Asymmetric Syntheses of β- and γ-Amino Acids

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by

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In fact it happens also in chemistry as in architecture that "beautiful" edifices, that is, symmetrical and simple, are also the most sturdy: in short, the same thing happens with molecules as with the cupolas of cathedrals or the arches of bridges. And it is also possible that the explanation is neither remote nor metaphysical: to say "beautiful" is to say "desirable", and ever since man has built he has wanted to build at the smallest expense and in the most durable fashion, and the aesthetic enjoyment he experiences when contemplating his work comes afterward.

Primo Levi
The Periodic Table

The work described in this thesis was carried out in the Chemistry Research Laboratory, University of Oxford from October 2011 until August 2015, 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

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This thesis is concerned with the development of new synthetic routes for the asymmetric syntheses of a range of β- and γ-amino acids.

Chapter 1 introduces the various biological activities displayed by cyclic β-amino acid containing compounds together with their occurrence in pharmaceutical molecules and β-peptides. Some of the most commonly used synthetic strategies for the preparation of carbocyclic β-amino acids are briefly described, with the focus on the formation and functionalisation of a five-membered carbocyclic ring.

Chapter 2 describes a full investigation into a highly diastereoselective Ireland-Claisen rearrangement of stereodefined allyl β-amino esters to access enantiopure α-substituted β-amino acid products. The synthetic utility of this methodology is highlighted by its application in the asymmetric syntheses of five previously inaccessible C(5)-substituted 1,2-*anti*-1,5-*syn*-transpentacins.

Chapter 3 delineates investigations into a highly diastereoselective conjugate addition-elimination protocol for the preparation of a cyclic β'-amino-α,β-unsaturated ester. Subsequent chemo- and diastereoselective conjugate addition reactions of Grignard reagents and lithium amides to this substrate enabled the asymmetric syntheses of four C(5)-substituted 1,2-*anti*-1,5-*syn*-transpentacins and two five-membered β,β'-diamines.

Chapter 4 details the extension of the protocol developed in Chapter 3 for the conjugate addition of Grignard reagents to a range of acyclic γ-(*N*,*N*-dibenzylamino)-substituted α,β-unsaturated esters. Elaboration of the β,γ-disubstituted γ-amino ester products culminated in the asymmetric syntheses of six β,γ-disubstituted γ-amino acids.

Chapter 5 chronicles the preparation of an azabicyclic α,β-unsaturated ester, following which attempts towards the asymmetric synthesis of various substituted pyrrolizidines using a conjugate addition protocol are subsequently described.

Chapter 6 contains full experimental procedures and characterisation data for all compounds synthesised in Chapters 2, 3, 4 and 5.

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List of abbreviations

~	Approximately
(±)	Racemic
α	Alpha
$[\alpha]_D$	Specific rotation
Ac	Acetyl
AG	*Aktiengesellschaft* meaning public limited company
AIBN	Azobisisobutyronitrile
app	Apparent
aq	Aqueous
Ar	Aryl
atm	Atmosphere
ATR	Attenuated total reflectance
β	Beta
9-BBN	9-Borabicyclo[3.3.1]nonane
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
br	Broad
Bu	Butyl
Bz	Benzoate
γ	Gamma
c	Concentration
^{13}C	Carbon
CAN	Ceric ammonium nitrate
Cbz	Carboxylbenzyl
CI	Chemical ionisation
cm	Centimetres
cm^{-1}	Wavenumber
conc	Concentrated
conv	Conversion
COSY	Correlation spectroscopy
Cp	Cyclopentadienyl
CSI	Chlorosulfonyl isocyanate
Cy	Cyclohexyl
δ	Delta
d	Doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*'-Dicyclohexylcarbodiimide
Dec	Decomposes
Deg	Degrees
DIBAL-H	Diisobutylaluminium hydride

DMAP	4-(Dimethylamino)pyridine
DMF	*N*,*N*-Dimethylformamide
DPP-4	Dipeptidyl peptidase-4
dr	Diastereoisomeric ratio
δ_H	Proton (^{1}H) NMR chemical shift
δ_C	Carbon (^{13}C) NMR chemical shift
ε	Epsilon
(*E*)	Entgegen
E1cB	Elimination, unimolecular, *via* conjugate base
E2	Elimination, bimolecular
ee	Enantiomeric excess
ent	Enantiomer
epi	Epimer
equiv	Equivalents
ESI	Electrospray ionisation
Et	Ethyl
exo	Bond is outside of the newly formed ring
Fmoc	Fluorenylmethylcarbonyl
FT	Fourier transform
g	Grams
gem	Geminal
Grubbs I	Grubbs catalyst, 1st generation
Grubbs II	Grubbs catalyst, 2nd generation
h	Hours
^{1}H	Proton
HIV	Human immunodeficiency virus type 1
HMBC	Heteronuclear multiple bond correlation
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz
^{i}	Iso
i	Ipso
ICA	Isopropylcyclohexylamide
IR	Infrared
J	Coupling constant
^3J	Vicinal coupling constant
K	Kelvin
KHMDS	Potassium bis(trimethylsilyl)amide
L	Litres
LA	Lewis acid

LC	Liquid chromatography
LDA	Lithium diisopropylamide
LiHMDS	Lithium bis(trimethylsilyl)amide
lit.	Literature
m	Meta
m	milli
m	Multiplet
M	Molar
$[M]^+$	Molecular ion
m-CPBA	3-Chloroperbenzoic acid
Me	Methyl
MeOH-d_4	Deuterated methanol
MHz	Megahertz
min	Minutes
mol	Moles
mp	Melting point
Ms	Methanesulfonyl
MS	Mass spectrometry
m/z	Mass to charge ratio
μ	Micro
n	Integer
n	Nano
NBS	*N*-Bromosuccinimide
Nu	Nucleophile
NMO	4-Methylmorpholine-*N*-oxide
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect spectroscopy
o	Ortho
OSu	Succinimide
p	Para
PCC	Pyridinium chlorochromate
Ph	Phenyl
PhMe-d_8	Deuterated toluene
ppm	Parts per million
Pr	Propyl
q	Quartet
quant	Quantitative
R	General alkyl or aryl group
(*R*)	Rectus
ref.	Reference
rt	Room temperature

^{s}, *sec*	Secondary
s	Singlet
(*S*)	Sinister
satd	Saturated
Su	Succinimide
^{t}, *tert*	Tertiary
t	Triplet
T	Temperature
TBDMS	*tert*-Butyldimethylsilyl
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy
TES	Triethylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMS	Trimethylsilyl
Tr	Trityl, triphenylmethyl
trig	sp^2 (trigonal) hybridisation at the ring closure point
Ts	*p*-Toluenesulfonyl
UV	Ultraviolet
ν_{max}	Infrared absorption
v/v	Volume to volume ratio
w/w	Weight to weight ratio
γ	Gamma
(*Z*)	Zusammen

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Appendix: X-ray crystal structure data

Chapter 1: Introduction

This chapter illustrates a brief overview of the role of β-amino acids in medicinal and peptide chemistry. Selected examples of existing strategies for the preparation of cyclic β-amino acids will also be presented, focusing solely on β-amino acids bearing a five-membered carbocyclic scaffold.

1.1. The importance of β-amino acids

The structure of a β-amino acid has been defined as having the α-amino group shifted to the β-carbon position, thereby enabling different functionalities to be attached to the scaffold between the amino and carboxyl groups.[1] In the early 1990s, relatively simple β-amino acids had been recognised as displaying potent biological activity,[2] for instance cispentacin (*cis*-2-aminocyclopentanecarboxylic acid) **1**, which was isolated from *Bacillus cereus*[3] and *Streptomyces setonii*,[4] exhibits potent *in vivo* antifungal activity against various *Candida* strains.[5] Later, Bayer AG[6] discovered that icofungipen **2** was an antifungal agent that could be used for the treatment of yeast infections.[7] Since then, a number of cyclic β-amino acid analogues possessing a cispentacin core subunit have been assessed for pharmacological activity, such as amipurimycin **4** (a nucleoside antibiotic isolated from *Streptomyces novoguineensis*),[8] CEP-28122 **6** (a potent inhibitor of anaplastic lymphoma kinase activity displaying *in vivo* antitumour activity),[9] and β-benzamido hydroxamic acid **5** (a tumour necrosis factor-α converting enzyme inhibitor being investigated for the treatment of inflammatory diseases).[10] Moreover, the six-membered carbocyclic β-amino acid analogue tilidine **3** is an opioid analgesic drug used for the management of acute pain.[11] Examples of acyclic β-amino acid derivatives exhibiting biological activity include CP-91149 **7** (a selective human liver glycogen phosphorylase *a* inhibitor that reduces blood glucose *in vivo* and is used in investigations of glycogenolysis inhibition for the treatment of type 2 diabetes)[12] and sitagliptin **9** (a DPP-4 inhibitor developed by Merck for the treatment of type 2 diabetes).[13] In addition, Pfizer discovered that maraviroc **8** displays antiviral activity against the HIV-1 infection by acting as a potent antagonist of the chemokine CCR5 receptor[14] which blocks the entry of HIV-1[15] (Figure 1).

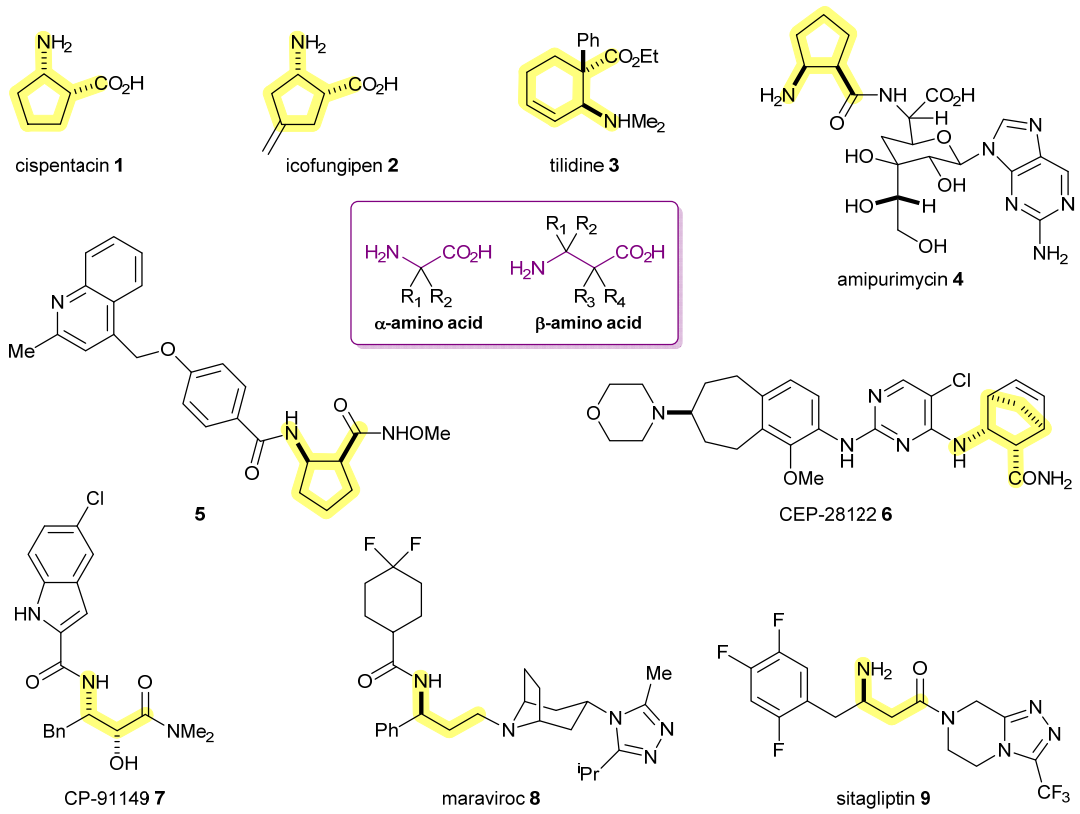


Figure 1. Representative examples of pharmacologically active β-amino acids and analogues thereof.

The incorporation of β-amino acids instead of α-amino acids into peptides[16,17] has also received a great deal of attention as a result of the privileged secondary structural characteristics[18] and biological activity[19,20] exhibited by oligomers of cyclic β-amino acid residues. For example, Reiser and co-workers utilised the conformationally rigid *cis*-2-aminocyclopropanecarboxylic acid subunit in the syntheses of α,β-peptides **10**.[21,22] β-Dipeptide **11** containing a four-membered carbocyclic β-amino acid residue[23,24] was reported to exhibit potent biological activity as a metallocarboxypeptidase B inhibitor.[25] Moreover, Gellman and co-workers incorporated the cyclic β-amino acid subunit transpentacin (*trans*-2-aminocyclopentanecarboxylic acid) **12** into β-peptides **13**, and reported that both peptides (hexamer or octamer) adopt a conformationally stable helical folding pattern defined by interwoven 12-membered-ring hydrogen bonds (12-helix) in the solid state and in solution.[26] Secondary structural characteristics of oligomers **14** derived from substituted transpentacin monomers have also been investigated by Davies and co-workers (Figure 2).[27]

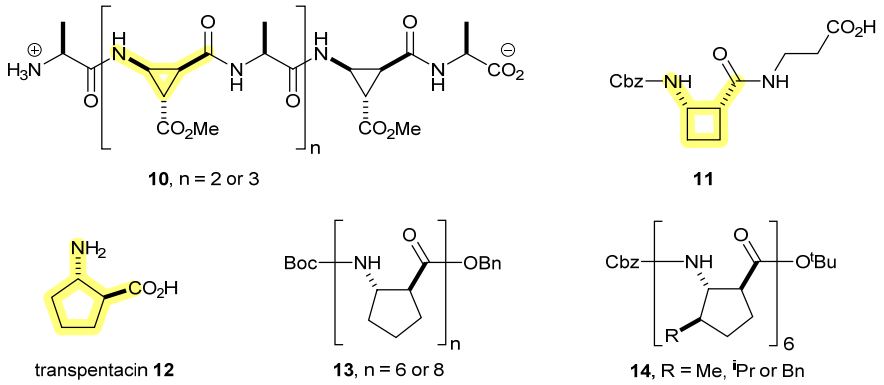


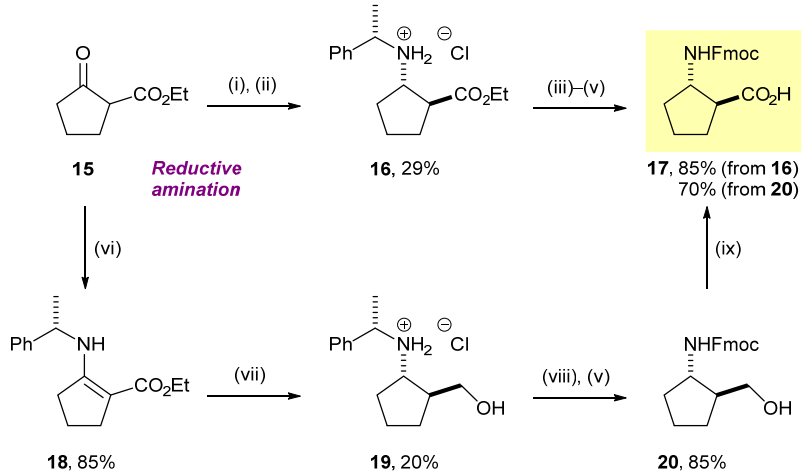
Figure 2. Structures of α,β-peptides **10**, β-dipeptide **11**, cyclic β-amino acid transpentacin **12**, β-peptides **13** and substituted analogues **14**.

1.2. Synthetic strategies towards cyclic β-amino acids

As was pointed out in a recent review by Fülöp and co-workers on carbocyclic β-amino acids,[28] a number of synthetic methods to construct and functionalise a five-membered carbocyclic ring have been identified. The following subsections cover representative examples of the strategies so far reported for the preparation of cyclic β-amino acids.

1.2.1. Reductive amination

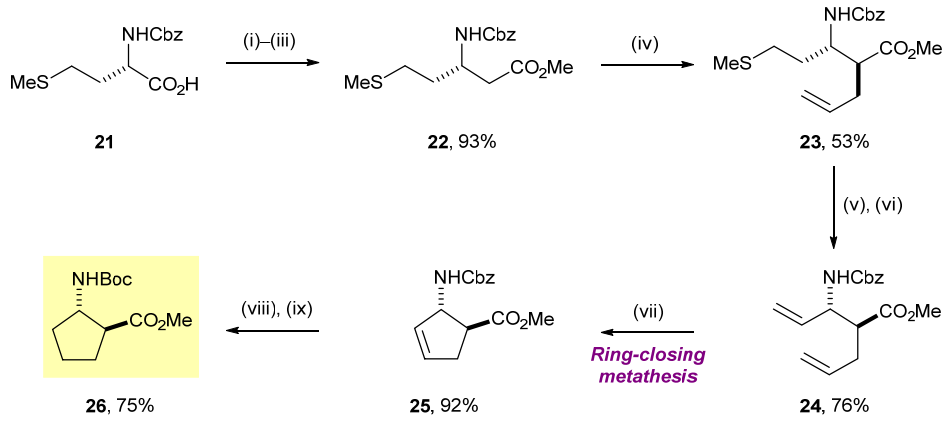
Gellman and co-workers[29] have expanded on Bartoli's original strategy[30] of reducing a cyclic β-enamino ester with sodium. (*S*)-α-Methylbenzylamine was used to prepare β-enamino ester **18** and reduction of **18** gave β-amino alcohol **19** in 20% isolated yield. Further elaboration to β-amino acid **17** proceeded in 10% overall yield from β-keto ester **15**. The authors also explored an alternative shorter route to **17** starting from the reductive amination of **15** with (*S*)-α-methylbenzylamine and $NaBH_3CN$, followed by sequential ester hydrolysis, hydrogenolysis and *N*-Fmoc-protection to afford **17** in an improved 25% overall yield from β-keto ester **15** (Scheme 1).



Scheme 1. *Reagents and conditions*: (i) (*S*)-α-methylbenzylamine, AcOH, rt, 2 h then $NaBH_3CN$, 72 °C, 13 h; (ii) 4.0 M HCl in dioxane, 0 °C, 1 h; (iii) $LiOH{\cdot}H_2O$, THF/MeOH/H_2O (v/v/v 6:3:1), 0 °C, 9 h; (iv) H_2, Pd/C, EtOH, rt, 48 h; (v) FmocOSu, $NaHCO_3$, acetone/H_2O (v/v 2:1), 0 °C, 1 h then rt, overnight; (vi) (*S*)-α-methylbenzylamine, TsOH, reflux, 16 h; (vii) Na, ^{i}PrOH, THF, rt, 7 h then 4.0 M HCl in dioxane, 0 °C, 2 h; (viii) Pd/C, NH_4CO_2H, MeOH, reflux, 4 h; (ix) NaOCl, TEMPO, $NaHCO_3$, KBr, Bu_4NBr, CH_2Cl_2, 0 °C, 1 h.

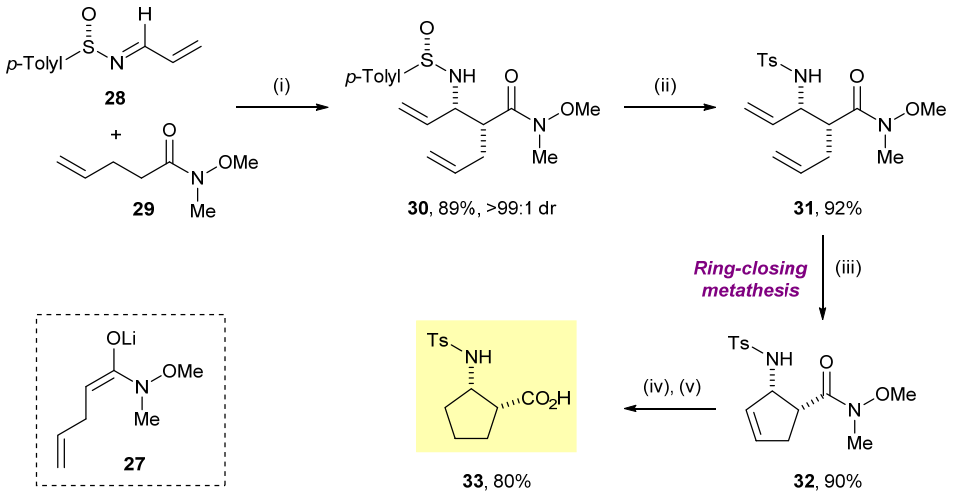
1.2.2. Ring-closing metathesis

Application of a ring-closing metathesis protocol for the synthesis of enantiopure cyclic β-amino esters has been described by Abell and co-workers.[31,32] For this purpose, *N*-Cbz-(*S*)-methionine **21** was used as the starting material to prepare the ring-closing metathesis precursor **24**. β-Amino ester **22** was synthesised by an Arndt-Eistert[33] homologation/esterification reaction sequence, and was then alkylated with allyl bromide to give *anti*-**23** in 49% overall yield (from **21**). Diene **24** was then prepared in 76% yield by subjecting **23** to H_2O_2 to promote oxidative elimination of the methylsulfanyl moiety. The formation of cyclic β-amino ester **25** was then carried out in the presence of Grubbs II in benzene to give **25** in 92% yield. Finally, tandem hydrogenolysis/reduction and *N*-Boc protection gave **26** in 26% overall yield, in nine steps from *N*-Cbz protected (*S*)-methionine **21** (Scheme 2).



Scheme 2. *Reagents and conditions*: (i) Et_3N, $ClCO_2Et$, THF, –15 °C, 15 min; (ii) CH_2N_2, 0 °C; (iii) AgBz, Et_3N, MeOH, –25 °C; (iv) LiCl, LDA, –78 °C, 1 h then allyl bromide, –78 °C, 2 h then rt, 16 h; (v) H_2O_2, AcOH, rt, 4 h; (vi) xylene, 200 °C, sealed tube, 16 h; (vii) Grubbs II, C_6H_6, rt, 2 h; (viii) H_2, Pd/C, MeOH, rt, 12 h; (ix) Boc_2O, $NaHCO_3$, MeOH, rt, 3 h.

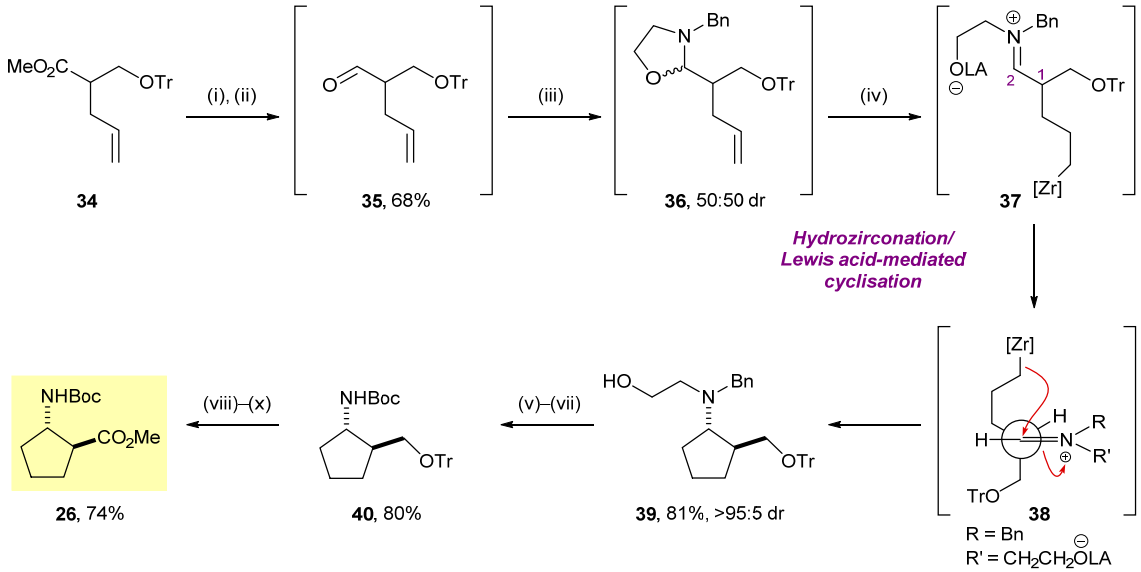
In addition, Davis and Theddu have adopted a ring-closing metathesis strategy for the synthesis of cyclic β-amino Weinreb amides as the key step in their synthesis of β-amino acids.[34] Treatment of lithium enolate **27** (derived from the deprotonation of *N*-methoxy-*N*-methyl 4-pentenamide **29** with LDA) with sulfinimine[35] **28** resulted in the formation of the *N*-sulfinyl β-amino Weinreb amide **30** in 89% isolated yield and >99:1 dr.[36] Conversion of the *N*-sulfinyl auxiliary to an *N*-tosyl group[37] *via* oxidation with *m*-CPBA proceeded to give **31**, which was in turn subjected to ring-closing metathesis conditions to give the cyclic β-amino Weinreb amide **32** in 83% overall yield (from **30**). Subsequent deprotection involving reduction of the double bond and hydrolysis of the amide group afforded *N*-tosyl protected β-amino acid **33** in five steps and 59% overall yield from **28** (Scheme 3).



Scheme 3. *Reagents and conditions*: (i) LDA, THF, –78 °C, 1 h; (ii) *m*-CPBA, CH_2Cl_2, rt, 1 h; (iii) Grubbs II, CH_2Cl_2, rt, 16 h; (iv) H_2 (1 atm), Pd/C, EtOH, rt, 16 h; (v) KOH, THF, reflux, 48 h.

1.2.3. Hydrozirconation/Lewis acid-mediated cyclisation

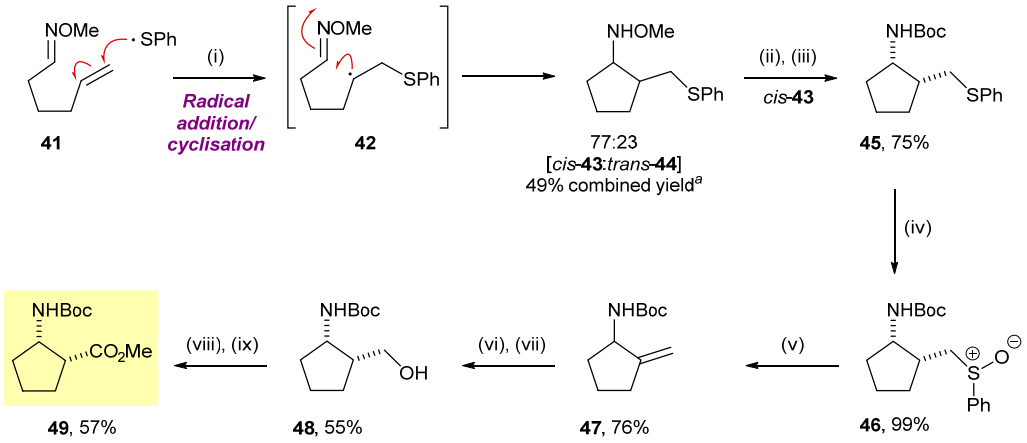
Szymoniak and co-workers showed the applicability of a tandem hydrozirconation/Lewis acid-mediated cyclisation sequence[38] for the synthesis of cyclic β-amino esters.[39] Treatment of methyl ester **34** with $LiAlH_4$ followed by oxidation of the resultant alcohol with PCC afforded aldehyde **35** in 68% yield. Subsequent reaction of **35** with *N*-benzylaminoethanol in refluxing toluene resulted in the formation of a 50:50 mixture of diastereoisomers of the substituted oxazolidine **36**. Hydrozirconation of the C=C bond within **36** using $Cp_2Zr(H)Cl$ in the presence of a stoichiometric amount of $BF_3{\cdot}OEt_2$ led exclusively to the *trans*-configured cyclopentane product **39** in 81% yield and >95:5 dr. The preference for the *trans*-isomer was rationalised by the authors by invoking a modified Felkin-Anh-type transition state model **38**, where the C(1)–CH_2OTr group adopts a perpendicular orientation to the C(2)-iminium moiety in order to minimise steric interactions. *N*-Debenzylation of **39** with Pd/C under a H_2 atmosphere was subsequently carried out, followed by $Pb(OAc)_4$ promoted oxidative cleavage of the hydroxyethyl moiety and *N*-Boc protection to furnish the *N*- and *O*-protected amino alcohol **40** in 80% yield over the three steps. Upon ruthenium-catalysed oxidation of the hydroxymethyl group (following deprotection of the alcohol with AcOH) and esterification of the corresponding carboxylic acid with $TMSCHN_2$, β-amino ester **26** was obtained in 33% overall yield from **34** (Scheme 4).



Scheme 4. *Reagents and conditions*: (i) $LiAlH_4$, EtO_2, 0 °C, 2 h; (ii) PCC, Celite, CH_2Cl_2, rt, 2 h; (iii) *N*-benzylaminoethanol, PhMe, reflux, 3 h; (iv) $Cp_2Zr(H)Cl$, CH_2Cl_2 then $BF_3{\cdot}OEt_2$, rt, 30 min; (v) H_2, Pd/C, rt, 12 h; (vi) $Pb(OAc)_4$, MeOH, CH_2Cl_2, 0 °C, 30 min then $NH_2OH{\cdot}HCl$, 0 °C, 30 min; (vii) Boc_2O, CH_2Cl_2, Et_3N, rt, 2 h; (viii) AcOH/H_2O (v/v 4:1), rt, 2 h; (ix) RuO_2, $NaIO_4$, acetone/H_2O (v/v 1:1), rt, 4 h; (x) $TMSCHN_2$ (2 M in Et_2O), MeOH, rt, 1 h.

1.2.4. Radical addition/cyclisation

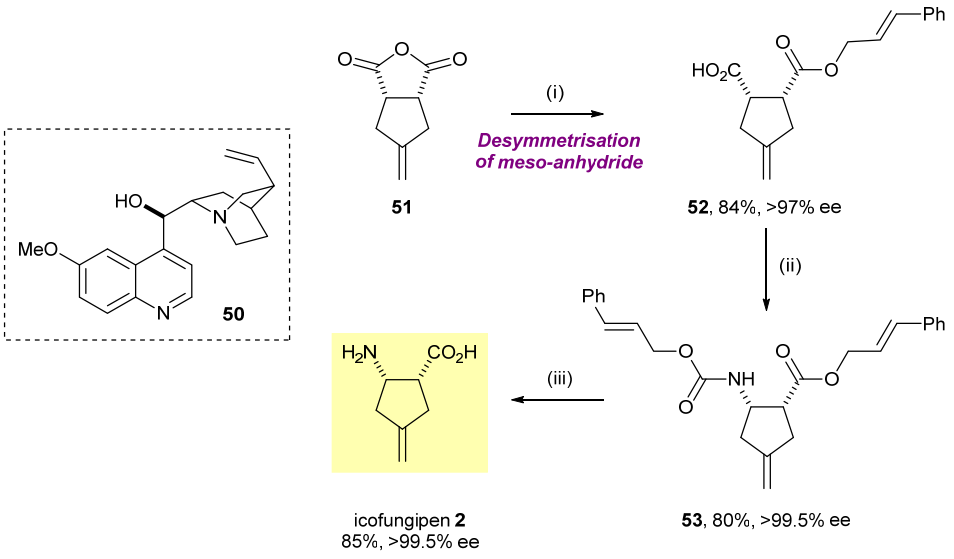
Oxime ethers have been reported to cyclise *via* a phenylsulfanyl radical addition/cyclisation pathway allowing access to cyclic β-amino esters.[40] Naito and co-workers subjected oxime ether **41** to a radical cyclisation protocol consisting of thiophenol and AIBN in refluxing benzene to promote a 5-*exo*-*trig* cyclisation of the alkyl radical species **42**, which resulted in a 77:23 mixture of *cis*- and *trans*-cyclopentane products **43** and **44**, respectively, in 49% combined isolated yield. Elaboration of *cis*-**43** through to β-amino ester **49** was achieved *via* reductive cleavage of the *N*-methoxy group followed by *N*-Boc protection to furnish **45** in 75% yield. Oxidation of **45** with *m*-CPBA resulted in the formation of the corresponding sulfoxide **46** which was then heated to reflux in the presence of NaOAc to give **47** in 75% yield over the two steps. Conversion of **47** into β-amino ester **49** was performed in 31% overall yield and a four step sequence involving the stereoselective hydroboration/oxidation of **47** followed by oxidation of **48** under ruthenium catalysis, and esterification of the intermediate carboxylic acid with diazomethane (Scheme 5).



Scheme 5. *Reagents and conditions*: (i) PhSH, AIBN, C_6H_6, reflux, 2 h; (ii) $LiAlH_4$, THF, reflux, 8 h; (iii) Boc_2O, Et_3N, CH_2Cl_2, rt, 5 h; (iv) *m*-CPBA, CH_2Cl_2, 0 °C, 4.5 h; (v) NaOAc, *o*-dichlorobenzene, reflux, 3 h; (vi) 9-BBN, THF, 0 °C, 7 h; (vii) 30% H_2O_2, 6.0 M aq NaOH, 0 °C then rt, 16 h; (viii) $RuO_2 \cdot H_2O$, $NaIO_4$, H_2O/acetone (v/v 3:2), rt, 7 h; (ix) CH_2N_2, MeOH, Et_2O, 0 °C then rt, 1 h. [[a] Individual yields for *cis*-**43** and *trans*-**44** were not reported.]

1.2.5. Desymmetrisation of *meso*-anhydrides

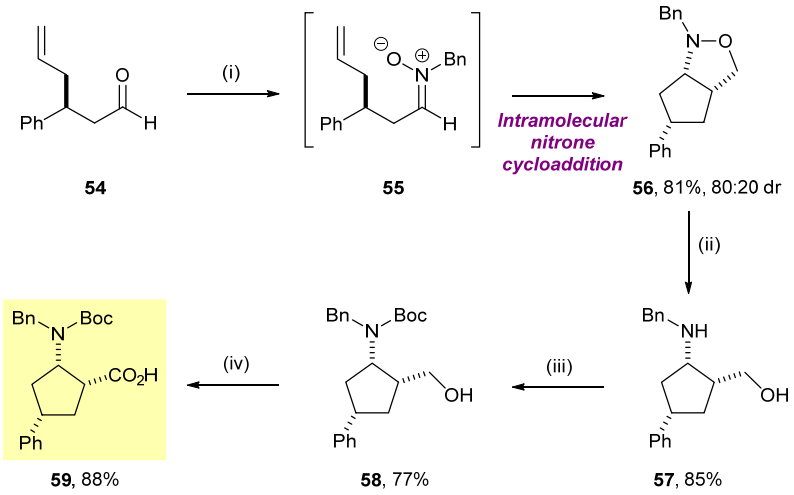
Another established method of accessing cyclic β-amino acids is by the enantioselective desymmetrisation of *meso*-anhydrides with alcohols.[41,42] For example, Mittendorf and co-workers have shown that the reaction of cyclic anhydride **51** with cinnamyl alcohol in the presence of 1.0 equiv of quinine **50** at –15 °C proceeded to give hemiester **52** in high enantiomeric excess (>97% ee).[6,43] The corresponding β-amino ester **53** was subsequently formed in 80% yield and >99.5% ee *via* a Curtius rearrangement of **52** with diphenylphosphoryl azide and treatment of the intermediate isocyanate with cinnamyl alcohol. One-pot deprotection of both the amide and carbamate groups within **53** using $Pd(OAc)_2$ and morpholine in EtOH gave enantiomerically pure icofungipen **2** in 57% yield over the three steps (Scheme 6).



Scheme 6. *Reagents and conditions*: (i) **50**, PhMe, –15 °C, 10 min then (*E*)-3-phenyl-2-propan-1-ol, –15 °C, overnight; (ii) $(PhO)_2PON_3$, Et_3N, PhMe, 90 °C, 30 min then (*E*)-3-phenyl-2-propan-1-ol, reflux, overnight; (iii) PPh_3, morpholine, EtOH, rt, 10 min then $Pd(OAc)_2$, reflux, 2 h then 3-mercapto-1,2,4-triazole, reflux, 1 h then 3 °C, 30 min.

1.2.6. Intramolecular nitrone cycloaddition

Beak and Whisler have applied an intramolecular nitrone-olefin cycloaddition reaction[44] to enantiopure β-allyl-substituted aldehydes, giving rise to cyclic β-amino acids.[45,46] The authors reported that condensation of **54** with *N*-benzylhydroxylamine hydrochloride presumably proceeds *via* the nitrone species **55** to give isoxazolidine **56** in 81% isolated yield and 80:20 dr. Isoxazolidine **56** was in turn subjected to Zn and AcOH to give the corresponding amino alcohol **57** in 85% yield. The synthesis was completed by an *N*-Boc protection step followed by a ruthenium-catalysed oxidation reaction with $NaIO_4$ affording the *N*-protected amino acid **59** in 68% isolated yield over the two steps (Scheme 7).

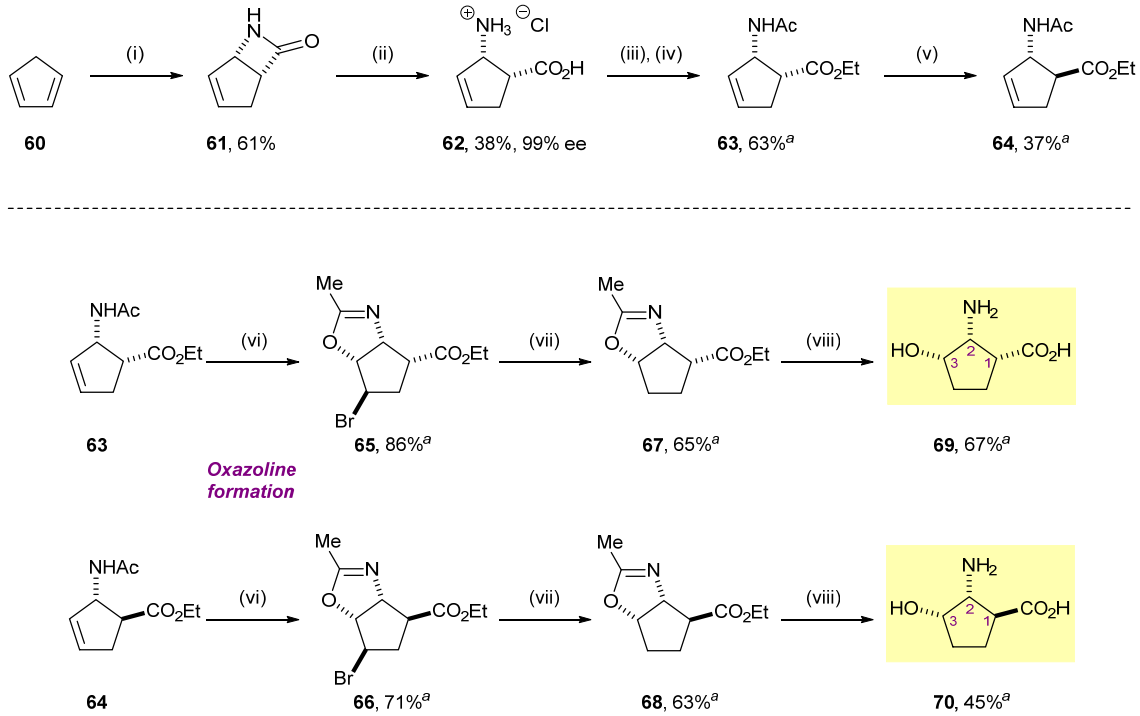


Scheme 7. *Reagents and conditions*: (i) BnNHOH·HCl, Et_3N, PhMe, molecular sieves, rt, overnight; (ii) Zn, AcOH, 55 °C, 3 h; (iii) Boc_2O, $NaHCO_3$, MeOH, rt, overnight; (iv) $RuCl_3$, $NaIO_4$, MeCN/CCl_4/H_2O (v/v/v 1:1:1.5), rt, overnight.

1.2.7. Enzymatic resolution

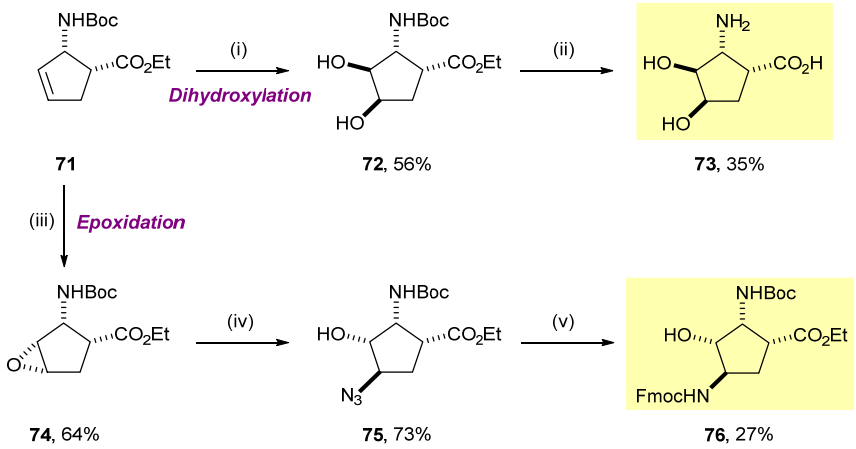
Fülöp and co-workers have adopted an enzymatic resolution and functionalisation procedure to facilitate the preparation of the C(3)-hydroxy substituted β-amino acids **69** and **70**.[47,48] For this purpose, the reaction of β-amino esters **63** and **64** with NBS was investigated. The synthesis of both diastereoisomers **63** and **64** was accomplished using β-lactam **61** as the precursor.[49] Treatment of cyclopentadiene **60** with chlorosulfonyl isocyanate (CSI) in Et_2O gave racemic bicyclic β-lactam **61** in 61% yield.[50] Enantioselective ring-opening of **61** using Lipolase (lipase B from *Candida antarctica*) followed by treatment with HCl gave **62** in 38% yield and 99% ee.[51,52] Subsequent esterification and acetylation enabled the formation of *cis*-**63** in 63% overall yield, which was also epimerised with NaOEt to provide *trans*-**64** in 37% yield. The authors reported that the reactions of both *cis*-**63** and *trans*-**64** with NBS proceeded regio- and diastereoselectively to furnish the bicyclic bromooxazoline products **65** and **66** in 86 and 71% yield, respectively. A subsequent radical reduction step provided the

corresponding oxazolines **67** and **68** in good yield. Finally, heating **67** and **68** in 20% aq HCl resulted in global deprotection affording β-amino acids **69** and **70** in 5 and 1% overall yield, respectively, in eight steps from **60** (Scheme 8).



Scheme 8. *Reagents and conditions*: (i) CSI, Et_2O, –10 °C, 3 h; (ii) Lipolase, $^{i}Pr_2O$, H_2O, 70 °C, 5 h; (iii) $SOCl_2$, EtOH, rt, 3 h, then reflux, 1 h; (iv) AcCl, Et_3N, $CHCl_3$, rt, 2 h; (v) NaOEt, EtOH, rt, 24 h; (vi) NBS, CH_2Cl_2, rt, 3 h; (vii) Bu_3SnH, CH_2Cl_2, 40 °C, 20 h; (viii) 20% aq HCl, reflux, 24 h then Dowex 50WX8. [[a] Yields quoted herein correspond to those obtained for the racemic series since the yields for the preparation of the enantiopure analogues were not reported.]

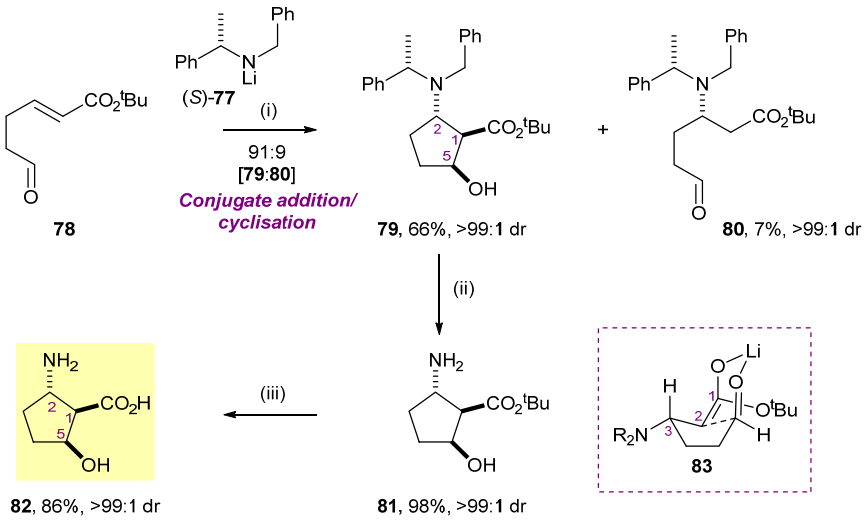
Fülöp and co-workers have also investigated the oxidative functionalisation of cyclic olefin substrates, such as β-amino ester **71**. Dihydroxylation of **71** using a catalytic amount of OsO_4 and 3.0 equiv of NMO (i.e., Upjohn conditions)[53] gave 3,4-dihydroxy substituted β-amino ester **72** in 56% yield.[47,54] Diol **72** was in turn deprotected to give β-amino acid **73** by treatment with 20% aq HCl in 20% overall yield. β-Amino ester **71** was also subjected to epoxidation conditions to give epoxide **74** in 64% yield.[55,56,57] Regioselective ring-opening of **74** with NaN_3 provided the C(4)-azido substituted β-amino ester **75** as the sole product in 73% yield. The synthesis was subsequently completed by a Staudinger reaction protocol followed by *in situ* treatment with FmocOSu to give β-amino ester **76** in 13% overall yield from **71** (Scheme 9).[48]



Scheme 9. *Reagents and conditions*: (i) OsO_4, NMO, acetone, rt, 4 h; (ii) 20% aq HCl, rt, 24 h; (iii) *m*-CPBA, CH_2Cl_2, 0 °C, 5 h; (iv) NaN_3, EtOH, 20 mol% NH_4Cl, H_2O, reflux, 4 h; (v) PPh_3, THF, H_2O, rt, 5 h then FmocOSu, Et_3N, rt, 12 h.

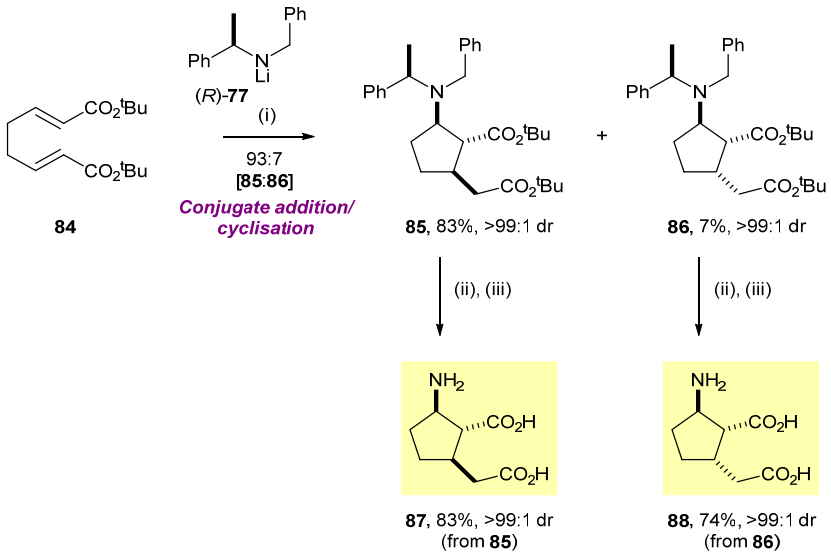
1.2.8. Lithium amide conjugate addition

Access to the C(5)-hydroxy substituted β-amino acid **82** from α,β-unsaturated-ε-aldehyde ester **78** *via* a diastereoselective conjugate addition/cyclisation protocol has been investigated by Davies and co-workers.[58,59,60] Under the optimised reaction conditions, treatment of **78** with lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*S*)-**77** gave a 91:9 product mixture of cyclic β-amino ester **79** and the corresponding acyclic β-amino ester **80**, from which **79** was isolated in 66% yield. The authors proposed that the (*Z*)-configured enolate[61] **83** minimises 1,3-allylic strain and the intramolecular aldol reaction with the tethered aldehyde proceeds *via* a boat-like transition state whereby lithium chelation between the aldehyde and enolate oxygen is present. Removal of the *N*-benzyl and *N*-(α-methylbenzyl) groups followed by ester hydrolysis upon treatment with TFA afforded β-amino acid **82** in 56% overall yield from **78** (Scheme 10).



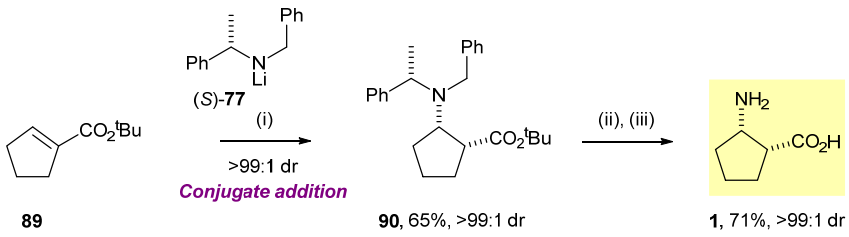
Scheme 10. *Reagents and conditions*: (i) (*S*)-**77**, THF, –78 °C, 2 h then –20 °C, 2 h; (ii) H_2 (5 atm), $Pd(OH)_2/C$, MeOH, rt, 16 h; (iii) TFA, CH_2Cl_2, rt, 16 h then Dowex 50WX8.

Davies and co-workers have also accomplished a high-yielding tandem diastereoselective conjugate addition/cyclisation reaction[62] leading to the synthesis of β-amino diacids.[63,64] For example, treatment of α,β-unsaturated *tert*-butyl diester **84** with (*R*)-**77** in THF at –78 °C furnished a 93:7 mixture of the target C(5)-epimeric cyclopentane products **85** and **86**, respectively. Following chromatographic separation, **85** and **86** were isolated in 83 and 7% yield, respectively, and were subsequently elaborated to β-amino diacids **87** and **98** in 83 and 74% yield *via* a two-step procedure involving hydrogenolysis followed by acid-catalysed ester hydrolysis (Scheme 11).



Scheme 11. *Reagents and conditions*: (i) (*R*)-**77**, THF, –78 °C, 2 h; (ii) H_2 (5 atm), Pd/C, AcOH, MeOH, rt, overnight; (iii) TFA, rt, 2 h then Dowex 50WX8.

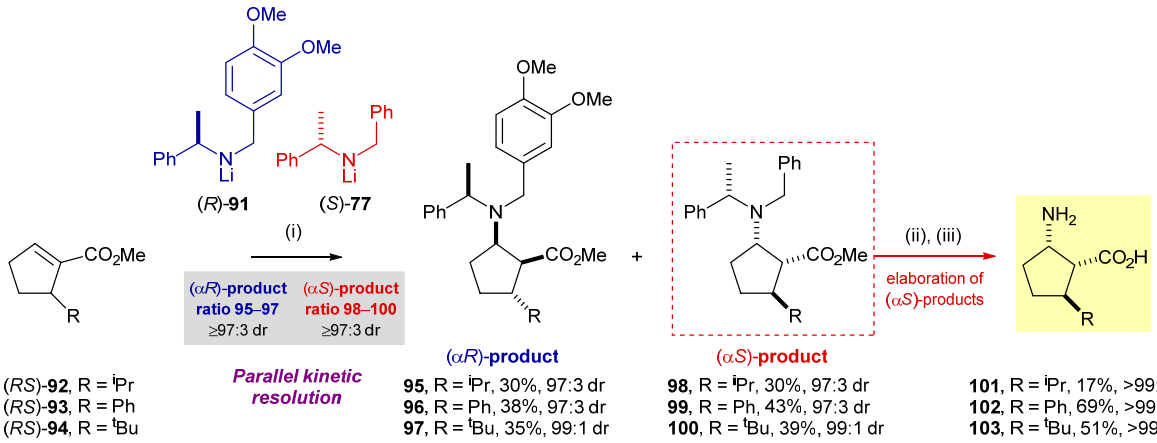
A highly diastereoselective conjugate addition reaction of enantiopure lithium amide to *tert*-butyl cyclopent-1-enecarboxylate **89** has been developed to access cyclic β-amino acids. For example, subjection of **89** to (*S*)-**77** in THF at –78 °C gave **90** in 65% isolated yield and >99:1 dr. Elaboration to cispentacin **1** was effected in just two chemical transformations: *N*-deprotection with Pd/C under a H_2 atmosphere followed by hydrolysis of the *tert*-butyl moiety to give **1** in 46% overall yield from **89** (Scheme 12).[65]



Scheme 12. *Reagents and conditions*: (i) (*S*)-**77**, THF, –78 °C, 2 h; (ii) H_2 (5 atm), Pd/C, AcOH, 50 °C, overnight; (iii) TFA, rt, 16 h then Dowex 50WX8.

The use of a parallel kinetic resolution strategy to afford a different class of substituted β-amino acids has also been demonstrated by Davies and co-workers.[66] A 50:50

pseudoenantiomeric mixture of lithium amides (*R*)-**91** and (*S*)-**77** were shown to react with racemic C(5)-substituted α,β-unsaturated esters **92**–**94** to give 50:50 mixtures of (α*R*)-β-amino esters **95**–**97** and (α*S*)-β-amino esters **98**–**100** in ≥97:3 dr in all cases (Scheme 13). To rationalise the stereochemical outcome of this reaction, the authors suggested that steric interactions between the lithium amides and the C(5)-substituent within α,β-unsaturated esters **92**–**94** favours addition on the face opposite to the C(5)-substituent. Subsequent protonation then occurs *anti* to the C(2)-amino group. The reaction sequence was continued with the (α*S*)-β-amino esters by subjection of **98**–**100** to hydrogenolysis conditions followed by acid-catalysed ester hydrolysis to furnish a range of 1,2-*syn*-1,5-*anti*-configured β-amino acids **101**–**103** in 5–30% overall yield (Scheme 13).[67]



Scheme 13. *Reagents and conditions*: (i) (*R*)-**91**/(*S*)-**77** (50:50 mixture), THF, –78 °C, 2 h; (ii) H_2 (5 atm), $Pd(OH)_2$/C, MeOH, rt, 24 h; (iii) 20% aq HCl, reflux, 16 h then Dowex 50WX8.

Davies and co-workers have also utilised the parallel kinetic resolution strategy for the asymmetric synthesis of C(3)-substituted β-amino acids.[68,69]

1.3. Project aims

The primary aim of this thesis is to develop new synthetic routes for the asymmetric synthesis of a range of C(5)-substituted cyclic β-amino acids that are inaccessible *via* the parallel kinetic resolution strategy. Initial studies will focus on using stereodefined allyl β-amino esters **104** in a diastereoselective Ireland-Claisen rearrangement protocol to access α-substituted β-amino esters **105**. It was envisaged that further elaboration using ring-closing metathesis would allow access to cyclic β-amino acids **106**. Subsequent investigations towards **106** will explore the diastereoselective conjugate addition reactions of organometallic reagents and lithium amides to enantiopure β'-amino-α,β-unsaturated ester **107**. Furthermore,

the use of a bicyclic scaffold as the α,β-unsaturated ester substrate in the lithium amide conjugate reaction was anticipated to access the azabicyclic β-amino acid **109** (Figure 3).

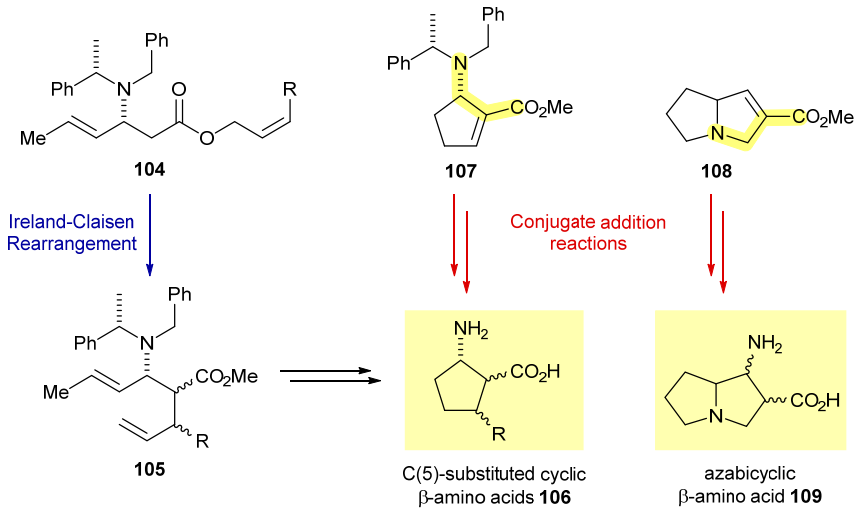


Figure 3. The Ireland-Claisen rearrangement of allyl β-amino esters **104** and conjugate addition reactions to α,β-unsaturated esters **107** and **108** as the key steps in the asymmetric synthesis of cyclic β-amino acids.

1.4. References and notes

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Chapter 2: Diastereoselective Ireland-Claisen rearrangements of substituted allyl β-amino esters and applications in the asymmetric synthesis of enantiopure C(5)-substituted transpentacins

This chapter details investigations into the diastereoselective Ireland-Claisen rearrangement of substituted allyl β-amino esters **110**, and the application of this methodology in the asymmetric synthesis of C(5)-substituted 1,2-*anti*-1,5-*syn*-transpentacins **111** (Figure 4).

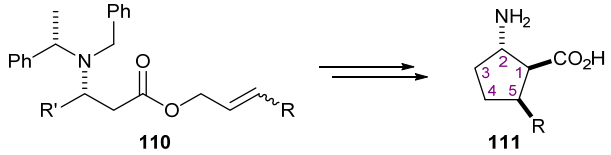


Figure 4. Diastereoselective Ireland-Claisen rearrangement of stereodefined allyl β-amino esters **110** utilised in the preparation of 1,2-*anti*-1,5-*syn*-transpentacins **111**.

2.1. Introduction

One of the most notable variants of the Claisen [3,3]-sigmatropic rearrangement is the Ireland-Claisen rearrangement which has been used as a powerful tool in organic synthesis.[1] Ireland and co-workers demonstrated the tuneable diastereoselectivity of the Ireland-Claisen rearrangement by the stereoselective enolisation of substituted allyl esters, such as **112**, with lithium amide bases in the presence or absence of HMPA, followed by trapping with silylating agents to promote a [3,3]-rearrangement of the resultant allyl trimethylsilyl ketene acetals **113** and **114**, and subsequently furnishing γ,δ-unsaturated carboxylic acids **115** and **116** (Figure 5).[2]

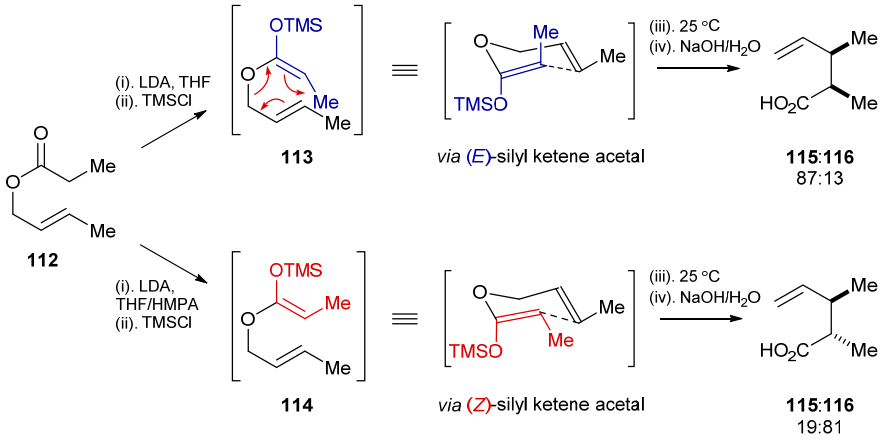
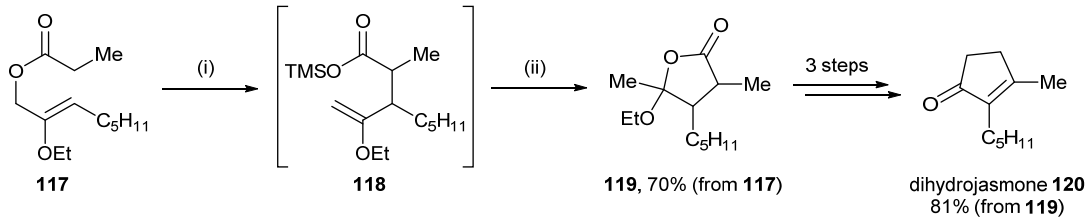


Figure 5. The Ireland-Claisen rearrangement of silyl ketene acetals **113** and **114** *via* chair-like transition states.

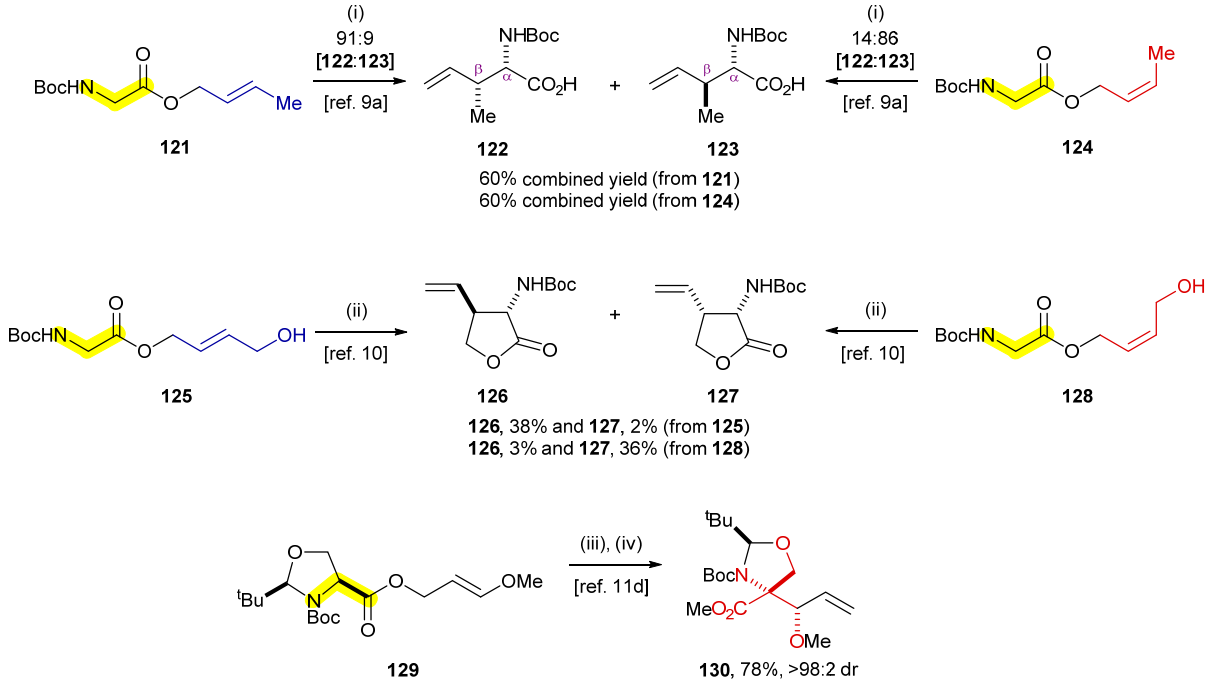
In 1972, Ireland and Mueller demonstrated the utility of the Ireland-Claisen rearrangement in their synthesis of dihydrojasmone **120**, a prostaglandin-like structure.[2a] Rearrangement of allyl ester **117** using LiICA and TMSCl generated **118**, which upon treatment with MsOH resulted in the formation of lactone **119**. Three additional steps were required for conversion of **119** to cyclopentenone **120** in 81% overall yield (Scheme 14). This landmark report has

been followed by many additional examples showcasing the power of the Ireland-Claisen rearrangement in target-directed synthesis.[3,4]



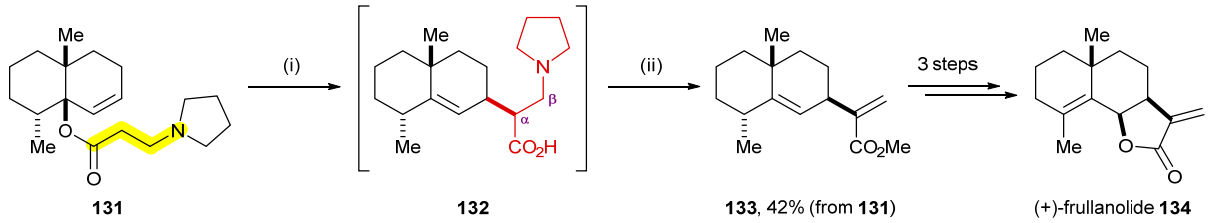
Scheme 14. *Reagents and conditions*: (i) LiICA, THF, –78 °C, TMSCl then 65 °C, 7 h; (ii) MsOH, EtOH.

This methodology has also been applied in the preparation of synthetically useful γ,δ-unsaturated-α-amino acids,[5] which have been used as enzyme inhibitors,[6] antibiotics[7] and as key components in cyclic peptides.[8] Bartlett and co-workers were the first to explore the influence of a nitrogen substituent in the α-position of the allyl ester.[9] It was found that under conditions of rearrangement, the *trans*-configuration of the allyl moiety in *N*-acylated glycine allyl ester **121** guides the reaction toward **122** in high diastereoselectivity (91:9 dr). Contrastingly, *cis*-configured allyl ester **124** gave predominantly **123** with high diastereoselectivity (86:14 dr) when exposed to identical conditions.[9a] Another example of the rearrangement of *N*-Boc protected allyl glycinates was demonstrated by Duthaler and Baumann in 1988.[10] The sequential treatment of (*E*)- or (*Z*)-configured allyl esters **125** and **128** with LiICA and TMSCl at –78 °C followed by heating under reflux for 1 h enabled the isolation of either the *trans*- or *cis*-substituted lactones **126** and **127**, respectively. More recently, Carbery and co-workers[11] reported the highly diastereoselective formation of the substituted β,β'-dihydroxy-α-amino acid[12] precursor **130** (containing a quaternary α-centre), using the Ireland-Claisen rearrangement[11d] of **129** as the key step *en route* to the synthesis of the immunosuppressant mycestericin G[13] (Scheme 15).



Scheme 15. *Reagents and conditions*: (i) LiICA, THF, –78 °C, 5 min then TMSCl, –78 °C then reflux, 1 h then MeOH, rt, overnight; (ii) HMDS, reflux, 4 h then LiICA, THF, –78 °C, 10 min then TMSCl, –78 °C, 30 min then reflux, 1 h; (iii) LiHMDS, TMSCl, THF, –78 °C then 23 °C, 16 h; (iv) CH_2N_2, Et_2O.

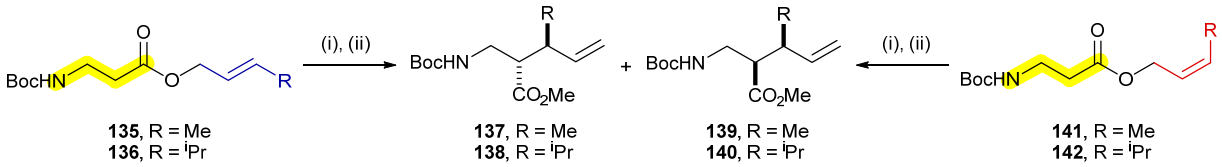
The Ireland-Claisen rearrangement has also been used to synthesise α-substituted β-amino acids.[14] As part of a synthetic strategy towards the sesquiterpene lactone (+)-frullanolide **134**,[15] Still and Schneider reported the first example of an Ireland-Claisen rearrangement of a β-amino allyl ester.[16] Treatment of **131** with LDA and TESCl in THF at –45 °C, followed by heating of the reaction mixture at reflux gave intermediate acid **132**, which subsequently underwent elimination and esterification affording α-substituted acrylic ester **133** as the only product in 42% yield (Scheme 16).



Scheme 16. *Reagents and conditions*: (i) LDA, TESCl, THF, –45 °C, 20 min then reflux, 20 min; (ii) Me_2SO_4, K_2CO_3, MeOH, rt, 2 h.

Following this precedent, Knight and co-workers sought to utilise the Ireland-Claisen rearrangement to access a wider scope of α-substituted β-amino acids.[17] Treatment of *N*-Boc protected allyl β-amino esters **135**, **136**, **141** and **142** with LDA and TMSCl at –78 °C followed by reaction under reflux in THF was reported to offer suitable conditions for rearrangement.[17a] The authors showed that rearrangement of *trans*-configured allyl esters **135** (R = Me) and **136** (R = ^{i}Pr) proceeded to give major diastereoisomers **137** and **138**, respectively, in high diastereoselectivity. Treatment of *cis*-**141** (R = Me) to identical

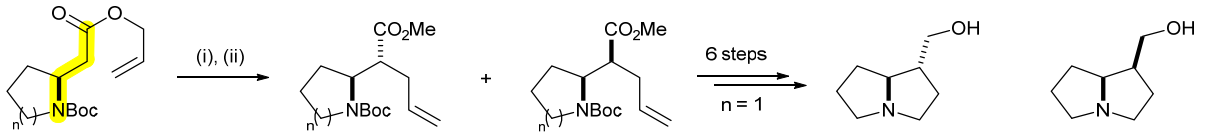
conditions for rearrangement gave predominantly **139** in 88:12 dr. However, when a bulkier substituent is present within the *cis*-configured allyl ester, such as in **142** (R = ^{i}Pr), the major diastereoisomer formed matched that resulting from the rearrangement of the *trans*-configured substrate **136** (Scheme 17).



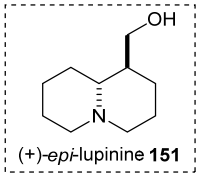
Substrate	R	rearrangement dr
135	Me	**137**:**139** 86:14
136	^{i}Pr	**138**:**140** 80:20
141	Me	**137**:**139** 12:88
142	^{i}Pr	**138**:**140** 81:19

Scheme 17. *Reagents and conditions*: (i) LDA, THF, –78 °C, 20 min then TMSCl, –78 °C, 20 min then reflux, 2 h; (ii) CH_2N_2, Et_2O, rt, overnight.

In subsequent studies by Knight and co-workers, homoproline-derived allyl β-amino ester **143** served as a valuable precursor to pyrrolizidine alkaloids.[18] Subjection of **143** to LiHMDS and TMSCl followed by esterification with CH_2N_2 gave a 67:33 diastereoisomeric mixture of **145** and **147**, respectively, in 78% total yield. The products were independently subjected to a six-step procedure to afford (–)-trachelantamidine **149** and (–)-isoretronecanol **150** in 13 and 11% overall yield from **145** and **147**, respectively. Furthermore, in an attempt to construct a quinolizidine[19] ring system, such as that within (+)-*epi*-lupinine **151**, an analogous reaction was performed using homopipecolic acid-derived allyl β-amino ester **144**.[20] Treatment of **144** to the rearrangement conditions followed by esterification was reported to give a 94:6 mixture of diastereoisomers **146** and **148** in 76% total isolated yield (Scheme 18).



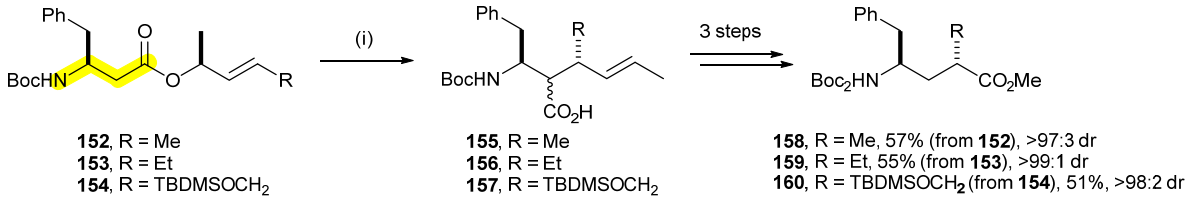
Substrate	n	rearrangement dr	total yield
143	1	**145**:**147** 67:33	78%
144	2	**146**:**148** 94:6	76%



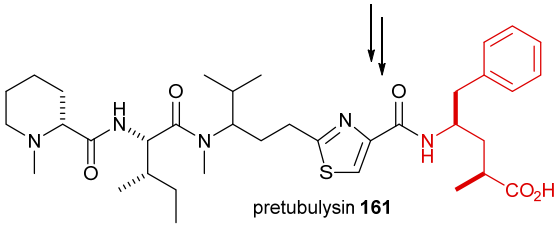
Scheme 18. *Reagents and conditions*: (i) LiHMDS, THF, –78 °C, 10 min then TMSCl, 20 min then rt, overnight (n = 1) or reflux, 6 h (n = 2); (ii) CH_2N_2, Et_2O, rt, overnight.

Despite this precedent, further examples of the Ireland-Claisen rearrangement of allyl β-amino esters are scarce in the literature. Kazmaier and Becker have only recently (in 2013) exploited the utility of allyl β-amino esters[21,22] in the synthesis of β-amino acid subunits found

in the antitumor-active compound pretubulysin **161**.[23] *trans*-Configured allyl β-amino esters **152**–**154** were subjected to LDA and TMSCl to afford the corresponding α,β-disubstituted β-amino acids **155**–**157** as mixtures of epimers at the CO_2H-bearing stereocentre in moderate diastereoselectivity (up to 67:33 dr). The diastereoselectivity of the rearrangement was unimportant as the carboxylic acid group was removed further along in the synthesis. As an application of this methodology, the key intermediates **155**–**157** were thereby elaborated to *N*-protected tubuphenylalanine esters **158**–**160** *via* a three-step procedure (Scheme 19).



Substrate	R	rearrangement dr for 155–157	combined yield
152	Me	67:33	93%
153	Ph	67:33	91%
154	$TBDMSOCH_2$	50:50	93%



Scheme 19. *Reagents and conditions*: (i) LDA, THF, –78 °C, 30 min then TMSCl, 60 min then 60 °C, 2 h.

2.2. Aim: proposed route to C(5)-substituted cyclic β-amino acids

The aim of this chapter is to outline the full potential of stereodefined allyl β-amino esters **110** in the Ireland-Claisen rearrangement. It was envisaged that **110** could be readily accessed using a conjugate addition reaction of the lithium amide reagent derived from enantiopure amine **162** to an allyl α,β-unsaturated ester **163**. Rearrangement of adducts **110** *via* the intermediacy of silyl ketene acetal **164** were expected to give **165**, and hence provide a useful method for the stereocontrolled synthesis of α-substituted β-amino esters **166**. In the case where R = $CH_3CH{=}CH–$, elaboration of **105** *via* ring-closing metathesis would afford cyclic β-amino esters **167** which could then undergo tandem hydrogenolysis/reduction and ester hydrolysis to give C(5)-substituted cyclic β-amino acids **106** (Figure 6).[24]

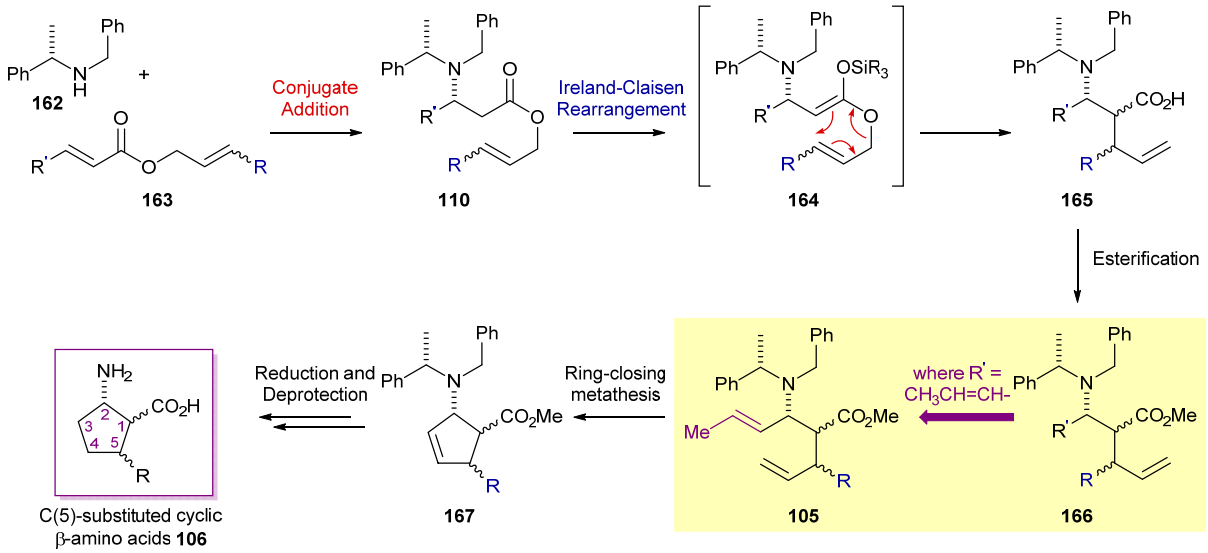
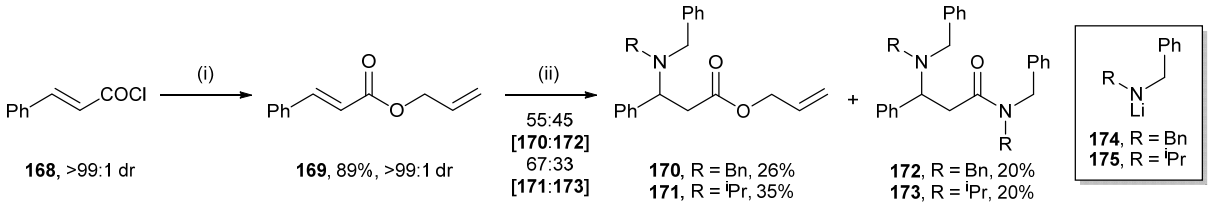


Figure 6. Proposed route through to C(5)-substituted cyclic β-amino acids **106** from allyl β-amino esters **110** *via* a diastereoselective Ireland-Claisen rearrangement.

2.3. Results and discussion

2.3.1. Model studies: Ireland-Claisen rearrangement of racemic allyl β-amino esters

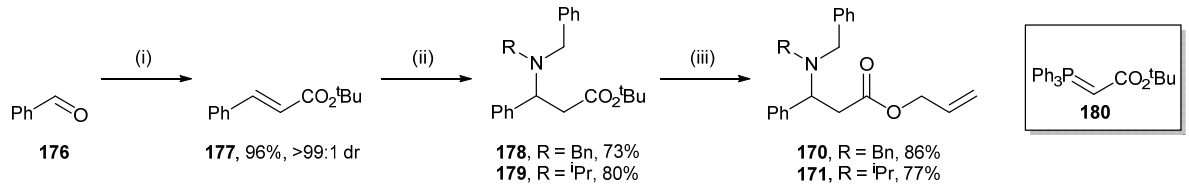
In the first instance, racemic allyl β-amino esters **170** and **171** were chosen as model systems for investigations into the diastereoselectivity of the Ireland-Claisen rearrangement. Esterification of cinnamoyl chloride **168** with allyl alcohol gave α,β-unsaturated ester **169** in 89% yield and >99:1 dr. Conjugate addition of lithium *N*,*N*-dibenzylamide[25] **174** to α,β-unsaturated ester **169** in THF at –78 °C for 2 h led to complete consumption of **169**, giving a 55:45 mixture of allyl β-amino ester **170** and the corresponding amide **172**, respectively, with **170** being isolated in 26% yield and **172** being isolated in 20% yield following chromatographic purification. Amide **172** is presumably the result of 1,2-addition of lithium amide **174** to α,β-unsaturated ester **169**, followed by conjugate addition of **174** to the resultant α,β-unsaturated amide.[26] Similarly, conjugate addition of lithium *N*-isopropyl-*N*-benzylamide[27] **175** to **169** led to a chromatographically separable 67:33 mixture of **171** and **173**, which were isolated in 35 and 20% yield, respectively (Scheme 20).



Scheme 20. *Reagents and conditions*: (i) allyl alcohol, Et_3N, CH_2Cl_2, rt, 16 h; (ii) **174** or **175**, THF, –78 °C, 2 h.

In order to eliminate competing 1,2-addition, an alternative protocol starting from *tert*-butyl cinnamate **177** (which was prepared from a Wittig reaction of **176** with ylid **180**)[28] to effect

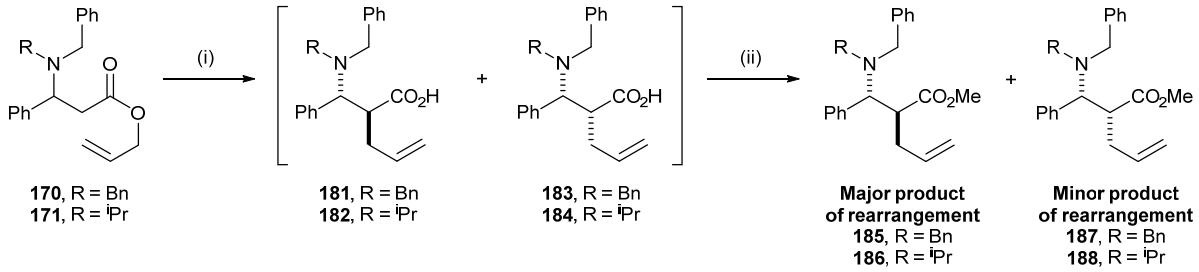
selective conjugate addition,[29] followed by transesterification to install the olefinic moiety was investigated. As expected, conjugate additions of lithium *N*,*N*-dibenzylamide **174** and lithium *N*-isopropyl-*N*-benzylamide **175** to **177** proceeded cleanly to give **178** and **179** as the sole products in 73 and 80% isolated yield, respectively. Subsequent transesterification of **178** and **179** with $SOCl_2$ in allyl alcohol gave the corresponding allyl β-amino esters **170** and **171** in 86 and 77% yield, respectively (Scheme 21).



Scheme 21. *Reagents and conditions*: (i) **180**, CH_2Cl_2, rt, 48 h; (ii) **174** or **175**, THF, –78 °C, 2 h; (iii) $SOCl_2$, allyl alcohol, 50 °C, 3 h.

With allyl β-amino esters **170** and **171** in hand, the Ireland-Claisen rearrangement was next investigated. The first reaction was carried out by treating **171** (R = ^{i}Pr) with TMSCl in THF at –78 °C[30] followed by the dropwise addition of LiHMDS,[31,32] and the reaction mixture was stirred at rt for 16 h. Unfortunately, this initial attempt was unsuccessful and led only to the recovery of starting material. In accord with literature precedent,[9b,17a,17b] the reaction mixture in THF was heated to reflux for 16 h to afford a 91:9 diastereoisomeric mixture of α-substituted β-amino acids **182** and **184**, respectively, in 34% conversion. Upon repetition of the reaction in PhMe at reflux, complete consumption of starting material was observed to give a mixture of **182** and **184** in 91:9 dr, respectively. Optimisation of the Ireland-Claisen rearrangement revealed that deprotonation with 3.0 equiv of LiHMDS and treatment of the resultant lithium (*E*)-β-amino enolate[29a,33] with 3.0 equiv of TMSCl, followed by heating the corresponding silyl ketene acetal at reflux in PhMe for 1 h, delivered a 91:9 mixture of diastereoisomers **182** and **184**. For ease of purification and handling, the crude product mixture was converted to the corresponding methyl esters **186** and **188** upon reaction with MeOH and $SOCl_2$ with no change in the diastereoisomeric ratio of products **186** and **188** [i.e., 91:9 dr for step (ii)], confirming that no epimerisation of the C(2)-stereogenic centres occurred during this transformation. The mixture of methyl esters **186** and **188** was subsequently isolated in 62% combined yield and 88:12 dr. Under the same reaction conditions, *N*,*N*-dibenzyl substituted β-amino ester **170** gave an 83:17 mixture of diastereoisomers **181** and **183**, respectively. On treatment with MeOH and $SOCl_2$ the

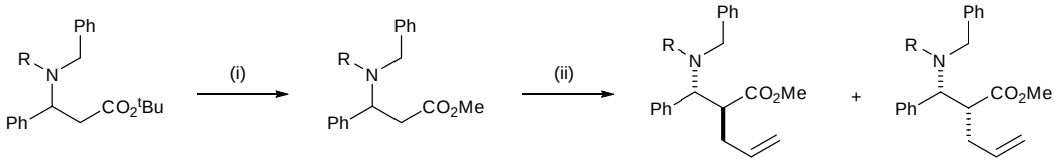
chromatographically inseparable mixture of methyl esters **185** and **187** were isolated in 40% combined yield, and 83:17 dr (Scheme 22).



Substrate	R	rearrangement dr: step (i)	esterification dr: step (ii)	combined isolated yield (dr)
170	Bn	**181**:**183** 83:17	**185**:**187** 83:17	**185**:**187**, 40% (83:17)
171	^{i}Pr	**182**:**184** 91:9	**186**:**188** 91:9	**186**:**188**, 62% (88:12)

Scheme 22. *Reagents and conditions*: (i) TMSCl, PhMe, –78 °C, 10 min then LiHMDS, –78 °C, 30 min then reflux, 1 h; (ii) $SOCl_2$, MeOH, 50 °C, 48 h.

In an attempt to ascertain the relative configurations within **185** and **186**, authentic samples of **185** and **186** were prepared *via* an α-alkylation strategy. It is well precedented that deprotonation of β-amino methyl esters using lithium amide bases followed by alkylation usually yields predominantly the *anti*-α-substituted diastereoisomer.[29a] Consequently, β-amino esters **178** and **179** were treated with $SOCl_2$ in MeOH to give the corresponding methyl esters **189** and **190** in 64 and 75% yield, respectively. As expected, reaction of both **189** and **190** with LiHMDS in THF at –78 °C for 2 h followed by addition of allyl bromide proceeded to full conversion. Allylation of β-amino ester **190** resulted in an 81:19 mixture of **186** and **188** with *anti*-**186** being isolated in 11% yield[34] and >99:1 dr. In marked contrast, an identical reaction using β-amino ester **189** was essentially non-selective, and exhaustive column purification resulted in the isolation of *anti*-**185** in 15% isolated yield and 98:2 dr (Scheme 23). Single crystal X-ray diffraction analysis[35] allowed unambiguous assignment of the relative *anti*-configuration within **185** (Figure 7). This analysis therefore also allowed the relative *syn*-configuration within **187** to be assigned. Furthermore, the ^{1}H NMR spectra of the samples of **185** obtained from the alkylation of **189** and the rearrangement of allyl β-amino ester **170** were found to be in complete agreement, thereby confirming the *anti*-configuration within **185**.



178, R = Bn
179, R = ^{i}Pr

189, R = Bn, 64%
190, R = ^{i}Pr, 75%

185, R = Bn
186, R = ^{i}Pr

187, R = Bn
188, R = ^{i}Pr

Substrate	R	alkylation dr	(±)-*anti* yield (dr)	(±)-*syn*:(±)-*anti* combined yield (dr)
189	Bn	**185**:**187** 54:46	15% (98:2)	**187**:**185**, 66% (39:61)
190	^{i}Pr	**186**:**188** 81:19	11% (>99:1)	**188**:**186**, 53% (24:76)

Scheme 23. *Reagents and conditions*: (i) $SOCl_2$, MeOH, 50 °C, 16 h; (ii) LiHMDS, THF, –78 °C, 2 h then allyl bromide, –78 °C rt, 16 h.

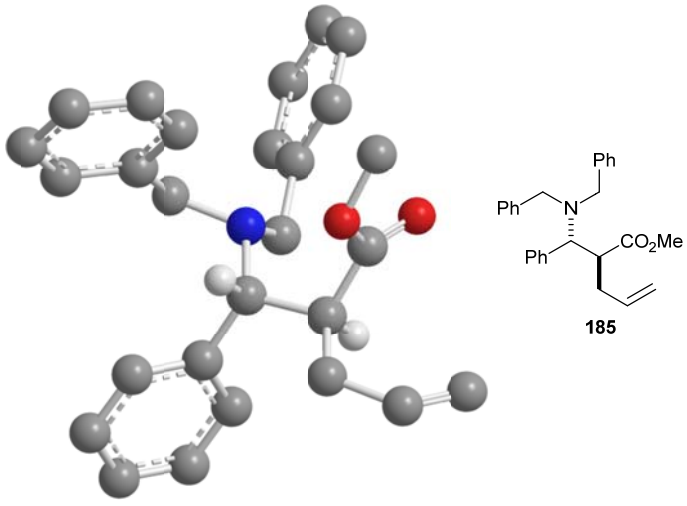
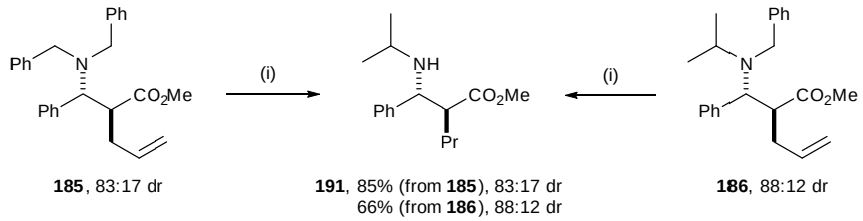


Figure 7. X-ray crystal structure of (*RS*,*SR*)-**185** (selected H atoms are omitted for clarity).

A series of hydrogenolytic/reductive alkylation chemical correlation experiments were next conducted in order to unambiguously establish the relative configurations within the β-amino ester products **186** and **188** from the Ireland-Claisen rearrangement of **171** (R = ^{i}Pr). Hydrogenolysis of a sample of *anti*-**185** (83:17 dr) in the presence of $Pd(OH)_2/C$[36] and acetone, effected the removal of the *N*-benzyl groups and *in situ* reductive alkylation to give *N*-isopropyl substituted β-amino ester *anti*-**191** in 85% yield and 83:17 dr (Scheme 24). Recrystallisation of an aliquot of **191** (83:17 dr) provided a diastereoisomerically pure (>99:1 dr) sample from which the relative configuration within **191** was confirmed unambiguously *via* single crystal X-ray diffraction analysis[35] (Figure 8). Subjection of **186** (88:12 dr) to identical hydrogenolysis/reductive alkylation conditions gave **191** in 66% yield and 88:12 dr (Scheme 24). The ^{1}H NMR spectra of the samples of **191** prepared from **185** and **186** were found to be identical and therefore served to confirm the relative *anti*-configurations within the major products of the Ireland-Claisen rearrangements of both **170** and **171** (*vide supra*).



Scheme 24. *Reagents and conditions*: (i) H_2 (1 atm), $Pd(OH)_2/C$, MeOH/acetone (v/v 9:1), rt, 16 h.

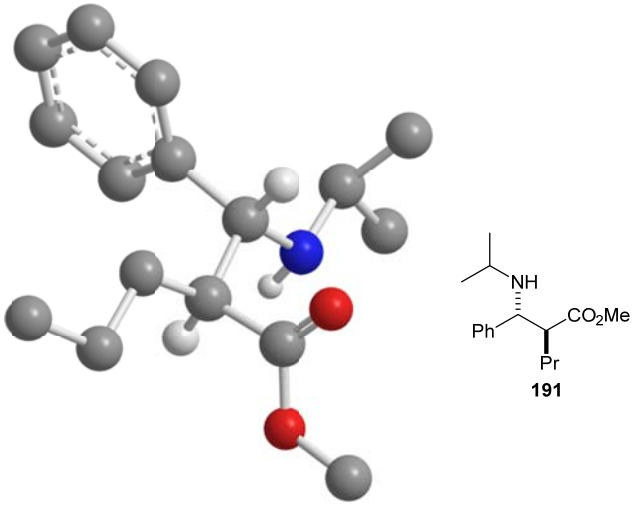
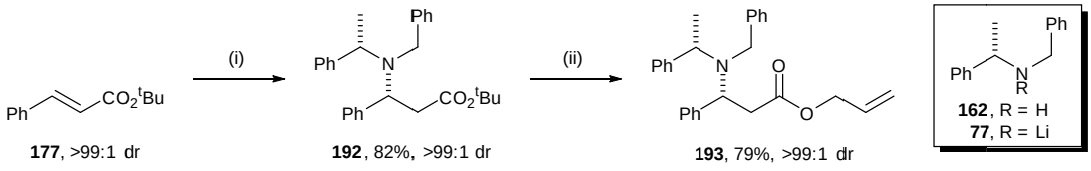


Figure 8. X-ray crystal structure of (*RS*,*SR*)-**191** (selected H atoms are omitted for clarity).

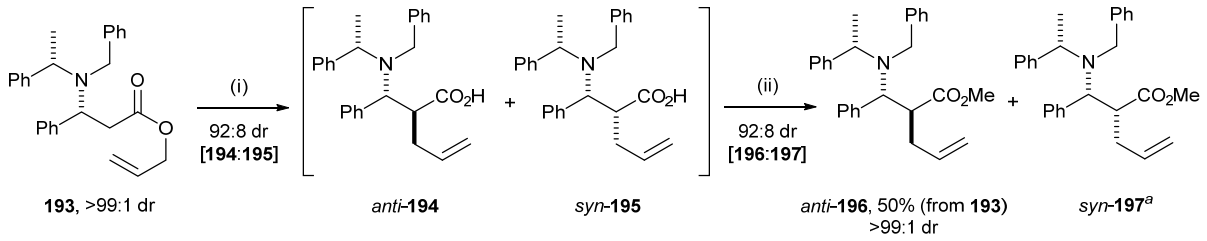
2.3.2. Ireland-Claisen rearrangement of enantiopure allyl β-amino esters

Having demonstrated that the rearrangement of allyl β-amino esters **170** and **171** preferentially promotes the formation of the *anti* diastereoisomer (~5:1 dr or ~10:1 dr), subsequent studies were focused on the use of the stereogenic *N*-α-methylbenzyl substituent to prepare enantiopure precursors to rearrangement as a means to provide access to enantiomerically pure α-substituted products. Consequently, α,β-unsaturated ester **177** was treated with lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*S*)-**77** [which was generated upon treatment of amine (*S*)-**162** with BuLi] to give the known β-amino ester **192**.[37] Subsequent transesterification of **192** upon treatment with $SOCl_2$ in allyl alcohol gave allyl β-amino ester **193** in 79% yield and >99:1 dr (Scheme 25).[38]



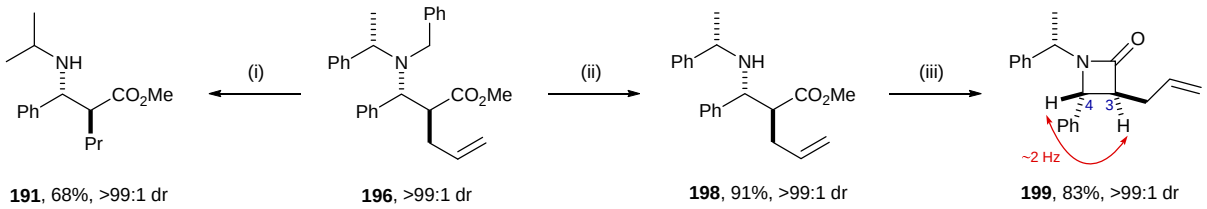
Scheme 25. *Reagents and conditions*: (i) (*S*)-**77**, THF, –78 °C, 2 h; (ii) $SOCl_2$, allyl alcohol, 50 °C, 3 h.

The Ireland-Claisen rearrangement of **193** under standard conditions proceeded in a highly diastereoselective manner to give a 92:8 mixture of *anti*-**194** and *syn*-**195**. Upon treatment of this mixture with $SOCl_2$ in MeOH, methyl ester **196** was isolated in 50% overall yield and >99:1 dr (Scheme 26).[39]



Scheme 26. *Reagents and conditions*: (i) TMSCl, PhMe, –78 °C, 10 min then LiHMDS, –78 °C, 30 min then reflux, 1 h; (ii) $SOCl_2$, MeOH, 50 °C, 48 h. [[a] *syn*-**197** was isolated in two separate fractions of 3 and 5% yield as 38:62 and 42:58 mixtures of **197** and **196**, respectively.]

The relative *anti*-configuration within β-amino ester **196** was first established by an oxidative *N*-debenzylation[40] reaction followed by a MeMgBr-mediated cyclisation,[41] which gave *trans*-β-lactam **199** in 76% yield over the two steps and >99:1 dr. The diagnostic value of the ^{1}H–^{1}H NMR ^3J coupling constant between the C(3)*H* and C(4)*H* protons within **199** ($^3J_{3,4}$ = 2.1 Hz) was supportive of the assigned *anti*-configuration ($^3J_{3,4}$ ^{1}H NMR coupling constants for *cis*-β-lactams are typically ~5 Hz).[42] Additionally, tandem hydrogenolysis and reductive alkylation of **196** gave *anti*-**191** in 68% yield and >99:1 dr (Scheme 27). The ^{1}H NMR spectroscopic data for **191** were identical to the samples of **191** previously synthesised (*vide supra*).



Scheme 27. *Reagents and conditions*: (i) H_2 (1 atm), $Pd(OH)_2$/C, MeOH/acetone (v/v 9:1), rt, 16 h; (ii) CAN, MeCN/H_2O (v/v 5:1), rt, 16 h; (iii) MeMgBr, Et_2O, 0 °C, 30 min.

An attempt at separating **194** and **195** by column chromatography was successful and resulted in the isolation of intermediate β-amino acid **194**. Once crystallised, the relative *anti*-configuration within **194** was proven unambiguously *via* single crystal X-ray diffraction analysis and the absolute configuration of **194** was assigned relative to the known (*S*)-configuration of the *N*-α-methylbenzyl fragment.[35] In addition, subsequent X-ray crystallographic analysis[35] of **196** also confirmed the assigned configuration within **196** and the absolute configuration of **196** was again assigned relative to the known (*S*)-configuration of the *N*-α-methylbenzyl fragment (Figure 9). The stereochemical outcome of the rearrangement of **193** is, therefore, in accordance with that seen for the rearrangement of allyl β-amino esters **170** and **171**. Taken together, the diastereoisomeric ratios on rearrangement of β-amino esters **170** (*N*,*N*-dibenzyl substituted, 83:17 dr), **171** (*N*-isopropyl-*N*-benzyl substituted, 91:9 dr) and **193** (*N*-benzyl-*N*-α-methylbenzyl substituted, 92:8 dr) demonstrate

that the (*S*)-α-methylbenzyl stereogenic centre does not exert a significant influence on the diastereoselectivity of the rearrangement.

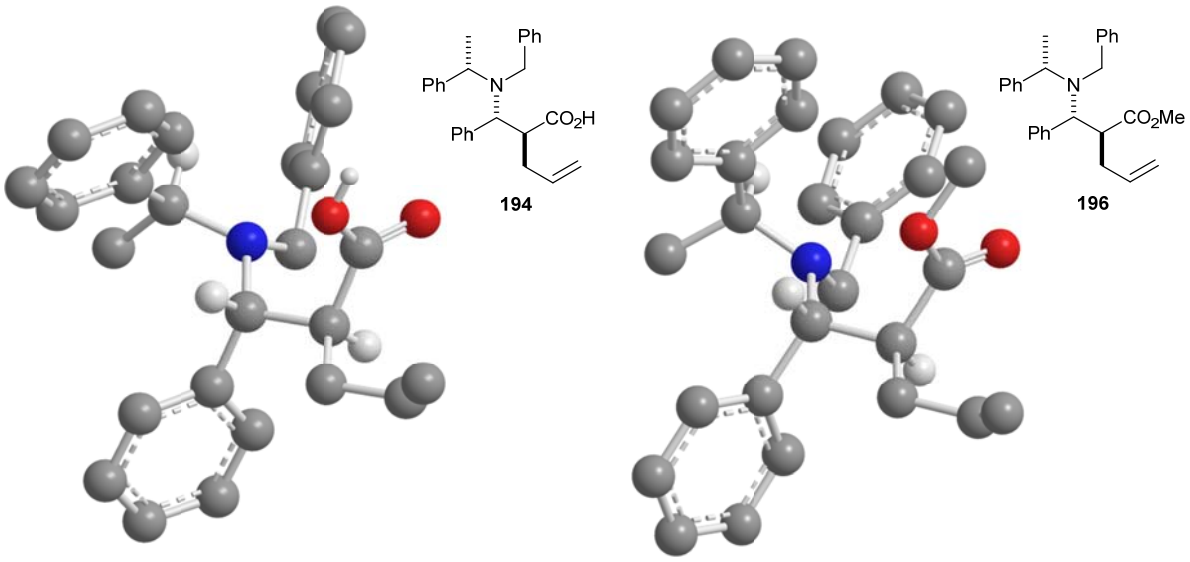
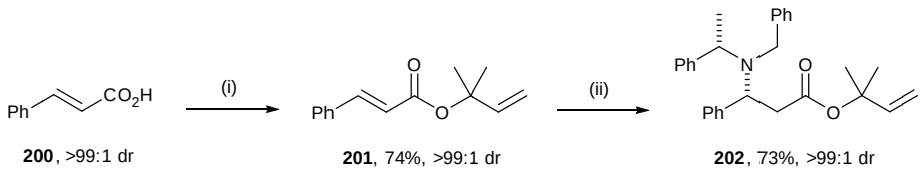


Figure 9. X-ray crystal structures of (2*S*,3*R*,α*S*)-**194** [*left*] and (2*S*,3*R*,α*S*)-**196** [*right*] (selected H atoms are omitted for clarity).

The effect of introducing two methyl substituents onto the allyl moiety of the α,β-unsaturated ester was investigated next. Substrate **201** was synthesised *via* a DCC/DMAP-mediated coupling[43] of *trans*-cinnamic acid **200** and 2-methylbut-3-en-2-ol. In contrast to allyl β-amino esters **170** and **171**, treatment of *gem*-dimethyl substituted **201** with lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*S*)-**77** gave exclusively β-amino ester **202**, which was isolated as a single diastereoisomer (>99:1 dr) in 73% yield (Scheme 28). Notably, no products arising from 1,2-addition were detected, consistent with the absence of products arising from 1,2-addition upon conjugate addition of lithium amides to *tert*-butyl esters.[14e] The sense of diastereocontrol in this reaction was initially assigned by reference to the lithium amide conjugate addition transition state mnemonic developed by Davies and co-workers[44] that has been used to reliably predict the stereochemical outcome of conjugate addition reactions of secondary lithium amides derived from α-methylbenzylamine to α,β-unsaturated esters.[14c,14e] Single crystal X-ray diffraction analysis[35] later served to unambiguously confirm the relative configuration within **202** and the absolute configuration of **202** was assigned relative to the known (*S*)-configuration of the *N*-α-methylbenzyl fragment (Figure 10).



Scheme 28. *Reagents and conditions*: (i) DMAP, DCC, 2-methylbut-3-en-2-ol, CH_2Cl_2, rt, 16 h; (ii) (*S*)-**77**, THF, –78 °C, 2 h.

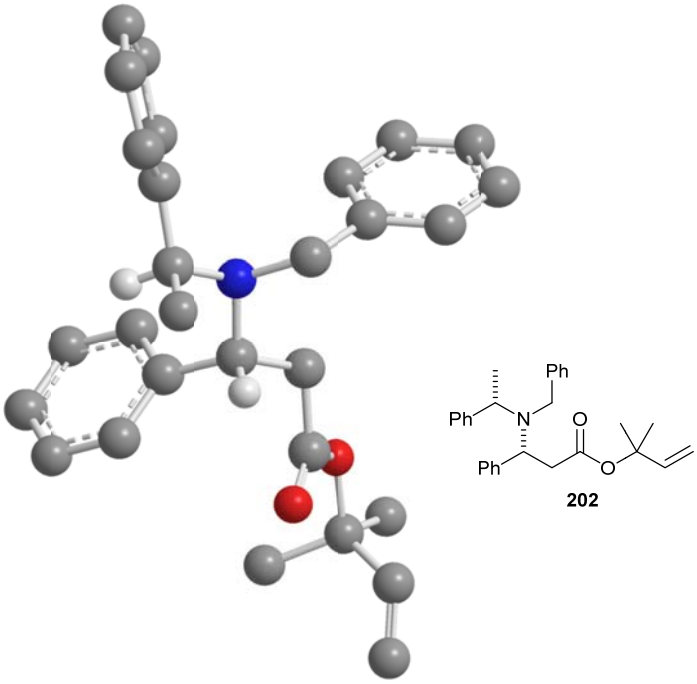
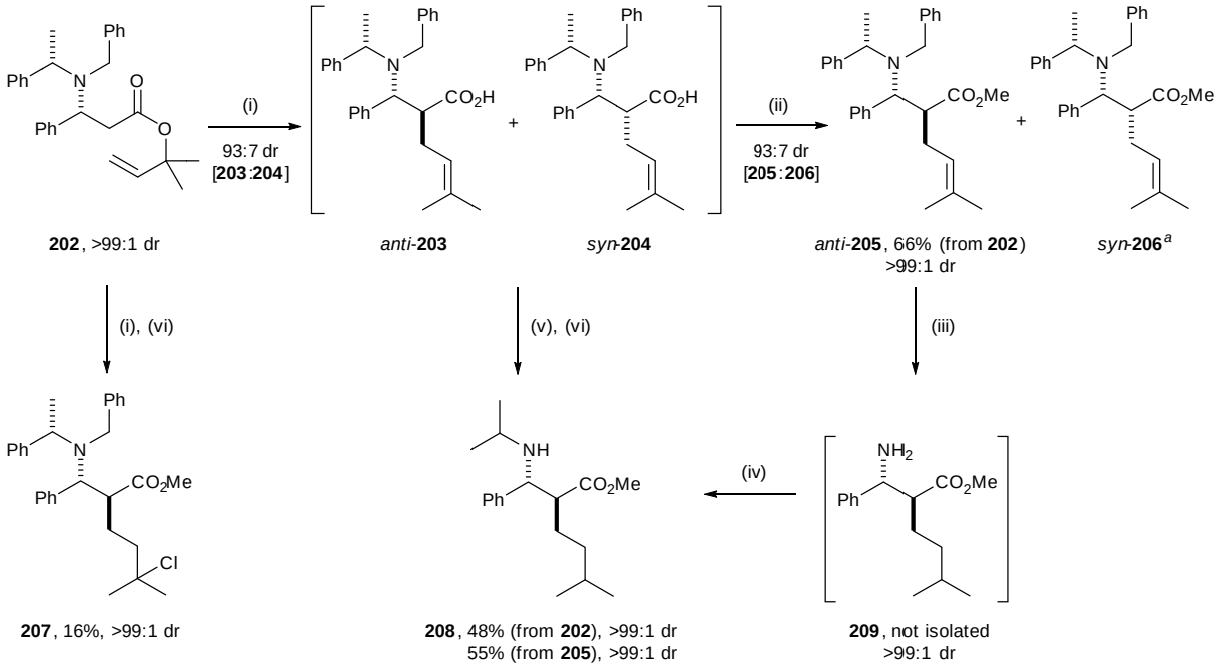


Figure 10. X-ray crystal structure of (3*R*,α*S*)-**202** (selected H atoms are omitted for clarity).

Under the optimised conditions, treatment of isoprenyl β-amino ester **202** with LiHMDS and TMSCl in PhMe induced an Ireland-Claisen rearrangement which gave predominantly **203** in high diastereoselectivity (93:7 dr). The stereochemical outcome of this reaction was initially assigned by analogy to the rearrangements of **170**, **171** and **193**. Attempted exposure of the 93:7 mixture of diastereoisomers **203** and **204**, respectively, to the usual acidic conditions previously employed for esterification to the corresponding methyl ester (i.e., $SOCl_2$ in MeOH) gave **207** predominantly, as a result of both esterification and hydrochlorination of the olefinic moiety. Chromatographic purification gave **207** in 16% isolated yield and >99:1 dr [along with an unidentifiable impurity (~10%)]. The use of MeI in the presence of DBU[45] proved effective at cleanly converting the crude reaction 93:7 mixture of **203** and **204**, respectively, to the corresponding β-amino methyl esters **205** and **206**, from which the major diastereoisomer **205** was isolated in 66% yield and >99:1 dr.[39] Moreover, the unchanged diastereoisomeric ratios for the rearrangement and esterification steps served to confirm that esterification of the crude reaction mixture of **203** and **204** with MeI and DBU proceeds without epimerisation of the C(2)-stereogenic centre. A series of hydrogenolytic/reductive alkylation reactions were next conducted in order to correlate the configurations of the C(2)-stereogenic centres within β-amino acid **203** and corresponding β-amino ester **205**. Hydrogenolysis of **205** (>99:1 dr) using Pearlman's catalyst [$Pd(OH)_2$/C] followed by reductive alkylation using $NaBH_3CN$ and acetone gave *anti*-**208** in 55% yield and >99:1 dr. Subjection of a 93:7 mixture of **203** and **204** to hydrogenolytic *N*-debenzylation conditions in

the presence of acetone, followed by treatment with $SOCl_2$ in MeOH at 50 °C for 48 h also gave *anti*-**208** in 48% yield and >99:1 dr over three steps from precursor **202** (Scheme 29). The ^{1}H and ^{13}C NMR spectra and specific rotations of the two samples of *anti*-**208** were found to be in complete agreement. In addition, the relative configuration within β-amino ester *anti*-**208** was later unambiguously secured by single crystal X-ray diffraction analysis[35] and the absolute configuration of **208** was assigned relative to the known (*S*)-configuration of the *N*-α-methylbenzyl fragment (Figure 11). The X-ray crystal structure of **208** also allowed the assigned configurations within **203** and **205** to be established.



Scheme 29. *Reagents and conditions*: (i) TMSCl, PhMe, –78 °C, 10 min then LiHMDS, –78 °C, 30 min then reflux, 1 h; (ii) DBU, MeI, MeCN, rt, 4 h; (iii) H_2 (1 atm), $Pd(OH)_2/C$, MeOH, rt, 15 h; (iv) acetone, $NaBH_3CN$, MeOH, rt, 22 h; (v) H_2 (1 atm), $Pd(OH)_2/C$, MeOH/acetone (v/v 9:1), rt, 22 h; (vi) $SOCl_2$, MeOH, 50 °C, 48 h. [[a] *syn*-**206** was isolated in a separate fraction of 12% yield as a 57:43 mixture of **206** and **205**, respectively.]

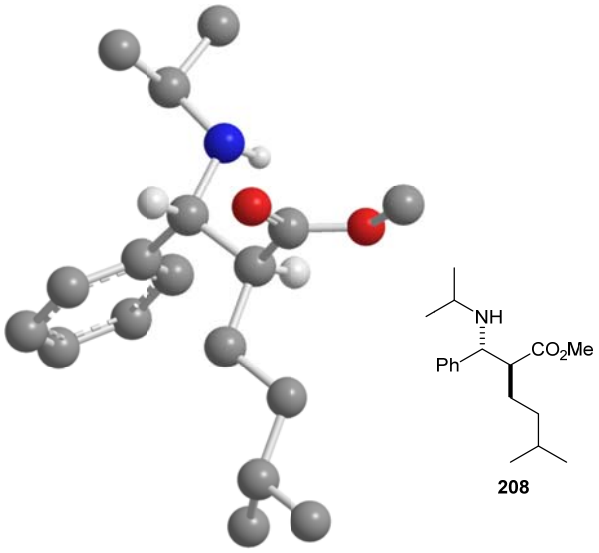
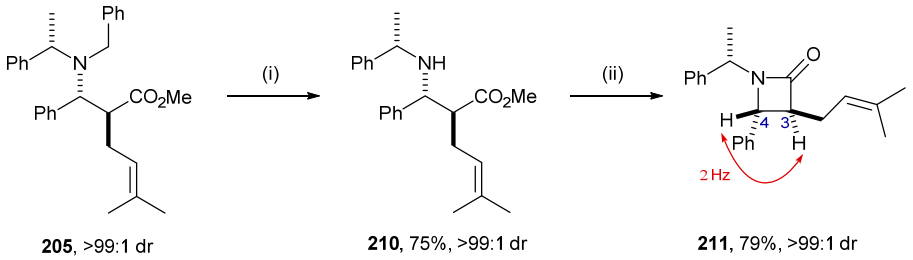


Figure 11. X-ray crystal structure of (2*S*,3*R*)-**208** (selected H atoms are omitted for clarity).

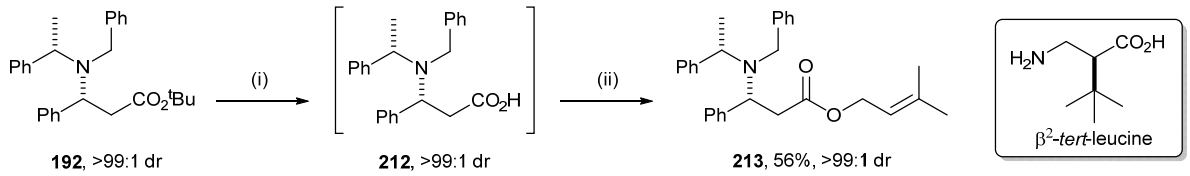
The relative *anti*-configuration within β-amino ester **205** was also assigned on the basis of an analogous series of transformations as those applied to β-amino ester **196** to convert it into the corresponding β-lactam (*vide supra*). Treatment of **205** with CAN[40,46] in MeCN/H_2O followed by MeMgBr[41] in Et_2O gave the *trans*-3,4-disubstituted β-lactam **211** in 59% overall yield and >99:1 dr. The relative *anti*-configuration within **211** was again assigned by inspection of a diagnostic ^1H–^1H ^3J coupling constant of 2.0 Hz between the C(3)*H* and C(4)*H* protons (Scheme 30).[46,33b]



205, >99:1 dr **210**, 75%, >99:1 dr **211**, 79%, >99:1 dr

Scheme 30. *Reagents and conditions*: (iv) CAN, MeCN/H_2O (v/v 5:1), rt, 16 h; (v) MeMgBr, Et_2O, 0 °C, 30 min.

The effect of terminal olefinic substitution on the diastereoselectivity of the Ireland-Claisen rearrangement was next probed. The trisubstituted olefin within the prenyl β-amino ester **213** was chosen as it was envisaged that **213** could be used to create a quaternary centre at the C(1')-position of the product (albeit not stereogenic in this case) *via* the rearrangement protocol. This would thus provide a route to C(2)-substituted β-amino esters with a scaffold analogous to β^2-*tert*-leucine[47] that is not easily accessible by a direct alkylation strategy. Treatment of **192** with TFA gave the corresponding β-amino acid **212**, and subsequent reaction with 3,3-dimethylallyl bromide[48] provided **213** in 56% yield over the two steps (Scheme 31).[49]

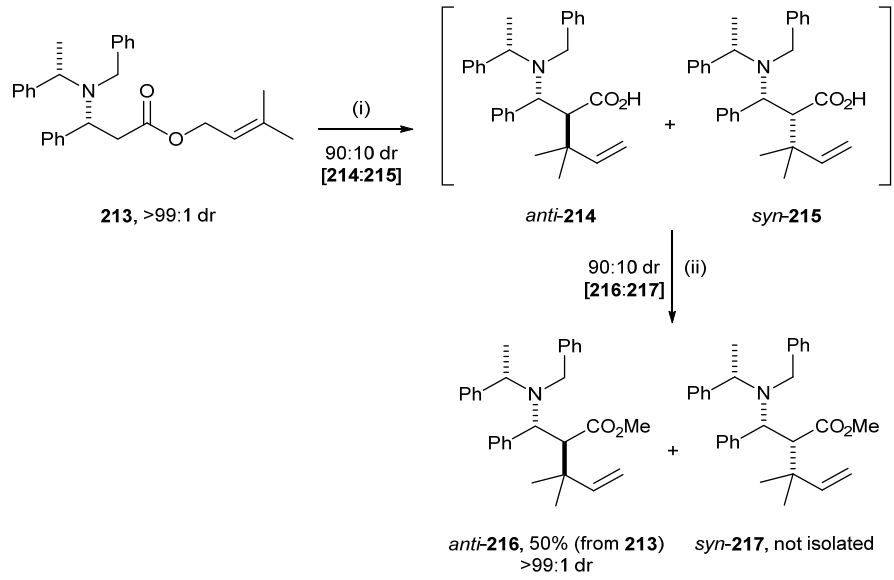


192, >99:1 dr **212**, >99:1 dr **213**, 56%, >99:1 dr

Scheme 31. *Reagents and conditions*: (i) TFA, CH_2Cl_2, rt, 16 h; (ii) 3,3-dimethylallyl bromide, DBU, MeCN, rt, 17 h.

With prenyl β-amino ester **213** in hand, rearrangement under optimised conditions proceeded to give β-amino acids bearing a quaternary centre at the C(1') position, as a 90:10 mixture of diastereoisomers **214** and **215**, respectively. Subjection of this mixture of **214** and **215** (90:10 dr) to $SOCl_2$ in MeOH in order to effect esterification to the corresponding β-amino methyl esters **216** and **217** gave no conversion. This is presumably due to the greater steric bulk inherent at the C(1')-position of **214** and **215**. Alternatively, rearrangement of **213** followed by

treatment with DBU and MeI effected esterification of the crude reaction mixture to give **216** in 50% isolated yield and >99:1 dr (Scheme 32). The configurations within **214** and **216** were assigned by analogy to those within **185**, **186**, **196** and **205**.



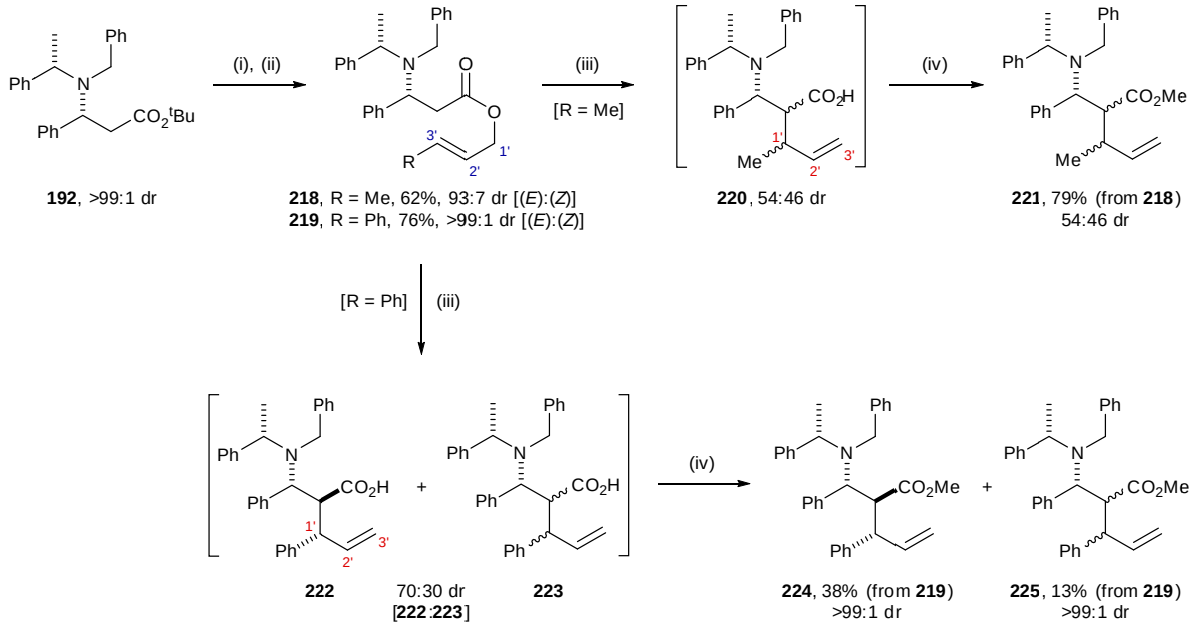
Scheme 32. *Reagents and conditions*: (i) TMSCl, PhMe, –78 °C, 10 min then LiHMDS, –78 °C, 30 min then reflux, 1 h; (iii) DBU, MeI, MeCN, rt, 8 h.

2.3.3. Evaluation of the Ireland-Claisen rearrangement for stereodefined allyl β-amino esters

2.3.3.1. Ireland-Claisen rearrangement of *trans*-configured β-amino esters

In order to examine the effect of a substituent at the C(3')-position (i.e., terminal position) of the allyl moiety in the Ireland-Claisen rearrangement, allyl β-amino esters **218** and **219** were prepared. Incorporation of a methyl or phenyl group at the C(3')-position was anticipated to generate a new stereocentre at the C(1')-position of the product, hence installing two new stereogenic centres in a single operation. Following a facile two-step procedure, β-amino ester **192** was reacted with TFA, and the resultant β-amino acid was esterified with commercially available crotyl alcohol [93:7 dr (*E*):(*Z*)] and cinnamyl alcohol [>99:1 dr (*E*):(*Z*)] to give *trans*-configured allyl esters **218** and **219** in 62 and 76% yield, respectively. Under the standard conditions of rearrangement, treatment of **218** [93:7 dr (*E*):(*Z*)] with LiHMDS and TMSCl produced an approximate 1:1 mixture of diastereoisomers **220**. Rearrangement of **219** [>99:1 dr (*E*):(*Z*)] gave a 70:30 diastereoisomeric ratio of products in favour of **222**. Exposure of the crude reaction mixture of **222** and **223** to MeI and DBU followed by column chromatography led to the isolation of **224** in 38% yield as a single diastereoisomer (>99:1 dr) and **225** in 13% yield and >99:1 dr (Scheme 33). In addition, chromatographic purification of **222** and **223** led to the successful isolation of a sample of diastereoisomerically-pure **222**, the

single crystal X-ray diffraction analysis[35] of which unambiguously confirmed the relative configuration within **222** and the absolute (2*S*,3*R*,1'*S*,α*S*)-configuration was assigned relative to the known (*S*)-configuration of the *N*-α-methylbenzyl fragment (Figure 12). However, the relative configuration within **223** and **225** could not be assigned in the absence of a crystalline derivative.



Scheme 33. *Reagents and conditions*: (i) TFA, CH_2Cl_2, rt, 16 h; (ii) $(COCl)_2$, CH_2Cl_2, DMF, 0 °C to rt, 1 h then crotyl alcohol [93:7 dr (*E*):(*Z*)] or cinnamyl alcohol [>99:1 dr (*E*):(*Z*)], CH_2Cl_2, 0 °C to rt, 16 h; (iii) LiHMDS, TMSCl, PhMe, –78 °C then reflux, 1 h; (iv) DBU, MeI, MeCN, rt, 16 h.

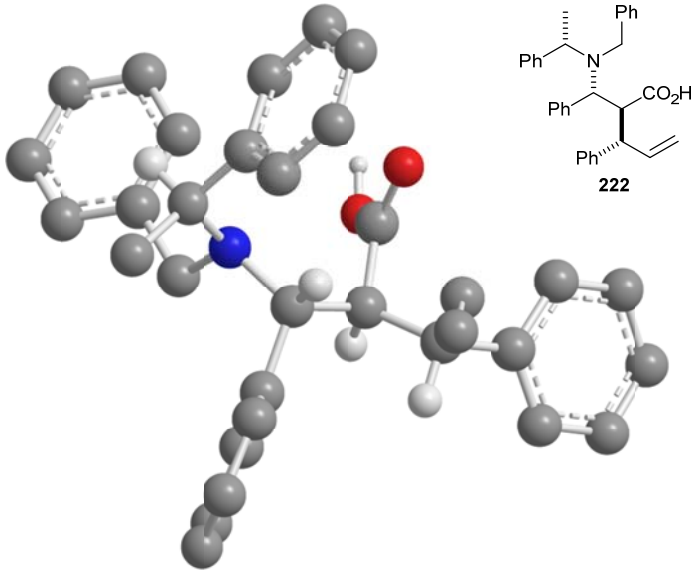
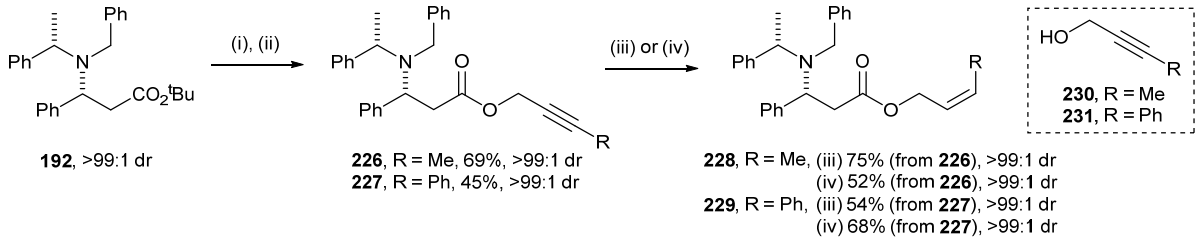


Figure 12. X-ray crystal structure of (2*S*,3*R*,1'*S*,α*S*)-**222** (selected H atoms are omitted for clarity).

2.3.3.2. Ireland-Claisen rearrangement of *cis*-configured β-amino esters: asymmetric synthesis of C(2)-substituted β-amino acids

Attention was next shifted to the synthesis of the *cis*-configured allyl β-amino esters. Efforts were initially focused on the preparation of propargyl β-amino ester substrates **226** and **227** to then prepare the corresponding *cis*-configured allyl β-amino esters **228** and **229**. This was

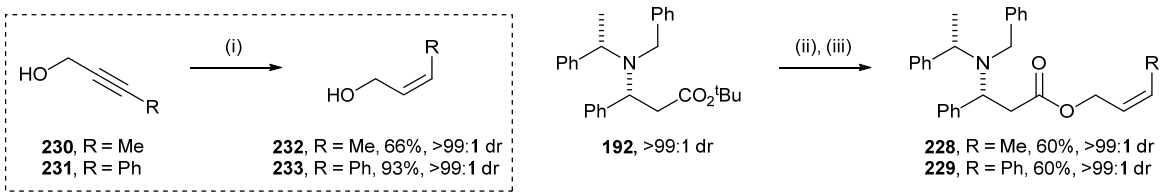
achieved by treating **192** with TFA followed by esterification with commercially available propargylic alcohols **230** and **231** to give β-amino esters **226** and **227** in 69 and 45% yield, respectively, and >99:1 dr in each case. Partial hydrogenation was then attempted using Lindlar catalyst,[50] in a procedure whereby **226** and **227** were stirred under a H_2 atmosphere in the presence of 20 mol% $Pd/CaCO_3$ and 0.9 equiv quinoline to give rearrangement precursors **228** and **229** in 52 and 24% yield over three steps, respectively, and >99:1 dr. However, the hydrogenation reactions could not be reproduced on a larger scale and ^1H NMR spectroscopic analyses of the crude reaction mixtures showed either over reduction or poor (*Z*)-selectivity. Alternatively, partial hydrogenation of **226** and **227** using the nickel boride catalyst[51] gave consistently *cis*-configured substrates **228** and **229** in 36 and 31% isolated yield, respectively, over the three steps and in >99:1 dr in both cases (Scheme 34).



Scheme 34. *Reagents and conditions*: (i) TFA, CH_2Cl_2, rt, 16 h; (ii) $(COCl)_2$, CH_2Cl_2, DMF, 0 °C to rt, 1 h then **230** or **231**, CH_2Cl_2, 0 °C to rt, 16 h; (iii) $Pd/CaCO_3$, quinoline, H_2 (1 atm), EtOAc, 4–72 h; (iv) $Ni(OAc)_2{\cdot}4H_2O$, $NaBH_4$, $(CH_2NH_2)_2$, H_2 (1 atm), MeOH, rt, 45 min.

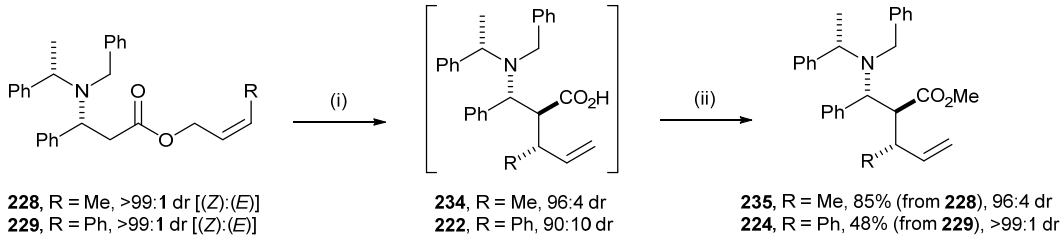
As the preparation of **228** and **229** was relatively low-yielding, an alternative way of making the *cis*-configured allyl β-amino esters was next investigated. Following several reports in the literature, the hydrogenation of alcohols **230** and **231** was attempted prior to esterification. Unfortunately, exhaustive efforts to prepare *cis*-allylic alcohols **232** and **233** from the corresponding alkynes **230** and **231** using Lindlar catalyst were also found to be irreproducible and capricious,[52] particularly on a large scale, giving either returned starting material or fully reduced alcohols.[53] Partial alkyne hydrogenation was instead successfully carried out using the borohydride-reduced nickel catalyst, which proved to be a more reliable protocol. Treatment of commercially available alkynes **230** and **231** with 0.25 mol% nickel(II) acetate and 0.25 mol% $NaBH_4$ in the presence of ethylenediamine resulted in completely (*Z*)-selective (>99:1 dr) hydrogenation of **230** and **231** to give **232** and **233** in 66 and 93% yield, respectively. Transformation of the *tert*-butyl group in **192** into a *cis*-stereodefined allyl unit was relatively straightforward with **192** being treated with TFA to give β-amino acid **212**, followed by esterification with alcohols **232** and **233** to give allyl

β-amino esters **228** and **229** both in 60% yield (over two steps) and >99:1 dr, thus representing the most efficient method for their preparation (Scheme 35).



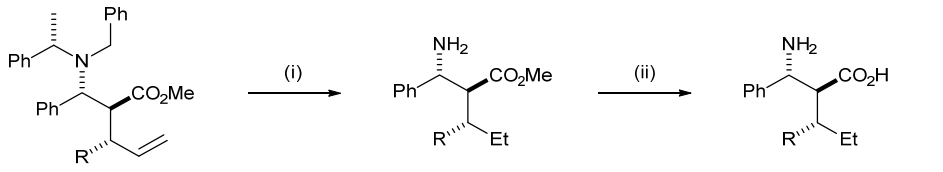
Scheme 35. *Reagents and conditions*: (i) $Ni(OAc)_2 \cdot 4H_2O$, $NaBH_4$, $(CH_2NH_2)_2$, H_2 (1 atm), MeOH, rt, 3.5 or 6 h; (ii) TFA, CH_2Cl_2, rt, 16 h; (iii) $(COCl)_2$, CH_2Cl_2, DMF, 0 °C to rt, 1 h then **232** or **233** [>99:1 dr (*Z*):(*E*)], CH_2Cl_2, 0 °C to rt, 16 h.

