The use of functionalised lithium amides in the total synthesis of alkaloids

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by

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The work described in this thesis was carried out in the Chemistry Research Laboratory, University of Oxford from August 2009 until September 2012, 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.

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Abstract

James A. Lee D.Phil. Thesis
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This thesis is concerned with the application of the conjugate addition of functionalised lithium amides in the asymmetric syntheses of (−)-morphine and all members of the homalium alkaloids.

Chapter 1 introduces the conjugate addition reaction as an important bond forming reaction, and explores its utility in the asymmetric synthesis of a variety of natural products. The conjugate addition of secondary lithium amides derived from α-methylbenzylamine is discussed, along with its application to the asymmetric synthesis of alkaloids.

Chapter 2 describes two distinct attempts towards the asymmetric synthesis of (−)-morphine, both reliant upon the lithium amide conjugate addition and an intramolecular Diels-Alder reaction to set the five required stereogenic centres. The use of the novel and highly functionalised reagent lithium (*R*)-*N*-[2′-(7-methoxybenzofuran-3-yl)ethyl]-*N*-(α-methylbenzyl)amide and its derivatives is reported.

Chapter 3 focuses on the use of the novel reagent lithium (*R*)-*N*-(3-chloroprop-1-yl)-*N*-(α-methylbenzyl)amide and its derivatives in the asymmetric synthesis of two of the homalium alkaloids, (−)-(*S*,*S*)-homaline and (−)-(*R*,*R*)-hopromine, culminating in the most efficient syntheses of these alkaloids to date. Further, a sample of the (4′*R*,4″*S*)-diastereoisomer of hopromine was synthesised, serving to confirm the proposed absolute configuration within natural (−)-(*R*,*R*)-hopromine.

Chapter 4 extends the methodology developed in chapter 3 to the asymmetric synthesis of all possible diastereoisomers of the remaining homalium alkaloids, (−)-hopromalinol and (−)-hoprominol. These syntheses were used to propose the absolute configurations within these alkaloids, and therefore represented the first asymmetric syntheses of natural (−)-(4′*S*,4″*R*,2‴*R*)-hopromalinol and (−)-(*R*,*R*,*R*)-hoprominol.

Chapter 5 contains full experimental procedures and characterisation data for all compounds synthesised in Chapters 2, 3 and 4.

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Abbreviations

~	Approximately
(±)	Racemic
$[\alpha]_D$	Specific rotation
(*R*)	Rectus
(*E*)	Entgegen
(*S*)	Sinister
(*Z*)	Zusammen
[P]	Protecting group
δ_C	^{13}C NMR chemical shift
δ_H	^{1}H NMR chemical shift
µ	Experimental absorption coefficient
µL	Microlitres
µmol	Micromoles
µwave	Microwave irradiation
ν_{max}	IR absorption maximum
σ	Standard deviation
^{13}C NMR	Carbon NMR
^{1}H NMR	Proton NMR
Å	Angstroms
AB	AB system
Ac	Acetyl
app	Apparent
aq	Aqueous
Ar	Aromatic
atm	Atmosphere(s)
ATR	Attentuated total reflectance
BHT	3,5-Di-*tert*-butyl-4-hydroxytoluene
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
Boc-ON	*tert*-Butyl (2-cyano-2-phenylvinyl)carbonate
bp	Boiling point
br	Broad
Bu	Butyl
Bz	Benzoyl

C	Celsius
c	Concentration
CAN	Ceric ammonium nitrate
Cbz	Carboxybenzyl
CI^+	Positive chemical ionisation
cm	Centimetres
cm^{-1}	Wavenumber
CoAS	Coenzyme A
conc.	Concentrated
COSY	Correlation spectroscopy
Cp	Cyclopentadienyl
Cy	Cyclohexyl
d	Doublet
dba	Dibenzylideneacetone
DEAD	Diethyl azodicarboxylate
dec	Decomposes
deg	Degrees
DIBAL-H	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMG	*N*,*N*-Dimethylglycine
DMPU	*N*,*N′*-Dimethylpropyleneurea
DMSO	Dimethylsulfoxide
dppp	1,3-Bis(diphenylphosphino)propane
dr	Diastereoisomeric ratio
ent	Enantiomer
er	Enantiomeric ratio
ESI^+	Postive electrospray ionisation
Et	Ethyl
eq	Equivalents
EWG	Electron withdrawing group
FI^+	Positive field ionisation
g	Grams
h	Hours
HMBC	Heteronuclear multiple bond correlation

HMPA	Hexamethylphosphoramide
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
HMQC	Heteronuclear multiple quantum correlation
i	Ipso
^{i}Bu	Isobutyl
IBX	2-Iodoxybenzoic acid
Ipc	Diisopinocampheyl
^{i}Pr	Isopropyl
IUPAC	International Union of Pure and Applied Chemistry
J	Coupling constant
K	Kelvin
KHMDS	Potassium bis(trimethylsilyl)amide
L	Litres
LCT	Liquid chromatography time of flight
LDA	Lithium diisopropylamide
lit.	Literature
M	Molar
M	Cell formula weight
m/z	Mass to charge ratio
Me	Methyl
MeOH-d_4	Deuterated methanol
MHz	Megahertz
min	Minute(s)
mol	Moles
MOM	Methoxymethyl
mp	Melting point
Ms	Methanesulfonyl
NADP$^+$	Nicotinamide adenine dinucleotide phosphate
NADPH	Nicotinamide adenine dinucleotide phosphate, reduced form
NOESY	Nuclear Overhauser Effect Spectroscopy
Nu	Nucleophile
o	Ortho
p	Para
Ph	Phenyl

PhMe-d_8	Deuterated toluene
Piv	Pivaloyl
PMP	*p*-Methoxyphenyl
PPA	Polyphosphoric acid
ppm	Parts per million
q	Quartet
quant	Quantitative
quin	Quintet
ref	Reference
rt	Room temperature
s	Singlet
SAH	*S*-Adenosyl homocysteine
SAM	*S*-Adenosyl methionine
sec	Second(s)
sol	Solvent
t	Triplet
TBAC	Tetrabutylammonium chloride
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
^{t}Bu	*tert*-Butyl
TEBAC	Triethylbenzylammonium chloride
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl
ToF	Time of flight
Ts	*p*-Toluenesulfonyl
UV	Ultraviolet
v	Volume
V	Unit cell volume
Z	Cell formula units

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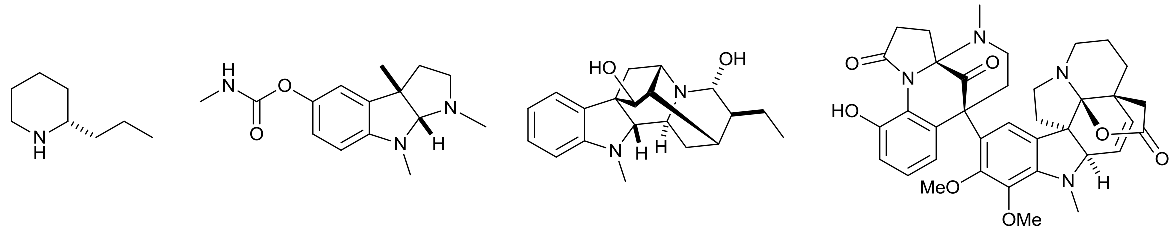
Chapter 1: Introduction

This thesis describes the conjugate addition of enantiopure lithium amides for the synthesis of complex alkaloids.

1.1 Alkaloids

Alkaloids may be defined as basic nitrogen containing compounds, commonly heterocyclic, that originate mostly in the plant kingdom, but do not exclude those of animal origin. Although the distinction is not clear, amino acids, peptides, proteins, nucleotides, nucleic acids and antibiotics are not normally regarded as alkaloids.[1] Alkaloids vary extensively in their intricacy, from the relatively simple hemlock alkaloid (+)-coniine **1** (the principal poison found in *Conium maculatum*),[2] to the increasingly complex alkaloids (−)-physostigmine **2** (a parasympathomimetic drug isolated from calabar bean, used to treat myasthenia gravis),[3] (+)-ajmaline **3** (an antiarrhythmic agent isolated from the roots of *Rauwolfia serpentina*)[4] and (+)-haplophytine **4** (the active ingredient in an insecticide used by the Aztecs, isolated from *Haplophyton cimicidum*)[5] (Figure 1).

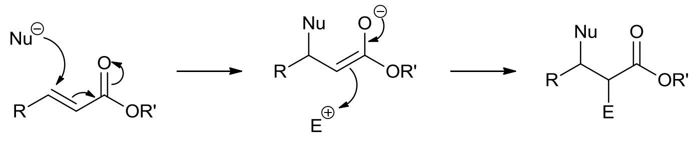


(+)-coniine **1** (–)-physostigmine **2** (+)-ajmaline **3** (+)-haplophytine **4**

Figure 1. Representative alkaloids **1**-**4**.

1.2 The conjugate addition reaction

The conjugate addition reaction, first reported by Sokoloff *et al*. in 1874,[6] involves the 1,4-addition of a nucleophile to an electrophilic olefin, for example an α,β-unsaturated ester, as in **5**, with reaction of the resultant enolate **6** with an electrophile to give the conjugate addition adduct **7** (Figure 2).



5 **6** **7**

Figure 2. The conjugate addition reaction.

The broad scope of this reaction is emphasised by the diversity of nucleophiles, olefins and electrophiles that partake in the reaction. Typical nucleophiles comprise of an array of organometallic reagents,[7] amines,[8] metal amides,[9] alkoxides,[10] phosphines,[11] thiols[12] and halides.[13] Compatible olefin activating groups incorporate aldehydes,[14] ketones,[15] esters,[16] amides,[17] nitriles,[18] nitro groups,[19] sulfones[20] and phosphonium salts.[21] Exemplary electrophiles include a proton,[22] carbonyl compounds,[23] electrophilic sources of oxygen,[24] nitrogen[25] or fluorine,[26] and alkyl halides.[27]

1.3 Asymmetry in the conjugate addition reaction

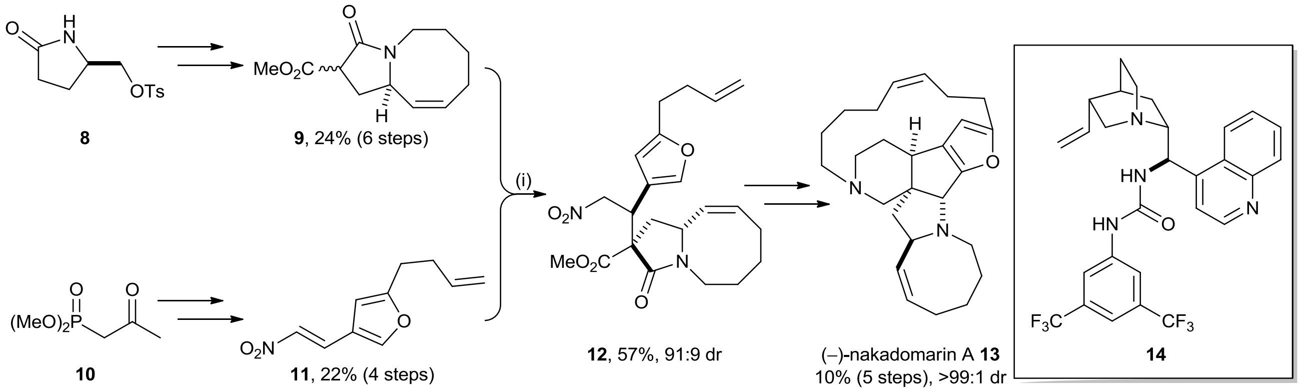
Depending on the nature of the nucleophile, electrophilic olefin, and electrophile, it is possible to form up to three new stereogenic centres following a conjugate addition reaction. Control over the configuration of these newly formed stereogenic centres therefore offers a powerful tool for asymmetric synthesis, and this area has been extensively investigated.[28] There are three main methods that have been employed to control the stereochemical outcome of the reaction: (i) conjugate addition of an achiral nucleophile to an achiral olefin in a chiral environment (for example, reaction in the presence of a chiral, non-racemic catalyst); (ii) conjugate addition of an achiral nucleophile to a chiral, non-racemic olefin; and (iii) conjugate addition of a chiral, non-racemic nucleophile to an achiral olefin. All of these methods have found use as stereodefining steps in the asymmetric synthesis of a variety of natural products and other enantiopure compounds.

1.3.1 Use of asymmetric catalysis in the conjugate addition reaction and its application in synthesis

Asymmetric catalysis represents a powerful tool for stereocontrol in the conjugate addition reaction as it requires neither the nucleophile nor the electrophilic olefin to contain any stereochemical information. There are three main methods to achieve asymmetric catalysis in the conjugate addition reaction depending on how the catalyst interacts with the components of the reaction.

1.3.1.1 Simultaneous catalytic activation of the nucleophile and electrophilic olefin

The use of a bifunctional catalyst that simultaneously activates both the nucleophilic and electrophilic components of the conjugate addition reaction is an elegant way to impart stereocontrol. The use of such a catalyst has been demonstrated by Dixon *et al.*[19] in their synthesis of (−)-nakadomarin A **13**, in which the key step was the conjugate addition of 1,3-dicarbonyl **9** to nitroolefin **11** using the cinchona derived organocatalyst **14**. 1,3-Dicarbonyl **9** was synthesised in 24% yield over six steps from tosylate **8**, whilst nitroolefin **11** was synthesised in 22% yield over four steps from phosphonate **10**. Reaction of **9** and **11** in the presence of **14** gave the desired conjugate addition adduct **12** in 57% yield and 91:9 dr. Further elaboration of **12** gave (−)-nakadomarin A **13** in 10% yield over five steps, and >99:1 dr (Scheme 1).



Scheme 1. *Reagents and conditions*: (i) **14** (15 mol%), PhMe, 30 °C, 8 days.

A transition state model has been proposed to rationalise the diastereoselectivity observed in this reaction. Hydrogen bonding between the nitro group within **11** and the urea group present in **14** serves to activate nitroolefin **11** towards nucleophilic attack. Simultaneously, 1,3-dicarbonyl **9** is deprotonated by the amine within **14**, and the corresponding enolate hydrogen bonds to the ammonium species, delivering the enolate to the *Re*-face of **11** (Figure 3).[29]

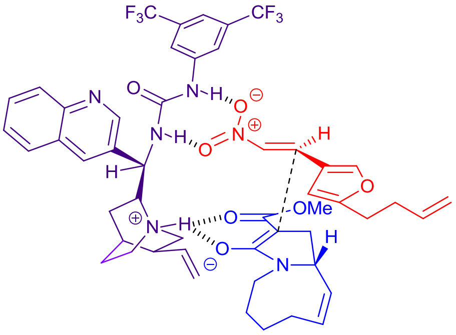
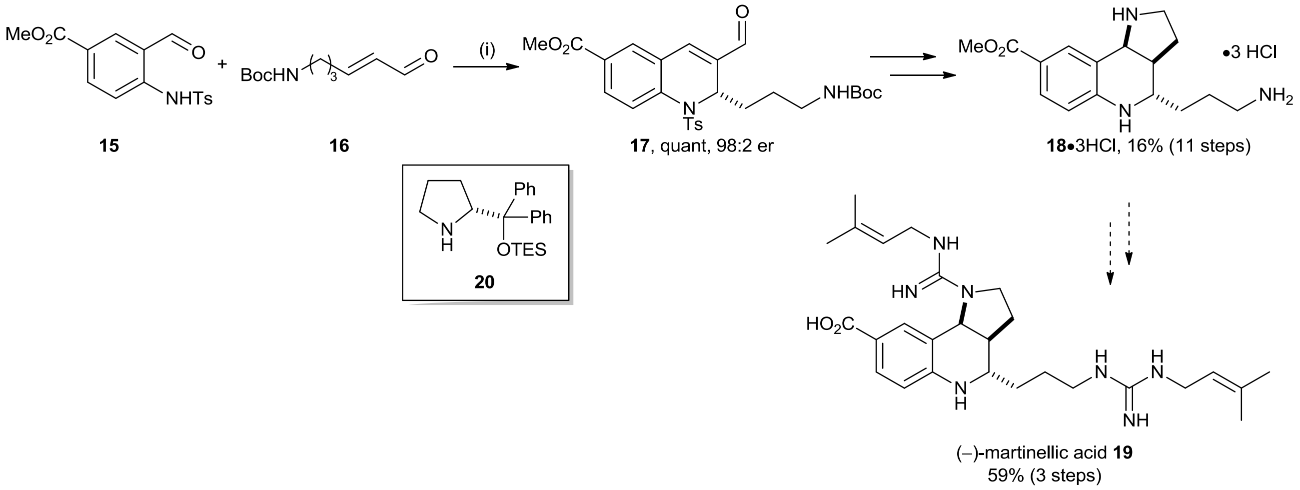


Figure 3. Proposed transition state for the diastereoselective conjugate addition of **9** to **11** in the presence of **14**.

1.3.1.2 Catalytic activation of the olefin

The second method for activation is for the chiral catalyst to bind to the electrophilic olefin, as is exemplified by Hamada *et al.* in their formal synthesis of (−)-martinellic acid **19**,[30] a pyrroloquinoline alkaloid isolated from the roots of *Martinella iquitoensis* that is the active ingredient in eye medication used by Amazon Indian tribes.[31] Conjugate addition of aniline **15** to α,β-unsaturated aldehyde **16**, catalysed by the proline derived pyrrolidine **20**, followed by spontaneous intramolecular aldol reaction, gave dihydroquinoline **17** in quantitative yield and 98:2 er. The formal synthesis was then completed in eleven steps to give the tricyclic core **18**·3HCl in 16% overall yield; the conclusion of the synthesis can be achieved in three steps from **18**·3HCl according to the procedure of Ma *et al.*,[32] giving (−)-martinellic acid **19** in 59% yield over three steps (Scheme 2).



Scheme 2. *Reagents and conditions*: (i) **20** (5 mol%), AcOH (5 mol%), MeCN, −20 °C, 24 h.

The high level of enantioselectivity observed in this reaction may be rationalised by the initial formation of the (*E*)-iminium ion **21**, which adopts an *s*-trans conformation, favoured in order to minimise steric interactions with the stereodirecting group within **21**. Nucleophilic attack of aniline **15** then occurs on the *Si*-face of **21**, the *Re*-face being blocked by the bulky stereodirecting group (Figure 4).[33]

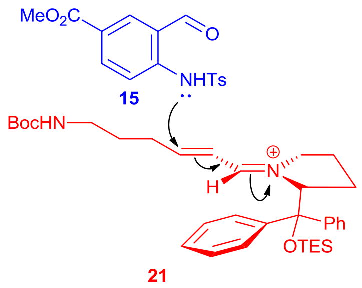
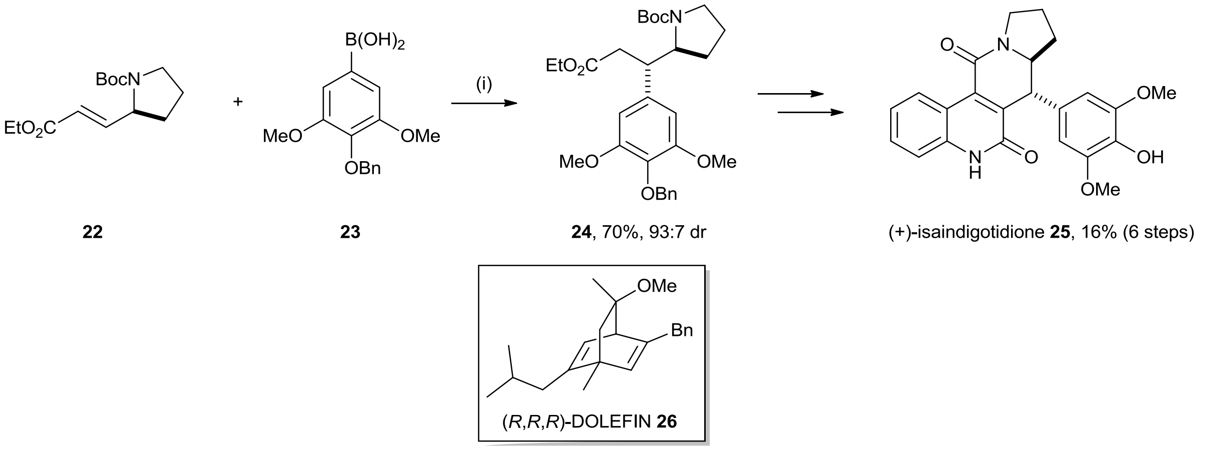


Figure 4. The proposed origin of the enantioselectivity observed in the conjugate addition of **15** to **21**.

1.3.1.3 Catalytic activation of the nucleophile

The final method for catalytic asymmetric conjugate addition occurs when the catalyst binds to the the nucleophile. An example of this mode of activation can be found in a synthesis of (+)-isaindigotidione **25**, an alkaloid isolated from the roots of *Isatis tinctoria*, a herb indigenous to China's Changjiang river valley used in traditional Chinese medicine.[34] The first step of this synthesis, as reported by Cuny and Hellal, involved the asymmetric conjugate addition of boronic acid **23** to α,β-unsaturated ester **22** using catalytic $[Rh(C_2H_4)_2Cl]_2$ in the presence of (*R*,*R*,*R*)-DOLEFIN **26**, which proceeded to give **24** in 70% yield and 93:7 dr, with the diastereoselectivity proposed to be under the dominant stereocontrol of the ligand.[35] A further six steps allowed the completion of the synthesis of (+)-isaindigotidione **25** in 16% overall yield from **24** (Scheme 3).[36]



Scheme 3. *Reagents and conditions*: (i) $[Rh(C_2H_4)_2Cl]_2$ (3 mol%), (*R*,*R*,*R*)-DOLEFIN **26** (7 mol%), $CsCO_3$, dioxane/H_2O (v/v 10:1), 60 °C, 24 h.

A catalytic cycle for this class of reaction has been proposed by Hayashi *et al.*[37] involving initial reversible solvolysis of rhodium dimer **27** to give the monomeric species **28**. Transmetallation of boronic acid **23** with rhodium species **28** gives **29**, which is followed by complexation of olefin **22** to give **30**. Conjugate addition of the complexed aryl group to the coordinated olefin gives **31**, with subsequent hydrolysis and solvolysis releasing the product **24** and regenerating the catalyst **28** (Figure 5).

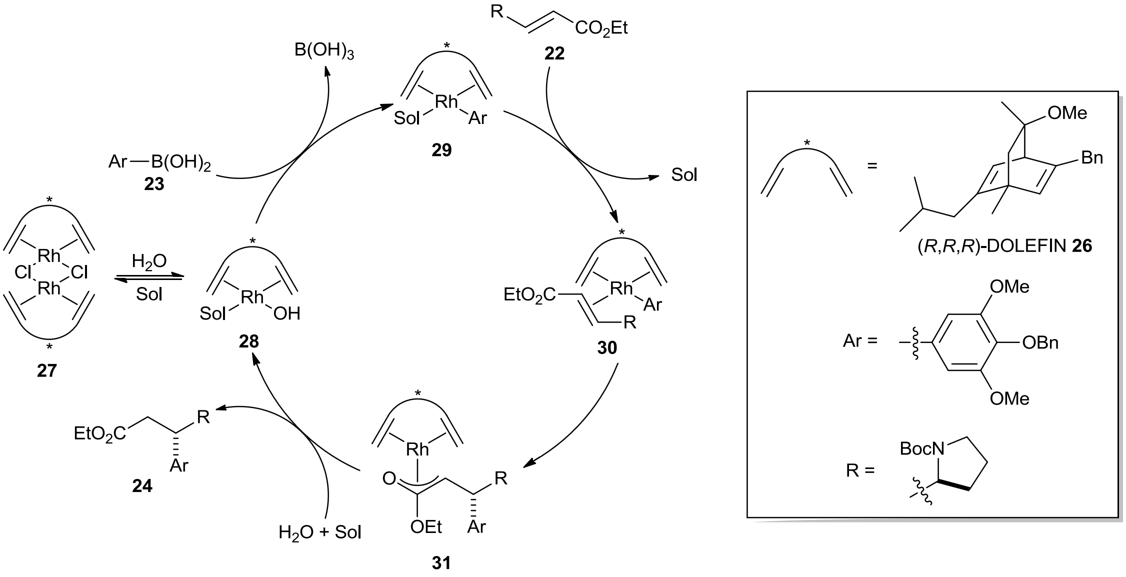


Figure 5. Proposed catalytic cycle for the rhodium-catalysed conjugate addition of organoboronic acids.

Hayashi has also proposed a model to rationalise the enantioselectivity observed when chiral diene ligands, similar to **26**, are used in the rhodium catalysed conjugate addition reaction.[38] In this model, it is suggested that steric repulsion between the carbonyl moiety and, in this case, either the isopropyl or benzyl groups,[39] favours complexation of the back face of the alkene within **32**. Subsequent attack of the *Re*-face with the aryl group then sets the configuration at the newly formed stereogenic centre (Figure 6).

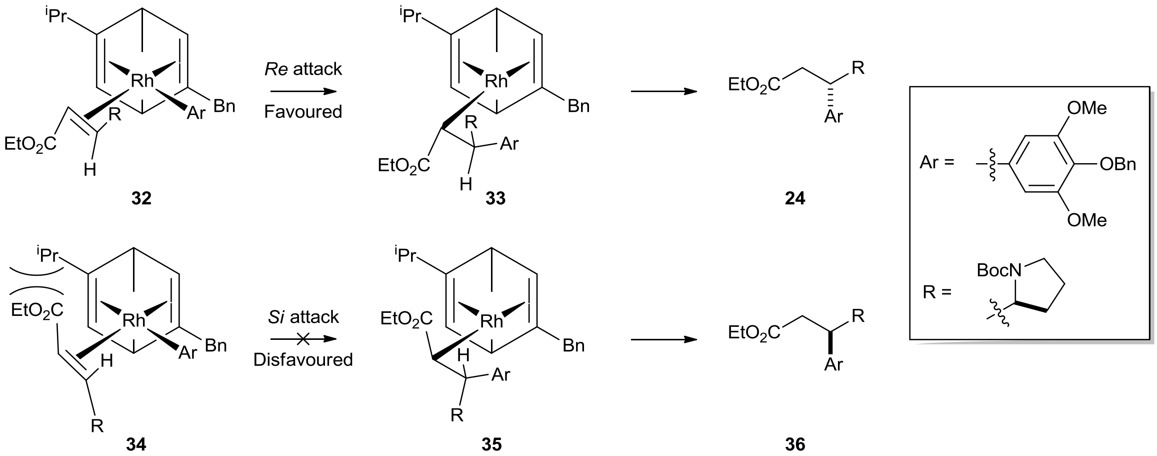


Figure 6. Hayashi’s proposed stereochemical rationale for the rhodium catalysed asymmetric conjugate addition of boronic acids to α,β-unsaturated esters.

1.3.2 Use of chiral olefins in the conjugate addition reaction and its application in synthesis

A vast array of chiral auxiliaries, for example **37**-**44**, has been used to direct the conjugate addition of a range of nucleophiles to electrophilic olefins;[28a] the majority of these chiral auxiliaries are derived from enantiopure alcohols and amines (Figure 7).[40]

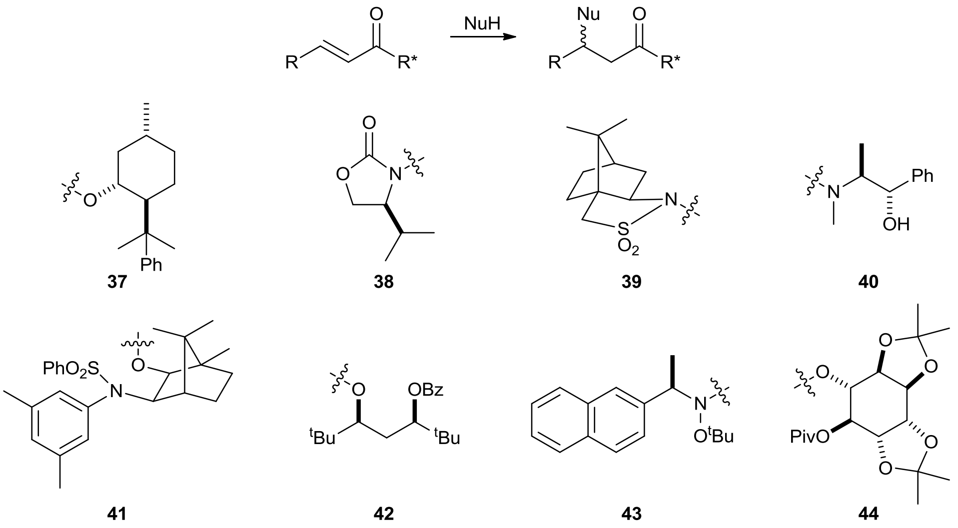
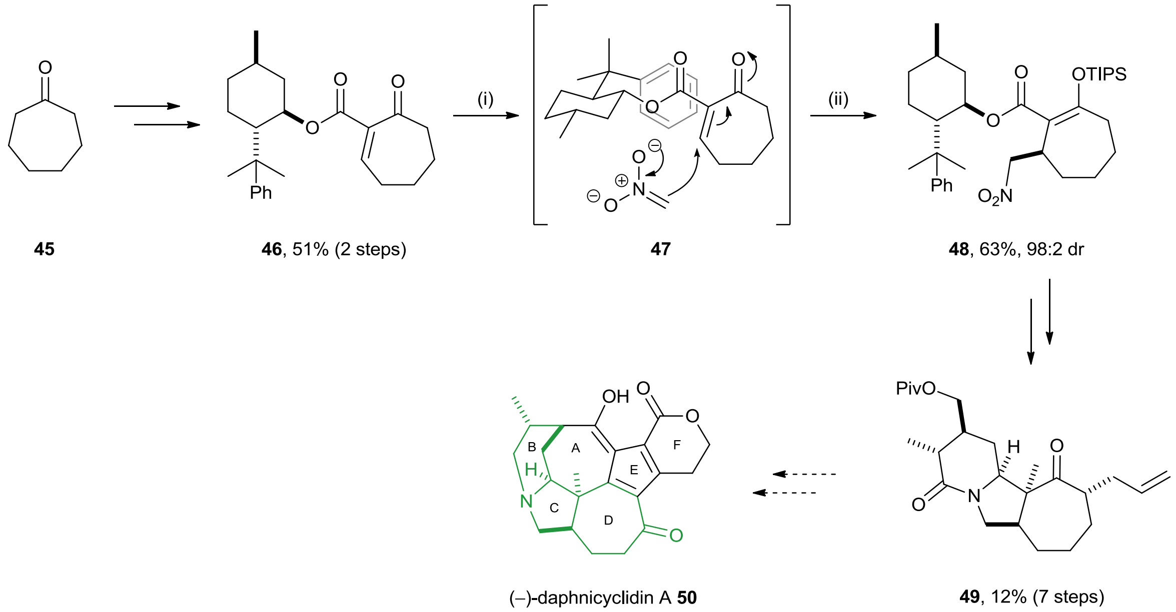


Figure 7. Exemplary chiral auxiliaries used to control diastereoselectivity in conjugate addition reactions.

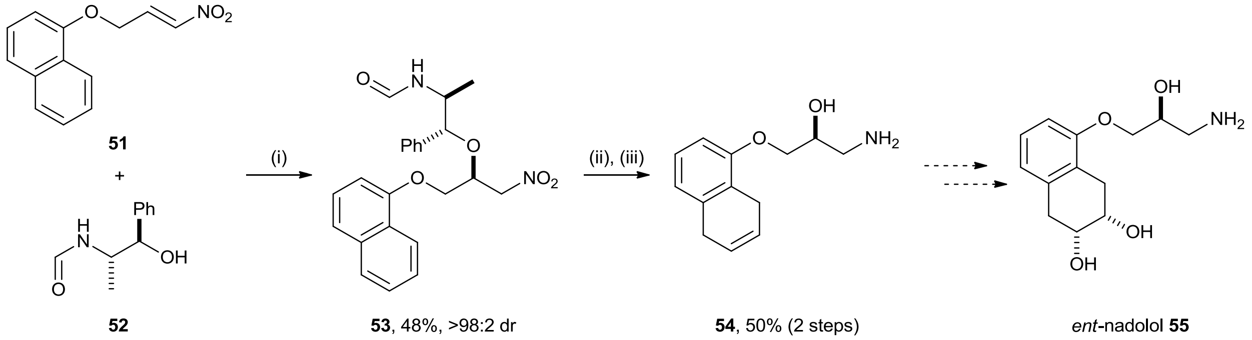
The use of such auxiliaries in synthesis to control the diastereofacial selectivity in conjugate addition reactions has been demonstrated by, amongst others, Iwabuchi *et al.*[41] In 2009, they reported the enantiocontrolled synthesis of the BCD ring system **49** of (−)-daphnicyclidin A **50**, a hexacylic alkaloid isolated in 2001 from the stems of *Daphniphyllum macropodum* and *Daphniphyllum teysmannii* by Kobayashi and co-workers.[42] The key enantioselective step in their synthesis consisted of the conjugate addition of lithium methyleneazinate to chiral α,β-unsaturated ester **46**, derived from Corey’s 8-phenylmenthol chiral auxiliary,[40a] with subsequent trapping of the intermediate enolate as the corresponding silyl enol ether **48**. Conjugate addition proceeded in 63% yield and 98:2 dr, with the absolute configuration within **48** being confirmed at a later stage of the synthesis via X-ray crystallographic analysis and ^{1}H NMR NOESY correlations of an advanced intermediate. Further elaboration of **48** gave the BCD ring system **49** of (−)-daphnicyclidin A **50** in 3.9% overall yield and twelve steps from cycloheptanone **45** (Scheme 4).



Scheme 4. *Reagents and conditions*: (i) BuLi, $MeNO_2$, THF, −78 °C, 1.5 h; (ii) TIPSOTf, HMPA, −78 to −10 °C, 9 h.

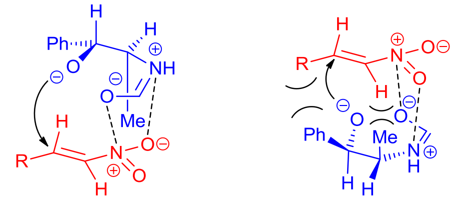
1.3.3 Use of chiral nucleophiles in the conjugate addition reaction and its application in synthesis

The conjugate addition of (1*R*,2*S*)-(−)-*N*-formylnorephedrine **52** (pioneered by Enders *et al.*)[43] to nitroolefin **51** has been identified as a potential route to *ent*-nadolol **55**, a non-selective beta-blocker used in the treatment of hypertension.[44] Treatment of **52** with NaH in THF followed by nitroolefin **51** gave β-oxynitroalkane **53** in 48% yield and >98:2 dr. Subsequent reduction of the nitro group within **53** with $NaBH_4$ and Pd/C followed immediately by Birch reduction of the resultant amine to remove the chiral auxiliary, with concomitant reduction of the naphthyl ring, gave **54** in 50% yield from **53**. It was then hypothesised that **54** could be readily converted into *ent*-nadolol **55**, although the conclusion of the synthesis was not reported (Scheme 5).[43]



Scheme 5. *Reagents and conditions*: (i) NaH, **52**, THF, rt, then **51**, −78 °C; (ii) $NaBH_4$, Pd/C, MeOH/THF (v/v 1:1), 0 °C, 2 h, then rt, 3 days; (iii) Na, NH_3, THF, −78 °C, 15 min.

To rationalise the stereochemical outcome of this reaction, Enders proposed that in the transition state there is significant electrostatic attraction between the formyl group within the anion of **52** and the nitro group within **51**, which controls the approach orientation of the alkoxide derived from **52**. The *Si*-diastereofacial selectivity is then determined by minimisation of steric interactions between the nitroalkene **51** and the norephedrine derived directing group in the two possible diastereotopic transition states **56** and **57** (Figure 8).



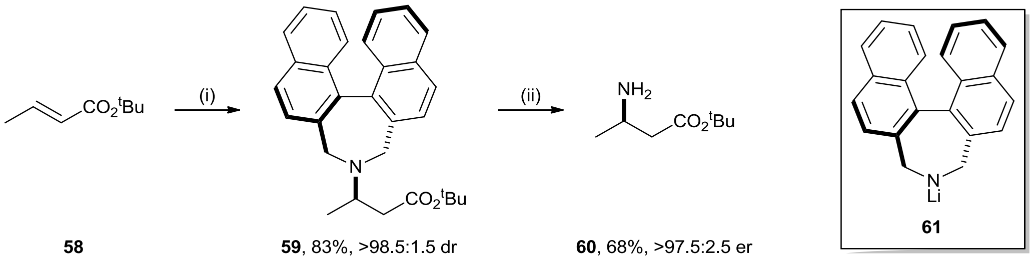
56 *Si* diastereofacial attack
Favoured

57 *Re* diastereofacial attack
Disfavoured

Figure 8. The diastereotopic transition states **56** and **57** proposed to rationalise the stereochemical outcome of the conjugate addition of the alkoxide generated from (1*R*,2*S*)-(−)-*N*-formylnorephedrine **52** to nitroolefins.

1.4 The conjugate addition of chiral lithium amides

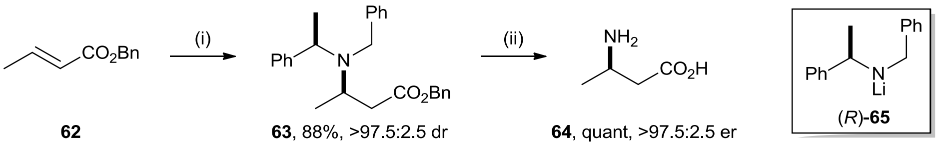
In 1986, Hawkins *et al*. showed that the conjugate addition of an enantiopure lithium amide to an α,β-unsaturated ester could proceed with high levels of diastereoselectivity. Lithium amide **61** was shown to react with a range α,β-unsaturated esters; for example, reaction of **61** with *tert*-butyl crotonate **58** gave **59** in 83% yield and >98.5:1.5 dr.[45] Subsequent removal of the binaphthyl group within **59** occurred upon hydrogenolyisis to yield β-amino ester **60** in 68% yield and >97.5:2.5 er (Scheme 6).[46]



58 **59**, 83%, >98.5:1.5 dr **60**, 68%, >97.5:2.5 er **61**

Scheme 6. *Reagents and conditions*: (i) **61**, THF, −78 °C, 30 min; (ii) Pd(OH)$_2$/C, morpholinium formate, EtOH, 50 °C, 5 h.

Following this, Davies and Ichihara reported the conjugate addition of lithium amide (*R*)-**65** to benzyl crotonate **62**, which proceeded in 88% yield and >97.5:2.5 dr. Subsequent hydrogenolytic removal of all the benzyl groups gave β-amino acid **64** in quantitative yield and >97.5:2.5 er (Scheme 7).[9]



62 **63**, 88%, >97.5:2.5 dr **64**, quant, >97.5:2.5 er (*R*)-**65**

Scheme 7. *Reagents and conditions*: (i) (*R*)-**65**, THF, −78 °C, 15 min; (ii) Pd(OH)$_2$/C, H$_2$ (5 atm), MeOH, 20 °C, 22 h.

A transition state mnemonic has been proposed by Davies *et al.*[47] in which the lithium atom coordinates to the carbonyl oxygen of the ester. The C(α)*Me* group then occupies the position above the C(3)*H* proton, and both benzyl groups point away from the α,β-unsaturated ester to minimise steric interactions (Figure 9).

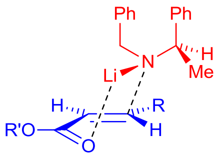
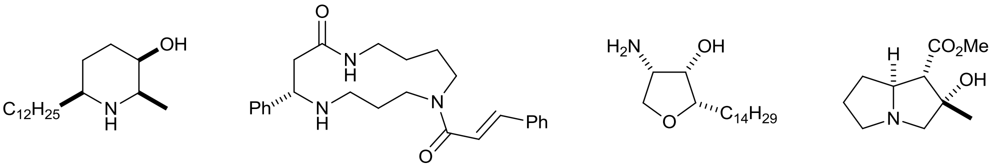


Figure 9. Transition state mnemonic for the lithium amide conjugate addition of (*R*)-**65**.

The conjugate addition of secondary lithium amides derived from α-methylbenzylamine[48] has since been extensively developed, primarily by Davies,[28b] amongst others,[49] and has proved valuable in the synthesis of a range of enantiopure, nitrogen containing compounds.

1.4.1 The lithium amide conjugate addition in alkaloid synthesis

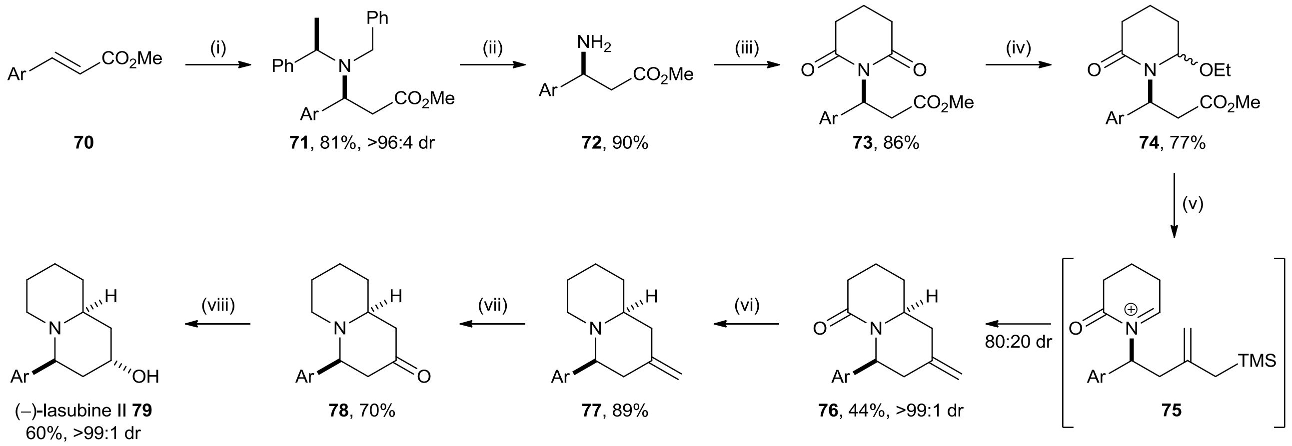
Alkaloids have been successfully synthesised using the conjugate addition of either enantiopode of lithium amide **65** to an α,β-unsaturated ester as the key stereodefining step in the synthesis, representative examples including the syntheses of (−)-deoxocassine **66**,[50] (+)-dihydroperiphylline **67**,[51] (+)-jaspine B **68**[52] and (−)-tussilagine **69**[53] (Figure 10).



(–)-deoxocassine **66** (+)-dihydroperiphylline **67** (+)-jaspine B **68** (–)-tussilagine **69**

Figure 10. Exemplary alkaloids synthesised using the conjugate addition of **65** to an α,β-unsaturated ester.

For example, Remuson *et al*. reported the synthesis of (−)-lasubine II **79**,[54] one of several related alkaloids isolated from plants of the *Lythraceae* family. The first step of the synthesis was the conjugate addition of (*R*)-**65** to α,β-unsaturated ester **70**, to give β-amino ester **71** in 81% yield and >96:4 dr. Hydrogenolytic removal of the *N*-benzyl groups followed by the sequential treatment of the resultant β-amino ester **72** with glutaric anhydride and acetyl chloride gave imide **73**. Reduction of imide **73** to hemiaminal ether **74** was achieved with $NaBH_4$ and EtOH to give **74** in 77% yield as a mixture or diastereoisomers. Treatment of **74** with $TMSCH_2MgCl$ and $CeCl_3$, followed by HCl gave methylenequinolizidinone **76** (via iminum ion **75**) in 80:20 dr, and 44% and >99:1 dr after purification. Reduction of the amide functionality within **76**, mediated by $LiAlH_4$, followed by oxidative cleavage of the double bond within **77** gave ketone **78** in 62% yield over two steps. Diastereoselective reduction of **78** with LS-Selectride® then gave (−)-lasubine II **79** in 60% yield and >99:1 dr (Scheme 8).[54]



Scheme 8. *Reagents and conditions*: (i) (*R*)-**65**, THF, 0 °C, 3 h; (ii) Pd(OH)$_2$/C, H$_2$ (4 atm), MeOH/H$_2$O/AcOH (v/v/v 40:4:1), rt, 3 days; (iii) glutaric anhydride, PhMe, reflux, 12 h, then AcCl, PhMe, reflux, 3 h; (iv) NaBH$_4$, EtOH, H$_2$SO$_4$, −10 °C, 2 h; (v) TMSCH$_2$MgCl, CeCl$_3$, 0 °C to rt, 3 days then HCl; (vi) LiAlH$_4$, THF, reflux, 12 h; (vii) OsO$_4$, Na$_3$H$_2$IO$_6$, AcOH/H$_2$O (v/v 4:1), 10 °C, 18 h; (viii) LS-Selectride®, THF, −78 °C, 12 h. [Ar = 3,4-dimethoxyphenyl].

More recently, alkaloids have been successfully synthesised using "functionalised" lithium amides, for which the substituent on the α-methylbenzyl moiety is retained in the target molecule, whether further functionalised or not. This increases both the step efficiency and atom economy of any potential synthesis.[55] A variety of these lithium amide reagents **80-83**[56] have been used in synthesis to target a range of different alkaloids, including (+)-pseudodistomin D **84**,[57] (−)-7a-*epi*-hyacinthacine A1 **85**,[58] (−)-codonopsinine **86**[59] and (−)-angustureine **87**[60] (Figure 11).

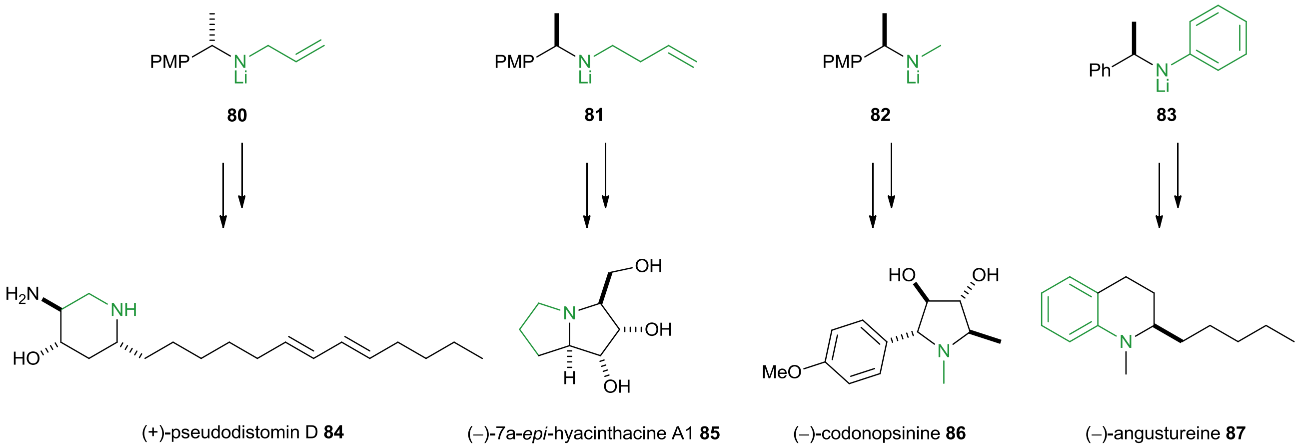
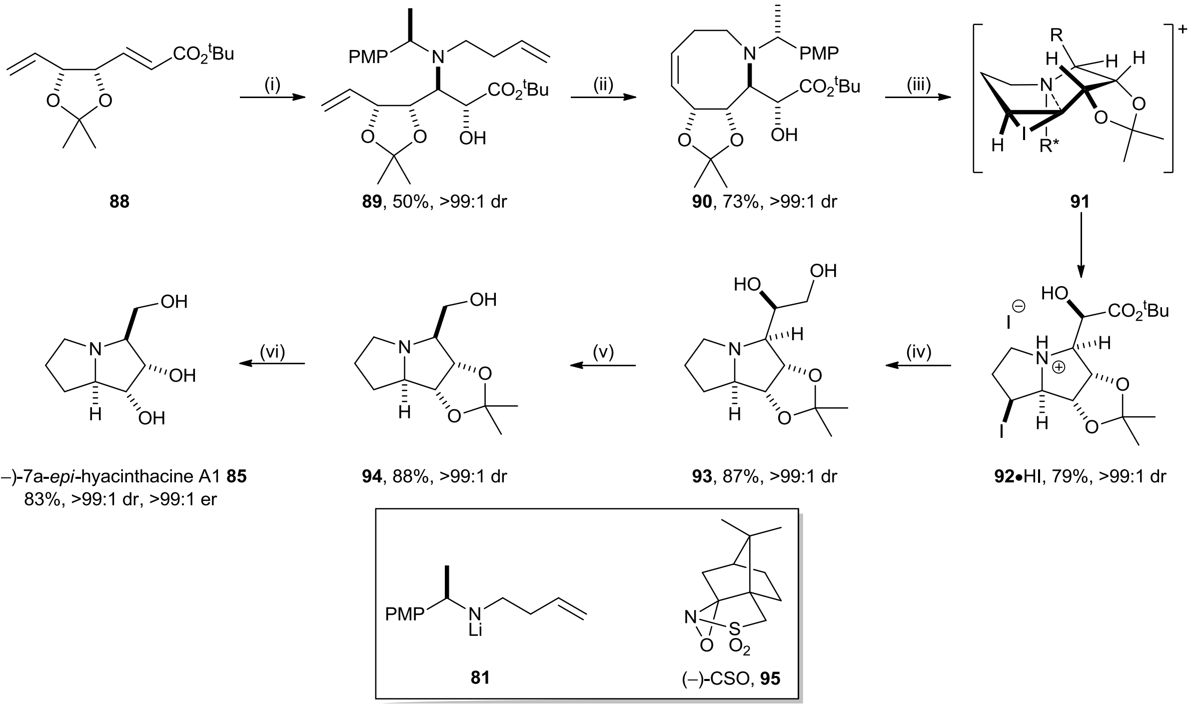


Figure 11. Exemplary alkaloids **84-87** that have been synthesised using "functionalised" lithium amides **80-83**.

In the synthesis of (−)-7a-*epi*-hyacinthacine A1 **85** reported by Davies *et al.*,[58] conjugate addition of **81** to the D-ribose derived α,β-unsaturated ester **88** followed by *in situ* enolate oxidation with (−)-CSO **95** gave α-hydroxy-β-amino ester **89** in 50% yield and >99:1 dr. Ring closing metathesis of **89** with Grubbs I catalyst gave hexahydroazocine **90** in 73% yield. Ring closing iodoamination of **90**, with concomitant *N*-debenzylation gave pyrrolizine **92**·HI in 79% yield and >99:1 dr; the stereochemical outcome of this reaction was hypothesised to occur due to reaction through iodonium **91**. Simultaneous reduction of both the ester moiety and C−I bond within **92**, mediated by LiAlH$_4$, gave diol **93** in 87% yield. Oxidative cleaveage of the diol within **93** followed by immediate reduction of the resultant aldehyde with NaBH$_4$ gave **94** in 88% yield. Finally, hydrolysis of the acetonide protecting group within **94** gave (−)-7a-*epi*-hyacinthacine A1 **85** in 83% yield (Scheme 9).[58]



Scheme 9. *Reagents and conditions*: (i) **81**, THF, −78 °C, 2 h, then (−)-CSO **95**, −78 °C to rt, 12 h; (ii) Grubbs I catalyst, CH_2Cl_2, 30 °C, 12 h; (iii) I_2, $NaHCO_3$, CH_2Cl_2, rt, 12 h; (iv) $LiAlH_4$, THF, −78 °C to rt, 12 h; (v) $NaIO_4$, MeOH/H_2O (v/v 5:1), rt, 4 h then, $NaBH_4$, rt, 4 h; (vi) HCl (3.0 M, aq), MeOH, reflux, 2 h, then Dowex 1X8 200-400.

1.5 Project aims

This thesis is concerned with the development of the conjugate addition of "functionalised" lithium amides to α,β-unsaturated esters as the key stereodefining step in the asymmetric syntheses of (−)-morphine **98** and the homalium alkaloids (−)-homaline **99**, (−)-hopromine **100**, (−)-hopromalinol **101** and (−)-hoprominol **102** (Figure 12).

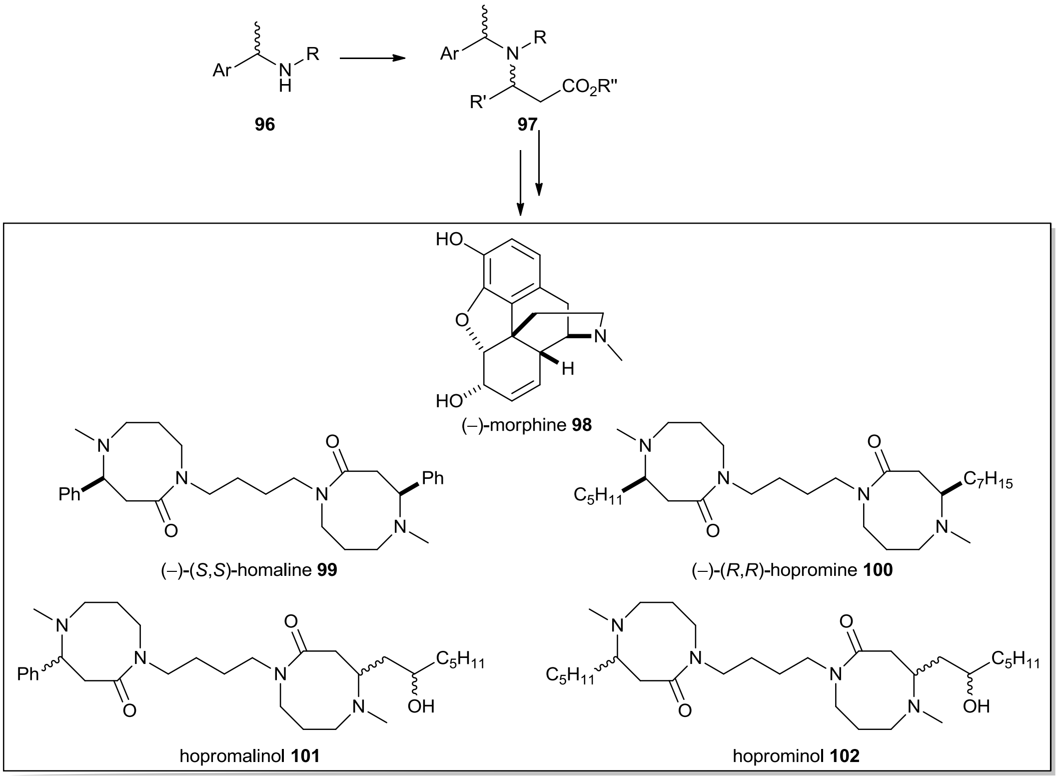


Figure 12. Targets for synthesis utilising "functionalised" lithium amides.

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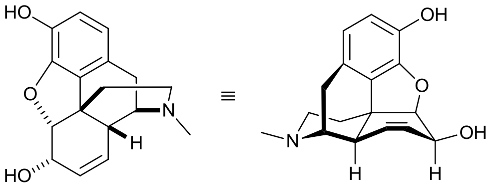
Chapter 2: Towards the asymmetric synthesis of (−)-morphine

2.1 Introduction

This chapter describes attempts to synthesise (−)-morphine **98** utilising the conjugate addition of functionalised lithium amides, including the use of the highly functionalised reagent lithium (*R*)-*N*-[2′-(7-methoxybenzofuran-3-yl)ethyl]-*N*-(α-methylbenzyl)amide **103** and its derivatives.

2.1.1 (−)-Morphine

(−)-Morphine **98** is the principal opiate alkaloid isolated from the latex (opium) of the immature seed head of the opium poppy *Papaver somniferum*, typically making up 10% of the dried mass of the latex, although the actual content varies widely depending on cultivar, with a (−)-morphine **98** content as high as 21.8% being reported two hours after the cutting of the seed head on one occasion (Figure 13).[1]



(–)-morphine **98**

Figure 13. The structure of (−)-morphine **98**.

The effects of opium were well known in ancient Greece,[2] but it was in the early 19th century that the isolation of the active component, (−)-morphine **98**, was independently reported by Séguin[3] and Sertürner.[1,4] Sertürner went on to report the first systematic studies on the effect of ingesting (−)-morphine **98** on the human body, hiring three seventeen year olds to take the pure opiate with him. Initial dosage of "*un demi-grain*"[5] of (−)-morphine **98** resulted in general redness, especially in the face. Successive dosage in half grain intervals lead to dizziness, nausea and eventual unconsciousness into a dream-like state.[6] These initial studies developed into a vast area of research into the chemistry and biology of (−)-morphine **98** that continues to this day, arguably spawning the entire field of medicinal chemistry.[7] These investigations revealed that (−)-morphine **98** is a powerful analgesic, leading to its wide use as such, with a total worldwide production of 416 tons in 2010.[8] Over the same time period, the illicit use of opiates increased substantially, in particular the use of heroin (diacetylmorphine), with an estimated 375 tons consumed by approximately 13 million people in 2009.[9]

On an industrial scale, (−)-morphine **98** is isolated from opium poppies by a series of acidic, alkaline and solvent extractions,[10] based on the Gregory process that was first reported in 1833.[11] In this procedure, poppy straw (the dry, harvested plant, excluding the roots, leaves and seeds), is pulverised and extracted multiple times with dilute sulfuric acid, filtering to remove any insoluble plant matter. The opium extracts are then concentrated to a thick syrup (poppy straw concentrate), to which a solution of concentrated calcium chloride is added, inducing the precipitation of impurities including calcium meconate, calcium lactate and calcium sulfate, among other minor alkaloids. The impurities are removed via filtration and the mother liquor is concentrated to give the "Gregory salt": a mixture of (−)-codeine **120** and (−)-morphine **98** hydrochloride salts. This mixture is then purified by recrystallisation from H_2O. Finally, the purified mixture of (−)-codeine **120** and (−)-morphine **98** hydrochloride salts is dissolved in water and (−)-morphine **98** is precipitated by the addition of ammonia, with the (−)-codeine **120** remaining in solution. The purity of the (−)-morphine **98** may be further improved by cycles of filtration through decolourising charcoal and recrystallisation of its hydrochloride salt.[1]

2.1.2 The biosynthetic origin of (−)-morphine

Robinson was the first to theorise that (−)-morphine **98** originated from the dimerisation of two L-tyrosine **104** derivatives, and his hypotheses regarding the biosynthesis of (−)-morphine **98** have largely been confirmed by the use of ^{14}C and ^{3}H labelling experiments.[1] The biosynthesis of (−)-morphine **98** is now almost completely elucidated, although the identity of all participating enzymes is not currently known. Starting with L-tyrosine **104**, metabolism via different pathways gives either dopamine **105** or 4-hydroxyphenylacetaldehyde **106**, both in two steps. Enzymatic controlled condensation of **105** and **106** gives iminium ion **107**, which spontaneously cyclises to (−)-norcoclaurine **108**. Successive *O*- and *N*-methylation mediated by SAM, followed by oxidation with NADPH and O_2 gives (*S*)-3-hydroxy-*N*-methylcoclaurine **110**. *O*-Methylation of **110** with SAM furnishes (+)-reticuline **111**, which is inverted to (−)-reticuline **111** via oxidation to the corresponding iminium ion, followed by enantioselective reduction with NADPH to give (−)-reticuline **111**. Oxidative coupling of the two phenolic moieties forms the quaternary stereogenic centre within (−)-morphine **98**, yielding (+)-salutaridine **113**. Reduction of **113** with NADPH gives salutaridinol **114**, which is acetylated with acetyl CoA, resulting in the spontaneous cyclisation to (−)-thebaine **116**. Oxidative demethylation of (−)-thebaine **116** gives (−)-neopinone **118**, which undergoes non-enzymatic equilibration to (−)-codeinone **119**. Reduction of (−)-codeinone **119** with NADPH gives (−)-codeine **120**, followed by demethylation to give (−)-morphine **98** (Figure 14).[12]

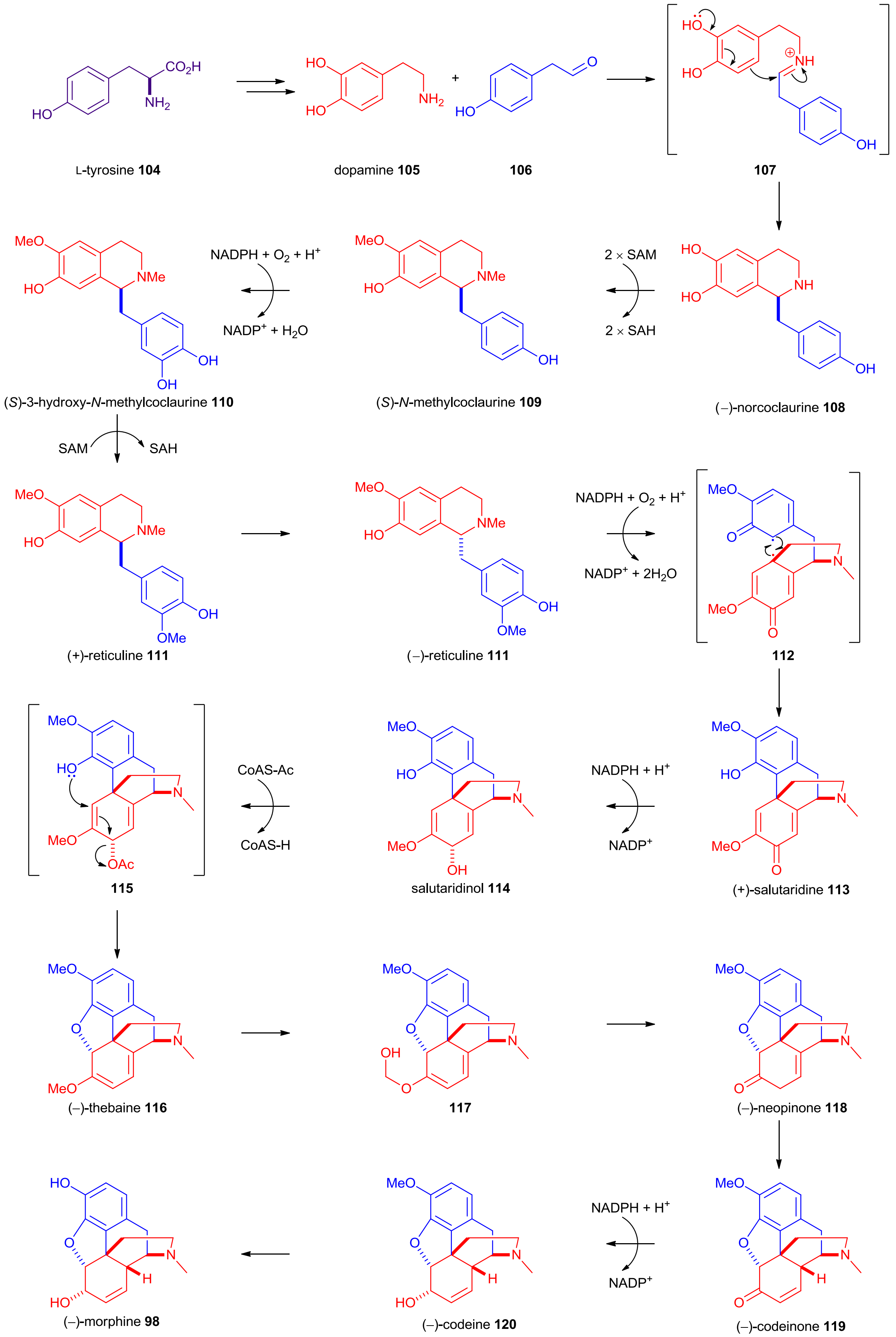
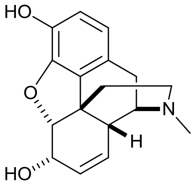


Figure 14. The biosynthesis of (−)-morphine **98**.

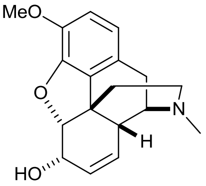
2.1.3 Previous syntheses of morphine

Although current methodology is unlikely to provide a total synthesis of (−)-morphine **98** that competes with the existing production of the opiate via the harvesting of opium poppies,[12a] this alkaloid has attracted numerous successful attempts at its synthesis. In 1952, Gates' landmark total synthesis of (−)-morphine **98**[13] served to confirm the structure originally proposed by Robinson in 1925,[14] with the crystal structure of morphine hydroiodide dihydrate subsequently being reported by Hodgkin and Mackay in 1955.[15] There have since been three other syntheses of morphine **98** (one enantioselective, one racemic, and one reliant on a resolution protocol), in addition to sixteen formal syntheses (five enantioselective, one enantiospecific, eight racemic and two reliant on a resolution protocol) (Figure 15).[16]

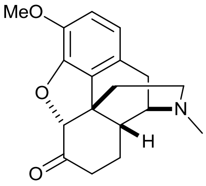
Principal Author	Year	Target	Strategy	Steps	Overall Yield [%]	Ref
Gates	1952	(–)-morphine **98**	resolution	29	0.001	13
Rice	1980	(±)-dihydrocodeinone **121**	racemic	10	29.00	17
Evans	1982	(±)-*O*-Me-β-dihydrothebainone **122**	racemic	12	16.67	18
Rapoport	1983	(±)-codeine **120**	racemic	26	1.15	19
Fuchs	1988	(±)-codeine **120**	racemic	22	1.53	20
Tius	1991	(±)-thebainone **123**	racemic	24	1.10	21
Parker	1992	(–)-dihydrocodeinone **121**	enantioselective	11	4.64	22
Overman	1994	(–)-dihydrocodeinone **121**	enantioselective	15	2.85	23
Mulzer	1996	(–)-dihydrocodeinone **121**	resolution	11	11.50	24
White	1999	(+)-codeine **120**	enantioselective	24	0.99	25
Ogasawara	2001	(–)-dihydrocodeinone ethylene acetal **124**	resolution	22	1.47	26
Taber	2002	(–)-morphine **98**	enantioselective	27	0.51	27
Trost	2002	(–)-codeine **120**	enantioselective	15	6.78	28
Trost	2005	(–)-morphine **98**	enantioselective	16	3.20	29
Fukuyama	2006	(±)-morphine **98**	racemic	22	9.22	30
Chida	2007	(–)-dihydroisocodeine **125**	enantiospecific	27	3.84	31
Guillou	2008	(±)-codeine **120**	racemic	15	0.58	32
Stork	2009	(±)-codeine **120**	racemic	22	2.13	33
Hudlicky	2009	(–)-codeine **120**	enantioselective	16	0.04	34
Magnus	2009	(±)-codeine **120**	racemic	14	19.85	35
Fukuyama	2010	(–)-morphine **98**	resolution	21	4.76	36



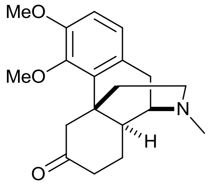
(–)-morphine **98**



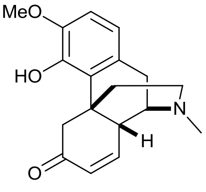
(–)-codeine **120**
1 step to **98**, 88%
see ref 37



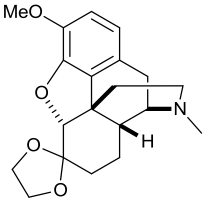
(–)-dihydrocodeinone **121**
7 steps to **98**, 37%
see ref 38, 39



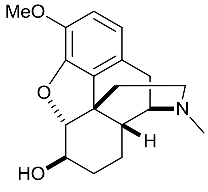
(–)-*O*-Me-β-dihydrothebainone **122**
10 steps to **98**, 0.16%
see ref 13b



(–)-thebainone **123**
4 steps to **98**, 4.2%
see ref 13b



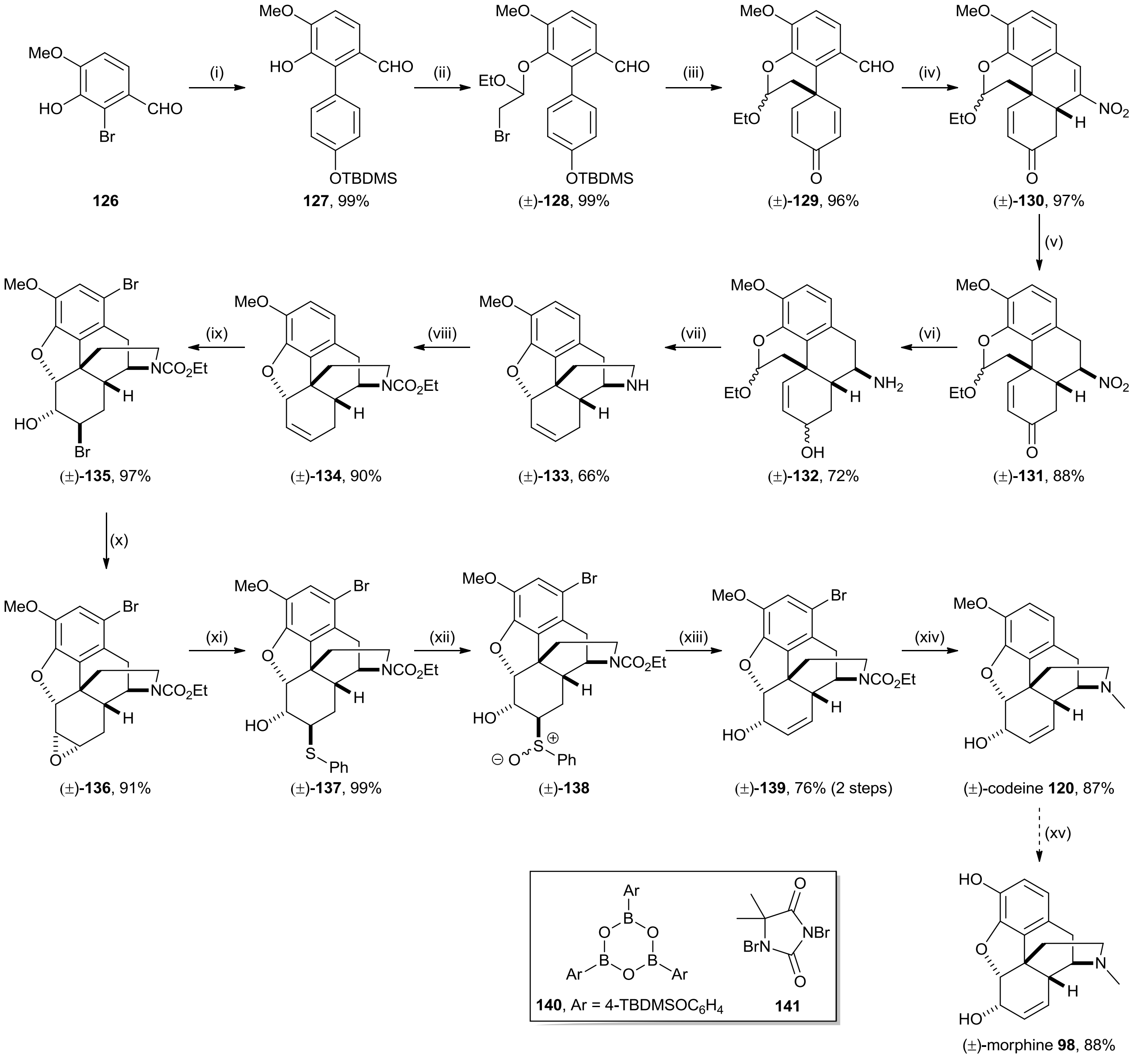
(–)-dihydrocodeinone ethylene acetal **124**
8 steps to **98**, 35%
see ref 24, 38, 39



(–)-dihydroisocodeine **125**
8 steps to **98**, 31%
see ref 22a, 38, 39

Figure 15. Previous syntheses, including formal, of morphine **98**.

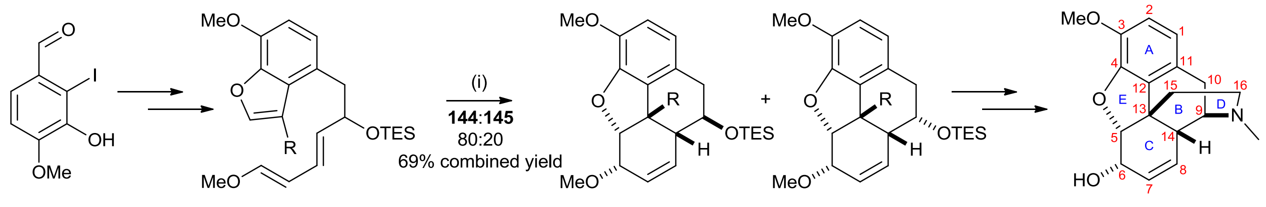
The most efficacious synthesis to date is arguably that of Magnus *et al.*[35] which provided (±)-codeine **120** in fourteen steps and 19.9% overall yield [and therefore (±)-morphine **98** in fifteen steps and 17.5% yield].[34] The synthesis begins with Suzuki coupling of aldehyde **126** with boronic acid trisanhydride **140**, giving biphenyl **127** in 99% yield. Reaction of **127** with ethyl vinyl ether and Br_2 gave racemic ether **128** in 99% yield. Removal of the silyl group within **128** with CsF resulted in the spontaneous formation of dienone **129** in 96% yield, with subsequent Henry reaction giving **130** in 97% yield. Reduction of **130** with $NaBH_3CN$ gave **131** in 88% yield; further reduction with $LiAlH_4$ then gave amine **132** in 72% yield. Hydrolysis of the acetal within **132** followed by spontaneous cyclisation and *in situ* reductive amination effected by $NaBH_3CN$ gave **133** in 66% yield. Acylation of **133** with EtOCOCl gave carbamate **134** in 90% yield, an intermediate in Taber's asymmetric synthesis of (−)-morphine **98**.[27] Hydroxybromination of the alkene within **134** with 5,5-dimethyl-1,3-dibromohydantoin **141** gave bromohydrin **135** in 97% yield (in which bromination of the aromatic ring also occurred). Treatment of **135** with KOH gave epoxide **136** in 91% yield, with subsequent epoxide ring opening with PhSNa giving thiol **137** in 99% yield. Oxidation of the thiol functionality within **137** gave sulfoxide **138** that was thermolysised to give olefin **139** in 76% yield over two steps. Finally, reduction of the ethyl carbamate moiety and C−Br bond within **139**, mediated by $LiAlH_4$, gave (±)-codeine **120** in 87% yield, completing the formal synthesis of (±)-morphine **98**. (±)-Morphine **98** could then be accessed by demethylation of (±)-codeine **120** using BBr_3 in 88% yield, according to the procedure of Rice[37] (Scheme 10).



Scheme 10. *Reagents and conditions*: (i) **140**, $Pd_2(dba)_3$, PCy_3, BHT, K_2CO_3, dioxane/H_2O (v/v 3:1), 80 °C, 1 h; (ii) ethyl vinyl ether, Br_2, $^iPr_2NEt$, CH_2Cl_2, 0 °C, 12 h; (iii) CsF, DMF, 130 °C, 1.5 h; (iv) $MeNO_2$, NH_4OAc, AcOH, reflux, 2.5 h; (v) $NaBH_3CN$, THF/AcOH (v/v 3:1), rt, 4 h; (vi) $LiAlH_4$, THF, −78 °C to rt, 8 h; (vii) HCl (1.0 M, aq), $NaBH_3CN$, dioxane, reflux, 5 h; (viii) EtOCOCl, NEt_3, CH_2Cl_2, 0 °C, 1 h; (ix) **141**, acetone/H_2O (v/v 10:1), rt, 12 h; (x) KOH, PhMe, 80 °C, 3 h; (xi) PhSNa, EtOH, 25 °C, 2 h; (xii) 30% aq H_2O_2, hexafluoroisopropanol, rt, 15 min; (xiii) PhMe, $NaHCO_3$, reflux, 2 h; (xiv) $LiAlH_4$, THF, 25 °C, 6 h; (xv) BBr_3, $CHCl_3$, rt, 15 min.

2.1.4 The Diels-Alder approach to the morphine skeleton

The possibility of constructing the cyclohexene C ring within (−)-morphine **98** using a Diels-Alder reaction between a tethered diene and a suitably substituted benzofuran has been identified as a synthetic strategy by several groups.[40] However, only Stork *et al.* have successfully completed the synthesis of (±)-codeine **120** (and therefore a formal synthesis of (±)-morphine **98**) using this approach. Starting from aldehyde **142**, the Diels-Alder precursor **143** was synthesised in 56% yield over six steps. Heating **143** in a mixture of decalin and NEt_3 at 240 °C for 24 h gave an 80:20 mixture of epimeric Diels-Alder adducts **144** and **145** in 69% combined yield. Reaction was observed to proceeded via an *endo* transition state, forming the correct relative configuration between the C(5), C(6), C(13) and C(14) stereogenic centres within **144** and **145**. The synthesis was subsequently completed in 5% yield over thirteen steps, relying on the stereochemistry at C(13) to impart the correct relative configuration at the C(9)-stereogenic centre within (±)-codeine **120** (Scheme 11).[33]



142 (±)-**143** 56% (6 steps) (±)-**144** (±)-**145** (±)-codeine **120** 5% (13 steps)

Scheme 11. *Reagents and conditions*: (i) NEt_3, decalin, 240 °C, 24 h. [R = CO_2Me].

2.2 Chapter aim

The aim of this chapter is to delineate an asymmetric synthesis of (−)-morphine **98** reliant on a Diels-Alder reaction to construct the C ring. It was envisaged that by initially forming the C(9)-stereogenic centre in an asymmetric fashion (as may readily be achieved utilising the conjugate addition of a lithium amide reagent derived from enantiopure α-methylbenzylamine), stereoinduction would impart the correct absolute configuration on the C(5), C(6), C(13) and C(14) stereogenic centres within (−)-morphine **98**, thereby improving on the strategy used by Stork *et al.*[33]

2.3 First retrosynthetic analysis of (−)-morphine

The first retrosynthetic analysis of (−)-morphine **98** commences by opening of the cyclohexene C ring to give Diels-Alder precursor **146**. Conversion of the diene within **146** to a Weinreb amide,[41] as in **148**, would allow the diene to be made in the forward sense via reduction of the Weinreb amide to an aldehyde, homologation with a Wittig salt similar to **147** and subsequent elimination of [P]OH to generate the diene **146**. Cleavage of the C−O bond within benzofuran **148** would generate alkene **149**, with reaction in the forward sense occurring upon treatment of **149** with I_2.[42] Disconnection of the disubstituted alkene **149** would give the β-amino hydroxamate **150**, with R = α-methylbenzyl; a Heck reaction[43] in the forward sense forming the desired eight membered ring. Disconnection of the C(3)−N bond within **150** reveals α,β-unsaturated hydroxamate **151**, which can be made in the forward sense via the conjugate addition of the lithium amide derived from **152**[44] to **151**, the second key stereocontrolled step. Disconnection of the olefin within **151** gives aldehyde **155**, itself originating from isovanillin derivative **156** via homologation. Aldehyde **156** can in turn be made via bromination of isovanillin **157** and protection of the acidic phenolic functionality (Figure 16).

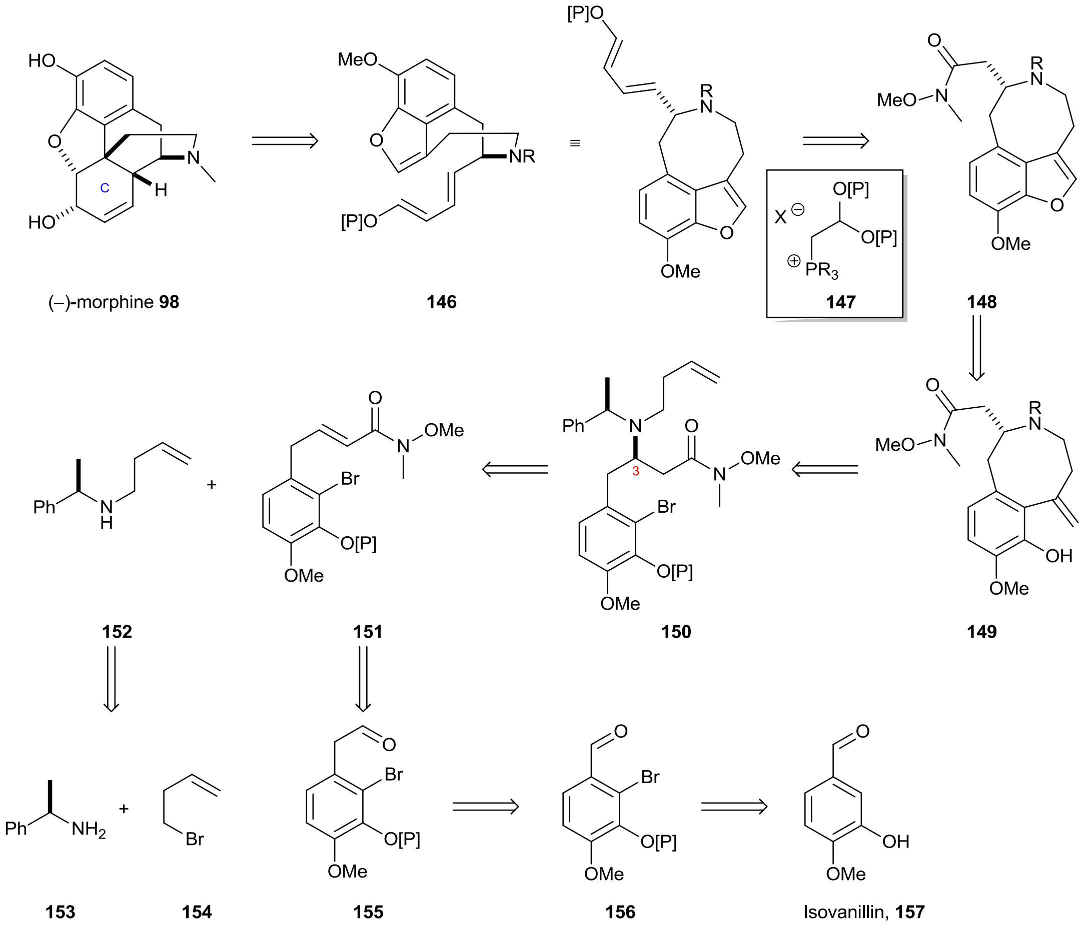
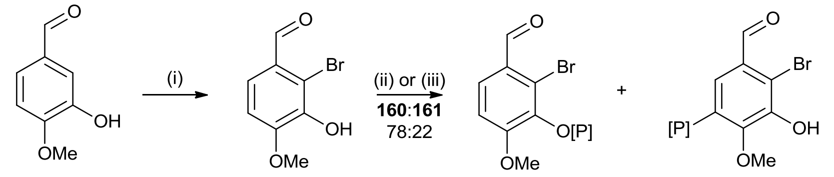


Figure 16. First retrosynthetic analysis of (−)-morphine **98**.

2.3.1 First attempted synthesis of (−)-morphine

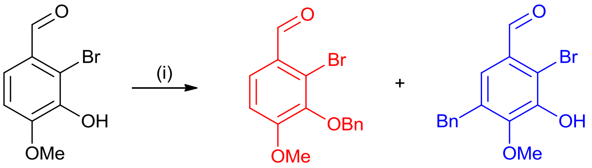
Initial synthetic endeavours were aimed at the synthesis of the isovanillin derivative **156**. Bromination of isovanillin **157** under literature conditions[20] with Br_2 and *in situ* generated catalytic $FeBr_3$ gave aldehyde **126** in 61% yield. Three potential protecting groups were originally chosen to protect the phenolic functionality: TES, allyl and benzyl. Treatment of **126** with TESCl and DMAP resulted in 53% conversion to **158**, isolated in 39% yield. The low yield is presumably due to the high steric congestion around the phenolic functionality. Allylation of **126** upon treatment with NaH and allyl bromide gave a 78:22 mixture of the desired *O*-allyl protected phenol **160** and the detrimental C(5)-allyl product **161**,[45] isolated in 45 and 20% yield, respectively (Scheme 12).



Isovanillin **157** **126**, 61% **158**, [P] = TES, 39% **159**, [P] = TES, 0%
160, [P] = Allyl, 45% **161**, [P] = Allyl, 20%

Scheme 12. *Reagents and conditions*: (i) Br_2, Fe, NaOAc, AcOH, rt, 1 h; (ii) TESCl, DMAP, CH_2Cl_2, rt, 48 h; (iii) NaH, DMF, rt, 1 h, then allyl bromide, rt, 24 h.

O-Benzyl protection of **126** was investigated more extensively, but again under a range of conditions[46] a mixture of the desired product **162** and the unwanted C(5)-benzylated product **163** was observed. The optimal conditions of deprotonation with NaH followed by benzylation with BnBr in DMF at rt gave an 83:17 mixture of **162** and **163** which were isolated in 51% and 15% yield, respectively. These conditions were therefore employed upon scale up (Scheme 13).



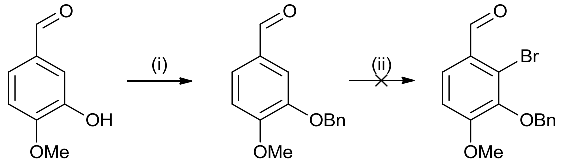
126 **162** **163**

Solvent	Base	X	162:163
DMF	NaH	Br	83:17
DMF	K_2CO_3	Br	63:37
DMF	Cs_2CO_3	Br	66:34
DMF	NEt_3	Br	36:64
Acetone	K_2CO_3	Br	64:36
Acetone	Cs_2CO_3	Br	51:49
Acetone	NEt_3	Br	45:55

Solvent	Base	X	162:163
DMF	K_2CO_3	OTs	62:38
DMF	Cs_2CO_3	OTs	64:36
DMF	NEt_3	OTs	12:88
Acetone	K_2CO_3	OTs	55:45
Acetone	Cs_2CO_3	OTs	31:69
Acetone	NEt_3	OTs	43:57
EtOH	K_2CO_3	Cl	82:18

Scheme 13. *Reagents and conditions*: (i) BnX, base, solvent, rt, 48 h.

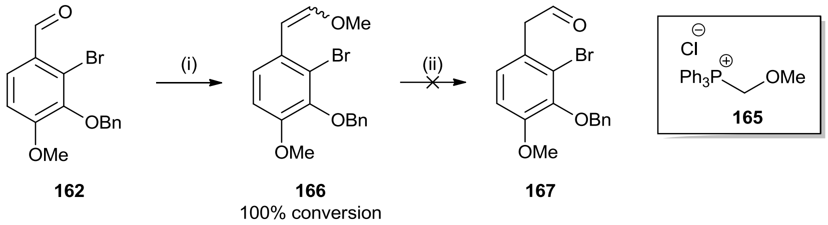
As a potential solution to the issues with regioselectivity encountered with the protection of **126**, it was envisaged that reversing the order of reactions [i.e., phenolic protection then C(2)-bromination] would allow access to **162**. Protection of isovanillin **157** with TES or an allyl group was not attempted due to the incompatibility of these protecting groups with the ensuing bromination reaction conditions. *O*-Benzyl protection, in contrast, was believed to be compatible with the bromination conditions. Thus, benzylation of isovanillin **157** gave **164** in 76% yield,[47] with no sign of any undesired S_EAr reactions occurring, as determined by inspection of the 400 MHz ^{1}H NMR spectrum of the crude reaction mixture. Bromination of **164**, however, did not result in the formation of **162**, so this route was abandoned (Scheme 14).



Isovanillin **157** **164**, 76% **162**

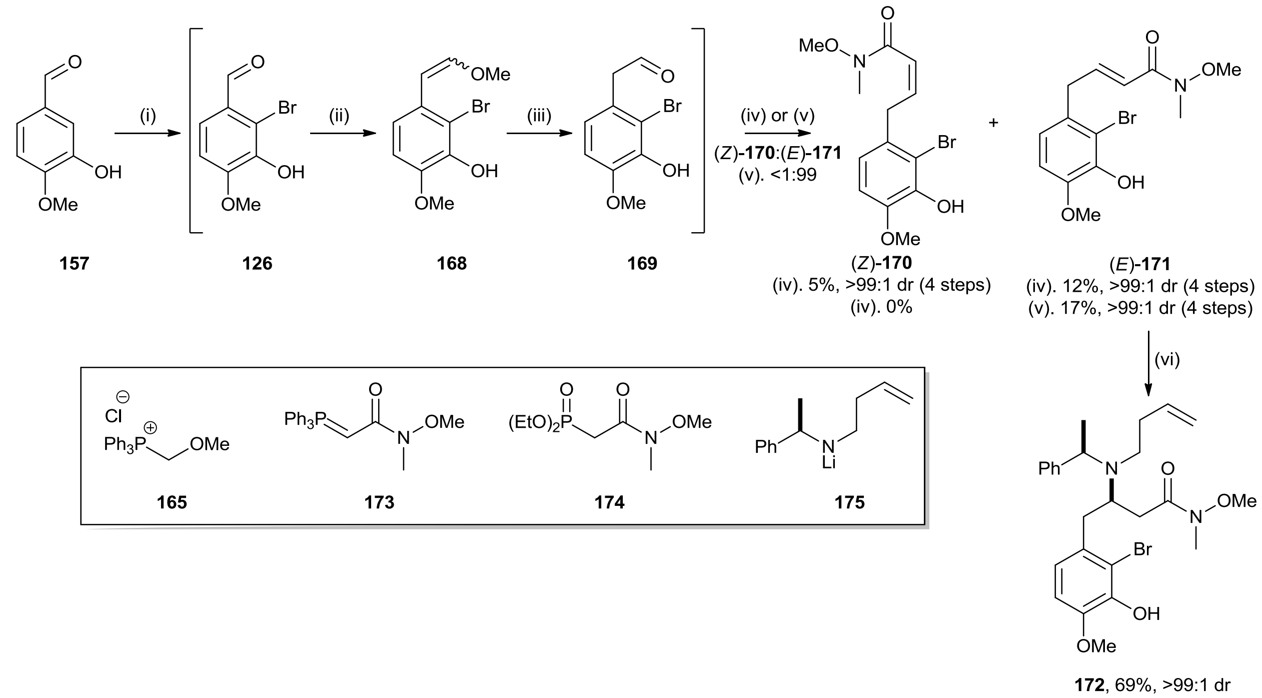
Scheme 14. *Reagents and conditions*: (i) BnBr, K_2CO_3, DMF, 60 °C, 16 h; (ii) Br_2, Fe, NaOAc, AcOH, rt, 1 h.

Using the original route to access **162**, further elaboration of this intermediate was attempted. Homologation of **162** with (methoxymethyl)triphenylphosphonium chloride **165** and KO^{t}Bu gave 100% conversion to enol ether **166** as a mixture of diastereoisomers.[48] Unfortunately, hydrolysis of enol ether **166** with HCO_2H[49] did not result in the formation of the desired aldehyde **167** (Scheme 15).



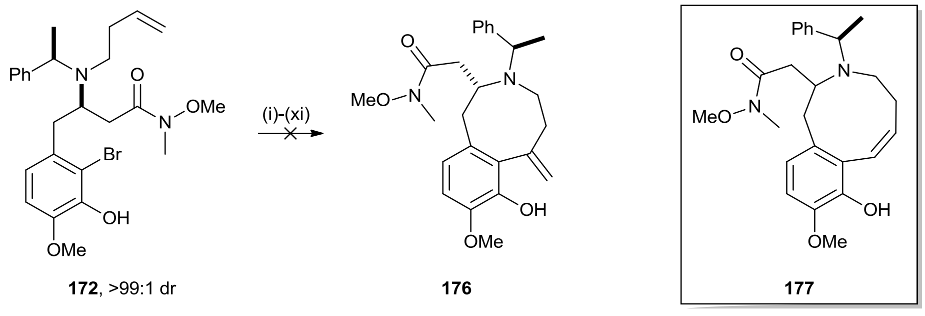
Scheme 15. *Reagents and conditions*: (i) **165**, KO^{t}Bu, THF, rt, 18 h; (ii) HCO_2H, CH_2Cl_2, rt, 48 h.

With a range of problems encountered in the synthesis of a protected, brominated isovanillin derivative **156**, attention turned to a protecting group free synthesis. Consequently, bromination of isovanillin **157** gave aldehyde **126** which was immediately treated with (methoxymethyl)triphenylphosphonium chloride **165** and KO^{t}Bu to give enol ether **168** as a 64:36 mixture of diastereoisomers, as determined by peak integration of the 400 MHz ^{1}H NMR spectrum of the crude reaction mixture. Subsequent hydrolysis of **168** with HCO_2H gave aldehyde **169** which was immediately subjected to Wittig olefination with **173**[50] to give (*Z*)-**170** and (*E*)-**171** in 5 and 12% yield, respectively, over four steps, both isolated in >99:1 dr.[51] Alternatively, Wadsworth-Emmons homologation of **169** with the anion generated from phosphonoacetamide **174**[52] and MeMgBr[53] gave α,β-unsaturated hydroxamate (*E*)-**171** in >99:1 dr, which was isolated in 15% yield and >99:1 dr over four steps. Conjugate addition of lithium amide **175**[54] to (*E*)-**171** gave β-amino hydroxamate **172** in 69% yield and >99:1 dr (Scheme 16). The sense of diastereocontrol in this conjugate addition reaction was assigned relative to the transition state mnemonic developed by Davies *et al.*[55] for the lithium amide conjugate addition reaction of secondary lithium amides derived from α-methylbenzylamine to α,β-unsaturated esters.



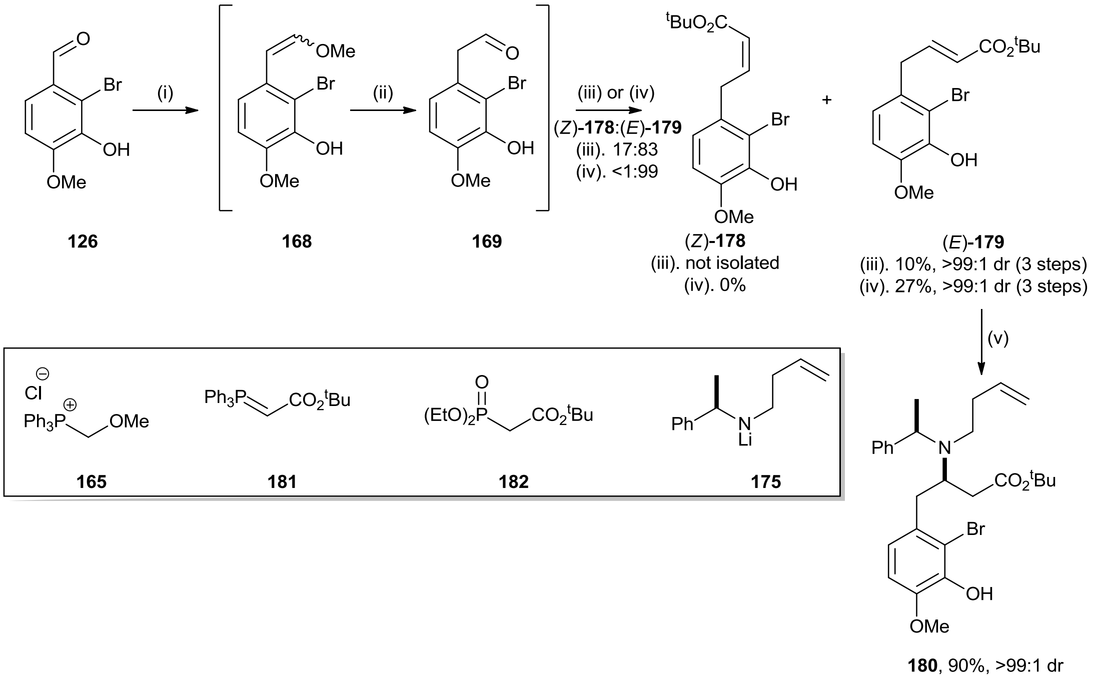
Scheme 16. *Reagents and conditions*: (i) Br_2, Fe, NaOAc, AcOH, rt, 1 h; (ii) **165**, KO^tBu, THF, rt, 18 h; (iii) HCO_2H, CH_2Cl_2, rt, 48 h; (iv) **173**, CH_2Cl_2, rt, 24 h; (v) **174**, MeMgBr, THF, rt, 15 min, then **169**, THF, reflux, 2.5 h; (vi) **175**, THF, −78 °C, 2 h.

The next step in the synthesis required the intramolecular Heck coupling of the aryl bromide functionality to the alkene within **172**. Three potential problems were identified with this reaction: firstly, the electron rich aromatic ring could hinder the oxidative addition of palladium into the Ar−Br bond; secondly, the large steric bulk around the Ar−Br bond could further hinder oxidative addition, especially if the ligands bound to the palladium are large; and finally, there are two potential regioisomers that could result from the Heck reaction, namely the desired compound with the exocyclic methylene group **176** and the corresponding undesired product with the endocyclic alkene **177**. Previous examples found in the literature, however, suggest that reaction could proceed to give the desired exocyclic alkene **176**.[56] To address the first two issues, reaction conditions that had been reported to be efficacious for electron rich aryl bromides and those for sterically encumbered reaction centres were trialled.[57] Unfortunately, under the wide range of coupling conditions examined, reaction only resulted in returned starting material, with neither **176** or **177** being detected by mass spectrometry or in the 400 MHz ^1H NMR spectra of the crude reaction mixtures (Scheme 17).



Scheme 17. *Reagents and conditions*: (i) $Pd(PPh_3)_4$, K_2CO_3, MeCN, reflux, 72 h; (ii) $Pd(OAc)_2$, MeCN, K_2CO_3, reflux, 72 h; (iii) $PdCl_2(PhCN)_2$, NaOAc, DMG, DMF, 130 °C, 16 h; (iv) $Pd(OAc)_2$, TBAC, Cy_2NH, DMF, 85 °C, 72 h; (v) $Pd(OAc)_2$, TBAC, K_2CO_3, DMF, rt, 72 h; (vi) $Pd_2(dba)_3$, Cy_2NH, PBu_3, DMF, rt, 72 h; (vii) $Pd_2(dba)_3$, Cy_2NH, PCy_3, DMF, rt, 72 h; (viii) $Pd_2(dba)_3$, Cy_2NMe, PBu_3, DMF, rt, 72 h; (ix) $Pd_2(dba)_3$, Cy_2NMe, PCy_3, DMF, rt, 72 h; (x) $Pd_2(dba)_3$, Cy_2NMe, PMe_3, DMF, rt, 72 h; (xi) $Pd_2(dba)_3$, Cy_2NMe, PMe_2Ph, DMF, rt, 72 h.

Reactions involving palladium in the presence of Weinreb amides are relatively sparse in the literature,[58,59] and it was therefore hypothesised that the Weinreb amide functionality within **172** was in some way sequestering the palladium, hence suppressing any reactivity. To test this hypothesis, the analogous *tert*-butyl ester **180** (the compatibility of *tert*-butyl esters with palladium coupling reactions is well established)[60] was synthesised. Following an equivalent procedure as for **171**, α,β-unsaturated ester (*E*)-**179** was synthesised from aldehyde **126** in 10% yield and >99:1 dr over three steps via Wittig homologation of **169** with **181**,[61] or in 27% yield and >99:1 dr over three steps via the Wadsworth-Emmons homologation of **169** with **182**.[62] Conjugate addition of lithium amide **175** to α,β-unsaturated ester (*E*)-**179** gave β-amino ester **180** in 90% yield and >99:1 dr (Scheme 18). The sense of diastereocontrol in this conjugate addition reaction was initially assigned relative to the transition state mnemonic developed by Davies *et al.*[55] The relative configuration within **180** was later unambiguously confirmed by single crystal X-ray diffraction analysis of the corresponding HBF_4 salt, with the absolute configuration assigned relative to the known (*R*)-configuration of the C(α)-stereogenic centre. The assignment of the absolute configuration within **180**·HBF_4 was further supported by the determination of a Flack *x* parameter[63,64] for the structure of **180**·HBF_4 of −0.05(2) (Figure 17). The (*R*,*R*)-configuration within β-amino hydroxamate **172** was therefore assigned by analogy.



Scheme 18. *Reagents and conditions*: (i) **165**, KO^tBu, THF, rt, 18 h; (ii) HCO_2H, CH_2Cl_2, rt, 48 h; (iii) **181**, CH_2Cl_2, rt, 24 h; (iv) **182**, MeMgBr, THF, rt, 15 min, then **169**, THF, reflux, 2.5 h; (v) **175**, THF, −78 °C, 2 h.

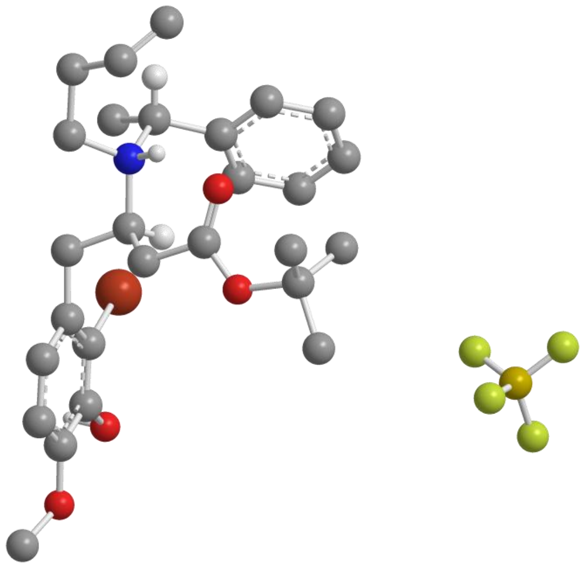
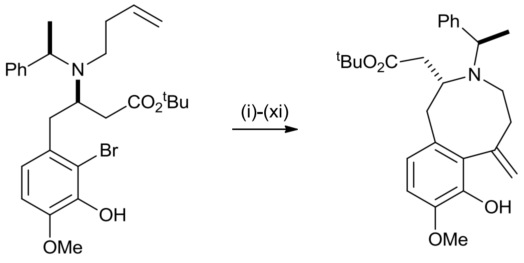


Figure 17. X-ray crystal structure of **180**·HBF_4 (selected H atoms are omitted for clarity).

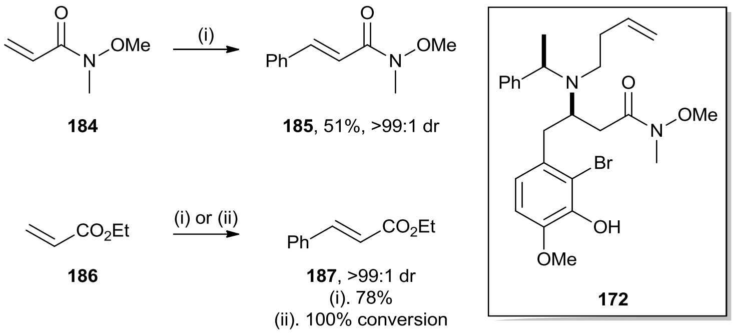
Heck reaction under a wide range of reaction conditions[57] was unsuccessful, with only starting material and no trace of the desired product **183** being detected by mass spectrometry or ^{1}H NMR spectroscopic analysis of the crude reaction mixtures (Scheme 19).



180 **183**

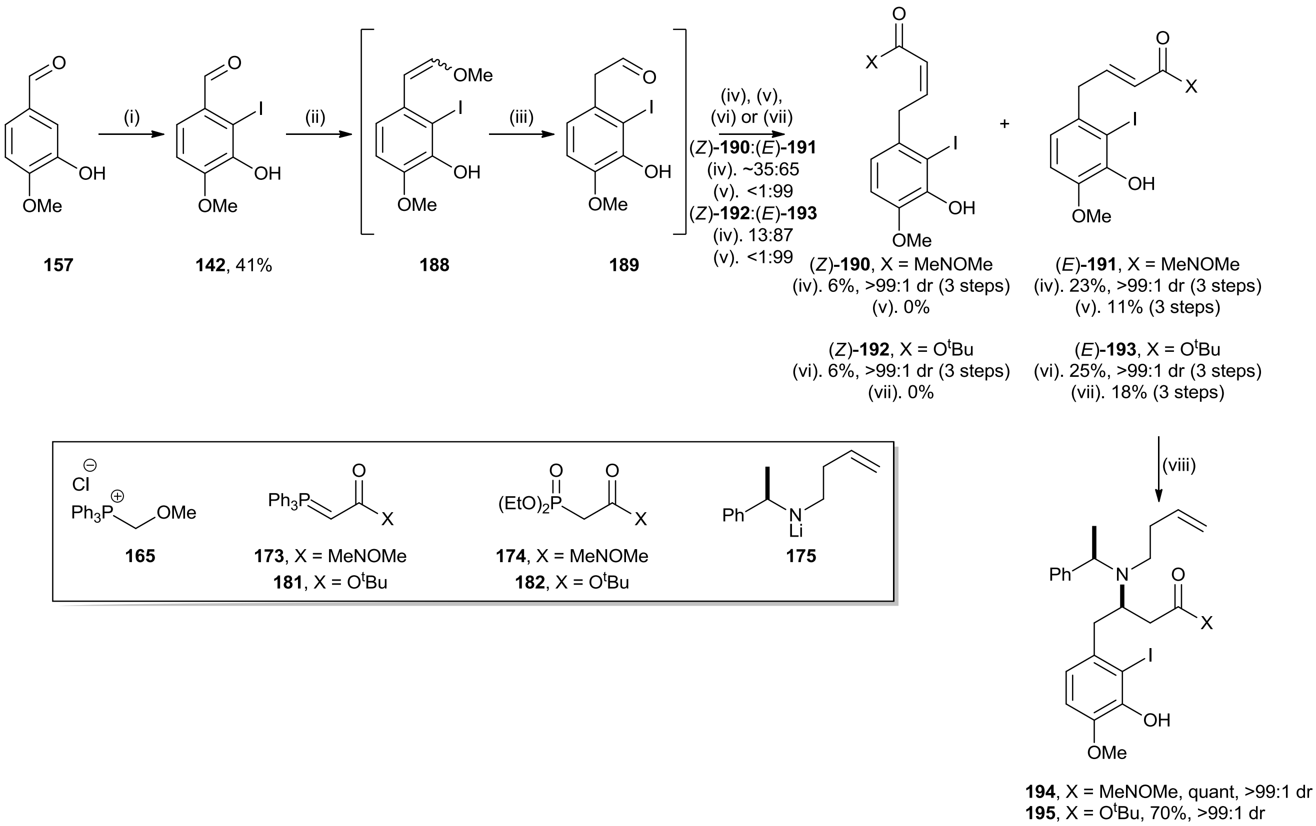
Scheme 19. *Reagents and conditions*: (i) $Pd(OAc)_2$, TBAC, Cy_2NMe, DMF, rt, 72 h; (ii) $Pd(OAc)_2$, TBAC, $NaHCO_3$, DMF, rt, 72 h; (iii) $Pd_2(dba)_3$, Cy_2NMe, PBu_3, DMF, rt, 72 h; (iv) $Pd_2(dba)_3$, Cy_2NMe, PCy_3, DMF, rt, 72 h; (v) $Pd_2(dba)_3$, Cy_2NMe, PMe_3, DMF, rt, 72 h; (vi) $Pd_2(dba)_3$, Cy_2NMe, PMe_2Ph, DMF, rt, 72 h; (vii) $Pd(OAc)_2$, TBAC, Cy_2NMe, DMF, 90 °C, 72 h; (viii) $Pd(OAc)_2$, TBAC, $NaHCO_3$, DMF, 90 °C, 72 h; (ix) $Pd_2(dba)_3$, Cy_2NMe, PBu_3, DMF, 90 °C, 72 h; (x) $Pd_2(dba)_3$, Cy_2NMe, PCy_3, DMF, 90 °C, 72 h; (xi) $PdCl_2(PhCN)_2$, NaOAc, DMG, DMF, 130 °C, 16 h.

To further confirm that the presence of the Weinreb amide functionality within **172** was not hindering the reaction, the Heck coupling between PhI and acrylate **184**[65] was achieved under Jeffery's conditions,[66] giving the desired α,β-unsaturated hydroxamate **185** in 51% yield and >99:1 dr. Finally, to investigate whether any other functionality within **172** was hindering reaction, the Heck coupling between PhI and ethyl acrylate **186** was performed, again under Jeffery's conditions, both in the presence and absence of a stoichiometric amount of β-amino hydroxamate **172**. Under both sets of conditions, complete conversion of PhI to ethyl cinnamate **187** was observed, providing strong evidence that any functionality within **172** was not sequestering the reactivity of the catalytic palladium species (Scheme 20).



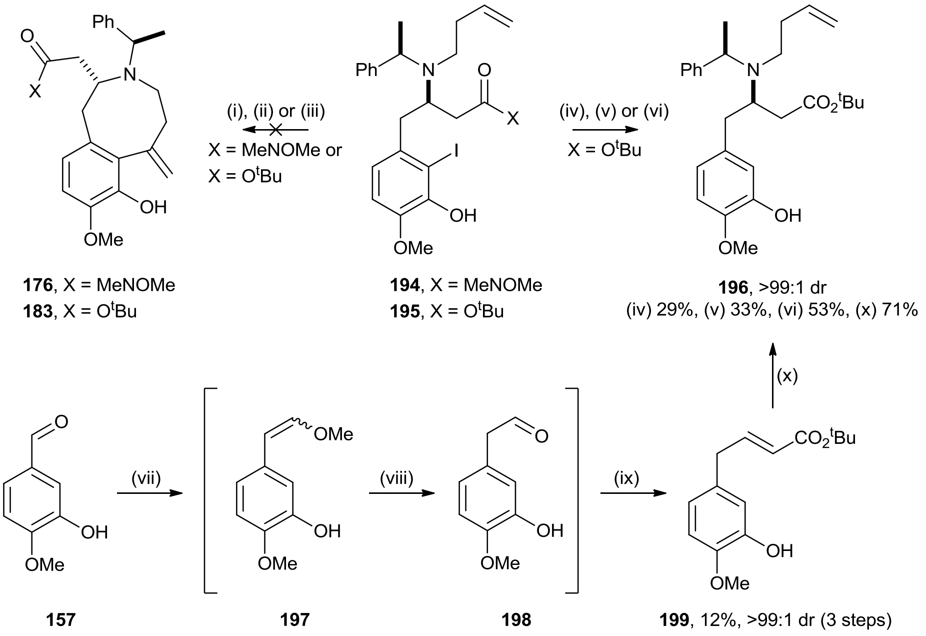
Scheme 20: *Reagents and conditions*: (i) PhI, Pd(OAc)$_2$, K$_2$CO$_3$, TBAC, DMF, rt, 72 h; (ii) PhI, **172**, Pd(OAc)$_2$, K$_2$CO$_3$, TBAC, DMF, rt, 72 h.

With the compatibility of all the functional groups within **172** to the reaction conditions established, and with the desired intramolecular Heck reaction still not occurring, the corresponding aryl iodides were synthesised as it was hypothesised that the weaker Ar−I bonds would allow oxidative addition to occur more readily.[67] Following a similar synthetic strategy as for bromides **172** and **180**, iodination of isovanillin **157** with ICl[68] gave aldehyde **142** in 41% yield. Ensuing homologation with Wittig reagent **173** gave a ~35:65 mixture of (*Z*)-**190** and (*E*)-**191**, which were isolated in 6 and 23% yield, respectively, over three steps and >99:1 dr in each case. The analogous homologation with the Wadsworth-Emmons reagent **174** gave (*E*)-**191** in >99:1 dr, which was isolated in >99:1 dr and 11% yield over three steps. For the corresponding *tert*-butyl ester, homologation with Wittig reagent **181** gave an 13:87 mixture of (*Z*)-**192** and (*E*)-**193**, which were isolated in 6 and 25% yield, respectively, over three steps and >99:1 dr in each case. Wadsworth-Emmons homologation with **182** gave (*E*)-**193** in >99:1 dr, which was isolated in 18% yield and >99:1 dr over three steps. Ensuing conjugate addition of lithium amide **175** to α,β-unsaturated hydroxamate (*E*)-**191** and α,β-unsaturated ester (*E*)-**193** gave β-amino carbonyls **194** and **195** in quantitative and 70% yield, respectively, both in >99:1 dr (Scheme 21).



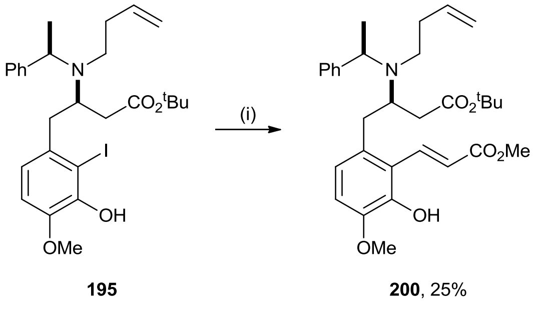
Scheme 21. *Reagents and conditions*: (i) ICl, pyridine, CH_2Cl_2, rt, 96 h; (ii) **165**, KO^tBu, THF, rt, 18 h; (iii) HCO_2H, CH_2Cl_2, rt, 48 h; (iv) **173**, CH_2Cl_2, rt, 24 h; (v) **174**, MeMgBr, THF, rt, 15 min, then **189**, THF, reflux, 2.5 h; (vi) **181**, CH_2Cl_2, rt, 24 h; (vii) **182**, MeMgBr, THF, rt, 15 min, then **189**, THF, reflux, 2.5 h; (viii) **175**, THF, −78 °C, 2 h.

Heck reaction of Weinreb amide **194** under a range of conditions again failed, only resulting in returned starting material. Treatment of ester **195** under the same selection of coupling reaction conditions also resulted in returned starting material. However, treatment of **195** under Jeffery's conditions[66] at elevated temperature resulted in the formation of proto-deiodonated **196**, which was isolated in 29% yield, with 5% returned starting material also isolated. An authentic sample of **196** was synthesised using comparable methodology to that used in the syntheses of **172**, **180**, **194** and **195** (*vide supra*), giving **196** in 9% overall yield from isovanillin, thus confirming the identity of **196**. The yield of **196** derived from the attempted Heck reaction of **195** could be improved by use of $Pd_2(dba)_3$, Cy_2NMe and PBu_3 in DMF at 90 °C, resulting in 33% yield of **196**, and further improvement was found by the use of $Pd(PPh_3)_4$ at elevated temperature, which gave 100% consumption of starting material, with **196** subsequently being isolated in 53% yield (Scheme 22).



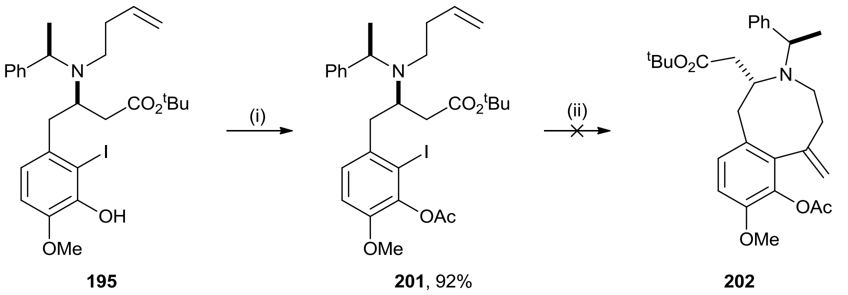
Scheme 22. *Reagents and conditions*: (i) $Pd_2(dba)_3$, Cy_2NMe, PMe_3, DMF, rt, 72 h; (ii) $Pd_2(dba)_3$, Cy_2NMe, PMe_2Ph, DMF, rt, 72 h; (iii) $Pd(OAc)_2$, TBAC, $NaHCO_3$, DMF, rt, 72 h; (iv) $Pd(OAc)_2$, TBAC, $NaHCO_3$, DMF, 90 °C, 48 h; (v) $Pd_2(dba)_3$, Cy_2NMe, PBu_3, DMF, 90 °C, 48 h; (vi) $Pd(PPh_3)_4$, K_2CO_3, MeCN, 90 °C, 48 h; (vii) **165**, KO^tBu, THF, rt, 18 h; (viii) HCO_2H, CH_2Cl_2, rt, 48 h; (ix) **182**, MeMgBr, THF, rt, 15 min, then **198**, THF, reflux, 2.5 h; (x) **175**, THF, −78 °C, 2 h.

Encouraged by the observation of β-amino ester **196**, whose formation requires oxidative addition of palladium into the Ar−I bond to have occurred, further investigations were initiated. Firstly, Heck coupling of iodide **195** to the more active coupling partner methyl acrylate was attempted. Under the optimal conditions for the formation of **196** from iodide **195**, Heck coupling proceeded to give **200** in 25% yield[69] (Scheme 23).



Scheme 23. *Reagents and conditions*: (i) methyl acrylate, $Pd(PPh_3)_4$, K_2CO_3, MeCN, 90 °C, 48 h.

With evidence that an intermolecular Heck reaction with **195** was possible, it was hypothesised that the rate of proto-depalladation is much greater than that for the formation of the corresponding eight membered ring. As all reactions were being performed under anhydrous conditions, it was believed that the source of the proton was the phenolic functionality adjacent to the site of oxidative addition. Removal of this acidic proton was therefore desirable, and was readily achieved by acetylation with Ac_2O and pyridine to give **201** in 92% yield. Unfortunately, attempted Heck reaction of **201** using the conditions developed for **195** resulted in returned starting material, suggesting that protection of the phenolic functionality prevented oxidative addition from occurring (Scheme 24).[70] Owing to this failure, endeavours along this synthetic route were abandoned in favour of an alternative strategy.



Scheme 24. *Reagents and conditions*: (i) Ac_2O, pyridine, rt, 16 h; (ii) $Pd(PPh_3)_4$, K_2CO_3, MeCN, 90 °C, 90 h.

2.4 Second retrosynthetic analysis of (−)-morphine

In the first proposed retrosynthetic analysis of (−)-morphine **98**, the key Diels-Alder step was near the conclusion of the synthesis, and with the limited literature precedent for Diels-Alder reactions of benzofurans, it was desirable to have this transformation earlier in the synthesis to enable assessment of it its feasibility. The following approach was therefore adopted: functional group interconversions of (−)-morphine **98** involving removal of the C(6)-hydroxyl group, addition of a carbonyl at C(10), and conversion of the *N*-methyl group into an α-methylbenzyl group gives **203**. In the forward sense, these reactions could be achieved by hydrogenolysis with *in situ* reductive alkylation, reduction of the C(10)-carbonyl, and oxidation of C(6) using SeO_2 to give the corresponding ketone; subsequent diastereoselective reduction would then give (−)-morphine **98**.[28] Breaking of the C(10)−C(11) bond opens the B ring, with ring closure in the forward sense occurring upon Friedel-Crafts acylation of **204**. A retro Diels-Alder reaction of the cyclohexene C ring followed by functional group interconversions (including the homologation of the carboxylic acid within **204**) reveals lithium amide adduct **205** as a possible intermediate, which can be readily synthesised from the conjugate addition of lithium amide **103** to α,β,γ,δ,ε,ζ-unsaturated ester **207**. The initial targets were therefore the requisite amine **206** and α,β,γ,δ,ε,ζ-unsaturated ester **207** (Figure 18).

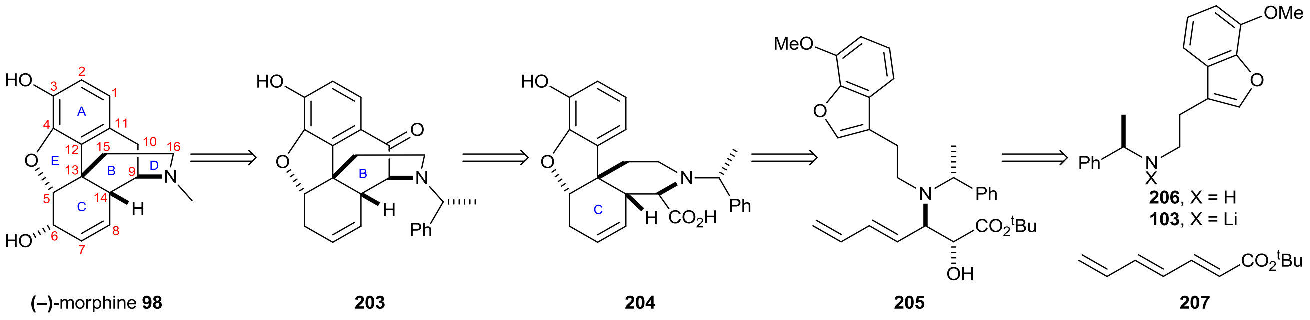
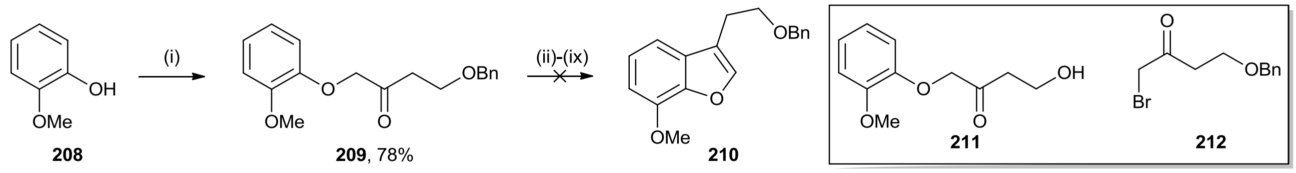


Figure 18. Summary of the second retrosynthetic analysis of (−)-morphine **98**.

