ENANTIORECOGNITION PHENOMENA IN ASYMMETRIC SYNTHESIS

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

by

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Declaration

The work described in this thesis was carried out in the Chemistry Research Laboratory, University of Oxford from October 2008 until November 2011, 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 investigations into applications of double asymmetric induction and parallel kinetic resolution in asymmetric synthesis.

Chapter 1 introduces enantiorecognition phenomena as a significant field in asymmetric synthesis. The main approaches in this field are described: double asymmetric induction, kinetic resolution, parallel kinetic resolution and dynamic kinetic resolution.

Chapter 2 describes investigations into the use of double asymmetric induction as a mechanistic probe to elucidate the reactive conformation of enantiopure α,β-unsaturated esters (derived from Corey's 8-phenylmenthol auxiliary) and hydroxamates [derived from (*S*)-*N*-1-(1'-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine] upon conjugate addition.

Chapter 3 describes investigations into the doubly diastereoselective organocatalytic intramolecular Michael cyclization of enantiopure enamides (derived from a 4-substituted-5,5-dimethyl-oxazolidin-2-one auxiliary) and α,β-unsaturated esters (derived from Corey's 8-phenylmenthol auxiliary) using α-methylbenzylamine and its derivatives as the chiral catalysts.

Chapter 4 describes investigations into parallel kinetic resolution of acyclic γ-amino-α,β-unsaturated esters utilising a 50:50 pseudoenantiomeric mixture of lithium amides. To highlight the synthetic utility of the resultant β,γ-diamino esters, their elaboration to a range of 5-substituted-4-amino-pyrrolidin-2-ones is demonstrated and a concise synthesis of natural product (±)-absouline is performed.

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

Acknowledgements

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I would like to thank my boyfriend Fan Lu and all my family for their love, support and encouragement. Thank you so much.

Abbreviations

The following abbreviations are used throughout this thesis:

Å	Angstroms
Ac	Acetyl
app	Apparent
aq	Aqueous
Ar	Aryl
atm	Atmosphere
ATR	Attenuated total reflectance
$[\alpha]_D$	Specific rotation
BBTO	Bis(tributyltin) oxide
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
bp	Boiling point
br	Broad
Bu	*n*-Butyl
^{t}Bu	*t*-Butyl
Bz	Benzoyl
c	Concentration
C	Celsius
Cbz	Carboxylbenzyl
CI	Chemical ionisation
cm^{-1}	Wavenumber
conc	Concentrated
conv	Conversion
CSA	Camphorsulfonic acid
CSO	Camphorsulfonyl oxaziridine
Cy	Cyclohexyl
d	Doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
DIBAL-H	Di(*iso*-butyl)aluminium hydride
DIPEA	Ethyldiisopropylamine
DIPT	Diisopropyl tartrate
DKR	Dynamic kinetic resolution
DMAC	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMBA	Dimethylbenzylamine
DMF	*N*,*N*-Dimethylformamide
DMS	Dimethylsulfide
DMSO	Dimethylsulfoxide
dr	Diastereoisomeric ratio
δ_H	Proton (^{1}H) NMR chemical shift
δ_C	Carbon (^{13}C) NMR chemical shift
δ_F	Fluorine (^{19}F) NMR chemical shift
E	Stereoselectivity factor
ee	Enantiomeric excess
ent	Enantiomeric

equiv	Equivalents
ESI	Electrospray ionisation
Et	Ethyl
FI	Field ionisation
g	Grams
GCT	Gas chromatograph/time-of-flight
gem	Geminal
Grubbs II	Benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene] dichloro(tricyclohexylphosphine)ruthenium
h	Hours
5-HT	5-Hydroxytryptamine
HMPA	Hexamethylphosphoramide
HRMS	High resolution mass spectrometry
Hz	Hertz
i	Ipso
i	Iso
IPA	Isopropyl alcohol
J	Joules
J	Coupling constant
k	Rate constant
K	Kelvin
KHMDS	Potassium hexamethyldisilazide
lit.	Literature
L	Litres
LDA	Lithium di(*iso*-propyl)amide
m	Meta
m	Metres
m	Milli
m	Multiplet
M	Molar
$[M]^+$	Molecular ion
Mes	Mesityl
mmHg	Millimetres of mercury
m-CPBA	*m*-Chloroperoxybenzoic acid
Me	Methyl
min	Minutes
MKR	Mutual kinetic resolution
mol	Moles
mp	Melting point
Ms	Methanesulfonyl
m/z	Mass to charge ratio
µ	Micro
n	Normal
Nap	Naphthyl
nbd	Norbomadiene
NBS	*N*-Bromosuccinimide
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
o	Ortho
p	Para
Ph	Phenyl
PKR	Parallel kinetic resolution
ppm	Parts per million

Pr	Propyl
^{i}Pr	*i*-Propyl
q	Quartet
quant	Quantitative
quin	Quintet
R	Unspecified organic group
ref.	Reference
rt	Room temperature
s	Singlet
satd	Saturated
sept	Septet
t	Tertiary
t	Triplet
T	Temperature
TBDPS	*tert*-Butyldiphenylsilyl
TBHP	*tert*-Butyl hydroperoxide
tert	Tertiary
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMP	Tetramethylpiperidide
Ts	*p*-Toluenesulphonyl
TSA	Toluenesulfonic acid
UV	Ultraviolet
V	Volume
v/v	Volume to volume ratio
ν_{max}	Infra red absorption
w/v	Weight to volume ratio (g per 100 mL)
w/w	Mass to mass ratio
X	Unspecified substitutent

Contents

CHAPTER 1
Introduction

1.1. Introduction

Enantiorecognition phenomena are of fundamental significance in the fields of both chemistry and biology. In the field of chemistry, for example, enantiorecognition phenomena are encountered when using double asymmetric induction,[1] or kinetic,[2] dynamic kinetic[3] and parallel kinetic resolution protocols (Fig. 1).[4]

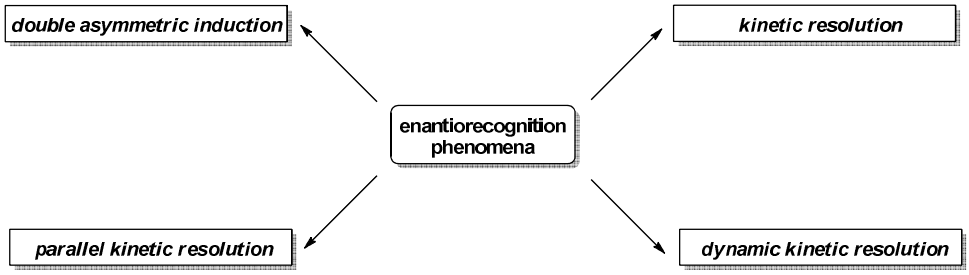


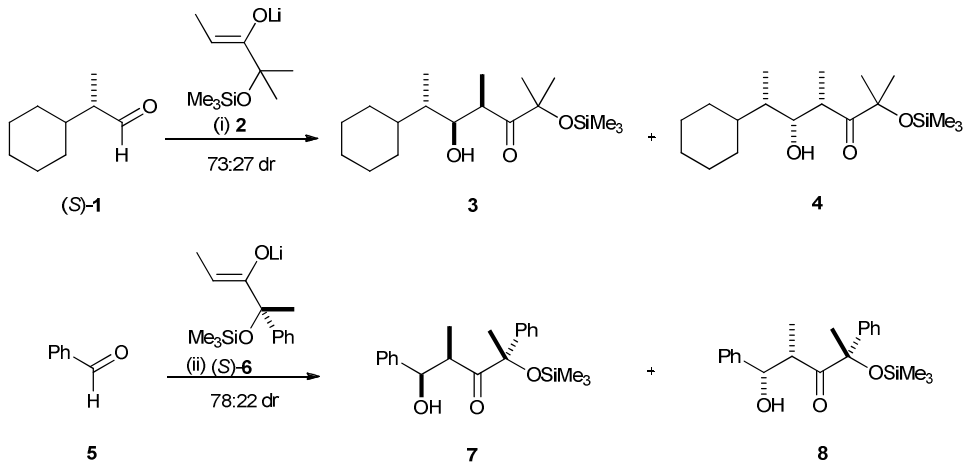
Fig. 1. Enantiorecognition phenomena in the field of chemistry.

1.2. Double asymmetric induction

Double asymmetric induction concerns the interaction of two chiral reactants, a substrate and a reagent.[5] The stereochemical analysis of double asymmetric induction may lead to the design of a strategy which is capable of constructing any new stereogenic centre on a chiral substrate in a predictable and controlled manner.[1a] This type of stereochemical effect was probably first described by Vavon (1950),[6] and Harada and Matsumoto (1966).[7] In 1968, Horeau, Kagan and Vigneron named the cumulative effect of two chiral auxiliaries in one reaction as "double induction".[8] Since then, the strategy of double asymmetric induction has found a use in such fields of organic chemistry as asymmetric nucleophilic addition reactions, asymmetric oxidation and reduction reactions, and asymmetric cycloaddition reactions.[1b]

1.2.1. The concept of "matched" and "mismatched" pairs

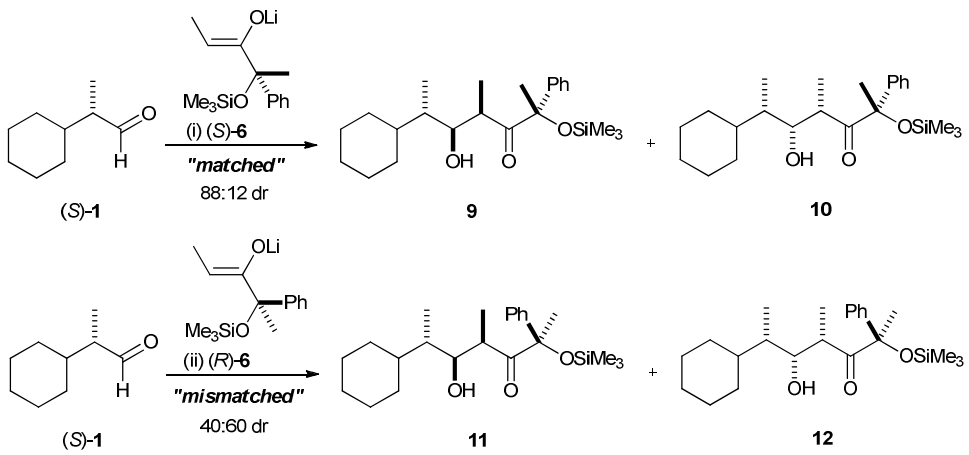
In a double asymmetric induction protocol, reactions can proceed under the stereocontrol of either the substrate or the reagent or both. In the case where the substrate and reagent favor production of the same diastereoisomeric product, Masamune originally termed this pairing of substrate and reagent as "matched", which generally leads to very high levels of diastereoselectivity. In the "mismatched" pairing (i.e., where substrate and reagent favor a different diastereoselective outcome), lower diastereoselectivity is often observed, and the stereochemical outcome of the reaction is dictated by the agent (substrate or reagent) with greater diastereofacial control.[5] For example, the following aldol reaction may be used to demonstrate the "matched" and "mismatched" interactions of two chiral reactants.[9] The reaction of chiral aldehyde (*S*)-**1** and achiral lithium enolate **2** gave a 73:27 mixture of two diastereoisomeric products **3** and **4**, reflecting the diastereoselectivity of substrate control alone. In a similar manner, reaction of achiral benzaldehyde **5** with chiral lithium enolate (*S*)-**6** gave a 78:22 mixture of two diastereoisomeric products **7** and **8**, reflecting the level of reagent control alone (Scheme 1).



Scheme 1. *Reagents and conditions*: (i) **2**, THF, −78 °C, 25 min; (ii) (*S*)-**6**, THF, −78 °C, 25 min.

In the corresponding double asymmetric induction protocol, the reaction of chiral aldehyde (*S*)-**1** and chiral lithium enolate (*S*)-**6** proceeds with an enhancement of diastereoselection, in which the substrate control and reagent control reinforce one another, giving diastereoisomeric products **9** and **10** in 88:12 dr. This reaction therefore represents the "matched" pairing. In contrast, the "mismatched" pairing of aldehyde (*S*)-**1** and lithium

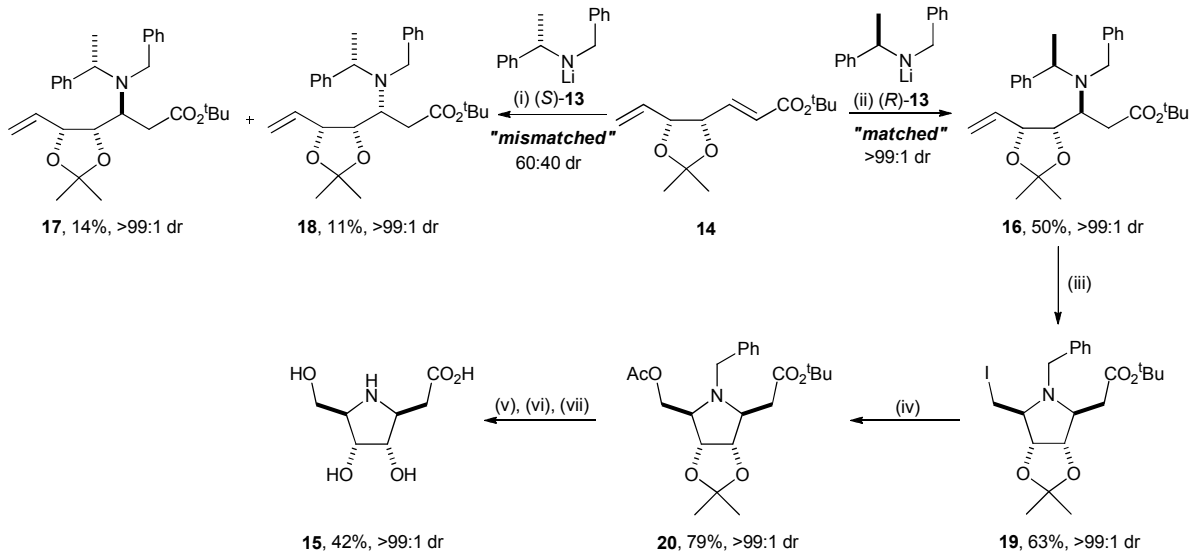
enolate (*R*)-**6** reacts with inferior diastereoselection, giving a 40:60 mixture of diastereoisomeric products **11** and **12** (Scheme 2).



Scheme 2. *Reagents and conditions*: (i) (*S*)-**6**, THF, −78 °C, 25 min; (ii) (*R*)-**6**, THF, −78 °C, 25 min.

1.2.2. Applications of double asymmetric induction

During the past 20 years, the field of double asymmetric induction has advanced and this strategy has been employed to effect many types of reactions with excellent stereochemical control, such as aldol-type reactions[10] (e.g., the Reformatsky reaction[11] and Mukaiyama reaction),[12] conjugate addition reactions,[13] epoxidation,[14] catalytic hydrogenation,[15] alkylation[16] and Diels-Alder reactions.[17] For example, Davies and co-workers have employed double asymmetric induction in the conjugate addition of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **13** to chiral α,β-unsaturated ester **14** in their synthesis of polyhydroxylated pyrrolidine **15**. The "matched" pair of lithium amide (*R*)-**13** and α,β-unsaturated ester **14** resulted in the formation of **16** in >99:1 dr, which was isolated as a single diastereoisomer in 50% yield. Meanwhile, the "mismatched" reaction of lithium amide (*S*)-**13** with α,β-unsaturated ester **14** gave addition products **17** and **18** in 60:40 dr, which were isolated in 14 and 11% yield, respectively. Further manipulation of **16** (the product of the "matched" reaction) gave iodide **19**, which is the key intermediate for the synthesis of polyhydroxylated pyrrolidine **15** (Scheme 3).[18]



Scheme 3. *Reagents and conditions*: (i) (*S*)-**13**, THF, −78 °C, 2 h; (ii) (*R*)-**13**, THF, −78 °C, 2 h; (iii) I_2, $NaHCO_3$, CH_3CN, −20 °C, 2 h, then rt, 20 h; (iv) AgOAc, toluene, rt, 2h; (v) $Pd(OH)_2/C$, H_2(1 atm), MeOH, rt, 15 h; (vi) K_2CO_3, MeOH, rt, 2 h; (vii) TFA, rt, 3 h, then Dowex 50WX8-200.

1.3. Kinetic resolution

In the kinetic resolution protocol, stoicheiometric resolving agents or asymmetric catalysts which react much faster with one enantiomer of a racemic substrate are used to furnish enantioenriched unreacted substrate and enantioenriched product. The efficiency of a kinetic resolution is given by the relative rates of reaction of the substrate enantiomers with the resolving agent to generate the product. The relative rate (also known as selectivity factor),[19] $E = k_{rel} = k_{fast}/k_{slow}$, can be calculated using Equation 1, if the reaction conversion and the ee of the recovered starting material are known. The ideal situation to yield enantiopure (i.e., resolved) starting material and enantiopure product is when E is very large and the reaction can be halted at 50% conversion. Generally, systems with $E > 10$ are synthetically useful.[20]

$$E = k_{rel} = \frac{k_{fast}}{k_{slow}} = \frac{\ln[(1-c)(1-ee)]}{\ln[(1-c)(1+ee)]}$$

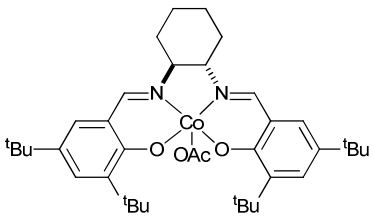
c = conversion
ee = ee of recovered starting material

Equation 1. The relative rate of reaction of two enantiomers in a kinetic resolution protocol.

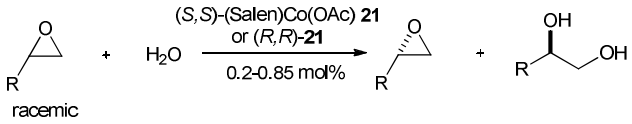
1.3.1. Kinetic resolutions using non-enzymatic catalysts

Whilst the use of enzymes for kinetic resolution has emerged as a popular strategy,[21] the widespread application of non-enzymatic catalysts for kinetic resolution to afford

enantiopure compounds in good yield has also gained popularity. Major developments using non-enzymatic catalysts for kinetic resolution include the hydrolytic kinetic resolution (HKR) of terminal racemic epoxides,[22] oxidative kinetic resolution via asymmetric epoxidation strategies,[23] kinetic resolution via enantioselective reduction of racemic ketones,[24] alcoholysis of racemic carbonyl derivatives,[25] and kinetic resolution via conjugate addition.[26] Numerous reports have recently appeared describing the use of Jacobsen's chiral salen complexes of Co and Cr for HKR of terminal racemic epoxides.[22] In HKR, water can be used as an effective nucleophile for the resolution of a series of racemic terminal epoxides. For example, HKR of racemic propylene epoxides catalyzed by Co(III)-salen complex (*S*,*S*)-**21** affords recovered epoxides in ≥98% ee and in yields approaching the theoretical maximum of 50%. High *E* values of HKR are observed, most being over 50 and several exceeding 200.[27] This protocol has been applied to a wide range of alkyl-, halo alkyl-, aryl-, and vinyl epoxides, and epoxides containing ω-sulfone,[28] and ω-diethyl phosphonate functionalities,[29] all of which afford enantioenriched epoxides in ≥ 93% ee. Some highly efficient cases have been used to produce hundreds of kilograms of resolved terminal epoxides (Fig. 2).[27]



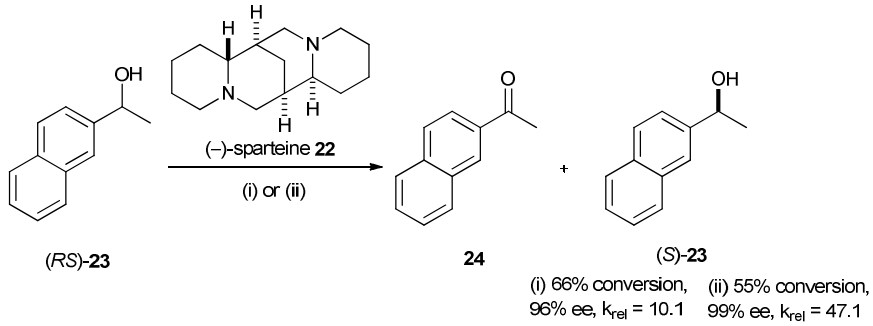
(*S*,*S*)-(Salen)Co(OAc) **21**



R	catalyst **21**	*E*	Epoxide ee (%)	Yield (%)
Me	(*S*,*S*)	> 400	> 98	44
CH_2Cl	(*S*,*S*)	50	98	44
$(CH_2)_3CH_3$	(*S*,*S*)	290	98	46
$(CH_2)_5CH_3$	(*S*,*S*)	260	99	45
$CH{=}CH_2$	(*S*,*S*)	30	99	29
$(CH_2)_2SO_2Ph$	(*S*,*S*)	-	> 99	48
Ph[a]	(*R*,*R*)	-	> 99	44
CF_3[a]	(*R*,*R*)	-	> 99	42
CH_2Ph[a]	(*R*,*R*)	-	> 99	46
CH_2F[a]	(*R*,*R*)	-	> 99	42
CH_2OBn[a]	(*R*,*R*)	-	> 99	48
CH_2OTBS[a]	(*R*,*R*)	-	> 99	47
CH_2CO_2Et[a]	(*R*,*R*)	-	> 99	44
CH_2OCO^nPr[a]	(*R*,*R*)	-	> 99	46
Ph(*p*-Cl)[a]	(*R*,*R*)	-	> 99	38
$CH_2PO(OEt)_2$[a]	(*R*,*R*)	-	93	42

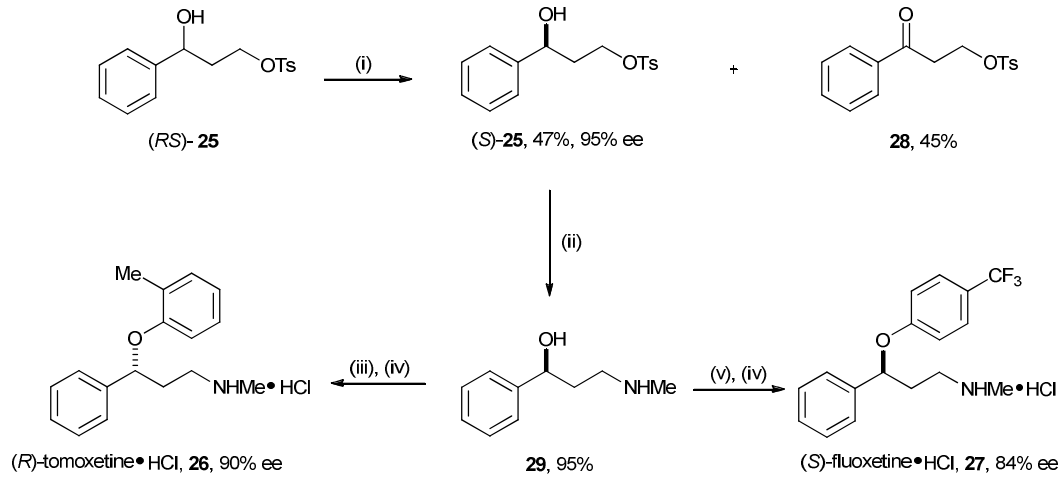
Fig. 2. Kinetic resolution of racemic epoxides using enantiopure (salen)Co(OAc) catalyst **21**. [[a] represented as the antipodes for ease of comparison]

Kinetic resolution strategies using chiral catalysts for enantioselective oxidation of one enantiomer of a racemic alcohol to its corresponding ketone have been reported. In 2001, Sigman *et al.* and Stoltz *et al.* independently reported that a Pd(II)-catalyzed oxidative kinetic resolution of a range of secondary racemic alcohols was achieved using (−)-sparteine **22** as a chiral ligand and molecular oxygen as the oxidant.[30,31] In a representative example, Sigman *et al.* found that using $Pd(OAc)_2$ gave the recovered alcohol (*S*)-**23** in 96% ee, whilst Stoltz *et al.* reported that the alternative use of $Pd(nbd)Cl_2$ increased the enantiopurity of the recovered alcohol (*S*)-**23** to 99% ee (Scheme 4).



Scheme 4. *Reagents and conditions*: (i) $Pd(OAc)_2$ (5 mol%), (−)-**22** (20 mol%), O_2 (1 atm), toluene, 60 °C, 24 h; (ii) $Pd(nbd)Cl_2$ (5 mol%), (−)-**22** (20 mol%), O_2 (1 atm), toluene, 80 °C, 112 h. [nbd = norbornadiene]

This protocol has been applied in the synthesis of (*S*)-3-phenyl-3-hydroxypropyltosylate **25**, which was used in the synthesis of the chiral drugs (*R*)-tomoxetine **26** and (*S*)-fluoxetine **27** (Scheme 5).[32]



Scheme 5. *Reagents and conditions*: (i) $Pd(OAc)_2$ (5 mol%), (−)-**22** (20 mol%), O_2 (1 atm), toluene, 80 °C, 36 h; (ii) 40% aq. $MeNH_2$, THF, 65 °C; (iii) *o*-cresol, PPh_3, DEAD, Et_2O, −10 to 0 °C; (iv) HCl (gas), Et_2O; (v) NaH, DMAC, 90 °C, *p*-$ClC_6H_4CF_3$, 100 °C.

Although developments in kinetic resolution protocols have been achieved, the inherent specificity of the procedures has limited their general application in organic synthesis. One fundamental problem with kinetic resolution is that the maximum product yield is only 50%. Moreover, the relative rate depends not only on the rate constants but also on the relative concentrations of both reactant and substrate. As the faster reacting enantiomer is removed from a kinetic resolution reaction, its concentration is reduced relative to the concentration of the slower reacting enantiomer, therefore the relative rate of the "mismatched" reaction will increase. The efficiency of a kinetic resolution approaching 50% conversion is markedly influenced by this concentration effect (known as mass action). In order to improve kinetic resolution procedures and to combat the effects of mass action, a number of processes have been developed, which can keep the relative concentrations of the reacting enantiomers constant throughout the reaction. In particular, dynamic kinetic resolution (DKR) and parallel kinetic resolution (PKR) protocols represent solutions to the problems associated with mass action.

1.4. Dynamic kinetic resolution

The overall yield of resolved products can be improved by conducting a DKR in which *in situ* racemisation of the substrate occurs. In order for the DKR to be efficient, the rate of racemisation must be faster than the rate of reaction with the undesired enantiomer of the substrate. Theoretically (although rarely observed practially) this strategy may result in complete conversion of a racemic substrate to a single enantiomerically pure product (Fig. 3).[3]

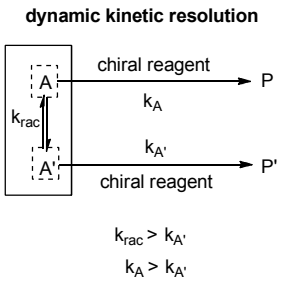
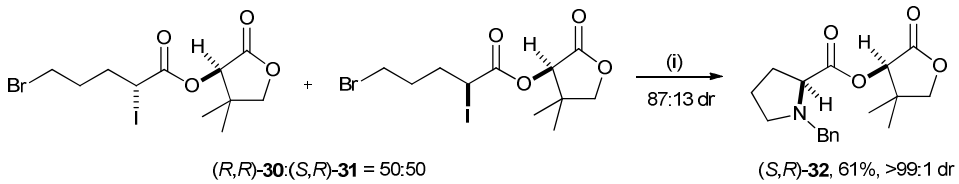


Fig. 3. Schematic representation of dynamic kinetic resolution. [A, A' = two enantiomeric substrates; P, P' = enantiomerically enriched products; k_A, $k_{A'}$ = reaction rates of the two enantiomers with reagent; k_{rac} = rate of racemisation]

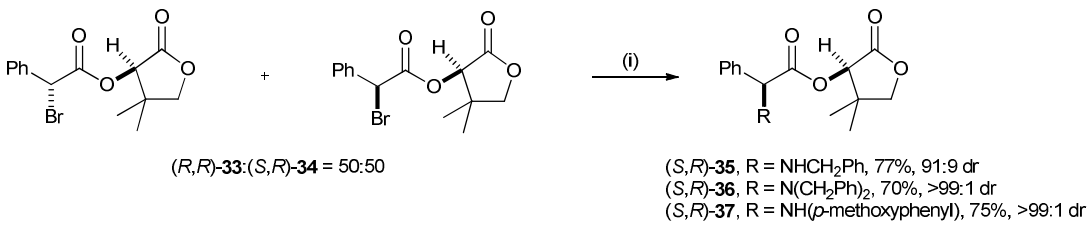
1.4.1. Dynamic kinetic resolution of alkyl halides

Although chiral alkyl halides with a halogen at a stereogenic centre are generally configurationally stable, for many α-halo carboxyl compounds, racemisation may be induced by additives such as polar solvents, base or halide sources. For example, in 1993, Durst *et al.* reported that reaction of a 50:50 mixture of **30** and **31** with benzylamine gave (*S*,*R*)-**32** as the major product in 87:13 dr, which was isolated as a single diastereoisomer in 61% yield. The authors suggested that the (*R*,*R*)-**30** diastereoisomer must react significantly faster than the (*S*,*R*)-**31** diastereoisomer. The greater than 50% yield of (*S*,*R*)-**32** was achieved by rapid racemisation of the α-iodide catalysed by the liberated bromide ion (Scheme 6).[33]



Scheme 6. *Reagents and conditions*: (i) benzylamine, Et_3N, THF, rt, 2 days.

More impressive DKR results were obtained when a 50:50 mixture of pantolactone esters **33** and **34** reacted with a range of nucleophiles in the presence of catalytic amount of tetrahexylammonium iodide. Reaction with benzylamine afforded (*S*,*R*)-**35** in 77% yield and in 91:9 dr. Moreover, using dibenzylamine and *p*-methoxyaniline gave (*S*,*R*)-**36** and (*S*,*R*)-**37** as single diastereoisomers in 70 and 75% isolated yield respectively (Scheme 7).[33] The application of the DKR strategy using the pantolactone auxiliary has also been extended to the synthesis of α-hydroxy esters[34] and 2,5-disubstituted pyrrolidines.[35]



Scheme 7. *Reagents and conditions*: (i) benzylamine, dibenzylamine, or *p*-methoxyaniline, tetrahexylammonium iodide, Et_3N, THF, rt, 2 days.

Other chiral auxiliaries have also been developed to effect this class of DKR, including *tert*-butyl (*S*)-*N*(1)-methyl-2-oxoimidazolidin-4-carboxylate **38**,[36] (4*R*,5*S*)-*N*(1),5-dimethyl -4-phenylimidazolidin-2-one **39**,[37] Oppolzer's chiral camphorsultam **40**[38] and Evans' (*S*)-4-isopropyl-oxazolidin-2-one **41** (Fig. 4).[39]

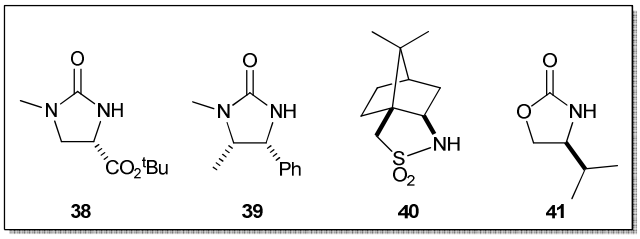
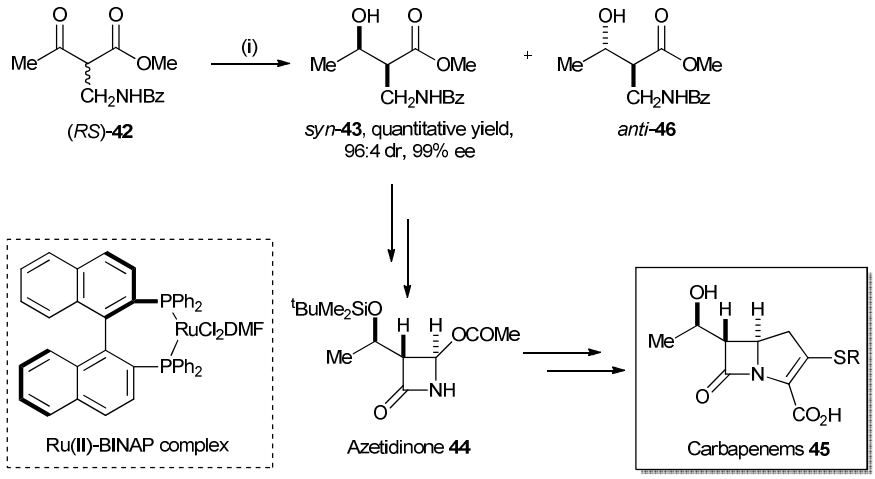


Fig. 4. Other effective chiral auxiliaries used for DKR of alkyl halides.

1.4.2. Dynamic kinetic resolution of 1,3-dicarbonyl compounds through asymmetric hydrogenation

The propensity for 2-substituted-1,3-dicarbonyl compounds to undergo racemisation via keto-enol tautomerism has long been recognised. When this property is coupled with asymmetric hydrogenation which reduces one enantiomer much faster than the other,[40] the resulting DKR can generate a variety of enantiomerically enriched α-substituted β-hydroxy carbonyl compounds. For example, Noyori and coworkers have demonstrated that use of a Ru(II)-BINAP catalytic system can effect DKR of α-substituted β-keto ester **42** with excellent control over enantioselectivity (99% ee) and diastereoselectivity (96:4 dr). In this reaction, the configuration of the catalyst determines which face of the ketone is reduced, and the substrate structure determines the stereochemistry at the β-carbon. The *syn*-β-hydroxy ester **43** generated in this DKR was used to synthesise azetidinone **44** on an industrial scale (120 ton/year), which is an important intermediate in the synthesis of carbapenem antibiotics **45** (Scheme 8).[41]



Scheme 8. *Reagents and conditions*: (i) [(*R*)-BINAP]$RuCl_2$(DMF), H_2 (100 atm), CH_2Cl_2, 50 °C.

1.5. Parallel kinetic resolution

Another approach to alleviate the problems associated with mass action is to minimize the relative build-up of the less-reactive substrate enantiomer by removing it in parallel during the course of the resolution reaction. This leads to a new strategy termed parallel kinetic resolution (PKR), in which each enantiomer (A and A') of the starting material is simultaneously converted into distinct products, P and Q, at similar rates.[20] When the two procedures work synergistically, the efficiency of the resolution is increased. PKR is powerful because the selectivity factor for it can be considerably lower than for a standard kinetic resolution to achieve the same result (Fig. 5).[4a]

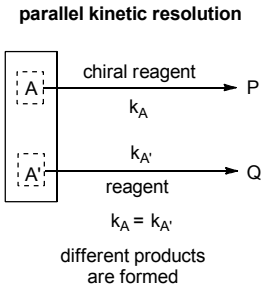
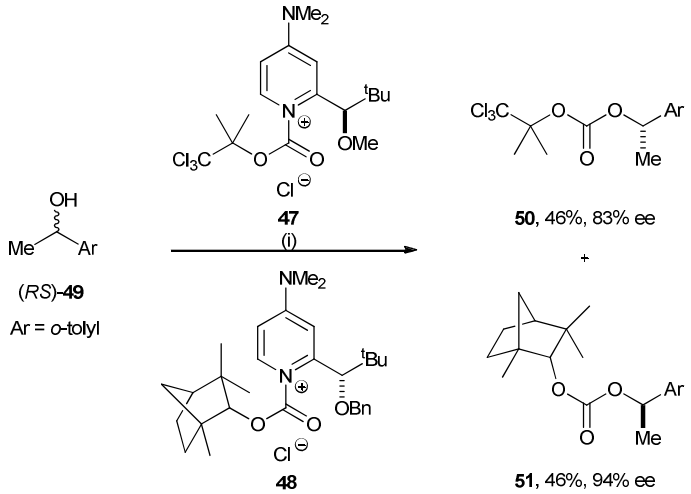


Fig. 5. Schematic representation of parallel kinetic resolution. [A, A' = two enantiomeric substrates; P = enantiomerically enriched product derived from A; k_A, $k_{A'}$ = reaction rates of the two enantiomers with reagent; Q = enantiomerically enriched product derived from A']

For PKR to be viable, the following guidelines need to be adhered to: (i) both complementary chiral reagents have to react independently without mutual interference; (ii) the two reactions need to have complementary stereocontrol and similar reaction rates to ensure that essentially racemic substrate is maintained throughout the process; and (iii) for ease of isolation, the complementary reactions must afford distinct and readily separable products. Subclasses of PKRs have been proposed, based on the structural relationship between both products, which include chemodivergent, regiodivergent and stereodivergent approaches.