Exposure of *cis*-configured allyl β-amino esters **228** and **229** to the rearrangement conditions resulted in strikingly different behaviour when compared to *trans*-configured allyl β-amino esters **218** and **219**. The levels of diastereocontrol upon rearrangement were found to be remarkably higher for **228** and **229**, with β-amino acids **234** and **222** being formed in 96:4 and 90:10 dr, respectively. Treatment of **234** and **222** with DBU and MeI gave the corresponding methyl esters **235** and **224** in 85 and 48% isolated yield, and 96:4 and >99:1 dr, respectively (Scheme 36). Notably, the ^1H and ^{13}C NMR spectra and specific rotation for **224** (R = Ph) matched those obtained for the sample of **224** derived from rearrangement of **219** (*vide supra*).



Scheme 36. *Reagents and conditions*: (i) LiHMDS, TMSCl, PhMe, –78 °C then reflux, 1 h; (ii) DBU, MeI, MeCN, rt, 16 h.

Elaboration of **235** and **224** to the C(2)-substituted β-amino acids **238** and **239** was pursued by *N*-debenzylation and concomitant hydrogenation in the presence of Pearlman's catalyst, which furnished primary amines **236** and **237** both in 76% isolated yield and 96:4 and >99:1 dr, respectively. These substrates were then subjected to acid-catalysed hydrolysis for five days[54] followed by purification on ion-exchange resin to afford the corresponding β-amino acids **238** and **239** in 96:4 and >99:1 dr, respectively, in six steps and 19 and 35% overall yield from **192** (Scheme 37).



235, R = Me, 96:4 dr
224, R = Ph, >99:1 dr

236, R = Me, 76%, 96:4 dr
237, R = Ph, 76%, >99:1 dr

238, R = Me, 91%, 96:4 dr
239, R = Ph, 88%, >99:1 dr

Scheme 37. *Reagents and conditions*: (i) $Pd(OH)_2/C$, H_2 (1 atm), MeOH, rt, 24 h; (ii) HCl (6.0 M aq), reflux, 5 days then DOWEX 50WX8.

2.3.4. The origin of diastereoselectivity observed in the Ireland-Claisen rearrangement of allyl β-amino esters

It is interesting to note that regardless of the geometry of the olefin, the rearrangement of *trans*- and *cis*-configured allyl β-amino esters (*E*)-**219** and (*Z*)-**229** proceeded to afford the same major diastereoisomeric product **222**. However, although *cis*-configured precursors **228** and **229** exhibited high stereocontrol upon rearrangement, the analogous reactions with *trans*-configured allyl esters **218** and **219** displayed moderate diastereoselectivity in the case of **219**, and essentially no diastereoselectivity with **218**. To address the origin of diastereoselectivity, these results were interpreted in terms of the possible transition states available for the rearrangement. It was predicted that the rearrangement of the (*E*)-*O*-silyl ketene acetal derived from (*Z*)-**229** (R^1 = H, R^2 = Ph) would proceed *via* a chair-like transition state[2b] **240**. Furthermore, the chair conformer in which 1,3-allylic strain between the C(3)-substituent and the C(1)–O bond is minimised, the rearrangement occurs on the face opposite the bulky *N*-benzyl-*N*-(α-methylbenzyl) group. The rearrangement of (*Z*)-**229** thereby results in the preferential formation of **222** as the major diastereoisomer. In marked contrast, the chair-like transition state is disfavoured for substrates such as (*E*)-**219** (R^1 = Ph, R^2 = H) when unfavourable *syn*-pentane interactions between the R^1 and C(3)-phenyl groups are encountered. In this case, a boat-like transition state **241**[11b,55,56] is favoured in which the bulky R^1 substituent occupies a pseudoequatorial position. In the boat-like transition state, 1,3-allylic strain between the C(3)-substituent and the C(1)–O bond is minimised and rearrangement occurs on the face opposite the bulky *N*-benzyl-*N*-(α-methylbenzyl) group to also afford **222** as the major product (Figure 13). Additionally, this stereochemical analysis provides an explanation for the slight erosion in diastereoselectivity observed for the rearrangement of (*Z*)-**229** (R^2 = Ph; 90:10 dr) when compared with the analogous reaction involving (*Z*)-**228** (R^2 = Me; 96:4 dr) presumably due to the increased steric congestion encountered by a larger R^2 group in an axial position with a chair-like transition state **240**. Furthermore, this rationale may account for the observed difference in diastereoselectivity

when (*E*)-**218** (R^1 = Me, R^2 = H) was subjected to the rearrangement conditions, and a significant erosion of diastereoselectivity was observed (54:46 dr). Presumably, in this case, the absence of any significant steric interactions does not bias any particular transition state.

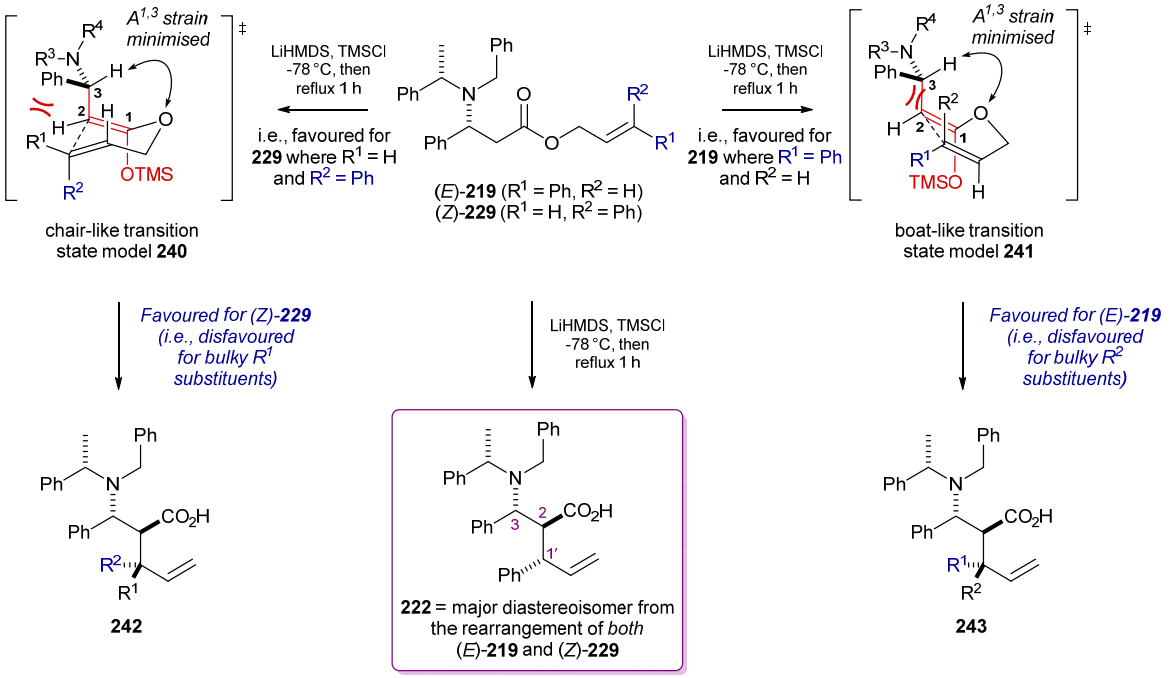


Figure 13. Postulated transition state models for the rearrangement of (*E*)-**219** and (*Z*)-**229**.

2.3.5. Application to the asymmetric synthesis of C(5)-substituted transpentacins

Following the successful investigation into the applicability of the Ireland-Claisen methodology in the asymmetric synthesis of β-amino esters bearing stereogenic C(2)-substituents, the transformation of allyl γ,δ-unsaturated-β-amino esters **104** into C(5)-substituted transpentacins **111** was next explored. It was anticipated that the products of rearrangement **244** could be easily elaborated to 1,2-*anti*-1,5-*syn*-transpentacins **111** by ring-closing metathesis, followed by hydrogenolytic reduction and deprotection (Figure 14).

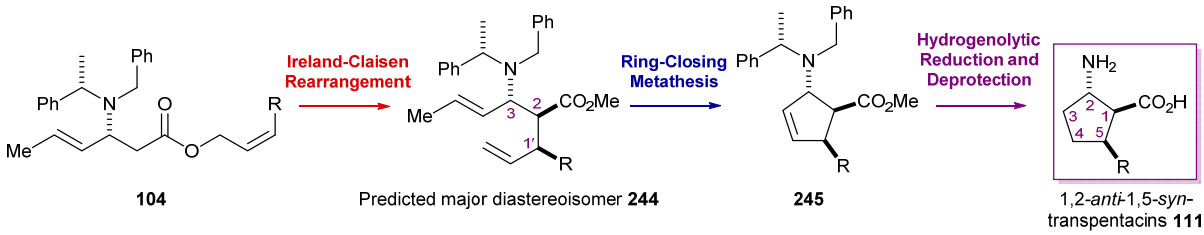
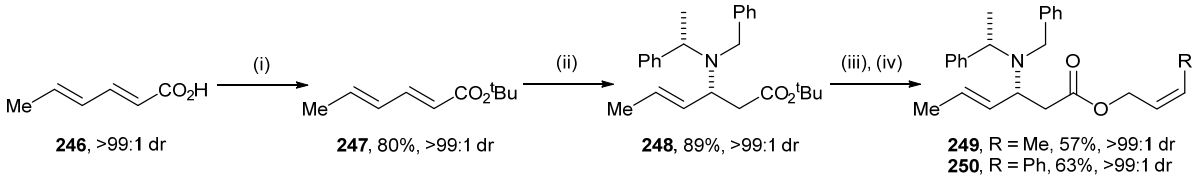


Figure 14. Proposed route through to 1,2-*anti*-1,5-*syn*-transpentacins **111** from *cis*-configured β-amino esters **104** *via* a diastereoselective Ireland-Claisen rearrangement.

2.3.5.1. Synthesis of requisite allyl β-amino esters

Allyl β-amino esters **249** (R = Me) and **250** (R = Ph) were first assessed in the Ireland-Claisen rearrangement. γ,δ-Unsaturated β-amino ester **248** has been reported by Davies and co-workers in their investigation into the synthesis of 5-membered ring scaffolds using the ring-closing metathesis of this substrate as the key step.[57] Following the established

procedure, sorbic acid [(*E*,*E*)-hexa-2,4-dienoic acid] **246** was first converted to **247** in 80% yield upon treatment with isobutylene and catalytic H_2SO_4. Conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*S*)-**77** to **247** gave the known β-amino ester **248**[58] which was isolated in 89% yield and >99:1 dr. The synthesis of rearrangement precursors **249** and **250** was then accomplished using the methodology previously described for allyl β-amino esters **218**, **219**, **228** and **229**: *tert*-butyl ester **248** was treated with TFA followed by esterification with the requisite *cis*-allylic alcohols **232** or **233** to give allyl β-amino esters **249** and **250** in 57 and 63% isolated yield over two steps and >99:1 dr (Scheme 38).

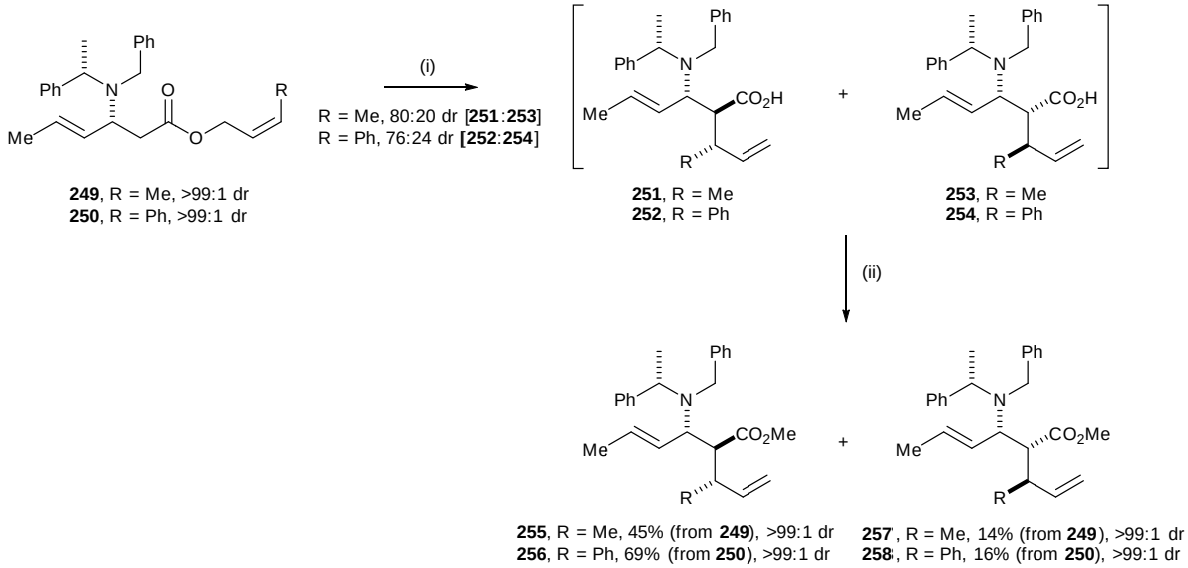


Scheme 38. *Reagents and conditions*: (i) isobutylene, H_2SO_4, CH_2Cl_2, 0 °C to rt, 48 h; (ii) (*S*)-**77**, THF, –78 °C, 2 h; (iii) TFA, CH_2Cl_2, rt, 16 h; (iv) $(COCl)_2$, CH_2Cl_2, DMF, 0 °C to rt, 1 h then *cis*-RCH=CHCH$_2$OH **232** (R = Me) or **233** (R = Ph) [>99:1 dr (*Z*):(*E*)], CH_2Cl_2, 0 °C to rt, 16 h.

2.3.5.2. Ireland-Claisen rearrangement

Treatment of allyl β-amino ester **250** (R = Ph) under the previously optimised Ireland-Claisen rearrangement conditions of LiHMDS and TMSCl in PhMe proceeded with high diastereoselectivity (76:24 dr) to give **252** and **254**, i.e., only two out of the four possible diastereoisomeric products. Esterification of the crude reaction mixture of **252** and **254** using MeI and DBU gave the corresponding methyl esters **256** and **258** in 69 and 16% isolated yield, respectively, and as single diastereoisomers (>99:1 dr) in each case (Scheme 39). The assignments of the relative configurations for the newly formed C(2)- and C(1')-stereogenic centres within products **256** and **258** were established by single crystal X-ray diffraction analysis of **256**·HBF_4 and **258**. The absolute (*S*,*S*,*S*,*S*,*E*)-configuration within **256** and the absolute (2*R*,3*S*,1'*R*,α*S*,*E*)-configuration within **258** were assigned in each case relative to the known (*S*)-configuration of the *N*-α-methylbenzyl fragment (Figure 15). The Ireland-Claisen rearrangement of **249** (R = Me) proceeded in a similar manner with high diastereoselectivity (80:20 dr). Following separation of the 80:20 product mixture of **251** and **253**, respectively, by column chromatography, individual esterification of **251** and **253** produced **255** and **257** in 45 and 14% yield over two steps, respectively, and >99:1 dr (Scheme 39). As **255** and **257** were not crystalline, the relative configurations within both products were assigned by analogy to that unambiguously proven for α-substituted β-amino esters **256** and **258**. These assignments were later confirmed unambiguously by chemical correlation and single crystal

X-ray diffraction analysis[35] of a derivative (*vide infra*). The stereochemical outcome of the rearrangements of **249** and **250** can, in both cases, be rationalised by considering a chair-like transition state model analogous to **240** (*vide supra*).



Scheme 39. *Reagents and conditions*: (i) LiHMDS, TMSCl, PhMe, –78 °C, 15 min, then reflux, 1 h; (ii) DBU, MeI, MeCN, rt, 16 h.

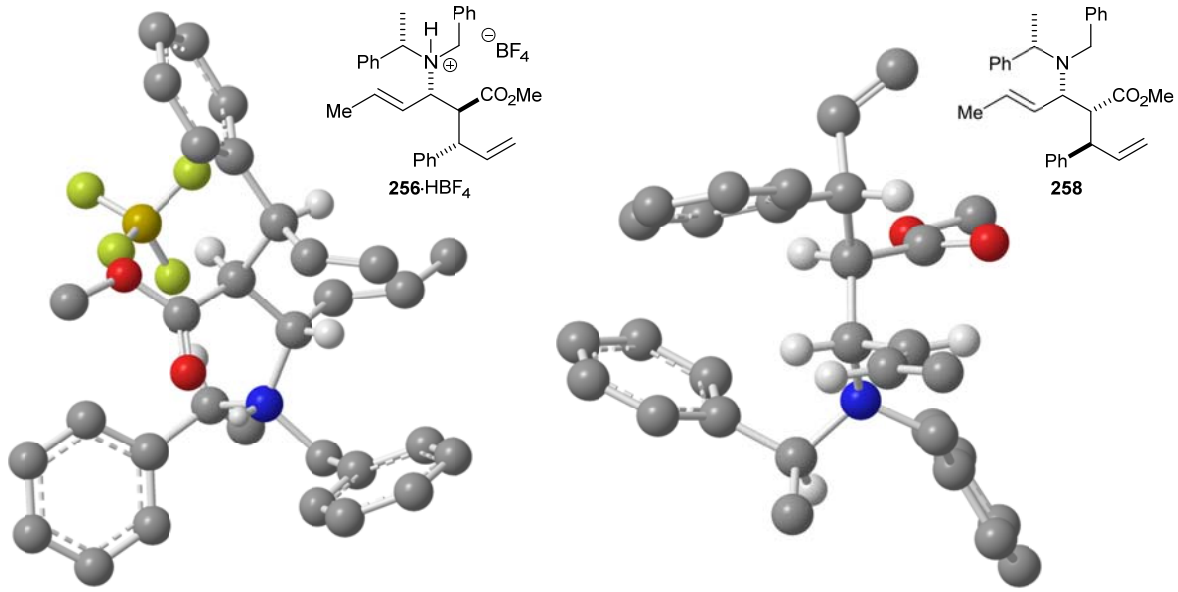
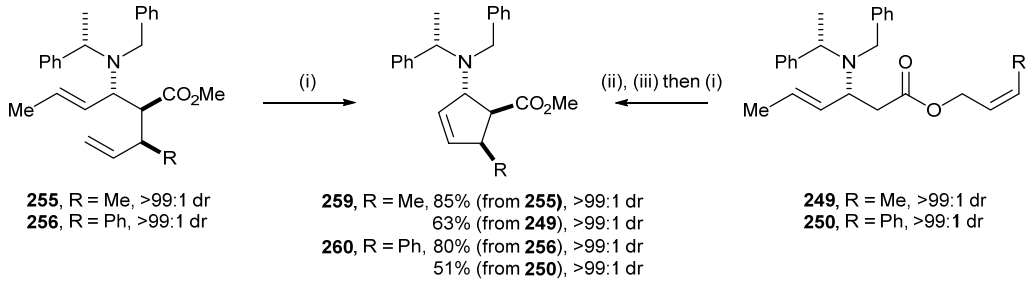


Figure 15. X-ray crystal structures of (*S*,*S*,*S*,*S*,*E*)-**256**·HBF_4 [*left*] and (2*R*,3*S*,1'***R***,α*S*,*E*)-**258** [*right*] (selected H atoms are omitted for clarity).

2.3.5.3. Ring-closing metathesis and chemical correlations

With β-amino methyl esters **255** and **256** (the major products of the Ireland-Claisen rearrangement of **249** and **250**) in hand, attention turned to the ring-closing metathesis step. Treatment of **255** and **256** with 40 mol% Grubbs I catalyst in CH_2Cl_2 at 40 °C and a concentration of 0.02 M gave **259** and **260** in 85 and 80% yield, respectively (i.e., 38 and 55% overall yield over three steps from allyl β-amino esters **249** and **250**). Increasing the isolated yield of **259** was possible by reacting the diastereoisomeric mixture of **251** and **253** prepared

from allyl β-amino ester **249** to esterification and ring-closing metathesis conditions,[59] followed by chromatographic purification, which gave **259** in 63% overall yield over three steps from **249** and >99:1 dr. Cyclic β-amino ester **260** could also be prepared without purification of any intermediates, giving **260** in 51% yield as a single diastereoisomer (>99:1 dr) over three steps from **250** (Scheme 40).[60]



Scheme 40. *Reagents and conditions*: (i) Grubbs I, CH_2Cl_2, 40 °C, 24 h; (ii) LiHMDS, TMSCl, PhMe, –78 °C, 15 min, then reflux, 1 h; (iii) DBU, MeI, MeCN, rt, 16 h.

The 1,2-*anti*-1,5-*syn*-configurations within **259** and **260** were assigned on the basis of the configurations of the starting materials **255** and **256**, and were supported by ^{1}H NMR nOe analyses. For both **259** and **260**, irradiation of CO_2*Me* showed nOe enhancements to both the C(2)*H* proton and the R group, which suggests that the ester and R (i.e., Me or Ph) groups are on the same face of the ring in each case. This result was corroborated by the observed reciprocal correlation between the C(1)*H* and C(5)*H* protons. In addition, irradiation of the C(1)*H* proton resulted in an enhancement of the *N*-benzyl protons (Figure 16).

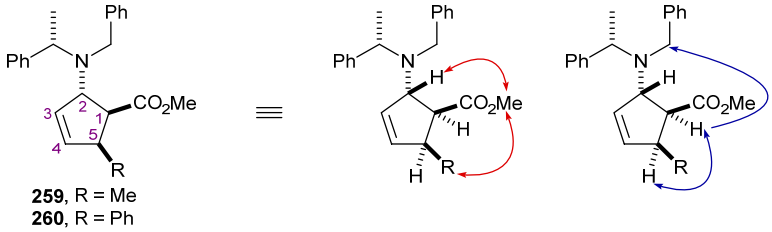
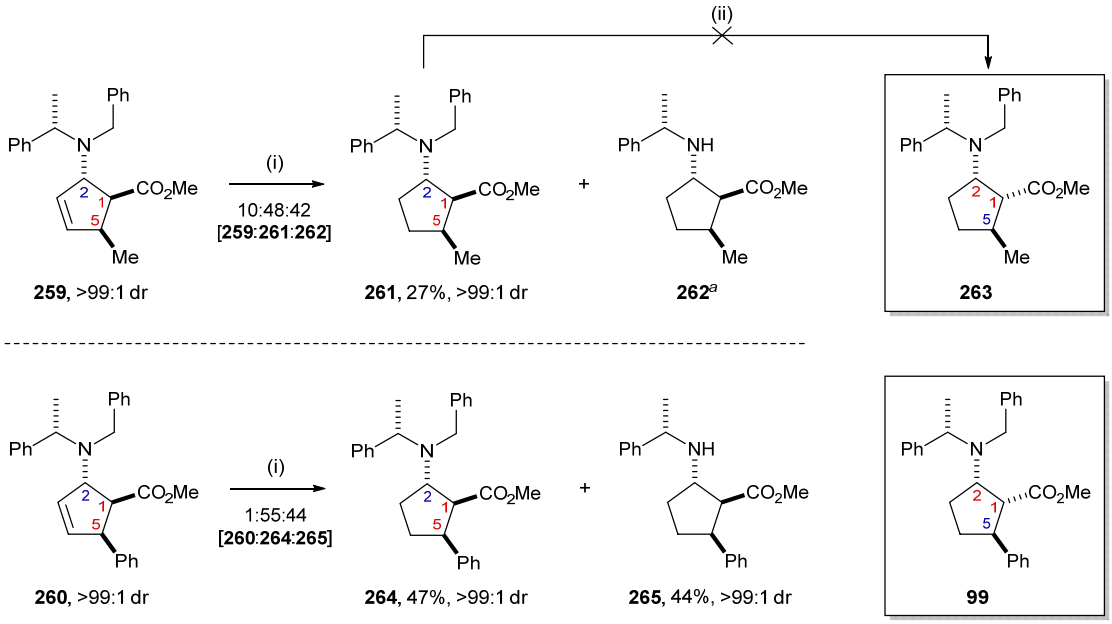


Figure 16. Representations of the ^{1}H NMR nOe correlations observed within **259** and **260**. [‘‘↔’’ represents reciprocal interaction.]

A series of chemical correlation experiments were next conducted in order to support the assigned 1,2-*anti*-1,5-*syn*-configuration. β-Amino esters **259** and **260** were subjected to selective hydrogenation conditions of 50% w/w Pd/C under 1 atm of H_2 for 7 and 15 min to give **261** and **264** in 27 and 47% isolated yield, respectively, and >99:1 dr in both cases (Scheme 41).[61] The ^{1}H NMR spectra of **261** and **264** were found to be significantly different to those of the known 1,2-*syn*-1,5-*anti*-epimers **263** and **99**, respectively.[62] Subsequent single crystal X-ray diffraction analysis[35] of **264** enabled the relative 1,2-*anti*-1,5-*syn*-configuration to be proven unambiguously and the absolute configuration was assigned relative to the known (*S*)-configuration of the *N*-α-methylbenzyl fragment (Figure 17). Additionally, in

another attempt to correlate to the 1,2-*syn*-1,5-*anti*-β-amino ester **263**, β-amino ester **261** was exposed to NaOMe in MeOH at room temperature for 2 days in an attempt to epimerise the C(1)*H* stereocentre.[63] However, analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed only returned starting material (Scheme 41).



Scheme 41. *Reagents and conditions*: (i) H_2 (1 atm), Pd/C, MeOH, rt, 7 or 15 min for **259** and **260**, respectively. [[a] **262** was isolated in 74% yield and >99:1 dr when the reaction was left to stir for 34 min]; (ii) NaOMe, MeOH, rt, 48 h.

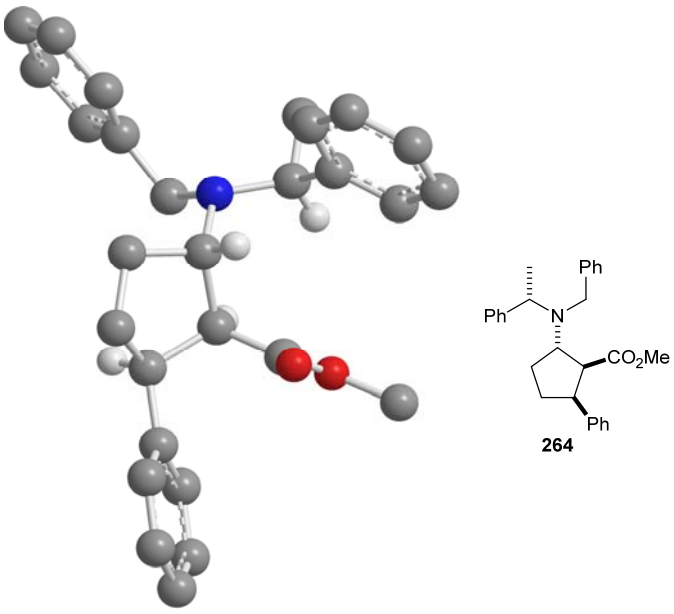
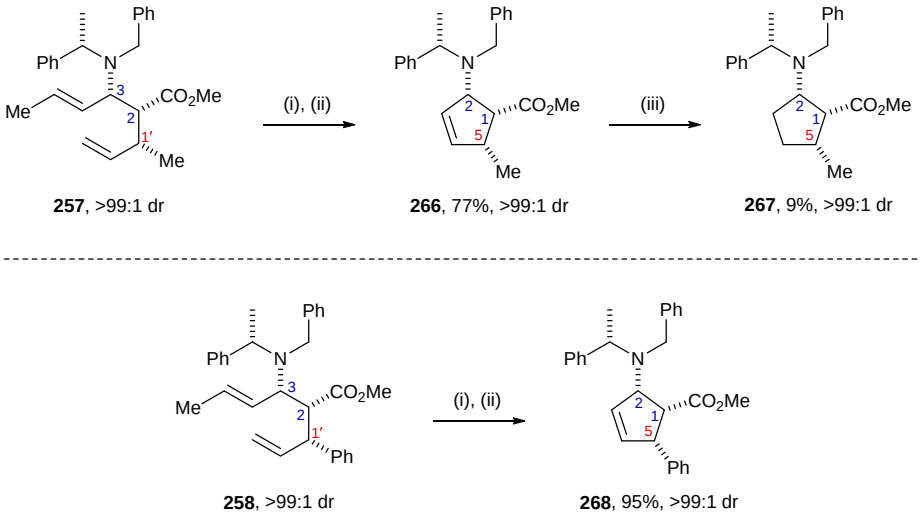


Figure 17. X-ray crystal structure of (*S*,*S*,*S*,*S*)-**264** (selected H atoms are omitted for clarity).

The relative configuration within **257** (the minor diastereoisomer resulting from the Ireland-Claisen rearrangement of **249**) was established by chemical correlation to the known saturated derivative **267**.[62] Ring-closing metathesis of **257** using Grubbs I catalyst afforded β-amino ester **266** in 77% yield and >99:1 dr.[64] Attempted selective hydrogenation of the double bond within **266** using 5 mol% Wilkinson's catalyst [$RhCl(PPh_3)_3$] in EtOAc proved

ineffective, and led only to the recovery of starting material. Alternatively, hydrogenation of **266** under 1 atm H_2 in the presence of 50% w/w Pd/C for 20 min, followed by exhaustive chromatographic purification of the complex crude reaction mixture gave **267** in 9% isolated yield as a single diastereoisomer (Scheme 42). Comparison of ^{1}H and ^{13}C NMR data for **267** showed complete agreement with those reported in the literature.[62,65] This correlation permitted confident assignment of the relative 1,2-*syn*-1,5-*syn*-configuration of **266** and hence established the configuration within the acyclic precursor **257**. The minor product **258** from the rearrangement of **250** was also treated with Grubbs I catalyst which gave **268** in 95% yield and >99:1 dr (Scheme 42).



Scheme 42. *Reagents and conditions*: (i) Grubbs I, CH_2Cl_2, 40 °C, 24 h; (ii) silica, $P(CH_2OH)_3$, Et_3N, CH_2Cl_2, rt, 30 min; (iii) H_2 (1 atm), Pd/C, MeOH, rt, 20 min.

^{1}H NMR nOe analyses of **266** and **268** were also carried out to support further the relative 1,2-*syn*-1,5-*syn*-configuration. In each case, irradiation of the C(1)*H* proton showed a strong enhancement to the signals corresponding to the C(2)*H* and C(5)*H* protons. Moreover, a reciprocal interaction between the C(2)*H* and C(5)*H* protons was also identified, suggesting that C(1)*H*, C(2)*H* and C(5)*H* occupy the same face of the ring system in each case. No correlation to the protons of the *N*-benzyl-*N*-(α-methylbenzyl) group was observed when C(1)*H* and C(5)*H* were irradiated. Additionally, irradiation of the methoxy group resulted in an nOe enhancement of the *N*-benzyl and R (i.e., Me or Ph) group signals (Figure 18).

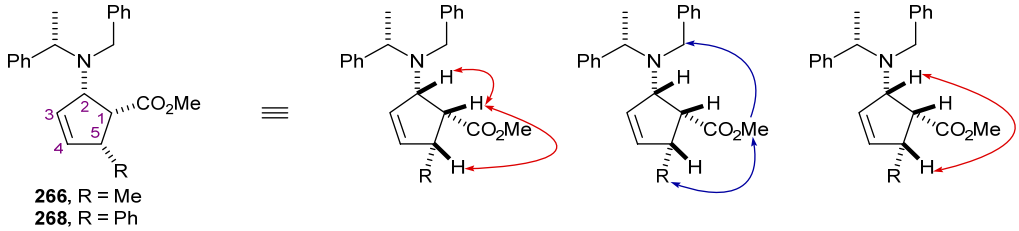
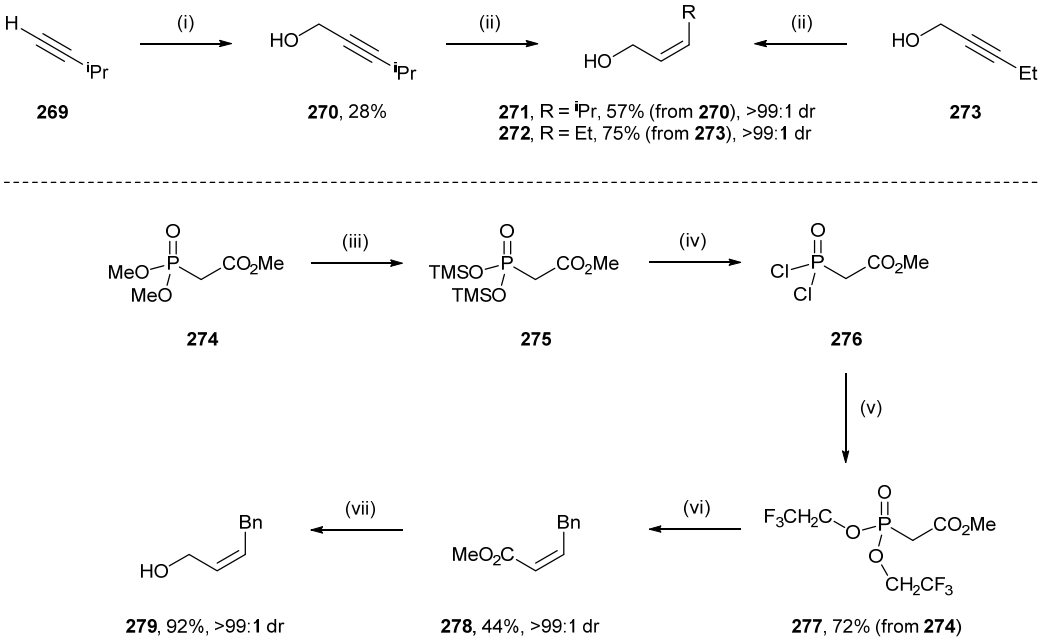


Figure 18. Representations of the ^{1}H NMR nOe correlations observed within **266** and **268**. [''↔'' represents reciprocal interaction.]

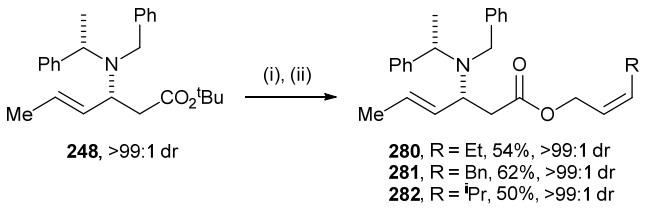
2.3.5.4. Substrate scope

The substrate scope of the rearrangement of allyl β-amino esters was next assessed. Following the conditions established for *cis*-configured alcohols **232** and **233**, partial reduction of commercially available alkyne **273** gave exclusively *cis*-alcohol **272** in 75% yield and >99:1 dr. In an analogous reaction, alkyne **270** (prepared from the deprotonation of **269** with BuLi followed by reaction with paraformaldehyde) afforded **271** in 57% yield and >99:1 dr. The benzyl-substituted analogue **279** was accessed using a Still-Gennari olefination[66] between 2-phenylacetaldehyde[67] and phosphonate ester **277** to give the known *cis*-α,β-unsaturated ester **278**[68] as the sole product. Reaction of **278** with DIBAL-H gave **279** in 29% overall yield (over five steps from **274**) and >99:1 dr (Scheme 43).



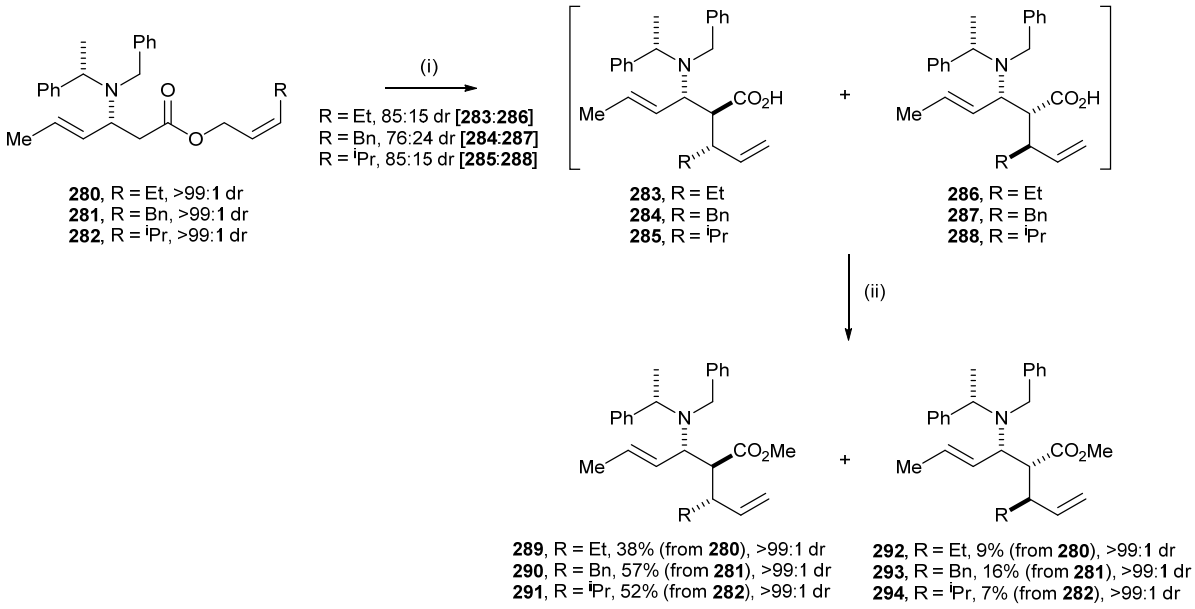
Scheme 43. *Reagents and conditions*: (i) BuLi, paraformaldehyde, THF, –78 °C, then rt, 16 h; (ii) $Ni(OAc)_2{\cdot}4H_2O$, $NaBH_4$, $(CH_2NH_2)_2$, H_2 (1 atm), MeOH, rt, 1.5 or 8 h; (iii) TMSCl, 80 °C, 4 days; (iv) $(COCl)_2$, DMF, CH_2Cl_2, rt, 1 h; (v) CF_3CH_2OH, Et_3N, DMAP, CH_2Cl_2, 0 °C, then rt, 16 h; (vi) KHMDS, 18-crown-6, THF, –78 °C, 25 min, then 2-phenylacetaldehyde, THF, –78 °C, 25 min; (vii) DIBAL-H, CH_2Cl_2, –78 °C, 15 min.

Following an analogous procedure to that used for the synthesis of allyl β-amino esters **249** and **250**, reaction of *tert*-butyl ester **248** with TFA followed by esterification with *cis*-alcohols **271**, **272** and **279** gave the rearrangement precursors **280**–**282** in 50–62% yield (over the two steps) and >99:1 dr in each case (Scheme 44).



Scheme 44. *Reagents and conditions*: (i) TFA, CH_2Cl_2, rt, 16 h; (ii) $(COCl)_2$, CH_2Cl_2, DMF, 0 °C to rt, 1 h then *cis*-RCH=CHCH$_2$OH **272** (R = Et), **279** (R = Bn) and **271** (R = ^{i}Pr), CH_2Cl_2, 0 °C to rt, 16 h.

In all cases, treatment of **280**–**282** with LiHMDS and TMSCl in PhMe afforded clean conversion to mixtures of products containing ~80:20 ratios of α-substituted β-amino acids **283**–**288**. The crude reaction mixtures were esterified using MeI and DBU, although isolation of methyl esters **289**–**294** using chromatographic purification was not possible. Alternatively, the isolation of diastereoisomerically pure (>99:1 dr) samples of **283**–**288** using column chromatography proved successful, with each β-amino acid diastereoisomer being then individually treated with MeI and DBU to give methyl esters **289**–**294** as single diastereoisomers (>99:1 dr) in each case (Scheme 45).



Scheme 45. *Reagents and conditions*: (i) LiHMDS, TMSCl, PhMe, –78 °C, 15 min, then reflux, 1 h; (ii) DBU, MeI, MeCN, rt, 16 h.

The (*S*,*S*,*S*,*S*,*E*)-configurations within the major products **289**–**291** were initially assigned by reference to the proposed transition state for this reaction manifold (*vide supra*) and by analogy to the established stereochemical outcome upon rearrangement of **249** (R = Me) and **250** (R = Ph). Additionally, the absolute (2*R*,3*S*,2'*R*,α*S*,*E*)-configurations within **292** (R = Et) and **287** (R = Bn) were secured by single crystal X-ray diffraction analyses[35] of **292**·HBF_4 and **287**, which therefore allowed the configurations of **286** and **293** to also be confidently assigned. In each case, the absolute configurations were again assigned relative to the known (*S*)-configuration of the *N*-α-methylbenzyl fragment (Figure 19).

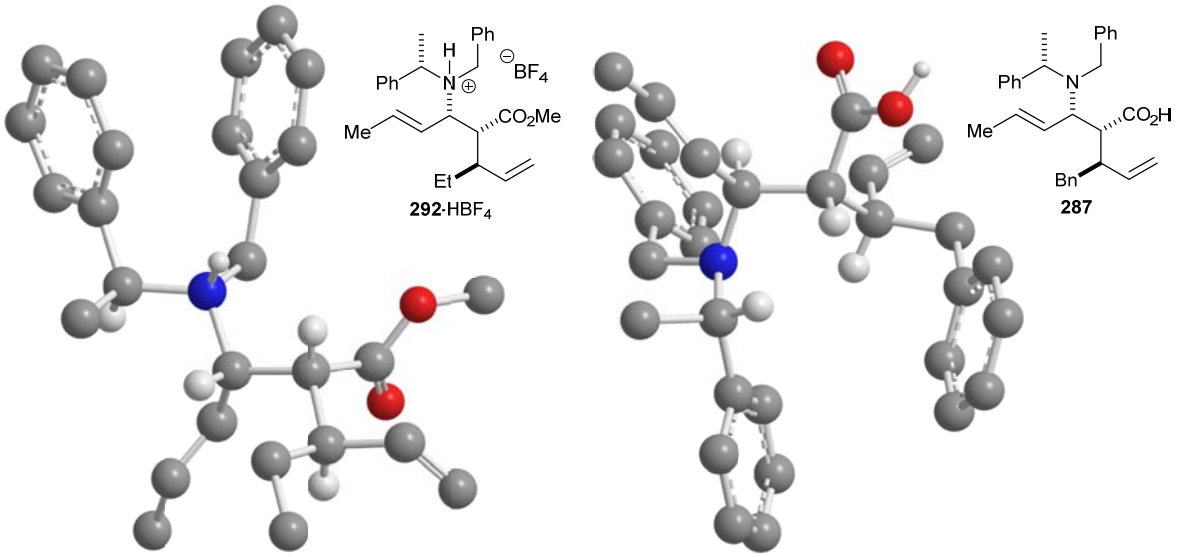
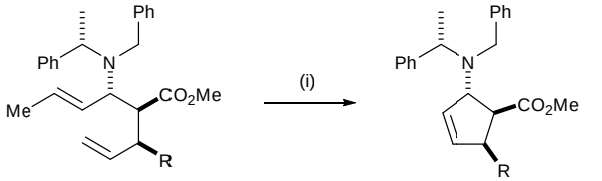


Figure 19. X-ray crystal structures of (2*R*,3*S*,2'*R*,α*S*,*E*)-**292**·HBF_4 [*left*] and (2*R*,3*S*,2'*R*,α*S*,*E*)-**287** [*right*] (the BF_4^- counterion and selected H atoms are omitted for clarity).

2.3.5.5. Elaboration to C(5)-substituted 1,2-*anti*-1,5-*syn*-transpentacins

The major diastereoisomers **289**–**291** were subjected to ring-closing metathesis using Grubbs I catalyst in CH_2Cl_2 to give the corresponding cyclic β-amino esters **295**–**297** in 38–96% yield and >99:1 dr in each case (Scheme 46).



289, R = Et, >99:1 dr
290, R = Bn, >99:1 dr
291, R = ^{i}Pr, >99:1 dr

295, R = Et, 62%, >99:1 dr
296, R = Bn, 96%, >99:1 dr
297, R = ^{i}Pr, 38%, >99:1 dr

Scheme 46. *Reagents and conditions*: (i) Grubbs I, CH_2Cl_2, 40 °C, 24–96 h.

The 1,2-*anti*-1,5-*syn*-configuration within **295**–**297** was assigned on the basis of the configurations of the starting materials **289**–**291** and was supported by ^{1}H NMR nOe analyses of **295**–**297**. In each case, irradiation of CO_2*Me* identified two correlations to proton signals corresponding to C(2)*H* and the R group (i.e., CH_2CH_3, CH_2Ph or $CHMe_2$) in the absence of enhancements to the protons of the *N*-benzyl-*N*-(α-methylbenzyl) group and the C(5)*H* proton. Moreover, reciprocal nOe enhancements between the C(1)*H* and C(5)*H* protons were observed together with a correlation between the C(1)*H* and C(α)*H* protons (Figure 20). Although coupling constants in conformationally flexible five-membered rings are not usually inherently indicative of stereochemistry,[69] it is interesting to note that in all cases, including **259** (R = Me) and **260** (R = Ph) a doublet of doublets for C(1)*H* was observed with ^{1}H–^{1}H ^3J coupling constants within the range of 5.4–6.0 Hz and 9.2–10.3 Hz. These results are consistent with values reported for cyclopentane compounds exhibiting a smaller coupling

constant for a *trans* configuration between protons,[69,70] and hence may in fact be diagnostic for this class of substrates.

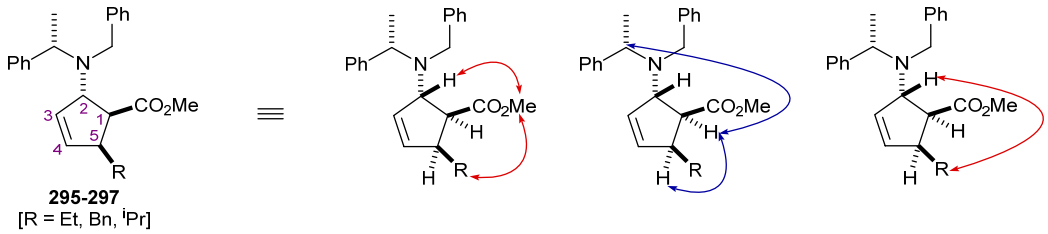
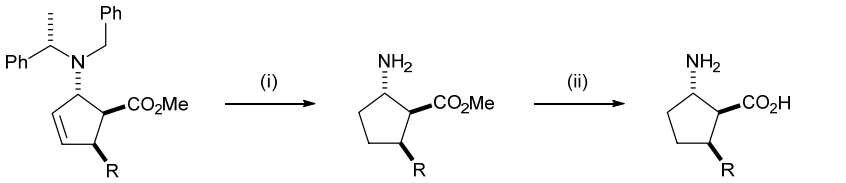


Figure 20. Representations of the ^{1}H NMR nOe correlations observed within **295–297**. [‘‘↔’’ represents reciprocal interaction.]

With the ring system now in place, elaboration of **259**, **260** and **295–297** to C(5)-substituted transpentacins **303–307** could be effected in just two chemical transformations. *N*-Deprotection was achieved by treatment of **259–260** with $Pd(OH)_2/C$ under a H_2 atmosphere to promote *N*-debenzylation and concomitant hydrogenation, which gave primary amines **298–302** as single diastereoisomers (>99:1 dr) in 40–87% yield. Hydrolysis of methyl esters **298–302** using 6.0 M aq HCl at reflux for 16 h and purification by ion exchange chromatography afforded β-amino acids **303–307** in 84% to quantitative yield (Scheme 47). The asymmetric synthesis of a range of five 1,2-*anti*-1,5-*syn*-transpentacins **303–307** was therefore concluded in 3–19% overall yield and nine steps from commercially available sorbic acid **246**.



259, R = Me, >99:1 dr
295, R = Et, >99:1 dr
296, R = Bn, >99:1 dr
297, R = ^{i}Pr, >99:1 dr
260, R = Ph, >99:1 dr

298, R = Me, 83%, >99:1 dr
299, R = Et, 67%, >99:1 dr
300, R = Bn, 69%, >99:1 dr
301, R = ^{i}Pr, 40%, >99:1 dr
302, R = Ph, 87%, >99:1 dr

303, R = Me, 84%, >99:1 dr
304, R = Et, 85%, >99:1 dr
305, R = Bn, quant, >99:1 dr
306, R = ^{i}Pr, 94%, >99:1 dr
307, R = Ph, 89%, >99:1 dr

Scheme 47. *Reagents and conditions*: (i) H_2 (1 atm), $Pd(OH)_2/C$, MeOH, rt, 24 h; (ii) HCl (6.0 M aq), reflux, 16 h then DOWEX 50WX8.

The relative 1,2-*anti*-1,5-*syn*-configurations within **301** (R = ^{i}Pr) and **302**[71] (R = Ph) were initially assigned on the basis of the configurations of their precursors and were also supported by ^{1}H NMR nOe analyses.[72] Irradiation of the C(1)*H* proton showed a correlation to the C(5)*H* proton in both **301** and **302**. The presence of an nOe enhancement between CO_2Me and $CHMe_2$ in **301**, and a reciprocal nOe between the protons of the phenyl group and the C(2)*H* proton in **302** was indicative of a 1,2-*anti*-1,5-*syn*-configuration (Figure 21).

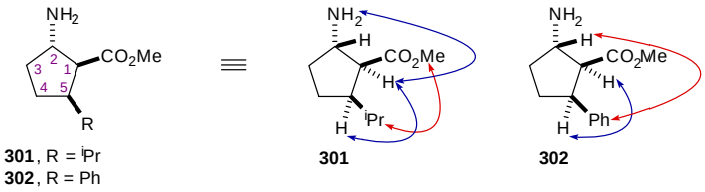


Figure 21. ^{1}H NMR nOe correlations observed within **301** and **302**. [''↔'' represents reciprocal interaction].

Subsequent single crystal X-ray diffraction analyses[35] of the 2,6-difluorobenzoic acid salt of **298**, the hydrochloride salt of **299** and the HBF_4 salt of **302** enabled the relative (*S*,*S*,*S*)-configurations to be proven unambiguously (Figure 22). Additionally, the determination of a Flack *x* parameter[73,74] of 0.005(11) for the crystal structure of **298**·2,6-difluorobenzoic acid provided support for the assigned absolute (*S*,*S*,*S*)-configuration within **298**. The absolute (1*S*,2*S*,5*R*)-configurations within primary β-amino esters **300** (R = Bn) and **301** (R = ^{i}Pr) were hence assigned by analogy, and this analysis also allowed the 1,2-*anti*-1,5-*syn*-configuration within intermediates **259**, **260** and **295**–**297** to be confirmed.

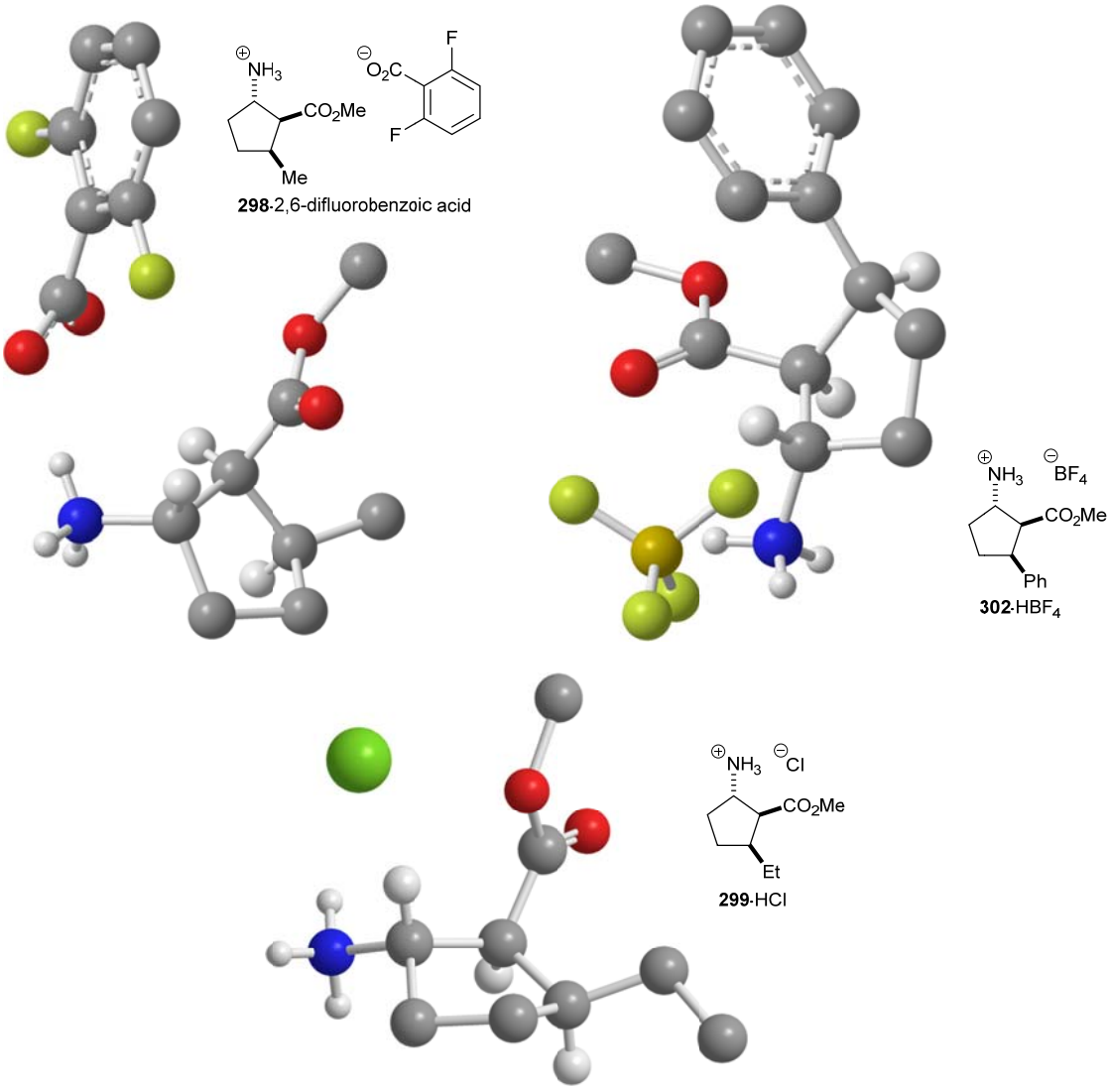


Figure 22. X-ray crystal structure of (*S*,*S*,*S*)-**298**·2,6-difluorobenzoic acid·$CHCl_3$ [*top left*], (*S*,*S*,*S*)-**302**·HBF_4 [*top right*] and (*S*,*S*,*S*)-**299**·HCl [*bottom*] (selected H atoms and $CHCl_3$ are omitted for clarity).

2.4. Conclusion

In conclusion, a highly diastereoselective Ireland-Claisen rearrangement protocol for a range of allyl β-amino esters to give α-substituted β-amino acid products has been successfully developed. The synthetic utility of this reaction manifold was highlighted by the asymmetric syntheses of a range of five novel C(5)-substituted transpentacins.

2.5. References and notes

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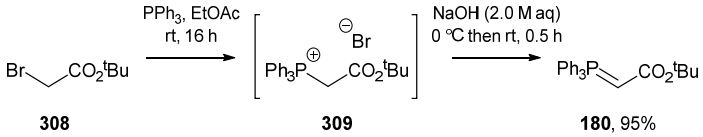
[27] Lithium *N*-isopropyl-*N*-benzylamide **175** was generated by reacting *N*-isopropyl-*N*-benzylamine with BuLi.

[28] PPh_3 was alkylated with *tert*-butyl bromoacetate **308** and the resultant ylid **309** was deprotonated using NaOH to give **180** in 95% yield.



308 **309** **180**, 95%

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[34] Only partial separation could be achieved by column chromatography.

[35] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr J. A. Lee, Chemistry Research laboratory, University of Oxford, U.K.

[36] Pearlman, W. M. *Tetrahedron Lett.* **1967**, 1663.

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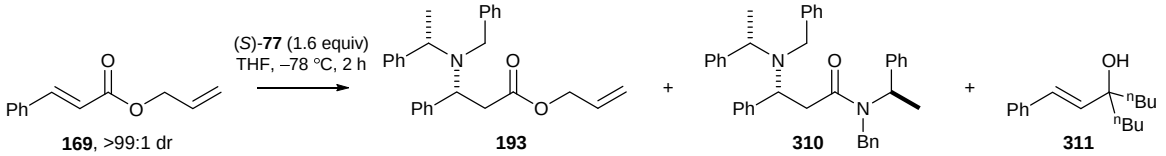
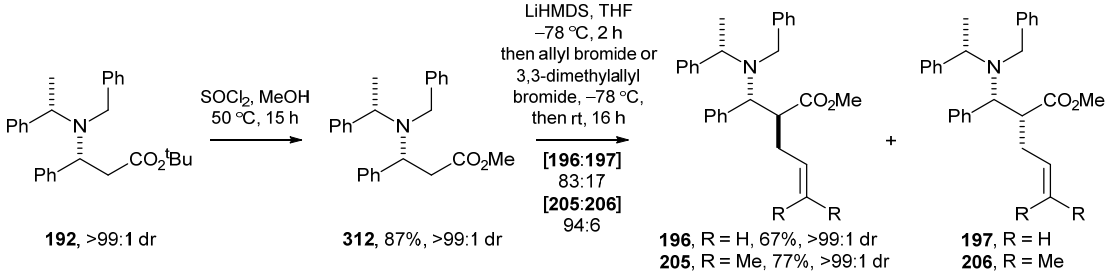
[38] Organolithium reagent *sec*-BuLi was chosen following a short study into premixing lithium amide reactions [i.e., *sec*-BuLi added dropwise to a solution of acceptor and enantiopure amine at –78 °C, and reaction mixture stirred at this temperature for 2 h] using α,β-unsaturated ester **169** as a model ester. Analysis of the ^{1}H NMR spectra for the premixing reactions showed that the propensity for 1,2-addition could be decreased to just 11% (entry 2). Adjustment of the reaction conditions led to the use of *sec*-BuLi resulting in 86 and 14% conversion to allyl β-amino ester **193** and **310**, respectively (entry 3). Moreover, similar levels of diastereoselectivity were observed for the premixing strategy as compared to standard lithium amide conditions. For examples of a pre-mix procedure used in the lithium amide reaction, see: (a) Baenziger, M.; Gobbi, L.; Riss, B. P.; Schaefer, F.; Vaupel, A. *Tetrahedron: Asymmetry* **2000**, *11*, 2231. (b) Kruchinin, D. *D.Phil. Thesis*, University of Oxford, **2006**.



Entry	Conditions	Organolithium reagent	^{1}H NMR crude analysis 193 % / dr	310 % / dr	311
1	Standard	^{n}BuLi	58 (>95:5 dr)	42 (>99:1 dr)	0
2	Pre-mix method	^{n}BuLi	62 (94:6 dr)	11 (>99:1 dr)	27
3	Pre-mix method	^{sec}BuLi	95 (92:8 dr)	5 (>99:1 dr)	0

[39] Authentic sample preparation proceeded *via* an allylation protocol: treatment of *tert*-butyl ester **192** with $SOCl_2$ in MeOH gave the corresponding methyl ester **312** in 87% yield. Subsequent allylation of **312** using LiHMDS and allyl bromide gave an 83:17 mixture of **196** and **197**, with *anti*-**196** being isolated in 67% yield and >99:1 dr. An analogous allylation reaction using 3,3-dimethylallyl bromide resulted in a 94:6 mixture of diastereoisomers whereby *anti*-**205** was obtained in 77% yield and >99:1 dr.



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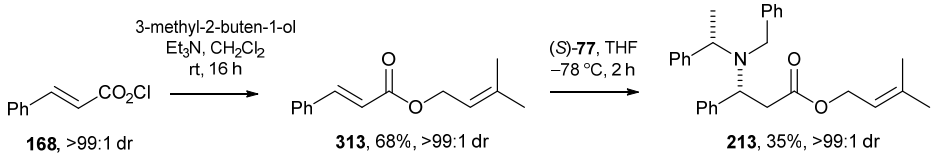
[49] Conjugate addition of (*S*)-**77** to α,β-unsaturated ester **313** (which was derived from reaction of cinnamoyl chloride **168** and 3-methyl-2-buten-1-ol) was carried out in a premixed solution [(*S*)-**77** and **313** were premixed in THF –78 °C prior to the addition of *sec*-BuLi] with *sec*-BuLi to give **213** in 35% yield and >99:1 dr.



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[53] The progress of the hydrogenation reaction was monitored by mass spectrometric analysis and TLC.

[54] Progress of hydrolysis was monitored by mass spectrometric analysis.

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[59] Formation of **259** required two consecutive ring-closing metathesis reactions. Reaction of **251** and **253** with Grubbs I catalyst gave 56% conversion to **259**. Resubjection of the crude reaction mixture to the RCM conditions gave 78% conversion to **259**.

[60] Formation of **260** required three consecutive ring-closing metathesis reactions. Reaction of **252** and **254** with Grubbs I catalyst gave 27% conversion to **260**. Resubjection of the crude reaction mixture to the RCM conditions twice more gave 51 and 69% conversion to **260**.

[61] ^{1}H–^{1}H NMR nOe analyses were attained for **261**, **262** and **265**. Most importantly, in each case reciprocal nOe enhancements were observed between the C(1)*H* and C(α)*H* protons, and between the C(1)*H* and C(5)*H* protons which further confirmed the assigned 1,2-*anti*-1,5-*syn*-configuration. ^{1}H–^{1}H NMR NOESY analysis was performed on **264** to assign the relative 1,2-*anti*-1,5-*syn*-configuration. Irradiation of the C(1)*H* proton showed reciprocal correlation to the C(5)*H* and the *N*-benzyl proton signals. Additionally, a NOESY enhancement from the CO_2*Me* group to the C(2)*H* proton was observed together with a reciprocal interaction between the C(5)*H* and the *N*-benzyl group protons.

[62] Davies, S. G.; Garner, A. C.; Long, M. J. C.; Morrison, R. M.; Roberts, P. M.; Savory, E. D.; Smith, A. D.; Sweet, M. J.; Withey, J. M. *Org. Biomol. Chem.* **2005**, 3, 2762.

[63] Epimerisation of **260** was also attempted under the same reaction conditions outlined for **261**. Unfortunately, only returned starting material was observed by ^{1}H NMR analysis of the crude reaction mixture.

[64] Attempted chromatographic purification of **266** on silica gel resulted in decomposition. Removal of Grubbs I catalyst was possible by using a mixture of $P(CH_2OH)_3$, triethylamine and silica gel in dichloromethane, see: Maynard, H. D.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, 4137.

[65] ^{1}H–^{1}H NMR nOe analysis was performed on **267** to further confirm the assigned 1,2-*syn*-1,5-*syn*-configuration. Reciprocal enhancement was observed between the C(1)*H* and C(2)*H* protons, and between the C(1)*H* and C(5)*H* protons. In addition, reciprocal correlation was identified for the protons of CO_2*Me* and those of the *N*-benzyl group.

[66] Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

[67] Reaction was also attempted with isobutyraldehyde and phosphonate **277**. However, this did not furnish the *cis*-α,β-unsaturated ester and gave instead returned starting material.

[68] Nicolaou, K. C.; Yue, E. W.; La Greca, S.; Nadin, A.; Yang, Z.; Leresche, J. E.; Tsuri, T.; Naniwa, Y.; De Riccardis, R. *Chem. Eur. J.* **1995**, 1, 467.

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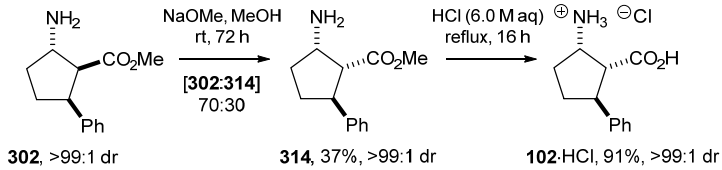
[70] The observation that *trans*-configured protons exhibit smaller ^{3}J coupling constants than *cis*-configured protons in five-membered rings has previously been identified; see: Constantino, M. G.; da Silva, G. V. J. *Tetrahedron* **1998**, *54*, 11363.

[71] Epimerisation of **302** using NaOMe in MeOH followed by acid-catalysed hydrolysis gave **102**·HCl in 34% yield and >99:1 dr over the two steps. The specific rotation together with the ^{1}H and ^{13}C NMR spectra of **102**·HCl were in complete agreement with those reported in the literature[62] and consistent with **302** and **314** being epimeric at C(1).



302, >99:1 dr **314**, 37%, >99:1 dr **102**·HCl, 91%, >99:1 dr

[72] ^{1}H–^{1}H nOe analysis could not be performed for **298** (R = Me) and **300** (R = Bn) due to unresolved resonances in the ^{1}H NMR spectrum.

[73] Flack, H. D. *Acta Crystallogr. A* **1983**, *39*, 876.

[74] Flack, H. D.; Bernardinelli, G. *J. Appl. Crystallogr.* **2000**, *33*, 1143.

Chapter 3: The asymmetric synthesis of enantiopure C(5)-substituted transpentacins *via* diastereoselective conjugate additions to a β'-amino-α,β-unsaturated ester

This chapter details investigations into a diastereoselective conjugate addition/elimination strategy to access β'-amino-α,β-unsaturated ester **107**, upon which conjugate addition reactions using Grignard reagents and lithium amides could be attempted. Development of this protocol culminated in a concise route to access C(5)-substituted 1,2-*anti*-1,5-*syn*-transpentacins **111** (Figure 23).

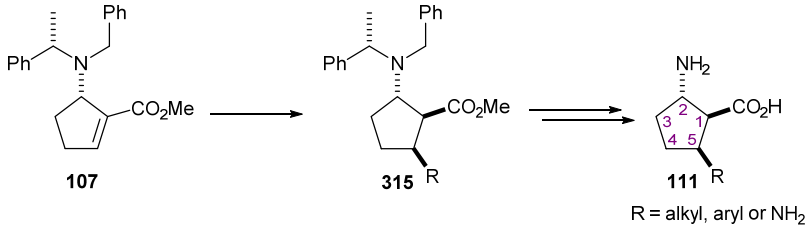
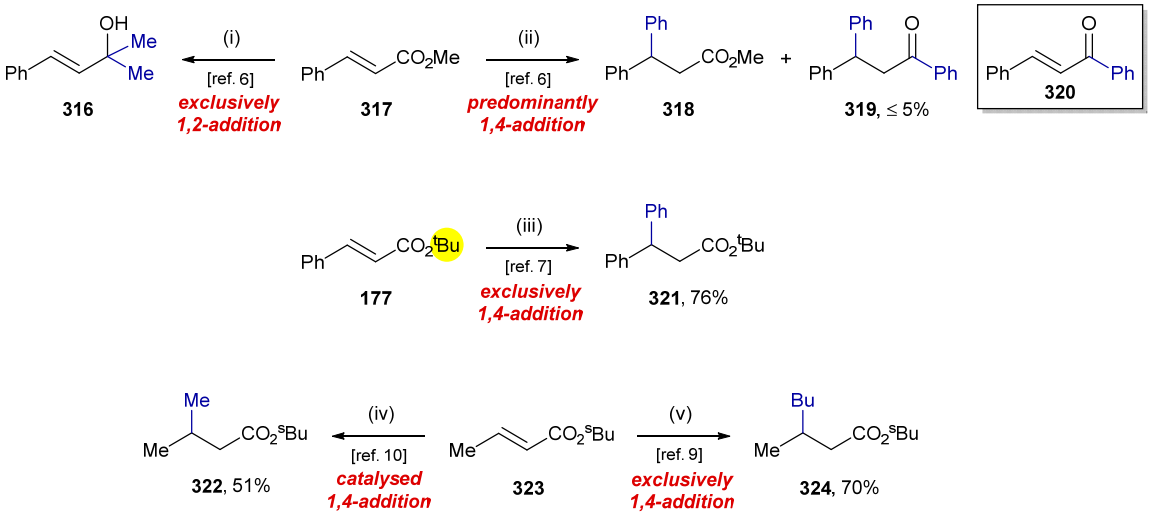


Figure 23. The utility of β'-amino-α,β-unsaturated ester **107** in the synthesis of C(5)-substituted 1,2-*anti*-1,5-*syn*-transpentacins **111**.

3.1. Introduction: conjugate addition reactions of Grignard reagents to α,β-unsaturated esters

In 1899, Barbier reported the observation of a tertiary alcohol product upon reacting a methyl ketone with methyl iodide in the presence of magnesium in Et_2O.[1] Thirteen years later, his student Victor Grignard[2] was awarded the Nobel Prize in Chemistry for the discovery of the so-called Grignard reagent, which has since greatly advanced the progress of organic chemistry.[3] During the delivery of his Nobel lecture, Grignard explained that "*the organic magnesium compounds can produce in certain cases a phenomenon of apparent fixing to an ethylene bond. This will happen when the double bond is near a functional group with a multiple bond, in position α,β called a conjugated position*".[4] Moreover, in distinguishing between the 1,2- and 1,4-addition pathways possible he continued to explain that "*these two reactions are independent and can occur in very variable proportions depending on the working conditions, the nature of the unsaturated compound and the nature of the magnesium compound*".[4] Kohler and Heritage were the first to perform a systematic study exploring the reaction between α,β-unsaturated esters and Grignard reagents.[5] For instance, treatment of methyl cinnamate **317** with MeMgI in Et_2O at –10 °C afforded 1,2-addition product **316**, whereas PhMgBr was shown to add to **317** in a predominantly 1,4-fashion to furnish **318**.[6] Only a trace amount (≤ 5%) of 1,2-addition was observed, as identified by the presence of ketone **319** (resulting from 1,2-addition of PhMgBr to α,β-unsaturated ester **317**, followed by

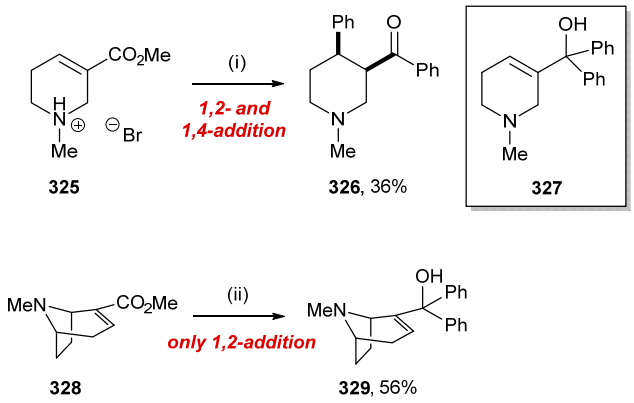
conjugate addition of PhMgBr to the resultant α,β-unsaturated ketone **320**) in the reaction mixture.[6] Following this, Hauser and co-workers[7] have shown that the *tert*-butyl group within **177** poses a steric constraint that completely prevents 1,2-addition of PhMgBr, thereby resulting in the exclusive formation of **321**, which was isolated in 76% isolated yield. In later studies, Munch-Peterson and co-workers investigated the scope of the conjugate addition reaction to α,β-unsaturated esters by employing various aliphatic Grignard reagents.[8] In particular, the reaction of BuMgBr with *sec*-butyl crotonate **323** proceeded with high regioselectivity giving the conjugate addition product **324** in 70% isolated yield.[9] In contrast, a switch to MeMgBr required the presence of a catalytic amount of CuCl in the reaction mixture to effect the isolation of **322** in 51% yield.[10] In the absence of any CuCl, a complex mixture of products resulting from the competitive 1,2-addition pathway was instead obtained (Scheme 48).[11,12,13]



Scheme 48. *Reagents and conditions*: (i) MeMgI, Et_2O, –10 °C, 2 h then rt, 1 h; (ii) PhMgBr, Et_2O, –10 °C, 2 h then rt, 1 h; (iii) PhMgBr, Et_2O, reflux, 4 h; (iv) MeMgBr, CuCl, Et_2O, –5 °C, 15 min then rt, 2 h; (v) BuMgBr, Et_2O, 0 °C, 15 min then rt, 2.5 h.

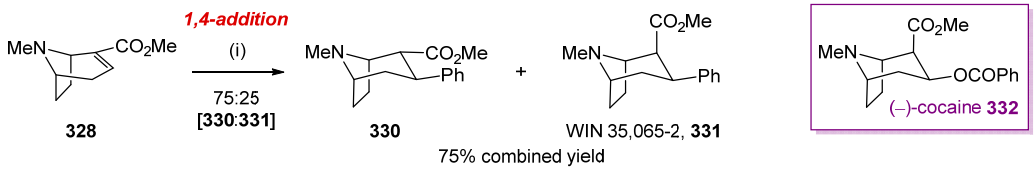
The chemoselectivity of non-catalysed conjugate addition reactions of Grignard reagents to α,β-unsaturated esters was further explored by Zaugg and co-workers in their work on α,β-unsaturated ester containing alkaloids.[14] The authors reported that the reaction of arecoline hydrobromide[15] **325** with PhMgBr did not yield the expected tertiary alcohol product **327** (which would have resulted from 1,2-addition to the ester group) but rather the *cis*-configured ketone **326** was isolated in 36% yield, as a consequence of sequential 1,2- and 1,4-addition reactions. However, in marked contrast, anhydroecgonine methyl ester[16] **328** was reported to give a complex mixture of products when exposed to identical conditions (i.e., upon treatment with PhMgBr) and clean conversion could only be affected by using the

organolithium reagent PhLi, which gave the 1,2-addition product **329** in 56% isolated yield (Scheme 49).



Scheme 49. *Reagents and conditions*: (i) PhMgBr, Et_2O, rt then reflux, 2 h; (ii) PhLi, Et_2O, rt then reflux, 2 h.

Further investigations by Clarke and co-workers towards the synthesis of analogues of (–)-cocaine **332** (e.g., WIN 35,065-2 **331**),[17,18] have demonstrated that anhydroecgonine methyl ester **328** can in fact undergo effective regioselective conjugate addition reactions with a range of aryl Grignard reagents in the absence of any copper salt.[19] For example, this was achieved by treating **328** with PhMgBr in Et_2O at –20 °C which furnished a 75:25 mixture of the 2-methoxycarbonyl-3-phenyltropanes **330** and **331**, respectively, in 75% combined yield (Scheme 50). Interestingly, the authors reported that the copper-catalysed reaction using either 5 mol% or 1.0 equiv of CuBr did not improve the yield and instead resulted in a complex mixture of unidentifiable products.



Scheme 50. *Reagents and conditions*: (i) PhMgBr, Et_2O, –20 °C, 1 h.

3.2. Aim: proposed route to C(5)-substituted cyclic β-amino acids

The synthesis of C(5)-substituted cyclic β-amino acids **338** *via* a diastereoselective Ireland-Claisen rearrangement[20] (see Chapter 2) instigated a study into alternative methods for their preparation to enhance further the structural diversity available for these cyclic β-amino acids. Reaction of the known cyclopentene carboxylates[21] **333** (R = H) or **334** (R = Ac) with a lithium amide reagent **77** was proposed to proceed with concomitant E1cB-type elimination to give β'-amino-α,β-unsaturated ester **107**. It was envisaged that **107** would provide an attractive scaffold for chemo- and diastereoselective conjugate addition reactions of lithium amides and organometallic reagents (e.g., Grignard reagents) to access a range of cyclic

β-amino esters **337**. Elaboration of these substrates *via* hydrogenolysis and ester hydrolysis would then afford C(5)-substituted cyclic β-amino acids **338** (Figure 24).

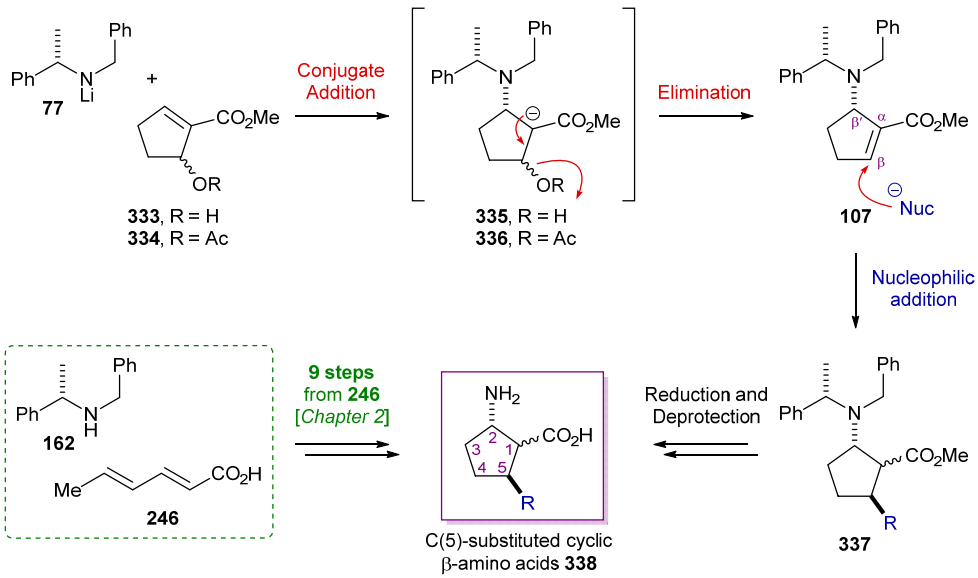
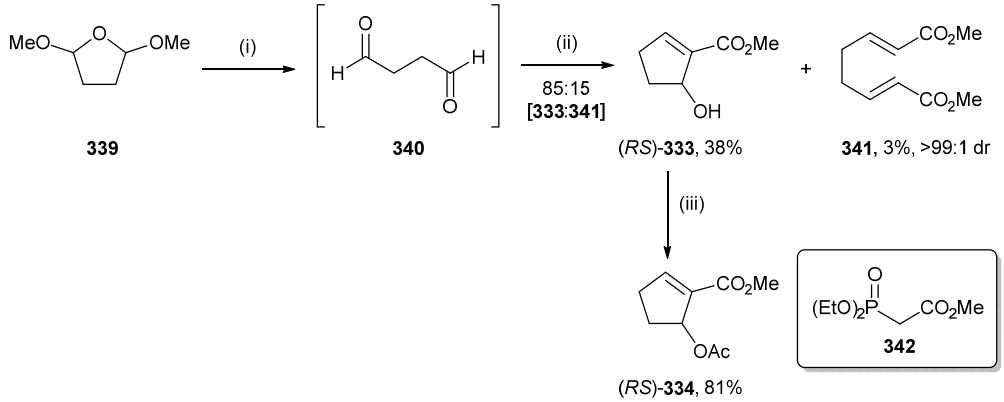


Figure 24. Proposed synthesis of C(5)-substituted cyclic β-amino acids **338** from cyclopentene carboxylates **333** or **334** *via* a diastereoselective conjugate addition/elimination reaction and subsequent diastereoselective conjugate additions to β'-amino-α,β-unsaturated ester **107**.

3.3. Results and discussion

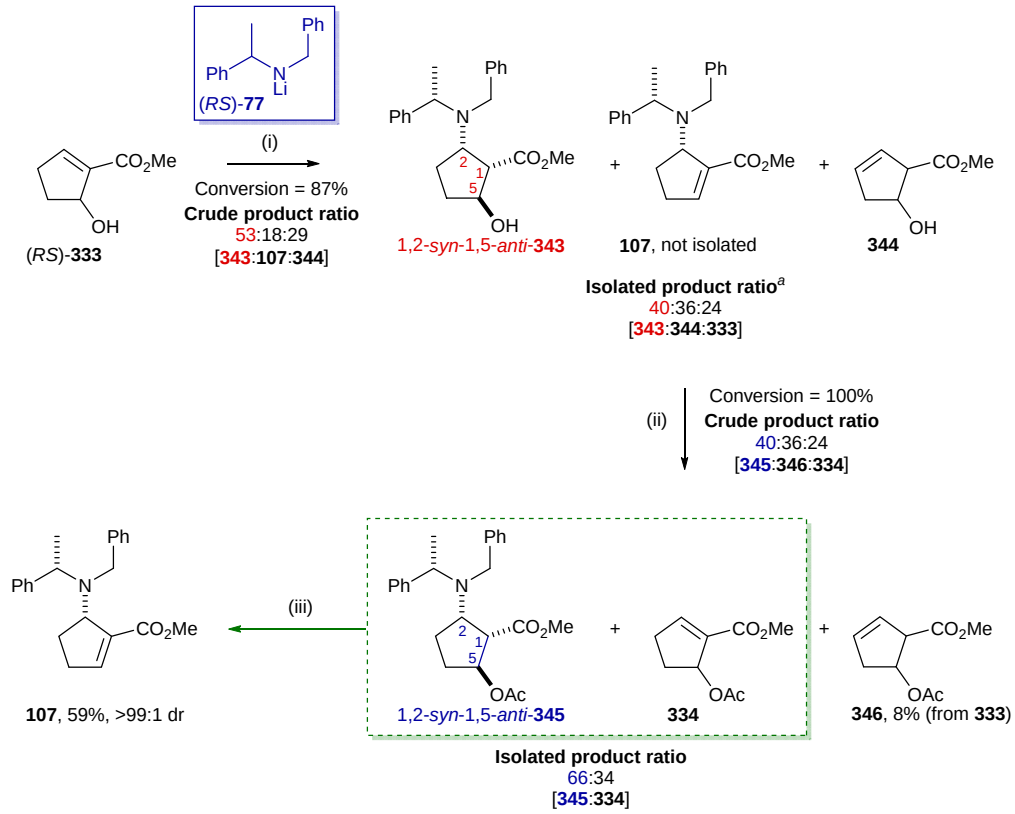
3.3.1. Synthesis of (*S*,*S*)-β'-amino-α,β-unsaturated ester

The preparation of methyl 5-hydroxycyclopentene-1-carboxylate (*RS*)-**333** has previously been achieved on >30 g scale[21] using literature conditions developed by Villiéras and co-workers.[22] Following this established procedure, dialdehyde **340** was generated *in situ* by reacting 2,5-dimethoxytetrahydrofuran **339** with 0.6 M aq HCl. Subsequent Wadsworth-Emmons reaction[23] of **340** using phosphonate[24] **342** gave an 85:15 mixture of (*RS*)-**333** and the corresponding diester **341**, respectively. Isolation of (*RS*)-**333** was achieved *via* chromatographic purification to give **333** in 38% yield over the two steps. Subsequent treatment of (*RS*)-**333** with Ac_2O in pyridine at rt gave (*RS*)-**334** in 81% yield (Scheme 51).



Scheme 51. *Reagents and conditions*: (i) HCl (0.6 M aq), 80 °C, 2.5 h; (ii) **342**, K_2CO_3 (6.5 M aq), rt, 36 h; (iii) Ac_2O, pyridine, CH_2Cl_2, rt, 16 h.

The possibility of high levels of enantiorecognition upon conjugate addition of chiral lithium amides to α,β-unsaturated esters (*RS*)-**333** (R = H) and (*RS*)-**334** (R = Ac) was investigated next. Davies and co-workers[25] have previously employed a mutual kinetic resolution[26] strategy (i.e., reaction of a racemic substrate with a racemic reagent) in order to establish the levels of enantiorecognition observed between a chiral substrate (i.e., an α,β-unsaturated ester) and a chiral reagent (i.e., a lithium amide). The conjugate addition of lithium (*RS*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*RS*)-**77** to (*RS*)-**333** was initially examined. Treatment of (*RS*)-**333** with (*RS*)-**77** in THF at –78 °C for 2 h resulted in a 53:18:29 mixture of C(5)-hydroxy substituted β-amino ester **343**, β'-amino-α,β-unsaturated ester **107** and β,γ-unsaturated ester **344** (which is presumably formed as a result of deprotonation at the γ-position within **333** by the basic lithium amide reagent), respectively, in 87% conversion. Subsequent acetylation to enable their separation gave a 40:36:24 mixture of **345**, **346** and **334**, respectively, following which chromatographic purification resulted in the isolation of a 66:34 mixture of the C(5)-acetoxy substituted β-amino ester **345** and the acetylated α,β-unsaturated ester **334** (Scheme 52). The relative configurations between the C(2) and C(α) stereogenic centres within **107**, **343** and **345** were initially assigned on the assumption that the conjugate addition reaction proceeds with the same sense of diastereoselectivity as when **77** is added to achiral α,β-unsaturated esters,[27] and this assignment was subsequently confirmed by single crystal X-ray diffraction analysis of the HBF_4 salt of enantiopure **107** (*vide infra*). Subjection of the 66:34 mixture of **345** and **334**, respectively, to NaOMe in MeOH resulted in full conversion of **345** to **107**. The fate of **334** in this reaction is, however, unknown. The ^{1}H and ^{13}C NMR spectroscopic data for this sample of **107** were identical to those for the sample of **107** isolated from the conjugate addition of (*RS*)-**77** to (*RS*)-**333**, thus establishing the relative configuration between the C(2) and C(α) stereogenic centres within **107** and therefore also those within **343** and **345**.



Scheme 52. *Reagents and conditions*: (i) (*RS*)-**77**, THF, –78 °C, 2 h; (ii) Ac_2O, pyridine, CH_2Cl_2, rt, 16 h; (iii) NaOMe, MeOH, rt, 16 h. [[a] Another fraction was isolated containing a 62:11:27 mixture of **343**, **344** and **333**, respectively.]

The relative 1,2-*syn*-1,5-*anti*-configurations within **343** and **345** were assigned on the basis of ^{1}H NMR nOe analyses. Irradiation of the C(1)*H* proton within **343** showed an nOe enhancement to the C(2)*H* proton, which suggests that the ester and *N*-benzyl-*N*-(α-methylbenzyl)amino groups are on the same face of the ring. This result was corroborated by the observed correlation from the C(5)*H* to the NCH_2Ph proton signals. Additionally, irradiation of the separate signals corresponding to the C(4)H_2 protons showed an interaction between the C(4)H_A and C(2)*H* protons together with an interaction between the C(4)H_B and C(5)*H* protons. ^{1}H NMR nOe analysis of **345** identified a reciprocal correlation between the C(1)*H* and C(2)*H* protons which is consistent with a *syn*-relationship between the ester and amino groups. The presence of a reciprocal nOe enhancement between the ester group and the C(5)*H* proton was indicative of a 1,5-*anti* configuration. Irradiation of the protons at C(3) and C(4) further complemented these results since correlations were observed between the C(2)*H* and C(3)H_A protons, and the C(2)*H* and C(4)H_A protons, together with enhancements between the C(3)H_B, C(4)H_B and C(5)*H* protons (Figure 25). The assigned relative 1,2-*syn*-1,5-*anti*-configurations within **343** and **345** thereby indicates that upon formation of **343**, protonation of the intermediate enolate occurs *anti* to the C(2)-amino group[28] in accordance with the synthesis of previously reported[25a,25b] cyclic β-amino esters resulting from conjugate addition

to analogous systems. It is important to note, however, that the level of enantiorecognition between α,β-unsaturated ester **333** and lithium amide **77** could not be quantified in this case as some elimination to **107** was observed together with γ-deprotonation of α,β-unsaturated ester **333** to form **344**.

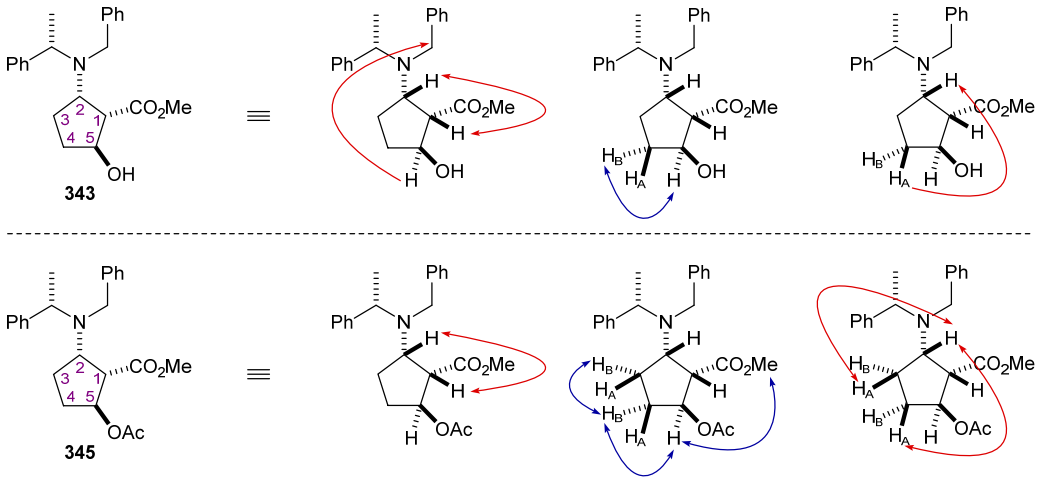
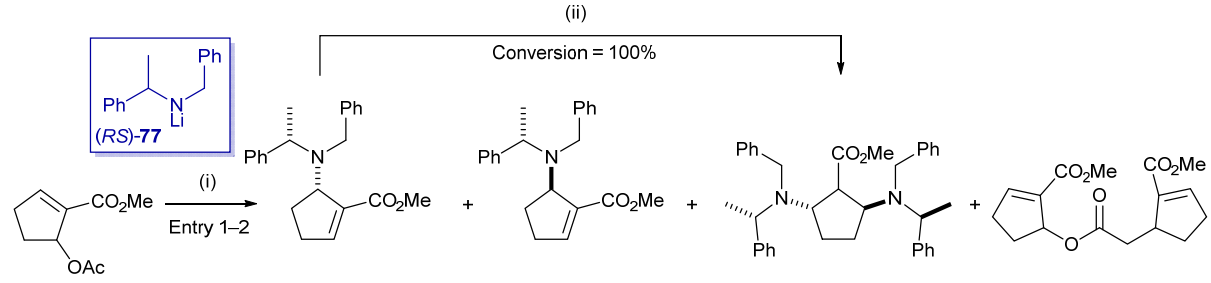


Figure 25. ^{1}H NMR nOe correlations observed within **343** and **345**. [''↔'' represents reciprocal interaction].

Conjugate addition of (*RS*)-**77** to (*RS*)-**334** was carried out under standard conditions (i.e., in THF at –78 °C for 2 h followed by the addition of satd aq NH_4Cl), and proceeded in full conversion to give a 60:5:35 mixture of diastereoisomers (*RS*,*RS*)-**107** and (*RS*,*SR*)-**347** alongside β,β'-diamino ester **348** [which is presumably formed as a result of a doubly diastereoselective conjugate addition of a second equivalent of the lithium amide reagent to **107**]. In an attempt to suppress the second conjugate addition pathway, an analogous reaction was performed using only 0.95 equiv of (*RS*)-**77**. ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed a 63:6:31 mixture of **107**, **347** and **349**, respectively, with no evidence of any β,β'-diamino ester **348** being formed. Exhaustive chromatographic purification of the crude reaction mixture allowed the isolation of (*RS*,*RS*)-**107** and (*RS*,*SR*)-**347** in 13 and 2% yield, respectively, as single diastereoisomers (>99:1 dr) in both cases, together with a sample of **349** in 13% isolated yield. An authentic sample of β,β'-diamino ester **348** was prepared upon conjugate addition of (*RS*)-**77** to β'-amino-α,β-unsaturated ester (*RS*,*RS*)-**107** in THF at –78 °C for 2 h, delivering solely **348** (>99:1 dr), which was isolated in 82% yield (Scheme 53). The sample of **348** proved to be crystalline, hence single crystal X-ray diffraction analysis[29] unambiguously confirmed the relative configuration within **348** (Figure 26).[30]



Entry	(*RS*)-77 equiv	Conversion	Crude product ratio [107 : 347 : 348 : 349]	Conjugate addition dr [107 : 347]	Isolated yield of 107 (dr)	Isolated yield of 347 (dr)
1	1.6	100	60 : 5 : 35 : 0	95 : 5[a]	-	-
2[b]	0.95	62	63 : 6 : 0 : 31	91 : 9	13% (>99:1 dr)	2% (>99:1 dr)

Scheme 53. *Reagents and conditions*: (i) (*RS*)-**77**, THF, –78 °C, 2 h; (ii) (*RS*)-**77** (1.6 equiv), THF, –78 °C, 2 h. [[a] The conjugate addition dr was calculated using (**107**+**348**):**347**. [b] A sample of **349** was also isolated from this reaction in 13% yield.]

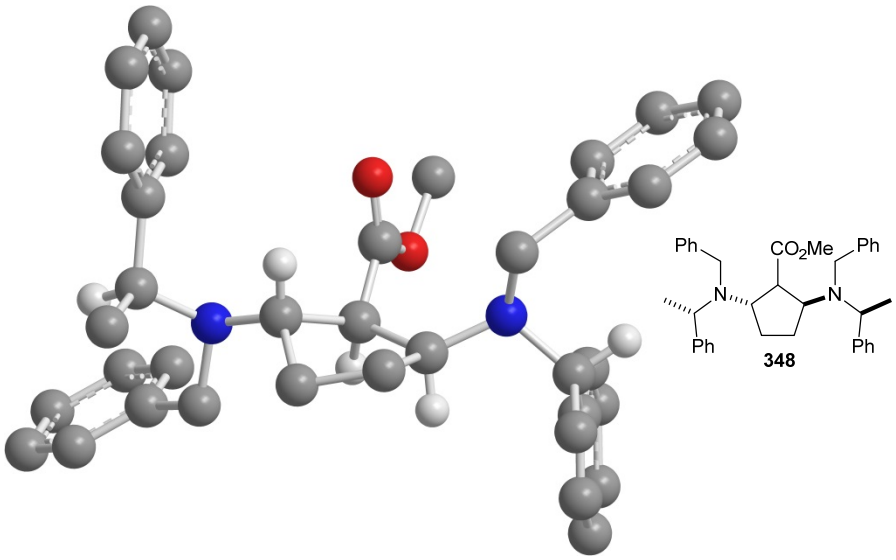
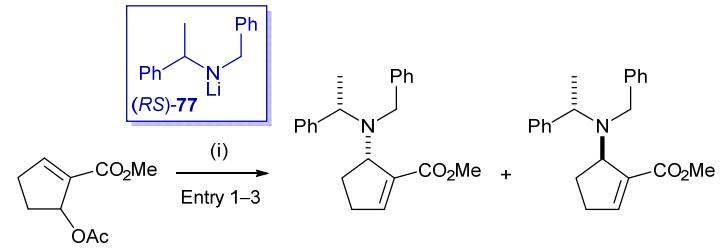


Figure 26. X-ray crystal structure of (*RS*,*RS*,*RS*,*RS*)-**348** (selected H atoms are omitted for clarity).

In an attempt to inhibit the formation of β,β'-diamino ester **348**, it was next envisaged that a silylating agent could be utilised to trap the intermediate enolate and prevent elimination of the acetoxy substituent prior to work-up.[31] To test this hypothesis (*RS*)-**334** was treated with 2.0 equiv of TMSCl followed by 1.6 equiv of (*RS*)-**77** in THF at –78 °C, and the reaction mixture was stirred for 2 h giving exclusively (*RS*,*RS*)-**107** and (*RS*,*SR*)-**347** in a 92:8 ratio, respectively, with elimination presumably occurring upon work-up in this case. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed no sign of β,β'-diamino ester **348**, and purification *via* flash column chromatography resulted in the isolation of **107** in 34% yield and >99:1 dr. However, despite **107** and **347** now being the only two products, the reaction proceeded to only 53% conversion, thereby indicating that the presence of TMSCl retards the rate of conjugate addition. In an attempt to force the reaction to conversion the amount of TMSCl was decreased to 1.2 equiv, which resulted in a 92:8 mixture of **107** and

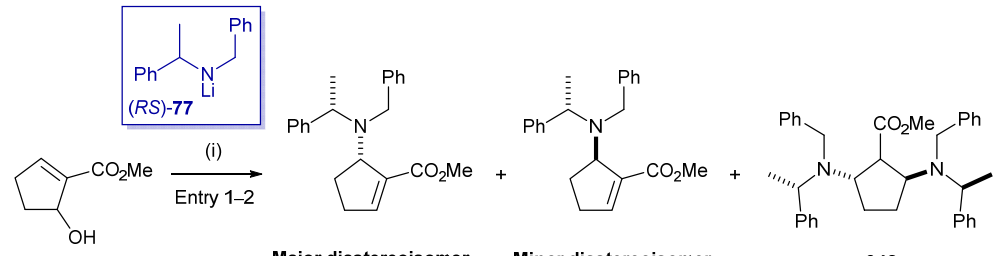
347, respectively, and a marginally improved conversion of 62%. Upon increasing the number of equivalents of (*RS*)-**77** to 6.0 equiv,[32] however, a 92:8 mixture of β,β'-diamino ester **348** and **107**, respectively, was obtained. Alternatively, using 2.0 equiv of (*RS*)-**77** and 1.2 equiv of TMSCl yielded predominantly **107** in 82% conversion, with **107** and **347** being isolated in 57 and 3% yield, respectively, and as single diastereoisomers (>99:1 dr) in each case (Scheme 54). Therefore, under optimised conditions, β'-amino-α,β-unsaturated ester (*RS*,*RS*)-**107** was prepared in four steps from commercially available **339**, in 18% overall yield and >99:1 dr. It is also important to note that the inclusion of TMSCl in the reaction mixture did not affect the level of diastereoselectivity.



Entry	(*RS*)-77 equiv	TMSCl equiv	Conversion	Crude product ratio [107 : 347]	Isolated yield of 107 (dr)	Isolated yield of 347 (dr)
1	1.6	2.0	53	92 : 8	34% (>99:1 dr)	-
2	1.6	1.2	62	92 : 8	-	-
3	2.0	1.2	82	91 : 9	57% (>99:1 dr)	3% (>99:1 dr)

Scheme 54. *Reagents and conditions*: (i) (*RS*)-**77**, TMSCl, THF, –78 °C, 2 h.

It was next decided to utilise TMSCl in the conjugate addition to the C(5)-hydroxy substituted analogue **333**. For the conjugate addition of 2.6 equiv[33] (*RS*)-**77** to (*RS*)-**333**, the addition of 2.2 equiv of TMSCl to the reaction mixture led to complete consumption of **333**, giving a 26:74 mixture of **107** and **348**, respectively, with β,β'-diamino ester **348** being isolated in 57% yield and >99:1 dr. Although the conjugate addition proceeded with high diastereoselectivity in this case, the reaction suffered from the second conjugate addition pathway to afford **348** as the major product. By contrast, when the reaction was carried out in the presence of 4.0 equiv of TMSCl, comparatively clean conversion to a 92:4:4 mixture of **107**, **347** and **348**, respectively, was obtained, from which **107** was isolated in 61% yield as a single diastereoisomer (>99:1 dr) (Scheme 55). Racemic β'-amino-α,β-unsaturated ester **107** was therefore prepared in three steps from commercially available **339**, in a slightly improved overall yield of 23%.

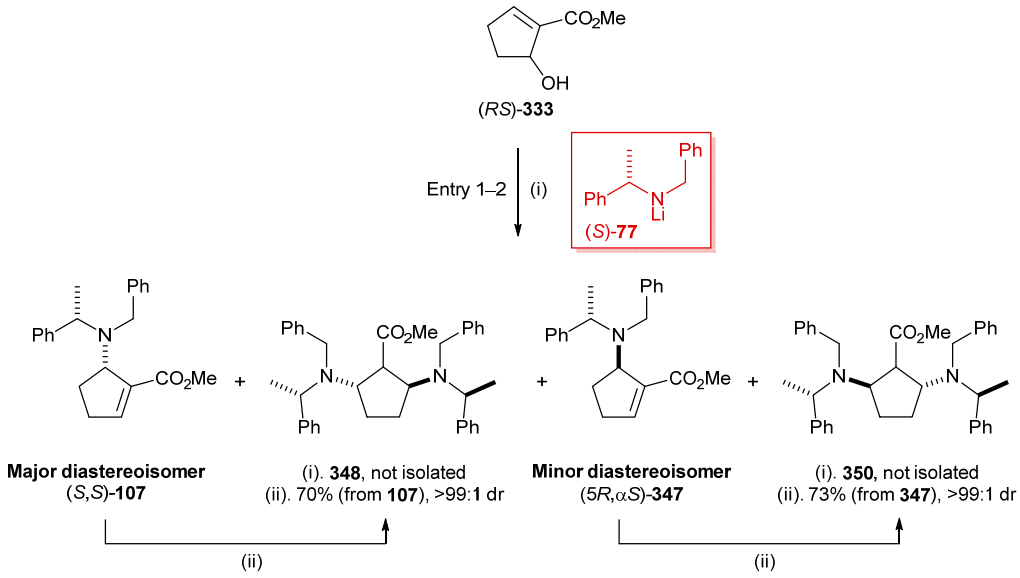


Entry	TMSCl equiv	Crude product ratio [107 : 347 : 348]	Conjugate addition dr[a]	Isolated yield of 107 (dr)	Isolated yield of 348 (dr)
1	2.2	26 : 0 : 74	>99:1	-	57% (>99:1 dr)
2	4.0	92 : 4 : 4	96:4	61% (>99:1 dr)	-

Scheme 55. *Reagents and conditions*: (i) (*RS*)-**77** (2.6 equiv), TMSCl, THF, –78 °C, 2 h. [[a] The conjugate addition dr was calculated using (**107**+**348**):**347**].

The reaction of (*RS*)-**333** with enantiopure lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*S*)-**77** was conducted next. Reaction of (*RS*)-**333** with (*S*)-**77** under conditions that matched the developed tandem conjugate addition/elimination protocol [i.e., with 2.6 equiv (*S*)-**77** and 4.0 equiv TMSCl] gave 100% conversion to a 78:15:6:1 mixture of **107**, **348**, **347** and **350**, respectively. The conjugate addition dr of 85:15 was determined by calculating the ratio between the sum of the major diastereoisomers and the sum of the minor diastereoisomers [i.e., (**107**+**348**):(**347**+**350**)]. Upon chromatographic purification of the crude reaction mixture, (*S*,*S*)-**107** was isolated in 49% yield and >99:1 dr. Authentic samples of β,β'-diamino esters **348** and **350** were accessed by separate conjugate addition reactions of (*S*)-**77** to β'-amino-α,β-unsaturated esters (*S*,*S*)-**107** and (5*R*,α*S*)-**347**, respectively, in THF at –78 °C, whereby both reactions proceeded with high diastereoselectivity (>99:1 dr in each case).[34] Chromatographic purification of the crude reaction mixtures resulted in the isolation of **348** and **350** in 70 and 73% yield, respectively, and >99:1 dr in both cases (Scheme 56). In the case of the conjugate addition of (*S*)-**77** to (*S*,*S*)-**107**, the anticipated senses of reagent and substrate control are co-operative (i.e., representing the doubly diastereoselective "matched" pairing). On the other hand, the experimental result obtained for the reaction of (5*R*,α*S*)-**347** with (*S*)-**77** indicates that the stereocontrol exerted by the substrate is completely dominant over that of the lithium amide, thereby representing the doubly diastereoselective "mismatched" pairing. Unfortunately, at only a 3-fold increase in scale (i.e., with 600 mg of **333**), reaction of (*RS*)-**333** with (*S*)-**77** under identical conditions gave a 40:52:7:1 mixture of **107**, **348**, **347** and **350**, respectively. To circumvent this problem, the solution of (*S*)-**77** in THF at –78 °C was added dropwise to a stirred solution of (*RS*)-**333** and TMSCl (5.0 equiv) in THF at –78 °C, such that (*S*)-**77** was kept at a lower concentration in the reaction mixture.

Consequently, this 'reverse addition' strategy proved successful in significantly reducing the amount of **348** formed, and the conjugate addition of (*S*)-**77** to (*RS*)-**333** could be conducted on larger scale (i.e., with ~3 g of **333**) to give crude 80:13:5:2 mixtures of **107**, **348**, **347** and **350**, respectively, in a consistent fashion. Diastereoisomers (*S*,*S*)-**107** and (5*R*,α*S*)-**347** were subsequently isolated in 50 and 9% yield, respectively, and >99:1 dr in both cases. This concluded the synthesis of enantiopure (*S*,*S*)-**107** in three steps from starting material **339**, 19% overall yield and >99:1 dr (Scheme 56). Furthermore, single crystal X-ray diffraction analysis[29] of the HBF_4 salt of **107** served to unambiguously establish the relative configuration within **107**, and the absolute (*S*,*S*)-configuration of **107** was assigned relative to the known (*S*)-configuration of the *N*-α-methylbenzyl fragment. In addition, the determination of a Flack *x* parameter[35,36] of 0.01(15) for the crystal structure of **107**·HBF_4 confirmed the assigned absolute configuration of **107** (Figure 27).



Entry	TMSCl equiv	Crude product ratio [107 : 348 : 347 : 350]	Conjugate addition dr [(107 + 348) : (347 + 350)]	Isolated yield of (*S*,*S*)-107 (dr)	Isolated yield of (5*R*,α*S*)-347 (dr)
1	4.0	78 : 15 : 6 : 1	85 : 15	49% (>99:1 dr)	-
2	5.0	80 : 13 : 5 : 2	85 : 15	50% (>99:1 dr)	9% (>99:1 dr)

Scheme 56. *Reagents and conditions*: (i) (*S*)-**77** (2.6 equiv), TMSCl, THF, –78 °C, 2 h; (ii) (*S*)-**77** (2.5 equiv), THF, –78 °C, 2 h.

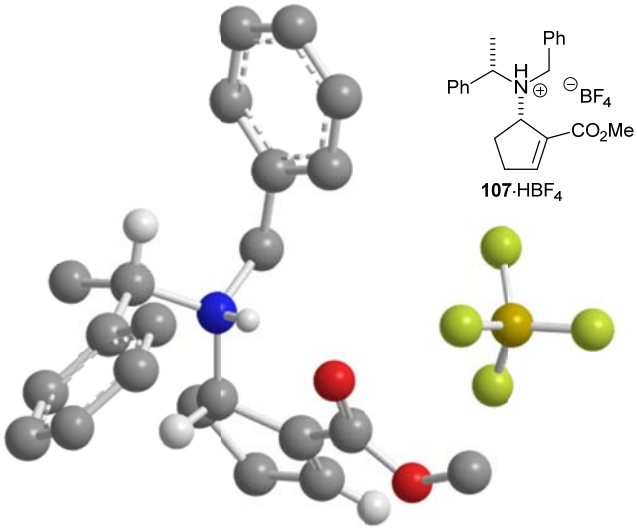
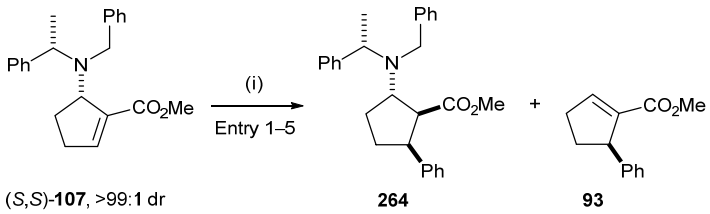


Figure 27. X-ray crystal structure of (*S*,*S*)-**107**·HBF_4 (selected H atoms are omitted for clarity).

3.3.2. Conjugate addition of organometallic reagents to (*S*,*S*)-β'-amino-α,β-unsaturated ester

With enantiopure β'-amino-α,β-unsaturated ester (*S*,*S*)-**107** in hand, the conjugate addition of organometallic reagents to **107** was next investigated. When the reaction of **107** with 2.0 equiv of PhMgBr was carried out in THF at –20 °C, the reaction proceeded to furnish C(5)-substituted β-amino ester **264** as the sole product in >95:5 dr and in a moderate conversion of 32%. Upon increasing the number of equivalents of PhMgBr to 10.0 equiv, 97% conversion to **264** was observed and **264** was subsequently isolated in 92% yield and >99:1 dr. Analysis of the ^{1}H NMR spectra of the crude reaction mixtures indicated that no products arising from a competing 1,2-addition pathway were formed. The specific rotation together with the ^{1}H and ^{13}C NMR spectra of the sample of **264** were found to be in complete agreement with those of the sample of 1,2-*anti*-1,5-*syn*-**264** prepared from the Ireland-Claisen rearrangement of allyl β-amino ester **250** (followed by esterification and hydrogenation), thereby confirming the relative configuration within **264** (see Chapter 2). β'-Amino ester **107** reacted less readily with PhMgBr in the presence of 0.1 equiv of cuprate reagent[37] $CuCl·(LiCl)_2$ at –20 °C resulting in the formation of **264** in only 12% conversion after 4 h. Subjection of **107** to PhMgBr and 0.1 equiv of $CuCl·(LiCl)_2$ at 0 °C for 4 h also proceeded to form **264**, but with only a partial conversion of 19%.[38,39] Moreover, this conjugate addition reaction was accompanied by the formation of β'-elimination product **93**. The organolithium reagent PhLi was next substituted for the Grignard reagent in the conjugate addition reaction with **107**.[40] The formation of a single product **264** in >95:5 dr was observed when **107** was treated with PhLi in THF at 0 °C. Chromatographic purification allowed the isolation of **264** in 62% yield and as a single diastereoisomer (Scheme 57). The ^{1}H and ^{13}C NMR spectra and

the specific rotation of the sample of **264** prepared using PhLi were found to be identical to the major product resulting from the reaction of **107** with PhMgBr. These results indicate that the reaction of organometallic reagents to **107** does not result in 1,2-addition and instead proceeds with addition at the β-position of the ester. Furthermore, the deleterious effect observed in this case upon using a copper source demonstrates that their use is not essential for achieving high chemoselectivity.



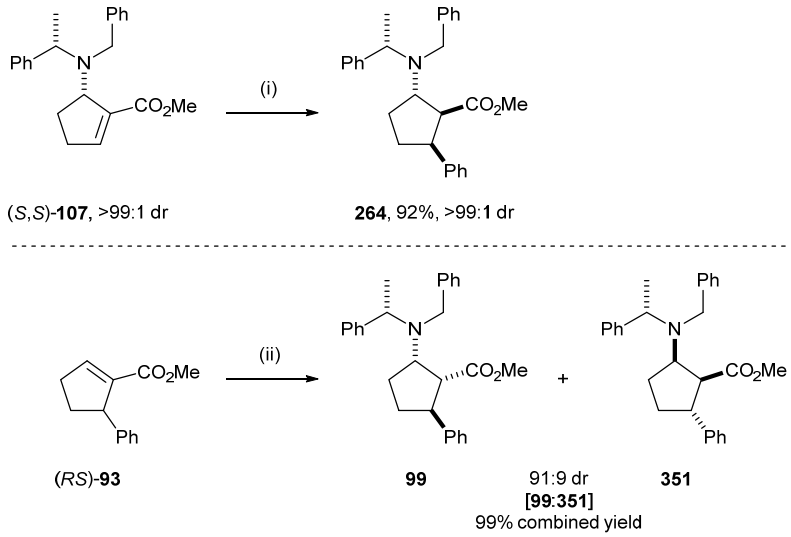
(*S*,*S*)-**107**, >99:1 dr **264** **93**

Entry	Additive	RM	Equiv RM	Temperature	Conversion	Crude product ratio [264 : 93]	Isolated yield of 264 (dr)
1	None	PhMgBr	2.0	–20 °C	32%	100 : 0	-
2	None	PhMgBr	10.0	–20 °C	97%	100 : 0	92% (>99:1)
3	$CuCl{\cdot}(LiCl)_2$	PhMgBr	2.0	–20 °C	12%	100 : 0	-
4	$CuCl{\cdot}(LiCl)_2$	PhMgBr	2.0	0 °C[a]	19%	47 : 53	-
5	None	PhLi	2.0	0 °C[b]	100%	100 : 0	62% (>99:1)

Scheme 57. *Reagents and conditions*: (i) organometallic reagent (RM), additive (0.1 equiv), THF, stated temperature, 4 h. [[a] The additive was added at –50 °C and the resultant solution was allowed to stir at –50 °C for 2 h followed by additional stirring at 0 °C for 4 h. [b] Reaction allowed to stir at 0 °C for 2 h.]

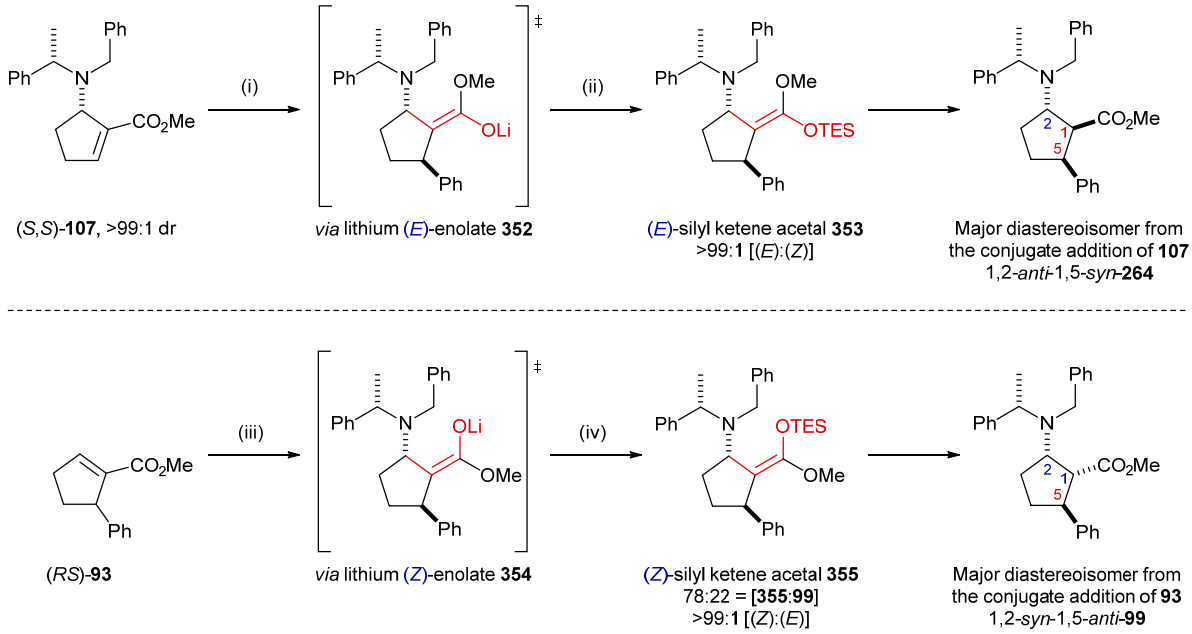
3.3.3. The origin of diastereoselectivity observed upon conjugate addition of organometallic reagents

The observation that β-amino ester **264** is the only product from the reaction of (*S*,*S*)-**107** with PhMgBr or PhLi illustrates that conjugate addition to the C(5) atom must occur preferentially *anti* to the C(2)-amino group. Such an approach was expected to be favoured as the large C(2)-amino substituent provides a diastereofacial bias towards attack on the least hindered face of the ring. Interestingly, the high preference for the 1,2-*anti*-1,5-*syn*-diastereoisomer **264** indicates that protonation of the resulting magnesium or lithium enolate takes place *syn* to the C(2)-amino group. This is in marked contrast to the known mutual kinetic resolution[25b] of (*RS*)-**77** with α,β-unsaturated ester (*RS*)-**93**[41] which forms a 91:9 mixture of **99** and **351**, respectively, as a result of preferential conjugate addition of **77** occurring *anti* to the C(5)-substituent and protonation of the corresponding enolates taking place *anti* to the C(2)-amino group[28] in both cases (Scheme 58).



Scheme 58. *Reagents and conditions*: (i) PhLi, THF, 0 °C, 2 h; (ii) (*RS*)-**77**, THF, –78 °C, 2 h.

In an attempt to provide some insight into the origin of diastereoselectivity observed upon protonation of these enolates, the β-amino enolate geometry for the conjugate addition of organometallic reagents to **107** was ascertained. Following the standard conjugate addition protocol, reaction of (*S*,*S*)-**107** with 1.0 equiv of PhMgBr and 1.6 equiv TESCl afforded a 79:21 mixture of starting material **107** and 1,2-*anti*-1,5-*syn*-**264**, respectively. Further efforts to isolate the *O*-silyl ketene acetal **353** by varying the quantities of PhMgBr and TESCl gave solely **264**, presumably due to the instability of the magnesium enolate. It was next decided to use PhLi in order to prepare the *O*-silyl ketene acetal **353**. Reaction of (*S*,*S*)-**107** with PhLi at 0 °C and subsequent treatment with TESCl before warming to room temperature gave solely *O*-silyl ketene acetal **353**. ^{1}H NMR spectroscopic analysis of the crude reaction mixture in anhydrous[42] benzene-d_6[43] revealed the presence of a single (*E*)-configured *O*-silyl ketene acetal **353** in >99:1 dr [(*E*):(*Z*)]. An authentic sample of (*Z*)-*O*-silyl ketene acetal[44] **355** was also prepared. Conjugate addition of (*RS*)-**77** to (*RS*)-**93** in THF at –78 °C was followed by the silylation of the intermediate lithium (*Z*)-β-amino enolate **354** using 3.0 equiv of TESCl to give a 78:22 mixture of *O*-silyl ketene acetal **355** and 1,2-*anti*-1,5-*syn*-**99**, respectively. ^{1}H NMR spectroscopic analysis of the crude reaction mixture identified the formation of the *O*-silyl ketene acetal **355** in >99:1 dr [(*Z*):(*E*)] (Scheme 59).



Scheme 59. *Reagents and conditions*: (i) PhLi, THF, 0 °C, 2 h; (ii) TESCl, 0 °C then rt, 30 min; (iii) (*RS*)-**77**, THF, –78 °C, 2 h; (iv) TESCl, –78 °C then rt, 30 min.

The geometries within *O*-silyl ketene acetals **353** and **355** were established by ^{1}H NMR NOESY analyses. Irradiation of the C(5)*H* proton in (*E*)-**353** showed a NOESY enhancement to the NCH_2Ph proton signals, which is consistent with an *anti*-relationship between the C(5)-phenyl and the C(2)-amino groups. A reciprocal interaction between the NCH_2Ph protons and the O*Me* group was also indicative of an (*E*)-configured *O*-silyl ketene acetal **353**. Contrastingly, ^{1}H NMR NOESY analysis of (*Z*)-**355** showed no correlation between the ester group and the protons of the C(2)-amino group. Irradiation of the C(α)*H* and the NCH_2Ph protons in **355** identified instead an enhancement to the Si(CH_2CH$_3$)$_3$ group, thereby illustrating a (*Z*)-geometry for the *O*-silyl ketene acetal **355** (Figure 28). These results collectively suggest that the observed differences in protonation diastereoselectivity for enolates (*E*)-**353** and (*Z*)-**355** (and the corresponding magnesium enolate) are not simply a function of the amino group.

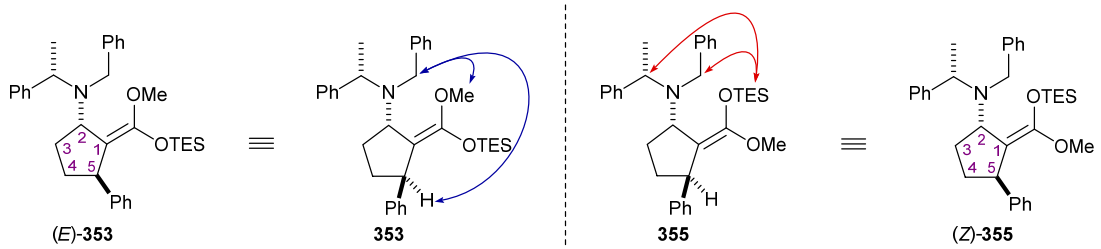
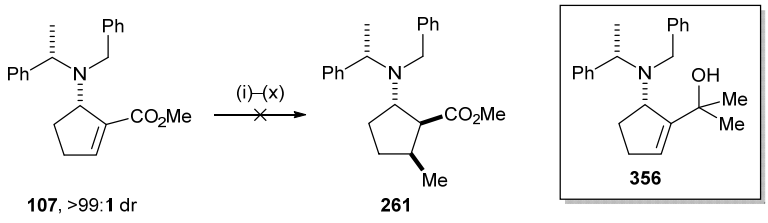


Figure 28. ^{1}H NMR NOESY correlations observed within *O*-silyl ketene acetals (*E*)-**353** and (*Z*)-**355**.

3.3.4. Evaluation of alternative Grignard reagents

The generality of the conjugate addition reaction for Grignard reagents was next investigated. Unfortunately, exhaustive attempts to incorporate a methyl group at the C(5)-position of the β'-amino ester **107** using a range of conditions proved fruitless. For instance, under reaction

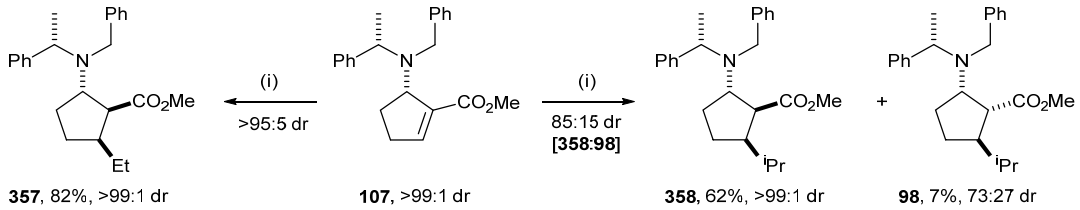
conditions analogous to those previously employed for the conjugate addition of PhMgBr to **107** (i.e., RMgX, THF, –20 °C, 4 h) only returned starting material was observed. A switch in the Grignard reagent to MeMgCl also gave returned starting material. Treatment of **107** with *in situ* prepared MeMgI in Et_2O resulted in a 58:42 mixture of starting material **107** and 1,2-addition product **356**, respectively, with no evidence of any products resulting from conjugate addition (such as **261**) in the ^{1}H NMR spectrum of the crude reaction mixture. In addition, the reactions using an organolithium reagent, such as MeLi proceeded to completion to give complex mixtures of products containing the 1,2-addition product **356** (Scheme 60). The possibility of introducing a *tert*-butyl group at the C(5)-position was also briefly examined. However, reaction of **107** with ^{t}BuMgCl in THF at –20 °C for 4 h only resulted in returned starting material.



Conditions	Result
(i)	Returned starting material
(ii)	Returned starting material
(iii)	Returned starting material
(iv)	Returned starting material
(v)	42% conversion to **356**
	356 isolated in 12% yield, >99:1 dr
(vi)	Complex mixture
(vii)	Returned starting material
(viii)	Returned starting material
(ix)	Complex mixture
(x)	Complex mixture

Scheme 60. *Reagents and conditions*: (i) MeMgBr, THF, –20 °C, 4 h; (ii) MeMgBr, CuI, THF, –35 °C, 3 h; (iii) MeMgCl, $CuCl{\cdot}(LiCl)_2$, THF, –20 °C, 4 h; (iv) MeMgCl, THF, –20 °C, 4 h; (v) Mg, MeI, Et_2O, –20 °C, 4 h; (vi) MeMgCl, CH_2Cl_2, 0 °C, 4 h; (vii) $MeAlCl_2$, THF, –20 °C, 2 h; (viii) MeMgBr, $MgBr_2$, THF, 0 °C, 4 h; (ix) MeLi, THF, –20 °C, 2 h; (x) MeLi, THF, –78 °C, 2 h.

In marked contrast, the corresponding conjugate addition reactions using EtMgBr and ^{i}PrMgBr were successful. Treatment of **107** with EtMgBr in THF at –20 °C afforded clean conversion to the C(5)-substituted β-amino ester **357** in >95:5 dr, and **357** was subsequently isolated in 82% yield and >99:1 dr. Following an analogous procedure, reaction of **107** with ^{i}PrMgBr afforded an 85:15 mixture of diastereoisomers **358** and **98**, respectively. Chromatographic purification allowed the isolation of **358** in 62% yield as a single diastereoisomer (>99:1 dr), together with a sample of the minor diastereoisomer **98**, which was isolated in 7% yield and 73:27 dr (Scheme 61).



Scheme 61. *Reagents and conditions*: (i) EtMgBr or ^{i}PrMgBr, THF, –20 °C, 4 h.

The 1,2-*anti*-1,5-*syn*-configurations within major products **357** and **358** were initially assigned by analogy to the established stereochemical outcome observed for the formation of **264** (R = Ph), and these assignments were also supported by ^{1}H NMR nOe analyses. For both **357** and **358**, the irradiation of the C(1)*H* proton showed a strong interaction to the C(5)*H* proton and an enhancement to the NC*H*$_2$Ph group. The presence of an nOe enhancement from the ester group to the C(2)*H* proton indicated a 1,2-*anti*-relationship between the ester and C(2)-amino groups. A similarly informative correlation between the C(5)*H* and the NC*H*$_2$Ph group protons further supported a 1,2-*anti*-1,5-*syn*-configuration.[45] ^{1}H NMR nOe analysis of **98** was also carried out in support of its assigned relative 1,2-*syn*-1,5-*anti*-configuration. Irradiation of the C(1)*H* proton identified two strong correlations to proton signals corresponding to C(2)*H* and the CH*Me*$_2$ group without affecting the protons of the NC*H*$_2$Ph group. This result was corroborated by the observed reciprocal correlation between the ester group and the C(5)*H* proton. A reciprocal nOe enhancement between the C(5)*H* and C(4)H_B protons together with a reciprocal correlation between the C(4)H_A proton and the CH*Me*$_2$ group further illustrated a *trans* configuration for the ester and ^{i}Pr groups (Figure 29).

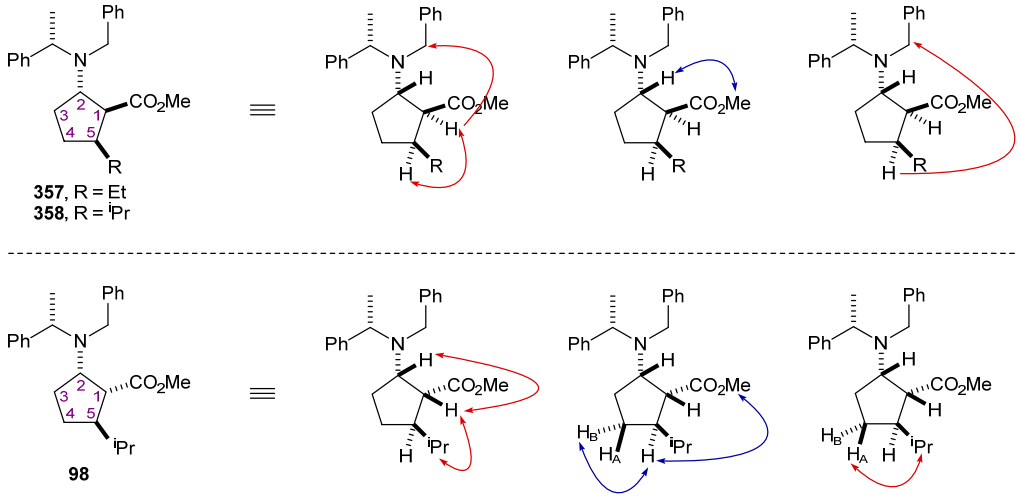
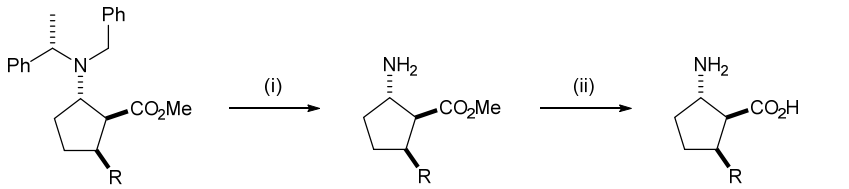


Figure 29. Representations of the ^{1}H NMR nOe correlations observed within **98**, **357** and **358**. [‘‘↔’’ represents reciprocal interaction].

3.3.4.1. Application to the synthesis of C(5)-substituted cyclic β-amino acids

Subjection of **357**, **358** and **264** to a two-step elaboration protocol resulted in a concise asymmetric synthesis of C(5)-substituted transpentacins **304**, **306** and **307**. Reaction of **357**,

358 and **264** with Pearlman's catalyst under a H_2 atmosphere effected hydrogenolytic *N*-debenzylation to afford primary amines **299**, **301** and **302** in 58–82% yield and >99:1 dr. The specific rotations and ^{1}H and ^{13}C NMR spectra for **299**, **301** and **302** were found to be entirely consistent with samples prepared from the rearrangement of allyl β-amino esters **280**, **282** and **250**, respectively, and hence permitted confident assignment of the absolute configurations within (*S*,*S*,*S*)-**299**, (1*S*,2*S*,5*R*)-**301** and (*S*,*S*,*S*)-**302** (see Chapter 2). Subjection of β-amino esters **299**, **301** and **302** to acid-catalysed hydrolyses and purification by ion exchange chromatography allowed the syntheses of C(5)-substituted β-amino acids **304**, **306** and **307** to be completed in six steps from commercially available 2,5-dimethoxytetrahydrofuran **339**, in 6–11% overall yield and >99:1 dr in each case (Scheme 62). In addition, although substrate tolerance for the conjugate addition protocol and the Ireland-Claisen rearrangement (see Chapter 2) is different, the former methodology exemplifies an alternative way of preparing 1,2-*anti*-1,5-*syn*-transpentacins using a shorter sequence of steps.



357, R = Et, >99:1 dr
358, R = ^{i}Pr, >99:1 dr
264, R = Ph, >99:1 dr

299, R = Et, 82%, >99:1 dr
301, R = ^{i}Pr, 58%, >99:1 dr
302, R = Ph, 61%, >99:1 dr

304, R = Et, 85%, >99:1 dr
306, R = ^{i}Pr, 94%, >99:1 dr
307, R = Ph, 89%, >99:1 dr

Scheme 62. *Reagents and conditions*: (i) H_2 (1 atm), $Pd(OH)_2$/C, MeOH, rt, 24 h; (ii) HCl (6.0 M aq), reflux, 16 h then DOWEX 50WX8.

3.3.5. Asymmetric synthesis of β,β'-diamino compounds

To expand the structural diversity of the monomeric cyclic β-amino acid derivatives available, the transformation of β,β'-diamino ester **348** into β,β'-diamino compounds **360** and **362** was next explored.[46] It was envisaged that **348** could be easily elaborated to **360** by hydrogenolytic reduction and deprotection. Furthermore, the synthesis of the β,β'-diamino alcohol **362** was expected to proceed *via* the reduction of the ester moiety followed by *N*-debenzylation (Figure 30).