2.4.1 Second attempted synthesis of (−)-morphine

Several synthetic routes to amine **206** were explored. Initially, it was envisaged that alkylation of guiacol **208** with bromide **212** followed by Lewis acid mediated cyclisation would yield benzofuran **210**, with subsequent manipulation resulting in the formation of amine **206**. The required alkylation of **208** with bromide **212**[71] proceeded to give **209** in 78% yield, but under a range of conditions[72] the required cyclisation failed to occur, with *O*-debenzylation to give **211** being observed in two cases (Scheme 25).

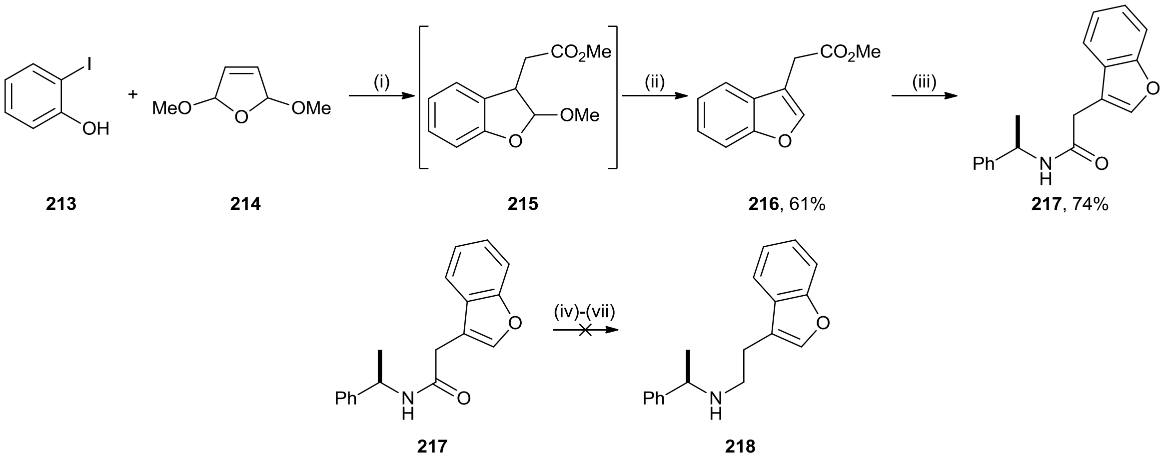


Conditions	Result
(ii)	**211** isolated in 67% yield
(iii)	Returned starting material
(iv)	Complex mixture
(v)	Returned starting material

Conditions	Result
(vi)	100% conversion to **211**
(vii)	Returned starting material
(viii)	Returned starting material
(ix)	Complex mixture

Scheme 25. *Reagents and conditions*: (i) NaH, DMF, rt, 1 h, then **212**, rt 16 h; (ii) BCl_3, CH_2Cl_2, −78 °C, 1 h; (iii) PPA, CH_2Cl_2, rt, 3 h; (iv) H_2SO_4, CH_2Cl_2, rt, 3 h; (v) $TiCl_4$, CH_2Cl_2, rt, 3 h; (vi) $AlCl_3$, CH_2Cl_2, rt, 3 h; (vii) $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt, 3 h; (viii) $InCl_3$, CH_2Cl_2, rt, 3 h; (ix) $BF_3{\cdot}OEt_2$, CH_2Cl_2, reflux, 18 h.

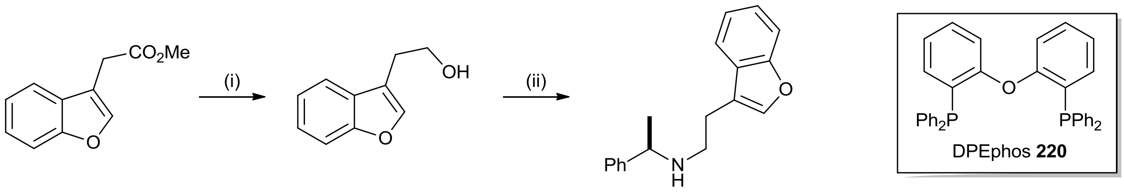
As an alternative synthetic route, Samizu and Ogasawara[73] have previously reported the synthesis of methyl 3-benzofuranylacetate **216** via a palladium mediated coupling between 2-iodophenol **213** and dihydrofuran **214** to give acetal **215**. Subsequent Lewis acid mediated elimination of MeOH then gives **216**, from which it was hypothesised that it would be possible to synthesise the C(7′)-demethoxy amine **218** as a model system. Following a modified procedure, Heck reaction[74] between iodide **213** and dihydrofuran **214** gave acetal **215**, which was immediately treated with $BF_3{\cdot}OEt_2$ to give benzofuran **216** in 61% yield over two steps. Heating benzofuran **216** in (*R*)-α-methylbenzylamine (*R*)-**153** then gave amide **217** in 74% yield. Unfortunately, under a range of conditions, amide **217** could not be completely reduced to amine **218**: treatment of **217** with nine equivalents of $LiAlH_4$ in THF at reflux for 88 h only resulted in 50% conversion to **218** (Scheme 26).



Conditions	Result
(iv)	Returned starting material
(v)	50% conversion to **218**
(vi)	Complex mixture
(vii)	Complex mixture

Scheme 26. *Reagents and conditions*: (i) $Pd(OAc)_2$, $^iPr_2NEt$, TEBAC, DMF, 80 °C, 18 h; (ii) $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt, 16 h; (iii) (*R*)-α-methylbenzylamine (*R*)-**153**, 130 °C, 16 h, then 150 °C, 10 h; (iv) $LiAlH_4$ (3.0 eq), Et_2O, reflux, 12 h; (v) $LiAlH_4$ (9.0 eq), THF, reflux, 88 h; (vi) DIBAL-H, PhMe, reflux, 18 h; (vii) $BH_3{\cdot}THF$, THF, rt, 60 h.

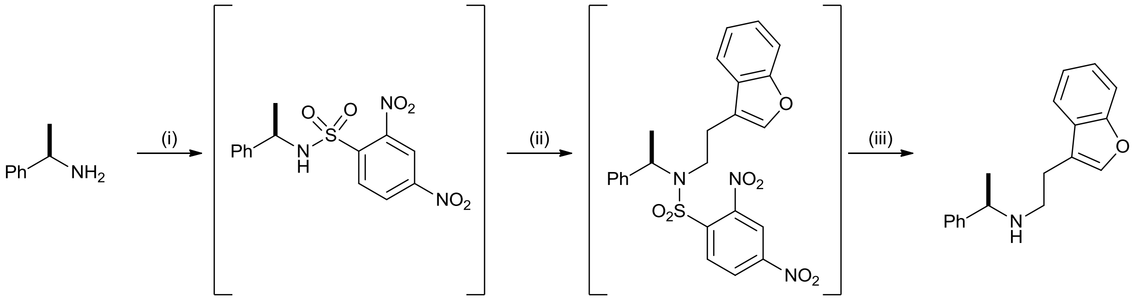
A variety of other strategies where therefore investigated for the conversion of **216** to **218**. Firstly, using the method of "hydrogen borrowing" developed by Williams *et al.*,[75] reaction of alcohol **219** (derived from reduction of ester **216** with $LiAlH_4$) with (*R*)-α-methylbenzylamine (*R*)-**153** in the presence of [Ru(*p*-cymene)Cl_2]$_2$ and DPEphos **220** gave amine **218** in 27% yield (Scheme 27).



216 **219**, 94% **218**, 27%

Scheme 27. *Reagents and conditions*: (i) $LiAlH_4$, Et_2O, rt, 1 h; (ii) (*R*)-α-methylbenzylamine (*R*)-**153**, [Ru(*p*-cymene)Cl_2]$_2$, DPEphos **220**, PhMe, 48 h.

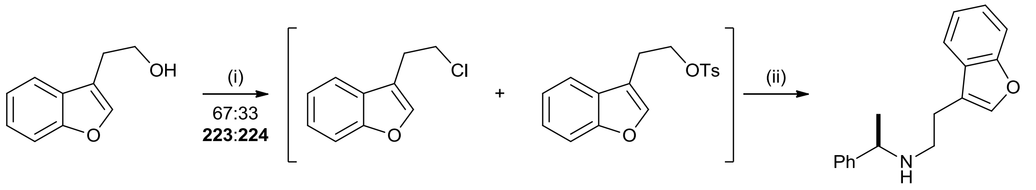
Secondly, using the chemistry developed by Fukuyama *et al.*,[76] reaction of (*R*)-α-methylbenzylamine (*R*)-**153** with 2,4-dinitrobenzenesulfonyl chloride gave sulfonamide **221**, which proved unstable to column chromatography, with **221** being isolated in ~90% purity. Subsequent Mitsunobu[77] reaction of **221** with alcohol **219** gave tertiary sulfonamide **222**, again in ~90% puritiy due to its incompatibility to chromatographic media. Ensuing removal of the dinosyl group with mercaptoacetic acid gave the desired amine **218** in 6% yield over three steps (Scheme 28).



(*R*)-**153** **221** **222** **218**, 6% (3 steps)

Scheme 28. *Reagents and conditions*: (i) 2,4-dinitrobenzenesulfonyl chloride, NEt_3, CH_2Cl_2, 0 °C to rt, 15 min; (ii) **219**, PPh_3, DEAD, THF, 0 °C to rt, 16 h; (iii) mercaptoacetic acid, NEt_3, CH_2Cl_2, rt, 1 h.

The third synthetic route to amine **218** involved treatment of alcohol **219** with TsCl to generate a 67:33 mixture of **223** and **224**. Treatment of this mixture with (*R*)-α-methylbenzylamine (*R*)-**153** in the presence of NaI gave **218** in 56% yield over two steps, and >99:1 er,[78] representing the most efficient synthesis of **218** from alcohol **219** (Scheme 29).

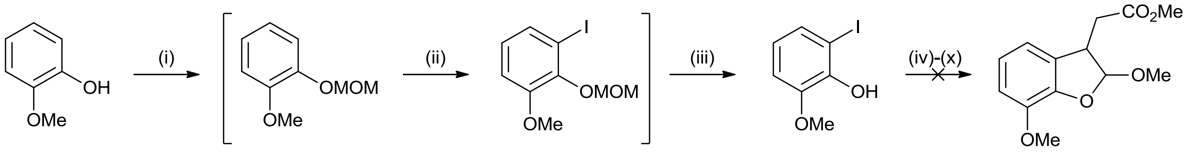


219 **223** **224** **218**, 56% (2 steps), >99:1 er

Scheme 29. *Reagents and conditions*: (i) TsCl, DMAP, pyridine, rt, 16 h; (ii) (*R*)-α-methylbenzylamine (*R*)-**153**, NaI, MeCN, reflux, 18 h.

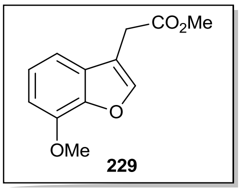
With an optimised synthetic route to model amine **218** available, attention turned to the synthesis of the desired C(7′)-methoxy substituted analogue **206**. If iodide **227** could be accessed, it was believed that a similar procedure as used for the synthesis of benzofuran **216** would be applicable to that of **229**. Following a modified literature procedure,[79] *O*-MOM protection of guiacol **208**, followed by directed lithiation of **225** upon treatment with BuLi and iodination with I_2 gave iodide **226**.

Subsequent hydrolysis of the *O*-MOM ether gave the desired iodide **227** in 53% yield over three steps. Treatment of **227** with dihydrofuran **214** under a range of conditions[56,57a,73,80] failed to give **228**, with either returned starting material or a complex mixture being observed (Scheme 30).



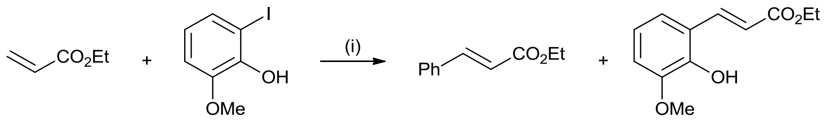
208 **225** **226** **227**, 53% (3 steps) **228**

Conditions	Result
(iv)	Returned starting material
(v)	Returned starting material
(vi)	Complex mixture
(vii)	Complex mixture
(viii)	Returned starting material
(ix)	Returned starting material
(x)	Returned starting material



Scheme 30. *Reagents and conditions*: (i) NaH, DMF, rt, 30 min, then MOMCl, 0 °C to rt, 16 h; (ii) BuLi, Et_2O, 0 °C, 1 h, then I_2, THF, 0 °C to rt, 16 h; (iii) HCl, THF/MeOH (v/v 1:1), rt, 48 h; (iv) **214**, $Pd(OAc)_2$, $^iPr_2NEt$, TEBAC, DMF, 60 °C, 6 h; (v) **214**, $Pd(OAc)_2$, $^iPr_2NEt$, TEBAC, DMF, 80 °C, 18 h; (vi) **214**, $Pd(OAc)_2$, PPh_3, K_2CO_3, TBAC, MeCN, 125 °C, 36 h; (vii) **214**, $PdCl_2(PhCN)_2$, DMF, NaOAc, DMG, 130 °C, 10 h; (viii) **214**, $Pd_2(dba)_3{\cdot}CHCl_3$, $P^tBu_3{\cdot}HBF_4$, Cy_2NMe, dioxane, rt, 40 h; (ix) **214**, $Pd(PPh_3)_4$, MeCN, K_2CO_3, 90 °C, 16 h; (x) **214**, $Pd_2(dba)_3{\cdot}CHCl_3$, KO^tBu, PhMe, 50 °C, 24 h.

It was hypothesised that iodide **227** was incompatible with the reaction conditions, possibly due to chelation of the palladium between the two oxygen atoms within **227**, making it unavailable to partake in the catalytic cycle. To test this hypothesis, reaction of PhI with two equivalents of ethyl acrylate **186** in the presence of iodide **227** was performed under coupling conditions screened for the attempted formation of acetal **228**. It was found that both PhI and iodide **227** reacted to give their corresponding acrylates **187** and **230** in 68 and 62% yield, respectively (Scheme 31). From this reaction, it is clear that iodide **227** is compatible with the reaction conditions and can partake in the Heck reaction. Furthermore, it is known that dihydrofuran **214** is also compatible with the coupling reaction conditions (*vide supra*), so the origin of the incompatibility of the combination of **227** and **214** to the reaction conditions is unknown.

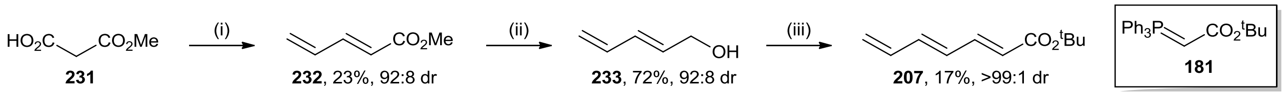


186 **227** **187**, 68% **230**, 62%

Scheme 31. *Reagents and conditions*: (i) PhI, $Pd(OAc)_2$, $^iPr_2NEt$, TEBAC, DMF, 60 °C, 6 h.

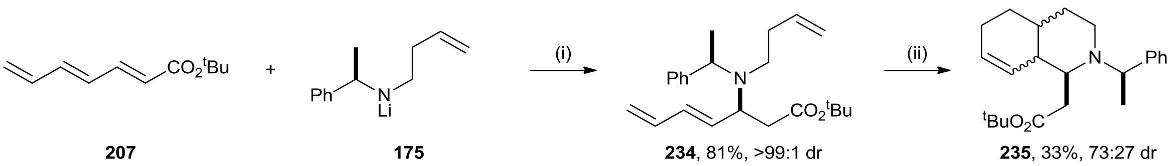
With the synthesis of amine **206** proving challenging, attention turned to the synthesis of the desired α,β,γ,δ,ε,ζ-unsaturated ester **207**, and investigating if the model amine **218** would be compatible in the lithium amide conjugate addition reaction. α,β,γ,δ,ε,ζ-Unsaturated ester **207** was synthesised from acrolein and monomethyl malonic acid **231**[81] via the Doebner modification[82] of the Knoevenagel condensation[83] to give diene **232**. Reduction of the ester functionality gave alcohol **233**, which was immediately subject to oxidation with IBX[84] in the presence of ylid **181**[85] to give α,β,γ,δ,ε,ζ-unsaturated ester **207** in 17% isolated yield and >99:1 dr (Scheme 32). The low yield of

207 can be attributed to both the instability of **207**[86] with respect to polymerisation via Diels-Alder reaction, and the complex mixture of alkenes observed in the Wittig reaction resulting in difficulties with the isolation of pure **207**.[87]



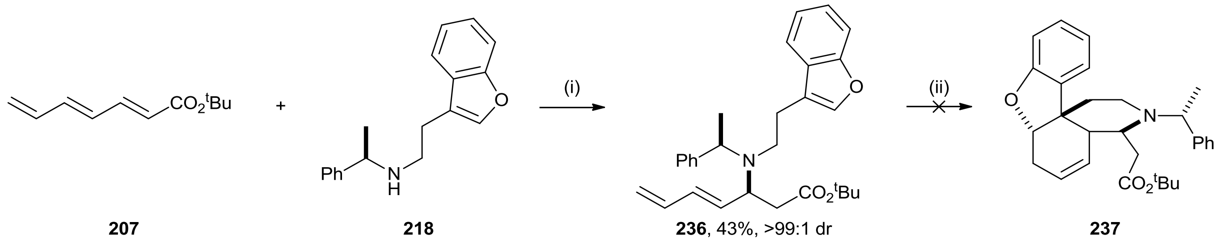
Scheme 32. *Reagents and conditions*: (i) acrolein, DMAP, pyridine, 50 °C, 18 h; (ii) DIBAL-H, CH_2Cl_2, 0 °C, 3 h; (iii) IBX, **181**, DMSO, rt, 24 h.

The conjugate addition of **175** to α,β,γ,δ,ε,ζ-unsaturated ester **207** was trialled as a model system for the conjugate addition of the lithium amide derived from **218**, giving **234** in 81% yield and >99:1 dr. Heating **234** in PhMe resulted in the intramolecular Diels-Alder reaction, yielding **235** in 33% yield and 73:27 dr (Scheme 33).



Scheme 33. *Reagents and conditions*: (i) THF, −78 °C, 2 h; (ii) PhMe, 130 °C, 64 h.

With the success of the model system, conjugate addition of the lithium amide derived from amine **218** to α,β,γ,δ,ε,ζ-unsaturated ester **207** gave β-amino ester **236** in 43% yield and >99:1 dr, showing that the benzofuran functionality within **218** is compatible with the reaction conditions. The sense of diastereocontrol in this conjugate addition reaction was assigned relative to the transition state mnemonic developed by Davies *et al.*[55] Unfortunately, attempts to promote the subsequent Diels-Alder reaction upon heating resulted in decomposition when temperatures of 200 °C were reached (Scheme 34).



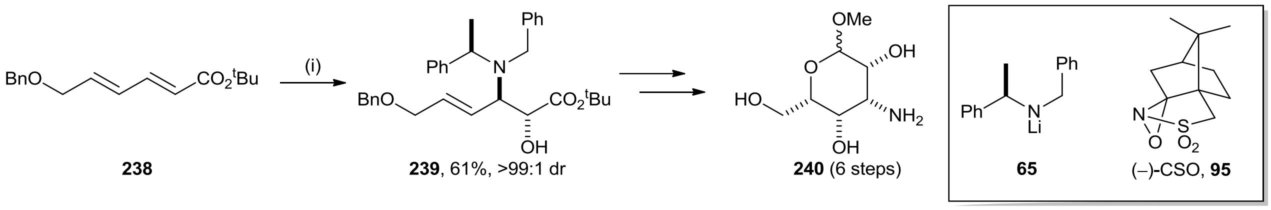
Scheme 34. *Reagents and conditions*: (i) **218**, BuLi, THF, −78 °C, 15 min, then **207**, THF, 2 h; (ii) PhMe, 130 °C, 16 h, then 150 °C, 24 h, then 170 °C, 24 h, then 200 °C, 66 h.

Encouraged by the successful conjugate addition of the lithium amide derived from **218** to **207**, renewed efforts towards amine **206** were initiated. Further, a practical alternative to the unstable α,β,γ,δ,ε,ζ-unsaturated ester **207** was sought.

2.4.2 Conjugate addition to an α,β,γ,δ-unsaturated ester

The conjugate addition of lithium (*R*)-*N*-benzyl-*N*-α-(methylbenzyl)amide **65** to α,β,γ,δ-unsaturated ester **238**, with *in situ* enolate oxidation with (−)-CSO **95** (a convenient aminohydroxylation procedure that typically proceeds in >95:5 dr)[55] has previously been reported, giving **239** in 61%

yield. Davies *et al*. then envisaged that further manipulation of **239** would allow access to amino sugar **240** in six steps (Scheme 35).[88]



Scheme 35. *Reagents and conditions*: (i) **65**, THF, −78 °C, 2 h, then (−)-CSO **95**, −78 °C to rt, 12 h.

Conjugate addition of lithium amide **103** to a similar α,β,γ,δ-unsaturated ester **241**, in which the C(6)-hydroxyl protecting group can be removed in the presence of the *N*-α-methylbenzyl and alkene functionalities within **242**, was considered ideal as this methodology obviates the need to synthesise an α,β,γ,δ,ε,ζ-unsaturated ester. Deprotection of the C(6)-hydroxyl group within β-amino ester **242** would then allow further elaboration to an electron deficient diene **245** via an oxidation/Wittig olefination protocol, the electronics of the system favouring an inverse electron demand Diels-Alder reaction (Figure 19).

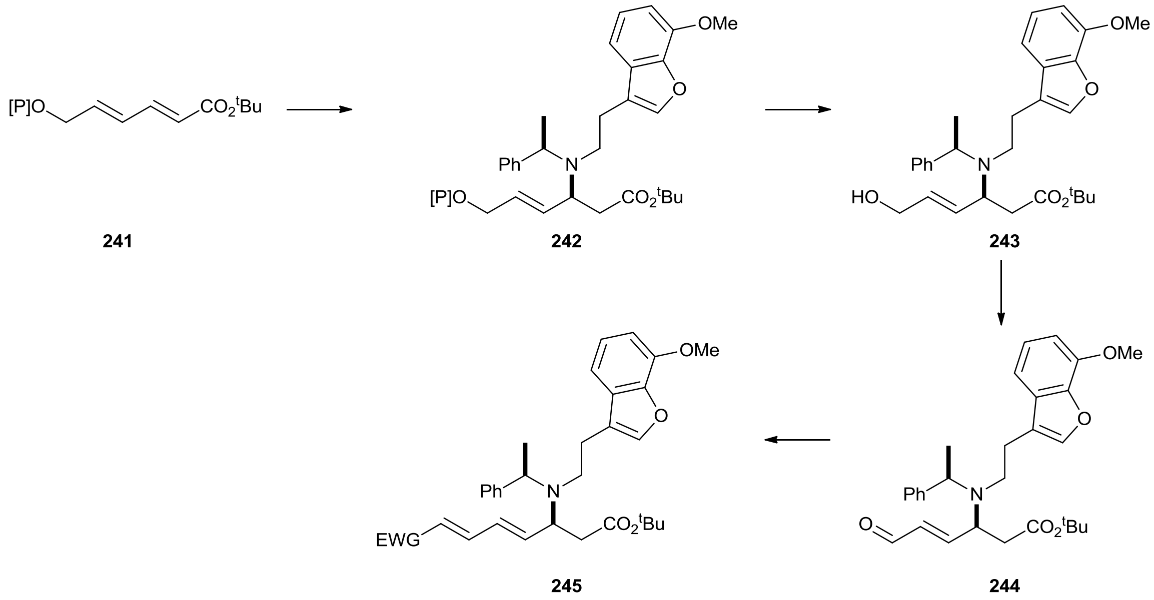
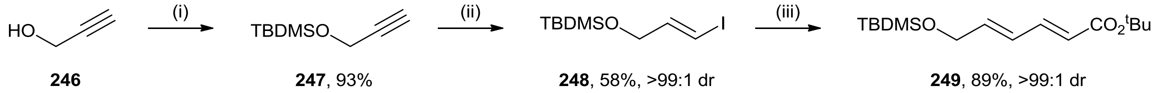


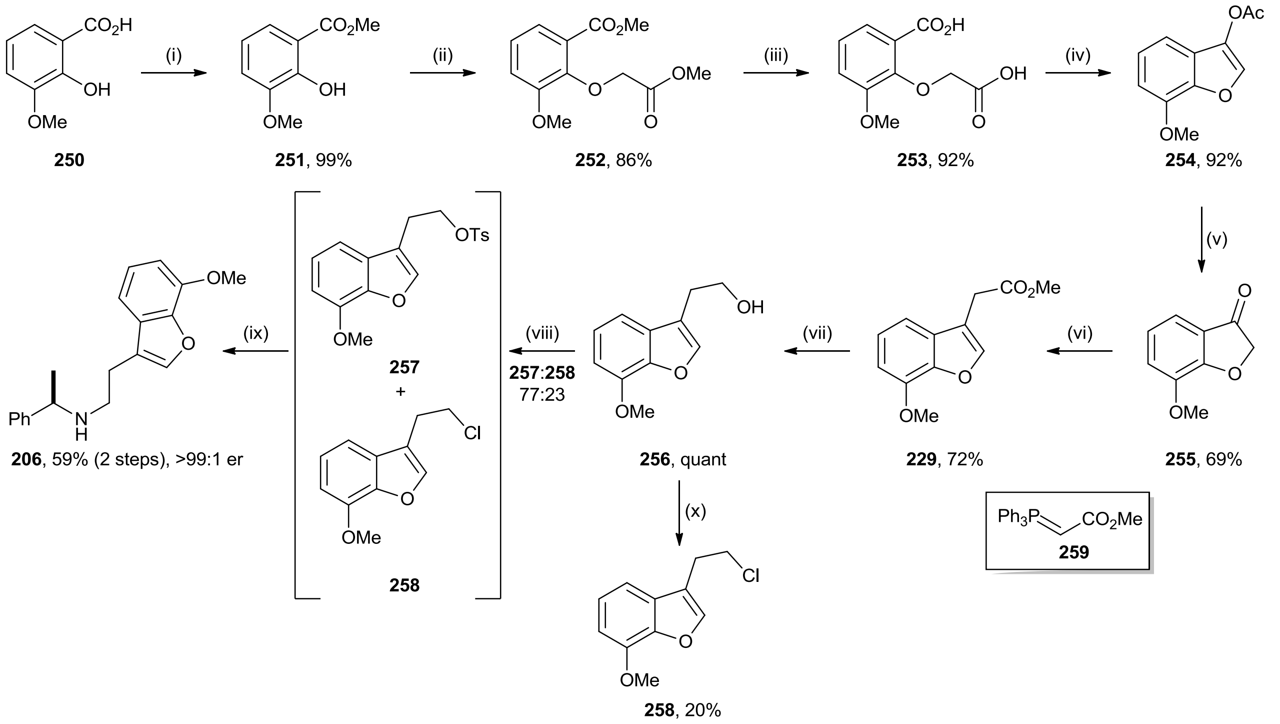
Figure 19. Proposed synthetic strategy.

The TBDMS protecting group is known to tolerate the reaction conditions of the lithium amide conjugate addition,[55] as such it was chosen as an ideal orthogonal protecting group that could readily be removed with a source of fluoride. α,β,γ,δ-Unsaturated ester **249** therefore became a synthetic target. Treatment of propargyl alcohol **246** with TBDMSCl and imidazole gave silyl ether **247** in 93% yield. Hydrozirconation of **247** with Schwartz's reagent Cp_2ZrHCl (generated *in situ* from Cp_2ZrCl_2 and DIBAL-H), followed by addition of I_2 gave iodide **248** in 58% yield and >99:1 dr.[89] Subsequent Heck reaction with *tert*-butyl acrylate under Jeffery's conditions[66] gave the desired α,β,γ,δ-unsaturated ester **249** in 89% yield and >99:1 dr (Scheme 36).



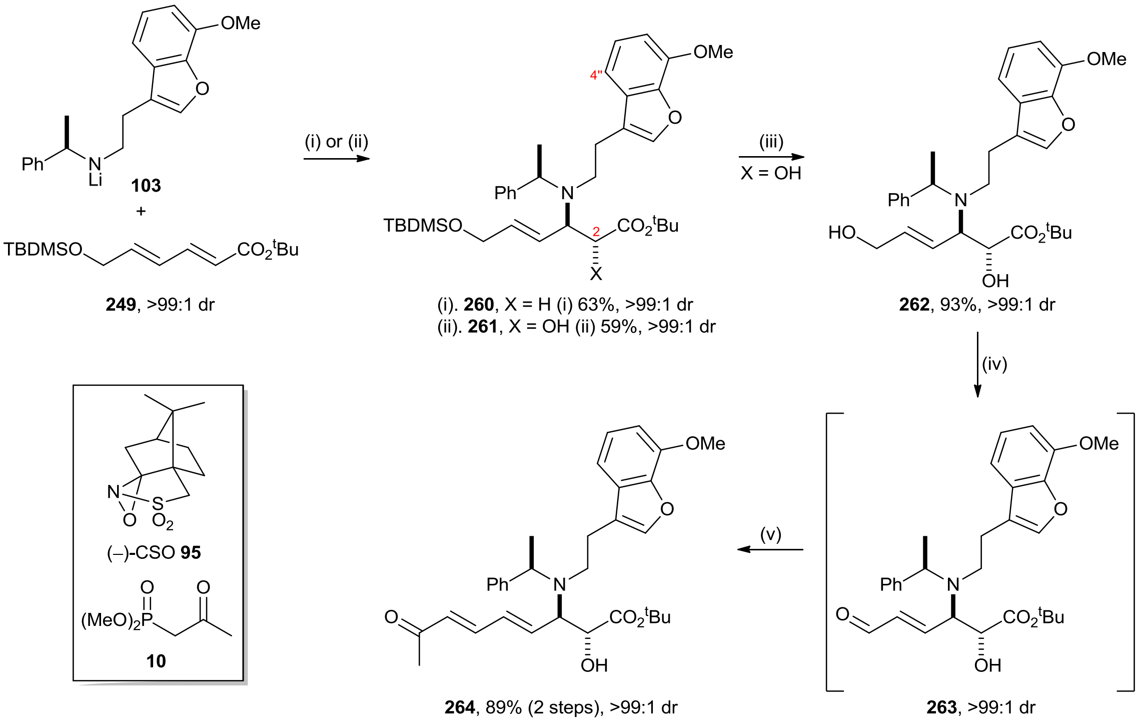
Scheme 36. *Reagents and conditions*: (i) TBDMSCl, imidazole, DMF, 0 °C to rt, 16 h; (ii) Cp_2ZrCl_2, DIBAL-H, THF, 0 °C, 30 min, then **247**, 0 °C to rt, 1 h, then I_2, −78 °C, 30 min; (iii) *tert*-butyl acrylate, $Pd(OAc)_2$, K_2CO_3, TBAC, DMF, rt, 16 h.

Ohno *et al.*[90] have reported the synthesis of benzofuran **229** from benzofuranone **255**, from which it was envisaged amine **206** could be synthesised. Following an analogous procedure as for model amine **218**, reduction of **229** mediated by $LiAlH_4$ should yield alcohol **256**, which could then be converted to amine **206** via tosylate **257**. Benzofuranone **255** is commercially available, but it could also be readily synthesised in multi-gram quantities following the procedure of Bryant and Huhn.[91] Starting with 2-hydroxy-3-methoxybenzoic acid **250**, formation of the corresponding methyl ester **251** occurred in 99% yield upon treatment with MeOH and conc. H_2SO_4. Alkylation of the phenolic functionality within **251** with methyl chloroacetate gave ether **252** in 86% yield, with subsequent hydrolysis of the methyl esters giving **253** in 92% yield. Treatment of **253** with Ac_2O at 125 °C resulted in the cyclisation of the furan ring to give **254** in 92% yield, and ensuing transesterification resulted in the formation of benzofuranone **255** in 69% yield. Wittig reaction of **255** with ylid **259**[92] under forcing conditions gave ester **229** in 57% yield. Reduction of ester **229** with $LiAlH_4$, followed by tosylation gave a 77:23 mixture of **257** and **258**;[93] an authentic sample of **258** was synthesised by reaction of alcohol **256** with PPh_3 and CCl_4.[94] Reaction of the 77:23 mixture of **257** and **258** with excess (*R*)-α-methylbenzylamine (*R*)-**153** in the presence of NaI gave amine **206** in 58% yield over two steps, and >99:1 er[95] (Scheme 37).



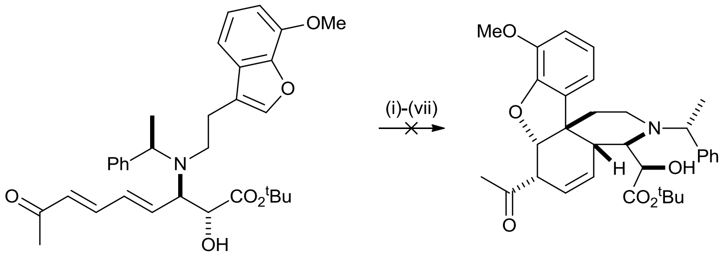
Scheme 37. *Reagents and conditions*: (i) MeOH, conc. H_2SO_4, reflux, 24 h; (ii) methyl chloroacetate, K_2CO_3, acetone, reflux, 48 h; (iii) NaOH, MeOH, reflux, 1 h; (iv) Ac_2O, NaOAc, AcOH, 125 °C, 3.75 h; (v) HCl, MeOH, reflux, 3.5 h; (vi) **259**, xylene, reflux, 72 h; (vii) $LiAlH_4$, Et_2O, rt, 16 h; (viii) TsCl, DMAP, pyridine, rt, 16 h; (ix) (*R*)-α-methylbenzylamine (*R*)-**153**, NaI, MeCN, reflux, 18 h; (x) CCl_4, PPh_3, MeCN, reflux, 24 h.

Conjugate addition of lithium amide **103** to α,β,γ,δ-unsaturated ester **249** proceeded to give β-amino ester **260** in 63% yield and >99:1 dr. As it was ultimately desirable to have a functional handle at the C(2)-position within **260** to enable formation of a bond between C(2) and C(4″) [corresponding to the C(10)−C(11) bond within (−)-morphine **98**], the analogous conjugate addition reaction involving the diastereoselective oxidation of the intermediate lithium enolate with (−)-CSO **95**[96,97] was also conducted to give α-hydroxy-β-amino ester **261** in 59% yield and >99:1 dr.[98,99] Deprotection of **261** with TBAF gave **262** in 93% yield, with subsequent chemoselective oxidation of the primary alcohol with IBX giving aldehyde **263** under optimised conditions. Aldehyde **263** was immediately subjected to Wadsworth-Emmons olefination with phosphonate **10**[100] in the presence of NaH to give α,β,γ,δ-unsaturated ketone **264** in 89% yield over two steps and >99:1 dr (Scheme 38).



Scheme 38. *Reagents and conditions*: (i) THF, −78 °C, 2 h; (ii) THF, −78 °C, 2 h, then (−)-CSO **95**, −78 °C to rt, 18 h; (iii) TBAF, THF, rt, 3 h; (iv) IBX, DMSO, rt, 1 h; (v) **10**, NaH, THF, rt, 1 h, then **263**, THF, rt, 18 h.

Unfortunately, under a range of conditions,[33,40a,40b,101] **264** failed to undergo an intramolecular Diels-Alder reaction, with either decomposition or returned starting material being observed (Scheme 39).

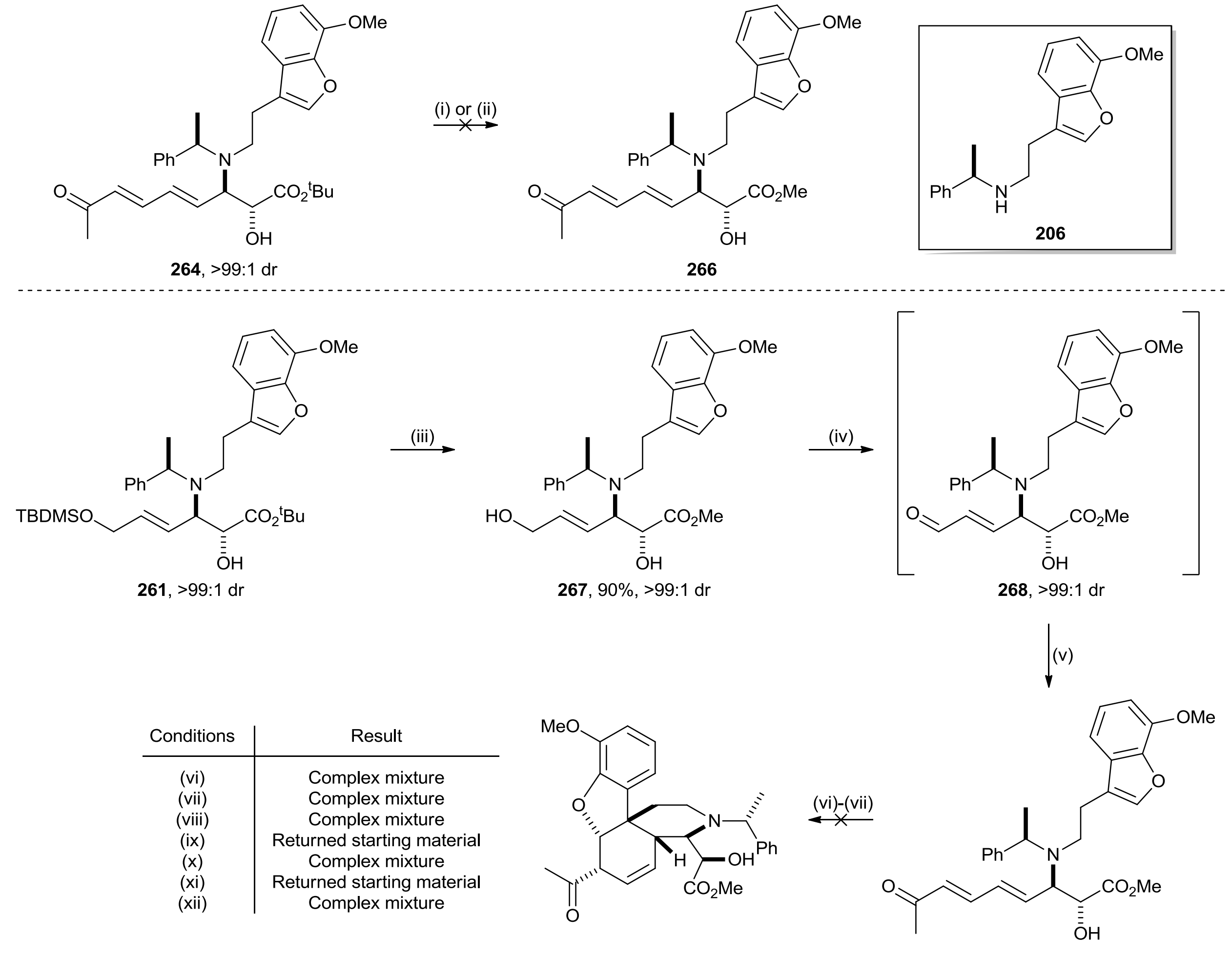


264 **265**

Conditions	Result
(i)	Complex mixture
(ii)	Complex mixture
(iii)	Returned starting material
(iv)	Complex mixture
(v)	Complex mixture
(vi)	Returned starting material
(vii)	Returned starting material

Scheme 39. *Reagents and conditions*: (i) PhMe, 110 °C, 18 h, then 130 °C, 9 h, then 170 °C, 16 h; (ii) NEt_3, decalin, 230 °C, 30 min; (iii) $AlCl_3$, CH_2Cl_2, 40 °C, 4 h; (iv) $AlCl_3$, THF, 40 °C, 5 h; (v) 1,3-dibromobenzene, 220 °C, 1 h; (vi) *N,O*-dimethylhydroxylammonium chloride (20 mol%), MeOH/H_2O (v/v 19:1), reflux, 40 h; (vii) Me_2AlCl, CH_2Cl_2, rt, 48 h.

It was hypothesised that high levels of steric congestion were preventing **264** being able to adopt the correct conformation to allow the Diels-Alder reaction to occur. It was envisaged that removing either the *tert*-butyl ester or α-methylbenzyl group would ease any detrimental steric interactions, and was therefore investigated. Attempted transesterification of **264** to the corresponding methyl ester failed upon treatment with K_2CO_3 in MeOH, with amine **206** being observed as a major product in the 400 MHz ^{1}H NMR spectrum of the crude reaction mixture, most likely arising from the retro-conjugate addition reaction. Alternative acidic transesterification conditions ($SOCl_2$ and MeOH) led to a complex mixture of products. In comparison, transesterification of the earlier intermediate **261** with $SOCl_2$ and MeOH proved successful, with concurrent deprotection of the silyl ether, giving methyl ester **267** in 90% yield. Oxidation of **267** with IBX (under the previously optimised conditions) followed by Wadsworth-Emmons olefination gave **266** in 22% yield over two steps. Attempted Diels-Alder reaction of **266** under a range of conditions[33,40a,40b,101] failed, with reaction resulting in either returned starting material **266** or decomposition (Scheme 40).



264, >99:1 dr

266

206

261, >99:1 dr

267, 90%, >99:1 dr

268, >99:1 dr

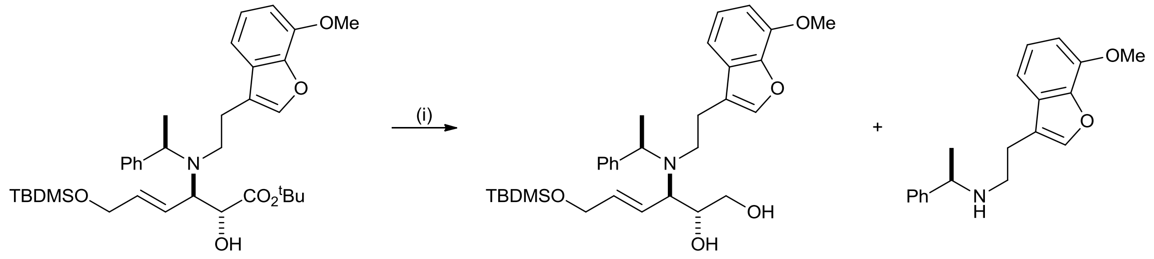
Conditions	Result
(vi)	Complex mixture
(vii)	Complex mixture
(viii)	Complex mixture
(ix)	Returned starting material
(x)	Complex mixture
(xi)	Returned starting material
(xii)	Complex mixture

269

266, 22% (2 steps), >99:1 dr

Scheme 40. *Reagents and conditions*: (i) $SOCl_2$, MeOH, rt, 5 h; (ii) K_2CO_3, MeOH, 50 °C, 5 h; (iii) $SOCl_2$, MeOH, rt, 25 h; (iv) IBX, DMSO, rt, 1 h; (v) **10**, NaH, THF, rt, 1 h, then **268**, THF, rt, 18 h; (vi) PhMe, 110 °C, 16 h, then 140 °C, 24 h, then 150 °C, 24 h; (vii) NEt_3, decalin, 230 °C, 30 min; (viii) *N*,*O*-dimethylhydroxylammonium chloride (20 mol%), MeOH/H_2O (v/v 19:1), reflux, 40 h; (ix) $AlCl_3$, CH_2Cl_2, 40 °C, 4 h; (x) $AlCl_3$, THF, 70 °C, 10 h; (xi) $ZnCl_2$, CH_2Cl_2, 40 °C, 4 h; (xii) $ZnCl_2$, THF, 70 °C, 10 h.

As an alternative to transesterification, reduction of ester **261** to the corresponding alcohol **270** was attempted in order to reduce steric congestion; the analogous reaction with θ-keto ester **264** was not attempted due to potential chemoselectivity problems between the ketone and ester functionalities within **264**. Reduction of **261** with DIBAL-H produced a complex mixture of products, from which the desired diol **270** was isolated in 5% yield, and amine **206** was isolated in 25% yield (Scheme 41).



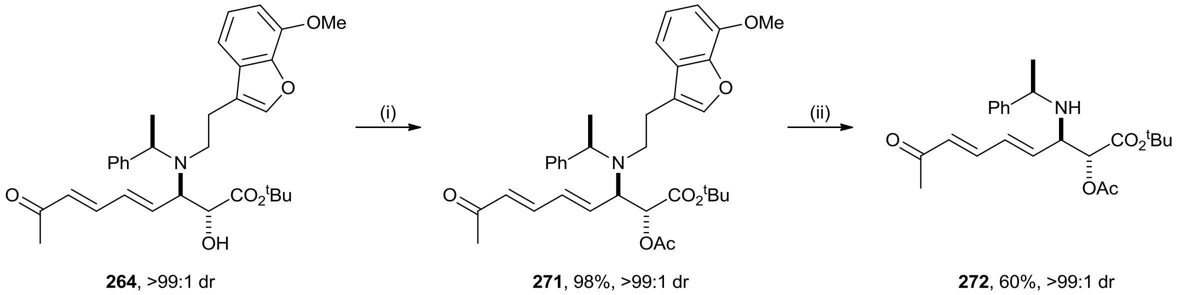
261

270, 5%, >99:1 dr

206, 25%

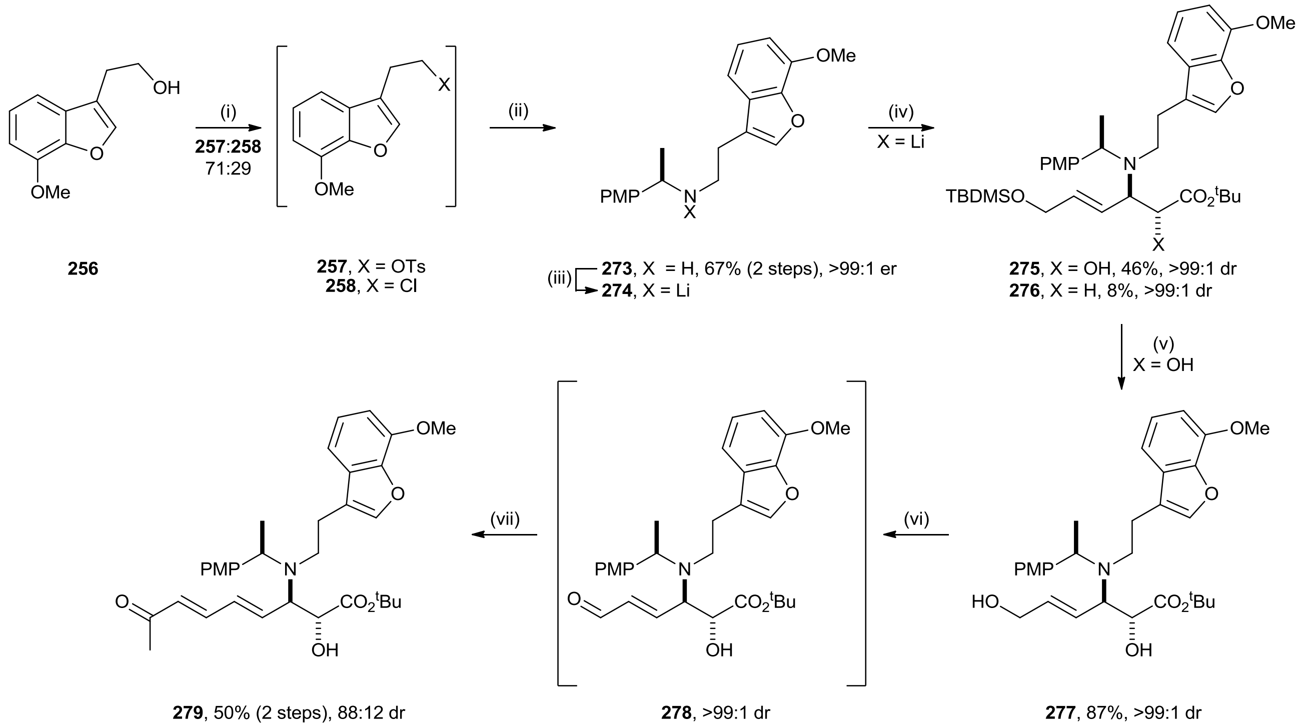
Scheme 41. *Reagents and conditions*: (i) DIBAL-H, CH_2Cl_2, rt, 5 h.

The low yield of this reaction meant that this synthetic route was not pursued further, and the focus of the project changed to the attempted removal of the *N*-α-methylbenzyl group within **264**. It was envisaged that the α-methylbenzyl group within **264** could be removed upon treatment with CAN.[102] It has previously been observed that it is necessary to protect the C(2)-hydroxy group within α-hydroxy-β-aminoesters as the corresponding acetate prior to treatment with CAN to prevent decomposition of the starting materials to a complex mixture of products.[103] Hence, acetylation of **264** was achieved with Ac_2O and pyridine in the presence of a catalytic amount of DMAP to give **271** in 98% yield. Subsequent treatment of **271** with 2.1 eq of CAN resulted in the formation of **272** as the only product, isolated in 60% yield (Scheme 42).



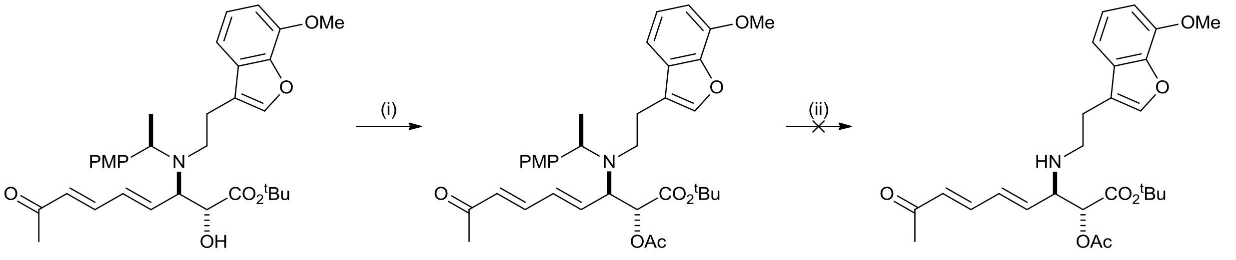
Scheme 42. *Reagents and conditions*: (i) Ac_2O, DMAP, pyridine, rt, 15 min; (ii) CAN, $MeCN/H_2O$ (v/v 4:1), rt, 30 min.

The inability to remove the α-methylbenzyl group within **264** led to the synthesis of **279**, incorporating the more labile *N*-α-methyl-4-methoxybenzyl group. Amine **273**[104] was synthesised in two steps and 67% overall yield, and >99:1 er,[105] from alcohol **256** using similar procedures as for the synthesis of **206**. Conjugate addition of lithium amide **274** to α,β,γ,δ-unsaturated ester **249** followed by enolate oxidation with (−)-CSO **95** gave **275** in 46% and >99:1 dr, in addition to β-amino ester **276**, which was isolated in 8% yield and >99:1 dr.[106] Deprotection of **275** with TBAF gave **277** in 87% yield, and subsequent oxidation of **277** with IBX gave α,β-unsaturated aldehyde **278**. Ensuing Wadsworth-Emmons homologation of **278** gave α,β,γ,δ-unsaturated ketone **279** in 50% yield and 88:12 dr over two steps (Scheme 43).



Scheme 43. *Reagents and conditions*: (i) TsCl, DMAP, pyridine, rt, 16 h; (ii) (*R*)-α-methyl-4-methoxybenzylamine **280**, NaI, MeCN, reflux, 18 h; (iii) BuLi, THF, −78 °C, 15 min; (iv) **249**, THF, −78 °C, 2 h, then (−)-CSO **95**, −78 °C to rt, 18 h; (v) TBAF, THF, rt, 3 h; (vi) IBX, DMSO, rt, 1 h; (vii) **10**, NaH, THF, rt, 1 h, then **278**, THF, rt, 18 h.

O-Acetyl protection of the C(2)-hydroxyl group within **279** with Ac_2O gave **281** in 42% yield. Attempted removal of the α-methyl-4-methoxybenzyl group within **281** with 2.1 eq of CAN returned starting material, even after extended reaction times. Resubjection of **281** to the reaction conditions with 6.0 eq of CAN resulted in the formation of a complex mixture of products (Scheme 44).

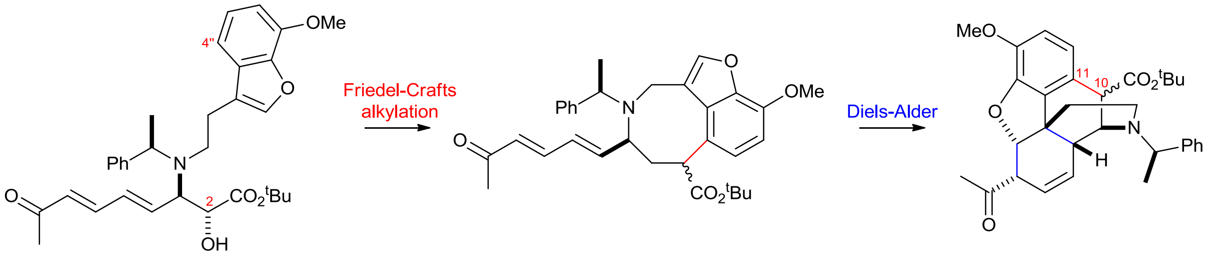


279, 88:12 dr **281**, 42%, 88:12 dr **282**

Scheme 44. *Reagents and conditions*: (i) Ac_2O, DMAP, pyridine, rt, 15 min; (ii) CAN (2.1 eq), $MeCN/H_2O$ (v/v 4:1), rt, 18 h, then CAN (6.0 eq), $MeCN/H_2O$ (v/v 4:1), rt, 18 h.

2.4.3 Friedel-Crafts approach

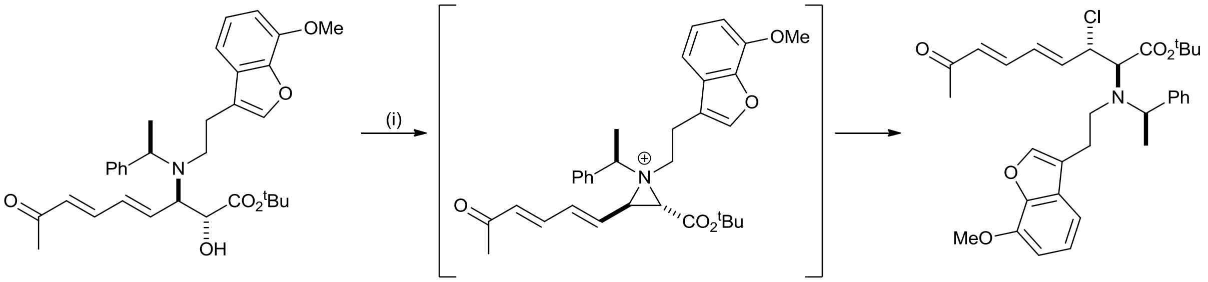
With the inability to remove the *N*-protecting groups within **264** and **279**, an alternative approach was sought. It was hypothesised that if the intramolecular Friedel-Crafts alkylation between C(4″) and C(2) within **264** [forming the C(10)–C(11) bond within the (−)-morphine skeleton **284**] could be achieved first, the resultant azocane **283** might allow the Diels-Alder reaction to proceed more readily, giving access to the (−)-morphine skeleton **284** (Figure 20).



264 **283** **284**

Figure 20. Alternative strategy for the formation of the (−)-morphine skeleton **284**.

Activation of the C(2)-hydroxyl group within **264** was achieved upon treatment with MsCl and NEt_3. In this case, α-amino-β-chloro ester **286** was isolated in 95% yield and >99:1 dr (Scheme 45).[107] The configuration within **286** was assigned by analogy to other occurrences of this rearrangement,[108] and is consistent with reaction via aziridinium ion **285** occurring via two consecutive inversions of configuration [one at C(2), one at C(3)].



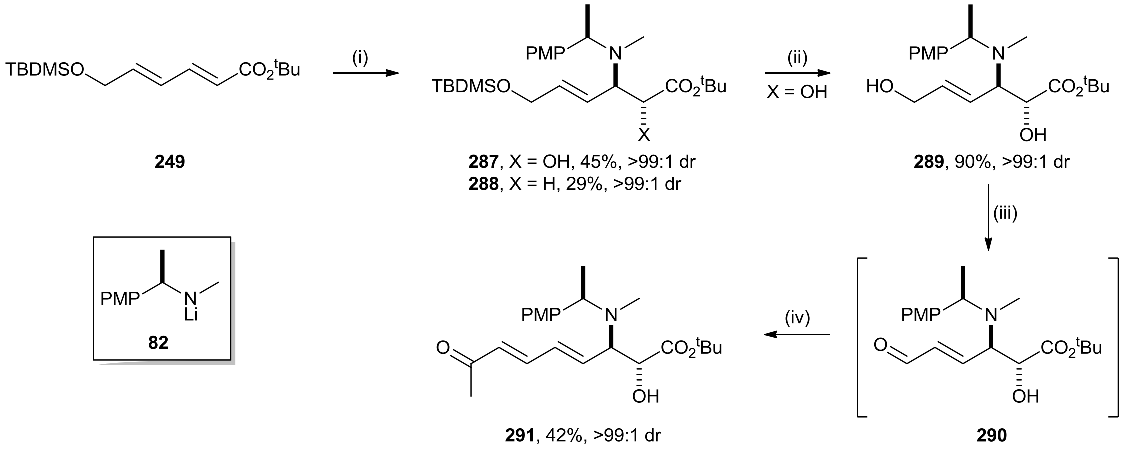
264, >99:1 dr **285** **286**, 95%, >99:1 dr

Scheme 45. *Reagents and conditions*: (i) MsCl, NEt_3, DMAP, CH_2Cl_2, rt, 16 h.

2.4.4 Use of lithium (*R*)-*N*-methyl-*N*-α-(methyl-4-methoxybenzyl)amide

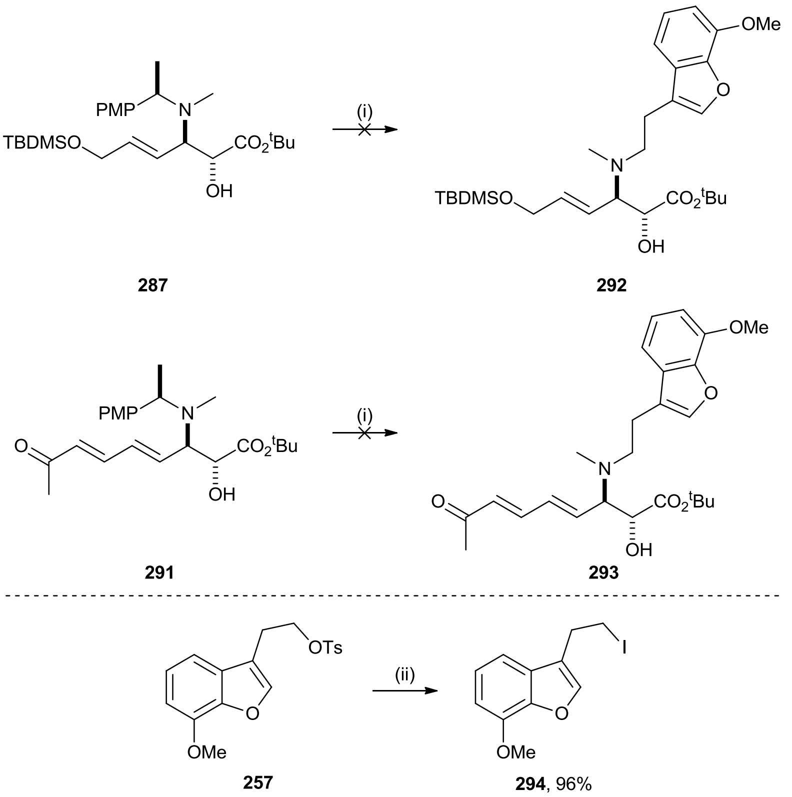
The preferential oxidative removal of the benzofuran moiety within **271** upon treatment with CAN, together with the failure of other reactions on substrates with the benzofuran moiety suggested that this functionality may be interfering with the desired course of reaction. As such, the analogous *N*-methyl series was investigated in the hope that the *N*-protecting group may be removed followed by alkylation with tosylate **257**.

Following an analogous procedure to that used for the synthesis of α-hydroxy-β-amino esters **264** and **279**, conjugate addition of **82**[109] to α,β,γ,δ-unsaturated ester **249** with *in situ* enolate oxidation with (−)-CSO **95**, gave α-hydroxy-β-amino ester **287** in 45% yield, along with β-amino ester **288** in 29% yield, both isolated in >99:1 dr.[110] The sense of diastereocontrol in this conjugate addition reaction was again assigned by reference to the transition state mnemonic developed by Davies *et al.*[55] Deprotection of **287** with TBAF gave allylic alcohol **289** in 90% yield, with subsequent oxidation with IBX and Wadsworth-Emmons homologation giving α,β,γ,δ-unsaturated ketone **291** in 42% yield and >99:1 dr (Scheme 46).



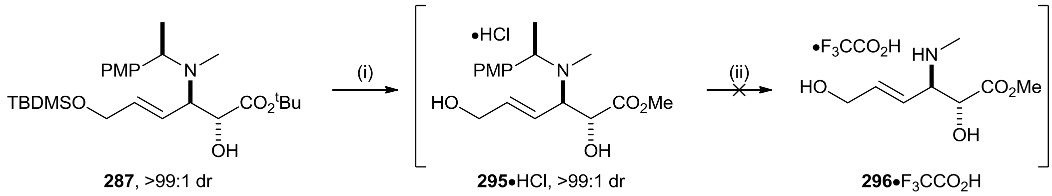
Scheme 46. *Reagents and conditions*: (i) **82**, THF, −78 °C, 2 h, then (−)-CSO **95**, −78 °C to rt, 18 h; (ii) TBAF, THF, rt, 3 h; (iii) IBX, DMSO, rt, 1 h; (iv) **10**, NaH, THF, rt, 1 h, then **290**, THF, rt, 18 h.

Attempted removal of the *N*-α-methyl-4-methoxybenzyl moieties within **287** and **291** by quaternisation of the nitrogen atom upon treatment with tosylate **257** under Finkelstein conditions failed, resulting in returned starting amines **287** and **291**, and iodide **294**. The formation of iodide **294** under the reaction conditions was confirmed by the synthesis of an authentic sample of **294** upon treatment of tosylate **257** with NaI in MeCN, giving **294** in 96% yield (Scheme 47).



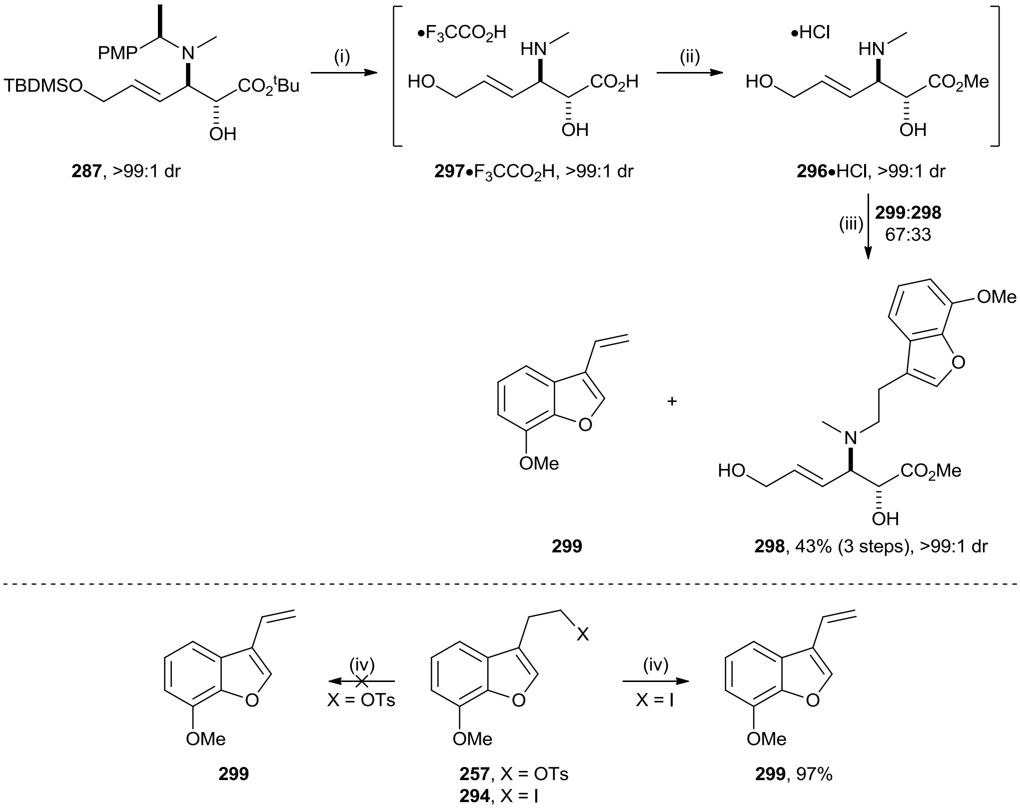
Scheme 47. *Reagents and conditions*: (i) **257**, NaI, MeCN, reflux, 24 h; (ii) NaI, MeCN, reflux, 24 h.

As an alternative protocol for the removal of the *N*-α-methyl-4-methoxybenzyl moiety within **287**, reaction of **287** with methanolic HCl gave **295**, which could not be isolated as it was unstable to chromatography. Methyl ester **295**·HCl was therefore immediately subject to treatment with F_3CCO_2H in an attempt to remove the *N*-α-methyl-4-methoxybenzyl moiety within **295**, but this resulted in a complex mixture of products (Scheme 48).



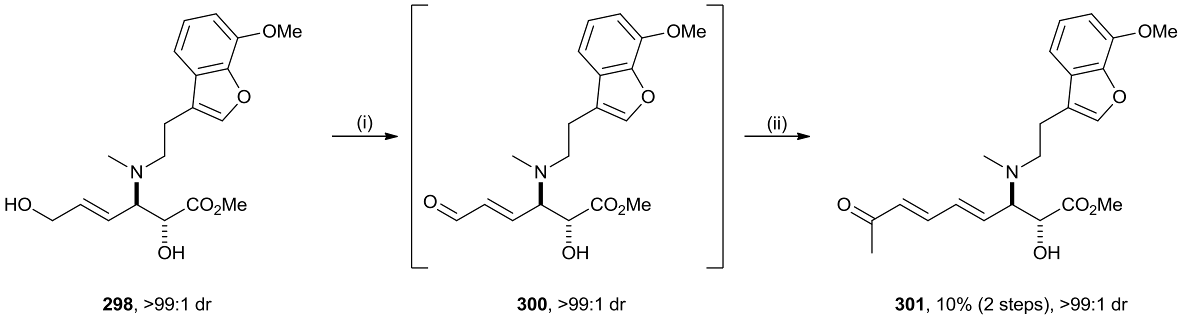
Scheme 48. *Reagents and conditions*: (i) $SOCl_2$, MeOH, reflux, 5 h; (ii) F_3CCO_2H, 65 °C, 2.5 h.

Reversing the order of reactions, treatment of **287** with F_3CCO_2H gave amino acid **297**·F_3CCO_2H which was immediately subject to esterification with MeOH and $SOCl_2$ to give **296**·HCl. Aqueous work up of **296**·HCl to generate the free base **296** resulted in substantial mass loss, suggesting that **296** is water soluble; subsequent reactions were therefore carried out on the crude sample of **296**·HCl. Attempted *N*-alkylation of **296**·HCl with tosylate **257** in the presence of NEt_3 gave returned tosylate **257**, with no amine **296** recovered, presumably due to its water solubility in the ensuing aqueous work up. In contrast, reaction under Finkelstein conditions gave a 67:33 mixture of alkene **299** and the desired tertiary amine **298**, which was isolated in 43% yield over three steps. The formation of alkene **299** in the reaction was confirmed by the synthesis of an authentic sample by treatment of iodide **294** with NEt_3, giving alkene **299** in 97% yield. Interestingly, subjection of tosylate **257** to the same reaction conditions did not result in the formation of any alkene **299** (Scheme 49).



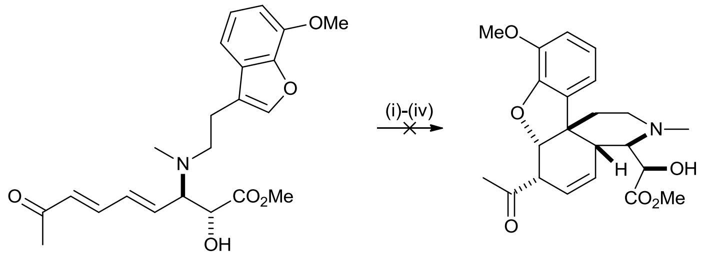
Scheme 49. *Reagents and conditions*: (i) F_3CCO_2H, 65 °C, 2.5 h; (ii) $SOCl_2$, MeOH, reflux, 5 h; (iii) **257**, NEt_3, NaI, MeCN, reflux, 24 h; (iv) NEt_3, MeCN, reflux, 24 h.

With α-hydroxy-β-amino ester **298** in hand, attention turned to its conversion to α,β,γ,δ-unsaturated ketone **301**. Under the previously optimised conditions, oxidation of **298** with IBX to α,β-unsaturated aldehyde **300**, followed by Wadsworth-Emmons homologation gave α,β,γ,δ-unsaturated ketone **301** in 10% yield and >99:1 dr over two steps (Scheme 50).



Scheme 50: *Reagents and conditions*: (i) IBX, DMSO, rt, 1 h; (ii) **10**, NaH, THF, rt, 1 h, then **300**, THF, rt, 18 h.

Attempted Diels-Alder reaction of **301** under a range of conditions[33,40a,40b,101] again failed to result in the formation of the desired Diels-Alder adduct **302** (Scheme 51).



301, >99:1 dr **302**

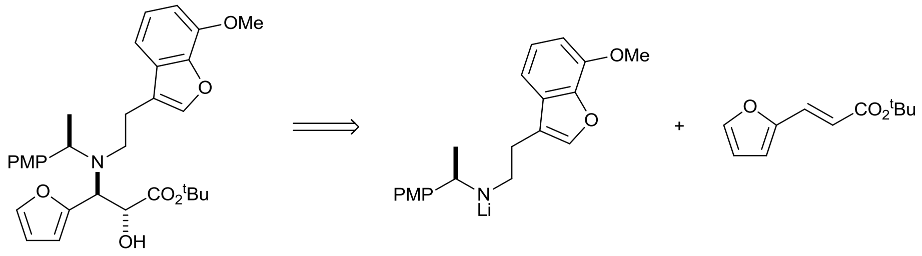
Conditions	Result
(i)	Complex mixture
(ii)	Complex mixture
(iii)	Returned starting material
(iv)	Complex mixture

Scheme 51: *Reagents and conditions*: (i) PhMe, 110 °C, 48 h; (ii) NEt_3, decalin, 190 °C, 30 min; (iii) $ZnCl_2$, CH_2Cl_2, 40 °C, 4 h; (iv) $ZnCl_2$, THF, 70 °C, 10 h.

The failure of the Diels-Alder reaction to occur under a range of conditions, together with the low yield for the synthesis of α,β,γ,δ-unsaturated ketone **301**, led to an alternative strategy being sort.

2.4.5 Use of *tert*-butyl (*E*)-3-(furan-2′-yl)acrylate

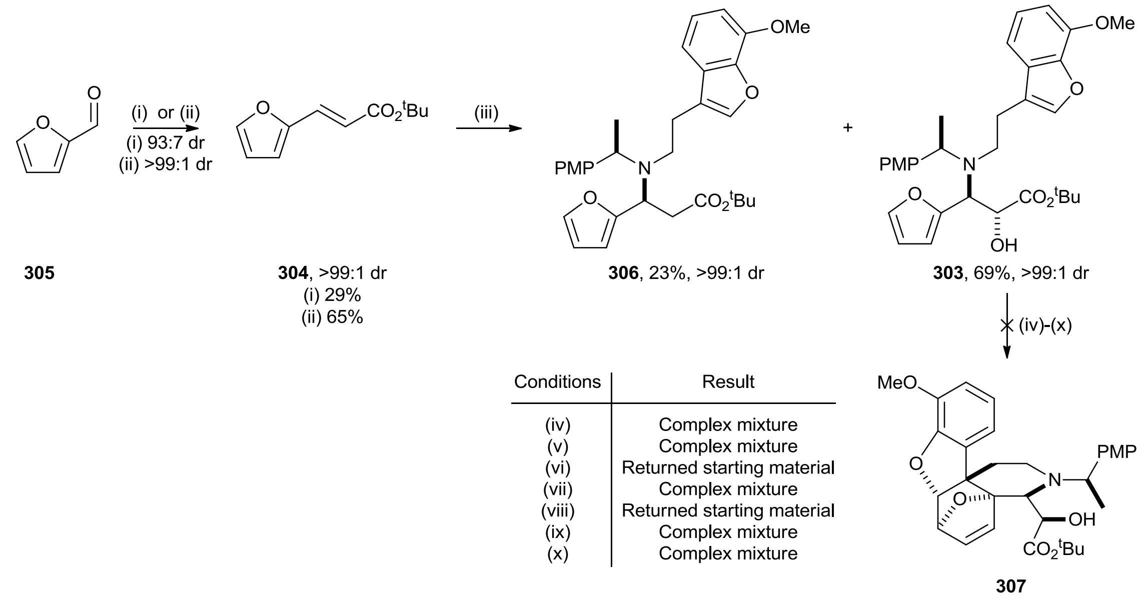
It was hypothesised that the conformations of the diene moieties within **264**, **266** and **301** were such that they were reluctant to adopt the required *s-cis* conformation required for a Diels-Alder reaction to occur. The intramolecular Diels-Alder reaction of a furan (in which the diene is held in the *s-cis* conformation) to a benzofuran has previously been identified as a potential route to access the C-ring within (−)-morphine **98**,[40b] and it was envisaged that a similar strategy could be used in this synthesis. Diels-Alder precursor **303** therefore became a target for synthesis, which could readily be accessed by the conjugate addition of lithium amide **274** to α,β-unsaturated ester **304** (Figure 21).



303 **274** **304**

Figure 21. Retrosynthetic analysis of **303**.

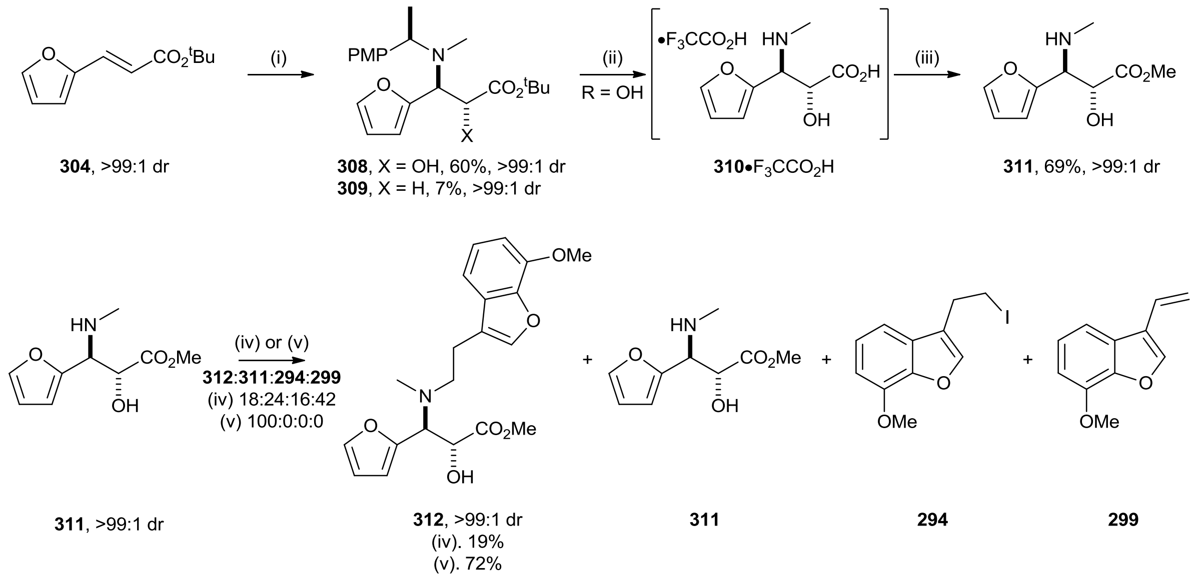
Wittig reaction between furfural **305** and **181** gave α,β-unsaturated ester **304** in 93:7 dr, with **304** being isolated in 29% yield and >99:1 dr.[111] Alternatively, MeMgBr mediated Wadsworth-Emmons homologation[53] with phosphonoacetate **182** gave **304** in >99:1 dr, with **304** isolated in 65% yield and >99:1 dr. Subsequent conjugate addition of lithium amide **274** [with *in situ* enolate oxidation with (−)-CSO **95**] gave α-hydroxy-β-amino ester **303** in 69% yield and >99:1 dr, along with β-amino ester **306** in 23% yield and >99:1 dr. The sense of diastereocontrol in this conjugate addition reaction was assigned by reference to the transition state mnemonic developed by Davies *et al.*[55] A range of conditions were screened in order to affect the intramolecular Diels-Alder reaction,[33,40a,40b] unfortunately none resulted in the formation of the desired product **307**, with either starting material being returned or reaction resulting in a complex mixture of products (Scheme 52).



Conditions	Result
(iv)	Complex mixture
(v)	Complex mixture
(vi)	Returned starting material
(vii)	Complex mixture
(viii)	Returned starting material
(ix)	Complex mixture
(x)	Complex mixture

Scheme 52: *Reagents and conditions*: (i) **181**, CH_2Cl_2, rt, 16 h; (ii) **182**, MeMgBr, THF, rt, 15 min, then **305**, THF, reflux, 18 h (iii) **274**, THF, −78 °C, 3 h, then (−)-CSO **95**, −78 °C to rt, 48 h; (iv) PhMe, 110 °C, 16 h, then 140 °C, 24 h; (v) HCl, PhMe, 110 °C, 24 h; (vi) NEt_3, decalin, 190 °C, 30 min; (vii) $AlCl_3$, CH_2Cl_2, rt, 4 h; (viii) $ZnCl_2$, CH_2Cl_2, rt, 4 h; (ix) $ZnCl_2$, CH_2Cl_2, 40 °C, 4 h; (x) $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt, 4 h.

It was again hypothesised that steric congestion meant that **303** could not access the required conformation to enable Diels-Alder reaction to occur; this steric congestion could be reduced by the synthesis of α-hydroxy-β-amino ester **312**. Conjugate addition of **82** to α-β-unsaturated ester **304** [again with *in situ* enolate oxidation with (−)-CSO **95**] gave α-hydroxy-β-amino ester **308** in 60% yield and >99:1 dr, and β-amino ester **309** in 7% yield and >99:1 dr. The sense of diastereocontrol in this conjugate addition reaction was initially assigned by reference to the transition state mnemonic developed by Davies *et al.*[55] The relative configuration within **308** was later unambiguously confirmed by X-ray diffraction analysis, with the absolute configuration assigned relative to the known (*R*)-configuration of the C(α)-stereogenic centre (Figure 22). Removal of the *N*-protecting group within **308** upon treatment with F_3CCO_2H gave **310**·F_3CCO_2H, which was immediately subjected to esterification with methanolic HCl to give **311** in 69% yield. Subsequent *N*-alkylation with **257** under Finkelstein conditions gave an 18:24:16:42 mixture of tertiary amine **312**, secondary amine **311**, iodide **294** and alkene **299**, with **312** isolated in 19% yield. The yield of tertiary amine **312** could be improved by excluding NaI from the reaction mixture (which is known to be pivotal in the detrimental formation of alkene **299**), with reaction proceeding to give **312** in 72% yield (Scheme 53).



Scheme 53. *Reagents and conditions*: (i) **82**, THF, −78 °C, 2 h, then (−)-CSO **95**, −78 °C to rt, 18 h; (ii) F_3CCO_2H, 65 °C, 2.5 h; (iii) $SOCl_2$, MeOH, 50 °C, 5 h; (iv) **257**, NaI, NEt_3, MeCN, reflux, 18 h; (v) **257**, NEt_3, MeCN, reflux, 48 h.

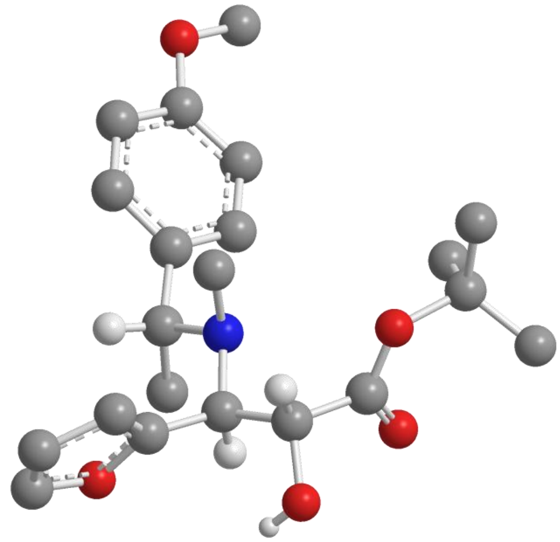
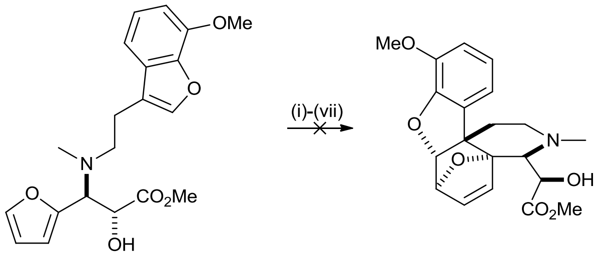


Figure 22. X-ray crystal structure of **308** (selected H atoms are omitted for clarity).

Again, a range of conditions were screened in order to affect the intramolecular Diels-Alder reaction of **312**, however all conditions trialled[33,40a,40b] resulted in either returned starting material or decomposition of **312** (Scheme 54).



Conditions	Result
(i)	Complex mixture
(ii)	Returned starting material
(iii)	Returned starting material
(iv)	Returned starting material
(v)	Complex mixture
(vi)	Returned starting material
(vii)	Complex mixture

Scheme 54: *Reagents and conditions*: (i) PhMe, 110 °C, 72 h; (ii) NEt_3, decalin, 190 °C, 30 min; (iii) HCl, PhMe, 110 °C, 24 h; (iv) $AlCl_3$, CH_2Cl_2, 40 °C, 4 h; (v) $AlCl_3$, THF, 70 °C, 10 h; (vi) $ZnCl_2$, CH_2Cl_2, 40 °C, 4 h; (vii) $ZnCl_2$, THF, 70 °C, 10 h.

2.5 Conclusion

A number of synthetic strategies to enable the asymmetric synthesis of (−)-morphine **98** have been attempted, reliant on the conjugate addition of a lithium amide reagent to an α,β-unsaturated carbonyl compound followed by an intramolecular Diels-Alder reaction as key steps. Initially, conjugate addition of lithium (*R*)-*N*-but-3-enyl-*N*-(α-methylbenzyl)amide **175** to a range of α,β-unsaturated carbonyls **172**, **180**, **194** and **195** provided a variety of β-amino esters in >99:1 dr. Attempted Heck reaction to form the required eight membered rings within **176** and **183** showed that these substrates **172**, **180**, **194** and **195** were resilient to a wide range of reaction conditions, and when oxidative addition was achieved, competing proto-depalladation hindered the desired reaction. Secondly, the use of highly functionalised amines related to (*R*)-*N*-[2′-(7-methoxybenzofuran-3-yl)ethyl]-*N*-(α-methylbenzyl)amine **206** have successfully been utilised in the lithium amide conjugate addition to a range of α,β-unsaturated esters, with reaction proceeding in excellent levels of diastereoselectivity. It is apparent that the intramolecular Diels-Alder reaction involving a benzofuran as the dienophile component is non-trivial, and further investigations are required if this strategy is to become an efficacious route to (−)-morphine **98**.

2.6 References and notes

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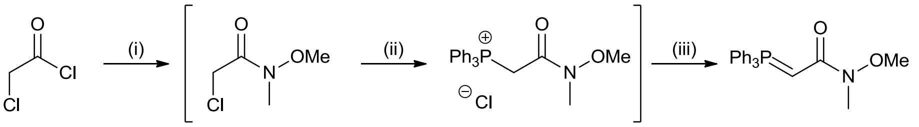
[50] **173** was made in two steps from chloroacetyl chloride **314**: treatment of **314** with *N*,*O*-dimethylhydroxylammonium chloride in the presence of $\mathrm{NEt_3}$ gave **315**, with subsequent reaction with $\mathrm{PPh_3}$ and deprotonation of the resultant ylid **316** with KOH giving **173** in 44% overall yield. See: Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001.

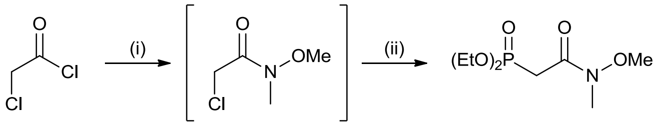


314 **315** **316** **173**, 44%

Reagents and conditions: (i) *N*,*O*-dimethylhydroxylammonium chloride, $\mathrm{NEt_3}$, $\mathrm{CH_2Cl_2}$, rt, 1 h; (ii) $\mathrm{PPh_3}$, MeCN, reflux, 15 h; (iii) KOH (2.0 M aq), $\mathrm{CH_2Cl_2}$, rt, 1 min.

[51] It was not possible to determine the crude (*E*):(*Z*) ratio of **171** and **170** by peak integration of the 400 MHz ^{1}H NMR due to peak overlap.

[52] **174** was made in two steps from chloroacetyl chloride **314**: treatment of **314** with *N*,*O*-dimethylhydroxylammonium chloride in the presence of $\mathrm{NEt_3}$ gave **315**, with subsequent Arbusov reaction with $\mathrm{P(OEt)_3}$ giving **174** in 39% overall yield. See: Nuzillard, J.-M.; Boudemdjel, A.; Massiot, G. *Tetrahedron Lett.* **1989**, *30*, 3779.



314 **315** **174**, 39%

Reagents and conditions: (i) *N*,*O*-dimethylhydroxylammonium chloride, $\mathrm{NEt_3}$, $\mathrm{CH_2Cl_2}$, rt, 1 h; (ii) $\mathrm{P(OEt)_3}$, 80 °C, 24 h.

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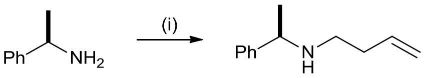
[54] Enantiopure (*R*)-α-methylbenzylamine (*R*)-**153** (99.5:0.5 er) is commercially available. Alkylation of (*R*)-α-methylbenzylamine (*R*)-**153** upon treatment with 4-bromobut-1-ene **154** in the presence of $\mathrm{K_2CO_3}$ gave *(R)-N-(α-methylbenzyl)but-3-en-1-amine **152** in 68% yield and >99:1 er*; subsequent deprotonation with BuLi in THF generated a yellow solution of lithium (*R*)-*N*-but-3-enyl-*N*-(α-methylbenzyl)amide **175**. The er of **152** was determined from the 400 MHz ^{1}H NMR spectrum in the presence of the chiral solvating agent (*R*)-*O*-acetylmandelic acid, and comparison with an authentic racemic sample.



(*R*)-**153** **152**, 68%, >99:1 er

Reagents and conditions: (i) 4-bromobut-1-ene **154**, $\mathrm{K_2CO_3}$, 50 °C, 12 h.

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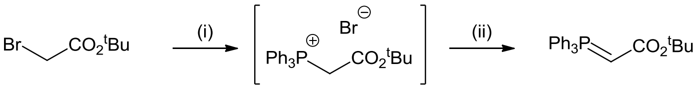
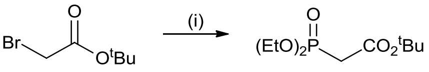
[61]**181** was made in 80% yield from the alkylation of $\mathrm{PPh_3}$ with *tert*-butyl bromoacetate **317**, followed by deprotonation of the resultant ylid **318** with NaOH.



317 **318** **181**, 80%

Reagents and conditions: (i) $\mathrm{PPh_3}$, EtOAc, rt, 12 h; (ii) NaOH (2.0 M aq), $\mathrm{CH_2Cl_2}$, rt, 1 min.

[62]**182** was made in 65% yield by an Arbusov reaction between $\mathrm{P(OEt)_3}$ and *tert*-butyl bromoacetate **317**.



317 **182**, 65%

Reagents and conditions: (i) $\mathrm{P(OEt)_3}$, 30 °C, 48 h.

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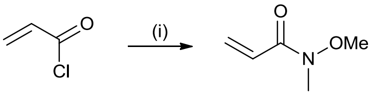
[65] Acrylate **184** was synthesised from acryloyl chloride **319** and *N*,*O*-dimethylhydroxylammonium chloride in 13% yield. See: Corminboeuf, O.; Renaud, P. *Org. Lett.* **2002**, *4*, 1735.



319 **184**, 13%

Reagents and conditions: (i) *N*,*O*-dimethylhydroxylammonium chloride, pyridine, $\mathrm{CHCl_3}$, 0 °C, 30 min.

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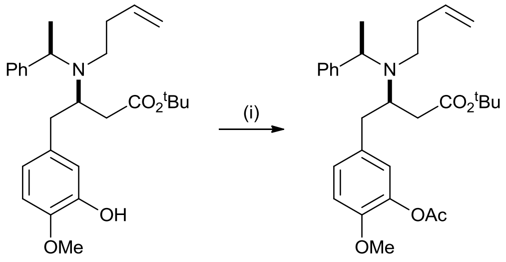
[69] There was evidence of the proto-deiodonated product **196** in the 400 MHz ^{1}H NMR of the crude reaction mixture, however due to peak overlap it was not possible to quantify the extent of conversion to **196**. Further, no **196** was isolated pure so it was also not possible to calculate a yield for its formation.

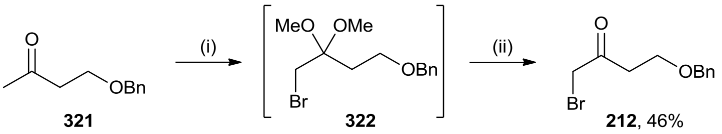
[70] An authentic sample of **320**, the product expected from proto-deiodonation of **201**, was synthesised in 70% yield by treatment of **196** with Ac_2O to enable comparison with the crude reaction mixture for the attempted Heck reaction of **201**.



196, >99:1 dr **320**, 70%, >99:1 dr

Reagents and conditions: (i) Ac_2O, pyridine, rt, 4 h.

[71] Bromide **212** was made in 46% yield over two steps from ketone **321** according a literature procedure. See: Jakob, B.; Voss, G.; Gerlach, H. *Tetrahedron: Asymmetry* **1996**, *7*, 3255.



321 **322** **212**, 46%

Reagents and conditions: (i) Br_2, MeOH, 0 °C, 2 h; (ii) H_2SO_4 (1.0 M aq), THF, reflux, 1.5 h.

[72] (a) Kim, I.; Lee, S.-H.; Lee, S. *Tetrahedron Lett.* **2008**, *49*, 6579. (b) Montfort, B.; Laude, B.; Verbel, J.; Cerutti, E.; *Bull. Soc. Chim. Fr.*, **1987**, *5*, 848.

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[78] The er of **218** was determined from the 400 MHz ^{1}H NMR spectrum in the presence of the chiral solvating agent (*R*)-*O*-acetylmandelic acid, and comparison with an authentic racemic sample.

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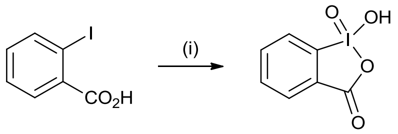
[80] (a) Hsin, L.-W.; Chang, L.-T.; Chen, C.-W.; Hsu, C.-H.; Chen, H.-W. *Tetrahedron* **2005**, *61*, 513. (b) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989. (c) Denmark, S. E.; Regens, C. S.; Kobayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 2774.

[81] Methyl potassium malonate is commercially available from Sigma Aldrich. Addition of excess HCl (2.0 M in Et_2O) to a suspension of methyl potassium malonate in $CHCl_3$ followed by stirring for 16 h, filtration and concentration *in vacuo* gave monomethyl malonate **231** in quantitative yield.

[82] Doebner, O. *Ber. Dtsch. Chem. Ges.* **1902**, *35*, 1136.

[83] Knoevenagel, E. *Ber. Dtsch. Chem. Ges.* **1898**, *31*, 2596.

[84] IBX was synthesised in 77% yield from 2-iodobenzoic acid **323**. See: Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537.



323 IBX, 77%

Reagents and conditions: (i) Oxone®, H_2O, 70 °C, 3 h.

[85] Maiti, A.; Yadav, J. S. *Synth. Commun.* **2001**, *31*, 1499.

[86] Subsequent reactions of **207** had to be carried out immediately after isolation.

[87] The crude (*E*):(*Z*) ratio for **207** could not be determined from the 400 MHz ^{1}H NMR due to multiple alkene components being present resulting in peak overlap.

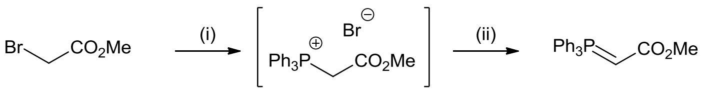
[88] Davies, S. G.; Maruani, A. *Unpublished result*.

[89] Huang, Z.; Negishi, E. *Org. Lett.* **2006**, *8*, 3675.

[90] Ohno, M.; Miyamoto, M.; Hoshi, K.; Takeda, T.; Yamada, N.; Ohtake, A. *J. Med. Chem.* **2005**, *48*, 5279.

[91] Bryant, W. M., III; Huhn, G. F. *Synth. Commun.* **1995**, *25*, 915.

[92] **259** was made in 87% yield from the alkylation of PPh_3 with methyl bromoacetate **324**, followed by deprotonation of the resultant ylid **325** with NaOH.



324 **325** **259**, 87%

Reagents and conditions: (i) PPh_3, EtOAc, rt, 3 h; (ii) NaOH (2.0 M aq), CH_2Cl_2, rt, 1 min.

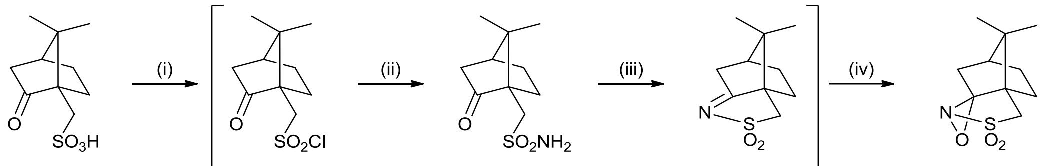
[93] Ding, R.; He, Y.; Wang, X.; Zu, J.; Chen, Y.; Feng, M.; Qi, C. *Molecules*, **2011**, *16*, 5665.

[94] Appel, R. *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 801.

[95] The er of **206** was determined from the 400 MHz ^{1}H NMR spectrum in the presence of the chiral solvating agent (*R*)-*O*-acetylmandelic acid, and comparison with an authentic racemic sample.

[96] Bunnage, M. E.; Davies, S. G.; Goodwin, C. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2373.

[97](−)-CSO **95** was synthesised in four steps and 73% overall yield from commercially available (−)-camphorsulfonic acid **326**. See: Towson, J. C.; Weismiller, M. C.; Lal, G. S.; Sheppard, A. C.; Kumar, A.; Davis, F. A. *Org. Synth.* **1990**, *69*, 158.



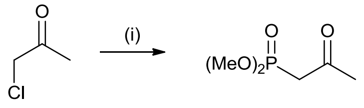
326 **327** **328** **329** (–)-CSO, **95**, 73%

Reagents and conditions: (i) $SOCl_2$, $CHCl_3$, reflux, 12 h; (ii) sat aq NH_4OH, $CHCl_3$, 0 °C, 4 h; (iii) Amberlyst® 15, PhMe, Dean-Stark, 16 h; (iv) CH_3CO_3H, K_2CO_3, Aliquat™ 336, CH_2Cl_2, 5 °C to rt, 16 h.

[98] β-Amino ester **260** was also isolated in 5% yield.

[99] Due to significant peak overlap in the 400 MHz ^{1}H NMR spectrum of the crude reaction mixture, it was not possible to determine the ratio of **260** and **261**, nor assess the levels of diastereoselectivity observed in this reaction.

[100] Phosphonate **10** was synthesised in 50% yield from chloroacetone **330** according a literature procedure. See: Pietruszka, J.; Witt, A. *Synthesis*, **2006**, *24*, 4266.



330 **10**, 50%

Reagents and conditions: (i) KI, MeCN, acetone, rt, 1 h, then $P(OMe)_3$, rt, 12 h, then 50 °C, 3 h.

[101] Cavill, J. L.; Peter, J.-U.; Tomkinson, N. C. O. *Chem. Commun.* **2003**, 728.

[102] The other methods commonly employed to remove the α-methylbenzyl group, which include hydrogenolysis, and reductive cleavage with Na in liquid NH_3, were considered to be incompatible with the other functional groups within **264**.

[103] Davies, S. G.; Foster, E. M. *Unpublished result.*

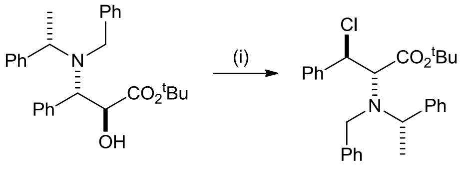
[104] Enantiopure (*R*)-α-methyl-4-methoxybenzylamine **280** (99.5:0.5 er) is commercially available.

[105] The er of **273** was determined from the 400 MHz ^{1}H NMR spectrum in the presence of the chiral solvating agent (*R*)-*O*-acetylmandelic acid, and comparison with an authentic racemic sample.

[106] Due to significant peak overlap in the 400 MHz ^{1}H NMR spectrum of the crude reaction mixture, it was not possible to determine the ratio of **275** and **276**, nor assess the levels of diastereoselectivity observed in this reaction.

[107] The regiochemical assignment within **286** was made with reference to the HMBC spectra.

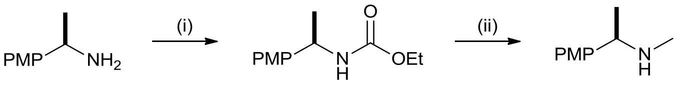
[108] Treatment of **331** with MsCl and pyridine gave **332**, whose relative and absolute configuration was confirmed by single crystal X-ray diffraction analysis. See: Hayward, A. Part II Thesis, *University of Oxford*, **2012**.



331 **332**

Reagents and conditions: (i) MsCl, pyridine, rt, 16 h.

[109] Acylation of (*R*)-α-methyl-4-methoxybenzylamine **280** with EtOCOCl gave **333** in 50% yield, subsequent reduction with $LiAlH_4$ gave **334** in 99% yield and >99:1 er. Deprotonation of **334** with BuLi in THF generated a yellow solution of lithium (*R*)-*N*-methyl-*N*-(α-methylbenzyl)amide **82**. The er of **334** was determined from the 400 MHz ^{1}H NMR spectrum in the presence of the chiral solvating agent (*R*)-*O*-acetylmandelic acid, and comparison with an authentic racemic sample. **334** was used immediately due to its propensity to oxidise upon contact with air.



280 **333**, 55% **334**, 99%, >99:1 er

Reagents and conditions: (i) EtOCOCl, NEt_3, Et_2O, 0 °C to rt, 2 h; (ii) $LiAlH_4$, THF, 60 °C, 24 h.

[110] Due to significant peak overlap in the 400 MHz ^{1}H NMR spectrum of the crude reaction mixture, it was not possible to determine the ratio of **287** and **288**, nor assess the levels of diastereoselectivity observed in this reaction.

[111] A diastereoisomerically impure fraction of **304** was also isolated in 32% yield and 87:13 dr.

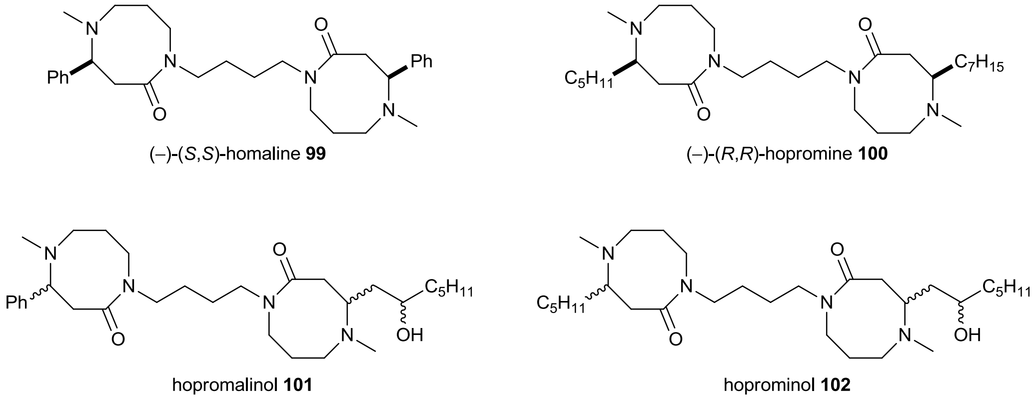
Chapter 3: Asymmetric synthesis of (−)-(*S*,*S*)-homaline and (−)-(*R*,*R*)-hopromine

3.1 Introduction

This chapter describes the total synthesis of two of the homalium alkaloids, (−)-(*S*,*S*)-homaline **99** and (−)-(*R*,*R*)-hopromine **100**, and introduces the use of the novel enantiopure lithium amide reagent lithium *N*-(3-chloroprop-1-yl)-*N*-(α-methylbenzyl)amide **335** and its derivatives.

3.2 The homalium alkaloids

The homalium alkaloids are a group of four structurally related alkaloids isolated from the leaves of *Homalium pronyense* Guillaum, a member of the Flacourtiaceae family, found in the forests of New Caledonia. They were first isolated and had their gross structures elucidated by Païs *et al.* in the early 1970s.[1] They possess *bis*-ζ-lactam structures, unique to this family of alkaloids, which have been postulated to be biosynthetically derived from spermine and fatty or cinnamic acid residues (Figure 23).[2]



(−)-(*S*,*S*)-homaline **99**

(−)-(*R*,*R*)-hopromine **100**

hopromalinol **101**

hoprominol **102**

Figure 23. The homalium alkaloids **99**-**102**.

3.2.1 Homaline and hopromine

(−)-(*S*,*S*)-Homaline **99** is the most extensively characterised member of this family of alkaloids, with its gross structure confirmed by X-ray crystallography.[3] The inherent symmetry present within homaline means that only the C_2 symmetric (*S*,*S*)- and (*R*,*R*)-stereoisomers are optically active, with the (*R*,*S*)-diastereoisomer being meso. The absolute (*S*,*S*)-configuration within (−)-homaline **99** was confirmed by chemical correlation in an enantiospecific total synthesis starting from methyl (*S*)-3-amino-3-phenylpropionate **343**, and subsequent comparison of the specific rotation of the synthetic sample with that of the naturally occurring alkaloid.[4,5] In comparison, hopromine **100** has four possible stereoisomers, comprising two pairs of enantiomers. The absolute (*R*,*R*)-configuration within (−)-hopromine **100** was established by Ensch and Hesse via an enantiospecific total synthesis from L-aspartic acid **389** and comparison of the specific rotation of the synthetic sample with that of the naturally occurring alkaloid.[2] It is noteworthy that only the (*R*,*R*)-stereoisomer was synthesised in this study, so this structural assignment does not allow for the coincidental matching of the magnitudes of the specific rotations of both possible (*R*,*R*)- and (*R*,*S*)-diastereoisomers.

3.2.2 Previous syntheses of homaline

The first total synthesis of (−)-(*S*,*S*)-homaline **99** was completed by Wasserman and Berger in 1983.[5] The key step in this synthesis was the ring expansion/transamidation reactions of both β-lactams within **337** to form the necessary ζ-lactams within (−)-(*S*,*S*)-homaline **99**. In turn, the required intermediate **337** was produced by reaction of *bis*-electrophile **338** with β-lactam **339** (Figure 24).

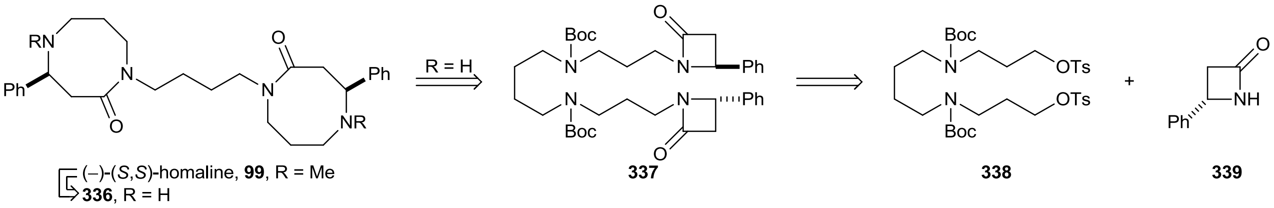
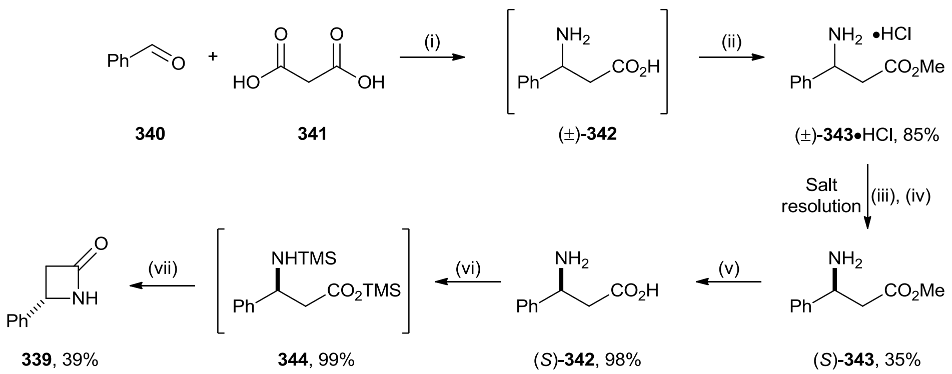


Figure 24. Key steps in Wasserman's retrosynthesis.

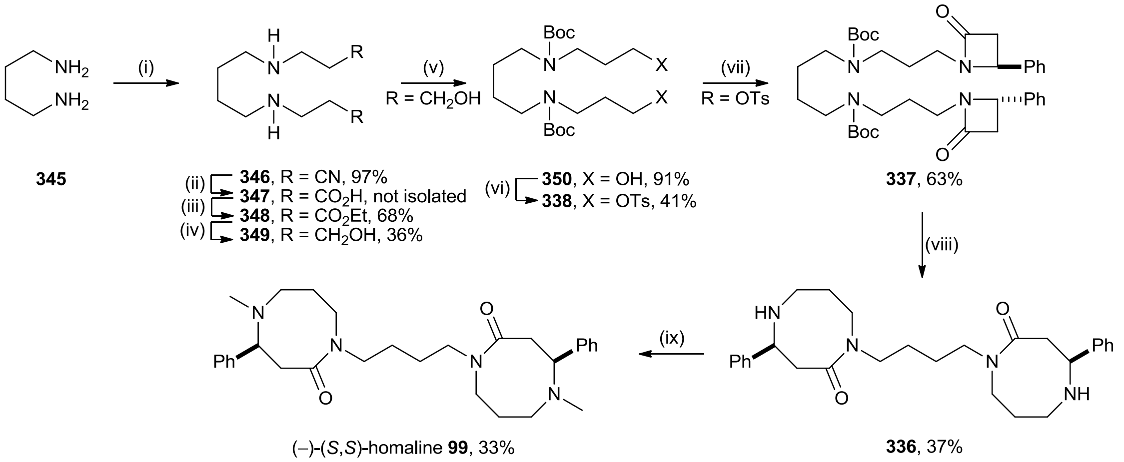
The required enantiopure β-lactam **339** was readily synthesised on a multigram scale via condensation of benzaldehyde **340**, malonic acid **341** and NH_4OAc to give racemic 3-phenyl-3-aminopropanoic acid **342**. Esterification of **342** upon treatment with methanolic HCl gave **343**·HCl in 85% yield. Subsequent resolution of **343** via recrystallisation of the L-(+)-tartaric acid salt, followed by generation of the free base upon treatment with aq NaOH gave enantiopure (*S*)-**343** in 35% overall yield. Further treatment with aq NaOH resulted in ester hydrolysis to give (*S*)-**342** in 98% yield. Treatment of (*S*)-**342** with TMSCl resulted in the formation of the unstable *bis*-silyated intermediate **344** in 99% yield that, upon reaction with EtMgBr, gave the desired β-lactam **339** in 39% yield (Scheme 55).



Scheme 55. *Reagents and conditions*: (i) NH_4OAc, BuOH; (ii) MeOH, HCl; (iii) L-(+)-tartaric acid, MeOH; (iv) NaOH (1.0 M, aq); (v) NaOH (40% aq), MeOH, rt, 16 h; (vi) TMSCl, PhH, rt, 30 min, then NEt_3, 80 °C, 4 h; (vii) EtMgBr, Et_2O, 0 °C, 3 h.

The required *bis*-electrophile **338** was synthesised in six steps from 1,4-diaminobutane **345**. Thus, conjugate addition of **345** to acrylonitrile gave **346** in 97% yield. Subsequent hydrolysis of the nitrile groups, esterification with ethanolic HCl, and reduction with $LiAlH_4$ gave diaminodiol **349** in 24% overall yield for the three step procedure. *N*-Boc protection of the amino functionalities within **349** with Boc-ON, followed by reaction of **350** with TsCl gave **338** in 37% yield over two steps.

Alkylation of β-lactam **339** with **338** gave **337** in 63% yield. Heating **337** in Ph_2O saturated with air promoted the ring expansion to give **336** in 37% yield. Finally, Eschweiler Clarke methylation of **336** gave (−)-(*S*,*S*)-homaline **99** in 33% yield, completing the synthesis in 0.7% overall yield over nine steps from 1,4-diaminobutane **345** (Scheme 56).



Scheme 56. *Reagents and conditions*: (i) acrylonitrile, 0 °C to rt, 2 h; (ii) HCl (6.0 M, aq), reflux, 10 h; (iii) EtOH, HCl, reflux, 12 h; (iv) $LiAlH_4$, THF, reflux, 1 h, then rt, 12 h; (v) Boc-ON, NEt_3, H_2O/dioxane (v/v 1:4), rt, 16 h; (vi) TsCl, pyridine, 4 °C, 36 h; (vii) **339**, NaH, DMF, rt, 40 min, then **338**, DMF, 90 °C, 16 h; (viii) Ph_2O, air, reflux, 3 h; (ix) formalin, HCO_2H, 100 °C, 2 h.

In contrast to Wasserman's synthesis, Crombie *et al.* envisaged that initial preparation of monomeric ζ-lactam **352** followed by *N*-alkylation with a 1,4-*bis*-electrophile to give **351** would allow access to (−)-(*S*,*S*)-homaline **XX**; a similar approach could also be used in the synthesis of the other alkaloids **100-102** (*vide infra*). The desired ζ-lactam **352** could be synthesised by a ring expansion/transamidation of **353**, similar to the approach used by Wasserman, with **353** originating from the same intermediate enantiopure β-lactam **339** (Figure 25).

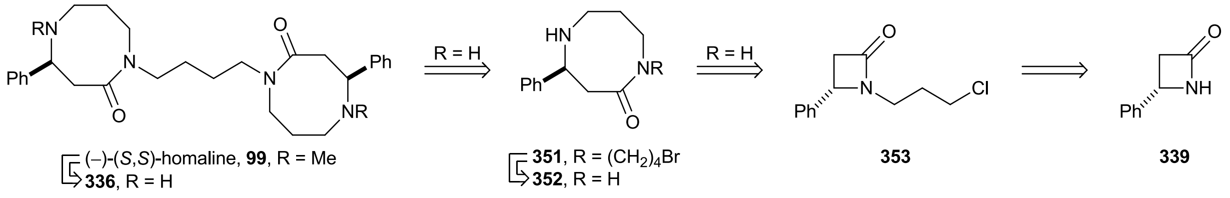
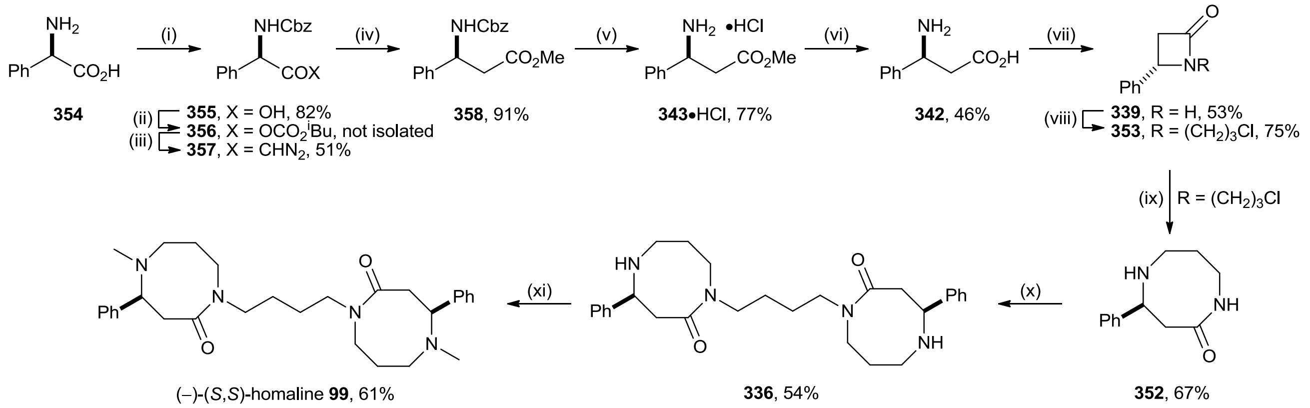


Figure 25. Key steps in Crombie's retrosynthesis of (−)-(*S*,*S*)-homaline **99**.

Starting from (*R*)-(−)-phenylglycine **354**, β-lactam **339** was synthesised in seven steps and 7% overall yield. *N*-Alkylation of **339** with 1-bromo-3-chloropropane **359** gave **353** in 75% yield, with reaction of **353** in liquid NH_3 affecting the simultaneous ring expansion/transamidation reaction to give ζ-lactam **352** in 67% yield. Reaction of **352** with 0.5 equivalents of 1,4-dibromobutane **360** followed by Borch methylation then gave (−)-(*S*,*S*)-homaline **99** in 33% yield over two steps, completing the synthesis in 1.2% overall yield over eleven steps from (*R*)-(−)-phenylglycine **354** (Scheme 57).[6]



Scheme 57. *Reagents and conditions*: (i) CbzCl, NaOH (2.0 M, aq), rt, 1 h; (ii) $^{i}BuO_2CCl$, *N*-methylmorpholine, THF, −5 °C, 30 min; (iii) CH_2N_2, Et_2O, 0 °C, 16 h; (iv) $PhCO_2Ag$, NEt_3, MeOH, rt, 3 h; (v) H_2 (1 atm), Pd/C, MeOH, conc. HCl, rt, 3-4 h; (vi) NaOH (10% aq); (vii) 2,2′-dithiodipyridine, PPh_3, MeCN, reflux, 12 h; (viii) 1-bromo-3-chloropropane **359**, KOH, DMSO, rt, 16 h; (ix) liquid NH_3, rt, 3 days; (x) 1,4-dibromobutane **360**, KOH, DMSO, rt, 16 h; (xi) formalin, $NaBH_3CN$, MeCN, AcOH, rt, 1 h.

Ensch and Hesse[2] adopted a different strategy to construct the ζ-lactam in their synthesis of (±)-homaline **99** and its meso stereoisomer **361**, namely the $Sb(OEt)_3$ mediated macrolactamisation[7] of diamine **363**, itself derived from commercially available 3-amino-3-phenylpropanoic acid **342** (Figure 26).

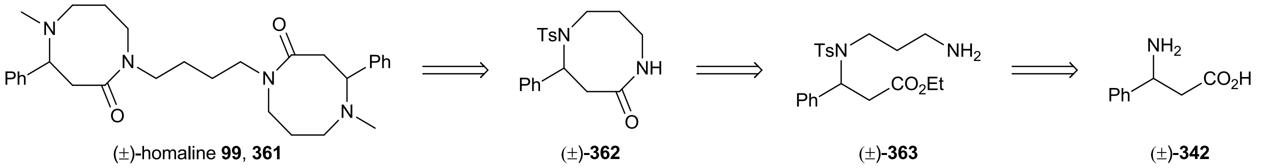
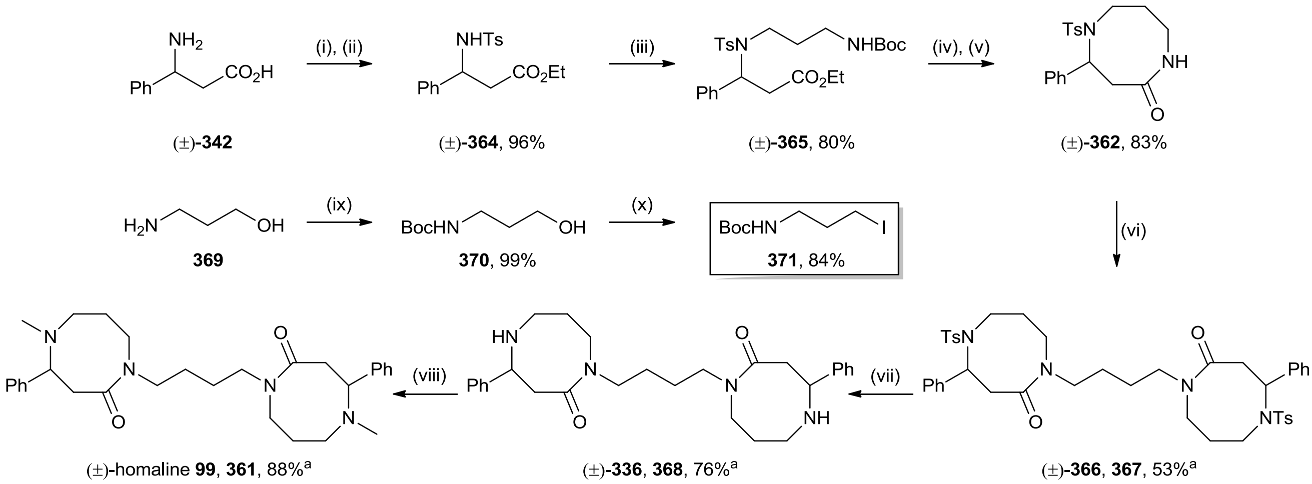


Figure 26. Key steps in Ensch and Hesse's retrosynthesis of (±)-homaline **99** and its meso stereoisomer **361**.

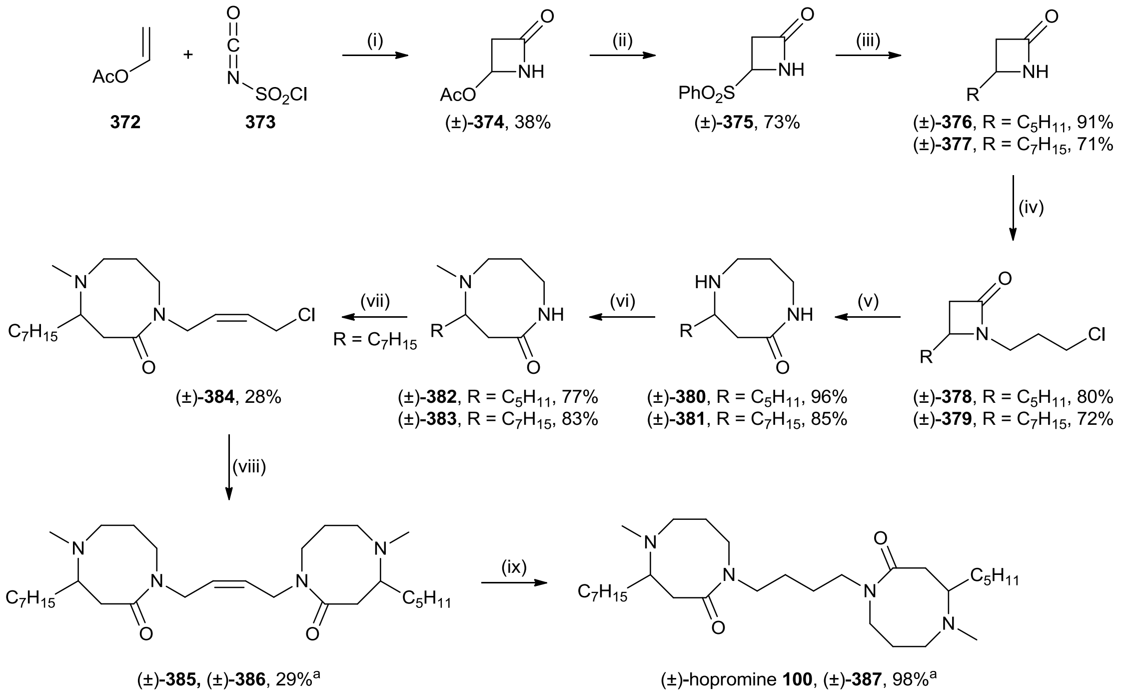
N-Tosylation followed by esterification of 3-amino-3-phenylpropanoic acid **342** with ethanolic HCl gave **364** in 96% yield over two steps. *N*-Alkylation of **364** with iodide **371** (derived from 3-aminopropan-1-ol **369** in 83% over two steps) gave the protected diamine **365** in 80% yield. Removal of the *N*-Boc group within **365** with F_3CCO_2H, followed by $Sb(OEt)_3$ mediated cyclisation afforded ζ-lactam **362** in 83% yield over two steps. Treatment of **362** with 0.5 equivalents of 1,4-dibromobutane **360** gave a mixture of (±)-**366** and **367** in 53% combined yield, with electrolytic detosylation of (±)-**366** and **367** affording (±)-**336** and **368** in 76% combined yield. Finally, Borch methylation of (±)-**336** and **368** gave a mixture of (±)-homaline **99** and its meso diastereoisomer **361** in 88% combined yield, completing the synthesis in 20% combined, overall yield, over eight steps from 3-phenyl-3-aminopropanoic acid **342** (Scheme 58).