1.5.1. Chemodivergent PKR

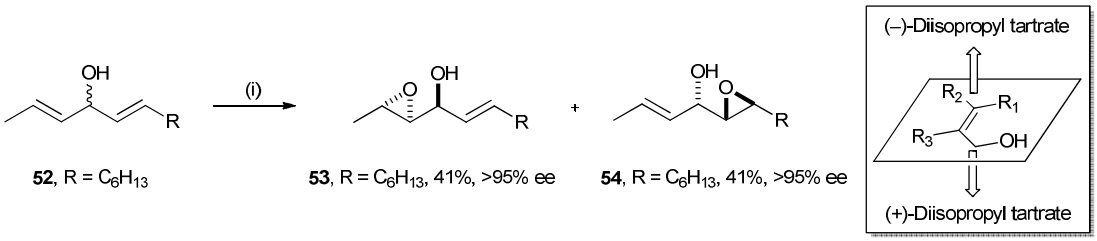
This class of PKR includes those reactions that yield two pseudoenantiomeric products which possess all the stereocenters with opposite configurations and differing structurally at a position far from them.[42] An elegant application of this strategy is using pseudoenantiomeric resolution reagents and the concept of "matched" and "mismatched" pairs.[1a] For example, Vedejs *et al.* have reported that the pseudoenantiomeric chiral DMAP-derived salts **47** and **48** can effect enantioselective acyl-transfer for PKR of racemic alcohol (*RS*)-**49**. The trichlorobutyl and fenchyl substituents of these chloroformates are significant since they are transferred to the resolved alcohol, and facilitate product separation. Although selectivity factors for kinetic resolution of (*RS*)-**49** with **47** and **48** are around 40, PKR of (*RS*)-**49** with **47** and **48** affords **50** in 46% yield and 83% ee and **51** in 46% yield and 94% ee (equivalent to selectivity factor $E > 125$), respectively (Scheme 9).[43]



Scheme 9. *Reagents and conditions*: (i) **47**, **48**, $MgBr_2$, Et_3N, CH_2Cl_2, rt, 36 h.

1.5.2. Regiodivergent PKR

In a regiodivergent PKR, the enantiomeric substrates with the same reacting functional group at different positions on the molecule react with chiral reagents via different pathways, affording regioisomeric products. Several cases of efficient regiodivergent PKR have been documented.[44] For example, Zhou and coworkers have described a regiodivergent PKR of secondary allylic alcohols in a Sharpless asymmetric epoxidation reaction. For example, when the PKR of (*RS*)-**52** was carried out with 1.0 equiv of *tert*-butyl hydroperoxide (TBHP) in the presence of $Ti(O^iPr)_4$ and L-(+)-diisopropyl tartrate (DIPT), regioisomeric epoxide products **53** and **54** were formed in good yield (≥40%) and in enantiopure form (>95% ee) (Scheme 10).[45]

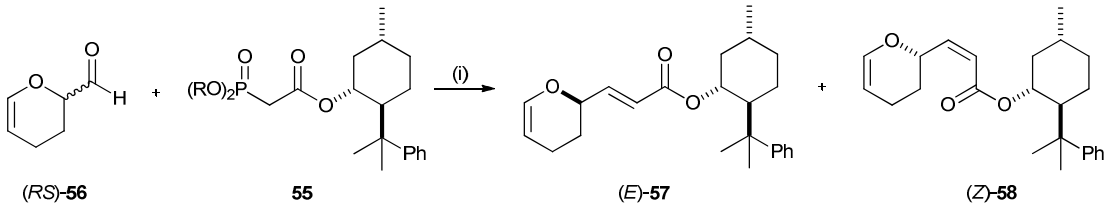


52, R = C_6H_{13} **53**, R = C_6H_{13}, 41%, >95% ee **54**, R = C_6H_{13}, 41%, >95% ee

Scheme 10. *Reagents and conditions*: (i) L-(+)-DIPT, TBHP, $Ti(O^iPr)_4$, CaH_2, silica gel, −25 °C, 6 h.

1.5.3. Stereodivergent PKR

This class of PKR includes those reactions which transform racemic substrates into diastereomeric products by introduction of a new stereocentre or by formation of geometric isomers of olefins. Several examples of PKR catalysed by enzymes are known.[46] Moreover, Rein *et al.* have reported that chiral phosphonates **55** (derived from Corey's 8-phenylmenthol auxiliary)[47] can effect PKR of racemic **56** though an asymmetric Wadsworth-Emmons reaction. These reactions show that each enantiomer of the substrate gives one different geometric isomer (*E*)-**57** and (*Z*)-**58**. It is noteworthy that partial racemization of the substrate must occur to allow for the relatively high chemical yield and modest to good levels of diastereoselectivity of each isomer, which is dependent on the phosphonate **55** used. Thus, this stereodivergent PKR has occurred in combination with a dynamic kinetic resolution process (Scheme 11).[48]



R	(*E*)/(*Z*) ratio crude	dr of (*E*) crude	dr of (*E*) isolated	yield of (*E*) %	dr of (*Z*) crude	dr of (*Z*) isolated	yield of (*Z*) %
Me	39:61	95:5	96:4	20	91:9	91:9	55
Et	73:27	92:8	92:8	70	82:18	81:19	24
^{i}Pr	95:5	84:16	87:13	89	72:28	69:31	3

Scheme 11. *Reagents and conditions*: (i) KHMDS, 18-crown-6, THF, −78 °C.

1.6. Thesis objectives

The aim of this project is to explore enantiorecognition phenomena in asymmetric synthesis. Double asymmetric induction and parallel kinetic resolution approaches were chosen to develop efficient protocols for asymmetric synthesis, and to achieve a better understanding of enantiorecognition phenomena.

It is the aim of Chapter 2 to investigate the use of double asymmetric induction as a mechanistic probe to elucidate the reactive conformation of enantiopure α,β-unsaturated esters (derived from Corey's 8-phenylmenthol chiral auxiliary **59**) and hydroxamates (derived from Davies's "chiral Weinreb amide auxiliary" **60**) upon conjugate addition of lithium amides (Fig. 6).

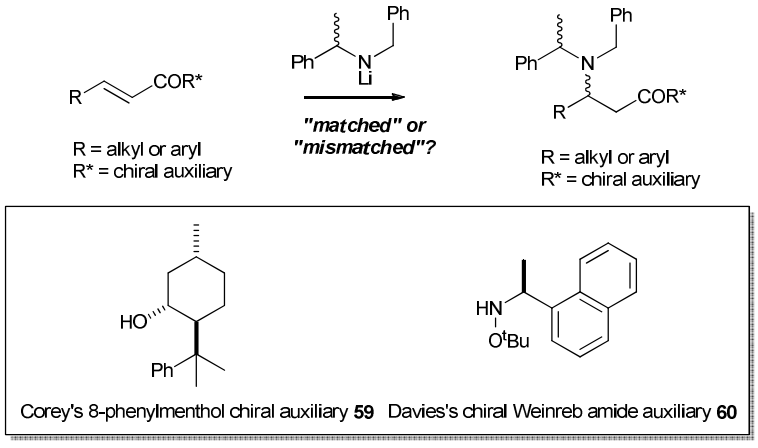


Fig. 6. The doubly diastereoselective conjugate addition of lithium amide to enantiopure α,β-unsaturated carbonyl compounds.

Chapter 3 aims to investigate the doubly diastereoselective intramolecular Michael cyclization of chiral enamides (derived from SuperQuat chiral auxiliaries **61**) and chiral α,β-unsaturated esters (derived from Corey's 8-phenylmenthol auxiliary **59**) with enantiopure amine organocatalysts (Fig. 7).

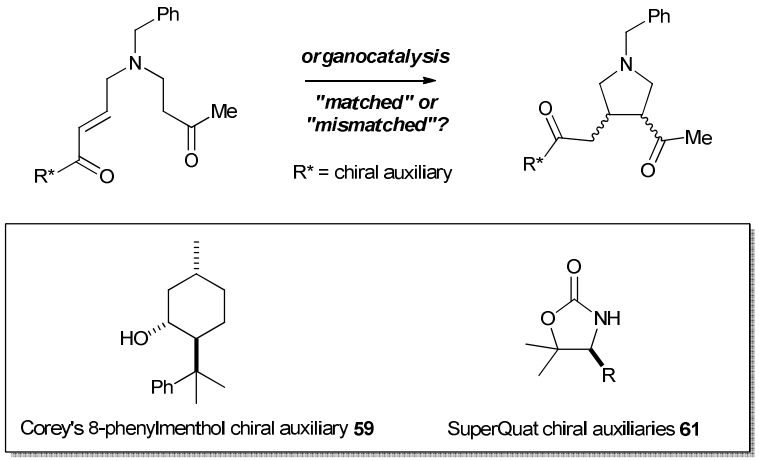


Fig. 7. Doubly diastereoselective organocatalytic Michael cyclisations of substrates incorporating chiral auxiliaries.

Finally, Chapter 4 describes investigations into the parallel kinetic resolution of acyclic γ-amino-α,β-unsaturated esters utilising a 50:50 pseudoenantiomeric mixture of lithium amides. The synthetic utility of the resulting β,γ-diamino esters is demonstrated by further elaboration to 4-amino-pyrrolidin-2-ones and the synthesis of (±)-absouline (Fig. 8).[49]

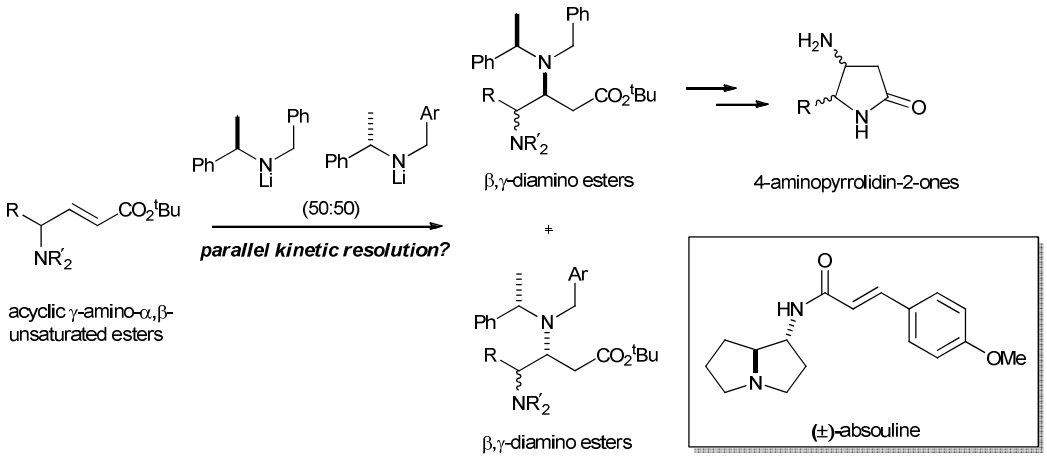


Fig. 8. Parallel kinetic resolution of acyclic γ-amino-α,β-unsaturated esters and elaboration of the resultant β,γ-diamino esters to 4-aminopyrrolidin-2-ones and (±)-absouline.

1.7. References and notes

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CHAPTER 2

Exploiting Double Asymmetric Induction as a Mechanistic Probe

2.1. Introduction

This chapter describes investigations into the use of double asymmetric induction as a mechanistic probe to elucidate the reactive conformation of enantiopure α,β-unsaturated carbonyl compounds upon conjugate addition (Fig. 9).

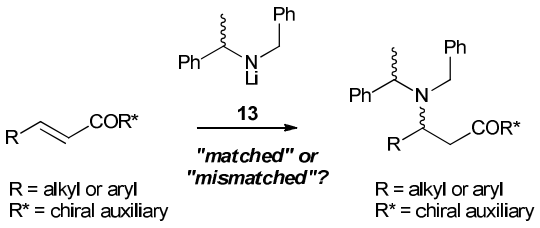
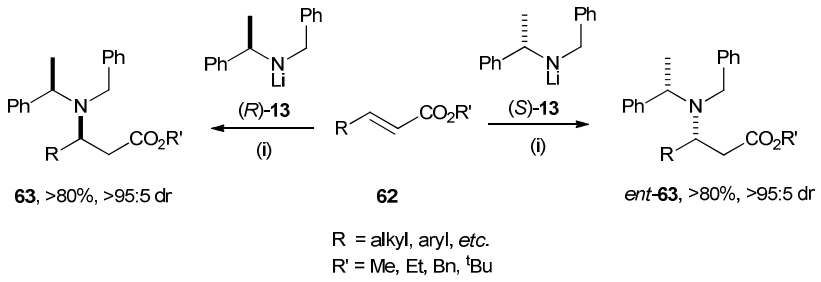


Fig. 9. The doubly diastereoselective conjugate addition of the antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **13** to enantiopure α,β-unsaturated carbonyl compounds.

2.1.1. Lithium amide conjugate addition

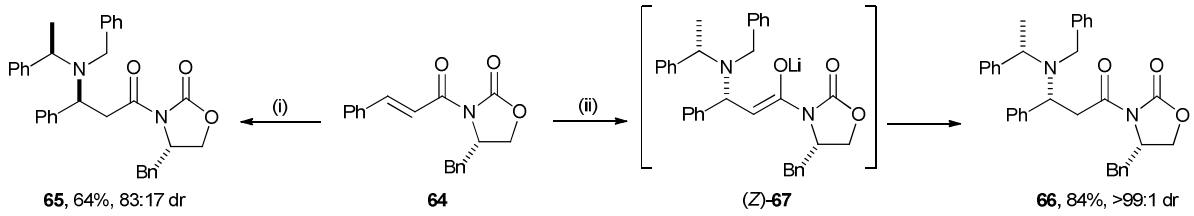
Davies and co-workers have pioneered the use of enantiomerically pure lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **13** as an enantiopure ammonia equivalent for the asymmetric synthesis of β-amino acids and their derivatives.[1] Conjugate addition of the antipodes of **13** to a range of α,β-unsaturated esters **62** proceeds with very high levels of diastereoselectivity to give the corresponding β-amino esters **63**, typically in >80% yield and >95:5 dr (Scheme 12). This methodology has found numerous applications, including in the total syntheses of natural products,[2] molecular recognition phenomena[3] and resolution protocols,[4] and has been reviewed.[5]



Scheme 12. *Reagents and conditions:* (i) (*R*)-**13** or (*S*)-**13**, THF, –78 °C.

2.1.2. Double Asymmetric Induction as a Mechanistic Probe

Using this conjugate addition methodology, Davies *et al*. have recently employed double asymmetric induction as a mechanistic probe to elucidate the reactive conformation of enantiopure *N*-enoyl oxazolidin-2-ones.[6,5] For example, the doubly diastereoselective conjugate addition of lithium amide (*R*)-**13** to *N*-enoyl oxazolidin-2-one **64** gave addition product **65** with relatively low diastereoselectivity (83:17 dr), representing the doubly diastereoselective "mismatched" pairing of chiral reagents. The corresponding conjugate addition of lithium amide (*S*)-**13** gave addition product **66** as a single diastereoisomer (>99:1 dr) in 84% yield, representing the doubly diastereoselective "matched" reaction pairing. An enolate trapping study conclusively determined that the "matched" conjugate addition of lithium amide (*S*)-**13** to *N*-enoyl oxazolidin-2-one **64** proceeded via lithium (*Z*)-β-aminoenolate **67**, the result of conjugate addition of lithium amide (*S*)-**13** to the *N*-enoyl oxazolidin-2-one **64** in an *s-cis* conformation (Scheme 13).



Scheme 13. *Reagents and conditions:* (i) (*R*)-**13**, THF, –78 °C, 2 h; (ii) (*S*)-**13**, THF, –78 °C, 2 h.

These data, in combination with the well established diastereofacial preference observed upon conjugate addition of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **13** to a range of achiral α,β-unsaturated esters and amides,[1] allowed the *anti-s-cis* form of *N*-enoyl oxazolidin-2-one **64** to be identified as the reactive conformation (Fig. 10).

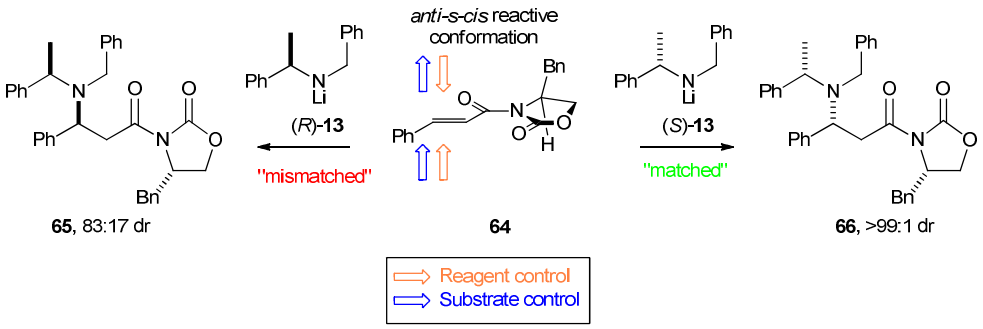


Fig. 10. The doubly diastereoselective conjugate addition of the antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **13** to enantiopure *N*-enoyl oxazolidin-2-one **64** in the *anti*-s-*cis* reactive conformation.

2.2. Project aims

Based on this precedent, it was envisaged that double asymmetric induction could be further exploited as a mechanistic probe to elucidate the reactive conformation of other chiral α,β-unsaturated carbonyl compounds upon conjugate addition. It was proposed to investigate the diastereoselectivity elicited upon conjugate addition of the antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **13** to enantiopure α,β-unsaturated esters **68** [derived from Corey's 8-phenylmenthol chiral auxiliary **59**[7]] and hydroxamates **69** [derived from (*S*)-*N*-1-(1'-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine **60**][8] (Fig. 11).

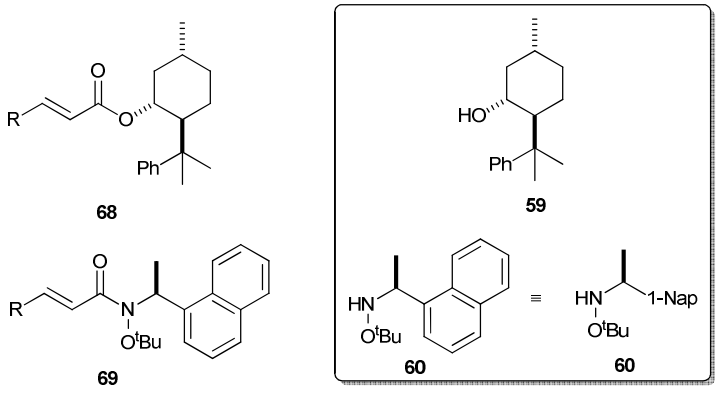
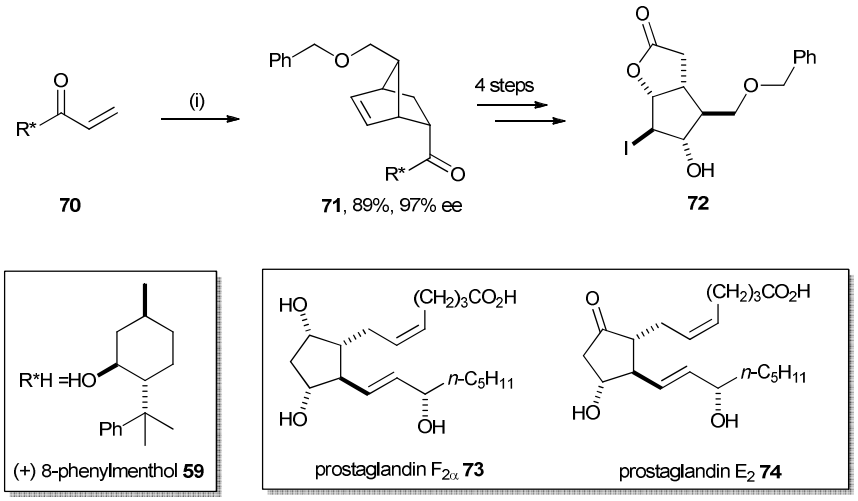


Fig. 11. Enantiopure α,β-unsaturated esters **68** [derived from Corey's 8-phenylmenthol chiral auxiliary **59**] and hydroxamates **69** [derived from (*S*)-*N*-1-(1'-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine **60**]. [1-Nap = 1-naphthyl].

2.3. Results and Discussion

2.3.1. Corey's 8-phenylmenthol auxiliary

In 1975, Corey *et al.* reported that (+)-8-phenylmenthol functioned as an exceptionally effective chiral auxiliary in the enantioselective synthesis of naturally occurring prostaglandins. Diastereoselective Diels-Alder reaction between **70** (the acrylate ester of (+)-8-phenylmenthol **59**) and 5-benzyloxymethylcyclopentadiene proceeded with high levels of asymmetric induction, giving **71** in 89% yield and 97% ee. Further manipulation of **71** gave **72**, which is the key intermediate for synthesis of prostaglandin $F_{2\alpha}$ **73** and prostaglandin E_2 **74** (Scheme 14).[7]



Scheme 14. *Reagents and conditions:* (i) 5-benzyloxymethylcyclopentadiene, $AlCl_3$, CH_2Cl_2, −55 °C, 1 h.

Since then, Corey's 8-phenylmenthol auxiliary **59** has shown considerable versatility in synthesis,[9] and has found use in, for example, nucleophilic addition reactions,[10] cycloadditions,[11] intermolecular ene reactions,[12] oxidation reactions,[13] reduction reactions,[14] rearrangement processes,[15] photochemical/radical reactions,[16] and as a resolving agent.[17]

2.3.2. Conjugate additions of achiral nucleophiles to α,β-unsaturated esters of Corey's auxiliary

α,β-Unsaturated esters of Corey's 8-phenylmenthol auxiliary **68** have also shown application as substrates in diastereoselective conjugate addition reactions.[18] In these systems, π-stacking of the aromatic moiety with the enoyl system is proposed to be crucial in determining the diastereofacial selectivity. It is therefore possible for an 8-phenylmenthyl α,β-unsaturated ester to undergo diastereoselective conjugate addition in any one of four possible conformations: two *s-cis* conformations **68A** and **68B**, and two *s-trans* conformations **68C** and **68D** (Fig. 12).[19]

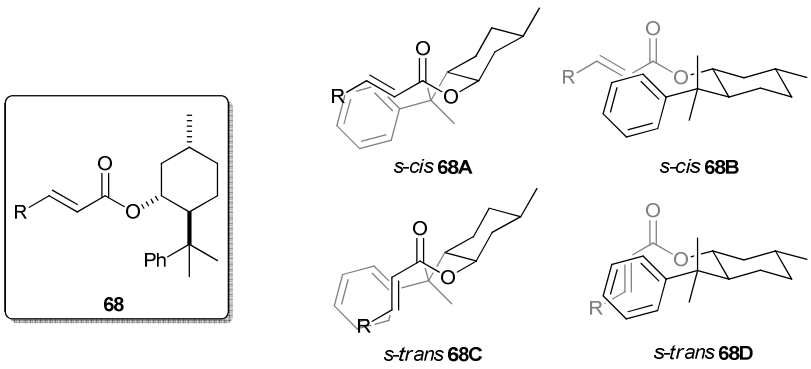
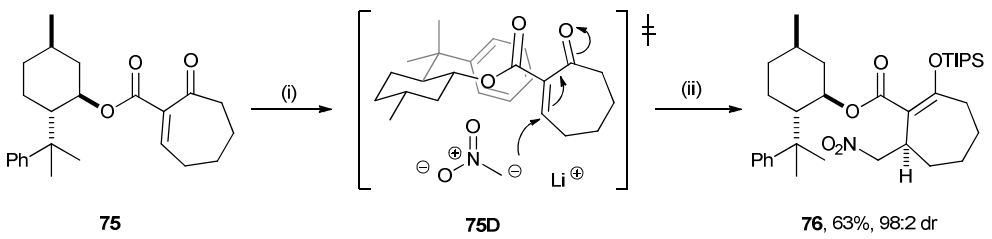


Fig. 12. Possible conformations of **68**: *s-cis* **68A** and **68B**, and *s-trans* **68C** and **68D**.

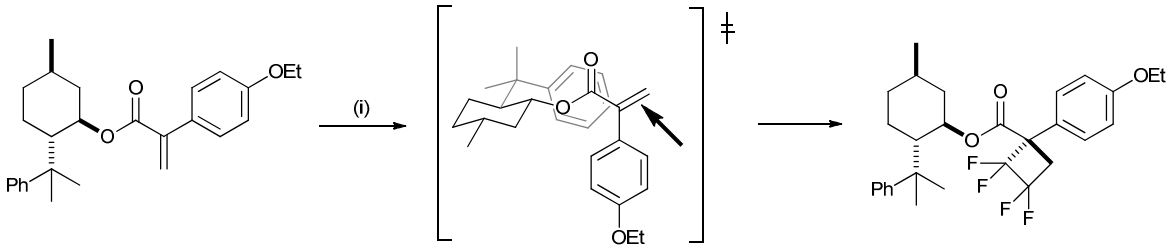
In some of the reported cases, a reactive conformation has been proposed to account for the asymmetric induction.[11b,15b,15c,18b] For instance, Ikeda *et al*. reported that conjugate addition of the lithium anion of nitromethane to **75** followed by addition of TIPSOTf gave **76** in 63% yield and 98:2 dr. Here, the *s-trans* conformation **75D** was proposed to be the reactive one, with addition of the lithium anion of nitromethane giving a transient enolate, which was trapped to afford silyl enol ether **76** (Scheme 15).[18e]



75 **75D** **76**, 63%, 98:2 dr

Scheme 15. *Reagents and conditions:* (i) BuLi, $MeNO_2$, THF, −78 °C; (ii) TIPSOTf, HMPA, −78 to 0 °C.

In another example, the addition of tetrafluoroethylene to acrylate **77** gave the major product **78** in 70% yield and 79:21 dr. Here, it was postulated that *s-cis* conformation **77B** was adopted to maximise the π-stacking interaction, with subsequent reaction on the least hindered face leading to **78** (Scheme 16).[11e]



77 **77B** **78**, 70%, 79:21 dr

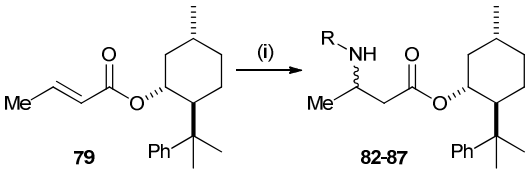
Scheme 16. *Reagents and conditions:* (i) tetrafluoroethylene, cyclohexane, 130 to 180 °C, 15 h.

In all these examples, however, it is noteworthy that the same product would result from attack on the least hindered face of both conformations *s-cis* **68A** and *s-trans* **68D**, whilst the diastereoisomeric product would result from attack on the least hindered face of either conformation *s-cis* **68B** or *s-trans* **68C**. Therefore, it follows that it is impossible to unambiguously determine the reactive conformation by assessment of the product distribution of single asymmetric transformations.

2.3.3. Conjugate additions of chiral nucleophiles to α,β-unsaturated esters of Corey's auxiliary

One pertinent example concerning the conjugate addition of amine nucleophiles to chiral α,β-unsaturated esters of Corey's auxiliary was reported by d'Angelo and Maddaluno who investigated the high pressure induced conjugate addition of primary amines to chiral

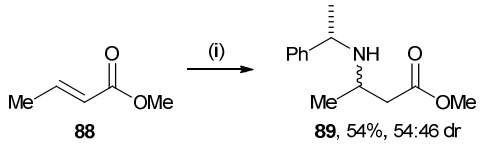
α,β-unsaturated esters such as **79**.[20] The authors noted that whilst moderate levels of diastereoselectivity were obtained upon conjugate addition of primary amines to **79**, "*the double diastereodifferentiation phenomenon was not observed*" upon addition of either (*R*)- or (*S*)-α-methylbenzylamine **80** to **79** (Scheme 17).



RNH_2	R	products	dr	combined yield (%)
(*R*)-**80**	(*R*)-CHMePh	**82:83**	75:25	60
(*S*)-**80**	(*S*)-CHMePh	**84:85**	80:20	60
81	Bn	**86:87**	80:20	90

Scheme 17. *Reagents and conditions:* (i) RNH_2, MeOH, 15 kbar, 50 °C, 24 h.

This finding is consistent with the poor diastereoselectivity observed upon thermal addition of (*S*)-α-methylbenzylamine **80** to methyl crotonate **88**, which has been reported to give a 54:46 epimeric mixture of β-amino esters **89** (Scheme 18).[21]

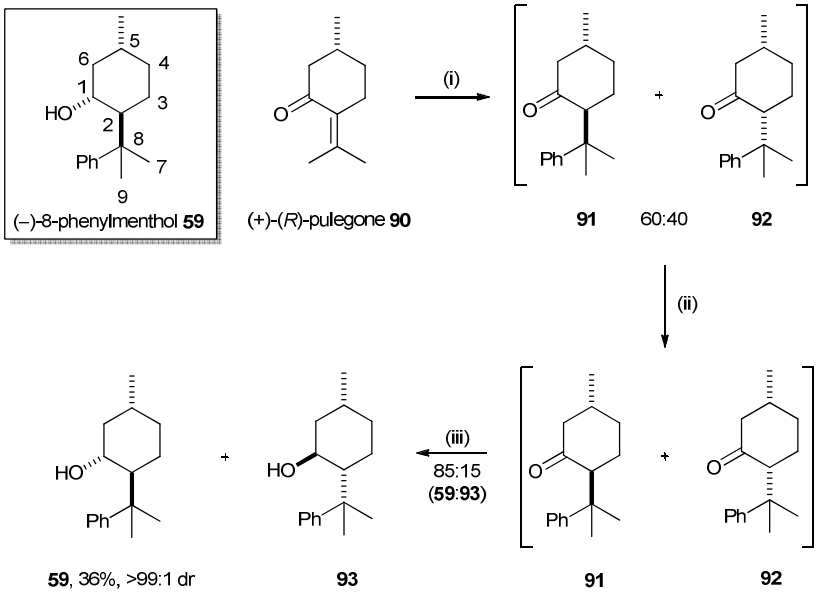


Scheme 18. *Reagents and conditions:* (i) (*S*)-α-methylbenzylamine **80**, MeOH, reflux, 96 h.

In contrast, the conjugate addition of secondary lithium amides such as lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **13** to a range of achiral α,β-unsaturated esters at –78 °C in THF has consistently been shown to proceed with extremely high levels of diastereoselectivity (typically >95:5 dr)[5] with the α,β-unsaturated esters in an *s-cis* conformation.[6b,22] Assuming that this preference also applies for conjugate addition to α,β-unsaturated esters of Corey's auxiliary **68**, the two *s-trans* conformations **68C** and **68D** can be discounted, and it was proposed that by employing the tool of double asymmetric induction, the reactive *s-cis* conformation **68A** or **68B** for conjugate addition can be elucidated.

2.3.4. Synthesis of Corey's 8-phenylmenthol auxiliary

In launching this investigation, (−)-8-phenylmenthol **59** was selected because of its easy access from the starting material (+)-(*R*)-pulegone **90**.[23] According to a literature procedure,[24] copper-catalyzed conjugate addition of phenylmagnesium bromide to (+)-(*R*)-pulegone **90** provided a 60:40 mixture of *trans*-ketone **91** and *cis*-ketone **92**, which was equilibrated upon treatment with ethanolic potassium hydroxide to give an 85:15 mixture of *trans*-**91**:*cis*-**92**.[25] Subsequent reduction of this mixture with sodium-isopropyl alcohol in refluxing toluene gave an 85:15 mixture of (−)-8-phenylmenthol **59** and its C(5)-epimer **93**, which shows opposite asymmetric induction to that of (−)-8-phenylmenthol **59**.[26] Thus, complete separation of the two diastereoisomers **59** and **93** is essential, and was accomplished by column chromatography to give (−)-8-phenylmenthol **59** in 36% overall yield and >99:1 dr. A 75:25 mixture of **59** and **93** was also isolated in 30% yield (Scheme 19).

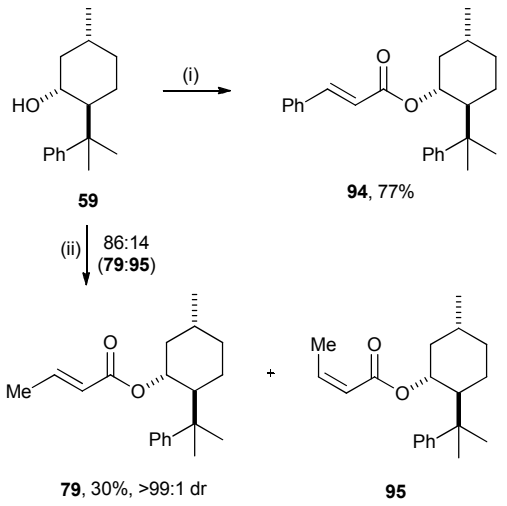


Scheme 19. *Reagents and conditions:* (i) PhMgBr, CuBr, Et_2O, −20 °C, 18 h; (ii) KOH, EtOH/H_2O, reflux, 3 h; (iii) Na, IPA, toluene, reflux, 8 h.

2.3.5. Synthesis of chiral α,β-unsaturated esters

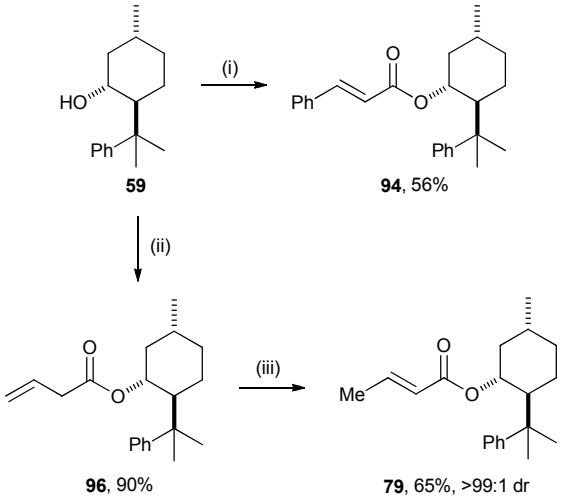
8-Phenylmenthyl crotonate **79** and 8-phenylmenthyl cinnamate **94** were selected as model substrates for this investigation, and their synthesis by coupling the requisite acid chlorides with (−)-8-phenylmenthol **59** was investigated. According to a literature procedure,[13] treatment of **59** with cinnamoyl chloride in the presence of catalytic DMAP gave **94** in 77%

isolated yield. However, application of these conditions to reaction of crotonoyl chloride with (−)-8-phenylmenthol **59** afforded an 86:14 mixture of 8-phenylmenthyl crotonate **79** and the corresponding isomer (Z)-**95**. 8-Phenylmenthyl crotonate **79** was isolated from this mixture in 30% yield and >99:1 dr upon chromatographic purification (Scheme 20).



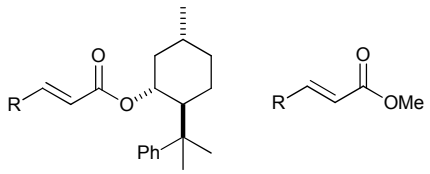
Scheme 20. *Reagents and conditions:* (i) cinnamoyl chloride, DMAP, THF, rt, 18 h; (ii) crotonoyl chloride, DMAP, THF, rt, 18 h.

As an alternative method for the preparation of α,β-unsaturated esters **79** and **94**, the use of the requisite acid chlorides in the presence of $^{i}Pr_2NEt$ was investigated. Under these conditions, reaction of (−)-8-phenylmenthol **59** and cinnamoyl chloride gave **94** in 56% isolated yield. Meanwhile, treatment of **59** with crotonoyl chloride in the presence of $^{i}Pr_2NEt$ gave β,γ-unsaturated ester **96** as the only product which was isolated in 90% yield. This result is consistent with observations of the deconjugation of double bonds in the crotonoylation of an alcohol reported by Ozeki and Kusaka,[27] which was found to be dependent on several factors such as the identities of the amine base and the alcohol used, the solvent and the temperature.[27] In this case, however, isomerisation of **96** was achieved upon treatment with DBU to give α,β-unsaturated ester **79** in 65% yield and >99:1 dr (Scheme 21).



Scheme 21. *Reagents and conditions:* (i) cinnamoyl chloride, $^{i}Pr_2NEt$, THF, rt, 18 h; (ii) crotonoyl chloride, $^{i}Pr_2NEt$, THF, rt, 18 h; (iii) DBU, THF, rt, 18 h.

At this stage, a comparative study of the ^{1}H NMR spectra for **79** and **94**, and the corresponding methyl esters **88** and **97**, proved to be informative. The peaks corresponding to the olefinic C(2)*H* and C(3)*H* protons within both esters **79** and **94** derived from Corey's 8-phenylmenthol auxiliary **59** are shifted upfield with respect to the corresponding resonances in the ^{1}H NMR spectra of methyl esters **88** and **97**. This analysis suggests that the phenyl group of the auxiliary effectively shields one face of the olefin, and is therefore consistent with the models invoked by previous investigators, in which π-stacking of the aromatic moiety of the auxiliary and that of the enoyl system is crucial in determining the diastereoselectivity (Fig. 13).[28]



79, R = Me
94, R = Ph

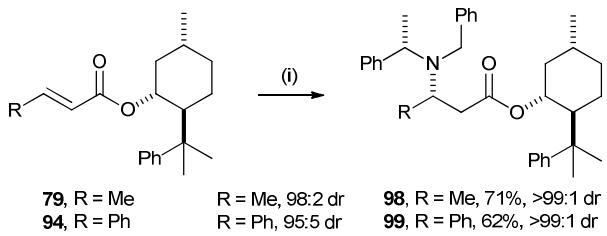
88, R = Me
97, R = Ph

Ester	R	δ_H (ppm) for C(2)*H*	δ_H (ppm) for C(3)*H*
79	Me	5.38	6.50
88	Me	5.76	6.81
94	Ph	5.81	7.20[a]
97	Ph	6.53	7.73

Fig. 13. ^{1}H NMR data for chiral α,β-unsaturated esters **79** and **94**, and the corresponding methyl esters **88** and **97**. [[a] approximate value (±0.05 ppm) due to peak overlap].

