Asymmetric Syntheses of Polycyclic Amines

A thesis submitted in partial fulfilment of the requirement
for the degree of Doctor of Philosophy

by

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The work described in this thesis was carried out in the Chemistry Research Laboratory, University of Oxford from September 2013 until June 2017, under the supervision of Professor Stephen G. Davies. All of the work is my own unless otherwise stated and has not been submitted previously for any other degree at this or any other university.

Ian Houlsby

June 2017

"The structure known, but not yet accessible by synthesis, is to the chemist what the unclimbed mountain, the uncharted sea, the untilled field, the unreached planet, are to other men… The unique challenge which chemical synthesis provides for the creative imagination and the skilled hand ensures that it will endure a long as men write books, paint pictures, and fashion things which are beautiful, or practical, or both."

Robert Woodward, 1963

Abstract

Ian Houlsby D. Phil. Thesis

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This thesis centres on the asymmetric synthesis of polycyclic amines, focussing on three distinct classes of polycyclic alkaloid natural products. The work aims to use common methodology of lithium amide conjugate additions as the source of asymmetry in all cases, and for each product class a single strategy is used to synthesise a variety compounds.

Chapter 1 describes the importance of the synthesis of polycyclic alkaloids, highlighting three classes of compounds and documenting prior synthetic strategies. The classes discussed are: the Hancock alkaloids, hydroxymethyl-substituted azabicycles, and the tetraponerine alkaloids.

Chapter 2 describes two separate synthetic strategies towards the Hancock alkaloid (–)-cuspareine, one using a benzyne mediated cyclisation and one a Buchwald-Hartwig cyclisation. The Buchwald-Hartwig methodology was also applied in the synthesis of two more Hancock alkaloids (–)-galipinine and (–)-galipeine; the synthesis of (–)-galipeine led to a reassignment of the structure of the natural product.

Chapter 3 describes work in the synthesis of four [x.y.0]-azabicycles with differing in ring sizes (x, y = 3, 4). The strategy employs sequential S_N2-like ring-closing reactions to form the bicyclic structures where pyrrolizidine, indolizidine and quinolizidine scaffolds can be accessed. Amongst the products are two natural alkaloids, (–)-lupinine and (+)-isoretronecanol.

Chapter 4 describes the synthesis of all eight tetraponerine alkaloids T1–8. Two sequential lithium amide conjugate addition reactions allow for the synthesis of the differing ring-sizes and diastereoisomers displayed by the eight alkaloids. Ring-closing metathesis and diamine condensation with 4-bromobutanal provide the ring-closing steps in the syntheses.

Chapter 5 contains full experimental procedures and characterisation data for all compounds synthesised in Chapters 2–4.

Acknowledgements

We're rarely given the opportunity to thank the people who have had an impact on our lives. I have no doubt that without the opportunity provided to me by Prof S. Davies, chemistry and I would still be strangers. The input and funding he has supplied over the years has given me the opportunity to undertake my D.Phil and progress as a synthetic chemist. His support did not come unaided and I'd love to thank the postdocs Jim, Paul and Ai for all their day to day help with lab work and writing up. You really made the whole process of working towards, and writing my D.Phil much easier. I know there are numerous people within the SGD group who I should thank, and here I can mention the specific people who have helped me out throughout the years. Currently in G10, the rules are upheld wonderfully by David and Matt who not only force me to close my fumehood and fill up acetone bottles, but have been good friends from the very start of my D.Phil, so I'd like to thank the pair of them for four excellent years and I hope that they do their best to finish up their work a little more promptly than I have.

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other kinds of spirits). For his similar support in distractions from work with trips to the pub, another guy I should thank is Stefan Verhoog who has been a good friend to me over the last few years.

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You really can never predict how your decisions will pan out over the years, but if it was up to me to restart my postgrad research I would choose to work here in the SGD group again. I will never forget my time here in Oxford and all the people and experiences that have shaped my work. I'm gonna leave you with my memories of fantastic music in the SGD labs G9 and G10, and I will let you in on my final thoughts as I finish my time here. I know these acknowledgements that you just read are a little rambling and incoherent, but that is for your benefit, so you can read down the first word of each line. Thank you all again for your support and taking time to read this.

Abbreviations

$[\alpha]_D$	Specific rotation
δ	NMR chemical shift
Δ	Reflux
ν_{max}	Infrared absorption maximum
Å	Angstrom
Ac	Acetyl
app	Apparent
Ar	Aryl
atm	Atmospheres
ATR	Attenuated total reflectance
aq	Aqueous
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene
1D NOE	1 Dimensional nuclear Overhauser effect
DIPEA	Diisopropylethylamine
DMSO	Dimethylsulfoxide
BMI	Butylmethylimidazolinium
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
br	Broad
Bu	Butyl
^{t}Bu	*tert*-Butyl
c	Concentration
°C	Degrees Celsius
Cbz	Carboxybenzyl
cm	Centimeters
cm^{-1}	Wavenumbers
CSO	Camphorsulfonyloxaziridine

Cy	Cyclohexyl
d	Doublet
DCC	*N*,*N*′-Dicyclohexylcarbodiimide
DEAD	Diethyl azodicarboxylate
deg	Degrees
DET	Diethyl tartrate
DIBAL-H	Diisobutylalumnium hydride
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
dr	Diastereomeric ratio
E	Electrophile
E	Entgegen
E_1	Elimination, unimolecular
ee	Enantiomeric excess
epi	Epimeric
er	Enantiomeric ratio
ESI^+	Positive electrospray ionisation
Et	Ethyl
equiv	Equivalents
FT	Fourier transform
g	Grams
GC	Gas chromatography
Grubbs I	Benzylidene-bis(tricyclohexylphosphine)dichlororuthenium
Grubbs II	(1,3-Bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro (phenylmethylene)(tricyclohexylphosphine)ruthenium
h	Hours
HIV	Human immunodeficiency virus
HMBC	Heteronuclear Multiple Bond Correlation

HMDS	Bis(trimethylsilyl)amide
HMPA	Hexamethylphosphoramide
HMPT	Hexamethylphosphorous triamide
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum coherence
Hz	Hertz
i	Ipso
IBX	2-Iodoxybenzoic acid
IR	Infrared
J	Coupling constant
L	Litres
μL	Microlitres
LC/MS	Liquid chromatography mass spectrometry
LDA	Lithium diisopropylamine
lit.	Literature
m	Multiplet
m	Meta
M	Molar/Molecular ion
m/*z*	Mass to charge ratio
m-CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
mg	Milligrams
MHz	Megahertz
min	Minutes
mL	Millilitres
mmol	Millimoles
Moc	Methyl carbonyl
mol	Moles
mp	Melting point

Ms	Methanesulfonyl
MS	Molecular sieves
nm	Nanometers
NMR	Nuclear magnetic resonance
o	Ortho
p	Para
PADA	Potassium azodicarboxylate
^{n}Pent	Normal pentyl
pH	Potential of hydrogen
Ph	Phenyl
PMP	*para*-Methoxyphenyl
PPA	Polyphosphoric acid
ppm	Parts per million
PPTS	Pyridinium *para*-toluenesulfonic acid
^{i}Pr	Isopropyl
^{n}Pr	Normal propyl
q	Quartet
quant	Quantitative
quin	Quintet
R	Unspecified organic group
R	Rectus
Rapoport's reagent	4-Formyl-1-methylpyridinium benzenesulfonate
Re	Rectus
Red-Al	Sodium bis(2-methoxyethoxy)aluminumhydride
Ref.	Reference
rt	Room temperature
s	Singlet
S	Sinister
S_N2	Substitution, nucleophilic, bimolecular

satd	Saturated
sext	Sextet
Si	Sinister
t	Triplet
T1–8	(+)-Tetraponerine 1–8
TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
temp	Temperature
tert	Tertiary
TIPS	Triisopropylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMS	Trimethylsilyl
ToF	Time of flight
Tol	*p*-Methylphenyl
Ts	*p*-Toluenesulfonyl
UV	Ultraviolet
v	Volume
w	Weight
Wilkinson's catalyst	Rhodium(I) tris(triphenylphosphine) chloride
X	Unspecified group
X-Phos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
Y	Unspecified group
Z	Zusammen

Contents

Chapter 1

Introduction

1.1 Natural product synthesis

For centuries, natural compounds have been a great source of therapeutic agents for mankind, being employed around the world in folk medicine using natural ingredients, principally plants, in the treatment of disease. Over the years, people began to challenge these remedies and started to look for an active ingredient in traditional medicines. Coinciding with the beginnings of synthetic organic chemistry that we know today, more chemical understanding arose in the 19th century from the isolation of key compounds from natural sources, such as morphine, caffeine, nicotine, quinine and strychnine.[1] Today, natural products still provide a vital source of medicinal compounds, either in their original state, or as starting points for the development of new therapeutic agents. Between 1981 and 2014, 65% of all new small-molecule therapeutic agents were derived from natural products, or directly mimicked the known action of a natural product.[2] Due to the difficulties associated with the extraction of products from natural sources, be it accessibility, abundance or efficiency, it is necessary for the synthetic chemistry community to develop efficient syntheses of the vast array of different structures prevalent in Nature.

1.2 Polycyclic amines

Alkaloids, which are loosely defined as, typically, plant derived compounds that react as alkalis and contain basic nitrogen atoms,[3] are an important class of natural products with a large variety of structure and activity. Within this broad category, the majority of compounds fall under the class of nitrogen heterocycles.[3] The synthesis of these compounds is both of interest in an academic setting (as they provide numerous synthetic challenges relating to their structural diversity and complexity) and for drug discovery purposes (as many commercial therapeutic agents are based on cyclic amines). For example, carmegliptin **1**, clopidogrel **2**, aplaviroc **3** and levetiracetam **4** are all commercial azacyclic drugs which are used in the treatment of Type II diabetes,[4] heart attacks,[5] HIV,[6] and epilepsy,[7] respectively (Figure 1).

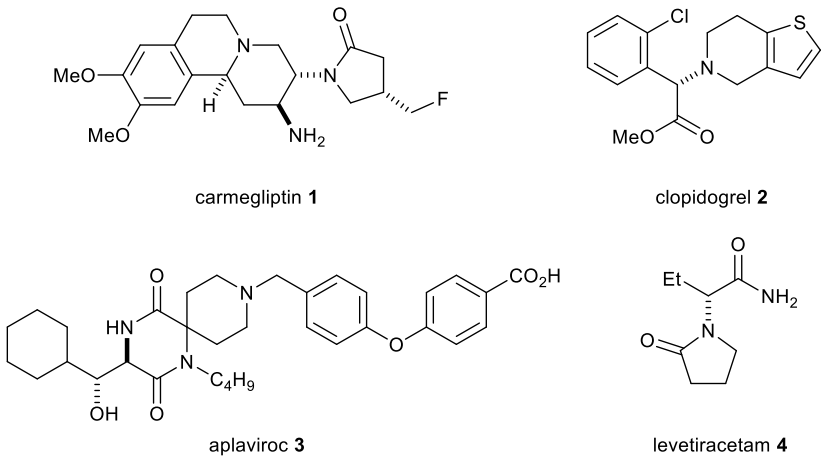


Figure 1 Examples of azacyclic therapeutic agents.

The following sections will describe three classes of azacycles, documenting their origins, uses and syntheses. These compounds comprise the Hancock alkaloids **5**, hydroxymethyl-azabicycles **6** and the tetraponerines **7** (Figure 2).

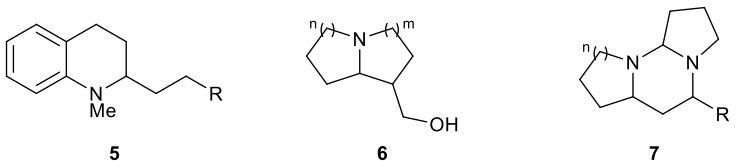


Figure 2 Core structures of the Hancock alkaloids **5**, hydroxymethyl-azabicycles **6** and the tetraponerines **7**.

1.3 The Hancock alkaloids

The Hancock alkaloids **8**–**11** (Figure 3) were isolated from the bark of the angostura tree, *Galipea officinalis* Hancock, in Venezuela in 1998–1999,[8,9] although studies in the early 20th century may have identified these compounds but provide no spectroscopic data.[10] Extracts from the bark have been used in Venezuelan folk medicine to treat a variety of illnesses including dyspepsia, dysentery, diarrhoea and fever.[11] More recently, studies have been done on the potency of these alkaloids as alternatives to chloroquine in the treatment of malaria, showing good *in vivo* anti-malarial activity for chloroquine-resistant strains.[12]

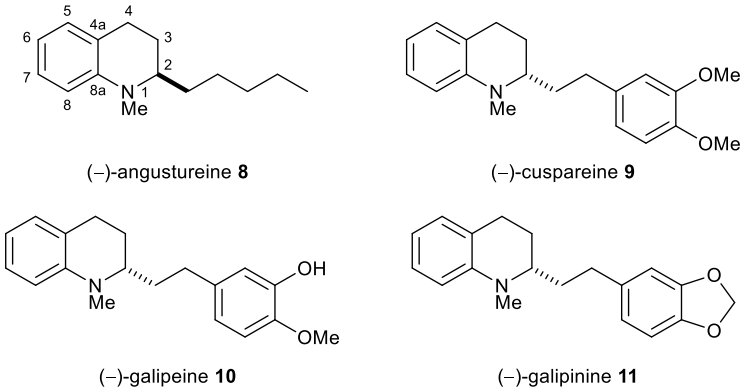
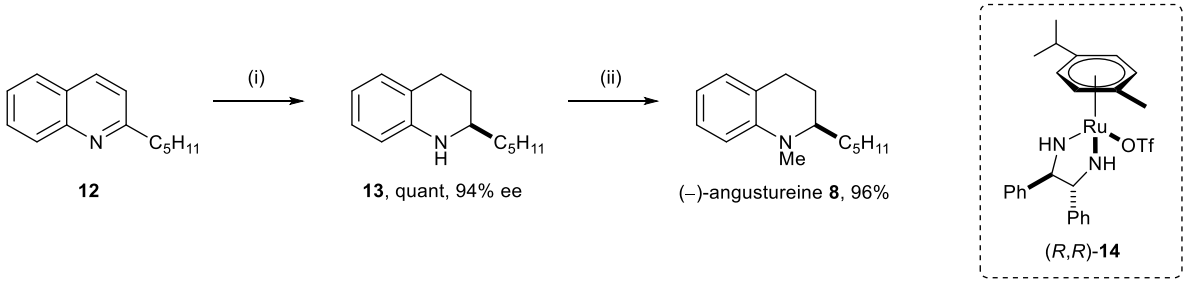


Figure 3 Structures of the Hancock alkaloids **8**–**11**.

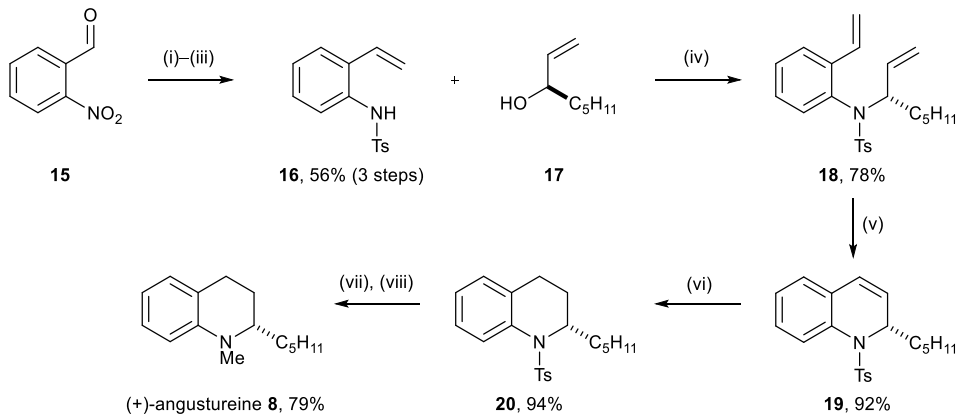
1.3.1 Selected syntheses

Due to the promising biological profile of the targets, the synthesis of any of these alkaloids has become a valuable testing ground for methodology in the construction of 1,2,3,4-tetrahydroquinolines. Typically, the key focus in any synthesis is on the production of an enantiopure 1,2,3,4-tetrahydroquinoline core, often with less attention being applied to the specific nature of the side chain. For this reason, angustureine **8** has attracted the most synthetic attention, with numerous publications documenting the asymmetric synthesis of either (+)- or (–)-angustureine **8** as the sole representative example.[13–23] One common method for the asymmetric synthesis of the 1,2,3,4-tetrahydroquinoline core is the asymmetric hydrogenation of substituted quinolines. An example of such a synthesis was published by Fan *et al*. in 2008.[16] Solvent free, asymmetric hydrogenation of 2-pentylquinoline **12** using H_2 at 80 atm in the presence of ruthenium catalyst (*R*,*R*)-**14** gave **13** in quantitative yield and 94% ee. Methylation of **13** upon reductive alkylation with formaldehyde provided (–)-angustureine **8** in 96% yield. This short and efficient synthesis demonstrates the power of asymmetric hydrogenation but has the disadvantage of requiring high pressure conditions (Scheme 1).



Scheme 1 *Reagents and conditions*: (i) (*R*,*R*)-**14**, H_2 (80 atm), rt, 72 h; (ii) H_2CO, $NaBH_3CN$, AcOH, MeCN, rt, 30 min.

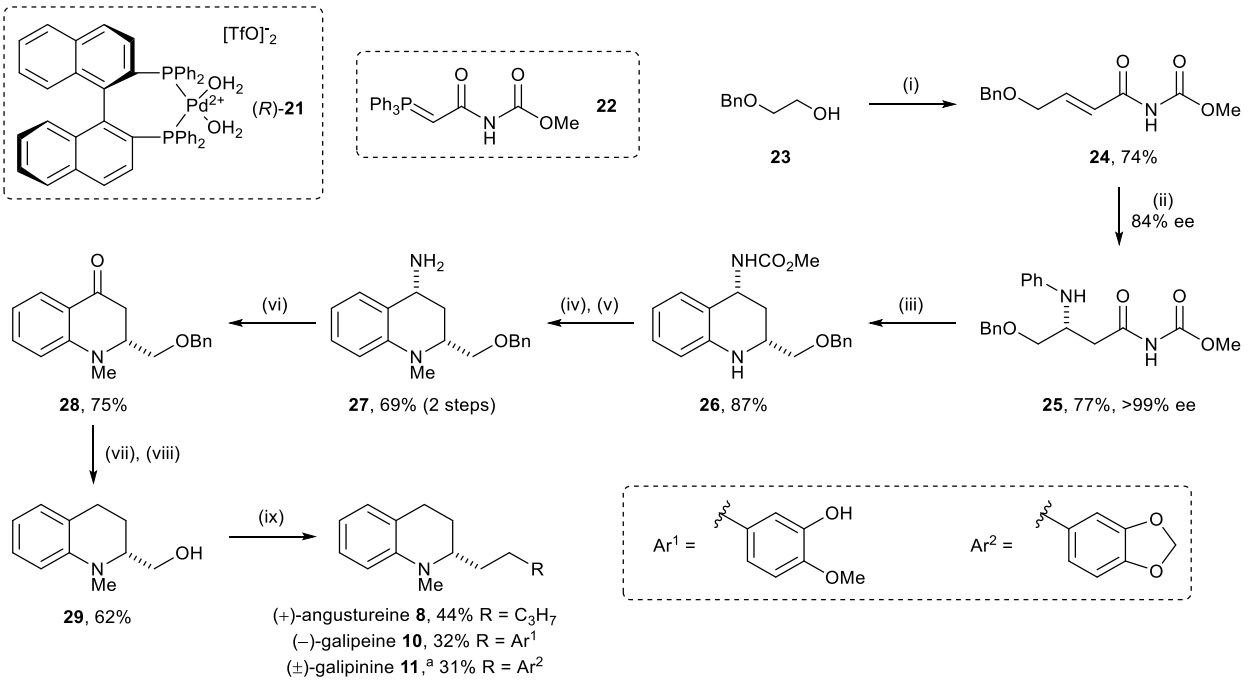
Other syntheses focus on constructing the 1,2,3,4-tetrahydroquinoline core from a ring-closing reaction, such as the work by Nishida *et al.*[13] Starting from 2-nitrobenzaldehyde **15**, vinyl aniline **16** was produced in 56% yield over three steps *via* a sequence of Wittig olefination, nitro reduction and *N*-tosylation. Subsequent Mitsonobu reaction of **16** with chiral alcohol **17** gave aniline **18** in 78% yield. Now the ring-closure could be performed, using a Grubbs II catalysed ring-closing metathesis reaction, which gave **19** in 92% yield. Hydrogenation of **19** using PtO_2 and H_2 gave 1,2,3,4-tetrahydroquinoline **20** in 94% yield. After *N*-deprotection of **20** and subsequent *N*-methylation, (+)-angustureine **8** was isolated in 79% yield over the two steps (Scheme 2). There are also numerous other examples of ring-closing reactions to form the cyclic core of Hancock alkaloids, such as hydroarylation of an alkyne,[14,24] aza-Michael reaction,[15] Friedel-Crafts type acylation,[17] copper catalysed C–N coupling,[20] Buchwald-Hartwig amination,[22,25,26] Mitsonobu reaction,[23] Diels-Alder reaction,[27] allylic amination,[28] Suzuki-Miyaura reaction,[29] and reductive condensation.[30]



Scheme 2 *Reagents and conditions*: (i) Ph_3PMeBr, KHMDS, THF, rt, 1 h; (ii) Zn powder, AcOH, rt, 16 h; (iii) TsCl, pyridine, CH_2Cl_2, rt, 1 h; (iv) DEAD, PPh_3, THF, rt, 2 h; (v) Grubbs II, CH_2Cl_2, 50 °C, 1 h; (vi) PtO_2, H_2, MeOH, rt, 12 h; (vii) anthracene sodium, DME, –65 °C, 10 min; (viii) MeI, K_2CO_3, THF, Δ, 10 h.

There are many examples of asymmetric syntheses of the other Hancock alkaloids: cusparine **9**,[25,29,31–36] galipeine **10**,[26,30,41] and galipinine **11**.[26,30,31,33,34,38–41] However, often, the syntheses of Hancock alkaloids involve construction of the full carbon skeleton before the key step, be it a ring-closing reaction or manipulation of a quinoline. This means that accessing many different *C*(2)-substituted 1,2,3,4-tetrahydroquinolines can be inefficient. One example of a route that employs late stage diversification of the side chain was published by Hii *et al.* in 2012.[30] The source of enantioselectivity in this synthesis was an aza-Michael addition in the presence of BINAP-complex (*R*)-**21**. Michael acceptor **24** was synthesised in 74% yield from *O*-benzylethane-1,2-diol **23** using a Swern oxidation and Wittig

olefination with ylid **22**. Treatment of **24** with aniline in the presence of (*R*)-**21** gave **25** in 77% yield and >99% ee after recrystallization. Reductive condensation of **25** promoted cyclisation to 1,2,3,4-tetrahydroquinoline **26** in 87% yield. *N*-Methylation of **26** and removal of the carbamate group using TMSI in MeCN gave **27** in 69% yield over the two steps. Treatment of **27** with Rapoport's reagent[42] furnished dihydroquinolinone **28** in 75% yield. Reduction of the carbonyl functionality within **28** using $LiAlH_4$ followed by hydrogenolytic *O*-debenzylation gave **29** in 62% yield. This intermediate was a suitable compound for derivatisation to install the different *C*(2) side chains. Through a three-step procedure of Swern oxidation, Wittig olefination and hydrogenation, the different side chains of (+)-angustureine **8**, (–)-galipeine **10** and (±)-galipinine **11** were installed giving the target alkaloids in 44, 32 and 31% yield, respectively, over the three transformations (Scheme 3).



Scheme 3 *Reagents and conditions*: (i) $(COCl)_2$, DMSO, CH_2Cl_2 –78 °C, 30 min then Et_3N, –78 °C to rt then **22**, CH_2Cl_2, rt, 16 h; (ii) $PhNH_2$, (*R*)-**21**, PheMe, 50 °C, 38 h; (iii) $MgCl_2$, $NaBH_4$, EtOH/THF (1:1 v/v), –10 °C, 30 min; (iv) H_2CO, $NaBH_3CN$, AcOH, MeCN, 0 °C, 1 h; (v) TMSI, MeCN, rt, 18 h; (vi) 4-formyl-1-methylpyridinium benzenesulfonate, CH_2Cl_2/DMF (1:1 v/v), rt, 1 h then DBU, rt, 1 h then oxalic acid, rt, 16 h; (vii) $LiAlH_4$, $AlCl_3$, THF, Δ; (viii) H_2, Raney Ni, EtOH/THF (7:8 v/v), Δ; (ix) $(COCl)_2$, DMSO, CH_2Cl_2 –78 °C, 1 h then Et_3N, –78 °C to rt then Ph_3P=CHR, THF, 0 °C, 16 h then H_2, Pd/C, EtOH/THF (1:1 v/v), rt, 16 h. [[a] reactions performed only on racemic **29**]

1.4 Hydroxymethyl substituted azabicycles

The term azabicycle covers many structures, fully including any bicyclic compound containing nitrogen. However, herein the term will be used to describe saturated bicyclic structures with a nitrogen atom at

the bridgehead position (i.e., compounds of type **34**–**36**). For the three permutations of 5- and 6-membered rings, the compounds are defined as pyrrolizidines **34** (n = m = 1, [3.3.0]-azabicycles), indolizidines **35** (n = 1, m = 2, [3.4.0]-azabicycles) and quinolizidines **36** (n = m = 2, [4.4.0]-azabicycles). For this work, the focus will be on a set of four analogous compounds **30**–**33**, which all have a single hydroxymethyl substituent on one ring adjacent to the bridgehead carbon atom (Figure 4). (–)-Lupinine **30** is one of the simplest compounds in a class of many quinolizidine alkaloids and was first isolated from a variety of lupin like plants from the family *Fabaceae*, and it has been implicated in the protection of the plant by its insecticidal properties.[43] It has been demonstrated that low concentrations of **30** in *Lupinus leuteus* provide a deterring affect to the red-legged earth mite, as well as other pests such as aphids and beetles. The pyrrolizidine homologue (+)-isoretronecanol **33**, which was first isolated and identified in 1942,[44,45] is produced by leguminous plants of the genus *Crotalaria*, and displays potent hepatotoxic effects.[46] The toxicity of pyrrolizidine alkaloids in general has been well studied[47] and so significant synthetic effort has been made in the production of numerous compounds containing the pyrrolizidine core. Completing the set are two indolizidine structures, **31** and **32**. (+)-5-*epi*-Tashiromine **32**[48] is the epimer of the natural product (+)-tashiromine which is produced by the plant *Maackia tashiroi* of the *Fabaceae* family and was first isolated in 1990 by Murakoshi *et al.*[49] 1-(Hydroxymethyl)indolizidine **31** has not been observed from natural sources but provides the bicyclic core for a set of alkaloids called the stellettamides **37**. The first example, stellettamide A, was isolated in 1990 by Fusetani *et al.*[50] from a marine sponge and displays potent antifungal and cytotoxic activity (Figure 4).

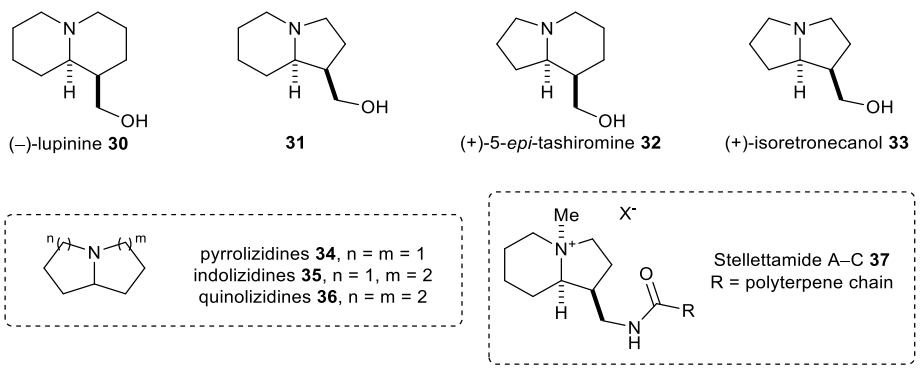
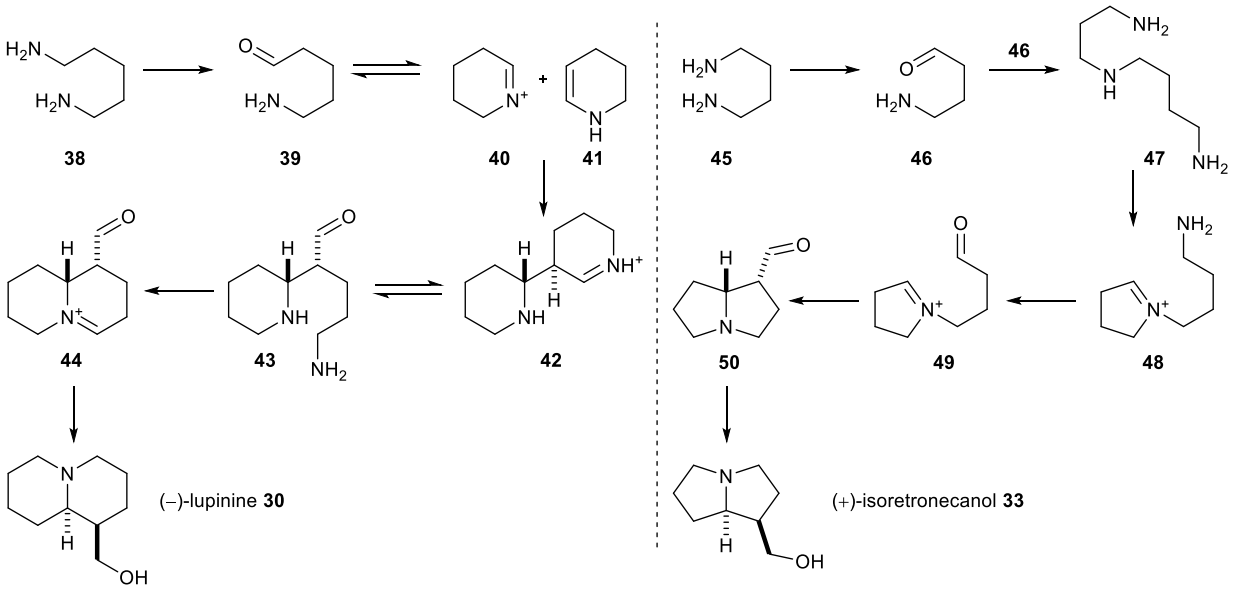


Figure 4 The structures of azabicycles **30**–**37**.

1.4.1 Biosynthesis

Studies have been conducted into exploring the biosyntheses of the natural products (–)-lupinine **30**[51] and (+)-isoretronecanol **33**,[52] using feeding studies with a variety of isotopically labelled compounds. Both syntheses are postulated to start from diamines: cadaverine **38** as a precursor for (–)-lupinine **30**, and putrescine **45** as a precursor for (+)-isoretronecanol **33**. For (–)-lupinine **30**, oxidation of **38** to amino aldehyde **39** is followed by dimerization of **40** and **41**, which produces iminium ion **42**. Following hydrolysis of **42**, oxidation of the corresponding amino aldehyde **43** results in cyclisation to iminium ion **44**, which can be reduced to (–)-lupinine **30**. Conversely, for (+)-isoretronecanol **33**, the dimerization of putrescine **45** results in the triamine spermidine **47**. Subsequent oxidation and cyclisation produces iminium **48**, which after further oxidation can undergo a Mannich-like reaction to form the pyrrolizidine core **50**. Lastly, reduction furnishes (+)-isoretronecanol **33** (Scheme 4).

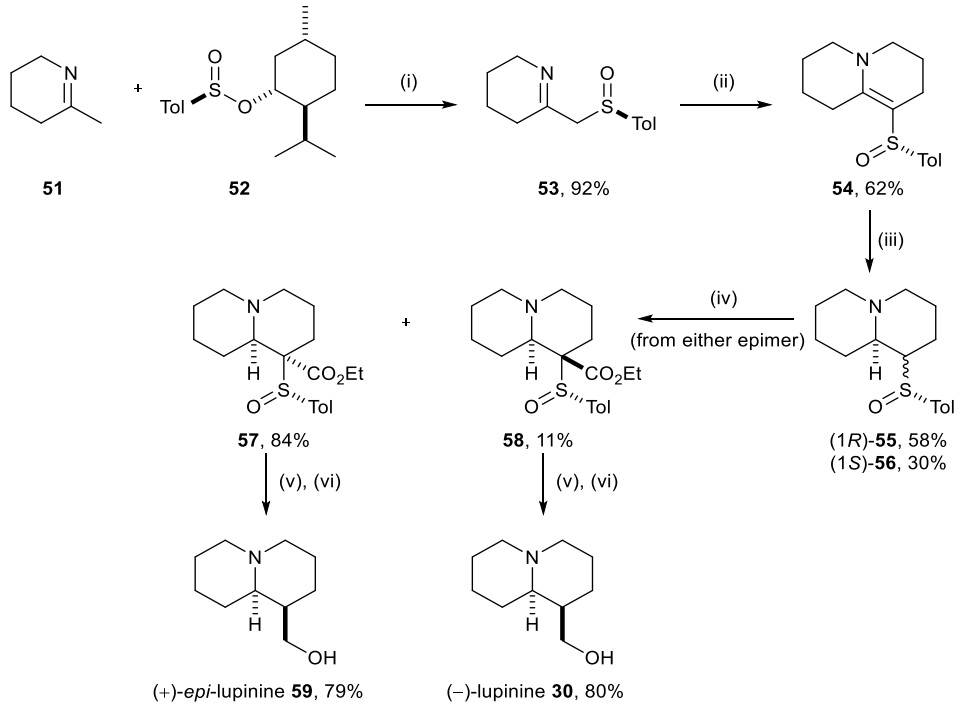


Scheme 4 Proposed biosynthetic pathways for the syntheses of (–)-lupinine **30** and (+)-isoretronecanol **33**.

1.4.2 Selected syntheses

Hydroxymethyl substituted azabicycles have attracted synthetic attention not only for their properties and biological activities in themselves, but also because they act as a good proving ground for methodology focussed on constructing chiral bicyclic scaffolds as they provide the base units for

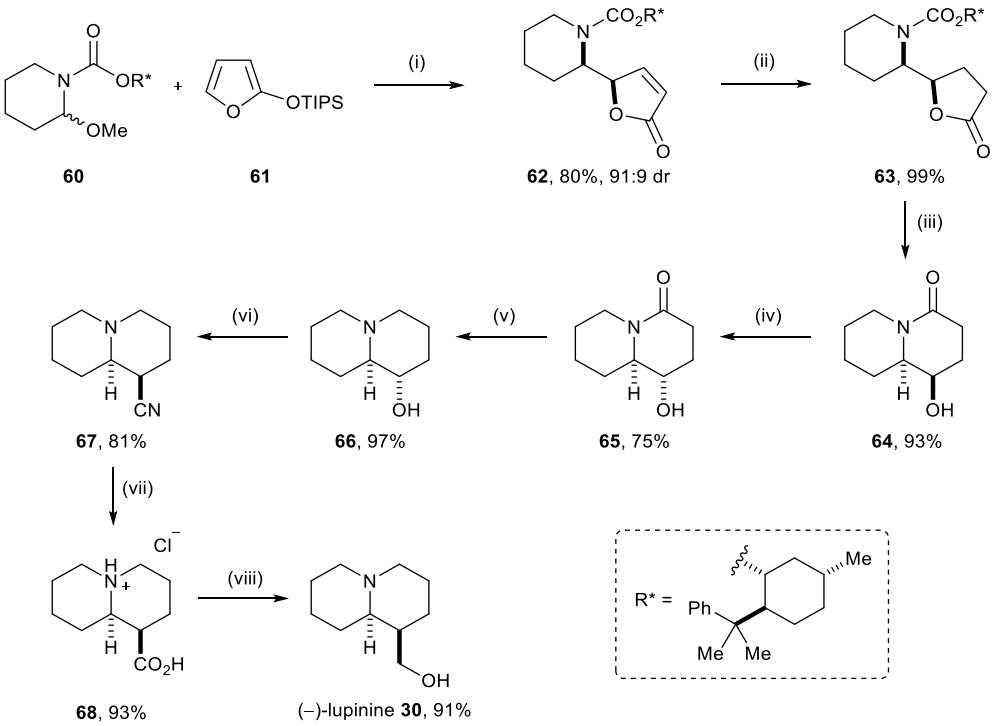
numerous, more functionalised alkaloids. The first asymmetric synthesis of (–)-lupinine **30** was reported in 1991,[53] where both (–)-lupinine and (+)-*epi*-lupinine[54] were targeted. The synthesis started with the lithiation of imine **51** and subsequent addition to chiral sulfinate ester **52** which gave, with inversion of configuration, sulfoxide **53** in 92% yield. Alkylation of **53** upon treatment with LDA and 1,3-diiodopropane was followed by cyclisation to give cyclic enamine **54** in 62% yield. The double bond within **54** was reduced with $NaBH_4$ under Luche conditions, producing a mixture of epimers **55** and **56**, however, treatment of either epimer with LDA and ethyl cyanoformate resulted in epimeric quinolizidines **57** and **58**, in 84 and 11% isolated yield, respectively. Ester **58** was then reduced using $LiAlH_4$ and the sulfoxide was removed with Raney Ni to give (–)-lupinine **30** in 80% yield (from **58**). An analogous procedure was used to produce (+)-*epi*-lupinine **59** in 79% yield from the epimeric precursor **57** (Scheme 5).



Scheme 5 *Reagents and conditions*: (i) LDA, THF, –10 °C, 2 h; (ii) LDA, 1,3-diiodopropane, THF, –78 °C to rt, 20 h; (iii) $CeCl_3$, $NaBH_4$, MeOH, 0 °C to rt, 2.5 h; (iv) LDA, ethyl cyanoformate, THF, –78 °C to rt, 2 h; (v) $LiAlH_4$, THF, Et_2O, 0 °C, 3 h; (vi) Raney Ni, EtOH, rt, 10 h.

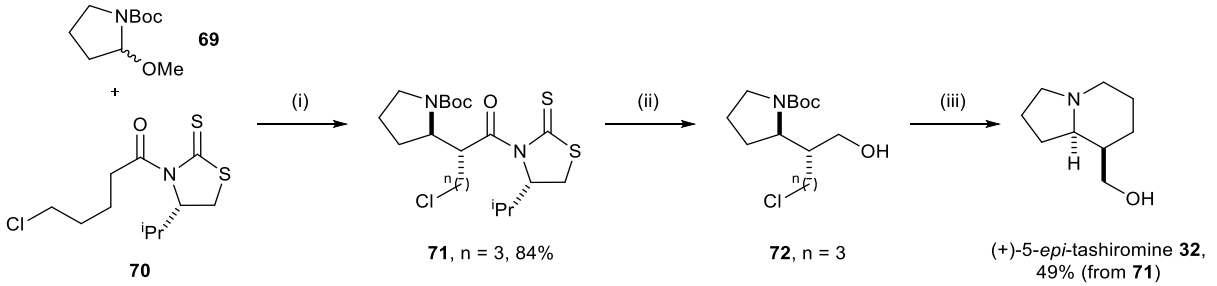
Often, the syntheses of bicyclic alkaloids start from a commercially available monocycle and build the second ring from the existing scaffold, such as the synthesis of (–)-lupinine **30** reported by Silvia Santos *et al.*[55] and the synthesis of (+)-5-*epi*-tashiromine **32** reported by Pilli *et al.*[56] The synthesis by Silvia Santos *et al.* started with the addition of siloxyfuran **61** to monocyclic methoxypiperidine **60** in the presence of butylmethylimidazolinium tetrafluoroborate (BMI·BF_4) which produced piperidine **62** in

80% yield and 91:9 dr. The source of asymmetry in this addition was the action of Corey's 8-phenylmenthyl derived chiral auxiliary denoted by R* (Scheme 6) attached to **60** *via* a carbamate linkage. Hydrogenation of the double bond within **62** gave **63** in 99% yield, which underwent an intramolecular migration upon treatment with NaOH in MeOH, producing quinolizinone **64**. Mitsonobu reaction of **64** gave **65** in 75% yield, which upon treatment with AlH_3 (formed using $LiAlH_4$ and $AlCl_3$) gave quinolizidine **66** in 97% yield. Further Mitsonobu chemistry allowed the installation of the nitrile functionality within **67**, with inversion of configuration at the *C*(1) stereocentre. Hydrolysis of **67** gave the corresponding carboxylic acid **68** in 93% yield and reduction of the acid functionality gave (–)-lupinine **30** in 91% yield (Scheme 6).



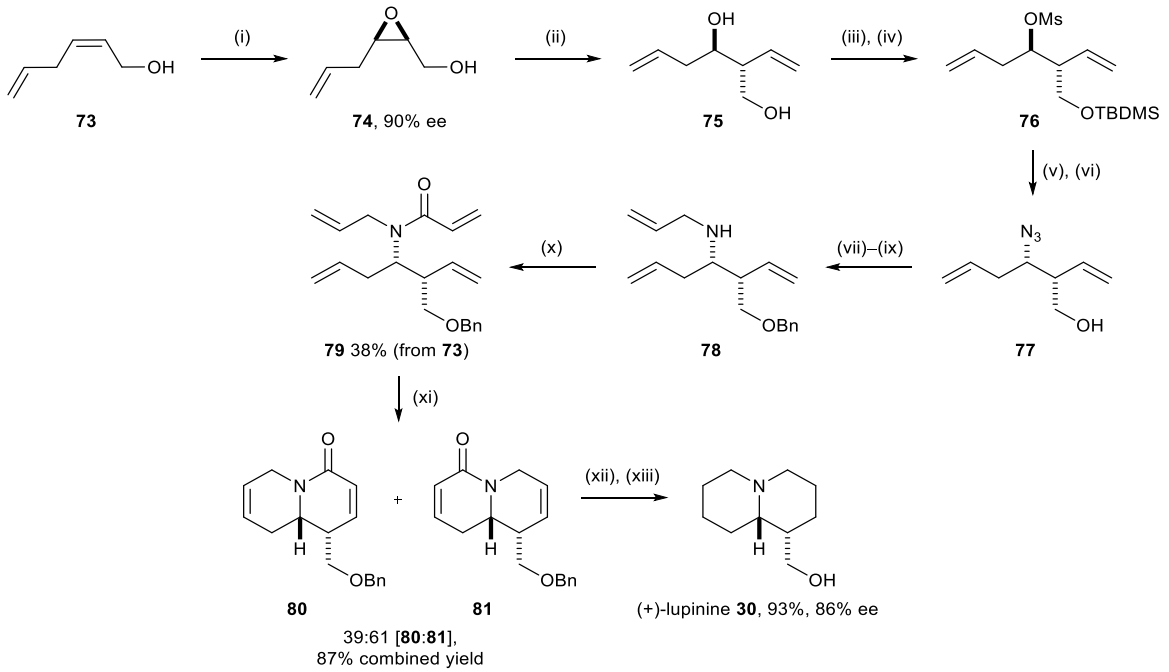
Scheme 6 *Reagents and conditions*: (i) TMSOTf, BMI·BF_4, THF/CH_2Cl_2 (1:1 v/v), –78 °C, 7 h; (ii) H_2 (1 atm), Pd/C, EtOAc, rt, 4 h; (iii) NaOH, MeOH, rt, 2 h; (iv) PPh_3, $ClCH_2CO_2H$, DEAD, CH_2Cl_2, rt, 6 h then K_2CO_3, MeOH; (v) $LiAlH_4$, $AlCl_3$, THF, rt, 10 min; (vi) PPh_3, acetone cyanohydrin, DEAD, PhMe, CH_2Cl_2, 0 °C, 1 h then rt, 40 min; (vii) HCl (6 M in $CHCl_3$), 60 °C, 2 h; (viii) $LiAlH_4$, $AlCl_3$, THF, rt, 20 min.

The short synthesis of (+)-5-*epi*-tashiromine **32** by Pilli *et al*. started with the addition of a chiral titanium enolate derived from **70** to monocyclic methoxypyrrolidine **69**, which gave pyrrolidine **71** in 84% yield. Cleavage of the chiral auxiliary using $LiBH_4$ gave hydroxychloride **72** which upon *N*-deprotection with Et_3SiH in TFA and basification underwent ring-closure to give (+)-5-*epi*-tashiromine **32** in 49% yield from **71** (Scheme 7).



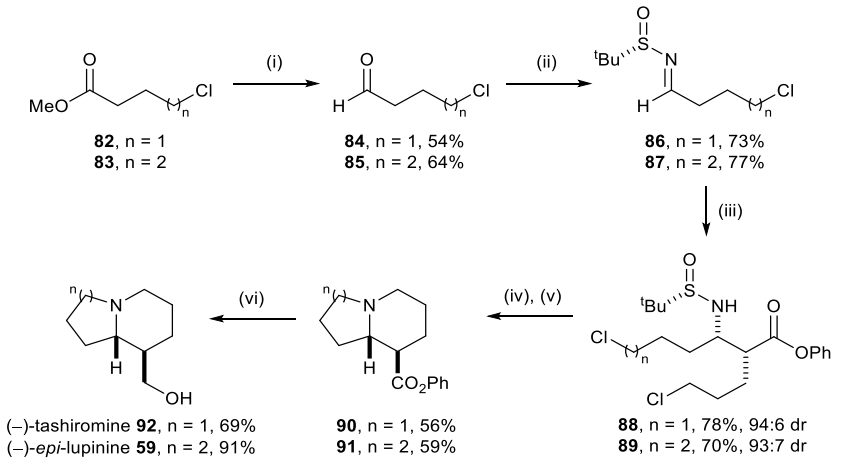
Scheme 7 *Reagents and conditions*: (i) $TiCl_4$, DIPEA, CH_2Cl_2, –23 °C, 1 h; (ii) $LiBH_4$, MeOH, THF, 0 °C, 1 h; (iii) TFA, Et_3SiH, rt, 24 h then $NaHCO_3$, H_2O, rt, 16 h.

Other synthetic efforts have focussed on taking a linear precursor and either performing sequential ring-closures, or a double ring-closure to form the bicyclic scaffolds. This is often an attractive proposal as the nature of the acyclic compounds can be modified and common ring-closing methodology can be used to access different bicyclic scaffolds. Three such examples of double ring-closures are in the works of Ma *et al*.,[57] Brown *et al*.[58] and Davies *et al*.[59] Ma *et al*. use ring-closing metathesis to produce (+)-lupinine **30** (and other diastereoisomers), as well as demonstrating that the methodology is applicable to larger ring sizes, synthesising [5.5.0]-azabicyclic compounds. Brown *et al*. use S_N2-like ring-closures to access either an indolizinde or quinolizidine core resulting in the syntheses of (–)-*epi*-lupinine **59** and (–)-tashiromine **92**. Finally, Davies *et al*. use a double reductive amination for the cyclisation step in the synthesis of (–)-isoretronecanol **33** [and its epimer (–)-trachelantamidine] and show that the methodology is suitable for the construction of polyhydroxylated pyrrolizidine structures besides the structurally simpler parent compounds.[60,61] For the synthesis of (+)-lupinine **30** by Ma *et al*., the stereogenic centres were introduced *via* Sharpless asymmetric epoxidation of allylic alcohol **73**, giving epoxide **74** in 90% ee. Ring-opening of **74** using vinylmagnesium bromide gave **75**, which was sequentially reacted with TBDMSCl (selectively forming the TBDMS ether on the primary alcohol within **75**) and MsCl to give mesylate **76**. An S_N2 reaction of **76** with NaN_3 gave the corresponding azide, with inversion of configuration, which after *O*-desilylation gave azide **77**. A three-step sequence employing *O*-benzylation, reduction with $LiAlH_4$, and *N*-allylation gave secondary amine **78**, which upon treatment with acryloyl chloride produced amide **79**; this sequence gave chiral tetraene **79** in 38% yield from amino alcohol **73**. Treatment of tetraene **79** with Grubbs II catalyst led to the formation of two isomeric products, **80** and **81**, in a combined yield of 87%. Reaction of this mixture under hydrogenation/hydrogenolysis conditions, followed by amide reduction gave (+)-lupinine **30** in 93% yield and 86% ee (Scheme 8).



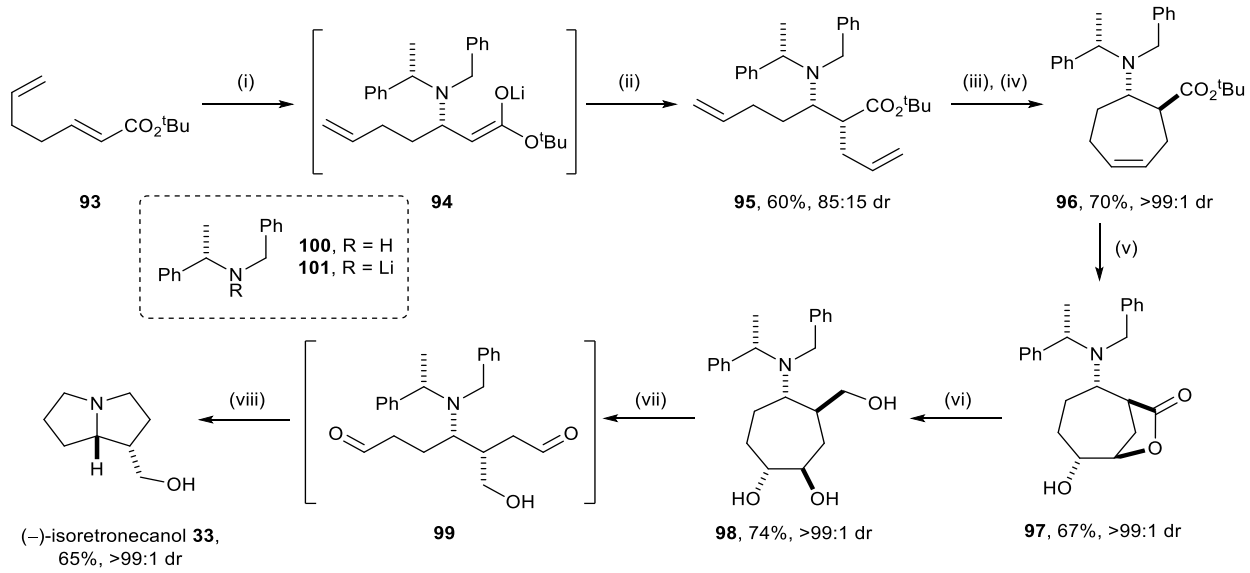
Scheme 8 *Reagents and conditions*: (i) ^{t}BuOOH, 4 Å MS, (–)-DET, Ti(O^{i}Pr)$_4$, CH_2Cl_2, –20 °C, 29 h; (ii) $CH_2CHMgBr$, CuI, Et_2O, –78 °C to –25 °C, 16 h; (iii) Et_3N, DMAP, TBDMSCl, CH_2Cl_2, –78 °C to rt, 3 h; (iv) MsCl, Et_3N, CH_2Cl_2, –78 °C to rt, 1.5 h; (v) NaN_3, HMPA, 40 °C, 2 h; (vi) TBAF, THF, rt; (vii) NaH, THF, rt, 30 min then BnBr, rt, 3.5 h; (viii) $LiAlH_4$, THF, –78 °C to rt, 2 h; (ix) allyl bromide, K_2CO_3, DMF, 0 °C to rt, 1 h; (x) acryloyl chloride, Et_3N, CH_2Cl_2, –78 °C to rt; (xi) Grubbs II, CH_2Cl_2, Δ, 6 h; (xii) H_2 (1 atm), Pd/C, 30 °C, 24 h; (xiii) $LiAlH_4$, THF, Δ, 4 h.

Brown *et al*. started their synthesis with the partial reduction of ω-chloro esters **82** (n = 1) and **83** (n = 2) with DIBAL-H to give aldehydes **84** and **85** in 54 and 64% yield, respectively. Condensation of these aldehydes with (S_S)-*tert*-butanesulfinamide gave sulfinyl imines **86** and **87** in 73 and 77% yield, respectively. Use of a diastereoselective imino-aldol reaction with phenyl 5-chloropentanoate and **86** gave **88** in 78% yield and 94:6 dr, with the minor diastereoisomer being the compound epimeric at the centre α to the ester; similar treatment of the longer homologue **87** gave **89** in 70% yield and 93:7 dr. After hydrolysis of the sulfinamide functionalities within **88** and **89** a Finkelstein reaction was used to activate the pendent chlorides within **88** and **89** to facilitate double ring-closure. This led to indolizinde **90** in 56% yield and quinolizidine **91** in 59% yield from their respective precursors **88** and **89**. Finally, reduction of the phenyl esters within **90** and **91** with $LiAlH_4$ gave (–)-tashiromine **92** and (–)-*epi*-lupinine **59** in 69 and 91% yield, respectively (Scheme 9).



Scheme 9 *Reagents and conditions*: (i) DIBAL-H, CH_2Cl_2, –78 °C, 1–2 h; (ii) (S_S)-*tert*-butanesulfinamide, $CuSO_4$, CH_2Cl_2, 40 °C, 16–18 h; (iii) Phenyl 5-chloropentanoate, LDA, –78 °C, 30 min then **86** or **87**, 1 h; (iv) HCl/dioxane, rt, 2 h; (v) K_2CO_3, NaI, MeCN, rt, 16 h; (vi) $LiAlH_4$, THF, rt, 16 h.

The synthesis of (–)-isoretronecanol by Davies *et al*. started from α,β-unsaturated ester **93** and employed a lithium amide conjugate addition reaction as the source of asymmetry. Upon conjugate addition of a suitable chiral lithium amide reagent to an α,β-unsaturated ester, a lithium (*Z*)-β-amino enolate[62] is formed and this reaction has been widely used by Davies *et al*.[63,64] in the generation of β-amino esters [where the intermediate lithium (*Z*)-β-amino enolate is treated with NH_4Cl, resulting in protonation at the α-centre], or for the production of α-substituted-β-amino esters [where the intermediate lithium (*Z*)-β-amino enolate is treated with a suitable electrophile]. In this case, a one-pot conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*S*)-**101** [generated from the treatment of the corresponding amine (*S*)-**100** with BuLi], followed by addition of allyl bromide to the intermediate lithium (*Z*)-β-amino enolate **94** gave β-amino ester **95** in 60% yield and 85:15 dr (epimeric at the α centre).[65] A two-step protocol was then used to both form the cycloheptene ring (Grubbs I catalysed ring-closing metathesis), and enrich the diastereomeric ratio by epimerising the α centre, which gave **96** in 70% yield and >99:1 dr. Using an ammonium ion-directed epoxidation, lactone **97** was produced in 67% yield from **96**, where an *in situ* ring-opening of the intermediate epoxide occurs. Reduction of **97** using $LiAlH_4$ gave triol **98** in 74% yield and >99:1 dr. This triol was then treated with $NaIO_4$ in MeOH, resulting in oxidative cleavage to the intermediate dialdehyde **99**; this was not isolated, but subjected to hydrogenolysis/hydrogenation conditions which facilitated *N*-deprotection and double reductive cyclisation to give (–)-isoretronecanol **33** in 65% yield and >99:1 dr (Scheme 10).



Scheme 10 *Reagents and conditions*: (i) (*S*)-**100**, BuLi, THF, –78 °C, 2 h; (ii) allyl bromide, THF, –78 °C to rt, 12 h; (iii) Grubbs I, CH_2Cl_2, 30 °C, 12 h; (iv) KHMDS, ^tBuOH, THF, rt, 16 h; (v) HBF_4, *m*-CPBA, CH_2Cl_2, rt, 48 h; (vi) $LiAlH_4$, THF, 0 °C, 2 h; (vii) $NaIO_4$, MeOH, rt, 1 h; (viii) H_2 (5 atm), $Pd(OH)_2/C$, MeOH/AcOH (20:1, v/v), rt, 24 h.

1.5 The tetraponerine alkaloids

The tetraponerine alkaloids are a set of eight natural products, named (+)-tetraponerine 1–8 (commonly abbreviated to T1–8), that are secreted as a venom cocktail by the ants *Tetraponera* sp.[66] They have attracted the attention of chemists and biologists alike since their discovery in 1986. The ants use these toxins in a unique manner, with their sting being adapted not to inject the venom, but to smear a liquid on the bodies of their enemies. The structures of the tetraponerines are also unique for ant toxins, containing tricyclic cores and an unusual aminal functionality. The eight alkaloids fall into two groups of four with distinct core scaffolds: T1 **102**, T2 **103**, T5 **106** and T6 **107** comprise of a [5-6-5] (rings [A-B-C]) structure (i.e., decahydrodipyrrolo-[1,2-*a*:1',2'-*c*]pyrimidines) with *C*(5)-alkyl substitution, and T3 **104**, T4 **105**, T7 **108** and T8 **109** comprise of a [6-6-5] structure (i.e., decahydro-5*H*-pyrido[1,2-*c*]-pyrrolo[1,2-*a*]pyrimadines) with *C*(5)-alkyl substitution (Figure 5).

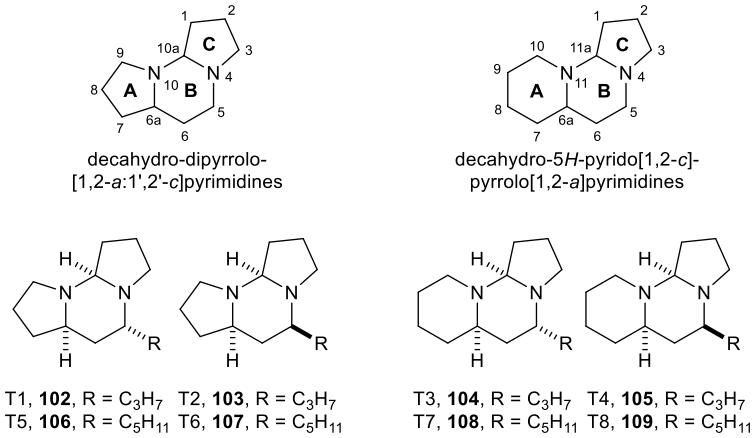


Figure 5 The structures of the tetraponerine alkaloids T1–8, **102**–**109**.

1.5.1 Isolation and structural elucidation

In 1986 Braekman *et al.*[66] observed the eight tetraponerines **102**–**109** by GC analysis of ant venom, but was only able to isolate T3–T8 **104**–**109** due to the low amounts of compound present in the mixtures; venom samples isolated from 1250 ants led to 2, 1.1, 3, 3, 3 and 6 mg of T3 **104**, T4 **105**, T5 **106**, T6 **107**, T7 **108** and T8 **109**, respectively. For these six compounds, the structures of T4 **105** and T8 **109** were correctly assigned, aided by the X-ray diffraction data of crystalline T8 **109**. The others, however, were originally misassigned, with a [6-6-5] structure being proposed for all the compounds: T3 **104** and T7 **108** were originally assigned as **110** and **112**, respectively, with the correct connectivity but the incorrect configuration; and T5 **106** and T6 **107** were assigned as **111** and **113**, respectively, incorrectly assuming a [6-6-5] core (Figure 6).

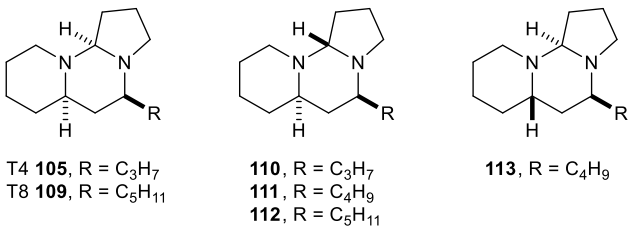
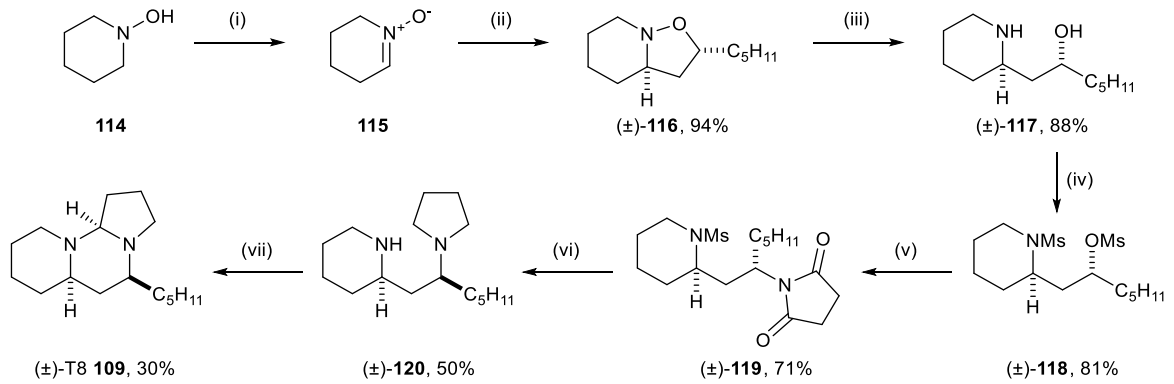


Figure 6 Originally proposed structures of the tetraponerine alkaloids T3–8 **104**–**109**.

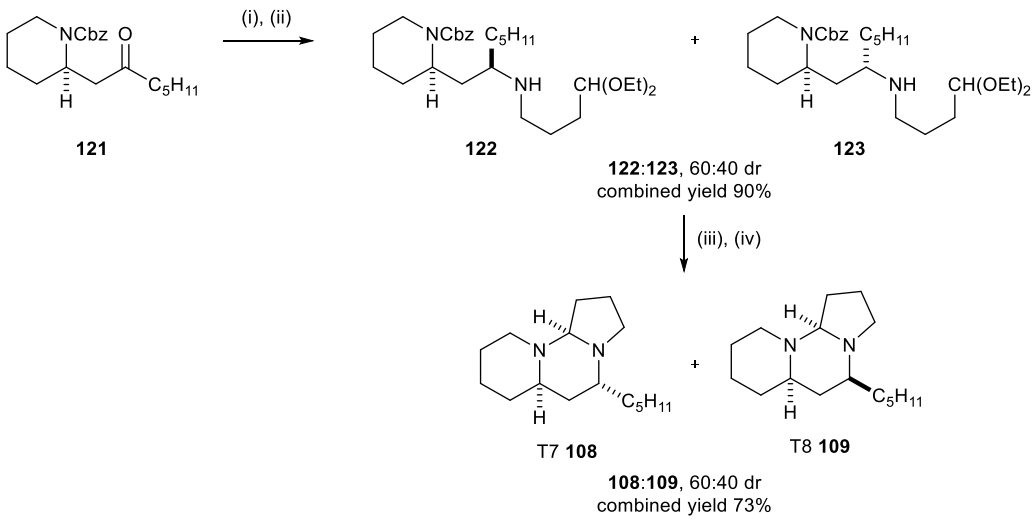
Shortly after isolation the first synthesis of a tetraponerine was completed by Braekman *et al.*,[67] confirming the structure of racemic T8 (±)-**109**. Starting from nitrone **115** (prepared from oxidation of 1-hydroxypiperidine **114**), a 1,3-dipolar cycloaddition with hept-1-ene resulted in isoxazolidine **116** in 94% yield. Reduction of **116** to amino alcohol **117** and *N*,*O*-dimesylation to give **118** proceeded in 88

and 81% yield, respectively. An S_N2 reaction with succinimide produced **119** in 71% yield, which contains all the necessary carbon atoms for T8 **109**. Various end-game conditions were trialled, with reduction of **119** with Red-Al to give **120**, and subsequent photocyclization to racemic T8 (±)-**109** being the most successful (Scheme 11).



Scheme 11 *Reagents and conditions*: (i) HgO, $CHCl_3$; (ii) hept-1-ene, $CHCl_3$, Δ; (iii) H_2, Raney Ni, MeOH; (iv) Ms_2O, NEt_3, CH_2Cl_2; (v) succinimide, K_2CO_3, HMPT, THF; (vi) Red-Al, PhMe; (vii) *N*-chlorosuccinimide, Et_3N, Et_2O, hν.

Later work, in 1995, on the synthesis of T8 and 5-*epi*-T8, led to the revision of the structures of T3 **104** and T7 **108** to those displayed in Figure 5.[68] In this synthesis of T8 **109**, a reductive amination was used on ketone **121**, producing a 60:40 mixture of epimeric amines **122** and **123**, respectively, in 90% yield. This mixture was deprotected and cyclised to produce a 60:40 mixture of two compounds which matched the data for the naturally isolated compounds T7 **108** and T8 **109**, respectively (Scheme 12). This confirmed that T7 **108** was, in fact, 5-*epi*-T8, and also led to the proposal that T3 **104** and T4 **105** were related as *C*(5) epimers.



Scheme 12 *Reagents and conditions*: (i) 4,4-diethoxybutylamine, Amberlyst A-15, 3 Å MS, rt, 25 h; (ii) $NaBH_4$, MeOH, rt, 4h; (iii) H_2, Pd/C, MeOH, rt, 7 h; (iv) 3% HCl, rt, 16 h.

At this stage, the structures of T5 **106** and T6 **107** were under scrutiny, and the structures of T1 **102** and T2 **103** were yet to be proposed. Braekman *et al.*[69] re-evaluated the ^{1}H and ^{13}C NMR data for T5 **106** and T6 **107** and concluded that they must consist of a [5-6-5] scaffold, managing to validate this theory by their total syntheses *via* analogous methods to those shown for T7 **108** and T8 **109**. Given the relationship between the [6-6-5] tetraponerines, the structures of T1 **102** and T2 **103** were now postulated, creating an analogous [5-6-5] series.

In these examples, no specific attention is given to the control of the aminal stereocentre. However, no 11a-*epi* compounds (in the [6-6-5] series) or 10a-*epi* compounds (in the [5-6-5] series) are observed; this can be attributed to the aminal forming reactions being governed by thermodynamic control and that the natural configuration is the more stable epimer. Theoretical studies have been conducted by González-Gómez *et al.*[70] into the configurations of an epimeric pair of tetraponerines T3 **104** and T4 **105**. A comprehensive screen of possible conformers of the different possible configurations of the aminal centres were considered and it was shown that the lowest energy conformers are those displayed by the natural products. Specifically conformer **105A** was shown to be the lowest energy for T4 **105**, whilst two low energy conformers, **104A** and **104B** were found for T3 **104**, linked by inversion of *N*(4) (Figure 7).

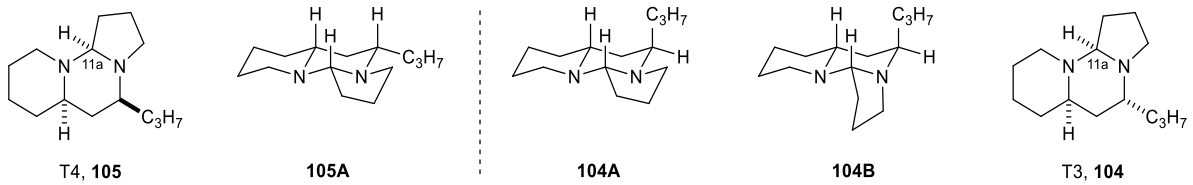
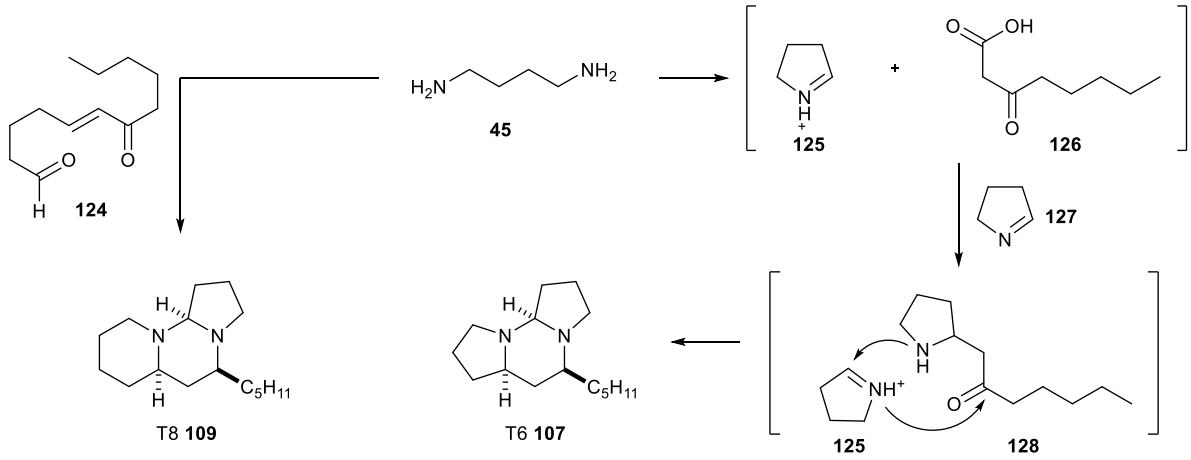


Figure 7 Lowest energy conformers of T3 **104** and T4 **105**.

1.5.2 Biosynthesis

As the tetraponerine skeletons are unique amongst natural products, research was done into the biosynthesis of the two different structural classes.[71,72] Feeding studies were conducted using ^{14}C labelled sodium acetate and ^{14}C labelled putrescine **45** followed by degradation studies of the isolated natural products, namely T6 **107** and T8 **109**. The acetate feeding showed that the entire carbon skeletons of the tetraponerines are produced from acetate, which can be converted into putrescine **45** *via* the tricarboxylic acid cycle. Feeding studies using putrescine **45** directly showed different results for the two core

scaffolds, the [5-6-5] tetraponerines (including T6 **107**) and the [6-6-5] tetraponerines (including T8 **109**), namely twice as much radioactive incorporation was observed for T6 **107** than for T8 **109**. Each product is believed to be synthesised from putrescine **45** and either compound **126** or **124** for T6 **107** or T8 **109**, respectively. It was concluded that for T8 **109** a single molecule of putrescine **45**, providing the carbons incorporated into the pyrrolidine ring, is added to olefin **124**, which provides all the remaining carbons for the natural product. In a contrasting biosynthesis, two molecules of putrescine **45**, *via* iminium **125** and imine **127**, are incorporated within T6 **107** (providing the carbons for both the pyrrolidine rings), with ketone **126** providing the remaining carbons (Scheme 13).

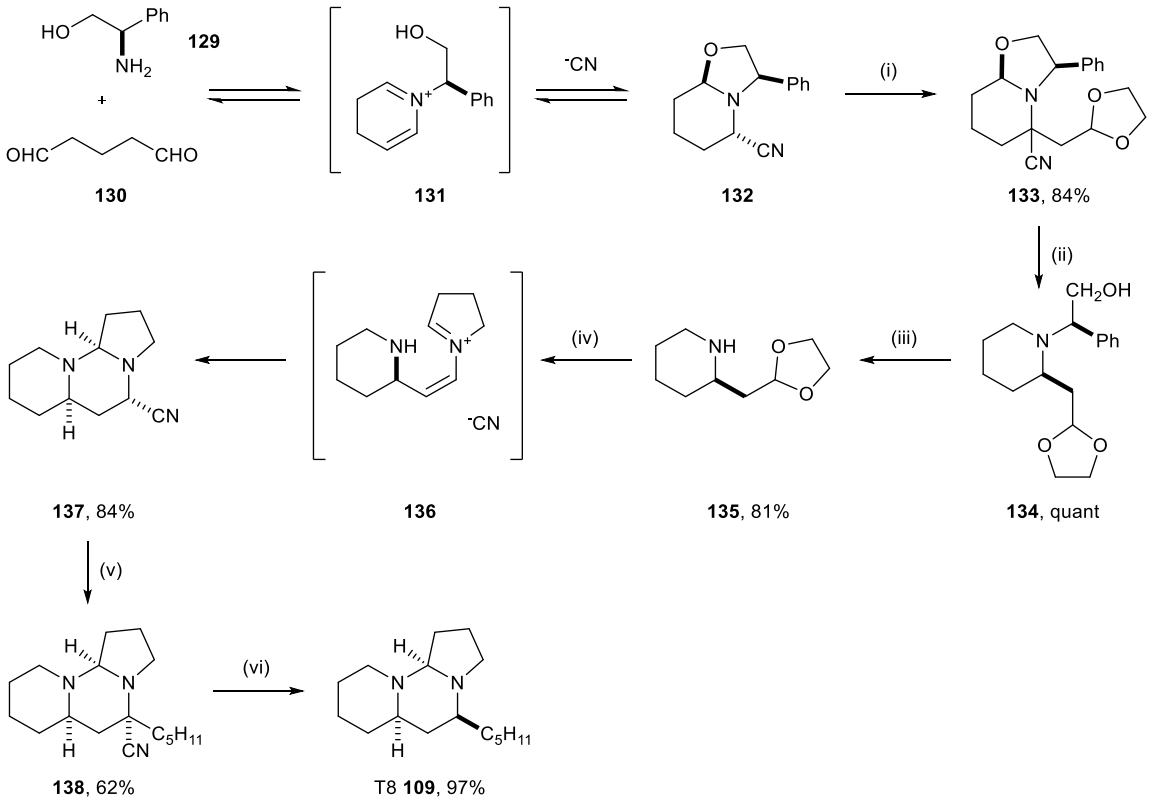


Scheme 13 Proposed biosynthetic pathways for the syntheses of T6 **107** and T8 **109**.[72]

1.5.3 Selected syntheses

Numerous syntheses of the tetraponerines have been reported, with T8 **109** attracting the most research.[67,68,73–82] Several methods used are only applicable to the synthesis of one of the two core scaffolds, or one set of diastereoisomers; however, two groups have published the syntheses of all eight compounds *via* common methodology.[70,77,80] The remaining publications focus on individual or a few selected tetraponerines, providing synthetic proof of their structures or new methodology for their syntheses.[69,83–87] Shortly after the first racemic synthesis of T8 **109**, Royer *et al.*[73] published the first enantioselective synthesis of a tetraponerine (also T8 **109** in this case), demonstrating the use of CN(*R*,*S*) methodology. This methodology is based around the notion that either an *R* or *S* stereocentre can be accessed from the elimination of the CN group within an α-amino nitrile. Condensation of

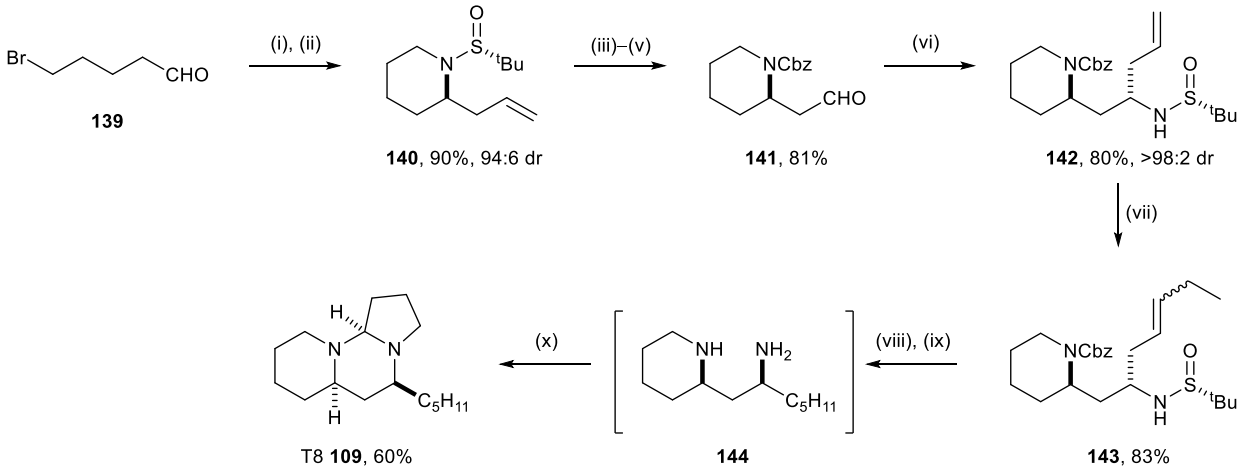
(*R*)-2-phenylglycinol **129** and malonaldehyde **130** in the presence of cyanide results in chiral hemiaminal ether **132**. Treatment of **132** with LDA and reaction of the resultant anion with 2-(bromomethyl)-1,2-dioxolane gave **133** in 84% yield, and reduction of **133** with $NaBH_4$ produced amine **134** in quantitative yield. Hydrogenolysis of the *N*-protecting group gave the masked β-amino aldehyde **135** in 81% yield. A second condensation, this time with 4-aminobutyraldehyde in the presence of cyanide, resulted in the core [6-6-5] scaffold of T8 **109** as cyano aminal **137**. Further deprotonation and alkylation gave **138** in 62% yield, which following elimination of the nitrile functionality, gave T8 **109** in 97% yield, completing the first asymmetric synthesis (Scheme 14). Following this, Royer *et al.*[77] published the syntheses of the remaining tetraponerines *via* analogous methodology.



Scheme 14 *Reagents and conditions*: (i) LDA, HMPA, THF, –78 °C then 2-(bromomethyl)-1,2-dioxolane; (ii) $NaBH_4$, EtOH, Δ, 2 h; (iii) H_2, Pd/C 10%, MeOH, 40 min; (iv) dilute HCl, rt, 16 h then 4-aminobutyraldehyde diethyl acetate, KCN, pH 2–3, rt, 2 h; (v) LDA, HMPA, THF, –78 °C then $Br(CH_2)_4CH_3$; (vi) Na, NH_3, –78 °C, 20 min.

The other methodology used in the syntheses of all eight compounds is documented by González-Gómez *et al.*[80] Below an example is described of one of their syntheses (also T8 **109**). In this case the source of enantioselectivity is in the use of (R_S)-*tert*-butanesulfinamide in an indium mediated aminoallylation of 5-bromopentanal **139**, followed by ring-closure to form piperidine **140** in 90% yield and 94:6 dr.[88] Hydrolysis of the sulfinamide with aq HCl, *N*-protection and oxidative cleavage of the olefinic

functionality resulted in β-amino aldehyde **141** in 81% yield. This aldehyde can then be used in a second aminoallylation, installing the second nitrogen and stereocentre within **142** in 80% yield. Cross metathesis using Grubbs II catalyst and (*Z*)-hex-3-ene elongates the carbon side chain yielding **143** in 83% yield. Hydrolysis of the sulfinamide, hydrogenation of the olefin, and hydrogenolysis of the *N*-carbamate provides diamine **144**, which was not isolated, but treated directly with 4-bromobutanal to give the natural product T8 **109** in 60% yield from **143** (Scheme 15). Applying this method to different starting materials and reagents allowed for the synthesis of the remaining tetraponerines.



Scheme 15 *Reagents and conditions*: (i) $Ti(OEt)_4$, In, THF, rt, 1 h then allyl bromide, 60 °C, 5 h; (ii) KHMDS, THF, 0 °C, 2 h; (iii) aq HCl, THF, rt, 1.5 h; (iv) aq NaOH, CbzCl, CH_2Cl_2, rt, 3 h; (v) OsO_4, $NaIO_4$, 2,6-lutidine, 1,4-dioxane/H_2O (3:1, v/v), rt, 1.5 h; (vi) (*R*S)-*tert*-butanesulfinamide, $Ti(OEt)_4$, In, THF, rt, 1 h then allyl bromide, 60 °C, 5 h; (vii) (*Z*)-hex-3-ene, Grubbs II, $Ti(O^iPr)_4$, CH_2Cl_2, 40 °C, 6 h; (viii) aq HCl, THF, rt, 1 h; (ix) H_2 (4 atm), Pd/C, MeOH, rt, 12 h; (x) 4-bromobutanal, K_2CO_3, CH_2Cl_2, rt, 4 h.

1.6 Thesis aim

The aim of this project was to synthesis a variety of cyclic amines, focussing on natural alkaloids and their close derivatives. The target compounds were the classes of: (1) the Hancock alkaloids (section 1.3); (2) hydroxymethyl substituted azabicycles (section 1.4); and (3) the tetraponerine alkaloids (section 1.5). The purpose of each synthesis was to demonstrate efficient methodology in the production of a variety of products (Figure 8). For each class of compounds a synthetic strategy was devised to target simultaneously a variety of compounds, differing in ring sizes, configuration or functionality using a lithium amide conjugate addition reaction as the key step to introduce asymmetry. This thesis will describe the work towards the Hancock alkaloids (Chapter 2), performing a single ring closure;

hydroxymethyl substituted azabicycles (Chapter 3), forming both rings in a variety of sizes; and the tetraponerines (Chapter 4), where the two different tricyclic cores will be formed covering the eight different structures.

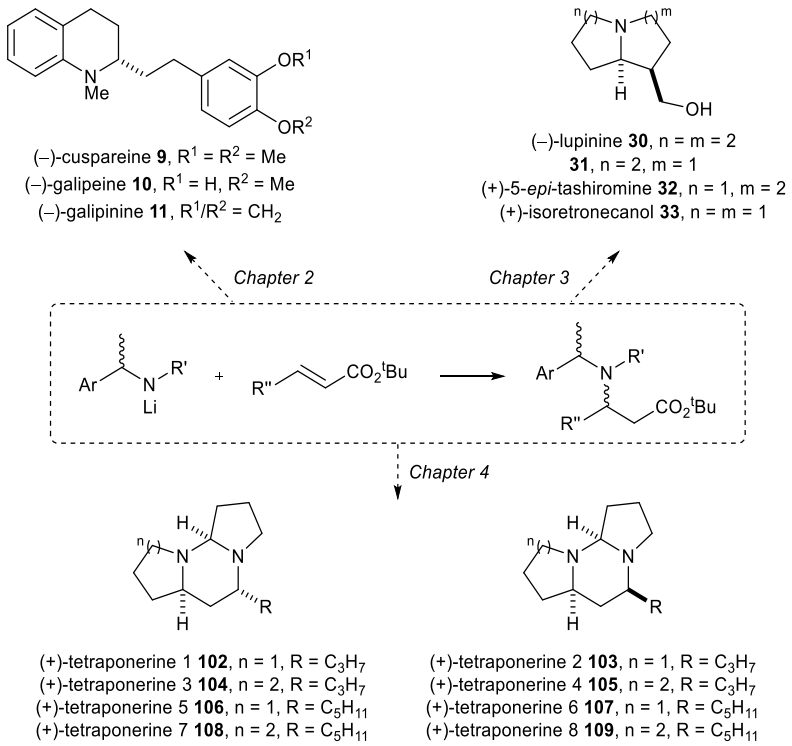


Figure 8 Thesis aim.

1.7 References and notes

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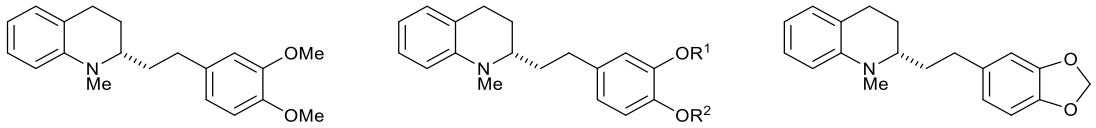
Chapter 2

Asymmetric Syntheses of Hancock Alkaloids

2.1 Introduction

This chapter describes the total asymmetric syntheses of three of the Hancock alkaloids: (–)-cuspareine **9**, (–)-galipeine **10** and (–)-galipinine **11** culminating in the structural revision of (–)-galipeine to the structure **145** (Figure 9).