Scheme 58. *Reagents and conditions*: (i) TsCl, NaOH (2.0 M, aq), rt, 16 h; (ii) $SOCl_2$, EtOH, 0 °C to rt, 2.5 h; (iii) Cs_2CO_3, **371**, DMF, 55 °C, 16 h; (iv) F_3CCO_2H, $CHCl_3$, 40 °C, 16 h; (v) $Sb(OEt)_3$, PhH, reflux, 16 h; (vi) 1,4-dibromobutane **360**, KOH, DMSO, rt, 16 h; (vii) electrolysis; (viii) formalin, $NaBH_3CN$, AcOH, MeOH, 0 °C to rt, 3.5 h; (ix) Boc_2O, Et_3N, CH_2Cl_2, reflux, 16 h; (x) I_2, PPh_3, imidazole, CH_2Cl_2 , rt, 3.5 h. [a combined yield].

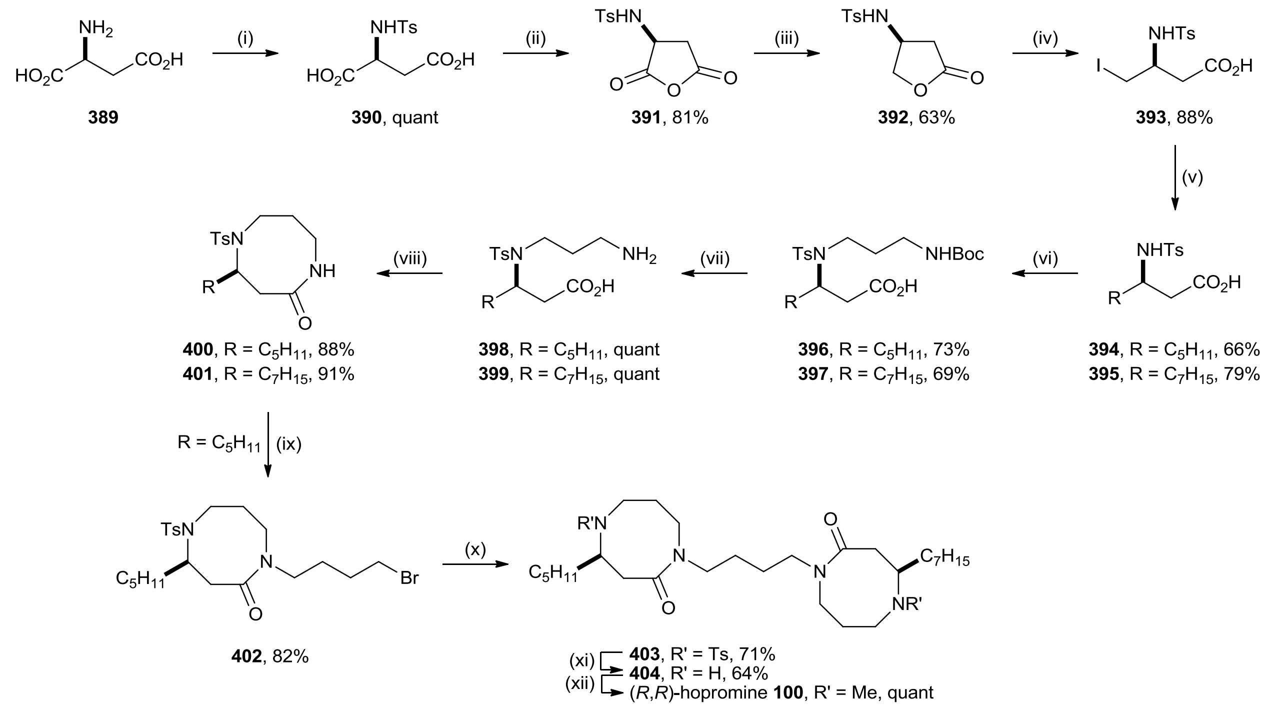
3.2.3 Previous syntheses of hopromine

Hopromine **100** has been synthesised twice previously, once by Crombie *et al.*[8] and once by Ensch and Hesse.[2] Following a similar strategy as for their synthesis of homaline **99**, Crombie's synthesis relied on the ring expansion/transamidation of β-lactams **378** and **379** followed by stepwise alkylation to give a mixture (±)-hopromine **100** and its diastereoisomer (±)-**387**. Thus, β-lactams **376** and **377** were prepared from the [2 + 2] cycloaddition of vinyl acetate **372** and chlorosulfonyl isocyanate **373** to give **374** in 38% yield. Displacement of the acetate group within **374** with $PhSO_2Na$ gave **375** in 73% yield, with subsequent displacement of the sulfonyl group with the appropriate Grignard reagent giving **376** and **377** in 91 and 71% yield, respectively. Proceeding as in their synthesis of homaline **99**, **376** and **377** were elaborated to ζ-lactams **382** and **383** in 59 and 51% yield, respectively, over three steps. Alkylation of **383** was achieved upon treatment with 2.5 equivalents of (*Z*)-1,4-dichlorobut-2-ene **388** in the presence of KHMDS to give **384** in 28% yield. Subsequent alkylation of **382** with **384** gave a mixture of (±)-**385** and (±)-**386** in 29% combined yield, with ensuing hydrogenation giving a mixture of (±)-hopromine **100** and (±)-**387** in 98% combined yield, completing the synthesis in 0.8% combined, overall yield, over nine steps from vinyl acetate **372** (Scheme 59).



Scheme 59. *Reagents and conditions*: (i) 20 °C, 30 min, then $NaHCO_3$, Na_2SO_3, H_2O, −40 °C; (ii) $PhSO_2Na$, H_2O, 100 °C, 15 min; (iii) RMgBr, −70 °C, THF, 35 min, then rt, 3.5 h; (iv) 1-bromo-3-chloropropane **359**, KOH, DMSO, rt, 18 h; (v) liquid NH_3, 10 days (R = C_5H_{11}) or 7 days (R = C_7H_{15}); (vi) formalin, $NaBH_3CN$, MeCN, AcOH, rt, 1 h; (vii) KHMDS, (*Z*)-1,4-dichlorobut-2-ene **388**, THF, rt, 50 h; (viii) KHMDS, **382**, THF, rt, 1 day, then NaH, 10 days; (ix) H_2 (1 atm), PtO_2, MeOH, conc. HCl, rt, 3 h. [a combined yield].

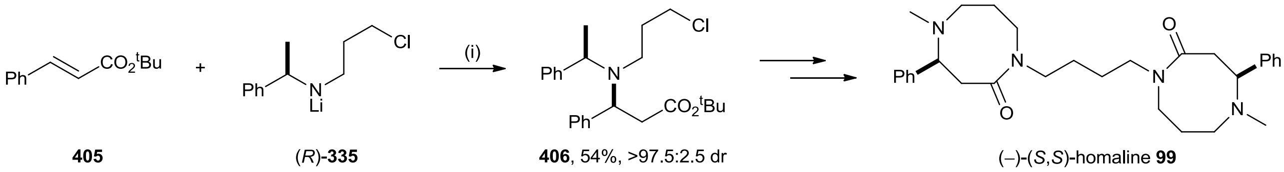
By analogy to their synthesis of homaline **99**, Ensch and Hesse's enantiospecific synthesis of (−)-(*R*,*R*)-hopromine **100** relied on the $Sb(OEt)_3$ mediated macrolactamisation of diamines **398** and **399** to form the desired ζ-lactams, followed by the stepwise alkylation and subsequent manipulation to give (−)-(*R*,*R*)-hopromine **100**. Starting from L-aspartic acid **389**, *N*-tosylation followed by reaction with $SOCl_2$ gave anhydride **391** in 81% yield over two steps. Regioselective reduction of one of the carbonyl groups followed by opening of the resultant lactone **392** with TMSI gave iodide **393** in 55% yield over two steps. Displacement of the iodide functionality within **393** with the appropriate organocuprate reagent gave **394** and **395** in 66 and 79% yield, respectively. Proceeding as in their synthesis of homaline **99**, the *N*-tosyl ζ-lactams **400** and **401** were generated in 64 and 63% yield, respectively. Alkylation of **400** with 1,4-dibromobutane **360** gave **402** in 82% yield, with the second alkylation between **401** and **402** proceeding to give **403** in 71% yield. Removal of the *N*-tosyl groups and subsequent Borch methylation gave (−)-(*R*,*R*)-hopromine **100** in 45% yield over two steps, completing the synthesis in 7.1% overall yield over ten steps (Scheme 60).



Scheme 60. *Reagents and conditions*: (i) TsCl, NaOH (4.0 M, aq), Et_2O, rt, 16 h; (ii) $SOCl_2$, EtOAc, rt, 4 h; (iii) $NaBH_4$, THF, 0 °C, 2 h then HCl, EtOH, reflux, 2 h; (iv) TMSI, EtOH, CH_2Cl_2, 0 °C to rt, 16 h; (v) RLi, $CuBr{\cdot}Me_2S$, Et_2O/THF (v/v 1:2) −65 to −45 °C, 5 h; (vi) Cs_2CO_3, **371**, DMF, 55 °C, 16 h; (vii) F_3CCO_2H, $CHCl_3$, 40 °C, 16 h; (viii) $Sb(OEt)_3$, PhH, reflux, 16 h; (ix) 1,4-dibromobutane **360**, KOH, DMSO, rt, 16 h; (x) **401**, KOH, DMSO, 0 °C to rt, 16 h; (xi) electrolysis; (xii) formalin, $NaBH_3CN$, AcOH, MeOH, 0 °C to rt, 4 h.

3.3 Chapter aim

Pilot studies within the Davies group[9] have shown that the conjugate addition of the novel lithium amide reagent, lithium (*R*)-*N*-(3-chloroprop-1-yl)-*N*-(α-methylbenzyl)amide (*R*)-**335** to *tert*-butyl cinnamate **405** proceeds with the high levels of diastereoselectivity normally observed in this reaction manifold.[10] It was envisaged that this reaction could be utilised as the key step in the asymmetric synthesis of (*S*,*S*)-(−)-homaline **99** (Scheme 61).



Scheme 61. *Reagents and conditions*: (i) THF, −78 °C, 2 h.

3.4 Asymmetric synthesis of (−)-(*S*,*S*)-homaline

Initial attempts to synthesise (−)-(*S*,*S*)-homaline **99** were based on the following retrosynthetic analysis. Replacement of the *N*-methyl groups with α-methylbenzyl groups and potentially adding a degree of unsaturation in the C_4 linker gives **407**, which in the forward sense could be subjected to hydrogenation/hydrogenolysis in the presence of formaldehyde to give (−)-(*S*,*S*)-homaline **99**. Disconnection of the C_4 linker either at the C−N or C=C bond gives **408**; in the forward sense this requires either alkylation of **408** (R = H) with a 1,4-*bis*-electrophile, or metathesis of **408** (R = allyl) to give **407**. Breaking of the amide bond within **408** gives diamine **409**, with reaction in the forward sense following Ensch and Hesse's $Sb(OEt)_3$ mediated macrolactamisation methodology.[2]

Diamine **409** could be derived from **410** by displacement of the chloride functionality. Chloride **410** can then be obtained from the conjugate addition of the functionalised lithium amide **412** to the corresponding cinnamate ester **411** (Figure 27).

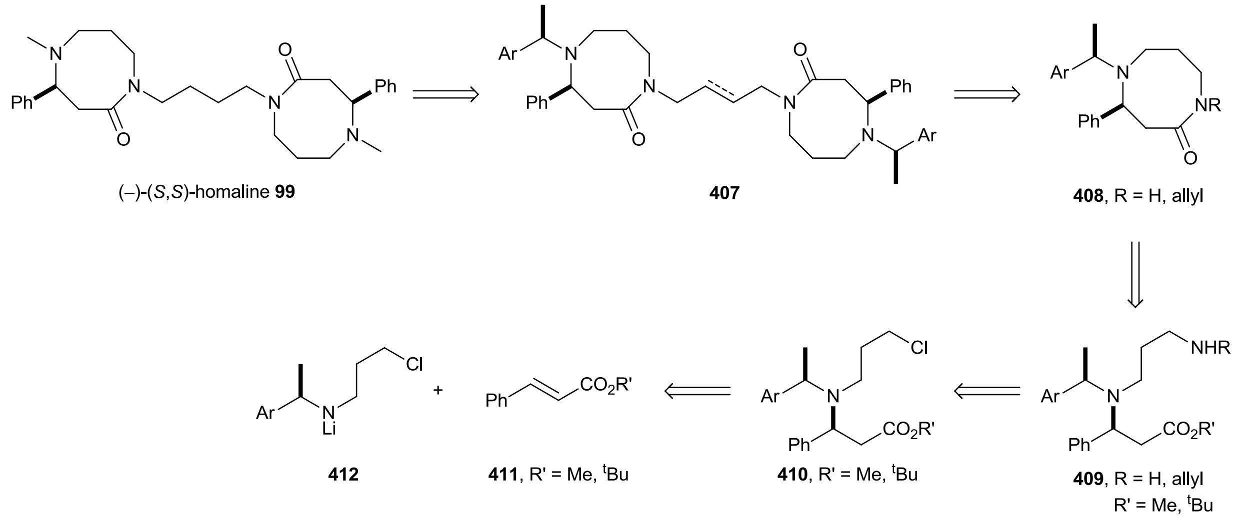
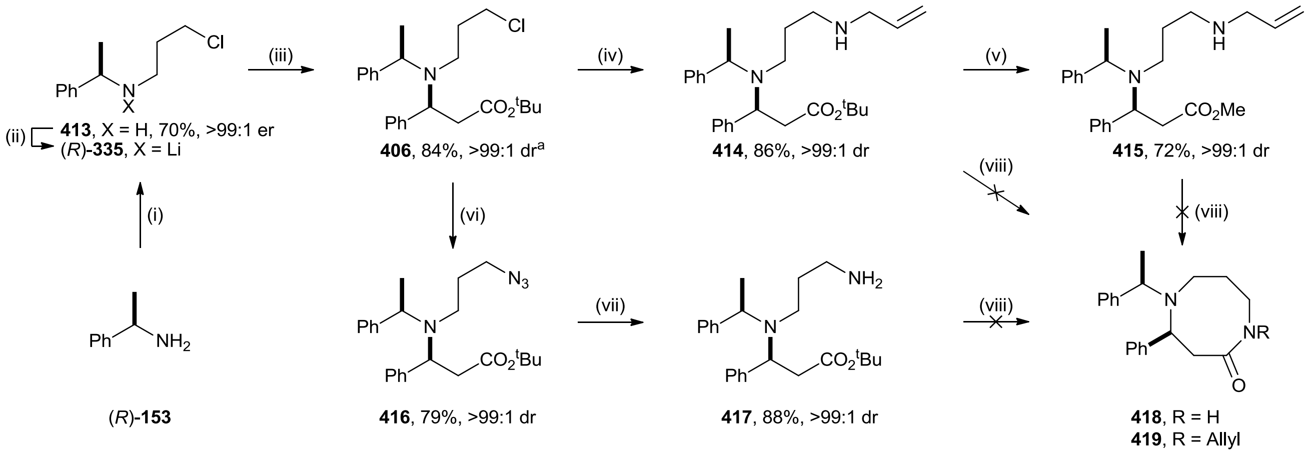


Figure 27. Initial retrosynthetic analysis of (−)-(*S*,*S*)-homaline **99**.

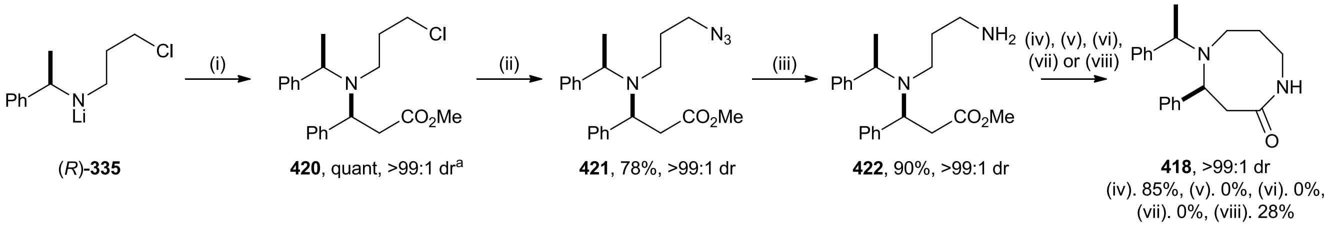
3.4.1 Use of lithium (*R*)-*N*-3-(chloroprop-1-yl)-*N*-(α-methylbenzyl)amide

It was initially decided to investigate the structural requirements for the $Sb(OEt)_3$ mediated macrolactamisation reaction by variation of the ester and C(3′)-amino functionalities. Efforts therefore focused on the synthesis of a range of ζ-lactam precursors **414**, **415** and **417**. Thus, amine **413** was prepared by alkylation of (*R*)-α-methylbenzylamine (*R*)-**153** with 1-bromo-3-chloropropane **359** in 70% yield and >99:1 er.[11] Treatment of **413** with BuLi generated a yellow solution of the corresponding lithium amide (*R*)-**335** which reacted with *tert*-butyl cinnamate **405** to give **406** in 84% yield and >99:1 dr. The sense of diastereocontrol in this conjugate addition reaction was assigned relative to the transition state mnemonic developed by Davies *et al.* for the lithium amide conjugate addition reaction of secondary lithium amides derived from α-methylbenzylamine to α,β-unsaturated esters.[12] Displacement of the chloride functionality within **406** with allylamine in the presence of NaI gave the first cyclisation precursor **414** in 86% yield. Transesterification of **414** with methanolic HCl gave the corresponding methyl ester **415** in 72% yield. Finally, displacement of the chloride functionality within **406** with NaN_3 (again in the presence of NaI) gave azide **416** in 79% yield, which was subjected to Staudinger reduction with PPh_3 to give **417** in 88% yield. Unfortunately, all of these substrates failed to cyclise upon treatment with $Sb(OEt)_3$ under the conditions used by Ensch and Hesse[2] to affect the macrolactamisation of **363**, **398** and **399** (*vide supra*) (Scheme 62).



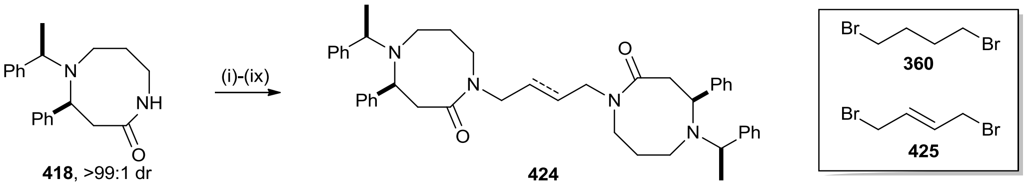
Scheme 62. *Reagents and conditions*: (i) 1-bromo-3-chloropropane **359**, MeCN, rt, 16 h; (ii) BuLi, THF, −78 °C, 15 min; (iii) *tert*-butyl cinnamate **405**, THF, −78 °C, 2 h; (iv) allylamine, NaI, 65 °C, 24 h; (v) $SOCl_2$, MeOH, reflux, 2 h; (vi) NaN_3, NaI, DMSO, 50 °C, 48 h; (vii) PPh_3, THF, rt, 30 min, then H_2O, 50 °C, 2 h; (viii) $Sb(OEt)_3$, PhMe, reflux, 18 h. [^{a} crude and isolated].

The failure of **414**, **415** and **417** to cyclise suggested that the presence of a primary amine functionality and an unhindered ester was prerequisite to cyclisation under these conditions, as was the case in previously reported examples of this reaction.[2] Therefore, the corresponding methyl ester **422** was synthesised via the conjugate addition of lithium amide (*R*)-**335** to methyl cinnamate **423** which gave **420** in quantitative yield and >99:1 dr. The sense of diastereoselectivity was again initially assigned by reference to the lithium amide conjugate addition transition state mnemonic,[12] and this assignment was later confirmed by chemical correlation and single crystal X-ray diffraction analysis. Treatment of **420** with NaN_3 and NaI gave **421** in 78% yield, with subsequent Staudinger reduction giving **422** in 90% yield. Macrolactamisation of **422** upon treatment with $Sb(OEt)_3$ gave ζ-lactam **418** in 85% yield. At this point, it was decided to examine the importance of $Sb(OEt)_3$ in the reaction manifold. A range of conditions were therefore screened to investigate the macrolactamisation of **422**: reaction with either NaOMe or $CsCO_3$, or in the absence of any base, failed to give any conversion to the desired ζ-lactam **418**. In contrast, reaction using $Fe(OEt)_3$ afforded the desired ζ-lactam **418** in 28% yield. However, no set of conditions were found that were more efficacious than the use of $Sb(OEt)_3$. Finally, it was found that ζ-lactam **418** could be synthesised without isolation of intermediates **420-422**, giving **418** in 69% overall yield over four steps (Scheme 63).



Scheme 63. *Reagents and conditions*: (i) methyl cinnamate **423**, THF, −78 °C, 2 h; (ii) NaN_3, NaI, DMSO, 50 °C, 24 h; (iii) PPh_3, THF, rt, 30 min, then H_2O, 50 °C, 2 h; (iv) $Sb(OEt)_3$, PhMe, reflux, 18 h; (v) PhMe, reflux, 18 h; (vi) NaOMe, PhMe, reflux, 18 h; (vii) $CsCO_3$, PhMe, reflux, 18 h; (viii) $Fe(OEt)_3$, PhMe, reflux, 18 h. [^{a} crude and isolated].

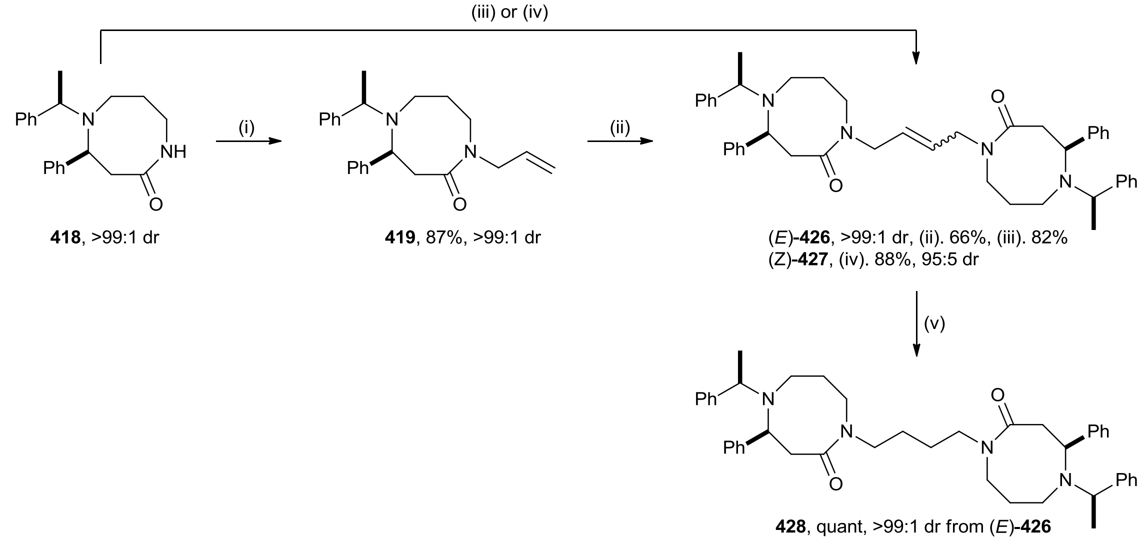
With ζ-lactam **418** in hand, attention turned to its *N*-alkylation with a 1,4-*bis*-electophile to give the (−)-(*S*,*S*)-homaline scaffold **424**. ζ-Lactam **418** initially proved resilient to *N*-alkylation under both literature conditions[2,6] used in similar systems or a range of novel conditions initially trialled, with reaction failing to result in any significant level of alkylation in every attempt (Scheme 64).



Alkyl halide	Conditions	Result
360	(i)	Returned starting material
360	(ii)	Returned starting material
360	(iii)	8% yield, >99:1 dr
360	(iv)	Returned starting material
425	(v)	Returned starting material
425	(vi)	Returned starting material
425	(vii)	Returned starting material
425	(viii)	Returned starting material
425	(ix)	Returned starting material

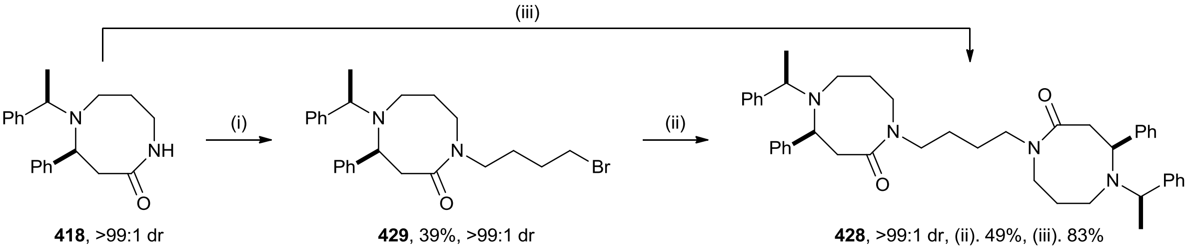
Scheme 64. *Reagents and conditions*: (i) NaH, DMF, rt, 1 h, then **360**, rt, 18 h; (ii) NaH, DMF, rt, 1 h, then **360**, 50 °C, 18 h; (iii) KOH, **360**, DMSO, 0 °C to rt, 16 h; (iv) K_2CO_3, **360** (solvent), 50 °C, 18 h; (v) NaH, DMF, rt, 1 h, then **425**, 50 °C, 18 h; (vi) NaH, 15-crown-5, NaI, DMF, rt, 1 h, then **425**, 50 °C, 18 h; (vii) KHMDS, DMF, 0 °C, 1 h, then **425**, rt, 18 h; (viii) KHMDS, DMSO, rt, 30 min, then **425**, rt, 18 h; (ix) KOH, **425**, DMSO, 0 °C to rt, 16 h.

After extensive optimisation, it was found that **418** could be allylated with allyl bromide under phase transfer conditions with microwave irradiation at 160 °C:[13] upon treatment of **418** with K_2CO_3, KOH, TBAC and allyl bromide, *N*-allyl ζ-lactam **419** was isolated in 87% yield. Metathesis of **419** using Grubbs II catalyst affected the condensation of **419** to give (*E*)-**426** in 82% yield. The (*E*)-configuration of the newly formed C=C double bond within **426** was confirmed by the synthesis of authentic samples of (*E*)-**426** and (*Z*)-**427** by alkylation of **418** with either (*E*)-1,4-dibromobut-2-ene **425** or (*Z*)-1,4-dichlorobut-2-ene **388**, and comparison of the 400 MHz ^{1}H NMR spectra of (*E*)-**426** and (*Z*)-**427** with that of the sample of (*E*)-**426** prepared from metathesis of **419**. In an attempt to debenzylate (*E*)-**426** (with concomitant hydrogenation of the C=C double bond), (*E*)-**426** was subjected to reaction with H_2 (5 atm) and $Pd(OH)_2/C$. This resulted in the quantitative hydrogenation of the C=C double bond to give **428**, with no debenzylation being observed (Scheme 65).



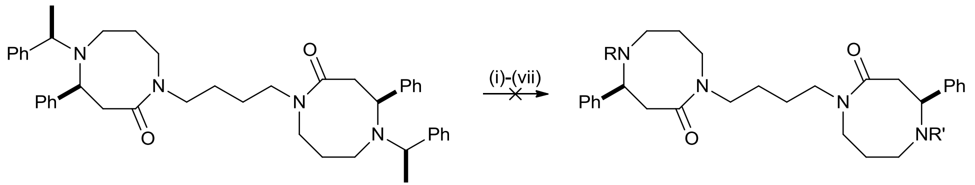
Scheme 65. *Reagents and conditions*: (i) allyl bromide, K_2CO_3, KOH, TBAC, 160 °C, µwave, 2 min; (ii) Grubbs II, CH_2Cl_2, 40 °C, 18 h; (iii) (*E*)-1,4-dibromobut-2-ene **425**, K_2CO_3, KOH, TEBAC, DMSO, rt, 72 h; (iv) (*Z*)-1,4-dichlorobut-2-ene **388** (95:5 dr), K_2CO_3, KOH, TEBAC, DMSO, rt, 96 h (v) H_2 (5 atm), $Pd(OH)_2/C$, MeOH, rt, 1 h.

A different route to **428** involved alkylation of ζ-lactam **418** with 1,4-dibromobutane **360** under similar, optimised phase transfer conditions (*vide supra*), giving bromide **429** in 39% yield. Reaction between bromide **429** and ζ-lactam **418** then gave *bis*-ζ-lactam **428** in 49% yield, providing a two step procedure to **428** in 19% overall yield. Alternatively, alkylation of ζ-lactam **418** with 0.5 equivalents of 1,4-dibromobutane **360** under similar conditions gave **428** in 83% yield, representing the most efficient route to **428** (Scheme 66).



Scheme 66. *Reagents and conditions*: (i) 1,4-dibromobutane **360**, K_2CO_3, KOH, TBAC, 160 °C, µwave, 110 sec; (ii) **418**, K_2CO_3, KOH, TBAC, PhMe, µwave, 7 min; (iii) 1,4-dibromobutane **360**, K_2CO_3, KOH, TBAC, PhMe, 160 °C, µwave, 15 min.

Unfortunately, exhaustive attempts to remove the α-methylbenzyl groups within **428** under a range of conditions,[14] with or without *in situ* reductive methylation, proved unreliable, giving either returned starting material or inseparable complex mixtures of products consisting of (−)-(*S*,*S*)-homaline **99**, **336** and **430** (Scheme 67). A second, analogous, strategy was therefore sought in which the acid labile *N*-(α-methyl-4-methoxybenzyl) protecting group was used.



428, >99:1 dr

(–)-(*S*,*S*)-homaline **99**, R = R' = Me
336, R = R' = H
430, R = H, R' = Me

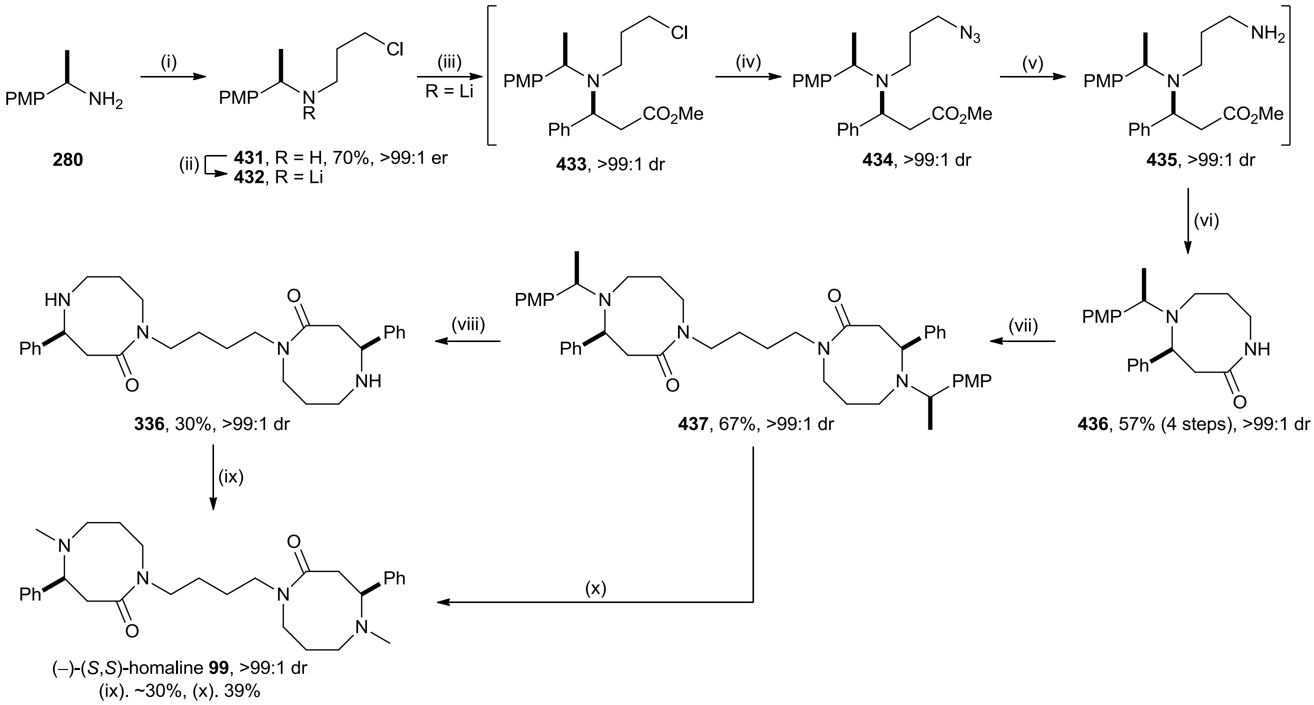
Conditions	Result
(i)	Complex mixture
(ii)	Complex mixture
(iii)	Complex mixture
(iv)	Complex mixture
(v)	Returned starting material
(vi)	Returned starting material
(vii)	Returned starting material

Scheme 67. *Reagents and conditions*: (i) $Pd(OH)_2/C$, H_2 (1 atm), AcOH, rt, 16 h; (ii) $Pd(OH)_2/C$, H_2 (1 atm), AcOH/formalin/MeOH (v/v/v 3:2:1), rt, 16 h; (iii) $Pd(OH)_2/C$, H_2 (5 atm), AcOH/formalin/MeOH (v/v/v 3:2:1), rt, 48 h; (iv) $Pd(OH)_2/C$, H_2, AcOH, rt, 18 h then formalin, MeOH, rt, 18 h; (v) HCO_2H, Et_3SiH, 90 °C, 16 h; (vi) $FeCl_3$, NaI, MeCN, rt, 18 h; (vii) MeI, rt, 1 month.

3.4.2 Use of lithium (*R*)-*N*-3-(chloroprop-1-yl)-*N*-(α-methyl-4′-methoxybenzyl)amide

Alkylation of (*R*)-α-methyl-(4-methoxybenzyl)amine **280** with 1-bromo-3-chloropropane **359** gave **431** in 70% yield and >99:1 er.[15] Conjugate addition of the corresponding lithium amide **432** to methyl cinnamate **423** gave **433** in >99:1 dr. The sense of diastereocontrol in this reaction was initially assigned by reference to the lithium amide conjugate addition transition state mnemonic,[12] and was later confirmed by chemical correlation and single crystal X-ray diffraction analysis. Displacement of the chloride functionality within **433** with NaN_3 in the presence of NaI gave azide **434**, with subsequent Staudinger reduction of **434** and $Sb(OEt)_3$ mediated macrolactamisation of **435** giving **436** in 57% yield over four steps. Alkylation of **436** with 0.5 equivalents of 1,4-dibromobutane **360** upon treatment with K_2CO_3, KOH and TBAI in PhMe at 160 °C in a microwave reactor (similar to the previously optimised conditions for the *N*-alkylation of **418**) gave **437** in 67% yield as a single diastereoisomer (>99:1 dr). Removal of the *N*-(α-methyl-4-methoxybenzyl) groups within **437** using F_3CCO_2H gave **336** in 30% yield, with subsequent Borch methylation[5] giving an approximately 95% pure sample of (*S*,*S*)-(−)-homaline **99** in 30% yield. This sample of (*S*,*S*)-(−)-homaline **99** was found to be chromatographically identical to other samples of (−)-(*S*,*S*)-homaline **99**, and displayed ^1H and ^{13}C NMR data consistent with the natural product. However, the value of the specific rotation for this sample of (*S*,*S*)-(−)-homaline **99** {$[\alpha]_D^{24}$ −16.8 (*c* 0.4 in $CHCl_3$)} was not in agreement with that of natural (−)-(*S*,*S*)-homaline **99** {lit.[1f] $[\alpha]_D^{20}$ −34 (*c* 1.0 in $CHCl_3$)}. It was, however, in close agreement with the value obtained for (−)-(*S*,*S*)-homaline **99** by Wasserman and Berger {lit.[5] $[\alpha]_D^{24}$ −15.4 (*c* 1.0 in $CHCl_3$)} for the same reductive methylation procedure. Alternatively, reaction of **437** under Eschweiler Clarke conditions effected both *N*-deprotection and *N*-methylation to give (*S*,*S*)-(−)-homaline **99** directly in 39% yield and >99:1 dr (Scheme 68). The spectroscopic data obtained for this sample of (–)-(*S*,*S*)-homaline **99**

{$[\alpha]_D^{24}$ −29.2 (*c* 1.0 in $CHCl_3$)} were in excellent agreement with those for the sample isolated from the natural source {lit.[1f] $[\alpha]_D^{20}$ −34 (*c* 1.0 in $CHCl_3$)} and other samples obtained by total synthesis.[4,5,6]

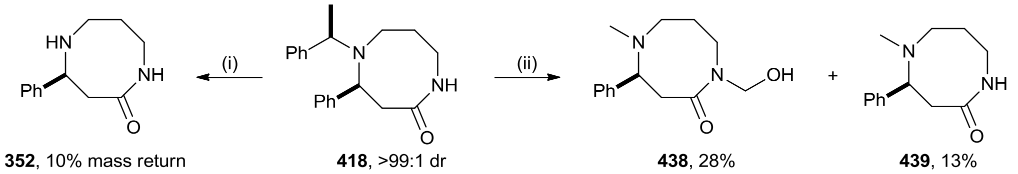


Scheme 68. *Reagents and conditions*: (i) 1-bromo-3-chloropropane **359**, MeCN, rt, 16 h; (ii) BuLi, THF, −78 °C, 15 min; (iii) methyl cinnamate **423**, THF, −78 °C, 2 h; (iv) NaN_3, NaI, DMSO, 50 °C, 24 h; (v) PPh_3, THF, rt, 30 min, then H_2O, 50 °C, 2 h; (vi) $Sb(OEt)_3$, PhMe, reflux, 18 h; (vii) 1,4-dibromobutane **360**, K_2CO_3, KOH, TBAI, PhMe, 160 °C, μwave, 15 min; (viii) F_3CCO_2H, 60 °C, 2.5 h; (ix) formalin, $NaBH_3CN$, AcOH, MeOH, 0 °C to rt, 3.5 h; (x) formalin, HCO_2H, reflux, 2.5 h. [[a] crude and isolated].

The optimal yield of (*S*,*S*)-(−)-homaline **99** from this route is therefore 10% over seven steps from commercially available starting materials. In an effort to improve the overall yield of (*S*,*S*)-(−)-homaline **99**, an alternative strategy reliant on early stage *N*-deprotection was investigated next.

3.4.3 Synthesis using an early deprotection strategy

With removal of the *N*-(α-methylbenzyl) or *N*-(α-methyl-4-methoxybenzyl) groups proving to be problematic in the latter stages of the above syntheses, an earlier deprotection strategy was deemed desirable. Three possible points in the synthesis were identified as being potentially amenable for this deprotection: *N*-debenzylation of the ζ-lactams **418** and **436**, *N*-debenzylation of the azido intermediate **421** (with simultaneous reduction of the azide) and *N*-debenzylation of the β-amino esters **420** and **433**. Hydrogenolytic *N*-debenzylation of ζ-lactam **418** over $Pd(OH)_2/C$ resulted in a poor crude mass return, whilst *N*-debenzylation of **418** with *in situ* reductive methylation with formalin gave hemiaminal **438** as the major product in 28% yield, in addition to **439** which was isolated in only 13% yield (Scheme 69). Comparison of the specific rotation of **439** {$[\alpha]_D^{24}$ +6.7 (*c* 1.0 in $CHCl_3$)} with that previously reported for an enantioenriched sample of *ent*-**439** {lit.[16,17] $[\alpha]_D^{24}$ −6.2 (*c* 0.9 in $CHCl_3$)} confirmed the absolute (*S*)-configuration within **439**. This also allowed the assigned absolute configurations within **418** and **420-422** to be confirmed.



Scheme 69. *Reagents and conditions*: (i) H_2 (1 atm), $Pd(OH)_2/C$, AcOH, rt, 18 h; (ii) H_2 (5 atm), $Pd(OH)_2/C$, AcOH/formalin/MeOH (v/v/v 3:2:1), rt, 72 h.

Furthermore, the structures of both **438** and **439** were confirmed by single crystal X-ray diffraction analysis, with the determination of a Flack *x* parameter[18,19] for **439** of 0.20(19), providing support for the assigned absolute (*S*)-configuration within **439** (Figure 28).

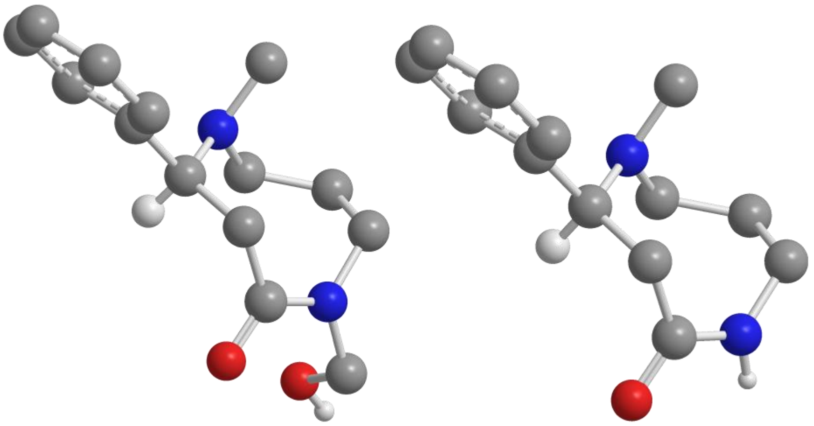
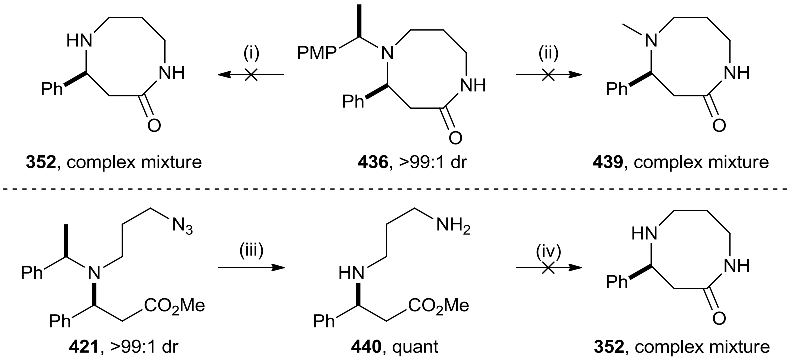


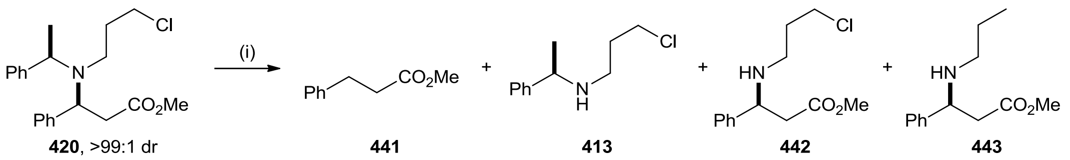
Figure 28. X-ray crystal structures of **438** [*left*] and **439** [*right*] (selected H atoms are omitted for clarity).

Attempted debenzylation of **436** with either F_3CCO_2H or under Eschweiler Clarke conditions resulted in complex mixtures of products from which **352** or **439** could not be isolated. Hydrogenolytic debenzylation of **421** with concurrent reduction of the azide functionality proceeded in quantitative yield to give **440**, but the ensuing $Sb(OEt)_3$ mediated macrolactamisation reaction resulted in a complex mixture from which **352** could not be isolated, suggesting that the presence of a tertiary amine is also essential for this reaction (Scheme 70).



Scheme 70. *Reagents and conditions*: (i) F_3CCO_2H, 60 °C, 2.5 h; (ii) formalin, HCO_2H, 100 °C, 2.5 h; (iii) H_2 (1 atm), $Pd(OH)_2/C$, MeOH, rt, 16 h; (iv) $Sb(OEt)_3$, PhMe, reflux, 18 h.

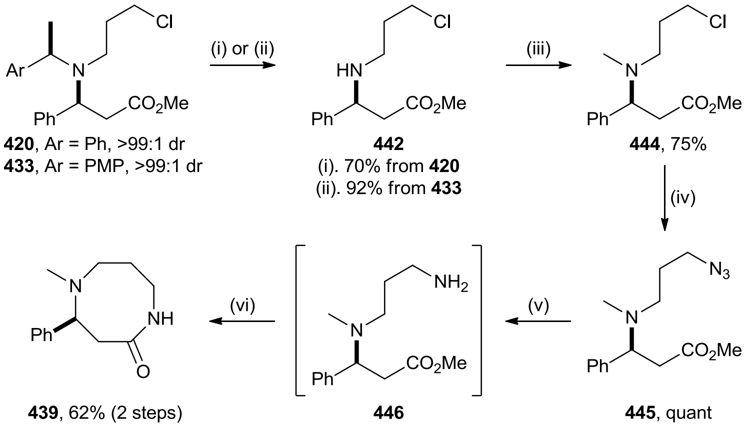
The final option was then considered: *N*-deprotection of β-amino esters **420** and **433**. Hydrogenolysis of **420** with H_2 and $Pd(OH)_2/C$ in EtOAc resulted in the cleavage of the C(3)−N bond, yielding **441** as the only observed product in the 400 MHz ^1H NMR spectrum of the crude reaction mixture. Upon changing the solvent to MeOH, selective cleavage of the desired C(α)−N bond was observed to give **442**, however, reduction of the C−Cl bond was also observed to give **443**, resulting in an 85:15 mixture of **442** and **443** respectively. Reaction in AcOH suppressed the reduction of the C−Cl bond, however, some cleavage of the C(3)−N bond was again observed, giving a 28:4:68 mixture of **441**:**413**:**442** (Scheme 71).



Solvent	Crude product ratio (**441**:**413**:**442**:**443**)
EtOAc	100:0:0:0
MeOH	0:0:85:15
AcOH	28:4:68:0

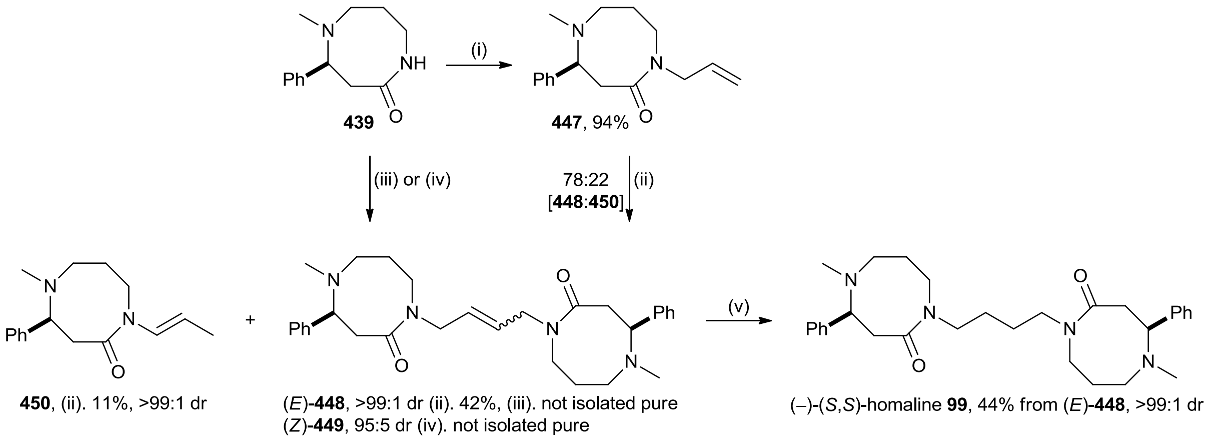
Scheme 71. *Reagents and conditions*: (i) H_2 (1 atm), $Pd(OH)_2/C$, solvent, rt, 16 h.

In comparison, hydrogenolysis of **420** in 1.0 M aq HCl proved successful, with only cleavage of the desired C(α)−N bond being observed, giving **442** in 70% yield. Alternatively, the *N*-(α-methyl-4-methoxybenzyl) group within **433** could be removed upon treatment with F_3CCO_2H to give **442** in 92% yield. Borch methylation of **442** gave **444** in 75% yield, with ensuing displacement of the chloride with NaN_3 in the presence of NaI giving **445** in quantitative yield. Staudinger reduction of **445** and $Sb(OEt)_3$ mediated macrolacamisation of **446** gave ζ-lactam **439** in 62% yield over two steps (Scheme 72).



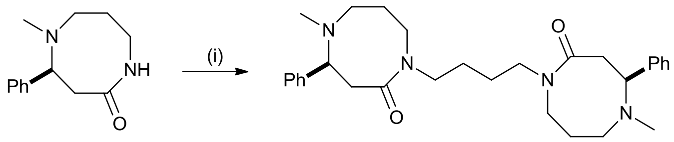
Scheme 72. *Reagents and conditions*: (i) **420**, H_2, $Pd(OH)_2/C$, HCl (1.0 M, aq), rt, 16 h; (ii) **433**, F_3CCO_2H, 65 °C, 2.5 h; (iii) $(CH_2O)_n$, $NaBH_3CN$, MeOH, rt, 16 h; (iv) NaN_3, NaI, DMSO, 50 °C, 24 h; (v) PPh_3, THF, rt, 30 min, then H_2O, 50 °C, 2 h; (vi) $Sb(OEt)_3$, PhMe, reflux, 18 h.

Unfortunately, ζ-lactam **439** could not be alkylated under the previously optimised conditions used for **418** and **436** (K_2CO_3, KOH and TBAC in PhMe at 160 °C in a microwave reactor), as only returned starting material was obtained. However, under different phase transfer conditions, **439** could be allylated with allyl bromide to give **447** in 94% yield. Metathesis of **447** using Grubbs II catalyst gave **448** in 42% yield and >99:1 dr, as well as 11% of the isomerised product (*E*)-**450**[20] and other, unidentified alkene containing products. The configuration of the newly formed C=C double bond within **448** was confirmed by the synthesis of authentic samples of (*E*)-**448** and (*Z*)-**449** by alkylation of **439** with either (*E*)-1,4-dibromobut-2-ene **425**[21] or (*Z*)-1,4-dichlorobut-2-ene **388**[22] and comparison of their 400 MHz ^{1}H NMR spectra with that of the sample of (*E*)-**448** prepared from metathesis of **447**. The stereochemistry of the newly formed C=C double bond within **450** was assigned by ^{1}H NMR ^3J coupling constant analyses, with a diagnostic *trans* ($J_{1',2'}$ = 14.7 Hz) olefinic coupling constant being observed.[23] It was hypothesised that **450** and **448** could be equilibrated by further exposure to the reaction conditions, however resubjection of **450** to Grubbs II catalyst did not produce any **448**. Similarly, resubjection of **448** to the reaction conditions did not produce any **450**, suggesting that both products **448** and **450** form irreversibly. Hydrogenation of (*E*)-**448** gave (−)-(*S*,*S*)-homaline **99** in 44% yield, concluding this synthesis in 10 steps and 5.2% overall yield from commercially available starting materials (Scheme 73). The spectroscopic data obtained for this sample of (–)-(*S*,*S*)-homaline **99** {$[\alpha]_D^{20}$ −32.5 (*c* 1.0 in $CHCl_3$)} were in excellent agreement with those for the sample isolated from the natural source,[1f] and other samples obtained by total synthesis.[4,5,6]



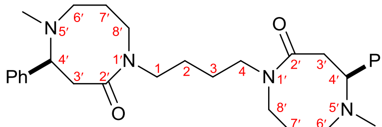
Scheme 73. *Reagents and conditions*: (i) allyl bromide, NaOH, K_2CO_3, TEBAC, THF, 75 °C, 18 h; (ii) Grubbs II (20 mol%), CH_2Cl_2, 40 °C, 40 h; (iii) (*E*)-1,4-dibromobut-2-ene **425**, K_2CO_3, KOH, TEBAC, DMSO, rt, 96 h; (iv) (*Z*)-1,4-dichlorobut-2-ene **388** (95:5 dr), K_2CO_3, KOH, TEBAC, DMSO, rt, 96 h; (v) H_2, $Pd(OH)_2/C$, EtOAc, rt, 2 h.

The above reaction conditions used for the allylation of **439** were not applicable to the alkylation of **439** with 1,4-dibromobutane **360**, which would generate (−)-(*S*,*S*)-homaline **99** in one step. However, reaction between **439** and 0.5 equivalents of 1,4-dibromobutane **360** and KOH in DMSO for 96 h (conditions that had previously failed for the alkylation of **418**), in this case successfully gave (−)-(*S*,*S*)-homaline **99** in 60% yield (Scheme 74). This third asymmetric synthesis of (−)-(*S*,*S*)-homaline **99** was therefore completed in 18% overall yield in eight steps from commercially available starting materials, representing the most efficient synthesis of (−)-(*S*,*S*)-homaline **99** to date. The spectroscopic data for this sample of (−)-(*S*,*S*)-homaline {$[\alpha]_D^{21}$ −28.1 (*c* 1.0 in $CHCl_3$)} were again in good agreement with those for the sample isolated from the natural source,[1f] and other samples obtained by total synthesis (Figure 29).[4,5,6]



439 (−)-(*S*,*S*)-homaline **99**, 60%, >99:1 dr

Scheme 74. *Reagents and conditions*: (i) 1,4-dibromobutane **360**, KOH, DMSO, rt, 96 h.



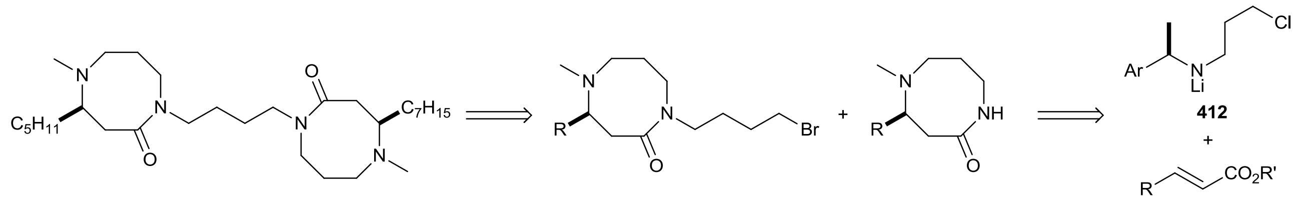
(−)–homaline **99**

Data	Païs	Wasserman	Matsuyama	Crombie	Hesse	Davies
mp	132 °C	132-133 °C	-	134-135 °C	-	115-117 °C
$[\alpha]_D$ (CHCl$_3$)	$[\alpha]_D^{20}$ −34 (*c* 1.0)	$[\alpha]_D^{24}$ −35 (*c* 0.92)	-	$[\alpha]_D^{22}$ −32 (*c* 0.95)	-	$[\alpha]_D^{24}$ −28.1 (*c* 1.0)
ν_{max} (C=O)	1620 cm^{-1}	1622 cm^{-1}	-	1625 cm^{-1}	1620 cm^{-1}	1630 cm^{-1}
^{1}H NMR	60 MHz, CDCl$_3$	270 MHz, CDCl$_3$	CDCl$_3$	CDCl$_3$	CDCl$_3$	400 MHz, CDCl$_3$
C(2)H_2	1.6-1.9 (8H, m)	1.54-1.92 (8H, m)	1.61-1.85 (8H, m)	1.50-1.90 (8H, m)	1.52-1.73 (6H, m)	1.57-1.67 (6H, m)
C(3)H_2						
2 × C(7')H_A					↓	↓
2 × C(7')H_B	↓	↓	↓	↓	1.74-1.90 (2H, m)	1.76-1.87 (2H, m)
2 × N*Me*	2.25 (6H, s)	2.26 (6H, s)	2.34 (6H, s)	2.26 (6H, s)	2.26 (6H, s)	2.26 (6H, s)
2 × C(3')H_A	2.30-4.15 (18H, m)	2.46-2.56 (4H, m)	2.56-2.62 (4H, m)	2.45-3.90 (16H, m)	2.45-2.60 (4H, m)	2.47-2.55 (4H, m)
2 × C(6')H_A		↓	↓		↓	↓
C(1)H_A		2.93-3.06 (4H, m)	3.03-3.38 (8H, m)		2.93-3.04 (2H, m)	2.93-3.08 (4H, m)
C(4)H_A					↓	
2 × C(6')H_B		↓			3.05-3.25 (4H, m)	↓
2 × C(3')H_B		3.16 (2H, t, *J* 12)			↓	3.16 (2H, t, *J* 12.1)
2 × C(8')H_A		3.33 (2H, dt, *J* 15, 3.5)	↓		3.32 (2H, m)	3.32 (2H, dt, *J* 15.4, 3.5)
C(1)H_B		3.80-3.90 (4H, m)	3.74-4.04 (4H, m)		3.70-3.93 (4H, m)	3.77-3.90 (4H, m)
C(4)H_B						
2 × C(8')H_B		↓	↓	↓	↓	↓
2 × C(4')*H*	↓	4.00 (2H, dd, *J* 12, 3.3)	4.09 (2H, dd *J* 11.8, 2.8)	4.00 (2H, dd, *J* 11.6, 3.2)	4.00 (2H, dd, *J* 11.6, 3.1)	4.00 (2H, dd, *J* 11.6, 3.0)
Ph	7.21 (10H, s)	7.20 (10H, m)	7.27-7.36 (10H, m)	7.30 (10H, s)	7.21-7.35 (10H, m)	7.23-7.34 (10H, m)
^{13}C NMR	-	-	100 MHz, CDCl$_3$	62.5 MHz, CDCl$_3$	CDCl$_3$	100 MHz, CDCl$_3$
C(2), *C*(3)	-	-	25.3	25.4	25.4	25.4
2 × *C*(7')	-	-	29.6	29.9	29.9	29.9
2 × *C*(3')	-	-	41.1	41.3	41.2	41.2
2 × N*Me*	-	-	43.8	43.6	43.6	43.7
C(1), *C*(4)	-	-	45.7	45.8	45.7	45.7
2 × *C*(8')	-	-	47.8	47.9	47.9	47.9
2 × *C*(6')	-	-	51.4	51.1	50.9	51.0
2 × *C*(4')	-	-	68.4	68.1	67.9	68.1
o,m,p-Ph	-	-	127.3, 127.6, 128.4	127.1, 127.5, 128.3	127.0, 127.4, 128.2	127.1, 127.5, 128.3
i-Ph	-	-	141.6	142.2	142.0	142.0
2 × *C*(2')	-	-	173.3	173.4	173.3	173.5

Figure 29. Comparison of the spectroscopic data for homaline **99**.

3.5 Asymmetric synthesis of (−)-(*R*,*R*)-hopromine

With the total asymmetric synthesis of (−)-(*S*,*S*)-homaline **99** complete, attention next turned to the synthesis of the unsymmetrical analogue (−)-(*R*,*R*)-hopromine **100**. A similar approach to that adopted for the synthesis of (−)-(*S*,*S*)-homaline **99** was envisioned to be applicable, with a stepwise alkylation strategy being used to couple the differentially substituted ζ-lactam scaffolds. Thus, the initial targets for synthesis were ζ-lactams **382** and **383**, which could be synthesised from α,β-unsaturated ester **453** via conjugate addition of a *N*-3-chloropropyl substituted lithium amide reagent **412** (Figure 30).



(−)-(*R*,*R*)-hopromine **100**

451, R = C_5H_{11}
452, R = C_7H_{15}

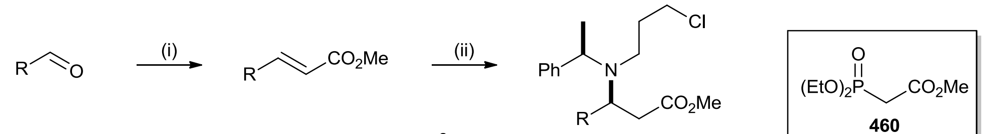
382, R = C_5H_{11}
383, R = C_7H_{15}

412

453

Figure 30. Key steps in the retrosynthesis of (−)-(*R*,*R*)-hopromine **100**.

Initially, the conjugate addition of lithium amide (*R*)-**335** to methyl esters **456** and **457** was investigated. MeMgBr mediated Wadsworth-Emmons[24] reaction between either of the requisite aldehydes hexanal **454** and octanal **455**, and methyl diethylphosphonoacetate **460** gave the corresponding α,β-unsaturated esters **456** and **457** in >99:1 dr and 62 and 54% isolated yield, respectively. Conjugate addition of (*R*)-**335** to **456** and **457** proceeded in >99:1 dr, although in both cases the crude reaction mixtures were contaminated with several other species that could not be separated from the desired β-amino esters (Scheme 75). It was hypothesised that a likely side reaction was the 1,2-addition of the lithium amide (*R*)-**335** to the methyl ester,[25] as has been previously observed,[10] and as such the corresponding, sterically more hindered, *tert*-butyl esters **461** and **462** were investigated.



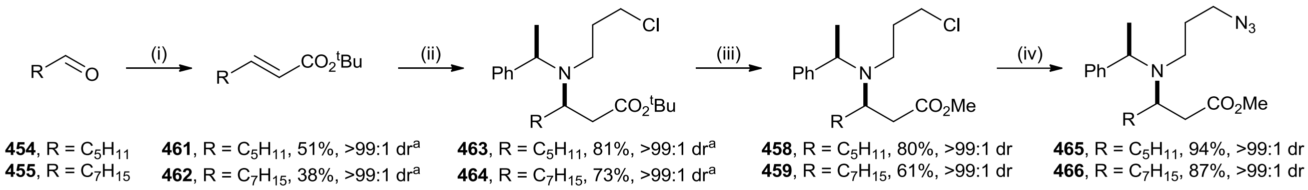
454, R = C_5H_{11}
455, R = C_7H_{15}

456, R = C_5H_{11}, 62%, >99:1 dr[a]
457, R = C_7H_{15}, 54%, >99:1 dr[a]

458, R = C_5H_{11}, >99:1 dr
459, R = C_7H_{15}, >99:1 dr

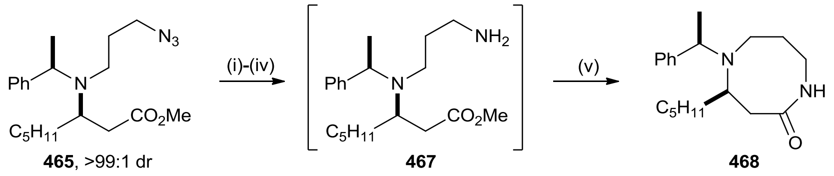
Scheme 75. *Reagents and conditions*: (i) MeMgBr, **460**, THF, rt, 15 min, then RCHO, reflux, 2.5 h; (ii) (*R*)-**335**, **456** or **457**, −78 °C, 2 h. [[a] crude and isolated].

MeMgBr mediated Wadsworth-Emmons reaction[24] between either hexanal **454** or octanal **455**, and *tert*-butyl diethylphosphonoacetate **182** gave the corresponding α,β-unsaturated esters **461** and **462** in >99:1 dr and 51 and 38% isolated yield, respectively. Conjugate addition of lithium amide (*R*)-**335** to α,β-unsaturated esters **461** and **462** gave β-amino esters **463** and **464** in 81 and 73% yield, respectively, and >99:1 dr in both cases. The sense of diastereoselectivity was initially assigned by reference to the lithium amide conjugate addition transition state mnemonic;[12] this assignment was later confirmed by chemical correlation, and single crystal X-ray diffraction analysis in the case of **463**. Transesterification of **463** and **464** to the corresponding methyl esters **458** and **459** was affected with methanolic HCl in 80 and 61% yield, respectively. Displacement of the chloride functionalities within **458** and **459** with NaN_3 gave the corresponding azides **465** and **466** in 94 and 87% yield (Scheme 76).



Scheme 76. *Reagents and conditions*: (i) MeMgBr, **182**, THF, rt, 15 min, then RCHO, reflux, 2.5 h; (ii) (*R*)-**335**, **461** or **462**, −78 °C, 2 h; (iii) $SOCl_2$, MeOH, reflux, 4 h; (iv) NaN_3, NaI, DMSO, 50 °C, 24 h. [^a crude and isolated].

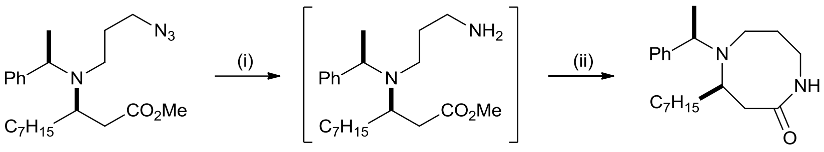
Staudinger reduction of azides **465** and **466** with PPh_3 gave complete conversion to diamines **467** and **469**, however, the resultant Ph_3PO could not be removed from the crude reaction mixture using the acid/base wash that had previously been successful for the C(3)-phenyl diamines **422**, **435** and **446**. The ensuing $Sb(OEt)_3$ mediated macrolactamisations on the crude reaction mixtures was unhindered by the presence of Ph_3PO, with full conversion to ζ-lactams **468** and **470** being observed, however, it was, not possible to separate **468** or **470** from the Ph_3PO by chromatography. A selection of phosphines was therefore examined for their effectiveness in the Staudinger reduction, the compatibility of the corresponding phosphine oxides with the macrolactamisation reaction, and the ease of separation of these phosphine oxides from the ζ-lactam products **468** and **470**. Using C(3)-pentyl substituted azide **465** as a representative system, reduction with PCy_3 yielded a complex mixture of products, whilst $P(OMe)_3$ returned starting material. Use of polymer supported PPh_3 resulted in incomplete conversion of **465** to diamine **467**, even after extended reaction times with 2.2 equivalents of reductant. In contrast, reaction with PBu_3 proved efficacious, with complete conversion to diamine **467** followed by $Sb(OEt)_3$ mediated macrolactamisation yielding ζ-lactam **468** in 98% yield over two steps, with **468** and Bu_3PO being separable by chromatography (Scheme 77).



Conditions	Result
(i)	Complex mixture
(ii)	Returned starting material
(iii)	91% conversion to **467**
(iv)	**468** isolated in 98% yield, >99:1 dr

Scheme 77. *Reagents and conditions*: (i) PCy_3, THF, rt, 1 h, then H_2O, 50 °C, 2 h; (ii) $P(OMe)_3$, THF, rt, 1 h, then H_2O, 50 °C, 2 h; (iii) polymer supported PPh_3 (2.2 eq), THF, 50 °C, 18 h, then H_2O, 50 °C, 24 h; (iv) PBu_3, THF, rt, 1 h, then H_2O, 50 °C, 2 h (v) $Sb(OEt)_3$, PhMe, reflux, 18 h.

A similar procedure, when applied to C(3)-heptyl substituted azide **466**, gave ζ-lactam **470** in 52% yield over two steps (Scheme 78). The overall yields of ζ-lactams **468** and **470** could be significantly improved if the intermediates **458**, **459**, **461-467** and **469** were used without purification, allowing access to **468** and **470** in 72 and 40% yield over six steps from the corresponding aldehydes **454** and **455**.



466, >99:1 dr **469**, >99:1dr **470**, 52%, >99:1 dr

Scheme 78. *Reagents and conditions*: (i) PBu_3, THF, rt, 1 h, then H_2O, 50 °C, 2 h; (ii) $Sb(OEt)_3$, PhMe, reflux, 18 h.

The relative configuration within **468** was unambiguously established via single crystal X-ray diffraction analysis of the corresponding hydrochloride salt **468**·HCl, with the absolute (*R*,*R*)-configuration within **468** being assigned from the known configuration of the (*R*)-α-methylbenzyl fragment, and is in accord with the lithium amide conjugate addition transition state mnemonic[12] (Figure 31). Additionally, the determination of a Flack *x* parameter[18,19] of 0.03(4) for the crystal structure of **468**·HCl allowed the absolute (*R*,*R*)-configuration within **468** to be confirmed. This analysis also allowed the (*R*,*R*)-configurations within intermediates **458**, **463**, **465** and **467** to be confirmed, and the absolute (*R*,*R*)-configurations within **470**, and therefore **459**, **464**, **466** and **469** were therefore assigned by analogy.

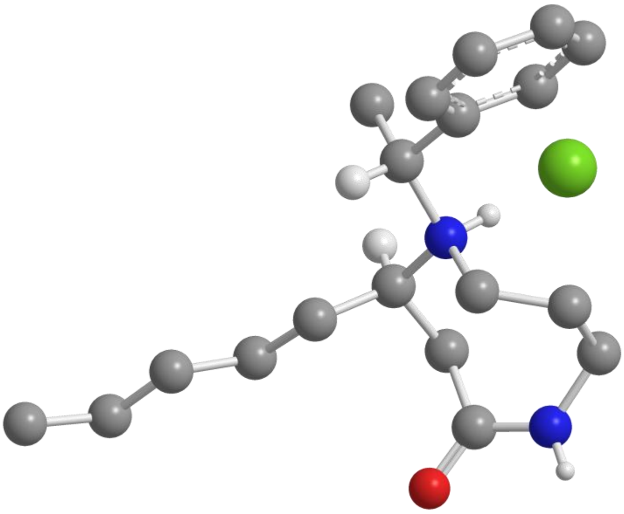
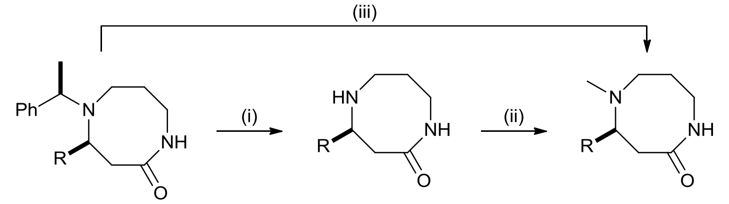


Figure 31. X-ray crystal structure of **468**·HCl (selected H atoms are omitted for clarity).

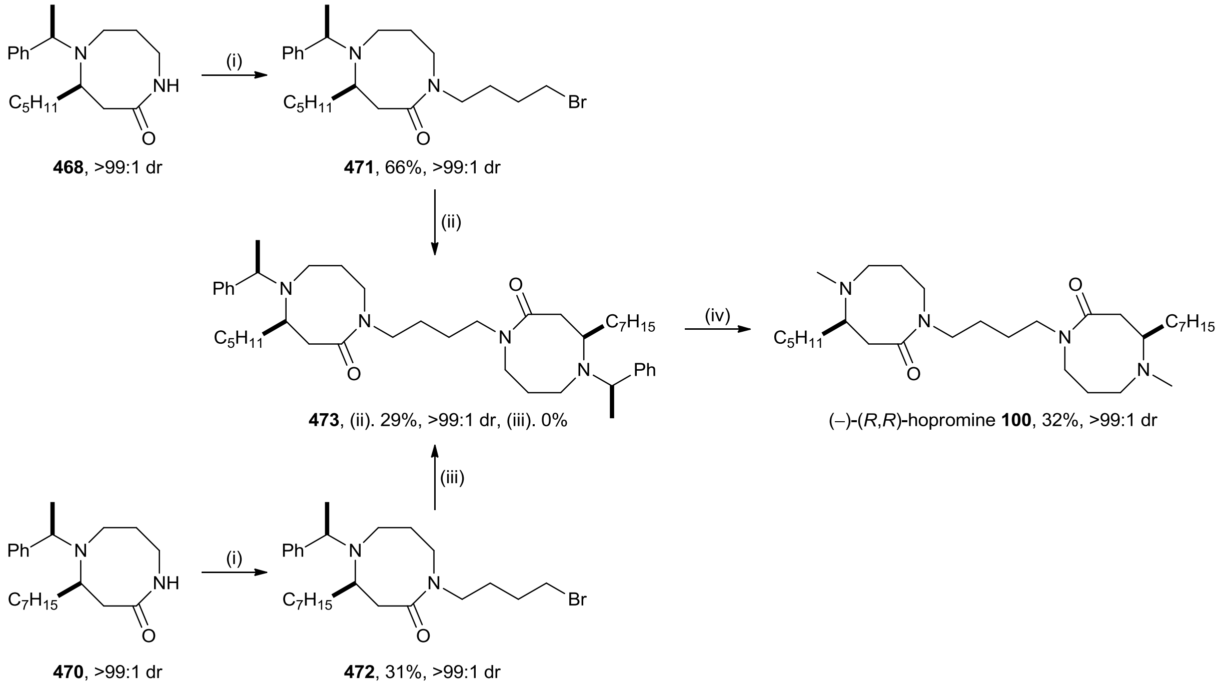
Two strategies were investigated for the *N*-α-methylbenzyl deprotection of **468** and **470** and subsequent *N*-methylation: a two step procedure involving hydrogenolysis of the *N*-α-methylbenzyl group followed by reductive methylation, or a one step procedure with hydrogenolysis and *in situ* reductive methylation. In contrast to the C(4)-phenyl substituted ζ-lactam **418**, the C(4)-alkyl substituted ζ-lactams **468** and **470** proved susceptible to hydrogenolysis, giving **380** and **381** in 95% and quantitative yield, respectively. Reductive methylation of **380** and **381** with $NaBH_3CN$ and $(CH_2O)_n$ gave the desired *N*-methyl ζ-lactams **382** and **383** in 36 and 83% yield, however, hydrogenolysis of **468** and **470** in the presence of $(CH_2O)_n$ gave **382** and **383** directly in quantitative and 98% yield, respectively (Scheme 79).



468, R = C_5H_{11}, >99:1 dr
470, R = C_7H_{15}, >99:1 dr
380, R = C_5H_{11}, 95%
381, R = C_7H_{15}, quant
382, R = C_5H_{11}, (ii). 36%, (iii). quant
383, R = C_7H_{15}, (ii). 83%, (iii). 98%

Scheme 79. *Reagents and conditions*: (i) H_2 (1 atm), $Pd(OH)_2/C$, MeOH, rt, 18 h; (ii) $NaBH_3CN$, $(CH_2O)_n$, MeOH, rt, 18 h; (iii) H_2 (1 atm), $Pd(OH_2)/C$, $(CH_2O)_n$, MeOH, rt, 72 h.

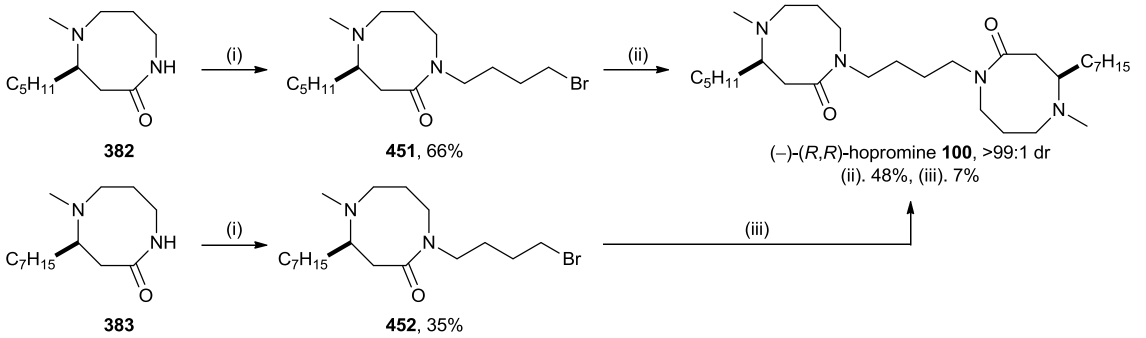
With the compatibility of the *N*(5)-α-methylbenzyl groups to undergo hydrogenolysis in the C(4)-alkyl substituted ζ-lactams **468** and **470** established, initial efforts towards completing the synthesis of (−)-(*R*,*R*)-hopromine **100** focused on the coupling of *N*-α-methylbenzyl ζ-lactams **468** and **470**. Alkylation of C(4)-heptyl substituted ζ-lactam **470** with 3.0 equivalents of 1,4-dibromobutane **360** gave **472** in 31% yield, however repeated attempts at the treatment of bromide **472** with C(4)-pentyl substituted ζ-lactam **468** failed to yield **473**. In contrast, monoalkylation of C(4)-pentyl substituted ζ-lactam **468** with 3.0 equivalents of 1,4-dibromobutane **360** gave **471** in 66% yield, with subsequent alkylation of C(4)-heptyl substituted ζ-lactam **470** with bromide **471** giving **473** in 29% yield. Tandem hydrogenolysis/*N*-methylation of **473** gave (−)-(*R*,*R*)-hopromine **100** in 32% yield and >99:1 dr, completing this synthesis in 4.4% overall yield over nine steps from commercially available starting materials (Scheme 80). The spectroscopic data obtained for this sample of (–)-(*R*,*R*)-hopromine **100** were in excellent agreement with those for the sample isolated from the natural source,[1f] and also the other samples obtained by total synthesis.[2,8]



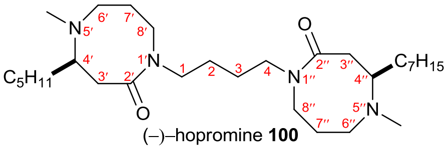
468, >99:1 dr
471, 66%, >99:1 dr
473, (ii). 29%, >99:1 dr, (iii). 0%
(−)-(*R*,*R*)-hopromine **100**, 32%, >99:1 dr
470, >99:1 dr
472, 31%, >99:1 dr

Scheme 80. *Reagents and conditions*: (i) 1,4-dibromobutane **360**, K_2CO_3, KOH, TEBAC, DMSO, rt, 24 h; (ii) **470**, KOH, DMSO, rt, 96 h; (iii) **468**, KOH, DMSO, rt, 96 h; (iv) H_2 (1 atm), $Pd(OH)_2/C$, $(CH_2O)_n$, MeOH, rt, 72 h.

An improved overall yield of (−)-(*R*,*R*)-hopromine **100** was noted when the alkylations were performed on the *N*(5)-methyl substituted ζ-lactams **382** and **383**. Thus, alkylation of C(4)-pentyl substituted ζ-lactam **382** with 3.0 equivalents of 1,4-dibromobutane **360** gave **451** in 66% yield, with subsequent alkylation of C(4)-heptyl substituted ζ-lactam **383** with bromide **451** giving (−)-(*R*,*R*)-hopromine **100** {$[\alpha]_D^{24}$ −13.8 (*c* 1.0 in $CHCl_3$)} in 48% yield and >99:1 dr. This was found to be superior to the alkylation of C(4)-heptyl substituted ζ-lactam **383**, which gave **452** in 35% yield, followed by alkylation of C(4)-pentyl substituted ζ-lactam **382** with bromide **452**, which gave (−)-(*R*,*R*)-hopromine **100** {$[\alpha]_D^{24}$ −11.2 (*c* 0.3 in $CHCl_3$)} in 7% yield and >99:1 dr (Scheme 81). The spectroscopic data obtained for these samples of (–)-(*R*,*R*)-hopromine **100** were in excellent agreement with those for the sample isolated from the natural source,[1f] and also the other samples obtained by total synthesis (Figure 32).[2,8] The former optimised conditions therefore allowed access to (−)-(*R*,*R*)-hopromine **100** in 23% overall yield over nine steps from commercially available starting materials, representing the most efficient synthesis of this natural product reported to date.



Scheme 81. *Reagents and conditions*: (i) 1,4-dibromobutane **360**, K_2CO_3, KOH, TEBAC, DMSO, rt, 24 h; (ii) **383**, KOH, DMSO, rt, 96 h; (iii) **382**, KOH, DMSO, rt, 96 h.

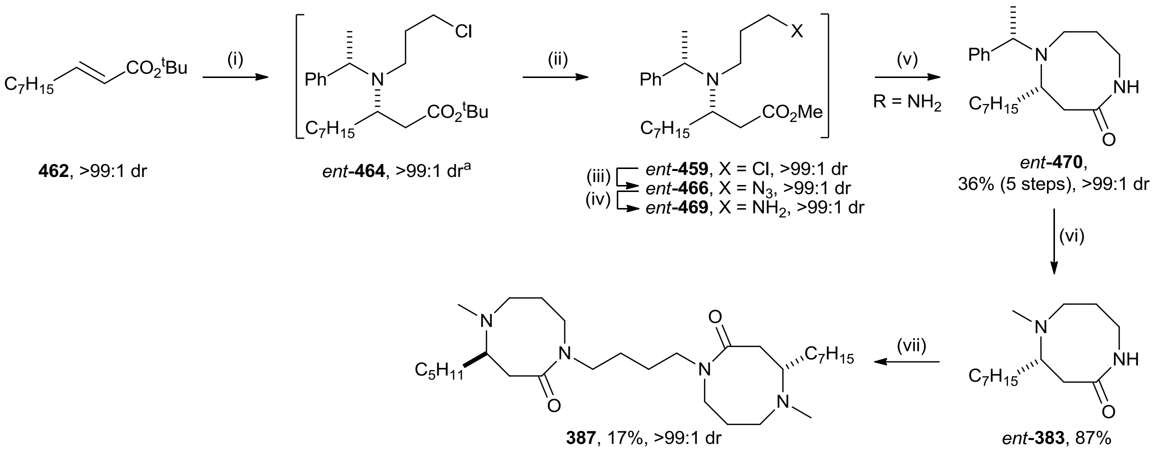


(−)-hopromine **100**

Data	Païs	Crombie	Hesse	Davies	
$[\alpha]_D$ ($CHCl_3$)	$[\alpha]_D^{20}$ −10 (*c* 3.0)	-	$[\alpha]_D^{21}$ −14.4 (*c* 2.1)	$[\alpha]_D^{24}$ −13.8 (*c* 1.0)	
ν_{max} (C=O)	1620 cm^{-1}	1625 cm^{-1}	1620 cm^{-1}	1635 cm^{-1}	
^1H NMR	60 MHz, $CDCl_3$	$CDCl_3$	$CDCl_3$	500 MHz, $CDCl_3$	500 MHz, PhMe-d_8, 363 K
$C(4')(CH_2)_4CH_3$, $C(4'')(CH_2)_6CH_3$	0.9 (6H, m)	0.88 (6H, m)	0.88 (6H, m)	0.85-0.92 (6H, m)	0.91 (6H, app t, *J* 7.3)
$C(2)H_2$	1.10-2.40 (28H, m)	1.10-2.00 (28H, m)	1.20-1.65 (26H, m)	1.21-1.45 (14H, m)	1.16-1.63 (28H, m)
$C(3)H_2$	↓	↓	1.68-1.88 (2H, m)	1.48-1.70 (12H, m)	↓
$C(7')H_2$	↓	↓	↓	1.79 (2H, br s)	↓
$C(7'')H_2$	↓	↓	↓	↓	↓
$C(4')(CH_2)_4CH_3$	↓	↓	↓	↓	↓
$C(4'')(CH_2)_6CH_3$	↓	↓	↓	↓	↓
N*Me*	2.42 (6H, s)	2.41 (6H, s)	2.41 (6H, m)	2.37-2.59 (12H, m)	2.33 (3H, s)
N*Me*	↓	↓	↓	↓	2.34 (3H, s)
$C(3')H_2$	2.45-3.80 (18H, m)	2.45-3.60 (18H, m)	2.44-2.56 (6H, m)	↓	2.27-2.47 (6H, m)
$C(6')H_A$	↓	↓	↓	↓	↓
$C(3'')H_2$	↓	↓	↓	↓	↓
$C(6'')H_A$	↓	↓	↓	↓	↓
$C(6')H_B$	↓	↓	2.82-2.96 (4H, m)	2.83-3.03 (4H, m)	2.66-2.77 (2H, m)
$C(6'')H_B$	↓	↓	↓	↓	↓
$C(4')H$	↓	↓	↓	↓	2.84-2.95 (2H, m)
$C(4'')H$	↓	↓	↓	↓	↓
$C(8')H_2$	↓	↓	3.20 (2H, m)[a]	3.16-3.53 (8H, m)	3.04-3.22 (4H, m)
$C(8'')H_2$	↓	↓	3.30-3.47 (6H, m)	↓	↓
$C(1)H_2$	↓	↓	↓	↓	3.22-3.43 (4H, m)
$C(4)H_2$	↓	↓	↓	↓	↓
^{13}C NMR	-	$CDCl_3$	$CDCl_3$	125 MHz, $CDCl_3$	125 MHz, PhMe-d_8, 363 K
$C(4')(CH_2)_4CH_3$, $C(4'')(CH_2)_6CH_3$	-	14.1, 14.1	13.9, 14.0	14.0, 14.1	14.0, 14.0
$C(2)$, $C(3)$, $C(7')$, $C(7'')$,	-	22.7, 25.3, 26.7, 27.0,	22.5, 25.2, 26.5, 26.9,	22.6, 24.6, 24.7, 25.3,	22.9, 26.0, 27.0, 27.4,
$C(4')(CH_2)_4CH_3$,	-	28.7, 29.3, 29.7,	28.6, 29.2, 29.5,	26.6, 27.0, 28.7, 29.3,	29.1, 29.6, 30.0, 31.5,
$C(4'')(CH_2)_6CH_3$	-	30.8, 31.9, 31.9	30.8, 31.7, 31.8	29.6, 30.9, 31.8, 31.9	31.6, 32.2, 32.3
$C(3')$, $C(3'')$	-	38.5	38.4	38.4	39.9
N(5')*Me*, N(5")*Me*	-	39.8	39.6	39.7	39.0
$C(1)$, $C(4)$	-	45.5	45.4	45.5	45.8
$C(6')$, $C(6'')$	-	47.1	47.1	47.3	47.2
$C(8')$, $C(8'')$	-	47.7	47.5	47.6	47.4
$C(4')$, $C(4'')$	-	63.3	63.2	63.3	63.6
$C(2')$, $C(2'')$	-	173.7	173.5	173.7	172.4

Figure 32. Comparison of the spectroscopic data for hopromine **100**. [[a] arbitrary assignment]

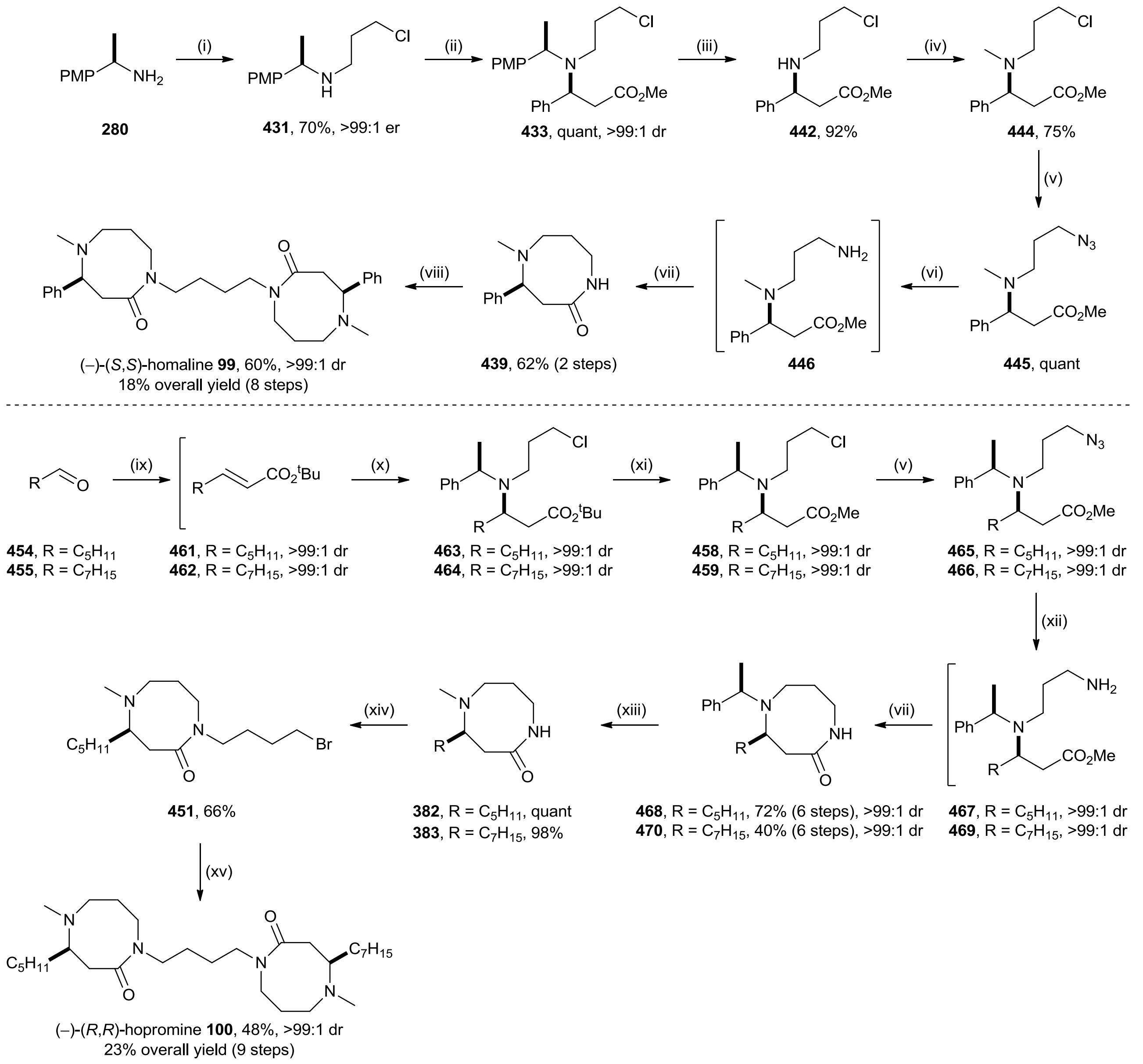
In order to unambiguously confirm Ensch and Hesse's stereochemical assignment of (−)-(*R*,*R*)-hopromine, it was decided to use this strategy to synthesise an authentic sample of the epimeric compound (4′*R*,4″*S*)-**387** so that its specific rotation could be compared with that of the sample of (−)-hopromine **100** isolated from the natural source. C(4)-Heptyl substituted ζ-lactam *ent*-**383** was therefore synthesised in 31% overall yield in six steps from α,β-unsaturated ester **462** and (*S*)-**335**,[26] using identical procedures as for the synthesis of **383**. Alkylation of this ζ-lactam *ent*-**383** with bromide **451** then gave **387** in 17% yield and >99:1 dr (Scheme 82). Comparison of the specific rotation of (4′*R*,4″*S*)-**387** {$[\alpha]_D^{24}$ +2.3 (*c* 0.8 in $CHCl_3$)} with that of natural (−)-hopromine **100** {lit.[1f] $[\alpha]_D^{20}$ −10 (*c* 3.0 in $CHCl_3$)} served to confirm the absolute (*R*,*R*)-configuration within (−)-hopromine **100**.



Scheme 82. *Reagents and conditions*: (i) (*S*)-**335**, −78 °C, 2 h; (ii) $SOCl_2$, MeOH, reflux, 4 h; (iii) NaN_3, NaI, DMSO, 50 °C, 24 h; (iv) PBu_3, THF, rt, 30 min, then H_2O, 50 °C, 2 h; (v) $Sb(OEt)_3$, PhMe, reflux, 18 h; (vi) H_2 (1 atm), $Pd(OH_2)/C$, $(CH_2O)_n$, MeOH, rt, 72 h; (vii) **451**, K_2CO_3, KOH, TEBAC, DMSO, rt, 96 h. [[a] crude and isolated].

3.6 Conclusion

The use of the novel amines (*R*)- and (*S*)-*N*-(3-chloroprop-1-yl)-*N*-(α-methylbenzyl)amine (*R*)-**413** and (*S*)-**413**, and (*R*)-*N*-(3-chloroprop-1-yl)-*N*-(α-methyl-4′-methoxybenzyl)amine (*R*)-**431** in the highly diastereoselective conjugate addition reaction have been used as the key steps in the syntheses of all of the optically active diastereoisomers of homaline **99** and hopromine **100**. The naturally occurring stereoisomers, (−)-(*S*,*S*)-homaline **99** and (−)-(*R*,*R*)-hopromine **100**, were synthesised from commercially available starting materials in 18% overall yield and eight steps, and 23% overall yield and nine steps, respectively. These syntheses therefore represent by far the most efficient strategies to access these alkaloids reported to date (Scheme 83).[27]



Scheme 83. *Reagents and conditions*: (i) 1-bromo-3-chloropropane **359**, MeCN, rt, 16 h; (ii) BuLi, THF, −78 °C, 15 min, then methyl cinnamate **423**, THF, −78 °C, 2 h; (iii) F_3CCO_2H, 65 °C, 2.5 h; (iv) $(CH_2O)_n$, $NaBH_3CN$, MeOH, rt, 16 h; (v) NaN_3, NaI, DMSO, 50 °C, 24 h; (vi) PPh_3, THF, rt, 30 min, then H_2O, 50 °C, 2 h; (vii) $Sb(OEt)_3$, PhMe, reflux, 18 h; (viii) 1,4-dibromobutane **360**, KOH, DMSO, rt, 96 h; (ix) MeMgBr, **182**, THF, rt, 15 min, then RCHO, reflux, 2.5 h; (x) (*R*)-**335**, **461** or **462**, −78 °C, 2 h; (xi) $SOCl_2$, MeOH, reflux, 4 h; (xii) PBu_3, THF, rt, 1 h, then H_2O, 50 °C, 2 h; (xiii) H_2 (1 atm), $Pd(OH_2)/C$, $(CH_2O)_n$, MeOH, rt, 72 h; (xiv) 1,4-dibromobutane **360**, K_2CO_3, KOH, TEBAC, DMSO, rt, 24 h; (xv) **383**, KOH, DMSO, rt, 96 h.

3.7 References and notes

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[11] The er of **413** was determined from the 400 MHz ^{1}H NMR spectrum in the presence of the chiral solvating agent (*S*)-*O*-acetylmandelic acid, and comparison with an authentic racemic sample.

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[15] The er of **431** was determined from the 400 MHz ^{1}H NMR spectrum in the presence of the chiral solvating agent (*S*)-*O*-acetylmandelic acid, and comparison with an authentic racemic sample.

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[17] The er for *ent*-**439** was not determined, however, the er for the precursor to *ent*-**439**, (*R*)-4-phenyl-1,5-diazocan-2-one **352**, was assessed to be 91:9 by chiral HPLC. See reference 7.

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[21] Approximately 37% conversion to (*E*)-**448** was observed under these conditions, and the remaining starting material could not be separated from the product so a pure sample of **448** was not isolated in this case.

[22] Approximately 64% conversion to (*Z*)-**449** was observed under these conditions, and the remaining starting material could not be separated from the product so a pure sample of **449** was not isolated in this case.

[23] For spectroscopic data on (*E*)- and (*Z*)-isomers of related compounds, see reference 20.

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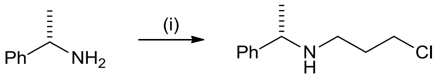
[25] There was evidence of the products arising from 1,2- and concomitant 1,4-addition of **335** to **456** and **457** in the mass spectrum of the crude reaction mixture, however neither were isolated upon purification of **458** or **459**, respectively.

[26] Enantiopure (*S*)-α-methylbenzylamine (*S*)-**153** (99.5:0.5 er) is commercially available. Alkylation of (*S*)-α-methylbenzylamine (*S*)-**153** with 1-bromo-3-chloropropane **359** gave (*S*)-**413** in 55% and >99:1 er. The er of (*S*)-**413** was determined from the 400 MHz ^{1}H NMR spectrum in the presence of the chiral solvating agent (*R*)-*O*-acetylmandelic acid, and comparison with an authentic racemic sample.



(*S*)-**153** (*S*)-**413**, 55%, >99:1 er

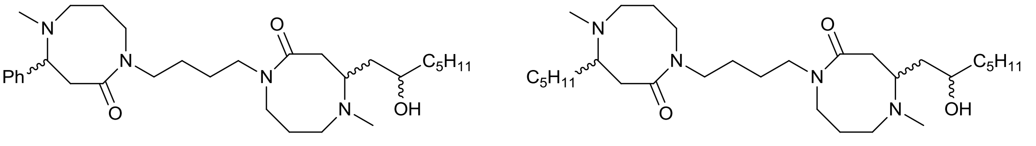
Reagents and conditions: (i) 1-bromo-3-chloropropane **359**, MeCN, rt, 16 h.

[27] (a) Davies, S. G.; Lee, J. A.; Roberts, P. M.; Stonehouse, J. P.; Thomson, J. E. *Tetrahedron Lett.* **2012**, *53*, 1119. (b) Davies, S. G.; Lee, J. A.; Roberts, P. M.; Stonehouse, J. P.; Thomson, J. E. *J. Org. Chem.* **2012**, *77*, 7028.

Chapter 4: Asymmetric synthesis of (−)-(4′*S*,4″*R*,2‴*R*)-hopromalinol and (−)-(*R*,*R*,*R*)-hoprominol

4.1 Introduction

With efficient routes for the asymmetric syntheses of (−)-(*S*,*S*)-homaline **99** and (−)-(*R*,*R*)-hopromine **100** established, it was envisaged that similar methodology could be applied to the syntheses of (−)-hopromalinol **101** and (−)-hoprominol **102** (Figure 33).



hopromalinol **101**

hoprominol **102**

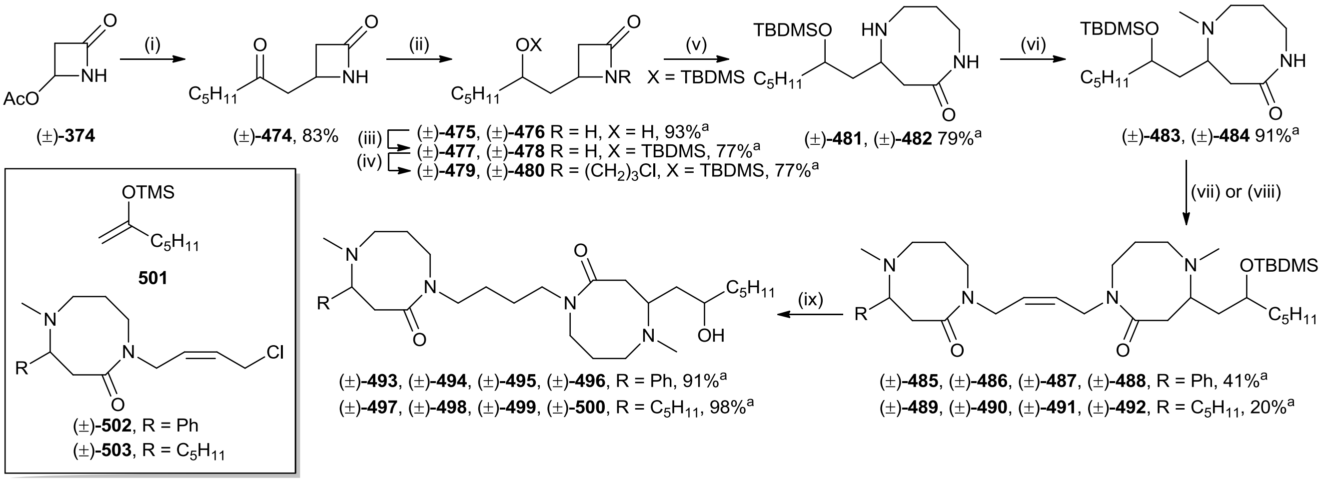
Figure 33. The structures of hopromalinol **101** and hoprominol **102**.

Despite being originally isolated over 40 years ago, no stereoselective or stereospecific total syntheses of either (−)-hopromalinol **101** or (−)-hoprominol **102** have been reported to date, so neither the absolute nor relative configurations of these alkaloids are known. It was therefore desirable to synthesise all four possible diastereoisomers of these alkaloids so that the spectroscopic data for the synthetic samples could be compared with those of the samples isolated from the natural source and hence allow the absolute configuration of these alkaloids to be established.[1]

4.2 Previous syntheses hopromalinol and hoprominol

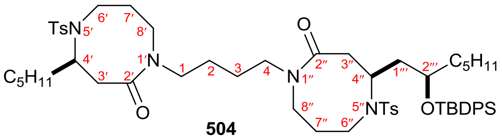
Hopromalinol **101** has been the target of a laboratory synthesis only once before, whilst hoprominol **102** has been the target of two laboratory syntheses. In 1993, Crombie *et al.*[2] reported that application of methodology similar to that developed for their synthesis of hopromine **100** allowed access to hopromalinol **101** and hoprominol **102**, although all starting materials were racemic, yielding the final products as complex mixtures of stereoisomers. The diastereomeric mixture of the desired C(2′)-silyl ether bearing ζ-lactam **483**/**484** was prepared by displacement of the acetate group within **374** with **501** (the kinetic silyl enol ether derived from heptan-2-one, LDA and TMSCl) to give **474** in 83% yield. Reduction of ketone **474** with $NaBH_4$ gave alcohol **475**/**476** in 93% yield, followed by TBDMS protection of the hydroxyl group (via *N*-protection followed by migration to oxygen mediated by BuLi and CuI) to give *O*-silyl ether **477**/**478** in 77% yield. Proceeding as in their previously reported synthesis of (−)-(*R*,*R*)-hopromine **100**,[2] β-lactam **477**/**478** was alkylated with 1-bromo-3-chloropropane **359** to give **479**/**480** in 77% yield. Subsequent transamidation and ring expansion upon treatment with liquid NH_3 gave ζ-lactam **481**/**482** in 79% yield; ensuing Borch methylation then gave ζ-lactam **483**/**484** in 91% yield. Alkylation of **483**/**484** with chloride **502** gave a mixture of (±)-**485**-(±)-**488** in 41% combined yield. Hydrogenation of this mixture, with *in situ* deprotection of the silyl ether, gave a mixture of the diastereoisomers of hopromalinol

(±)-**493**-(±)-**496** in 91% combined yield. Similarly alkylation of **483**/**484** with chloride **503** gave a mixture of (±)-**489**-(±)-**492** in 20% combined yield; hydrogenation then gave a mixture of the diastereoisomers of hoprominol (±)-**497**-(±)-**500** in 98% combined yield. Hopromalinol and hoprominol were therefore synthesised in 4.7 and 2.5% overall yield, both in nine steps and as a mixture of diastereoisomers (Scheme 84). The complex mixture of stereoisomers formed using this synthetic strategy meant that it was not possible to assign either the relative or absolute configurations within (−)-hopromalinol **101** or (−)-hoprominol **102**. Further, it was not possible to confidently confirm the structures of (±)-**493**-(±)-**496** or (±)-**497**-(±)-**500** by ^{1}H NMR spectroscopy;[3] however, comparison of the fragmentation patterns in the mass spectrometric data of (±)-**493**-(±)-**496** and (±)-**497**-(±)-**500** with those reported by Païs *et al.*[1] for the natural products showed good correlation, and these data were relied upon to corroborate the successful syntheses of **101** and **102**.



Scheme 84. *Reagents and conditions*: (i) **501**, $ZnCl_2$, CH_2Cl_2, rt, 20 h; (ii) $NaBH_4$, MeOH, 0 °C, 1 h; (iii) BuLi, TBDMSCl, THF, 0 °C to rt, 6 h, then BuLi, CuI, THF, −20 °C to rt, 16 h; (iv) KOH, Bu_4NHSO_3, 1-bromo-3-chloropropane **359**, THF, rt, 3.5 days; (v) liquid NH_3, rt, 13 days; (vi) formalin, $NaBH_3CN$, MeCN, AcOH, rt, 1 h; (vii) KHMDS, **502**, THF, rt, 20 h, then NaH, 9 days; (viii) KHMDS, **503**, THF, rt, 24 h, then NaH, 17 days; (ix) H_2 (1 atm), PtO_2, MeOH, conc. HCl, rt, 3 h. [[a] combined yield].

In 2003, the homochirality between (−)-(*S*,*S*)-homaline **99** and (−)-(*R*,*R*)-hopromine **100**, led Ensch and Hesse[4] to hypothesise that "*all members of the homalium family share the same three-dimensional orientation of the residues at their corresponding stereogenic centers of the lactam rings*". This was the basis for their synthesis of the protected (*R*,*R*,*R*)-hoprominol derivative **504**, although no attempt was reported to deprotect **504** and correlate it with the natural product, and it was not rationalised why the (2‴*R*)-configuration was targeted in this synthesis (Figure 34).



504

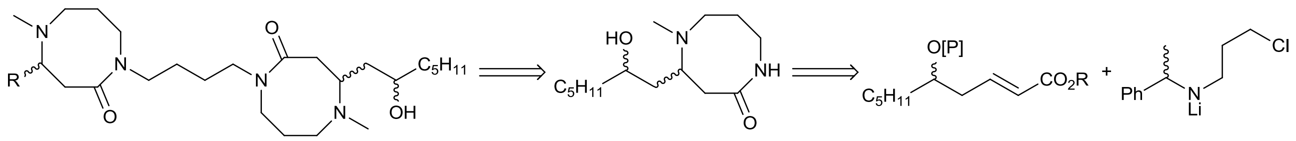
Figure 34. The (*R*,*R*,*R*)-hoprominol derivative **504** prepared by Ensch and Hesse.

4.3 Chapter aim

With the limitations of the previously reported synthetic endeavours towards hopromalinol **101** and hoprominol **102** in mind, it was envisaged that the methodology developed for the asymmetric synthesis of (*R*,*R*)-(−)-hopromine **100**, utilising the conjugate addition of lithium amide **335** to an α,β-unsaturated ester (*vide supra*), would allow the asymmetric syntheses of the four possible diastereoisomers of both hopromalinol **493-496** and hoprominol **497-500** to be completed. Comparison of both the signs and magnitudes of the specific rotations[5] of these synthetic samples with those reported for the natural products[1] would then potentially allow the absolute configurations within (−)-hopromalinol **101** and (−)-hoprominol **102** to be determined.

4.4 Syntheses of hoprominol and hopromalinol

Retrosynthetic analyses of hopromalinol **101** and hoprominol **102** (similar to those for (−)-(*S*,*S*)-homaline **99** and (−)-(*R*,*R*)-hopromine **100**) revealed the need for ζ-lactam **505**, itself originating from the conjugate addition of lithium amide **335** to protected α,β-unsaturated ester **506** (Figure 35).



hopromalinol **101**, R = Ph
hoprominol **102**, R = C_5H_{11}

505

506

335

Figure 35. Retrosynthetic analysis of hopromalinol **101** and hoprominol **102**.

Although it was desired to synthesise all possible diastereoisomers of hopromalinol **493-496** and hoprominol **497-500** for the unambiguous assignment of stereochemistry, the initial targets for synthesis were the two C(2′)-epimeric ζ-lactams **507** and **508**, in which the C(4)-stereogenic centre has the absolute (*R*)-configuration, in agreement with Ensch and Hesse's[4] hypothesis regarding the homochirality between the homalium alkaloids. Once an efficient route to (4*R*)-configured ζ-lactams **507** and **508** had been developed, the corresponding enantiomers *ent*-**507** and *ent*-**508** could be synthesised by performing the reaction sequence in the antipodal series. Stepwise coupling of all four ζ-lactams **507**, **508**, *ent*-**507** and *ent*-**508** with ζ-lactams **382**, **418**, **439** and **468** [previously prepared during the syntheses of (*S*,*S*)-(−)-homaline **99** and (*R*,*R*)-(−)-hopromine **100**] would then allow access to all diastereoisomers of hopromalinol **493-496** and hoprominol **497-500** (Figure 36).

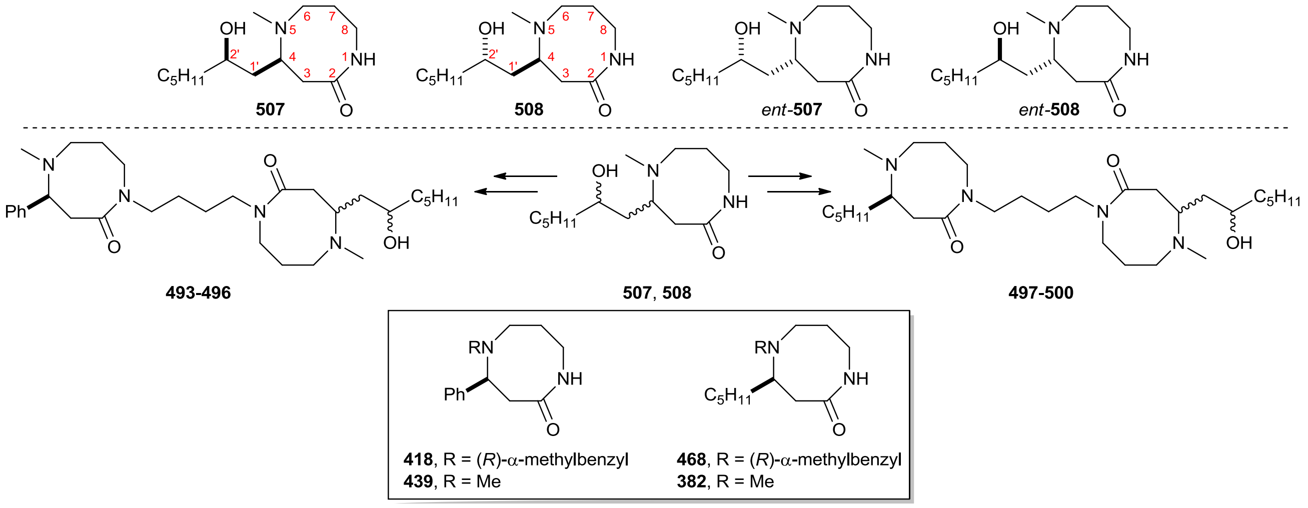
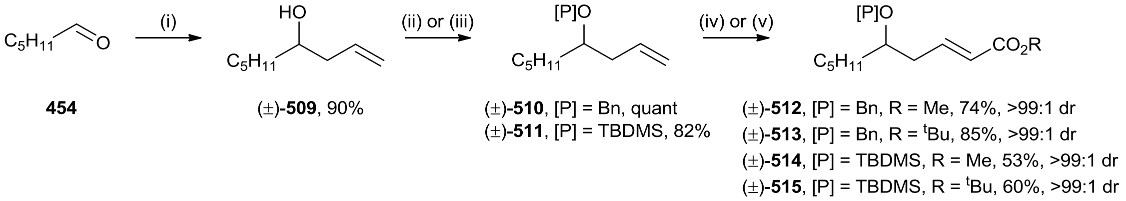


Figure 36. The initial ζ-lactam targets for synthesis **507**, **508** (and *ent*-**507** and *ent*-**508**), and the strategy for the synthesis of all the diastereoisomers of hopromalinol **493-496** and hoprominol **497-500**.

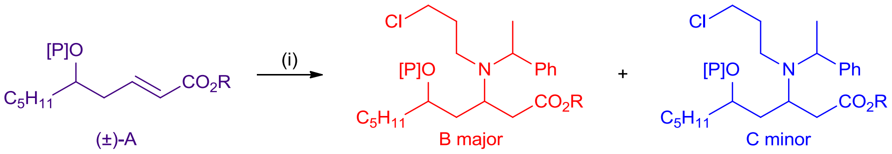
4.4.1 Protecting group strategy

It was envisaged that the conjugate addition of (*R*)- or (*S*)-**335** to a suitably protected racemic α,β-unsaturated ester, followed by separation of the resultant diastereoisomers, would allow rapid access to the enantio- and diastereomerically pure β-amino esters required for the syntheses of ζ-lactams **507**, **508**, *ent*-**507** and *ent*-**508**. A range of protected α,β-unsaturated esters **512-515** was therefore produced so that methods for the separation of the diastereomeric conjugate addition products could be investigated. Addition of allylmagnesium chloride to hexanal **454** gave allylic alcohol **509** in 90% yield. Protection of the resulting hydroxyl group as either the benzyl or TBDMS ether gave **510** and **511** in quantitative and 82% yield, respectively. Metathesis of **510** or **511** with either methyl acrylate or *tert*-butyl acrylate and Grubbs II catalyst afforded **512-515** in 53 to 85% yield, and >99:1 dr in each case (Scheme 85).



Scheme 85. *Reagents and conditions*: (i) allymagnesium chloride, THF, 0 °C, 1 h; (ii) NaH, THF, rt, 1 h then BnBr, THF, rt, 16 h; (iii) TBDMSCl, DMF, imidazole, rt, 18 h; (iv) methyl acrylate, Grubbs II, CH_2Cl_2, 40 °C, 16 h; (v) *tert*-butyl acrylate, Grubbs II, CH_2Cl_2, 40 °C, 16 h.

Conjugate addition of (±)-**335**[6] to α,β-unsaturated esters **512-515** was investigated in the first instance: conjugate addition of (±)-**335** to methyl esters **512** and **514** led to incomplete consumption of **512** and **514**, giving chromatographically inseparable mixtures of diastereoisomeric β-amino esters **516**, **517**, **520** and **521**, and starting α,β-unsaturated esters **512** and **514**, among other unidentified alkene containing products. In comparison, reaction of (±)-**335** with *tert*-butyl esters **513** and **515** gave complete conversion to the desired β-amino esters **518**, **519**, **522** and **523**, with no evidence of deleterious side products. The diastereoisomeric conjugate addition products **518** and **519** proved separable by chromatography in this one case (Scheme 86). At this stage, the relative configuration was not established and the pairs of diastereoisomeric β-amino esters **516**-**523** observed in these reactions were tentatively assigned as being a mixture of C(5)-epimers (*vide infra*).



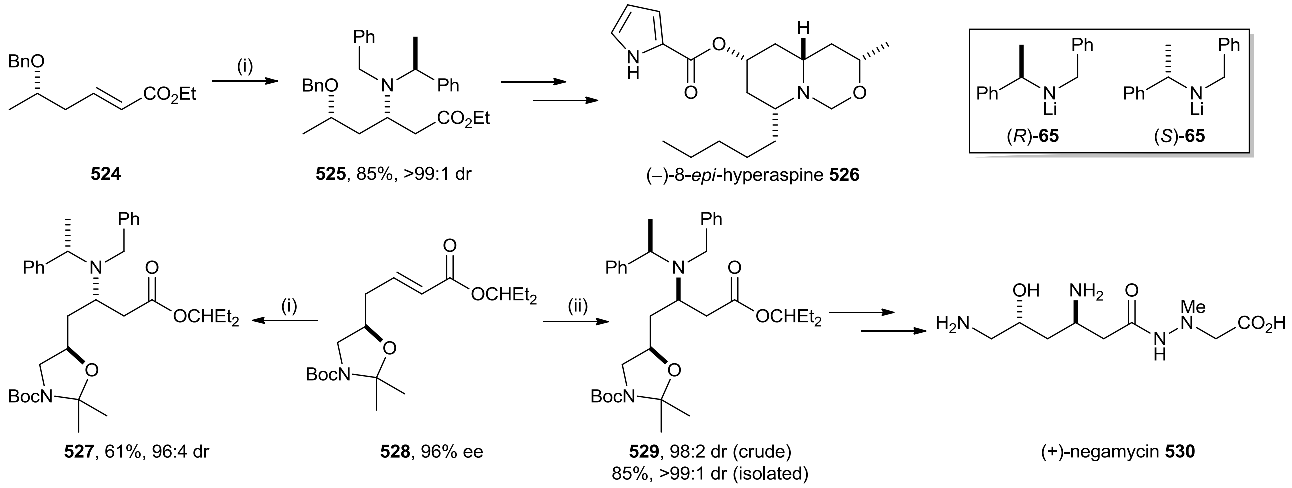
A	[P]	R	B	C	Crude ratio A:B:C	Yield B	Yield C	Yield (B:C)	Total yield
512	Bn	Me	**516**	**517**	37:34:29	-	-	-	-
513	Bn	^{t}Bu	**518**	**519**	0:52:48	24	11	43 (34:66)	78
514	TBDMS	Me	**520**	**521**	9:57:34	-	-	52 (45:55)	52
515	TBDMS	^{t}Bu	**522**	**523**	0:59:41	-	-	66 (61:39)	66

Scheme 86. *Reagents and conditions*: (i) **512**, **513**, **514** or **515**, (±)-**335**, −78 °C, 2 h.

The ability to separate the diastereoisomeric β-amino esters **518** and **519** shows that the use of the C(5)-benzyloxy α,β-unsaturated *tert*-butyl ester **513** is most suitable for the planned synthetic strategy, and further studies therefore focused on its use.

4.4.2 Directing ability of a C(5)-oxo stereogenic centre in the lithium amide conjugate addition reaction

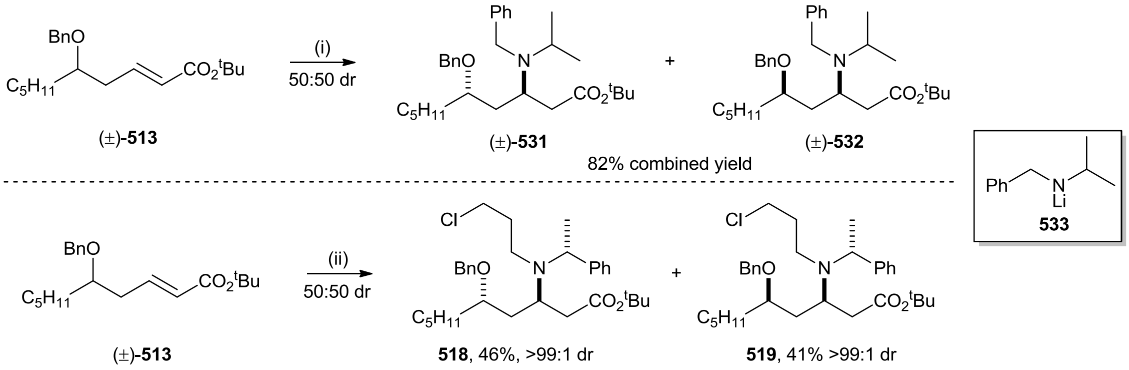
The high levels of diastereoselectivity observed upon the conjugate addition of secondary lithium amides derived from α-methylbenzylamine to α,β-unsaturated esters leads to the possibility of double asymmetric induction being observed upon addition to a chiral α,β-unsaturated ester. This double asymmetric induction has been studied with a range of chiral α,β-unsaturated esters, and varying levels of "matching" and "mismatching" effects have been observed.[7] There are two previously reported examples of the conjugate addition of a lithium amide derived from α-methylbenzyl amine to an α,β-unsaturated ester with an isolated C(5)-oxy stereogenic centre. Firstly, Ma and Zhu reported the conjugate addition of (*S*)-**65** to enantiopure α,β-unsaturated ester (*S*)-**524** (which occurred in 85% yield and >99:1 dr) in their synthesis of (−)-8-*epi*-hyperaspine **526**.[8] Secondly, Davies and Ichihara reported that the conjugate addition of (*R*)-**65** to α,β-unsaturated ester **528** [a key step in their synthesis of (+)-negamycin **530**] proceeded in 98:2 dr, corresponding to the "matched" reaction pairing. Similar reaction of **528** with (*S*)-**65** proceeded in 61% yield and 96:4 dr, corresponding to the "mismatched" reaction pairing. In this case, however, the very high reagent control exhibited by lithium amide **65** dictated the stereochemical outcome and overwhelmed the inherent substrate control exhibited by α,β-unsaturated ester **528** (Scheme 87).



Scheme 87. *Reagents and conditions*: (i) (*S*)-**65**, THF, −78 °C, 2 h; (ii) (*R*)-**65**, THF, −78 °C, 2 h.