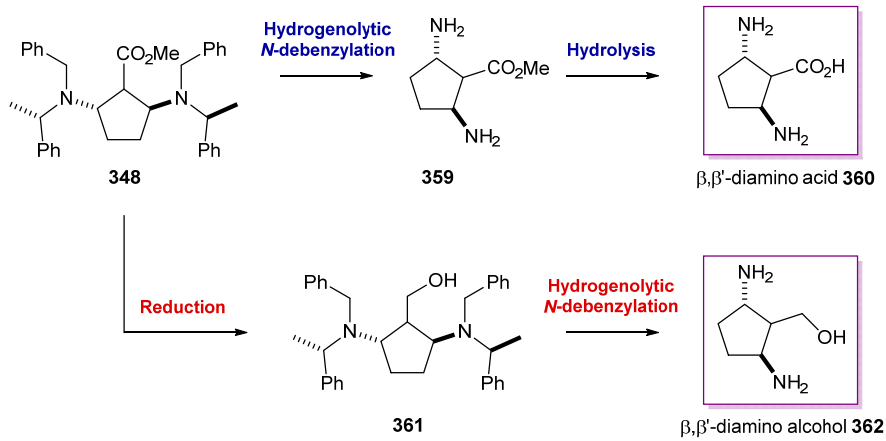
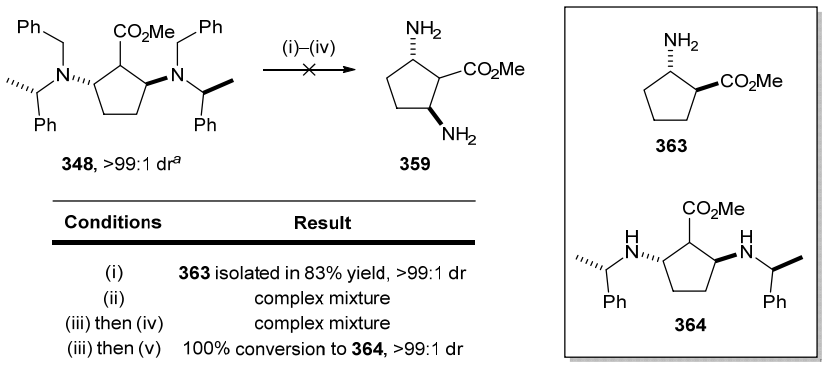


Figure 30. Proposed route through to β,β'-diamino compounds **360** and **362** from β,β'-diamino ester **348**.

Unfortunately, hydrogenolytic *N*-debenzylation of β,β'-diamino ester **348** [which was obtained in >99:1 dr upon conjugate addition of (*S*)-**77** to (*S*,*S*)-**107**][47] in the presence of $Pd(OH)_2/C$ did not result in the formation of **359**. Analysis of the ^1H NMR spectrum of the crude reaction mixture showed the β-amino ester **363** as the only product formed, which most likely arises from a retro-conjugate addition pathway. Following purification by flash column chromatography **363** was isolated in 83% yield and >99:1 dr.[48] Further attempts at forming **359** proved unsuccessful and led only to a complex mixture of products. Mass spectrometric analyses of these crude reaction mixtures also indicated the presence of β-amino ester **363**. In addition, treatment of the HCl salt of **348** with Pd/C under a H_2 atmosphere in methanolic HCl for 24 h gave full conversion to only the *N*-debenzylated product **364** (Scheme 63).

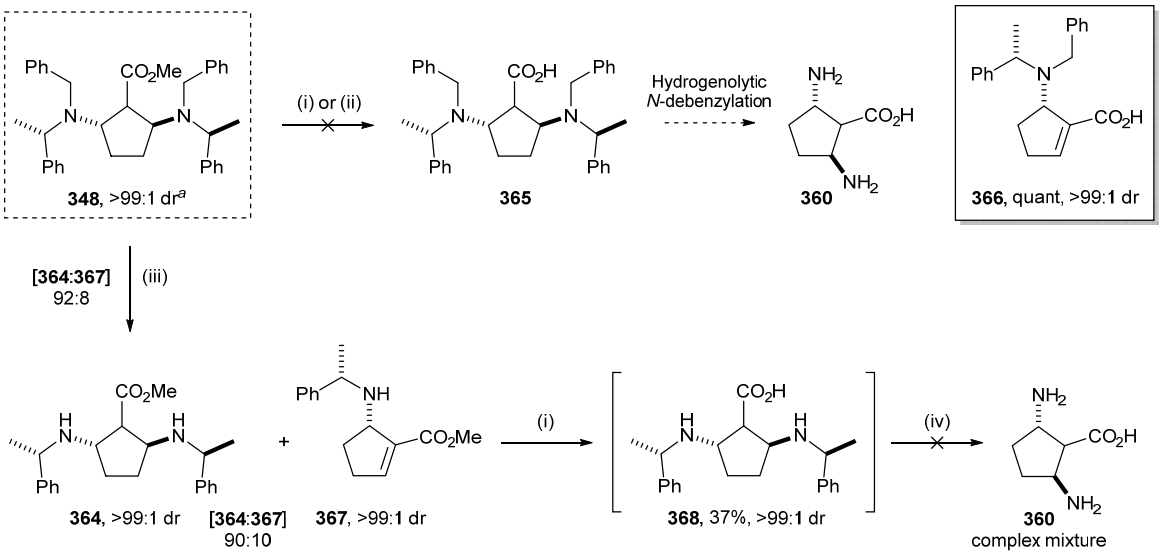


Conditions	Result
(i)	**363** isolated in 83% yield, >99:1 dr
(ii)	complex mixture
(iii) then (iv)	complex mixture
(iii) then (v)	100% conversion to **364**, >99:1 dr

Scheme 63. *Reagents and conditions*: (i) H_2 (5 atm), $Pd(OH)_2/C$, MeOH, rt, 24 h; (ii) H_2 (1 atm), Pd/C, MeOH, rt, 24 h; (iii) HCl (2.0 M in Et_2O), rt, 0.5 h; (iv) H_2 (1 atm), $Pd(OH)_2/C$, HCl (1.25 M in MeOH), rt, 24 h; (v) H_2 (1 atm), Pd/C, HCl (1.25 M in MeOH), rt, 24 h. [[a] >95% purity].

With the removal of the *N*-α-methylbenzyl and *N*-benzyl groups proving to be problematic, an alternative strategy was investigated. It was envisaged that hydrolysis of the methyl ester group within **348** to the corresponding carboxylic acid **365** would inhibit the retro-conjugate addition pathway in the following hydrogenolytic *N*-debenzylation step. Unfortunately, attempted acid-catalysed hydrolysis of **348** to the corresponding carboxylic acid **365** led to the sole formation of **366** in quantitative yield and >99:1 dr, whereas base-catalysed hydrolysis of

348 gave returned starting material. Alternatively, oxidative *N*-debenzylation[49] of **348** with CAN followed by chromatographic purification resulted in a 90:10 mixture of **364** and **367**, respectively. Acid-catalysed hydrolysis of the mixture of **364** and **367** in 6.0 M aq HCl proved successful with only the hydrolysis of the methyl ester being observed; and after purification **368** was isolated in 37% yield and >99:1 dr. However, treatment of **368** under a H_2 atmosphere in the presence of Pearlman's catalyst failed to yield any **360**, and instead returned a complex mixture of unidentified products (Scheme 64).



Scheme 64. *Reagents and conditions*: (i) HCl (6.0 M aq), reflux, 16 h; (ii) LiOH (58 equiv), MeOH/H_2O/THF (v/v 7:2:1), reflux, 24 h; (iii) CAN, MeCN/H_2O (v/v 5:1), rt, 16 h; (iv) H_2 (1 atm), $Pd(OH)_2$/C, MeOH, rt, 48 h. [[a] >95% purity].

The relative configurations within **364** and **368** were supported by ^{1}H NMR NOESY analyses.[50] Irradiation of the C(1)*H* proton in both **364** and **368** showed correlations to the C(5)*H* proton and the C(α)*H* proton of the C(2)-amino group. For **364**, this result was corroborated by the observed reciprocal correlation between the C(5)*H* and the C(4)H_B protons together with a NOESY enhancement between the C(4)H_A and the C(2)*H* protons. Additionally, reciprocal enhancements between the C(5)*H* and the C(4)H_B protons in **368**, together with a reciprocal correlation between the C(4)H_B proton and the C(α)*H* proton of the C(2)-amino group were indicative of the assigned 2,5-*anti* relationship within **368** (Figure 31).

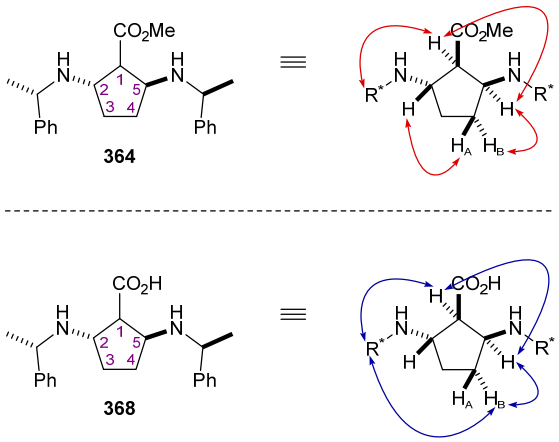
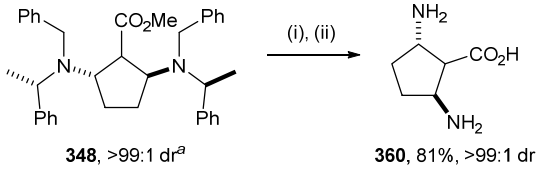


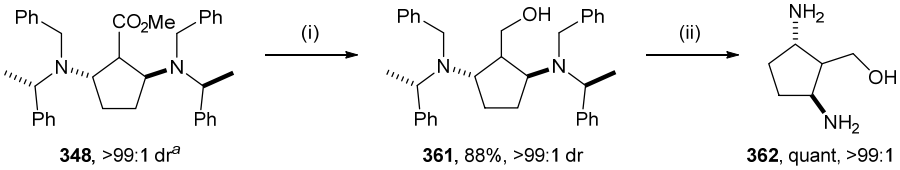
Figure 31. ^{1}H NMR NOESY correlations observed within **364** and **368**. [''↔'' represents reciprocal interaction; R* = α-methylbenzyl].

N-Deprotection of the β,β'-diamino ester **348** was finally achieved using oxidative debenzylation conditions ($NaBrO_3/Na_2S_2O_4$)[51] in a biphasic system.[52,53] Upon optimised conditions, treatment of **348** with 10 equiv of $NaBrO_3$ and 8.3 equiv of $Na_2S_2O_4$ followed by 2.0 M aq HCl effected the removal of both the *N*-α-methylbenzyl and *N*-benzyl groups, and the hydrolysis of the methyl ester. Subsequent purification by ion exchange chromatography afforded β,β'-diamino acid **360** in 81% isolated yield and >99:1 dr, completing this synthesis in 11% overall yield and five steps from commercially available **339** (Scheme 65).



Scheme 65. *Reagents and conditions*: (i) $NaBrO_3$, $Na_2S_2O_4$, H_2O/EtOAc (v/v 3:1), rt, 18 h; (ii) HCl (2.0 M aq), rt, 0.5 h then DOWEX 50WX8. [[a] >95% purity].

Elaboration of **348** to the β,β'-diamino alcohol **362** was next pursued. Reduction of the ester functionality within **348** upon treatment with DIBAL-H gave **361**, which was isolated in 88% yield and >99:1 dr.[54] Treatment of **361** with 10 equiv of $NaBrO_3$ and 8.3 equiv of $Na_2S_2O_4$ under identical conditions to **348** followed by purification on ion-exchange resin resulted in **362** being isolated in ~80% purity. Alternatively, **361** was subjected to *N*-debenzylation and concomitant hydrogenation conditions with Pearlman's catalyst, which furnished β,β'-diamino alcohol **362** in quantitative yield as a single diastereoisomer (>99:1 dr), in six steps and 12% overall yield from commercially available starting materials (Scheme 66).



Scheme 66. *Reagents and conditions*: (i) DIBAL-H, PhMe, –78 °C, 2 h; (ii) H_2 (1 atm), $Pd(OH)_2$/C, MeOH, rt, 24 h. [[a] >95% purity].

3.3.6. Asymmetric synthesis of the C(5)-hydroxymethyl substituted analogue

It was next envisaged that the C(5)-hydroxymethyl substituted β-amino acid **371** could be accessed in short order starting with the conjugate addition reaction of vinyl magnesium bromide to β'-amino-α,β-unsaturated ester **107**. Ozonolysis of a salt of **369** (to prevent *N*-oxidation) followed by a reductive work-up would then be expected to reveal the hydroxymethyl group at the C(5)-position of β-amino ester **370**, with hydrogenolytic reduction and deprotection as the last step to access 1,2-*anti*-1,5-*syn*-transpentacin **371** (Figure 32).

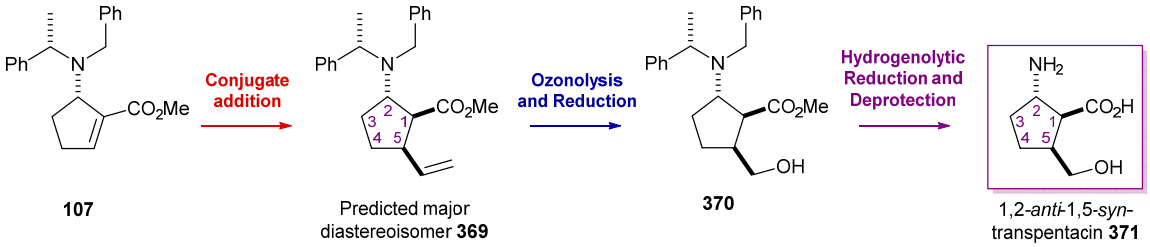
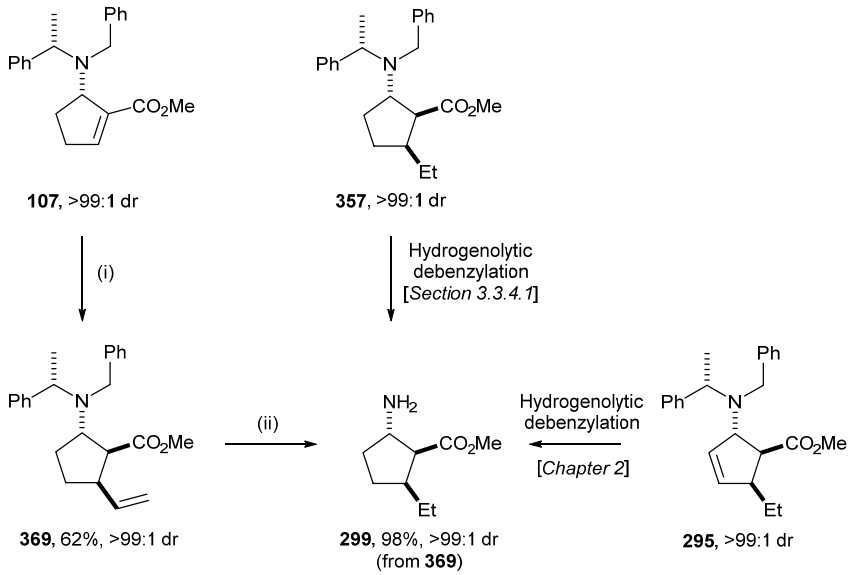


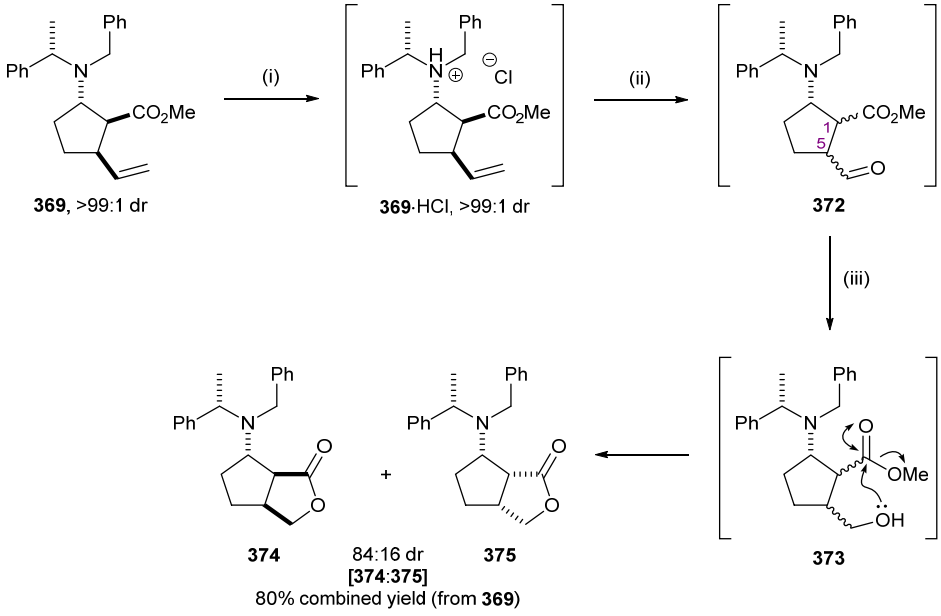
Figure 32. Proposed route through to 1,2-*anti*-1,5-*syn*-transpentacin **371** *via* a conjugate addition reaction to **107**.

Treatment of **107** with vinyl magnesium bromide in THF at –20 °C afforded clean conversion to C(5)-vinyl substituted β-amino ester **369** in >95:5 dr, and **369** was subsequently isolated in 62% yield and >99:1 dr. The configuration within **369** was initially assigned by analogy to those within **264**, **357** and **358**. A chemical correlation experiment was conducted next in order to unambiguously establish the relative 1,2-*anti*-1,5-*syn*-configuration within **369**. *N*-Debenzylation and concomitant hydrogenation of **369** in the presence of Pearlman's catalyst furnished primary amine **299** in 98% isolated yield and >99:1 dr (Scheme 67). The ^{1}H and ^{13}C NMR spectra and specific rotations of the sample of **299** were found to be identical to the hydrogenolytic reduction product arising from **295** (see Chapter 2) and the hydrogenolytic product resulting from the *N*-protected β-amino ester **357** (see Section 3.3.4.1).



Scheme 67. *Reagents and conditions*: (i) vinyl magnesium bromide, THF, –20 °C, 4 h; (ii) H_2 (1 atm), $Pd(OH)_2/C$, MeOH, rt, 24 h.

With C(5)-substituted β-amino ester **369** in hand, the elaboration of the vinyl group to the hydroxymethyl moiety was investigated next. The hydrochloride salt of **369** was reacted with O_3 at –78 °C to effect ozonolysis[55] of the double bond followed by *in situ* reduction using $NaBH_4$ to give C(5)-hydroxymethyl substituted β-amino ester **373**. However, upon chromatographic purification an 84:16 mixture of γ-lactone **374** and a compound which was tentatively assigned as its diastereoisomer **375**, respectively, was obtained. The formation of lactones **374** and **375** can be rationalised as proceeding *via* attack of the C(5)-hydroxy group at the methyl ester carbonyl, and presumably epimerisation of the enolisable stereogenic centres at C(1) and C(5) within **373** also occurs at a competitive rate (Scheme 68).



Scheme 68. *Reagents and conditions*: (i) HCl (2.0 M in Et_2O), rt; (ii) O_3, CH_2Cl_2/MeOH (v/v 2:1), –78 °C, 5 mins; (iii) $NaBH_4$, –78 °C then rt, 5 h.

The assigned connectivity within γ-lactone **374** was supported by full ^{1}H and ^{13}C NMR spectroscopic analyses, and most importantly a long-range ^{1}H–^{13}C HMBC heteronuclear correlation experiment. Notably, the protons of the C(3)H_2 group at δ_H = 3.89 ppm show connectivity to the *C*(1) carbonyl group at δ_C = 179.6 ppm which confirms ring-closure to a lactone framework. In addition, the IR spectrum of the mixture of **374** and **375** identified a diagnostic carbonyl absorption band at 1759 cm^{-1} indicating the presence of γ-lactones.[56] Furthermore, the relative configuration of the stereogenic centres at C(6), C(6a) and C(3a) within **374** was assigned by ^{1}H NMR nOe analysis. Irradiation of the C(6a)*H* proton showed an nOe enhancement to the C(α)*H* proton of the amino group and a correlation to the NCH_2Ph group protons, hence demonstrating a *trans* orientation for the C(6)*H* and C(6a)*H* protons. Another series of enhancements were similarly instructive with the irradiation of the C(3a)*H* proton resulting in strong correlations to the C(6a)*H* and NCH_2Ph proton signals, thereby suggesting that C(3a)*H* and C(6a)*H* are on the same face of the bicyclic system (Figure 33).

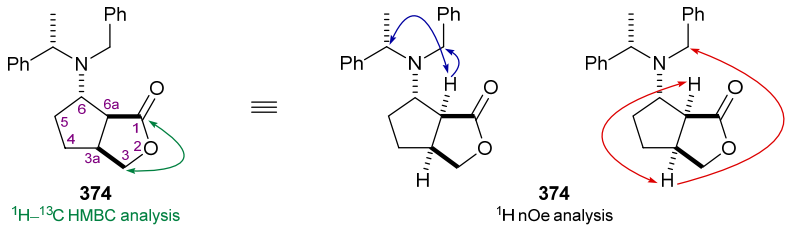
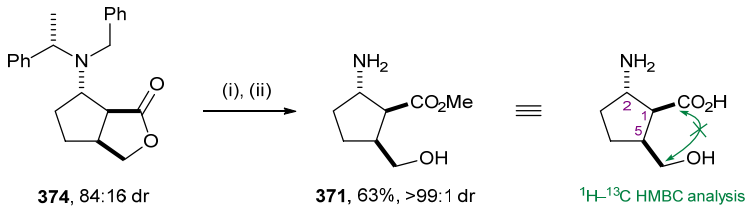


Figure 33. Representation of the ^{1}H–^{13}C HMBC and ^{1}H NMR nOe correlations observed within major diastereoisomer **374**. [''↔'' represents reciprocal interaction].

To complete the synthesis of the C(5)-hydroxymethyl substituted β-amino acid **371**, hydrogenolytic removal of the *N*-α-methylbenzyl and *N*-benzyl groups was next attempted. Subjection of the 84:16 sample of **374** and **375**, respectively, to the optimised debenzylation conditions with $NaBrO_3$/$Na_2S_2O_4$ for 14 h effected *N*-debenzylation to **374**.[57] Treatment of the aqueous layer with 2.0 M aq HCl followed by purification of the crude reaction mixture by ion exchange chromatography afforded diastereoisomerically-pure **371** in 63% isolated yield (i.e., 6% overall yield in seven steps from commercially available **339**) as a single diastereoisomer (>99:1 dr).[58] ^{1}H–^{13}C HMBC analysis of **371** showed no correlation between the *C*(1) carbonyl group and the C(5)CH_2OH protons. The presence of a carbonyl IR absorption band at 1653 cm^{-1}, which is typically diagnostic for amino acids in their zwitterionic form,[56] was also noted (Scheme 69).



Scheme 69. *Reagents and conditions*: (i) $NaBrO_3$, $Na_2S_2O_4$, H_2O/EtOAc (v/v 3:1), rt, 14 h; (ii) HCl (2.0 M aq), rt, 0.5 h then DOWEX 50WX8.

3.4. Conclusion

In conclusion, a highly diastereoselective conjugate addition/elimination protocol to access β'-amino-α,β-unsaturated ester **107** from **339** has been successfully developed. The ability of **107** to provide a scaffold for the highly chemo- and diastereoselective conjugate addition reactions of Grignard reagents enabled the asymmetric syntheses of a range of four C(5)-substituted 1,2-*anti*-1,5-*syn*-transpentacins **304**, **306**, **307** and **371**. Furthermore, a second lithium amide conjugate addition reaction to **107** demonstrated an efficient synthetic strategy to allow access to β,β'-diamino compounds **360** and **362** (Figure 34).

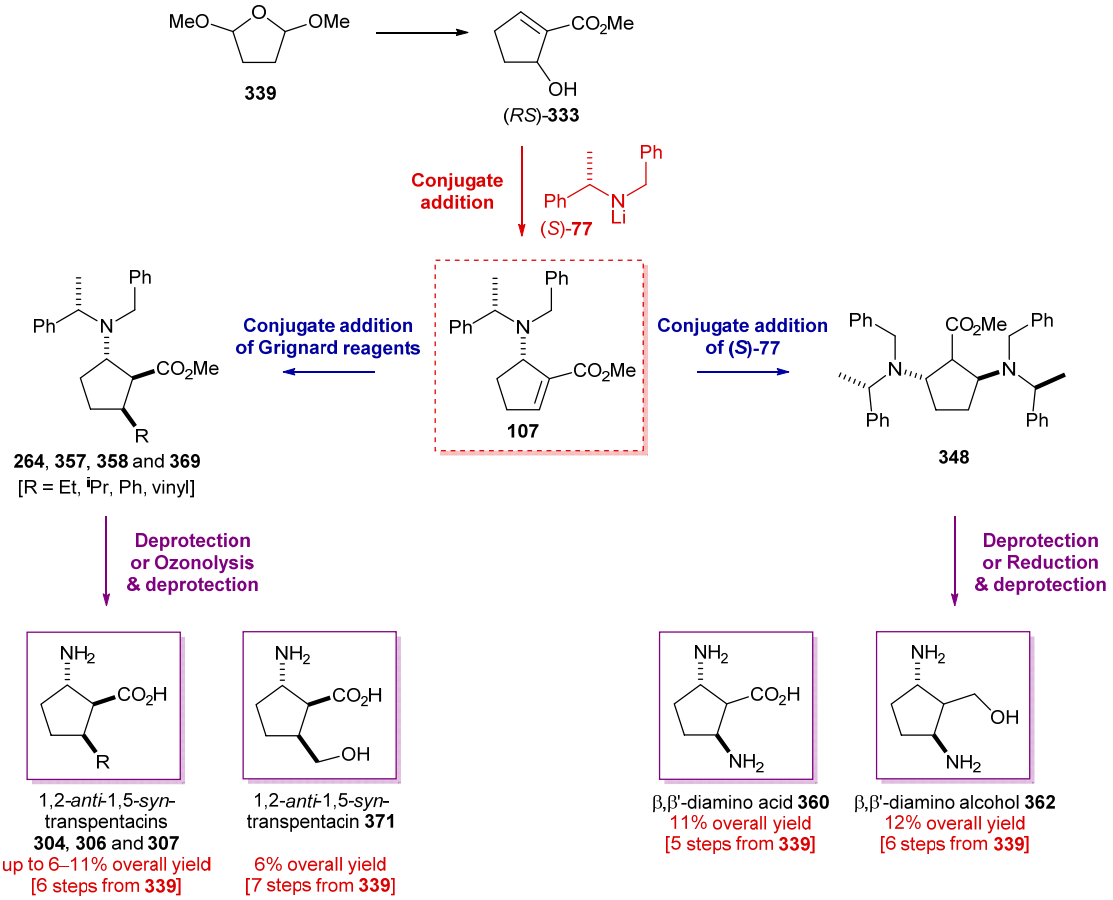


Figure 34. Route through to 1,2-*anti*-1,5-*syn*-transpentacins **304**, **306**, **307** and **371**, and β,β'-diamino compounds **360** and **362** from commercially available **339**.

3.5. References and notes

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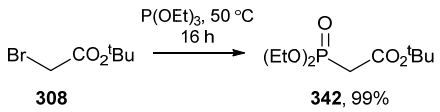

308 **342**, 99%

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[30] ^{1}H–^{1}H NMR nOe analysis was initially performed on **348** to assign its relative configuration. Reciprocal enhancements were observed between the C(1)*H* and C(5)*H* protons, and between the C(1)*H* proton and the C(α)*H* proton of the C(2)-amino group. In addition, a reciprocal nOe correlation was identified between the C(2)*H* proton and the C(5)-NCH_2Ph group protons.

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[33] An additional 1.0 equiv of (*RS*)-**77** was added since 1.0 equiv would be required for the deprotonation of the hydroxyl group, and an extra equiv of TMSCl was also added [i.e., 2.6 equiv (*RS*)-**77** and 2.2 equiv TMSCl]. For an example of a conjugate addition reaction to α,β-unsaturated-ε- and ζ-alcohols, see: Davies, S. G.; Díez, D.; Dominguez, S. H.; Garrido, N. M.; Kruchinin, D.; Price, P. D.; Smith, A. D. *Org. Biomol. Chem.* **2005**, *3*, 1284.

[34] ^{1}H–^{1}H NMR nOe analysis was performed on **350** to assign the relative configuration. Reciprocal enhancement was observed between the C(1)*H* and C(5)*H* protons. Another enhancement was observed between the CO_2*Me* group and C(2)*H* proton. In addition, an nOe correlation was identified for the C(2)*H* proton and the C(α)*Me* of the C(5)-amino group.

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[38] Mass spectrometric analysis of an aliquot of the reaction mixture following stirring at –50 °C for 2 h showed the presence of starting material and no indication of **264** being formed.

[39] Reaction of 2.0 equiv PhMgBr to (*S*,*S*)-**107** at 0 °C for 4 h resulted in 46% conversion to **264**.

[40] Only a few examples highlighting the conjugate addition of an organolithium reagent to α,β-unsaturated esters have previously been reported, since reactions of organolithium reagents and α,β-unsaturated esters generally provide 1,2-addition products; for example, see: (a) Cooke, Jr., M. P. *J. Org. Chem.* **1986**, *51*, 1637. (b) Frey, L. F.; Tillyer, R. D.; Caille, A.-S.; Tschaen, D. M.; Dolling, U.-H.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1998**, *63*, 3120.

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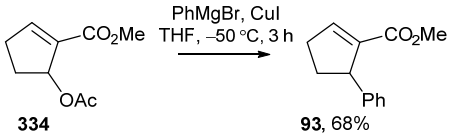

334 **93**, 68%

[42] C_6D_6 was dried over molecular sieves prior to use.

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[54] ^{1}H–^{1}H NMR NOESY analysis was performed on **361** to assign its relative configuration. Reciprocal enhancement was noted between the C(1)*H* and C(5)*H* protons, and between the C(1)*H* proton and the C(α)*H* proton of the C(2)-amino group. Moreover, a NOESY enhancement was identified for the C(5)*H* proton and the C(2)-NC*H*$_2$Ph group.

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[57] The progress of *N*-debenzylation to the *N*-deprotected γ-lactone was monitored by mass spectrometric analysis. In addition, the mass spectrum of the aqueous layer upon work-up gave evidence for the presence of the *N*-deprotected lactone which suggests that it is water-soluble. No attempt was made to characterise and assign a dr, and was instead taken through to the next step (i.e., treatment with 2.0 M aq HCl) to furnish amino acid **371**.

[58] ^{1}H–^{1}H NMR NOESY analysis was performed on **371** to assign its relative configuration. Irradiation of the C(1)*H* proton showed a correlation to the C(5)*H* proton. The presence of a NOESY enhancement between the C(2)*H* and C(5)C*H*$_2$OH protons was indicative of a 1,2-*anti*-1,5-*syn*-configuration.

Chapter 4: Conjugate addition reactions of Grignard reagents to acyclic γ-amino-α,β-unsaturated esters

This chapter details investigations into the conversion of α-amino acids **376** into β,γ-disubstituted γ-amino acids **378** ($\gamma^{3,4}$-amino acids) using chemo- and diastereoselective conjugate addition reactions of Grignard reagents to acyclic γ-amino-α,β-unsaturated esters **377** (Figure 35).

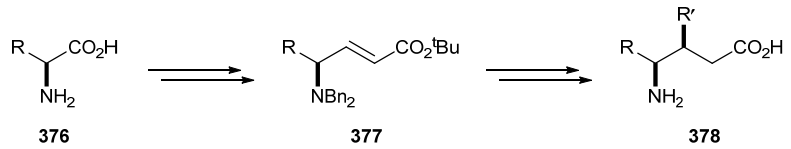
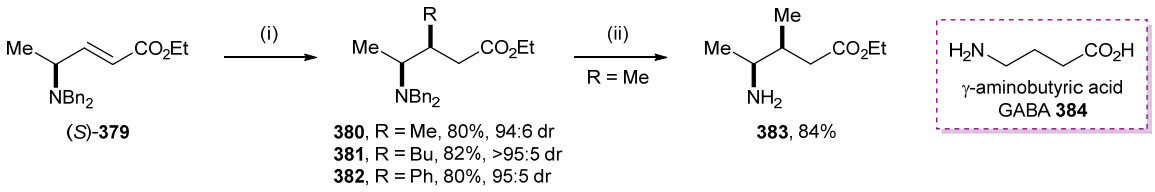


Figure 35. Diastereoselective conjugate addition reactions of Grignard reagents to γ-amino-α,β-unsaturated esters **377** for the synthesis of β,γ-disubstituted γ-amino acids **378**.

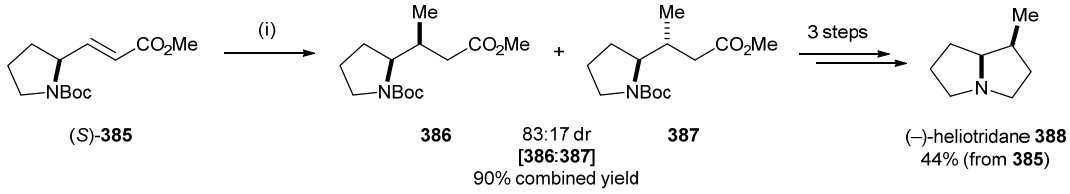
4.1. Introduction: conjugate addition reactions to acyclic γ-amino-α,β-unsaturated esters

Reetz and Röhrig have investigated conjugate addition reactions of a range of organocopper reagents to enantiopure γ-amino-α,β-unsaturated esters.[1,2,3] In particular, the reactions of [(*S*)-alanine derived] *N*,*N*-dibenzyl protected α,β-unsaturated ester (*S*)-**379** with Me_2CuLi, Bu_2CuLi or Ph_2CuLi in the presence of 1.1 equiv of TMSCl all proceeded with high diastereoselectivity (≥94:6 dr) to give the *syn*-configured β,γ-disubstituted γ-amino esters **380**–**382** in 80–82% isolated yield. Interestingly, the authors reported that no conjugate addition could be effected in the absence of any silylating agent.[4] β,γ-Disubstituted γ-amino ester **380** was then chosen for an *N*-debenzylation step to access **383**, the partially deprotected analogue of γ-aminobutyric acid (GABA) **384**,[5,6] which was isolated in 84% yield (Scheme 70).



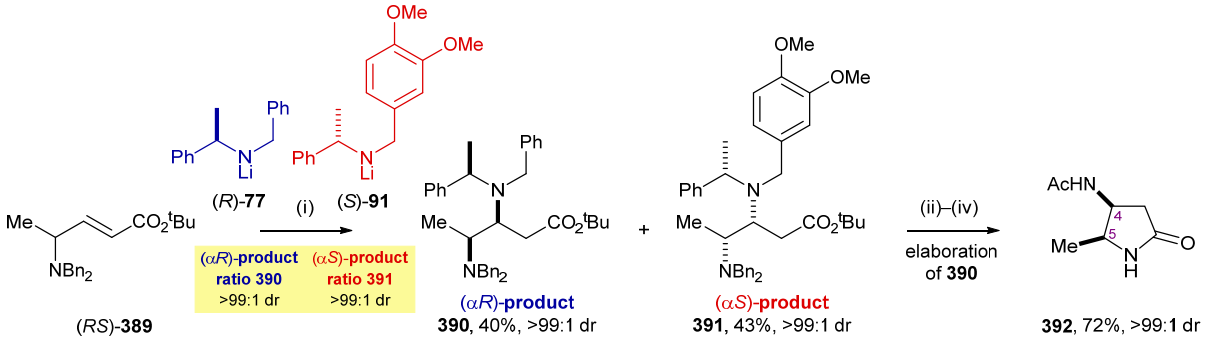
Scheme 70. *Reagents and conditions*: (i) R_2CuLi, TMSCl, THF, –78 °C, 12–20 h; (ii) H_2 (1 atm), Pd, MeOH/AcOH (v/v 5:1), rt.

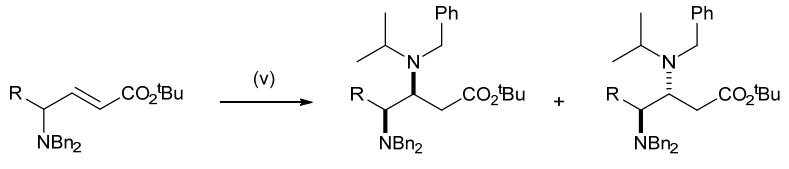
As part of a synthetic strategy towards the pyrrolizidine alkaloid (–)-heliotridane **388**,[7] Taddei and co-workers reported the conjugate addition of organocopper reagents to (*S*)-proline derived ester **385**.[8] For example, treatment of **385** with Me_2CuLi in Et_2O gave predominantly *syn*-configured β-substituted γ-amino ester **386** with high diastereoselectivity (83:17 dr),[9] and the 83:17 mixture of **386** and **387**, respectively, underwent cyclisation and reduction furnishing **388** in three steps and 44% overall yield from **385** (Scheme 71).



Scheme 71. *Reagents and conditions*: (i) Me_2CuLi, TMSCl, Et_2O, –40 °C, 30 min then rt.

More recently, Davies and co-workers[10] have developed a parallel kinetic resolution strategy to access 5-substituted 4-aminopyrrolidin-2-ones from racemic γ-amino-α,β-unsaturated esters bearing a non-α-branched alkyl substituent at the γ-position. For example, treatment of (*RS*)-**389** with a 50:50 pseudoenantiomeric mixture of enantiopure lithium amides (*R*)-**77** and (*S*)-**91** in THF at –78 °C for 2 h gave β,γ-diamino esters **390** and **391** in 40 and 43% isolated yield, respectively, and >99:1 dr in both cases. Three additional steps were required for conversion of **390** to 5-methyl-4-aminopyrrolidin-2-one[11] **392**, which was isolated in 29% overall yield from **389**. This protocol could not, however, be utilised for substrate (*RS*)-**393** (R = Ph) as indicated by the low level of substrate control obtained upon reaction with an achiral lithium amide reagent. Reaction of **393** with lithium *N*-isopropyl-*N*-benzylamide proceeded to give a 27:73 mixture of **395** and **397**, respectively, with *anti*-**397** being isolated in 48% yield and >99:1 dr. In addition, only a trace amount (<5%) of conjugate addition was observed when α-branched substrate (*RS*)-**394** (R = ^{i}Pr) was reacted with this achiral lithium amide (Scheme 72).

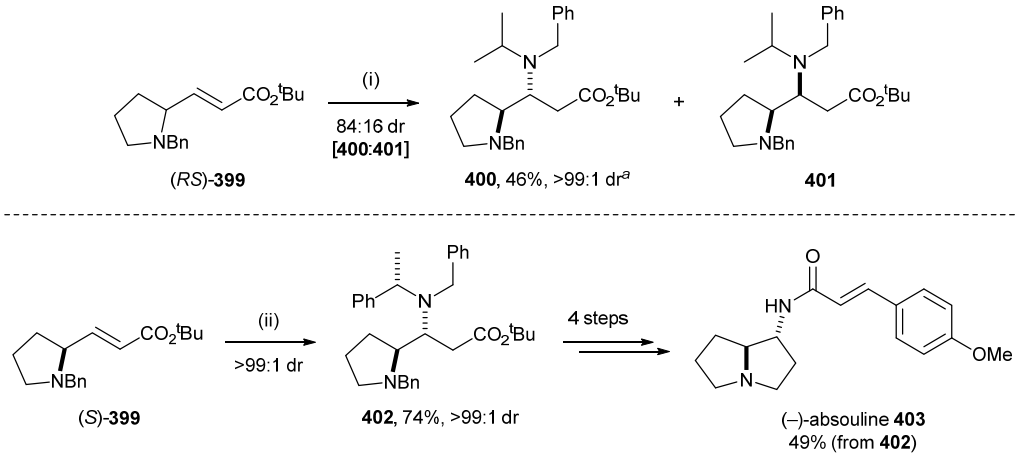




Substrate	R	addition dr	(±)-*syn* yield (dr)	(±)-*anti* yield (dr)
393	Ph	**395**:**397** 27:73	15% (>99:1)	48% (>99:1)
394	^{i}Pr	<5% conversion	-	-

Scheme 72. *Reagents and conditions*: (i) (*R*)-**77**/(*S*)-**91** (50:50 mixture), THF, –78 °C, 2 h; (ii) H_2 (5 atm), $Pd(OH)_2$/C, HCl (1.25 M in MeOH), rt, 48 h; (iii) HCl (3.0 M aq), 90 °C, 18 h; (iv) Ac_2O, pyridine, rt, 12 h; (v) LiN^iPrBn, THF, –78 °C, 2 h.

In subsequent studies by Davies and co-workers,[12] the conjugate addition of (*RS*)-proline derived γ-amino-α,β-unsaturated ester (*RS*)-**399** with lithium *N*-isopropyl-*N*-benzylamide was reported to proceed with moderate diastereoselectivity to give an 84:16 mixture of β,γ-diamino esters **400** and **401**, respectively. As an application of this methodology, enantiopure (*S*)-proline derived ester (*S*)-**399** served as a valuable precursor to the pyrrolizidine alkaloid, (–)-absouline[13] **403**. Treatment of (*S*)-**399** with enantiopure lithium amide (*S*)-**77** was reported to give **402** as the only product in 74% isolated yield. Subsequent elaboration of **402** to **403** was achieved *via* a four-step procedure in 49% overall yield (Scheme 73).



Scheme 73. *Reagents and conditions*: (i) LiN^{i}PrBn, THF, –78 °C, 2 h; (ii) (*S*)-**77**, THF, –78 °C, 2 h. [[a] **400** was also isolated as a separate fraction of 16% yield as an 80:20 mixture of **400** and **401**, respectively.]

4.2. Aim: proposed route to β,γ-disubstituted γ-amino acids

The aim of the work reported in this chapter is to apply the chemo- and diastereoselective Grignard reagent protocol developed in Chapter 3 to a range of acyclic γ-amino-α,β-unsaturated esters **377** that have previously been employed as substrates for parallel kinetic resolution.[10] It was envisaged that conjugate addition of **377** (which can be readily accessed from enantiopure α-amino acids **376**) would result in the synthesis of disubstituted γ-amino esters **404**, and elaboration of **404** *via* hydrogenolysis and ester hydrolysis would afford β,γ-disubstituted γ-amino acids **378** (Figure 36).

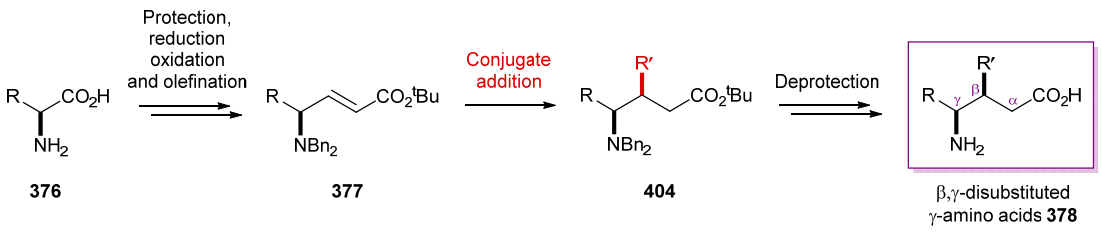
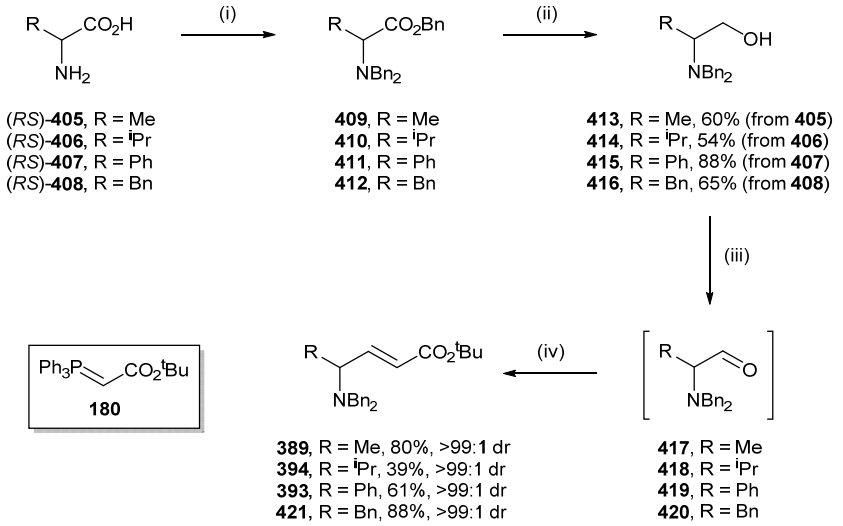


Figure 36. Proposed asymmetric synthesis of β,γ-disubstituted γ-amino acids **378** from α-amino acids **376** *via* a diastereoselective conjugate addition reaction.

4.3. Results and discussion

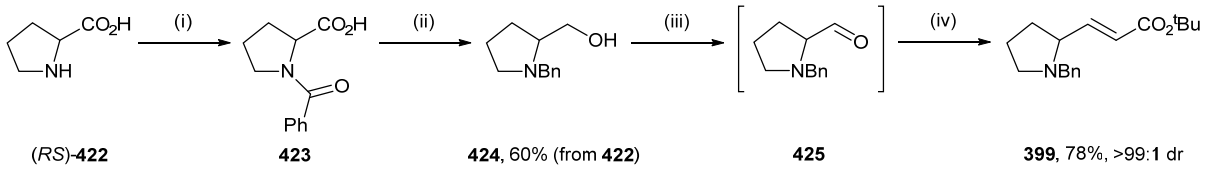
4.3.1. Substrate synthesis

In the first instance, racemic *N*-protected γ-amino-α,β-unsaturated esters[10] **389**, **393**, **394** and **421** were chosen as model systems for the conjugate addition reactions of Grignard reagents, since sufficient quantities for test reactions were available within the laboratory as a result of previous work into the parallel kinetic resolution of these substrates (*vide supra*). The syntheses of known substrates **389**, **393**, **394** and **421** were carried out using a four-step protocol from a range of commercially available α-amino acids **405**–**408**. (*RS*)-Alanine (R = Me) **405**, (*RS*)-valine (R = ^{i}Pr) **406**, (*RS*)-phenylglycine (R = Ph) **407** and (*RS*)-phenylalanine (R = Bn) **408** were first converted to **409**–**412** upon reaction with BnBr in aq K_2CO_3 at reflux. Treatment of **409**–**412** with $LiAlH_4$ effected reduction of the ester moiety to give the *N*,*N*-dibenzyl substituted amino alcohols **413**–**416** in 54–88% isolated yield over the two steps. Subsequent one-pot oxidation/olefination involving the *in situ* treatment of aldehydes **417**–**420**[14] with ylid **180** gave γ-amino-α,β-unsaturated esters **389**, **393**, **394** and **421** in 21–57% overall yield from α-amino acids **405**–**408** and >99:1 dr (Scheme 74).



Scheme 74. *Reagents and conditions*: (i) BnBr, K_2CO_3, H_2O, reflux, 3 h; (ii) $LiAlH_4$, THF, 0 °C then reflux, 1 h; (iii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C, 1 h; (iv) **180**, rt, 16 h.

An alternative benzylation procedure utilising benzoyl chloride has previously been reported for the preparation of the (*RS*)-proline derived α,β-unsaturated ester **399**.[12] Reaction of (*RS*)-proline **422** with benzoyl chloride followed by global reduction of **423** with $LiAlH_4$ resulted in the formation of the *N*-benzyl protected amino alcohol **424** in 60% isolated yield over the two steps. Subsequent Wittig reaction of aldehyde **425** (which was accessed *via* Swern oxidation of **424**) with ylid **180** afforded the known γ-amino-α,β-unsaturated ester **399**,[10] which was isolated in 47% yield (over four steps from **422**) and >99:1 dr (Scheme 75).

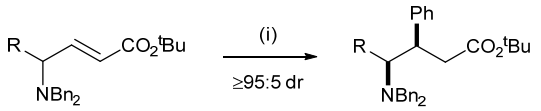


Scheme 75. *Reagents and conditions*: (i) PhCOCl, NaOH, H_2O, 0 °C, 2 h; (ii) $LiAlH_4$, THF, 0 °C then reflux, 1 h; (iii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C, 1 h; (iv) **180**, rt, 16 h.

4.3.2. Conjugate addition reactions

Racemic γ-amino-α,β-unsaturated ester **426** (R = Et)[15] was initially chosen to investigate the conjugate addition reaction with PhMgBr. Treatment of **426** with 10 equiv of PhMgBr in THF at –20 °C for 4 h[16] afforded β-phenyl-γ-amino ester **429** in only 22% conversion, although **429** was formed with high diastereoselectivity (95:5 dr). Conjugate addition of PhMgBr (10 equiv) to **426** in THF at 0 °C for 4 h afforded full conversion to **429** in 95:5 dr, and **429** was subsequently isolated in 69% yield and >99:1 dr. Upon decreasing the number of equivalents of PhMgBr to 4.0 equiv, however, only starting material was returned. γ-Amino-α,β-unsaturated esters **389**, **394**, **421** and **427** were next subjected to the conjugate addition reaction conditions optimised for **426**. Substrates **389** (R = Me) and **421** (R = Bn) furnished the corresponding β-phenyl-γ-amino esters **428** and **431** in high diastereoselectivity (95:5 dr), however, the reactions proceeded in only 50 and 35% conversion, respectively, after 4 h. Chromatographic purification of the crude reaction mixtures resulted in the isolation of diastereoisomerically pure (>99:1 dr) samples of **428** and **431** in 29 and 19% yield, respectively (Scheme 76). Once recrystallised, the relative *syn*-configurations within **428** and **431** were proven unambiguously *via* single crystal X-ray diffraction analysis (Figure 37).[17] Unfortunately, treatment of **394** (R = ^{i}Pr) under identical conditions afforded only returned starting material. In contrast, the conjugate addition of PhMgBr to **427** (R = CH_2OBn)[18] proceeded with a higher conversion of 83% to give β-phenyl-γ-amino ester **432**, which was subsequently isolated in 55% yield and >99:1 dr. As the preparation of **428**–**432** was relatively low-yielding, the conjugate addition reactions were next repeated using Et_2O as the solvent. Using these conditions the reactions proceeded in full conversion with the exception of **394** (R = ^{i}Pr), which gave a 73:27 mixture of β-phenyl-γ-amino ester **430** and unreacted starting material **394**, respectively. In addition, all α,β-unsaturated esters **389**, **394**, **421**, **426** and **427** gave the corresponding *syn*-configured β-phenyl-γ-amino esters **428**–**432** in high diastereoselectivity (>95:5 dr), and subsequent purification gave **428**–**432** in 56% to quantitative yield and >99:1 dr in each case (Scheme 76). The relative *syn*-configuration within **430** (R = ^{i}Pr) was subsequently established by single crystal X-ray diffraction analysis

(Figure 37).[17] As described in Section 4.1., Reetz and Röhrig obtained *syn*-configured β-phenyl-γ-amino ester **380** in 80% isolated yield and 95:5 dr upon reaction of α,β-unsaturated ester **379** with Ph_2CuLi in the presence of TMSCl (*vide supra*). The authors also reported a similar reaction for the ethyl ester equivalent of **421**, which gave the corresponding β-phenyl-γ-amino ester in 78% yield and 95:5 dr.[1] In comparison, this study required solely PhMgBr to furnish **428** and **431** in superior yields and >99:1 dr following chromatographic purification.



(*RS*)-**389**, R = Me, >99:1 dr
(*RS*)-**426**, R = Et, >99:**1** dr
(*RS*)-**394**, R = ^{i}Pr, >99:1 dr
(*RS*)-**421**, R = Bn, >99:1 dr
(*RS*)-**427**, R = CH_2OBn, >99:1 dr

428, R = Me, >99:**1** dr
429, R = Et, >99:1 dr
430, R = ^{i}Pr, >99:1 dr
431, R = Bn, >99:1 dr
432, R = CH_2OBn, >99:**1** dr

Substrate	R	Solvent	Conversion	Isolated yield of 428–432 (dr)
389	Me	THF	50%	29% (>99:1)
426	Et	THF	100%	69% (>99:1)
394	^{i}Pr	THF	0%	-
421	Bn	THF	35%	19% (>99:1)
427	CH_2OBn	THF	83%	55% (>99:1)
389	Me	Et_2O	100%	quant (>99:1)
426	Et	Et_2O	100%	78% (>99:1)
394	^{i}Pr	Et_2O	73%	56% (>99:1)
421	Bn	Et_2O	100%	88% (>99:1)
427	CH_2OBn	Et_2O	100%	70% (>99:1)

Scheme 76. *Reagents and conditions*: (i) PhMgBr (10 equiv), stated solvent, 0 °C, 4 h.

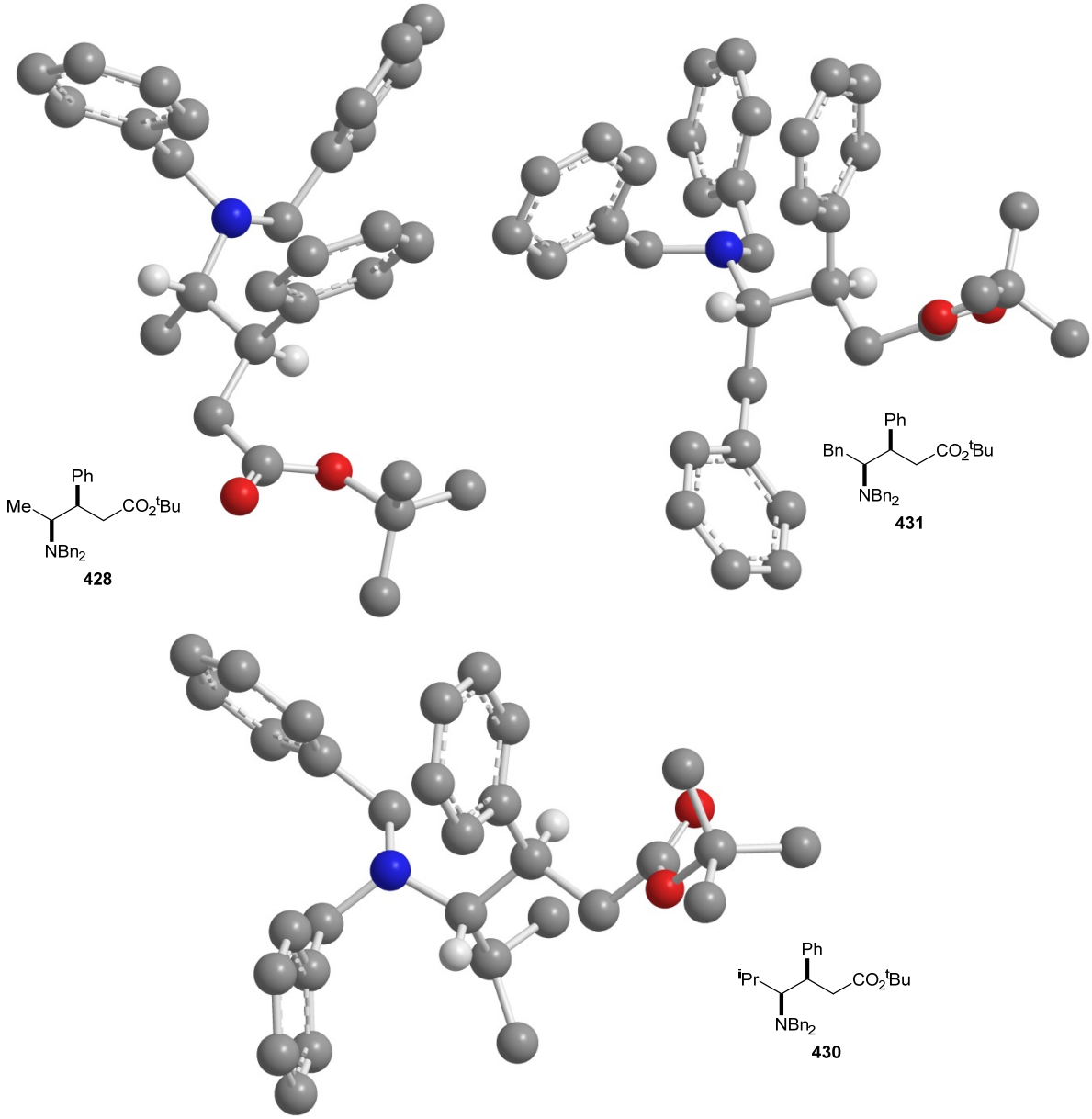
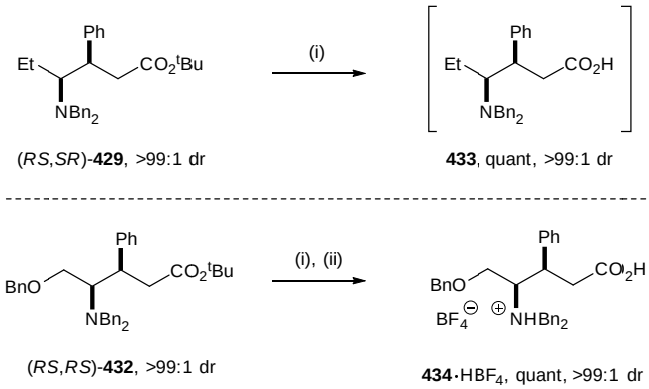


Figure 37. X-ray crystal structures of (*RS*,*SR*)-**428**, (*RS*,*SR*)-**430** and (*RS*,*SR*)-**431** (selected H atoms are omitted for clarity).

In the cases of **429** (R = Et) and **432** (R = CH_2OBn), hydrolysis of the *tert*-butyl ester moieties produced crystalline derivatives. Treatment of **429** with TFA gave γ-amino acid **433** in quantitative yield and >99:1 dr, and application of this procedure to **432** followed by formation of the corresponding HBF_4 salt gave **434**·HBF_4 in quantitative yield and >99:1 dr (Scheme 77). Single crystal X-ray diffraction analyses of **433** and **434**·HBF_4 thereby allowed the relative *syn*-configurations within **429** and **432** to be unambiguously determined (Figure 38).[17]



Scheme 77. *Reagents and conditions*: (i) TFA, CH_2Cl_2, rt, 16 h; (ii) $HBF_4{\cdot}OEt_2$, Et_2O, rt, 5 min.

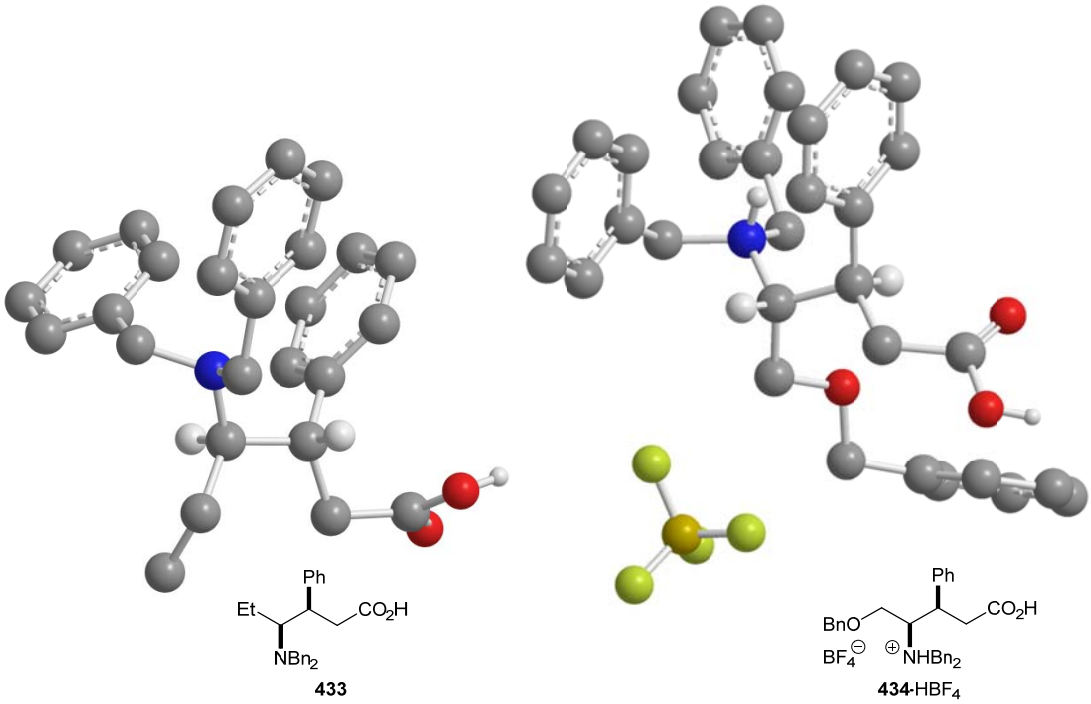


Figure 38. X-ray crystal structures of (*RS*,*SR*)-**433** and (*RS*,*RS*)-**434**·HBF_4 (selected H atoms are omitted for clarity).

In order to rationalise the inherent substrate diastereofacial control of the conjugate addition reactions, single crystal X-ray diffraction analysis of γ-amino-α,β-unsaturated ester **427** (R = CH_2OBn)[17] was conducted and the crystallographic data was compared with that previously reported[19] for **389** (R = Me). The structures of **389** and **427** indicated that they both adopt preferred solid state conformations similar to **377A**,[20] whereby the hydrogen atom at the C(4) position lies almost perpendicular to the plane of the α,β-unsaturated ester [H–C(4)–C(3) = 100.7° for **389** and 97.9° for **427**]. In addition, the C(4)–Me group within **389** and the C(4)–CH_2OBn group within **427** occupy the most sterically congested position whereas the C(4)–NBn_2 group occupies the least hindered position in both cases. Conjugate addition to **377** in conformation **377A** may then be expected to occur on the less hindered *Si*[21] face of the α,β-unsaturated ester. This rationale is consistent with the experimentally observed outcome upon conjugate addition of PhMgBr to γ-amino-α,β-unsaturated esters **389**, **394**, **421**, **426** and

427 which gave in each case *syn*-configured β,γ-disubstitued γ-amino esters **428**–**432** exclusively (Figure 39).

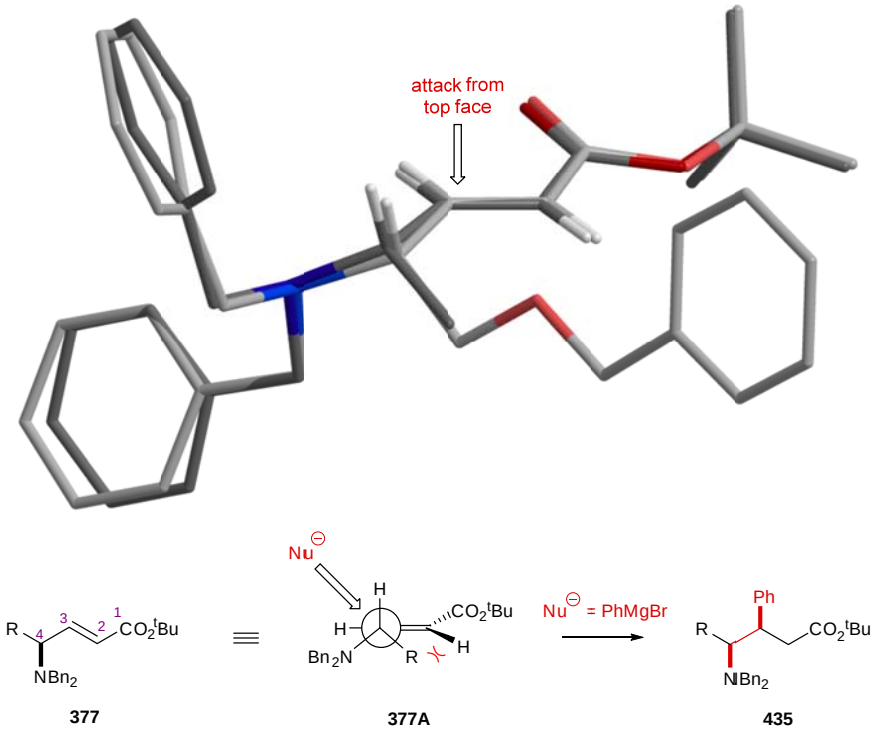
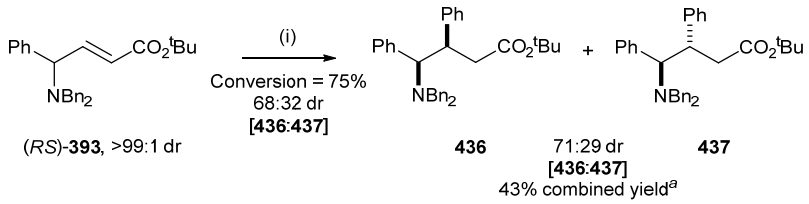


Figure 39. Overlay of the X-ray crystal structures of (*RS*)-**389** (R = Me) and (*RS*)-**427** (R = CH_2OBn) (selected H atoms are omitted for clarity) and suggested favoured conformation **377A** for the conjugate addition of PhMgBr to γ-amino-α,β-unsaturated ester **377**.

The conjugate addition of PhMgBr to γ-phenyl substituted γ-amino-α„β-unsaturated ester **393** proved to be far less diastereoselective, by analogy to previous investigations[10] concerning the conjugate addition of lithium amides to the same substrate (*vide supra*). Treatment of **393** with PhMgBr in Et_2O at 0 °C led to a 68:32 mixture of the epimeric β-phenyl-γ-amino esters **436** and **437**, respectively, in 75% conversion; although attempted chromatographic separation of **436** and **437** was found to be ineffective, with a mixture of **436** and **437** being subsequently isolated in 43% yield and 71:29 dr (Scheme 78). The relative *syn*-configuration within the major product **436** was initially assigned by analogy to that unambiguously proven for β-phenyl-γ-amino esters **428**–**432**. Recrystallisation of an aliquot of **436** and **437** (71:29 dr) provided a diastereoisomerically pure (>99:1 dr) sample of **436** allowing its relative *syn*-configuration to be established unambiguously *via* single crystal X-ray diffraction analysis (Figure 40).[17] This allowed the relative *anti*-configuration of the minor diastereoisomer **437** to also be assigned.



Scheme 78. *Reagents and conditions*: (i) PhMgBr, Et_2O, 0 °C, 4 h. [[a] Another fraction was isolated in 19% yield and 60:40 dr (**436**:**437**)].

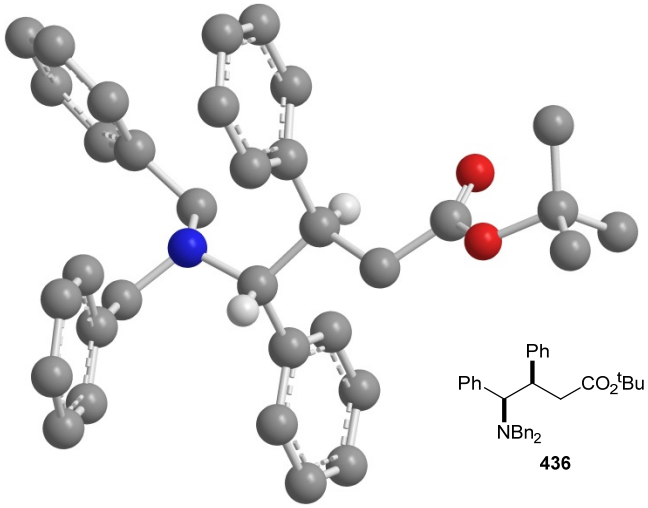
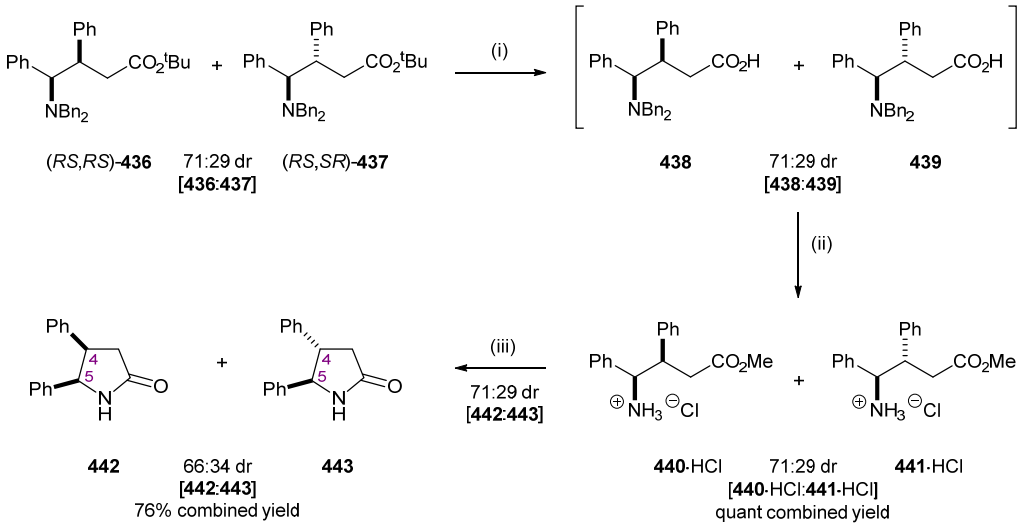


Figure 40. X-ray crystal structure of (*RS*,*RS*)-**436** (selected H atoms are omitted for clarity).

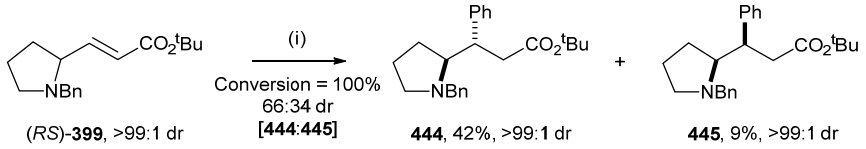
The relative configuration within the minor diastereoisomer **437** was next confirmed by chemical correlation to the known *trans*-γ-lactam **443**.[22] The 71:29 diastereoisomeric mixture of **436** and **437**, respectively, was treated with TFA to give a 71:29 mixture of the corresponding γ-amino acids **438** and **439**, respectively. As **438** and **439** proved to be chromatographically inseparable, the crude reaction mixture was subjected to an *N*-debenzylation reaction with $Pd(OH)_2/C$ under a H_2 atmosphere in methanolic HCl to provide a 71:29 mixture of γ-amino methyl ester hydrochloride salts **440**·HCl and **441**·HCl, respectively, in quantitative combined yield over the two steps. Further elaboration of this mixture to γ-lactams **442** and **443** was achieved in 76% combined yield and 66:34 dr upon treatment with K_2CO_3 in PhMe at reflux for 16 h, followed by purification by flash column chromatography (Scheme 79). Comparison of ^{1}H and ^{13}C NMR data for the minor diastereoisomer *trans*-**443** showed complete agreement with those reported in the literature.[23] Furthermore, analysis of the ^{1}H NMR spectrum for **442** and **443** identified two proton signals as doublets corresponding to C(5)*H*.[24] For *trans*-**443** this proton chemical shift appeared at δ 4.63 ppm with a ^{1}H–^{1}H ^3J coupling constant of 7.3 Hz, whereas C(5)*H* in *cis*-**442** was detected at δ 4.95 ppm with a slightly higher ^3J coupling constant of 7.6 Hz. The observed higher chemical shift and coupling constant values for C(5)*H* have previously been known to

be indicative of a *syn*-configuration between the C(4)*H* and C(5)*H* protons in 4,5-disubstituted γ-lactams.[25]



Scheme 79. *Reagents and conditions*: (i) TFA, CH_2Cl_2, rt, 16 h; (ii) H_2 (1 atm), $Pd(OH)_2/C$, HCl (1.25 M in MeOH), rt, 16 h; (iii) K_2CO_3, PhMe, reflux, 16 h.

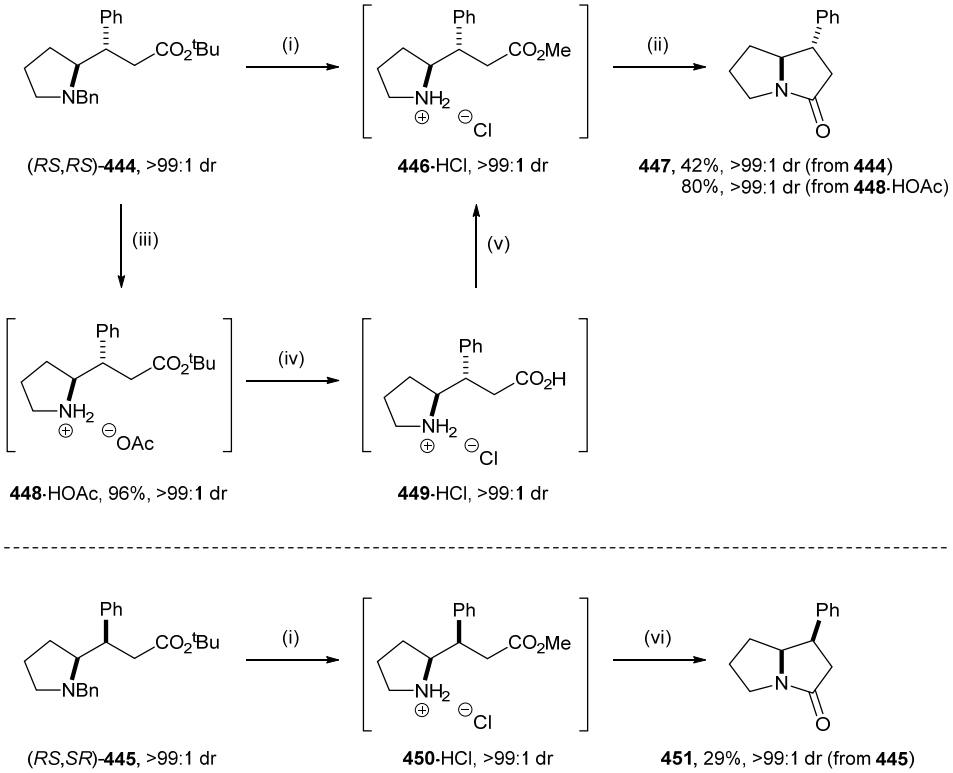
The conjugate addition of PhMgBr to the (*RS*)-proline derived γ-amino-α,β-unsaturated ester **399** led to complete consumption of **399**, giving a 66:34 mixture of diastereoisomers **444** and **445**, respectively. Upon chromatographic purification of the reaction mixture, *anti*-**444** was isolated in 42% yield and >99:1 dr, together with *syn*-**445** in 9% yield and >99:1 dr (Scheme 80). It is interesting to note that this experimental result differs greatly from that obtained for the conjugate addition to *N*-Boc protected γ-amino-α,β-unsaturated methyl ester **385**, whereby the *syn*-configured product was obtained in high diastereoselectivity (*vide supra*).[8]



Scheme 80. *Reagents and conditions*: (i) PhMgBr, Et_2O, 0 °C, 4 h.

The configurations of the newly formed stereogenic centres within **444** and **445** were assigned *via* a combination of chemical correlation and single crystal X-ray diffraction analysis. *N*-Debenzylation of **444** with Pearlman's catalyst under 1 atm of H_2 in methanolic HCl furnished **446**·HCl in >99:1 dr. Treatment of **446**·HCl with K_2CO_3 in PhMe at reflux proceeded to give pyrrolizidin-3-one **447**, which was isolated in 42% yield (over two steps from **444**) and >99:1 dr. Concurrent efforts were also directed at preparing **447** by hydrogenolysis of **444** in the presence of AcOH, which gave **448**·HOAc in 96% yield and >99:1 dr. Subsequent acid-catalysed hydrolysis of **448**·HOAc followed by esterification and cyclisation gave pyrrolizidin-3-one **447** in 77% yield (over four steps from **444**) and >99:1 dr. In both cases, the ^1H and ^{13}C NMR spectra of the sample of **447** were found to be identical to

those reported in the literature.[26] A similar sequence of reactions was next applied to **445** with the aim of preparing **451**. Treatment of **445** with $Pd(OH)_2/C$ under a H_2 atmosphere followed by a basic work-up with $NaHCO_3$ enabled cyclisation of **445** to give **451** in 29% yield (over two steps from **445**) and >99:1 dr (Scheme 81).[27] Once again, comparison of the ^1H and ^{13}C NMR spectra of **451** with those reported in the literature were found to be in complete agreement.[26] Additionally, the relative *anti*-configuration within **448**·HOAc was unambiguously secured *via* single crystal X-ray diffraction analysis of **448**·HOAc (Figure 41).[17] These data therefore also confirmed the relative configurations within **444**–**447** and **449**–**451**.



Scheme 81. *Reagents and conditions*: (i) H_2 (1 atm), $Pd(OH)_2/C$, HCl (1.25 M in MeOH), rt, 24 h; (ii) K_2CO_3, PhMe, reflux, 16 h; (iii) H_2 (1 atm), $Pd(OH)_2/C$, MeOH/AcOH (v/v 40:1), rt, 24 h; (iv) HCl (3.0 M aq), reflux, 16 h; (v) HCl (1.25 M in MeOH), reflux, 16 h; (vi) $NaHCO_3$, CH_2Cl_2, rt, 30 min.

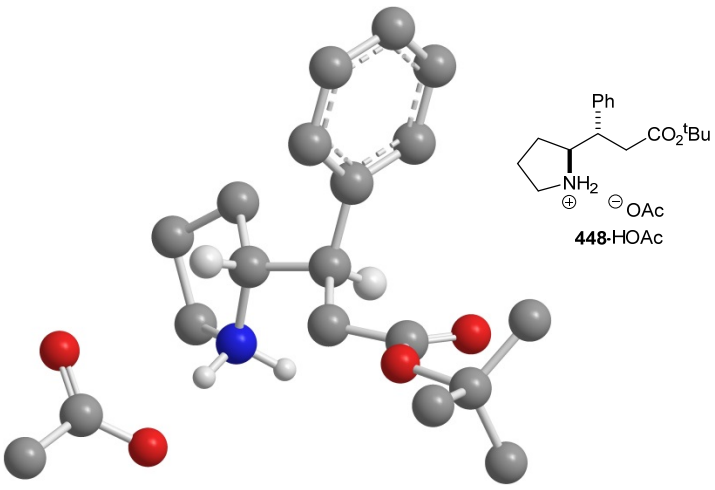
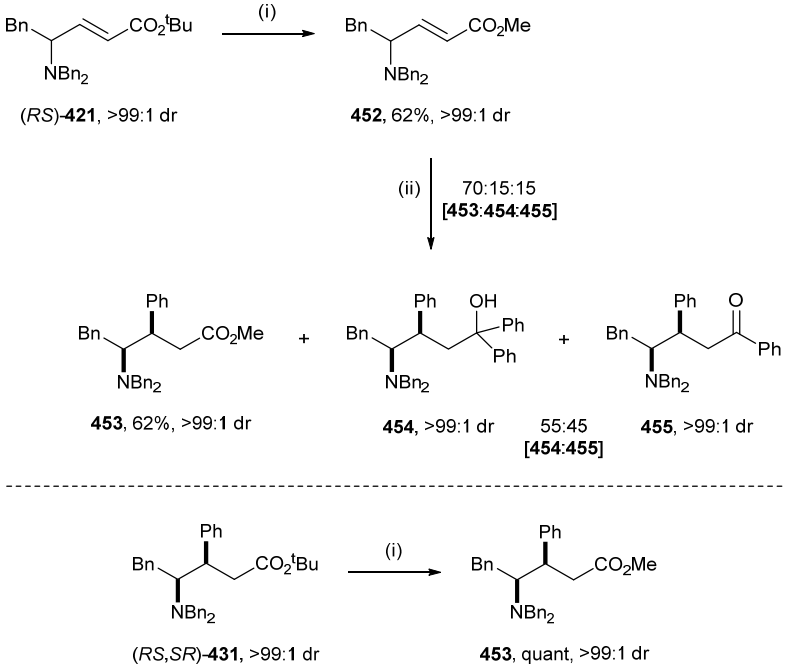


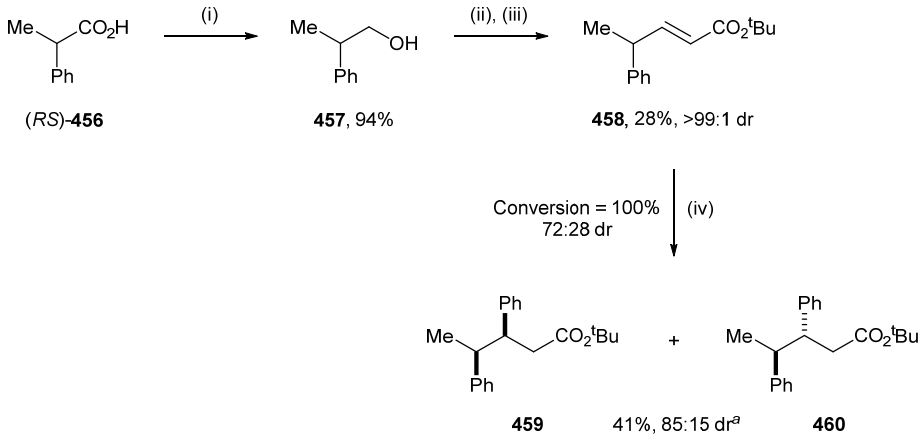
Figure 41. X-ray crystal structure of (*RS*,*RS*)-**448**·HOAc (selected H atoms are omitted for clarity).

It was next decided to investigate whether the bulky (*tert*-butyl) ester group is a requirement for high chemoselectivity in these conjugate addition reactions. γ-Amino methyl ester **452** was prepared by transesterification of *tert*-butyl ester **421** with $SOCl_2$ in MeOH to give **452** in 62% yield and >99:1 dr. Reaction of **452** with PhMgBr under conditions that matched the developed conjugate addition protocol for *tert*-butyl esters **389**, **394**, **421**, **426** and **427** gave at 100% conversion a crude 70:15:15 ratio of **453**, **454** and **455**, respectively. As a consequence of the ester group no longer posing a steric constraint to 1,2-addition, ketone **455** was presumably formed *via* 1,2-addition of PhMgBr to the carbonyl moiety within **452**, followed by 1,4-addition to the resultant α,β-unsaturated ketone. Moreover, a second 1,2-addition of PhMgBr to ketone **455** is presumably responsible for the formation of tertiary alcohol **454**. Chromatographic purification of the reaction mixture allowed the isolation of **453** in 62% yield as a single diastereoisomer (>99:1 dr), together with a 55:45 mixture of **454** and **455**, respectively. The stereochemical outcome for this reaction was tentatively assigned by analogy to the conjugate additions of PhMgBr to **389**, **394**, **421**, **426** and **427**. In order to verify the assigned *syn*-configuration within **453**, an authentic sample was prepared by transesterification of *tert*-butyl ester **431** in $SOCl_2$ and MeOH, which furnished methyl ester **453** in quantitative yield and >99:1 dr (Scheme 82). The ^{1}H and ^{13}C NMR spectra of the sample of **453** prepared by this method were found to be in complete agreement with the data obtained from the conjugate addition reaction of PhMgBr to α,β-unsaturated ester **452**.



Scheme 82. *Reagents and conditions*: (i) $SOCl_2$, MeOH, 50 °C, 16 h; (ii) PhMgBr, Et_2O, 0 °C, 4 h.

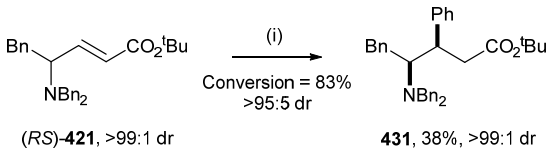
In order to probe whether the *N*,*N*-dibenzylamino substituent is playing an active role in achieving high diastereoselectivity in the conjugate addition reactions, γ-phenyl substituted α,β-unsaturated ester **458** (bearing no amino group) was synthesised. Reduction of commercially available 2-phenylpropionic acid (*RS*)-**456** with $LiAlH_4$ gave the corresponding alcohol **457**. Swern oxidation of **457** and olefination of the resultant aldehyde with ylid **180** gave α,β-unsaturated ester (*RS*)-**458** in 26% overall yield (from **456**) and >99:1 dr. Under reaction conditions analogous to those employed for the conjugate addition of PhMgBr to γ-amino α,β-unsaturated esters **389**, **394**, **421**, **426** and **427** was subjected to PhMgBr in Et_2O at 0 °C for 4 h. In contrast to the results obtained for **428**–**432**, however, ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed a 72:28 diastereoisomeric ratio of conjugate addition products **459** and **460**. Subsequent purification by flash column chromatography resulted in an inseparable 85:15 mixture of diastereoisomers being isolated in 41% combined yield; the relative configurations within **459** and **460** could therefore not be assigned unambiguously (Scheme 83). This result supports the notion that the amino group present within the α,β-unsaturated esters is a prerequisite for high diastereoselectivity upon conjugate addition.



Scheme 83. *Reagents and conditions*: (i) $LiAlH_4$, THF, 0 °C then reflux, 1 h; (ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C, 1 h; (iii) **180**, rt, 16 h; (iv) PhMgBr, Et_2O, 0 °C, 4 h. [[a] Another fraction containing **459** and **460** was isolated in 21% yield and 54:46 dr.]

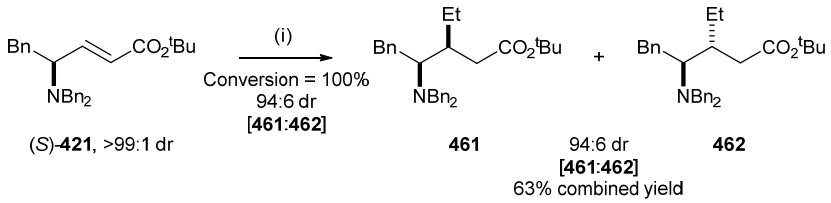
4.3.3. Evaluation of alternative organometallic reagents

It was next decided to substitute PhMgBr with PhLi in the conjugate addition reaction with γ-amino-α,β-unsaturated ester (*RS*)-**421**. Treatment of **421** with PhLi in Et_2O at 0 °C proceeded to 83% conversion to give the *syn*-configured β,γ-disubstituted γ-amino ester **431** in 38% isolated yield as a single diastereoisomer (>99:1 dr) (Scheme 84).



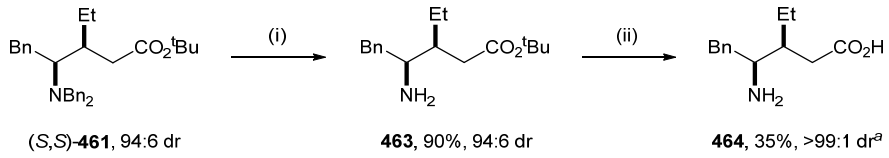
Scheme 84. *Reagents and conditions*: (i) PhLi, Et_2O, 0 °C, 2 h.

The generality of the 1,4-conjugate addition reaction to γ-amino-α,β-unsaturated esters was also surmised by assessing the chemoselectivity of the reaction using an alkyl Grignard reagent. For this purpose, EtMgBr was chosen as a representative example of an alkyl Grignard reagent, since the conjugate addition reaction of MeMgBr to the β'-amino-α,β-unsaturated ester investigated in Chapter 3 proved unsuccessful. Reaction of (*S*,*E*)-**421** with EtMgBr in Et_2O at 0 °C proceeded to completion to give a 94:6 mixture of diastereoisomers **461** and **462**, respectively, following which chromatographic purification allowed the isolation of **461** in 63% yield and 94:6 dr (Scheme 85). The *syn*-configuration within the major product **461** was assigned by analogy to the established stereochemical outcome observed for the formation of β-phenyl-γ-amino esters **428**–**432**.



Scheme 85. *Reagents and conditions*: (i) EtMgBr, Et_2O, 0 °C, 4 h.

Elaboration of **461** to β-ethyl-γ-amino acid **464** was pursued by *N*-debenzylation under a H_2 atmosphere in the presence of $Pd(OH)_2/C$, which afforded primary amine **463** in 90% isolated yield and 94:6 dr. γ-Amino *tert*-butyl ester **461** was then subjected to acid-catalysed hydrolysis using TFA, and subsequent purification on ion-exchange resin furnished the corresponding γ-amino acid[28] **464** in >99:1 dr, in seven steps and 8% overall yield from (*S*)-phenylalanine **408** (Scheme 86).

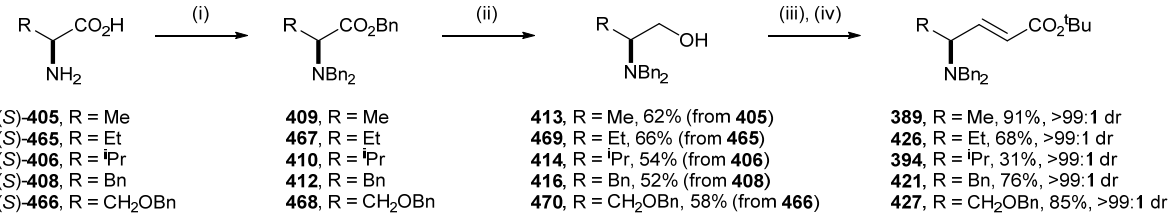


Scheme 86. *Reagents and conditions*: (i) H_2 (1 atm), $Pd(OH)_2/C$, MeOH, rt, 24 h; (ii) TFA, CH_2Cl_2, rt, 16 h then HCl (6.0 M aq), rt, 30 min then DOWEX 50WX8. [[a] Another fraction was isolated in 38% yield and 94:6 dr.]

4.3.4. Application to the asymmetric synthesis of enantiopure γ-amino acids and γ-lactams

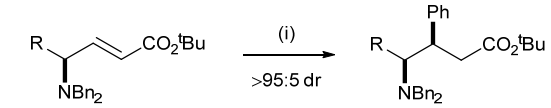
Following the successful development of a protocol for the conjugate addition of PhMgBr to racemic γ-amino-α,β-unsaturated esters **389**, **394**, **421**, **426** and **427**, transformation of the

corresponding enantiopure β,γ-disubstituted ester products into γ-amino acids was next assessed. The synthesis of enantiopure γ-amino-α,β-unsaturated esters **389**, **394**, **421**, **426** and **427** was accomplished using the methodology previously described for the racemic analogues. Starting with α-amino acids **405**, **406**, **408**, **465** and **466**, sequential benzylation, ester reduction, oxidation and olefination afforded **389**, **394**, **421**, **426** and **427** in 17–56% isolated yield (over four steps from the α-amino acids) and >99:1 dr (Scheme 87).



Scheme 87. *Reagents and conditions*: (i) BnBr, K_2CO_3, H_2O, reflux, 3 h; (ii) $LiAlH_4$, THF, 0 °C then reflux, 1 h; (iii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C, 1 h; (iv) **180**, rt, 16 h.

As in the racemic series, reaction of (*S*)-**389** (R = Me), (*S*)-**426** (R = Et), (*S*)-**421** (R = Bn) and (*R*)-**427** (R = CH_2OBn) with PhMgBr at 0 °C proceeded in full conversion to deliver the corresponding β-phenyl-γ-amino esters **428**, **429**, **431** and **432** with high diastereoselectivity (>95:5 dr) in each case. Upon chromatographic purification of the crude reaction mixtures **428**, **429**, **431** and **432** were isolated in 79–91% yield and >99:1 dr. Meanwhile, treatment of the γ-isopropyl substituted α,β-unsaturated ester (*S*)-**394** with PhMgBr proceeded to a moderate 69% conversion after stirring the reaction mixture for 4 h at 0 °C, and β-phenyl-γ-amino ester **430** was subsequently isolated in 47% yield and >99:1 dr (Scheme 88).

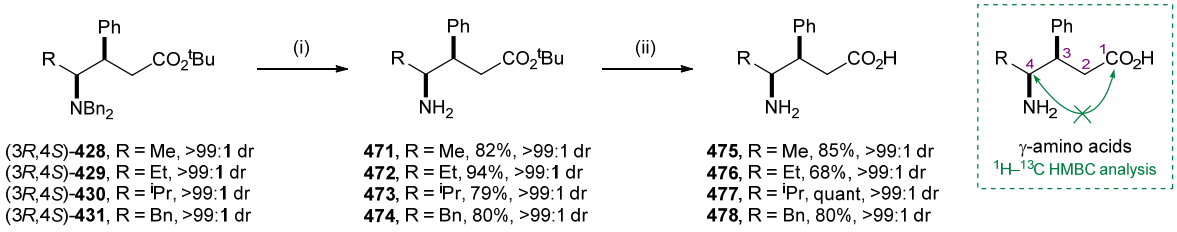


Substrate	R	Conversion	Isolated yield of 428–432 (dr)
389	Me	100%	81% (>99:1)
426	Et	100%	79% (>99:1)
394	iPr	69%	47% (>99:1)
421	Bn	100%	91% (>99:1)
427	CH_2OBn	100%	83% (>99:1)

Scheme 88. *Reagents and conditions*: (i) PhMgBr, Et_2O, 0 °C, 4 h.

With the phenyl group installed at the β-position, elaboration of γ-amino esters **428**–**431** to the corresponding γ-amino acids **475**–**478** could be effected in just two chemical transformations. *N*-Deprotection was achieved by treatment of **428**–**431** with Pearlman's catalyst under a H_2 atmosphere which gave primary amines **471**–**474** as single

diastereoisomers (>99:1 dr) in 79–94% yield. Hydrolysis of *tert*-butyl esters **471**–**474** using TFA in CH_2Cl_2 at rt for 16 h and purification by ion exchange chromatography furnished γ-amino acids **475**–**478** in 68% to quantitative yield. The preparation of γ-amino acids as opposed to γ-lactams was supported by the observation of carbonyl IR absorption bands at 1545–1553 cm^{-1} which are typically diagnostic for amino acids in their zwitterionic form. Furthermore, ^{1}H–^{13}C HMBC analyses for **475**–**478** showed no corrrelation between the *C*(1) carbonyl group and the C(4)*H* proton signal (Scheme 89). The asymmetric synthesis of a range of four γ-substituted β-phenyl-γ-amino acids **475**–**478** was therefore concluded in 6–32% overall yield and seven steps from commercially available α-amino acids **405**, **465**, **406** and **408**.



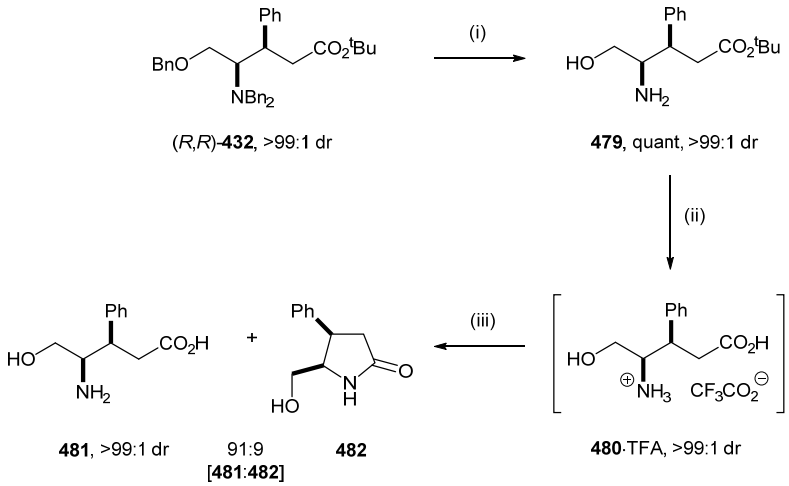
(3*R*,4*S*)-**428**, R = Me, >99:**1** dr
(3*R*,4*S*)-**429**, R = Et, >99:**1** dr
(3*R*,4*S*)-**430**, R = ^{i}Pr, >99:**1** dr
(3*R*,4*S*)-**431**, R = Bn, >99:**1** dr

471, R = Me, 82%, >99:1 dr
472, R = Et, 94%, >99:**1** dr
473, R = ^{i}Pr, 79%, >99:1 dr
474, R = Bn, 80%, >99:1 dr

475, R = Me, 85%, >99:1 dr
476, R = Et, 68%, >99:1 dr
477, R = ^{i}Pr, quant, >99:1 dr
478, R = Bn, 80%, >99:1 dr

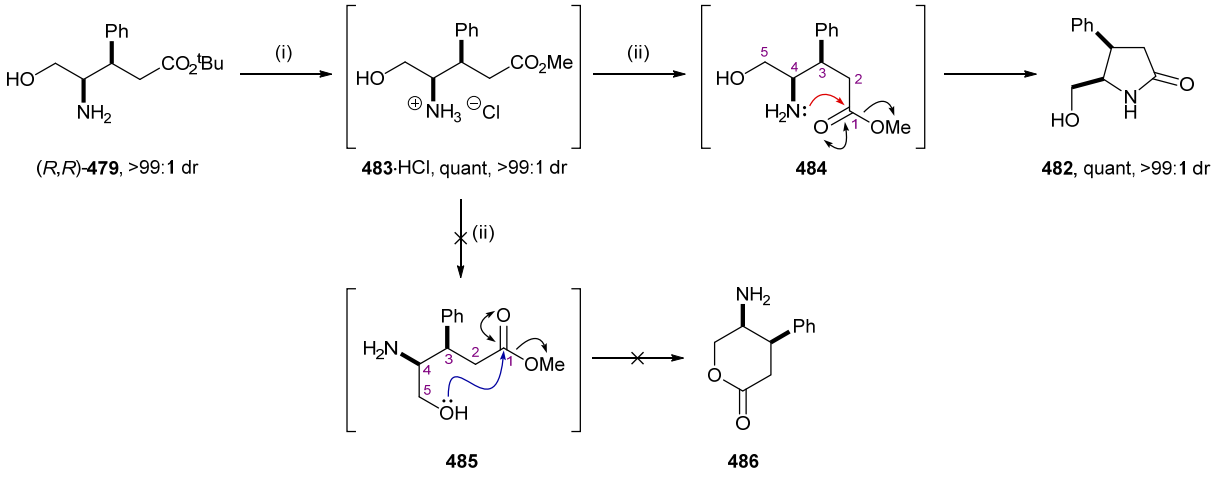
Scheme 89. *Reagents and conditions*: (i) H_2 (1 atm), $Pd(OH)_2/C$, MeOH, rt, 24 h; (ii) TFA, CH_2Cl_2, rt, 16 h then HCl (6.0 M aq), rt, 30 min then DOWEX 50WX8.

The elaboration of β,γ-disubstituted γ-amino ester **432** (R = CH_2OBn) was next attempted. Hydrogenolysis of the *N*,*N*-dibenzylamino moiety within **432** using $Pd(OH)_2/C$ gave primary amine **479** in quantitative yield and >99:1 dr. Subsequent acid-catalysed hydrolysis gave **480**·TFA as a single diastereoisomer (>99:1 dr). However, purification of the crude reaction mixture *via* ion-exchange chromatography resulted in the isolation of a 91:9 mixture of γ-amino acid **481** and γ-lactam **482**, respectively (Scheme 90). The formation of **480**·TFA was confirmed by full ^{1}H and ^{13}C NMR spectroscopic analyses, including a ^{1}H–^{13}C HMBC experiment. The identity of the minor product **482** was subsequently confirmed by the synthesis of an authentic sample (*vide infra*).



Scheme 90. *Reagents and conditions*: (i) H_2 (1 atm), $Pd(OH)_2/C$, MeOH, rt, 24 h; (ii) TFA, CH_2Cl_2, rt, 16 h; (iii) HCl (6.0 M aq), rt, 30 min then DOWEX 50WX8.

Treatment of **479** with a solution of methanolic HCl proceeded to give **483**·HCl in quantitative yield and >99:1 dr. Subsequent reaction of **483**·HCl with K_2CO_3 in PhMe resulted in the formation of γ-lactam **482** in quantitative yield (over the two steps) and >99:1 dr. The cyclisation step can be simply rationalised by attack of the C(4)-amino group at the ester. The absence of any δ-lactone **486** in the ^{1}H NMR spectrum of the crude reaction mixture discounts the possible competing attack of the C(5)-hydroxyl group at the ester (Scheme 91). γ-Lactam **482** was therefore prepared in 41% overall yield and eight steps from commercially available (*S*)-*O*-benzyl serine **466**.



Scheme 91. *Reagents and conditions*: (i) HCl (1.25 M in MeOH), reflux, 16 h; (ii) K_2CO_3, PhMe, reflux, 16 h.

The assigned connectivity within γ-lactam **482** was confirmed by ^{1}H and ^{13}C NMR spectroscopic analyses, and most importantly a ^{1}H–^{13}C HMBC experiment. Notably, the C(5)*H* proton at δ_H = 4.01 ppm showed connectivity to the *C*(2) carbonyl group at δ_C = 181.0 ppm which confirms ring-closure to a lactam framework. In addition, no correlation between the C(5)CH_2OH protons and the *C*(1) carbonyl group was observed. The assignment of a *syn*-configuration within **482** was supported by ^{1}H NMR NOESY analysis. Irradiation of the

C(5)CH_2OH proton signals showed a NOESY enhancement to the phenyl group protons in the absence of an enhancement to the C(4)*H* proton. This result was corroborated by the observed reciprocal correlation between the C(4)*H* and C(5)*H* protons, thereby suggesting that the hydroxymethyl and phenyl groups occupy the same face of the ring system (Figure 42).

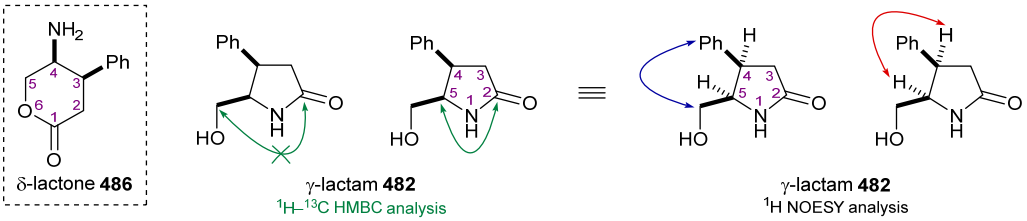


Figure 42. Representation of ^{1}H–^{13}C HMBC and ^{1}H NMR NOESY correlations observed within **482**. [''↔'' represents reciprocal interaction].

4.4. Conclusion

In conclusion, treatment of a range of γ-*N*,*N*-dibenzylamino-substituted α,β-unsaturated esters (prepared from enantiopure α-amino acids) with Grignard reagents resulted in highly chemo- and diastereoselective conjugate addition reactions to give the corresponding *syn*-configured β,γ-disubstituted γ-amino esters. The synthetic utility of this reaction was subsequently highlighted in the concise asymmetric syntheses of a range of six β,γ-disubstituted γ-amino acids.

4.5. References and notes

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[5] Analogues of the neurotransmitter GABA exhibit important pharmacological functions on the central nervous system; see: (a) Kerr, D. I. B.; Ong, J. *Pharmac. Ther.* **1995**, *67*, 187. (b) Bryans, J. S.; Wustrow, D. J. *Med. Res. Rev.* **1999**, *19*, 149. (c) Thorpe, A. J.; Taylor, C. P. In *Comprehensive Medicinal Chemistry II*; Taylor, J. B.; Triggle, D. J., Eds.; Elsevier Ltd., 2007; Vol. 8, pp 227.

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[9] The authors also reported the conjugate addition of R_2CuLi (R = vinyl) to **385** which gave *syn*-configured β-vinyl-γ-amino ester in 89% yield and 86:14 dr.

[10] Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E.; Yin, J. *Org. Lett.* **2012**, *14*, 218.

[11] 4-Aminopyrrolidin-2-ones can be used to access synthetically useful β,γ-amino acids; see: Bouillére, F.; Guillot, R.; Kouklovsky, C.; Alezra, V. *Org. Biomol. Chem.* **2011**, *9*, 394.

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[15] Sample of γ-amino-α,β-unsaturated ester **426** (R = Et) was provided by Dr J. Yin.

[16] Optimised conditions for the conjugate addition of PhMgBr to β'-amino-α,β-unsaturated ester (see Chapter 3).

[17] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research laboratory, University of Oxford, U.K.

[18] Sample of γ-amino-α,β-unsaturated ester **427** (R = CH_2OBn) was provided by Dr J. Yin.

[19] Single crystal X-ray diffraction analysis has previously been utilised to rationalise the *syn*-selectivity obtained for the reactions of γ-amino-α,β-unsaturated esters with lithium amides; see: Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E.; Yin, J. *Org. Lett.* **2012**, *14*, 218.

[20] A similar model has previously been used to provide insight on the selectivity of the conjugate addition reactions of organocopper reagents and organocuprates to γ-alkoxy-α,β-unsaturated esters, see: (a) Yamamoto, Y.; Chounan, Y.; Nishii, S.; Ibuka, T.; Kitahara, H. *J. Am. Chem. Soc.* **1992**, *114*, 7652. (b) Kireev, A. S.; Manpadi, M.; Kornienko, A. *J. Org. Chem.* **2006**, *71*, 2630.

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[23] The authors reported that the relative *trans*-configuration within **443** was established by single crystal X-ray diffraction analysis; see: Escalante, J.; González-Tototzin, M. A. *Tetrahedron: Asymmetry* **2003**, *14*, 981.

[24] Unfortunately, ^1H–^1H NMR NOESY analysis performed on the mixture of **442** and **443** proved inconclusive as NOESY enhancements were observed between the C(4)*H* and C(5)*H* protons for both *cis*-**442** and *trans*-**443**.

[25] (a) Yee, N. K. *Tetrahedron Lett.* **1997**, *38*, 5091. (b) Leśniak, S.; Nazarski, R. B.; Pasternak, B. *Tetrahedron* **2009**, *65*, 6364.

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[27] An analogous reaction was set-up for the major diastereoisomer *anti*-**444**, and treatment of **444** with Pearlman's catalyst under an atmosphere of H_2 followed by a basic work-up resulted in the formation of *trans*-**447** in 52% yield and >99:1 dr.

[28] The formation of γ-amino acid **464** was confirmed by ^1H–^{13}C HMBC analysis which showed no correlation between the *C*(1) carbonyl group and the C(4)*H* proton signal.

Chapter 5: Towards the asymmetric synthesis of azabicyclic β-amino acids

This chapter details attempts towards the asymmetric synthesis of functionalised azabicyclic β-amino acids **109** and **488**, utilising the conjugate addition of a lithium amide reagent to azabicyclic α,β-unsaturated esters **108** and **487** as the key step (Figure 43).

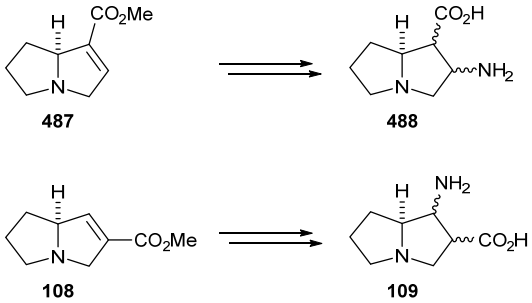
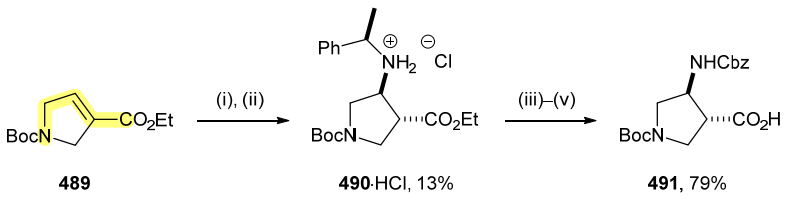


Figure 43. Conjugate addition reactions to azabicyclic α,β-unsaturated esters **108** and **487** to access azabicyclic β-amino acids **109** and **488**.

5.1. Introduction: conjugate addition reactions to azacyclic α,β-unsaturated esters

The synthesis of azacyclic β-amino acids, for their incorporation into β-peptides,[1] was initially investigated by Gellman and co-workers.[2] The authors reported that subjection of α,β-unsaturated ester **489** to a conjugate addition protocol whereby treatment of **489** with (*R*)-α-methylbenzylamine in H_2O at 55 °C for 67 h resulted in the formation of four diastereoisomers,[3] from which **490**·HCl was isolated in 13% yield following exhaustive chromatographic purification and treatment with 4 M HCl in dioxane. *N*-Debenzylation of **490**·HCl upon treatment with Pd/C under a H_2 atmosphere was subsequently carried out, followed by *N*-Cbz protection and base-catalysed ester hydrolysis to furnish the orthogonally protected β-amino acid **491** in 79% yield over the three steps (Scheme 92).

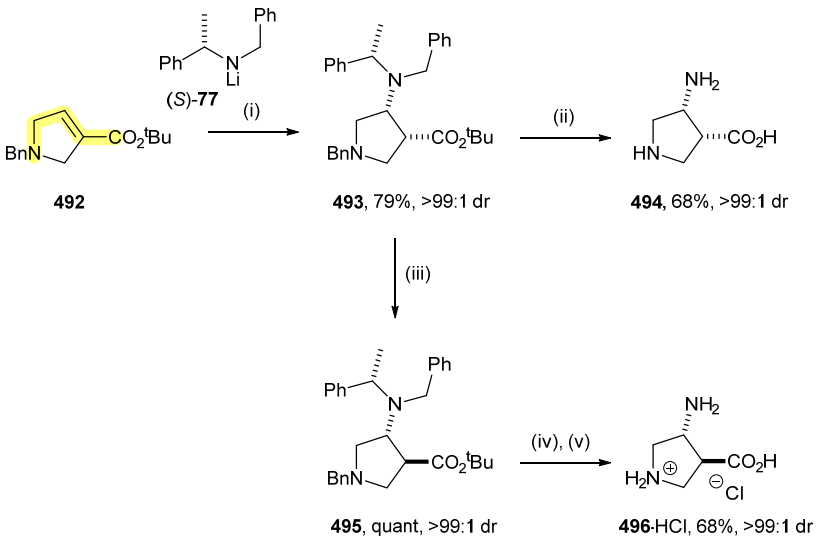


489 **490**·HCl, 13% **491**, 79%

Scheme 92. *Reagents and conditions*: (i) (*R*)-α-methylbenzylamine, H_2O, 55 °C, 67 h; (ii) HCl (4.0 M in dioxane), EtOAc, rt; (iii) H_2 (50 psi), Pd/C, EtOH, rt, 22 h; (iv) Cbz-OSu, $NaHCO_3$, acetone/H_2O (v/v 2:1), rt, 14 h; (v) $LiOH·H_2O$, MeOH/H_2O (v/v 3:1), 0 °C, 15 h.

Davies and co-workers later demonstrated a highly diastereoselective conjugate addition reaction leading to the synthesis of fully deprotected azacyclic β-amino acids **494** and **496**·HCl.[4] Treatment of azacyclic α,β-unsaturated ester **492** with (*S*)-**77** in THF at –78 °C furnished β-amino ester **493** in 79% yield and >99:1 dr. Hydrogenolytic removal of the *N*-benzyl and *N*-α-methylbenzyl groups followed by acid-catalysed hydrolysis afforded azacyclic β-amino acid **494** in 68% yield. The epimeric azacyclic β-amino acid **496**·HCl was

synthesised upon reaction of **493** with KO^{t}Bu in ^{t}BuOH, which gave β-amino ester **495** in quantitative yield and >99:1 dr. Subsequent elaboration to **496**·HCl proceeded in 68% yield *via* a two-step procedure involving hydrogenolysis and ester hydrolysis (Scheme 93).



Scheme 93. *Reagents and conditions*: (i) (*S*)-**77**, THF, –78 °C, 3 h; (ii) H_2 (5 atm), $Pd(OH)_2$/C, EtOH/H_2O/HCl (v/v/v 6:3:1), rt, overnight then HCl (1.0 M aq), 70 °C, 4 h then DOWEX 50WX8; (iii) KO^{t}Bu, ^{t}BuOH, reflux, 3 h; (iv) H_2 (5 atm), $Pd(OH)_2$/C, EtOH/H_2O/HCl (v/v/v 6:3:1), rt, overnight; (v) HCl (1.0 M aq), 70 °C, 4 h.

5.2. Aim: proposed route to azabicyclic β-amino acids

The aim of this chapter is to delineate an asymmetric synthesis of azabicyclic β-amino acids **109** and **488**. Building on previous studies by Davies and co-workers,[4,5] it was envisaged that an azabicyclic α,β-unsaturated ester would provide an attractive scaffold for diastereoselective conjugate addition reactions of lithium amides, thereby allowing access to the regioisomeric β-amino esters **498** and **500**. Consequently, elaboration of these substrates *via* hydrogenolysis and ester hydrolysis would afford azabicyclic β-amino acids **109** and **488** (Figure 44).

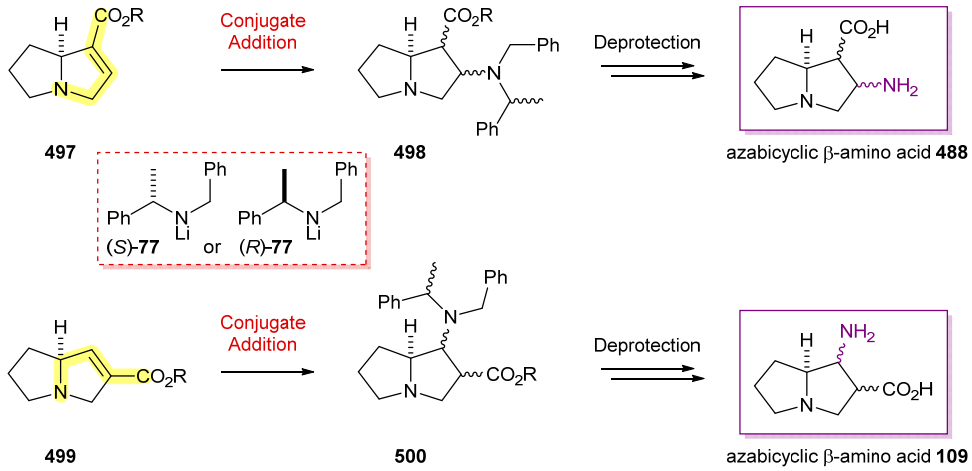
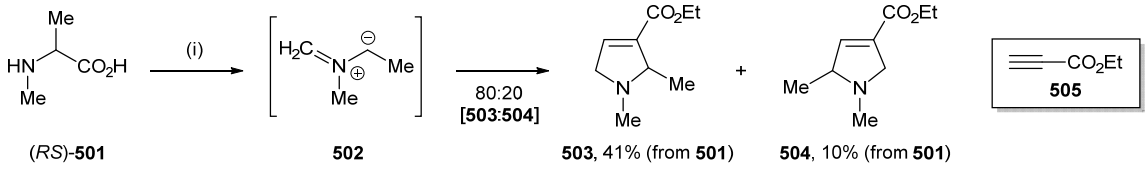


Figure 44. Proposed route through to azabicyclic β-amino acids **109** and **488** from azabicyclic α,β-unsaturated esters **497** and **499**.

5.3. Results and Discussion

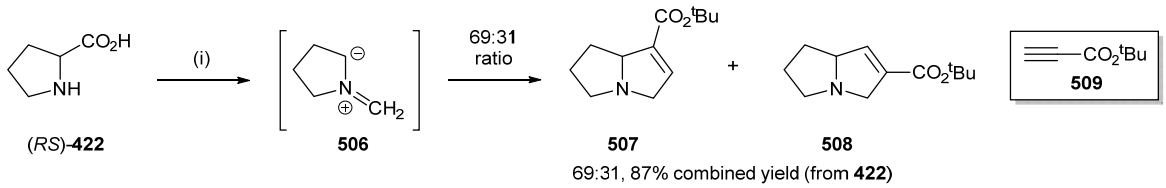
5.3.1. Synthesis of racemic azabicyclic α,β-unsaturated esters and their assessment in the conjugate addition reaction with lithium (*RS*)-*N*-benzyl-*N*-(α-methylbenzyl)amide

The utility of 1,3-dipolar cycloadditions for the construction of a pyrrolidine ring has been identified by several groups.[6] For instance, Johnson and co-workers[6b] have shown that reaction of *N*-methyl-(*RS*)-alanine (*RS*)-**501** with ethyl propiolate **505** in the presence of paraformaldehyde[7] proceeded *via* azomethine ylide[8] **502** to give an 80:20 mixture of dihydropyrroles **503** and **504**, respectively. Chromatographic purification was subsequently required for the isolation of **503** and **504** in 41 and 10% yield, respectively (Scheme 94).



Scheme 94. *Reagents and conditions*: (i) paraformaldehyde, **505**, $MgSO_4$, PhMe, 90 °C, 3.5 h.

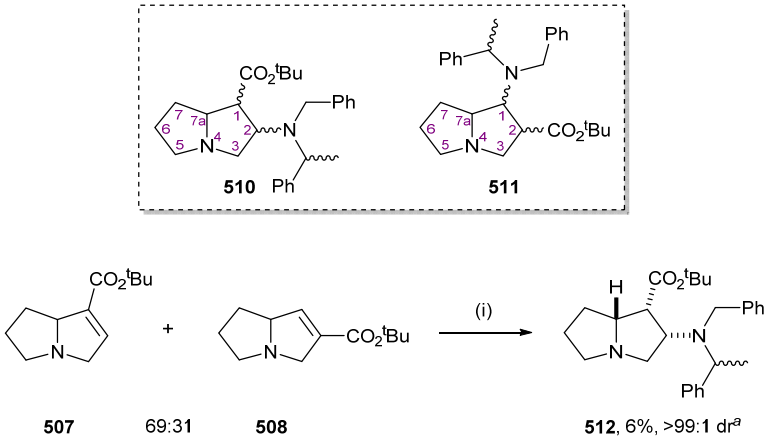
It was thereby decided to adopt the above protocol in order to investigate the preparation of azabicyclic α,β-unsaturated esters **507** and **508**. In the present case, the decarboxylative condensation pathway of (*RS*)-proline (*RS*)-**422** was utilised in conjunction with the 1,3-dipolar cycloaddition of the resultant azomethine ylide **506** with *tert*-butyl propiolate **509**.[9] Azomethine ylide **506** was generated *in situ* by reacting (*RS*)-**422** with paraformaldehyde in PhMe at reflux. Subsequent 1,3-dipolar cycloaddition of **506** with **509**[10] gave a chromatographically inseparable 69:31 mixture of **507** and **508** in 87% combined yield (Scheme 95).[11] Unfortunately, attempts at improving the regioselectivity by changing the reaction solvent to MeCN[12] or adding $ZnCl_2$ to the reaction mixture were not productive, with similar crude ratios being observed in each case.



Scheme 95. *Reagents and conditions*: (i) paraformaldehyde, **509**, PhMe, reflux, 3 h.

As α,β-unsaturated esters **507** and **508** are racemic, investigating the effects of double asymmetric induction upon conjugate addition of either antipode of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **77** was not possible and therefore their mutual kinetic resolution with (*RS*)-**77** was evaluated instead. The 69:31 regioisomeric mixture of **507** and **508** was subsequently treated with 1.6 equiv of lithium amide (*RS*)-**77** under standard conditions for

the conjugate addition of lithium amides to α,β-unsaturated esters (i.e., in THF at –78 °C for 2 h followed by the addition of satd aq NH_4Cl). Analysis of the ^1H NMR spectrum of the crude reaction mixture revealed the presence of multiple C(α)*Me* group containing products and no remaining starting material. However, purification *via* flash column chromatography resulted only in the isolation of **512** in 6% yield as a single diastereoisomer (>99:1 dr). No product corresponding to the connectivity within β-amino ester **511** [i.e., an amino group at the C(1) position] arising from conjugate addition to regioisomer **508** was isolated (Scheme 96).



Scheme 96. *Reagents and conditions*: (i) (*RS*)-**77**, THF, –78 °C, 2 h. [[a] 80% purity].

The connectivity within β-amino ester **512** was assigned by full ^1H and ^{13}C NMR spectroscopic analyses, and most importantly a long-range ^1H–^{13}C HMBC heteronuclear correlation experiment. The HMBC correlation of the C(7a)*H* proton at δ_H = 4.19 ppm to the *C*O$_2^t$Bu carbonyl carbon at δ_C = 170.3 ppm established the position of the ester group at C(1). In addition, resonances corresponding to the C(3)H_2 group at δ_H = 3.08 and 3.38 ppm were correlated with the *C*(2) carbon at δ_C = 65.9 ppm, with no correlation to the *C*O$_2^t$Bu carbonyl group being observed, thereby supporting the presence of the amino group at C(2). Furthermore, the relative configuration of the stereogenic centres at C(1), C(2) and C(7a) within **512** was assigned by ^1H NMR nOe analysis. A reciprocal interaction between the C*Me*$_3$ group and the C(α)*H* proton was indicative of a *syn*-relationship between the ester and amino groups. Another series of enhancements were similarly instructive with the irradiation of the C(1)*H* proton resulting in strong correlations to the C(2)*H* and C(7a)*H* proton signals, and the irradiation of the C(7a)*H* proton showing an nOe enhancement to the C(2)*H* proton. These results collectively suggest that C(1)*H*, C(2)*H* and C(7a)*H* protons are on the same face of the bicyclic system (Figure 45).

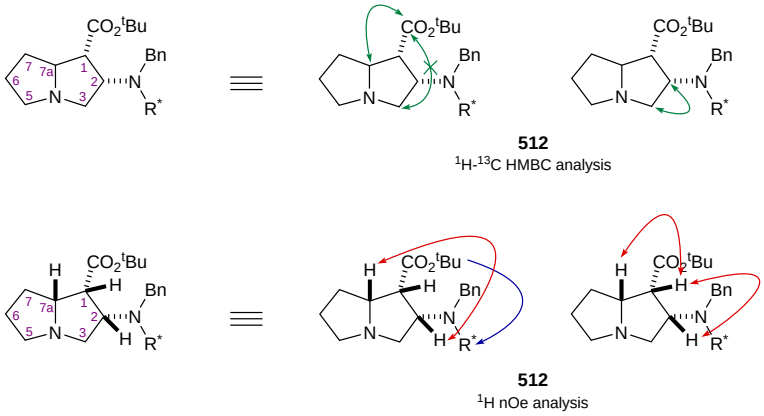
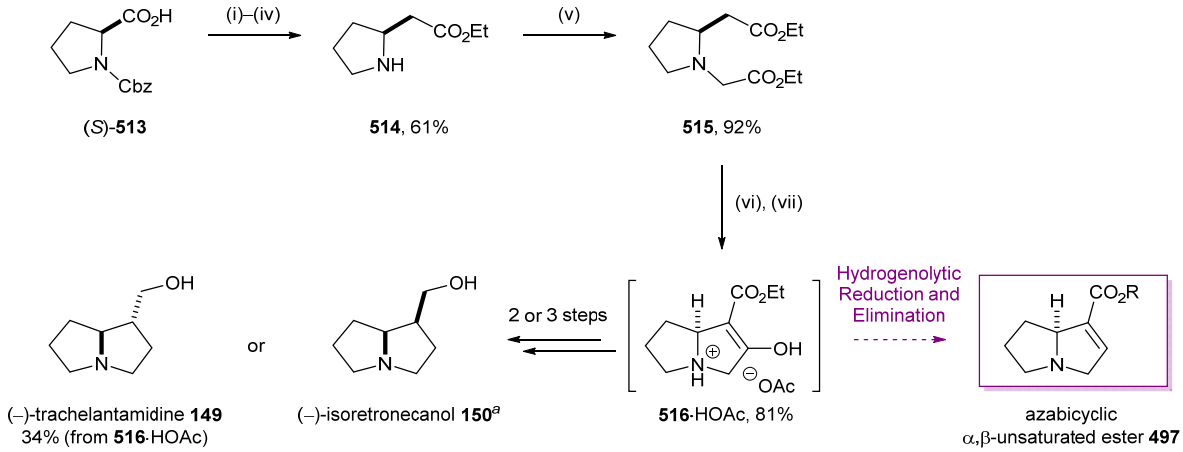


Figure 45. Representation of the $^{1}H–^{13}C$ HMBC and ^{1}H NMR nOe correlations observed within **512**. [‘‘↔’’ represents reciprocal interaction; R^{*} = α-methylbenzyl].

Owing to the fact that the azabicyclic α,β-unsaturated ester could not be synthesised regioselectively and that the conjugate addition reaction resulted in an azabicyclic β-amino ester in poor yield, it was not possible to conclude anything about the level of enantiorecognition observed between these chiral substrates and the chiral lithium amide reagent. Therefore, synthetic endeavours within this route were not pursued further and an alternative strategy for the synthesis of a single regioisomeric azabicyclic α,β-unsaturated ester was next investigated.

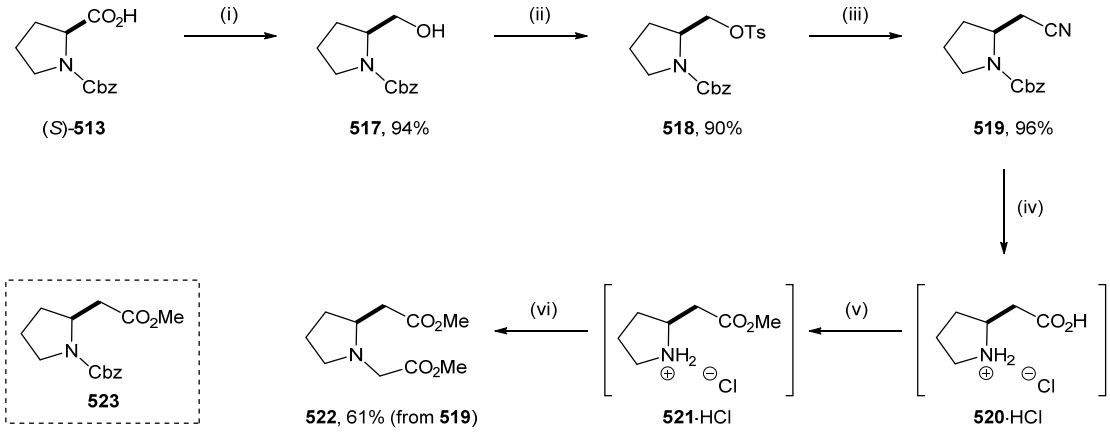
5.3.2. Synthesis of a single regioisomeric azabicyclic α,β-unsaturated ester

As a potential solution to the regioselectivity problem encountered with in the preparation of α,β-unsaturated esters **507** and **508**, it was envisaged that adopting a route developed by Benn and Rüeger[13] for their syntheses of (–)-trachelantamidine **149** and (–)-isoretronecanol **150** would allow access to only one regioisomer **497**. The authors reported a five-step reaction sequence to prepare diethyl ester **515** in 56% overall yield from commercially available *N*-Cbz-protected (*S*)-proline (*S*)-**513**. The azabicyclic ring system was subsequently constructed upon Dieckmann cyclisation of **515**. For the present case, it was anticipated that the Dieckmann product **516**·HOAc could be readily converted to an azabicyclic α,β-unsaturated ester **497** by sequential hydrogenolytic reduction and elimination (Scheme 97).



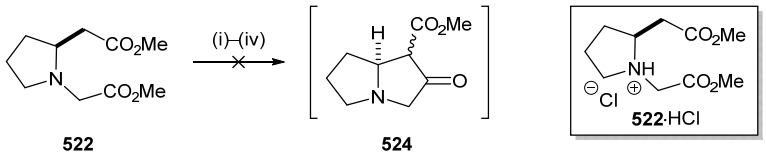
Scheme 97. *Reagents and conditions*: (i) $BH_3 \cdot Me_2S$; (ii) *p*-TsCl, pyridine; (iii) NaCN, DMSO; (iv) HCl/EtOH; (v) ethyl bromoacetate, Na_2CO_3; (vi) NaOEt; (vii) $AcOH/H_2O$. [[a] Yield for the elaboration of **516**·HOAc to **150** was not reported.]

Efforts were therefore next focused on the preparation of diester **522** from *N*-Cbz-protected (*S*)-proline (*S*)-**513**. Homologation of **513** was achieved by a reduction/tosylation/cyanide displacement reaction sequence. Reduction of the carboxylic acid moiety[14] within **513** upon treatment with $BH_3 \cdot Me_2S$ in THF gave *N*-Cbz-protected (*S*)-prolinol **517** in 94% yield. Subsequent treatment of **517** with *p*-TsCl[15] followed by reaction with KCN at 90 °C for 6 h[16,17] furnished nitrile **519**, which was isolated in 81% yield (over 3 steps from **513**). Treatment of **519** with $SOCl_2$ in MeOH at reflux for 16 h failed to yield any *N*-Cbz-protected methyl ester **523**, and instead resulted in the formation of a complex mixture of products. Alternatively, acid-catalysed hydrolysis[18] of **519** in 9.0 M aq HCl proved successful, with both hydrolysis of the nitrile group and removal of the *N*-Cbz group being observed under these conditions. Esterification of **520**·HCl gave methyl ester **521**·HCl and was followed by *N*-alkylation using methyl bromoacetate to give diester **522** in 6 steps and 50% overall yield from commercially available (*S*)-**513** (Scheme 98).



Scheme 98. *Reagents and conditions*: (i) $BH_3 \cdot Me_2S$, THF, 0 °C then rt, 16 h; (ii) *p*-TsCl, pyridine, 0 °C then rt, 16 h; (iii) KCN, DMSO, 90 °C, 6 h; (iv) HCl (9.0 M aq), reflux, 64 h; (v) 1.25 M HCl/MeOH, reflux, 4 h; (vi) Na_2CO_3, methyl bromoacetate, MeOH, reflux, 16 h.

With diester **522** in hand, attention turned to the condensation step to access β-keto ester **524**. Unfortunately, cyclisation of **522** proved fruitless in every attempt with only returned starting material (as the corresponding hydrochloride salt **522**·HCl)[19] being observed. Repeated attempts at the treatment of **522** with freshly prepared NaOMe in PhMe at rt failed to yield **524**. Following literature conditions,[20,21] reaction of **522** with NaOMe in refluxing PhMe for 30 min up to 5 h only resulted in the formation of **522**·HCl. Diester **522** also failed to cyclise upon treatment with KHMDS in PhMe under the conditions used by Trauner and co-workers[22] to affect condensation of a functionalised pyrrolidine diethyl ester (Scheme 99). No trace of β-keto ester **524** (or its tautomer) could be detected by mass spectrometry or ^{1}H NMR spectroscopic analysis in the crude reaction mixtures, so the route was consequently abandoned.