2.3.6. Conjugate additions of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide 13

The doubly diastereoselective conjugate additions of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **13**[29] to α,β-unsaturated esters **79** and **94** were first investigated. Both reactions proceeded with high diastereoselectivity, giving β-amino esters **98** and **99** in 98:2 and 95:5 dr, respectively. In both cases, the major diastereoisomeric products were isolated as single diastereoisomers (>99:1 dr) after chromatographic purification (Scheme 22).



Scheme 22. *Reagents and conditions:* (i) (*S*)-**13**, THF, –78 °C, 2 h.

The relative configuration within **98** was unambiguously established by single crystal X-ray diffraction analysis,[30] with the absolute (3*S*,1'*R*,2'*S*,5'*R*,α*S*)-configuration assigned relative to the known configurations of both the (+)-(*R*)-pulegone derived auxiliary **59** and the (*S*)-α-methylbenzyl stereocentre (Fig. 14). It is noteworthy that the relative configurations of the C(3) and C(α)-stereogenic centres within **98** are consistent with those predicted by the transition state mnemonic that was developed to rationalise the exceptional diastereofacial bias of this class of lithium amide conjugate addition.[1b,5] These observations, combined with the very high levels of diastereoselectivity observed in the conjugate addition reactions suggest that these are the doubly diastereoselective "matched" reaction pairings.

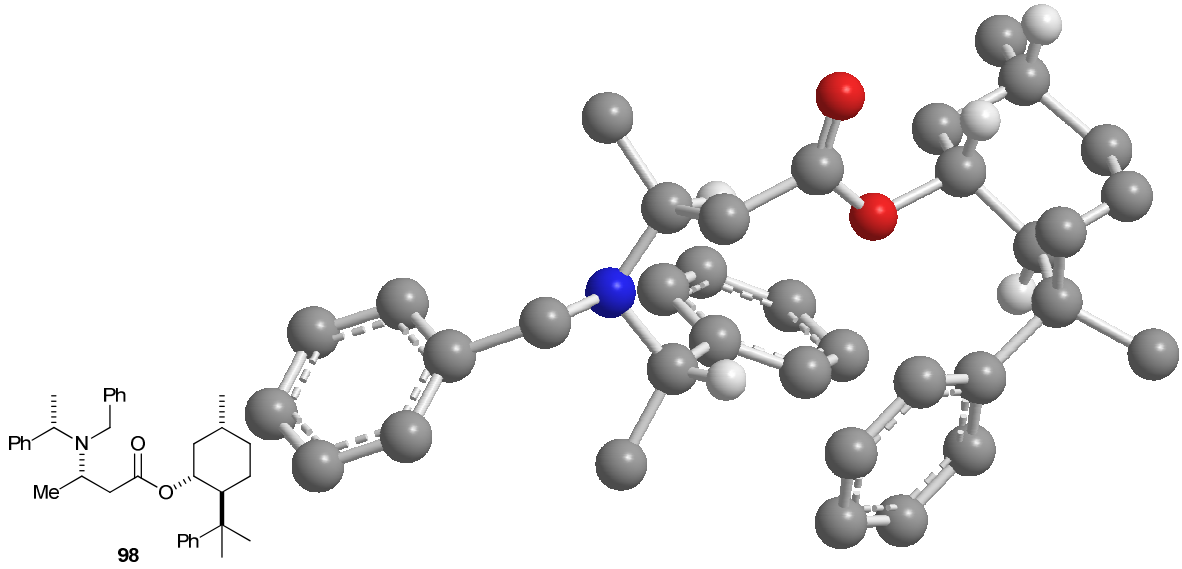
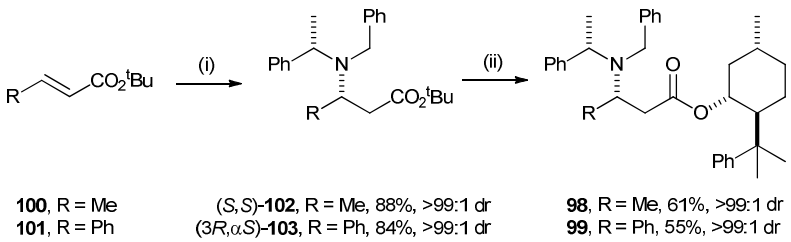


Fig. 14. X-ray crystal structure of (3*S*,1'*R*,2'*S*,5'*R*,α*S*)-**98** (selected H atoms are omitted for clarity).

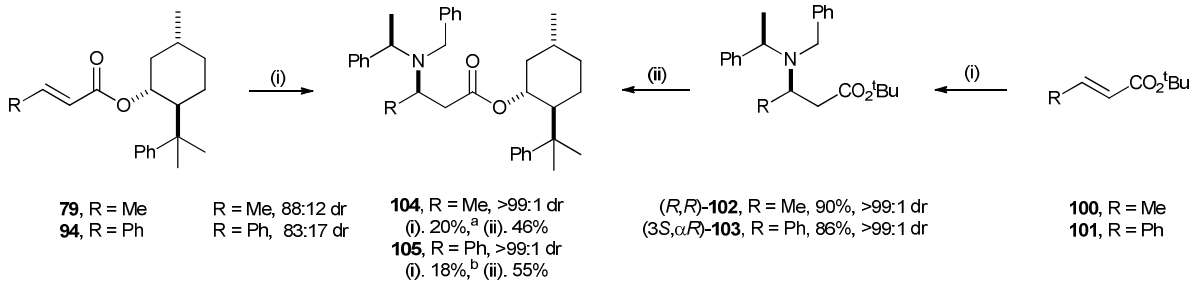
The configuration at C(3) within β-amino ester **99** was unambiguously established by a separate chemical synthesis: β-amino ester (3*R*,α*S*)-**103** [obtained from the conjugate addition of lithium amide (*S*)-**13** to *tert*-butyl cinnamate **101**][31] was treated with TFA to give the corresponding carboxylic acid, which was coupled with Corey's auxiliary **59** via the intermediacy of the corresponding acid chloride. The spectroscopic properties, including specific rotation value, of the sample of β-amino ester **99** prepared in this manner were identical to the major diastereoisomer arising from the conjugate addition of lithium amide (*S*)-**13** to **94**, providing unequivocal evidence of the sense of stereoinduction observed in this reaction. An analogous sequence of transformations applied to β-amino ester (*S*,*S*)-**102** (derived from *tert*-butyl crotonate **100**)[1a,b] gave β-amino ester **98**, thus confirming that no epimerisation of the C(3)-stereogenic centre occurs during this sequence of transformations (Scheme 23).



Scheme 23. *Reagents and conditions:* (i) (*S*)-**13**, THF, –78 °C, 2 h; (ii) TFA/CH_2Cl_2 (v/v 1:1), rt, 2 h, then $(COCl)_2$, DMF, CH_2Cl_2, 0 °C to rt, 1 h then **59**, CH_2Cl_2, rt, 18 h.

2.3.7. Conjugate additions of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide 13

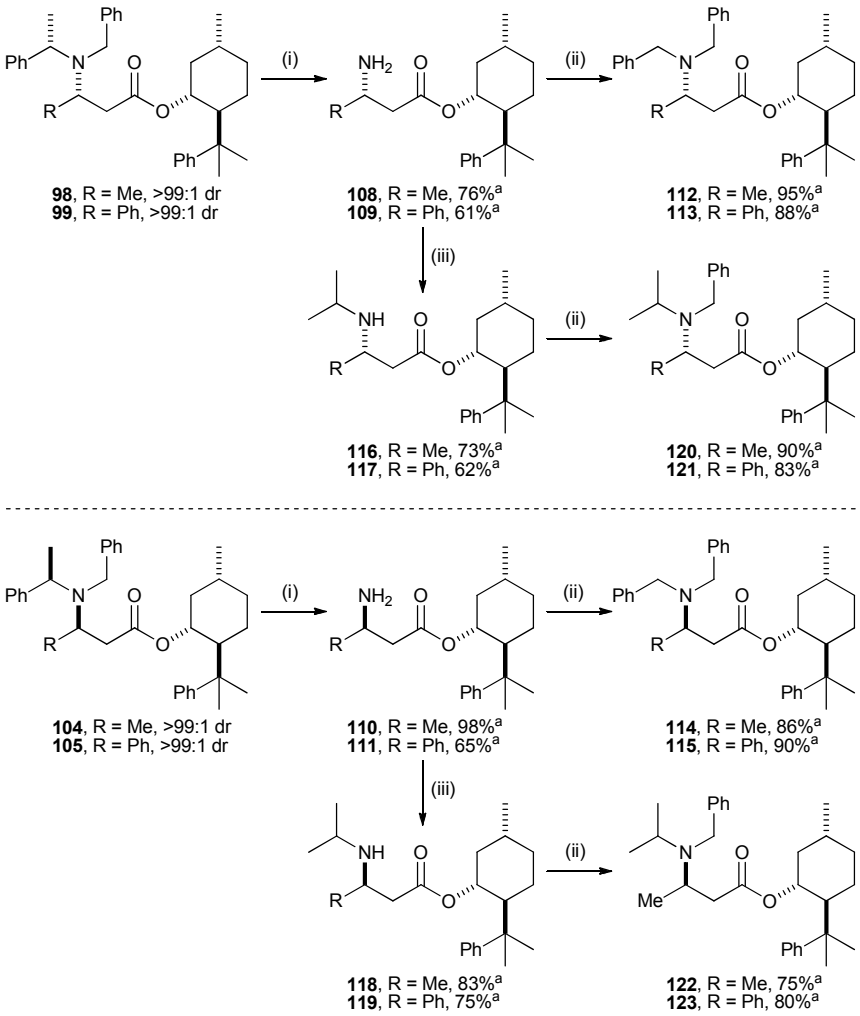
Upon conjugate addition of lithium amide (*R*)-**13** to both α,β-unsaturated esters **79** and **94** only modest levels of diastereoselectivity were observed, giving **104** and **105** as the major products in 88:12 and 83:17 dr, respectively. In both cases, partial separation of the diastereoisomeric products of conjugate addition was achieved upon chromatographic purification, with the major diastereoisomeric products being isolated as single diastereoisomers (>99:1 dr), along with mixed fractions. The configurations at C(3) within β-amino esters **104** and **105** were established unambiguously by a separate chemical synthesis in each case. β-Amino esters (*R*,*R*)-**102** and (3*S*,α*R*)-**103** [obtained from the conjugate addition of lithium amide (*R*)-**13** to *tert*-butyl crotonate **100** and *tert*-butyl cinnamate **101** respectively][31,1a,b] were treated with TFA to give the corresponding carboxylic acids, which were coupled with Corey's auxiliary **59**, via the intermediacy of the corresponding acid chlorides. The spectroscopic properties, including specific rotation values, of the samples of β-amino esters **104** and **105** prepared in this manner were identical to the major diastereoisomers arising from the conjugate addition of lithium amide (*R*)-**13** to α,β-unsaturated esters **79** and **94**, providing unequivocal evidence of the sense of stereoinduction observed in these reaction pairings. These results suggest that it is the stereocontrol of the lithium amide (*R*)-**13** and not the 8-phenylmenthol chiral auxiliary that has the dominant influence in determining the diastereoselectivity of these doubly diastereoselective "mismatched" reactions (Scheme 24).



Scheme 24. *Reagents and conditions:* (i) (*R*)-**13**, THF, –78 °C, 2 h; (ii) TFA/CH_2Cl_2 (v/v 1:1), rt, 2 h, then $(COCl)_2$, DMF, CH_2Cl_2, 0 °C to rt, 1 h then **59**, CH_2Cl_2, rt, 18 h. [[a] An 85:15 mixture of **104** and its C(3)-epimer was also isolated in 50% combined yield; [b]An 83:17 mixture of **105** and its C(3)-epimer was also isolated in 70% combined yield].

2.3.8. Conjugate additions of lithium dibenzylamide 106 and lithium *N*-isopropyl-*N*-benzylamide 107

It was next proposed to explore the conjugate additions of achiral lithium dibenzylamide **106**[32] and lithium *N*-isopropyl-*N*-benzylamide **107**[4] to α,β-unsaturated esters **79** and **94** in order to assess the extent of substrate control offered by the 8-phenylmenthol auxiliary in these systems. Initially, authentic samples of all the diastereoisomeric products of the proposed conjugate additions were prepared in order to facilitate subsequent analysis of the outcomes of the conjugate addition reactions. The *N*-benzyl and *N*-α-methylbenzyl groups within β-amino esters **98**, **99**, **104** and **105** were removed via hydrogenolysis in the presence of Pearlman's catalyst [$Pd(OH)_2$/C] to give **108**-**111** in 61-98% yield as single diastereoisomers (>99:1 dr) in each case. β-Amino esters **108**-**111** were then treated with BnBr in the presence of K_2CO_3 at 100 °C to provide authentic samples of the *N*,*N*-dibenzyl substituted β-amino esters **112**-**115** in 86-95% yield and >99:1 dr. β-Amino esters **108**-**111** were also subjected to a reductive amination procedure to give single diastereoisomers of the *N*-isopropyl substituted analogues **116**-**119** in 62-83% yield and >99:1 dr. Finally, treatment of **116**-**119** with BnBr provided access to authentic samples of the *N*-isopropyl-*N*-benzyl substituted β-amino esters **120**-**123** in 75-90% yield and >99:1 dr (Scheme 25).



Scheme 25. *Reagents and conditions:* (i) H_2 (5 atm), $Pd(OH)_2/C$, MeOH, AcOH, rt, 18 h; (ii) BnBr, K_2CO_3, 100 °C, 7 h; (iii) acetone, $NaBH_3CN$, MeOH, rt, 18 h. [[a] isolated in >99:1 dr].

The relative configuration within **112** was confirmed by single crystal X-ray diffraction analysis,[30] with the absolute (3*S*,1'*R*,2'*S*,5'*R*)-configuration within **112** assigned relative to the known configuration of the (+)-(*R*)-pulegone derived auxiliary **59** (Fig. 15).

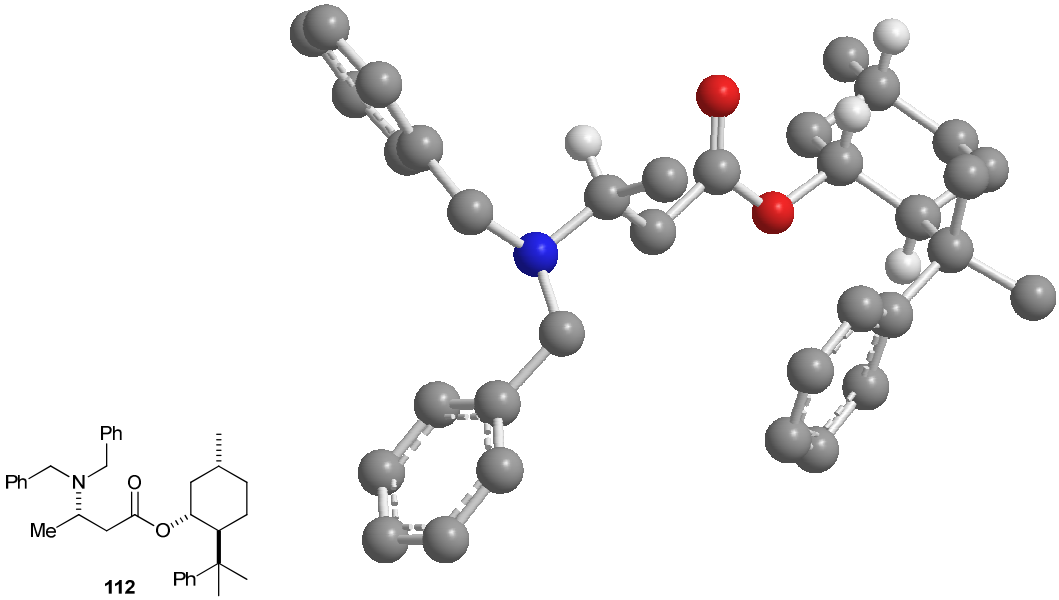
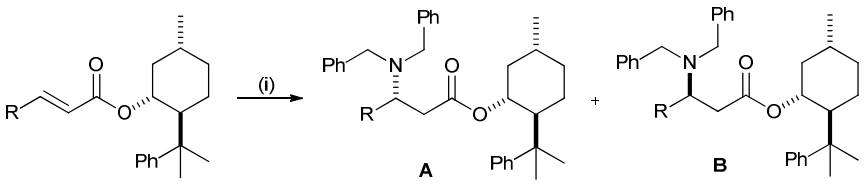


Fig. 15. X-ray crystal structure of (3*S*,1'*R*,2'*S*,5'*R*)-**112** (selected H atoms are omitted for clarity).

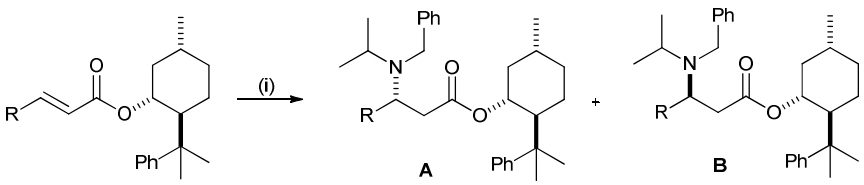
With these authentic samples in hand, the conjugate additions of lithium dibenzylamide **106**[33] to both α,β-unsaturated esters **79** and **94** were examined. These conjugate addition reactions proceeded with modest levels of diastereoselectivity to give a mixture of **112** and **114** in 78:22 dr, and a mixture of **113** and **115** in 65:35 dr. In the case of addition to **79**, the major diastereoisomeric product **112** was isolated in 25% yield and >99:1 dr, along with a 63:37 mixture of **114** and **112**, respectively, in 10% yield. The conjugate addition products **113** and **115** (derived from **94**) proved to be inseparable, and were therefore isolated as a 65:35 mixture in 85% combined yield. The spectroscopic properties of **112**-**115** were identical to those of the authentic samples previously prepared, providing unequivocal evidence of the sense of stereoinduction observed in these reactions (Scheme 26).



Substrate	R	A	B	crude dr (A:B)	yield of A (dr A:B) %	yield of B (dr B:A) %
79	Me	**112**	**114**	78:22	25 (>99:1)	10 (63:37)
94	Ph	**113**	**115**	65:35	85 (65:35)	–

Scheme 26. *Reagents and conditions:* (i) lithium dibenzylamide **106**, THF, –78 °C, 2 h.

Upon conjugate addition of lithium *N*-isopropyl-*N*-benzylamide **107** [34] to both α,β-unsaturated esters **79** and **94**, similar levels of diastereoselectivity were observed, and a 72:28 mixture of **120** and **122**, and an 80:20 mixture of **121** and **123**, were obtained, respectively. In the case of conjugate addition to **79**, the major diastereoisomeric product **120** was isolated as a single diastereoisomer (>99:1 dr) in 9% yield after chromatographic purification, along with a mixed fraction (containing **120** and **122** in 83:17 dr) in 40% combined yield. In the conjugate addition of **107** to **94**, separation of the diastereoisomeric products could not be achieved, and thus **121** and **123** were isolated as an 80:20 mixture in 78% combined yield. The spectroscopic properties of the conjugate products **120**-**123** were identical to those of the authentic samples previously prepared, providing unequivocal evidence of the sense of stereoinduction observed in these reaction pairings (Scheme 27).



Substrate	R	A	B	crude dr (A:B)	yield of A (dr A:B) %
79	Me	**120**	**122**	72:28	9 (>99:1)[a]
94	Ph	**121**	**123**	80:20	78 (80:20)

Scheme 27. *Reagents and conditions:* (i) lithium *N*-isopropyl-*N*-benzylamide **107**, THF, –78 °C, 2 h. [[a] An 83:17 mixture of **120** and **122** was also isolated in 40% combined yield]

2.3.9. The origins of diastereoselectivity observed upon conjugate addition of both antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide 13 to 8-phenylmenthyl α,β-unsaturated esters

Considering the double asymmetric induction observed upon conjugate addition of the antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **13** to both chiral α,β-unsaturated esters **79** and **94**, in the "matched" cases conjugate addition of lithium amide (*S*)-**13** to α,β-unsaturated ester **79** results in the preferential formation of β-amino ester **98** in 98:2 dr, and conjugate addition of lithium amide (*S*)-**13** to α,β-unsaturated ester **94** results in the preferential formation of β-amino ester **99** in 95:5 dr. In the "mismatched" cases, conjugate addition of lithium amide (*R*)-**13** to α,β-unsaturated ester **79** results in the formation of β-amino ester **104** in 88:12 dr, and the conjugate addition of lithium amide (*R*)-**13** to α,β-unsaturated ester **94** results in the formation of β-amino ester **105** in 83:17 dr. These empirical "matched" and "mismatched" product distributions cannot be achieved if the reaction were to proceed through *s-cis* conformations **79A** and **94A**, but are consistent with addition of lithium amides (*S*)-**13** and (*R*)-**13** to α,β-unsaturated esters **79** and **94** in *s-cis* conformations **79B** and **94B**. In this model, the preferential addition of lithium amide (*S*)-**13** to the *Re* face of the double bond at C(3) within **94B** (reagent control) coincides with addition opposite to the bulky stereodirecting group of the auxiliary (substrate control), and is consistent with the formation of β-amino ester **99** in the "matched" reaction. An analogous argument is able to rationalise preferential formation of β-amino ester **98** from **79B**. The formation of β-amino esters **104** and **105** as the major diastereoisomers in the "mismatched" cases may occur via approach of the lithium amide (*R*)-**13** on the same face as the stereodirecting phenyl group of the auxiliary in conformations **79B** and **94B**, although these data do not discount the possibility that the formation of β-amino esters **104** and **105** may occur via preferential addition of lithium amide (*R*)-**13** to α,β-unsaturated esters **79** and **94** in an alternative conformation (Fig. 16).

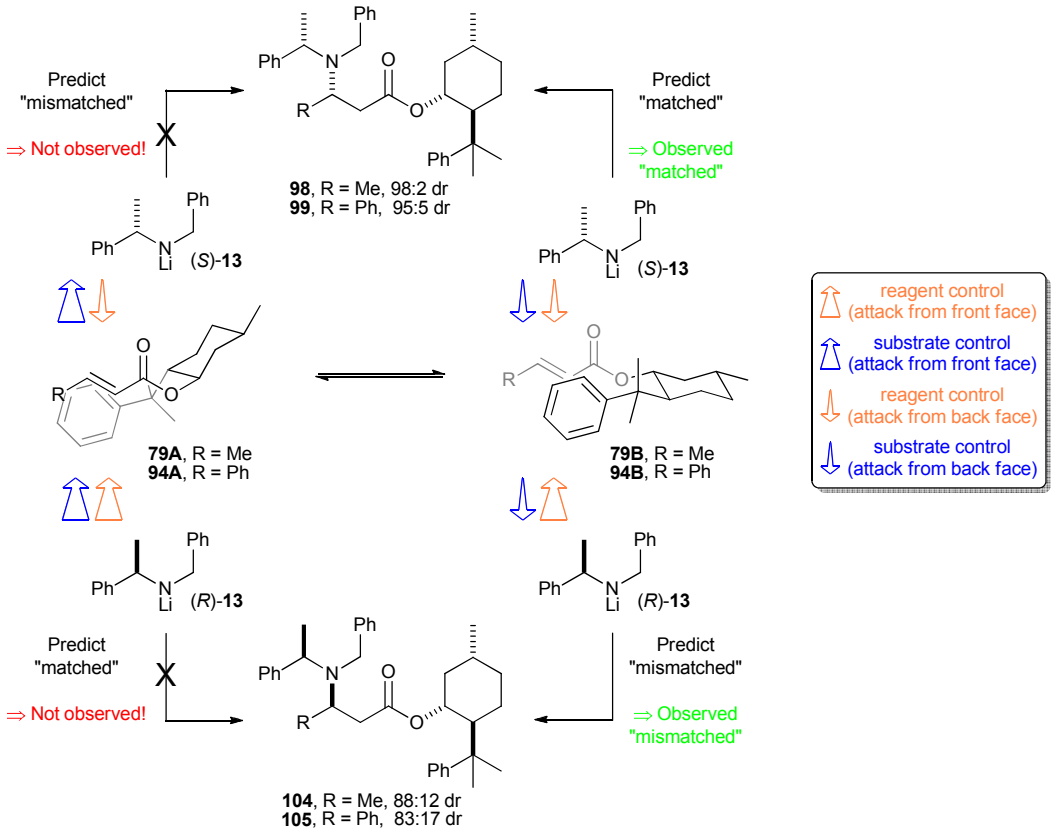
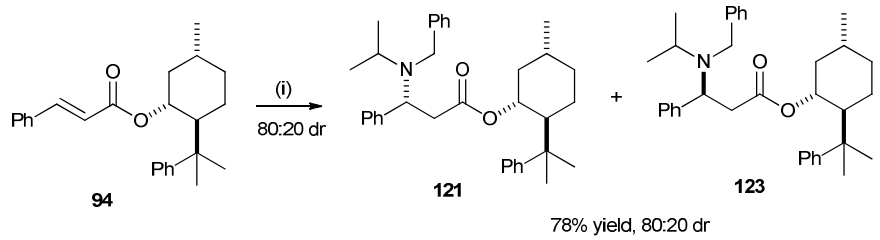


Fig. 16. Model to rationalise the observed "matched" and "mismatched" double asymmetric induction; given the observed "matched" and "mismatched" reaction pairings, the reactive conformation cannot be **79A** and **94A**.

2.3.10. The origins of diastereoselectivity observed upon conjugate additions of achiral lithium amides to 8-phenylmenthyl α,β-unsaturated esters

In addition, it is useful to consider the modest diastereoselectivities (ranging from 65:35 dr to 80:20 dr) upon the conjugate addition of both achiral lithium amides **106** and **107** to both α,β-unsaturated esters **79** and **94**. For ease of discussion, the conjugate addition of *N*-isopropyl-*N*-benzylamide **107** to α,β-unsaturated ester **94** proceeding in 80:20 dr is illustrated below (Scheme 28).



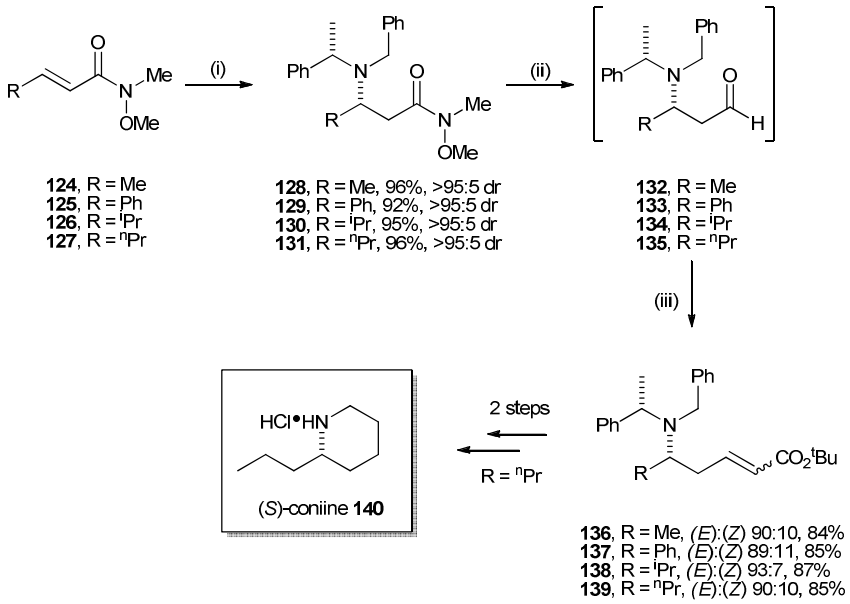
Scheme 28. *Reagents and conditions:* (i) **107**, THF, –78 °C, 2 h.

A number of mechanistic scenarios may account for the product distribution: (i) The conjugate addition of *N*-isopropyl-*N*-benzylamide **107** takes place with exclusive diastereofacial selectivity (opposite to the stereodirecting phenyl group of the auxiliary) to an unequilibrating 80:20 mixture of **94B** and **94A** conformers of **94**; (ii) The conjugate addition of *N*-isopropyl-*N*-benzylamide **107** takes place to a rapidly equilibrating mixture of **94B** and **94A** conformers, with unknown diastereofacial selectivity; or (iii) The conjugate addition of *N*-isopropyl-*N*-benzylamide **107** exclusively takes place to conformer **94B** with modest (80:20 dr) facial selectivity.

If the reaction proceeded under scenario (i), neither conjugate addition of (*S*)-**13** nor (*R*)-**13** to α,β-unsaturated ester **94** would be expected to lead to a highly diastereoselective reaction. Obviously, the high level of diastereoselectivity (95:5 dr) arising from conjugate addition of (*S*)-**13** proves this is not the case. If the reaction proceeded under scenario (ii), conjugate addition of both antipodes of lithium amide **13** to α,β-unsaturated ester **94** would have proceeded with equal and high levels of diastereocontrol (Curtin-Hammett control). This possibility has been eliminated by the observation of double asymmetric induction (i.e., "matching" and "mismatching") in these systems. Thus, after eliminating scenarios (i) and (ii), it may be concluded that the conjugate addition of *N*-isopropyl-*N*-benzylamide **107** should exclusively take place to conformer **94B**, with modest diastereofacial selectivity. It follows that this mechanistic scenario should also apply to other conjugate additions of achiral lithium amides **106** and **107** to both α,β-unsaturated esters **79** and **94**.

2.3.11. Weinreb amides

N-Methoxy-*N*-methyl amides (Weinreb amides) were introduced by Nahm and Weinreb in 1981.[35] These compounds were shown to have a main advantage over other carboxylic acid derivatives: over-addition products derived from reaction with an excess of organometallic and hydride reducing agents are limited and therefore they show great utility for the direct synthesis of aldehydes and ketones. Since then, Weinreb amides have enjoyed ever-increasing use in organic synthesis.[36] Within this area, previous investigations by Davies *et al*. have shown that conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **13** to a range of α,β-unsaturated Weinreb amides **124**-**127** proceeds efficiently, with high levels of diastereoselectivity (>95:5 dr), to generate the β-amino Weinreb amides **128**-**131**. Subsequent transformation into the corresponding β-amino aldehydes **132**-**135** can be achieved by treatment with DIBAL-H. Trapping of the aldehydes via Wadsworth-Emmons reaction furnishes α,β-unsaturated-δ-amino esters **136**-**139**. This approach was employed for the synthesis of 2-substituted piperidines such as the alkaloid (*S*)-coniine **140** (Scheme 29).[2c]



Scheme 29. *Reagents and conditions:* (i) (*S*)-**13**, THF, –78 °C, 2 h; (ii) DIBAL-H, hexanes, THF, 0 °C then acetone, $C_4H_4KNaO_6$ (satd aq); (iii) $(EtO)_2POCH_2CO_2{}^tBu$, BuLi, THF, –78 °C to rt.

2.3.12. *N*-1-(1'-Naphthyl)ethyl-*O*-*tert*-butylhydroxamate: a chiral Weinreb amide equivalent

Davies and co-workers have recently demonstrated that *N*-acyl derivatives of *N*-1-(1'-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine **60** are able to act as chiral Weinreb amide equivalents.[8a,37] The alkylations of enolates derived from *N*-1-(1'-naphthyl)ethyl-*O*-*tert*-butylhydroxamates such as **141** proceed with high levels of diastereoselectivity (>95:5 dr) to give access to the corresponding enantiopure α-stereogenic aldehydes **143** or ketones **144** in >95% ee following treatment of the intermediate hydroxamates **142** with either $LiAlH_4$ or MeLi respectively (Fig. 17). This route offers a convenient synthesis of α-stereogenic aldehydes and ketones in a single reductive operation. This property of the chiral auxiliary makes it superior to many other chiral auxiliaries, such as Oppolzer's sultam[38,39] and Evans's oxazolidinones,[40,41] cleavage of which to generate aldehydes usually requires at least two synthetic steps.[42,43]

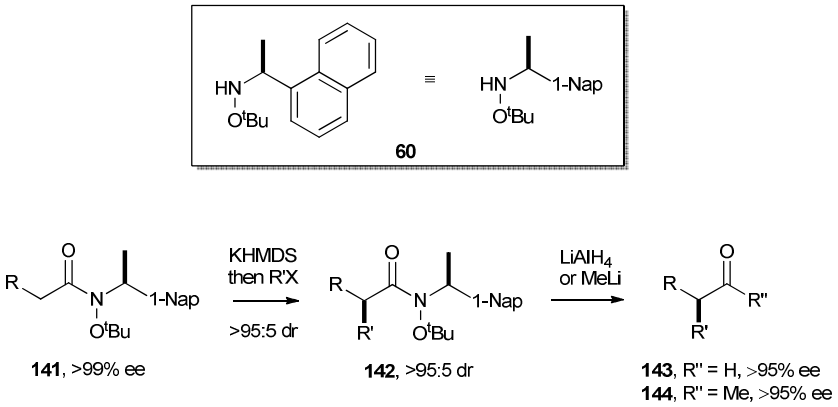


Fig. 17. Alkylation of chiral Weinreb amide equivalents **141**, derived from *N*-1-(1'-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine **60**, and conversion to enantiopure aldehydes **143** and ketones **144**.

A 'chiral relay'[44] mechanism was proposed to rationalise the observed stereochemical outcome in these reactions, and this was subsequently validated by a combination of evidence gained through experimental observations (including modification of the auxiliary structure), physical measurements, and molecular mechanics calculations.[8b] It was shown that deprotonation of **141** with KHMDS leads to a non-chelated (*Z*)-enolate **145** with the oxygen atoms adopting an *anti*-periplanar conformation. The configuration of the *N*-1-(1′-naphthyl)ethyl group dictates the position of the *O*-*tert*-butyl group and the

configuration adopted by the pyramidal nitrogen atom. Subsequent enolate alkylation occurs on the face *anti* to both the *O*-*tert*-butyl group (steric control) and *N*-lone pair (stereoelectronic control) (Fig. 18).

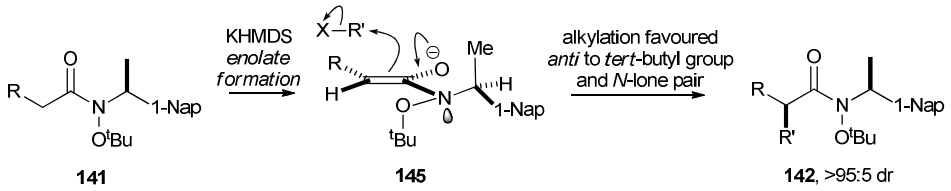


Fig. 18. The proposed 'chiral relay' mechanism in the alkylation of chiral Weinreb amide equivalents **141**.

Based on these studies, it was envisaged that α,β-unsaturated hydroxamates **69** [derived from (*S*)-*N*-1-(1'-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine **60**] may undergo conjugate addition reactions with high levels of diastereocontrol at the β-position. In order to evaluate this hypothesis, the conjugate addition of the antipodes of **13**, and achiral lithium amides **106** and **107**, to α,β-unsaturated hydroxamates **146** was proposed, and it was also anticipated that the tool of double asymmetric induction could be used to identify the reactive conformation of **69** in this case (Fig. 19).

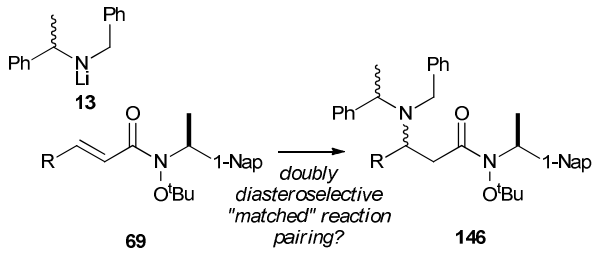
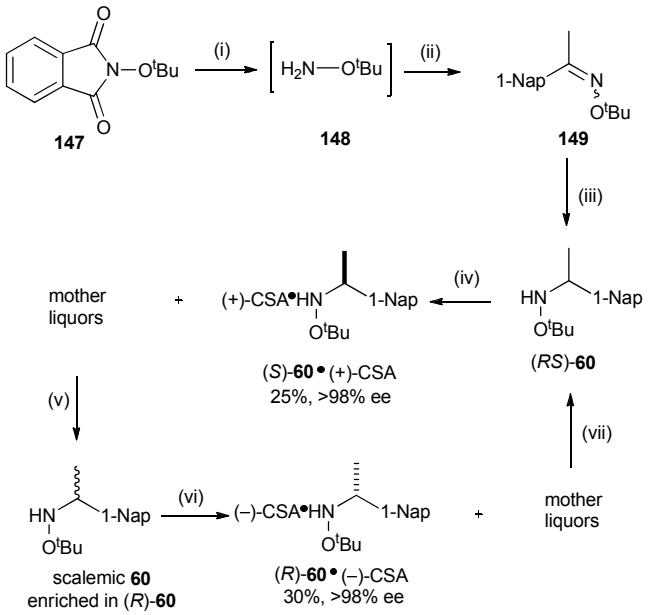


Fig. 19. Proposed doubly diastereoselective conjugate addition of the antipodes of **13** to α,β-unsaturated hydroxamates **69**. [1-Nap = 1-naphthyl].