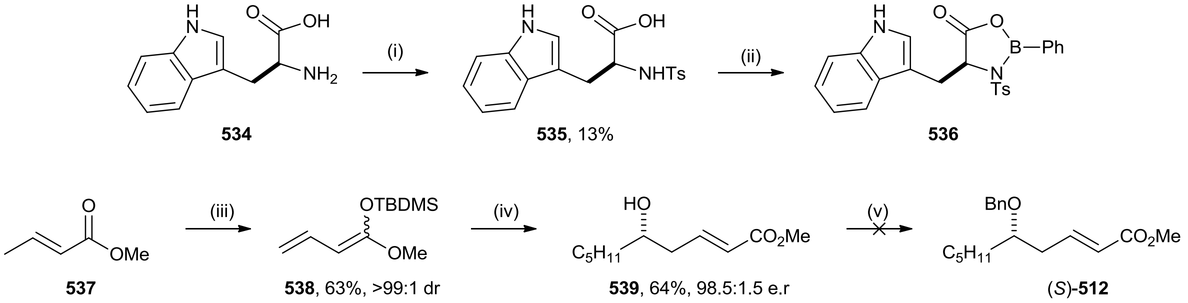
4.4.3 Stereochemical assignment of β-amino esters 518 and 519

In order to assess the level of substrate control in the conjugate addition reactions of α,β-unsaturated ester **513**, the addition of achiral lithium *N*-isopropyl-*N*-benzylamide **533** to α,β-unsaturated ester (±)-**513** was investigated. This gave a 50:50 mixture of the corresponding diastereoisomeric products **531** and **532** which could not be separated by chromatography and were therefore isolated in 82% combined yield, and 50:50 dr. These results demonstrate that the stereo-directing ability of the C(5)-oxy stereogenic centre is extremely low, and is consistent with the previous observations of Davies and co workers.[9,10,11] Finally, conjugate addition of enantiopure (*R*)-**335** to (±)-**513** led to a 50:50 mixture of chromatographically separable diastereoisomers **518** and **519** in 46 and 41% yield, respectively (Scheme 88).



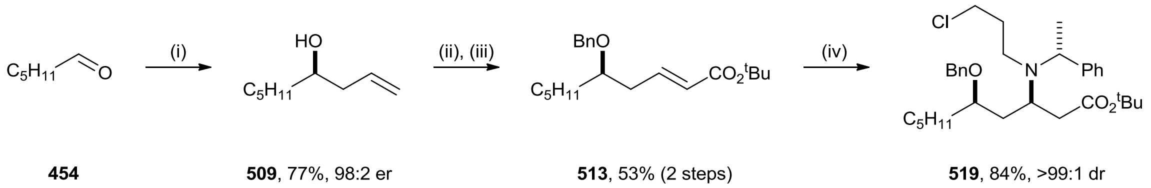
Scheme 88. *Reagents and conditions*: (i) **533**, THF, −78 °C, 2 h; (ii) (*R*)-**335**, THF, −78 °C, 2 h.

With the poor substrate control elicited by α,β-unsaturated ester **513** established, the two diastereoisomeric products produced in the reaction of (*R*)-**335** to (±)-**513** were confidently assigned as the two C(5)-epimers **518** and **519**. The absolute configurations within **518** and **519** were assigned by chemical correlation via the conjugate addition of lithium amide (*R*)-**335** to an enantiopure sample of α,β-unsaturated ester **513** or similar. Initially, the asymmetric vinylogous Mukaiyama Aldol reaction developed by Kalesse *et al.*[12] was chosen as a potential route to (*S*)-**512**. The desired pre-catalyst, **535**, was made by treatment of L-tryptophan **534** with TsCl, albeit in poor yield due to difficulties in its purification via chromatography. The active catalyst **536** was then made by reaction of **535** with PhBCl$_2$, which when combined with hexanal **454** and ketene acetal **538** (produced in 63% yield from methyl crotonate **537**) gave (*S*)-**539** in 64% yield and 98.5:1.5 er.[13] The absolute configuration within **539** was assigned by reference to the proposed transition state for this reaction manifold.[12] Attempted protection of the C(5)-hydroxyl group upon treatment with NaH and BnBr gave a complex mixture of products, presumably arising from polymerisation of **539** (Scheme 89). Due to the problems encountered with the purification of **535** and the inability to protect the C(5)-hydroxyl group within **539**,[14] an alternative route was sought.



Scheme 89. *Reagents and conditions*: (i) TsCl, NEt$_3$, THF/H$_2$O (v/v 19:1), 0 °C to rt, 2 h; (ii) PhBCl$_2$, CH$_2$Cl$_2$, rt, 1 h; (iii) LDA, DMPU, THF, −78 °C, 15 min, then TBDMSCl, THF, −78 °C to rt, 3 h; (iv) hexanal **454**, **536**, butyronitrile, −78 °C, 3 h; (v) NaH, THF, rt, 1 h then BnBr, THF, rt, 16 h.

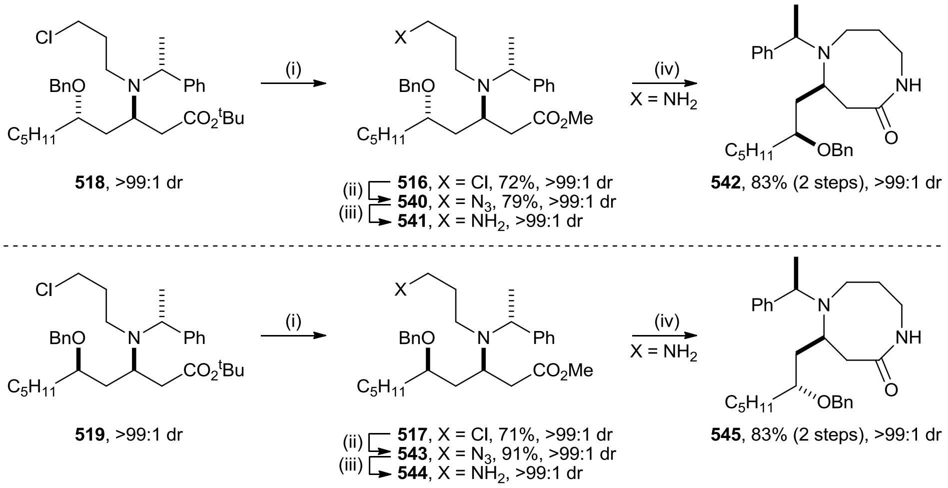
Brown allylation[15] of hexanal **454** with (−)-Ipc$_2$BCH$_2$CH=CH$_2$ gave alcohol (*R*)-**509** in 77% yield and 98:2 er.[16] The absolute configuration within (*R*)-**509** was assigned by comparison of the specific rotation of this sample with that of a sample of known configuration reported in the literature {$[\alpha]_D^{20}$ +9.0 (*c* 1.0 in CHCl$_3$); lit.[17] $[\alpha]_D^{25}$ +8.9 (*c* 1.1 in CHCl$_3$)}. This stereochemical outcome is in agreement with previously reported examples of this reaction,[15,18] and the transition state mnemonic developed to rationalise the enantioselectivity observed in this reaction manifold.[19] Subsequent *O*-benzyl protection of (*R*)-**509** followed by cross metathesis of (*R*)-**510** with *tert*-butyl acrylate and Grubbs II catalyst afforded α,β-unsaturated ester (*R*)-**513** in 53% yield over two steps. Conjugate addition of (*R*)-**335** to α,β-unsaturated ester (*R*)-**513** then gave **519** as the sole product in 84% yield and >99:1 dr. Given the very high reagent control and predictable sense of diastereoselectivity observed upon conjugate addition of secondary lithium amides derived from α-methylbenzylamine to α,β-unsaturated esters,[7] and the extremely low substrate control observed upon conjugate addition of lithium *N*-isopropyl-*N*-benzylamide **533** to (±)-**513**, the (*R*)-configuration of the newly formed C(3)-stereogenic centre within **519** was confidently assigned by reference to the well established transition state mnemonic[20] (Scheme 90).



Scheme 90. *Reagents and conditions*: (i) (−)-Ipc$_2$BCl, allylmagnesium bromide, Et$_2$O, −78 °C to rt, 1 h; (ii) NaH, THF, rt, 1 h then BnBr, THF, rt, 16 h; (iii) *tert*-butyl acrylate, Grubbs II, CH$_2$Cl$_2$, 40 °C, 16 h; (iv) (*R*)-**335**, THF, −78 °C, 2 h.

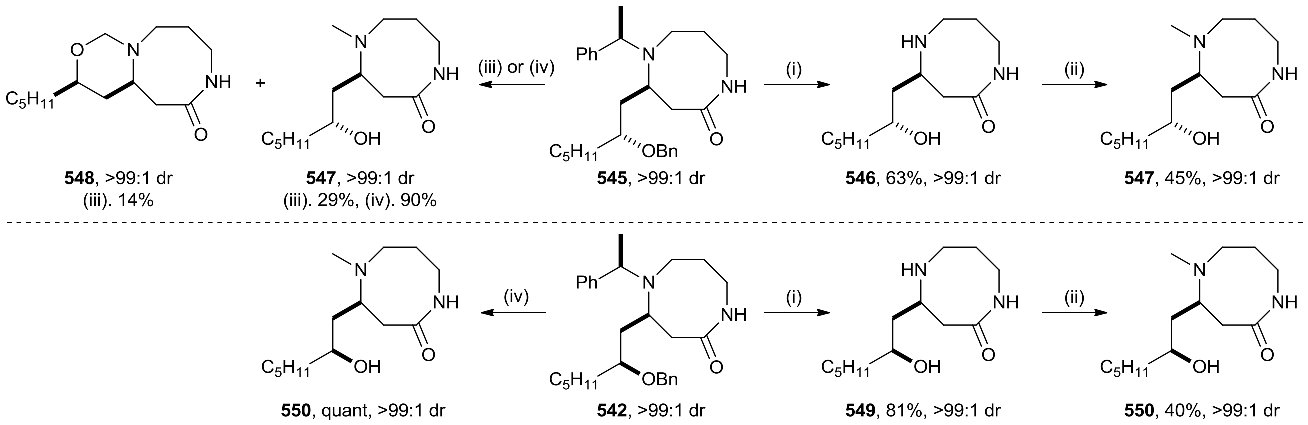
4.4.4 Synthesis of the required C(2′)-hydroxy ζ-lactams

Confident in the stereochemical assignments of the C(5)-stereogenic centres within **518** and **519**, derivatisation of **518** and **519** to ζ-lactams **542** and **545** was next pursued. Transesterification of **518** and **519** with $SOCl_2$ and MeOH gave methyl esters **516** and **517** in 72 and 71% yield, respectively. Displacement of the chloride functionalities within **516** and **517** with NaN_3 gave **540** and **543** in 79 and 91% yield, respectively. Staudinger reduction of **540** and **543** with PBu_3 gave diamines **541** and **544**, with subsequent macrolactamisation giving ζ-lactams **542** and **545**, both in 83% yield over two steps (Scheme 91). Isolation of all the intermediates in this reaction sequence proved beneficial as the analogous procedures performed without isolation of the intermediates gave ζ-lactams **542** and **545** in 44 and 32% yield over four steps, respectively, from β-amino esters **518** and **519**, in contrast to 47 and 54% yield, respectively, with isolation of intermediates.



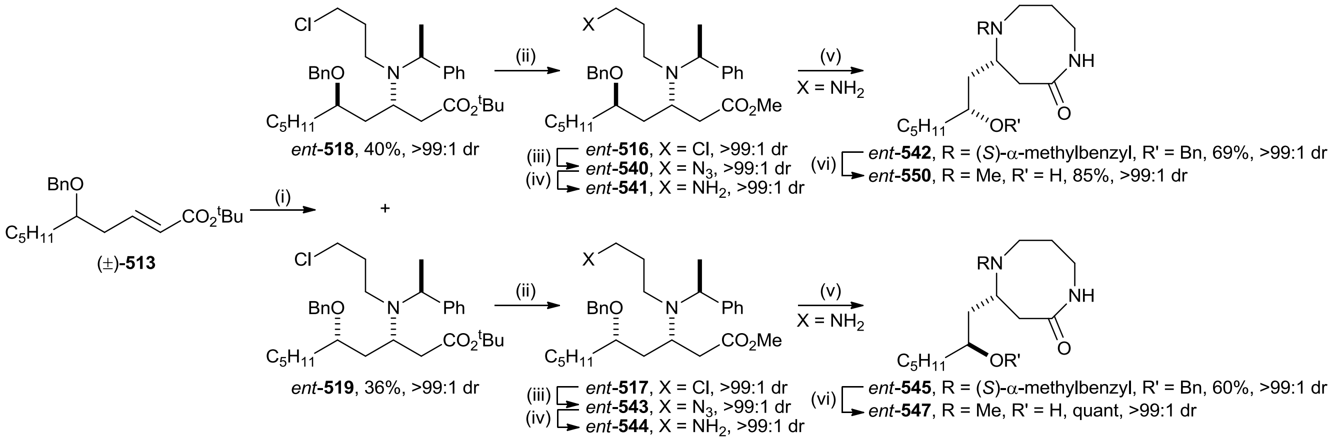
Scheme 91. *Reagents and conditions*: (i) $SOCl_2$, MeOH, reflux, 4 h; (ii) NaN_3, NaI, DMSO, 50 °C, 24 h; (iii) PBu_3, THF, rt, 30 min, then H_2O, 50 °C, 2 h; (iv) $Sb(OEt)_3$, PhMe, reflux, 18 h.

Two strategies were investigated for the deprotection of the C(2′)-benzyloxy substituted ζ-lactams **542** and **545**. Firstly, a stepwise protocol of hydrogenolysis of **545** and **542** gave **546** and **549** in 63 and 81% yield, respectively, with subsequent reductive alkylation giving the corresponding *N*-methyl ζ-lactams **547** and **550** in 45 and 40% yield. Alternatively, attempted tandem hydrogenolysis and reductive methylation of **545** using MeOH as solvent gave an 85:15 mixture of **547** and **548**, which were isolated in 29 and 14% yield, respectively, after purification. Upon changing the solvent to AcOH, the formation of **548** was completely suppressed and **547** was formed in 90% yield. Reaction of the C(2′)-epimeric ζ-lactam **542** under identical conditions gave **550** in quantitative yield (Scheme 92).



Scheme 92. *Reagents and conditions*: (i) H_2 (1 atm), $Pd(OH)_2/C$, MeOH, rt, 24 h; (ii) $NaBH_3CN$, $(CH_2O)_n$, MeOH, rt, 18 h; (iii) H_2 (1 atm), $Pd(OH)_2/C$, $(CH_2O)_n$, MeOH, rt, 72 h; (iv) H_2 (1 atm), $Pd(OH)_2/C$, $(CH_2O)_n$, AcOH, rt, 24 h.

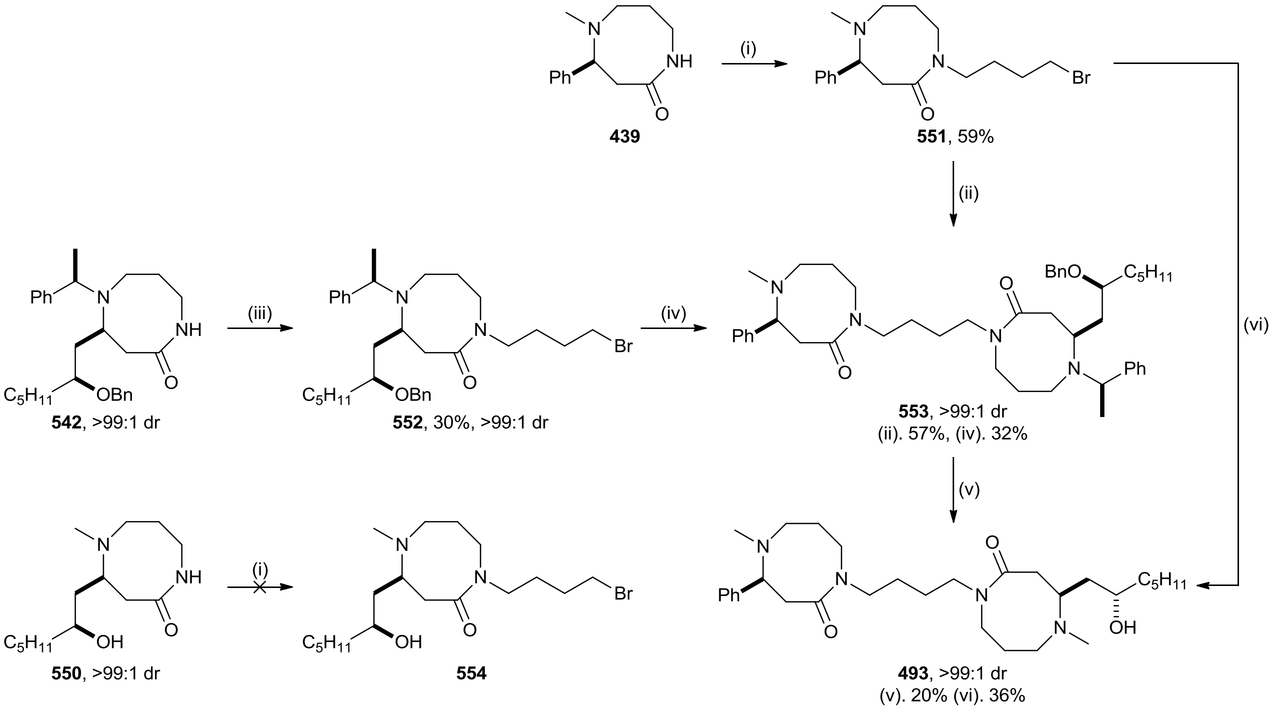
With the (4*R*)-configured ζ-lactams **547** and **550** successfully synthesised, analogous procedures were used to synthesise the corresponding (4*S*)-configured ζ-lactams *ent*-**547** and *ent*-**550** so that samples of all possible diastereoisomers of hopromalinol **493-496** and hoprominol **497-500** could be produced. Conjugate addition of lithium (*S*)-*N*-(3-chloroprop-1-yl)-*N*-(α-methylbenzyl)amide (*S*)-**335** to (±)-**513** gave a 50:50 mixture of *ent*-**518** and *ent*-**519**, with *ent*-**518** and *ent*-**519** being isolated in 40 and 36% yield, respectively, both in >99:1 dr. Subsequent conversion of *ent*-**518** and *ent*-**519** to the corresponding ζ-lactams *ent*-**542** and *ent*-**545** using the standard four step procedure gave *ent*-**542** and *ent*-**545** in 69 and 60% yield, respectively. Tandem hydrogenolysis with *in situ* reductive methylation then gave *ent*-**547** and *ent*-**550** in 85% and quantitative yield, respectively (Scheme 93).



Scheme 93. *Reagents and conditions*: (i) (*S*)-**335**, THF, −78 °C, 2h; (ii) $SOCl_2$, MeOH, reflux, 4 h; (iii) NaN_3, NaI, DMSO, 50 °C, 24 h; (iv) PBu_3, THF, 30 min, H_2O, 50 °C, 2 h; (v) $Sb(OEt)_3$, PhMe, reflux, 18 h; (vi) H_2 (1 atm), $Pd(OH)_2/C$, $(CH_2O)_n$, AcOH, rt, 24 h.

4.4.5 Asymmetric synthesis of the hopromalinol diastereoisomer (4′*S*,4″*R*,2‴*S*)-493

In the earlier reported synthesis of (−)-(*R*,*R*)-hopromine **100**, all possible permutations of the order of alkylation/debenzylation of lactams **382**, **383**, **468** and **470** were explored in order to find the optimum synthesis. The large number of permutations available in the syntheses of all diastereoisomers of hopromalinol **493-496** and hoprominol **497-500** meant that a similar approach was impractical, so a representative system was chosen upon which to model the other diastereoisomers. Four possible routes[21] to (4′*S*,4″*R*,2‴*S*)-**493** were therefore explored: alkylation of C(4)-phenyl substituted ζ-lactam **439** with 1,4-dibromobutane **360** gave **551** in 59% yield, then treatment of bromide **551** with C(2′)-benzyloxy substituted ζ-lactam **542** gave **553** in 57% yield and >99:1 dr. Alternatively, reversing the order of steps and treating C(2′)-benzyloxy substituted ζ-lactam **542** with 1,4-dibromobutane **360** gave **552** in 30% yield, with subsequent reaction of **552** with C(4)-phenyl substituted ζ-lactam **439** giving **553** in 32% yield. Tandem hydrogenolysis/reductive methylation of **553** then gave **493** in 20% yield and >99:1 dr. However, reaction of **551** with C(2′)-hydroxy lactam **550** gave **493** directly in 36% yield. Finally, treatment of C(2′)-hydroxy ζ-lactam **550** with 1,4-dibromobutane **360** resulted in the formation of a complex mixture of products (Scheme 94).

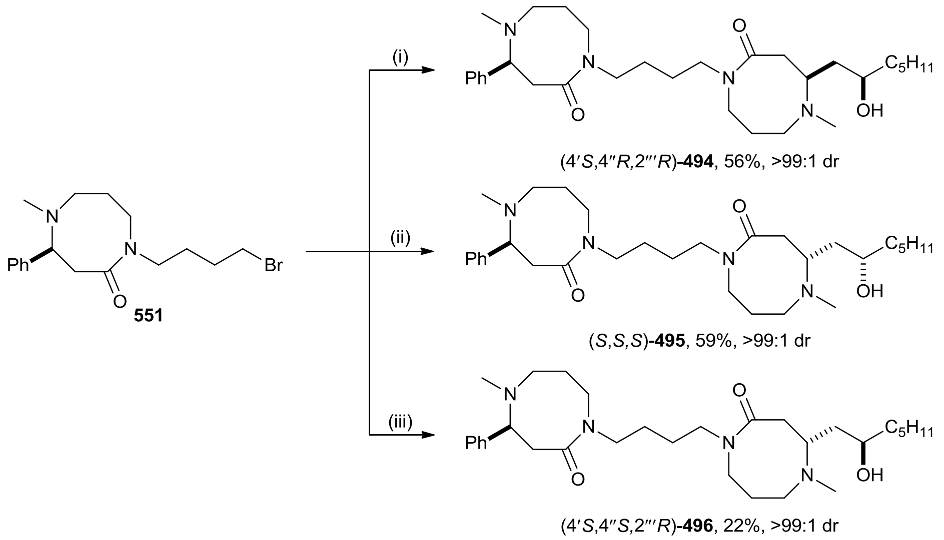


Scheme 94. *Reagents and conditions*: (i) 1,4-dibromobutane **360**, KOH, DMSO, rt, 18 h; (ii) **542**, KOH, DMSO, rt, 96 h; (iii) 1,4-dibromobutane **360**, K_2CO_3, KOH, TEBAC, DMSO, rt, 24 h; (iv) **439**, K_2CO_3, KOH, TEBAC, DMSO, rt, 96 h; (v) H_2 (1 atm), $Pd(OH)_2/C$, $(CH_2O)_n$, AcOH, rt, 24 h; (vi) **550**, K_2CO_3, KOH, TEBAC, DMSO, rt, 48 h.

In agreement with the synthesis of (−)-(*R*,*R*)-hopromine **100**, the most efficient route to **493** was found to be stepwise alkylation of *N*-methyl ζ-lactams **439** and **550**, giving **493** in 36% yield from ζ-lactam **542**. In contrast, the two routes corresponding to the stepwise alkylation of *O*-benzyl ζ-lactam **542**, proceeded in 11 and 1.9% yield, respectively. It was therefore decided to adopt the former of the three strategies for the synthesis of the remaining alkaloid diastereoisomers.

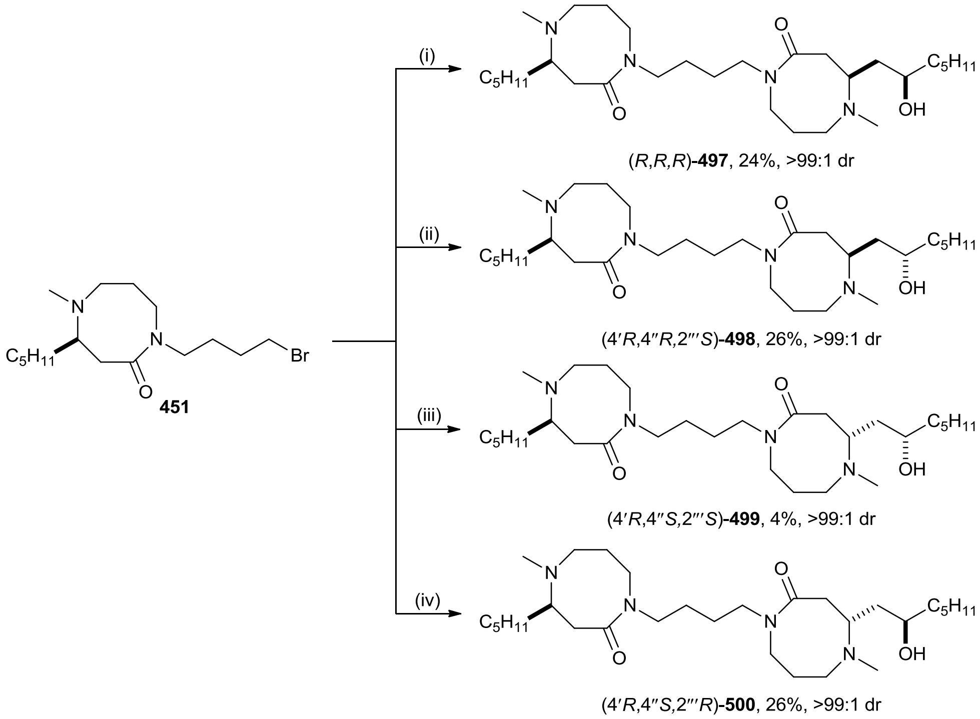
4.4.6 Asymmetric synthesis of the remaining diastereoisomers: total synthesis of (−)-(4′*S*,4″*R*,2‴*R*)-hopromalinol (−)-(*R*,*R*,*R*)-hoprominol

Alkylation of the remaining C(2′)-hydroxy lactam stereoisomers **547**, *ent*-**547** and *ent*-**550** with bromide **551** resulted in the synthesis of **494**-**496** in 22-56% yield, concluding the syntheses of all four targets corresponding to hopromalinol (Scheme 95).



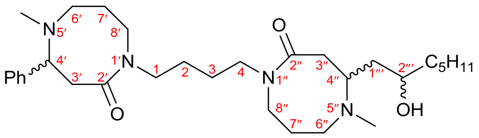
Scheme 95: *Reagents and conditions*: (i) **547**, K_2CO_3, KOH, TEBAC, DMSO, rt, 48 h; (ii) *ent*-**547**, K_2CO_3, KOH, TEBAC, DMSO, rt, 60 h; (iii) *ent*-**550**, K_2CO_3, KOH, TEBAC, DMSO, rt, 60 h.

Similarly, alkylation of lactams **547**, **550**, *ent*-**547** and *ent*-**550** with bromide **451** [an intermediate in the synthesis of (−)-(*R*,*R*)-hopromine **100**] gave **497**-**500** in 4-26% yield, corresponding to all four diastereoisomers of hoprominol (Scheme 96).

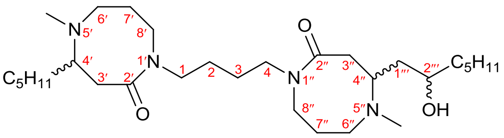


Scheme 96: *Reagents and conditions*: (i) **547**, K_2CO_3, KOH, TEBAC, DMSO, rt, 48 h; (ii) **550**, K_2CO_3, KOH, TEBAC, DMSO, rt, 48 h; (iii) *ent*-**547**, K_2CO_3, KOH, TEBAC, DMSO, rt, 60 h; (iv) *ent*-**550**, K_2CO_3, KOH, TEBAC, DMSO, rt, 60 h.

Unfortunately, only limited NMR data for both natural (−)-hopromalinol **102** and (−)-hoprominol **101** are available in the literature,[1] and attempts to acquire authentic samples for comparison were not successful. It was therefore necessary to compare the values for the specific rotations of the synthetic samples with those reported for the natural products: (−)-hopromalinol **102** {lit.[1] $[\alpha]_D^{20}$ −17 (*c* 2.5 in $CHCl_3$)} and (−)-hoprominol **101** {lit.[1] $[\alpha]_D^{20}$ −19 (*c* 2 in $CHCl_3$)} (Figure 37).



(−)-hopromalinol
natural sample: $[\alpha]_D^{20}$ −17 (*c* 2.5 in CHCl$_3$)



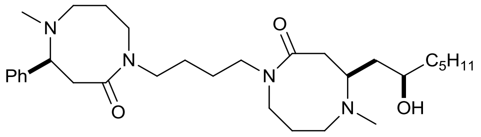
(−)-hoprominol
natural sample: $[\alpha]_D^{20}$ −19 (*c* 2 in CHCl$_3$)

	absolute configuration			specific rotation
	C(4′)	C(4″)	C(2‴)	$[\alpha]_D^{24}$ (*c* 1.0 in CHCl$_3$)
493	*S*	*R*	*S*	−9.3
494	*S*	*R*	*R*	−16.8
495	*S*	*S*	*S*	+2.1
496	*S*	*S*	*R*	−7.1

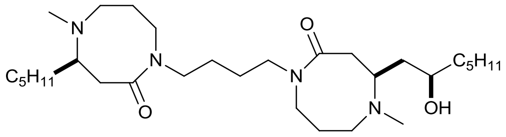
	absolute configuration			specific rotation
	C(4′)	C(4″)	C(2‴)	$[\alpha]_D^{24}$ (*c* 1.0 in CHCl$_3$)
497	*R*	*R*	*R*	−17.5
498	*R*	*R*	*S*	−18.4
499	*R*	*S*	*S*	+5.8
500	*R*	*S*	*R*	−2.4

Figure 37: Comparison of the specific rotations of all diastereoisomers of hopromalinol **493-496** and hoprominol **497-500**.

Comparison of the values for the specific rotations of **493-496** with that of naturally occurring (−)-hopromalinol **101** revealed that only (−)-(2′*S*,4″*R*,4‴*R*)-**494** is in good agreement with both the magnitude and sign of the reported value; the remaining diastereoisomers **493**, **495** and **496** all have specific rotations that are too small in magnitude to be consistent with either enantiomer of the natural product. The absolute (2′*S*,4″*R*,4‴*R*)-configuration can therefore be confidently assigned to natural (−)-hopromalinol. In contrast, comparison of the specific rotations for **497-500** reveal that both the (*R*,*R*,*R*)- and (2′*R*,4″*R*,4‴*S*)-diastereoisomers **497** and **498** have specific rotations of similar magnitude and sign to natural (−)-hoprominol **102**, and therefore the absolute configuration cannot be unambiguously assigned in the absence of an authentic sample. This study does, however, serve to confirm the hypothesis that all the homalium alkaloids are homochiral with respect to the C(4)-stereogenic centres within the ζ-lactam rings. Given this observed homochirality, it may also be reasoned that (−)-hopromalinol **101** and (−)-hoprominol **102** are homochiral with respect to their C(2‴)-stereogenic centers; on this basis it may be proposed that (−)-hoprominol contains the absolute (*R*,*R*,*R*)-configuration (Figure 38).



(−)-(4′*S*,4″*R*,2‴*R*)-hopromalinol **494**

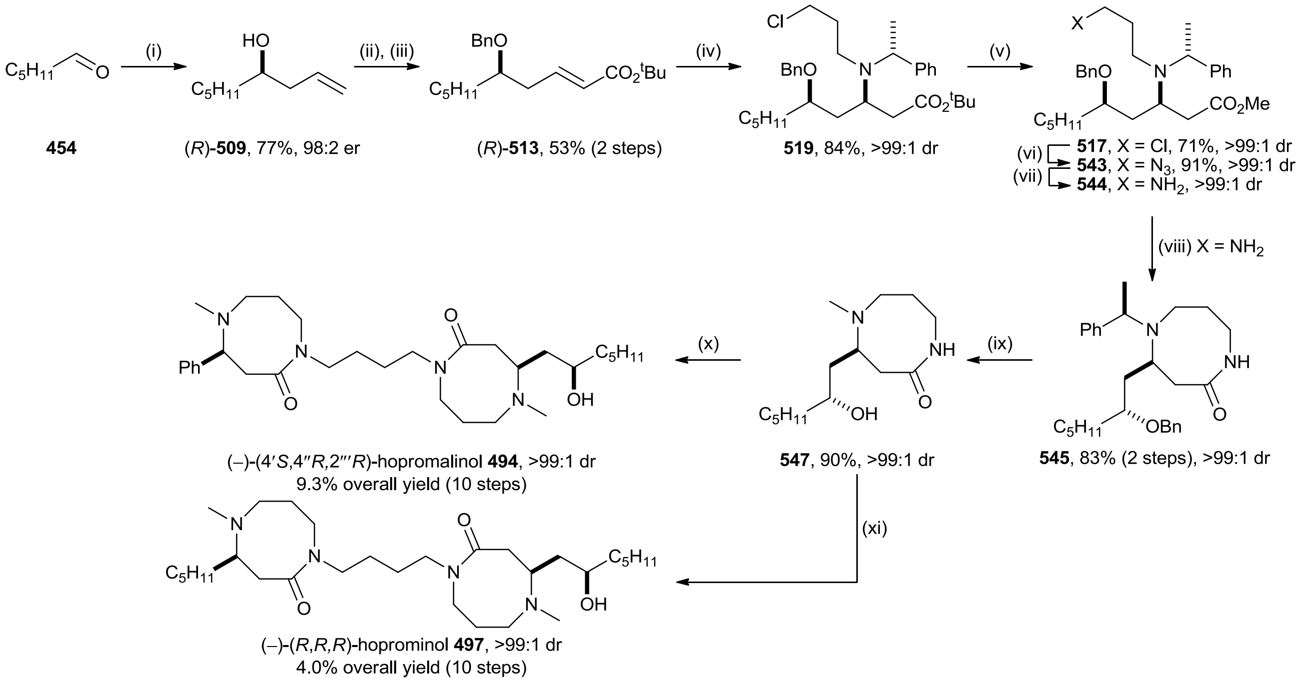


(−)-(*R*,*R*,*R*)-hoprominol **497**

Figure 38: Proposed structures of (−)-hopromalinol **101** and (−)-hoprominol **102**.

4.7 Conclusion

The highly diastereoselective conjugate addition of lithium amides (*R*)- and (*S*)-*N*-(3-chloroprop-1-yl)-*N*-(α-methylbenzyl)amide (*R*)-**335** and (*S*)-**335** to α,β-unsaturated ester **513** enabled the first asymmetric syntheses of all the diastereoisomers of hopromalinol **493-496** and hoprominol **497-500** to be completed. This allowed the absolute configurations within these alkaloids to be proposed, with the naturally occurring diastereoisomers (−)-(2′*S*,4″*R*,4‴*R*)-hopromalinol **494** and (−)-(*R*,*R*,*R*)-hoprominol **497** being synthesised in 9.3 and 4.0% overall yield, respectively both in ten steps from hexanal **454** (Scheme 97).[22]



Scheme 97: *Reagents and conditions*: (i) (−)-Ipc$_2$BCl, allylmagnesium bromide, Et$_2$O, −78 °C to rt, 1 h; (ii) NaH, THF, rt, 1 h then BnBr, THF, rt, 16 h; (iii) *tert*-butyl acrylate, Grubbs II, CH$_2$Cl$_2$, 40 °C, 16 h; (iv) (*R*)-**335**, THF, −78 °C, 2 h; (v) SOCl$_2$, MeOH, reflux, 4 h; (vi) NaN$_3$, NaI, DMSO, 50 °C, 24 h; (vii) PBu$_3$, THF, rt, 30 min, then H$_2$O, 50 °C, 2 h; (viii) Sb(OEt)$_3$, PhMe, reflux, 18 h; (ix) H$_2$ (1 atm), Pd(OH)$_2$/C, (CH$_2$O)$_n$, AcOH, rt, 24 h; (x) **551**, K$_2$CO$_3$, KOH, TEBAC, DMSO, rt, 96 h; (xi) **451**, K$_2$CO$_3$, KOH, TEBAC, DMSO, rt, 96 h.

4.8 References and notes

[1] Païs, M.; Sarfati, R.; Jarreau, F. X.; Goutarel, R. *Tetrahedron* **1973**, *29*, 1001.

[2] Crombie, L.; Haigh, D.; Jones, R. C. F.; Mat-Zin, A. R. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2055.

[3] The ^{1}H NMR spectra of (±)-**493**-(±)-**496** and (±)-**497**-(±)-**500** were reported to be broad at rt, which further complicated analysis of the spectra; no ^{13}C NMR data were reported. See reference 2.

[4] Ensch, C.; Hesse, M. *Helv. Chim. Acta* **2003**, *86*, 233.

[5] There are only limited ^{1}H and no ^{13}C NMR spectroscopic data reported for the natural products. See reference 1.

[6] (±)-**413** was synthesised in 57% yield from (±)-**153** using an analogous procedure to the synthesis of (*R*)-**443**. Treatment with BuLi in THF generated a yellow solution of lithium (±)-*N*-(3-chloropropyl)-*N*-(α-methylbenzyl)amide (±)-**335**.

[7] Davies, S. G.; Smith, A. D.; Price, P. D. *Tetrahedron: Asymmetry* **2005**, *16*, 2833.

[8] Ma, D.; Zhu, W. *Tetrahedron Lett.* **2003**, *44*, 8609.

[9] Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1996**, *7*, 1919.

[10] Davies, S. G.; Ichihara, O.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2011**, *67*, 216.

[11] These results are also consistent with the approximately 45:55 mixture of diastereoisomers observed in the conjugate addition of (±)-**335** to racemic esters **512**-**515** (Scheme 86).

[12] Simsek, S.; Horzella, M.; Kalesse, M.; *Org. Lett.* **2007**, *9*, 5637.

[13] The er of **539** was determined according to the procedure of Feringa *et al.* See: Feringa, B. L.; Smaardijk, A.; Wynberg, H. *J. Am. Chem. Soc.* **1985**, *107*, 4798.

[14] It proved necessary to protect the C(5)-hydroxy substituent in the lithium amide conjugate addition reaction. Reaction of **539** with 2.6 equivalents of **335** without protection of the C(5)-hydroxyl group resulted in a complex mixture of products, again presumably due to deprotonation of the alcohol with subsequent polymerisation of **539**.

[15] Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092.

[16] The er of **509** was determined according to the procedure of Feringa *et al.* See reference 13.

[17] Das, B.; Laxminarayana, K.; Krishnaiah, M.; Kumar, D. N. *Helv. Chim. Acta* **2009**, *92*, 1840.

[18] Marco, J. A.; García-Pla, J.; Carda, M.; Murga, J.; Falomir, E.; Trigili, C.; Notararigo, S.; Díaz, J. F.; Barasoain, I. *Eur. J. Med. Chem.* **2011**, *46*, 1630.

[19] Brown, H. C.; Jadhav, P. K.; *J. Org. Chem.* **1984**, *49*, 4089.

[20] Costello, J. F.; Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1994**, *5*, 1999.

[21] Reactions using (4*S*,α*R*)-4-phenyl-*N*(5)-(α-methylbenzyl)-1,5-diazocan-2-one **418** were not attempted due to the known incompatibility of the *N*(5)-α-methylbenzyl group to hydrogenolysis.

[22] Davies, S. G.; Lee, J. A.; Roberts, P. M.; Stonehouse, J. P.; Thomson, J. E. *J. Org. Chem.* **2012**, *77*, 9724.

Chapter 5: Experimental

5.1 General experimental

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under vacuum before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[1] H_2O was purified by an Elix® UV-10 system. BuLi was used as a solution in hexanes and titrated against diphenylacetic acid before use. MeMgBr and allylmagnesium bromide were used as a solutions in Et_2O and titrated against (*E*)-2-(2′-phenylhydrazonomethyl)phenol before use.[2] NaH was used as a 60% dispersion in mineral oil. TBAF was used as a solution in THF. 1,4-Dibromobutane was distilled from $CaCl_2$ before use. DMPU was distilled from BaO before use. Diisopropylamine was distilled from CaH_2 before use. Formalin describes a 37% aq solution of formaldehyde stabilised with 12% MeOH. All other reagents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$ unless otherwise stated. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), 1% aq $KMnO_4$ or Dragendorff's reagent. Flash column chromatography was performed on Kieselgel 60 silica. Elemental analyses were recorded by the Elemental Analysis Service at London Metropolitan University. Melting points were recorded on either a Gallenkamp Hot Stage apparatus or a Leica Galen III and are uncorrected. Optical rotations were recorded on either a Perkin-Elmer 241 or Perkin-Elmer 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 a Bruker Tensor 27 FT-IR spectrometer as either a thin film on NaCl plates (film), a KBr disc (KBr) or using an ATR module (ATR), as stated. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers at the frequency and in the deuterated solvent stated. Spectra were recorded at rt unless otherwise stated. The field was locked by external referencing to the relevant deuteron resonance. Resonances in the ^{13}C NMR spectra which are broad have their corresponding chemical shifts italicised in the list of assignments. ^1H-^1H COSY, ^1H-^{13}C HMQC and ^1H-^{13}C HMBC analyses were used to establish atom connectivity. Low-resolution mass spectra were recorded on either a Micromass LCT Premier instrument or an Agilent Quadrupole 6120 LC/MS. Accurate mass measurements were run on either a Bruker MicroToF internally calibrated with polyalanine, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m × 0.25 mm) using amyl acetate as a lock mass.

5.2 Experimental

General procedure 1: Wittig reaction with (methoxymethyl)triphenylphosphonium chloride 165.

KO^{t}Bu was added to the requisite aldehyde and **165** in THF at rt and the resultant mixture stirred for 24 h. Sat aq NH_4Cl was added and the aqueous layer extracted twice with Et_2O. The combined organic extracts were washed with brine, then dried and concentrated *in vacuo*.

General procedure 2: enol ether hydrolysis.

HCO_2H was added to the requisite enol ether in CH_2Cl_2 at rt and the resultant mixture stirred in the dark for 48 h. H_2O was added and the aqueous layer extracted twice with CH_2Cl_2. The combined organic extracts were dried and concentrated *in vacuo*.

General procedure 3: Wittig reaction.

The requisite ylid was added to the requisite aldehyde in CH_2Cl_2 at rt and the resultant mixture stirred for 24 h. The reaction mixture was then concentrated *in vacuo*.

General procedure 4: MeMgBr mediated Wadsworth-Emmons reaction.

MeMgBr was added dropwise to the requisite phosphonate in THF at rt and the resultant mixture stirred for 15 min. The requisite aldehyde in THF was added via cannula and the resultant mixture heated at reflux for 3 h. The reaction mixture was then partitioned between sat aq NH_4Cl and Et_2O and the aqueous layer extracted twice with EtOAc. The combined organic extracts were washed with brine, then dried and concentrated *in vacuo*.

General procedure 5: lithium amide conjugate addition with NH_4Cl quench.

BuLi was added to the requisite amine in THF at −78 °C and the resultant mixture was stirred at –78 °C for 15 min. The requisite α,β-unsaturated ester in THF at −78 °C was then added via cannula and the resultant mixture was stirred at –78 °C for 2 h. Sat aq NH_4Cl was added, the reaction mixture allowed to warm to rt over 15 min and then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 and 10% aq citric acid, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic extracts were washed with sat aq $NaHCO_3$ and brine, then dried and concentrated *in vacuo*.

General procedure 6: Heck reaction under Jeffery′s conditions.

$Pd(OAc)_2$ was added to the requisite halide, alkene, TBAC, and K_2CO_3 in DMF at rt and the resultant mixture stirred in the dark for 72 h. The reaction mixture was then partitioned between H_2O and

Et_2O and the aqueous layer extracted twice with Et_2O. The combined organic extracts were washed twice with H_2O and once with brine, then dried and concentrated *in vacuo*.

General procedure 7: lithium amide conjugate addition with (−)-CSO 95 quench.

BuLi was added to the requisite amine in THF at −78 °C and the resultant mixture was stirred at –78 °C for 15 min. The requisite α,β-unsaturated ester in THF at −78 °C was then added via cannula and the resultant mixture was stirred at –78 °C for 2 h. (−)-CSO **95** was added and the reaction mixture was allowed to warm to rt over 16 h and then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 and 10% aq citric acid, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic extracts were washed with sat aq $NaHCO_3$ and brine, then dried and concentrated *in vacuo*.

General procedure 8: *O*-silyl deprotection with TBAF.

TBAF was added to the requisite silyl ether in THF at rt and the resultant mixture stirred for 3 h. The reaction mixture was partitioned between H_2O and Et_2O and the aqueous layer extracted twice with Et_2O. The combined organic extracts were washed with brine, then dried and concentrated *in vacuo*.

General procedure 9: oxidation with IBX.

IBX was added to the requisite alcohol in DMSO at rt and the resultant mixture stirred for 1 h. The reaction mixture was then partitioned between H_2O and EtOAc and the aqueous layer extracted twice with EtOAc. The combined organic extracts were washed twice with H_2O and once with brine, then dried and concentrated *in vacuo*.

General procedure 10: NaH mediated Wadsworth-Emmons reaction.

NaH was added to **10** in THF at rt and the resultant mixture stirred for 1 h. The requisite aldehyde in THF was added via cannula and the resultant mixture stirred at rt for 18 h. The reaction mixture was partitioned between H_2O and EtOAc and the aqueous layer extracted twice with EtOAc. The combined organic extracts were washed with brine, then dried and concentrated *in vacuo*.

General procedure 11: *tert*-butyl ester to methyl ester transesterification.

$SOCl_2$ was added to MeOH at rt and the resultant mixture was stirred for 1 min. The requisite *tert*-butyl ester in MeOH was added and the resultant mixture heated at reflux for 4 h. The reaction mixture was allowed to cool to rt and concentrated *in vacuo*. The residue was partitioned between sat aq $NaHCO_3$ and CH_2Cl_2 and the aqueous layer extracted twice with CH_2Cl_2. The combined organic extracts were dried and concentrated *in vacuo*.

General procedure 12: NaN_3 displacement.

NaN_3 and NaI were added to the requisite amine in DMSO and the resultant mixture stirred and heated at 50 °C for 24 h. The reaction mixture was allowed to cool to rt, and then partitioned between Et_2O and H_2O. The aqueous layer was extracted twice with Et_2O and the combined organic extracts washed twice with H_2O and once with brine, then dried and concentrated *in vacuo*.

General procedure 13: Staudinger reduction.

PPh_3 or PBu_3 was added to the requisite amine in THF at rt and the resultant mixture stirred for 30 min. H_2O was added and the reaction mixture was heated at 50 °C for 2 h before being allowed to cool to rt and concentrated *in vacuo*.

General procedure 14: macrolactamisation.

The requisite amine in PhMe was added to a two necked round bottomed flask fitted with an open pressure equalising dropping funnel part filled with activated 4 Å molecular sieves and a condenser attached to the top of the dropping funnel. A glass stopper was placed in the second neck, the reaction vessel insulated with cotton wool and the solution heated at reflux such that the PhMe vapour condensed above the level of the molecular sieves for 2 h. The resultant solution was allowed to cool for 5 min and then $Sb(OEt)_3$ or $Fe(OEt)_3$ was added. The resultant mixture was heated at reflux for 18 h then allowed to cool to rt. Sat aq NH_4Cl was added and the reaction mixture was stirred at rt for 15 min and then filtered through Celite® (eluent EtOAc). The aqueous layer was extracted once with EtOAc and the combined organic extracts were dried and concentrated *in vacuo*.

General procedure 15: *N*-alkylation of amide.

Powdered KOH, K_2CO_3 and TEBAC were added to the requisite amide and alkyl bromide in DMSO at rt and the resultant mixture stirred for the stated time. The reaction mixture was partitioned between H_2O and $CHCl_3$ and the aqueous layer extracted twice with $CHCl_3$. The combined organic extracts were washed twice with H_2O and once with brine, then dried and concentrated *in vacuo*.

General procedure 16: *N*-alkylation of amide 2.

Powdered KOH was added to the requisite amide and alkyl bromide in DMSO at rt and the resultant mixture stirred for the stated time. The reaction mixture was partitioned between H_2O and $CHCl_3$ and the aqueous layer extracted twice with $CHCl_3$. The combined organic extracts were washed twice with H_2O and once with brine, then dried and concentrated *in vacuo*.

General procedure 17: hydrogenolysis.

$Pd(OH)_2/C$ (20% w/w) was added to the requisite substrate [and $(CH_2O)_n$ if stated] in the stated degassed solvent at rt and the resultant mixture was stirred under H_2 (1 atm) for the stated time. The reaction mixture was then degassed, filtered through Celite® (eluent EtOAc then MeOH) and concentrated *in vacuo*.

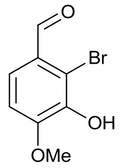
General procedure 18: reductive methylation.

$NaBH_3CN$ was added to the requisite amine and $(CH_2O)_n$ in MeOH at rt and the resultant mixture was stirred for 18 h and then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 and H_2O, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic extracts were washed with brine, then dried and concentrated *in vacuo*.

General procedure 19: cross methathesis.

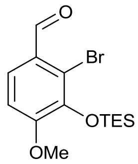
Grubbs II catalyst and the requisite acrylate were added to a degassed solution of the requisite alkene in CH_2Cl_2 (EtOH stabilised) at rt and the resultant mixture heated at 40 °C for 24 h. The reaction mixture was then concentrated *in vacuo*.

2-Bromo-3-hydroxy-4-methoxybenzaldehyde 126



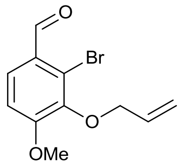
Br_2 (0.36 mL, 7.08 mmol) in AcOH (1.5 mL) was added dropwise to isovanillin **157** (1.00 g, 6.57 mmol), NaOAc (1.08 g, 13.1 mmol) and Fe powder (31 mg, 556 μmol) in AcOH (6 mL) at rt. The resultant mixture was stirred for 1 h and then added to H_2O (15 mL). The resultant precipitate was collected via filtration and washed with H_2O (50 mL). Purification via flash column chromatography (eluent 30-40 °C petrol/acetone, 5:1) gave **126** as a white solid (928 mg, 61%);[3] mp 195-200 °C; {lit.[3] mp 196-200 °C}; δ_H (400 MHz, $CDCl_3$) 4.02 (3H, s, O*Me*), 6.10 (1H, s, O*H*), 6.94 (1H, d, *J* 8.5, C(6)*H*), 7.59 (1H, d, *J* 8.5, C(5)*H*), 10.27 (1H, s, C*H*O).

2-Bromo-3-(triethylsilyloxy)-4-methoxybenzaldehyde 158

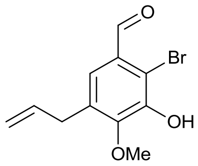


TESCl (0.17 mL, 1.04 mmol) was added to **126** (200 mg, 866 μmol), DMAP (11 mg, 86 μmol) and imidazole (88 mg, 1.30 mmol) in CH_2Cl_2 (8 mL) at rt and the resultant mixture stirred for 96 h. H_2O (10 mL) was added the aqueous layer extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with H_2O (30 mL) and brine (30 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/acetone, 5:1) gave **158** as a colourless oil (116 mg, 39%); ν_{max} (ATR) 1667 (C=O); δ_H (400 MHz, $CDCl_3$) 0.77 (6H, q, *J* 8.2, Si(C*H*$_2$CH$_3$)$_3$), 0.98 (9H, t, *J* 8.2, Si(CH$_2$C*H*$_3$)$_3$), 3.88 (3H, s, O*Me*), 6.87 (1H, d, *J* 8.7, C(5)*H*), 7.57 (1H, d, *J* 8.7, C(6)*H*), 10.24 (1H, s, C*H*O); δ_C (100 MHz, $CDCl_3$) 5.6 (Si(*C*H$_2$CH$_3$)$_3$), 6.7 (Si(CH$_2$*C*H$_3$)$_3$), 55.6 (O*Me*), 109.8 (*C*(5)), 120.5 (*C*(2)), 123.5 (*C*(6)), 127.4 (*C*(1)), 143.2 (*C*(3)), 156.2 (*C*(4)), 191.5 (*C*HO).[4]

2-Bromo-3-allyloxy-4-methoxybenzaldehyde 160 and 2-bromo-3-hydroxy-4-methoxy-5-allyl-benzaldehyde 161



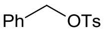
160



161

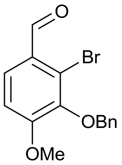
A solution of **126** (200 mg, 866 µmol) in DMF (4 mL) was added to NaH (52 mg, 1.30 mmol) in DMF (4 mL) at rt and the resultant mixture stirred for 1 h. Allyl bromide (0.11 mL, 1.30 mmol) was added and the reaction mixture stirred at rt for 24 h. The reaction mixture was partitioned between H_2O (10 mL) and CH_2Cl_2 (10 mL) and the aqueous layer extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with H_2O (2 × 20 mL) and brine (20 mL), then dried and concentrated *in vacuo* to give a 78:22 mixture of **160** and **161**. Purification via flash column chromatography (eluent 30-40 °C/Et_2O, 15:2) gave **161** as a white solid (48 mg, 20%); mp 58-60 °C; ν_{max} (ATR) 1691 (C=O); δ_H (400 MHz, $CDCl_3$) 3.95 (3H, s, O*Me*), 4.54 (2H, dd, *J* 6.1, 1.3, C(5)C*H*$_2$), 5.27 (1H, app d, *J* 10.4, CH=C*H*$_A$), 5.39 (1H, dd, *J* 17.2, 1.3, CH=C*H*$_B$), 6.07-6.17 (1H, m, C*H*=CH$_2$), 7.16 (1H, s, C(6)*H*), 10.20 (1H, s, C*H*O); δ_C (100 MHz, $CDCl_3$) 56.5 (O*Me*), 74.1 (C(5)*C*H$_2$), 117.0 (*C*(6)), 119.0 (CH=*C*H$_2$), 120.8 (*C*(2)), 122.4 (*C*(5)), 125.2 (*C*(1)), 133.0 (*C*H=CH$_2$), 145.3 (*C*(3)), 156.8 (*C*(4)), 190.6 (*C*HO); *m/z* (CI^+) 273 ($[M(^{81}Br)+H]^+$, 77%), 271 ($[M(^{79}Br)+H]^+$, 100%); HRMS (CI^+) $C_{11}H_{12}{}^{81}BrO_3{}^+$ ($[M(^{81}Br)+H]^+$) requires 272.9944; found 272.9935; $C_{11}H_{12}{}^{79}BrO_3{}^+$ ($[M(^{79}Br)+H]^+$) requires 270.9964; found 270.9977. Further elution gave **160** as a white solid (105 mg, 45%);[5] mp 73-75 °C; {lit.[5] mp 75-78 °C}; δ_H (400 MHz, $CDCl_3$) 3.96 (3H, s, O*Me*), 4.57 (2H, d, *J* 5.8, OC*H*$_2$), 5.28 (1H, dd, *J* 9.2, 1.2, CH=C*H*$_A$), 5.41 (1H, app dq, *J* 17.4, 1.2, CH=C*H*$_B$), 6.11-6.21 (1H, m, C*H*=CH$_2$), 6.97 (1H, d, *J* 8.6, C(6)*H*), 7.75 (1H, d, *J* 8.6, C(5)*H*), 10.27 (1H, s, C*H*O).

Benzyl tosylate 555[6]

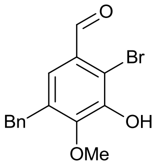


K_2CO_3 (10.0 g, 72.4 mmol), BnOH (2.07 mL, 20.0 mmol) and TsCl (5.72 g, 30 mmol) were ground in a mortar and pestle for 5 min. KOH (5.60 g, 100 mmol) was added and the resultant mixture ground for 2 min. Et_2O (100 mL) was added, the reaction mixture ground for 30 sec, then filtered and concentrated *in vacuo* to give **555** as a colourless oil (3.59 g, 68%); δ_H (400 MHz, $CDCl_3$) 2.46 (3H, s, C(4)*Me*), 5.06 (2H, s, PhC*H*$_2$), 7.24-7.39 (7H, m, C(2)*H*, C(6)*H*, *Ph*), 7.81 (2H, d, *J* 8.2, C(3)*H*, C(5)*H*).

2-Bromo-3-benzyloxy-4-methoxybenzaldehyde 162 and 2-bromo-3-hydroxy-4-methoxy-5-benzylbenzaldehyde 163



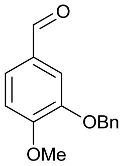
162



163

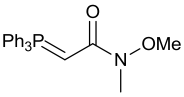
A solution of **126** (15.0 g, 64.9 mmol) in DMF (100 mL) was added to NaH (3.90 g, 97.4 mmol) in DMF (100 mL) at rt and the resultant mixture stirred for 15 min. BnBr (11.6 mL, 97.4 mmol) was added and the resultant mixture stirred at rt for 48 h. The reaction mixture was partitioned between H_2O (150 mL) and CH_2Cl_2 (150 mL) and the aqueous layer extracted with CH_2Cl_2 (2 × 150 mL). The combined organic extracts were washed with H_2O (2 × 250 mL) and brine (250 mL), then dried and concentrated *in vacuo* to give an 83:17 mixture of **162** and **163**. Purification via flash column chromatography (eluent 30-40°C petrol/Et_2O, 15:2) gave **163** as a colourless oil (3.13g, 15%); ν_{max} (film) 3439 (O−H); 1692 (C=O); δ_H (400 MHz, $CDCl_3$) 3.95 (3H, s, O*Me*), 5.03 (2H, s, C(5)C*H*$_2$), 7.18 (1H, s, C(6)*H*), 7.34-7.42 (3H, m, *Ph*), 7.51-7.56 (2H, m, *Ph*), 10.21 (1H, s, C*H*O); δ_C (100 MHz, $CDCl_3$) 56.5 (O*Me*), 74.8 (C(5)*C*H$_2$), 117.1 (*C*(6)), 121.0 (*C*(2)), 122.4 (*C*(5)), 125.3 (*C*(1)), 128.4, 128.5 (*o*,*m*,*p*-*Ph*), 136.3 (*i*-*Ph*), 145.3 (*C*(3)), 156.9 (*C*(4)), 190.6 (*C*HO); *m/z* (CI^+) 340 ($[M(^{81}Br)+NH_4]^+$, 10%), 338 ($[M(^{79}Br)+NH_4]^+$, 16%), 323 ($[M(^{81}Br)+H]^+$, 46%), 321 ($[M(^{81}Br)+H]^+$, 100%); HRMS (ESI^+) $C_{15}H_{14}{}^{81}BrO_3{}^+$ ($[M(^{81}Br)+H]^+$) requires 323.0100; found 323.0115.[7] Further elution gave **162** as a white solid (10.6 g, 51%);[8] mp 72-74 °C; {lit.[9] mp 77-79 °C}; δ_H (400 MHz, $CDCl_3$) 3.97 (3H, s, O*Me*), 5.06 (2H, s, OC*H*$_2$), 6.99 (1H, d, *J* 8.7, C(6)*H*), 7.33-7.43 (3H, m, *Ph*), 7.53-7.58 (2H, m, *Ph*), 7.77 (1H, d, *J* 8.7, C(5)*H*), 10.27 (1H, s, C*H*O).

3-Benzyloxy-4-methoxybenzaldehyde 164



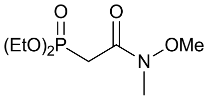
BnBr (1.17 mL, 9.86 mmol) was added to isovanillin **157** (1.00 g, 6.57 mmol) and K_2CO_3 (1.82 g, 13.1 mmol) in DMF (10 mL) at rt and the resultant mixture stirred and heated at 60 °C for 16 h. The reaction mixture was allowed to cool to rt and then partitioned between H_2O (30 mL) and Et_2O (30 mL). The aqueous layer was extracted with Et_2O (2 × 40 mL), the combined organic extracts were washed with H_2O (2 × 50 mL) and brine (50 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 3:1) gave **164** as a white solid (1.20 g, 76%);[10] mp 58-60 °C; {lit.[11] mp 59-60 °C}; δ_H (400 MHz, $CDCl_3$) 3.98 (3H, s, O*Me*), 5.21 (2H, s, PhC*H*$_2$), 7.01 (1H, d, *J* 7.9, C(5)*H*), 7.31-7.41 (3H, m, *Ph*, *Ar*), 7.46-7.49 (4H, m, *Ph*, *Ar*), 9.83 (1H, s, C*H*O).

N-Methoxy-*N*-methyl triphenylphosphenylideneacetamide 173



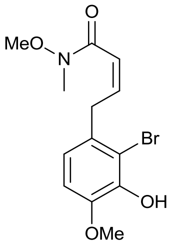
NEt_3 (28.0 mL, 200 mmol) was added dropwise to **314** (8.00 mL, 100 mmol) and *N*,*O*-dimethylhydroxylammonium chloride (9.75 g, 100 mmol) in CH_2Cl_2 (250 mL) at rt and the resultant mixture stirred for 1 h. The reaction mixture was filtered (eluent CH_2Cl_2) and the filtrate washed with 2.0 M aq HCl (200 mL), brine (300 mL) and sat aq $NaHCO_3$ (300 mL), then dried (Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved in MeCN (100 mL) and PPh_3 (21.8 g, 83.0 mmol) added. The resultant mixture was heated at reflux for 15 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (200 mL) and 2.0 M aq KOH (200 mL), and the organic layer was washed with 2.0 M aq KOH (100 mL) and brine (200 mL). The combined aqueous extracts were extracted with CH_2Cl_2 (200 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification via recrystallisation (EtOAc:hexane, 1:1) gave **173** as a yellow solid (16.1 g, 44%);[12] mp 163-165 °C; {lit.[12] mp 176-177 °C}; δ_H (400 MHz, $CDCl_3$) 2.05 (1H, s, PC*H*), 3.08 (3H, s, N*Me*), 3.74 (3H, s, O*Me*), 7.42-7.49 (6H, m, *Ph*), 7.51-7.57 (3H, m, *Ph*), 7.64-7.72 (6H, m, *Ph*).

N-Methoxy-*N*-methyl (diethylphosphono)acetamide 174

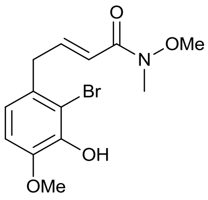


NEt$_3$ (28.0 mL, 200 mmol) was added dropwise to **314** (8.00 mL, 100 mmol) and *N*,*O*-dimethylhydroxylammonium chloride (9.75 g, 100 mmol) in CH$_2$Cl$_2$ (250 mL) at rt and the resultant mixture stirred for 1 h. The reaction mixture was filtered (eluent CH$_2$Cl$_2$) and the filtrate washed with 2.0 M aq HCl (200 mL), brine (300 mL) and sat aq NaHCO$_3$ (300 mL), then dried (Na$_2$SO$_4$) and concentrated *in vacuo*. P(OEt)$_3$ (17.1 mL, 99.7 mmol) was added to the residue and the resultant mixture heated at 80 °C for 24 h. Purification via distillation gave **174** as a yellow oil (9.25 g, 39%); bp 167-169 °C (4 mbar); {lit.[13] bp 124 °C (1 mbar)}; δ_H (400 MHz, CDCl$_3$) 1.35 (6H, t, *J* 7.3, P(OCH$_2$C*H*$_3$)$_2$), 3.18 (2H, d, *J* 22.2, PC*H*$_2$), 3.22 (3H, s, N*Me*), 3.78 (3H, s, O*Me*), 4.16-4.23 (4H, m, P(OC*H*$_2$CH$_3$)$_2$).

N-Methoxy-*N*-methyl (*Z*)- and (*E*)-4-(2′-bromo-3′-hydroxy-4′-methoxyphenyl)but-2-enamide (*Z*)-170 and (*E*)-171



(*Z*)-**170**



(*E*)-**171**

Method A - step 1: Following *general procedure 1*, KO^{t}Bu (10.0 g, 89.1 mmol), **126** (5.00 g, 21.6 mmol) and **165** (7.50 g, 21.8 mmol) were reacted in THF (150 mL) to give **168** as a brown oil (11.0 g).

Step 2: Following *general procedure 2*, HCO$_2$H (12.5 mL) and **168** (11.0 g) were reacted in CH$_2$Cl$_2$ (45 mL) to give **169** as a brown oil (10.2 g).

Step 3: Following *general procedure 3*, **173** (7.86 g, 21.6 mmol) and **169** (10.2 g) were reacted in CH$_2$Cl$_2$ (200 mL). Purification via flash column chromatography (gradient elution, 20% → 55% EtOAc in 30-40 °C petrol) gave (*Z*)-**170** as a yellow oil (350 mg, 5% over 3 steps, >99:1 dr); ν_{max} (film) 3293 (O−H), 1647 (C=O), 1621 (C=C); δ_H (400 MHz, CDCl$_3$) 3.26 (3H, s, N*Me*), 3.71 (3H, s, NO*Me*), 3.89 (3H, s, C(4′)O*Me*), 4.09 (2H, d, *J* 7.5, C(4)*H*$_2$), 5.98 (1H, s, O*H*), 6.22 (1H, ABdt, *J* 11.5, 7.2, C(3)*H*), 6.36 (1H, br ABd, *J* 11.5, C(2)*H*), 6.77 (1H, ABd, *J* 8.3, C(5′)*H*), 6.89 (1H, ABd, *J* 8.3, C(6′)*H*); δ_C (100 MHz, CDCl$_3$) *31.9* (N*Me*), 35.0 (*C*(4)), 56.2 (C(4′)O*Me*), 61.6 (NO*Me*), 109.8 (*C*(5′)), 110.9 (*C*(2′)), *118.3* (*C*(2)), 120.6 (*C*(6′)), 132.2 (*C*(1′)), 143.4, 145.8 (*C*(3′), *C*(4′)), *144.4* (*C*(3)), *167.2* (*C*(1)); *m/z* (ESI$^+$) 354 ([M(^{81}Br)+Na]$^+$, 100%), 352

([M(^{79}Br)+Na]$^+$, 96%), 332 ([M(^{81}Br)+H]$^+$, 32%), 330 ([M(^{79}Br)+H]$^+$, 36%); HRMS (ESI$^+$) $C_{13}H_{16}{}^{81}BrNNaO_4^+$ ([M(^{81}Br)+Na]$^+$) requires 354.0134; found 354.0135; $C_{13}H_{16}{}^{79}BrNNaO_4^+$ ([M(^{79}Br)+Na]$^+$) requires 352.0155; found 352.0157. Further elution gave (*E*)-**171** as a yellow oil (856 mg, 12% over 3 steps, >99:1 dr); ν_{max} (film) 3419 (O−H), 1670 (C=O); δ_H (400 MHz, $CDCl_3$) 3.06 (3H, s, N*Me*), 3.46 (2H, d, *J* 6.3, C(4)*H*$_2$), 3.49 (3H, s, NO*Me*), 3.59 (3H, s, C(4′)O*Me*), 6.27 (1H, d, *J* 15.4, C(2)*H*), 6.50-6.58 (2H, m, C(5′)*H*, C(6′)*H*), 6.86-6.98 (1H, m, C(3)*H*), 7.14 (1H, s, O*H*); δ_C (100 MHz, $CDCl_3$) *32.2* (N*Me*), 38.2 (*C*(4)), 56.1 (C(4′)O*Me*), 61.7 (NO*Me*), 109.7 (*C*(5′)), 111.1 (*C*(2′)), 119.9 (*C*(2)), 120.3 (*C*(6′)), 132.0 (*C*(1′)), 143.7, 146.1 (*C*(3′), *C*(4′)), 144.5 (*C*(3)), 166.5 (*C*(1)); *m/z* (ESI$^+$) 354 ([M(^{81}Br)+Na]$^+$, 100%), 352 ([M(^{79}Br)+Na]$^+$, 95%), 332 ([M(^{81}Br)+H]$^+$, 56%), 330 ([M(^{79}Br)+H]$^+$, 55%); HRMS (ESI$^+$) $C_{13}H_{16}{}^{81}BrNNaO_4^+$ ([M(^{81}Br)+Na]$^+$) requires 354.0134; found 354.0130; $C_{13}H_{16}{}^{79}BrNNaO_4^+$ ([M(^{79}Br)+Na]$^+$) requires 352.0155; found 352.0151.

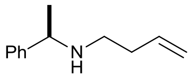
Method B - step 1: Br_2 (18.0 mL, 354 mmol) in AcOH (75 mL) was added dropwise to isovanillin **157** (50.0 g, 329 mmol), NaOAc (54.0 g, 655 mmol) and Fe powder (1.55 g, 27.8 mmol) in AcOH (300 mL) at 0 °C and the resultant mixture allowed to warm to rt over 2 h. The reaction mixture was added to H_2O (500 mL), the resultant precipitate was collected via filtration and then washed with H_2O (1.0 L) to give **126** as a yellow solid (64.5 g).

Step 2: Following *general procedure 1*, KO^{t}Bu (100 g, 891 mmol), **126** (50.0 g) and **165** (75.0 g, 218 mmol) were reacted in THF (1.5 L) to give **168** as a brown oil (67.0 g).

Step 3: Following *general procedure 2*, HCO_2H (75.0 mL) and **168** (67.0 g) were reacted in CH_2Cl_2 (250 mL) to give **169** as a brown oil (65.8 g).

Step 4: Following *general procedure 4*, MeMgBr (3.0 M, 100 mL, 300 mmol), **174** (73.4 mL, 331 mmol) and **169** (65.8 g) were reacted in THF (1.50 L) to give **171** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 1:1) gave **171** as a yellow oil (18.4 g, 17% over 4 steps, >99:1 dr).

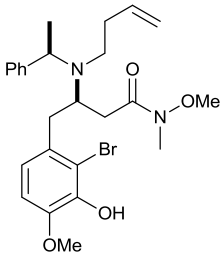
(*R*)-*N*-(α-Methylbenzyl)but-3-en-1-amine 152



4-Bromobut-1-ene (75.0 g, 555 mmol) was added to (*R*)-α-methylbenzylamine (*R*)-**153** (177 mL, 1.39 mol, 99.5:0.5 er) and K_2CO_3 (92.1 g, 666 mmol) at rt and the resultant mixture stirred and heated at 50 °C for 12 h. The reaction mixture was allowed to cool to rt, H_2O (1.5 L) and Et_2O (1.5 L) were added and the aqueous layer extracted with Et_2O (2 × 750 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O/NEt_3, 29:70:1) gave **152** as a yellow oil (65.8 g, 68%, >99:1 er);[14] $[\alpha]_D^{24}$ +42.1

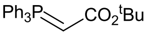
(*c* 1.0 in $CHCl_3$); {lit.[14] $[\alpha]_D^{25}$ +41.6 (*c* 1.0, $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.36 (3H, d, *J* 6.6, C(α)*Me*), 2.24 (2H, m, C(2)H_2), 2.54 (2H, m, C(1)H_2), 3.77 (1H, q, *J* 6.6, C(α)*H*), 5.06 (2H, m, C(4)H_2), 5.75 (1H, m, C(3)*H*), 7.22-7.36 (5H, m, *Ph*).

N-Methoxy-*N*-methyl (*R*,*R*)-3-[*N*′-but-3″-enyl-*N*′-(α-methylbenzyl)amino]-4-(2′-bromo-3′-hydroxy-4′-methoxyphenyl)butanamide 172



Following *general procedure 5*, **152** (25.4 g, 145 mmol, >99:1 er), BuLi (2.5 M, 57.0 mL, 143 mmol) and **171** (18.4 g, 55.8 mmol, >99:1 dr) were reacted in THF (1.0 L) to give **172** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 1:9) gave **172** as a yellow oil that solidified to a brown solid upon prolonged sonication under vacuum (19.5 g, 69%, >99:1 dr); $C_{25}H_{33}BrN_2O_4$ requires C, 59.4; H, 6.6; N, 5.5%; found C, 59.4; H, 6.5; N, 5.5%; mp 69-71 °C; $[\alpha]_D^{25}$ −2.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3406 (O−H), 1641 (C=O); δ_H (400 MHz, $CDCl_3$) 1.32 (3H, d, *J* 6.8, C(α)*Me*), 2.21-2.30 (3H, m, C(2″)H_2, C(2)H_A), 2.33-2.43 (1H, m, C(2)H_B), 2.61-2.70 (1H, m, C(1″)H_A), 2.75-2.81 (2H, m, C(1″)H_B, C(4)H_A), 2.94-2.99 (1H, dd, *J* 13.4, 6.8, C(4)H_B), 3.04 (3H, s, N*Me*), 3.38 (3H, s, NO*Me*), 3.79-3.86 (1H, m, C(3)*H*), 3.89 (3H, s, C(4′)O*Me*), 4.02 (1H, q, *J* 6.8, C(α)*H*), 4.97 (1H, app d, *J* 9.9, C(4″)H_A), 5.03 (1H, app d, *J* 17.2, C(4″)H_B), 5.73-5.84 (1H, m, C(3″)*H*), 6.75 (1H, ABd, *J* 8.5, C(6′)*H*), 6.78 (1H, ABd, *J* 8.5, C(5′)*H*), 7.15-7.31 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.8 (C(α)*Me*), 32.1 (N*Me*), 33.8 (*C*(2)), 34.8 (*C*(2″)), 38.2 (*C*(4)), 45.7 (*C*(1″)), 55.5 (*C*(3)), 56.4 (C(4′)O*Me*), 57.3 (*C*(α)), 60.9 (NO*Me*), 109.4 (*C*(5′)), 111.6 (*C*(2′)), 115.3 (*C*(4″)), 122.0 (*C*(6′)), 126.4, 127.7, 127.9 (*Ph*), 132.5 (*C*(1′)), 137.2 (*C*(3″)), 142.8 (*i-Ph*), 145.1, 145.3 (*C*(3′), *C*(4′)), 173.3 (*C*(1)); *m/z* (ESI^+) 507 ($[M(^{81}Br)+H]^+$, 100%), 505 ($[M(^{79}Br)+H]^+$, 95%); HRMS (ESI^+) $C_{25}H_{34}{}^{81}BrN_2O_4{}^+$ ($[M(^{81}Br)+H]^+$) requires 507.1676; found 507.1680; $C_{25}H_{34}{}^{79}BrN_2O_4{}^+$ ($[M(^{79}Br)+H]^+$) requires 505.1696; found 505.1695.

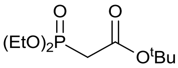
tert-Butyl triphenylphosphenylidene acetate 181



317 (50.0 g, 256 mmol) was added to PPh_3 (67.2 g, 256 mmol) in EtOAc (330 mL) at rt and the resultant mixture stirred for 12 h. The resultant precipitate was collected via filtration, washed with Et_2O (200 mL), and then added to 2.0 M aq NaOH (330 mL) and CH_2Cl_2 (300 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL) and concentrated *in vacuo* to a volume of ~100 mL.

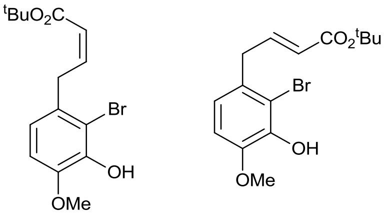
30-40 °C petrol (~200 mL) was added and the resultant precipitate collected via filtration to give **181** as a white solid (76.7 g, 80%);[15] mp 148-150 °C; {lit.[16] mp 151-152 °C}; δ_H (400 MHz, $CDCl_3$) 1.23 (9H, br s, C*Me*$_3$), 2.68 (1H, br s, PC*H*), 7.37-7.72 (15H, m, *Ph*).

***tert*-Butyl diethylphosphonoacetate 182**



$P(OEt)_3$ (34.9 mL, 204 mmol) was added to **317** (36.1 g, 185 mmol) at rt and the resultant mixture stirred and heated at 30 °C for 48 h. The reaction mixture was then concentrated *in vacuo* to give **182** as a colourless oil (30.2 g, 65%);[17] δ_H (400 MHz, $CDCl_3$) 1.35 (6H, t, *J* 7.2, $P(OCH_2CH_3)_2$), 1.48 (9H, s, C*Me*$_3$), 2.89 (2H, d, *J* 21.2, PCH_2), 4.17 (4H, m, $P(OCH_2CH_3)_2$).

***tert*-Butyl (*Z*)- and (*E*)-4-(2′-bromo-3′-hydroxy-4′-methoxyphenyl)but-2-enoate (*Z*)-178 and (*E*)-179**



(*Z*)-**178** (*E*)-**179**

Method A - step 1: Following *general procedure 1*, KO^{t}Bu (10.0 g, 81.9 mmol), **126** (5.00 g, 21.6 mmol) and **165** (7.50 g, 21.9 mmol) were reacted in THF (150 mL) to give **168** as a brown oil (11.0 g).

Step 2: Following *general procedure 2*, HCO_2H (12.5 mL) and **168** (11.0 g) were reacted in CH_2Cl_2 (45 mL) to give **169** as a brown oil (10.2 g).

Step 3: Following *general procedure 3*, **181** (8.15 g, 21.6 mmol) and **169** (10.2 g) were reacted in CH_2Cl_2 (200 mL) to give an 17:83 mixture of (*Z*)-**178** and (*E*)-**179**. Purification via flash column chromatography (gradient elution, 20% → 55% EtOAc in 30-40 °C petrol) gave an impure sample of (*Z*)-**178** as a yellow oil (204 mg); δ_H (400 MHz, $CDCl_3$) [selected peaks] 4.07 (2H, dd, *J* 7.3, 1.9, C(4)*H*$_2$), 5.79 (1H, dt, *J* 11.4, 1.9, C(2)*H*), 6.20 (1H, dt, *J* 11.4, 7.3, C(3)*H*); *m/z* (ESI$^+$) 367 ([M(^{81}Br)+Na]$^+$, 98%), 365 ([M(^{79}Br)+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{15}H_{19}{}^{81}BrNaO_4{}^+$ ([M(^{81}Br)+Na]$^+$) requires 367.0338; found 367.0334; $C_{15}H_{19}{}^{79}BrNaO_4{}^+$ ([M(^{79}Br)+Na]$^+$) requires 365.0359; found 365.0352. Further elution gave (*E*)-**179** as a yellow oil (741 mg, 10% over 3 steps, >99:1 dr); $C_{15}H_{19}BrO_4$ requires C, 52.5; H, 5.6%; found, C, 52.5; H, 5.7%; ν_{max} (film) 3389 (O−H), 1694 (C=O), 1650 (C=C); δ_H (400 MHz, $CDCl_3$) 1.47 (9H, s, C*Me*$_3$), 3.58 (2H, dd, *J* 6.5, 1.7, C(4)*H*$_2$), 3.91 (3H, s, O*Me*), 5.68 (1H, dt, *J* 15.7, 1.7, C(2)*H*), 6.00 (1H, s, O*H*), 6.74 (1H, ABd, *J* 8.2, C(5′)*H*), 6.79 (1H, ABd, *J* 8.2, C(6′)*H*), 6.96 (1H, dt, *J* 15.7, 6.5, C(3)*H*);

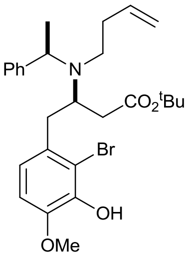
δ_C (100 MHz, CDCl$_3$) 28.1 (C*Me*$_3$), 37.9 (*C*(4)), 56.0 (O*Me*), 80.3 (*C*Me$_3$), 109.7 (*C*(5′)), 110.9 (*C*(2′)), 120.9 (*C*(6′)), 124.2 (*C*(2)), 130.5 (*C*(1′)), 143.4, 145.9 (*C*(3′), *C*(4′)), 144.8 (*C*(3)), 165.9 (*C*(1)); *m/z* (ESI$^+$) 367 ([M(^{81}Br)+Na]$^+$, 88%), 365 ([M(^{79}Br)+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{15}H_{19}{}^{81}BrNaO_4^+$ ([M(^{81}Br)+Na]$^+$) requires 367.0338; found 367.0328; $C_{15}H_{19}{}^{79}BrNaO_4^+$ ([M(^{79}Br)+Na]$^+$) requires 365.0359; found 365.0348.

Method B - step 1: Following *general procedure 1*, KO^{t}Bu (5.75 g, 51.1 mmol), **126** (3.83 g, 16.5 mmol) and **165** (5.75 g, 16.7 mmol) were reacted in THF (115 mL) to give **168** as a brown oil (6.80 g).

Step 2: Following *general procedure 2*, HCO$_2$H (7.60 mL) and **168** (6.80 g) were reacted in CH$_2$Cl$_2$ (25 mL) to give **169** as a brown oil (6.70 g).

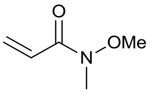
Step 3: Following *general procedure 4*, MeMgBr (3.0 M, 9.3 mL, 27.9 mmol), **182** (6.51 mL, 27.8 mmol) and **169** (6.70 g) were reacted in THF (350 mL) to give **179** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/Et$_2$O, 2:1) gave **179** as a colourless oil (1.53 g, 27% over 3 steps, >99:1 dr).

tert-Butyl (*R*,*R*)-3-[*N*-but-3″-enyl-*N*-(α-methylbenzyl)amino]-4-(2′-bromo-3′-hydroxy-4′-methoxyphenyl)butanoate 180



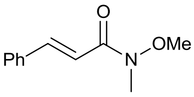
Following *general procedure 5*, **152** (1.33 g, 7.60 mmol, >99:1 er), BuLi (2.4 M, 3.1 mL, 7.45 mmol) and **179** (1.00 g, 2.92 mmol, >99:1 dr) were reacted in THF (50 mL) to give **180** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/Et$_2$O, 1:1) gave **180** as a yellow solid (1.37 g, 90%, >99:1 dr); $C_{27}H_{36}BrNO_4$ requires C, 62.55; H, 7.0; N, 2.7%; found C, 62.6; H, 7.0; N, 2.6%; mp 54-56 °C; $[\alpha]_D^{21}$ −10.2 (*c* 1.0 in CHCl$_3$); ν_{max} (film) 1722 (C=O); δ_H (400 MHz, CDCl$_3$) 1.36 (3H, d, *J* 7.2, C(α)*Me*), 1.38 (9H, s, C*Me*$_3$), 2.10-2.26 (4H, m, C(2)*H*$_2$, C(2″)*H*$_2$), 2.59-2.77 (3H, m, C(1″)*H*$_2$, C(4)*H*$_A$), 2.97 (1H, ABdd, *J* 13.1, 6.1, C(4)*H*$_B$), 3.74-3.78 (1H, m, C(3)*H*), 3.88 (3H, s, O*Me*), 3.98 (1H, q, *J* 7.2, C(α)*H*), 4.94-5.01 (2H, m, C(4″)*H*$_2$), 5.68-5.78 (1H, m, C(3″)*H*), 6.02 (1H, br s, O*H*), 6.72 (1H, ABd, *J* 8.5, C(6′)*H*), 6.76 (1H, ABd, *J* 8.5, C(5′)*H*), 7.19-7.31 (5H, m, *Ph*); δ_C (100 MHz, CDCl$_3$) 20.1 (C(α)*Me*), 28.0 (C*Me*$_3$), 35.0 (*C*(2″)), 37.8 (*C*(2)), 38.3 (*C*(4)), 45.9 (*C*(1″)), 56.0 (*C*(3)), 56.3 (O*Me*), 57.8 (*C*(α)), 80.0 (*C*Me$_3$), 109.4 (*C*(5′)), 111.5 (*C*(2′)), 115.3 (*C*(4″)), 122.0 (*C*(6′)), 126.6, 127.7, 127.9 (*o,m,p-Ph*), 132.0 (*C*(1′)), 137.0 (*C*(3″)), 143.0 (*i-Ph*), 145.0, 145.4 (*C*(3′), *C*(4′)), 171.8 (*C*(1)); *m/z* (ESI$^+$) 520 ([M(^{81}Br)+H]$^+$, 100%), 518 ([M(^{79}Br)+H]$^+$, 95%); HRMS (ESI$^+$) $C_{27}H_{37}{}^{81}BrNO_4{}^+$ ([M(^{81}Br)+H]$^+$) requires 520.1880; found 520.1883; $C_{27}H_{37}{}^{79}BrNO_4{}^+$ ([M(^{79}Br)+H]$^+$) requires 518.1900; found 518.1899.

N-Methoxy-*N*-methyl acrylamide 184



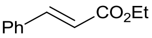
Pyridine (2.17 mL, 26.8 mmol) was added to acryloyl chloride **319** (1.00 mL, 12.3 mmol) and *N*,*O*-dimethylhydroxylammonium chloride (1.12 g, 13.4 mmol) in $CHCl_3$ (40 mL) at 0 °C and the resultant mixture stirred at 0 °C for 30 min. The reaction mixture was concentrated *in vacuo* and the residue partitioned between CH_2Cl_2 (20 mL) and brine (20 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL) and the combined organic extracts dried (Na_2SO_4) and then concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 1:2) gave **184** as a yellow oil (180 mg, 13%);[18] δ_H (400 MHz, $CDCl_3$) 3.27 (3H, s, N*Me*), 3.72 (3H, s, O*Me*), 5.76 (1H, dd, *J* 10.8, 2.3, C(3)H_A), 6.44 (1H, dd, *J* 17.3, 2.3, C(3)H_B), 6.74 (1H, dd, *J* 17.3, 10.8, C(2)*H*).

N-Methoxy-*N*-methyl cinnamamide 185



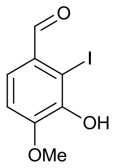
Following *general procedure 6*, PhI (48 µL, 430 µmol), **184** (81 mg, 704 µmol), $Pd(OAc)_2$ (4 mg, 18 µmol), TBAC (120 mg, 430 µmol) and K_2CO_3 (150 mg, 1.09 mmol) were reacted in DMF (3 mL) to give **185** in >99:1 dr. Purification via flash column chromatography (gradient elution, 10% → 100% Et_2O in 30-40 °C petrol) gave **185** as a yellow oil (42 mg, 51%, >99:1 dr);[19] δ_H (400 MHz, $CDCl_3$) 3.32 (3H, s, N*Me*), 3.77 (3H, s, O*Me*), 7.05 (1H, d, *J* 15.8, C(2)*H*), 7.33-7.42 (3H, m, *Ph*), 7.55-7.60 (2H, m, *Ph*), 7.75 (1H, d, *J* 15.8, C(3)*H*).

Ethyl cinnamate 187



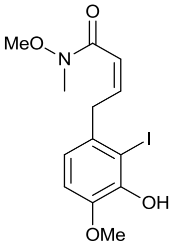
Following *general procedure 6*, PhI (0.11 mL, 1.00 mmol), ethyl acrylate **186** (0.22 mL, 704 µmol), $Pd(OAc)_2$ (9 mg, 40 µmol), TBAC (278 mg, 1.00 mmol) and K_2CO_3 (346 mg, 2.50 mmol) were reacted in DMF (10 mL) to give **187** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 9:1) gave **187** as a colourless oil (137 mg, 78%, >99:1 dr);[20] δ_H (400 MHz, $CDCl_3$) 1.35 (3H, t, *J* 7.2, OCH_2CH_3), 4.28 (2H, q, *J* 7.2, OCH_2CH_3), 6.45 (1H, d, *J* 16.0, C(2)*H*), 7.37-7.42 (3H, m, *Ph*), 7.51-7.56 (2H, m, *Ph*), 7.70 (1H, d, *J* 16.0, C(3)*H*).

2-Iodo-3-hydroxy-4-methoxybenzaldehyde 142

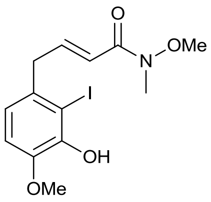


A solution of ICl (5.36 g, 33.0 mmol) in CH_2Cl_2 (30 mL) was added to isovanillin **157** (5.00 g, 33.0 mmol) in pyridine (20 mL) at 0 °C over 15 min and the resultant mixture allowed to warm to rt and stirred for 96 h. The reaction mixture was partitioned between sat aq $CuSO_4$ (100 mL) and CH_2Cl_2 (50 mL) and the aqueous layer extracted with CH_2Cl_2 (50 mL). The combined organic extracts were washed with sat aq $CuSO_4$ (50 mL), H_2O (100 mL), 5% aq $NaHSO_3$ (100 mL) and brine (100 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 2:1) gave **142** as a white solid (3.74 g, 41%);[21] mp 171-173 °C; {lit.[22] mp 167-169 °C}; δ_H (400 MHz, $CDCl_3$) 4.01 (3H, s, O*Me*), 6.30 (1H, s, O*H*), 6.94 (1H, d, *J* 8.5, C(6)*H*), 7.57 (1H, d, *J* 8.5, C(5)*H*), 10.05 (1H, s, C*H*O).

N-Methoxy-*N*-methyl (*Z*)- and (*E*)-4-(2′-iodo-3′-hydroxy-4′-methoxyphenyl)but-2-enamide (*Z*)-190 and (*E*)-191



(*Z*)-**190**



(*E*)-**191**

Method A - step 1: Following *general procedure 1*, KO^{t}Bu (2.12 g, 18.9 mmol), **142** (1.75 g, 6.29 mmol) and **165** (2.19 g, 6.38 mmol) were reacted in THF (45 mL) to give **188** as a brown oil (3.34 g).

Step 2: Following *general procedure 2*, HCO_2H (8.0 mL) and **188** (3.34 g) were reacted in CH_2Cl_2 (13 mL) to give **189** as a brown oil (3.50 g).

Step 3: Following *general procedure 3*, **173** (2.29 g, 6.30 mmol) and **189** (3.50 g) were reacted in CH_2Cl_2 (200 mL) to give ~35:65 mixture of (*Z*)-**190** and (*E*)-**191**. Purification via flash column chromatography (gradient elution, 20% → 55% EtOAc in 30-40 °C petrol) gave (*Z*)-**190** as a yellow oil (139 mg, 6% over 3 steps, >99:1 dr); ν_{max} (ATR) 3332 (O−H), 1648 (C=O); δ_H (400 MHz, $CDCl_3$) 3.24 (3H, s, N*Me*), 3.69 (3H, s, NO*Me*), 3.84 (3H, s, C(4′)O*Me*), 4.09 (2H, d, *J* 7.0, C(4)H_2), 6.17 (2H, dt, *J* 11.6, 7.0, C(3)*H*), 6.31-6.39 (2H, m, C(2)*H*, O*H*), 6.75 (1H, ABd, *J* 8.1, C(5′)*H*), 6.87 (1H, ABd, *J* 8.1, C(6′)*H*); δ_C (100 MHz, $CDCl_3$) *32.1* (N*Me*), 39.4 (*C*(4)), 56.4 (C(4′)O*Me*), 61.7 (NO*Me*), 88.2 (*C*(2′)), 110.6 (*C*(6′)), *118.4* (*C*(2)), 120.8 (*C*(5′)), 135.8 (*C*(1′)), 144.4, 145.7

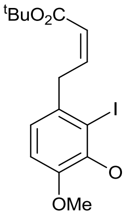
(*C*(3′), *C*(4′)), *144.6* (*C*(3)), *167.3* (*C*(1)); *m/z* (ESI$^+$) 400 ([M+Na]$^+$, 100%), 378 ([M+H]$^+$, 8%); HRMS (ESI$^+$) $C_{13}H_{16}INNaO_4^+$ ([M+Na]$^+$) requires 400.0016; found 400.0009. Further elution gave (*E*)-**191** as a yellow oil (546 mg, 23% over 3 steps, >99:1 dr); ν_{max} (film) 3211 (O−H), 1639 (C=O); δ_H (400 MHz, $CDCl_3$) 3.16 (3H, s, N*Me*), 3.57 (2H, d, *J* 6.8, C(4)*H*$_2$), 3.60 (3H, s, NO*Me*), 3.75 (3H, s, C(4′)O*Me*), 6.35 (1H, d, *J* 15.4, C(2)*H*), 6.65 (1H, ABd, *J* 8.2, C(6′)*H*), 6.68 (1H, ABd, *J* 8.2, C(5′)*H*), 6.75 (1H, s, O*H*), 6.98 (1H, dt, *J* 15.4, 6.8, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 32.4 (N*Me*), 42.7 (*C*(4)), 56.3 (C(4′)O*Me*), 61.9 (NO*Me*), 88.7 (*C*(2′)), 110.6 (*C*(6′)), 120.2 (*C*(2)), 120.5 (*C*(5′)), 133.8 (*C*(1′)), 144.6, 145.9 (*C*(3′), *C*(4′)), 144.8 (*C*(3)), 166.7 (*C*(1)); *m/z* (ESI$^+$) 400 ([M+Na]$^+$, 100%), 378 ([M+H]$^+$, 33%); HRMS (ESI$^+$) $C_{13}H_{16}INNaO_4^+$ ([M+Na]$^+$) requires 400.0016; found 400.0024.

Method B - step 1: Following *general procedure 1*, KO^{t}Bu (1.64 g, 14.6 mmol), **142** (1.32 g, 4.75 mmol) and **165** (1.64 g, 4.77 mmol) were reacted in THF (35 mL) to give **188** as a brown oil (1.11 g).

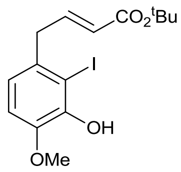
Step 2: Following *general procedure 2*, HCO_2H (1.24 mL) and **188** (1.11 g) were reacted in CH_2Cl_2 (4.5 mL) to give **189** as a brown oil (956 mg).

Step 3: Following *general procedure 4*, MeMgBr (2.4 M, 2.73 mL, 6.54 mmol), **174** (1.57 g, 6.54 mmol) and **189** (956 mg) were reacted in THF (100 mL) to give (*E*)-**191** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 1:1) gave (*E*)-**191** as a yellow oil (203 mg, 11% over 3 steps, >99:1 dr).

***tert*-Butyl (*Z*)- and (*E*)-4-(2′-iodo-3′-hydroxy-4′-methoxyphenyl)but-2-enoate (*Z*)-192 and (*E*)-193**



(*Z*)-**192**



(*E*)-**193**

Method A - step 1: Following *general procedure 1*, KO^{t}Bu (2.12 g, 18.9 mmol), **142** (1.75 g, 6.29 mmol) and **165** (2.19 g, 6.38 mmol) were reacted in THF (45 mL) to give **188** as a brown oil (3.34 g).

Step 2: Following *general procedure 2*, HCO_2H (8.0 mL) and **188** (3.34 g) were reacted in CH_2Cl_2 (13 mL) to give **189** as a brown oil (3.50 g).

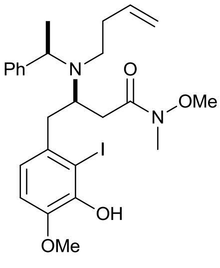
Step 3: Following *general procedure 3*, **181** (2.37 g, 6.30 mmol) and **189** (3.50 g) were reacted in CH_2Cl_2 (200 mL) to give an 17:83 mixture of (*Z*)-**192** and (*E*)-**193**. Purification via flash column chromatography (gradient elution, 15% → 35% Et_2O in 30-40 °C petrol) gave (*Z*)-**192** as a colourless oil (147 mg, 6% over 3 steps, >99:1 dr); *ν*$_{max}$ (ATR) 3467 (O−H), 1707 (C=O); δ_H (400 MHz, $CDCl_3$) 1.51 (9H, s, C*Me*$_3$), 3.86 (3H, s, O*Me*), 4.08 (2H, dd, *J* 7.1, 1.5, C(4)*H*$_2$), 5.79 (1H, d, *J* 11.5, C(2)*H*), 6.16 (1H, dt, *J* 11.5, 7.1, C(3)*H*), 6.27 (1H, s, O*H*), 6.77 (1H, ABd, *J* 8.2, C(6′)*H*), 6.82 (1H, ABd, *J* 8.2, C(5′)*H*); δ_C (100 MHz, $CDCl_3$) 28.3 (C*Me*$_3$), 39.2 (*C*(4)), 56.4 (O*Me*), 80.4 (*C*Me$_3$), 88.2 (*C*(2′)), 110.5 (*C*(5′)), 120.5 (*C*(6′)), 122.0 (*C*(2)), 135.5 (*C*(1′)), 144.4, 145.7 (*C*(3′), *C*(4′)), 145.6 (*C*(3)), 165.9 (*C*(1)); *m/z* (ESI^+) 413 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{15}H_{19}INaO_4^+$ ($[M+Na]^+$) requires 413.0220; found 413.0216. Further elution gave (*E*)-**193** as a white solid (622 mg, 25% over 3 steps, >99:1 dr); $C_{15}H_{19}IO_4$ requires C, 46.2; H, 4.9%; found C, 46.3; H, 4.8%; mp 128-130 °C; *ν*$_{max}$ (film) 3393 (O−H), 1696 (C=O); δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s, C*Me*$_3$), 3.56 (2H, d, *J* 6.5, C(4)*H*$_2$), 3.81 (3H, s, O*Me*), 5.67 (1H, d, *J* 15.6, C(2)*H*), 6.45 (1H, s, O*H*), 6.69 (1H, ABd, *J* 7.5, C(6′)*H*), 6.74 (1H, ABd, *J* 7.5, C(5′)*H*), 6.90 (1H, dt, *J* 15.6, 6.5, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 28.1 (C*Me*$_3$), 42.3 (*C*(4)), 56.3 (O*Me*), 80.2 (*C*Me$_3$), 88.4 (*C*(2′)), 110.5 (*C*(5′)), 120.7 (*C*(6′)), 124.2 (*C*(2)), 133.7 (*C*(1′)), 144.6, 145.9 (C(3′), C(4′)), 145.2 (*C*(3)), 165.9 (*C*(1)); *m/z* (ESI^+) 413 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{15}H_{19}INaO_4^+$ ($[M+Na]^+$) requires 413.0220; found 413.0214.

Method B - step 1: Following *general procedure 1*, KO^{t}Bu (1.64 g, 14.6 mmol), **142** (1.32 g, 4.75 mmol) and **165** (1.64 g, 4.77 mmol) were reacted in THF (35 mL) to give **188** as a brown oil (1.11 g).

Step 2: Following *general procedure 2*, HCO_2H (1.24 mL) and **188** (1.11 g) were reacted in CH_2Cl_2 (4.5 mL) to give **189** as a brown oil (956 mg).

Step 3: Following *general procedure 3*, MeMgBr (2.4 M, 2.73 mL, 6.54 mmol), **182** (1.54 mL, 6.54 mmol) and **189** (956 mg) were reacted in THF (100 mL) to give **193** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 2:1) gave **193** as a white solid (331 mg, 18% over 3 steps, >99:1 dr).

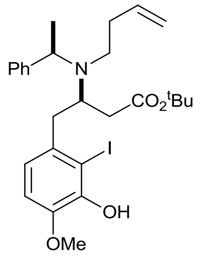
N-methoxy-*N*-methyl (*R*,*R*)-3-[*N′*-but-3″-enyl-*N′*-(α-methylbenzyl)amino]-4-(2′-iodo-3′-hydroxy-4′-methoxyphenyl)butanamide 194



Following *general procedure 5*, **152** (217 mg, 1.24 mmol, >99:1 er), BuLi (2.1 M, 0.58 mL, 1.22 mmol) and **191** (180 mg, 461 μmol, >99:1 dr) were reacted in THF (10 mL) to give **194** in

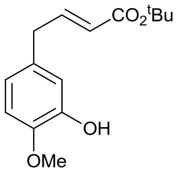
>99:1 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/Et$_2$O, 1:9) gave **194** as a yellow gum (265 mg, quant, >99:1 dr); $[\alpha]_D^{21}$ −6.3 (*c* 0.7 in CHCl$_3$); ν_{max} (ATR) 1656 (C=O); δ_H (400 MHz, CDCl$_3$) 1.33 (3H, d, *J* 6.8, C(α)*Me*), 2.26 (3H, app q, *J* 7.3, C(2″)H_2, C(2)H_A), 2.40-2.47 (1H, m, C(2)H_B), 2.62-2.70 (1H, m, C(1″)H_A), 2.78-2.85 (2H, m, C(4)H_A, C(1″)H_B), 2.98-3.09 (1H, m, C(4)H_B) overalapping 3.01 (3H, br s, N*Me*), 3.39 (3H, br s, NO*Me*), 3.80-3.90 (1H, m, C(3)*H*), 3.90 (3H, s, C(4′)O*Me*), 4.03 (1H, q, *J* 6.8, C(α)*H*), 4.96-5.05 (2H, m, C(4″)H_2), 5.73-5.84 (1H, m, C(3″)*H*), 6.75-6.80 (2H, m, C(5′)*H*, C(6′)*H*), 7.16-7.29 (5H, m, *Ph*); δ_C (100 MHz, CDCl$_3$) 19.9 (C(α)*Me*), 32.1 (N*Me*), 33.8 (*C*(2)), 34.9 (*C*(2″)), 42.3 (*C*(4)), 45.7 (*C*(1″)), 55.9 (*C*(3)), 56.4 (C(4′)O*Me*), 57.3 (*C*(α)), 60.9 (NO*Me*), 89.6 (*C*(2′)), 110.1 (*C*(5′)), 115.3 (*C*(4″)), 121.8 (*C*(6′)), 126.4, 127.7, 127.9 (*o,m,p-Ph*), 135.7 (*C*(1′)), 137.2 (*C*(3″)), 144.1 (*i-Ph*), 145.2, 145.3 (*C*(3′), *C*(4′)), 173.2 (*C*(1)); *m/z* (ESI$^+$) 553 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{34}IN_2O_4^+$ ([M+H]$^+$) requires 553.1558; found 553.1560.

***tert*-Butyl (*R*,*R*)-3-[*N*-but-3″-enyl-*N*-(α-methylbenzyl)amino]-4-(2′-iodo-3′-hydroxy-4′-methoxyphenyl)butanoate 195**



Following *general procedure 5*, **152** (351 mg, 2.00 mmol, >99:1 er), BuLi (2.1 M, 0.93 mL, 1.96 mmol) and **193** (300 mg, 0.77 mmol, >99:1 dr) were reacted in THF (14 mL) to give **195** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/Et$_2$O, 1:1) gave **195** as a yellow gum (305 mg, 70%, >99:1 dr); $[\alpha]_D^{25}$ −12.1 (*c* 1.0 in CHCl$_3$); ν_{max} (film) 3509 (O−H), 1723 (C=O); δ_H (400 MHz, CDCl$_3$) 1.35-1.40 (12H, m, C*Me*$_3$, C(α)*Me*), 2.12-2.21 (3H, m, C(2)H_A, C(2″)H_2), 2.28 (1H, ABdd, *J* 14.7, 7.6, C(2)H_B), 2.61-2.82 (3H, m, C(4)H_A, C(1″)H_2), 3.04 (1H, ABdd, *J* 13.5, 5.9, C(4)H_B), 3.76-3.83 (1H, m, C(3)*H*), 3.87 (3H, s, O*Me*), 4.01 (1H, q, *J* 6.8, C(α)*H*), 4.94-5.02 (2H, m, C(4″)H_2), 5.69-5.79 (1H, m, C(3″)*H*), 6.74 (1H, ABd, *J* 8.3, C(6′)*H*), 6.77 (1H, ABd, *J* 8.3, C(5′)*H*), 7.20-7.35 (5H, m, *Ph*); δ_C (100 MHz, CDCl$_3$) 20.2 (C(α)*Me*), 28.1 (C*Me*$_3$), 35.0 (*C*(2″)), 38.2 (*C*(2)), 41.8 (*C*(4)), 45.9 (*C*(1″)), 56.3 (*C*(3)), 56.4 (O*Me*), 57.7 (*C*(α)), 89.4 (*C*(2′)), 110.3 (*C*(5′)), 115.3 (*C*(4″)), 121.8 (*C*(6′)), 126.6, 127.8, 128.0 (*o,m,p-Ph*), 135.2 (*C*(1′)), 137.1 (*C*(3″)), 144.2 (*i-Ph*), 145.1, 145.4 (*C*(3′), *C*(4′)), 171.8 (*C*(1)); *m/z* (ESI$^+$) 566 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{37}INO_4^+$ ([M+H]$^+$) requires 566.1762; found 556.1760.

tert-Butyl (*E*)-4-(3′-hydroxy-4′-methoxyphenyl)but-2-enoate 199

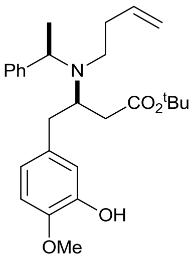


Step 1: Following *general procedure 1*, KO^tBu (4.52 g, 40.3 mmol), **157** (2.00 g, 13.1 mmol) and **165** (4.52 g, 13.2 mmol) were reacted in THF (90 mL) to give **197** as a yellow solid (3.18 g).

Step 2: Following *general procedure 2*, HCO_2H (4.9 mL) and **197** (3.18 g) were reacted in CH_2Cl_2 (15 mL) to give **198** as a brown oil (2.96 g).

Step 3: Following *general procedure 4*, MeMgBr (2.6 M, 10.1 mL, 26.3 mmol), **182** (6.20 mL, 26.3 mmol) and **198** (2.96 g) were reacted in THF (250 mL) to give **199** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 2:1) gave **199** as a white solid (412 mg, 12% over 3 steps, >99:1 dr); mp 62-64 °C; ν_{max} (KBr) 3430 (O−H), 1709 (C=O), 1651 (C=C); δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, C*Me*$_3$), 3.39 (2H, dd, *J* 6.5, 1.5, C(4)*H*$_2$), 3.87 (3H, s, O*Me*), 5.72 (1H, dd, *J* 15.6, 1.5, C(2)*H*), 6.66 (1H, ABdd, *J* 8.2, 2.2, C(6′)*H*), 6.76 (1H, d, *J* 2.2, C(2′)*H*), 6.80 (1H, ABd, *J* 8.2, C(5′)*H*), 6.96 (1H, dt, *J* 15.6, 6.5, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 28.1 (C*Me*$_3$), 37.2 (*C*(4)), 56.0 (O*Me*), 80.2 (*C*Me$_3$), 110.8 (*C*(5′)), 115.1 (*C*(2′)), 120.2 (*C*(6′)), 123.8 (*C*(2)), 131.1 (*C*(1′)), 145.3, 145.7 (*C*(3′), *C*(4′)), 146.3 (*C*(3)), 165.9 (*C*(1)); *m/z* (ESI^+) 815 ($[3M+Na]^+$, 38%), 551 ($[2M+Na]^+$, 100%), 287 ($[M+Na]^+$, 61%); HRMS (CI^+) $C_{15}H_{20}NaO_4^+$ ($[M+Na]^+$) requires 287.1254; found 287.1254.

tert-Butyl (*R*,*R*)-3-[*N*-but-3″-enyl-*N*-(α-methylbenzyl)amino]-4-(3′-hydroxy-4′-methoxyphenyl)butanoate 196



Method A: Following *general procedure 5*, **152** (545 mg, 3.11 mmol, >99:1 er), BuLi (2.5 M, 1.22 mL, 3.06 mmol) and **199** (314 mg, 1.20 mmol, >99:1 dr) were reacted in THF (15 mL) to give **196** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 3:7) gave **196** as a colourless oil (375 mg, 71%, >99:1 dr); $C_{27}H_{37}NO_4$ requires C, 73.8; H, 8.5; N, 3.2%; found C, 73.8; H, 8.5; N, 3.1%; $[\alpha]_D^{25}$ −12.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3437 (O−H), 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.34 (3H, d, *J* 6.8, C(α)*Me*), 1.40 (9H, s, C*Me*$_3$), 2.02-2.21 (2H, m, C(2″)*H*$_2$) overlapping 2.15 (2H, app d, *J* 6.8, C(2)*H*$_2$), 2.43 (1H, ABdd, *J* 13.3, 8.1, C(4)*H*$_A$), 2.57-2.65

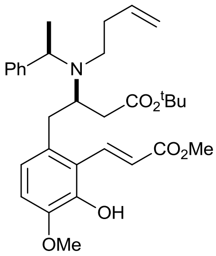
(2H, m, C(1″)*H*$_2$), 2.74 (1H, ABdd, *J* 13.3, 6.1, C(4)*H*$_B$), 3.57 (1H, app quin, *J* 7.1, C(3)*H*), 3.88 (3H, s, O*Me*), 3.93 (1H, q, *J* 6.8, C(α)*H*), 4.93-5.01 (2H, m, C(4″)*H*$_2$), 5.58 (1H, s, O*H*), 5.67-5.77 (1H, m, C(3″)*H*), 6.63 (1H, ABdd, *J* 8.1, 1.8, C(6′)*H*), 6.74 (1H, d, *J* 1.8, C(2′)*H*), 6.77 (1H, ABd, *J* 8.1, C(5′)*H*), 7.18-7.32 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.4 (C(α)*Me*), 28.1 (C*Me*$_3$), 35.2 (*C*(2″)), 37.5 (*C*(4)), 38.2 (*C*(2)), 46.1 (*C*(1″)), 56.0 (O*Me*), 58.0 (*C*(3)), 58.7 (*C*(α)), 80.0 (*C*Me$_3$), 110.5 (*C*(5′)), 115.2 (*C*(4″)), 115.6 (*C*(2′)), 120.8 (*C*(6′)), 126.6, 127.7, 128.0 (*o,m,p-Ph*), 133.4 (*C*(1′)), 137.1 (*C*(3″)), 144.9 (*i-Ph*), 145.1, 145.3 (*C*(3′), *C*(4′)), 172.0 (*C*(1)); *m/z* (ESI$^+$) 901 ([2M+Na]$^+$, 70%); 462 ([M+Na]$^+$, 100%), 440 ([M+H]$^+$, 74%); HRMS (ESI$^+$) $C_{27}H_{38}NO_4^+$ ([M+H]$^+$) requires 440.2795; found 440.2793.

Method B: $Pd(OAc)_2$ (2 mg, 9 µmol) in DMF (10 mL) was added to **195** (100 mg, 177 µmol, >99:1 dr), TBAC (49 mg, 177 µmol) and $NaHCO_3$ (37 mg, 443 µmol) at rt and the resultant mixture stirred and heated at 90 °C for 48 h. The reaction mixture as allowed to cool to rt and then partitioned between H_2O (20 mL) and Et_2O (20 mL). The aqueous layer was extracted with Et_2O (2 × 20 mL) and the combined organic extracts were washed with H_2O (2 × 30 mL) and brine (30 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 9% → 75% Et_2O in 30-40 °C petrol) gave **196** as a yellow oil (23 mg, 29%, >99:1 dr).

Method C: $Pd_2(dba)_3 \cdot CHCl_3$ (9 mg, 9 µmol) in DMF (10 mL) was added to **195** (100 mg, 177 µmol, >99:1 dr), Cy_2NMe (75 µL, 354 µmol) and PBu_3 (9 µL, 35 µmol) at rt and the resultant mixture was stirred and heated at 90 °C for 48 h. The reaction mixture was allowed to cool to rt and then partitioned between H_2O (20 mL) and Et_2O (20 mL). The aqueous layer was extracted with Et_2O (2 × 20 mL) and the combined organic extracts were washed with H_2O (2 × 30 mL) and brine (30 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 9% → 75% Et_2O in 30-40 °C petrol) gave **196** as a yellow oil (26 mg, 33%, >99:1 dr).

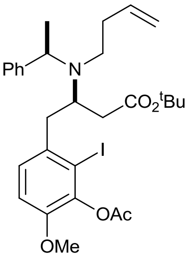
Method D: $Pd(PPh_3)_4$ (10 mg, 9 µmol) in MeCN (10 mL) was added to **195** (100 mg, 177 µmol, >99:1 dr) and K_2CO_3 (73 mg, 531 µmol) at rt and the resultant mixture sealed in a tube. The reaction mixture was stirred and heated at 90 °C for 48 h. The reaction mixture was allowed to cool to rt and then Et_2O (10 mL) was added. The resultant mixture was filtered through Celite® (eluent Et_2O then H_2O) and the aqueous layer was extracted with Et_2O (2 × 15 mL). The combined organic extracts were washed with H_2O (30 mL) and brine (30 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 9% → 75% Et_2O in 30-40 °C petrol) gave **196** as a yellow oil (41 mg, 53%, >99:1 dr).

***tert*-Butyl (*R*,*R*,*E*)-3-[*N*-but-3″-enyl-*N*-(α-methylbenzyl)amino]-4-[2′-(3‴-methoxy-3‴-oxoprop-1‴-en-1‴-yl)-3′-hydroxy-4′-methoxyphenyl]butanoate 200**



$Pd(PPh_3)_4$ (10 mg, 9 µmol) in MeCN (2 mL) was added to **195** (100 mg, 177 µmol, >99:1 dr) and K_2CO_3 (73 mg, 531 µmol) at rt and the resultant mixture sealed in a tube. The reaction mixture was heated at 90 °C for 72 h. The reaction mixture was allowed to cool to rt and then Et_2O (10 mL) was added. The resultant mixture was filtered through Celite® (eluent Et_2O) and the filtrate concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 6% → 48% Et_2O in 30-40 °C petrol) gave **200** as a yellow oil (23 mg, 25%, >99:1 dr); $[\alpha]_D^{24}$ −10.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1718 (C=O), 1627 (C=C); δ_H (400 MHz, $CDCl_3$) 1.35 (9H, s, C*Me*$_3$), 1.37 (3H, d, *J* 6.7, C(α)*Me*), 2.03-2.18 (4H, m, C(2)*H*$_2$, C(2″)*H*$_2$), 2.56-2.70 (3H, m, C(4)*H*$_A$, C(1″)*H*$_2$), 3.06 (1H, dd, *J* 13.4, 5.5, C(4)*H*$_B$), 3.57-3.64 (1H, m, C(3)*H*), 3.80 (3H, s, C(3‴)O*Me*), 3.90 (3H, s, C(4′)O*Me*), 3.98 (1H, q, *J* 6.7, C(α)*H*), 4.90-4.97 (2H, m, C(4″)*H*$_2$), 5.70 (1H, app tt, *J* 10.2, 6.8, C(3″)*H*), 6.33 (1H, br s, O*H*), 6.68 (1H, ABd, *J* 8.2, C(6′)*H*), 6.78 (1H, ABd, *J* 8.2, C(5′)*H*), 6.92 (1H, d, *J* 16.0, C(2‴)*H*), 7.17-7.31 (5H, m, *Ph*), 7.90 (1H, d, *J* 16.0, C(1‴)*H*); δ_C (100 MHz, $CDCl_3$) 19.9 (C(α)*Me*), 28.0 (C*Me*$_3$), 34.7 (*C*(2″)), 35.5 (*C*(4)), 38.2 (*C*(2)), 46.1 (*C*(1″)), 51.5 (C(3‴)O*Me*), 56.2 (C(4′)O*Me*), 57.1 (*C*(3)), 57.6 (*C*(α)), 80.0 (*C*Me$_3$), 111.1 (*C*(5′)), 115.1 (*C*(4″)), 121.9 (*C*(6′)), 122.9 (*C*(2‴)), 126.6, 127.7, 127.9 (*o,m,p-Ph*), 128.3, 128.6 (*C*(1′), *C*(2′)), 137.0 (*C*(3″)), 138.2 (*C*(1‴)), 144.7 (*i-Ph*), 145.0, 145.7 (*C*(3′), *C*(4′)), 168.2 (*C*(3‴)), 171.7 (*C*(1)); *m/z* (ESI^+) 546 ($[M+Na]^+$, 19%), 524 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{31}H_{42}NO_6^+$ ($[M+H]^+$) requires 524.3007; found 524.2991.

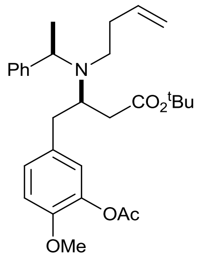
***tert*-Butyl (*R*,*R*)-3-[*N*-but-3″-enyl-*N*-(α-methylbenzyl)amino]-4-(2′-iodo-3′-acetoxy-4′-methoxyphenyl)butanoate 201**



Ac_2O (0.31 mL, 3.22 mmol) was added to **195** (913 mg, 1.61 mmol) in pyridine (11 mL) at rt and the resultant mixture stirred for 16 h. The reaction mixture was partitioned between sat aq $CuSO_4$

(40 mL) and CH_2Cl_2 (40 mL) and the aqueous layer extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extracts were washed with H_2O (60 mL) and brine (60 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 15% → 65% Et_2O in 30-40 °C petrol) gave **201** as a yellow oil (900 mg, 92%, >99:1 dr); $C_{29}H_{38}INO_5$ requires C, 57.3; H, 6.3; N, 2.3%; found C, 57.4; H, 6.2; N, 2.2%; $[\alpha]_D^{24}$ −11.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1775 (C(3′)OC=O), 1722 (C(1)=O); δ_H (400 MHz, $CDCl_3$) 1.34 (3H, d, *J* 6.8, C(α)*Me*), 1.39 (9H, s, C*Me*$_3$), 2.06-2.25 (4H, m, C(2)*H*$_2$, C(2″)*H*$_2$), 2.39 (3H, s, CO*Me*), 2.59-2.76 (2H, m, C(4)*H*$_2$), 2.80 (1H, ABdd, *J* 13.6, 8.6, C(1″)*H*$_A$), 3.00 (1H, ABdd, *J* 13.6, 6.6, C(1″)*H*$_B$), 3.76 (1H, app quin, *J* 7.1, C(3)*H*), 3.82 (3H, s, C(4′)O*Me*), 3.97 (1H, q, *J* 6.8, C(α)*H*), 4.93-5.03 (2H, m, C(4″)*H*$_2$), 5.74 (1H, app td, *J* 10.4, 6.8, C(3″)*H*), 6.88 (1H, ABd, *J* 8.5, C(5′)*H*), 7.04 (1H, ABd, *J* 8.5, C(6′)*H*), 7.19-7.32 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.1 (C(α)*Me*), 21.0 (*Me*CO), 28.1 (C*Me*$_3$), 34.9 (*C*(2″)), 38.1 (*C*(2)), 42.1 (*C*(4)), 45.8 (*C*(1″)), 56.1 (*C*(3)), 56.2 (C(4′)O*Me*), 57.8 (*C*(α)), 80.1 (*C*Me$_3$), 99.3 (*C*(2′)), 111.8 (*C*(5′)), 115.3 (*C*(4″)), 126.7 (*C*(6′)), 127.7, 128.0, 128.2 (*o,m,p-Ph*), 135.4 (*C*(1′)), 137.0 (*C*(3″)), 140.4 (*i-Ph*), 144.7 (*C*(4′)), 149.7 (*C*(3′)), 167.9 (*C*OMe), 171.7 (*C*(1)); *m/z* (ESI^+) 630 ($[M+Na]^+$, 60%), 608 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{29}H_{39}INO_5^+$ ($[M+H]^+$) requires 608.1867; found 608.1868.

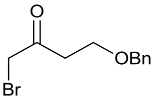
tert-Butyl (*R*,*R*)-3-[*N*-but-3″-enyl-*N*-(α-methylbenzyl)amino]-4-(3′-acetoxy-4′-methoxyphenyl)butanoate 320



Ac_2O (43 μL, 455 μmol) was added to **196** (50 mg, 114 μmol) in pyridine (1 mL) at rt and the resultant mixture stirred for 4 h. The reaction mixture was partitioned between CH_2Cl_2 (20 mL) and sat aq $CuSO_4$ (20 mL) and the aqueous layer extracted with CH_2Cl_2 (2 × 15 mL). The combined organic extracts were washed with H_2O (40 mL) and brine (40 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 15% → 65% Et_2O in 30-40 °C petrol) gave **320** as a yellow oil (37 mg, 70%, >99:1 dr); $[\alpha]_D^{24}$ −15.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1769 (C(3′)OC=O), 1725 (C(1)=O); δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, *J* 6.8, C(α)*Me*), 1.41 (9H, s, C*Me*$_3$), 2.05-2.24 (2H, m, C(2″)*H*$_2$), 2.10 (2H, d, *J* 6.6, C(2)*H*$_2$), 2.33 (3H, s, CO*Me*), 2.48 (1H, ABdd, *J* 13.5, 7.1, C(4)*H*$_A$), 2.61 (2H, t, *J* 7.6, C(1″)*H*$_2$), 2.71 (1H, ABdd, *J* 13.5, 7.1, C(4)*H*$_B$), 3.54 (1H, app quin, *J* 6.8, C(3)*H*), 3.83 (3H, s, O*Me*), 3.90 (1H, q, *J* 6.8, C(α)*H*), 4.94-5.03

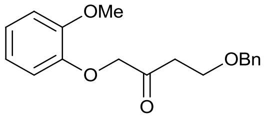
(2H, m, C(4″)H_2), 5.69-5.79 (1H, m, C(3″)*H*), 6.85 (1H, s, C(2′)*H*), 6.88 (1H, ABd, *J* 8.3, C(6′)*H*), 6.98 (1H, ABd, *J* 8.3, C(5′)*H*), 7.19-7.28 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.3 (C(α)*Me*), 20.7 (CO*Me*), 28.1 (C*Me*$_3$), 35.0 (*C*(2″)), 37.5 (*C*(4)), 37.9 (*C*(2)), 46.0 (*C*(1″)) 56.0 (O*Me*), 57.5 (*C*(3)), 58.6 (*C*(α)), 80.1 (*C*Me$_3$), 112.1 (*C*(6′)), 115.3 (*C*(4″)), 123.8 (*C*(2′)), 126.7, 127.5, 127.7 (*o,m,p-Ph*), 128.0 (*C*(5′)), 132.9 (*C*(1′)), 137.0 (*C*(3″)), 139.3 (*C*(4′)), 144.6 (*i-Ph*), 149.3 (*C*(3′)), 169.0 (*C*OMe), 171.9 (*C*(1)); *m/z* (ESI$^+$) 504 ([M+Na]$^+$, 35%), 482 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{40}NO_5^+$ ([M+H]$^+$) requires 482.2901; found 482.2894.