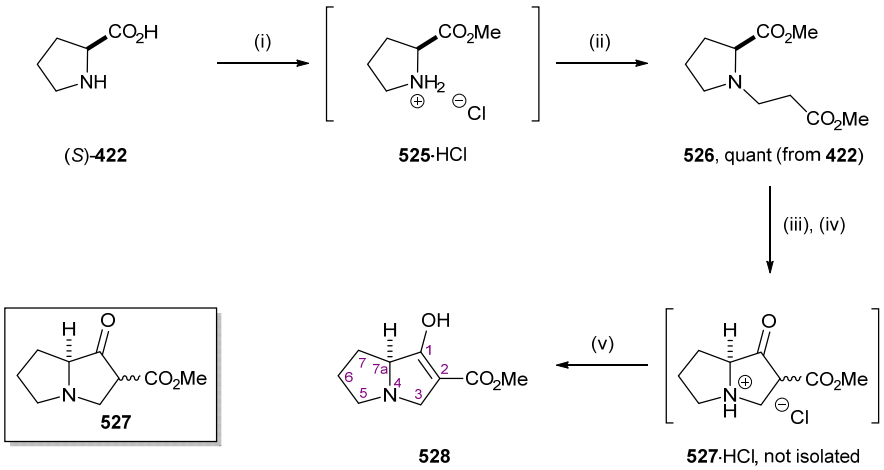
522 **524** **522**·HCl

Conditions	Result
(i)	Returned starting material as **522**·HCl
(ii)	Returned starting material as **522**·HCl
(iii)	Returned starting material as **522**·HCl
(iv)	Returned starting material as **522**·HCl

Scheme 99. *Reagents and conditions*: (i) NaOMe, PhMe, rt, 1.5 h then HCl (1.0 M aq), rt, 30 min; (ii) NaOMe, PhMe, rt, 1.5 h then reflux, 30 min then HCl (1.0 M aq), rt, 30 min; (iii) NaOMe, PhMe, reflux, 5 h then HCl (1.0 M aq), rt, 30 min; (iv) KHMDS, PhMe, 0 °C then rt, 1.5 h.

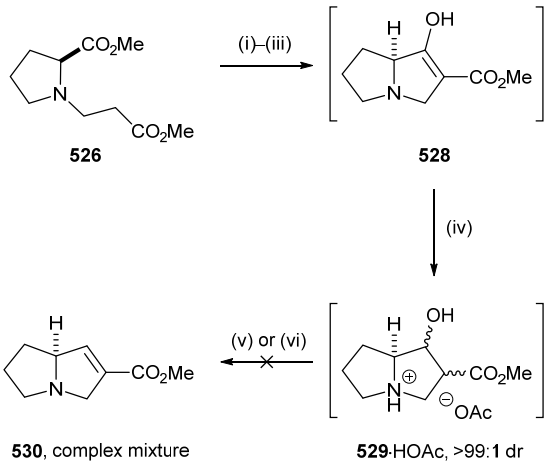
As the preparation of **524** was proving difficult, attention was next shifted to the synthesis of the regioisomeric β-keto ester **527** following a similar approach (i.e., using a Dieckmann cyclisation as the key step). Starting from (*S*)-proline **422**, treatment with a solution of anhydrous HCl in MeOH proceeded to give the corresponding methyl ester **525**·HCl, which was subsequently reacted with methyl 3-bromopropionate to afford **526** in quantitative yield over the two steps. In contrast to diester **522**, cyclisation of **526** was achieved upon treatment with 2.0 equiv of KHMDS in PhMe.[22,23] After stirring at rt for 1.5 h,[24] the reaction mixture was treated with 1.0 M aq HCl to afford **527**·HCl. The pH of the reaction mixture was then adjusted to ~9 by dropwise addition of 1.0 M aq NH_4OH, and ^{1}H NMR spectroscopic analysis showed that the reaction had proceeded to 100% conversion to furnish enol **528** (Scheme 100). It is noteworthy that full ^{1}H and ^{13}C NMR analysis of the crude product mixture in D_2O revealed solely the existence of the enol tautomer **528** as opposed to β-keto ester **527**. Notably, the ^{13}C NMR spectrum identified signals for *C*(1) and *C*(2) at δ_C = 177.2 ppm and

84.5 ppm, respectively. In addition, the IR spectrum of **528** showed diagnostic hydroxyl and carbonyl absorption bands at 3399 cm^{-1} and 1679 cm^{-1}, respectively, thereby confirming the structural assignment of enol **528**.



Scheme 100. *Reagents and conditions*: (i) 1.25 M HCl/MeOH, reflux, 16 h; (ii) methyl 3-bromopropionate, Na_2CO_3, MeOH, reflux, 16 h; (iii) KHMDS, PhMe, 0 °C, 30 min then rt, 1.5 h; (iv) HCl (1.0 M aq), rt, 30 min; (v) NH_4OH (1.0 M aq), rt, 30 min.

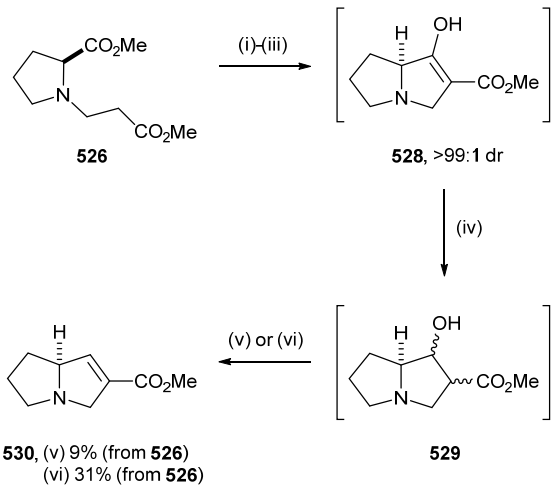
Subjection of the crude reaction mixture of **528** to hydrogenation conditions of 10% w/w Adam's catalyst (PtO_2)[25,26] in a solution of AcOH under 1 atm of H_2 for 16 h promoted full conversion to **529**·HOAc (>99:1 dr) as the sole product of undetermined configuration at C(1) and C(2). When **529**·HOAc was reacted with 1.5 equiv of $POCl_3$,[27] no α,β-unsaturated ester **530** could be isolated and a complex mixture of products was instead observed. The preparation of **530** was next attempted *via* mesylation and base-induced elimination.[28] However, mesylation of **529**·HOAc upon treatment with MsCl and Et_3N also returned a complex mixture of products (Scheme 101).



Scheme 101. *Reagents and conditions*: (i) KHMDS, PhMe, 0 °C, 30 min then rt, 1.5 h; (ii) HCl (1.0 M aq), rt, 30 min; (iii) NH_4OH (1.0 M aq), rt, 30 min; (iv) PtO_2, H_2 (1 atm), AcOH, H_2O, rt, 16 h; (v) $POCl_3$, pyridine, 0 °C, 12 min; (vi) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, 1 h then rt, 3 h.

A different set of conditions *en route* to **530** was next sought. Following reduction of **528** (prepared from **526**) with $NaBH_4$, analysis of the crude reaction mixture by ^1H NMR

spectroscopy revealed the presence of β-hydroxy ester **529**[29] as a mixture of at least three diastereoisomers identified by three CO_2Me ^1H NMR proton signals, with no remaining starting material. Dehydration of **529** was initially attempted using $POCl_3$ in the presence of pyridine. These set of reaction conditions resulted in the formation of α,β-unsaturated ester **530** as the only product, which was subsequently isolated in 9% yield (over three steps). Alternatively, reaction of **529** with MsCl and Et_3N gave **530** in an improved yield of 31% (from **526**) after chromatographic purification, representing the most efficient route to **530** (Scheme 102).[30] The synthesis of **530** was therefore completed in five steps from commercially available **422**, without isolation of intermediates **525**·HCl, **527**·HCl, **528** and **529**, in 31% overall yield.



Scheme 102. *Reagents and conditions*: (i) KHMDS, PhMe, 0 °C, 30 min then rt, 1.5 h; (ii) HCl (1.0 M aq), rt, 30 min; (iii) NH_4OH (1.0 M aq), rt, 30 min; (iv) $NaBH_4$, MeOH, 0 °C then rt, 48 h; (v) $POCl_3$, pyridine, 0 °C, 12 min; (vi) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, 1 h then rt, 3 h.

5.3.3. Predicting the effects of double asymmetric induction in the conjugate addition reactions of enantiopure lithium amides to azabicyclic α,β-unsaturated ester 530

Upon conjugate addition of a lithium amide reagent to azabicyclic α,β-unsaturated ester **530**, it was anticipated that **530** would adopt conformation **530A** whereby the ring encompassing the α,β-unsaturated ester moiety would be somewhat planar.[31] In this conformation, conjugate addition of lithium *N*,*N*-dibenzylamide **174** to **530** was expected to show a clear diastereofacial preference for the formation of azabicyclic β-amino ester **531** *via* attack of **174** on the less hindered face of α,β-unsaturated ester **530**. By analogy to the formation of previously reported[4] β-amino esters resulting from conjugate addition to azacyclic α,β-unsaturated esters, protonation of the intermediate lithium (*Z*)-β-amino enolate[32] was expected to occur *anti* to the C(1)-amino group to give **531**. Furthermore, based upon the known sense of reagent control observed for the conjugate addition of either antipode of

lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **77** to achiral α,β-unsaturated esters[33] in combination with the anticipated sense of substrate control provided by **530**, it was predicted that the conjugate addition of (*S*)-**77** would be the doubly diastereoselective "matched" pairing of chiral substrate and chiral reagent to give azabicyclic β-amino ester **532** as the major product [following protonation of the lithium (*Z*)-β-amino enolate[32] *anti* to the C(1)-amino group]. In contrast, it was anticipated that the conjugate addition of (*R*)-**77** to **530** would be the doubly diastereoselective "mismatched" pairing of chiral substrate and chiral reagent (Figure 46).

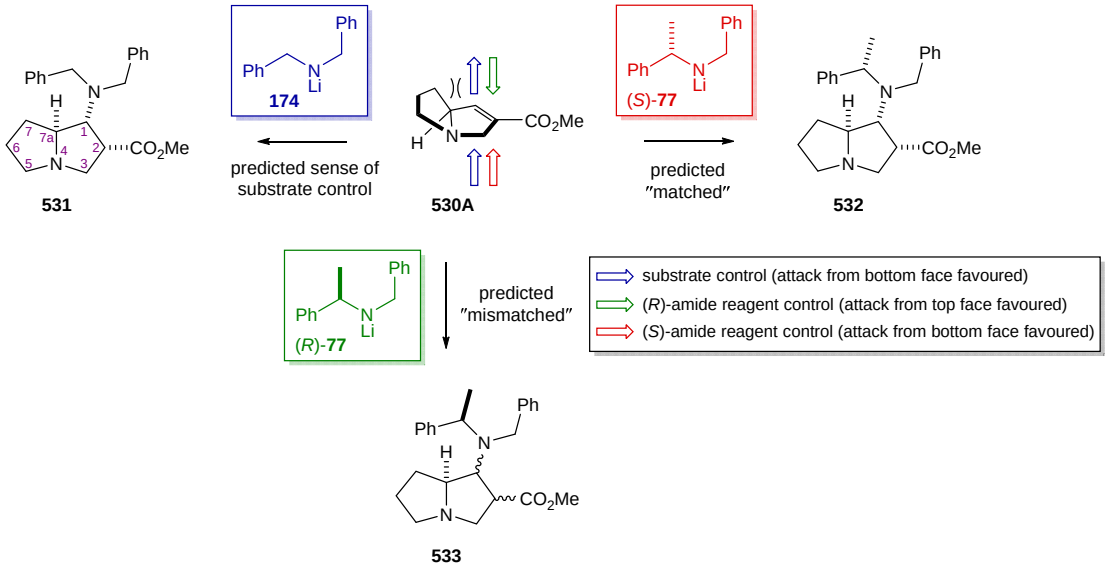
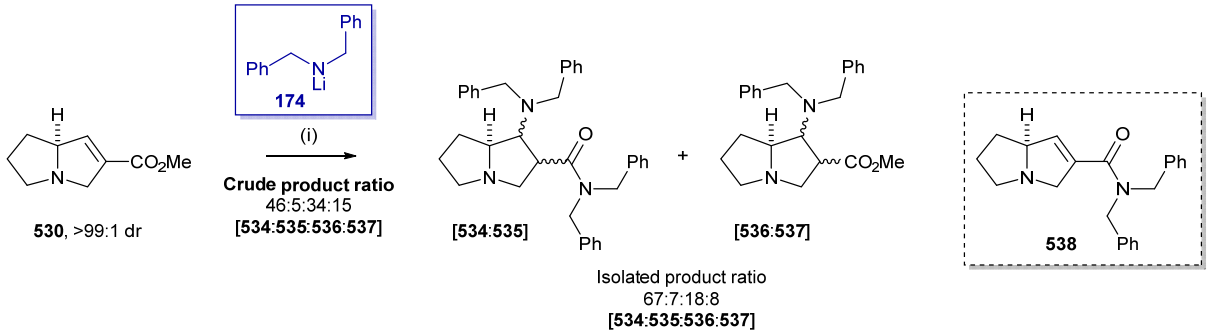


Figure 46. Model to predict double diastereoselectivity in the conjugate addition of lithium amides **174**, (*R*)-**77** and (*S*)-**77** to azabicyclic α,β-unsaturated ester **530**.

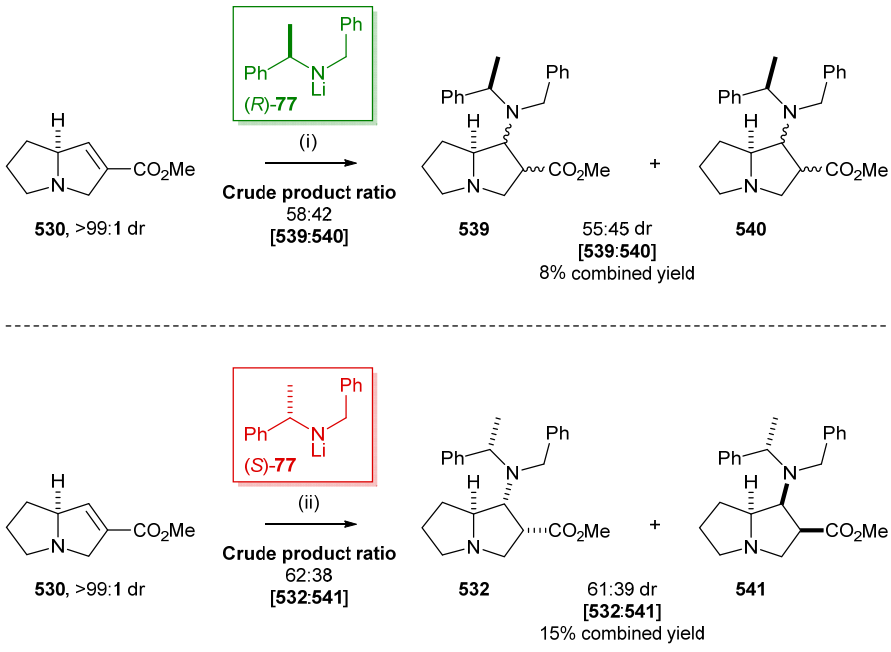
5.3.4. Conjugate additions of lithium amides to azabicyclic α,β-unsaturated ester 530

The evaluation of substrate control in the conjugate addition reaction of lithium *N*,*N*-dibenzylamide **174** to azabicyclic α,β-unsaturated ester **530** was investigated first. Reaction of **530** with 1.6 equiv of **174** resulted in a 46:5:34:15 mixture of **534**, **535**, **536** and **537**, respectively, as the only products with no sign of remaining starting material in the crude reaction mixture, as determined by ^{1}H NMR spectroscopic analysis. Amides **534** and **535** were presumably formed *via* a competing 1,2-addition pathway followed by 1,4-addition to the resultant α,β-unsaturated amide **538**. Attempted separation of the product mixture *via* flash column chromatography proved unsuccessful and resulted in the isolation of a 67:7:18:8 mixture of **534**, **535**, **536** and **537**, respectively (Scheme 103).[34] Unfortunately, it was not possible to assign configurations to **534**–**537** due to ^{1}H NMR proton signal overlap in various deuterated solvents, thus the substrate control could not be discerned from these data.



Scheme 103. *Reagents and conditions*: (i) **174** (1.6 equiv), THF, –78 °C, 2 h.

The conjugate additions of (*R*)-**77** and (*S*)-**77** to α,β-unsaturated ester **530** were next examined. Initially, both reactions gave solely returned starting material when 1.6 equiv of lithium amide was used, with no evidence of any products resulting from conjugate addition in the ^{1}H NMR and mass spectra of the crude reaction mixtures. In an effort to force the reaction to conversion, **530** was treated with 6.0 equiv of (*R*)-**77**. Although the reaction proceeded with complete consumption of starting material, a complex mixture of products was obtained, from which a 58:42 diastereoisomeric mixture of β-amino esters **539** and **540** could be identified. Upon purification by flash column chromatography, a 55:45 mixture of **539** and **540** was isolated in only 8% combined yield. The conjugate addition of 6.0 equiv of (*S*)-**77** to **530** proceeded to afford a complex mixture of products composed of unidentified compounds and a 62:38 mixture of β-amino esters **532** and **541**, respectively, with no starting material being detected. Chromatographic purification of the crude reaction mixture resulted in the isolation of an inseparable 61:39 mixture of **532** and **541**, respectively, in 15% combined yield (Scheme 104).



Scheme 104. *Reagents and conditions*: (i) (*R*)-**77** (6.0 equiv), THF, –78 °C, 2 h; (ii) (*S*)-**77** (6.0 equiv), THF, –78 °C, 2 h.

Unfortunately, the configurations of **539** and **540** formed during the conjugate addition of (*R*)-**77** to **530** could not be assigned by ^{1}H NMR nOe analysis due to unresolved resonances in the ^{1}H NMR spectrum in various deuterated solvents. The assignment of the relative configuration of the C(1), C(2) and C(7a) stereogenic centres within **532**, however, was possible by ^{1}H NMR NOESY and nOe analyses. Irradiation of the C(1)*H* proton showed an nOe enhancement to the C(2)*H* proton, hence demonstrating a *cis* orientation for the amino and ester groups. Additionally, irradiation of the C(7a)*H* proton identified two correlations to proton signals corresponding to the C(α)*H* and the NCH_2Ph group protons, thereby suggesting that the C(7a)*H* proton and the amino group are on the same face of the ring. Another series of enhancements were similarly instructive with the irradiation of the C(7)H_B proton resulting in reciprocal correlations to CO_2Me and the C(7a)*H* proton, and the irradiation of the C(7)H_A proton showing a reciprocal enhancement to the C(2)*H* proton. Moreover, ^{1}H NMR nOe enhancements between the C(5)H_A and C(1)*H* protons were observed together with a correlation between the C(5)H_B and the C(7a)*H* protons. Furthermore, the relative configuration within **541** was tentatively assigned by ^{1}H NOESY analysis. The presence of a reciprocal correlation between CO_2Me and the C(α)*H* proton was consistent with a *syn*-relationship between the ester and amino groups. Additionally, irradiation of the proton at C(1) further complemented this result since an nOe enhancement was observed between the C(1)*H* and C(2)*H* protons (Figure 47).

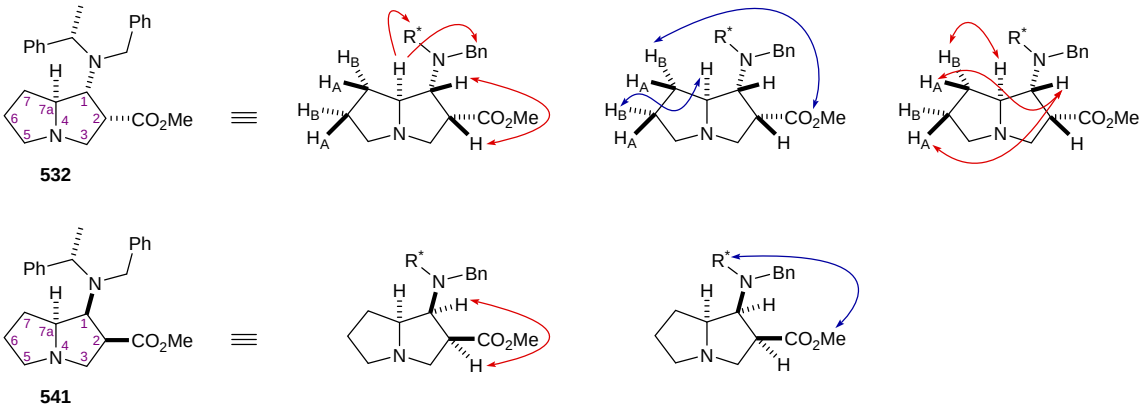


Figure 47. Representation of ^{1}H NMR NOESY and nOe correlations observed within **532** and **541**. [''↔'' represents reciprocal interaction; R* = (*S*)-α-methylbenzyl].

The absolute configurations within (1*R*,2*R*,7a*S*,α*S*)-**532** and (1*S*,2*S*,7a*S*,α*S*)-**541** were assigned in each case relative to the known configuration of the (*S*)-proline derived C(7a) stereogenic centre. The assigned relative 1,2-*syn*-configurations within **532** and **541** illustrates that protonation of the intermediate lithium (*Z*)-β-amino enolate[32] occurred *anti* to the C(1)-amino group in both cases, as predicted.[35] However, it is evident that the diastereoselectivity

observed for the conjugate addition of (*S*)-**77** to **530** (62:38 dr) is not consistent with that predicted for a doubly diastereoselective[36] "matched" pairing of reagent and substrate and therefore this substrate does not conform to the classical "matching" and "mismatching" pattern usually exhibited by this class of reaction.[37,38] The low isolated yields and poor diastereoselectivities observed upon conjugate addition of (*R*)-**77** or (*S*)-**77** to azabicyclic α,β-unsaturated ester **530**, therefore, precluded the synthesis of the target azabicyclic β-amino acids **109** and **488**. Consequently, further studies were directed towards the use of an alternative nucleophile in conjugate addition to **530**.

5.3.5. Conjugate addition of a Grignard reagent to azabicyclic α,β-unsaturated ester 530

Transformation of azabicyclic α,β-unsaturated ester **530** into 1-phenyl-2-carboxy pyrrolizidine **543** was next explored using the protocol developed in Chapter 3. Thus, reaction of **530** with PhMgBr was proposed to proceed with 1,4-addition to give **542**. It was thereby envisaged that **542** could be readily elaborated to **543** *via* ester hydrolysis (Figure 48).

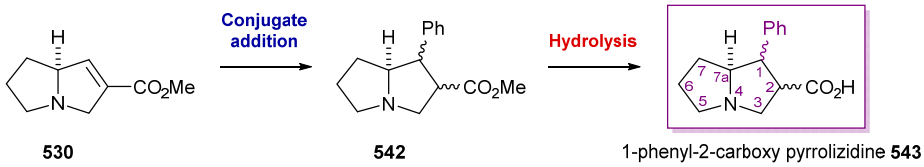
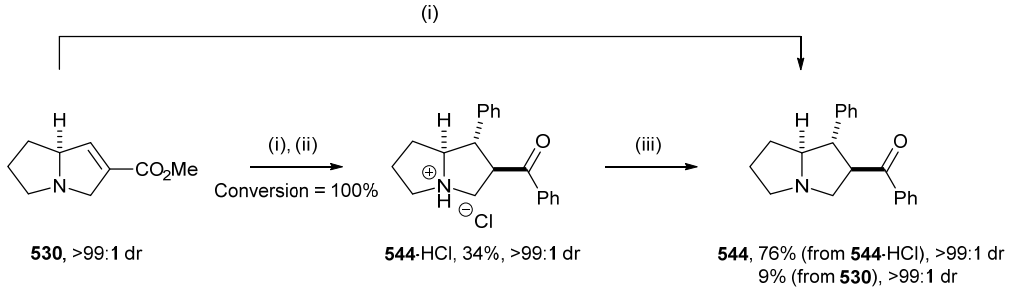


Figure 48. Proposed route through to 1-phenyl-2-carboxy pyrrolizidine **543**.

Under reaction conditions analogous to those previously employed for the conjugate addition of PhMgBr to β'-amino-α,β-unsaturated ester **107** (see Chapter 3), **530** was treated with 10.0 equiv of PhMgBr in THF at –20 °C for 4 h which gave clean conversion to 1-phenyl-2-benzoyl pyrrolizidine **544**, as a consequence of sequential 1,2- and 1,4-addition reactions. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture indicated that no conjugate addition product **542**, arising from exclusive 1,4-addition to α,β-unsaturated ester **530**, was formed. Upon chromatographic purification, **544** was obtained as a single diastereoisomer (>99:1 dr), albeit in only 9% yield. A superior yield was obtained when the hydrochloride salt of **544** was prepared and purified by column chromatography, which gave **544**·HCl in 34% isolated yield and >99:1 dr. Subsequent treatment of **544**·HCl to a basic work-up with $NaHCO_3$ gave **544** in a slightly improved overall yield of 26% (from **530**) and >99:1 dr (Scheme 105).



Scheme 105. *Reagents and conditions*: (i) PhMgBr (10 equiv), THF, –20 °C, 4 h; (ii) HCl (1.0 M in Et_2O), rt; (iii) $NaHCO_3$, CH_2Cl_2, rt, 30 min.

The relative configuration within **544** was assigned by ^{1}H NMR NOESY analysis. Irradiation of the C(7a)*H* proton showed a correlation to the protons of the phenyl group at C(1) and a reciprocal correlation to the C(7)H_B proton. This result was corroborated by the observed reciprocal correlation between the C(7)H_A and the C(1)*H* protons. Additionally, a correlation between the C(2)*H* proton and the phenyl group at C(1), together with a reciprocal nOe enhancement between the C(2)*H* and the C(7a)*H* protons were indicative of a 1,2-*anti* relationship within **544** (Figure 49). It is noteworthy that the stereochemical outcome of the reaction of **530** with PhMgBr is consistent with the anticipated sense of substrate control (see Section 5.3.3).

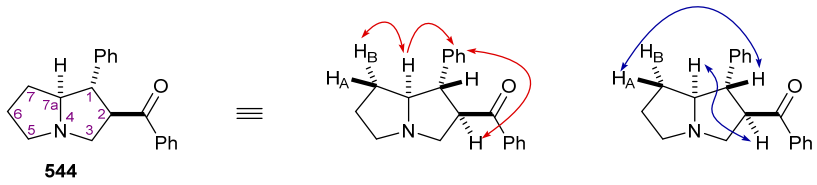


Figure 49. Representation of ^{1}H NMR NOESY correlations observed within **544**. [‘‘↔’’ represents reciprocal interaction].

5.4. Conclusion

In conclusion, a strategy starting from (*S*)-proline was developed to access azabicyclic α,β-unsaturated ester **530**, upon which conjugate addition reactions could be attempted. Conjugate addition of lithium amides to **530** provided inseparable mixtures of β-amino esters **545** in low to moderate diastereoselectivity. Furthermore, attempted conjugate addition of a Grignard reagent to access 1-phenyl-2-carboxy pyrrolizidine **543** furnished instead 1-phenyl-2-benzoyl pyrrolizidine **544**, owing to a competitive 1,2-addition pathway followed by 1,4-addition to the resultant α,β-unsaturated ketone. It is thereby apparent that conjugate addition reactions to this azabicyclic scaffold are not as straightforward when compared to previously reported[4,5] γ-amino-α,β-unsaturated esters, and further investigations concerning the asymmetric synthesis of such azabicyclic β-amino acids are required. An azabicyclic β-amino ester **548** could alternatively be synthesised from β-keto ester **527** *via* reductive

amination with benzylamine **546** followed by diastereoselective reduction of the resultant imine **547**. The deprotection of azabicyclic β-amino ester **548** into azabicyclic β-amino acid **109** could then also be explored. Alternatively, azabicyclic β-amino ester **551** could be obtained from the conjugate addition of a lithium amide reagent to azacyclic α,β-unsaturated ester **549**, followed by ring-closing metathesis. Subsequent reduction and deprotection of **551** would then reveal the target azabicyclic β-amino acid **109** (Figure 50).

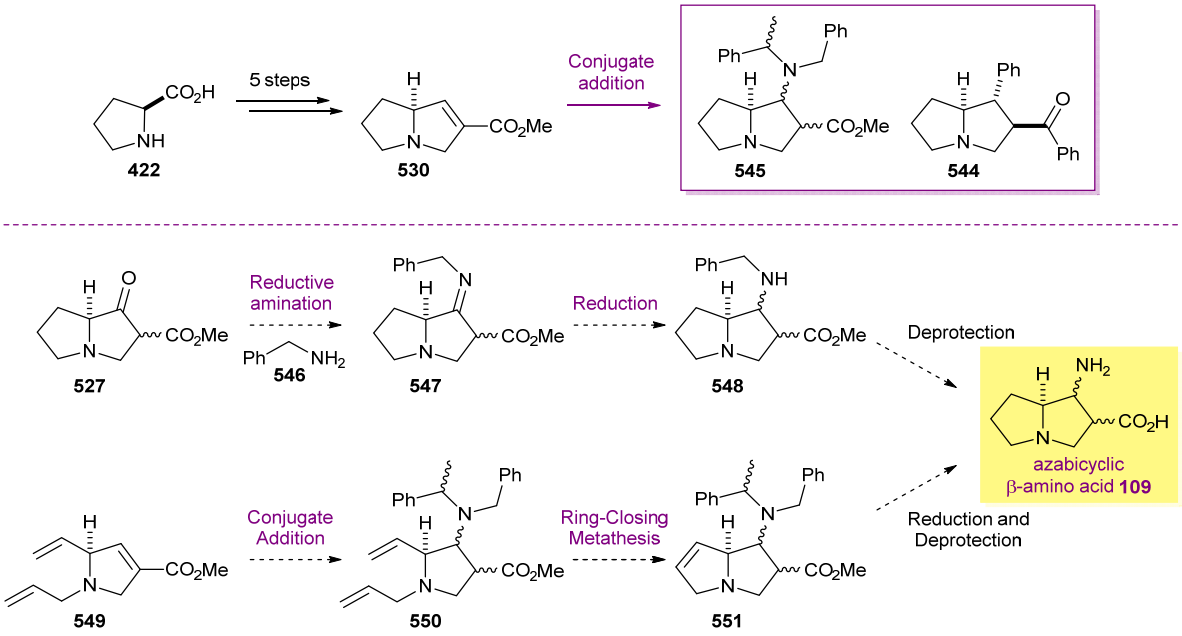


Figure 50. Products of conjugate addition **544** and **545** from azabicyclic α,β-unsaturated ester **530** and potential synthetic strategies for the preparation of azabicyclic β-amino acid **109**.

5.5. Summary

Two synthetic approaches have been developed for the asymmetric synthesis of previously inaccessible C(5)-substituted 1,2-*anti*-1,5-*syn*-transpentacins **111**. Firstly, the Ireland-Claisen rearrangement of stereodefined β-amino allyl esters **104** provided access to enantiopure α-substituted β-amino ester products **244**, which were then elaborated to **111** by ring-closing metathesis, followed by hydrogenolytic reduction and deprotection. An alternative route to **111** made use of a diastereoselective conjugate addition/elimination strategy to furnish enantiopure β'-amino-α,β-unsaturated ester **107**. Chemo- and diastereoselective conjugate addition reactions of organometallic reagents and lithium amides to **107**, followed by deprotection enabled the asymmetric synthesis of 1,2-*anti*-1,5-*syn*-transpentacins **111** and β,β'-diamino compounds **552** in short sequence. Subsequent studies focused on investigating conjugate addition reactions to γ-amino-α,β-unsaturated esters **555** to access γ-amino acids **554** and azabicyclic β-amino acid **109**. Chemo- and diastereoselective conjugate addition reactions of Grignard reagents to acyclic γ-amino-α,β-unsaturated esters **377** resulted in

syn-configured β,γ-disubstituted γ-amino esters **553**. Subsequent elaboration of **553** *via* hydrogenolysis and ester hydrolysis proceeded to afford β,γ-disubstituted γ-amino acids **554**. Reaction of the corresponding azabicyclic α,β-unsaturated ester **530** with lithium amides gave mixtures of substituted pyrrolizidines **545** in poor diastereoselectivity. However, conjugate addition of PhMgBr to **530** resulted in the exclusive formation of 1-phenyl-2-benzoyl pyrrolizidine **544** as a consequence of 1,2-addition followed by 1,4-addition (Figure 51).

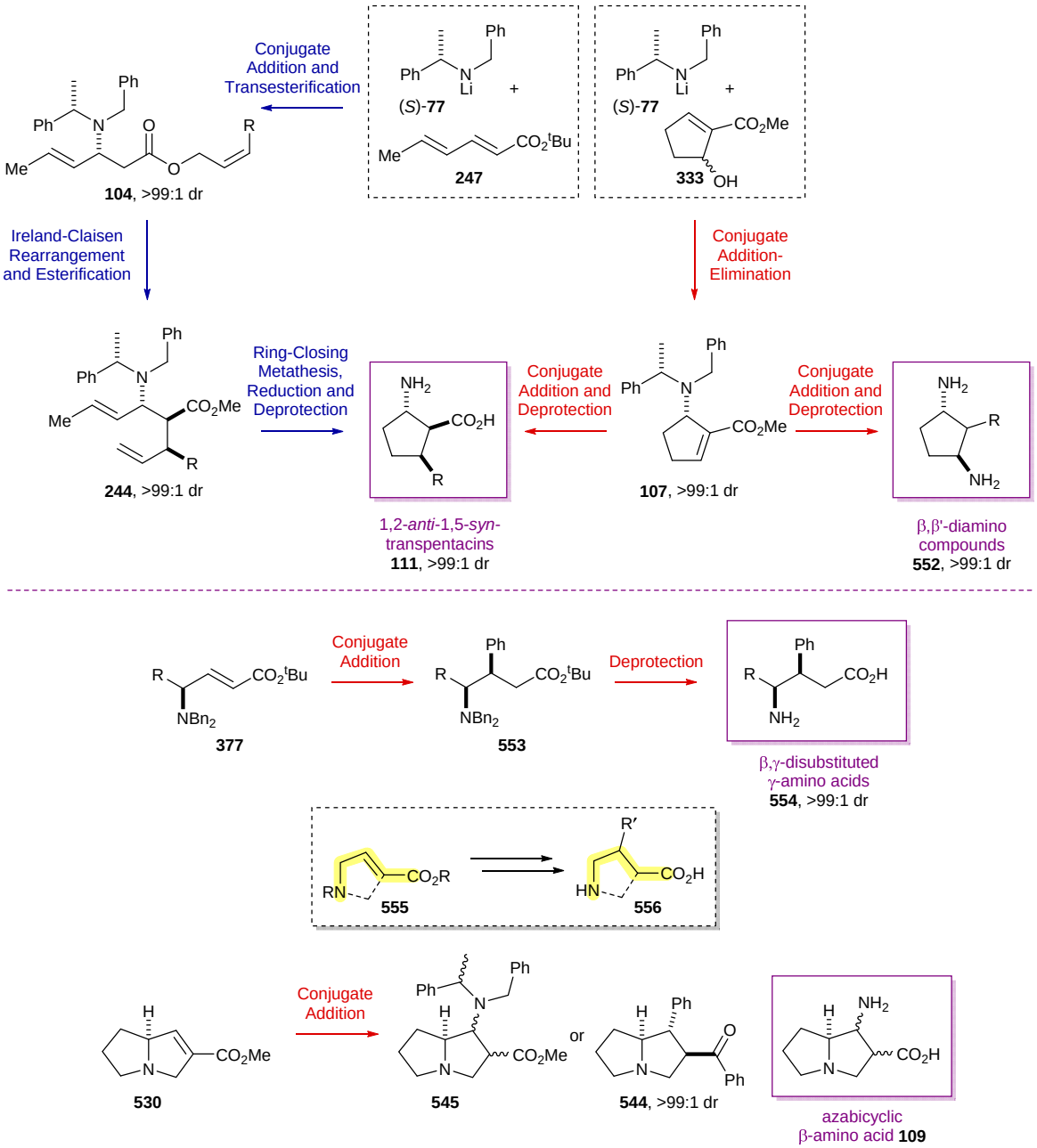


Figure 51. Summary of synthetic strategies towards the preparation of C(5)-substituted 1,2-*anti*-1,5-*syn*-transpentacins **111**, β,β'-diamino compounds **552**, β,γ-disubstituted γ-amino acids **554** and azabicyclic β-amino acid **109**.

5.6. References and notes

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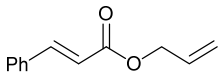
Chapter 6: Experimental

6.1. 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 a flow of nitrogen prior to use. Solvents were dried according to the procedure outlined by Grubbs and co-workers[1] or by storage over molecular sieves. Water was purified by an Elix® UV-10 system. BuLi was supplied as a solution in hexanes and titrated against diphenylacetic acid prior to use. All other solvents (analytical or HPLC grade) and reagents were used as supplied. Organic layers were dried over $MgSO_4$ and the dessicant removed by filtration prior to concentration *in vacuo*. 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 on a glass column, or on a Biotage SP4 flash column chromatography platform. Melting points were recorded on a Leica Gallen III apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 or 341 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer using an ATR module (ATR) with selected characteristic peaks reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated. The field was locked by external referencing to the relevant deuteron resonance. Chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. ^1H–^1H COSY, ^1H–^{13}C HSQC and ^1H–^{13}C HMBC analyses were used to establish atom connectivity. Low-resolution mass spectra were recorded on either a Micromass LCT Premier or Agilent Quadrupole 6120 LC/MS spectrometer. Accurate mass measurements were run on a Bruker MicroToF internally calibrated with polyalanine.

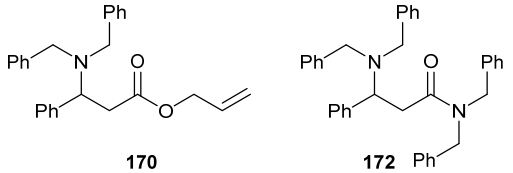
6.2. Experimental for Chapter 2

Prop-2'-en-1'-yl (*E*)-3-phenylprop-2-enoate 169



Et_3N (16.6 mL, 120 mmol) was added dropwise to a stirred solution of cinnamoyl chloride **168** (10.0 g, 60.0 mmol, >99:1 dr) and allyl alcohol (6.15 mL, 90.0 mmol) in CH_2Cl_2 (100 mL) at 0 °C. The resultant mixture was allowed to warm to rt and stirred at rt for 16 h. The reaction mixture was then washed with H_2O (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed sequentially with 1.0 M aq HCl (200 mL), 10% aq NaOH (200 mL) and brine (200 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent, 30–40 °C petrol/Et_2O, 99:1) gave **169** as a colourless oil (10.1 g, 89%, >99:1 dr);[2] ν_{max} (ATR) 2943 (C–H), 1711 (C=O), 1637 (C=C); δ_H (400 MHz, $CDCl_3$) 4.60–4.62 (2H, m, C(1')H_2), 5.17 (1H, dd, *J* 10.4, 1.4, C(3')H_A), 5.27 (1H, dd, *J* 17.2, 1.4, C(3')H_B), 5.85–5.94 (1H, m, C(2')*H*), 6.36 (1H, d, *J* 16.0, C(2)*H*), 7.26–7.28 (3H, m, *Ph*), 7.40–7.42 (2H, m, *Ph*), 7.62 (1H, d, *J* 16.0, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 65.1 (*C*(1')), 117.7 (*C*(2)), 118.1 (*C*(3')), 128.0, 128.8, 130.2 (*o*,*m*,*p*-*Ph*), 132.2 (*C*(2')), 134.2 (*i*-*Ph*), 144.9 (*C*(3)), 166.4 (*C*(1)); *m*/*z* (ESI^+) 211 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{12}H_{12}NaO_2^+$ ($[M+Na]^+$) requires 211.0730; found 211.0727.

Prop-2'-en-1'-yl (*RS*)-3-(*N*,*N*-dibenzylamino)-3-phenyl-propanoate 170 and *N*,*N*-dibenzyl (*RS*)-3-(*N*',*N*'-dibenzylamino)-3-phenyl propionamide 172



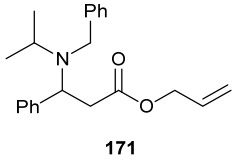
170 **172**

Method A: $SOCl_2$ (2.15 mL, 29.9 mmol) was added dropwise to a stirred solution of **178** (4.00 g, 9.96 mmol) in allyl alcohol (40 mL) at 0 °C and the resultant mixture was stirred at 50 °C for 3 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*, the residue was dissolved in CH_2Cl_2 (150 mL), and the resultant solution was washed with satd aq $NaHCO_3$ (3 × 150 mL). The organic layer was then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **170** as a colourless oil (3.30 g, 86%); ν_{max} (ATR) 2934 (C–H), 1735 (C=O), 1602 (C=C); δ_H (400 MHz, $CDCl_3$) 2.69 (1H, dd, *J* 14.4, 7.3, C(2)H_A), 3.07 (1H, dd, *J* 14.4, 7.3, C(2)H_B),

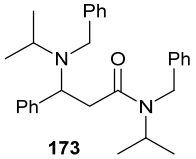
3.11 (2H, d, *J* 13.9, N(C*H*$_A$H$_B$Ph)$_2$), 3.69 (2H, d, *J* 13.9, N(CH$_A$*H*$_B$Ph)$_2$), 4.25 (1H, t, *J* 7.3, C(3)*H*), 4.38–4.55 (2H, m, C(1')*H*$_2$), 5.09–5.17 (2H, m, C(3')*H*$_2$), 5.69–5.79 (1H, m, C(2')*H*), 7.12–7.31 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 36.6 (*C*(2)), 53.7 (N(*C*H$_2$Ph)$_2$), 58.9 (*C*(3)), 65.3 (*C*(1')), 118.3 (*C*(3')), 126.9, 127.5, 128.1, 128.2, 128.6, 128.8 (*o*,*m*,*p*-*Ph*), 132.1 (*C*(2')), 137.4, 139.5 (*i*-*Ph*), 171.3 (*C*(1)); *m*/*z* (ESI$^+$) 408 ([M+Na]$^+$, 100%), 386 ([M+H]$^+$, 70%); HRMS (ESI$^+$) $C_{26}H_{28}NO_2^+$ ([M+H]$^+$) requires 386.2115; found 386.2101.

Method B: BuLi (2.0 M in hexanes, 0.82 mL, 1.65 mmol) was added dropwise to a solution of dibenzylamine (335 mg, 1.70 mmol) in THF (7 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of **169** (200 mg, 1.06 mmol, >99:1 dr) in THF (3 mL) at −78 °C was then added dropwise *via* cannula, and the reaction mixture was stirred at −78 °C for 2 h. Satd aq NH_4Cl (2 mL) was then added and the reaction mixture was allowed to warm to rt. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic extracts were washed sequentially with 10% aq citric acid (20 mL), satd aq $NaHCO_3$ (20 mL) and brine (20 mL), then dried and concentrated *in vacuo* to give a 55:45 mixture of **170** and **172**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petrol/EtOAc, 99:1) gave **170** as a colourless oil (105 mg, 26%). Further elution (eluent 30–40 °C petrol/EtOAc, 93:7) gave **172** as a colourless oil (111 mg, 20%);[3] δ_H (400 MHz, $CDCl_3$) 2.91 (2H, d, *J* 7.3, C(2)*H*$_2$), 3.42 (4H, d, *J* 14.0, N(C*H*$_2$Ph)$_2$), 3.42 (4H, d, *J* 17.2, PhC*H*$_2$NCO), 4.36–4.45 (3H, m, PhC*H*$_2$NCO, C(3)*H*), 6.90–6.93 (4H, m, *Ph*), 7.06–7.29 (21H, m, *Ph*).

Prop-2'-en-1'-yl (*RS*)-3-(*N*-isopropyl-*N*-benzylamino)-3-phenylpropanoate 171 and *N*-isopropyl-*N*-benzyl (*RS*)-3-(*N*-isopropyl-*N*-benzylamino-3-phenylpropionamide 173



171



173

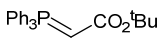
Method A: $SOCl_2$ (2.44 mL, 33.9 mmol) was added dropwise to a stirred solution of **179** (4.00 g, 11.3 mmol) in allyl alcohol (40 mL) at 0 °C and the resultant mixture was stirred at 50 °C for 3 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*, the residue was dissolved in CH_2Cl_2 (150 mL), and the resultant solution was washed with satd aq $NaHCO_3$ (3 × 150 mL). The organic layer was then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **171** as a colourless oil (2.94 g, 77%); ν_{max} (ATR) 2965, 2934 (C–H), 1735 (C=O), 1601 (C=C); δ_H

(400 MHz, $CDCl_3$) 0.71 (3H, d, *J* 6.6, CH*Me*$_A$), 0.98 (3H, d, *J* 6.6, CH*Me*$_B$), 2.55 (1H, dd, *J* 14.4, 8.5, C(2)*H*$_A$), 2.87 (1 H, dd, *J* 14.4, 6.9, C(2)*H*$_B$), 3.01 (1H, septet, *J* 6.6, C*H*Me$_2$), 3.61 (2H, d, *J* 15.1, NC*H*$_2$Ph), 4.25 (1H, dd, *J* 8.5, 6.9, C(3)*H*), 4.29–4.40 (2H, m, C(1')*H*$_2$), 5.04–5.10 (2H, m, C(3')*H*$_2$), 5.62–5.71 (1H, m, C(2')*H*), 7.12–7.31 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.4, 21.4 (CH*Me*$_2$), 38.9 (*C*(2)), 47.9 (*C*HMe$_2$), 49.3 (N*C*H$_2$Ph), 60.0 (*C*(3)), 65.0 (*C*(1')), 118.0 (*C*(3')), 126.5, 127.1, 128.0, 128.1 (*o*,*m*,*p*-*Ph*), 132.1 (*C*(2')), 141.3, 141.8 (*i*-*Ph*), 171.5 (*C*(1)); *m*/*z* (ESI$^+$) 360 ([M+Na]$^+$, 100%), 338 ([M+H]$^+$, 90%); HRMS (ESI$^+$) $C_{22}H_{28}NO_2^+$ ([M+H]$^+$) requires 338.2115; found 338.2104.

Method B: BuLi (2.0 M in hexanes, 0.82 mL, 1.65 mmol) was added dropwise to a solution of *N*-isopropyl-*N*-benylamine (254 mg, 1.70 mmol) in THF (7 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of **169** (200 mg, 1.06 mmol, >99:1 dr) in THF (3 mL) at −78 °C was then added dropwise *via* cannula, and the reaction mixture was stirred at −78 °C for 2 h. Satd aq NH_4Cl (2 mL) was then added and the reaction mixture was allowed to warm to rt. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic extracts were washed sequentially with 10% aq citric acid (20 mL), satd aq $NaHCO_3$ (20 mL) and brine (20 mL), then dried and concentrated *in vacuo* to give a 67:33 mixture of **171** and **173**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petrol/EtOAc, 99:1) gave **171** as a colourless oil (126 mg, 35%). Further elution (eluent 30–40 °C petrol/EtOAc, 93:7) gave **173** as a colourless oil (103 mg, 20%);[3] ν_{max} (film) 2967, 2932 (C–H), 1638 (C=O), 1494 (C=C); δ_H (400 MHz, $CDCl_3$) *Rotamer 1*: 0.73–0.79 (6H, m, NCH*Me*$_A$, CONCH*Me*$_A$), 0.85–0.89 (6H, m, NCH*Me*$_B$, CONCH*Me*$_B$), 2.26 (1H, dd, *J* 14.8, 9.7, C(2)*H*$_A$), 2.45 (1H, dd, *J* 14.8, 3.9, C(2)*H*$_B$), 2.86 (1H, app dt, *J* 12.9, 6.6, NC*H*Me$_2$), 3.45 (1H, d, *J* 15.9, NC*H*$_A$H$_B$Ph), 3.72 (1H, d, *J* 15.9, NCH$_A$*H*$_B$Ph), 3.79–3.89 (2H, m, CONC*H*$_2$Ph), 4.38–4.40 (1H, m, C(3)*H*), 4.60 (1H, m, CONC*H*Me$_2$), 6.71–6.79 (2H, m, *Ph*), 7.01–7.41 (13H, m, *Ph*); *Rotamer 2*: 0.67 (3H, d, *J* 6.6, CONCH*Me*$_A$), 0.73–0.79 (6H, m, NCH*Me*$_A$, CONCH*Me*$_B$), 1.00 (3H, d, *J* 6.6, NCH*Me*$_B$), 2.67–2.80 (2H, m, C(2)*H*$_2$), 2.99–3.06 (1H, m, NC*H*Me$_2$), 3.58 (1H, d, *J* 15.7, NC*H*$_A$H$_B$Ph), 3.66–3.74 (1H, m, CONC*H*Me$_2$), 3.79–3.89 (1H, m, NCH$_A$*H*$_B$Ph), 4.17 (1H, d, *J* 16.2, CONCH$_A$*H*$_B$Ph), 4.35 (1H, d, *J* 16.2, CONCH$_A$*H*$_B$Ph), 4.38–4.40 (1H, m, C(3)*H*), 6.71–6.79 (2H, m, *Ph*), 7.01–7.41 (13H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) *Rotamer 1*: 16.6 (CONCH*Me*$_A$), 19.9 (NCH*Me*$_A$), 21.0 (NCH*Me*$_B$, CONH*Me*$_B$), 40.2 (*C*(2)), 45.2 (CONCHMe$_2$), 45.5 (CONCH$_2$Ph), 48.9 (NCHMe$_2$), 49.3 (NCH$_2$Ph, CONCH$_2$Ph), 62.3 (*C*(3)), 125.6, 126.5, 127.1, 127.8, 127.9,

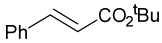
128.0, 128.0, 128.3 (*o*,*m*,*p*-*Ph*), 138.3, 139.3, 143.1 (*i*-*Ph*), 171.8 (*C*(1)); *Rotamer 2*: 17.1 (CONCH*Me*$_B$), 19.9 (NCH*Me*$_B$), 21.2 (CONCH*Me*$_A$), 21.4 (NCH*Me*$_B$), 383.7 (*C*(2)), 43.5 (CON*C*H$_2$Ph), 48.5 (CON*C*HMe$_2$), 48.7 (N*C*HMe$_2$), 61.8 (*C*(3)), 126.0, 126.0, 126.2, 126.7, 126.9, 127.6, 128.3 (*o*,*m*,*p*-*Ph*), 142.3, 143.2 (*i*-*Ph*), 170.9 (*C*(1)); *m*/*z* (ESI$^+$) 429 ([M+H]$^+$, 100%), 451 ([M+Na]$^+$, 70%); HRMS (ESI$^+$) $C_{29}H_{37}N_2O^+$ ([M+H]$^+$) requires 429.2900; found 429.2884.

tert-Butyl (triphenylphosphoranylidene)acetate 180



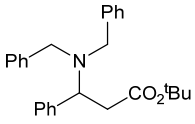
tert-Butyl bromoacetate **308** (50.0 g, 256 mmol) was added dropwise to a stirred solution of PPh_3 (67.2 g, 256 mmol) in EtOAc (330 mL) at rt, and the resultant mixture was stirred at rt for 16 h. The resultant white precipitate was then collected by filtration and washed with Et_2O (100 mL). The solid residue was added portionwise to 2.0 M aq NaOH (330 mL) at 0 °C and the resultant solution was stirred at rt for 0.5 h, followed by extraction with CH_2Cl_2 (3 × 200 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give **180** as a white solid (91.7 g, 95%);[4] mp 151 °C; {lit.[5] mp 148 °C}; δ_H (400 MHz, $CDCl_3$) 1.17 (9H, br s, C*Me*$_3$), 2.62 (1H, br s, C(2)*H*), 7.33–7.58 (15H, m, *Ph*).

tert-Butyl (*E*)-3-phenylprop-2-enoate [_tert_-Butyl cinnamate] 177



tert-Butyl (triphenylphosphoranylidene)acetate **180** (40.0 g, 106 mmol) was added portionwise to a solution of **176** (10.3 mL, 101 mmol) in CH_2Cl_2 (200 mL), and the resultant solution was stirred at rt for 48 h. The reaction mixture was then concentrated *in vacuo* and purification *via* flash column chromatography (gradient elution, 1%→5% Et_2O in 30–40 °C petrol) gave **177** as a colourless oil (20.9 g, 96%, >99:1 dr);[6] δ_H (400 MHz, $CDCl_3$) 1.47 (9H, s, C*Me*$_3$), 6.30 (1H, d, *J* 16.0, C(2)*H*), 7.28–7.32 (3H, m, *Ph*), 7.42–7.45 (2H, m, *Ph*), 7.52 (1H, d, *J* 16.0, C(3)*H*).

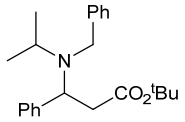
tert-Butyl (*RS*)-3-(*N*,*N*-dibenzylamino)-3-phenylpropanoate 178



BuLi (2.0 M in hexanes, 11.4 mL, 22.8 mmol) was added dropwise to a solution of *N*,*N*-dibenzylamine (4.64 g, 23.4 mmol) in THF (99 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of **177** (3.00 g, 14.7 mmol, >99:1 dr) in THF (60 mL) at −78 °C was added dropwise *via* cannula, and the resultant mixture was stirred at

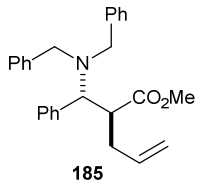
−78 °C for 2 h. Satd aq NH_4Cl (20 mL) was then added and the reaction mixture was allowed to warm to rt. The aqueous layer was extracted with Et_2O (3 × 100 mL) and the combined organic extracts were washed sequentially with 10% aq citric acid (100 mL), satd aq $NaHCO_3$ (100 mL) and brine (100 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 99:1) gave **178** as a white solid (4.30 g, 73%);[7] mp 64 °C; {lit.[7] mp 64–66 °C}; δ_H (400 MHz, $CDCl_3$) 1.26 (9H, s, CMe_3), 2.64 (1H, dd, *J* 14.4, 8.6, C(2)H_A), 2.92 (1H, dd, *J* 14.4, 7.1, C(2)H_B), 3.21 (1H, d, *J* 13.7, NCH_AH$_B$Ph), 3.64 (1H, d, *J* 13.7, NCH$_A$$H_B$Ph), 4.20 (1H, dd, *J* 8.6, 7.1, C(3)*H*), 7.13–7.30 (15H, m, *Ph*).

***tert*-Butyl (*RS*)-3-(*N*-isopropyl-*N*-benzylamino)-3-phenylpropanoate 179**

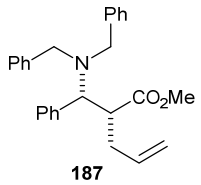


BuLi (2.0 M in hexanes, 15.2 mL, 30.4 mmol) was added dropwise to a solution of *N*-isopropyl-*N*-benzylamine (4.68 g, 31.3 mmol) in THF (99 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of **177** (4.00 g, 19.6 mmol, >99:1 dr) in THF (60 mL) at −78 °C was added dropwise *via* cannula, and the resultant mixture was stirred at −78 °C for 2 h. Satd aq NH_4Cl (20 mL) was then added and the reaction mixture was allowed to warm to rt. The aqueous layer was extracted with Et_2O (3 × 100 mL) and the combined organic extracts were washed sequentially with 10% aq citric acid (100 mL), satd aq $NaHCO_3$ (100 mL) and brine (100 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 99:1) gave **179** as a colourless oil (5.51 g, 80%);[8] δ_H (400 MHz, $CDCl_3$) 0.77 (3H, d, *J* 6.5, CHMe_A), 0.97 (3H, d, *J* 6.5, CHMe_B), 1.18 (9H, s, CMe_3), 2.46 (1H, dd, *J* 14.4, 9.4, C(2)H_A), 2.71 (1H, dd, *J* 14.4, 6.0, C(2)H_B), 2.97 (1H, app septet, *J* 6.5, C*H*Me$_2$), 3.50 (1H, d, *J* 15.2, NCH_AH$_B$Ph), 3.72 (1H, d, *J* 15.2, NCH$_A$$H_B$Ph), 4.20 (1H, dd, *J* 9.4, 6.0, C(3)*H*), 7.08–7.33 (10H, m, *Ph*).

Methyl (*RS*,*SR*)-2-(prop-2'-en-1'-yl)-3-(*N*,*N*-dibenzylamino)-3-phenylpropanoate 185 and methyl (*RS*,*RS*)-2-(prop-2'-en-1'-yl)-3-(*N*,*N*-dibenzylamino)-3-phenylpropanoate 187



185



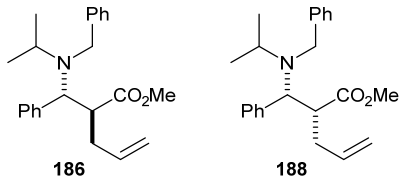
187

Method A: TMSCl (0.9 mL, 7.8 mmol) was added dropwise to a solution of **170** (1.00 g, 2.59 mmol) in PhMe (10 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 10 min. LiHMDS (1.0 M in THF, 7.8 mL, 7.8 mmol) was added dropwise and the resultant solution was stirred at −78 °C for 30 min. The reaction mixture was heated at reflux for 1 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 (100 mL) and 1.0 M aq HCl (100 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed brine (150 mL), then dried and concentrated *in vacuo*. The residue was then dissolved in MeOH (20 mL), the resultant solution was cooled to 0 °C, and $SOCl_2$ (5.6 mL, 77.8 mmol) was added dropwise. The reaction mixture was heated at 50 °C for 48 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (100 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (3 × 100 mL). The organic extract was then dried and concentrated *in vacuo* to give an 83:17 mixture of **185** and **187**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 99:1) gave **185** as a pale yellow oil (51 mg, 40%, 83:17 dr). Data for major diastereoisomer **185**: δ_H (400 MHz, $CDCl_3$) 1.69–1.73 (1H, m, C(1')H_A), 1.90–1.99 (1H, m, C(1')H_B), 2.86 (2H, d, *J* 13.6, N(C$H_A$$H_B$Ph)$_2$), 3.33 (1H, app td, *J* 11.5, 3.3, C(2)*H*), 3.67 (3H, s, O*Me*), 3.83–3.89 (3H, m, C(3)*H*, N(C$H_A$$H_B$Ph)$_2$), 4.79–4.82 (2H, m, C(3')H_2), 5.47–5.57 (1H, m, C(2')*H*), 7.08–7.36 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 34.8 (*C*(1')), 48.4 (*C*(2)), 51.4 (O*Me*), 53.7 (N(*C*H_2Ph)$_2$), 64.5 (*C*(3)), 116.6 (*C*(3')), 126.9, 127.7, 128.1, 128.2, 128.9, 129.4 (*o*,*m*,*p*-*Ph*), 133.9 (*i*-*Ph*), 135.0 (*C*(2')), 139.3 (*i*-*Ph*), 174.0 (*C*(1)). Data for minor diastereoisomer **187**: δ_H (400 MHz, $CDCl_3$) 2.22 (1H, ddd, *J* 14.0, 10.9, 8.1, C(1')H_A), 2.93 (2H, d, *J* 13.4, N(C$H_A$$H_B$Ph)$_2$), 3.08–3.12 (1H, m, C(1')H_B), 3.14 (3H, s, O*Me*), 3.24 (1H, td, *J* 10.9, 3.5, C(2)*H*), 3.75–3.82 (3H, m, C(3)*H*, N(C$H_A$$H_B$Ph)$_2$), 4.91–5.02 (2H, m, C(3')H_2), 5.64–5.74 (1H, m, C(2')*H*), 7.07–7.35 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 35.0 (*C*(1')), 48.1 (*C*(2)), 51.0 (O*Me*), 53.8 (N(*C*H_2Ph)$_2$), 63.4 (*C*(3)), 116.6 (*C*(3')), 127.0, 127.8, 128.0, 128.4, 128.8, 129.4 (*o*,*m*,*p*-*Ph*), 134.7 (*i*-*Ph*), 135.6

(*C*(2')), 139.4 (*i-Ph*), 174.0 (*C*(1)). Data for mixture: ν_{max} (ATR) 2948, 2839 (C–H), 1738 (C=O), 1603 (C=C); *m*/*z* (ESI$^+$) 422 ([M+Na]$^+$, 40%), 400 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{30}NO_2^+$ ([M+H]$^+$) requires 400.2271; found 400.2253.

Method B: LiHMDS (1.0 M in THF, 3.56 mL, 3.56 mmol) was added dropwise to a solution of **189** (508 mg, 1.19 mmol) in THF (5 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 2 h. Allyl bromide (465 μL, 5.35 mmol) was then added dropwise at −78 °C, and the resultant solution was allowed to warm to rt over 16 h. Satd aq NH_4Cl (0.5 mL) was then added and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic extracts were washed with brine (20 mL), then dried and concentrated *in vacuo* to give a 54:46 mixture of **185** and **187**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 93:7) gave **185** as a colourless oil (72 mg, 15%, 98:2 dr). Further elution (eluent 30–40 °C petrol/Et_2O, 93:7) gave a 39:61 mixture of **187** and **185**, respectively, as a colourless oil (312 mg, 66%).

Methyl (*RS*,*SR*)-2-(prop-2'-en-1'-yl)-3-(*N*-isopropyl-*N*-benzyl-amino)-3-phenylpropanoate 186 and methyl (*RS*,*RS*)-2-(prop-2'-en-1'-yl)-3-(*N*-isopropyl-*N*-benzyl-amino)-3-phenylpropanoate 188



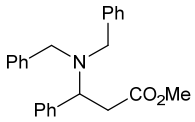
186 188

Method A: TMSCl (1.12 mL, 8.89 mmol) was added dropwise to a solution of **171** (1.00 g, 2.96 mmol) in PhMe (10 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 10 min. LiHMDS (1.0 M in THF, 8.89 mL, 8.89 mmol) was added dropwise and the resultant solution was stirred at −78 °C for 30 min. The reaction mixture was allowed to warm to rt then heated at reflux for 1 h, before being allowed to cool to rt and concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 (100 mL) and 1.0 M aq HCl (100 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed with brine (150 mL), then dried and concentrated *in vacuo*. The residue was then dissolved in MeOH (10 mL), the resultant solution was cooled to 0 °C, and $SOCl_2$ (6.39 mL, 88.9 mmol) was added dropwise. The reaction mixture was then heated at 50 °C for 48 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (100 mL), the resultant solution was washed with satd aq $NaHCO_3$ (3 × 100 mL), then dried and concentrated *in vacuo* to give a 91:9 mixture of **186** and **188**, respectively. Purification

via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 99:1) gave **186** as a pale yellow oil (640 mg, 62%, 88:12 dr). Data for major diastereoisomer **186**: δ_H (400 MHz, $CDCl_3$) 0.42 (3H, d, *J* 6.6, CH*Me*$_A$Me$_B$), 1.01 (3H, d, *J* 6.6, CHMe$_A$*Me*$_B$), 1.70–1.74 (1H, m, C(1')*H*$_A$), 1.87–1.95 (1H, m, C(1')*H*$_B$), 3.22–3.30 (2H, m, C(2)*H*, C*H*Me$_2$), 3.28 (1H, d, *J* 14.2, NCH$_A$*H*$_B$Ph), 3.60 (3H, s, O*Me*), 3.80 (1H, d, *J* 14.2, NC*H*$_A$H$_B$Ph), 3.84 (1H, d, *J* 11.6, C(3)*H*), 4.78–4.82 (2H, m, C(3')*H*$_2$), 5.47–5.57 (1H, m, C(2')*H*), 7.17–7.30 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.8, 22.7 (CH*Me*$_2$), 34.7 (*C*(1')), 47.4 (*C*(2)), 49.2 (*C*HMe$_2$), 49.5 (N*C*H$_2$Ph), 51.2 (O*Me*), 64.3 (*C*(3)), 116.4 (*C*(3')), 126.7, 127.4, 127.9, 128.3, 129.0, 129.1 (*o*,*m*,*p*-*Ph*), 135.2 (*C*(2')), 137.8, 140.4 (*i*-*Ph*), 174.4 (*C*(1)). Data for minor diastereoisomer **188**: δ_H (400 MHz, $CDCl_3$) 0.46 (3H, d, *J* 6.7, CH*Me*$_A$Me$_B$), 1.06 (3H, d, *J* 6.7, CHMe$_A$*Me*$_B$), 2.00–2.06 (1H, m, C(1')*H*$_A$), 2.86–2.92 (1H, m, C(1')*H*$_B$), 3.08 (1H, dt, *J* 11.2, 3.4, C(2)*H*), 3.14–3.19 (1H, m, C*H*Me$_2$), 3.15 (3H, s, O*Me*), 3.34 (1H, d, *J* 14.2, NC*H*$_A$H$_B$Ph), 3.72–3.76 (2H, m, NCH$_A$*H*$_B$Ph, C(3)*H*), 4.87–4.96 (2H, m, C(3')*H*$_2$), 5.58–5.68 (1H, m, C(2')*H*), 7.15–7.34 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.4, 22.8 (CH*Me*$_2$), 35.5 (*C*(1')), 47.7 (*C*(2)), 48.8 (C*H*Me$_2$), 49.2 (N*C*H$_2$Ph), 50.9 (O*Me*), 63.3 (*C*(3)), 116.2 (*C*(3')), 126.8, 127.2, 127.8, 128.2, 128.9 (*o*,*m*,*p*-*Ph*), 136.0 (*C*(2')), 138.4, 140.6 (*i*-*Ph*), 174.4 (*C*(1)). Data for mixture: ν_{max} (ATR) 2964 (C–H), 1738 (C=O), 1602 (C=C); *m*/*z* (ESI^+) 374 ($[M+Na]^+$, 50%), 352 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{23}H_{30}NO_2^+$ ($[M+H]^+$) requires 352.2271; found 352.2260.

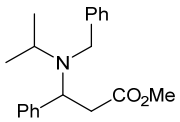
Method B: LiHMDS (1.0 M in THF, 2.27 mL, 2.27 mmol) was added dropwise to a solution of **190** (236 mg, 0.76 mmol) in THF (2.5 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 2 h. Allyl bromide (198 μL, 2.27 mmol) was then added dropwise at −78 °C, and the resultant solution was allowed to warm to rt over 16 h. Satd aq NH_4Cl (0.5 mL) was then added and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic extracts were washed with brine (20 mL), then dried and concentrated *in vacuo* to give an 81:19 mixture of **186** and **188**, respectively. Purification *via* flash column chromatography (eluent, 30–40 °C petrol/Et_2O, 98:2) gave **186** as a colourless oil (30 mg, 11%, >99:1 dr). Further elution (eluent, 30–40 °C petrol/Et_2O, 98:2) gave a 24:76 mixture of **188** and **186**, respectively (140 mg, 53%).

Methyl (*RS*)-3-(*N*,*N*-dibenzylamino)-3-phenylpropanoate 189



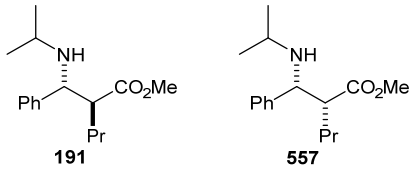
$SOCl_2$ (0.51 mL, 7.1 mmol) was added dropwise to a solution of **178** (950 mg, 2.37 mmol) in MeOH (23 mL) at 0 °C and the resultant mixture was then stirred at 50 °C for 16 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*, the residue was dissolved in CH_2Cl_2 (20 mL), and the resultant solution was washed with satd aq $NaHCO_3$ (3 × 25 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **189** as a colourless oil (649 mg, 64%);[9] δ_H (400 MHz, $CDCl_3$) 2.63 (1H, dd, *J* 14.4, 7.1, C(2)H_A), 3.05 (1H, dd, *J* 14.4, 8.9, C(2)H_B), 3.07 (1H, d, *J* 13.6, NC$H_A$$H_B$Ph), 3.53 (3H, s, O*Me*), 3.69 (1H, d, *J* 13.6, NC$H_A$$H_B$Ph), 4.21 (1H, dd, *J* 8.9, 7.1, C(3)*H*), 7.11–7.30 (15H, m, *Ph*).

Methyl (*RS*)-3-(*N*-isopropyl-*N*-benzylamino)-3-phenylpropanoate 190



$SOCl_2$ (0.31 mL, 4.24 mmol) was added dropwise to a solution of **179** (500 mg, 9.96 mmol) in MeOH (12 mL) at 0 °C and the reaction mixture was then stirred at 50 °C for 16 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (20 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (3 × 25 mL). The organic layer was then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 99:1) gave **190** as a colourless oil (330 mg, 75%); ν_{max} (ATR) 2964 (C–H), 1738 (C=O); δ_H (400 MHz, $CDCl_3$) 0.68 (3H, d, *J* 6.6, CH*Me*$_A$), 0.98 (3H, d, *J* 6.6, CH*Me*$_B$), 2.51 (1H, dd, *J* 14.5, 7.7, C(2)H_A), 2.86 (1H, dd, *J* 14.5, 7.7, C(2)H_B), 3.02 (1H, septet, *J* 6.6, C*H*Me$_2$), 3.43 (3H, s, O*Me*), 3.45 (1H, d, *J* 15.2, NC$H_A$$H_B$Ph), 3.72 (1H, d, *J* 15.2, NCH$_A$$H_B$Ph), 4.22 (1H, app t, *J* 7.7, C(3)*H*), 7.12–7.30 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.4, 21.5 (CH*Me*$_2$), 38.7 (*C*(2)), 47.7 (*C*HMe$_2$), 49.3 (N*C*H$_2$Ph), 51.4 (O*Me*), 59.8 (*C*(3)), 126.5, 127.1, 128.0, 128.1, 128.1, 128.1 (*o*,*m*,*p*-*Ph*), 141.2, 141.7 (*i*-*Ph*), 172.2 (*C*(1)); *m*/*z* (ESI$^+$) 312 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{26}NO_2^+$ ([M+H]$^+$) requires 312.1958; found 312.1949.

Methyl (*RS*,*SR*)-2-propyl-3-(*N*-isopropylamino)-3-phenylpropanoate 191 and methyl (*RS*,*RS*)-2-propyl-3-(*N*-isopropylamino)-3-phenylpropanoate 557

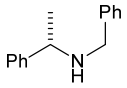


Method A: $Pd(OH)_2/C$ (50 mg, 50% w/w) was added to a degassed solution of **185** (100 mg, 0.25 mmol, 83:17 dr) in MeOH/acetone (2.5 mL, v/v 9:1) at rt. The resultant suspension was stirred vigorously under H_2 (1 atm) at rt for 16 h. The reaction mixture was then filtered through Celite® (eluent EtOAc) and the filtrate was washed with satd aq $NaHCO_3$ (10 mL), then dried and concentrated *in vacuo* to give an 83:17 mixture of **191** and **557**, respectively. Purification *via* flash column chromatography (eluent, 30–40 °C petrol/Et_2O, 93:7) gave **191** as a colourless oil (56 mg, 85%, 83:17 dr). Data for major diastereoisomer **191**: δ_H (400 MHz, $CDCl_3$) 0.67 (3H, t, *J* 7.2, C(3')H_3), 0.81 (3H, d, *J* 6.2, CHMe_AMe$_B$), 0.86 (3H, d, *J* 6.2, CHMe$_A$$Me_B$), 0.91–1.18 (3H, m, C(1')H_A, C(2')H_2), 1.32–1.42 (1H, m, C(1')H_B), 1.51 (1H, br s, N*H*), 2.40 (1H, dt, *J* 12.4, 6.2, C*H*Me$_2$), 2.51 (1H, dt, *J* 10.1, 3.5, C(2)*H*), 3.64 (3H, s, O*Me*), 3.70 (1H, d, *J* 10.1, C(3)*H*), 7.13–7.19 (3H, m, *Ph*), 7.24–7.27 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.7 (*C*(3')), 20.6 (*C*(1')), 21.6, 24.2 (CH*Me*$_2$), 32.1 (*C*(2')), 45.2 (*C*HMe$_2$), 51.3 (O*Me*), 53.6 (*C*(2)), 62.4 (*C*(3)), 127.2, 127.3, 128.4 (*o*,*m*,*p*-*Ph*), 142.3 (*i*-*Ph*), 175.7 (*C*(1)). Data for minor diastereoisomer **557**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.57–1.65 (2H, m, C(1')H_2), 3.34 (3H, s, O*Me*), 3.79 (1H, d, *J* 7.8, C(3)*H*); δ_C (100 MHz, $CDCl_3$) [selected peaks] 13.9 (*C*(3')), 20.9 (*C*(1')), 21.7 (CHMe_AMe$_B$), 30.8 (*C*(2')), 45.5 (*C*HMe$_2$), 51.0 (O*Me*), 53.4 (*C*(2)), 61.8 (*C*(3)), 127.0, 128.0 (*o*,*m*,*p*-*Ph*), 142.2 (*i*-*Ph*), 174.8 (*C*(1)). Data for mixture: ν_{max} (ATR) 3326 (N–H), 2960, 2872 (C–H), 1735 (C=O), 1602 (C=C); *m*/*z* (ESI^+) 286 ($[M+Na]^+$, 5%), 264 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{16}H_{26}NO_2^+$ ($[M+H]^+$) requires 264.1958; found 264.1956.

Method B: $Pd(OH)_2/C$ (120 mg, 50% w/w) was added to a degassed solution of **186** (240 mg, 0.68 mmol, 88:12 dr) in MeOH/acetone (6 mL, v/v 9:1) at rt. The resultant suspension was stirred vigorously under H_2 (1 atm) at rt for 16 h. The reaction mixture was then filtered through Celite® (eluent EtOAc) and the filtrate was washed with satd aq $NaHCO_3$ (10 mL), then dried and concentrated *in vacuo* to give an 88:12 mixture of **191** and **557**. Purification *via* flash column chromatography (eluent, 30–40 °C petrol/Et_2O, 93:7) gave **191** as a colourless oil (101 mg, 66%, 88:12 dr).

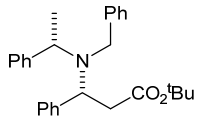
Method C: $Pd(OH)_2/C$ (87 mg, 50% w/w by substrate) was added to a degassed solution of **196** (173 mg, 0.42 mmol, >99:1 dr) in MeOH/acetone (4 mL, v/v 9:1) at rt. The resultant suspension was stirred vigorously under H_2 (1 atm) at rt for 16 h. The reaction mixture was then filtered through Celite® (eluent EtOAc) and the filtrate was washed with satd aq $NaHCO_3$ (10 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent, 30–40 °C petrol/Et_2O, 93:7) gave **191** as a colourless oil which solidified upon standing (75 mg, 68%, >99:1 dr); mp 47–50 °C; $[\alpha]_D^{20}$ +23.4 (*c* 1.0 in $CHCl_3$).

(*S*)-*N*-Benzyl-*N*-(α-methylbenzyl)amine 162



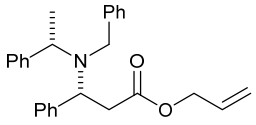
PhCHO **176** (41.9 mL, 413 mmol) was added to a solution of (*S*)-α-methylbenzylamine (50.0 mL, 393 mmol) in EtOH (250 mL) at rt and the resultant mixture was heated at reflux for 2 h before being cooled to 0 °C. $NaBH_4$ (14.9 g, 393 mmol) was then added portionwise and the resultant suspension was stirred at rt for 48 h. The reaction mixture was then concentrated *in vacuo* to half its original volume at which point the residue was partitioned between H_2O (250 mL) and CH_2Cl_2 (375 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 150 mL) and the combined organic extracts were dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (75 mL) and the resultant solution was added dropwise to a flask containing 10 M aq HCl (50 mL) and Et_2O (500 mL) at 0 °C. The reaction mixture was allowed to stir at 0 °C for 1 h then the white precipitate was collected by filtration, washed with Et_2O (125 mL), and dissolved in CH_2Cl_2 (500 mL). The resultant organic solution was dried and concentrated *in vacuo*. Purification *via* recrystallisation from CH_2Cl_2/*n*-pentane (525 mL, v/v 1:2) gave **162**·HCl (78.0 g) as a white solid. The free amine **162** was regenerated quantitatively by treatment of **162**·HCl with 2.0 M aq NaOH (250 mL), followed by extraction with CH_2Cl_2 (2 × 400 mL). The combined organic extracts were dried and concentrated *in vacuo* to give (*S*)-**162** as a colourless oil (66.0 g, 80%, >99:1 er);[10] $[\alpha]_D^{20}$−53.5 (*c* 1.0 in $CHCl_3$); {lit.[7] for *ent*-**162** $[\alpha]_D^{27}$+46.4 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, *J* 6.6, C(α)*Me*), 1.50 (1H, br s, N*H*), 3.52 (1H, d, *J* 13.2, NCH_AH_BPh), 3.59 (1H, d, *J* 13.2, NCH_AH_BPh), 3.74 (1H, q, *J* 6.6, C(α)*H*), 7.14–7.30 (10H, m, *Ph*).

***tert*-Butyl (3*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 192**



BuLi (2.4 M in hexanes, 14.5 mL, 34.2 mmol) was added dropwise to a solution of (*S*)-**162** (7.50 g, 35.3 mmol) in THF (149 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of **177** (4.50 g, 22.0 mmol, >99:1 dr) in THF (59 mL) at −78 °C was added dropwise *via* cannula, and the reaction mixture was stirred at −78 °C for 2 h. Satd aq NH_4Cl (20 mL) was then added and the reaction mixture was allowed to warm to rt. The aqueous layer was extracted with Et_2O (3 × 100 mL) and the combined organic extracts were washed sequentially with 10% aq citric acid (100 mL), satd aq $NaHCO_3$ (100 mL) and brine (100 mL), then dried and concentrated *in vacuo* to give **192** in 95:5 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 99:1) gave **192** as a colourless oil (7.50 g, 82%, >99:1 dr);[3] $[\alpha]_D^{20}$ −5.7 (*c* 1.0 in $CHCl_3$); {lit.[3] $[\alpha]_D^{23}$ −4.0 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.14 (9H, s, C*Me*$_3$), 1.18 (3H, d, *J* 6.9, C(α)*Me*), 2.38–2.49 (2H, m, C(2)H_2), 3.58 (1H, d, *J* 15.1, NCH_AH$_B$Ph), 3.62 (1H, d, *J* 15.1, NCH$_A$$H_B$Ph), 3.92 (1H, q, *J* 6.9, C(α)*H*), 4.32 (1H, dd, *J* 9.9, 5.3, C(3)*H*), 7.08–7.35 (15H, m, *Ph*).

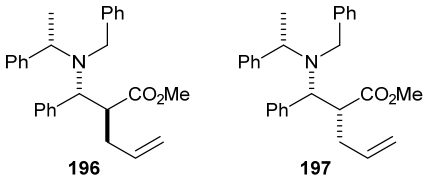
Prop-2'-en-1'-yl (3*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-3-phenylpropanoate 193



$SOCl_2$ (0.94 mL, 13.1 mmol) was added dropwise to a solution of **192** (1.82 g, 4.38 mmol, >99:1 dr) in allyl alcohol (18 mL) at 0 °C and the resultant mixture was stirred at 50 °C for 3 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (100 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (3 × 150 mL). The organic layer was then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **193** as a colourless oil (1.39 g, 79%, >99:1 dr); $[\alpha]_D^{20}$ −4.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2971, 2935 (C–H), 1733 (C=O), 1601 (C=C); δ_H (400 MHz, $CDCl_3$) 1.14 (3H, d, *J* 6.8, C(α)*Me*), 2.52 (1H, dd, *J* 14.6, 9.6, C(2)H_A), 2.61 (1H, dd, *J* 14.6, 5.4, C(2)H_B), 3.58 (1H, d, *J* 14.6, NCH_AH$_B$Ph), 3.65 (1H, d, *J* 14.6, NCH$_A$$H_B$Ph), 3.92 (1H, q, *J* 6.8, C(α)*H*), 4.24–4.32 (2H, m, C(1')H_2), 4.38 (1H, dd, *J* 9.6, 5.4, C(3)*H*), 5.00–5.04 (2H, m, C(3')H_2), 5.56–5.66 (1H, m, C(2')*H*), 7.07–7.32 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.8 (C(α)*Me*), 37.5 (*C*(2)), 50.7

(N*C*H$_2$Ph), 56.7 (*C*(α)), 59.3 (*C*(3)), 64.9 (*C*(1')), 118.0 (*C*(3')), 126.6, 126.8, 127.2, 127.8, 128.0, 128.0, 128.1, 128.1, 128.2 (*o*,*m*,*p*-*Ph*), 132.0 (*C*(2')), 141.3, 141.6, 143.9 (*i*-*Ph*), 171.4 (*C*(1)); *m*/*z* (ESI$^+$) 422 ([M+Na]$^+$, 100%), 400 ([M+H]$^+$, 90%); HRMS (ESI$^+$) $C_{27}H_{29}NNaO_2^+$ ([M+Na]$^+$) requires 422.2091; found 422.2091.

Methyl (2*S*,3*R*,α*S*)-2-(prop-2'-en-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 196 and methyl (2*R*,3*R*,α*S*)-2-(prop-2'-en-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 197



Method A: LiHMDS (1.0 M in THF, 4.0 mL, 4.0 mmol) was added dropwise to a solution of **312** (500 mg, 1.34 mmol, >99:1 dr) in THF (5 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 2 h. Allyl bromide (525 μL, 6.03 mmol) was then added dropwise at −78 °C, and the resultant solution was allowed to warm to rt over 16 h. Satd aq NH_4Cl (0.5 mL) was added and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic extracts were washed with brine (20 mL), then dried and concentrated *in vacuo* to give an 83:17 mixture of **196** and **197**, respectively. Purification *via* flash column chromatography (eluent, 30–40 °C petrol/Et_2O, 98:2) gave **196** as a colourless oil which solidified upon standing (370 mg, 67%, >99:1 dr); mp 79–81 °C; $[\alpha]_D^{20}$ +27.4 (*c* in $CHCl_3$); ν_{max} (ATR) 2977 (C–H), 1737 (C=O), 1642 (C=C); δ_H (400 MHz, $CDCl_3$) 0.83 (3H, d, *J* 7.0, C(α)*Me*), 1.60–1.64 (1H, m, C(1')*H*$_A$), 1.80–1.88 (1H, m, C(1')*H*$_B$), 3.21 (1H, dt, *J* 11.3, 3.4, C(2)*H*), 3.45 (3H, s, O*Me*), 3.56 (1H, d, *J* 13.7, NC*H*$_A$H$_B$Ph), 3.92 (1H, d, *J* 11.3, C(3)*H*), 4.07–4.14 (1H, m, C(α)*H*), 4.12 (1H, d, *J* 13.7, NCH$_A$*H*$_B$Ph), 4.73–4.78 (2H, m, C(3')*H*$_2$), 5.39–5.49 (1H, m, C(2')*H*), 7.13–7.32 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.9 (C(α)*Me*), 34.8 (*C*(1')), 49.3 (*C*(2)), 50.7 (N*C*H$_2$Ph), 51.2 (O*Me*), 55.3 (*C*(α)), 63.4 (*C*(3)), 116.4 (*C*(3')), 126.4, 126.8, 127.5, 127.7, 128.0, 128.2, 128.4, 129.0, 129.1 (*o*,*m*,*p*-*Ph*), 135.0 (*C*(2')), 138.8, 139.8, 144.0 (*i*-*Ph*), 174.0 (*C*(1)); *m*/*z* (ESI$^+$) 436 ([M+Na]$^+$, 100%), 414 ([M+H]$^+$, 80%); HRMS (ESI$^+$) $C_{28}H_{31}NNaO_2^+$ ([M+Na]$^+$) requires 436.2247; found 436.2234. Further elution (eluent, 30–40 °C petrol/Et_2O, 98:2) gave a 28:72 mixture of **196** and **197**, respectively (36 mg, 7%). Data for minor diastereoisomer **197**: δ_H (400 MHz, $CDCl_3$) 0.88 (3H, d, *J* 6.8, C(α)*Me*), 1.80–1.91 (2H, m, C(1')*H*$_2$), 3.09 (1H, td, *J* 11.2, 3.2, C(2)*H*), 3.14 (3H, s, O*Me*), 3.54 (1H, d, *J* 13.8, NC*H*$_A$H$_B$Ph), 3.83 (1H, d, *J* 11.4, C(3)*H*), 3.87 (1H, d, *J* 13.8,

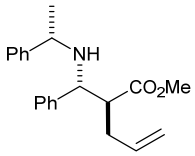
NCH_AH_BPh), 4.06–4.11 (1H, m, C(α)*H*), 4.86–4.91 (2H, m, C(3')H_2), 5.56 (1H, ddt, *J* 17.1, 10.0, 7.1, C(2')*H*), 7.14–7.32 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.9 (C(α)*Me*), 35.3 (*C*(1')), 49.3 (*C*(2)), 50.6 (NCH_2Ph), 50.9 (O*Me*), 55.9 (*C*(α)), 62.5 (*C*(3)), 116.3 (*C*(3')), 126.7, 127.0, 127.3, 127.8, 128.0, 128.2, 128.3, 128.9, 129.1 (*o*,*m*,*p*-*Ph*), 135.9 (*C*(2')), 138.8, 140.0, 144.5 (*i*-*Ph*), 174.3 (*C*(1)). Data for mixture: ν_{max} (ATR) 2948 (C–H), 1737 (C=O), 1641 (C=C); *m*/*z* (ESI^+) 414 ($[M+H]^+$, 100%), 436 ($[M+Na]^+$, 50%); HRMS (ESI^+) $C_{28}H_{31}NNaO_2^+$ ($[M+Na]^+$) requires 436.2247; found 436.2235.

Method B – Step 1: TMSCl (1.3 mL, 10.4 mmol) was added dropwise to a solution of **193** (1.39 g, 3.48 mmol, >99:1 dr) in PhMe (14 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 10 min. LiHMDS (1.0 M in THF, 10.4 mL, 10.4 mmol) was then added dropwise and the resultant solution was stirred at −78 °C for 30 min. The reaction mixture was stirred at reflux for 1 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (100 mL) and 1.0 M aq HCl (100 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed with brine (150 mL), then dried and concentrated *in vacuo* to give **194** as an orange oil (1.39 g, 92:8 dr). Purification of an aliquot *via* flash column chromatography (eluent, 30–40 °C petrol/Et_2O, 75:25) gave **194** as a white solid; $[\alpha]_D^{20}$ +73.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3100–2600 (O–H), 2934, 2849 (C–H), 1708 (C=O), 1603 (C=C); δ_H (400 MHz, $CDCl_3$) 1.05 (3H, d, *J* 7.1, C(α)*Me*), 1.62–1.69 (1H, m, C(1')H_A), 2.31–2.35 (1H, m, C(1')H_B), 3.04 (1H, ddd, *J* 11.3, 6.8, 3.8, C(2)*H*), 3.60 (1H, d, *J* 13.5, NCH_AH_BPh), 4.07 (1H, app q, *J* 6.8, C(3)*H*), 4.16–4.20 (1H, m, C(α)*H*), 4.18 (1H, d, *J* 13.5, NCH_AH_BPh), 4.57–4.76 (2H, m, C(3')H_2), 5.38–5.48 (1H, m, C(2')*H*), 7.16–7.41 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.9 (C(α)*Me*), 32.9 (*C*(1')), 44.5 (*C*(2)), 51.0 (NCH_2Ph), 57.6 (*C*(3)), 61.6 (*C*(α)), 117.4 (*C*(3')), 127.7, 127.8, 128.4, 128.4, 128.6, 128.7, 129.4, 129.7 (*o*,*m*,*p*-*Ph*), 134.1 (*C*(2')), 135.8, 136.3, 140.2 (*i*-*Ph*), 175.9 (*C*(1)); *m*/*z* (ESI^+) 422 ($[M+Na]^+$, 100%), 400 ($[M+H]^+$, 30%); *m*/*z* (ESI^-) 398 ($[M-H]^-$, 40%); HRMS (ESI^+) $C_{27}H_{30}NO_2^+$ ($[M+H]^+$) requires 400.2271; found 400.2268.

Method B – Step 2: The residue of **194** (92:8 dr) was dissolved in MeOH (15 mL) and the resultant solution was cooled to 0 °C. $SOCl_2$ (7.5 mL, 104 mmol) was then added dropwise and the reaction mixture was allowed to warm to rt, then heated at 50 °C for 48 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (100 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (3 × 100 mL), then

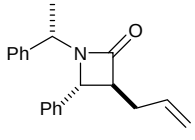
dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent, 30–40 °C petrol/Et_2O, 98:2) gave **196** as a colourless oil which solidified upon standing (718 mg, 50% from **193**, >99:1 dr); $[\alpha]_D^{20}$ +26.1 (*c* in $CHCl_3$). Further elution gave second (44 mg, 3%, 62:38 dr) and third (30 mg, 5%, 58:42 dr) fractions of **196** as colourless oils.

Methyl (2*S*,3*R*,α*S*)-2-(prop-2'-en-1'-yl)-3-[*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 198



CAN (696 mg, 1.27 mmol) was added to a stirred solution of **196** (250 mg, 0.60 mmol, >99:1 dr) in MeCN/H_2O (7 mL, v/v 5:1) at rt and the resultant mixture was stirred at rt for 16 h. Satd aq $NaHCO_3$ (15 mL) and Et_2O (20 mL) were then added and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic extracts were washed with brine (50 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent, 30–40 °C petrol/Et_2O, 95:5) gave **198** as a colourless oil (179 mg, 91%, >99:1 dr); $[\alpha]_D^{20}$ −5.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3320 (N–H), 2970, 2949 (C–H), 1735 (C=O), 1642, 1603 (C=C); δ_H (400 MHz, $CDCl_3$) 1.16 (3H, d, *J* 6.3, C(α)*Me*), 1.74 (1H, br s, N*H*), 1.83–1.88 (1H, m, C(1')H_A), 2.10–2.17 (1H, m, C(1')H_B), 2.62 (1H, app td, *J* 9.9, 6.9, C(2)*H*), 3.43 (1H, q, *J* 6.3, C(α)*H*), 3.63 (3H, s, O*Me*), 3.83 (1H, d, *J* 9.9, C(3)*H*), 4.83–4.88 (2H, m, C(3')H_2), 5.49–5.59 (1H, m, C(2')*H*), 7.08–7.25 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 21.8 (C(α)*Me*), 34.2 (*C*(1')), 51.3 (O*Me*), 53.3 (*C*(2)), 54.4 (*C*(α)), 61.9 (*C*(3)), 116.6 (*C*(3')), 126.5, 126.8, 127.3, 127.4, 128.2, 128.5 (*o*,*m*,*p*-*Ph*), 135.0 (*C*(2')), 141.3, 146.2 (*i*-*Ph*), 174.7 (*C*(1)); *m*/*z* (ESI^+) 346 ($[M+Na]^+$, 100%), 324 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{21}H_{26}NO_2^+$ ($[M+H]^+$) requires 324.1958; found 324.1949.

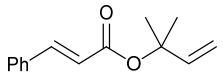
(3*S*,4*R*,α*S*)-*N*(1)-(α-Methylbenzyl)-3-(prop-2'-en-1'-yl)-4-phenylazetidin-2-one 199



MeMgBr (2.0 M in Et_2O, 90 μL, 0.18 mmol) was added dropwise to a solution of **198** (50.0 mg, 0.15 mmol, >99:1 dr) in Et_2O (2 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 30 min. Satd aq NH_4Cl (2 mL) was then added and the aqueous layer was extracted with Et_2O (2 × 5 mL). The combined organic extracts were then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent, 30–40 °C

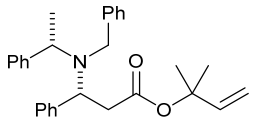
petrol/Et_2O, 80:20) gave **199** as a colourless oil (30 mg, 83%, >99:1 dr); $[\alpha]_D^{20}$ +34.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2979, 2934 (C–H), 1746 (C=O), 1603 (C=C); δ_H (400 MHz, $CDCl_3$) 1.22 (3H, d, *J* 7.3, C(α)*Me*), 2.20–2.29 (1H, m, C(1')H_A), 2.38–2.45 (1H, m, C(1')H_B), 3.00 (1H, ddd, *J* 8.8, 5.1, 2.0, C(3)*H*), 3.87 (1H, d, *J* 2.0, C(4)*H*), 4.85–4.90 (2H, m, C(3')H_2), 4.97 (1H, q, *J* 7.3, C(α)*H*), 5.57–5.67 (1H, m, C(2')*H*), 7.14–7.27 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.6 (C(α)*Me*), 32.3 (*C*(1')), 51.9 (*C*(α)), 58.4 (*C*(3)), 59.8 (*C*(4)), 117.1 (*C*(3')), 127.3, 128.8, 127.7, 128.3, 128.5, 128.6 (*o*,*m*,*p*-*Ph*), 134.1 (*C*(2')), 139.5, 140.0 (*i*-*Ph*), 170.0 (*C*(2)); *m*/*z* (ESI^+) 314 ($[M+Na]^+$, 100%), 292 ($[M+H]^+$, 40%); HRMS (ESI^+) $C_{20}H_{21}NNaO^+$ ($[M+Na]^+$) requires 314.1515; found 314.1509.

2'-Methylbut-3'-en-2'-yl (*E*)-3-phenylprop-2-enoate 201



DMAP (8.25 g, 67.0 mmol) was added to a stirred solution of *trans*-cinnamic acid **200** (10.0 g, 67.5 mmol) in CH_2Cl_2 (100 mL) at rt. The resultant solution was cooled to 0 °C and DCC (7.66 g, 37.1 mmol) was added. After stirring at 0 °C for 10 min, 2-methylbut-3-en-2-ol (11.6 g, 135 mmol) was added and the reaction mixture was allowed to warm to rt over 16 h. The reaction mixture was then filtered and concentrated *in vacuo*. The residue was then dissolved in CH_2Cl_2 (100 mL) and the resultant solution was washed sequentially with 0.5 M aq HCl (2 × 150 mL), satd aq $NaHCO_3$ (150 mL) and brine (150 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent, 30–40 °C petrol/Et_2O, 99:1) gave **201** as a colourless oil (10.7 g, 74%, >99:1 dr);[11] δ_H (400 MHz, $CDCl_3$) 1.51 (6H, s, C(2')Me_2), 5.02 (1H, dd, *J* 10.9, 0.7, C(4')H_A), 5.13 (1H, dd, *J* 17.6, 0.7, C(4')H_B), 6.06 (1H, dd, *J* 17.6, 10.9, C(3')*H*), 6.29 (1H, d, *J* 16.0, C(2)*H*), 7.24–7.27 (5H, m, *Ph*), 7.51 (1H, d, *J* 16.0, C(3)*H*).

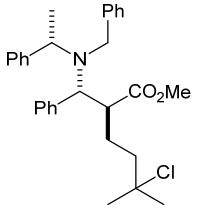
2'-Methylbut-3'-en-2'-yl (3*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 202



BuLi (2.0 M in hexanes, 14.3 mL, 28.7 mmol) was added dropwise to a solution of (*S*)-**162** (6.25 g, 29.6 mmol) in THF (132 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of **201** (4.00 g, 18.5 mmol, >99:1 dr) in THF (52 mL) at −78 °C was then added dropwise *via* cannula, and the resultant mixture was stirred at −78 °C

for 2 h. Satd aq NH_4Cl (20 mL) was then added and the reaction mixture was allowed to warm to rt. The aqueous layer was extracted with Et_2O (3 × 100 mL) and the combined organic extracts were washed sequentially with 10% aq citric acid (100 mL), satd aq $NaHCO_3$ (100 mL) and brine (100 mL), then dried and concentrated *in vacuo* to give **202** in >95:5 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 99:1) gave **202** as a colourless oil which solidified upon standing (5.78 g, 73%, >99:1 dr); mp 60–62 °C; $[\alpha]_D^{20}$ −8.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2976, 2934 (C–H), 1728 (C=O), 1602 (C=C); δ_H (400 MHz, $CDCl_3$) 1.34 (3H, d, *J* 7.0, C(α)*Me*), 1.35 (3H, s, C(2')*Me*$_A$), 1.37 (3H, s, C(2')*Me*$_B$), 2.61–2.64 (2H, m, C(2)*H*$_2$), 3.76 (2H, app s, NC*H*$_2$Ph), 4.07 (1H, q, *J* 7.0, C(α)*H*), 4.51 (1H, dd, *J* 8.3, 6.6, C(3)*H*), 4.98–5.04 (2H, m, C(4')*H*$_2$), 5.87 (1H, dd, *J* 17.4, 10.9, C(3')*H*), 7.22–7.42 (11H, m, *Ph*), 7.49–7.51 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.2 (C(α)*Me*), 26.1 (C(2')*Me*$_2$), 38.2 (*C*(2)), 50.8 (N*C*H$_2$Ph), 57.0 (*C*(α)), 59.6 (*C*(3)), 80.5 (*C*(2')), 112.2 (*C*(4')), 126.5, 126.8, 127.1, 127.8, 127.9, 128.1, 128.2 (*o,m,p-Ph*), 141.6, 141.6 (*i-Ph*), 142.4 (*C*(3')), 144.0 (*i-Ph*), 170.6 (*C*(1)); *m*/*z* (ESI$^+$) 428 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{34}NO_2^+$ ([M+H]$^+$) requires 428.2584; found 428.2569.

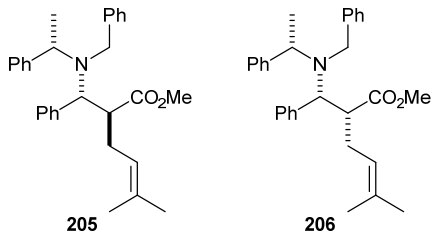
Methyl (2*S*,3*R*,α*S*)-2-(3'-chloro-3'-methylbutyl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 207



TMSCl (443 μL, 3.51 mmol) was added dropwise to a solution of **202** (500 mg, 1.17 mmol) in PhMe (5 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 10 min. LiHMDS (1.0 M in THF, 3.5 mL, 3.51 mmol) was added dropwise at −78 °C and the resultant solution was stirred at −78 °C for 30 min. The reaction mixture was then heated at reflux for 1 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 (50 mL) and 1.0 M aq HCl (50 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extracts were washed brine (50 mL), then dried and concentrated *in vacuo*. The residue was then dissolved in MeOH (10 mL), and $SOCl_2$ (2.5 mL, 35.1 mmol) was added dropwise to the resultant solution at 0 °C. The reaction mixture was stirred at 50 °C for 48 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was then dissolved in CH_2Cl_2 (50 mL) and the resultant solution was washed with

satd aq $NaHCO_3$ (3 × 50 mL). The organic layer was then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent, 30–40 °C petrol/Et_2O, 98:2) gave **207** as a pale yellow oil (91 mg, 16%, >99:1 dr); $[\alpha]_D^{20}$+14.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2970, 2947 (C–H), 1736 (C=O), 762 (C–Cl); δ_H (400 MHz, $CDCl_3$) 0.83 (3H, d, *J* 6.8, C(α)*Me*), 1.06–1.18 (1H, m, C(1')H_A), 1.22 (3H, s, C(3')Me_A), 1.25 (3H, s, C(3')Me_B), 1.29–1.34 (1H, m, C(1')H_B), 1.36–1.44 (2H, m, C(2')H_2), 3.08 (1H, dt, *J* 11.1, 3.0, C(2)*H*), 3.47 (3H, s, O*Me*), 3.54 (1H, d, *J* 14.2, NC$H_A$$H_B$Ph), 3.95 (1H, d, *J* 11.1, C(3)*H*), 4.06–4.12 (1H, m, C(α)*H*), 4.08 (1H, d, *J* 14.2, NCH$_A$$H_B$Ph), 7.12–7.31 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.0 (C(α)*Me*), 25.9 (*C*(1')), 31.7, 32.3 (C(3')Me_2), 43.4 (*C*(2')), 49.3 (*C*(2)), 50.7 (N*C*H_2Ph), 51.3 (O*Me*), 55.3 (*C*(α)), 63.7 (*C*(3)), 70.1 (*C*(3')), 126.4, 126.8, 127.5, 127.7, 128.0, 128.2, 128.4, 129.0 (*o*,*m*,*p*-*Ph*), 138.6, 139.8, 144.1 (*i*-*Ph*), 174.5 (*C*(1)); *m*/*z* (ESI^+) 480 ([M(^{37}Cl)+H]$^+$, 50%), 478 ([M(^{35}Cl)+H]$^+$, 100%); 502 ([M(^{37}Cl)+Na]$^+$, 75%), 500 ([M(^{35}Cl)+Na]$^+$, 25%); HRMS (ESI^+) $C_{30}H_{36}ClNNaO_2^+$ ([M+Na]$^+$) requires 500.2327; found 500.2323.

Methyl (2*S*,3*R*,α*S*)-2-(3'-methylbut-2'-en-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 205 and methyl (2*R*,3*R*,α*S*)-2-(3'-methylbut-2'-en-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 206



Method A: LiHMDS (1.0 M in THF, 19.9 mL, 19.9 mmol) was added dropwise to a solution of **312** (2.47 g, 6.68 mmol, >99:1 dr) in THF (25 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 2 h. 3,3-Dimethylallyl bromide (3.44 mL, 29.8 mmol) was then added dropwise at −78 °C, and the resultant solution was allowed to warm to rt over 16 h. Satd aq NH_4Cl (5 mL) was added and the aqueous layer was extracted with Et_2O (2 × 80 mL). The combined organic extracts were washed with brine (200 mL), then dried and concentrated *in vacuo* to give a 94:6 mixture of **205** and **206**, respectively. Purification *via* flash column chromatography (eluent, 30–40 °C petrol/Et_2O, 93:7) gave **205** as a colourless oil which solidified upon standing (2.24 g, 77%, >99:1 dr); $[\alpha]_D^{20}$ +3.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2969, 2946 (C–H), 1737 (C=O), 1602 (C=C); δ_H (400 MHz, $CDCl_3$) 0.81 (3H, d, *J* 7.1, C(α)*Me*), 1.23 (3H, s, C(3')Me_A), 1.46 (3H, s, C(3')Me_B), 1.49–1.55 (1H, m, C(1')H_A), 1.77–1.86 (1H, m, C(1')H_B), 3.11 (1H, app td, *J* 11.3, 3.4, C(2)*H*), 3.42 (3H, s, O*Me*), 3.53

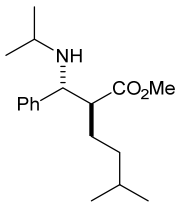
(1H, d, *J* 13.9, NC*H*$_A$H$_B$Ph), 3.91 (1H, d, *J* 11.3, C(3)*H*), 4.06–4.11 (1H, m, C(α)*H*), 4.09 (1H, d, *J* 13.9, NCH$_A$*H*$_B$Ph), 4.76–4.80 (1H, m, C(2')*H*), 7.09–7.30 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.0 (C(α)*Me*), 17.4 (C(3')*Me*$_A$), 25.6 (C(3')*Me*$_B$), 29.3 (*C*(1')), 49.7 (*C*(2)), 50.6 (N*C*H$_2$Ph), 51.1 (O*Me*), 55.2 (*C*(α)), 63.3 (*C*(3)), 120.6 (*C*(2')), 126.3, 126.8, 127.4, 127.7, 127.9, 128.1, 128.3, 128.9, 129.0 (*o*,*m*,*p*-*Ph*), 133.4 (*C*(3')), 139.0, 139.8, 144.1 (*i*-*Ph*), 174.4 (*C*(1)); *m*/*z* (ESI$^+$) 464 ([M+Na]$^+$, 40%), 442 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{36}NO_2^+$ ([M+H]$^+$) requires 442.2741; found 442.2734. Further elution (eluent, 30–40 °C petrol/Et_2O, 93:7) gave a 58:42 mixture of **205** and **206**, respectively (228 mg, 8%). Data for minor diastereoisomer **206**: δ_H (400 MHz, $CDCl_3$) 0.85 (3H, d, *J* 6.9, C(α)*Me*), 1.41 (3H, s, C(3')*Me*$_A$), 1.57 (3H, s, C(3')*Me*$_B$), 1.79–1.87 (1H, m, C(1')*H*$_A$), 2.70–2.73 (1H, m, C(1')*H*$_B$), 3.01 (1H, app td, *J* 11.1, 3.6, C(2)*H*), 3.13 (3H, s, O*Me*), 3.54 (1H, d, *J* 13.9, NC*H*$_A$H$_B$Ph), 3.83 (1H, d, *J* 11.1, C(3)*H*), 3.89 (1H, d, *J* 13.9, NCH$_A$*H*$_B$Ph), 4.07–4.10 (1H, m, C(α)*H*), 4.86–4.89 (1H, m, C(2')*H*), 7.12–7.33 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.6 (C(α)*Me*), 17.6 (C(3')*Me*$_A$), 25.8 (C(3')*Me*$_B$), 29.8 (*C*(1')), 49.5 (*C*(2)), 50.6 (N*C*H$_2$Ph), 51.0 (O*Me*), 55.6 (*C*(α)), 62.6 (*C*(3)), 121.2 (*C*(2')), 126.7, 127.0, 127.2, 127.9, 128.0, 128.1, 128.3, 129.0, 129.2 (*o*,*m*,*p*-*Ph*), 133.3 (*C*(3')), 139.1, 140.1, 144.6 (*i*-*Ph*), 174.7 (*C*(1)). Data for mixture: ν_{max} (ATR) 2929, 2853 (C–H), 1736 (C=O), 1603 (C=C); *m*/*z* (ESI$^+$) 464 ([M+Na]$^+$, 60%), 442 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{36}NO_2^+$ ([M+H]$^+$) requires 442.2741; found 442.2742.

Method B − Step 1: TMSCl (89 μL, 0.70 mmol) was added dropwise to a solution of **202** (100 mg, 0.23 mmol, >99:1 dr) in PhMe (1 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 10 min. LiHMDS (1.0 M in THF, 0.70 mL, 0.70 mmol) was then added dropwise and the resultant mixture was stirred at −78 °C for 30 min. The reaction mixture was then allowed to warm to rt, then heated at reflux for 1 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and 1.0 M aq HCl (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed brine (25 mL), then dried and concentrated *in vacuo* to give **203** as a pale orange solid (100 mg, 93:7 dr); mp 146–148 °C; $[\alpha]_D^{20}$ +58.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2969, 2929 (C–H), 1706 (C=O), 1602 (C=C); δ_H (400 MHz, $CDCl_3$) 1.03 (3H, d, *J* 7.0, C(α)*Me*), 1.05 (3H, s, C(3')*Me*$_A$), 1.42 (3H, s, C(3')*Me*$_B$), 1.68–1.75 (1H, m, C(1')*H*$_A$), 2.16 (1H, app d, *J* 14.4, C(1')*H*$_B$), 2.98–3.04 (1H, m, C(2)*H*), 3.60 (1H, d, *J* 13.2, NC*H*$_A$H$_B$Ph), 4.08 (1H, q, *J* 7.0, C(α)*H*), 4.15 (1H, d, *J* 11.6, C(3)*H*), 4.17 (1H, d, *J* 13.2, NCH$_A$*H*$_B$Ph),

4.69–4.72 (1H, m, C(2')*H*), 7.16–7.27 (10H, m, *Ph*), 7.31–7.38 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.8 (C(α)*Me*), 17.6 (C(3')*Me*$_A$), 25.6 (C(3')*Me*$_B$), 27.4 (*C*(1')), 45.2 (*C*(2)), 50.9 (N*C*H_2Ph), 57.4 (*C*(α)), 61.7 (*C*(3)), 119.9 (*C*(2')), 127.7, 127.7, 128.3, 128.3, 128.5, 128.6, 129.4, 129.8 (*o*,*m*,*p*-*Ph*), 133.8 (*C*(3')), 136.2, 136.4, 140.3 (*i*-*Ph*), 176.6 (*C*(1)); *m*/*z* (ESI^+) 450 ($[M+Na]^+$, 10%), 428 ($[M+H]^+$, 100%); *m*/*z* (ESI^-) 426 ($[M-H]^-$ 100%); HRMS (ESI^+) $C_{29}H_{34}NO_2^+$ ($[M+H]^+$) requires 428.2584; found 428.2573.

Method B − Step 2: The residue of **203** (50 mg, 93:7 dr) was dissolved in MeCN (500 μL) and the resultant solution was treated sequentially with DBU (18 μL, 0.12 mmol) and MeI (9 μL, 0.14 mmol), and the resultant mixture was stirred at rt for 4 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (5 mL) and 2.0 M aq HCl (5 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were then washed sequentially with satd aq $NaHCO_3$ (15 mL) and brine (15 mL), then dried and concentrated *in vacuo* to give a 93:7 mixture of **205** and **206**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **205** as a colourless oil (34 mg, 66% from **202**, >99:1 dr); $[\alpha]_D^{20}$ +4.3 (*c* 1.0 in $CHCl_3$). Further elution gave **205** as a colourless oil (6 mg, 12%, 43:57 dr).

Methyl (2*S*,3*R*)-2-(3'-methylbutyl)-3-(*N*-isopropylamino)-3-phenylpropanoate 208



Method A – Step 1: $Pd(OH)_2/C$ (75 mg, 50% w/w) was added to a degassed solution of **205** (150 mg, 0.34 mmol, >99:1 dr) in MeOH (3.4 mL) at rt. The resultant mixture was stirred vigorously under H_2 (1 atm) at rt for 15 h. The reaction mixture was then filtered through Celite® (eluent EtOAc) and the filtrate was washed with satd aq $NaHCO_3$ (10 mL), then dried and concentrated *in vacuo* to give **209** as a yellow solid (76 mg, >99:1 dr).

Method A – Step 2: Acetone (44 μL, 0.61 mmol) and $NaBH_3CN$ (77 mg, 1.22 mmol) were added sequentially to a solution of the residue of **209** (76 mg, >99:1 dr) in MeOH (4 mL) at rt, and the resultant mixture was stirred at rt for 22 h. The reaction mixture was then concentrated *in vacuo*, the residue was partitioned between CH_2Cl_2 (10 mL) and H_2O (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried and concentrated *in vacuo*. Purification *via* flash column

chromatography (eluent 30–40 °C petrol/Et_2O, 93:7) gave **208** as a colourless oil which solidified upon standing (49 mg, 55% from **205**, >99:1 dr); mp 47–49 °C; $[\alpha]_D^{20}$ +12.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3324 (N–H), 2956, 2870 (C–H), 1735 (C=O); δ_H (400 MHz, $CDCl_3$) 0.63 (3H, d, *J* 6.7, C(3')*Me*$_A$), 0.66 (3H, d, *J* 6.7, C(3')*Me*$_B$), 0.81 (3H, d, *J* 6.2, NHCH*Me*$_A$Me$_B$), 0.86 (3H, d, *J* 6.2, NHCHMe$_A$*Me*$_B$), 0.90–0.96 (2H, m, C(2')*H*$_2$), 0.97–1.06 (1H, m, C(1')*H*$_A$), 1.24–1.32 (1H, m, C(3')*H*), 1.33–1.41 (1H, m, C(1')*H*$_B$), 2.44–2.51 (1H, m, NHC*H*Me$_2$), 2.46 (1H, td, *J* 10.0, 3.4, C(2)*H*), 3.64 (3H, s, O*Me*), 3.71 (1H, d, *J* 10.0, C(3)*H*), 7.17–7.20 (3H, m, *Ph*), 7.24–7.27 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.6, 21.9, 22.7, 24.2 (C(3')*Me*$_2$, NHCH*Me*$_2$), 27.7 (*C*(3')), 27.8 (*C*(1')), 36.4 (*C*(2')), 45.2 (NH*C*H(Me)$_2$), 51.4 (O*Me*), 53.9 (*C*(2)), 62.3 (*C*(3)), 127.2, 127.3, 128.4 (*o*,*m*,*p*-*Ph*), 142.3 (*i*-*Ph*), 175.7 (*C*(1)); *m*/*z* (ESI$^+$) 314 ([M+Na]$^+$, 10%), 292 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{30}NO_2^+$ ([M+H]$^+$) requires 292.2271; found 292.2263.

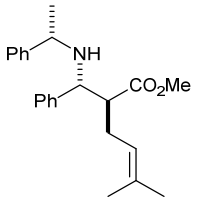
Method B – Step 1: TMSCl (443 μL, 3.51 mmol) was added dropwise to a solution of **202** (500 mg, 1.17 mmol, >99:1 dr) in PhMe (5 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 10 min. LiHMDS (1.0 M in THF, 3.5 mL, 3.51 mmol) was then added dropwise and the resultant mixture was stirred at −78 °C for 30 min. The reaction mixture was then allowed to warm to rt, then heated at reflux for 1 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and 1.0 M aq HCl (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed brine (25 mL), then dried and concentrated *in vacuo* to give **203** as a pale orange solid (63 mg, 93:7 dr).

Method B – Step 2: $Pd(OH)_2$/C (32 mg, 50% w/w) was added to a degassed solution of the residue of **203** (63 mg, 93:7 dr) in MeOH/acetone (1.6 mL, v/v 9:1) at rt. The resultant suspension was stirred vigorously under H_2 (1 atm) at rt for 22 h. The reaction mixture was then filtered through Celite® (eluent EtOAc) and the filtrate was washed with satd aq $NaHCO_3$ (10 mL), then dried and concentrated *in vacuo* to give a yellow oil (39 mg).

Method B – Step 3: The residue (39 mg) was dissolved in MeOH (0.4 mL), and the resultant solution was cooled to 0 °C then $SOCl_2$ (300 μL, 4.25 mmol) was added dropwise. The reaction mixture was allowed to warm to rt then heated at 50 °C for 48 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was then dissolved in CH_2Cl_2 (10 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (3 × 10 mL). The organic layer was then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent,

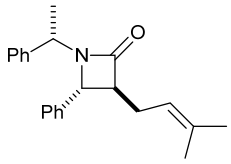
30–40 °C petrol/ Et_2O, 92:8) gave **208** as a colourless oil (20 mg, 48% from **202**, >99:1 dr); $[\alpha]_D^{20}$ +11.1 (*c* 1.0 in $CHCl_3$).

Methyl (2*S*,3*R*,α*S*)-2-(3'-methylbut-2'-en-1'-yl)-3-[*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 210



CAN (782 mg, 1.43 mmol) was added to a stirred solution of **205** (300 mg, 0.68 mmol, >99:1 dr) in MeCN/H_2O (8.3 mL, v/v 5:1) at rt and the resultant mixture was stirred at rt for 16 h. Satd aq $NaHCO_3$ (15 mL) and Et_2O (20 mL) were then added and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic extracts were washed with brine (50 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent, 30–40 °C petrol/Et_2O, 95:5) gave **210** as a colourless oil (180 mg, 75%, >99:1 dr); $[\alpha]_D^{20}$ −26.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3319 (N–H), 2968, 2927 (C–H), 1737 (C=O), 1603 (C=C); δ_H (400 MHz, $CDCl_3$) 1.16 (3H, d, *J* 6.5, C(α)*Me*), 1.35 (3H, s, C(3')*Me*$_A$), 1.53 (3H, s, C(3')*Me*$_B$), 1.70–1.78 (2H, m, C(1')*H*$_A$, N*H*), 2.07–2.15 (1H, m, C(1')*H*$_B$), 2.52 (1H, app dt, *J* 9.9, 4.2, C(2)*H*), 3.42 (1H, q, *J* 6.5, C(α)*H*), 3.63 (3H, s, O*Me*), 3.83 (1H, d, *J* 9.9, C(3)*H*), 4.87 (1H, app t, *J* 7.2, C(2')*H*), 7.07–7.24 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.5 (C(3')*Me*$_A$), 21.8 (C(α)*Me*), 25.7 (C(3')*Me*$_B$), 28.7 (*C*(1')), 51.3 (O*Me*), 53.9 (*C*(2)), 54.3 (*C*(α)), 61.9 (*C*(3)), 120.6 (*C*(2')), 126.5, 126.8, 127.3, 127.3, 128.2, 128.5 (*o*,*m*,*p*-*Ph*), 133.5 (*C*(3')), 141.6, 146.4 (*i*-*Ph*), 175.2 (*C*(1)); *m*/*z* (ESI$^+$) 352 ($[M+H]^+$, 100%), 374 ($[M+Na]^+$, 10%); HRMS (ESI$^+$) $C_{23}H_{30}NO_2^+$ ($[M+H]^+$) requires 352.2271; found 352.2271.

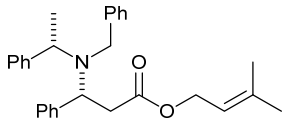
(3*S*,4*R*,α*S*)-*N*(1)-(α-Methylbenzyl)-3-(3'-methylbut-2'-en-1'-yl)-4-phenylazetidin-2-one 211



MeMgBr (3.0 M in Et_2O, 0.16 mL, 0.48 mmol) was added dropwise to a solution of **210** (100 mg, 0.28 mmol, >99:1 dr) in Et_2O (4 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 30 min. Satd aq NH_4Cl (4 mL) was then added and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic extracts were then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent, 30–40 °C petrol/Et_2O, 83:17)

gave **211** as a colourless oil (72 mg, 79%, >99:1 dr); $[\alpha]_D^{20}$ −11.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2976 (C–H), 1746 (C=O), 1603 (C=C); δ_H (400 MHz, $CDCl_3$) 1.19 (3H, d, *J* 7.3, C(α)*Me*), 1.47 (3H, s, C(3')*Me*$_A$), 1.52 (3H, s, C(3')*Me*$_B$), 2.17–2.34 (2H, m, C(1')*H*$_2$), 2.94 (1H, ddd, *J* 7.5, 5.4, 2.0, C(3)*H*), 3.83 (1H, d, *J* 2.0, C(4)*H*), 4.92–4.96 (1H, m, C(2')*H*), 4.99 (1H, q, *J* 7.3, C(α)*H*), 7.13–7.27 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.7 (C(3')*Me*$_A$), 18.5 (C(α)*Me*), 25.6 (C(3')*Me*$_B$), 26.0 (*C*(1')), 51.6 (*C*(α)), 59.0 (*C*(3)), 59.3 (*C*(4)), 119.3 (*C*(2')), 126.6, 127.2, 127.5, 128.1, 128.4, 128.6 (*o*,*m*,*p*-*Ph*), 134.3 (*C*(3')), 139.7, 140.0 (*i*-*Ph*), 170.3 (*C*(2)); *m*/*z* (ESI^+) 320 ($[M+H]^+$, 10%), 342 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{22}H_{25}NNaO^+$ ($[M+Na]^+$) requires 342.1828; found 342.1829.

3'-Methylbut-2'-en-1'-yl (3*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 213



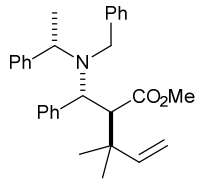
Method A: *Step 1*: TFA (0.9 mL) was added to a stirred solution of **192** (200 mg, 0.48 mmol, >99:1 dr) in CH_2Cl_2 (1.9 mL) at rt, and the resultant mixture was stirred at rt for 16 h. Satd aq $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL) were then added and the aqueous layer was extracted with CH_2Cl_2 (10 mL). The combined organic extracts were then concentrated *in vacuo* to give an orange oil (109 mg, >99:1 dr).

Step 2: A solution of the residue (109 mg, >99:1 dr) in MeCN (2 mL) was treated sequentially with DBU (144 μL, 0.96 mmol) and 3,3-dimethylallyl bromide (134 μL, 1.16 mmol) at rt. The resultant mixture was stirred at rt for 17 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and 2.0 M aq HCl (20 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then washed sequentially with satd aq $NaHCO_3$ (30 mL) and brine (30 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 99:1) gave **213** as a colourless oil (115 mg, 56% from **192**, >99:1 dr); $[\alpha]_D^{20}$ −9.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2971, 2933 (C–H), 1731 (C=O); δ_H (400 MHz, $CDCl_3$) 1.15 (3H, d, *J* 6.7, C(α)*Me*), 1.51 (3H, s, C(3')*Me*$_A$), 1.61 (3H, s, C(3')*Me*$_B$), 2.48 (1H, dd, *J* 14.8, 9.6, C(2)*H*$_A$), 2.58 (1H, dd, *J* 14.8, 5.4, C(2)*H*$_B$), 3.56–3.66 (2H, m, NC*H*$_2$Ph), 3.92 (1H, q, *J* 6.7, C(α)*H*), 4.24–4.34 (2H, m, C(1')*H*$_2$), 4.37 (1H, dd, *J* 9.6, 5.4, C(3)*H*), 5.02–5.06 (1H, m, C(2')*H*), 7.07–7.26 (11H, m, *Ph*), 7.31–7.34 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.8 (C(α)*Me*), 17.9 (C(3')*Me*$_A$), 25.7 (C(3')*Me*$_B$), 37.7 (*C*(2)), 50.7 (N*C*H$_2$Ph), 56.8 (*C*(α)), 59.5 (*C*(3)), 61.1

(*C*(1')), 118.5 (*C*(2')), 126.5, 126.8, 127.1, 127.8, 128.0, 128.1, 128.1, 128.2 (*o,m,p-Ph*), 138.7 (*C*(3')), 141.4, 141.7, 144.0 (*i-Ph*), 171.8 (*C*(1)); *m/z* (ESI$^+$) 450 ([M+Na]$^+$, 10%), 428 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{34}NO_2^+$ ([M+H]$^+$) requires 428.2584; found 428.2567.

Method B: *sec*-BuLi (1.2 M in cyclohexane, 3.0 mL, 3.60 mmol) was added dropwise to a stirred solution of (*S*)-**162** (782 mg, 3.70 mmol) and **313** (500 mg, 2.31 mmol) in THF (23 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 2 h. Satd aq NH_4Cl (2 mL) was then added and the reaction mixture was allowed to warm to rt. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic extracts were washed sequentially with 10% aq citric acid (20 mL), satd aq $NaHCO_3$ (20 mL) and brine (20 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 99:1) gave **213** as a colourless oil (341 mg, 35%, >99:1 dr); $[\alpha]_D^{20}$ −11.7 (*c* 1.0 in $CHCl_3$).

Methyl (2*S*,3*R*,α*S*)-2-(2'-methylbut-3'-en-2'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 216

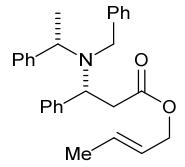


Step 1: TMSCl (101 μL, 0.81 mmol) was added dropwise to a solution of **213** (115 mg, 0.27 mmol, >99:1 dr) in PhMe (1 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 10 min. LiHMDS (1.0 M in THF, 0.8 mL, 0.80 mmol) was then added dropwise and the resultant mixture was stirred at −78 °C for 30 min. The reaction mixture was heated at reflux for 1 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and 1.0 M aq HCl (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with brine (25 mL), then dried and concentrated *in vacuo* to give **214** as a pale orange solid (117 mg, 90:10 dr); ν_{max} (ATR) 2969 (C–H), 1737 (C=O), 1638, 1602 (C=C); δ_H (400 MHz, $CDCl_3$) 0.74 (3H, s, C(2')*Me*$_A$), 0.75 (3H, s, C(2')*Me*$_B$), 0.82 (3H, d, *J* 7.1, C(α)*Me*), 3.21 (1H, d, *J* 11.1, C(2)*H*), 3.64 (1H, d, *J* 13.1, NC*H*$_A$H$_B$Ph), 3.95–4.01 (1H, m, C(α)*H*), 4.14 (1H, d, *J* 11.1, C(3)*H*), 4.38 (1H, d, *J* 13.1, NCH$_A$*H*$_B$Ph), 4.42–4.46 (2H, m, C(4')*H*$_2$), 5.47 (1H, dd, *J* 17.2, 11.1, C(3')*H*), 7.12–7.41 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.1 (C(α)*Me*), 24.9, 26.3 (C(2')*Me*$_2$), 38.3 (*C*(2')), 51.3 (N*C*H$_2$Ph), 56.4 (*C*(α)), 58.5 (*C*(2)), 59.9 (*C*(3)), 110.7 (*C*(4')), 127.0, 127.1, 127.7, 127.7, 128.3, 129.1, 129.3 (*o,m,p-Ph*), 138.7, 139.1, 141.5 (*i-Ph*), 145.5

(*C*(3')), 178.3 (*C*(1)); *m*/*z* (ESI$^+$) 450 ([M+Na]$^+$, 5%), 428 ([M+H]$^+$, 100%); *m*/*z* (ESI$^-$) 426 ([M−H]$^-$, 100%); HRMS (ESI$^+$) $C_{29}H_{34}NO_2^+$ ([M+H]$^+$) requires 428.2584; found 428.2570.

Step 2: A solution of the residue of **214** (117 mg, 90:10 dr) in MeCN (1.2 mL) was treated sequentially with DBU (40 μl, 0.27 mmol) and MeI (40 μL, 0.64 mmol) at rt. The reaction mixture was stirred at rt for 8 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (5 mL) and 2.0 M aq HCl (5 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were then washed sequentially with satd aq $NaHCO_3$ (15 mL) and brine (15 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **216** as a colourless oil (60 mg, 50% from **213**, >99:1 dr); $[\alpha]_D^{20}$ +21.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3027, 2969 (C–H), 1737 (C=O), 1494 (C=C); δ_H (400 MHz, $CDCl_3$) 0.58 (3H, s, C(2')*Me*$_A$), 0.65 (3H, s, C(2')*Me*$_B$), 0.78 (3H, d, *J* 7.1, C(α)*Me*), 3.21 (1H, d, *J* 11.4, C(2)*H*), 3.27 (3H, br s, O*Me*), 3.53 (1H, d, *J* 13.6, NC*H*$_A$H$_B$Ph), 4.10 (1H, d, *J* 11.4, C(3)*H*), 4.11–4.16 (2H, m, NCH$_A$*H*$_B$Ph, C(α)*H*), 4.34–4.41 (2H, m, C(4')*H*$_2$), 5.48 (1H, dd, *J* 17.3, 10.7, C(3')*H*), 7.10–7.40 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.5 (C(α)*Me*), 25.7 (C(2')*Me*$_2$), 38.5 (*C*(2')), 50.6 (O*Me*), 51.0 (N*C*H$_2$Ph), 53.4 (*C*(α)), 55.5 (*C*(2)), 60.1 (*C*(3)), 110.3 (*C*(4')), 126.2, 126.7, 127.4, 127.6, 127.8, 128.2, 128.9 (*o*,*m*,*p*-*Ph*), 139.1, 139.6 (*i*-*Ph*), 145.7 (*C*(3')), 173.0 (*C*(1)); *m*/*z* (ESI$^+$) 464 ([M+Na]$^+$, 20%), 442 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{36}NO_2^+$ ([M+H]$^+$) requires 442.2741; found 442.2724.

(*E*)-But-2'-en-1'-yl (3*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 218

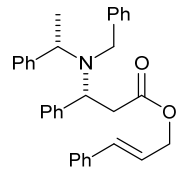


Step 1: TFA (4.6 mL) was added to a solution of **192** (1.00 g, 2.41 mmol, >99:1 dr) in CH_2Cl_2 (9.3 mL) at rt, and the resultant mixture was stirred at rt for 16 h. Satd aq $NaHCO_3$ (100 mL) and CH_2Cl_2 (100 mL) were then added and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give a yellow oil (1.05 g, >99:1 dr).

Step 2: A solution of the residue (1.05 g, >99:1 dr) in CH_2Cl_2 (10 mL) was treated sequentially with $(COCl)_2$ (0.22 mL, 2.53 mmol) and DMF (8 μL, 0.10 μmol) at 0 °C. The reaction mixture was allowed to warm to rt over 1 h then concentrated *in vacuo*. A solution of

crotyl alcohol [240 mg, 3.37 mmol, 93:7 dr (*E*):(*Z*)] was then added to a solution of the residue in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred at rt for 16 h. Satd aq $NaHCO_3$ (100 mL) was then added and the resultant mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (300 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 0% → 6% Et_2O in 30–40 °C petrol) gave **218** as a colourless oil (613 mg, 62%, 93:7 dr); $[\alpha]_D^{20}$ −16.1 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 3028 (C–H), 1732 (C=O), 1493 (C=C); δ_H (400 MHz, $CDCl_3$) 1.14 (3H, d, *J* 6.8, C(α)*Me*), 1.56 (3H, d, *J* 6.8, C(4')H_3), 2.48 (1H, dd, *J* 14.6, 9.4, C(2)H_A), 2.59 (1H, dd, *J* 14.6, 5.4, C(2)H_B), 3.57 (1H, d, *J* 14.6, NC$H_A$$H_B$Ph), 3.65 (1H, d, *J* 14.6, NC$H_A$$H_B$Ph), 3.92 (1H, q, *J* 6.8, C(α)*H*), 4.19–4.24 (2H, m, C(1')H_2), 4.36 (1H, dd, *J* 9.4, 5.4, C(3)*H*), 5.23–5.30 (1H, m, C(2')*H*), 5.47–5.55 (1H, m, C(3')*H*), 7.06–7.26 (11H, m, *Ph*), 7.31–7.34 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.7 (C(α)*Me*), 17.7 (*C*(4')), 37.7 (*C*(2)), 50.7 (N*C*H_2Ph), 56.7 (*C*(α)), 59.4 (*C*(3)), 64.9 (*C*(1')), 124.9 (*C*(2')), 126.5, 126.8, 127.2, 127.8, 128.0, 128.1, 128.1, 128.1, 128.2 (*o*,*m*,*p*-*Ph*), 130.9 (*C*(3')), 141.4, 141.7, 144.0 (*i*-*Ph*), 171.5 (*C*(1)); *m*/*z* (ESI^+) 414 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{28}H_{32}NO_2^+$ ($[M+H]^+$) requires 414.2428; found 414.2418.

(*E*)-3'-Phenylprop-2'-en-1'-yl (3*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 219

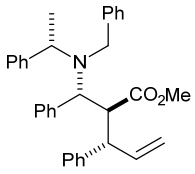


Step 1: TFA (8 mL) was added to a solution of **192** (1.70 g, 4.09 mmol, >99:1 dr) in CH_2Cl_2 (16 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with $NaHCO_3$ (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give a yellow oil (1.75 g, >99:1 dr).