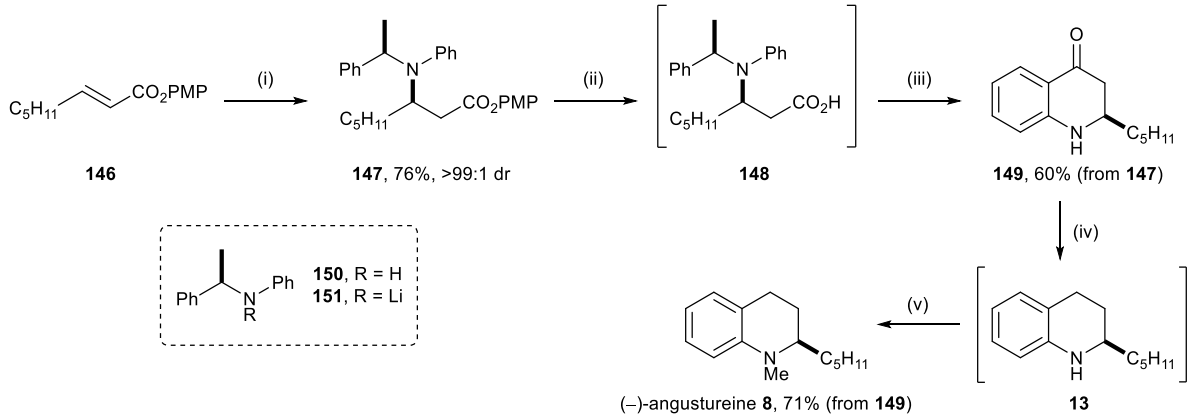


(–)-cuspareine, **9** (–)-galipeine (originally proposed) **10**, R^1 = H, R^2 = Me (–)-galipeine (revised structure) **145**, R^1 = Me, R^2 = H (–)-galipinine, **11**

Figure 9 Structures of the Hancock alkaloids **9**–**11** and **145**.

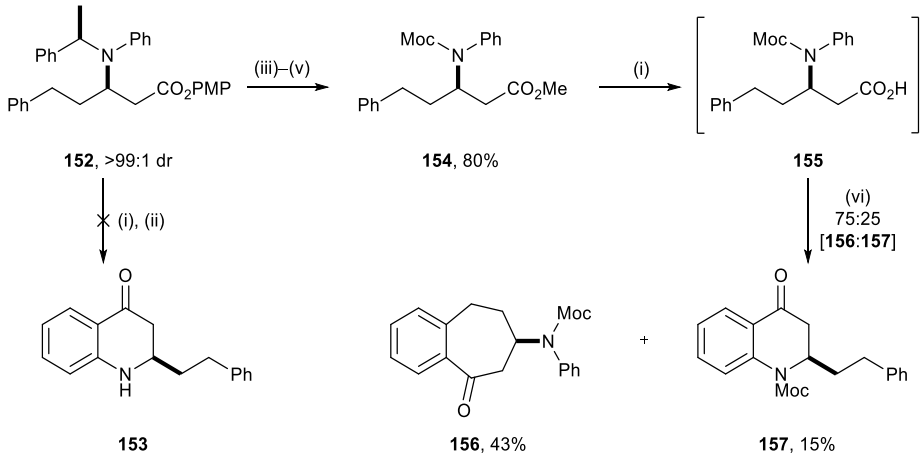
2.2 Previous work

Previously within the Davies group, work has been done on the asymmetric synthesis of (–)-angustureine **8**[1] and towards the syntheses of the remaining three alkaloids in this series.[2] For the synthesis of (–)-angustureine **8**, the conjugate addition of lithium anilide **151** to α,β-unsaturated ester **146** gave β-amino ester **147** in 76% yield and >99:1 dr. Saponification of **147** gave carboxylic acid **148** which, upon treatment with PPA, underwent both cyclisation and *N*-debenzylation to give dihydroquinolinone **149** in 60% yield (from **147**). Reduction of **149** using $LiAlH_4$ and subsequent *N*-methylation resulted in (–)-angustureine **8** in 71% yield over the final two steps (Scheme 16).



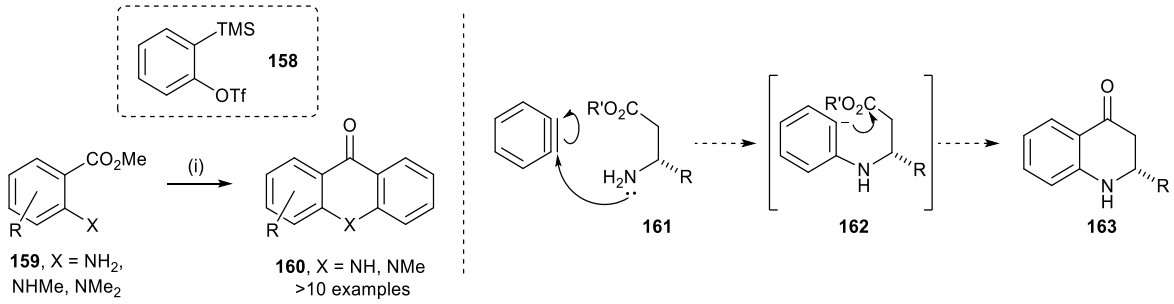
Scheme 16 *Reagents and conditions*: (i) **150**, BuLi, THF, –78 °C, 2 h; (ii) LiOH, THF/H_2O (1:1 v/v), 40 °C, 3 h; (iii) PPA, 100 °C, 16 h; (iv) $LiAlH_4$, THF, Δ, 16 h; (v) MeI, K_2CO_3, THF, Δ, 16 h.

This synthetic sequence was also trialled for the remaining Hancock alkaloids, all of which would require a β-amino ester analogous to **147** but containing an δ-aryl functionality, so it was decided to use δ-phenyl-β-amino ester **152** as a model compound for the targets **9**–**11**. However, treatment of **152** under the saponification/cyclisation conditions used for the synthesis of **149** did not lead to the cyclisation product **153**. A second protocol was trialled using a Friedel-Crafts acylation, which required the use of a carbamate-protected amine. Hydrogenolytic *N*-deprotection, *N*-Moc protection and transesterification of **152** gave methyl ester **154** in 80% yield over the three steps. Saponification to the carboxylic acid and Friedel-Crafts reaction of the corresponding acyl chloride resulted in a 75:25 mixture of **156** and **157**, respectively (Scheme 17).[2] This reaction demonstrated that the δ-phenyl substituent was participating in the reaction to give **156** as the major product, and so this strategy would not be applicable to the syntheses of **9**–**11**.



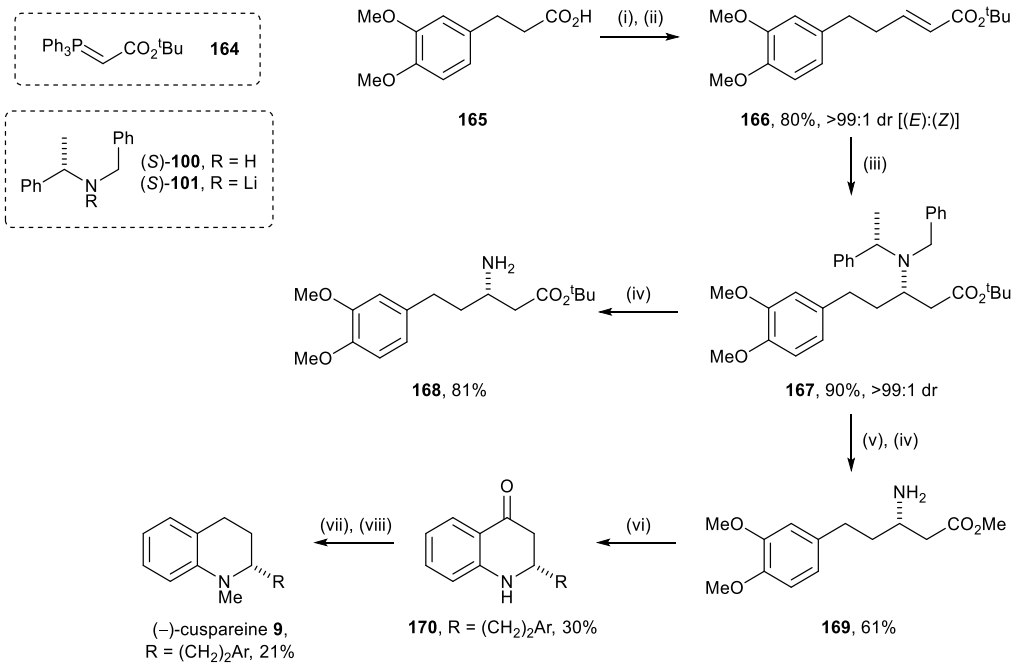
Scheme 17 *Reagents and conditions*: (i) LiOH, THF/H_2O (1:1 v/v), 40 °C, 3 h; (ii) PPA, 100 °C, 16 h; (iii) $Pd(OH)_2/C$, H_2 (1 atm), EtOAc, 4 h; (iv) MocCl, K_2CO_3, Δ, 16 h; (v) MeOH, $SOCl_2$, Δ, 2 h; (vi) $(COCl)_2$, CH_2Cl_2, rt, 2 h then $AlCl_3$, CH_2Cl_2, rt, 16 h.

Davies *et al*. proposed a second synthetic strategy, based on work by Larock *et al*.[3] employing benzyne (generated from the treatment of silyl triflate **158** with CsF) to achieve cyclisations of anilines **159** (X = NH_2, NHMe, NMe_2) to give acridones **160** (X = NH, NMe). It was postulated that treatment of β-amino ester **161** with benzyne would result in initial nucleophilic addition of the amine to give aryl anion **162**, which could subsequently react with the ester functionality to give cyclised dihydroquinolinone **163** (Scheme 18).



Scheme 18 *Reagents and conditions*: (i) **158**, CsF, MeCN, 65 °C, 24 h.

It was reported that the synthesis of (–)-cuspareine **9** started with reduction of carboxylic acid **165** with $LiAlH_4$, followed by an oxidation/olefination procedure which gave α,β-unsaturated ester **166** in 80% isolated yield and >99:1 dr. Conjugate addition of lithium amide (*S*)-**101** to **166** gave β-amino ester **167** in 90% yield and >99:1 dr. Hydrogenolysis of **167** gave β-amino *tert*-butyl ester **168** in 81% yield, and transesterification of **167** followed by hydrogenolysis gave β-amino methyl ester **169** in 61% yield. From these β-amino esters a cyclisation protocol was attempted using **158** and CsF to generate benzyne *in situ*. Reaction of **168** under these conditions was reported to give rise to no cyclised product, but for the reaction of **169**, dihydroquinolinone **170** was isolated in 30% yield. Reduction and *N*-methylation of **170** then gave (–)-cuspareine **9** in 21% yield (Scheme 19).[2,4]



Scheme 19 *Reagents and conditions*: (i) $LiAlH_4$, THF, 0 °C, 16 h; (ii) IBX, EtOAc, 70 C, 3 h then **164**, rt, 16 h; (iii) (*S*)-**101**, THF, –78 °C, 2 h; (iv) H_2 (5 atm), $Pd(OH)_2/C$, MeOH, rt, 16 h; (v) $SOCl_2$, MeOH, 50 °C, 16 h; (vi) **158**, CsF, MeCN, rt, 16 h; (vii) $LiAlH_4$, THF, Δ, 24 h; (viii) MeI, K_2CO_3, THF, Δ, 16 h. [Ar = 3,4-$(MeO)_2C_6H_4$]

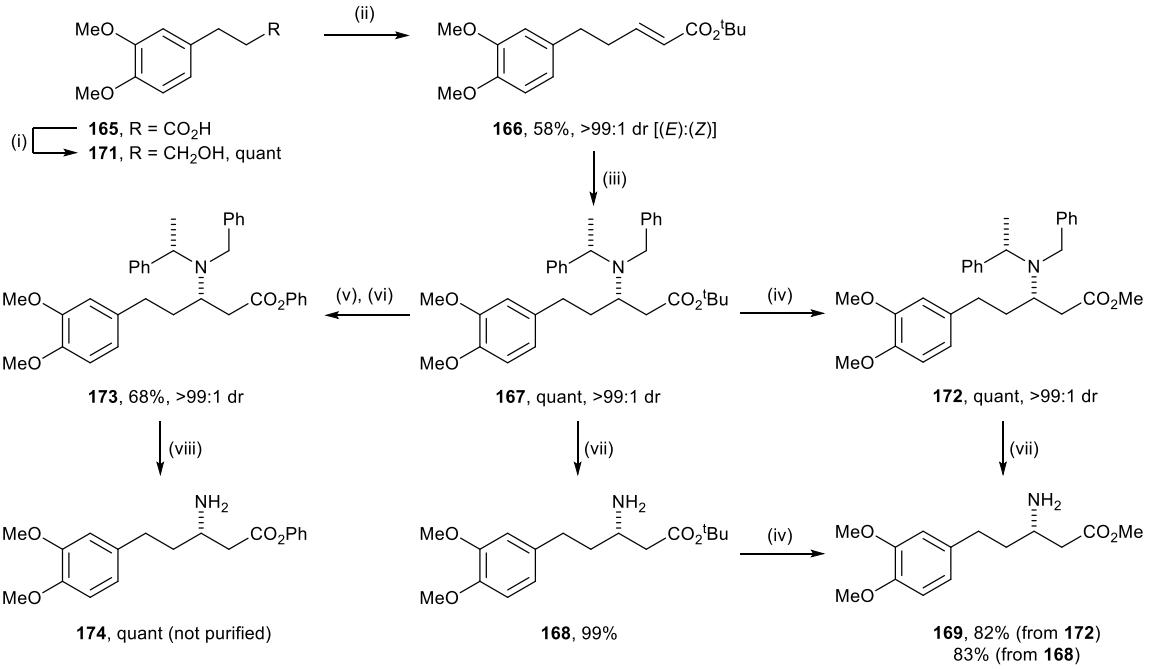
2.3 Chapter aim

Given the previous partial success of cyclisation to dihydroquinolinone **170**, the aim was to investigate further this reaction, namely the fate of the material in the reaction with *tert*-butyl ester **168** and analysis of other products formed in the reaction with methyl ester **169**. The ultimate goal was to then synthesise the natural products (–)-cuspareine **9**, (–)-galipeine (originally proposed structure) **10** and (–)-galipinine **11**, starting with the established procedures developed by Davies *et al*.[2]

2.4 Synthesis of cyclisation precursors

The earlier work conducted within the Davies group had demonstrated that the nature of the ester group was significant in the cyclisation reaction; hence a variety of esters was synthesised, namely *tert*-butyl, methyl and phenyl esters. Reduction of commercially available 3-(3',4'-dimethoxyphenyl)propanoic acid **165** gave alcohol **171** in quantitative yield. Oxidation of **171** under Swern conditions followed by Wittig reaction of the resultant aldehyde with ylid **164** gave α,β-unsaturated *tert*-butyl ester **166** in 58% yield and >99:1 dr [(*E*):(*Z*)] after purification; subsequently, conjugate addition of lithium amide (*S*)-**101** to **166** gave β-amino ester **167** in quantitative yield as a single diastereoisomer (>99:1 dr). Hydrogenolysis

of **167** resulted in primary β-amino *tert*-butyl ester **168** in 99% yield. The corresponding tertiary β-amino methyl ester **172** was accessed by transesterification of **167** using $SOCl_2$ in MeOH in quantitative yield. Primary amine **169** could then either be accessed through hydrogenolysis of β-amino methyl ester **172** in 82% yield, or transesterification of *tert*-butyl ester **168** in 83% yield. The final target, primary β-amino phenyl ester **174** was also synthesised from *tert*-butyl ester **167**. Saponification of **167** and treatment of the resultant carboxylic acid with DCC and PhOH gave phenyl ester **173** in 68% yield over the two steps, and hydrogenolysis of **173** gave **174** in quantitative yield (β-amino phenyl ester **174** was not purified as suitable flash column chromatography conditions could not be determined by TLC analysis). These reactions allow the efficient syntheses of any of the primary β-amino esters: *tert*-butyl ester **168**, methyl ester **169** or phenyl ester **174** (Scheme 20).

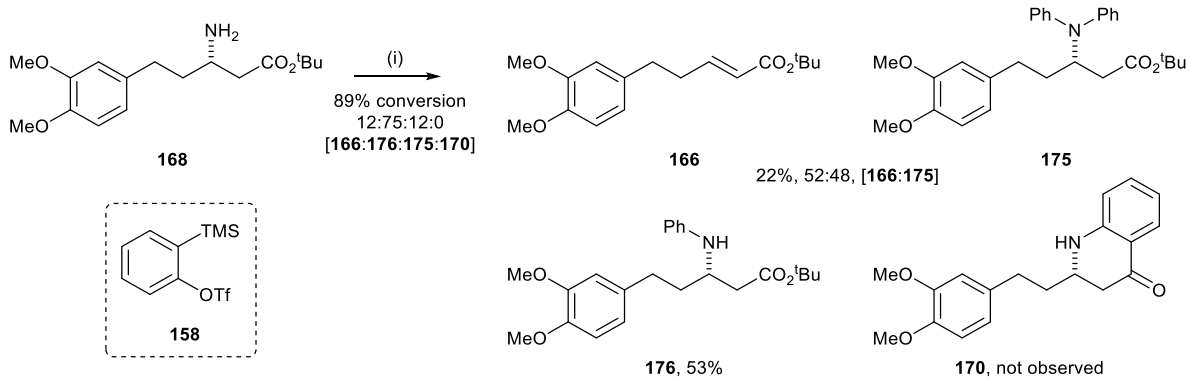


Scheme 20 *Reagents and conditions*: (i) $NaBH_4$, $BF_3{\cdot}OEt_2$, THF, 0 °C, 1 h; (ii) $(COCl)_2$, DMSO, CH_2Cl_2 –78 °C, 40 min then Et_3N, –78 °C to rt, 30 min then **164**, rt, 16 h; (iii) (*S*)-**100**, BuLi, THF, –78 °C, 2 h; (iv) $SOCl_2$, MeOH, 50 °C, 16 h; (v) TFA/CH_2Cl_2 (1:2, v/v), rt, 16 h; (vi) DCC, PhOH, CH_2Cl_2, rt, 16 h; (vii) $Pd(OH)_2$/C, H_2 (5 atm), MeOH, rt, 16 h; (viii) $Pd(OH)_2$/C, H_2 (5 atm), EtOAc, rt, 16 h.

2.5 Benzyne mediated cyclisations

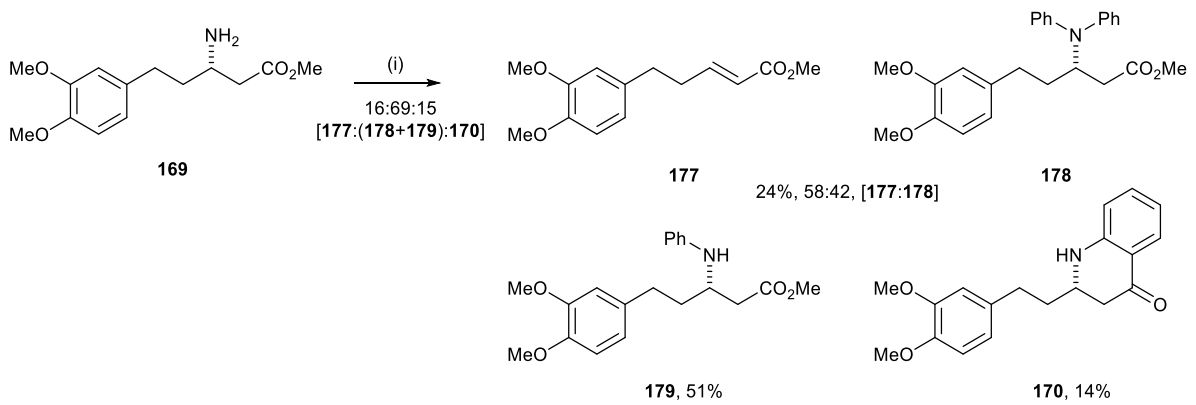
β-Amino *tert*-butyl ester **168** was first investigated in a benzyne mediated cyclisation. Although this reaction was unsuccessfully performed previously,[2] no documentation was made as to the product distribution. Treatment of **168** with benzyne precursor **158** and CsF in MeCN under conditions reported

by Okuma *et al*.[5] gave 89% conversion to a 12:75:12 mixture of α,β-unsaturated ester **166**, β-*N*-phenyl amino ester **176** and β-*N*,*N*-diphenyl amino ester **175**, respectively, with no dihydroquinolinone **170** being observed. This demonstrates that under these conditions, benzyne is being successfully generated and nucleophilic addition of amine **168** to benzyne is occurring, but is being followed by protonation of the resultant aryl anion as the major pathway to give **176**. A small amount of **166** is observed, which is presumably formed from a retro-aza-Michael type process with loss of the amine fragment, the identity of which was not determined in this reaction (Scheme 21).



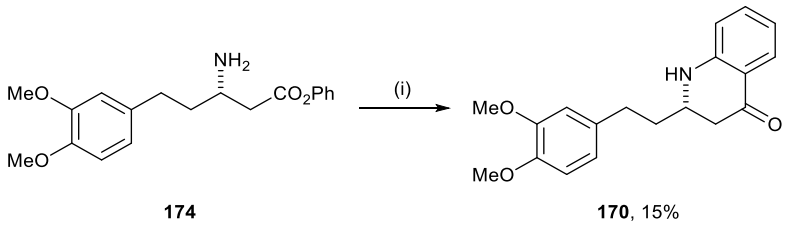
Scheme 21 *Reagents and conditions*: (i) **158**, CsF, MeCN, rt, 16 h.

The incorporation of *N*-phenyl units in the reaction, but no observed cyclisation suggested the limiting factor was the reaction of the intermediate aryl anion with the *tert*-butyl ester functionality; hence, the methyl ester analogue **169** was investigated as a less bulky substituent may lead to a faster rate of cyclisation. Repetition of the reaction using methyl ester **169** gave quantitative conversion to a mixture of products containing **170** and **177**–**179**. Peak overlap in the ^{1}H NMR spectrum of the crude reaction mixture precluded determination of a **178** to **179** ratio but the ratio of **177**:[**178**+**179**]:**170** was 16:69:15. This reaction demonstrated that although a similar process of *N*-arylation and protonation to give *N*-phenyl compounds and elimination to give α,β-unsaturated ester **177**, some cyclisation of the intermediate aryl anion is observed in this case, giving dihydroquinolinone **170**, which is consistent with the more reactive ester functionality (Scheme 22).



Scheme 22 *Reagents and conditions*: (i) **158**, CsF, MeCN, rt, 16 h.

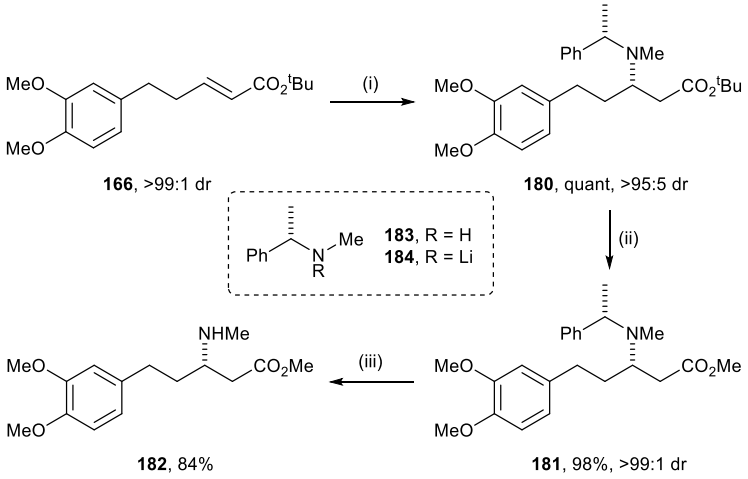
As the increase in reactivity of the ester group had proved successful in promoting a small amount of the desired reactivity, the more electrophilic phenyl ester **174** was subjected to the benzyne conditions. The reaction proceeded to full conversion but due to numerous overlapping signals in the ^{1}H NMR spectrum of the crude reaction mixture no ratio for the product distribution could be obtained. However, dihydroquinolinone **170** was isolated in 15% yield; it was also tentatively assigned that the crude reaction mixture contained similar *N*-arylated compounds, as observed with the benzyne reaction on esters **168** and **169** (Scheme 23).



Scheme 23 *Reagents and conditions*: (i) **158**, CsF, MeCN, rt, 16 h.

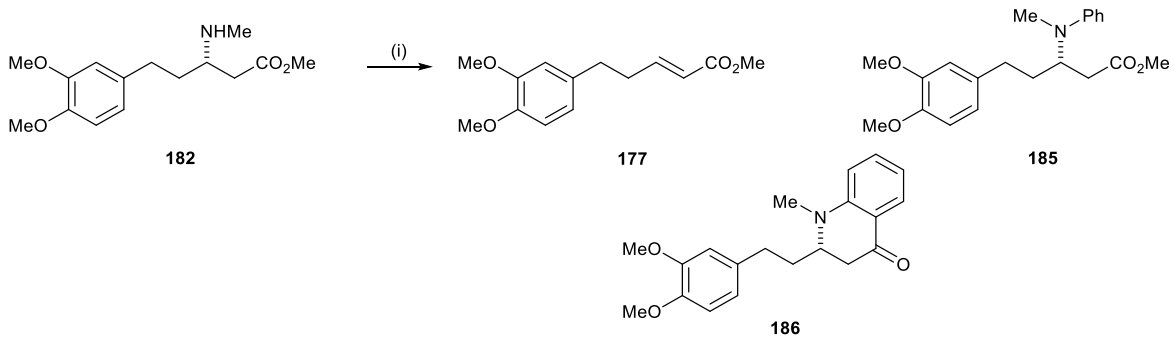
2.5.1 Benzyne mediated cyclisations with secondary amines

As the natural products contain the *N*-methyl functionality, it was proposed that an *N*-methyl substituted lithium amide reagent **184** could be used to install the desired alkyl group at this stage. Conjugate addition of lithium amide **184** to α,β-unsaturated ester **166** gave β-amino ester **180** in quantitative yield and >95:5 dr. Subsequent transesterification to methyl ester **181** was achieved in 98% yield and hydrogenolysis gave the target *N*-methyl β-amino ester **182** in 84% yield (Scheme 24). The corresponding phenyl ester was not investigated in this case due to the similarity of the reactivity of **169** and **174**.



Scheme 24 *Reagents and conditions*: (i) **183**, BuLi, THF, –78 °C, 2 h; (ii) $SOCl_2$, MeOH, 50 °C, 16 h; (iii) $Pd(OH)_2/C$, H_2 (5 atm), MeOH, rt, 16 h.

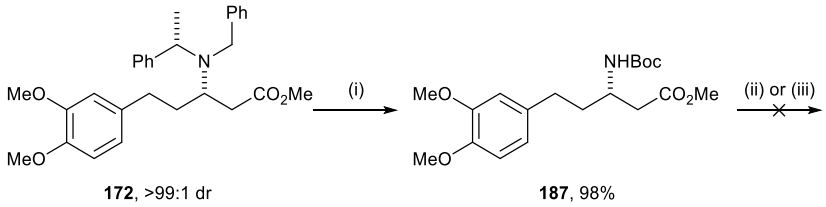
The cyclisation reaction undertaken with β-amino ester **182** gave quantitative conversion to a 37:51:12 ratio of **177**, **185** and **186**, respectively, again showing a majority of *N*-phenylation and elimination, with a small proportion of desired cyclisation (**186** being isolated in 12% yield). These results were very similar to the reaction of the primary amine **169** with benzyne, where the dihydroquinoline product **170** was isolated in only 14% yield. Performing the reaction in THF, another solvent commonly used for benzyne chemistry, gave, at rt, only returned starting material. This was accompanied by quantitative returned benzyne precursor **158**, consistent with negligible generation of benzyne under these conditions. To force the formation of benzyne, the reaction was heated at 65 °C. Now, no starting material remained and a 50:37:13 ratio of **177**, **185** and **186**, respectively, was formed; a similar result to the reaction in MeCN at rt (Scheme 25).



Entry	Reagents and Conditions	Solvent	Temp	Conversion / %	Ratio [**177**:**185**:**186**]	Notes
1	(i)	MeCN	rt	100	37:51:12	**186** isolated in 12% yield
2	(i)	THF	rt	0	-	Returned **158**
3	(i)	THF	65 °C	100	50:37:13	-

Scheme 25 *Reagents and conditions*: (i) **158**, CsF, solvent, temp, 16 h.

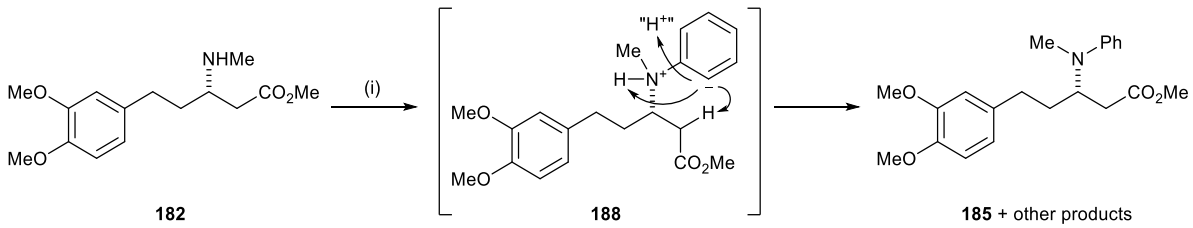
Additionally, an *N*-Boc protected amine was synthesised as it was envisaged that the *N*-Boc functionality could be easily reduced to an *N*-Me group at a later stage in the synthesis and that the acidic *N*-H proton could be easily removed before the reaction. Hydrogenolysis of **172** in the presence of $(Boc)_2O$ gave *N*-Boc amine **187** in 98% yield. (Scheme 26). Deprotonation of **187** using NaH to from the sodium amide, and this was subjected directly to the benzyne reaction conditions. In this case, the benzyne precursor **158** was fully consumed but no conversion of **187** was observed, implying benzyne was being generated but the desired reactivity was not occurring. The reaction was also repeated on **187** without prior deprotonation (to rule out any interference of NaH or Na salts in the reaction conditions) and the same result was observed: no reaction of the starting material but full consumption of the precursor **158**. It was therefore concluded that the amide N was not nucleophilic enough to add into benzyne and initiate the reaction.



Scheme 26 *Reagents and conditions*: (i) $Pd(OH)_2/C$, $(Boc)_2O$, H_2 (5 atm), MeOH, rt, 24 h; (ii) NaH, **158**, CsF, MeCN, rt, 16 h; (iii) **158**, CsF, MeCN, rt, 16 h.

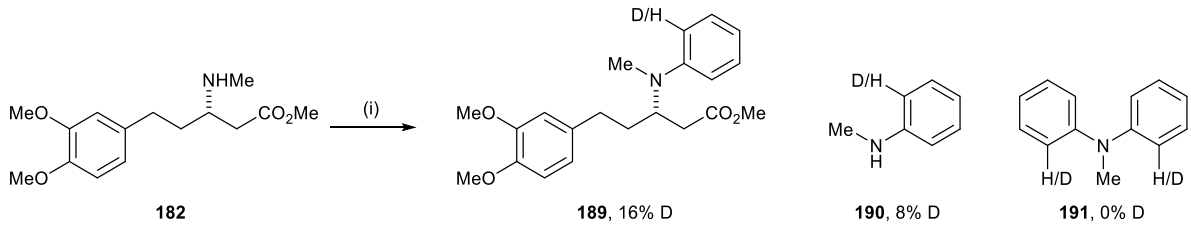
2.6 Deuteration studies

As the most significant issue with these reactions was the protonation of aryl anions, giving *N*-phenyl compounds, deuteration studies were undertaken to ascertain the main sources of protonation of the intermediate aryl anion **188**. The studies were conducted on *N*-Me amine **182**, where the most obvious potential acidic protons are the *N*-H proton, the *C*(2) protons α to the carbonyl, the solvent or some other adventitious proton source (Scheme 27).



Scheme 27 *Reagents and conditions*: (i) **158**, CsF, MeCN, rt, 16 h.

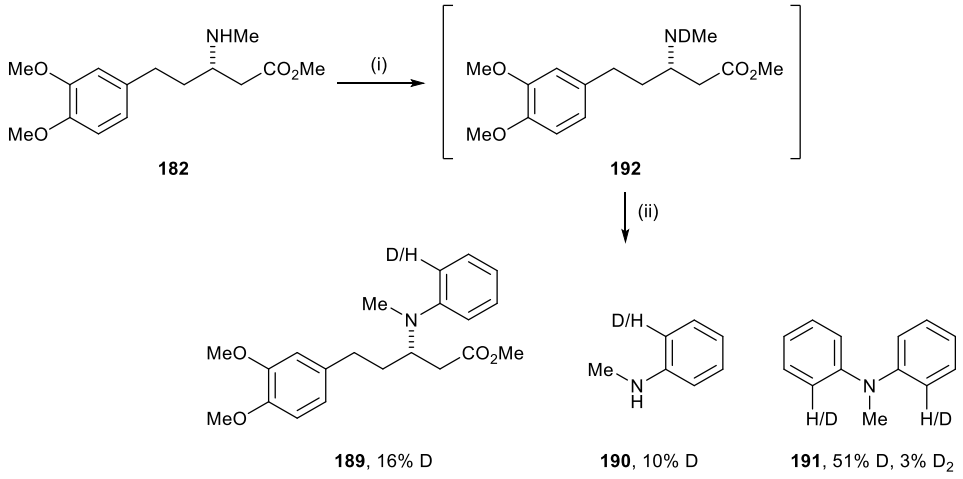
The initial experiment conduct was repetition of the reaction conditions using MeCN-d_3. Analysis of the crude reaction mixture was conducted using HRMS where the ratio of molecular ions $[M(D)+H]^+$ and $[M(H)+H]^+$ could be used to quantify deuterium incorporation within any component of the reaction. The compounds analysed were *N*-phenyl amine **189**, *N*-methyl aniline **190** and *N*-phenyl-*N*-methyl aniline **191**, where the two aniline compounds **190** and **191** are the potential eliminated amines that arise in the formation of α,β-unsaturated ester **177** in the original reaction. HRMS analysis showed the following levels of deuteration: **189** [16% M(D)], **190** [8% M(D)] and **191** [0% M(D)] (Scheme 28). This demonstrated that protonation can occur from the solvent, although there is still significant protonation arising from other sources.



182 **189**, 16% D **190**, 8% D **191**, 0% D

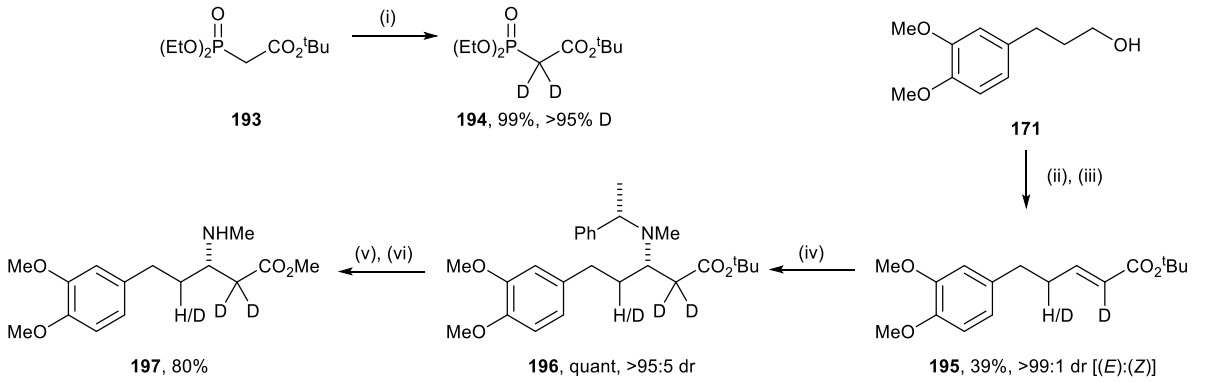
Scheme 28 *Reagents and conditions*: (i) **158**, CsF, MeCN-d_3, rt, 16 h.

Next, the possibility of proton transfer from the *N*-H functionality was considered. The deuterated compound **192** was formed *in situ* from repeated co-evaporation of **182** from MeOH-d_4, and was then subjected directly to the reaction conditions. Similar HRMS analysis showed the following levels of deuteration: **189** [16% M(D)], **190** [10% M(D)] and **191** [51% M(D), 3% M(D_2)] (Scheme 29). This demonstrated that proton transfer can occur between the *N*-H proton and the intermediate aryl anion **188** although it was not possible to ascertain the percentage transfer as it was not possible to determine the level of *N*-deuteration within **192**.



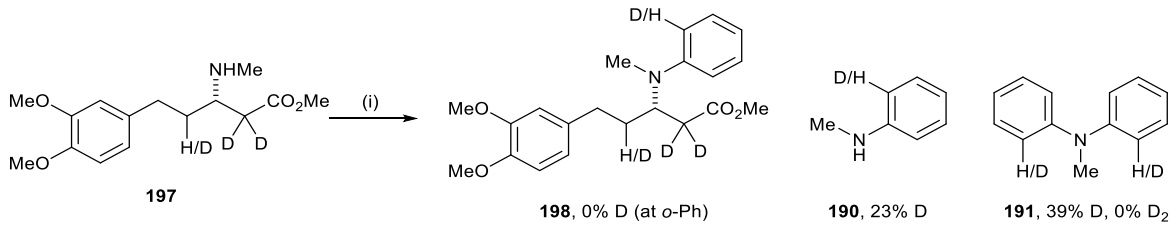
Scheme 29 *Reagents and conditions*: (i) MeOH-d_4; (ii) **158**, CsF, MeCN, rt, 16 h.

Finally, the *C*(2) deuterated compound was prepared in a similar fashion to work previously reported by Davies *et al*.[6] A deuterated Wadsworth-Emmons reagent **194** was prepared from phosphonate **193**, using K_2CO_3 in D_2O, in 99% yield with >95% D incorporation. Reaction of **194** with the aldehyde generated from Swern oxidation of alcohol **171** gave α,β-unsaturated ester **195** in 39% yield with 99% D incorporation at *C*(2). ^{1}H and ^{2}D NMR spectroscopy also indicated some D incorporation at *C*(4) (~20%); and HRMS analysis also indicated multiply deuterated species [66% M(D), 32% M(D_2), 1% M(D_3)]. This was consistent with some α-deuteration of the intermediate aldehyde (exchange with the solvent, D_2O) prior to olefination. Lithium amide conjugate addition of **184** to **195** and quenching with D_2O gave β-amino ester **196** in quantitative yield with >95% D being observed at *C*(2), with a similar amount of *C*(4) deuteration being detected to **195** (~20% by ^{1}H and ^{2}D NMR). Transesterification of **196** and hydrogenolysis of the resultant methyl ester gave **197** in 80% yield over the two steps with 88% D incorporation at *C*(2), and again ~20% D at *C*(4). The slight erosion in the deuterium labelling at *C*(2) could be attributable to the reaction of **196** in acidic MeOH, possibly allowing proton exchange α to the ester with the solvent (Scheme 30).



Scheme 30 *Reagents and conditions*: (i) K_2CO_3, D_2O, rt, 16 h; (ii) $(COCl)_2$, DMSO, CH_2Cl_2 –78 °C, 40 min then Et_3N, –78 °C to rt, 30 min; (iii) **194**, K_2CO_3, D_2O, 30 h, 50 °C; (iv) **183**, BuLi, THF, –78 °C, 2 h then D_2O, –78 °C to rt; (v) $SOCl_2$, MeOH, 50 °C, 16 h; (vi) $Pd(OH)_2/C$, H_2 (5 atm), MeOH, rt, 16 h.

Performing the benzyne cyclisation reaction on **197** gave the following levels of deuteration: **190** [23% M(D)] and **191** [39% M(D)] (HRMS analysis) and **198** (0% D at *o*-Ph, ^{1}H NMR analysis), demonstrating that transfer is occurring between the *C*(2) deuterons and the aryl anion, but that they are not incorporated at the *o*-Ph position within **198** (Scheme 31).



Scheme 31 *Reagents and conditions*: (i) **158**, CsF, MeCN, rt, 16 h.

With the information from product distributions and deuteration studies a potential pathway for the formation of the major products **185** and **177** was proposed. Initial benzyne addition to **182** gives the putative ammonium **199**, which has four possible protonation events: A, C(2)*H* deprotonation; B, N*H* deprotonation; C, solvent deprotonation; and D, protonation from unknown sources. Studies using MeCN-d_3 and *N*-D **192** show that B and C are possible pathways (leading to *N*-phenyl amine **185** amongst other products). C(2)D_2 studies show that that pathway A leads to enolate **200** (R = H) where elimination must occur to give α,β-unsaturated ester **177** and *N*-methyl aniline **202** (which may possibly further arylate to give *N*-phenyl-*N*-methyl aniline **203**). For pathways B, C and D, phenyl amine **185** will be produced (N*H* loss after pathways C and D). This is either untouched (observed in the final reaction mixture) or arylated with a second equivalent of benzyne; this results in ammonium **204**. Now, two new pathways are possible: A, C(2)*H* deprotonation; and B, protonation from solvent or unknown sources. Pathway A leads to enolate **201** (R = Ph) which, as with **200** (R = H), will fragment, this time giving

α,β-unsaturated ester **177** and *N*-phenyl-*N*-methyl aniline **203**. If pathway B occurs ammonium **205** is formed, which would presumably also fragment resulting in the same compounds **177** and **203** (Figure 10). The formation of partially deuterated products **190** and **191** in all three deuteration studies is entirely consistent with these postulations.

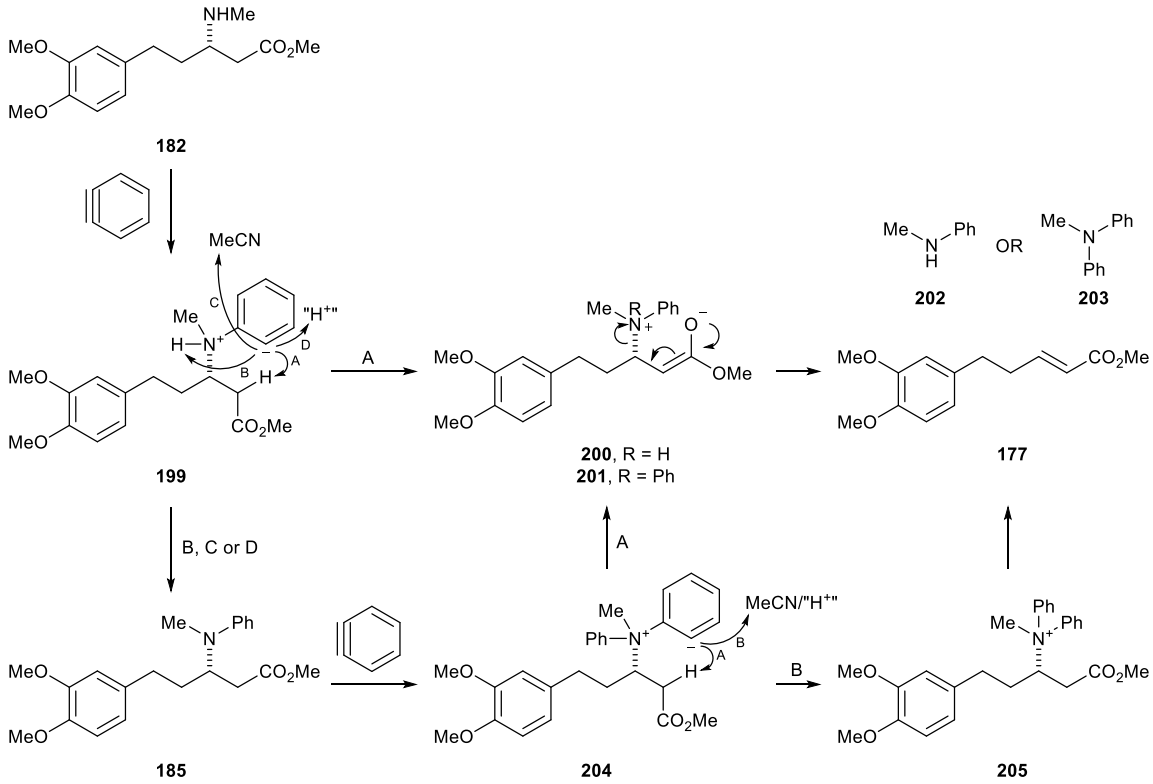
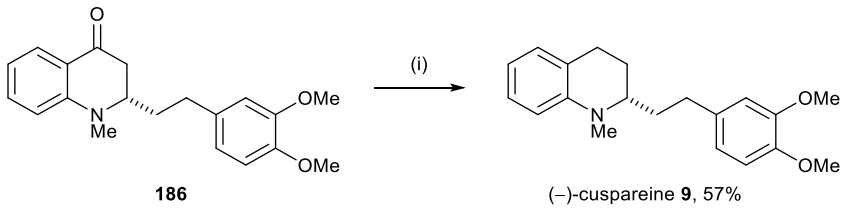


Figure 10 Potential pathways for the formation of products **177**, **185**, **202** and **203**.

2.7 Synthesis of (–)-cuspareine

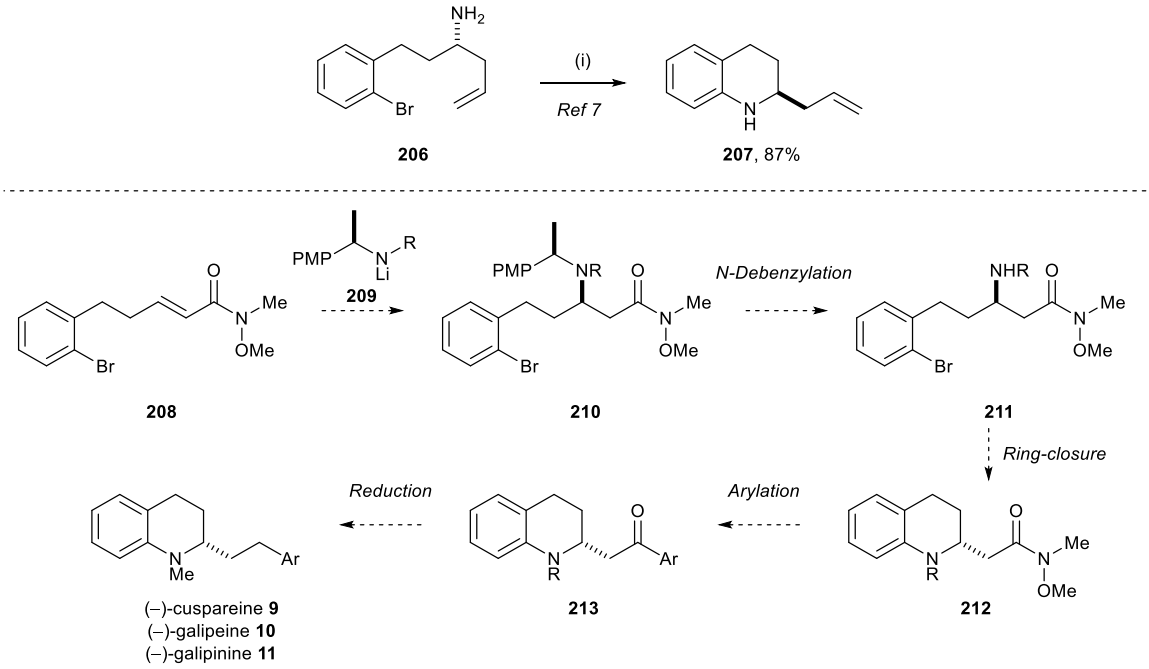
Although the cyclisation reaction requires further optimisation to be synthetically viable, the synthesis of (–)-cuspareine **9** was completed to demonstrate that the dihydroquinolinones produced in the cyclisation reactions were suitable compounds for the synthesis of the desired alkaloids. Dihydroquinolinone **186** was treated with $LiAlH_4$ at reflux resulting in complete deoxygenation to give (–)-cuspareine **9** in 57% yield (Scheme 32). This completed the asymmetric total synthesis of (–)-cuspareine **9** in 3.3% overall yield over seven steps from commercially available 3-(3',4'-dimethoxyphenyl)propanoic acid **165**, thereby confirming the stereochemical assignment of the synthetic precursors **180**–**182** and **186**.



Scheme 32 *Reagents and conditions*: (i) $LiAlH_4$, THF, Δ, 16 h.

2.8 Second synthetic strategy: Buchwald-Hartwig cyclisation

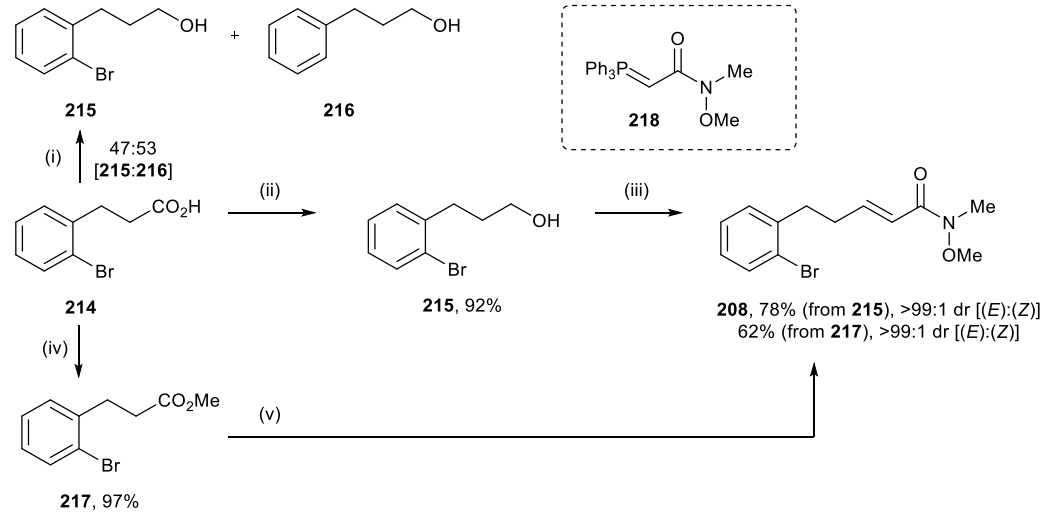
As the benzyne cyclisation reaction proved problematic, a second synthetic strategy was devised. Work towards the synthesis of (–)-angustureine **8** by Yus *et al.*[7] demonstrates the use of a Buchwald-Hartwig coupling reaction in the formation of tetrahydroquinoline **207** in 87% yield from aryl bromide **206** (Scheme 33). It was envisaged that a similar ring-closing protocol could be used from β-amino amide **211** and so a second synthetic strategy towards (–)-cuspareine **9**, (–)-galipeine (originally proposed structure) **10** and (–)-galipinine **11** was devised. Taking α,β-unsaturated amide **208** and performing a lithium amide conjugate addition with a *p*-methoxy-α-methylbenzyl derived lithium amide **209** could lead to β-amino amide **210**. Now, the specific nature of the *p*-methoxyaryl functionality allows for *N*-debenzylation to **210**: work by Davies *et al.*[8] has demonstrated that under suitable hydrogenolysis conditions to *N*-debenzylate an α-methylbenzyl protected amine, debromination of aryl bromides will also occur, in similar systems. However, acidic *N*-deprotection of a *p*-methoxy-α-methylbenzyl protected amine is compatible with the aryl bromide functionality. Buchwald-Hartwig reaction of **211** would give tetrahydroquinoline **212** which, containing the Weinreb amide functionality, is a suitable compound for diversification by the mono-addition of a variety of aryl groups to **212** and will allow access to the structural diversity within the target alkaloids. Reduction of the carbonyl within **213** (and any necessary manipulation of *N*-protecting groups) would lead to the target compounds **9–11** (Scheme 33).



Scheme 33 *Reagents and conditions*: (i) $Pd(OAc)_2$, PPh_3, Cs_2CO_3, PhMe, Δ, 21 h. Proposed synthetic plan.

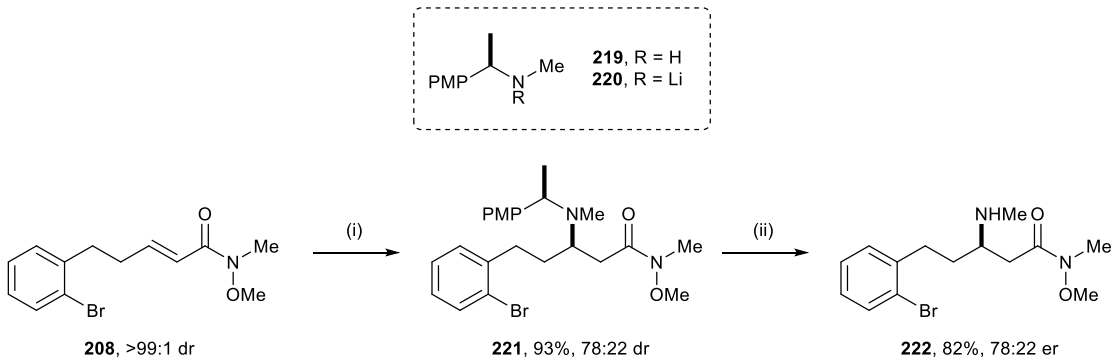
2.9 Synthesis of tetrahydroquinoline core

Starting with commercially available 3-(2'-bromophenyl)propanoic acid **214**, initially a reduction using $LiAlH_4$ was attempted. This resulted in significant competitive debromination,[9] and gave a 47:53 mixture of **215** and **216**, respectively. Milder reduction conditions ($NaBH_4$ in the presence of $BF_3{\cdot}OEt_2$) gave alcohol **215** in 92% yield. Swern oxidation of **215** followed by treatment of the resultant aldehyde with ylid **218** gave α,β-unsaturated amide **208** in 78% yield and >99:1 dr [(*E*):(*Z*)] after purification by flash column chromatography; **208** was assigned as the (*E*)-olefin by the characteristic ^{1}H NMR ^3J coupling constant of 15.4 Hz between the C(2)*H* and C(3)*H* protons. Another reaction sequence could also be used to access **208** from **214**, employing an esterification reaction to give methyl ester **217** in 97% yield and subsequent reduction of **217** with DIBAL-H and olefination of the intermediate aldehyde with **218**, gave α,β-unsaturated amide **208** in 62% yield and >99:1 dr [(*E*):(*Z*)] (Scheme 34).



Scheme 34 *Reagents and conditions*: (i) $LiAlH_4$, THF, Δ, 2 h; (ii) $NaBH_4$, BF_3OEt_2, THF, 0 °C, 1 h; (iii) $(COCl)_2$, DMSO, CH_2Cl_2 –78 °C, 40 min then Et_3N, –78 °C to rt, 30 min then **218**, rt, 16 h; (iv) $SOCl_2$, MeOH, Δ, 3 h; (v) DIBAL-H, PhMe, –78 °C, 1 h then MeOH, **218**, –78 °C to rt, 16 h.

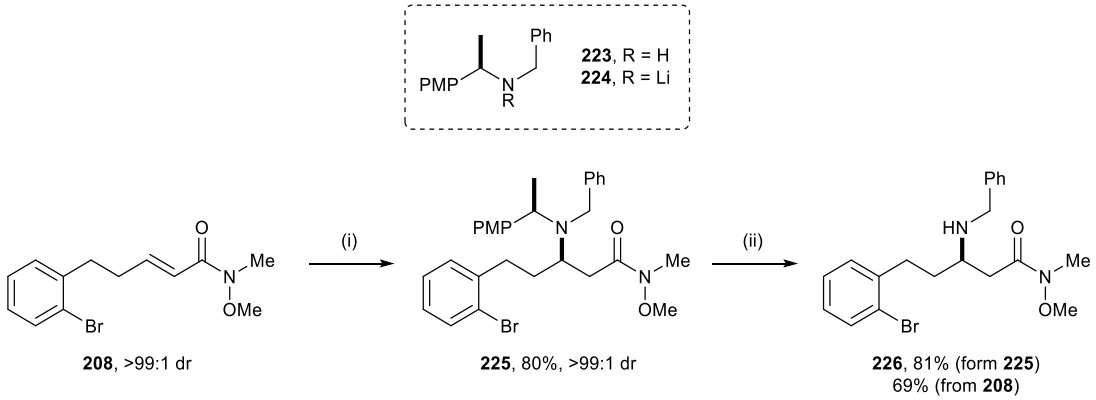
As the target compounds contain an *N*-methyl functionality it was hoped that an *N*-methyl substituted lithium amide reagent **220** could be used to install the desired functionality at this stage. Upon conjugate addition of **220** to α,β-unsaturated amide **208**, an inseparable 78:22 mixture of products **221** was formed, isolated in 93% combined yield. It was established that these were diastereoisomers by *N*-deprotection of **221**; this gave secondary amine **222** which was formed as a single compound, and isolated in 82% yield and 78:22 er,[10] reinforcing the assignment of **221** as a 78:22 mixture of diastereoisomers. The major compound **221** was tentatively assigned as the (*R*,*R*)-compound based on Davies's transition state mnemonic for lithium amide conjugate addition (Scheme 35).[11]



Scheme 35 *Reagents and conditions*: (i) **219**, BuLi, THF, –78 °C, 2 h; (ii) Et_3SiH, HCO_2H, 90 °C, 16 h.

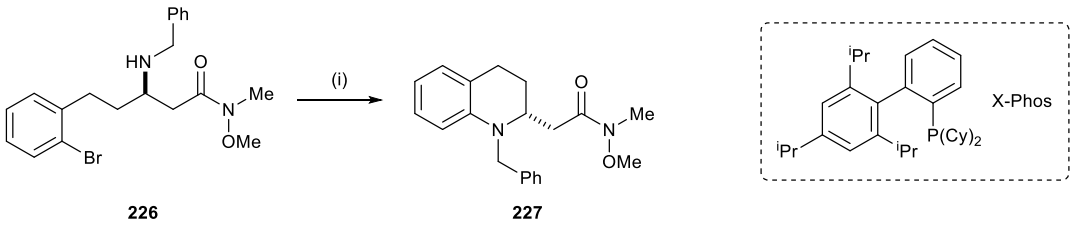
As these diastereoisomers could not be separated, a lithium amide conjugate addition was performed using *N*-benzyl lithium amide **224**, which gave β-amino amide **225** in 80% yield and as a single diastereoisomer (>99:1 dr). *N*-Deprotection of **225** using Et_3SiH in formic acid gave secondary amine **226** in 81% (65% overall yield from **208**) and a telescoped two-step procedure (without purification of

β-amino ester **225**) gave **226** in a slightly superior yield of 69% (from **208**) over the two steps (Scheme 36).



Scheme 36 *Reagents and conditions*: (i) **223**, BuLi, THF, –78 °C, 2 h; (ii) Et_3SiH, HCO_2H, 90 °C, 16 h.

At this stage, a Buchwald-Hartwig cyclisation could be undertaken. Amine **226** was treated with Yus's conditions [5 mol% of $Pd(OAc)_2$ and PPh_3][7] which gave tetrahydroquinoline **227** but in only 43% conversion, where **227** could be isolated in 37% yield. Increasing the catalyst loading to 15 mol% resulted in full conversion, with **227** being isolated in 79% yield, and exchange of PPh_3 for X-Phos (at 5 mol% loading) also gave full conversion, with **227** being isolated in quantitative yield (Scheme 37).



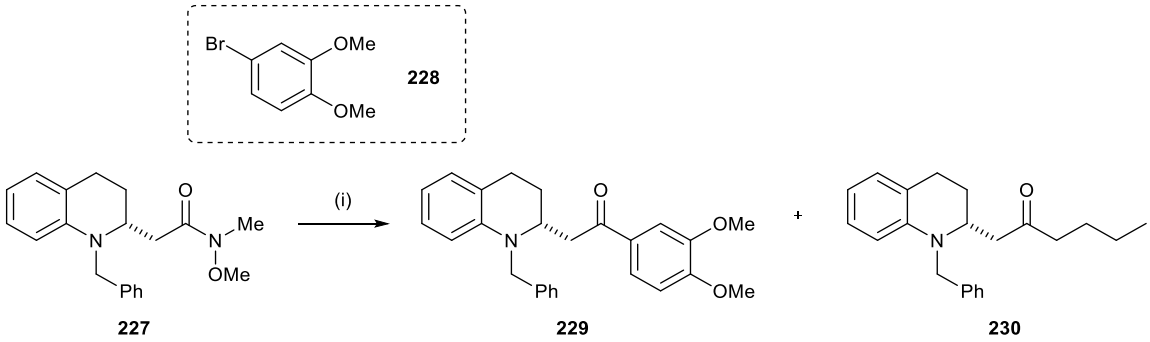
Entry	Reagents and Conditions	mol% of catalyst	Ligand	Conversion / %	Isolated yield of **227** / %
1	(i)	5	PPh_3	43	37
2	(i)	15	PPh_3	100	79
3	(i)	5	X-Phos	100	quant

Scheme 37 *Reagents and conditions*: (i) $Pd(OAc)_2$, ligand, Cs_2CO_3, PhMe, Δ, 24 h.

2.10 Synthesis of (–)-cuspareine

The Weinreb amide functionality within tetrahydroquinoline **227** was used so an aryl lithium reagent could be added without over addition to the corresponding diaryl alcohol. Initially, trials were conducted towards the synthesis of (–)-cuspareine **9** where a 3,4-dimethoxy aryl substituent is required. The first

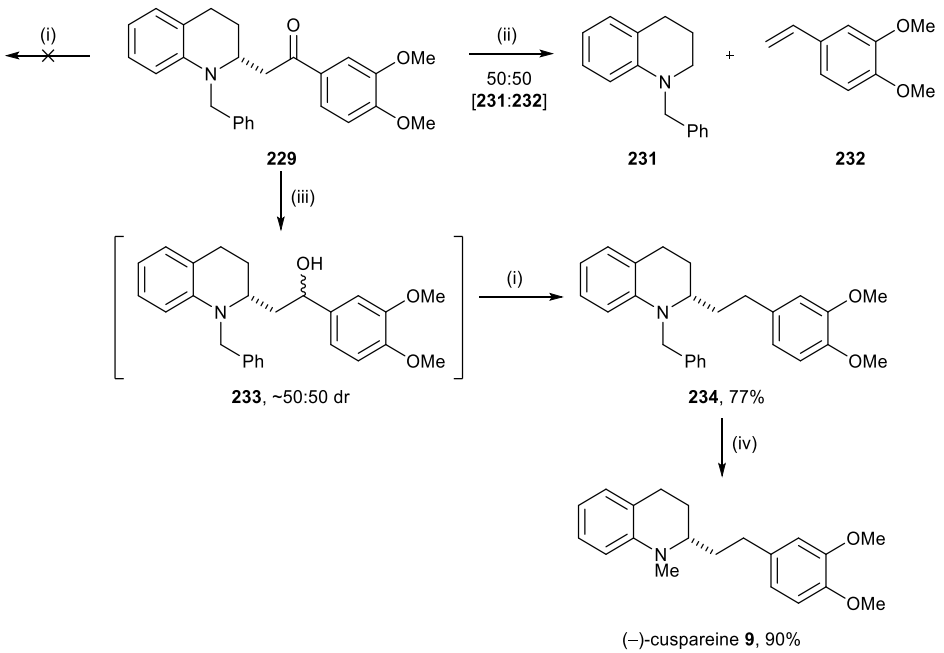
conditions tried were using 1.0 equiv of aryl bromide **228** and 1.0 equiv of BuLi to generate an aryl lithium reagent at –78 °C. Addition of amide **227** to this mixture at –78 °C gave, after 1.5 h of reaction time, 40% conversion to the target compound **229** (which was isolated in 39% yield). Repetition of this procedure but performing the reaction for 16 h at –78 °C gave a similar conversion of 43% and repetition for 1.5 h but at 0 °C gave a slightly lower conversion of 33%. As neither longer reaction time or higher reaction temperature resulted in a significant increase in product, attention was turned to stoichiometry of the reaction. One plausible explanation was that some of the BuLi was being consumed in an elimination reaction with the BuBr that is formed from the lithium halogen exchange (although this is not often a problem when using ^{n}BuLi). When an additional equivalent of BuLi was added, butyl-addition was observed to give **230**, thus demonstrating the BuLi was not being consumed by this possible pathway. A 1:1 ratio of aryl bromide **228** and BuLi was maintained but with increasing equivalents of the aryl lithium species being used compared with amide **227**. 2.0 Equiv gave 59% conversion with **229** being isolated in 55% yield, and 7.0 equiv gave >95% conversion, with **229** being isolated in 79% yield (Scheme 38). This procedure, although requiring an excess of aryl bromide **228**, gave **229** in good yield and allowed for continued synthesis towards the target alkaloid.



Entry	Equiv of **228**	Equiv of BuLi	Temp / °C	Time / h	Conversion / %	Isolated yield of **229** / %	Notes
1	1	1	–78	1.5	40	39	-
2	1	2	–78	1.5	84	22	29:71 [**229**:**230**]
3	2	2	–78	1.5	59	55	-
4	7	7	–78	1.5	>95	79	-
5	1	1	0	1.5	33	-	-
6	1	1	–78	16	43	-	-

Scheme 38 *Reagents and conditions*: (i) **228**, BuLi, THF, –78 °C, 30 min then **227**, temp, time.

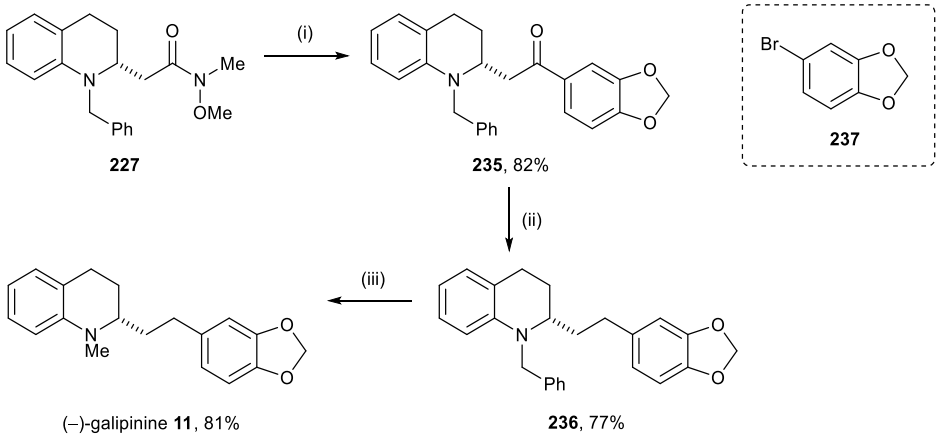
Similar aryl ketones to **229** have been reduced using Et_3SiH in TFA at rt,[12] however, use of these conditions upon **229** gave no reaction, returning only starting material. Heating the reaction to 70 °C led to fragmentation of the molecule giving a 50:50 mixture of tetrahydroquinoline **231** and styrene **232**, which is consistent with a retro-Mannich type reaction of the β-amino ketone and subsequent reduction of the resultant acetophenone. Reduction of the ketone within **229** using $LiAlH_4$ gave alcohol **233** (~50:50 dr) which, upon treatment with Et_3SiH in TFA at rt gave the target tetrahydroquinoline **234** in 77% yield. One-pot hydrogenolysis and reductive alkylation replaced the *N*-benzyl functionality with *N*-methyl and so gave (–)-cuspareine **9** in 90% yield (Scheme 39). The spectroscopic data for (–)-cuspareine **9** were in good agreement with literature values {$[\alpha]_D^{25}$ –27.8 (*c* 1.0 in $CHCl_3$); lit.[13] for a sample isolated from the natural source $[\alpha]_D$ –22.8 (*c* 0.0135 in $CHCl_3$); lit.[12] $[\alpha]_D^{24}$ –27.2 (*c* 0.87 in $CHCl_3$)}. This completed the synthesis of (–)-cuspareine **9** in 27.1% overall yield over nine steps from commercially available 3-(2'-bromophenyl)propanoic acid **214**, confirming the stereochemical assignments of the synthetic precursors **225**–**227**, **229** and **234**.



Scheme 39 *Reagents and conditions*: (i) Et_3SiH, TFA, rt, 16 h; (ii) Et_3SiH, TFA, 70 °C, 16 h; (iii) $LiAlH_4$, THF, Δ, 16 h; (iv) Pd/C, H_2 (1 atm), CH_2O, MeOH, 24 h.

2.11 Synthesis of (–)-galipinine

Treatment of Weinreb amide **227** with an aryl lithium derived from aryl bromide **237** gave aryl ketone **235** in 82% yield. Reaction of **235** under the two-step conditions of $LiAlH_4$ followed by Et_3SiH in TFA gave the deoxygenated compound **236** in 77% yield. Finally, *N*-debenzylation and *in situ* reductive alkylation gave (–)-galipinine **11** in 81% yield (Scheme 40). The spectroscopic data for (–)-galipinine **11** were in good agreement with literature values {$[\alpha]_D^{25}$ –23.7 (*c* 1.0 in $CHCl_3$); lit.[13] for a sample isolated from the natural source $[\alpha]_D$ –33.4 (*c* 0.0055 in $CHCl_3$); lit.[14] $[\alpha]_D^{24}$ –21.8 (*c* 0.75 in $CHCl_3$)}. This concluded the asymmetric total synthesis of (–)-galipinine **11** in 25.3% overall yield over nine steps from commercially available 3-(2'-bromophenyl)propanoic acid **214**, confirming the stereochemical assignments of the synthetic precursors **225**–**227**, **235** and **236**.



Scheme 40 *Reagents and conditions*: (i) **237**, BuLi, THF, –78 °C, 30 min then **227**, –78 °C, 1.5 h; (ii) $LiAlH_4$, THF, Δ, 16 h then Et_3SiH, TFA, rt, 16 h; (iii) Pd/C, H_2 (1 atm), CH_2O, MeOH, 24 h.

2.12 Comparison of ^1H and ^{13}C NMR data for (–)-cuspareine and (–)-galipinine

The following tables (1, 2) display the ^1H and ^{13}C NMR data for the Hancock alkaloids **9** and **11**, with comparison to literature data and data from naturally isolated sources. Where data was left unassigned in the original manuscript, an assignment has been made here for the ease of comparison.[15][16]

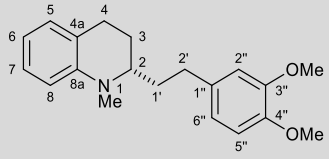
	^{1}H NMR shifts / ppm, multiplicity, *J* / Hz				^{13}C NMR shifts / ppm		
	(–)-Cuspareine **9** 						
Assignment	This work $CDCl_3$	Ref 15 $CDCl_3$	Ref 13 Natural $CDCl_3$	Assignment	This work $CDCl_3$	Ref 15 $CDCl_3$	Ref 13 Natural $CDCl_3$
C(2)*H*	3.26–3.33, m	3.30, dq, 4.5, 8.5	3.25, m	*C*(2)	58.6	58.4	58.3
C(3)H_2	1.87–2.00, m	1.87–2.02, m	1.92, m	*C*(3)	24.5	24.4	24.4
C(4)H_A	2.64–2.73, m	2.63–2.75, m	2.64, m	*C*(4)	23.7	23.6	23.6
C(4)H_B	2.80–2.91, m	2.86, ddd, 17.5, 12.0, 6.0	2.82, m	*C*(4a)	121.9	121.7	121.8
C(5)*H*	6.98, d, 7.3	6.99, dd, 7.0, 1.5	6.97, d, 7.1	*C*(5)	128.8	128.7	128.7
C(6)*H*	6.59, t, 7.3	6.61, ddd, 7.5, 7.5, 1.5	6.67, m	*C*(6)	115.5	115.4	115.5
C(7)*H*	7.06–7.11, m	7.07–7.12, m	7.97, t, 7.7	*C*(7)	127.3	127.1	127.2
C(8)*H*	6.53, d, 8.2	6.54, d, 8.0	6.61, dd, 7.8, 1.7	*C*(8)	110.7	110.6	110.7
C(1')H_A	1.68–1.79, m	1.75, dddd, 14.0, 10.0, 9.0, 5.5	1.69, m	*C*(8a)	145.4	145.3	145.4
C(1')H_B	1.87–2.00, m	1.87–2.02, m	1.91, m	*C*(1')	33.2	33.1	33.2
C(2')H_A	2.53, ddd, 13.9, 10.1, 6.4	2.55, ddd, 14.0, 10.0, 6.5	2.49, m	*C*(2')	32.1	31.9	32.1
C(2')H_B	2.64–2.73, m	2.63–2.75, m	2.60, m	*C*(1")	134.8	134.6	134.7
C(2")*H*	6.70–6.75, m	6.70–6.76, m	6.70, m	*C*(2")	111.7	111.6	111.6
C(5")*H*	6.79, d, 8.0	6.80, d, 8.0	6.70, m	*C*(3")/*C*(4")	147.3	147.2	147.2
C(6")*H*	6.70–6.75, m	6.70–6.76, m	6.70, m	*C*(3")/*C*(4")	149.0	148.9	148.9
N*Me*	2.92, s	2.93, s	2.89, s	*C*(5")	111.4	111.3	111.3
O*Me*	3.86, s	3.87, s	3.84, s	*C*(6")	120.2	120.0	120.1
O*Me*	3.87, s	3.88, s	3.86, s	N*Me*	38.3	38.1	38.1
-	-	-	-	O*Me*	56.0	55.9	55.9
-	-	-	-	O*Me*	56.1	55.9	55.9

Table 1 Comparison of ^{1}H and ^{13}C NMR data for (–)-cuspareine **9**.[17]

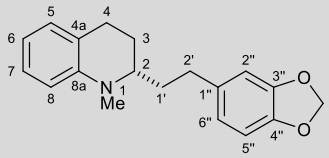
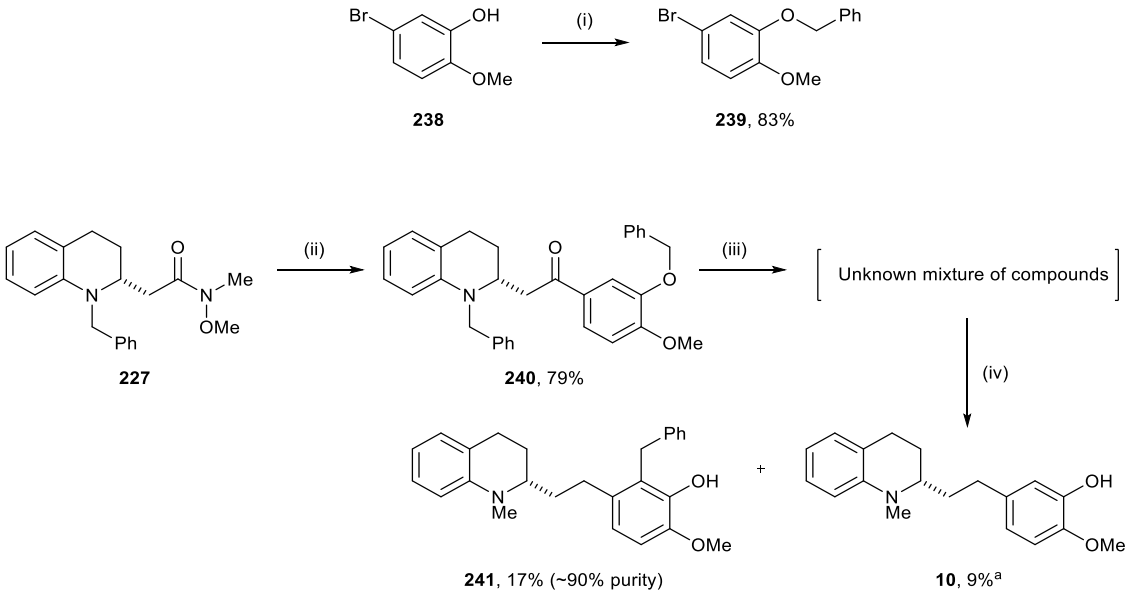
	^{1}H NMR shifts / ppm, multiplicity, *J* / Hz				^{13}C NMR shifts / ppm		
	(–)-Galipinine **11** 						
Assignment	This work $CDCl_3$	Ref 16 $CDCl_3$	Ref 13 Natural $CDCl_3$	Assignment	This work $CDCl_3$	Ref 16 $CDCl_3$	Ref 13 Natural $CDCl_3$
C(2)*H*	3.16–3.23, m	3.24–3.29, m	3.27, m	*C*(2)	58.4	58.3	58.4
C(3)H_2	1.84–1.96, m	1.84–1.97, m	1.95, m	*C*(3)	24.5	24.4	24.4
C(4)H_A	2.59–2.72, m	2.60–2.70, m	2.68, m	*C*(4)	23.7	23.6	23.6
C(4)H_B	2.83, td, 10.9, 6.2	2.80–2.87, m	2.85, m	*C*(4a)	121.9	121.7	122.7
C(5)*H*	6.97, d, 7.4	6.97, d, 7.2	6.97, d, 7.2	*C*(5)	128.8	128.7	128.7
C(6)*H*	6.59, td, 7.4, 1.0	6.59, t, 7.2	6.60, t, 7.3	*C*(6)	115.6	115.0	115.4
C(7)*H*	7.05–7.11, m	7.08, t, 7.5	7.03,t, 7.9	*C*(7)	127.2	127.2	127.1
C(8)*H*	6.52, d, 8.2	6.52, d, 8.3	6.52, d, 8.1	*C*(8)	110.8	110.7	110.7
C(1')H_A	1.65–1.74, m	1.66–1.73, m	1.72, m	*C*(8a)	145.4	145.3	145.3
C(1')H_B	1.84–1.96, m	1.84–1.97, m	1.94, m	*C*(1')	33.3	33.2	33.1
C(2')H_A	2.50, ddd, 13.9, 9.9, 6.6	2.47–2.53, m	2.51, m	*C*(2')	32.2	32.1	31.9
C(2')H_B	2.59–2.72, m	2.60–2.70, m	2.63, m	*C*(1")	136.0	135.9	135.9
C(2")*H*	6.68, d, 1.6	6.68, s	6.70, m	*C*(2")	108.9	108.8	108.8
C(5")*H*	6.72, d, 7.9	6.71–6.73, m	6.70, m	*C*(3")/*C*(4")	145.7	145.6	145.7
C(6")*H*	6.63, dd, 7.9, 1.6	6.63–6.64, m	6.70, m	*C*(3")/*C*(4")	147.7	147.6	147.6
N*Me*	2.91, s	2.9, s	2.91, s	*C*(5")	108.3	108.2	108.2
OCH_2O	5.92, s	5.91, s	5.90, s	*C*(6")	121.1	121.0	121.0
-	-	-	-	N*Me*	38.2	38.1	38.1
-	-	-	-	OCH_2O	100.9	100.8	100.8

Table 2 Comparison of ^{1}H and ^{13}C NMR data for (–)-galipinine **11**.[17]

2.13 Synthesis and structural reassignment of (–)-galipeine

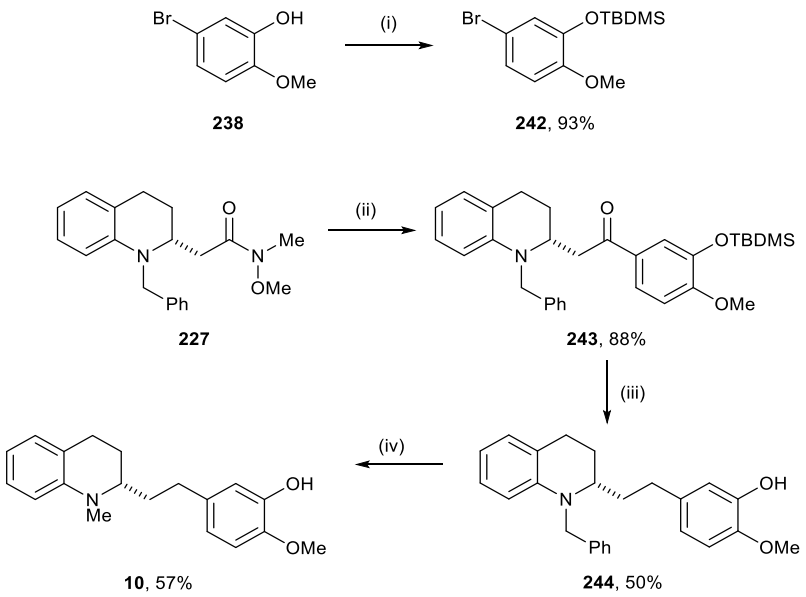
Two syntheses of the structure originally reported for (–)-galipeine **10** have been reported[18,19] but in both cases the data (most notably the ^{13}C NMR data for the substituted phenol ring) do not match the data for the naturally isolated compound,[20] despite claims made within the two manuscripts. It was therefore decided to synthesise our own authentic sample of **10** and the alternative regioisomer. The proposed structure **10** contains a free hydroxyl functionality, which may cause problems in the formation of an aryl lithium. For this reason, an *O*-benzyl protected aryl bromide **239** was prepared from 2-methoxy-5-bromophenol **238** in 83% isolated yield after purification by recrystallization. Treatment of amide **227** with the aryl lithium generated from **239** gave aryl ketone **240** in 79% yield. Upon reaction under the same conditions used for the reduction of **229** and **235**, followed by hydrogenolysis, two compounds were isolated: **10** in 9% yield and *o*-benzylphenol **241** in 17% yield (~90% purity). The compound could be confidently assigned as the *C*(2")-benzyl substituted species as C(5")*H* and C(6")*H* display a ^{3}J coupling constant of 8.3 Hz to one another in the ^{1}H NMR spectrum. The presence of this species is consistent with debenzylation of **240** under the acidic reaction conditions and Friedel-Crafts reaction of the resultant phenol with the benzyl cation (Scheme 41).



Scheme 41 *Reagents and conditions*: (i) BnBr, K_2CO_3, Me_2CO, Δ, 16 h; (ii) **239**, BuLi, THF, –78 °C, 30 min then **227**, –78 °C, 1.5 h; (iii) $LiAlH_4$, THF, Δ, 16 h then Et_3SiH, TFA, rt, 16 h; (iv) Pd/C, H_2 (1 atm), CH_2O, MeOH, 24 h. [[a] further impure mixtures of **10** and **241** were obtained]

As the *O*-benzyl functionality was proving to be problematic the reaction sequence was repeated using a silyl protected aryl bromide **242**. Addition of the corresponding aryl lithium to amide **227** proceeded

in 88% yield giving aryl ketone **243**, which upon reduction gave phenol **244** in 50% yield (where *O*-desilylation has also occurred under the reaction conditions). Treatment of **244** under the hydrogenolysis/reductive alkylation conditions gave tetrahydroquinoline **10** in 57% yield (Scheme 42). Upon examination of the data for **10**, this compound was found to be identical to the two previous synthetic samples, but again does not match the isolation data for (–)-galipeine {$[\alpha]_D^{25}$ –26.2 (*c* 1.0 in $CHCl_3$); lit.[20] for a sample isolated from the natural source $[\alpha]_D$ –13.6; lit.[18] for a synthetic sample of **10** $[\alpha]_D^{24}$ –26.1 (*c* 0.44 in $CHCl_3$)}; although it is difficult to draw conclusions about the value of specific rotation for the naturally isolated compound as no solvent, concentration or temperature were recorded.



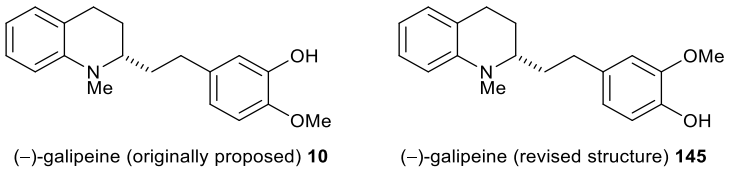
Scheme 42 *Reagents and conditions*: (i) TBDMSCl, imidazole, DMF, rt, 16 h; (ii) **242**, BuLi, THF, –78 °C, 30 min then **227**, –78 °C, 1.5 h; (iii) $LiAlH_4$, THF, Δ, 16 h then Et_3SiH, TFA, rt, 16 h; (iv) Pd/C, H_2 (1 atm), CH_2O, MeOH, 24 h.