1-Bromo-4-benzyloxybutan-2-one 212



Br_2 (7.77 mL, 152 mmol) was added to 4-benzyloxybutan-2-one **321** (26.3 mL, 151 mmol) in MeOH (100 mL) at 4 °C and the resultant mixture stirred for 1.5 h. 1.0 M aq K_2CO_3 (260 mL) was added and the reaction mixture concentrated *in vacuo* to a volume of ~250 mL. Et_2O (250 mL) and PhMe (250 mL) were added, and the organic layer washed with 1.0 M aq K_2CO_3 (400 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved in THF (525 mL) and 1.0 M aq H_2SO_4 (315 mL) was added. The reaction mixture was heated at reflux for 1.5 h and then allowed to cool to rt. Et_2O (400 mL) was added and the organic layer washed with 2.0 M aq K_2CO_3 (400 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 9:1) gave **212** as a yellow oil (18.0 g, 46%);[23] δ_H (400 MHz, $CDCl_3$) 2.93 (2H, t, *J* 6.1, C(3)H_2), 3.78 (2H, t, *J* 6.1, C(4)H_2), 3.96 (2H, s, C(1)H_2), 4.52 (2H, s, PhCH_2), 7.27-7.39 (5H, m, *Ph*).

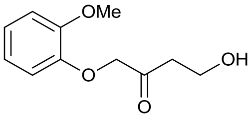
1-(2′-Methoxyphenoxy)-4-benzyloxybutan-2-one 209



NaH (326 mg, 13.6 mmol) was added to **208** (1.53 g, 12.3 mmol) in DMF (40 mL) at rt and the reaction mixture stirred for 15 min. A solution of **212** (3.17 g, 12.3 mmol) in DMF (40 mL) was added and the reaction mixture was stirred at rt for 16 h. The reaction mixture was partitioned between H_2O (40 mL) and Et_2O (60 mL) and the aqueous layer extracted with Et_2O (2 × 60 mL). The combined organic extracts were washed with H_2O (2 × 100 mL) and brine (100 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 2:1) gave **209** as a white solid (2.87 g, 78%); $C_{18}H_{20}O_4$ requires C, 72.0; H, 6.7%; found C, 72.1; H, 6.6%; mp 37-39 °C; ν_{max} (ATR) 1728 (C=O); δ_H (400 MHz, $CDCl_3$)

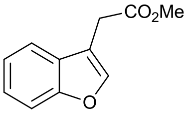
2.89 (2H, t, *J* 6.1, C(3)*H*$_2$), 3.81 (2H, t, *J* 6.1, C(4)*H*$_2$), 3.88 (3H, s, C(2′)O*Me*), 4.53 (2H, s, OC*H*$_2$Ph), 4.68 (2H, s, C(1)*H*$_2$), 6.76 (1H, ABdd, *J* 7.9, 1.6, C(3′)*H*), 6.83 (1H, app td, *J* 7.5, 1.7, C(4′)*H*), 6.92 (1H, app dd, *J* 7.9, 1.7, C(6′)*H*), 6.97 (1H, app ABtd, *J* 7.2, 1.6, C(5′)*H*), 7.28-7.37 (5H, m, *Ph*); δ_C (100 MHz, CDCl$_3$) 39.3 (*C*(3)), 55.8 (O*Me*), 65.0 (*C*(4)), 73.3 (O*C*H$_2$Ph), 74.5 (*C*(1)), 112.1 (*C*(6′)), 114.2 (*C*(3′)), 120.8 (*C*(4′)), 122.4 (*C*(5′)), 127.7, 127.8, 128.4 (*o,m,p-Ph*), 138.0 (*i-Ph*), 147.3 (*C*(2′)), 149.6 (*C*(1′)), 206.0 (*C*(2)); *m/z* (ESI$^+$) 623 ([2M+Na]$^+$, 100%), 323 ([M+Na]$^+$, 97%); HRMS (ESI$^+$) $C_{18}H_{20}NaO_4^+$ ([M+Na]$^+$) requires 323.1259; found 323.1254.

1-(2′-Methoxyphenoxy)-4-hydroxybutan-2-one 211



BCl$_3$ (1.0 M in CH$_2$Cl$_2$, 0.54 mL, 540 µmol) was added to **209** (135 mg, 449 µmol) in CH$_2$Cl$_2$ (3 mL) at −78 °C and the reaction mixture allowed to warm to rt over 1 h. The reaction mixture was partitioned between H$_2$O (5 mL) and CH$_2$Cl$_2$ (5 mL) and the aqueous layer extracted with CH$_2$Cl$_2$ (2 × 5 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatograph (eluent Et$_2$O) gave **211** as a yellow oil (63 mg, 67%); ν_{max} (ATR) 3534 (O−H), 1724 (C=O); δ_H (400 MHz, CDCl$_3$) 2.91 (2H, t, *J* 5.4, C(3)*H*$_2$), 3.89 (3H, s, C(2′)O*Me*), 3.93 (2H, br t, *J* 5.4, C(4)*H*$_2$), 4.63 (2H, s, C(1)*H*$_2$), 6.80 (1H, ABdd, *J* 7.9, 1.4, C(3′)*H*), 6.89 (1H, app td, *J* 7.9, 1.5, C(4′)*H*), 6.94 (1H, ABdd, *J* 8.0, 1.5, C(6′)*H*), 7.01 (1H, app ABtd, *J* 7.2, 1.4, C(5′)*H*); δ_C (100 MHz, CDCl$_3$) 41.2 (*C*(3)), 55.8 (C(2′)O*Me*), 57.5 (*C*(4)), 74.3 (*C*(1)), 112.2 (*C*(6′)), 114.4 (*C*(3′)), 120.9 (*C*(4′)), 122.7 (*C*(5′)), 147.2, 149.6 (*C*(1′), *C*(2′)), 208.7 (*C*(2)); *m/z* (ESI$^+$) 425 ([2M+Na−H$_2$O]$^+$, 100%), 233 ([M+Na]$^+$, 10%); HRMS (ESI$^+$) $C_{11}H_{14}NaO_4^+$ ([M+Na]$^+$) requires 233.0790; found 233.0777.

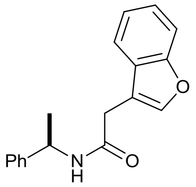
Methyl (benzofuran-3-yl)acetate 216



Step 1: Pd(OAc)$_2$ (480 mg, 2.14 mmol) in DMF (300 mL) was added to **213** (25.0 g, 114 mmol), **214** (20.8 mL, 171 mmol), ^{i}Pr$_2$NEt (39.7 mL, 228 mmol) and TEBAC (26.0 g, 114 mmol) at rt and the resultant mixture stirred and heated at 80 °C for 18 h. The reaction mixture was allowed to cool to rt, partitioned between H$_2$O (200 mL) and Et$_2$O (200 mL) and the aqueous layer extracted with Et$_2$O (2 × 300 mL). The combined organic extracts were washed with H$_2$O (2 × 400 mL) and brine (400 mL), then dried and concentrated *in vacuo* to give **215** as a brown oil (30.1 g).

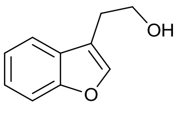
Step 2: $BF_3{\cdot}OEt_2$ (38.0 mL, 308 mmol) was added to **215** (30.1 g) in CH_2Cl_2 (400 mL) at 0 °C and the resultant mixture allowed to warm to rt over 18 h. Sat aq $NaHCO_3$ (400 mL) was added and the aqueous layer extracted with CH_2Cl_2 (2 × 300 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 3:1) gave **216** as a yellow oil (13.2 g, 61% over 2 steps);[24] δ_H (400 MHz, $CDCl_3$) 3.78 (2H, app d, *J* 1.0, C*H*$_2$), 3.79 (3H, s, O*Me*), 7.29-7.34 (1H, m, C(6)*H*), 7.37 (1H, td, *J* 8.2, 1.4, C(5)*H*), 7.53-7.56 (1H, m, C(7)*H*), 7.61-7.64 (1H, m, C(4)*H*), 7.69 (1H, br s, C(2)*H*).

(*R*)-*N*-(α-Methylbenzyl)(benzofuran-3-yl)acetamide 217



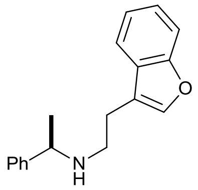
(*R*)-α-Methylbenzylamine (*R*)-**153** (1.40 mL, 11.0 mmol, 99.5:0.5 er) was added to **216** (1.40 g, 7.36 mmol) at rt and the resultant mixture stirred and heated at 130 °C for 16 h, and then heated at 150 °C for 10 h. The reaction mixture was then allowed to cool to rt. Purification via flash column chromatography (gradient elution, 25% → 75% EtOAc in 30-40 °C petrol) gave **217** as a white solid (1.53 g, 74%); $C_{18}H_{17}NO_2$ requires C, 77.4; H, 6.1; N, 5.0%; found C, 77.5; H, 6.0; N, 4.9%; mp 114-116 °C; $[\alpha]_D^{25}$ +9.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1646 (C=O); δ_H (400 MHz, $CDCl_3$) 1.39 (3H, d, *J* 7.1, C(α)*Me*), 3.58 (2H, s, C*H*$_2$), 5.14 (1H, app quin, *J* 7.3, C(α)*H*), 6.41 (1H, br d, *J* 7.8, N*H*), 7.18-7.36 (7H, m, *Ph*, *Ar*), 7.49-7.56 (3H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 21.7 (C(α)*Me*), 31.7 (*C*H$_2$), 48.9 (*C*(α)), 111.7 (*C*(7)), 114.1 (*C*(3)), 119.7 (*C*(4)), 122.8, 124.8, 126.1, 127.3, 127.4, 128.6 (*Ar*, *o,m,p-Ph*), 143.1 (*C*(2), *i-Ph*), 155.4 (*C*(7a)), 169.0 (*C*O); *m/z* (FI^+) 279 ($[M]^+$, 100%), HRMS (FI^+) $C_{18}H_{17}NO_2^+$ ($[M]^+$) requires 279.1254; found 279.1253.

2-(Benzofuran-3′-yl)ethanol 219



$LiAlH_4$ (150 mg, 3.94 mmol) was added to **216** (750 mg, 3.94 mmol) in Et_2O (8 mL) at 0 °C and the resultant mixture stirred for 1 h. Ice (~1 g) was cautiously added, followed by H_2O (10 mL), and the aqueous layer extracted with Et_2O (2 × 15 mL). The combined organic extracts were washed with 1.0 M aq HCl (20 mL), dried and concentrated *in vacuo* to give **219** as a yellow oil (602 mg, 94%);[25] δ_H (400 MHz, $CDCl_3$) 2.97 (2H, app dt, *J* 6.3, 1.0, C(2)*H*$_2$), 3.95 (1H, app q, *J* 4.8, C(1)*H*$_2$), 7.27 (1H, dd, *J* 7.5, 1.0, C(7′)*H*), 7.32 (1H, app td, *J* 7.6, 1.1, C(6′)*H*), 7.48-7.51 (1H, m, C(5′)*H*), 7.53 (1H, br s, C(2′)*H*), 7.57-7.60 (1H, m, C(4′)*H*).

(*R*)-*N*-[(Benzofuran-3′-yl)ethyl]-*N*-(α-methylbenzyl)amine 218



Method A: A solution of **219** (162 mg, 1.00 mmol) and (*R*)-α-methylbenzylamine (*R*)-**153** (121 mg, 1.00 mmol, 99.5:0.5 er) in PhMe (1 mL) was added to [Ru(*p*-cymene)Cl_2]$_2$ (16 mg, 26 μmol), DPEPhos **220** (28 mg, 52 μmol) and activated 3 Å molecular sieves (~500 mg) at rt. The resultant mixture was stirred for 10 min, then heated at reflux for 24 h. The reaction mixture was allowed to cool to rt and then concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 25% → 72% Et_2O in 30-40 °C petrol) gave **218** as a brown oil (73 mg, 27%); $[\alpha]_D^{24}$ +49.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3060 (N−H); δ_H (400 MHz, $CDCl_3$) 1.38 (3H, d, *J* 6.6, C(α)*Me*), 2.81-2.90 (4H, m, C(1)H_2, C(2)H_2), 3.84 (4H, q, *J* 6.6, C(α)*H*), 7.21-7.35 (7H, m, *Ph*, *Ar*), 7.45-7.51 (3H, m, *Ph*, *Ar*); δ_C (100 MHz, $CDCl_3$) 24.2 (*C*(2)), 24.2 (C(α)*Me*), 46.5 (*C*(1)), 58.2 (*C*(α)), 111.5 (*C*(7′)), 118.0 (*C*(3′)), 119.6 (*C*(4′)), 122.3 (*C*(5′)), 124.2 (*C*(6′)), 126.6, 127.0, 128.5 (*o,m,p-Ph*), 128.0 (*C*(3a′)), 141.7 (*C*(2′)), 145.1 (*i-Ph*), 155.4 (*C*(7a′)); *m/z* (ESI$^+$) 288 ([M+Na]$^+$, 70%), 266 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{20}NO^+$ ([M+H]$^+$) requires 266.1539; found 266.1540.

Method B - step 1: 2,4-Dinitrobenzenesulfonyl chloride (3.81 g, 14.3 mmol) was added to (*R*)-α-methylbenzylamine (*R*)-**153** (2.00 mL, 15.7 mmol, 99.5:0.5 er) and NEt_3 (2.19 mL, 15.7 mmol) in CH_2Cl_2 (30 mL) at 0 °C and the resultant mixture stirred and allowed to warm to rt over 15 min. 1.0 M aq HCl (20 mL) was added and the aqueous layer extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were washed with brine (50 mL), and then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 1:1) gave **221** as a brown solid of ~90% purity (2.34 g); δ_H (400 MHz, $CDCl_3$) 1.58 (3H, d, *J* 7.1, C(α)*Me*), 4.74 (1H, app quin, *J* 7.6, C(α)*H*), 5.91 (1H, d, *J* 8.6, N*H*), 7.03-7.14 (5H, m, *Ph*), 8.10 (1H, dd, *J* 8.6, 2.0, C(5′)*H*), 8.45-8.51 (2H, m, C(3′)*H*, C(6′)*H*); δ_C (100 MHz, $CDCl_3$) 23.4 (C(α)*Me*), 55.4 (*C*(α)), 119.7 (*C*(3′)), 126.1, 126.3, 128.5 (*o,m,p-Ph*), 126.3 (*C*(5′)), 132.4 (*C*(6′)), 139.7, 140.9 (*C*(1′), *i-Ph*), 149.1 (*C*(2′), *C*(4′)); *m/z* (ESI$^+$) 374 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{13}N_3NaO_6S^+$ ([M+Na]$^+$) requires 374.0417; found 374.0416.

Step 2: DEAD (0.17 mL, 924 μmol) was added to PPh_3 (242 mg, 924 μmol), **219** (150 mg, 924 μmol) and **221** (271 mg, ~90% purity) in THF (5 mL) at 0 °C and the resultant mixture stirred and allowed to warm to rt over 16 h. The reaction mixture was filtered through Celite® (eluent Et_2O) and the filtrate concentrated *in vacuo*. Purification via flash column chromatography (eluent

30-40 °C petrol/Et_2O, 7:3) gave **222** as a brown solid of ~90% purity (116 mg); δ_H (400 MHz, $CDCl_3$) 1.62 (3H, d, *J* 7.1, C(α)*Me*), 2.43 (1H, dd, *J* 13.9, 11.4, C(2)H_A), 2.85 (1H, dd, *J* 13.9, 11.1, C(2)H_B), 3.41-3.63 (2H, m, C(1)H_2), 5.40 (1H, q, *J* 7.1, C(α)*H*), 7.18-7.48 (10H, m, C(2′)*H*, C(4′)*H*, C(5′)*H*, C(6′)*H*, C(7′)*H*, *Ph*), 8.13 (1H, d, *J* 8.8, C(6″)*H*), 8.32 (1H, dd, *J* 8.8, 2.2, C(5″)H), 8.40 (1H, d, *J* 2.2, C(3″)*H*); δ_C (100 MHz, $CDCl_3$) 17.5 (C(α)*Me*), 25.5 (*C*(2)), 45.0 (*C*(1)), 56.7 (*C*(α)), 111.5 (*C*(7′)), 116.5 (*C*(3′)), 119.4 (*C*(3″)), 119.6 (*C*(4′)), 122.6 (*C*(5′)), 124.4 (*C*(6′)), 125.9 (*C*(6″)), 127.7, 128.6, 128.9 (*o,m,p-Ph*), 127.4 (*C*(3′a)), 132.4 (*C*(5″)), 138.9 (*C*(4″)), 139.1 (*C*(2″)), 141.9 (*C*(2′)), 147.9 (*i-Ph*), 149.4 (*C*(1″)), 155.1 (*C*(7′a)).

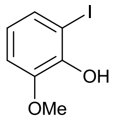
Step 3: Mercaptoacetic acid (21 µL, 303 µmol) was added to **222** (100 mg, ~90% purity) and NEt_3 (56 µL, 402 µmol) in CH_2Cl_2 (1 mL) at rt and the resultant mixture stirred for 1 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between EtOAc (5 mL) and sat aq $NaHCO_3$ (5 mL). The aqueous layer was extracted with EtOAc (5 mL) and the combined organic extracts dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O:NEt_3, 50:49:1) gave **218** as a yellow oil (22 mg, 6% over 3 steps).

Method C - Step 1: TsCl (26.4 g, 86.3 mmol) was added to **219** (7.00 g, 43.2 mmol) and DMAP (30 mg, 246 µmol) in pyridine (200 mL) at rt and the resultant mixture was stirred for 18 h. The reaction mixture was concentrated *in vacuo* and the residue partitioned between Et_2O (200 mL) and H_2O (200 mL). The aqueous layer was extracted with Et_2O (2 × 100 mL) and the combined organic extracts washed with 2.0 M aq HCl (300 mL), sat aq $NaHCO_3$ (200 mL) and brine (200 mL), then dried and concentrated *in vacuo* to give a 67:33 mixture of **223**:**224** (7.17 g). Purification of an aliquot via flash column chromatography (gradient elution, 0% → 11% Et_2O in 30-40 °C petrol) gave **223** as a colourless oil; ν_{max} (ATR) 2961 (C−H); δ_H (400 MHz, $CDCl_3$) 3.19 (2H, t, *J* 7.1, C(1′)H_2), 3.82 (2H, t, *J* 7.1, C(2′)H_2), 7.25-7.38 (2H, m, C(4)*H*, C(6)*H*), 7.49-7.61 (3H, m, C(2)*H*, C(5)*H*, C(7)*H*); δ_C (100 MHz, $CDCl_3$) 27.4 (*C*(1′)), 43.4 (*C*(2′)), 111.7 (*C*(7)), 116.7 (*C*(3)), 119.3 (*C*(4)), 122.6 (*C*(5)), 124.5 (*C*(6)), 127.6 (*C*(3a)), 142.3 (*C*(2)), 155.3 (*C*(7a)); *m/z* (FI^+) 182 ($[M(^{37}Cl)]^+$, 32%), 180 ($[M(^{35}Cl)]^+$, 100%); HRMS (FI^+) $C_{10}H_9{}^{37}ClO^+$ ($[M(^{37}Cl)]^+$) requires 182.0315; found 182.0331; $C_{10}H_9{}^{35}ClO^+$ ($[M(^{35}Cl)]^+$) requires 180.0336; found 180.0340. Further elution gave **224** as a white solid; mp 50-52 °C; ν_{max} (ATR) 2960 (C−H); δ_H (400 MHz, $CDCl_3$) 2.39 (3H, s, C(4″)*Me*), 3.04 (2H, t, *J* 6.6, C(1′)H_2), 4.30 (2H, t, *J* 6.6, C(2′)H_2), 7.17-7.22 (3H, m, C(5)*H*, C(3″)*H*, C(5″)*H*), 7.29 (1H, t, *J* 7.3, C(6)*H*), 7.39-7.46 (3H, m, C(2)*H*, C(4)*H*, C(7)*H*), 7.66 (2H, d, *J* 8.1, C(2″)*H*, C(6″)*H*); δ_C (100 MHz, $CDCl_3$) 21.6 (C(4″)*Me*), 23.7 (*C*(1′)), 68.9 (*C*(2′)), 111.5 (*C*(7)), 115.0 (*C*(3)), 119.2 (*C*(4)), 122.5 (*C*(5)), 124.4 (*C*(6)), 127.4 (*C*(3a)), 127.7 (*C*(2″), *C*(6″)), 129.7

(*C*(3″), *C*(5″)), 132.6 (*C*(4″)), 142.4 (*C*(2)), 144.8 (*C*(1″)), 155.2 (*C*(7a)); *m/z* (ESI$^+$) 339 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{17}H_{16}NaO_4S^+$ ([M+Na]$^+$) requires 339.0662; found 339.0654.

Step 2: NaI (25.0 g, 167 mmol) and (*R*)-α-methylbenzylamine (*R*)-**153** (13.0 mL, 101 mmol, 99.5:0.5 er) were added to the 67:33 mixture of **223**:**224** (7.17 g) in MeCN (250 mL) and the resultant mixture was stirred and heated at reflux for 48 h. The reaction mixture was allowed to cool to rt and partitioned between EtOAc (250 mL) and sat aq $NaHCO_3$ (250 mL). The aqueous layer was extracted with EtOAc (250 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O/NEt_3, 70:29:1) gave **218** as a yellow oil (6.43 g, 56% over 2 steps, >99:1 er).

2-Iodo-6-methoxyphenol 227



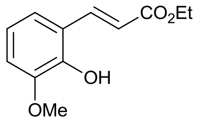
Step 1: NaH (528 mg, 13.2 mmol) was added to **208** (0.97 mL, 8.82 mmol) in DMF (10 mL) at rt and the resultant mixture stirred for 30 min. The reaction mixture was cooled to 0 °C, MOMCl (1.00 mL, 13.2 mmol) was added and the resultant mixture allowed to warm to rt over 16 h. The reaction mixture was partitioned between H_2O (30 mL) and Et_2O (30 mL) and the aqueous layer extracted with Et_2O (2 × 30 mL). The combined organic extracts were washed with 10% aq NaOH (40 mL) and brine (40 mL), then dried and concentrated *in vacuo* to give **225** as a yellow oil (1.61 g); δ_H (400 MHz, $CDCl_3$) 3.53 (3H, s, CH_2OMe), 3.89 (3H, s, C(2)O*Me*), 5.25 (2H, s, OC*H*$_2$), 6.88 (2H, m, C(3)*H*, C(5)*H*), 6.98-7.03 (1H, m, C(4)*H*), 7.17 (1H, dd, *J* 8.2, 1.7, C(6)*H*).

Step 2: BuLi (2.5 M, 7.42 mL, 18.5 mmol) was added to **225** (1.61 g) in Et_2O (14 mL) at 0 °C and the resultant mixture stirred for 1 h. I_2 (12.7 g, 50.0 mmol) in THF (50 mL) was added and the resultant mixture allowed to warm to rt over 16 h. The reaction mixture was partitioned between sat aq $Na_2S_2O_3$ (40 mL) and Et_2O (40 mL) and the aqueous layer extracted with Et_2O (40 mL). The combined organic extracts were dried and concentrated *in vacuo* to give **226** as a brown oil (2.22 g); δ_H (400 MHz, $CDCl_3$) 3.69 (3H, s, CH_2OMe), 3.84 (3H, s, C(6)O*Me*), 5.18 (2H, s, OC*H*$_2$), 6.81 (1H, app ABt, *J* 8.2, C(4)*H*), 6.90 (1H, ABdd, *J* 8.2, 1.4, C(5)*H*), 7.38 (1H, dd, *J* 7.9, 1.4, C(3)*H*).

Step 3: 2.0 M aq HCl (4.8 mL) was added to **226** (2.22 g) in THF (30 mL) and MeOH (30 mL) at rt and the resultant mixture was stirred for 48 h and then concentrated *in vacuo*. The residue was partitioned between H_2O (30 mL) and CH_2Cl_2 (30 mL) and the aqueous layer extracted with Et_2O (30 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 3:1) gave **227** as a yellow solid

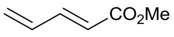
(1.28 g, 53%);[26] mp 54-56 °C {lit.[26] mp 58-60 °C}; δ_H (400 MHz, $CDCl_3$) 3.90 (3H, s, C(6)O*Me*), 6.10 (1H, s, O*H*), 6.64 (1H, app t, *J* 8.9, C(4)*H*), 6.84 (1H, dd, *J* 7.9, 1.4, C(5)*H*), 7.30 (1H, dd, *J* 8.2, 1.4, C(3)*H*).

Ethyl (*E*)-3-(2′-hydroxy-3′-methoxyphenyl)acrylate 230



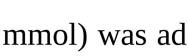
$Pd(OAc)_2$ (2 mg, 5 µmol) in DMF (0.8 mL) was added to **227** (100 mg, 400 µmol), PhI (44 µL, 400 µmol), ethyl acrylate **186** (88 µL, 800 µmol), TEBAC (91 mg, 400 µmol) and $^{i}Pr_2NEt$ (0.15 mL, 800 µmol) at rt and the resultant mixture stirred and heated at 60 °C for 6 h. The reaction mixture was allowed to cool to rt, filtered through Celite® (eluent Et_2O) and then partitioned between H_2O (15 mL) and Et_2O (15 mL). The aqueous layer was extracted with Et_2O (2 × 15 mL) and the combined organic extracts were washed with H_2O (2 × 30 ml) and brine (30 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 9:1) gave **187** as a colourless oil (48 mg, 68%, >99:1 dr). Further elution gave **230** as a colourless oil (55 mg, 62%, >99:1 dr);[27] δ_H (400 MHz, $CDCl_3$) 1.34 (3H, t, *J* 7.2, OCH_2CH_3), 3.91 (3H, s, O*Me*), 4.27 (2H, q, *J* 7.2, OCH_2CH_3), 6.21 (1H, s, O*H*), 6.61 (1H, d, *J* 16.0, C(2)*H*), 6.82-8.88 (2H, m, C(4′)*H*, C(5′)*H*), 7.09 (1H, dd, *J* 6.8, 2.7, C(6′)*H*), 7.96 (1H, d, *J* 16.0, C(3)*H*).

Methyl (*E*)-penta-2,4-dienoate 232



Acrolein (3.38 mL, 45.6 mmol) and DMAP (420 mg, 3.44 mmol) were added to **231** (7.32 g, 62.0 mmol) in pyridine (14 mL) and the resultant mixture stirred and heated at 50 °C for 18 h. The reaction mixture was added to H_2O (25 mL) and the aqueous layer extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with 15% aq HCl (40 mL), then dried and concentrated *in vacuo* to give **232** in 92:8 dr. Purification via distillation gave **232** as a colourless oil (1.18 g, 23%, 92:8 dr);[28] bp 47-49°C (25 mbar); {lit.[28] bp 45 °C (20 mbar)}; δ_H (400 MHz, $CDCl_3$) 3.76 (3H, s, O*Me*), 5.49-5.53 (1H, m, C(5)H_A), 5.60-5.66 (1H, m, C(5)H_B), 5.93 (1H, app dt, *J* 15.4, 0.7, C(2)*H*), 6.42-6.52 (1H, m, C(4)*H*), 7.28 (1H, app ddt, *J* 15.4, 10.9, 0.7, C(3)*H*).

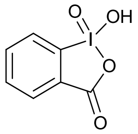
(*E*)-Penta-2,4-dien-1-ol 233



DIBAL-H (1.0 M in CH_2Cl_2, 100 mL, 100 mmol) was added to **232** (5.38 g, 48.0 mmol, 92:8 dr) in CH_2Cl_2 (150 mL) at 0 °C and the resultant mixture stirred at 0 °C for 3 h. Ice (~2 g) was cautiously added, the resultant mixture dried, filtered through a plug of silica (eluent Et_2O), and then concentrated *in vacuo* to give **233** as a colourless oil (2.91 g, 72%, 92:8 dr);[29] δ_H (400 MHz, $CDCl_3$)

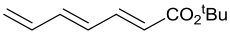
4.21 (2H, d, *J* 5.8, C(1)H_2), 5.12 (1H, app d, *J* 9.6, C(5)H_A), 5.24 (1H, dd, *J* 16.0, 1.1, C(5)H_B), 5.87 (1H, dt, *J* 15.0, 5.8, C(2)*H*), 6.24-6.42 (2H, m, C(3)*H*, C(4)*H*).

2-Iodoxybenzoic acid [IBX]



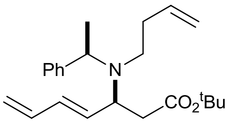
2-Iodobenzoic acid **323** (73.5 g, 297 mmol) was added to a mechanically stirred solution of Oxone® (543 g, 889 mmol) in H_2O (1.5 L) and the resultant mixture heated at 70 °C for 3 h. The reaction mixture was allowed to cool to rt and the precipitated collected via filtration. The filter cake was washed with H_2O (2 × 250 mL), acetone (250 mL) and Et_2O (250 mL), then dried *in vacuo* to give IBX as a white solid (63.9 g, 77%);[30] mp 217 °C (dec); {lit.[31] mp 232 °C (dec)}; δ_H (400 MHz, DMSO–d_6) 7.83-7.86 (1H, m, *Ar*), 7.99-8.05 (2H, m, *Ar*), 8.14-8.16 (1H, m, *Ar*).

***tert*-Butyl (*E*,*E*)-hepta-2,4,6-trienoate 207**



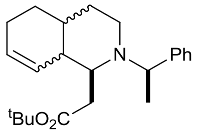
IBX (14.5 g, 51.8 mmol) was added to **233** (2.91 g, 34.5 mmol) and **181** (19.5 g, 51.8 mmol) in DMSO (100 mL) at rt and the resultant mixture stirred for 24 h. Et_2O (50 mL) and H_2O (50 mL) were added, the resultant mixture filtered and the aqueous layer extracted with Et_2O (2 × 100 mL). The combined organic extracts were washed with H_2O (2 × 150 mL) and brine (150 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography gave **207** as a white solid (1.07 g, 17%, >99:1 dr); mp 57 °C (dec); ν_{max} (film) 1708 (C=O), 1627 (C=C); δ_H (400 MHz, $CDCl_3$) 1.49 (9H, s, C*Me*$_3$), 5.29 (1H, app d, *J* 10.1, C(7)H_A), 5.39 (1H, app d, *J* 16.7, C(7)H_B), 5.83 (1H, d, *J* 15.2, C(2)*H*), 6.30 (1H, ABdd, *J* 14.7, 11.3, C(4)*H*), 6.41 (1H, app ABdt, *J* 16.7, 10.1, C(6)*H*), 6.52 (1H, ABdd, *J* 14.7, 10.9, C(5)*H*), 7.20 (1H, dd, *J* 15.2, 11.3, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 28.1 (C*Me*$_3$), 80.3 (*C*Me$_3$), 121.1 (*C*(7)), 123.6 (*C*(2)), 130.5 (*C*(4)), 136.3 (*C*(6)), 140.2 (*C*(5)), 143.0 (*C*(3)), 166.3 (*C*(1)).[32]

***tert*-Butyl (3*S*,α*R*,*E*)-3-[*N*-but-3″-enyl-*N*-(α-methylbenzyl)amino]hepta-4,6-dienoate 234**



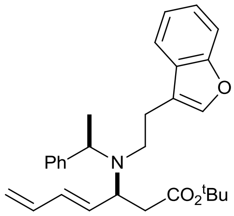
Following *general procedure 5*, **152** (1.56 g, 8.88 mmol, >99:1 er), BuLi (2.5 M, 3.44 mL, 8.60 mmol) and **207** (1.00 g, 4.90 mmol, >99:1 dr) were reacted in THF (100 mL) to give **234** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 25:1) gave **234** as a yellow oil (1.60 g, 81%, >99:1 dr); $[\alpha]_D^{25}$ −7.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1730 (C=O); δ_H (400 MHz, $CDCl_3$) 1.41 (3H, d, *J* 6.7, C(α)*Me*), 1.42 (9H, s, C*Me*$_3$), 2.00-2.14 (2H, m, C(2′)H_2), 2.35 (1H, ABdd, *J* 14.4, 8.1, C(2)H_A), 2.46 (1H, ABdd, *J* 14.4, 6.6, C(2)H_B), 2.50-2.63 (2H, m, C(1′)H_2), 3.90 (1H, app q, *J* 7.3, C(3)*H*), 3.97 (1H, q, *J* 6.7, C(α)*H*), 4.90-4.97 (2H, m, C(4′)H_2), 5.07 (1H, app d, *J* 10.4, C(7)H_A), 5.17 (1H, app d, *J* 17.0, C(7)H_B), 5.62-5.72 (1H, m, C(3′)*H*), 5.76 (1H, dd, *J* 15.4, 5.5, C(4)*H*), 6.14 (1H, ABdd, *J* 15.4, 10.4, C(5)*H*), 6.34 (1H, app ABdt, *J* 17.0, 10.4, C(6)*H*), 7.20-7.25 (1H, m, *Ph*), 7.31 (2H, t, *J* 7.8, *Ph*), 7.36-7.41 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.7 (C(α)*Me*), 28.1 (CMe_3), 35.0 (*C*(2′)), 39.7 (*C*(2)), 46.7 (*C*(1′)), 57.2 (*C*(3)), 58.2 (*C*(α)), 80.2 (*C*Me_3), 115.2 (*C*(4′)), 116.6 (*C*(7)), 126.6, 127.7, 128.0 (*o,m,p-Ph*), 132.0 (*C*(5)), 134.0 (*C*(4)), 136.8 (*C*(3′)), 137.0 (*C*(6)), 145.2 (*i-Ph*), 171.1 (*C*(1)); *m/z* (ESI$^+$) 356 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{34}NO_2^+$ ([M+H]$^+$) requires 356.2584; found 356.2577.

***tert*-Butyl (1*S*,α*R*)-2-[*N*(2)-(α-methylbenzyl)-1,2,3,4,4a,5,6,8a-octahydroisoquinolin-1-yl]acetate 235**



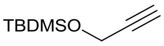
234 (100 mg, 281 µmol) in PhMe (10 mL) was heated at 130 °C in a sealed tube for 64 h. The reaction mixture was allowed to cool to rt and then concentrated *in vacuo* to give **235** in 73:27 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 19:1) gave **235** as a yellow oil (33 mg, 33%, 73:27 dr); ν_{max} (ATR) 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.31 (6H, d, *J* 6.5, 2 × C(α)*Me*), 1.33 (2 × 18H, s, CMe_3), 1.59-2.76 (23H, m, 2 × C(3)H_A, C(3)H_B, 2 × C(4)H_2, 2 × C(4a)*H*, 2 × C(5)H_2, 2 × C(6)H_2, 2 × C(8a)*H*, 2 × C(1)CH_2), 2.88-2.96 (1H, m, C(3)H_B), 3.08-3.14 (1H, m, C(1)*H*), 3.56-3.61 (1H, m, C(1)*H*), 3.64 (1H, q, *J* 6.5, C(α)*H*), 3.89 (1H, q, *J* 6.8, C(α)*H*), 5.33-5.40 (2H, m, 2 × C(8)*H*), 5.61-5.69 (2H, m, 2 × C(7)*H*), 7.17-7.37 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 21.2, 24.8, 25.7, 27.0, 28.1, 29.5, 30.3, 30.9, 32.0, 33.0, 38.5, 41.8, 42.2, 42.5 (2 × *C*(3), 2 × *C*(4), 2 × *C*(4a), 2 × *C*(5), 2 × *C*(6), 2 × *C*(8a), 2 × C(1)*C*H_2), 22.0, 22.2 (2 × C(α)*Me*), 27.8, 28.0 (2 × CMe_3), 55.5, 57.6 (2 × *C*(1)), 59.2, 60.0 (2 × *C*(α)), 79.9 (2 × *C*Me_3), 126.0, 126.7, 127.1, 127.3, 128.2, 128.5 (2 × *C*(7), *o,m,p-Ph*), 131.4 (2 × *C*(8)), 145.9 (2 × *i-Ph*), 172.9 (2 × *C*O); *m/z* (ESI$^+$) 356 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{34}NO_2^+$ ([M+H]$^+$) requires 356.2584; found 356.2575.

***tert*-Butyl (3*S*,α*R*,*E*)-3-{*N*-[2′-(benzofuran-3″-yl)ethyl]-*N*-[α-methylbenzyl]amino} hepta-4,6-dienoate 236**



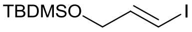
Following *general procedure 5*, **218** (118 mg, 445 μmol, >99:1 er), BuLi (2.5 M, 0.17 mL, 425 μmol) and **207** (73 mg, 405 μmol, >99:1 dr) were reacted in THF (2 mL) to give **236** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 20:1) gave **236** as a yellow oil (76 mg, 43%, >99:1 dr); $[\alpha]^{24}_{D}$ +19.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1726 (C=O), 1601 (C=C); δ_H (400 MHz, $CDCl_3$) 1.45 (3H, d, *J* 6.6, C(α)*Me*), 1.48 (9H, s, C*Me*$_3$), 2.44 (1H, ABdd, *J* 14.4, 7.6, C(2)*H*$_A$), 2.54-2.87 (5H, m, C(2)*H*$_B$, C(1′)*H*$_2$, C(2′)*H*$_2$), 3.98-4.10 (2H, m, C(3)*H*, C(α)*H*), 5.09 (1H, app d, *J* 10.1, C(7)*H*$_A$), 5.20 (1H, app d, *J* 15.9, C(7)*H*$_B$), 5.78 (1H, dd, *J* 15.2, 7.3, C(4)*H*), 6.19 (1H, dd, *J* 15.2, 10.4, C(5)*H*), 6.33 (1H, app dt, *J* 16.7, 10.4, C(6)*H*), 7.14-7.21 (2H, m, *Ph*, *Ar*), 7.23-7.31 (3H, m, *Ph*, *Ar*), 7.32-7.38 (2H, m, *Ph*, *Ar*), 7.41-7.47 (3H, m, *Ph*, *Ar*); δ_C (100 MHz, $CDCl_3$) 19.5 (C(α)*Me*), 25.4 (*C*(2′)), 28.1 (C*Me*$_3$), 39.9 (*C*(2)), 47.5 (*C*(1′)), 57.7 (*C*(3)), 59.1 (*C*(α)), 80.4 (*C*Me$_3$), 111.3 (*C*(7″)), 116.9 (*C*(7)), 118.5 (*C*(3″)), 119.6 (*C*(4″)), 122.1 (*C*(5″)), 124.0 (*C*(6″)), 126.9, 127.9, 128.2 (*o*,*m*,*p*-*Ph*), 128.1 (*C*(3a″)), 132.3 (*C*(5)), 133.4 (*C*(4)), 136.6 (*C*(6)), 141.3 (*C*(2″)), 145.4 (*i*-*Ph*), 155.2 (*C*(7a″)) 171.1 (*C*(1)); *m/z* (ESI^+) 446 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{29}H_{36}NO_3{}^+$ ($[M+H]^+$) requires 446.2690; found 446.2680.

3-(*tert*-Butyldimethylsiloxy)propyne 247



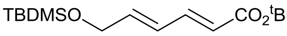
TBDMSCl (13.6 g, 90.2 mmol) was added to propargylic alcohol **246** (5.00 mL, 85.9 mmol) and imidazole (7.31 g, 107 mmol) in DMF (30 mL) at 0 °C and the resultant mixture allowed to warm to rt over 16 h. The reaction mixture was partitioned between H_2O (50 mL) and Et_2O (50 mL) and the aqueous layer extracted with Et_2O (2 × 50 mL). The combined organic extracts were washed with H_2O (2 × 100 mL) and brine (100 mL), then dried and concentrated *in vacuo*. Purification via distillation gave **247** as a colourless oil (13.7 g, 93%);[33] bp 52-54 °C (20 mbar); {lit.[33] bp 52 °C (19 mbar)}; δ_H (400 MHz, $CDCl_3$) 0.14 (6H, s, Si*Me*$_2$), 0.92 (9H, s, C*Me*$_3$), 2.40 (1H, t, *J* 2.4, C(1)*H*), 4.33 (2H, d, *J* 2.4, C(3)*H*$_2$).

(*E*)-1-Iodo-3-(*tert*-butyldimethylsiloxy)prop-1-ene 248



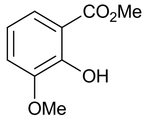
DIBAL-H (1.0 M in THF, 32.4 mL, 32.4 mmol) was added to ZrCp$_2$Cl$_2$ (9.44 g, 32.4 mmol) in THF (60 mL) at 0 °C and the resultant mixture stirred at 0 °C for 30 min. A solution of **247** (5.00 g, 29.4 mmol) in THF (15 mL) was added and the reaction mixture allowed to warm to rt and stirred until homogeneous (~1 h). The reaction mixture was cooled to −78 °C and I_2 (9.71 g, 38.2 mmol) in THF (50 mL) was added and the reaction mixture stirred for at −78 °C for 30 min. The reaction mixture was partitioned between 1.0 M aq HCl (100 mL) and Et$_2$O (150 mL) and the aqueous layer extracted with Et$_2$O (2 × 150 mL). The combined organic extracts were washed with sat aq $Na_2S_2O_3$ (300 mL), sat aq $NaHCO_3$ (300 mL) and brine (300 mL), then dried and concentrated *in vacuo* to give **248** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 °C petrol) gave **248** as a yellow oil (5.12 g, 58%, >99:1 dr);[34] δ_H (400 MHz, CDCl$_3$) 0.08 (6H, s, Si*Me*$_2$), 0.91 (9H, s, C*Me*$_3$), 4.12 (2H, dd, *J* 4.7, 1.9, C(3)*H*$_2$), 6.30 (1H, dt, *J* 14.3, 1.9, C(1)*H*), 6.61 (1H, dt, *J* 14.3, 4.7, C(2)*H*).

***tert*-Butyl (*E*,*E*)-6-(*tert*-butyldimethylsilyloxy)hexa-2,4-dienoate 249**



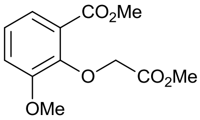
Following *general procedure 6*, **248** (5.11 g, 17.1 mmol), *tert*-butyl acrylate (10.0 mL, 68.5 mmol), Pd(OAc)$_2$ (192 mg, 857 μmol), TBAC (4.75 g, 17.1 mmol) and K_2CO_3 (5.92 g, 42.8 mmol) were reacted in DMF (100 mL) to give **249** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/Et$_2$O, 19:1) gave **249** as a colourless oil (4.56 g, 89%, >99:1 dr); ν_{max} (film) 1711 (C=O), 1649, 1620 (C=C); δ_H (400 MHz, CDCl$_3$) 0.07 (6H, s, Si*Me*$_2$), 0.91 (9H, s, SiC*Me*$_3$), 1.48 (9H, s, OC*Me*$_3$), 4.28 (2H, d, *J* 2.7, C(6)*H*$_2$), 5.79 (1H, dd, *J* 15.4, 2.1, C(2)*H*), 6.12 (1H, dt, *J* 15.1, 2.7, C(5)*H*), 6.33-6.40 (1H, m, C(4)*H*), 7.19 (1H, dd, *J* 15.4, 11.2, C(3)*H*); δ_C (100 MHz, CDCl$_3$) −5.4 (Si*Me*$_2$), 18.3 (Si*C*Me$_3$), 25.8 (SiC*Me*$_3$), 28.1 (OC*Me*$_3$), 62.9 (*C*(6)), 80.2 (O*C*Me$_3$), 122.7 (*C*(2)), 126.9 (*C*(4)), 141.0 (*C*(5)), 143.0 (*C*(3)), 166.5 (*C*(1)); *m/z* (ESI$^+$) 619 ([2M+Na]$^+$, 100%), 321 ([M+Na]$^+$, 63%); HRMS (ESI$^+$) $C_{16}H_{30}NaO_3Si^+$ ([M+Na]$^+$) requires 321.1862; found 321.1854.

Methyl 2-hydroxy-3-methoxybenzoate 251



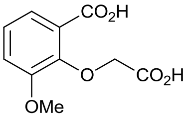
Conc. H_2SO_4 (8.25 mL) was added to **250** (50.0 g, 298 mmol) in MeOH (175 mL) and the resultant mixture stirred and heated at reflux for 24 h. The reaction mixture was allowed to cool to rt and then H_2O (300 mL) added and the resultant mixture cooled to 0 °C. The resultant precipitate was collected via filtration, washed with H_2O (200 mL) and dried *in vacuo* to give **251** as an off white solid (53.5 g, 99%);[35] mp 58-60 °C; {lit.[35] mp 68 °C}; δ_H (400 MHz, $CDCl_3$) 3.92 (3H, s, C(3)O*Me*), 3.96 (3H, s, CO_2*Me*), 6.84 (1H, app ABt, *J* 8.0, C(5)*H*), 7.06 (1H, ABd, *J* 7.9, C(4)*H*); 7.44 (1H, dd, *J* 8.2, 1.5, C(6)*H*), 11.02 (1H, br s, O*H*).

Methyl 2-(2′-methoxy-2′-oxoethoxy)-3-methoxybenzoate 252



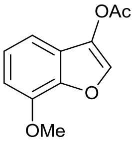
Methyl chloroacetate (52.0 mL, 593 mmol) was added to **251** (53.5 g, 294 mmol) and K_2CO_3 (102 g, 738 mmol) in acetone (535 mL) and the resultant mixture stirred and heated at reflux for 48 h. The reaction mixture was allowed to cool to rt, filtered and the filter cake washed with acetone (50 mL). The filtrate was concentrated *in vacuo* to a volume of ~200 mL, allowed to cool to rt and H_2O (620 mL) added over 1.5 h. The resultant mixture was stirred for 16 h and the resultant precipitate collected via filtration, washed with H_2O (300 mL) and then dried *in vacuo* to give **252** as an off white solid (64.1 g, 86%);[35] mp 62-63 °C; {lit.[35] mp 76 °C}; δ_H (400 MHz, $CDCl_3$) 3.82 (3H, s, O*Me*), 3.87 (3H, s, O*Me*), 3.90 (3H, s, O*Me*), 4.69 (2H, s, C(1′)H_2), 7.06 (1H, ABdd, *J* 8.2, 1.7, C(4)*H*), 7.13 (1H, app t, *J* 7.9, C(5)*H*), 7.33 (1H, ABdd, *J* 7.7, 1.7, C(6)*H*).

2-(Carboxymethoxy)-3-methoxybenzoic acid 253



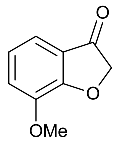
12% aq NaOH (315 mL) was added to **252** (64.1 g, 252 mmol) in MeOH (125 mL) at 60 °C and the resultant mixture stirred and heated at reflux for 1 h. The reaction mixture was allowed to cool to rt and acidified to pH 2 with 22% aq HCl (136 mL). The resultant precipitate was collected via filtration, washed with water (270 mL), and dried *in vacuo* to give **253** as a white solid (52.6 g, 92%);[35] mp 174-176 °C; {lit.[35] mp 188 °C}; δ_H (400 MHz, MeOH-d_4) 3.92 (3H, s, O*Me*), 4.76 (2H, s, OCH_2), 7.19 (1H, app ABt, *J* 8.2, C(5)*H*), 7.29 (1H, ABdd, *J* 8.2, 1.5, C(4)*H*), 7.43 (1H, dd, *J* 7.9, 1.5, C(6)*H*).

7-Methoxybenzofuran-3-yl acetate 254



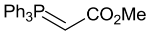
NaOAc (30.0 g, 366 mmol) was added to **253** (52.6 g, 232 mmol) in Ac_2O (260 mL) and AcOH (40 mL) at rt and the resultant mixture stirred and heated at reflux for 3.75 h. The reaction mixture was allowed to cool to 60 °C and H_2O (60 mL) was added dropwise over 45 min and the resultant mixture was allowed to cool to rt and stirred for 16 h. H_2O (640 mL) was added dropwise over 45 min and the resultant mixture stirred for 1.5 h. The resultant precipitate was collected via filtration, washed with H_2O (1.0 L), and dried *in vacuo* to give **254** as a white solid (44.3 g, 92%);[35] mp 65-67 °C; {lit.[35] mp 70 °C}; δ_H (400 MHz, $CDCl_3$) 2.38 (3H, s, *Ac*), 4.02 (3H, s, O*Me*), 6.84 (1H, d, *J* 7.5, C(6)*H*), 7.15-7.22 (2H, m, C(4)*H*, C(5)*H*), 8.04 (1H, s, C(2)*H*).

7-Methoxybenzofuran-3(2*H*)-one 255



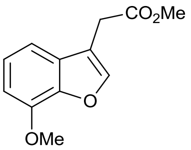
1.0 M aq HCl (66.0 mL) was added to **254** (44.3 g, 215 mmol) in MeOH (350 mL) and H_2O (190 mL) at rt and the resultant mixture heated at reflux for 3.5 h. The mixture was allowed to cool to 65 °C, activated charcoal (6.30 g) added and the resultant mixture stirred for 10 min. The resultant mixture was filtered whilst hot and the filtrate allowed to cool to rt and stirred for 16 h. H_2O (315 mL) was added over 45 min and the resultant mixture cooled to 0 °C. The resultant precipitate was collected via filtration, washed with H_2O (200 mL), and dried *in vacuo* to give **255** as an orange solid (24.4 g, 69%);[35] mp 50-52 °C; {lit.[35] mp 81 °C}; δ_H (400 MHz, $CDCl_3$) 3.97 (3H, s, O*Me*), 4.69 (2H, s, C(2)H_2), 7.04 (1H, app ABt, *J* 7.7, C(5)*H*), 7.12 (1H, ABd, *J* 7.9, C(6)*H*), 7.27 (1H, d, *J* 7.7, C(4)*H*).

Methyl triphenylphosphenylidene acetate 259



Methyl bromoacetate **324** (50.0 g, 327 mmol) was added to PPh_3 (85.7 g, 327mmol) in EtOAc (300 mL) at rt and the resultant mixture stirred for 12 h. The resultant precipitate was collected via filtration, washed with Et_2O (200 mL), and then added to 2.0 M aq NaOH (500 mL) and CH_2Cl_2 (300 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL) and the combined organic extracts dried and concentrated *in vacuo* to a volume of ~100 mL. 30-40 °C petrol (~200 mL) was added and the resultant precipitate collected via filtration to give **259** as a white solid (95.3 g, 87%);[36] mp 159-160 °C; {lit.[36] mp 165 °C}; δ_H (400 MHz, $CDCl_3$) 2.93 (1H, br s, PC*H*), 3.58 (3H, br s, CO_2*Me*), 7.42-7.73 (15H, m, *Ph*).

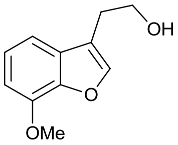
Methyl 2′-(7-methoxybenzofuran-3-yl)acetate 229



259 (34.2 g, 102 mmol) was added to **255** (15.0 g, 91.4 mmol) in xylene (300 mL) at rt and the resultant mixture stirred and heated at reflux for 72 h and then concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 3:1) gave **229** as a yellow oil

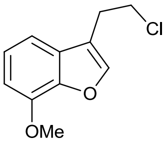
(14.5 g, 72%);[37] δ_H (400 MHz, $CDCl_3$) 3.71 (2H, d, *J* 1.0, C(2′)H_2), 3.74 (3H, s, CO_2Me), 4.02 (3H, s, C(7)O*Me*), 6.83 (1H, dd, *J* 7.5, 1.4, C(6)*H*), 7.14-7.21 (2H, m, C(4)*H*, C(5)*H*), 7.65 (1H, s, C(2)*H*).

2′-(7-methoxybenzofuran-3-yl)ethanol 256



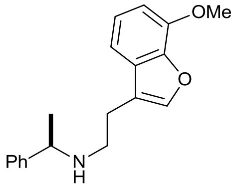
$LiAlH_4$ (2.44 g, 64.3 mmol) was added to **229** (14.5 g, 65.8 mmol) in Et_2O (270 mL) and the reaction mixture stirred at rt for 16 h. Ice (~5 g) was cautiously added followed by H_2O (50 mL) and the aqueous layer extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with 1.0 M aq HCl (300 mL), dried and concentrated *in vacuo* to give **256** as a colourless oil (12.6 g, quant);[38] δ_H (400 MHz, $CDCl_3$) 2.95 (2H, t, *J* 6.3, C(2′)H_2), 3.93 (2H, t, *J* 6.3, C(1′)H_2), 4.02 (3H, s, O*Me*), 6.83 (1H, dd, *J* 6.1, 2.7, C(6)*H*), 7.16-7.21 (2H, m, C(4)*H*, C(5)*H*), 7.54 (1H, s, C(2)*H*).

2′-(7-Methoxybenzofuran-3-yl)ethyl chloride 258



CCl_4 (0.64 mL, 6.63 mmol) was added to **256** (322 mg, 1.68 mmol) and PPh_3 (1.75 g, 6.67 mmol) in MeCN (11 mL) at rt and the resultant mixture stirred and heated at reflux for 24 h. The reaction mixture was allowed to cool to rt and then concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 1% → 20% Et_2O in 30-40 °C petrol) gave **258** as a yellow oil (70 mg, 20%); ν_{max} (ATR) 2961 (C−H); δ_H (400 MHz, $CDCl_3$) 3.15 (2H, t, *J* 7.2, C(2′)H_2), 3.79 (2H, t, *J* 7.2, C(1′)H_2), 4.02 (3H, s, O*Me*), 6.83 (1H, d, *J* 7.6, C(6)*H*), 7.13-7.22 (2H, m, C(4)*H*, C(5)*H*), 7.54 (1H, s, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 27.4 (*C*(2′)), 43.3 (*C*(1′)), 56.1 (O*Me*), 106.6 (*C*(6)), 111.5 (*C*(4)), 117.1 (*C*(3)), 123.4 (*C*(5)), 129.3 (*C*(3a)), 142.3 (*C*(2)), 144.6 (*C*(7a)), 145.7 (*C*(7)); *m/z* (ESI^+) 235 ($[M(^{37}Cl)+Na]^+$, 34%), 233 ($[M(^{35}Cl)+Na]^+$, 100%); HRMS (ESI^+) $C_{11}H_{11}{}^{37}ClNaO_2{}^+$ ($[M(^{37}Cl)+Na]^+$) requires 235.0310; found 235.0327; $C_{11}H_{11}{}^{35}ClNaO_2{}^+$ ($[M(^{35}Cl)+Na]^+$) requires 233.0340; found 233.0350.

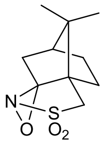
(*R*)-*N*-[2′-(7-Methoxybenzofuran-3-yl)ethyl]-*N*-(α-methylbenzyl)amine 206



Step 1: TsCl (25.4 g, 133 mmol) was added to **256** (12.6 g, 65.6 mmol) and DMAP (30 mg, 246 μmol) in pyridine (320 mL) at rt and the resultant mixture was stirred for 18 h. The reaction mixture was partitioned between H_2O (300 mL) and Et_2O (300 mL) and the aqueous layer extracted with Et_2O (2 × 200 mL). The combined organic extracts were washed with 5.0 M aq HCl (1.0 L), sat aq $NaHCO_3$ (500 mL) and brine (500 mL), then dried and concentrated *in vacuo* to give a 77:23 mixture of **257**:**258** (15.1 g). Purification of an aliquot via flash column chromatography (gradient elution, 0% → 11% Et_2O in 30-40 °C petrol) gave **258** as a colourless oil. Further elution gave **257** as a white solid; mp 73-75 °C; ν_{max} (ATR) 2978 (C−H); δ_H (400 MHz, $CDCl_3$) 2.39 (3H, s, C(4″)*Me*), 3.02 (2H, t, *J* 6.7, C(1′)H_2), 4.01 (3H, s, O*Me*), 4.29 (2H, t, *J* 6.7, C(2′)H_2), 6.80 (1H, d, *J* 7.8, C(6)*H*), 6.99 (1H, d, *J* 7.1, C(4)*H*), 7.12 (1H, app t, *J* 7.8, C(5)*H*), 7.21 (2H, d, *J* 8.2, C(3″)*H*, C(5″)*H*), 7.39 (1H, s, C(2)*H*), 7.66 (2H, d, *J* 8.2, C(2″)*H*, C(6″)*H*); δ_C (100 MHz, $CDCl_3$) 21.6 (C(4″)*Me*), 23.7 (*C*(1′)), 56.0 (O*Me*), 68.8 (*C*(2′)), 106.5 (*C*(6)), 111.5 (*C*(4)), 115.4 (*C*(3)), 123.4 (*C*(5)), 127.7 (*C*(2″), *C*(6″)), 129.1 (*C*(3a)), 129.6 (*C*(3″), *C*(5″)), 132.6 (*C*(1″)), 142.4 (*C*(2)), 144.5 (*C*(7a)), 144.7 (*C*(4″)), 145.5 (*C*(7)); *m/z* (ESI^+) 715 ($[2M+Na]^+$, 30%), 369 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{18}H_{18}NaO_5S^+$ ($[M+Na]^+$) requires 369.0767; found 369.0754.

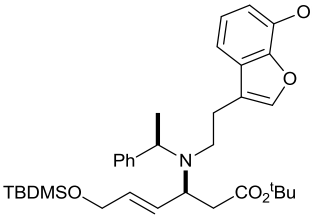
Step 2: NaI (45.5 g, 304 mmol) and (*R*)-α-methylbenzylamine (*R*)-**153** (23.0 mL, 178 mmol, 99.5:0.5 er) were added to the 77:23 mixture of **257**:**258** (15.1 g) in MeCN (450 mL) at rt, the resultant mixture was stirred and heated at reflux for 62 h and then allowed to cool to rt. The reaction mixture was partitioned between EtOAc (450 mL) and sat aq $NaHCO_3$ (450 mL) and the aqueous layer extracted with EtOAc (450 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 45% → 100% Et_2O in 30-40 °C petrol, doped with 1% NEt_3) gave **206** as a yellow oil (11.4 g, 59%, >99:1 er); $[\alpha]_D^{24}$ +41.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3320 (N−H); δ_H (400 MHz, $CDCl_3$) 1.36 (3H, d, *J* 6.6, C(α)*Me*), 2.77-2.90 (4H, m, C(1′)H_2, C(2′)H_2), 3.81 (1H, q, *J* 6.6, C(α)*H*), 4.01 (3H, s, O*Me*), 6.81 (1H, d, *J* 7.1, C(6)*H*), 7.10 (1H, ABd, *J* 6.6, C(4)*H*), 7.15 (1H, app ABt, *J* 7.8, C(5)*H*), 7.22-7.35 (5H, m, *Ph*), 7.45 (1H, s, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 24.4 (C(α)*Me*), 24.5 (*C*(2′)), 46.6 (*C*(1′)), 56.0 (O*Me*), 58.2 (*C*(α)), 106.4 (*C*(6)), 112.0 (*C*(4)), 118.5 (*C*(3)), 123.1 (*C*(5)), 126.5, 126.9, 128.5 (*o,m,p-Ph*), 129.8 (*C*(3a)), 141.8 (*C*(2)), 144.6, 145.5, 145.6 (*C*(7), *C*(7a), *i-Ph*); *m/z* (ESI$^+$) 318 ([M+Na]$^+$, 39%), 296 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{22}NO_2^+$ ([M+H]$^+$) requires 296.1645; found 296.1641.

(−)-Camphorsulfonyloxaziridine [(−)-CSO] 95



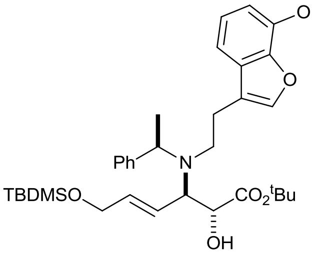
$SOCl_2$ (252 mL, 3.47 mol) was added dropwise to **326** (200 g, 861 mmol) in $CHCl_3$ (1.0 L) at rt and the resultant mixture was heated at reflux for 12 h. The reaction mixture was concentrated *in vacuo* and the residue dissolved in $CHCl_3$ (1.0 L). The resultant mixture was added dropwise to 35% aq NH_3 (2.0 L) at 0 °C and the resultant mixture stirred at 0 °C for 4 h. The aqueous layer was extracted with CH_2Cl_2 (2 × 1.0 L), and the combined organic extracts dried and concentrated *in vacuo*. The residue was dissolved in PhMe (1.0 L), Amberlyst® 15 (12 g) was added to the resultant solution and the reaction vessel fitted with a Dean-Stark apparatus. The reaction mixture was stirred and heated at reflux for 16 h, then filtered whilst hot though Celite® (eluent hot $CHCl_3$) and the filtrate concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (1.5 L), and 2.0 M aq K_2CO_3 (750 mL) and Aliquat™ 336 (~16 g) were added and the resultant mixture was cooled to 5 °C. $MeCO_3H$ (39% in AcOH, 217 mL, 1.06 mol) was added dropwise and the resultant mixture allowed to warm to rt over 16 h. Na_2SO_3 (30.0 g, 238 mmol) was added and the phases rapidly separated. The organic layer was washed with 1.0 M aq NaOH (800 mL), H_2O (800 mL) and sat aq $NaHCO_3$ (800 mL), then dried and concentrated *in vacuo*. The residue was dissolved in hot CH_2Cl_2 (~300 mL) and 30-40 °C petrol (~300 mL) was added. The resultant suspension was allowed to cool to rt and the resultant precipitate collected via filtration to give **95** as a white solid. Similar recrystallisation of the mother liquor gave a second crop of **95** (144.5 g, 73%);[39] mp 164-166 °C; {lit.[39] mp 165-167 °C}; $[\alpha]_D^{24}$ −45.4 (*c* 1.0 in $CHCl_3$); {lit.[39] $[\alpha]_D^{25}$ −43.6 (*c* 2.2, $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.05 (3H, s, Me_A), 1.19 (3H, s, Me_B), 1.52-1.54 (1H, m, C*H*), 1.79 (1H, d, *J* 15.7 CH_A), 1.89-2.15 (4H, m, 2 × CH_2), 2.63-2.65 (1H, m, CH_B), 3.11 (1H, d, *J* 14.0, CH_AH_BSO$_2$), 3.28 (1H, d, *J* 14.0, CH$_A$$H_BSO_2$).

***tert*-Butyl (3*S*,α*R*,*E*)-3-{[*N*-2′-(7″-methoxybenzofuran-3″-yl)ethyl]-*N*-[α-methylbenzyl]amino}-6-(*tert*-butyldimethylsilyloxy)hex-4-enoate 260**



Following *general procedure 5*, **206** (158 mg, 536 μmol, >99:1 er), BuLi (2.5 M, 0.21 mL, 519 μmol) and **249** (100 mg, 355 μmol, >99:1 dr) were reacted in THF (4 mL) to give **260** in >99:1 dr. Purification via flash column chromatography (gradient elution, 0% → 11% Et_2O in 30-40 °C petrol) gave **260** as a colourless oil (126 mg, 63%, >99:1 dr); $[\alpha]_D^{24}$ +0.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 0.08 (6H, s, Si*Me*$_2$), 0.92 (9H, s, SiC*Me*$_3$), 1.44 (3H, d, *J* 6.6, C(α)*Me*), 1.47 (9H, s, OC*Me*$_3$), 2.42 (1H, ABdd, *J* 14.4, 7.3, C(2)H_A), 2.51-2.85 (5H, m, C(2)H_B, C(1′)H_2, C(2′)H_2), 3.97-4.08 (2H, m, C(3)*H*, C(α)*H*) overlapping 3.99 (3H, s, O*Me*), 4.17 (2H, d, *J* 4.0, C(6)H_2), 5.69 (1H, ABdt, *J* 15.7, 8.6, C(5)*H*), 5.78 (1H, ABdd, *J* 15.7, 6.8, C(4)*H*), 6.77 (1H, d, *J* 7.8, C(6″)*H*), 6.79 (1H, d, *J* 7.8, C(4″)*H*), 7.08 (1H, app t, *J* 7.8, C(5″)*H*), 7.23-7.28 (2H, m, *Ph*), 7.33 (2H, t, *J* 7.6, *Ph*), 7.40-7.44 (2H, m, C(2″)*H*, *Ph*); δ_C (100 MHz, $CDCl_3$) −5.2 (Si*Me*$_2$), 18.4 (Si*C*Me$_3$), 19.5 (C(α)*Me*), 25.3 (*C*(2′)), 25.9 (SiC*Me*$_3$), 28.1 (OC*Me*$_3$), 40.0 (*C*(2)), 47.3 (*C*(1′)), 56.0 (O*Me*), 57.3 (*C*(α)), 59.0 (*C*(3)), 63.4 (*C*(6)), 80.3 (O*C*Me$_3$), 106.2 (*C*(6″)), 112.0 (*C*(4″)), 119.0 (*C*(3″)), 122.9 (*C*(5″)), 126.8, 127.9, 128.1 (*o,m,p-Ph*), 129.0 (*C*(4)), 129.9 (*C*(3a″)), 131.2 (*C*(5)), 141.3 (*C*(2″)), 144.4, 145.4, 145.6 (*C*(7″), *C*(7a″), *i-Ph*), 171.2 (*C*(1)); *m/z* (ESI^+) 616 ($[M+Na]^+$, 32%), 594 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{35}H_{52}NO_5Si^+$ ($[M+H]^+$) requires 594.3609; found 594.3603.

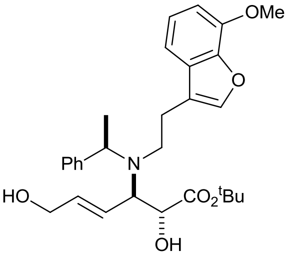
***tert*-Butyl (*R*,*R*,*R*,*E*)-2-hydroxy-3-{*N*-[2′-(7″-methoxybenzofuran-3″-yl)ethyl]-*N*-[α-methylbenzyl]amino}-6-(*tert*-butyldimethylsilyloxy)hex-4-enoate 261**



Following *general procedure 7*, **206** (8.00 g, 27.1 mmol, >99:1 er), BuLi (2.5 M, 10.4 mL, 26.0 mmol), **249** (6.75 g, 22.6 mmol, >99:1 dr) and (−)-CSO **95** (6.21 g, 27.1 mmol) were reacted in THF (270 mL). Purification via flash column chromatography (eluent, 30-40 °C petrol/Et_2O, 5:1) gave **260** as a yellow oil (861 mg, 5%, >99:1 dr). Further elution gave **261** as a yellow oil (8.12 g, 59%, >99:1 dr); $[\alpha]_D^{24}$ −24.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3505 (O−H), 1724 (C=O);

δ_H (400 MHz, CDCl$_3$) 0.07 (3H, s, Si*Me*$_A$), 0.08 (3H, s, Si*Me*$_B$), 0.91 (9H, s, SiC*Me*$_3$), 1.42 (3H, d, *J* 6.8, C(α)*Me*), 1.44 (9H, s, OC*Me*$_3$), 2.65-2.78 (2H, m, C(2′)*H*$_2$), 2.86-2.94 (1H, m, C(1′)*H*$_A$), 3.06-3.21 (2H, m, C(1′)*H*$_B$, O*H*), 3.69 (1H, dd, *J* 9.1, 3.0, C(3)*H*), 4.00 (3H, s, O*Me*), 4.17 (2H, d, *J* 4.8, C(6)*H*$_2$), 4.22-4.28 (2H, m, C(2)*H*, C(α)*H*), 5.71 (1H, ABdt, *J* 15.4, 4.8, C(5)*H*), 5.91 (1H, ABdd, *J* 15.4, 9.1, C(4)*H*), 6.78 (1H, d, *J* 7.8, C(6″)*H*), 6.92 (1H, d, *J* 7.8, C(4″)*H*), 7.10 (1H, app t, *J* 7.8, C(5″)*H*), 7.24-7.28 (1H, m, *Ph*), 7.34 (3H, t, *J* 7.3, *Ph*), 7.44-7.47 (2H, m, C(2″)*H*, *Ph*); δ_C (100 MHz, CDCl$_3$) −5.3 (Si*Me*$_2$), 16.1 (C(α)*Me*), 18.4 (Si*C*Me$_3$), 25.1 (*C*(2′)), 25.9 (SiC*Me*$_3$), 28.0 (OC*Me*$_3$), 47.3 (*C*(1′)), 56.0 (O*Me*), 58.2 (*C*(α)), 63.3 (*C*(6)), 63.7 (*C*(3)), 74.0 (*C*(2)), 82.2 (O*C*Me$_3$), 106.2 (*C*(6″)), 112.1 (*C*(4″)), 118.8 (*C*(3″)), 122.9 (*C*(5″)), 125.2 (*C*(4)), 126.8, 128.0, 128.1 (*o,m,p-Ph*), 130.0 (*C*(3a″)), 133.9 (*C*(5)), 141.5 (*C*(2″)), 144.4, 144.5, 145.4 (*C*(7″), *C*(7a″), *i-Ph*), 172.4 (*C*(1)); *m/z* (ESI$^+$) 632 ([M+Na]$^+$, 52%), 610 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{35}H_{52}NO_6Si^+$ ([M+H]$^+$) requires 610.3558; found 610.3564.

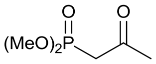
***tert*-Butyl (*R*,*R*,*R*,*E*)-2,6-dihydroxy-3-{[2′-(7″-methoxybenzofuran-3″-yl)ethyl][α-methylbenzyl]amino}hex-4-enoate 262**



Following *general procedure 8*, TBAF (1.0 M, 9.02 mL, 9.02 mmol) and **261** (5.00 g, 8.20 mmol, >99:1 dr) were reacted in THF (90 mL). Purification via flash column chromatography (gradient elution, 35 → 100% EtOAc in 30-40 °C petrol) gave **262** as a white gum (3.79 g, 93%, >99:1 dr); $C_{29}H_{37}NO_6$ requires C, 70.3; H, 7.5; N, 2.8%; found C, 70.4; H, 7.5; N, 2.8%; $[\alpha]_D^{24}$ −25.3 (*c* 1.0 in CHCl$_3$); ν_{max} (ATR) 3447 (O−H), 1726 (C=O); δ_H (400 MHz, CDCl$_3$) 1.38-1.47 (12H, m, C*Me*$_3$, C(α)*Me*), 1.91 (1H, br s, O*H*), 2.64-2.77 (2H, m, C(2′)*H*$_2$), 2.86-2.95 (1H, m, C(1′)*H*$_A$), 3.06-3.15 (1H, m, C(1′)*H*$_B$), 3.23 (1H, br s, O*H*), 3.67 (1H, dd, *J* 8.8, 3.0, C(3)*H*), 3.99 (3H, s, O*Me*), 4.10 (2H, d, *J* 5.0, C(6)*H*$_2$), 4.18-4.25 (2H, m, C(2)*H*, C(α)*H*), 5.75 (1H, ABdt, *J* 15.6, 5.0, C(5)*H*), 5.90 (1H, ABdd, *J* 15.6, 8.8, C(4)*H*), 6.77 (1H, d, *J* 7.7, C(6″)*H*), 6.92 (1H, d, *J* 7.7, C(4″)*H*), 7.10 (1H, app t, *J* 7.8, C(5″)*H*), 7.23-7.28 (1H, m, *Ph*), 7.31-7.36 (3H, m, *Ph*), 7.42-7.45 (2H, m, *Ph*, C(2″)*H*); δ_C (100 MHz, CDCl$_3$) 16.2 (C(α)*Me*), 25.2 (*C*(2′)), 28.0 (C*Me*$_3$), 47.4 (*C*(1′)), 56.0 (O*Me*), 58.4 (*C*(α)), 63.0 (*C*(6)), 63.7 (*C*(3)), 74.0 (*C*(2)), 82.4 (*C*Me$_3$), 106.2 (*C*(6″)), 112.1 (*C*(4″)), 118.8 (*C*(3″)), 122.9 (*C*(5″)), 126.8 (*C*(4)), 126.9, 128.0, 128.2 (*o,m,p-Ph*), 130.0 (*C*(3a″)), 133.5 (*C*(5)), 141.5 (*C*(2″)), 144.3, 144.5, 145.5 (*C*(7″), *C*(7a″), *i-Ph*), 172.6 (*C*(1)); *m/z* (ESI$^+$)

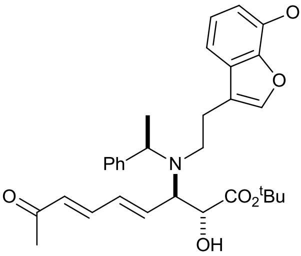
518 ([M+Na]$^+$, 66%), 496 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{37}NNaO_6^+$ ([M+Na]$^+$) requires 518.2513; found 518.2526.

Dimethyl (2-oxopropyl)phosphonate 10



Chloroacetone (39.0 mL, 490 mmol) was added to KI (82.0 g, 490 mmol) in MeCN (125 mL) and acetone (100 mL) at rt and the resultant mixture stirred for 1 h. $P(OMe)_3$ (58.0 mL, 490 mmol) was added dropwise and the resultant mixture was stirred at rt for 12 h, then heated at 50 °C for 3 h. The reaction mixture was allowed to cool to rt, filtered through Celite® (eluent acetone) and then concentrated *in vacuo*. Purification via distillation gave **10** as a yellow oil (40.5 g, 50%);[40] bp 112-115 °C (5 mbar); {lit.[40] bp 69-70 °C (0.5 mbar)}; δ_H (400 MHz, $CDCl_3$) 2.33 (3H, s, C(3)H_3), 3.12 (2H, d, *J* 22.9, C(1)H_2), 3.80 (6H, d, *J* 11.3, (O*Me*)$_2$).

***tert*-Butyl (*R*,*R*,*R*,*E*,*E*)-2-hydroxy-3-{*N*-[2′-(7″-methoxybenzofuran-3″-yl)ethyl]-*N*-[α-methylbenzyl]amino}-8-oxonona-4,6-dienoate 264**

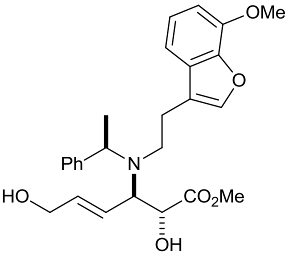


Step 1: Following *general procedure 9*, IBX (399 mg, 1.42 mmol) and **262** (443 mg, 830 μmol, >99:1 dr) were reacted in DMSO (9 mL) to give **263** as a yellow oil (473 mg, >99:1 dr); δ_H (400 MHz, $CDCl_3$) 1.37 (9H, s, C*Me*$_3$), 1.54 (3H, d, *J* 6.8, C(α)*Me*), 2.79-2.88 (2H, m, C(2′)H_2), 3.03-3.13 (1H, m, C(1′)H_A), 3.18-3.29 (1H, m, C(1′)H_B), 3.90 (1H, dd, *J* 7.9, 2.1, C(3)*H*), 4.01 (3H, s, C(7″)O*Me*), 4.19-4.25 (2H, m, C(2)*H*, C(α)*H*), 6.12 (1H, dd, *J* 15.8, 7.9, C(5)*H*), 6.79 (1H, d, *J* 7.9, C(6″)*H*), 6.86 (1H, dd, *J* 15.8, 7.9, C(4)*H*), 7.01 (1H, d, *J* 7.9, C(4″)*H*), 7.13 (1H, app t, *J* 7.9, C(5″)*H*), 7.31-7.43 (6H, m, C(2″)*H*, *Ph*), 9.43 (1H, d, *J* 7.9, C(6)*H*).

Step 2: Following *general procedure 10*, NaH (71 mg, 1.78 mmol), **10** (310 mg, 1.87 mmol) and **263** (473 mg, >99:1 dr) were reacted in THF (20 mL) to give **264** in >99:1 dr. Purification via flash column chromatography (gradient elution, 15% → 85% Et_2O in 30-40 °C petrol) gave **264** as a yellow solid (423 mg, 89% over 2 steps, >99:1 dr); $C_{32}H_{39}NO_6$ requires C, 72.0; H, 7.4; N, 2.6%; found C, 72.0; H, 7.4; N, 2.5%; mp 36-38 °C; $[\alpha]_D^{24}$ −8.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3442 (O−H), 1732 (C(1)=O), 1667 (C(8)=O), 1627, 1591 (C=C); δ_H (400 MHz, $CDCl_3$) 1.39 (9H, s, C*Me*$_3$), 1.42 (3H, d, *J* 6.8, C(α)*Me*), 2.27 (3H, s, C(9)H_3), 2.77 (2H, app t, *J* 7.6, C(2′)H_2), 2.95-3.03 (1H, m, C(1′)H_A), 3.12-3.20 (1H, m, C(1′)H_B), 3.74 (1H, dd, *J* 8.1, 2.8, C(3)*H*), 4.00 (3H, s, O*Me*), 4.21-4.26

(2H, m, C(2)*H*, C(α)*H*), 6.04 (1H, d, *J* 15.8, C(7)*H*), 6.20 (1H, ABdd, *J* 15.4, 10.1, C(5)*H*), 6.28 (1H, ABdd, *J* 15.4, 8.1, C(4)*H*), 6.78 (1H, d, *J* 7.8, C(6″)*H*), 6.96 (1H, d, *J* 6.8, C(4″)*H*), 7.01 (1H, dd, *J* 15.8, 10.1, C(6)*H*), 7.11 (1H, app t, *J* 7.8, C(5″)*H*), 7.24-7.29 (1H, m, *Ph*), 7.31-7.38 (3H, m, *Ph*), 7.41-7.45 (2H, m, *Ph*, C(2″)*H*); δ_C (100 MHz, $CDCl_3$) 16.6 (C(α)*Me*), 25.1 (*C*(2′)), 26.9 (*C*(9)), 28.0 (C*Me*$_3$), 47.3 (*C*(1′)), 56.0 (O*Me*), 58.4 (*C*(α)), 63.3 (*C*(3)), 73.8 (*C*(2)), 82.8 (*C*Me$_3$), 106.3 (*C*(6″)), 112.0 (*C*(4″)), 118.6 (*C*(3″)), 123.0 (*C*(5″)), 127.1, 127.9, 128.3 (*o,m,p-Ph*), 129.9 (*C*(3a″)), 130.8 (*C*(7)), 131.6 (*C*(5)), 139.6 (*C*(4)), 141.6 (*C*(2″)), 142.6 (*C*(6)), 143.9, 144.5, 145.5 (*C*(7″), *C*(7a″), *i-Ph*), 172.3 (*C*(1)), 198.7 (*C*(8)); *m/z* (ESI$^+$) 556 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{40}NO_6^+$ ([M+H]$^+$) requires 534.2850; found 534.2848.

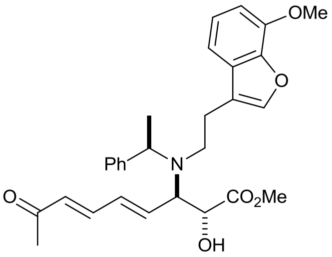
Methyl (*R,R,R,E*)-2,6-dihydroxy-3-{*N*-[2′-(7″-methoxybenzofuran-3″-yl)ethyl]-*N*-[α-methylbenzyl]amino}hex-4-enoate 267



$SOCl_2$ (0.48 mL, 6.58 mmol) was added to MeOH (1.5 mL) at rt and the resultant mixture stirred for 1 min. **261** (400 mg, 646 µmol, >99:1 dr) in MeOH (1.5 mL) was added and the reaction mixture stirred at rt for 25 h. Sat aq $NaHCO_3$ (5 mL) and CH_2Cl_2 (10 mL) were added and the aqueous layer extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 15% → 80% EtOAc in 30-40 °C petrol) gave **267** as a colourless oil (265 mg, 90%, >99:1 dr); $[\alpha]_D^{24}$ −31.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3401 (O−H), 1739 (C=O), 1625 (C=C); δ_H (400 MHz, $CDCl_3$) 1.39 (3H, d, *J* 6.7, C(α)*Me*), 2.33 (1H, br s, O*H*), 2.59-2.74 (2H, m, C(2′)*H*$_2$), 2.80-2.88 (1H, m, C(1′)*H*$_A$), 2.97-3.05 (1H, m, C(1′)*H*$_B$), 3.44 (1H, br s, O*H*), 3.67 (1H, dd, *J* 9.0, 4.6, C(3)*H*), 3.69 (3H, s, CO$_2$*Me*), 3.98 (3H, s, C(7″)O*Me*), 4.11 (2H, d, *J* 5.0, C(6)*H*$_2$), 4.18 (1H, q, *J* 6.7, C(α)*H*), 4.31 (1H, d, *J* 4.6, C(2)*H*), 5.80 (1H, ABdt, *J* 15.5, 5.0, C(5)*H*), 5.91 (1H, ABdd, *J* 15.5, 9.0, C(4)*H*), 6.77 (1H, d, *J* 7.8, C(6″)*H*), 6.89 (1H, d, *J* 7.8, C(4″)*H*), 7.10 (1H, app t, *J* 7.8, C(5″)*H*), 7.24-7.29 (1H, m, *Ph*), 7.31-7.37 (3H, m, *Ph*), 7.40-7.43 (2H, m, C(2″)*H*, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.6 (C(α)*Me*), 25.0 (*C*(2′)), 47.7 (*C*(1′)), 52.2 (CO$_2$*Me*), 56.0 (C(7″)O*Me*), 58.2 (*C*(α)), 62.9 (*C*(6)), 64.3 (*C*(3)), 73.5 (*C*(2)), 106.3 (*C*(6″)), 111.9 (*C*(4″)), 118.6 (*C*(3″)), 123.0 (*C*(5″)), 126.9 (*C*(4)), 127.0, 127.9, 128.3 (*o,m,p-Ph*), 129.8 (*C*(3a″)), 134.1 (*C*(5)), 141.5 (*C*(2″)), 143.9, 144.5, 145.5

(*C*(7″), *C*(7a″), *i-Ph*), 173.6 (*C*(1)); *m/z* (ESI$^+$) 929 ([2M+Na]$^+$, 98%), 476 ([M+Na]$^+$, 100%), 454 ([M+H]$^+$, 95%); HRMS (ESI$^+$) $C_{26}H_{32}NO_6^+$ ([M+H]$^+$) requires 454.2224; found 454.2217.

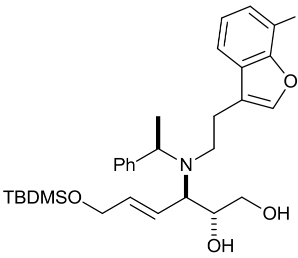
Methyl (*R*,*R*,*R*,*E*,*E*)-2-hydroxy-3-{*N*-[2′-(7″-methoxybenzofuran-3″-yl)ethyl]-*N*-[α-methylbenzyl]amino}-8-oxonona-4,6-dienoate 266



Step 1: Following *general procedure 9*, IBX (187 mg, 674 µmol) and **267** (191 mg, 422 µmol, >99:1 dr) were reacted in DMSO (3.6 mL) to give **268** as a yellow oil (132 mg).

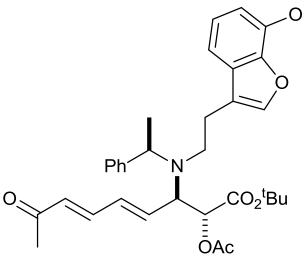
Step 2: Following *general procedure 10*, NaH (36 mg, 833 µmol), **10** (162 mg, 883 µmol) and **268** (132 mg) were reacted in THF (7 mL) to give **266** in >99:1 dr. Purification via flash column chromatography (gradient elution, 15% → 85% Et_2O in 30-40 °C petrol) gave **266** as a yellow oil (46 mg, 22% over 2 steps, >99:1 dr); $[\alpha]_D^{24}$ −20.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3442 (O−H), 1745 (C=O), 1733 (C=O), 1667 (C=C); δ_H (400 MHz, $CDCl_3$) 1.41 (3H, d, *J* 6.8, C(α)*Me*), 2.27 (3H, s, C(9)H_3), 2.67-2.82 (2H, m, C(2′)H_2), 2.88-2.97 (1H, m, C(1′)H_A), 3.01-3.11 (1H, m, C(1′)H_B), 3.70 (3H, s, CO_2*Me*), 3.72-3.79 (1H, m, C(3)*H*), 4.00 (3H, s, C(7″)O*Me*), 4.21 (1H, q, *J* 6.8, C(α)*H*), 4.31 (1H, d, *J* 4.0, C(2)*H*), 6.09 (1H, d, *J* 15.9, C(7)*H*), 6.22-6.34 (2H, m, C(5)*H*, C(4)*H*), 6.79 (1H, d, *J* 7.8, C(6″)*H*), 6.94 (1H, d, *J* 7.8, C(4″)*H*), 7.04 (1H, dd, *J* 15.9, 9.9, C(6)*H*), 7.12 (1H, app t, *J* 7.9, C(5″)), 7.24-7.31 (1H, m, *Ph*), 7.32-7.38 (3H, m, *Ph*), 7.39-7.44 (2H, m, C(2″)*H*, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.1 (C(α)*Me*), 25.0 (C(2′)) 27.1 (*C*(9)), 47.7 (*C*(1′)), 52.5 (CO_2*Me*), 56.0 (C(7″)O*Me*), 58.5 (*C*(α)), 63.8 (*C*(3)), 73.5 (*C*(2)), 106.4 (*C*(6″)), 111.9 (*C*(4″)), 118.4 (*C*(3″)), 123.1 (*C*(5″)), 127.2, 127.8, 128.3 (*o,m,p-Ph*), 129.8 (*C*(3a″)), 131.1 (*C*(7)), 132.0 (*C*(5)), 139.2 (*C*(4)), 141.6 (*C*(2″)), 142.3 (*C*(6)), 143.6, 144.5, 145.5 (*C*(7″), *C*(7a″), *i-Ph*), 173.3 (*C*(1)), 198.5 (*C*(8)); *m/z* (ESI$^+$) 514 ([M+Na]$^+$, 98%), 492 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{34}NO_6^+$ ([M+H]$^+$) requires 492.2381; found 492.2372.

(*R*,*R*,*R*,*E*)-3-{*N*-[2′-(7″-Methoxybenzofuran-3″-yl)ethyl]-*N*-[α-methylbenzyl]amino}-6-(*tert*-butyldimethylsilyloxy)hex-4-en-1,2-diol 270



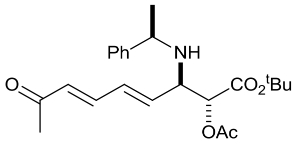
DIBAL-H (1.0 M in CH_2Cl_2, 1.13 mL, 1.13 mmol) was added to **261** (200 mg, 323 µmol, >99:1 dr) in CH_2Cl_2 (5 mL) at rt and resultant mixture was stirred for 5 h. Sat aq Na_2SO_4 (3 mL) was added and the aqueous layer extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were washed with brine (15 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 25% → 85% EtOAc in 30-40 °C petrol) gave **270** as a yellow oil (8 mg, 5%, >99:1 dr); $[\alpha]_D^{24}$ −8.2 (*c* 0.8 in $CHCl_3$); ν_{max} (ATR) 3423 (O−H); δ_H (500 MHz, $CDCl_3$) 0.08 (6H, s, SiMe_2), 0.91 (9H, s, CMe_3), 1.41 (3H, d, *J* 6.8, C(α)*Me*), 2.61-2.76 (2H, m, C(2′)H_2), 2.82-2.89 (1H, m, C(1′)H_A), 2.96-3.03 (1H, m, C(1′)H_B), 3.35 (1H, app t, *J* 8.5, C(3)*H*), 3.52 (1H, ABdd, *J* 11.4, 5.0, C(1)H_A), 3.58 (1H, ABdd, *J* 11.4, 5.4, C(1)H_B), 3.65-3.71 (1H, m, C(2)*H*), 4.00 (3H, s, O*Me*), 4.14 (1H, q, *J* 6.8, C(α)*H*), 4.22 (2H, d, *J* 3.8, C(6)H_2), 5.82 (1H, ABdt, *J* 15.5, 3.8, C(5)*H*), 5.87-5.93 (1H, m, C(4)*H*), 6.79 (1H, d, *J* 7.6, C(6″)*H*), 6.89 (1H, d, *J* 7.3, C(4″)*H*), 7.12 (1H, app t, *J* 7.9, C(5″)*H*), 7.27-7.45 (6H, m, C(2″)*H*, *Ph*); δ_C (125 MHz, $CDCl_3$) −5.3 (SiMe_2), 15.5 (C(α)*Me*), 18.3 (*C*Me_3), 24.7 (*C*(2′)), 25.8 (CMe_3), 47.8 (*C*(1′)), 56.0 (O*Me*), 58.5 (*C*(α)), 63.0 (*C*(6)), 63.7 (*C*(3)), 65.2 (*C*(1)), 70.8 (*C*(2)), 106.4 (*C*(6″)), 111.8 (*C*(4″)), 118.4 (*C*(3″)), 123.1 (*C*(5″)), 125.9 (*C*(4)), 127.3, 128.1, 128.4 (*o,m,p-Ph*), 129.6 (*C*(3a″)), 135.5 (*C*(5)), 141.4, 144.5, 145.5 (C(2″), *C*(7″), *C*(7a″), *i-Ph*); *m/z* (ESI^+) 540 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{31}H_{46}NO_5Si^+$ ($[M+H]^+$) requires 540.3140; found 540.3135. Further elution gave **206** as a yellow oil (24 mg, 25%).

tert-Butyl (*R*,*R*,*R*,*E*,*E*)-2-acetoxy-3-{-*N*-[2′-(7″-methoxybenzofuran-3″-yl)ethyl]-*N*-[α-methylbenzyl]amino}-8-oxonona-4,6-dienoate 271



Ac_2O (18 µL, 190 µmol) was added to **264** (50 mg, 93.7 µmol, >99:1 dr) and DMAP (5 mg, 40.9 µmol) in pyridine (0.5 mL) at rt and the resultant was mixture stirred for 15 min. The reaction mixture was partitioned between sat aq $CuSO_4$ (5 mL) and CH_2Cl_2 (5 mL), and the aqueous layer extracted with CH_2Cl_2 (5 mL). The combined organic extracts were washed with H_2O (10 mL) and brine (10 mL), then dried and concentrated *in vacuo* to give **271** as a yellow oil (53 mg, 98%, >99:1 dr); $[\alpha]_D^{24}$ −6.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1744 (C=O), 1669 (C=C); δ_H (400 MHz, $CDCl_3$) 1.37 (9H, s, C*Me*$_3$), 1.45 (3H, d, *J* 6.7, C(α)*Me*), 2.04 (3H, s, CO*Me*), 2.27 (3H, s, C(9)*H*$_3$), 2.72 (2H, t, *J* 7.6, C(2′)*H*$_2$), 2.98-3.05 (2H, m, C(1′)*H*$_2$), 3.94 (1H, app br t, *J* 4.8, C(3)*H*), 3.99 (3H, s, C(7″)O*Me*), 4.14 (1H, q, *J* 6.7, C(α)*H*), 5.12 (1H, d, *J* 3.8, C(2)*H*), 6.07 (1H, d, *J* 15.7, C(7)*H*), 6.19-6.30 (2H, m, C(4)*H*, C(5)*H*), 6.79 (1H, d, *J* 7.8, C(6″)*H*), 6.93 (1H, d, *J* 7.6, C(4″)*H*), 7.02 (1H, dd, *J* 15.7, 9.4, C(6)*H*), 7.12 (1H, app t, *J* 7.8, C(5″)*H*), 7.25-7.30 (1H, m, *Ph*), 7.32-7.38 (3H, m, C(2″)*H*, *Ph*), 7.39-7.45 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.0 (C(α)*Me*), 20.7 (CO*Me*), 25.4 (*C*(2′)), 27.1 (*C*(9)), 27.9 (C*Me*$_3$), 47.6 (*C*(1′)), 56.0 (C(7″)O*Me*), 59.3 (*C*(α)), 61.3 (*C*(3)), 74.9 (*C*(2)), 82.5 (*C*Me$_3$), 106.3 (*C*(6″)), 111.8 (*C*(4″)), 118.5 (*C*(3″)), 123.1 (*C*(5″)), 127.2, 127.7, 128.4 (*o,m,p-Ph*), 129.7 (*C*(3a″)), 131.0 (*C*(7)), 132.1 (*C*(5)), 138.8 (*C*(4)), 141.4 (*C*(2″)), 142.4 (*C*(6)), 143.9, 144.5, 145.6 (C(7″), C(7a″), *i-Ph*), 167.4 (*C*OMe), 170.1 (*C*(1)), 198.6 (*C*(8)); *m/z* (ESI^+) 598 ($[M+Na]^+$, 100%), 576 ($[M+H]^+$, 63%); HRMS (ESI^+) $C_{34}H_{41}NNaO_7^+$ ($[M+Na]^+$) requires 598.2775; found 598.2773.

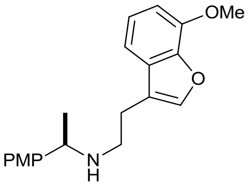
***tert*-Butyl (*R*,*R*,*R*,*E*,*E*)-2-acetoxy-3-[*N*-(α-methylbenzyl)amino]-8-oxonona-4,6-dienoate 272**



CAN (100 mg, 183 μmol) was added to **271** (50 mg, 87 μmol, >99:1 dr) in MeCN (2 mL) and H_2O (0.5 mL) at rt and the resultant mixture was stirred for 30 min. Sat aq $NaHCO_3$ (5 mL) and Et_2O (5 mL) were added and the resultant mixture was stirred for 10 min. The aqueous layer was extracted with Et_2O (2 × 5 mL) and the combined organic extracts were washed with brine (20 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 75% → 100% Et_2O in 30-40 °C petrol) gave **272** as a yellow oil (21 mg, 60%, >99:1 dr); $[\alpha]_D^{24}$ +0.6 (*c* 0.7 in $CHCl_3$); ν_{max} (ATR) 1744 (C=O), 1669 (C=C); δ_H (500 MHz, $CDCl_3$) 1.35 (3H, br s, C(α)*Me*), 1.40 (9H, s, C*Me*$_3$), 2.18 (3H, s, CO*Me*), 2.27 (3H, s, C(9)*H*$_3$), 3.64 (1H, dd, *J* 7.3, 2.2, C(3)*H*), 3.89 (1H, br q, *J* 6.0, C(α)*H*), 5.21 (1H, br s, C(2)*H*), 6.01 (1H, br dd, *J* 15.3, 7.6, C(4)*H*), 6.10 (1H, d, *J* 15.7, C(7)*H*), 6.29 (1H, dd, *J* 15.3, 10.7, C(5)*H*), 7.04 (1H, dd, *J* 15.7, 10.7, C(6)*H*), 7.22-7.29 (1H, m, *Ph*), 7.31-7.38 (4H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 21.2 (CO*Me*), *24.2* (C(α)*Me*), 27.5 (*C*(9)), 28.4 (C*Me*$_3$), *55.4* (*C*(α)), 58.4 (*C*(3)), 83.2 (*C*Me$_3$), 127.2, *127.8*, 129.0 (*o,m,p-Ph*), *131.5* (*C*(5), *C*(7)), *140.4* (*C*(4)), *142.8* (*C*(6)), 170.8 (*C*(1), *C*OMe), 199.0 (*C*(8));[41] *m/z* (ESI^+)

424 ($[M+Na]^+$, 91%), 402 ($[M+H]^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{31}NNaO_5^+$ ($[M+Na]^+$) requires 424.2094; found 424.2082.

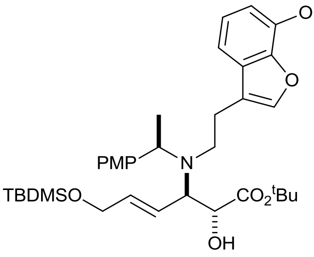
(*R*)-*N*-[2-(7′-Methoxybenzofuran-3′-yl)ethyl]-*N*-(α-methyl-4″-methoxybenzyl)amine 273



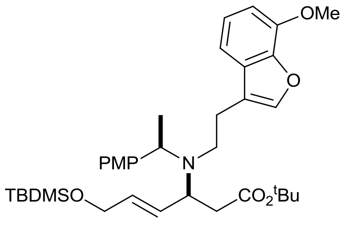
Step 1: TsCl (7.95 g, 41.7 mmol) was added to **256** (4.00 g, 20.8 mmol) and DMAP (189 mg, 1.55 mmol) in pyridine (100 mL) at rt and the resultant mixture was stirred for 18 h. The reaction mixture was partitioned between H_2O (100 mL) and Et_2O (100 mL) and the aqueous layer was extracted with Et_2O (2 × 100 mL). The combined organic extracts were washed with 2.0 M aq HCl (400 mL), sat aq $NaHCO_3$ (200 mL) and brine (200 mL), then dried and concentrated *in vacuo* to give a 71:29 mixture of **257**:**258** (5.23 g).

Step 2: NaI (7.39 g, 49.3 mmol) and (*R*)-α-methyl-4-methoxybenzylamine **280** (8.71 mL, 59.0 mmol, 99.5:0.5 er) were added to the 71:29 mixture of **257**:**258** (5.23 g) in MeCN (75 mL) and the resultant mixture stirred and heated at reflux for 48 h, then allowed to cool to rt. The reaction mixture was partitioned between EtOAc (75 mL) and sat aq $NaHCO_3$ (75 mL) and the aqueous layer extracted with EtOAc (75 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (eluent Et_2O) gave **273** as a yellow oil (3.93 g, 67% over 2 steps, >99:1 er); $C_{20}H_{23}NO_3$ requires C, 73.8; H, 7.1; N, 4.3%; found C, 73.9; H, 7.2; N, 4.2%; $[\alpha]_D^{24}$ −23.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3312 (N−H); δ_H (400 MHz, $CDCl_3$) 1.33 (3H, d, *J* 6.6, C(α)*Me*), 2.77-2.88 (4H, m, C(1)H_2, C(2)H_2), 3.76 (1H, q, *J* 6.6, C(α)*H*), 3.80 (3H, s, C(4″)O*Me*), 4.01 (3H, s, C(7′)O*Me*), 6.81 (1H, d, *J* 7.1, C(6′)*H*), 6.84-6.88 (2H, m, C(3″)*H*, C(5″)*H*), 7.10 (1H, ABd, *J* 7.8, C(4′)*H*), 7.15 (1H, app ABt, *J* 7.6, C(5′)*H*), 7.18-7.22 (2H, m, C(2″)*H*, C(6″)*H*), 7.45 (1H, s, C(2′)*H*); δ_C (100 MHz, $CDCl_3$) 24.4 (C(α)*Me*), 24.5 (*C*(2)), 46.5 (*C*(1)), 55.2 (C(4″)O*Me*), 56.0 (C(7′)O*Me*), 57.5 (*C*(α)), 106.4 (*C*(6′)), 112.0 (*C*(4′)), 113.8 (*C*(3″), *C*(5″)), 118.6 (*C*(3′)), 123.1 (*C*(5′)), 127.5 (*C*(2″), *C*(6″)), 129.8 (*C*(3a′)), 137.6 (*C*(1″)), 141.7 (*C*(2′)), 144.6, 145.6 (*C*(7′), *C*(7a′)), 158.5 (*C*(4″)); *m/z* (ESI$^+$) 348 ($[M+Na]^+$, 4%), 326 ($[M+H]^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{24}NO_3^+$ ($[M+H]^+$) requires 326.1751; found 326.1751.

tert-Butyl (*R*,*R*,*R*,*E*)-2-hydroxy-3-{*N*-[2′-(7″-methoxybenzofuran-3″-yl)ethyl]-*N*-[α-methyl-4‴-methoxybenzyl]amino}-6-(*tert*-butyldimethylsilyloxy)hex-4-enoate 275 and *tert*-Butyl (3*S*,α*R*,*E*)-3-{*N*-[2′-(7″-methoxybenzofuran-3″-yl)ethyl]-*N*-[α-methyl-4‴-methoxybenzyl]amino}-6-(*tert*-butyldimethylsilyloxy)hex-4-enoate 276



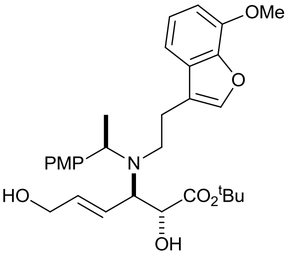
275



276

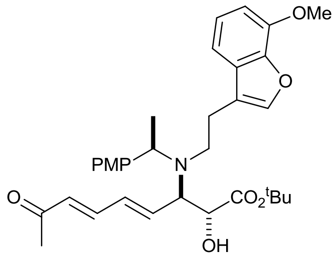
Following *general procedure 7*, **273** (3.00 g, 9.22 mmol, >99:1 er), BuLi (2.4 M, 3.68 mL, 8.84 mmol), **249** (2.29 g, 7.68 mmol, >99:1 dr) and (−)-CSO **95** (2.11 g, 9.22 mmol) were reacted in THF (90 mL). Purification via flash column chromatography (gradient elution, 17% → 30% Et_2O in 30-40 °C petrol) gave **276** as a yellow oil (383 mg, 8%, >99:1 dr); $[\alpha]_D^{24}$ +4.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 0.09 (6H, s, Si*Me*$_2$), 0.93 (9H, s, SiC*Me*$_3$), 1.42 (3H, d, *J* 6.9, C(α)*Me*), 1.48 (9H, s, OC*Me*$_3$), 2.42 (1H, ABdd, *J* 14.4, 7.6, C(2)H_A), 2.52-2.88 (5H, m, C(2)H_B, C(1′)H_2, C(2′)H_2), 3.81 (3H, s, C(4‴)O*Me*), 3.94-3.98 (1H, m, C(3)*H*) 3.98 (3H, s, C(7″)O*Me*), 4.04 (1H, q, *J* 6.9, C(α)*H*), 4.18 (2H, d, *J* 4.3, C(6)H_2), 5.52-5.82 (2H, m, C(4)*H*, C(5)*H*), 6.77 (1H, d, *J* 8.1, C(6″)*H*), 6.84-6.88 (3H, m, C(4″)*H*, C(3‴)*H*, C(5‴)*H*), 7.09 (1H, app t, *J* 7.8, C(5″)*H*), 7.30-7.34 (3H, m, C(2″)*H*, C(2‴)*H*, C(3‴)*H*); δ_C (100 MHz, $CDCl_3$) −5.2 (Si*Me*$_2$), 18.4 (Si*C*Me$_3$), 19.5 (C(α)*Me*), 25.3 (*C*(2′)), 25.9 (SiC*Me*$_3$), 28.2 (OC*Me*$_3$), 40.0 (*C*(2)), 47.1 (*C*(1′)), 55.2 (C(4‴)O*Me*), 56.0 (C(7″)O*Me*), 57.2 (*C*(α)), 58.2 (*C*(3)), 63.4 (*C*(6)), 80.2 (*C*Me$_3$), 106.2 (*C*(6″)), 112.1 (*C*(4″)), 113.4 (*C*(3‴), *C*(5‴)), 119.0 (*C*(3″)), 122.8 (*C*(5″)), 128.7 (*C*(4)), 128.8 (C(2‴), C(6‴)), 129.2 (*C*(1‴)), 130.0 (*C*(3a″)), 131.1 (*C*(5)), 141.3 (*C*(2″)), 144.5, 145.5 (*C*(7″), *C*(7a″)), 158.5 (*C*(4‴)), 171.2 (*C*(1)); *m/z* (ESI^+) 646 ($[M+Na]^+$, 100%), 624 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{36}H_{54}NO_6Si^+$ ($[M+H]^+$) requires 624.3715; found 624.3707. Further elution gave **275** as a yellow oil (2.24 g, 46%, >99:1 dr); $C_{36}H_{53}NO_7Si$ requires C, 67.6; H, 8.35; N, 2.2%; found C, 67.5; H, 8.45; N, 2.2%; $[\alpha]_D^{24}$ −24.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 0.06 (3H, s, SiMe_A), 0.07 (3H, s, SiMe_B), 0.90 (9H, s, SiC*Me*$_3$), 1.37 (3H, d, *J* 6.8, C(α)*Me*), 1.44 (9H, s, OC*Me*$_3$), 2.63-2.77 (2H, m, C(2′)H_2), 2.82-2.91 (1H, m, C(1′)H_A), 3.02-3.12 (1H, m, C(1′)H_B), 3.15-3.21 (1H, br m, O*H*), 3.66 (1H, dd, *J* 8.8, 3.0, C(3)*H*), 3.81 (3H, s, C(4‴)O*Me*), 4.00 (3H, s, C(7″)O*Me*), 4.14-4.23 (4H, m, C(2)*H*, C(6)H_2, C(α)*H*), 5.70 (1H, app dt, *J* 15.4, 4.8, C(5)*H*), 5.84-5.93 (1H, m, C(4)*H*), 6.77 (1H, d, *J* 7.6, C(6″)*H*), 6.86 (2H, d, *J* 8.5, C(3‴)*H*, C(5‴)*H*), 6.93 (1H, d, *J* 7.8, C(4″)*H*), 7.10 (1H, app t, *J* 7.8, C(5″)*H*), 7.34 (3H, m, C(2″)*H*, C(2‴)*H*, C(6‴)*H*); δ_C (100 MHz, $CDCl_3$) −5.3 (Si*Me*$_2$), 15.9 (C(α)*Me*), 18.3 (Si*C*Me$_3$), 25.1 (*C*(2′)), 25.9 (SiC*Me*$_3$), 28.0 (OC*Me*$_3$), 47.1 (*C*(1′)), 55.2 (C(4‴)O*Me*), 56.0 (C(7″)O*Me*), 57.5 (*C*(α)), 63.3 (*C*(6)), 63.7 (*C*(3)), 74.0 (*C*(2)), 82.1 (*C*Me$_3$), 106.2 (*C*(6″)), 112.1 (*C*(4″)), 113.4 (*C*(3‴), *C*(5‴)), 118.8 (*C*(3″)), 122.8 (*C*(5″)), 125.3 (*C*(4)), 129.0 (*C*(2‴), *C*(6‴)), 130.0 (*C*(3a″)), 133.9 (*C*(5)), 136.4 (*C*(1‴)), 141.5 (*C*(2″)), 144.4, 145.4 (*C*(7″), *C*(7a″)), 158.4 (*C*(4‴)), 172.4 (*C*(1)); *m/z* (ESI^+) 662 ($[M+Na]^+$, 100%), 640 ($[M+H]^+$, 91%), 506 ($[M-C_9H_{10}O]^+$, 71%); HRMS (ESI^+) $C_{36}H_{54}NO_7Si^+$ ($[M+H]^+$) requires 640.3664; found 640.3673.

***tert*-Butyl (*R*,*R*,*R*,*E*)-2,6-dihydroxy-3-{*N*-[2′-(7″-methoxybenzofuran-3″-yl)ethyl]-*N*-[α-methyl-4‴-methoxybenzyl]amino}hex-4-enoate 277**



Following *general procedure 8*, TBAF (1.0 M, 1.29 mL, 1.29 mmol) and **275** (750 mg, 1.17 mmol, >99:1 dr) were reacted in THF (13 mL). Purification via flash column chromatography (gradient elution, 50 → 100% Et_2O in 30-40 °C petrol) gave **277** as a white solid (705 mg, 87%, >99:1 dr); mp 36-39 °C; $[\alpha]_D^{24}$ −30.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3455 (O−H), 1727 (C=O); δ_H (400 MHz, $CDCl_3$) 1.37 (3H, d, *J* 6.7, C(α)*Me*), 1.42 (9H, s, C*Me*$_3$), 2.09 (1H, br s, O*H*), 2.62-2.76 (2H, m, C(2′)*H*$_2$), 2.82-2.92 (1H, m, C(1′)*H*$_A$), 3.03-3.12 (1H, m, C(1′)*H*$_B$), 3.30 (1H, br s, O*H*), 3.65 (1H, dd, *J* 9.0, 3.0, C(3)*H*), 3.80 (3H, s, C(4‴)O*Me*), 3.99 (3H, s, C(7″)O*Me*), 4.09 (2H, app br s, C(6)*H*$_2$), 4.16 (1H, q, *J* 6.7, C(α)*H*), 4.21 (1H, d, *J* 3.0, C(2)*H*), 5.74 (1H, ABdt, *J* 15.6, 5.1, C(5)*H*), 5.89 (1H, ABdd, *J* 15.6, 9.0, C(4)*H*), 6.76 (1H, d, *J* 7.8, C(6″)*H*), 6.85 (2H, d, *J* 8.6, C(3‴)*H*, C(5‴)*H*), 6.93 (1H, d, *J* 7.6, C(4″)*H*), 7.09 (1H, app t, *J* 7.8, C(5″)*H*), 7.31-7.36 (3H, m, C(2″)*H*, C(2‴)*H*, C(6‴)*H*); δ_C (100 MHz, $CDCl_3$) 16.0 (C(α)*Me*), 25.1 (*C*(2′)), 28.0 (C*Me*$_3$), 47.2 (*C*(1′)), 55.2 (C(4‴)O*Me*), 56.0 (C(7″)O*Me*), 57.7 (*C*(α)), 63.0 (*C*(6)), 63.7 (*C*(3)), 74.0 (*C*(2)), 82.3 (*C*Me$_3$), 106.2 (*C*(6″)), 112.1 (*C*(4″)), 113.5 (*C*(3‴), *C*(5‴)), 118.8 (*C*(3″)), 122.9 (*C*(5″)), 126.9 (*C*(4)), 129.0 (*C*(2‴), *C*(6‴)), 130.0 (*C*(3a″)), 133.5 (*C*(5)), 136.2 (*C*(1‴)), 141.5 (*C*(2″)), 144.4, 145.4 (*C*(7″), *C*(7a″)), 158.5 (*C*(4‴)), 172.6 (*C*(1)); *m/z* (ESI^+) 548 ($[M+Na]^+$, 100%), 526 ($[M+H]^+$, 93%), 392 ($[M-C_9H_{10}O]^+$, 90%); HRMS (ESI^+) $C_{30}H_{40}NO_7^+$ ($[M+H]^+$) requires 526.2799; found 526.2807.

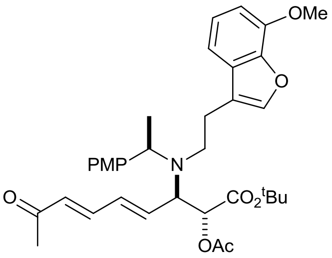
tert-Butyl (*R*,*R*,*R*,*E*,*E*)-2-hydroxy-3-{[2′-(7″-methoxybenzofuran-3″-yl)ethyl][α-methyl-4‴-methoxybenzyl]amino}-8-oxonona-4,6-dienoate 279



Step 1: Following *general procedure 9*, IBX (317 mg, 1.13 mmol) and **277** (350 mg, 666 µmol, >99:1 dr) were reacted in DMSO (7.0 mL) to give **278** as a yellow oil (420 mg, >99:1 dr); δ_H (400 MHz, $CDCl_3$) 1.36-1.41 (12H, m, C(α)*Me*, CMe_3), 2.80-2.87 (2H, m, C(2′)H_2), 3.01-3.10 (1H, m, C(1′)H_{A}), 3.16-3.26 (1H, m, C(1′)H_{B}), 3.81 (3H, s, C(4‴)O*Me*), 3.89 (1H, dd, *J* 7.9, 2.4, C(3)*H*), 4.01 (3H, s, C(7″)O*Me*), 4.13 (1H, q, *J* 7.2, C(α)*H*), 4.21 (1H, d, *J* 2.4, C(2)*H*), 6.12 (1H, dd, *J* 15.9, 7.9, C(5)*H*), 6.78-6.89 (4H, m, C(4)*H*, C(6″)*H*, C(3‴)*H*, C(5‴)*H*), 7.03 (1H, d, *J* 7.7, C(4″)*H*), 7.13 (1H, app t, *J* 7.7, C(5″)*H*), 7.31 (2H, d, *J* 8.7, C(2‴)*H*, C(6‴)*H*), 7.41 (1H, s, C(2″)*H*), 9.43 (1H, d, *J* 7.9, C(6)*H*).

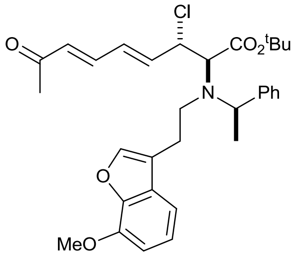
Step 2: Following *general procedure 10*, NaH (57 mg, 1.40 mmol), **10** (244 mg, 1.47 mmol, >99:1 dr) and **278** (132 mg) were reacted in THF (13 mL) to give **279** in 88:12 dr. Purification via flash column chromatography (gradient elution, 30% → 100% Et_2O in 30-40 °C petrol) gave **279** as a yellow oil (188 mg, 50% over 2 steps, 88:12 dr); ν_{max} (ATR) 3485 (O−H), 1727 (C(1)=O), 1668 (C(8)=O), 1626, 1591 (C=C); δ_H (400 MHz, $CDCl_3$) 1.36-1.41 (12H, m, C(α)*Me*, CMe_3), 2.26 (3H, s, C(9)H_3), 2.75 (2H, t, *J* 8.1, C(2′)H_2), 2.92-2.99 (1H, m, C(1′)H_{A}), 3.09-3.17 (1H, m, C(1′)H_{B}), 3.73 (1H, dd, *J* 8.1, 2.8, C(3)*H*), 3.80 (3H, s, C(4‴)O*Me*), 3.99 (3H, s, C(7″)O*Me*), 4.15-4.20 (2H, m, C(2)*H*, C(α)*H*), 6.04 (1H, d, *J* 15.8, C(7)*H*), 6.17-6.31 (2H, m, C(4)*H*, C(5)*H*), 6.77 (1H, d, *J* 7.6, C(6″)*H*), 6.86 (2H, d, *J* 8.6, C(3‴)*H*, C(5‴)*H*), 6.97 (1H, d, *J* 7.8, C(4″)*H*), 7.01 (1H, dd, *J* 15.8, 10.1, C(6)*H*), 7.10 (1H, app t, *J* 7.8, C(5″)*H*), 7.32 (1H, d, *J* 8.6, C(2‴)*H*, C(6‴)*H*), 7.38 (1H, s, C(2″)*H*); δ_C (100 MHz, $CDCl_3$) 16.5 (C(α)*Me*), 25.1 (*C*(2′)), 26.9 (*C*(9)), 28.0 (CMe_3), 47.2 (*C*(1′)), 55.2 (C(4‴)O*Me*), 56.0 (C(7″)O*Me*), 57.9 (*C*(α)), 63.2 (*C*(3)), 73.8 (*C*(2)), 82.7 (*C*Me_3), 106.2 (*C*(6″)), 112.0 (*C*(4″)), 113.5 (*C*(3‴), *C*(5‴)), 118.7 (*C*(3″)), 122.9 (*C*(5″)), 128.9 (*C*(2‴), *C*(6‴)), 129.9 (*C*(3a″)), 130.8 (*C*(7)), 131.5 (*C*(5)), 135.9 (*C*(1‴)), 139.8 (*C*(4)), 141.6 (*C*(2″)), 142.6 (*C*(6)), 144.5, 145.5 (*C*(7″), *C*(7a″)), 158.6 (*C*(4‴)), 172.3 (*C*(1)), 198.6 (*C*(8)); *m/z* (ESI^+) 586 ($[M+Na]^+$, 100%), 564 ($[M+H]^+$, 97%), 430 ($[M-C_9H_{10}O]^+$, 94%); HRMS (ESI^+) $C_{33}H_{42}NO_7{}^+$ ($[M+H]^+$) requires 564.2956; found 564.2972.

tert-Butyl (*R*,*R*,*R*,*E*,*E*)-2-acetoxy-3-{*N*-[2′-(7″-methoxybenzofuran-3″-yl)ethyl]-*N*-[α-methyl-4‴-methoxybenzyl]amino}-8-oxonona-4,6-dienoate 281



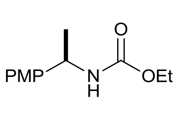
Ac_2O (36 µL, 357 µmol) was added to **279** (106 mg, 188 µmol, 88:12 dr) and DMAP (10 mg, 82 µmol) in pyridine (1 mL) at rt and the resultant mixture stirred for 15 min. The reaction mixture was partitioned between sat aq $CuSO_4$ (5 mL) and CH_2Cl_2 (5 mL) and the aqueous layer extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were washed with sat aq $CuSO_4$ (15 mL), H_2O (15 mL) and brine (15 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 40% → 100% Et_2O in 30-40 °C petrol) gave **281** as a yellow oil (48 mg, 42%, 88:12 dr); ν_{max} (ATR) 1743 (C=O), 1669 (C=C); δ_H (400 MHz, $CDCl_3$) 1.37 (9H, s, CMe_3), 1.40 (3H, d, *J* 6.8, C(α)*Me*), 2.04 (3H, s, CO*Me*), 2.26 (3H, s, C(9)H_3), 2.70 (2H, t, *J* 7.0, C(2′)H_2), 2.99 (2H, t, *J* 7.0, C(1′)H_2), 3.80 (3H, s, C(4‴)O*Me*), 3.89-3.94 (1H, m, C(3)*H*), 3.98 (3H, s, C(7″)O*Me*), 4.09 (1H, q, *J* 6.8, C(α)*H*), 5.10 (1H, d, *J* 4.0, C(2)*H*), 6.06 (1H, d, *J* 15.8, C(7)*H*), 6.19-6.30 (2H, m, C(4)*H*, C(5)*H*), 6.78 (1H, d, *J* 7.8, C(6″)*H*), 6.87 (2H, d, *J* 8.6, C(3‴)*H*, C(5‴)*H*), 6.94 (1H, d, *J* 7.8, C(4″)*H*), 7.02 (1H, dd, *J* 15.8, 9.4, C(6)*H*), 7.11 (1H, app t, *J* 7.8, C(5″)*H*), 7.31 (2H, d, *J* 8.6, C(2‴)*H*, C(6‴)*H*), 7.36 (1H, s, C(2″)*H*); δ_C (100 MHz, $CDCl_3$) 17.9 (C(α)*Me*), 20.7 (CO*Me*), 25.4 (*C*(2′)), 27.1 (*C*(9)), 27.9 (CMe_3), 47.4 (*C*(1′)), 55.2 (C(4‴)O*Me*), 56.0 (C(7″)O*Me*), 58.5 (*C*(α)), 61.2 (*C*(3)), 75.1 (*C*(2)), 82.4 (*C*Me_3), 106.3 (*C*(6″)), 111.8 (*C*(4″)), 113.7 (*C*(3‴), *C*(5‴)), 118.6 (*C*(3″)), 123.1 (*C*(5″)), 128.7 (*C*(2‴), *C*(6‴)), 129.7 (*C*(3a″)), 131.0 (*C*(7)), 132.0 (*C*(5)), 135.8 (*C*(1‴)), 138.9 (*C*(4)), 141.4 (*C*(2″)), 142.4 (*C*(6)), 144.5, 145.5 (*C*(7″), *C*(7a″)), 158.7 (*C*(4‴)), 167.5 (MeCO_2), 170.1 (*C*(1)), 198.5 (*C*(8)); *m/z* (ESI$^+$) 628 ($[M+Na]^+$, 48%), 606 ($[M+H]^+$, 4%), 472 ($[M-C_9H_{10}O]^+$, 100%); HRMS (ESI$^+$) $C_{35}H_{43}NNaO_8^+$ ($[M+Na]^+$) requires 628.2881; found 628.2872.

***tert*-Butyl (2*R*,3*S*,α*R*,*E*,*E*)-2-{*N*-[2′-(7″-methoxybenzofuran-3″-yl)ethyl]-*N*-[α-methylbenzyl]amino}-3-chloro-8-oxonona-4,6-dienoate 286**



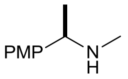
MsCl (14 µL, 187 µmol) was added to **264** (50 mg, 94 µmol, >99:1 dr), NEt_3 (52 µL, 375 µmol) and DMAP (2 mg, 16 µmol) in CH_2Cl_2 (1 mL) at rt and the resultant mixture stirred for 16 h. The reaction mixture was partitioned between H_2O (5 mL) and CH_2Cl_2 (5 mL) and the aqueous layer extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with sat aq $NaHCO_3$ (20 mL) and then dried and concentrated *in vacuo* to give **286** in >99:1 dr. Purification via flash column chromatography (gradient elution, 0% → 100% Et_2O in 30-40 °C petrol) gave **286** as a yellow oil (49 mg, 95%, >99:1 dr); $[\alpha]_{\mathrm{D}}^{24}$ −38.0 (*c* 1.0 in $CHCl_3$); $\nu_{\max}$ (ATR) 1724 (C=O), 1669 (C=C); δ_H (400 MHz, $CDCl_3$) 1.47 (3H, d, *J* 6.8, C(α)*Me*), 1.54 (9H, s, C*Me*$_3$), 2.30 (3H, s, C(9)H_3), 2.76-2.90 (2H, m, C(2′)H_2), 3.01-3.08 (1H, m, C(1′)H_A), 3.28-3.37 (1H, m, C(1′)H_B), 3.48 (1H, d, *J* 10.6, C(2)*H*), 4.01 (3H, s, O*Me*), 4.25 (1H, q, *J* 6.8, C(α)*H*), 4.52 (1H, app t, *J* 9.9, C(3)*H*), 5.37 (1H, dd, *J* 15.1, 9.1, C(4)*H*), 5.86 (1H, dd, *J* 15.1, 10.9, C(5)*H*), 6.01 (1H, d, *J* 15.7, C(7)*H*), 6.77-6.84 (2H, m, C(6)*H*, C(6″)*H*), 7.07 (1H, ABd, *J* 7.8, C(4″)*H*), 7.17 (1H, app t, *J* 8.1, C(5″)*H*), 7.28-7.38 (5H, m, *Ph*), 7.40 (1H, s, C(2″)*H*); δ_C (100 MHz, $CDCl_3$) 14.9 (C(α)*Me*), 23.6 (*C*(2′)), 27.4 (*C*(9)), 28.0 (C*Me*$_3$), 46.6 (*C*(1′)), 56.0 (O*Me*), 57.7 (*C*(α)), 59.1 (*C*(3)), 65.3 (*C*(2)), 82.1 (*C*Me$_3$), 106.4 (*C*(6″)), 111.8 (*C*(4″)), 118.3 (*C*(3″)), 123.3 (*C*(5″)), 127.4, 128.2, 128.4 (*o,m,p-Ph*), 129.7 (*C*(3a″)), 131.3 (*C*(5)), 131.4 (*C*(7)), 140.2 (*C*(4)), 141.4 (*C*(6)), 141.7 (*C*(2″)), 142.7, 144.6, 145.6 (*C*(7″), *C*(7a″), *i-Ph*), 170.2 (*C*(1)), 198.3 (*C*(8)); *m/z* (ESI$^+$) 554 ([M(^{37}Cl)+H]$^+$, 100%) 552 ([M(^{35}Cl)+H]$^+$, 48%); HRMS (ESI$^+$) $C_{32}H_{38}{}^{37}ClNNaO_5{}^+$ ([M(^{37}Cl)+Na]$^+$) requires 576.2305; found 576.2317; $C_{32}H_{38}{}^{35}ClNNaO_5{}^+$ ([M(^{35}Cl)+Na]$^+$) requires 574.2331; found 574.2333.