2.3.13. Synthesis of the antipodes of *N*-1-(1'-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine 60

According to a literature procedure,[8a] the synthesis of the antipodes of *N*-1-(1'-naphthyl)-ethyl-*O*-*tert*-butylhydroxylamine **60** was initiated by the release of *O*-*tert*-butylhydroxyl-amine **148** from *N*-*tert*-butoxyphthalimide **147** (available "in house") using a stoicheiometric amount of methylhydrazine. Subsequent condensation of **148** with 1-acetylnaphthalene under acidic conditions gave the corresponding oxime ether **149** as an

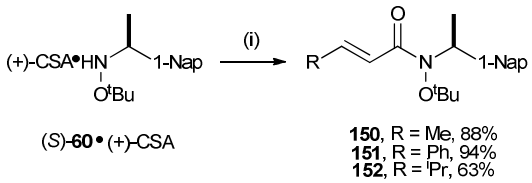
87:13 mixture of geometric isomers, which was treated with borane-pyridine complex and ethanolic HCl to afford hydroxylamine (*RS*)-**60**. Addition of (+)-camphorsulfonic acid [(+)-CSA] to (*RS*)-**60** in acetone at −30 °C furnished the single diastereoisomeric salt (*S*)-**60**·(+)-CSA as crystals. The mother liquors were basified, extracted and treated with (−)-CSA under identical conditions to furnish the antipode (*R*)-**60**·(−)-CSA as a single diastereoisomer. After recrystallization from acetone and repetition of the process to obtain a second crop, (*S*)-**60**·(+)-CSA and (*R*)-**60**·(−)-CSA were obtained in 25 and 30% overall yield, respectively (Scheme 30).



Scheme 30. *Reagents and conditions:* (i) $MeNHNH_2$, CH_2Cl_2, rt, 12 h; (ii) 1-acetylnaphthalene, EtOH, AcOH, reflux, 12 h; (iii) BH_3·pyridine, HCl, EtOH, 0 °C to rt, 2 h; (iv) (+)-CSA, acetone, −30 °C, 12 h; (v) 1.0 M aq NaOH; (vi) (−)-CSA, acetone, −30 °C, 12 h; (vii) 1.0 M aq NaOH. [1-Nap = 1-naphthyl].

2.3.14. Synthesis of chiral α,β-unsaturated hydroxamates

Enantiopure α,β-unsaturated hydroxamates **150**, **151** and **152** were prepared in 63-94% yield by reaction of (*S*)-**60**·(+)-CSA with crotonoyl, cinnamoyl and 4-methylpent-2-enoyl chlorides, respectively. The 400 MHz ^{1}H NMR spectra of **150**, **151** and **152** were exceptionally broad in $CDCl_3$ at rt and some resonances of low intensity were present in the 100 MHz ^{13}C NMR spectra. These characteristics of the NMR spectra were indicative of these compounds being rotameric in $CDCl_3$ at rt. However, ^{1}H NMR spectroscopic analysis of **150**, **151** and **152** at 343 K in PhMe-d_8 revealed that peak coalescence had occurred (Scheme 31).



Scheme 31. *Reagents and conditions:* (i) RCH=CHCOCl, K_2CO_3, CH_2Cl_2, rt, 18 h. [1-Nap = 1-naphthyl].

2.3.15. Conformations of chiral α,β-unsaturated hydroxamates

The solid state conformations of **150** and **151** were also investigated by single crystal X-ray diffraction (Fig. 20).[30] In both cases the conformation of the "chiral Weinreb amide" auxiliary was found to be consistent with previous observations concerning this class of hydroxamates:[45] i.e., that the oxygen atoms adopt an *anti*-periplanar conformation, the *O-tert*-butyl group is approximately perpendicular to this plane, the nitrogen atom is pyramidalized, and the nitrogen lone pair lies *syn*-periplanar to the *O-tert*-butyl group. This conformational preference is consistent with hydroxylamine itself for which the lowest energy conformation has lone pairs and bonds eclipsed to minimise lone pair-lone pair interactions.[46] A search of the Cambridge Structural Database reveals that Weinreb amides show a similar conformational preference in the solid state.[8b] It is notable that these structures also bear a notable resemblance to that proposed for enolate **145**. Assuming that **150**, **151** and **152** adopt similar conformations in solution it may therefore be reasoned that their reactive conformations upon conjugate addition are similar also. In this case the conjugate addition of lithium amide (*R*)-**13** would be predicted to be the doubly diastereoselective "matched" reaction pairing with nucleophilic attack preferentially occurring on the face *anti* to both the *O-tert*-butyl group and *N*-lone pair.

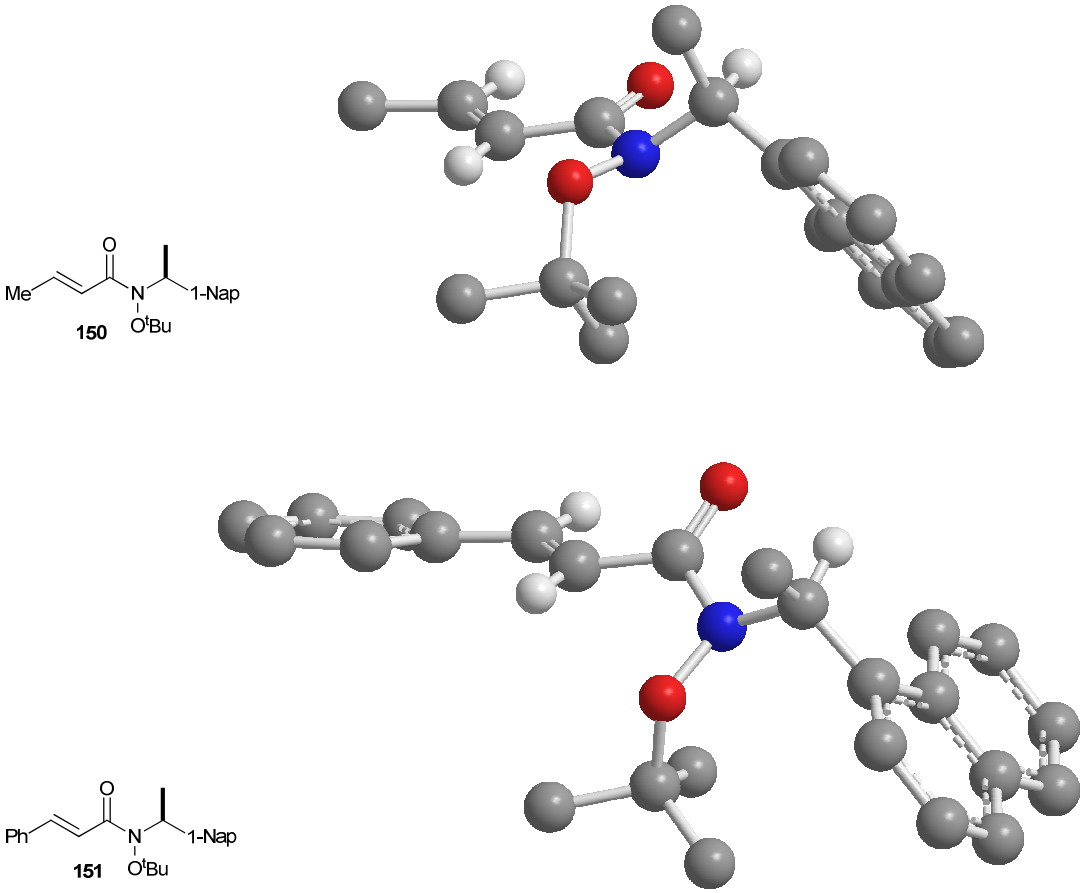
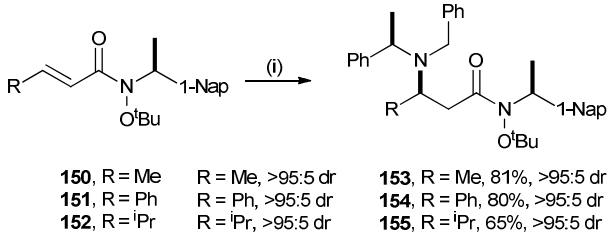


Fig. 20. X-ray crystal structures of **150** and **151** (selected H atoms are omitted for clarity). [1-Nap = 1-naphthyl].

2.3.16. Conjugate additions of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide 13

The conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **13** to enantiopure α,β-unsaturated hydroxamates **150**, **151** and **152** were first investigated. The conjugate additions of (*R*)-**13** to **150**, **151** and **152** gave, in each case, the corresponding β-amino hydroxamates **153**, **154** and **155** in >95:5 dr,[47] representing the doubly diastereoselective "matched" reaction pairings (Scheme 32).



Scheme 32. *Reagents and conditions:* (i) (*R*)-**13**, THF, –78 °C, 2 h.

The relative configuration within **153** was unambiguously assigned by single crystal X-ray diffraction analysis,[30] with the absolute (3*R*,1'*S*,α*R*)-configuration assigned relative to the known configurations of both the (*R*)-α-methylbenzyl stereocentre and the (*S*)-*N*-1-(1'-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine **60** derived "chiral Weinreb amide" auxiliary (Fig. 21). This analysis also confirmed that the relative configurations of the C(3) and C(α)-stereogenic centres within **153** was in accord with that predicted by the transition state mnemonic for lithium amide conjugate addition reaction.[1b,5]

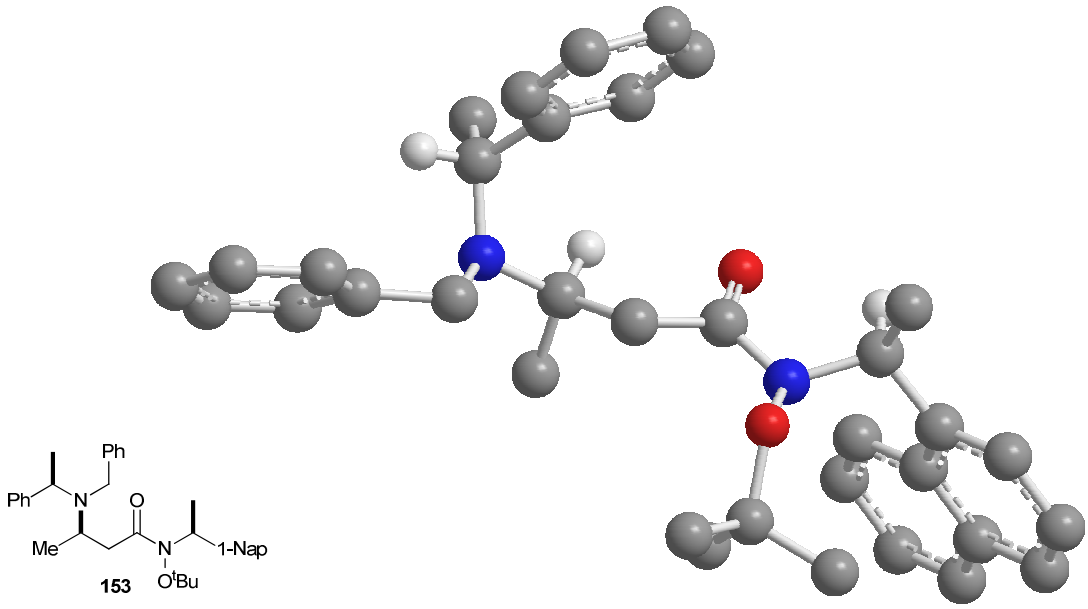
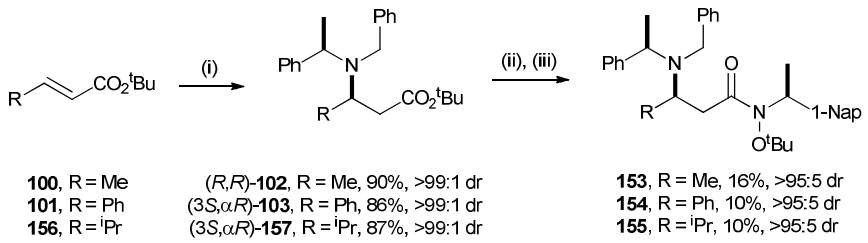


Fig. 21. X-ray crystal structure of (3*R*,1'*S*,α*R*)-**153** (selected H atoms are omitted for clarity). [1-Nap = 1-naphthyl].

The configurations at C(3) within **154** and **155** were established unambiguously by a separate chemical synthesis in each case: β-amino esters (3*S*,α*R*)-**103** and (3*S*,α*R*)-**157** [obtained from the conjugate addition of lithium amide (*R*)-**13** to *tert*-butyl cinnamate **101** and *tert*-butyl 4-methylpent-2-enoate **156** respectively][31] were hydrolysed with TFA then the resultant carboxylic acids were coupled with (*S*)-*N*-1-(1'-naphthyl)ethyl-*O*-*tert*-butyl-hydroxylamine **60** to give authentic samples of **154** and **155** as single diastereoisomers (>95:5 dr), although the overall yields obtained in the coupling step were relatively low. The spectroscopic properties, including specific rotation values, of the samples of **154** and **155** prepared in this manner were consistent with the major diastereoisomers arising from the conjugate addition of lithium amide (*R*)-**13** to α,β-unsaturated hydroxamates **151** and **152**, providing unequivocal evidence of the sense of stereoinduction observed in these reaction pairings. An analogous sequence of transformations applied to β-amino ester (*R*,*R*)-**102**

(derived from *tert*-butyl crotonate **100**)[1a,b] gave β-amino ester **153**, thus confirming that no epimerisation of the C(3) stereogenic centre occurs during this sequence of transformations (Scheme 33).



100, R = Me
101, R = Ph
156, R = ^{i}Pr

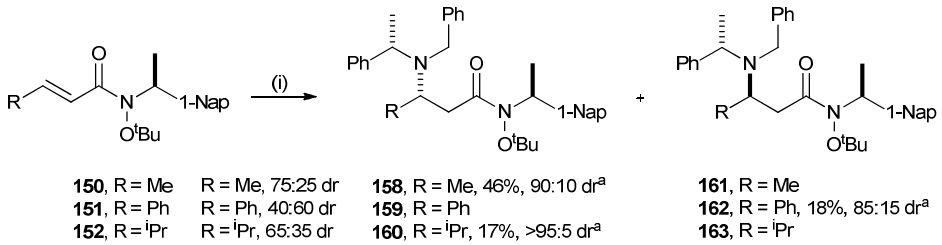
(*R*,*R*)-**102**, R = Me, 90%, >99:1 dr
(3*S*,α*R*)-**103**, R = Ph, 86%, >99:1 dr
(3*S*,α*R*)-**157**, R = ^{i}Pr, 87%, >99:1 dr

153, R = Me, 16%, >95:5 dr
154, R = Ph, 10%, >95:5 dr
155, R = ^{i}Pr, 10%, >95:5 dr

Scheme 33. *Reagents and conditions:* (i) (*R*)-**13**, THF, –78 °C, 2 h; (ii) TFA/CH_2Cl_2 (v/v 1:1), rt, 2 h; (iii) $(COCl)_2$, DMF, CH_2Cl_2, rt, 1 h then (*S*)-**60**·(+)-CSA, K_2CO_3, CH_2Cl_2, 16 h. [1-Nap = 1-naphthyl]

2.3.17. Conjugate additions of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide 13

The levels of diastereoselectivity observed upon conjugate addition of lithium amide (*S*)-**13** to α,β-unsaturated hydroxamates **150**, **151** and **152** were much lower, representing the doubly diastereoselective "mismatched" reaction pairings. Upon conjugate addition of lithium amide (*S*)-**13** to α,β-unsaturated hydroxamate **150**, modest levels of diastereoselectivity was observed, giving **158** as the major product in 75:25 dr. Purification of the crude reaction mixture gave **158** in 46% yield and 90:10 dr, along with a 60:40 mixture of **158**:**161** in 30% combined yield. Conjugate addition of lithium amide (*S*)-**13** to α,β-unsaturated hydroxamate **152** proceeded with modest levels of diastereoselectivity to give **160**:**163** in 65:35 dr. The major product **160** was isolated as a single diastereoisomer (>95:5 dr) in 17% yield upon purification, along with a 68:32 mixture of **160**:**163** in 25% combined yield. Meanwhile, in the case of the C(3)-phenyl substituted α,β-unsaturated hydroxamate **151** conjugate addition of lithium amide (*S*)-**13** gave a 40:60 mixture of **159** and **162**. Upon purification the major diastereoisomer **162** was isolated in 18% yield and 85:15 dr, along with a 50:50 mixture of **159** and **162** in 40% combined yield (Scheme 34).



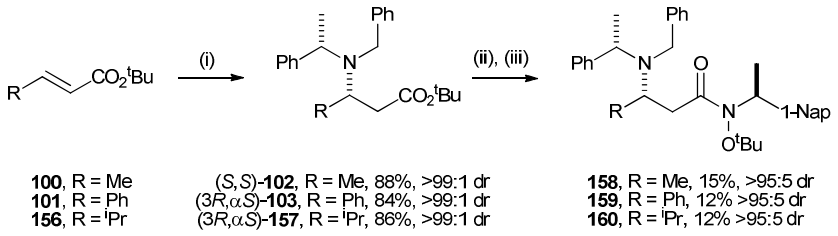
150, R = Me R = Me, 75:25 dr
151, R = Ph R = Ph, 40:60 dr
152, R = ^{i}Pr R = ^{i}Pr, 65:35 dr

158, R = Me, 46%, 90:10 dr[a]
159, R = Ph
160, R = ^{i}Pr, 17%, >95:5 dr[a]

161, R = Me
162, R = Ph, 18%, 85:15 dr[a]
163, R = ^{i}Pr

Scheme 34. *Reagents and conditions:* (i) (*S*)-**13**, THF, –78 °C, 2 h. [[a] mixed fractions were also isolated]

The configurations at C(3) within **158**, **159** and **160** were established unambiguously by a separate chemical synthesis in each case, thereby also confirming the assigned configurations within **161**, **162** and **163**: β-amino esters (*S*,*S*)-**102**, (3*R*,α*S*)-**103** and (3*R*,α*S*)-**157** [obtained from the conjugate addition of lithium amide (*S*)-**13** to *tert*-butyl crotonate **100**, *tert*-butyl cinnamate **101** and *tert*-butyl 4-methylpent-2-enoate **156**, respectively][31] were hydrolysed to the carboxylic acids with TFA. Subsequent coupling with (*S*)-*N*-1-(1'-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine **60** gave authentic samples of **158**, **159** and **160** as single diastereoisomers (>95:5 dr), although the overall yields obtained in the coupling step were relatively low. The spectroscopic properties, including specific rotation values, of the samples of **158**, **159** and **160** prepared in this manner were consistent with the major diastereoisomers[48] arising from the conjugate addition of lithium amide (*S*)-**13** to α,β-unsaturated hydroxamates **100**, **101** and **156**, providing unequivocal evidence of the sense of stereoinduction observed in these reaction pairings. The results of conjugate addition of lithium amide (*S*)-**13** to both C(3)-methyl substituted α,β-unsaturated hydroxamate **100** and C(3)-isopropyl substituted α,β-unsaturated hydroxamate **156** suggest that it is the stereocontrol of the lithium amide (*S*)-**13** and not the chiral Weinreb amide auxiliary that dominates the diastereoselectivity of these "mismatched" reactions. Meanwhile, in the case of C(3)-phenyl substituted α,β-unsaturated hydroxamate **101**, the conjugate addition of (*S*)-**13** proceeded under the predominant stereocontrol of the chiral Weinreb amide auxiliary (Scheme 35).



100, R = Me
101, R = Ph
156, R = ^{i}Pr

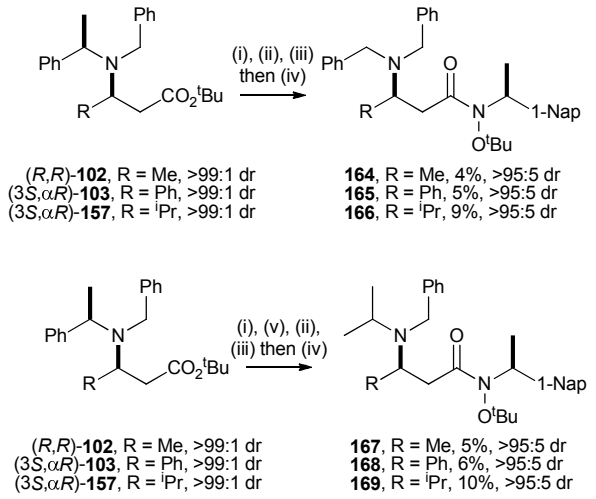
(*S*,*S*)-**102**, R = Me, 88%, >99:1 dr
(3*R*,α*S*)-**103**, R = Ph, 84%, >99:1 dr
(3*R*,α*S*)-**157**, R = ^{i}Pr, 86%, >99:1 dr

158, R = Me, 15%, >95:5 dr
159, R = Ph, 12% >95:5 dr
160, R = ^{i}Pr, 12% >95:5 dr

Scheme 35. *Reagents and conditions:* (i) (*S*)-**13**, THF, –78 °C, 2 h; (ii) TFA/CH_2Cl_2 (v/v 1:1), rt, 2 h; (iii) $(COCl)_2$, DMF, CH_2Cl_2, rt, 1 h then (*S*)-**60**·(+)-CSA, K_2CO_3, CH_2Cl_2, 16 h. [1-Nap = 1-naphthyl]

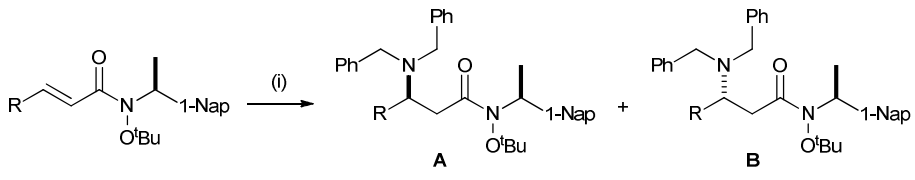
2.3.18. Conjugate additions of achiral lithium amides

To assess the extent of substrate control in these systems, the conjugate additions of achiral lithium dibenzylamide **106**[32] and lithium *N*-isopropyl-*N*-benzylamide **107**[4] to α,β-unsaturated hydroxamates **150**, **151** and **152** were also conducted. Initially, authentic samples of the diastereoselective products of conjugate additions were prepared in order to facilitate subsequent assignment of stereochemical outcomes of conjugate addition reactions. It was anticipated that the conjugate products **153**, **154** and **155** derived from addition of (*R*)-**13** to α,β-unsaturated hydroxamates **150**, **151** and **152** could be converted to authentic samples via *N*-deprotection and *N*-alkylation. Hydrogenolysis of **153** was first attempted. However, this reaction was not successful and returned a complex mixture of products: ^{1}H NMR spectroscopic and mass spectrometric analyses of the crude reaction mixture indicated the presence of products arising from cleavage of the N–O, N–C(1') and *N*-benzyl bonds. The preparation of authentic samples from β-amino esters (*R*,*R*)-**102**, (3*S*,α*R*)-**103** and (3*S*,α*R*)-**157** was therefore investigated. Thus, hydrogenolysis of (*R*,*R*)-**102**, (3*S*,α*R*)-**103** and (3*S*,α*R*)-**157** followed by bis-alkylation of the resultant β-amino esters with BnBr, ester hydrolysis, and coupling with (*S*)-*N*-1-(1'-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine **60** gave authentic samples of **164**, **165** and **166** in 4-9% yield and >95:5 dr in each case. Similarly, hydrogenolysis of (*R*,*R*)-**102**, (3*S*,α*R*)-**103** and (3*S*,α*R*)-**157** followed by reductive alkylation of the resultant β-amino esters with acetone, alkylation with BnBr, ester hydrolysis, and coupling with (*S*)-*N*-1-(1'-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine **60** gave authentic samples of **167**, **168** and **169** in >95:5 dr and 5-10% isolated yield (Scheme 36).



Scheme 36. *Reagents and conditions:* (i) H_2 (5 atm), $Pd(OH)_2/C$, MeOH, rt, 36 h; (ii) BnBr, K_2CO_3, 100 °C, 7 h; (iii) TFA/CH_2Cl_2 (v/v 1:1), rt, 2 h; (iv) $(COCl)_2$, DMF, CH_2Cl_2, 0 °C to rt, 1 h then (*S*)-**60**·(+)-CSA, K_2CO_3, CH_2Cl_2, 18 h; (v) acetone, $NaBH_3CN$, MeOH, rt, 16 h. [1-Nap = 1-naphthyl].

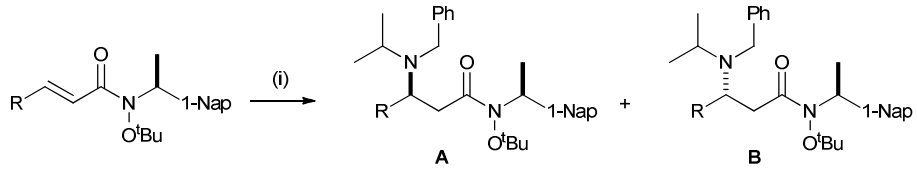
The conjugate additions of lithium dibenzylamide **106** to α,β-unsaturated hydroxamates **150**, **151** and **152** all proceeded with the same sense of stereoinduction and with modest levels of diastereoselectivity to give the diastereoisomeric conjugate addition products **164** and **170** in 80:20 dr, **165** and **171** in 70:30 dr, and **166** and **172** in 80:20 dr, respectively. In the cases of hydroxamates **150** and **151**, separation of the diastereoisomeric products could not be achieved upon purification, even after exhaustive flash column chromatography. In the case of the C(3)-isopropyl substituted α,β-unsaturated hydroxamate **152**, upon purification of the crude reaction mixture, the diastereoisomeric purity of the major product **166** was slightly increased. The spectroscopic properties of the major diastereoisomeric products **164**, **165** and **166** were consistent with the authentic samples prepared, providing unequivocal evidence of the sense of stereoinduction observed in these reaction pairings (Scheme 37).



Substrate	R	A	B	conv (%)	crude dr (A:B)	yield of A (dr A:B) %
150	Me	**164**	**170**	83	80:20	66 (80:20)
151	Ph	**165**	**171**	92	70:30	62 (70:30)
152	^{i}Pr	**166**	**172**	71	80:20	60 (88:12)

Scheme 37. *Reagents and conditions:* (i) lithium dibenzylamide **106**, THF, –78 °C, 2 h.

Similarly, the same diastereofacial preference and modest levels of diastereoselectivity (≥80:20 dr) were observed in the conjugate additions of lithium *N*-isopropyl-*N*-benzylamide **107** to α,β-unsaturated hydroxamates **150**, **151** and **152**. In the cases of hydroxamates **150** and **151**, separation of the diastereoisomeric products could not be achieved upon chromatographic purification. In the case of the C(3)-isopropyl substituted α,β-unsaturated hydroxamate **152**, the diastereoisomeric purity of the major product **169** was slightly increased upon purification of the crude reaction mixture. The spectroscopic properties of the major diastereoisomeric products **167**, **168** and **169** were in accord with the authentic samples prepared, providing unequivocal evidence of the sense of stereoinduction observed in these reaction pairings (Scheme 38).



Substrate	R	A	B	conv (%)	crude dr (A:B)	yield of A (dr A:B) %
150	Me	**167**	**173**	83	80:20	70 (80:20)
151	Ph	**168**	**174**	65	80:20	60 (80:20)
152	^{i}Pr	**169**	**175**	66	85:15	48 (90:10)

Scheme 38. *Reagents and conditions:* (i) lithium *N*-isopropyl-*N*-benzylamide **107**, THF, –78 °C, 2 h.

2.3.19. The origins of diastereoselectivity observed upon conjugate addition to α,β-unsaturated hydroxamates

As predicted, the conjugate addition of lithium amide (*R*)-**13** to enantiopure α,β-unsaturated hydroxamates **150**, **151** and **152** proceeded with high diastereoselectivity (>95:5 dr in each case) and represents the doubly diastereoselective "matched" reaction pairings, whereas reaction of lithium amide (*S*)-**13** with α,β-unsaturated hydroxamates **150**, **151** and **152** proceeded with much poorer levels of diastereoselectivity and represents the "mismatched" reaction pairings. These empirical "matched" and "mismatched" product distributions are consistent with the preferential addition of lithium amide (*R*)-**13** to the *Si* face of the double bond (reagent control) within *s-cis* reactive conformation of α,β-unsaturated hydroxamate **151**, which coincides with addition opposite to the stereodirecting *tert*-butyl group and *N*-lone pair within the auxiliary (substrate control). An analogous argument is able to

rationalise preferential formation of β-amino hydroxamates **153** and **155** from **150** and **152**. The poor diastereoselectivity observed in the "mismatched" cases may occur via approach of lithium amide (*S*)-**13** on the same face as the stereodirecting *tert*-butyl group of the auxiliary, although these data do not discount the possibility that preferential addition of lithium amide (*S*)-**13** to α,β-unsaturated hydroxamates **150**, **151** and **152** proceeds via an alternative conformation of the α,β-unsaturated hydroxamate. These findings are consistent with the previous observations of Davies *et al*. concerning the alkylation of enolates derived from *N*-1-(1'-naphthyl)ethyl-*O*-*tert*-butylhydroxamate [8] in that a 'chiral relay'[44] mechanism may be proposed to rationalise the observed stereochemical outcome of the reaction: the configuration of the *N*-1-(1'-naphthyl)ethyl group dictates the position of the *O*-*tert*-butyl group and also the configuration adopted by the pyramidal nitrogen atom. A fully staggered arrangement is adopted in which minimisation of steric interactions between the C(1')-methyl and *O*-*tert*-butyl groups leaves the C(1')-hydrogen and carbonyl oxygen atoms eclipsing, minimising *syn*-pentane interactions. Minimisation of lone pair-lone pair repulsion controls the configuration of the pyramidal nitrogen atom; the doubly diastereoselective "matched" conjugate addition of lithium amide (*R*)-**13** then occurs on the opposite face to both the nitrogen lone-pair and the bulky *O*-*tert*-butyl group (Fig. 22).

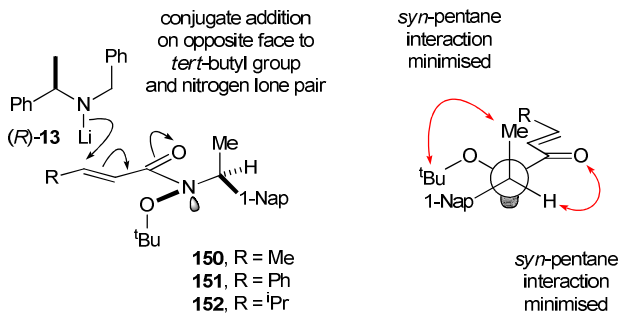


Fig. 22. The proposed 'chiral relay' mechanism in the doubly diastereoselective conjugate addition of (*R*)-**13** to α,β-unsaturated hydroxamates **150** (R = Me), **151** (R = Ph), and **152** (R = ^{i}Pr). [1-Nap = 1-naphthyl].

2.4. Conclusions

In conclusion, the doubly diastereoselective conjugate additions of the antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide to a range of enantiopure α,β-unsaturated esters and enantiopure α,β-unsaturated hydroxamates has been used as a mechanistic probe to determine the reactive conformations in these systems. In all cases, conjugate addition occurs with the α,β-unsaturated carbonyl compounds adopting *s-cis* reactive conformations. High levels of diastereoselectivity (≥95:5 dr) were observed in the doubly diastereoselective "matched" reaction pairings. In all but one case the dominant stereocontrolling element in the "mismatched" reaction pairings was found to be the lithium amide reagent. Intermediate levels of diastereoselectivity were observed upon conjugate addition of achiral lithium amides, providing an indication of the level of substrate control in these systems. In the doubly diastereoselective "matched" cases the known diastereofacial preference exerted by lithium *N*-benzyl-*N*-(α-methylbenzyl)amide was found to be in accord with conjugate addition to the face opposite to the stereodirecting groups within these auxiliaries (i.e., the phenyl group within Corey's 8-phenylmenthol auxiliary and both the *tert*-butyl group and *N*-lone pair within Davies's 'chiral Weinreb amide' auxiliary).

2.5. References and notes

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[45] Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 733577, 745789 and 745790; see also Refs. 8a,c.

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[47] Due to the highly rotameric nature of all the β-amino hydroxamates described herein more accurate determinations of the reaction diastereoselectivities were not possible.

[48] The conjugate addition of (*S*)-**13** to **151** produced a 60:40 mixture of **162** and **159** respectively. In this case the spectroscopic data for the authentic sample of **159** were consistent with the minor diastereoisomer from the conjugate addition reaction.

CHAPTER 3

Doubly Diastereoselective Organocatalytic Michael Cyclisation

3.1. Introduction

This chapter describes investigations into doubly diastereoselective organocatalytic Michael cyclisations of substrates incorporating chiral auxiliaries (Fig. 23).

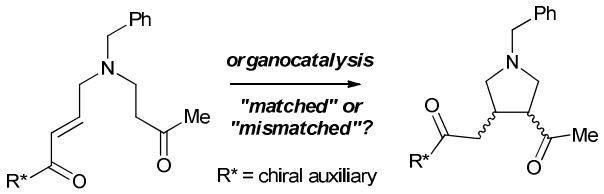
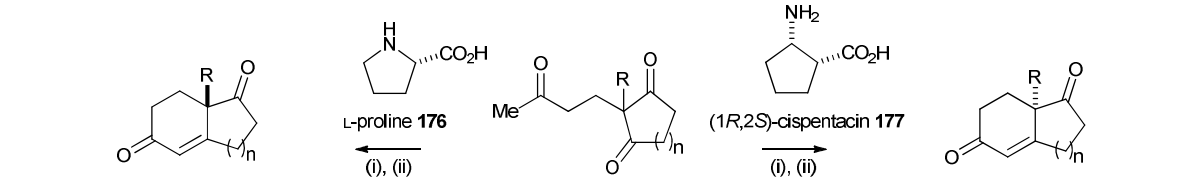


Fig. 23. Doubly diastereoselective organocatalytic Michael cyclisations of substrates incorporating chiral auxiliaries.

3.1.1. Organocatalysis

Organocatalysis (the use of relatively simple chiral organic molecules to catalyse organic transformations) is a popular field within the domain of asymmetric synthesis. As a complementary tool to organometallic and enzymatic catalysis, organocatalytic methodology is often less expensive, safer and more environmentally conscious.[1] The advent of organocatalysis may have arisen due to several factors.[2] For instance, organocatalytic reactions are generally less sensitive to oxygen and moisture than the organometallic alternatives and thus there are no special requirements for specific reaction vessels, experimental techniques or ultra-dry reagents and anhydrous solvents. Furthermore, a variety of organocatalysts are readily available as single enantiomers from the chiral pool, or can be synthesized in either enantiomeric form, and are usually more stable than enzymes, organometallic catalysts or other bio-organic catalysts.[3] In addition, organocatalysis can be classified as 'green chemistry' as it utilises non-toxic and environmentally friendly compounds, increasing the safety of catalysis in biological and chemical research across industrial and academic institutions. In the expanding field of organocatalysis, a range of catalysts of varying structural complexity have been developed, which include imidazolidinones,[4] phosphines,[5] peptides,[6] *N*-heterocyclic carbenes,[7] thioureas[8] and bifunctional catalyst systems.[9] Among the most readily available proteinogenic α-amino

acid derived organocatalysts, proline and its derivatives have received the most attention for a series of asymmetric transformations such as aldol,[10] Mannich[11] and Michael reactions.[12] The first widely recognised catalytic asymmetric application of proline **176** concerned the enantioselective Hajos-Parrish-Eder-Sauer-Wiechert reaction in which the enantioselective cyclisation of triketone **178** produces enone product (*S*)-**181** in quantitative yield and 93% ee.[13] However, in 2005, Davies and co-workers reported that the β-amino acid cispentacin **177** promoted the Hajos-Parrish-Eder-Sauer-Wiechert reaction with levels of enantioselectivity comparable to or higher than proline. It was reported that cyclisation of **178** catalysed by (1*R*,2*S*)-cispentacin **177** gave enone (*R*)-**181** in 94% yield and comparable enantioselectivity (90% ee) to L-proline **176** which gave enone (*S*)-**181** in 93% ee. Cyclisations of **179** and **180** promoted by (1*R*,2*S*)-cispentacin **177** gave the corresponding enones (*R*)-**182** and (*R*)-**183** in higher yields and with higher levels of enantioselectivity than using L-proline **176** for the same cyclisation {formation of **182**: cispentacin **177** 78% ee [(*R*)], L-proline **176** 74% ee [(*S*)]; formation of **183**: cispentacin **177** 86% ee [(*R*)], L-proline **176** 72% ee [(*S*)]} (Scheme 39).[14]



Scheme 39. *Reagents and conditions*: (i) catalyst (30 mol%), DMF, rt; (ii) *p*-TsOH, toluene, reflux.

3.1.2. Organocatalytic enantiorecognition processes

Countless examples of organocatalytic transformations involving achiral substrates have been reported in the literature,[15] although the use of chiral substrates is described much less frequently.[16] It has been shown that the use of chiral substrates with chiral reagents can offer high levels of diastereoselectivity in many non-organocatalytic systems, such as asymmetric aldol,[17] Michael addition,[18] epoxidation,[19] hydrogenation,[20] Diels-Alder[21] and Baylis-Hillman[22] reactions, as "matching" and "mismatching" effects result in increased levels of stereoinduction for the "matched" pair. There are several options to create doubly diastereoselective reaction manifolds in an organocatalytic system, utilising any combination of chiral substrates, chiral organocatalysts, or both (Fig. 24).