The NMR data for all the Hancock alkaloids are extremely similar, with the only significant deviations being observable in the ^{13}C NMR shifts of the variable aryl ring (excluding obvious differences in side groups). The ^{13}C NMR shifts for *C*(1")–*C*(6") are displayed in Table 3 for tetrahydroquinoline **10**, both previous synthetic samples of **10** and naturally occurring (–)-galipeine. For (–)-galipeine the peaks at 120.9 and 134.0 ppm are >1 ppm out from any synthetic sample, moreover the assignments for the peaks that are very similar in carbon shift differ between the isolated sample and this study. For **10** *C*(2") = 114.6 ppm, *C*(5") = 110.7 ppm; for (–)-galipeine *C*(2") = 110.8 ppm, *C*(5") = 114.3 ppm. The assignment of the ^{13}C peaks done in this study is secure, being confirmed by HSQC and HMBC analysis, with the 4"-methoxy functionality being confirmed by 1D NOE NMR spectroscopy. Additionally, the

structure of **10** was confirmed by single crystal X-ray diffraction (see Appendix 1). The original isolation paper by Jacquemond-Collet *et al*. assigns the 4"-methoxy functionality based on HMBC interactions, namely: (1) $^{3}J_{C(4")–OMe}$, (2) $^{2}J_{C(4")–C(5")H}$ and (3) $^{2}J_{C(3")–C(2")H}$. It was proposed that the methoxy group has been incorrectly placed, and the interactions (2) and (3) are, in fact, ^{3}J HMBC interactions, namely $^{3}J_{C(3")–C(5")H}$ and (3) $^{3}J_{C(4")–C(2")H}$, leading to a new proposal of 3"-methoxy compound **145** as the true structure of (–)-galipeine (Figure 11).

^{13}C NMR shifts / ppm			
This study **10**	Ref 18 **10**	Ref 19 **10**	Ref 20 (–)-Galipeine
110.7	110.7	110.6	110.8
114.6	114.5	114.5	114.3
119.7	119.6	119.5	120.9
135.5	135.4	135.3	134.0
144.9	144.8	144.7	143.7
145.6	145.5	145.5	146.5

Table 3 Comparison of selected ^{13}C NMR data for **10** and (–)-galipeine.

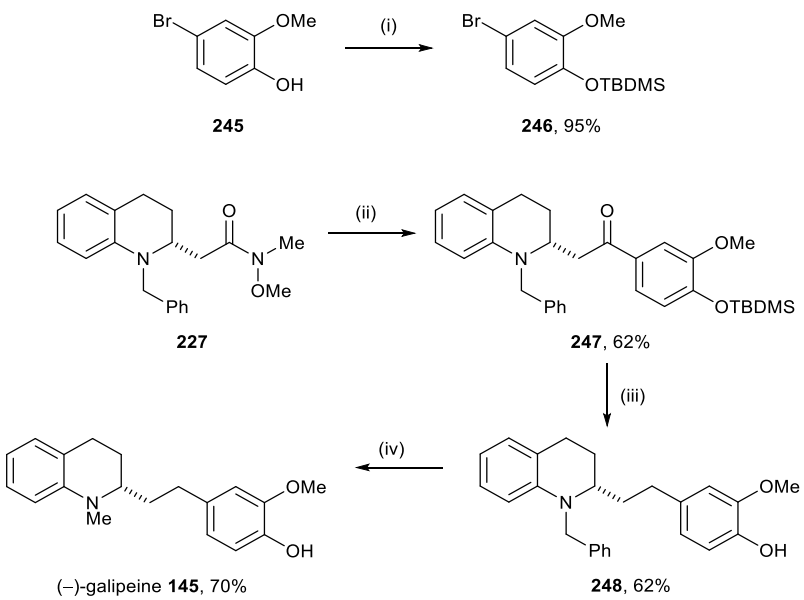


(–)-galipeine (originally proposed) **10** (–)-galipeine (revised structure) **145**

Figure 11 Newly proposed structure of (–)-galipeine.

To prove this assignment, a synthetic sample of **145** was prepared. Addition of the aryl lithium derived from aryl bromide **246** to Weinreb amide **227** gave ketone **247** in 62% yield after purification. Deoxygenation and concomitant *O*-desilylation, using the same conditions as for previous compounds, gave phenol **248** in 62% yield. Finally, hydrogenolysis/reductive alkylation revealed the target compound **145** in 70% yield (Scheme 43). The NMR data for this isomer were unambiguously fully assigned based on HSQC, HMBC and 1D NOE techniques and comparison with the natural product data [specifically, excellent agreement of ^{13}C NMR data for *C*(1")–*C*(6")] confirmed the structure of (–)-galipeine as the 3-methoxy regioisomer **145** {$[\alpha]_D^{25}$ –22.3 (*c* 1.0 in $CHCl_3$), –22.0 (*c* 0.2 in $CHCl_3$), –14.0 (*c* 1.0 in MeOH); lit.[20] for a sample isolated from the natural source $[\alpha]_D$ –13.6}. As there was no solvent, temperature or concentration reported for the specific rotation of the natural product it is difficult to compare values, however, a negative value for both samples may indicate that the natural compound is indeed the (*S*) configuration. This completed the first asymmetric synthesis of naturally occurring (–)-

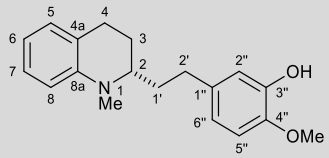
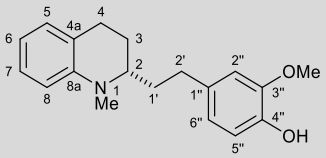
galipeine **145** in 13.3% overall yield over nine steps from commercially available 3-(2'-bromophenyl)propanoic acid **214**, confirming the stereochemical assignments of the synthetic precursors **225**–**227**, **247** and **248**.



Scheme 43 *Reagents and conditions*: (i) TBDMSCl, imidazole, DMF, rt, 16 h; (ii) **246**, BuLi, THF, –78 °C, 30 min then **227**, –78 °C, 1.5 h; (iii) $LiAlH_4$, THF, Δ, 16 h then Et_3SiH, TFA, rt, 16 h; (iv) Pd/C, H_2 (1 atm), CH_2O, MeOH, 24 h.

2.13.1 Comparison of ^{1}H and ^{13}C NMR data for (–)-galipeine

The following tables (4, 5) display the ^{1}H and ^{13}C NMR data for the Hancock alkaloid **145**, with comparison to literature data and data from naturally isolated sources. Where data was left unassigned in the original manuscript, assignment has been made here for the ease of comparison.

	^{1}H NMR shifts / ppm, multiplicity, *J* / Hz			
	10 		(–)-Galipeine **145** 	
Assignment	This work $CDCl_3$	Ref 18 $CDCl_3$	This work $CDCl_3$	Ref 20 Natural $CDCl_3$
C(2)*H*	3.24–3.30, m	3.23–3.39, m	3.26–3.33, m	3.26, m
C(3)H_2	1.84–1.99, m	1.86–2.04, m	1.86–2.00, m	1.92, m
C(4)H_A	2.59–2.72, m	2.60–2.79, m	2.62–2.73, m	2.68, m
C(4)H_B	2.84, ddd, 17.6, 11.7, 5.2	2.82–2.92, m	2.86, ddd, 17.5, 11.6, 6.1	2.82, m
C(5)*H*	6.98, d, 7.2	7.02, d, 7.2	6.99, d, 7.3	6.96, d, 7.3
C(6)*H*	6.59, td, 7.3, 1.0	6.63, t, 7.2	6.60, td, 7.3, 0.9	6.57, td, 7.3, 0.9
C(7)*H*	7.05–7.10, m	7.12, t, 8.0	7.07–7.12, m	7.06, t, 8.2
C(8)*H*	6.52, d, 8.1	6.57, d, 8.0	6.54, d, 8.1	6.51, d, 8.2
C(1')H_A	1.66–1.76, m	1.67–1.84, m	1.68–1.78, m	1.87, m
C(1')H_B	1.84–1.99, m	1.86–2.04, m	1.86–2.00, m	1.87, m

C(2')H_A	2.49, ddd, 13.9, 9.9, 6.6	2.46–2.60, m	2.52, ddd, 13.9, 10.2, 6.4	1.70, m[a]
C(2')H_B	2.59–2.72, m	2.60–2.79, m	2.62–2.73, m	1.70, m[a]
C(2")*H*	6.75–6.79, m	6.76–6.88, m	6.67–6.71, m	6.65, s
C(5")*H*	6.75–6.79, m	6.76–6.88, m	6.84, d, 8.5	6.80, d, 7.2
C(6")*H*	6.66, dd, 8.2, 2.1	6.70, dd, 8.2, 2.0	6.67–6.71, m	6.65, dd, 7.1, 1.9
N*Me*	2.90, s	2.94, s	2.92, s	2.89, s
O*Me*	3.87, s	3.91, s	3.88, s	3.85, s
O*H*	5.56, s	5.61, s	5.47, s	-

Table 4 Comparison of ^{1}H NMR data for **10** and (–)-galipeine **145**. [[a] These protons are assigned as benzylic protons in the original manuscript and we propose a mistake has been made in reporting the ppm values]

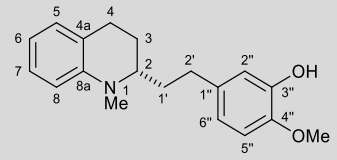
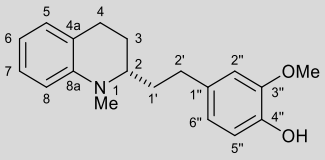
	^{13}C NMR shifts / ppm			
	10 		(–)-Galipeine **145** 	
Assignment	This work $CDCl_3$	Ref 18 $CDCl_3$	This work $CDCl_3$	Ref 20 Natural $CDCl_3$
C(2)	58.3	58.2	58.5	58.5
C(3)	24.5	24.4	24.5	24.4
C(4)	23.7	23.6	23.7	23.6
C(4a)	121.9	121.8	121.8	121.8
C(5)	128.8	128.8	128.8	128.8
C(6)	115.5	115.4	115.5	115.4
C(7)	127.2	127.1	127.2	127.2
C(8)	110.7	110.6	110.7	110.7
C(8a)	145.5	145.4	145.4	145.4
C(1')	33.0	32.9	33.3	33.2
C(2')	31.7	31.6	32.1	32.1
C(1")	135.5	135.4	134.0	134.0
C(2")	114.6	114.5	110.8	110.8
C(3")	145.6	145.5	146.5	146.5
C(4")	144.9	144.8	143.8	143.7
C(5")	110.7	110.7	114.3	114.3
C(6")	119.7	119.6	120.9	120.9
N*Me*	38.1	38.0	38.2	38.2
O*Me*	56.1	56.0	56.0	56.0

Table 5 Comparison of ^{13}C NMR data for **10** and (–)-galipeine **145**.

2.14 Conclusion

In conclusion, two different routes to the Hancock alkaloids have been investigated. Firstly, the synthesis of (–)-cuspareine **9** was completed employing a lithium amide conjugate addition reaction to access enantiopure β-amino ester **180**, then a benzyne mediated cyclisation reaction to give dihydroquinolinone **186** which upon reduction revealed the target alkaloid. Secondly a lithium amide conjugate addition reaction and Buchwald-Hartwig cyclisation was used to give tetrahydroquinoline **227**, a key intermediate in the divergent synthesis of three natural Hancock alkaloids and one unnatural isomer. Aryl lithium additions to **227**, followed by deoxygenation and protecting group manipulation led to the syntheses of (–)-cuspareine **9** and (–)-galipinine **11** in 27.1 and 25.3% overall yields, respectively, over nine steps. Comparison of data for (–)-galipeine with synthetic samples showed several differences. Synthesis of the reported structure shared these differences with the natural alkaloid and data analysis revealed a likely

origin for the discrepancy. Synthesis of the revised structure confirmed this reassignment, providing the first total synthesis of (–)-galipeine **145** in 13.3% overall yield over nine steps (Figure 12).

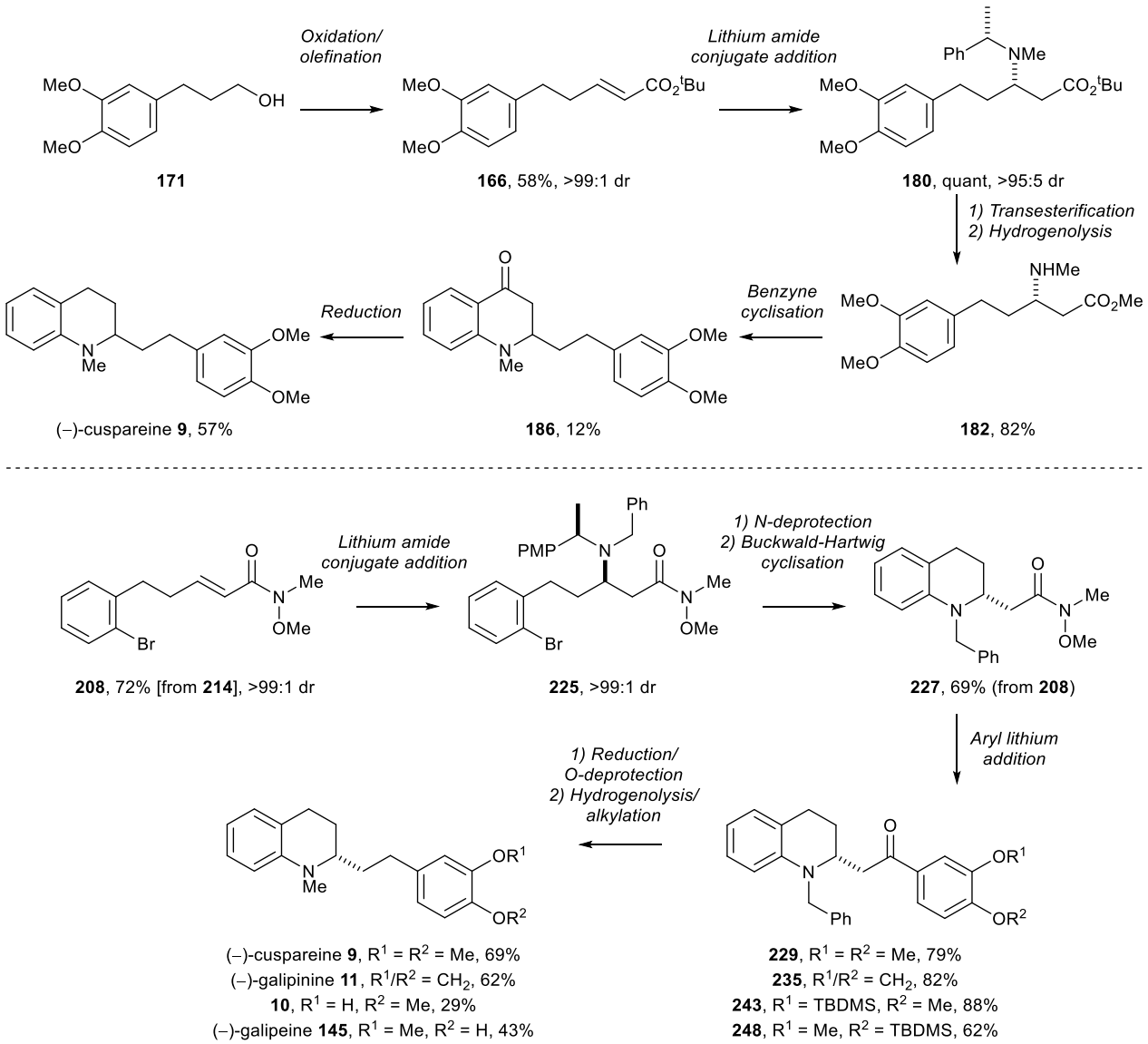


Figure 12 Summary of the asymmetric syntheses of **9**–**11** and **145**.

2.15 References and notes

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[17] We believe a mistake has been made in the reporting of the ^{13}C NMR shifts in the aryl units of (–)-cuspareine **9** and (–)-galipinine **11**, where data have been transposed; corrected values are displayed here.
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Chapter 3

Asymmetric Syntheses of Hydroxymethyl Substituted Azabicycles

3.1 Introduction

This chapter describes the asymmetric syntheses of four hydroxymethyl substituted [x.y.0]-azabicycles **30–33**, covering the four possible permutations of 5- and 6-membered rings: a quinolizidine **30**, two indolizidines **31** and **32**, and a pyrrolizidine **33**. This work aims to use the same methodology to synthesise all of the structures, such that the choice of ring size can be achieved simply through the use of homologous starting materials or reagents (Figure 13).

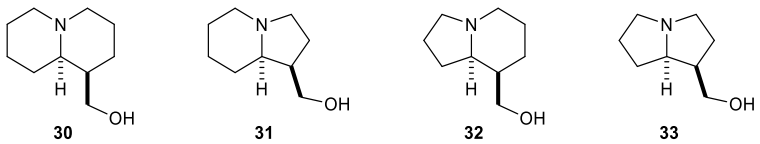


Figure 13 Azabicyclic alkaloids **30**–**33**.

3.2 Previous work

Preliminary work was previously conducted within the Davies group[1] towards the synthesis of azabicycles **252** (n = 1, 2; m = 1, 2). The strategy for the synthesis of the azabicyclic motifs **252** involved either: (1) alkylation of an enantiopure β-amino ester such as **250** (which is readily available from the diastereoselective conjugate addition of an enantiopure lithium amide reagent to an α,β-unsaturated ester **249**),[2] followed by a double ring-closure of **251**, in which both benzylic *N*-protecting groups are lost during the one-pot tandem cyclisation process (i.e., Route A, Figure 14); or (2) sequential ring-closure/concomitant *N*-debenzylation of **250** to give pyrrolidine (n = 1) or piperidine (n = 2) **253**, followed by alkylation of these azacyclic templates **253** and ring-closure/concomitant *N*-debenzylation of **254** to give the corresponding azabicyclic scaffold **252** (i.e., Route B, Figure 14).

Initially Route A was investigated, focussing on the formation of α-alkyl-β-amino esters **251**. Two methods were proposed, starting from α,β-unsaturated esters **249** (n = 1, 2), employing either a "tandem" or "stepwise" lithium amide conjugate addition/α-alkylation. The "tandem" reaction sequence involves the lithium amide conjugate addition to α,β-unsaturated esters **249** to produce intermediate lithium (*Z*)-β-amino enolates,[3] followed by reaction with a suitable electrophile, to give α-alkyl-β-amino esters **251**. The "stepwise" approach would involve a lithium amide conjugate addition to the α,β-unsaturated esters **249** followed by protonation of the intermediate lithium (*Z*)-β-amino enolates to give **250**. Subsequent deprotonation of **250** with a suitable base generates the corresponding lithium (*E*)-β-amino enolates,[3] which upon treatment with an electrophile would undergo α-alkylation to give α-alkyl-β-amino esters **251** (Figure 14).

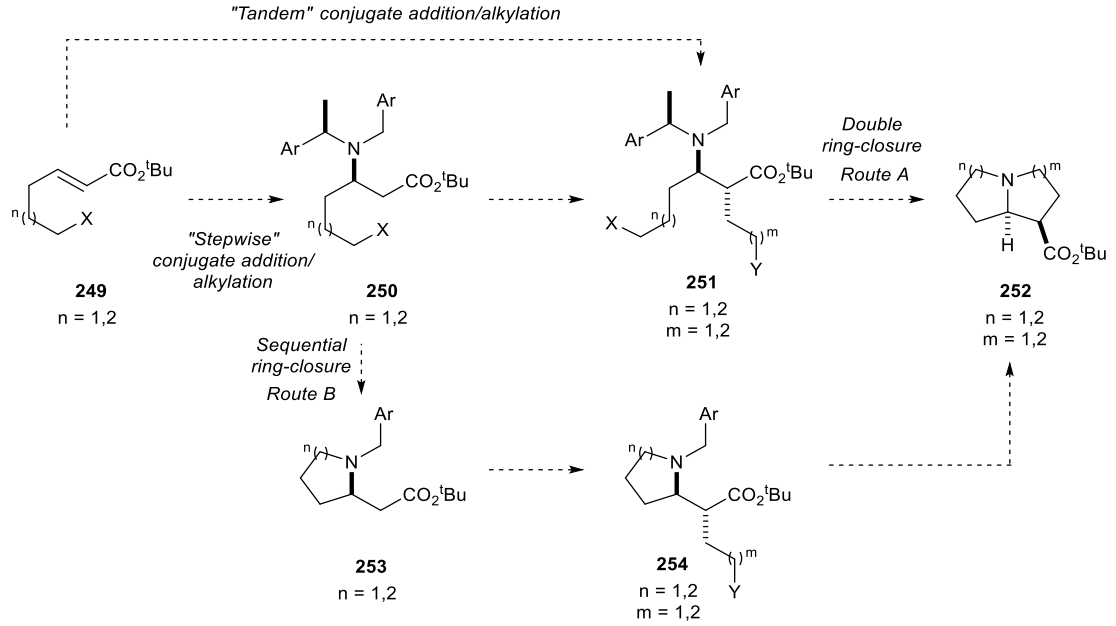
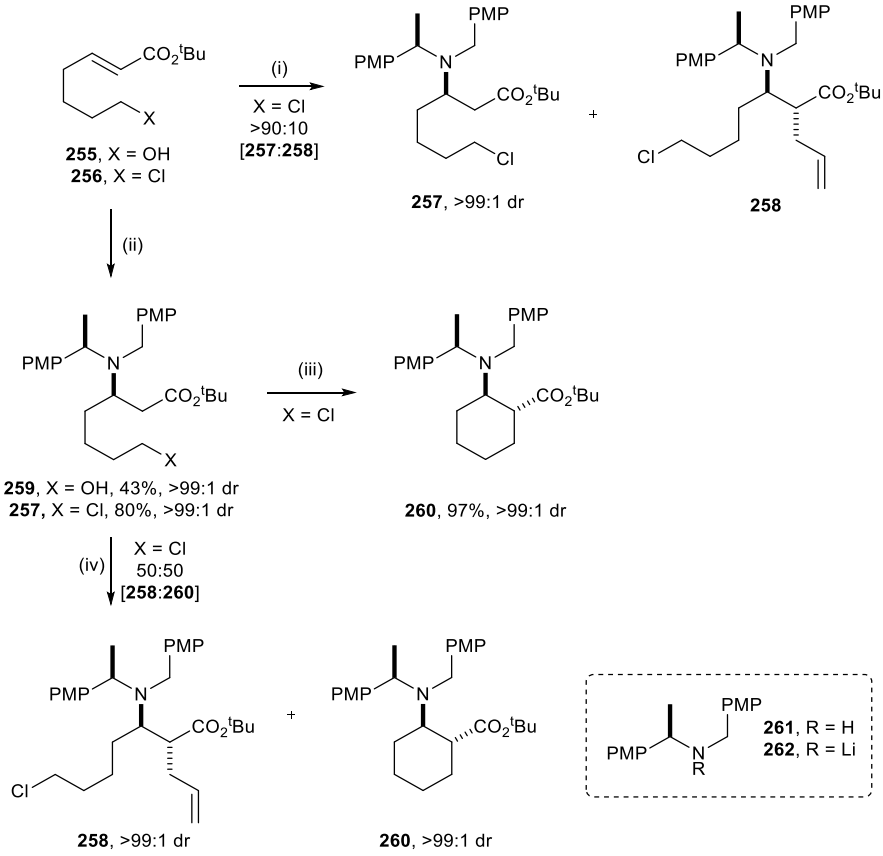


Figure 14 Two proposed synthetic routes to azabicycles **252**.

It was shown that reaction of the lithium amide **262** (derived from deprotonation of enantiopure amine **261** with BuLi) with ζ-hydroxy-α,β-unsaturated ester **255** (X = OH) and ζ-chloro-α,β-unsaturated ester **256** (X = Cl) gave the corresponding β-amino ester products **259** (X = OH) and **257** (X = Cl), respectively, in 43 and 80% yield as single diastereoisomers (>99:1 dr) in each case. The specific choice of the aryl substituents in this synthesis was to aid with cyclisation/*N*-deprotection in subsequent steps. As these conjugate additions were completely diastereoselective any erosion in dr upon alkylation in the "tandem" approach would be due to mixtures of *C*(2)-epimers being formed. Attempted "tandem" conjugate addition and allylation was, however, unsuccessful for both substrates **255** and **256**, with a

complex mixture being produced for the reaction with ζ-alcohol **255**, and less than 10% of the anticipated product being observed upon reaction of ζ-chloride **256**, with the majority of the mixture being **257**, the product of enolate protonation (Scheme 44). For the "stepwise" approach, β-amino ester **257** was deprotonated with LiHMDS and the resultant enolate was treated with either allyl bromide or $Br(CH_2)_3OTBDMS$. For the allylation procedure a 50:50 mixture of the α-allyl product **258** and cyclic β-amino ester **260** was formed (from the intramolecular reaction of the intermediate enolate with the pendant ζ-chloro-functionality) and in the attempted alkylation with $Br(CH_2)_3OTBDMS$, only **260** was produced, in 97% yield (Scheme 44).

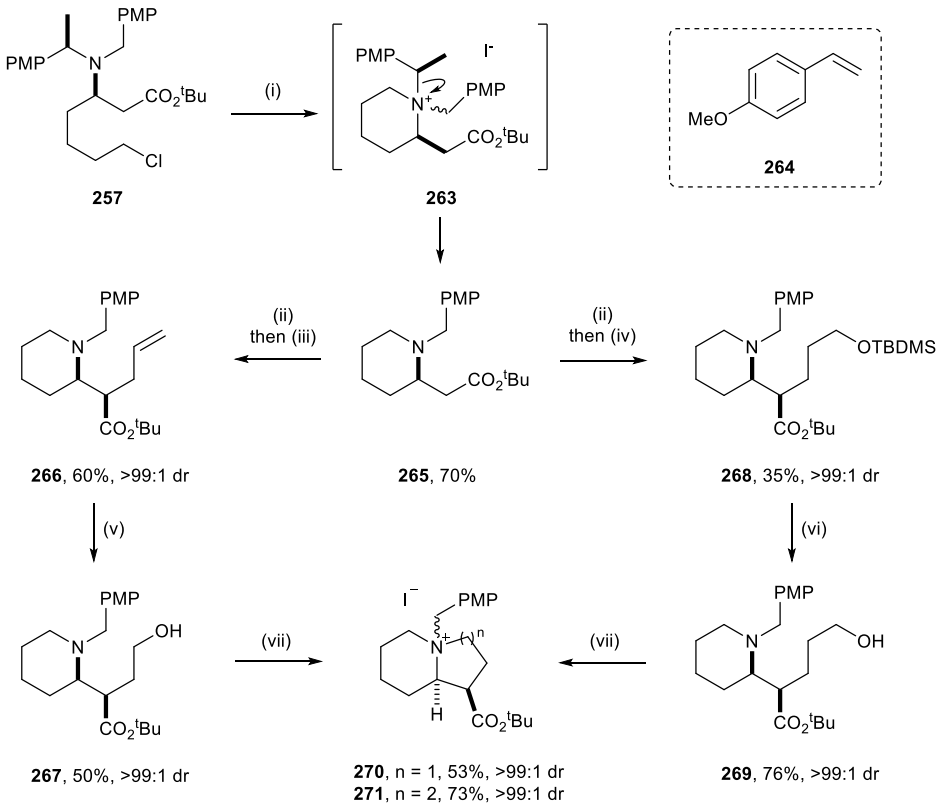


Scheme 44 *Reagents and conditions*: (i) **262** (1.6 or 2.6 equiv), THF, −78 °C, 2 h then allyl bromide, −78 °C to rt, 16 h; (ii) **262** (1.6 or 2.6 equiv), THF, −78 °C, 2 h then NH_4Cl (satd aq), −78 °C to rt, 15 min; (iii) LiHMDS, THF, −78 °C, 1 h then $Br(CH_2)_3OTBDMS$, −78 °C to rt, 16 h; (iv) LiHMDS, THF, −78 °C, 1 h then allyl bromide, −78 °C to rt, 16 h.

As neither the "stepwise" nor "tandem" routes were looking promising, it was decided that Route A would not be viable and so attention was turned to Route B.

Route B was evaluated, starting from the β-amino-ω-chloro ester **257**. Treatment of **257** with NaI promoted Finkelstein reaction and cyclisation to give piperidine **265** in 70% yield. This reaction outcome is consistent with cyclisation to give the intermediate ammonium ion **263**, followed by fragmentation,

with the selective loss of the α-methyl-*p*-methoxybenzyl cation in an E_1-type process to give **265**, and *p*-methoxystyrene **264** (the choice of *p*-methoxy functionality in the *N*-protecting groups was to facilitate this deprotection). Now, treatment of **265** with LiHMDS followed by either allyl bromide or $Br(CH_2)_3OTBDMS$ resulted in alkylated products **266** and **268**, with **266** being isolated in 60% yield, and **268** being isolated in a more modest 35% yield.[4] Treatment of olefin **266** under ozonolysis conditions, or treatment of **268** with TBAF gave the corresponding alcohols **267** and **269**, respectively. When either of these alcohols was subjected to Appel conditions, cyclisation was observed to give bicyclic ammonium salts **270** (n = 1) and **271** (n = 2) in 53 and 73% yield, respectively (Scheme 45). In neither case was fragmentation observed (with loss of the *p*-methoxybenzyl cation) to give the corresponding bicyclic target, and only quaternary ammonium ions were observed.



Scheme 45 *Reagents and conditions*: (i) NaI, MeCN, Δ, 16 h; (ii) LiHMDS, THF, –78 °C, 1 h; (iii) allyl bromide, –78 °C to rt, 16 h; (iv) $Br(CH_2)_3OTBDMS$, –78 °C to rt, 16 h; (v) HCl (2.0 M in Et_2O), Et_2O, 15 min then O_3, CH_2Cl_2, –78 °C then $NaBH_4$, –78 °C to rt, 16 h; (vi) TBAF, THF, rt, 12 h; (vii) I_2, imidazole, PPh_3, MeCN, 80 °C, 16 h.

Various attempts to remove the *N*-*p*-methoxybenzyl group, such as resubjection to the Appel conditions, reductive conditions using Et_3SiH or $LiAlH_4$, or treatment with Na and NH_3 were all unsuccessful. This showed that this cyclisation methodology had potential to produce bicyclic products, but further

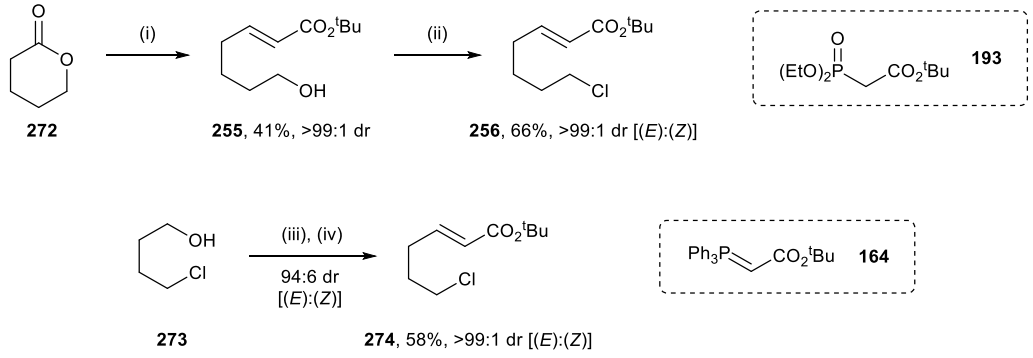
optimisation was needed to affect the final *N*-deprotection step and apply the optimised protocols in the synthesis of all possible ring systems.

3.3 Chapter aim

Given the previous efforts towards the synthesis of the bicyclic amines **30–33**, it was decided that using the established set of reactions to from monocyclic amines **265** and **277** would be the best route to pursue (i.e. Route B). As it had also been shown that the diastereoselective alkylation of these compounds was possible, this route should be viable for the asymmetric synthesis of **30–33** and so optimisation of the early work, and completion of the second cyclisation/*N*-deprotection sequence was undertaken.

3.4 Preparation of enantiopure pyrrolidine and piperidine scaffolds

The requisite β-amino esters were prepared according to the established procedures.[1] This synthesis started with a one-pot DIBAL-H/Wadsworth-Emmons procedure on commercially available δ-valerolactone **272** to produce α,β-unsaturated ester **255**[5] in 41% yield as a single diastereoisomer (>99:1 dr [(*E*):(*Z*)]). An Appel reaction was then employed to afford chloride **256** in 66% yield from **255**. For the synthesis of the homologous α,β-unsaturated ester **274**, previous work[1] had shown that the one-pot DIBAL-H/Wadsworth-Emmons procedure applied to γ-butyrolactone resulted in poor yield (14%), and so was not suitable for efficient production of material. It was therefore decided to access ε-chloro ester **274** from an oxidation/Wittig procedure from commercially available 4-chlorobutan-1-ol **273**, which gave **274** in 94:6 dr [(*E*):(*Z*)]; after purification by flash column chromatography **274** was isolated in 58% yield and >99:1 dr [(*E*):(*Z*)] (Scheme 46).

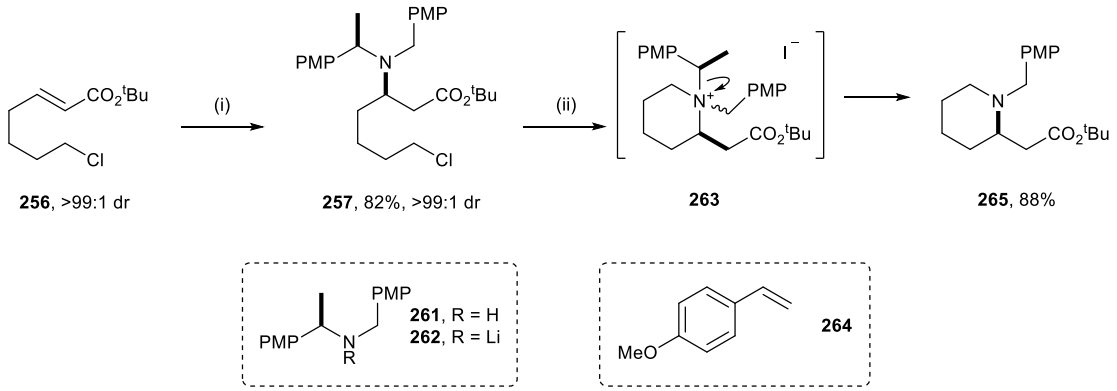


272 **255**, 41%, >99:1 dr **256**, 66%, >99:1 dr [(*E*):(*Z*)]

273 **274**, 58%, >99:1 dr [(*E*):(*Z*)]

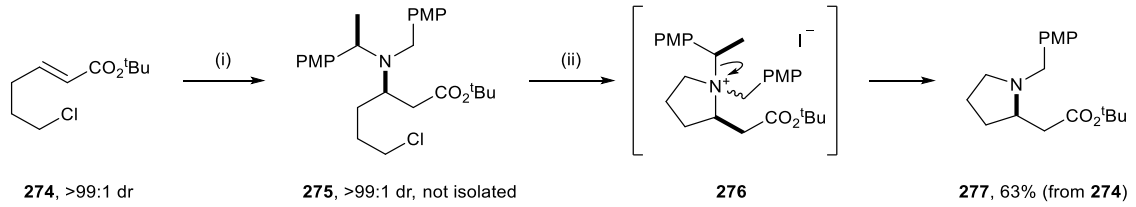
Scheme 46 *Reagents and conditions*: (i) **193**, BuLi, DIBAL-H, THF, –78 °C to rt, 16 h; (ii) CCl_4, PPh_3, Et_3N, MeCN, Δ, 24 h; (iii) IBX, EtOAc, 70 °C, 3 h; (iv) **164**, EtOAc, rt, 16 h.

With **256** in hand, the conjugate addition of lithium amide **262** was performed, and gave **257** in 82% yield and >99:1 dr. Finkelstein reaction of **257**, according to the established procedure,[1] was then used to form piperidine **265** in 88% yield, with *p*-methoxystyrene **264** also being isolated in 53% yield, consistent with the initial formation of ammonium intermediate **263** and selective loss of the α-methyl-*p*-methoxybenzyl cation in an E_1-type process (Scheme 47).



Scheme 47 *Reagents and conditions*: (i) **261**, BuLi, THF, –78 °C, 2 h; (ii) NaI, MeCN, Δ, 24 h.

The analogous shorter α,β-unsaturated ester **274** underwent diastereoselective lithium amide conjugate addition with **262**, to afford **275** in >99:1 dr. Subsequent Finkelstein reaction of **275** gave pyrrolidine **277** in 63% yield over the 2 steps from **274** (Scheme 48).

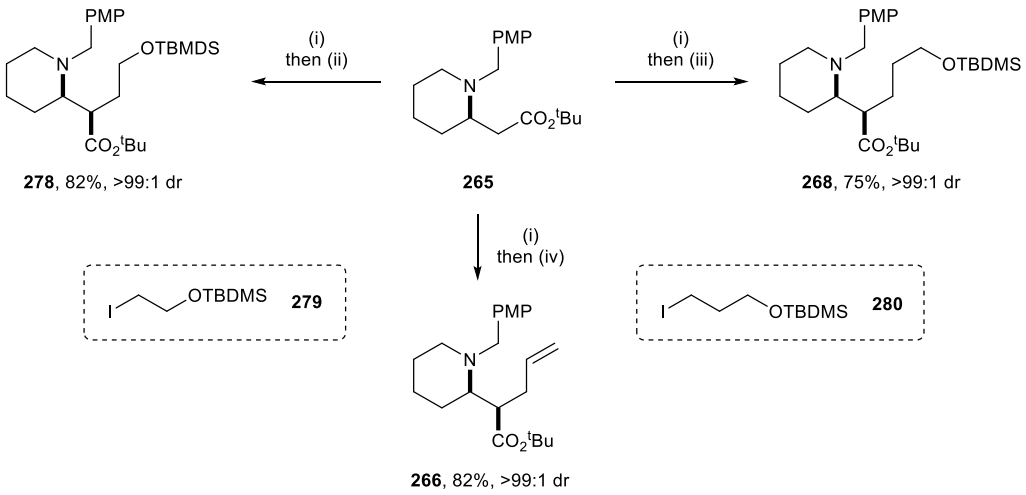


Scheme 48 *Reagents and conditions*: (i) **261**, BuLi, THF, –78 °C, 2 h; (ii) NaI, MeCN, Δ, 24 h.

3.5 α-Alkylation and the elaboration to cyclisation precursors

Alkylation of **265**, upon treatment with LiHMDS and a variety of electrophiles, was used to install either a masked 2-hydroxyethyl (in the case of **278** and **266**) or 3-hydroxypropyl (in the case of **268**) unit in 75–82% yield. All of these alkylations proceeded with high diastereoselectivity, with only a single diastereoisomer (>99:1 dr) being observed in each case. Initially, the relative configurations of the alkylation products were tentatively assigned by analogy to previous alkylations on similar systems[6] and

were subsequently unambiguously assigned by chemical correlation upon elaboration to the target azabicyclic species (Scheme 49).



Scheme 49 *Reagents and conditions*: (i) LiHMDS, THF, –78 °C, 1 h; (ii) **279**, –78 °C to rt, 16 h; (iii) **280**, –78 °C to rt, 16 h; (iv) allyl bromide, –78 °C to rt, 16 h.

One plausible explanation for the origin of the high diastereoselectivity of these alkylations is shown below (Figure 15). Deprotonation of *tert*-butyl ester **265** with LiHMDS at –78 °C would be predicted to lead to the predominant formation of a lithium (*E*)-β-amino enolate (Ireland model),[7] for which **281** is presumably the low energy conformer due to the minimisation of 1,3-allylic strain. The diastereofacial selectivity of the alkylation would then be determined by the relative steric bulk of the two β-substituents over the *Re* and *Si* faces of *C*(2). As the system is constrained within a ring system, *C*(4) is held away from the *Re* face of the enolate, resulting in very little steric crowding. The *Si* face, however, is likely to be sterically blocked by the equatorial R substituent (i.e. *p*-methoxybenzyl group). This results in a significant difference in steric bulk across the two faces of the enolate, with preference for an electrophile approaching from the *Re* face at *C*(2), leading to the observed products **266**, **268** and **278**.[8]

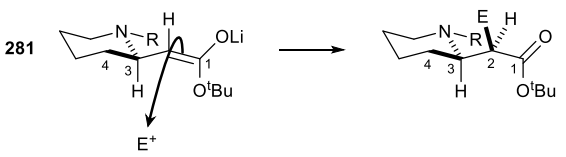
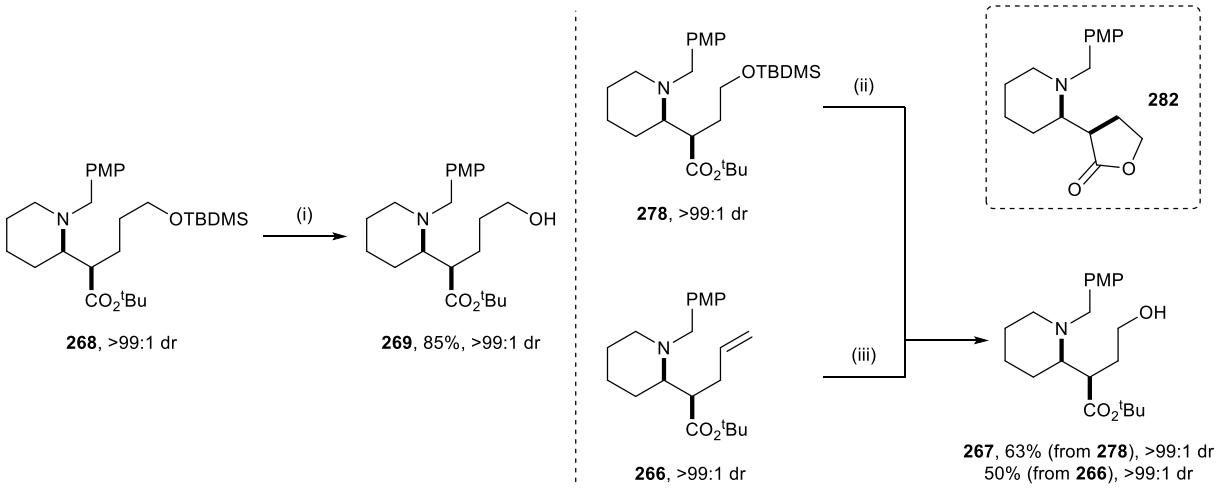


Figure 15 Potential origin of alkylation selectivity. [R = CH_2PMP, E^+ = electrophile].

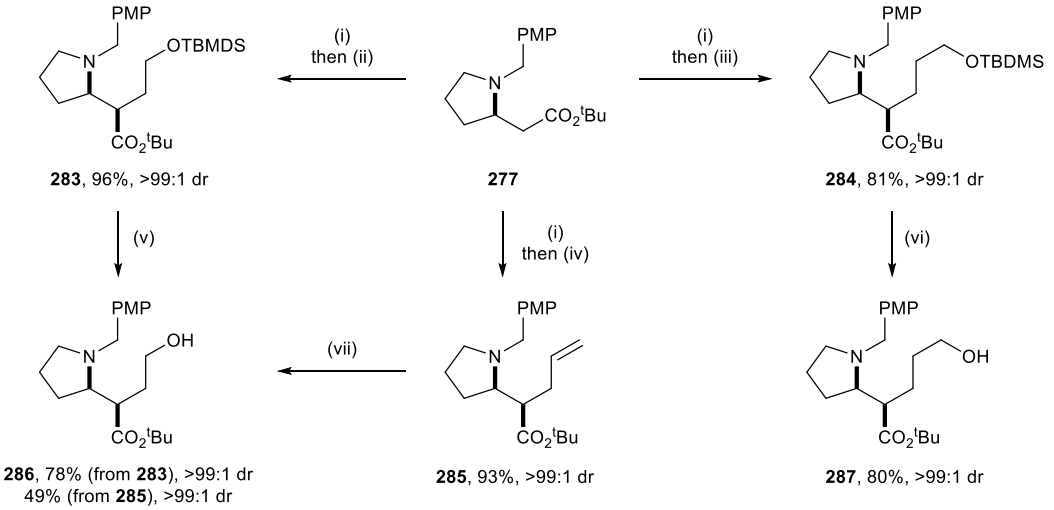
To unmask the alcohol functionality within **268**, TBAF was used to remove the silyl group to give **269** in 85% yield. However, when these conditions were applied to the *O*-deprotection of **278**, only the known lactone **282**[1] was observed. However, *O*-desilylation of **278** was achieved with catalytic PPTS in a

mixture of CH_2Cl_2 and MeOH, which gave **267** in 63% yield but due to the long reaction time required was not considered to be synthetically viable. However, **267** could also be accessed from the ozonolysis of the terminal olefinic unit within **266**: this was achieved by first protecting the amine as the corresponding HCl salt, before treating the reaction mixture with ozone, followed by a reductive work-up using $NaBH_4$ to produce **267** in 50% yield (Scheme 50).



Scheme 50 *Reagents and conditions*: (i) TBAF, THF, rt, 4 h; (ii) PPTS, CH_2Cl_2/MeOH (3:1 v/v), 50 °C, 7 days; (iii) HCl, Et_2O, rt, 15 min then O_3, CH_2Cl_2, –78 °C then $NaBH_4$, –78 °C to rt, 16 h.

As with the piperidine series, pyrrolidine **277** underwent smooth α-alkylation with a variety of electrophiles: alkylation of **277** with iodide **280** led to the installation of the masked 3-hydroxypropyl unit within **284** in 81% yield and as a single diastereoisomer (>99:1 dr). Similarly, allylation of **277** or alkylation of **277** with iodide **279** produced the masked 2-hydroxyethyl functionalities within **285** and **283** in 93 and 96% yield, respectively, as single diastereoisomers (>99:1 dr) in each case. δ-Hydroxy ester **287** could be accessed through the TBAF *O*-deprotection of silyl ether **284** in 80% yield, whereas γ-hydroxy ester **286** was available either through ozonolysis of **285** in 49% yield (overall yield of 46% from pyrrolidine **277**), or *via O*-silyl deprotection of **283** with PPTS which gave **286** in 78% yield (overall yield of 75% from **277**) (Scheme 51).

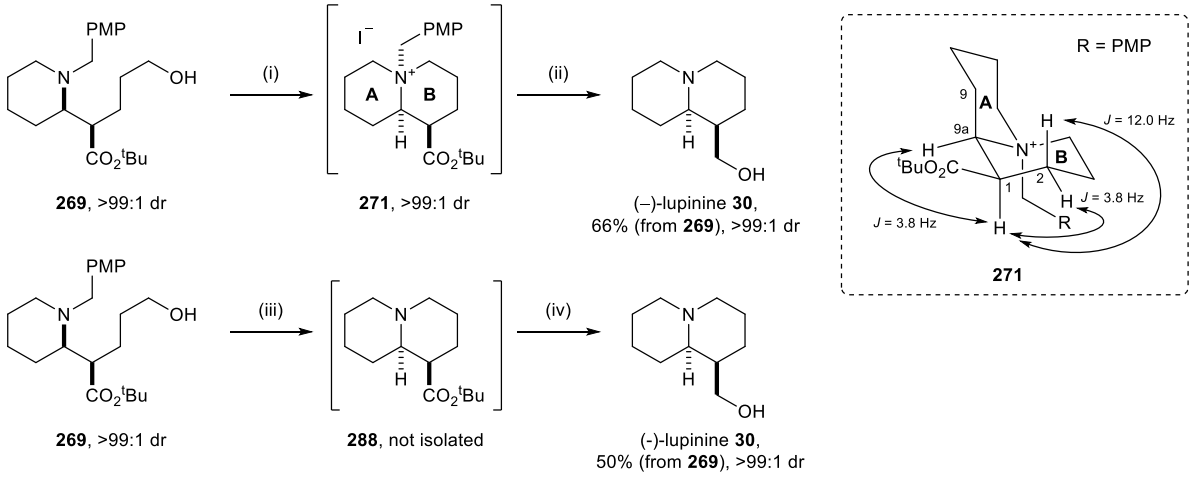


Scheme 51 *Reagents and conditions*: (i) LiHMDS, THF, –78 °C, 1 h; (ii) **279**, –78 °C to rt, 16 h; (iii) **280**, –78 °C to rt, 16 h; (iv) allyl bromide, –78 °C to rt, 16 h; (v) PPTS, CH_2Cl_2/MeOH (3:1 v/v), 50 °C, 10 days; (vi) TBAF, THF, rt, 4 h; (vii) HCl, Et_2O, rt, 15 min then O_3, CH_2Cl_2, –78 °C then $NaBH_4$, –78 °C to rt, 16 h.

3.6 Elaboration to azabicyclic alkaloids

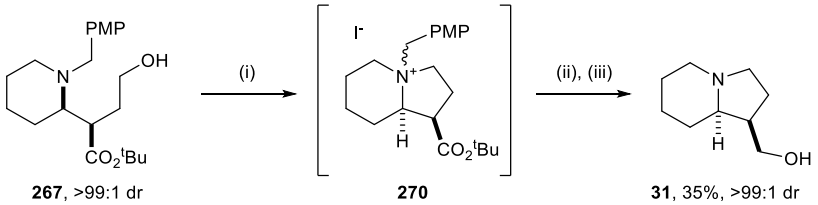
With alcohol **269** in hand, the second cyclisation was attempted. As observed previously, treatment of **269** with I_2, imidazole and polymer-supported PPh_3 led, initially, to quaternary ammonium species **271**. The relative configuration at the nitrogen atom within **271** was tentatively assigned by ^{1}H NMR ^3J coupling constant analysis: the ^{1}H NMR ^3J coupling constants of $^3J_{1,2}$ = 12.0, 3.8 Hz and $^3J_{1,9a}$ = 3.8 Hz indicate an axial proton at *C*(1) with respect to ring **B** and this, along with the relative configuration between *C*(1) and *C*(9a), places the *C*(9) substituent in an axial position with respect to ring **B**. This indicates that rings **A** and **B** define a *cis*-decalin type structure and hence allow assignment of the configuration at the *N* atom; it follows that **271** is the preferred conformation in solution. However, subjection to longer reaction times under the Appel conditions resulted in *N*-deprotection, furnishing amine **288**, which could be treated with $LiAlH_4$ to reduce the ester functionality, producing (–)-lupinine **30** in 50% yield as a single diastereoisomer (>99:1 dr). It was also possible to treat the intermediate ammonium **271** with $LiAlH_4$ which both reduced the ester and aided in removal of the *p*-methoxybenzyl group, producing (–)-lupinine **30** in 66% yield (Scheme 52). Although the exact nature of this *N*-deprotection was not determined, it is plausible that this proceeded *via* a direct S_N2 attack of hydride at the benzylic site; or purely that the benzylic cation was quenched by hydride, driving the equilibrium of the dissociation forward. Data for (–)-lupinine **30** were in agreement with literature vaules[9,10] $\{[\alpha]_D^{20}$

–12.0 (*c* 0.4 in EtOH); lit.[11] $[\alpha]_D$ –18.3 (*c* 0.27 in EtOH); lit.[9] for *ent*-**30**: $[\alpha]_D^{30}$ +12.7 (*c* 0.35 in EtOH)}. Overall, the total synthesis of (–)-lupinine **30** was completed in 8% yield over 8 steps from commercially available starting materials.



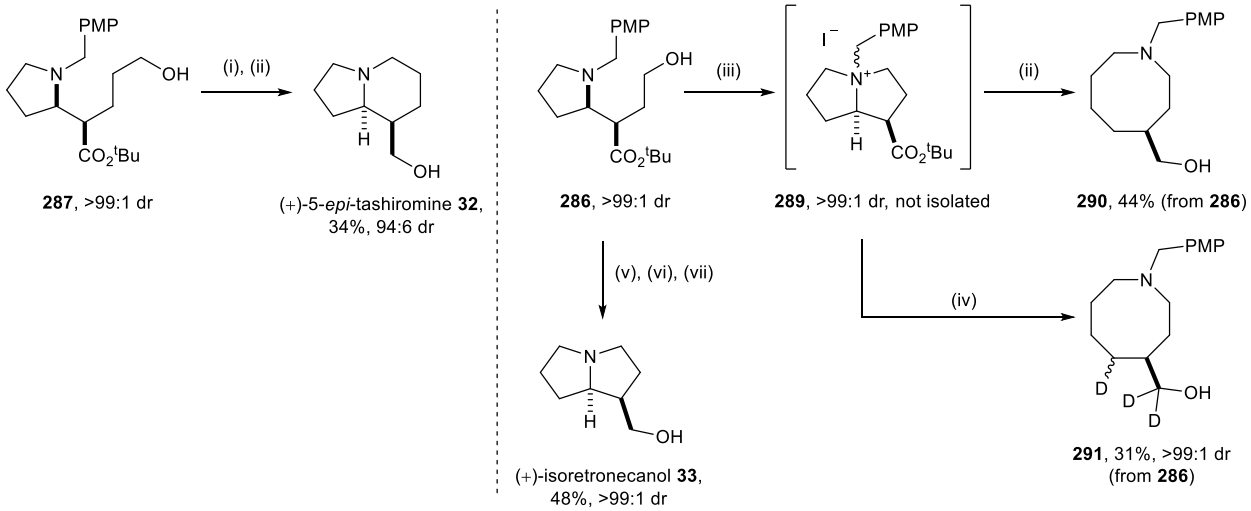
Scheme 52 *Reagents and conditions*: (i) I_2, imidazole, polymer-supported PPh_3, PhMe/MeCN (4:1 v/v), 65 °C, 16 h; (ii) $LiAlH_4$, THF, Δ, 48 h; (iii) I_2, imidazole, polymer-supported PPh_3, PhMe/MeCN (4:1 v/v), 65 °C, 60 h; (iv) $LiAlH_4$, THF, Δ, 16 h.

Initial attempts at the second cyclisation on γ-hydroxy ester **267** resulted in negligible product formation which was attributed to very slow *N*-debenzylation of the intermediate ammonium **270** and, unlike previously, direct reduction of **270** with $LiAlH_4$ was not successful, returning a complex mixture including *N*-benzyl substituted products. For this reason, an additional hydrogenolytic step was added, after cyclisation, to effect *N*-deprotection of **270** before the final ester reduction step upon treatment with $LiAlH_4$. Employing this three-step protocol provided (*R*,*R*)-1-(hydroxymethyl)octahydroindolizine **31** in 35% yield as a single compound (>99:1 dr) (Scheme 53), and completed the synthesis in 3% over 9 steps from commercially available starting materials. Data for (*R*,*R*)-1-(hydroxymethyl)octahydroindolizine **31** were in good agreement with literature values[6,12] {$[\alpha]_D^{20}$ –37.5 (*c* 0.1 in EtOH); lit.[6] $[\alpha]_D^{23}$ –35.8 (*c* 0.5 in EtOH)}.



Scheme 53 *Reagents and conditions*: (i) I_2, imidazole, polymer-supported PPh_3, PhMe/MeCN (4:1 v/v), rt, 16 h; (ii) $Pd(OH)_2/C$, H_2 (5 atm), MeOH, rt, 4 days; (iii) $LiAlH_4$, THF, Δ, 48 h.

Employing the same end-game to **287** provided (+)-5-*epi*-tashiromine **32** in 94:6 dr (Scheme 54), completing the asymmetric synthesis in 8% yield over 8 steps. A similar approach to the synthesis of **33**, however, gave an unexpected result. Treatment of quaternary ammonium species **289** with $LiAlH_4$ resulted in ring-opening of the pyrrolizidine core to give azocane **290** in 44% yield. Repeating this procedure, but with $LiAlD_4$ as the reducing agent, resulted in the formation of **291**, which was isolated in 31% yield and >99:1 dr. One plausible mechanism for this process could be an S_N2-type attack of deuteride at *C*(7a), opening the bicyclic structure; such a stereospecific mechanism is consistent with the formation of **291** as a single diastereoisomer. This ring-expansion pathway could be circumvented by removal of the *p*-methoxybenzyl group, by hydrogenolysis of the intermediate ammonium **289** prior to treatment with $LiAlH_4$. This three-step procedure afforded (+)-isoretronecanol **33** in 48% yield and as a single diastereoisomer (>99:1 dr) (Scheme 54). This concluded the asymmetric synthesis of (+)-isoretronecanol **33** in 13% over 9 steps from commercially available starting materials. Data for both **32** and **33** were in agreement with literature values; for (+)-5-*epi*-tashiromine **32**[13] {$[\alpha]_D^{20}$ +2.3 (*c* 0.4 in EtOH); lit.[14] $[\alpha]_D^{20}$ +1.1 (in EtOH); lit.[15] for *ent*-**32** $[\alpha]_D$ –0.96 (*c* 0.31 in EtOH); for **32**·HCl $[\alpha]_D^{20}$ +19.6 (*c* 0.3 in EtOH); lit.[16] for **32**·HCl $[\alpha]_D^{20}$ +26.0 (*c* 0.5 in EtOH)}; for (+)-isoretronecanol **33**[17] {$[\alpha]_D^{20}$ +58.3 (*c* 0.6 in EtOH); lit.[18] $[\alpha]_D^{26}$ +55 (*c* 0.055 in EtOH); lit.[19] for *ent*-**33** $[\alpha]_D^{20}$ –65.7 (*c* 1.88 in EtOH)}.



Scheme 54 *Reagents and conditions*: (i) I_2, imidazole, polymer-supported PPh_3, PhMe/MeCN (4:1 v/v), 65 °C, 36 h; (ii) $LiAlH_4$, THF, Δ, 60 h; (iii) I_2 , imidazole, polymer-supported PPh_3, PhMe/MeCN (4:1 v/v), rt, 16 h then 65 °C, 60 h; (iv) $LiAlD_4$, THF, Δ, 60 h; (v) I_2, imidazole, polymer-supported PPh_3, PhMe/MeCN (4:1 v/v), rt, 16 h; (vi) $Pd(OH)_2/C$, H_2 (5 atm), MeOH, rt, 6 days; (vii) $LiAlH_4$, THF, Δ, 16 h.

3.7 Comparison of ^{1}H and ^{13}C NMR data for 30–33

The spectroscopic data and specific rotations for **30**–**33** were in good agreement with literature values, thereby confirming the assigned configuration of all synthetic precursors **257**, **265**–**269**, **275**, **277**, **278** and **283**–**287**. The ^{1}H and ^{13}C NMR data for **30**–**33** are displayed in Tables 6–13 with comparisons with literature values.

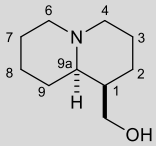
	^{1}H NMR shifts / ppm, multiplicity, *J* / Hz				
	(–)-Lupinine **30** 				
Assignment	This work C_6D_6	Ref 10 C_6D_6	Assignment	This work C_6D_6	Ref 10 C_6D_6
C(1)*H*	1.15–1.25, m	1.24, br s	C(7)H_A	1.25–1.44, m	1.34, dsext, 13, 3
C(2)H_A	1.25–1.44, m	1.36, m	C(7)H_B	1.25–1.44, m	1.42, qt, 12.8, 3.6
C(2)H_B	1.63–1.80, m	1.79, m	C(8)H_A	0.94–1.06, m	1.05, qt, 12.9, 3.7
C(3)H_A	1.25–1.44, m	1.36, m	C(8)H_B	1.49–1.58, m	1.58, m
C(3)H_B	2.23–2.37, m	2.35, tdt, 14.5, 12.8, 4.4	C(9)H_A	1.15–1.25, m	1.26, dquin, 12.8, 3
C(4)H_A	1.63–1.80, m	1.76, ddd, 12.9, 11.2, 3.3	C(9)H_B	1.63–1.80, m	1.73, tdd, 12.8, 11.7, 3.8
C(4)H_B	2.44–2.56, m	2.58, ddt, 11.2, 4.4, 1.9	C(9a)*H*	1.63–1.80, m	1.80, dt, 11, 3
C(6)H_A	1.49–1.58, m	1.57, td, 12, 3	CH_AOH	3.75, app d, 10.7	3.80, ddd, 10.8, 1.9, 0.6
C(6)H_B	2.44–2.56, m	2.52, dddd, 11.4, 3.6, 2.7, 1.9	CH_BOH	4.18, dd, 10.7, 4.8	4.22, ddd, 10.8, 4.9, 1.6

Table 6 Comparison of ^{1}H NMR data for (–)-lupinine **30**.

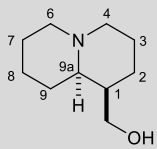
	^{13}C NMR shifts / ppm	
	(–)-Lupinine **30** 	
Assignment	This work C_6D_6	Ref 10 C_6D_6
C(1)	38.9	38.8
C(2)	31.6	31.6
C(3)	23.3	23.2
C(4)	57.4	57.4
C(6)	57.3	57.3
C(7)	25.9	25.9
C(8)	25.0	25.0
C(9)	29.9	30.0
C(9a)	65.2	65.2
*C*OH	65.7	65.6

Table 7 Comparison of ^{13}C NMR data for (–)-lupinine **30**.

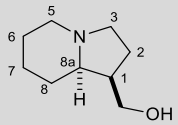
	^{1}H NMR shifts / ppm, multiplicity, *J* / Hz				
	(*R*,*R*)-1-(hydroxymethyl)octahydroindolizine **31** 				
Assignment	This work $CDCl_3$	Ref 12 $CDCl_3$	Assignment	This work $CDCl_3$	Ref 12 $CDCl_3$
C(1)*H*	2.00–2.12, m	0.95–2.55, m	C(6)H_B	1.59–1.64, m	0.95–2.55, m
C(2)H_A	1.76–1.87, m	0.95–2.55, m	C(7)H_A	1.17–1.22, m	0.95–2.55, m
C(2)H_B	1.91–2.00, m	0.95–2.55, m	C(7)H_B	1.76–1.87, m	0.95–2.55, m
C(3)H_A	2.00–2.12, m	0.95–2.55, m	C(8)H_A	1.42–1.57, m	0.95–2.55, m
C(3)H_B	3.13, app dd, 9.0, 2.8	2.95–3.30, m	C(8)H_B	1.76–1.87, m	0.95–2.55, m
C(5)H_A	1.76–1.87, m	0.95–2.55, m	C(8a)*H*	2.00–2.12, m	0.95–2.55, m
C(5)H_B	3.06–3.11, m	2.95–3.30, m	CH_AOH	3.46, dd, 10.2, 2.8	3.33–3.65, m
C(6)H_A	1.42–1.57, m	0.95–2.55, m	CH_BOH	3.85, dd, 10.2, 2.4	3.33–3.65, m

Table 8 Comparison of ^{1}H NMR data for (*R*,*R*)-1-(hydroxymethyl)octahydroindolizine **31**.

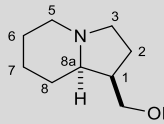
	^{13}C NMR shifts / ppm	
	(*R*,*R*)-1-(hydroxymethyl) octahydroindolizine **31** 	
Assignment	This work $CDCl_3$	Ref 12 $CDCl_3$
C(1)	41.1	41.2
C(2)	25.5	25.6
C(3)	54.1	53.8
C(5)	53.8	53.3
C(6)	25.5	26.9
C(7)	24.3	24.2
C(8)	26.9	29.5
C(8a)	66.4	64.7
*C*OH	64.7	64.2

Table 9 Comparison of ^{13}C NMR data for (*R*,*R*)-1-(hydroxymethyl)octahydroindolizine **31**, corrected ^{13}C NMR data from Ref 12 are displayed here.[6]

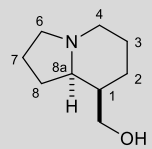
	^{1}H NMR shifts / ppm, multiplicity, *J* / Hz				
	(+)-5-*epi*-tashiromine **32** 				
Assignment	This work $CDCl_3$	Ref 13 $CDCl_3$	Assignment	This work $CDCl_3$	Ref 13 $CDCl_3$
C(1)*H*	1.64–1.81, m	1.67–2.12,[a] m	C(6)H_B	3.05–3.11, m	3.07–3.15, m
C(2)H_A	1.46–1.59, m	1.45–1.63, m	C(7)H_A	1.46–1.59, m	1.45–1.63, m
C(2)H_B	1.83–2.09, m	1.67–2.12,[a] m	C(7)H_B	1.83–2.09, m	1.67–2.12,[a] m
C(3)H_A	1.64–1.81, m	1.67–2.12,[a] m	C(8)H_A	1.64–1.81, m	1.67–2.12,[a] m
C(3)H_B	1.64–1.81, m	1.67–2.12,[a] m	C(8)H_B	1.83–2.09, m	1.67–2.12,[a] m
C(4)H_A	1.83–2.09, m	1.67–2.12,[a] m	C(8a)*H*	2.20–2.26, m	2.24–2.32, m
C(4)H_B	2.96–3.02, m	3.00–3.05, m	CH_AOH	3.71, ddd, 10.8, 1.8, 0.8	3.74, br d, 10.7
C(6)H_A	1.83–2.09, m	1.67–2.12,[a] m	CH_BOH	4.14, ddd, 10.8, 4.2, 1.2	4.18, dd, 10.7, 4.0

Table 10 Comparison of ^{1}H NMR data for (+)-5-*epi*-tashiromine **32** [[a] reported as δ_H 1.67–1.95 (6H, m) and δ_H 1.96–2.12 (3H, m)].

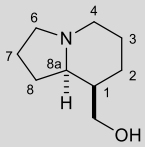
	^{13}C NMR shifts / ppm	
	(+)-5-*epi*-tashiromine **32** 	
Assignment	This work $CDCl_3$	Ref 13 $CDCl_3$
C(1)	35.4	35.3
C(2)	30.6	30.6
C(3)	20.9	20.8
C(4)	54.6	54.5
C(6)	53.7	53.5
C(7)	23.3	23.3
C(8)	25.9	25.8
C(8a)	66.9	66.8
*C*OH	65.6	65.7

Table 11 Comparison of ^{13}C NMR data for (+)-5-*epi*-tashiromine **32**.

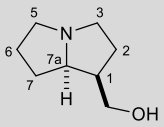
	^{1}H NMR shifts / ppm, multiplicity, *J* / Hz				
	(+)-Isoretronecanol **33** 				
Assignment	This work $CDCl_3$	Ref 17 $CDCl_3$	Assignment	This work $CDCl_3$	Ref 17 $CDCl_3$
C(1)*H*	2.38–2.52, m	2.33–2.50, m	C(6)H_A	1.67–1.76, m	1.60–1.92, m
C(2)H_A	1.45–1.57, m	1.33–1.55, m	C(6)H_B	1.77–1.91, m	1.60–1.92, m
C(2)H_B	1.77–1.91, m	1.60–1.92, m	C(7)H_A	1.35–1.45, m	1.33–1.55, m
C(3)H_A	2.62, ddd, 11.1, 7.7, 3.4	2.54–2.63, m	C(7)H_B	1.67–1.76, m	1.60–1.92, m
C(3)H_B	2.95–3.04, m	2.89–3.00, m	C(7a)*H*	3.52, app dt, 9.9, 6.9	3.42–3.51, m
C(5)H_A	2.38–2.52, m	2.33–2.50, m	CH_AOH	3.64, dd, 10.6, 7.3	3.52–3.66, m
C(5)H_B	3.10–3.17, m	3.05–3.12, m	CH_BOH	3.67, dd, 10.6, 7.3	3.52–3.66, m

Table 12 Comparison of ^{1}H NMR data for (+)-isoretronecanol **33**.

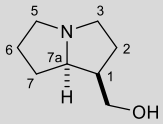
	^{13}C NMR shifts / ppm	
	(+)-Isoretronecanol **33** 	
Assignment	This work $CDCl_3$	Ref 17 $CDCl_3$
C(1)	44.2	44.1
C(2)	27.4	26.9
C(3)	54.1	53.7
C(5)	55.7	55.3
C(6)	26.7	26.1
C(7)	26.1	25.6
C(7a)	66.6	65.8
*C*OH	63.5	62.4

Table 13 Comparison of ^{13}C NMR data for (+)-isoretronecanol **33**.

3.8 Conclusion

In conclusion the concise asymmetric syntheses of (–)-lupinine **30**, (*R*,*R*)-1-(hydroxymethyl)octahydroindolizine **31**, (+)-5-*epi*-tashiromine **32** and (+)-isoretronecanol **33** have been completed in 6–15% yield in nine steps or fewer from commercially available starting materials.[20] The key steps involve: (1) the diastereoselective conjugate addition of an enantiopure lithium amide reagent to the homologous α,β-unsaturated esters **256** and **274**, (2) ring-closure under Finkelstein conditions to either pyrrolidine **275** (n = 1) or piperidine **257** (n = 2) scaffolds with concomitant *N*-deprotection, (3) diastereoselective α-alkylation of these azacycles and (4) ring-closure of alcohols **267**, **269**, **286** and **287** and reduction to afford the desired enantiopure azabicycles **30**–**33** (Figure 16).

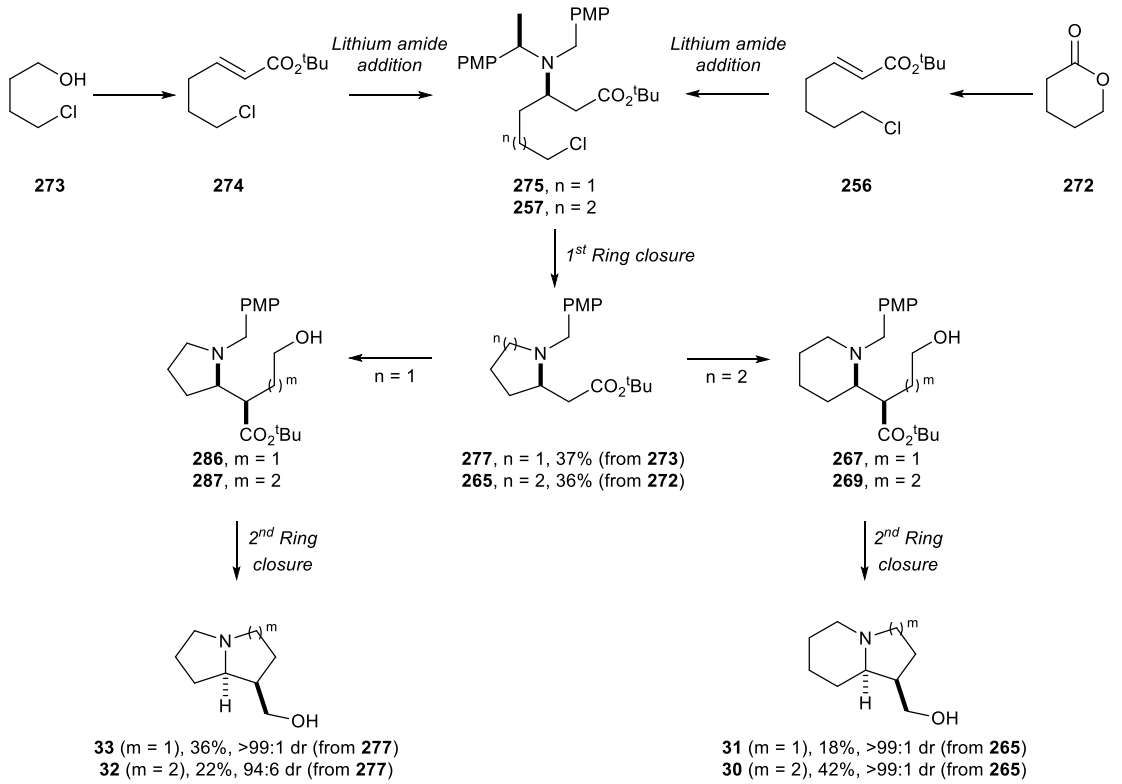


Figure 16 Summary of the asymmetric syntheses of **30**–**33**.

3.9 References and notes

[1] Schofield, T. M. *Part II Thesis*, University of Oxford, **2012**.
[2] Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Tetrahedron: Asymmetry* **2012**, *23*, 1111.
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[5] Davies, S. G.; Hughes, D. G.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E.; Williams, O. M. H. *Synlett* **2010**, 567.
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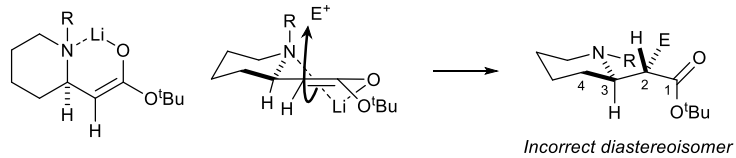
[8] Consideration was also given to possible formation of a lithium (*Z*)-enolate and subsequent reaction of the enolate *via* a chelated model. The presumed reactivity (Fürst-Plattner rule on a *trans*-decalin like structure) of this conformation is shown here and would result in the other diastereoisomer than is experimentally observed. This, however, does not rule out a mechanism *via* non Fürst-Plattner reactivity or through a different conformer.



Incorrect diastereoisomer

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Chapter 4

Asymmetric Syntheses of the Tetraponerine Alkaloids

4.1 Chapter aim

This chapter describes the asymmetric syntheses of tetraponerines 1–8 **102**–**109**. The synthetic strategy was to use common methodology for the syntheses of the different ring sizes, diastereoisomers and alkyl substitutions within the tetraponerine alkaloid family. Starting with *tert*-butyl sorbate **294**, a lithium amide conjugate addition could be employed to access either an *N*-allyl or *N*-but-3-enyl substituted β-amino ester **295** (n = 1, 2),[1] which could be subjected to a ring-closing metathesis reaction to give the corresponding dihydropyrrole **296** (n = 1) or tetrahydropyridine **296** (n = 2), respectively.[1] Homologation to **297** would give chiral α,β-unsaturated esters as precursors for a second lithium amide conjugate addition using lithium amide (*R*/*S*)-**101**, which would allow the installation of the second nitrogen, and treatment of the intermediate lithium (*Z*)-β-amino enolate[2] with camphorsulfonyloxaziridine (CSO) would result in enolate oxidation to give the corresponding α-hydroxy-β-amino esters **298**.[3] By analogy to the stereochemical outcome observed upon conjugate addition reactions to α,β-unsaturated esters bearing remote stereogenic centres (in which little or no substrate control is observed),[4] it was postulated that the diastereoselectivity of this conjugate addition step would be predominantly controlled by the lithium amide reagent (rather than the substrate), and thus employing either antipode of the lithium amide **101** would give rise to both desired configurations at *C*(3). Reduction of the ester moiety within **298** and oxidative cleavage of the resultant diol followed by olefination would provide olefin **299**. Global hydrogenation/hydrogenolysis of **299** would give the corresponding diamines **300** (n = 1, 2) which could be reacted with 4-bromobutanal **293** (according to the procedure of González-Gómez *et al.*)[5] to give the target alkaloids **301** (Figure 17).

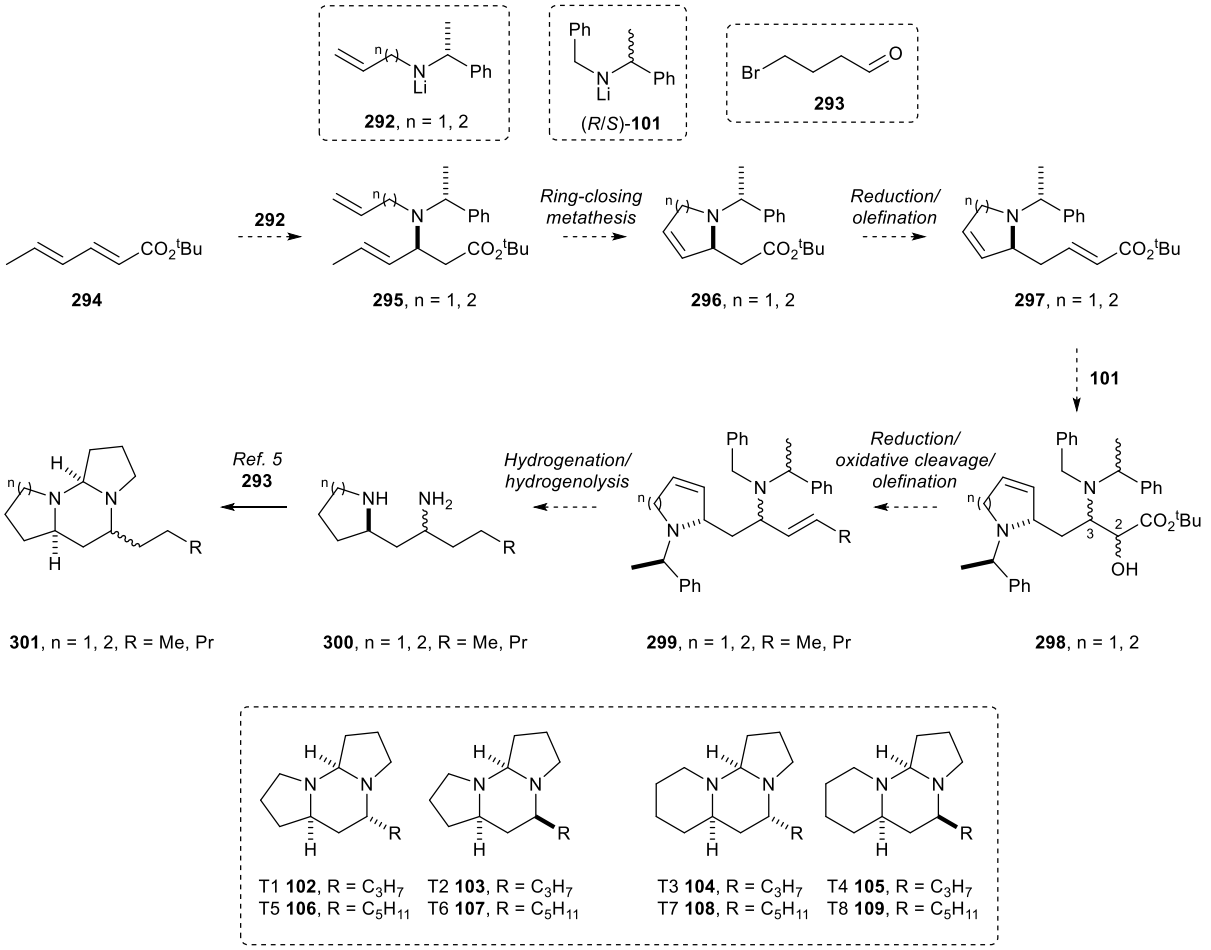


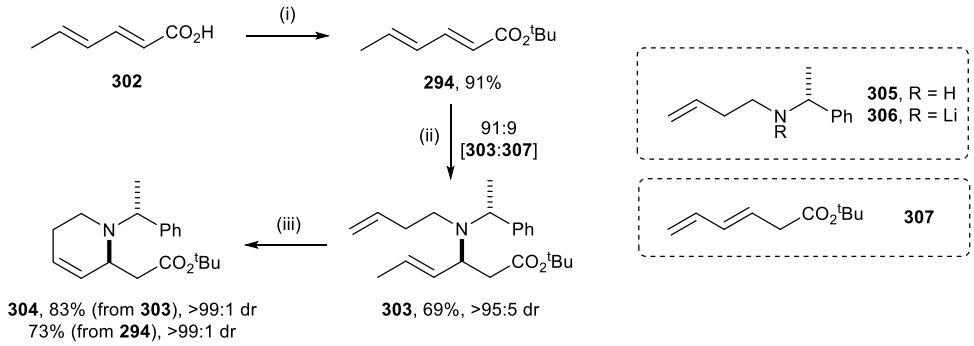
Figure 17 Proposed synthetic route to tetraponerines **301**.

The synthetic route requires the installation of olefinic units to produce **297** and **299**, at two different stages. These would formally be installed by an olefination of an amino aldehyde. β-Amino aldehydes are known to be unstable and are susceptible to side reactions,[6] so some attention must be given to these steps. In the generation of **297**, a model system was used to initially trial reactions and for **299**, this synthetic route proceeds *via* an α-amino aldehyde, avoiding the potentially problematic β-amino aldehyde functionality. Initial work was undertaken on the synthesis of T4 **105**, which would be used for route optimisation. The reaction sequence developed could then be applied to the other seven tetraponerines, to produce the entire family *via* common, divergent methodology.

4.2 Synthesis of α,β-unsaturated ester

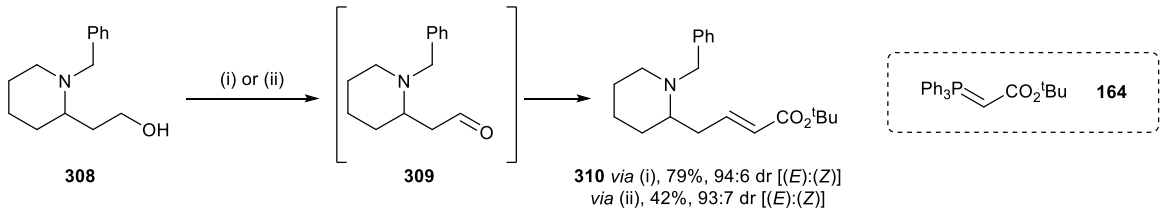
Tetrahydropyridine **304** was prepared according to a known[1] sequence of reactions. *tert*-Butyl sorbate **294** was produced in 91% yield from commercially available sorbic acid **302** by acid catalysed esterification with isobutylene. Treatment of α,β-unsaturated ester **294** with the enantiopure lithium

amide reagent **306** gave a 91:9 ratio of β-amino ester **303** and β,γ,δ,ε-diunsaturated ester **307**, which could be separated by flash column chromatography to give **303** in 69% yield and >95:5 dr (Scheme 55). The production of **307** is consistent with deprotonation of **294** at the ε-position by the basic lithium amide reagent followed by protonation of the resultant enolate at the α-position upon aqueous work up. Grubbs I catalyst was used to afford tetrahydropyridine **304** in 83% yield, as a single diastereoisomer (>99:1 dr) after purification. A superior overall yield of **304** (73%, as opposed to 57% overall yield for the two-step process, from **294**) could be achieved by employing a telescoped, two-step synthesis to perform the conjugate addition reaction and ring-closing metathesis, without a significant loss of material in the purification of the intermediate amine **303** (Scheme 55).



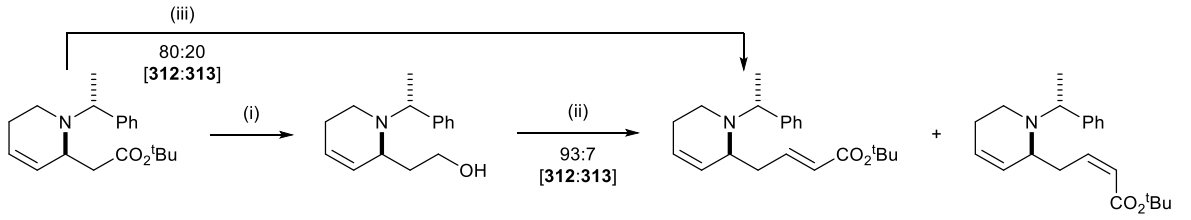
Scheme 55 *Reagents and conditions*: (i) isobutylene, H_2SO_4, CH_2Cl_2, 0 °C to rt, 48 h; (ii) **305**, BuLi, THF, –78 °C, 2 h; (iii) Grubbs I, CH_2Cl_2, 40 °C, 48 h.

The next steps were focussed on installing another α,β-unsaturated ester unit prior to the second lithium amide conjugate addition. Early work was performed on a model system, namely alcohol **308**,[7] to find viable methodology for installing the α,β-unsaturated ester functionality. Oxidation of alcohol **308** with IBX gave aldehyde **309**, which after addition of ylid **164** to the same flask to obviate isolation of **309** gave α,β-unsaturated ester **310** in 42% yield. A similar protocol, but employing a Swern oxidation to generate aldehyde **309**, gave **310** in 79% yield from **308** (Scheme 56).



Scheme 56 *Reagents and conditions*: (i) $(COCl)_2$, DMSO, CH_2Cl_2 –78 °C, 40 min then Et_3N, –78 °C to rt, 30 min then **164**, rt, 16 h; (ii) IBX, EtOAc, 70 °C, 3 h then **164**, rt, 16 h.