Ethyl (*R*)-*N*-(α-methyl-4-methoxybenzyl)carbamate 333



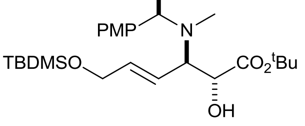
EtOCOCl (15.8 mL, 165 mmol) in Et_2O (100 mL) was added dropwise to **280** (25.0 g, 165 mmol, 99.5:0.5 er) and NEt_3 (27.5 mL, 197 mmol) in Et_2O (150 mL) at 0 °C and the resultant mixture allowed to warm to rt over 2 h. The reaction mixture was filtered through Celite® (eluent Et_2O) and the filtrate washed with 1.0 M aq HCl (150 mL), sat aq $NaHCO_3$ (150 mL) and brine (150 mL), then dried and concentrated *in vacuo* to give **333** as a white solid (20.1 g, 55%); mp 74-76 °C; $[\alpha]_D^{24}$ +80.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3357 (N−H); 1687 (C=O); δ_H (400 MHz, $CDCl_3$) 1.22 (3H, t, *J* 7.1, CH_2CH_3), 1.46 (3H, d, *J* 6.8, C(α)*Me*), 3.80 (3H, s, O*Me*), 4.04-4.06 (2H, m, CH_2CH_3), 4.75-4.84 (1H, m, C(α)*H*), 4.93 (1H, br s, N*H*), 6.87 (2H, d, *J* 8.6, C(3)*H*, C(5)*H*), 7.24 (2H, d, *J* 8.6, C(2)*H*, C(6)*H*); δ_C (100 MHz, $CDCl_3$) 14.6 (CH_2CH_3), 22.4 (C(α)*Me*), 49.9 (*C*(α)), 55.3 (O*Me*), 60.7 (CH_2CH_3), 113.9 (*C*(3), *C*(5)), 127.1 (*C*(2), *C*(6)), 135.8 (*C*(1)), 155.8 (*C*(4)), 158.7 (CO_2Et); *m/z* (ESI^+) 469 ($[2M+Na]^+$, 7%), 246 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{12}H_{17}NNaO_3$ ($[M+Na]^+$) requires 246.1011; found 246.1098.

(*R*)-*N*-Methyl-*N*-(α-methyl-4′-methoxybenzyl)amine 334

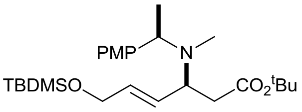


A solution of **333** (7.00 g, 31.4 mmol) in THF (50 mL) was added to $LiAlH_4$ (2.37 g, 62.5 mmol) in THF (160 mL) at 0 °C and the resultant mixture heated at 60 °C for 36 h, then allowed to cool to rt. Sat aq Na_2SO_4 (10 mL) was added cautiously, the reaction mixture filtered through Celite® (eluent EtOAc) and then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (50 mL) and 1.0 M aq HCl (50 mL) and the organic layer extracted with 1.0 M aq HCl (50 mL). The combined aqueous extracts were washed with CH_2Cl_2 (25 mL). 35% aq NH_4OH (100 mL) was added to the aqueous layer and the aqueous layer extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried and concentrated *in vacuo* to give **334** as a yellow oil (5.12 g, 99%, >99:1 er);[42] $[\alpha]_D^{24}$ +57.8 (*c* 1.0 in $CHCl_3$); {lit.[42] $[\alpha]_D^{23}$ +56.7 (neat)}; δ_H (400 MHz, $CDCl_3$) 1.34 (3H, d, *J* 6.5, C(α)*Me*), 2.30 (1H, s, N*Me*), 3.60 (1H, q, *J* 6.5, C(α)*H*), 3.81 (3H, s, O*Me*), 6.86-6.89 (2H, m, C(3)*H*, C(5)*H*), 7.21-7.24 (2H, m, C(2)*H*, C(6)*H*).

tert-Butyl (*R*,*R*,*R*,*E*)-2-hydroxy-3-[*N*-methyl-*N*-(α-methyl-4′-methoxybenzyl)amino]-6-(*tert*-butyldimethylsilyloxy)-hex-4-enoate 287 and *tert*-butyl (3*S*,α*R*,*E*)-3-[*N*-methyl-*N*-(α-methyl-4′-methoxybenzyl)amino]-6-(*tert*-butyldimethylsilyloxy)hex-4-enoate 288



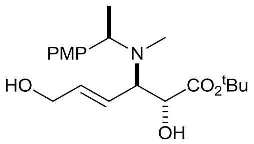
287



288

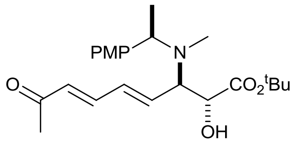
Following *general procedure 7*, **334** (2.38 g, 14.4 mmol, >99:1 er), BuLi (2.2 M, 6.36 mL, 14.0 mmol), **249** (2.69 g, 9.01 mmol, >99:1 dr) and (−)-CSO **95** (3.30 g, 14.4 mmol) were reacted in THF (100 mL). Purification via flash column chromatography (gradient elution, 25% → 60% Et_2O in 30–40 °C petrol) gave **288** as a yellow oil (1.23 g, 29%, >99:1 dr); $[\alpha]_D^{24}$ +22.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3495 (O−H); 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 0.08 (6H, s, $SiMe_2$), 0.92 (9H, s, SiC*Me*$_3$), 1.33 (3H, d, *J* 6.6, C(α)*Me*), 1.44 (9H, s, OC*Me*$_3$), 2.05 (3H, s, N*Me*), 2.33 (1H, ABdd, *J* 13.7, 7.8, C(2)*H*$_A$), 2.54 (1H, ABdd, *J* 13.7, 6.8, C(2)*H*$_B$), 3.58 (1H, q, *J* 6.6, C(α)*H*), 3.70 (3H, s, O*Me*), 3.89 (1H, app q, *J* 5.6, C(3)*H*), 4.17 (2H, br s, C(6)*H*$_2$), 5.67-5.72 (2H, m, C(4)*H*, C(5)*H*), 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$_3$) −5.2 (Si*Me*$_2$), 18.4 (C(α)*Me*), 20.5 (Si*C*Me$_3$), 25.9 (SiC*Me*$_3$), 28.1 (OC*Me*$_3$), 33.2 (N*Me*), 38.6 (*C*(2)), 55.2 (O*Me*), 57.5 (*C*(3)), 60.7 (*C*(α)), 63.4 (*C*(6)), 80.0 (O*C*Me$_3$), 113.5 (*C*(3′), *C*(5′)), 128.0 (*C*(4)), 131.6 (*C*(5)), 128.3 (*C*(2′), *C*(6′)), 138.0 (*C*(1′)), 158.3 (*C*(4′)), 171.4 (*C*(1)); *m/z* (ESI$^+$) 486 ([M+Na]$^+$, 11%), 464 ([M+H]$^+$, 100%); HRMS (ESI$^+$) C$_{26}$H$_{46}$NO$_4$Si$^+$ ([M+H]$^+$) requires 464.3191; found 464.3186. Further elution gave **287** as a yellow oil (1.94 g, 45%, >99:1 dr); $[\alpha]_D^{24}$ −0.5 (*c* 1.0 in CHCl$_3$); ν_{max} (ATR) 3495 (O−H), 1724 (C=O); δ$_H$ (400 MHz, CDCl$_3$) 0.05 (6H, s, Si*Me*$_2$), 0.89 (9H, s, SiC*Me*$_3$), 1.31 (3H, d, *J* 6.6, C(α)*Me*), 1.44 (9H, s, OC*Me*$_3$), 2.17 (3H, s, N*Me*), 3.32 (1H, br s, O*H*), 3.49 (1H, dd, *J* 8.1, 3.3, C(3)*H*), 3.80 (3H, s, O*Me*), 3.89 (1H, q, *J* 6.6, C(α)*H*), 4.16 (2H, d, *J* 3.8, C(6)*H*$_2$), 4.31 (1H, d, *J* 3.3, C(2)*H*), 5.68-5.84 (2H, m, C(4)*H*, C(5)*H*), 6.85 (2H, d, *J* 8.5, C(3′)*H*, C(5′)*H*), 7.25 (2H, d, *J* 8.5, C(2′)*H*, C(6′)*H*); δ$_C$ (100 MHz, CDCl$_3$) −5.3 (Si*Me*$_2$), 16.0 (C(α)*Me*), 18.3 (Si*C*Me$_3$), 25.9 (SiC*Me*$_3$), 28.1 (OC*Me*$_3$), 33.6 (N*Me*), 55.2 (O*Me*), 58.8 (*C*(α)), 63.3 (*C*(6)), 65.4 (*C*(3)), 71.4 (*C*(2)), 81.9 (O*C*Me$_3$), 113.5 (*C*(2′), *C*(6′)), 124.6 (*C*(4)), 128.7 (*C*(3′), *C*(5′)), 134.3 (*C*(5)), 136.1 (*C*(1′)), 158.4 (*C*(4′)), 172.2 (*C*(1)); *m/z* (ESI$^+$) 502 ([M+Na]$^+$, 10%), 480 ([M+H]$^+$, 100%); HRMS (ESI$^+$) C$_{26}$H$_{46}$NO$_5$Si$^+$ ([M+H]$^+$) requires 480.3140; found 480.3132.

***tert*-Butyl (*R*,*R*,*R*,*E*)-2,6-dihydroxy-3-[*N*-methyl-*N*-(α-methyl-4′-methoxybenzyl)amino]hex-4-enoate 289**



Following *general procedure 8*, TBAF (1.0 M, 2.28 mL, 2.28 mmol) and **287** (1.00 g, 2.08 mmol, >99:1 dr) were reacted in THF (22 mL). Purification via flash column chromatography (gradient elution, 1% → 5% MeOH in CHCl$_3$) gave **289** as a yellow oil (687 mg, 90%, >99:1 dr); $[\alpha]_D^{24}$ −14.0 (*c* 1.0 in CHCl$_3$); ν_{max} (ATR) 3433 (O−H), 1731 (C=O); δ$_H$ (400 MHz, CDCl$_3$) 1.27 (3H, d, *J* 6.6, C(α)*Me*), 1.40 (9H, s, C*Me*$_3$), 2.13 (3H, s, N*Me*), 3.46-3.51 (1H, m, C(3)*H*), 3.73 (3H, s, O*Me*), 3.78 (1H, q, *J* 6.6, C(α)*H*), 4.06 (2H, d, *J* 3.5, C(6)*H*$_2$), 4.28 (1H, d, *J* 4.0, C(2)*H*), 5.74-5.80 (2H, m, C(4)*H*, C(5)*H*), 6.79 (2H, d, *J* 8.6, C(3′)*H*, C(5′)*H*), 7.20 (2H, d, *J* 8.6, C(2′), C(6′)); δ$_C$ (100 MHz, CDCl$_3$) 17.0 (C(α)*Me*), 28.0 (C*Me*$_3$), 33.8 (N*Me*), 55.1 (O*Me*), 59.3 (*C*(α)), 62.6 (*C*(6)), 65.1 (*C*(3)), 71.6 (*C*(2)), 81.9 (*C*Me$_3$), 113.4 (*C*(3′), *C*(5′)), 125.6 (*C*(4)), 128.7 (*C*(2′), *C*(6′)), 134.3 (*C*(5)), 136.2 (*C*(1′)), 158.4 (*C*(4′)), 172.5 (*C*(1)); *m/z* (ESI^+) 388 ($[M+Na]^+$, 15%), 366 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{32}NO_5^+$ ($[M+H]^+$) requires 366.2275; found 336.2271.

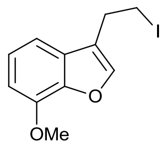
tert-Butyl (*R*,*R*,*R*,*E*,*E*)-2-hydroxy-3-[*N*-methyl-*N*-(α-methyl-4′-methoxybenzyl)amino]-8-oxonona-4,6-dienoate 291



Step 1: Following *general procedure 9*, IBX (369 mg, 1.32 mmol) and **289** (284 mg, 777 µmol, >99:1 dr) were reacted in DMSO (8.1 mL) to give **290** as a yellow oil (246 mg, >99:1 dr); δ_H (400 MHz, $CDCl_3$) 1.41 (12H, m, C(α)*Me*, C*Me*$_3$), 2.41 (3H, br s, N*Me*), 3.78-3.94 (2H, m, C(3)*H*, C(α)*H*), 3.80 (3H, s, C(4′)O*Me*), 4.50 (1H, br s, C(2)*H*), 6.24 (1H, dd, *J* 15.4, 7.7, C(5)*H*), 6.75-6.83 (1H, m, C(4)*H*), 6.86 (2H, d, *J* 8.4, C(3′)*H*, C(5′)*H*), 7.27-7.30 (2H, m, C(2′)*H*, C(6′)*H*), 9.54 (1H, d, *J* 8.0, C(6)*H*).

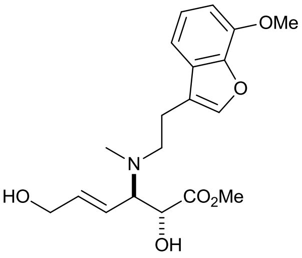
Step 2: Following *general procedure 10*, NaH (67 mg, 2.79 mmol), **10** (285 mg, 1.72 mmol) and **290** (246 mg, >99:1 dr) were reacted in THF (16 mL) to give **291** in >99:1 dr. Purification via flash column chromatography (gradient elution, 0% → 2.5% MeOH in $CHCl_3$) gave **291** as a yellow oil (131 mg, 42% over 2 steps, >99:1 dr); $[\alpha]_D^{24}$ −6.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3460 (O−H), 1731 (C(1)=O), 1688 (C(8)=O); δ_H (400 MHz, $CDCl_3$) 1.32 (3H, d, *J* 6.8, C(α)*Me*), 1.40 (9H, s, C*Me*$_3$), 2.23 (3H, s, C(9)H_3), 2.23 (3H, s, N*Me*), 3.10 (1H, br s, O*H*), 3.59 (1H, dd, *J* 8.0, 3.4, C(3)*H*), 3.78 (3H, s, C(4′)O*Me*), 3.82 (1H, q, *J* 6.8, C(α)*H*), 4.35 (1H, d, *J* 3.4, C(2)*H*), 6.07 (1H, d, *J* 15.7, C(7)*H*), 6.21 (1H, ABdd, *J* 15.3, 8.0, C(4)*H*), 6.30 (1H, ABdd, *J* 15.3, 10.1, C(5)*H*), 6.84 (2H, d, *J* 8.7, C(3′)*H*, C(5′)*H*), 7.07 (1H, dd, *J* 15.7, 10.1, C(6)*H*), 7.24 (2H, d, *J* 8.7, C(2′)*H*, C(6′)*H*); δ_C (100 MHz, $CDCl_3$) 17.0 (C(α)*Me*), 26.9 (*C*(9)), 28.0 (C*Me*$_3$), 33.8 (N*Me*), 55.2 (O*Me*), 59.7 (*C*(α)), 65.3 (*C*(3)), 71.1 (*C*(2)), 82.5 (*C*Me$_3$), 113.6 (*C*(3′), *C*(5′)), 128.6 (*C*(2′), *C*(6′)), 130.8 (*C*(7)), 131.9 (*C*(5)), 135.7 (*C*(1′)), 139.0 (*C*(4)), 142.6 (*C*(6)), 158.6 (*C*(4′)), 172.2 (*C*(1)), 198.7 (*C*(8)); *m/z* (ESI^+) 426 ($[M+Na]^+$, 68%), 404 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{23}H_{33}NNaO_5^+$ ($[M+Na]^+$) requires 426.2251; found 426.2247.

2′-(7-Methoxybenzofuran-3-yl)ethyl iodide 294



NaI (80 mg, 534 µmol) was added to **257** (30 mg, 87 µmol) in MeCN (0.5 mL) at rt and the resultant mixture heated at reflux for 18 h. The reaction mixture was allowed to cool to rt and then partitioned between EtOAc (10 mL) and sat aq $NaHCO_3$ (10 mL). The aqueous layer was extracted with EtOAc (10 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give **294** as a yellow oil (25 mg, 96%); ν_{max} (ATR) 2939 (C−H); δ_H (400 MHz, $CDCl_3$) 3.27 (2H, t, *J* 7.6, C(1′)H_2), 3.44 (2H, t, *J* 7.6, C(2′)H_2), 4.02 (3H, s, O*Me*), 6.83 (1H, d, *J* 7.8, C(6)*H*), 7.13 (1H, d, *J* 7.8, C(4)*H*), 7.19 (1H, app t, *J* 7.8, C(5)*H*), 7.54 (1H, s, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 3.6 (*C*(1′)), 28.5 (*C*(2′)), 56.1 (O*Me*), 106.6 (*C*(6)), 111.5 (*C*(4)), 119.6 (*C*(3)), 123.4 (*C*(5)), 129.0 (*C*(3a)), 141.8 (*C*(2)), 144.6, 145.7 (*C*(7), *C*(7a)); *m/z* (FI^+) 302 ($[M]^+$, 100%); HRMS (FI^+) $C_{11}H_{11}IO_2^+$ ($[M]^+$) requires 301.9804; found 301.9814.

Methyl (*R*,*R*,*E*)-2,6-dihydroxy-3-{*N*-methyl-*N*-[2′-(7″-methoxybenzofuran-3″-yl)ethyl]amino}-hex-4-enoate 298



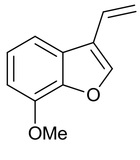
Method A - step 1: F_3CCO_2H (32 mL) was added to **287** (3.24 g, 6.74 mmol, >99:1 dr) at rt and the resultant mixture stirred and heated at 65 °C for 2.5 h and then concentrated *in vacuo*. The residue was dissolved in MeOH (65 mL) and $SOCl_2$ (2.00 mL, 27.6 mmol) added.

Step 2: The resultant mixture was heated at reflux for 5 h and then concentrated *in vacuo* to give methyl (*R*,*R*,*E*)-2,6-dihydroxy-3-(*N*-methylamino)-hex-4-enoate hydrochloride **296**·HCl as a brown gum (3.20 g); δ_H (400 MHz, CD_3OD) 2.67 (3H, s, N*Me*), 3.77 (3H, s, CO_2*Me*), 4.06 (1H, dd, *J* 9.8, 3.0, C(3)*H*), 4.13 (2H, dd, *J* 4.3, 1.9, C(6)H_2), 4.64 (1H, d, *J* 3.0, C(2)*H*), 5.75 (1H, ddt, *J* 15.5, 9.8, 1.9, C(4)*H*), 6.15 (1H, dt, *J* 15.5, 4.3, C(5)*H*); δ_C (100 MHz, CD_3OD) 31.0 (N*Me*), 52.3 (CO_2*Me*), 61.3 (*C*(6)), 63.5 (*C*(3)), 70.3 (*C*(2)), 117.9 (*C*(4)), 142.4 (*C*(5)), 171.1 (*C*(1)); *m/z* (ESI^+) 190 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_8H_{15}NNaO_4^+$ ($[M+Na]^+$) requires 212.0893; found 212.0895.

Step 3: **257** (333 mg, 961 µmol) was added to **296**·HCl (428 mg), NaI (287 mg, 1.91 mmol) and NEt_3 (0.27 mL, 1.93 mmol) in MeCN (4.4 mL) at rt and the resultant mixture heated at reflux for 18 h and then allowed to cool to rt. The reaction mixture was partitioned between EtOAc (15 mL) and sat aq $NaHCO_3$ (15 mL), and the aqueous phase extracted with EtOAc (2 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 1% → 5% MeOH in CH_2Cl_2) gave **298** as a colourless oil (137 mg, 43% over 3 steps, >99:1 dr); $[\alpha]_D^{24}$ −15.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3405 (O−H), 1741 (C=O), 1625 (C=C); δ_H (400 MHz, $CDCl_3$) 2.44 (3H, s, N*Me*), 2.77-2.92 (4H, m, C(1′)H_2, C(2′)H_2), 3.35 (1H, dd, *J* 8.4, 4.3, C(3)*H*), 3.73 (3H, s, CO_2*Me*), 4.00 (3H, s, C(7″)O*Me*), 4.11 (2H, d, *J* 4.2, C(6)H_2), 4.46 (1H, d, *J* 4.3, C(2)*H*), 5.72-5.84 (2H, m, C(4)*H*, C(5)*H*), 6.80 (1H, dd, *J* 7.5, 1.2, C(6″)*H*), 7.12-7.19 (2H, m, C(4″)*H*, C(5″)*H*), 7.46 (1H, s, C(2″)*H*); δ_C (100 MHz, $CDCl_3$) 21.7 (*C*(2′)), 38.9 (N*Me*), 53.4 (CO_2*Me*), 54.1 (*C*(1′)), 56.0 (C(7″)O*Me*), 62.8 (*C*(6)), 68.7 (*C*(3)), 71.9 (*C*(2)), 106.4 (*C*(6″)), 111.8 (*C*(4″)), 118.4 (*C*(3″)), 123.1 (*C*(5″)), 125.1 (*C*(4)), 129.8 (*C*(3a″)), 135.4 (*C*(5)), 141.6 (*C*(2″)), 144.5, 145.6 (*C*(7″), *C*(7a″)), 173.5 (*C*(1)); *m/z* (ESI^+) 386 ($[M+Na]^+$, 100%); 364 ($[M+H]^+$, 78%); HRMS (ESI^+) $C_{19}H_{26}NO_6^+$ ($[M+H]^+$) requires 364.1755; found 364.1747.

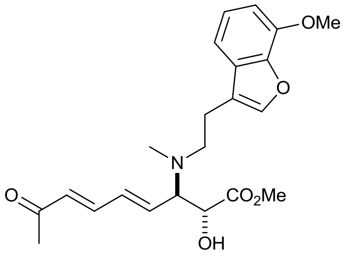
Method B: $SOCl_2$ (0.1 mL, 1.38 mmol) was added to **287** (100 mg, 208 µmol) in MeOH (2 mL) at rt and the resultant mixture heated at reflux for 5 h. The reaction mixture was allowed to cool to rt and then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (5 mL) and sat aq $NaHCO_3$ (5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were washed with brine (20 mL), dried and concentrated *in vacuo* to give methyl (*R*,*R*,*R*,*E*)-2,6-dihydroxy-3-[*N*-methyl-*N*-(α-methyl-4′-methoxybenzyl)amino]hex-4-enoate **295** as a yellow oil (86 mg, >99:1 dr); δ_H (400 MHz, $CDCl_3$) 1.32 (3H, d, *J* 6.5, C(α)*Me*), 2.15 (3H, s, N*Me*), 3.57-3.62 (1H, m, C(3)*H*), 3.73 (3H, s, CO_2*Me*), 3.79 (3H, s, C(4′)O*Me*), 3.87 (1H, q, *J* 6.5, C(α)*H*), 4.11 (2H, app s, C(6)H_2), 4.52 (1H, d, *J* 4.3, C(2)*H*), 5.81-5.86 (2H, m, C(4)*H*, C(5)*H*), 6.85 (2H, d, *J* 8.3, C(2′)*H*, C(6′)*H*), 7.24 (2H, d, *J* 8.3, C(3′)*H*, C(5′)*H*); δ_C (100 MHz, $CDCl_3$) 15.9 (C(α)*Me*), 33.6 (N*Me*), 52.2 (CO_2*Me*), 55.2 (C(4′)O*Me*), 59.3 (*C*(α)), 62.7 (*C*(6)), 65.7 (*C*(3)), 71.7 (*C*(2)), 113.6 (*C*(3′), *C*(5′)), 125.2 (*C*(4)), 128.8 (*C*(2′), *C*(6′)), 135.1 (*C*(5), *C*(1′)), 158.6 (*C*(4′)), 173.3 (*C*(1)); *m/z* (ESI^+) 346 ($[M+Na]^+$, 17%); 324 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{17}H_{25}NNaO_5^+$ ($[M+Na]^+$) requires 346.1625; found 346.1617. The residue was dissolved in F_3CCO_2H (1.0 mL) at rt and the resultant solution heated at 65 °C for 2.5 h and then concentrated *in vacuo* to give a complex mixture of products.

7-Methoxy-3-vinylbenzofuran 299



NEt_3 (23 µL, 165 µmol) was added to **294** (25 mg, 83 µmol) in MeCN (0.5 mL) at rt and the resultant mixture heated at reflux for 24 h. The reaction mixture was allowed to cool to rt and then partitioned between EtOAc (5 mL) and sat aq $NaHCO_3$ (5 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **299** as a white solid (14 mg, 97%); mp 31-33 °C; ν_{max} (ATR) 1624 (C=C); δ_H (400 MHz, $CDCl_3$) 4.02 (3H, s, O*Me*), 5.37 (1H, app d, *J* 11.3, CH=CH_AH$_B$), 5.84 (1H, app d, *J* 17.8, CH=CH$_A$$H_B$), 6.78 (1H, dd, *J* 17.8, 11.3, C*H*=CH$_2$), 6.85 (1H, d, *J* 7.8, C(6)*H*), 7.23 (1H, t, *J* 7.8, C(5)*H*), 7.43 (1H, d, *J* 7.8, C(4)*H*), 7.68 (1H, s, C(2)*H*); δ_C (100 MHz, CDCl$_3$) 56.0 (O*Me*), 106.7 (*C*(6)), 113.1 (*C*(4)), 115.1 (CH=*C*H$_2$), 120.0 (*C*(3)), 123.8 (*C*(5)), 126.4 (*C*H=CH$_2$), 127.5 (*C*(3a)), 143.4 (*C*(2)), 145.1, 145.6 (*C*(7), *C*(7a)); *m/z* (FI$^+$) 174 ([M]$^+$, 100%); HRMS (FI$^+$) $C_{11}H_{10}O_2^+$ ([M]$^+$) requires 174.0681; found 174.0684.

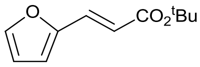
Methyl (*R*,*R*,*E*,*E*)-2-hydroxy-3-{*N*-methyl-*N*-[2′-(7″-methoxybenzofuran-3″-yl)ethyl]amino}-8-oxonona-4,6-dienoate 301



Step 1: Following *general procedure 9*, IBX (181 mg, 646 µmol) and **298** (137 mg, 377 µmol, >99:1 dr) were reacted in DMSO (4.0 mL) to give **300** as a yellow oil (104 mg, >99:1 dr); *m/z* (ESI$^+$) 384 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{23}NNaO_6^+$ ([M+Na]$^+$) requires 384.1418; found 384.1418.

Step 2: Following *general procedure 10*, NaH (32 mg, 800 µmol), **10** (140 mg, 843 µmol) and **300** (104 mg, >99:1 dr) were reacted in THF (9 mL). Purification via flash column chromatography (gradient elution, 50% → 100% Et$_2$O in 30-40 °C petrol) gave **301** as a yellow oil (15 mg, 10% over 2 steps, >99:1 dr); $[\alpha]_D^{24}$ +8.4 (*c* 0.3 in CHCl$_3$); ν_{max} (ATR) 3442 (O−H), 1741 (C=O), 1667 (C=C), 1627 (C=C); δ_H (400 MHz, CDCl$_3$) 2.28 (3H, s, C(9)H_3), 2.52 (3H, s, N*Me*), 2.82-3.02 (4H, m, C(1′)H_2, C(2′)H_2), 3.52 (1H, br s, C(3)*H*), 3.74 (3H, s, CO$_2$*Me*), 4.01 (3H, s, C(7″)O*Me*), 4.59 (1H, br s, C(2)*H*), 6.09 (1H, app d, *J* 15.7, C(7)*H*), 6.15 (1H, ABdd, *J* 15.4, 9.1, C(4)*H*), 6.29 (1H, ABdd, *J* 15.4, 10.6, C(5)*H*), 6.81 (1H, d, *J* 7.3, C(6″)*H*), 7.04 (1H, dd, *J* 15.7, 10.6, C(6)*H*), 7.12 (1H, ABd, *J* 7.7, C(4″)*H*), 7.17 (1H, app ABt, *J* 7.5, C(5″)*H*), 7.48 (1H, s, C(2″)*H*); δ_C (125 MHz, CDCl$_3$) 21.9 (*C*(2′)), 27.1 (*C*(9)), 39.0 (N*Me*), 52.6 (*C*O$_2$Me), 54.2 (*C*(1′)), 56.0 (C(7″)O*Me*), 68.9 (*C*(3)), 71.7 (*C*(2)), 106.4 (*C*(6″)), 111.7 (*C*(4″)), *118.3* (*C*(3″)), 123.2 (*C*(5″)), 129.7 (*C*(3a″)), 131.4 (*C*(7)), *133.1* (*C*(5)), *137.2* (*C*(4)), 141.6 (*C*(2″)), 141.9 (*C*(6)), 144.5, 145.6 (*C*(7″), *C*(7a″)), 173.1 (*C*(1)), 198.5 (*C*(8)); *m/z* (ESI$^+$) 424 ([M+Na]$^+$, 94%), 402 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{28}NO_6^+$ ([M+H]$^+$) requires 402.1911; found 402.1905.

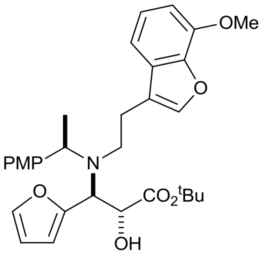
tert-Butyl (*E*)-3-(furan-2′-yl)acrylate 304



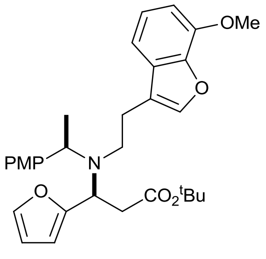
Method A: Following *general procedure 3*, **181** (25.0 g, 66.4 mmol) and **305** (5.00 mL, 60.4 mmol) were reacted in CH_2Cl_2 (250 mL) to give **304** in 93:7 dr. Purification via flash column chromatography (eluent 30-40° C petrol/Et_2O, 19:1) gave **304** as a colourless oil (3.71 g, 32%, 87:13 dr). Further elution gave **304** as a colourless oil (3.36 g, 29%, >99:1 dr);[43] δ_H (400 MHz, $CDCl_3$) 1.52 (9H, s, C*Me*$_3$), 6.26 (1H, d, *J* 15.8, C(2)*H*), 6.45-6.47 (1H, m, C(4′)*H*), 6.57 (1H, d, *J* 3.4, C(3′)*H*), 7.33 (1H, d, *J* 15.8, C(3)*H*), 7.45-7.47 (1H, m, C(5′)*H*).

Method B: Following *general procedure 4*, **182** (2.88 g, 11.4 mmol), MeMgBr (3.0 M in Et_2O, 3.64 mL, 10.9 mmol) and **305** (500 mg, 5.20 mmol) were reacted in THF (50 mL) to give **304** in >99:1 dr. Purification via flash column chromatography (eluent 30-40° C petrol/Et_2O, 19:1) gave **304** as a colourless oil (661 mg, 65%, >99:1 dr).

tert-Butyl (2*R*,3*S*,α*R*)-2-hydroxy-3-{*N*-[2′-(7″-methoxybenzofuran-3″-yl)ethyl]-*N*-[α-methyl-4‴-methoxybenzyl]amino}-3-(furan-2‴′-yl)propanoate 303 and *tert*-butyl (3*S*,α*R*)-3-{*N*-[2′-(7″-methoxybenzofuran-3″-yl)ethyl]-*N*-[α-methyl-4‴-methoxybenzyl]amino}-3-(furan-2‴′-yl)propanoate 303



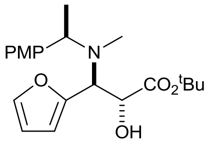
303



306

BuLi (2.3 M, 0.10 mL, 230 µmol) was added to **273** (79 mg, 243 µmol, >99:1 er) in THF (1 mL) at −78 °C and the resultant mixture was stirred at –78 °C for 15 min. **304** (39 mg, 201 µmol) in THF (2 mL) at −78 °C was then added via cannula and the resultant mixture was stirred at –78 °C for 3 h. (−)-CSO **95** (60 mg, 262 µmol) was added and the reaction mixture was allowed to warm to rt over 48 h and then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 and 10% aq citric acid, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic extracts were washed with sat aq $NaHCO_3$ and brine, then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40° C petrol/Et_2O, 4:1) gave **306** as a yellow oil (24 mg, 23%, >99:1 dr); $[\alpha]_D^{24}$ −20.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1729 (C=O); δ_H (400 MHz, $CDCl_3$) 1.22 (3H, d, *J* 6.6, C(α)*Me*), 1.49 (9H, m, C*Me*$_3$), 2.44-2.55 (1H, m, C(2′)H_A), 2.57-2.68 (1H, m, C(2′)H_B), 2.73-2.90 (4H, m, C(2)H_2, C(1′)H_2), 3.83 (3H, s, C(4‴)O*Me*), 3.98 (3H, s, C(7″)O*Me*), 4.04 (1H, q, *J* 6.6, C(α)*H*), 4.73 (1H, app t, *J* 7.8, C(3)*H*), 6.19 (1H, d, *J* 2.8, C(3⁗)*H*), 6.35 (1H, dd, *J* 2.8, 1.77, C(4⁗)*H*), 6.77 (1H, d, *J* 8.1, C(6″)*H*), 6.80 (1H, d, *J* 7.8, C(4″)*H*), 6.88 (2H, d, *J* 8.6, C(2‴)*H*, C(6‴)*H*), 7.09 (1H, app t, *J* 7.8, C(5″)*H*), 7.28 (1H, s, C(2″)*H*), 7.36 (2H, d, *J* 8.6, C(3‴)*H*, C(5‴)*H*), 7.41 (1H, app s, C(5⁗)*H*); δ_C (100 MHz, CDCl$_3$) 18.3 (C(α)*Me*), 24.3 (*C*(2′)), 28.1 (C*Me*$_3$), 38.6 (*C*(2)), 47.4 (*C*(1′)), 52.7 (*C*(3)), 55.2 (C(4‴)O*Me*), 56.0 (C(7″)O*Me*), 57.5 (C(α)), 80.6 (*C*Me$_3$), 106.2 (*C*(6″)), 107.0 (*C*(3⁗)), 110.2 (*C*(4⁗)), 112.0 (*C*(4″)), 113.4 (*C*(3‴), *C*(5‴)), 119.0 (*C*(3″)), 122.8 (*C*(5″)), 128.8 (*C*(2‴), *C*(6‴)), 130.0 (*C*(3a″)), 137.6 (*C*(1‴)), 141.4 (*C*(2″)), 141.5 (*C*(5⁗)), 144.4, 145.5 (*C*(7″), *C*(7a″)), 155.2 (*C*(2⁗)), 158.4 (*C*(4‴)), 170.8 (*C*(1)); *m/z* (ESI$^+$) 542 ([M+Na]$^+$, 33%), 520 ([M+H]$^+$, 100%), 386 ([M−C$_9$H$_{10}$O]$^+$, 96%); HRMS (ESI$^+$) C$_{31}$H$_{38}$NO$_6$$^+$ ([M+H]$^+$) requires 520.2694; found 520.2681. Further elution gave **303** as a yellow oil (74 mg, 69%, >99:1 dr); $[\alpha]_D^{24}$ −27.1 (*c* 1.0 in CHCl$_3$); ν_{max} (ATR) 3494 (O−H), 1728 (C=O); δ_H (400 MHz, CDCl$_3$) 1.26 (3H, d, *J* 6.6, C(α)*Me*), 1.35 (9H, s, C*Me*$_3$), 2.61-2.70 (1H, m, C(2′)H_A), 2.72-2.81 (1H, m, C(2′)H_B), 2.89-2.99 (1H, m, C(1′)H_A), 3.08 (1H, d, *J* 5.1, O*H*), 3.11-3.20 (1H, m, C(1′)H_B), 3.82 (3H, s, C(4‴)O*Me*), 4.00 (3H, s, C(7″)O*Me*), 4.17 (1H, q, *J* 6.6, C(α)*H*), 4.34-4.41 (2H, m, C(2)*H*, C(3)*H*), 6.33 (2H, app s, C(3⁗)*H*, C(4⁗)*H*), 6.78 (1H, d, *J* 7.8, C(6″)*H*), 6.88 (2H, d, *J* 8.6, C(3‴)*H*, C(5‴)*H*), 6.95 (1H, d, *J* 7.8, C(4″)*H*), 7.11 (1H, app t, *J* 7.8, C(5″)*H*), 7.35-7.39 (4H, m, C(2″)*H*, C(2‴)*H*, C(6‴)*H*, C(5⁗)*H*); δ_C (100 MHz, CDCl$_3$) 16.0 (C(α)*Me*), 24.6 (*C*(2″)), 27.8 (C*Me*$_3$), 45.0 (*C*(1″)), 55.2 (C(4‴)O*Me*), 56.0 (C(7″)O*Me*), 57.9 (*C*(α)), 58.4 (*C*(3)), 74.1 (*C*(2)), 82.4 (*C*Me$_3$), 106.2 (*C*(6″)), 109.3 (*C*(3⁗)), 110.3 (*C*(4⁗)), 112.1 (*C*(4″)), 113.5 (*C*(2‴), *C*(6‴)), 118.8 (*C*(3″)), 122.9 (*C*(5″)), 129.0 (*C*(3‴), *C*(5‴)), 130.0 (*C*(3a″)), 136.4 (*C*(1‴)), 141.3 (*C*(2″)), 141.5 (*C*(5⁗)), 144.4, 145.4 (*C*(7″), *C*(7″a)), 152.2 (*C*(2⁗)), 158.5 (*C*(4‴)), 172.1 (*C*(1)); *m/z* (ESI$^+$) 558 ([M+Na]$^+$, 32%), 536 ([M+H]$^+$, 31%), 402 ([M−C$_9$H$_{10}$O]$^+$, 100%); HRMS (ESI$^+$) C$_{31}$H$_{38}$NO$_7$$^+$ ([M+H]$^+$) requires 536.2643; found 536.2632.

***tert*-Butyl (2*R*,3*S*,α*R*)-2-hydroxy-3-[*N*-methyl-*N*-(α-methyl-4′-methoxybenzyl)amino]-3-(furan-2″-yl)propanoate 308 and *tert*-butyl (3*S*,α*R*)-3-[*N*-methyl-*N*-(α-methyl-4′-methoxybenzyl)amino]-3-(furan-2″-yl)propanoate 309**



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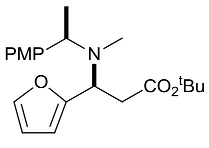


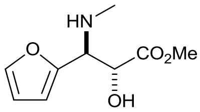
309

Following *general procedure 7*, **334** (4.54 g, 27.5 mmol, >99:1 er), BuLi (2.4 M, 11.0 mL, 26.4 mmol), **304** (4.11 g, 21.2 mmol, >99:1 dr) and (−)-CSO **95** (6.80 g, 29.7 mmol) were reacted in THF (160 mL). Purification via flash column chromatography (gradient elution, 10% → 50% Et$_2$O in 30-40 °C petrol) gave **309** as a yellow oil (528 mg, 7%, >99:1 dr);[44] $[\alpha]_D^{24}$ +16.8 (*c* 0.2 in $CHCl_3$); ν_{max} (ATR) 1731 (C=O); δ_H (400 MHz, $CDCl_3$) 1.41 (3H, d, *J* 6.6, C(α)*Me*), 1.44 (9H, s, CMe_3), 2.00 (3H, s, N*Me*), 2.69 (1H, ABdd, *J* 14.4, 7.3, C(2)H_A), 2.81 (1H, ABdd, *J* 14.4, 8.1, C(2)H_B), 3.54 (1H, q, *J* 6.6, C(α)*H*), 3.76 (3H, s, O*Me*), 4.65 (1H, app t, *J* 7.8, C(3)*H*), 6.15 (1H, d, *J* 3.2, C(3″)*H*), 6.32 (1H, dd, *J* 3.2, 1.8, C(4″)*H*), 6.83 (2H, d, *J* 8.7, C(2′)*H*, C(6′)*H*), 7.25 (2H, d, *J* 8.7, C(3′)*H*, C(5′)*H*), 7.37-7.39 (1H, m, C(5″)*H*); δ_C (100 MHz, $CDCl_3$) 21.2 (C(α)*Me*), 28.1 (CMe_3), 34.3 (N*Me*), 37.3 (*C*(2)), 53.4 (C(α)), 55.1 (O*Me*), 61.1 (*C*(3)), 80.2 (*C*Me_3), 107.3 (*C*(3″)), 109.8 (*C*(4″)), 113.6 (*C*(3′), *C*(5′)), 128.2 (*C*(2′), *C*(6′)), 138.2 (*C*(1′)), 141.6 (*C*(5″)), 154.2 (*C*(2″)), 158.4 (*C*(4′)), 170.7 (*C*(1)); *m/z* (ESI^+) 382 ($[M+Na]^+$, 8%), 360 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{21}H_{30}NO_4^+$ ($[M+H]^+$) requires 360.2169; found 360.2160. Further elution gave **308** as a white solid (4.74 g, 60%, >99:1 dr); mp 65-67 °C, $[\alpha]_D^{24}$ +8.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3472 (O−H), 1731 (C=O); δ_H (400 MHz, $CDCl_3$) 1.36 (3H, d, *J* 6.6, C(α)*Me*), 1.39 (9H, s, CMe_3), 2.18 (3H, s, N*Me*), 3.60 (1H, q, *J* 6.8, C(α)*H*), 3.75 (3H, s, O*Me*), 4.32 (1H, d, *J* 5.4, C(3)*H*), 4.53 (1H, d, *J* 5.4, C(2)*H*), 6.30-6.35 (2H, m, C(3″)*H*, C(4″)*H*), 6.83 (2H, d, *J* 8.6, C(3′)*H*, C(5′)*H*), 7.24 (2H, d, *J* 8.6, C(2′)*H*, C(6′)*H*), 7.36 (1H, app s, C(5″)*H*); δ_C (100 MHz, $CDCl_3$) 18.5 (C(α)*Me*), 27.9 (CMe_3), 35.1 (N*Me*), 55.1 (O*Me*), 60.4 (*C*(α)), 60.5 (*C*(3)), 71.8 (*C*(2)), 81.9 (*C*Me_3), 109.3 (*C*(3″)), 110.1 (*C*(4″)), 113.5 (*C*(3′), *C*(5′)), 128.5 (*C*(2′), *C*(6′)), 136.7 (*C*(1′)), 141.7 (*C*(5″)), 151.6 (*C*(2″)), 158.4 (*C*(4′)), 172.2 (*C*(1)); *m/z* (ESI^+) 398 ($[M+Na]^+$, 3%), 376 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{21}H_{29}NNaO_5^+$ ($[M+Na]^+$) requires 398.1938; found 398.1923.

X-ray crystal structure determination for **308**. Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-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.[45]

X-ray crystal structure data for **308** [$C_{21}H_{29}NO_5$]: M = 375.46, monoclinic, space group $P\ 2_1$, a = 12.8788(6) Å, b = 6.0581(3) Å, c = 13.3000(7) Å, β = 91.797(2)°, V = 1037.17(9) Å^3, Z = 2, μ = 0.085 mm^{-1}, colourless block, crystal dimensions = 0.10 × 0.12 × 0.32 mm^3. A total of 2571 unique reflections were measured for $5 < \theta < 27$ and 2250 reflections were used in the refinement. The final parameters were wR_2 = 0.149 and R_1 = 0.073 [$I > -3.0\sigma(I)$].

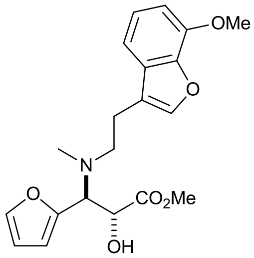
Methyl (2*R*,3*S*)-2-hydroxy-3-(*N*-methylamino)-3-(furan-2′-yl)propanoate 311



Step 1: F_3CCO_2H (11 mL) was added to **308** (1.09 g, 3.30 mmol, >99:1 dr) at rt and the resultant mixture stirred and heated at 65 °C for 2.5 h and then concentrated *in vacuo* to give **310**·F_3CCO_2H as a purple oil (1.20 g, >99:1 dr); δ_H (400 MHz, CD_3OD) 2.65 (3H, s, N*Me*), 3.30-3.34 (1H, m, N*H*), 3.74-3.77 (1H, m, O*H*), 4.76-4.79 (1H, m, C(2)*H*), 4.82 (1H, d, *J* 3.8, C(3)*H*), 6.48-6.51 (1H, m, C(4′)*H*), 6.74 (1H, d, *J* 3.0, C(3′)*H*), 7.60-7.62 (1H, m, C(5′)*H*); δ_C (100 MHz, CD_3OD) 30.8 (N*Me*), 58.2 (*C*(3)), 69.1 (*C*(2)), 111.0 (*C*(4′)), 112.7 (*C*(3′)), 144.5 (*C*(5′)), 145.2 (*C*(2′)), 171.8 (*C*(1)).

Step 2: $SOCl_2$ (0.60 mL, 5.37 mmol) was added to **310**·F_3CCO_2H (1.15 g) in MeOH (20 mL) and the resultant mixture heated at 50 °C for 5 h. The reaction mixture was allowed to cool to rt and then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (30 mL) and sat aq $NaHCO_3$ (30 mL), and the aqueous layer extracted with CH_2Cl_2 (30 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 1% → 5% MeOH in CH_2Cl_2) gave **311** as a yellow oil (400 mg, 69%, >99:1 dr); $[\alpha]_D^{24}$ −32.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3322 (N−H, O−H), 1739 (C=O); δ_H (400 MHz, $CDCl_3$) 2.38 (3H, s, N*Me*), 2.69 (2H, br s, N*H*, O*H*), 3.69 (3H, s, O*Me*), 4.01 (1H, d, *J* 3.8, C(3)*H*), 4.53 (1H, d, *J* 3.8, C(2)*H*), 6.21 (1H, d, *J* 3.0, C(3′)*H*), 6.31 (1H, dd, *J* 3.0, 1.8, C(4′)*H*), 7.35 (1H, app s, C(5′)*H*); δ_C (100 MHz, $CDCl_3$) 34.0 (N*Me*), 52.4 (O*Me*), 60.4 (*C*(3)), 71.9 (*C*(2)), 108.0 (*C*(3′)), 110.1 (*C*(4′)), 142.3 (*C*(5′)), 151.8 (*C*(2′)), 172.9 (*C*(1)); *m/z* (ESI^+) 421 ($[2M+Na]^+$, 15%), 222 ($[M+Na]^+$, 33%), 200 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_9H_{13}NNaO_4^+$ ($[M+Na]^+$) requires 222.0737; found 222.0734.

Methyl (2*R*,3*S*)-2-hydroxy-3-{*N*-[2′-(7″-methoxybenzofuran-3″-yl)ethyl]-*N*-methylamino}-3-(furan-2‴-yl)propanoate 312

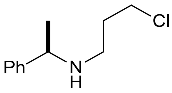


Method A: **257** (670 mg, 1.93 mmol) was added to **311** (350 mg, 1.76 mmol, >99:1 dr), NaI (579 mg, 3.86 mmol) and NEt_3 (0.27 mL, 1.93 mmol) in MeCN (9.0 mL) at rt and the resultant mixture heated at reflux for 18 h and then allowed to cool to rt. The reaction mixture was partitioned between EtOAc (20 mL) and sat aq $NaHCO_3$ (20 mL) and the aqueous phase extracted with EtOAc (2 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 1% → 5% MeOH in CH_2Cl_2) gave

312 as a colourless oil (124 mg, 19%, >99:1 dr); $[\alpha]_D^{24}$ −6.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3448 (O−H), 1740 (C=O); δ_H (400 MHz, $CDCl_3$) 2.39 (3H, s, N*Me*), 2.70-2.90 (4H, m, C(1′)H_2, C(2′)H_2), 3.70 (3H, s, CO_2*Me*), 4.00 (3H, s, C(7″)O*Me*), 4.07 (1H, d, *J* 6.3, C(3)*H*), 4.69 (1H, d, *J* 6.3, C(2)*H*), 6.31 (1H, ABd, *J* 3.0, C(3‴)*H*), 6.33-6.35 (1H, m, C(4‴)*H*), 6.80 (1H, d, *J* 7.8, C(6″)*H*), 7.10 (1H, ABdd, *J* 7.6, 1.0, C(4″)*H*), 7.16 (1H, app ABt, *J* 7.8, C(5″)*H*), 7.38-7.40 (1H, m, C(5‴)*H*), 7.44 (1H, s, C(2″)*H*); δ_C (100 MHz, $CDCl_3$) 22.1 (*C*(2′)), 39.1 (N*Me*), 52.4 (CO_2*Me*), 54.5 (*C*(1′)), 56.0 (C(7″)O*Me*), 64.6 (*C*(3)), 71.5 (*C*(2)), 106.3 (*C*(6″)), 109.8 (*C*(3‴)), 110.1 (*C*(4‴)), 111.9 (*C*(4″)), 118.5 (*C*(3″)), 123.1 (*C*(5″)), 129.9 (*C*(3a″)), 141.6 (*C*(2″)), 142.4 (*C*(5‴)), 144.5, 145.5 (*C*(7″), *C*(7a″)), 150.3 (*C*(2‴)), 173.4 (*C*(1)); *m/z* (ESI^+) 396 ($[M+Na]^+$, 37%), 374 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{24}NO_6^+$ ($[M+H]^+$) requires 374.1598; found 374.1586.

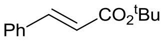
Method B: **257** (50 mg, 144 μmol) was added to **311** (29 mg, 144 μmol, >99:1 dr) and NEt_3 (20 μL, 144 μmol) in MeCN (1.5 mL) at rt and the resultant mixture heated at reflux for 48 h and then allowed to cool to rt. The reaction mixture was partitioned between EtOAc (5 mL) and sat aq $NaHCO_3$ (5 mL) and the aqueous phase extracted with EtOAc (2 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 1% → 5% MeOH in CH_2Cl_2) gave **312** as a colourless oil (39 mg, 72%, >99:1 dr).

(*R*)-*N*-(3-Chloroprop-1-yl)-*N*-(α-methylbenzyl)amine (*R*)-413



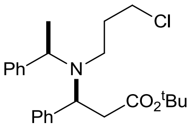
(*R*)-α-Methylbenzylamine (*R*)-**153** (32.2 mL, 253 mmol) was added to 1-bromo-3-chloropropane **359** (10.0 mL, 101 mmol, 99.5:0.5 er) in MeCN (80 mL) at rt and the resultant mixture stirred for 16 h. The reaction mixture was basified to pH 9 with sat aq $NaHCO_3$ then extracted with EtOAc (3 × 100 mL). The combined organic extracts were then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40° C petrol/Et_2O, 3:7) gave (*R*)-**413** as a yellow oil (13.9 g, 70%, >99:1 er);[46] $[\alpha]_D^{24}$ +59.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3337 (N−H); δ_H (400 MHz, $CDCl_3$) 1.37 (3H, d, *J* 6.7, C(α)*Me*), 1.91 (2H, app quin, *J* 6.6, C(2)H_2), 2.58 (1H, ABdt, *J* 11.9, 6.8, C(1)H_A), 2.68 (1H, ABdt, *J* 11.9, 6.6, C(1)H_B), 3.55-3.66 (2H, m, C(3)H_2), 3.78 (1H, q, *J* 6.7, C(α)*H*), 7.24-7.28 (1H, m, *Ph*), 7.31-7.37 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 24.5 (C(α)*Me*), 33.2 (*C*(2)), 43.2 (*C*(3)), 44.8 (*C*(1)), 58.3 (*C*(α)), 126.5, 126.9, 128.5 (*o,m,p-Ph*), 145.6 (*i-Ph*); *m/z* (ESI^+) 200 ($[M(^{37}Cl)+H]^+$, 19%), 198 ($[M(^{35}Cl)+H]^+$, 47%), 162 ($[M-Cl]^+$, 100%); HRMS (ESI^+) $C_{11}H_{17}{}^{37}ClN^+$ ($[M(^{37}Cl)+H]^+$) requires 200.1015; found 200.1013; $C_{11}H_{17}{}^{35}ClN^+$ ($[M(^{35}Cl)+H]^+$) requires 198.1044; found 198.1045.

tert-Butyl cinnamate 405



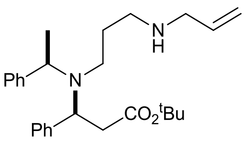
Benzaldehyde **340** (1.00 mL, 9.84 mmol) was added to **181** (4.07 g, 10.8 mmol) in CH_2Cl_2 (30 mL) at rt and the resultant mixture stirred for 20 h before being concentrated *in vacuo*. Purification via flash column chromatography gave **405** as a colourless oil (1.62 g, 81%, >99:1 dr);[47] δ_H (400 MHz, $CDCl_3$) 1.54 (9H, s, C*Me*$_3$), 6.38 (1H, d, *J* 16.0, C(2)*H*), 7.36-7.41 (3H, m, *Ph*), 7.50-7.54 (2H, m, *Ph*), 7.60 (1H, d, *J* 16.0, C(3)*H*).

tert-Butyl (3*S*,α*R*)-3-[*N*-(3′-chloropropyl)-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 406



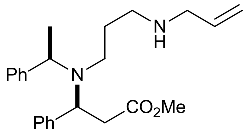
Following *general procedure 5*, (*R*)-**413** (1.55 g, 7.83 mmol, >99:1 er), BuLi (2.5 M, 3.04 mL, 7.59 mmol) and **405** (1.00 mL, 4.90 mmol) were reacted in THF (40 mL). Purification via flash column chromatography (gradient elution, 0% → 8% Et_2O in 30-40 °C petrol) gave **406** as a yellow oil (1.65 g, 84%, >99:1 dr);[46] $[\alpha]_D^{20}$ −4.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 1.22 (3H, s, C(α)*Me*), 1.35 (9H, s, C*Me*$_3$), 1.71-1.84 (2H, m, C(2′)*H*$_2$), 2.65-2.71 (3H, m, C(2)*H*$_A$, C(1′)*H*$_2$), 2.83 (1H, app dd, *J* 14.7, 6.6, C(2)*H*$_B$), 3.22-3.32 (2H, m, C(3′)*H*$_2$), 4.02 (1H, q, *J* 6.7, C(α)*H*), 4.44 (1H, dd, *J* 8.6, 6.6, C(3)*H*), 7.25-7.43 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.7 (C(α)*Me*), 27.9 (C*Me*$_3$), 33.1 (*C*(2′)), 38.5 (*C*(2)), 43.3 (*C*(3′)), 43.9 (*C*(1′)), 57.1 (*C*(α)), 58.7 (*C*(3)), 80.3 (*C*Me$_3$), 126.8, 127.2, 127.7, 128.1, 128.2 (*o,m,p-Ph*), 141.4, 144.8 (*i-Ph*), 171.2 (*C*(1)); *m/z* (ESI$^+$) 426 ([M(^{37}Cl)+Na]$^+$, 24%), 424 ([M(^{35}Cl)+Na]$^+$, 58%), 404 ([M(^{37}Cl)+H]$^+$, 55%), 402 ([M(^{35}Cl)+H, 100%); HRMS (ESI$^+$) $C_{24}H_{33}{}^{37}ClNO_2^+$ ([M(^{37}Cl)+H]$^+$) requires 404.2165; found 404.2163; $C_{24}H_{33}{}^{35}ClNO_2^+$ ([M(^{35}Cl)+H]$^+$) requires 402.2194; found 402.2182.

tert-Butyl (3*S*,α*R*)-3-{*N*-[3′-(*N*′-allylamino)propyl]-*N*-[α-methylbenzyl]amino}-3-phenylpropanoate 414



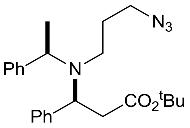
NaI (182 mg, 1.21 mmol) was added to **406** (163 mg, 405 μmol, >99:1 dr) in allyl amine (1.22 mL, 16.3 mmol) at rt and the resultant mixture was heated at 65 °C for 24 h and then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (25 mL) and sat aq $NaHCO_3$ (25 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extracts were washed with brine (75 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent CH_2Cl_2/MeOH, 19:1) gave **414** as a yellow oil (147 mg, 86%, >99:1 dr); $C_{27}H_{38}N_2O_2$ requires C, 76.7; H, 9.1; N, 6.6%; found C, 76.7; H, 9.0; N, 6.7%; $[\alpha]_D^{24}$ −4.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1727 (C=O); δ_H (400 MHz, $CDCl_3$) 1.21 (3H, d, *J* 6.8, C(α)*Me*), 1.27 (9H, s, C*Me*$_3$), 1.52-1.64 (2H, m, C(2′)*H*$_2$), 2.28-2.50 (3H, m, C(1′)*H*$_2$, N*H*), 2.56 (2H, app t, *J* 6.8, C(3′)*H*$_2$), 2.64-2.67 (2H, m, C(2)*H*$_2$), 3.02 (2H, d, *J* 6.0, NC*H*$_2$CH=CH$_2$), 3.98 (1H, q, *J* 6.8, C(α)*H*), 4.38 (1H, dd, *J* 8.6, 6.6, C(3)*H*), 5.06-5.14 (2H, m, CH=C*H*$_2$), 5.75-5.85 (1H, m, C*H*=CH$_2$), 7.20-7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.6 (C(α)*Me*), 28.0 (C*Me*$_3$), 29.4 (*C*(2′)), 38.0 (*C*(2)), 44.0 (*C*(3′)), 47.0 (*C*(1′)), 52.0 (N*C*H$_2$CH=CH$_2$), 56.8 (*C*(α)), 59.4 (*C*(3)), 80.3 (*C*Me$_3$), 116.4 (CH=*C*H$_2$), 126.7, 127.1, 127.7, 128.1, 128.2 (*o,m,p-Ph*), 135.9 (*C*H=CH$_2$), 141.7, 144.6 (*i-Ph*), 171.2 (*C*(1)); *m/z* (ESI$^+$) 423 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{39}N_2O_2^+$ ([M+H]$^+$) requires 423.3006; found 423.3008.

Methyl (3*S*,α*R*)-3-{*N*-[3′-(*N*′-allylamino)propyl]-*N*-[α-methylbenzyl]amino}-3-phenylpropanoate 415



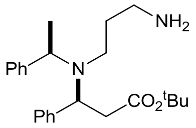
Following *general procedure 11*, **414** (900 mg, 1.19 mmol, >99:1 dr) in MeOH (4.5 mL) and $SOCl_2$ (0.90 mL, 12.4 mmol) in MeOH (4.5 mL) were reacted. Purification via flash column chromatography (gradient elution, 1% → 5% MeOH in CH_2Cl_2) gave **415** as a yellow oil (585 mg, 72%, >99:1 dr); $C_{27}H_{38}N_2O_2$ requires C, 76.7; H, 9.0; N, 6.6%; found C, 76.7; H, 9.0; N, 6.7%; $[\alpha]_D^{24}$ −1.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1739 (C=O); δ_H (400 MHz, $CDCl_3$) 1.17 (3H, d, *J* 6.8, C(α)*Me*), 1.56 (2H, app quin, *J* 7.1, C(2′)*H*$_2$), 2.28-2.39 (2H, m, C(1′)*H*$_2$), 2.56 (2H, t, *J* 7.1, C(3′)*H*$_2$), 2.70 (1H, ABdd, *J* 14.9, 8.6, C(2)*H*$_A$), 2.79 (1H, ABdd, *J* 14.9, 6.3, C(2)*H*$_B$), 3.03 (2H, app d, *J* 6.1, NC*H*$_2$CH=CH$_2$), 3.52 (3H, s, O*Me*), 4.00 (1H, q, *J* 6.8, C(α)*H*), 4.44-4.48 (1H, m, C(3)*H*), 5.03-5.12 (2H, m, CH=C*H*$_2$), 5.75-5.85 (1H, m, C*H*=CH$_2$), 7.18-7.38 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.7 (C(α)*Me*), 29.5 (*C*(2′)), 36.8 (*C*(2)), 43.9 (*C*(3′)), 46.9 (*C*(1′)), 51.5 (O*Me*), 52.2 (N*C*H$_2$CH=CH$_2$), 56.7 (*C*(α)), 58.9 (*C*(3)), 116.0 (CH=*C*H$_2$), 126.8, 127.2, 127.7, 127.9, 128.1, 128.3 (*o,m,p-Ph*), 136.4 (*C*H=CH$_2$), 141.5, 144.6 (*i-Ph*), 172.4 (*C*(1)); *m/z* (ESI$^+$) 381 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{33}N_2O_2^+$ ([M+H]$^+$) requires 381.2537; found 381.2526.

tert-Butyl (3*S*,α*R*)-3-[*N*-(3′-azidopropyl)-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 416



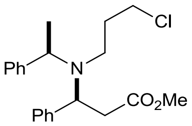
Following *general procedure 13*, NaN_3 (129 mg, 1.99 mmol), NaI (298 mg, 1.99 mmol) and **406** (400 mg, 995 µmol, >99:1 dr) were reacted in DMSO (2 mL) for 48 h. Purification via flash column chromatography (gradient elution, 3% → 9% Et_2O in 30-40 °C petrol) gave **416** as a yellow oil (323 mg, 79%, >99:1 dr); $[\alpha]_D^{24}$ −0.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2095 (N≡N), 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 1.18 (3H, d, *J* 6.8, C(α)*Me*), 1.32 (9H, s, C*Me*$_3$), 1.48-1.62 (2H, m, C(2′)*H*$_2$), 2.58 (2H, t, *J* 7.1, C(1′)*H*$_2$), 2.64 (1H, ABdd, *J* 14.7, 8.5, C(2)*H*$_A$), 2.79 (1H, ABdd, *J* 14.7, 6.6, C(2)*H*$_B$), 2.91-3.03 (2H, m, C(3′)*H*$_2$), 3.98 (1H, q, *J* 6.8, C(α)*H*), 4.39 (1H, dd, *J* 8.5, 6.6, C(3)*H*), 7.22-7.41 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.6 (C(α)*Me*), 27.9 (C*Me*$_3$), 29.1 (*C*(2′)), 38.4 (*C*(2)), 43.5 (*C*(1′)), 49.4 (*C*(3′)), 57.0 (*C*(α)), 59.6 (*C*(3)), 80.4 (*C*Me$_3$), 126.8, 127.2, 127.7, 128.0, 128.1, 128.2 (*o,m,p-Ph*), 141.3, 144.8 (*i-Ph*), 171.2 (*C*(1)); *m/z* (ESI^+) 431 ($[M+Na]^+$, 46%), 409 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{24}H_{33}N_4O_2^+$ ($[M+H]^+$) requires 409.2598; found 409.2600.

***tert*-Butyl (3*S*,α*R*)-3-[*N*-(3′-aminopropyl)-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 417**



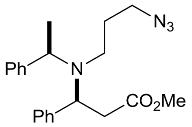
Following *general procedure 13*, **416** (270 mg, 660 µmol, >99:1 dr) and PPh_3 (192 mg, 730 µmol) were reacted in THF (1.3 mL) and H_2O (0.27 mL). The residue was partitioned between CH_2Cl_2 (10 mL) and 2.0 M aq HCl (5 mL). The organic layer was extracted with 2.0 M aq HCl (2 × 5 mL) and the combined aqueous layers washed with CH_2Cl_2 (15 mL). The aqueous layer was basified to pH 12 by addition of solid KOH and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give **417** as a colourless oil (222 mg, 88%, >99:1 dr); $[\alpha]_D^{24}$ −3.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.17 (3H, d, *J* 6.8, C(α)*Me*), 1.29 (9H, s, C*Me*$_3$), 1.48 (2H, app quin, *J* 6.8, C(2′)*H*$_2$), 2.39-2.46 (2H, m, C(1′)*H*$_2$), 2.53 (2H, app td, *J* 6.8, 2.5, C(3′)*H*$_2$), 2.63 (1H, ABdd, *J* 14.6, 8.8, C(2)*H*$_A$), 2.71 (1H, ABdd, *J* 14.6, 6.2, C(2)*H*$_B$), 3.98 (1H, q, *J* 6.8, C(α)*H*), 4.39 (1H, dd, *J* 8.8, 6.2, C(3)*H*), 7.20-7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.4 (C(α)*Me*), 27.9 (C*Me*$_3$), 33.2 (*C*(2′)), 38.3 (*C*(2)), 39.7 (*C*(3′)), 43.4 (*C*(1′)), 56.7 (*C*(α)), 59.4 (*C*(3)), 80.3 (*C*Me$_3$), 126.7, 127.1, 127.8, 128.0, 128.1, 128.2 (*o,m,p-Ph*), 141.6, 144.8 (*i-Ph*), 171.3 (*C*(1)); *m/z* (ESI^+) 405 ($[M+Na]^+$, 18%), 383 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{24}H_{35}N_2O_2^+$ ($[M+H]^+$) requires 383.2693; found 383.2682.

Methyl (3*S*,α*R*)-3-[*N*-(3′-chloropropyl)-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 420



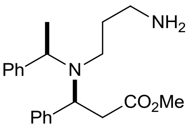
Following *general procedure 5*, (*R*)-**413** (5.00 g, 25.3 mmol, >99:1 er), BuLi (2.2 M, 9.8 mL, 24.5 mmol) and **423** (2.56 g, 15.8 mmol) were reacted in THF (250 mL) to give **420** as a yellow oil (5.68 g, quant, >99:1 dr); $C_{21}H_{26}ClNO_2$ requires C, 70.1; H, 7.3; N, 3.9%; found C, 70.2; H, 7.2; N, 3.8%; $[\alpha]_D^{24}$ −7.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1738 (C=O); δ_H (400 MHz, $CDCl_3$) 1.18 (3H, d, *J* 6.8, C(α)*Me*), 1.69-1.81 (2H, m, C(2′)H_2), 2.67 (2H, t, *J* 6.8, C(1′)H_2), 2.71 (1H, ABdd, *J* 14.9, 8.2, C(2)H_A), 2.87 (1H, ABdd, *J* 14.9, 6.8, C(2)H_B), 3.21-3.31 (2H, m, C(3′)H_2), 3.58 (3H, s, O*Me*), 3.99 (1H, q, *J* 6.8, C(α)*H*), 4.45 (1H, ABdd, *J* 8.2, 6.8, C(3)*H*), 7.22-7.38 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.9 (C(α)*Me*), 32.8 (*C*(2′)), 37.2 (*C*(2)), 43.2 (*C*(3′)), 43.8 (*C*(1′)), 51.6 (O*Me*), 57.1 (*C*(α)), 59.3 (*C*(3)), 126.9, 127.4, 127.7, 128.0, 128.2, 128.4 (*o,m,p-Ph*), 141.2, 144.7 (*i-Ph*), 172.3 (*C*(1)); *m/z* (ESI$^+$) 384 ([M(^{37}Cl)+Na], 66%), 382 ([M(^{35}Cl)+Na]$^+$, 100%), 362 ([M(^{37}Cl)+H], 44%), 360 ([M(^{35}Cl)+H]$^+$, 72%); HRMS (ESI$^+$) $C_{21}H_{27}{}^{37}ClNO_2^+$ ([M(^{37}Cl)+H]$^+$) requires 362.1695; found 362.1697; $C_{21}H_{27}{}^{35}ClNO_2^+$ ([M(^{35}Cl)+H]$^+$) requires 360.1725; found 360.1721.

Methyl (3*S*,α*R*)-3-[(*N*-3′-azidopropyl)-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 421



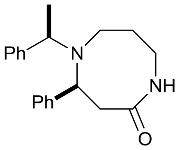
Following *general procedure 12*, NaN_3 (1.08 g, 16.7 mmol, >99:1 dr), NaI (2.49 g, 16.7 mmol) and **420** (3.00 g, 8.36 mmol, >99:1 dr) were reacted in DMSO (15 mL). Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 8:2) gave **421** as a yellow oil (2.38 g, 78%, >99:1 dr); $C_{21}H_{26}N_4O_2$ requires C, 68.8; H, 7.15; N, 15.3%; found C, 68.9; H, 7.1; N, 15.2%; $[\alpha]_D^{24}$ −9.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2096 (N≡N), 1738 (C=O); δ_H (400 MHz, $CDCl_3$) 1.20 (3H, d, *J* 6.8, C(α)*Me*), 1.50-1.66 (2H, m, C(2′)H_2), 2.62 (2H, t, *J* 6.8, C(1′)H_2), 2.73 (1H, ABdd, *J* 14.8, 8.1, C(2)H_A), 2.90 (1H, ABdd, *J* 14.8, 6.8, C(2)H_B), 2.95-3.06 (2H, m, C(3′)H_2), 3.61 (3H, s, O*Me*), 4.02 (1H, q, *J* 6.8, C(α)*H*), 4.49 (1H, app t, *J* 7.6, C(3)*H*), 7.24-7.41 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.8 (C(α)*Me*), 30.0 (*C*(2′)), 37.1 (*C*(2)), 43.5 (*C*(1′)), 49.4 (*C*(3′)), 51.6 (O*Me*), 57.0 (*C*(α)), 59.3 (*C*(3)), 126.9, 127.4, 127.6, 127.9, 128.2, 128.4 (*o,m,p-Ph*), 141.2, 144.7 (*i-Ph*), 172.3 (*C*(1)); *m/z* (ESI$^+$) 389 ([M+Na]$^+$, 100%), 367 ([M+H]$^+$, 74%); HRMS (ESI$^+$) $C_{21}H_{27}N_4O_2^+$ ([M+H]$^+$) requires 367.2129; found 367.2129.

Methyl (3*S*,α*R*)-3-[*N*-(3′-aminopropyl)-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 422



Following *general procedure 13*, **421** (1.20 g, 3.24 mmol, >99:1 dr) and PPh_3 (948 mg, 3.60 mmol) were reacted in THF (6.6 mL) and H_2O (1.2 mL). The residue was partitioned between CH_2Cl_2 (40 mL) and 2.0 M aq HCl (25 mL). The organic layer was extracted with 2.0 M aq HCl (2 × 25 mL) and the combined aqueous layers were washed with CH_2Cl_2 (50 mL). The aqueous layer was basified to pH 12 by the addition of solid KOH and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give **422** as a colourless oil (1.19 g, 90%, >99:1 dr); $[\alpha]_D^{20}$ −9.9 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1736 (C=O); δ_H (400 MHz, $CDCl_3$) 1.17 (3H, d, *J* 6.8, C(α)*Me*), 1.52 (2H, app t, *J* 7.0, C(2′)H_2), 2.44-2.48 (2H, m, C(3′)H_2), 2.57 (2H, t, *J* 7.3, C(1′)H_2), 2.71 (1H, ABdd, *J* 14.9, 8.5, C(2)H_A), 2.82 (1H, ABdd, *J* 14.9, 6.7, C(2)H_B), 3.56 (3H, s, O*Me*), 4.02 (1H, q, *J* 6.8, C(α)*H*), 4.46 (1H, dd, *J* 8.5, 6.7, C(3)*H*), 7.21-7.42 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.5 (C(α)*Me*), 33.4 (*C*(2′)), 37.0 (*C*(2)), 39.8 (*C*(3′)), 43.3 (*C*(1′)), 51.5 (O*Me*), 56.5 (*C*(α)), 58.9 (*C*(3)), 126.7, 127.2, 127.7, 127.9, 128.1, 128.3 (*o,m,p-Ph*), 141.6, 144.7 (*i-Ph*), 172.4 (*C*(1)); *m/z* (ESI^+) 363 ($[M+Na]^+$, 76%), 341 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{21}H_{29}N_2O_2^+$ ($[M+H]^+$) requires 341.2224; found 341.2213.

(4*S*,α*R*)-4-Phenyl-*N*(5)-(α-methylbenzyl)-1,5-diazocan-2-one 418

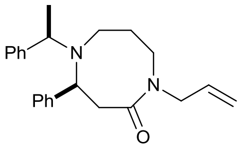


Method A: Following *general procedure 14*, **422** (1.19 g, 3.50 mmol, >99:1 dr) and $Sb(OEt)_3$ (0.72 mL, 4.18 mmol) were reacted in PhMe (350 mL). Purification via flash column chromatography (gradient elution, 50% → 100% EtOAc in 30-40 °C petrol) gave **418** as a white solid (915 mg, 85%, >99:1 dr); mp 46-48 °C; $[\alpha]_D^{24}$ +22.4 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1662 (C=O); δ_H (400 MHz, $CDCl_3$) 1.00-1.07 (1H, m, C(7)H_A), 1.16-1.30 (4H, m, C(7)H_B, C(α)*Me*), 2.57-2.70 (2H, m, C(6)H_2), 3.04-3.16 (3H, m, C(8)H_A, C(3)H_2), 3.46-3.58 (1H, m, C(8)H_B), 3.99 (1H, q, *J* 6.8, C(α)*H*), 4.55 (1H, br s, C(4)*H*), 6.59 (1H, br t, *J* 7.1, N*H*), 7.18-7.44 (10H, m, *Ph*); δ_H (500 MHz, PhMe-d_8, 363 K) 0.74-0.81 (1H, m, C(7)H_A), 1.03-1.11 (1H, m, C(7)H_B), 1.18 (3H, d, *J* 6.6, C(α)*Me*), 2.48-2.56 (2H, m, C(3)H_A, C(6)H_A), 2.59-2.65 (1H, m, C(8)H_A), 2.79 (1H, app t, *J* 11.7, C(3)H_B), 2.92 (1H, ddd, *J* 15.8, 8.5, 2.8, C(6)H_B), 3.05-3.14 (1H, m, C(8)H_B), 3.96 (1H, q, *J* 6.6, C(α)*H*), 4.51 (1H, dd, *J* 11.0, 3.8, C(4)*H*), 5.94 (1H, br s, N*H*), 7.04-7.11 (2H, m, *Ph*), 7.14-7.21 (4H, m, *Ph*), 7.24-7.28 (2H, m, *Ph*), 7.30-7.34 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 33.2 (*C*(7)), *41.2*

(*C*(3)), *46.8* (*C*(8)), *60.7* (*C*(α)), *62.8* (*C*(4)), 126.8, 127.0, 127.2, 128.0, 128.1, 128.6 (*o,m,p-Ph*), 143.1, *145.5* (*i-Ph*), 176.7 (*C*(2));[48] δ_C (125 MHz, PhMe-d_8, 363 K) 16.5 (C(α)*Me*), 33.8 (*C*(7)), 41.8 (*C*(6)), 41.9 (*C*(3)), 46.7 (*C*(8)), 61.2 (*C*(α)), 63.5 (*C*(4)), 126.9, 127.0, 127.6, 128.1, 128.4, 128.6 (*o,m,p-Ph*), 144.3, 146.0 (*i-Ph*), 175.0 (*C*(2)); *m/z* (ESI$^+$) 948 ([3M+Na]$^+$, 46%), 639 ([2M+Na]$^+$, 100%), 331 ([M+Na]$^+$, 82%), 309 ([M+H]$^+$, 66%); HRMS (ESI$^+$) $C_{20}H_{25}N_2O^+$ ([M+H]$^+$) requires 309.1961; found 309.1960.

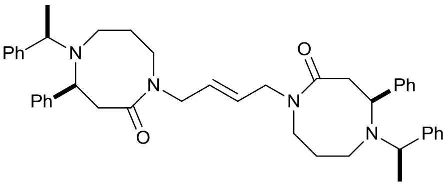
Method A: Following *general procedure 14*, **422** (200 mg, 587 µmol, >99:1 dr) and $Fe(OEt)_3$ (135 mg, 705 µmol) were reacted in PhMe (60 mL). Purification via flash column chromatography (gradient elution, 80% → 100% EtOAc in 30-40 °C petrol) gave **418** as a white solid (51 mg, 28%, >99:1 dr).

(4*S*,α*R*)-*N*(1)-Allyl-4-phenyl-*N*(5)-(α-methylbenzyl)-1,5-diazocan-2-one 419



Allyl bromide (2.50 mL, 28.9 mmol) was added to **418** (750 mg, 2.34 mmol, >99:1 dr), KOH (545 mg, 9.71 mmol) TBAC (5 mg, 22.0 µmol) under N_2 and sealed in a tube. The resultant mixture was heated at 160 °C in a microwave reactor for 2 min before being cooled to rt. The reaction mixture was partitioned between H_2O (20 mL) and CH_2Cl_2 (20 mL) and the aqueous layer extracted with CH_2Cl_2 (2 × 30 ml). The combined organic extracts were washed with brine (40 mL), dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 10% → 65% EtOAc in 30-40 °C petrol) gave **419** as a yellow oil (709 mg, 87%, >99:1 dr); $C_{23}H_{28}N_2O$ requires C, 79.3; H, 8.1; N, 8.0%; found C, 79.4; H, 7.9; N, 7.9%; $[\alpha]_D^{24}$ −4.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1635 (C=O); δ_H (400 MHz, $CDCl_3$) 0.92-0.99 (1H, m, C(7)H_A), 1.20-1.32 (1H, m, C(7)H_B), 1.24 (3H, d, *J* 6.6, C(α)*Me*), 2.52 (1H, br s, C(6)H_A), 2.67 (1H, dd, *J* 12.9, 3.8, C(3)H_A), 3.04-3.19 (3H, m, C(3)H_B, C(6)H_B, C(8)H_A), 3.49 (1H, dd, *J* 15.2, 7.1, CH_AH$_B$CH=CH$_2$), 3.75 (1H, app br t, *J* 13.6, C(8)H_B), 3.95 (1H, q, *J* 6.6, C(α)*H*), 4.52-4.61 (2H, m, C(4)*H*, CH$_A$$H_B$CH=CH$_2$), 5.12-5.18 (2H, m, $CH_2CH{=}CH_2$), 5.76-5.87 (1H, m, $CH_2CH{=}CH_2$), 7.17-7.31 (4H, m, *Ph*), 7.33-7.38 (4H, m, *Ph*), 7.40-7.45 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 30.3 (*C*(7)), *43.1* (*C*(3)), *46.7* (*C*(8)), 48.3 ($CH_2CH{=}CH_2$), *60.7* (*C*(α)), *63.5* (*C*(4)), 117.2 ($CH_2CH{=}CH_2$), 126.8, 127.0, 127.2, 127.9, 128.0, 128.6 (*o,m,p-Ph*), 143.4, *145.6* (*i-Ph*), 173.2 (*C*(2));[49] *m/z* (ESI$^+$) 371 ([M+Na]$^+$, 38%), 349 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{29}N_2O^+$ ([M+H]$^+$) requires 349.2274; found 349.2266.

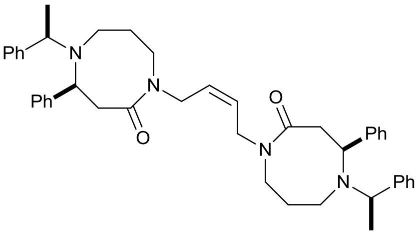
(4′*S*,α*R*,*E*)-1,4-Di[2′-oxo-4′-phenyl-*N*(5′)-α-methylbenzyl-1′,5′-diazocan-*N*(1′)-yl]but-2-ene 426



Method A: Grubbs II (120 mg, 143 μmol) was added to a degassed solution of **419** (500 mg, 143 mmol, >99:1 dr) in CH_2Cl_2 (7 mL, EtOH stabilised) at rt and the reaction mixture heated at 40 °C for 18 h. The reaction mixture was the concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 0% → 7% MeOH in CH_2Cl_2) gave **426** as a yellow solid (394 mg, 82%, >99:1 dr); mp 64-67 °C; $[\alpha]_D^{20}$ −7.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1637 (C=O); δ_H (400 MHz, $CDCl_3$) 0.91-1.01 (2H, m, 2 × C(7′)H_A), 1.19-1.28 (2H, m, 2 × C(7′)H_B) overlapping 1.24 (6H, d, *J* 6.6, 2 × C(α)*Me*), 2.42-2.57 (2H, m, 2 × C(6′)H_A), 2.65 (2H, dd, *J* 12.6, 3.3, 2 × C(8′)H_A), 3.03-3.18 (6H, m, 2 × C(3′)H_A, 2 × C(6′)H_B, 2 × C(8′)H_B), 3.44 (2H, br d, *J* 12.1, C(1)H_A, C(4)H_A), 3.74 (2H, br t, *J* 11.9, 2 × C(3′)H_B), 3.95 (2H, br q, *J* 6.6, 2 × C(α)*H*), 4.40-4.66 (4H, m, C(1)H_B, C(4)H_B, 2 × C(4′)*H*), 5.54-5.59 (2H, m, C(2)*H*, C(3)*H*), 7.19-7.45 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 30.2 (2 × *C*(7′)), 46.9 (2 × *C*(3′)), 126.8, 127.0, 127.1, 127.9, 128.0, 128.6 (*o,m,p-Ph*), 143.3 (*i-Ph*), 172.2 (2 × *C*(2′));[50] *m/z* (ESI^+) 691 ($[M+Na]^+$, 95%), 669 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{44}H_{53}N_4O_2^+$ ($[M+H]^+$) requires 669.4163; found 669.4161.

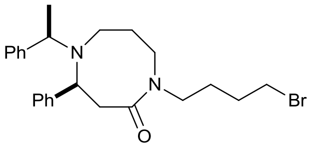
Method B: Following *general procedure 15*, **418** (244 mg, 791 μmol), **425** (85 mg, 397 μmol), KOH (177 mg, 3.15 mmol), K_2CO_3 (132 mg, 955 μmol) and TEBAC (22 mg, 98.3 μmol) were reacted in DMSO (4.0 mL) for 72 h. Purification via column chromatography (gradient elution, 0% → 2% MeOH in $CHCl_3$) gave **426** as a white solid (175 mg, 66%, >99:1 dr); mp 67-69 °C; $[\alpha]_D^{20}$ −7.9 (*c* 1.0 in $CHCl_3$).

(4′*S*,α*R*,*Z*)-1,4-Di[2′-oxo-4′-phenyl-*N*(5′)-α-methylbenzyl-1′,5′-diazocan-*N*(1′)-yl]but-2-ene 427



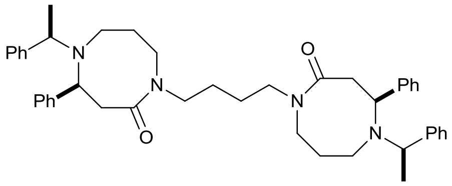
Following *general procedure 15*, **418** (134 mg, 344 μmol, >99:1 dr), **388** (23 μL, 219 μmol, 95:5 dr), KOH (97 mg, 1.73 mmol), K_2CO_3 (72 mg, 524 μmol) and TEBAC (13 mg, 54 μmol) were reacted in DMSO (3.8 mL) for 96 h. Purification via flash column chromatography (gradient elution, 0% → 7% MeOH in CH_2Cl_2) gave **427** as a yellow oil (128 mg, 88%, 95:5 dr); $[\alpha]_D^{24}$ −5.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1628 (C=O); δ_H (400 MHz, $CDCl_3$) 0.94-1.07 (2H, m, 2 × C(7′)H_A), 1.18-1.31 (6H, m, 2 × C(7′)H_B, 2 × C(α)*Me*), 2.61 (2H, dd, *J* 12.3, 3.4, 2 × C(8′)H_A), 3.01-3.21 (6H, m, 2 × C(3′)H_A, 2 × C(6′)H_B, 2 × C(8′)H_B), 3.62 (2H, dd, *J* 14.7, 5.1, C(1)H_A, C(4)H_A), 3.74-3.86 (2H, m, 2 × C(3′)H_B), 3.93 (2H, br q, *J* 6.7, 2 × C(α)*H*), 4.37-4.65 (4H, m, C(1)H_B, C(4)H_B, 2 × C(4′)*H*), 5.58 (2H, br t, *J* 4.4, C(2)*H*, C(3)*H*), 7.17-7.50 (20H, m, *Ph*); δ_C (100 MHz, CDCl$_3$) 30.5 (2 × *C*(7)), 42.3 (*C*(1), *C*(4)), *43.5* (2 × *C*(8′)), *46.9* (2 × *C*(3′)), *60.4* (2 × *C*(α)), *63.6* (2 × *C*(4′)), 126.8, 127.0, 127.2, 127.9, 128.0, 128.1, 128.5, 128.6 (*C*(2), *C*(3), *o,m,p-Ph*), 143.4, 145.4 (*i-Ph*), 173.4 (2 × *C*(1′));[51] *m/z* (ESI$^+$) 669 ([M+H]$^+$, 15%), 565 ([M−C$_8$H$_7$]$^+$, 100%), 461 ([M−C$_{16}$H$_{15}$]$^+$, 46%); HRMS (ESI$^+$) $C_{44}H_{53}N_4O_2^+$ ([M+H]$^+$) requires 669.4163; found 669.4159.

(4*S*,α*R*)-*N*(1)-(4′-Bromobutyl)-4-phenyl-*N*(5)-(α-methylbenzyl)-1,5-diazocan-2-one 429



1,4-Dibromobutane **360** (0.5 mL, 4.19 mmol) was added to **418** (150 mg, 0.486 mmol), KOH (109 mg, 1.94 mmol), K$_2$CO$_3$ (269 mg, 1.94 mmol) and TBAC (16 mg, 0.049 mmol) under N$_2$ and sealed in a tube. The resultant mixture was heated at 160 °C in a microwave reactor for 2 min before being cooled to rt. The reaction mixture was partitioned between H$_2$O (20 mL) and CH$_2$Cl$_2$ (20 mL) and the aqueous layer extracted with CH$_2$Cl$_2$ (2 × 30 ml). The combined organic extracts were washed with brine (40 mL), dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 30% → 80% Et$_2$O in 30-40 °C petrol) gave **429** as a yellow oil (83 mg, 39%, >99:1 dr); $[\alpha]_D^{24}$ −8.3 (*c* 1.0 in CHCl$_3$); ν_{max} (film) 1633 (C=O); δ_H (400 MHz, CDCl$_3$) 0.94-1.02 (1H, m, C(7)H_A), 1.19-1.31 (1H, m, C(7)H_B) overlapping 1.22 (3H, d, *J* 6.8, C(α)*Me*), 1.62-1.76 (2H, m, C(3′)H_2), 1.87 (2H, app quin, *J* 7.3, C(2′)H_2), 2.38-2.56 (1H, m, C(6)H_A), 2.62 (1H, dd, *J* 12.6, 3.3, C(3)H_A), 2.81-2.87 (1H, m, C(1′)H_A), 3.04-4.15 (3H, m, C(3)H_B, C(6)H_B, C(8)H_A), 3.44 (2H, t, *J* 6.8, C(4′)H_2), 3.59 (1H, br t, *J* 12.9, C(8)H_B), 3.88-3.96 (2H, m, C(α)*H*, C(1′)H_B), 4.50 (1H, br s, C(4)*H*), 7.17-7.29 (4H, m, *Ph*), 7.33-7.36 (4H, m, *Ph*), 7.39-7.43 (2H, m, *Ph*); δ_C (100 MHz, CDCl$_3$) 26.6 (*C*(7)), 30.0 (*C*(2′)), 30.6 (*C*(3′)), 33.6 (*C*(4′)), *43.2* (*C*(3)), 44.9 (*C*(1′)), *46.7* (*C*(6)), 47.6 (*C*(8)), *60.5* (*C*(α)), *63.4* (*C*(4)), 126.8, 127.0, 127.2, 127.9, 128.0, 128.6 (*o,m,p-Ph*), 143.3, *145.5* (*i-Ph*), 173.4 (*C*(2));[52] *m/z* (ESI$^+$) 467 ([M(^{81}Br)+Na]$^+$, 94%), 465 ([M(^{79}Br)+Na]$^+$, 100%), 445 ([M(^{81}Br)+H]$^+$, 58%), 443 ([M(^{79}Br)+H]$^+$, 61%); HRMS (ESI$^+$) $C_{24}H_{31}{}^{81}BrN_2NaO^+$ ([M+Na]$^+$) requires 467.1492; found 467.1487, $C_{24}H_{31}{}^{79}BrN_2NaO^+$ ([M+H]$^+$) requires 465.1512; found 465.1506.

(4′*S*,α*R*)-1,4-Di[2′-oxo-4′-phenyl-*N*(5′)-α-methylbenzyl-1′,5′-diazocan-1′-yl]butane 428



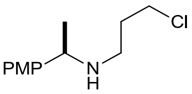
Method A: 1,4-Dibromobutane **360** (0.29 mL, 2.43 mmol) was added to **418** (1.50 g, 4.86 mmol, >99:1 dr), KOH (1.10 g, 19.5 mmol), K_2CO_3 (2.69 g, 19.5 mmol), and TBAC (135 mg, 486 μmol) in PhMe (16 mL) at rt under N_2 and sealed in a tube. The resultant mixture was heated at 160 °C in a microwave reactor for 15 min before being cooled to rt. The reaction mixture was partitioned between H_2O (20 mL) and EtOAc (20 mL) and the aqueous layer was extracted with EtOAc (2 × 30 ml). The combined organic extracts were washed with brine (40 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 40% → 100% EtOAc in 30-40 °C petrol) gave **428** as a yellow oil (1.36 g, 83%, >99:1 dr); $[\alpha]_D^{24}$ +4.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1614 (C=O); δ_H (400 MHz, $CDCl_3$) 0.95-1.04 (2H, m, 2 × C(7′)H_A), 1.20-1.33 (8H, m, 2 × C(α)*Me*, 2 × C(7′)H_B), 1.53-1.59 (4H, m, C(2)H_2, C(3)H_2), 2.57-2.65 (2H, m, 2 × C(6′)H_A), 2.78-2.86 (2H, m, C(1)H_A, C(4)H_A), 3.02-3.19 (8H, m, 2 × C(3′)H_A, 2 × C(8′)H_2, 2 × C(6′)H_B), 3.80 (2H, br t, *J* 11.9, 2 × C(3′)H_B), 3.90-4.01 (4H, m, 2 × C(α)*H*, C(1)H_B, C(4)H_B), 4.42-4.60 (2H, m, 2 × C(4′)*H*), 7.17-7.47 (20H, m, *Ph*); δ_H (500 MHz, PhMe-d_8, 363 K) 0.74-0.80 (2H, m, 2 × C(7′)H_A), 1.13 (6H, d, *J* 6.6, 2 × C(α)*Me*), 1.17-1.27 (2H, m, 2 × C(7′)H_B), 1.51-1.57 (4H, m, C(2)H_2, C(3)H_2), 2.40-2.47 (2H, m, 2 × C(6′)H_A), 2.56 (2H, dd, *J* 12.6, 3.8, C(1)H_A, C(4)H_A), 2.77-2.94 (8H, m, 2 × C(3′)H_A, 2 × C(6′)H_B, 2 × C(8′)H_2), 3.45 (2H, t, *J* 13.6, 2 × C(3′)H_B), 3.89-3.98 (4H, m, 2 × C(α)*H*, C(1)H_B, C(4)H_B), 4.47 (2H, dd, *J* 11.0, 3.5, 2 × C(4′)*H*), 7.02-7.08 (4H, m, *Ph*), 7.15 (8H, app t, *J* 7.9, *Ph*), 7.22-7.29 (8H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.3 (*C*(2), *C*(3)), 30.5 (2 × *C*(7′)), 45.5 (*C*(1), *C*(4)), 126.7, 127.0, 127.1, 127.2, 127.9, 128.0, 128.1, 128.6, 128.7 (*o,m,p-Ph*), 173.3 (2 × *C*(2′));[53] δ_C (125 MHz, PhMe-d_8, 363 K) *16.5* (2 × C(α)*Me*), 26.3 (*C*(2), *C*(3)), 31.4 (2 × *C*(7′)), 43.7 (2 × *C*(3′)), 46.1 (*C*(1), *C*(4)), 46.9 (2 × *C*(8′)), 47.9 (2 × *C*(6′)), 61.2 (2 × *C*(α)), 64.3 (2 × *C*(4′)), 127.3, 127.4, 128.0, 128.6, 128.9, 129.1 (*o,m,p-Ph*), 145.0, 146.5 (*i-Ph*), 172.5 (2 × *C*(2′)); *m/z* (ESI^+) 693 ($[M+Na]^+$, 41%), 671 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{44}H_{55}N_4O_2^+$ ($[M+H]^+$) requires 671.4320; found 671.4312.

Method B: Following *general procedure 17*, **426** (20 mg, 30 μmol), $Pd(OH)_2/C$ (10 mg) and H_2 (5 atm) were reacted in MeOH (1.0 mL) for 1 h. The residue was partitioned between CH_2Cl_2 (5 mL) and sat aq $NaHCO_3$ (5 mL), the aqueous layer extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated *in vacuo* to give **428** as a yellow oil (21 mg, quant, >99:1 dr); $[\alpha]_D^{24}$ +4.2 (*c* 1.0 in $CHCl_3$).

Method C: Powdered KOH (53 mg, 95 µmol) was added to DMSO (1 mL) at rt and the resultant mixture stirred for 15 min. The reaction mixture as cooled to 0 °C and 1,4-dibromobutane **360** (26 µL, 21 µmol) and **418** (132 mg, 428 µmol, >99:1 dr) were added. The resultant mixture was allowed to warm to rt over 18 h. The reaction mixture was partitioned between Et_2O (2 mL) and sat aq NH_4Cl (2 mL) and the aqueous layer extracted with Et_2O (2 × 5 mL). The combined organic extracts were washed with H_2O (2 × 10 mL) and brine (10 mL), then dried (Na_2SO_4) and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 35% → 100% Et_2O in 30-40 °C petrol) gave **428** as a yellow oil (12 mg, 8%, >99:1 dr).

Method D: **418** (50 mg, 181 µmol, >99:1 dr) was added to **429** (80 mg, 181 µmol, >99:1 dr), K_2CO_3 (100 mg, 724 µmol), KOH (40 mg, 768 µmol) and TBAC (5 mg, 18 µmol) in PhMe (0.6 mL) at rt under N_2 and sealed in a tube. The resultant mixture was heated at 160 °C in a microwave reactor for 7 min before being cooled to rt and partitioned between H_2O (5 mL) and CH_2Cl_2 (5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 ml) and the combined organic extracts were washed with brine (20 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 40% → 100% EtOAc in 30-40 °C petrol) gave **428** as a yellow oil (59 mg, 49%, >99:1 dr).

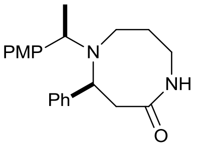
(*R*)-*N*-3-(Chloroprop-1-yl)-*N*-(α-methyl-4′-methoxybenzyl)amine 431



(*R*)-*N*-α-Methyl-4-methoxybenzyl amine **280** (5.00 g, 33.1 mmol, 99.5:0.5 er) was added to 1-bromo-3-chloropropane **359** (1.81 mL, 18.3 mmol) in MeCN (10 mL) at rt and the resultant mixture stirred for 16 h. The reaction mixture was basified to pH 9 with sat aq $NaHCO_3$ and then extracted with EtOAc (3 × 100 mL). The combined organic extracts were then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent Et_2O) gave **431** as a yellow oil (2.90 g, 70%, >99:1 er); $C_{12}H_{18}ClNO$ requires C, 63.3; H, 8.0; N, 6.15%; found C, 63.5; H, 7.9; N, 6.1%; $[\alpha]_D^{24}$ +28.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3323 (N−H); δ_H (400 MHz, $CDCl_3$) 1.34 (3H, d, *J* 6.7, C(α)*Me*), 1.89 (2H, app quin, *J* 6.8, C(2)H_2), 2.56 (1H, dt, *J* 11.9, 6.8, C(1)H_A), 2.66 (1H, dt, *J* 11.9, 6.6, C(1)H_B), 3.54-3.65 (2H, m, C(3)H_2), 3.73 (1H, q, *J* 6.7, C(α)*H*), 3.80 (3H, s, O*Me*), 6.86-6.89 (2H, m, C(3′)*H*, C(5′)*H*), 7.22-7.25 (2H, m, C(2′)*H*, C(6′)*H*); δ_C (100 MHz, $CDCl_3$) 24.4 (C(α)*Me*), 33.1 (*C*(2)), 43.2 (*C*(3)), 44.7 (*C*(1)), 55.2 (O*Me*), 57.6 (*C*(α)), 113.8 (*C*(3′), *C*(5′)), 127.5 (*C*(2′), *C*(6′)), 137.7 (*C*(1′)), 158.5 (*C*(4′)); *m/z* (ESI^+) 252 ($[M(^{37}Cl)+Na]^+$, 4%), 250

([M(^{35}Cl)+Na]$^+$, 10%), 230 ([M(^{37}Cl)+H]$^+$, 40%), 228 ([M(^{35}Cl)+H]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{19}{}^{37}ClNO^+$ ([M(^{37}Cl)+H]$^+$) requires 230.1120; found 230.1119; $C_{12}H_{19}{}^{35}ClNO^+$ ([M(^{35}Cl)+H]$^+$) requires 228.1150; found 228.1145.

(4*S*,α*R*)-4-Phenyl-*N*(5)-(α-methyl-4′-methoxybenzyl)-1,5-diazocan-2-one 436



Step 1: Following *general procedure 5*, **431** (3.00 g, 13.2 mmol, >99:1 er), BuLi (2.5 M, 5.12 mL, 12.8 mmol) and **423** (1.33 g, 8.23 mmol) were reacted in THF (75 mL) to give **433** (3.37 g, >99:1 dr). Purification of an aliquot via flash column chromatography (gradient elution, 2% → 20% Et_2O in 30-40 °C petrol) gave **433** as a colourless oil; $C_{22}H_{28}ClNO_3$ requires C, 67.8; H, 7.2; N, 3.6%; found C, 67.9; H, 7.0; N, 3.3%; $[\alpha]_D^{24}$ −3.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1737 (C=O); δ_H (400 MHz, $CDCl_3$) 1.18 (3H, d, *J* 6.8, C(α)*Me*), 1.69-1.85 (2H, m, C(2′)H_2), 2.68 (2H, t, *J* 7.1, C(1′)H_2), 2.73 (1H, dd, *J* 14.9, 8.2, C(2)H_A), 2.90 (1H, dd, *J* 14.9, 6.7, C(2)H_B), 3.23-3.33 (2H, m, C(3′)H_2), 3.59 (3H, s, CO_2*Me*), 3.81 (3H, s, O*Me*), 3.98 (1H, q, *J* 6.8, C(α)*H*), 4.48 (1H, dd, *J* 8.2, 6.7, C(3)*H*), 6.87-6.91 (2H, m, C(3″)*H*, C(5″)*H*), 7.27-7.32 (3H, m, C(2″)*H*, C(6″)*H*, *Ph*), 7.33-7.39 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.9 (C(α)*Me*), 32.9 (*C*(2′)), 37.1 (*C*(2)), 43.2 (*C*(3′)), 43.6 (*C*(1′)), 51.5 (CO_2*Me*), 55.2 (O*Me*), 56.4 (*C*(α)), 59.2 (*C*(3)), 113.5 (*C*(3″), *C*(5″)), 127.3 (*C*(2″), *C*(6″)), 128.0, 128.4, 128.7 (*o,m,p-Ph*), 136.6 (*C*(1″)), 141.4 (*i-Ph*), 158.5 (*C*(4″)), 172.3 (*C*(1)); *m/z* (ESI$^+$) 414 ([M(^{37}Cl)+Na]$^+$, 35%), 412 ([M(^{35}Cl)+Na]$^+$, 100%), 392 ([M(^{37}Cl)+H]$^+$, 21%), 390 ([M(^{35}Cl)+H]$^+$, 84%); HRMS (ESI$^+$) $C_{22}H_{29}{}^{37}ClNO_3{}^+$ ([M(^{37}Cl)+H]$^+$) requires 392.1801; found 392.1804; $C_{22}H_{29}{}^{35}ClNO_3{}^+$ ([M(^{35}Cl)+H]$^+$) requires 390.1830; found 390.1819.

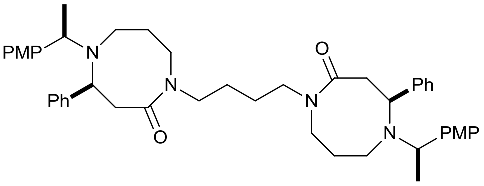
Step 2: Following *general procedure 12*, NaN_3 (1.07 g, 16.5 mmol), NaI (2.47 g, 16.5 mmol) and **433** (3.00 g, >99:1 dr) were reacted in DMSO (20 mL) to give **434** (2.93 g, >99:1 dr). Purification of an aliquot via flash column chromatography (gradient elution, 2% → 20% Et_2O in 30-40 °C petrol) gave **434** as a yellow oil; $[\alpha]_D^{24}$ −3.4 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2096 (N≡N), 1738 (C=O); δ_H (400 MHz, $CDCl_3$) 1.17 (3H, d, *J* 6.8, C(α)*Me*), 1.48-1.64 (2H, m, C(2′)H_2), 2.59 (2H, t, *J* 6.8, C(1′)H_2), 2.73 (1H, dd, *J* 14.9, 8.1, C(2)H_A), 2.89 (1H, dd, *J* 14.9, 6.8, C(2)H_B), 2.95-3.05 (2H, m, C(3′)H_2), 3.60 (3H, s, CO_2*Me*), 3.82 (3H, s, C(4′)O*Me*), 3.97 (1H, q, *J* 6.8, C(α)*H*), 4.45-4.49 (1H, m, C(3)*H*), 6.87-6.90 (2H, m, C(3″)*H*, C(5″)*H*), 7.28-7.31 (2H, m, C(2″)*H*, C(6″)*H*), 7.34-7.38 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.8 (C(α)*Me*), 29.0 (*C*(2′)), 37.1 (*C*(2)), 43.3 (*C*(1′)), 49.4 (*C*(3′)), 51.6 (CO_2*Me*), 55.2 (C(4′)O*Me*), 56.3 (*C*(α)), 59.2 (*C*(3)), 113.5 (*C*(3″), *C*(5″)), 127.3 (*C*(2″), *C*(6″)), 127.9, 128.4, 128.7 (*o,m,p-Ph*), 136.6 (*C*(1″)), 141.3 (*i-Ph*), 158.4 (*C*(4″)), 172.3 (*C*(1)); *m/z* (ESI$^+$)

419 ([M+Na]$^+$, 100%), 397 ([M+H]$^+$, 94%); HRMS (ESI$^+$) $C_{22}H_{29}N_4O_3^+$ ([M+H]$^+$) requires 397.2234; found 397.2232.

Step 3: Following *general procedure 13*, **434** (2.69 g, >99:1 dr) and PPh_3 (1.78 g, 6.77 mmol) were reacted in THF (10 mL) and H_2O (2.7 mL). The residue was partitioned between CH_2Cl_2 (100 mL) and 2.0 M aq HCl (25 mL). The organic layer was extracted with 2.0 M aq HCl (2 × 25 mL) and the combined aqueous layers washed with CH_2Cl_2 (50 mL). The aqueous layer was then basified to pH 12 by addition of solid KOH and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give **435** as a colourless oil (1.95 g, >99:1 dr); δ_H (400 MHz, $CDCl_3$) 1.15 (3H, d, *J* 6.8, C(α)*Me*), 1.50 (2H, quin, *J* 6.9, C(2′)H_2), 2.46 (2H, td, *J* 6.9, 2.7, C(3′)H_2), 2.54 (2H, t, *J* 7.9, C(1′)H_2), 2.70 (1H, ABdd, *J* 14.9, 8.7, C(2)H_A), 2.81 (1H, ABdd, *J* 14.9, 6.5, C(2)H_B), 3.57 (3H, s, CO_2*Me*), 3.81 (3H, s, C(4′)O*Me*), 3.96 (1H, q, *J* 6.8, C(α)*H*), 4.45 (1H, dd, *J* 8.7, 6.5, C(3)*H*), 6.86 (2H, d, *J* 8.5, C(3″)*H*, C(5″)*H*), 7.24-7.36 (7H, m, *Ph*, C(2″)*H*, C(6″)*H*).

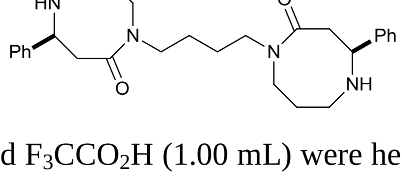
Step 4: Following *general procedure 14*, **435** (1.95 g, >99:1 dr) and $Sb(OEt)_3$ (1.07 mL, 6.31 mmol) were reacted in PhMe (600 mL). Purification via flash column chromatography (eluent EtOAc) gave **436** as a colourless oil (1.31 g, 57% over 4 steps, >99:1 dr); $C_{21}H_{26}N_2O_2$ requires C, 74.5; H, 7.7; N, 8.3%; found C, 74.4; H, 7.6; N, 8.2%; $[\alpha]_D^{20}$ +21.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1663 (C=O); δ_H (400 MHz, $CDCl_3$) 0.99-1.08 (1H, m, C(7)H_A), 1.20-1.30 (1H, m, C(7)H_B) overlapping 1.21 (3H, d, *J* 6.3, C(α)*Me*), 2.51-2.66 (2H, m, C(2)H_A, C(6)H_A), 2.98-3.17 (3H, m, C(2)H_B, C(6)H_B, C(8)H_A), 3.49 (1H, app br q, *J* 9.9, C(8)H_B), 3.74 (3H, s, C(4′)O*Me*), 3.93 (1H, q, *J* 6.3, C(α)*H*), 4.49 (1H, br s, C(4)*H*), 6.81 (2H, d, *J* 8.3, C(3′)*H*, C(5′)*H*), 7.02 (1H, br t, *J* 6.8, N*H*), 7.21-7.41 (7H, m, C(2′)*H*, C(6′)*H*, *Ph*); δ_C (125 MHz, PhMe-d_8, 363 K) 16.8 (C(α)*Me*), 33.8 (*C*(7)), 41.9 (*C*(6)), 42.0 (*C*(3)), 46.6 (*C*(8)), 54.9 (C(4′)O*Me*), 60.4 (*C*(α)), 63.4 (*C*(4)), 114.0 (*C*(3′), C(5′)), 127.0, 127.6, 128.6, 129.4 (*o,m,p-Ph*, *C*(2′), *C*(6′)), 138.0, 144.4 (*i-Ph*), 159.3 (*C*(4′)), 175.7 (*C*(2));[54] *m/z* (ESI$^+$) 699 ([2M+Na]$^+$, 100%), 361 ([M+Na]$^+$, 79%), 339 ([M+H]$^+$, 76%); HRMS (ESI$^+$) $C_{21}H_{26}N_2NaO_2^+$ ([M+Na]$^+$) requires 361.1886; found 361.1880.

(4′*S*,α*R*)-1,4-Di[2′-oxo-4′-phenyl-*N*(5′)-(α-methyl-4″-methoxybenzyl)-1′,5′-diazocan-1′-yl]butane 437



1,4-Dibromobutane (88 µL, 739 µmol) was added to **436** (500 mg, 1.48 mmol, >99:1 dr), K_2CO_3 (818 mg, 5.92 mmol), KOH (332 mg, 5.92 mmol) and TBAI (55 mg, 148 µmol) in PhMe (8 mL) at rt under N_2 and sealed in a tube. The resultant mixture was heated at 160 °C in a microwave reactor for 15 min before being cooled to rt and partitioned between H_2O (5 mL) and EtOAc (5 mL). The aqueous layer was extracted with EtOAc (2 × 10 ml) and the combined organic extracts were washed with brine (20 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 70% → 100% EtOAc in 30-40 °C petrol) gave **437** as a white solid (363 mg, 67%, >99:1 dr); mp 46-49 °C; $[\alpha]_D^{24}$ +20.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1661 (C=O); δ_H (500 MHz, $CDCl_3$) 0.96-1.04 (2H, m, 2 × C(7′)H_A), 1.19 (6H, d, *J* 6.5, 2 × C(α)*Me*), 1.27-1.37 (2H, m, 2 × C(7′)H_B), 1.56 (4H, br s, C(2)H_2, C(3)H_2), 2.45 (2H, br s, 2 × C(6′)H_A), 2.78-2.86 (2H, m, C(1)H_A, C(4)H_A), 3.02 (2H, br s, 2 × C(3′)H_A), 3.06-3.17 (4H, m, 2 × C(6′)H_B, 2 × C(8′)H_A), 3.78-3.84 (8H, m, 2 × C(4″)O*Me*, 2 × C(8′)H_B), 3.88 (2H, q, *J* 6.5, 2 × C(α)*H*), 3.90-3.98 (2H, m, C(1)H_B, C(4)H_B), 4.44 (2H, br s, 2 × C(4′)*H*), 6.82 (4H, d, *J* 8.8, 2 × C(3″)*H*, 2 × C(5″)*H*), 7.22-7.28 (6H, m, 2 × C(2″)*H*, 2 × C(5″)*H*, *Ph*), 7.32-7.37 (4H, m, *Ph*), 7.38-7.44 (4H, m, *Ph*);[55] δ_C (125 MHz, $CDCl_3$) *15.1* (2 × C(α)*Me*), 25.3 (*C*(2), *C*(3)), 30.6 (2 × *C*(7′)), *43.4* (2 × *C*(3′)), 45.4 (*C*(1), *C*(4)), *47.5* (2 × (*C*(8′)), 55.2 (2 × C(4″)O*Me*), *59.5* (2 × *C*(α)), *63.7* (2 × *C*(4′)), 113.2 (2 × *C*(3″), 2 × (*C*(5″)), 126.9, 127.1, 128.6, 129.0 (2 × *C*(2″), 2 × *C*(6″), *o,m,p-Ph*), *137.5* (2 × *C*(1″)), 143.6 (*i-Ph*), 158.3 (2 × *C*(4″)), 170.3 (2 × *C*(1′));[56] *m/z* (ESI^+) 753 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{46}H_{58}N_4NaO_4^+$ ($[M+Na]^+$) requires 753.4350; found 753.4358.

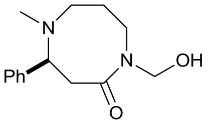
(*S*,*S*)-1,4-Di[2′-oxo-4′-phenyl-1′,5′-diazocan-*N*(1′)-yl]butane 336



437 (50 mg, 78 µmol, >99:1 dr) and F_3CCO_2H (1.00 mL) were heated at 60 °C for 2.5 h and then the reaction mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc (5 mL) and sat aq $NaHCO_3$ (5 mL) and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic extracts were washed with brine (10 mL), then dried and concentrated *in vacuo*. Purification via column chromatography (gradient elution, 0% → 10% MeOH in $CHCl_3$)

gave **336** as a colourless oil (11 mg, 30%, >99:1 dr);[57] $[\alpha]_D^{24}$ −32.5 (*c* 0.5 in $CHCl_3$); {lit.[57] $[\alpha]_D^{20}$ −30 (*c* 1.3 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.59-1.68 (2H, m, 2 × C(7′)H_A), 1.76-1.84 (6H, m, C(2)H_2, C(3)H_2, 2 × C(7′)H_B), 2.38 (2H, dd, *J* 12.3, 8.9, 2 × C(3′)H_A), 2.50 (2H, dd, *J* 12.3, 1.7, 2 × C(3′)H_B), 2.89-3.04 (4H, m, 2 × C(6′)H_2), 3.13-3.32 (4H, m, C(1)H_2, C(4)H_2), 3.83-3.92 (2H, m, 2 × C(8′)H_A), 3.95-4.23 (4H, m, 2 × C(4′)*H*, 2 × C(8′)H_B), 7.23-7.43 (10H, m, *Ph*).

(*S*)-*N*(1)-(Hydroxymethyl)-4-phenyl-*N*(5)-methyl-1,5-diazocan-2-one 438



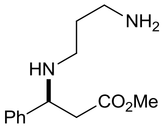
$Pd(OH)_2/C$ (200 mg) was added to a degassed solution of **418** (200 mg, 648 µmol, >99:1 dr) in AcOH (10 mL), MeOH (3.4 mL) and formalin (6.4 mL) at rt and the resultant mixture was stirred under H_2 (5 atm) for 72 h. The reaction mixture was degassed, filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was partitioned between EtOAc (15 mL) and sat aq $NaHCO_3$ (15 mL). The aqueous layer was extracted with EtOAc (2 × 15 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent CH_2Cl_2/MeOH, 19:1) gave **438** as a white solid (45 mg, 28%, >99:1 dr); mp 94-97 °C; $[\alpha]_D^{24}$ −5.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3357 (O−H), 1631 (C=O); δ_H (400 MHz, $CDCl_3$) 1.67-1.75 (1H, m, C(7)H_A), 1.85-1.96 (1H, m, C(7)H_B), 2.25 (3H, s, N*Me*), 2.51-2.57 (2H, m, C(6)H_A, C(3)H_A), 2.97 (1H, ddd, *J* 15.4, 7.1, 3.3, C(6)H_B), 3.14 (1H, app t, *J* 11.9, C(3)H_B), 3.49 (1H, dt, *J* 15.4, 3.8, C(8)H_A), 3.88-4.00 (2H, m, C(4)*H*, C(8)H_B), 4.11 (1H, br s, O*H*), 4.77 (1H, ABd, *J* 10.3, N(1)C$H_A$$H_B$OH), 5.02 (1H, ABd, *J* 10.3, N(1)C$H_A$$H_B$OH), 7.23-7.35 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 31.1 (*C*(7)), 41.5 (*C*(3)), 43.8 (N*Me*), 48.6 (*C*(8)), 51.5 (*C*(6)), 68.4 (*C*(4)), 72.9 (N(1)*C*H_2OH), 127.3, 127.5, 128.4 (*o,m,p-Ph*), 141.8 (*i-Ph*), 175.5 (*C*(2)); *m/z* (ESI^+) 271 ($[M+Na]^+$, 100%), 249 ($[M+H]^+$, 41%); HRMS (ESI^+) $C_{14}H_{21}N_2O_2^+$ ($[M+H]^+$) requires 249.1598; found 249.1599. Further elution gave **439** as a white solid (18 mg, 13%, >99:1 dr).

X-ray crystal structure determination for **438**. Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-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.[45]

X-ray crystal structure data for **438** [$C_{14}H_{20}N_2O_2$]: *M* = 248.32, monoclinic, space group *P* 2_1, *a* = 6.0224(3) Å, *b* = 6.8706(3) Å, *c* = 15.3642(6) Å, *β* = 93.565(2)°, *V* = 634.50(5) Å^3, *Z* = 2, μ = 0.088 mm^{-1}, colourless plate, crystal dimensions = 0.08 × 0.19 × 0.22 mm^3. A total of 1545 unique reflections were measured for $5 < \theta < 27$ and 1545 reflections were used in the refinement. The final parameters were $wR_2 = 0.105$ and $R_1 = 0.058$ [$I > -3.0\sigma(I)$].

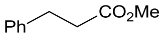
Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 880489. Copies of these data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif., or on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

Methyl (*S*)-3-(3′-aminopropylamino)-3-phenylpropanoate 440



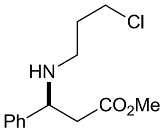
Following *general procedure 17*, **421** (100 mg, 273 µmol, >99:1 dr), and $Pd(OH)_2/C$ (50 mg) were reacted in MeOH (1 mL) for 16 h to give **440** as a yellow oil (65 mg, quant); $[\alpha]_D^{24}$ −10.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3294 (N−H), 1733 (C=O); δ_H (400 MHz, $CDCl_3$) 1.58 (2H, app t, *J* 6.8, C(2′)H_2), 2.43-2.76 (7H, m, C(2)H_2, C(1′)H_2, C(3′)H_2, N*H*), 3.66 (3H, s, O*Me*), 4.07 (1H, dd, *J* 8.7, 5.3, C(3)*H*), 7.18-7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 33.7 (*C*(2′)), 40.4 (*C*(3′)), 42.8 (*C*(2)), 45.3 (*C*(1′)), 51.6 (O*Me*), 59.7 (*C*(3)), 126.9, 127.4, 128.6 (*o,m,p-Ph*), 142.8 (*i-Ph*), 172.4 (*C*(1)); *m/z* (ESI^+) 237 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{13}H_{21}N_2O_2^+$ ($[M+H]^+$) requires 237.1598; found 237.1597.

Methyl 3-phenylpropanoate 441



Following *general procedure 17*, **420** (100 mg, 278 µmol, >99:1 dr), and $Pd(OH)_2/C$ (50 mg) were reacted in EtOAc (1 mL) for 16 h. Purification via flash column chromatography (gradient elution, 2% → 6% Et_2O in 30-40 °C petrol) gave **441** as a colourless oil (21 mg, 46%);[58] δ_H (400 MHz, $CDCl_3$) 2.64 (2H, t, *J* 8.0, C(2)*H*), 2.97 (2H, t, *J* 8.0, C(3)*H*), 3.68 (3H, s, O*Me*), 7.19-7.33 (5H, m, *Ph*).

Methyl (*S*)-3-(3′-chloropropylamino)-3-phenylpropanoate 442

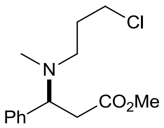


Method A: Following *general procedure 17*, **420** (1.00 g, 2.78 mmol, >99:1 dr), and $Pd(OH)_2/C$ (500 mg) were reacted in 1.0 M aq HCl (10 mL) for 18 h. The residue was partitioned between CH_2Cl_2 (20 mL) and sat aq $NaHCO_3$ (20 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give **442** as a yellow oil

(496 mg, 70%); $[\alpha]_D^{24}$ −29.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3347 (N−H), 1735 (C=O); δ_H (400 MHz, $CDCl_3$) 1.83-1.95 (2H, m, C(2′)H_2), 2.54-2.67 (3H, m, C(1′)H_2, C(2)H_A), 2.72 (1H, ABdd, *J* 15.7, 8.7 C(2)H_B), 3.54-3.64 (2H, m, C(3′)H_2), 3.66 (3H, s, O*Me*), 4.09 (1H, dd, *J* 8.7, 5.3, C(3)*H*), 7.25-7.36 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 32.7 (*C*(2′)), 42.7 (*C*(2)), 42.9 (*C*(3′)), 44.2 (*C*(1′)), 51.7 (O*Me*), 59.4 (*C*(3)), 126.9, 127.6, 128.6 (*o,m,p-Ph*), 142.3 (*i-Ph*), 172.2 (*C*(1)); *m/z* (ESI^+) 280 ($[M(^{37}Cl)+Na]^+$, 9%), 278 ($[M(^{35}Cl)+Na]^+$, 26%), 258 ($[M(^{37}Cl)+H]^+$, 47%), 256 ($[M(^{35}Cl)+H]^+$, 100%); HRMS (ESI^+) $C_{13}H_{19}{}^{37}ClNO_2{}^+$ ($[M(^{37}Cl)+H]^+$) requires 258.1069; found 256.1068; $C_{13}H_{19}{}^{35}ClNO_2{}^+$ ($[M(^{35}Cl)+H]^+$) requires 256.1099; found 256.1096.

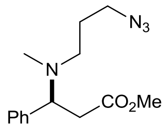
Method B: **433** (958 mg, 2.66 mmol, >99:1 dr) and F_3CCO_2H (9.6 mL) were heated at 60 °C for 2.5 h and then the reaction mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc (20 mL) and sat aq $NaHCO_3$ (20 mL) and then the aqueous layer was extracted with EtOAc (2 × 20 mL). 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/Et_2O, 3:7) gave **442** as a yellow oil (581 mg, 92%); $[\alpha]_D^{24}$ −28.5 (*c* 1.0 in $CHCl_3$).

