} (film) 2959 (C-H), 2901 (C-H), 1749 (C=O), 1745 (C=O), 1720 (C=O), 1710 (C=O);

rac-**286**; δ_H (500 MHz, CD_2Cl_2) 1.83 – 1.88 (1H, m, C(3)*H*), 2.25 – 2.35 (2H, m, CH_2C(O)), 2.46 – 2.53 (1H, m, C(1′)*H*), 3.03 (1H, dt, *J* 4.6, 1.3, C(7a)*H*), 3.04 – 3.11 (1H, m, C(6)*H*), 3.16 – 3.20 (1H, m, (C(3a)*H*), 3.26 (1H, d, *J* 1.6, C(4″)H_A), 3.27 (1H, d, *J* 1.6, C(4″)H_B), 4.23 (1H, d, *J* 15.0, NCH_APh), 4.75 (1H, d, *J* 3.8, C(7)*H*), 4.97 (1H, d, *J* 15.0, NCH_BPh), 5.12 (2H, s, OCH_2Ph), 5.13 (2H, s, C(6″)H_2), 5.83 (1H, dt, *J* 15.7, 1.6, C(2″)*H*), 6.15 – 6.28 (2H, m, C(4)*H*, C(5)*H*), 6.89 – 6.97 (1H, m, C(3″)*H*), 7.22 – 7.39 (15H, m, *Ph*); δ_C (126 MHz, CD_2Cl_2) 37.1 (C(1′)), 37.6 (C(4″)), 38.9 (*C*H_2C(O)), 39.5 (C(3a)), 40.1 (C(6)), 44.7 (N*C*H_2Ph), 45.5 (C(3)), 61.0 (C(7a)), 66.8 (O*C*H_2Ph),

67.2 (C(6″)), 74.7 (C(7)), 124.6 (C(2″)), 128.0 (C(5)), 132.2 (C(4)), 140.7 (C(3″)), 165.3 (C(1″)), 171.6 (C(5″)),171.6 (*C*O_2Bn), 177.4 (C(2)); m/z (ESI$^+$) 606 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{37}H_{36}O_7N^+$ ([M+H]+, requires 606.2487; found 606.2488.

rac-**285**; δ_H (500 MHz, CD_2Cl_2) 1.83 – 1.88 (1H, m, C(3)*H*), 2.25 – 2.35 (2H, m, CH_2C(O)), 2.46 – 2.53 (1H, m, C(1′)*H*), 2.99 (1H, dt, *J* 4.6, 1.3, C(7a)*H*), 3.04 – 3.11 (1H, m, C(6)*H*), 3.14 (1H, dd, *J* 2.3, 1.6, C(2″)H_A), 3.15 (1H, dd, *J* 2.3, 1.6, C(2″)H_B), 3.16 – 3.20 (1H, m, (C(3a)*H*), 4.19 (1H, d, *J* 15.0, NCH_APh), 4.71 (1H, d, *J* 3.8, C(7)*H*), 4.94 (1H, d, *J* 15.0, NCH_BPh), 5.12 (2H, s, OCH_2Ph), 5.17 (2H, s, C(6″)H_2), 5.94 (1H, dt, *J* 15.7, 1.6, C(4″)*H*), 6.15 – 6.28 (2H, m, C(4)*H*, C(5)*H*), 6.89 – 6.97 (1H, m, C(3″)*H*), 7.22 – 7.39 (15H, m, *Ph*); δ_C (126 MHz, CD_2Cl_2) 37.0 (C(1′)), 37.6 (C(2″)), 38.8 (*C*H_2C(O)), 39.5 (C(3a)), 39.9 (C(6)), 44.7 (N*C*H_2Ph), 45.4 (C(3)), 60.9 (C(7a)), 66.6 (C(6″)), 66.8 (O*C*H_2Ph), 75.2 (C(7)), 124.8 (C(4″)), 128.1 (C(5)), 132.0 (C(4)), 140.1 (C(3″)), 165.7 (C(5″)), 171.5 (C(1″)), 171.5 (*C*O_2Bn), 177.4 (C(2)); m/z (ESI$^+$) 606 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{37}H_{36}O_7N^+$ ([M+H]+, requires 606.2487; found 606.2488.