Taking these results on board, alcohol **311** was synthesised in 94% yield from **304** upon reduction with $LiAlH_4$. A one-pot Swern oxidation/Wittig olefination was attempted (having given the best results on the model system) and gave a 93:7 mixture of (*E*)-**312** and (*Z*)-**313**, respectively, from which α,β-unsaturated ester (*E*)-**312** was isolated in only 46% yield (additionally, (*Z*)-**313** was isolated in 3% yield). The olefin geometries within both (*E*)-**312** and (*Z*)-**313** were unambiguously assigned from the diagnostic ^{1}H NMR ^3J coupling constants of 15.5 Hz between the C(2)*H* and C(3)*H* protons within (*E*)-**312**, and 11.4 Hz between the C(2)*H* and C(3)*H* protons within (*Z*)-**313**. An alternative procedure was trialled, whereby β-amino ester **304** was reduced with DIBAL-H and the intermediate aldehyde was then subjected to *in situ* Wittig reaction, which gave an 80:20 mixture of α,β-unsaturated esters (*E*)-**312** and (*Z*)-**313**, respectively, from which (*E*)-**312** was isolated in 72% yield and >99:1 dr, along with (*Z*)-**313** in 14% yield and >99:1 dr. Whilst the diastereoselectivity of the olefination reaction under these conditions is lower, the total yield of (*E*)-**312** is greater, resulting in a more synthetically useful reaction sequence (Scheme 57).

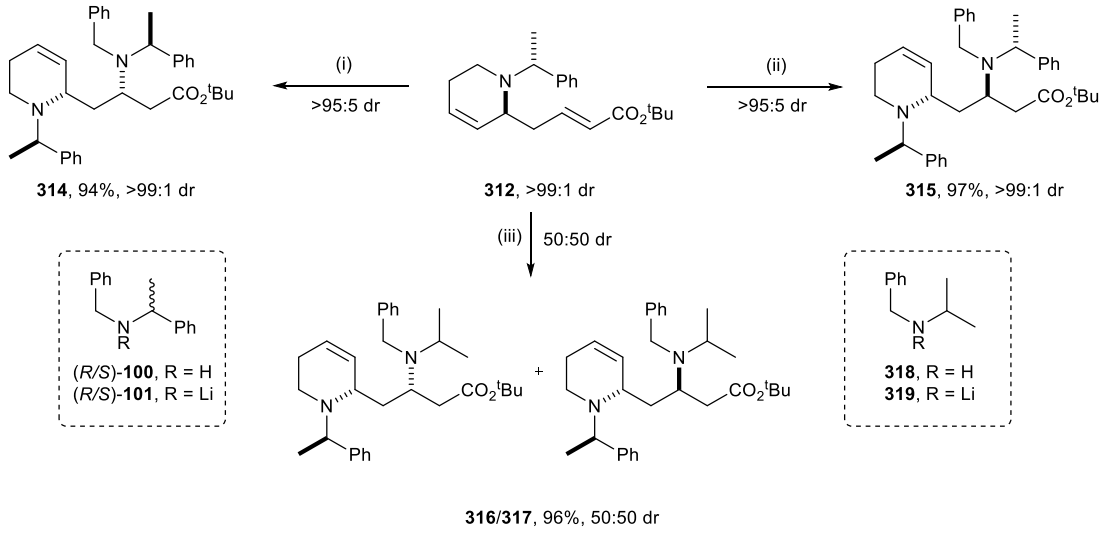


Scheme 57 *Reagents and conditions*: (i) $LiAlH_4$, THF, 0 °C to rt, 16 h; (ii) $(COCl)_2$, DMSO, CH_2Cl_2 –78 °C, 40 min then Et_3N, –78 °C to rt, 30 min then **164**, rt, 16 h; (iii) DIBAL-H, PhMe, –78 °C, 1 h then MeOH, –78 °C to rt then **164**, rt, 16 h.

4.3 Lithium amide conjugate additions

The next synthetic step was an aminohydroxylation of α,β-unsaturated ester **312**, where following conjugate addition of a lithium amide reagent to **312** the intermediate lithium (*Z*)-β-amino enolate was treated with CSO, resulting in oxidation at the α-centre. As two new stereogenic centres are being formed in this reaction, this gives rise to potentially four diastereomeric products, which may be difficult to distinguish from one another by, for example, ^{1}H NMR spectroscopy. To first understand the selectivity involved in formation of the β-amino centre, the reaction was initially studied with a protonation work-up, i.e. after the conjugate addition of a lithium amide reagent, the intermediate lithium

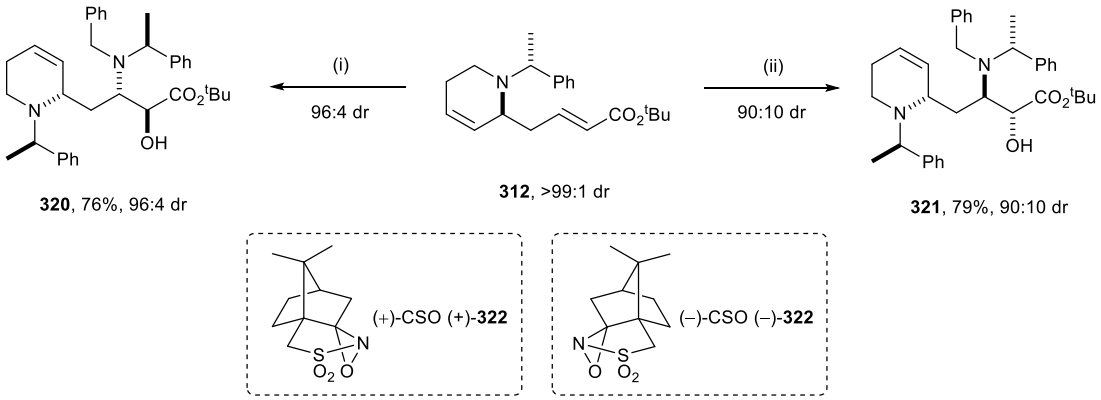
(*Z*)-β-amino enolate was treated with NH_4Cl, resulting in protonation at the α-centre. Although the stereoselectivity of the next lithium amide conjugate addition reaction was expected to proceed under the dominant stereocontrol of the chiral lithium amide reagent, the δ-stereocentre within α,β-unsaturated ester **312** could bias the diastereofacial selectivity to some extent. To probe the level of this inherent substrate control, achiral lithium amide **319** was initially used in the reaction. Upon conjugate addition of lithium amide **319** to α,β-unsaturated ester **312**, a 50:50 mixture of two diastereomeric β-amino ester adducts **316**/**317** was produced. This result demonstrated that there is negligible inherent diastereofacial selectivity and reagent control was therefore expected to dominate the stereochemical outcome upon conjugate addition of the chiral lithium amide reagents (*R*)-**101** or (*S*)-**101**. In the event of conjugate addition of chiral lithium amides (*R*)-**101** or (*S*)-**101**, the β-amino ester adducts **314** (isolated in 94% yield) and **315** (isolated in 97% yield), were produced as single diastereoisomers (Scheme 58). The absolute configuration of the newly formed *C*(3) centres within both **314** and **315** were therefore assigned from Davies' transition state mnemonic for lithium amide conjugate additions,[8] and these assignments were later confirmed by chemical correlation to the target alkaloids (*vide infra*).



Scheme 58 *Reagents and conditions*: (i) (*S*)-**100**, BuLi, THF, –78 °C, 2 h; (ii) (*R*)-**100**, BuLi, THF, –78 °C, 2 h; (iii) **318**, BuLi, THF, –78 °C, 2 h.

As these conjugate additions were completely diastereoselective, any diastereoisomeric mixtures formed during the corresponding aminohydroxylation process would be mixtures of *C*(2) epimers. Repetition of the conjugate addition reaction using (*S*)-**101** and treatment of the intermediate lithium (*Z*)-β-amino enolate with (+)-CSO (+)-**322** gave α-hydroxy-β-amino ester **320** in 76% yield and 96:4 dr. Similar reaction of **312** with (*R*)-**101** and (–)-**322** gave α-hydroxy-β-amino ester **321** in 79% yield and 90:10 dr.

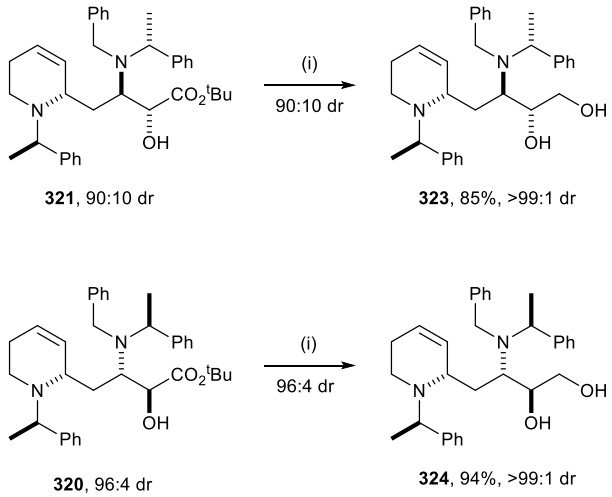
The *C*(2)-*C*(3) *anti*-configurations of **320** and **321** were tentatively assigned by analogy to many prior examples of this reaction by Davies *et al*. on achiral α,β-unsaturated esters,[3] although the configuration at the *C*(2) centre will ultimately be inconsequential as the synthetic plan was to oxidise the compounds in subsequent steps (Scheme 59).



Scheme 59 *Reagents and conditions*: (i) (*S*)-**100**, BuLi, THF, –78 °C, 2 h then (+)-**322**, –78 °C to rt, 16 h; (ii) (*R*)-**100**, BuLi, THF, –78 °C, 2 h then (–)-**322**, –78 °C to rt, 16 h.

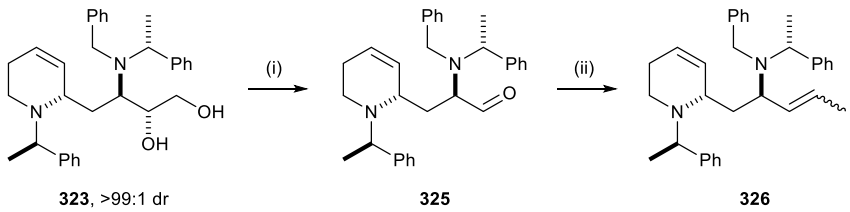
4.4 Side chain installation

At this stage, the requisite stereogenic centres within the tetraponerines have been established. This leaves functional group manipulations to install an alkyl chain, tandem hydrogenation/hydrogenolysis, and the final ring-closing reaction following the procedure of González-Gómez *et al.*[5] to generate the aminal stereocentre under thermodynamic control. Initially, work was focussed upon manipulation of α-hydroxy-β-amino esters **320** and **321**. Reduction of **320** and **321** with $LiAlH_4$ produced diols **324** and **323**, respectively, which were isolated as single compounds in 94 and 85% yield, respectively. The synthetic plan at this stage was to use an oxidative cleavage reaction to produce the corresponding aldehydes to **323** and **324** which after either *in situ* or subsequent Wittig reaction would result in formation of the target olefins (Scheme 60).



Scheme 60 *Reagents and conditions*: (i) $LiAlH_4$, THF, rt, 16 h.

Treatment of diol **323** with $NaIO_4$ in MeOH resulted in a complex mixture that could not be purified by flash column chromatography. A two-step protocol of the diol cleavage and Wittig reaction was also attempted but again only a complex mixture was formed. Changing the solvent to CH_2Cl_2 resulted in only returned starting material **323** and oxidation with periodic acid led to another complex mixture. Attempts with $Pb(OAc)_4$ as the oxidising agent were similarly unsuccessful in EtOAc. In PhMe, however, an aldehydic species was observed in the ^1H NMR spectrum of the crude reaction mixture (δ_H = 9.24 ppm). Unfortunately, treatment of this crude reaction mixture with Ph_3P=CHMe did not result in formation of olefin **326** (Scheme 61).



Entry	Reagents and Conditions		Notes
	(i) rt, 1 h	(ii) THF 0 °C to rt, 16 h	
1	$NaIO_4$, MeOH	N/A	complex mixture
2	$NaIO_4$, MeOH	Ph_3P=CHMe	complex mixture
3	$NaIO_4$, CH_2Cl_2	N/A	no reaction
4	H_5IO_6, H_2O/CH_2Cl_2	N/A	complex mixture
5	$Pb(OAc)_4$, EtOAc	N/A	complex mixture
6	$Pb(OAc)_4$, PhMe	N/A	aldehyde observed by ^1H NMR
7	$Pb(OAc)_4$, PhMe	Ph_3P=CHMe	complex mixture

Scheme 61 *Reagents and conditions*: See Table.

As the oxidative cleavage was not successful with conditions that have been shown to work for other 3-amino-1,2-diols,[9,10] a second synthetic strategy was devised (Figure 18). Taking β-amino esters **327** and applying a reduction procedure to generate aldehydes, followed by olefination could lead to olefins **328**. From here, an analogous strategy to the previous route was suggested to progress towards the final compounds.

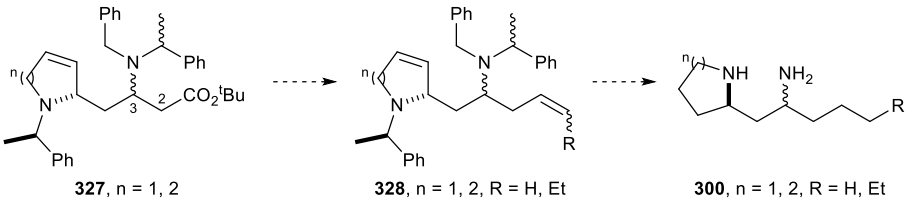
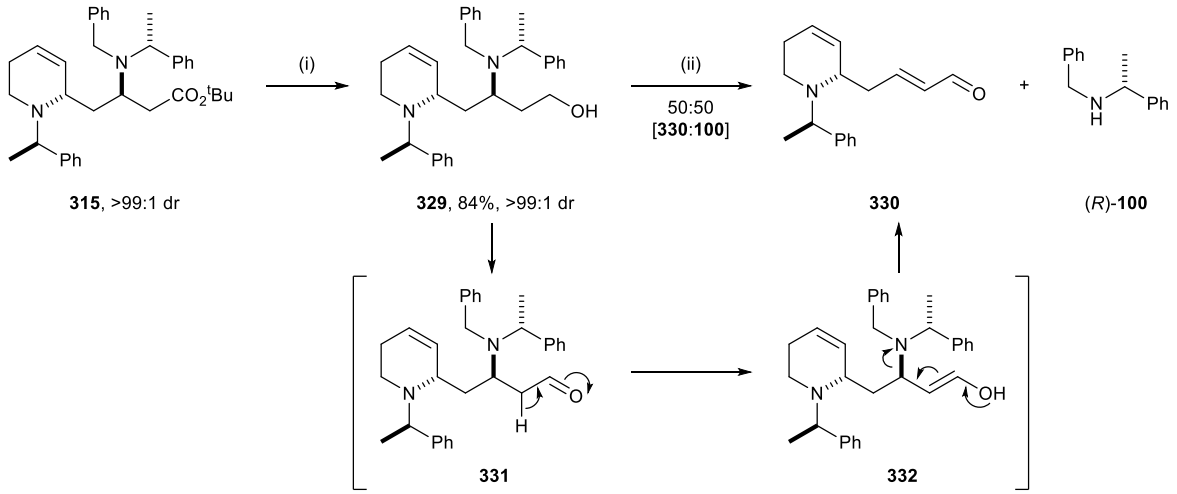


Figure 18 Second proposed synthetic route to diamines **300**.

4.5 Synthesis of (+)-tetraponerine 4

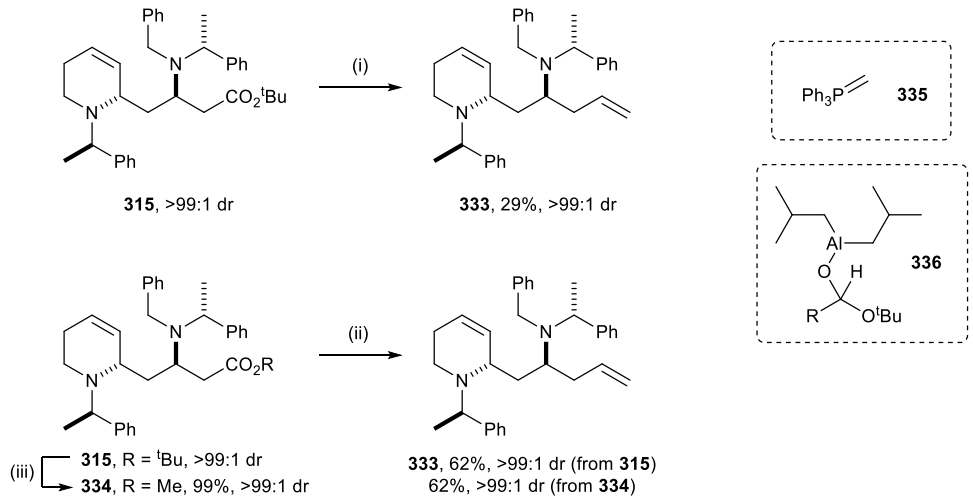
Reduction of **315** with $LiAlH_4$ gave alcohol **329** in 84% yield, as a single compound (>99:1 dr), but treatment of this alcohol under Swern oxidation conditions did not give the β-amino aldehyde **331**. Instead, a 50:50 mixture of the known secondary amine (*R*)-**100** and a species tentatively assigned as aldehyde **330**, was produced, consistent with a retro-Michael reaction of the intermediate β-amino aldehyde **331** (Scheme 62).



Scheme 62 *Reagents and conditions*: (i) $LiAlH_4$, THF, 0 °C to rt, 16 h; (ii) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 40 min then Et_3N, –78 °C to rt, 30 min.

It was proposed that the intermediate aldehyde **331** could be subjected to an *in situ* Wittig olefination, keeping reaction temperatures low to disfavour degradation pathways. Attention was focussed on a one-

pot DIBAL-H reduction/Wittig olefination procedure, where the intermediate aldehyde **331**, resulting from the reduction of **315**, would be reacted with ylid **335** (generated from the treatment of methyltriphenylphosphonium iodide with KHMDS) at –78 °C. This gave olefin **333** in 29% yield. It is generally accepted that upon reduction of esters with DIBAL-H, the initially generated species is a hemiacetal (such as **336**) that is stable under the reaction conditions at –78 °C, and only decomposes to the desired aldehyde on warming or on quenching of the reaction. It is hypothesised that this is the reason for the poor yield of the reaction, as the aldehyde **331** is not produced at low temperatures, but only when the reaction mixture is warmed and as **331** is unstable at ambient temperatures, the reaction fails. For this reason, it was decided to add MeOH to the reaction at –78 °C, before the addition of ylid **335**.[11] This would, hopefully, free the aldehyde *in situ* at –78 °C and allow the Wittig reaction to proceed before warming to rt. In practice, this method gave **333** in an improved yield of 62% from ester **315**. The reaction was also attempted on methyl ester **334**, which was formed in 99% yield from **315** using $SOCl_2$ in MeOH. This made no change to the reaction outcome, also affording olefin **333** in 62% yield (Scheme 63).

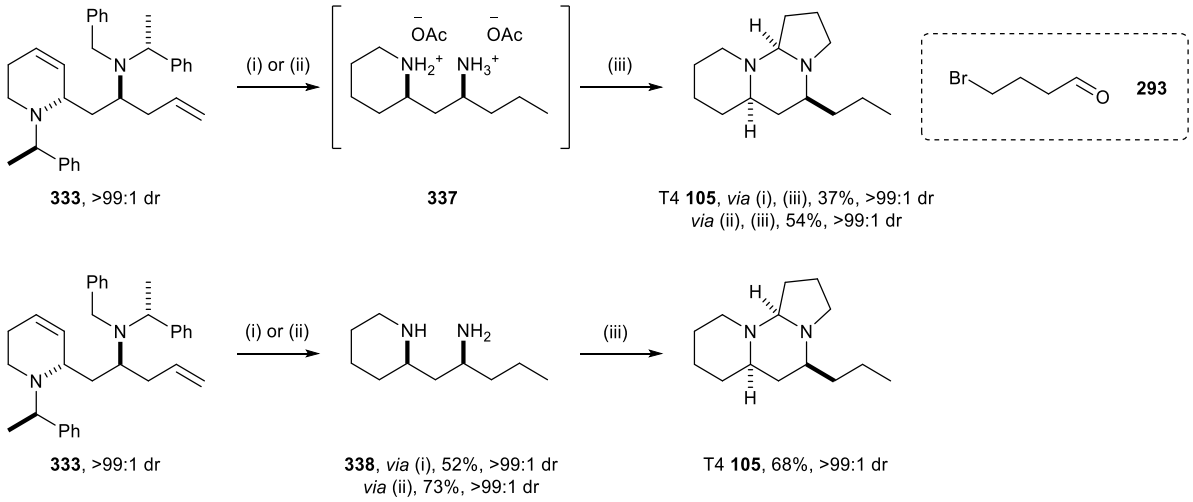


Scheme 63 *Reagents and conditions*: (i) DIBAL-H, PhMe, –78 °C, 1 h then **335**, –78 °C to rt, 16 h; (ii) DIBAL-H, PhMe, –78 °C, 1 h then MeOH, –78 °C then **335**, –78 °C to rt, 16 h; (iii) $SOCl_2$, MeOH, 50 °C, 16 h.

4.5.1 End-game ring closures

For the end-game, hydrogenation/hydrogenolysis of **333** using $Pd(OH)_2/C$ in a mixture of $MeOH/H_2O/AcOH$ led to, initially, the diacetate salt **337**. This was treated under González-Gómez's conditions (i.e. bromobutanal **293** and K_2CO_3 in CH_2Cl_2)[5] to form (+)-tetraponerine 4 **105** in 37% yield

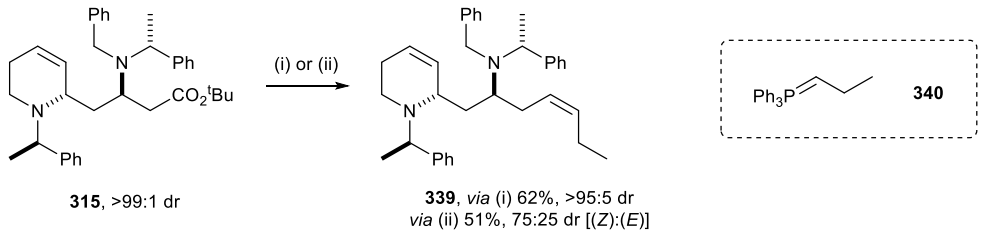
and as a single diastereoisomer (>99:1 dr). As the yield of this final step was not as high as desired, the two-step process was broken down into the individual reactions. It was found that the hydorgenation/hydrogenolysis of **333** gave diamine **338** in 52% yield after basification and purification, and the final step proceeded in 68% yield, an overall yield of 35% from **333**. As the limiting factor in these final steps seemed to be the reduction/debenzylation, a more potent catalyst was trialled. Treatment of **333** under the hydrogenation/hydrogenolysis conditions, but using Pd black as the catalyst, gave diamine **338** in an improved yield of 73%. Employing this reaction in the two-step process also increased the overall yield, by a similar fraction, to 54% (Scheme 64). This concluded the asymmetric synthesis of (+)-tetraponerine 4 **105** as a single diastereoisomer (>99:1 dr) in 15.5% yield over eight steps. The spectroscopic data and specific rotation value for this synthetic sample of (+)-tetraponerine 4 **105** were in good agreement with literature values[5,12] {$[\alpha]_D^{25}$ +90.8 (*c* 1.0 in $CHCl_3$); lit.[12] for a sample isolated from the natural source $[\alpha]_D^{20}$ +94 (*c* 0.2 in $CHCl_3$); lit.[13] $[\alpha]_D^{20}$ +96 (*c* 2.0 in $CHCl_3$)} and so secured the configurations of all synthetic precursors **303**, **304**, **311**–**313**, **315** and **333**. As the highest overall yield of **105** from **333** was achieved using Pd black for the reduction to ammonium **337** and subsequent condensation with **293** (54% yield), this protocol was taken forward for use in the syntheses of the other tetraponerines.



Scheme 64 *Reagents and conditions*: (i) $Pd(OH)_2/C$, H_2 (5 atm), $MeOH/H_2O/AcOH$, rt, 48 h; (ii) Pd, H_2 (5 atm), $MeOH/H_2O/AcOH$, rt, 48 h; (iii) **293**, K_2CO_3, CH_2Cl_2, rt, 2 h.

4.6 Syntheses of (+)-tetraponerine 3, (+)-tetraponerine 7 and (+)-tetraponerine 8

Attention was now turned to the synthesis of the remaining [6-6-5] ring tetraponerines, T3 **104**, T7 **108** and T8 **109**. Starting with ester **315**, from the route to T4 **105**, the DIBAL-H reduction/Wittig olefination procedure was employed using ylid **340** (generated from the treatment of propyltriphenylphosphonium bromide with KHMDS) to form olefin **339** in 62% yield (Scheme 65). An alternative procedure was also used where **340** was generated from the treatment of propyltriphenylphosphonium bromide with BuLi. This resulted in a slightly lower yield of 51%, but also produced **339** in 75:25 dr [(*Z*):(*E*)]; although the configuration of this olefin is ultimately inconsequential, as both diastereoisomers will converge upon the same compound after hydrogenation this mixture allowed for the assignment of the configuration of the olefin within **339**. For the mixture, the γ-effect[14] can be observed; this is where the allylic carbons of (*Z*)-olefins appear ~6 ppm lower in the ^{13}C NMR spectrum than their (*E*)-olefin counterparts. For **339**, the ^{13}C chemical shift of $C(3)_{minor} - C(3)_{major}$ = 5.8 ppm and $C(6)_{minor} - C(6)_{major}$ = 4.9 ppm, showing the major component is the one with the lower chemical shifts at *C*(3) and *C*(6), allowing tentative assignment of $\mathbf{339}_{major}$ as the (*Z*)-olefin (and for the sample of **339** at >95:5 dr).

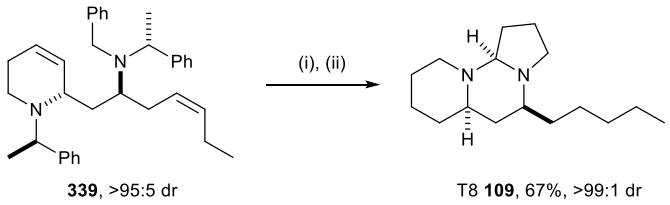


315, >99:1 dr

339, *via* (i) 62%, >95:5 dr
via (ii) 51%, 75:25 dr [(*Z*):(*E*)]

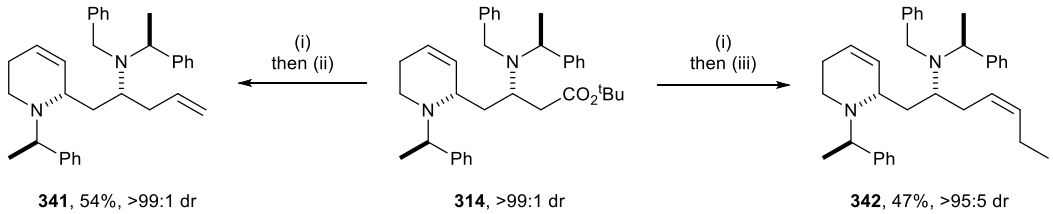
Scheme 65 *Reagents and conditions*: (i) DIBAL-H, PhMe, –78 °C, 1 h then MeOH, –78 °C then **340** (formed using KHMDS), –78 °C to rt, 16 h; (ii) DIBAL-H, PhMe, –78 °C, 1 h then MeOH, –78 °C then **340** (formed using BuLi), –78 °C to rt, 16 h.

Reaction of **339** under the palladium catalysed hydrogenation/hydrogenolysis conditions, followed by condensation with **293**, gave (+)-tetraponerine 8 **109** in 67% yield and >99:1 dr (Scheme 66). The spectroscopic data, melting point and specific rotation value for **109** were in good agreement with literature values[12,15] {mp 38–40 °C; lit.[16] mp 40 °C; $[\alpha]_D^{25}$ +93.0 (*c* 1.0 in $CHCl_3$); lit.[12] for a sample isolated from the natural source $[\alpha]_D^{20}$ +102 (*c* 0.2 in $CHCl_3$); lit.[13] $[\alpha]_D^{20}$ +101 (*c* 2.0 in $CHCl_3$)}. This completed the total asymmetric synthesis of T8 **109** in 19.3% over eight steps from commercially available sorbic acid **302**, confirming the configurations of all synthetic precursors **303**, **304**, **311**–**313**, **315** and **339**.



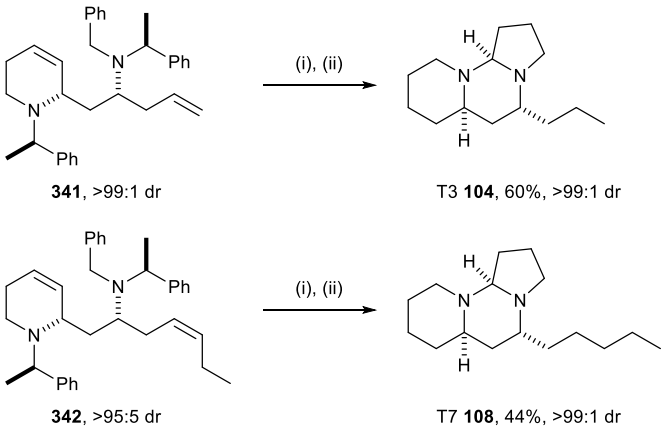
Scheme 66 *Reagents and conditions*: (i) Pd, H_2 (5 atm), MeOH/H_2O/AcOH, rt, 48 h then $Pd(OH)_2$/C, H_2 (5 atm), MeOH/H_2O/AcOH, rt, 16 h; (ii) **293**, K_2CO_3, CH_2Cl_2, rt, 2 h.

Treatment of β-amino ester **314** [formed from the conjugate addition of (*S*)-**101** to α,β-unsaturated ester **312**] with either ylid **335** or **340**, under the reduction/olefination conditions, gave **341** and **342** in 54 and 47% yield, respectively (Scheme 67). The geometry of the olefin within **342** was tentatively assigned as (*Z*) by analogy to the (*Z*)-olefin **339** formed upon treatment of **315** with ylid **340**.



Scheme 67 *Reagents and conditions*: (i) DIBAL-H, PhMe, –78 °C, 1 h then MeOH, –78 °C; (ii) **335**, –78 °C to rt, 16 h; (iii) **340**, –78 °C to rt, 16 h.

Taking both compounds **341** and **342**, and subjecting them to the final steps led to the last two [6-6-5] ring tetraponerines, (+)-tetraponerine 3 **104** and (+)-tetraponerine 7 **108**, in 60 and 44% respectively, both being isolated as single compounds (>99:1 dr) (Scheme 68). For both compounds the characterisation data were in good agreement with literature values;[5,12,15] {for **104**: $[\alpha]_D^{25}$ +30.9 (*c* 1.0 in $CHCl_3$); lit.[12] for a sample isolated from the natural source $[\alpha]_D^{20}$ +27 (*c* 0.07 in $CHCl_3$); lit.[16] $[\alpha]_D^{20}$ +31 (*c* 3.1 in $CHCl_3$); lit.[5] $[\alpha]_D^{20}$ +35 (*c* 0.49 in $CHCl_3$); for **108**: $[\alpha]_D^{25}$ +30.4 (*c* 0.8 in $CHCl_3$); lit.[12] for a sample isolated from the natural source $[\alpha]_D^{20}$ +30 (*c* 0.22 in $CHCl_3$); lit.[13] $[\alpha]_D^{20}$ +29.5 (*c* 2.2 in $CHCl_3$)}. This completed the asymmetric total syntheses of T3 **104** and T7 **108**, as single compounds (>99:1 dr), in 14.6 and 9.3% overall yields, respectively, in eight steps from commercially available starting material, confirming the configurations of all synthetic precursors **303**, **304**, **311**–**314**, **341** and **342**.



Scheme 68 *Reagents and conditions*: (i) Pd, H_2 (5 atm), MeOH/H_2O/AcOH, rt, 48 h; (ii) **293**, K_2CO_3, CH_2Cl_2, rt, 2 h.

4.7 Syntheses of (+)-tetraponerine 1, (+)-tetraponerine 2, (+)-tetraponerine 5 and (+)-tetraponerine 6

Having completed the syntheses of T3 **104**, T4 **105**, T7 **108** and T8 **109**, the four tetraponerines with a [6-6-5] scaffold **343**, attention was turned to the remaining four: those consisting of a [5-6-5] scaffold **346**. The syntheses of the [6-6-5] compounds **343** passed through the key tetrahydropyridine **304**, where the ring size was determined by the choice of the but-3-enyl substituted lithium amide **306**. Employing an analogous route, but starting with allyl amide **344**, would result in the corresponding dihydropyrrole intermediate **345**. From here, the same reaction sequence as for the tetrahydropyridine analogues could then be employed to synthesise the remaining compounds (Figure 19).

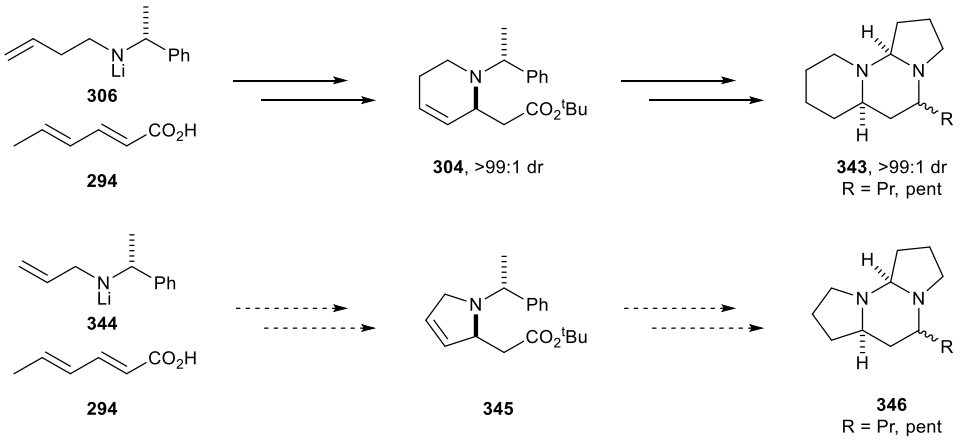
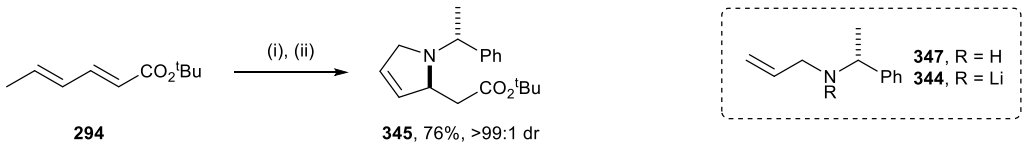


Figure 19 Synthetic route to tetraponerines **343** and planned synthetic route to tetraponerines **346**.

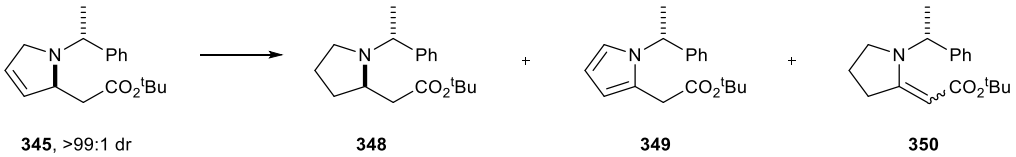
4.8 Synthesis of α,β-unsaturated ester

Dihydropyrrole **345** was prepared according to established procedures.[1] A lithium amide conjugate addition reaction using *tert*-butyl sorbate **294** and the lithium amide **344**, followed by Grubbs I catalyst mediated ring-closing metathesis, gave dihydropyrrole **345** in 76% yield over the two steps, as a single compound (>99:1 dr) after purification (Scheme 69).



Scheme 69 *Reagents and conditions*: (i) **347**, BuLi, THF, –78 °C, 2 h; (ii) Grubbs I, CH_2Cl_2, rt, 24 h.

Originally, it was imagined that **345** would be a suitable compound to pursue the rest of the synthesis with. However, on subsequent reactions the products were becoming contaminated with pyrrole containing species. This was attributed to oxidation of **345** over time, or during reaction conditions (the ease of oxidation of **345** has previously been reported).[1] For this reason, it was decided to remove the olefin unit at this stage, so that further reactions could be undertaken on a saturated pyrrolidine, which would be less prone to oxidation. Previous work[1] had shown that this reduction could be achieved using Wilkinson's catalyst; however, initial attempts at the use of this procedure did not prove as efficient as the original work. Optimisation was therefore undertaken (Scheme 70). Initially, palladium based hydrogenation was attempted, under mild conditions, so as not to cause *N*-deprotection. However, using either Pd/C or $Pd(OH)_2/C$ as the catalyst resulted predominantly in oxidation to pyrrole **349**, with a rearranged product tentatively assigned as **350**, also being observed. Wilkinson's catalyst was also trialled, and a marked difference was observed with solvent variation, producing various ratios of pyrrolidine **348**, pyrrole **349** and the side product **350** (Scheme 70). Taking the most promising conditions (Wilkinson's catalyst in EtOAc, similar to the original conditions reported in Ref 1) and purifying the reaction mixture by column chromatography, produced known pyrrolidine **348** in 50% yield as a single compound. Reductions using potassium azodicarboxylate (PADA) were also attempted and looked initially successful, with 12% conversion to pyrrolidine **348** being observed after 1 h. However, lengthening the reaction time did not significantly improve the conversion, and oxidation product **349** was also observed.

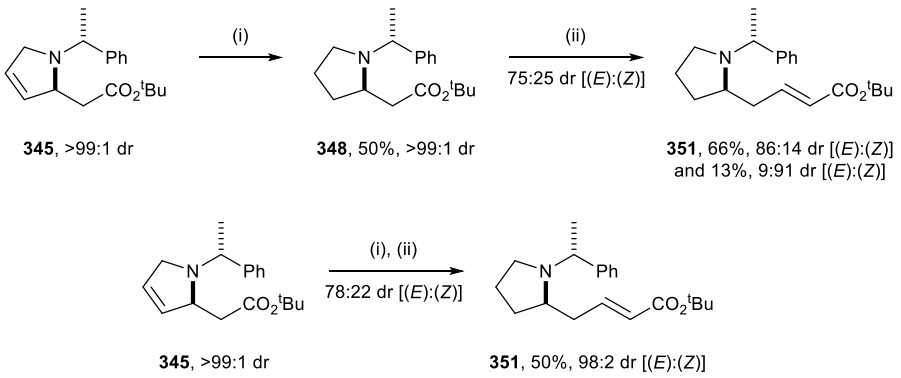


345, >99:1 dr **348** **349** **350**

Entry	Reagents and Conditions	Solvent	Conversion / %	Ratio **348**:**349**:**350**	Notes
1	(i)	MeOH	100	0:72:28	-
2	(ii)	MeOH	100	0:75:25	-
3	(iii)	MeOH	13	92:8:0	-
4	(iv)	MeOH	36	75:25:0	-
5	(v)	PhH	49	88:0:12	-
6	(v)	MeOH	100	82:0:18	-
7	(v)	EtOAc	100	88:0:12	**348** isolated in 50%, >99:1 dr
8	(v)	THF	18	-	18% unknown material
9	(v)	MeCN	0	-	-

Scheme 70 *Reagents and conditions*: (i) $Pd(OH)_2/C$, H_2 (1 atm), solvent, rt, 2 h; (ii) Pd/C, H_2 (1 atm), solvent, rt, 2 h; (iii) PADA, AcOH, solvent, rt, 1 h; (iii) PADA, AcOH, solvent, rt, 1 h; (iv) PADA, AcOH, solvent, rt, 3 days; (v) Wilkinson's catalyst, H_2 (1 atm), solvent, rt, 16 h.

With the best reduction conditions (Wilkinson's catalyst, EtOAc), material could be acquired to employ the same DIBAL-H reduction/Wittig olefination procedure, as was used earlier, to give α,β-unsaturated ester **351** in 86:14 dr [(*E*):(*Z*)] in 60% isolated yield (with another fraction of 9:91 dr [(*E*):(*Z*)] being isolated in 13% yield). Assignments as to the geometry of the double bonds were made on the characteristic ^{1}H NMR ^3J coupling constants of 15.6 Hz between the C(2)*H* and C(3)*H* protons in the (*E*)-isomer and 11.6 Hz in the (*Z*)-isomer. A telescoped synthesis, subjecting the crude reaction mixture from the hydrogenation directly to the reduction/olefination procedure, increased the efficiency, with a sample of **351** in 98:2 dr [(*E*):(*Z*)] being isolated in 50% yield by exhaustive chromatographic purification (Scheme 71).



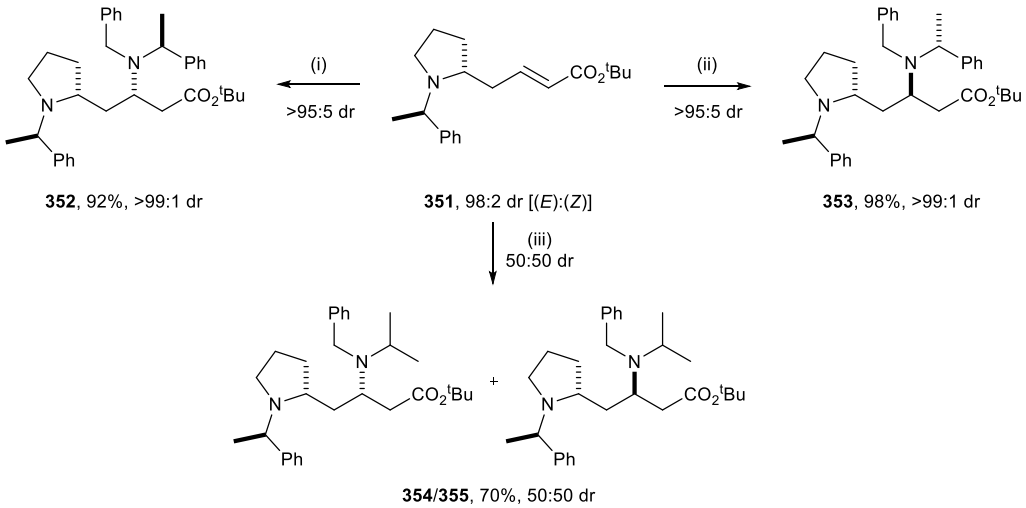
345, >99:1 dr **348**, 50%, >99:1 dr **351**, 66%, 86:14 dr [(*E*):(*Z*)] and 13%, 9:91 dr [(*E*):(*Z*)]

345, >99:1 dr **351**, 50%, 98:2 dr [(*E*):(*Z*)]

Scheme 71 *Reagents and conditions*: (i) Wilkinson's, H_2 (1 atm), EtOAc, rt, 16 h; (ii) DIBAL-H, PhMe, –78 °C, 1 h then MeOH, –78 °C then **164**, –78 °C to rt, 16 h.

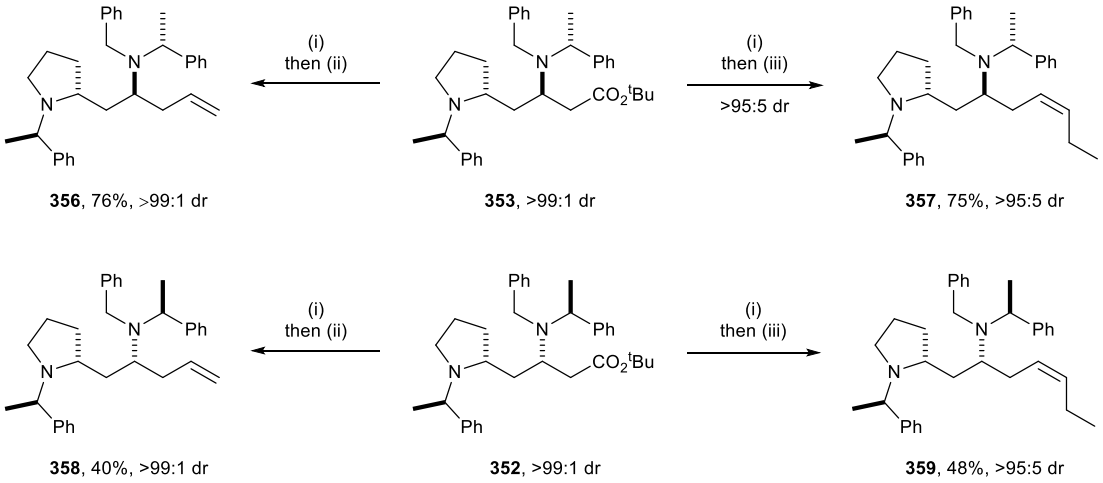
4.9 Second lithium amide conjugate addition and end-game

As with α,β-unsaturated ester **312**, initial investigation was done to ascertain any inherent diastereofacial selectivity within **351**. Upon conjugate addition of lithium amide **319** to α,β-unsaturated ester **351**, a 50:50 mixture of two diastereomeric β-amino ester adducts **354**/**355** was observed and isolated in 70% combined yield. As with **312**, this demonstrates that there is negligible inherent diastereofacial selectivity. Conjugate addition of the chiral amides (*R*)-**101** and (*S*)-**101** to **351** gave β-amino esters **352** and **353**, respectively, in 92 and 98% yield, respectively (Scheme 72)



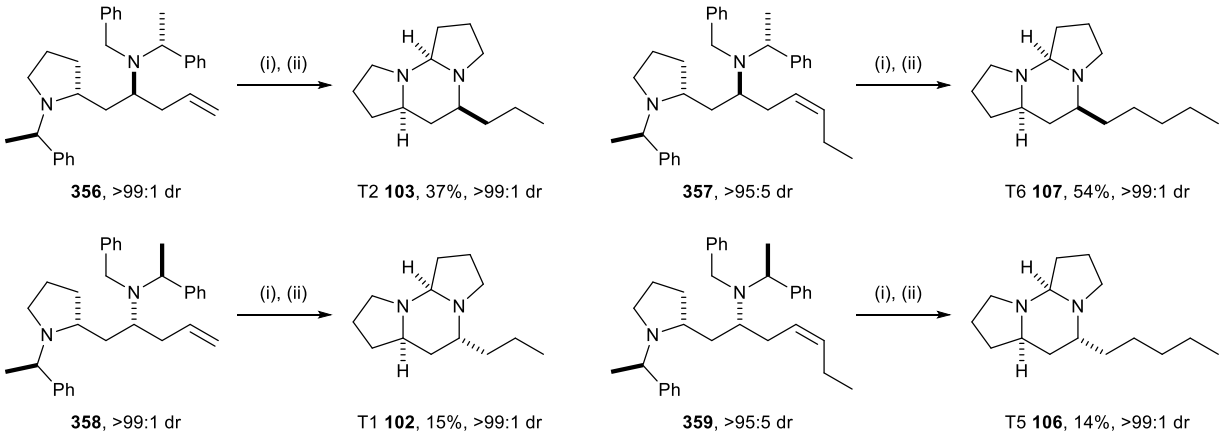
Scheme 72 *Reagents and conditions*: (i) (*S*)-**100**, BuLi, THF, –78 °C, 2 h; (ii) (*R*)-**100**, BuLi, THF, –78 °C, 2 h; (iii) **318**, BuLi, THF, –78 °C, 2 h.

At this stage, the stereocentres within **352** and **353** are set up to produce either T1 **102** and T5 **106** or T2 **103** and T6 **107**, respectively, and so the divergent DIBAL-H reduction/Wittig olefination procedure with either yild **335** or **340** was employed. This allowed access to the four olefins, **356–359** in 40–76% yield, that can undergo the final cyclisation steps (Scheme 73).



Scheme 73 *Reagents and conditions*: (i) DIBAL-H, PhMe, –78 °C, 1 h then MeOH, –78 °C; (ii) **335**, –78 °C to rt, 16 h; (iii) **340**, –78 °C to rt, 16 h.

Treatment of **356**–**359** under the standard end-game reaction sequence (hydrogenation/hydrogenolysis followed by condensation with bromobutanal **293**) produced the four remaining tetraponerines. (+)-Tetraponerine 2 **103** and (+)-tetraponerine 6 **107** were produced in 37 and 54% yield from **356** and **357**, respectively, and reaction of their diastereoisomers, **358** and **359**, gave (+)-tetraponerine 1 **102** and (+)-tetraponerine 5 **106** in 15 and 14% yield, respectively. (Scheme 74). Data for T1 **102**, T2 **103** and T5 **106** were in good agreement with literature values {for **102**: $[\alpha]_D^{25}$ +14.4 (*c* 0.13 in $CHCl_3$); lit.[16] $[\alpha]_D^{20}$ +11 (*c* 0.14 in $CHCl_3$); lit.[17] $[\alpha]_D^{20}$ +14 (*c* 0.498 in $CHCl_3$); for **103**: $[\alpha]_D^{25}$ +44.2 (*c* 1.0 in $CHCl_3$); lit.[16] $[\alpha]_D^{20}$ +36 (*c* 1.79 in $CHCl_3$); lit.[17] $[\alpha]_D^{20}$ +47 (*c* 0.232 in $CHCl_3$); for **106**: $[\alpha]_D^{25}$ +12.4 (*c* 0.13 in $CHCl_3$); lit.[12] for a sample isolated from the natural source $[\alpha]_D^{20}$ +10 (*c* 0.2 in $CHCl_3$); lit.[16] $[\alpha]_D^{20}$ +10 (*c* 0.24 in $CHCl_3$); lit.[17] $[\alpha]_D^{20}$ +14 (*c* 1.6 in $CHCl_3$)}, thereby confirming the assigned configurations of all synthetic precursors **345**, **348**, **351**–**353** and **356**–**359**. Although the ^1H and ^{13}C NMR data for T6 **107** matched reported values, a discrepancy was observed for the specific rotation value {for **107**: $[\alpha]_D^{25}$ +66.3 (*c* 1.0 in $CHCl_3$); lit.[12] for a sample isolated from the natural source $[\alpha]_D^{20}$ +35 (*c* 0.15 in $CHCl_3$); lit.[17] $[\alpha]_D^{20}$ +40 (*c* 0.75 in $CHCl_3$)}. The specific rotation for a sample of the hydrochloride salt of T6 **107** was also obtained {for **107**·HCl $[\alpha]_D^{25}$ +9.2 (*c* 1.0 in $CHCl_3$)}, and therefore one plausible explanation for the discrepancy between the data could be due to isolation of non-stoichiometric ammonium species in previous studies. This concluded the asymmetric total syntheses of T1 **102**, T2 **103**, T5 **106** and T6 **107** in 1.9, 9.7, 2.1 and 14.0% overall yield, respectively, in nine steps from commercially available materials.



Scheme 74 *Reagents and conditions*: (i) Pd, H_2 (5 atm), MeOH/H_2O/AcOH, rt, 48 h; (ii) **293**, K_2CO_3, CH_2Cl_2, rt, 2 h.

4.10 Comparison of ^{1}H and ^{13}C NMR data for (+)-tetraponerines 1–8

The following tables (14–21) display the ^{1}H and ^{13}C NMR data for all tetraponerines, with comparisons to literature data and, where available, data from naturally isolated sources. Consecutive ^{1}H multiplets in the region δ_H 1.00–2.00 ppm have been combined for clarity.

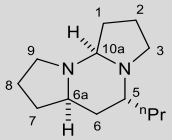
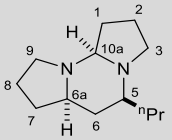
	^{1}H NMR shifts / ppm, multiplicity, *J* / Hz				
	(+)-Tetraponerine 1 **102** 			(+)-Tetraponerine 2 **103** 	
Assignment	This work C_6D_6	This work $CDCl_3$	Ref 16 $CDCl_3$	This work C_6D_6	Ref 17 C_6D_6
C(1)H_A	1.23–1.91, m	1.24–1.96, m	1.25–1.95, m	1.27–1.97, m	1.25–2.07, m
C(1)H_B					
C(2)H_A					
C(2)H_B					
C(3)H_A	2.82–2.91, m	2.82, td, 7.9, 3.0	2.81, dd, 4.9, 6.7	2.29–2.36, m	2.43, td, 8.7, 5.1
C(3)H_B	3.21, q, 7.7	3.08, q, 7.9	3.09, q, 7.4	3.01–3.07, m	2.93–3.17, m
C(5)*H*	2.82–2.91, m	2.91–3.01, m	2.96, m	2.39–2.46, m	2.51–2.60, m
C(6)H_A	1.23–1.91, m	1.24–1.96, m	1.25–1.95, m	1.27–1.97, m	1.25–2.07, m
C(6)H_B					
C(6a)*H*	1.91–2.02, m	2.00–2.10, m	2.06, m		
C(7)H_A	1.23–1.91, m	1.24–1.96, m	1.25–1.95, m		
C(7)H_B					
C(8)H_A					
C(8)H_B					
C(9)H_A					
C(9)H_B	2.82–2.91, m	2.91–3.01, m	2.96, m	2.93, td, 8.5, 2.5	2.93–3.17, m
C(10a)*H*	3.48, t, 2.3	3.39, app d, 3.7	3.39, br d, 4.5	2.86, t, 5.3	
C(1')H_A	1.23–1.91, m	1.24–1.96, m	1.25–1.95, m	1.27–1.97, m	1.25–2.07, m
C(1')H_B					
C(2')H_A					
C(2')H_B					
C(3')H_3	0.96, t, 7.3	0.90, t, 7.3	0.91, t, 7.2	0.92, t, 7.2	1.01, t, 7.1

Table 14 Comparison of ^{1}H NMR data for (+)-tetraponerine 1 **102** and (+)-tetraponerine 2 **103**.

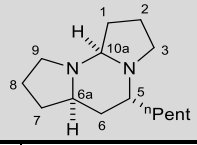
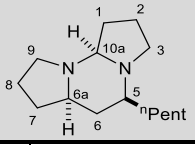
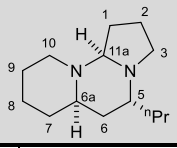
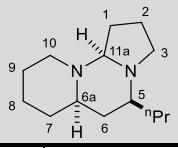
	^{1}H NMR shifts / ppm, multiplicity, *J* / Hz					
	(+)-Tetraponerine 5 **106** 			(+)-Tetraponerine 6 **107** 		
Assignment	This work C_6D_6	Ref 18 C_6D_6	Natural Break, 1988[a]	This work C_6D_6	Ref 18 C_6D_6	Natural Break, 1988[a]
C(1)H_A	1.28–2.01, m	1.35	-	1.23–1.98, m	1.77	-
C(1)H_B		1.79				
C(2)H_A		1.75			1.60	
C(2)H_B		1.85			1.80	
C(3)H_A	2.83–2.92, m	2.87	2.7–2.9, m	2.31–2.38, m	2.34, m	2.34, ddd, 9, 9, 5
C(3)H_B	3.23, q, 7.8	3.22, q, 8.0	3.22, ddd, 7, 7, 7	3.03–3.10, m	3.05, m	3.06, ddd, 9, 9, 4
C(5)*H*	2.83–2.92, m	2.84	2.7–2.9, m	2.39–2.46, m	2.42, m	2.43, m
C(6)H_A	1.28–2.01, m	1.34	-	1.23–1.98, m	1.34	-
C(6)H_B		1.80			1.43	
C(6a)*H*		1.98, m			1.88, m	
C(7)H_A		1.34			1.40	
C(7)H_B		1.62			1.70	
C(8)H_A		1.37			1.48	
C(8)H_B		1.58			1.68	
C(9)H_A		1.73, m			1.93, q, 8.5	
C(9)H_B	2.83–2.92, m	2.86	2.7–2.9, m	2.94, td, 8.5, 2.5	2.93, ddd, 8.5, 8.5, 2.2	2.94, ddd, 8, 8, 2.5
C(10a)*H*	3.51, t, 2.1	3.50, dd, 1.8, 1.8	3.50, dd, 4, 3	2.87, t, 5.3	2.86, dd, 6.5, 4.5	2.88, dd, 5, 5
C(1')H_A	1.28–2.01, m	1.32	-	1.23–1.98, m	1.37	-
C(1')H_B		1.76			1.60	
C(2')H_A		1.32			1.38	
C(2')H_B		1.52			1.40	
C(3')H_A		1.24			1.27	
C(3')H_B		1.32				
C(4')H_2		1.30			1.30	
C(5')H_3	0.93, t, 6.8	0.90, t, 6.5	0.93, t, 7	0.91, t, 7.0	0.90, t, 6.5	0.91, t, 7

Table 15 Comparison of ^{1}H NMR data for (+)-tetraponerine 5 **106** and (+)-tetraponerine 6 **107** [[a] the structures of **106** and **107** were original erroneously reported and so reassignment has been done here for data comparison].

	^{1}H NMR shifts / ppm, multiplicity, *J* / Hz					
	(+)-Tetraponerine 3 **104** 			(+)-Tetraponerine 4 **105** 		
Assignment	This work C_6D_6	Ref 5 C_6D_6	Ref 12 Natural C_6D_6	This work C_6D_6	Ref 5 C_6D_6	Ref 12 Natural C_6D_6
C(1)H_2	1.15–1.84, m	1.01–1.86, m	1.75	1.13–1.77, m	1.05–1.86, m	1.72
C(2)H_A			1.66			1.46
C(2)H_B			1.78			1.70
C(3)H_A	2.72–2.86, m	2.69–2.85, m	2.77	2.02, dd, 16.3, 8.6	2.04, dd, 15.9, 8.5	2.0, q, 8
C(3)H_B	3.17, app q, 7.5	3.20, dd, 14.6, 7.4	3.15, br q, 6.5	3.13, td, 8.6, 2.2	3.16, td, 8.2, 2.2	3.12, ddd, 8, 8, 2.5
C(5)*H*	2.72–2.86, m	2.69–2.85, m	2.80, br q, 6.5	2.11, ddd, 14.6, 7.4, 3.6	2.13, ddd, 10.7, 7.1, 3.4	2.09, m
C(6)H_A	1.09, dt, 12.7, 1.9	1.01–1.86, m	1.09, br d, 12.5	1.13–1.77, m	1.05–1.86, m	1.30
C(6)H_B	1.91, ddd, 12.7, 11.9, 5.3	1.87–1.97, m	1.90, br ddd, 12.5, 12.5, 5.5			1.43
C(6a)*H*	1.99–2.07, m	1.98–2.08, m	2.0, m			1.68
C(7)H_A	1.15–1.84, m	1.01–1.86, m	1.28			1.32
C(7)H_B			1.32			1.42
C(8)H_A			1.17			1.15
C(8)H_B			1.55			1.60
C(9)H_A			1.45			1.48
C(9)H_B			1.55			1.65
C(10)H_A						1.70
C(10)H_B	2.72–2.86, m	2.69–2.85, m	2.76	2.80–2.85, m	2.83, d, 8.1	2.80, ddd, 9.5, 2.5, 2.5
C(11a)*H*	3.30, t, 3.5	3.28, dd, 4.8, 2.2	3.28, dd, 4.9, 2	2.31, dd, 7.8, 5.6	2.35, t, 6.3	2.29, dd, 8, 6
C(1')H_A	1.15–1.84, m	1.01–1.86, m	1.32	1.13–1.77, m	1.05–1.86, m	1.32

C(1')H_B			1.74			1.50
C(2')H_A			1.33			1.22
C(2')H_B			1.43			1.36
C(3')H_3	0.95, t, 7.2	0.93, t, 7.1	0.90, t, 6.5	0.89, t, 7.1	0.88, t,7.1	0.89, t, 6.5

Table 16 Comparison of ^{1}H NMR data for (+)-tetraponerine 3 **104** and (+)-tetraponerine 4 **105**.

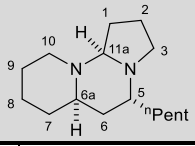
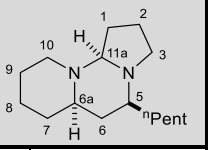
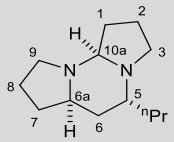
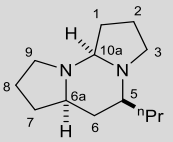
	^{1}H NMR shifts / ppm, multiplicity, *J* / Hz					
	(+)-Tetraponerine 7 **108** 			(+)-Tetraponerine 8 **109** 		
Assignment	This work C_6D_6	Ref 15 C_6D_6	Ref 12 Natural C_6D_6	This work C_6D_6	Ref 15 C_6D_6	Ref 12 Natural C_6D_6
C(1)H_A	1.17–1.86, m	1.15–1.85, m	1.72	1.16–1.78, m	1.14–1.78, m	1.74
C(1)H_B			1.82			
C(2)H_A			1.65			1.48
C(2)H_B			1.82			1.70
C(3)H_A	2.74–2.86, m	2.73–2.85, m	2.78, ddd, 8, 8, 2	2.05, dd, 16.3, 8.5	2.01–2.07, m	2.05, q, 8
C(3)H_B	3.15–3.21, m	3.14–3.22, m	3.22, br q, 8	3.15, td, 8.5, 2.2	3.12–3.19, m	3.16, ddd, 8, 8, 2
C(5)*H*	2.74–2.86, m	2.73–2.85, m	2.80	2.12, ddd, 14.6, 7.3, 3.6	2.09–2.15, m	2.12, m
C(6)H_A	1.13, dt, 12.9, 1.9	1.12, ddd, 13.0, 2.5, 1.5	1.10, br d, 12	1.16–1.78, m	1.14–1.78, m	1.35
C(6)H_B	1.93, ddd, 12.9, 11.9, 5.4	1.94, ddd, 13.0, 11.8, 5.4	1.98, br ddd, 12, 12, 5.4			1.50
C(6a)*H*	2.02–2.09, m	2.02–2.08, m	2.05, br t, 11			1.72
C(7)H_A	1.17–1.86, m	1.15–1.85, m	1.34			1.43
C(7)H_B			1.42			1.60
C(8)H_A			1.16			1.18
C(8)H_B			1.58			1.60
C(9)H_A			1.44			1.50
C(9)H_B			1.48			1.65
C(10)H_A			1.52			1.72
C(10)H_B	2.74–2.86, m	2.73–2.85, m	2.76	2.81–2.86, m	2.81–2.87, m	2.83, ddd, 10, 2.5, 2.5
C(11a)*H*	3.33, t, 3.6	3.32, dd, 4.8, 2.7	3.31, dd, 5.5, 2	2.31, dd, 7.9, 5.7	2.31, dd, 7.9, 5.8	2.32, dd, 8, 6
C(1')H_A	1.17–1.86, m	1.15–1.85, m	1.34	1.16–1.78, m	1.14–1.78, m	1.38
C(1')H_B			1.74			1.46
C(2')H_A			1.28			1.25
C(2')H_B			1.40			1.45
C(3')H_2			1.28			1.25
C(4')H_2			1.30			1.28
C(5')H_3	0.93, t, 6.9	0.92, t, 7.0	0.92, t, 7	0.90, t, 7.0	0.9, t, 7.1	0.90, t, 7

Table 17 Comparison of ^{1}H NMR data for (+)-tetraponerine 7 **108** and (+)-tetraponerine 8 **109**.

	^{13}C NMR shifts / ppm				
	(+)-Tetraponerine 1 **102** 			(+)-Tetraponerine 2 **103** 	
Assignment	This work C_6D_6	This Work $CDCl_3$	Royer (1st) $CDCl_3$	This work C_6D_6	Ref 17 C_6D_6
C(1)	30.1	29.7	29.6	29.3	28.9
C(2)	22.0	21.3	21.2	21.0	20.8
C(3)	51.0	50.4	50.2	45.8	45.5
C(5)	53.7	53.6	53.5	59.4	59.1
C(6)	30.1	29.4	29.4	33.4	32.7
C(6a)	58.3	58.3	58.3	64.2	63.8
C(7)	31.6	31.0	30.9	30.6	30.4
C(8)	20.4	20.2	20.1	21.3	21.1
C(9)	50.0	50.1	49.9	49.2	48.6
C(10a)	76.5	76.9	76.8	83.4	83.0
C(1')	35.4	34.0	33.9	37.0	36.5

C(2')	20.8	20.6	20.5	19.3	19.3
C(3')	14.5	14.3	14.2	14.7	14.6

Table 18 Comparison of ^{13}C NMR data for (+)-tetraponerine 1 **102** and (+)-tetraponerine 2 **103**.

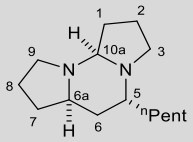
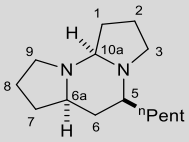
	^{13}C NMR shifts / ppm					
	(+)-Tetraponerine 5 **106** 			(+)-Tetraponerine 6 **107** 		
Assignment	This work C_6D_6	Ref 18 C_6D_6	Natural Break, 1988[a] C_6D_6	This work C_6D_6	Ref 18 C_6D_6	Natural Break, 1988[a] C_6D_6
C(1)	30.1/30.2	30.1	30.2	29.3	29.2	29.3
C(2)	22.0	22.0	22.0	21.0	20.8	21.0
C(3)	51.1	51.0	51.0	45.9	45.9	45.9
C(5)	54.1	54.1	54.1	59.7	59.6	59.7
C(6)	30.1/30.2	30.0	30.1	33.5	33.3	33.5
C(6a)	58.3	58.3	58.3	64.2	64.0	64.2
C(7)	31.6	31.5	31.6	30.7	30.5	30.7
C(8)	20.4	20.4	20.4	21.3	21.1	21.3
C(9)	50.1	50.0	50.0	49.2	49.1	49.2
C(10a)	76.5	76.0	76.5	83.5	83.2	83.4
C(1')	33.2	33.1	33.2	34.8	34.6	34.8
C(2')	27.5	27.4	27.4	25.9	25.9	25.9
C(3')	32.5	32.5	32.5	32.7	32.5	32.7
C(4')	23.2	23.2	23.2	23.4	23.0	23.1
C(5')	14.4	14.4	14.4	14.4	14.3	14.3

Table 19 Comparison of ^{13}C NMR data for (+)-tetraponerine 5 **106** and (+)-tetraponerine 6 **107** [[a] data have been reassigned for comparison].

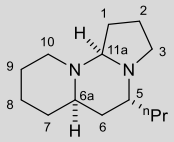
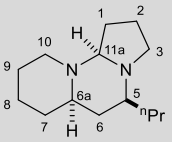
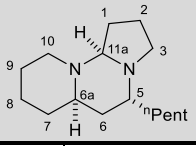
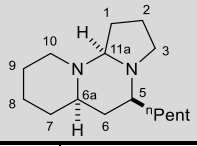
	^{13}C NMR shifts / ppm					
	(+)-Tetraponerine 3 **104** 			(+)-Tetraponerine 4 **105** 		
Assignment	This work C_6D_6	Ref 5 C_6D_6	Ref 12 Natural C_6D_6	This work C_6D_6	Ref 5 C_6D_6	Ref 12 Natural C_6D_6
C(1)	30.6	30.4	30.6	29.7	30.0	29.7
C(2)	22.2	22.2	22.2	20.2	20.8	20.3
C(3)	50.6	50.7	50.6	49.0	49.2	48.9
C(5)	53.0	52.8	53.0	61.1	61.4	61.1
C(6)	32.2	32.0	32.2	38.0	37.9	37.9
C(6a)	56.7	56.8	56.7	62.7	63.3	62.7
C(7)	34.3	33.9	34.3	33.0	33.2	33.0
C(8)	25.3	25.1	25.2	25.1	25.5	25.1
C(9)	26.6	26.2	26.6	26.3	26.5	26.2
C(10)	51.0	50.8	51.0	51.6	51.9	51.5
C(11a)	75.4	75.7	75.5	85.6	86.0	85.5
C(1')	33.4	33.2	33.3	36.9	37.3	36.9
C(2')	20.7	20.7	20.7	18.7	19.3	18.7
C(3')	14.5	14.5	14.5	14.8	15.3	14.8

Table 20 Comparison of ^{13}C NMR data for (+)-tetraponerine 3 **104** and (+)-tetraponerine 4 **105**.

	^{13}C NMR shifts / ppm					
	(+)-Tetraponerine 7 **108** 			(+)-Tetraponerine 8 **109** 		
Assignment	This work C_6D_6	Ref 15 C_6D_6	Ref 12 Natural C_6D_6	This work C_6D_6	Ref 15 C_6D_6	Ref 12 Natural C_6D_6

C(1)	30.6	30.6	30.5	29.8	29.8	29.3
C(2)	22.2	22.2	22.2	20.2	20.2	19.9
C(3)	50.7	50.7	50.7	49.0	49.1	49.7
C(5)	53.3	53.3	53.3	61.4	61.4	61.6
C(6)	32.3	32.2	32.2	38.0	38.0	37.6
C(6a)	56.7	56.7	56.8	62.7	62.7	62.6
C(7)	34.3	34.3	34.0	34.6	34.6	34.2
C(8)	25.3	25.3	25.1	25.2	25.1	24.7
C(9)	26.6	26.6	26.4	26.3	26.3	25.8
C(10)	51.0	51.0	50.9	51.6	51.6	51.3
C(11a)	75.5	75.5	75.6	85.6	85.6	85.4
C(1')	31.1	31.2	31.0	33.0	33.0	32.6
C(2')	27.4	27.4	27.4	25.2	25.2	24.9
C(3')	32.5	32.5	32.5	32.8	32.8	32.2
C(4')	23.2	23.3	23.2	23.2	23.2	22.9
C(5')	14.4	14.5	14.4	14.4	14.4	14.2

Table 21 Comparison of ^{13}C NMR data for (+)-tetraponerine 7 **108** and (+)-tetraponerine 8 **109**.

4.11 Conclusion

In conclusion, all eight tetraponerines were synthesised as single compounds (>99:1 dr) in an asymmetric and divergent manner from commercially available sorbic acid **302** in 1.9–19.3% overall yield in nine steps or fewer. The key synthetic steps involved were: (1) a diastereoselective lithium amide conjugate addition and ring closing metathesis for afford monocycles **304** and **345**, (2) chain homologation and a second diastereoselective lithium amide conjugate addition allowing for each epimer of the tetraponerines to be accessed, (3) functional group manipulation to install variable length alkyl chains and (4) deprotection and condensation of the resultant diamines with 4-bromobutanal **293** to produce the complete family of tetraponerines (Figure 20).

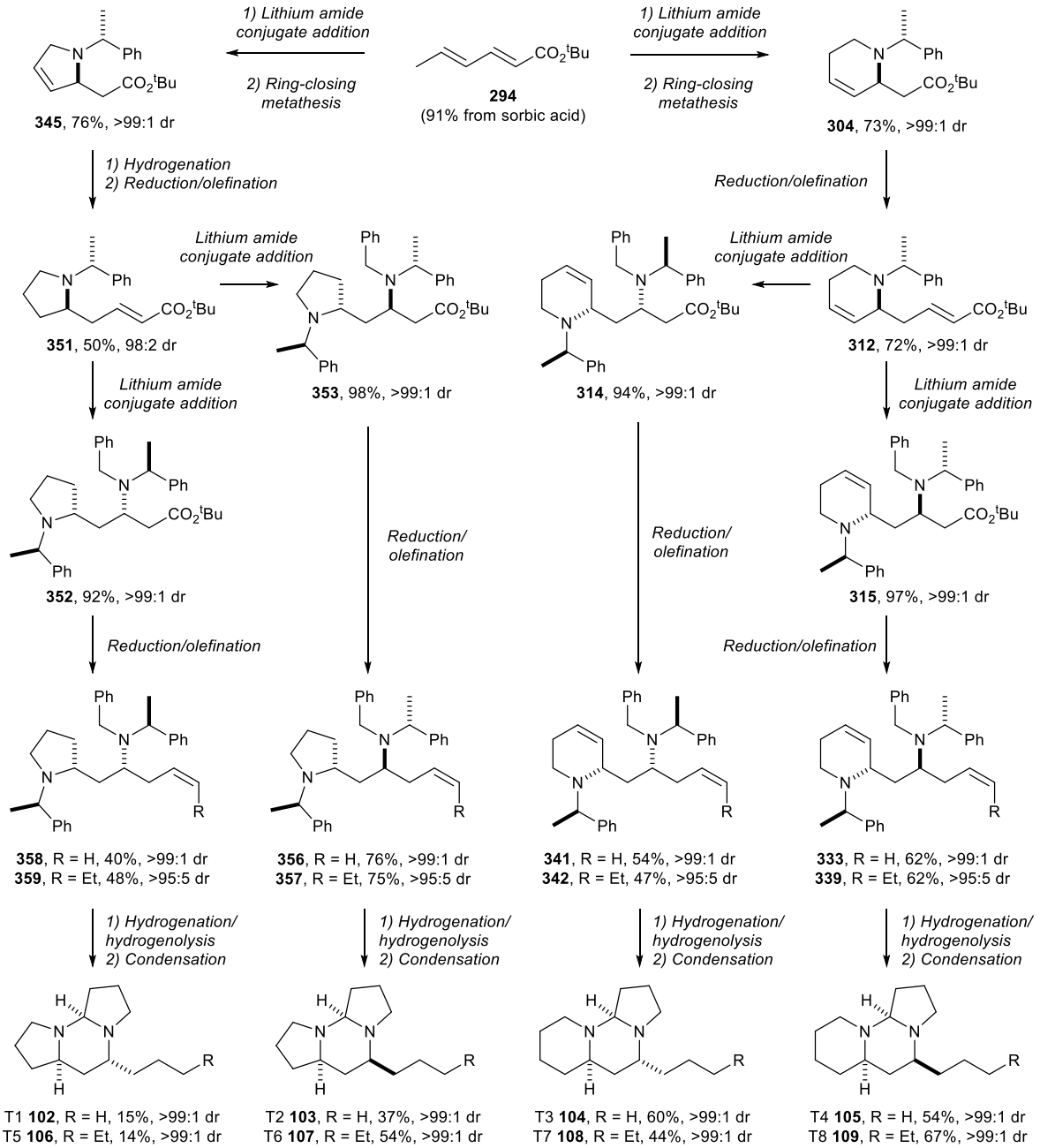


Figure 20 Summary of the asymmetric syntheses of **102**–**109**.

4.12 References and notes

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Chapter 5

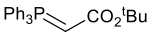
Experimental

5.1 General experimental

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs *et al*.[1] Water was purified by an Elix® UV-10 system. BuLi was supplied as a solution in hexanes and titrated against Ph_2CHCO_2H before use. All other solvents and reagents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm) and 1% aq $KMnO_4$. Flash column chromatography was performed on Kieselgel 60 silica. For biphasic eluents, the aqueous phase was removed prior to flash column chromatography. Melting points were recorded on a Gallenkamp Hot Stage or Leica Gallen III apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 or 341 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded on Bruker Tensor 27 FT-IR spectrometer on a diamond ATR module (ATR). Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated and at rt unless otherwise specified. The field was locked by external referencing to the relevant deuteron resonance. Chemical shifts (δ) are reported in ppm and coupling constants (J) in Hz. Low-resolution mass spectra were recorded on either a Micromass LCT Premier or Agilent Quadrupole 6120 LC/MS spectrometer. Accurate mass measurements were run on a Bruker MicroToF internally calibrated with polyalanine.

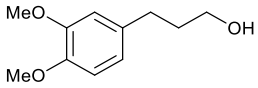
5.2 Experimental data for Chapter 2

tert-Butyl (triphenylphosphoranylidene)acetate 164



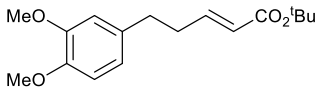
PPh_3 (40.0 g, 150 mmol) was added to a stirred solution of *tert*-butyl bromoacetate (22.5 mL, 150 mmol) in EtOAc (200 mL) at rt and the resultant solution was stirred at rt for 16 h. The resultant suspension was filtered and the precipitate was washed with Et_2O (50 mL), then added portionwise to 2 M aq NaOH (200 mL) and the resultant suspension was stirred at rt for 10 min. The resultant mixture was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **164** as a white solid (46.8 g, 81%);[2] mp 150–154 °C; δ_H (400 MHz, $CDCl_3$) 1.26 (9H, s, C*Me*$_3$), 2.70 (1H, br s, C(2)*H*), 7.35–7.73 (15H, m, *Ph*).

3-(3',4'-Dimethoxyphenyl)-propan-1-ol 171



$BF_3{\cdot}Et_2O$ (11.9 mL, 95.1 mmol) was added dropwise to a stirred solution of $NaBH_4$ (3.18 g, 95.1 mmol) and **165** (10.0 g, 47.6 mmol) in THF (100 mL) at 0 °C. The resultant mixture was stirred at 0 °C for 1 h then MeOH (60 mL) and aq HCl (1.0 M, 60 mL) were added sequentially. The resultant mixture was extracted with EtOAc (3 × 100 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **171** as a colourless oil (9.30 g, quant);[3] δ_H (400 MHz, $CDCl_3$) 1.84–1.92 (2H, m, C(2)H_2), 2.31 (1H, br s, O*H*), 2.65 (2H, t, *J* 7.7, C(3)H_2), 3.69 (2H, t, *J* 6.4, C(1)H_2), 3.85 (3H, s, O*Me*), 3.87 (3H, s, O*Me*), 6.71–6.75 (2H, m, C(2')*H*, C(5')*H*), 6.79 (1H, d, *J* 8.7, C(6')*H*).

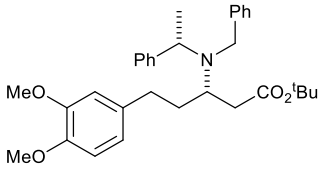
tert-Butyl 5-(3',4'-dimethoxyphenyl)pent-2-enoate 166



DMSO (4.3 mL, 61 mmol) was added to a stirred solution of $(COCl)_2$ (2.6 mL, 31 mmol) in CH_2Cl_2 (120 mL) at –78 °C and was stirred at –78 °C for 20 min. **171** (3.00 g, 15.3 mmol) was added and the resultant mixture was stirred at –78 °C for 40 min then Et_3N (12.8 mL, 91.7 mmol) was added. The reaction mixture was allowed to warm to rt over 30 min, **164** (5.75 g, 15.3 mmol) was added and the resultant

mixture was stirred for 16 h. Satd aq K_2CO_3 (100 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (300 mL) then dried and concentrated *in vacuo* to give **166** in >95:5 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 75:25:1) gave **166** as a pale yellow oil (2.57g, 58%, >99:1 dr); ν_{max} (ATR) 2976, 2934, 2835 (C–H), 1709 (C=O); δ_H (400 MHz, $CDCl_3$) 1.47 (9H, s, C*Me*$_3$), 2.43–2.50 (2H, m, C(4)*H*$_2$), 2.70 (2H, t, *J* 7.8, C(5)*H*$_2$), 3.85 (3H, s, O*Me*), 3.86 (3H, s, O*Me*), 5.76 (1H, d, *J* 15.7, C(2)*H*), 6.67–6.73 (2H, m, C(5')*H*, C(6')*H*), 6.79 (1H, d, *J* 8.1, C(2')*H*), 6.89 (1H, dt, *J* 15.7, 6.9, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 28.3 (C*Me*$_3$), 34.2 (*C*(4)), 34.2 (*C*(5)), 55.9, 56.0 (2 × O*Me*), 80.2 (O*C*Me$_3$), 111.3 (*C*(2')), 111.7 (*C*(5')), 120.2 (*C*(6')), 123.7 (*C*(2)), 133.7 (*C*(1')), 147.0 (*C*(3)), 147.4, 148.9 (*C*(3'), *C*(4')), 166.1 (*C*(1)); *m/z* (ESI$^+$) 315 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{17}H_{24}NaO_4^+$ ([M+Na]$^+$) requires 315.1578; found 315.1564.

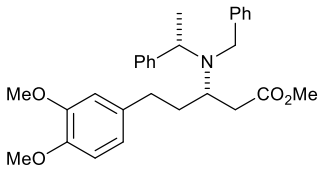
***tert*-Butyl (*S*,*S*)-3-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-5-(3',4'-dinethoxyphenyl)pentanoate 167**



BuLi (2.3 M in hexanes, 1.2 mL, 2.7 mmol) was added dropwise to a stirred solution of (*S*)-**100**[4] (578 mg, 2.74 mmol, >99:1 er) in THF (7 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. A solution of **166** (500 mg, 1.71 mmol, >99:1 dr) in THF (3 mL) at –78 °C was then added and the resultant mixture was stirred at –78 °C for 2 h. Satd aq NH_4Cl (2 mL) was added and the reaction mixture was allowed to warm to rt, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (15 mL) and 10% aq citric acid (15 mL), and the organic layer was washed with satd aq $NaHCO_3$ (15 mL) and brine (15 mL), then dried and concentrated *in vacuo* to give **167** in >99:1 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 80:24:1) gave **167** as a colourless oil (866 mg, quant, >99:1 dr); $[\alpha]_D^{25}$ +13.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3027, 2934, 2833 (C–H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.36–1.38 (12H, m, C(α)*Me*, C*Me*$_3$), 1.54–1.75 (2H, m, C(4)*H*$_2$), 1.91–1.99 (2H, m, C(2)*H*$_2$), 2.52 (1H, ddd, *J* 13.9, 10.7, 6.3, C(5)*H*$_A$), 2.97 (1H, ddd, *J* 13.9, 10.7, 5.0, C(5)*H*$_B$), 3.37–3.44 (1H, m, C(3)*H*), 3.55 (1H, d, *J* 15.1, NC*H*$_A$H$_B$Ph), 3.80–3.89 (8H, m, NCH$_A$*H*$_B$Ph, C(α)*H*, 2 × O*Me*), 6.64–6.68 (2H, m, C(2')*H*, C(6')*H*), 6.76 (1H, d, *J* 8.7, C(5')*H*), 7.22–

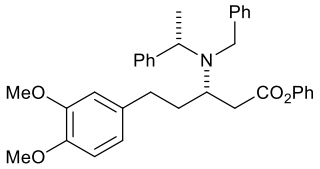
7.39 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.5 (C(α)*Me*), 28.2 (C*Me*$_3$), 33.4 (*C*(5)), 36.1 (*C*(4)), 37.7 (*C*(2)), 50.2 (N*C*H$_2$Ph), 54.1 (*C*(3)), 55.9, 56.1 (2 × OMe), 58.6 (*C*(α)Me), 80.2 (O*C*Me$_3$), 111.3 (*C*(5')), 111.8 (*C*(2')), 120.2 (*C*(6')), 126.8, 127.1 (2 × *p-Ph*), 128.1, 128.3, 128.3, 128.4 (2 × *o,m-Ph*), 135.6 (*C*(1')), 142.0, 143.0 (2 × *i-Ph*), 147.1, 148.9 (*C*(3'), *C*(4')), 172.2 (*C*(1)); *m/z* (ESI$^+$) 504 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{42}NO_4^+$ ([M+H]$^+$) requires 504.3108; found 504.3104.

Methyl (*S*,*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-(3',4'-dimethoxyphenyl)pentanoate 172



$SOCl_2$ (0.15 mL, 2.1 mmol) was added dropwise to a stirred solution of **167** (107 mg, 0.21 mmol, >99:1 dr) in MeOH (2 mL) at 0 °C. The resultant solution was stirred at 50 °C for 16 h then cooled to rt and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and aq NaOH (1.0 M, 10 mL). The organic layer was dried and concentrated *in vacuo* to give **172** as a colourless oil (98 mg, quant, >99:1 dr); $[\alpha]_D^{25}$ +16.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3027, 2935, 2834 (C–H), 1734 (C=O); δ_H (400 MHz, $CDCl_3$) 1.34 (3H, d, *J* 7.0, C(α)*Me*), 1.56–1.66 (1H, m, C(4)H_A), 1.72–1.83 (1H, m, C(4)H_B), 2.05–2.13 (2H, m, C(2)H_2), 2.54 (1H, ddd, *J* 13.9, 10.3, 5.6, C(5)H_A), 2.90 (1H, ddd, *J* 13.9, 10.3, 5.4, C(5)H_B), 3.37–3.44 (1H, m, C(3)*H*), 3.52 (3H, s, CO_2*Me*), 3.62 (1H, d, *J* 14.8, NCH_AH$_B$Ph), 3.82 (1H, d, *J* 14.8, NCH$_A$$H_B$Ph), 3.83 (3H, s, ArO*Me*), 3.86 (3H, s, ArO*Me*), 3.87 (1H, q, *J* 7.0, C(α)*H*), 6.65 (1H, d, *J* 1.8, C(2')*H*), 6.68 (1H, ddd, *J* 8.1, 1.8, C(6')*H*), 6.78 (1H, d, *J* 8.1, C(5')*H*), 7.22–7.38 (8H, m, *Ph*), 7.44–7.49 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.1 (C(α)*Me*), 33.3 (*C*(5)), 36.0 (*C*(4)), 36.6 (*C*(2)), 50.1 (N*C*H$_2$Ph), 51.5 (CO_2*Me*), 53.9 (*C*(3)), 55.9, 56.1 (2 × ArOMe), 58.1 (*C*(α)Me), 111.4 (*C*(5')), 112.0 (*C*(2')), 120.3 (*C*(6')), 126.9, 127.1 (2 × *p-Ph*), 128.1, 128.3, 128.4, 128.5 (2 × *o,m-Ph*), 135.2 (*C*(1')), 141.6, 143.1 (2 × *i-Ph*), 147.2, 148.9 (*C*(3'), *C*(4')), 173.2 (*C*(1)); *m/z* (ESI$^+$) 462 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{36}NO_4^+$ ([M+H]$^+$) requires 462.2639; found 462.2635.