Methyl (*S*)-3-[*N*-(3′-chloropropyl)-*N*-methylamino]-3-phenylpropanoate 444



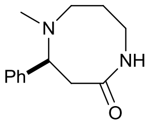
Following *general procedure 18*, **442** (675 mg, 2.64 mmol), $(CH_2O)_n$ (159 mg, 5.28 mmol) and $NaBH_3CN$ (664 mg, 10.6 mmol) were reacted in MeOH (27 mL). Purification via flash column chromatography (gradient elution, 60% → 100% EtOAc in 30-40 °C petrol) gave **444** as a yellow oil (573 mg, 75%); $[\alpha]_D^{24}$ −5.3 (*c* 0.4 in $CHCl_3$); ν_{max} (ATR) 1737 (C=O); δ_H (400 MHz, $CDCl_3$) 1.85-1.93 (2H, m, C(2′)H_2), 2.14 (3H, s, N*Me*), 2.38-2.45 (1H, m, C(1′)H_A), 2.49-2.55 (1H, m, C(1′)H_B), 2.70 (1H, ABdd, *J* 14.8, 7.1, C(2)H_A), 3.00 (1H, ABdd, *J* 14.8, 8.3, C(2)H_B), 3.57 (2H, t, *J* 6.3, C(3′)H_2), 3.64 (3H, s, O*Me*), 4.17 (1H, app t, *J* 7.8, C(3)*H*), 7.23-7.36 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 30.4 (*C*(2′)), 37.3 (N*Me*, *C*(2)), 42.9 (*C*(3′)), 50.7 (*C*(1′)), 51.6 (O*Me*), 64.5 (*C*(3)), 127.5, 128.1, 128.3 (*o,m,p-Ph*), 137.9 (*i-Ph*), 172.3 (*C*(1)); *m/z* (ESI^+) 294 ($[M(^{37}Cl)+Na]^+$, 11%), 292 ($[M(^{35}Cl)+Na]^+$, 31%), 272 ($[M(^{37}Cl)+H]^+$, 53%), 270 ($[M(^{35}Cl)+H]^+$, 100%); HRMS (ESI^+) $C_{14}H_{21}{}^{37}ClNO_2{}^+$ ($[M(^{37}Cl)+H]^+$) requires 272.1226; found 272.1227; HRMS (ESI^+) $C_{14}H_{21}{}^{35}ClNO_2{}^+$ ($[M(^{35}Cl)+H]^+$) requires 270.1255; found 270.1250.

Methyl (*S*)-3-[*N*-(3′-azidopropyl)-*N*-methylamino]-3-phenylpropanoate 445



Following *general procedure 12*, NaN_3 (1.21 g, 18.6 mmol), NaI (2.79 g, 18.6 mmol) and **444** (2.51 g, 9.31 mmol) were reacted in DMSO (40 mL). Purification via flash column chromatography (gradient elution, 10% → 50% Et_2O in 30-40 °C petrol) gave **445** as a yellow oil (2.57 g, quant, >99:1 dr); $[\alpha]_D^{24}$ −4.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2096 (N≡N), 1739 (C=O); δ_H (400 MHz, $CDCl_3$) 1.71 (2H, app quind, *J* 6.7, 2.7, C(2′)H_2), 2.14 (3H, s, N*Me*), 2.30-2.36 (1H, m, C(1′)H_A), 2.41-2.48 (1H, m, C(1′)H_B), 2.70 (1H, ABdd, *J* 14.9, 7.2, C(2)H_A), 2.99 (1H, ABdd, *J* 14.9, 8.4, C(2)H_B), 3.31 (2H, t, *J* 6.8, C(3′)H_2), 3.64 (3H, s, O*Me*), 4.16 (1H, app t, *J* 7.9, C(3)*H*), 7.21-7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 26.7 (*C*(2′)), 37.2 (*C*(2)), 37.3 (N*Me*), 49.2 (*C*(3′)), 50.7 (*C*(1′)), 51.6 (O*Me*), 64.3 (*C*(3)), 127.5, 128.1, 128.2 (*o,m,p-Ph*), 137.9 (*i-Ph*), 172.3 (*C*(1)); *m/z* (ESI^+) 299 ($[M+Na]^+$, 49%), 277 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{14}H_{21}N_4O_2^+$ ($[M+H]^+$) requires 277.1659; found 277.1654.

(*S*)-4-Phenyl-*N*(5)-methyl-1,5-diazocan-2-one 439



Step 1: Following *general procedure 13*, **445** (2.40 g, 8.69 mmol) and PPh_3 (2.51 g, 9.55 mmol) were reacted in THF (25 mL) and H_2O (7.2 mL) to give **446** as a yellow oil (5.15 g, >99:1 dr); δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.55-1.62 (2H, m, C(2′)H_2), 2.15 (3H, s, N*Me*), 2.29-2.35 (1H, m, C(1′)H_A), 2.39-2.46 (1H, m, C(1′)H_B), 2.67-2.72 (3H, m, C(2)H_A, C(3′)H_2), 3.00 (1H, app dd, *J* 14.9, 8.0, C(2)H_B), 3.63 (3H, s, O*Me*), 4.16 (1H, app t, *J* 7.9, C(3)*H*).

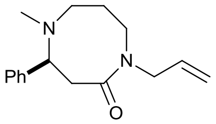
Step 2: Following *general procedure 14*, **446** (5.15 g, >99:1 dr) and $Sb(OEt)_3$ (1.49 mL, 8.77 mmol) were reacted in PhMe (750 mL). Purification via flash column chromatography (gradient elution, 0% → 10% MeOH in EtOAc) gave **439** as a white solid (1.18 g, 62% over 2 steps);[59,60] mp 97-99 °C; $[\alpha]_D^{24}$ +6.7 (*c* 1.0 in $CHCl_3$); {lit.[61,62] for enantiomer $[\alpha]_D^{25}$ −6.2 (*c* 0.9 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.54-1.64 (1H, m, C(7)H_A), 1.67-1.78 (1H, m, C(7)H_B), 2.31 (3H, s, N*Me*), 2.46 (1H, ABdd, *J* 12.6, 3.8, C(3)H_A), 2.53 (1H, ddd, *J* 15.4, 6.8, 2.8, C(6)H_A), 2.99-3.04 (1H, m, C(6)H_B), 3.08 (1H, app ABt, *J* 12.1, C(3)H_B), 3.24-3.34 (1H, m, C(8)H_A), 3.46-3.57 (1H, m, C(8)H_B), 4.05 (1H, dd, *J* 8.3, 3.5, C(4)*H*), 6.94 (1H, br t, *J* 6.3, N*H*), 7.21-7.35 (5H, m, *Ph*).

X-ray crystal structure determination for **439**. 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.[45]

X-ray crystal structure data for **439** [$C_{13}H_{18}N_2O$]: M = 218.30, monoclinic, space group $P\ 2_1$, a = 6.0474(2) Å, b = 6.8974(2) Å, c = 13.9812(4) Å, β = 96.696(3)°, V = 579.19(3) $Å^3$, Z = 2, μ = 0.632 mm^{-1}, colourless plate, crystal dimensions = 0.05 × 0.11 × 0.23 mm^3. A total of 6077 reflections were measured for $5 < \theta < 77$ and 5458 reflections were used in the refinement. The final parameters were $wR_2 = 0.084$ and $R_1 = 0.034$ [$I > -3.0\sigma(I)$].

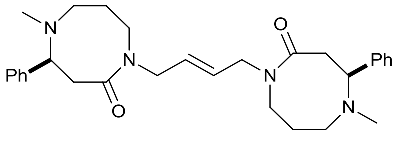
Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 880488. Copies of these data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif., or on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

(*S*)-*N*(1)-Allyl-4-phenyl-*N*(5)-methyl-1,5-diazocan-2-one 447

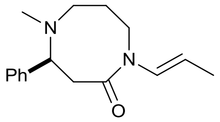


Allyl bromide (0.24 mL, 2.80 mmol) was added to **439** (500 mg, 2.29 mmol), K_2CO_3 (380 mg, 2.75 mmol), NaOH (387 mg, 9.68 mmol) and TEBAC (69 mg, 298 μmol) in THF (14 mL) at rt. The resultant mixture was heated at 75 °C for 18 h, then filtered through Celite® (eluent EtOAc) and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 60% → 100% EtOAc in 30-40 °C petrol) gave **447** as a yellow oil (555 mg, 94%); $[\alpha]_D^{24}$ −31.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1633 (C=O); δ_H (400 MHz, $CDCl_3$) 1.55-1.64 (1H, m, C(7)H_A), 1.77-1.88 (1H, m, C(7)H_B), 2.28 (3H, s, N*Me*), 2.52 (1H, ddd, *J* 15.4, 7.8, 3.0, C(6)H_A), 2.58 (1H, dd, *J* 12.9, 3.3, C(3)H_A), 2.98 (1H, ddd, *J* 15.4, 7.8, 3.0, C(6)H_B), 3.19 (1H, app t, *J* 12.1, C(3)H_B), 3.33 (1H, dt, *J* 15.4, 3.8, C(8)H_A), 3.68 (1H, dd, *J* 15.2, 6.8, C$H_A$$H_B$CH=$CH_2$), 3.79-3.86 (1H, m, C(8)H_B), 4.03 (1H, dd, *J* 11.6, 3.3, C(4)*H*), 4.45 (1H, dd, *J* 15.2, 5.3, C$H_A$$H_B$CH=$CH_2$), 5.16-5.24 (2H, m, CH_2CH=CH_2), 5.79-5.89 (1H, m, CH_2C*H*=CH_2), 7.22-7.36 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 29.6 (*C*(7)), 41.1 (*C*(3)), 43.7 (N*Me*), 47.1 (*C*(8)), 48.5 (*C*H_2CH=CH_2), 51.1 (*C*(6)), 68.1 (*C*(4)), 117.2 (CH_2CH=*C*H_2), 127.1, 127.5, 128.3 (*o,m,p-Ph*), 133.9 (CH_2*C*H=CH_2), 141.9 (*i-Ph*), 173.3 (*C*(2)); *m/z* (ESI^+) 539 ($[2M+Na]^+$, 100%), 517 ($[2M+H]^+$, 13%), 281 ($[M+Na]^+$, 96%) 259 ($[M+H]^+$, 90%); HRMS (ESI^+) $C_{16}H_{23}N_2O^+$ ($[M+H]^+$) requires 259.1805; found 259.1803.

(*S*,*E*)-1,4-Di[2′-oxo-4′-phenyl-*N*(5′)-methyl-1′,5′-diazocan-1′-yl]but-2-ene 448 and (*S*,*E*)-1-(prop-1′-en-1′-yl)-4-phenyl-*N*(5)-methyl-1,5-diazocan-2-one 450



448

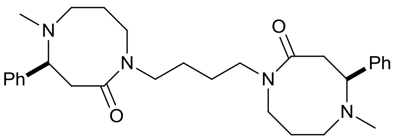


450

Method A: Grubbs II (75 mg, 88.6 µmol) was added to a degassed solution of **447** (229 mg, 886 µmol) in CH_2Cl_2 (3 mL, EtOH stabilised) at rt and the resultant mixture was heated at 40 °C for 16 h. The reaction mixture was then concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 0% → 10% MeOH in CH_2Cl_2) gave **450** as a brown oil (26 mg, 11%); $[\alpha]_D^{24}$ +14.4 (*c* 0.4 in $CHCl_3$); ν_{max} (ATR) 1644 (C=O); δ_H (400 MHz, $CDCl_3$) 1.75 (3H, dd, *J* 6.6, 1.5, C(3′)H_3), 1.80-1.93 (2H, m, C(7)H_2), 2.24 (3H, s, N*Me*), 2.50 (1H, ABddd, *J* 15.3, 8.3, 2.8, C(6)H_A), 2.64 (1H, ABdd, *J* 13.1, 3.3, C(3)H_A), 2.93 (1H, ABddd, *J* 15.3, 6.8, 3.3, C(6)H_B), 3.25 (1H, br t, *J* 12.1, C(3)H_B), 3.75 (1H, ABdt, *J* 15.4, 3.5, C(8)H_A), 3.94-4.05 (2H, m, C(4)*H*, C(8)H_B), 5.11 (1H, dq, *J* 14.7, 6.6, C(2′)*H*), 7.19-7.37 (6H, m, C(1′)*H*, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.5 (*C*(3′)), 28.6 (*C*(7)), 42.1 (*C*(3)), 43.8 (N*Me*), 44.3 (*C*(8)), 51.4 (*C*(6)), 68.9 (*C*(4)), 106.5 (*C*(2′)), 126.5, 127.5, 128.4 (*o,m,p-Ph*), 127.3 (*C*(1′)), 171.7 (*C*(2));[63] *m/z* (ESI^+) 539 ($[2M+Na]^+$, 100%), 517 ($[2M+H]^+$, 6%), 281 ($[M+Na]^+$, 82%) 259 ($[M+H]^+$, 71%); HRMS (ESI^+) $C_{16}H_{23}N_2O^+$ ($[M+H]^+$) requires 259.1805; found 259.1805. Further elution gave **448** as a brown oil (92 mg, 42%, >99:1 dr) $[\alpha]_D^{24}$ −29.2 (*c* 0.8 in $CHCl_3$); ν_{max} (ATR) 1631 (C=O); δ_H (400 MHz, $CDCl_3$) 1.55-1.68 (2H, m, 2 × C(7′)H_A), 1.74-1.87 (2H, m, 2 × C(7′)H_B), 2.27 (6H, s, 2 × N*Me*), 2.46-2.59 (4H, m, 2 × C(3′)H_A, 2 × C(6′)H_A), 2.98 (2H, app ddd, *J* 15.2, 7.8, 2.8, 2 × C(6′)H_B), 3.18 (2H, app t, *J* 12.1, 2 × C(3′)H_B), 3.31 (2H, app dt, *J* 15.4, 3.5, 2 × C(8′)H_A), 3.68 (2H, dd, *J* 15.7, 3.3, C(1)H_A, C(4)H_A), 3.81 (2H, app t, *J* 13.4, 2 × C(8′)H_B), 4.01 (2H, dd, *J* 11.6, 3.0, 2 × C(4′)*H*), 4.41 (2H, app d, *J* 13.4, C(1)H_B, C(4)H_B), 5.65 (2H, t, *J* 3.3, C(2)*H*, C(3)*H*), 7.23-7.35 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 29.6 (2 × *C*(7′)), 41.0 (2 × *C*(3′)), 43.7 (2 × N*Me*), *47.3* (2 × *C*(8′)), 47.4 (*C*(1), *C*(4)), 51.1 (2 × (*C*(6′)), 68.1 (2 × *C*(4′)), 127.2, 127.5, 128.3 (*o,m,p-Ph*), 128.5 (*C*(2), *C*(3)), 141.7 (*i-Ph*), 173.3 (2 × *C*(2′)); *m/z* (ESI^+) 511 ($[M+Na]^+$, 69%), 489 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{30}H_{41}N_4O_2^+$ ($[M+H]^+$) requires 489.3224; found 489.3233.

Method B: Following *general procedure 15*, **439** (75 mg, 344 µmol), **425** (37 mg, 172 µmol), KOH (77 mg, 1.37 mmol), K_2CO_3 (57 mg, 415 µmol) and TEBAC (10 mg, 42.8 µmol) were reacted in DMSO (3.0 mL) for 96 h. Purification via flash column chromatography (eluent PhMe/isoproylalcohol/35% aq NH_4OH, 94:5:1) gave an 80:20 mixture of **439**:**448** as a yellow oil.

(*S*,*S*)-1,4-Di[2′-oxo-4′-phenyl-*N*(5′)-methyl-1′,5′-diazocan-*N*(1′)-yl]butane [(−)-homaline] 99



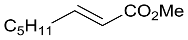
Method A: Formalin (2.71 mL) was added to a stirred mixture of **437** (50 mg, 78 µmol, >99:1 dr) in HCO_2H (2.28 mL) at rt and the resultant mixture was heated at reflux for 2.5 h and then allowed to cool to rt. 1.0 M aq NaOH was added to the reaction mixture until pH >13 was achieved, and the aqueous layer was extracted with $CHCl_3$ (3 × 10 mL). The combined organic extracts were then dried and concentrated *in vacuo*. Purification via column chromatography (gradient elution, 0% → 13% MeOH in Et_2O) gave (−)-(*S*,*S*)-homaline **99** as a white solid (15 mg, 39%, >99:1 dr);[64] mp 113–116 °C; {lit.[64] mp 132 °C (Et_2O)}; $[\alpha]_D^{24}$ −29.2 (*c* 1.0 in $CHCl_3$); {lit.[5] $[\alpha]_D^{20}$ −34 (*c* 1.0 in $CHCl_3$)}; ν_{max} (film) 1630 (C=O); δ_H (400 MHz, $CDCl_3$) 1.57–1.67 (6H, m, C(2)H_2, C(3)H_2, 2 × C(7′)H_A), 1.76–1.87 (2H, m, 2 × C(7′)H_B), 2.26 (6H, s, 2 × N*Me*), 2.47–2.55 (4H, m, 2 × C(3′)H_A, 2 × C(6′)H_A), 2.93–3.08 (4H, m, C(1)H_A, C(4)H_A, 2 × C(6′)H_B), 3.16 (2H, app t, *J* 12.1, 2 × C(3′)H_B), 3.32 (2H, app dt, *J* 15.4, 3.5, 2 × C(8′)H_A), 3.77–3.90 (4H, m, C(1)H_B, C(4)H_B, 2 × C(8′)H_B), 4.00 (2H, dd, *J* 11.6, 3.0, 2 × C(4′)*H*), 7.23–7.34 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.4 (*C*(2), *C*(3)), 29.9 (2 × *C*(7′)), 41.2 (2 × *C*(3′)), 43.7 (2 × N*Me*), 45.7 (*C*(1), *C*(4)), 47.9 (2 × *C*(8′)), 51.0 (2 × *C*(6′)), 68.1 (2 × *C*(4′)), 127.1, 127.5, 128.3 (*o,m,p-Ph*), 142.0 (*i-Ph*), 173.5 (2 × *C*(2′)); *m/z* (ESI$^+$) 982 ($[2M+H]^+$, 43%), 513 ($[M+Na]^+$, 100%), 491 ($[M+H]^+$, 96%); HRMS (ESI$^+$) $C_{30}H_{43}N_4O_2^+$ ($[M+H]^+$) requires 491.3381; found 491.3389.

Method B:[7] Formalin (0.81 mL) was added to **336** (25 mg, 54 µmol, >99:1 dr) in AcOH (2.5 mL) at 0 °C and the resultant mixture was stirred for 15 min. $NaBH_3CN$ (65 mg, 1.03 mmol) in MeOH (0.43 mL) was added and the resultant mixture was allowed to warm to rt over 3.5 h. The reaction mixture was cooled to 0 °C, 2.0 M aq HCl (2 mL) was added and the resultant mixture concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (5 mL) and sat aq Na_2CO_3 (5 mL), the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL), and the combined organic extracts were washed with brine (10 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 0% → 4% MeOH in $CHCl_3$) gave (−)-(*S*,*S*)-homaline **99** as a white solid (8 mg, ~30%, >99:1 dr);[64] mp 115–117 °C; $[\alpha]_D^{21}$ −16.8 (*c* 0.4 in $CHCl_3$).

Method C: Following *general procedure 17*, **448** (57 mg, 117 µmol, >99:1 dr) and $Pd(OH)_2$/C were reacted in EtOAc (1 mL) for 2 h. Purification via column chromatography (gradient elution, 1% → 10% MeOH in Et_2O) gave (−)-(*S*,*S*)-homaline **99** as a white solid (25 mg, 44%, >99:1 dr); mp 122–124 °C; $[\alpha]_D^{24}$ −32.5 (*c* 1.0 in $CHCl_3$).

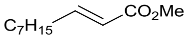
Method D: Following *general procedure 16*, **439** (100 mg, 458 µmol), 1,4-dibromobutane **360** (28 µL, 234 µmol) and KOH (103 mg, 1.84 mmol) were reacted in DMSO (0.92 mL) for 96 h. Purification via column chromatography (gradient elution, 0% → 2.5% MeOH in CH_2Cl_2) gave (−)-(*S*,*S*)-homaline **99** as a white solid (67 mg, 60%, >99:1 dr); mp 115–117 °C; $[\alpha]_D^{21}$ −28.1 (*c* 1.0 in $CHCl_3$).

Methyl (*E*)-oct-2-enoate 456



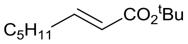
Following *general procedure 4*, **460** (1.68 mL, 9.16 mmol), MeMgBr (3.0 M in Et_2O, 2.92 mL, 8.75 mmol) and **454** (1 mL, 8.33 mmol) were reacted in THF (50 mL) to give **456** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 °C petrol) gave **456** as a colourless oil (810 mg, 62%, >99:1 dr);[65] δ_H (400 MHz, $CDCl_3$) 0.87-0.91 (3H, m, C(8)H_3), 1.24-1.36 (6H, m, C(5)H_2, C(6)H_2, C(7)H_2), 2.20 (2H, app qd, *J* 7.2, 1.5, C(4)H_2), 3.73 (3H, s, O*Me*), 5.83 (1H, dt, *J* 15.7, 1.4, C(2)*H*), 6.98 (1H, dt, *J* 15.7, 7.2, C(3)*H*).

Methyl (*E*)-dec-2-enoate 457



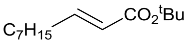
Following *general procedure 4*, **460** (1.68 mL, 9.16 mmol), MeMgBr (3.0 M in Et_2O, 2.92 mL, 8.75 mmol) and **455** (1.30 mL, 8.33 mmol) were reacted in THF (50 mL) to give **457** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 °C petrol) gave **457** as a colourless oil (835 mg, 54%, >99:1 dr);[65] δ_H (400 MHz, $CDCl_3$) 0.86-0.91 (3H, m, C(10)H_3), 1.24-1.35 (10H, m, C(5)H_2, C(6)H_2, C(7)H_2, C(8)H_2, C(9)H_2), 2.20 (2H, app qd, *J* 7.2, 1.4, C(4)H_2), 3.73 (3H, s, O*Me*), 5.82 (1H, dt, *J* 15.6, 1.4, C(2)*H*), 6.98 (1H, dt, *J* 15.6, 7.2, C(3)*H*).

tert-Butyl (*E*)-oct-2-enoate 461



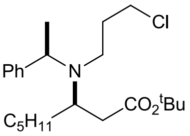
Following *general procedure 4*, **182** (10.7 mL, 45.7 mmol), MeMgBr (2.5 M, 17.5 mL, 43.7 mmol) and **454** (5 mL, 41.6 mmol) were reacted in THF (300 mL) to give **461** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 °C petrol) gave **461** as a colourless oil (4.18 g, 51%, >99:1 dr);[66] δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.8, C(8)H_3), 1.25-1.60 (6H, m, C(5)H_2, C(6)H_2, C(7)H_2) overlapping 1.49 (9H, s, CMe_3), 2.17 (2H, app q, *J* 7.0, C(4)H_2), 5.74 (1H, dt, *J* 15.7, 1.6, C(2)*H*), 6.87 (1H, dt, *J* 15.7, 7.0, C(3)*H*).

tert-Butyl (*E*)-dec-2-enoate 462



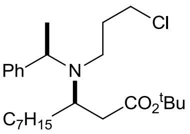
Following *general procedure 4*, **182** (10.7 mL, 45.7 mmol), MeMgBr (2.5 M, 17.5 mL, 43.7 mmol) and **455** (6.5 mL, 41.6 mmol) were reacted in THF (300 mL) to give **462** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 °C petrol) gave **462** as a colourless oil (3.57 g, 38%, >99:1 dr);[67] δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.8, C(10)H_3), 1.22-1.48 (10H, m, C(5)H_2, C(6)H_2, C(7)H_2, C(8)H_2, C(9)H_2), 1.49 (9H, s, C*Me*$_3$), 2.17 (2H, app q, *J* 7.2, C(4)H_2), 5.74 (1H, dt, *J* 15.6, 1.5, C(2)*H*), 6.87 (1H, dt, *J* 15.6, 6.8, C(3)*H*).

***tert*-Butyl (*R*,*R*)-3-[*N*-(3′-chloropropyl)-*N*-(α-methylbenzyl)amino]octanoate 463**



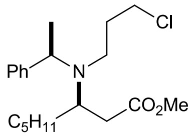
Following *general procedure 5*, (*R*)-**413** (6.67 g, 33.7 mmol, >99:1 er), BuLi (2.5 M, 13.1 mL, 32.7 mmol) and **461** (4.18 g, 21.1 mmol) were reacted in THF (300 mL) to give **463** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 19:1) gave **463** as a yellow oil (6.75 g, 81%, >99:1 dr); $[\alpha]_D^{24}$ −13.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.3, C(8)H_3), 1.17-1.35 (7H, m, C(4)H_A, C(5)H_2, C(6)H_2, C(7)H_2), 1.40-1.48 (13H, m, C*Me*$_3$, C(4)H_B, C(α)*Me*), 1.85 (2H, app quin, *J* 6.6, C(2′)H_2), 2.00 (1H, ABdd, *J* 14.7, 7.8, C(2)H_A), 2.06 (1H, ABdd, *J* 14.7, 5.3, C(2)H_B), 2.55-2.68 (2H, m, C(1′)H_2), 3.17-3.24 (1H, m, C(3)*H*), 3.50 (2H, td, *J* 6.3, 1.0, C(3′)H_2), 3.87 (1H, q, *J* 6.8, C(α)*H*), 7.19-7.25 (1H, m, *Ph*), 7.26-7.34 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(8)), 20.6 (C(α)*Me*), 22.7, 26.6, 31.9, 32.6 (*C*(4), *C*(5), *C*(6), *C*(7)), 28.0 (C*Me*$_3$), 33.1 (*C*(2′)), 38.1 (*C*(2)), 42.9 (*C*(1′)), 43.3 (*C*(3′)), 55.3 (*C*(3)), 58.7 (*C*(α)), 79.9 (*C*Me$_3$), 126.8, 127.7, 128.1 (*o*,*m*,*p-Ph*), 144.5 (*i-Ph*), 172.3 (*C*(1)); *m/z* (ESI$^+$) 420 ([M(^{37}Cl)+Na]$^+$, 67%), 418 ([M(^{35}Cl)+Na]$^+$, 100%), 398 ([M(^{37}Cl)+H]$^+$, 77%), 396 ([M(^{35}Cl)+H]$^+$, 72%); HRMS (ESI$^+$) $C_{23}H_{39}{}^{37}ClNO_2^+$ ([M(^{37}Cl)+H]$^+$) requires 398.2634; found 398.2626; HRMS (ESI$^+$) $C_{23}H_{39}{}^{35}ClNO_2^+$ ([M(^{35}Cl)+H]$^+$) requires 396.2664; found 396.2664.

***tert*-Butyl (*R*,*R*)-3-[*N*-(3′-chloropropyl)-*N*-(α-methylbenzyl)amino]decanoate 464**



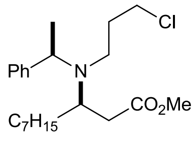
Following *general procedure 5*, (*R*)-**413** (4.99 g, 25.2 mmol, >99:1 er), BuLi (2.5 M, 9.72 mL, 24.3 mmol) and **462** (3.57 g, 15.7 mmol) were reacted in THF (230 mL) to give **464** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 19:1) gave **464** as a yellow oil (4.85 g, 73%, >99:1 dr); $[\alpha]_D^{24}$ −13.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1727 (C=O); δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 6.6, C(10)H_3), 1.20-1.35 (12H, m, C(4)H_2, C(5)H_2, C(6)H_2, C(7)H_2, C(8)H_2, C(9)H_2), 1.40-1.44 (12H, m, C*Me*$_3$, C(α)*Me*), 1.85 (2H, app quin, *J* 6.6, C(2′)H_2), 2.00 (1H, ABdd, *J* 14.6, 8.1, C(2)H_A), 2.06 (1H, ABdd, *J* 14.6, 5.3, C(2)H_B), 2.55-2.68 (2H, m, C(1′)H_2), 3.17-3.24 (1H, m, C(3)*H*), 3.49 (2H, app td, *J* 8.6, 1.2, C(3′)H_2), 3.87 (1H, q, *J* 7.1, C(α)*H*), 7.20-7.24 (1H, m, *Ph*), 7.26-7.34 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(10)), 20.6 (C(α)*Me*), 22.7, 27.0, 29.3, 29.6, 31.9, 32.6 (*C*(4), *C*(5), *C*(6), *C*(7), *C*(8), *C*(9)), 28.0 (CMe_3), 33.1 (*C*(2′)), 38.1 (*C*(2)), 42.9 (*C*(1′)), 43.3 (*C*(3′)), 55.3 (*C*(3)), 58.7 (*C*(α)), 79.9 (*C*Me_3), 126.8, 127.7, 128.1 (*o,m,p-Ph*), 144.5 (*i-Ph*), 172.2 (*C*(1)); *m/z* (ESI$^+$) 448 ([M(^{37}Cl)+Na]$^+$, 12%), 446 ([M(^{35}Cl)+Na]$^+$, 34%), 426 ([M(^{37}Cl)+H]$^+$, 91%), 424 ([M(^{35}Cl)+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{42}{}^{37}ClNO_2{}^+$ ([M(^{37}Cl)+H]$^+$) requires 426.2947; found 426.2951; $C_{25}H_{43}{}^{35}ClNO_2{}^+$ ([M(^{35}Cl)+H]$^+$) requires 424.2977; found 424.2969.

Methyl (*R*,*R*)-3-[*N*-(3′-chloropropyl)-*N*-(α-methylbenzyl)amino]octanoate 458



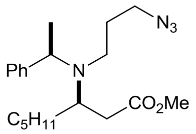
Following *general procedure 11*, **463** (1.00 g, 2.53 mmol, >99:1 dr) in MeOH (7.5 mL) and $SOCl_2$ (0.25 mL, 3.45 mmol) in MeOH (7.5 mL) were reacted. Purification via flash column chromatography (gradient elution, 0% → 6% Et_2O in 30-40 °C petrol) gave **458** as a yellow oil (717 mg, 80%, >99:1 dr); $[\alpha]_D^{24}$ −12.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1737 (C=O); δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.3, C(8)H_3), 1.20-1.53 (8H, m, C(4)H_2, C(5)H_2, C(6)H_2, C(7)H_2) overlapping 1.41 (3H, d, *J* 6.8, C(α)*Me*), 1.86 (2H, app quin, *J* 6.6, C(2′)H_2), 2.10-2.19 (2H, m, C(2)H_2), 2.59-2.72 (2H, m, C(1′)H_2), 3.23 (1H, app quin, *J* 6.6, C(3)*H*), 3.51 (2H, t, *J* 6.1, C(3′)H_2), 3.57 (3H, s, O*Me*), 3.90 (1H, q, *J* 6.8, C(α)*H*), 7.20-7.26 (1H, m, *Ph*), 7.27-7.32 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(8)), 20.0 (C(α)*Me*), 22.7, 26.8, 31.9, 32.8 (*C*(4), *C*(5), *C*(6), *C*(7)), 32.9 (*C*(2′)), 37.0 (*C*(2)), 42.8 (*C*(1′)), 43.3 (*C*(3′)), 51.3 (O*Me*), 55.4 (*C*(3)), 58.3 (*C*(α)), 126.8, 127.7, 128.1 (*o,m,p-Ph*), 144.4 (*i-Ph*), 173.3 (*C*(1)); *m/z* (ESI$^+$) 378 ([M(^{37}Cl)+Na]$^+$, 22%), 376 ([M(^{35}Cl)+Na]$^+$, 64%), 356 ([M(^{37}Cl)+H]$^+$, 59%), 354 ([M(^{35}Cl)+H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{33}{}^{37}ClNO_2{}^+$ ([M(^{37}Cl)+H]$^+$) requires 356.2165; found 356.2173; $C_{20}H_{33}{}^{35}ClNO_2{}^+$ ([M(^{35}Cl)+H]$^+$) requires 354.2194; found 354.2196.

Methyl (*R*,*R*)-3-[*N*-(3′-chloropropyl)-*N*-(α-methylbenzyl)amino]decanoate 459



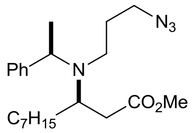
Following *general procedure 11*, **464** (1.00 g, 2.36 mmol, >99:1 dr) in MeOH (7.5 mL) and $SOCl_2$ (0.25 mL, 3.45 mmol) in MeOH (7.5 mL) were reacted. Purification via flash column chromatography (gradient elution, 0% → 6% Et_2O in 30-40 °C petrol) gave **459** as a yellow oil (550 mg, 61%, >99:1 dr); $[\alpha]_D^{24}$ −15.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1737 (C=O); δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 6.8, C(10)H_3), 1.21-1.63 (12H, m, C(4)H_2, C(5)H_2, C(6)H_2, C(7)*H*$_2$, C(8)*H*$_2$, C(9)*H*$_2$), 1.41 (3H, d, *J* 7.0, C(α)*Me*), 1.86 (2H, app quin, *J* 6.6, C(2′)*H*$_2$), 2.09-2.19 (2H, m, C(2)*H*$_2$), 2.58-2.72 (2H, m, C(1′)*H*$_2$), 3.23 (1H, app quin, *J* 6.8, C(3)*H*), 3.51 (2H, t, *J* 6.3, C(3′)*H*$_2$), 3.57 (3H, s, O*Me*), 3.89 (1H, q, *J* 7.0, C(α)*H*), 7.20-7.25 (1H, m, *Ph*), 7.29-7.30 (4H, m, *Ph*); δ_C (100 MHz, CDCl$_3$) 14.1 (*C*(10)), 20.0 (C(α)*Me*), 22.7, 29.2, 29.3, 29.6, 31.9, 32.8 (*C*(4), *C*(5), *C*(6), *C*(7), *C*(8), *C*(9)), 32.9 (*C*(2′)), 37.0 (*C*(2)), 42.8 (*C*(1′)), 43.3 (*C*(3′)), 51.3 (O*Me*), 55.4 (*C*(3)), 58.3 (*C*(α)), 126.8, 127.7, 128.1 (*o,m,p-Ph*), 144.4 (*i-Ph*), 173.3 (*C*(1)); *m/z* (ESI$^+$) 406 ([M(^{37}Cl)+Na]$^+$, 14%), 404 ([M(^{35}Cl)+Na]$^+$, 37%), 384 ([M(^{37}Cl)+H]$^+$, 61%), 382 ([M(^{35}Cl)+H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{37}{}^{37}ClNO_2^+$ ([M(^{37}Cl)+H]$^+$) requires 384.2478; found 384.2494; $C_{22}H_{37}{}^{35}ClNO_2^+$ ([M(^{35}Cl)+H]$^+$) requires 382.2507; found 382.2506.

Methyl (*R*,*R*)-3-[*N*-(3′-azidopropyl)-*N*-(α-methylbenzyl)amino]octanoate 465



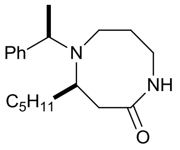
Following *general procedure 12*, NaN$_3$ (367 mg, 5.65 mmol, >99:1 dr), NaI (847 mg, 5.65 mmol) and **458** (1.00 g, 2.83 mmol) were reacted in DMSO (6 mL). Purification via flash column chromatography (eluent 30-40 °C petrol/Et$_2$O, 30:1) gave **465** as a yellow oil (959 mg, 94%, >99:1 dr); $[\alpha]_D^{25}$ −22.3 (*c* 1.0 in CHCl$_3$); ν_{max} (film) 2096 (N≡N), 1737 (C=O); δ_H (400 MHz, CDCl$_3$) 0.90 (3H, t, *J* 7.3, C(8)*H*$_3$), 1.20-1.55 (8H, m, C(4)*H*$_2$, C(5)*H*$_2$, C(6)*H*$_2$, C(7)*H*$_2$) overlapping 1.40 (3H, d, *J* 6.8, C(α)*Me*), 1.60-1.72 (2H, m, C(2′)*H*$_2$), 2.11-2.21 (2H, m, C(2)*H*$_2$), 2.52-2.63 (2H, m, C(1′)*H*$_2$), 3.20-3.27 (3H, m, C(3)*H*, C(3′)*H*$_2$), 3.58 (3H, s, O*Me*), 3.89 (3H, q, *J* 6.8, C(α)*H*), 7.20-7.26 (1H, m, *Ph*), 7.28-7.30 (4H, m, *Ph*); δ_C (100 MHz, CDCl$_3$) 14.1 (*C*(8)), 19.9 (C(α)*Me*), 22.7, 26.8, 31.9, 32.7 (*C*(4), *C*(5), *C*(6), *C*(7)), 29.2 (*C*(2′)), 37.0 (*C*(2)), 42.8 (*C*(1′)), 49.4 (*C*(3′)), 51.3 (O*Me*), 55.4 (*C*(3)), 58.3 (*C*(α)), 126.8, 127.7, 128.1 (*o,m,p-Ph*), 144.6 (*i-Ph*), 173.3 (*C*(1)); *m/z* (ESI$^+$) 383 ([M+Na]$^+$, 28%), 361 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{33}N_4O_2^+$ ([M+H]$^+$) requires 361.2598; found 361.2597.

Methyl (*R*,*R*)-3-[(3′-azidopropyl)(α-methylbenzyl)amino]decanoate 466



Following *general procedure 12*, NaN$_3$ (367 mg, 5.65 mmol), NaI (847 mg, 5.65 mmol) and **459** (1.08 g, 2.83 mmol, >99:1 dr) were reacted in DMSO (6 mL). Purification via flash column chromatography (eluent 30-40 °C petrol/Et$_2$O, 30:1) gave **466** as a yellow oil (958 mg, 87%, >99:1 dr); $C_{22}H_{36}N_4O_2$ requires C, 68.0; H, 9.3; N, 14.4%; found C, 68.1; H, 9.1; N, 14.3%; $[\alpha]_D^{24}$ −20.9 (*c* 1.0 in CHCl$_3$); ν_{max} (film) 2096 (N≡N), 1737 (C=O); δ_H (400 MHz, CDCl$_3$) 0.90 (3H, t, *J* 7.1, C(10)H_3), 1.22-1.53 (12H, m, C(4)H_2, C(5)H_2, C(6)H_2, C(7)H_2, C(8)H_2, C(9)H_2) overlapping 1.40 (3H, d, *J* 6.8, C(α)*Me*), 1.61-1.69 (2H, m, C(2′)H_2), 2.11-2.21 (2H, m, C(2)H_2), 2.53-2.61 (2H, m, C(1′)H_2), 3.20-3.26 (3H, m, C(3)*H*, C(3′)H_2), 3.58 (3H, s, O*Me*), 3.89 (1H, q, *J* 6.8, C(α)*H*), 7.20-7.26 (1H, m, *Ph*), 7.28-7.31 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(10)), 19.8 (C(α)*Me*), 22.7, 27.1, 29.3, 29.7, 31.9, 32.7 (*C*(4), *C*(5), *C*(6), *C*(7), *C*(8), *C*(9)), 29.2 (*C*(2′)), 37.1 (*C*(2)), 42.8 (*C*(1′)), 49.4 (*C*(3′)), 51.3 (O*Me*), 55.4 (*C*(3)), 58.3 (*C*(α)), 126.8, 127.7, 128.1 (*o,m,p-Ph*), 144.6 (*i-Ph*), 173.3 (*C*(1)); *m/z* (ESI^+) 411 ($[M+Na]^+$, 15%), 389 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{22}H_{37}N_4O_2^+$ ($[M+H]^+$) requires 389.2911; found 389.2914.

(*R*,*R*)-4-Pentyl-*N*(5)-(α-methylbenzyl)-1,5-diazocan-2-one 468



Step 1: Following *general procedure 13*, **465** (100 mg, 277 µmol, >99:1 dr) and PBu_3 (74 µL, 297 µmol) were reacted in THF (1 mL) and H_2O (0.3 mL) to give **467** as a yellow oil (158 mg, >99:1 dr); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.2, C(8)H_3), 1.18-1.54 (8H, m, C(4)H_2, C(5)H_2, C(6)H_2, C(7)H_2) overlapping 1.40 (3H, d, *J* 6.9, C(α)*Me*), 1.60 (2H, app quin, *J* 6.8, C(2′)H_2), 2.15 (2H, app dd, *J* 6.3, 2.1, C(2)H_2), 2.54 (2H, app q, *J* 7.7, C(3′)H_2), 2.66 (2H, app td, *J* 7.0, 3.8, C(1′)H_2), 3.22 (1H, app quin, *J* 6.7, C(3)*H*), 3.56 (3H, s, O*Me*), 3.93 (1H, q, *J* 6.9, C(α)*H*), 7.19-7.25 (1H, m, *Ph*), 7.28-7.33 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.0 (*C*(8)), 19.7 (C(α)*Me*), 22.6, 26.7, 31.9, 32.8, 33.5 (*C*(4), *C*(5), *C*(6), *C*(7), *C*(2′)), 37.0 (*C*(2)), 40.0 (*C*(1′)), 42.9 (*C*(3′)), 51.3 (*C*(3)), 55.2 (O*Me*), 57.9 (*C*(α)), 126.6, 127.7, 128.0 (*o,m,p-Ph*), 144.6 (*i-Ph*), 173.4 (*C*(1)); *m/z* (ESI^+) 335 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{35}N_2O_2^+$ ($[M+H]^+$) requires 335.2693; found 335.2692.

Step 2: Following *general procedure 14*, **467** (158 mg, >99:1 dr) and $Sb(OEt)_3$ (57 µL, 333 µmol) were reacted in PhMe (20 mL). Purification via flash column chromatography (gradient elution, 10% → 100% EtOAc in 30-40 °C petrol) gave **468** as a colourless oil (82 mg, 98% over 2 steps, >99:1 dr); $C_{19}H_{30}N_2O$ requires C, 75.45; H, 10.0; N, 9.3%; found C, 75.55; H, 10.0; N, 9.25%; $[\alpha]_D^{24}$ +3.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1661 (C=O); δ_H (400 MHz, $CDCl_3$) 0.86 (3H, t, *J* 6.8, C(5′)H_3), 0.97-1.06 (1H, m, C(7)H_A), 1.12-1.54 (9H, m, C(7)H_B, C(1′)H_2, C(2′)H_2, C(3′)H_2, C(4′)H_2) overlapping 1.27 (3H, d, *J* 6.4, C(α)*Me*), 2.43 (2H, d, *J* 7.1, C(3)H_2), 2.46-2.55 (1H, m, C(6)H_A), 2.81 (1H, br t, *J* 12.9, C(6)H_B), 3.20 (2H, br s, C(8)H_2), 3.44 (1H, br s, C(4)*H*), 3.74 (1H, q, *J* 6.4, C(α)*H*), 6.83 (1H, br s, N*H*), 7.12-7.16 (1H, m, *Ph*), 7.22 (2H, app t, *J* 7.8, *Ph*), 7.29-7.33 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.0 (*C*(5′)), *21.9* (C(α)*Me*), 22.6, 26.5, 28.2 (*C*(2′), *C*(3′), *C*(4′)), 32.1 (*C*(7)), 32.4 (*C*(1′)), *37.9* (*C*(3)), *42.6* (*C*(8)), *45.9* (*C*(6)), 56.5 (*C*(4)), 62.6 (*C*(α)), 126.8, 128.0

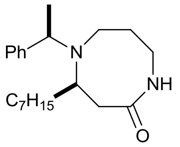
(*o,m,p-Ph*), 146.5 (*i-Ph*), 177.1 (*C*(2)); *m/z* (ESI$^+$) 930 ([3M+Na]$^+$, 36%), 627 ([2M+Na]$^+$, 100%), 325 ([M+Na]$^+$, 23%), 303 ([M+H]$^+$, 34%); HRMS (ESI$^+$) $C_{19}H_{31}N_2O^+$ ([M+H]$^+$) requires 303.2431; found 303.2435.

X-ray crystal structure determination for **468**·HCl. Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-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.[45]

X-ray crystal structure data for **468**·HCl [$C_{19}H_{31}ClN_2O$]: M = 338.92, triclinic, space group $P\ 1$, a = 7.2921(4) Å, b = 7.3234(4) Å, c = 9.7967(6) Å, α = 102.695(3)°, β = 94.987(3)°, γ = 109.832(2)°, V = 472.62(5) Å^3, Z = 1, μ = 0.209 mm^{-1}, colourless block, crystal dimensions = 0.10 × 0.16 × 0.18 mm^3. A total of 3477 unique reflections were measured for $5 < \theta < 27$ and 3477 reflections were used in the refinement. The final parameters were wR_2 = 0.074 and R_1 = 0.032 [$I > -3.0\sigma(I)$], with Flack enantiopole = 0.03(4).[68]

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 880490. Copies of these data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif., or on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

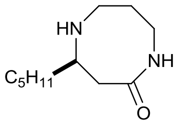
(*R*,*R*)-4-Heptyl-*N*(5)-(α-methylbenzyl)-1,5-diazocan-2-one 470



Step 1: Following *general procedure 13,* **466** (7.66 g, 19.7 mmol, >99:1 dr) and PBu_3 (5.42 mL, 21.7 mmol) were reacted in THF (75 mL) and H_2O (22 mL) to give **469** as a yellow oil (11.2 g, >99:1 dr); δ_H (400 MHz, $CDCl_3$) 0.85 (3H, t, *J* 7.1, C(10)*H*$_2$), 1.18-1.68 (14H, m, C(4)*H*$_2$, C(5)*H*$_2$, C(6)*H*$_2$, C(7)*H*$_2$, C(8)*H*$_2$, C(9)*H*$_2$, C(2′)*H*$_2$) overlapping 1.39 (3H, d, *J* 7.2, C(α)*Me*), 2.11 (2H, app t, *J* 6.8, C(2)*H*$_2$), 2.49 (2H, app q, *J* 7.3, C(3′)*H*$_2$), 2.61 (2H, td, *J* 7.1, 1.5, C(1′)*H*$_2$), 3.18 (1H, app quin, *J* 6.6, C(3)*H*), 3.52 (3H, s, O*Me*), 3.88 (1H, q, *J* 7.2, C(α)*H*), 7.14-7.30 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(10)), 19.6 (C(α)*Me*), 22.6, 25.8, 29.2, 29.6, 31.8, 32.8, 33.4 (*C*(4), *C*(5), *C*(6), *C*(7), *C*(8), *C*(9), *C*(2′)), 37.0 (*C*(2)), 40.0 (*C*(1′)), 42.9 (*C*(3′)), 51.3 (*C*(3)), 55.2 (O*Me*), 57.9 (*C*(α)), 126.7, 127.7, 128.0 (*o,m,p-Ph*), 144.6 (*i-Ph*), 173.4 (*C*(1)); *m/z* (ESI$^+$) 363 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{39}N_2O_2^+$ ([M+H]$^+$) requires 363.3006; found 363.3006.

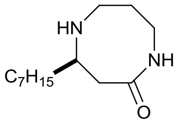
Step 2: Following *general procedure 14*, **469** (11.2 g, >99:1 dr) and $Sb(OEt)_3$ (4.02 mL, 23.7 mmol) were reacted in PhMe (2.00 L). Purification via flash column chromatography (gradient elution, 60% → 100% EtOAc in 30-40 °C petrol) gave **470** as a white solid (3.38 g, 52% over 2 steps, >99:1 dr); mp 47-49 °C; $[\alpha]_D^{24}$ +3.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1658 (C=O); δ_H (400 MHz, $CDCl_3$) 0.87 (3H, t, *J* 7.1, C(7′)H_3), 0.99-1.07 (1H, m, C(7)H_A), 1.12-1.54 (13H, m, C(7)H_B, C(1′)H_2, C(2′)H_2, C(3′)H_2, C(4′)H_2, C(5′)H_2, C(6′)H_2) overlapping 1.29 (3H, d, *J* 6.6, C(α)*Me*), 2.45 (2H, d, *J* 7.3, C(3)H_2), 2.52 (1H, dt, *J* 15.4, 3.0, C(6)H_A), 2.79-2.82 (1H, m, C(6)H_B), 3.22 (2H, br s, C(8)H_2), 3.45 (1H, br s, C(4)*H*), 3.75 (1H, q, *J* 6.6, C(α)*H*), 6.60 (1H, t, *J* 7.1, N*H*), 7.15-7.18 (1H, m, *Ph*), 7.22-7.26 (2H, m, *Ph*), 7.32-7.34 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(7′)), 21.9 (C(α)*Me*), 22.6, 26.9, 28.3, 29.3, 30.0, 31.8, 32.4 (*C*(7), *C*(1′), *C*(2′), *C*(3′), *C*(4′), *C*(5′), *C*(6′)), 37.9 (*C*(3)), *42.6* (*C*(8)), *45.9* (*C*(6)), 56.5 (*C*(4)), 62.7 (*C*(α)), 126.8, 128.0, 128.1 (*o,m,p-Ph*), 146.5 (*i-Ph*), 177.0 (*C*(2)); *m/z* (ESI^+) 683 ($[2M+Na]^+$, 100%), 353 ($[M+Na]^+$, 25%), 331 ($[M+H]^+$, 49%); HRMS (ESI^+) $C_{21}H_{35}N_2O^+$ ($[M+H]^+$) requires 331.2744; found 331.2742.

(*R*)-4-Pentyl-1,5-diazocan-2-one 380



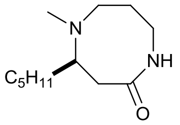
Following *general procedure 17*, **468** (200 mg, 661 μmol, >99:1 dr) and $Pd(OH)_2/C$ (100 mg) were reacted in MeOH (3 mL) for 24 h to give **380** as a colourless oil (125 mg, 95%);[69] $[\alpha]_D^{24}$ +39.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1655 (C=O); δ_H (400 MHz, $CDCl_3$) 0.75 (3H, t, *J* 6.9, C(5′)H_3), 1.11-1.27 (6H, m, C(2′)H_2, C(3′)H_2, C(4′)H_2), 1.34-1.40 (2H, m, C(1′)H_2), 1.47-1.59 (2H, m, C(7)H_2), 2.25 (1H, app d, *J* 12.3, C(3)H_A), 2.32-2.43 (2H, m, C(3)H_B, C(6)H_A), 2.79-2.85 (1H, m, C(4)*H*), 3.01 (1H, dt, *J* 14.8, 4.1, C(6)H_B), 3.10-3.17 (1H, m, C(8)H_A), 3.40-3.53 (2H, m, C(8)H_B, N(5)*H*), 7.06 (1H, br s, N(1)*H*); δ_C (100 MHz, $CDCl_3$) 13.9 (*C*(5′)), 22.4, 25.9, 31.6 (*C*(2′), *C*(3′), *C*(4′)), 33.3 (*C*(7)), 36.2 (*C*(1′)), 39.9 (*C*(8)), 40.4 (*C*(3)), 43.3 (*C*(6)), 58.8 (*C*(4)), 176.7 (*C*(2)); *m/z* (ESI^+) 221 ($[M+Na]^+$, 15%), 199 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{11}H_{23}N_2O^+$ ($[M+H]^+$) requires 199.1805; found 199.1797.

(*R*)-4-Heptyl-1,5-diazocan-2-one 381



Following *general procedure 17*, **470** (100 mg, 303 μmol, >99:1 dr) and $Pd(OH)_2/C$ (50 mg) were reacted in MeOH (3.0 mL) for 24 h to give **381** as a colourless oil (69 mg, quant);[69] $[\alpha]_D^{24}$ +34.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3234 (N−H), 1656 (C=O); δ_H (400 MHz, $CDCl_3$) 0.83 (3H, t, *J* 6.7, C(7′)H_3), 1.16-1.35 (10H, m, C(2′)H_2, C(3′)H_2, C(4′)H_2, C(5′)H_2, C(6′)H_2), 1.39-1.47 (2H, m, C(1′)H_2), 1.49-1.67 (2H, m, C(7)H_2), 2.29-2.57 (4H, m, C(3)H_2, N(5)*H*, C(6)H_A), 2.83-2.92 (1H, m, C(4)*H*), 3.08 (1H, dt, *J* 14.9, 4.0, C(6)H_B), 3.15-3.25 (1H, m, C(8)H_A), 3.50-3.61 (1H, m, C(8)H_B), 6.64 (1H, br s, N(1)*H*); δ_C (100 MHz, $CDCl_3$) 14.0 (*C*(7′)), 22.6, 26.3, 29.1, 29.5, 31.7 (*C*(2′), *C*(3′), *C*(4′), *C*(5′), *C*(6′)), 33.8 (*C*(7)), 36.8 (*C*(1′)), 39.9 (*C*(8)), 41.1 (*C*(3)), 43.5 (*C*(6)), 59.0 (*C*(4)), 176.9 (*C*(2)); *m/z* (ESI$^+$) 702 ([3M+Na]$^+$, 84%), 475 ([2M+Na]$^+$, 100%), 453 ([2M+H]$^+$, 96%), 227 ([M+H]$^+$, 65%); HRMS (ESI$^+$) $C_{13}H_{27}N_2O^+$ ([M+H]$^+$) requires 227.2118; found 227.2123.

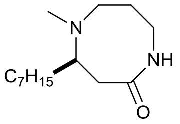
(*R*)-4-Pentyl-*N*(5)-methyl-1,5-diazocan-2-one 382



Method A: Following *general procedure 17*, **468** (100 mg, 331 µmol, >99:1 dr), $(CH_2O)_n$ (20 mg, 666 µmol) and $Pd(OH)_2/C$ (50 mg) were reacted in MeOH (1.3 mL) for 72 h to give **382** as a colourless oil (71 mg, quant);[69] $[\alpha]^{24}_{D}$ −0.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1660 (C=O); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.8, C(5′)H_3), 1.26-1.41 (7H, m, C(1′)H_A, C(2′)H_2, C(3′)H_2, C(4′)H_2), 1.47-1.60 (2H, m, C(7)H_A, C(1′)H_B), 1.68-1.80 (1H, m, C(7)H_B), 2.43 (2H, d, *J* 7.2, C(3)H_2), 2.46 (3H, s, N*Me*), 2.54 (1H, app dt, *J* 15.4, 4.3, C(6)H_A), 2.90-3.04 (2H, m, C(4)*H*, C(6)H_B), 3.29-3.33 (2H, m, C(8)H_2), 5.60 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 14.0 (*C*(5′)), 22.6, 26.6, 31.9 (C(2′), C(3′), C(4′)), 30.3 (*C*(1′)), 31.4 (*C*(7)), 37.5 (*C*(3)), 40.6 (N*Me*), 42.2 (*C*(8)), 47.3 (*C*(6)), 62.9 (*C*(4)), 177.2 (*C*(2)); *m/z* (ESI$^+$) 447 ([2M+Na]$^+$, 100%), 425 ([2M+H]$^+$, 12%), 235 ([M+Na]$^+$, 14%), 213 ([M+H]$^+$, 26%); HRMS (ESI$^+$) $C_{12}H_{25}N_2O^+$ ([M+H]$^+$) requires 213.1961; found 213.1963.

Method B: Following *general procedure 18*, **380** (965 mg, 4.87 mmol), $(CH_2O)_n$ (231 mg, 7.69 mmol) and $NaBH_3CN$ (970 mg, 29.5 mmol) were reacted in MeOH (40 mL). Purification via flash column chromatography (gradient elution, 0% → 5% MeOH in CH_2Cl_2) gave **382** as a colourless oil (373 mg, 36%); $[\alpha]^{24}_{D}$ −0.5 (*c* 1.0 in $CHCl_3$).

(*R*)-4-Heptyl-5-methyl-1,5-diazocan-2-one 383

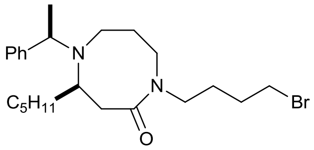


Following *general procedure 17*, **470** (109 mg, 331 µmol, >99:1 dr), $(CH_2O)_n$ (20 mg, 666 µmol) and $Pd(OH)_2/C$ (50 mg) were reacted in MeOH (1.3 mL) for 72 h to give **383** as a colourless oil (78 mg, 98%);[69] $[\alpha]^{24}_{D}$ −0.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1659 (C=O); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.3, C(7′)H_3), 1.22-1.41 (11H, m, C(1′)H_A, C(2′)H_2, C(3′)H_2, C(4′)H_2, C(5′)H_2, C(6′)H_2), 1.47-1.67

(2H, m, C(1′)*H*$_B$, C(7)*H*$_A$), 1.68-1.79 (1H, m, C(7)*H*$_B$), 2.42 (2H, d, *J* 7.0, C(3)*H*$_2$), 2.46 (3H, s, N*Me*), 2.54 (1H, dt, *J* 15.2, 4.1, C(6)*H*$_A$), 2.90-3.04 (2H, m, C(4)*H*, C(6)*H*$_B$), 3.28-3.34 (2H, m, C(8)*H*$_2$), 5.64 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(7′)), 22.6, 26.9, 29.2, 29.7, 31.8 (*C*(2′), *C*(3′), *C*(4′), *C*(5′), *C*(6′)), 30.3 (*C*(1′), 31.4 (*C*(7)), 37.5 (*C*(3)), 40.7 (N*Me*), 42.3 (*C*(8)), 47.4 (*C*(6)), 62.9 (*C*(4)), 177.1 (*C*(2)); *m/z* (ESI^+) 744 ($[3M+Na]^+$, 74%) 503 ($[2M+Na]^+$, 100%), 481 ($[2M+H]^+$, 36%), 263 ($[M+Na]^+$, 92%), 241 ($[M+H]^+$, 87%); HRMS (ESI^+) $C_{14}H_{29}N_2O^+$ ($[M+H]^+$) requires 241.2274; found 241.2277.

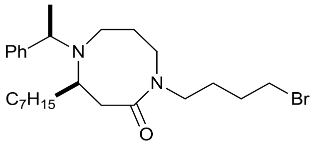
Method B: Following *general procedure 18*, **381** (989 mg, 4.37 mmol), $(CH_2O)_n$ (231 mg, 7.69 mmol) and $NaBH_3CN$ (970 mg, 29.5 mmol) were reacted in MeOH (40 mL). Purification via flash column chromatography (gradient elution, 0% → 5% MeOH in CH_2Cl_2) gave **383** as a colourless oil (875 mg, 83%); $[\alpha]_D^{24}$ −0.4 (*c* 1.0 in $CHCl_3$).

(*R*,*R*)-*N*(1)-(4′-Bromobutyl)-4-pentyl-*N*(5)-(α-methylbenzyl)-1,5-diazocan-2-one 471



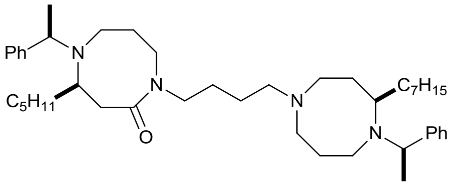
Following *general procedure 15*, **468** (150 mg, 496 μmol, >99:1 dr), 1,4-dibromobutane **360** (0.18 mL, 1.48 mmol), KOH (111 mg, 1.97 mmol), K_2CO_3 (83 mg, 600 μmol) and TEBAC (14 mg, 61.8 μmol) were reacted in DMSO (1.0 mL) for 24 h. Purification via flash column chromatography (gradient elution, 20% → 50% Et_2O in 30-40 °C petrol) gave **471** as a yellow oil (143 mg, 66%, >99:1 dr); $[\alpha]_D^{24}$ −16.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1636 (C=O); δ_H (500 MHz, PhMe-d_8, 363 K) 0.81-0.91 (1H, m, C(7)*H*$_A$), 0.92 (3H, t, *J* 7.3, C(5″)*H*$_3$), 1.11-1.20 (1H, m, C(7)*H*$_B$), 1.24-1.61 (8H, m, C(1″)*H*$_2$, C(2″)*H*$_2$, C(3″)*H*$_2$, C(4″)*H*$_2$), 1.27 (3H, d, *J* 6.5, C(α)*Me*), 1.53 (2H, app quin, *J* 7.6, C(2′)*H*$_2$), 1.67 (2H, app quin, *J* 7.6, C(3′)*H*$_2$), 2.34 (1H, ABdd, *J* 12.3, 8.8, C(3)*H*$_A$), 2.41-2.52 (2H, m, C(3)*H*$_B$, C(6)*H*$_A$), 2.57-2.67 (1H, m, C(6)*H*$_B$), 2.97-3.15 (3H, m, C(8)*H*$_2$, C(1′)*H*$_A$), 3.15 (2H, t, *J* 6.9, C(4′)*H*$_2$), 3.32-3.48 (2H, m, C(4)*H*, C(1′)*H*$_B$), 3.71 (1H, q, *J* 6.5, C(α)*H*), 7.06-7.12 (1H, m, *Ph*), 7.18 (2H, app t, *J* 7.6, *Ph*), 7.23-7.29 (2H, m, *Ph*); δ_C (125 MHz, PhMe-d_8, 363 K) 13.9 (*C*(5″)), 21.3 (C(α)*Me*), 22.9, 26.9, 27.2, 29.3, 30.7, 32.5 (*C*(7), *C*(2′), *C*(3′), *C*(2″), *C*(3″), *C*(4″)), 30.5 (*C*(1″)) 33.0 (*C*(4′)), 39.3 (*C*(3)), 45.0 (*C*(1′), *C*(6)), 47.8 (*C*(8)), 57.5 (*C*(4)), 62.8 (*C*(α)), 127.1, 128.2 (*o,m,p-Ph*), 146.8 (*i-Ph*), 172.4 (*C*(2)); *m/z* (ESI^+) 461 ($[M(^{81}Br)+Na]^+$, 83%), 459 ($[M(^{79}Br)+Na]^+$, 82%), 439 ($[M(^{81}Br)+H]^+$, 100%), 437 ($[M(^{79}Br)+H]^+$, 93%); HRMS (ESI^+) $C_{23}H_{38}{}^{81}BrN_2O^+$ ($[M(^{81}Br)+H]^+$) requires 439.2142; found 439.2155; $C_{23}H_{38}{}^{79}BrN_2O^+$ ($[M(^{79}Br)+H]^+$) requires 437.2162; found 437.2174.

(*R*,*R*)-1-(4′-Bromobutyl)-4-heptyl-5-(α-methylbenzyl)-1,5-diazocan-2-one 472



Following *general procedure 15*, **470** (233 mg, 706 µmol, >99:1 dr), 1,4-dibromobutane **360** (0.25 mL, 2.12 mmol), KOH (158 mg, 2.81 mmol), K_2CO_3 (118 mg, 854 µmol) and TEBAC (20 mg, 88.0 µmol) were reacted in DMSO (2.0 mL) for 18 h. Purification via flash column chromatography (gradient elution, 25% → 60% Et_2O in 30-40 °C petrol) gave **472** as a yellow oil (101 mg, 31%, >99:1 dr); $[\alpha]_D^{24}$ −11.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1628 (C=O); δ_H (500 MHz, PhMe-d_8, 363 K) 0.83-0.90 (1H, m, C(7)H_A), 0.92 (3H, t, *J* 7.3, C(7″)H_3), 1.12-1.22 (1H, m, C(7)H_B), 1.23-1.48 (12H, m, C(1″)H_2, C(2″)H_2, C(3″)H_2, C(4″)H_2, *C*(5″)H_2, *C*(6″)H_2), 1.27 (3H, d, *J* 6.6, C(α)*Me*), 1.53 (2H, app quin, *J* 7.6, C(2′)H_2), 1.66 (2H, app quin, *J* 7.6, C(3′)H_2), 2.35 (1H, ABdd, *J* 12.3, 8.8, C(3)H_A), 2.43-2.52 (2H, m, C(3)H_B, C(6)H_A), 2.63 (1H, app dt, *J* 12.6, 2.5, C(6)H_B), 2.98-3.14 (2H, m, C(8)H_2, C(1′)H_A), 3.15 (2H, t, *J* 6.6, C(4′)H_2), 3.33-3.47 (2H, m, C(4)*H*, C(1′)H_B), 3.72 (1H, q, *J* 6.6, C(α)*H*), 7.07-7.12 (1H, m, *Ph*), 7.18 (2H, t, *J* 7.6, *Ph*), 7.24-7.29 (2H, m, *Ph*); δ_C (125 MHz, PhMe-d_8, 363 K) 14.0 (*C*(7″)), 21.3 (C(α)*Me*), 22.9, 27.2, 27.3, 29.4, 29.6, 30.3, 30.5, 30.7, 32.2 (*C*(7), *C*(2′), *C*(3′), *C*(1″), *C*(2″), *C*(3″), *C*(4″), *C*(5″), *C*(6″)), 33.0 (*C*(4′)), 39.3 (*C*(3)), 45.0 (*C*(1′), *C*(6)), 47.8 (*C*(8)), 57.5 (*C*(4)), 62.8 (*C*(α)), 127.1, 128.3 (*o*,*m*,*p*-*Ph*), 146.8 (*i*-*Ph*), 172.3 (*C*(2)); *m/z* (ESI$^+$) 489 ([M(^{81}Br)+Na]$^+$, 40%), 487 ([M(^{79}Br)+Na]$^+$, 47%), 467 ([M(^{81}Br)+H]$^+$, 100%), 465 ([M(^{79}Br)+H]$^+$, 95%); HRMS (ESI$^+$) $C_{25}H_{42}{}^{81}BrN_2O^+$ ([M(^{81}Br)+H]$^+$) requires 467.2455; found 467.2464; $C_{25}H_{42}{}^{79}BrN_2O^+$ ([M(^{79}Br)+H]$^+$) requires 465.2475; found 465.2483.

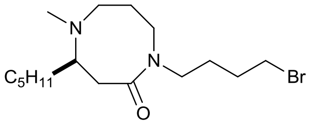
(*R*,*R*,*R*,*R*)-1-[2′-Oxo-4′-pentyl-*N*(5′)-(α-methylbenzyl)-1′,5′-diazocan-*N*(1′)-yl]-4-[2″-oxo-4″-heptyl-*N*(5″)-(α′-methylbenzyl)-1″,5″-diazocan-*N*(1″)-yl]butane 473



Following *general procedure 16*, **472** (91 mg, 275 µmol, >99:1 dr), **471** (109 mg, 249 µmol, >99:1 dr), KOH (62 mg, 1.10 mmol) were reacted in DMSO (1.0 mL) for 96 h. Purification via flash column chromatography (gradient elution, 0% → 2% MeOH in CH_2Cl_2) gave **473** as a yellow oil (50 mg, 29%, >99:1 dr); $[\alpha]_D^{24}$ −23.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1630 (C=O); δ_H (500 MHz, PhMe-d_8, 363 K) 0.89-0.98 (6H, br m, C(4′)$(CH_2)_4CH_3$, C(4″)$(CH_2)_6CH_3$), 1.20-1.53 (30H, br m, C(7′)H_2, C(7″)H_2, C(α)*Me*, C(α′)*Me*, C(4′)$(CH_2)_4CH_3$, C(4″)$(CH_2)_6CH_3$), 1.57-1.65

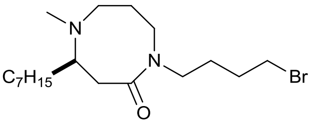
(4H, br m, C(2)H_2, C(3)H_2), 2.35-2.44 (2H, br m, C(3′)H_A, C(3″)H_A), 2.46-2.58 (4H, br m, C(3′)H_B, C(3″)H_B, C(6′)H_A, C(6″)H_A), 2.63-2.73 (2H, br m, C(6′)H_B, C(6″)H_B), 3.07-3.18 (2H, br m, C(8′)H_A, C(8″)H_A), 3.24 (4H, br s, C(8′)H_B, C(8″)H_B, C(1)H_A, C(4)H_A), 3.38 (2H, br s, C(4′)*H*, C(4″)*H*), 3.59 (2H, br s, C(1)H_B, C(4)H_B), 3.72-3.79 (2H, br m, C(α)*H*, C(α′)*H*), 7.08-7.14 (2H, br m, *Ph*), 7.18-7.24 (4H, br m, *Ph*), 7.27-7.33 (4H, br m, *Ph*); δ_C (125 MHz, PhMe-d_8, 363 K) 13.9, 14.0 (C(4′)(CH$_2$)$_4$*C*H$_3$, C(4″)(CH$_2$)$_6$*C*H$_3$), 21.3 (C(α)*Me*, C(α′)*Me*), 22.9, 22.9, 26.9, 27.3, 29.5, 29.5, 29.6, 30.3, 30.6, 30.6, 32.2, 32.5 (*C*(7′), *C*(7″), C(4′)(*C*H$_2$)$_4$CH$_3$, C(4″)(*C*H$_2$)$_6$CH$_3$), 26.2 (*C*(2), *C*(3)), 39.4 (*C*(3′), *C*(3″)), *45.0* (*C*(6′), *C*(6″)), 46.0 (*C*(1), *C*(4)), *47.9* (*C*(8′), *C*(8″)), 57.5, 57.5 (*C*(4′), *C*(4″)), 62.7 (*C*(α), *C*(α′)), 127.1, 128.3, 128.3 (*o,m,p-Ph*), 146.9 (*i-Ph*), 172.3 (*C*(2′), *C*(2″)); *m/z* (ESI$^+$) 710 ([M+Na]$^+$, 100%), 688 ([M+H]$^+$, 94%); HRMS (ESI$^+$) $C_{44}H_{71}N_4O_2^+$ ([M+H]$^+$) requires 687.5572; found 687.5591.

(*R*)-*N*(1)-(4′-Bromobutyl)-4-pentyl-*N*(5)-methyl-1,5-diazocan-2-one 451



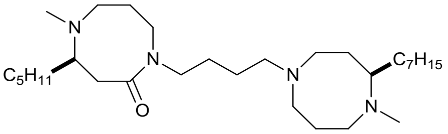
Following *general procedure 15*, **382** (423 mg, 1.99 mmol), 1,4-dibromobutane **360** (0.71 mL, 6.00 mmol), KOH (446 mg, 7.94 mmol), K_2CO_3 (333 mg, 2.41 mmol) and TEBAC (56 mg, 248 μmol) were reacted in DMSO (6 mL) for 24 h. Purification via flash column chromatography (eluent Et$_2$O) gave **451** as a colourless oil (456 mg, 66%); $[\alpha]_\mathrm{D}^{24}$ −8.1 (*c* 1.0 in CHCl$_3$); ν_max (ATR) 1634 (C=O); δ_H (400 MHz, CDCl$_3$) 0.89 (3H, t, *J* 7.0, C(5″)H_3), 1.23-1.92 (14H, m, C(7)H_2, C(2′)H_2, C(3′)H_2, C(1″)H_2, C(2″)H_2, C(3″)H_2, C(4″)H_2), 2.42 (3H, s, N*Me*), 2.46-2.56 (3H, m, C(3)H_2, C(6)H_A), 2.83-3.00 (2H, m, C(4)*H*, C(6)H_B), 3.26-3.51 (6H, m, C(8)H_2, C(1′)H_2, C(4′)H_2); δ_C (100 MHz, CDCl$_3$) 14.0 (*C*(5″)), 22.6, 26.5, 26.6, 28.8, 29.9, 31.9 (*C*(2′), *C*(3′), *C*(1″), *C*(2″), *C*(3″), *C*(4″)), *30.5* (*C*(7)) 33.7 (*C*(4′)), 38.4 (*C*(3)), *40.0* (N*Me*), 44.8 (*C*(8)), *47.1* (*C*(6)), *47.7* (*C*(1′)), 63.2 (*C*(4)), 173.8 (*C*(2)); *m/z* (ESI$^+$) 349 ([M(^{81}Br)+H]$^+$, 100%), 347 ([M(^{79}Br)+H]$^+$, 94%); HRMS (ESI$^+$) $C_{16}H_{32}{}^{81}BrN_2O^+$ ([M(^{81}Br)+H]$^+$) requires 349.1672; found 349.1678; $C_{16}H_{32}{}^{79}BrN_2O^+$ ([M(^{79}Br)+H]$^+$) requires 347.1693; found 347.1694.

(*R*)-1-(4′-Bromobutyl)-4-heptyl-5-methyl-1,5-diazocan-2-one 452



Following *general procedure 16*, **383** (165 mg, 687 μmol), 1,4-dibromobutane **360** (0.24 mL, 2.06 mmol), KOH (155 mg, 2.76 mmol) were reacted in DMSO (1.4 mL) for 24 h. Purification via flash column chromatography (gradient elution, 50% → 100% Et$_2$O in 30-40 °C petrol) gave **452** as a colourless oil (83 mg, 35%); $[\alpha]_D^{24}$ −10.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1631 (C=O); δ_H (400 MHz, $CDCl_3$) 0.86 (3H, t, *J* 6.8, C(7″)H_3), 1.20-1.90 (18H, m, C(7)H_2, C(2′)H_2, C(3′)H_2, C(1″)H_2, C(2″)H_2, C(3″)H_2, C(4″)H_2, C(5″)H_2, C(6″)H_2), 2.40 (3H, s, N*Me*), 2.44-2.54 (3H, m, C(3)H_2, C(6)H_A), 2.81-2.96 (2H, m, C(4)*H*, C(6)H_B), 3.24-3.47 (6H, m, C(8)H_2, C(1′)H_2, C(4′)H_2); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(7″)), 22.6, 26.5, 27.0, *28.7*, 29.3, 29.7, 29.9, 31.8 (*C*(2′), *C*(3′), *C*(1″), *C*(2″), *C*(3″), *C*(4″), *C*(5″), *C*(6″)), *30.3* (*C*(7)), 33.7 (*C*(4′)), *38.3* (*C*(3)), *40.1* (N*Me*), 44.8 (*C*(8)), *47.3* (*C*(6)), *47.6* (*C*(1′)), 63.3 (*C*(4)), 173.7 (*C*(2)); *m/z* (ESI^+) 399 ($[M(^{81}Br)+Na]^+$, 39%), 397 ($[M(^{79}Br)+Na]^+$, 44%), 377 ($[M(^{81}Br)+H]^+$, 100%), 375 ($[M(^{79}Br)+H]^+$, 89%); HRMS (ESI^+) $C_{18}H_{36}{}^{81}BrN_2O^+$ ($[M(^{81}Br)+H]^+$) requires 377.1985; found 377.1982, $C_{18}H_{36}{}^{79}BrN_2O^+$ ($[M(^{79}Br)+H]^+$) requires 375.2006; found 375.2002.

(*R*,*R*)-1-[2′-Oxo-4′-pentyl-*N*(5′)-methyl-1′,5′-diazocan-*N*(1′)-yl]-4-[2″-oxo-4″-heptyl-*N*(5″)-methyl-1″,5″-diazocan-*N*(1″)-yl]butane [(−)-hopromine] 100

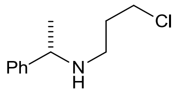


Method A: Following *general procedure 17*, **473** (17 mg, 25 μmol), $(CH_2O)_n$ (3 mg, 99.0 μmol) and $Pd(OH)_2/C$ (9 mg) were reacted in MeOH (1.0 mL) for 72 h. Purification via column chromatography (gradient elution, 0% → 2.5% MeOH in $CHCl_3$) gave (−)-(*R*,*R*)-hopromine **100** as a colourless oil (4 mg, 32%, >99:1 dr);[64] $[\alpha]_D^{24}$ −12.1 (*c* 0.1 in $CHCl_3$); {lit.[64] $[\alpha]_D^{20}$ −10 (*c* 3 in $CHCl_3$)}; {lit.[70] $[\alpha]_D^{20}$ −14.4 (*c* 2.1 in $CHCl_3$)}; ν_{max} (ATR) 1635 (C=O); δ_H (500 MHz, $CDCl_3$) 0.85-0.92 (6H, m, C(4′)$(CH_2)_4CH_3$, C(4″)$(CH_2)_6CH_3$), 1.21-1.45 (14H, m), 1.48-1.70 (12H, m) and 1.79 (2H, br s, C(2)H_2, C(3)H_2, C(7′)H_2, C(7″)H_2, C(4′)$(CH_2)_4CH_3$, C(4″)$(CH_2)_6CH_3$), 2.37-2.59 (12H, m, C(3′)H_2, N(5′)*Me*, C(6′)H_A, C(3″)H_2, N(5″)*Me*, C(6″)H_A), 2.83-3.03 (4H, m, C(4′)*H*, C(6′)H_B, C(4″)*H*, C(6″)H_B), 3.16-3.53 (8H, m, C(1)H_2, C(4)H_2, C(8′)H_2, C(8″)H_2); δ_C (125 MHz, $CDCl_3$) 14.0, 14.1 (C(4′)$(CH_2)_4CH_3$, C(4″)$(CH_2)_6CH_3$), 22.6, 24.6, 24.7, 25.3, 26.6, 27.0, *28.7*, 29.3, 29.6, *30.9*, 31.8, 31.9 (*C*(2), *C*(3), *C*(7′), *C*(7″), C(4′)$(CH_2)_4CH_3$, C(4″)$(CH_2)_6CH_3$), *38.4* (N(5′)*Me*, N(5″)*Me*), *39.7* (*C*(3′), *C*(3″)), 45.5 (*C*(1), *C*(4)), 47.3 (*C*(6′), *C*(6″)), 47.6 (*C*(8′), *C*(8″)), *63.3* (*C*(4′), *C*(4″)), *173.7* (*C*(2′), *C*(2″)); δ_H (500 MHz, PhMe-d_8, 363 K) 0.91 (6H, app t, *J* 7.3, C(4′)$(CH_2)_4CH_3$, C(4″)$(CH_2)_6CH_3$), 1.16-1.63 (28H, m, C(2)H_2, C(3)H_2, C(7′)H_2, C(7″)H_2, C(4′)$(CH_2)_4CH_3$, C(4″)$(CH_2)_6CH_3$), 2.27-2.47 (6H, m, C(3′)H_2, C(6′)H_A, C(3″)H_2, C(6″)H_A) overlapping 2.33 (3H, s, N*Me*) and 2.34 (3H, s, N*Me*), 2.66-2.77 (2H, m, C(6′)H_B, C(6″)H_B), 2.84-2.95 (2H, m, C(4′)*H*, C(4″)*H*), 3.04-3.22 (4H, m, C(8′)H_2, C(8″)H_2), 3.22-3.43 (4H, m, C(1)H_2, C(4)H_2); δ_C (125 MHz, PhMe-d_8, 363 K) 14.0, 14.0 (C(4′)$(CH_2)_4CH_3$, C(4″)(CH$_2$)$_6$*C*H$_3$), 22.9, 26.0, 27.0, 27.4, 29.1, 29.6, 30.0, 31.5, 31.6, 32.2, 32.3 (*C*(2), *C*(3), *C*(7′), *C*(7″), C(4′)(*C*H$_2$)$_4$CH$_3$, C(4″)(*C*H$_2$)$_6$CH$_3$), 39.0 (N(5′)*Me*, N(5″)*Me*), 39.9 (*C*(3′), *C*(3″)), 45.8 (*C*(1), *C*(4)), 47.2 (*C*(6′), *C*(6″)), 47.4 (*C*(8′), *C*(8″)), 63.6 (*C*(4′), *C*(4″)), 172.4 (*C*(2′), *C*(2″)); *m/z* (ESI$^+$) 529 ([M+Na]$^+$, 100%), 507 ([M+H]$^+$, 66%); HRMS (ESI$^+$) $C_{30}H_{59}N_4O_2^+$ ([M+H]$^+$) requires 507.4633; found 507.4640.

Method B: Following *general procedure 16*, **383** (57 mg, 238 μmol), **451** (75 mg, 216 μmol) and KOH (48 mg, 864 μmol) were reacted in DMSO (0.5 mL) for 96 h. Purification via column chromatography (gradient elution, 0% → 2.5% MeOH in CHCl$_3$) gave (−)-(*R*,*R*)-hopromine **100** as a colourless oil (53 mg, 48%, >99:1 dr); $[\alpha]_D^{24}$ −13.8 (*c* 1.0 in CHCl$_3$).

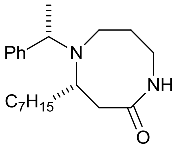
Method C: Following *general procedure 16*, **382** (32 mg, 149 μmol), **452** (51 mg, 136 μmol) and KOH (34 mg, 598 μmol) were reacted in DMSO (0.6 mL) for 96 h. Purification via column chromatography (gradient elution, 0% → 2.5% MeOH in CHCl$_3$) gave (−)-(*R*,*R*)-hopromine **100** as a colourless oil (5 mg, 7%, >99:1 dr); $[\alpha]_D^{24}$ −11.2 (*c* 0.3 in CHCl$_3$).

(*S*)-*N*-(3-Chloroprop-1-yl)-*N*-(α-methylbenzyl)amine (*S*)-413



(*S*)-α-Methylbenzylamine (*S*)-**153** (16.1 mL, 127 mmol) was added to 1-bromo-3-chloropropane **359** (5.00 mL, 50.5 mmol) in MeCN (40 mL) at rt and the resultant mixture was stirred for 16 h. The reaction mixture was basified to pH 9 with sat aq NaHCO$_3$ and then extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40° C petrol/Et$_2$O, 3:7) gave (*S*)-**413** as a yellow oil (5.45 g, 55%, >99:1 er); $[\alpha]_D^{24}$ −57.7 (*c* 1.0 in CHCl$_3$).

(*S*,*S*)-4-Heptyl-*N*(5)-(α-methylbenzyl)-1,5-diazocan-2-one *ent*-470



Step 1: Following *general procedure 5*, (*S*)-**413** (5.25 g, 26.6 mmol, >99:1 er), BuLi (2.5 M, 10.2 mL, 25.6 mmol) and **462** (4.80 g, 21.2 mmol) were reacted in THF (270 mL) to give *ent*-**464** as a yellow oil (5.41 g, >99:1 dr).

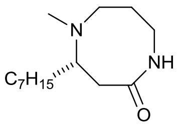
Step 2: Following *general procedure 11*, *ent*-**464** (5.41 g, >99:1 dr) in MeOH (40 mL) and SOCl$_2$ (1.35 mL, 18.6 mmol) in MeOH (40 mL) were reacted to give *ent*-**459** as a yellow oil (4.93 g, >99:1 dr).

Step 3: Following *general procedure 12*, NaN$_3$ (1.66 g, 25.5 mmol), NaI (3.83 g, 25.6 mmol) and *ent*-**459** (4.93 g, >99:1 dr) were reacted in DMSO (27 mL) to give *ent*-**466** as a yellow oil (4.74 g, >99:1 dr).

Step 4: Following *general procedure 13*, *ent*-**466** (4.74 g, >99:1 dr) and PBu$_3$ (3.50 mL, 14.0 mmol) were reacted in THF (50 mL) and H$_2$O (14 mL) to give *ent*-**469** as a yellow oil (7.31 g, >99:1 dr).

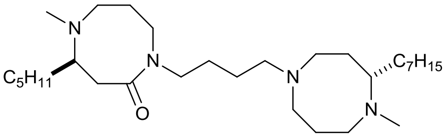
Step 5: Following *general procedure 13*, *ent*-**469** (7.31 g, >99:1 dr) and Sb(OEt)$_3$ (2.28 mL, 13.4 mmol) were reacted in PhMe (1.10 L). Purification via flash column chromatography (gradient elution, 60% → 100% EtOAc in 30-40 °C petrol) gave *ent*-**470** as a white solid (2.53 g, 36% over 5 steps, >99:1 dr); mp 45-47 °C; $[\alpha]_D^{24}$ −3.1 (*c* 1.0 in CHCl$_3$).

(*S*)-4-Heptyl-*N*(5)-methyl-1,5-diazocan-2-one *ent*-383



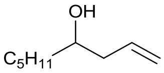
Following *general procedure 17*, *ent*-**470** (2.50 g, 7.56 mmol, >99:1 dr), (CH$_2$O)$_n$ (459 mg, 15.3 mmol) and Pd(OH)$_2$/C (1.15 g) were reacted in MeOH (25 mL) for 72 h to give *ent*-**383** as a colourless oil (1.58 g, 87%);[69] $[\alpha]_D^{24}$ +0.4 (*c* 1.0 in CHCl$_3$).

(4′*R*,4″*S*)-1-[2′-Oxo-4′-pentyl-*N*(5′)-methyl-1′,5′-diazocan-*N*(1′)-yl]-4-[2″-oxo-4″-heptyl-*N*(5″)-methyl-1″,5″-diazocan-*N*(1″)-yl]butane 387



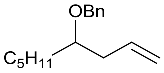
Following *general procedure 15*, *ent*-**383** (30 mg, 127 µmol), **451** (40 mg, 115 µmol), KOH (26 mg, 457 µmol), K$_2$CO$_3$ (19 mg, 138 µmol) and TEBAC (3 mg, 14.3 µmol) were reacted in DMSO (0.75 mL) for 96 h. Purification via column chromatography (gradient elution, 0% → 4% MeOH in CHCl$_3$) gave **387** as a yellow oil (10 mg, 17%, >99:1 dr); $[\alpha]_D^{24}$ +2.3 (*c* 0.8 in CHCl$_3$); ν_{max} (ATR) 1636 (C=O); δ_H (500 MHz, PhMe-*d*$_8$, 363 K) 0.92 (6H, br s, C(4′)(CH$_2$)$_4$C*H*$_3$, C(4″)(CH$_2$)$_6$C*H*$_3$), 1.22-1.60 (28H, m, C(2)*H*$_2$, C(3)*H*$_2$, C(7′)*H*$_2$, C(7″)*H*$_2$, C(4′)(C*H*$_2$)$_4$CH$_3$, C(4″)(C*H*$_2$)$_6$CH$_3$), 2.30-2.49 (12H, m, C(3′)*H*$_2$, N(5′)*Me*, C(6′)*H*$_A$, C(3″)*H*$_2$, N(5″)*Me*, C(6″)*H*$_A$), 2.68-2.77 (2H, m, C(6′)*H*$_B$, C(6″)*H*$_B$), 2.92 (2H, br s, C(4′)*H*, C(4″)*H*), 3.07-3.22 (4H, m, C(8′)*H*$_2$, C(8″)*H*$_2$), 3.24-3.32 (2H, m, C(1)*H*$_A$, C(4)*H*$_A$), 3.35-3.43 (2H, m, C(1)*H*$_B$, C(4)*H*$_B$); δ_C (125 MHz, PhMe-*d*$_8$, 363 K) 13.9, 14.0 (C(4′)(CH$_2$)$_4$*C*H$_3$, C(4″)(CH$_2$)$_6$*C*H$_3$), 22.9, 26.0, 26.7, 27.4, 29.1, 29.6, 30.0, 30.1, *31.4*, *31.5*, 32.2, 32.3 (*C*(2), *C*(3), *C*(7′), *C*(7″), C(4′)(*C*H$_2$)$_4$CH$_3$, C(4″)(*C*H$_2$)$_6$CH$_3$), 39.0 (N(5′)*Me*, N(5″)*Me*), 39.9 (*C*(3′), *C*(3″)), 45.8 (*C*(1), *C*(4)), 47.2 (*C*(6′), *C*(6″)), 47.4 (*C*(8′), *C*(8″)), 63.7 (*C*(4′), *C*(4″)), 172.3 (*C*(2′), *C*(2″)); *m/z* (ESI$^+$) 529 ([M+Na]$^+$, 89%), 507 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{59}N_4O_2^+$ ([M+H]$^+$) requires 507.4633; found 507.4617.

(*RS*)-Non-1-en-4-ol 509



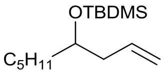
Allylmagnesium bromide (1.0 M, 50 mL, 50 mmol) was added to **454** (5.70 mL, 4.75 mmol) in THF (125 mL) at 0 °C and the resultant mixture was stirred and allowed to warm to rt over 1 h. Sat aq NH_4Cl (50 mL) was added and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic extracts were washed with brine (100 mL), dried and concentrated *in vacuo* to give **509** as a colourless oil (6.02g, 90%);[71] δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.1, C(9)H_3), 1.26-1.52 (8H, m, C(5)H_2, C(6)H_2, C(7)H_2, C(8)H_2), 2.14 (1H, ABt, *J* 14.0, 7.9, C(3)H_A), 2.29-2.35 (1H, m, C(3)H_B), 3.62-3.69 (1H, m, C(4)*H*), 5.12-5.18 (2H, m, C(1)H_2), 5.79-5.89 (1H, m, C(2)*H*).

(*RS*)-4-(Benzyloxy)non-1-ene 510



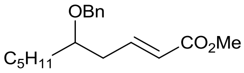
NaH (1.55 g, 38.7 mmol) was added to **509** (5.00 g, 35.2 mmol) in THF (100 mL) at rt and the resultant mixture stirred for 1 h. BnBr (4.39 mL, 36.9 mmol) was added and the resultant mixture stirred at rt for 18 h. H_2O (50 mL) was cautiously added and the aqueous layer extracted with Et_2O (2 × 50 mL). The combined organic extracts were dried and concentrated *in vacuo* to give **510** as a colourless oil (8.16 g, quant);[72] δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.2, C(9)H_3), 1.21-1.57 (8H, m, C(6)H_2, C(7)H_2, C(8)H_2, C(9)H_2), 2.30-2.36 (2H, m, C(3)H_2), 3.44 (1H, app quin, *J* 5.8, C(4)*H*), 4.50 (1H, ABd, *J* 11.6, OC$H_A$$H_B$Ph), 4.57 (1H, ABd, *J* 11.6, OC$H_A$$H_B$Ph), 5.05-5.12 (2H, m, C(1)H_2), 5.81-5.92 (1H, m, C(2)*H*), 7.26-7.37 (5H, m, *Ph*).

(*RS*)-4-[(*tert*-Butyldimethylsilyl)oxy]non-1-ene 511



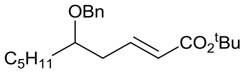
TBDMSCl (558 mg, 3.70 mmol) was added to **509** (500 mg, 3.52 mmol) and imidazole (300 mg, 4.40 mmol) in DMF (1.5 mL) at rt and the resultant mixture stirred for 16 h. The reaction mixture was partitioned between Et_2O (10 mL) and H_2O (10 mL) and the aqueous layer extracted with Et_2O (2 × 10 mL). The combined organic extracts were washed with H_2O (2 × 30 mL) and brine (30 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol) gave **511** as a colourless oil (744 mg, 82%);[73] δ_H (400 MHz, $CDCl_3$) 0.05 (6H, s, SiMe_2), 0.89 (12H, m, C(9)H_3, CMe_3), 1.21-1.45 (8H, m, C(5)H_2, C(6)H_2, C(7)H_2, C(8)H_2), 2.15-2.26 (2H, m, C(3)H_2), 3.68 (1H, app quin, *J* 5.6, C(4)*H*), 5.00-5.07 (2H, m, C(1)H_2), 5.77-5.87 (1H, m, C(2)*H*).

Methyl (*RS*,*E*)-5-(benzyloxy)dec-2-enoate 512



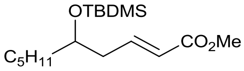
Following *general procedure 19*, Grubbs II catalyst (92 mg, 108 μmol), methyl acrylate (0.48 mL, 3.28 mmol) and **510** (500 mg, 2.15 mmol) were reacted in CH_2Cl_2 (6 mL). Purification via flash column chromatography (gradient elution, 0% → 10% Et_2O in 30-40 °C petrol) gave **512** as a colourless oil (461 mg, 74%, >99:1 dr); ν_{max} (ATR) 1724 (C=O), 1658 (C=C); δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.1, C(10)H_3), 1.23-1.65 (8H, m, C(6)H_2, C(7)H_2, C(8)H_2, C(9)H_2), 2.46 (2H, app t, *J* 6.6, C(4)H_2), 3.53 (1H, app quin, *J* 5.8, C(5)*H*), 3.74 (3H, s, O*Me*), 4.51 (1H, ABd, *J* 11.6, OCH_AH_BPh), 4.56 (1H, ABd, *J* 11.6, OCH_AH_BPh), 5.90 (1H, d, *J* 15.6, C(2)*H*), 7.02 (1H, dt, *J* 15.6, 7.6, C(3)*H*), 7.26-7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.0 (*C*(10)), 22.6, 25.0, 31.8, 34.0 (*C*(6), *C*(7), *C*(8), *C*(9)), 36.8 (*C*(4)), 51.4 (O*Me*), 71.1 (O*C*H_2Ph), 77.7 (*C*(5)), 123.0 (*C*(2)), 127.6, 127.8, 128.4 (*o*,*m*,*p*-*Ph*), 138.5 (*i*-*Ph*), 145.9 (*C*(3)), 166.8 (*C*(1)); *m/z* (ESI^+) 313 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{18}H_{26}NaO_3^+$ ($[M+Na]^+$) requires 313.1774; found 313.1764.

***tert*-Butyl (*RS*,*E*)-5-(benzyloxy)dec-2-enoate 513**



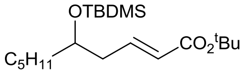
Following *general procedure 19*, Grubbs II catalyst (121 mg, 143 μmol), *tert*-butyl acrylate (4.87 mL, 33.2 mmol) and **510** (3.37 g, 14.5 mmol) were reacted in CH_2Cl_2 (33 mL). Purification via flash column chromatography (gradient elution, 0% → 5% Et_2O in 30-40 °C petrol) gave **513** as a colourless oil (4.10 g, 85%, >99:1 dr); $C_{21}H_{32}O_3$ requires C, 75.9; H, 9.7%; found C, 75.9; H, 9.6%; ν_{max} (ATR) 1713 (C=O), 1653 (C=C); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.1, C(10)H_3), 1.22-1.60 (8H, m, C(6)H_2, C(7)H_2, C(8)H_2, C(9)H_2) overlapping 1.50 (9H, s, CMe_3), 2.41-2.46 (2H, m, C(4)H_2), 3.51 (1H, app quin, *J* 5.6, C(5)*H*), 4.50 (1H, ABd, *J* 11.5, OCH_AH_BPh), 4.56 (1H, ABd, *J* 11.5, OCH_AH_BPh), 5.81 (1H, dt, *J* 15.6, 1.3, C(2)*H*), 6.90 (1H, dt, *J* 15.6, 7.3, C(3)*H*), 7.26-7.41 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.0 (*C*(10)), 22.6, 25.0, 31.8, 34.0 (C(6), C(7), C(8), C(9)), 28.2 (CMe_3), 36.7 (*C*(4)), 71.1 (O*C*H_2Ph), 77.9 (*C*(5)), 80.1 (*C*Me_3), 125.1 (*C*(2)), 127.6, 127.8, 128.3 (*o*,*m*,*p*-*Ph*), 138.6 (*i*-*Ph*), 144.2 (*C*(3)), 165.8 (*C*(1)); *m/z* (ESI^+) 687 ($[2M+Na]^+$, 23%), 355 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{21}H_{32}NaO_3^+$ ($[M+Na]^+$) requires 355.2244; found 355.2246.

Methyl (*RS*,*E*)-5-[(*tert*-butyldimethylsilyl)oxy]dec-2-enoate 514



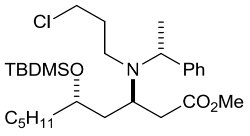
Following *general procedure 19*, Grubbs II catalyst (46 mg, 54 µmol), methyl acrylate (0.24 mL, 2.70 mmol) and **511** (276 mg, 1.08 mmol) were reacted in CH_2Cl_2 (3 mL). Purification via flash column chromatography (gradient elution, 0% → 5% Et_2O in 30-40 °C petrol) gave **514** as a colourless oil (181 mg, 53%, >99:1 dr); ν_{max} (ATR) 1728 (C=O), 1659 (C=C); δ_H (400 MHz, $CDCl_3$) 0.05 (6H, s, Si*Me*$_2$), 0.87-0.91 (12H, m, C(10)*H*$_3$, SiC*Me*$_3$), 1.21-1.46 (8H, m, C(6)*H*$_2$, C(7)*H*$_2$, C(8)*H*$_2$, C(9)*H*$_2$), 2.28-2.41 (2H, m, C(4)*H*$_2$), 3.74 (3H, s, O*Me*), 3.77 (1H, app quin, *J* 5.8, C(5)*H*), 5.84 (1H, d, *J* 15.7, C(2)*H*), 6.94-7.02 (1H, m, C(3)*H*); δ_C (100 MHz, $CDCl_3$) −4.5 (Si*Me*$_2$), 14.0 (*C*(10)), 18.1 (*C*Me$_3$), 22.6, 24.9, 31.9, 37.2 (*C*(6), *C*(7), *C*(8), *C*(9)), 25.8 (*CMe*$_3$), 40.2 (*C*(4)), 51.4 (O*Me*), 71.3 (*C*(5)), 122.8 (*C*(2)), 146.4 (*C*(3)), 166.9 (*C*(1)); *m/z* (ESI$^+$) 337 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{17}H_{34}NaO_3Si^+$ ([M+Na]$^+$) requires 337.2169; found 337.2174.

tert-Butyl (*RS*,*E*)-5-[(*tert*-butyldimethylsilyl)oxy]dec-2-enoate 515

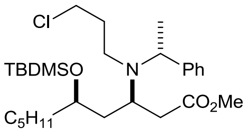


Following *general procedure 19*, Grubbs II catalyst (46 mg, 54 µmol), *tert*-butyl acrylate (0.40 mL, 2.70 mmol) and **511** (276 mg, 1.08 mmol) were reacted in CH_2Cl_2 (3 mL). Purification via flash column chromatography (gradient elution, 0% → 5% Et_2O in 30-40 °C petrol) gave **515** as a colourless oil (227 mg, 60%, >99:1 dr); ν_{max} (ATR) 1715 (C=O), 1655 (C=C); δ_H (400 MHz, $CDCl_3$) 0.04 (6H, s, Si*Me*$_2$), 0.87-0.90 (12H, m, C(10)*H*$_3$, SiCMe$_3$), 1.22-1.37 (6H, m, C(7)*H*$_2$, C(8)*H*$_2$, C(9)*H*$_2$), 1.39-1.45 (2H, m, C(6)*H*$_2$), 1.48 (9H, s, OC*Me*$_3$), 2.23-2.36 (2H, m, C(4)*H*$_2$), 3.74 (1H, app quin, *J* 5.8, C(5)*H*), 5.74 (1H, d, *J* 15.7, C(2)*H*), 6.81-6.89 (1H, m, C(3)*H*); δ_C (100 MHz, $CDCl_3$) −4.6 (Si*Me*$_2$), 14.0 (*C*(10)), 18.1 (Si*C*Me$_3$), 22.6, 24.9, 31.9, 37.3 (*C*(6), *C*(7), *C*(8), *C*(9)), 25.8 (Si*CMe*$_3$), 28.1 (O*CMe*$_3$), 40.0 (*C*(4)), 71.4 (*C*(5)), 79.9 (O*C*Me$_3$), 124.9 (*C*(2)), 144.9 (*C*(3)), 165.8 (*C*(1)); *m/z* (ESI$^+$) 735 ([2M+Na]$^+$, 41%), 379 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{40}NaO_3Si^+$ ([M+Na]$^+$) requires 379.2639; found 379.2647.

Methyl (3*RS*,5*SR*,α*RS*)-3-[*N*-(3′-chloropropyl)-*N*-(α-methylbenzyl)amino]-5-[(*tert*-butyldimethylsilyl)oxy]decanoate 520 and methyl (*RS*,*RS*,*RS*)-3-[*N*-(3′-chloropropyl)-*N*-(α-methylbenzyl)amino]-5-[(*tert*-butyldimethylsilyl)oxy]decanoate 521



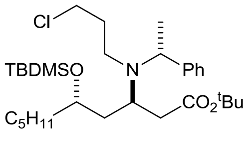
520



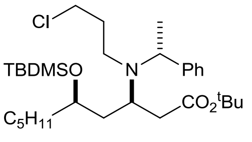
521

Following *general procedure 5*, (±)-**413** (75 mg, 381 µmol), BuLi (2.5 M, 0.15 mL, 369 µmol) and **514** (75 mg, 238 µmol) were reacted in THF (2 mL) to give a 9:57:34 mixture of **514**, **520** and **521**.[74] Purification via flash column chromatography (gradient elution, 0% → 7% Et_2O in 30-40 °C petrol) gave a 52:45 mixture of **520**:**521**[74] as a colourless oil (64 mg, 52%).[75] Data for mixture: ν_{max} (ATR) 1738 (C=O); δ_H (400 MHz, $CDCl_3$) 0.06 (6H, s, Si*Me*$_2$), 0.07 (6H, s, Si*Me*$_2$), 0.88-0.94 (6H, m, 2 × C(10)*H*$_3$) overlapping 0.89 (9H, s, C*Me*$_3$), 0.91 (9H, s, C*Me*$_3$), 1.21-1.51 (18H, m, 2 × C(4)*H*$_A$, 2 × C(6)*H*$_2$, 2 × C(7)*H*$_2$, 2 × C(8)*H*$_2$, 2 × C(9)*H*$_2$) overlapping 1.41 (6H, d, *J* 7.1, 2 × C(α)*Me*), 1.68-1.92 (6H, m, 2 × C(4)*H*$_B$, 2 × C(2′)*H*$_2$), 2.23-2.35 (4H, m, 2 × C(2)*H*$_2$), 2.61-2.69 (4H, m, 2 × C(1′)*H*$_2$), 3.33-3.51 (6H, m, 2 × C(3)*H*, 2 × C(3′)*H*$_2$), 3.56 (6H, s, O*Me*), 3.65-3.73 (2H, m, 2 × C(5)*H*), 3.88-3.96 (2H, m, 2 × C(α)*H*), 7.19-7.32 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) −4.5, −4.4, −4.3, −4.1 (4 × Si*Me*), 14.1 (2 × *C*(10)), 18.0, 18.1 (2 × *C*Me$_3$), 19.0, 19.1 (2 × C(α)*Me*), 22.6, 24.5, 24.6, 32.0, 32.1 (2 × *C*(7), 2 × *C*(8), 2 × *C*(9)), 25.9 (2 × C*Me*$_3$), 32.7, 32.9 (2 × *C*(2′)), 37.5, 37.6 (2 × *C*(6)), 38.7, 38.8 (2 × *C*(2)), 39.9 (2 × *C*(4)), 43.0, 43.2, 43.3, 43.4 (2 × *C*(1′), 2 × *C*(3′)), 51.2, 51.3 (2 × O*Me*), 52.6, 53.4 (2 × *C*(3)), 58.0, 58.1 (2 × *C*(α)), 70.0, 71.2 (2 × *C*(5)), 70.0, 71.2 (2 × *C*(5)), 126.7, 126.8, 127.8, 128.0, 128.1 (*o,m,p-Ph*), 144.5, 145.1 (*i-Ph*), 172.8, 172.9 (2 × *C*(1)); *m/z* (ESI$^+$) 536 ([M(^{37}Cl)+Na]$^+$, 87%), 534 ([M(^{35}Cl)+Na]$^+$, 100%), 514 ([M(^{37}Cl)+H]$^+$, 100%), 512 ([M(^{35}Cl)+H]$^+$, 88%); HRMS (ESI$^+$) $C_{28}H_{51}{}^{37}ClNO_3Si^+$ ([M+H]$^+$) requires 514.3295; found 514.3301, $C_{28}H_{51}{}^{35}ClNO_3Si^+$ ([M+H]$^+$) requires 512.3321; found 512.3316.

tert-Butyl (3*RS*,5*SR*,α*RS*)-3-[*N*-(3′-chloropropyl)-*N*-(α-methylbenzyl)amino]-5-[(*tert*-butyldimethylsilyl)oxy]decanoate 522 and *tert*-butyl (*RS*,*RS*,*RS*)-3-[*N*-(3′-chloropropyl)-*N*-(α-methylbenzyl)amino]-5-[(*tert*-butyldimethylsilyl)oxy]decanoate 523



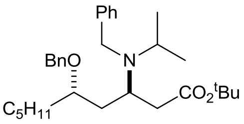
522



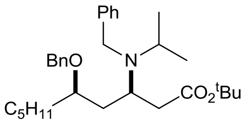
523

Following *general procedure 5*, (±)-**413** (67 mg, 338 µmol), BuLi (2.5 M, 0.13 mL, 326 µmol) and **515** (75 mg, 210 µmol) were reacted in THF (2 mL) to give a 59:41 mixture of **522**:**523**.[74] Purification via flash column chromatography (gradient elution, 0% → 4% Et_2O in 30-40 °C petrol) gave a 61:39 mixture of **522**:**523**[74] as a colourless oil (66 mg, 66%). Data for mixture: ν_{max} (ATR) 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 0.05-0.10 (12H, m, 2 × Si*Me*$_2$), 0.88-0.92 (6H, m, 2 × C(10)*H*$_3$), 0.90 (9H, s, SiC*Me*$_3$) overlapping 0.91 (9H, s, SiC*Me*$_3$), 1.21-1.39 (18H, m, 2 × C(4)*H*$_A$, 2 × C(6)*H*$_2$, 2 × C(7)*H*$_2$, 2 × C(8)*H*$_2$, 2 × C(9)*H*$_2$), 1.41 (6H, d, *J* 6.8, 2 × C(α)*Me*), 1.44 (9H, s, OC*Me*$_3$), 1.45 (9H, s, OC*Me*$_3$), 1.65-1.83 (6H, m, 2 × C(4)*H*$_B$, 2 × C(2′)*H*$_2$), 2.18-2.31 (4H, m, 2 × C(2)*H*$_2$), 2.54-2.66 (4H, m, 2 × C(1′)*H*$_2$), 3.32-3.43 (6H, m, 2 × C(3)*H*, 2 × C(3′)*H*$_2$), 3.69 (2H, app quin, *J* 5.8, 2 × C(5)*H*), 3.90 (2H, q, *J* 6.8, C(α)*H*), 7.18-7.38 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (2 × *C*(10)), 18.0, 18.1 (2 × Si*C*Me$_3$), 19.9, 20.5 (2 × *C*(α)Me), 22.7, 24.5, 24.6, 30.9, 32.1 (2 × *C*(7), 2 × *C*(8), 2 × *C*(9)), 26.0 (SiC*Me*$_3$), 28.1 (2 × OC*Me*$_3$), 32.9, 33.2 (2 × *C*(2′)), 37.3, 37.5 (2 × *C*(6)), 38.6, 39.4 (2 × *C*(2)), 40.1 (2 × *C*(4)), 43.3, 43.3, 43.4, 43.7 (2 × *C*(1′), 2 × *C*(3′)), 52.9, 53.8 (2 × *C*(3)), 58.5, 58.6 (2 × *C*(α)), 70.0, 71.1 (2 × *C*(5)), 80.0 (2 × *C*Me$_3$), 126.8, 127.8, 128.0 (*o,m,p-Ph*), 145.0, 145.3 (*i-Ph*), 171.7, 171.8 (2 × *C*(1)); *m/z* (ESI^+) 578 ($[M(^{37}Cl)+Na]^+$, 75%), 576 ($[M(^{35}Cl)+Na]^+$, 98%), 556 ($[M(^{37}Cl)+H]^+$, 100%), 554 ($[M(^{35}Cl)+H]^+$, 89%); HRMS (ESI^+) $C_{31}H_{57}{}^{37}ClNO_3Si^+$ ($[M+H]^+$) requires 556.3764; found 556.3770, $C_{31}H_{57}{}^{35}ClNO_3Si^+$ ($[M+H]^+$) requires 554.3791; found 554.3782.

tert-Butyl (3*RS*,5*SR*)-3-(*N*-benzyl-*N*-isopropylamino)-5-(benzyloxy)decanoate 531 and *tert*-butyl (*RS*,*RS*)-3-(*N*-benzyl-*N*-isopropylamino)-5-(benzyloxy)decanoate 532



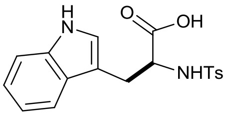
531



532

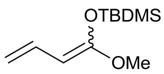
Following *general procedure 5*, *N*-isopropylbenzylamine (0.30 mL, 1.77 mmol), BuLi (2.5 M, 0.69 mL, 1.72 mmol) and **513** (369 mg, 1.11 mmol) were reacted in THF (5 mL) to give a 50:50 mixture of **531**:**532**. Purification via flash column chromatography (gradient elution, 1% → 9% Et_2O in 30-40 °C petrol) gave a 50:50 mixture of **531**:**532** as a colourless oil (411 mg, 82%). Data for mixture: ν_{max} (ATR) 1723 (C=O); δ_H (400 MHz, $CDCl_3$) 0.95-1.00 (6H, m, 2 × C(10)*H*$_3$), 1.11 (3H, app d, *J* 3.0, NCH*Me*$_A$), 1.12 (3H, app d, *J* 3.0, NCH*Me*$_B$), 1.15 (6H, app t, *J* 6.7, NCH*Me*$_2$), 1.23-1.66 (18H, m, 2 × C(4)*H*$_A$, 2 × C(6)*H*$_2$, 2 × C(7)*H*$_2$, 2 × C(8)*H*$_2$, 2 × C(9)*H*$_2$) overlapping 1.50 (9H, s, C*Me*$_3$) and 1.54 (9H, s, C*Me*$_3$), 1.73 (1H, ABddd, *J* 14.4, 8.3, 3.5, C(4)*H*$_B$), 2.02 (1H, ddd, *J* 13.9, 8.1, 5.3, C(4)*H*$_B$), 2.24-2.32 (2H, m, C(2)*H*$_2$), 2.66 (2H, app td, *J* 13.6, 5.6, C(2)*H*$_2$), 2.99-3.14 (2H, m, 2 × NC*H*Me$_2$), 3.35-3.43 (1H, m, C(3)*H*), 3.50-3.58 (2H, m, C(3)*H*, C(5)*H*), 3.61 (1H, ABd, *J* 14.2, NC*H*$_A$H$_B$Ph), 3.63-3.70 (1H, m, C(5)*H*) overlapping 3.64 (1H, ABd, *J* 14.2, NC*H*$_A$H$_B$Ph), 3.77 (2H, app ABd, *J* 14.2, 2 × NCH$_A$*H*$_B$Ph), 4.27 (1H, ABd, *J* 11.1, OCH_AH_BPh), 4.50 (1H, ABd, *J* 11.1, OCH_AH_BPh), 4.54 (1H, ABd, *J* 11.5, OCH_AH_BPh), 4.58 (1H, ABd, *J* 11.5, OCH_AH_BPh), 7.22-7.47 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1, 14.1 (2 × *C*(10)), 19.5, 19.8, 21.7, 21.8 (2 × NCH*Me*$_2$), 22.7, 22.8, 24.8, 24.9, 32.1, 32.2, 33.7, 33.9 (2 × C(6), 2 × C(7), 2 × C(8), 2 × C(9)) 28.1, 28.2 (2 × C*Me*$_3$), 37.4, 38.3 (2 × *C*(4)), 39.2, 39.9 (2 × *C*(2)), 47.5, 48.3 (2 × N*C*HMe$_2$), 49.1, 49.3 (2 × N*C*H$_2$Ph), 51.5, 52.1 (2 × *C*(3)), 70.3, 71.0 (2 × O*C*H$_2$Ph), 76.9, 77.1 (2 × *C*(5)), 80.1, 80.1 (2 × *C*Me$_3$), 126.8, 127.1, 127.4, 127.6, 127.8, 128.1, 128.1, 128.1, 128.3, 128.7, 128.9 (*o,m,p-Ph*), 139.2, 139.4, 141.4, 141.7 (*i-Ph*), 172.1, 172.3 (2 × *C*(1)); *m/z* (ESI$^+$) 986 ([2M+Na]$^+$, 75%), 504 ([M+Na]$^+$, 100%), 482 ([M+H]$^+$, 78%); HRMS (ESI$^+$) $C_{31}H_{48}NO_3^+$ ([M+H]$^+$) requires 482.3629; found 482.3614.

(*S*)-*N*-Tosyl tryptophan 535



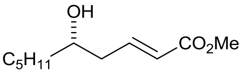
TsCl (9.30 g, 49.0 mmol) in THF (90 mL) was added to (*S*)-tryptophan **534** (10.0 g, 49.0 mmol) and NEt$_3$ (17.0 mL, 94.5 mmol) in THF (90 mL) and H$_2$O (10 mL) at 0 °C and the resultant mixture stirred at 0 °C for 5 min. The reaction mixture was allowed to warm to rt and stirred for 2 h. The reaction mixture was partitioned between Et$_2$O (200 mL) and H$_2$O (100 mL) and the aqueous layer extracted with Et$_2$O (200 mL). 1.0 M aq HCl (100 mL) was added to the aqueous layer and the aqueous layer was then extracted with EtOAc (3 × 150 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 2% → 10% MeOH in PhMe) gave **535** as a white solid (2.32 g, 13%);[76] mp 145-146 °C; $[\alpha]_D^{24}$ −44.4 (*c* 1.0 in EtOH); {lit.[76] $[\alpha]_D^{25}$ −41.6 (*c* 1.0 in EtOH)}; δ_H (400 MHz, $CDCl_3$) 2.30 (3H, s, Ar*Me*), 2.97 (1H, ABdd, *J* 14.4, 8.4, C(2)H_A), 3.19 (1H, ABdd, *J* 14.4, 5.4, C(2)H_B), 4.04 (1H, dd, *J* 8.4, 5.4, C(1)*H*), 6.93 (1H, td, *J* 7.0, 0.9, *Ar*), 6.99 (1H, s, *Ar*), 7.01-7.08 (3H, m, *Ar*), 7.26 (1H, dq, *J* 8.0, 0.9, *Ar*), 7.36 (1H, dd, *J* 8.0, 0.9, *Ar*), 7.38-7.42 (2H, m, *Ar*).

***tert*-Butyl(1-methoxybutadienyloxy)dimethylsilane 538**



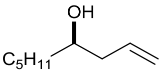
BuLi (2.5 M, 23.8 mL, 59.6 mmol) was added to diisopropylamine (8.70 mL, 62.1 mmol) in THF (100 mL) at 0 °C and the resultant mixture stirred at 0 °C for 15 min. The reaction mixture was cooled to −78 °C and then DMPU (9.34 mL, 74.4 mmol) was added and the resultant mixture stirred for 15 min at −78 °C. Methyl crotonate **537** (5.00 mL, 49.6 mmol) was added at −78 °C and the resultant mixture stirred for 15 min at −78 °C. TBDMSCl (9.34 g, 62.1 mmol) in THF (10 mL) was added and the resultant mixture stirred at −78 °C for 45 min. The reaction mixture was allowed to warm to rt and then stirred for 2 h. The reaction mixture was partitioned between sat aq $NaHCO_3$ (50 mL) and 30-40 °C petrol (100 mL) and the aqueous layer extracted with 30-40 °C petrol (100 mL). The combined organic extracts were washed with sat aq $NaHCO_3$ (100 mL) and brine (200 mL), and then dried and concentrated *in vacuo*. Purification via distillation gave **538** as a colourless oil (6.66 g, 63%, >99:1 dr);[76] bp 64-68 °C (2 mbar); {lit.[76] bp 54-58 °C (0.3 mbar)}; δ_H (400 MHz, $CDCl_3$) 0.18 (6H, s, Si*Me*$_2$), 0.96 (9H, s, C*Me*$_3$), 3.58 (3H, s, O*Me*), 4.49 (1H, d, *J* 10.2, C(2)*H*), 4.61 (1H, ddd, *J* 10.1, 2.1, 0.7, C(4)H_A), 4.86 (1H, ddd, *J* 17.1, 2.1, 0.7, C(4)H_B), 6.54 (1H, dt, *J* 17.1, 10.2, C(3)*H*).

Methyl (*S*,*E*)-5-hydroxydec-2-enoate 539



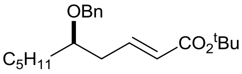
$PhBCl_2$ (0.19 mL, 1.65 mmol) was added to **535** (591 mg, 1.65 mmol) in CH_2Cl_2 (15 mL) at rt and the resultant mixture was stirred for 1 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in butyronitrile (6.0 mL) and the resultant mixture was cooled to −78 °C. **538** (423 mg, 1.98 mmol), hexanal **454** (0.20 mL, 1.65 mmol), IPA (0.15 mL, 1.98 mmol) in butyronitrile (1.5 mL) was added over 10 min and the resultant mixture stirred at −78 °C for 3 h. Sat aq $NaHCO_3$ (20 mL) was added and the aqueous layer extracted with Et_2O (2 × 30 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 10% → 30% Et_2O in 30-40 °C petrol) gave **539** as a colourless oil (211 mg, 64%, 98.5:1.5 er); $[\alpha]_D^{24}$ +2.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3434 (O−H), 1705 (C=O), 1657 (C=C); δ_H (400 MHz, $CDCl_3$) 0.85 (3H, t, *J* 6.8, C(10)H_3), 1.18-1.48 (8H, m, C(6)H_2, C(7)H_2, C(8)H_2, C(9)H_2), 2.25-2.41 (2H, m, C(4)H_2), 2.74 (1H, br s, O*H*), 3.67-3.74 (1H, m, C(5)*H*) overlapping 3.68 (3H, s, O*Me*), 5.86 (1H, d, *J* 15.7, C(2)*H*), 6.96 (1H, dt, *J* 15.7, 7.3, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 14.0 (*C*(10)), 22.6, 25.2, 31.7, 37.0 (*C*(6), *C*(7), *C*(8), *C*(9)), 40.1 (*C*(4)), 51.5 (O*Me*), 70.5 (*C*(5)), 123.1 (*C*(2)), 146.1 (*C*(3)), 167.0 (*C*(1)); *m/z* (ESI^+) 223 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{11}H_{20}NaO_3^+$ ($[M+Na]^+$) requires 223.1305; found 223.1302.

(*R*)-Non-1-en-4-ol 509



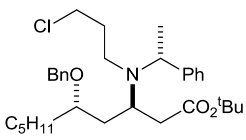
Allylmagnesium bromide (1.0 M, 11 mL, 11.0 mmol) was added to (−)-Ipc_2BCl (4.24 g, 13.2 mmol) in Et_2O (60 mL) at −78 °C and the reaction mixture stirred and allow to warm to 0 °C over 1 h. The stirring was ceased and the mother liquor was carefully transferred to another flask via cannula such that the white precipitate remained in the original flask. The resultant solution was cooled to −78 °C and hexanal **454** (1.08 mL, 8.79 mmol) in Et_2O (30 mL) was added and the resultant solution stirred at −78 °C for 1 h. Phosphate pH 7 buffer (60 mL), MeOH (60 mL) and 30% H_2O_2 (30 mL) were sequentially added and the resultant mixture stirred for 30 min. The reaction mixture was added to sat aq $NaHCO_3$ (100 mL) and the aqueous layer extracted with Et_2O (2 × 100 mL). The combined organic extracts were washed with sat aq $Na_2S_2O_3$ (100 mL), dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 2% → 10% Et_2O in 30-40 °C petrol) gave (*R*)-**509** as a colourless oil (959 mg, 77%, 98:2 er); $[\alpha]^{24}_{D}$ +9.0 (*c* 1.0 in $CHCl_3$); {lit.[77] $[\alpha]^{25}_{D}$ +8.9 (*c* 1.1 in $CHCl_3$)}.

***tert*-Butyl (*R*,*E*) 5-(benzyloxy)dec-2-enoate 513**

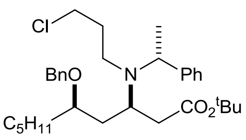


NaH (155 mg, 3.87 mmol) was added to (*R*)-**509** (500 mg, 3.52 mmol) in THF (5 mL) at rt and the resultant mixture stirred for 1 h. BnBr (0.44 mL, 3.69 mmol) was added and the resultant mixture stirred at rt for 18 h. H_2O (5 mL) was cautiously added and the aqueous layer extracted with Et_2O (2 × 5 mL). The combined organic extracts were dried and concentrated *in vacuo* to give (*R*)-**510** as a colourless oil (707 mg). Grubbs II catalyst (22 mg, 26 μmol) and *tert*-butyl acrylate (0.89 mL, 6.08 mmol) were added to a degassed solution of (*R*)-**510** (615 mg, 2.65 mmol) in CH_2Cl_2 (6 mL, EtOH stabilised) at rt and the resultant mixture heated at 40 °C for 24 h. The reaction mixture was then concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 0% → 5% Et_2O in 30-40 °C petrol) gave **513** as a colourless oil (539 mg, 53% over 2 steps, >99:1 dr); $[\alpha]^{20}_{D}$ +10.9 (*c* 1.0 in $CHCl_3$).