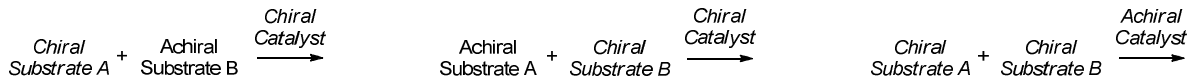
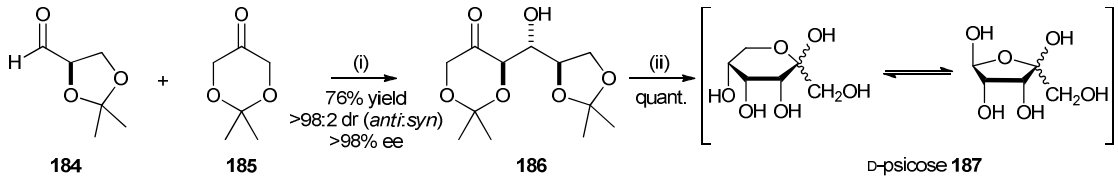


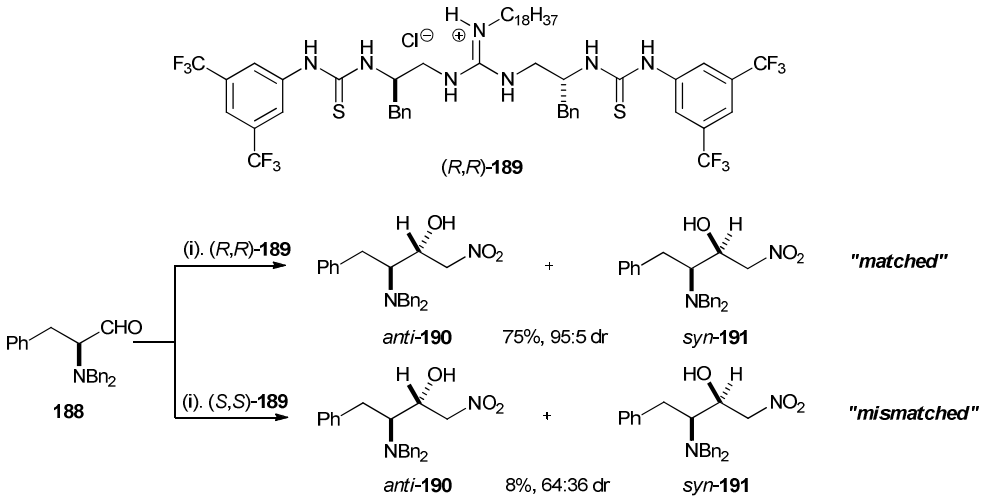
Fig. 24. Examples of several options for creating doubly diastereoselective organocatalytic reaction manifolds.

The use of chiral electrophiles in doubly diastereoselective organocatalytic C–C bond forming processes has previously been studied.[23] For example, Enders *et al.* used D-proline **176** to catalyse the aldol reaction between ketone **185** and chiral aldehyde **184** in their organocatalytic synthesis of D-psicose **187**, with aldol product **186** being isolated in 76% yield and excellent diastereo- and enantioselectivity.[16] However, in this system, the level of stereoinduction with the antipode of the catalyst was not discussed (Scheme 40).



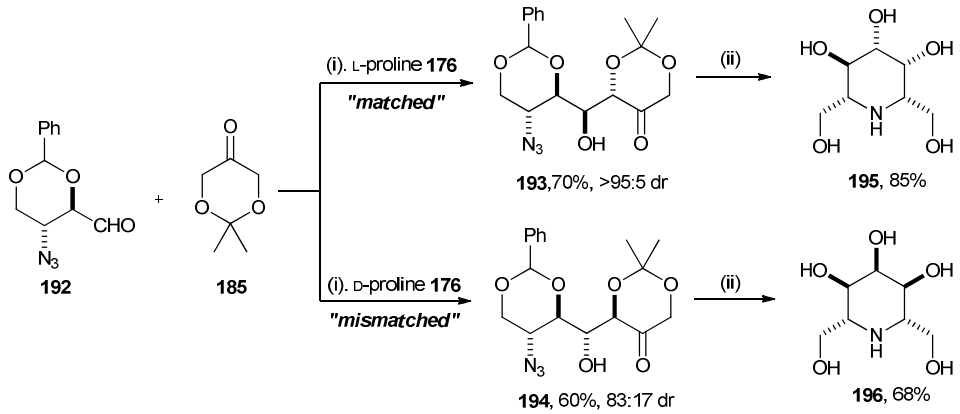
Scheme 40. *Reagents and conditions*: (i) D-proline **176** (30 mol%), DMF, rt; (ii) *p*-TsOH, toluene, reflux.

The concept of double asymmetric induction has also played a decisive role in the stereochemical outcome for organocatalytic reactions. For example, Sohtome *et al*. reported that the doubly diastereoselective phenomenon was observed in the Henry reaction of α-substituted aldehyde **188** using guanidine-thiourea bifunctional catalyst **189**. The reaction catalysed by (*S*,*S*)-**189** gave the nitro alcohol products *anti*-**190** and *syn*-**191** in 8% combined yield and with relatively low diastereoselectivity (64:36 dr, respectively), representing the doubly diastereoselective "mismatched" pairing of chiral reagents, whereas the corresponding reaction in the presence of catalyst (*R*,*R*)-**189**, gave *anti*-**190** in 75% yield and 95:5 dr, representing the doubly diastereoselective "matched" reaction pairing (Scheme 41).[24]



Scheme 41. *Reagents and conditions*: (i) (*R*,*R*)-**189** or (*S*,*S*)-**189** (10 mol%), CH_3NO_2, KI, KOH, toluene/H_2O (v/v 1:1), 0 °C, 24 h.

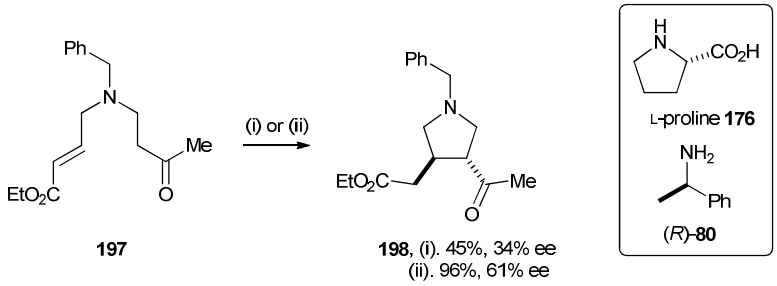
Calderón *et al*. also reported a doubly diastereoselective organocatalytic aldol reaction as the key step in their synthesis of ring azasugars **195** and **196**. In this study, the reaction of aldehyde (*R*)-**192** and ketone **185** in the presence of L-proline **176** gave *anti*-(*S*,*S*)-aldol product **193** in >95:5 dr and 70% isolated yield. Meanwhile, D-proline **176** catalysis afforded the *anti*-(*R*,*R*)-aldol product **194** as major product with moderate diastereoselectivity (83:17 dr). These results demonstrate that the diastereoselectivities of the two chiral components are reinforcing with the aldehyde (*R*)-**192**/L-proline **176** combination representing the doubly diastereoselective "matched" reaction pairing. Reversing the absolute configuration of one of the two chiral components leads to the "mismatched" pairing (Scheme 42).[25]



Scheme 42. *Reagents and conditions*: (i) D-proline **176** or L-proline **176** (10 mol%), DMF, 4 °C, 96 h; (ii) H_2 (45 psi), 10% Pd/C, MeOH/HCl, rt, 48 h.

3.1.3. Organocatalytic Michael cyclisation

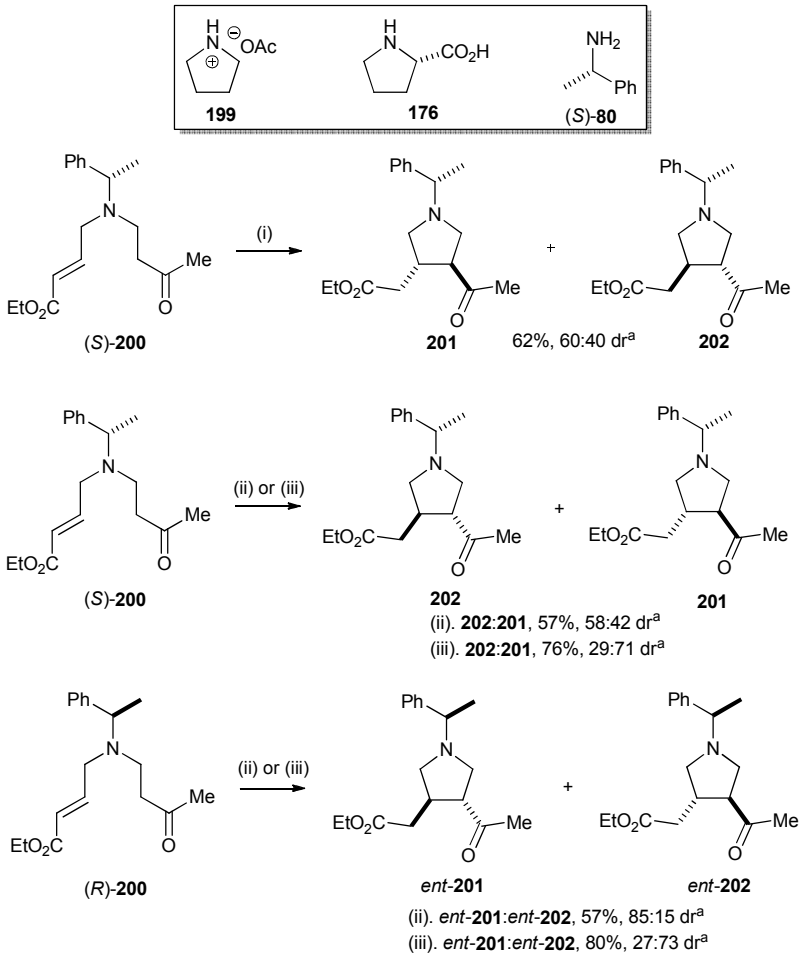
Momose *et al.* have reported organocatalytic Michael cyclisations for the enantioselective construction of 3,4-disubstituted pyrrolidines. For example, cyclisation of **197** to give *trans*-pyrrolidine **198** was catalysed by L-proline **176**, giving *trans*-pyrrolidine **198** in 45% yield and 34% ee. However, with (*R*)-α-methylbenzylamine **80** as the catalyst, cyclisation of **197** gave *trans*-pyrrolidine **198** in 96% yield and 61% ee. The authors proposed that the organocatalytic cyclisation reaction proceeded via a mechanism in which the chiral amine catalysts condensed with the ketone moiety within the cyclisation substrate **197** to form a transient enamine intermediate, which undergoes a diastereoselective Michael addition to the pendant α,β-unsaturated ester functionality. Subsequent *in situ* hydrolysis of the cyclisation product would then give pyrrolidine **198** (Scheme 43).[26]



Scheme 43. *Reagents and conditions*: (i) L-proline **176** (100 mol%), DMF, rt, 7 days; (ii) (*R*)-α-methylbenzylamine **80** (100 mol %), THF, 5 Å molecular sieves, 5 °C, 13 days.

Davies and co-workers have shown that the incorporation of a chiral fragment within this type of substrate leads to an enhancement in diastereoselectivity for the "matched" pairing of chiral substrate and chiral catalyst with respect to the enantioselectivity observed using chiral catalysts and achiral substrates. In these studies, the contribution of the chiral *N*-α-methylbenzyl fragment within the substrate upon the level of stereoinduction (i.e., the level of substrate control) was assessed by treating (*S*)-**200** with an achiral catalyst **199** to give two diastereoisomeric *trans*-pyrrolidine products **201** and **202** in 62% combined yield and 60:40 dr, respectively. With L-proline **176** as the catalyst, cyclisation of chiral substrate (*S*)-**200** afforded a 58:42 mixture of two diastereoisomeric products **202** and **201**, respectively, in 57% combined yield. Meanwhile, cyclisation of (*S*)-**200** catalysed by (*S*)-α-methylbenzylamine **80** gave a 29:71 mixture of **202** and **201**, respectively, in 76% combined yield. Similarly, cyclisation of (*R*)-**200** catalyzed by L-proline **176** gave an 85:15 mixture of *ent*-**201** and *ent*-**202** in 57% combined yield, whereas catalysis with

(*S*)-α-methylbenzylamine **80** showed the opposite sense of stereoinduction, giving *ent*-**202** as the major product (73:27 dr) in 80% yield (Scheme 44).[27]



Scheme 44. *Reagents and conditions*: (i) pyrrolidinium acetate **199**, DMF, rt, 7 days; (ii) L-proline **176**, DMF, rt, 7 days; (iii) (*S*)-α-methylbenzylamine **80**, THF, rt, 7 days. [[a] dr of isolated product is the same as crude dr]

3.2. Project aims

It was anticipated that other analogous chiral substrates and organocatalysts may be used to explore doubly diastereoselective effects in these systems. It was proposed to investigate the diastereoselectivity elicited upon intramolecular Michael cyclisation of chiral enamides **203** [derived from a SuperQuat chiral auxiliary **61**] and chiral α,β-unsaturated esters **205** [derived from Corey's 8-phenylmenthol chiral auxiliary **59**[28]] in the hope that superior levels of diastereoselectivity would be observed relative to the cyclisation of the ethyl ester counterparts **197** and **200** (Fig. 25).

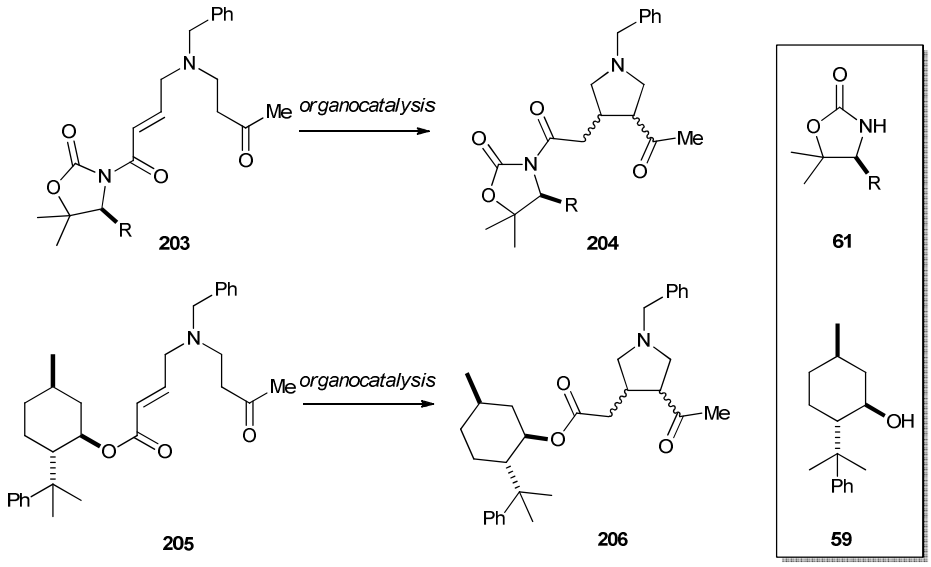


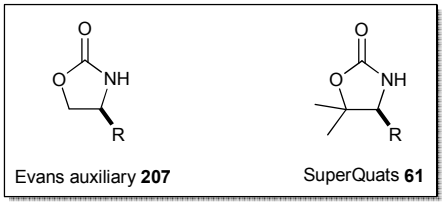
Fig. 25. Proposed intramolecular Michael cyclisation of chiral enamides **203** (derived from a SuperQuat chiral auxiliary **61**) and chiral α,β-unsaturated esters **205** (derived from Corey's 8-phenylmenthol chiral auxiliary **59**).

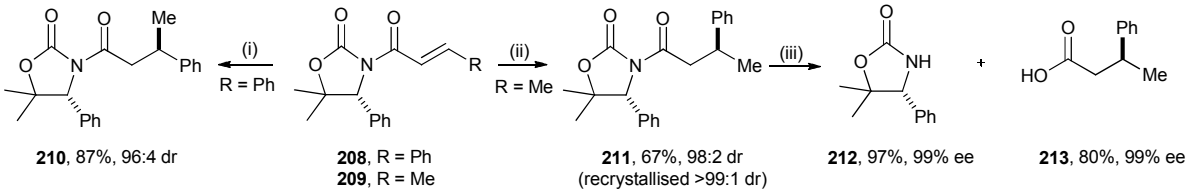
3.3. Synthesis of cyclisation substrates

3.3.1. The SuperQuat chiral auxiliaries

Evans's 4-substituted oxazolidin-2-ones **207**[29] are used to control the stereoselectivity of a wide range of chemistry including aldol reactions, 1,4-conjugate additions, hydroxylation reactions, halogenation reactions, Diels-Alder reactions, ene reactions, cyclopropanations, α-amino acid syntheses and iterative propionate homologation reactions.[30] When using Evans's auxiliary for asymmetric synthesis, the general strategy involves attachment of an acyl fragment to the N(3) atom within the oxazolidinone, followed by stereoselective reaction, and finally removal of the chiral acyl fragment. Although these auxiliaries often excel in ease of acylation and the level of diastereocontrol, removal of the acyl fragment is problematic due to competing endocyclic cleavage.[31] While this endocyclic cleavage problem may be ameliorated by using LiOOH as the nucleophile, the use of this reagent on a large scale is undesirable.[31] Davies and co-workers have developed a new class of chiral auxiliary, 4-substituted-5,5-dimethyl-oxazolidin-2-ones (SuperQuats) **61**, which has addressed the problems associated with Evans's auxiliary by incorporating a *gem*-dimethyl group at the C(5) position. The presence of the *gem*-dimethyl group at the C(5) position enhances the diastereoselectivity by serving to direct the conformation of the stereocontrolling group at C(4), and also confers superior cleavage properties to the corresponding *N*-acyl fragment by serving to protect the oxazolidin-2-one carbonyl from nucleophilic attack.[32] These properties have allowed SuperQuat **61** to act as an efficient

chiral auxiliary in a range of chemistry, such as alkylation of enolates derived from *N*-acyl SuperQuats[32] and conjugate additions.[33] For example, Davies and co-workers have shown (*R*)-4-phenyl-5,5-dimethyl-oxazolidin-2-one **212** to be an effective chiral auxiliary for stereoselective conjugate additions to attached α,β-unsaturated *N*-acyl moieties. Conjugate addition of organocuprate reagents to **208** and **209** proceeded with high levels of diastereoselectivity to give **210** in 87% yield and 96:4 dr, and **211** as a single diastereoisomer (>99:1 dr) in 67% yield (after recrystallisation), respectively. Subsequent hydrolysis of **211** gave enantiopure acid **213** in 80% yield and 99% ee and recovered SuperQuat **212** in 97% yield, indicating that endocyclic cleavage pathway was completely suppressed and no loss of stereochemical integrity was observed at the stereogenic centre within **211** upon cleavage of the chiral auxiliary (Scheme 45).[33]

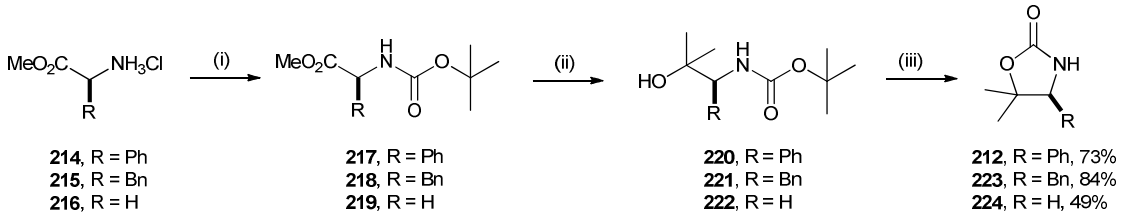




Scheme 45. *Reagents and conditions*: (i) CuBr, DMS, MeMgBr, THF, –40 °C, 1 h; (ii) CuBr, DMS, PhMgBr, THF, –40 °C, 1 h; (iii) LiOH, THF/H_2O (v/v 3:1), 0 °C, 1 h.

3.3.2. Syntheses of SuperQuat chiral auxiliaries

A versatile protocol for the synthesis of SuperQuat auxiliaries on multigram scale has been developed by Davies and co-workers.[32] Following this procedure, α-amino methyl esters **214**, **215** and **216** were reacted with Boc_2O under basic conditions to give *N*-Boc α-amino esters **217**, **218** and **219**, which were treated with excess Grignard reagent to afford *N*-Boc-protected amino alcohols **220**, **221** and **222**, respectively. Subjection of amino alcohols **220**, **221** and **222** to base catalysed cyclisation with KO^{t}Bu gave SuperQuat auxiliaries **212**, **223** and **224** in ≥49% yield over 3 steps (Scheme 46).



Scheme 46. *Reagents and conditions*: (i) Boc_2O, $NaHCO_3$, EtOH, 0 °C to rt, 48 h; (ii) MeMgBr, Et_2O, 0 °C to rt, 48 h; (iii) KO^tBu, THF, 0 °C, 30 min.

3.3.3. The cross metathesis strategy

The initial approach to cyclisation substrates **203** focused on a cross metathesis strategy to couple two olefinic fragments **225** and **226**, as this convergent strategy would enable late-stage diversification in the synthesis. It was anticipated that one fragment **225** could be synthesised via *N*-acylation of a SuperQuat auxiliary **61**, and the other fragment **226** could be derived from alkylation of *N*-allyl-*N*-benzylamine **227** (Fig. 26).

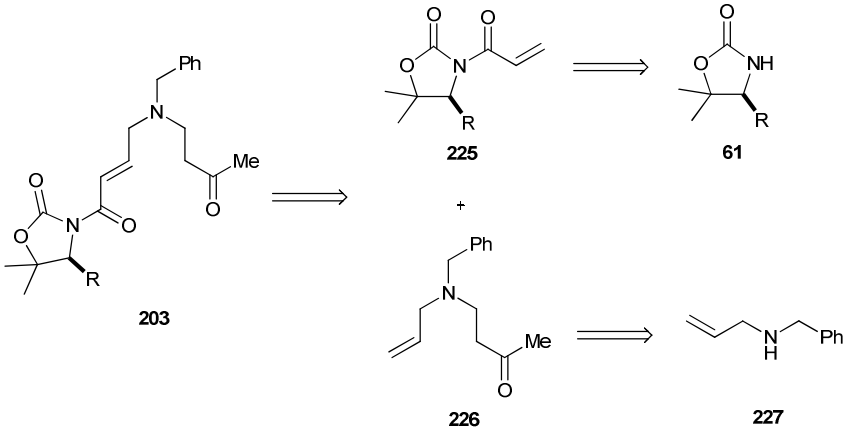
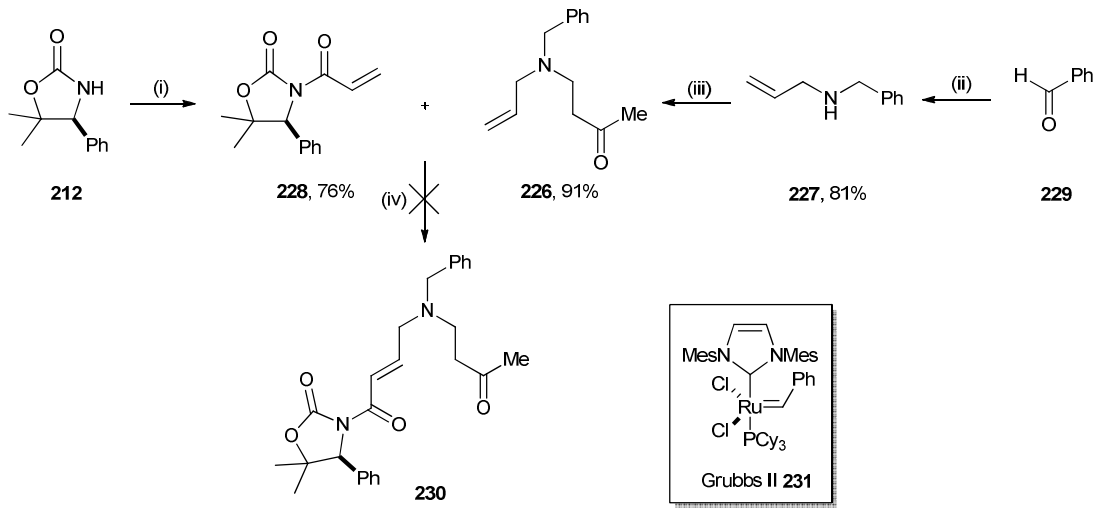


Fig. 26. Retrosynthetic analysis of substrate **203**.

The C(4)-phenyl substituted SuperQuat auxiliary **212** was selected as a model system for optimisation of the substrate synthesis. *N*-Acryloyl oxazolidin-2-one **228** was prepared from **212** via treatment with acrylic anhydride under basic conditions to give **228** in 76% yield. Reductive amination of benzaldehyde **229** with allylamine gave *N*-allyl-*N*-benzylamine **227** in 81% yield, which was reacted with methyl vinyl ketone to give **226** in 91% yield. With the two olefinic fragments **226** and **228** in hand, a cross metathesis reaction with Grubbs II **231** was investigated. However, upon refluxing **226**, **228** and Grubbs II **231** in toluene for 48 h, a complex mixture was obtained without any evidence for the formation of coupling product **230**, according to analysis of the ^{1}H NMR spectrum of the crude reaction mixture (Scheme 47).



Scheme 47. *Reagents and conditions:* (i) acrylic acid, acryloyl chloride, Et_3N, Et_2O, 0 °C to rt, 70 min, then LiCl, Et_3N, rt, 4 h; (ii) allyl amine, EtOH, reflux, 3 h, then $NaBH_4$, rt, 72 h; (iii) methyl vinyl ketone, CH_2Cl_2, rt, 16 h; (iv) Grubbs II **231** (10 mol%), toluene, reflux, 48 h.

3.3.4. The alkylation strategy I

The next synthetic strategy focused on amine **232** as the key intermediate which could undergo alkylation with methyl vinyl ketone, by analogy to the route which was previously utilized by Davies *et al.*[27] It was expected that amine **232** could be synthesized via alkylation of benzylamine **81** with the requisite bromide **233** (Fig. 27).

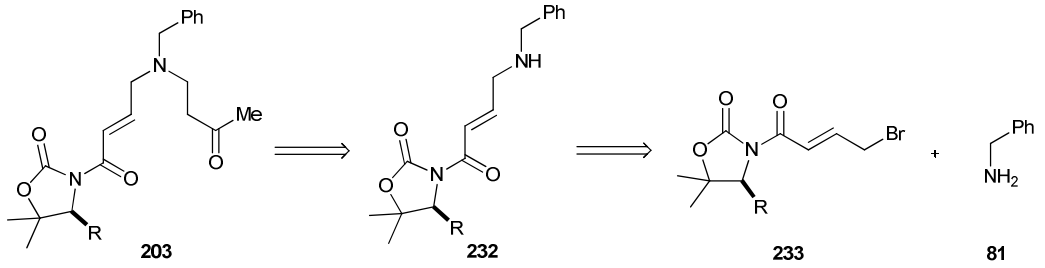
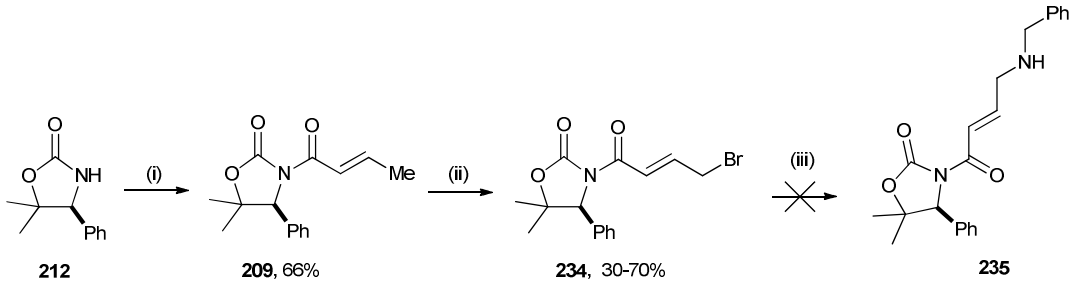


Fig. 27. Retrosynthetic analysis of substrate **203**.

According to a literature procedure,[33] *N*-crotonoyl oxazolidin-2-one **209** was prepared via treatment of SuperQuat **212** with BuLi, followed by addition of crotonoyl chloride. Allylic bromination of **209** under Wöhl-Ziegler conditions was found to give inconsistent yields of **234** ranging between 30 and 70%. Subsequent alkylation of benzylamine **81** with bromide **234** repeatedly gave complex mixtures of products (as determined by inspection of the ^{1}H NMR spectra of the crude reaction mixtures) which may have been due to a competing *N*-dialkylation pathway (Scheme 48).



Scheme 48. *Reagents and conditions:* (i) crotonoyl chloride, BuLi, THF, −78 °C to rt, 3 h; (ii) NBS, benzoyl peroxide, CCl_4, reflux, 2 h; (iii) $BnNH_2$ **81**, CH_2Cl_2, rt, 18 h.

Due to the complex nature of the reaction mixture observed from attempted alkylation of benzylamine **81** with bromide **234**, this approach was abandoned in favour of a synthesis which incorporated a nitrogen protecting group at an early stage.

3.3.5. The alkylation strategy II

It was envisaged that key intermediate **236** could be accessed via coupling a SuperQuat auxiliary with acid **237**, which in turn could be accessed by hydrolysis of methyl ester **238**. The *N*-Boc protecting group was chosen to protect the amino functionality as it would be compatible with the subsequent base mediated ester hydrolysis reaction. It was proposed that methyl ester **238** could be synthesized via alkylation of benzylamine **81** with bromide **239**, followed by *N*-Boc protection (Fig. 28).

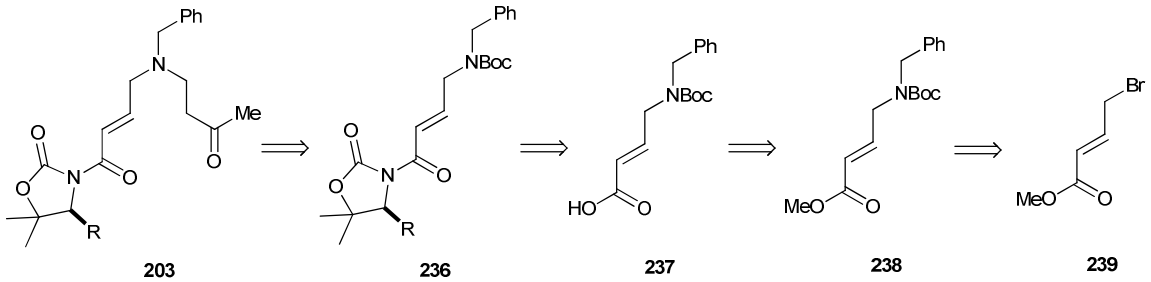
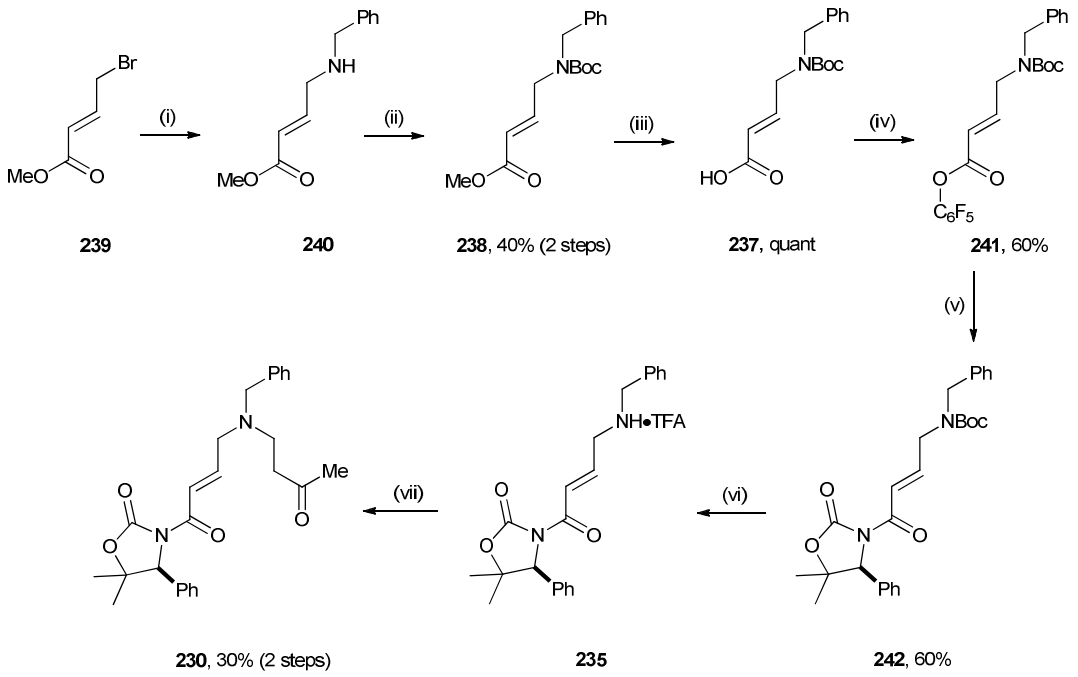


Fig. 28. Retrosynthetic analysis of substrate **203**.

This approach was initiated by alkylation of benzylamine **81** with methyl 4-bromocrotonate **239**,[27] followed by *N*-Boc protection to afford methyl ester **238** in 40% yield over 2 steps.[34] Conversion of **238** to acid **237** under basic conditions was achieved in quantitative yield. Direct acylation of SuperQuat **212** with acid **237** through *in situ* activation by conversion to either the corresponding acid chloride or mixed anhydride was not successful. However, when pentafluorophenyl ester **241** was employed as the acylating agent, key intermediate

242 was furnished in 60% yield.[35] Subsequent deprotection of the *N*-Boc group within **242** with 20 equivalents of TFA generated **235** as its TFA salt, which was treated with excess methyl vinyl ketone and Et_3N to afford substrate **230** in 30% yield over 2 steps (Scheme 49).



Scheme 49. *Reagents and conditions:* (i) $BnNH_2$ **81**, DIPEA, CH_2Cl_2, rt, 3 h; (ii) Boc_2O, DIPEA, 0 °C to rt, 3 h; (iii) NaOH (2.0 M aq), THF, rt, 16 h; (iv) DCC, C_6F_5OH, EtOAc, rt, 60 h; (v) **212**, BuLi, THF, −78 °C, 2 h; (vi) TFA, CH_2Cl_2, rt, 2 h; (vii) methyl vinyl ketone, Et_3N, CH_2Cl_2, rt, 1 h.

Although this route for the synthesis of substrate **230** was successful, it proved somewhat lengthy and low yielding (seven steps with an overall yield of 18%). Further optimisation was therefore carried out in an attempt to shorten the synthetic route and improve the overall yield for the formation of cyclisation precursor **203**.

3.3.6. The convergent strategy

It was envisaged that substrate **203** could be accessed via alkylation of amine **244** with the requisite bromide **233**, which could be derived from coupling the requisite SuperQuat with 4-bromocrotonic acid **243** in order to avoid the problematic bromination of *N*-crotonoyl oxazolidin-2-one **209** (Fig. 29).

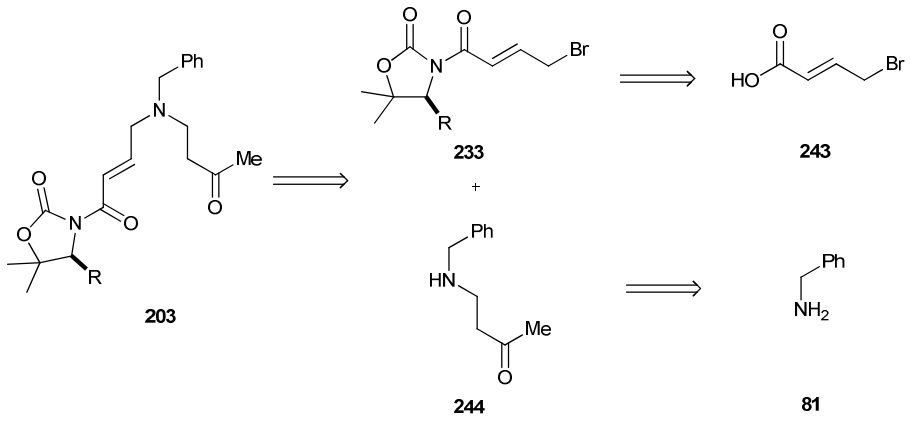
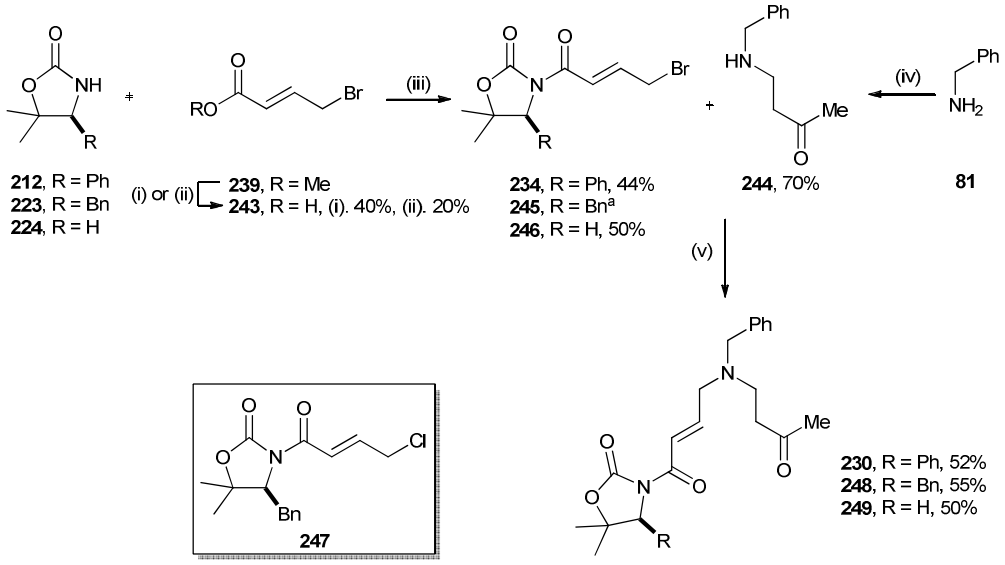


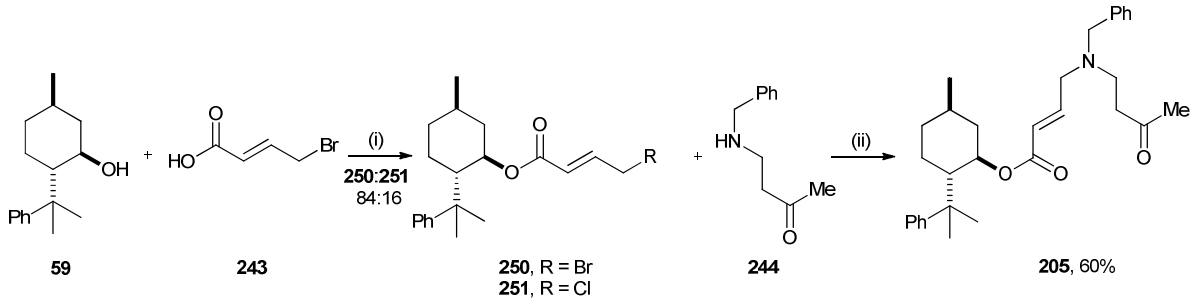
Fig. 29. Retrosynthetic analysis of substrate **203**.