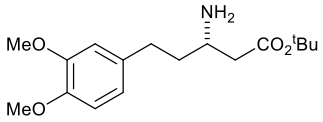
Phenyl (*S*,*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-(3',4'-dimethoxyphenyl)pentanoate 173



Step 1: **167** (374 mg, 0.743 mmol, >99:1 dr) was stirred in CH_2Cl_2/TFA (2:1, 5.4 mL) at rt for 16 h. The reaction mixture was concentrated *in vacuo* then satd aq $NaHCO_3$ (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried and concentrated *in vacuo*.

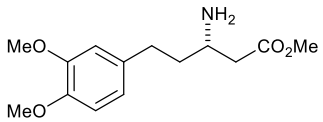
Step 2: DCC (169 mg, 0.817 mmol) was added to the residue from the previous step in CH_2Cl_2 (5 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 30 min. PhOH (70 mg, 0.74 mmol) was added and the reaction mixture was allowed to warm to rt and stirred for 16 h. EtOAc (10 mL) was added and the resultant mixture was filtered through Celite® (eluent EtOAc) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 66:33:1) gave **173** as a colourless oil (263 mg, 68%, >99:1 dr); $[\alpha]_D^{25}$ +14.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3027, 2933, 2834 (C–H), 1752 (C=O); δ_H (400 MHz, $CDCl_3$) 1.40 (3H, d, *J* 7.0, C(α)*Me*), 1.70–1.90 (2H, m, C(4)H_2), 2.21–2.30 (2H, m, C(2)H_2), 2.61 (1H, ddd, *J* 14.0, 10.0, 6.2, C(5)H_A), 2.98 (1H, ddd, *J* 14.0, 10.1, 5.3, C(5)H_B), 3.53–3.61 (1H, m, C(3)*H*), 3.66 (1H, d, *J* 14.9, NC$H_A$$H_B$Ph), 3.80 (3H, s, O*Me*), 3.86 (3H, s, O*Me*), 3.90 (1H, d, *J* 14.9, NCH$_A$$H_B$Ph), 3.93 (1H, q, *J* 7.0, C(α)*H*), 6.65–6.71 (2H, m, C(2')*H*, C(6')*H*), 6.77 (1H, d, *J* 8.0, C(5')*H*), 6.93 (2H, d, *J* 7.8, *o*-O*Ph*), 7.21 (1H, t, *J* 7.4, *p*-O*Ph*), 7.25–7.41 (10H, m, *m*-O*Ph*, *Ph*), 7.49–7.53 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.1 (C(α)*Me*), 33.2 (*C*(5)), 36.0 (*C*(4)), 36.7 (*C*(2)), 50.2 (N*C*H$_2$Ph), 54.0 (*C*(3)), 55.9, 56.1 (2 × OMe), 58.3 (*C*(α)Me), 111.3 (*C*(5')), 111.8 (*C*(2')), 120.3 (*C*(6')), 121.6 (*o*-O*Ph*), 125.9, 126.9, 127.3 (*p*-O*Ph*, 2 × *p*-*Ph*), 128.1, 128.4, 128.4, 128.5, 129.5 (*m*-O*Ph*, 2 × *o*,*m*-*Ph*), 135.1 (*C*(1')), 141.5, 142.7 (2 × *i*-*Ph*), 147.2, 148.9 (*C*(3'), *C*(4')), 150.7 (*i*-O*Ph*), 171.4 (*C*(1)); *m/z* (ESI$^+$) 524 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{34}H_{38}NO_4^+$ ([M+H]$^+$) requires 524.2795; found 524.2814.

***tert*-Butyl (*S*)-3-amino-5-(3',4'-diemthoxyphenyl)pentanoate 168**



$Pd(OH)_2/C$ (200 mg, 40% w/w) was added to a stirred, degassed solution of **167** (500 mg, 0.993 mmol, >99:1 dr) in MeOH (2 mL). The resultant mixture was stirred under an atmosphere of H_2 (5 atm) at rt for 16 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH), and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent Et_2O/NH_4OH, 100:1) gave **168** as a colourless oil (303 mg, 99%); $[\alpha]_D^{25}$ +1.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2975, 2934, 2836 (C–H), 1721 (C=O), 1516 (Ar); δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s, C*Me*$_3$), 1.57–1.76 (2H, m, C(4)*H*$_2$), 2.22 (1H, dd, *J* 15.5, 8.7, C(2)*H*$_A$), 2.40 (1H, dd, *J* 15.5, 4.2, C(2)*H*$_B$), 2.59 (1H, ddd, *J* 13.9, 9.7, 6.3, C(5)*H*$_A$), 2.68 (1H, ddd, *J* 13.9, 10.2, 5.9, C(5)*H*$_B$), 3.17 (1H, app sep, *J* 4.2, C(3)*H*), 3.84 (3H, s, O*Me*), 3.86 (3H, s, O*Me*), 6.70–6.73 (2H, m, C(2')*H*, C(6')*H*), 6.78 (1H, d, *J* 8.6, C(5')*H*); δ_C (100 MHz, $CDCl_3$) 28.3 (C*Me*$_3$), 32.2 (*C*(5)), 39.6 (*C*(4)), 44.1 (*C*(2)), 48.2 (*C*(3)), 55.9, 56.1 (2 × OMe), 80.7 (O*C*Me$_3$), 111.4, 111.8 (*C*(2'), *C*(5')), 120.2 (*C*(6')), 134.7 (*C*(1')), 147.3, 149.0 (*C*(3'), *C*(4')), 172.0 (*C*(1)); *m/z* (ESI^+) 310 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{17}H_{28}NO_4^+$ ($[M+H]^+$) requires 310.2013; found 310.2010.

Methyl (*S*)-3-amino-5-(3',4'-dimethoxyphenyl)pentanoate 169

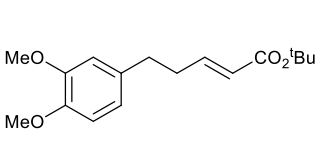


Method A: $Pd(OH)_2/C$ (200 mg, 40% w/w) was added to a stirred, degassed solution of **172** (500 mg, 1.08 mmol, >99:1 dr) in MeOH (2 mL). The resultant mixture was stirred under an atmosphere of H_2 (5 atm) at rt for 16 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH), and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent Et_2O/NH_4OH, 100:1) gave **169** as a colourless oil (237 mg, 82%); $[\alpha]_D^{25}$ –1.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2949, 2837 (C–H), 1731 (C=O), 1516 (Ar); δ_H (400 MHz, $CDCl_3$) 1.58–1.78 (2H, m, C(4)*H*$_2$), 2.30 (1H, dd, *J* 15.6, 8.8, C(2)*H*$_A$), 2.49 (1H, dd, *J* 15.6, 4.1, C(2)*H*$_B$), 2.58 (1H, ddd, *J* 13.9, 9.9, 6.4, C(5)*H*$_A$), 2.68 (1H, ddd, *J* 13.9, 9.6, 5.9, C(5)*H*$_B$), 3.20 (1H, app sep, *J* 4.1, C(3)*H*), 3.67 (3H, s, CO$_2$*Me*), 3.84 (3H, s, ArO*Me*), 3.85 (3H, s, ArO*Me*), 6.69–6.73 (2H, m, C(2')*H*, C(6')*H*), 6.78 (1H, d, *J* 8.5, C(5')*H*); δ_C (100 MHz,

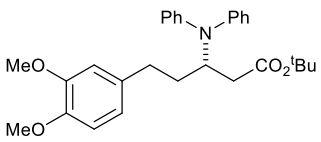
$CDCl_3$) 32.2 (*C*(5)), 39.6 (*C*(4)), 42.7 (*C*(2)), 48.1 (*C*(3)), 51.7 (CO_2*Me*), 55.9, 56.0 (2 × ArO*Me*), 111.4, 111.8 (*C*(2'), *C*(5')), 120.2 (*C*(6')), 134.4 (*C*(1')), 147.4, 149.0 (*C*(3'), *C*(4')), 173.0 (*C*(1)); *m/z* (ESI^+) 268 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{14}H_{22}NO_4^+$ ($[M+H]^+$) requires 268.1543; found 268.1542.

Method B: $SOCl_2$ (2.88 mL, 40.4 mmol) was added dropwise to a stirred solution of **168** (1.25 g, 4.04 mmol) in MeOH (30 mL) at 0 °C. The resultant solution was stirred at 50 °C for 16 h then cooled to rt and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (100 mL) and aq NaOH (1.0 M, 100 mL) and the organic layer was dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent Et_2O/NH_4OH, 100:1) gave **169** as a colourless oil (893 mg, 83%).

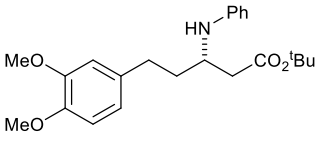
tert-Butyl 5-(3',4'-dimethoxyphenyl)pent-2-enoate 166, _tert_-butyl (_S_)-3-(_N_,_N_-diphenylamino)-5-(3',4'-dimethoxyphenyl)pentanoate 175 and _tert_-butyl (_S_)-3-(_N_-phenylamino)-5-(3',4'-dimethoxyphenyl)pentanoate 176



166



175

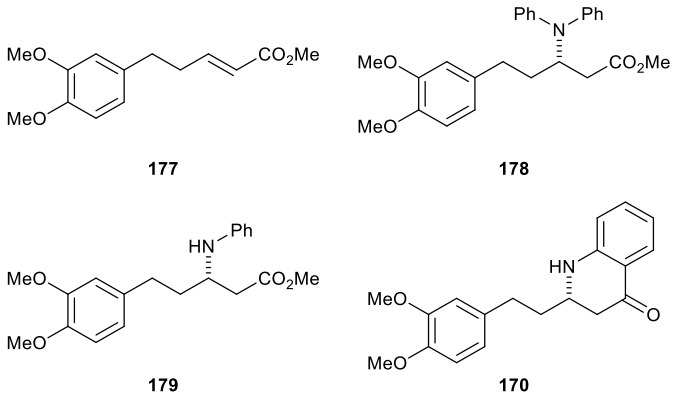


176

CsF (147 mg, 0.970 mmol) was dried *in vacuo* at 200 °C for 6 h, then cooled to rt and placed under N_2 (1 atm). **168** (100 mg, 0.323 mmol) in MeCN (1.6 mL) was added, followed by 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **158** (0.12 mL, 0.49 mmol) and the resultant suspension was stirred at rt for 16 h. Satd aq Na_2CO_3 (2 mL) was added, the resultant mixture was extracted with EtOAc (3 × 5 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give a 12:75:12 ratio of **166**, **176** and **175**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 75:25:1 to 0:100:1) gave a 52:48 mixture of **166** and **175** as a colourless oil (26 mg, 22%). Data for **175**: δ_H (400 MHz, $CDCl_3$) 1.35 (9H, s, OCMe_3), 1.64–1.74 (1H, m, C(4)H_A), 1.79–1.90 (1H, m, C(4)H_B), 2.36 (1H, dd, *J* 14.8, 7.9, C(2)H_A), 2.42–2.49 (1H, m, C(5)H_A), 2.59–2.79 (2H, m, C(2)H_B, C(5)H_B), 3.76 (3H, s, O*Me*), 3.83 (3H, s, O*Me*), 4.53–4.61 (1H, m, C(3)*H*), 6.56 (1H, d, *J* 1.7, C(2')*H*), 6.64 (1H, dd, *J* 8.1, 1.7, C(6')*H*), 6.75 (1H, d, *J* 8.1, C(5')*H*), 6.92 (4H, d, *J* 8.0, *o*-*Ph*), 6.99 (2H, t, *J* 7.3, *p*-*Ph*), 7.23–7.28 (4H, m, *m*-*Ph*); δ_C (100 MHz, $CDCl_3$) 28.1 (CMe_3), 32.7 (*C*(5)), 35.6 (*C*(4)), 40.6 (*C*(2)), 54.3 (*C*(3)), 55.8, 56.0 (2 × O*Me*), 80.8 (O*C*Me$_3$), 111.3, 111.9 (*C*(2'), *C*(5')), 120.3 (*C*(6')),

122.2 (*p-Ph*), 123.1 (*o-Ph*), 129.4 (*m-Ph*), 134.3 (*C*(1')), 146.6 (*i-Ph*), 147.3, 148.9 (*C*(3'), *C*(4')), 171.3 (*C*(1)); *m/z* (ESI$^+$) 462 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{36}NO_4^+$ ([M+H]$^+$) requires 462.2639; found 462.2636. Data for mixture: ν_{max} (ATR) 2978, 2933, 2834 (C–H), 1714 (C=O). Further elution gave **176** as a colourless oil (66 mg, 53%); $[\alpha]_D^{25}$ –16.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3383 (N–H), 3002, 2975, 2934, 2835 (C–H), 1721 (C=O); δ_H (400 MHz, $CDCl_3$) 1.41 (9H, s, OC*Me*$_3$), 1.85–1.92 (2H, m, C(4)*H*$_2$), 2.42 (1H, dd, *J* 14.8, 6.0, C(2)*H*$_A$), 2.49 (1H, dd, *J* 14.8, 5.0, C(2)*H*$_B$) 2.64–2.78 (2H, m, C(5)*H*$_2$), 3.71–3.80 (1H, m, C(3)*H*), 3.80 (3H, s, O*Me*), 3.86 (3H, s, O*Me*), 6.58 (2H, d, *J* 7.8, *o-Ph*), 6.67–6.73 (3H, m, C(2')*H*, C(6')*H*, *p-Ph*), 6.80 (1H, d, *J* 8.0, C(5')*H*), 6.16 (2H, t, *J* 7.8, *m-Ph*); δ_C (100 MHz, $CDCl_3$) 28.1 (C*Me*$_3$), 32.0 (*C*(5)), 36.7 (*C*(4)), 40.6 (*C*(2)), 49.7 (*C*(3)), 55.8, 56.0 (2 × O*Me*), 80.8 (O*C*Me$_3$), 111.3 (*C*(2')), 111.8 (*C*(5')), 113.5 (*C*(2"), *C*(6")), 117.5 (*C*(4")), 120.3 (*C*(6')), 129.4 (*C*(3"), *C*(5")), 134.2 (*C*(1')), 147.3, 147.3, 148.9 (*C*(3'), *C*(4'), *C*(1")), 171.3 (*C*(1)); *m/z* (ESI$^+$) 386 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{32}NO_4^+$ ([M+H]$^+$) requires 386.2326; found 386.2320.

(*S*)-2-[2'-(3'',4''-Dimethoxyphenyl)ethanyl]-2,3-dihydroquinolin-4(1*H*)-one 170, methyl 5-(3',4'-dimethoxyphenyl)pent-2-enoate 177, methyl (*S*)-3-(*N*,*N*-diphenylamino)-5-(3',4'-dimethoxyphenyl)pentanoate 178 and methyl (*S*)-3-(*N*-phenylamino)-5-(3',*4*'-dimethoxyphenyl)pentanoate 179



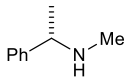
Method A: CsF (170 mg, 1.12 mmol) was dried *in vacuo* at 200 °C for 6 h, then cooled to rt and placed under N_2 (1 atm). **169** (100 mg, 0.374 mmol) in MeCN (1.9 mL) was added, followed by 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **158** (0.14 mL, 0.56 mmol) and the resultant suspension was stirred at rt for 16 h. Satd aq Na_2CO_3 (2 mL) was added, the resultant mixture was extracted with EtOAc (3 × 5 mL) and the combined organic extracts were dried and concentrated *in*

vacuo to give a 16:69:15 ratio of **177**, [**178+179**] and **170**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 75:25:1 to 0:100:1) gave a 58:42 mixture of **177** and **178** as a yellow oil (29 mg, 24%). Data for **178**: δ_H (400 MHz, $CDCl_3$) 1.69–1.80 (1H, m, C(4)H_A), 1.84–1.94 (1H, m, C(4)H_B), 2.45–2.54 (1H, m, C(2)H_A), 2.59–2.67 (1H, m, C(5)H_A), 2.70–2.82 (2H, m, C(2)H_B, C(5)H_B), 3.60 (3H, s, CO_2*Me*), 3.78 (3H, s, ArO*Me*), 3.86 (3H, s, ArO*Me*), 4.57–4.65 (1H, m, C(3)*H*), 6.56 (1H, d, *J* 1.7, C(2')*H*), 6.64 (1H, dd, *J* 8.1, 1.7, C(6')*H*), 6.76 (1H, d, *J* 8.1, C(5')*H*), 6.92 (4H, d, *J* 7.7, *o-Ph*), 6.97–7.03 (2H, m, *p-Ph*), 7.25–7.29 (4H, m, *m-Ph*); δ_C (100 MHz, $CDCl_3$) 32.6 (*C*(5)), 35.6 (*C*(4)), 38.9 (*C*(2)), 51.8 (CO_2*Me*), 54.3 (*C*(3)), 55.8, 56.0 (2 × ArO*Me*), 111.3 (*C*(5')), 111.7 (*C*(2')), 120.2 (*C*(6')), 122.3 (*p-Ph*), 123.1 (*o-Ph*), 129.4 (*m-Ph*), 134.1 (*C*(1')), 146.5 (*i-Ph*), 147.3, 148.9 (*C*(3'), *C*(4')), 172.4 (*C*(1)); *m/z* (ESI^+) 420 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{26}H_{30}NO_4^+$ ($[M+H]^+$) requires 420.2169; found 420.2168. Data for mixture: ν_{max} (ATR) 2997, 2949, 2835 (C–H), 1722 (C=O). Further elution gave **179** as a yellow oil (62 mg, 51%); $[\alpha]_D^{25}$ –12.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3393 (N–H), 2951, 2934, 2907, 2834 (C–H), 1733 (C=O); δ_H (400 MHz, $CDCl_3$) 1.86–1.93 (2H, m, C(4)H_2), 2.50–2.61 (2H, m, C(2)H_2), 2.64–2.81 (2H, m, C(5)H_2), 3.64 (3H, s, CO_2*Me*), 3.76–3.82 (1H, m, C(3)*H*) overlapping 3.80 (3H, s, ArO*Me*), 3.86 (3H, s, ArO*Me*), 6.58 (2H, d, *J* 7.8, *o-Ph*), 6.66–6.73 (3H, m, C(2')*H*, C(6')*H*, *p-Ph*), 6.79 (1H, d, *J* 8.1, C(5')*H*), 7.16 (2H, t, *J* 7.8, *m-Ph*); δ_C (100 MHz, $CDCl_3$) 32.0 (*C*(5)), 36.7 (*C*(4)), 39.1 (*C*(2)), 49.6 (*C*(3)), 51.7 (CO_2*Me*), 55.8, 56.0 (2 × ArO*Me*), 111.3 (*C*(5')), 111.8 (*C*(2')), 113.6 (*o-Ph*), 117.7 (*p-Ph*), 120.3 (*C*(6')), 129.4 (*m-Ph*), 134.1 (*C*(1')), 147.2, 147.3, 148.9 (*C*(3'), *C*(4'), *i-Ph*), 172.4 (*C*(1)); *m/z* (ESI^+) 344 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{26}NO_4^+$ ($[M+H]^+$) requires 344.1856; found 344.1859. Further elution gave **170** as a yellow oil (16 mg, 14%); $[\alpha]_D^{25}$ –89.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3349 (N–H), 2958, 2934, 2909, 2834 (C–H), 1672 (C=O); δ_H (400 MHz, $CDCl_3$) 1.88–2.04 (2H, m, C(1')H_2), 2.54 (1H, dd, *J* 16.1, 12.1, C(3)H_A), 2.61–2.79 (3H, m, C(3)H_B, C(2')H_2), 3.63–3.71 (1H, m, C(2)*H*), 3.86 (6H, s, 2 × O*Me*), 4.26 (1H, br s, N*H*), 6.56 (1H, d, *J* 8.2, C(8)*H*), 6.70–6.76 (3H, m, C(6)*H*, C(2")*H*, C(6")*H*), 6.81 (1H, d, *J* 8.1, C(5")*H*), 7.26–7.31 (1H, m, C(7)*H*), 7.81 (1H, dd, *J* 7.9, 1, C(5)*H*); δ_C (100 MHz, $CDCl_3$) 31.7 (*C*(2')), 36.7 (*C*(1')), 44.0 (*C*(3)), 53.2 (*C*(2)), 56.0, 56.1 (2 × O*Me*), 111.5 (*C*(5")), 111.6 (*C*(2")), 115.9 (*C*(8)), 118.1 (*C*(6)), 119.2 (*C*(4a)), 120.2 (*C*(6")), 127.6 (*C*(5)), 133.5 (*C*(1")), 135.4 (*C*(7)), 147.6, 149.2, 151.4 (*C*(8a), *C*(3"), *C*(4")), 193.9 (*C*(4)); *m/z* (ESI^+) 312 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{19}H_{22}NO_3^+$ ($[M+H]^+$) requires 312.1594; found 312.1596.

Method B – Step 1: $Pd(OH)_2/C$ (99 mg, 40% w/w) was added to a stirred, degassed solution of **173** (248 mg, 0.474 mmol, >99:1 dr) in EtOAc (2 mL). The resultant mixture was stirred under an atmosphere of H_2 (5 atm) at rt for 24 h. The reaction mixture was then filtered through a short plug of Celite® (eluent EtOAc), and concentrated *in vacuo* to give **174** as a colourless oil (163 mg, quant).

Step 2: CsF (104 mg, 0.683 mmol) was dried *in vacuo* at 200 °C for 6 h, then cooled to rt and placed under N_2 (1 atm). **174** (75 mg, 0.228 mmol) in MeCN (1.5 mL) was added, followed by 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **158** (83 μL, 0.34 mmol) and the resultant suspension was stirred at rt for 16 h. Satd aq Na_2CO_3 (2 mL) was added, the resultant mixture was extracted with EtOAc (3 × 5 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 50:50:1) gave **170** as a yellow oil (11 mg, 15 %).

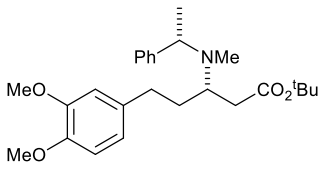
(*S*)-*N*-Methyl-*N*-(α-methylbenzyl)amine 183



Step 1: Ethyl chloroformate (19.1 mL, 200 mmol) in Et_2O (150 mL) at 0 °C was added to a stirred solution of (*S*)-α-methylbenzylamine (25.8 mL, 200 mmol) and Et_3N (33.5 mL, 240 mmol) in Et_2O (150 mL) at 0 °C. The resultant mixture was stirred and allowed to warm to rt over 2 h then washed sequentially with aq HCl (1.0 M, 500 mL), satd aq $NaHCO_3$ (500 mL) and brine (500 mL). The organic extract was dried and concentrated *in vacuo* to give ethyl (*S*)-*N*-(α-methylbenzyl)carbamate as a white solid (35.6 g, 92%).

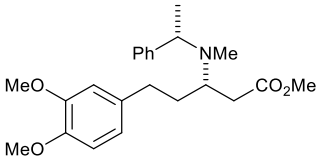
Step 2: $LiAlH_4$ (2.4 M in THF, 21.6 mL, 51.7 mmol) was added dropwise to a stirred solution of ethyl (*S*)-*N*-(α-methylbenzyl)carbamate (5.00 g, 25.9 mmol, >99:1 er) in THF (150 mL) at 0 °C. The resultant mixture was heated at reflux for 24 h then cooled to 0 °C. Aq NaOH (2.0 M, 25 mL) was then added and the resultant mixture was stirred at rt for 1 h. The reaction mixture was then filtered through Celite® (eluent EtOAc), then concentrated *in vacuo* to give **183** as a colourless oil (3.13 g, 90%, >99:1 er);[5,6] $[\alpha]_D^{25}$ –62.6 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.38 (3H, d, *J* 6.6, C(α)*H*), 2.33 (3H, s, N*Me*), 3.66 (1H, q, *J* 6.6, C(α)*Me*),7.24–7.38 (5H, m, *Ph*).

tert-Butyl (*S*,*S*)-3-[*N*-methyl-*N*-(α-methylbenzyl)amino]-5-(3',4'-dimethoxyphenyl)pentanoate 180



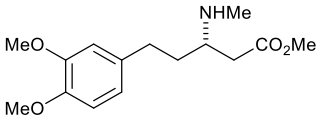
BuLi (2.3 M in hexanes, 3.1 mL, 7.2 mmol) was added dropwise to a stirred solution of **183** (1.00 g, 7.40 mmol, >99:1 er) in THF (15 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. A solution of **166** (1.35 g, 4.62 mmol, >99:1 dr) in THF (5 mL) at –78 °C was then added and the resultant mixture was stirred at –78 °C for 2 h. Satd aq NH_4Cl (5 mL) was added and the reaction mixture was allowed to warm to rt, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (40 mL) and 10% aq citric acid (40 mL), and the organic layer was washed with satd aq $NaHCO_3$ (40 mL) and brine (40 mL), then dried and concentrated *in vacuo* to give **180** in >95:5 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 50:50:1) gave **180** as a pale yellow oil (2.01 g, quant, >95:5 dr); $[\alpha]_D^{25}$ +0.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2975, 2934, 2835, 2787 (C–H), 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.32 (3H, d, *J* 6.6, C(α)*Me*), 1.40 (9H, s, C*Me*$_3$), 1.47–1.58 (1H, m, C(4)H_A), 1.66–1.76 (1H, m, C(4)H_B), 2.14 (1H, dd, *J* 13.9, 7.9, C(2)H_A) overlapping 2.16 (3H, s, N*Me*), 2.34–2.44 (1H, m, C(5)H_A) overlapping 2.43 (1H, dd, *J* 13.9, 5.7, C(2)H_B), 2.66 (1H, ddd, *J* 13.9, 10.4, 5.6, C(5)H_B), 3.17–3.25 (1H, m, C(3)*H*), 3.61 (1H, q, *J* 6.6, C(α)*H*), 3.85 (6H, s, 2 × O*Me*), 6.63–6.67 (2H, m, C(2')*H*, C(6')*H*), 6.76 (1H, d, *J* 8.6, C(5')*H*), 7.18–7.33 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.9 (C(α)*Me*), 28.2 (C*Me*$_3$), 31.9 (N*Me*), 32.8 (*C*(5)), 33.4 (*C*(4)), 36.6 (*C*(2)), 55.9, 56.1 (2 × O*Me*), 56.1 (*C*(3)), 62.2 (*C*(α)Me), 80.1 (O*C*Me$_3$), 111.3 (*C*(5')), 111.8 (*C*(2')), 120.1 (*C*(6')), 126.9 (*p-Ph*), 127.6, 128.3 (*o*,*m-Ph*), 135.5 (*C*(1')), 146.0, 147.1, 148.9 (*C*(3'), *C*(4'), *i-Ph*), 172.5 (*C*(1)); *m/z* (ESI$^+$) 428 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{38}NO_4^+$ ([M+H]$^+$) requires 428.2795; found 428.2787.

Methyl (*S*,*S*)-3-[*N*-methyl-*N*-(α-methylbenzyl)amino]-5-(3',4'-dimethoxyphenyl)pentanoate 181



$SOCl_2$ (3.3 mL, 45 mmol) was added dropwise to a stirred solution of **180** (1.94 g, 4.53 mmol, >95:5 dr) in MeOH (40 mL) at 0 °C. The resultant solution was stirred at 50 °C for 16 h then cooled to rt and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (100 mL) and aq NaOH (1.0 M, 100 mL) and the organic layer was dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 50:50:1) gave **181** as a colourless oil (1.71 g, 98%, >99:1 dr); $[\alpha]_D^{25}$ –4.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3028, 2998, 2980, 2970, 2933, 2906, 2834 (C–H), 1735 (C=O); δ_H (400 MHz, $CDCl_3$) 1.30 (3H, d, *J* 6.6, C(α)*Me*), 1.49–1.61 (1H, m, C(4)H_A), 1.68–1.79 (1H, m, C(4)H_B), 2.17 (3H, s, N*Me*), 2.28 (1H, dd, *J* 14.0, 7.5, C(2)H_A), 2.41 (1H, ddd, *J* 14.0, 10.5, 5.5, C(5)H_A), 2.52 (1H, dd, *J* 14.0, 6.5, C(2)H_B), 2.67 (1H, ddd, *J* 14.0, 10.4, 5.6, C(5)H_B), 3.24–3.33 (1H, m, C(3)*H*), 3.61 (1H, q, *J* 6.6, C(α)*H*) overlapping 3.64 (3H, s, CO_2*Me*), 3.85 (3H, s, ArO*Me*), 3.86 (3H, s, ArO*Me*), 6.65–6.69 (2H, m, C(2')*H*, C(6')*H*), 6.77 (1H, d, *J* 7.9, C(5')*H*), 7.18–7.30 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 22.0 (C(α)*Me*), 31.8 (N*Me*), 32.8 (*C*(5)), 33.4 (*C*(4)), 35.5 (*C*(2)), 51.6 (CO_2*Me*), 55.9, 55.9, 56.1 (*C*(3), 2 × ArO*Me*), 62.2 (*C*(α)Me), 111.3 (*C*(5')), 111.8 (*C*(2')), 120.1 (*C*(6')), 126.9 (*p*-*Ph*), 127.4, 128.3 (*o*,*m*-*Ph*), 135.2 (*C*(1')), 146.0, 147.2, 148.9 (*C*(3'), *C*(4'), *i*-*Ph*), 173.6 (*C*(1)); *m/z* (ESI^+) 386 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{23}H_{32}NO_4^+$ ($[M+H]^+$) requires 386.2326; found 386.2320.

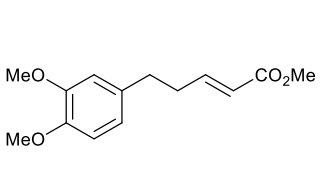
Methyl (*S*)-3-(*N*-methylamino)-5-(3',4'-dimethoxyphenyl)pentanoate 182



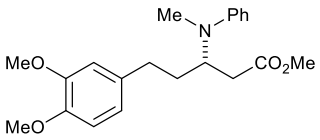
$Pd(OH)_2$/C (245 mg, 40% w/w) was added to a stirred, degassed solution of **181** (613 mg, 1.59 mmol, >99:1 dr) in MeOH (2 mL). The resultant mixture was stirred under an atmosphere of H_2 (5 atm) at rt for 16 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH), and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent Et_2O/NH_4OH, 100:1) gave **182** as a colourless oil (326 mg, 84%); $[\alpha]_D^{25}$ +4.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3340 (N–H), 2981, 2951,

2933, 2906, 2886 (C–H), 1733 (C=O); δ_H (400 MHz, $CDCl_3$) 1.41 (1H, br s, N*H*), 1.66–1.84 (2H, m, C(4)H_2), 2.40 (3H, s, N*Me*), 2.47 (2H, dd, *J* 6.3, 1.3, C(2)H_2), 2.62 (1H, t, *J* 8.2, C(5)H_2), 2.92 (1H, quin, *J* 6.3, C(3)*H*), 3.68 (3H, s, CO_2Me), 3.85 (3H, s, ArO*Me*), 3.87 (3H, s, ArO*Me*), 6.70–6.74 (2H, m, C(2')*H*, C(6')*H*), 6.79 (1H, d, *J* 8.5, C(5')*H*); δ_C (100 MHz, $CDCl_3$) 31.8 (*C*(5)), 33.4 (N*Me*), 36.0 (*C*(4)), 38.4 (*C*(2)), 51.7 (CO_2Me), 56.0, 56.0, 56.1 (*C*(3), 2 × ArO*Me*), 111.4, 111.8 (*C*(2'), *C*(5')), 120.2 (*C*(6')), 134.7 (*C*(1')), 147.3, 149.0 (*C*(3'), *C*(4')), 173.0 (*C*(1)); *m/z* (ESI^+) 282 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{15}H_{24}NO_4^+$ ($[M+H]^+$) requires 282.1700; found 282.1701.

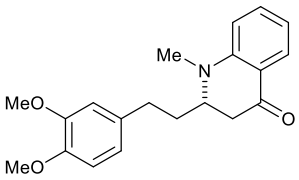
Methyl 5-(2',3'-diemthoxyphenyl)pent-2-enoate 177, methyl (*S*)-3-(*N*-phenyl-*N*-methylamino)-5-(3',4'-dimethoxyphenyl)pentanoate 185 and (*S*)-2-[2'-(3'',4''-dimethoxyphenyl)ethanyl]-1-methyl-2,3-dihydroquinolin-4(1*H*)-one 186



177



185



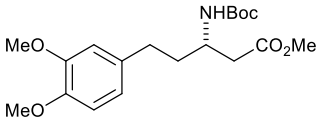
186

Method A: CsF (810 mg, 5.33 mmol) was dried *in vacuo* at 200 °C for 6 h, then cooled to rt and placed under N_2 (1 atm). **182** (500 mg, 1.78 mmol) in MeCN (9 mL) was added, followed by 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **158** (0.65 mL, 2.7 mmol) and the resultant suspension was stirred at rt for 16 h. Satd aq Na_2CO_3 (10 mL) was added, the resultant mixture was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give a 37:51:12 ratio of **177**, **185** and **186**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 75:25:1 to 0:100:1) gave **177** as a colourless oil (127 mg, 29%, >99:1 dr); ν_{max} (ATR) 2987, 2949, 2836 (C–H), 1720 (C=O); δ_H (400 MHz, $CDCl_3$) 2.47–2.54 (2H, m, C(4)H_2), 2.72 (2H, t, *J* 7.7, C(5)H_2), 3.72 (3H, s, CO_2Me), 3.85 (3H, s, ArO*Me*), 3.87 (3H, s, ArO*Me*), 5.84 (1H, dt, *J* 15.7, 1.5, C(2)*H*), 6.69 (1H, d, *J* 2.0, C(2')*H*), 6.71 (1H, dd, *J* 8.1, 2, C(6')*H*), 6.79 (1H, d, *J* 8.1, C(5')*H*), 7.00 (1H, dt, *J* 15.7, 6.9, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 34.1 (*C*(5)), 34.2 (*C*(4)), 51.6 (CO_2Me), 56.0, 56.0 (2 × ArO*Me*), 111.4 (*C*(5')), 111.8 (*C*(2')), 120.3 (*C*(6')), 121.6 (*C*(2)), 133.5 (*C*(1')), 147.5 (*C*(4')), 148.6 (*C*(3)), 149.0 (*C*(3')), 167.1 (*C*(1)); *m/z* (ESI^+) 273 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{14}H_{18}NaO_4^+$ ($[M+Na]^+$) requires 273.1097; found 273.1096. Further elution gave **185** as

a yellow oil (298 mg, 47%); $[\alpha]_D^{25}$ –10.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2981, 2889 (C–H), 1735 (C=O); δ_H (400 MHz, $CDCl_3$) 1.78–1.88 (1H, m, C(4)H_A), 1.92–2.03 (1H, m, C(4)H_B), 2.42–2.52 (2H, m, C(2)H_A, C(5)H_A), 2.56–2.64 (2H, m, C(2)H_B, C(5)H_B), 2.77 (3H, s, N*Me*), 3.53 (3H, s, CO_2*Me*), 3.75 (3H, s, ArO*Me*), 3.85 (3H, s, ArO*Me*), 4.27–4.36 (1H, m, C(3)*H*), 6.57 (1H, d, *J* 1.9, C(2')*H*), 6.65 (1H, dd, *J* 8.2, 1.9, C(6')*H*), 6.72 (1H, t, *J* 7.2, *p-Ph*), 6.76 (1H, d, *J* 8.2, C(5')*H*), 6.80 (2H, d, *J* 8.4, *o-Ph*), 7.21 (2H, dd, *J* 8.4, 7.2, *m-Ph*); δ_C (100 MHz, $CDCl_3$) 30.2 (N*Me*), 32.3 (*C*(5)), 34.8 (*C*(4)), 37.7 (*C*(2)), 51.7 (CO_2*Me*), 55.3, 55.8 (2 × ArO*Me*), 56.1 (*C*(3)), 111.3 (*C*(5')), 112.0 (*C*(2')), 113.8 (*o-Ph*), 117.3 (*p-Ph*), 120.2 (*C*(6')), 129.2 (*m-Ph*), 134.6 (*C*(1')), 147.3, 148.8, 150.4 (*C*(3'), *C*(4'), 2 × *i-Ph*), 172.4 (*C*(1)); *m/z* (ESI^+) 358 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{21}H_{28}NO_4^+$ ($[M+H]^+$) requires 358.2013; found 358.2013. Further elution gave **186** as a yellow oil (67 mg, 12%); $[\alpha]_D^{25}$ –255.2 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 2938, 2833 (C–H), 1670 (C=O); δ_H (400 MHz, $CDCl_3$) 1.89–1.93 (2H, m, C(1')H_2), 2.46 (1H, dt, *J* 14.3, 8.2, C(2')H_A), 2.67 (1H, ddd, *J* 14.3, 9.1, 6.3, C(2')H_B) overlapping 2.73 (1H, dd, *J* 16.2, 2.3, C(3)H_A), 3.00 (3H, s, N*Me*) overlapping 3.01 (1H, dd, *J* 16.2, 6.1, C(3)H_B), 3.51–3.57 (1H, m, C(2)*H*), 3.84 (3H, s, O*Me*), 3.85 (3H, s, O*Me*), 6.59 (1H, d, *J* 8.6, C(8)*H*), 6.63–6.71 (3H, m, C(6)*H*, C(2")*H*, C(6")*H*), 6.77 (1H, d, *J* 8.1, C(5")*H*), 7.38 (1H, ddd, *J* 8.6, 7.1, 1.8, C(7)*H*), 7.86 (1H, dd, *J* 7.8, 1.8, C(5)*H*); δ_C (100 MHz, $CDCl_3$) 30.2 (*C*(1')), 31.8 (*C*(2')), 38.2 (N*Me*), 41.4 (*C*(3)), 56.0, 56.1 (2 × O*Me*), 60.9 (*C*(2)), 111.4 (*C*(5")), 111.6 (*C*(2")), 113.0 (*C*(8)), 116.3 (*C*(6)), 119.3 (*C*(4a)), 120.2 (*C*(6")), 127.7 (*C*(5)), 133.6 (*C*(1")), 136.0 (*C*(7)), 147.5, 149.1 (*C*(3"), *C*(4")), 150.3 (*C*(8a)), 193.4 (*C*(4)); *m/z* (ESI^+) 326 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{24}NO_3^+$ ($[M+H]^+$) requires 326.1751; found 326.1752.

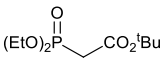
Method B: CsF (79 mg, 0.52 mmol) was dried *in vacuo* at 200 °C for 6 h, then cooled to rt and placed under N_2 (1 atm). **182** (49 mg, 0.17 mmol) in THF (0.9 mL) was added, followed by 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **158** (63 μL, 0.26 mmol) and the resultant suspension was stirred at 65 °C for 16 h. The reaction was cooled to rt then satd aq Na_2CO_3 (2 mL) was added, the resultant mixture was extracted with EtOAc (3 × 5 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give a 50:37:13 ratio of **177**, **185** and **186**, respectively.

Methyl (*S*)-3-[*N*-(*tert*-butoxycarbonyl)amino]-5-(3',4'-dimethoxyphenyl)pentanoate 187



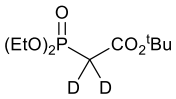
$Pd(OH)_2/C$ (388 mg, 40% w/w) was added to a stirred, degassed solution of **172** (970 mg, 2.10 mmol, >99:1 dr) and $(Boc)_2O$ (866 mg, 3.15 mmol) in MeOH (3 mL). The resultant mixture was stirred under an atmosphere of H_2 (5 atm) at rt for 16 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH), and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:1) gave **187** as a white solid (754 mg, 98%); mp 66–67 °C; $[\alpha]_D^{25}$ –8.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3366 (N–H), 3003, 2978, 2952, 2934, 2907, 2835 (C–H), 1738, 1712 (C=O); δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s, C*Me*$_3$), 1.72–1.89 (2H, m, C(4)*H*$_2$), 2.47–2.70 (4H, m, C(2)*H*$_2$, C(5)*H*$_2$), 3.67 (3H, s, CO_2*Me*), 3.84 (3H, s, ArO*Me*), 3.87 (3H, s, ArO*Me*), 3.90–4.01 (1H, m, C(3)*H*), 5.00 (1H, d, *J* 9.5, N*H*), 6.69–6.73 (1H, m, C(2')*H*, C(6')*H*), 6.78 (1H, d, *J* 8.7, C(5')*H*); δ_C (100 MHz, $CDCl_3$) 28.5 (C*Me*$_3$), 32.3 (*C*(5)), 36.7 (*C*(4)), 39.3 (*C*(2)), 47.4 (*C*(3)), 51.8 (CO_2*Me*), 56.0, 56.0 (2 × ArO*Me*), 79.5 (O*C*Me$_3$), 111.4, 111.9 (*C*(2'), *C*(5')), 120.2 (*C*(6')), 134.2 (*C*(1')), 147.4 (*C*(3')), 149.0 (*C*(4')), 155.5 (N*C*O), 172.3 (*C*(1)); *m/z* (ESI^+) 390 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{19}H_{29}NNaO_6^+$ ($[M+Na]^+$) requires 390.1887; found 390.1882.

***tert*-Butyl 2-(diethoxyphosphoryl)acetate 193**



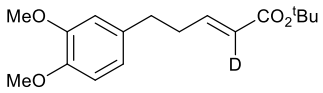
tert-Butyl 2-bromoacetate (27.3 mL, 185 mmol) and triethylphosphite (34.7 mL, 204 mmol) were stirred at 35 °C for 72 h. The mixture was concentrated *in vacuo* to give **193** as a colourless oil (46.7 g, quant);[7] δ_H (400 MHz, $CDCl_3$) 1.34 (6H, t, *J* 7.2, P(OCH_2CH_3)$_2$), 1.47 (9H, s, C*Me*$_3$), 2.88 (2H, d, *J* 21.5, C*H*$_2$P), 4.09–4.25 (4H, m, P(OCH_2CH_3)$_2$).

***tert*-Butyl 2,2-dideutero-2-(diethoxyphosphoryl)acetate 194**



193 (10.0 g, 39.6 mmol) and K_2CO_3 (16.4 g, 119 mmol) were stirred in D_2O (25 mL, 99.9% D) at rt for 16 h. The resultant mixture was extracted with Et_2O (3 × 30 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **194** as a colourless oil (9.95 g, 99%, >95% D [^{1}H NMR]);[8] δ_H (400 MHz, $CDCl_3$) 1.34 (6H, t, *J* 7.1, $P(OCH_2CH_3)_2$), 1.47 (9H, s, CMe_3), 4.12–4.20 (4H, m, $P(OCH_2CH_3)_2$).

***tert*-Butyl 2-deutero-5-(3',4'-dimethoxyphenyl)pent-2-enoate 195**

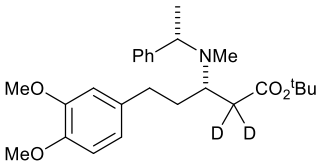


Step 1: DMSO (2.6 mL, 41 mmol) was added to a stirred solution of $(COCl)_2$ (1.8 mL, 20 mmol) in CH_2Cl_2 (75 mL) at –78 °C and was stirred at –78 °C for 20 min. **171** (2.00 g, 10.2 mmol) was added and the resultant mixture was stirred at –78 °C for 40 min then Et_3N (8.5 mL, 61 mmol) was added. The reaction mixture was allowed to warm to rt over 30 min, H_2O was added (100 mL) and the mixture was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were dried and concentrated *in vacuo*.

Step 2: **194** (5.19 g, 20.4 mmol) and K_2CO_3 (8.51 g, 61.6 mmol) were added to the residue from the previous step in D_2O (15 mL) and the resultant mixture was stirred at 50 °C for 36 h. The reaction mixture was cooled to rt, extracted with Et_2O (3 × 15 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 75:25:1) gave **195** as a pale yellow oil (1.16 g, 39%, >99:1 dr, 99% C(2)D, 23% C(4)D [^{1}H NMR], 66% D, 32% D_2, 1% D_3 [HRMS]); ν_{max} (ATR) 2934, 2835 (C–H), 1707 (C=O); δ_H (400 MHz, $CDCl_3$) 1.47 (9H, s, CMe_3), 2.43–2.50 (1.6H, m, C(4)H_2), 2.71 (2H, t, *J* 8.0, C(5)H_2), 3.86 (3H, s, O*Me*), 3.87 (3H, s, O*Me*), 6.68–6.74 (2H, m, C(5')*H*, C(6')*H*), 6.79 (1H, d, *J* 8.2, C(2')*H*), 6.86–6.91 (1H, m, C(3)*H*); δ_D (77 MHz, $CHCl_3$) 2.44 (0.4D, br s, C(4)*D*), 5.79 (1D, br s, C(2)*D*); δ_C (100 MHz, $CDCl_3$) 28.1 (CMe_3), 34.0 (*C*(4)), 34.0 (*C*(5)), 55.7 (O*Me*), 55.9 (O*Me*), 80.0 ($OCMe_3$), 111.2

(*C*(2')), 111.6 (*C*(5')), 120.1 (*C*(6')), 123.2 (t, *J* 24.5, *C*(2)), 133.5 (*C*(1')), 146.7 (*C*(3)), 147.3, 148.8 (*C*(3'), *C*(4')), 165.9 (*C*(1)); *m/z* (ESI$^+$) 316 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{17}H_{23}DNaO_4^+$ ([M(D)+Na]$^+$, 100%) requires 316.1630; found 316.1630; $C_{17}H_{24}NaO_4^+$ ([M(H)+Na]$^+$, 2%) requires 316.1567; found 315.1569.

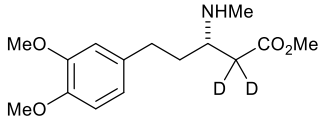
***tert*-Butyl (*S*,*S*)-2,2-dideutero-3-[*N*-methyl-*N*-(α-methylbenzyl)amino]-5-(3',4'-dimethoxyphenyl)pentanoate 196**



BuLi (2.3 M in hexanes, 2.3 mL, 5.4 mmol) was added dropwise to a stirred solution of **183** (752 mg, 5.56 mmol, >99:1 er) in THF (15 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. A solution of **195** (1.02 g, 3.48 mmol, >99:1 dr) in THF (3 mL) at –78 °C was then added and the resultant mixture was stirred at –78 °C for 2 h. Satd aq NH_4Cl (3 mL) was added and the reaction mixture was allowed to warm to rt, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (30 mL) and 10% aq citric acid (30 mL), and the organic layer was washed with satd aq $NaHCO_3$ (30 mL) and brine (30 mL), then dried and concentrated *in vacuo* to give **196** in >95:5 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 50:50:1) gave **196** as a pale yellow oil (1.50 g, quant, >95:5 dr, >95% C(2)D, 18% C(4)D [^{1}H NMR], 5% D, 57% D_2, 32% D_3, 6% D_4 [HRMS]); $[\alpha]_D^{25}$ +1.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2974, 2935, 2834, 2785 (C–H), 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.34 (3H, d, *J* 6.7, C(α)*Me*), 1.43 (9H, s, C*Me*$_3$), 1.50–1.61 (0.9H, m, C(4)H_A), 1.69–1.79 (0.9H, m, C(4)H_B), 2.19 (3H, s, N*Me*), 2.38–2.47 (1H, m, C(5)H_A), 2.65–2.74 (1H, m, C(5)H_B), 3.21–3.26 (1H, m, C(3)*H*), 3.64 (1H, q, *J* 6.7, C(α)*H*), 3.87 (3H, s, O*Me*), 3.87 (3H, s, O*Me*), 6.66–6.70 (2H, m, C(2')*H*, C(6')*H*), 6.79 (1H, d, *J* 8.7, C(5')*H*), 7.21–7.34 (5H, m, *Ph*); δ_D (77 MHz, $CDCl_3$) 1.54 (0.1D, br s, C(4)D_A), 1.71 (0.1D, br s, C(4)D_B), 2.14 (1D, br s, C(2)D_A), 2.42 (1D, br s, C(2)D_B); δ_C (100 MHz, $CDCl_3$) 21.9 (C(α)*Me*), 28.2 (C*Me*$_3$), 31.8 (N*Me*), 32.7 (*C*(5)), 33.2 (*C*(4)), 36.0* (*C*(2)), 55.9, 56.0 (2 × O*Me*), 62.1 (*C*(α)Me), 80.0 (O*C*Me$_3$), 111.3 (*C*(5')), 111.7 (*C*(2')), 120.1 (*C*(6')), 126.8 (*p-Ph*), 127.5, 128.2 (*o,m-Ph*), 135.4 (*C*(1')), 145.9, 147.1, 148.8 (*C*(3'), *C*(4'), *i-Ph*), 172.5 (*C*(1)); *m/z* (ESI$^+$) 430 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{36}D_2NO_4^+$ ([M(D_2)+H]$^+$, 100%) requires 430.2921; found

430.2918; $C_{26}H_{37}DNO_4^+$ ([M(HD)+H]$^+$, 9%) requires 429.2858; found 429.2858. *central point of multiplet

Methyl (*S*)-2,2-dideutero-3-(*N*-methylamino)-5-(3',4'-dimethoxyphenyl)pentanoate 197



Step 1: $SOCl_2$ (0.8 mL, 12 mmol) was added dropwise to a stirred solution of **196** (500 mg, 1.16 mmol) in MeOH (10 mL) at 0 °C. The resultant solution was stirred at 50 °C for 16 h then cooled to rt and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and aq NaOH (1.0 M, 20 mL) and the organic layer was dried and concentrated *in vacuo*.

Step 2: $Pd(OH)_2/C$ (160 mg, 40% w/w) was added to a stirred, degassed solution of the residue from the previous step in MeOH (2 mL). The resultant mixture was stirred under an atmosphere of H_2 (5 atm) at rt for 16 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH), and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent Et_2O/NH_4OH, 100:1) gave **197** as a colourless oil (263 mg, 80%, 88% C(2)D, 18% C(4)D [^{1}H NMR], 9% D, 62% D_2, 26% D_3, 3% D_4 [HRMS]); $[\alpha]_D^{25}$ +5.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3335 (N–H), 2937, 2837, 2795 (C–H), 1732 (C=O); δ_H (400 MHz, $CDCl_3$) 1.28 (1H, br s, N*H*), 1.61–1.79 (1.6H, m, C(4)H_2), 2.35 (3H, s, N*Me*), 2.37–2.43 (0.2H, m, C(2)H_2), 2.57 (1H, t, *J* 7.6, C(5)H_2), 2.85 (1H, t, *J* 5.8, C(3)*H*), 3.62 (3H, s, CO_2Me), 3.79 (3H, s, ArO*Me*), 3.81 (3H, s, ArO*Me*), 6.65–6.69 (2H, m, C(2')*H*, C(6')*H*), 6.73 (1H, d, *J* 8.7, C(5')*H*); δ_D (77 MHz, $CDCl_3$) 1.67 (0.1D, br s, C(4)D_A), 1.74 (0.1D, br s, C(4)D_B), 2.41 (2D, br s, C(2)D_2); δ_C (100 MHz, $CDCl_3$) 31.5 (*C*(5)), 33.1 (N*Me*), 35.7 (*C*(4)), 37.6* (*C*(2)), 51.4 (CO_2Me), 55.6, 55.6, 55.7 (*C*(3), 2 × ArO*Me*), 111.1, 111.5 (*C*(2'), *C*(5')), 119.9 (*C*(6')), 134.5 (*C*(1')), 147.0, 148.7 (*C*(3'), *C*(4')), 172.0 (*C*(1)); *m/z* (ESI$^+$) 284 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{15}H_{22}D_2NO_4^+$ ([M(D_2)+H]$^+$, 100%) requires 284.1825; found 284.1825; $C_{15}H_{23}DNO_4^+$ ([M(HD)+H]$^+$, 14%) requires 283.1763; found 283.1766. *central point of multiplet

Deuteration studies:

Reaction of 182

CsF (76 mg, 0.50 mmol) was dried *in vacuo* at 200 °C for 6 h, then cooled to rt and placed under N_2 (1 atm). **182** (47 mg, 0.17 mmol) in MeCN-d_3 (0.9 mL) was added, followed by 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **158** (61 μL, 0.25 mmol) and the resultant suspension was stirred at rt for 16 h. Satd aq Na_2CO_3 (2 mL) was added, the resultant mixture was extracted with EtOAc (3 × 5 mL) and the combined organic extracts were dried and concentrated *in vacuo*. HRMS (ESI^+) **189** $C_{21}H_{27}DNO_4$ ($[M(D)+H]^+$, 42%) requires 359.2046; found 359.2062; $C_{21}H_{28}NO_4$ ($[M(H)+H]^+$, 100%) requires 358.2013; found 358.2015; **191** $C_{13}H_{14}N$ ($[M(H)+H]^+$, 100%) requires 184.1121; found 184.1124; **190** C_7H_9DN ($[M(D)+H]^+$, 17%) requires 109.0843; found 109.0873; $C_7H_{10}N$ ($[M(H)+H]^+$, 100%) requires 108.0808; found 108.0811.

Reaction of 192

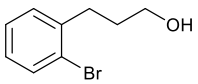
CsF (86 mg, 0.57 mmol) was dried *in vacuo* at 200 °C for 6 h, then cooled to rt and placed under N_2 (1 atm). **192** (53 mg, 0.19 mmol) in MeCN (1.0 mL) was added, followed by 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **158** (69 μL, 0.28 mmol) and the resultant suspension was stirred at rt for 16 h. Satd aq Na_2CO_3 (2 mL) was added, the resultant mixture was extracted with EtOAc (3 × 5 mL) and the combined organic extracts were dried and concentrated *in vacuo*. HRMS (ESI^+) **189** $C_{21}H_{27}DNO_4$ ($[M(D)+H]^+$, 43%) requires 359.2046; found 359.2067; $C_{21}H_{28}NO_4$ ($[M(H)+H]^+$, 100%) requires 358.2013; found 358.2018; **191** $C_{13}H_{12}D_2N$ ($[M(D_2)+H]^+$, 18%) requires 186.1246; found 186.1242; $C_{13}H_{13}DN$ ($[M(HD)+H]^+$, 100%) requires 185.1184; found 185.1183; $C_{13}H_{14}N$ ($[M(H_2)+H]^+$, 80%) requires 184.1121; found 184.1124; **190** C_7H_9DN ($[M(D)+H]^+$, 19%) requires 109.0843; found 109.0873; $C_7H_{10}N$ ($[M(H)+H]^+$, 100%) requires 108.0808; found 108.0811.

Reaction of 197

CsF (134 mg, 0.879 mmol) was dried *in vacuo* at 200 °C for 6 h, then cooled to rt and placed under N_2 (1 atm). **197** (83 mg, 0.29 mmol) in MeCN (1.5 mL) was added, followed by 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **158** (0.11 mL, 0.44 mmol) and the resultant suspension was stirred at rt for 16

h. Satd aq Na_2CO_3 (2 mL) was added, the resultant mixture was extracted with EtOAc (3 × 5 mL) and the combined organic extracts were dried and concentrated *in vacuo*. HRMS (ESI$^+$) **191** $C_{13}H_{13}DN$ ([M(D)+H]$^+$, 78%) requires 185.1184; found 185.1185; $C_{13}H_{14}N$ ([M(H)+H]$^+$, 100%) requires 184.1121; found 184.1123; **190** C_7H_9DN ([M(D)+H]$^+$, 37%) requires 109.0843; found 109.0873; $C_7H_{10}N$ ([M(H)+H]$^+$, 100%) requires 108.0808; found 108.0811.

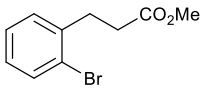
3-(2'-Bromophenyl)propan-1-ol 215



Method A: $LiAlH_4$ (2.4 M in THF, 1.36 mL, 3.27 mmol) was added dropwise to a stirred solution of **214** (500 mg, 2.18 mmol) in THF (7 mL) at 0 °C. The resultant solution was heated at reflux for 2 h then cooled to 0 °C. Aq NaOH (2.0 M, 1 mL) was then added and the resultant mixture was stirred at rt for 1 h. The reaction mixture was then filtered through Celite® (eluent EtOAc), then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 50:50:1) gave a 47:53 mixture of **215** and **216**, respectively (360 mg). Data for **216**:[9] δ_H (400 MHz, $CDCl_3$) 1.27 (1H, t, *J* 4.7, O*H*), 1.86–1.94 (2H, m, C(2)H_2), 2.72 (2H, t, *J* 7.4, C(3)H_2), 3.66–3.73 (2H, m, C(1)H_2), 7.17–7.31 (5H, m, *Ph*).

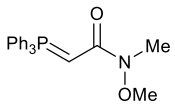
Method B: $BF_3{\cdot}Et_2O$ (0.84 mL, 6.7 mmol) was added dropwise to a stirred solution of **214** (771 mg, 3.37 mmol) and $NaBH_4$ (225 mg, 6.74 mmol) in THF (7 mL) at 0 °C. The resultant mixture was stirred at 0 °C for 1 h then MeOH (4 mL) and aq HCl (1.0 M, 4 mL) were added sequentially. The resultant mixture was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 50:50:1) gave **215** as a colourless oil (664 mg, 92%);[10] δ_H (400 MHz, $CDCl_3$) 1.37 (1H, t, *J* 5.8, O*H*), 1.87–1.96 (2H, m, C(2)H_2), 2.85 (2H, t, *J* 7.8, C(3)H_2), 3.72 (1H, app q, *J* 5.8, C(1)H_2), 7.04–7.11 (1H, m, C(4')*H*), 7.23–7.29 (2H, m, C(5')*H*, C(6')*H*), 7.55 (1H, d, *J* 8.1, C(3')*H*).

Methyl 3-(2'-bromophenyl)propanoate 217



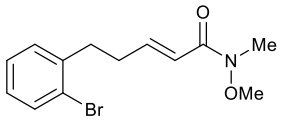
$SOCl_2$ (0.32 mL, 4.4 mmol) was added dropwise to a stirred solution of **214** (500 mg, 2.18 mmol) in MeOH (4 mL) at 0 °C. The resultant solution was heated at reflux for 3 h then cooled to rt and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and H_2O (10 mL). The organic layer was washed with satd aq $NaHCO_3$ (10 mL), dried and concentrated *in vacuo* to give **217** as a colourless oil (513 mg, 97%);[11] δ_H (400 MHz, $CDCl_3$) 2.65 (2H, t, *J* 7.8, C(2)H_2), 3.06 (2H, t, *J* 7.8, C(3)H_2), 3.68 (3H, s, O*Me*), 7.05–7.10 (1H, m, C(4')*H*), 7.20–7.26 (2H, m, C(5')*H*, C(6')*H*), 7.53 (1H, d, *J* 8.0, C(3')*H*).

***N*-Methoxy-*N*-methyl triphenylphosphenylideneacetamide 218**



Bromoacetyl bromide (2.2 mL, 25 mmol) was added dropwise to a stirred solution of K_2CO_3 (7.45 g, 53.9 mmol) and *N*-methoxy-*N*-methylamine hydrochloride (1.05 g, 10.8 mmol) in MeCN (25 mL) at rt and the resultant mixture was stirred at rt for 1 h then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (50 mL) and H_2O (50 mL) and the organic extract was dried and concentrated *in vacuo*. The residue was dissolved in EtOAc (20 mL), PPh_3 (2.59 g, 9.86 mmol) was added and the resultant suspension was stirred at rt for 16 h. The mixture was separated by filtration and the filter cake was the washed with Et_2O (50 mL). The solid residue was then partitioned between CH_2Cl_2 (20 mL) and aq NaOH (2.0 M, 10 mL) and the organic extract was dried and concentrated *in vacuo* to give **218** as a pale yellow solid (2.68 g, 68%);[12] mp 162–166 °C {lit.[12] mp 176–177 °C}; δ_H (400 MHz, $CDCl_3$) 3.08 (3H, s, N*Me*), 3.53 (1H, br s, C*H*), 3.73 (3H, s, O*Me*), 7.42–7.49 (6H, m, *Ph*), 7.50–7.56 (3H, m, *Ph*), 7.64–7.71 (6H, m, *Ph*).

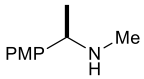
(*E*)-5-(2'-Bromophenyl)-*N*-methoxy-*N*-methylpent-2-enamide 208



Method A: DMSO (0.53 mL, 7.4 mmol) was added to a stirred solution of $(COCl)_2$ (0.32 mL, 3.7 mmol) in CH_2Cl_2 (10 mL) at –78 °C and was stirred at –78 °C for 20 min. **215** (400 mg, 1.86 mmol) was added and the resultant mixture was stirred at –78 °C for 40 min, then Et_3N (1.7 mL, 11 mmol) was added. The reaction mixture was allowed to warm to rt over 30 min, **218** (1.01 g, 2.79 mmol) was added and the resultant mixture was stirred for 16 h. Satd aq K_2CO_3 (20 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine (60 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 50:50:1) gave **208** as a pale yellow oil (435 mg, 78%, >99:1 dr); ν_{max} (ATR) 2935 (C–H), 1663 (C=O), 1632 (C=C); δ_H (400 MHz, $CDCl_3$) 2.61 (2H, app q, *J* 7.5, C(4)H_2), 2.95 (2H, t, *J* 7.5, C(5)H_2), 3.28 (3H, s, N*Me*), 3.70 (3H, s, O*Me*), 6.54 (1H, d, *J* 15.4, C(2)*H*), 7.02–7.14 (2H, m, C(3)*H*, C(4')*H*), 7.23–7.32 (2H, m, C(5')*H*, C(6')*H*), 7.58 (1H, d, *J* 7.9, C(3')*H*); δ_C (100 MHz, $CDCl_3$) 32.5 (*C*(4)), 32.6 (N*Me*), 35.1 (*C*(5)), 61.8 (O*Me*), 119.6 (*C*(2)), 124.5 (*C*(2')), 127.6 (*C*(5')), 128.0 (*C*(4')), 130.6 (*C*(6')), 133.0 (*C*(3')), 140.4 (*C*(1')), 146.2 (*C*(3)), 166.9 (*C*(1)); *m/z* (ESI^+) 298 ([M(^{79}Br)+H]$^+$, 100%), 300 ([M(^{81}Br)+H]$^+$, 100%); HRMS (ESI^+) $C_{13}H_{27}{}^{79}BrNO_2^+$ ([M(^{79}Br)+H]$^+$) requires 298.0437; found 298.0435; $C_{13}H_{27}{}^{81}BrNO_2^+$ ([M(^{81}Br)+H]$^+$) requires 300.0417; found 300.0414.

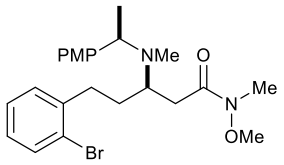
Method B: DIBAL-H (1.0 M in PhMe, 0.45 mL, 0.45 mmol) was added dropwise to a stirred solution of **217** (100 mg, 0.411 mmol) in PhMe (2 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 1 h. MeOH (85 μL, 2.1 mmol) and **218** (224 mg, 0.617 mmol) were added sequentially, and the resultant mixture was allowed to warm to rt and stirred at rt for 16 h. The reaction mixture was then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 50:50:1) gave **208** as a pale yellow oil (76 mg, 62%, >99:1 dr).

(*R*)-*N*-Methyl-*N*-(α-methyl-*p*-methoxybenzyl)amine 219



$LiAlH_4$ (2.4 M in THF, 9.3 mL, 22 mmol) was added dropwise to a stirred solution of ethyl (*R*)-*N*-(α-methyl-*p*-methoxybenzyl)carbamate[13] (2.50 g, 11.2 mmol, >99:1 er) in THF (70 mL) at 0 °C. The resultant mixture was heated at reflux for 24 h then cooled to 0 °C. Aq NaOH (2.0 M, 10 mL) was then added and the resultant mixture was stirred at rt for 1 h. The reaction mixture was then filtered through Celite® (eluent EtOAc), then concentrated *in vacuo* to give **219** as a yellow oil (1.70 g, 92%, >99:1 er);[5,14] $[\alpha]_D^{25}$ +66.8 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.33 (3H, d, *J* 6.6, C(α)*Me*), 2.29 (3H, s, N*Me*), 3.59 (1H, q, *J* 6.6, C(α)*H*), 3.80 (3H, s, O*Me*), 6.87 (2H, d, *J* 8.6, C(3')*H*, C(5')*H*), 7.22 (2H, d, *J* 8.6, C(2')*H*, C(6')*H*).

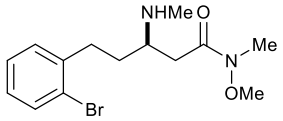
(*R*,*R*)-3-[*N*-Methyl-*N*-(*α*-methyl-*p*-methoxybenzyl)amino]-5-(2'-bromophenyl)-*N*-methoxy-*N*-methylpentanamide 221



BuLi (2.3 M in hexanes, 3.9 mL, 9.1 mmol) was added dropwise to a stirred solution of **219** (1.55 g, 9.39 mmol, >99:1 er) in THF (20 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. A solution of **208** (1.75 g, 5.87 mmol, >99:1 dr) in THF (5 mL) at –78 °C was then added and the resultant mixture was stirred at –78 °C for 2 h. Satd aq NH_4Cl (5 mL) was added and the reaction mixture was allowed to warm to rt, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and 10% aq citric acid (20 mL), and the organic layer was washed with satd aq $NaHCO_3$ (20 mL) and brine (20 mL), then dried and concentrated *in vacuo* to give **221** in 78:22 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 66:33:1) gave **221** as a colourless oil (2.53 g, 93%, 78:22 dr). Data for major compound: δ_H (400 MHz, $CDCl_3$) 1.34 (3H, d, *J* 6.7, C(α)*Me*), 1.46–1.57 (1H, m, C(4)H_A), 1.70–1.82 (1H, m, C(4)H_B), 2.25 (3H, s, C(3)N*Me*), 2.29–2.71 (3H, m, C(2)H_2, C(5)H_A), 2.91–3.02 (1H, m, C(5)H_B), 3.15 (3H, s, C(1)N*Me*), 3.34–3.41 (1H, m, C(3)*H*), 3.58–3.66 (4H, m, C(α)*H*, NO*Me*), 3.79 (3H, s, ArO*Me*), 6.81–6.86 (2H, m, C(3")*H*, C(5")*H*), 6.99–7.05 (1H, m, C(4')*H*), 7.14–7.28 (4H, m, C(5')*H*, C(6')*H*, C(2")*H*, C(6")*H*), 7.48–7.53 (1H, m, C(3')*H*); δ_C (100 MHz, $CDCl_3$) 22.1 (C(α)*Me*), 32.0, 32.2 (*C*(2), *C*(4), 2 × N*Me*), 33.9 (*C*(5)), 55.3 (NO*Me*), 55.6 (*C*(3)), 61.3 (ArO*Me*, *C*(α)Me), 113.6 (*C*(3"), *C*(5")), 124.5 (*C*(2')), 127.4, 127.5 (*C*(3'), *C*(4')), 128.5 (*C*(2"), *C*(6")), 130.4

(*C*(6')), 132.7 (*C*(5')), 138.3 (*C*(1")), 142.3 (*C*(1')), 158.5 (*C*(4")), 173.9 (*C*(1)). Data for minor compound: δ_H (400 MHz, $CDCl_3$) 1.34 (3H, d, *J* 6.7, C(α)*Me*), 1.46–1.57 (1H, m, C(4)H_A), 1.60–1.73 (1H, m, C(4)H_B), 2.10 (3H, s, C(3)N*Me*), 2.29–2.71 (3H, m, C(2)H_2, C(5)H_A), 2.91–3.02 (1H, m, C(5)H_B), 3.18 (3H, s, C(1)N*Me*), 3.34–3.41 (1H, m, C(3)*H*), 3.58–3.66 (4H, m, C(α)*H*, NO*Me*), 3.80 (3H, s, ArO*Me*), 6.81–6.86 (2H, m, C(3")*H*, C(5")*H*), 6.99–7.05 (1H, m, C(4')*H*), 7.14–7.28 (4H, m, C(5')*H*, C(6')*H*, C(2")*H*, C(6")*H*), 7.48–7.53 (1H, m, C(3')*H*); δ_C (100 MHz, $CDCl_3$) 21.8 (C(α)*Me*), 32.2, 32.4, 32.6 (*C*(2), *C*(4), 2 × N*Me*), 33.9 (*C*(5)), 55.0, 55.3 (*C*(3), NO*Me*), 61.3, 61.8 (ArO*Me*, *C*(α)Me), 113.7 (*C*(3"), *C*(5")), 124.5 (*C*(2')), 127.4, 127.5 (*C*(3'), *C*(4')), 128.4 (*C*(2"), *C*(6")), 130.6 (*C*(6')), 132.8 (*C*(5')), 138.7 (*C*(1")), 142.3 (*C*(1')), 158.4 (*C*(4")), 173.9 (*C*(1)). Data for mixture: ν_{max} (ATR) 2968, 2934, 2864, 2835 (C–H), 1658 (C=O); *m/z* (ESI^+) 463 ([M(^{79}Br)+H]$^+$, 100%), 465 ([M(^{81}Br)+H]$^+$, 100%); HRMS (ESI^+) $C_{23}H_{32}{}^{79}BrN_2O_3^+$ ([M(^{79}Br)+H]$^+$) requires 463.1591; found 493.1588; $C_{23}H_{32}{}^{81}BrN_2O_3^+$ ([M(^{81}Br)+H]$^+$) requires 465.1570; found 465.1568.

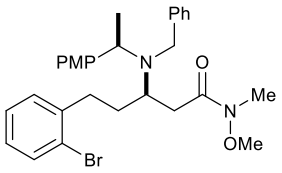
(*R*)-3-(*N*-Methylamino)-5-(2'-bromophenyl)-*N*-methoxy-*N*-methylpentanamide 222



Et_3SiH (0.26 mL, 1.6 mmol) was added to a stirred solution of **221** (500 mg, 1.08 mmol, 78:22 dr) in HCO_2H (4 mL) and the resultant solution was heated at 90 °C for 16 h. The resultant mixture was cooled to rt and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and satd aq $NaHCO_3$ (10 mL) and the organic extract was washed with brine (10 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$/MeOH/NH_4OH, 90:9:1) gave **222** as a colourless oil (290 mg, 82%, 78:22 er);[15] ν_{max} (ATR) 3326 (N–H), 2936, 2861, 2795 (C–H), 1655 (C=O); δ_H (400 MHz, $CDCl_3$) 1.68–1.87 (2H, m, C(4)H_2), 2.43 (3H, s, C(3)N*Me*), 2.63 (2H, d, *J* 6.0, C(2)H_2), 2.76–2.82 (2H, m, C(5)H_2), 3.05 (1H, quin, *J* 6.0, C(3)*H*), 3.19 (3H, s, C(1)N*Me*), 3.69 (3H, s, O*Me*), 7.02–7.07 (1H, m, C(4')*H*), 7.20–7.26 (2H, m, C(5')*H*, C(6')*H*), 7.51 (1H, d, *J* 7.6, C(3')*H*); δ_C (100 MHz, $CDCl_3$) 32.2 (C(1)N*Me*), 32.6 (*C*(5)), 33.4 (C(3)N*Me*), 33.9 (*C*(4)), 35.8 (*C*(2)), 55.9 (*C*(3)), 61.4 (O*Me*), 124.5 (*C*(2')), 127.7, 127.7 (*C*(4'), *C*(5')), 130.4 (*C*(6')), 132.9 (*C*(3')), 141.6 (*C*(1')), 173.4 (*C*(1)); *m/z* (ESI^+) 329 ([M(^{79}Br)+H]$^+$, 100%), 331 ([M(^{81}Br)+H]$^+$, 100%); HRMS (ESI^+)

$C_{14}H_{22}{}^{79}BrN_2O_2^+$ ([M(^{79}Br)+H]$^+$) requires 329.0859; found 329.0860; $C_{14}H_{22}{}^{81}BrN_2O_2^+$ ([M(^{81}Br)+H]$^+$) requires 331.0839; found 331.0839.

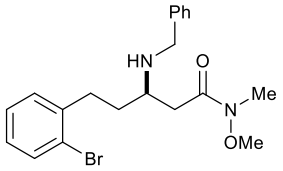
(*R*,*R*)-3-[*N*-Benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amino]-5-(2'-bromophenyl)-*N*-methoxy-*N*-methylpentanamide 225



BuLi (2.3 M in hexanes, 0.45 mL, 1.0 mmol) was added dropwise to a stirred solution of **223**[4] (259 mg, 1.07 mmol, >99:1 er) in THF (2 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. A solution of **208** (200 mg, 0.671 mmol, >99:1 dr) in THF (1 mL) at –78 °C was then added and the resultant mixture was stirred at –78 °C for 2 h. Satd aq NH_4Cl (1 mL) was added and the reaction mixture was allowed to warm to rt, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and 10% aq citric acid (10 mL), and the organic layer was washed with satd aq $NaHCO_3$ (10 mL) and brine (10 mL), then dried and concentrated *in vacuo* to give **225** in >95:5 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 50:50:1) gave **225** as a pale yellow oil (273 mg, 80%, >99:1 dr); $[\alpha]_D^{25}$ +21.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2998, 2981, 2969, 2932, 2905, 2886, 2868 (C–H), 1659 (C=O); δ_H (400 MHz, $CDCl_3$) 1.39 (3H, d, *J* 7.0, C(α)*Me*), 1.55–1.66 (1H, m, C(4)H_A), 1.73–1.84 (1H, m, C(4)H_B), 2.00 (1H, d, *J* 14.0, C(2)H_A), 2.21–2.31 (1H, m, C(2)H_B), 2.70 (1H, ddd, *J* 13.8, 11.8, 5.0, C(5)H_A), 3.07 (3H, s, N*Me*), 3.19 (1H, ddd, *J* 13.8, 11.6, 4.9, C(5)H_B), 3.43 (3H, s, NO*Me*), 3.59–3.66 (1H, m, C(3)*H*), 3.60 (1H, d, *J* 14.8, NCH_AH_BPh), 3.79 (3H, s, ArO*Me*), 3.87 (1H, q, *J* 7.0, C(α)*H*), 3.93 (1H, d, *J* 14.8, NCH$_A$$H_B$Ph), 6.85 (2H, d, *J* 8.6, C(3")*H*, C(5")*H*), 6.99–7.05 (1H, m, C(4')*H*), 7.16–7.28 (5H, m, C(5')*H*, C(6')*H*, C(2")*H*, C(6")*H*, *p-Ph*), 7.36 (2H, t, *J* 7.5, *m-Ph*), 7.50 (1H, d, *J* 7.8, C(3')H), 7.54 (2H, d, *J* 7.5, *o-Ph*); δ_C (100 MHz, $CDCl_3$) 20.1 (C(α)*Me*), 32.3 (N*Me*), 33.9 (*C*(2)), 34.1 (*C*(4)), 34.4 (*C*(5)), 50.3 (N*C*H$_2$Ph), 53.0 (*C*(3)), 55.4 (NO*Me*), 56.8 (*C*(α)Me), 61.0 (ArO*Me*), 113.6 (*C*(3"), *C*(5")), 124.6 (*C*(2')), 126.8 (*p-Ph*), 127.4 (*C*(4')), 127.5 (*C*(5')), 128.5, 128.5 (*o,m-Ph*), 129.1 (*C*(2"), *C*(6")), 130.4 (*C*(6')), 132.7 (*C*(3')), 135.2 (*C*(1")), 141.7 (*i-Ph*), 142.3 (*C*(1')), 158.6 (*C*(4")), 173.5 (*C*(1)); *m/z* (ESI$^+$) 539 ([M(^{79}Br)+H]$^+$, 100%), 541 ([M(^{81}Br)+H]$^+$, 100%);

HRMS (ESI$^+$) $C_{29}H_{36}{}^{79}BrN_2O_3^+$ ([M(^{79}Br)+H]$^+$) requires 539.1904; found 539.1902; $C_{29}H_{36}{}^{81}BrN_2O_3^+$ ([M(^{81}Br)+H]$^+$) requires 541.1883; found 541.1882.

(*R*)-3-(*N*-Benzylamino)-5-(2'-bromophenyl)-*N*-methoxy-*N*-methylpentanamide 226



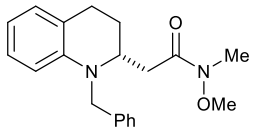
Method A: Et_3SiH (25 μL, 0.16 mmol) was added to a stirred solution of **225** (87 mg, 1.10 mmol, >99:1 dr) in HCO_2H (0.6 mL) and the resultant solution was heated at 90 °C for 16 h. The resultant mixture was cooled to rt and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (5 mL) and satd aq $NaHCO_3$ (5 mL) and the organic extract was washed with brine (5 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 50:50:1) gave **226** as a colourless oil (35 mg, 81%); $[\alpha]_D^{25}$ –7.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3324 (N–H), 3085, 3027, 2965, 2935, 2861 (C–H), 1658 (C=O); δ_H (400 MHz, $CDCl_3$) 1.79–1.89 (2H, m, C(4)H_2), 2.67 (2H, d, *J* 5.8, C(2)H_2), 2.80–2.86 (2H, m, C(5)H_2), 3.16–3.23 (1H, m, C(3)*H*), 3.18 (3H, s, N*Me*), 3.67 (3H, s, O*Me*), 3.81 (1H, d, *J* 12.9, NCH_AH$_B$Ph), 3.85 (1H, d, *J* 12.9, NCH$_A$$H_B$Ph), 7.01–7.08 (1H, m, C(4')*H*), 7.20–7.39 (7H, m, C(5')*H*, C(6')*H*, *Ph*), 7.52 (1H, d, *J* 7.8, C(3')*H*); δ_C (100 MHz, $CDCl_3$) 32.2 (*C*(3)), 32.6 (*C*(5)), 34.5 (*C*(4)), 36.5 (*C*(2)), 51.2 (N*C*H$_2$Ph), 53.9 (N*Me*), 61.4 (O*Me*), 124.5 (*C*(2')), 127.0, 127.6, 127.7 (*C*(4'), *C*(5'), *p-Ph*), 128.4, 128.5 (*o*,*m-Ph*), 130.5 (*C*(6')), 132.9 (*C*(3')), 140.8 (*i-Ph*), 141.7 (*C*(1')), 173.4 (*C*(1)); *m/z* (ESI$^+$) 405 ([M(^{79}Br)+H]$^+$, 100%), 407 ([M(^{81}Br)+H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{26}{}^{79}BrN_2O_2^+$ ([M(^{79}Br)+H]$^+$) requires 405.1172; found 405.1169; $C_{20}H_{26}{}^{81}BrN_2O_2^+$ ([M(^{81}Br)+H]$^+$) requires 407.1152; found 407.1148.

Method B – Step 1: BuLi (2.3 M in hexanes, 6.9 mL, 16 mmol) was added dropwise to a stirred solution of **223** (3.98 g, 16.5 mmol, >99:1 er) in THF (30 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. A solution of **208** (3.07 g, 10.3 mmol, >99:1 dr) in THF (10 mL) at –78 °C was then added and the resultant mixture was stirred at –78 °C for 2 h. Satd aq NH_4Cl (10 mL) was added and the reaction mixture was allowed to warm to rt, then concentrated *in vacuo*. The residue was partitioned

between CH_2Cl_2 (50 mL) and 10% aq citric acid (50 mL), and the organic layer was washed with satd aq $NaHCO_3$ (50 mL) and brine (50 mL), then dried and concentrated *in vacuo* to give **225** in >95:5 dr.

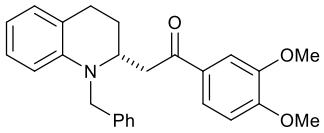
Method B – Step 2: Et_3SiH (3.3 mL, 21.0 mmol) was added to a stirred solution of **225** from the previous step in HCO_2H (40 mL) and the resultant solution was heated at 90 °C for 16 h. The resultant mixture was cooled to rt and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (50 mL) and satd aq $NaHCO_3$ (50 mL) and the organic extract was washed with brine (50 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 50:50:1) gave **226** as a colourless oil (2.89 g, 69% from **208**).

(*R*)-2-[*N*(1')-Benzyl-1',2',3',4'-tetrahydroquinolin-2'-yl]-*N*-methoxy-*N*-methylacetamide 227



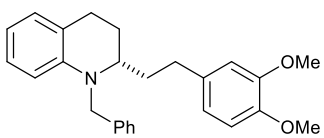
$Pd(OAc)_2$ (26 mg, 0.12 mmol) was added to a stirred solution of **226** (943 mg, 2.33 mmol), X-Phos (163 mg, 0.349 mmol) and Cs_2CO_3 (1.51 g, 4.65 mmol) in PhMe (30 mL) and the resultant mixture was heated at reflux for 24 h. The resultant mixture was cooled to rt and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (100 mL) and H_2O (100 mL) and the organic extract was then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 50:50:1) gave **227** as a pale yellow solid (751 mg, quant); mp 58–60 °C; $[\alpha]_D^{25}$ –11.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3027, 2968, 2935, 2865 (C–H), 1658 (C=O); δ_H (400 MHz, $CDCl_3$) 1.97–2.13 (2H, m, C(3')H_2), 2.71 (2H, d, *J* 6.5, C(2)H_2), 2.78 (1H, dt, *J* 16.5, 3.7, C(4')H_A), 2.97 (1H, ddd, *J* 16.5, 12.8, 5.7, C(4')H_B), 3.16 (3H, s, N*Me*), 3.58 (3H, s, O*Me*), 4.04–4.10 (1H, m, C(2')*H*), 4.53 (1H, d, *J* 17.2, NC$H_A$$H_B$Ph), 4.59 (1H, d, *J* 17.2, NC$H_A$$H_B$Ph), 6.45 (1H, d, *J* 7.7, C(8')*H*), 6.60 (1H, t, *J* 7.7, C(6')*H*), 6.97 (1H, t, *J* 7.7, C(7')*H*), 7.04 (1H, d, *J* 7.7, C(5')*H*), 7.19–7.33 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 23.7 (*C*(4')), 25.4 (*C*(3')), 32.2 (N*Me*), 35.0 (*C*(2)), 54.0 (N*C*H_2Ph), 55.0 (*C*(2')), 61.4 (O*Me*), 111.9 (*C*(8')), 116.0 (*C*(6')), 121.4 (*C*(4'a)), 126.5 (*o-Ph*), 126.8 (*p-Ph*), 127.3 (*C*(7')), 128.7 (*m-Ph*), 129.2 (*C*(5')), 139.2 (*i-Ph*), 144.2 (*C*(8'a)), 172.6 (*C*(1)); *m/z* (ESI$^+$) 325 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{25}N_2O_2^+$ ([M+H]$^+$) requires 325.1911; found 325.1909.