Further elution gave *rac*-**284** (98 mg, 64%, >95:5 dr); ν_{max} (film) 3359 (O-H), 2982 (C-H), 2902 (C-H), 1751 (C=O), 1722 (C=O); δ_H (400 MHz, CD_2Cl_2) 1.81 – 1.85 (1H, m, C(3)*H*), 2.25 – 2.30 (2H, m, CH_2C(O)), 2.38 (1H, dddd, *J* 7.4, 6.7, 3.5, 1.5, C(1′)*H*), 2.93 (1H, dt, *J* 4.6, 1.3, C(7a)*H*), 3.01 (1H, dddt, *J* 5.4, 4.0, 2.7, 1.4, C(6)*H*), 3.20 – 3.27 (1H, m, C(3a)*H*), 3.57 – 3.63 (1H, m, C(7)*H*), 4.09 (1H, d, *J* 15.0, NCH_APh), 4.78 (1H, d, *J* 15.0, NCH_BPh), 5.12 (2H, s, OCH_2Ph), 6.22 (1H, dddt, *J* 8.3, 6.2, 1.4, 0.7), 6.28 (1H, ddd, *J* 8.1, 6.4, 1.6), 7.26 – 7.39 (10H, m, *Ph*); δ_C (126 MHz, CD_2Cl_2) 37.5 (C(1′)) , 39.1 (*C*H_2C(O)), 39.6 (C(3a)), 43.8 (C(6)), 45.5 (N*C*H_2Ph), 45.6 (C(3)), 63.6 (C(7a)), 66.7 (O*C*H_2Ph), 71.9 (C(7)), 128.0, 128.6 (2 × *m-Ph*), 128.4, 128.6, 128.9, 129.1 (2 × *o*, *m-Ph*), 129.9 (C(4)), 131.7 (C(5)), 136.5, 137.3 (2 × *i-Ph*), 171.7 (*C*O_2Bn), 177.4 (C(2)); m/z (ESI$^+$) 426 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{25}O_4NNa^+$ ([M+Na]+, requires 426.1676; found 426.1679.

(*R*)-*N*-Allyl-*N*-(α-methylbenzyl)amine 287

^{n}BuLi (2.5 M in hexanes, 17.4 mL, 43.5 mmol) was added dropwise to a stirred solution of (*R*)-*N*-(α-methylbenzyl)amine (5.80 mL, 45.6 mol, 99% ee) in THF (80 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 1 h. Allyl bromide (3.89 mL, 44.7 mmol) was added dropwise over 30 min and the resultant mixture was stirred at 0 °C for 2 h. Satd aq NH_4Cl (20 mL) and brine (20 mL) were then added, the aqueous layer was extracted with EtOAc (3 × 20 mL), and the combined organic extracts were dried and concentrated *in vacuo*. Purification by flash column chromatography (eluent Et_2O/30–40 °C petrol, 7:3) gave **287** as a pale yellow oil (3.60 g, 49%, 99% ee); $[\alpha]_D^{22}$ +63.3 (*c* 1.0 in $CHCl_3$); {lit.[140] $[\alpha]_D^{22}$ +63.0 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, MeOD) 1.36 (3H, d, *J* 6.7, C(α)*Me*), 2.95 – 3.10 (2H, m, C(1)H_2), 3.77 (1H, q, *J* 6.7, C(α)*H*), 5.03 – 5.14 (2H, m, C(3)H_2), 5.80 – 5.95 (1H, m, C(2)*H*), 7.16 – 7.39 (5H, m, *Ph*).

(*R*,*R*,*R*)-6-(*N*-(α-Methylbenzyl)amino)cyclohexa-2,4-dien-1-ol 289 and (*S*,*S*,*R*)-6-(-*N*-(α-methylbenzyl)amino)cyclohexa-2,4-dien-1-ol 221

(*R*)-α-methylbenzylamine (0.47 mL, 3.7 mmol) was added to a solution of benzene oxide (35 mg, 0.37 mmol) in MeOH (0.35 mL) and the resultant solution was heated at 65 °C for 7 days. The orange solution was then concentrated in vacuo. Purification via flash column chromatography (eluent $CHCl_3$/Ammonia, ca. 7 N solution in MeOH, 200:1) gave **289** as a yellow oil (31 mg, 40%, >95:5 dr); ν_{max} (film) 3659 (O-H), 2985 (C-H), 2882 (C-H); δ_H (400 MHz, MeOD) 1.37 (3H, d, *J* 6.7, C(α)*Me*), 3.36 (1H, ddd, *J* 9.7, 3.6, 2.2, C(6)*H*), 4.03 (1H, q, *J* 6.7, C(α)*H*), 4.29 (1H, ddd, *J* 9.7, 3.3, 1.9, C(1)*H*), 5.60 (1H, ddt, *J* 9.4, 3.5, 1.1, C(2)*H*), 5.77 – 5.91 (3H, m, C(3)*H*), 7.23– 7.39 (5H, m, *Ph*); δ_C (101 MHz, MeOD) 30.7 (C(α)*Me*), 57.6 (C(α)), 60.1 (C(6)), 70.1 (C(1)), 124.9 (C(3)), 125.6 (C(4)), 128.3 (*o*-Ph), 128.9 (*p*-Ph), 129.8 (C(5)), 132.5 (*m*-Ph), 133.6 (C(2)), 146.5 (*i*-Ph); m/z (ESI$^+$) 216 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{18}ON^+$ ([M+H]$^+$) requires 216.1383; found 216.1384. Further elution gave **221** as a yellow oil (32 mg, 40%, >95:5 dr); ν_{max} (film) 3658 (O-H),