Step 2: A solution of the residue (1.75 g, >99:1 dr) in CH_2Cl_2 (18 mL) was treated sequentially with $(COCl)_2$ (0.37 μL, 4.29 mmol) and DMF (14 μL, 0.18 μmol) at 0 °C. The reaction mixture was allowed to warm to rt over 1 h then concentrated *in vacuo*. A solution of cinnamyl alcohol [770 mg, 5.73 mmol, >99:1 dr(*E*):(*Z*)] was then added to a solution of the residue in CH_2Cl_2 (18 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred at rt for 16 h. Satd aq $NaHCO_3$ (100 mL) was then added and the resultant mixture was

extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (300 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 0% → 6% Et_2O in 30–40 °C petrol) gave **219** as a colourless oil (1.47 g, 76%, >99:1 dr); $[\alpha]_D^{20}$ −14.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3027, 2935 (C–H), 1732 (C=O), 1494 (C=C); δ_H (400 MHz, $CDCl_3$) 1.33 (3H, d, *J* 6.9, C(α)*Me*), 2.72 (1H, dd, *J* 14.6, 9.6, C(2)H_A), 2.82 (1H, dd, *J* 14.6, 5.8, C(2)H_B), 3.77 (1H, d, *J* 14.6, NC$H_A$$H_B$Ph), 3.85 (1H, d, *J* 14.6, NC$H_A$$H_B$Ph), 4.12 (1H, q, *J* 6.9, C(α)*H*), 4.57–4.67 (3H, m, C(3)*H*, C(1')H_2), 6.09–6.16 (1H, dt, *J* 15.8, 6.4, C(2')*H*), 6.56 (1H, d, *J* 15.8, C(3')*H*), 7.25–7.44 (16H, m, *Ph*), 7.52–7.54 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.8 (C(α)*Me*), 37.7 (*C*(2)), 50.7 (N*C*H_2Ph), 56.7 (*C*(α)), 59.4 (*C*(3)), 64.8 (*C*(1')), 123.1 (*C*(2')), 126.5, 126.6, 126.8, 127.2, 127.8, 127.9, 128.0, 128.0, 128.1, 128.1, 128.2, 128.5, (*o*,*m*,*p*-*Ph*), 133.8 (*C*(3')), 136.2, 141.3, 141.6, 144.0 (*i*-*Ph*), 171.5 (*C*(1)); *m*/*z* (ESI^+) 476 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{33}H_{33}NNaO_2^+$ ($[M+Na]^+$) requires 498.2404; found 498.2388.

Methyl (2*S*,3*R*,1'*S*,α*S*)-2-(1'-phenylprop-2'-en-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 224



*Method A (from **229**) – Step 1*: TMSCl (780 μL, 6.18 mmol) was added dropwise to a solution of **229** (980 mg, 2.06 mmol, >99:1 dr) in PhMe (9.8 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 10 min. LiHMDS (1.0 M in THF, 6.31 mL, 6.31 mmol) was added dropwise at −78 °C and the resultant mixture was stirred at −78 °C for 15 min. The reaction mixture was then heated at reflux for 1 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (200 mL) and 1.0 M aq HCl (150 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL). The combined organic extracts were washed with brine (150 mL), then dried and concentrated *in vacuo* to give **222** as an off-white solid (962 mg, 90:10 dr).

Method A – Step 2: A solution of the residue of **222** (962 mg, 90:10 dr) in MeCN (9.8 mL) was treated sequentially with DBU (0.62 mL, 4.12 mmol) and MeI (0.28 mL, 4.53 mmol) at rt. The resultant mixture was stirred at rt for 16 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (50 mL) and 2.0 M aq HCl (50 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were then washed

sequentially with satd aq $NaHCO_3$ (100 mL) and brine (100 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **224** as a colourless oil (487 mg, 48% from **229**, >99:1 dr); $[\alpha]_D^{20}$ +28.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3027, 2946 (C–H), 1736 (C=O), 1494 (C=C); δ_H (400 MHz, $CDCl_3$) 0.83 (3H, d, *J* 6.9, C(α)*Me*), 2.96 (1H, dd, *J* 9.6, 4.4, C(1')*H*), 3.20 (3H, s, O*Me*), 3.49 (1H, d, *J* 14.0, NC$H_A$$H_B$Ph), 3.53 (1H, dd, *J* 11.7, 4.4, C(2)*H*), 4.01 (1H, d, *J* 14.0, NC$H_A$$H_B$Ph), 4.15 (1H, d, *J* 11.7, C(3)*H*), 4.16 (1H, q, *J* 6.9, C(α)*H*), 4.36 (1H, dd, *J* 16.9, 1.7, C(3')H_A), 4.80 (1H, dd, *J* 10.0, 1.7, C(3')H_B), 6.22 (1H, app dt, *J* 16.9, 10.0, C(2')*H*), 6.87–6.89 (2H, m, *Ph*), 6.99–7.33 (18H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.1 (C(α)*Me*), 49.3 (*C*(1')), 50.8 (O*Me*), 50.9 (N*C*H_2Ph), 54.5 (*C*(2)), 55.5 (*C*(α)), 61.7 (*C*(3)), 117.7 (*C*(3')), 126.3, 126.4, 126.8, 127.3, 127.6, 127.7, 127.9, 128.1, 128.3, 128.3, 129.0, 129.6 (*o,m,p-Ph*), 135.5 (*C*(2')), 137.4, 139.6, 142.7, 144.3 (*i-Ph*), 172.6 (*C*(1)); *m/z* (ESI^+) 490 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{34}H_{35}NNaO_2^+$ ($[M+Na]^+$) requires 512.2560; found 512.2541.

*Method B (from **219**) – Step 1*: TMSCl (956 μL, 7.57 mmol) was added dropwise to a solution of **219** (1.20 g, 2.52 mmol, >99:1 dr) in PhMe (12 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 10 min. LiHMDS (1.0 M in THF, 7.57 mL, 7.57 mmol) was added dropwise at −78 °C and the resultant mixture was stirred at −78 °C for 15 min. The reaction mixture was heated at reflux for 1 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 (200 mL) and 1.0 M aq HCl (150 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL). The combined organic extracts were washed with brine (150 mL), then dried and concentrated *in vacuo* to give a 70:30 mixture of **222** and **223**, respectively. Purification *via* flash column chromatography (gradient elution, 0% → 8% acetone in 30–40 °C petrol) gave **222** as a white solid (632 mg, >99:1 dr); mp 77–79 °C; $[\alpha]_D^{20}$ +57.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3028, 2971 (C–H), 1704 (C=O), 1494 (C=C); δ_H (400 MHz, $CDCl_3$) 0.95 (3H, d, *J* 7.0, C(α)*Me*), 3.03 (1H, dd, *J* 9.9, 3.4, C(1')*H*), 3.51 (1H, dd, *J* 11.7, 3.4, C(2)*H*), 3.58 (1H, d, *J* 13.5, NC$H_A$$H_B$Ph), 4.07 (1H, q, *J* 7.0, C(α)*H*), 4.19 (1H, d, *J* 13.5, NC$H_A$$H_B$Ph), 4.23 (1H, d, *J* 11.7, C(3)*H*), 4.52 (1H, dd, *J* 17.1, 1.8, C(3')H_A), 4.87 (1H, dd, *J* 9.9, 1.8, C(3')H_B), 6.09 (1H, app dt, *J* 17.1, 9.9, C(2')*H*), 6.98–7.01 (3H, m, *Ph*), 7.06–7.14 (5H, m, *Ph*), 7.16–7.21 (3H, m, *Ph*), 7.36–7.39 (9H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.5 (C(α)*Me*), 48.6 (*C*(1')), 51.0 (N*C*H_2Ph), 52.3 (*C*(2)), 56.9 (*C*(α)), 61.5 (*C*(3)), 118.0 (*C*(3')), 126.3, 127.3, 127.3, 127.4, 128.0, 128.1, 128.3, 128.5, 128.5, 128.6, 129.2, 129.9 (*o,m,p-Ph*), 135.9 (*C*(2')), 136.8, 137.5, 141.2, 142.6 (*i-Ph*), 176.1

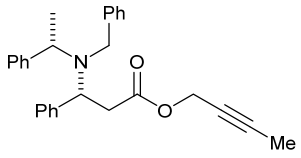
(*C*(1)); *m*/*z* (ESI$^+$) 476 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{33}H_{34}NO_2^+$ ([M+H]$^+$) requires 476.2584; found 476.2571. Further elution (eluent 30–40 °C petrol/acetone, 92:8) gave **223** as a yellow oil (175 mg, >99:1 dr); $[\alpha]_D^{20}$ +39.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3029, 2928 (C–H), 1707 (C=O), 1494 (C=C); δ_H (400 MHz, $CDCl_3$) 0.96 (3H, d, *J* 7.0, C(α)*Me*), 3.05 (1H, dd, *J* 7.7, 3.6, C(1')*H*), 3.33 (1H, dd, *J* 11.4, 3.6, C(2)*H*), 3.55 (1H, d, *J* 13.2, NCH_AH$_B$Ph), 4.03 (1H, q, *J* 7.0, C(α)*H*), 4.12 (1H, d, *J* 13.2, NCH$_A$$H_B$Ph), 4.16 (1H, app d, *J* 11.4, C(3)*H*), 4.55 (1H, app d, *J* 17.1, C(3')H_A), 4.77 (1H, d, *J* 10.0, C(3')H_B), 6.30–6.38 (1H, m, C(2')*H*), 6.75–6.78 (2H, m, *Ph*), 6.94–7.02 (3H, m, *Ph*), 7.09–7.28 (12H, m, *Ph*), 7.35–7.41 (3H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.7 (C(α)*Me*), 49.5 (*C*(1')), 50.5 (*C*(2)), 51.1 (N*C*H$_2$Ph), 57.9 (*C*(α)), 60.9 (*C*(3)), 113.9 (*C*(3')), 126.4, 128.0, 128.0, 128.1, 128.4, 128.6, 128.6, 128.8, 128.8, 128.8, 129.5, 130.1 (*o*,*m*,*p*-*Ph*), 135.0, 135.2, 138.9, 139.5 (*i*-*Ph*), 141.2 (*C*(2')), 174.0 (*C*(1)); *m*/*z* (ESI$^+$) 476 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{33}H_{34}NO_2^+$ ([M+H]$^+$) requires 476.2584; found 476.2579.

*Method B – Step 2 (for **224**)*: A solution of **222** (472 mg) in MeCN (4.7 mL) was treated sequentially with DBU (296 μL, 1.98 mmol) and MeI (135 μL, 2.18 mmol) at rt. The reaction mixture was stirred at rt for 16 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (50 mL) and 2.0 M aq HCl (50 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were then washed sequentially with satd aq $NaHCO_3$ (100 mL) and brine (100 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **224** as a colourless oil (350 mg, 38% from **219**, >99:1 dr).

*Method B – Step 2 (for **225**)*: A solution of **223** (150 mg) in MeCN (1.5 mL) was treated sequentially with DBU (94 μL, 0.63 mmol) and MeI (43 μL, 0.69 mmol) at rt. The reaction mixture was stirred at rt for 16 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and 2.0 M aq HCl (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then washed sequentially with satd aq $NaHCO_3$ (40 mL) and brine (40 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **225** as a colourless oil (133 mg, 13% from **219**, >99:1 dr); $[\alpha]_D^{20}$ +33.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3028, 2946 (C–H), 1739 (C=O), 1494 (C=C); δ_H (400 MHz, $CDCl_3$) 0.98 (3H, d, *J* 6.9, C(α)*Me*), 3.28 (3H, s, O*Me*), 3.38 (1H, app t, *J* 8.1, C(1')*H*), 3.67 (1H, d, *J* 13.9, NCH_AH$_B$Ph), 3.83 (1H, dd, *J* 11.2, 8.1, C(2)*H*), 4.18 (1H, d, *J* 13.9, NCH$_A$$H_B$Ph), 4.24 (1H, d, *J* 11.2,

C(3)*H*), 4.32 (1H, q, *J* 6.9, C(α)*H*), 4.58–4.68 (2H, m, C(3')H_2), 5.55–5.64 (1H, m, C(2')*H*), 7.01–7.03 (2H, m, *Ph*), 7.15–7.47 (18H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.4 (C(α)*Me*), 50.8 (O*Me*), 50.9 (N*C*H_2Ph), 51.4 (*C*(1')), 54.0 (*C*(2)), 55.9 (*C*(α)), 62.3 (*C*(3)), 114.4 (*C*(3')), 126.2, 126.3, 126.6, 127.4, 127.7, 127.7, 127.8, 128.0, 128.1, 128.4, 128.9, 129.9 (*o*,*m*,*p*-*Ph*), 138.2, 139.0, 139.6 (*i*-*Ph*), 141.1 (*C*(2')), 144.4 (*i*-*Ph*), 172.6 (*C*(1)); *m*/*z* (ESI^+) 490 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{34}H_{36}NO_2^+$ ($[M+H]^+$) requires 490.2741; found 490.2750.

But-2'-yn-1'-yl (3*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 226

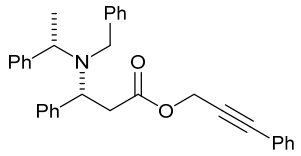


Step 1: TFA (9.2 mL) was added to a stirred solution of **192** (2.00 g, 4.82 mmol, >99:1 dr) in CH_2Cl_2 (16 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with CH_2Cl_2 (100 mL) and the resultant mixture was washed with satd aq $NaHCO_3$ (150 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give a yellow oil (1.66 g).

Step 2: A stirred solution of the residue (1.66 g) in CH_2Cl_2 (20 mL) was cooled to 0 °C and treated sequentially with $(COCl)_2$ (0.43 mL, 5.06 mmol) and DMF (20 μL, 0.26 μmol). The reaction mixture was then allowed to warm to rt over 1 h and concentrated *in vacuo*. The residue was dissolved in in CH_2Cl_2 (25 mL), the resultant solution was cooled to 0 °C, and a solution of 2-butyn-1-ol **230** (405 mg, 5.78 mmol, >99:1 dr) in CH_2Cl_2 (2 mL) was then added. The reaction mixture was allowed to warm to rt and stirred at rt for 16 h. Satd aq $NaHCO_3$ (100 mL) was then added and the resultant mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (200 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 96:4) gave **226** as a colourless oil (1.37 g, 69% from **192**, >99:1 dr); $[\alpha]_D^{20}$ −6.74 (*c* 1.08 in $CHCl_3$); ν_{max} (ATR) 3028 (C–H), 1738 (C=O), 1159, 699; δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, *J* 6.9, C(α)*Me*), 1.88 (3H, app t, *J* 2.5, C(4')H_3), 2.69 (1H, dd, *J* 15.0, 9.4, C(2)H_A), 2.80 (1H, dd, *J* 15.0, 5.8, C(2)H_B), 3.75 (1H, d, *J* 14.6, NC$H_A$$H_B$Ph), 3.83 (1H, d, *J* 14.6, NC$H_A$$H_B$Ph), 4.10 (1H, q, *J* 6.9, C(α)*H*), 4.46–4.61 (3H, m, C(1')H_2, C(3)*H*), 7.25–7.44 (11H, m, *Ph*), 7.48–7.52 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 3.6 (*C*(4')), 15.7 (C(α)*Me*), 37.3 (*C*(2)), 50.6 (N*C*H_2Ph), 52.6 (*C*(1')), 56.6 (*C*(α)), 59.1 (*C*(3)), 73.0 (*C*(3')), 82.9 (*C*(2')), 126.6,

126.8, 127.2, 127.8, 128.0, 128.1, 128.1, 128.1, 128.2 (*o*,*m*,*p*-*Ph*), 141.2, 141.5, 143.9 (*i*-*Ph*), 171.0 (*C*(1)); *m*/*z* (ESI$^+$) 412 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{29}NNaO_2^+$ ([M+Na]$^+$) requires 434.2091; found 434.2077.

3'-Phenylprop-2'-yn-1'-yl (3*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 227

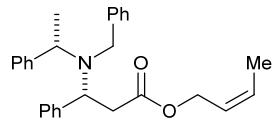


Step 1: TFA (4.6 mL) was added to a stirred solution of **192** (1.00 g, 2.41 mmol, >99:1 dr) in CH_2Cl_2 (9.3 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with CH_2Cl_2 (100 mL) and the resultant mixture was washed with satd aq $NaHCO_3$ (150 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give a yellow oil (1.01 g);

Step 2: A stirred solution of the residue (1.01 g) in CH_2Cl_2 (10 mL) was cooled to 0 °C and treated sequentially with $(COCl)_2$ (0.22 mL, 2.53 mmol) and DMF (20 μL, 0.26 μmol). The reaction mixture was then allowed to warm to rt over 1 h and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (25 mL), the resultant solution was cooled to 0 °C, and a solution of 3-phenyl-2-propyn-1-ol **231** (382 mg, 2.89 mmol, >99:1 dr) in CH_2Cl_2 (2 mL) was then added. The reaction mixture was allowed to warm to rt and stirred at rt for 16 h. Satd aq $NaHCO_3$ (100 mL) was then added and the resultant mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (200 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 97:3) gave **227** as a colourless oil (513 mg, 45% from **192**, >99:1 dr); $[\alpha]_D^{20}$ −10.1 (*c* 1.01 in $CHCl_3$); ν_{max} (ATR) 3028 (C–H), 1741 (C=O), 1161, 699; δ_H (400 MHz, $CDCl_3$) 1.15 (3H, d, *J* 6.8, C(α)*Me*), 2.55 (1H, dd, *J* 15.0, 9.1, C(2)H_A), 2.66 (1H, dd, *J* 15.0, 5.7, C(2)H_B), 3.59 (1H, d, *J* 14.7, NCH_AH$_B$Ph), 3.67 (1H, d, *J* 14.7, NCH$_A$$H_B$Ph), 3.93 (1H, q, *J* 6.8, C(α)*H*), 4.41 (1H, dd, *J* 9.1, 5.7, C(3)*H*), 4.58 (1H, d, *J* 15.7, C(1')H_A), 4.68 (1H, d, *J* 15.7, C(1')H_B), 7.08–7.27 (14H, m, *Ph*), 7.32–7.36 (6H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.8 (C(α)*Me*), 37.4 (*C*(2)), 50.7 (N*C*H$_2$Ph), 52.6 (*C*(1')), 56.7 (*C*(α)), 59.1 (*C*(3)), 82.9 (*C*(3')), 86.3 (*C*(2')), 122.2 (*i*-*Ph*), 126.6, 126.9, 127.3, 127.8, 128.0, 128.1, 128.1, 128.2, 128.2, 128.3, 128.7, 131.8 (*o*,*m*,*p*-*Ph*), 141.2, 141.5, 143.9 (*i*-*Ph*), 171.0 (*C*(1)); *m*/*z* (ESI$^+$) 474

([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{33}H_{31}NNaO_2^+$ ([M+Na]$^+$) requires 496.2247; found 496.2244.

(*Z*)-But-2'-en-1'-yl (3*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 228



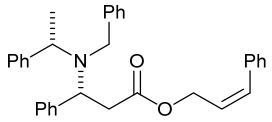
Method A – Step 1: TFA (7 mL) was added to a solution of **192** (1.60 g, 3.85 mmol, >99:1 dr) in CH_2Cl_2 (15 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with $NaHCO_3$ (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give a yellow oil (1.58 g, >99:1 dr).

Method A – Step 2: A solution of the residue (1.58 g, >99:1 dr) in CH_2Cl_2 (16 mL) was treated sequentially with $(COCl)_2$ (0.35 mL, 4.05 mmol) and DMF (13 μL, 0.17 μmol) at 0 °C. The reaction mixture was allowed to warm to rt over 1 h then concentrated *in vacuo*. A solution of **232** (0.39 g, 5.39 mmol, >99:1 dr) was then added to a solution of the residue in CH_2Cl_2 (16 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred at rt for 16 h. Satd aq $NaHCO_3$ (100 mL) was then added and the resultant mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (300 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 0% → 7% Et_2O in 30–40 °C petrol) gave **228** as a colourless oil (960 mg, 60% from **192**, >99:1 dr); $[\alpha]_D^{20}$ –8.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3028 (C–H), 1732 (C=O), 1493 (C=C); δ_H (400 MHz, $CDCl_3$) 1.25 (3H, d, *J* 6.8, C(α)*Me*), 1.61–1.63 (3H, m, C(4')H_3), 2.59 (1H, dd, *J* 14.6, 9.4, C(2)H_A), 2.69 (1H, dd, *J* 14.6, 5.6, C(2)H_B), 3.68 (1H, d, *J* 14.8, NCH_AH$_B$Ph), 3.75 (1H, d, *J* 14.8, NCH$_A$$H_B$Ph), 4.02 (1H, q, *J* 6.8, C(α)*H*), 4.40–4.51 (3H, m, C(3)*H*, C(1')H_2), 5.31–5.38 (1H, m, C(2')*H*), 5.61–5.70 (1H, m, C(3')*H*), 7.17–7.37 (11H, m, *Ph*), 7.41–7.45 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.0 (*C*(4')), 15.8 (C(α)*Me*), 37.6 (*C*(2)), 50.7 (N*C*H$_2$Ph), 56.7 (*C*(α)), 59.4 (*C*(3)), 59.9 (*C*(1')), 124.1 (*C*(2')), 126.5, 126.8, 127.1, 127.8, 128.0, 128.0, 128.1, 128.1, 128.2 (*o*,*m*,*p*-*Ph*), 129.3 (*C*(3')), 141.4, 141.7, 144.0 (*i*-*Ph*), 171.6 (*C*(1)); *m*/*z* (ESI$^+$) 414 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{31}NNaO_2^+$ ([M+Na]$^+$) requires 436.2247; found 436.2234.

Method B: $NaBH_4$ (83 mg, 2.19 mmol) was added portionwise to a stirred solution of $Ni(OAc)_2{\cdot}4H_2O$ (540 mg, 2.19 mmol) in MeOH (20 mL) at 0 °C, and the resultant black

mixture was stirred and allowed to warm to rt over 15 min. $(CH_2NH_2)_2$ (3.65 mL, 54.7 mmol) and a solution of **226** (900 mg, 2.19 mmol) in MeOH (20 mL) were added sequentially at rt and the resultant suspension was then vigorously stirred under H_2 (1 atm) at rt. The progress of the hydrogenation reaction was closely monitored by MS analysis. Once complete (45 min) the reaction mixture was filtered through Celite® (eluent EtOAc) and the filtrate was concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **228** as a colourless oil (468 mg, 52%, >99:1 dr); $[\alpha]_D^{20}$ –6.2 (*c* 1.0 in $CHCl_3$).

(*Z*)-3'-Phenylprop-2'-en-1'-yl (3*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 229



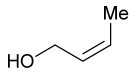
Method A – Step 1: TFA (2 mL) was added to a solution of **192** (500 mg, 1.20 mmol, >99:1 dr) in CH_2Cl_2 (4 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with CH_2Cl_2 (50 mL) and washed with $NaHCO_3$ (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give a yellow oil (475 mg, >99:1 dr).

Method A – Step 2: A solution of the residue (475 mg, >99:1 dr) in CH_2Cl_2 (5 mL) was treated sequentially with $(COCl)_2$ (108 μL, 1.26 mmol) and DMF (4 μL, 0.05 μmol) at 0 °C. The reaction mixture was allowed to warm to rt over 1 h then concentrated *in vacuo*. A solution of **233** (226 mg, 1.69 mmol, >99:1 dr) was then added to a solution of the residue in CH_2Cl_2 (5 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred at this temperature for 16 h. Sat aq $NaHCO_3$ (50 mL) was then added and the resultant mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with brine (150 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 0% → 10% Et_2O in 30–40 °C petrol) gave **229** as a colourless oil (342 mg, 60% from **192**, >99:1 dr); $[\alpha]_D^{20}$ –12.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3027, 2969 (C–H), 1733 (C=O), 1494 (C=C); δ_H (400 MHz, $CDCl_3$) 1.12 (3H, d, *J* 6.9, C(α)*Me*), 2.51 (1H, dd, *J* 14.7, 9.4, C(2)H_A), 2.60 (1H, dd, *J* 14.7, 5.6, C(2)H_B), 3.57 (1H, d, *J* 14.8, NC$H_A$$H_B$Ph), 3.64 (1H, d, *J* 14.8, NC$H_A$$H_B$Ph), 3.91 (1H, q, *J* 6.9, C(α)*H*), 4.37 (1H, dd, *J* 9.4, 5.6, C(3)*H*), 4.51–4.60 (2H, m, C(1')H_2), 5.45 (1H, dt, *J* 11.7, 6.6, C(2')*H*), 6.44–6.47 (1H, m, C(3')*H*), 7.02–7.25 (16H, m, *Ph*), 7.31–7.33 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.9 (C(α)*Me*), 37.5 (*C*(2)), 50.7

(N*C*H$_2$Ph), 56.7 (*C*(α)), 59.3 (*C*(3)), 61.3 (*C*(1')), 125.7 (*C*(2')), 126.6, 126.8, 127.2, 127.4, 127.8, 128.0, 128.0, 128.1, 128.1, 128.2, 128.3, 128.6 (*o,m,p-Ph*), 132.6 (*C*(3')), 135.9, 141.3, 141.6, 143.9 (*i-Ph*), 171.5 (*C*(1)); *m*/*z* (ESI$^+$) 476 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{33}H_{33}NNaO_2^+$ ([M+Na]$^+$) requires 498.2404; found 498.2382.

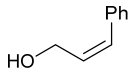
Method B: $NaBH_4$ (6 mg, 0.15 mmol) was added portionwise to a stirred solution of $Ni(OAc)_2{\cdot}4H_2O$ (37 mg, 0.15 mmol) in MeOH (1.6 mL) at 0 °C and the resultant black mixture was stirred and allowed to warm to rt over 15 min. $(CH_2NH_2)_2$ (0.25 mL, 3.70 mmol) and a solution of **227** (70 mg, 0.15 mmol) in MeOH (1.6 mL) were added sequentially at rt and the resultant suspension was then vigorously stirred under H_2 (1 atm) at rt. The progress of the hydrogenation reaction was closely monitored by MS analysis. Once complete (45 min) the reaction mixture was filtered through Celite® (eluent EtOAc) and the filtrate was concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **229** as a colourless oil (48 mg, 68%, >99:1 dr); $[\alpha]_D^{20}$ –12.1 (*c* 1.0 in $CHCl_3$).

(*Z*)-2-Buten-1-ol 232



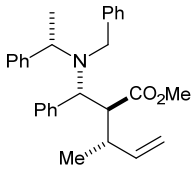
$NaBH_4$ (2.02 g, 53.5 mmol) was added portionwise to a stirred solution of $Ni(OAc)_2{\cdot}4H_2O$ (13.3 g, 53.5 mmol) in MeOH (263 mL) at 0 °C, and the resultant black mixture was allowed to warm to rt over 15 min. $(CH_2NH_2)_2$ (8.87 mL, 133 mmol) and a solution of **230** (15.0 g, 214 mmol) in MeOH (113 mL) were added sequentially at rt and the resultant suspension was then vigorously stirred under H_2 (1 atm) at rt. The progress of the hydrogenation reaction was closely monitored by TLC analysis [R_f (**230**) = 0.50, R_f (**232**) = 0.40; eluent 30–40 °C petrol/Et_2O, 50:50]. Once complete (~6 h) the reaction mixture was filtered through Celite® (eluent Et_2O) and the solvent was removed by distillation. Et_2O (200 mL) was then added to the residue and the resultant pink suspension was filtered through Celite® (eluent Et_2O) and the solvent was again removed by distillation to give **232** as an orange oil (10.2 g, 66%, >99:1 dr);[12] δ_H (400 MHz, $CDCl_3$) 1.62–1.68 (3H, m, C(4)H_3), 1.90 (1H, br s, O*H*), 4.15–4.21 (2H, m, C(1)H_2), 5.54–5.63 (2H, m, C(2)*H*, C(3)*H*).

(*Z*)-3-Phenylprop-2-en-1-ol 233



$NaBH_4$ (355 mg, 9.39 mmol) was added portionwise to a stirred solution of $Ni(OAc)_2{\cdot}4H_2O$ (2.35 g, 9.44 mmol) in MeOH (88 mL) at 0 °C, and the resultant black mixture was stirred and allowed to warm to rt over 15 min. $(CH_2NH_2)_2$ (1.56 mL, 23.3 mmol) and a solution of **231** (5.00 g, 37.8 mmol) in MeOH (38 mL) were added sequentially at rt and the resultant suspension was then vigorously stirred under H_2 (1 atm) at rt. The progress of the hydrogenation reaction was closely monitored by TLC analysis [R_f (**231**) = 0.50, R_f (**233**) = 0.39; eluent 30–40 °C petrol/Et_2O, 50:50]. Once complete (~3.5 h) the reaction mixture was filtered through Celite® (eluent EtOAc) and the filtrate was concentrated *in vacuo*. EtOAc (200 mL) was then added to the residue and the resultant pink suspension was filtered through Celite® (eluent EtOAc) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 80:20) gave **233** as a pale yellow oil (4.70 g, 93%, >99:1 dr);[13,14] δ_H (400 MHz, $CDCl_3$) 1.90 (1H, br s, O*H*), 4.45 (2H, dd, *J* 6.6, 1.8, C(1)H_2), 5.88 (1H, ddd, *J* 11.8, 6.6, 6.4, C(2)*H*), 6.56–6.60 (1H, m, C(3)*H*), 7.20–7.23 (2H, m, *Ph*), 7.26–7.30 (1H, m, *Ph*), 7.34–7.38 (2H, m, *Ph*).

Methyl (2*S*,3*R*,1'*S*,α*S*)-2-(but-3'-en-2'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 235

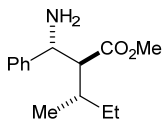


Step 1: TMSCl (541 μL, 5.08 mmol) was added dropwise to a solution of **228** (590 mg, 1.69 mmol, >99:1 dr) in PhMe (7 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 10 min. LiHMDS (1.0 M in THF, 4.28 mL, 4.28 mmol) was added dropwise at −78 °C and the resultant mixture was stirred at −78 °C for 15 min. The reaction mixture was then heated at reflux for 1 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (200 mL) and 1.0 M aq HCl (150 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL). The combined organic extracts were washed with brine (150 mL), then dried and concentrated *in vacuo* to give **234** as an orange oil (582 mg, 96:4 dr); $[\alpha]_D^{20}$ +59.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3029, 2965 (C–H), 1704 (C=O), 1494 (C=C); δ_H (400 MHz, $CDCl_3$) 1.13–1.19 (6H, m, C(1')H_3, C(α)*Me*), 1.94–2.02 (1H, m, C(2')*H*), 3.11 (1H, dd, *J* 11.6, 2.5, C(2)*H*), 3.66 (1H, d, *J* 13.4, NCH_AH_BPh), 4.16 (1H, q, *J*

6.9, C(α)*H*), 4.23–4.28 (2H, m, NCH_AH_BPh, C(3)*H*), 4.47–4.51 (1H, m, C(4')H_A), 4.70–4.73 (1H, m, C(4')H_B), 5.58–5.67 (1H, m, C(3')*H*), 7.25–7.49 (15H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 13.9 (C(α)*Me*), 20.1 (*C*(1')), 38.1 (*C*(2')), 50.8 (*C*(2)), 51.1 (NCH_2Ph), 57.5 (*C*(α)), 61.4 (*C*(3)), 115.5 (*C*(4')), 127.6, 128.2, 128.3, 128.6, 128.7, 129.4, 130.0 (*o*,*m*,*p*-*Ph*), 136.4, 136.6 (*i*-*Ph*), 139.2 (*C*(3')), 140.4 (*i*-*Ph*), 175.5 (*C*(1)); *m*/*z* (ESI^+) 414 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{28}H_{32}NO_2^+$ ($[M+H]^+$) requires 414.2428; found 414.2432.

Step 2: A solution of the residue of **234** (582 mg, 96:4 dr) in MeCN (5.9 mL) was treated sequentially with DBU (0.51 mL, 3.39 mmol) and MeI (0.23 mL, 3.73 mmol) at rt. The resultant mixture was stirred at rt for 16 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (50 mL) and 2.0 M aq HCl (50 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were then washed sequentially with satd aq $NaHCO_3$ (100 mL) and brine (100 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **235** as a colourless oil (517 mg, 85% from **228**, 96:4 dr); $[\alpha]_D^{20}$ +98.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3027, 2968 (C–H), 1736 (C=O), 1494 (C=C); δ_H (400 MHz, $CDCl_3$) 0.78 (3H, d, *J* 7.1, C(1')H_3), 0.85 (3H, d, *J* 6.9, C(α)*Me*), 1.79–1.88 (1H, m, C(2')*H*), 3.22 (1H, dd, *J* 12.0, 4.2, C(2)*H*), 3.43 (3H, s, O*Me*), 3.46 (1H, d, *J* 14.2, NCH_AH_BPh), 3.98 (1H, d, *J* 14.2, NCH_AH_BPh), 4.06 (1H, d, *J* 12.0, C(3)*H*), 4.13 (1H, q, *J* 6.9, C(α)*H*), 4.22–4.27 (1H, m, C(4')H_A), 4.62 (1H, dd, *J* 10.0, 2.0, C(4')H_B), 5.62 (1H, app dt, *J* 17.2, 10.0, C(3')*H*), 7.08–7.17 (4H, m, *Ph*), 7.19–7.29 (11H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.2 (C(α)*Me*), 19.6 (*C*(1')), 37.5 (*C*(2')), 50.7 (NCH_2Ph), 50.8 (O*Me*), 53.4 (*C*(2)), 55.8 (*C*(α)), 61.5 (*C*(3)), 115.2 (*C*(4')), 126.3, 126.6, 127.3, 127.6, 127.9, 128.0, 128.1, 128.9, 129.5 (*o*,*m*,*p*-*Ph*), 137.7 (*i*-*Ph*), 138.8 (*C*(3')), 139.8, 144.3 (*i*-*Ph*), 172.9 (*C*(1)); *m*/*z* (ESI^+) 428 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{29}H_{34}NO_2^+$ ($[M+H]^+$) requires 428.2584; found 428.2583.

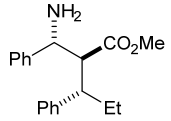
Methyl (2*S*,3*R*,1'*S*)-2-(but-2'-yl)-3-amino-3-phenylpropanoate 236



$Pd(OH)_2$/C (100 mg, 50% w/w by substrate) was added to a degassed solution of **235** (200 mg, 0.47 mmol, 96:4 dr) in MeOH (6 mL) at rt. The resultant suspension was stirred vigorously under H_2 (1 atm) at rt for 24 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (15 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (15 mL). The aqueous

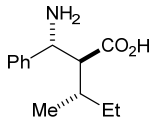
layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$/MeOH, 99:1) gave **236** as a colourless oil (83 mg, 76%, 96:4 dr); $[\alpha]_D^{20}$ +33.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3386 (N–H), 2963 (C–H), 1727 (C=O), 1154; δ_H (400 MHz, $CDCl_3$) 0.81 (3H, t, *J* 7.4, C(4')H_3), 0.96 (3H, d, *J* 6.7, C(1')H_3), 0.99–1.07 (1H, m, C(3')H_A), 1.45–1.60 (2H, m, C(2')*H*, C(3')H_B), 1.70 (2H, br s, NH_2), 2.57 (1H, dd, *J* 7.8, 6.7, C(2)*H*), 3.59 (3H, s, O*Me*), 4.26 (1H, d, *J* 7.8, C(3)*H*), 7.24–7.28 (3H, m, *Ph*), 7.30–7.36 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.6 (*C*(4')), 17.2 (*C*(1')), 25.8 (*C*(3')), 34.2 (*C*(2')), 51.0 (O*Me*), 55.1 (*C*(3)), 59.4 (*C*(2)), 126.3, 127.1, 128.4 (*o*,*m*,*p*-*Ph*), 144.2 (*i*-*Ph*), 174.6 (*C*(1)); *m*/*z* (ESI^+) 236 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{14}H_{22}NO_2^+$ ($[M+H]^+$) requires 236.1645; found 236.1643.

Methyl (2*S*,3*R*,1'*S*)-2-(1'-phenylpropyl)-3-amino-3-phenylpropanoate 237



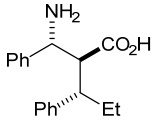
$Pd(OH)_2$/C (200 mg, 50% w/w by substrate) was added to a degassed solution of **224** (400 mg, 0.82 mmol, >99:1 dr) in MeOH (12 mL) at rt. The resultant suspension was stirred vigorously under H_2 (1 atm) at rt for 24 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (15 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), then the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$/^{i}PrOH, 99:1) gave **237** as a pale yellow oil (184 mg, 76%, >99:1 dr); $[\alpha]_D^{20}$ +4.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3397 (N–H), 3027, 2962 (C–H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 0.59 (3H, t, *J* 7.3, C(3')H_3), 1.44–1.56 (2H, m, C(2')H_2), 1.66 (2H, br s, NH_2), 2.89 (1H, app td, *J* 10.0, 4.4, C(2)*H*), 2.91–2.97 (1H, m, C(1')*H*), 3.39 (3H, s, O*Me*), 3.66 (1H, d, *J* 4.4, C(3)*H*), 7.02–7.05 (2H, m, *Ph*), 7.08–7.12 (1H, m, *Ph*), 7.15–7.20 (5H, m, *Ph*), 7.25–7.29 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.0 (*C*(3')), 27.2 (*C*(2')), 47.3 (*C*(1')), 51.0 (O*Me*), 54.8 (*C*(3)), 59.4 (*C*(2)), 125.8, 126.7, 126.8, 128.0, 128.2, 128.6 (*o*,*m*,*p*-*Ph*), 141.7, 144.3 (*i*-*Ph*), 174.4 (*C*(1)); *m*/*z* (ESI^+) 298 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{19}H_{23}NNaO_2^+$ ($[M+Na]^+$) requires 320.1621; found 320.1611.

(2*S*,3*R*,1'*S*)-2-(But-2'-yl)-3-amino-3-phenylpropanoic acid 238



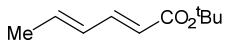
A solution of **236** (63 mg, 0.27 mmol, 96:4 dr) in 6.0 M aq HCl (8.8 mL) was heated at reflux for 5 days. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in H_2O (2 mL) and purified on DOWEX 50WX8 ion exchange resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) to give **238** as a white solid (54 mg, 91%, 96:4 dr); mp 190–192 °C; $[\alpha]_D^{20}$ +27.1 (*c* 0.3 in H_2O); ν_{max} (ATR) 3604, 2965 (C–H), 1649 (C=O), 1498 (C=C); δ_H (400 MHz, MeOH-d_4) 0.88 (3H, t, *J* 7.2, C(4')H_3), 1.10 (3H, d, *J* 6.8, C(1')H_3), 1.06–1.17 (1H, m, C(3')H_A), 1.50–1.64 (2H, m, C(2')*H*, C(3')H_B), 2.49–2.52 (1H, m, C(2)*H*), 4.51 (1H, d, *J* 6.4, C(3)*H*), 7.38–7.52 (5H, m, *Ph*); δ_C (100 MHz, MeOH-d_4) 12.3 (*C*(4')), 17.7 (*C*(1')), 27.7 (*C*(3')), 36.1 (*C*(2')), 56.1 (*C*(3)), 59.1 (*C*(2)), 128.5, 130.0, 130.3 (*o*,*m*,*p*-*Ph*), 139.0 (*i*-*Ph*), 179.4 (*C*(1)); *m*/*z* (ESI^+) 222 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{13}H_{19}NNaO_2^+$ ($[M+Na]^+$) requires 244.1308; found 244.1314.

(2*S*,3*R*,1'*S*)-2-(1'-Phenylpropyl)-3-amino-3-phenylpropanoic acid 239



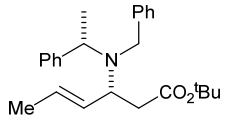
A solution of **237** (73 mg, 0.24 mmol, >99:1 dr) in 6.0 M aq HCl (10 mL) was heated at reflux for 5 days. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in H_2O (2 mL) and purified on DOWEX 50WX8 ion exchange resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) to give **239** as a white solid (61 mg, 88%, >99:1 dr); mp 209–211 °C (sub.); $[\alpha]_D^{20}$ −19.6 (*c* 0.2 in H_2O); ν_{max} (ATR) 2957 (C–H), 1613, 1571, 1496; δ_H (500 MHz, D_2O) 0.57 (3H, t, *J* 7.3, C(3')H_3), 1.47–1.56 (1H, m, C(2')H_A), 1.60–1.67 (1H, m, C(2')H_B), 2.71 (1H, td, *J* 10.8, 3.7, C(1')*H*), 2.84 (1H, dd, *J* 10.8, 3.7, C(2)*H*), 4.05 (1H, d, *J* 3.7, C(3)*H*), 7.10–7.12 (2H, m, *Ph*), 7.27–7.34 (6H, m, *Ph*), 7.36–7.39 (2H, m, *Ph*); δ_C (125 MHz, D_2O) 11.1 (*C*(3')), 27.1 (*C*(2')), 47.1 (*C*(1')), 54.1 (*C*(3)), 58.6 (*C*(2)), 126.0, 127.1, 128.5, 128.8, 129.0, 129.1 (*o*,*m*,*p*-*Ph*), 136.3, 141.3 (*i*-*Ph*), 179.1 (*C*(1)); *m*/*z* (ESI^+) 284 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{18}H_{22}NO_2^+$ ($[M+H]^+$) requires 284.1645; found 284.1645.

***tert*-Butyl (*E*,*E*)-hexa-2,4-dienoate 247**



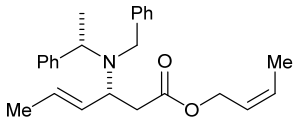
Conc. H_2SO_4 (5.0 mL) was added dropwise to a solution of **246** (50.0 g, 446 mmol) in CH_2Cl_2 (1 L) at 0 °C. Isobutylene (300 mL) was condensed at −78 °C and added dropwise. After stirring for 1 h at 0 °C the reaction mixture was allowed to warm to rt over 48 h. The reaction mixture was washed with satd aq $NaHCO_3$ solution (5 × 500 mL) and the combined aqueous washes were extracted with CH_2Cl_2 (2 × 500 mL). The combined organic extracts were washed with brine (500 mL), then dried and concentrated *in vacuo* to give **247** as a colourless oil (60.0 g, 80%, >99:1 dr);[15] δ_H (400 MHz, $CDCl_3$) 1.49 (9H, s, C*Me*$_3$), 1.84 (3H, d, *J* 5.8, C(6)*H*$_3$), 5.71 (1H, d, *J* 15.3, C(2)*H*), 6.05–6.21 (2H, m, C(4)*H*, C(5)*H*), 7.16 (1H, dd, *J* 15.3, 10.1, C(3)*H*).

***tert*-Butyl (3*R*,α*S*,*E*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 248**



BuLi (2.0 M in hexanes, 23.0 mL, 46.1 mmol) was added dropwise to a stirred solution of (*S*)-**162** (10.1 g, 47.6 mmol) in THF (165 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of **247** (5.0 g, 29.7 mmol, >99:1 dr) in THF (65 mL) at −78 °C was then added dropwise *via* cannula, and the reaction mixture was stirred at −78 °C for 2 h. Satd aq NH_4Cl (20 mL) was then added and the reaction mixture was allowed to warm to rt. The aqueous layer was extracted with Et_2O (3 × 100 mL) and the combined organic extracts were washed sequentially with 10% aq citric acid (100 mL), satd aq $NaHCO_3$ (100 mL) and brine (100 mL), then dried and concentrated *in vacuo* to give **248** in >95:5 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 99:1) gave **248** as a colourless oil (10.1 g, 89%, >99:1 dr); $[\alpha]_D^{20}$ +23.6 (*c* 1.0 in $CHCl_3$); {lit.[16] for *ent*-**248** $[\alpha]_D^{23}$ −23.3 (*c* 2.04 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.37 (9H, s, C*Me*$_3$), 1.38 (3H, d, *J* 6.8, C(α)*Me*), 1.68–1.71 (3H, m, C(6)*H*$_3$), 2.23 (1H, dd, *J* 14.1, 9.4, C(2)*H*$_A$), 2.35 (1H, dd, *J* 14.1, 5.6, C(2)*H*$_B$), 3.67 (2H, app s, NC*H*$_2$Ph), 3.72–3.79 (1H, m, C(3)*H*), 4.01 (1H, q, *J* 6.8, C(α)*H*), 5.48–5.59 (2H, m, C(4)*H*, C(5)*H*), 7.17–7.23 (2H, m, *Ph*), 7.26–7.34 (6H, m, *Ph*), 7.38–7.41 (2H, m, *Ph*).

(*Z*)-But-2'-en-1'-yl (3*R*,α*S*,*E*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 249

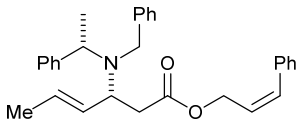


Step 1: TFA (10 mL) was added to a stirred solution of **248** (2.50 g, 6.59 mmol, >99:1 dr) in CH_2Cl_2 (20 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with CH_2Cl_2 (100 mL) and the resultant mixture was washed with satd aq $NaHCO_3$ (150 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give a yellow oil (2.20 g); δ_H (400 MHz, $CDCl_3$) 1.49 (3H, d, *J* 6.9, C(α)*Me*), 1.71–1.73 (3H, m, C(6)H_3), 2.21 (1H, dd, *J* 17.2, 4.4, C(2)H_A), 2.39 (1H, dd, *J* 17.2, 11.5, C(2)H_B), 3.67 (1H, d, *J* 13.6, NCH_AH$_B$Ph), 3.80 (1H, ddd, *J* 11.5, 7.9, 4.4, C(3)*H*), 3.92 (1H, d, *J* 13.6, NCH$_A$$H_B$Ph), 4.09 (1H, q, *J* 6.9, C(α)*H*), 5.47–5.54 (1H, m, C(4)*H*), 5.61–5.70 (1H, m, C(5)*H*), 7.17–7.29 (10H, m, *Ph*).

Step 2: A stirred solution of the residue (2.20 g) in CH_2Cl_2 (25 mL) was cooled to 0 °C and treated sequentially with $(COCl)_2$ (0.6 mL, 6.92 mmol) and DMF (20 μL, 0.26 μmol). The reaction mixture was then allowed to warm to rt over 1 h and concentrated *in vacuo*. The residue was dissolved in in CH_2Cl_2 (25 mL), the resultant solution was cooled to 0 °C, and a solution of **232** (670 mg, 9.23 mmol, >99:1 dr) was then added. The reaction mixture was allowed to warm to rt and stirred at rt for 16 h. Satd aq $NaHCO_3$ (100 mL) was then added and the resultant mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (200 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **249** as a colourless oil (1.42 g, 57% from **248**, >99:1 dr); $[\alpha]_D^{20}$ +15.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3028, 1734 (C=O), 1494 (C=C), 1171, 699; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, *J* 6.9, C(α)*Me*), 1.58 (3H, dt, *J* 6.9, 0.9, C(4')H_3), 1.61 (3H, d, *J* 5.4, C(6)H_3), 2.24 (1H, dd, *J* 14.3, 8.2, C(2)H_A), 2.38 (1H, dd, *J* 14.3, 6.5, C(2)H_B), 3.57 (1H, d, *J* 14.6, NCH_AH$_B$Ph), 3.62 (1H, d, *J* 14.6, NCH$_A$$H_B$Ph), 3.90–3.95 (1H, m, C(3)*H*), 3.92 (1H, q, *J* 6.9, C(α)*H*), 4.35–4.40 (1H, m, C(1')H_A), 4.45–4.50 (1H, m, C(1')H_B), 5.31–5.39 (1H, m, C(2')*H*), 5.41–5.52 (2H, m, C(4)*H*, C(5)*H*), 5.55–5.64 (1H, m, C(3')*H*), 7.09–7.14 (2H, m, *Ph*), 7.17–7.21 (4H, m, *Ph*), 7.24–7.29 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.1 (*C*(4')), 16.8 (C(α)*Me*), 18.0 (*C*(6)), 38.6 (*C*(2)), 50.3 (NCH_2Ph), 56.8 (*C*(3)), 56.8 (*C*(α)), 59.8 (*C*(1')), 124.4 (*C*(2')), 126.5, 126.6 (*o*,*m*,*p*-*Ph*), 127.1 (*C*(5)), 127.8, 127.9, 128.0, 128.3 (*o*,*m*,*p*-*Ph*), 129.1 (*C*(3')), 131.1 (*C*(4)),

141.3, 144.3 (*i-Ph*), 171.7 (*C*(1)); *m*/*z* (ESI$^+$) 378 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{32}NO_2^+$ ([M+H]$^+$) requires 378.2428; found 378.2434.

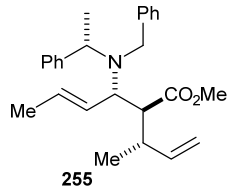
(*Z*)-3'-Phenylprop-2'-en-1'-yl (3*R*,α*S*,*E*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 250

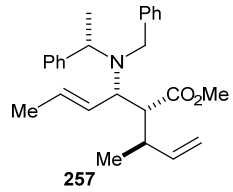


Step 1: TFA (10 mL) was added to a stirred solution of **248** (2.55 g, 6.70 mmol, >99:1 dr) in CH_2Cl_2 (20 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with CH_2Cl_2 (100 mL) and the resultant mixture was washed with $NaHCO_3$ (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give a yellow oil (2.50 g).

Step 2: A stirred solution of the residue (2.50 g) in CH_2Cl_2 (25 mL) was cooled to 0 °C and treated sequentially with $(COCl)_2$ (0.6 mL, 7.06 mmol) and DMF (20 μL, 0.26 μmol). The reaction mixture was then allowed to warm to rt over 1 h and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (25 mL), the resultant solution was cooled to 0 °C, and a solution of **233** (1.26 g, 9.41 mmol, >99:1 dr) was then added. The reaction mixture was allowed to warm to rt and stirred at rt for 16 h. Satd aq $NaHCO_3$ (100 mL) was then added and the resultant mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (200 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **250** as a colourless oil (1.86 g, 63% from **248**, >99:1 dr); $[\alpha]_D^{20}$ +5.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3027, 1735 (C=O), 1494 (C=C), 1167, 699; δ_H (400 MHz, $CDCl_3$) 1.39 (3H, d, *J* 6.8, C(α)*Me*), 1.71 (3H, d, *J* 5.3, C(6)H_3), 2.36 (1H, dd, *J* 14.2, 8.1, C(2)H_A), 2.51 (1H, dd, *J* 14.2, 6.8, C(2)H_B), 3.68 (1H, d, *J* 14.6, NCH_AH$_B$Ph), 3.74 (1H, d, *J* 14.6, NCH$_A$$H_B$Ph), 3.80–3.85 (1H, m, C(3)*H*), 4.02 (1H, q, *J* 6.8, C(α)*H*), 4.64–4.69 (1H, m, C(1')H_A), 4.75–4.80 (1H, m, C(1')H_B), 5.51–5.60 (2H, m, C(4)*H*, C(5)*H*), 5.63–5.72 (1H, m, C(2')*H*), 6.64 (1H, d, *J* 11.6, C(3')*H*), 7.16–7.23 (6H, m, *Ph*), 7.25–7.32 (5H, m, *Ph*), 7.35–7.40 (4H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 16.7 (C(α)*Me*), 18.0 (*C*(6)), 38.6 (*C*(2)), 50.3 (N*C*H$_2$Ph), 56.8 (*C*(α)), 56.7 (*C*(3)), 61.3 (*C*(1')), 126.1 (*C*(2')), 126.6, 126.6 (*o*,*m*,*p-Ph*), 127.2 (*C*(5)), 127.4, 127.8, 127.9, 128.1, 128.3, 128.4, 128.7 (*o*,*m*,*p-Ph*), 131.1 (*C*(4)), 132.4 (*C*(3')), 136.1, 141.3, 144.3 (*i-Ph*), 171.6 (*C*(1)); *m*/*z* (ESI$^+$) 440 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{34}NO_2^+$ ([M+H]$^+$) requires 440.2584; found 440.2566.

Methyl (*S*,*S*,*S*,*S*,*E*)-2-(but-3'-en-2'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 255 and methyl (2*R*,3*S*,2'*R*,α*S*,*E*)-2-(but-3'-en-2'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 257





Step 1: TMSCl (3.01 mL, 23.8 mmol) was added dropwise to a stirred solution of **249** (3.00 g, 7.90 mmol, >99:1 dr) in PhMe (30 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 10 min. LiHMDS (1.0 M in THF, 23.8 mL, 23.8 mmol) was added dropwise at −78 °C and the resultant solution was stirred at −78 °C for 15 min. The reaction mixture was then stirred at reflux for 1 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 (200 mL) and 1.0 M aq HCl (150 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL) and the combined organic extracts were washed brine (150 mL), then dried and concentrated *in vacuo* to give an 80:20 mixture of **251** and **253**, respectively. Purification *via* flash column chromatography (gradient elution, 0% → 8% acetone in 30–40 °C petrol) gave **253** as a yellow oil (574 mg, >99:1 dr); $[\alpha]_D^{20}$ +12.9 (*c* 0.7 in $CHCl_3$); ν_{max} (ATR) 2965 (C–H), 1703 (C=O), 1494 (C=C), 699; δ_H (400 MHz, $CDCl_3$) 0.75 (3H, d, *J* 6.9, C(1')H_3), 1.34 (3H, d, *J* 6.9, C(α)*Me*), 1.60–1.62 (3H, m, C(6)H_3), 2.24 (1H, app t, *J* 6.9, C(2)*H*), 2.42–2.50 (1H, m, C(2')*H*), 3.45–3.49 (1H, m, C(3)*H*), 3.52 (1H, d, *J* 14.1, NCH_AH$_B$Ph), 3.75 (1H, d, *J* 14.1, NCH$_A$$H_B$Ph), 4.09 (1H, q, *J* 6.9, C(α)*H*), 4.64–4.74 (2H, m, C(4')H_2), 5.43–5.59 (3H, m, C(4)*H*), C(5)*H*, C(3')*H*), 7.08–7.33 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.2 (C(α)*Me*), 17.5 (*C*(1')), 18.0 (*C*(6)), 35.2 (*C*(2')), 51.9 (N*C*H$_2$Ph), 53.1 (*C*(2)), 57.2 (*C*(α)), 61.7 (*C*(3)), 113.6 (*C*(4')), 127.0 (*o*,*m*,*p*-*Ph*), 127.2 (*C*(4)), 127.3, 128.3, 128.3, 128.8 (*o*,*m*,*p*-*Ph*), 130.8 (*C*(5), 139.6 (*i*-*Ph*), 141.1 (*C*(3')), 142.5 (*i*-*Ph*), 177.0 (*C*(1)); *m*/*z* (ESI^+) 378 ($[M+H]^+$, 100%), 400 ($[M+Na]^+$, 4%); HRMS (ESI^+) $C_{25}H_{31}NNaO_2^+$ ($[M+Na]^+$) requires 400.2247; found 400.2239. Further elution (eluent 30–40 °C petrol/acetone, 92:8) gave **251** as a yellow oil (1.79 g, >99:1 dr); $[\alpha]_D^{20}$ +15.2 (*c* 0.8 in $CHCl_3$); ν_{max} (ATR) 2966 (C–H), 1704 (C=O), 1495 (C=C), 698; δ_H (400 MHz, $CDCl_3$) 1.07 (3H, d, *J* 7.1, C(1')H_3), 1.45 (3H, d, *J* 7.0, C(α)*Me*), 1.77–1.79 (3H, m, C(6)H_3), 2.16–2.19 (1H, m, C(2)*H*), 2.37–2.44 (1H, m, C(2')*H*), 3.62 (1H, d, *J* 13.6, NCH_AH$_B$Ph), 3.68 (1H, app t, *J* 10.4, C(3)*H*), 3.87 (1H, d, *J* 13.6, NCH$_A$$H_B$Ph), 3.99 (1H, q, *J* 7.0, C(α)*H*), 4.64–4.75 (2H, m, C(4')H_2), 5.37 (1H, ddd, *J* 15.4, 9.8, 1.7, C(4)*H*), 5.54–5.61 (1H, m,

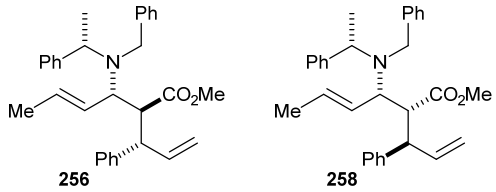
C(3')*H*), 5.61–5.68 (1H, m, C(5)*H*), 7.13–7.23 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.8 (C(α)*Me*), 18.1 (*C*(6)), 19.2 (*C*(1')), 37.6 (*C*(2')), 49.2 (*C*(2)), 50.8 (N*C*H_2Ph), 59.4 (*C*(3)), 60.5 (*C*(α)), 114.7 (*C*(4')), 126.2 (*C*(4)), 127.8, 127.9, 128.3, 128.5, 128.5, 129.4 (*o*,*m*,*p*-*Ph*), 133.5 (*C*(5)), 135.4, 140.0 (*i*-*Ph*), 140.3 (*C*(3')), 174.4 (*C*(1)); *m*/*z* (ESI^+) 378 ($[M+H]^+$, 100%), 400 ($[M+Na]^+$, 5%); HRMS (ESI^+) $C_{25}H_{31}NNaO_2^+$ ($[M+Na]^+$) requires 400.2247; found 400.2241.

Step 2 (*for* ***255***): A solution of **251** (1.79 g) in MeCN (8 mL) was treated sequentially with DBU (1.42 ml, 9.48 mmol) and MeI (0.65 mL, 10.4 mmol) at rt. The reaction mixture was stirred at rt for 16 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (80 mL) and 2.0 M aq HCl (80 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were then washed sequentially with satd aq $NaHCO_3$ (150 mL) and brine (150 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **255** as a colourless oil (1.39 g, 45% from **249**, >99:1 dr); $[\alpha]_D^{20}$ −10.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3026, 2966 (C–H), 1734 (C=O), 1495 (C=C), 1150, 699; δ_H (400 MHz, $CDCl_3$) 0.85 (3H, d, *J* 7.1, C(1')H_3), 1.30 (3H, d, *J* 6.9, C(α)*Me*), 1.68 (3H, ddd, *J* 6.1, 1.0, 0.8, C(6)H_3), 2.15–2.23 (1H, m, C(2')*H*), 2.59–2.63 (1H, m, C(2)*H*), 3.34 (3H, s, O*Me*), 3.42–3.48 (1H, m, C(3)*H*), 3.47 (1H, d, *J* 13.9, NC$H_A$$H_B$Ph), 3.71 (1H, d, *J* 13.9, NC$H_A$$H_B$Ph), 4.03 (1H, q, *J* 6.9, C(α)*H*), 4.65–4.76 (2H, m, C(4')H_2), 5.24–5.31 (1H, m, C(5)*H*), 5.36–5.44 (1H, m, C(4)*H*), 5.59–5.68 (1H, m, C(3')*H*), 7.04–7.22 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.7 (C(α)*Me*), 18.0 (*C*(6)), 19.6 (*C*(1')), 37.4 (*C*(2')), 50.3 (N*C*H_2Ph), 50.6 (O*Me*), 54.0 (*C*(2)), 56.1 (*C*(α)), 60.5 (*C*(3)), 114.6 (*C*(4')), 126.2, 126.4, 127.6, 127.8, 127.9 (*o*,*m*,*p*-*Ph*), 128.2 (*C*(5)), 128.9 (*o*,*m*,*p*-*Ph*), 130.0 (*C*(4)), 139.2 (*C*(3')), 140.2, 144.6 (*i*-*Ph*), 173.0 (*C*(1)); *m*/*z* (ESI^+) 392 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{26}H_{33}NNaO_2^+$ ($[M+Na]^+$) requires 414.2404; found 414.2405.

Step 2 (*for* ***257***): A solution of **253** (573 mg, >99:1 dr) in MeCN (5.7 mL) was treated sequentially with DBU (454 μl, 3.04 mmol) and MeI (208 μL, 3.34 mmol) at rt. The reaction mixture was stirred at rt for 16 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (50 mL) and 2.0 M aq HCl (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (150 mL) and brine (150 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **257** as a colourless oil (438 mg, 14% from **249**, >99:1 dr); $[\alpha]_D^{20}$ −8.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR)

2968 (C–H), 1732 (C=O), 1494 (C=C), 1153, 700; δ_H (400 MHz, $CDCl_3$) 0.77 (3H, d, *J* 6.8, C(1')H_3), 1.42 (3H, d, *J* 6.8, C(α)*Me*), 1.75–1.77 (3H, m, C(6)H_3), 2.48 (1H, dd, *J* 8.2, 6.4, C(2)*H*), 2.56–2.65 (1H, m, C(2')*H*), 3.49–3.54 (1H, m, C(3)*H*), 3.56 (3H, s, O*Me*), 3.70 (1H, d, *J* 14.4, NC$H_A$$H_B$Ph), 3.78 (1H, d, *J* 14.4, NC$H_A$$H_B$Ph), 4.05 (1H, q, *J* 6.8, C(α)*H*), 4.75–4.83 (2H, m, C(4')H_2), 5.45–5.61 (2H, m, C(3')*H*, C(5)*H*), 5.69–5.75 (1H, m, C(4)*H*), 7.22–7.27 (2H, m, *Ph*), 7.30–7.36 (6H, m, *Ph*), 7.41–7.43 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.7 (C(α)*Me*), 17.7 (*C*(1')), 18.0 (*C*(6)), 35.9 (*C*(2')), 50.7 (O*Me*), 50.9 (NCH_2Ph), 55.4 (*C*(2)), 57.1 (*C*(α)), 59.3 (*C*(3)), 113.6 (*C*(4')), 126.6, 126.6, 127.9, 128.0, 128.0 (*o*,*m*,*p*-*Ph*), 128.2 (*C*(4)), 128.8 (*o*,*m*,*p*-*Ph*), 129.2 (*C*(5)), 140.4 (*C*(3')), 141.1, 144.3 (*i*-*Ph*), 173.7 (*C*(1)); *m*/*z* (ESI$^+$) 392 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{33}NNaO_2^+$ ([M+Na]$^+$) requires 414.2404; found 414.2408.

Methyl (*S*,*S*,*S*,*S*,*E*)-2-(1'-phenylprop-2'-en-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino] hex-4-enoate 256 and methyl (2*R*,3*S*,1'*R*,α*S*,*E*)-2-(1'-phenylprop-2'-en-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 258

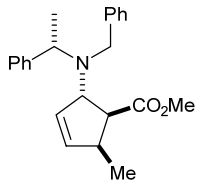


Step 1: TMSCl (2.18 mL, 17.3 mmol) was added dropwise to a stirred solution of **250** (2.53 g, 5.75 mmol, >99:1 dr) in PhMe (25.3 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 10 min. LiHMDS (1.0 M in THF, 17.3 mL, 17.3 mmol) was added dropwise at −78 °C and the resultant solution was stirred at −78 °C for 15 min. The reaction mixture was then stirred at reflux for 1 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 (200 mL) and 1.0 M aq HCl (150 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL) and the combined organic extracts were washed with brine (150 mL), then dried and concentrated *in vacuo* to give a 76:24 mixture of **252** and **254**, respectively as a brown oil (2.00 g).

Step 2: A solution of the residue in MeCN (25.3 mL) was treated sequentially with DBU (1.72 mL, 11.5 mmol) and MeI (0.79 mL, 12.7 mmol) at rt. The reaction mixture was stirred at rt for 16 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (200 mL) and 2.0 M aq HCl (200 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were then washed sequentially with satd aq

$NaHCO_3$ (250 mL) and brine (250 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 0% → 2% Et_2O in 30–40 °C petrol) gave **258** as a white solid (413 mg, 16% from **250**, >99:1 dr); mp 82–83 °C; $[\alpha]_D^{20}$ +26.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3028, 1731 (C=O), 1494 (C=C), 1167, 699; δ_H (400 MHz, $CDCl_3$) 1.11 (3H, d, *J* 6.8, C(α)*Me*), 1.62–1.64 (3H, m, C(6)H_3), 2.86 (1H, dd, *J* 10.8, 5.4, C(2)*H*), 2.96 (1H, dd, *J* 9.9, 5.4, C(3)*H*), 3.21–3.26 (1H, m, C(1')*H*), 3.51 (1H, d, *J* 14.0, NC$H_A$$H_B$Ph), 3.53 (3H, s, O*Me*), 3.63 (1H, d, *J* 14.0, NC$H_A$$H_B$Ph), 3.81 (1H, q, *J* 6.8, C(α)*H*), 4.72–4.76 (2H, m, C(3')H_2), 4.92 (1H, dq, *J* 15.4, 6.5, C(5)*H*), 5.57–5.66 (1H, m, C(2')*H*), 5.79 (1H, ddd, *J* 15.4, 9.9, 1.7, C(4)*H*), 6.47–6.49 (2H, m, *Ph*), 6.95–7.03 (3H, m, *Ph*), 7.12–7.31 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.9 (C(α)*Me*), 18.0 (C(6)), 50.2 (*C*(1')), 51.1 (O*Me*), 51.5 (N*C*H_2Ph), 54.6 (*C*(2)), 56.0 (*C*(α)), 59.8 (*C*(3)), 115.0 (*C*(3')), 126.0, 126.4, 126.6 (*o*,*m*,*p*-*Ph*), 126.9 (*C*(4)), 127.8, 127.9, 128.1, 128.1, 128.3, 128.7 (*o*,*m*,*p*-*Ph*), 130.6 (*C*(5)), 139.6 (*C*(2')), 140.3, 141.2, 144.0 (*i*-*Ph*), 174.6 (*C*(1)); *m*/*z* (ESI^+) 454 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{31}H_{35}NNaO_2^+$ ($[M+Na]^+$) requires 476.2560; found 476.2550. Further elution gave **256** as a colourless oil which solidified upon standing (1.81 g, 69% from **250**; >99:1 dr); mp 63–64 °C; $[\alpha]_D^{20}$ −65.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3027, 1737 (C=O), 1494 (C=C), 1166, 699; δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, *J* 6.9, C(α)*Me*), 1.52–1.54 (3H, m, C(6)H_3), 3.03 (1H, dd, *J* 10.8, 6.6, C(2)*H*), 3.21 (3H, s, O*Me*), 3.22–3.27 (1H, m, C(3)*H*), 3.44 (1H, d, *J* 13.9, NC$H_A$$H_B$Ph), 3.54 (1H, t, *J* 10.8, C(1')*H*), 3.70 (1H, d, *J* 13.9, NC$H_A$$H_B$Ph), 4.01 (1H, q, *J* 6.9, C(α)*H*), 4.73–4.85 (2H, m, C(3')H_2), 4.99–5.06 (1H, m, C(4)*H*), 5.35 (1H, dq, *J* 15.3, 6.4, C(5)*H*), 5.94–6.04 (1H, m, C(2')*H*), 6.94–7.20 (2H, m, *Ph*), 7.01–7.23 (13H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.4 (C(α)*Me*), 18.0 (C(6)), 50.3 (N*C*H_2Ph), 50.4 (*C*(3)), 50.7 (O*Me*), 54.7 (*C*(2)), 55.8 (*C*(α)), 61.6 (*C*(1')), 116.2 (*C*(3')), 126.1, 126.2, 126.5, 127.6, 127.8, 127.8, 127.9, 128.2 (*o*,*m*,*p*-*Ph*), 128.5 (*C*(4)), 129.0 (*o*,*m*,*p*-*Ph*), 129.9 (*C*(5)), 137.5 (*C*(2')), 140.0, 142.9, 144.6 (*i*-*Ph*), 172.9 (*C*(1)); *m*/*z* (ESI^+) 454 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{31}H_{35}NNaO_2^+$ ($[M+Na]^+$) requires 476.2560; found 476.2553.

Methyl (*S*,*S*,*S*,*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-methylcyclopent-3-ene-1-carboxylate 259



*Method A (from **255**)*: Grubbs I catalyst (589 mg, 0.72 mmol) was added to a degassed solution of **255** (530 mg, 1.79 mmol, >99:1 dr) in CH_2Cl_2 (71 mL) at rt and the resultant mixture was heated at 40 °C for 24 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **259** as a colourless oil (530 mg, 85%, >99:1 dr); $[\alpha]_D^{20}$ +190.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3028, 2969 (C–H), 1734 (C=O), 1493 (C=C), 1170, 699; δ_H (400 MHz, $CDCl_3$) 0.76 (3H, d, *J* 7.1, C(5)*Me*), 1.26 (3H, d, *J* 6.9, C(α)*Me*), 2.83 (1H, dd, *J* 9.2, 5.6, C(1)*H*), 2.29–2.98 (1H, m, C(5)*H*), 3.38 (3H, s, O*Me*), 3.57 (1H, d, *J* 15.0, NCH_AH_BPh), 3.62 (1H, d, *J* 15.0, NCH_AH_BPh), 3.77 (1H, q, *J* 6.9, C(α)*H*), 4.41–4.44 (1H, m, C(2)*H*), 5.53–5.55 (1H, m, C(4)*H*), 5.58–5.60 (1H, m, C(3)*H*), 7.08–7.24 (8H, m, *Ph*), 7.30–7.33 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.4 (C(5)*Me*), 16.4 (C(α)*Me*), 41.1 (*C*(5)), 50.1 (N*C*H_2Ph), 50.5 (*C*(1)), 51.0 (O*Me*), 57.7 (*C*(α)), 67.3 (*C*(2)), 126.5, 126.5, 127.7, 127.8, 128.1 (*o*,*m*,*p*-*Ph*), 131.7 (*C*(3)), 136.9 (*C*(4)), 141.7, 143.9 (*i*-*Ph*), 173.9 (*C*O_2Me); *m*/*z* (ESI^+) 350 ($[M+H]^+$, 100%), 372 ($[M+Na]^+$, 10%); HRMS (ESI^+) $C_{23}H_{28}NO_2^+$ ($[M+H]^+$) requires 350.2115; found 350.2118.

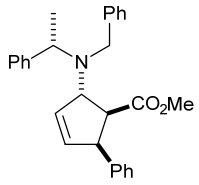
*Method B (from **249**) – Step 1:* TMSCl (0.20 mL, 1.59 mmol) was added dropwise to a stirred solution of **249** (200 mg, 0.53 mmol) in PhMe (2 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 10 min. LiHMDS (1.0 M in THF, 1.59 mL, 1.59 mmol) was added dropwise at −78 °C and the resultant solution was stirred at −78 °C for 15 min. The reaction mixture was then stirred at reflux for 1 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 (20 mL) and 1.0 M aq HCl (15 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with brine (15 mL), then dried and concentrated *in vacuo* to give an 80:20 mixture of **251** and **253** as an orange oil (223 mg).

*Method B (from **249**) – Step 2*: A solution of the residue of **251** and **253** (223 mg) in MeCN (2 mL) was treated sequentially with DBU (0.16 mL, 1.06 mmol) and MeI (0.07 mL, 1.17 mmol) at rt. The reaction mixture was stirred at rt for 16 h, then concentrated *in vacuo*.

The residue was partitioned between CH_2Cl_2 (20 mL) and 2.0 M aq HCl (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (25 mL) and brine (25 mL), then dried and concentrated *in vacuo* to give an 80:20 mixture of **255** and **257** as an orange oil (165 mg).

*Method B (from **249**) – Step 3*: Grubbs I catalyst (139 mg, 0.17 mmol) was added to a degassed solution of the residue of **255** and **257** (165 mg) in CH_2Cl_2 (16.5 mL) at rt and the resultant mixture was heated at 40 °C for 24 h. The reaction mixture was allowed to cool to rt and concentrated *in vacuo*. Resubjection of the crude reaction mixture to these reaction conditions gave **259**. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **259** as a colourless oil (107 mg, 63% from **249**, >99:1 dr); $[\alpha]_D^{20}$ +191.3 (*c* 1.0 in $CHCl_3$).

Methyl (*S*,*S*,*S*,*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-phenylcyclopent-3-ene-1-carboxylate 260



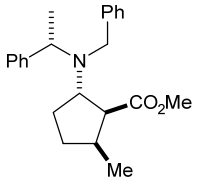
*Method A (from **256**)*: Grubbs I catalyst (121 mg, 0.15 mmol) was added to a degassed solution of **256** (167 mg, 0.37 mmol, >99:1 dr) in CH_2Cl_2 (120 mL) at rt and the resultant mixture was heated at 40 °C for 24 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **260** as a colourless oil which solidified upon standing (122 mg, 80%, >99:1 dr); mp 72–73 °C; $[\alpha]_D^{20}$ +208.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3028, 1728 (C=O), 1493 (C=C), 699; δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, *J* 6.9, (C(α)*Me*), 2.78 (3H, s, O*Me*), 3.10 (1H, dd, *J* 10.3, 5.4, C(1)*H*), 3.64 (1H, d, *J* 14.8, NC$H_A$$H_B$Ph), 3.72 (1H, d, *J* 14.8, NC$H_A$$H_B$Ph), 3.81 (1H, q, *J* 6.9, C(α)*H*), 4.13–4.17 (1H, m, C(5)*H*), 4.62–4.64 (1H, m, C(2)*H*), 5.69 (1H, app dt, *J* 5.7, 2.2, C(4)*H*), 5.89 (1H, ddd, *J* 5.7, 2.2, 2.1, C(3)*H*), 6.91–6.93 (2H, m, *Ph*), 7.02–7.26 (11H, m, *Ph*), 7.34–7.36 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.0 (C(α)*Me*), 50.1 (NCH_2Ph), 50.7 (O*Me*), 52.2 (*C*(1)), 53.4 (*C*(5)), 58.0 (*C*(α)), 67.3 (*C*(2)), 126.6, 126.6, 126.7, 127.7, 127.7, 127.9, 128.1, 128.2, 128.5 (*o*,*m*,*p*-*Ph*), 133.7 (*C*(4)), 134.7 (*C*(3)), 140.0, 141.6, 143.6 (*i*-*Ph*), 172.7 (*C*O_2Me); *m*/*z* (ESI^+) 412 ($[M+H]^+$, 100%), 434 ($[M+Na]^+$, 10%); HRMS (ESI^+) $C_{28}H_{29}NNaO_2^+$ ($[M+Na]^+$) requires 434.2091; found 434.2073.

*Method B (from **250**) – Step 1:* TMSCl (0.17 mL, 1.37 mmol) was added dropwise to a stirred solution of **250** (200 mg, 0.45 mmol) in PhMe (2 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 10 min. LiHMDS (1.0 M in THF, 1.37 mL, 1.37 mmol) was added dropwise at −78 °C and the resultant solution was stirred at −78 °C for 15 min. The reaction mixture was then stirred at reflux for 1 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 (20 mL) and 1.0 M aq HCl (15 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic extracts were washed with brine (15 mL), then dried and concentrated *in vacuo* to give to give a 76:24 mixture of **252** and **254** as an orange oil (199 mg).

*Method B (from **250**) – Step 2*: A solution of the residue of **252** and **254** (199 mg) in MeCN (2 mL) was treated sequentially with DBU (0.14 mL, 0.91 mmol) and MeI (0.06 mL, 1.00 mmol) at rt. The reaction mixture was stirred at rt for 16 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and 2.0 M aq HCl (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then washed sequentially with satd aq $NaHCO_3$ (25 mL) and brine (25 mL), then dried and concentrated *in vacuo* to give a 76:24 mixture of **256** and **258** as an orange oil (237 mg).

*Method B (from **250**) – Step 3*: Grubbs I catalyst (82 mg, 0.10 mmol) was added to a degassed solution of the residue of **256** and **258** (237 mg) in CH_2Cl_2 (20 mL) at rt and the resultant mixture was heated at 40 °C for 24 h. The resultant mixture was allowed to cool to rt and concentrated *in vacuo*. Resubjection of the crude reaction mixture to these reaction conditions twice more gave **260**. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **260** as a colourless oil (96 mg, 51% from **250**, >99:1 dr).

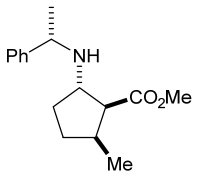
Methyl (*S*,*S*,*S*,*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-methylcyclopentane-1-carboxylate 261



Pd/C (25 mg, 50% w/w) was added to a degassed solution of **259** (50 mg, 0.14 mmol, >99:1 dr) in MeOH (3.6 mL) at rt. The resultant suspension was stirred vigorously under H_2 (1 atm) at rt for 7 min. The reaction mixture was then filtered through Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo* to give a 10:48:42 mixture of **259**, **261** and **262**, respectively. Purification *via* flash column chromatography (eluent, 30–40 °C petrol/Et_2O,

98:2) gave **261** as a colourless oil (14 mg, 27%, >99:1 dr); $[\alpha]_D^{20}$ +25.7 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 3028, 2969 (C–H), 1734 (C=O), 1453, 699; δ_H (400 MHz, $CDCl_3$) 0.76 (3H, d, *J* 6.9, C(5)*Me*), 1.22 (3H, d, *J* 6.9, C(α)*Me*), 1.18–1.28 (1H, m, C(4)H_A), 1.50–1.67 (2H, m, C(3)H_A, C(4)H_B), 1.75–1.84 (1H, m, C(3)H_B), 2.03–2.14 (1H, m, C(5)*H*), 2.67 (1H, dd, *J* 9.7, 6.5, C(1)*H*), 3.39 (3H, s, O*Me*), 3.67 (2H, app s, NCH_2Ph), 3.68–3.76 (2H, m, C(2)*H*, C(α)*H*), 7.09–7.26 (8H, m, *Ph*), 7.34–7.36 (2H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 16.1 (C(5)*Me*), 16.9 (C(α)*Me*), 29.6 (*C*(4)), 33.2 (*C*(3)), 37.1 (*C*(5)), 50.4 (N*C*H_2Ph), 51.0 (O*Me*), 51.5 (*C*(1)), 58.2 (*C*(α)), 62.9 (*C*(2)), 126.5, 126.6, 127.6, 127.9, 128.1, 128.2 (*o*,*m*,*p*-*Ph*), 141.9, 144.4 (*i*-*Ph*), 175.3 (*C*O_2Me); δ_H (500 MHz, C_6D_6) 0.99 (3H, d, *J* 6.9, C(5)*Me*), 1.28 (3H, d, *J* 6.8, C(α)*Me*), 1.38–1.50 (2H, m, C(3)H_A, C(4)H_A), 1.50–1.59 (1H, m, C(4)H_B), 1.83–1.93 (1H, m, C(3)H_B), 1.91–1.99 (1H, m, C(5)*H*), 2.89 (1H, dd, *J* 9.6, 6.1, C(1)*H*), 3.42 (3H, s, O*Me*), 3.64 (1H, d, *J* 15.1, NC$H_A$$H_B$Ph), 3.69 (1H, d, *J* 15.1, NC$H_A$$H_B$Ph), 3.93 (1H, q, *J* 6.8, C(α)*H*), 4.08 (1H, td, *J* 8.4, 6.1, C(2)*H*), 7.17–7.24 (2H, m, *Ph*), 7.30–7.31 (2H, m, *Ph*), 7.34–7.37 (2H, m, *Ph*), 7.46–7.48 (2H, m, *Ph*), 7.57–7.59 (2H, m, *Ph*); δ_C (125 MHz, C_6D_6) 16.3 (C(5)*Me*), 17.9 (C(α)*Me*), 30.2 (*C*(3)), 33.3 (*C*(4)), 37.6 (*C*(5)), 50.7 (N*C*H_2Ph), 50.8 (O*Me*), 51.3 (*C*(1)), 59.3 (*C*(α)), 63.6 (*C*(2)), 126.9, 127.0, 127.9, 128.1, 128.3, 128.6 (*o*,*m*,*p*-*Ph*), 142.6, 144.8 (*i*-*Ph*), 174.9 (*C*O_2Me); *m*/*z* (ESI^+) 352 ($[M+H]^+$, 100%), 374 ($[M+Na]^+$, 3%); HRMS (ESI^+) $C_{23}H_{29}NNaO_2^+$ ($[M+Na]^+$) requires 374.2091; found 374.2092.

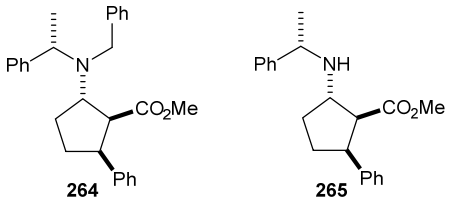
Methyl (*S*,*S*,*S*,*S*)-2-[*N*-(α-methylbenzyl)amino]-5-methylcyclopentane-1-carboxylate 262



Pd/C (25 mg, 50% w/w) was added to a degassed solution of **259** (50 mg, 0.14 mmol, >99:1 dr) in MeOH (3.6 mL) at rt. The resultant suspension was stirred vigorously under H_2 (1 atm) at rt for 34 min. The reaction mixture was then filtered through Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo* to give a 74:26 mixture of **262** and **298**, respectively. Purification *via* flash column chromatography (eluent, 30–40 °C petrol/Et_2O, 50:50) gave **262** as a pale yellow oil (28 mg, 74%, >99:1 dr); $[\alpha]_D^{20}$ −20.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3330 (N–H), 2959 (C–H), 1729 (C=O), 1453, 701; δ_H (400 MHz, $CDCl_3$) 0.82 (2H, d, *J* 6.9, C(5)*Me*), 1.08–1.24 (3H, m, C(3)H_A, C(4)H_A, N*H*), 1.26 (3H, d, *J* 6.6, C(α)*Me*), 1.68–1.74 (1H, m, C(4)H_B), 1.83–1.90 (1H, m, C(3)H_B), 2.26–2.37 (1H, m, C(5)*H*), 2.60–2.64 (1H, m, C(1)*H*), 3.26–3.31 (1H, m, C(2)*H*), 3.55 (3H, s, O*Me*), 3.71 (1H, q, *J* 6.6,

C(α)*H*), 7.13–7.25 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.4 (C(5)*Me*), 24.6 (C(α)*Me*), 32.6 (*C*(4)), 33.6 (*C*(3)), 36.4 (*C*(5)), 51.1 (O*Me*), 55.3 (*C*(1)), 56.8 (*C*(α)), 60.0 (*C*(2)), 126.6, 126.9, 128.3 (*o*,*m*,*p*-*Ph*), 145.6 (*i*-*Ph*), 175.1 (CO_2Me); *m*/*z* (ESI^+) 262 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{16}H_{23}NNaO_2^+$ ($[M+Na]^+$) requires 284.1621; found 284.1620.

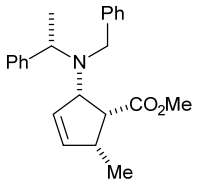
Methyl (*S*,*S*,*S*,*S*)-5-phenyl-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]cyclopentane-1-carboxylate 264 and methyl (*S*,*S*,*S*,*S*)-5-phenyl-2-[*N*-(α-methylbenzyl)amino] cyclopentane-1-carboxylate 265



Pd/C (22 mg, 50% w/w by substrate) was added to a degassed solution of **260** (44 mg, 0.11 mmol, >99:1 dr) in MeOH (3.2 mL) at rt. The resultant suspension was vigorously stirred under H_2 (1 atm) at rt for 15 min. The reaction mixture was then degassed, filtered through Celite® (eluent MeOH) and concentrated *in vacuo* to give a 1:55:44 mixture of **260**, **264** and **265**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 97:3) gave **264** as a white solid (20 mg, 47%, >99:1 dr); $[\alpha]_D^{20}$ −20.9 (*c* 0.5 in $CHCl_3$); mp 101–102 °C; ν_{max} (ATR) 2948 (C–H), 1729 (C=O), 1158, 698; δ_H (400 MHz, $CDCl_3$) 1.25 (3H, d, *J* 6.7, C(α)*Me*), 1.68–1.76 (1H, m, C(3)H_A), 1.78–1.86 (1H, m, C(4)H_A), 1.92–2.03 (2H, m, C(3)H_B, C(4)H_B), 2.93 (3H, s, O*Me*), 2.99 (1H, dd, *J* 10.6, 5.5, C(1)*H*), 3.23 (1H, app td, *J* 10.6, 5.5, C(5)*H*), 3.75–3.84 (4H, m, NCH_2Ph, C(α)*H*, C(2)*H*), 7.01–7.41 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.7 (C(α)*Me*), 29.0 (*C*(4)), 30.7 (*C*(3)), 48.7 (*C*(5)), 50.7 (N*C*H_2Ph), 50.8 (O*Me*), 52.5 (*C*(1)), 58.7 (*C*(α)), 63.2 (*C*(2)), 126.3, 126.6, 126.7, 127.6, 127.8, 127.8, 128.0, 128.0, 128.2 (*o*,*m*,*p*-*Ph*), 140.4, 141.8, 144.2 (*i*-*Ph*), 174.6 (CO_2Me); *m*/*z* (ESI^+) 414 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{28}H_{31}NNaO_2^+$ ($[M+Na]^+$) requires 436.2247; found 436.2227. Further elution (eluent 30–40 °C petrol/Et_2O, 40:60) gave **265** as a colourless oil (16 mg, 44%, >99:1 dr); $[\alpha]_D^{20}$ −113.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2953 (C–H), 1728 (C=O), 1452 (C=C), 700; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, *J* 6.6, C(α)*Me*), 1.31–1.39 (1H, m, C(3)H_A), 1.92 (1H, br s, N*H*), 1.87–2.02 (2H, m, C(4)H_2), 2.04–2.11 (1H, m, C(3)H_B), 2.99 (1H, dd, *J* 9.8, 4.9, C(1)*H*), 3.10 (3H, s, O*Me*), 3.35–3.41 (1H, m, C(2)*H*), 3.45–3.52 (1H, m, C(5)*H*), 3.77 (1H, q, *J* 6.6, C(α)*H*), 7.08–7.11 (3H, m, Ph), 7.15–7.26 (7H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 24.6 (C(α)*Me*), 29.6 (*C*(4)), 34.1 (*C*(3)), 47.7 (*C*(5)), 50.9 (O*Me*), 56.7

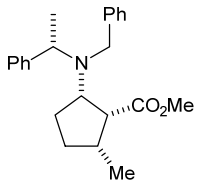
(*C*(1)), 56.9 (*C*(α)), 60.2 (*C*(2)), 126.4, 126.6, 127.0, 127.8, 128.0, 128.4 (*o*,*m*,*p*-*Ph*), 140.9, 145.4 (*i*-*Ph*), 174.3 (*C*O_2Me); *m*/*z* (ESI$^+$) 324 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{26}NO_2^+$ ([M+H]$^+$) requires 324.1958; found 324.1945.

Methyl (1*R*,2*S*,5*R*,α*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-methylcyclopent-3-ene-1-carboxylate 266



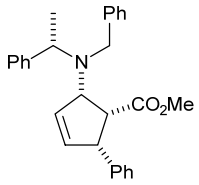
Grubbs I catalyst (72 mg, 0.09 mmol) was added to a degassed solution of **257** (85 mg, 0.22 mmol, >99:1 dr) in CH_2Cl_2 (8.6 mL) at rt and the resultant mixture was heated at 40 °C for 24 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (10 mL) and $P(CH_2OH)_3$ (539 mg, 4.34 mmol), Et_3N (0.06 mL, 0.43 mmol) and excess silica (~200 mg) were added sequentially. The resultant mixture was left to stir at rt for 30 min, then filtered and concentrated *in vacuo* to give **266** as an orange oil (58 mg, 77%, >99:1 dr);[17] $[\alpha]_D^{20}$ −22.5 (*c* 0.8 in $CHCl_3$); ν_{max} (ATR) 2966 (C–H), 1737 (C=O), 1494 (C=C), 1161, 699; δ_H (400 MHz, $CDCl_3$) 0.98 (3H, d, *J* 7.3, C(5)*Me*), 1.28 (3H, d, *J* 6.6, C(α)*Me*), 2.55–2.65 (1H, m, C(5)*H*), 2.88 (1H, app t, *J* 8.2, C(1)*H*), 3.54 (3H, s, O*Me*), 3.76 (1H, d, *J* 14.4, NCH_AH_BPh), 3.86 (1H, q, *J* 6.6, C(α)*H*), 4.01–4.05 (1H, m, C(2)*H*), 4.06 (1H, d, *J* 14.4, NCH_AH_BPh), 5.56 (1H, dt, *J* 5.7, 2.4, C(4)*H*), 5.79 (1H, ddd, *J* 5.7, 2.4, 2.3, C(3)*H*), 7.10–7.37 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.0 (C(α)*Me*), 15.7 (C(5)*Me*), 40.0 (*C*(5)), 50.7 (O*Me*), 52.6 (N*C*H_2Ph), 54.1 (*C*(1)), 56.0 (*C*(α)), 66.7 (*C*(2)), 126.4, 126.5, 127.8, 127.9, 128.1, 128.3 (*o*,*m*,*p*-*Ph*), 130.4 (*C*(3)), 135.8 (*C*(4)), 141.4, 144.2 (*i*-*Ph*), 172.5 (*C*O_2Me); δ_H (400 MHz, C_6D_6) 0.85 (3H, d, *J* 7.3, C(5)*Me*), 0.95 (3H, d, *J* 6.9, C(α)*Me*), 2.07–2.18 (1H, m, C(5)*H*), 2.82 (1H, t, *J* 8.2, C(1)*H*), 3.24 (3H, s, O*Me*), 3.58 (1H, d, *J* 14.3, NCH_AH_BPh), 3.82 (1H, q, *J* 6.9, C(α)*H*), 3.87–3.91 (1H, m, C(2)*H*), 4.16 (1H, d, *J* 14.3, NCH_AH_BPh), 5.26 (1H, dt, *J* 5.9, 2.3, C(4)*H*), 5.51–5.54 (1H, m, C(3)*H*), 6.91–7.37 (10H, m, *Ph*); δ_C (100 MHz, C_6D_6) 11.6 (C(α)*Me*), 15.7 (C(5)*Me*), 39.9 (*C*(5)), 50.1 (O*Me*), 52.6 (N*C*H_2Ph), 53.7 (*C*(1)), 56.0 (*C*(α)), 66.5 (*C*(2)), 126.5, 126.6, 128.0, 128.2, 128.5 (*Ph*), 130.3 (*C*(3)), 135.7 (*C*(4)), 141.7, 144.3 (*i*-Ph), 171.7 (*C*O_2Me); *m*/*z* (ESI$^+$) 350 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{27}NNaO_2^+$ ([M+Na]$^+$) requires 372.1934; found 372.1925.

Methyl (1*R*,2*S*,5*R*,α*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-methylcyclopentane-1-carboxylate 267



Pd/C (29 mg, 50% w/w by substrate) was added to a degassed solution of **266** (58 mg, 0.17 mmol, >99:1 dr) in MeOH (4.2 mL) at rt. The resultant suspension was vigorously stirred under H_2 (1 atm) at rt for 20 min. The reaction mixture was then degassed, filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **267** as a colourless oil (5 mg, 9%, >99:1 dr); $[\alpha]_D^{20}$ −26.1 (*c* 0.3 in $CHCl_3$);[18] ν_{max} (ATR) 2959 (C–H), 1730 (C=O), 699; δ_H (400 MHz, $CDCl_3$) 0.92 (3H, d, *J* 7.1, C(5)*Me*), 1.33 (3H, d, *J* 6.9, C(α)*Me*), 1.53–1.63 (1H, m, C(4)H_A), 1.67–1.78 (2H, m, C(3)H_A, C(4)H_B), 2.00–2.08 (1H, m, C(5)*H*), 2.10–2.18 (1H, m, C(3)H_B), 2.85 (1H, t, *J* 6.2, C(1)*H*), 3.24–3.31 (1H, m, C(2)*H*), 3.62 (3H, s, O*Me*), 3.64 (1H, d, *J* 15.2, NC$H_A$$H_B$Ph), 3.80 (1H, d, *J* 15.2, NCH$_A$$H_B$Ph), 4.16 (1H, q, *J* 6.9, C(α)*H*), 7.15–7.42 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 15.5 (C(α)*Me*), 16.1 (C(5)*Me*), 27.7 (*C*(3)), 29.9 (*C*(4)), 34.9 (*C*(5)), 50.8 (O*Me*), 51.6 (N*C*H_2Ph), 53.8 (*C*(1)), 57.8 (*C*(α)), 65.5 (*C*(2)), 126.2, 126.6, 127.8, 127.9, 128.0, 128.0 (*o*,*m*,*p*-*Ph*), 142.8, 143.1 (*i*-*Ph*), 173.8 (*C*O_2Me); *m*/*z* (ESI^+) 352 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{23}H_{30}NO_2^+$ ($[M+H]^+$) requires 352.2271; found 352.2258.

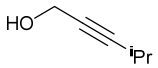
Methyl (1*R*,2*S*,5*R*,α*S*)-5-phenyl-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]cyclopent-3-ene-1-carboxylate 268



Grubbs I catalyst (152 mg, 0.19 mmol) was added to a degassed solution of **258** (210 mg, 0.46 mmol, >99:1 dr) in CH_2Cl_2 (21 mL) at rt and the resultant mixture was heated at 40 °C for 24 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (25 mL) and $P(CH_2OH)_3$ (1.15 g, 9.26 mmol), Et_3N (0.13 mL, 0.93 mmol) and excess silica (~200 mg) were added sequentially. The resultant mixture was left to stir at rt for 30 minutes, then filtered and concentrated *in vacuo* to give **268** as an orange oil (182 mg, 95%, >99:1 dr);[19] $[\alpha]_D^{20}$ −28.4 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 2947

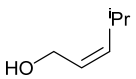
(C–H), 1731 (C=O), 1494 (C=C), 1163, 698; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, *J* 6.6, C(α)*Me*), 3.03 (3H, s, O*Me*), 3.18 (1H, app t, *J* 8.2, C(1)*H*), 3.79–3.89 (2H, m, C(5)*H*, C(α)*H*), 3.84 (1H, d, *J* 14.6, NCH_AH_BPh), 4.10–4.13 (1H, m, C(2)*H*), 4.16 (1H, d, *J* 14.6, NCH_AH_BPh), 5.89–5.90 (1H, m, C(3)*H*), 6.04–6.07 (1H, m, C(4)*H*), 7.01–7.42 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.7 (C(α)*Me*), 50.4 (O*Me*), 50.7 (*C*(5)), 52.7 (NCH_2Ph), 56.0 (*C*(α)), 57.4 (*C*(1)), 66.7 (*C*(2)), 126.3, 126.4, 126.5, 127.7, 127.9, 127.9, 128.0, 128.1, 128.2 (*o*,*m*,*p*-*Ph*), 131.5 (*C*(3)), 133.0 (*C*(4)), 140.2, 141.3, 144.0 (*i*-*Ph*), 171.4 (*C*O_2Me); δ_H (500 MHz, C_6D_6) 1.30 (3H, d, *J* 6.9, C(α)*Me*), 3.12 (3H, s, O*Me*), 3.46 (1H, app t, *J* 8.0, C(1)*H*), 3.56–3.60 (1H, m, C(5)*H*), 3.98 (1H, d, *J* 14.5, NCH_AH_BPh), 4.14 (1H, q, *J* 6.9, C(α)*H*), 4.23–4.27 (1H, m, C(2)*H*), 4.56 (1H, d, *J* 14.5, NCH_AH_BPh), 5.88–5.90 (1H, m, C(3)*H*), 6.05–6.07 (1H, m, C(4)*H*), 7.07–7.68 (15H, m, *Ph*); δ_C (125 MHz, C_6D_6) 11.7 (C(α)*Me*), 50.3 (O*Me*), 51.0 (*C*(5)), 53.2 (N*C*H_2Ph), 56.5 (*C*(α)), 58.0 (*C*(1)), 67.1 (*C*(2)), 126.6, 126.9, 127.0, 127.0, 128.4, 128.5, 128.6, 128.9, 128.9 (*o*,*m*,*p*-*Ph*), 140.8, 142.0, 144.7 (*i*-*Ph*), 171.2 (*C*O_2Me); *m*/*z* (ESI^+) 412 ($[M+H]^+$, 100%), 442 ($[M+Na]^+$, 5%); HRMS (ESI^+) $C_{28}H_{29}NNaO_2^+$ ($[M+Na]^+$) requires 434.2091; found 434.2091.

4-Methylpent-2-yn-1-ol 270



BuLi (2.0 M in hexanes, 6.45 mL, 12.9 mmol) was added dropwise to a solution of **269** (660 mg, 9.69 mmol) in THF (8.2 mL) at −78 °C. Paraformaldehyde (290 mg, 9.69 mmol) was then added at −78 °C and the resultant suspension was allowed to warm to rt. The reaction mixture was then stirred at rt for 16 h. Satd aq NH_4Cl (2 mL) was added and the reaction mixture was allowed to warm to rt. The aqueous layer was extracted with Et_2O (3 × 20 mL) and the combined organic extracts were washed brine (50 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent, 30–40 °C petrol/Et_2O, 95:5) gave **270** as a yellow oil (266 mg, 28%);[20] δ_H (400 MHz, $CDCl_3$) 1.04 (6H, d, *J* 7.0, C(4)Me_2), 1.56 (1H, app t, *J* 6.0, O*H*), 2.42–2.50 (1H, m, C(4)*H*), 4.12 (2H, dd, *J* 6.0, C(1)H_2).

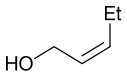
(*Z*)-4-Methylpent-2-en-1-ol 271



$NaBH_4$ (20 mg, 0.53 mmol) was added portionwise to a stirred solution of $Ni(OAc)_2 \cdot 4H_2O$ (132 mg, 0.53 mmol) in MeOH (4.6 mL) at 0 °C, and the resultant black mixture was allowed

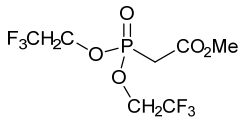
to warm to rt over 15 min. $(CH_2NH_2)_2$ (88 μL, 1.32 mmol) and a solution of **270** (208 mg, 2.12 mmol) in MeOH (2 mL) were added sequentially at rt and the resultant suspension was then vigorously stirred under H_2 (1 atm) at rt. The progress of the hydrogenation reaction was closely monitored by TLC analysis [R_f (**270**) = 0.53, R_f (**271**) = 0.23; eluent 30–40 °C petrol/Et_2O, 80:20]. Once complete (~1.5 h) the reaction mixture was filtered through Celite® (eluent Et_2O) and the filtrate was concentrated *in vacuo*. Et_2O (20 mL) was then added to the residue and the resultant pink suspension was filtered through Celite® (eluent Et_2O) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 95:5) gave **271** as a pale yellow oil (120 mg, 57%, >99:1 dr);[21] δ_H (400 MHz, $CDCl_3$) 0.90 (6H, d, *J* 6.7, C(4)*Me*$_2$), 1.21 (1H, t, *J* 5.4, O*H*), 2.51–2.60 (1H, m, C(4)*H*), 4.12–4.15 (2H, m, C(1)*H*$_2$), 5.28–5.33 (1H, m, C(3)*H*), 5.38–5.44 (1H, m, C(2)*H*).

(*Z*)-Pent-2-en-1-ol 272



$NaBH_4$ (830 mg, 21.9 mmol) was added portionwise to a stirred solution of $Ni(OAc)_2 \cdot 4H_2O$ (7.28 g, 29.3 mmol) in MeOH (148 mL) at 0 °C, and the resultant black mixture was allowed to warm to rt over 15 min. $(CH_2NH_2)_2$ (4.66 mL, 69.8 mmol) and a solution of 2-pentyn–1-ol **273** (9.47 g, 113 mmol) in MeOH (75 mL) were added sequentially at rt and the resultant suspension was then vigorously stirred under H_2 (1 atm) at rt. The progress of the hydrogenation reaction was closely monitored by TLC analysis [R_f (**273**) = 0.53, R_f (**272**) = 0.45; eluent 30–40 °C petrol/Et_2O, 50:50]. Once complete (~8 h) the reaction mixture was filtered through Celite® (eluent Et_2O) and the solvent was removed by distillation. Et_2O (200 mL) was then added to the residue and the resultant pink suspension was filtered through Celite® (eluent Et_2O) and the solvent was again removed by distillation to give **272** as an orange oil (7.24 g, 75%, >99:1 dr);[22] ν_{max} (ATR) 3291 (O–H), 2961, 2874 (C–H), 1569, 1481 (C=C); δ_H (400 MHz, $CDCl_3$) 0.99 (3H, t, *J* 7.5, C(5)*H*$_3$), 1.59 (1H, br s, O*H*), 2.06–2.13 (2H, m, C(4)*H*$_2$), 4.18–4.20 (2H, m, C(1)*H*$_2$), 5.50–5.60 (2H, m, C(2)*H*, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 14.2 (*C*(5)), 20.6 (*C*(4)), 57.9 (*C*(1)), 128.1 (*C*(2)), 133.9 (*C*(3)).

Methyl bis(2,2,2-trifluoroethyl)phosphonoacetate 277

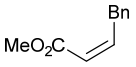


Step 1: TMSCl (29.3 mL, 232 mmol) was added to trimethylphosphonoacetate **274** (8.43 g, 46.2 mmol) at rt in a screw-cap pressure tube. The reaction mixture was heated at 80 °C for 4 days, then allowed to cool to rt and concentrated *in vacuo* to give **275** as a colourless oil (15.4 g); δ_H (400 MHz, $CDCl_3$) 0.30 (18H, s, Si*Me*$_3$), 2.90 (2H, d, *J* 22.4, C(2)*H*$_2$), 3.72 (3H, s, CO_2*Me*).

Step 2: A solution of residue of **275** (15.4 g) in CH_2Cl_2 (94 mL) was treated sequentially with DMF (4 drops) and $(COCl)_2$ (9.79 mL, 116 mmol) at rt. The reaction mixture was stirred at rt for 1 h, then concentrated *in vacuo* to give **276** as an orange oil (9.79 g); δ_H (400 MHz, $CDCl_3$) 3.77 (2H, d, *J* 19.0, C(2)*H*$_2$), 3.86 (3H, d, *J* 0.8, CO_2*Me*).

Step 3: A solution of Et_3N (38.7 mL, 278 mmol) and CF_3CH_2OH (13.5 mL, 185 mmol) in CH_2Cl_2 (46.5 mL) was added dropwise to a solution of residue of **276** (9.79 g) in CH_2Cl_2 (46.5 mL) at 0 °C. DMAP (113 mg, 0.93 mmol) was added at 0 °C and the reaction mixture was then allowed to warm to rt and stirred at rt for further 16 h. Brine (200 mL) and CH_2Cl_2 (200 mL) were then added and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/EtOAc, 67:33) gave **277** as a pale yellow oil (10.6 g, 72% from **274**);[23] δ_H (400 MHz, $CDCl_3$) 3.17 (2H, d, *J* 20.8, C(2)*H*$_2$), 3.78 (3H, s, CO_2*Me*), 4.42–4.51 (4H, m, (POC*H*$_2$CF$_3$)$_2$).

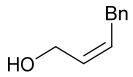
Methyl (*Z*)-4-phenylbut-2-enoate 278



KHMDS (38 mL, 0.5 M in PhMe, 19 mmol) was added dropwise to a solution of **277** (3.00 g, 9.43 mmol) and 18-crown-6 (12.3 g, 46.7 mmol) in THF (136 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 25 min. 2-Phenylacetaldehyde (1.70 g, 14.1 mmol) was then added portionwise at −78 °C over a period of 5 min and the resultant suspension was stirred at −78 °C for 25 min. Satd aq NH_4Cl (10 mL) was added and the reaction mixture was allowed to warm to rt. The aqueous layer was extracted with Et_2O (3 × 50 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent, 30–40 °C petrol/Et_2O, 98:2) gave **278** as a colourless oil (0.73 g,

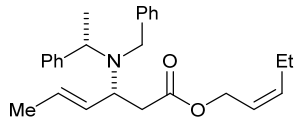
44%, >99:1 dr);[24] δ_H (400 MHz, $CDCl_3$) 3.77 (3H, s, CO_2Me), 4.04 (2H, dd, *J* 7.6, 1.7, C(4)H_2), 5.88 (1H, dt, *J* 11.4, 1.7, C(2)*H*), 6.38 (1H, dt, *J* 11.4, 7.6, C(3)*H*), 7.21–7.25 (3H, m, *Ph*), 7.30–7.34 (2H, m, *Ph*).

(*Z*)-4-Phenylbut-2-en-1-ol 279



DIBAL-H (42.7 mL, 1.0 M in CH_2Cl_2, 42.7 mmol) was added dropwise to a solution of **278** (1.71 g, 9.70 mmol, >99:1 dr) in CH_2Cl_2 (14 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 15 min. EtOAc (71 mL) and satd aq Rochelle's salt (71 mL) were then added sequentially at −78 °C. The reaction mixture was then allowed to warm to rt and stirred at rt for 16 h. The aqueous layer was separated and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with satd aq Rochelle's salt (3 × 150 mL) and brine (150 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent, 30–40 °C petrol/EtOAc, 90:10) gave **279** as a pale yellow oil (1.32 g, 92%, >99:1 dr);[24] δ_H (400 MHz, $CDCl_3$) 1.51 (1H, br s, O*H*), 3.46 (2H, app d, *J* 5.6, C(4)H_2), 4.30–4.37 (2H, m, C(1)H_2), 5.72–5.80 (2H, m, C(2)*H*, C(3)*H*), 7.19–7.24 (3H, m, *Ph*), 7.29–7.33 (2H, m, *Ph*).

(*Z*)-Pent-2'-en-1'-yl (3*R*,α*S*,*E*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 280

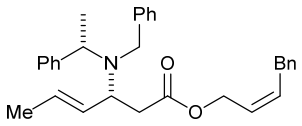


Step 1: TFA (8 mL) was added to a solution of **248** (2.00 g, 5.27 mmol, >99:1 dr) in CH_2Cl_2 (16 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with $NaHCO_3$ (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give a yellow oil (1.97 g, >99:1 dr).

Step 2: A solution of the residue (1.97 g, >99:1 dr) in CH_2Cl_2 (21 mL) was treated sequentially with $(COCl)_2$ (0.53 mL, 6.18 mmol) and DMF (18 μL, 0.24 μmol) at 0 °C. The reaction mixture was allowed to warm to rt over 1 h then concentrated *in vacuo*. A solution of **272** (0.72 g, 8.41 mmol, >99:1 dr) in CH_2Cl_2 (2 mL) was then added to a solution of the residue in CH_2Cl_2 (21 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred at rt for 16 h. Satd aq $NaHCO_3$ (100 mL) was then added and the resultant mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine

(300 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **280** as a colourless oil (1.30 g, 54% from **248**, >99:1 dr); $[\alpha]_D^{20}$ +5.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2966 (C–H), 1733 (C=O), 1494 (C=C); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.5, C(5')H_3), 1.29 (3H, d, *J* 6.9, C(α)*Me*), 1.61 (3H, d, *J* 5.4, C(6)H_3), 1.99 (2H, qdd, *J* 7.5, 7.5, 1.3, C(4')H_2), 2.23 (1H, dd, *J* 14.2, 8.2, C(2)H_A), 2.38 (1H, dd, *J* 14.2, 6.6, C(2)H_B), 3.57 (1H, d, *J* 14.6, NC$H_A$$H_B$Ph), 3.62 (1H, d, *J* 14.6, NC$H_A$$H_B$Ph), 3.69–3.74 (1H, m, C(3)*H*), 3.92 (1H, q, *J* 6.9, C(α)*H*), 4.34–4.39 (1H, m, C(1')H_A), 4.44–4.49 (1H, m, C(1')H_B), 5.26–5.33 (1H, m, C(2')*H*), 5.39–5.55 (3H, m, C(4)*H*, C(5)*H*, C(3')*H*), 7.09–7.14 (2H, m, *Ph*), 7.17–7.22 (4H, m, *Ph*), 7.24–7.29 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.0 (*C*(5')), 16.8 (C(α)*Me*), 18.0 (*C*(6)), 20.8 (*C*(4')), 38.6 (*C*(2)), 50.3 (N*C*H_2Ph), 56.7 (*C*(3)), 56.8 (*C*(α)), 60.0 (*C*(1')), 122.9 (*C*(2')), 126.5, 126.6 (*o*,*m*,*p*-*Ph*), 127.1 (*C*(5)), 127.8, 127.9, 128.0, 128.3 (*o*,*m*,*p*-*Ph*), 131.1 (*C*(4)), 136.5 (*C*(3')), 141.3, 144.3 (*i*-*Ph*), 171.7 (*C*(1)); *m*/*z* (ESI^+) 392 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{26}H_{34}NO_2^+$ ($[M+H]^+$) requires 392.2584; found 392.2584.

(*Z*)-4'-Phenylbut-2'-en-1'-yl (3*R*,α*S*,*E*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 281

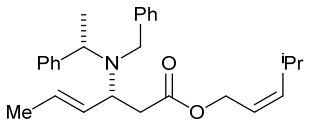


Step 1: TFA (18 mL) was added to a solution of **248** (4.13 g, 10.9 mmol, >99:1 dr) in CH_2Cl_2 (33 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with CH_2Cl_2 (100 mL) and washed with $NaHCO_3$ (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give a yellow oil (4.31 g, >99:1 dr).

Step 2: A solution of the residue (4.31 g, >99:1 dr) in CH_2Cl_2 (43 mL) was treated sequentially with $(COCl)_2$ (0.98 mL, 11.4 mmol) and DMF (33 μL, 0.43 μmol) at 0 °C. The reaction mixture was allowed to warm to rt over 1 h then concentrated *in vacuo*. A solution of **279** (2.26 g, 15.3 mmol, >99:1 dr) was then added to a solution of the residue in CH_2Cl_2 (43 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred at rt for 16 h. Satd aq $NaHCO_3$ (100 mL) was then added and the resultant mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (300 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 0% → 5% Et_2O in 30–40 °C petrol) gave **281** as a colourless oil (3.04 g, 62% from

248, >99:1 dr); $[\alpha]_D^{20}$ +7.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3027, 2935 (C–H), 1733 (C=O), 1494 (C=C); δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, *J* 6.8, C(α)*Me*), 1.62 (3H, d, *J* 5.2, C(6)H_3), 2.26 (1H, dd, *J* 14.2, 8.1 C(2)H_A), 2.41 (1H, dd, *J* 14.2, 6.6, C(2)H_B), 3.35 (2H, d, *J* 7.6, C(4')H_2), 3.58 (1H, d, *J* 14.6, NC$H_A$$H_B$Ph), 3.64 (1H, d, *J* 14.6, NC$H_A$$H_B$Ph), 3.71–3.76 (1H, m, C(3)*H*), 3.94 (1H, q, *J* 6.8, C(α)*H*), 4.47 (1H, dd, *J* 12.8, 6.8, C(1')H_A), 4.58 (1H, dd, *J* 12.8, 7.2, C(1')H_B), 5.41–5.54 (3H, m, C(5)*H*, C(2')*H*, C(4)*H*), 5.66–5.74 (1H, m, C(3')*H*), 7.08–7.15 (5H, m, *Ph*), 7.19–7.24 (6H, m, *Ph*), 7.26–7.30 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.8 (C(α)*Me*), 18.0 (*C*(6)), 33.7 (*C*(4')), 38.6 (*C*(2)), 50.3 (N*C*H_2Ph), 56.7 (*C*(3)), 56.8 (*C*(α)), 59.9 (*C*(1')), 124.4 (*C*(2')), 126.1, 126.5, 126.6, 127.8, 127.9, 128.0, 128.3, 128.3, 128.5 (*o*,*m*,*p*-*Ph*), 127.1 (*C*(5)), 131.0 (*C*(4)), 132.9 (*C*(3')), 139.8, 141.3, 144.3 (*i*-*Ph*), 171.6 (*C*(1)); *m*/*z* (ESI^+) 454 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{31}H_{36}NO_2^+$ ($[M+H]^+$) requires 454.2741; found 454.2741.

(*Z*)-4'-Methylpent-2'-en-1'-yl (3*R*,α*S*,*E*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 282

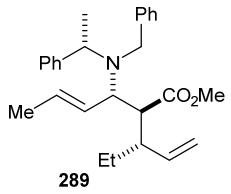


Step 1: TFA (4 mL) was added to a solution of **248** (0.95 g, 2.50 mmol, >99:1 dr) in CH_2Cl_2 (8 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with $NaHCO_3$ (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give a yellow oil (900 mg, >99:1 dr).

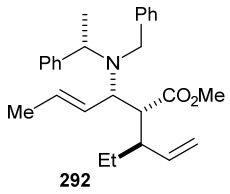
Step 2: A solution of the residue (900 mg, >99:1 dr) in CH_2Cl_2 (9 mL) was treated sequentially with $(COCl)_2$ (0.2 mL, 2.62 mmol) and DMF (8 μL, 0.10 μmol) at 0 °C. The reaction mixture was allowed to warm to rt over 1 h then concentrated *in vacuo*. A solution of **271** (350 mg, 3.49 mmol, >99:1 dr) was then added to a solution of the residue in CH_2Cl_2 (9 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred at rt for 16 h. Satd aq $NaHCO_3$ (100 mL) was then added and the resultant mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (300 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 0% → 5% Et_2O in 30–40 °C petrol) gave **282** as a colourless oil (510 mg, 50% from **248**, >99:1 dr); $[\alpha]_D^{20}$ +12.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2962 (C–H), 1734 (C=O), 1494 (C=C); δ_H (400 MHz, $CDCl_3$) 0.87 (6H, app d, *J* 6.8, C(5')H_3, C(4')*Me*), 1.29 (3H, d, *J* 6.9, C(α)*Me*),

1.61–1.62 (3H, m, C(6)H_3), 2.23 (1H, dd, *J* 14.3, 6.6, C(2)H_A), 2.38 (1H, dd, *J* 14.3, 8.0, C(2)H_B), 2.47–2.56 (1H, m, C(4')*H*), 3.57 (1H, d, *J* 14.4, NC$H_A$$H_B$Ph), 3.62 (1H, d, *J* 14.4, NCH$_A$$H_B$Ph), 3.69–3.74 (1H, m, C(3)*H*), 3.92 (1H, q, *J* 6.9, C(α)*H*), 4.37 (1H, ddd, *J* 12.7, 6.8, 1.2, C(1')H_A), 4.47 (1H, ddd, *J* 12.7, 6.8, 1.2, C(1')H_B), 5.17–5.23 (1H, m, C(2')*H*), 5.31–5.37 (1H, m, C(3')*H*), 5.39–5.46 (1H, m, C(5)*H*), 5.46–5.52 (1H, m, C(4)*H*), 7.09–7.15 (2H, m, *Ph*), 7.17–7.31 (8H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.8 (C(α)*Me*), 18.0 (*C*(6)), 23.0 (*C*(5'), C(4')*Me*), 26.9 (*C*(4')), 38.6 (*C*(2)), 50.3 (N*C*H$_2$Ph), 56.7 (*C*(3)), 56.8 (*C*(α)), 60.2 (*C*(1')), 121.1 (*C*(2')), 126.5, 126.6 (*o,m,p-Ph*), 127.1 (*C*(5)), 127.8, 127.9, 128.0, 128.3 (*o,m,p-Ph*), 131.0 (*C*(4)), 141.3 (*i-Ph*), 142.2 (*C*(3')), 144.3 (*i-Ph*), 171.7 (*C*(1)); *m*/*z* (ESI$^+$) 406 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{36}NO_2^+$ ([M+H]$^+$) requires 406.2741; found 406.2745.

Methyl (*S*,*S*,*S*,*S*,*E*)-2-(pent-1'-en-3'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 289 and methyl (2*R*,3*S*,2'*R*,α*S*,*E*)-2-(pent-1'-en-3'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 292



289



292

Step 1: TMSCl (1.94 mL, 15.3 mmol) was added dropwise to a solution of **280** (2.00 g, 5.11 mmol, >99:1 dr) in PhMe (20 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 10 min. LiHMDS (1.0 M in THF, 15.3 mL, 15.3 mmol) was added dropwise at −78 °C and the resultant mixture was stirred at −78 °C for 15 min. The reaction mixture was stirred at reflux for 1 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 (200 mL) and 1.0 M aq HCl (150 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL) and the combined organic extracts were washed with brine (150 mL), then dried and concentrated *in vacuo* to give an 85:15 mixture of **283** and **286**, respectively. Purification *via* flash column chromatography (gradient elution, 0% → 5% acetone in 30–40 °C petrol) gave **286** as a yellow oil (308 mg, >99:1 dr); $[\alpha]_D^{20}$ –7.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2965 (C–H), 1702 (C=O), 1494 (C=C); δ_H (400 MHz, $CDCl_3$) 0.61 (3H, t, *J* 7.3, C(5')H_3), 0.97–1.08 (1H, m, C(4')H_A), 1.09–1.16 (1H, m, C(4')H_B), 1.34 (3H, d, *J* 6.8, C(α)*Me*), 1.61 (3H, d, *J* 4.9, C(6)H_3), 2.17–2.24 (1H, m, C(3')*H*), 2.39 (1H, app t, *J* 6.5, C(2)*H*), 3.47 (1H, dd, *J* 8.4, 7.5, C(3)*H*), 3.53 (1H, d, *J* 14.2, NC$H_A$$H_B$Ph), 3.74 (1H, d, *J* 14.2, NCH$_A$$H_B$Ph), 4.06 (1H, q, *J* 6.8, C(α)*H*), 4.65 (1H, dd, *J* 17.1, 1.7, C(1')H_A), 4.83 (1H,

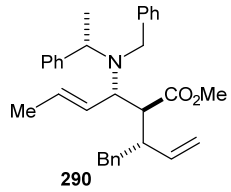
dd, *J* 10.3, 1.7, C(1')*H*$_B$), 5.38–5.45 (1H, m, C(2')*H*), 5.47–5.56 (2H, m, C(4)*H*, C(5)*H*), 7.08–7.12 (3H, m, *Ph*), 7.14–7.18 (3H, m, *Ph*), 7.23–7.31 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.7 (*C*(5')), 15.0 (C(α)*Me*), 18.0 (*C*(6)), 25.0 (*C*(4')), 43.7 (*C*(3')), 51.7 (N*C*H$_2$Ph), 52.0 (*C*(2)), 57.7 (*C*(α)), 62.0 (*C*(3)), 116.0 (*C*(1')), 126.9, 127.1 (*o*,*m*,*p*-*Ph*), 127.5 (*C*(4)), 128.2, 128.2, 128.3, 128.8 (*o*,*m*,*p*-*Ph*), 130.6 (*C*(5)), 139.0 (*C*(2')), 140.0, 143.0 (*i*-*Ph*), 177.3 (*C*(1)); *m*/*z* (ESI$^+$) 392 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{33}NNaO_2^+$ ([M+Na]$^+$) requires 414.2404; found 414.2404. Further elution (eluent 30–40 °C petrol/acetone, 95:5) gave **283** as a yellow oil (1.11 g, >99:1 dr); $[\alpha]_D^{20}$ +26.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2964 (C–H), 1703 (C=O), 1495 (C=C); δ_H (400 MHz, $CDCl_3$) 0.64 (3H, t, *J* 7.5, C(5')*H*$_3$), 1.41–1.55 (1H, m, C(4')*H*$_A$), 1.47 (3H, d, *J* 7.0, C(α)*Me*), 1.63–1.75 (1H, m, C(4')*H*$_B$), 1.81 (3H, dd, *J* 6.5, 1.5, C(6)*H*$_3$), 1.86–1.93 (1H, m, C(3')*H*), 2.13 (1H, dd, *J* 11.1, 1.8, C(2)*H*), 3.64 (1H, d, *J* 13.5, NC*H*$_A$H$_B$Ph), 3.72 (1H, app t, *J* 10.0, C(3)*H*), 3.85 (1H, d, *J* 13.5, NCH$_A$*H*$_B$Ph), 3.96 (1H, q, *J* 7.0, C(α)*H*), 4.65 (1H, dd, *J* 17.2, 2.1, C(1')*H*$_A$), 4.78 (1H, dd, *J* 10.1, 2.1, C(1')*H*$_B$), 5.38 (1H, app ddd, *J* 15.4, 10.0, 1.5, C(4)*H*), 5.51 (1H, app dt, *J* 17.2, 10.1, C(2')*H*), 5.67 (1H, dq, *J* 15.4, 6.5, C(5)*H*), 7.15–7.25 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.3 (*C*(5')), 17.2 (C(α)*Me*), 18.3 (*C*(6)), 26.5 (*C*(4')), 46.0 (*C*(3')), 47.1 (*C*(2)), 51.1 (N*C*H$_2$Ph), 59.9 (*C*(α)), 60.6 (*C*(3)), 116.6 (*C*(1')), 126.0 (*C*(4)), 128.0, 128.1, 128.3, 128.6, 128.6, 129.6 (*o*,*m*,*p*-*Ph*), 133.9 (*C*(5)), 135.2 (*i*-*Ph*), 138.8 (*C*(4')), 140.0 (*i*-*Ph*), 174.0 (*C*(1)); *m*/*z* (ESI$^+$) 392 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{33}NNaO_2^+$ ([M+Na]$^+$) requires 414.2404; found 414.2404.

Step 2 (*for **289***): A solution of **283** (906 mg) in MeCN (4 mL) was treated sequentially with DBU (692 µl, 4.63 mmol) and MeI (317 µL, 5.09 mmol) at rt. The reaction mixture was stirred at rt for 16 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (80 mL) and 2.0 M aq HCl (80 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic extracts were then washed sequentially with satd aq $NaHCO_3$ (150 mL) and brine (150 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **289** as a colourless oil (791 mg, 38% from **280**, >99:1 dr); $[\alpha]_D^{20}$ +4.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2967 (C–H), 1733 (C=O), 1495 (C=C); δ_H (400 MHz, $CDCl_3$) 0.70 (3H, t, *J* 7.3, C(5')*H*$_3$), 0.98–1.09 (1H, m, C(4')*H*$_A$), 1.18–1.28 (1H, m, C(4')*H*$_B$), 1.31 (3H, d, *J* 6.9, C(α)*Me*), 1.68–1.70 (3H, m, C(6)*H*$_3$), 1.84 (1H, m, C(3')*H*), 2.68 (1H, dd, *J* 11.5, 4.5, C(2)*H*), 3.35 (3H, s, O*Me*), 3.43–3.48 (1H, m, C(3)*H*), 3.47 (1H, d, *J* 14.2, NC*H*$_A$H$_B$Ph), 3.71 (1H, d, *J* 14.2, NCH$_A$*H*$_B$Ph), 4.03 (1H, q, *J* 6.9, C(α)*H*), 4.63 (1H, dd, *J* 17.1, 2.1, C(1')*H*$_A$), 4.81 (1H, dd, *J*

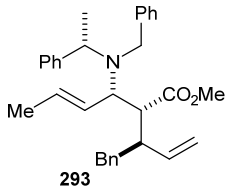
10.1, 2.1, C(1')H_B), 5.22–5.28 (1H, m, C(4)*H*), 5.34–5.42 (1H, m, C(5)*H*), 5.50 (1H, dt, *J* 17.1, 10.1, C(2')*H*) 7.05–7.13 (2H, m, *Ph*), 7.14–7.22 (8H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.9 (*C*(5')), 16.9 (C(α)*Me*), 18.0 (*C*(6)), 26.4 (*C*(4')), 45.6 (*C*(3')), 50.3 (N*C*H_2Ph), 50.6 (O*Me*), 52.3 (*C*(2)), 56.3 (*C*(α)), 60.4 (*C*(3)), 116.4 (*C*(1')), 127.9 (*C*(4)), 126.2, 126.4, 127.6, 127.8, 128.1, 128.9 (*o,m,p-Ph*), 130.1 (*C*(5)), 137.5 (*C*(2')), 140.3, 144.7 (*i-Ph*), 173.2 (*C*(1)); *m*/*z* (ESI^+) 406 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{27}H_{36}NO_2^+$ ($[M+H]^+$) requires 406.2741; found 406.2746.

Step 2 (*for **292***): A solution of **286** (256 mg) in MeCN (1.0 mL) was treated sequentially with DBU (196 μL, 1.31 mmol) and MeI (90 μL, 1.44 mmol) at rt. The reaction mixture was stirred at rt for 16 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (50 mL) and 2.0 M aq HCl (50 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were then washed sequentially with satd aq $NaHCO_3$ (150 mL) and brine (150 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **292** as a white solid (179 mg, 9% from **280**, >99:1 dr); $[\alpha]_D^{20}$ –19.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2966 (C–H), 1732 (C=O), 1494 (C=C); δ_H (400 MHz, $CDCl_3$) 0.55 (3H, t, *J* 7.5, C(5')H_3), 0.84–0.95 (1H, m, C(4')H_A), 0.97–1.06 (1H, m, C(4')H_B), 1.30 (3H, d, *J* 6.9, C(α)*Me*), 1.63 (3H, dd, *J* 6.4, 1.5, C(6)H_3), 2.18–2.25 (1H, m, C(3')*H*), 2.45 (1H, dd, *J* 8.6, 6.1, C(2)*H*), 3.39–3.42 (1H, m, C(3)*H*), 3.44 (3H, s, O*Me*), 3.57 (1H, d, *J* 14.0, NC$H_A$$H_B$Ph), 3.65 (1H, d, *J* 14.0, NC$H_A$$H_B$Ph), 3.90 (1H, q, *J* 6.9, C(α)*H*), 4.64 (1H, dd, *J* 17.1, 2.0, C(1')H_A), 4.80 (1H, dd, *J* 10.3, 2.0, C(1')H_B), 5.34–5.40 (1H, m, C(2')*H*), 5.40–5.47 (1H, m, C(5)*H*), 5.55–5.61 (1H, m, C(4)*H*), 7.09–7.14 (2H, m, *Ph*), 7.17–7.24 (6H, m, *Ph*), 7.30–7.31 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.4 (*C*(5')), 16.6 (C(α)*Me*), 18.1 (*C*(6)), 24.9 (*C*(4')), 44.0 (*C*(3')), 50.7 (O*Me*), 50.9 (N*C*H_2Ph), 53.6 (*C*(2)), 57.9 (*C*(α)), 59.9 (*C*(3)), 116.1 (*C*(1')), 127.9 (*C*(4)), 126.5, 126.6, 128.0, 128.0, 128.1, 128.8 (*o,m,p-Ph*), 129.3 (*C*(5)), 138.7 (*C*(2')), 141.3, 144.6 (*i-Ph*), 173.9 (*C*(1)); *m*/*z* (ESI^+) 406 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{27}H_{36}NO_2^+$ ($[M+H]^+$) requires 406.2741; found 406.2745.

Methyl (*S*,*S*,*S*,*S*,*E*)-2-(1'-phenylbut-3'-en-2'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino] hex-4-enoate 290 and methyl (2*R*,3*S*,2'*R*,α*S*,*E*)-2-(1'-phenylbut-3'-en–2'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 293



290



293

Step 1: TMSCl (1.11 mL, 8.80 mmol) was added dropwise to a solution of **281** (1.33 g, 2.93 mmol, >99:1 dr) in PhMe (13 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 10 min. LiHMDS (1.0 M in THF, 8.80 mL, 8.80 mmol) was then added dropwise and the resultant mixture was stirred at −78 °C for 15 min. The reaction mixture was allowed to warm to rt then then heated at reflux for 1 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 (150 mL) and 1.0 M aq HCl (100 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 150 mL). The combined organic extracts were washed with brine (150 mL), then dried and concentrated *in vacuo* to give a 76:24 mixture of **284** and **287**, respectively. Purification *via* flash column chromatography (gradient elution, 0% → 12% acetone in 30–40 °C petrol) gave **287** as a yellow oil (360 mg, >99:1 dr); $[\alpha]_D^{20}$ –21.3 (*c* 0.8 in $CHCl_3$); ν_{max} (ATR) 2928 (C–H), 1704 (C=O), 1494 (C=C); δ_H (400 MHz, $CDCl_3$) 1.38 (3H, d, *J* 6.6, C(α)*Me*), 1.58–1.59 (3H, m, C(6)H_3), 2.42–2.47 (1H, m, C(1')H_A), 2.49–2.57 (1H, m, C(2')*H*), 2.67–2.69 (1H, m, C(2)*H*), 2.78 (1H, dd, *J* 12.8, 6.5, C(1')H_B), 3.40 (1H, dd, *J* 10.0, 5.9, C(3)*H*), 3.55 (1H, d, *J* 14.0, NC$H_A$$H_B$Ph), 3.63 (1H, d, *J* 14.0, NC$H_A$$H_B$Ph), 4.11 (1H, q, *J* 6.6, C(α)*H*), 4.54 (1H, app d, *J* 17.5, C(4')H_A), 4.82 (1H, app d, *J* 10.2, C(4')H_B), 5.25–5.32 (1H, m, C(4)*H*), 5.48–5.57 (1H, m, C(5)*H*), 5.67 (1H, ddd, *J* 17.5, 10.2, 8.2, C(3')*H*), 6.91–6.93 (2H, m, *Ph*), 7.04–7.28 (13H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.2 (C(α)*Me*), 17.9 (*C*(6)), 39.3 (*C*(1')), 44.2 (*C*(2)), 50.2 (*C*(2')), 51.2 (N*C*H_2Ph), 56.9 (*C*(α)), 62.4 (*C*(3)), 116.1 (*C*(4')), 125.9, 126.9, 127.2 (*o*,*m*,*p*-*Ph*), 127.9 (*C*(4)), 128.1, 128.2, 128.2, 128.3, 128.8, 129.4 (*o*,*m*,*p*-*Ph*), 130.8 (*C*(5)), 138.5 (*C*(3')), 139.4, 140.2, 142.0 (*i*-*Ph*), 176.6 (*C*(1)); *m*/*z* (ESI$^+$) 454 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{36}NO_2^+$ ([M+H]$^+$) requires 454.2741; found 454.2754. Further elution (eluent 30–40 °C petrol/acetone, 88:12) gave **284** as a yellow oil (1.15 g, >99:1 dr); $[\alpha]_D^{20}$ +13.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3027, 2933 (C–H), 1704 (C=O), 1495 (C=C); δ_H (400 MHz, $CDCl_3$) 1.43 (3H, d, *J* 6.9, C(α)*Me*), 1.76 (3H, dd, *J* 6.4, 0.9, C(6)H_3), 2.02 (1H, app d, *J* 11.0, C(2)*H*), 2.29 (1H, app q, *J* 8.0, C(2')*H*), 2.79 (1H, dd, *J* 13.4, 6.6, C(1')H_A), 3.14 (1H, dd, *J* 13.4, 9.3, C(1')H_B), 3.54 (1H, d, *J*

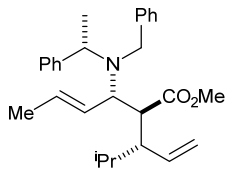
13.6, NCH_AH_BPh), 3.65–3.70 (2H, m, NCH_AH_BPh, C(3)*H*), 3.89 (1H, q, *J* 6.9, C(α)*H*), 4.64 (1H, app d, *J* 17.1, C(4')H_A), 4.77 (1H, dd, *J* 10.2, 1.7, C(4')H_B), 5.07 (1H, dd, *J* 14.8, 10.1, C(4)*H*), 5.53–5.61 (1H, m, C(5)*H*), 5.61–5.70 (1H, m, C(3')*H*), 7.02–7.03 (2H, m, *Ph*), 7.07–7.11 (3H, m, *Ph*), 7.14–7.25 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.9 (C(α)*Me*), 18.4 (*C*(6)), 40.0 (*C*(1')), 44.4 (*C*(2)), 46.1 (*C*(2')), 51.0 (N*C*H_2Ph), 59.9 (*C*(α)), 60.4 (*C*(3)), 116.9 (*C*(4')), 125.7 (*C*(4)), 125.9, 128.1, 128.2, 128.3, 128.4, 128.8, 128.9, 129.5, 129.6 (*o*,*m*,*p*-*Ph*), 134.3 (*C*(5)), 134.6 (*i*-*Ph*), 138.5 (*C*(3')), 139.6, 140.6 (*i*-*Ph*), 174.0 (*C*(1)); *m*/*z* (ESI^+) 454 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{31}H_{36}NO_2^+$ ($[M+H]^+$) requires 454.2741; found 454.2763.