(*R*)-*N*(1)-Benzyl-2-[2'-oxo-2'-(3'',4''-dimethoxyphenyl)ethanyl]-1,2,3,4-tetrahydroquinoline 229



BuLi (2.3 M in hexanes, 0.47 mL, 1.1 mmol) was added dropwise to a stirred solution of **228** (234 mg, 1.08 mmol) in THF (1 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. A solution of **227** (50 mg, 0.15 mmol) in THF (0.5 mL) at –78 °C was then added and the resultant mixture was stirred at –78 °C for 1.5 h. Satd aq NH_4Cl (0.5 mL) was added and the reaction mixture was warmed to rt and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (5 mL) and H_2O (5 mL) and the organic extract was dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 80:24:1) gave **229** as an orange oil (49 mg, 79%); $[\alpha]_D^{25}$ –12.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3028, 2962, 2933, 2900, 2838 (C–H), 1669 (C=O); δ_H (400 MHz, $CDCl_3$) 1.95–2.02 (1H, m, C(3)H_A), 2.10 (1H, tt, *J* 13.0, 4.8, C(3)H_B), 2.75–2.83 (1H, m, C(4)H_A), 2.98 (1H, ddd, *J* 16.6, 13.0, 5.7, C(4)H_B), 3.15 (1H, dd, *J* 15.9, 8.2, C(1')H_A), 3.23 (1H, dd, *J* 15.9, 5.1, C(1')H_B), 3.90 (3H, s, O*Me*), 3.94 (3H, s, O*Me*), 4.17–4.24 (1H, m, C(2)*H*), 4.49 (1H, d, *J* 17.0, NC$H_A$$H_B$Ph), 4.56 (1H, d, *J* 17.0, NC$H_A$$H_B$Ph), 6.47 (1H, d, *J* 7.8, C(8)*H*), 6.63 (1H, td, *J* 7.8, 0.9, C(6)*H*), 6.84 (1H, d, *J* 8.3, C(5")*H*), 6.98 (1H, t, *J* 7.8, C(7)*H*), 7.05 (1H, d, *J* 7.8, C(5)*H*), 7.19–7.32 (5H, m, *Ph*), 7.46–7.52 (2H, m, C(2")*H*, C(6")*H*); δ_C (100 MHz, $CDCl_3$) 23.6 (*C*(4)), 25.6 (*C*(3)), 40.8 (*C*(1')), 54.3 (N*C*H_2Ph), 55.1 (*C*(2)), 56.1, 56.2 (2 × O*Me*), 110.1, 110.1 (*C*(2"), *C*(5")), 112.1 (*C*(8)), 116.2 (*C*(6)), 121.3 (*C*(4a)), 123.0 (*C*(6")), 126.5 (*o-Ph*), 126.9 (*p-Ph*), 127.4 (*C*(7)), 128.7 (*m-Ph*), 129.3 (*C*(5)), 130.5 (*C*(1")), 139.0 (*i-Ph*), 144.2 (*C*(8a)), 149.2 (*C*(3")), 153.5 (*C*(4")), 197.8 (*C*(2')); *m/z* (ESI^+) 402 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{26}H_{28}NO_3^+$ ($[M+H]^+$) requires 402.2064; found 402.2061.

(*S*)-*N*(1)-benzyl-2-[2'-(3'',4''-dimethoxyphenyl)ethanyl]-1,2,3,4-tetrahydroquinoline 234

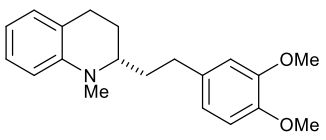


Step 1: $LiAlH_4$ (2.4 M in THF, 0.42 mL, 1.0 mmol) was added dropwise to a stirred solution of **229** (200 mg, 0.498 mmol) in THF (3.5 mL) at 0 °C. The resultant mixture was heated at reflux for 16 h then allowed to cool to rt. Aq NaOH (2.0 M, 0.5 mL) was then added and the resultant mixture was heated at

reflux for 3 h. The reaction mixture was then allowed to cool to rt and filtered through Celite® (eluent EtOAc), then concentrated *in vacuo*.

Step 2: Et_3SiH (0.80 mL, 4.89 mmol) was added to a stirred solution of the residue from the previous step in TFA (2.5 mL) and the resultant solution was stirred at rt for 16 h. The resultant mixture was concentrated *in vacuo* and the residue was then partitioned between CH_2Cl_2 (10 mL) and satd aq $NaHCO_3$ (10 mL). The organic extract was dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 75:25:1) gave **234** as a yellow oil (148 mg, 77%); $[\alpha]_D^{25}$ +1.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3024, 3000, 2934, 2835 (C–H), 1601, 1515, 1498 (Ar); δ_H (400 MHz, $CDCl_3$) 1.79–1.98 (2H, m, C(1')H_2), 1.98–2.09 (2H, m, C(3)H_2), 2.50 (1H, ddd, *J* 14.0, 9.8, 6.6, C(2')H_A), 2.66 (1H, ddd, *J* 14.0, 10.0, 5.6, C(2')H_B), 2.76 (1H, dt, *J* 16.2, 3.9, C(4)H_A), 2.94 (1H, ddd, *J* 16.2, 12.0, 5.9, C(4)H_B), 3.38–3.45 (1H, m, C(2)*H*), 3.84 (3H, s, O*Me*), 3.85 (3H, s, O*Me*), 4.43 (1H, d, *J* 17.0, NC$H_A$$H_B$Ph), 4.57 (1H, d, *J* 17.0, NCH$_A$$H_B$Ph), 6.43 (1H, d, *J* 7.6, C(8)*H*), 6.58 (1H, t, *J* 7.6, C(6)*H*), 6.64 (1H, d, *J* 2.0, C(2")*H*), 6.68 (1H, dd, *J* 8.1, 2.0, C(6")*H*), 6.77 (1H, d, *J* 8.1, C(5")*H*), 6.96 (1H, t, *J* 7.6, C(7)*H*), 7.02 (1H, d, *J* 7.6, C(5)*H*), 7.19–7.32 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 23.8 (*C*(4)), 24.4 (*C*(3)), 32.0 (*C*(2')), 33.9 (*C*(1')), 54.3 (N*C*H_2Ph), 56.0, 56.0 (2 × OMe), 57.5 (*C*(2)), 111.3 (*C*(5")), 111.6 (*C*(2")), 111.9 (*C*(8)), 115.7 (*C*(6)), 120.1 (*C*(6")), 121.7 (*C*(4a)), 126.6 (*o*/*m*-*Ph*), 126.8 (*p*-*Ph*), 127.2 (*C*(7)), 128.7 (*o*/*m*-*Ph*), 129.1 (*C*(5)), 134.6 (*C*(1")), 139.4 (*i*-*Ph*), 144.6 (*C*(8a)), 147.3, 149.0 (*C*(3"), *C*(4")); *m/z* (ESI$^+$) 388 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{30}NO_2^+$ ([M+H]$^+$) requires 388.2271; found 388.2276.

(*S*)-*N*(1)-Methyl-2-[2'-(3'',4''-dimethoxyphenyl)ethanyl]-1,2,3,4-tetrahydroquinoline [(–)-cuspareine] 9

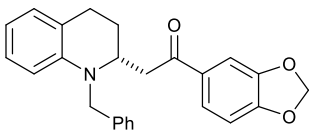


Method A: $LiAlH_4$ (2.4 M in THF, 61 μL, 0.15 mmol) was added dropwise to a stirred solution of **186** (24 mg, 0.074 mmol) in THF (0.5 mL) at 0 °C. The resultant mixture was heated at reflux for 16 h then allowed to cool to rt. Aq NaOH (2.0 M, 0.2 mL) was then added and the resultant mixture was heated at reflux for 3 h. The reaction mixture was then allowed to cool to rt and filtered through Celite® (eluent

EtOAc), then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 75:25:1) gave **9** as a colourless oil (13 mg, 57%).

Method B: Pd/C (26 mg, 40% w/w) was added to a stirred solution of **234** (64 mg, 0.17 mmol) and CH_2O (37% in H_2O, 1.2 mL, 1.7 mmol) in degassed MeOH (3 mL). The resultant mixture was stirred under H_2 (1 atm) at rt for 24 h. The reaction mixture was filtered through a short plug of Celite® (eluent MeOH) then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 75:25:1) gave **9** as a colourless oil (46 mg, 90%); $[\alpha]_D^{25}$ –27.8 (*c* 1.0 in $CHCl_3$); {lit.[16] for a sample isolated from the natural source $[\alpha]_D$ –22.8 (*c* 0.0135 in $CHCl_3$); lit.[17] $[\alpha]_D^{24}$ –27.2 (*c* 0.87 in $CHCl_3$)}; ν_{max} (ATR) 2981, 2971, 2934 (C–H), 1602, 1514, 1500 (Ar); δ_H (400 MHz, $CDCl_3$) 1.68–1.79 (1H, m, C(1')H_A), 1.87–2.00 (3H, m, C(3)H_2, C(1')H_B), 2.53 (1H, ddd, *J* 13.9, 10.1, 6.4, C(2')H_A), 2.64–2.73 (2H, m, C(4)H_A, C(2')H_B), 2.80–2.91 (1H, m, C(4)H_B), 2.92 (3H, s, N*Me*), 3.26–3.33 (1H, m, C(2)*H*), 3.86 (3H, s, O*Me*), 3.87 (3H, s, O*Me*), 6.53 (1H, d, *J* 8.2, C(8)*H*), 6.59 (1H, t, *J* 7.3, C(6)*H*), 6.70–6.75 (2H, m, C(2")*H*, C(6")*H*), 6.79 (1H, d, *J* 8.0, C(5")*H*), 6.98 (1H, d, *J* 7.3, C(5)*H*), 7.06–7.11 (1H, m, C(7)*H*); δ_C (100 MHz, $CDCl_3$) 23.7 (*C*(4)), 24.5 (*C*(3)), 32.1 (*C*(2')), 33.2 (*C*(1')), 38.3 (N*Me*), 56.0, 56.1 (2 × O*Me*), 58.6 (*C*(2)), 110.7 (*C*(8)), 111.4 (*C*(5")), 111.7 (*C*(2")), 115.5 (*C*(6)), 120.2 (*C*(6")), 121.9 (*C*(4a)), 127.3 (*C*(7)), 128.8 (*C*(5)), 134.8 (*C*(1")), 145.4 (*C*(8a)), 147.3, 149.0 (*C*(3"), *C*(4")); *m/z* (ESI^+) 312 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{26}NO_2^+$ ($[M+H]^+$) requires 312.1958; found 312.1958.

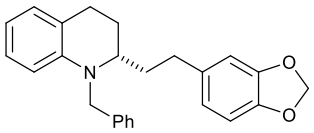
(*R*)-*N*(1)-Benzyl-2-[2'-oxo-2'-(3'',4''-methylenedioxyphenyl)ethanyl]-1,2,3,4-tetrahydroquinoline 235



BuLi (2.3 M in hexanes, 2.4 mL, 5.4 mmol) was added dropwise to a stirred solution of **237** (1.08 g, 5.39 mmol) in THF (15 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. A solution of **227** (250 mg, 0.771 mmol) in THF (2 mL) at –78 °C was then added and the resultant mixture was stirred at –78 °C for 1.5 h. Satd aq NH_4Cl (3 mL) was added and the reaction mixture was warmed to rt and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and H_2O (20 mL) and

the organic extract was dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 75:25:1) gave **235** as a yellow oil (244 mg, 82%); $[\alpha]_D^{25}$ –6.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3036, 3027, 2927 (C–H), 1671 (C=O); δ_H (400 MHz, $CDCl_3$) 1.97 (1H, ddt, *J* 13.1, 5.7, 2.8, C(3)H_A), 2.11 (1H, tt, *J* 13.1, 5.0, C(3)H_B), 2.79 (1H, ddd, *J* 16.8, 5.0, 2.8, C(4)H_A), 2.96 (1H, ddd, *J* 16.8, 13.1, 5.7, C(4)H_B), 3.12 (1H, dd, *J* 16.0, 8.0, C(1')H_A), 3.18 (1H, dd, *J* 16.0, 5.3, C(1')H_B), 4.16–4.23 (1H, m, C(2)*H*), 4.49 (1H, d, *J* 17.0, NC$H_A$$H_B$Ph), 4.57 (1H, d, *J* 17.0, NC$H_A$$H_B$Ph), 6.04 (2H, s, OC$H_2$O), 6.48 (1H, d, *J* 8.1, C(8)*H*), 6.64 (1H, td, *J* 7.3, 0.9, C(6)*H*), 6.81 (1H, d, *J* 8.2, C(5")*H*), 6.97–7.02 (1H, m, C(7)*H*), 7.06 (1H, d, *J* 7.3, C(5)*H*), 7.21–7.73 (5H, m, *Ph*), 7.39 (1H, d, *J* 1.7, C(2")*H*), 7.46 (1H, dd, *J* 8.2, 1.7, C(6")*H*); δ_C (100 MHz, $CDCl_3$) 23.6 (*C*(4)), 25.5 (*C*(3)), 41.0 (*C*(1')), 54.2 (N*C*H_2Ph), 54.9 (*C*(2)), 102.0 (O*C*H_2O), 107.9, 108.0 (*C*(2"), *C*(5")), 112.1 (*C*(8)), 116.2 (*C*(6)), 121.3 (*C*(4a)), 124.7 (*C*(6")), 126.6 (*o-Ph*), 126.9 (*p-Ph*), 127.3 (*C*(7)), 128.7 (*m-Ph*), 129.3 (*C*(5)), 132.2 (*C*(1")), 138.9 (*i-Ph*), 144.2 (*C*(8a)), 148.4 (*C*(3")), 152.0 (*C*(4")), 197.3 (*C*(2')); *m/z* (ESI^+) 386 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{25}H_{24}NO_3^+$ ($[M+H]^+$) requires 386.1751; found 386.1752.

(*S*)-*N*(1)-Benzyl-2-[2'-(3'',4''-methylenedioxyphenyl)ethanyl]-1,2,3,4-tetrahydroquinoline 236

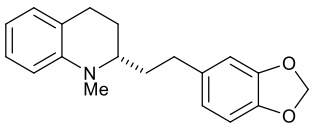


Step 1: $LiAlH_4$ (2.4 M in THF, 0.27 mL, 0.53 mmol) was added dropwise to a stirred solution of **235** (103 mg, 0.267 mmol) in THF (2.0 mL) at 0 °C. The resultant mixture was heated at reflux for 16 h then allowed to cool to rt. Aq NaOH (2.0 M, 0.3 mL) was then added and the resultant mixture was heated at reflux for 3 h. The reaction mixture was then allowed to cool to rt and filtered through Celite® (eluent EtOAc), then concentrated *in vacuo*.

Step 2: Et_3SiH (0.43 mL, 2.7 mmol) was added to a stirred solution of the residue from the previous step in TFA (1.3 mL) and the resultant solution was stirred at rt for 16 h. The resultant mixture was concentrated *in vacuo* and the residue was then partitioned between CH_2Cl_2 (10 mL) and satd aq $NaHCO_3$ (10 mL). The organic extract was dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 100:5:1) gave **236** as a colourless oil (76 mg, 77%); $[\alpha]_D^{25}$ +4.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3027, 2936 (C–H), 1601, 1500, 1490 (Ar); δ_H (400 MHz,

$CDCl_3$) 1.76–1.97 (2H, m, C(1')H_2), 1.98–2.06 (2H, m, C(3)H_2), 2.47 (1H, ddd, *J* 14.0, 9.7, 6.8, C(2')H_A), 2.62 (1H, ddd, *J* 14.0, 9.7, 5.4, C(2')H_B), 2.76 (1H, dt, *J* 16.4, 4.0, C(4)H_A), 2.93 (1H, ddd, *J* 16.4, 11.5, 6.5, C(4)H_B), 3.36–3.42 (1H, m, C(2)*H*), 4.41 (1H, d, *J* 17.0, NC$H_A$$H_B$Ph), 4.57 (1H, d, *J* 17.0, NC$H_A$$H_B$Ph), 5.91 (2H, s, OC$H_2$O), 6.43 (1H, d, *J* 8.0, C(8)*H*), 6.56–6.61 (2H, m, C(6)*H*, C(6")*H*), 6.62 (1H, d, *J* 1.6, C(2")*H*), 6.70 (1H, d, *J* 7.8, C(5")*H*), 6.95 (1H, t, *J* 8.0, C(7)*H*), 7.02 (1H, d, *J* 7.3, C(5)*H*), 7.19–7.32 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 23.7 (*C*(4)), 24.4 (*C*(3)), 32.1 (*C*(2')), 33.9 (*C*(1')), 54.3 (N*C*H_2Ph), 57.3 (*C*(2)), 100.9 (O*C*H_2O), 108.3 (*C*(5")), 108.8 (*C*(2")), 112.0 (*C*(8)), 115.8 (*C*(6)), 121.1 (*C*(6")), 121.8 (*C*(4a)), 126.6 (*o*/*m*-*Ph*), 126.8 (*p*-*Ph*), 127.2 (*C*(7)), 128.7 (*o*/*m*-*Ph*), 129.1 (*C*(5)), 135.8 (*i*-*Ph*), 139.4 (*C*(1")), 144.6 (*C*(8a)), 145.8, 147.7 (*C*(3"), *C*(4")); *m/z* (ESI^+) 372 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{25}H_{26}NO_2^+$ ($[M+H]^+$) requires 372.1958; found 372.1961.

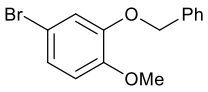
(*S*)-*N*(1)-Methyl-2-[2'-(3'',4''-methylenedioxyphenyl)ethanyl]-1,2,3,4-tetrahydroquinoline [(–)-galipinine] 11



Pd/C (30 mg, 40% w/w) was added to a stirred solution of **236** (73 mg, 0.19 mmol) and CH_2O (37% in H_2O, 0.15 mL, 2.0 mmol) in degassed MeOH (4 mL). The resultant mixture was stirred under H_2 (1 atm) at rt for 24 h. The reaction mixture was filtered through a short plug of Celite® (eluent MeOH) then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 90:9:1) gave **11** as a colourless oil (47 mg, 81%); $[\alpha]_D^{25}$ –23.7 (*c* 1.0 in $CHCl_3$); {lit.[16] for a sample isolated from the natural source $[\alpha]_D$ –33.4 (*c* 0.0055 in $CHCl_3$); lit.[18] for *ent*-**11** $[\alpha]_D^{24}$ +21.8 (*c* 0.75 in $CHCl_3$)}; ν_{max} (ATR) 2934, 2891 (C–H), 1602, 1500, 1489 (Ar); δ_H (400 MHz, $CDCl_3$) 1.65–1.74 (1H, m, C(1')H_A), 1.84–1.96 (3H, m, C(3)H_2, C(1')H_B), 2.50 (1H, ddd, *J* 13.9, 9.9, 6.6, C(2')H_A), 2.59–2.72 (2H, m, C(4)H_A, C(2')H_B), 2.83 (1H, td, *J* 10.9, 6.2, C(4)H_B), 2.91 (3H, s, N*Me*), 3.16–3.23 (1H, m, C(2)*H*), 5.92 (2H, s, OCH_2O), 6.52 (1H, d, *J* 8.2, C(8)*H*), 6.59 (1H, td, *J* 7.4, 1.0, C(6)*H*), 6.63 (1H, dd, *J* 7.9, 1.6, C(6")*H*), 6.68 (1H, d, *J* 1.6, C(2")*H*), 6.72 (1H, d, *J* 7.9, C(5")*H*), 6.97 (1H, d, *J* 7.4, C(5)*H*), 7.05–7.11 (1H, m, C(7)*H*); δ_C (100 MHz, $CDCl_3$) 23.7 (*C*(4)), 24.5 (*C*(3)), 32.2 (*C*(2')), 33.3 (*C*(1')), 38.2 (N*Me*), 58.4 (*C*(2)), 100.9 (O*C*H_2O), 108.3 (*C*(5")), 108.9 (*C*(2")), 110.8 (*C*(8)),

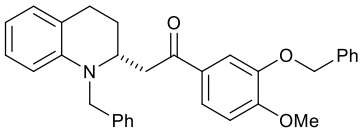
115.6 (*C*(6)), 121.1 (*C*(6")), 121.9 (*C*(4a)), 127.2 (*C*(7)), 128.8 (*C*(5)), 136.0 (*C*(1")), 145.4 (*C*(8a)), 145.7, 147.7 (*C*(3"), *C*(4")); *m/z* (ESI$^+$) 296 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{22}NO_2^+$ ([M+H]$^+$) requires 296.1645; found 296.1644.

1-Methoxy-2-benzyloxy-4-bromobenzene 239



BnBr (2.1 mL, 18 mmol) was added to a stirred solution of 2-methoxy-5-bromophenol **238** (3.00 g, 14.8 mmol) and K_2CO_3 (4.09 g, 29.6 mmol) in Me_2CO (9 mL). The resultant mixture was heated at reflux for 16 h then cooled to rt, filtered through Celite® (eluent Me_2CO) and concentrated *in vacuo*. The residue was recrystallized from EtOAc to give **239** as a white solid (3.58 g, 83%);[19] mp 106–107 °C; {lit.[19] mp 106–107 °C}; δ_H (400 MHz, $CDCl_3$) 3.86 (3H, s, O*Me*), 5.11 (2H, s, OCH_2Ph), 6.76 (1H, d, *J* 8.3, C(6)*H*), 7.02–7.06 (2H, m, C(3)*H*, C(5)*H*), 7.30–7.45 (5H, m, *Ph*).

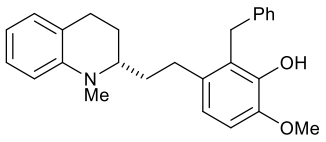
(*R*)-*N*(1)-Benzyl-2-[2'-oxo-2'-(3''-benzyloxy-4''-methoxyphenyl)ethanyl]-1,2,3,4-tetrahydroquinoline 240



BuLi (2.3 M in hexanes, 2.2 mL, 5.0 mmol) was added dropwise to a stirred solution of **239** (1.47 g, 5.03 mmol) in THF (15 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. A solution of **227** (233 mg, 0.718 mmol) in THF (2 mL) at –78 °C was then added and the resultant mixture was stirred at –78 °C for 1.5 h. Satd aq NH_4Cl (3 mL) was added and the reaction mixture was warmed to rt and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and H_2O (20 mL) and the organic extract was dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 75:25:1) gave **240** as a yellow oil (271 mg, 79%); $[\alpha]_D^{25}$ –15.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3029, 2931 (C–H), 1668, 1597, 1497 (Ar); δ_H (400 MHz, $CDCl_3$) 1.93–2.00 (1H, m, C(3)H_A), 2.11 (1H, tt, *J* 13.0, 4.8, C(3)H_B), 2.79 (1H, ddd, *J* 16.7, 4.8, 2.7, C(4)H_A), 2.96 (1H, ddd, *J* 16.7, 13.0, 5.5, C(4)H_B), 3.09 (1H, dd, *J* 15.8, 8.2, C(1')H_A), 3.19 (1H, dd, *J* 15.8, 5.1, C(1')H_B), 3.95 (3H, s, O*Me*), 4.16–4.22 (1H, m, C(2)*H*), 4.46 (1H, d, *J* 17.1, NCH_AH_BPh), 4.54 (1H, d,

J 17.1, NCH$_A$*H*$_B$Ph), 5.12 (1H, d, *J* 12.2, OC*H*$_A$H$_B$Ph), 5.16 (1H, d, *J* 12.2, OCH$_A$*H*$_B$Ph), 6.47 (1H, d, *J* 7.6, C(8)*H*), 6.65 (1H, t, *J* 7.6, C(6)*H*), 6.88 (1H, d, *J* 8.9, C(5")*H*), 7.00 (1H, t, *J* 7.6, C(7)*H*), 7.07 (1H, d, *J* 7.6, C(5)*H*), 7.20–7.40 (8H, m, *Ph*), 7.44–7.48 (2H, m, *Ph*), 7.50–7.54 (2H, m, C(2")*H*, C(6")*H*); δ_C (100 MHz, $CDCl_3$) 23.6 (*C*(4)), 25.6 (*C*(3)), 40.8 (*C*(1')), 54.2 (N*C*H$_2$Ph), 55.1 (*C*(2)), 56.2 (O*Me*), 70.9 (O*C*H$_2$Ph), 110.6 (*C*(5")), 112.1 (*C*(8)), 112.7 (*C*(2")), 116.2 (*C*(6)), 121.3 (*C*(4a)), 123.3 (*C*(6")), 126.5 (*o*/*m*-*Ph*), 126.9 (*p*-*Ph*), 127.4 (*C*(7)), 127.6 (*o*/*m*-*Ph*), 128.2 (*p*-*Ph*), 128.7, 128.7 (2 × *o*/*m*-*Ph*), 129.3 (*C*(5)), 130.4 (*C*(1")), 136.6, 139.0 (2 × *i*-*Ph*), 144.1 (*C*(8a)), 148.1 (*C*(3")), 154.1 (*C*(4")), 197.8 (*C*(2')); *m/z* (ESI$^+$) 478 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{32}NO_3^+$ ([M+H]$^+$) requires 478.2377; found 478.2379.

(*S*)-*N*(1)-Methyl-2-[2'-(2''-benzyl-3''-hydroxy-4''-methoxyphenyl)ethanyl]-1,2,3,4-tetrahydroquinoline 241



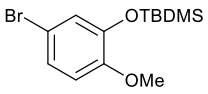
Step 1: $LiAlH_4$ (2.0 M in THF, 0.56 mL, 1.1 mmol) was added dropwise to a stirred solution of **240** (268 mg, 0.561 mmol) in THF (4.0 mL) at 0 °C. The resultant mixture was heated at reflux for 16 h then allowed to cool to rt. Aq NaOH (2.0 M, 0.7 mL) was then added and the resultant mixture was heated at reflux for 3 h. The reaction mixture was then allowed to cool to rt and filtered through Celite® (eluent EtOAc), then concentrated *in vacuo*.

Step 2: Et_3SiH (0.90 mL, 5.6 mmol) was added to a stirred solution of the residue from the previous step in TFA (2.8 mL) and the resultant solution was stirred at rt for 16 h. The resultant mixture was concentrated *in vacuo* and the residue was then partitioned between CH_2Cl_2 (10 mL) and satd aq $NaHCO_3$ (10 mL). The organic extract was dried and concentrated *in vacuo.*

Step 3: Pd/C (75 mg, 40% w/w) was added to a stirred solution of the residue from the previous step and CH_2O (37% in H_2O, 0.42 mL, 5.6 mmol) in degassed MeOH (4 mL). The resultant mixture was stirred under H_2 (1 atm) at rt for 24 h. The reaction mixture was filtered through a short plug of Celite® (eluent MeOH) then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 66:33:1) gave **241** as a colourless oil (36 mg, 17%, ~90% purity); ν_{max} (ATR) 3523

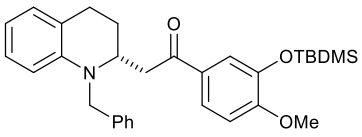
(O–H), 3024, 2935, 2839 (C–H), 1601, 1491 (Ar); δ_H (400 MHz, $CDCl_3$) 1.46–1.57 (1H, m, C(1')H_A), 1.62–1.72 (1H, m, C(1')H_B), 1.81–1.87 (2H, m, C(3)H_2), 2.40–2.75 (4H, m, C(4)H_2, C(2')H_2), 2.76 (3H, s, N*Me*), 3.14–3.20 (1H, m, C(2)*H*), 3.85 (3H, s, O*Me*), 4.04 (1H, d, *J* 15.5, CH_AH$_B$Ph), 4.10 (1H, d, *J* 15.5, CH$_A$$H_B$Ph), 5.74 (1H, s, O*H*), 6.46 (1H, d, *J* 8.1, C(8)*H*), 6.56 (1H, td, *J* 7.3, 1.0, C(6)*H*), 6.66 (1H, d, *J* 8.3, C(6")*H*), 6.71 (1H, d, *J* 8.3, C(5")*H*), 6.93 (1H, d, *J* 7.1, C(5)*H*), 7.02–7.02 (1H, m, C(7)*H*), 7.10–7.26 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 23.7 (*C*(4)), 24.5 (*C*(3)), 29.1 (*C*(2')), 31.6 (*C*H$_2$Ph), 33.0 (*C*(1')), 38.1 (N*Me*), 56.1 (O*Me*), 58.9 (*C*(2)), 108.8 (*C*(5")), 110.6 (*C*(8)), 115.4 (*C*(6)), 119.8 (*C*(6")), 121.9 (*C*(2")), 124.6 (*C*(4a)), 125.8 (*p-Ph*), 127.2 (*C*(7)), 128.2, 128.4 (*o,m-Ph*), 128.7 (*C*(5)), 134.4 (*C*(1")), 140.9 (*i-Ph*), 144.1, 144.7, 145.4 (*C*(8a), *C*(3"), *C*(4")); *m/z* (ESI$^+$) 388 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{30}NO_2^+$ ([M+H]$^+$) requires 388.2271; found 388.2277. Further elution gave **10** as a colourless oil (15 mg, 9%).

1-Methoxy-2-*tert*-butyldimethylsilyloxy-4-bromobenzene 242



TBDMSCl (1.50 g, 10.0 mmol) was added to a stirred solution of 2-methoxy-5-bromophenol **238** (2.00 g, 9.85 mmol) and imidazole (1.36 g, 20.0 mmol) in DMF (5 mL) and the resultant mixture was stirred at rt for 16 h. H_2O (15 mL) was added and the resultant mixture was extracted with hexane (5 × 15 mL). The combined organic extracts were dried and concentrated *in vacuo* to give **242** as a colourless oil (2.92 g, 93%);[20] δ_H (400 MHz, $CDCl_3$) 0.15 (6H, s, Si*Me*$_2$), 0.99 (9H, s, SiC*Me*$_3$), 3.78 (3H, s, O*Me*), 6.71 (1H, d, *J* 8.6, C(6)*H*), 6.98 (1H, d, *J* 2.4, C(3)*H*), 7.02 (1H, dd, *J* 8.6, 2.4, C(5)*H*).

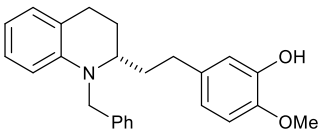
(*R*)-*N*(1)-Benzyl-2-[2'-Oxo-2'-(3''-*tert*-butyldimethylsilyloxy-4''-methoxyphenyl)ethanyl]-1,2,3,4-tetrahydroquinoline 243



BuLi (2.3 M in hexanes, 1.9 mL, 4.3 mmol) was added dropwise to a stirred solution of **242** (1.37 g, 4.32 mmol) in THF (15 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. A solution of **227** (200 mg, 0.616 mmol) in THF (2 mL) at –78 °C was then added and the resultant mixture was

stirred at –78 °C for 1.5 h. Satd aq NH_4Cl (3 mL) was added and the reaction mixture was warmed to rt and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and H_2O (20 mL) and the organic extract was dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 85:17:1) gave **243** as a yellow oil (273 mg, 88%); $[\alpha]_D^{25}$ –7.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2953, 2930, 2857 (C–H), 1671 (C=O); δ_H (400 MHz, $CDCl_3$) 0.15 (6H, s, Si*Me*$_2$), 0.99 (9H, s, SiC*Me*$_3$), 1.97 (1H, ddt, *J* 13.1, 5.7, 2.9, C(3)H_A), 2.09 (1H, tt, *J* 13.1, 4.8, C(3)H_B), 2.74–2.81 (1H, m, C(4)H_A), 2.96 (1H, ddd, *J* 16.7, 13.1, 5.7, C(4)H_B), 3.15 (2H, d, *J* 6.7, C(1')H_2), 3.86 (3H, s, O*Me*), 4.15–4.21 (1H, m, C(2)*H*), 4.49 (1H, d, *J* 17.2, NCH_AH$_B$Ph), 4.56 (1H, d, *J* 17.2, NCH$_A$$H_B$Ph), 6.45 (1H, d, *J* 8.2, C(8)*H*), 6.62 (1H, td, *J* 7.3, 0.9, C(6)*H*), 6.83 (1H, d, *J* 8.5, C(5")*H*), 6.95–7.00 (1H, m, C(7)*H*), 7.04 (1H, d, *J* 7.3, C(5)*H*), 7.18–7.31 (5H, m, *Ph*), 7.43 (1H, d, *J* 2.2, C(2")*H*), 7.49 (1H, dd, *J* 8.5, 2.2, C(6")*H*); δ_C (100 MHz, $CDCl_3$) –4.5 (Si*Me*$_2$), 18.6 (Si*C*Me$_3$), 23.7 (*C*(4)), 25.6 (*C*(3)), 25.8 (SiC*Me*$_3$), 40.9 (*C*(1')), 54.2 (N*C*H$_2$Ph), 55.1 (*C*(2)), 55.6 (O*Me*), 110.9 (*C*(5")), 112.0 (*C*(8)), 116.1 (*C*(6)), 120.4 (*C*(2")), 121.3 (*C*(4a)), 123.5 (*C*(6")), 126.5 (*o*/*m*-*Ph*), 126.9 (*p*-*Ph*), 127.4 (*C*(7)), 128.7 (*o*/*m*-*Ph*), 129.3 (*C*(5)), 130.7 (*C*(1")), 139.0 (*i*-*Ph*), 144.2 (*C*(8a)), 145.1 (*C*(3")), 155.6 (*C*(4")), 197.8 (*C*(2')); *m/z* (ESI$^+$) 502 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{40}NO_3Si^+$ ([M+H]$^+$) requires 502.2772; found 502.2768.

(*S*)-*N*(1)-Benzyl-2-[2'-(3''-hydroxy-4''-methoxyphenyl)ethanyl]-1,2,3,4-tetrahydroquinoline 244

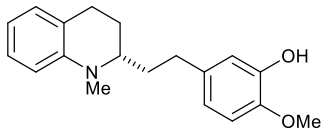


Step 1: $LiAlH_4$ (2.0 M in THF, 0.46 mL, 0.91 mmol) was added dropwise to a stirred solution of **243** (229 mg, 0.456 mmol) in THF (3.2 mL) at 0 °C. The resultant mixture was heated at reflux for 16 h then allowed to cool to rt. Aq NaOH (2.0 M, 0.5 mL) was then added and the resultant mixture was heated at reflux for 3 h. The reaction mixture was then allowed to cool to rt then concentrated *in vacuo*. The residue was dissolved in Et_2O and filtered through a short plug of silica (eluent Et_2O), then concentrated *in vacuo*.

Step 2: Et_3SiH (0.73 mL, 4.6 mmol) was added to a stirred solution of the residue from the previous step in TFA (2.2 mL) and the resultant solution was stirred at rt for 16 h. The resultant mixture was concentrated *in vacuo* and the residue was then partitioned between CH_2Cl_2 (10 mL) and satd aq $NaHCO_3$

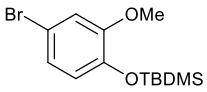
(10 mL). The organic extract was dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 75:25:1) gave **244** as a pale yellow oil (85 mg, 50%); $[\alpha]_D^{25}$ +0.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3513 (O–H), 3027, 2980, 2971, 2933, 2860 (C–H), 1600, 1510, 1498 (Ar); δ_H (400 MHz, $CDCl_3$) 1.77–2.09 (4H, m, C(3)H_2, C(1')H_2), 2.45 (1H, ddd, *J* 14.0, 9.6, 6.8, C(2')H_A), 2.61 (1H, ddd, *J* 14.0, 9.6, 5.4, C(2')H_B), 2.75 (1H, dt, *J* 16.5, 3.9, C(4)H_A), 2.93 (1H, ddd, *J* 16.5, 12.3, 5.9, C(4)H_B), 3.35–3.42 (1H, m, C(2)*H*), 3.85 (3H, s, O*Me*), 4.40 (1H, d, *J* 17.0, NC$H_A$$H_B$Ph), 4.56 (1H, d, *J* 17.0, NC$H_A$$H_B$Ph), 5.54 (1H, s, O*H*), 6.41 (1H, d, *J* 8.0, C(8)*H*), 6.55–6.62 (2H, m, C(6)*H*, C(6")*H*), 6.72–6.75 (2H, m, C(2")*H*, C(5")*H*), 6.94 (1H, t, *J* 8.0, C(7)*H*), 7.01 (1H, d, *J* 7.3, C(5)*H*), 7.19–7.31 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 23.7 (*C*(4)), 24.3 (*C*(3)), 31.7 (*C*(2')), 33.7 (*C*(1')), 54.2 (N*C*H_2Ph), 56.1 (O*Me*), 57.3 (*C*(2)), 110.7 (*C*(5")), 111.9 (*C*(8)), 114.6 (*C*(2")), 115.7 (*C*(6)), 119.6 (*C*(6")), 121.7 (*C*(4a)), 126.6 (*o*/*m*-*Ph*), 126.8 (*p*-*Ph*), 127.2 (*C*(7)), 128.7 (*o*/*m*-*Ph*), 129.1 (*C*(5)), 135.3 (*C*(1")), 139.4 (*i*-*Ph*), 144.6, 144.9, 145.6 (*C*(8a), *C*(3"), *C*(4")); *m/z* (ESI$^+$) 374 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{28}NO_2^+$ ([M+H]$^+$) requires 374.2115; found 374.2115.

(*S*)-*N*(1)-Methyl-2-[2'-(3''-hydroxy-4''-methoxyphenyl)ethanyl]-1,2,3,4-tetrahydroquinoline 10



Pd/C (27 mg, 40% w/w) was added to a stirred solution of **244** (68 mg, 0.18 mmol) and CH_2O (37% in H_2O, 0.13 mL, 1.8 mmol) in degassed MeOH (3 mL). The resultant mixture was stirred under H_2 (1 atm) at rt for 24 h. The reaction mixture was filtered through a short plug of Celite® (eluent MeOH) then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 66:33:1) gave **10** as a pale orange solid (31 mg, 57%); mp 134–138 °C; $[\alpha]_D^{25}$ –26.2 (*c* 1.0 in $CHCl_3$); {lit.[21] $[\alpha]_D^{24}$ –26.1 (*c* 0.44 in $CHCl_3$)}; ν_{max} (ATR) 3501 (O–H), 2980, 2934 (C–H), 1601, 1510, 1501 (Ar); δ_H (400 MHz, $CDCl_3$) 1.66–1.76 (1H, m, C(1')H_A), 1.84–1.99 (3H, m, C(3)H_2, C(1')H_B), 2.49 (1H, ddd, *J* 13.9, 9.9, 6.6, C(2')H_A), 2.59–2.72 (2H, m, C(4)H_A, C(2')H_B), 2.84 (1H, ddd, *J* 17.6, 11.7, 5.2, C(4)H_B), 2.90 (3H, s, N*Me*), 3.24–3.30 (1H, m, C(2)*H*), 3.87 (3H, s, O*Me*), 5.56 (1H, s, O*H*), 6.52 (1H, d, *J* 8.1, C(8)*H*), 6.59 (1H, td, *J* 7.3, 1.0, C(6)*H*), 6.66 (1H, dd, *J* 8.2, 2.1, C(6")*H*), 6.75–6.79 (2H, m, C(2")*H*, C(5")*H*), 6.98 (1H, d, *J* 7.2, C(5)*H*), 7.05–7.10 (1H, m, C(7)*H*); δ_C (100 MHz,

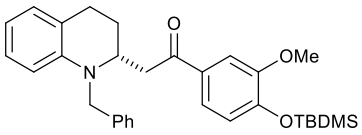
$CDCl_3$) 23.7 (*C*(4)), 24.5 (*C*(3)), 31.7 (*C*(2')), 33.0 (*C*(1')), 38.1 (N*Me*), 56.1 (O*Me*), 58.3 (*C*(2)), 110.7, 110.7 (*C*(8), *C*(5")), 114.6 (*C*(2")), 115.5 (*C*(6)), 119.7 (*C*(6")), 121.9 (*C*(4a)), 127.2 (*C*(7)), 128.8 (*C*(5)), 135.5 (*C*(1")), 144.9 (*C*(4")), 145.5 (*C*(8a)), 145.6 (*C*(3")); *m/z* (ESI^+) 298 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{19}H_{24}NO_2^+$ ($[M+H]^+$) requires 298.1802; found 298.1800.



1-Methoxy-2-*tert*-butyldimethylsilyloxy-5-bromobenzene 246

TBDMSCl (1.50 g, 10.0 mmol) was added to a stirred solution of 2-methoxy-4-bromophenol **245** (2.00 g, 9.85 mmol) and imidazole (1.36 g, 20.0 mmol) in DMF (5 mL) and the resultant mixture was stirred at rt for 16 h. H_2O (15 mL) was added and the resultant mixture was extracted with hexane (5 × 15 mL). The combined organic extracts were dried and concentrated *in vacuo* to give **246** as a colourless oil (2.98 g, 95%);[22] δ_H (400 MHz, $CDCl_3$) 0.14 (6H, s, Si*Me*$_2$), 0.98 (9H, s, SiC*Me*$_3$), 3.79 (3H, s, O*Me*), 6.71 (1H, d, *J* 8.3, C(3)*H*), 6.93 (1H, dd, *J* 8.3, 2.4, C(4)*H*), 6.95 (1H, d, *J* 2.4, C(6)*H*).

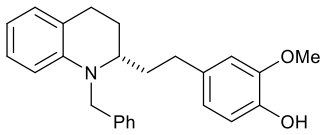
(*R*)-*N*(1)-Benzyl-2-[2'-oxo-2'-(3''-methoxy-4''-*tert*-butyldimethylsilyloxyphenyl)ethanyl]-1,2,3,4-tetrahydroquinoline 247



BuLi (2.3 M in hexanes, 2.4 mL, 5.4 mmol) was added dropwise to a stirred solution of **246** (1.71 g, 5.39 mmol) in THF (19 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. A solution of **227** (250 mg, 0.771 mmol) in THF (2 mL) at –78 °C was then added and the resultant mixture was stirred at –78 °C for 1.5 h. Satd aq NH_4Cl (4 mL) was added and the reaction mixture was warmed to rt and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and H_2O (20 mL) and the organic extract was dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 90:9:1) gave **247** as a yellow oil (239 mg, 62%); $[\alpha]_D^{25}$ –11.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2953, 2930, 2857 (C–H), 1672 (C=O); δ_H (400 MHz, $CDCl_3$) 0.17 (6H, s, Si*Me*$_2$), 0.99 (9H, s, SiC*Me*$_3$), 1.98 (1H, ddt, *J* 13.3, 5.7, 2.8, C(3)H_A), 2.10 (1H, tt, *J* 13.3, 4.9, C(3)H_B), 2.74–2.82 (1H, m, C(4)H_A), 2.97 (1H, ddd, *J* 17.1, 13.3, 5.7, C(4)H_B), 3.13 (1H, dd, *J* 16.1, 8.3, C(1')H_A),

3.21 (1H, dd, *J* 16.1, 5.1, C(1')H_B), 3.81 (3H, s, O*Me*), 4.16–4.22 (1H, m, C(2)*H*), 4.48 (1H, d, *J* 17.1, NCH_AH$_B$Ph), 4.55 (1H, d, *J* 17.1, NCH$_A$$H_B$Ph), 6.45 (1H, d, *J* 8.3, C(8)*H*), 6.62 (1H, td, *J* 7.3, 0.9, C(6)*H*), 6.83 (1H, d, *J* 8.3, C(5")*H*), 6.95–7.00 (1H, m, C(7)*H*), 7.04 (1H, d, *J* 7.3, C(5)*H*), 7.18–7.31 (5H, m, *Ph*), 7.38 (1H, dd, *J* 8.3, 2.0, C(6")*H*), 7.44 (1H, d, *J* 2.0, C(2")*H*); δ_C (100 MHz, $CDCl_3$) –4.4 (Si*Me*$_2$), 18.6 (Si*C*Me$_3$), 23.7 (*C*(4)), 25.6 (*C*(3)), 25.8 (SiC*Me*$_3$), 40.9 (*C*(1')), 54.3 (N*C*H$_2$Ph), 55.0 (*C*(2)), 55.6 (O*Me*), 111.1 (*C*(2")), 112.1 (*C*(8)), 116.2 (*C*(6)), 120.4 (*C*(5")), 121.3 (*C*(4a)), 122.7 (*C*(6")), 126.6 (*o*/*m*-*Ph*), 126.9 (*p*-*Ph*), 127.4 (*C*(7)), 128.7 (*o*/*m*-*Ph*), 129.4 (*C*(5)), 131.4 (*C*(1")), 139.0 (*i*-*Ph*), 144.2 (*C*(8a)), 150.3, 151.2 (*C*(3"), *C*(4")), 198.0 (*C*(2')); *m/z* (ESI$^+$) 502 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{40}NO_3Si^+$ ([M+H]$^+$) requires 502.2772; found 502.2768.

(*S*)-*N*(1)-Benzyl-2-[2'-(3''-methoxy-4''-hydroxyphenyl)ethanyl]-1,2,3,4-tetrahydroquinoline 248

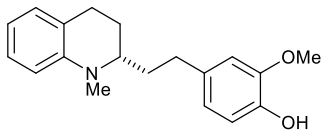


Step 1: $LiAlH_4$ (2.4 M in THF, 0.47 mL, 0.95 mmol) was added dropwise to a stirred solution of **247** (238 mg, 0.474 mmol) in THF (3.3 mL) at 0 °C. The resultant mixture was heated at reflux for 16 h then allowed to cool to rt. Aq NaOH (2.0 M, 0.5 mL) was then added and the resultant mixture was heated at reflux for 3 h. The reaction mixture was then allowed to cool to rt and filtered through Celite® (eluent EtOAc), then concentrated *in vacuo*.

Step 2: Et_3SiH (0.76 mL, 4.7 mmol) was added to a stirred solution of the residue from the previous step in TFA (2.3 mL) and the resultant solution was stirred at rt for 16 h. The resultant mixture was concentrated *in vacuo* and the residue was then partitioned between CH_2Cl_2 (10 mL) and satd aq $NaHCO_3$ (10 mL). The organic extract was dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 50:50:1) gave **248** as a pale yellow oil (109 mg, 62%); $[\alpha]_D^{25}$ +0.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3102, 3026, 2934 (C–H), 1605, 1530 (Ar); δ_H (400 MHz, $CDCl_3$) 1.78–2.08 (4H, m, C(3)H_2, C(1')H_2), 2.47 (1H, ddd, *J* 13.9, 9.9, 6.6, C(2')H_A), 2.64 (1H, ddd, *J* 13.9, 10.6, 5.1, C(2')H_B), 2.76 (1H, dt, *J* 16.5, 3.9, C(4)H_A), 2.94 (1H, ddd, *J* 16.5, 11.9, 6.2, C(4)H_B), 3.38–3.44 (1H, m, C(2)*H*), 3.84 (3H, s, O*Me*), 4.42 (1H, d, *J* 17.1, NCH_AH$_B$Ph), 4.57 (1H, d, *J* 17.1, NCH$_A$$H_B$Ph), 5.45 (1H, s, O*H*), 6.43 (1H, d, *J* 8.2, C(8)*H*), 6.58 (1H, td, *J* 7.3, 1.1, C(6)*H*), 6.61 (1H, d,

J 1.9, C(2")*H*), 6.63 (1H, dd, *J* 8.0, 1.9, C(6")*H*), 6.81 (1H, d, *J* 8.0, C(5")*H*), 6.93–6.98 (1H, m, C(7)*H*), 7.02 (1H, d, *J* 7.3, C(5)*H*), 7.19–7.32 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 23.8 (*C*(4)), 24.4 (*C*(3)), 32.1 (*C*(2')), 34.0 (*C*(1')), 54.3 (N*C*H_2Ph), 56.0 (O*Me*), 57.5 (*C*(2)), 110.8 (*C*(2")), 111.9 (*C*(8)), 114.3 (*C*(5")), 115.7 (*C*(6)), 120.9 (*C*(6")), 121.7 (*C*(4a)), 126.6 (*o*/*m*-*Ph*), 126.8 (*p*-*Ph*), 127.2 (*C*(7)), 128.7 (*o*/*m*-*Ph*), 129.1 (*C*(5)), 133.9 (*C*(1")), 139.4 (*i*-*Ph*), 143.8, 144.6, 146.5 (*C*(8a), *C*(3"), *C*(4")); *m/z* (ESI^+) 374 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{25}H_{28}NO_2^+$ ($[M+H]^+$) requires 374.2115; found 374.2118.

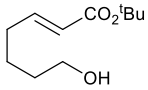
(*S*)-*N*(1)-Methyl-2-[2'-(3''-methoxy-4''-hydroxyphenyl)ethanyl]-1,2,3,4-tetrahydroquinoline [(–)-galipeine] 145



Pd/C (42 mg, 40% w/w) was added to a stirred solution of **248** (106 mg, 0.284 mmol) and CH_2O (37% in H_2O, 0.21 mL, 2.84 mmol) in degassed MeOH (5 mL). The resultant mixture was stirred under H_2 (1 atm) at rt for 24 h. The reaction mixture was filtered through a short plug of Celite® (eluent MeOH) then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 66:33:1) gave **145** as a colourless oil (59 mg, 70%); $[\alpha]_D^{25}$ –22.3 (*c* 1.0 in $CHCl_3$), –22.0 (*c* 0.2 in $CHCl_3$), –14.0 (*c* 1.0 in MeOH); {lit.[23] for a sample isolated from the natural source $[\alpha]_D$ –13.6}; ν_{max} (ATR) 3510 (O–H), 2935, 2860, 2844 (C–H), 1602, 1514, 1500 (Ar); δ_H (400 MHz, $CDCl_3$) 1.68–1.78 (1H, m, C(1')H_A), 1.86–2.00 (3H, m, C(3)H_2, C(1')H_B), 2.52 (1H, ddd, *J* 13.9, 10.2, 6.4, C(2')H_A), 2.62–2.73 (2H, m, C(4)H_A, C(2')H_B), 2.86 (1H, ddd, *J* 17.5, 11.6, 6.1, C(4)H_B), 2.92 (3H, s, N*Me*), 3.26–3.33 (1H, m, C(2)*H*), 3.88 (3H, s, O*Me*), 5.47 (1H, s, O*H*), 6.54 (1H, d, *J* 8.1, C(8)*H*), 6.60 (1H, td, *J* 7.3, 0.9, C(6)*H*), 6.67–6.71 (2H, m, C(2")*H*, C(6")*H*), 6.84 (1H, d, *J* 8.5, C(5")*H*), 6.99 (1H, d, *J* 7.3, C(5)*H*), 7.07–7.12 (1H, m, C(7)*H*); δ_C (100 MHz, $CDCl_3$) 23.7 (*C*(4)), 24.5 (*C*(3)), 32.1 (*C*(2')), 33.3 (*C*(1')), 38.2 (N*Me*), 56.0 (O*Me*), 58.5 (*C*(2)), 110.7 (*C*(8)), 110.8 (*C*(2")), 114.3 (*C*(5")), 115.5 (*C*(6)), 120.9 (*C*(6")), 121.8 (*C*(4a)), 127.2 (*C*(7)), 128.8 (*C*(5)), 134.0 (*C*(1")), 143.8 (*C*(4")), 145.4 (*C*(8a)), 146.5 (*C*(3")); *m/z* (ESI^+) 298 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{19}H_{24}NO_2^+$ ($[M+H]^+$) requires 298.1802; found 298.1801.

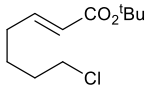
5.3 Experimental data for Chapter 3

tert-Butyl 7-hydroxyhept-2-enoate 255



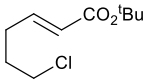
BuLi (2.3 M in hexanes, 38.7 mL, 88.9 mmol) was added dropwise to a stirred solution of **193** (22.4 g, 88.9 mmol) in THF (75 mL) at –78 °C and the resultant mixture was stirred for 30 min at –78 °C. δ-Valerolactone **272** (7.50 mL, 80.8 mmol) was added followed by the dropwise addition of DIBAL-H (1.0 M in THF, 80.8 mL, 80.8 mmol). The resultant solution was allowed to warm to rt over 16 h. The reaction was quenched with Rochelle salt (80 mL) and then concentrated *in vacuo*. The residue was partitioned between EtOAc (100 mL) and aq HCl (0.5 M, 100 mL). The organic fraction was washed sequentially with satd aq K_2CO_3 (100 mL) and brine (100 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:2) gave **255** as a colourless oil (6.71 g, 41%, >99.1 dr);[24] δ_H (400 MHz, $CDCl_3$) 1.41 (9H, s, C*Me*$_3$), 1.44–1.58 (4H, m, C(5)*H*$_2$, C(6)*H*$_2$), 2.14 (2H, app q, *J* 6.9, C(4)*H*$_2$), 3.59 (2H, t, *J* 6.2, C(7)*H*$_2$), 5.68 (1H, d, *J* 15.5, C(2)*H*), 6.78 (1H, dt, *J* 15.5, 6.9, C(3)*H*).

tert-Butyl 7-chlorohept-2-enoate 256



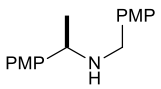
CCl_4 (12.9 mL, 134 mmol) was added dropwise to a stirred solution of **255** (6.71 g, 33.5 mmol, >99:1 dr), PPh_3 (8.79 g, 33.5 mmol) and Et_3N (18.7 mL, 134 mmol) in MeCN (180 mL). The resultant solution was heated to reflux for 24 h before being cooled and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **256** as a pale yellow oil (4.86 g, 66%, >99:1 dr);[24] δ_H (400 MHz, $CDCl_3$) 1.41 (9H, s, C*Me*$_3$), 1.50–1.59 (2H, m, C(5)*H*$_2$), 1.69–1.78 (2H, m, C(6)*H*$_2$), 2.11–2.18 (2H, m, C(4)*H*$_2$), 3.47 (2H, t, *J* 6.5, C(7)*H*$_2$), 5.69 (1H, dt, *J* 15.5, 1.4, C(2)*H*), 6.77 (1H, dt, *J* 15.5, 6.9, C(3)*H*).

tert-Butyl (_E_)-6-chlorohex-2-enoate 274



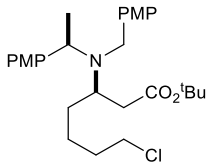
IBX (3.87 g, 13.8 mmol) was added to a stirred solution of **273** (1.00 g, 9.21 mmol) in EtOAc (20 mL) and the resultant mixture was heated at 70 °C for 3 h. The reaction mixture was then allowed to cool to rt, cooled further to 0 °C, and filtered. The filtrate was added to a solution of **164** (3.74 g, 9.21 mmol) in EtOAc (10 mL) and the resultant mixture was stirred at rt for 16 h, then concentrated *in vacuo* to give **274** in 94:6 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **274** as a colourless oil (1.10 g, 58%, >99:1 dr); ν_{max} (ATR) 2979, 2935, 2873 (C−H), 1712 (C=O); δ_H (400 MHz, $CDCl_3$) 1.49 (9H, s, C*Me*$_3$), 1.90–1.99 (2H, m, C(5)*H*$_2$), 2.32–2.40 (2H, m, C(4)*H*$_2$), 3.56 (2H, dt, *J* 6.5, 2.6, C(6)*H*$_2$), 5.80 (1H, dt, *J* 15.5, 1.5, C(2)*H*), 6.82 (1H, dt, *J* 15.5, 7.0, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 28.1 (C*Me*$_3$), 29.0 (*C*(4)), 30.8 (*C*(5)), 44.0 (*C*(6)), 80.2 (*C*Me$_3$), 124.2 (*C*(2)), 145.6 (*C*(3)), 165.8 (*C*(1)); *m/z* (ESI$^+$) 229 ([M(^{37}Cl)+Na]$^+$, 25%), 227 ([M(^{35}Cl)+Na]$^+$, 100%); HRMS (CI$^+$) $C_{10}H_{21}{}^{37}ClNO_2^+$ ([M(^{37}Cl)+NH_4]$^+$) requires 224.1226; found 224.1215. HRMS (CI$^+$) $C_{10}H_{21}{}^{35}ClNO_2^+$ ([M(^{35}Cl)+NH_4]$^+$) requires 222.1255; found 222.1249.

(_R_)-_N_-(α-Methyl-_p_-methoxybenzyl)-_N_-(_p_-methoxybenzyl)amine 261



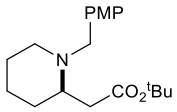
p-Anisaldehyde (7.87 mL, 65.5 mmol) was added to a stirred solution of (*R*)-*p*-methoxy-α-methylbenzylamine (10.0 mL, 68.8 mmol, >99% ee) in EtOH (50 mL) and the resultant mixture was heated to reflux for 2 h. The reaction mixture was cooled to 0 °C, then $NaBH_4$ (596 mg, 15.8 mmol) was added and the resultant mixture was stirred for 48 h. The reaction mixture was partitioned between CH_2Cl_2 (100 mL) and H_2O (100 mL) and the organic layer was washed with brine (100 mL), then dried and concentrated *in vacuo* to give **261** as a colourless oil (17.7 g, 99%, >99:1 er);[5,25] $[\alpha]_D^{20}$ +46 (*c* 0.1 in MeOH); {lit.[25] $[\alpha]_D^{20}$ +37.8 (*c* 0.1 in MeOH)}; δ_H (400 MHz, $CDCl_3$) 1.33 (3H, d, *J* 6.4, C(α)*Me*), 3.53 (1H, d, *J* 13.1, C*H*$_A$H$_B$Ar), 3.57 (1H, d, *J* 13.1, CH$_A$*H*$_B$Ar), 3.75 (1H, q, *J* 6.4, C(α)*H*), 3.80 (3H, s, O*Me*), 3.81 (3H, s, O*Me*), 6.85 (2H, d, *J* 8.6, C(3')*H*, C(5')*H*), 6.89 (2H, d, *J* 8.6, C(3")*H*, C(5")*H*), 7.19 (2H, d, *J* 8.6, C(2')*H*, C(6')*H*), 7.27 (2H, d, *J* 8.6, C(2")*H*, C(6")*H*).

***tert*-Butyl (*R*,*R*)-3-[*N*-(*p*-methoxybenzyl)-*N*-(α-methyl-*p*-methoxybenzyl)amino]-7-chloroheptanoate 257**



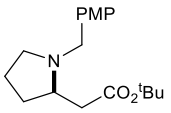
BuLi (2.3 M in hexanes, 3.1 mL, 7.1 mmol) was added dropwise to a stirred solution of **261** (1.98 g, 7.31 mmol, >99:1 er) in THF (40 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. A solution of **256** (1.00 g, 4.57 mmol, >99:1 dr) in THF (40 mL) at –78 °C was added *via* cannula, and the resultant mixture was stirred at –78 °C for 2 h. Satd aq NH_4Cl (4 mL) was added and the reaction mixture was allowed to warm to rt, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (40 mL) and 10% aq citric acid (40 mL), and the organic layer was washed with satd aq $NaHCO_3$ (40 mL) and brine (40 mL), then dried and concentrated *in vacuo* to give **257** in >99:1 dr. Purification *via* flash column chromatography (eluent 30–40°C petrol/Et_2O, 15:1) gave **257** as a colourless oil (1.84 g, 82%, >99:1 dr); $[\alpha]_D^{20}$ +34.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2970, 2933, 2868, 2835 (C−H), 1720 (C=O); δ_H (400 MHz, $CDCl_3$) 1.20–1.55 (4H, m, C(4)H_2, C(5)H_2), 1.33 (3H, d, *J* 7.1, C(α)*Me*), 1.42 (9H, s, CMe_3), 1.65–1.80 (2H, m, C(6)H_2), 1.87 (1H, dd, *J* 14.7, 9.4, C(2)H_A), 1.96 (1H, dd, *J* 14.7, 3.0, C(2)H_B), 3.25–3.35 (1H, m, C(3)*H*), 3.41 (1H, d, *J* 14.8, NC$H_A$$H_B$Ar), 3.53 (2H, t, *J* 6.3, C(7)H_2), 3.71 (1H, d, *J* 14.8, NCH$_A$$H_B$Ar), 3.76–3.81 (1H, q, *J* 7.1, C(α)*H*), 3.81 (3H, s, O*Me*), 3.83 (3H, s, O*Me*), 6.86 (2H, d, *J*, 8.7, C(3')*H*, C(5')*H*), 6.90 (2H, d, *J*, 8.6, C(3")*H*, C(5")*H*), 7.23 (2H, d, *J*, 8.7, C(2')*H*, C(6')*H*), 7.33 (2H, d, *J*, 8.6, C(2")*H*, C(6")*H*); δ_C (100 MHz, $CDCl_3$) 20.6 (C(α)*Me*), 24.2, 32.4, 32.7 (*C*(4), *C*(5), *C*(6)), 28.1 (CMe_3), 37.7 (*C*(2)), 45.1 (*C*(7)), 49.3 (N*C*H$_2$Ar), 53.2 (*C*(3)), 55.2, 55.3 (2 × O*Me*), 57.1 (*C*(α)), 80.0 (*C*Me$_3$), 113.4, 113.7 (*C*(3'), *C*(5'), *C*(3"), *C*(5")), 128.9, 129.1 (*C*(2'), *C*(6'), *C*(2"), *C*(6")), 133.7, 135.0 (*C*(1'), *C*(1")), 158.4, 158.5 (*C*(4'), *C*(4")), 172.2 (*C*(1)); *m*/*z* (ESI$^+$) 492 ([M(^{37}Cl)+H]$^+$, 35%), 490 ([M(^{35}Cl)+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{41}{}^{37}ClNO_4^+$ ([M(^{37}Cl)+H]$^+$) requires 492.2689; found 492.2698; HRMS (ESI$^+$) $C_{28}H_{41}{}^{35}ClNO_4^+$ ([M(^{35}Cl)+H]$^+$) requires 490.2719; found 490.2719.

tert-Butyl (_R_)-2-[_N_(1')-(_p_-methoxybenzyl)piperidin-2'-yl]acetate 265



NaI (844 mg, 5.63 mmol) was added to a stirred solution of **257** (1.38 g, 2.82 mmol, >99:1 dr) in MeCN (65 mL) and the resultant mixture was heated at reflux for 24 h. The reaction mixture was then allowed to cool to rt and diluted with Et_2O (65 mL). The resultant mixture was washed with H_2O (50 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/acetone, 15:1) gave *p*-methoxystyrene **264** as a colourless oil (200 mg, 53%);[26] δ_H (400 MHz, $CDCl_3$) 3.82 (3H, s, O*Me*), 5.14 (1H, d, *J* 10.9, CH=CH_AH_B), 5.62 (1H, d, *J* 17.6, CH=CH_AH_B), 6.67 (1H, dd, *J* 17.6, 10.9, C*H*=CH_2), 6.87 (2H, *J* 8.6, C(3)*H*, C(5)*H*), 7.35 (2H, *J* 8.6, C(2)*H*, C(6)*H*). Further elution (eluent 30–40 °C petrol/acetone, 3:1) gave **257** as a yellow oil (793 mg, 88%); $[\alpha]_D^{20}$ +20.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2976, 2932, 2857, 2835, 2797 (C−H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.35–1.55 (4H, m, C(3')H_A, C(4')H_2, C(5')H_A), 1.45 (9H, s, CMe_3), 1.58–1.65 (1H, m, C(5')H_B), 1.75–1.80 (1H, m, C(3')H_B), 2.11–2.18 (1H, m, C(6')H_A), 2.33 (1H, dd, *J* 14.5, 8.0, C(2)H_A), 2.55–2.70 (2H, m, C(2)H_B, C(6')H_B), 2.91 (1H, m, C(2')*H*), 3.30 (1H, d, *J* 13.5, NCH_AH_BAr), 3.73 (1H, d, *J* 13.5, NCH_AH_BAr), 3.80 (3H, s, O*Me*), 6.85 (2H, d, *J* 8.6, C(3")*H*, C(5")*H*), 7.23 (2H, d, *J* 8.6, C(2")*H*, C(6")*H*); δ_C (100 MHz, $CDCl_3$) 22.3, 25.3 (*C*(4'), *C*(5')), 28.1 (C*Me*$_3$), 31.0 (*C*(3')), 37.3 (*C*(2)), 50.0 (*C*(6')), 55.2 (*C*(2')), 57.6 (N*C*H_2Ar), 57.8 (O*Me*), 80.2 (*C*Me_3), 113.5 (*C*(3"), *C*(5")), 129.9 (*C*(2"), *C*(6")), 131.4 (*C*(1")), 158.5 (*C*(4")), 172.3 (*C*(1)); *m/z* (ESI$^+$) 320 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{30}NO_3^+$ ([M+H]$^+$) requires 320.2220; found 320.2220.

tert-Butyl (_R_)-2-[_N_(1')-(_p_-methoxybenzyl)pyrrolidin-2'-yl]-acetate 277

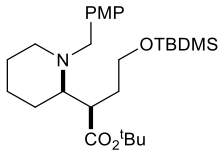


Step 1: BuLi (2.3 M in hexanes, 11.9 mL, 27.5 mmol) was added dropwise to a solution of **261** (7.73 g, 28.4 mmol, >99:1 er) in THF (120 mL) at −78 °C, and the resultant mixture was stirred at –78 °C for 30 min. A solution of **274** (3.63 g, 17.7 mmol, >99:1 dr) in THF (120 mL) at −78 °C was added *via* cannula, and the resultant mixture was stirred at −78 °C for 2 h. Satd aq NH_4Cl (40 mL) was added and the reaction

mixture was allowed to warm to rt and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (100 mL) and 10% aq citric acid (100 mL), and the organic layer was washed with satd aq $NaHCO_3$ (100 mL) and brine (100 mL), then dried and concentrated *in vacuo* to give **275** as a yellow oil; δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, *J* 6.8, C(α)*Me*), 1.35–1.40 (10H, m, C(4)H_A, CMe_3), 1.50–1.64 (1H, m, C(4)H_B), 1.80–1.95 (3H, m, C(2)H_2, C(5)H_A), 2.06–2.15 (1H, m, C(5)H_B), 3.25–3.33 (1H, C(3)*H*), 3.39 (1H, d, *J* 14.8, NCH_AH$_B$Ar), 3.43–3.50 (2H, m, C(6)H_2), 3.71 (1H, d, *J* 14.8, NCH$_A$$H_B$Ar), 3.76 (1H, q, *J* 6.8, C(α)*H*), 3.80 (3H, s, O*Me*), 3.82 (3H, s, O*Me*), 6.85–6.89 (4H, m, *Ar*), 7.21–7.31 (4H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 20.6 (C(α)*Me*), 28.0 (CMe_3), 30.2 (*C*(5)), 30.7 (*C*(4)), 37.5 (*C*(2)), 45.2 (*C*(6)), 49.3 (N*C*H$_2$Ar), 52.9 (*C*(3)), 55.2 (O*Me*), 55.3 (O*Me*), 56.9 (*C*(α)), 80.1 (*C*Me$_3$), 113.5, 113.7, 128.9, 129.2, 133.4, 134.8, 158.4, 158.6 (*Ar*), 172.1 (*C*(1)); *m/z* (ESI$^+$) 498 ([M(^{35}Cl)+Na]$^+$, 100%), 500 ([M(^{37}Cl)+Na]$^+$, 30%); HRMS (ESI$^+$) $C_{27}H_{38}{}^{35}ClNNaO_4^+$ ([M(^{35}Cl)+Na]$^+$) requires 498.2382; found 498.2369; $C_{27}H_{38}{}^{37}ClNNaO_4^+$ ([M(^{37}Cl)+Na]$^+$) requires 500.2352; found 500.2359.

Step 2: NaI (5.30 g, 35.5 mmol) was added to a stirred solution of the residue of **275** from the previous step in MeCN (300 mL) and the resultant mixture was heated at reflux for 24 h. The reaction mixture was then allowed to cool to rt and partitioned between CH_2Cl_2 (300 mL) and H_2O (200 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 300 mL) and the combined organic extracts were washed with brine (500 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/acetone/NH_4OH, 90:9:1) gave **277** as a colourless oil (3.40 g, 63% from **274**); $[\alpha]_D^{20}$ +54.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2975, 2965, 2932, 2875, 2835, 2802 (C−H), 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 1.45 (9H, s, CMe_3), 1.54–1.76 (3H, m, C(3')H_A, C(4')H_2), 1.98–2.08 (1H, m, C(3')H_B), 2.09–2.18 (1H, m, C(5')H_A), 2.22 (1H, dd, *J* 14.5, 8.9, C(2)H_A), 2.62 (1H, dd, *J* 14.5, 4.3, C(2)H_B), 2.74–2.89 (2H, m, C(2')*H*, C(5')H_B), 3.20 (1H, d, *J* 12.7, NCH_AH$_B$Ar), 3.79 (3H, s, O*Me*), 3.91 (1H, d, *J* 12.7, NCH$_A$$H_B$Ar), 6.84 (2H, d, *J* 8.5, C(3")*H*, C(5")*H*); 7.22 (2H, d, *J* 8.5, C(2")*H*, C(6")*H*); δ_C (100 MHz, $CDCl_3$) 22.0 (*C*(4')), 28.1 (CMe_3), 30.8 (*C*(3')), 41.1 (*C*(2)), 53.7 (*C*(5')), 55.2 (O*Me*), 57.8 (N*C*H$_2$Ar), 60.8 (*C*(2')), 80.2 (*C*Me$_3$), 113.5 (*C*(3"), *C*(5")), 130.0 (*C*(2"), *C*(6")), 131.4 (*C*(1")), 158.5 (*C*(4")), 171.8 (*C*(1)); *m/z* (ESI$^+$) 306 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{28}NO_3^+$ ([M+H]$^+$) requires 306.2064; found 306.2064.

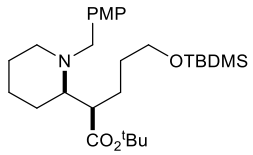
***tert*-Butyl (*R,R*)-2-[*N*(1')-(*p*-methoxybenzyl)piperidin-2'-yl]-4-(*tert*-butyldimethylsiloxy)butanoate 278**



LiHMDS (1.0 M in THF, 6.42 mL, 6.42 mmol) was added to a stirred solution of **265** (410 mg, 1.28 mmol) in THF (20 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 1 h. **279** (2.57 g, 8.98 mmol) was then added and the resultant mixture was allowed to warm to rt and stirred at rt for 16 h. Satd aq NH_4Cl (6 mL) was then added and the reaction mixture was concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and H_2O (20 mL), and the organic layer was then dried and concentrated *in vacuo.* Purification *via* flash column chromatography (eluent 30–40 °C petrol/Me_2CO/NH_4OH, 100:4:1) gave **278** as a pale yellow oil (504 mg, 82%, >99:1 dr); $[\alpha]_D^{20}$ +15.6 (*c* 2.0 in $CHCl_3$); ν_{max} (ATR) 2933, 2857, 2802 (C–H), 1728 (C=O); δ_H (400 MHz, $CDCl_3$) –0.03 (3H, s, Si*Me*$_A$), 0.00 (3H, s, Si*Me*$_B$), 0.82 (9H, s, SiC*Me*$_3$), 1.17–1.42 (3H, m, C(3')*H*$_A$, C(4')*H*$_A$, C(5')*H*$_A$), 1.42–1.56 (2H, m, C(3')*H*$_B$, C(4')*H*$_B$), 1.46 (9H, s, OC*Me*$_3$), 1.62–1.71 (1H, m, C(5')*H*$_B$), 1.80–1.89 (1H, m, C(3)*H*$_A$), 1.90–2.01 (2H, m, C(3)*H*$_B$, C(6')*H*$_A$), 2.59 (1H, m, C(2')*H*), 2.83 (1H, dt, *J* 12.2, 4.0, C(6')*H*$_B$), 3.17–3.28 (2H, m, C(2)*H*, NC*H*$_A$H$_B$Ar), 3.53 (1H, app td, *J* 9.8, 4.7, C(4)*H*$_A$), 3.69–3.76 (1H, m, C(4)*H*$_B$), 3.79 (3H, s, O*Me*), 3.97 (1H, d, *J* 13.0, NCH$_A$*H*$_B$Ar), 6.82 (2H, d, *J* 8.6, C(3")*H*, C(5")*H*), 7.23 (2H, d, *J* 8.6, C(2")*H*, C(6")*H*); δ_C (100 MHz, $CDCl_3$) –5.4, –5.3 (Si*Me*$_2$), 18.4 (Si*C*Me$_3$), 24.0 (*C*(4')), 24.6 (*C*(5')), 25.9 (*C*(3')), 26.0 (SiC*Me*$_3$), 28.2 (*C*(3)), 28.3 (OC*Me*$_3$), 43.4 (*C*(2)), 51.3 (*C*(6')), 55.3 (O*Me*), 56.4 (N*C*H$_2$Ar), 61.7 (*C*(4)), 62.3 (*C*(2')), 80.1 (O*C*Me$_3$), 113.4 (*C*(3"), *C*(5")), 130.5 (*C*(2"), *C*(6")), 131.2 (*C*(1")), 158.5 (*C*(4")), 174.2 (*C*(1)); *m/z* (ESI$^+$) 478 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{48}NO_4Si^+$ ([M+H]$^+$) requires 478.3347; found 478.3333.

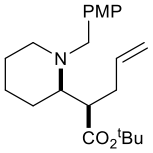
tert-Butyl (_R_,_R_)-2-[_N_(1')-(_p_-methoxybenzyl)piperidin-2'-yl]-5-(_tert_-butyldimethylsiloxy)pe

ntanoate 268



LiHMDS (1.0 M in THF, 5.15 mL, 5.15 mmol) was added to a stirred solution of **265** (235 mg, 0.736 mmol) in THF (10 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 1 h. **280** (1.10 g, 3.68 mmol) was then added and the resultant mixture was allowed to warm to rt and stirred at rt for 16 h. Satd aq NH_4Cl (5 mL) was then added and the reaction mixture was concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and H_2O (5 mL), and the organic layer was then dried and concentrated *in vacuo.* Purification *via* flash column chromatography (eluent 30–40 °C petrol/acetone/NH_4OH, 100:5:1) gave **268** as a colourless oil (271 mg, 75%, >99:1 dr); $[\alpha]_D^{20}$ +24.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2930, 2857 (C−H), 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 0.04 (6H, s, Si*Me*$_2$), 0.89 (9H, s, SiC*Me*$_3$), 1.26–1.70 (10H, m, C(3)*H*$_2$, C(4)*H*$_2$, C(3')*H*$_2$, C(4')*H*$_2$, C(5')*H*$_2$), 1.47 (9H, s, OC*Me*$_3$), 2.07–2.14 (1H, m, C(6')*H*$_A$), 2.64–2.68 (1H, m, C(2')*H*), 2.82–2.87 (1H, m, C(6')*H*$_B$), 2.87–2.93 (1H, m, C(2)*H*), 3.38 (1H, d, *J* 13.1, NC*H*$_A$H$_B$Ar), 3.56–3.68 (2H, m, C(5)*H*$_2$), 3.80 (3H, s, O*Me*), 3.82 (1H, d, *J* 13.1, NCH$_A$*H*$_B$Ar), 6.83 (2H, d, *J* 8.5, C(3")*H*, C(5")*H*), 7.23 (2H, d, *J* 8.5, C(2")*H*, C(6")*H*); δ_C (100 MHz, $CDCl_3$) −5.1 (Si*Me*$_2$), 18.5 (Si*C*Me$_3$), 23.1, 23.3, 24.6 (*C*(4), *C*(4'), *C*(5')), 26.1 (SiC*Me*$_3$), 28.4 (OC*Me*$_3$), 31.7 (*C*(3), *C*(3')), 47.6 (*C*(2)), 49.8 (*C*(6')), 55.4 (O*Me*), 56.5 (N*C*H$_2$Ar), 62.6 (*C*(2')), 63.5 (*C*(5)), 80.1 (O*C*Me$_3$), 113.5 (*C*(3"), *C*(5")), 130.2 (*C*(2"), *C*(6")), 131.7 (*C*(1")), 158.6 (*C*(4")), 174.4 (*C*(1)); *m/z* (ESI$^+$) 492 ([M+H]$^+$, 100%), 436 ([M−C_4H_8]$^+$, 25%); HRMS (ESI$^+$) $C_{28}H_{50}NO_4Si^+$ ([M+H]$^+$) requires 492.3504; found 492.3498.

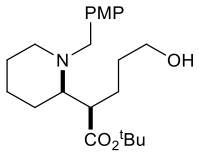
tert-Butyl (_R_,_R_)-2-[_N_(1')-(_p_-methoxybenzyl)piperidin-2'-yl]pent-4-enoate 266



LiHMDS (1.0 M in THF, 0.78 mL, 0.78 mmol) was added to a stirred solution of **265** (50 mg, 0.16 mmol) in THF (2 mL) at −78 °C and the resultant mixture was stired at −78 °C for 1 h. Allyl bromide

(0.10 mL, 1.1 mmol) was added and the resultant mixture was allowed to warm to rt and stirred at rt for 16 h. Satd aq NH_4Cl (0.5 mL) was then added and the reaction mixture was concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (5 mL) and H_2O (5 mL), and the organic layer was then dried and concentrated *in vacuo.* Purification *via* flash column chromatography (eluent 30–40 °C petrol/acetone, 15:1) gave **266** as an orange oil (44 mg, 82%, >99:1 dr); $[\alpha]_D^{20}$ +25.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3075, 2976, 2934, 2858, 2835 (C−H), 1727 (C=O); δ_H (400 MHz, $CDCl_3$) 1.23–1.70 (6H, m, C(3')H_2, C(4')H_2, C(5')H_2), 1.45 (9H, s, CMe_3), 2.02–2.10 (1H, m, C(6')H_A), 2.34–2.40 (2H, m, C(3)H_2), 2.63–2.69 (1H, m, C(2')*H*), 2.81–2.87 (1H, m, C(6')H_B), 2.97 (1H, dt, *J* 8.2, 6.1, C(2)*H*), 3.32 (1H, d, *J* 13.1, NCH_AH$_B$Ar), 3.79 (3H, s, O*Me*), 3.85 (1H, d, *J* 13.1, NCH$_A$$H_B$Ar), 4.96 (1H, dd, *J* 10.1, 1.2, C(5)H_A), 5.04 (1H, dd, *J* 17.1, 1.2, C(5)H_B), 5.80 (1H, ddt, *J* 17.1, 10.1, 6.8, C(4)*H*), 6.83 (2H, d, *J* 8.6, C(3")*H*, C(5")*H*), 7.23 (2H, d, *J* 8.6, C(2")*H*, C(6")*H*); δ_C (100 MHz, $CDCl_3$) 23.4, 23.6, 24.9 (*C*(3'), *C*(4'), *C*(5')), 28.2 (CMe_3), 30.3 (*C*(3)), 47.4 (*C*(2)), 50.2 (*C*(6')), 55.2 (O*Me*), 56.4 (N*C*H$_2$Ar), 62.2 (*C*(2')), 80.2 (*C*Me$_3$), 113.4 (*C*(3"), *C*(5")), 115.7 (*C*(4)), 130.1 (*C*(2"), *C*(6")), 130.0 (*C*(1")), 137.1 (*C*(5)), 158.5 (*C*(4")), 173.5 (*C*(1)); *m/z* (ESI$^+$) 360 ([M+H]$^+$, 100%), 304 ([M−C_4H_8]$^+$, 70%); HRMS (ESI$^+$) $C_{22}H_{34}NO_3^+$ ([M+H]$^+$) requires 360.2533; found 360.2530.

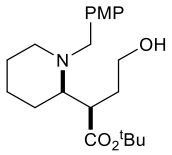
***tert*-Butyl (*R*,*R*)-2-[*N*(1')-(*p*-methoxybenzyl)piperidin-2'-yl]-5-hydroxypentanoate 269**



TBAF (1.0 M in THF, 2.70 mL, 2.70 mmol) was added dropwise to a stirred solution of **268** (265 mg, 0.539 mmol, >99:1 dr) in THF (10 mL). The resultant solution was stirred at rt for 4 h, then partitioned between Et_2O (10 mL) and H_2O (10 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic extracts were washed with brine (30 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40°C petrol/acetone/NH_4OH, 85:17:1) gave **269** as a yellow oil (173 mg, 85%, >99:1 dr); $[\alpha]_D^{20}$ +30.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3414 (O−H), 3032, 2933, 2860, 2836, 2724 (C−H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.25–1.45 (3H, m, C(3')H_A, C(4')H_A, C(5')H_A), 1.46 (9H, s, CMe_3), 1.47–1.61 (4H, m, C(3)H_2, C(4)H_2), 1.61–1.80 (3H, m, C(3')H_B, C(4')H_B, C(5')H_B), 2.03–2.10 (1H, m, C(6')H_A), 2.60–2.66 (1H, m, C(2')*H*), 2.80–2.92 (2H, m, C(2)*H*,

C(6')H_B), 3.34 (1H, d, *J* 13.1, NC$H_A$$H_B$Ar), 3.54–3.65 (2H, m, C(5)H_2), 3.78 (3H, s, O*Me*), 3.83 (1H, d, *J* 13.1, NCH$_A$$H_B$Ar), 6.83 (2H, d, *J* 8.4, C(3")*H*, C(5")*H*), 7.22 (2H, d, *J* 8.4, C(2")*H*, C(6")*H*); δ_C (100 MHz, $CDCl_3$) 21.7, 23.4, 23.7 (*C*(3'), *C*(4'), *C*(5')), 24.9 (*C*(3)), 28.1 (C*Me*$_3$), 31.6 (*C*(4)), 47.5 (*C*(2)), 50.5 (*C*(6')), 55.2 (O*Me*), 56.6 (N*C*H$_2$Ar), 62.4 (*C*(5)), 62.6 (*C*(2')), 80.3 (*C*Me$_3$), 113.4 (*C*(3"), *C*(5")), 130.1 (*C*(2"), *C*(6")), 131.2 (*C*(1")), 158.5 (*C*(4")), 174.5 (*C*(1)); *m/z* (ESI$^+$) 378 ([M+H]$^+$, 100%), 322 ([M–C_4H_8]$^+$, 25%); HRMS (ESI$^+$) $C_{22}H_{36}NO_4^+$ [M+H]$^+$ requires 378.2639; found 378.2633.

tert-Butyl (*R,R*)-2-[*N*(1')-(*p*-methoxybenzyl)piperidin-2'-yl]-4-hydroxybutanoate 267

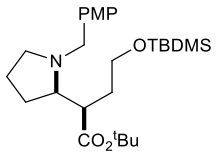


Method A: HCl (2.0 M in Et_2O, 2.9 mL, 5.8 mmol) was added dropwise to a stirred solution of **266** (300 mg, 0.834 mmol, >99:1 dr) in Et_2O (5 mL) at rt. The resultant mixture was stirred at rt for 15 min then concentrated *in vacuo* to give **266**·HCl. The residue was dissolved in CH_2Cl_2 (150 mL) and the resultant solution was cooled to −78 °C and degassed with O_2 for 5 min. O_3 was bubbled through the solution until it was seen to turn blue, then the reaction mixture was purged with O_2 until the solution turned colourless. $NaBH_4$ (155 mg, 4.17 mmol) was then added portionwise, and the reaction mixture was allowed to warm to rt and stirred at rt for 16 h. The reaction mixture was then washed sequentially with satd aq $NaHCO_3$ (20 mL), H_2O (10 mL) and brine (10 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/EtOAc, 5:1 to 1:2) gave **267** as a yellow oil (150 mg, 50%, >99:1 dr); $[\alpha]_D^{20}$ +32.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3490 (O–H), 3065, 2975, 2935, 2860, 2836 (C−H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.16–1.23 (1H, m, C(4')H_A), 1.40–1.46 (1H, m, C(3')H_A), 1.47 (9H, s, C*Me*$_3$), 1.49–1.57 (2H, m, C(5')H_2), 1.60–1.75 (2H, m, C(3')H_B, C(4')H_B), 1.84–2.00 (2H, m, C(3)H_A, C(6')H_A), 2.05–2.16 (1H, m, C(3)H_B), 2.66–2.72 (1H, m, C(2')*H*), 2.84–2.91 (1H, m, C(6')H_B), 3.21–3.27 (1H, m, C(2)*H*), 3.34 (1H, d, *J* 13.0, NC$H_A$$H_B$Ar), 3.60–3.66 (1H, m, C(4)H_A), 3.74–3.79 (1H, m, C(4)H_B), 3.79 (3H, s, O*Me*) 4.12 (1H, d, *J* 13.0, NCH$_A$$H_B$Ar), 6.85 (2H, d, *J* 8.6, C(3")*H*, C(5")*H*), 7.26 (2H, d, *J* 8.6, C(2")*H*, C(6")*H*); δ_C (125 MHz, $CDCl_3$) 24.1 (*C*(4')), 25.1 (*C*(3')), 26.1 (*C*(5')), 28.2 (C*Me*$_3$), 29.4 (*C*(3)), 46.2 (*C*(2)), 52.7 (*C*(6')), 55.4 (O*Me*), 57.7 (N*C*H$_2$Ar), 61.6 (*C*(4)), 62.6 (*C*(2')), 80.8 (*C*Me$_3$), 113.8 (*C*(3"), *C*(5")), 129.2 (*C*(1")), 130.8 (*C*(2"), *C*(6")), 158.9 (*C*(4")), 173.9

(*C*(1)); *m/z* (ESI$^+$) 364 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{34}NO_4^+$ ([M+H]$^+$) requires 364.2482; found 364.2472.