The key intermediate 4-bromocrotonic acid **243** was prepared by BBTO[36] or $Ba(OH)_2$[37] mediated hydrolysis of ester **239** in 40 and 20% yield, respectively. Acylation of SuperQuat **212** with the acyl bromide derived from acid **243** afforded bromide **234** in 44% yield. Meanwhile, amine **244** was synthesized in 70% yield by conjugate addition of benzylamine **81** to methyl vinyl ketone. Subsequent Finkelstein alkylation of amine **244** with bromide **234** gave substrate **230** in 52% yield. This approach for the synthesis of substrate **230** proved to be the most practical, despite the lower overall yield (3 steps with an overall yield of 9%) so it was therefore applied to enantiopure SuperQuat **223** to give substrate **248** in 11% overall yield. The achiral SuperQuat containing substrate **249** was also prepared in 10% overall yield to enable assessment of the extent of catalyst control during the organocatalytic cyclisation reaction in these systems (Scheme 50).



Scheme 50. *Reagents and conditions:* (i) BBTO, toluene, reflux, 6 h; (ii) $Ba(OH)_2$, $EtOH/H_2O$ (v/v 1:3), −11 °C, 16 h; (iii) $(COBr)_2$ or $(COCl)_2$, DMF, CH_2Cl_2, rt, 2 h, then BuLi, THF, −78 °C, 2 h; (iv) methyl vinyl ketone, CH_2Cl_2, rt, 16 h; (v) DIPEA, NaI, acetone, rt, 3 h. [[a] an 84:16 mixture of bromide **245** and chloride **247** was isolated in this case]

This synthetic protocol was also applied to the preparation of substrate **205** containing Corey's 8-phenylmenthol chiral auxiliary **59**. Thus, treatment of **59** with the acyl chloride derived from acid **243** gave an 84:16 mixture of bromide **250** and chloride **251**, then Finkelstein alkylation of amine **244** with this mixture afforded substrate **205** in 60% yield (Scheme 51).



Scheme 51. *Reagents and conditions:* (i) $(COCl)_2$, DMF, CH_2Cl_2, rt, 2 h, then DIPEA, THF, rt, 18 h; (ii) DIPEA, NaI, acetone, rt, 3 h.

3.4. Organocatalytic cyclisation reactions

With substrates **205**, **230**, **248** and **249** in hand, organocatalytic cyclisation reactions were investigated. Since Momose *et al*. reported that the Michael cyclisation of **197** catalysed by α-methylbenzylamine **80** proceeded with the highest degree of stereoselectivity,[26a] it was proposed to explore the analogous chiral amines **252** and **253** (as well as α-methylbenzylamine **80**) as catalysts in this investigation (Fig. 30).

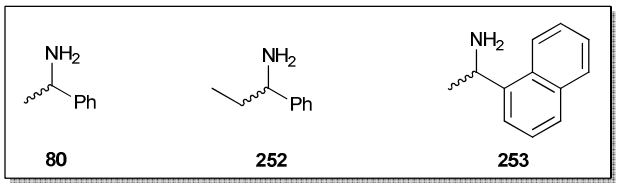
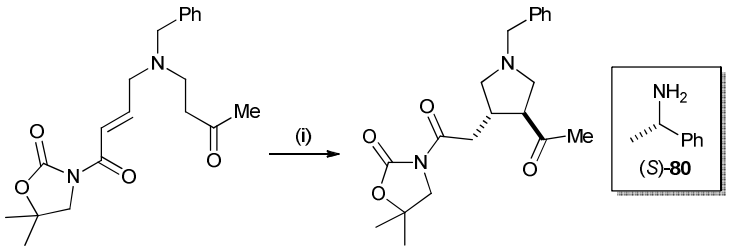


Fig. 30. Chiral amine catalysts **80**, **252** and **253** in this investigation.

3.4.1. Organocatalytic cyclisation of substrate 249

In order to assess the sense and magnitude of stereocontrol offered by the chiral catalyst [(*S*)-α-methylbenzylamine **80**] in these systems (i.e., the level of catalyst control), it was proposed to explore the cyclisation reactions of substrate **249** incorporating achiral SuperQuat **234**. Cyclisation of **249** catalysed by (*S*)-α-methylbenzylamine **80** gave **254** as a single diastereoisomer in 38% yield and 40% ee. The corresponding cyclisation with acetate salt (*S*)-**80**·HOAc gave **254** again as a single diastereoisomer in 61% yield and 30% ee. In

each case, the enantiopurity of **254** was determined by a ^{1}H NMR chiral shift experiment in the presence of chiral solvating agent (*S*)-*O*-acetyl mandelic acid. These results suggest that high diastereoselectivity is observed in the cyclisation of **249** (favouring production of the *trans*-isomer **254**), but that the chiral catalyst (*S*)-α-methylbenzylamine **80** offers only modest levels of enantiocontrol (Scheme 52).

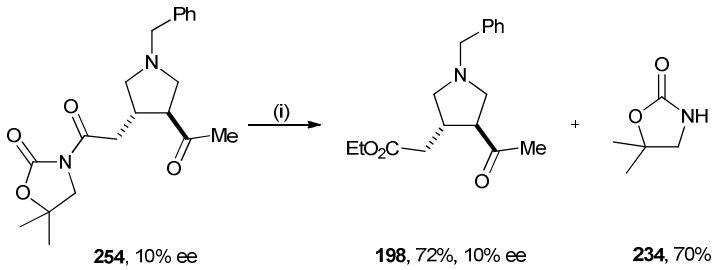


249 **254**

Catalyst	Time (h)	Conversion (%)	ee	Yield (%)
(*S*)-**80**	24	100	40	38
(*S*)-**80**•HOAc	24	100	30	61

Scheme 52. *Reagents and conditions:* (i) catalyst (100 mol%), THF, rt.

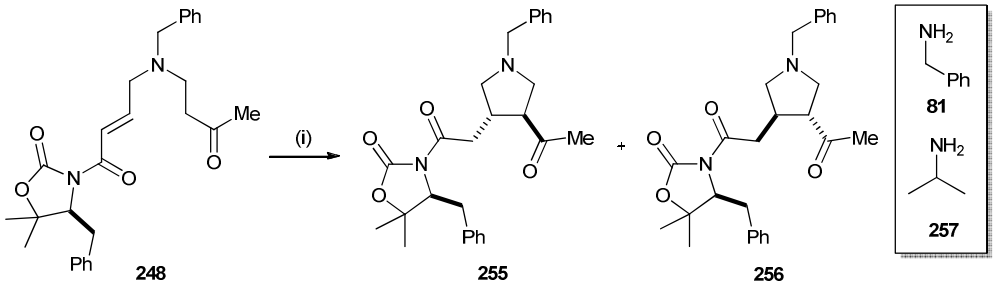
The absolute configuration within cyclisation product **254** was determined by chemical correlation: treatment of **254** (10% ee)[38] with LiOEt gave ethyl ester **198** as a single diastereoisomer in 72% yield and 10% ee.[39] The ^{1}H and ^{13}C NMR spectroscopic properties of **198** prepared in this manner were identical to those reported in the literature,[27] providing unequivocal evidence of the *trans*-relative configuration within **198**. The absolute (*S*,*S*)-configuration within the major enantiomeric product **198** could be assigned by comparing the specific rotation value for this sample of **198** with that of an authentic sample reported in the literature[27,26a] {for (*S*,*S*)-**198** (10% ee), $[\alpha]_D^{23}$ −1.2 (*c* 0.50 in $CHCl_3$); for (*S*,*S*)-**198** (41% ee), lit.[27] $[\alpha]_D^{22}$ −5.1 (*c* 1.0 in $CHCl_3$); for (*S*,*S*)-**198** (62% ee), lit.[26a] $[\alpha]_D^{25}$ −5.5 (*c* 0.85 in $CHCl_3$)}. Since the ee of SuperQuat containing species **254** is identical to the ee of ethyl ester **198**, it is evident that this cleavage process proceeds without erosion of the stereochemical integrity of **254**, and therefore, the absolute (3"*S*,4"*S*)-configuration within **254** (albeit in relatively low ee) could be unambiguously assigned (Scheme 53).



Scheme 53. *Reagents and conditions:* (i) LiOEt, EtOH, 0 °C to rt, 3 h.

3.4.2. Organocatalytic cyclisation of substrate 248

In order to assess the extent of control offered by the SuperQuat auxiliary **223** in this system (i.e., the extent of substrate control), it was proposed to explore the cyclisation reactions of **248** catalysed by the achiral amines benzylamine **81** and isopropylamine **257**. According to the standard cyclisation protocol,[26a] reactions catalysed by benzylamine **81** and the corresponding acetate salt **81**·HOAc proceeded with modest levels of diastereoselectivity, giving mixtures of **255** and **256** in 60:40 and 63:37 dr, respectively. Similarly, for the reactions catalysed by isopropylamine **257** and the corresponding acetate salt **257**·HOAc, the same level of diastereoselectivity (68:32 dr) was observed in both cases. These results suggest that the SuperQuat auxiliary **223** only offered modest levels of stereocontrol (Scheme 54).



Catalyst	Time (h)	Conversion (%)	crude dr (**255**:**256**)	Yield (%)[a]
81	24	100	60:40	10
81•HOAc	24	100	63:37	64
257	24	100	68:32	10
257•HOAc	24	100	68:32	75

Scheme 54. *Reagents and conditions:* (i) catalyst (100 mol%), THF, rt. [[a] dr of isolated product is the same as crude dr]

3.4.3. Relative configurations of cyclisation products

Recrystallisation of a mixture of **255** and **256** (68:32 dr) from chloroform gave small crystals which enabled the relative configuration within the major diastereoisomer **255** to be

unambiguously established by single crystal X-ray diffraction analysis. The absolute (*S*,*S*,*S*)-configuration within **255** was therefore assigned relative to the known (*S*)-configuration of the L-phenylalanine derived SuperQuat auxiliary **223** (Fig. 31). The ^{1}H NMR data of the single crystal used for the X-ray diffraction analysis were identical to those for the major diastereoisomer **255** arising from the organocatalytic cyclisation reactions of **248**, providing unequivocal evidence of the sense of stereoinduction observed in these reactions.

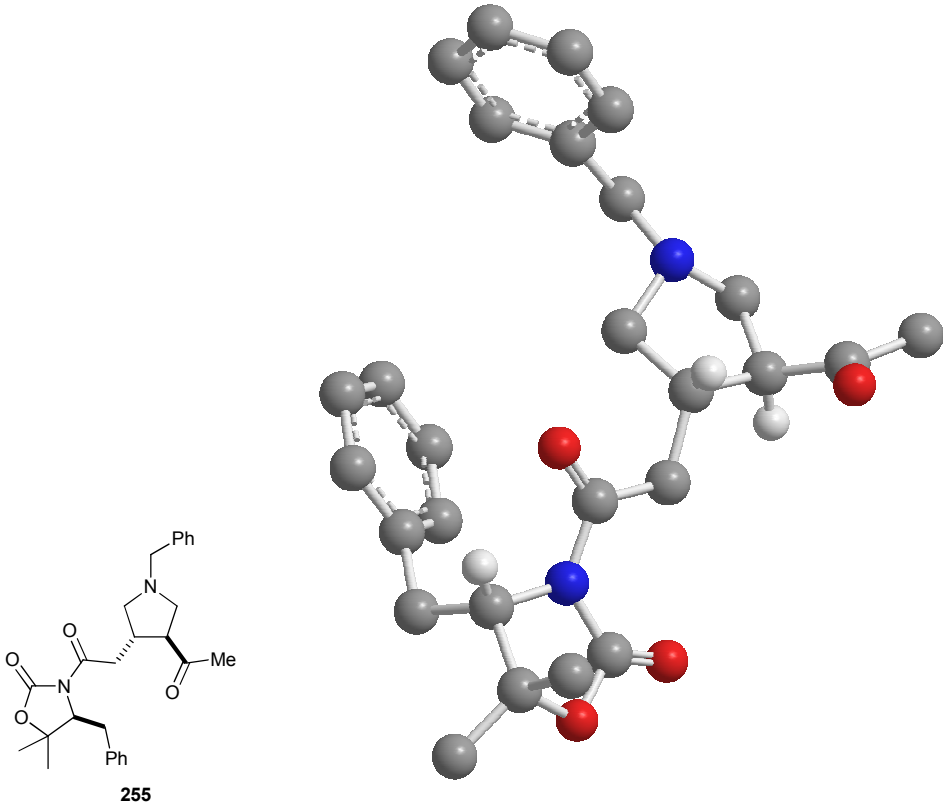
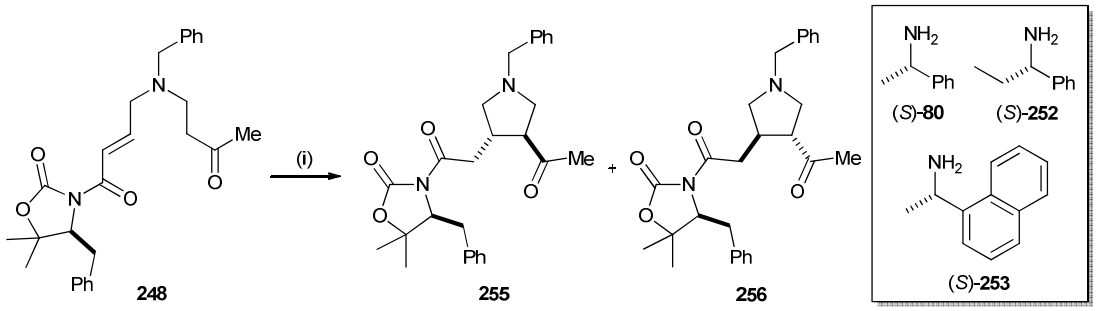


Fig. 31. X-ray crystal structure of (*S*,*S*,*S*)-**255** (selected H atoms are omitted for clarity).

3.4.4. Investigation of "matching" and "mismatching" effects

Previous results have shown that both the chiral catalyst (*S*)-α-methylbenzylamine **80** and the SuperQuat auxiliary **223** offer modest levels of stereocontrol in these cyclisation reactions. It was proposed to combine both stereodirecting components together to explore the "matching" and "mismatching" effects in the hope that superior levels of diastereoselectivity would be observed. From the known stereoselectivity of cyclisation of achiral substrate **249** with chiral catalyst (*S*)-**80**, and chiral substrate **248** with achiral catalysts **81** and **257**, it was envisaged that the combination of chiral substrate **248** with chiral catalyst (*S*)-**80** would represent the "matched" combination. Thus, cyclisation reactions of substrate **248** with the catalysts (*S*)-α-methylbenzylamine **80**,

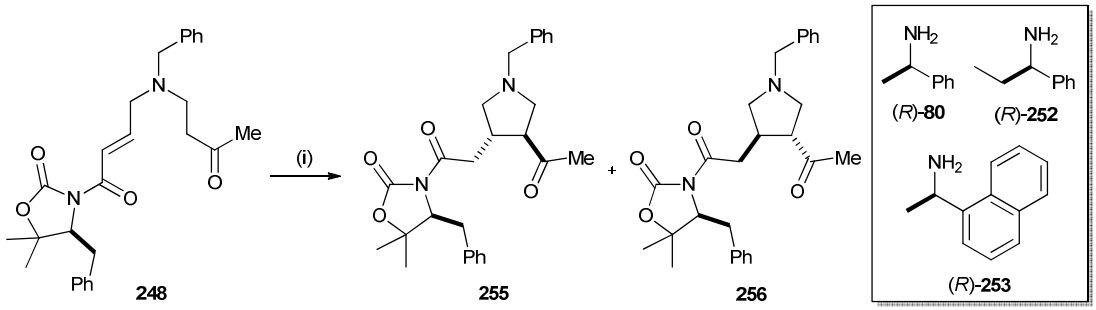
(*S*)-α-ethylbenzylamine **252**, (*S*)-1-(1'-naphthyl)ethylamine **253**, and the corresponding acetate salts **80**·HOAc, **252**·HOAc and **253**·HOAc were investigated next. All of these reactions gave mixtures of **255** and **256** in modest diastereoselectivity (80:20 dr in all but one case) with quantitative conversion. In the case of (*S*)-1-(1'-naphthyl)ethylamine **253**, a reaction time of 120 h was required for the cyclisation reaction to reach completion. The diastereoselectivities observed in these doubly diastereoselective organocatalytic cyclisations are slightly higher than the selectivities observed for the single asymmetric cyclisations, suggesting a slight co-operative effect (i.e., that this is indeed the "matched" pairing), although unfortunately the levels of diastereoselectivity are not at a synthetically useful level (Scheme 55).



Catalyst	Time (h)	Conversion (%)	crude dr (**255**:**256**)	Yield (%)[a]
(*S*)-**80**	24	100	73:27	38
(*S*)-**80**•HOAc	24	100	80:20	80
(*S*)-**252**	24	100	80:20	30
(*S*)-**252**•HOAc	24	100	80:20	86
(*S*)-**253**	120	100	80:20	50
(*S*)-**253**•HOAc	24	100	80:20	80

Scheme 55. *Reagents and conditions:* (i) catalyst (100 mol%), THF, rt. [[a] dr of isolated product is the same as crude dr]

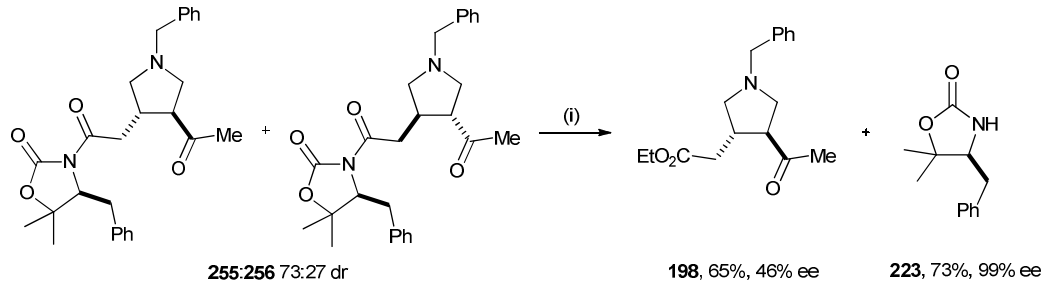
Upon cyclisation of substrate **248** catalysed by (*R*)-α-methylbenzylamine **80**, (*R*)-α-ethylbenzylamine **252**, (*R*)-1-(1'-naphthyl)ethylamine **253**, and the corresponding acetate salts **80**·HOAc, **252**·HOAc and **253**·HOAc, low levels of diastereoselectivity were observed, giving mixtures of **255** and **256** in ≤58:42 dr. The cyclisation using (*R*)-1-(1'-naphthyl)ethylamine **253** also required 120 h to reach completion. These diastereoselectivities suggest that these pairings are "mismatched" (Scheme 56).



Catalyst	Time (h)	Conversion (%)	crude dr (**255**:**256**)	Yield (%)[a]
(*R*)-**80**	24	100	58:42	30
(*R*)-**80**•HOAc	24	100	58:42	85
(*R*)-**252**	24	100	50:50	20
(*R*)-**252**•HOAc	24	100	56:44	80
(*R*)-**253**	120	100	50:50	45
(*R*)-**253**•HOAc	24	100	50:50	84

Scheme 56. *Reagents and conditions:* (i) catalyst (100 mol%), THF, rt. [[a] dr of isolated product is the same as crude dr]

The relative configurations within cyclisation products **255** and **256** were also confirmed by chemical correlation: cleavage of SuperQuat **223** from a 73:27 mixture of **255** and **256** (46% de) gave quantitative conversion to **198** which was isolated in 65% yield and 46% ee.[39] The ^{1}H and ^{13}C NMR spectroscopic properties of **198** prepared in this manner were identical to those reported in the literature,[27] providing unequivocal evidence of the *trans*-relative configurations within both **255** and **256**. This analysis also allows the absolute (*S*,*S*,*S*)- and (4*S*,3"*R*,4"*R*)-configurations within **255** and **256** to be confirmed (Scheme 57).

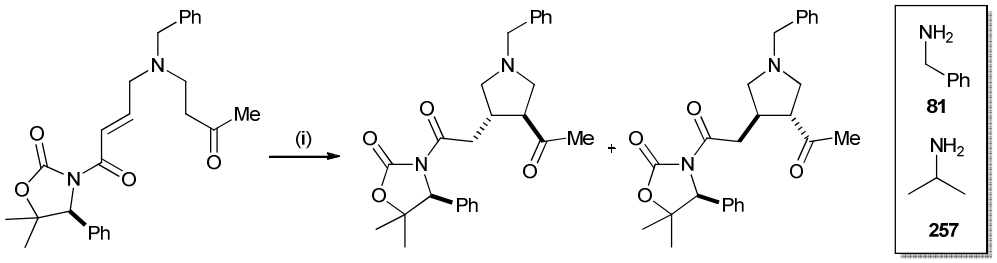


Scheme 57. *Reagents and conditions:* (i) LiOEt, EtOH, 0 °C to rt, 3 h.

In summary, the results from cyclisation of substrate **248** catalysed by the antipodes of α-methylbenzylamine **80**, α-ethylbenzylamine **252** and 1-(1'-naphthyl)ethylamine **253** show no significant effects of "matching" and "mismatching" in this system.

3.4.5. Organocatalytic cyclisation of substrate 230

The effect of incorporation of an alternative phenyl stereodirecting group within the SuperQuat auxiliary was next investigated. The cyclisation reactions of **230** catalysed by achiral catalysts benzylamine **81** and isopropylamine **257** were explored first in order to assess the extent of substrate control offered by the C(4)-phenyl substituted SuperQuat auxiliary **212**. In the cyclisation reactions catalysed by benzylamine **81** and the corresponding acetate salt **81**·HOAc, very low levels of diastereoselectivity (50:50 and 55:45 dr) were observed. Similarly, in the case of the reactions catalysed by isopropylamine **257** and the corresponding acetate salt **257**·HOAc, the same sense and same level of diastereoselectivity (55:45 dr) was observed in both cases. This indicates that the C(4)-phenyl substituted SuperQuat auxiliary **212** provided very poor stereocontrol in this system (Scheme 58).



230 **258** **259**

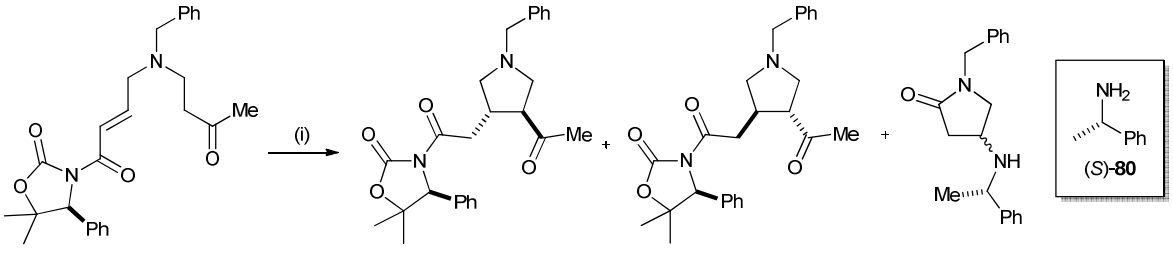
Catalyst	Time (h)	Conversion (%)	crude dr (**258**:**259**)	Yield (%)[a]
81	24	100	50:50	15
81•HOAc	24	100	55:45	55
257	24	100	55:45	36
257•HOAc	24	100	55:45	60

Scheme 58. *Reagents and conditions:* (i) catalyst (100 mol%), THF, rt. [[a] dr of isolated product is the same as crude dr]

3.4.6. Investigation of "matching" and "mismatching" effects

Previous results have shown that chiral catalyst (*S*)-α-methylbenzylamine **80** offers modest levels of stereocontrol and SuperQuat auxiliary **212** provides very poor levels of stereocontrol in cyclisation reactions, respectively. It was proposed to explore the "matching" and "mismatching" effects of the chiral catalysts and substrate **230** in this system. Cyclisation reactions of substrate **230** catalysed by (*S*)-α-methylbenzylamine **80** and the corresponding acetate salt **80**·HOAc proceeded with modest levels of diastereoselectivity (≥73:27 dr) with **258** as the major product in each case. The reaction catalysed by

(*S*)-α-methylbenzylamine **80** gave a 73:27 mixture of **258** and **259** which were inseparable upon chromatographic purification, along with by-product **260** in 60% yield and 75:25 dr. Use of the corresponding acetate salt **80**·HOAc increased the yield up to 75%, and employing water as a co-solvent shortened the reaction time to 7 h (Scheme 59).

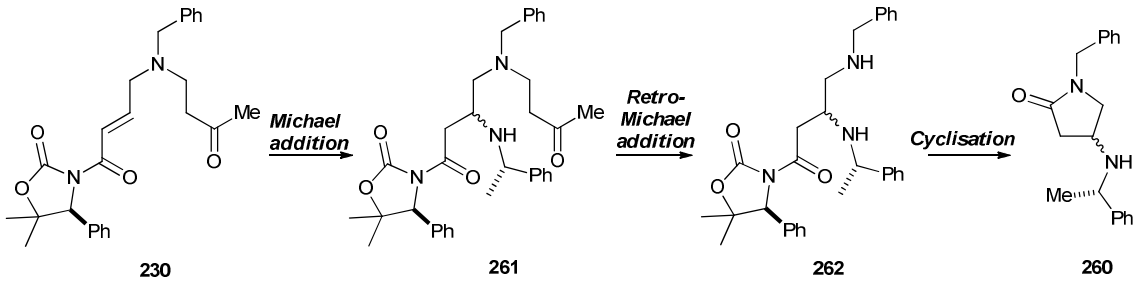


230 258 259 260

Catalyst	Time (h)	Conversion (%)	crude dr (**258**:**259**)	Yield (%)[a]	Yield of **260** (dr) %
(*S*)-**80**	24	100	73:27	25	60 (75:25)
(*S*)-**80**•HOAc	24	100	73:27	75	-
(*S*)-**80**•HOAc[b]	7	98	77:23	64	-

Scheme 59. *Reagents and conditions:* (i) catalyst (100 mol%), THF, rt. [[a] dr of isolated product is the same as crude dr; [b] 5 vol% of H_2O was added]

A possible mechanism was proposed to account for the formation of by-product **260**. It involves Michael addition of (*S*)-α-methylbenzylamine **80** to the substrate **230**, followed by retro-Michael addition to afford secondary amine **262**, which cyclises with loss of SuperQuat **212** to form **260**. The dr of by-product **260** would therefore represent the diastereoselectivity observed upon conjugate addition of (*S*)-**80** to **230** (Fig. 32).

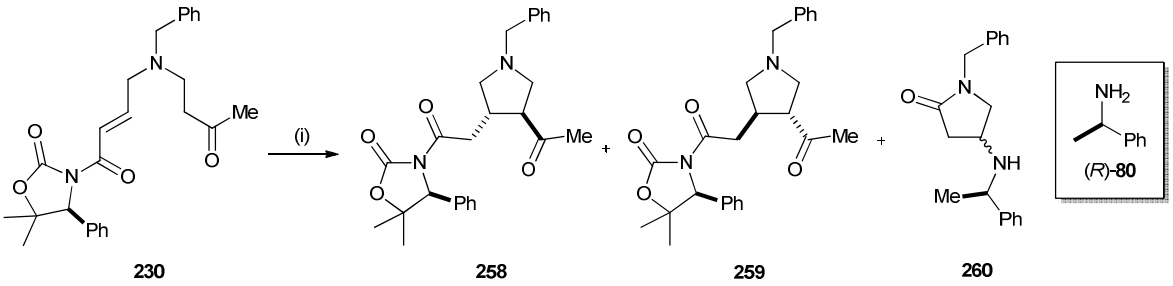


230 261 262 260

Fig. 32. Proposed mechanism for formation of by-product **260**.

Cyclisation reactions of substrate **230** catalysed by (*R*)-α-methylbenzylamine **80** and the corresponding acetate salt **80**·HOAc were next examined. In the reaction catalysed by (*R*)-α-methylbenzylamine **80**, very low diastereoselectivity (49:51 dr) was observed, giving **258** and **259** in 14% combined yield, along with by-product **260** in 63% yield and in 49:51 dr. Use of acetate salt (*R*)-**80**·HOAc increased the yield to 77% without changing the

diastereoselectivity. The addition of water as a co-solvent shortened the reaction time to 7 h (Scheme 60).

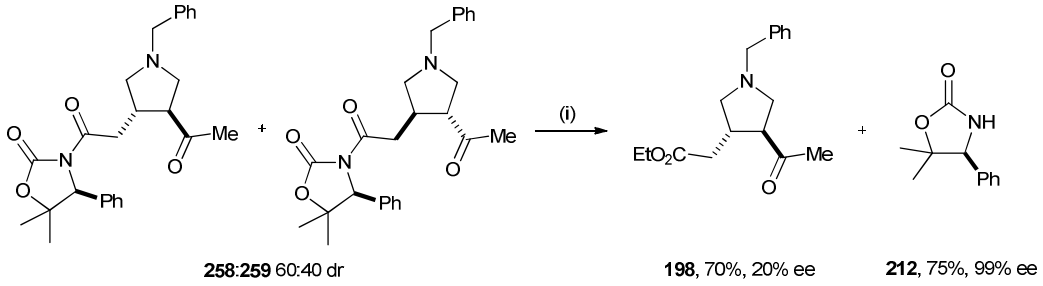


230 **258** **259** **260**

Catalyst	Time (h)	Conversion (%)	crude dr (**258**:**259**)	Yield (%)[a]	Yield of **260** (dr) %
(*R*)-**80**	24	100	49:51	14	63 (49:51)
(*R*)-**80**•HOAc	24	100	45:55	77	-
(*R*)-**80**•HOAc[b]	7	97	45:55	66	-

Scheme 60. *Reagents and conditions:* (i) catalyst (100 mol%), THF, rt. [[a] dr of isolated product is the same as crude dr; [b] 5 vol% of H_2O was added]

The relative configurations within cyclisation products **258** and **259** were again confirmed by chemical correlation: cleavage of SuperQuat **212** from a 60:40 mixture of **258** and **259** (20% de) gave ethyl ester **198** in 70% yield and 20% ee,[39] in addition to SuperQuat **212** in 75% isolated yield. The spectroscopic properties of **198** prepared in this manner were identical to those reported in the literature,[27] providing unequivocal evidence of the *trans*-relative configurations within both **258** and **259**. This analysis also allowed the absolute (*S*,*S*,*S*)-configuration within the major diastereoisomer **258** and the absolute (4*S*,3"*R*,4"*R*)-configuration within the minor diastereoisomer **259**, resulting from cyclisation of **230**, to be assigned (Scheme 61).



258:**259** 60:40 dr **198**, 70%, 20% ee **212**, 75%, 99% ee

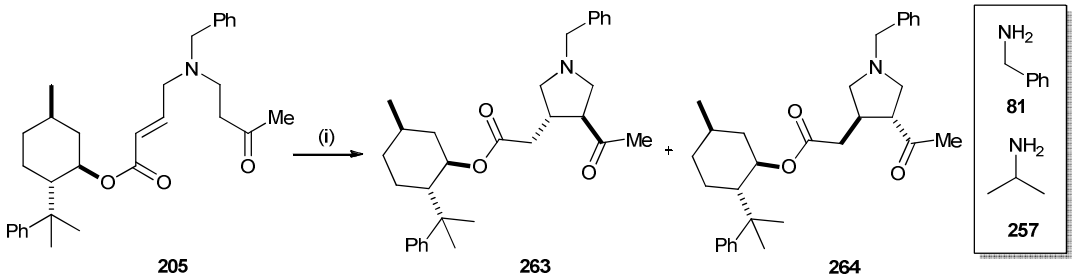
Scheme 61. *Reagents and conditions:* (i) LiOEt, EtOH, 0 °C to rt, 3 h.

Several characteristic features were gleaned from these results: generally, use of an ammonium salt as the catalyst dramatically improved the yield, possibly due to the modest

acidity facilitating enamine formation.[40] Cyclisation reactions were also accelerated by the addition of water as a co-solvent. In related systems, it has been postulated that water could facilitate both the enamine formation and also the hydrolysis step which follows the C–C bond forming process.[41] After analysing the results of cyclisation reactions of substrate **230** catalysed by the antipodes of α-methylbenzylamine **80**, it was noteworthy that no significant "matching" and "mismatching" effects between the substrate and catalyst were observed in this system, consistent with the moderate to poor levels of substrate control observed upon cyclisation of either **230** or **248** catalysed by benzylamine **81** and isopropylamine **257**.

3.4.7. Organocatalytic cyclisation of substrate 205

In order to assess the extent of substrate control offered by the Corey's 8-phenylmenthol auxiliary **59**, the cyclisation reactions of substrate **205** catalysed by achiral catalysts benzylamine **81** and isopropylamine **257** were investigated first. In the cyclisation reactions catalysed by benzylamine **81** and the corresponding acetate salt **81**·HOAc, the same level of diastereoselectivity (63:37 dr) was observed in both cases. Similarly, cyclisation catalysed by isopropylamine **257** and the corresponding acetate salt **257**·HOAc showed modest levels of diastereoselectivity, giving mixtures of **263** and **264** in 65:35 and 67:33 dr, respectively. These results suggest that Corey's 8-phenylmenthol auxiliary **59** only offered modest levels of stereocontrol in this system (Scheme 62).



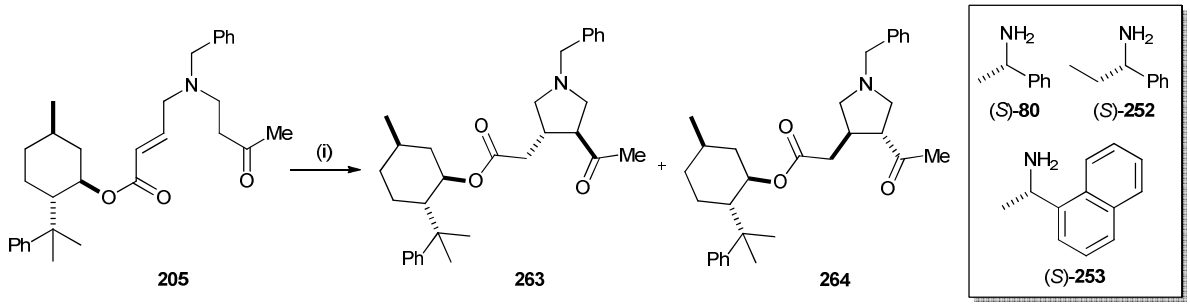
205 263 264

Catalyst	Time (days)	Conversion (%)	crude dr (**263**:**264**)	Yield (%)[a]
81	14	100	63:37	75
81•HOAc	14	95	63:37	84
257	14	98	65:35	80
257•HOAc	14	90	67:33	84

Scheme 62. *Reagents and conditions:* (i) catalyst (100 mol%), THF, rt. [[a] dr of isolated product is the same as crude dr]

3.4.8. Investigation of "matching" and "mismatching" effects

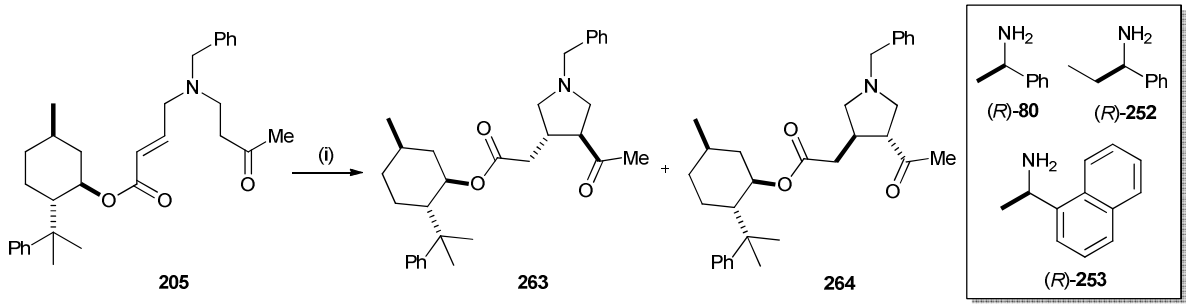
In an attempt to improve the diastereoselectivity of cyclisation reactions in this system, it was proposed to explore any "matching" and "mismatching" effects upon cyclisation of substrate **205** with catalysts (*S*)-α-methylbenzylamine **80**, (*S*)-α-ethylbenzylamine **252**, (*S*)-1-(1'-naphthyl)ethylamine **253**, and the corresponding acetate salts **80**·HOAc, **252**·HOAc and **253**·HOAc. These reactions gave mixtures of **263** and **264** in modest diastereoselectivity (≥60:40 dr) and 38-85% combined yield. In this system, reaction times of 5-12 days were required to achieve completion (Scheme 63).