2980 (C-H), 2888 (C-H); δ_H (400 MHz, MeOD) 1.41 (3H, d, *J* 6.7, C(α)*Me*), 3.20 (1H, dt, *J* 12.2, 2.4, C(6)*H*), 4.08 (1H, q, *J* 6.7, C(α)*H*), 4.27 (1H, dddt, *J* 12.2, 2.7, 2.1, 0.6, C(1)*H*), 5.75 (1H, ddq, *J* 9.6, 2.8, 0.9, C(2)*H*), 5.81 – 5.86 (1H, m, C(3)*H*), 5.87 – 5.93 (1H, m, C(4)*H*), 5.98 (1H, ddq, *J* 9.8, 2.8, 1.0, C(5)*H*), 7.21 – 7.37 (5H, m, *Ph*); δ_C (101 MHz, MeOD) 24.3 (C(α)*Me*), 55.7 (*C*(α)), 59.0 (C(6)), 72.2 (C(1)), 124.9 (C(3)), 125.1 (C(4)), 127.9 (*o-Ph*), 128.3 (*p-Ph*), 128.7 (C(5)), 129.7 (*m-Ph*), 132.0 (C(2)), 145.0 (*i-Ph*); m/z (ESI^+) 216 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{14}H_{18}ON^+$ ($[M+H]^+$) requires 216.1383; found 216.1385.

Methyl 7-(*N*-(α-methylbenzyl)amino)-2-oxo-2,3,3a,6,7,7a-hexahydro-3,6-methanobenzofuran-8-carboxylate 294

Step 1: Maleic anhydride (31 mg, 0.32 mmol) was added to a solution of **221** (56 mg, 0.26 mmol) in CH_2Cl_2 (1.30 mL) at rt and stirred for 4 day at 40 °C. The mix was then concentrated in vacuo.

Step 2: Trimethylsilyldiazomethane (2.0 M in hexanes, 80 μL, 0.16 mmol) was added to a solution of the residue from the previous step (25 mg, 0.08 mmol) in (benzene/MeOH, 10:1, 8.0 mL), and the resultant mixture stirred at rt for 2.5 h. The mixture was then concentrated in vacuo, and then portioned between H_2O (10 mL) and $CHCl_3$ (10 mL). The aqueous layer was then extracted with $CHCl_3$ (2 × 10 mL) then the combined organics were dried (Na_2SO_4) and concentrated in vacuo. Purification via flash column chromatography (eluent Chloroform/MeOH 10:0.1) gave **294** as a clear oil (26 mg, 99%, >95:5 dr); $[\alpha]_D^{25}$ −26.8 (*c* 1.0 in MeOH); ν_{max} (film) 3051 (N-H), 2938 (C-H), 2894 (C-H), 1762 (C=O), 1745 (C=O); δ_H (500 MHz, MeOD) 1.31 (3H, d, *J* 6.5, C(α)*Me*), 2.52 – 2.62 (2H, m, C(3)*H*, C(1′)*H*), 3.24 (1H, ddt, *J* 6.1, 2.9, 1.4, C(6)*H*), 3.30 – 3.32 (1H, m, C(7)*H*), 3.53 (3H, s, CO_2*Me*), 3.59 – 3.67 (1H, m, C(3a)*H*), 3.92 (1H, q, *J* 6.5, C(α)*H*), 4.16 (1H, dt, *J* 5.3, 1.1, C(7a)*H*), 6.19 (1H, ddd, *J* 8.0, 6.5, 1.4, C(4)*H*), 6.64 (1H, ddt, *J* 7.9, 6.8, 1.0, C(5)*H*), 7.21 – 7.28 (1H, m, *p-Ph*), 7.30 – 7.38 (4H, m *o,m-Ph*); δ_C (126 MHz, MeOD) 24.1 (C(α)*Me*), 37.7 (C(6)),

40.7 (C(3)), 43.2 (C(3a)), 46.5 (C(1′)), 52.4 (CO_2*Me*), 56.1 (*C*(α)), 56.8 (C(7)), 84.3 (C(7a)), 127.3 (C(4)), 128.1 (*o-Ph*), 128.3 (*p-Ph*), 129.6 (*m-Ph*), 137.4 (C(5)), 145.7 (*i-Ph*), 173.5 (*C*O_2Me), 180.0 (C(2)); m/z (ESI$^+$) 350 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{21}O_4NNa^+$ ([M+Na]$^+$) requires 350.1363; found 350.1361

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