Step 2 (*for* ***290***): A solution of **284** (1.15 g, >99:1 dr) in MeCN (12 mL) was treated sequentially with DBU (758 μl, 5.07 mmol) and MeI (347 μL, 5.58 mmol) at rt. The resultant mixture was stirred at rt for 16 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (80 mL) and 2.0 M aq HCl (80 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were then washed sequentially with satd aq $NaHCO_3$ (150 mL) and brine (150 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **290** as a pale yellow oil (777 mg, 57% from **281**, >99:1 dr); $[\alpha]_D^{20}$ –12.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3027, 2935 (C–H), 1734 (C=O), 1495 (C=C); δ_H (400 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6.9, C(α)*Me*), 1.67 (3H, dd, *J* 6.4, 1.5, C(6)H_3), 2.26–2.33 (1H, m, C(2')*H*), 2.38 (1H, dd, *J* 13.4, 8.2, C(1')H_A), 2.55 (1H, dd, *J* 13.4, 6.6, C(1')H_B), 2.72 (1H, dd, *J* 11.4, 3.8, C(2)*H*), 3.42 (3H, s, O*Me*), 3.45 (1H, d, *J* 14.0, NCH_AH_BPh), 3.46–3.52 (1H, m, C(3)*H*), 3.66 (1H, d, *J* 14.0, NCH_AH_BPh), 3.98 (1H, q, *J* 6.9, C(α)*H*), 4.50 (1H, dd, *J* 17.1, 2.1, C(4')H_A), 4.74 (1H, dd, *J* 10.2, 2.1, C(4')H_B), 5.15–5.22 (1H, m, C(4)*H*), 5.36 (1H, app dq, *J* 15.3, 6.4, C(5)*H*), 5.57–5.66 (1H, m, C(3')*H*), 6.98–7.01 (2H, m, *Ph*), 7.06–7.22 (13H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.9 (C(α)*Me*), 18.0 (*C*(6)), 40.1 (*C*(1')), 45.6 (*C*(2')), 50.3 (N*C*H_2Ph), 50.7 (O*Me*), 51.6 (*C*(2)), 56.3 (*C*(α)), 60.4 (*C*(3)), 116.6 (*C*(4')), 125.8, 126.2, 126.4, 127.6, 127.8, 127.9 (*o*,*m*,*p*-*Ph*), 127.9 (*C*(4)), 128.0, 128.9, 129.2 (*o*,*m*,*p*-*Ph*), 130.3 (*C*(5)), 137.0 (*C*(3')), 139.9, 140.2, 144.6 (*i*-*Ph*), 173.0 (*C*(1)); *m*/*z* (ESI^+) 468 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{32}H_{38}NO_2^+$ ($[M+H]^+$) requires 468.2897; found 468.2907.

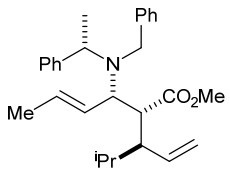
Step 2 (*for* ***293***): A solution of **287** (359 mg, >99:1 dr) in MeCN (3.6 mL) was treated sequentially with DBU (237 μL, 1.58 mmol) and MeI (108 μL, 1.74 mmol) at rt. The resultant mixture was stirred at rt for 16 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (50 mL) and 2.0 M aq HCl (50 mL), and the aqueous layer was extracted

with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were then washed sequentially with satd aq $NaHCO_3$ (150 mL) and brine (150 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 2% Et_2O in 30–40 °C petrol) gave **293** as a yellow oil (221 mg, 16% from **281**, >99:1 dr); $[\alpha]_D^{20}$ +15.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3028, 2950 (C–H), 1732 (C=O), 1496 (C=C); δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, *J* 7.0, C(α)*Me*), 1.63–1.65 (3H, m, C(6)H_3), 2.25 (1H, dd, *J* 13.7, 8.8, C(1')H_A), 2.39 (1H, dd, *J* 13.7, 6.4, C(1')H_B), 2.56 (1H, dd, *J* 8.8, 5.4, C(2)*H*), 2.63–2.70 (1H, m, C(2')*H*), 3.43–3.49 (1H, m, C(3)*H*), 3.48 (3H, s, O*Me*), 3.51 (1H, d, *J* 14.4, NC$H_A$$H_B$Ph), 3.58 (1H, d, *J* 14.4, NCH$_A$$H_B$Ph), 3.85 (1H, q, *J* 7.0, C(α)*H*), 4.35–4.40 (1H, m, C(4')H_A), 4.66 (1H, dd, *J* 10.4, 2.1, C(4')H_B), 5.37–5.45 (1H, m, C(3')*H*), 5.40–5.48 (1H, m, C(5)*H*), 5.51–5.57 (1H, m, C(4)*H*), 6.87–6.89 (2H, m, *Ph*), 7.02–7.27 (13H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.0 (C(α)*Me*), 18.1 (*C*(6)), 38.7 (*C*(1')), 43.8 (*C*(2')), 50.7 (N*C*H$_2$Ph), 50.8 (O*Me*), 53.0 (*C*(2)), 57.0 (*C*(α)), 59.6 (*C*(3)), 116.1 (*C*(4')), 125.8 (*C*(4)), 126.6 (*C*(5)), 127.9, 128.0, 128.0, 128.1, 128.1, 128.3, 129.0, 129.3, 129.3 (*o,m,p-Ph*), 138.0 (*C*(3')), 140.0, 140.9, 144.4 (*i-Ph*), 173.4 (*C*(1)); *m*/*z* (ESI$^+$) 468 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{38}NO_2^+$ ([M+H]$^+$) requires 468.2897; found 468.2904.

Methyl (*S*,*S*,*S*,*S*,*E*)-2-(4'-methylpent-1'-en-3'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino] hex-4-enoate 291 and methyl (2*R*,3*S*,2'*R*,α*S*,*E*)-2-(4'-methylpent-1'-en-3'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 294



291



294

Step 1: TMSCl (476 μL, 3.77 mmol) was added dropwise to a solution of **282** (509 mg, 1.26 mmol, >99:1 dr) in PhMe (5 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 10 min. LiHMDS (1.0 M in THF, 3.76 mL, 3.76 mmol) was added dropwise at −78 °C and the resultant mixture was stirred at −78 °C for 15 min. The reaction mixture was then stirred at reflux for 1 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 (200 mL) and 1.0 M aq HCl (150 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL) and the combined organic extracts were washed with brine (150 mL), then dried and concentrated *in vacuo* to give an 85:15 mixture of **285** and **288**, respectively. Purification *via* flash column chromatography (gradient elution, 0% → 6% acetone in 30–40 °C petrol) gave **288** as a yellow oil (81 mg, >99:1 dr); $[\alpha]_D^{20}$ –9.7

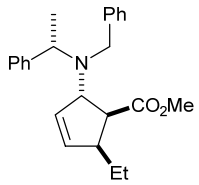
(*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2962 (C–H), 1701 (C=O), 1494 (C=C); δ_H (400 MHz, $CDCl_3$) 0.34 (3H, d, *J* 6.7, C(4')*Me*$_A$), 0.54 (3H, d, *J* 6.7, C(4')*Me*$_B$), 1.25 (3H, d, *J* 6.8, C(α)*Me*), 1.33–1.43 (1H, m, C(4')*H*), 1.57 (3H, d, *J* 6.4, C(6)*H*$_3$), 1.91–1.97 (1H, m, C(3')*H*), 2.47 (1H, app t, *J* 7.0, C(2)*H*), 3.34 (1H, dd, *J* 9.4, 7.0, C(3)*H*), 3.47 (1H, d, *J* 14.4, NC*H*$_A$H$_B$Ph), 3.69 (1H, d, *J* 14.4, NCH$_A$*H*$_B$Ph), 3.93 (1H, q, *J* 6.8, C(α)*H*), 4.51–4.56 (1H, m, C(1')*H*$_A$), 4.74–4.77 (1H, m, C(1')*H*$_B$), 5.38–5.47 (2H, m, C(5)*H*, C(2')*H*), 5.54–5.61 (1H, m, C(4)*H*), 7.03–7.20 (8H, m, *Ph*), 7.27–7.29 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.6 (C(α)*Me*), 17.6 (*C*(4')*Me*$_A$), 17.9 (*C*(6)), 21.2 (C(4')*Me*$_B$), 27.6 (*C*(4')), 49.0 (*C*(3')), 51.1 (*C*(2)), 51.5 (N*C*H$_2$Ph), 57.3 (*C*(α)), 61.0 (*C*(3)), 117.5 (*C*(1')), 126.7, 126.8 (*o,m,p-Ph*), 127.6 (*C*(4)), 128.0, 128.1, 128.3, 128.8 (*o,m,p-Ph*), 130.2 (*C*(5)), 136.1 (*C*(2')) 140.6, 143.7 (*i-Ph*), 179.2 (*C*(1)); *m*/*z* (ESI$^+$) 406 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{36}NO_2^+$ ([M+H]$^+$) requires 406.2741; found 406.2748. Further elution (eluent 30–40 °C petrol/acetone, 94:6) gave **285** as a yellow oil (382 mg, >99:1 dr); $[\alpha]_D^{20}$ +5.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2960 (C–H), 1702 (C=O), 1495 (C=C); δ_H (400 MHz, $CDCl_3$) 0.57 (3H, d, *J* 6.7, C(4')*Me*$_A$), 0.64 (3H, d, *J* 6.7, C(4')*Me*$_B$), 1.40 (1H, app td, *J* 10.0, 1.7, C(3')*H*), 1.48 (3H, d, *J* 7.1, C(α)*Me*), 1.83 (3H, dd, *J* 6.5, 1.8, C(6)*H*$_3$), 2.14–2.24 (C(2)*H*, C(4')*H*), 3.67 (1H, d, *J* 13.4, NC*H*$_A$H$_B$Ph), 3.74–3.79 (1H, m, C(3)*H*), 3.78 (1H, d, *J* 13.4, NCH$_A$*H*$_B$Ph), 3.91 (1H, q, *J* 7.1, C(α)*H*), 4.59 (1H, dd, *J* 17.3, 2.5, C(1')*H*$_A$), 4.79 (1H, dd, *J* 10.0, 2.5, C(1')*H*$_B$), 5.33 (1H, app ddd, *J* 15.5, 9.6, 1.8, C(4)*H*), 5.52 (1H, ddd, *J* 17.3, 10.2, 10.0, C(2')*H*), 5.66 (1H, dq, *J* 15.5, 6.5, C(5)*H*), 7.15–7.27 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.9 (C(α)*Me*), 18.3 (*C*(6)), 20.6, 22.1 (C(4')*Me*$_2$), 28.4 (*C*(4')), 43.9 (*C*(2)), 51.4 (N*C*H$_2$Ph), 52.2 (*C*(3')), 60.6 (*C*(α)), 60.6 (*C*(3)), 117.0 (*C*(1')), 125.7 (*C*(4)), 128.0, 128.1, 128.1, 128.7, 128.7, 129.6 (*o,m,p-Ph*), 134.2 (*C*(5)), 135.1 (*i-Ph*), 138.5 (*C*(2')), 140.3 (*i-Ph*), 174.0 (*C*(1)); *m*/*z* (ESI$^+$) 406 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{36}NO_2^+$ ([M+H]$^+$) requires 406.2741; found 406.2747.

*Step 2 (for **291**)*: A solution of **285** (382 mg, >99:1 dr) in MeCN (3.9 mL) was treated sequentially with DBU (281 μL, 1.88 mmol) and MeI (129 μL, 2.07 mmol) at rt. The reaction mixture was stirred at rt for 16 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (50 mL) and 2.0 M aq HCl (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic extracts were then washed sequentially with satd aq $NaHCO_3$ (150 mL) and brine (150 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **291** as a colourless oil (272 mg, 52% from **282**, >99:1 dr); $[\alpha]_D^{20}$ +1.2 (*c* 1.0 in $CHCl_3$); ν_{max}

(ATR) 2958 (C–H), 1737 (C=O), 1495 (C=C); δ_H (400 MHz, $CDCl_3$) 0.65 (3H, d, *J* 6.6, C(4')*Me*$_A$), 0.80 (3H, d, *J* 6.6, C(4')*Me*$_B$), 1.22–1.29 (1H, m, C(4')*H*), 1.31 (3H, d, *J* 6.9, C(α)*Me*), 1.58 (1H, app td, *J* 9.5, 3.8, C(3')*H*), 1.69 (3H, dd, *J* 6.4, 1.2, C(6)*H*$_3$), 2.83 (1H, dd, *J* 11.4, 3.8, C(2)*H*), 3.34 (3H, s, O*Me*), 3.42–3.48 (1H, m, C(3)*H*), 3.48 (1H, d, *J* 13.9, NC*H*$_A$H$_B$Ph), 3.71 (1H, d, *J* 13.9, NCH$_A$*H*$_B$Ph), 4.03 (1H, q, *J* 6.9, C(α)*H*), 4.58 (1H, dd, *J* 17.1, 2.5, C(1')*H*$_A$), 4.80 (1H, dd, *J* 10.2, 2.5, C(1')*H*$_B$), 5.17–5.24 (1H, m, C(4)*H*), 5.31–5.40 (1H, m, C(5)*H*), 5.51 (1H, dt, *J* 17.1, 10.2, C(2')*H*), 7.05–7.12 (2H, m, *Ph*), 7.13–7.23 (8H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.2 (C(α)*Me*), 18.1 (*C*(6)), 21.0 (C(4')*Me*$_B$), 21.3 (C(4')*Me*$_A$), 30.0 (*C*(4')), 49.6 (*C*(2)), 50.5 (N*C*H$_2$Ph), 50.6 (O*Me*), 51.2 (*C*(3')), 56.5 (*C*(α)), 60.7 (*C*(3)), 116.8 (*C*(1')), 126.1, 126.4, 127.6, 127.8, 127.9, 129.0 (*o*,*m*,*p*-*Ph*), 128.1 (*C*(4)), 130.2 (*C*(5)), 136.9 (*C*(2')), 140.3, 144.8 (*i*-*Ph*), 173.3 (*C*(1)); *m*/*z* (ESI^+) 420 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{28}H_{38}NO_2^+$ ($[M+H]^+$) requires 420.2897; found 420.2900.

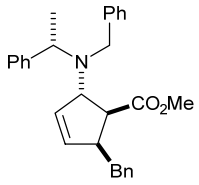
*Step 2 (for **294**)*: A solution of **288** (72 mg, >99:1 dr) in MeCN (0.7 mL) was treated sequentially with DBU (53 μL, 0.36 mmol) and MeI (24 μL, 0.39 mmol) at rt. The reaction mixture was stirred at rt for 16 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and 2.0 M aq HCl (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then washed sequentially with satd aq $NaHCO_3$ (40 mL) and brine (40 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **294** as a white solid (44 mg, 7% from **282**, >99:1 dr); $[\alpha]_D^{20}$ –27.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2960 (C–H), 1731 (C=O), 1494 (C=C); δ_H (400 MHz, $CDCl_3$) 0.30 (3H, d, *J* 6.7, C(4')*Me*$_A$), 0.57 (3H, d, *J* 6.7, C(4')*Me*$_B$), 1.28 (3H, d, *J* 6.7, C(α)*Me*), 1.34 (1H, dd, *J* 11.9, 6.7, C(4')*H*), 1.65 (3H, dd, *J* 6.4, 1.5, C(6)*H*$_3$), 2.00 (1H, ddd, *J* 9.9, 7.6, 5.2, C(3')*H*), 2.56 (1H, app t, *J* 7.6, C(2)*H*), 3.36 (1H, dd, *J* 9.9, 7.6, C(3)*H*), 3.44 (3H, s, O*Me*), 3.56 (1H, d, *J* 14.2, NC*H*$_A$H$_B$Ph), 3.69 (1H, d, *J* 14.2, NCH$_A$*H*$_B$Ph), 3.90 (1H, q, *J* 6.7, C(α)*H*), 4.61 (1H, dd, *J* 17.1, 2.3, C(1')*H*$_A$), 4.84 (1H, dd, *J* 9.9, 2.3, C(1')*H*$_B$), 5.40–5.52 (2H, m, C(5)*H*, C(2')*H*), 5.68–5.75 (1H, m, C(4)*H*), 7.10–7.13 (2H, m, *Ph*), 7.17–7.27 (6H, m, *Ph*), 7.33–7.35 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.2 (C(α)*Me*), 17.2 (C(4')*Me*$_A$), 18.1 (*C*(6)), 21.2 (C(4')*Me*$_B$), 27.5 (*C*(4')), 49.3 (*C*(3')), 50.8 (O*Me*), 51.1 (N*C*H$_2$Ph), 52.1 (*C*(2)), 57.2 (*C*(α)), 59.8 (*C*(3)), 117.4 (*C*(1')), 126.6, 126.6 (*o*,*m*,*p*-*Ph*), 127.9 (*C*(4)), 128.0, 128.1, 128.2, 128.8 (*o*,*m*,*p*-*Ph*), 129.5 (*C*(5)), 136.1 (*C*(2')), 141.3, 144.5 (*i*-*Ph*), 174.5 (*C*(1)); *m*/*z* (ESI^+) 420 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{28}H_{38}NO_2^+$ ($[M+H]^+$) requires 420.2897; found 420.2898.

Methyl (*S*,*S*,*S*,*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-ethylcyclopent-3-ene-1-carboxylate 295



Grubbs I catalyst (292 mg, 0.36 mmol) was added to a degassed solution of **289** (360 mg, 0.89 mmol, >99:1 dr) in CH_2Cl_2 (36 mL) at rt and the resultant mixture was heated at 40 °C for 24 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **295** as a colourless oil (200 mg, 62%, >99:1 dr); $[\alpha]_D^{20}$ +198.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2965 (C–H), 1729 (C=O), 1493 (C=C); δ_H (400 MHz, $CDCl_3$) 0.75 (3H, t, *J* 7.3, C(2')H_3), 0.97–1.08 (1H, m, C(1')H_A), 1.18–1.29 (1H, m, C(1')H_B), 1.27 (3H, d, *J* 7.0, C(α)*Me*), 2.67–2.75 (1H, m, C(5)*H*), 2.89 (1H, dd, *J* 9.4, 6.0, C(1)*H*), 3.37 (3H, s, O*Me*), 3.58 (1H, d, *J* 15.4, NC$H_A$$H_B$Ph), 3.62 (1H, d, *J* 15.4, NC$H_A$$H_B$Ph), 3.77 (1H, q, *J* 7.0, C(α)*H*), 4.35–4.38 (1H, m, C(2)*H*), 5.64–5.66 (1H, m, C(4)*H*), 5.70–5.73 (1H, m, C(3)*H*), 7.09–7.25 (8H, m, *Ph*), 7.31–7.33 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.5 (*C*(2')), 16.3 (C(α)*Me*), 24.5 (*C*(1'), 48.4 (*C*(5)), 50.1 (N*C*H_2Ph), 50.6 (*C*(1)), 51.1 (O*Me*), 57.8 (*C*(α)), 67.5 (*C*(2)), 126.5, 126.5, 127.7, 127.8, 128.1, 128.1 (*o*,*m*,*p*-*Ph*), 132.5 (*C*(4)), 134.8 (*C*(3)), 141.7, 144.0 (*i*-*Ph*), 174.1 (*C*O_2Me); *m*/*z* (ESI^+) 364 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{24}H_{30}NO_2^+$ ($[M+H]^+$) requires 364.2271; found 364.2275.

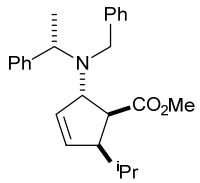
Methyl (*S*,*S*,*S*,*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-benzylcyclopent-3-ene-1-carboxylate 296



Grubbs I catalyst (282 mg, 0.34 mmol) was added to a degassed solution of **290** (400 mg, 0.86 mmol, >99:1 dr) in CH_2Cl_2 (40 mL) at rt and the resultant mixture was heated at 40 °C for 48 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **296** as a colourless oil (349 mg, 96%, >99:1 dr); $[\alpha]_D^{20}$ +185.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3027, 2946 (C–H), 1730 (C=O), 1494 (C=C); δ_H (400 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6.9, C(α)*Me*), 2.23 (1H, dd, *J* 13.2, 10.6, C(1')H_A), 2.58 (1H, dd, *J* 13.2, 5.6, C(1')H_B), 2.95 (1H, dd, *J* 9.4,

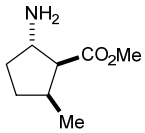
5.6, C(1)*H*), 3.11–3.19 (1H, m, C(5)*H*), 3.34 (3H, s, O*Me*), 3.60 (2H, app s, NC*H*$_2$Ph), 3.78 (1H, q, *J* 6.9, C(α)*H*), 4.43–4.46 (1H, m, C(2)*H*) 5.45 (1H, app dt, *J* 5.6, 2.1, C(4)*H*), 5.66 (1H, app dt, *J* 5.6, 2.1, C(3)*H*), 6.98–7.01 (2H, m, *Ph*), 7.05–7.25 (11H, m, *Ph*), 7.30–7.33 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.2 (C(α)*Me*), 37.7 (*C*(1')), 47.9 (*C*(5)), 50.1 (NCH_2Ph), 50.3 (*C*(1)), 51.2 (O*Me*), 57.7 (*C*(α)), 67.8 (*C*(2)), 126.0, 126.6, 126.6, 127.7, 127.9, 128.1, 128.1, 128.2, 128.8 (*o*,*m*,*p*-*Ph*), 132.6 (*C*(3)), 134.6 (*C*(4)), 140.1, 141.6, 144.0 (*i*-*Ph*), 174.0 (*C*O_2Me); *m*/*z* (ESI$^+$) 426 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{32}NO_2^+$ ([M+H]$^+$) requires 426.2428; found 426.2439.

Methyl (*S*,*S*,*S*,*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-isopropylcyclopent-3-ene-1-carboxylate 297



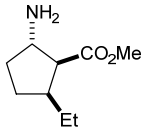
Grubbs I catalyst (197 mg, 0.24 mmol) was added to a degassed solution of **291** (251 mg, 0.60 mmol, >99:1 dr) in CH_2Cl_2 (25 mL) at rt and the resultant mixture was heated at 40 °C for 48 h then concentrated *in vacuo*. The residue was dissolved in degassed CH_2Cl_2 (25 mL) and Grubbs I catalyst (197 mg, 0.24 mmol) was added to the resultant solution. The reaction mixture was heated at 40 °C for 48 h then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **297** as a colourless oil (85 mg, 38%, >99:1 dr); $[\alpha]_D^{20}$ +204.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2958 (C–H), 1734 (C=O), 1494 (C=C); δ_H (400 MHz, $CDCl_3$) 0.68 (3H, d, *J* 6.6, C(1')*Me*$_A$), 0.75 (3H, d, *J* 6.6, C(1')*Me*$_B$), 1.26 (3H, d, *J* 6.9, C(α)*Me*), 1.55–1.63 (1H, m, C(1')*H*), 2.65 (1H, app t, *J* 8.0, C(5)*H*), 2.96 (1H, dd, *J* 9.2, 5.9, C(1)*H*), 3.38 (3H, s, O*Me*), 3.62 (2H, app s, NC*H*$_2$Ph), 3.81 (1H, q, *J* 6.9, C(α)*H*), 4.28 (1H, d, *J* 5.9, C(2)*H*), 5.68–5.71 (2H, m, C(3)*H*, C(4)*H*), 7.10–7.15 (2H, m, *Ph*), 7.18–7.25 (6H, m, *Ph*), 7.31–7.33 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.5 (C(α)*Me*), 20.0 (C(1')*Me*$_A$), 22.7 (C(1')*Me*$_B$), 28.8 (*C*(1')), 50.0 (NCH_2Ph), 50.5 (*C*(1)), 51.2 (O*Me*), 54.1 (*C*(5)), 58.2 (*C*(α)), 68.3 (*C*(2)), 126.5, 127.7, 127.8, 128.0, 128.1 (*o*,*m*,*p*-*Ph*), 133.1 (*C*(3)), 133.4 (*C*(4)), 141.9, 144.3 (*i*-*Ph*), 174.4 (*C*O_2Me); *m*/*z* (ESI$^+$) 378 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{32}NO_2^+$ ([M+H]$^+$) requires 378.2428; found 378.2437.

Methyl (*S*,*S*,*S*)-2-amino-5-methylcyclopentane-1-carboxylate 298



$Pd(OH)_2/C$ (250 mg, 50% w/w by substrate) was added to a degassed solution of **259** (500 mg, 1.43 mmol, >99:1 dr) in MeOH (36 mL) at rt. The resultant suspension was vigorously stirred under H_2 (1 atm) at rt for 24 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (25 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (25 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic extracts were then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$/MeOH, 98:2) gave **298** as a white solid (188 mg, 83%, >99:1 dr); mp 65–67 °C; $[\alpha]_D^{20}$ +52.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2962 (C–H), 1732 (C=O), 1484; δ_H (400 MHz, $CDCl_3$) 0.82 (3H, d, *J* 7.2, C(5)*Me*), 1.22–1.33 (2H, m, C(4)H_2), 1.53 (2H, br s, NH_2), 1.84–1.96 (1H, m, C(3)H_A), 1.99–2.09 (1H, m, C(3)H_B), 2.38–2.49 (2H, m, C(1)*H*, C(5)*H*), 3.56–3.65 (1H, m, C(2)*H*), 3.63 (3H, s, O*Me*); δ_C (125 MHz, $CDCl_3$) 17.5 (C(5)*Me*), 32.0 (*C*(4)), 34.1 (*C*(3)), 35.4 (*C*(5)), 51.3 (O*Me*), 54.2 (*C*(2)), 58.0 (*C*(1)), 174.4 (*C*O_2Me); *m*/*z* (ESI^+) 158 ($[M+H]^+$, 100%), 180 ($[M+Na]^+$, 5%); HRMS (ESI^+) $C_8H_{16}NO_2^+$ ($[M+H]^+$) requires 158.1176; found 158.1175.

Methyl (*S*,*S*,*S*)-2-amino-5-ethylcyclopentane-1-carboxylate 299



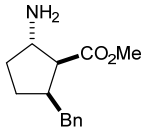
Method A: $Pd(OH)_2/C$ (87 mg, 50% w/w) was added to a degassed solution of **295** (173 mg, 0.48 mmol, >99:1 dr) in MeOH (12 mL) at rt. The resultant suspension was stirred vigorously under H_2 (1 atm) at rt for 24 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (15 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$/MeOH, 94:6) gave **299** as a white solid (55 mg, 67%, >99:1 dr); mp 64–66 °C; $[\alpha]_D^{20}$ +15.7 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 3344 (N–H), 2959, 2932 (C–H), 1730 (C=O); δ_H (400 MHz, $CDCl_3$) 0.80 (3H, t, *J* 7.3, C(2')H_3), 1.01–1.12 (1H, m, C(1')H_A), 1.23–1.39 (3H,

m, C(3)H_A, C(4)H_A, C(1')H_B), 1.81–1.91 (1H, m, C(4)H_B), 2.00–2.09 (3H, m, C(3)H_B, NH_2), 2.13–2.23 (1H, m, C(5)*H*), 2.53 (1H, dd, *J* 9.1, 7.1, C(1)*H*), 3.54–3.65 (1H, m, C(2)*H*), 3.62 (3H, s, O*Me*); δ_C (100 MHz, $CDCl_3$) 12.4 (*C*(2')), 24.7 (*C*(1')), 29.2 (*C*(4)), 34.0 (*C*(3)), 42.9 (*C*(5)), 51.2 (O*Me*), 54.9 (*C*(2)), 57.4 (*C*(1)), 174.5 (*C*O_2Me); *m*/*z* (ESI^+) 172 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_9H_{18}NO_2^+$ ($[M+H]^+$) requires 172.1332; found 172.1336.

*Method B (from **357**)*: $Pd(OH)_2$/C (50 mg, 50% w/w) was added to a degassed solution of **357** (100 mg, 0.27 mmol, >99:1 dr) in MeOH (7 mL) at rt. The resultant suspension was stirred vigorously under H_2 (1 atm) at rt for 24 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (15 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give **299** as a yellow oil (38 mg, 82%, >99:1 dr); $[\alpha]_D^{20}$+45.4 (*c* 1.0 in $CHCl_3$).

*Method C (from **369**)*: $Pd(OH)_2$/C (45 mg, 50% w/w) was added to a degassed solution of **369** (89 mg, 0.24 mmol, >99:1 dr) in MeOH (6 mL) at rt. The resultant suspension was stirred vigorously under H_2 (1 atm) at rt for 24 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (15 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give **299** as a yellow oil (41 mg, 98%, >99:1 dr); $[\alpha]_D^{20}$+47.5 (*c* 1.0 in $CHCl_3$).

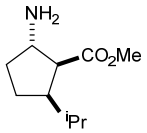
Methyl (1*S*,2*S*,5*R*)-2-amino-5-benzylcyclopentane-1-carboxylate 300



$Pd(OH)_2$/C (99 mg, 50% w/w by substrate) was added to a degassed solution of **296** (197 mg, 0.46 mmol, >99:1 dr) in MeOH (14 mL) at rt. The resultant suspension was stirred vigorously under H_2 (1 atm) at rt for 24 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (15 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$/MeOH, 98:2) gave **300** as a white solid (74 mg, 69%, >99:1 dr); mp 65–67 °C; $[\alpha]_D^{20}$ +32.4 (*c* 1.0 in

$CHCl_3$); ν_{max} (ATR) 3365 (N–H), 2950 (C–H), 1727 (C=O); δ_H (400 MHz, $CDCl_3$) 1.18–1.29 (1H, m, C(3)H_A), 1.36–1.45 (3H, m, C(4)H_A, NH_2), 1.64–1.72 (1H, m, C(4)H_B), 2.02–2.09 (1H, m, C(3)H_B), 2.26–2.33 (1H, m, C(1')H_A), 2.52–2.58 (1H, m, C(1)*H*), 2.59–2.68 (2H, m, C(1')H_B, C(5)*H*), 3.59 (3H, s, O*Me*), 3.62–3.68 (1H, m, C(2)*H*), 7.06–7.12 (3H, m, *Ph*), 7.17–7.21 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 29.4 (*C*(4)), 34.1 (*C*(3)), 37.7 (*C*(1')), 42.5 (*C*(5)), 51.3 (O*Me*), 55.1 (*C*(2)), 57.5 (*C*(1)), 125.9, 128.2, 128.8 (*o*,*m*,*p*-*Ph*), 140.5 (*i*-*Ph*), 174.4 (*C*O_2Me); *m*/*z* (ESI^+) 234 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{14}H_{20}NO_2^+$ ($[M+H]^+$) requires 234.1489; found 234.1495.

Methyl (1*S*,2*S*,5*R*)-2-amino-5-isopropylcyclopentane-1-carboxylate 301

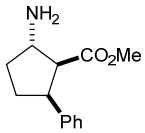


Method A: $Pd(OH)_2$/C (43 mg, 50% w/w by substrate) was added to a degassed solution of **297** (85 mg, 0.23 mmol, >99:1 dr) in MeOH (6 mL) at rt. The resultant suspension was stirred vigorously under H_2 (1 atm) at rt for 24 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (15 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$/MeOH, 99:1) gave **301** as a colourless oil (17 mg, 40%, >99:1 dr); $[\alpha]_D^{20}$ +16.1 (*c* 0.2 in $CHCl_3$); ν_{max} (ATR) 3392 (N–H), 2956 (C–H), 1721 (C=O), 1477; δ_H (700 MHz, $CDCl_3$) 0.81 (3H, d, *J* 3.6, C(1')*Me*$_A$), 0.85 (3H, d, *J* 3.6, C(1')*Me*$_B$), 1.24–1.30 (1H, m, C(3)H_A), 1.44–1.53 (2H, m, C(4)H_A, C(1')*H*), 1.71 (2H, br s, NH_2), 1.79–1.83 (1H, m, C(4)H_B), 1.93–1.98 (1H, m, C(5)*H*), 2.15–2.19 (1H, m, C(3)H_B), 2.59 (1H, dd, *J* 8.1, 3.2, C(1)*H*), 3.53–3.55 (1H, m, C(2)*H*), 3.59 (3H, s, O*Me*); δ_C (176 MHz, $CDCl_3$) 21.5 (C(1')*Me*$_A$), 22.3 (C(1')*Me*$_B$), 28.5 (*C*(4)), 29.7 (*C*(1')), 34.8 (*C*(3)), 49.9 (*C*(5)), 51.2 (O*Me*), 56.6 (*C*(2)), 56.8 (*C*(1)), 175.0 (*C*O_2Me); *m*/*z* (ESI^+) 186 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{10}H_{20}NO_2^+$ ($[M+H]^+$) requires 186.1489; found 186.1493.

*Method B (from **358**)*: $Pd(OH)_2$/C (50 mg, 50% w/w by substrate) was added to a degassed solution of **358** (100 mg, 0.26 mmol, >99:1 dr) in MeOH (7 mL) at rt. The resultant suspension was stirred vigorously under H_2 (1 atm) at rt for 24 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (15 mL) and the resultant solution was washed with satd aq $NaHCO_3$

(15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$/MeOH, 98:2) gave **301** as a colourless oil (28 mg, 58%, >99:1 dr); $[\alpha]_D^{20}$+6.3 (*c* 0.2 in $CHCl_3$).

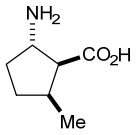
Methyl (*S*,*S*,*S*)-2-amino-5-phenylcyclopentane-1-carboxylate 302



Method A: $Pd(OH)_2$/C (300 mg, 50% w/w by substrate) was added to a degassed solution of **260** (600 mg, 1.47 mmol, >99:1 dr) in MeOH (42 mL) at rt. The resultant suspension was vigorously stirred under H_2 (1 atm) at rt for 24 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (25 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (25 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give **302** as a white solid (277 mg, 87%, >99:1 dr); mp 56–60 °C; $[\alpha]_D^{20}$ −15.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2950 (C–H), 1728 (C=O), 1206; δ_H (400 MHz, $CDCl_3$) 1.46–1.56 (3H, m, C(3)H_A, NH_2), 1.98–2.08 (1H, m, C(4)H_A), 2.16–2.22 (1H, m, C(4)H_B), 2.23–2.33 (1H, m, C(3)H_B), 2.85 (1H, dd, *J* 10.0, 7.5, C(1)*H*), 3.24 (3H, s, O*Me*), 3.63–3.69 (1H, m, C(5)*H*), 3.83–3.89 (1H, m, C(2)*H*), 7.14–7.19 (3H, m, *Ph*), 7.24–7.27 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 30.7 (*C*(3)), 34.9 (*C*(4)), 47.1 (*C*(5)), 51.0 (O*Me*), 55.0 (*C*(2)), 59.5 (*C*(1)), 126.4, 127.9, 128.0 (*o*,*m*,*p*-*Ph*), 142.1 (*i*-*Ph*), 173.6 (*C*O_2Me); *m*/*z* (ESI^+) 220 ($[M+H]^+$, 100%), 242 ($[M+Na]^+$, 5%); HRMS (ESI^+) $C_{13}H_{17}NNaO_2^+$ ($[M+Na]^+$) requires 242.1151; found 242.1154.

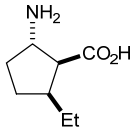
*Method B (from **264**)*: $Pd(OH)_2$/C (42 mg, 50% w/w by substrate) was added to a degassed solution of **264** (84 mg, 0.20 mmol, >99:1 dr) in MeOH (10.8 mL) at rt. The resultant suspension was vigorously stirred under H_2 (1 atm) at rt for 24 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (10 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic extracts were then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$/MeOH, 98:2) gave **302** as a white solid (27 mg, 61%, >99:1 dr); $[\alpha]_D^{20}$ −14.7 (*c* 1.0 in $CHCl_3$).

(*S*,*S*,*S*)-2-Amino-5-methylcyclopentane-1-carboxylic acid 303



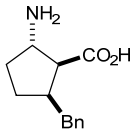
A solution of **298** (50 mg, 0.32 mmol, >99:1 dr) in 6.0 M aq HCl (7 mL) was heated at reflux for 16 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in H_2O (2 mL) and purified on DOWEX 50WX8 ion exchange resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) to give **303** as a white solid (48 mg, 84%, >99:1 dr); mp 214–219 °C (dec.); $[\alpha]_D^{20}$ +67.0 (*c* 1.0 in H_2O); ν_{max} (ATR) 3428 (O–H, N–H), 2970 (C–H), 1576 (C=O); δ_H (400 MHz, D_2O) 0.76 (3H, d, *J* 7.3, C(5)*Me*), 1.26–1.35 (1H, m, C(4)H_A), 1.44–1.53 (1H, m, C(3)H_A), 1.84–1.92 (1H, m, C(4)H_B), 2.08–2.17 (1H, m, C(3)H_B), 2.32–2.42 (1H, m, C(5)*H*), 2.61 (1H, app t, *J* 8.2, C(1)*H*), 3.73 (1H, app q, *J* 8.1, C(2)*H*); δ_C (100 MHz, D_2O) 16.3 (C(5)*Me*), 29.1 (*C*(4)), 31.6 (*C*(3)), 35.6 (*C*(5)), 53.8 (*C*(2)), 56.2 (*C*(1)), 179.7 (*C*O_2H); *m*/*z* (ESI^+) 144 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_7H_{14}NO_2^+$ ($[M+H]^+$) requires 144.1019; found 144.1023.

(*S*,*S*,*S*)-2-Amino-5-ethylcyclopentane-1-carboxylic acid 304



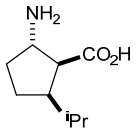
A solution of **299** (35 mg, 0.20 mmol, >99:1 dr) in 6.0 M aq HCl (5 mL) was heated at reflux for 16 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in H_2O (2 mL) and purified on DOWEX 50WX8 ion exchange resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) to give **304** as a white solid (27 mg, 85%, >99:1 dr); mp 202–204 °C; $[\alpha]_D^{20}$ +73.3 (*c* 1.0 in H_2O); ν_{max} (ATR) 3399 (O–H, N–H), 2960 (C–H), 1629 (C=O), 1570; δ_H (400 MHz, D_2O) 0.75 (3H, t, *J* 7.3, C(2')H_3), 0.92–1.03 (1H, m, C(1')H_A), 1.23–1.33 (1H, m, C(1')H_B), 1.35–1.43 (1H, m, C(4)H_A), 1.44–1.53 (1H, m, C(3)H_A), 1.81–1.89 (1H, m, C(4)H_B), 2.08–2.17 (2H, m, C(3)H_B, C(5)*H*), 2.65 (1H, dd, *J* 8.8, 7.7, C(1)*H*), 3.71 (1H, app q, *J* 7.7, C(2)*H*); δ_C (100 MHz, D_2O) 11.8 (*C*(2')), 23.5 (*C*(1')), 28.2 (*C*(4)), 28.9 (*C*(3)), 42.6 (*C*(5)), 53.8 (*C*(2)), 55.8 (*C*(1)), 179.5 (*C*O_2H); *m*/*z* (ESI^+) 158 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_8H_{16}NO_2^+$ ($[M+H]^+$) requires 158.1176; found 158.1173.

(1*S*,2*S*,5*R*)-2-Amino-5-benzylcyclopentane-1-carboxylic acid 305



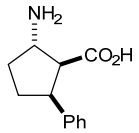
A solution of **300** (28 mg, 0.12 mmol, >99:1 dr) in 6.0 M aq HCl (4 mL) was heated at reflux for 16 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in H_2O (2 mL) and purified on DOWEX 50WX8 ion exchange resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) to give **305** as a white solid (26 mg, quant, >99:1 dr); mp 213–215 °C; $[\alpha]_D^{20}$ +4.7 (*c* 1.0 in H_2O); ν_{max} (ATR) 3363 (O–H, N–H), 3045 (C–H), 1571 (C=O), 1402; δ_H (400 MHz, D_2O) 1.35–1.45 (1H, m, C(4)H_A), 1.45–1.54 (1H, m, C(3)H_A), 1.58–1.66 (1H, m, C(4)H_B), 2.15–2.24 (2H, m, C(3)H_B, C(1')H_A), 2.52–2.61 (1H, m, C(5)*H*), 2.72 (1H, dd, *J* 13.2, 4.0, C(1')H_B), 2.77 (1H, app t, *J* 7.9, C(1)*H*), 3.83 (1H, app q, *J* 7.9, C(2)*H*), 7.15–7.21 (3H, m, *Ph*), 7.24–7.28 (2H, m, *Ph*); δ_C (176 MHz, D_2O) 27.8 (*C*(4)), 28.6 (*C*(3)), 36.2 (*C*(1')), 42.5 (*C*(5)), 53.8 (*C*(2)), 55.8 (*C*(1)), 126.2, 128.6, 129.1 (*o,m,p-Ph*), 141.1 (*i-Ph*), 179.0 (*C*O_2H); *m*/*z* (ESI^+) 220 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{13}H_{18}NO_2^+$ ($[M+H]^+$) requires 220.1332; found 220.1337.

(1*S*,2*S*,5*R*)-2-Amino-5-isopropylcyclopentane-1-carboxylic acid 306



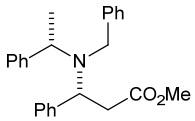
A solution of **301** (20 mg, 0.11 mmol, >99:1 dr) in 6.0 M aq HCl (2.8 mL) was heated at reflux for 16 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in H_2O (2 mL) and purified on DOWEX 50WX8 ion exchange resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) to give **306** as a white solid (17 mg, 94%, >99:1 dr); mp 200–204 °C (dec.); $[\alpha]_D^{20}$ +6.0 (*c* 0.2 in H_2O); ν_{max} (ATR) 3419 (O–H, N–H), 2953 (C–H), 1634 (C=O), 1510; δ_H (700 MHz, D_2O) 0.79 (3H, d, *J* 6.6, C(1')*Me*$_A$), 0.87 (3H, d, *J* 6.6, C(1')*Me*$_B$), 1.48–1.58 (3H, m, C(3)H_A, C(4)H_A, C(1')*H*), 1.83–1.87 (1H, m, C(4)H_B), 1.92–1.97 (1H, m, C(5)*H*), 2.21–2.25 (1H, m, C(3)H_B), 2.73 (1H, dd, *J* 8.6, 4.4, C(1)*H*), 3.75 (1H, app td, *J* 7.3, 4.4, C(2)*H*); δ_C (176 MHz, D_2O) 20.3 (C(1')*Me*$_A$), 21.8 (C(1')*Me*$_B$), 27.4 (*C*(4)), 29.1 (*C*(1')), 30.1 (*C*(3)), 49.4 (*C*(5)), 55.0 (*C*(1)), 55.2 (*C*(2)), 180.3 (*C*O_2H); *m*/*z* (ESI^+) 172 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_9H_{18}NO_2^+$ ($[M+H]^+$) requires 172.1332; found 172.1335.

(*S*,*S*,*S*)-2-Amino-5-phenylcyclopentane-1-carboxylic acid 307



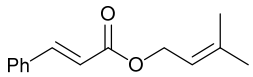
A solution of **302** (161 mg, 0.74 mmol, >99:1 dr) in 6.0 M aq HCl (23 mL) was heated at reflux for 16 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in H_2O (3 mL) and purified on DOWEX 50WX8 ion exchange resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) to give **307** as a white solid (134 mg, 89%, >99:1 dr); mp 215–218 °C (dec.); $[\alpha]_D^{20}$ +17.5 (*c* 0.5 in H_2O); ν_{max} (ATR) 3469, 3030 (O–H, N–H), 2944 (C–H), 1567 (C=O), 700; δ_H (400 MHz, D_2O) 1.61–1.71 (1H, m, C(3)H_A), 1.89–1.98 (1H, m, C(4)H_A), 2.11–2.20 (1H, m, C(4)H_B), 2.29–2.37 (1H, m, C(3)H_B), 2.94–2.98 (1H, m, C(1)*H*), 3.53–3.59 (1H, m, C(5)*H*), 3.90 (1H, app q, *J* 8.3, C(2)*H*), 7.11–7.27 (5H, m, *Ph*); δ_C (125 MHz, D_2O) 29.4 (*C*(3)), 30.1 (*C*(4)), 46.4 (*C*(5)), 53.9 (*C*(2)), 56.7 (*C*(1)), 126.7, 128.0, 128.4 (*o*,*m*,*p*-*Ph*), 141.8 (*i*-*Ph*), 177.9 (CO_2H); *m*/*z* (ESI^+) 206 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{12}H_{15}NNaO_2^+$ ($[M+Na]^+$) requires 228.0995; found 228.0994.

Methyl (3*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 312



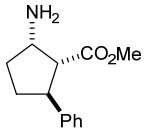
$SOCl_2$ (0.11 mL, 1.6 mmol) was added dropwise to a solution of **192** (200 mg, 0.53 mmol, >99:1 dr) in MeOH (4.8 mL) at 0 °C and the resultant mixture was then stirred at 50 °C for 15 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*, the residue was dissolved in CH_2Cl_2 (100 mL), and the resultant solution was washed with satd aq $NaHCO_3$ (3 × 150 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 99:1) gave **312** as a colourless oil (157 mg, 87%, >99:1 dr);[25] $[\alpha]_D^{20}$+1.6 (*c* 1.0 in $CHCl_3$); {lit.[25] for *ent*-**312** $[\alpha]_D^{20}$−4.2 (*c* 1.1 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.14 (3H, d, *J* 7.0, C(α)*Me*), 2.49 (1H, dd, *J* 15.0, 9.4, C(2)H_A), 2.62 (1H, dd, *J* 15.0, 5.8, C(2)H_B), 3.40 (3H, s, O*Me*), 3.59 (1H, d, *J* 14.4, NC$H_A$$H_B$Ph), 3.68 (1H, d, *J* 14.4, NC$H_A$$H_B$Ph), 3.93 (1H, q, *J* 7.0, C(α)*H*), 4.37 (1H, dd, *J* 9.4, 5.8, C(3)*H*), 7.09–7.35 (15H, m, *Ph*).

3'-Methylbut-2'-en-1'-yl (*E*)-3-phenylprop-2-enoate 313



Et_3N (16.6 mL, 120 mmol) was added dropwise to a stirred solution of cinnamoyl chloride **168** (10.0 g, 60.0 mmol, >99:1 dr) and 3-methyl-2-buten-1-ol (4.73 mL, 90.0 mmol) in CH_2Cl_2 (100 mL) at 0 °C. The resultant mixture was allowed to warm to rt and stirred at rt for 16 h. The reaction mixture was then washed with water (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed sequentially with 1.0 M aq HCl (200 mL), 10% aq NaOH (200 mL) and brine (200 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent, 30–40 °C petrol/Et_2O, 99:1) gave **313** as a colourless oil (8.88 g, 68%, >99:1 dr); ν_{max} (ATR) 2972, 2933 (C–H), 1708 (C=O), 1578 (C=C); δ_H (400 MHz, $CDCl_3$) 1.66 (3H, s, C(3')*Me*$_A$), 1.70 (3H, s, C(3')*Me*$_B$), 4.63 (2H, d, *J* 7.1, C(1')*H*$_2$), 5.34 (1H, t, *J* 7.1, C(2')*H*), 6.36 (1H, d, *J* 16.2, C(2)*H*), 7.27–7.29 (3H, m, *Ph*), 7.41–7.43 (2H, m, *Ph*), 7.60 (1H, d, *J* 16.2, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 18.0 (C(3')*Me*$_A$), 25.7 (C(3')*Me*$_B$), 61.4 (*C*(1')), 118.1 (*C*(2)), 118.6 (*C*(2')), 128.0, 128.8, 130.1 (*o*,*m*,*p*-*Ph*), 134.4 (*i*-*Ph*), 139.1 (*C*(3')), 144.6 (*C*(3)), 166.9 (*C*(1)); *m*/*z* (ESI^+) 239 ($[M+Na]^+$, 25%); HRMS (ESI^+) $C_{14}H_{16}NaO_2^+$ ($[M+Na]^+$) requires 239.1043; found 239.1036.

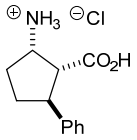
Methyl (1*R*,2*S*,5*R*)-2-amino-5-phenylcyclopentane-1-carboxylate 314



Na (230 mg, 10.0 mmol) was added portionwise to a solution of **302** (50 mg, 0.23 mmol) in dry MeOH (5 mL) at 0 °C and the resultant reaction mixture was allowed to warm to rt and stirred at rt for 72 h. The reaction mixture was then partitioned between sat aq NH_4Cl (3 mL) and EtOAc (5 mL) and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic extracts were then concentrated *in vacuo* and the residue was dissolved in CH_2Cl_2 (5 mL). The resultant solution was washed with sat aq $NaHCO_3$ (5 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were dried and concentrated *in vacuo* to give a 70:30 mixture of **302** and **314**, respectively. Purification *via* flash column chromatography (eluent $CHCl_3$/MeOH, 98:2) gave **314** as a colourless oil (18 mg, 37%, >99:1 dr); $[\alpha]_D^{20}$ +4.6 (*c* 0.85 in $CHCl_3$); ν_{max} (ATR) 3376 (N–H), 2951 (C–H), 1730 (C=O), 1168, 701; δ_H (400 MHz, $CDCl_3$) 1.46 (2H, br s, N*H*$_2$), 1.59–1.68

(1H, m, C(3)H_A), 1.68–1.78 (1H, m, C(4)H_A), 2.22–2.30 (2H, m, C(3)H_B, C(4)H_B), 2.99 (1H, dd, *J* 10.0, 7.6, C(1)*H*), 3.59–3.64 (1H, m, C(5)*H*), 3.67 (3H, s, O*Me*), 3.81–3.86 (1H, m, C(2)*H*), 7.18–7.32 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 32.5 (*C*(3)), 35.7 (*C*(4)), 46.3 (*C*(5)), 51.6 (O*Me*), 55.2 (*C*(2)), 58.0 (*C*(1)), 126.3, 127.2, 128.5 (*o*,*m*,*p*-*Ph*), 144.0 (*i*-*Ph*), 173.7 (*C*O_2Me); *m*/*z* (ESI$^+$) 220 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{18}NO_2^+$ ([M+H]$^+$) requires 220.1332; found 220.1331.

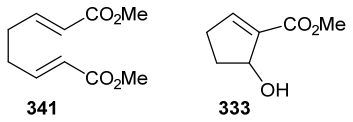
(1*R*,2*S*,5*R*)-2-Amino-5-phenylcyclopentane-1-carboxylate hydrochloride 102·HCl



A solution of **314** (4 mg, 20 μmol, >99:1 dr) in 6.0 M aq HCl (0.6 mL) was heated at reflux for 16 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo* to give **102**·HCl as a white solid (4 mg, 91%, >99:1 dr);[18] $[\alpha]_D^{20}$ +67.6 (*c* 0.85 in H_2O); {lit.[18] $[\alpha]_D^{20}$+76.3 (*c* 1.2 in H_2O)}; δ_H (400 MHz, D_2O) 1.71–1.86 (2H, m, C(4)H_A, C(3)H_A), 2.14–2.23 (1H, m, C(4)H_B), 2.30–2.39 (1H, m, C(3)H_B), 3.12 (1H, dd, *J* 11.2, 7.2, C(1)*H*), 3.33–3.42 (1H, m, C(5)*H*), 3.97–4.01 (1H, m, C(2)*H*), 7.17–7.30 (5H, m, *Ph*).

6.3. Experimental for Chapter 3

Dimethyl (*E*,*E*)-octa-2,6-dienedioate 341 and methyl (*RS*)-5-hydroxy-1-cyclopentene-1-carboxylate 333

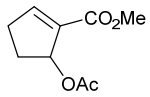


341 **333**

A solution of 2,5-dimethoxytetrahydrofuran **339** (18.5 mL, 143 mmol) in 0.6 M aq HCl (117 mL) was stirred at 80 °C for 2.5 h. The reaction mixture was cooled to 0 °C, and then neutralised with 10% aq (140 mL) $KHCO_3$ until the pH value reached 7. This solution was treated sequentially with 6.5 M aq K_2CO_3 (1.1 mL), **342** (30.0 g, 143 mmol) and another portion of 6.5 M aq K_2CO_3 (44 mL) at 0 °C. The resultant mixture was allowed to warm to rt and stirred at rt for 36 h. The reaction mixture was then extracted with Et_2O (3 × 100 mL), and the combined organic extracts were washed with brine (300 mL), then dried and concentrated *in vacuo* to give an 85:15 mixture of **333** and **341**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petrol/EtOAc, 95:5) gave **341** as a yellow oil (862 mg, 3%, >99:1 dr);[26] δ_H (400 MHz, $CDCl_3$) 2.34–2.36 (4H, m, C(4)H_2, C(5)H_2), 3.69

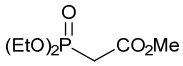
(6H, s, O*Me*), 5.82 (2H, d, *J* 15.7, C(2)*H*, C(7)*H*), 6.86–6.93 (2H, m, C(3)*H*, C(6)*H*). Further elution (gradient elution, 5% → 10% EtOAc in 30–40 °C petrol) gave **333** as a yellow oil (7.7 g, 38%); ν_{max} (ATR) 3418 (O–H), 2952 (C–H), 1720 (C=O); δ_H (400 MHz, $CDCl_3$) 1.82–1.93 (1H, m, C(4)H_A), 2.30–2.39 (1H, m, C(4)H_B), 2.37–2.45 (1H, m, C(3)H_A), 2.60–2.70 (1H, m, C(3)H_B), 2.85 (1H, d, *J* 2.5, O*H*), 3.77 (3H, s, O*Me*), 5.06–5.09 (1H, m, C(5)*H*), 6.90–6.92 (1H, m, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 30.7 (*C*(3)), 31.8 (*C*(4)), 51.4 (O*Me*), 75.1 (*C*(5)), 137.6 (*C*(1)), 146.7 (*C*(2)), 165.3 (*C*O_2Me); *m*/*z* (ESI^+) 143 ($[M+H]^+$, 76%), 160 ($[M+NH_4]^+$, 100%); HRMS (ESI^+) $C_7H_{11}O_3^+$ ($[M+H]^+$) requires 143.0703; found 143.0708.

Methyl (*RS*)-5-acetoxycyclopentene-1-carboxylate 334



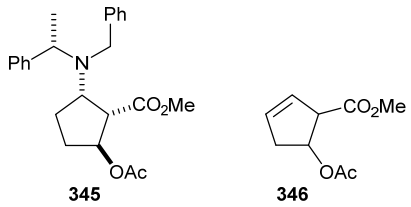
Ac_2O (5.27 mL, 55.7 mmol) was added dropwise to a solution of **333** (3.96 g, 27.9 mmol) and pyridine (3.31 g, 41.8 mmol) in CH_2Cl_2 (28 mL) at rt and the resultant mixture was stirred at rt for 16 h. Brine (100 mL) and CH_2Cl_2 (100 mL) were added and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were then washed with brine (150 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/EtOAc, 90:10) gave **334** as a colourless oil (4.17 g, 81%);[18] δ_H (400 MHz, $CDCl_3$) 1.87–1.94 (1H, m, C(4)H_A), 2.04 (3H, s, CO*Me*), 2.34–2.52 (2H, m, C(3)H_A, C(4)H_B), 2.63–2.73 (1H, m, C(3)H_B), 3.75 (3H, s, O*Me*), 5.96–5.99 (1H, m, C(5)*H*), 7.10–7.12 (1H, m, C(2)*H*).

Methyl diethylphosphonoacetate 342



A mixture of methyl bromoacetate (45.9 g, 300 mmol) and $P(OEt)_3$ (49.8 g, 300 mmol) was heated at 50 °C for 2 h, then allowed to cool to rt and concentrated *in vacuo* to give **342** (62.6 g, 99%); δ_H (400 MHz, $CDCl_3$) 1.29–1.33 (6H, m, $P(OCH_2CH_3)_2$), 2.94 (2H, d, *J* 21.5, PCH_2), 3.71 (3H, app d, *J* 0.5, O*Me*), 4.10–4.18 (4H, m, $P(OCH_2CH_3)_2$).

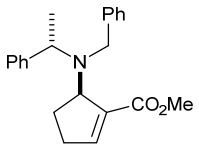
Methyl (*RS*,*RS*,*RS*,*RS*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-acetoxycyclopentane-1-carboxylate 345 and methyl (*RS*)-5-acetoxycyclopent-2-ene-1-carboxylate 346



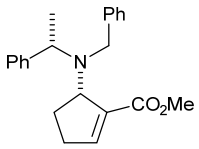
Step 1: BuLi (2.0 M in hexanes, 2.43 mL, 4.85 mmol) was added dropwise to a stirred solution of (*RS*)-**162** (1.04 g, 4.92 mmol) in THF (6.6 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of **333** (200 mg, 1.41 mmol) in THF (2.6 mL) at −78 °C was added dropwise *via* cannula, and the reaction mixture was stirred at −78 °C for 2 h. Satd aq NH_4Cl (2 mL) was then added and the reaction mixture was allowed to warm to rt, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (25 mL) and 10% aq citric acid (25 mL), and the organic extract was washed sequentially with satd aq $NaHCO_3$ (25 mL) and brine (25 mL), then dried and concentrated *in vacuo* to give a 46:25:13:16 mixture of **343**, **344**, **333** and **107**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 70:30) gave a 40:36:24 mixture of **343**, **344** and **333**, respectively, as a yellow oil (62 mg). Further elution (eluent 30–40 °C petrol/Et_2O, 70:30) gave a 62:11:27 mixture of **343**, **344** and **333**, respectively, as a yellow oil (27 mg). Data for **343**: δ_H (500 MHz, $CDCl_3$) 1.24 (3H, d, *J* 6.9, C(α)*Me*), 1.30–1.38 (1H, m, C(4)H_A), 1.70–1.75 (1H, m, C(3)H_A), 1.84–1.92 (1H, m, C(3)H_B), 2.09–2.15 (1H, m, C(4)H_B), 2.73 (1H, dd, *J* 9.5, 5.7, C(1)*H*), 3.36–3.59 (1H, m, C(2)*H*), 3.60 (1H, d, *J* 14.5, NC$H_A$$H_B$Ph), 3.62 (3H, s, O*Me*), 3.74 (1H, d, *J* 14.5, NC$H_A$$H_B$Ph), 3.90 (1H, q, *J* 6.9, C(α)*H*), 4.46–4.50 (1H, m, C(5)*H*), 7.11–7.31 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 14.4 (C(α)*Me*), 27.0 (*C*(3)), 33.1 (*C*(4)), 51.6 (O*Me*), 51.6 (N*C*H_2Ph), 56.7 (*C*(α)), 57.5 (*C*(1)), 60.5 (*C*(2)), 74.5 (*C*(5)), 126.7, 126.7, 127.9, 128.0, 128.2, 128.3 (*o*,*m*,*p*-*Ph*), 141.2, 143.1 (*i*-*Ph*), 173.6 (*C*O_2Me). Data for **344**:[27] δ_H (500 MHz, $CDCl_3$) 2.28–2.32 (1H, m, C(4)H_A), 2.72–2.75 (1H, m, C(4)H_B), 3.42–3.43 (1H, m, C(1)*H*), 3.64 (3H, s, O*Me*), 4.64–4.67 (1H, m, C(5)*H*), 5.62–5.65 (1H, m, C(3)*H*), 5.73–5.76 (1H, m, C(2)*H*); δ_C (125 MHz, $CDCl_3$) 41.2 (*C*(4)), 51.5 (*C*(1)), 51.7 (O*Me*), 74.9 (*C*(5)), 126.0 (*C*(3)), 131.2 (*C*(2)), 173.6 (*C*O_2Me). Data for mixture: ν_{max} (ATR) 3408 (O–H), 2949 (C–H), 1728 (C=O), 1493 (C=C), 1163, 698; *m*/*z* (ESI$^+$) 354 ([M(**343**)+H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{28}NO_3^+$ ([M(**343**)+H]$^+$) requires 354.2064; found 354.2064.

Step 2: Ac_2O (82 μL, 0.87 mmol) and pyridine (53 μL, 0.65 mmol) were added dropwise to a 40:36:24 mixture of **343**, **344** and **333**, respectively, (62 mg) in CH_2Cl_2 (0.4 mL) at rt and the resultant mixture was stirred at rt for 16 h. Brine (5 mL) and CH_2Cl_2 (5 mL) were then added and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were washed with brine (15 mL), then dried and concentrated *in vacuo* to give a 40:36:24 mixture of **345**, **346** and **334**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 95:5) gave **107** as a colourless oil (8 mg, >99:1 dr). Further elution (eluent 30–40 °C petrol/Et_2O, 95:5) gave **346** as an orange oil (14 mg, 8% from **333**); ν_{max} (ATR) 2957 (C–H), 1724 (C=O), 1233; δ_H (500 MHz, $CDCl_3$) 1.98 (3H, s, CO*Me*), 2.32 (1H, app ddt, *J* 17.8, 2.2, 1.2, C(4)H_A), 2.90 (1H, ddd, *J* 17.8, 7.3, 2.2, C(4)H_B), 3.52–3.54 (1H, m, C(1)*H*), 3.65 (3H, s, O*Me*), 5.50–5.53 (1H, m, C(5)*H*), 5.63–5.65 (1H, m, C(3)*H*), 5.77–5.80 (1H, m, C(2)*H*); δ_C (125 MHz, $CDCl_3$) 21.1 (CO*Me*), 39.5 (*C*(4)), 52.2 (O*Me*), 57.3 (*C*(1)), 76.0 (*C*(5)), 126.7 (*C*(3)), 131.4 (*C*(2)), 170.6 (*C*OMe), 172.5 (*C*O_2Me); *m*/*z* (ESI^+) 207 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_9H_{12}NaO_4^+$ ($[M+Na]^+$) requires 207.0628; found 207.0628. Further elution (eluent 30–40 °C petrol/Et_2O, 95:5) gave a 66:34 mixture of **345** and **334**, respectively, as a yellow oil (14 mg, >99:1 dr). Data for **345**: δ_H (500 MHz, $CDCl_3$) 1.27 (3H, d, *J* 6.9, C(α)*Me*), 1.35–1.45 (1H, m, C(4)H_A), 1.65–1.72 (1H, m, C(3)H_A), 1.78–1.87 (1H, m, C(3)H_B), 1.88 (3H, s, CO*Me*), 2.19–2.27 (1H, m, C(4)H_B), 2.83 (1H, dd, *J* 8.8, 3.8, C(1)*H*), 3.45 (1H, ddd, *J* 10.7, 8.8, 3.8, C(2)*H*), 3.57 (1H, d, *J* 14.5, NC$H_A$$H_B$Ph), 3.64 (3H, s, O*Me*), 3.80 (1H, d, *J* 14.5, NC$H_A$$H_B$Ph), 3.99 (1H, q, *J* 6.9, C(α)*H*), 5.15–5.20 (1H, m, C(5)*H*), 7.18–7.33 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 15.3 (C(α)*Me*), 21.0 (CO*Me*), 27.4 (*C*(3)), 30.3 (*C*(4)), 51.3 (N*C*H_2Ph), 51.7 (O*Me*), 54.1 (*C*(1)), 57.2 (*C*(α)), 62.0 (*C*(2)), 76.5 (*C*(5)), 126.5, 126.7, 127.9, 128.0, 128.0, 128.1 (*o*,*m*,*p*-*Ph*), 141.5, 142.7 (*i*-*Ph*), 170.5 (*C*OMe), 173.0 (*C*O_2Me). Data for mixture: ν_{max} (ATR) 2951 (C–H), 1736 (C=O), 1493 (C=C), 1238, 700; *m*/*z* (ESI^+) 396 ($[M(\mathbf{345})+H]^+$, 100%); HRMS (ESI^+) $C_{24}H_{29}NNaO_4^+$ ($[M(\mathbf{345})+Na]^+$) requires 418.1989; found 418.1990.

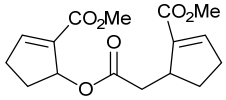
Methyl (5*RS*,α*SR*)-5-[*N*-benzyl-*N*-(α-methylbenzyl)amino]cyclopent-1-ene-1-carboxylate 347, methyl (*RS*,*RS*)-5-[*N*-benzyl-*N*-(α-methylbenzyl)amino]cyclopent-1-ene-1-carboxylate 107 and methyl (*RS*)-5-[2'-(2''-methoxycarbonylcyclopent-2''-en-1''-yl)acetoxy]cyclopentene-1-carboxylate 349



347



107



349

Method A: BuLi (2.0 M in hexanes, 0.49 mL, 0.97 mmol) was added dropwise to a stirred solution of (*RS*)-**162** (217 mg, 1.03 mmol) in THF (6.6 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of **334** (200 mg, 1.08 mmol) in THF (2.6 mL) at −78 °C was added dropwise *via* cannula, and the reaction mixture was stirred at −78 °C for 2 h. Satd aq NH_4Cl (2 mL) was then added and the reaction mixture was allowed to warm to rt, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (25 mL) and 10% aq citric acid (25 mL), and the organic extract was washed sequentially with satd aq $NaHCO_3$ (25 mL) and brine (25 mL), then dried and concentrated *in vacuo* to give a 38:39:4:19 mixture of **334**, **107**, **347** and **349**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **347** as a colourless oil (6 mg, 2%, >99:1 dr); ν_{max} (ATR) 2970 (C–H), 1721 (C=O), 1493 (C=C), 700; δ_H (400 MHz, $CDCl_3$) 1.24–1.30 (1H, m, C(4)H_A), 1.31 (3H, d, *J* 6.9, C(α)*Me*), 1.47–1.57 (1H, m, C(4)H_B), 2.14–2.29 (2H, m, C(3)H_2), 3.38 (1H, d, *J* 14.8, NC$H_A$$H_B$Ph), 3.49 (1H, d, *J* 14.8, NC$H_A$$H_B$Ph), 3.69 (1H, q, *J* 6.9, C(α)*H*), 3.70 (3H, s, O*Me*), 4.51 (1H, app d, *J* 9.2, C(5)*H*), 6.64–6.66 (1H, m, C(2)*H*), 7.10–7.28 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.3 (C(α)*Me*), 23.8 (*C*(4)), 32.1 (*C*(3)), 49.4 (N*C*H_2Ph), 51.1 (O*Me*), 58.6 (*C*(α)), 61.8 (*C*(5)), 126.3, 126.8, 127.9, 128.0, 128.0, 128.1 (*o*,*m*,*p*-*Ph*), 137.7 (*C*(1)), 141.8, 143.1 (*i*-*Ph*), 144.9 (*C*(2)), 165.6 (*C*O_2Me); *m*/*z* (ESI^+) 336 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{22}H_{26}NO_2^+$ ($[M+H]^+$) requires 336.1958; found 336.1963. Further elution (eluent 30–40 °C petrol/Et_2O, 98:2) gave **107** as a colourless oil (47 mg, 13%, >99:1 dr); ν_{max} (ATR) 2970, 2946 (C–H), 1717 (C=O), 1494 (C=C), 698; δ_H (400 MHz, $CDCl_3$) 1.19 (3H, d, *J* 6.9, C(α)*Me*), 1.72–1.89 (2H, m, C(4)H_2), 2.12–2.21 (1H, m, C(3)H_A), 2.25–2.35 (1H, m, C(3)H_B), 3.42 (3H, s, O*Me*), 3.48 (2H, app s, NCH_2Ph), 3.82 (1H, q, *J* 6.9, C(α)*H*), 4.11 (1H, ddd, *J* 7.0, 5.0, 3.7, C(5)*H*), 6.55–6.57 (1H, m, C(2)*H*), 7.00–7.05 (2H, m, *Ph*), 7.09–7.21 (8H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.4 (C(α)*Me*), 26.2 (*C*(4)), 31.8 (*C*(3)), 49.6 (N*C*H_2Ph), 51.0 (O*Me*), 57.1 (*C*(α)), 62.6 (*C*(5)),

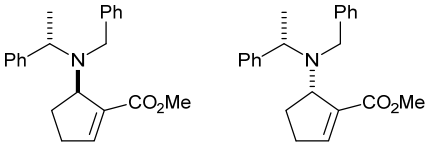
126.4, 126.5, 127.6, 128.0, 128.1, 128.4 (*o,m,p-Ph*), 138.2 (*C*(1)), 141.5, 144.5 (*i-Ph*), 144.8 (*C*(2)), 165.8 (*C*O_2Me); *m*/*z* (ESI$^+$) 336 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{26}NO_2^+$ ([M+H]$^+$) requires 336.1958; found 336.1965. Further elution (eluent 30–40 °C petrol/Et_2O, 90:10) gave **334** as a colourless oil (25 mg, 13%, >99:1 dr). Further elution (eluent 30–40 °C petrol/Et_2O, 80:20) gave **349** as a pale yellow oil (44 mg, 13%); ν_{max} (ATR) 2955 (C–H), 1717 (C=O), 1437 (C=C), 748; δ_H (400 MHz, $CDCl_3$) 1.69–1.77 (1H, m, C(5")H_A), 1.86–1.94 (1H, m, C(4)H_A), 2.18–2.28 (2H, m, C(2')H_A, C(5")H_B), 2.33–2.55 (4H, m, C(4")H_2, C(3)H_A, C(4)H_B), 2.62–2.71 (1H, m, C(3)H_B), 2.82–2.87 (1H, m, C(2')H_B), 3.29–3.37 (1H, m, C(1")*H*), 3.71 (3H, s, C(2")CO_2*Me*), 3.73 (3H, s, C(1)CO_2*Me*), 5.96–6.01 (1H, m, C(5)*H*), 6.79–6.80 (1H, m, C(3")*H*), 7.10–7.11 (1H, m, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 29.5 (*C*(5")), 31.1 (*C*(4)), 31.3 (*C*(4")), 31.3 (*C*(3)), 38.4 (*C*(2')), 40.8 (*C*(1")), 51.3 (CO_2*Me*), 51.5 (CO_2*Me*), 134.8 (*C*(1)), 137.8 (*C*(2")), 145.2 (*C*(3")), 150.1 (*C*(2)), 164.0 (C(1)*C*O_2Me), 165.1 (C(2")*C*O_2Me), 172.2 (*C*(1')); *m*/*z* (ESI$^+$) 331 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{20}NaO_6^+$ ([M+Na]$^+$) requires 331.1152; found 331.1146.

Method B: BuLi (2.0 M in hexanes, 1.05 mL, 2.11 mmol) was added dropwise to a stirred solution of (*RS*)-**162** (457 mg, 2.16 mmol) in THF (6.6 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of **334** (200 mg, 1.08 mmol) and TMSCl (164 μL, 1.29 mmol) in THF (2.6 mL) at −78 °C was added dropwise *via* cannula, and the reaction mixture was stirred at −78 °C for 2 h. Satd aq NH_4Cl (2 mL) was then added and the reaction mixture was allowed to warm to rt, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (25 mL) and 10% aq citric acid (25 mL), and the organic extract was washed sequentially with satd aq $NaHCO_3$ (25 mL) and brine (25 mL), then dried and concentrated *in vacuo* to give an 18:75:7 mixture of **334**, **107** and **347**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **347** as a pale yellow oil (12 mg, 3%, >99:1 dr). Further elution (eluent 30–40 °C petrol/Et_2O, 98:2) gave **107** as a pale yellow oil (205 mg, 57%, >99:1 dr).

Method C: BuLi (2.0 M in hexanes, 1.79 mL, 3.59 mmol) was added dropwise to a stirred solution of (*RS*)-**162** (773 mg, 3.66 mmol) in THF (6.6 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of **333** (200 mg, 1.41 mmol) and TMSCl (710 μL, 5.63 mmol) in THF (2.6 mL) at −78 °C was added dropwise *via* cannula, and the reaction mixture was stirred at −78 °C for 2 h. Satd aq NH_4Cl (2 mL) was then added and the reaction mixture was allowed to warm to rt, then concentrated *in vacuo*. The residue was

partitioned between CH_2Cl_2 (25 mL) and 10% aq citric acid (25 mL), and the organic extract was washed sequentially with satd aq $NaHCO_3$ (25 mL) and brine (25 mL), then dried and concentrated *in vacuo* to give a 92:4:4 mixture of **107**, **347** and **348**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **107** as a yellow oil (289 mg, 61%, >99:1 dr).

Methyl (5*R*,α*S*)-5-[*N*-benzyl-*N*-(α-methylbenzyl)amino]cyclopent-1-ene-1-carboxylate 347 and methyl (*S*,*S*)-5-[*N*-benzyl-*N*-(α-methylbenzyl)amino]cyclopent-1-ene-1-carboxylate 107

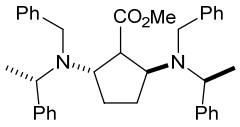


Method A: BuLi (2.0 M in hexanes, 1.79 mL, 3.59 mmol) was added dropwise to a stirred solution of (*S*)-**162** (773 mg, 3.66 mmol) in THF (6.6 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of **333** (200 mg, 1.41 mmol) and TMSCl (710 μL, 5.63 mmol) in THF (2.6 mL) at −78 °C was added dropwise *via* cannula, and the reaction mixture was stirred at −78 °C for 2 h. Satd aq NH_4Cl (2 mL) was then added and the reaction mixture was allowed to warm to rt, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (25 mL) and 10% aq citric acid (25 mL), and the organic extract was washed sequentially with satd aq $NaHCO_3$ (25 mL) and brine (25 mL), then dried and concentrated *in vacuo* to give a 78:15:6:1 mixture of **107**, **348**, **347** and **350**, respectively. Purification *via* flash column chromatography (gradient elution, 6% Et_2O in 30–40 °C petrol) gave a 51:32:17 mixture of **347**, **107** and **348**, respectively as a pale yellow oil (107 mg). Further elution (eluent 30–40 °C petrol/Et_2O, 94:6) gave **107** as a pale yellow oil (231 mg, 49%, >99:1 dr); $[\alpha]_D^{20}$ +21.5 (*c* 1.0 in $CHCl_3$).

Method B: BuLi (2.0 M in hexanes, 10.8 mL, 21.5 mmol) was added dropwise to a stirred solution of (*S*)-**162** (4.64 g, 21.9 mmol) in THF (39.6 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. The resultant solution was then added dropwise *via* cannula to a solution of **333** (1.20 g, 8.44 mmol) and TMSCl (5.33 mL, 42.2 mmol) in THF (15.6 mL) at −78 °C and the reaction mixture was stirred at −78 °C for 2 h. Satd aq NH_4Cl (20 mL) was then added and the reaction mixture was allowed to warm to rt, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (100 mL) and 10% aq citric acid (100 mL), and the organic extract was washed sequentially with satd aq $NaHCO_3$

(100 mL) and brine (100 mL), then dried and concentrated *in vacuo* to give an 80:13:5:2 mixture of **107**, **348**, **347** and **350** respectively. Purification *via* flash column chromatography (gradient elution, 6% Et_2O in 30–40 °C petrol) gave **347** as a colourless oil (243 mg, 9%, >99:1 dr); $[\alpha]_D^{20}$ −119.0 (*c* 1.0 in $CHCl_3$). Further elution (eluent 30–40 °C petrol/Et_2O, 94:6) gave **107** as a pale yellow oil (879 mg, 50%, >99:1 dr); $[\alpha]_D^{20}$ +23.3 (*c* 1.0 in $CHCl_3$).

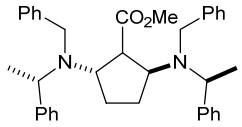
Methyl (*RS*,*RS*,*RS*,*RS*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-[*N*'-benzyl-*N*'-(α'-methylbenzyl)amino]cyclopentane-1-carboxylate 348



Method A: BuLi (2.0 M in hexanes, 1.79 mL, 3.58 mmol) was added dropwise to a solution of (*RS*)-**162** (773 mg, 3.66 mmol) in THF (6.6 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of **333** (200 mg, 1.41 mmol) and TMSCl (391 μL, 3.09 mmol) in THF (2.6 mL) at −78 °C was added dropwise *via* cannula, and the reaction mixture was stirred at −78 °C for 2 h. Satd aq NH_4Cl (2 mL) was then added and the reaction mixture was allowed to warm to rt, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (25 mL) and 10% aq citric acid (25 mL), and the organic extract was washed sequentially with satd aq $NaHCO_3$ (25 mL) and brine (25 mL), then dried and concentrated *in vacuo* to give a 74:26 mixture of **348** and **107**, respectively. Purification *via* flash column chromatography (gradient elution, 2% → 10% Et_2O in 30–40 °C petrol) gave **348** as a colourless oil (326 mg, 57%, >99:1 dr). ν_{max} (ATR) 2970 (C–H), 1725 (C=O), 1493, 699; δ_H (400 MHz, $CDCl_3$) 1.11 (3H, d, *J* 6.9, C(α')*Me*), 1.23 (3H, d, *J* 6.9, C(α)*Me*), 1.26–1.35 (1H, m, C(4)H_A), 1.35–1.42 (1H, m, C(3)H_A), 1.45–1.55 (1H, m, C(3)H_B), 1.66–1.73 (1H, m, C(4)H_B), 2.73 (1H, dd, *J* 8.8, 4.4, C(1)*H*), 3.03 (1H, ddd, *J* 12.1, 8.8, 5.6, C(2)*H*), 3.35 (1H, d, *J* 15.3, NCH_AH$_B$Ph), 3.43–3.52 (2H, m, N'CH_2Ph), 3.47 (3H, s, O*Me*), 3.53–3.59 (1H, m, C(5)*H*), 3.64 (1H, q, *J* 6.9, C(α')*H*), 3.78 (1H, d, *J* 15.3, NCH$_A$$H_B$Ph), 4.01 (1H, q, *J* 6.9, C(α)*H*), 7.05–7.31 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.3 (C(α)*Me*), 18.7 (C(α')*Me*), 29.0 (*C*(3)), 29.1 (*C*(4)), 50.3 (*C*(1)), 50.6 (N'*C*H$_2$Ph), 51.1 (N*C*H$_2$Ph), 51.3 (O*Me*), 57.6 (C(α)), 59.4 (*C*(α')), 62.0 (*C*(5)), 64.8 (*C*(2)), 126.2, 126.5, 126.6, 126.8, 127.4, 127.7, 127.7, 127.9, 127.9, 128.0, 128.1, 128.2 (*o*,*m*,*p*-*Ph*), 141.9, 142.1, 142.3, 144.4 (*i*-*Ph*), 175.4 (*C*O$_2$Me); *m*/*z* (ESI$^+$) 547 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{37}H_{43}N_2O_2^+$ ([M+H]$^+$) requires 547.3319; found 547.3325.

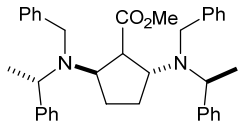
Method B: BuLi (2.0 M in hexanes, 0.23 mL, 0.46 mmol) was added dropwise to a solution of (*RS*)-**162** (101 mg, 0.48 mmol) in THF (3.3 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of **107** (100 mg, 0.29 mmol, >99:1 dr) in THF (1.3 mL) at −78 °C was added dropwise *via* cannula, and the reaction mixture was stirred at −78 °C for 2 h. Satd aq NH_4Cl (2 mL) was then added and the reaction mixture was allowed to warm to rt, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (25 mL) and 10% aq citric acid (25 mL), and the organic extract was washed sequentially with satd aq $NaHCO_3$ (25 mL) and brine (25 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 5% Et_2O in 30–40 °C petrol) gave **348** as a colourless oil (133 mg, 82%, >99:1 dr). Further elution (gradient elution, 6% Et_2O in 30–40 °C petrol) gave **107** as a pale yellow oil (13 mg, >99:1 dr).

Methyl (*S*,*S*,*S*,*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-[*N*'-benzyl-*N*'-(α'-methylbenzyl)amino]cyclopentane-1-carboxylate 348



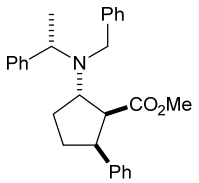
BuLi (2.0 M in hexanes, 0.73 mL, 1.46 mmol) was added dropwise to a solution of (*S*)-**162** (315 mg, 1.49 mmol) in THF (6.6 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of (*S*,*S*)-**107** (200 mg, 0.60 mmol, >99:1 dr) in THF (2.6 mL) at −78 °C was added dropwise *via* cannula, and the reaction mixture was stirred at −78 °C for 2 h. Satd aq NH_4Cl (2 mL) was then added and the reaction mixture was allowed to warm to rt, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (25 mL) and 10% aq citric acid (25 mL), and the organic extract was washed sequentially with satd aq $NaHCO_3$ (25 mL) and brine (25 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 6% Et_2O in 30–40 °C petrol) gave **348** as a colourless oil (228 mg, 70%, >99:1 dr); $[\alpha]_D^{20}$ −67.3 (*c* 1.0 in $CHCl_3$). Further elution (gradient elution, 6% Et_2O in 30–40 °C petrol) gave **107** as a yellow oil (10 mg, >99:1 dr).

Methyl (2*R*,5*R*,α*S*,α'*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-[*N*'-benzyl-*N*'-(α'-methylbenzyl)amino]cyclopentane-1-carboxylate 350



BuLi (2.0 M in hexanes, 0.37 mL, 0.74 mmol) was added dropwise to a solution of (*S*)-**162** (158 mg, 0.75 mmol) in THF (3.3 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of (5*R*,α*S*)-**347** (100 mg, 0.30 mmol, >99:1 dr) in THF (1.3 mL) at −78 °C was added dropwise *via* cannula, and the reaction mixture was stirred at −78 °C for 2 h. Satd aq NH_4Cl (2 mL) was then added and the reaction mixture was allowed to warm to rt, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (25 mL) and 10% aq citric acid (25 mL), and the organic extract was washed sequentially with satd aq $NaHCO_3$ (25 mL) and brine (25 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **350** as a colourless oil (119 mg, 73%, >99:1 dr); $[\alpha]_D^{28}$ −35.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3026, 2970 (C–H), 1725 (C=O), 1493, 748, 699; δ_H (500 MHz, C_6D_6) 1.06–1.12 (1H, m, C(3)H_A), 1.14–1.20 (1H, m, C(4)H_A), 1.22 (3H, d, *J* 6.9, C(α)*Me*), 1.28 (3H, d, *J* 6.9, C(α')*Me*), 1.37–1.49 (2H, m, C(3)H_B, C(4)H_B), 3.21 (1H, dd, *J* 9.1, 5.6, C(1)*H*), 3.33–3.39 (1H, m, C(2)*H*), 3.55 (3H, s, O*Me*), 3.57–3.65 (3H, m, NCH_2Ph, N'C$H_A$$H_B$Ph), 3.76 (1H, d, *J* 14.8, N'CH$_A$$H_B$Ph), 3.82 (1H, q, *J* 6.9, C(α')*H*), 3.93–3.98 (1H, m, C(5)*H*), 4.17 (1H, q, *J* 6.9, C(α)*H*), 7.05–7.22 (20H, m, *Ph*); δ_C (125 MHz, C_6D_6) 13.2 (C(α)*Me*), 15.8 (C(α')*Me*), 28.6 (*C*(3)), 28.6 (*C*(4)), 50.5 (N'*C*H$_2$Ph), 50.9 (O*Me*), 51.9 (*C*(1)), 53.0 (N*C*H$_2$Ph), 56.6 (*C*(α)), 57.4 (*C*(α')), 61.8 (*C*(5)), 63.7 (*C*(2)), 126.5, 126.6, 126.7, 126.8, 127.6, 127.8, 128.0, 128.0, 128.1, 128.1, 128.2, 128.3 (*o*,*m*,*p*-*Ph*), 141.5, 141.7, 143.4, 143.8 (*i*-Ph), 174.7 (*C*O$_2$Me); *m*/*z* (ESI$^+$) 547 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{37}H_{43}N_2O_2^+$ ([M+H]$^+$) requires 547.3319; found 547.3317.

Methyl (*S*,*S*,*S*,*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-phenylcyclopentane-1-carboxylate 264

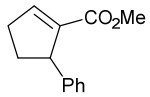


Method A: PhMgBr (1.0 M in THF, 1.49 mL, 1.49 mmol) was added dropwise to a stirred solution of (*S*,*S*)-**107** (50 mg, 0.15 mmol, >99:1 dr) in THF (0.9 mL) at −20 °C, and the

resultant mixture was stirred at −20 °C for 4 h. Satd aq NH_4Cl (1 mL) was then added and the reaction mixture was allowed to warm to rt. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic extracts were washed with brine (20 mL), then dried and concentrated *in vacuo* to give **264** in >95:5 dr. Purification *via* flash column chromatography (gradient elution, 5% Et_2O in 30–40 °C petrol) gave **264** as a white solid (57 mg, 92%, >99:1 dr); $[\alpha]_D^{20}$ −23.6 (*c* 0.5 in $CHCl_3$).

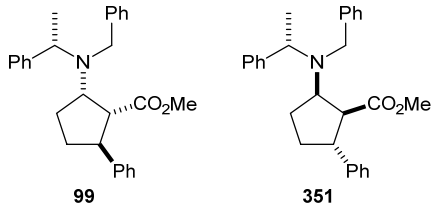
Method B: PhLi (1.8 M in Bu_2O, 0.66 mL, 0.60 mmol) was added dropwise to a stirred solution of (*S*,*S*)-**107** (100 mg, 0.30 mmol, >99:1 dr) in THF (1.8 mL) at 0 °C, and the resultant solution was stirred at 0 °C for 2 h. Satd aq NH_4Cl (1 mL) was then added and the reaction mixture was allowed to warm to rt. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic extracts were washed with brine (20 mL), then dried and concentrated *in vacuo* to give **264** in >95:5 dr. Purification *via* flash column chromatography (gradient elution, 5% Et_2O in 30–40 °C petrol) gave **264** as a colourless oil (77 mg, 62%, >99:1 dr); $[\alpha]_D^{20}$ −43.0 (*c* 0.5 in $CHCl_3$).

Methyl (*RS*)-5-phenyl-1-cyclopentene-1-carboxylate 93



CuI (34 mg, 0.18 mmol) was added to a stirred solution of **334** (660 mg, 3.57 mmol) in THF at −50 °C. After 5 min, PhMgBr (1.0 M in THF, 7.1 mL, 7.14 mmol) was then added dropwise and the resultant solution was stirred at −50 °C for 3 h. Satd aq NH_4Cl (2 mL) was then added and the reaction mixture was allowed to warm to rt. The aqueous layer was extracted with Et_2O (3 × 20 mL) and the combined organic extracts were washed with brine (50 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **93** as a yellow oil (493 mg, 68%);[18] δ_H (400 MHz, $CDCl_3$) 1.81–1.90 (1H, m, C(4)H_A), 2.39–2.51 (2H, m, C(3)H_A, C(4)H_B), 2.54–2.68 (1H, m, C(3)H_B), 3.53 (3H, s, O*Me*), 4.05–4.08 (1H, m, C(5)*H*), 6.91–6.93 (1H, m, C(2)*H*), 7.08–7.13 (3H, m, *Ph*), 7.19–7.22 (2H, m, *Ph*).

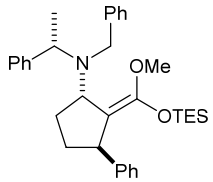
Methyl (1*RS*,2*SR*,5*SR*,α*SR*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-phenylcyclopentane-1-carboxylate 99 and methyl (1*SR*,2*RS*,5*RS*,α*SR*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-phenylcyclopentane-1-carboxylate 351



99 **351**

BuLi (2.0 M in hexanes, 0.99 mL, 1.98 mmol) was added dropwise to a stirred solution of (*RS*)-**162** (420 mg, 1.98 mmol) in THF (10 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of **93** (200 mg, 0.99 mmol) in THF (2 mL) at −78 °C was added dropwise *via* cannula, and the reaction mixture was stirred at −78 °C for 2 h. Satd aq NH_4Cl (1 mL) was then added and the reaction mixture was allowed to warm to rt. The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic extracts were then dried and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (50 mL) and 10% aq citric acid (50 mL) and the organic layer was washed sequentially with satd aq $NaHCO_3$ (50 mL) and brine (50 mL), then dried and concentrated *in vacuo* to give a 91:9 mixture of **99** and **351**, respectively, as a colourless oil (165 mg, 99%);[18] Data for major diastereoisomer **99**: δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, *J* 6.8, C(α)*Me*), 1.41–1.49 (2H, m, C(4)H_A), 1.75–1.81 (1H, m, C(3)H_A), 1.98–2.14 (2H, m, C(3)H_B, C(4)H_B), 2.88 (1H, dd, *J* 9.4, 8.8, C(1)*H*), 3.44–3.59 (2H, m, C(2)*H*, C(5)*H*), 3.61 (3H, s, O*Me*), 3.84 (2H, app s, NCH_2Ph), 3.95 (1H, q, *J* 6.8, C(α)*H*), 6.99–7.37 (15H, m, *Ph*).

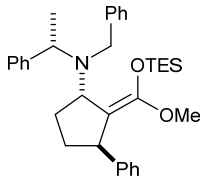
(1*S*,3*R*,α*S*,*E*)-[*N*-Benzyl-*N*-(α-methylbenzyl)-amino]-2-[methoxy(triethylsiloxy)methylene]-3-phenylcyclopentane 353



PhLi (1.8 M in Bu_2O, 80 μL, 0.15 mmol) was added dropwise to a stirred solution of **107** (50 mg, 0.15 mmol) in THF (0.9 mL) at 0 °C, and the resultant solution was stirred at 0 °C for 2 h. TESCl (40 μL, 0.24 mmol) was then added dropwise and the reaction mixture was allowed to warm to rt over 30 min before being concentrated *in vacuo* to give **353** [(*E*):(*Z*) ratio >99:1 dr] as a yellow oil. Data for **353**: δ_H (400 MHz, C_6D_6) [selected peaks][28] 0.61–0.72 (6H, m, Si(CH_2CH$_3$)$_3$), 0.94–0.98 (9H, m, Si(CH$_2$CH_3)$_3$), 1.21 (3H, d, *J* 6.9, C(α)*Me*),

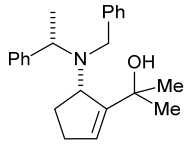
1.76–1.80 (1H, m, C(5)H_A), 1.99–2.04 (1H, m, C(5)H_B), 3.47 (3H, s, O*Me*), 3.53–3.56 (1H, m, C(3)*H*), 3.55–3.58 (1H, m, C(1)*H*), 3.80 (1H, d, *J* 14.4, NC$H_A$$H_B$Ph), 3.93 (1H, d, *J* 14.4, NCH$_A$$H_B$Ph), 4.17 (1H, q, *J* 6.8, C(α)*H*), 7.13–7.35 (15H, m, *Ph*); δ_C (125 MHz, C_6D_6) [selected peaks][29] 14.4 (C(α)*Me*), 29.7 (*C*(5)), 32.6 (*C*(4)), 52.4 (O*Me*), 52.8 (N*C*H$_2$Ph), 54.3 (*C*(3)), 57.1 (*C*(α)), 73.8 (*C*(1)), 156.5 (C(2)*C*OMe).

(*1RS*,*3SR*,*αRS*,*Z*)-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-2-[methoxy(triethylsiloxy)methylene]-3-phenylcyclopentane 355



BuLi (2.0 M in hexanes, 0.25 mL, 0.49 mmol) was added dropwise to a stirred solution of (*RS*)-**162** (105 mg, 0.49 mmol) in THF (2.5 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of **93** (50 mg, 0.25 mmol) in THF (0.5 mL) at −78 °C was added dropwise *via* cannula, and the reaction mixture was stirred at −78 °C for 2 h. TESCl (125 μL, 0.74 mmol) was then added dropwise and the reaction mixture was allowed to warm to rt over 30 min before being concentrated *in vacuo* to give a 78:22 mixture of **355** [(*Z*):(*E*) ratio >99:1 dr] and **99**, respectively, as a yellow oil. Data for **355**: δ_H (400 MHz, C_6D_6) 0.52–0.60 (6H, m, Si(CH_2CH$_3$)$_3$), 0.99 (9H, t, *J* 7.3, Si(CH$_2$CH_3)$_3$), 1.42 (3H, d, *J* 6.6, C(α)*Me*), 1.50–1.57 (1H, m, C(4)H_A), 1.70–1.79 (1H, m, C(5)H_A), 1.85–1.91 (1H, m, C(5)H_B), 2.48–2.58 (1H, m, C(4)H_B), 2.73 (3H, s, O*Me*), 3.38 (1H, dd, *J* 8.9, 2.3, C(3)*H*), 3.75 (1H, d, *J* 15.5, NC$H_A$$H_B$Ph), 3.84 (1H, d, *J* 15.5, NCH$_A$$H_B$Ph), 4.23 (1H, q, *J* 6.6, C(α)*H*), 4.33 (1H, app d, *J* 5.9, C(1)*H*), 7.08–7.27 (15H, m, *Ph*); δ_C (100 MHz, C_6D_6) 13.6 (C(α)*Me*), 30.2 (*C*(5)), 35.7 (*C*(4)), 46.3 (*C*(3)), 49.9 (N*C*H$_2$Ph), 56.4 (O*Me*), 58.4 (*C*(α)), 63.4 (*C*(1)), 102.8 (*C*(2)), 126.8, 127.2, 127.2, 127.6, 127.8, 127.8, 128.1, 128.1, 128.4 (*o*,*m*,*p*-*Ph*), 144.3, 145.5, 147.6 (*i*-*Ph*), 153.1 (C(2)*C*OMe).

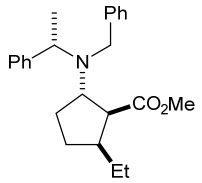
(*S*,*S*)-1-(2'-Propan-2'-ol)-5-[*N*-benzyl-*N*-(α-methylbenzyl)amino]cyclopent-1-ene 356



MeI (0.93 mL, 14.9 mmol) was added dropwise to a suspension of magnesium turnings (73 mg, 3.0 mmol) in Et_2O (1.5 mL) with gentle heating to initiate formation of the Grignard reagent. Once an exothermic reaction had commenced the remaining MeI (148 μL, 2.4 mmol)

was added to this solution. **107** (100 mg, 0.30 mmol, >99:1 dr) in Et_2O (0.7 mL) was added dropwise over 15 min at −20 °C, and the resultant solution was stirred at −20 °C for 4 h. Satd aq NH_4Cl (1 mL) was then added and the reaction mixture was allowed to warm to rt. The aqueous layer was extracted with Et_2O (3 × 15 mL) and the combined organic extracts were washed with brine (40 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **356** as a pale yellow oil (12 mg, 12%, >99:1 dr); $[\alpha]_D^{28}$ +25.0 (*c* 0.2 in $CHCl_3$); ν_{max} (ATR) 3263 (O–H), 2973, 2929 (C–H), 1162, 701; δ_H (400 MHz, $CDCl_3$) 0.50 (3H, s, C(1')H_3), 1.27 (3H, s, C(3')H_3), 1.31 (3H, t, *J* 6.9, C(α)*Me*), 1.79–1.89 (1H, m, C(4)H_A), 2.08–2.16 (1H, m, C(4)H_B), 2.18–2.23 (1H, m, C(3)H_A), 2.27–2.35 (1H, m, C(3)H_B), 3.49 (1H, d, *J* 12.6, NCH_AH$_B$Ph), 3.75 (1H, d, *J* 12.6, NCH$_A$$H_B$Ph), 3.87 (1H, q, *J* 6.9, C(α)*H*), 4.17 (1H, d, *J* 9.2, C(5)*H*), 5.60 (1H, s, C(2)*H*), 6.53 (1H, brs, O*H*), 7.10–7.43 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 10.3 (C(α)*Me*), 23.6 (*C*(4)), 27.9 (*C*(3')), 28.7 (*C*(1')), 30.1 (*C*(3)), 47.6 (N*C*H$_2$Ph), 54.0 (*C*(α)), 60.4 (*C*(5)), 69.1 (*C*(2')), 125.3 (*C*(2)), 126.1, 126.3, 127.1, 127.6, 127.6, 128.8 (*o*,*m*,*p*-*Ph*), 137.7 (*C*(1)), 141.5, 146.6 (*i*-Ph); *m*/*z* (ESI$^+$) 336 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{30}NO^+$ ([M+H]$^+$) requires 336.2322; found 336.2321.

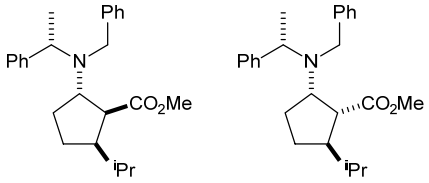
Methyl (*S*,*S*,*S*,*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-ethylcyclopentane-1-carboxylate 357



EtMgBr (0.9 M in THF, 9.90 mL, 8.95 mmol) was added dropwise to a stirred solution of **107** (300 mg, 0.89 mmol, >99:1 dr) in THF (5.4 mL) at −20 °C, and the resultant solution was stirred at −20 °C for 4 h. Satd aq NH_4Cl (2 mL) was then added and the reaction mixture was allowed to warm to rt. The aqueous layer was extracted with Et_2O (3 × 20 mL) and the combined organic extracts were washed with brine (50 mL), then dried and concentrated *in vacuo* to give **357** in >95:5 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 99:1) gave **357** as a colourless oil (269 mg, 82%, >99:1 dr); $[\alpha]_D^{20}$ +39.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2961 (C–H), 1728 (C=O), 1157, 698; δ_H (400 MHz, $CDCl_3$) 0.74 (3H, t, *J* 7.4, C(2')H_3), 0.95–1.07 (1H, m, C(1')H_A), 1.20 (3H, d, *J* 6.8, C(α)*Me*), 1.14–1.29 (2H, m, C(1')H_B, C(4)H_A), 1.54 (1H, app tdd, *J* 12.1, 9.7, 6.9, C(3)H_A), 1.67 (1H, app dt, *J* 12.1, 6.2, C(4)H_B), 1.75–1.87 (2H, m, C(3)H_B, C(5)*H*), 2.72 (1H, dd, *J* 9.7, 6.0,

C(1)*H*), 3.37 (3H, s, O*Me*), 3.59–3.65 (1H, m, C(2)*H*), 3.67 (2H, app s, NCH_2Ph), 3.73 (1H, q, *J* 6.8, C(α)*H*), 7.08–7.26 (8H, m, *Ph*), 7.34–7.36 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.8 (*C*(2')), 17.2 (C(α)*Me*), 24.1 (*C*(1')), 29.9 (*C*(3)), 30.5 (*C*(4)), 45.1 (*C*(5)), 50.4 (N*C*H_2Ph), 50.6 (*C*(1)), 50.9 (O*Me*), 58.4 (*C*(α)), 63.4 (*C*(2)), 126.5, 126.6, 127.6, 127.9, 128.0, 128.1 (*o*,*m*,*p*-*Ph*), 141.9, 144.4 (*i*-*Ph*), 175.5 (*C*O_2Me); δ_H (500 MHz, C_6D_6) 0.82 (3H, t, *J* 7.4, C(2')H_3), 1.16 (3H, d, *J* 6.8, C(α)*Me*), 1.11–1.20 (1H, m, C(1')H_A), 1.26–1.34 (1H, m, C(4)H_A), 1.36–1.47 (2H, m, C(3)H_A, C(1')H_B), 1.50–1.55 (1H, m, C(4)H_B), 1.59–1.67 (1H, m, C(5)*H*), 1.74–1.79 (1H, m, C(3)H_B), 2.85 (1H, dd, *J* 9.5, 5.6, C(1)*H*), 3.30 (3H, s, O*Me*), 3.54 (2H, d, *J* 15.1, NC$H_A$$H_B$Ph), 3.61 (2H, d, *J* 15.1, NC$H_A$$H_B$Ph), 3.82 (1H, q, *J* 6.8, C(α)*H*), 3.92 (1H, ddd, *J* 9.5, 7.8, 5.6, C(2)*H*), 7.06–7.14 (2H, m, *Ph*), 7.17–7.20 (2H, m, *Ph*), 7.23–7.26 (2H, m, *Ph*), 7.35–7.37 (2H, m, *Ph*), 7.46–7.48 (2H, m, *Ph*); δ_C (125 MHz, C_6D_6) 12.8 (*C*(2')), 17.9 (C(α)*Me*), 24.2 (*C*(1')), 30.1 (*C*(3)), 30.4 (*C*(4)), 45.3 (*C*(5)), 50.1 (*C*(1)), 50.4 (O*Me*), 50.5 (N*C*H_2Ph), 59.2 (*C*(α)), 63.8 (*C*(2)), 126.6, 126.6, 127.6, 128.0, 128.0, 128.2 (*o*,*m*,*p*-*Ph*), 142.3, 144.6 (*i*-*Ph*), 174.9 (*C*O_2Me); *m*/*z* (ESI^+) 366 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{24}H_{32}N_2O^+$ ($[M+H]^+$) requires 366.2428; found 366.2421.

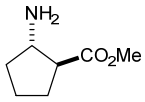
Methyl (1*S*,2*S*,5*R*,α*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-isopropylcyclopentane-1-carboxylate 358 and methyl (1*R*,2*S*,5*R*,α*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-isopropylcyclopentane-1-carboxylate 98



^{i}PrMgBr (1.0 M in THF, 8.94 mL, 8.94 mmol) was added dropwise to a stirred solution of **107** (300 mg, 0.89 mmol, >99:1 dr) in THF (5.4 mL) at −20 °C, and the resultant solution was stirred at −20 °C for 4 h. Satd aq NH_4Cl (3 mL) was then added and the reaction mixture was allowed to warm to rt. The aqueous layer was extracted with Et_2O (3 × 30 mL) and the combined organic extracts were washed with brine (80 mL), then dried and concentrated *in vacuo* to give an 85:15 mixture of **358** and **98**, respectively. Purification *via* flash column chromatography (gradient elution, 4% Et_2O in 30–40 °C petrol) gave **358** as a colourless oil (212 mg, 62%, >99:1 dr); $[\alpha]_D^{20}$ +2.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2957 (C–H), 1728 (C=O), 1157, 700; δ_H (400 MHz, $CDCl_3$) 0.75 (3H, d, *J* 6.4, C(1')*Me*$_A$), 0.78 (3H, d, *J* 6.4, C(1')*Me*$_B$), 1.17 (3H, d, *J* 6.7, C(α)*Me*), 1.25–1.38 (2H, m, C(4)H_A, C(1')*H*), 1.46–1.59 (2H, m, C(3)H_A,

C(5)*H*), 1.63–1.69 (1H, m, C(4)H_B), 1.78–1.84 (1H, m, C(3)H_B), 2.80 (1H, dd, *J* 9.2, 4.5, C(1)*H*), 3.41 (3H, s, O*Me*), 3.52 (1H, ddd, *J* 9.2, 7.9, 4.5, C(2)*H*), 3.68 (1H, d, *J* 15.2, NC$H_A$$H_B$Ph), 3.73–3.77 (2H, m, NC$H_A$$H_B$Ph, C(α)*H*), 7.09–7.28 (8H, m, *Ph*), 7.39–7.41 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.0 (C(α)*Me*), 21.8 (C(1')*Me*$_A$), 22.3 (C(1')*Me*$_B$), 29.6 (*C*(1')), 29.6 (*C*(4)), 30.7 (*C*(3)), 49.7 (*C*(1)), 50.7 (N*C*H_2Ph), 51.1 (O*Me*), 52.7 (*C*(5)), 58.9 (*C*(α)), 64.7 (*C*(2)), 126.5, 126.6, 127.4, 127.9, 128.0, 128.2 (*o*,*m*,*p*-*Ph*), 142.1, 144.7 (*i*-*Ph*), 176.4 (*C*O_2Me); *m*/*z* (ESI$^+$) 380 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{34}NO_2^+$ ([M+H]$^+$) requires 380.2584; found 380.2587. Further elution (eluent 30–40 °C petrol/Et_2O, 96:4) gave a 73:27 mixture of **98** and **358**, respectively, as a colourless oil (23 mg, 7%). Data for minor diastereoisomer **98**: δ_H (500 MHz, $CDCl_3$) 0.70 (3H, d, *J* 6.6, C(1')*Me*$_A$), 0.71 (3H, d, *J* 6.6, C(1')*Me*$_B$), 0.93–1.02 (1H, m, C(4)H_A), 1.25 (3H, d, *J* 6.9, C(α)*Me*), 1.29–1.34 (1H, m, C(1')*H*), 1.52–1.58 (1H, m, C(3)H_A), 1.71–1.77 (1H, m, C(4)H_B), 1.78–1.85 (1H, m, C(3)H_B), 2.01 (1H, app dq, *J* 10.1, 7.4, C(5)*H*), 2.52 (1H, dd, *J* 9.4, 6.3, C(1)*H*), 3.14 (1H, ddd, *J* 11.2, 9.4, 6.3, C(2)*H*), 3.62 (3H, s, O*Me*), 3.66 (1H, d, *J* 14.8, NC$H_A$$H_B$Ph), 3.78 (1H, d, *J* 14.8, NC$H_A$$H_B$Ph), 3.98 (1H, q, *J* 6.9, C(α)*H*), 7.10–7.41 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 14.9 (C(α)*Me*), 20.1 (C(1')*Me*$_A$), 20.9 (C(1')*Me*$_B$), 28.3 (*C*(4)), 29.9 (*C*(3)), 33.1 (*C*(1')), 49.4 (*C*(5)), 51.5 (O*Me*), 51.7 (N*C*H_2Ph), 52.1 (*C*(1)), 56.9 (*C*(α)), 63.7 (*C*(2)), 126.4, 126.6, 127.8, 128.0, 128.0, 128.1 (*o*,*m*,*p*-*Ph*), 141.9, 143.0 (*i*-*Ph*), 176.2 (*C*(1)). Data for mixture: ν_{max} (ATR) 2955 (C–H), 1728 (C=O), 1157, 700; *m*/*z* (ESI$^+$) 380 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{34}NO_2^+$ ([M+H]$^+$) requires 380.2584; found 380.2586.

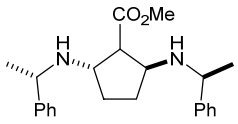
Methyl (*S*,*S*)-2-aminocyclopentane-1-carboxylate 363



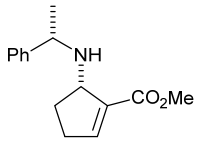
$Pd(OH)_2$/C (183 mg, 50% w/w by substrate) was added to a degassed solution of **348** (366 mg, 0.73 mmol, >99:1 dr, >95% purity) in MeOH (26 mL) at rt. The resultant suspension was stirred vigorously under H_2 (5 atm) at rt for 24 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$/MeOH, 95:5) gave **363** as a yellow oil (80 mg, 83%, >99:1 dr); $[\alpha]_D^{28}$ +76.4 (*c* 0.2 in $CHCl_3$); ν_{max} (ATR) 3262 (N–H), 2959, 2922 (C–H), 1732 (C=O), 1553; δ_H (400 MHz, $CDCl_3$) 1.40–1.50 (1H, m, C(3)H_A), 1.58–1.83 (3H, m, C(4)H_2, C(5)H_A), 1.95–2.04 (2H, m, C(3)H_B, C(5)H_B), 2.52 (1H, app q, *J* 8.3, C(1)*H*), 3.46 (1H, app q, *J* 7.8, C(2)*H*), 3.64 (3H, s, O*Me*), 3.72 (2H, br s, NH_2); δ_C (100 MHz, $CDCl_3$) 22.7 (*C*(4)),

28.2 (*C*(5)), 34.3 (*C*(3)), 51.8 (O*Me*), 52.3 (*C*(1)), 56.6 (*C*(2)), 175.3 (*C*O_2Me); *m*/*z* (ESI$^+$) 144 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_7H_{14}NO_2^+$ ([M+H]$^+$) requires 144.1019; found 144.1019.

Methyl (*S*,*S*,*S*,*S*)-2-[*N*-(α-methylbenzyl)amino]-5-[*N*'-(α'-methylbenzyl)amino]cyclopentane-1-carboxylate 364 and methyl (*S*,*S*)-5-[*N*-(α-methylbenzyl)amino]cyclopent-1-ene-1-carboxylate 367



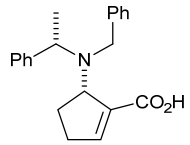
364



367

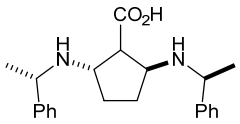
CAN (2.64 g, 4.81 mmol) was added to a stirred solution of **348** (526 mg, 0.96 mmol, >99:1 dr, >95% purity) in MeCN/H_2O (14.5 mL, v/v 5:1) at rt and the resultant mixture was stirred at rt for 16 h. Satd aq $NaHCO_3$ (30 mL) and Et_2O (40 mL) were then added and the aqueous layer was extracted with Et_2O (2 × 40 mL). The combined organic extracts were washed with brine (50 mL), then dried and concentrated *in vacuo* to give a 92:8 mixture of **364** and **367**, respectively. Purification *via* flash column chromatography (eluent $CHCl_3$/MeOH, 99:1) gave a 90:10 mixture of **364** and **367**, respectively, as an orange oil (188 mg). Data for **364**: δ_H (400 MHz, $CDCl_3$) 0.96–1.07 (1H, m, C(3)H_A), 1.15 (3H, d, *J* 6.6, C(α')*Me*), 1.21 (3H, d, *J* 6.6, C(α)*Me*), 1.36–1.42 (1H, m, C(4)H_A), 1.64–1.70 (1H, m, C(4)H_B), 1.77–1.84 (1H, m, C(3)H_B), 2.77 (1H, dd, *J* 8.5, 5.0, C(1)*H*), 3.10–3.14 (1H, m, C(5)*H*), 3.14–3.20 (1H, m, C(2)*H*), 3.62 (3H, s, O*Me*), 3.63–3.66 (1H, m, C(α')*H*), 3.74 (1H, q, *J* 6.6, C(α)*H*), 7.12–7.25 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 24.7 (C(α)*Me*), 24.9 (C(α')*Me*), 31.9 (*C*(3)), 32.3 (*C*(4)), 51.4 (O*Me*), 54.0 (*C*(1)), 56.4 (*C*(α)), 56.5 (*C*(α')), 58.9 (*C*(5)), 60.3 (*C*(2)), 126.6, 126.6, 126.9, 126.9, 128.3, 128.4 (*o*,*m*,*p*-*Ph*), 145.2, 145.8 (*i*-*Ph*), 174.9 (*C*O_2Me). Data for **367**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.18 (3H, d, *J* 6.6, C(α)*Me*), 3.83 (1H, q, *J* 6.6, C(α)*H*), 4.00–4.03 (1H, m, C(5)*H*), 6.74–6.76 (1H, m, C(2)*H*); δ_C (100 MHz, $CDCl_3$) [selected peaks] 25.1 (C(α)*Me*), 51.5 (O*Me*), 145.9 (*C*(2)), 174.7 (*C*O_2Me). Data for mixture: $[\alpha]_D^{20}$ −135.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3330 (N–H), 2959 (C–H), 1722 (C=O), 1451, 701; *m*/*z* (ESI$^+$) 367 ([M(**364**)+H]$^+$, 100%), 246 ([M(**367**)+H]$^+$, 17%); HRMS (ESI$^+$) $C_{23}H_{31}N_2O_2^+$ ([M(**364**)+H]$^+$) requires 367.2380; found 367.2373.

(*S*,*S*)-5-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]cyclopent-1-ene-1-carboxylic acid 366



A stirred solution of **348** (100 mg, 0.18 mmol, >99:1 dr, >95% purity) in 6.0 M aq HCl (14 mL) was heated at reflux for 16 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (25 mL) and the resultant solution was washed sequentially with 10% aq citric acid (25 mL), satd aq $NaHCO_3$ (25 mL) and brine (25 mL), then dried and concentrated *in vacuo* to give **366** as an orange oil (59 mg, quant, >99:1 dr); $[\alpha]_D^{20}$+16.3 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 2965, 2928 (C–H), 1717 (C=O), 1452, 700; δ_H (400 MHz, $CDCl_3$) 1.35 (3H, d, *J* 7.1, C(α)*Me*), 2.03–2.19 (2H, m, C(3)H_2), 2.31–2.41 (1H, m, C(4)H_A), 2.42–2.52 (1H, m, C(4)H_B), 3.57 (1H, d, *J* 12.9, NCH_AH$_B$Ph), 3.66 (1H, d, *J* 12.9, NCH$_A$$H_B$Ph), 4.01 (1H, q, *J* 7.1, C(α)*H*), 4.16–4.22 (1H, m, C(5)*H*), 6.83–6.85 (1H, m, C(2)*H*), 7.05–7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.6 (C(α)*Me*), 24.4 (*C*(3)), 31.1 (*C*(4)), 49.2 (N*C*H$_2$Ph), 55.2 (*C*(α)), 61.7 (*C*(5)), 127.9, 128.1, 128.5, 128.9, 129.7 (*o*,*m*,*p*-*Ph*), 134.1, 135.9 (*i*-*Ph*), 139.7 (*C*(1)), 144.6 (*C*(2)), 165.5 (*C*O$_2$H); *m*/*z* (ESI^+) 322 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{21}H_{24}NO_2^+$ ($[M+H]^+$) requires 322.1802; found 322.1803.

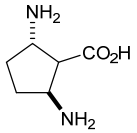
(*S*,*S*,*S*,*S*)-2-[*N*-(α-Methylbenzyl)amino]-5-[*N*'-(α'-methylbenzyl)amino]cyclopentane-1-carboxylic acid 368



A stirred solution of a 90:10 mixture of **364** and **367**, respectively, (100 mg) in 6.0 M aq HCl (14 mL) was heated at reflux for 16 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (25 mL) and the resultant solution was washed sequentially with satd aq $NaHCO_3$ (25 mL) and brine (25 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$/MeOH, 90:10) gave **368** as a colourless oil (36 mg, 37%, >99:1 dr); $[\alpha]_D^{20}$−29.6 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 3333 (O–H, N–H), 2963 (C–H), 1578 (C=O), 1383, 700; δ_H (400 MHz, $CDCl_3$) 0.88–0.98 (1H, m, C(4)H_A), 1.27 (3H, d, *J* 6.6, C(α)*Me*), 1.40–1.55 (3H, m, C(3)H_2, C(4)H_B), 1.54 (3H, d, *J* 6.6, C(α')*Me*), 2.58 (1H, app t, *J* 6.9, C(1)*H*), 3.19 (1H, app q, *J* 7.3, C(5)*H*), 3.29–3.34 (1H, m, C(2)*H*), 3.86 (1H, q, *J* 6.6, C(α)*H*), 3.92 (1H, q, *J* 6.6,

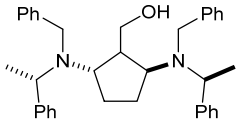
C(α')*H*), 7.06–7.48 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.6 (C(α)*Me*), 23.8 (C(α')*Me*), 28.8 (*C*(3)), 30.3 (*C*(4)), 51.0 (*C*(1)), 56.0 (C(5)), 57.1 (*C*(α)), 57.5 (*C*(α')), 61.2 (*C*(2)), 126.9, 127.0, 127.4, 128.3, 128.5, 129.0 (*o*,*m*,*p*-*Ph*), 139.3, 144.8 (*i*-*Ph*), 177.3 (CO_2H); *m*/*z* (ESI^+) 353 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{22}H_{29}N_2O_2^+$ ($[M+H]^+$) requires 353.2224; found 353.2223.

(*S*,*S*)-2,5-Diaminocyclopentane-1-carboxylic acid 360



A solution of $NaBrO_3$ (116 mg, 0.77 mmol) in H_2O (1 mL) was added dropwise to a solution of **348** (42 mg, 76.8 μmol, >99:1 dr, >95% purity) in EtOAc (1.1 mL) at rt and the resultant mixture was stirred at rt for 10 min. A solution of $Na_2S_2O_4$ (111 mg, 0.64 mmol) in H_2O (2 mL) was then added dropwise at rt over 15 min with stirring continued at rt for 18 h. Satd aq $Na_2S_2O_3$ (3 mL) and EtOAc (3 mL) were then added and the aqueous layer was extracted with EtOAc (2 × 5 mL) and then acidified with 2.0 M aq HCl until the pH value reached 1. After stirring the acidified aqueous layer for 30 mins, the solution was then concentrated *in vacuo* to half its original volume at which point the resultant suspension was filtered. The filtrate was subsequently concentrated *in vacuo* and the residue was dissolved in H_2O (10 mL) and purified on DOWEX 50WX8 ion exchange resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) to give **360** as a white solid (9 mg, 81%, >99:1 dr); mp 197–199 °C; $[\alpha]_D^{20}$+70.4 (*c* 0.5 in H_2O); ν_{max} (ATR) 3350 (O–H, N–H), 2954 (C–H), 1440 (C=O), 1129; δ_H (400 MHz, D_2O) 1.67–1.76 (1H, m, C(3)H_A), 1.76–1.85 (1H, m, C(4)H_A), 2.26–2.38 (2H, m, C(3)H_B, C(4)H_B), 3.01 (1H, dd, *J* 9.1, 7.8, C(1)*H*), 3.82–3.88 (1H, m, C(2)*H*), 3.93 (1H, app td, *J* 7.8, 5.5, C(5)*H*); δ_C (100 MHz, D_2O) 27.2 (*C*(3)), 27.7 (*C*(4)), 50.5 (*C*(5)), 51.0 (*C*(1)), 53.0 (*C*(2)), 175.4 (CO_2H); *m*/*z* (ESI^+) 145 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_6H_{13}N_2O_2^+$ ($[M+H]^+$) requires 145.0972; found 145.0972.

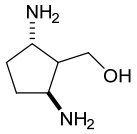
(*S*,*S*,*S*,*S*)-2-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-5-[*N*'-benzyl-*N*'-(α'-methylbenzyl)amino]-1-(hydroxymethyl)cyclopentane 361



DIBAL-H (0.66 mL, 1.0 M in PhMe, 0.66 mmol) was added dropwise to a solution of **348** (142 mg, 0.26 mmol, >99:1 dr, >95% purity) in PhMe (1 mL) at −78 °C and the resultant

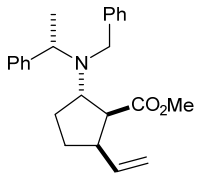
mixture was stirred at −78 °C for 2 h. MeOH (1 mL) was added carefully at −78 °C and the reaction mixture was allowed to warm to rt, then the resultant solution was washed with satd aq Rochelle's salt (4 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL) and the combined organic extracts were then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent, 30–40 °C petrol/Et_2O, 92:8) gave **361** as a colourless oil (119 mg, 88%, >99:1 dr); $[\alpha]_D^{20}$ −9.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3331 (O–H), 2963, 2930 (C–H), 1026, 698; δ_H (400 MHz, $CDCl_3$) 1.18 (3H, d, *J* 6.9, C(α)*Me*), 1.30 (3H, d, *J* 6.9, C(α')*Me*), 1.41–1.50 (2H, m, C(3)H_A, C(4)H_A), 1.55–1.64 (2H, m, C(3)H_B, C(4)H_B), 1.94–2.02 (1H, m, C(1)*H*), 2.76 (1H, app q, *J* 7.6, C(2)*H*), 3.13–3.19 (1H, m, C(5)*H*), 3.27–3.31 (3H, m, N'CH_AH$_B$Ph, CH_2OH), 3.52 (1H, d, *J* 14.2, NCH_AH$_B$Ph), 3.62 (1H, d, *J* 14.2, NCH$_A$$H_B$Ph), 3.74 (1H, q, *J* 6.9, C(α)*H*), 3.78 (1H, d, *J* 14.2, N'CH$_A$$H_B$Ph), 3.90 (1H, q, *J* 6.9, C(α')*H*), 7.07–7.33 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (C(α')*Me*), 14.6 (C(α)*Me*), 27.3 (*C*(3)), 28.2 (*C*(4)), 46.0 (*C*(1)), 50.4 (NCH_2Ph), 52.9 (N'CH_2Ph), 56.8 (*C*(α)), 57.3 (*C*(α')), 60.1 (*C*(5)), 60.5 (*C*(2)), 63.9 (CH_2OH), 126.7, 126.8, 126.9, 127.2, 127.7, 127.9, 128.1, 128.2, 128.2, 128.5, 128.5, 128.5 (*o*,*m*,*p*-*Ph*), 140.6, 141.2, 141.5, 144.3 (*i*-*Ph*); *m*/*z* (ESI^+) 519 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{36}H_{43}N_2O^+$ ($[M+H]^+$) requires 519.3370; found 519.3369.

(*S*,*S*)-2,5-(Diaminocyclopentyl)methanol 362



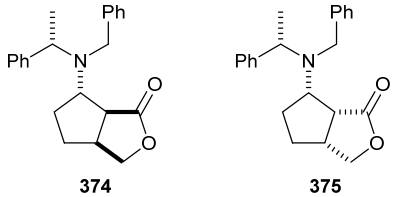
$Pd(OH)_2$/C (30 mg, 50% w/w by substrate) was added to a degassed solution of **361** (60 mg, 0.12 mmol, >99:1 dr) in MeOH (10 mL) at rt. The resultant suspension was stirred vigorously under H_2 (1 atm) at rt for 24 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo* to give **362** as a white solid (15 mg, quant, >99:1 dr); $[\alpha]_D^{28}$ +64.0 (*c* 0.3 in MeOH); ν_{max} (ATR) 3347 (O–H, N–H), 2919 (C–H), 1513, 1025; δ_H (400 MHz, MeOH-d_4) 1.63–1.83 (2H, m, C(3)H_A, C(4)H_A), 2.27–2.36 (3H, m, C(1)*H*, C(3)H_B, C(4)H_B), 3.35 (1H, s, O*H*), 3.64 (1H, app q, *J* 7.7, C(2)*H*), 3.82–3.88 (1H, m, C(5)*H*), 3.88 (2H, d, *J* 5.6, CH_2OH); δ_C (100 MHz, MeOH-d_4) 30.1 (*C*(3)), 31.0 (*C*(4)), 48.9 (*C*(1)), 53.9 (*C*(2)), 54.1 (*C*(5)), 59.9 (CH_2OH); *m*/*z* (ESI^+) 131 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_6H_{15}N_2O^+$ ($[M+H]^+$) requires 131.1179; found 131.1179.

Methyl (1*S*,2*S*,5*R*,α*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-vinylcyclopentane-1-carboxylate 369



Vinyl magnesium bromide (1.0 M in THF, 18.6 mL, 18.6 mmol) was added dropwise to a stirred solution of **107** (624 mg, 1.86 mmol, >99:1 dr) in THF (11 mL) at −20 °C, and the resultant solution was stirred at −20 °C for 4 h. Satd aq NH_4Cl (5 mL) was then added and the reaction mixture was allowed to warm to rt. The aqueous layer was extracted with Et_2O (3 × 25 mL) and the combined organic extracts were washed with brine (80 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave **369** as a colourless oil (420 mg, 62%, >99:1 dr); $[\alpha]_D^{20}$ +18.6 (*c* 1.3 in $CHCl_3$); ν_{max} (ATR) 2949 (C–H), 1727 (C=O), 1156, 699; δ_H (400 MHz, $CDCl_3$) 1.23 (3H, d, *J* 6.8, C(α)*Me*), 1.46–1.71 (3H, m, C(4)H_2, C(3)H_A), 1.80–1.87 (1H, m, C(3)H_B), 2.57–2.66 (1H, m, C(5)*H*), 2.79 (1H, dd, *J* 9.8, 6.4, C(1)*H*), 3.36 (3H, s, O*Me*), 3.65–3.71 (3H, m, C(2)*H*, NCH_2Ph), 3.75 (1H, q, *J* 6.8, C(α)*H*), 4.82–4.92 (2H, m, C(2')H_2), 5.51–5.60 (1H, m, C(1')*H*), 7.09–7.27 (8H, m, *Ph*), 7.35–7.37 (2H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 16.9 (C(α)*Me*), 29.6 (*C*(3)), 30.8 (*C*(4)), 46.7 (*C*(5)), 50.4 (*C*(2)), 51.0 (O*Me*), 51.7 (*C*(1)), 58.3 (*C*(α)), 63.1 (N*C*H_2Ph), 115.3 (*C*(2')), 126.5, 126.6, 127.6, 127.9, 128.1, 128.2 (*o*,*m*,*p*-*Ph*), 138.1 (*C*(1')), 141.7, 144.3 (*i*-Ph), 174.7 (*C*O_2Me); *m*/*z* (ESI^+) 364 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{24}H_{30}NO_2^+$ ($[M+H]^+$) requires 364.2271; found 364.2264.

(*S*,*S*,*S*,*S*)-6-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]hexahydro-1*H*-cyclopenta[*c*]furan-1-one 374 and (3a*R*,6*S*,6a*R*,α*S*)-6-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hexahydro-1*H*-cyclopenta[*c*]furan-1-one 375

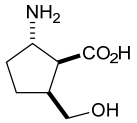


A sample of **369** (103 mg, 0.28 mmol, >99:1 dr) was co-evaporated with 2.0 M HCl in Et_2O (3 × 2 mL). The residue was dissolved in CH_2Cl_2/MeOH (34 mL, v/v 2:1) and the resultant solution was cooled to −78 °C and degassed with N_2 and O_2 before O_3 was bubbled through until a persistent blue colour was observed (~5 min). O_2 was then bubbled through the

reaction mixture until the solution became colourless. $NaBH_4$ (108 mg, 2.8 mmol) was added and the reaction mixture was allowed to warm to rt and stirred at rt for 5 h. Satd aq NH_4Cl (2 mL) was then added and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were washed with satd aq $NaHCO_3$ (25 mL) and brine (25 mL), then dried and concentrated *in vacuo*. The residue was dissolved in EtOAc (25 mL) and the resultant solution filtered through silica (eluent EtOAc) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 90:10) gave an 84:16 mixture of **374** and **375**, respectively, as a pale yellow oil (76 mg, 80%). Data for major diastereoisomer **374**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.18–1.22 (1H, m, C(4)H_A), 1.25 (3H, d, *J* 6.9, C(α)*Me*), 1.63–1.73 (1H, m, C(5)H_A), 1.80–1.88 (1H, m, C(5)H_B), 1.90–1.98 (1H, m, C(4)H_B), 2.59–2.68 (1H, m, C(3a)*H*), 2.78–2.81 (1H, m, C(6a)*H*), 3.61–3.67 (3H, m, C(6)*H*, NCH_2Ph), 3.89 (1H, dd, *J* 9.3, 1.7, C(3)H_A), 4.03 (1H, q, *J* 6.9, C(α)*H*), 4.15 (1H, dd, *J* 9.3, 6.6, C(3)H_B); δ_C (100 MHz, $CDCl_3$) 17.9 (C(α)*Me*), 30.4 (*C*(4)), 32.6 (*C*(5)), 40.3 (*C*(3a)), 47.4 (*C*(6a)), 50.7 (N*C*H_2Ph), 59.6 (*C*(α)), 65.4 (*C*(6)), 71.7 (*C*(3)), 126.5, 126.7, 127.4, 128.0, 128.0, 128.2 (*o,m,p-Ph*), 142.3, 144.3 (*i-Ph*), 179.6 (*C*(1)); δ_H (500 MHz, C_6D_6) [selected peaks] 0.47–0.56 (1H, m, C(4)H_A), 1.19 (3H, d, *J* 6.9, C(α)*Me*), 1.22–1.29 (2H, m, C(4)H_B, C(5)H_A), 1.47–1.52 (1H, m, C(5)H_B), 1.75–1.82 (1H, m, C(3a)*H*), 2.45 (1H, dd, *J* 9.0, 4.0, C(6a)*H*), 3.25 (1H, dd, *J* 9.1, 1.7, C(3)H_A), 3.44 (1H, d, *J* 9.1, 6.6, C(3)H_B), 3.48 (2H, app d, *J* 4.1, NCH_2Ph); 3.72 (1H, td, *J* 7.6, 4.0, C(6)*H*), 4.07 (1H, q, *J* 6.8, C(α)*H*); δ_C (125 MHz, C_6D_6) 19.8 (C(α)*Me*), 30.3 (*C*(4)), 33.3 (*C*(5)), 40.7 (*C*(3a)), 47.2 (*C*(6a)), 51.3 (N*C*H_2Ph), 61.1 (*C*(α)), 65.9 (*C*(6)), 71.2 (*C*(3)), 127.2, 127.5, 128.1, 128.7, 128.9, 129.0 (*o,m,p-Ph*), 143.6, 145.5 (*i-Ph*), 179.2 (*C*(1)). Data for minor diastereoisomer **375**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.10–1.15 (1H, m, C(4)H_A), 1.43 (3H, d, *J* 6.9, C(α)*Me*), 1.46–1.54 (1H, m, C(5)H_A), 1.61–1.65 (1H, m, C(5)H_B), 2.69–2.76 (1H, m, C(3a)*H*), 2.91 (1H, dd, *J* 8.9, 3.8, C(6a)*H*), 3.60–3.61 (1H, m, C(6)*H*), 3.87 (1H, q, *J* 6.9, C(α)*H*), 3.92 (1H, dd, *J* 9.3, 1.7, C(3)H_A), 4.20 (1H, dd, *J* 9.3, 6.3, C(3)H_B); δ_C (100 MHz, $CDCl_3$) [selected peaks] 14.6 (C(α)*Me*), 30.4 (*C*(4)), 32.1 (*C*(5)), 40.7 (*C*(3a)), 47.7 (*C*(6a)), 50.6 (N*C*H_2Ph), 57.5 (*C*(α)), 63.2 (*C*(6)), 71.1 (*C*(3)), 126.6, 126.8, 127.9, 128.3 (*o,m,p-Ph*), 141.2, 143.6 (*i-Ph*); δ_H (500 MHz, C_6D_6) [selected peaks] 1.12–1.15 (1H, m, C(5)H_A), 1.33–1.40 (1H, m, C(5)H_B), 1.50 (3H, d, *J* 6.8, C(α)*Me*), 3.28–3.30 (1H, m, C(3)H_A), 3.50–3.52 (1H, m, C(3)H_B), 3.67–3.70 (1H, m, C(6)*H*), 3.91 (1H, q, *J* 6.8, C(α)*H*); δ_C (125 MHz, C_6D_6) [selected peaks] 14.6 (C(α)*Me*), 30.1(*C*(4)), 33.0 (*C*(5)), 41.1 (*C*(3a)), 47.6 (*C*(6a)), 51.2 (N*C*H_2Ph),

58.3 (*C*(α)), 63.3 (*C*(6)), 70.6 (*C*(3)), 127.4, 127.6, 128.8, 129.0 (*o,m,p-Ph*), 142.2, 144.5 (*i-Ph*), 179.4 (*C*(1)). Data for mixture: $[\alpha]_D^{20}$ +44.5 (*c* 0.8 in $CHCl_3$); ν_{max} (ATR) 2968 (C–H), 1759 (C=O), 1162, 699; δ_H (400 MHz, $CDCl_3$) [selected peaks] 7.10–7.43 (12H, m, *Ph*); δ_H (500 MHz, C_6D_6) [selected peaks] 7.07–7.65 (12H, m, *Ph*); *m*/*z* (ESI^+) 336 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{22}H_{26}NO_2^+$ ($[M+H]^+$) requires 336.1958; found 336.1963.