***tert*-Butyl (3*R*,5*S*,α*R*)-3-[*N*-(3′-chloropropyl)-*N*-(α-methylbenzyl)amino]-5-(benzyloxy)decanoate 518 and *tert*-butyl (*R*,*R*,*R*)-3-[*N*-(3′-chloropropyl)-*N*-(α-methylbenzyl)amino]-5-(benzyloxy)decanoate 519**



518

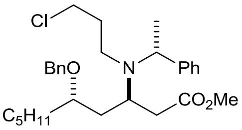


519

Method A: Following *general procedure 5*, (*R*)-**413** (6.60 g, 33.4 mmol, >99:1 er), BuLi (2.5 M, 12.9 mL, 32.4 mmol) and (±)-**513** (6.95 g, 20.9 mmol) were reacted in THF (190 mL) to give a 50:50 mixture of **518** and **519**. Purification via flash column chromatography (gradient elution, 5% → 6.25% Et_2O in 30-40 °C petrol) gave **518** as a colourless oil (5.11 g, 46%, >99:1 dr); $C_{32}H_{48}ClNO_3$ requires C, 72.5; H, 9.1; N, 2.6%; found C, 72.4; H, 9.2; N, 2.65%; $[\alpha]^{24}_{D}$ −11.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1718 (C=O); δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, *J* 7.3, C(10)H_3), 1.25-1.46 (6H, m, C(7)H_2, C(8)H_2, C(9)H_2) overlapping 1.38 (9H, s, CMe_3) and 1.40 (3H, d, *J* 6.9, C(α)*Me*), 1.54-1.62 (4H, m, C(4)H_2, C(6)H_2), 1.85 (2H, app quin, *J* 6.3, C(2′)H_2), 2.03-2.06 (2H, m, C(2)H_2), 2.56-2.68 (2H, m, C(1′)H_2), 3.44-3.55 (3H, m, C(3)*H*, C(3′)H_2), 3.56-3.61 (1H, m, C(5)*H*), 3.88 (1H, q, *J* 6.9, C(α)*H*), 4.31 (1H, ABd, *J* 11.2, OCH_AH$_\text{B}$Ph), 4.52 (1H, ABd, *J* 11.2, OCH$_\text{A}$$H_\text{B}$Ph), 7.18-7.35 (10H, m, *Ph*); δ_C (100 MHz, CDCl$_3$) 14.1 (*C*(10)), 20.4 (C(α)*Me*), 22.7, 24.5, 32.2 (*C*(7), *C*(8), *C*(9)), 28.0 (C*Me*$_3$), 32.9 (*C*(2′)), 33.5, 37.5 (*C*(4), *C*(6)), 38.6 (*C*(2)), 42.8 (*C*(1′)), 43.2 (*C*(3′)), 52.8 (*C*(3)), 58.5 (*C*(α)), 69.8 (O*C*H$_2$Ph), 76.6 (*C*(5)), 80.0 (*C*Me$_3$), 126.9, 127.1, 127.5, 127.9, 128.1, 128.2 (*o,m,p-Ph*), 139.2, 144.0 (*i-Ph*), 172.0 (*C*(1)); *m/z* (ESI$^+$) 554 ([M(^{37}Cl)+Na]$^+$, 11%), 552 ([M(^{35}Cl)+Na]$^+$, 26%), 532 ([M(^{37}Cl)+H]$^+$, 97%), 530 ([M(^{35}Cl)+H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{49}{}^{37}ClNO_3^+$ ([M(^{37}Cl)+H]$^+$) requires 532.3366; found 532.3392; $C_{32}H_{49}{}^{35}ClNO_3^+$ ([M(^{35}Cl)+H]$^+$) requires 530.3395; found 530.3400. Further elution gave **519** as a colourless oil (4.57 g, 41%, >99:1 dr); $C_{32}H_{48}ClNO_3$ requires C, 72.5; H, 9.1; N, 2.6%; found C, 72.45; H, 9.1; N, 2.5%; $[\alpha]_\text{D}^{24}$ −16.2 (*c* 1.0 in CHCl$_3$); ν_max (ATR) 1724 (C=O); δ_H (500 MHz, CDCl$_3$) 0.91 (3H, t, *J* 7.3, C(10)H_3), 1.20-1.47 (9H, m, C(4)H_A, C(6)H_2, C(7)H_2, C(8)H_2, C(9)H_2) overlapping 1.40 (3H, d, *J* 6.8, C(α)*Me*) and 1.42 (9H, s, C*Me*$_3$), 1.71-1.80 (1H, m, C(2′)H_A), 1.82-1.91 (2H, m, C(4)H_B, C(2′)H_B), 2.09 (1H, ABdd, *J* 14.5, 7.3, C(2)H_A), 2.19 (1H, ABdd, *J* 14.5, 6.3, C(2)H_B), 2.57-2.69 (2H, m, C(1′)H_2), 3.37-3.50 (4H, m, C(3)*H*, C(5)*H*, C(3′)H_2), 3.85 (1H, q, *J* 6.8, C(α)*H*), 4.53 (2H, app s, OCH_2Ph), 7.20-7.25 (1H, m, *Ph*), 7.26-7.32 (5H, m, *Ph*), 7.32-7.40 (4H, m, *Ph*); δ_C (125 MHz, CDCl$_3$) 13.1 (*C*(10)), 19.6 (C(α)*Me*), 21.7, 23.8, 31.1, 32.7 (*C*(6), *C*(7), *C*(8), *C*(9)), 27.1 (C*Me*$_3$), 32.3 (*C*(2′)), 35.8 (*C*(4)), 37.1 (*C*(2)), 42.4, 42.4 (*C*(1′), *C*(3′)), 51.8 (*C*(3)), 57.9 (*C*(α)), 69.9 (O*C*H$_2$Ph), 75.7 (*C*(5)), 79.1 (*C*Me$_3$), 125.9, 126.4, 126.8, 126.8, 127.1, 127.3 (*o,m,p-Ph*), 137.9, 143.8 (*i-Ph*), 170.8 (*C*(1)); *m/z* (ESI$^+$) 554 ([M(^{37}Cl)+Na]$^+$, 36%), 552 ([M(^{35}Cl)+Na]$^+$, 94%), 532 ([M(^{37}Cl)+H]$^+$, 100%), 530 ([M(^{35}Cl)+H]$^+$, 93%); HRMS (ESI$^+$) $C_{32}H_{49}{}^{37}ClNO_3^+$ ([M(^{37}Cl)+H]$^+$) requires 532.3366; found 532.3389; $C_{32}H_{49}{}^{35}ClNO_3^+$ ([M(^{35}Cl)+H]$^+$) requires 530.3395; found 530.3399.

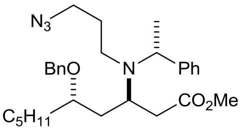
Method B: Following *general procedure 5*, (*R*)-**413** (190 mg, 962 μmol, >99:1 er), BuLi (2.3 M, 0.41 mL, 931 μmol) and (*R*)-**513** (200 mg, 602 μmol) were reacted in THF (5 mL). Purification via flash column chromatography (gradient elution, 2% → 10% Et$_2$O in 30-40 °C petrol) gave **519** as a colourless oil (267 mg, 84%, >99:1 dr).

Methyl (3*R*,5*S*,α*R*)-3-[*N*-(3′-chloropropyl)-*N*-(α-methylbenzyl)amino]-5-(benzyloxy)decanoate 516



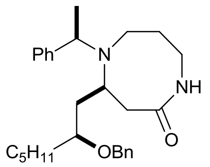
Following *general procedure 11*, **518** (5.93 g, 11.2 mmol, >99:1 dr) in MeOH (45 mL) and $SOCl_2$ (1.36 mL, 18.6 mmol) in MeOH (45 mL) were reacted. Purification via flash column chromatography (gradient elution, 0% → 6% Et_2O in 30-40 °C petrol) gave **516** as a colourless oil (3.91 g, 72%, >99:1 dr); $C_{29}H_{42}ClNO_3$ requires C, 71.4; H, 8.7; N, 2.9%; found C, 71.4; H, 8.7; N, 2.8%; $[\alpha]_D^{24}$ −11.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1733 (C=O); δ_H (400 MHz, $CDCl_3$) 0.95 (3H, t, *J* 7.1, C(10)H_3), 1.29-1.45 (6H, m, C(7)H_2, C(8)H_2, C(9)H_2) overlapping 1.42 (3H, d, *J* 6.9, C(α)*Me*), 1.52-1.74 (4H, m, C(4)H_2, C(6)H_2), 1.84-1.93 (2H, m, C(2′)H_2), 2.17 (1H, ABdd, *J* 14.5, 6.1, C(2)H_A), 2.24 (1H, ABdd, *J* 14.5, 7.8, C(2)H_B), 2.61-2.75 (2H, m, C(1′)H_2), 3.47-3.63 (4H, m, C(3)*H*, C(5)*H*, C(3′)H_2), 3.57 (3H, s, O*Me*), 3.92 (1H, q, *J* 6.9, C(α)*H*), 4.36 (1H, ABd, *J* 11.5, OC$H_A$$H_B$Ph), 4.56 (1H, ABd, *J* 11.5, OC$H_A$$H_B$Ph), 7.20-7.26 (1H, m, *Ph*), 7.26-7.33 (5H, m, *Ph*), 7.34-7.40 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(10)), 19.9 (C(α)*Me*), 22.7, 24.7, 32.2 (*C*(7), *C*(8), *C*(9)), 32.9 (*C*(2′)), 33.7, 37.8 (*C*(4), *C*(6)), 37.5 (*C*(2)), 42.8 (*C*(3′)), 43.2 (*C*(1′)), 51.4 (O*Me*), 52.8 (*C*(3)), 58.3 (*C*(α)), 69.8 (O*C*H_2Ph), 76.9 (*C*(5)), 127.0, 127.3, 127.5, 127.8, 128.2, 128.3 (*o,m,p-Ph*), 139.1, 144.0 (*i-Ph*), 173.0 (*C*(1)); *m/z* (FI^+) 489 ($[M(^{37}Cl)]^+$, 32%), 487 ($[M(^{35}Cl)]^+$, 100%); HRMS (FI^+) $C_{29}H_{42}{}^{37}ClNO_3^+$ ($[M(^{37}Cl)]^+$) requires 489.2818; found 489.2833; $C_{29}H_{42}{}^{35}ClNO_3^+$ ($[M(^{35}Cl)]^+$) requires 487.2848; found 487.2867.

Methyl (3*R*,5*S*,α*R*)-3-[*N*-(3′-azidopropyl)-*N*-(α-methylbenzyl)amino]-5-(benzyloxy)decanoate 540



Following *general procedure 12*, NaN_3 (783 mg, 12.0 mmol), NaI (1.80 g, 12.0 mmol) and **516** (2.94 g, 6.02 mmol, >99:1 dr) were reacted in DMSO (10 mL). Purification via flash column chromatography (gradient elution, 0% → 6% Et_2O in 30-40 °C petrol) gave **540** as a yellow oil (2.36 g, 79%, >99:1 dr); $[\alpha]_D^{24}$ −9.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2095 (N≡N), 1736 (C=O); δ_H (400 MHz, $CDCl_3$) 0.93 (3H, t, *J* 6.8, C(10)H_3), 1.27-1.43 (6H, m, C(7)H_2, C(8)H_2, C(9)H_2) overlapping 1.39 (3H, d, *J* 6.8, C(α)*Me*), 1.50-1.75 (6H, m, C(4)H_2, C(6)H_2, C(2′)H_2), 2.19 (1H, ABdd, *J* 14.5, 6.3, C(2)H_A), 2.25 (1H, ABdd, *J* 14.5, 7.3, C(2)H_B), 2.58 (2H, t, *J* 7.6, C(1′)H_2), 3.23 (2H, t, *J* 6.6, C(3′)H_2), 3.50-3.59 (2H, m, C(3)*H*, C(5)*H*), 3.56 (3H, s, O*Me*), 3.90 (1H, q, *J* 6.8, C(α)*H*), 4.34 (1H, ABd, *J* 11.4, OCH_AH$_B$Ph), 4.53 (1H, ABd, *J* 11.4, OCH$_A$$H_B$Ph), 7.19-7.25 (1H, m, *Ph*), 7.25-7.31 (5H, m, *Ph*), 7.32-7.38 (4H, m, *Ph*); δ_C (100 MHz, CDCl$_3$) 14.1 (*C*(10)), 19.7 (C(α)*Me*), 22.7, 24.7, 29.2, 32.1, 33.7, 37.6 (*C*(4), *C*(6), *C*(7), *C*(8), *C*(9), *C*(2′)), 37.7 (*C*(2)), 42.9 (*C*(1′)), 49.4 (*C*(3′)), 51.4 (O*Me*), 53.0 (*C*(3)), 58.3 (*C*(α)), 69.9 (O*C*H$_2$Ph), 77.0 (*C*(5)), 127.0, 127.3, 127.5, 127.8, 128.2, 128.3 (*o,m,p-Ph*), 139.0, 144.1 (*i-Ph*), 173.0 (*C*(1)); *m/z* (ESI$^+$) 517 ([M+Na]$^+$, 100%) 495 ([M+H]$^+$, 95%); HRMS (ESI$^+$) $C_{29}H_{43}N_4O_3^+$ ([M+H]$^+$) requires 495.3330; found 495.3331.

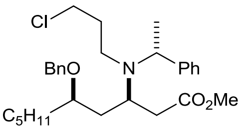
(4*R*,2′*S*,α*R*)-4-[2′-(Benzyloxy)heptyl]-*N*(5)-(α-methylbenzyl)-1,5-diazocan-2-one 542



Following *general procedure 13*, **540** (2.55 g, 5.16 mmol, >99:1 dr) and PBu$_3$ (1.32 mL, 5.28 mmol) were reacted in THF (15 mL) and H_2O (1.7 mL) to give **541** as a yellow oil (3.54 g, >99:1 dr); δ_H (400 MHz, CDCl$_3$) [selected peaks] 2.13-2.24 (2H, m, C(2)H_2), 2.52 (2H, td, *J* 7.3, 2.4, C(3′)H_2), 2.59-2.67 (2H, m, C(1′)H_2), 3.47-3.58 (2H, m, C(3)*H*, C(5)*H*) overlapping 3.54 (3H, s, O*Me*), 3.92 (1H, q, *J* 6.8, C(α)*H*), 4.32 (1H, ABd, *J* 11.4, OCH_AH$_B$Ph), 4.51 (1H, ABd, *J* 11.4, OCH$_A$$H_B$Ph), 7.16-7.36 (10H, m, *Ph*).

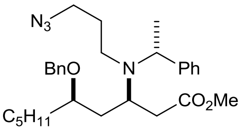
Following *general procedure 14*, **541** (3.54 g, >99:1 dr) and Sb(OEt)$_3$ (0.87 mL, 5.12 mmol) were reacted in PhMe (450 mL). Purification via flash column chromatography (eluent EtOAc) gave **542** as a yellow oil (1.86 g, 83% over 2 steps, >99:1 dr); $C_{28}H_{40}N_2O_2$ requires C, 77.0; H, 9.2; N, 6.4%; found C, 76.9; H, 9.2; N, 6.4%; $[\alpha]_D^{24}$ +2.5 (*c* 1.0 in CHCl$_3$); ν_{max} (ATR) 1658 (C=O); δ_H (400 MHz, CDCl$_3$) 0.90 (3H, t, *J* 6.8, C(7′)H_3), 1.02-1.12 (1H, m, C(7)H_A), 1.19-1.63 (12H, m, C(7)H_B, C(3′)H_2, C(4′)H_2, C(5′)H_2, C(6′)H_2, C(α)*Me*), 1.63-1.72 (1H, m, C(1′)H_A), 1.85 (1H, br s, C(1′)H_B), 2.50-2.61 (3H, m, C(3)H_2, C(6)H_A), 2.81-2.90 (1H, m, C(6)H_B), 3.17-3.32 (2H, m, C(8)H_2), 3.46 (1H, app quin, *J* 5.8, C(2′)*H*), 3.54-3.64 (1H, m, C(4)*H*), 3.74 (1H, q, *J* 6.5, C(α)*H*), 4.50 (1H, ABd, *J* 11.4, OCH_AH$_B$Ph), 4.55 (1H, ABd, *J* 11.4, OCH$_A$$H_B$Ph), 5.55-5.66 (1H, m, N*H*), 7.19-7.24 (1H, m, *Ph*), 7.25-7.30 (4H, m, *Ph*), 7.31-7.39 (5H, m, *Ph*); δ_C (100 MHz, CDCl$_3$) 14.2 (*C*(7′)), *21.9* (C(α)*Me*), 22.7, 24.8, 32.0, 34.0 (*C*(3′), *C*(4′), *C*(5′), *C*(6′)), 32.4 (*C*(7)), 33.2 (*C*(1′)), *38.8* (*C*(3)), *42.5* (*C*(8)), *45.6* (*C*(6)), *54.2* (*C*(4)), *62.5* (*C*(α)), 70.5 (O*C*H$_2$Ph), 77.5 (*C*(2′)), 126.9, 127.4, 127.9, 128.0, 128.1, 128.3 (*o,m,p-Ph*), 138.9, *146.2* (*i-Ph*), 176.9 (*C*(2)); *m/z* (ESI$^+$) 896 ([2M+Na]$^+$, 100%), 874 ([2M+H]$^+$, 18%), 459 ([M+Na]$^+$, 96%), 437 ([M+H]$^+$, 94%); HRMS (ESI$^+$) $C_{28}H_{41}N_2O_2^+$ ([M+H]$^+$) requires 437.3163; found 437.3175.

Methyl (*R*,*R*,*R*)-3-[*N*-(3′-chloropropyl)-*N*-(α-methylbenzyl)amino]-5-(benzyloxy)decanoate 517



Following *general procedure 11*, **519** (3.45 g, 10.8 mmol) in MeOH (25 mL) and $SOCl_2$ (0.79 mL, 10.8 mmol) in MeOH (25 mL) were reacted. Purification via flash column chromatography (gradient elution, 0% → 6% Et_2O in 30-40 °C petrol) gave **517** as a yellow oil (2.25 g, 71%, >99:1 dr); $C_{29}H_{42}ClNO_3$ requires C, 71.4; H, 8.7; N, 2.9%; found C, 71.3; H, 8.6; N, 2.7%; $[\alpha]_D^{24}$ −30.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1735 (C=O); δ_H (400 MHz, $CDCl_3$) 0.94 (3H, t, *J* 7.3, C(10)H_3), 1.26-1.59 (9H, m, C(4)H_A, C(6)H_2, C(7)H_2, C(8)H_2, C(9)H_2) overlapping 1.41 (3H, d, *J* 6.8, C(α)*Me*), 1.75-1.83 (1H, m, C(2′)H_A), 1.85-1.96 (2H, m, C(4)H_B, C(2′)H_B), 2.22 (1H, ABdd, *J* 14.4, 6.3, C(2)H_A), 2.29 (1H, ABdd, *J* 14.4, 7.3, C(2)H_B), 2.63-2.75 (2H, m, C(1′)H_2), 3.41-3.47 (1H, m, C(5)*H*), 3.51 (2H, app t, *J* 6.3, C(3)*H*, C(3′)H_2), 3.54 (3H, s, O*Me*), 3.90 (1H, q, *J* 6.8, C(α)*H*), 4.49 (1H, ABd, *J* 11.5, OCH_AH$_B$Ph), 4.59 (1H, ABd, *J* 11.5, OCH$_A$$H_B$Ph), 7.21-7.26 (1H, m, *Ph*), 7.26-7.33 (5H, m, *Ph*), 7.34-7.40 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(10)), 19.0 (C(α)*Me*), 22.7, 24.7, 32.1, 33.7 (*C*(6), *C*(7), *C*(8), *C*(9)), 33.0 (*C*(2′)), 37.3 (*C*(4)), 37.4 (*C*(2)), 43.1 (*C*(1′)), 43.3 (*C*(3′)), 51.4 (O*Me*), 52.3 (*C*(3)), 58.4 (*C*(α)), 71.0 (O*C*H_2Ph), 76.7 (*C*(5)), 126.8, 127.5, 127.8, 127.8, 128.1, 128.3 (*o,m,p-Ph*), 144.7, 138.9 (*i-Ph*), 172.9 (*C*(1)); *m/z* (ESI^+) 512 ($[M(^{37}Cl)+Na]^+$, 34%) 510 ($[M(^{35}Cl)+Na]^+$, 81%), 490 ($[M(^{37}Cl)+H]^+$, 44%), 488 ($[M(^{35}Cl)+H]^+$, 100%); HRMS (ESI^+) $C_{29}H_{43}{}^{37}ClNO_3^+$ ($[M(^{37}Cl)+H]^+$) requires 490.2896; found 490.2905; $C_{29}H_{43}{}^{35}ClNO_3^+$ ($[M(^{35}Cl)+H]^+$) requires 488.2926; found 488.2921.

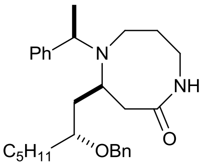
Methyl (*R*,*R*,*R*)-3-[*N*-(3′-azidopropyl)-*N*-(α-methylbenzyl)amino]-5-(benzyloxy)decanoate 543



Following *general procedure 12*, NaN_3 (557 mg, 8.56 mmol), NaI (1.28 g, 8.56 mmol) and **517** (2.09 g, 4.28 mmol, >99:1 dr) were reacted in DMSO (8 mL). Purification via flash column chromatography (gradient elution, 0% → 6% Et_2O in 30-40 °C petrol) gave **543** as a yellow oil (1.93 g, 91%, >99:1 dr); $C_{29}H_{42}N_4O_3$ requires C, 70.4; H, 8.6; N, 11.3%; found C, 70.5; H, 8.4; N, 11.3%; $[\alpha]_D^{24}$ −33.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2095 (N≡N), 1737 (C=O); δ_H (400 MHz, $CDCl_3$) 0.94 (3H, t, *J* 7.3, C(10)H_3), 1.26-1.62 (10H, m, C(4)H_A, C(6)H_2, C(7)H_2, C(8)H_2, C(9)H_2, C(2′)H_A) overlapping 1.41 (3H, d, *J* 6.8, C(α)*Me*), 1.64-1.73 (1H, m, C(2′)H_B), 1.84-1.91 (1H, m, C(4)H_B), 2.23 (1H, ABdd, *J* 14.4, 6.3, C(2)H_A), 2.29 (1H, ABdd, *J* 14.4, 7.6, C(2)H_B), 2.54-2.66 (2H, m, C(1′)H_2), 3.23 (2H, t, *J* 6.6, C(3′)H_2), 3.39-3.46 (1H, m, C(5)*H*), 3.52-3.59 (1H, m, C(3)*H*), 3.55

(3H, s, O*Me*), 3.90 (1H, q, *J* 6.8, C(α)*H*), 4.48 (1H, ABd, *J* 11.4, OC*H*$_{\mathrm{A}}$H$_{\mathrm{B}}$Ph), 4.60 (1H, ABd, *J* 11.4, OCH$_{\mathrm{A}}$*H*$_{\mathrm{B}}$Ph), 7.21-7.26 (1H, m, *Ph*), 7.27-7.33 (5H, m, *Ph*), 7.34-7.40 (4H, m, *Ph*); δ_{C} (100 MHz, CDCl$_3$) 14.1 (*C*(10)), 18.9 (C(α)*Me*), 22.7, 24.7, 32.1, 33.7 (*C*(6), *C*(7), *C*(8), *C*(9)), 29.2 (*C*(2′)), 37.1 (*C*(4)), 37.5 (*C*(2)), 43.0 (*C*(1′)), 49.4 (*C*(3′)), 51.4 (O*Me*), 52.2 (*C*(3)), 58.3 (*C*(α)), 71.0 (O*C*H$_2$Ph), 76.7 (*C*(5)), 126.8, 127.5, 127.8, 127.9, 128.1, 128.3 (*o,m,p-Ph*), 138.9, 144.8 (*i-Ph*), 172.9 (*C*(1)); *m/z* (ESI$^+$) 517 ([M+Na]$^+$, 100%) 495 ([M+H]$^+$, 97%); HRMS (ESI$^+$) C$_{29}$H$_{43}$N$_4$O$_3^+$ ([M+H]$^+$) requires 495.3330; found 495.3326.

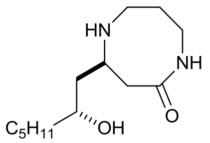
(*R*,*R*,*R*)-4-[2′-(Benzyloxy)heptyl]-*N*(5)-(α-methylbenzyl)-1,5-diazocan-2-one 545



Following *general procedure 13*, **543** (2.45 g, 4.95 mmol, >99:1 dr) and PBu$_3$ (1.32 mL, 5.28 mmol) were reacted in THF (15mL) and H$_2$O (1.7 mL) to give **544** as a yellow oil (3.48 g, >99:1 dr); δ_{H} (400 MHz, CDCl$_3$) [selected peaks] 2.17 (1H, ABdd, *J* 14.3, 6.7, C(2)*H*$_{\mathrm{A}}$), 2.25 (1H, ABdd, *J* 14.3, 7.2, C(2)*H*$_{\mathrm{B}}$), 2.48-2.65 (4H, m, C(1′)*H*$_2$, C(3′)*H*$_2$), 3.35-3.50 (2H, m, C(3)*H*, C(5)*H*), 3.52 (3H, s, O*Me*), 3.91 (1H, q, *J* 6.8, C(α)*H*), 4.45 (1H, ABd, *J* 11.4, OC*H*$_{\mathrm{A}}$H$_{\mathrm{B}}$Ph), 4.55 (1H, ABd, *J* 11.4, OCH$_{\mathrm{A}}$*H*$_{\mathrm{B}}$Ph), 7.17-7.37 (10H, m, *Ph*).

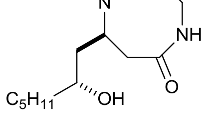
Following *general procedure 14*, **544** (3.48 g, >99:1 dr) and Sb(OEt)$_3$ (0.87 mL, 5.12 mmol) were reacted in PhMe (450 mL). Purification via flash column chromatography (eluent EtOAc) gave **545** as a yellow oil (1.80 g, 83% over 2 steps, >99:1 dr); $[\alpha]^{24}_{\mathrm{D}}$ −16.9 (*c* 1.0 in CHCl$_3$); ν_{max} (ATR) 1661 (C=O); δ_{H} (400 MHz, CDCl$_3$) 0.91 (3H, t, *J* 7.0, C(7′)*H*$_3$), 1.06-1.16 (1H, br m, C(7)*H*$_{\mathrm{A}}$), 1.24-1.45 (7H, m, C(7)*H*$_{\mathrm{B}}$, C(4′)*H*$_2$, C(5′)*H*$_2$, C(6′)*H*$_2$) overlapping 1.37 (3H, d, *J* 6.6, C(α)*Me*), 1.49-1.59 (1H, m, C(1′)*H*$_{\mathrm{A}}$), 1.62-1.76 (3H, m, C(1′)*H*$_{\mathrm{B}}$, C(3′)*H*$_2$), 2.33 (1H, br s, C(3)*H*$_{\mathrm{A}}$), 2.49 (1H, ABdd, *J* 12.4, 4.3, C(3)*H*$_{\mathrm{B}}$), 2.52-2.60 (1H, m, C(6)*H*$_{\mathrm{A}}$), 2.77 (1H, br t, *J* 13.1, C(6)*H*$_{\mathrm{B}}$), 3.12-3.23 (1H, br m, C(8)*H*$_{\mathrm{A}}$), 3.39 (1H, br s, C(8)*H*$_{\mathrm{B}}$), 3.49-3.58 (1H, m, C(2′)*H*), 3.69-3.83 (2H, m, C(4)*H*, C(α)*H*), 4.44 (1H, ABd, *J* 11.4, OC*H*$_{\mathrm{A}}$H$_{\mathrm{B}}$Ph), 4.62 (1H, ABd, *J* 11.4, OCH$_{\mathrm{A}}$*H*$_{\mathrm{B}}$Ph), 5.51 (1H, br s, N*H*), 7.19-7.24 (1H, m, *Ph*), 7.25-7.30 (4H, m, *Ph*), 7.31-7.35 (5H, m, *Ph*); δ_{C} (100 MHz, CDCl$_3$) 14.2 (*C*(7′)), *22.7* (C(α)*Me*), 24.7, 32.4 (*C*(4′), *C*(5′), *C*(6′)),[78] 32.2 (*C*(7)), 33.5 (*C*(3′)), 34.4 (*C*(1′)), 38.3 (*C*(3)), *41.7* (*C*(8)), *45.0* (*C*(6)), *52.4* (*C*(4)), 62.6 (*C*(α)), 71.1 (O*C*H$_2$Ph), 76.7 (*C*(2′)), 126.8, 127.4, 127.8, 128.0, 128.1, 128.3 (*o,m,p-Ph*), 138.9, *146.2* (*i-Ph*), 176.7 (*C*(2)); δ_{H} (500 MHz, PhMe–*d*$_8$, 363 K) 0.78-0.85 (1H, m, C(7)*H*$_{\mathrm{A}}$), 0.94 (3H, t, *J* 6.6, C(7′)*H*$_3$), 1.10-1.19 (1H, m, C(7)*H*$_{\mathrm{B}}$), 1.30-1.84 (10H, m, C(1′)*H*$_2$, C(3′)*H*$_2$, C(4′)*H*$_2$, C(5′)*H*$_2$, C(6′)*H*$_2$) overlapping 1.34 (3H, d, *J* 6.6, C(α)*Me*), 2.25 (1H, ABdd, *J* 12.5, 7.6, C(3)*H*$_{\mathrm{A}}$), 2.41 (1H, ABdd, *J* 12.5, 4.1, C(3)H_B), 2.46 (1H, ABdt, *J* 14.1, 3.2, C(6)H_A), 2.65 (1H, ABtd, *J* 14.1, 2.8, C(6)H_B), 2.69-2.76 (1H, m, C(8)H_A), 3.07-3.16 (1H, m, C(8)H_B), 3.55-3.62 (1H, m, C(2′)*H*), 3.70-3.79 (2H, m, C(4)*H*, C(α)*H*), 4.36 (1H, ABd, *J* 11.7, OCH_AH_BPh), 4.53 (1H, ABd, *J* 11.7, OCH_AH_BPh), 5.72 (1H, br s, N*H*), 7.05-7.13 (2H, m, *Ph*), 7.16 (2H, app t, *J* 7.6, *Ph*), 7.20 (2H, t, *J* 7.3, *Ph*), 7.29 (4H, app dd, *J* 14.5, 7.3, *Ph*); δ_C (125 MHz, PhMe–d_8, 363 K) 14.0 (*C*(7′)), 20.6 (C(α)*Me*), 22.9, 25.0, 33.2, 34.6, 34.9 (*C*(1′), *C*(3′), *C*(4′), *C*(5′), *C*(6′)), 32.5 (*C*(7)), 38.5 (*C*(3)), 41.2 (*C*(8)), 44.3 (*C*(6)), 53.1 (*C*(4)), 63.1 (*C*(α)), 71.4 (O*C*H$_2$Ph), 77.4 (*C*(2′)), 126.9, 127.4, 128.0, 128.2, 128.4, 128.4 (*o,m,p-Ph*), 139.9, 146.6 (*i-Ph*), 174.9 (*C*(2)); *m/z* (ESI$^+$) 896 ([2M+Na]$^+$, 97%) 459 ([M+Na]$^+$, 100%), 437 ([M+H]$^+$, 91%); HRMS (ESI$^+$) $C_{28}H_{41}N_2O_2^+$ ([M+H]$^+$) requires 437.3163; found 437.3159.

(*R*,*R*)-4-[2′-(Hydroxy)heptyl]-1,5-diazocan-2-one 546



Following *general procedure 17*, **545** (140 mg, 321 µmol, >99:1 dr) and Pd(OH)$_2$/C (70 mg) were reacted in MeOH (2.1 mL) for 24 h to give **546** as a white solid (49 mg, 63%, >99:1 dr); mp 84-86 °C $[\alpha]_D^{24}$ +7.9 (*c* 1.0 in CHCl$_3$); ν_{max} (ATR) 3289 (N−H, O−H), 1651 (C=O); δ_H (400 MHz, CDCl$_3$) 0.84 (3H, t, *J* 7.3, C(7′)H_3), 1.18-1.55 (10H, m, C(1′)H_2, C(3′)H_2, C(4′)H_2, C(5′)H_2, C(6′)H_2), 1.61-1.74 (2H, m, C(7)H_2), 2.36 (1H, ABdd, *J* 12.5, 2.7, C(3)H_A), 2.53 (1H, ABdd, *J* 12.5, 9.7, C(3)H_B), 2.63-2.71 (1H, m, C(6)H_A), 3.06 (1H, dt, *J* 10.4, 4.4, C(6)H_B), 3.21-3.31 (2H, m, C(4)*H*, C(8)H_A), 3.40-3.50 (1H, m, C(8)H_B), 3.59-3.99 (3H, br m, C(2′)*H*, N(5)*H*, O*H*), 6.88 (1H, br s, N(1)*H*); δ_C (100 MHz, CDCl$_3$) 14.0 (*C*(7′)), 22.6, 25.0, 31.8, 38.0 (*C*(3′), *C*(4′), *C*(5′), *C*(6′)), 33.9 (*C*(7)), 40.9 (*C*(3)), 41.0 (*C*(8)), 41.4 (*C*(1′)), 42.8 (*C*(6)), 58.9 (*C*(4)), 72.4 (*C*(2′)), 175.9 (*C*(2)); *m/z* (ESI$^+$) 750 ([3M+Na]$^+$, 44%), 507 ([2M+Na]$^+$, 100%), 485 ([M+H]$^+$, 93%), 265 ([M+Na]$^+$, 51%), 243 ([M+H]$^+$, 97%); HRMS (ESI$^+$) $C_{13}H_{27}N_2O_2^+$ ([M+H]$^+$) requires 243.2067; found 243.2071.

(*R*,*R*)-4-[2′-(Hydroxy)heptyl]-*N*(5)-methyl-1,5-diazocan-2-one 547

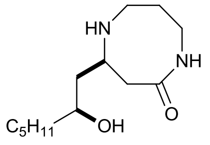


Method A: Following *general procedure 18*, **546** (97 mg, 400 µmol, >99:1 dr), (CH$_2$O)$_n$ (24 mg, 799 µmol) and NaBH$_3$CN (101 mg, 1.61 mmol) were reacted in MeOH (4 mL). Purification via flash column chromatography (eluent CH$_2$Cl$_2$/MeOH, 19:1) gave **547** as a colourless oil (46 mg, 45%, >99:1 dr); $[\alpha]_D^{24}$ −1.2 (*c* 1.0 in CHCl$_3$); ν_{max} (ATR) 3291 (O−H), 1657 (C=O); δ_H (400 MHz, CDCl$_3$) 0.79 (3H, t, *J* 6.5, C(7′)H_3), 1.12-1.40 (9H, m, C(1′)H_A, C(3′)H_2, C(4′)H_2, C(5′)H_2, C(6′)H_2), 1.43-2.57 (2H, m, C(7)H_A, C(1′)H_B), 1.88-1.99 (1H, m, C(7)H_B), 2.20-2.43 (2H, m, C(3)H_2), 2.45 (3H, s, N*Me*), 2.72 (1H, app br d, *J* 15.4, C(6)H_A), 2.97 (1H, app br t, *J* 12.4, C(6)H_B), 3.17-3.34 (3H, m, C(4)*H*, C(8)H_2), 3.68 (1H, br s, C(2′)*H*), 7.18 (1H, br s, N*H*); δ_C (100 MHz, CDCl$_3$) 14.0 (*C*(7′)), 22.6, 25.0, 29.6, 31.8, 37.9 (*C*(7), *C*(1′), *C*(3′), *C*(4′), *C*(5′), *C*(6′)),[79] *36.7* (*C*(3)), *39.0* (N*Me*), *41.9* (*C*(8)), *45.4* (*C*(6)), 63.4 (*C*(4)), 72.5 (*C*(2′)), 176.5 (*C*(2)); *m/z* (ESI$^+$) 535 ([2M+Na]$^+$, 25%), 279 ([M+Na]$^+$, 59%), 257 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{29}N_2O_2^+$ ([M+Na]$^+$) requires 257.2224; found 257.2219.

Method B: Following *general procedure 17*, **545** (150 mg, 344 μmol, >99:1 dr), $(CH_2O)_n$ (21 mg, 699 μmol) and Pd(OH)$_2$/C (75 mg) were reacted in MeOH (2.0 mL) for 72 h. Purification via flash column chromatography (gradient elution, 1% → 8% MeOH in CH$_2$Cl$_2$) gave **548** as a colourless oil (12 mg, 14%, >99:1 dr); $[\alpha]_D^{24}$ −26.7 (*c* 0.6 in CHCl$_3$); ν_{max} (ATR) 1663 (C=O); δ_H (500 MHz, CDCl$_3$) 0.88 (3H, t, *J* 7.3, CH_3), 1.23-1.55 (10H, m, C(4)H_2, C(3)CH_2CH_2CH_2CH_2), 1.59-1.66 (1H, m, C(9)H_A), 1.69-1.78 (1H, m, C(9)H_B), 2.27 (1H, br s, C(5)H_A), 2.59 (1H, br t, *J* 10.7, C(5)H_B), 2.85 (2H, br s, C(10)H_2), 3.21-3.47 (4H, m, C(3)*H*, C(4a)*H*, C(8)H_2), 4.23 (1H, br d, *J* 9.2, C(1)H_A), 4.46 (1H, ABd, *J* 9.2, C(1)H_B), 5.98 (1H, br s, N*H*); δ_C (125 MHz, CDCl$_3$) 14.0 (*C*H$_3$), 22.6, 24.7, 31.8, *33.2* (C(3)*C*H$_2$*C*H$_2$*C*H$_2$*C*H$_2$), *33.7* (*C*(9)), 36.2 (*C*(4)), *38.7* (*C*(5)), *42.8* (*C*(8)), *47.4* (*C*(10)), *58.6* (*C*(4a)), 77.0 (*C*(3)), 87.7 (*C*(1)), 175.3 (*C*(6)); *m/z* (ESI$^+$) 531 ([2M+Na]$^+$, 88%), 509 ([2M+H]$^+$, 54%), 277 ([M+Na]$^+$, 100%), 255 ([M+H]$^+$, 86%); HRMS (ESI$^+$) $C_{14}H_{27}N_2O_2^+$ ([M+H]$^+$) requires 255.2067; found 255.2068. Further elution gave **547** as a colourless oil (26 mg, 29%, >99:1 dr).

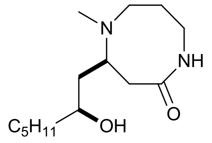
Method C: Following *general procedure 17,* **545** (750 mg, 1.72 mmol, >99:1 dr), $(CH_2O)_n$ (98 mg, 3.26 mmol) and Pd(OH)$_2$/C (375 mg) were reacted in AcOH (11.3 mL) for 24 h. The residue was partitioned between CHCl$_3$ (10 mL) and sat aq NaHCO$_3$ (10 mL). The aqueous layer was extracted with CHCl$_3$ (2 × 10 mL) and the combined organic extracts were dried (Na$_2$SO$_4$) and concentrated *in vacuo* to give **547** as a colourless oil (395 mg, 90%, >99:1 dr).

(4*R*,2′*S*)-4-[2′-(Hydroxy)heptyl]-1,5-diazocan-2-one 549



Following *general procedure 17,* **542** (160 mg, 366 μmol, >99:1 dr) and Pd(OH)$_2$/C (80 mg) were reacted in MeOH (2 mL) to give **549** as a colourless oil (72 mg, 81%, >99:1 dr); $[\alpha]_D^{24}$ +13.4 (*c* 1.0 in CHCl$_3$); ν_{max} (ATR) 3298 (N−H, O−H), 1649 (C=O); δ_H (400 MHz, CDCl$_3$) 0.83 (3H, t, *J* 6.8, C(7′)H_3), 1.16-1.77 (12H, m, C(7)H_2, C(1′)H_2, C(3′)H_2, C(4′)H_2, C(5′)H_2, C(6′)H_2), 2.37 (1H, app ABd, *J* 12.1, C(3)H_{A}), 2.51-2.63 (2H, m, C(3)H_{B}, C(6)H_{A}), 3.03-3.12 (1H, m, C(6)H_{B}), 3.20-3.30 (1H, m, C(8)H_{A}), 3.30-3.39 (1H, m, C(4)*H*), 3.41-3.54 (1H, m, C(8)H_{B}), 3.69-3.77 (1H, m, C(2′)*H*), 4.06 (2H, br s, N(5)*H*, O*H*), 6.86 (1H, br s, N(1)*H*); δ_{C} (100 MHz, $CDCl_3$) 14.0 (*C*(7′)), 22.6, 25.5, 31.8, 33.2, 37.5 (*C*(7), *C*(3′), *C*(4′), *C*(5′), *C*(6′)), 39.6 (*C*(3)), 40.4 (*C*(8)), 41.8 (*C*(1′)), 43.1 (*C*(6)), 55.7 (*C*(4)), 68.7 (*C*(2′)), 176.4 (*C*(2)); *m/z* (ESI^+) 750 ($[3M+Na]^+$, 10%), 727 ($[3M+H]^+$, 4%), 507 ($[2M+Na]^+$, 100%), 265 ($[M+Na]^+$, 24%), 243 ($[M+H]^+$, 22%); HRMS (ESI^+) $C_{13}H_{27}N_2O_2^+$ ($[M+H]^+$) requires 243.2067; found 243.2066.

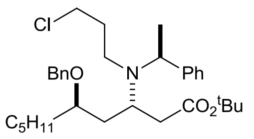
(4*R*,2′*S*)-4-[2′-(Hydroxy)heptyl]-*N*(5)-methyl-1,5-diazocan-2-one 550

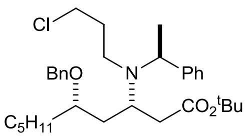


Method A: Following *general procedure 18*, **549** (70 mg, 289 µmol, >99:1 dr), $(CH_2O)_n$ (17 mg, 578 µmol) and $NaBH_3CN$ (73 mg, 1.16 mmol) were reacted in MeOH (3 mL). Purification via flash column chromatography (eluent CH_2Cl_2/MeOH, 19:1) gave **550** as a colourless oil (30 mg, 40%, >99:1 dr); $[\alpha]_{\mathrm{D}}^{24}$ −1.2 (*c* 1.0 in $CHCl_3$); $\nu_{\max}$ (ATR) 3293 (O−H), 1654 (C=O); δ_{H} (400 MHz, $CDCl_3$) 0.79 (3H, t, *J* 6.6, C(7′)H_3), 1.15-1.50 (10H, m, C(7)H_{A}, C(1′)H_{A}, C(3′)H_2, C(4′)H_2, C(5′)H_2, C(6′)H_2), 1.70-1.85 (2H, m, C(7)H_{B}, C(1′)H_{B}), 2.40 (5H, app s, C(3)H_2, N*Me*), 2.57 (1H, br dt, *J* 15.4, 3.5, C(6)H_{A}), 2.85 (1H, app br t, *J* 12.1, C(6)H_{B}), 3.16-3.28 (3H, m, C(4)*H*, C(8)H_2), 3.57 (1H, br s, C(2′)*H*), 3.89 (1H, br s, O*H*), 7.05 (1H, br t, *J* 6.6, N*H*); δ_{C} (100 MHz, $CDCl_3$) 14.0 (*C*(7′)), 22.6, 25.6, 30.4, 31.9, *36.9*, 37.7 (*C*(7), *C*(1′), *C*(3′), *C*(4′), *C*(5′), *C*(6′)), *37.2* (*C*(3)), *40.1* (N*Me*), *41.6* (*C*(8)), *45.7* (*C*(6)), 60.0 (*C*(4)), 70.0 (*C*(2′)), 177.1 (*C*(2)); *m/z* (ESI^+) 535 ($[2M+Na]^+$, 44%), 279 ($[M+Na]^+$, 65%), 257 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{14}H_{29}N_2O_2^+$ ($[M+Na]^+$) requires 257.2224; found 257.2220.

Method B: Following *general procedure 17*, **542** (154 mg, 353 µmol, >99:1 dr), $(CH_2O)_n$ (20 mg, 666 µmol) and $Pd(OH)_2/C$ (77 mg) were reacted in AcOH (2.3 mL) for 24 h. The residue was partitioned between $CHCl_3$ (10 mL) and sat aq $NaHCO_3$ (10 mL). The aqueous layer was extracted with $CHCl_3$ (2 × 10 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give **550** as a colourless oil (90 mg, quant, >99:1 dr).

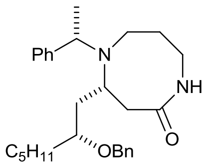
***tert*-Butyl (3*S*,5*R*,α*S*)-3-[*N*-(3′-chloropropyl)-*N*-(α-methylbenzyl)amino]-5-(benzyloxy)decanoate *ent*-518 and *tert*-Butyl (*S*,*S*,*S*)-3-[*N*-(3′-chloropropyl)-*N*-(α-methylbenzyl)amino]-5-(benzyloxy)decanoate *ent*-519**


ent-**518**


ent-**519**

Following *general procedure 5*, (*S*)-**413** (5.44 g, 27.6 mmol, >99:1 er), BuLi (2.1 M, 12.6 mL, 26.5 mmol) and (±)-**513** (6.91 g, 20.8 mmol) were reacted in THF (190 mL) to give a 50:50 mixture of *ent*-**518**:*ent*-**519**. Purification via flash column chromatography (gradient elution, 5% → 6.25% Et_2O in 30-40 °C petrol) gave *ent*-**518** as a yellow oil (4.36 g, 40%, >99:1 dr); $[\alpha]_D^{24}$ +13.3 (*c* 1.0 in $CHCl_3$). Further elution gave *ent*-**519** as a yellow oil (3.94 g, 36%, >99:1 dr); $[\alpha]_D^{24}$ +16.7 (*c* 1.0 in $CHCl_3$).

(4*S*,2′*R*,α*S*)-4-[2′-(Benzyloxy)heptyl]-*N*(5)-(α-methylbenzyl)-1,5-diazocan-2-one *ent*-542



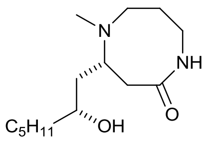
Following *general procedure 11*, *ent*-**518** (4.36 g, 8.22 mmol, >99:1 dr) in MeOH (35 mL) and $SOCl_2$ (1.05 mL, 14.5 mmol) in MeOH (35 mL) were reacted to give *ent*-**516** as a yellow oil (4.20 g, >99:1 dr).

Following *general procedure 12*, NaN_3 (1.16 g, 17.9 mmol), NaI (2.68 g, 17.9 mmol) and *ent*-**516** (4.20 g, >99:1 dr) were reacted in DMSO (10 mL) to give *ent*-**540** as a yellow oil (3.66 g, >99:1 dr).

Following *general procedure 13*, *ent*-**540** (3.66 g, >99:1 dr) and PBu_3 (2.03 mL, 8.13 mmol) were reacted in THF (30 mL) and H_2O (8.0 mL) to give *ent*-**541** as a yellow oil (3.46 g, >99:1 dr).

Following *general procedure 14*, *ent*-**541** (3.46 g, >99:1 dr) and $Sb(OEt)_3$ (1.50 mL, 8.77 mmol) were reacted in PhMe (650 mL). Purification via flash column chromatography (eluent EtOAc) gave *ent*-**542** as a yellow oil (2.48 g, 69% over 4 steps, >99:1 dr); $[\alpha]_D^{24}$ +16.0 (*c* 1.0 in $CHCl_3$).

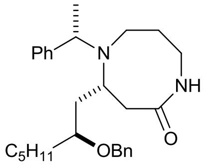
(*S*,*R*)-4-[2′-(Hydroxy)heptyl]-*N*(5)-methyl-1,5-diazocan-2-one *ent*-550



Following *general procedure 17*, *ent*-**542** (50 mg, 115 µmol, >99:1 dr), $(CH_2O)_n$ (7 mg, 233 µmol) and $Pd(OH)_2/C$ (25 mg) were reacted in AcOH (0.75 mL) for 24 h. The residue was partitioned between $CHCl_3$ (4 mL) and sat aq $NaHCO_3$ (4 mL) and the aqueous layer was extracted with $CHCl_3$

(2 × 4 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give *ent*-**550** as a colourless oil (25 mg, 85%, >99:1 dr); $[\alpha]_D^{24}$ +1.3 (*c* 1.0 in $CHCl_3$).

(*S*,*S*,*S*)-4-[2′-(Benzyloxy)heptyl]-*N*(5)-(α-methylbenzyl)-1,5-diazocan-2-one *ent*-545



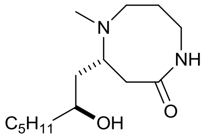
Following *general procedure 11*, *ent*-**519** (3.69 g, 6.96 mmol, >99:1 dr) in MeOH (30 mL) and $SOCl_2$ (0.91 mL, 12.5 mmol) in MeOH (30 mL) were reacted to give *ent*-**517** as a yellow oil (3.61 g, >99:1 dr).

Following *general procedure 12*, NaN_3 (1.16 g, 17.9 mmol, >99:1 dr), NaI (2.68 g, 17.9 mmol) and *ent*-**517** (3.61 g) were reacted in DMSO (10 mL) to give *ent*-**543** as a yellow oil (3.18 g, >99:1 dr).

Following *general procedure 13*, *ent*-**543** (3.18 g, >99:1 dr) and PBu_3 (1.77 mL, 7.09 mmol) were reacted in THF (30 mL) and H_2O (8.0 mL) to give *ent*-**544** as a yellow oil (3.05 g, >99:1 dr).

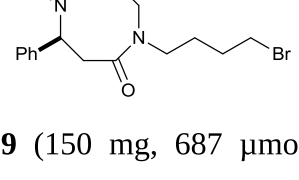
Following *general procedure 14*, *ent*-**544** (3.05 g, >99:1 dr) and $Sb(OEt)_3$ (1.31 mL, 7.71 mmol) were reacted in PhMe (550 mL). Purification via flash column chromatography (eluent EtOAc) gave *ent*-**545** as a yellow oil (1.81 g, 60% over 4 steps, >99:1 dr); $[\alpha]_D^{24}$ −2.7 (*c* 1.0 in $CHCl_3$).

(*S*,*S*)-4-[2′-(Hydroxy)heptyl]-*N*(5)-methyl-1,5-diazocan-2-one *ent*-547



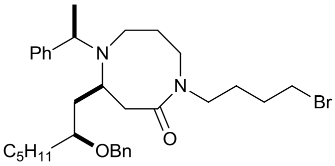
Following *general procedure 17*, *ent*-**545** (1.75 g, 4.01 mmol, >99:1 dr), $(CH_2O)_n$ (229 mg, 7.63 mmol) and $Pd(OH)_2/C$ (875 mg) were reacted in AcOH (25 mL) for 24 h. The residue was partitioned between $CHCl_3$ (30 mL) and sat aq $NaHCO_3$ (30 mL) and the aqueous layer was extracted with $CHCl_3$ (2 × 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give *ent*-**547** as a colourless oil (1.03 g, quant, >99:1 dr); $[\alpha]_D^{24}$ +1.1 (*c* 1.0 in $CHCl_3$).

(*S*)-1-(4′-Bromobutyl)-4-phenyl-5-methyl-1,5-diazocan-2-one 551



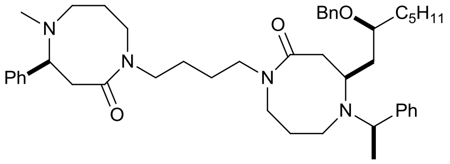
Following *general procedure 16*, **439** (150 mg, 687 μmol), 1,4-dibromobutane **360** (0.24 mL, 2.01 mmol) and KOH (155 mg, 2.76 mmol) were reacted in DMSO (1.4 mL) for 18 h. Purification via flash column chromatography (gradient elution, 50% → 100% Et_2O in 30-40 °C petrol) gave **551** as a yellow oil (143 mg, 59%); $[\alpha]_D^{24}$ −15.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1635 (C=O); δ_H (400 MHz, $CDCl_3$) 1.57-1.95 (6H, m, C(7)H_2, C(2′)H_2, C(3′)H_2), 2.27 (3H, s, N*Me*), 2.45-2.56 (2H, m, C(3)H_A, C(6)H_A), 2.99 (1H, ddd, *J* 15.4, 7.8, 3.0, C(6)H_B), 3.11-3.20 (2H, m, C(3)H_B, C(1′)H_A), 3.30 (1H, app dt, *J* 15.4, 3.5, C(8′)H_A), 3.41-3.51 (2H, m, C(4′)H_2), 3.68-3.75 (1H, m, C(1′)H_B), 3.85 (1H, app br t, *J* 13.5, C(8)H_B), 4.00 (1H, dd, *J* 11.6, 3.3, C(4)*H*), 7.22-7.35 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 26.7 (*C*(7)), 29.9 (*C*(3′)), 30.0 (*C*(2′)), 33.7 (*C*(4′)), 41.1 (*C*(3)), 43.8 (N*Me*), 45.3 (*C*(1′)), 48.1 (*C*(8)), 50.9 (*C*(6)), 67.9 (*C*(4)), 127.2, 127.5, 128.3 (*o,m,p-Ph*), 141.7 (*i-Ph*), 173.5 (*C*(2)); *m/z* (ESI^+) 377 ([M(^{81}Br)+Na]$^+$, 96%), 375 ([M(^{79}Br)+Na]$^+$, 95%), 355 ([M(^{81}Br)+H]$^+$, 100%), 353 ([M(^{79}Br)+H]$^+$, 94%); HRMS (ESI^+) $C_{17}H_{26}{}^{81}BrN_2O^+$ ([M(^{81}Br)+H]$^+$) requires 355.1203; found 355.1202; $C_{17}H_{26}{}^{79}BrN_2O^+$ ([M(^{79}Br)+H]$^+$) requires 353.1223; found 353.1219.

(4*R*,2″*S*,α*R*)-*N*(1)-(4′-Bromobutyl)-4-[2″-(benzyloxy)heptyl]-*N*(5)-(α-methylbenzyl)-1,5-diazocan-2-one 552



Following *general procedure 16*, **542** (500 mg, 1.15 mmol, >99:1 dr), 1,4-dibromobutane **360** (0.41 mL, 3.43 mmol) and KOH (260 mg, 4.63 mmol) were reacted in DMSO (2.5 mL) for 24 h. Purification via flash column chromatography (gradient elution, 50% → 100% Et_2O in 30-40 °C petrol) gave **552** as a yellow oil (116 mg, 30%, >99:1 dr); $[\alpha]_D^{24}$ −11.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1634 (C=O); δ_H (500 MHz, PhMe–d_8, 363 K) 0.84-0.92 (1H, m, C(7)H_A) overlapping 0.92 (3H, t, *J* 7.3, C(7″)H_3), 1.13-1.23 (1H, m, C(7)H_B), 1.25-1.38 (4H, m, C(5″)H_2, C(6″)H_2) overlapping 1.30 (3H, d, *J* 6.6, C(α)*Me*), 1.39-1.68 (9H, m, C(2′)H_2, C(3′)H_2, C(1″)H_A, C(3″)H_2, C(4″)H_2), 1.89-2.00 (1H, m, C(1″)H_B), 2.41 (1H, ABdd, *J* 12.6, 8.5, C(3)H_A), 2.50 (1H, ABdt, *J* 15.5, 3.2, C(6)H_A), 2.55-2.67 (2H, m, C(3)H_B, C(6)H_B), 2.95-3.04 (1H, m, C(8)H_A), 3.08-3.20 (2H, m, C(8)H_B, C(1′)H_A), 3.13 (2H, t, *J* 6.6, C(4′)H_2), 3.35 (1H, br s, C(1′)H_B), 3.48-3.58 (2H, m, C(4)*H*, C(2″)*H*), 3.72 (1H, q, *J* 6.6, C(α)*H*), 4.52 (1H, ABd, *J* 11.9, OCH_AH_BPh), 4.56 (1H, ABd, *J* 11.9, OCH_AH_BPh), 7.07-7.13 (2H, m, *Ph*), 7.15-7.24 (4H, m, *Ph*), 7.23-7.28 (2H, m, *Ph*), 7.39-7.44 (2H, m, *Ph*); δ_C (125 MHz, PhMe–d_8, 363 K) 14.0 (*C*(7″)), 21.3 (C(α)*Me*), 22.9, 25.2, 27.2, 30.6, 32.4, 34.6 (*C*(2′), *C*(3′), *C*(3″), *C*(4″), *C*(5″), *C*(6″)), 30.4 (*C*(7)), 33.0 (*C*(4′)), 34.3 (*C*(1″)), 40.3 (*C*(3)), *44.8* (*C*(1′)), 45.1 (*C*(6)), *47.6* (*C*(8)), 54.9 (*C*(4)), 62.7 (*C*(α)), 70.9 (O*C*H_2Ph), 77.9 (*C*(2″)), 127.2, 127.3, 128.1, 128.3, 128.3, 128.3 (*o,m,p-Ph*), 140.1, 146.6 (*i-Ph*), 172.4 (*C*(2)); *m/z* (ESI^+) 573 ([M(^{81}Br)+H]$^+$, 100%), 571 ([M(^{79}Br)+H]$^+$, 94%); HRMS (ESI^+) $C_{32}H_{48}{}^{81}BrN_2O_2{}^+$ ([M(^{81}Br)+H]$^+$) requires 573.2873; found 573.2876; $C_{32}H_{48}{}^{79}BrN_2O_2{}^+$ ([M(^{79}Br)+H]$^+$) requires 571.2894; found 571.2880.

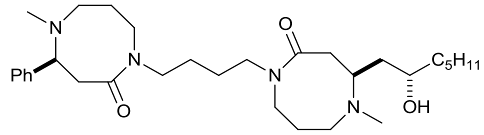
(4′*S*,4″*R*,2‴*S*,α*R*)-1-[2′-Oxo-4′-phenyl-*N*(5′)-methyl-1′,5′-diazocan-*N*(1′)-yl)-4-{2″-oxo-4″-[2‴-(benzyloxy)heptyl]-*N*(5″)-(α-methylbenzyl)-1″,5″-diazocan-*N*(1′)-yl}butane 553



Method A: Following *general procedure 15*, **439** (28 mg, 128 µmol), **552** (60 mg, 105 µmol, >99:1 dr), KOH (28 mg, 504 µmol), K$_2$CO$_3$ (21 mg, 153 µmol) and TEBAC (4 mg, 15.7 µmol) were reacted in DMSO (1.2 mL) for 96 h. Purification via column chromatography (gradient elution, 0% → 5% MeOH in CHCl$_3$) gave **553** as a colourless oil (24 mg, 32%, >99:1 dr); $[\alpha]_D^{24}$ −14.8 (*c* 1.0 in CHCl$_3$); ν_{max} (ATR) 1636 (C=O); δ_H (500 MHz, PhMe–d_8, 363 K) 0.91-1.00 (1H, br s, C(7″)H_A), 0.92 (3H, t, *J* 6.9, C(7‴)H_3), 1.20-1.37 (6H, m, C(7″)H_B, CH_2), 1.31 (3H, d, *J* 6.6, C(α)*Me*), 1.41-1.52 (2H, m, CH_2), 1.53-1.71 (8H, m, C(7′)H_A, CH_2), 1.98 (1H, br s, C(7′)H_B), 2.18 (3H, s, N*Me*), 2.40 (1H, ddd, *J* 15.1, 7.9, 2.8, C(6′)H_A), 2.43-2.49 (1H, m, C(3″)H_A), 2.51-2.57 (2H, m, C(1)H_A, C(3′)H_A,), 2.59-2.75 (3H, m, C(1)H_B, C(6′)H_B, C(3″)H_B), 2.90 (1H, t, *J* 11.8, C(3′)H_B), 2.99-3.13 (2H, m, C(4)H_A, C(6″)H_A), 3.26 (2H, br s, C(4)H_B, C(8″)H_A), 3.45-3.61 (5H, m, C(8′)H_2, C(4″)*H*, C(8″)H_B, C(2‴)*H*), 3.71-3.78 (2H, m, C(α)*H*, C(6″)H_B), 3.99 (1H, dd, *J* 11.4, 3.2, C(4′)*H*), 4.54-4.58 (2H, m, OCH_2Ph), 7.05-7.12 (3H, m, *Ph*), 7.13-7.23 (8H, m, *Ph*), 7.26-7.30 (2H, m, *Ph*), 7.40-7.44 (2H, m, *Ph*); δ_C (125 MHz, PhMe–d_8, 363 K) 14.0 (*C*(7‴)), 21.4 (C(α)*Me*), 22.9, 25.2, 26.1, 26.2, 30.4, 30.5, 30.6, 32.4, 34.5 (*C*(1), *C*(2), *C*(3), *C*(4), *C*(1‴), *C*(3‴), *C*(4‴), *C*(5‴), *C*(6‴)), 30.4 (*C*(7″)), 34.6 (*C*(7′)), 40.4 (*C*(3″)), 41.8 (*C*(3′)), 43.2 (N*Me*), 45.9 (*C*(8′)), 46.2 (*C*(6″)), 47.7 (*C*(8″)), 51.3 (*C*(6′)), 54.9 (*C*(4″)), 62.6 (*C*(α)), 68.6 (*C*(4′)), 70.8 (O*C*H$_2$Ph), 77.9 (*C*(2‴)), 127.0, 127.1, 127.3, 127.8, 128.1, 128.3, 128.4, 129.0 (*o*,*m*,*p*-*Ph*), 140.2, 143.5, 146.6 (*i*-*Ph*), 172.3, 172.4 (*C*(1′), *C*(1″)); *m/z* (ESI$^+$) 731 ([M+Na]$^+$, 55%), 709 ([M+H]$^+$, 94%); HRMS (ESI$^+$) C$_{45}$H$_{64}$N$_4$NaO$_3^+$ ([M+Na]$^+$) requires 731.4871; found 731.4873.

Method B: Following *general procedure 16*, **542** (89 mg, 204 µmol, >99:1 dr), **551** (62 mg, 175 µmol) and KOH (45 mg, 802 µmol) were reacted in DMSO (0.5 mL) for 96 h. Purification via flash column chromatography (gradient elution, 0% → 2.5% MeOH in CH$_2$Cl$_2$) gave **553** as a yellow oil (71 mg, 57%, >99:1 dr).

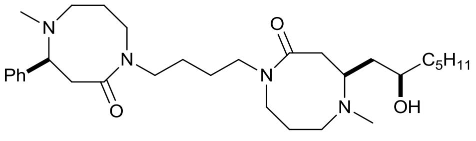
(4′*S*,4″*R*,2‴*S*)-1-[2′-Oxo-4′-phenyl-*N*(5′)-methyl-1′,5′-diazocan-*N*(1′)-yl]-4-{2″-oxo-4″-[2‴-(hydroxy)heptyl]-*N*(5″)-methyl-1″,5″-diazocan-*N*(1″)-yl}butane 493



Method A: Following *general procedure 17*, **553** (24 mg, 34 µmol, >99:1 dr), (CH$_2$O)$_n$ (2 mg, 67 µmol) and Pd(OH)$_2$/C (12 mg) were reacted in AcOH (0.5 mL) for 18 h. The residue was partitioned between CHCl$_3$ (5 mL) and sat aq NaHCO$_3$ (5 mL). The aqueous layer was extracted with CHCl$_3$ (2 × 5 mL) and the combined organic extracts were dried (Na$_2$SO$_4$) and concentrated *in vacuo*. Purification via column chromatography (gradient elution, 1% → 4% MeOH in CHCl$_3$) gave **493** as a colourless oil (4 mg, 20%, >99:1 dr); $[\alpha]^{24}_{D}$ −9.8 (*c* 0.3 in CHCl$_3$); ν_{max} (ATR) 3401 (O−H), 1625 (C=O); δ_H (500 MHz, PhMe–d_8, 363 K) 0.89-0.97 (3H, m, C(7‴)*H*), 1.26-1.73 (18H, m, C(2)H_2, C(3)H_2, C(7′)H_2, C(7″)H_2, C(1‴)H_2, C(3‴)H_2, C(4‴)H_2, C(5‴)H_2, C(6‴)H_2), 2.18 (3H, s, N(5′)*Me*), 2.30 (3H, s, N(5″)*Me*), 2.31-2.44 (2H, m, C(3″)H_A, C(6″)H_A), 2.51-2.67 (4H, m, C(3′)H_A, C(3″)H_B, C(6′)H_2), 2.72 (1H, ddd, *J* 15.5, 7.6, 2.8, C(6″)H_B), 2.91 (1H, app t, *J* 11.4, C(3′)H_B), 2.96-3.12 (4H, m, C(1)H_A, C(8′)H_A, C(4″)*H*, C(8″)H_A), 3.19-3.33 (2H, m, C(4)H_A, C(8′)H_B), 3.34-3.41 (1H, m, C(4)H_B), 3.50 (1H, br t, *J* 12.9, C(8″)H_B), 3.62-3.70 (2H, m, C(1)H_B, C(2‴)*H*), 3.99 (1H, dd, *J* 11.4, 3.2, C(4′)*H*), 7.05-7.09 (1H, m, *Ph*), 7.14-7.20 (4H, m, *Ph*); δ_C (125 MHz, PhMe–d_8, 363 K) 14.2 (*C*(7‴)), 23.2, 26.0, 26.1, 26.4, 29.0, 30.3, 30.6, 32.6, 38.3 (*C*(2), *C*(3), *C*(7′), *C*(7″), *C*(1‴), *C*(3‴), *C*(4‴), *C*(5‴), C(6‴)), 38.7 (*C*(3″)), 39.5 (N(5″)*Me*), 42.0 (*C*(3′)), 43.4 (N(5′)*Me*), 46.0 (*C*(4)), 46.4 (*C*(1), *C*(6″)), 47.1 (*C*(8′)), 48.1 (*C*(8″)), 51.5 (*C*(6′)), 62.0 (*C*(4″)), 68.8 (*C*(4′)), 70.2 (*C*(2‴)), 128.0, 128.4, 128.6 (*o,m,p-Ph*), 143.5 (*i-Ph*), 172.7 (*C*(2″)), 173.2 (*C*(2′)); *m/z* (ESI$^+$) 551 ([M+Na]$^+$, 100%), 529 ([M+H]$^+$, 92%); HRMS (ESI$^+$) $C_{31}H_{52}N_4NaO_3^+$ ([M+Na]$^+$) requires 551.3932; found 551.3918.

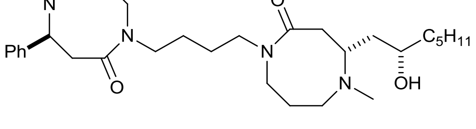
Method B: Following *general procedure 15*, **551** (39 mg, 152 µmol), **550** (49 mg, 138 µmol, >99:1 dr), KOH (34 mg, 609 µmol), K$_2$CO$_3$ (26 mg, 185 µmol) and TEBAC (4 mg, 19.0 µmol) were reacted in DMSO (0.75 mL) for 48 h. Purification via column chromatography (gradient elution, 1% → 4% MeOH in CHCl$_3$) gave **493** as a colourless oil (26 mg, 36%, >99:1 dr); $[\alpha]^{24}_{D}$ −9.3 (*c* 1.0 in CHCl$_3$).

(4′*S*,4″*R*,2‴*R*)-1-[2′-Oxo-4′-phenyl-*N*(5′)-methyl-1′,5′-diazocan-*N*(1′)-yl]-4-{2″-oxo-4″-[2‴-(hydroxy)heptyl]-*N*(5″)-methyl-1″,5″-diazocan-*N*(1″)-yl}butane [(−)-hopromalinol] 494



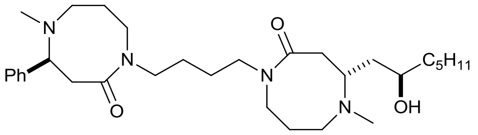
Following *general procedure 15*, **551** (49 mg, 138 μmol), **547** (39 mg, 152 μmol, >99:1 dr), KOH (34 mg, 609 μmol), K_2CO_3 (26 mg, 185 μmol) and TEBAC (4 mg, 19.0 μmol) were reacted in DMSO (0.75 mL) for 48 h. Purification via column chromatography (gradient elution, 1% → 4% MeOH in $CHCl_3$) gave **494** as a colourless oil (41 mg, 56%, >99:1 dr); $[\alpha]_D^{24}$ −16.8 (*c* 1.0 in $CHCl_3$); {lit.[64] $[\alpha]_D^{20}$ −17 (*c* 3 in $CHCl_3$)}; ν_{max} (ATR) 3385 (O−H), 1623 (C=O); δ_H (500 MHz, PhMe–d_8, 363 K) 0.90 (3H, br s, C(7‴)H_3), 1.11-1.19 (1H, m, C(7′)H_A), 1.20-1.61 (17H, m, C(2)H_2, C(3)H_2, C(7′)H_B, C(7″)H_2, C(1‴)H_2, C(3‴)H_2, C(4‴)H_2, C(5‴)H_2, C(6‴)H_2), 2.15 (3H, s, N(5′)*Me*), 2.24 (3H, s, N(5″)*Me*), 2.28-2.41 (4H, m, C(6′)H_A, C(3″)H_2, C(6″)H_A), 2.51 (1H, dd, *J* 12.6, 2.6, C(3′)H_A), 2.64-2.75 (3H, m, C(6′)H_B, C(6″)H_B, O*H*), 2.87 (1H, app t, *J* 12.0, C(3′)H_B), 2.93-3.04 (3H, m, C(1)H_A, C(8′)H_A, C(8″)H_A), 3.05-3.20 (3H, m, C(4)H_A, C(4″)*H*, C(8′)H_B), 3.34-3.43 (1H, m, C(4)H_B), 3.46 (1H, app t, *J* 13.4, C(8″)H_B), 3.62-3.76 (2H, m, C(1)H_B, C(2‴)*H*), 3.96 (1H, dd, *J* 11.4, 2.5, C(4′)*H*), 7.02-7.08 (1H, m, *Ph*), 7.10-7.17 (4H, m, *Ph*); δ_C (125 MHz, PhMe–d_8, 363 K) 14.2 (*C*(7‴)), 23.2, 25.8, 26.0, 26.3, 28.3, 30.3, 30.6, 32.7, 38.8 (*C*(2), *C*(3), *C*(7′), *C*(7″), *C*(1‴), *C*(3‴), *C*(4‴), *C*(5‴), C(6‴)), 38.6 (*C*(3″)), 39.4 (N(5″)*Me*), 42.0 (*C*(3′)), 43.4 (N(5′)*Me*), 46.1 (*C*(4)), 46.3, 46.3 (*C*(1), *C*(6″)), 47.6 (*C*(8′)), 48.0 (*C*(8″)), 51.5 (*C*(6′)), 63.0 (*C*(4″)), 68.8 (*C*(4′)), 71.9 (*C*(2‴)), 127.3, 128.0, 128.6 (*o,m,p-Ph*), 143.6 (*i-Ph*), 172.4 (*C*(2″)), 172.7 (*C*(2′)); *m/z* (ESI^+) 551 ($[M+Na]^+$, 89%), 529 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{31}H_{53}N_4O_3^+$ ($[M+H]^+$) requires 529.4112; found 529.4120.

(*S*,*S*,*S*)- 1-[2′-Oxo-4′-phenyl-*N*(5′)-methyl-1′,5′-diazocan-*N*(1′)-yl]-4-{2″-oxo-4″-[2‴-(hydroxy)heptyl]-*N*(5″)-methyl-1″,5″-diazocan-*N*(1″)-yl}butane 495



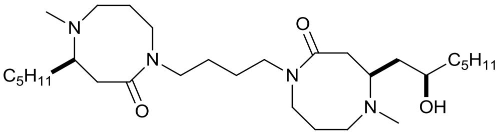
Following *general procedure 15*, **551** (93 mg, 262 μmol), *ent*-**547** (74 mg, 289 μmol, >99:1 dr), KOH (65 mg, 1.15 mmol), K_2CO_3 (48 mg, 349 μmol) and TEBAC (8 mg, 36 μmol) were reacted in DMSO (1.4 mL) for 60 h. Purification via column chromatography (gradient elution, 1% → 4% MeOH in $CHCl_3$) gave **495** as a white solid (82 mg, 59%, >99:1 dr); mp 110-115 °C; $[\alpha]_D^{24}$ +2.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3409 (O−H), 1625 (C=O); δ_H (500 MHz, PhMe–d_8, 363 K) 0.93 (3H, br t, *J* 6.9, C(7‴)H_3), 1.19-1.25 (1H, m, C(7′)H_A), 1.26-1.66 (17H, m, C(2)H_2, C(3)H_2, C(7′)H_B, C(7″)H_2, C(1‴)H_2, C(3‴)H_2, C(4‴)H_2, C(5‴)H_2, C(6‴)H_2), 2.19 (3H, s, N(5′)*Me*), 2.29 (3H, s, N(5″)*Me*), 2.33-2.50 (4H, m, C(6′)H_A, C(6″)H_A, C(3″)H_2), 2.54 (1H, dd, *J* 12.6, 3.2, C(3′)H_A), 2.70-2.77 (2H, m, C(6′)H_B, C(6″)H_B), 2.92 (1H, br t, *J* 12.3, C(3′)H_B), 2.97-3.10 (3H, m, C(1)H_A, C(8′)H_A, C(8″)H_A), 3.12-3.38 (4H, m, C(4)H_2, C(8′)H_B, C(4″)*H*), 3.51 (1H, app br t, *J* 12.9, C(8″)H_B), 3.64-3.71 (1H, m, C(1)H_B), 3.77 (1H, br s, C(2‴)*H*), 3.99 (1H, dd, *J* 11.0, 3.2, C(4′)*H*), 7.06-7.12 (1H, m, *Ph*), 7.14-7.21 (4H, m, *Ph*); δ_C (125 MHz, PhMe–d_8, 363 K) 14.2 (*C*(7‴)), 23.2, 25.8, 26.0, 26.3, 28.3, 30.3, 30.6, 32.7, 38.8 (*C*(2), *C*(3), *C*(7′), *C*(7″), *C*(1‴), *C*(3‴), *C*(4‴), *C*(5‴), C(6‴)), 38.5 (*C*(3″)), *39.6* (N(5″)*Me*), 42.0 (*C*(3′)), 43.4 (N(5′)*Me*), 46.1 (*C*(4)), 46.3 (*C*(1)), 46.4 (*C*(6″)), 47.5 (*C*(8′)), 48.0 (*C*(8″)), 51.5 (*C*(6′)), 62.9 (*C*(4″)), 68.8 (*C*(4′)), 71.6 (*C*(2‴)), 127.3, 128.0, 128.6 (*o,m,p-Ph*), 143.5 (*i-Ph*), 172.4 (*C*(2″)), 172.7 (*C*(2′)); *m/z* (ESI$^+$) 551 ([M+Na]$^+$, 100%), 529 ([M+H]$^+$, 88%); HRMS (ESI$^+$) $C_{31}H_{52}N_4NaO_3^+$ ([M+Na]$^+$) requires 551.3932; found 551.3918.

(4′*S*,4″*S*,2‴*R*)-1-[2′-Oxo-4′-phenyl-*N*(5′)-methyl-1′,5′-diazocan-*N*(1′)-yl]-4-{2″-oxo-4″-[2‴-(hydroxy)heptyl]-*N*(5″)-methyl-1″,5″-diazocan-*N*(1″)-yl}butane 496



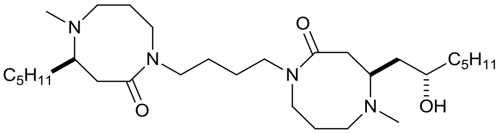
Following *general procedure 15*, **551** (93 mg, 262 μmol), *ent*-**550** (74 mg, 289 μmol, >99:1 dr), KOH (65 mg, 1.15 mmol), K_2CO_3 (48 mg, 349 μmol) and TEBAC (8 mg, 36 μmol) were reacted in DMSO (1.4 mL) for 60 h. Purification via column chromatography (gradient elution, 1% → 4% MeOH in $CHCl_3$) gave **496** as a white solid (31 mg, 22%, >99:1 dr); mp 120-122 °C; $[\alpha]_D^{24}$ −7.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3401 (O−H), 1623 (C=O); δ_H (500 MHz, PhMe–d_8, 363 K) 0.89 (3H, br s, C(7‴)H_3), 1.19-1.71 (18H, m, C(2)H_2, C(3)H_2, C(7′)H_2, C(7″)H_2, C(1‴)H_2, C(3‴)H_2, C(4‴)H_2, C(5‴)H_2, C(6‴)H_2), 2.15 (3H, s, N(5′)*Me*), 2.28 (3H, s, N(5″)*Me*), 2.29-2.41 (2H, m, C(3″)H_A, C(6″)H_A), 2.46-2.73 (5H, m, C(3′)H_A, C(6′)H_2, C(3″)H_B, C(6″)H_B), 2.88 (1H, app t, *J* 12.0, C(3′)H_B), 2.93-3.03 (3H, m, C(1)H_A, C(8′)H_A, C(8″)H_A), 3.04-3.17 (2H, m, C(4)H_A, C(4″)*H*), 3.21-3.30 (1H, m, C(8′)H_B), 3.36-3.54 (2H, m, C(4)H_B, C(8″)H_B), 3.59-3.71 (2H, m, C(1)H_B, C(2‴)*H*), 3.96 (1H, d, *J* 10.1, C(4′)*H*), 7.01-7.08 (1H, m, *Ph*), 7.10-7.18 (4H, m, *Ph*); δ_C (125 MHz, PhMe–d_8, 363 K) 14.2 (*C*(7‴)), 23.2, 26.0, 26.1, 26.3, 29.0, 30.3, 30.6, 32.6, 38.2 (*C*(2), *C*(3), *C*(7′), *C*(7″), *C*(1‴), *C*(3‴), *C*(4‴), *C*(5‴), C(6‴)), 38.5 (*C*(3″)), 39.5 (N(5″)*Me*), 42.0 (*C*(3′)), 43.4 (N(5′)*Me*), 45.9 (*C*(4)), 46.3 (*C*(1), *C*(6″)), 47.1 (*C*(8′)), 48.0 (*C*(8″)), 51.5 (*C*(6′)), 62.0 (*C*(4″)), 68.8 (*C*(4′)), 70.2 (*C*(2‴)), 127.3, 128.0, 128.6 (*o,m,p-Ph*), 143.5 (*i-Ph*), 172.7 (*C*(2″)), 173.2 (*C*(2′)); *m/z* (ESI$^+$) 551 ([M+Na]$^+$, 100%), 529 ([M+H]$^+$, 88%); *m/z* (ESI$^+$) 551 ([M+Na]$^+$, 100%), 529 ([M+H]$^+$, 96%); HRMS (ESI$^+$) $C_{31}H_{53}N_4O_3^+$ ([M+H]$^+$) requires 529.4112; found 529.4099.

(*R*,*R*,*R*)-1-[2′-Oxo-4′-pentyl-*N*(5′)-methyl-1′,5′-diazocan-*N*(1′)-yl]-4-{2″-oxo-4″-[2‴-(hydroxy)heptyl]-*N*(5″)-methyl-1″,5″-diazocan-*N*(1″)-yl}butane [(−)-hoprominol] 497



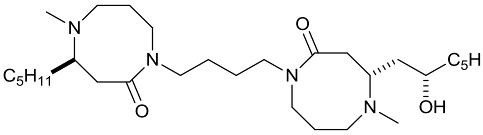
Following *general procedure 15*, **451** (48 mg, 138 µmol), **547** (39 mg, 152 µmol, >99:1 dr), KOH (34 mg, 609 µmol), K_2CO_3 (26 mg, 185 µmol) and TEBAC (4 mg, 19 µmol) were reacted in DMSO (0.75 mL) for 48 h. Purification via column chromatography (gradient elution, 1% → 4% MeOH in $CHCl_3$) gave **497** as a colourless oil (17 mg, 24%, >99:1 dr); $[\alpha]_D^{24}$ −17.5 (c 1.0 in $CHCl_3$); {lit.[64] $[\alpha]_D^{20}$ −19 (*c* 2 in $CHCl_3$)}; ν_{max} (ATR) 3390 (O−H), 1626 (C=O); δ_H (500 MHz, PhMe–d_8, 363 K) 0.88-0.99 (6H, m, C(7‴)H_3, C(4′)(CH_2)$_4$CH_3), 1.15-1.63 (26H, m, C(2)H_2, C(3)H_2, C(7′)H_2, C(7″)H_2, C(1‴)H_2, C(3‴)H_2, C(4‴)H_2, C(5‴)H_2, C(6‴)H_2, C(4′)(CH_2)$_4$), 2.26 (3H, s, N*Me*), 2.31-2.46 (6H, m, C(3′)H_2, C(6′)H_A, C(3″)H_2, C(6″)H_A), 2.33 (3H, s, N*Me*), 2.72 (2H, app ddd, *J* 15.1, 10.4, 3.2, C(6′)H_B, (6″)H_B), 2.87-2.95 (1H, m, C(4′)*H*), 2.98-3.42 (10H, m, C(1)H_2, C(4)H_2, C(8′)H_2, C(4″)*H*, C(8″)H_2), 3.72-3.79 (1H, m, C(2‴)*H*); δ_C (125 MHz, PhMe–d_8, 363 K) 14.2, 14.2 (*C*(7‴), C(4′)(CH_2)$_4$*C*H_3), 23.1, 23.2, 25.8, 26.1, 26.3, 27.2, 28.3, 29.4, 30.3, 31.7, 32.5, 32.7, 38.6 (*C*(2), *C*(3), *C*(7′), *C*(7″), *C*(1‴), *C*(3‴), *C*(4‴), *C*(5‴), *C*(6‴), C(4′)(*C*H_2)$_4$), 38.8, 39.2 (*C*(3′), *C*(3″)), 39.4 (N*Me*), 40.2 (N*Me*), 46.0, 46.1, 46.2, 47.5, 47.5, 47.7 (*C*(1), *C*(4), *C*(6′), *C*(6″), *C*(8′), *C*(8″)), 63.1 (*C*(4″)), 63.9 (*C*(4′)), 71.9 (*C*(2‴)), 172.3, 172.7 (*C*(2′), *C*(2″)); *m/z* (ESI^+) 545 ($[M+Na]^+$, 100%), 523 ($[M+H]^+$, 98%); HRMS (ESI^+) $C_{30}H_{59}N_4O_3^+$ ($[M+H]^+$) requires 523.4582; found 523.4577.

(4′*R*,4″*R*,2‴*S*)-1-[2′-Oxo-4′-pentyl-*N*(5′)-methyl-1′,5′-diazocan-*N*(1′)-yl]-4-{2″-oxo-4″-[2‴-(hydroxy)heptyl]-*N*(5″)-methyl-1″,5″-diazocan-*N*(1″)-yl}butane 498



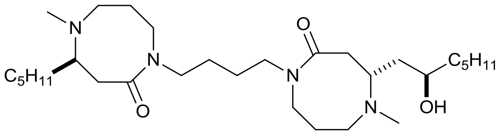
Following *general procedure 15*, **451** (48 mg, 138 µmol), **550** (39 mg, 152 µmol, >99:1 dr), KOH (34 mg, 609 µmol), K_2CO_3 (26 mg, 185 µmol) and TEBAC (4 mg, 19.0 µmol) were reacted in DMSO (0.75 mL) for 48 h. Purification via column chromatography (gradient elution, 1% → 4% MeOH in $CHCl_3$) gave **498** as a colourless oil (19 mg, 26%, >99:1 dr); $[\alpha]_D^{24}$ −18.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3399 (O−H), 1626 (C=O); δ_H (500 MHz, PhMe–d_8, 363 K) 0.88-0.97 (6H, m, C(7‴)H_3, C(4′)(CH_2)$_4$CH_3), 1.21-1.63 (26H, m, C(2)H_2, C(3)H_2, C(7′)H_2, C(7″)H_2, C(1‴)H_2, C(3‴)H_2, C(4‴)H_2, C(5‴)H_2, C(6‴)H_2, C(4′)(CH_2)$_4$), 2.31 (3H, s, N*Me*), 2.32-2.47 (4H, m, C(3′)H_2, C(6′)H_A, C(6″)H_A) overlapping 2.33 (3H, s, N*Me*), 2.51-2.58 (2H, m, C(3″)H_2), 2.64 (1H, app ddd, *J* 15.5, 11.0, 2.8, C(6″)H_B), 2.72 (1H, app ddd, *J* 14.8, 10.1, 3.5, C(6′)H_B), 2.87-2.96 (1H, m, C(4′)*H*), 3.01 (1H, dt, *J* 15.5, 4.7, C(8″)H_A), 3.07-3.43 (8H, m, C(1)H_2, C(4)H_2, C(8′)H_2, C(4″)*H*, C(8″)H_B), 3.61-3.69 (1H, m, C(2‴)*H*); δ_C (125 MHz, PhMe–d_8, 363 K) 14.2, 14.2 (*C*(7‴), C(4′)$(\mathrm{CH_2})_4C\mathrm{H_3}$), 23.1, 23.2, 26.1, 26.1, 26.2, 27.2, 29.1, 29.4, 30.3, 32.5, 32.7, 38.3, 38.7 (*C*(2), *C*(3), *C*(7′), *C*(7″), *C*(1‴), *C*(3‴), *C*(4‴), *C*(5‴), *C*(6‴), *C*(7‴), C(4′)$(C\mathrm{H_2})_4$), 39.2, 39.5 (*C*(3′), *C*(3″)), 40.2 (N*Me*), 40.8 (N*Me*), 46.0, 46.0, 46.3, 47.2, 47.5, 47.7 (*C*(1), *C*(4), *C*(6′), *C*(6″), *C*(8′), *C*(8″)), 61.9 (*C*(4″)), 63.9 (*C*(4′)), 70.2 (*C*(2‴)), 172.7, 173.2 (*C*(2′), *C*(2″)); *m/z* (ESI$^+$) 545 ([M+Na]$^+$, 100%), 523 ([M+H]$^+$, 95%); HRMS (ESI$^+$) $\mathrm{C_{30}H_{59}N_4O_3}^+$ ([M+H]$^+$) requires 523.4582; found 523.4577.

(4′*R*,4″*S*,2‴*S*)-1-[2′-Oxo-4′-pentyl-*N*(5′)-methyl-1′,5′-diazocan-*N*(1′)-yl]-4-{2″-oxo-4″-[2‴-(hydroxy)heptyl]-*N*(5″)-methyl-1″,5″-diazocan-*N*(1″)-yl}butane 499



Following *general procedure 15*, **451** (175 mg, 504 µmol), *ent*-**547** (142 mg, 554 µmol, >99:1 dr), KOH (125 mg, 2.23 mmol), $\mathrm{K_2CO_3}$ (92 mg, 664 µmol) and TEBAC (15 mg, 66 µmol) were reacted in DMSO (2.9 mL) for 60 h. Purification via column chromatography (gradient elution, 1% → 4% MeOH in $\mathrm{CHCl_3}$), and further purification via supercritical fluid chiral HPLC (Chiralpak AD-H 250 × 10 mm column, eluent methanol/$\mathrm{CO_2}$/diethanolamine, 49.9:50:0.1)[80] gave **499** as a colourless oil (11 mg, 4%, >99:1 dr); $[\alpha]_\mathrm{D}^{24}$ +5.8 (*c* 1.0 in $\mathrm{CHCl_3}$); ν_max (ATR) 3405 (O−H), 1622 (C=O); δ_H (500 MHz, PhMe–d_8, 363 K) 0.88-1.01 (6H, m, C(7‴)H_3, C(4′)$(\mathrm{CH_2})_4C H_3$), 1.14-1.68 (26H, m, C(2)H_2, C(3)H_2, C(7′)H_2, C(7″)H_2, C(1‴)H_2, C(3‴)H_2, C(4‴)H_2, C(5‴)H_2, C(6‴)H_2, C(4′)$(CH_2)_4$), 2.26 (3H, s, N*Me*), 2.28-2.50 (6H, m, C(3′)H_2, C(6′)H_A, C(3″)H_2, C(6″)H_A) overlapping 2.34 (3H, s, N*Me*), 2.72 (2H, app t, *J* 12.5, C(6′)H_B, C(6″)H_B), 2.91 (1H, br s, C(4′)*H*), 2.99-3.44 (9H, m, C(1)H_2, C(4)H_2, C(8′)H_2, C(4″)*H*, C(8″)H_2), 3.76 (1H, br s, C(2‴)*H*), 3.95 (1H, br s, O*H*); δ_C (125 MHz, PhMe–d_8, 363 K) 14.2, 14.2 (*C*(7′), *C*(7″)), 23.1, 23.2, 25.8, 26.1, 26.3, 27.3, 28.3, 29.4, 31.7, 32.5, 32.7, 38.6, 38.7 (*C*(2), *C*(3), *C*(7′), *C*(7″), *C*(1‴), *C*(3‴), *C*(4‴), *C*(5‴), *C*(6‴), C(4′)$(C\mathrm{H_2})_4$), 38.8, 39.3 (*C*(3′), *C*(3″)), 39.3 (N*Me*), 40.2 (N*Me*), 46.0, 46.1, 46.2, 47.4, 47.5, 47.7 (*C*(1), *C*(4), *C*(6′), *C*(6″), *C*(8′), *C*(8″)), 63.1 (*C*(4″)), 63.9 (*C*(4′)), 71.9 (*C*(2‴)), 172.3, 172.7 (*C*(2′), *C*(2″)); *m/z* (ESI$^+$) 545 ([M+Na]$^+$, 62%), 523 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $\mathrm{C_{30}H_{59}N_4O_3}^+$ ([M+H]$^+$) requires 523.4582; found 523.4588.

(4′*R*,4″*S*,2‴*R*)-1-[2′-Oxo-4′-pentyl-*N*(5′)-methyl-1′,5′-diazocan-*N*(1′)-yl]-4-{2″-oxo-4″-[2‴-(hydroxy)heptyl]-*N*(5″)-methyl-1″,5″-diazocan-*N*(1″)-yl}butane 500



Following *general procedure 15,* **451** (91 mg, 262 µmol), *ent*-**550** (74 mg, 289 µmol, >99:1 dr), KOH (65 mg, 1.15 mmol), K_2CO_3 (48 mg, 349 µmol) and TEBAC (8 mg, 36 µmol) were reacted in DMSO (1.4 mL) for 60 h. Purification via column chromatography (gradient elution, 1% → 4% MeOH in $CHCl_3$) gave **500** as a colourless oil (36 mg, 26%, >99:1 dr); $[\alpha]^{24}_{\mathrm{D}}$ −2.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3391 (O−H), 1625 (C=O); δ_{H} (500 MHz, PhMe–d_8, 363 K) 0.89-0.95 (6H, m, C(7‴)H_3, C(4′)(CH$_2$)$_4$CH_3), 1.23-1.73 (26H, m, C(2)H_2, C(3)H_2, C(7′)H_2, C(7″)H_2, C(1‴)H_2, C(3‴)H_2, C(4‴)H_2, C(5‴)H_2, C(6‴)H_2, C(4′)(CH_2)$_4$), 2.30 (3H, s, N*Me*), 2.32-2.46 (4H, m, C(3′)H_2, C(6′)H_{A}, C(6″)H_{A}) overlapping 2.33 (3H, s, N*Me*), 2.52-2.57 (2H, m, C(3″)H_2), 2.63 (1H, app ddd, *J* 14.8, 11.0, 3.2, C(6″)H_{B}), 2.72 (1H, app ddd, *J* 13.9, 10.1, 2.8, C(6′)H_{B}), 2.88-2.93 (1H, m, C(4′)*H*), 3.00 (1H, dt, *J* 15.1, 4.7, C(8″)H_{A}), 3.05-3.42 (8H, m, C(1)H_2, C(4)H_2, C(8′)H_2, C(4″)*H*, C(8″)H_{B}), 3.61-3.67 (1H, m, C(2‴)*H*); δ_{C} (125 MHz, PhMe–d_8, 363 K) 14.2, 14.2 (*C*(7‴), C(4′)(CH$_2$)$_4$*C*H$_3$), 23.1, 23.2, 26.1, 26.1, 26.2, 27.2, 29.1, 29.4, 31.7, 32.5, 32.7, 38.3, 38.7 (*C*(2), *C*(3), *C*(7′), *C*(7″), *C*(1‴), *C*(3‴), *C*(4‴), *C*(5‴), *C*(6‴), C(4′)(*C*H$_2$)$_4$), 39.2, 39.5 (*C*(3′), *C*(3″)), 40.2 (N*Me*), 40.8 (N*Me*), 45.9, 46.0, 46.2, 47.1, 47.5, 47.7 (*C*(1), *C*(4), *C*(6′), *C*(6″), *C*(8′), *C*(8″)), 61.9 (*C*(4″)), 63.9 (*C*(4′)), 70.3 (*C*(2‴)), 172.7, 173.2 (*C*(2′), *C*(2″)); *m/z* (ESI$^+$) 545 ([M+Na]$^+$, 58%), 523 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{59}N_4O_3^+$ ([M+H]$^+$) requires 523.4582; found 523.4574.

5.3 References and notes

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[50] No other resonances were observed in the 100 MHz ^{13}C NMR spectrum of **426** at rt.

[51] No other resonances were observed in the 100 MHz ^{13}C NMR spectrum of **427** at rt.

[52] A resonance corresponding to C(α)*Me* was not observed in the 100 MHz ^{13}C NMR spectrum of **429** at rt.

[53] No other resonances were observed in the 100 MHz ^{13}C NMR spectrum of **428** at rt.

[54] A resonance corresponding to C(1′) was not observed in the 125 MHz ^{13}C NMR spectrum of **436** at 363 K.

[55] A resonance corresponding to 2 × C(3′)H_B was not observed in the 500 MHz ^{1}H NMR spectrum of **437** at rt.

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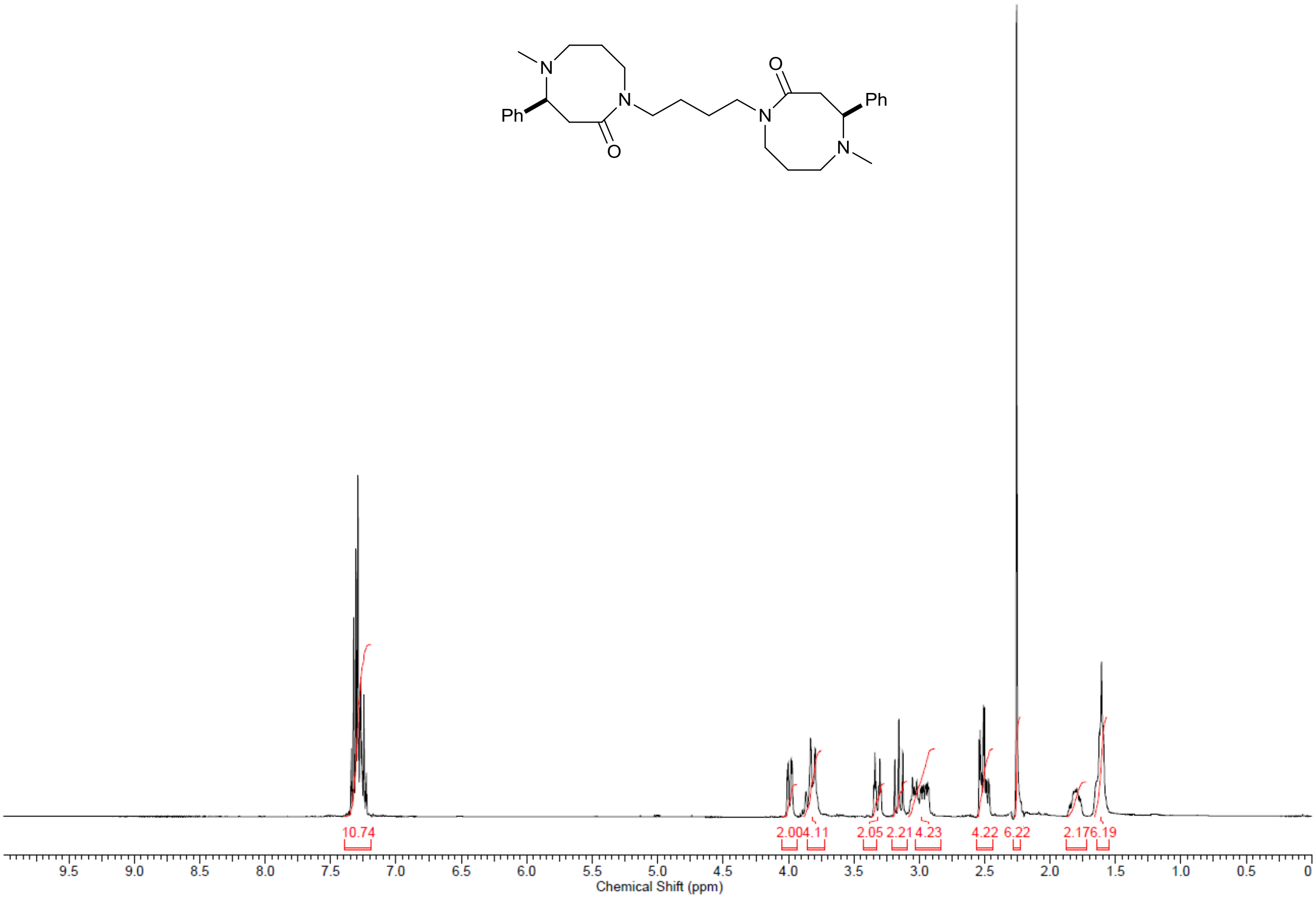
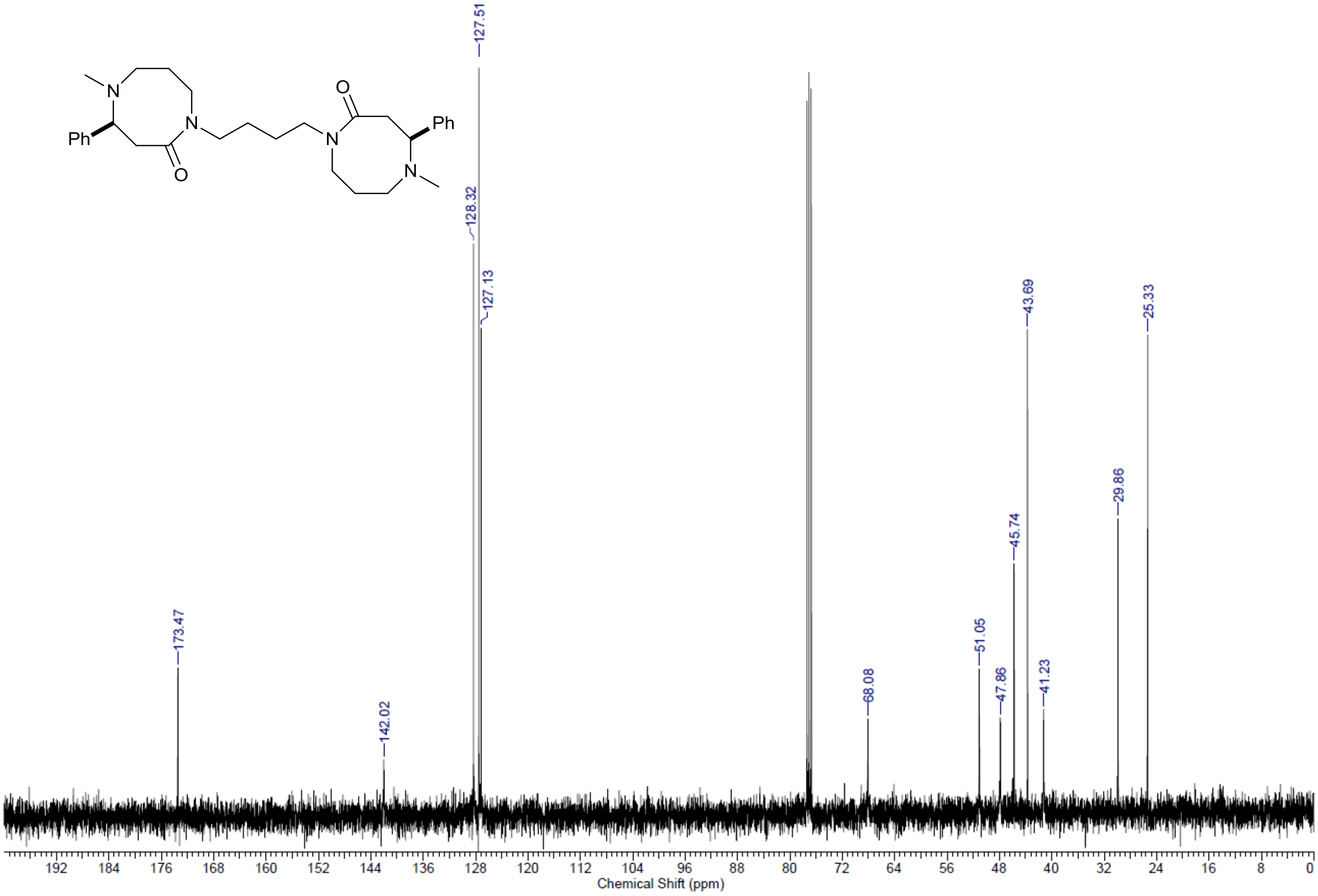
[80] HPLC purification was performed by Dr. J. P. Stonehouse.

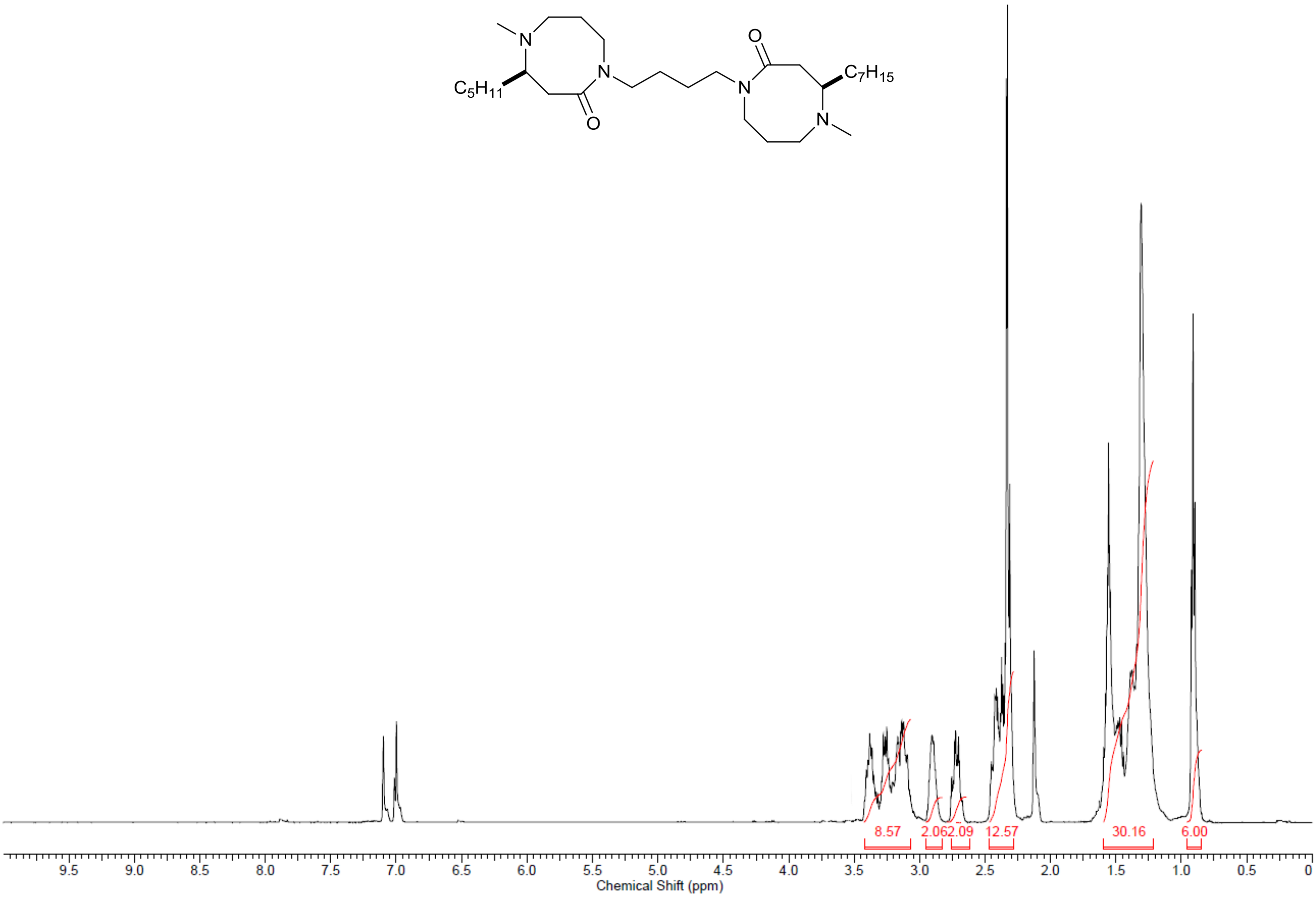
(*S*,*S*)-1,4-Di[2′-oxo-4′-phenyl-*N*(5′)-methyl-1′,5′-diazocan-*N*(1′)-yl]butane [(−)-homaline] 99 (400 MHz, ^{1}H, CDCl$_3$)



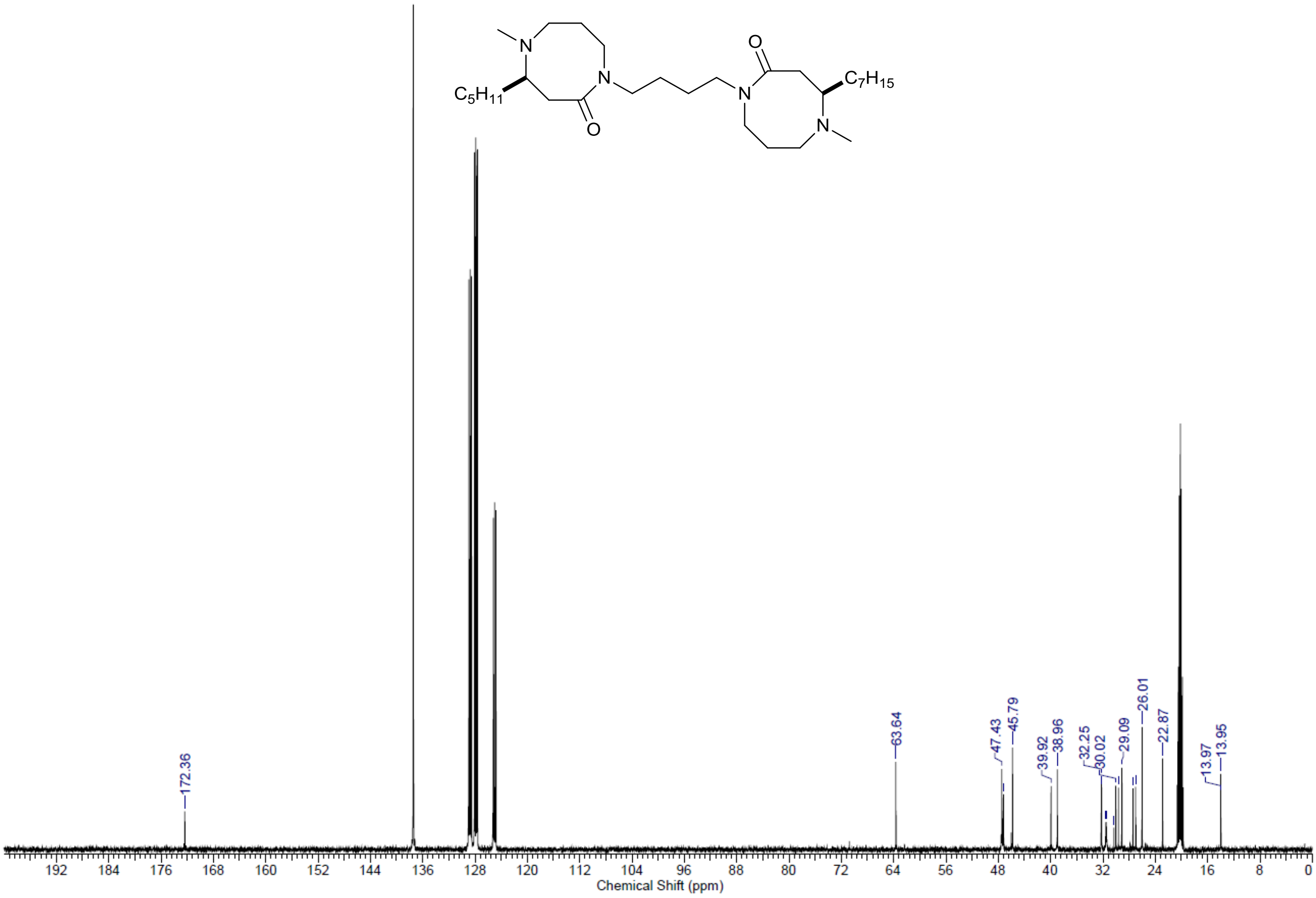
(*S*,*S*)-1,4-Di[2′-oxo-4′-phenyl-*N*(5′)-methyl-1′,5′-diazocan-*N*(1′)-yl]butane [(−)-homaline] 99 (100 MHz, ^{13}C, CDCl$_3$)



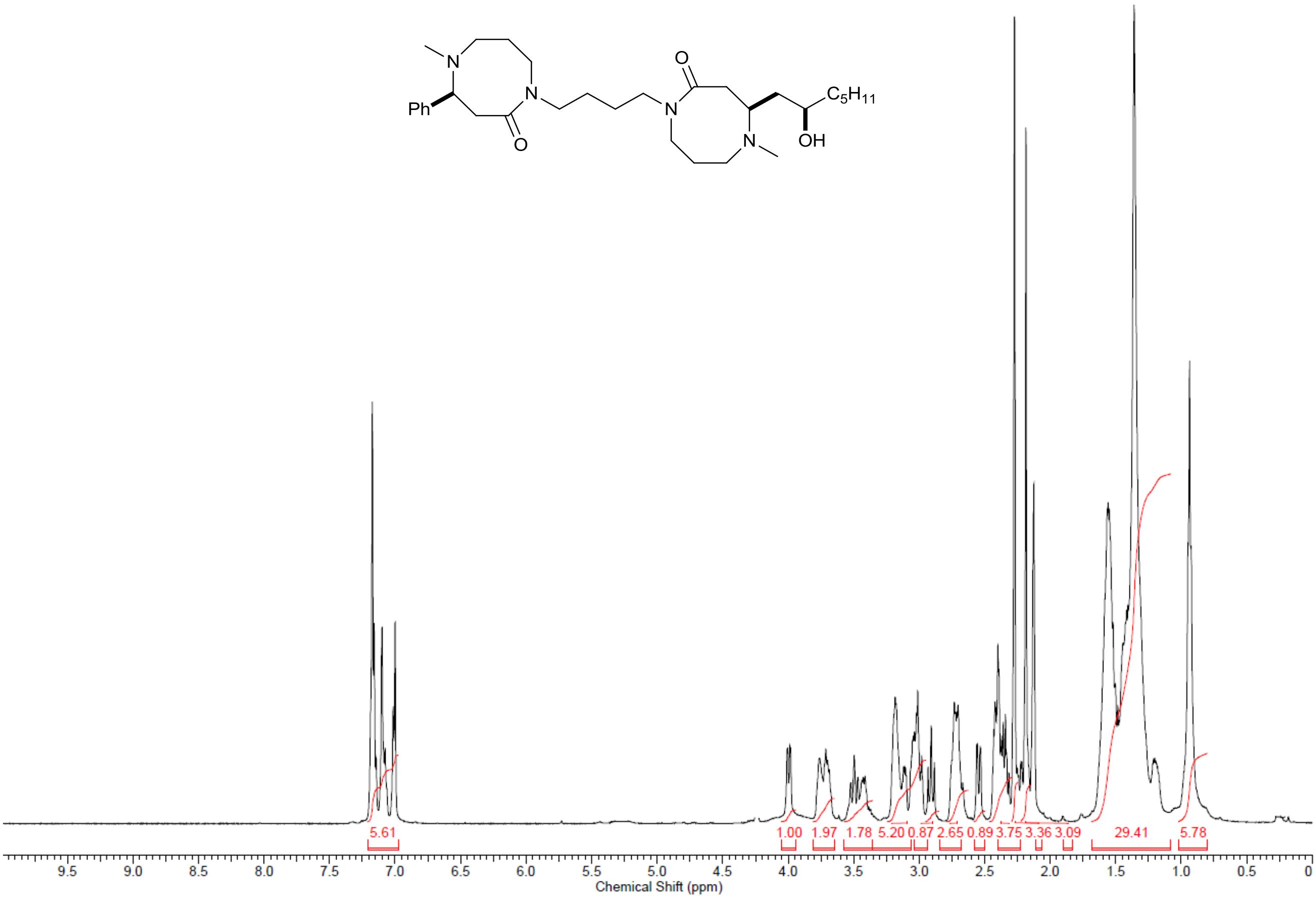
(***R***,***R***)-1-[2′-Oxo-4′-pentyl-*N*(5′)-methyl-1′,5′-diazocan-*N*(1′)-yl]-4-[2″-oxo-4″-heptyl-*N*(5″)-methyl-1″,5″-diazocan-*N*(1″)-yl]butane [(−)-hopromine] 100 (500 MHz, ^{1}H, PhMe-d_8, 363 K)



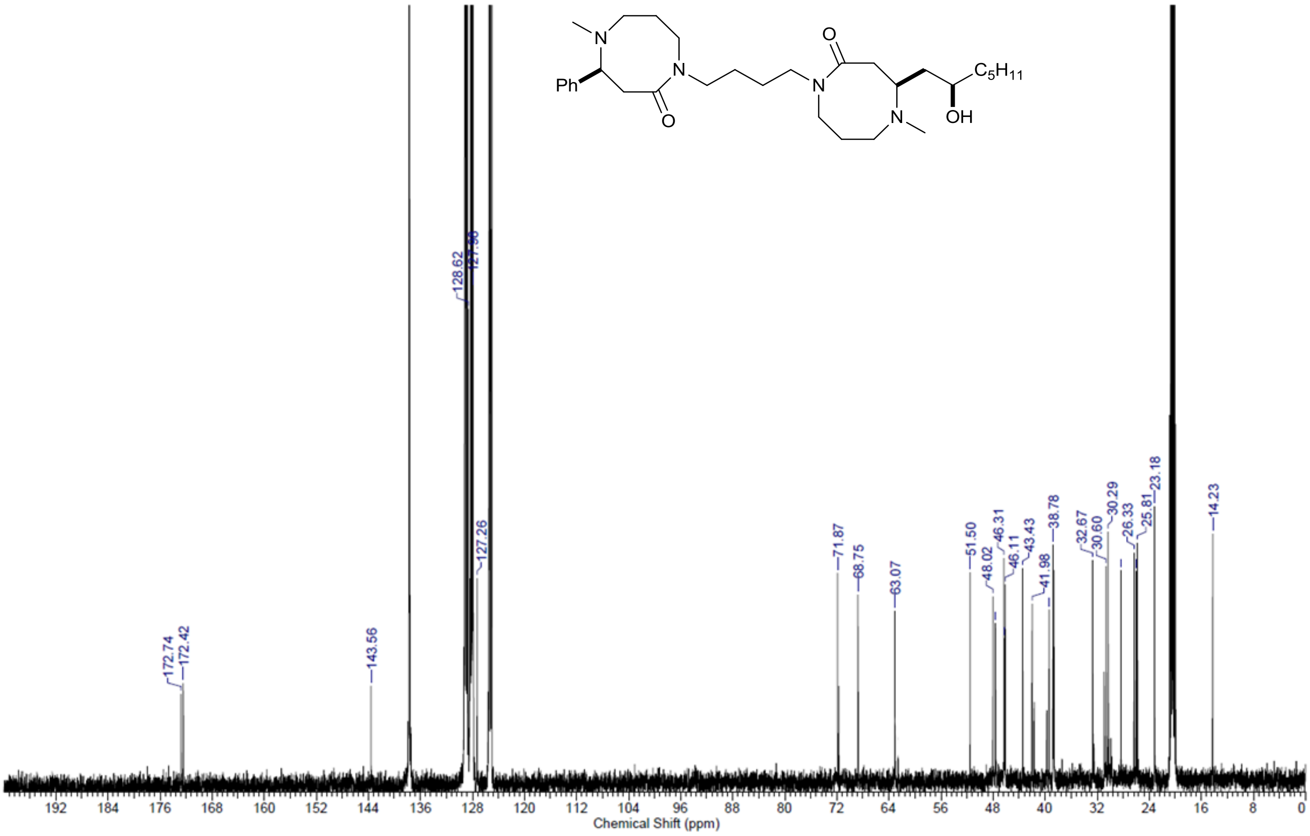
(***R***,***R***)-1-[2′-Oxo-4′-pentyl-*N*(5′)-methyl-1′,5′-diazocan-*N*(1′)-yl]-4-[2″-oxo-4″-heptyl-*N*(5″)-methyl-1″,5″-diazocan-*N*(1″)-yl]butane [(−)-hopromine] 100 (125 MHz, ^{13}C, PhMe-d_8, 363 K)



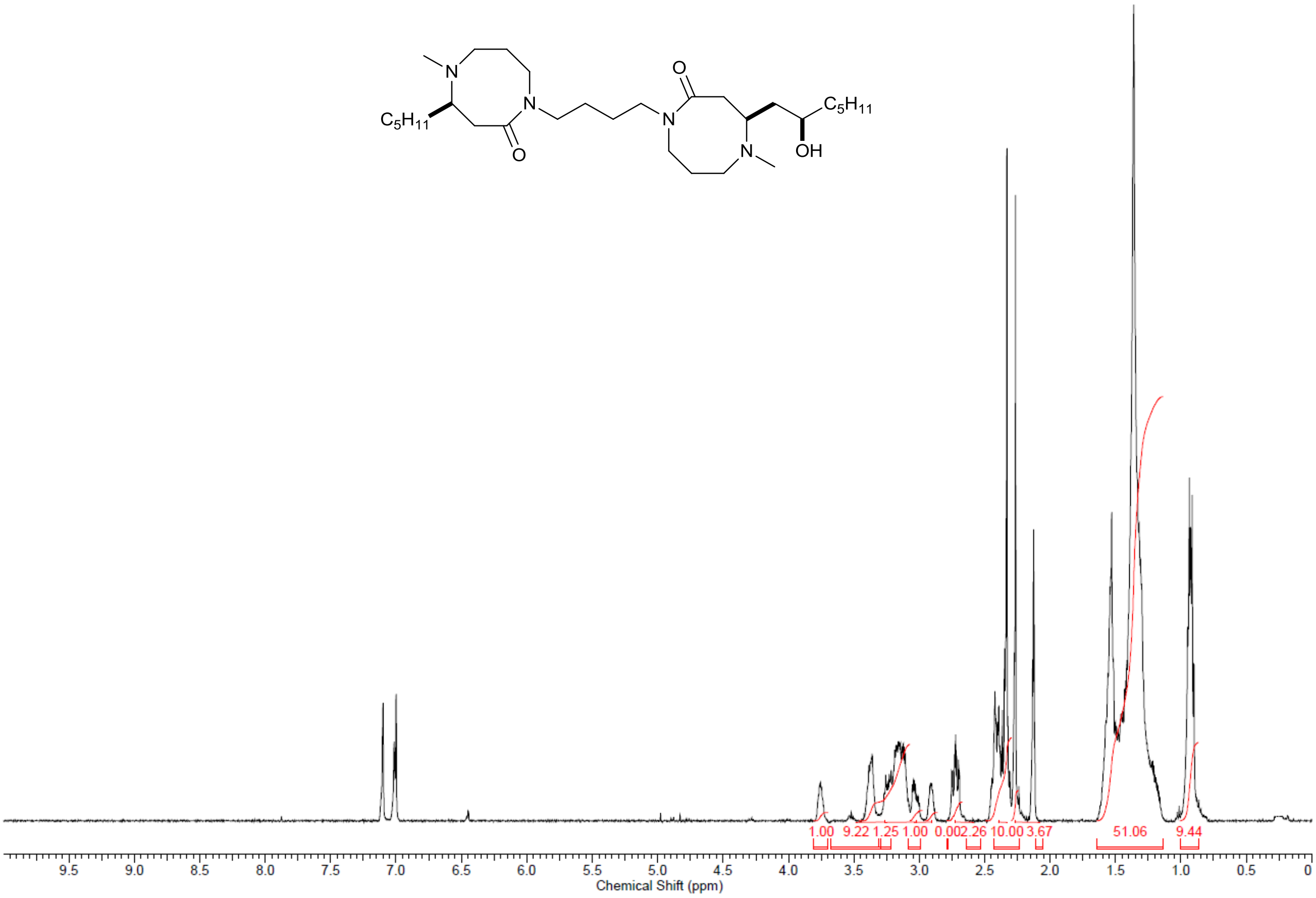
(4′*S*,4″*R*,2‴*R*)-1-[2′-Oxo-4′-phenyl-*N*(5′)-methyl-1′,5′-diazocan-*N*(1′)-yl]-4-[2″-oxo-4″-(2‴-hydroxyheptyl)-*N*(5″)-methyl-1″,5″-diazocan-*N*(1″)-yl]butane [(−)-horpomalinol] 494 (500 MHz ^{1}H, PhMe-d_8, 363 K)



(4′*S*,4″*R*,2‴*R*)-1-[2′-Oxo-4′-phenyl-*N*(5′)-methyl-1′,5′-diazocan-*N*(1′)-yl]-4-[2″-oxo-4″-(2‴-hydroxyheptyl)-*N*(5″)-methyl-1″,5″-diazocan-*N*(1″)-yl]butane [(−)-horpomalinol] 494 (125 MHz ^{13}C, PhMe-d_8, 363 K)



(*R*,*R*,*R*)-1-[2′-Oxo-4′-pentyl-*N*(5′)-methyl-1′,5′-diazocan-*N*(1′)-yl]-4-[2″-oxo-4″-(2‴-hydroxyheptyl)-*N*(5″)-methyl-1″,5″-diazocan-*N*(1″)-yl]butane [(−)-hoprominol] 497 (500 MHz ^{1}H, PhMe-d_8, 363 K)



(*R*,*R*,*R*)-1-[2′-Oxo-4′-pentyl-*N*(5′)-methyl-1′,5′-diazocan-*N*(1′)-yl]-4-[2″-oxo-4″-(2‴-hydroxyheptyl)-*N*(5″)-methyl-1″,5″-diazocan-*N*(1″)-yl]butane 497 [(−)-hoprominol] (125 MHz ^{13}C, PhMe-d_8, 363 K)