Method B: PPTS (88 mg, 0.34 mmol) was added to a stirred solution of **278** (111 mg, 0.232 mmol, >99:1 dr) in CH_2Cl_2/MeOH (3:1, 4 mL). The resultant mixture was stirred at 50 °C for 7 days, then allowed to cool to rt and partitioned between CH_2Cl_2 (5 mL) and H_2O (5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Me_2CO/NH_4OH, 80:20:1) gave **267** as a yellow oil (53 mg, 63%, >99:1 dr).

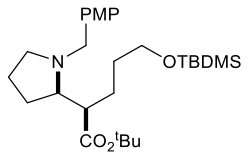
tert-Butyl (*R*,*R*)-2-[*N*(1')-(*p*-methoxybenzyl)pyrrolidin-2'-yl]-4-(_tert_-butyldimethylsiloxy) butanoate 283



LiHMDS (1.0 M in THF, 2.46 mL, 2.46 mmol) was added to a stirred solution of **277** (150 mg, 0.491 mmol) in THF (6 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 1 h. **279** (984 mg, 3.44 mmol) was then added and the resultant mixture was allowed to warm to rt and stirred at rt for 16 h. Satd aq NH_4Cl (2 mL) was added the reaction mixture was concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and H_2O (5 mL), and the organic layer was then dried and concentrated *in vacuo.* Purification *via* flash column chromatography (eluent 30–40 °C petrol/Me_2CO/NH_4OH, 100:5:1) gave **283** as a pale yellow oil (219 mg, 96%, >99:1 dr); $[\alpha]_D^{20}$ +30.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2970, 2955, 2857 (C–H), 1727 (C=O); δ_H (400 MHz, $CDCl_3$) 0.04 (6H, s, Si*Me*$_2$), 0.88 (9H, s, SiC*Me*$_3$), 1.45 (9H, s, OC*Me*$_3$), 1.52–1.61 (2H, m, C(4')*H*$_2$), 1.61–1.71 (2H, m, C(3')*H*$_2$), 1.74–1.85 (1H, m, C(3)*H*$_A$), 2.01–2.11 (1H, m, C(3)*H*$_B$), 2.09 (1H, app q, *J* 8.6, C(5')*H*$_A$), 2.72–2.88 (3H, m, C(2)*H*, C(2')*H*, C(5')*H*$_B$), 3.14 (1H, d, *J* 12.8, NC*H*$_A$H$_B$Ar), 3.58 (1H, td, *J* 9.3, 5.7, C(4)*H*$_A$), 3.68–3.75 (1H, m, C(4)*H*$_B$), 3.79 (3H, s, O*Me*), 3.97 (1H, d, *J* 12.8, NC*H*$_A$H$_B$Ar), 6.79 (2H, d, *J* 8.6, C(3")*H*, C(5")*H*), 7.19 (2H, d, *J* 8.6, C(2")*H*, C(6")*H*); δ_C (100 MHz, $CDCl_3$) –5.2, –5.1 (2 × Si*Me*), 18.5 (Si*C*Me$_3$), 22.8 (*C*(4')), 26.1 (SiC*Me*$_3$), 26.5 (*C*(3')), 28.4 (OC*Me*$_3$), 28.6 (*C*(3)), 44.5 (*C*(2)), 53.7 (*C*(5')), 55.4 (O*Me*), 57.7 (N*C*H$_2$Ar), 61.9 (*C*(4)), 64.7 (*C*(2')), 80.2 (O*C*Me$_3$), 113.6 (*C*(3"), *C*(5")), 130.1

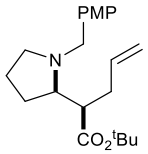
(*C*(2''), *C*(6'')), 132.0 (*C*(1'')), 158.6 (*C*(4'')), 174.4 (*C*(1)); *m/z* (ESI$^+$) 464 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{46}NO_4Si^+$ ([M+H]$^+$) requires 464.3191; found 464.3181.

tert-Butyl (*R*,*R*)-2-[*N*(1')-(*p*-methoxybenzyl)pyrrolidin-2'-yl]-5-(_tert_-butyldimethylsiloxy) pentanoate 284



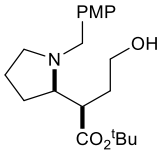
LiHMDS (1.0 M in THF, 2.56 mL, 2.56 mmol) was added to a stirred solution of **277** (111 mg, 0.365 mmol) in THF (5 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 1 h. **280** (548 mg, 1.83 mmol) was then added and the resultant mixture was allowed to warm to rt and stirred at rt for 16 h. Satd aq NH_4Cl (2 mL) was then added and the reaction mixture was concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and H_2O (10 mL), and the organic layer was then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/acetone/NH_4OH, 90:9:1) gave **284** as a pale yellow oil (141 mg, 81%, >99:1 dr); $[\alpha]_D^{20}$ +29.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2954, 2931, 2858 (C−H), 1742 (C=O); δ_H (400 MHz, $CDCl_3$) 0.06 (6H, s, Si*Me*$_2$), 0.90 (9H, s, SiC*Me*$_3$), 1.45 (9H, s, OC*Me*$_3$), 1.50–1.79 (8H, m, C(3)*H*$_2$, C(4)*H*$_2$, C(3')*H*$_2$, C(4')*H*$_2$), 2.09–2.14 (1H, m, C(5')*H*$_A$), 2.43–2.51 (1H, m, C(2)*H*), 2.78–2.90 (2H, m, C(2')*H*, C(5')*H*$_B$), 3.21 (1H, d, *J* 13.0, NC*H*$_A$H$_B$Ar), 3.59–3.68 (2H, m, C(5)*H*$_2$), 3.79 (3H, s, O*Me*), 3.95 (1H, d, *J* 13.0, NCH$_A$*H*$_B$Ar), 6.83 (2H, d, *J* 8.4, C(3'')*H*, C(5'')*H*), 7.22 (2H, d, *J* 8.4, C(2'')*H*, C(6'')*H*); δ_C (100 MHz, $CDCl_3$) −5.1 (Si*Me*$_2$), 18.5 (Si*C*Me$_3$), 22.8, 23.1 (*C*(4), *C*(4')), 26.1 (SiC*Me*$_3$), 27.0, 31.6 (*C*(3), *C*(3')), 28.3 (OC*Me*$_3$), 49.5 (*C*(2)), 53.9 (*C*(5')), 55.4 (O*Me*), 58.4 (N*C*H$_2$Ar), 63.5 (*C*(5)), 65.3 (*C*(2')), 80.2 (O*C*Me$_3$), 113.6 (*C*(3''), *C*(5'')), 129.9 (*C*(2''), *C*(6'')), 132.2 (*C*(1'')), 158.6 (*C*(4'')), 174.6 (*C*(1)); *m/z* (ESI$^+$) 478 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{48}NO_4Si^+$ ([M+H]$^+$) requires 478.3347; found 478.3340.

***tert*-Butyl (*R,R*)-2-[*N*(1')-(*p*-methoxybenzyl)pyrrolidin-2'-yl]pent-4-enoate 285**



LiHMDS (1.0 M in THF, 3.67 mL, 3.67 mmol) was added to a stirred solution of **277** (224 mg, 0.735 mmol) in THF (10 mL) at −78 °C and the resultant mixture was stirred at –78 °C for 1 h. Allyl bromide (0.45 mL, 5.14 mmol) was then added and the resultant mixture was allowed to warm to rt and stirred at rt for 16 h. Satd aq NH_4Cl (5 mL) was then added and the reaction mixture was concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (15 mL) and H_2O (10 mL), the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic extracts were washed with brine (30 mL), then dried and concentrated *in vacuo* to give **285** as an orange oil (232 mg, 93%, >99:1 dr); $[\alpha]_D^{20}$ +31.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3016, 3005, 2971, 2947, 2871, 2805 (C−H), 1739 (C=O); δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s, C*Me*$_3$), 1.58–1.67 (2H, m, C(4')*H*$_2$), 1.69–1.77 (2H, m, C(3')*H*$_2$), 2.13 (1H, app q, *J* 8.6, C(5')*H*$_A$), 2.30–2.48 (2H, m, C(3)*H*$_2$), 2.52–2.60 (1H, m, C(2)*H*), 2.80–2.90 (2H, m, C(2')*H*, C(5')*H*$_B$), 3.21 (1H, d, *J* 13.0, NC*H*$_A$H$_B$Ar), 3.80 (3H, s, O*Me*), 3.94 (1H, d, *J* 13.0, NCH$_A$*H*$_B$Ar), 4.98 (1H, dd, *J* 10.2, 1.2, C(5)*H*$_A$), 5.06 (1H, dd, *J* 17.0, 1.2, C(5)*H*$_B$), 5.82 (1H, ddt, *J* 17.0, 10.2, 6.8, C(4)*H*), 6.84 (2H, d, *J* 8.5, C(3")*H*, C(5")*H*), 7.23 (2H, d, *J* 8.5, C(2")*H*, C(6")*H*); δ_C (100 MHz, $CDCl_3$) 22.9 (*C*(4')), 26.7 (*C*(3')), 28.1 (C*Me*$_3$), 30.4 (*C*(3)), 49.0 (*C*(2)), 53.8 (*C*(5')), 55.2 (O*Me*), 58.0 (N*C*H$_2$Ar), 64.7 (*C*(2')), 80.2 (*C*Me$_3$), 113.5 (*C*(3"), *C*(5")), 115.6 (*C*(4)), 129.7 (*C*(2"), *C*(6")), 131.9 (*C*(1")), 137.0 (*C*(5)), 158.5 (*C*(4")), 173.7 (*C*(1)); *m/z* (ESI$^+$) 346 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{32}NO_3^+$ ([M+H]$^+$) requires 346.2377; found 346.2381.

***tert*-Butyl (*R,R*)-2-[*N*(1')-(*p*-methoxybenzyl)pyrrolidin-2'-yl]-4-hydroxybutanoate 286**

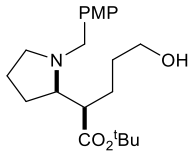


Method A: HCl (2.0 M in Et_2O, 6.4 mL, 13 mmol) was added dropwise to a stirred solution of **285** (1.14 g, 3.30 mmol, >99:1 dr) in Et_2O (5 mL) at rt. The resultant mixture was stirred at rt for 15 min then concentrated *in vacuo* to give **285**·HCl. The residue was dissolved in CH_2Cl_2 (50 mL) and the resultant

solution was cooled to −78 °C and degassed with O_2 for 5 min. O_3 was bubbled through the solution until it was seen to turn blue, then the reaction mixture was purged with O_2 until the solution turned colourless. $NaBH_4$ (602 mg, 15.9 mmol) was added portionwise, and the reaction mixture was allowed to warm to rt and stirred at rt for 16 h. The reaction mixture was then filtered and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (50 mL) and the resultant solution was washed sequentially with $NaHCO_3$ (50 mL), H_2O (50 mL) and brine (50 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/acetone/NH_4OH, 80:20:1) gave **286** as a yellow oil (567 mg, 49%, >99:1 dr); $[\alpha]_D^{20}$ +34.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3415 (O–H), 2969, 2935, 2877, 2835 (C–H), 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s, C*Me*$_3$), 1.64–1.75 (2H, m, C(4')*H*$_2$), 1.76–1.86 (2H, m, C(3')*H*$_2$), 1.87–1.94 (2H, m, C(3)*H*$_2$), 2.17–2.23 (1H, m, C(5')*H*$_A$), 2.65–2.71 (1H, m, C(2)*H*), 2.86–2.96 (2H, m, C(2')*H*, C(5')*H*$_B$); 3.31 (1H, d, *J* 12.6, NC*H*$_A$H$_B$Ar), 3.47–3.54 (1H, m, C(4)*H*$_A$), 3.72 (1H, dt, *J* 11.6, C(4)*H*$_B$), 3.79 (3H, s, O*Me*), 4.00 (1H, d, *J* 12.6, NCH$_A$*H*$_B$Ar), 6.86 (2H, d, *J* 8.6, C(3")*H*, C(5")*H*); 7.25 (2H, d, *J* 8.6, C(2")*H*, C(6")*H*); δ_C (100 MHz, $CDCl_3$) 22.7 (*C*(4')), 25.7 (*C*(3')), 28.2 (C*Me*$_3$), 29.5 (*C*(3)), 48.0 (*C*(2)), 53.8 (*C*(5')), 55.4 (O*Me*), 58.2 (N*C*H$_2$Ar), 61.8 (*C*(4)), 64.2 (*C*(2')), 80.7 (*C*Me$_3$), 113.9 (*C*(3"), *C*(5")), 129.4 (*C*(1")), 130.8 (*C*(2"), *C*(6")), 159.1 (*C*(4")), 173.9 (*C*(1)); *m/z* (ESI$^+$) 350 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{32}NO_4^+$ ([M+H]$^+$) requires 350.2326; found 350.2318.

Method B: PPTS (154 mg, 0.615 mmol) was added to a stirred solution of **283** (190 mg, 0.410 mmol, >99:1 dr) in CH_2Cl_2/MeOH (3:1, 4 mL). The resultant mixture was stirred at 50 °C for 10 days, then allowed to cool to rt and partitioned between CH_2Cl_2 (5 mL) and H_2O (5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Me_2CO/NH_4OH, 80:20:1) gave **286** as a yellow oil (111 mg, 78%, >99:1 dr).

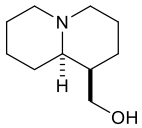
***tert*-Butyl (*R*,*R*)-2-[*N*(1')-(*p*-methoxybenzyl)pyrrolidin-2'-yl]-5-hydroxypentanoate 287**



TBAF (1.0 M in THF, 4.90 mL, 4.90 mmol) was added dropwise to a solution of **284** (468 mg, 0.980 mmol, >99:1 dr) in THF (25 mL). The resultant mixture was stirred at rt for 4 h, then partitioned between

Et_2O (25 mL) and H_2O (25 mL). The aqueous layer was extracted with Et_2O (3 × 20 mL) and the combined organic extracts were washed with brine (60 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/acetone/NH_4OH, 80:20:1) gave **287** as a colourless oil (286 mg, 80%, >99:1 dr); $[\alpha]_D^{20}$ +30.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3416 (O–H), 2976, 2934, 2872, 2835 (C–H), 1742 (C=O); δ_H (400 MHz, $CDCl_3$) 1.45 (9H, s, C*Me*$_3$), 1.49–1.67 (4H, m, C(4)*H*$_2$, C(4')*H*$_2$), 1.67–1.79 (4H, m, C(3)*H*$_2$, C(3')*H*$_2$), 1.92 (1H, br s, O*H*), 2.15 (1H, app q, *J* 8.5, C(5')*H*$_A$), 2.44–2.50 (1H, m, C(2)*H*), 2.79–2.91 (2H, m, C(2')*H*, C(5')*H*$_B$), 3.25 (1H, d, *J* 13.0, NC*H*$_A$H$_B$Ar), 3.61 (1H, dt, *J* 10.7, 6.3, C(5)*H*$_A$), 3.65 (1H, dt, *J* 10.7, 6.3, C(5)*H*$_B$), 3.79 (3H, s, O*Me*), 3.91 (1H, d, *J* 13.0, NCH$_A$*H*$_B$Ar), 6.84 (2H, d, *J* 8.6, C(3")*H*, C(5")*H*), 7.22 (2H, d, *J* 8.6, C(2")*H*, C(6")*H*); δ_C (100 MHz, $CDCl_3$) 21.6 (*C*(3)), 23.1 (*C*(4')), 26.7 (*C*(3')), 28.3 (C*Me*$_3$), 31.4 (*C*(4)), 48.6 (*C*(2)), 54.0 (*C*(5')), 55.4 (O*Me*), 58.2 (N*C*H$_2$Ar), 62.5 (*C*(5)), 65.2 (*C*(2')), 80.5 (*C*Me$_3$), 113.7 (*C*(3"), *C*(5")), 130.1 (*C*(2"), *C*(6")), 131.7 (*C*(1")), 158.7 (*C*(4")), 174.7 (*C*(1)); *m/z* (ESI$^+$) 364 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{34}NO_4^+$ ([M+H]$^+$) requires 364.2482; found 364.2474.

(*R*,*R*)-1-(Hydroxymethyl)octahydro-1*H*-quinolizine [(–)-lupinine] 30



Method A – Step 1: I_2 (548 mg, 2.16 mmol), imidazole (147 mg, 2.16 mmol) and polymer-supported PPh_3 (720 mg, ~3.2 mmol/g,) were added to a solution of **269** (163 mg, 0.432 mmol, >99:1 dr) in PhMe/MeCN (4:1, 5 mL). The resultant mixture was heated at 65 °C for 16 h, then allowed to cool to rt, filtered and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (10 mL) and the resultant solution was washed with satd aq $Na_2S_2O_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were then concentrated *in vacuo* to give **271** as a brown oil.

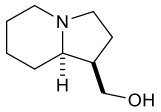
Method A – Step 2: $LiAlH_4$ (1.0 M in THF, 0.59 mL, 0.59 mmol) was added to a stirred solution of **271** (95 mg, >99:1 dr) in THF (4 mL) at 0 °C. The resultant mixture was heated at reflux for 48 h then allowed to cool to rt. Aq NaOH (2.0 M, 0.5 mL) was then added and the resultant mixture was heated at reflux for 3 h. The reaction mixture was then allowed to cool to rt and filtered through Celite® (eluent CH_2Cl_2), then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent

$CHCl_3$/MeOH/NH_4OH, 200:25:2) gave **30** as a pale yellow oil (26 mg, 66% from **269**, >99:1 dr); $[\alpha]_D^{20}$ –12.0 (*c* 0.4 in EtOH); {lit.[27] $[\alpha]_D$ –18.3 (*c* 0.27 in EtOH); lit.[28] for *ent*-**30** $[\alpha]_D^{30}$ +12.7 (*c* 0.35 in EtOH)}; ν_{max} (ATR) 3323 (O–H), 2933, 2857, 2807, 2763 (C–H); δ_H (400 MHz, C_6D_6) 0.94–1.06 (1H, m, C(8)H_A), 1.15–1.25 (2H, m, C(1)*H*, C(9)H_A), 1.25–1.44 (4H, m, C(2)H_A, C(3)H_A, C(7)H_2), 1.49–1.58 (2H, m, C(6)H_A, C(8)H_B), 1.63–1.80 (4H, m, C(2)H_B, C(4)H_A, C(9)H_B, C(9a)*H*), 2.23–2.37 (1H, m, C(3)H_B), 2.44–2.56 (2H, m, C(4)H_B, C(6)H_B), 3.75 (1H, app d, *J* 10.7, CH_AH$_B$OH), 4.18 (1H, dd, *J* 10.7, 4.8, CH$_A$$H_B$OH); δ_C (100 MHz, C_6D_6) 23.3 (*C*(3)), 25.0 (*C*(8)), 25.9 (*C*(7)), 29.9 (*C*(9)), 31.6 (*C*(2)), 38.9 (*C*(1)), 57.3 (*C*(6)), 57.4 (*C*(4)), 65.2 (*C*(9a)), 65.7 (*C*H_2OH); *m/z* (ESI^+) 170 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{10}H_{20}NO^+$ ($[M+H]^+$) requires 170.1539; found 170.1541.

Method B – Step 1: I_2 (343 mg, 1.35 mmol), imidazole (92 mg, 1.35 mmol) and polymer-supported PPh_3 (450 mg, ~3.2 mmol/g) were added to a solution of **269** (102 mg, 0.27 mmol, >99:1 dr) in PhMe/MeCN (4:1, 5 mL). The resultant mixture was heated at 65 °C for 60 h, then allowed to cool to rt, filtered and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (5 mL) and the resultant solution was washed sequentially with satd aq $Na_2S_2O_3$ (5 mL) and satd aq $NaHCO_3$ (5 mL). The combined aqueous layers were extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were then concentrated *in vacuo* to give **288** as a brown oil.

Method B – Step 2: $LiAlH_4$ (1.0 M in THF, 0.81 mL, 0.81 mmol) was added to a stirred solution of **288** (118 mg, >99:1 dr) in THF (2.5 mL) at 0 °C. The resultant mixture was heated at reflux for 16 h then allowed to cool to rt. Aq NaOH (2.0 M, 0.8 mL) was then added and the resultant mixture was heated at reflux for 3 h. The reaction mixture was then allowed to cool to rt and filtered through Celite® (eluent CH_2Cl_2), then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$/MeOH/NH_4OH, 200:25:2) gave **30** as a pale yellow oil (23 mg, 50% from **269**, >99:1 dr); $[\alpha]_D^{20}$ –9.5 (*c* 0.4 in EtOH).

(*R*,*R*)-1-(Hydroxymethyl)octahydroindolizine 31

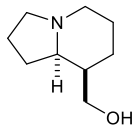


Step 1: I_2 (185 mg, 0.73 mmol), imidazole (46 mg, 0.73 mmol) and polymer-supported PPh_3 (243 mg, ~3.2 mmol/g,) were added to a stirred solution of **267** (53 mg, 0.15 mmol, >99:1 dr) in PhMe/MeCN (4:1, 4 mL). The resultant mixture was stirred at rt for 16 h, then filtered and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (5 mL) and the resultant solution was washed with satd aq $Na_2S_2O_3$ (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL) and the combined organic extracts were then concentrated *in vacuo* to give a brown oil.

Step 2: $Pd(OH)_2/C$ (39 mg, 50% w/w) was added to a solution of the residue in MeOH (2 mL) and the resultant mixture was degassed for 10 min. The reaction mixture was placed under an atmosphere of H_2 (~5 atm) and stirred at rt for 4 days, then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo* to give a brown oil.

Step 3: $LiAlH_4$ (1.0 M in THF, 0.29 mL, 0.29 mmol) was added to a stirred solution of the residue in THF (1 mL) at 0 °C. The resultant mixture was heated at reflux for 16 h then allowed to cool to rt. Aq NaOH (2.0 M, 1 mL) was then added and the resultant mixture was heated at reflux for 3 h. The reaction mixture was then allowed to cool to rt and filtered through Celite® (eluent CH_2Cl_2), then concentrated *in vacuo*. Purification *via* flash column chromatography on neutral alumina (eluent 30–40 °C petrol/Me_2CO/NH_4OH, 90:9:1) gave **31** as a colourless oil (8 mg, 35% from **267**, >99:1 dr); $[\alpha]_D^{20}$ –37.5 (*c* 0.1 in EtOH); {lit.[29] $[\alpha]_D^{23}$ –35.8 (*c* 0.5 in EtOH)}; ν_{max} (ATR) 3455 (O–H), 3016, 2970, 2927, 2854 (C–H); δ_H (400 MHz, $CDCl_3$) 1.17–1.22 (1H, m, C(7)H_A), 1.42–1.57 (2H, m, C(6)H_A, C(8)H_A), 1.59–1.64 (1H, m, C(6)H_B), 1.76–1.87 (4H, m, C(2)H_A, C(5)H_A, C(7)H_B, C(8)H_B), 1.91–2.00 (1H, m, C(2)H_B), 2.00–2.12 (2H, m, C(1)*H*, C(3)H_A, C(8a)*H*), 3.06–3.11 (1H, m, C(5)H_B), 3.13 (1H, app dd, *J* 9.0, 2.8, C(3)H_B), 3.46 (1H, dd, *J* 10.2, 2.8, CH_AH$_B$OH), 3.85 (1H, dd, *J* 10.2, 2.4, CH$_A$$H_B$OH); δ_C (100 MHz, $CDCl_3$) 24.3 (*C*(7)), 25.5 (*C*(2)), 25.5 (*C*(6)), 26.9 (*C*(8)), 41.1 (*C*(1)), 53.8 (*C*(5)), 54.1 (*C*(3)), 64.7 (*C*H_2OH), 66.4 (*C*(8a)); *m/z* (ESI^+) 156 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_9H_{18}NO^+$ ($[M+H]^+$) requires 156.1383; found 156.1382.

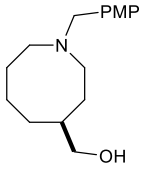
(*R*,*R*)-1-(Hydroxymethyl)octahydro-1*H*-indolizine [(+)-5-*epi*-tashiromine] 32



Step 1: I_2 (999 mg, 3.93 mmol), imidazole (248 mg, 3.93 mmol) and polymer-supported PPh_3 (1.31 g, ~3.2 mmol/g,) were added to a solution of **287** (286 mg, 0.787 mmol, >99:1 dr) in PhMe/MeCN (4:1, 15 mL). The resultant mixture was heated at 65 °C for 36 h, then allowed to cool to rt, filtered and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (10 mL) and the resultant solution was washed with satd aq $Na_2S_2O_3$ (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were then concentrated *in vacuo* to give a brown oil.

Step 2: $LiAlH_4$ (1.0 M in THF, 3.93 mL, 3.93 mmol) was added to a stirred solution of the residue in THF (10 mL) at 0 °C. The resultant mixture was heated at reflux for 60 h then allowed to cool to rt. Aq NaOH (2.0 M, 4 mL) was then added and the resultant mixture was heated at reflux for 3 h. The reaction mixture was then allowed to cool to rt and filtered through Celite® (eluent CH_2Cl_2), then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$/MeOH/NH_4OH, 200:25:2) gave **32** as a yellow oil (42 mg, 34% from **287**, 94:6 dr); $[\alpha]_D^{20}$ +2.3 (*c* 0.4 in EtOH); {lit.[30] $[\alpha]_D^{20}$ +1.1 (in EtOH); lit.[31] for *ent*-**32** $[\alpha]_D$ –0.96 (*c* 0.31 in EtOH)}; ν_{max} (ATR) 3366 (O–H), 2930, 2856, 2787, 2729 (C–H); δ_H (400 MHz, $CDCl_3$) 1.46–1.59 (2H, m, C(2)H_A, C(7)H_A), 1.64–1.81 (4H, m, C(1)*H*, C(3)H_2, C(8)H_A), 1.83–2.09 (5H, m, C(2)H_B, C(4)H_A, C(6)H_A, C(7)H_B, C(8)H_B), 2.20–2.26 (1H, m, C(8a)*H*), 2.96–3.02 (1H, m, C(4)H_B), 3.05–3.11 (1H, m, C(6)H_B), 3.71 (1H, ddd, *J* 10.8, 1.8, 0.8, CH_AH$_B$OH), 4.14 (1H, ddd, *J* 10.8, 4.2, 1.2, CH$_A$$H_B$OH); δ_C (100 MHz, $CDCl_3$) 20.9 (*C*(3)), 23.3 (*C*(7)), 25.9 (*C*(8)), 30.6 (*C*(2)), 35.4 (*C*(1)), 53.7 (*C*(6)), 54.6 (*C*(4)), 65.6 (*C*H_2OH), 66.9 (*C*(8a)); *m/z* (ESI$^+$) 156 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_9H_{18}NO^+$ ([M+H]$^+$) requires 156.1383; found 156.1381.

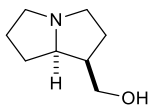
(*S*)-*N*(1)-Benzyl-4-(hydroxymethyl)azocane 290



Step 1: I_2 (925 mg, 3.65 mmol), imidazole (229 mg, 3.65 mmol) and polymer-supported PPh_3 (1.22 g, ~3.2 mmol/g,) were added to a stirred solution of **286** (255 mg, 0.730 mmol, >99:1 dr) in PhMe/MeCN (4:1, 10 mL). The resultant mixture was stirred at rt for 16 h, then heated at 65 °C for 60 h before being allowed to cool to rt, filtered and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (10 mL) and the resultant solution was washed with satd aq $Na_2S_2O_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were then concentrated *in vacuo* to give a brown oil.

Step 2: $LiAlH_4$ (1.0 M in THF, 3.65 mL, 3.65 mmol) was added to a stirred solution of the residue in THF (3 mL) at 0 °C. The resultant mixture was heated at reflux for 60 h then allowed to cool to rt. Aq NaOH (2.0 M, 3 mL) was then added and the resultant mixture was heated at reflux for 3 h. The reaction mixture was then allowed to cool to rt and filtered through Celite® (eluent CH_2Cl_2), then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$/MeOH/NH_4OH, 100:2:1) gave **290** as a colourless oil (85 mg, 44% from **286**); $[\alpha]_D^{20}$ +3.7 (*c* 1.0 in EtOH); ν_{max} (ATR) 3357 (O–H), 2921, 2853, 2805 (C–H); δ_H (400 MHz, $CDCl_3$) 1.32–1.44 (1H, m, C(3)H_A), 1.44–1.80 (7H, m, C(3)H_B, C(5)H_2, C(6)H_2, C(7)H_2), 1.80–1.88 (1H, m, C(4)*H*), 2.47–2.60 (3H, m, C(2)H_A, C(8)H_2), 2.62–2.70 (1H, m, C(2)H_B), 3.40 (1H, dd, *J* 10.4, 6.3, CH_AH$_B$OH), 3.44 (1H, dd, *J* 10.4, 6.3, CH$_A$$H_B$OH), 3.53 (2H, app s, NC$H_2$Ar), 3.79 (3H, s, O*Me*), 6.84 (2H, d, *J* 8.6, C(3')*H*, C(5')*H*), 7.25 (2H, d, *J* 8.6, C(2')*H*, C(6')*H*); δ_C (100 MHz, $CDCl_3$) 25.0 (*C*(6)), 28.2 (*C*(7)), 30.2 (*C*(3)), 30.7 (*C*(5)), 39.8 (*C*(4)), 52.9 (*C*(2)), 54.0 (*C*(8)), 55.3 (O*Me*), 63.0 (NCH_2Ar), 68.6 (CH_2OH), 113.6 (*C*(3'), *C*(5')), 130.2 (*C*(2'), *C*(6')), 132.2 (*C*(1')), 158.6 (*C*(4')); *m/z* (ESI$^+$) 264 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{26}NO_2^+$ ([M+H]$^+$) requires 264.1958; found 264.1955.

(*R*,*R*)-1-(Hydroxymethyl)hexahydropyrrolizine [(+)-isoretronecanol] 33



Step 1: I_2 (780 mg, 3.08 mmol), imidazole (194 mg, 3.08 mmol) and polymer-supported PPh_3 (1.02 g, ~3.2 mmol/g,) were added to a stirred solution of **286** (215 mg, 0.615 mmol, >99:1 dr) in PhMe/MeCN (4:1, 9 mL). The resultant mixture was stirred at rt for 16 h, then filtered and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (10 mL) and the resultant solution was washed with satd aq $Na_2S_2O_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were then concentrated *in vacuo* to give a brown oil.

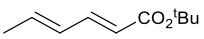
Step 2: $Pd(OH)_2/C$ (158 mg, 50% w/w) was added to a solution of the residue in MeOH (3 mL) and the resultant mixture was degassed for 10 min. The reaction mixture was placed under an atmosphere of H_2 (~5 atm) and stirred at rt for 3 days, then filtered through a short plug of Celite® (eluent MeOH). A further portion of $Pd(OH)_2/C$ (158 mg, 50% w/w) was added and the resultant mixture was degassed for 10 min. The reaction mixture was placed under at atmosphere of H_2 (~5 atm) and stirred at rt for 3 days, then then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo* to give a brown oil.

Step 3: $LiAlH_4$ (1.0 M in THF, 1.23 mL, 1.23 mmol) was added to a stirred solution of the residue in THF (5 mL) at 0 °C. The resultant mixture was heated at reflux for 16 h then allowed to cool to rt. Aq NaOH (2.0 M, 2 mL) was then added and the resultant mixture was heated at reflux for 3 h. The reaction mixture was then allowed to cool to rt and filtered through Celite® (eluent CH_2Cl_2), then concentrated *in vacuo*. Purification *via* flash column chromatography on neutral alumina (eluent $CHCl_3$/MeOH/ NH_4OH, 90:9:1) gave **33** as a colourless oil (42 mg, 48% from **286**, >99:1 dr); $[\alpha]_D^{20}$ +58.3 (*c* 0.6 in EtOH); { lit.[32] $[\alpha]_D^{26}$ +55 (*c* 0.055 in EtOH); lit.[33] for *ent*-**33** $[\alpha]_D^{20}$ –65.7 (*c* 1.88 in EtOH)}; ν_{max} (ATR) 3362 (O–H), 2956, 2873 (C–H); δ_H (400 MHz, $CDCl_3$) 1.35–1.45 (1H, m, C(7)H_A), 1.47–1.57 (1H, m, C(2)H_A), 1.67–1.76 (2H, m, C(6)H_A, C(7)H_B), 1.77–1.91 (2H, m, C(2)H_B, C(6)H_B), 2.38–2.52 (2H, m, C(1)*H*, C(5)H_A), 2.62 (1H, ddd, *J* 11.1, 7.7, 3.4, C(3)H_A), 2.95–3.04 (2H, m, C(3)H_B, O*H*), 3.10–3.17 (1H, m, C(5)H_B), 3.52 (1H, app dt, *J* 9.9, 6.9, C(7a)*H*), 3.64 (1H, dd, *J* 10.6, 7.3, CH_AH$_B$OH), 3.67 (1H, dd,

J 10.6, 7.3, CH_AH_BOH); δ_C (100 MHz, $CDCl_3$) 26.1 (*C*(7)), 26.7 (*C*(6)), 27.4 (*C*(2)), 44.2 (*C*(1)), 54.1 (*C*(3)), 55.7 (*C*(5)), 63.5 (*C*H_2OH), 66.6 (*C*(7a)); *m/z* (ESI^+) 142 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_8H_{16}NO^+$ ($[M+H]^+$) requires 142.1226; found 142.1226.

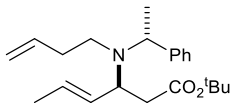
5.3 Experimental data for Chapter 4

tert-Butyl (*E*,*E*)-hexa-2,4-dienoate [*tert*-butyl sorbate] 294



Condensed isobutylene (180 mL) at –78 °C was added to a stirred solution of sorbic acid **302** (30.0 g, 268 mmol) and conc aq H_2SO_4 (3.00 mL) in CH_2Cl_2 (600 mL) at 0 °C, and the resultant mixture was allowed to warm to rt and stirred at rt for 48 h. The reaction mixture was washed with satd aq $NaHCO_3$ (5 × 300 mL) and the combined aqueous washings were extracted with CH_2Cl_2 (2 × 300 mL). The combined organic extracts were washed with brine (500 mL), then dried and concentrated *in vacuo* to give **294** as a pale yellow oil (41.1 g, 91%, >99:1 dr);[34] δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, C*Me*$_3$), 1.84 (3H, d, *J* 5.9, C(6)*H*$_3$), 5.70 (1H, d, *J* 15.4, C(2)*H*), 6.04–6.21 (2H, m, C(4)*H*, C(5)*H*), 7.15 (1H, dd, *J* 15.4, 10.0, C(3)*H*).

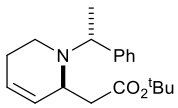
tert-Butyl (3*S*,*αR*,*E*)-3-[*N*-(but-3'-en-1'-yl)-*N*-(α-methylbenzyl)amino]hex-4-enoate 303



BuLi (2.3 M in hexanes, 2.00 mL, 4.61 mmol) was added dropwise to a stirred solution of **305**[4] (833 mg, 4.76 mmol, >99:1 er) in THF (5 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. A solution of **294** (500 mg, 2.97 mmol, >99:1 dr) in THF (2 mL) at –78 °C was added and the resultant mixture was stirred at –78 °C for 2 h. Satd aq NH_4Cl (2 mL) was added and the reaction mixture was allowed to warm to rt, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and 10% aq citric acid (10 mL), and the organic layer was washed with satd aq $NaHCO_3$ (10 mL) and brine (10 mL), then dried and concentrated *in vacuo* to give a 91:9 mixture of **303** and **307**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **303** as a pale yellow oil (708 mg, 69%, >99:1 dr);[34] $[\alpha]_D^{25}$ –15.4 (*c* 2.0 in $CHCl_3$); {lit.[34] $[\alpha]_D^{20}$ –14.6 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.36 (3H, d, *J* 6.7, C(α)*Me*), 1.40 (9H, s, C*Me*$_3$), 1.69 (3H, d,

J 5.0, C(6)H_3), 1.96–2.08 (2H, m, C(2')H_2), 2.28 (1H, dd, *J* 14.1, 8.2, C(2)H_A), 2.40 (1H, dd, *J* 14.1, 6.6, C(2)H_B), 2.44–2.58 (2H, m, C(1')H_2), 3.75–3.81 (1H, m, C(3)*H*), 3.93 (1H, q, *J* 6.7, C(α)*H*), 4.86–4.94 (2H, m, C(4')H_2), 5.45–5.58 (2H, m, C(4)*H*, C(5)*H*), 5.64 (1H, ddt, *J* 17.0, 10.3, 6.8, C(3')*H*), 7.17–7.23 (1H, m, *Ph*), 7.25–7.30 (2H, m, *Ph*), 7.32–7.37 (2H, m, *Ph*).

tert-Butyl (2'*S*,α*R*)-2-[*N*(1')-(α-methylbenzyl)-1',2',5',6'-tetrahydropyridin-2'-yl]acetate 304

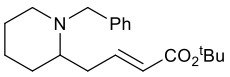


Method A: Grubbs I catalyst (301 mg, 0.366 mmol) was added to a stirred, degassed solution of **303** (3.14 g, 9.14 mmol, >99:1 dr) in CH_2Cl_2 (EtOH stabilised, 300 mL) at rt. The resultant mixture was stirred at rt for 16 h, then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 90:9:1) gave **304** as a pale yellow oil (2.30 g, 83%, >99:1 dr);[34] $[\alpha]_D^{25}$ +41.5 (*c* 1.0 in $CHCl_3$); {lit.[34] $[\alpha]_D^{25}$ +41.8 (*c* 1.5 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.38 (3H, d, *J* 6.6, C(α)*Me*), 1.48 (9H, s, C*Me*$_3$), 1.66–1.75 (1H, m, C(5')H_A), 2.04–2.16 (1H, m, C(5')H_B), 2.37 (1H, dd, *J* 14.2, 6.8, C(2)H_A), 2.43–2.50 (1H, m, C(6')H_A), 2.59 (1H, dd, *J* 14.2, 7.3, C(2)H_B), 2.84 (1H, ddd, *J* 13.9, 9.5, 4.7, C(6')H_B), 3.70–3.77 (1H, m, C(2')*H*), 3.89 (1H, q, *J* 6.6, C(α)*H*), 5.62–5.67 (1H, m, C(3')*H*), 5.78–5.85 (1H, m, C(4')*H*), 7.20–7.34 (5H, m, *Ph*).

Method B – Step 1: BuLi (2.3 M in hexanes, 20.0 mL, 46.1 mmol) was added dropwise to a stirred solution of **305** (8.33 g, 47.6 mmol, >99:1 er) in THF (70 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. A solution of **294** (5.00 g, 29.7 mmol, >99:1 dr) in THF (10 mL) at –78 °C was then added and the resultant mixture was stirred at –78 °C for 2 h. Satd aq NH_4Cl (20 mL) was added and the reaction mixture was allowed to warm to rt, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (50 mL) and 10% aq citric acid (50 mL), and the organic layer was washed with satd aq $NaHCO_3$ (50 mL) and brine (50 mL), then dried and concentrated *in vacuo* to give **303** in >95:5 dr.

Method B – Step 2: Grubbs I catalyst (854 mg, 1.04 mmol) was added to a stirred, degassed solution of the residue of **303** from the previous step in CH_2Cl_2 (EtOH stabilised, 900 mL) at rt. The resultant solution was stirred at rt for 16 h, then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 90:9:1) gave **304** as a pale yellow oil (6.55 g, 73% from **294**, >99.1 dr).

tert-Butyl (*E*)-4-[*N*(1')-benzylpiperidin-2'-yl]but-2-enoate 310

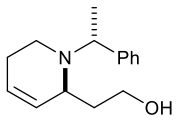


Method A: DMSO (70 µL, 0.985 mmol) was added to a stirred solution of $(COCl)_2$ (36 µL, 0.429 mmol) in CH_2Cl_2 (5 mL) at –78 °C and was stirred at –78 °C for 20 min. **308**[35] (54 mg, 0.246 mmol) was added and the resultant mixture was stirred at –78 °C for 40 min then Et_3N (0.21 mL, 1.48 mmol) was added. The reaction mixture was allowed to warm to rt over 30 min, **164** (93 mg, 0.246 mmol) was added and the resultant mixture was stirred for 16 h. Satd aq K_2CO_3 (5 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (30 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Me_2CO/NH_4OH, 100:5:1) gave **310** as a colourless oil (56 mg, 79%, 94:6 dr); ν_{max} (ATR) 2933 (C–H), 1707 (C=O); δ_H (400 MHz, $CDCl_3$) 1.17–1.29 (1H, m, C(4')H_A), 1.31–1.47 (12H, m, C(3')H_A, C(5')H_2, CMe_3), 1.52–1.62 (2H, m, C(4')H_B, C(3')H_B), 1.98 (1H, ddd, *J* 12.1, 9.0, 3.7, C(6')H_A), 2.37–2.44 (3H, m, C(4)H_2, C(2')*H*), 2.63 (1H, dt, *J* 12.1, 4.2, C(6')H_B), 3.16 (1H, d, *J* 13.4, NC$H_A$$H_B$Ph), 3.88 (1H, d, *J* 13.4, NC$H_A$$H_B$Ph), 5.71 (1H, d, *J* 13.5, C(2)*H*), 6.85 (1H, dt, *J* 15.5, 7.1, C(3)*H*), 7.12–7.26 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 23.2 (*C*(4')), 25.4 (*C*(5')), 28.3 (CMe_3), 30.7 (*C*(3')), 34.2 (*C*(4)), 51.5 (*C*(6')), 58.3 (NCH_2Ph), 59.7 (*C*(2')), 80.2 (O*C*Me$_3$), 124.7 (*C*(2)), 126.9 (*p-Ph*), 128.3, 128.9 (*o*,*m-Ph*), 139.5 (*i-Ph*), 145.7 (*C*(3)), 166.0 (*C*(1)); *m/z* (ESI$^+$) 316 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{30}NO_2^+$ ([M+H]$^+$) requires 316.2271; found 316.2273.

Method B: IBX (103 mg, 0.369 mmol) was added to a stirred solution of **308** (54 mg, 0.246 mmol) in EtOAc (5 mL) and the suspension was heated to 70 °C for 3 h. After cooling to 0 °C the mixture was filtered and **164** (93 mg, 0.246 mmol) was added to the filtrate. The resulting mixture was stirred at rt

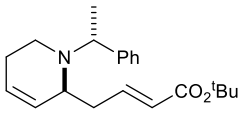
for 16 h before being concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Me_2CO/NH_4OH, 100:5:1) gave **310** as a colourless oil (30 mg, 42%, 93:7 dr).

(2'*S*,α*R*)-2-[*N*(1')-(α-Methylbenzyl)-1',2',5',6'-tetrahydropyridin-2'-yl]ethan-1-ol 311

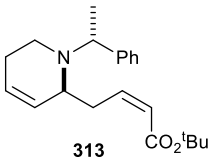


$LiAlH_4$ (2.4 M in THF, 3.18 mL, 7.63 mmol) was added to a stirred solution of **304** (2.30 g, 7.63 mmol, >99:1 dr) in THF (70 mL) at 0 °C. The resultant mixture was allowed to warm to rt and stirred at rt for 16 h. Aq NaOH (2.0 M, 7 mL) was then added and the resultant mixture was stirred at rt for 3 h. The reaction mixture was filtered through Celite® (eluent CH_2Cl_2), then concentrated *in vacuo* to give **311** as a pale yellow oil (1.66 g, 94%, >99:1 dr); $[\alpha]_D^{25}$ –3.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3393 (O–H), 3026, 2970, 2839, (C–H), 1454 (C=C); δ_H (400 MHz, $CDCl_3$) 1.49 (3H, d, *J* 6.6, C(α)*Me*), 1.73–1.88 (2H, m, C(2)H_A, C(5')H_A), 1.88–1.97 (1H, m, C(2)H_B), 2.04–2.14 (1H, m, C(5')H_B), 2.34 (1H, app dt, *J* 13.4, 4.5, C(6')H_A), 3.02 (1H, ddd, *J* 13.4, 8.9, 4.7, C(6')H_B), 3.59–3.66 (1H, m, C(2')*H*), 3.85–3.96 (2H, m, C(1)H_2), 4.05 (1H, q, *J* 6.6, C(α)*H*), 5.50–5.56 (1H, m, C(3')*H*), 5.84–5.97 (1H, m, C(4')*H*), 6.36 (1H, br s, O*H*), 7.24–7.39 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.3, 21.4 (*C*(5'), C(α)*Me*), 32.9 (*C*(2)), 40.0 (*C*(6')), 56.2 (*C*(2')), 57.6 (*C*(α)), 63.0 (*C*(1)), 126.4 (*C*(4')), 127.4 (*p-Ph*), 127.8, 128.5 (*o,m-Ph*), 128.5 (*C*(3')), 142.6 (*i-Ph*); *m/z* (ESI^+) 232 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{15}H_{22}NO^+$ ($[M+H]^+$) requires 232.1696; found 232.1696.

***tert*-Butyl (2'*S*,α*R*,*E*)-4-[*N*(1')-(α-methylbenzyl)-1',2',5',6'-tetrahydropyridin-2'-yl]but-2-enoate 312 and *tert*-Butyl (2'*S*,α*R*,*Z*)-4-[*N*(1')-(α-methylbenzyl)-1',2',5',6'-tetrahydropyridin-2'-yl]but-2-enoate 313**



312



313

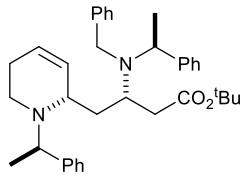
Method A: DMSO (0.61 mL, 8.65 mmol) was added to a stirred solution of $(COCl)_2$ (0.37 mL, 4.32 mmol) in CH_2Cl_2 (50 mL) at –78 °C and was stirred at –78 °C for 20 min. **311** (500 mg, 2.16 mmol, >99:1 dr) was added and the resultant mixture was stirred at –78 °C for 40 min, then Et_3N (1.81 mL, 13.0

mmol) was added. The reaction mixture was allowed to warm to rt over 30 min, **164** (814 mg, 2.16 mmol) was added, and the resultant mixture was stirred at rt for 16 h. Satd aq K_2CO_3 (300 mL) was then added and the reaction mixture was extracted with CH_2Cl_2 (3 × 300 mL). The combined organic extracts were washed with brine (500 mL), then dried and concentrated *in vacuo* to give a 93:7 mixture of **312** and **313**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 90:9:1) gave **313** as a pale yellow oil (19 mg, 3%, >99:1 dr); $[\alpha]_D^{25}$ +57.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2975, 2931 (C–H), 1712 (C=O), 1639 (C=C); δ_H (400 MHz, $CDCl_3$) 1.34 (3H, d, *J* 6.8, C(α)*Me*), 1.47 (9H, s, C*Me*$_3$), 1.84–1.94 (1H, m, C(5')H_A), 1.96–2.05 (1H, m, C(5')H_B), 2.23 (1H, ddd, *J* 12.1, 7.2, 5.7, C(6')H_A), 2.65–2.73 (1H, m, C(4)H_A), 2.92 (1H, app dt, *J* 12.1, 5.6, C(6')H_B), 3.16–3.26 (2H, m, C(4)H_B, C(2')*H*), 4.00 (1H, q, *J* 6.8, C(α)*H*), 5.46–5.51 (1H, m, C(3')*H*), 5.73 (1H, d, *J* 11.4, C(2)*H*), 5.73–5.78 (1H, m, C(4')*H*), 6.30 (1H, app dt, *J* 11.4, 7.5, C(3)*H*), 7.17–7.34 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.9 (C(α)*Me*), 24.3 (*C*(5')), 28.4 (C*Me*$_3$), 32.1 (*C*(4)), 40.8 (*C*(6')), 54.9 (*C*(2')), 57.1 (*C*(α)), 80.1 (*C*Me$_3$), 122.0 (*C*(2)), 126.5 (*C*(4')), 126.9 (*p-Ph*), 128.1, 128.1 (*o*,*m-Ph*), 130.1 (*C*(3')), 142.6 (*i-Ph*), 146.7 (*C*(3)), 166.4 (*C*(1)); *m/z* (ESI$^+$) 328 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{30}NO_2^+$ ([M+H]$^+$) requires 328.2271; found 328.2273. Further elution gave **312** as a yellow oil (322 mg, 46%, >99:1 dr); $[\alpha]_D^{25}$ +65.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2979, 2932 (C–H), 1713 (C=O), 1651 (C=C); δ_H (400 MHz, $CDCl_3$) 1.38 (3H, d, *J* 6.7, C(α)*Me*), 1.49 (9H, s, C*Me*$_3$), 1.82–1.93 (1H, m, C(5')H_A), 2.03–2.15 (1H, m, C(5')H_B), 2.36–2.55 (3H, m, C(4)H_2, C(6')H_A), 2.88 (1H, ddd, *J* 12.7, 7.8, 4.8, C(6')H_B), 3.23–3.31 (1H, m, C(2')*H*), 3.95 (1H, q, *J* 6.7, C(α)*H*), 5.53–5.58 (1H, m, C(3')*H*), 5.77 (1H, d, *J* 15.5, C(2)*H*), 5.77–5.83 (1H, m, C(4')*H*), 6.90 (1H, ddd, *J* 15.5, 8.0, 6.7, C(3)*H*), 7.21–7.35 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.4 (C(α)*Me*), 23.9 (*C*(5')), 28.3 (C*Me*$_3$), 35.9 (*C*(4)), 40.7 (*C*(6')), 54.6 (*C*(2')), 57.9 (*C*(α)), 80.1 (*C*Me$_3$), 124.3 (*C*(2)), 126.5 (*C*(4')), 127.0 (*p-Ph*), 127.9, 128.3 (*o*,*m-Ph*), 129.5 (*C*(3')), 143.4 (*i-Ph*), 145.9 (*C*(3)), 166.1 (*C*(1)); *m/z* (ESI$^+$) 328 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{30}NO_2^+$ ([M+H]$^+$) requires 328.2271; found 328.2271.

Method B: DIBAL-H (1.0 M in PhMe, 7.30 mL, 7.30 mmol) was added dropwise to a stirred solution of **304** (2.00 g, 6.64 mmol, >99:1 dr) in PhMe (20 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 1 h. MeOH (1.34 mL, 33.2 mmol) and **164** (2.50 g, 6.64 mmol) were added sequentially, and the resultant mixture was allowed to warm to rt and stirred at rt for 16 h. The reaction mixture was then

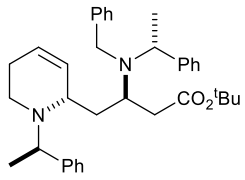
concentrated *in vacuo* to give an 80:20 mixture of **312** and **313**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 90:9:1) gave **313** as a pale yellow oil (313 mg, 14%, >99:1 dr). Further elution gave **312** as a yellow oil (1.57 g, 72%, >99:1 dr).

***tert*-Butyl (3*S*,2'*S*,α*S*,α'*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-[*N*(1')-(α'-methylbenzyl)-1',2',5',6'-tetrahydropyridin-2'-yl]butanoate 314**



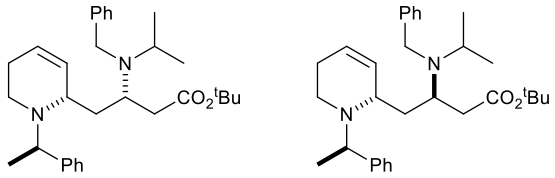
BuLi (2.3 M in hexanes, 0.64 mL, 1.47 mmol) was added dropwise to a stirred solution of (*S*)-**100**[4] (318 mg, 1.51 mmol, >99:1 er) in THF (2 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. A solution of **312** (308 mg, 0.941 mmol, >99:1 dr) in THF (1 mL) at –78 °C was added and the resultant mixture was stirred at –78 °C for 2 h. Satd aq NH_4Cl (0.5 mL) was added and the reaction mixture was allowed to warm to rt, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (5 mL) and 10% aq citric acid (5 mL), and the organic layer was washed with satd aq $NaHCO_3$ (5 mL) and brine (5 mL), then dried and concentrated *in vacuo* to give **314** in >95:5 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 90:9:1) gave **314** as a pale yellow oil (476 mg, 94%, >99:1 dr); $[\alpha]_D^{25}$ +68.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3064, 3025, 2973, 2932 (C–H), 1722 (C=O), 1609 (C=C); δ_H (400 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6.6, C(α')*Me*), 1.40 (3H, d, *J* 6.9, C(α)*Me*), 1.44 (9H, s, C*Me*$_3$), 1.55–1.73 (3H, m, C(4)*H*$_2$, C(5')*H*$_A$), 2.03–2.14 (1H, m, C(5')*H*$_B$), 2.17 (1H, dd, *J* 14.4, 6.6, C(2)*H*$_A$), 2.30 (1H, dd, *J* 14.4, 6.6, C(2)*H*$_B$), 2.41 (1H, app dd, *J* 13.7, 3.5, C(6')*H*$_A$), 2.76 (1H, ddd, *J* 13.7, 10.4, 4.8, C(6')*H*$_B$), 3.28–3.35 (1H, m, C(2')*H*), 3.55–3.63 (1H, m, C(3)*H*), 3.63 (1H, d, *J* 15.0, NC*H*$_A$H$_B$Ph), 3.76 (1H, d, *J* 15.0, NCH$_A$*H*$_B$Ph), 3.82 (1H, q, *J* 6.6, C(α')*H*), 4.01 (1H, q, *J* 6.9, C(α)*H*), 5.55–5.61 (1H, m, C(3')*H*), 5.71–5.77 (1H, m, C(4')*H*), 7.17–7.39 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.6 (C(α)*Me*), 21.5 (*C*(5')), 22.5 (C(α')*Me*), 28.3 (C*Me*$_3$), 36.6 (*C*(4)), 39.8, 39.9 (*C*(2), *C*(6')), 49.8 (N*C*H$_2$Ph), 52.9 (*C*(2')), 54.3 (*C*(3)), 58.1 (*C*(α')), 58.9 (*C*(α)), 80.0 (*C*Me$_3$), 125.3 (*C*(4')), 126.6, 126.8, 126.9 (3 × *p-Ph*), 127.7, 128.1, 128.2, 128.3, 128.3, 128.5 (3 × *o,m-Ph*), 130.4 (*C*(3')), 141.9, 143.9, 145.7 (3 × *i-Ph*), 172.3 (*C*(1)); *m/z* (ESI$^+$) 539 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{36}H_{47}N_2O_2^+$ ([M+H]$^+$) requires 539.3632; found 539.3631.

***tert*-Butyl (3*R*,2'*S*,α*R*,α'*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-[*N*(1')-(α'-methylbenzyl)-1',2',5',6'-tetrahydropyridin-2'-yl]butanoate 315**



BuLi (2.3 M in hexanes, 0.58 mL, 1.33 mmol) was added dropwise to a stirred solution of (*R*)-**100**[4] (289 mg, 1.37 mmol, >99:1 er) in THF (2 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. A solution of **312** (280 mg, 0.855 mmol, >99:1 dr) in THF (1 mL) at –78 °C was added and the resultant mixture was stirred at –78 °C for 2 h. Satd aq NH_4Cl (0.5 mL) was added and the reaction mixture was allowed to warm to rt, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (5 mL) and 10% aq citric acid (5 mL), and the organic layer was washed with satd aq $NaHCO_3$ (5 mL) and brine (5 mL), then dried and concentrated *in vacuo* to give **315** in >95:5 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 90:9:1) gave **315** as a pale yellow oil (449 mg, 97%, >99:1 dr); $[\alpha]_D^{25}$ +23.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3025, 2973, 2931, 2837 (C–H), 1722 (C=O), 1618 (C=C); δ_H (400 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6.8, C(α')*Me*), 1.29 (3H, d, *J* 6.9, C(α)*Me*), 1.32 (9H, s, C*Me*$_3$), 1.39–1.50 (2H, m, C(4)*H*$_A$, C(5')*H*$_A$), 1.90–2.00 (1H, m, C(4)*H*$_B$), 2.06 (1H, dd, *J* 14.1, 7.7, C(2)*H*$_A$), 2.03–2.19 (1H, m, C(5')*H*$_B$), 2.18 (1H, dd, *J* 14.1, 5.4, C(2)*H*$_B$), 2.48 (1H, app dd, *J* 13.8, 5.3, C(6')*H*$_A$), 2.81 (1H, ddd, *J* 13.8, 11.0, 4.7, C(6')*H*$_B$), 3.47–3.59 (2H, m, C(3)*H*, C(2')*H*), 3.58 (1H, d, *J* 14.7, NC*H*$_A$H$_B$Ph), 3.83 (1H, d, *J* 14.7, NCH$_A$*H*$_B$Ph), 3.84 (1H, q, *J* 6.8, C(α')*H*), 3.92 (1H, q, *J* 6.9, C(α)*H*), 5.40–5.47 (1H, m, C(3')*H*), 5.71–5.77 (1H, m, C(4')*H*), 7.17–7.43 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.5 (C(α)*Me*), 20.9 (*C*(5')), 22.9 (C(α')*Me*), 28.2 (C*Me*$_3$), 38.3, 38.5 (*C*(2), *C*(4)), 40.3 (*C*(6')), 50.4 (N*C*H$_2$Ph), 50.9 (*C*(2')), 52.7 (*C*(3)), 58.2 (*C*(α')), 58.6 (*C*(α)), 80.1 (*C*Me$_3$), 125.7 (*C*(4')), 126.6, 126.8, 127.0 (3 × *p*-*Ph*), 127.6, 128.2, 128.2, 128.3, 128.3, 128.6 (3 × *o*,*m*-*Ph*), 129.6 (*C*(3')), 142.1, 144.2, 146.2 (3 × *i*-*Ph*), 172.1 (*C*(1)); *m/z* (ESI$^+$) 539 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{36}H_{47}N_2O_2^+$ ([M+H]$^+$) requires 539.3632; found 539.3648.

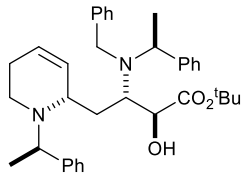
tert-Butyl (3*R*,2'*S*,α*R*)-3-[*N*-benzyl-*N*-isopropylamino]-4-[*N*(1')-(α-methylbenzyl)-1',2',5',6'-tetrahydropyridin-2'-yl]butanoate and _tert_-butyl (3*S*,2'*S*,α*R*)-3-[*N*-benzyl-*N*-isopropylamino]-4-[*N*(1')-(α-methylbenzyl)-1',2',5',6'-tetrahydropyridin-2'-yl]butanoate 316 and 317



BuLi (2.3 M in hexanes, 0.44 mL, 1.00 mmol) was added dropwise to a stirred solution of *N*-benzyl-*N*-isopropylamine **318** (155 mg, 1.04 mmol) in THF (2 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. A solution of **312** (212 mg, 0.647 mmol, >99:1 dr) in THF (1 mL) at –78 °C was added and the resultant mixture was stirred at –78 °C for 2 h. Satd aq NH_4Cl (0.5 mL) was added and the reaction mixture was allowed to warm to rt, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and 10% aq citric acid (10 mL), and the organic layer was washed with satd aq $NaHCO_3$ (10 mL) and brine (10 mL), then dried and concentrated *in vacuo* to give a 50:50 mixture of **316** and **317** as a colourless oil (296 mg, 96%). Data for **316**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.05–1.11 (6H, m, NCH*Me*$_2$), 1.35 (3H, d, *J* 6.5, C(α)*Me*), 1.36–1.63 (2H, m, C(4)H_A, C(5')H_A), 1.50 (9H, s, C*Me*$_3$), 1.84–1.98 (1H, m, C(4)H_B), 2.04–2.17 (1H, m, C(5')H_B), 2.42–2.57 (3H, m, C(2)H_2, C(6')H_A), 2.72–2.84 (1H, m, C(6')H_B), 2.91–3.02 (1H, m, NC*H*Me$_2$), 3.32–3.43 (1H, m, C(2')*H*), 3.52–3.61 (1H, m, C(3)*H*), 3.65 (1H, d, *J* 14.5, NCH_AH$_B$Ph), 3.73 (1H, d, *J* 14.5, NCH$_A$$H_B$Ph), 3.84 (1H, q, *J* 6.5, C(α)*H*), 5.33–5.43 (1H, m, C(3')*H*), 5.69–5.79 (1H, m, C(4')*H*), 7.19–7.43 (10H, m, *Ph*). Data for **317**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.05–1.11 (6H, m, NCH*Me*$_2$), 1.35 (3H, d, *J* 6.5, C(α)*Me*), 1.36–1.63 (2H, m, C(4)H_A, C(5')H_A), 1.46 (9H, s, C*Me*$_3$), 1.68 (1H, app dt, *J* 14.2, 5.2, C(4)H_B), 2.04–2.17 (1H, m, C(5')H_B), 2.29 (1H, dd, *J* 13.7, 6.2, C(2)H_A), 2.40–2.57 (2H, m, C(2)H_B, C(6')H_A), 2.72–2.84 (1H, m, C(6')H_B), 2.91–3.02 (1H, m, NC*H*Me$_2$), 3.32–3.43 (1H, m, C(2')*H*), 3.52–3.61 (1H, m, C(3)*H*), 3.66 (2H, s, NCH_2Ph), 3.84 (1H, q, *J* 6.5, C(α)*H*), 5.49–5.55 (1H, m, C(3')*H*), 5.69–5.79 (1H, m, C(4')*H*), 7.19–7.43 (10H, m, *Ph*). Data for mixture of **316** and **317**: ν_{max} (ATR) 3024, 2967, 2931, 2837 (C–H), 1724 (C=O), 1602 (C=C); δ_C (100 MHz, $CDCl_3$) 20.2, 20.4, 20.8, 20.9, 21.1, 21.8, 22.7, 23.0, 28.3, 28.3, 36.5, 37.4, 39.8, 39.9, 40.2, 40.4, 47.8, 49.3, 49.4, 50.0, 51.2, 51.9, 52.4, 53.9, 58.0, 58.2, 80.0, 80.1, 125.4, 125.7, 126.6, 126.6, 126.8, 126.8, 127.5, 127.6, 128.1, 128.1, 128.3, 128.3 ,128.5,

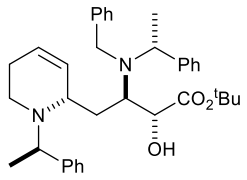
129.0, 129.8, 130.2, 141.8, 142.3, 145.9, 146.2, 172.3, 172.6; *m/z* (ESI$^+$) 477 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{45}N_2O_2^+$ ([M+H]$^+$) requires 477.3476; found 477.3471.

tert-Butyl (2*S*,3*S*,2'*S*,α*S*,α'*R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-[*N*(1')-(α'-methylbenzyl)-1',2',5',6'-tetrahydropyridin-2'-yl]butanoate 320



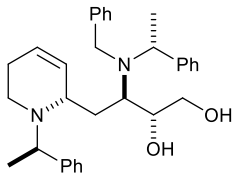
BuLi (2.3 M in hexanes, 1.03 mL, 2.37 mmol) was added dropwise to a stirred solution of (*S*)-**100**[4] (517 mg, 2.45 mmol, >99:1 er) in THF (4 mL) at –78 °C and the resultant mixture was stirred for 30 min. A solution of **312** (500 mg, 1.53 mmol, >99:1 dr) in THF (2 mL) at –78 °C was added and the resultant mixture was stirred at –78 °C for 2 h. (+)-CSO (+)-**322** (596 mg, 2.60 mmol) was added and the reaction mixture was allowed to warm to rt over 16 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and 10% aq citric acid (10 mL) then the organic layer was washed with satd aq Na_2CO_3 (10 mL) and brine (10 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 85:17:1) gave **320** as a colourless oil (645 mg, 76%, 96:4 dr); $[\alpha]_D^{25}$ +36.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3062, 3026, 2974, 2932, 2849 (C–H), 1730 (C=O); δ_H (400 MHz, $CDCl_3$) 1.33 (3H, d, *J* 7.0, C(α)*Me*), 1.38 (3H, d, *J* 6.4, C(α')*Me*), 1.41–1.51 (1H, m, C(5')H_A), 1.56 (9H, s, CMe_3), 1.62–1.72 (2H, m, C(4)H_2), 1.96–2.08 (1H, m, C(5')H_B), 2.41 (1H, dd, *J* 14.3, 5.1, C(6')H_A), 2.60–2.70 (1H, m, C(6')H_B), 3.26 (1H, d, *J* 9.1, C(2')*H*), 3.45–3.52 (1H, m, C(3)*H*), 3.72 (1H, q, *J* 6.4, C(α')*H*), 3.75 (1H, d, *J* 15.2, NCH_AH$_B$Ph), 3.86 (1H, d, *J* 9.4, C(2)*H*), 3.90 (1H, d, *J* 15.2, NCH$_A$$H_B$Ph), 4.10 (1H, q, *J* 7.0, C(α)*H*), 5.34 (1H, d, *J* 10.0, C(3')*H*), 5.80 (1H, dd, *J* 10.0, 4.5, C(4')*H*), 7.19–7.38 (13H, m, *Ph*), 7.45 (2H, d, *J* 7.4, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.8 (C(α')*Me*), 19.3 (*C*(5')), 22.5 (C(α)*Me*), 28.3 (CMe_3), 32.7 (*C*(4)), 39.3 (*C*(6')), 50.1 (N*C*H$_2$Ph), 54.9 (*C*(2')), 58.4 (*C*(α')Me), 61.1 (*C*(α)Me), 62.4 (*C*(3)), 74.4 (*C*(2)), 80.7 (O*C*Me$_3$), 125.8 (*C*(4')), 126.7, 127.2, 127.3 (3 × *p-Ph*), 127.5, 128.2, 128.2, 128.2, 128.3, 128.7, 128.7 (*C*(3'), 3 × *o,m-Ph*), 141.9, 143.6, 144.2 (3 × *i-Ph*), 174.0 (*C*(1)); *m/z* (ESI$^+$) 555 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{36}H_{47}N_2O_3^+$ ([M+H]$^+$) requires 555.3581; found 555.3580.

tert-Butyl (2*R*,3*R*,2'*S*,α*R*,α'*R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-[*N*(1')-(α'-methylbenzyl)-1',2',5',6'-tetrahydropyridin-2'-yl]butanoate 321



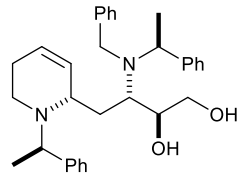
BuLi (2.3 M in hexanes, 1.03 mL, 2.37 mmol) was added dropwise to a stirred solution of (*R*)-**100**[4] (517 mg, 2.45 mmol, >99:1 er) in THF (4 mL) at –78 °C and the resultant mixture was stirred for 30 min. A solution of **312** (500 mg, 1.53 mmol, >99:1 dr) in THF (2 mL) at –78 °C was added and the resultant mixture was stirred at –78 °C for 2 h. (–)-CSO (–)-**322** (596 mg, 2.60 mmol) was added and the reaction mixture was allowed to warm to rt over 16 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and 10% aq citric acid (10 mL) then the organic layer was washed with satd aq Na_2CO_3 (10 mL) and brine (10 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 85:17:1) gave **321** as a colourless oil (669 mg, 79%, 90:10 dr); $[\alpha]_D^{25}$ –4.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3025, 2838 (C–H), 1719 (C=O); δ_H (400 MHz, $CDCl_3$) 1.33 (3H, d, *J* 6.5, C(α)*Me*), 1.38 (3H, d, *J* 7.0, C(α')*Me*), 1.46 (9H, s, C*Me*$_3$), 1.48–1.69 (2H, m, C(4)*H*$_A$, C(5')*H*$_A$), 2.01 (1H, app quintet, *J* 6.9, C(4)*H*$_B$), 2.08–2.20 (1H, m, C(5')*H*$_B$), 2.54 (1H, dd, *J* 14.0, 5.1, C(6')*H*$_A$), 2.91 (1H, ddd, *J* 14.0, 11.0, 4.8, C(6')*H*$_B$), 3.50–3.56 (1H, m, C(3)*H*), 3.59–3.66 (1H, m, C(2')*H*), 3.77 (1H, d, *J* 14.7, NC*H*$_A$H$_B$Ph), 3.86 (1H, q, *J* 6.5, C(α)*H*), 3.97–4.04 (2H, m, C(2)*H*, C(α')*H*), 4.14 (1H, d, *J* 14.7, NCH$_A$*H*$_B$Ph), 5.39–5.45 (1H, m, C(3')*H*), 5.78 (1H, d, *J* 9.9, C(4')*H*), 7.20–7.39 (13H, m, *Ph*), 7.51 (2H, d, *J* 7.3, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.2 (C(α')*Me*), 20.6 (*C*(5')), 22.6 (C(α)*Me*), 28.2 (C*Me*$_3$), 34.1 (*C*(4)), 40.1 (*C*(6')), 50.6 (*C*(2')), 51.7 (N*C*H$_2$Ph), 56.4 (*C*(3)), 58.2, 58.3 (*C*(α)Me, *C*(α')Me), 70.5 (*C*(2)), 82.0 (*C*Me$_3$), 126.2 (*C*(4')), 126.8, 126.9, 127.3 (3 × *p-Ph*), 127.5, 128.3, 128.4, 128.4, 128.4, 128.8 (3 × *o,m-Ph*), 129.4 (*C*(3')), 141.9, 143.7, 145.7 (3 × *i-Ph*), 174.1 (*C*(1)); *m/z* (ESI$^+$) 555 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{36}H_{47}N_2O_3^+$ ([M+H]$^+$) requires 555.3581; found 555.3576.

(2*R*,3*R*,2'*S*,α*R*,α'*R*)-2-Hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-[*N*(1')-(α'-methyl-benzyl)-1',2',5',6'-tetrahydropyridin-2'-yl]butan-1-ol 323



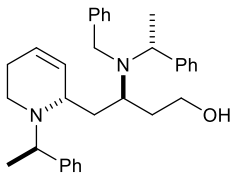
$LiAlH_4$ (2.4 M in THF, 1.00 mL, 2.42 mmol) was added to a stirred solution of **321** (669 mg, 1.21 mmol, 90:10 dr) in THF (5 mL) at 0 °C. The resulting mixture was stirred at rt for 16 h. Aq NaOH (2.0 M, 1 mL) was then added and the resultant mixture was stirred for 3 h. The reaction mixture was filtered through Celite® (eluent CH_2Cl_2), then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent Et_2O/NH_4OH, 100:1) gave **323** as a white foam (497 mg, 85%, >99:1 dr); mp 49–53 °C; $[\alpha]_D^{25}$ +1.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3392 (O–H), 3026, 2970 (C–H); δ_H (400 MHz, $CDCl_3$) 1.45 (6H, app t, *J* 6.8, C(α)*Me*, C(α')*Me*), 1.94–2.00 (2H, m, C(5')H_2), 2.07 (1H, ddd, *J* 15.1, 6.1, 2.1, C(4)H_A), 2.16–2.32 (2H, m, C(4)H_B, C(6')H_A), 2.99–3.08 (2H, m, C(3)*H*, C(6')H_B), 3.21 (1H, dd, *J* 10.8, 6.6, C(1)H_A), 3.43–3.49 (1H, m, C(2')*H*), 3.54 (1H, dd, *J* 10.8, 4, C(1)H_B), 3.60–3.66 (1H, m, C(2)*H*), 3.83 (1H, d, *J* 13.8, NC$H_A$$H_B$Ph), 3.96 (1H, d, *J* 13.8, NC$H_A$$H_B$Ph), 3.99 (1H, q, *J* 6.8, C(α)*H*), 4.11 (1H, q, *J* 6.8, C(α')*H*), 5.45 (1H, d, *J* 9.4, C(3')*H*), 5.75–5.81 (1H, m, C(4')*H*), 7.19–7.39 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.7 (C(α)*Me*), 19.6 (C(α')*Me*), 23.5 (*C*(5')), 32.8 (*C*(4)), 40.6 (*C*(6')), 51.6 (N*C*H_2Ph), 54.0 (*C*(2')), 56.2 (*C*(3)), 57.5 (*C*(α')Me), 57.6 (*C*(α)Me), 66.0 (*C*(1)), 71.7 (*C*(2)), 126.4 (*C*(4')), 127.2, 127.2, 127.7 (3 × *p-Ph*), 128.2, 128.3, 128.4, 128.5, 128.6, 128.6, 129.1 (*C*(3'), 3 × *o,m-Ph*), 139.8, 140.5, 143.8 (3 × *i-Ph*); *m/z* (ESI^+) 485 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{32}H_{41}N_2O_2^+$ ($[M+H]^+$) requires 485.3163; found 485.3160.

(2*S*,3*S*,2'*S*,α*S*,α'*R*)-2-Hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-[*N*(1')-(α'-methyl-benzyl)-1',2',5',6'-tetrahydropyridin-2'-yl]butan-1-ol 324



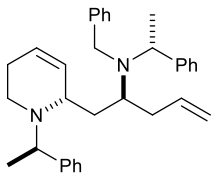
$LiAlH_4$ (2.4 M in THF, 0.97 mL, 2.32 mmol) was added to a stirred solution of **320** (645 mg, 1.16 mmol, 96:4 dr) in THF (5 mL) at 0 °C. The resulting mixture was stirred at rt for 16 h. Aq NaOH (2.0 M, 1 mL) was then added and the resultant mixture was stirred for 3 h. The reaction mixture was filtered through Celite® (eluent CH_2Cl_2), then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent Et_2O/NH_4OH, 100:1) gave **324** as a white foam (530 mg, 94%, >99:1 dr); mp 48–57 °C; $[\alpha]_D^{25}$ +61.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3390 (O–H), 3061, 3026, 2971, 2935 (C–H); δ_H (400 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6.3, C(α')*Me*), 1.44 (3H, d, *J* 6.9, C(α)*Me*), 1.46–1.54 (1H, m, C(5')H_A), 1.85 (1H, ddd, *J* 15.1, 10.4, 7.2, C(4)H_A), 1.97 (1H, d, *J* 15.1, C(4)H_B), 2.00–2.11 (1H, m, C(5')H_B), 2.49 (1H, dd, *J* 14.4, 5.1, C(6')H_A), 2.68–2.83 (2H, m, C(3)*H*, C(6')H_B), 3.15–3.21 (1H, m, C(1)H_A), 3.42 (1H, d, *J* 10.2, C(2')*H*), 3.46–3.56 (2H, m, C(1)H_B, C(2)*H*), 3.74 (1H, q, *J* 6.3, C(α')*H*), 3.82 (1H, d, *J* 13.9, NCH_AH$_B$Ph), 3.87 (1H, d, *J* 13.9, NCH$_A$$H_B$Ph), 4.01 (1H, q, *J* 6.9, C(α)*H*), 5.59 (1H, d, *J* 10.1, C(3')*H*), 5.90 (1H, dd, *J* 10.1, 4.6, C(4')*H*), 7.20–7.44 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (C(α)*Me*), 19.2 (*C*(5')), 22.6 (C(α')*Me*), 34.0 (*C*(4)), 39.3 (*C*(6')), 51.1 (N*C*H$_2$Ph), 55.4 (*C*(2')), 57.3 (*C*(α)Me), 58.5 (*C*(α')Me), 60.3 (*C*(3)), 67.1 (*C*(1)), 72.2 (*C*(2)), 126.1 (*C*(4')), 127.3, 127.4, 127.4, 127.5, 128.1, 128.3, 128.3, 128.6, 128.9, 129.2 (*C*(3'), 3 × *o*,*m*,*p*-*Ph*), 140.2, 143.2, 143.7 (3 × *i*-*Ph*); *m/z* (ESI^+) 485 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{32}H_{41}N_2O_2^+$ ($[M+H]^+$) requires 485.3163; found 485.3160.

(3*R*,2'*S*,α*R*,α'*R*)-3-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-4-[*N*(1')-(α'-methylbenzyl)-1',2',5',6'-tetrahydropyridin-2'-yl]butan-1-ol 329



$LiAlH_4$ (2.4 M in THF, 0.31 mL, 0.752 mmol) was added to a stirred solution of **315** (405 mg, 0.752 mmol, >99:1 dr) in THF (7 mL) at 0 °C. The resulting mixture was stirred at rt for 16 h. Aq NaOH (2.0 M, 0.3 mL) was then added and the resultant mixture was stirred for 3 h. The reaction mixture was filtered through Celite® (eluent CH_2Cl_2), then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 66:33:1) gave **329** as a colourless oil (297 mg, 84%, >99:1 dr); $[\alpha]_D^{25}$ –38.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3416 (O–H), 3061, 3025, 2932 (C–H); δ_H (400 MHz, $CDCl_3$) 1.23 (3H, d, *J* 6.4, C(α')*Me*), 1.40 (1H, ddd, *J* 13.5, 10.5, 3.0, C(4)H_A), 1.47–1.72 (3H, m, C(2)H_2, C(5')H_A), 1.49 (3H, d, *J* 7.0, C(α)*Me*), 2.62 (1H, m, C(4)H_B), 2.10–2.21 (1H, m, C(5')H_B), 2.63 (1H, dd, *J* 14.1, 5.2, C(6')H_A), 2.96 (1H, ddd, *J* 14.1, 11.7, 4.3, C(6')H_B), 3.10 (1H, br s, O*H*), 3.23 (1H, ddd, *J* 10.8, 7.6, 3.4, C(1)H_A), 3.26–3.32 (1H, m, C(2')*H*), 3.42–3.56 (2H, m, C(1)H_B, C(3)*H*), 3.67 (1H, d, *J* 13.4, NC$H_A$$H_B$Ph), 3.83 (1H, q, *J* 6.4, C(α')*H*), 3.94 (1H, d, *J* 13.4, NC$H_A$$H_B$Ph), 3.97 (1H, q, *J* 7.0, C(α)*H*), 5.56–5.62 (1H, m, C(3')*H*), 5.83–5.89 (1H, m, C(4')*H*), 7.23–7.40 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.9 (C(α)*Me*), 20.2 (*C*(5')), 23.0 (C(α')*Me*), 33.7 (*C*(2)), 36.9 (*C*(4)), 40.4 (*C*(6')), 50.4 (N*C*H_2Ph), 51.7 (*C*(2')), 52.3 (*C*(3)), 56.5 (*C*(α)Me), 58.3 (*C*(α')Me), 62.3 (*C*(1)), 125.9 (*C*(4')), 126.9, 127.1, 127.2 (3 × *p-Ph*), 127.6, 128.1, 128.4, 128.6, 128.6, 129.4 (3 × *o,m-Ph*), 130.3 (*C*(3')), 140.7, 144.1, 146.1 (3 × *i-Ph*); *m/z* (ESI^+) 469 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{32}H_{41}N_2O^+$ ($[M+H]^+$) requires 469.3213; found 469.3219.

(2*S*,2'*S*,α*R*,α'*R*)-1-[*N*(1')-(α-Methylbenzyl)-1',2',5',6'-tetrahydropyridin-2'-yl]-2-[*N*-benzyl-*N*-(α'-methylbenzyl)amino]pent-4-ene 333



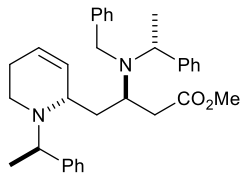
Method A: DIBAL-H (1.0 M in PhMe, 0.20 mL, 0.20 mmol) was added dropwise to a stirred solution of **315** (100 mg, 0.185 mmol, >99:1 dr) in PhMe (2 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 1 h. MeOH (38 μL, 0.93 mmol) and **335**[36] (0.31 M in PhMe/THF, 6.6 mL, 2.0 mmol) were added sequentially, and the resultant mixture was allowed to warm to rt and stirred at rt for 16 h, then concentrated *in vacuo*. The residue was dissolved in Et_2O (10 mL) and the resultant solution was filtered through a short plug of Celite® (eluent Et_2O) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 100:5:1) gave **333** as a colourless oil (25 mg, 29%, >99:1 dr); $[\alpha]_D^{25}$ +28.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3358, 2961 (C–H), 1596 (C=C); δ_H (400 MHz, $CDCl_3$) 1.26 (3H, d, *J* 6.4, C(α)*Me*), 1.37 (3H, d, *J* 6.9, C(α')*Me*), 1.46–1.57 (2H, m, C(1)H_A, C(5')H_A), 1.89–2.01 (2H, m, C(3)H_A, C(1)H_B), 2.05–2.16 (2H, m, C(3)H_B, C(5')H_B), 2.49 (1H, app dd, *J* 14.0, 5.2, C(6')H_A), 2.86 (1H, ddd, *J* 14.0, 11.2, 4.6, C(6')H_B), 3.12 (1H, app quintet, *J* 6.4, C(2)*H*), 3.38–3.46 (1H, m, C(2')*H*), 3.73 (1H, d, *J* 14.7, NC$H_A$$H_B$Ph), 3.82 (1H, q, *J* 6.4, C(α)*H*), 3.84 (1H, d, *J* 14.7, NC$H_A$$H_B$Ph), 3.96 (1H, q, *J* 6.9, C(α')*H*), 4.85–4.93 (2H, m, C(5)H_2), 5.46–5.52 (1H, m, C(3')*H*), 5.59 (1H, ddt, *J* 17.0, 10.2, 7.0, C(4)*H*), 5.72–5.79 (1H, m, C(4')*H*), 7.18–7.34 (11H, m, *Ph*), 7.36–7.41 (2H, m, *Ph*), 7.42–7.46 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.9 (C(α')*Me*), 20.6 (*C*(5')), 22.9 (C(α)*Me*), 36.4 (*C*(3)), 37.9 (*C*(1)), 40.2 (*C*(6')), 50.3 (N*C*H_2Ph), 51.3 (*C*(2')), 53.8 (*C*(2)), 57.3 (*C*(α')Me), 58.1 (*C*(α)Me), 115.3 (*C*(5)), 125.5 (*C*(4')), 126.5, 126.6, 126.6 (3 × *p-Ph*), 127.4, 127.9, 128.1, 128.2, 128.2, 128.5 (3 × *o,m-Ph*), 130.0 (*C*(3')), 137.9 (*C*(4)), 142.2, 144.7, 146.1 (3 × *i-Ph*); *m/z* (ESI^+) 465 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{33}H_{41}N_2^+$ ($[M+H]^+$) requires 465.3264; found 465.3258.

Method B: DIBAL-H (1.0 M in PhMe, 0.20 mL, 0.20 mmol) was added dropwise to a stirred solution of **315** (100 mg, 0.185 mmol, >99:1 dr) in PhMe (2 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 1 h. MeOH (38 μL, 0.93 mmol) and **335**[36] (0.31 M in PhMe/THF, 6.6 mL, 2.0 mmol) were added sequentially, and the resultant mixture was allowed to warm to rt and stirred at rt for 16 h, then

concentrated *in vacuo*. The residue was dissolved in Et_2O (10 mL) and the resultant solution was filtered through a short plug of Celite® (eluent Et_2O) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 100:5:1) gave **333** as a colourless oil (54 mg, 62%, >99:1 dr).