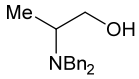
(*S*,*S*,*S*)-2-Amino-5-(hydroxymethyl)cyclopentane-1-carboxylic acid 371



A solution of $NaBrO_3$ (117 mg, 0.78 mmol) in H_2O (1 mL) was added dropwise to a solution of **374** (26 mg, 77.5 μmol, 84:16 dr) in EtOAc (0.7 mL) at rt and the resultant mixture was stirred at rt for 10 min. A solution of $Na_2S_2O_4$ (112 mg, 0.64 mmol) in H_2O (1.9 mL) was then added dropwise at rt over 15 min with stirring continued at rt for 14 h. Satd aq $Na_2S_2O_3$ (3 mL) and EtOAc (3 mL) were then added and the aqueous layer was extracted with EtOAc (2 × 5 mL), then acidified with 2.0 M aq HCl until the pH value reached 1. After stirring the acidified aqueous layer for 30 mins, the solution was then concentrated *in vacuo* to half its original volume at which point the resultant suspension was filtered. The filtrate was subsequently concentrated *in vacuo* and the residue was dissolved in H_2O (10 mL) and purified on DOWEX 50WX8 ion exchange resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) to give **371** as a white solid (8 mg, 63%, >99:1 dr); mp 222–224 °C (dec.); $[\alpha]_D^{20}$+91.3 (*c* 0.2 in H_2O); ν_{max} (ATR) 3451, 3229 (O–H, N–H), 2860, 2592 (C–H), 1653 (C=O), 1188; δ_H (400 MHz, D_2O) 1.48–1.60 (2H, m, C(3)H_A, C(4)H_A), 1.87–1.97 (1H, m, C(4)H_B), 2.14–2.21 (1H, m, C(3)H_B), 2.42–2.51 (1H, m, C(5)*H*), 2.73 (1H, dd, *J* 9.0, 8.3, C(1)*H*), 3.28 (1H, dd, *J* 10.9, 9.0, CH_AH$_B$OH), 3.50 (1H, dd, *J* 10.9, 5.0, CH$_A$$H_B$OH), 3.74 (1H, app q, *J* 8.3, C(2)*H*); δ_C (100 MHz, D_2O) 26.4 (*C*(4)), 28.8 (*C*(3)), 42.1 (*C*(5)), 53.5 (*C*(1)), 53.9 (*C*(2)), 62.5 (*C*H_2OH), 178.4 (*C*O_2H); *m*/*z* (ESI^+) 160 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_7H_{14}NO_3^+$ ($[M+H]^+$) requires 160.0968; found 160.0967.

6.4. Experimental for Chapter 4

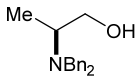
(*RS*)-2-(*N*,*N*-Dibenzylamino)propan-1-ol 413



Step 1: A solution of (*RS*)-**405** (5.00 g, 56.0 mmol) in H_2O (100 mL) was treated sequentially with K_2CO_3 (23.2 g, 168 mmol) and BnBr (20.0 mL, 168 mmol) at rt and the resultant mixture was heated at reflux for 3 h. The reaction mixture was then allowed to cool to rt and extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with brine (300 mL), then dried and concentrated *in vacuo* to give (*RS*)-**409** as a pale yellow oil (19.0 g).

Step 2: A solution of the residue (19.0 g) in THF (19 mL) was then added dropwise *via* cannula to a suspension of $LiAlH_4$ (3.90 g, 104 mmol) in THF (60 mL) at 0 °C and the resultant mixture was heated at reflux for 1 h. The reaction mixture was then cooled to 0 °C and cautiously treated with 2.0 M aq NaOH until a white suspension was obtained. The reaction mixture was then allowed to warm to rt, filtered through Celite® (eluent Et_2O) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 90:10) gave (*RS*)-**413** as a colourless oil (8.65 g, 60% from (*RS*)-**405**);[30] δ_H (400 MHz, $CDCl_3$) 0.91 (3H, d, *J* 6.7, C(3)H_3), 2.87–2.96 (1H, m, C(2)*H*), 3.07 (1H, br s, O*H*), 3.24–3.28 (1H, m, C(1)H_A), 3.28 (2H, d, *J* 13.4, N(C$H_A$$H_B$Ph)$_2$), 3.39 (1H, app t, *J* 10.5, C(1)H_B), 3.75 (2H, d, *J* 13.4, N(C$H_A$$H_B$Ph)$_2$), 7.15–7.26 (10H, m, *Ph*).

(*S*)-2-(*N*,*N*-Dibenzylamino)propan-1-ol 413

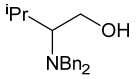


Step 1: A solution of (*S*)-**405** (5.00 g, 56.0 mmol) in H_2O (100 mL) was treated sequentially with K_2CO_3 (23.2 g, 168 mmol) and BnBr (20.0 mL, 168 mmol) at rt and the resultant mixture was heated at reflux for 3 h. The reaction mixture was then allowed to cool to rt and extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with brine (300 mL), then dried and concentrated *in vacuo* to give (*S*)-**409** as a pale yellow oil (18.5 g).

Step 2: A solution of the residue (18.5 g) in THF (19 mL) was then added dropwise *via* cannula to a suspension of $LiAlH_4$ (3.90 g, 104 mmol) in THF (60 mL) at 0 °C and the resultant mixture was heated at reflux for 1 h. The reaction mixture was then cooled to 0 °C and cautiously treated with 2.0 M aq NaOH until a white suspension was obtained. The reaction mixture was then allowed to warm to rt, filtered through Celite® (eluent Et_2O) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C

petrol/Et_2O, 90:10) gave (*S*)-**413** as a colourless oil (8.82 g, 62% from (*S*)-**405**);[30] $[\alpha]_D^{20}$ +86.1 (*c* 1.0 in $CHCl_3$); {lit.[30] $[\alpha]_D^{20}$ +88.2 (*c* 1.0 in $CHCl_3$)}.

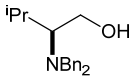
(*RS*)-2-(*N*,*N*-Dibenzylamino)-3-methylbutan-1-ol 414



Step 1: A solution of (*RS*)-**406** (5.00 g, 42.7 mmol) in H_2O (100 mL) was treated sequentially with K_2CO_3 (17.7 g, 128 mmol) and BnBr (15.2 mL, 128 mmol) at rt and the resultant mixture was heated at reflux for 3 h. The reaction mixture was then allowed to cool to rt and extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with brine (300 mL), then dried and concentrated *in vacuo* to give (*RS*)-**410** as a pale yellow oil (14.5 g).

Step 2: A solution of the residue (14.5 g) in THF (15 mL) was then added dropwise *via* cannula to a suspension of $LiAlH_4$ (2.94 g, 77.4 mmol) in THF (35 mL) at 0 °C and the resultant mixture was heated at reflux for 1 h. The reaction mixture was then cooled to 0 °C and cautiously treated with 2.0 M aq NaOH until a white suspension was obtained. The reaction mixture was then allowed to warm to rt, filtered through Celite® (eluent Et_2O) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 90:10) gave (*RS*)-**414** as a colourless oil (6.48 g, 54% from (*RS*)-**406**);[31] δ_H (400 MHz, $CDCl_3$) 0.93 (3H, d, *J* 6.7, C(3)*Me*$_A$), 1.18 (3H, d, *J* 6.7, C(3)*Me*$_B$), 2.06–2.14 (1H, m, C(3)*H*), 2.57 (1H, ddd, *J* 9.8, 7.8, 4.6, C(2)*H*), 3.04 (1H, br s, O*H*), 3.47 (1H, app t, *J* 10.4, C(1)H_A), 3.60 (1H, dd, *J* 10.4, 4.6, C(1)H_B), 3.72 (2H, d, *J* 13.2, N(CH_AH$_B$Ph)$_2$), 3.92 (2H, d, *J* 13.2, N(CH$_A$$H_B$Ph)$_2$), 7.26–7.36 (10H, m, *Ph*).

(*S*)-2-(*N*,*N*-Dibenzylamino)-3-methylbutan-1-ol 414

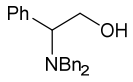


Step 1: A solution of (*S*)-**406** (5.00 g, 42.7 mmol) in H_2O (100 mL) was treated sequentially with K_2CO_3 (17.7 g, 128 mmol) and BnBr (15.2 mL, 128 mmol) at rt and the resultant mixture was heated at reflux for 3 h. The reaction mixture was then allowed to cool to rt and extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with brine (300 mL), then dried and concentrated *in vacuo* to give (*S*)-**410** as a pale yellow oil (14.5 g).

Step 2: A solution of the residue (14.5 g) in THF (15 mL) was then added dropwise *via* cannula to a suspension of $LiAlH_4$ (2.94 g, 77.4 mmol) in THF (35 mL) at 0 °C and the resultant mixture was heated at reflux for 1 h. The reaction mixture was then cooled to 0 °C and cautiously treated with 2.0 M aq NaOH until a white suspension was obtained. The

reaction mixture was then allowed to warm to rt, filtered through Celite® (eluent Et_2O) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 90:10) gave (*S*)-**414** as a colourless oil (6.48 g, 54% from (*S*)-**406**);[31] $[\alpha]_D^{20}$ +23.4 (*c* 1.0 in $CHCl_3$); {lit.[30] $[\alpha]_D^{20}$ +21.5 (*c* 1.0 in $CHCl_3$)}.

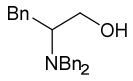
(*RS*)-2-(*N*,*N*-Dibenzylamino)-2-phenylethan-1-ol 415



Step 1: A solution of (*RS*)-**407** (5.00 g, 33.0 mmol) in H_2O (100 mL) was treated sequentially with K_2CO_3 (13.7 g, 99.0 mmol) and BnBr (12.0 mL, 99.0 mmol) at rt and the resultant mixture was heated at reflux for 3 h. The reaction mixture was then allowed to cool to rt and extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with brine (300 mL), then dried and concentrated *in vacuo* to give (*RS*)-**411** as a pale yellow oil (13.0 g).

Step 2: A solution of the residue (13.0 g) in THF (13 mL) was then added dropwise *via* cannula to a suspension of $LiAlH_4$ (2.34 g, 61.7 mmol) in THF (30 mL) at 0 °C and the resultant mixture was heated at reflux for 1 h. The reaction mixture was then cooled to 0 °C and cautiously treated with 2.0 M aq NaOH (100 mL). The reaction mixture was then allowed to warm to rt, filtered through Celite® (eluent Et_2O) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 90:10) gave (*RS*)-**415** as a colourless oil (9.27 g, 88% from (*RS*)-**407**);[31] δ_H (400 MHz, $CDCl_3$) 3.08 (1H, br s, O*H*), 3.18 (2H, d, *J* 13.3, $N(CH_AH_BPh)_2$), 3.65 (1H, dd, *J* 10.6, 5.0, C(2)*H*), 3.97 (2H, d, *J* 13.3, $N(CH_AH_BPh)_2$), 3.97–4.00 (1H, m, C(1)H_A), 4.19 (1H, app t, *J* 10.6, C(1)H_B), 7.28–7.33 (4H, m, *Ph*), 7.36–7.41 (8H, m, *Ph*), 7.42–7.49 (3H, m, *Ph*).

(*RS*)-2-(*N*,*N*-Dibenzylamino)-3-phenylpropan-1-ol 416

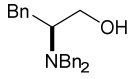


Step 1: A solution of (*RS*)-**408** (5.00 g, 30.3 mmol) in H_2O (100 mL) was treated sequentially with K_2CO_3 (12.6 g, 90.9 mmol) and BnBr (10.8 mL, 90.9 mmol) at rt and the resultant mixture was heated at reflux for 3 h. The reaction mixture was then allowed to cool to rt and extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with brine (300 mL), then dried and concentrated *in vacuo* to give (*RS*)-**412** as a yellow oil (12.2 g).

Step 2: A solution of the residue (12.2 g) in THF (13 mL) was then added dropwise *via* cannula to a suspension of $LiAlH_4$ (2.23 g, 58.8 mmol) in THF (35 mL) at 0 °C and the resultant mixture was heated at reflux for 1 h. The reaction mixture was then cooled to 0 °C

and cautiously treated with 2.0 M aq NaOH until a white suspension was obtained. The reaction mixture was then allowed to warm to rt, filtered through Celite® (eluent Et_2O) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 90:10) gave (*RS*)-**416** as a colourless oil (6.49 g, 65% from (*RS*)-**408**);[30] δ_H (400 MHz, $CDCl_3$) 2.47–2.53 (1H, m, C(3)H_A), 3.11 (1H, br s, O*H*), 3.11–3.21 (2H, m, C(1)H_A, C(3)H_B), 3.41 (1H, dd, *J* 10.5, 4.4, C(2)*H*), 3.56 (2H, d, *J* 13.3, N(C$H_A$$H_B$Ph)$_2$), 3.58 (1H, app t, *J* 10.5, C(1)H_B), 4.00 (2H, d, *J* 13.3, N($CH_A$$H_B$Ph)$_2$), 7.16–7.18 (2H, m, *Ph*), 7.24–7.42 (13H, m, *Ph*).

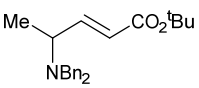
(*S*)-2-(*N*,*N*-Dibenzylamino)-3-phenylpropan-1-ol 416



Step 1: A solution of (*S*)-**408** (5.00 g, 30.3 mmol) in H_2O (100 mL) was treated sequentially with K_2CO_3 (12.6 g, 90.9 mmol) and BnBr (10.8 mL, 90.9 mmol) at rt and the resultant mixture was heated at reflux for 3 h. The reaction mixture was then allowed to cool to rt and extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with brine (300 mL), then dried and concentrated *in vacuo* to give (*S*)-**412** as a yellow oil (12.0 g).

Step 2: A solution of the residue (12.0 g) in THF (13 mL) was then added dropwise *via* cannula to a suspension of $LiAlH_4$ (2.23 g, 58.8 mmol) in THF (35 mL) at 0 °C and the resultant mixture was heated at reflux for 1 h. The reaction mixture was then cooled to 0 °C and cautiously treated with 2.0 M aq NaOH until a white suspension was obtained. The reaction mixture was then allowed to warm to rt, filtered through Celite® (eluent Et_2O) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 90:10) gave (*S*)-**416** as a colourless oil (5.22 g, 52% from (*S*)-**408**);[30] $[\alpha]_D^{20}$ +44.6 (*c* 1.0 in $CHCl_3$); {lit.[30] $[\alpha]_D^{20}$ +47.0 (*c* 1 in $CHCl_3$)}.

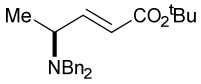
***tert*-Butyl (*RS*,*E*)-4-(*N*,*N*-dibenzylamino)pent-2-enoate 389**



DMSO (0.91 mL, 13 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (0.99 mL, 12 mmol) in CH_2Cl_2 (34 mL) at −78 °C. After 10 min, a solution of (*RS*)-**413** (2.50 g, 9.79 mmol) in CH_2Cl_2 (6.8 mL) at −78 °C was added dropwise *via* cannula and the resultant solution was stirred at −78 °C for 1 h. Et_3N (2.73 mL, 19.5 mmol) was then added at −78 °C and the reaction mixture was allowed to warm to rt over a period of 1 h. **180** (3.70 g, 9.79 mmol) was added and the resultant mixture was stirred at rt for 16 h. Satd aq $NaHCO_3$

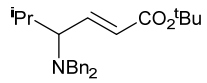
(100 mL) was then added and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (300 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave (*RS*,*E*)-**389** as a colourless oil (2.76 g, 80%, >99:1 dr);[32] δ_H (400 MHz, $CDCl_3$) 1.15 (3H, d, *J* 6.9, C(5)H_3), 1.43 (9H, s, CMe_3), 3.34–3.41 (1H, m, C(4)*H*), 3.51 (2H, d, *J* 14.0, N(CH_AH$_B$Ph)$_2$), 3.56 (2H, d, *J* 14.0, N(CH$_A$$H_B$Ph)$_2$), 5.75 (1H, app dd, *J* 15.9, 1.2, C(2)*H*), 6.90 (1H, dd, *J* 15.9, 5.8, C(3)*H*), 7.13–7.19 (3H, m, *Ph*), 7.21–7.23 (3H, m, *Ph*), 7.30–7.32 (4H, m, *Ph*).

***tert*-Butyl (*S*,*E*)-4-(*N*,*N*-dibenzylamino)pent-2-enoate 389**



DMSO (1.81 mL, 25.4 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (1.99 mL, 23.5 mmol) in CH_2Cl_2 (68 mL) at −78 °C. After 10 min, a solution of (*S*)-**413** (5.00 g, 19.6 mmol) in CH_2Cl_2 (13.6 mL) at −78 °C was added dropwise *via* cannula and the resultant solution was stirred at −78 °C for 1 h. Et_3N (5.46 mL, 39.2 mmol) was then added at −78 °C and the reaction mixture was allowed to warm to rt over a period of 1 h. **180** (7.37 g, 19.6 mmol) was added and the resultant mixture was stirred at rt for 16 h. Satd aq $NaHCO_3$ (100 mL) was then added and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (300 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave (*S*,*E*)-**389** as a colourless oil (6.25 g, 91%, >99:1 dr); $[\alpha]_D^{20}$ −127.4 (*c* 1.1 in $CHCl_3$).

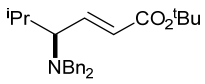
***tert*-Butyl (*RS*,*E*)-4-(*N*,*N*-dibenzylamino)-5-methylhex-2-enoate 394**



DMSO (0.98 mL, 13.8 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (1.08 mL, 12.7 mmol) in CH_2Cl_2 (80 mL) at −78 °C. After 10 min, a solution of (*RS*)-**414** (3.00 g, 10.6 mmol) in CH_2Cl_2 (16 mL) at −78 °C was added dropwise *via* cannula and the resultant solution was stirred at −78 °C for 1 h. Et_3N (2.95 mL, 21.2 mmol) was then added at −78 °C and the reaction mixture was allowed to warm to rt over a period of 1 h. **180** (3.99 g, 10.6 mmol) was added and the resultant mixture was stirred at rt for 16 h. Satd aq $NaHCO_3$ (100 mL) was then added and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (300 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2)

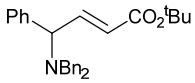
gave (*RS*,*E*)-**394** as a colourless oil (1.58 g, 39%, >99:1 dr);[32] δ_H (400 MHz, $CDCl_3$) 0.65 (3H, d, *J* 6.6, C(5)*Me*$_A$), 1.00 (3H, d, *J* 6.6, C(5)*Me*$_B$), 1.47 (9H, s, C*Me*$_3$), 1.81–1.93 (1H, m, C(5)*H*), 2.52 (1H, t, *J* 10.3, C(4)*H*), 3.23 (2H, d, *J* 13.7, NC*H*$_2$Ph), 3.83 (2H, d, *J* 13.7, NC*H*$_2$Ph), 5.60 (1H, d, *J* 15.6, C(2)*H*), 6.71 (1H, dd, *J* 15.6, 10.3, C(3)*H*), 7.13–7.33 (10H, m, *Ph*).

***tert*-Butyl (*S*,*E*)-4-(*N*,*N*-dibenzylamino)-5-methylhex-2-enoate 394**



DMSO (1.96 mL, 27.6 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (2.16 mL, 25.4 mmol) in CH_2Cl_2 (160 mL) at −78 °C. After 10 min, a solution of (*S*)-**414** (6.00 g, 21.2 mmol) in CH_2Cl_2 (32 mL) at −78 °C was added dropwise *via* cannula and the resultant solution was stirred at −78 °C for 1 h. Et_3N (5.90 mL, 42.4 mmol) was then added at −78 °C and the reaction mixture was allowed to warm to rt over a period of 1h. **180** (7.98 g, 21.2 mmol) was added and the resultant mixture was stirred at rt for 16 h. Satd aq $NaHCO_3$ (100 mL) was then added and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (300 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave (*S*,*E*)-**394** as a colourless oil (2.48 g, 31%, >99:1 dr);[32] $[\alpha]_D^{20}$ −93.9 (*c* 1.0 in $CHCl_3$).

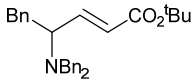
***tert*-Butyl (*RS*,*E*)-4-(*N*,*N*-dibenzylamino)-4-phenylbut-2-enoate 393**



DMSO (0.77 mL, 10.9 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (0.85 mL, 10.0 mmol) in CH_2Cl_2 (65 mL) at −78 °C. After 10 min, a solution of (*RS*)-**415** (2.65 g, 8.35 mmol) in CH_2Cl_2 (12 mL) at −78 °C was added dropwise *via* cannula and the resultant solution was stirred at −78 °C for 1 h. Et_3N (2.33 mL, 16.7 mmol) was then added at −78 °C and the reaction mixture was allowed to warm to rt over a period of 1 h. **180** (3.14 g, 8.35 mmol) was added and the resultant mixture was stirred at rt for 16 h. Satd aq $NaHCO_3$ (100 mL) was then added and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (300 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave (*RS*,*E*)-**393** as a white solid (2.11 g, 61%, >99:1 dr);[32] mp 148–149 °C {lit.[32] mp 144–146 °C}; δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s, C*Me*$_3$), 3.51 (2H, d, *J* 13.8, N(C*H*$_A$H$_B$Ph)$_2$), 3.55 (2H, d, *J* 13.8, N(CH$_A$*H*$_B$Ph)$_2$), 4.33 (1H, d, *J* 8.1, C(4)*H*), 5.84 (1H, d, *J* 15.7, C(2)*H*),

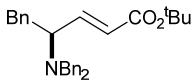
7.05 (1H, dd, *J* 15.7, 8.1, C(3)*H*), 7.14–7.20 (3H, m, *Ph*), 7.21–7.28 (5H, m, *Ph*), 7.30–7.33 (7H, m, *Ph*).

***tert*-Butyl (*RS*,*E*)-4-(*N*,*N*-dibenzylamino)-5-phenylpent-2-enoate 421**



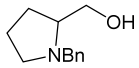
DMSO (1.11 mL, 15.7 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (1.23 mL, 14.5 mmol) in CH_2Cl_2 (90 mL) at −78 °C. After 10 min, a solution of (*RS*)-**416** (4.00 g, 12.1 mmol) in CH_2Cl_2 (20 mL) at −78 °C was added dropwise *via* cannula and the resultant solution was stirred at −78 °C for 1 h. Et_3N (3.36 mL, 24.1 mmol) was then added at −78 °C and the reaction mixture was allowed to warm to rt over a period of 1 h. **180** (4.54 g, 12.1 mmol) was added and the resultant mixture was stirred at rt for 16 h. Satd aq $NaHCO_3$ (100 mL) was then added and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (300 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave (*RS*,*E*)-**421** as a yellow oil (4.55 g, 88%, >99:1 dr);[32] δ_H (400 MHz, $CDCl_3$) 1.43 (9H, s, C*Me*$_3$), 2.71 (1H, dd, *J* 13.8, 7.5, C(5)*H*$_A$), 3.00 (1H, dd, *J* 13.8, 7.5, C(5)*H*$_B$), 3.44 (2H, d, *J* 14.1, N(C*H*$_A$H$_B$Ph)$_2$), 3.47 (1H, app q, *J* 7.5, C(4)*H*), 3.75 (2H, d, *J* 14.1, N(CH$_A$*H*$_B$Ph)$_2$), 5.72 (1H, d, *J* 15.7, C(2)*H*), 6.88 (1H, dd, *J* 15.7, 7.5, C(3)*H*), 7.12–7.19 (15H, m, *Ph*).

***tert*-Butyl (*S*,*E*)-4-(*N*,*N*-dibenzylamino)-5-phenylpent-2-enoate 421**



DMSO (1.39 mL, 19.6 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (1.53 mL, 18.1 mmol) in CH_2Cl_2 (112 mL) at −78 °C. After 10 min, a solution of (*S*)-**416** (5.68 g, 15.1 mmol) in CH_2Cl_2 (25 mL) at −78 °C was added dropwise *via* cannula and the resultant solution was stirred at −78 °C for 1 h. Et_3N (4.21 mL, 30.2 mmol) was then added at −78 °C and the reaction mixture was allowed to warm to rt over a period of 1 h. **180** (5.68 g, 15.1 mmol) was added and the resultant mixture was stirred at rt for 16 h. Satd aq $NaHCO_3$ (100 mL) was then added and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (300 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave (*S*,*E*)-**421** as a colourless oil (4.92 g, 76%, >99:1 dr);[32] $[\alpha]_D^{20}$ −56.8 (*c* 1.0 in $CHCl_3$).

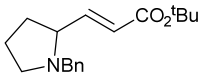
(*RS*)-(*N*(1')-Benzylpyrrolidin-2'-yl)methanol 424



Step 1: (*RS*)-**422** (5.00 g, 43 mmol) was added dropwise to a stirred solution of NaOH (1.74 g, 44.0 mmol) in H_2O (75 mL) at 0 °C. The resultant solution was then treated simultaneously with benzoyl chloride (5.00 mL, 43 mmol) and a solution of NaOH (1.74 g, 44 mmol) in H_2O (5 mL), and the resultant mixture was stirred at 0 °C for 2 h, then washed with Et_2O (2 × 50 mL). The aqueous layer was acidified with cold 6.0 M aq HCl until the pH value reached 2, then extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine (300 mL), then dried and concentrated *in vacuo* to give (*RS*)-**423** as a colourless oil (9.63 g).

Step 2: A solution of the residue (9.63 g) in THF (8.5 mL) was then added dropwise *via* cannula to a suspension of $LiAlH_4$ (3.00 g, 79 mmol) in THF (100 mL) at 0 °C and the resultant mixture was heated at reflux for 1 h. The reaction mixture was then cooled to 0 °C and cautiously treated with 2.0 M aq NaOH until a white suspension was obtained. The reaction mixture was then allowed to warm to rt, filtered through Celite® (eluent Et_2O) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C $CHCl_3$/MeOH, 90:10) gave (*RS*)-**424** as an orange oil (4.98 g, 60 % from (*RS*)-**422**);[33] δ_H (400 MHz, $CDCl_3$) 1.70–1.77 (2H, m, C(4')H_2), 1.83–1.91 (1H, m, C(3')H_A), 1.92–2.02 (1H, m, C(3')H_B), 2.29–2.36 (1H, m, C(5')H_A), 2.77 (1H, ddt, *J* 8.8, 5.9, 3.1, C(2')*H*), 2.78 (1H, br s, O*H*), 2.99–3.03 (1H, m, C(5')H_B), 3.39 (1H, d, *J* 13.0, NCH_AH$_B$Ph), 3.45–3.48 (1H, m, C(1)H_A), 3.70 (1H, dd, *J* 10.6, 3.5, C(1)H_B), 4.01 (1H, d, *J* 13.0, NCH$_A$$H_B$Ph), 7.27–7.38 (5H, m, *Ph*).

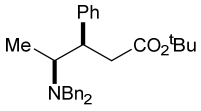
***tert*-Butyl (*RS*,*E*)-3-(*N*(1')-benzylpyrrolidin-2'-yl)propenoate 399**



DMSO (1.89 mL, 26.6 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (2.08 mL, 24.5 mmol) in CH_2Cl_2 (122 mL) at −78 °C. After 10 min, a solution of (*RS*)-**424** (3.91 g, 24.4 mmol) in CH_2Cl_2 (49 mL) at −78 °C was added dropwise *via* cannula and the resultant solution was stirred at −78 °C for 1 h. Et_3N (5.72 mL, 40.9 mmol) was then added at −78 °C and the reaction mixture was allowed to warm to rt over a period of 1 h. **180** (7.72 g, 20.4 mmol) was added and the resultant mixture was stirred at rt for 16 h. Satd aq $NaHCO_3$ (100 mL) was then added and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL).

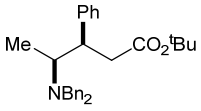
The combined organic extracts were washed with brine (300 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave (*RS*,*E*)-**399** as a colourless oil (4.00 g, 78%, >99:1 dr);[34] δ_H (400 MHz, $CDCl_3$) 1.42 (9H, s, C*Me*$_3$), 1.57–1.80 (3H, m, C(3')*H*$_A$, C(4')*H*$_2$), 1.88–1.97 (1H, m, C(3')*H*$_B$), 2.10 (1H, app q, *J* 8.8, C(5')*H*$_A$), 2.87–2.96 (2H, m, C(2')*H*, C(5')*H*$_B$), 3.11 (1H, d, *J* 13.0, NC*H*$_A$H$_B$Ph), 3.86 (1H, d, *J* 13.0, NCH$_A$*H*$_B$Ph), 5.83 (1H, d, *J* 15.6, C(2)*H*), 6.72 (1H, dd, *J* 15.6, 8.1, C(3)*H*), 7.14–7.18 (1H, m, *Ph*), 7.23–7.24 (4H, m, *Ph*).

***tert*-Butyl (*RS*,*SR*)-3-phenyl-4-(*N*,*N*-dibenzylamino)pentanoate 428**



PhMgBr (3.0 M in Et_2O, 0.47 mL, 1.40 mmol) was added dropwise to a stirred solution of (*RS*,*E*)-**389** (50 mg, 0.14 mmol, >99:1 dr) in Et_2O (0.9 mL) at 0 °C, and the resultant solution was stirred at 0 °C for 4 h. Satd aq NH_4Cl (1 mL) was then added dropwise at 0 °C and the reaction mixture was allowed to warm to rt. The resultant suspension was filtered under reduced pressure (eluent Et_2O) and the filtrate was washed with brine (25 mL), then dried and concentrated *in vacuo* to give (*RS*,*SR*)-**428** in >95:5 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave (*RS*,*SR*)-**428** as a colourless oil (66 mg, quant, >99:1 dr); ν_{max} (ATR) 2975, 2799 (C–H), 1726 (C=O), 1146, 697; δ_H (500 MHz, $CDCl_3$) 1.08 (3H, d, *J* 6.6, C(5)*H*$_3$), 1.09 (9H, s, C*Me*$_3$) 2.19 (1H, dd, *J* 14.5, 10.1, C(2)*H*$_A$), 2.47 (1H, dd, *J* 14.5, 5.2, C(2)*H*$_B$), 2.83 (1H, dq, *J* 10.3, 6.6, C(4)*H*), 3.13–3.18 (1H, m, C(3)*H*), 3.18 (2H, d, *J* 13.7, N(C*H*$_A$H$_B$Ph)$_2$), 3.61 (2H, d, *J* 13.7, N(CH$_A$*H*$_B$Ph)$_2$), 6.85–6.86 (6H, m, *Ph*), 7.08–7.16 (9H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 10.1 (*C*(5)), 27.7 (C*Me*$_3$), 41.1 (*C*(2)), 46.9 (*C*(3)), 53.2 (N(*C*H$_2$Ph)$_2$), 56.6 (*C*(4)), 80.1 (*C*Me$_3$), 126.1, 126.6, 127.6, 127.9, 127.9, 128.9, 128.9, 128.9, 129.0 (*o*,*m*,*p*-*Ph*), 139.8, 139.8, 142.7 (*i*-*Ph*), 171.7 (*C*(1)); *m*/*z* (ESI$^+$) 430 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{36}NO_2^+$ ([M+H]$^+$) requires 430.2741; found 430.2731.

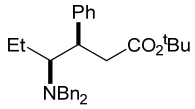
***tert*-Butyl (3*R*,4*S*)-3-phenyl-4-(*N*,*N*-dibenzylamino)pentanoate 428**



PhMgBr (3.0 M in Et_2O, 19.0 mL, 56.9 mmol) was added dropwise to a stirred solution of (*S*,*E*)-**389** (2.00 g, 5.69 mmol, >99:1 dr) in Et_2O (28 mL) at 0 °C, and the resultant solution was stirred at 0 °C for 4 h. Satd aq NH_4Cl (10 mL) was then added dropwise at 0 °C and the

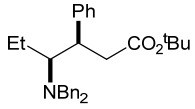
reaction mixture was allowed to warm to rt. The resultant suspension was filtered under reduced pressure (eluent Et_2O) and the filtrate was washed with brine (100 mL), then dried and concentrated *in vacuo* to give (3*R*,4*S*)-**428** in >95:5 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave (3*R*,4*S*)-**428** as a colourless oil (1.98 g, 81%, >99:1 dr); $[\alpha]_D^{20}$ −58.3 (*c* 1.0 in $CHCl_3$).

***tert*-Butyl (*RS*,*SR*)-3-phenyl-4-(*N*,*N*-dibenzylamino)hexanoate 429**



PhMgBr (3.0 M in Et_2O, 1.83 mL, 5.50 mmol) was added dropwise to a stirred solution of (*RS*,*E*)-**426** (200 mg, 0.55 mmol, >99:1 dr) in Et_2O (3.6 mL) at 0 °C, and the resultant solution was stirred at 0 °C for 4 h. Satd aq NH_4Cl (1 mL) was then added dropwise at 0 °C and the reaction mixture was allowed to warm to rt. The resultant suspension was filtered under reduced pressure (eluent Et_2O) and the filtrate was washed with brine (30 mL), then dried and concentrated *in vacuo* to give (*RS*,*SR*)-**429** in >95:5 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave (*RS*,*SR*)-**429** as a colourless oil (191 mg, 78%, >99:1 dr); ν_{max} (ATR) 2975, 2931 (C–H), 1726 (C=O), 1147, 698; δ_H (500 MHz, $CDCl_3$) 0.97 (3H, t, *J* 7.5, C(6)H_3), 1.08 (9H, s, CMe_3), 1.38–1.46 (1H, m, C(5)H_A), 1.65–1.74 (1H, m, C(5)H_B), 2.40 (1H, dd, *J* 14.7, 10.6, C(2)H_A), 2.49 (1H, dd, *J* 14.7, 5.0, C(2)H_B), 2.64 (1H, app dt, *J* 7.6, 5.8, C(4)*H*), 3.32 (1H, ddd, *J* 10.6, 7.6, 5.0, C(3)*H*), 3.37 (2H, d, *J* 13.7, N(C$H_A$$H_B$Ph)$_2$), 3.49 (2H, d, *J* 13.7, N(C$H_A$$H_B$Ph)$_2$), 6.97–7.02 (6H, m, *Ph*), 7.07–7.15 (9H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.5 (*C*(6)), 20.0 (*C*(5)), 27.7 (CMe_3), 40.0 (*C*(2)), 44.5 (*C*(3)), 54.0 (N(*C*H_2Ph)$_2$), 63.0 (*C*(4)), 80.0 (*C*Me$_3$), 126.1, 126.6, 127.8, 127.9, 127.9, 127.9, 128.9, 129.0, 129.0 (*o*,*m*,*p*-*Ph*), 140.0, 140.0, 142.7 (*i*-*Ph*), 171.8 (*C*(1)); *m*/*z* (ESI$^+$) 444 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{38}NO_2^+$ ([M+H]$^+$) requires 444.2897; found 444.2884.

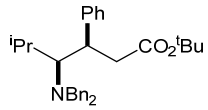
***tert*-Butyl (3*R*,4*S*)-3-phenyl-4-(*N*,*N*-dibenzylamino)hexanoate 429**



PhMgBr (3.0 M in Et_2O, 15.9 mL, 47.6 mmol) was added dropwise to a stirred solution of (*S*,*E*)-**426** (1.74 g, 4.76 mmol) in Et_2O (31.6 mL) at 0 °C, and the resultant solution was stirred at 0 °C for 4 h. Satd aq NH_4Cl (10 mL) was then added dropwise at 0 °C and the reaction mixture was allowed to warm to rt. The resultant suspension was filtered under

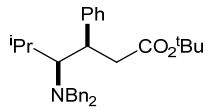
reduced pressure (eluent Et_2O) and the filtrate was washed with brine (100 mL), then dried and concentrated *in vacuo* to give (3*R*,4*S*)-**429** in >95:5 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave (3*R*,4*S*)-**429** as a colourless oil (1.67 g, 79%, >99:1 dr); $[\alpha]_D^{20}$ −108.0 (*c* 1.0 in $CHCl_3$).

***tert*-Butyl (*RS*,*SR*)-3-phenyl-4-(*N*,*N*-dibenzylamino)-5-methylhexanoate 430**



PhMgBr (3.0 M in Et_2O, 4.40 mL, 13.2 mmol) was added dropwise to a stirred solution of (*RS*,*E*)-**394** (500 mg, 1.32 mmol, >99:1 dr) in Et_2O (28 mL) at 0 °C, and the resultant solution was stirred at 0 °C for 4 h. Satd aq NH_4Cl (2 mL) was then added dropwise at 0 °C and the reaction mixture was allowed to warm to rt. The resultant suspension was filtered under reduced pressure (eluent Et_2O) and the filtrate was washed with brine (50 mL), then dried and concentrated *in vacuo* to give (*RS*,*SR*)-**430** in >95:5 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave (*RS*,*SR*)-**430** as a colourless oil which solidified upon standing (336 mg, 56%, >99:1 dr); mp 89–90 °C; ν_{max} (ATR) 2974 (C–H), 1727 (C=O), 1147, 698; δ_H (500 MHz, $CDCl_3$) 0.99 (3H, d, *J* 7.1, C(5)*Me*$_A$), 1.02 (3H, d, *J* 7.1, C(5)*Me*$_B$), 1.07 (9H, s, C*Me*$_3$), 2.15 (1H, dtd, *J* 14.1, 7.1, 2.8, C(5)*H*), 2.23 (1H, dd, *J* 14.1, 11.4, C(2)*H*$_A$), 2.53 (1H, dd, *J* 14.1, 4.3, C(2)*H*$_B$), 2.68 (1H, dd, *J* 9.6, 2.8, C(4)*H*), 3.38 (2H, d, *J* 13.5, N(C*H*$_A$H$_B$Ph)$_2$), 3.46 (2H, d, *J* 13.5, N(CH$_A$*H*$_B$Ph)$_2$), 3.49–3.53 (1H, m, C(3)*H*), 6.93–6.94 (4H, m, *Ph*), 7.00–7.02 (2H, m, *Ph*), 7.10–7.18 (9H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.0 (C(5)*Me*$_A$), 22.5 (*C*(5)*Me*$_B$), 26.4 (*C*(5)), 27.7 (C*Me*$_3$), 41.4 (*C*(2)), 42.7 (*C*(3)), 54.3 (N(*C*H$_2$Ph)$_2$), 64.5 (*C*(4)), 80.0 (*C*Me$_3$), 126.2, 126.7, 127.7, 127.8, 129.3, 129.3 (*o*,*m*,*p*-*Ph*), 140.0, 140.0, 142.9 (*i*-*Ph*), 171.4 (*C*(1)); *m*/*z* (ESI^+) 458 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{31}H_{40}NO_2^+$ ($[M+H]^+$) requires 458.3054; found 458.3037.

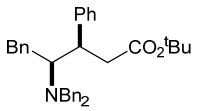
***tert*-Butyl (3*R*,4*S*)-3-phenyl-4-(*N*,*N*-dibenzylamino)-5-methylhexanoate 430**



PhMgBr (3.0 M in Et_2O, 13.5 mL, 40.5 mmol) was added dropwise to a stirred solution of (*S*,*E*)-**394** (1.54 g, 4.05 mmol, >99:1 dr) in Et_2O (28 mL) at 0 °C, and the resultant solution was stirred at 0 °C for 4 h. Satd aq NH_4Cl (10 mL) was then added dropwise at 0 °C and the reaction mixture was allowed to warm to rt. The resultant suspension was filtered under reduced pressure (eluent Et_2O) and the filtrate was washed with brine (100 mL), then dried

and concentrated *in vacuo* to give (3*R*,4*S*)-**430** in >95:5 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave (3*R*,4*S*)-**430** as a colourless oil (880 mg, 47%, >99:1 dr); $[\alpha]_D^{20}$ −93.9 (*c* 1.1 in $CHCl_3$).

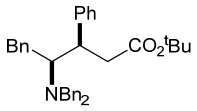
***tert*-Butyl (*RS*,*SR*)-3,5-diphenyl-4-(*N*,*N*-dibenzylamino)pentanoate 431**



Method A: PhMgBr (3.0 M in Et_2O, 0.40 mL, 1.20 mmol) was added dropwise to a stirred solution of (*RS*,*E*)-**421** (50 mg, 0.12 mmol, >99:1 dr) in Et_2O (0.9 mL) at 0 °C, and the resultant solution was stirred at 0 °C for 4 h. Satd aq NH_4Cl (1 mL) was then added dropwise at 0 °C and the reaction mixture was allowed to warm to rt. The resultant suspension was filtered under reduced pressure (eluent Et_2O) and the filtrate was washed with brine (25 mL), then dried and concentrated *in vacuo* to give (*RS*,*SR*)-**431** in >95:5 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave (*RS*,*SR*)-**431** as a white solid (52 mg, 88%, >99:1 dr); mp 65–67 °C; ν_{max} (ATR) 2930 (C–H), 1724 (C=O), 1143, 698; δ_H (400 MHz, $CDCl_3$) 1.02–1.03 (9H, m, C*Me*$_3$), 2.17–2.24 (1H, m, C(2)H_A), 2.36–2.41 (1H, m, C(2)H_B), 2.64–2.69 (1H, m, C(5)H_A), 3.12–3.19 (2H, m, C(4)*H*, C(5)H_B), 3.33–3.37 (3H, m, C(3)*H*, N(CH_AH$_B$Ph)$_2$), 3.61 (2H, d, *J* 14.0, N(CH$_A$$H_B$Ph)$_2$), 6.87–6.88 (4H, m, *Ph*), 6.97–6.98 (2H, m, *Ph*), 7.09–7.15 (12H, m, *Ph*), 7.19–7.23 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.7 (C*Me*$_3$), 33.8 (*C*(5)), 40.7 (*C*(2)), 46.0 (*C*(3)), 54.0 (N(*C*H$_2$Ph)$_2$), 63.0 (*C*(4)), 80.0 (*C*Me$_3$), 125.9, 126.2, 126.7, 127.7, 127.9, 127.9, 127.9, 128.5, 128.9, 128.9, 129.1, 129.1 (*o*,*m*,*p*-*Ph*), 139.5, 139.5, 141.3, 142.3 (*i*-*Ph*), 171.5 (*C*(1)); *m*/*z* (ESI$^+$) 506 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{35}H_{40}NO_2^+$ ([M+H]$^+$) requires 506.3054; found 506.3054.

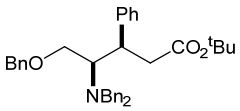
Method B: PhLi (1.8 M in Bu_2O, 1.30 mL, 2.34 mmol) was added dropwise to a stirred solution of (*RS*,*E*)-**421** (100 mg, 0.23 mmol, >99:1 dr) in Et_2O (1.8 mL) at 0 °C, and the resultant solution was stirred at 0 °C for 2 h. Satd aq NH_4Cl (1 mL) was then added dropwise at 0 °C and the reaction mixture was allowed to warm to rt. The resultant suspension was filtered under reduced pressure (eluent Et_2O) and the filtrate was washed with brine (25 mL), then dried and concentrated *in vacuo* to give (*RS*,*SR*)-**431** in >95:5 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave (*RS*,*SR*)-**431** as a colourless oil (45 mg, 38%, >99:1 dr).

***tert*-Butyl (3*R*,4*S*)-3,5-diphenyl-4-(*N*,*N*-dibenzylamino)pentanoate 431**



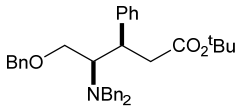
PhMgBr (3.0 M in Et_2O, 16.5 mL, 49.4 mmol) was added dropwise to a stirred solution of (*S*,*E*)-**421** (2.11 g, 4.94 mmol, >99:1 dr) in Et_2O (38 mL) at 0 °C, and the resultant solution was stirred at 0 °C for 4 h. Satd aq NH_4Cl (10 mL) was then added dropwise at 0 °C and the reaction mixture was allowed to warm to rt. The resultant suspension was filtered under reduced pressure (eluent Et_2O) and the filtrate was washed with brine (100 mL), then dried and concentrated *in vacuo* to give (3*R*,4*S*)-**431** in >95:5 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave (3*R*,4*S*)-**431** as a colourless oil (2.28 g, 91%, >99:1 dr); $[\alpha]_D^{20}$ −56.4 (*c* 1.1 in $CHCl_3$).

***tert*-Butyl (*RS*,*RS*)-3-phenyl-4-(*N*,*N*-dibenzylamino)-5-(benzyloxy)pentanoate 432**



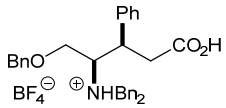
PhMgBr (3.0 M in Et_2O, 0.37 mL, 1.10 mmol) was added dropwise to a stirred solution of (*RS*,*E*)-**427** (50 mg, 0.11 mmol, >99:1 dr) in Et_2O (0.9 mL) at 0 °C, and the resultant solution was stirred at 0 °C for 4 h. Satd aq NH_4Cl (1 mL) was then added dropwise at 0 °C and the reaction mixture was allowed to warm to rt. The resultant suspension was filtered under reduced pressure (eluent Et_2O) and the filtrate was washed with brine (25 mL), then dried and concentrated *in vacuo* to give (*RS*,*RS*)-**432** in >95:5 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 96:4) gave (*RS*,*RS*)-**432** as a colourless oil (41 mg, 70%, >99:1 dr); ν_{max} (ATR) 2929 (C–H), 1725 (C=O), 1148, 698; δ_H (400 MHz, $CDCl_3$) 1.06 (9H, s, C*Me*$_3$), 2.26 (1H, dd, *J* 14.5, 10.7, C(2)*H*$_A$), 2.55 (1H, dd, *J* 14.5, 4.5, C(2)*H*$_B$), 2.92 (1H, app dt, *J* 10.2, 4.5, C(4)*H*), 3.32 (2H, d, *J* 13.7, N(C*H*$_A$H$_B$Ph)$_2$), 3.45 (1H, app td, *J* 10.2, 4.5, C(3)*H*), 3.66 (1H, dd, *J* 10.2, 4.0, C(5)*H*$_A$), 3.69 (2H, d, *J* 13.7, N(CH$_A$*H*$_B$Ph)$_2$), 3.73 (1H, dd, *J* 10.2, 4.0, C(5)*H*$_B$), 4.47 (1H, d, *J* 12.2, OC*H*$_A$H$_B$Ph), 4.54 (1H, d, *J* 12.2, OCH$_A$*H*$_B$Ph), 6.85–6.90 (6H, m, *Ph*), 7.08–7.14 (9H, m, *Ph*), 7.21–7.27 (1H, m, *Ph*), 7.30–7.36 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.7 (C*Me*$_3$), 40.5 (*C*(2)), 43.0 (*C*(3)), 54.4 (N(*C*H$_2$Ph)$_2$), 60.5 (*C*(4)), 67.4 (*C*(5)), 73.2 (O*C*H$_2$Ph), 79.9 (*C*Me$_3$), 126.2, 126.6, 127.6, 127.6, 127.7, 127.9, 128.4, 129.0, 129.2 (*o*,*m*,*p*-*Ph*), 13.8, 139.8, 142.2 (*i*-*Ph*), 171.6 (*C*(1)); *m*/*z* (ESI$^+$) 536 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{36}H_{42}NO_3^+$ ([M+H]$^+$) requires 536.3159; found 536.3148.

tert-Butyl (*R*,*R*)-3-phenyl-4-(*N*,*N*-dibenzylamino)-5-(benzyloxy)pentanoate 432



PhMgBr (3.0 M in Et_2O, 14.6 mL, 43.7 mmol) was added dropwise to a stirred solution of (*R*,*E*)-**427** (2.00 g, 4.37 mmol, >99:1 dr) in Et_2O (36 mL) at 0 °C, and the resultant solution was stirred at 0 °C for 4 h. Satd aq NH_4Cl (10 mL) was then added carefully at 0 °C and the reaction mixture was allowed to warm to rt. The resultant suspension was filtered under reduced pressure (eluent Et_2O) and the filtrate was washed with brine (100 mL), then dried and concentrated *in vacuo* to give (*R*,*R*)-**432** in >95:5 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 96:4) gave (*R*,*R*)-**432** as a colourless oil (1.94 g, 83%, >99:1 dr); $[\alpha]_D^{20}$ −13.6 (*c* 1.0 in $CHCl_3$).

(*RS*,*RS*)-3-Phenyl-4-(*N*,*N*-dibenzylammonium)-5-(benzyloxy)pentanoic acid tetrafluoroborate 434·HBF$_4$

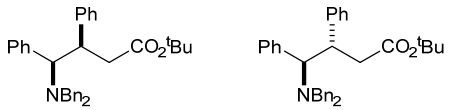


Step 1: TFA (0.23 mL) was added to a stirred solution of (*RS*,*RS*)-**432** (50 mg, 0.09 mmol, >99:1 dr) in CH_2Cl_2 (0.47 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with CH_2Cl_2 (10 mL) and the resultant mixture was washed with $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give (*RS*,*RS*)-**434** as a colourless oil (59 mg, >99:1 dr); ν_{max} (ATR) 3028, 2857 (C–H), 1706 (C=O), 698; δ_H (400 MHz, $CDCl_3$) 2.36 (1H, dd, *J* 15.9, 9.3, C(2)H_A), 2.66 (1H, dd, *J* 15.9, 4.9, C(2)H_B), 2.93–2.98 (1H, m, C(4)*H*), 3.26 (2H, d, *J* 13.7, N(CH_AH$_B$Ph)$_2$), 3.44 (1H, app td, *J* 9.3, 4.9, C(3)*H*), 3.62 (2H, d, *J* 13.7, N(CH_AH$_B$Ph)$_2$), 3.66–3.72 (2H, m, C(5)H_2), 4.41 (1H, d, *J* 12.1, OCH_AH$_B$Ph), 4.49 (1H, d, *J* 12.1, OCH$_A$$H_B$Ph), 6.85–7.30 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 38.7 (*C*(2)), 42.3 (*C*(3)), 54.4 (N(*C*H$_2$Ph)$_2$), 60.0 (*C*(4)), 67.2 (*C*(5)), 73.2 (O*C*H$_2$Ph), 126.4, 126.7, 127.7, 127.7, 127.9, 127.9, 127.9, 127.9, 128.4, 128.8, 129.0, 129.0 (*o*,*m*,*p*-*Ph*), 138.1, 139.5, 142.0 (*i*-*Ph*), 178.1 (*C*(1)); *m*/*z* (ESI$^+$) 480 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{34}NO_3^+$ ([M+H]$^+$) requires 480.2533; found 480.2520.

Step 2: HBF$_4$·OEt$_2$ (14 μl, 0.10 mmol) was added in one portion to a stirred solution of (*RS*,*RS*)-**434** (59 mg, >99:1 dr) in Et_2O (2 mL) at rt and the resultant mixture was stirred at rt for 5 min. The reaction mixture was then concentrated *in vacuo* to give (*RS*,*RS*)-**434**·HBF$_4$ as

a white solid (53 mg, quant, >99:1 dr); mp 65–67 °C; ν_{max} (ATR) 3524 (O–H, N–H), 3148 (C–H), 1733, 1714 (C=O), 1060, 700; δ_H (400 MHz, $CDCl_3$) 2.54 (1H, dd, *J* 16.6, 9.2, C(2)H_A), 2.70 (1H, dd, *J* 16.6, 3.9, C(2)H_B), 3.72 (1H, app td, *J* 9.7, 4.2, C(3)*H*), 4.03–4.11 (3H, m, C(4)*H*, C(5)H_A, NCH_AH$_B$Ph), 4.17 (1H, dd, *J* 13.3, 8.9, NCH_CH$_D$Ph), 4.30 (1H, d, *J* 11.5, C(5)H_B), 4.40–4.49 (2H, m, NCH$_A$$H_BPh, NCH_C$$H_D$Ph), 4.51 (1H, d, *J* 11.3, OCH_AH$_B$Ph), 4.67 (1H, d, *J* 11.3, OCH$_A$$H_B$Ph), 5.28 (1H, br s, N*H*), 6.64–7.32 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 37.2 (*C*(2)), 39.6 (*C*(3)), 54.9, 56.8 (N(*C*H$_2$Ph)$_2$), 73.4 (O*C*H$_2$Ph), 128.2, 128.5, 128.6, 129.0, 129.3, 129.5, 129.7, 129.8, 129.9, 130.0, 130.2, 130.4 (*o*,*m*,*p*-*Ph*), 135.8, 136.7 (*i*-*Ph*), 174.0 (*C*(1)); *m*/*z* (ESI$^+$) 480 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{34}NO_3^+$ ([M+H]$^+$) requires 480.2533; found 480.2523.

***tert*-Butyl (*RS*,*RS*)-3,4-diphenyl-4-(*N*,*N*-dibenzylamino)butanoate 436 and *tert*-butyl (*RS*,*SR*)-3,4-diphenyl-4-(*N*,*N*-dibenzylamino)butanoate 437**

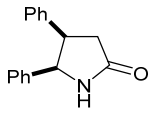


436 **437**

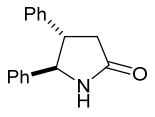
PhMgBr (3.0 M in Et_2O, 4.00 mL, 12.1 mmol) was added dropwise to a stirred solution of (*RS*,*E*)-**393** (500 mg, 1.21 mmol) in Et_2O (18 mL) at 0 °C, and the resultant solution was stirred at 0 °C for 4 h. Satd aq NH_4Cl (2 mL) was then added dropwise at 0 °C and the reaction mixture was allowed to warm to rt. The resultant suspension was filtered under reduced pressure (eluent Et_2O) and the filtrate was washed with brine (60 mL), then dried and concentrated *in vacuo* to give a 68:32 mixture of (*RS*,*RS*)-**436** and (*RS*,*SR*)-**437**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave a 71:29 mixture of (*RS*,*RS*)-**436** and (*RS*,*SR*)-**437**, respectively, as a colourless oil (258 mg, 43%). Data for major diastereoisomer (*RS*,*RS*)-**436**: δ_H (400 MHz, $CDCl_3$) 1.01 (9H, s, C*Me*$_3$), 1.99–2.11 (2H, m, C(2)H_2), 2.84 (2H, d, *J* 13.7, N(CH_AH$_B$Ph)$_2$), 3.71–3.85 (4H, m, N(CH$_A$$H_B$Ph)$_2$, C(3)*H*, C(4)*H*), 6.78–7.41 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.7 (C*Me*$_3$), 41.6 (*C*(2)), 44.2 (*C*(3)), 53.3 (N(*C*H$_2$Ph)$_2$), 66.4 (*C*(4)), 80.0 (*C*Me$_3$), 126.7, 127.5, 127.8, 127.9, 127.9, 128.3, 128.4, 128.7, 128.9, 129.0, 129.0, 129.3 (*o*,*m*,*p*-*Ph*), 135.7, 139.5, 139.5, 141.6 (*i*-*Ph*), 171.3 (*C*(1)). Data for minor diastereoisomer (*RS*,*SR*)-**437**: δ_H (400 MHz, $CDCl_3$) 1.12 (9H, s, C*Me*$_3$), 2.35 (1H, dd, *J* 14.8, 10.5, C(2)H_A), 2.95 (2H, d, *J* 13.7, N(CH_AH$_B$Ph)$_2$), 3.61 (1H, dd, *J* 14.8, 3.4, C(2)H_B), 3.71–3.85 (2H, m, C(3)*H*, C(4)*H*), 3.96 (2H, d, *J* 13.7, N(CH_AH$_B$Ph)$_2$), 6.78–7.41 (20H, m, Ph); δ_C (100 MHz, $CDCl_3$) [selected

peaks] 27.8 (C*Me*$_3$), 40.9 (*C*(2)), 43.9 (*C*(3)), 53.7 (N(*C*H$_2$Ph)$_2$), 66.4 (*C*(4)), 80.1 (*C*Me$_3$), 126.0, 126.5, 126.8, 127.0, 127.5, 127.7, 129.4, 129.8 (*o*,*m*,*p*-*Ph*), 134.7, 139.7, 139.7, 141.6 (*i*-*Ph*), 172.5 (*C*(1)). Data for mixture: ν_{max} (ATR) 2930 (C–H), 1725 (C=O), 1144, 698; *m*/*z* (ESI$^+$) 492 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{34}H_{38}NO_2^+$ ([M+H]$^+$) requires 492.2897; found 492.2882. Further elution gave a 60:40 mixture of (*RS*,*RS*)-**436** and (*RS*,*SR*)-**437**, respectively, as a colourless oil (112 mg, 19%).

(*RS*,*RS*)-4,5-Diphenylpyrrolidin-2-one 442 and (*RS*,*SR*)-4,5-diphenylpyrrolidin-2-one 443



442



443

Step 1: TFA (0.8 mL) was added to a stirred solution of a 71:29 mixture of (*RS*,*RS*)-**436** and (*RS*,*SR*)-**437**, respectively, (179 mg, 0.36 mmol) in CH_2Cl_2 (1.7 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with CH_2Cl_2 (20 mL) and the resultant mixture was washed with $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give a 71:29 mixture of (*RS*,*RS*)-**438** and (*RS*,*SR*)-**439**, respectively, as a pale yellow oil (158 mg). Data for major diastereoisomer (*RS*,*RS*)-**438**: δ_H (500 MHz, $CDCl_3$) 2.17 (2H, app d, *J* 7.7, C(2)*H*$_2$), 2.83 (2H, d, *J* 13.6, N(C*H*$_A$H$_B$Ph)$_2$), 3.71–3.74 (3H, m, N(CH$_A$*H*$_B$Ph)$_2$, C(4)*H*), 3.79–3.86 (1H, m, C(3)*H*), 6.75–7.38 (20H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 40.0 (*C*(2)), 43.5 (*C*(3)), 53.3 (N(*C*H$_2$Ph)$_2$), 66.1 (*C*(4)), 126.8, 126.8, 127.9, 127.9, 127.9, 128.1, 128.3, 128.5, 128.9, 129.1, 129.1, 129.1 (*o*,*m*,*p*-*Ph*), 135.4, 139.3, 141.4 (*i*-*Ph*), 177.2 (*C*(1)). Data for minor diastereoisomer (*RS*,*SR*)-**439**: δ_H (500 MHz, $CDCl_3$) 2.39 (1H, dd, *J* 16.0, 8.9, C(2)*H*$_A$), 2.93 (2H, d, *J* 13.6, NC*H*$_2$Ph), 3.61 (1H, dd, *J* 16.0, 3.3, C(2)*H*$_B$), 3.79–3.86 (2H, m, C(3)*H*, C(4)*H*), 3.95 (2H, d, *J* 13.6, NC*H*$_2$Ph), 6.75–7.38 (20H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 39.7 (*C*(2)), 42.8 (*C*(3)), 53.8 (N(*C*H$_2$Ph)$_2$), 66.3 (*C*(4)), 126.2, 127.0, 127.0, 127.1, 127.5, 127.7, 128.0, 128.3, 128.4, 128.7, 129.4, 130.0 (*o*,*m*,*p*-*Ph*), 134.2, 139.2, 141.6 (*i*-*Ph*), 178.4 (*C*(1)). Data for mixture: ν_{max} (ATR) 3029, 2833 (C–H), 1707 (C=O), 750, 699; *m*/*z* (ESI$^+$) 458 ([M+Na]$^+$, 2%), 436 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{30}NO_2^+$ ([M+H]$^+$) requires 436.2271; found 436.2262.

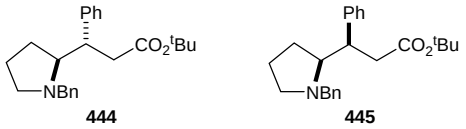
Step 2: Pd(OH)$_2$/C (65 mg, 50% w/w by substrate) was added to a degassed solution of a 71:29 mixture of (*RS*,*RS*)-**438** and (*RS*,*SR*)-**439**, respectively, (130 mg) in 1.25 M HCl/MeOH

(3 mL) at rt. The resultant suspension was vigorously stirred under H_2 (1 atm) at rt for 16 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo* to give a 71:29 mixture of (*RS*,*RS*)-**440**·HCl and (*RS*,*SR*)-**441**·HCl, respectively, as a white solid (91 mg, quant from (*RS*,*RS*)-**436** and (*RS*,*SR*)-**437**). Data for major diastereoisomer (*RS*,*RS*)-**440**·HCl: δ_H (500 MHz, $CDCl_3$) 2.24–2.27 (1H, m, C(2)H_A), 2.53–2.57 (1H, m, C(2)H_B), 3.28 (3H, s, O*Me*), 3.60–3.68 (1H, m, C(3)*H*), 4.51–4.59 (1H, m, C(4)*H*), 6.94–7.56 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 38.3 (*C*(2)), 46.8 (*C*(3)), 51.1 (O*Me*), 59.7 (*C*(4)), 128.1, 128.4, 128.7, 128.7, 129.4, 129.5 (*o*,*m*,*p*-*Ph*), 135.8, 138.3 (*i*-Ph), 171.7 (*C*(1)). Data for minor diastereoisomer (*RS*,*SR*)-**441**·HCl: δ_H (500 MHz, $CDCl_3$) 2.80–2.84 (1H, m, C(2)H_A), 2.98–3.01 (1H, m, C(2)H_B), 3.44 (3H, s, O*Me*), 3.69–3.74 (1H, m, C(3)*H*), 4.58–4.62 (1H, m, C(4)*H*), 6.94–7.56 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 37.5 (*C*(2)), 46.4 (*C*(3)), 51.3 (O*Me*), 59.2 (*C*(4)), 127.4, 127.9, 128.7, 128.9, 129.7 (*o*,*m*,*p*-*Ph*), 135.6, 138.1 (*i*-*Ph*), 171.9 (*C*(1)). Data for mixture: ν_{max} (ATR) 2921 (C–H), 1726 (C=O), 760, 700; *m*/*z* (ESI^+) 270 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{17}H_{20}NO_2^+$ ($[M+H]^+$) requires 270.1489; found 270.1483.

Step 3: K_2CO_3 (165 mg, 1.19 mmol) was added to a stirred solution of a 71:29 mixture of (*RS*,*RS*)-**440**·HCl and (*RS*,*SR*)-**441**·HCl, respectively, (91 mg, 0.30 mmol) in PhMe (10 mL) and the resultant suspension was heated at reflux for 16 h. The reaction mixture was allowed to cool to rt and then filtered through Celite® (eluent PhMe/MeOH, 75:25 v/v) and concentrated *in vacuo* to give a 71:29 mixture of (*RS*,*RS*)-**442** and (*RS*,*SR*)-**443**, respectively. Purification *via* flash column chromatography (eluent $CHCl_3$/MeOH, 98:2) gave a 66:34 mixture of (*RS*,*RS*)-**442** and (*RS*,*SR*)-**443**, respectively, as a yellow oil (54 mg, 76%).[35] Data for major diastereoisomer (*RS*,*RS*)-**442**: δ_H (500 MHz, $CDCl_3$) 2.59–2.65 (1H, m, C(3)H_A), 2.72 (1H, dd, *J* 16.9, 8.8, C(3)H_B), 3.97 (1H, app q, *J* 8.8, C(4)*H*), 4.95 (1H, d, *J* 7.6, C(5)*H*), 6.36 (1H, br s, N*H*), 6.71–6.74 (2H, m, *Ph*), 6.77–6.78 (2H, m, *Ph*), 6.98–7.00 (3H, m, *Ph*), 7.02–7.05 (3H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 35.2 (*C*(3)), 46.7 (*C*(4)), 62.7 (*C*(5)), 126.6, 128.0, 128.1, 128.2, 128.2, 128.9 (*o*,*m*,*p*-*Ph*), 137.8, 138.0 (*i*-*Ph*), 178.1 (*C*(2)). Data for minor diastereoisomer (*RS*,*SR*)-**443**: δ_H (500 MHz, $CDCl_3$) 2.59–2.65 (1H, m, C(3)H_A), 2.80 (1H, dd, *J* 17.1, 8.9, C(3)H_B), 3.30–3.36 (1H, m, C(4)*H*), 4.63 (1H, d, *J* 7.3, C(5)*H*), 6.32 (1H, br s, N*H*), 7.08–7.27 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 38.6 (*C*(3)), 51.2 (*C*(4)), 66.0 (*C*(5)), 125.9, 125.9, 126.9, 127.4, 127.4, 127.6 (*o*,*m*,*p*-*Ph*), 140.5, 140.6 (*i*-*Ph*), 176.7 (*C*(2)). Data for mixture: ν_{max} (ATR) 3216 (N–H), 3031 (C–H), 1688 (C=O), 697; *m*/*z* (ESI^+) 260

([M+Na]$^+$, 50%), 238 ([M+H]$^+$, 50%); HRMS (ESI$^+$) $C_{16}H_{16}NO^+$ ([M+H]$^+$) requires 238.1226; found 238.1221.

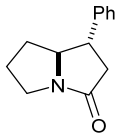
***tert*-Butyl (*RS*,*RS*)-3-(*N*(1')-benzylpyrrolidin-2'-yl)-3-phenylpropanoate 444 and *tert*-Butyl (*RS*,*SR*)-3-(*N*(1')-benzylpyrrolidin-2'-yl)-3-phenylpropanoate 445**



PhMgBr (3.0 M in Et_2O, 6.15 mL, 18.4 mmol) was added dropwise to a stirred solution of (*RS*,*E*)-**399** (530 mg, 1.84 mmol) in Et_2O (9.5 mL) at 0 °C, and the resultant solution was stirred at 0 °C for 4 h. Satd aq NH_4Cl (2 mL) was then added carefully at 0 °C and the reaction mixture was allowed to warm to rt. The resultant suspension was filtered under reduced pressure (eluent Et_2O) and the filtrate was washed with brine (50 mL), then dried and concentrated *in vacuo* to give a 66:34 mixture of (*RS*,*RS*)-**444** and (*RS*,*SR*)-**445**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 94:6) gave (*RS*,*RS*)-**444** as a white solid (280 mg, 42%, >99:1 dr); mp 69–70 °C; ν_{max} (ATR) 2973, 2789 (C–H), 1725 (C=O), 1146, 700; δ_H (400 MHz, $CDCl_3$) 1.18 (9H, s, C*Me*$_3$), 1.30–1.38 (1H, m, C(4')*H*$_A$), 1.39–1.52 (2H, m, C(3')*H*$_A$, C(4')*H*$_B$), 1.57–1.64 (1H, m, C(3')*H*$_B$), 2.10 (1H, app td, *J* 9.3, 6.4, C(5')*H*$_A$), 2.49 (1H, dd, *J* 14.9, 9.8, C(2)*H*$_A$), 2.74–2.79 (2H, m, C(2')*H*, C(5')*H*$_B$), 2.81 (1H, dd, *J* 14.9, 6.3, C(2)*H*$_B$), 3.15 (1H, app dt, *J* 9.8, 6.3, C(3)*H*), 3.31 (1H, d, *J* 13.2, NC*H*$_A$H$_B$Ph), 4.02 (1H, d, *J* 13.2, NCH$_A$*H*$_B$Ph), 7.07–7.24 (8H, m, *Ph*), 7.27–7.29 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 23.4 (*C*(4')), 27.6 (*C*(3')), 27.8 (C*Me*$_3$), 39.1 (*C*(2)), 46.3 (*C*(3)), 54.1 (*C*(5')), 60.6 (N*C*H$_2$Ph), 68.2 (*C*(2')), 79.9 (*C*Me$_3$), 126.2, 126.6, 127.7, 128.1, 128.5, 128.8 (*o*,*m*,*p*-*Ph*), 140.1, 141.6 (*i*-*Ph*), 172.1 (*C*(1)); *m*/*z* (ESI$^+$) 366 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{32}NO_2^+$ ([M+H]$^+$) requires 366.2428; found 366.2416. Further elution (eluent 30–40 °C petrol/Et_2O, 94:6) gave (*RS*,*SR*)-**445** as a yellow oil (59 mg, 9%, >99:1 dr); ν_{max} (ATR) 3028, 2789 (C–H), 1724 (C=O), 1144, 699; δ_H (400 MHz, $CDCl_3$) 1.18 (9H, s, C*Me*$_3$), 1.43–1.55 (2H, m, C(3')*H*$_A$, C(4')*H*$_2$), 1.55–1.66 (1H, m, C(3')*H*$_B$), 2.07 (1H, app q, *J* 8.5, C(5')*H*$_A$), 2.57 (1H, dd, *J* 15.5, 11.4, C(2)*H*$_A$), 2.64–2.69 (1H, m, C(2')*H*), 2.83 (1H, app dt, *J* 8.5, 4.8, C(5')*H*$_B$), 2.93 (1H, dd, *J* 15.5, 4.2, C(2)*H*$_B$), 3.19 (1H, d, *J* 13.0, NC*H*$_A$H$_B$Ph), 3.39 (1H, app dt, *J* 11.3, 4.2, C(3)*H*), 4.02 (1H, d, *J* 13.0, NCH$_A$*H*$_B$Ph), 7.10–7.29 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 22.8 (*C*(4')), 26.4 (*C*(3')), 27.9 (C*Me*$_3$), 34.7 (*C*(2)), 44.0 (*C*(3)), 54.3 (*C*(5')), 59.0 (N*C*H$_2$Ph), 68.3 (*C*(2')), 80.0 (*C*Me$_3$), 126.3, 126.7, 128.1, 128.1, 128.2, 128.8

(*o*,*m*,*p*-*Ph*), 139.9, 142.2 (*i*-*Ph*), 172.6 (*C*(1)); *m*/*z* (ESI$^+$) 366 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{32}NO_2^+$ ([M+H]$^+$) requires 366.2428; found 366.2429.

(*RS*,*RS*)-1-Phenylhexahydro-3*H*-pyrrolizidin-3-one 447



Method A – Step 1: $Pd(OH)_2$/C (50 mg, 50% w/w by substrate) was added to a degassed solution of (*RS*,*RS*)-**444** (100 mg, 0.27 mmol, >99:1 dr) in MeOH/AcOH (2 mL, 40:1 v/v) at rt. The resultant suspension was stirred vigorously under H_2 (1 atm) at rt for 24 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated *in vacuo* to give (*RS*,*RS*)-**448**·HOAc as a pale yellow solid (88 mg, 96%, >99:1 dr); mp 148–150 °C; ν_{max} (ATR) 3413 (N–H), 2976, 2930 (C–H), 1723, 1690 (C=O), 1147, 702; δ_H (400 MHz, $CDCl_3$) 1.12 (9H, s, C*Me*$_3$), 1.47–1.52 (1H, m, C(3')*H*$_A$), 1.55–1.62 (1H, m, C(3')*H*$_B$), 1.69–1.79 (1H, m, C(4')*H*$_A$), 1.83–1.89 (1H, m, C(4')*H*$_B$), 2.64 (1H, dd, *J* 15.2, 10.5, C(2)*H*$_A$), 2.99 (1H, dd, *J* 15.2, 4.4, C(2)*H*$_B$), 3.22–3.30 (3H, m, C(3)*H*, C(5')*H*$_2$), 3.55–3.61 (1H, m, C(2')*H*), 7.11–7.24 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 23.7 (*C*(4')), 27.7 (C*Me*$_3$), 30.4 (*C*(3')), 40.1 (*C*(2)), 45.0 (*C*(5')), 45.3 (*C*(3)), 63.8 (*C*(2')), 80.6 (*C*Me$_3$), 127.4, 128.0, 128.6 (*o*,*m*,*p*-*Ph*), 140.2 (*i*-*Ph*), 170.8 (*C*(1)); *m*/*z* (ESI$^+$) 276 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{17}H_{26}NO_2^+$ ([M+H]$^+$) requires 276.1958; found 276.1951.

Method A – Step 2: A solution of (*RS*,*RS*)-**448**·HOAc (59 mg, 0.17 mmol, >99:1 dr) in 3.0 M aq HCl (7 mL) was heated at reflux for 16 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo* to give (*RS*,*RS*)-**449**·HCl as an orange oil (78 mg, >99:1 dr); ν_{max} (ATR) 3371 (O–H, N–H), 2953 (C–H), 1721 (C=O), 1405, 758, 703; δ_H (400 MHz, MeOH-d_4) 1.54–1.74 (2H, m, C(3')*H*$_2$), 1.86–2.06 (2H, m, C(4')*H*$_2$), 2.83 (1H, dd, *J* 16.1, 9.7, C(2)*H*$_A$), 2.98 (1H, dd, *J* 16.1, 5.0, C(2)*H*$_B$), 3.34–3.44 (3H, m, C(3)*H*, C(5')*H*$_2$), 3.80–3.86 (1H, m, C(2')*H*), 7.26–7.38 (5H, m, *Ph*); δ_C (100 MHz, MeOH-d_4) 24.1 (*C*(4')), 31.0 (*C*(3')), 40.0 (*C*(2)), 45.8 (*C*(3)), 47.0 (*C*(5')), 66.0 (*C*(2')), 128.9, 129.2, 130.1 (*o*,*m*,*p*-*Ph*), 141.4 (*i*-*Ph*), 174.8 (*C*(1)); *m*/*z* (ESI$^+$) 220 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{18}NO_2^+$ ([M+H]$^+$) requires 220.1332; found 220.1329.

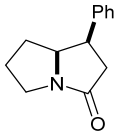
Method A – Step 3: A solution of (*RS*,*RS*)-**449**·HCl (78 mg, >99:1 dr) in 1.25 M HCl/MeOH (10 mL) was heated to reflux for 16 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo* to give (*RS*,*RS*)-**446**·HCl as brown oil (68 mg).

Method A – Step 4: K_2CO_3 (97 mg, 0.70 mmol) was added to a stirred solution of (*RS*,*RS*)-**446**·HCl (68 mg) in PhMe (3 mL) and the resultant suspension was heated at reflux for 16 h. The reaction mixture was allowed to cool to rt and then filtered through Celite® (eluent PhMe/MeOH, 75:25 v/v) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$/MeOH, 99:1) gave (*RS*,*RS*)-**447** as an orange oil (28 mg, 80% from (*RS*,*RS*)-**448**·HOAc, >99:1 dr);[36] ν_{max} (ATR) 3519 (N–H), 2948, 2881 (C–H), 1687 (C=O), 1415, 701; δ_H (500 MHz, $CDCl_3$) 1.45–1.53 (1H, m, C(7)H_A), 1.95–2.00 (1H, m, C(6)H_A), 2.01–2.12 (2H, m, C(6)H_B, C(7)H_B), 2.75 (1H, dd, *J* 16.2, 8.4, C(2)H_A), 2.89–2.95 (1H, m, C(2)H_B), 3.03–3.08 (1H, m, C(5)H_A), 3.22 (1H, app dt, *J* 11.7, 8.4, C(1)*H*), 3.56 (1H, dt, *J* 11.5, 7.6, C(5)H_B), 3.88 (1H, app td, *J* 8.4, 5.8, C(7a)*H*), 7.18–7.21 (3H, m, *Ph*), 7.27–7.30 (2H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 27.0 (*C*(6)), 31.3 (*C*(7)), 41.3 (*C*(5)), 43.1 (*C*(2)), 48.5 (*C*(3)), 68.6 (*C*(7a)), 127.0, 127.1, 128.8 (*o*,*m*,*p*-*Ph*), 140.5 (*i*-*Ph*), 173.1 (*C*(1)); *m*/*z* (ESI^+) 202 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{13}H_{16}NO^+$ ($[M+H]^+$) requires 202.1226; found 202.1226.

Method B – Step 1: $Pd(OH)_2$/C (100 mg, 50% w/w by substrate) was added to a degassed solution of (*RS*,*RS*)-**444** (200 mg, 0.55 mmol, >99:1 dr) in 1.25 M HCl/MeOH (9.4 mL) at rt. The resultant suspension was stirred vigorously under H_2 (1 atm) at rt for 24 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated *in vacuo* to give (*RS*,*RS*)-**446**·HCl as an orange oil (148 mg, >99:1 dr).

Method B – Step 2: K_2CO_3 (303 mg, 2.19 mmol) was added to a stirred solution of (*RS*,*RS*)-**446**·HCl (148 mg, 0.55 mmol, >99:1 dr) in PhMe (31 mL) and the resultant suspension was heated at reflux for 16 h. The reaction mixture was allowed to cool to rt and then filtered through Celite® (eluent PhMe/MeOH, 75:25 v/v) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$/MeOH, 99:1) gave (*RS*,*RS*)-**447** as a colourless oil (46 mg, 42% from (*RS*,*RS*)-**444**, >99:1 dr).

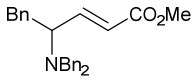
(*RS*,*SR*)-1-Phenylhexahydro-3*H*-pyrrolizidin-3-one 451



$Pd(OH)_2$/C (65 mg, 50% w/w by substrate) was added to a degassed solution of (*RS*,*SR*)-**445** (130 mg, 0.36 mmol, >99:1 dr) in 1.25 M HCl/MeOH (6.1 mL) at rt. The resultant suspension was stirred vigorously under H_2 (1 atm) at rt for 24 h. The reaction mixture was then filtered

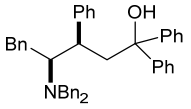
through Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (20 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (20 mL) at rt for 30 min. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$/MeOH, 99:1) gave (*RS*,*SR*)-**451** as a pale yellow oil (21 mg, 29% from (*RS*,*SR*)-**445**, >99:1 dr);[36] ν_{max} (ATR) 2971, 2879 (C–H), 1673 (C=O), 1416, 701; δ_H (400 MHz, $CDCl_3$) 0.80–0.90 (1H, m, C(7)H_A), 1.42 (1H, app dtd, *J* 12.7, 6.7, 3.4, C(7)H_B), 1.76 (1H, app ddt, *J* 12.1, 8.1, 4.2, C(6)H_A), 1.82–1.90 (1H, m, C(6)H_B), 2.60 (1H, dd, *J* 16.7, 2.2, C(2)H_A), 2.98–3.04 (1H, m, C(5)H_A), 3.13 (1H, dd, *J* 16.7, 8.7, C(2)H_B), 3.44 (1H, app dt, *J* 11.4, 7.8, C(5)H_B), 3.62 (1H, ddd, *J* 9.1, 8.7, 2.2, C(1)*H*), 4.20 (1H, app dt, *J* 9.1, 6.7, C(7a)*H*), 7.02–7.04 (2H, m, *Ph*), 7.16–7.27 (3H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 26.3 (*C*(7)), 26.7 (*C*(6)), 41.4 (*C*(5)), 41.6 (*C*(2)), 41.7 (*C*(1)), 65.9 (*C*(7a)), 127.0, 127.6, 128.6 (*o*,*m*,*p*-*Ph*), 140.6 (*i*-*Ph*), 174.2 (*C*(3)); *m*/*z* (ESI^+) 202 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{13}H_{16}NO^+$ ($[M+H]^+$) requires 202.1226; found 202.1225.

Methyl (*RS*,*E*)-4-(*N*,*N*-dibenzylamino)-5-phenylpent-2-enoate 452

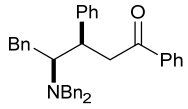


$SOCl_2$ (2.60 mL, 36.9 mmol) was added dropwise to a solution of (*RS*,*E*)-**421** (527 mg, 1.23 mmol) in MeOH (5.4 mL) at 0 °C and the reaction mixture was then stirred at 50 °C for 16 h. The resultant mixture was concentrated *in vacuo*, and the residue was dissolved in CH_2Cl_2 (20 mL). The resultant solution was washed with satd aq $NaHCO_3$ (3 × 25 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave (*RS*,*E*)-**452** as a colourless oil (475 mg, 62%, >99:1 dr); ν_{max} (ATR) 2948 (C–H), 1722 (C=O), 1268, 696; δ_H (400 MHz, $CDCl_3$) 2.91 (1H, dd, *J* 13.7, 7.8, C(5)H_A), 3.21 (1H, dd, *J* 13.7, 7.3, C(5)H_B), 3.63 (2H, d, *J* 13.9, N(C$H_A$$H_B$Ph)$_2$), 3.68 (1H, app q, *J* 7.8, C(4)*H*), 3.86 (3H, s, O*Me*), 3.95 (2H, d, *J* 13.9, N(C$H_A$$H_B$Ph)$_2$), 5.99 (1H, d, *J* 15.7, C(2)*H*), 7.13–7.15 (2H, m, *Ph*), 7.14–7.20 (1H, m, C(3)*H*), 7.29–7.40 (13H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 37.1 (*C*(5)), 51.5 (O*Me*), 53.5 (N(*C*H_2Ph)$_2$), 60.2 (*C*(4)), 123.1 (*C*(2)), 126.1, 126.8, 128.1, 128.2, 128.2, 128.2, 128.4, 128.4, 129.3 (*o*,*m*,*p*-*Ph*), 138.4, 139.3, 139.3 (*i*-*Ph*), 146.6 (*C*(3)), 166.4 (*C*(1)); *m*/*z* (ESI^+) 386 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{26}H_{28}NO_2^+$ ($[M+H]^+$) requires 386.2115; found 386.2105.

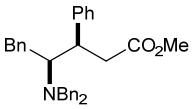
(*RS*,*SR*)-1,1,3,5-Tetraphenyl-4-(*N*,*N*-dibenzylamino)pentan-1-ol 454, (*RS*,*SR*)-1,3,5-triphenyl-4-(*N*,*N*-dibenzylamino)pentan-1-one 455 and methyl (*RS*,*SR*)-3,5-diphenyl-4-(*N*,*N*-dibenzylamino)pentanoate 453



454



455



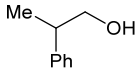
453

*Method A (from **452**)*: PhMgBr (3.0 M in Et_2O, 0.86 mL, 2.59 mmol) was added dropwise to a stirred solution of (*RS*,*E*)-**452** (100 mg, 0.26 mmol, >99:1 dr) in Et_2O (1.8 mL) at 0 °C, and the resultant solution was stirred at 0 °C for 4 h. Satd aq NH_4Cl (1 mL) was then added carefully at 0 °C and the reaction mixture was allowed to warm to rt. The resultant suspension was filtered under reduced pressure (eluent Et_2O) and the filtrate was washed with brine (50 mL), then dried and concentrated *in vacuo* to give a 15:15:70 mixture of (*RS*,*SR*)-**454**, (*RS*,*SR*)-**455** and (*RS*,*SR*)-**453**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave a 55:45 mixture of (*RS*,*SR*)-**454** and (*RS*,*SR*)-**455**, respectively, as a colourless oil (28 mg). Data for (*RS*,*SR*)-**454**: δ_H (500 MHz, $CDCl_3$) [selected peaks] 2.71 (1H, dd, *J* 8.3, 6.4, C(5)H_A), 3.00 (1H, dd, *J* 17.7, 5.1, C(2)H_A), 3.09 (1H, dd, *J* 17.7, 8.1, C(2)H_B), 3.21–3.24 (1H, m, C(5)H_B), 3.32 (2H, d, *J* 13.6, N(C$H_A$$H_B$Ph)$_2$), 3.32–3.35 (1H, m, C(4)*H*), 3.62 (2H, d, *J* 13.6, N($CH_A$$H_B$Ph)$_2$), 3.65–3.69 (1H, m, C(3)*H*); δ_C (125 MHz, $CDCl_3$) [selected peaks] 33.7 (*C*(5)), 43.3 (*C*(2)), 43.7 (*C*(3)), 54.4 (N(*C*H_2Ph)$_2$), 62.7 (*C*(4)), 78.6 (*C*(1)). Data for (*RS*,*SR*)-**455**: δ_H (500 MHz, $CDCl_3$) [selected peaks] 2.31 (1H, dd, *J* 14.5, 9.1, C(2)H_A), 2.50 (1H, dd, *J* 14.7, 8.0, C(5)H_A), 2.65 (1H, dd, *J* 14.5, 2.7, C(2)H_B), 2.72–2.76 (1H, m, C(3)*H*), 3.14 (1H, dd, *J* 14.7, 4.2, C(5)H_B), 3.20 (2H, d, *J* 13.7, N(C$H_A$$H_B$Ph)$_2$), 3.24–3.28 (1H, m, C(4)*H*), 3.44 (2H, d, *J* 13.7, N($CH_A$$H_B$Ph)$_2$); δ_C (125 MHz, $CDCl_3$) [selected peaks] 33.3 (*C*(2)), 44.8 (*C*(3)), 45.0 (*C*(5)), 54.5 (N(*C*H_2Ph)$_2$), 63.4 (*C*(4)), 198.5 (*C*(1)); Data for mixture: *m*/*z* (ESI^+) 510 ($[M+H]^+$, 34%), 588 ($[M+H]^+$, 66%); HRMS (ESI^+) $C_{43}H_{42}NO^+$ ($[M+H]^+$) requires 588.3261; found 588.3259. Further elution (eluent 30–40 °C petrol/Et_2O, 98:2) gave (*RS*,*SR*)-**453** as a white solid (75 mg, 62%, >99:1 dr); ν_{max} (ATR) 3027 (C–H), 1736 (C=O), 1161, 697; δ_H (400 MHz, $CDCl_3$) 2.32 (1H, dd, *J* 15.9, 9.5, C(2)H_A), 2.53 (1H, dd, *J* 15.9, 5.3, C(2)H_B), 2.65 (1H, dd, *J* 14.4, 7.6, C(5)H_A), 3.16 (1H, dd, *J* 14.4, 4.9, C(5)H_B), 3.22–3.25 (1H, m, C(4)*H*), 3.27 (3H, s, O*Me*), 3.31 (2H, d, *J* 13.9, N(C$H_A$$H_B$Ph)$_2$), 3.32–3.37 (1H, m, C(3)*H*), 3.56 (2H, d, *J* 13.9, N($CH_A$$H_B$Ph)$_2$), 6.94–7.00 (6H, m, *Ph*), 7.09–7.16 (12H, m, *Ph*),

7.21–7.25 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 33.5 (*C*(5)), 38.7 (*C*(2)), 44.9 (*C*(3)), 51.3 (O*Me*), 54.3 (N(*C*H_2Ph)$_2$), 62.2 (*C*(4)), 126.0, 126.4, 126.7, 127.9, 128.0, 128.0, 128.0, 128.5, 128.8, 128.9, 128.9, 129.1 (*o*,*m*,*p*-*Ph*), 139.5, 139.5, 141.0, 142.1 (*i*-*Ph*), 172.6 (*C*(1)); *m*/*z* (ESI$^+$) 464 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{34}NO_2^+$ ([M+H]$^+$) requires 464.2584; found 464.2575.

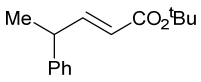
*Method B (from (RS,SR)-**431**)*: $SOCl_2$ (0.52 mL, 7.29 mmol) was added dropwise to a solution of (*RS*,*SR*)-**431** (123 mg, 0.24 mmol, >99:1 dr) in MeOH (1.2 mL) at 0 °C and the reaction mixture was then stirred at 50 °C for 16 h. The resultant mixture was concentrated *in vacuo*, and the residue was dissolved in CH_2Cl_2 (10 mL). The resultant solution was washed with satd aq $NaHCO_3$ (3 × 15 mL), then dried and concentrated *in vacuo* to give (*RS*,*SR*)-**453** as a yellow oil (113 mg, quant, >99:1 dr).

(*RS*)-2-Phenyl-1-propanol 457



A solution of (*RS*)-**456** (3.00 g, 19.9 mmol) in THF (6.9 mL) was added dropwise *via* cannula to a suspension of $LiAlH_4$ (1.41 g, 37.2 mmol) in THF (21.7 mL) at 0 °C and the resultant mixture was heated at reflux for 1 h. The reaction mixture was then cooled to 0 °C and cautiously treated with 2.0 M aq NaOH until a white suspension was obtained. The reaction mixture was then allowed to warm to rt, filtered through Celite® (eluent Et_2O) and concentrated *in vacuo* to give (*RS*)-**457** as a colourless oil (2.72 g, 94%);[37] δ_H (400 MHz, $CDCl_3$) 1.20 (3H, d, *J* 7.0, C(3)H_3), 1.36 (1H, s, O*H*), 2.88 (1H, app sextet, *J* 7.0, C(2)*H*), 3.63 (2H, d, *J* 7.0, C(1)H_2), 7.14–7.18 (3H, m, *Ph*), 7.24–7.29 (2H, m, *Ph*).

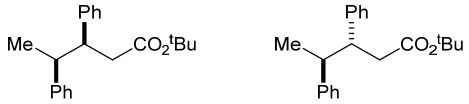
***tert*-Butyl (*RS*,*E*)-4-phenylpent-2-enoate 458**



DMSO (1.74 mL, 24.4 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (1.90 mL, 22.6 mmol) in CH_2Cl_2 (63 mL) at −78 °C. After 10 min, a solution of (*RS*)-**457** (2.56 g, 18.8 mmol) in CH_2Cl_2 (11.6 mL) at −78 °C was added dropwise *via* cannula and the resultant solution was stirred at −78 °C for 1 h. Et_3N (5.24 mL, 37.6 mmol) was then added at −78 °C and the reaction mixture was allowed to warm to rt over a period of 1 h. **180** (7.07 g, 18.8 mmol) was added and the resultant mixture was stirred at rt for 16 h. Satd aq $NaHCO_3$ (100 mL) was then added and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (300 mL), then dried and concentrated

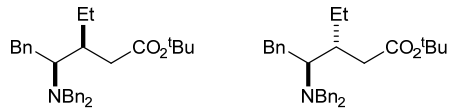
in vacuo. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 99:1) gave (*RS*,*E*)-**458** as a colourless oil (1.31 g, 28%, >99:1 dr);[38] δ_H (400 MHz, $CDCl_3$) 1.35 (3H, d, *J* 7.0, C(5)H_3), 1.40 (9H, s, CMe_3), 3.48–3.55 (1H, m, C(4)*H*), 5.65 (1H, dd, *J* 15.7, 1.5, C(2)*H*), 6.93 (1H, dd, *J* 15.7, 6.6, C(3)*H*), 7.12–7.19 (3H, m, *Ph*), 7.23–7.27 (2H, m, *Ph*).

tert-Butyl (*RS*,*RS*)-3,4-diphenylpentanoate and _tert_-butyl (*RS*,*SR*)-3,4-diphenylpentanoate 459 and 460



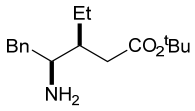
PhMgBr (3.0 M in Et_2O, 2.73 mL, 8.18 mmol) was added dropwise to a stirred solution of (*RS*,*E*)-**458** (190 mg, 0.82 mmol, >99:1 dr) in Et_2O (3.4 mL) at 0 °C, and the resultant solution was stirred at 0 °C for 4 h. Satd aq NH_4Cl (1 mL) was then added carefully at 0 °C and the reaction mixture was allowed to warm to rt. The resultant suspension was filtered under reduced pressure (eluent Et_2O) and the filtrate was washed with brine (50 mL), then dried and concentrated *in vacuo* to give a 72:28 mixture of **459** and **460**. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 99:1) gave an 85:15 mixture of **459** and **460** as a colourless oil (103 mg, 41%). Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 1.13 (9H, s, CMe_3), 1.21 (3H, d, *J* 7.1, C(5)H_3), 2.47 (1H, dd, *J* 15.0, 10.2, C(2)H_A), 2.62 (1H, dd, *J* 15.0, 5.9, C(2)H_B), 2.93 (1H, app quintet, *J* 7.1, C(4)*H*), 3.22 (1H, app dt, *J* 10.2, 5.9, C(3)*H*), 6.84–6.89 (4H, m, *Ph*), 6.98–7.09 (6H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 18.4 (*C*(5)), 27.7 (CMe_3), 39.0 (*C*(2)), 45.0 (*C*(4)), 48.8 (*C*(3)), 80.1 (*C*Me_3), 126.0, 126.1, 127.5, 127.7, 128.0 128.6 (*o*,*m*,*p*-*Ph*), 145.4 (*i*-*Ph*), 171.8 (*C*(1)). Data for minor diastereoisomer: δ_H (400 MHz, $CDCl_3$) 0.95 (3H, d, *J* 6.9, C(5)H_3), 1.04 (9H, s, CMe_3), 2.19–2.30 (2H, m, C(2)H_2), 2.75 (1H, qd, *J* 10.2, 6.9, C(4)*H*), 3.08 (1H, app td, *J* 10.2, 5.9, C(3)*H*), 7.12–7.25 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 20.5 (*C*(5)), 27.6 (CMe_3), 41.2 (*C*(2)), 46.0 (*C*(4)), 49.6 (*C*(3)), 79.8 (*C*Me_3), 126.4, 126.4, 127.5, 127.7, 128.3, 128.5 (*o*,*m*,*p*-*Ph*), 142.5, 145.4 (*i*-*Ph*), 171.6 (*C*(1)). Data for mixture: ν_{max} (ATR) 2975 (C–H), 1726 (C=O), 1143, 699; *m*/*z* (ESI^+) 333 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{21}H_{26}NaO_2^+$ ($[M+Na]^+$) requires 333.1825; found 333.1819. Further elution gave a second fraction of **459** and **460** as a colourless oil (52 mg, 21%, 54:46 dr).

***tert*-Butyl (*S*,*S*)-3-ethyl-4-(*N*,*N*-dibenzylamino)-5-phenylpentanoate 461** and ***tert*-butyl (3*R*,4*S*)-3-ethyl-4-(*N*,*N*-dibenzylamino)-5-phenylpentanoate 462**



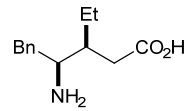
EtMgBr (0.9 M in THF, 37.1 mL, 33.4 mmol) was added dropwise to a stirred solution of (*S*,*E*)-**421** (1.43 g, 3.34 mmol, >99:1 dr) in Et_2O (26 mL) at 0 °C, and the resultant solution was stirred at 0 °C for 4 h. Satd aq NH_4Cl (10 mL) was then added dropwise at 0 °C and the reaction mixture was allowed to warm to rt. The resultant suspension was filtered under reduced pressure (eluent Et_2O) and the filtrate was washed with brine (100 mL), then dried and concentrated *in vacuo* to give a 94:6 mixture of (*S*,*S*)-**461** and (3*R*,4*S*)-**462**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave a 94:6 mixture of (*S*,*S*)-**461** and (3*R*,4*S*)-**462**, respectively, as a colourless oil (964 mg, 63%). Data for major diastereoisomer (*S*,*S*)-**461**: δ_H (400 MHz, $CDCl_3$) 0.64 (3H, t, *J* 7.5, C(2')H_3), 1.27–1.34 (1H, m, C(1')H_A), 1.30 (9H, s, CMe_3), 1.41–1.51 (1H, m, C(1')H_B), 1.94 (1H, dd, *J* 15.4, 8.1, C(2)H_A), 2.06–2.14 (1H, m, C(3)*H*), 2.34 (1H, dd, *J* 15.4, 4.4, C(2)H_B), 2.58 (1H, dd, *J* 13.7, 5.6, C(5)H_A), 2.84 (1H, dd, *J* 13.7, 7.6, C(5)H_B), 2.88–2.93 (1H, m, C(4)*H*), 3.54 (2H, d, *J* 13.8, N(C$H_A$$H_B$Ph)$_2$), 3.63 (2H, d, *J* 13.8, N(C$H_A$$H_B$Ph)$_2$), 7.03–7.21 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.5 (*C*(2')), 24.9 (*C*(1')), 28.0 (CMe_3), 33.3 (*C*(5)), 37.7 (*C*(3)), 37.7 (*C*(2)), 54.2 (N(*C*H_2Ph)$_2$), 61.0 (*C*(4)), 80.0 (*C*Me_3), 125.8, 126.7, 128.0, 128.0, 128.2, 128.8, 128.8, 128.8, 129.3 (*o*,*m*,*p*-*Ph*), 140.0, 140.0, 141.2 (*i*-*Ph*), 172.9 (*C*(1)). Data for minor diastereoisomer (3*R*,4*S*)-**462**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 0.43 (3H, t, *J* 7.5, C(2')H_3), 2.05–2.07 (1H, m, C(3)*H*), 2.76–2.79 (1H, m, C(4)*H*), 2.97–3.03 (1H, m, C(5)H_A), 3.37 (2H, d, *J* 13.8, N(C$H_A$$H_B$Ph)$_2$), 3.72 (2H, d, *J* 13.8, N(C$H_A$$H_B$Ph)$_2$), 7.03–7.21 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) [selected peaks] 10.4 (*C*(2')), 24.1 (*C*(1')), 28.0 (CMe_3), 33.5 (*C*(5)), 37.5 (*C*(2)), 39.3 (*C*(3)), 54.4 (N(*C*H_2Ph)$_2$), 61.0 (*C*(4)), 79.8 (*C*Me_3), 125.7, 126.7, 126.9, 127.8, 128.2, 129.0, 129.2 (*o*,*m*,*p*-*Ph*), 140.0, 140.0, 141.6 (*i*-*Ph*), 173.5 (*C*(1)). Data for mixture: $[\alpha]_D^{20}$ +10.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2965, 2931 (C–H), 1724 (C=O), 1150, 697; *m*/*z* (ESI$^+$) 458 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{40}NO_2^+$ ([M+H]$^+$) requires 458.3054; found 458.3044.

***tert*-Butyl (*S*,*S*)-3-ethyl-4-amino-5-phenylpentanoate 463**



$Pd(OH)_2/C$ (221 mg, 50% w/w by substrate) was added to a degassed solution of (*S*,*S*)-**461** (442 mg, 0.97 mmol, 94:6 dr) in MeOH (32 mL) at rt. The resultant suspension was stirred vigorously under H_2 (1 atm) at rt for 24 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (25 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (25 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give (*S*,*S*)-**463** as a pale yellow oil (242 mg, 90%, 94:6 dr); $[\alpha]_D^{20}$ −22.8 (*c* 1.1 in $CHCl_3$); ν_{max} (ATR) 3370 (N–H), 2964, 2929 (C–H), 1725 (C=O), 1150, 700; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.5, C(2')H_3), 1.07 (2H, br s, NH_2), 1.24–1.35 (1H, m, C(1')H_A), 1.37 (9H, s, CMe_3), 1.43–1.54 (1H, m, C(1')H_B), 1.77–1.84 (1H, m, C(3)*H*), 2.13 (1H, dd, *J* 14.9 , 6.9, C(2)H_A), 2.30 (1H, dd, *J* 13.4, 10.1, C(5)H_A), 2.38 (1H, dd, *J* 14.9, 6.6, C(2)H_B), 2.74 (1H, dd, *J* 13.4, 3.6, C(5)H_B), 3.02 (1H, app dt, *J* 10.1, 3.6, C(4)*H*), 7.10–7.17 (3H, m, *Ph*), 7.19–7.25 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.9 (*C*(2')), 22.6 (*C*(1')), 28.1 (CMe_3), 36.8 (*C*(2)), 40.6 (*C*(5)), 42.4 (*C*(3)), 54.7 (*C*(4)), 80.1 (*C*Me_3), 126.2, 128.5, 129.1 (*o*,*m*,*p*-*Ph*), 140.0 (*i*-*Ph*), 173.1 (*C*(1)); *m*/*z* (ESI^+) 278 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{17}H_{28}NO_2^+$ ($[M+H]^+$) requires 278.2115; found 278.2108.

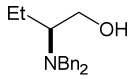
(*S*,*S*)-3-Ethyl-4-amino-5-phenylpentanoic acid 464



TFA (0.23 mL) was added to a stirred solution of (*S*,*S*)-**463** (50 mg, 0.18 mmol, 94:6 dr) in CH_2Cl_2 (0.5 mL) at rt, and the resultant mixture was stirred at rt for 16 h. Satd aq $NaHCO_3$ (5 mL) and CH_2Cl_2 (5 mL) were then added and the aqueous layer was extracted with CH_2Cl_2 (5 mL). The aqueous layer was then concentrated *in vacuo*, following which the residue was dissolved in 6.0 M aq HCl (25 mL) and the resultant solution was stirred at rt for 30 min, then concentrated *in vacuo*. The residue was dissolved in H_2O (2 mL) and purified on DOWEX 50WX8 ion exchange resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) to give (*S*,*S*)-**464** as a white solid (14 mg, 35%, >99:1 dr); mp 198–200 °C (dec.); $[\alpha]_D^{20}$ −19.2 (*c* 0.5 in 1.0 M aq HCl); ν_{max} (ATR) 3100 (O–H, N–H), 2957 (C–H), 1538 (C=O), 1381, 701; δ_H (500 MHz, D_2O) 0.90 (3H, t, *J* 7.3, C(2')H_3), 1.25–1.34 (1H, m, C(1')H_A), 1.50–1.58 (1H, m,

C(1')H_B), 1.89–1.95 (1H, m, C(3)*H*), 2.29 (1H, dd, *J* 15.8, 5.7, C(2)H_A), 2.41 (1H, dd, *J* 15.8, 6.8, C(2)H_B), 2.76 (1H, dd, *J* 14.3, 9.7, C(5)H_A), 3.00 (1H, dd, *J* 14.3, 5.5, C(5)H_B), 3.54–3.57 (1H, m, C(4)*H*), 7.24–7.29 (3H, m, *Ph*), 7.32–7.35 (2H, m, *Ph*); δ_C (125 MHz, D_2O) 11.1 (*C*(2')), 21.3 (*C*(1')), 35.6 (*C*(5)), 38.8 (*C*(2)), 38.8 (*C*(3)), 56.6 (*C*(4)), 127.4, 129.1, 129.3 (*o*,*m*,*p*-*Ph*), 136.3 (*i*-*Ph*), 181.2 (*C*(1)); *m*/*z* (ESI$^+$) 222 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{20}NO_2^+$ ([M+H]$^+$) requires 222.1489; found 222.1485. Further elution (eluent 1.0 M aq NH_4OH) gave (*S*,*S*)-**464** as a white solid (15 mg, 38%, 94:6 dr).

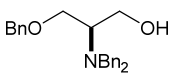
(*S*)-2-(*N*,*N*-Dibenzylamino)butan-1-ol 469



Step 1: A solution of (*S*)-**465** (5.00 g, 48.5 mmol) in H_2O (100 mL) was treated sequentially with K_2CO_3 (20.1 g, 145 mmol) and BnBr (17.3 mL, 145 mmol) at rt and the resultant mixture was heated at reflux for 3 h. The reaction mixture was then allowed to cool to rt and extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with brine (300 mL), then dried and concentrated *in vacuo* to give (*S*)-**467** as a pale yellow oil (16.8 g).

Step 2: A solution of the residue (16.8 g) in THF (18 mL) was then added dropwise *via* cannula to a suspension of $LiAlH_4$ (3.68 g, 97.0 mmol) in THF (40 mL) at 0 °C and the resultant mixture was heated at reflux for 1 h. The reaction mixture was then cooled to 0 °C and cautiously treated with 2.0 M aq NaOH until a white suspension was obtained. The reaction mixture was then allowed to warm to rt, filtered through Celite® (eluent Et_2O) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 90:10) gave (*S*)-**469** as a colourless oil (8.56 g, 66% from (*S*)-**465**);[39] $[\alpha]_D^{20}$ +62.0 (*c* 1.00 in $CHCl_3$); {lit.[39] for *ent*-**469** $[\alpha]_D^{20}$ −55.5 (*c* 1.68 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 0.96 (3H, t, *J* 7.6, C(4)H_3), 1.23–1.34 (1H, m, C(3)H_A), 1.85 (1H, dqd, *J* 13.5, 7.6, 4.1, C(3)H_B), 2.77 (1H, app tt, *J* 9.7, 5.0, C(2)*H*), 3.23 (1H, s, O*H*), 3.43–3.49 (1H, m, C(1)H_A), 3.47 (2H, d, *J* 13.2, N(C$H_A$$H_B$Ph)$_2$), 3.58 (1H, dd, *J* 10.6, 5.0, C(1)H_B), 3.87 (2H, d, *J* 13.2, N(C$H_A$$H_B$Ph)$_2$), 7.27–7.39 (10H, m, *Ph*).

(*R*)-2-(*N*,*N*-Dibenzylamino)-3-(benzyloxy)propan-1-ol 470

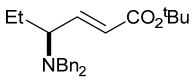


Step 1: A solution of (*S*)-**466** (5.00 g, 25.6 mmol) in H_2O (100 mL) was treated sequentially with K_2CO_3 (10.6 g, 76.8 mmol) and BnBr (9.1 mL, 76.8 mmol) at rt and the resultant mixture was heated at reflux for 3 h. The reaction mixture was then allowed to cool to rt and

extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with brine (300 mL), then dried and concentrated *in vacuo* to give (*S*)-**468** as a pale yellow oil (12.4 g).

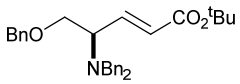
Step 2: A solution of the residue (12.4 g) in THF (13 mL) was then added dropwise *via* cannula to a suspension of $LiAlH_4$ (1.94 g, 51.2 mmol) in THF (27 mL) at 0 °C and the resultant mixture was heated at reflux for 1 h. The reaction mixture was then cooled to 0 °C and cautiously treated with 2.0 M aq NaOH until a white suspension was obtained. The reaction mixture was then allowed to warm to rt, filtered through Celite® (eluent Et_2O) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent chloroform/methanol, 99:1) gave (*R*)-**470** as a colourless oil (5.37 g, 58% from (*S*)-**466**);[31] $[\alpha]_D^{20}$ +84.9 (*c* 1.1 in $CHCl_3$); {lit.[31] $[\alpha]_D^{20}$ +90.3 (*c* 1.5 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 2.97 (1H, br s, O*H*), 3.18–3.24 (1H, m, C(2)*H*), 3.56–3.62 (3H, m, C(1)H_2, C(3)H_A), 3.66 (2H, d, *J* 13.4, N(C$H_A$$H_B$Ph)$_2$), 3.80 (1H, dd, *J* 9.8, 6.3, C(3)H_B), 3.93 (2H, d, *J* 13.4, N(C$H_A$$H_B$Ph)$_2$), 4.57 (1H, d, *J* 12.1, OC$H_A$$H_B$Ph), 4.61 (1H, d, *J* 12.1, OC$H_A$$H_B$Ph), 7.28–7.46 (15H, m, *Ph*).

***tert*-Butyl (*S*,*E*)-4-(*N*,*N*-dibenzylamino)hex-2-enoate 426**



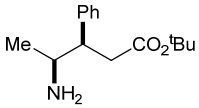
DMSO (1.70 mL, 24.1 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (1.90 mL, 22.3 mmol) in CH_2Cl_2 (100 mL) at −78 °C. After 10 min, a solution of (*S*)-**469** (5.00 g, 18.6 mmol) in CH_2Cl_2 (20 mL) at −78 °C was added dropwise *via* cannula and the resultant solution was stirred at −78 °C for 1 h. Et_3N (5.20 mL, 37.1 mmol) was then added at −78 °C and the reaction mixture was allowed to warm to rt over a period of 1 h. **180** (6.99 g, 18.6 mmol) was added and the resultant mixture was stirred at rt for 16 h. Satd aq $NaHCO_3$ (100 mL) was then added and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (300 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 98:2) gave (*S*,*E*)-**426** as a colourless oil (4.58 g, 68%, >99:1 dr);[32] $[\alpha]_D^{20}$ −123.0 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.83 (3H, t, *J* 7.4, C(6)H_3), 1.38–1.51 (1H, m, C(5)H_A), 1.45 (9H, s, CMe_3), 1.64–1.75 (1H, m, C(5)H_B), 2.99 (1H, app q, *J* 7.8, C(4)*H*), 3.35 (2H, d, *J* 13.8, N(C$H_A$$H_B$Ph)$_2$), 3.74 (2H, d, *J* 13.8, N(C$H_A$$H_B$Ph)$_2$), 5.68 (1H, dd, *J* 15.6, 0.9, C(2)*H*), 6.82 (1H, dd, *J* 15.6, 8.5, C(3)*H*), 7.13–7.31 (10H, m, *Ph*).

***tert*-Butyl (*R*,*E*)-4-(*N*,*N*-dibenzylamino)-5-(benzyloxy)pent-2-enoate 427**



DMSO (1.02 mL, 14.4 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (1.13 mL, 13.3 mmol) in CH_2Cl_2 (57 mL) at −78 °C. After 10 min, a solution of (*R*)-**470** (4.00 g, 11.1 mmol) in CH_2Cl_2 (12 mL) at −78 °C was added dropwise *via* cannula and the resultant solution was stirred at −78 °C for 1 h. Et_3N (3.09 mL, 22.1 mmol) was then added at −78 °C and the reaction mixture was allowed to warm to rt over a period of 1 h. **180** (4.17 g, 11.1 mmol) was added and the resultant mixture was stirred at rt for 16 h. Satd aq $NaHCO_3$ (100 mL) was then added and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (300 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 96:4) gave (*R*,*E*)-**427** as a yellow oil which solidified upon standing (4.28 g, 85%, >99:1 dr);[32] mp 60–62 °C {lit.[32] mp 56–57 °C}; $[\alpha]_D^{20}$ −57.2 (*c* 1.1 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.57 (9H, s, C*Me*$_3$), 3.59–3.70 (2H, m, C(4)*H*, C(5)H_A), 3.66 (2H, d, *J* 13.8, N(CH_AH$_B$Ph)$_2$), 3.80–3.84 (1H, m, C(5)H_B), 3.83 (2H, d, *J* 13.8, N(CH$_A$$H_B$Ph)$_2$), 4.52 (2H, app s, OC$H_2$Ph), 5.98 (1H, d, *J* 15.8, C(2)*H*), 6.98 (1H, dd, *J* 15.8, 6.6, C(3)*H*), 7.24–7.43 (15H, m, *Ph*).

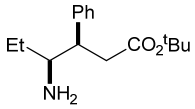
***tert*-Butyl (3*R*,4*S*)-3-phenyl-4-aminopentanoate 471**



$Pd(OH)_2$/C (500 mg, 50% w/w by substrate) was added to a degassed solution of (3*R*,4*S*)-**428** (1.00 g, 2.33 mmol, >99:1 dr) in MeOH (69 mL) at rt. The resultant suspension was stirred vigorously under H_2 (1 atm) at rt for 24 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2/^{i}PrOH (25 mL, 9:1) and the resultant solution was washed with satd aq $NaHCO_3$ (25 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give (3*R*,4*S*)-**471** as a colourless oil (475 mg, 82%, >99:1 dr); $[\alpha]_D^{20}$ −34.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3367 (N–H), 2976 (C–H), 1723 (C=O), 1145, 702; δ_H (400 MHz, $CDCl_3$) 1.02 (3H, d, *J* 6.4, C(5)H_3), 1.15 (9H, s, C*Me*$_3$), 1.47 (2H, br s, NH_2), 2.44 (1H, dd, *J* 14.8, 9.8, C(2)H_A), 2.64 (1H, dd, *J* 14.8, 5.9, C(2)H_B), 2.83 (1H, dt, *J* 9.8, 6.4, C(3)*H*), 2.99 (1H, app quintet, *J* 6.4, C(4)*H*), 7.11–7.14 (3H, m, *Ph*), 7.19–7.23 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.3 (*C*(5)), 27.5 (C*Me*$_3$), 38.8 (*C*(2)),

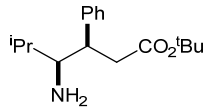
50.2 (*C*(3)), 50.8 (*C*(4)), 126.5, 128.0, 128.4 (*o*,*m*,*p*-*Ph*), 140.9 (*i*-*Ph*), 171.4 (*C*(1)); *m*/*z* (ESI$^+$) 272 ([M+Na]$^+$, 5%), 250 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{15}H_{24}NO_2^+$ ([M+H]$^+$) requires 250.1802; found 250.1796.

***tert*-Butyl (3*R*,4*S*)-3-phenyl-4-aminohexanoate 472**



$Pd(OH)_2$/C (500 mg, 50% w/w by substrate) was added to a degassed solution of (3*R*,4*S*)-**429** (1.00 g, 2.25 mmol, >99:1 dr) in MeOH (69 mL) at rt. The resultant suspension was stirred vigorously under H_2 (1 atm) at rt for 24 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2/^{i}PrOH (25 mL, 9:1) and the resultant solution was washed with satd aq $NaHCO_3$ (25 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give (3*R*,4*S*)-**472** as a colourless oil (561 mg, 94%, >99:1 dr); $[\alpha]_D^{20}$ −64.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3383 (N–H), 2974, 2931 (C–H), 1724 (C=O), 1145, 701; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.4, C(6)H_3), 1.01–1.14 (1H, m, C(5)H_A), 1.17 (9H, s, CMe_3), 1.46 (1H, ddd, *J* 13.7, 7.4, 4.1, C(5)H_B), 2.50 (1H, dd, *J* 14.8, 9.3, C(2)H_A), 2.67 (1H, dd, *J* 14.8, 6.3, C(2)H_B), 2.69–2.74 (1H, m, C(4)*H*), 2.98 (1H, app dt, *J* 9.3, 6.3, C(3)*H*), 7.10–7.15 (3H, m, *Ph*), 7.18–7.24 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 10.5 (*C*(6)), 27.6 (CMe_3), 28.1 (*C*(5)), 38.8 (*C*(2)), 47.8 (*C*(3)), 56.2 (*C*(4)), 79.8 (*C*Me$_3$), 126.4, 127.9, 128.6 (*o*,*m*,*p*-*Ph*), 140.7 (*i*-*Ph*), 171.5 (*C*(1)); *m*/*z* (ESI$^+$) 264 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{26}NO_2^+$ ([M+H]$^+$) requires 264.1958; found 264.1952.

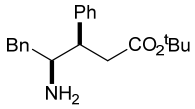
***tert*-Butyl (3*R*,4*S*)-3-phenyl-4-amino-5-methylhexanoate 473**



$Pd(OH)_2$/C (350 mg, 50% w/w by substrate) was added to a degassed solution of (3*R*,4*S*)-**430** (700 mg, 1.53 mmol, >99:1 dr) in MeOH (48 mL) at rt. The resultant suspension was stirred vigorously under H_2 (1 atm) at rt for 24 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (25 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (25 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give (3*R*,4*S*)-**473** as a pale yellow oil which solidified

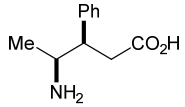
upon standing (334 mg, 79%, >99:1 dr); mp 102–103 °C; $[\alpha]_D^{20}$ −51.3 (*c* 1.1 in $CHCl_3$); ν_{max} (ATR) 3207 (N–H), 2963 (C–H), 1723 (C=O), 1146, 702; δ_H (500 MHz, $CDCl_3$) 0.82 (3H, d, *J* 6.7, C(5)*Me*$_A$), 0.88(2H, br s N*H*$_2$), 0.97 (3H, d, *J* 6.7, C(5)*Me*$_B$), 1.15 (9H, s, C*Me*$_3$), 1.57–1.65 (1H, m, C(5)*H*), 2.45 (1H, dd, *J* 14.5, 9.7, C(2)*H*$_A$), 2.58 (1H, dd, *J* 7.3, 5.1, C(4)*H*), 2.64 (1H, dd, *J* 14.5, 6.4, C(2)*H*$_B$), 3.05 (1H, dt, *J* 9.7, 6.4, C(3)*H*), 7.11–7.23 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.9 (C(5)*Me*$_A$), 21.0 (C(5)*Me*$_B$), 27.7 (C*Me*$_3$), 30.0 (*C*(5)), 39.7 (*C*(2)), 46.0 (*C*(3)), 60.2 (*C*(4)), 80.0 (*C*Me$_3$), 126.6, 128.1, 128.8 (*o*,*m*,*p*-*Ph*), 141.4 (*i*-*Ph*), 171.6 (*C*(1)); *m*/*z* (ESI^+) 300 ($[M+Na]^+$, 5%), 278 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{17}H_{28}NO_2^+$ ($[M+H]^+$) requires 278.2115; found 278.2105.

***tert*-Butyl (3*R*,4*S*)-3,5-diphenyl-4-aminopentanoate 474**



$Pd(OH)_2$/C (500 mg, 50% w/w by substrate) was added to a degassed solution of (3*R*,4*S*)-**431** (1.00 g, 1.98 mmol, >99:1 dr) in MeOH (69 mL) at rt. The resultant suspension was stirred vigorously under H_2 (1 atm) at rt for 24 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (25 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (25 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give (3*R*,4*S*)-**474** as a colourless oil which solidified upon standing (513 mg, 80%, >99:1 dr); mp 39–40 °C; $[\alpha]_D^{20}$ −40.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3380 (N–H), 2977, 2929 (C–H), 1723 (C=O), 1146, 701; δ_H (400 MHz, $CDCl_3$) 0.99 (2H, br s, N*H*$_2$), 1.18 (9H, s, C*Me*$_3$), 2.21 (1H, dd, *J* 13.2, 9.5, C(5)*H*$_A$), 2.59 (1H, dd, *J* 14.9, 9.0, C(2)*H*$_A$), 2.79 (1H, dd, *J* 14.9, 5.9, C(2)*H*$_B$), 2.85 (1H, dd, *J* 13.2, 2.8, C(5)*H*$_B$), 3.06–3.13 (2H, m, C(3)*H*, C(4)*H*), 7.07–7.25 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.7 (C*Me*$_3$), 38.9 (*C*(2)), 42.2 (*C*(5)), 48.1 (*C*(3)), 56.3 (*C*(4)), 126.2, 126.7, 128.1, 128.4, 128.7, 129.1 (*o*,*m*,*p*-*Ph*), 139.3, 140.5 (*i*-*Ph*), 171.5 (*C*(1)); *m*/*z* (ESI^+) 348 ($[M+Na]^+$, 5%), 326 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{21}H_{28}NO_2^+$ ($[M+H]^+$) requires 326.2115; found 326.2111.

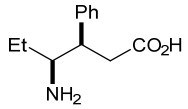
(3*R*,4*S*)-3-Phenyl-4-aminopentanoic acid 475



TFA (0.9 mL) was added to a stirred solution of (3*R*,4*S*)-**471** (200 mg, 0.80 mmol, >99:1 dr) in CH_2Cl_2 (1.9 mL) at rt, and the resultant mixture was stirred at rt for 16 h. Satd aq $NaHCO_3$

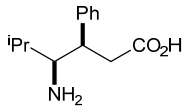
(10 mL) and CH_2Cl_2 (10 mL) were then added and the aqueous layer was extracted with CH_2Cl_2 (10 mL). The aqueous layer was then concentrated *in vacuo*, following which the residue was dissolved in 6.0 M aq HCl (25 mL) and the resultant solution was stirred at rt for 30 min, then concentrated *in vacuo*. The residue was dissolved in H_2O (4 mL) and purified on DOWEX 50WX8 ion exchange resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) to give (3*R*,4*S*)-**475** as a white solid (131 mg, 85%, >99:1 dr); mp 162–164 °C; $[\alpha]_D^{20}$ −13.5 (*c* 0.6 in H_2O); ν_{max} (ATR) 3031 (O–H, N–H), 2737 (C–H), 1549 (C=O), 1385, 698; δ_H (400 MHz, D_2O) 1.23 (3H, d, *J* 6.6, C(5)H_3), 2.38 (1H, dd, *J* 14.5, 10.0, C(2)H_A), 2.59 (1H, dd, *J* 14.5, 5.3, C(2)H_B), 3.03 (1H, app td, *J* 10.0, 5.3, C(3)*H*), 3.36–3.43 (1H, m, C(4)*H*), 7.18–7.23 (3H, m, *Ph*), 7.26–7.30 (2H, m, *Ph*); δ_C (100 MHz, D_2O) 16.2 (*C*(5)), 40.4 (*C*(2)), 47.0 (*C*(3)), 52.2 (*C*(4)), 127.9, 128.2, 129.2 (*o*,*m*,*p*-*Ph*), 139.1 (*i*-*Ph*), 179.7 (*C*(1)); *m*/*z* (ESI^+) 216 ($[M+Na]^+$, 5%), 194 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{11}H_{16}NO_2^+$ ($[M+H]^+$) requires 194.1176; found 194.1173.

(3*R*,4*S*)-3-Phenyl-4-aminohexanoic acid 476



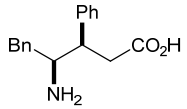
TFA (1.0 mL) was added to a stirred solution of (3*R*,4*S*)-**472** (220 mg, 0.84 mmol, >99:1 dr) in CH_2Cl_2 (2.0 mL) at rt, and the resultant mixture was stirred at rt for 16 h. Satd aq $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL) were then added and the aqueous layer was extracted with CH_2Cl_2 (10 mL). The aqueous layer was then concentrated *in vacuo*, following which the residue was dissolved in 6.0 M aq HCl (25 mL) and the resultant solution was stirred at rt for 30 min, then concentrated *in vacuo*. The residue was dissolved in H_2O (4 mL) and purified on DOWEX 50WX8 ion exchange resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) to give (3*R*,4*S*)-**476** as a white solid (117 mg, 68%, >99:1 dr); mp 144–146 °C; $[\alpha]_D^{20}$ −10.5 (*c* 0.6 in H_2O); ν_{max} (ATR) 3030 (O–H, N–H), 2819 (C–H), 1550 (C=O), 1394, 696; δ_H (400 MHz, D_2O) 0.92 (3H, t, *J* 7.5, C(6)H_3), 1.60 (1H, app dquintet, *J* 14.9, 7.5, C(5)H_A), 1.76 (1H, dqd, *J* 14.9, 7.5, 4.5, C(5)H_B), 2.45 (1H, dd, *J* 14.6, 10.0, C(2)H_A), 2.62 (1H, dd, *J* 14.6, 5.3, C(2)H_B), 3.19 (1H, app td, *J* 10.0, 5.3, C(3)*H*), 3.36 (1H, td, *J* 7.5, 4.5, C(4)*H*), 7.22–7.27 (3H, m, *Ph*), 7.31–7.34 (2H, m, *Ph*); δ_C (100 MHz, D_2O) 8.2 (*C*(6)), 23.0 (*C*(5)), 40.3 (*C*(2)), 44.4 (*C*(3)), 57.2 (*C*(4)), 128.0, 128.4, 129.2 (*o*,*m*,*p*-*Ph*), 138.8 (*i*-*Ph*), 179.6 (*C*(1)); *m*/*z* (ESI^+) 208 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{12}H_{18}NO_2^+$ ($[M+H]^+$) requires 208.1332; found 208.1329.

(3*R*,4*S*)-3-Phenyl-4-amino-5-methylhexanoic acid 477



TFA (0.4 mL) was added to a stirred solution of (3*R*,4*S*)-**473** (85 mg, 0.39 mmol, >99:1 dr) in CH_2Cl_2 (0.8 mL) at rt, and the resultant mixture was stirred at rt for 16 h. Satd aq $NaHCO_3$ (5 mL) and CH_2Cl_2 (5 mL) were then added and the aqueous layer was extracted with CH_2Cl_2 (5 mL). The aqueous layer was then concentrated *in vacuo*, following which the residue was dissolved in 6.0 M aq HCl (25 mL) and the resultant solution was stirred at rt for 30 min, then concentrated *in vacuo*. The residue was dissolved in H_2O (2 mL) and purified on DOWEX 50WX8 ion exchange resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) to give (3*R*,4*S*)-**477** as a white solid (68 mg, quant, >99:1 dr); mp 155–156 °C; $[\alpha]_D^{20}$ −23.6 (*c* 0.5 in 1.0 M aq HCl); ν_{max} (ATR) 3030 (O–H, N–H), 2876 (C–H), 1553 (C=O), 1391, 700; δ_H (500 MHz, D_2O) 0.96 (3H, d, *J* 6.9, C(5)*Me*$_A$), 1.07 (3H, d, *J* 6.9, C(5)*Me*$_B$), 2.18 (1H, td, *J* 6.9, 3.9, C(5)*H*), 2.50 (1H, dd, *J* 14.3, 9.9, C(2)*H*$_A$), 2.72 (1H, dd, *J* 14.3, 5.1, C(2)*H*$_B$), 3.29 (1H, app td, *J* 9.9, 5.1, C(3)*H*), 3.39 (1H, dd, *J* 9.9, 3.9, C(4)*H*), 7.29–7.33 (3H, m, *Ph*), 7.36–7.40 (2H, m, *Ph*); δ_C (100 MHz, D_2O) 14.4 (C(5)*Me*$_A$), 19.4 (C(5)*Me*$_B$), 27.0 (*C*(5)), 40.7 (*C*(2)), 43.5 (*C*(3)), 61.5 (*C*(4)), 128.1, 128.6, 129.3 (*o,m,p-Ph*), 138.8 (*i-Ph*), 179.2 (*C*(1)); *m*/*z* (ESI$^+$) 244 ([M+Na]$^+$, 14%), 222 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{19}NNaO_2^+$ ([M+Na]$^+$) requires 244.1308; found 244.1297.

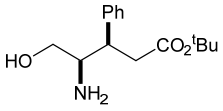
(3*R*,4*S*)-3,5-Diphenyl-4-aminopentanoic acid 478



TFA (0.9 mL) was added to a stirred solution of (3*R*,4*S*)-**474** (200 mg, 0.61 mmol, >99:1 dr) in CH_2Cl_2 (1.9 mL) at rt, and the resultant mixture was stirred at rt for 16 h. Satd aq $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL) were then added and the aqueous layer was extracted with CH_2Cl_2 (10 mL). The aqueous layer was then concentrated *in vacuo*, following which the residue was dissolved in 6.0 M aq HCl (25 mL) and the resultant solution was stirred at rt for 30 min, then concentrated *in vacuo*. The residue was dissolved in H_2O (4 mL) and purified on DOWEX 50WX8 ion exchange resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) to give (3*R*,4*S*)-**478** as a white solid (133 mg, 80%, >99:1 dr); mp 187–188 °C; $[\alpha]_D^{20}$ −30.3 (*c* 0.6 in H_2O); ν_{max} (ATR) 3031 (O–H, N–H), 2851 (C–H), 1545 (C=O), 1393, 699; δ_H (500 MHz, D_2O) 2.58–2.63 (1H, m, C(2)*H*$_A$, C(5)*H*$_A$), 2.79 (1H, dd, *J* 14.7, 5.4,

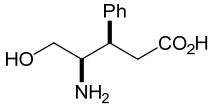
C(2)H_B), 3.15 (1H, dd, *J* 14.3, 4.0, C(5)H_B), 3.18–3.23 (1H, m, C(3)*H*), 3.53–3.57 (1H, m, C(4)*H*), 7.22–7.36 (10H, m, *Ph*); δ_C (125 MHz, D_2O) 37.7 (*C*(5)), 40.3 (*C*(2)), 46.6 (*C*(3)), 57.0 (*C*(4)), 127.2, 127.6, 128.6, 128.9, 129.0, 129.4 (*o*,*m*,*p*-*Ph*), 137.0, 139.5 (*i*-*Ph*), 180.2 (*C*(1)); *m*/*z* (ESI^+) 270 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{17}H_{20}NO_2^+$ ($[M+H]^+$) requires 270.1489; found 270.1488.

***tert*-Butyl (*R*,*R*)-3-phenyl-4-amino-5-hydroxypentanoate 479**



$Pd(OH)_2$/C (306 mg, 50% w/w by substrate) was added to a degassed solution of (*R*,*R*)-**432** (613 mg, 1.14 mmol, >99:1 dr) in MeOH (45 mL) at rt. The resultant suspension was stirred vigorously under H_2 (1 atm) at rt for 24 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (25 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (25 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give (*R*,*R*)-**479** as a colourless oil (303 mg, quant, >99:1 dr); $[\alpha]_D^{20}$ −25.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3360 (O–H, N–H), 2977 (C–H), 1722 (C=O), 1145, 702; δ_H (400 MHz, $CDCl_3$) 1.18 (9H, s, C*Me*$_3$), 1.91 (2H, br s, NH_2), 2.49 (1H, dd, *J* 15.1, 8.8, C(2)H_A), 2.64 (1H, dd, *J* 15.1, 6.4, C(2)H_B), 2.87–2.92 (1H, m, C(4)*H*), 3.02 (1H, app q, *J* 7.4, C(3)*H*), 3.27–3.31 (1H, m, C(5)H_A), 3.57–3.60 (1H, m, C(5)H_B), 7.12–7.17 (3H, m, *Ph*), 7.21–7.25 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.8 (C*Me*$_3$), 39.0 (*C*(2)), 45.6 (*C*(3)), 56.7 (*C*(4)), 64.5 (*C*(5)), 127.0, 128.5, 128.6 (*o*,*m*,*p*-*Ph*), 140.8 (*i*-*Ph*), 171.6 (*C*(1)); *m*/*z* (ESI^+) 266 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{15}H_{24}NO_3^+$ ($[M+H]^+$) requires 266.1751; found 266.1748.