Catalyst	Time (days)	Conversion (%)	crude dr (**263**:**264**)	Yield (%)[a]
(*S*)-**80**	7	100	79:21	38
(*S*)-**80**•HOAc	7	84	68:32	79
(*S*)-**252**	7	100	73:27	80
(*S*)-**252**•HOAc	12	98	65:35	85
(*S*)-**253**	5	100	85:15	72
(*S*)-**253**•HOAc	6	94	60:40	75

Scheme 63. *Reagents and conditions:* (i) catalyst (100 mol%), THF, rt. [[a] dr of isolated product is the same as crude dr]

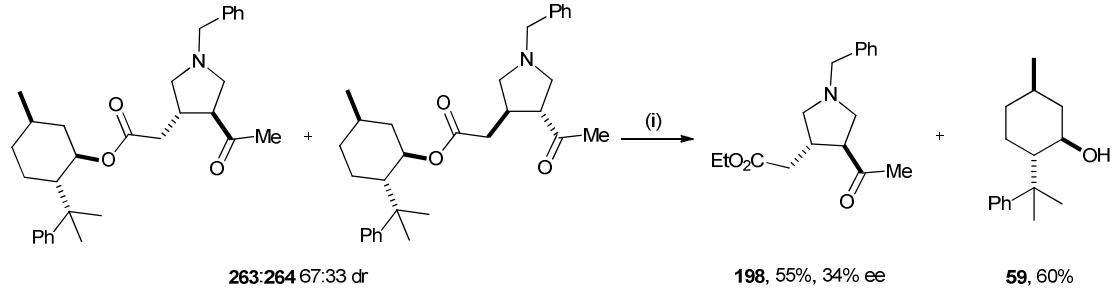
Upon cyclisation of substrate **205** catalysed by (*R*)-α-methylbenzylamine **80**, (*R*)-α-ethylbenzylamine **252**, (*R*)-1-(1'-naphthyl)ethylamine **253**, and the corresponding acetate salts **80**·HOAc, **252**·HOAc and **253**·HOAc, low levels of diastereoselectivity were observed, giving mixtures of **263** and **264** ranging from 55:45 to 67:33 dr. Similarly, long reaction times (5-12 days) were again required for the cyclisation reactions to reach completion (Scheme 64).



Catalyst	Time (days)	Conversion (%)	crude dr (**252**:**253**)	Yield (%)[a]
(*R*)-**80**	7	100	64:36	56
(*R*)-**80**•HOAc	7	85	60:40	75
(*R*)-**252**	7	100	67:33	75
(*R*)-**252**•HOAc	12	97	60:40	80
(*R*)-**253**	5	100	55:45	80
(*R*)-**253**•HOAc	6	95	55:45	72

Scheme 64. *Reagents and conditions:* (i) catalyst (100 mol%), THF, rt. [[a] dr of isolated product is the same as crude dr]

In this system, the relative configurations within cyclisation products **263** and **264** were also determined by chemical correlation: treatment of a 67:33 mixture of **263** and **264** (34% de) with LiOEt gave quantitative conversion to **198** which was isolated in 55% yield and 34% ee.[39] The spectroscopic data for the sample of **198** prepared in this manner were consistent with those of the samples of **198** isolated previously and also those reported in the literature for **198**,[27] providing unequivocal evidence of the *trans*-relative configurations within both **263** and **264**. This analysis also allowed the absolute (3'*S*,4'*S*,1"*R*,2"*S*,5"*R*)-configuration within the major diastereoisomer **263** and the absolute (3'*R*,4'*R*,1"*R*,2"*S*,5"*R*)-configuration within the minor diastereoisomer **264** to be assigned (Scheme 65).



Scheme 65. *Reagents and conditions:* (i) LiOEt, EtOH, 0 °C to rt, 3 h.

The results of these cyclisation reactions have again shown that no significant "matching" and "mismatching" effects were observed in this system.

3.5. Conclusions

In conclusion, the synthetic approach for the preparation of cyclisation substrates incorporating either SuperQuat auxiliaries, or Corey's 8-phenylmenthol auxiliary was developed. A series of organocatalysts were employed to catalyse intramolecular Michael cyclisations of these substrates. The results of the cyclisation reactions show that employing acetate salt of the amine organocatalysts dramatically improves the yield, and the cyclisation reactions could be accelerated by the use of water as a co-solvent. In these doubly diastereoselective systems, some evidence of "matching" and "mismatching" effects were observed. However, due to the modest levels of diastereoselectivity, these double asymmetric induction phenomena were not able to magnify stereocontrol to synthetically useful levels.

3.6. References and Notes

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[39] The ee of **198** was determined by a ^{1}H NMR chiral shift experiment in the presence of chiral solvating agent (*S*)-*O*-acetyl mandelic acid, and confirmed by comparing the specific rotation value for **198** with that of an authentic sample reported in the literature; see: Refs 26a, 27.
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CHAPTER 4

Parallel Kinetic Resolution of Acyclic γ-Amino-α,β-unsaturated Esters

4.1. Introduction

This chapter describes investigations into the parallel kinetic resolution of acyclic γ-amino-α,β-unsaturated esters **265** utilising a 50:50 pseudoenantiomeric mixture of lithium amides **13** and **266**, and demonstrates the synthetic utility of the β,γ-diamino ester products **267** by further elaboration into 4-aminopyrrolidin-2-ones **269** (Fig. 33).

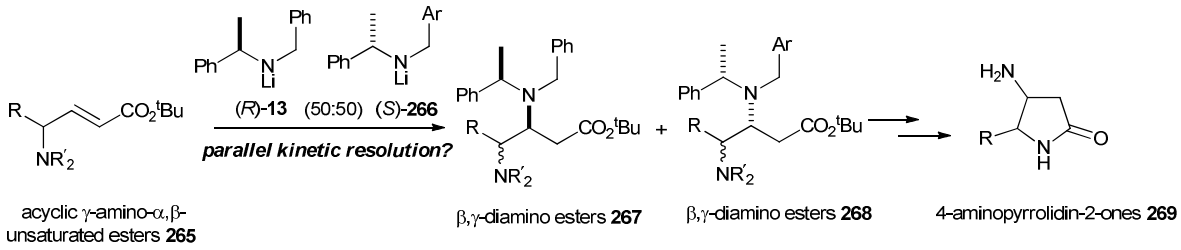


Fig. 33. Parallel kinetic resolution of acyclic γ-amino-α,β-unsaturated esters **265**, and elaboration of the resultant β,γ-diamino esters **267** to 4-aminopyrrolidin-2-ones **269**.

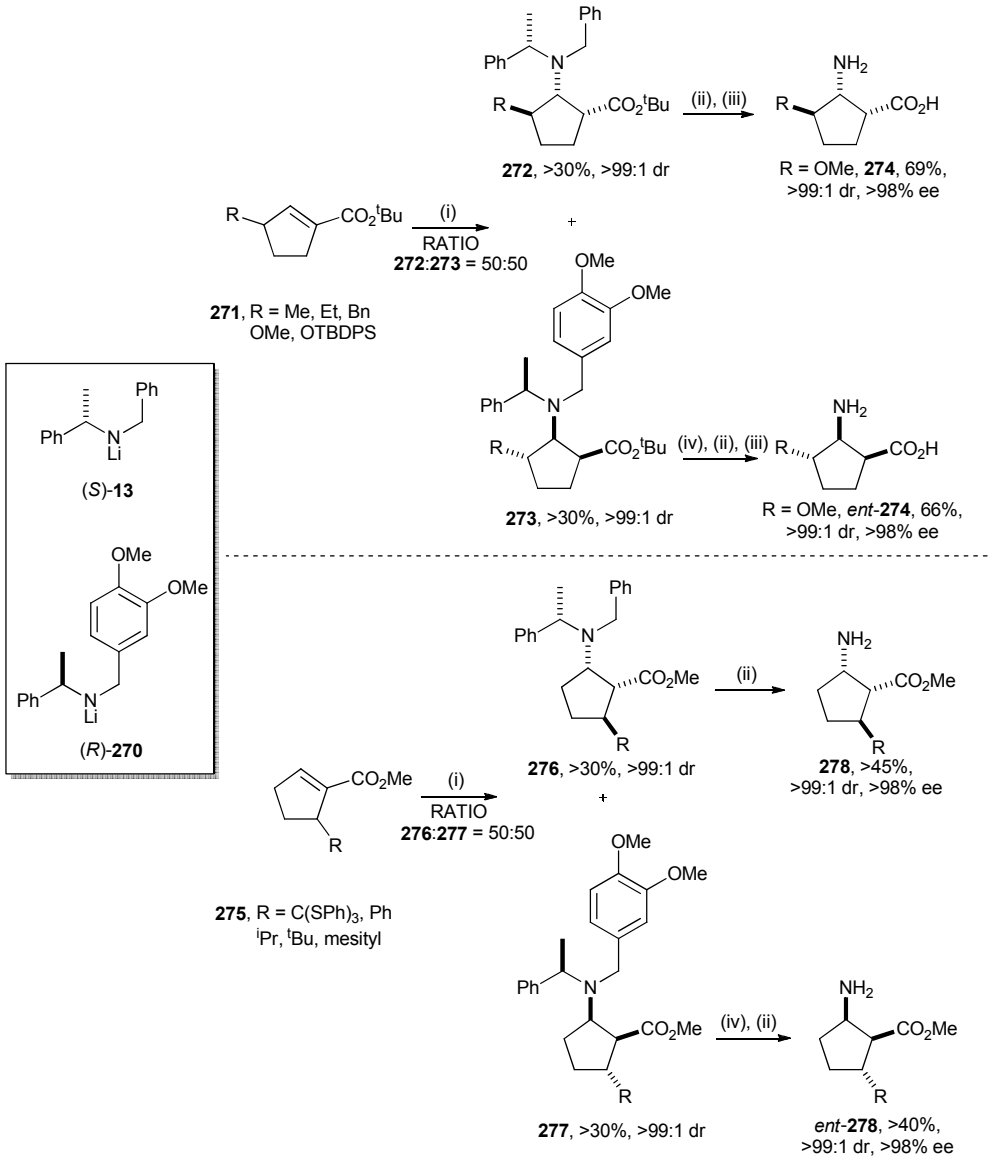
4.1.1. Kinetic resolution

Kinetic resolution is a venerable concept within organic chemistry. It was first observed by Marckwald and McKenzie in 1899, during the esterification of racemic mandelic acid with optically active (−)-menthol.[1] Such is the importance of kinetic resolution that over 100 years later it, together with dynamic kinetic resolution (DKR)[2] and parallel kinetic resoluion (PKR)[3] are employed widely in the preparation of enantiomerically pure materials on both laboratory and industrial scales.

4.1.2. PKR of cyclic α,β-unsaturated esters using lithium amides

Davies and co-workers have established an efficient PKR of a range of 3-alkyl, 3-oxy- and 5-alkyl-substituted cyclopent-1-enecarboxylates, utilising a 50:50 pseudoenantiomeric mixture of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*S*)-**13** and lithium (*R*)-*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amide (*R*)-**270**. In these systems, the exceptionally high diastereofacial control of lithium amides (*S*)-**13** and (*R*)-**270**, combined with high levels of substrate bias for conjugate addition of lithium amides to occur *anti* to the 3- or 5-

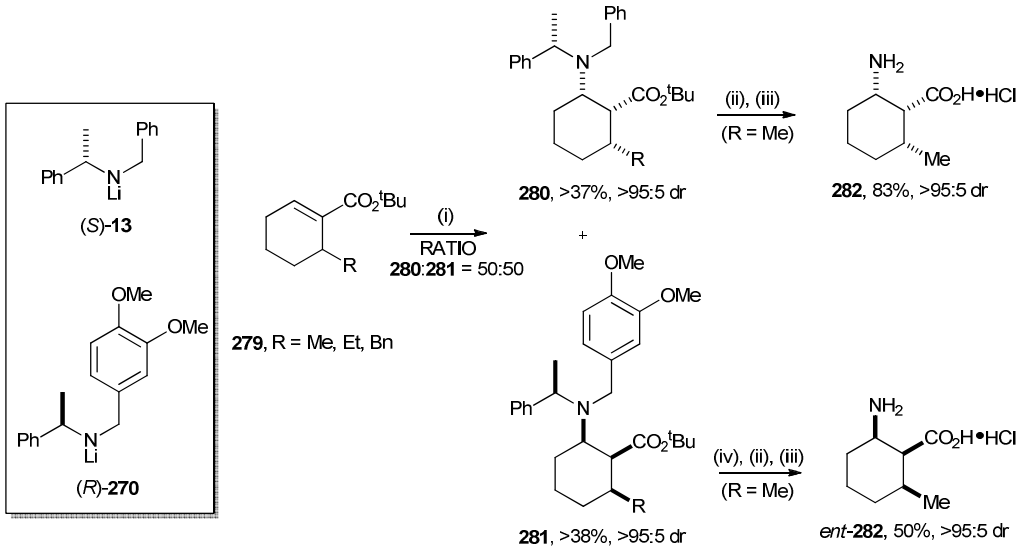
substituent, allowed efficient PKR to be achieved. High diastereofacial selectivity upon kinetic protonation of the intermediate enolates *anti* to the amino group gave access to single diastereoisomers (>99:1 dr) of both enantiomeric series of 3- or 5-substituted 2-amino-cyclopentanecarboxylates **272**, **273**, **276** and **277**, which were easily separable by chromatography. Subsequent deprotection of the β-amino esters **272**, **273**, **276** and **277** furnished a range of enantiomeric 3- or 5-substituted cispentacins **274** and **278** in >99:1 dr and high enantiomeric purity (Scheme 66).[4]



Scheme 66. *Reagents and conditions:* (i) (*S*)-**13**, (*R*)-**270**, THF, –78 °C, 2 h, then NH_4Cl (satd aq); (ii) $Pd(OH)_2/C$, MeOH, H_2 (5 atm), rt, 24 h; (iii) TFA, CH_2Cl_2, rt, 16 h, then HCl, Et_2O, then Dowex 50WX8-200; (iv) DDQ, CH_2Cl_2/H_2O (v/v 3:1), rt, 48 h.

This versatile protocol was further extended to the synthesis of 6-alkyl-substituted cishexacin derivatives via PKR of *tert*-butyl (*RS*)-6-alkylcyclohex-1-enecarboxylates upon

treatment with a 50:50 pseudoenantiomeric mixture of lithium amides (*S*)-**13** and (*R*)-**270**. In this system, preferential addition of the lithium amide occurred *syn* to the 6-alkyl substituent, with subsequent protonation *anti* to the newly installed amino substituent furnishing the all *syn* products **280** and **281** in high yield and >95:5 dr. *N*-Debenzylation and ester hydrolysis of the PKR products **280** and **281** afforded the enantiomers of 6-methyl-substituted cishexacin **282**, isolated as the corresponding hydrochloride salt (Scheme 67).[5]

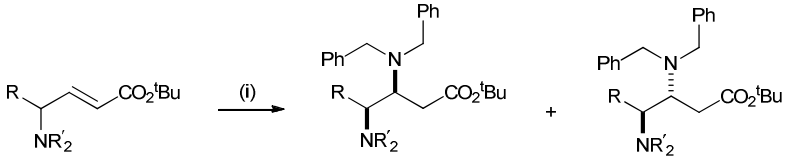


Scheme 67. *Reagents and conditions:* (i) (*S*)-**13**, (*R*)-**270**, THF, –78 °C, 2 h, then NH_4Cl (satd aq); (ii) $Pd(OH)_2/C$, MeOH, H_2 (5 atm), rt, 24 h; (iii) TFA, CH_2Cl_2, rt, 16 h, then HCl, Et_2O; (iv) DDQ, CH_2Cl_2/H_2O (v/v 3:1), rt, 48 h.

4.1.3. Kinetic resolution of acyclic α,β-unsaturated esters using lithium amides

This PKR protocol has thus far been limited to these cyclic α,β-unsaturated esters, due to the requirement for high levels of substrate control. However, studies by Davies and co-workers have evaluated the levels of diastereofacial control of a range of acyclic γ-amino-α,β-unsaturated esters upon conjugate addition of achiral lithium dibenzylamide **106**. Conjugate addition of lithium dibenzylamide **106** to *N*,*N*-diallyl protected γ-amino-α,β-unsaturated esters **284**, **285** and **286** proceeded with modest to good diastereoselectivity (75:25 to 96:4 dr). In these cases, the major diastereoisomeric products 3,4-*syn*-**289**, 3,4-*syn*-**290** and 3,4-*syn*-**291** were isolated as single diastereoisomers (>99:1 dr) in ≥56% yield after chromatographic purification. It was notewothy that in the case of **286** (R = ^{i}Pr), a longer reaction time (4 h) was required for reaction completion, suggesting that the presence of the isopropyl group at C(4) retarded the addition of lithium dibenzylamide **106** to the C(3)

position within **286**. Meanwhile, conjugate addition of lithium dibenzylamide **106** to α,β-unsaturated ester **287** (R = Ph) gave a 22:78 mixture of 3,4-*syn*-**292** and 3,4-*anti*-**297**, indicating opposite diastereofacial selectivity as compared to α,β-unsaturated esters **283**-**286**. Upon conjugate addition of lithium dibenzylamide **106** to *N*,*N*-dibenzyl protected α,β-unsaturated ester **283**, higher levels of diastereoselectivity (92:8 dr) were observed when compared with the modest diastereoselectivity (86:14 dr) derived from the addition to *N*,*N*-diallyl protected α,β-unsaturated ester **284**. The relative configurations within (±)-**289**, (±)-**291** and (±)-**297** were assigned by ^{1}H NMR NOE analysis of the corresponding 4-aminopyrrolidin-2-one derivatives (Scheme 68).[6]

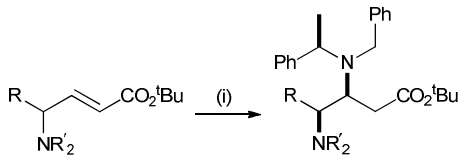


(±)-**283**-**287** (±)-3,4-*syn*-**288**-**292** (±)-3,4-*anti*-**293**-**297**

Substrate	R	R′	3,4-*syn*:3,4-*anti* ratio		(±)-3,4-*syn* yield (dr) %	(±)-3,4-*anti* yield (dr) %
283	Me	Bn	**288**:**293**	92:8	**288**, 85 (>99:1)	**293**, 9 (>99:1)
284	Me	Allyl	**289**:**294**	86:14	**289**, 78 (>99:1)	**294**, 8 (>99:1)
285	Et	Allyl	**290**:**295**	96:4	**290**, 93 (>99:1)	-
286	^{i}Pr	Allyl	**291**:**296**	75:25[a]	**291**, 56 (>99:1)	-
287	Ph	Allyl	**292**:**297**	22:78	**292**, 14 (>99:1)	**297**, 66 (>99:1)

Scheme 68. *Reagents and conditions:* (i) lithium dibenzylamide **106**, THF, –78 °C, 2 h. [[a] 4 h for reaction completion]

Based on this study, Davies and co-workers investigated the mutual kinetic resolution of γ-amino-α,β-unsaturated esters **283** and **285** (which offered very high levels of substrate control upon conjugate addition of lithium dibenzylamide **106**). Conjugate addition of lithium amide (*RS*)-**13** to α,β-unsaturated esters **283** and **285** gave, in each case, essentially a single diastereoisomeric product (3*RS*,4*RS*,α*SR*)-**298** and (3*RS*,4*RS*,α*SR*)-**299** in >99:1 dr, indicating very high levels of enantiorecognition between substrate and reagent, and consistent with *E* >99 in each case (Scheme 69).[6]



(±)-**283**, **285** (3*RS*,4*RS*,α*SR*)-**298**, **299**

Substrate	R	R′	diastereomeric ratio	*E*	(3*RS*,4*RS*,α*SR*) yield (dr) %
283	Me	Bn	>99:1	>99	**298**, 90 (>99:1)
285	Et	Allyl	>99:1	>99	-[a]

Scheme 69. *Reagents and conditions:* (i) (*RS*)-**13**, THF, –78 °C, 2 h. [[a] chromatographic purification of **299** was not attempted in this case]

Close inspection of the results for addition of lithium dibenzylamide **106** and lithium amide (*RS*)-**13** to γ-amino-α,β-unsaturated esters **283** and **285** revealed that the diastereoselectivities for the addition of the achiral lithium amide to α,β-unsaturated esters **283** and **285** are lower than those for the diastereoselectivity observed during the MKR of α,β-unsaturated esters **283** and **285**. More recent studies by Davies *et al*. have shown that lithium dibenzylamide **106** is not always an ideal achiral model for the addition of chiral lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **13** owing to its greater reactivity towards conjugate addition,[4c,e] and these observations may be reflective of that fact.

4.2. Project aims

Building on these initial results, it was anticipated that γ-amino-α,β-unsaturated esters **265** may be useful substrates for the PKR protocol employing a 50:50 pseudoenantiomeric mixture of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*R*)-**13** and lithium (*S*)-*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amide (*S*)-**270**. The resultant enantiopure β,γ-diamino ester products **267** and **300** could be further elaborated for the preparation of 4-aminopyrrolidin-2-ones **269**, which are valuable building blocks for β,γ-diamino acids and natural products (Fig. 34).[7]

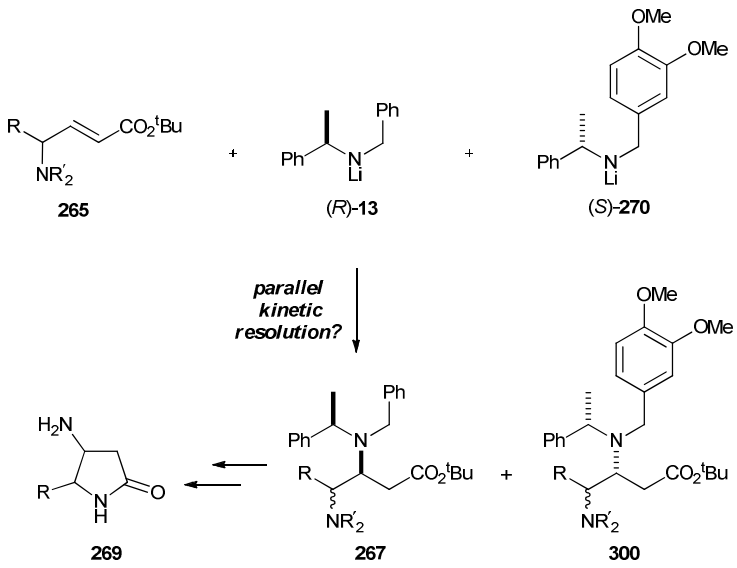
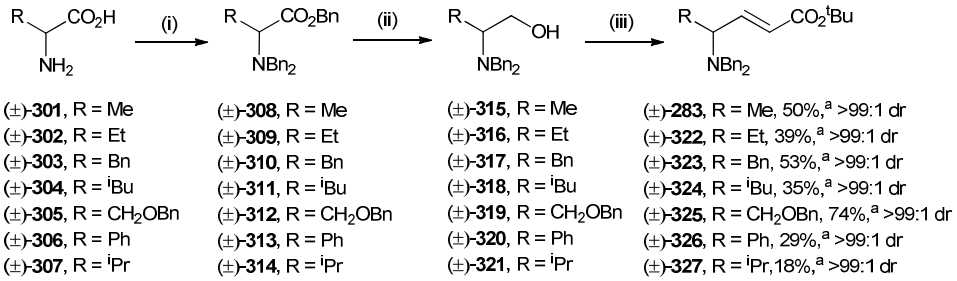


Fig. 34. Proposed parallel kinetic resolution of acyclic γ-amino-α,β-unsaturated esters **265** using (*R*)-**13** and (*S*)-**270**, and further elaboration to 4-aminopyrrolidin-2-ones **269**.

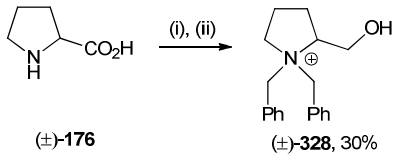
4.3. Preparation of γ-amino-α,β-unsaturated esters

Initial investigations were directed towards the preparation of a range of racemic *N*-protected γ-amino-α,β-unsaturated esters. Given the observations that *N*-benzyl protection results in very high substrate control upon conjugate addition of lithium dibenzylamide **106** to γ-amino-α,β-unsaturated ester **283** (*vide supra*), *N*,*N*-dibenzyl protection was selected for these studies. Reetz *et al*. originally demonstrated that α-amino acids could be elaborated to the corresponding γ-amino-α,β-unsaturated ethyl ester, [8] and a modification of this approach was utilized by Davies *et al.* for the synthesis of γ-amino-α,β-unsaturated *tert*-butyl ester **283**.[6] For the present study, the α-amino acids selected for investigation were: (±)-alanine **301**, R = Me; (±)-α-aminobutyric acid **302**, R = Et; (±)-phenylalanine **303**, R = Bn; (±)-leucine **304**, R = ^{i}Bu; (±)-*O*-benzyl serine **305**, R = CH_2OBn;[9] (±)-phenylglycine **306**, R = Ph; (±)-valine **307**, R = ^{i}Pr; and (±)-proline **176**. Exhaustive benzylation of (±)-**301**-**307** was achieved upon treatment with BnBr in boiling aq K_2CO_3 to give the racemic *N*,*N*-dibenzyl protected α-amino benzyl esters (±)-**308**-**314**. Subsequent reduction of esters (±)-**308**-**314** with $LiAlH_4$ gave the corresponding *N*,*N*-dibenzyl protected α-amino alcohols (±)-**315**-**321**. Swern oxidation of α-amino alcohols (±)-**315**-**321** and olefination of the resultant aldehydes then gave the desired racemic γ-amino-α,β-unsaturated esters (±)-**283** and (±)-**322**-**327** in 18-74% overall yield (Scheme 70).



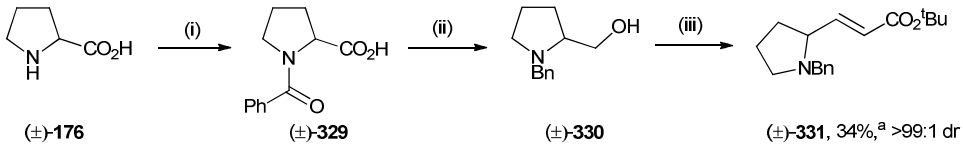
Scheme 70. *Reagents and conditions:* (i) BnBr, K_2CO_3, H_2O, reflux, 3 h; (ii) $LiAlH_4$, THF, reflux, 1 h; (iii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 1 h, then $Ph_3P{=}CHCO_2{}^tBu$, CH_2Cl_2, rt, 18 h. [[a] yield over 3 steps]

However, this general procedure did not apply to (±)-proline **176**, as benzylation of (±)-proline **176** gave a complex mixture of products. Upon reduction of this crude reaction mixture with $LiAlH_4$, *N*,*N*-dibenzyl α-amino alcohol **328** was isolated as the only product in 30% overall yield. This observation suggests that competing *N*,*N*-dibenzylation occurs upon treatment of proline with BnBr in boiling aq K_2CO_3 (Scheme 71).



Scheme 71. *Reagents and conditions:* (i) BnBr, K_2CO_3, H_2O, reflux, 3 h; (ii) $LiAlH_4$, THF, reflux, 1 h.

Thus, an alternative approach was adopted, whereby treatment of (±)-proline **176** with benzoyl chloride, followed by reduction with $LiAlH_4$ afforded *N*-benzyl protected α-amino alcohol (±)-**330**. Swern oxidation of α-amino alcohol (±)-**330** and olefination of the resultant aldehyde then gave racemic γ-amino-α,β-unsaturated ester (±)-**331** in 34% overall yield (Scheme 72).



Scheme 72. *Reagents and conditions:* (i) PhCOCl, NaOH, H_2O, 0 °C, 2 h; (ii) $LiAlH_4$, THF, reflux, 1 h; (iii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 1 h, then $Ph_3P{=}CHCO_2{}^tBu$, CH_2Cl_2, rt, 18 h. [[a] yield over 3 steps]

4.4. Strategy

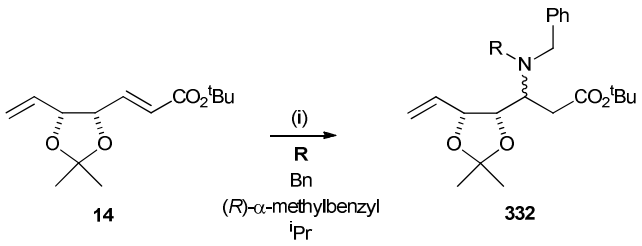
When investigating PKR using the conjugate addition of lithium amides,[3] in order to fully understand the levels of diastereoselectivity observed, Davies *et al*. have suggested that it is prudent to follow a strategy of first investigating the levels of substrate control offered by

the chiral α,β-unsaturated ester upon conjugate addition of an achiral lithium amide.[5] The levels of enantiorecognition between the chiral α,β-unsaturated ester (substrate) and lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **13** (chiral reagent) are then evaluated by investigation of their mutual kinetic resolution (MKR), i.e., addition of racemic lithium amide (*RS*)-**13** to racemic α,β-unsaturated ester substrate. This approach eliminates any complicating effects of mass action and allows the maximum levels of enantiodiscrimination (as quantified by the optimal stereoselectivity factor, *E*)[10] to be very simply determined by analysis of the product distribution by ^{1}H NMR spectroscopy. Finally, having identified those substrates that undergo efficient MKR upon addition of racemic lithium amide (*RS*)-**13**, their PKR employing a 50:50 pseudoenantiomeric mixture of enantiopure lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*R*)-**13** and enantiopure lithium (*S*)-*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amide (*S*)-**270** may be performed. It was therefore resolved to apply this approach to investigate the potential of racemic γ-amino-α,β-unsaturated esters as substrates for the PKR protocol.

4.5. Evaluation of substrate control

4.5.1. Lithium *N*-benzyl-*N*-isopropylamide 107: an alternative achiral model for lithium *N*-benzyl-*N*-(α-methylbenzyl)amide 13

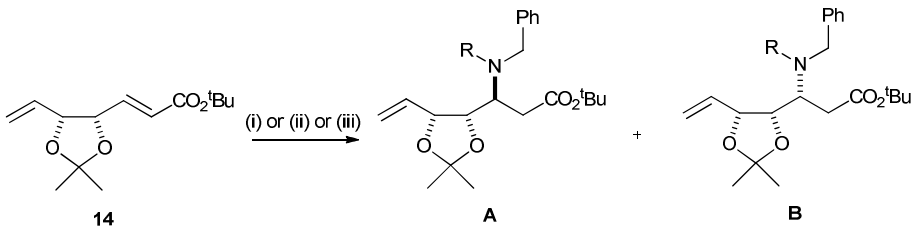
Since lithium dibenzylamide **106** may not be the best model for the addition of chiral lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **13** (*vide supra*), an improved achiral lithium amide model was sought to reflect more appropriately the sense and magnitude of stereoinduction observed upon evaluation of substrate control. Davies and co-workers have recently shown that lithium *N*-benzyl-*N*-isopropylamide **107** is able to very closely mimic the steric bias of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **13** upon conjugate addition to chiral α,β-unsaturated esters.[4c,e] For example, the product distribution derived from one-pot competition experiments have demonstrated that the rates of addition of lithium amides to chiral α,β-unsaturated ester **14** are in the order lithium dibenzylamide **106** >> lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **13** ~ lithium *N*-benzyl-*N*-isopropylamide **107**. This suggests that the similar steric bias of lithium *N*-benzyl-*N*-isopropylamide **107** and lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **13** is manifest in the similar rates of addition (Scheme 73).[11]



Lithium amides	Ratio of addition products
106 *vs* **107**	19:1
106 *vs* (*R*)-**13**	12:1
107 *vs* (*R*)-**13**	1:1

Scheme 73. *Reagents and conditions:* (i) (*R*)-**13**, lithium *N*-benzyl-*N*-isopropylamide **107**, lithium dibenzylamide **106**, THF, –78 °C, 2 h.

In accordance with these observations, addition of lithium amide (*R*)-**13** and lithium *N*-benzyl-*N*-isopropylamide **107** to α,β-unsaturated ester **14** gave single diastereoisomers (>99:1 dr) of the corresponding β-amino esters **16** and **333**, indicating very high levels of substrate control.[11] Meanwhile, conjugate addition of lithium dibenzylamide **106** proceeded with modest diastereoselectivity, giving **334** and **335** in 67:33 dr (Scheme 74).

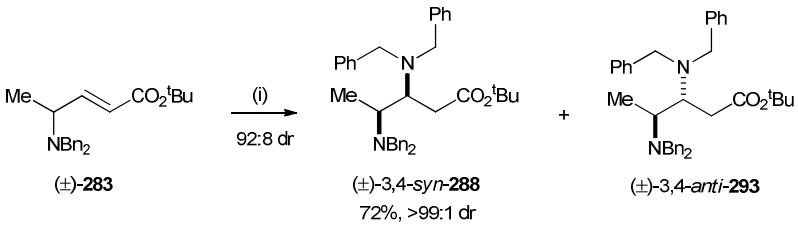


conditions	R	crude dr (A:B)	A (%)	B (%)
(i)	(*R*)-α-methylbenzyl	>99:1	**16**, 50	-
(ii)	iPr	>99:1	**333**, 55	-
(iii)	Bn	67:33	**334**, 54	**335**, 9

Scheme 74. *Reagents and conditions:* (i) (*R*)-**13**, THF, –78 °C, 2 h; (ii) lithium *N*-benzyl-*N*-isopropylamide **107**, THF, –78 °C, 2 h; (iii) lithium dibenzylamide **106**, THF, –78 °C, 2 h.

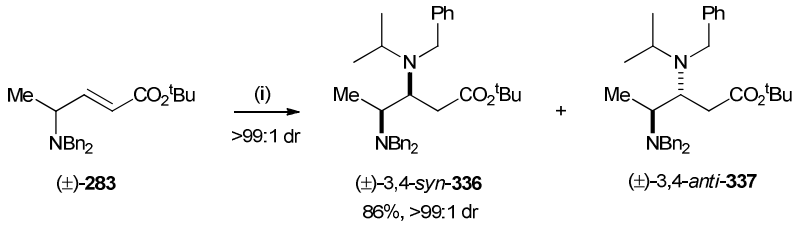
4.5.2. Conjugate addition of lithium dibenzylamide 106 and lithium *N*-benzyl-*N*-isopropylamide 107 to α,β-unsaturated ester 283

Initially, conjugate addition of lithium dibenzylamide **106** to α,β-unsaturated ester **283** was reexamined. This reaction proceeded with high diastereoselectivity, giving β,γ-diamino ester 3,4-*syn*-**288** in 92:8 dr, consistent with the data previously reported by Davies and co-workers.[6] Chromatographic purification of the crude reaction mixture gave 3,4-*syn*-**288** in 72% isolated yield as a single diastereoisomer (Scheme 75).[6]



Scheme 75. *Reagents and conditions:* (i) lithium dibenzylamide **106**, THF, –78 °C, 2 h.

Conjugate addition of lithium *N*-benzyl-*N*-isopropylamide **107** to α,β-unsaturated ester **283** was then examined. This reaction gave β,γ-diamino ester 3,4-*syn*-**336** as a single diastereoisomer (>99:1 dr), suggesting very high levels of substrate control. Comparison of the diastereoselectivity of conjugate addition of lithium dibenzylamide **106** (92:8 dr), lithium *N*-benzyl-*N*-isopropylamide **107** (>99:1 dr) and lithium *N*-benzyl-*N*-(α-methylbenzyl)amide (*RS*)-**13** (>99:1 dr, *vide supra*) towards γ-amino-α,β-unsaturated ester **283** show the behaviour of lithium *N*-benzyl-*N*-isopropylamide **107** is more like that of lithium amide (*RS*)-**13**, so lithium *N*-benzyl-*N*-isopropylamide **107** was used for evaluation of substrate control in all subsequent investigations (Scheme 76).