Method C: DIBAL-H (1.0 M in PhMe, 0.41 mL, 0.41 mmol) was added dropwise to a stirred solution of **334** (184 mg, 0.370 mmol, >99:1 dr) in PhMe (3 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 1 h. MeOH (81 μL, 1.9 mmol) and **335**[36] (0.31 M in PhMe/THF, 11.9 mL, 3.70 mmol) were added sequentially, and the resultant mixture was allowed to warm to rt and stirred at rt for 16 h, then concentrated *in vacuo*. The residue was dissolved in Et_2O (20 mL) and the resultant solution was filtered through a short plug of Celite® (eluent Et_2O) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 100:5:1) gave **333** as a colourless oil (107 mg, 62%, >99:1 dr).

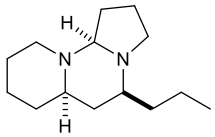
Methyl (3*R*,2'*S*,α*R*,α'*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-[*N*(1')-(α'-methylbenzyl)-1',2',5',6'-tetrahydropyridin-2'-yl]butanoate 334



$SOCl_2$ (0.28 mL, 3.77 mmol) was added dropwise to a stirred solution of **315** (203 mg, 0.377 mmol) in MeOH (5 mL) at 0 °C. The resultant solution was stirred at 50 °C for 16 h then cooled to rt and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and aq NaOH (1.0 M, 10 mL). The organic layer was dried and concentrated *in vacuo* to give **334** as a colourless oil (186 mg, 99%, >99:1 dr); $[\alpha]_D^{25}$ +9.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3025 (C–H), 1737 (C=O); δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, *J* 6.5, C(α')*Me*), 1.40 (3H, d, *J* 6.9, C(α)*Me*), 1.45–1.60 (2H, m, C(4)H_A, C(5')H_A), 2.02 (1H, ddd, *J* 13.5, 8.5, 4.7, C(4)H_B), 2.08–2.20 (1H, m, C(5')H_B), 2.27 (1H, dd, *J* 14.0, 5.7, C(2)H_A), 2.33 (1H, dd, *J* 14.0, 7.7, C(2)H_B), 2.52 (1H, dd, *J* 13.9, 5.0, C(6')H_A), 2.87 (1H, ddd, *J* 13.9, 11.1, 4.6, C(6')H_B), 3.36–3.42 (1H, m, C(2')*H*), 3.44 (3H, s, O*Me*), 3.70–3.77 (3H, m, C(3)*H*, NCH_2Ph), 3.84 (1H, q, *J* 6.5, C(α')*H*), 3.92 (1H, q, *J* 6.9, C(α)*H*), 5.52–5.58 (1H, m, C(3')*H*), 5.78–5.83 (1H, m, C(4')*H*), 7.20–7.37

(13H, m, *Ph*), 7.43 (2H, d, *J* 7.5, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.3 (C(α)*Me*), 20.6 (*C*(5')), 22.8 (C(α')*Me*), 37.7 (*C*(2)), 38.0 (*C*(4)), 40.2 (*C*(6')), 50.3 (N*C*H_2Ph), 51.4 (*C*(2')), 51.4 (O*Me*), 52.1 (*C*(3)), 57.2 (*C*(α)Me), 58.1 (*C*(α')Me), 126.0 (*C*(4')), 126.8, 126.8, 126.8 (3 × *p-Ph*), 127.6, 128.0, 128.3, 128.4, 128.4, 128.9 (3 × *o,m-Ph*), 129.8 (*C*(3')), 141.6, 144.3, 146.2 (3 × *i-Ph*), 173.1 (*C*(1)); *m/z* (ESI^+) 497 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{33}H_{41}N_2O_2^+$ ($[M+H]^+$) requires 497.3163; found 497.3160.

(5*S*,6a*R*,11a*S*)-5-Propyldecahydro-5*H*-pyrido[1,2-*c*]pyrrolo[1,2-*a*]pyrimidine [(+)-tetraponerine 4] 105

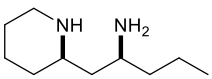


Method A: $Pd(OH)_2/C$ (226 mg, 100% w/w) was added to a stirred, degassed solution of **333** (226 mg, 0.486 mmol, >99:1 dr) in MeOH/H_2O/AcOH (10:1:1, 2 mL). The resultant mixture was stirred under an atmosphere of H_2 (5 atm) at rt for 48 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH/H_2O/AcOH, 10:1:1), and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (5 mL), then K_2CO_3 (201 mg, 1.46 mmol) and 4-bromobutanal **293** (146 mg, 0.973 mmol) were added to the resultant solution. The reaction mixture was stirred at rt for 2 h, then H_2O (2 mL) and satd aq $NaHCO_3$ (10 mL) were added. The reaction mixture was then extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Me_2CO/NH_4OH, 90:9:1) gave **105** as a colourless oil (40 mg, 37% from **333**, >99:1 dr); $[\alpha]_D^{25}$ +90.8 (*c* 1.0 in $CHCl_3$); {lit.[37] for a sample isolated from the natural source $[\alpha]_D^{20}$ +94 (*c* 0.2 in $CHCl_3$); lit.[38] $[\alpha]_D^{20}$ +96 (*c* 2.0 in $CHCl_3$)}; ν_{max} (ATR) 2933, 2855, 2793 (C–H); δ_H (400 MHz, C_6D_6) 0.89 (3H, t, *J* 7.1, C(3')H_3), 1.13–1.29 (2H, m, C(9)H_A, C(2')H_A), 1.30–1.56 (9H, m, C(2)H_A, C(6)H_2, C(7)H_2, C(8)H_A, C(1')H_2, C(2')H_B), 1.59–1.77 (7H, m, C(1)H_2, C(2)H_B, C(6a)*H*, C(8)H_B, C(9)H_B, C(10)H_A), 2.02 (1H, dd, *J* 16.3, 8.6, C(3)H_A), 2.11 (1H, ddd, *J* 14.6, 7.4, 3.6, C(5)*H*), 2.31 (1H, dd, *J* 7.8, 5.6, C(11a)*H*), 2.80–2.85 (1H, m, C(10)H_B), 3.13 (1H, app td, *J* 8.6, 2.2, C(3)H_B); δ_C (100 MHz, C_6D_6) 14.8 (*C*(3')), 18.7 (*C*(2')), 20.2 (*C*(2)), 25.1 (*C*(9)), 26.3 (*C*(8)), 29.7 (*C*(1)), 33.0 (*C*(7)), 36.9 (*C*(1')), 38.0 (*C*(6)), 49.0 (*C*(3)), 51.6 (*C*(10)), 61.1 (*C*(5)), 62.7 (*C*(6a)), 85.6 (*C*(11a)); *m/z* (ESI^+) 223 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{14}H_{27}N_2^+$ ($[M+H]^+$) requires 223.2169; found 223.2169.

Method B: Palladium black (24 mg, 20% w/w) was added to a stirred, degassed solution of **333** (121 mg, 0.261 mmol, >99:1 dr) in MeOH/H_2O/AcOH (10:1:1, 2 mL). The resultant mixture was stirred under an atmosphere of H_2 (5 atm) at rt for 48 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH/H_2O/AcOH, 10:1:1), and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (2 mL), then K_2CO_3 (108 mg, 0.781 mmol) and 4-bromobutanal **293** (79 mg, 0.52 mmol) were added to the resultant solution. The reaction mixture was stirred at rt for 2 h, then H_2O (2 mL) and satd aq $NaHCO_3$ (10 mL) were added. The reaction mixture was then extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Me_2CO/NH_4OH, 90:9:1) gave **105** as a colourless oil (31 mg, 54% from **333**, >99:1 dr).

Method C: K_2CO_3 (88 mg, 0.63 mmol) and 4-bromobutanal **293** (64 mg, 0.42 mmol) were added to a stirred solution of **338** (36 mg, 0.21 mmol, >99:1 dr) in CH_2Cl_2 (2 mL) at rt, and the resultant mixture was stirred at rt for 2 h. H_2O (2 mL) and satd aq $NaHCO_3$ (10 mL) were added, and the resultant mixture was extracted with CH_2Cl_2 (3 × 5 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Me_2CO/NH_4OH, 90:9:1) gave **105** as a colourless oil (32 mg, 68% from **338**, >99:1 dr).

(2*S*,2'*R*)-1-(Piperidin-2'-yl)-2-aminopentane 338

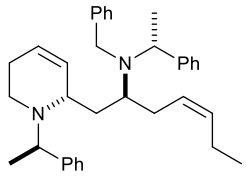


Method A: $Pd(OH)_2$/C (325 mg, 100% w/w) was added to a stirred, degassed solution of **333** (325 mg, 0.699 mmol) in MeOH/H_2O/AcOH (10:1:1, 2 mL). The resultant mixture was stirred under an atmosphere of H_2 (5 atm) at rt for 48 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH/H_2O/AcOH, 10:1:1) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$/MeOH/NH_4OH 10:1:1) gave **338** as a colourless oil (62 mg, 52%, >99:1 dr); $[\alpha]_D^{25}$ –3.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3292 (N–H), 2930, 2860 (C–H); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.9, C(5)H_3), 1.02–1.13 (1H, m, C(3')H_A), 1.17–1.46 (8H, m, C(1)H_2, C(3)H_2, C(4)H_2, C(4')H_A, C(5')H_A), 1.53–1.68 (2H, m, C(3')H_B, C(4')H_B), 1.72–1.80 (1H, m, C(5')H_B), 2.55–2.66 (2H, m, C(2')*H*, C(6')H_A), 2.75–2.82 (1H, m, C(2)*H*), 3.01–3.07 (1H, m, C(6')H_B); δ_C (100 MHz, $CDCl_3$) 14.3 (*C*(5)),

19.2 (*C*(4)), 25.0 (*C*(5')), 26.7 (*C*(4')), 33.4 (*C*(3')), 42.1 (*C*(3)), 45.5 (*C*(1)), 47.1 (*C*(6')), 49.9 (*C*(2)), 56.1 (*C*(2')); *m/z* (ESI$^+$) 171 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{10}H_{23}N_2^+$ ([M+H]$^+$) requires 171.1856; found 171.1856.

Method B: Palladium black (15 mg, 20% w/w) was added to a stirred, degassed solution of **333** (75 mg, 0.16 mmol) in MeOH/H_2O/AcOH (10:1:1, 2 mL). The resultant mixture was stirred under an atmosphere of H_2 (5 atm) at rt for 48 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH/H_2O/AcOH, 10:1:1) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$/MeOH/NH_4OH 10:1:1) gave **338** as a colourless oil (20 mg, 73%, >99:1 dr).

(2*S*,2'*S*,α*R*,α'*R*,*Z*)-1-[*N*(1')-(α-Methylbenzyl)-1',2',5',6'-tetrahydropyridin-2'-yl]-2-[*N*-benzyl-*N*-(α'-methylbenzyl)amino]hept-4-ene 339

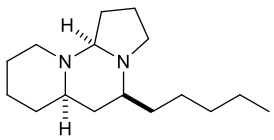


Method A: DIBAL-H (1.0 M in PhMe, 0.53 mL, 0.53 mmol) was added dropwise to a stirred solution of **315** (260 mg, 0.483 mmol, >99:1 dr) in PhMe (4 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 1 h. MeOH (98 μL, 2.41 mmol) and **340**[39] (0.31 M in PhMe/THF, 15.6 mL, 4.83 mmol) were added sequentially, and the resultant mixture was allowed to warm to rt and stirred at rt for 16 h, then concentrated *in vacuo*. The residue was dissolved in Et_2O (20 mL) and the resultant solution was filtered through a short plug of Celite® (eluent Et_2O) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 100:5:1) gave **339** as a pale yellow oil (148 mg, 62%, >95:5 dr [(*Z*):(*E*)]); $[\alpha]_D^{25}$ +36.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3024, 2931, 2838 (C–H), 1580, 1493, 1453 (C=C); δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, *J* 7.5, C(7)H_3), 1.26 (3H, d, *J* 6.4, C(α')*Me*), 1.36 (3H, d, *J* 6.9, C(α)*Me*), 1.46–1.58 (2H, m, C(1)H_A, C(5')H_A), 1.89–2.16 (6H, m, C(1)H_B, C(3)H_2, C(6)H_2, C(5')H_B), 2.49 (1H, dd, *J* 14.0, 5.2, C(6')H_A), 2.87 (1H, ddd, *J* 14.0, 11.2, 4.7, C(6')H_B), 3.06 (1H, app quintet, *J* 6.4, C(2)*H*), 3.40–3.47 (1H, m, C(2')*H*), 3.73 (1H, d, *J* 14.8, NC$H_A$$H_B$Ph), 3.81 (1H, q, *J* 6.4, C(α')*H*), 3.86 (1H, d, *J* 14.8, NC$H_A$$H_B$Ph), 3.98 (1H, q, *J* 6.9, C(α)*H*), 5.10–5.19 (1H, m, C(4)*H*), 5.25–5.33 (1H, m, C(5)*H*), 5.44–5.50 (1H, m, C(3')*H*), 5.71–5.78 (1H, m, C(4')*H*), 7.19–7.35 (11H, m,

Ph), 7.37–7.41 (2H, m, *Ph*), 7.42–7.46 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.3 (*C*(7)), 18.5 (C(α)*Me*), 20.8 (*C*(5')), 20.9 (*C*(6)), 23.0 (C(α')*Me*), 29.6 (*C*(3)), 38.3 (*C*(1)), 40.3 (*C*(6')), 50.5 (N*C*H_2Ph), 51.6 (*C*(2')), 54.5 (*C*(2)), 57.7 (*C*(α)), 58.2 (*C*(α')), 125.5 (*C*(4')), 126.5, 126.7, 126.7 (3 × *p-Ph*), 127.6, 128.0, 128.0, 128.2, 128.3, 128.3, 128.6 (*C*(4), 3 × *o,m-Ph*), 130.2 (*C*(3')), 131.9 (*C*(5)), 142.6, 145.2, 146.3 (3 × *i-Ph*); *m/z* (ESI$^+$) 493 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{35}H_{45}N_2^+$ ([M+H]$^+$) requires 493.3577; found 493.3568.

Method B: DIBAL-H (1.0 M in PhMe, 0.20 mL, 0.20 mmol) was added dropwise to a stirred solution of **315** (100 mg, 0.185 mmol, >99:1 dr) in PhMe (2 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 1 h. MeOH (38 μL, 0.93 mmol) and **340**[40] (0.62 M in hexanes, 3.0 mL, 1.9 mmol) were added sequentially, and the resultant mixture was allowed to warm to rt and stirred at rt for 16 h, then concentrated *in vacuo*. The residue was dissolved in Et_2O (20 mL) and the resultant solution was filtered through a short plug of Celite® (eluent Et_2O) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 100:5:1) gave **339** as a pale yellow oil (47 mg, 51%, 75:25 dr [(*Z*):(*E*)]).

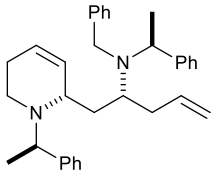
(5*S*,6a*R*,11a*S*)-5-Pentyldecahydro-5*H*-pyrido[1,2-*c*]pyrrolo[1,2-*a*]pyrimidine [(+)-tetraponerine 8] 109



Palladium black (26 mg, 20% w/w) was added to a stirred, degassed solution of **339** (130 mg, 0.297 mmol, >95:5 dr) in MeOH/H_2O/AcOH (10:1:1, 2 mL). The resultant mixture was stirred under an atmosphere of H_2 (5 atm) at rt for 48 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH/H_2O/AcOH, 10:1:1) and concentrated *in vacuo*. The residue was dissolved in MeOH/H_2O/AcOH (10:1:1, 2 mL) and the resultant solution was degassed. $Pd(OH)_2$/C (65 mg, 50% w/w) was added and the resultant mixture was stirred under an atmosphere of H_2 (5 atm) at rt for 24 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH/H_2O/AcOH, 10:1:1) and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (2 mL), then K_2CO_3 (110 mg, 0.792 mmol) and 4-bromobutanal **293** (80 mg, 0.53 mmol) were added to the resultant solution. The reaction

mixture was stirred at rt for 2 h, then H_2O (2 mL) and satd aq $NaHCO_3$ (10 mL) were added. The reaction mixture was then extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Me_2CO/NH_4OH, 90:9:1) gave **109** as a white solid (44 mg, 67% from **339**, >99:1 dr); mp 38–40 °C; {lit.[41] mp 40 °C}; $[\alpha]_D^{25}$ +93.0 (*c* 1.0 in $CHCl_3$); {lit.[37] for a sample isolated from the natural source $[\alpha]_D^{20}$ +102 (*c* 0.2 in $CHCl_3$); lit.[38] $[\alpha]_D^{20}$ +101 (*c* 2.0 in $CHCl_3$)}; ν_{max} (ATR) 2931, 2857 (C–H); δ_H (400 MHz, C_6D_6) 0.90 (3H, t, *J* 7.0, C(5')H_3), 1.16–1.67 (17H, m, C(2)H_A, C(6)H_2, C(7)H_2, C(8)H_2, C(9)H_2, C(1')H_2, C(2')H_2, C(3')H_2, C(4')H_2), 1.68–1.78 (5H, m, C(1)H_2, C(2)H_B, C(6a)*H*, C(10)H_A), 2.04 (1H, app dd, *J* 16.3, 8.5, C(3)H_A), 2.12 (1H, app ddd, *J* 14.6, 7.3, 3.6, C(5)*H*), 2.31 (1H, dd, *J* 7.9, 5.7, C(11a)*H*), 2.81–2.86 (1H, m, C(10)H_B), 3.15 (1H, app td, *J* 8.5, 2.2, C(3)H_B); δ_C (100 MHz, C_6D_6) 14.4 (*C*(5')), 20.2 (*C*(2)), 23.2 (*C*(4')), 25.2 (*C*(9)), 25.2 (*C*(2')), 26.3 (*C*(8)), 29.7 (*C*(1)), 32.8 (*C*(3')), 33.0 (*C*(7)), 34.6 (*C*(1')), 38.0 (*C*(6)), 49.0 (*C*(3)), 51.6 (*C*(10)), 61.4 (*C*(5)), 62.7 (*C*(6a)), 85.6 (*C*(11a)); *m/z* (ESI$^+$) 251 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{31}N_2^+$ ([M+H]$^+$) requires 251.2482; found 251.2472.

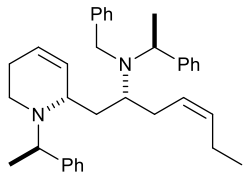
(2*R*,2'*S*,*αS*,*α'R*)-1-[*N*(1')-(*α*-Methylbenzyl)-1',2',5',6'-tetrahydropyridin-2'-yl]-2-[*N*-benzyl-*N*-(*α'*-methylbenzyl)amino]pent-4-ene 341



DIBAL-H (1.0 M in PhMe, 0.78 mL, 0.78 mmol) was added dropwise to a stirred solution of **314** (383 mg, 0.711 mmol, >99:1 dr) in PhMe (6 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 1 h. MeOH (144 μL, 3.55 mmol) and **335**[36] (0.31 M in PhMe/THF, 22.9 mL, 7.11 mmol) were added sequentially, and the resultant mixture was allowed to warm to rt and stirred at rt for 16 h, then concentrated *in vacuo*. The residue was dissolved in Et_2O (30 mL) and the resultant solution was filtered through a short plug of Celite® (eluent Et_2O) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 100:5:1) gave **341** as a pale yellow oil (180 mg, 54%, >99:1 dr); $[\alpha]_D^{25}$ +52.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3061, 3025, 2933, 2836 (C–H), 1601, 1492, 1452 (C=C); δ_H (400 MHz, $CDCl_3$) 1.26 (3H, d, *J* 6.6, C(α)*Me*), 1.34 (3H, d, *J* 6.9, C(α')*Me*), 1.58–1.76 (3H, d, C(1)H_2, C(5')H_A), 1.90–1.99 (1H, m, C(3)H_A), 2.00–2.15 (2H, m, C(3)H_B, C(5')H_B), 2.46 (1H,

ddd, *J* 13.4, 5.4, 2.6, C(6')H_A), 2.83 (1H, ddd, *J* 13.4, 9.9, 4.7, C(6')H_B), 2.93 (1H, app quintet, *J* 6.2, C(2)*H*), 3.24–3.30 (1H, m, C(2')*H*), 3.73 (1H, d, *J* 14.8, NC$H_A$$H_B$Ph), 3.81 (1H, d, *J* 14.8, NCH$_A$$H_B$Ph), 3.82 (1H, q, *J* 6.6, C(α)*H*), 3.96 (1H, q, *J* 6.9, C(α')*H*), 4.86–4.88 (1H, m, C(5)H_A), 4.89–4.92 (1H, m, C(5)H_B), 5.54–5.65 (2H, m, C(4)*H*, C(3')*H*), 5.72–5.77 (1H, m, C(4')*H*), 7.18–7.37 (13H, m, *Ph*), 7.42–7.46 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.2 (C(α')*Me*), 22.2 (*C*(5')), 22.5 (C(α)*Me*), 36.8 (*C*(1)), 37.1 (*C*(3)), 40.1 (*C*(6')), 50.1 (N*C*H$_2$Ph), 53.1 (*C*(2')), 55.1 (*C*(2)), 57.6 (*C*(α')), 58.3 (*C*(α)), 115.2 (*C*(5)), 125.2 (*C*(4')), 126.6, 126.8, 126.8 (3 × *p-Ph*), 127.7, 128.1, 128.3, 128.3, 128.3, 128.5 (3 × *o*,*m-Ph*), 130.6 (*C*(3')), 138.1 (*C*(4)), 142.3, 144.4, 145.5 (3 × *i-Ph*); *m/z* (ESI$^+$) 465 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{33}H_{41}N_2^+$ ([M+H]$^+$) requires 465.3264; found 465.3259.

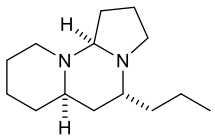
(2*R*,2'*S*,α*S*,α'*R*,*Z*)-1-[*N*(1')-(α-Methylbenzyl)-1',2',5',6'-tetrahydropyridin-2'-yl]-2-[*N*-benzyl-*N*-(α'-methylbenzyl)amino]hept-4-ene 342



DIBAL-H (1.0 M in PhMe, 0.77 mL, 0.77 mmol) was added dropwise to a stirred solution of **314** (377 mg, 0.700 mmol, >99:1 dr) in PhMe (6 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 1 h. MeOH (142 μL, 3.50 mmol) and **340**[39] (0.31 M in PhMe/THF, 22.6 mL, 7.00 mmol) were added sequentially, and the resultant mixture was allowed to warm to rt and stirred at rt for 16 h, then concentrated *in vacuo*. The residue was dissolved in Et_2O (30 mL) and the resultant solution was filtered through a short plug of Celite® (eluent Et_2O) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 100:5:1) gave **342** as a pale yellow oil (162 mg, 47%, >95:5 dr [(*Z*):(*E*)]); $[\alpha]_D^{25}$ +59.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2970 (C–H), 1493, 1453 (C=C); δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.5, C(7)H_3), 1.26 (3H, d, *J* 6.6, C(α)*Me*), 1.34 (3H, d, *J* 6.9, C(α')*Me*), 1.60–1.80 (3H, m, C(1)H_2, C(5')H_A), 1.91 (2H, app quintet, *J* 7.5, C(6)H_2), 1.97 (2H, app t, *J* 6.8, C(3)H_2), 2.04–2.15 (1H, m, C(5')H_B), 2.47 (1H, ddd, *J* 13.1, 5.3, 3.1, C(6')H_A), 2.80–2.92 (2H, m, C(2)*H*, C(6')H_B), 3.20–3.26 (1H, m, C(2')*H*), 3.73 (1H, d, *J* 14.8, NC$H_A$$H_B$Ph), 3.81 (1H, d, *J* 14.8, NCH$_A$$H_B$Ph), 3.83 (1H, q, *J* 6.6, C(α)*H*), 3.98 (1H, q, *J* 6.9, C(α')*H*), 5.12–5.19 (1H, m, C(4)*H*), 5.25–5.32 (1H, m, C(5)*H*), 5.56–5.61 (1H, m, C(3')*H*), 5.71–5.77 (1H, m, C(4')*H*), 7.17–7.44 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$)

14.3 (*C*(7)), 18.3 (C(α')*Me*), 20.9 (*C*(6)), 22.3 (C(α)*Me*), 22.6 (*C*(5')), 30.0 (*C*(3)), 36.8 (*C*(1)), 40.2 (*C*(6')), 50.0 (N*C*H$_2$Ph), 53.2 (*C*(2')), 55.5 (*C*(2)), 57.6 (*C*(α')), 58.2 (*C*(α)), 125.1 (*C*(4')), 126.6, 126.7, 126.8 (3 × *p-Ph*), 127.8, 128.0, 128.1, 128.2, 128.2, 128.3, 128.5 (*C*(4), 3 × *o*,*m-Ph*), 130.8 (*C*(3')), 131.8 (*C*(5)), 142.4, 144.7, 145.2 (3 × *i-Ph*); *m/z* (ESI$^+$) 493 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{35}H_{45}N_2^+$ ([M+H]$^+$) requires 493.3577; found 493.3565.

(5*R*,6a*R*,11a*S*)-5-Propyldecahydro-5*H*-pyrido[1,2-*c*]pyrrolo[1,2-*a*]pyrimidine [(+)-tetraponerine 3] 104

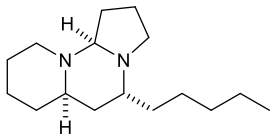


Palladium black (23 mg, 20% w/w) was added to a stirred, degassed solution of **341** (115 mg, 0.248 mmol, >99:1 dr) in MeOH/H$_2$O/AcOH (10:1:1, 2 mL). The resultant mixture was stirred under an atmosphere of H$_2$ (5 atm) at rt for 48 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH/H$_2$O/AcOH, 10:1:1) and concentrated *in vacuo*. The residue was dissolved in CH$_2$Cl$_2$ (2 mL), then K$_2$CO$_3$ (102 mg, 0.741 mmol) and 4-bromobutanal **293** (75 mg, 0.49 mmol) were added to the resultant solution. The reaction mixture was stirred at rt for 2 h, then H$_2$O (2 mL) and satd aq NaHCO$_3$ (10 mL) were added. The reaction mixture was then extracted with CH$_2$Cl$_2$ (3 × 5 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Me$_2$CO/NH$_4$OH, 90:9:1) gave **104** as a colourless oil (33 mg, 60% from **341**, >99:1 dr); $[\alpha]_D^{25}$ +30.9 (*c* 1.0 in CHCl$_3$); {lit.[37] for a sample isolated from the natural source $[\alpha]_D^{20}$ +27 (*c* 0.07 in CHCl$_3$); lit.[41] $[\alpha]_D^{20}$ +31 (*c* 3.1 in CHCl$_3$); lit.[42] $[\alpha]_D^{20}$ +35 (*c* 0.49 in CHCl$_3$)}; ν_{max} (ATR) 2954, 2928, 2859, 2802 (C–H); δ_H (400 MHz, C$_6$D$_6$) 0.95 (3H, t, *J* 7.2, C(3')*H*$_3$), 1.09 (1H, app dt, *J* 12.7, 1.9, C(6)*H*$_A$), 1.15–1.28 (1H, m, C(9)*H*$_A$), 1.27–1.48 (5H, m, C(7)*H*$_2$, C(1')*H*$_A$, C(2')*H*$_2$), 1.48–1.84 (9H, m, C(1)*H*$_2$, C(2)*H*$_2$, C(8)*H*$_2$, C(9)*H*$_B$, C(10)*H*$_A$, C(1')*H*$_B$), 1.91 (1H, ddd, *J* 12.7, 11.9, 5.3, C(6)*H*$_B$), 1.99–2.07 (1H, m, C(6a)*H*), 2.72–2.86 (3H, m, C(3)*H*$_A$, C(5)*H*, C(10)*H*$_B$), 3.17 (1H, app q, *J* 7.5, C(3)*H*$_B$), 3.30 (1H, app t, *J* 3.5, C(11a)*H*); δ_C (100 MHz, C$_6$D$_6$) 14.5 (*C*(3')), 20.7 (*C*(2')), 22.2 (*C*(2)), 25.3 (*C*(9)), 26.6 (*C*(8)), 30.6 (*C*(1)), 32.2 (*C*(6)), 33.4 (*C*(1')), 34.3 (*C*(7)), 50.6 (*C*(3)), 51.0

(*C*(10)), 53.0 (*C*(5)), 56.7 (*C*(6a)), 75.4 (*C*(11a)); *m/z* (ESI$^+$) 223 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{27}N_2^+$ ([M+H]$^+$) requires 223.2169; found 223.2168.

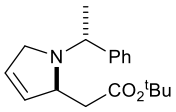
(5*R*,6a*R*,11a*S*)-5-Pentyldecahydro-5*H*-pyrido[1,2-*c*]pyrrolo[1,2-*a*]pyrimidine

[(+)-tetraponerine 7] 108



Palladium black (22 mg, 20% w/w) was added to a stirred, degassed solution of **342** (108 mg, 0.219 mmol, >95:5 dr) in MeOH/H_2O/AcOH (10:1:1, 2 mL). The resultant mixture was stirred under an atmosphere of H_2 (5 atm) at rt for 48 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH/H_2O/AcOH, 10:1:1) and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (2 mL), then K_2CO_3 (91 mg, 0.66 mmol) and 4-bromobutanal **293** (66 mg, 0.44 mmol) were added to the resultant solution. The reaction mixture was stirred at rt for 2 h, then H_2O (2 mL) and satd aq $NaHCO_3$ (10 mL) were added. The reaction mixture was then extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Me_2CO/NH_4OH, 90:9:1) gave **108** as a colourless oil (24 mg, 44% from **342**, >99:1 dr); $[\alpha]_D^{25}$ +30.4 (*c* 0.8 in $CHCl_3$); {lit.[37] for a sample isolated from the natural source $[\alpha]_D^{20}$ +30 (*c* 0.22 in $CHCl_3$); lit.[38] $[\alpha]_D^{20}$ +29.5 (*c* 2.2 in $CHCl_3$)}; ν_{max} (ATR) 2928, 2856 (C–H); δ_H (400 MHz, C_6D_6) 0.93 (3H, t, *J* 6.9, C(5')H_3), 1.13 (1H, app dt, *J* 12.9, 1.9, C(6)H_A), 1.17–1.86 (19H, m, C(1)H_2, C(2)H_2, C(7)H_2, C(8)H_2, C(9)H_2, C(10)H_A, C(1')H_2, C(2')H_2, C(3')H_2, C(4')H_2), 1.93 (1H, ddd, *J* 12.9, 11.9, 5.4, C(6)H_B), 2.02–2.09 (1H, m, C(6a)*H*), 2.74–2.86 (3H, m, C(3)H_A, C(5)*H*, C(10)H_B), 3.15–3.21 (1H, m, C(3)H_B), 3.33 (1H, app t, *J* 3.6, C(11a)*H*); δ_C (100 MHz, C_6D_6) 14.4 (*C*(5')), 22.2 (*C*(2)), 23.2 (*C*(4')), 25.3 (*C*(8)), 26.6 (*C*(9)), 27.4 (*C*(2')), 30.6 (*C*(1)), 31.1 (*C*(1')), 32.3 (*C*(6)), 32.5 (*C*(3')), 34.3 (*C*(7)), 50.7 (*C*(3)), 51.0 (*C*(10)), 53.3 (*C*(5)), 56.7 (*C*(6a)), 75.5 (*C*(11a)); *m/z* (ESI$^+$) 251 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{31}N_2^+$ ([M+H]$^+$) requires 251.2482; found 251.2480.

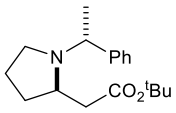
***tert*-Butyl (2'*S*,*αR*)-2-[*N*(1')-(*α*-methylbenzyl)-2',5'-dihydro-1*H*-pyrrol-2'-yl]acetate 345**



BuLi (2.3 M in hexanes, 36.1 mL, 82.9 mmol) was added dropwise to a stirred solution of **347**[4] (13.8 g, 85.6 mmol, >99:1 er) in THF (125 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. A solution of **294** (9.00 g, 53.5 mmol, >99:1 dr) in THF (25 mL) at –78 °C was added dropwise *via* cannula and the resultant mixture was stirred at –78 °C for 2 h. Satd aq NH_4Cl (20 mL) was added and the reaction mixture was allowed to warm to rt, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (100 mL) and 10% aq citric acid (100 mL), and the organic layer was washed with satd aq $NaHCO_3$ (100 mL) and brine (100 mL), then dried and concentrated *in vacuo.*

Step 2: Grubbs I catalyst (1.62 g, 1.97 mmol) was added to a stirred, degassed solution of the residue from the previous step in CH_2Cl_2 (EtOH stabilised, 1.6 L) at rt. The resultant mixture was stirred at rt for 16 h, then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 90:9:1) gave **345** as a pale yellow oil (11.7 g, 76%, >99:1 dr);[43] $[\alpha]_D^{25}$ +99.0 (*c* 1.0 in $CHCl_3$); {lit.[44] for *ent*-**345**: $[\alpha]_D^{24}$ –132.0 (*c* 0.99 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.43 (3H, d, *J* 6.7, C(α)*Me*), 1.46 (9H, s, C*Me*$_3$), 2.33 (1H, dd, *J* 14.5, 8.9, C(2)H_A), 2.59 (1H, dd, *J* 14.5, 4.0, C(2)H_B), 3.34–3.41 (1H, m, C(5')H_A), 3.57–3.63 (1H, m, C(5')H_B), 3.85 (1H, q, *J* 6.7, C(α)*H*), 4.10–4.18 (1H, m, C(2')*H*), 5.68–5.76 (2H, m, C(3')*H*, C(4')*H*), 7.19–7.34 (5H, m, *Ph*).

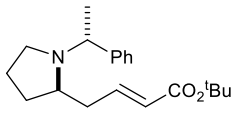
***tert*-Butyl (*R*,*R*)-2-[*N*(1')-(*α*-methylbenzyl)pyrrolidin-2'-yl]acetate 348**



$RhCl(PPh_3)_3$ (6.4 mg, 7.0 μmol) was added to a degassed solution of **345** (100 mg, 0.348 mmol, >99:1 dr) in EtOAc (2 mL) and the resultant mixture was stirred under H_2 (1 atm) at rt for 16 h. The reaction mixture then concentrated *in vacuo* to give an 88:12 mixture of **348** and **350**, respectively. Data for **350**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.47 (9H, s, C*Me*$_3$), 1.52 (3H, d, *J* 7.0, C(α)*Me*), 1.77–1.93 (2H, m, C(4')H_2), 2.99–3.13 (2H, m, C(3')H_A, C(5')H_A), 3.21–3.31 (2H, m, C(3')H_B, C(5')H_B), 4.65 (1H, s, C(2)*H*), 4.89 (1H, q, *J* 7.0, C(α)*H*), 7.21–7.36 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) [selected peaks] 16.5

(C(α)*Me*), 21.1 (*C*(4')), 28.9 (C*Me*$_3$), 32.9 (*C*(3')), 46.9 (*C*(5')), 52.6 (*C*(α)Me), 77.6 (*C*Me$_3$), 80.1 (*C*(2)), 126.9 (*o*/*m*-*Ph*), 127.5 (*p*-*Ph*), 128.7 (*o*/*m*-*Ph*), 140.6 (*i*-*Ph*), 164.2 (*C*(1)), 169.7 (*C*(2')). Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 90:9:1) gave **348** as a colourless oil (50 mg, 50%, >99:1 dr);[44] $[\alpha]_D^{25}$ +57.0 (*c* 1.0 in $CHCl_3$); {lit.[44] for *ent*-**348**: $[\alpha]_D^{23}$ –56.1 (*c* 1.6 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.44 (3H, d, *J* 6.8, C(α)*Me*), 1.44 (9H, s, C*Me*$_3$), 1.55–1.64 (2H, m, C(3')H_A, C(4')H_A), 1.65–1.77 (1H, m, C(4')H_B), 1.79–1.89 (1H, m, C(3')H_B), 2.18 (1H, dd, *J* 14.2, 9.9, C(2)H_A), 2.39 (1H, td, *J* 8.8, 6.9, C(5')H_A), 2.58 (1H, dd, *J* 14.2, 3.5, C(2)H_B), 2.76–2.82 (1H, m, C(5')H_B), 3.00–3.09 (1H, m, C(2')*H*), 3.76 (1H, q, *J* 6.8, C(α)*H*), 7.21–7.35 (5H, m, *Ph*).

***tert*-Butyl (*R*,*R*,*E*)-4-[*N*(1')-(α-methylbenzyl)pyrrolidin-2'-yl]but-2-enoate 351**

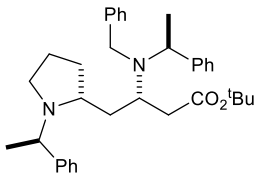


Method A: DIBAL-H (1.0 M in PhMe, 0.57 mL, 0.57 mmol) was added dropwise to a stirred solution of **348** (151 mg, 0.522 mmol, >99:1 dr) in PhMe (2 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 1 h. MeOH (0.11 mL, 2.61 mmol) and **164** (196 mg, 0.522 mmol) were added sequentially, and the resultant mixture was allowed to warm to rt and stirred at rt for 16 h. The reaction mixture was then concentrated *in vacuo* to give **351** in 75:25 dr [(*E*):(*Z*)]. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 85:17:1) gave (*Z*)-**351** as a pale yellow oil (22 mg, 13%, 9:91 dr [(*E*):(*Z*)]); δ_H (400 MHz, $CDCl_3$) 1.44 (3H, d, *J* 6.8, C(α)*Me*), 1.46–1.60 (2H, m, C(3')H_A, C(4')H_A), 1.50 (9H, s, C*Me*$_3$), 1.65–1.77 (2H, m, C(3')H_B, C(4')H_B), 2.37 (1H, app q, *J* 8.2, C(5')H_A), 2.65–2.79 (2H, m, C(4)H_A, C(2')*H*), 2.84–2.90 (1H, m, C(5')H_B), 2.94–3.03 (1H, m, C(4)H_B), 3.87 (1H, q, *J* 6.8, C(α)*H*), 5.75 (1H, dt, *J* 11.6, 1.7, C(2)*H*), 6.18 (1H, dt, *J* 11.6, 7.2, C(3)*H*), 7.21–7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 22.0 (C(α)*Me*), 22.6 (*C*(4')), 28.4 (C*Me*$_3$), 29.9 (*C*(3')), 32.6 (*C*(4)), 49.0 (*C*(5')), 58.9 (*C*(2')), 59.2 (*C*(α)), 80.1 (*C*Me$_3$), 122.5 (*C*(2)), 126.9 (*p*-*Ph*), 128.1, 128.2 (*o*,*m*-*Ph*), 142.4 (*i*-*Ph*), 146.2 (*C*(3)), 166.2 (*C*(1)); ν_{max} (ATR) 2972, 2873 (C–H), 1713 (C=O), 1651 (C=C); *m/z* (ESI$^+$) 316 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{30}NO_2^+$ ([M+H]$^+$) requires 316.2271; found 316.2269. Further elution (eluent 30–40 °C petrol/Et_2O/NH_4OH, 85:17:1) gave (*E*)-**351** as a colourless oil (108 mg, 66%, 86:14 dr [(*E*):(*Z*)]).

Method B – Step 1: $RhCl(PPh_3)_3$ (320 mg, 0.348 mmol) was added to a degassed solution of **345** (5.00 g, 17.4 mmol) in EtOAc (100 mL) and the resultant mixture was stirred under H_2 (1 atm) at rt for 16 h. The reaction mixture was then concentrated *in vacuo* to give **348**.

Method B – Step 2: DIBAL-H (1.0 M in PhMe, 19.1 mL, 19.1 mmol) was added dropwise to a stirred solution of the residue of **348** from the previous step in PhMe (70 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 1 h. MeOH (3.57 mL, 87.0 mmol) and **164** (6.55 g, 17.4 mmol) were added sequentially, and the resultant mixture was allowed to warm to rt and stirred at rt for 16 h. The reaction mixture was then concentrated *in vacuo* to give **351** in 78:22 dr [(*E*):(*Z*)]. Purification *via* exhaustive flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 85:17:1) gave (*E*)-**351** as a colourless oil (2.76 g, 50% from **345**, 98:2 dr [(*E*):(*Z*)]); $[\alpha]_D^{25}$ +82.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2972, 2873 (C–H), 1713 (C=O); δ_H (400 MHz, $CDCl_3$) 1.44 (3H, d, *J* 6.8, C(α)*Me*), 1.48 (9H, s, C*Me*$_3$), 1.48–1.81 (4H, m, C(3')H_2, C(4')H_2), 2.18 (1H, app dt, *J* 14.2, 9.0, C(4)H_A), 2.40 (1H, app td, *J* 8.7, 7.2, C(5')H_A), 2.50 (1H, dddd, *J* 14.2, 7.0, 3.3, 1.5, C(4)H_B), 2.70–2.78 (1H, m, C(2')*H*), 2.80–2.86 (1H, m, C(5')H_B), 3.80 (1H, q, *J* 6.8, C(α)*H*), 5.76 (1H, dt, *J* 15.6, 1.5, C(2)*H*), 6.83 (1H, app dt, *J* 15.6, 7.0, C(3)*H*), 7.21–7.34 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 22.2 (C(α)*Me*), 22.7 (*C*(4')), 28.3 (C*Me*$_3$), 30.2 (*C*(3')), 37.6 (*C*(4)), 49.9 (*C*(5')), 58.7 (*C*(2')), 60.3 (*C*(α)), 80.2 (*C*Me$_3$), 124.4 (*C*(2)), 127.0 (*p-Ph*), 128.0, 128.2 (*o,m-Ph*), 142.9 (*i-Ph*), 145.9 (*C*(3)), 166.1 (*C*(1)); *m/z* (ESI^+) 316 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{30}NO_2^+$ ($[M+H]^+$) requires 316.2271; found 316.2270.

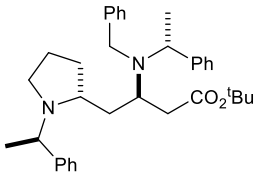
tert-Butyl (3*S*,2'*R*,α*S*,α'*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-[*N*(1')-(α'-methylbenzyl)-pyrrolidin-2'-yl]butanoate 352



BuLi (2.3 M in hexanes, 0.85 mL, 1.97 mmol) was added dropwise to a stirred solution of (*S*)-**100**[4] (429 mg, 2.03 mmol, >99:1 er) in THF (3 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. A solution of **351** (400 mg, 1.27 mmol, 98:2 dr [(*E*):(*Z*)]) in THF (2 mL) at –78 °C was added and the resultant mixture was stirred at –78 °C for 2 h. Satd aq NH_4Cl (1 mL) was added and the reaction

mixture was allowed to warm to rt, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and 10% aq citric acid (10 mL), and the organic layer was washed with satd aq $NaHCO_3$ (10 mL) and brine (10 mL), then dried and concentrated *in vacuo* to give **352** in >95:5 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 85:17:1) gave **352** as a pale yellow oil (615 mg, 92%, >99:1 dr); $[\alpha]_D^{25}$ +72.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3027, 2972, 2932, 2801 (C–H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.34 (3H, d, *J* 6.9, C(α)*Me*), 1.38 (9H, s, C*Me*$_3$), 1.42 (3H, d, *J* 6.9, C(α')*Me*), 1.41–1.47 (1H, m, C(3')*H*$_A$), 1.52–1.78 (4H, m, C(4)*H*$_A$, C(3')*H*$_B$, C(4')*H*$_2$), 1.84 (1H, ddd, *J* 13.0, 9.8, 2.5, C(4)*H*$_B$), 1.93 (1H, dd, *J* 15.1, 6.6, C(2)*H*$_A$), 2.10 (1H, dd, *J* 15.1, 5.8, C(2)*H*$_B$), 2.32–2.47 (2H, m, C(2')*H*, C(5')*H*$_A$), 2.79–2.85 (1H, m, C(5')*H*$_B$), 3.31–3.39 (1H, m, C(3)*H*), 3.62 (1H, d, *J* 14.8, NC*H*$_A$H$_B$Ph), 3.75 (1H, d, *J* 14.8, NCH$_A$*H*$_B$Ph), 3.80 (1H, q, *J* 6.9, C(α')*H*), 3.91 (1H, q, *J* 6.9, C(α)*H*), 7.17–7.40 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.8 (C(α)*Me*), 21.9 (C(α')*Me*), 22.7 (*C*(4')), 28.2 (C*Me*$_3$), 30.9 (*C*(3')), 38.8 (*C*(4)), 39.0 (*C*(2)), 49.2 (*C*(5')), 50.4 (N*C*H$_2$Ph), 53.4 (*C*(3)), 58.2 (*C*(2')), 58.6 (*C*(α)), 59.8 (*C*(α')), 80.1 (*C*Me$_3$), 126.6, 126.9, 127.0 (3 × *p-Ph*), 128.1, 128.1, 128.1, 128.2, 128.2, 128.5 (3 × *o,m-Ph*), 141.8, 142.5, 144.1 (3 × *i-Ph*), 172.1 (*C*(1)); *m/z* (ESI$^+$) 527 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{35}H_{47}N_2O_2^+$ ([M+H]$^+$) requires 527.3632; found 527.3627.

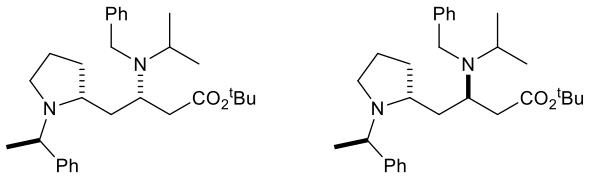
***tert*-Butyl (*R*,*R*,*R*,*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-[*N*(1')-(α'-methylbenzyl)-pyrrolidin-2'-yl]butanoate 353**



BuLi (2.3 M in hexanes, 0.85 mL, 1.96 mmol) was added dropwise to a stirred solution of (*R*)-**100**[4] (429 mg, 2.03 mmol, >99:1 er) in THF (3 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. A solution of **351** (400 mg, 1.27 mmol, 98:2 dr [(*E*):(*Z*)]) in THF (2 mL) at –78 °C was added and the resultant mixture was stirred at –78 °C for 2 h. Satd aq NH_4Cl (1 mL) was added and the reaction mixture was allowed to warm to rt, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and 10% aq citric acid (10 mL), and the organic layer was washed with satd aq $NaHCO_3$ (10 mL) and brine (10 mL), then dried and concentrated *in vacuo* to give **353** in >95:5 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 85:17:1) gave **353** as a pale

yellow oil (655 mg, 98%, >99:1 dr); $[\alpha]_D^{25}$ +45.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3027, 2971, 2932, 2872 (C–H), 1723 (C=O); δ_H (400 MHz, $CDCl_3$) 1.13 (1H, ddd, *J* 13.7, 10.9, 2.7, C(4)H_A), 1.32 (3H, d, *J* 7.0, C(α)*Me*), 1.38 (3H, obsc d, C(α')*Me*), 1.40 (9H, s, CMe_3), 1.42–1.50 (1H, m, C(3')H_A), 1.53–1.74 (3H, m, C(3')H_B, C(4')H_2), 1.75–1.83 (2H, m, C(2)H_2), 1.92 (1H, ddd, *J* 13.7, 10.8, 2.7, C(4)H_B), 2.42 (1H, app q, *J* 8.1, C(5')H_A), 2.73–2.79 (1H, m, C(5')H_B), 3.10–3.18 (1H, m, C(2')*H*), 3.34–3.41 (1H, m, C(3)*H*), 3.44 (1H, d, *J* 14.8, NC$H_A$$H_B$Ph), 3.73–3.81 (2H, m, C(α)*H*, C(α')*H*), 3.87 (1H, d, *J* 14.8, NC$H_A$$H_B$Ph), 7.16–7.40 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.8 (C(α)*Me*), 23.0 (C(α')*Me*), 23.1 (*C*(4')), 28.2 (CMe_3), 29.8 (*C*(3')), 37.9 (*C*(2)), 38.8 (*C*(4)), 50.4 (N*C*H_2Ph), 50.7 (*C*(5')), 51.8 (*C*(3)), 57.1 (*C*(α)), 57.5 (*C*(2')), 61.0 (*C*(α')), 80.1 (*C*Me$_3$), 126.7, 126.8, 127.1 (3 × *p-Ph*), 127.9, 128.2, 128.2, 128.3, 128.4, 128.5 (3 × *o*,*m-Ph*), 141.1, 142.5, 144.2 (3 × *i-Ph*), 172.1 (*C*(1)); *m/z* (ESI$^+$) 527 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{35}H_{47}N_2O_2^+$ ([M+H]$^+$) requires 527.3632; found 527.3626.

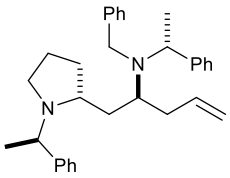
***tert*-Butyl (*R*,*R*,*R*)-3-[*N*-benzyl-*N*-isopropylamino]-4-[*N*(1')-(α-methylbenzyl)pyrrolidin-2'-yl]-butanoate and *tert*-butyl (3*S*,2'*R*,α*R*)-3-[*N*-benzyl-*N*-isopropylamino]-4-[*N*(1')-(α-methylbenzyl)-pyrrolidin-2'-yl]butanoate 354 and 355.**



BuLi (2.3 M in hexanes, 0.11 mL, 0.25 mmol) was added dropwise to a stirred solution of *N*-benzyl-*N*-isopropylamine **318** (38 mg, 0.25 mmol) in THF (0.5 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. A solution of **351** (50 mg, 0.159 mmol, 98:2 dr [(*E*):(*Z*)]) in THF (0.5 mL) at –78 °C was added and the resultant mixture was stirred at –78 °C for 2 h. Satd aq NH_4Cl (0.2 mL) was added and the reaction mixture was allowed to warm to rt, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (5 mL) and 10% aq citric acid (5 mL), and the organic layer was washed with satd aq $NaHCO_3$ (5 mL) and brine (5 mL), then dried and concentrated *in vacuo* to give a 50:50 mixture of **354** and **355**. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 85:17:1) gave a 50:50 mixture of **354** and **355** as a colourless oil (52 mg, 70%). Data for **354**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 0.96–1.06 (6H, m, NCH*Me*$_2$), 1.07–1.31 (2H, m, C(4)H_A, C(3')H_A), 1.34–1.41 (1H, m, C(3')H_B), 1.39 (3H, d, *J* 6.7, C(α)*Me*), 1.45 (9H, s, CMe_3),

1.48–1.62 (2H, m, C(4')H_2), 1.87 (1H, ddd, *J* 13.5, 10.2, 3.8, C(4)H_B), 2.10–2.18 (1H, m, C(2)H_A), 2.33–2.42 (1H, m, C(5')H_A), 2.64 (1H, dd, *J* 13.8, 3.8, C(2)H_B), 2.70 (1H, ddd, *J* 9.2, 7.4, 3.7, C(5')H_B), 2.87–2.97 (2H, m, C(2')*H*, NC*H*Me$_2$), 3.11 (1H, app tt, *J* 14.5, 3.8, C(3)*H*), 3.43 (1H, d, *J* 14.1, NCH_AH$_B$Ph), 3.70 (1H, d, *J* 14.1, NCH$_A$$H_B$Ph), 3.74 (1H, q, *J* 6.7, C(α)*H*), 7.17–7.40 (10H, m, *Ph*). Data for **355**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 0.96–1.06 (6H, m, NCH*Me*$_2$), 1.45 (3H, d, *J* 6.9, C(α)*Me*), 1.45 (9H, s, C*Me*$_3$), 1.46–1.63 (3H, m, C(4)H_A, C(3')H_A, C(4')H_A), 1.67–1.87 (3H, m, C(4)H_B, C(3')H_B, C(4')H_B), 2.10–2.18 (1H, m, C(2)H_A), 2.27–2.43 (3H, m, C(2)H_B, C(2')*H*, C(5')H_A), 2.82–2.97 (2H, m, C(5')H_B, NC*H*Me$_2$), 3.22–3.29 (1H, m, C(3)*H*), 3.62 (1H, d, *J* 14.6, NCH_AH$_B$Ph), 3.75 (1H, d, *J* 14.6, NCH$_A$$H_B$Ph), 3.84 (1H, q, *J* 6.9, C(α)*H*), 7.17–7.40 (10H, m, *Ph*). Data for mixture of **354** and **355**: ν_{max} (ATR) 3026, 2966, 2932, 2871 (C–H), 1724 (C=O); δ_C (100 MHz, $CDCl_3$) 18.8, 19.8, 21.4, 21.7, 22.5, 22.8, 22.9, 23.0, 28.2, 28.2, 29.6, 30.5, 37.4, 37.8, 39.2, 40.0, 46.8, 48.7, 48.9, 49.1, 49.3, 50.4, 52.6, 52.9, 57.5, 58.2, 59.4, 61.0, 80.1, 80.2, 126.6, 126.6, 126.7, 127.0, 127.9, 128.0, 128.0, 128.1, 128.1, 128.2, 128.6, 129.0, 141.1, 141.8, 142.1, 144.2, 172.4, 172.4; *m/z* (ESI$^+$) 465 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{45}N_2O_2^+$ ([M+H]$^+$) requires 465.3476; found 465.3475.

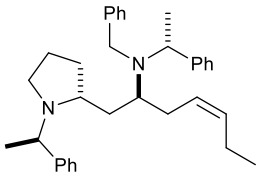
(2*S*,2'*R*,α*R*,α'*R*)-1-[*N*(1')-(α-Methylbenzyl)pyrrolidin-2'-yl]-2-[*N*-benzyl-*N*-(α'-methylbenzyl)-amino]pent-4-ene 356



DIBAL-H (1.0 M in PhMe, 0.59 mL, 0.59 mmol) was added dropwise to a stirred solution of **353** (284 mg, 0.539 mmol, >99:1 dr) in PhMe (5 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 1 h. MeOH (109 μL, 2.70 mmol) and **335**[36] (0.31 M suspension in PhMe/THF 17.4 mL, 5.39 mmol) were added sequentially, and the resultant mixture was allowed to warm to rt and stirred at rt for 16 h, then concentrated *in vacuo*. The residue was dissolved in Et_2O (40 mL) and the resultant solution was filtered through a short plug of Celite® (eluent Et_2O) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 90:9:1) gave **356** as a colourless oil (185 mg, 76%, >99:1 dr); $[\alpha]_D^{25}$ +76.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3026, 2970, 2933, 2870, 2803 (C–H), 1638, 1601, 1493, 1452 (C=C); δ_H (400 MHz, $CDCl_3$) 1.21–1.31 (2H, m, C(1)H_A, C(3')H_A), 1.27 (3H, d, *J* 7.0,

C(α')*Me*), 1.37 (3H, d, *J* 6.8, C(α)*Me*), 1.48–1.72 (4H, m, C(3)H_A, C(3')H_B, C(4')H_2), 1.72–1.80 (1H, m, C(3)H_B), 1.85 (1H, ddd, *J* 13.7, 9.9, 3.3, C(1)H_B), 2.36 (1H, app q, *J* 8.2, C(5')H_A), 2.73–2.81 (2H, m, C(2)*H*, C(5')H_B), 2.99–3.08 (1H, m, C(2')*H*), 3.57 (1H, d, *J* 15.0, NC$H_A$$H_B$Ph), 3.79 (1H, q, *J* 6.8, C(α)*H*), 3.83 (1H, q, *J* 7.0, C(α')*H*), 3.92 (1H, d, *J* 15.0, NCH$_A$$H_B$Ph), 4.81 (1H, d, *J* 17.1, C(5)H_A), 4.87 (1H, d, *J* 10.3, C(5)H_B), 5.46–5.57 (1H, m, C(4)*H*), 7.16–7.36 (13H, m, *Ph*), 7.39–7.43 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.8 (C(α')*Me*), 22.7 (C(α)*Me*), 22.9 (*C*(4')), 30.3 (*C*(3')), 35.9 (*C*(3)), 37.6 (*C*(1)), 50.1 (*C*(5')), 50.4 (N*C*H$_2$Ph), 55.0 (*C*(2)), 57.4 (*C*(α')), 57.9 (*C*(2')), 60.5 (*C*(α)), 116.1 (*C*(5)), 126.6, 126.8, 127.0 (3 × *p-Ph*), 128.1, 128.1, 128.1, 128.2, 128.4, 128.4 (3 × *o,m-Ph*), 137.4 (*C*(4)), 141.8, 143.6, 143.7 (3 × *i-Ph*); *m/z* (ESI$^+$) 453 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{41}N_2^+$ ([M+H]$^+$) requires 453.3264; found 453.3259.

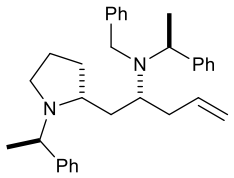
(2*S*,2'*R*,α*R*,α'*R*,*Z*)-1-[*N*(1')-(α-Methylbenzyl)pyrrolidin-2'-yl]-2-[*N*-benzyl-*N*-(α'-methylbenzyl)-amino]hept-4-ene 357



DIBAL-H (1.0 M in PhMe, 0.53 mL, 0.53 mmol) was added dropwise to a stirred solution of **353** (255 mg, 0.484 mmol, >99:1 dr) in PhMe (5 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 1 h. MeOH (98 μL, 2.42 mmol) and **340**[39] (0.31 M suspension in PhMe/THF 15.6 mL, 4.84 mmol) were added sequentially, and the resultant mixture was allowed to warm to rt and stirred at rt for 16 h, then concentrated *in vacuo*. The residue was dissolved in Et_2O (40 mL) and the resultant solution was filtered through a short plug of Celite® (eluent Et_2O) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 90:9:1) gave **357** as a colourless oil (174 mg, 75%, >95:5 dr [(*Z*):(*E*)]); $[\alpha]_D^{25}$ +78.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3061, 3026, 2966, 2932, 2872 (C–H), 1602, 1493, 1453 (C=C); δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.5, C(7)H_3), 1.16–1.30 (2H, m, C(1)H_A, C(3')H_A), 1.27 (3H, d, *J* 7.0, C(α')*Me*), 1.38 (3H, d, *J* 6.8, C(α)*Me*), 1.51–1.65 (3H, m, C(3')H_B, C(4')H_2), 1.72–1.95 (5H, m, C(1)H_B, C(3)H_2, C(6)H_2), 2.39 (1H, app q, *J* 7.9, C(5')H_A), 2.69–2.81 (2H, m, C(2)*H*, C(5')H_B), 2.98–3.06 (1H, m, C(2')*H*), 3.60 (1H, d, *J* 15.1, NC$H_A$$H_B$Ph), 3.80 (1H, q, *J* 6.8, C(α)*H*), 3.86 (1H, q, *J* 7.0, C(α')*H*), 3.96 (1H, d, *J* 15.1, NCH$_A$$H_B$Ph), 5.03–5.12 (1H, m, C(4)*H*),

5.24–5.32 (1H, m, C(5)*H*), 7.18–7.37 (13H, m, *Ph*), 7.40–7.43 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.3 (*C*(7)), 20.8 (*C*(6)), 21.1 (C(α')*Me*), 22.6 (C(α)*Me*), 22.8 (*C*(4')), 28.7 (*C*(3)), 30.2 (*C*(3')), 37.5 (*C*(1)), 50.0 (*C*(5')), 50.5 (N*C*H_2Ph), 55.8 (*C*(2)), 57.8 (*C*(α')), 57.8 (*C*(2')), 60.3 (*C*(α)), 126.5, 126.8, 126.9 (3 × *p-Ph*), 127.5 (*C*(4)), 128.0, 128.1, 128.1, 128.2, 128.3, 128.4 (3 × *o,m-Ph*), 132.5 (*C*(5)), 142.1, 143.7, 144.3 (3 × *i-Ph*); *m/z* (ESI$^+$) 481 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{34}H_{45}N_2^+$ ([M+H]$^+$) requires 481.3577; found 481.3574.

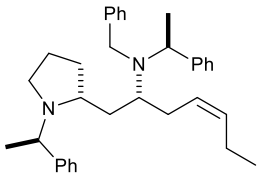
(2*R*,2'*R*,α*S*,α'*R*)-1-[*N*(1')-(α-Methylbenzyl)pyrrolidin-2'-yl]-2-[*N*-benzyl-*N*-(α'-methylbenzyl)-amino]pent-4-ene 358



DIBAL-H (1.0 M in PhMe, 0.65 mL, 0.65 mmol) was added dropwise to a stirred solution of **352** (200 mg, 0.380 mmol, >99:1 dr) in PhMe (5 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 1 h. MeOH (46 μL, 1.1 mmol) and **335**[36] (0.31 M suspension in PhMe/THF, 6.1 mL, 1.9 mmol) were added sequentially, and the resultant mixture was allowed to warm to rt and stirred at rt for 16 h, then concentrated *in vacuo*. The residue was dissolved in Et_2O (40 mL) and the resultant solution was filtered through a short plug of Celite® (eluent Et_2O) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 85:17:1) gave **358** as a colourless oil (68 mg, 40%, >99:1 dr); $[\alpha]_D^{25}$ +56.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3026, 2968, 2932, 2872 (C–H), 1638, 1602, 1493, 1452 (C=C); δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, *J* 6.9, C(α)*Me*), 1.43 (3H, d, *J* 6.8, C(α')*Me*), 1.42–1.48 (1H, m, C(3')H_A), 1.52–1.76 (4H, m, C(1)H_A, C(3')H_B, C(4')H_2), 1.82–1.90 (2H, m, C(1)H_B, C(3)H_A), 1.99–2.08 (1H, m, C(3)H_B), 2.36–2.48 (2H, m, C(2')*H*, C(5')H_A), 2.62–2.70 (1H, m, C(2)*H*), 2.81–2.87 (1H, m, C(5')H_B), 3.74 (1H, d, *J* 14.7, NC$H_A$$H_B$Ph), 3.79 (1H, d, *J* 14.7, NC$H_A$$H_B$Ph), 3.83 (1H, q, *J* 6.8, C(α')*H*), 3.97 (1H, q, *J* 6.9, C(α)*H*), 4.80–4.86 (2H, m, C(5)H_2), 5.52 (1H, ddt, *J* 15.8, 11.4, 7.0, C(4)*H*), 7.16–7.35 (13H, m, *Ph*), 7.39–7.43 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.9 (C(α)*Me*), 21.9 (C(α')*Me*), 22.4 (*C*(4')), 30.5 (*C*(3')), 36.7 (*C*(3)), 37.6 (*C*(1)), 48.8 (*C*(5')), 50.2 (N*C*H_2Ph), 55.4 (*C*(2)), 57.1 (*C*(α)), 58.5 (*C*(2')), 59.3 (*C*(α')), 115.3 (*C*(5)), 126.6, 126.7, 127.0 (3 × *p-Ph*), 128.0, 128.0, 128.1,

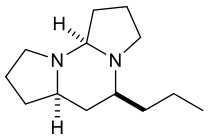
128.2, 128.3, 128.5 (3 × *o*,*m*-*Ph*), 138.1 (*C*(4)), 142.1, 142.3, 144.8 (3 × *i*-*Ph*); *m/z* (ESI$^+$) 453 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{41}N_2^+$ ([M+H]$^+$) requires 453.3264; found 453.3259.

(2*R*,2'*R*,α*S*,α'*R*,*Z*)-1-[*N*(1')-(α-Methylbenzyl)pyrrolidin-2'-yl]-2-[*N*-benzyl-*N*-(α'-methylbenzyl)-amino]hept-4-ene 359

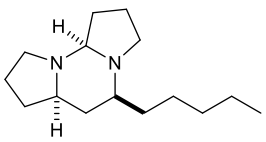


DIBAL-H (1.0 M in PhMe, 1.0 mL, 1.0 mmol) was added dropwise to a stirred solution of **352** (242 mg, 0.459 mmol, >99:1 dr) in PhMe (5 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 1 h. MeOH (93 μL, 2.3 mmol) and **340**[39] (0.31 M suspension in PhMe/THF, 14.8 mL, 4.59 mmol) were added sequentially, and the resultant mixture was allowed to warm to rt and stirred at rt for 16 h, then concentrated *in vacuo*. The residue was dissolved in Et_2O (40 mL) and the resultant solution was filtered through a short plug of Celite® (eluent Et_2O) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O/NH_4OH, 85:17:1) gave **359** as a pale yellow oil (106 mg, 48%, >95:5 dr [(*Z*):(*E*)]); $[\alpha]_D^{25}$ +53.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3025, 2964, 2932, 2872 (C–H), 1602, 1493, 1453 (C=C); δ_H (400 MHz, $CDCl_3$) 0.86 (3H, t, *J* 7.5, C(7)H_3), 1.32 (3H, d, *J* 6.8, C(α)*Me*), 1.41–1.47 (1H, m, C(1)H_A), 1.44 (3H, d, *J* 6.8, C(α')*Me*), 1.53–1.77 (4H, m, C(1)H_B, C(3')H_A, C(4')H_2), 1.79–1.92 (4H, m, C(3)H_A, C(6)H_2, C(3')H_B), 1.93–2.03 (1H, m, C(3)H_B), 2.36–2.45 (2H, m, C(2')*H*, C(4')H_A), 2.58–2.66 (1H, m, C(2)*H*), 2.84 (1H, ddd, *J* 9.1, 7.8, 2.4, C(4')H_B), 3.73 (1H, d, *J* 14.8, NCH_AH$_B$Ph), 3.77 (1H, d, *J* 14.8, NCH$_A$$H_B$Ph), 3.85 (1H, q, *J* 6.8, C(α')*H*), 3.99 (1H, q, *J* 6.8, C(α)*H*), 5.09 (1H, app dtt, *J* 10.8, 6.8, 1.4, C(4)*H*), 5.23 (1H, app dtt, *J* 10.8, 7.1, 1.6, C(5)*H*), 7.15–7.41 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.2 (*C*(7)), 18.0 (C(α)*Me*), 20.9 (*C*(6)), 21.9 (C(α')*Me*), 22.4 (*C*(4')), 29.7 (*C*(3)), 30.6 (*C*(1)), 37.4 (*C*(3')), 48.7 (*C*(5')), 50.1 (N*C*H$_2$Ph), 55.9 (*C*(2)), 57.0 (*C*(α)), 58.6 (*C*(2')), 59.2 (*C*(α')), 126.6, 126.6, 127.0 (3 × *p*-*Ph*), 128.0, 128.1, 128.2, 128.2, 128.2, 128.3, 128.6 (*C*(4), 3 × *o*,*m*-*Ph*), 131.7 (*C*(5)), 142.2, 142.3, 145.0 (3 × *i*-*Ph*); *m/z* (ESI$^+$) 481 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{34}H_{45}N_2^+$ ([M+H]$^+$) requires 481.3577; found 481.3571.

(5*S*,6a*R*,10a*S*)-5-Propyldecahydrodipyrrolo[1,2-*a*:1',2'-*c*]pyrimidine [(+)-tetraponerine 2] 103



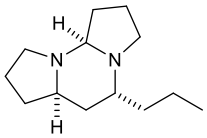
Palladium black (37 mg, 20% w/w) was added to a stirred, degassed solution of **356** (183 mg, 0.404 mmol, >99:1 dr) in MeOH/H_2O/AcOH (10:1:1, 2 mL). The resultant mixture was stirred under an atmosphere of H_2 (5 atm) at rt for 48 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH/H_2O/AcOH, 10:1:1) and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (2 mL), then K_2CO_3 (168 mg, 1.21 mmol) and 4-bromobutanal **293** (123 mg, 0.81 mmol) were added to the resultant solution. The reaction mixture was stirred at rt for 2 h, then H_2O (2 mL) and satd aq $NaHCO_3$ (10 mL) were added. The reaction mixture was then extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Me_2CO/NH_4OH, 90:9:1) gave **103** as a colourless oil (31 mg, 37% from **356**, >99:1 dr); $[\alpha]_D^{25}$ +44.2 (*c* 1.0 in $CHCl_3$); {lit.[41] $[\alpha]_D^{20}$ +36 (*c* 1.79 in $CHCl_3$); lit.[45] $[\alpha]_D^{20}$ +47 (*c* 0.232 in $CHCl_3$)}; ν_{max} (ATR) 2957, 2931, 2871, 2786 (C–H); δ_H (400 MHz, C_6D_6) 0.92 (3H, t, *J* 7.2, C(3')H_3), 1.27–1.83 (14H, m, C(1)H_2, C(2)H_2, C(6)H_2, C(7)H_2, C(8)H_2, C(1')H_2, C(2')H_2), 1.83–1.97 (2H, m, C(9)H_A, C(6a)*H*), 2.29–2.36 (1H, m, C(3)H_A), 2.39–2.46 (1H, m, C(5)*H*), 2.86 (1H, app t, *J* 5.3, C(10a)*H*), 2.93 (1H, app td, *J* 8.5, 2.5, C(9)H_B), 3.01–3.07 (1H, m, C(3)H_B); δ_C (100 MHz, C_6D_6) 14.7 (*C*(3')), 19.3 (*C*(2')), 21.0 (*C*(2)), 21.3 (*C*(8)), 29.3 (*C*(1)), 30.6 (*C*(7)), 33.4 (*C*(6)), 37.0 (*C*(1')), 45.8 (*C*(3)), 49.2 (*C*(9)), 59.4 (*C*(5)), 64.2 (*C*(6a)), 83.4 (*C*(10a)); *m/z* (ESI$^+$) 209 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{25}N_2^+$ ([M+H]$^+$) requires 209.2012; found 209.2012.



(5*S*,6a*R*,10a*S*)-5-Pentyldecahydrodipyrrolo[1,2-*a*:1',2'-*c*]pyrimidine [(+)-tetraponerine 6] 107

Palladium black (31 mg, 20% w/w) was added to a stirred, degassed solution of **357** (155 mg, 0.322 mmol, >95:5 dr [(*E*):(*Z*)]) in MeOH/H_2O/AcOH (10:1:1, 2 mL). The resultant mixture was stirred under

an atmosphere of H_2 (5 atm) at rt for 48 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH/H_2O/AcOH, 10:1:1) and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (2 mL), then K_2CO_3 (134 mg, 0.970 mmol) and 4-bromobutanal **293** (98 mg, 0.65 mmol) were added to the resultant solution. The reaction mixture was stirred at rt for 2 h, then H_2O (2 mL) and satd aq $NaHCO_3$ (10 mL) were added. The reaction mixture was then extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Me_2CO/NH_4OH, 90:9:1) gave **107** as a pale yellow oil (41 mg, 54% from **357**, >99:1 dr); $[\alpha]_D^{25}$ +66.3 (*c* 1.0 in $CHCl_3$); {lit.[37] for a sample isolated from the natural source $[\alpha]_D^{20}$ +35 (*c* 0.15 in $CHCl_3$); lit.[45] $[\alpha]_D^{20}$ +40 (*c* 0.75 in $CHCl_3$)}; ν_{max} (ATR) 2955, 2928, 2857, 2785 (C–H); δ_H (400 MHz, C_6D_6) 0.91 (3H, t, *J* 7.0, C(5')H_3), 1.23–1.54 (11H, m, C(6)H_2, C(7)H_A, C(8)H_A, C(1')H_A, C(2')H_2, C(3')H_2, C(4')H_2), 1.54–1.98 (9H, m, C(1)H_2, C(2)H_2, C(6a)*H*, C(7)H_B, C(8)H_B, C(9)H_A, C(1')H_B), 2.31–2.38 (1H, m, C(3)H_A), 2.39–2.46 (1H, m, C(5)*H*), 2.87 (1H, app t, *J* 5.3, C(10a)*H*), 2.94 (1H, app td, *J* 8.5, 2.5, C(9)H_B), 3.03–3.10 (1H, m, C(3)H_B); δ_C (100 MHz, C_6D_6) 14.4 (*C*(5')), 21.0 (*C*(2)), 21.3 (*C*(8)), 23.2 (*C*(4')), 25.9 (*C*(2')), 29.3 (*C*(1)), 30.6 (*C*(7)), 32.7 (*C*(3')), 33.5 (*C*(6)), 34.8 (*C*(1')), 45.9 (*C*(3)), 49.2 (*C*(9)), 59.7 (*C*(5)), 64.2 (*C*(6a)), 83.5 (*C*(10a)); *m/z* (ESI^+)

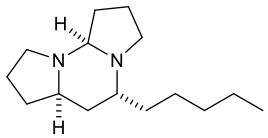


237 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{15}H_{29}N_2^+$ ($[M+H]^+$) requires 237.2325; found 237.2326.

(5*R*,6a*R*,10a*S*)-5-Propyldecahydrodipyrrolo[1,2-*a*:1',2'-*c*]pyrimidine [(+)-tetraponerine 1] 102

Palladium black (29 mg, 20% w/w) was added to a stirred, degassed solution of **358** (145 mg, 0.320 mmol, >99:1 dr) in MeOH/H_2O/AcOH (10:1:1, 2 mL). The resultant mixture was stirred under an atmosphere of H_2 (5 atm) at rt for 48 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH/H_2O/AcOH, 10:1:1) and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (2 mL), then K_2CO_3 (133 mg, 0.962 mmol) and 4-bromobutanal **293** (96 mg, 0.64 mmol) were added to the resultant solution. The reaction mixture was stirred at rt for 2 h, then H_2O (2 mL) and satd aq $NaHCO_3$ (10 mL) were added. The reaction mixture was then extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column

chromatography (eluent 30–40 °C petrol/Me_2CO/NH_4OH, 90:9:1) gave **102** as a colourless oil (10 mg, 15% from **358**, >99:1 dr); $[\alpha]_D^{25}$ +14.4 (*c* 0.13 in $CHCl_3$); {lit.[41] $[\alpha]_D^{20}$ +11 (*c* 0.14 in $CHCl_3$); lit.[45] $[\alpha]_D^{20}$ +14 (*c* 0.498 in $CHCl_3$)}; ν_{max} (ATR) 2927 (C–H); δ_H (400 MHz, C_6D_6) 0.96 (3H, t, *J* 7.3, C(3')H_3), 1.23–1.45 (6H, m, C(1)H_A, C(6)H_A, C(7)H_A, C(8)H_A, C(1')H_A, C(2')H_A), 1.49–1.69 (3H, m, C(7)H_B, C(8)H_B, C(2')H_B), 1.69–1.91 (6H, m, C(1)H_B, C(2)H_2, C(6)H_B, C(9)H_A, C(1')H_B), 1.91–2.02 (1H, m, C(6a)*H*), 2.82–2.91 (3H, m, C(3)H_A, C(5)*H*, C(9)H_B), 3.21 (1H, app q, *J* 7.7, C(3)H_B), 3.48, (1H, app t, *J* 2.3, C(10a)*H*); δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.3, C(3')H_3), 1.24–1.43 (3H, m, C(7)H_A, C(2')H_2), 1.43–1.96 (12H, m, C(1)H_2, C(2)H_2, C(6)H_2, C(7)H_B, C(8)H_2, C(9)H_A, C(1')H_2), 2.00–2.10 (1H, m, C(6a)*H*), 2.82 (1H, td, *J* 7.9, 3.0, C(3)H_A), 2.91–3.01 (2H, m, C(5)*H*, C(9)H_B), 3.08 (1H, app q, *J* 7.9, C(3)H_B), 3.39 (1H, app d, *J* 3.7, C(10a)*H*); δ_C (100 MHz, C_6D_6) 14.5 (*C*(3')), 20.4 (*C*(8)), 20.8 (*C*(2')), 22.0 (*C*(2)), 30.1, 30.1 (*C*(1), *C*(6)), 31.6 (*C*(7)), 35.4 (*C*(1')), 50.0 (*C*(9)), 51.0 (*C*(3)), 53.7 (*C*(5)), 58.3 (*C*(6a)), 76.5 (*C*(10a)); δ_C (100 MHz, $CDCl_3$) 14.3 (*C*(3')), 20.1 (*C*(8)), 20.6 (*C*(2')), 21.3 (*C*(2)), 29.4 (*C*(6)), 29.7 (*C*(1)), 31.0 (*C*(7)), 34.0 (*C*(1')), 50.1 (*C*(9)), 50.3 (*C*(3)), 53.6 (*C*(5)), 58.3 (*C*(6a)), 76.9 (*C*(10a));[46] *m/z* (ESI^+) 209 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{13}H_{25}N_2^+$ ($[M+H]^+$) requires 209.2012;



found 209.2013.

(5*R*,6a*R*,10a*S*)-5-Pentyldecahydrodipyrrolo[1,2-*a*:1',2'-*c*]pyrimidine [(+)-tetraponerine 5] 106

Palladium black (31 mg, 20% w/w) was added to a stirred, degassed solution of **359** (154 mg, 0.330 mmol) in MeOH/H_2O/AcOH (10:1:1, 2 mL). The resultant mixture was stirred under an atmosphere of H_2 (5 atm) at rt for 48 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH/H_2O/AcOH, 10:1:1) and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (2 mL), then K_2CO_3 (137 mg, 0.991 mmol) and 4-bromobutanal **293** (99 mg, 0.66 mmol) were added to the resultant solution. The reaction mixture was stirred at rt for 2 h, then H_2O (2 mL) and satd aq $NaHCO_3$ (10 mL) were added. The reaction mixture was then extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Me_2CO/NH_4OH, 90:9:1) gave **106** as a colourless oil (11 mg, 14% from **359**,

>99:1 dr); $[\alpha]_D^{25}$ +12.4 (*c* 0.13 in $CHCl_3$); {lit.[37] for a sample isolated from the natural source $[\alpha]_D^{20}$ +10 (*c* 0.2 in $CHCl_3$); lit.[41] $[\alpha]_D^{20}$ +10 (*c* 0.24 in $CHCl_3$); lit.[45] $[\alpha]_D^{20}$ +14 (*c* 1.6 in $CHCl_3$)}; ν_{max} (ATR) 2980, 2930 (C–H); δ_H (400 MHz, C_6D_6) 0.93 (3H, t, *J* 6.8, C(5')H_3), 1.28–1.46 (10H, m, C(1)H_A, C(6)H_A, C(7)H_A, C(8)H_A, C(1')H_A, C(2')H_A, C(3')H_2, C(4')H_2), 1.50–1.69 (3H, m, C(7)H_B, C(8)H_B, C(2')H_B), 1.69–1.92 (6H, m, C(1)H_B, C(2)H_2, C(6)H_B, C(9)H_A, C(1')H_B), 1.94–2.01 (1H, m, C(6a)*H*), 2.83–2.92 (3H, m, C(3)H_A, C(5)*H*, C(9)H_B), 3.23 (1H, app q, *J* 7.8, C(3)H_B), 3.51 (1H, app t, *J* 2.1, C(10a)*H*); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.8, C(5')H_3), 1.22–1.42 (7H, m, C(7)H_A, C(2')H_2, C(3')H_2, C(4')H_2), 1.43–1.96 (12H, m, C(1)H_2, C(2)H_2, C(6)H_2, C(7)H_B, C(8)H_2, C(9)H_A, C(1')H_2), 2.01–2.10 (1H, m, C(6a)*H*), 2.82 (1H, app td, *J* 8.0, 2.8, C(3)H_A), 2.89–3.01 (2H, m, C(5)*H*, C(9)H_B), 3.08 (1H, app q, *J* 8.0, C(3)H_B), 3.39 (1H, app d, *J* 3.5, C(10a)*H*); δ_C (100 MHz, C_6D_6) 14.4 (*C*(5')), 20.4 (*C*(8)), 22.0 (*C*(2)), 23.2 (*C*(4')), 27.5 (*C*(2')), 30.1, 30.2 (*C*(1), *C*(6)), 31.6 (*C*(7)), 32.5 (*C*(3')), 33.2 (*C*(1')), 50.0 (*C*(9)), 51.1 (*C*(3)), 54.1 (*C*(5)), 58.3 (*C*(6a)), 76.5 (*C*(10a)); δ_C (100 MHz, $CDCl_3$) 14.3 (*C*(5')), 20.2 (*C*(8)), 21.3 (*C*(2)), 22.8 (*C*(4')), 27.2 (*C*(2')), 29.4 (*C*(6)), 29.7 (*C*(1)), 31.0 (*C*(7)), 31.7 (*C*(1')), 32.1 (*C*(3')), 50.0 (*C*(9)), 50.3 (*C*(3)), 53.9 (*C*(5)), 58.3 (*C*(6a)), 76.8 (*C*(10a));[46] *m/z* (ESI^+) 237 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{15}H_{29}N_2^+$ ($[M+H]^+$) requires 237.2325; found 237.2324.

5.5 References and notes

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[35] Piperidine **308** was taken from lab stock.
[36] The solution of **335** was prepared on the requisite scale by the addition of KHMDS (0.5 M in PhMe, 1.0 equiv) to stirred suspension of methyltriphenylphosponium iodide (1.0 M in THF, 1.0 equiv) at rt and the resultant suspension was stirred at rt for 1 h.
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[39] The solution of **340** was prepared on the requisite scale by the addition of KHMDS (0.5 M in PhMe, 1.0 equiv) to stirred suspension of propyltriphenylphosponium bromide (1.0 M in THF, 1.0 equiv) at rt and the resultant suspension was stirred at rt for 1 h.
[40] The solution of **340** was prepared on the requisite scale by the addition of BuLi (2.30 M in hexanes, 1.0 equiv) to propyltriphenylphosponium bromide (1.0 equiv) at rt and the resultant suspension was stirred at rt for 1 h.
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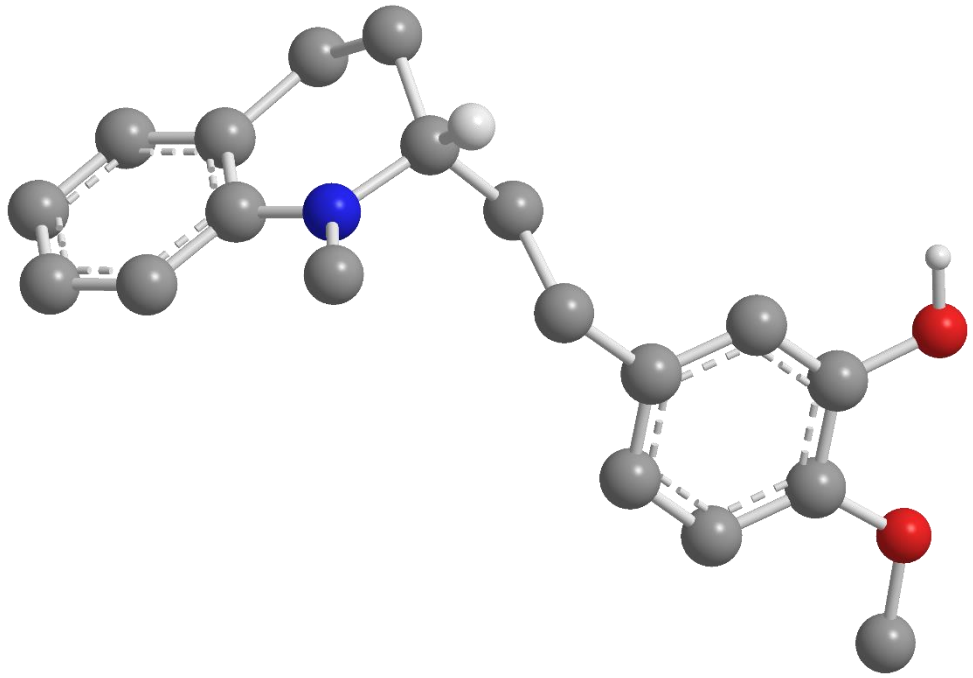
[46] For both (+)-tetraponerine 1 **102** and (+)-tetraponerine 5 **106**, the resonance corresponding to *C*(10a) in their ^{13}C NMR spectra (in $CDCl_3$) was partially obscured by the solvent peak.

Appendix 1: X-Ray Crystal Structure Data for (*S*)-10

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 10

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 **10** [$C_{19}H_{23}NO_2$]: M = 297.4, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 6.61954(8) Å, b = 13.75433(17) Å, c = 16.9835(2) Å, V = 1546.30(3) Å^3, Z = 4, μ = 0.648 mm^{-1}, colourless block, crystal dimensions = 0.26 × 0.27 × 0.30 mm^3. A total of 3210 unique reflections were measured for 4 < θ < 76 and 2528 reflections were used in the refinement. The final parameters were wR_2 = 0.078 and R_1 = 0.031 [I>–3.0σ(I)], with Flack enantiopole = –0.1(2).[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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