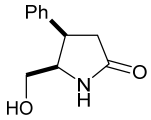
(*R*,*R*)-3-Phenyl-4-amino-5-hydroxypentanoic acid 481



TFA (0.2 mL) was added to a stirred solution of (*R*,*R*)-**479** (46 mg, 0.17 mmol, >99:1 dr) in CH_2Cl_2 (0.8 mL) at rt, and the resultant mixture was stirred at rt for 16 h. An aliquot of the reaction mixture was then concentrated *in vacuo* to give (*R*,*R*)-**480**·TFA as a colourless oil; ν_{max} (ATR) 3406 (O–H, N–H), 2928 (C–H), 1667 (C=O), 1182, 1131, 702; δ_H (500 MHz, D_2O) 2.68 (1H, dd, *J* 15.6, 10.3, C(2)H_A), 2.83 (1H, dd, *J* 15.6, 4.7, C(2)H_B), 3.27 (1H, app td, *J* 10.3, 4.7, C(3)*H*), 3.52 (1H, ddd, *J* 10.3, 6.0, 3.4, C(4)*H*), 3.70 (1H, dd, *J* 12.6, 6.0,

C(5)H_A), 3.85 (1H, dd, *J* 12.6, 3.4, C(5)H_B), 7.23–7.33 (5H, m, *Ph*); δ_C (125 MHz, D_2O) 36.9 (*C*(2)), 41.2 (*C*(3)), 56.6 (*C*(4)), 59.2 (*C*(5)), 128.3, 128.5, 129.4 (*o*,*m*,*p*-*Ph*), 137.4 (*i*-*Ph*), 175.3 (*C*(1)); *m*/*z* (ESI$^+$) 210 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{11}H_{16}NO_3^+$ ([M+H]$^+$) requires 210.1125; found 210.1124. Satd aq $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL) were then added to the residue and the aqueous layer was extracted with CH_2Cl_2 (10 mL). The aqueous layer was then concentrated *in vacuo*, following which the residue was dissolved in 6.0 M aq HCl (25 mL) and the resultant solution was stirred at rt for 30 min, then concentrated *in vacuo*. The residue was dissolved in H_2O (4 mL) and purified on DOWEX 50WX8 ion exchange resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) to give a 91:9 mixture of (*R*,*R*)-**481** and (*R*,*R*)-**482**, respectively, as a white solid (22 mg). Data for (*R*,*R*)-**481**: δ_H (400 MHz, D_2O) 2.49 (1H, dd, *J* 14.6, 10.0, C(2)H_A), 2.68 (1H, dd, *J* 14.6, 5.3, C(2)H_B), 3.25 (1H, app td, *J* 10.0, 5.3, C(3)*H*), 3.52 (1H, ddd, *J* 10.0, 6.3, 3.4, C(4)*H*), 3.74 (1H, dd, *J* 12.7, 6.3, C(5)H_A), 3.89 (1H, dd, *J* 12.7, 3.4, C(5)H_B), 7.26–7.38 (5H, m, *Ph*); δ_C (125 MHz, D_2O) 40.3 (*C*(2)), 42.3 (*C*(3)), 57.2 (*C*(4)), 59.4 (*C*(5)), 128.2, 128.3, 129.3 (*o*,*m*,*p*-*Ph*), 138.5 (*i*-*Ph*), 179.1 (*C*(1)). Data for mixture: ν_{max} (ATR) 3330, 3120 (O–H, N–H), 2933 (C–H), 1665 (C=O), 702; *m*/*z* (ESI$^+$) 210 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{11}H_{16}NO_3^+$ ([M+H]$^+$) requires 210.1125; found 210.1122.

(*R*,*R*)-Phenyl-5-(hydroxymethyl)pyrrolidin-2-one 482



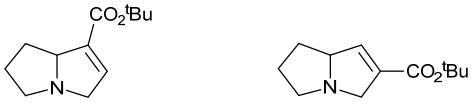
Step 1: A solution of (*R*,*R*)-**479** (30 mg, 0.11 mmol, >99:1 dr) in 1.25 M HCl/MeOH (1 mL) was heated at reflux for 16 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo* to give (*R*,*R*)-**483**·HCl as a white solid (29 mg, quant, >99:1 dr); mp 164–166 °C; $[\alpha]_D^{20}$ −3.39 (*c* 1.0 in MeOH); ν_{max} (ATR) 3383 (O–H, N–H), 2927, (C–H), 1732 (C=O), 698; δ_H (400 MHz, MeOD) 2.84 (1H, dd, *J* 15.7, 9.8, C(2)H_A), 2.97 (1H, dd, *J* 15.7, 4.9, C(2)H_B), 3.50–3.56 (1H, m, C(3)*H*), 3.53 (3H, s, O*Me*), 3.60 (1H, ddd, *J* 8.7, 5.4, 3.4, C(4)*H*), 3.79 (1H, dd, *J* 11.9, 5.4, C(5)H_A), 3.91 (1H, dd, *J* 11.9, 3.4, C(5)H_B), 7.33–7.44 (5H, m, *Ph*); δ_C (100 MHz, MeOD) 37.8 (*C*(2)), 43.0 (*C*(3)), 52.3 (O*Me*), 58.1 (*C*(4)), 60.6 (*C*(5)), 129.4, 129.7, 130.4 (*o*,*m*,*p*-*Ph*), 139.7 (*i*-*Ph*), 173.4 (*C*(1)); *m*/*z* (ESI$^+$) 224 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{18}NO_3^+$ ([M+H]$^+$) requires 224.1281; found 224.1278.

Step 2: K_2CO_3 (63 mg, 0.45 mmol) was added to a stirred solution of (*R*,*R*)-**483**·HCl (29 mg, 0.11 mmol, >99:1 dr) in PhMe (3 mL) and the resultant suspension was heated at reflux for

16 h. The reaction mixture was allowed to cool to rt and then filtered through Celite® (eluent PhMe/MeOH, 75:25 v/v) and concentrated *in vacuo* to give (*R*,*R*)-**482** as a white solid (22 mg, quant, >99:1 dr); mp 136–138 °C; $[\alpha]_D^{20}$ −138.7 (*c* 1.1 in MeOH); ν_{max} (ATR) 3438, 3334 (N–H, O–H), 2934, (C–H), 1677 (C=O), 1641 (N–H), 1046, 703; δ_H (400 MHz, MeOH-d_4) 2.50 (1H, dd, *J* 16.6, 8.6, C(3)H_A), 2.69 (1H, dd, *J* 16.6, 8.6, C(3)H_B), 3.02 (1H, dd, *J* 11.3, 7.2, CH_AH$_B$OH), 3.11 (1H, dd, *J* 11.3, 3.6, CH$_A$$H_B$OH), 3.76 (1H, app q, *J* 8.6, C(4)*H*), 3.85 (1H, app td, *J* 7.2, 3.6, C(5)*H*), 7.13–7.25 (5H, m, *Ph*); δ_C (100 MHz, MeOH-d_4) 37.2 (*C*(3)), 43.9 (*C*(4)), 61.3 (*C*(5)), 63.6 (*C*H$_2$OH), 128.3, 129.2, 129.7 (*o*,*m*,*p*-*Ph*), 139.9 (*i*-*Ph*), 180.7 (*C*(2)); δ_H (500 MHz, D$_2$O) 2.63 (1H, dd, *J* 17.0, 8.7, C(3)H_A), 2.80 (1H, dd, *J* 17.0, 9.1, C(3)H_B), 3.13 (1H, dd, *J* 11.8, 7.1, CH_AH$_B$OH), 3.22 (1H, dd, *J* 11.8, 3.8, CH$_A$$H_B$OH), 3.90 (1H, app q, *J* 8.7, C(4)*H*), 4.01 (1H, app td, *J* 7.1, 3.8, C(5)*H*), 7.25–7.28 (3H, m, *Ph*), 7.32–7.35 (2H, m, *Ph*); δ_C (125 MHz, D$_2$O) 35.3 (*C*(3)), 41.7 (*C*(4)), 59.5 (*C*(5)), 61.6 (*C*H$_2$OH), 127.3, 127.9, 128.6 (*o*,*m*,*p*-*Ph*), 138.1 (*i*-*Ph*), 181.0 (*C*(2)); *m*/*z* (ESI$^+$) 192 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{11}H_{14}NO_2^+$ ([M+H]$^+$) requires 192.1019; found 192.1017.

6.5. Experimental for Chapter 5

tert-Butyl (2,3,5,7a)-tetrahydro-1*H*-pyrrolizine-7-carboxylate 507 and *tert*-butyl (2,3,5,7a)-tetrahydro-1*H*-pyrrolizine-6-carboxylate 508

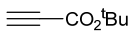


507 **508**

(*RS*)-Proline (*RS*)-**422** (183 mg, 1.59 mmol) and paraformaldehyde (48 mg, 1.59 mmol) were added sequentially to a stirred solution of **509** (100 mg, 0.79 mmol) in PhMe (20 mL) at rt and the resultant mixture was stirred at reflux for 3 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo* to give a 69:31 mixture of **507** and **508**. Purification *via* flash column chromatography (gradient elution, 2% MeOH in EtOAc) gave a 69:31 mixture of **507** and **508** as a yellow oil (145 mg, 87%); Data for major regioisomer: δ_H (400 MHz, $CDCl_3$) 1.42 (9H, s, C*Me*$_3$), 1.48–1.58 (1H, m, C(1)H_A), 1.65–1.72 (2H, m, C(2)H_2), 2.04–2.12 (1H, m, C(1)H_B), 2.39–2.45 (1H, m, C(3)H_A), 3.04 (1H, dt, *J* 9.7, 5.0, C(3)H_B), 3.37–3.43 (1H, m, C(5)H_A), 3.87–3.94 (1H, m, C(5)H_B), 4.21–4.29 (1H, m, C(7a)*H*), 6.50–6.52 (1H, m); δ_C (100 MHz, $CDCl_3$) 25.7 (*C*(2)), 28.1 (C*Me*$_3$), 31.3 (*C*(1)), 56.9 (*C*(3)), 61.9 (*C*(5)), 70.3 (*C*(7a)), 80.6 (*C*Me$_3$), 137.9, 141.7, 163.2 (*C*O$_2$^{t}Bu). Data for

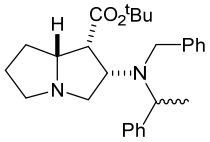
minor regioisomer: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.42 (9H, s, C*Me*$_3$), 1.92–2.00 (1H, m, C(1)*H*$_A$), 2.45–2.49 (1H, m, C(3)*H*$_A$), 3.43–3.48 (1H, m, C(5)*H*$_A$); δ_C (100 MHz, $CDCl_3$) [selected peaks] 25.5 (*C*(2)), 28.1 (C*Me*$_3$), 30.4 (*C*(1)), 56.9 (*C*(3)), 60.8 (*C*(5)), 71.8 (*C*(7a)), 80.6 (*C*Me$_3$), 134.2, 138.5, 163.3 (*C*O$_2$^{t}Bu). Data for mixture: ν_{max} (ATR) 2975 (C–H), 1693 (C=O), 1151, 712; *m*/*z* (ESI$^+$) 210 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{20}NO_2^+$ ([M+H]$^+$) requires 210.1489; found 210.1487.

***tert*-Butyl propiolate 509**



Conc. H_2SO_4 (1.0 mL) was added dropwise to a solution of propiolic acid (7.0 g, 101 mmol) in CH_2Cl_2 (70 mL) at 0 °C. Isobutylene (45 mL) was condensed at −78 °C and added dropwise. After stirring for 1 h at 0 °C the reaction mixture was allowed to warm to rt over 48 h. The pH of the reaction mixture was then adjusted to >7 by dropwise addition of cold 1.0 M aq NaOH. The organic layer was separated and extracted with 2.0 M aq NaOH (2 × 100 mL), and the combined organic extracts were then dried and concentrated *in vacuo* to give **509** as a pale yellow oil (12.2 g, 97%);[40] δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s, C*Me*$_3$), 2.69 (1H, s, C(3)*H*).

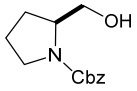
***tert*-Butyl (1*S*,2*S*,7a*R*,α*RS*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-(3,5,6,7)-tetrahydro-1*H*-pyrrolizine-1-carboxylate 512**



BuLi (2.0 M in hexanes, 0.37 mL, 0.74 mmol) was added dropwise to a solution of (*RS*)-**162** (162 mg, 0.77 mmol) in THF (3 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of a 69:31 mixture of **507** and **508** (100 mg, 0.48 mmol, >99:1 dr) in THF (2 mL) at −78 °C was then added dropwise *via* cannula, and the reaction mixture was stirred at −78 °C for 2 h. Satd aq NH_4Cl (2 mL) was then added and the reaction mixture was allowed to warm to rt, then concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 5% MeOH in EtOAc) gave **512** as a yellow oil (13 mg, 6%, 80% purity); ν_{max} (ATR) 2976 (C–H), 1720 (C=O), 1152, 701; δ_H (400 MHz, $CDCl_3$) 1.43 (3H, d, *J* 6.9, C(α)*Me*), 1.50 (9H, s, C*Me*$_3$), 1.68–1.76 (1H, m, C(7)*H*$_A$), 1.98–2.05 (1H, m, C(7)*H*$_B$), 2.06–2.11 (2H, m, C(6)*H*$_2$), 2.81–2.86 (1H, m, C(5)*H*$_A$), 3.08 (1H, dd, *J* 12.2, 10.4, C(3)*H*$_A$), 3.14 (1H, app t, *J* 6.3, C(1)*H*), 3.31 (1H, d, *J* 15.5, NC*H*$_A$H$_B$Ph), 3.38 (1H, dd,

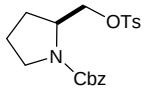
J 10.4, 6.3, C(3)H_B), 3.46–3.50 (1H, m, C(5)H_B), 3.65 (1H, dt, *J* 12.2, 6.3, C(2)*H*), 4.04 (1H, d, *J* 15.5, NCH_AH_BPh), 4.14 (1H, q, *J* 6.9, C(α)*H*), 4.20 (1H, app q, *J* 8.0, C(7a)*H*), 7.15–7.36 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.6 (C(α)*Me*), 26.0 (*C*(7)), 27.7 (*C*(6)), 28.2 (CMe_3), 49.9 (*C*(1)), 51.6 (NCH_2Ph), 53.8 (*C*(3)), 54.2 (*C*(5)), 58.2 (*C*(α)), 65.8 (*C*(7a)), 65.9 (*C*(2)), 82.9 (CMe_3), 127.2, 127.8, 127.9, 127.9, 128.4, 128.7 (*o*,*m*,*p*-*Ph*), 139.9, 140.5 (*i*-Ph), 170.3 ($CO_2{}^tBu$); *m*/*z* (ESI^+) 421 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{27}H_{37}N_2O_2^+$ ($[M+H]^+$) requires 421.2850; found 421.2842.

(*S*)-(*N*-Benzyloxycarbonyl)-2-(pyrrolidin-2'-yl)ethanol 517



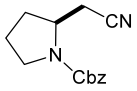
$BH_3{\cdot}Me_2S$ (32.0 mL, 337 mmol) was added dropwise to a solution of **513** (21.0 g, 84.2 mmol) in THF (105 mL) at 0 °C and the resultant mixture was allowed to warm to rt and stirred at rt for 16 h. Water (100 mL) was then added slowly and the resultant mixture was extracted with EtOAc (250 mL). The organic extract was washed sequentially with brine (2 × 250 mL), satd aq $NaHCO_3$ (250 mL) and water (250 mL), then dried and concentrated *in vacuo* to give **517** as a colourless oil (19.8 g, 94%);[41] $[\alpha]_D^{28}$ −37.9 (*c* 1.0 in $CHCl_3$); {lit.[41] $[\alpha]_D$ −41.8 (*c* 1.4 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.61–1.69 (1H, m, C(3')H_A), 1.74–1.91 (1H, m, C(4')H_2), 1.93–2.05 (1H, m, C(3')H_B), 3.37–3.43 (1H, m, C(5')H_A), 3.50–3.56 (1H, m, C(5')H_B), 3.63–3.67 (2H, m, C(2)H_2), 3.98–4.04 (0.8H, m, C(2')*H*), 3.90–3.96 (0.2H, m, C(2')*H*), 4.49 (1H, app t, *J* 5.1, O*H*), 5.13 (1H, d, *J* 12.4, OCH_AH_BPh), 5.17 (1H, d, *J* 12.4, OCH_AH_BPh), 7.32–7.38 (5H, m, *Ph*).

(*S*)-(*N*-Benzyloxycarbonyl)-2-(pyrrolidin-2'-yl)tosylate 518



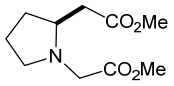
p-Toluenesulfonyl chloride (4.87 g, 25.5 mmol) was added to a solution of **517** (5.00 g, 21.3 mmol) in pyridine (27 mL) at 0 °C and the resultant mixture was allowed to warm to rt and stirred at rt for 16 h. The reaction mixture was then diluted with EtOAc (150 mL) and washed sequentially with 1.0 M aq HCl (3 × 200 mL), sat aq $NaHCO_3$ (3 × 200 mL) and brine (2 × 200 mL), then dried and concentrated *in vacuo* to give **518** as a colourless oil (7.46 g, 90%);[41] $[\alpha]_D^{28}$ −35.8 (*c* 1.0 in $CHCl_3$); {lit.[41] $[\alpha]_D$ −42.6 (*c* 1.02 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.80–1.88 (1H, m, C(4')H_A), 1.92–2.05 (3H, m, C(3')H_2, C(4')H_B), 2.44–2.45 (3H, m, $PhCH_3$), 3.34–3.47 (2H, m, C(5')H_2), 3.93–4.23 (3H, m, C(2')*H*, C(2)H_2), 4.99–5.13 (2H, m, OCH_2Ph), 7.29–7.39 (7H, m, *Ph*), 7.71–7.80 (2h, m, *Ph*).

(*S*)-(*N*-Benzyloxycarbonyl)-2-(pyrrolidin-2'-yl)acetonitrile 519



KCN (3.51 g, 53.9 mmol) was added to a solution of **518** (7.00 g, 18.0 mmol) in DMSO (105 mL) and the reaction mixture was then stirred at 90 °C for 6 h. The reaction mixture was then allowed to cool to rt, diluted with EtOAc (150 mL) and washed with NH_4Cl (150 mL). The organic extract was washed sequentially with $NaHCO_3$ (3 × 250 mL) and brine (250 mL), then dried and concentrated *in vacuo* to give **519** as a brown oil (4.23 g, 96%); $[\alpha]_D^{28}$ +17.8 (*c* 0.9 in $CHCl_3$); ν_{max} (ATR) 2971, 2884 (C–H), 2249 (C≡N), 1699 (C=O), 1411, 699; δ_H (400 MHz, $CDCl_3$) 1.86–1.99 (2H, m, C(3')H_A, C(4')H_A), 2.02–2.10 (1H, m, C(4')H_B), 2.15–2.24 (1H, m, C(3')H_B), 2.59 (0.4H, dd, *J* 16.7, 7.5, C(2)H_A), 2.66 (0.4H, dd, *J* 16.7, 3.6, C(2)H_B), 2.77 (0.6H, dd, *J* 16.6, 3.3, C(2)H_A), 2.88 (0.6H, dd, *J* 16.6, 7.2, C(2)H_B), 3.50–3.56 (2H, m, C(5')H_2), 4.06–4.12 (1H, m, C(2')*H*), 5.11–5.21 (2H, m, OCH_2Ph), 7.33–7.44 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) Rotamer 1: 22.0 (*C*(2)), 23.5 (*C*(4')), 30.2 (*C*(3')), 46.8 (*C*(5')), 54.1 (*C*(2')), 66.8 (O*C*H_2Ph), 117.7 (*C*(1)), 127.7, 127.9, 128.4 (*o*,*m*,*p*-*Ph*), 136.3 (*i*-Ph), 154.7 (*C*O_2Bn); Rotamer 2: 22.7 (*C*(4')), 23.0 (*C*(2)), 31.0 (*C*(3')), 47.1 (*C*(5')), 53.4 (*C*(2')), 67.1 (O*C*H_2Ph), 117.4 (*C*(1)), 128.0, 128.1, 128.5 (*o*,*m*,*p*-*Ph*), 136.1 (*i*-Ph), 154.2 (*C*O_2Bn); *m*/*z* (ESI$^+$) 267 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{16}N_2NaO_2^+$ ([M+Na]$^+$) requires 267.1104; found 267.1102.

(*S*)-*N*(1)-(2'-Methoxy-2'-oxoethyl)-2-(2''-methoxy-2''-oxoethyl)pyrrolidine 522



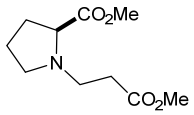
Step 1: A stirred solution of **519** (2.40 g, 9.82 mmol) in 9.0 M aq HCl (79 mL) was heated at reflux for 64 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo* to give **520**·HCl as a pale orange solid (1.25 g); mp 175–176 °C; $[\alpha]_D^{28}$ +32.0 (*c* 0.8 in MeOH); ν_{max} (ATR) 2950 (C–H, O–H, N–H), 1727 (C=O), 1393, 1166; δ_H (400 MHz, MeOH-d_4) 1.71–1.81 (1H, m, C(3')H_A), 1.98–2.08 (1H, m, C(4')H_A), 2.09–2.17 (1H, m, C(4')H_B), 2.26–2.34 (1H, m, C(3')H_B), 2.91 (2H, app d, *J* 7.0, C(2)H_2), 3.34–3.38 (2H, m, C(5')H_2), 3.90 (1H, dq, *J* 9.4, 7.0, C(2')*H*); δ_C (100 MHz, MeOH-d_4) 24.7 (*C*(4')), 31.3 (*C*(3')), 37.0 (*C*(2)), 46.7 (*C*(5')), 57.9 (*C*(2')), 173.7 (*C*(1)); *m*/*z* (ESI$^+$) 130 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_6H_{12}NO_2^+$ ([M+H]$^+$) requires 130.0863; found 130.0862.

Step 2: A solution of the residue (1.25 g) in 1.25 M HCl/MeOH (30 mL) was heated at reflux for 4 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo* to

521·HCl as an orange oil (1.30 g); $[\alpha]_D^{28}$ +27.5 (*c* 0.9 in MeOH); ν_{max} (ATR) 3410 (N–H), 2953 (C–H), 1734 (C=O), 1212; δ_H (400 MHz, MeOH-d_4) 1.72–1.82 (1H, m, C(3')H_A), 1.99–2.09 (1H, m, C(4')H_A), 2.09–2.18 (1H, m, C(4')H_B), 2.31 (1H, dtd, *J* 13.0, 7.2, 4.0, C(3')H_B), 2.98 (2H, d, *J* 7.1, C(2)H_2), 3.37–3.42 (2H, m, C(5')H_2), 3.77 (3H, s, O*Me*), 3.91–3.98 (1H, m, C(2')*H*); δ_C (100 MHz, MeOH-d_4) 24.6 (*C*(4')), 31.3 (*C*(3')), 37.0 (*C*(2)), 46.7 (*C*(5')), 52.9 (O*Me*), 57.7 (*C*(2')), 172.5 (*C*(1)); *m*/*z* (ESI^+) 144 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_7H_{14}NO_2^+$ ($[M+H]^+$) requires 144.1019; found 144.1018.

Step 3: A solution of the residue (1.30 g) in MeOH (100 mL) was treated sequentially with Na_2CO_3 (1.25 g, 11.8 mmol) and methyl bromoacetate (0.46 mL, 4.86 mmol), and the resultant mixture was heated at reflux for 16 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$/MeOH, 90:10) gave **522** as a pale yellow oil (1.28 g, 61% from **519**); $[\alpha]_D^{28}$ −42.6 (*c* 0.8 in $CHCl_3$); ν_{max} (ATR) 2953 (C–H), 1734 (C=O), 1197, 1168; δ_H (400 MHz, $CDCl_3$) 1.47–1.55 (1H, m, C(3)H_A), 1.65–1.81 (2H, m, C(4)H_2), 1.96–2.05 (1H, m, C(3)H_B), 2.26 (1H, dd, *J* 15.2, 8.3, C(1")H_A), 2.41 (1H, app q, *J* 8.8, C(5)H_A), 2.52 (1H, dd, *J* 15.2, 5.1, C(1")H_B), 2.94–3.01 (1H, m, C(2)*H*), 3.12 (1H, ddd, *J* 8.8, 7.5, 3.2, C(5)H_B), 3.20 (1H, d, *J* 16.8, C(1')H_A), 3.48 (1H, d, *J* 16.8, C(1')H_B), 3.59 (3H, s, O*Me*), 3.64 (3H, s, O*Me*); δ_C (100 MHz, $CDCl_3$) 22.5 (*C*(4)), 30.9 (*C*(3)), 39.3 (*C*(1")), 51.2, 51.3 (O*Me*), 53.8 (*C*(5)), 54.2 (*C*(1')), 59.6 (*C*(2)), 171.2, 172.3 (*C*O_2Me); *m*/*z* (ESI^+) 216 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{10}H_{18}NO_4^+$ ($[M+H]^+$) requires 216.1230; found 216.1230.

(*S*)-*N*(1)-(3'-Methoxy-3'-oxopropyl)-2-methoxycarbonylpyrrolidine 526

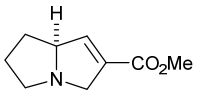


Step 1: A solution of (*RS*)-**422** (3.50 g, 30.4 mmol) in 1.25 M HCl/MeOH (50 mL) was heated at reflux for 16 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo* to **525**·HCl as pale yellow oil (5.00 g).

Step 2: Na_2CO_3 (3.84 g, 36.2 mmol) and methyl 3-bromopropionate (4.00 mL, 36.2 mmol) were added sequentially to a solution of **525**·HCl (5.00 g, 30.2 mmol) in MeOH (100 mL) and the resultant mixture was heated at reflux for 16 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo* to give **526** as a pale yellow oil (6.50 g, quant); $[\alpha]_D^{25}$ −74.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2953 (C–H), 1732 (C=O), 1194, 1169; δ_H (400 MHz, $CDCl_3$) 1.67–1.76 (1H, m, C(4)H_A), 1.78–1.88 (2H, m, C(3)H_A, C(4)H_B), 1.96–2.06

(1H, m, C(3)H_B), 2.31 (1H, app q, *J* 7.9, C(5)H_A), 2.42–2.46 (2H, m, C(2')H_2), 2.62–2.69 (1H, m, C(1')H_A), 2.90–2.97 (1H, m, C(1')H_B), 3.05 (1H, td, *J* 7.9, 3.3, C(5)H_B), 3.13 (1H, dd, *J* 8.8, 5.3, C(2)*H*), 3.57 (3H, s, O*Me*), 3.62 (3H, s, O*Me*); δ_C (100 MHz, $CDCl_3$) 23.0 (*C*(4)), 29.1 (*C*(3)), 33.3 (*C*(2')), 49.6 (*C*(1')), 51.3 (O*Me*), 51.5 (O*Me*), 53.0 (*C*(5)), 65.4 (*C*(2)), 172.3 (*C*O_2Me), 174.2 (*C*O_2Me); *m*/*z* (ESI^+) 216 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{10}H_{18}NO_4^+$ ($[M+H]^+$) requires 216.1230; found 216.1230.

Methyl (*S*)-(2,3,5,7a)-tetrahydro-1*H*-pyrrolizine-6-carboxylate 530



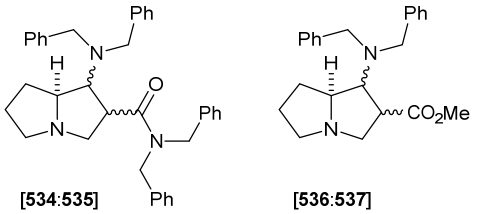
Step 1: KHMDS (0.5 M in PhMe, 74 mL, 37.2 mmol) was added dropwise to a stirred solution of **526** (4.00 g, 18.6 mmol) in PhMe (40 mL) at 0 °C, and the resultant mixture was stirred at 0 °C for 30 min. The reaction mixture was allowed to warm to rt and stirred at this temperature for 1.5 h. 1.0 M aq HCl (150 mL) was added the reaction mixture was stirred at rt for 0.5 h. The aqueous layer was basified with 1.0 M aq NH_4OH until the pH value reached 9, then concentrated *in vacuo* to give **528** as a brown oil; ν_{max} (ATR) 2952 (C–H), 1679 (C=O), 1451, 1268; *m*/*z* (ESI^+) 184 ($[M+H]^+$, 100%); δ_H (500 MHz, D_2O) 1.98–2.29 (4H, m, C(6)H_2, C(7)H_2), 3.25 (1H, dt, *J* 11.6, 7.0, C(5)H_A), 3.69 (3H, s, O*Me*), 3.71–3.75 (1H, m, C(5)H_B), 3.77 (1H, d, *J* 8.2, C(7a)*H*), 3.99 (1H, d, *J* 12.3, C(3)H_A), 4.50 (1H, d, *J* 12.3, C(3)H_B), 7.18 (1H, br s, O*H*); δ_C (100 MHz, D_2O) 24.4 (*C*(6)), 27.9 (*C*(7)), 51.0 (O*Me*), 56.4 (*C*(3)), 57.4 (*C*(5)), 71.3 (*C*(7a)), 84.5 (*C*(2)), 167.2 (*C*O_2Me), 177.2 (*C*(1)); HRMS (ESI^+) $C_9H_{14}NO_3^+$ ($[M+H]^+$) requires 184.0968; found 184.0967.

Step 2: $NaBH_4$ (1.40 g, 37.2 mmol) was added portionwise to a stirred solution of **528** in MeOH (160 mL) at 0 °C, and the resultant suspension was allowed to warm to rt and stirred at this temperature for 48 h. Water (150 mL) and Et_2O (150 mL) were then added and the aqueous layer was concentrated *in vacuo* to give **529** as a brown solid; Data for mixture: ν_{max} (ATR) 3130, 3049 (O–H), 2955 (C–H), 1734 (C=O), 1400, 1209; *m*/*z* (ESI^+) 186 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_9H_{16}NO_3^+$ ($[M+H]^+$) requires 186.1125; found 186.1126.

Step 3: A solution of **529** in CH_2Cl_2 (52 mL) was treated sequentially with Et_3N (14.9 mL, 107 mmol), DMAP (112 mg, 0.92 mmol) and MsCl (3.62 mL, 46.8 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, then allowed to warm to rt and stirred at this temperature for 3 h. Water (150 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were then dried and concentrated *in*

vacuo. Purification *via* flash column chromatography (eluent EtOAc/MeOH, 95:5) gave **530** as an orange oil (487 mg, 31% from **526**, >99:1 dr); $[\alpha]_D^{25}$ −1.2 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 2957 (C–H), 1725 (C=O), 1262, 1112; δ_H (500 MHz, $CDCl_3$) 1.59–1.66 (1H, m, C(1)H_A), 1.78–1.86 (2H, m, C(2)H_2), 2.07–2.14 (1H, m, C(1)H_B), 2.58–2.63 (1H, m, C(3)H_A), 3.30–3.34 (1H, m, C(3)H_B), 3.59–3.63 (1H, m, C(5)H_A), 3.70 (3H, s, O*Me*), 4.19–4.22 (1H, m, C(5)H_B), 4.59 (1H, m, C(7a)*H*), 6.61–6.62 (1H, m, C(7)*H*); δ_C (125 MHz, $CDCl_3$) 25.3 (*C*(2)), 30.1 (*C*(1)), 51.9 (O*Me*), 56.9 (*C*(3)), 60.2 (*C*(5)), 72.5 (*C*(7a)), 131.6 (*C*(6)), 141.2 (*C*(7)), 163.4 (*C*O_2Me); *m*/*z* (ESI^+) 168 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_9H_{14}NO_2^+$ ($[M+H]^+$) requires 168.1019; found 168.1020.

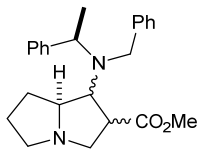
Methyl (*S*)-*N*,*N*-dibenzyl-1-(*N*,*N*-dibenzylamino)-(3,5,6,7)-tetrahydro-1*H*-pyrrolizine-2-carboxamide [**534**:**535**] **and methyl (*S*)-1-(*N*,*N*-dibenzylamino)-(3,5,6,7)-tetrahydro-1*H*-pyrrolizine-2-carboxylate** [**536**:**537**]



BuLi (2.0 M in hexanes, 0.46 mL, 0.93 mmol) was added dropwise to a solution of dibenzylamine (189 mg, 0.96 mmol) in THF (4 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of **530** (100 mg, 0.60 mmol, >99:1 dr) in THF (2 mL) at −78 °C was then added dropwise *via* cannula, and the reaction mixture was stirred at −78 °C for 2 h. Satd aq NH_4Cl (2 mL) was then added and the reaction mixture was allowed to warm to rt, then concentrated *in vacuo* to give a 46:5:34:15 mixture of **534**, **535**, **536** and **537**, respectively. Purification *via* flash column chromatography (gradient elution, 5% MeOH in EtOAc) gave a 67:7:18:8 mixture of **534**, **535**, **536** and **537**, respectively, as an orange oil (22 mg). Data for **534**: δ_H (500 MHz, $CDCl_3$) 1.10–1.15 (1H, m, C(7)H_A), 1.56–1.61 (1H, m, C(6)H_A), 1.67–1.74 (1H, m, C(6)H_B), 2.03–2.10 (1H, m, C(7)H_B), 2.21 (1H, td, *J* 9.8, 5.8, C(5)H_A), 2.78–2.84 (1H, m, C(3)H_A), 3.00 (1H, dt, *J* 10.4, 8.5, C(2)*H*), 3.17–3.21 (1H, m, C(5)H_B), 3.29 (1H, dd, *J* 8.5, 2.5, C(1)*H*), 3.31 (2H, d, *J* 13.2, N(C$H_A$$H_B$Ph)$_2$), 3.81 (1H, d, *J* 17.7, NC$H_A$$H_B$Ph), 3.86 (1H, d, *J* 14.7, NC$H_A$$H_B$Ph), 3.89 (2H, d, *J* 13.2, N(C$H_A$$H_B$Ph)$_2$), 3.92–3.97 (1H, m, C(3)H_B), 3.99–4.01 (1H, m, C(7a)*H*), 4.04 (1H, d, *J* 17.7, NC$H_A$$H_B$Ph), 5.36 (1H, d, *J* 14.7, NC$H_A$$H_B$Ph); δ_C (125 MHz, $CDCl_3$) [selected peaks] 26.1 (*C*(6)), 33.6 (*C*(7)), 43.6 (*C*(7)), 49.0, 49.4, 55.5, 55.5 (N*C*H_2Ph), 56.9 (*C*(5)), 58.3 (*C*(3)), 63.7 (*C*(7a)),

67.4 (*C*(1)), 126.0, 126.9, 128.1, 128.1, 128.2, 128.2, 128.5, 128.9, 129.4, 129.4, 129.5 (*o*,*m*,*p*-*Ph*), 136.5, 137.0, 139.3, 139.3 (*i*-Ph), 170.6 (*C*O). Data for **536**: δ_H (500 MHz, $CDCl_3$) [selected peaks] 1.40–1.46 (1H, m, C(6)H_A), 1.48–1.53 (1H, m, C(7)H_A), 1.88–1.94 (2H, m, C(6)H_B, C(7)H_B), 3.54–3.59 (2H, m, C(1)*H*, C(2)*H*), 3.68 (3H, s, O*Me*), 3.70–3.72 (1H, m, C(7a)*H*), 4.29 (1H, d, *J* 17.4, NCH_AH$_B$Ph), 4.42 (1H, d, *J* 14.6, NCH_AH$_B$Ph), 4.56 (1H, d, *J* 17.4, NCH$_A$$H_B$Ph), 4.84 (1H, d, *J* 14.6, NCH$_A$$H_B$Ph); δ_C (125 MHz, $CDCl_3$) [selected peaks] 30.4 (*C*(7)), 30.5 (*C*(6)), 44.2 (*C*(2)), 49.8 (N*C*H$_2$Ph), 50.4 (N*C*H$_2$Ph), 52.1 (CO_2*Me*), 65.4 (*C*(1)), 68.7 (*C*(7a)), 126.4, 127.1, 127.5, 127.7, 128.7, 129.2 (*o*,*m*,*p*-*Ph*), 136.5, 139.2 (*i*-Ph), 172.2 (*C*O). Data for mixture: ν_{max} (ATR) 2924 (C–H), 1732, 1647 (C=O), 749, 699; *m*/*z* (ESI$^+$) 365 ([M+H]$^+$, 24%), 530 ([M+H]$^+$, 76%); HRMS (ESI$^+$) $C_{36}H_{40}N_3O^+$ ([M+H]$^+$) requires 530.3166; found 530.3156.

Methyl (7a*S*,α*R*)-1-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-(3,5,6,7)-tetrahydro-1*H*-pyrrolizine-2-carboxylate 539 and 540

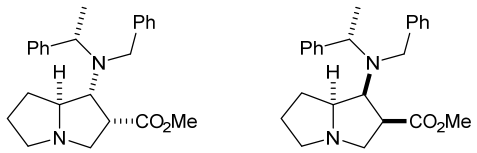


539 and **540**

BuLi (2.0 M in hexanes, 2.76 mL, 5.52 mmol) was added dropwise to a solution of (*R*)-**162** (758 mg, 3.59 mmol) in THF (2.5 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of **530** (100 mg, 0.60 mmol, >99:1 dr) in THF (1.3 mL) at −78 °C was then added dropwise *via* cannula, and the reaction mixture was stirred at −78 °C for 2 h. Satd aq NH_4Cl (2 mL) was then added and the reaction mixture was allowed to warm to rt, then concentrated *in vacuo* to give a 58:42 mixture of **539** and **540**, respectively. Purification *via* flash column chromatography (gradient elution, 5% MeOH in EtOAc) gave a 55:45 mixture of **539** and **540**, respectively, as a yellow oil (18 mg, 8%). Data for **539**: δ_H (400 MHz) [selected peaks] 1.29 (3H, d, *J* 6.9, C(α)Me), 1.67–1.72 (1H, m, C(7)H_A), 1.88–2.21 (2H, m, C(6)H_2), 2.21–2.26 (1H, m, C(7)H_B), 2.87–2.96 (2H, m, C(3)H_2), 3.48–3.56 (2H, m, C(1)*H*, C(2)*H*), 3.68 (3H, s, O*Me*), 4.00–4.06 (3H, m, C(α)*H*, NCH_2Ph), 4.09–4.16 (1H, m, C(7a)*H*); δ_C (100 MHz, $CDCl_3$) 19.3 (C(α)*Me*), 24.6 (*C*(6)), 29.3 (*C*(7)), 46.0 (*C*(2)), 50.5 (N*C*H$_2$Ph), 52.6 (O*Me*), 54.0 (*C*(3)), 56.6 (*C*(5)), 59.1 (*C*(α)), 66.0 (*C*(7a)), 67.8 (*C*(1)), 140.4, 143.6 (*i*-Ph), 171.3 (*C*O_2Me). Data for **540**: δ_H (400 MHz) [selected peaks] 1.32 (3H, d, *J* 6.9, C(α)*Me*), 1.80–1.86 (1H, m, C(7)H_A), 1.88–2.21 (1H, m, C(6)H_2), 2.30–2.36 (1H, m, C(7)H_B), 2.67–2.71 (1H, m, C(5)H_A), 2.73–2.79 (1H, m, C(5)H_B),

3.11–3.16 (1H, m, C(2)*H*), 3.48–3.56 (2H, m, C(1)*H*, C(3)H_A), 3.80 (3H, s, O*Me*), 3.86–4.00 (3H, m, NCH_2Ph, C(α)*H*), 4.44–4.49 (1H, m, C(7a)*H*); δ_C (100 MHz, $CDCl_3$) 16.1 (C(α)*Me*), 25.0 (*C*(6)), 30.5 (*C*(7)), 46.4 (*C*(2)), 51.0 (N*C*H_2Ph), 52.6 (O*Me*), 54.1 (*C*(3)), 56.6 (*C*(5)), 57.9 (*C*(α)), 65.1 (*C*(1)), 65.8 (*C*(7a)), 139.4, 142.4 (*i*-Ph), 169.9 (*C*O_2Me). Data for mixture: ν_{max} (ATR) 2960, 2926 (C–H), 1734 (C=O), 701; δ_H (400 MHz) [selected peaks] 7.25–7.54 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) [selected peaks] 127.2, 127.3, 127.4, 127.6, 127.6, 127.7, 127.9, 128.1, 128.5, 128.5, 128.6, 128.6 (*o*,*m*,*p*-*Ph*); *m*/*z* (ESI^+) 379 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{24}H_{31}N_2O_2^+$ ($[M+H]^+$) requires 379.2380; found 379.2375.

Methyl (1*R*,2*R*,7a*S*,α*S*)-1-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-(3,5,6,7)-tetrahydro-1*H*-pyrrolizine-2-carboxylate 532 and methyl (1*S*,2*S*,7a*S*,α*S*)-1-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-(3,5,6,7)-tetrahydro-1*H*-pyrrolizine-2-carboxylate 541

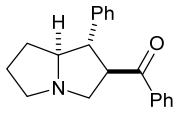


532 **541**

BuLi (2.0 M in hexanes, 2.76 mL, 5.52 mmol) was added dropwise to a solution of (*S*)-**162** (1.21 g, 5.71 mmol) in THF (4 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of **530** (159 mg, 0.95 mmol, >99:1 dr) in THF (2 mL) at −78 °C was then added dropwise *via* cannula, and the reaction mixture was stirred at −78 °C for 2 h. Satd aq NH_4Cl (2 mL) was then added and the reaction mixture was allowed to warm to rt, then concentrated *in vacuo* to give a 62:38 mixture of **532** and **541**, respectively. Purification *via* flash column chromatography (gradient elution, 5% MeOH in EtOAc) gave a 61:39 mixture of **532** and **541**, respectively, as a yellow oil (53 mg, 15%). Data for **532**: δ_H (500 MHz, $CDCl_3$) 1.23 (3H, d, *J* 6.7, C(α)*Me*), 1.62–1.70 (1H, m, C(7)H_A), 1.81 (1H, app dt, *J* 13.1, 6.5, C(6)H_A), 1.98 (1H, app dt, *J* 13.1, 6.5, C(6)H_B), 2.20 (1H, app dt, *J* 13.1, 6.5, C(7)H_B), 2.57–2.64 (1H, m, C(5)H_A), 2.75 (1H, dd, *J* 12.4, 7.2, C(3)H_A), 3.06 (1H, app q, *J* 7.2, C(2)*H*), 3.38 (1H, app t, *J* 7.2, C(1)*H*), 3.57–3.65 (1H, m, C(5)H_B), 3.68 (3H, s, O*Me*), 3.87 (1H, dd, *J* 12.4, 7.2, C(3)H_B), 3.95 (1H, q, *J* 6.7, C(α)*H*), 4.21–4.26 (1H, m, C(7a)*H*); δ_C (125 MHz, $CDCl_3$) 15.7 (C(α)*Me*), 25.2 (*C*(6)), 30.8 (*C*(7)), 46.6 (*C*(2)), 51.2 (N*C*H_2Ph), 52.3 (O*Me*), 55.0 (*C*(3)), 56.6 (*C*(5)), 57.7 (*C*(α)), 65.4 (*C*(1)), 65.6 (*C*(7a)), 127.7, 128.1, 128.3, 128.4, 128.4, 128.5 (*o*,*m*,*p*-*Ph*), 139.7, 142.6 (*i*-Ph), 170.5 (*C*O_2Me). Data for **541**: δ_H (500 MHz, $CDCl_3$) [selected peaks] 1.34 (3H, d, *J* 7.1, C(α)*Me*), 1.50–1.60 (2H, m, C(6)H_A, C(7)H_B), 1.69–1.76 (1H, m, C(6)H_B), 2.85 (1H, dd, *J* 12.7, 7.4, C(3)H_A), 3.34 (1H, app q, *J*

7.4, C(2)*H*), 3.53–3.57 (1H, m, C(1)*H*), 3.80 (3H, s, O*Me*); δ_C (125 MHz, $CDCl_3$) [selected peaks] 16.3 (C(α)*Me*), 24.7 (*C*(6)), 30.4 (*C*(7)), 47.7 (*C*(2)), 51.9 (N*C*H_2Ph), 52.4 (O*Me*), 55.2 (*C*(3)), 56.2 (*C*(α)), 56.6 (*C*(5)), 63.7 (*C*(1)), 65.5 (*C*(7a)), 127.2, 127.3, 127.4, 127.6, 128.0, 128.6 (*o*,*m*,*p*-*Ph*), 138.9, 141.1 (*i*-Ph), 170.3 (*C*O_2Me). Data for mixture: ν_{max} (ATR) 2963, 2926 (C–H), 1733 (C=O), 732, 700; *m*/*z* (ESI^+) 379 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{24}H_{31}N_2O_2^+$ ($[M+H]^+$) requires 379.2380; found 379.2370.

Phenyl [(1*S*,2*R*,7a*S*)-1-phenylhexahydro-1*H*-pyrrolizin-2-yl]methanone 544



Step 1: PhMgBr (1.0 M in THF, 9.75 mL, 9.75 mmol) was added dropwise to a stirred solution of **530** (163 mg, 0.97 mmol, >99:1 dr) in THF (3.5 mL) at −20 °C, and the resultant mixture was stirred at −20 °C for 4 h. Satd aq NH_4Cl (10 mL) was then added and the reaction mixture was allowed to warm to rt. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. The residue was then co-evaporated with 2.0 M HCl in Et_2O (3 × 10 mL) to give **544**·HCl in >95:5 dr. Purification *via* flash column chromatography (gradient elution, 5% MeOH in EtOAc) gave **544**·HCl as a pale yellow solid (108 mg, 34%, >99:1 dr); mp 58–60 °C; $[\alpha]_D^{25}$ +0.70 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2929 (C–H), 1677 (C=O), 1449, 701; δ_H (400 MHz, $CDCl_3$) 1.77–1.88 (1H, m, C(7)H_A), 1.98–2.22 (3H, m, C(7)H_B, C(6)H_2), 3.02–3.06 (1H, m, C(5)H_A), 3.10 (1H, app t, *J* 11.0, C(3)H_A), 3.34 (1H, app t, *J* 11.0, C(1)*H*), 3.44 (1H, ddd, *J* 11.4, 8.3, 6.5, C(5)H_B), 4.07 (1H, dd, *J* 11.0, 7.0, C(3)H_B), 4.36–4.41 (1H, m, C(7a)*H*), 4.57 (1H, app td, *J* 11.0, 7.0, C(2)*H*), 10–7.22 (4H, m, *Ph*), 7.25–7.27 (2H, m, *Ph*), 7.38–7.42 (2H, m, *Ph*), 7.65–7.68 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 24.7 (*C*(6)), 29.3 (*C*(7)), 53.9 (*C*(2)), 54.3 (*C*(5)), 54.7 (*C*(1)), 57.3 (*C*(3)), 72.6 (*C*(7a)), 127.7, 128.4, 128.5, 128.9, 133.8 (*o*,*m*,*p*-*Ph*), 135.5, 136.5 (*i*-Ph), 196.7 (*C*OPh); *m*/*z* (ESI^+) 292 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{22}NO^+$ ($[M+H]^+$) requires 292.1696; found 292.1690.

Step 2: A solution of **544**·HCl (45 mg, 0.14 mmol, >99:1 dr) in CH_2Cl_2 (5 mL) was washed with satd aq $NaHCO_3$ (5 mL) at rt for 30 min. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give **544** as a pale yellow solid (30 mg, 76%, >99:1 dr); $[\alpha]_D^{25}$ +1.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2924 (C–H), 1736 (C=O), 1449, 700; δ_H (400 MHz, $CDCl_3$) 1.69–1.75 (1H, m, C(7)H_A), 1.80–1.92 (2H, m, C(7)H_B, C(6)H_A), 1.94–2.04 (1H, m, C(6)H_B), 2.74–2.80 (1H, m,

C(5)H_A), 2.85 (1H, app t, *J* 10.3, C(3)H_A), 3.03–3.09 (1H, m, C(5)H_B), 3.34 (1H, app t, *J* 10.3, C(1)*H*), 3.72 (1H, dd, *J* 10.3, 7.7, C(3)H_B), 3.82–3.87 (1H, m, C(7a)*H*), 4.33 (1H, td, *J* 10.3, 7.7, C(2)*H*), 7.09–7.13 (1H, m, *Ph*), 7.17–7.24 (4H, m, *Ph*), 7.28–7.32 (2H, m, *Ph*), 7.41–7.45 (1H, m, *Ph*), 7.73–7.75 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.2 (*C*(6)), 30.3 (*C*(7)), 54.4 (*C*(1)), 54.9 (*C*(5)), 56.1 (*C*(2)), 58.8 (*C*(3)), 72.8 (*C*(7a)), 127.0, 127.8, 128.4, 128.6, 128.7, 133.4 (*o*,*m*,*p*-*Ph*), 136.5, 140.0 (*i*-Ph), 198.8 (*C*OPh); *m*/*z* (ESI^+) 292 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{22}NO^+$ ($[M+H]^+$) requires 292.1696; found 292.1697.

6.6. References and notes

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[28] C(4)H_2 signals are omitted due to unreliability of assignment resulting for the presence of excess Bu_2O.

[29] Aromatic carbon signals are omitted due to unreliability of assignment resulting for the presence of excess PhLi.

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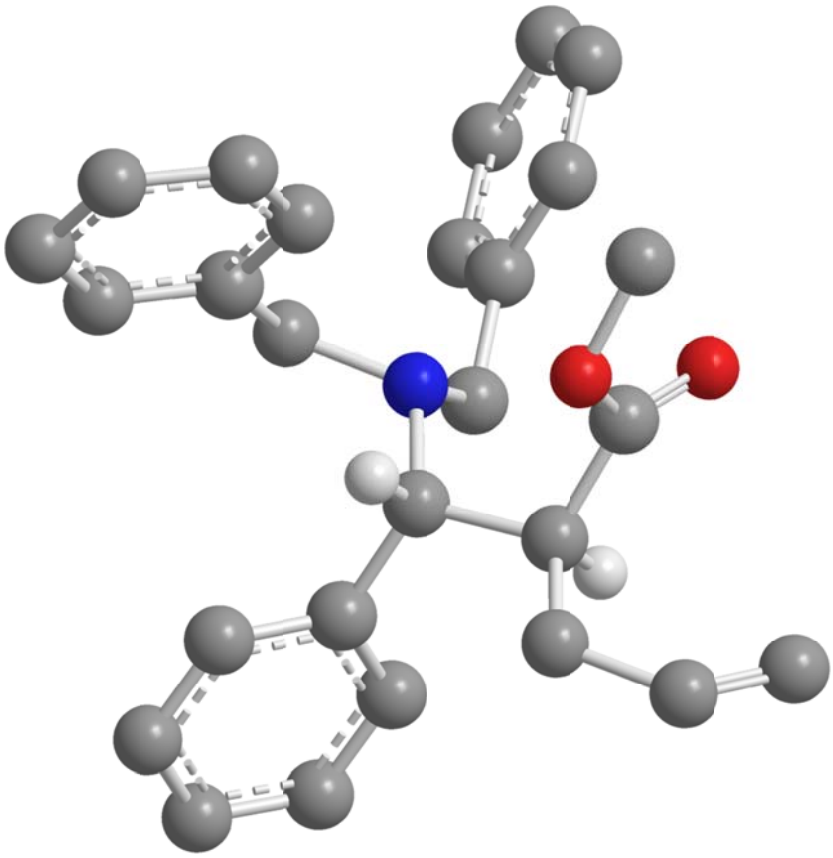
X-Ray crystal structure data for (*RS*,*SR*)-185

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 185

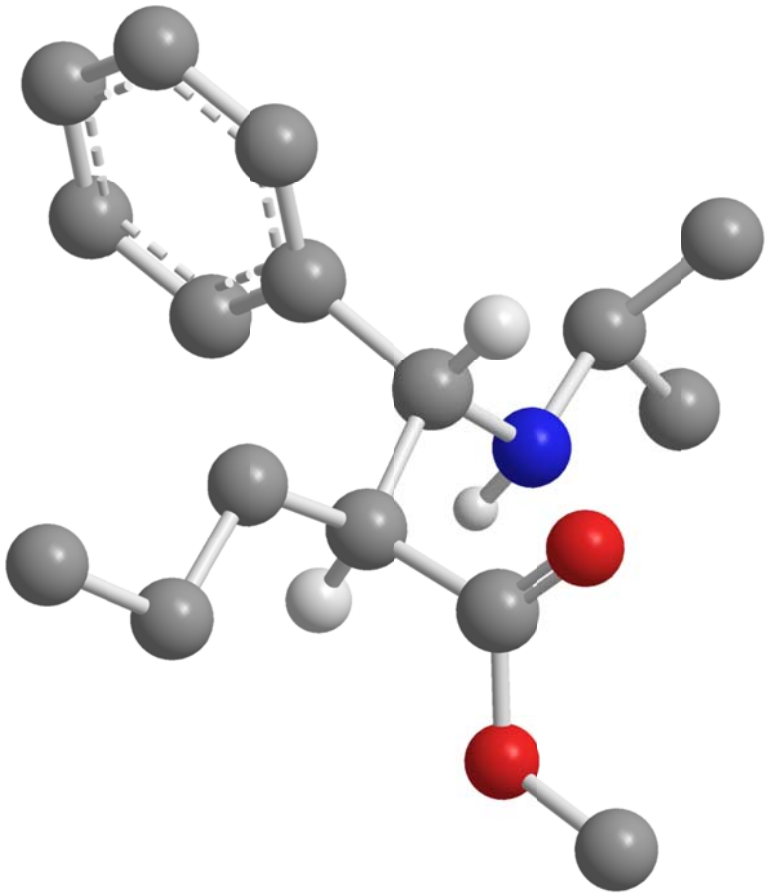
Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions.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

X-ray crystal structure data for **185** [$C_{27}H_{29}NO_2$]: M = 399.53, triclinic, space group $P\,\bar{1}$, a = 10.0503(2) Å, b = 10.9520(2) Å, c = 11.2054(3) Å, α = 74.3842(8)°, β = 68.6115(8)°, γ = 80.1552(12)°, V = 1102.40(4) Å^3, Z = 2, μ = 0.075 mm^{-1}, colourless block, crystal dimensions = 0.17 × 0.22 × 0.27 mm^3. A total of 5018 unique reflections were measured for $5 < \theta < 27$ and 3448 reflections were used in the refinement. The final parameters were wR_2 = 0.109 and R_1 = 0.053 [$I > -3.0\sigma(I)$]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

[1] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

X-Ray crystal structure data for (*RS*,*SR*)-191

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 191

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.[2]

X-ray crystal structure data for **191** [$C_{16}H_{25}NO_2$]: M = 263.38, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 8.66504(13) Å, b = 9.818(2) Å, c = 18.4067(4) Å, V = 1592.04(5) Å^3, Z = 4, μ = 0.562 mm^{-1}, colourless plate, crystal dimensions = 0.05 × 0.19 × 0.21 mm^3. A total of 7321 unique reflections were measured for $5 < \theta < 76$ and 7067 reflections were used in the refinement. The final parameters were wR_2 = 0.083 and R_1 = 0.034 [$I > -3.0\sigma(I)$], with Flack enantiopole = −0.02(13).[3] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

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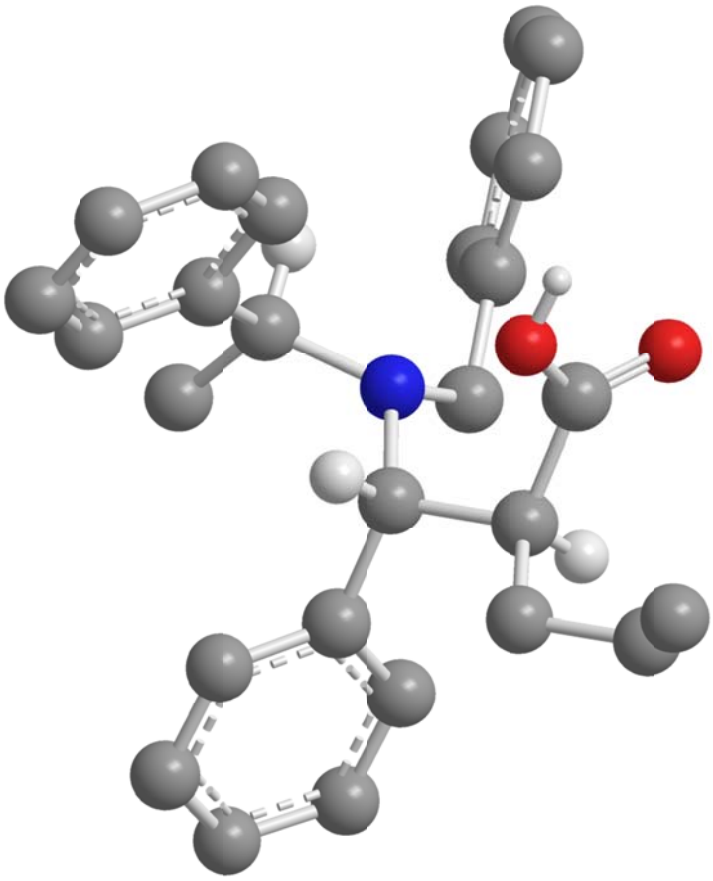
[2] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

[3] Flack, H. D.; Bernardinelli, G. *Acta. Crystallogr., Sect. A* **1999**, *55*, 908.

X-Ray crystal structure data for (2*S*,3*R*,α*S*)-194

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 194

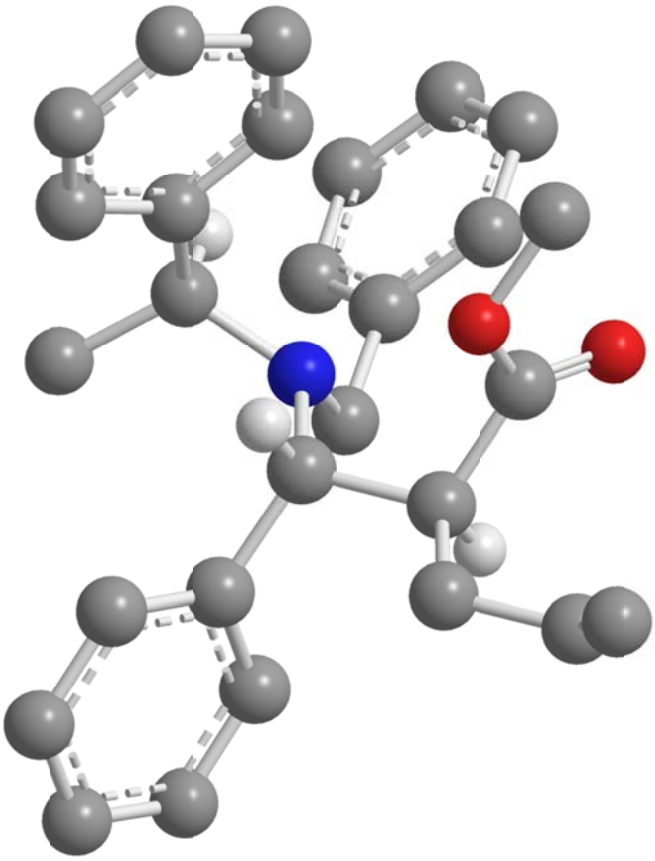
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[4]

X-ray crystal structure data for **194** [$C_{27}H_{29}NO_2$]: M = 399.53, trigonal, space group $P\ 3_1$, a = 11.2376(1) Å, c = 31.9939(3) Å, V = 3499.01(5) Å^3, Z = 6, μ = 0.553 mm^{-1}, colourless block, crystal dimensions = 0.23 × 0.24 × 0.27 mm^3. A total of 25381 unique reflections were measured for 5 < θ < 77 and 22493 reflections were used in the refinement. The final parameters were wR_2 = 0.172 and R_1 = 0.068 [I>−3.0σ(I)], with Flack enantiopole = 0.07(14).[5] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

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

X-Ray crystal structure data for (2*S*,3*R*,α*S*)-196

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 196

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.[6]

X-ray crystal structure data for **196** [$C_{28}H_{31}NO_2$]: M = 413.56, monoclinic, space group $P\,2_1$, a = 9.7215(3) Å, b = 13.5384(2) Å, c = 10.1187(3) Å, β = 116.959(3)°, V = 1187.05(6) Å^3, Z = 2, μ = 0.559 mm^{-1}, colourless block, crystal dimensions = 0.25 × 0.31 × 0.40 mm^3. A total of 10522 unique reflections were measured for 5 < θ < 77 and 9573 reflections were used in the refinement. The final parameters were wR_2 = 0.101 and R_1 = 0.038 [I>−3.0σ(I)], with Flack enantiopole = −0.02(15).[7] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

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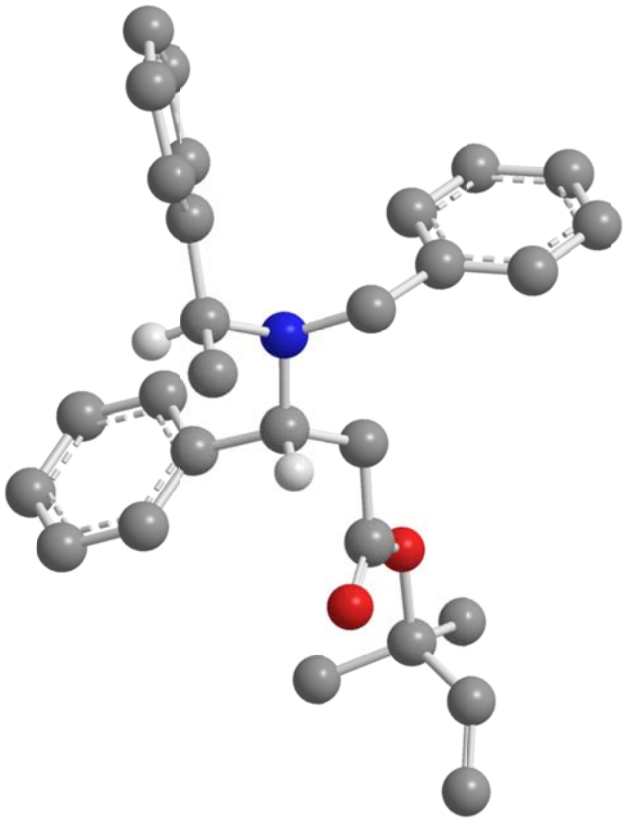
[6] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

[7] Flack, H. D.; Bernardinelli, G. *Acta. Crystallogr., Sect. A* **1999**, *55*, 908.

X-Ray crystal structure data for (3*R*,α*S*)-202

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 202

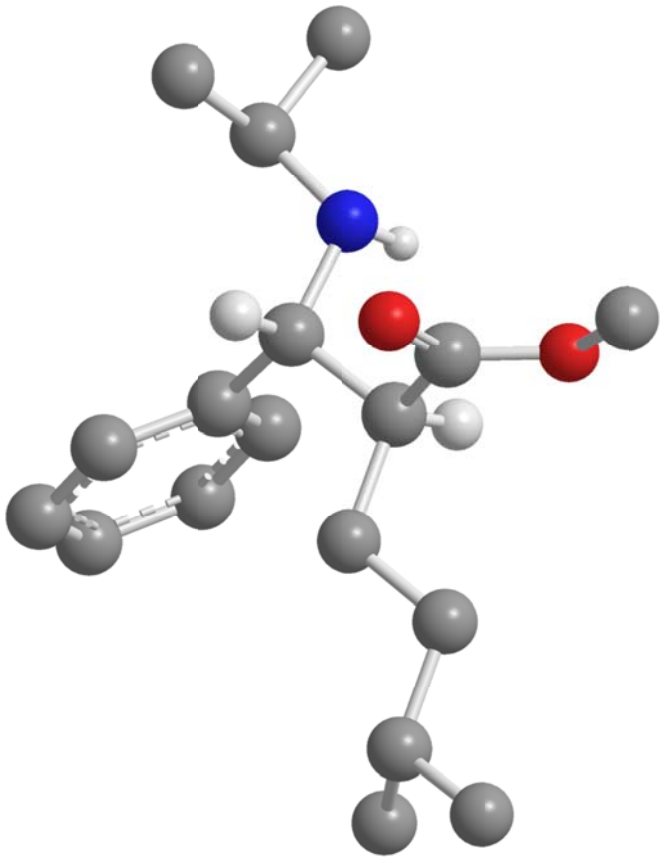
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[8]

X-ray crystal structure data for **202** [$C_{29}H_{33}NO_2$]: M = 427.59, monoclinic, space group $P\ 2_1$, a = 10.27494(11) Å, b = 10.27815(10) Å, c = 12.21513(16) Å, β = 107.2702(13)°, V = 1231.85(3) Å^3, Z = 2, μ = 0.554 mm^{-1}, colourless block, crystal dimensions = 0.15 × 0.18 × 0.19 mm^3. A total of 11386 unique reflections were measured for $5 < \theta < 77$ and 10142 reflections were used in the refinement. The final parameters were wR_2 = 0.076 and R_1 = 0.029 [I>−3.0σ(I)], with Flack enantiopole = −0.09(10).[9] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

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

X-Ray crystal structure data for (2*S*,3*R*)-208

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 208

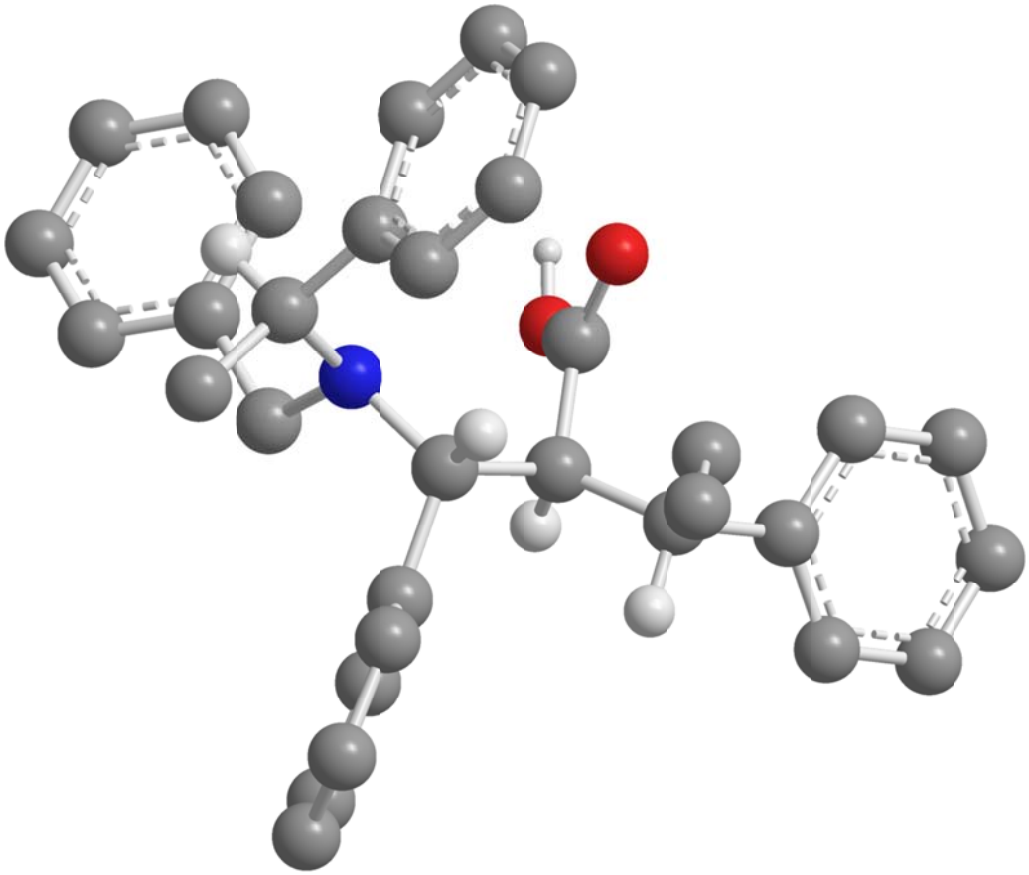
Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[10]

X-ray crystal structure data for **208** [$C_{18}H_{29}NO_2$]: M = 582.87, monoclinic, space group $P\,2_1$, a = 12.4852(2) Å, b = 9.9345(2) Å, c = 15.0329(3) Å, β = 100.0163(9)°, V = 1836.17(6) Å^3, Z = 4, μ = 0.067 mm^{-1}, colourless block, crystal dimensions = 0.27 × 0.33 × 0.38 mm^3. A total of 4416 unique reflections were measured for $5 < \theta < 27$ and 4002 reflections were used in the refinement. The final parameters were wR_2 = 0.101 and R_1 = 0.049 [$I > -3.0\sigma(I)$]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

[10] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

X-Ray crystal structure data for (2*S*,3*R*,1'*S*,α*S*)-222

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 222·½Me$_2$CO

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.[11]

X-ray crystal structure data for **222**·½Me$_2$CO [$C_{34.5}H_{36}NO_{2.5}$]: M = 504.67, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 12.3150(1) Å, b = 15.4817(2) Å, c = 29.8380(3) Å, V = 5687.45(10) Å^3, Z = 8, μ = 0.571 mm^{-1}, colourless plate, crystal dimensions = 0.15 × 0.21 × 0.26 mm^3. A total of 11951 unique reflections were measured for $3 < \theta < 77$ and 11907 reflections were used in the refinement. The final parameters were wR_2 = 0.118 and R_1 = 0.045 [I>–3.0σ(I)], with Flack enantiopole = 0.02(16).[12] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

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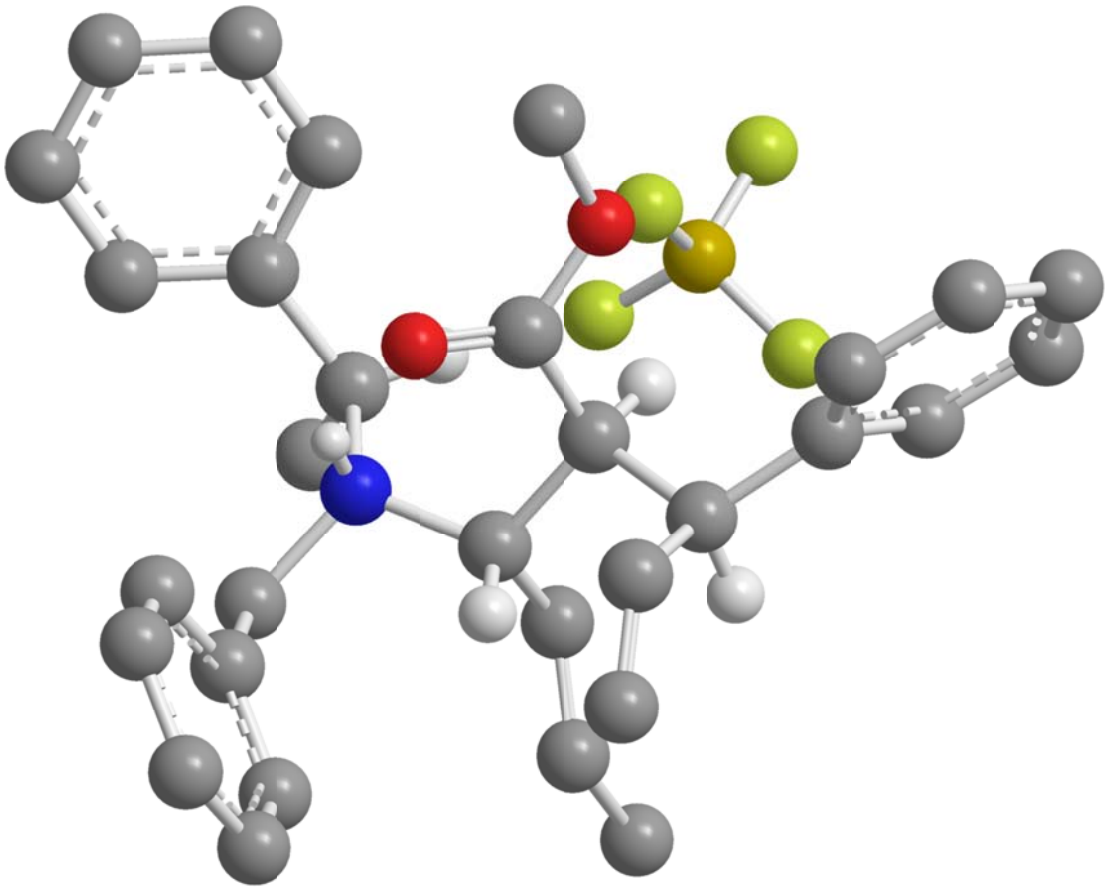
[11] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

[12] Flack, H. D.; Bernardinelli, G. *Acta. Crystallogr., Sect. A* **1999**, *55*, 908.

X-Ray crystal structure data for (*S*,*S*,*S*,*S*,*E*)-256·HBF_4

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 256·HBF_4

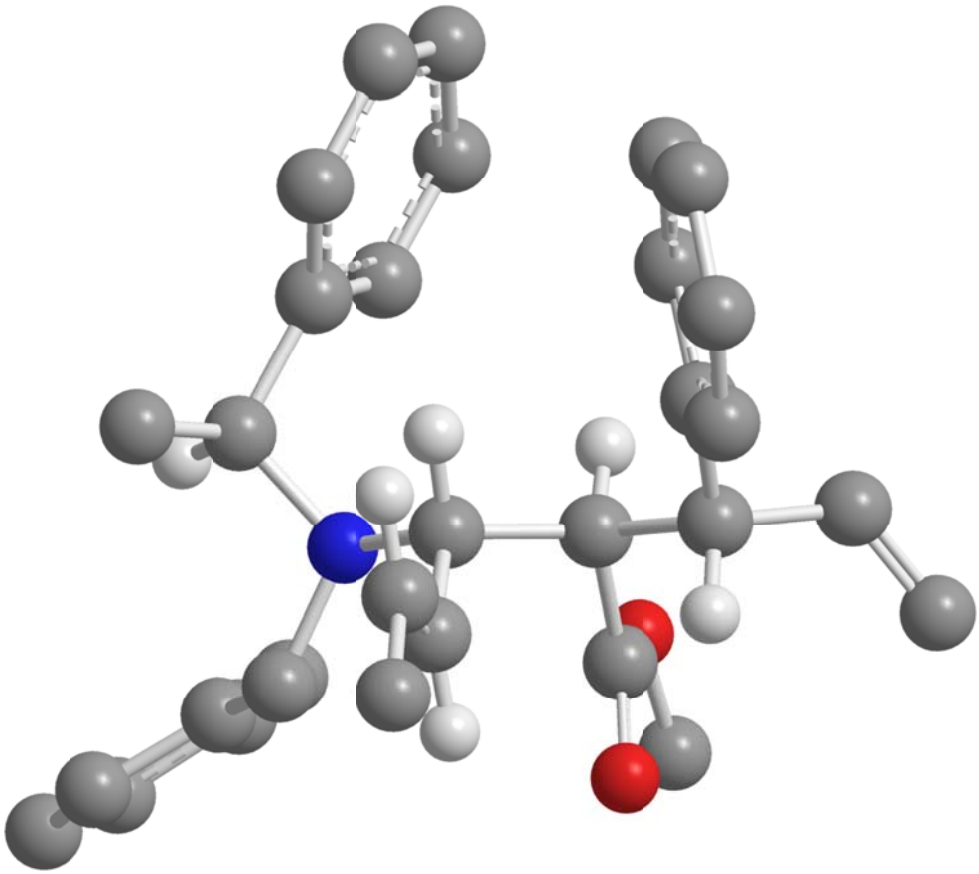
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[13]

X-ray crystal structure data for **256**·HBF_4 [$C_{31}H_{36}BF_4NO_2$]: M = 541.43, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 9.33249(10) Å, b = 15.31121(15) Å, c = 20.0967(2) Å, V = 2871.65(5) Å^3, Z = 4, μ = 0.784 mm^{-1}, colourless block, crystal dimensions = 0.23 × 0.26 × 0.30 mm^3. A total of 6010 unique reflections were measured for $4 < \theta < 77$ and 5068 reflections were used in the refinement. The final parameters were wR_2 = 0.102 and R_1 = 0.038 [I>–3.0σ(I)], with Flack enantiopole = –0.03 (14).[14] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

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

X-Ray crystal structure data for (2*R*,3*S*,1'*R*,α*S*,*E*)-258

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 258

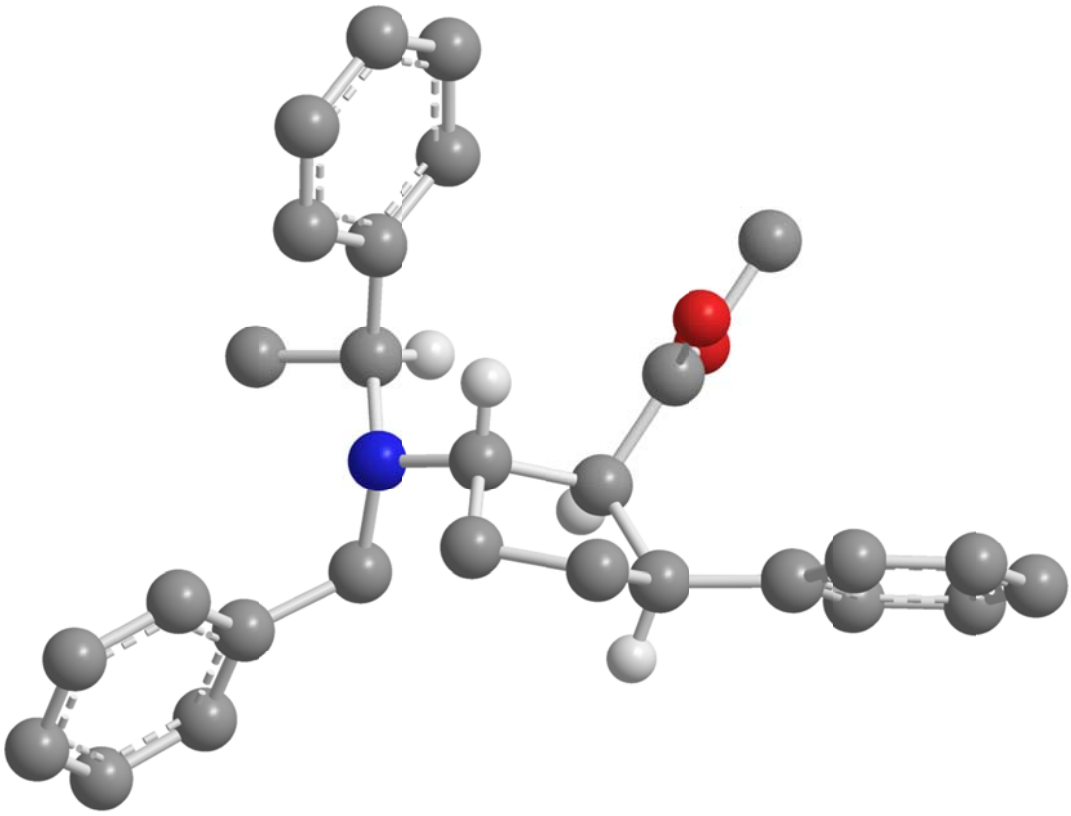
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[15]

X-ray crystal structure data for **258** [$C_{31}H_{35}NO_2$]: M = 453.62, monoclinic, space group $P\ 2_1$, a = 7.9925(2) Å, b = 16.7779(4) Å, c = 10.6442(3) Å, β = 111.582(3)°, V = 1327.29(7) Å^3, Z = 2, μ = 0.541 mm^{-1}, colourless plate, crystal dimensions = 0.05 × 0.20 × 0.24 mm^3. A total of 4653 unique reflections were measured for $4 < \theta < 77$ and 4635 reflections were used in the refinement. The final parameters were wR_2 = 0.086 and R_1 = 0.035 [I>–3.0σ(I)], with Flack enantiopole = 0.1(2).[16] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

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

X-Ray crystal structure data for (*S*,*S*,*S*,*S*)-264

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 264

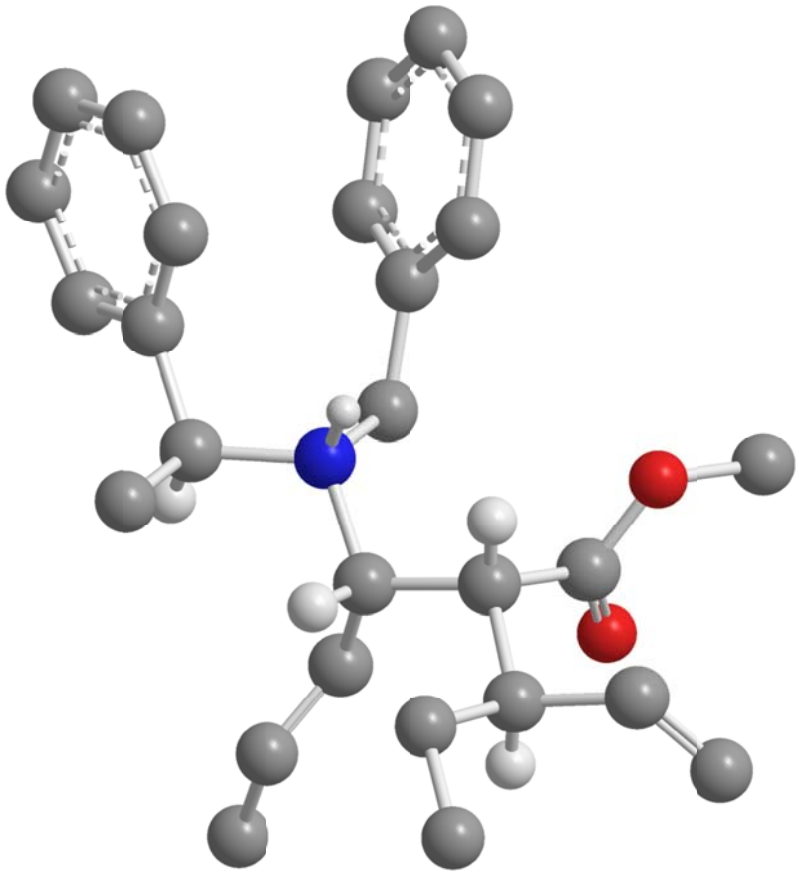
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[17]

X-ray crystal structure data for **264** [$C_{28}H_{31}NO_2$]: M = 413.56, monoclinic, space group $P\ 2_1$, a = 13.3768(12) Å, b = 6.1273(4) Å, c = 15.0922(17) Å, β = 110.373(12)°, V = 1159.6(2) Å^3, Z = 2, μ = 0.572 mm^{-1}, colourless block, crystal dimensions = 0.23 × 0.23 × 0.26 mm^3. A total of 2394 unique reflections were measured for $4 < \theta < 76$ and 2255 reflections were used in the refinement. The final parameters were wR_2 = 0.110 and R_1 = 0.043 [I>–3.0σ(I)], with Flack enantiopole = 0.0(4).[18] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

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

X-Ray crystal structure data for (2*R*,3*S*,2'*R*,α*S*,*E*)-292·HBF_4

(the BF_4^- counterion and selected H atoms are omitted for clarity)



X-ray crystal structure determination for 292·HBF_4

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.[19]

X-ray crystal structure data for **292**·HBF_4 [$C_{27}H_{36}BF_4NO_2$]: M = 493.39, monoclinic, space group $P\ 2_1$, a = 8.93933(11) Å, b = 14.19427(18) Å, c = 10.40085(16) Å, β = 98.8420(13)°, V = 1304.05(3) Å^3, Z = 2, μ = 0.808 mm^{-1}, colourless block, crystal dimensions = 0.08 × 0.10 × 0.19 mm^3. A total of 5399 unique reflections were measured for 4 < θ < 76 and 5377 reflections were used in the refinement. The final parameters were wR_2 = 0.070 and R_1 = 0.029 [I>–3.0σ(I)], with Flack enantiopole = 0.03(9).[20] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

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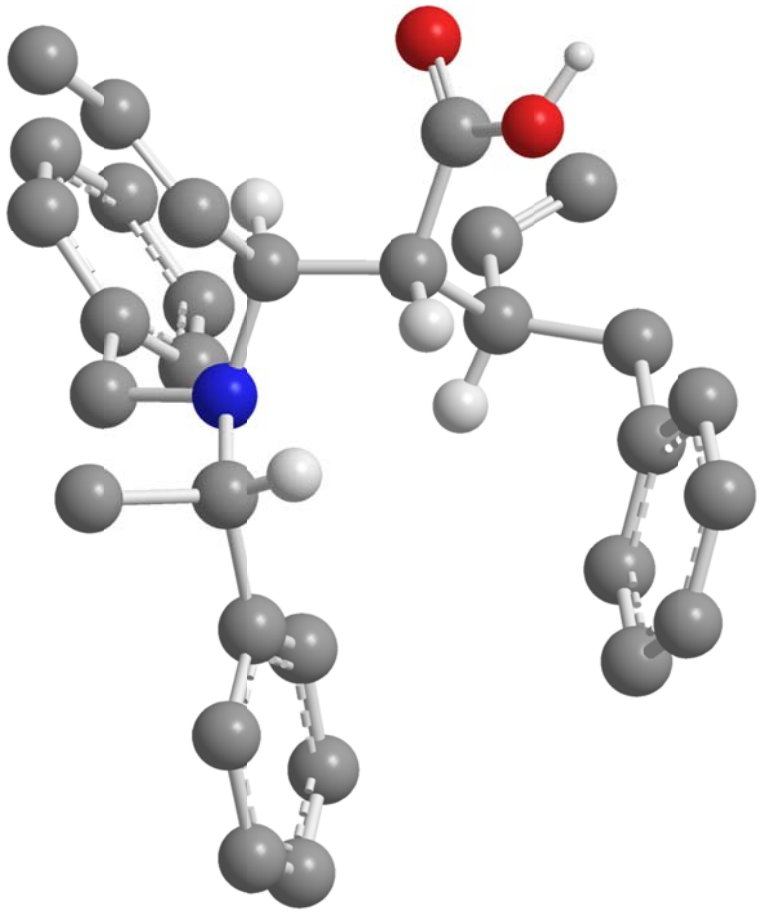
[19] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

[20] Flack, H. D.; Bernardinelli, G. *Acta. Crystallogr., Sect. A* **1999**, *55*, 908.

X-Ray crystal structure data for (2*R*,3*S*,2'*R*,α*S*,*E*)-287

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 287

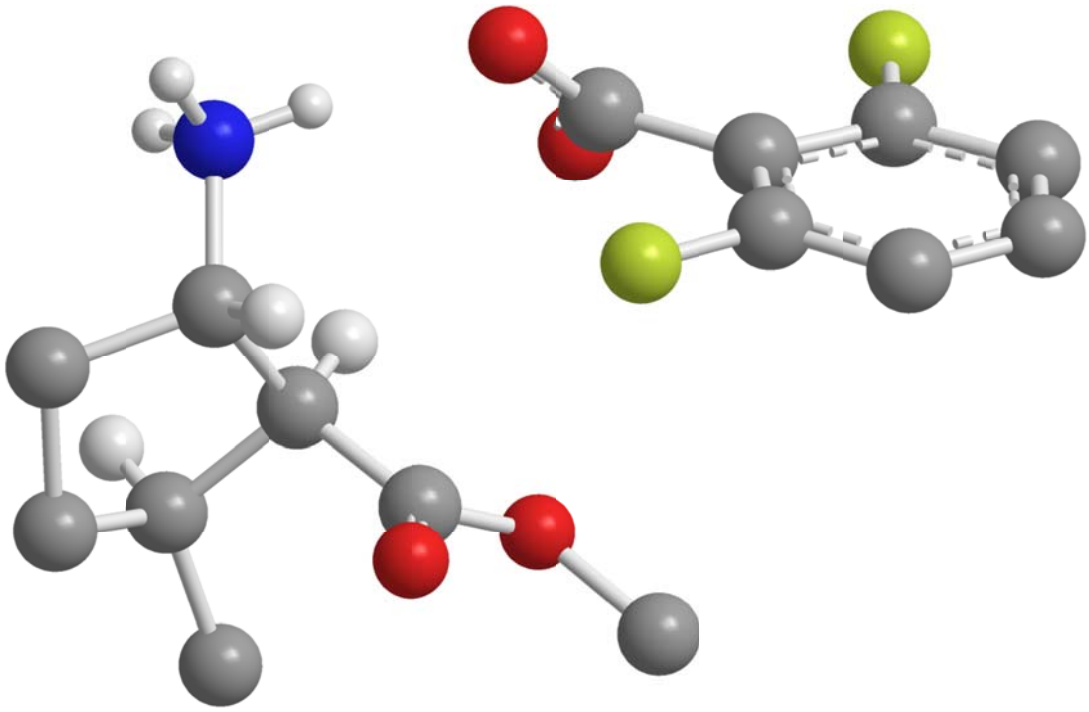
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[21]

X-ray crystal structure data for **287** [$C_{31}H_{35}NO_2$]: M = 453.62, orthorhombic, space group $P\ 2\ 2_1\ 2_1$, a = 10.7026(7) Å, b = 15.0868(9) Å, c = 16.8872(8) Å, V = 2726.8(3) Å^3, Z = 4, μ = 0.527 mm^{-1}, colourless prism, crystal dimensions = 0.08 × 0.11 × 0.19 mm^3. A total of 5681 unique reflections were measured for $3 < \theta < 77$ and 5154 reflections were used in the refinement. The final parameters were wR_2 = 0.205 and R_1 = 0.079 **[***I*>–3.0σ(*I*)], with Flack enantiopole = –0.7(4).[22] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

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

X-Ray crystal structure data for (*S*,*S*,*S*)-298·2,6-difluorobenzoic acid

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 298·2,6-difluorobenzoic acid

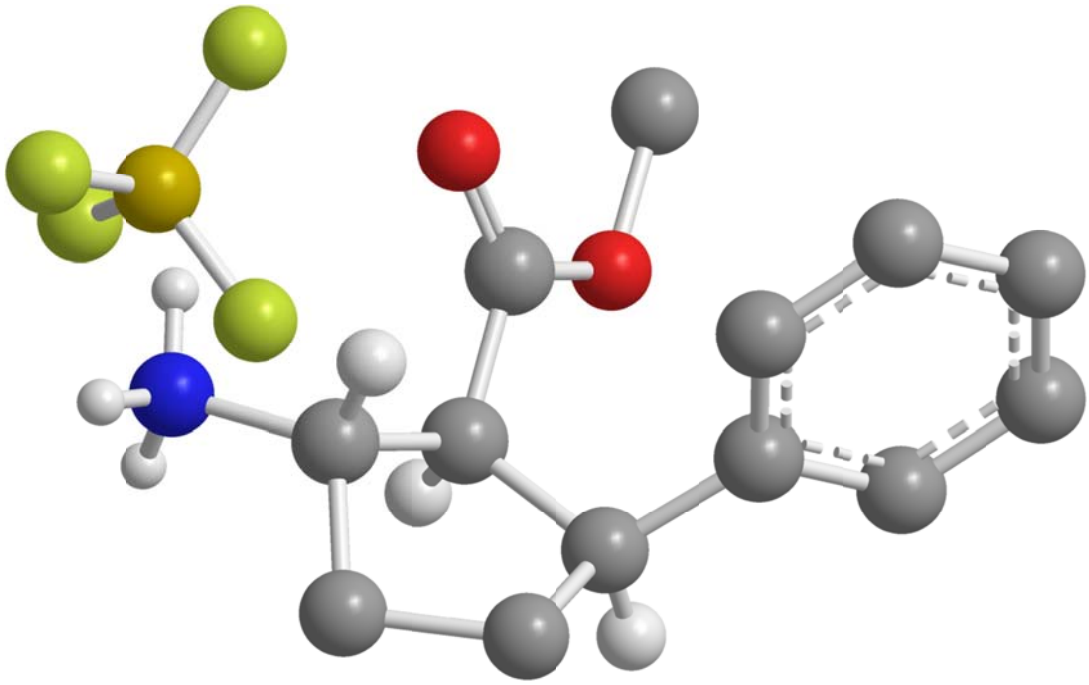
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[23]

X-ray crystal structure data for **298**·2,6-difluorobenzoic acid [$C_{16}H_{20}Cl_3F_2NO_4$]: M = 434.69, monoclinic, space group $C\ 2$, a = 25.0016(5) Å, b = 6.6915(1) Å, c = 12.9605(2) Å, β = 110.830(2)°, V = 2026.55(7) Å^3, Z = 4, μ = 4.425 mm^{-1}, colourless prism, crystal dimensions = 0.11 × 0.12 × 0.29 mm^3. A total of 4226 unique reflections were measured for 3 < θ < 76 and 4207 reflections were used in the refinement. The final parameters were wR_2 = 0.082 and R_1 = 0.033 [I>–3.0σ(I)], with Flack enantiopole = 0.005(11).[24] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

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

X-Ray crystal structure data for (*S*,*S*,*S*)-302·HBF_4

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 302·HBF_4

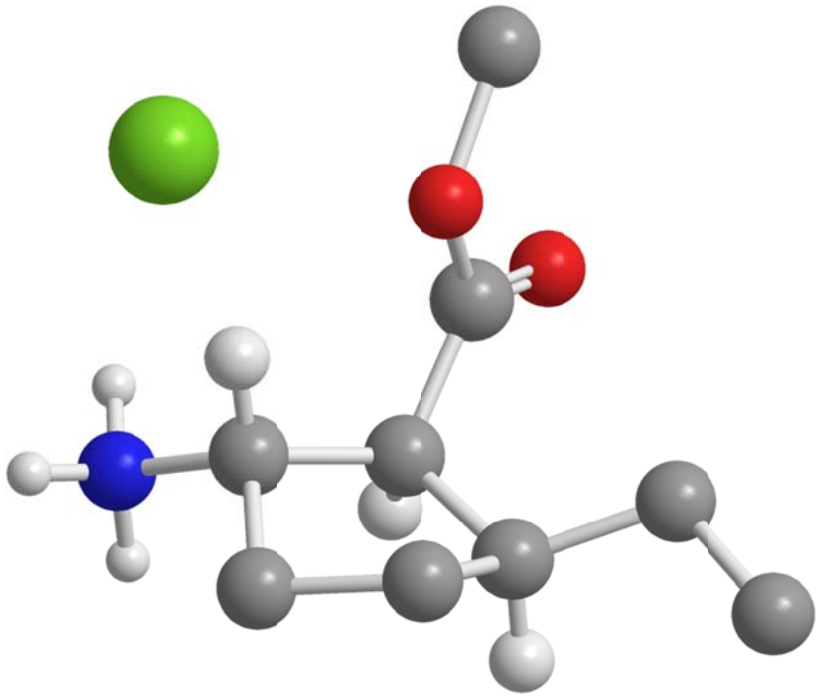
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[25]

X-ray crystal structure data for **302**·HBF_4 [$C_{13}H_{18}BF_4NO_2$]: M = 307.09, monoclinic, space group $P\ 2_1$, a = 5.5150(2) Å, b = 7.6423(3) Å, c = 17.2563(6) Å, β = 90.531(3)°, V = 727.27(5) Å^3, Z = 2, μ = 1.099 mm^{-1}, colourless block, crystal dimensions = 0.22 × 0.23 × 0.27 mm^3. A total of 2045 unique reflections were measured for $5 < \theta < 76$ and 2038 reflections were used in the refinement. The final parameters were wR_2 = 0.091 and R_1 = 0.036 [I>–3.0σ(I)], with Flack enantiopole = –0.03(16).[26] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

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

X-Ray crystal structure data for (*S*,*S*,*S*)-299·HCl

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 299·HCl

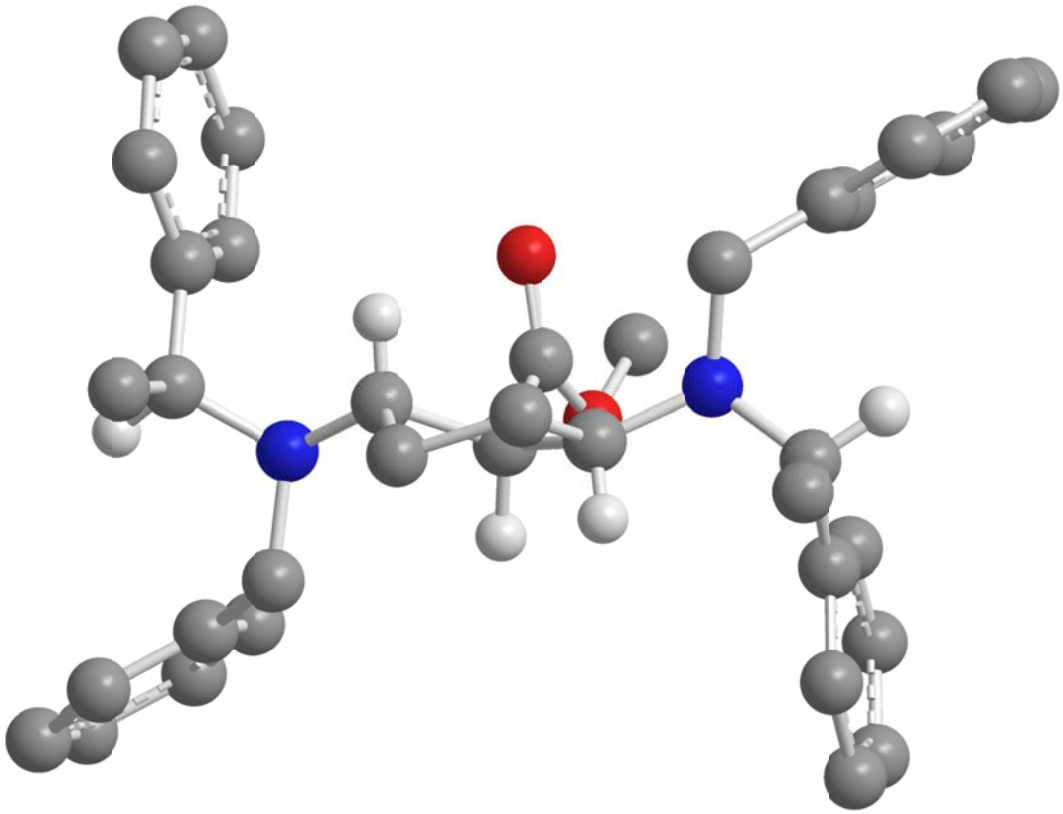
Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[27]

X-ray crystal structure data for **299**·HCl [$C_9H_{18}ClNO_2$]: M = 207.70, monoclinic, space group $P\,2_1$, a = 5.4210(1) Å, b = 8.9375(3) Å, c = 11.4409(3) Å, β = 101.8270(12)°, V = 542.55(3) Å^3, Z = 2, μ = 0.323 mm^{-1}, colourless block, crystal dimensions = 0.21 × 0.23 × 0.24 mm^3. A total of 2115 unique reflections were measured for $5 < \theta < 27$ and 2115 reflections were used in the refinement. The final parameters were wR_2 = 0.056 and R_1 = 0.025 [I>–3.0σ(I)], with Flack enantiopole = 0.03(5).[28] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

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

X-Ray crystal structure data for (*RS*,*RS*,*RS*,*RS*)-348

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 348

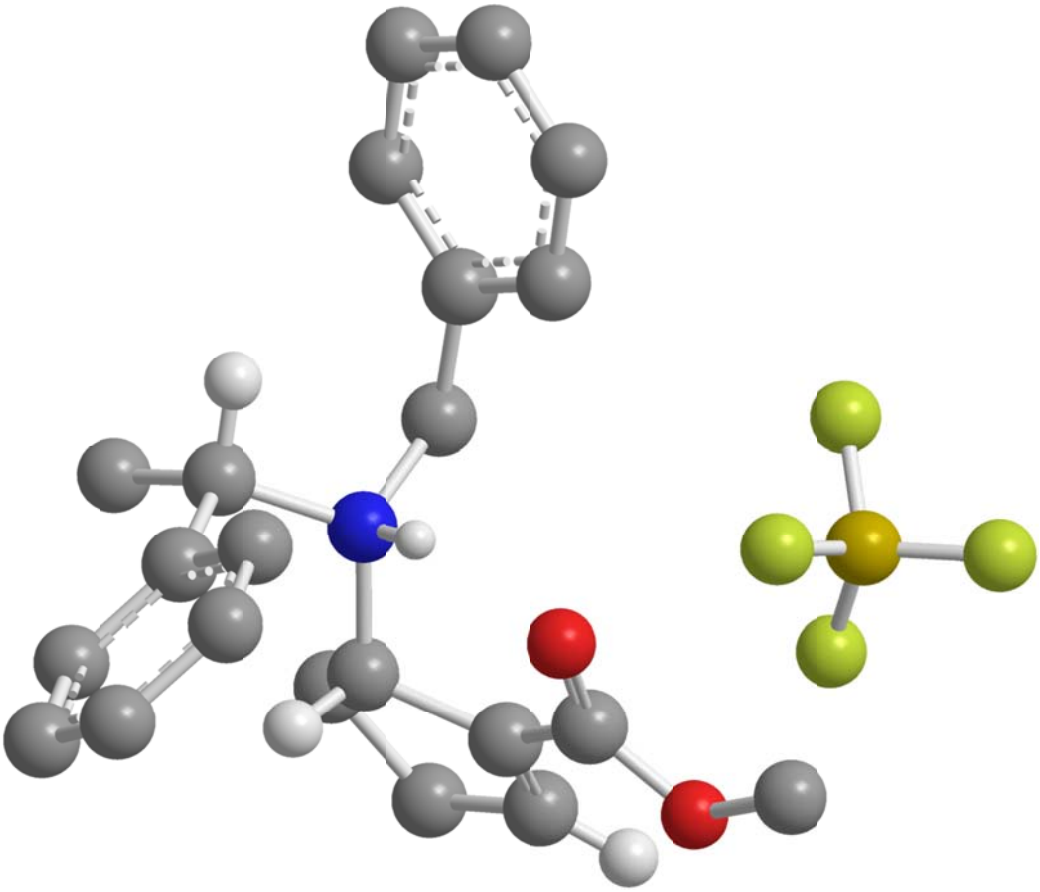
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[29]

X-ray crystal structure data for **348** [$C_{37}H_{42}N_2O_2$]: M = 546.75, triclinic, space group $P\,{-1}$, a = 11.0332(4) Å, b = 11.8682(4) Å, c = 13.0393(5) Å, α = 113.467(3)°, β = 93.853(3)°, γ = 97.767(3)°, V = 1538.01(10) Å^3, Z = 2, μ = 0.560 mm^{-1}, colourless block, crystal dimensions = 0.12 × 0.15 × 0.15 mm^3. A total of 6379 unique reflections were measured for $4 < \theta < 77$ and 6352 reflections were used in the refinement. The final parameters were wR_2 = 0.166 and R_1 = 0.066 [I>–3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

[29] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

X-Ray crystal structure data for (*S*,*S*)-107·HBF_4

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for (*S*,*S*)-107·HBF_4

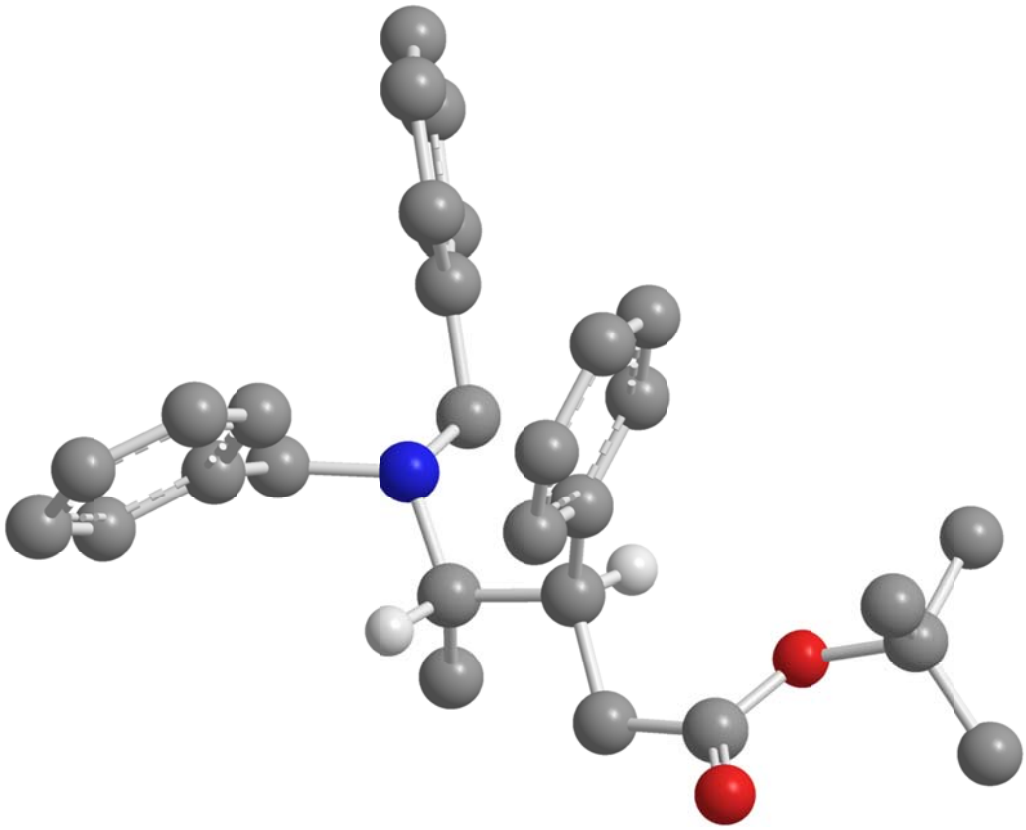
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[30]

X-ray crystal structure data for (*S*,*S*)-**107**·HBF_4 [$C_{22}H_{26}BF_4NO_2$]: M = 423.26, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 9.01661(14) Å, b = 12.8158(2) Å, c = 18.3303(3) Å, V = 2118.15(6) Å^3, Z = 4, μ = 0.908 mm^{-1}, colourless block, crystal dimensions = 0.07 × 0.09 × 0.19 mm^3. A total of 4200 unique reflections were measured for 4 < θ < 75 and 3487 reflections were used in the refinement. The final parameters were wR_2 = 0.098 and R_1 = 0.040 [I>–3.0σ(I)], with Flack enantiopole = –0.01(15).[31] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

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

X-Ray crystal structure data for (*RS*,*SR*)-428

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 428

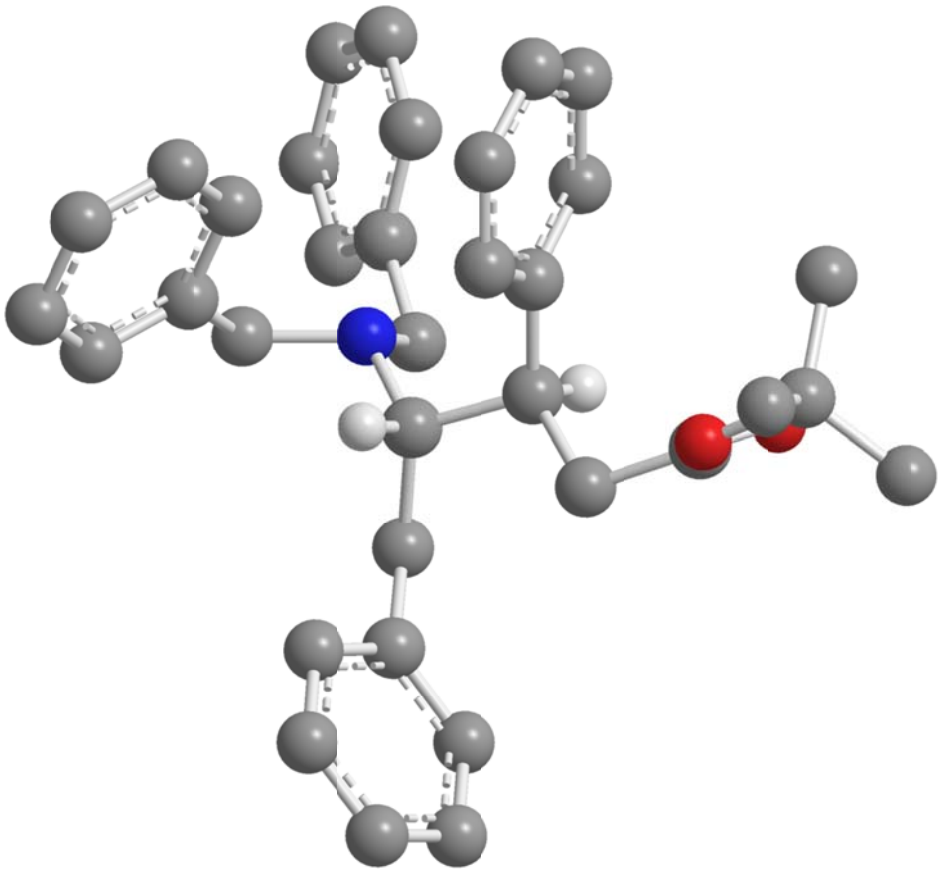
Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[32]

X-ray crystal structure data for **428** [$C_{29}H_{35}NO_2$]: M = 429.60, triclinic, space group $P\,\bar{1}$, a = 11.3749(2) Å, b = 13.4512(2) Å, c = 17.3862(3) Å, α = 88.4903(8)°, β = 88.3140(8)°, γ = 69.5533(8)°, V = 2491.15(7) Å^3, Z = 4, μ = 0.071 mm^{-1}, colourless block, crystal dimensions = 0.28 × 0.30 × 0.31 mm^3. A total of 11339 unique reflections were measured for $5 < \theta < 27$ and 11338 reflections were used in the refinement. The final parameters were wR_2 = 0.128 and R_1 = 0.083 [$I > -3.0\sigma(I)$]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

[32] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

X-Ray crystal structure data for (*RS*,*SR*)-431

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 431

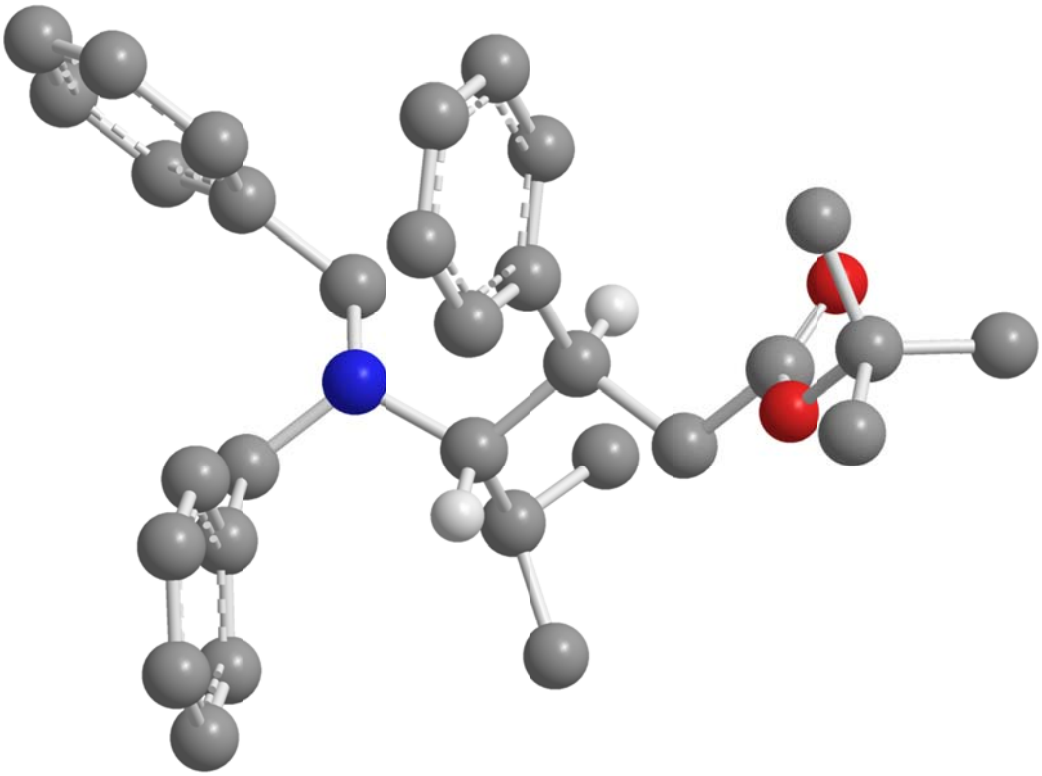
Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[33]

X-ray crystal structure data for **431** [$C_{35}H_{39}NO_2$]: M = 505.70, triclinic, space group $P\ -1$, a = 9.3391(3) Å, b = 12.3200(3) Å, c = 15.1402(5) Å, α = 75.9123(12)°, β = 74.1538(12)°, γ = 77.4766(11)°, V = 1604.15(8) Å^3, Z = 2, μ = 0.064 mm^{-1}, colourless plate, crystal dimensions = 0.10 × 0.21 × 0.29 mm^3. A total of 7277 unique reflections were measured for $5 < \theta < 27$ and 6012 reflections were used in the refinement. The final parameters were wR_2 = 0.210 and R_1 = 0.113 [I>–3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

[33] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

X-Ray crystal structure data for (*RS*,*SR*)-430

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 430

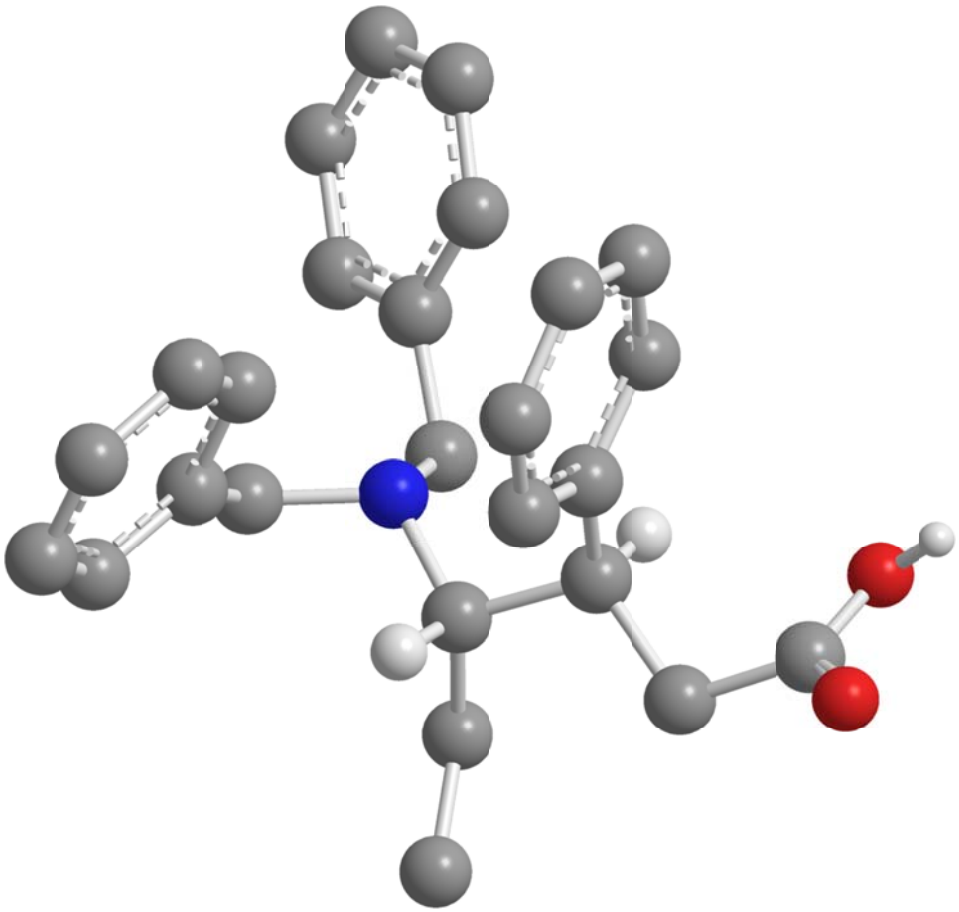
Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[34]

X-ray crystal structure data for **430** [$C_{31}H_{39}NO_2$]: M = 457.66, triclinic, space group $P\ -1$, a = 9.8685(2) Å, b = 10.7697(2) Å, c = 14.6816(4) Å, α = 88.0968(9)°, β = 73.0115(9)°, γ = 67.3548(10)°, V = 1371.67(5) Å^3, Z = 2, μ = 0.068 mm^{-1}, colourless plate, crystal dimensions = 0.09 × 0.18 × 0.21 mm^3. A total of 6235 unique reflections were measured for $5 < \theta < 27$ and 6235 reflections were used in the refinement. The final parameters were wR_2 = 0.119 and R_1 = 0.095 [I>–3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

[34] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

X-Ray crystal structure data for (*RS*,*SR*)-433

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 433

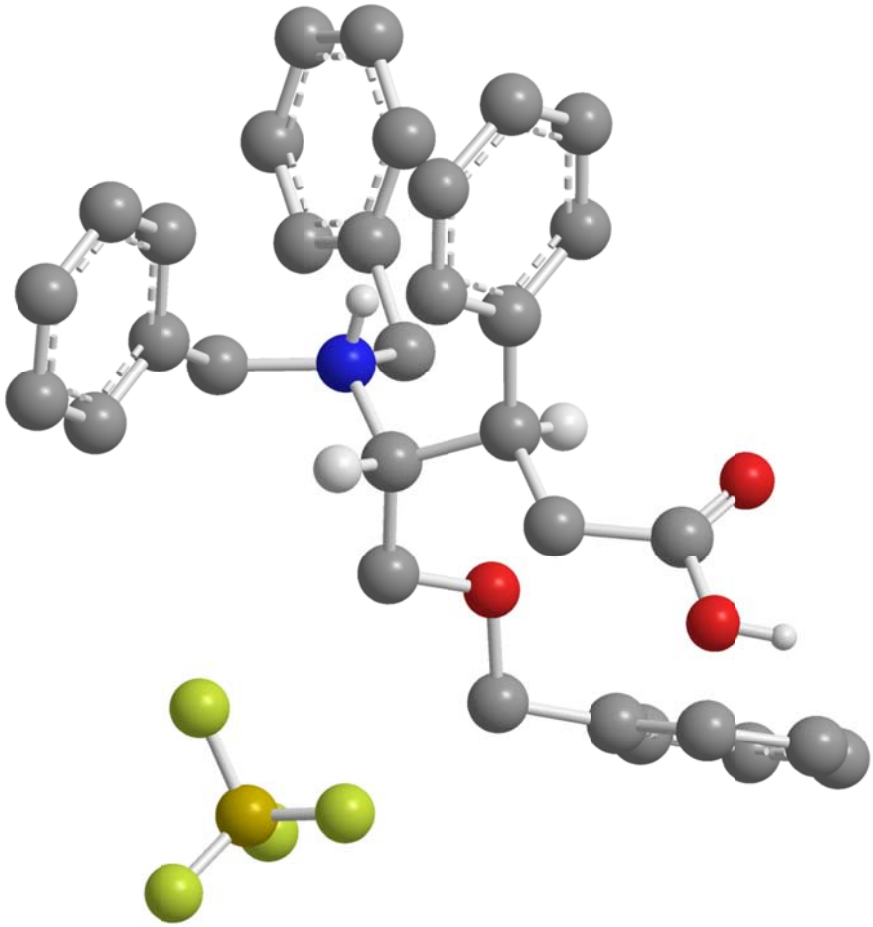
Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[35]

X-ray crystal structure data for **433** [$C_{26}H_{29}NO_2$]: M = 387.52, monoclinic, space group $P\ 2_1/a$, a = 14.3154(5) Å, b = 10.1148(4) Å, c = 15.2122(6) Å, β = 94.2843(15)°, V = 2196.53(14) Å^3, Z = 4, μ = 0.073 mm^{-1}, colourless plate, crystal dimensions = 0.09 × 0.22 × 0.26 mm^3. A total of 4917 unique reflections were measured for $5 < \theta < 27$ and 4917 reflections were used in the refinement. The final parameters were wR_2 = 0.205 and R_1 = 0.114 [I>–3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

[35] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

X-Ray crystal structure data for (*RS*,*RS*)-434·HBF_4

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 434·HBF_4

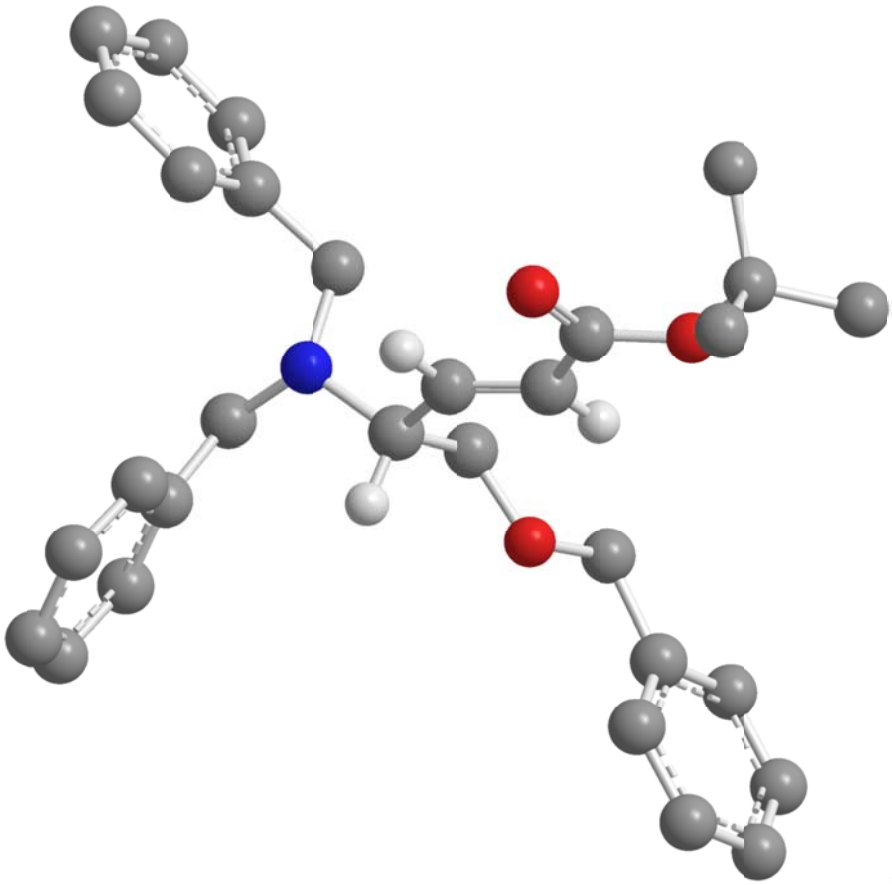
Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[36]

X-ray crystal structure data for **434**·HBF_4 [$C_{32}H_{34}BF_4NO_3$]: M = 567.43, monoclinic, space group $P\ 2_1/n$, a = 12.1811(3) Å, b = 20.9841(7) Å, c = 12.4206(4) Å, β = 115.5211(12)°, V = 2865.04(15) Å^3, Z = 4, μ = 0.100 mm^{-1}, colourless block, crystal dimensions = 0.21 × 0.30 × 0.39 mm^3. A total of 6494 unique reflections were measured for $5 < \theta < 27$ and 6494 reflections were used in the refinement. The final parameters were wR_2 = 0.169 and R_1 = 0.137 [I>–3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

[36] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

X-Ray crystal structure data for (*RS*)-427

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 427

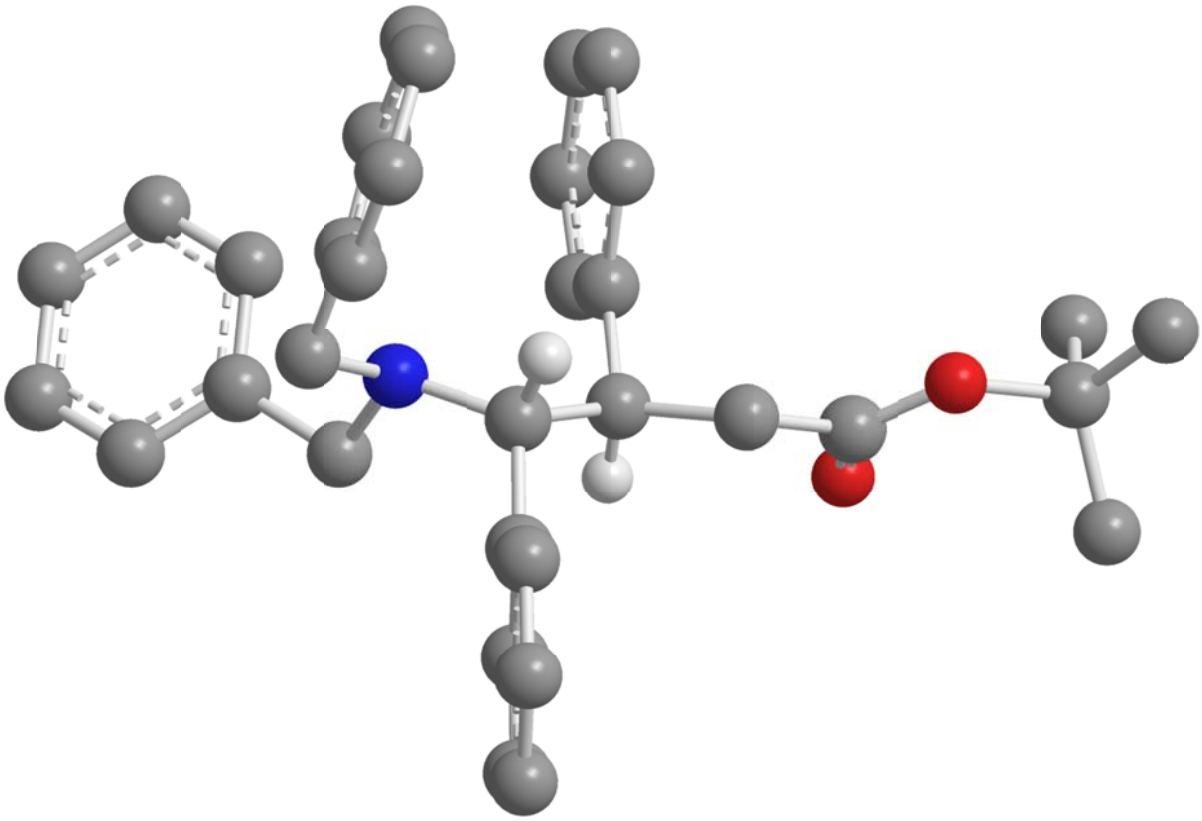
Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[37]

X-ray crystal structure data for **427** [$C_{30}H_{35}NO_3$]: M = 457.61, monoclinic, space group $P\ 2_1/c$, a = 16.4738(3) Å, b = 6.1221(1) Å, c = 25.8753(5) Å, β = 96.4963(8)°, V = 2592.88(8) Å^3, Z = 4, μ = 0.075 mm^{-1}, colourless prism, crystal dimensions = 0.08 × 0.11 × 0.23 mm^3. A total of 5873 unique reflections were measured for $5 < \theta < 27$ and 4829 reflections were used in the refinement. The final parameters were wR_2 = 0.103 and R_1 = 0.079 [$I > -3.0\sigma(I)$]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

[37] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

X-Ray crystal structure data for (*RS*,*RS*)-436

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 436

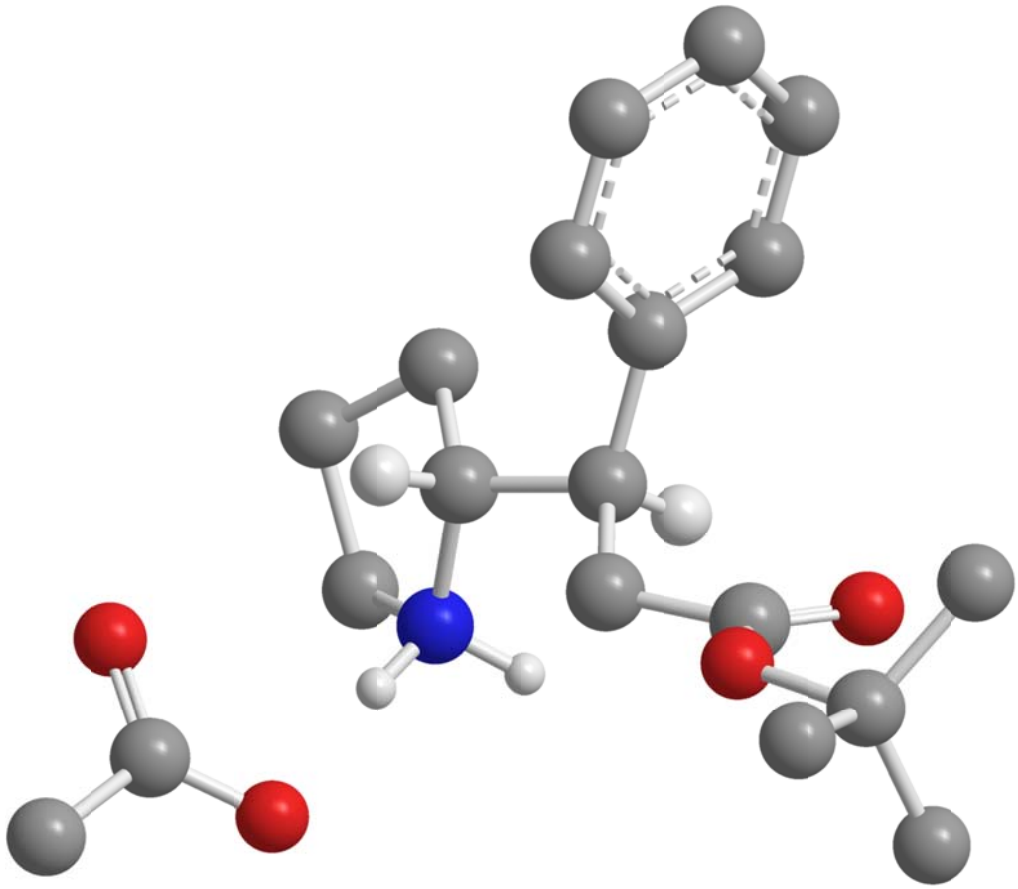
Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[38]

X-ray crystal structure data for **436**: $[C_{34}H_{37}NO_2]$: M = 491.67, triclinic, space group $P\,{-1}$, a = 11.3392(3) Å, b = 11.8581(4) Å, c = 13.8557(4) Å, α = 71.3386(17)°, β = 76.5426(17)°, γ = 65.4505(13)°, V = 1594.75(9) Å^3, Z = 2, μ = 0.063 mm^{-1}, colourless block, crystal dimensions = 0.22 × 0.28 × 0.33 mm^3. A total of 7222 unique reflections were measured for $5 < \theta < 27$ and 6551 reflections were used in the refinement. The final parameters were wR_2 = 0.202 and R_1 = 0.098 [I>–3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

[38] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

X-Ray crystal structure data for (*RS*,*RS*)-448·HOAc

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 448·HOAc

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.[39]

X-ray crystal structure data for **448**·HOAc [$C_{19}H_{29}NO_4$]: M = 335.44, monoclinic, space group *I 2*/a, a = 30.0750(9) Å, b = 5.62853(16) Å, c = 22.5665(7) Å, β = 98.643(3)°, V = 3776.6(2) Å^3, Z = 8, μ = 0.660 mm^{-1}, colourless block, crystal dimensions = 0.09 × 0.09 × 0.15 mm^3. A total of 3916 unique reflections were measured for 4 < θ < 76 and 3902 reflections were used in the refinement. The final parameters were wR_2 = 0.109 and R_1 = 0.042 [I>–3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

[39] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.