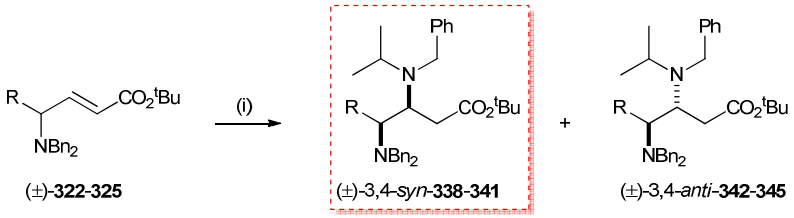


Scheme 76. *Reagents and conditions:* (i) lithium *N*-benzyl-*N*-isopropylamide **107**, THF, –78 °C, 2 h.

4.5.3. Conjugate addition of lithium *N*-benzyl-*N*-isopropylamide 107 to α,β-unsaturated esters 322-325

The behaviour of lithium *N*-benzyl-*N*-isopropylamide **107** towards γ-amino-α,β-unsaturated esters (±)-**322**-**325** (R = Et, Bn, ^{i}Bu, CH_2OBn) was next investigated. Addition of lithium *N*-benzyl-*N*-isopropylamide **107** to γ-amino-α,β-unsaturated esters (±)-**322**-**324** resulted in >95% conversion to the corresponding β,γ-amino esters (±)-**338**-**340** (≥94:6 dr in all cases), indicating very high levels of substrate control. Chromatographic purification allowed isolation of β,γ-amino esters (±)-**338**-**340** in 67-86% yield, and in ≥97:3 dr. Meanwhile, conjugate addition to γ-amino-α,β-unsaturated ester (±)-**325** resulted in an

88:12 mixture of 3,4-*syn*-**341** and 3,4-*anti*-**345**, which were isolated in 60 and 5% yield, as single diastereoisomers (>99:1 dr) in both cases (Scheme 77).



Substrate	R	3,4-*syn*:3,4-*anti* ratio		(±)-3,4-*syn* yield (dr) %	(±)-3,4-*anti* yield (dr) %
322	Et	**338**:**342**	94:6	**338**, 67 (>99:1)	-
323	Bn	**339**:**343**	97:3	**339**, 78 (97:3)	-
324	^{i}Bu	**340**:**344**	98:2	**340**, 72 (98:2)	-
325	CH_2OBn	**341**:**345**	88:12	**341**, 60 (>99:1)	**345**, 5 (>99:1)[a]

Scheme 77. *Reagents and conditions:* (i) lithium *N*-benzyl-*N*-isopropylamide **107**, THF, –78 °C, 2 h. [[a] A 68:32 mixture of **341** and **345** was also isolated in 17% combined yield]

The relative 3,4-*syn*-configuration within (±)-**339** (R = Bn) was unambiguously established by single crystal X-ray diffraction analysis of the corresponding hydrochloride salt (±)-**339**·HCl (Fig. 35). [12] The relative configurations within (±)-**341** and (±)-**345** were unambiguously proven by single crystal X-ray diffraction analysis of a derivative (*vide infra*). The relative 3,4-*syn*-configurations within (±)-**338** and (±)-**340** were assigned by analogy.[13]

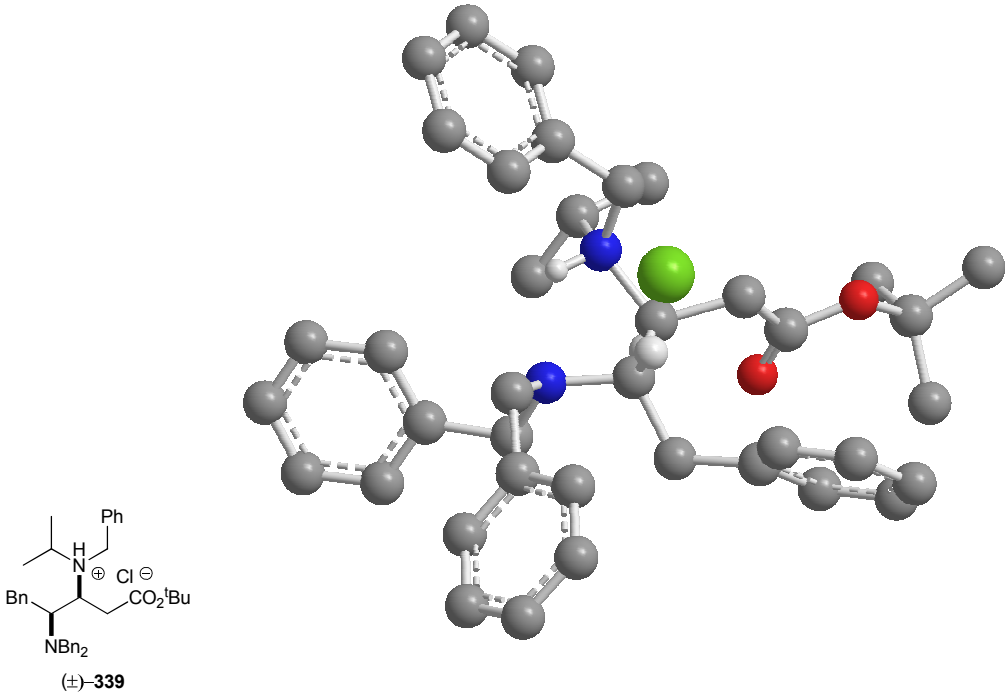
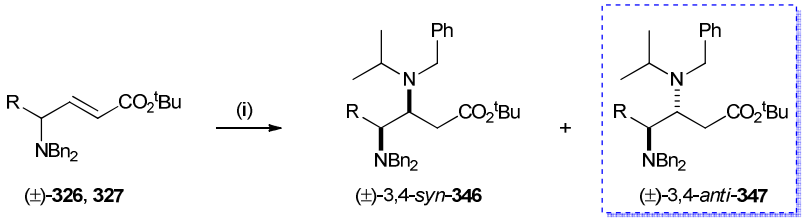


Fig. 35. X-ray crystal structure of (3*RS*,4*RS*)-**339**·HCl (selected H atoms are omitted for clarity).

4.5.4. Conjugate addition of lithium *N*-benzyl-*N*-isopropylamide 107 to α,β-unsaturated esters 326, 327 and 331

Conjugate addition of lithium *N*-benzyl-*N*-isopropylamide **107** to C(4)-phenyl substituted γ-amino-α,β-unsaturated ester (±)-**326** proceeded with low levels of substrate control to give a 27:73 mixture of 3,4-*syn*-**346** and 3,4-*anti*-**347**, which were isolated in 15 and 48% yield as single diastereoisomers (>99:1 dr). The relative 3,4-*anti*-configuration within **347** was unambiguously established by single crystal X-ray diffraction analysis (Fig. 36),[12] which therefore allowed the relative 3,4-*syn*-configuration within **346** to be assigned unambiguously. Meanwhile, in the case of the C(4)-isopropyl substituted γ-amino-α,β-unsaturated ester (±)-**327**, a very low level of conversion (5%) was observed, even over extended reaction times and when the amount of lithium amide was increased from 1.6 equiv to 10 equiv. This result is consistent with the observations of Davies and Epstein concerning the reduced reactivity of the analogous C(4)-isopropyl *N*,*N*-diallyl γ-amino-α,β-unsaturated ester (±)-**286** towards conjugate addition of lithium dibenzylamide **106** (*vide supra*) (Scheme 78).[6]



(±)-**326**, **327** (±)-3,4-*syn*-**346** (±)-3,4-*anti*-**347**

Substrate	R	3,4-*syn*:3,4-*anti* ratio	(±)-3,4-*syn* yield (dr) %	(±)-3,4-*anti* yield (dr) %
326	Ph	**346**:**347** 27:73	**346**, 15 (>99:1)	**347**, 48 (>99:1)
327	^{i}Pr	<5% conversion	-	-

Scheme 78. *Reagents and conditions:* (i) lithium *N*-benzyl-*N*-isopropylamide **107**, THF, –78 °C, 2 h.

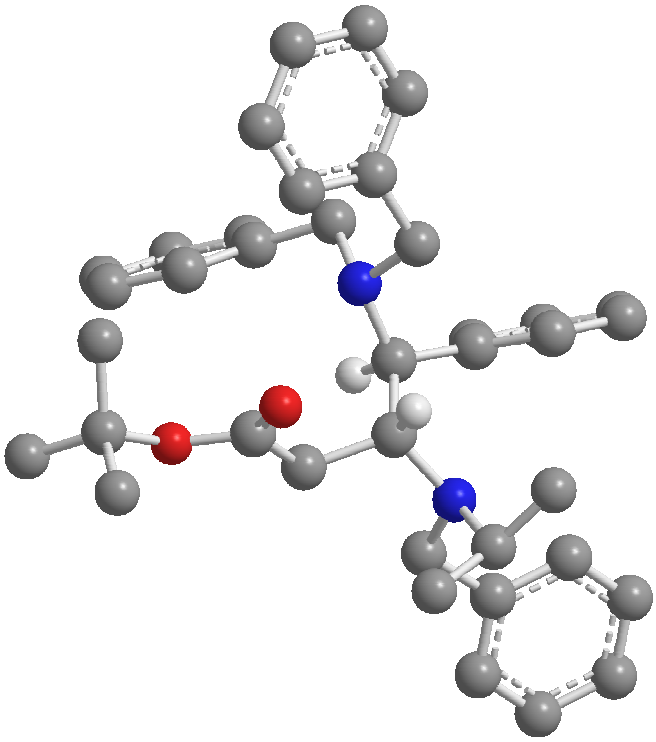
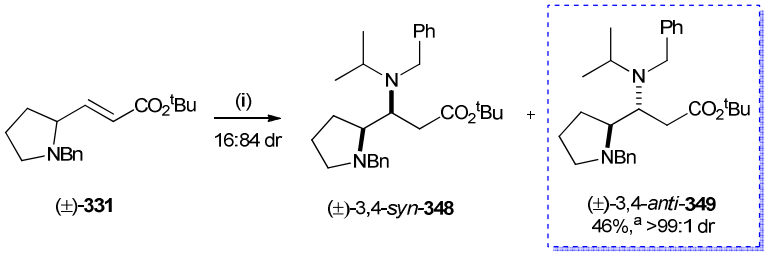


Fig. 36. X-ray crystal structure of (*RS*,*SR*)-**347** (selected H atoms are omitted for clarity).

In the case of γ-amino-α,β-unsaturated ester (±)-**331** [derived from (±)-proline], the conjugate addition of achiral lithium amide **107** proceeded with moderate levels of diastereoselectivity, giving 3,4-*syn*-**348** and 3,4-*anti*-**349** in 16:84 dr, respectively. Upon purification, the major product 3,4-*anti*-**349** was isolated in 46% yield as a single diastereoisomer (>99:1 dr), along with a mixed fraction. The relative configurations within (±)-**348** and (±)-**349** were unambiguously assigned by ^{1}H NMR NOE analyses of derivatives, and by chemical correlation (*vide infra*) (Scheme 79).

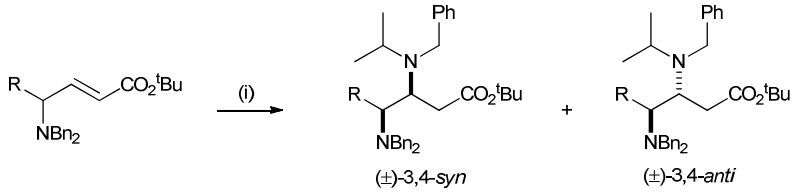


Scheme 79. *Reagents and conditions:* (i) lithium *N*-benzyl-*N*-isopropylamide **107**, THF, –78 °C, 2 h. [[a] an 80:20 mixture of **349** and **348** was also isolated in 16% combined yield].

4.5.5. Origin of diastereofacial selectivity

The results of these studies demonstrate that addition of lithium *N*-benzyl-*N*-isopropylamide **107** to chiral α,β-unsaturated esters (±)-**283** and (±)-**322**-**325** [which do not possess an α-

branched substituent on C(4)] give high levels of substrate control in favor of production of the corresponding 3,4-*syn*-diastereoisomer. Meanwhile, addition of lithium *N*-benzyl-*N*-isopropylamide **107** to chiral α,β-unsaturated esters (±)-**326** and (±)-**327** [possessing much larger C(4)-substituents] results in low levels of substrate control in the case of (±)-**326** (R = Ph) and favors production of the 3,4-*anti*-diastereoisomer, whilst addition to (±)-**327** (R = ^{i}Pr) fails completely. In the case of α,β-unsaturated ester (±)-**331** [derived from (±)-proline], moderate levels of substrate control were observed, favoring production of the 3,4-*anti*-diastereoisomer (Scheme 80).



Substrate	R	3,4-*syn*:3,4-*anti* ratio	(±)-3,4-*syn* yield (dr) %	(±)-3,4-*anti* yield (dr) %
283	Me	**336**:**337** >99:1	**336**, 86 (>99:1)	-
322	Et	**338**:**342** 94:6	**338**, 67 (>99:1)	-
323	Bn	**339**:**343** 97:3	**339**, 78 (97:3)	-
324	^{i}Bu	**340**:**344** 98:2	**340**, 72 (98:2)	-
325	CH_2OBn	**341**:**345** 88:12	**341**, 60 (>99:1)	**345**, 5 (>99:1)
326	Ph	**346**:**347** 27:73	**346**, 15 (>99:1)	**347**, 48 (>99:1)
327	^{i}Pr	<5% conversion	-	-
331	$-(CH_2)_3-$[a]	**348**:**349** 16:84	-	**349**, 46 (>99:1)

Scheme 80. *Reagents and conditions:* (i) lithium *N*-benzyl-*N*-isopropylamide **107**, THF, –78 °C, 2 h. [[a] R = $-(CH_2)_3-$ refers to the proline derived α,β-unsaturated ester, i.e., *tert*-butyl (*RS*,*E*)-3-(1'-benzylpyrrolidin-2'-yl)acrylate **331**].

The conjugate addition of a range of nucleophiles to a range of chiral α,β-unsaturated esters with a stereogenic centre at the γ-position has been extensively investigated in the literature.[14] A range of arguments have been put forward to rationalise the diastereocontrol observations, which include consideration of steric, electronic and chelation effects. Often, a modified Felkin-Anh model (i.e., one in which the α,β-unsaturated ester replaces the carbonyl group)[15] is invoked to rationalise the diastereocontrol, although the conformational preference of the substituents around the allylic stereocenter may be biased by steric effects (approach *anti* to the largest allylic substituent), stereoelectronic effects (approach *anti* to the best electron acceptor), and minimization of 1,3-allylic strain (preferred orientation of an allylic C–H in the same plane as the α-vinylic hydrogen). However, one simple model which is successfully able to rationalize the diastereoselectivity in the present case was derived

from analysis of the single crystal X-ray diffraction of chiral α,β-unsaturated ester **283**. The preferred solid state conformation of **283** has the C(4)-hydrogen atom almost perpendicular to the plane of the α,β-unsaturated system, with the bulky C(4)-*N*,*N*-dibenzylamino substituent occupying the less hindered "outside" position and the C(4)-methyl group in the more hindered "inside" position (Fig. 37).[12]

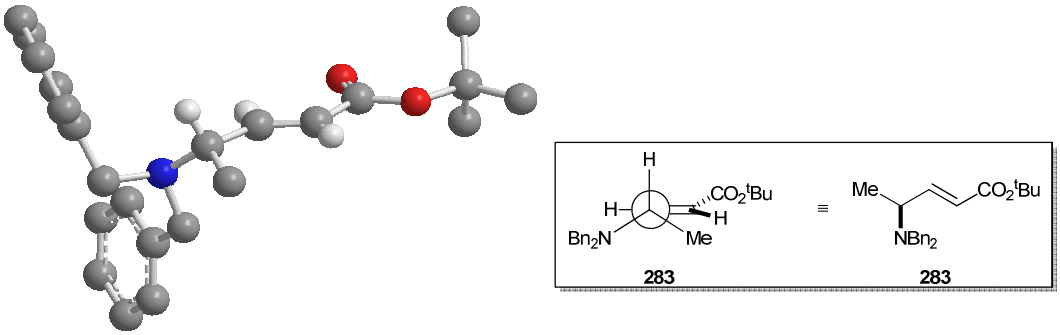


Fig. 37. X-ray crystal structure of (±)-**283** (selected H atoms are omitted for clarity; (*S*)-enantiomer depicted).

Assuming that **283** adopts a similar conformation in solution, conjugate addition of lithium *N*-benzyl-*N*-isopropylamide **107** to chiral α,β-unsaturated ester **283** in this conformation would be predicted to occur on the least hindered *Si* face past the "small" hydrogen substituent to give the 3,4-*syn*-diastereoisomer **336**, as observed experimentally. A similar analysis applied to chiral α,β-unsaturated esters (±)-**322**-**325** (R = Et, Bn, ^{i}Bu, CH_2OBn) would also successfully rationalise the observed substrate diastereofacial control, leading to the corresponding 3,4-*syn*-diastereoisomers (±)-**338**-**341** (Fig. 38).

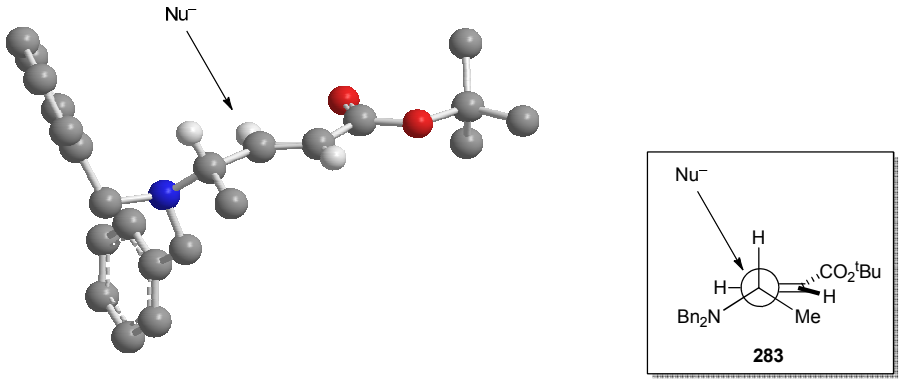


Fig. 38. Substrate diastereofacial control rationalisation.

In the case of α,β-unsaturated esters **326**, **327** and **331**, the increased steric bulk of the C(4)-phenyl and C(4)-isopropyl substituents or the cyclic constraints of the pyrrolidine ring may serve to disfavour analogous conformations, thereby providing a rationale for the differing behaviour observed upon conjugate addition of lithium *N*-benzyl-*N*-isopropylamide **107**. It may be that **326**, **327** and **331** adopt conformations **326A**, **327A** and **331A**, respectively, in which 1,3-allylic strain is minimised. However, this results in both faces being shielded: one face by the C(4)-amino substituent, the other by the C(4)-alkyl substituent. The conjugate addition of lithium *N*-benzyl-*N*-isopropylamide **107** to **326A** and **331A** may then preferentially occur over the smaller group (Ph or the alkyl group of the proline ring) in preference to the more sterically demanding C(4)-amino group, resulting in formation of the major diastereoisomers **347** and **349**, respectively. It is possible that, in the case of **327** (R = ^{i}Pr), the very large steric congestion around C(4) precludes addition of the sterically demanding lithium amide to C(3) (Fig. 39).

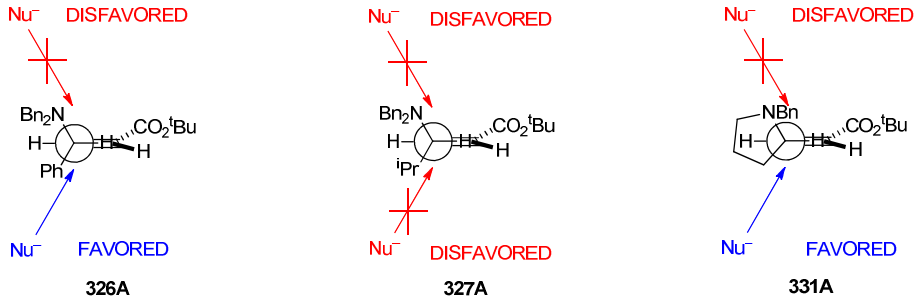
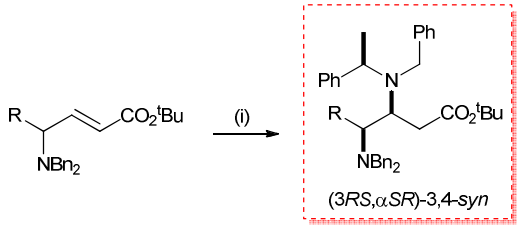


Fig. 39. Substrate diastereofacial control rationalisation for chiral γ-amino-α,β-unsaturated esters **326**, **327** and **331**.

4.6. Mutual kinetic resolution

Having demonstrated that conjugate addition of lithium *N*-benzyl-*N*-isopropylamide **107** to γ-amino-α,β-unsaturated esters (±)-**283** and (±)-**322**-**325** proceeds with high levels of substrate control, the mutual kinetic resolution of esters (±)-**283** and (±)-**322**-**325** with lithium (*RS*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*RS*)-**13** was next investigated in order to determine the maximum value of the stereoselectivity factor, *E*. In mutual kinetic resolutions, the effects of mass action are negated and the magnitude of the stereoselectivity factor (*E*) for the reaction is allowed to be calculated independent of the reaction conversion, and is generally identical to the ratio of products.[10] Given the high substrate control observations upon conjugate addition of lithium *N*-benzyl-*N*-isopropylamide **107** to α,β-unsaturated

esters (±)-**283** and (±)-**322**-**325**, and the known high reagent control of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **13**, high levels of enantiorecognition were expected. Indeed, addition of 1.6 equiv of lithium amide (*RS*)-**13** to (±)-**283** and (±)-**322**-**325** gave, in each case, the corresponding (3*RS*,α*SR*)-3,4-*syn*-diastereoisomers **298** and **350**-**353** in ≥95:5 dr. The identity of the minor diastereoisomeric product in these cases was not determined.[16] Purification facilitated isolation of diastereoisomerically pure (>99:1 dr) samples of **298**, **350**, **352** and **353** in ≥75% yield, with the exception of the γ-benzyl substituted case, where one sample of **351** was isolated in 13% yield and >99:1 dr, and another sample was isolated in 70% yield and 95:5 dr. The results of these mutual kinetic resolutions demonstrate that the expected high levels of enantiorecognition are present between lithium (*RS*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **13** and chiral α,β-unsaturated esters (±)-**283** and (±)-**322**-**325** (*E* >19 in each case), suggesting that PKR of these esters via this conjugate addition protocol may be achieved.[17] The diastereoselectivities observed in these MKR reactions were identical (within experimental error) to those observed in the conjugate additions of lithium *N*-benzyl-*N*-isopropylamide **107** to the corresponding substrates,[18,19] consistent with lithium *N*-benzyl-*N*-isopropylamide **107** being able to closely mimic the behaviour of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **13** in this case (Scheme 81).

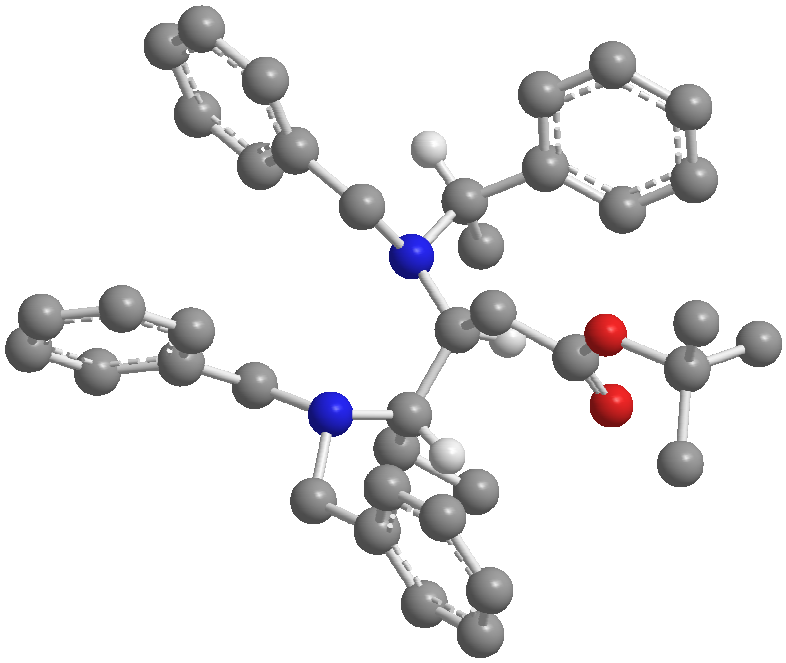


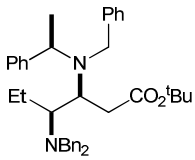
Substrate	R	diastereomeric ratio	*E*	(3*RS*,α*SR*)-3,4-*syn* yield (dr) %
283	Me	>99:1	>99	**298**, 83 (>99:1)
322	Et	95:5	19	**350**, 77 (>99:1)
323	Bn	96:4	24	**351**, 13 (>99:1)[a]
324	^{i}Bu	99:1	99	**352**, 77 (>99:1)
325	CH_2OBn	>99:1	>99	**353**, 75 (>99:1)

Scheme 81. *Reagents and conditions:* (i) (*RS*)-**13**, THF, –78 °C, 2 h. [[a] (3*RS*,4*RS*,α*SR*)-**351** was also isolated in 70% yield and in 95:5 dr]

The relative (3*RS*,4*RS*,α*SR*)-configurations within (±)-**350** and (±)-**352** were unambiguously established by single crystal X-ray diffraction analyses (Fig. 40 and 41),[12,12] and therefore the relative (3*RS*,α*SR*)-3,4-*syn*-configurations within (±)-**298**, (±)-**351** and (±)-**353** were

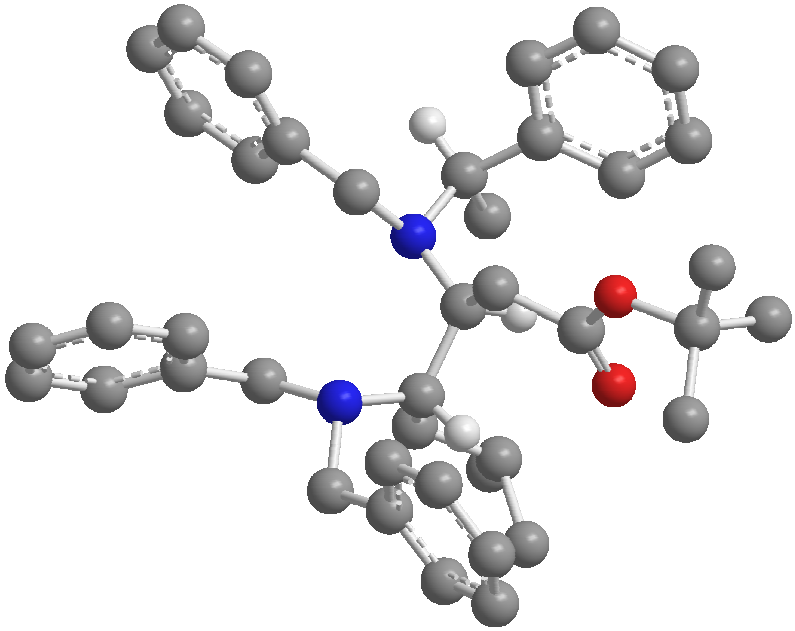
assigned by analogy. It is notable that the relative configurations of the C(3) and C(α)-stereogenic centres within both (±)-**350** and (±)-**352** are in accordance with that predicted by the transition state mnemonic that was developed to rationalise the exceptional facial bias of this class of lithium amide.[20]

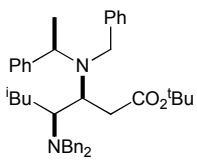




(±)-**350**

Fig. 40. X-ray crystal structure of (3*RS*,4*RS*,α*SR*)-**350** (selected H atoms are omitted for clarity).

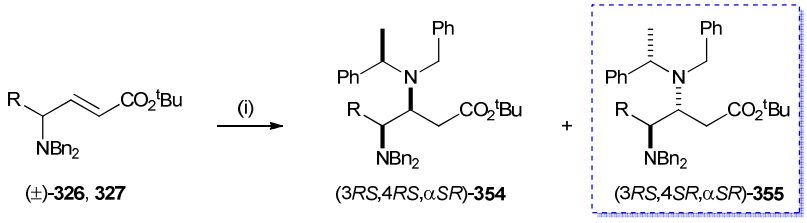




(±)-**352**

Fig. 41. X-ray crystal structure of (3*RS*,4*RS*,α*SR*)-**352** (selected H atoms are omitted for clarity).

Next, investigations concentrated upon the mutual kinetic resolution of γ-amino-α,β-unsaturated esters (±)-**326** (R = Ph) and (±)-**327** (R = ^{i}Pr). Addition of (*RS*)-**13** to α,β-unsaturated ester (±)-**326** gave a 45:55 mixture of diastereoisomeric products, which were isolated as single diastereoisomers (>99:1 dr) in 5 and 12% yield, respectively. In this case, the relative (3*RS*,4*SR*,α*SR*)-configuration within the major diastereoisomeric product **355** was tentatively assigned on the basis of the substrate control observed upon conjugate addition of lithium *N*-benzyl-*N*-isopropylamide **107**. The relative (3*RS*,4*RS*,α*SR*)-configuration within the minor diastereoisomeric product **354** was assigned on the basis of low substrate control but high reagent control. This product distribution is consistent with low levels of enantiorecognition between (*RS*)-**13** and α,β-unsaturated ester (±)-**326** (*E* = 1.2), indicating that α,β-unsaturated ester (±)-**326** is not a suitable substrate for PKR using enantiomerically pure lithium amides. Meanwhile, and unsurprisingly, α,β-unsaturated ester (±)-**327** proved recalcitrant to addition of lithium amide (*RS*)-**13**, even over extended reaction times and when the amount of lithium amide was increased from 1.6 equiv to 10 equiv (Scheme 82).



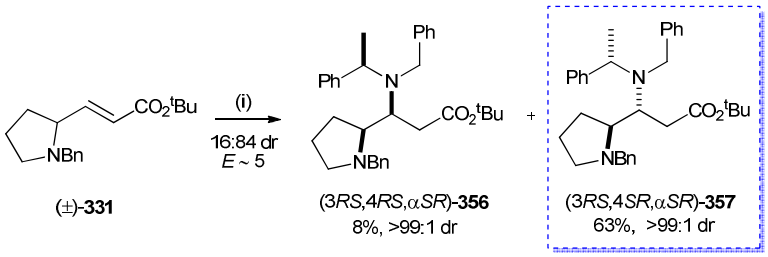
(±)-**326**, **327** (3*RS*,4*RS*,α*SR*)-**354** (3*RS*,4*SR*,α*SR*)-**355**

Substrate	R	diastereomeric ratio	(3*RS*,4*RS*,α*SR*) yield (dr) %	(3*RS*,4*SR*,α*SR*) yield (dr) %
326	Ph	**354**:**355** 45:55	**354**, 5 (>99:1)	**355**, 12 (>99:1)[a]
327	^{i}Pr	<5% conversion	-	-

Scheme 82. *Reagents and conditions:* (i) (*RS*)-**13**, THF, –78 °C, 2 h. [[a] a 42:58 mixture of (3*RS*,4*RS*,α*SR*)-**354** and (3*RS*,4*SR*,α*SR*)-**355** was also isolated in 70% combined yield]

In the MKR of γ-amino-α,β-unsaturated ester (±)-**331** [derived from (±)-proline **176**], addition of (*RS*)-**13** to (±)-**331** proceeded with same level of diastereoselectivity as shown upon addition of lithium *N*-benzyl-*N*-isopropylamide **107**, giving a 16:84 mixture of (3*RS*,4*RS*,α*SR*)-**356** and (3*RS*,4*SR*,α*SR*)-**357**, which were isolated as single diastereoisomers (>99:1 dr) in 8 and 63% yield respectively. The relative configurations within (±)-**356** and (±)-**357** were assigned by ^{1}H NMR NOE analyses of derivatives, and by chemical correlation (*vide infra*). This product distribution is consistent with low levels of

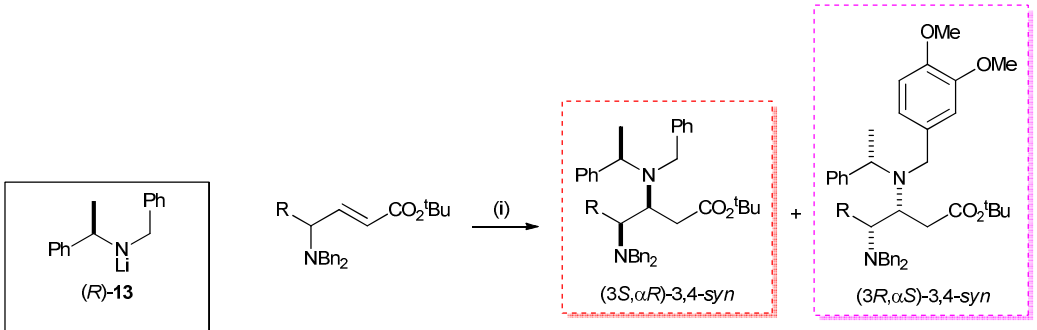
enantiorecognition between (*RS*)-**13** and α,β-unsaturated ester (±)-**331** (*E* ~5), suggesting γ-amino-α,β-unsaturated ester (±)-**331** is not a suitable substrate for PKR using enantiomerically pure lithium amides (Scheme 83).



Scheme 83. *Reagents and conditions:* (i) lithium (*RS*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (±)-**13**, THF, –78 °C, 2 h.

4.7. Parallel kinetic resolution

Having successfully established the mutual kinetic resolutions of γ-amino-α,β-unsaturated esters (±)-**283** and (±)-**322**-**325** with lithium (*RS*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **13**, the PKR of these esters using a 50:50 pseudoenantiomeric mixture of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **13** (2.0 equiv) and lithium (*S*)-*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amide **270** (2.0 equiv)[21] was next investigated. These reactions produced, in each case, a 50:50 mixture of the corresponding (α*R*)-adducts **298** and **350**-**353** in ≥95:5 dr and the (α*S*)-adducts **358**-**362** in ≥95:5 dr. The product distribution observed in PKR reactions were the same (within experimental error) as those derived from mutual kinetic resolution of the corresponding substrates, consistent with the complementary diastereoselectivities of the two pseudoenantiomeric lithium amides. Due to the disparate polarities of the *N*-benzyl and *N*-3,4-dimethoxybenzyl groups, the diastereoisomeric ester products were readily separable by flash column chromatography, allowing isolation of (α*R*)-**298** and **350**-**353** in >99:1 dr and 31-42% yield, and (α*S*)-**358**-**362** in >99:1 dr and 40-43% yield. In each case, the product of conjugate addition of lithium amide (*R*)-**13** was spectroscopically identical to the major diastereoisomer formed in the corresponding MKR reaction (Scheme 84).



Substrate	R	(αR) product ratio	(αS) product ratio	(3S,αR)-3,4-*syn* product yield (dr) %	(3R,αS)-3,4-*syn* product yield (dr) %
283	Me	**298**, >99:1	**358**, >99:1	**298**, 40 (>99:1)	**358**, 43 (>99:1)
322	Et	**350**, 95:5	**359**, 95:5	**350**, 31 (>99:1)	**359**, 40 (>99:1)
323	Bn	**351**, 96:4	**360**, 96:4	**351**, 42 (>99:1)	**360**, 43 (>99:1)
324	^{i}Bu	**352**, 98:2	**361**, >99:1	**352**, 39 (>99:1)	**361**, 43 (>99:1)
325	CH_2OBn	**353**, >99:1	**362**, >99:1	**353**, 37 (>99:1)	**362**, 40 (>99:1)

Scheme 84. *Reagents and conditions:* (i) (*R*)-**13**, (*S*)-**270**, THF, –78 °C, 2 h.

The relative configuration within β,γ-diamino ester **358** [the product of conjugate addition of lithium (*S*)-*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amide **270** to α,β-unsaturated esters (±)-**283**] was unambiguously established via single crystal X-ray diffraction analysis, with the absolute (3*R*,4*R*,α*S*)-configuration being assigned from the known (*S*)-configuration of the α-methylbenzyl stereocentre (Fig. 42).[12] The relative configurations of the C(3) and C(α)-stereogenic centres within **358** are again in accordance with those predicted by the transition state mnemonic for this class of lithium amide.[20] Given the pseudoenantiomeric nature of lithium amides (*R*)-**13** and (*S*)-**270**, this analysis also allows the assigned relative (3*RS*,4*RS*,α*SR*)-configuration within racemic **298** to be unambiguously confirmed, with the absolute (3*S*,4*S*,α*R*)-configuration within enantiopure **298** following from the known (*R*)-configuration of the α-methylbenzyl stereocentre. By similar reasoning, given the known relative configurations within racemic **350** (R = Et) and **352** (R = ^{i}Bu), the absolute (3*S*,4*S*,α*R*)-configurations within enantiopure **350** and **352** may be assigned from the known (*R*)-configuration of the α-methylbenzyl stereocentre and hence the absolute (3*R*,4*R*,α*S*)-configurations within **359** and **361** can be unambiguously assigned. The absolute (3*S*,4*S*,α*R*)-configuration within **351** (R = Bn) and the absolute (3*R*,4*R*,α*S*)-configuration within **360** were therefore assigned by analogy. Similarly, the absolute (3*S*,4*R*,α*R*)-configuration within **353** (R = CH_2OBn) and the absolute (3*R*,4*S*,α*S*)-configuration within **362** were also assigned by analogy.

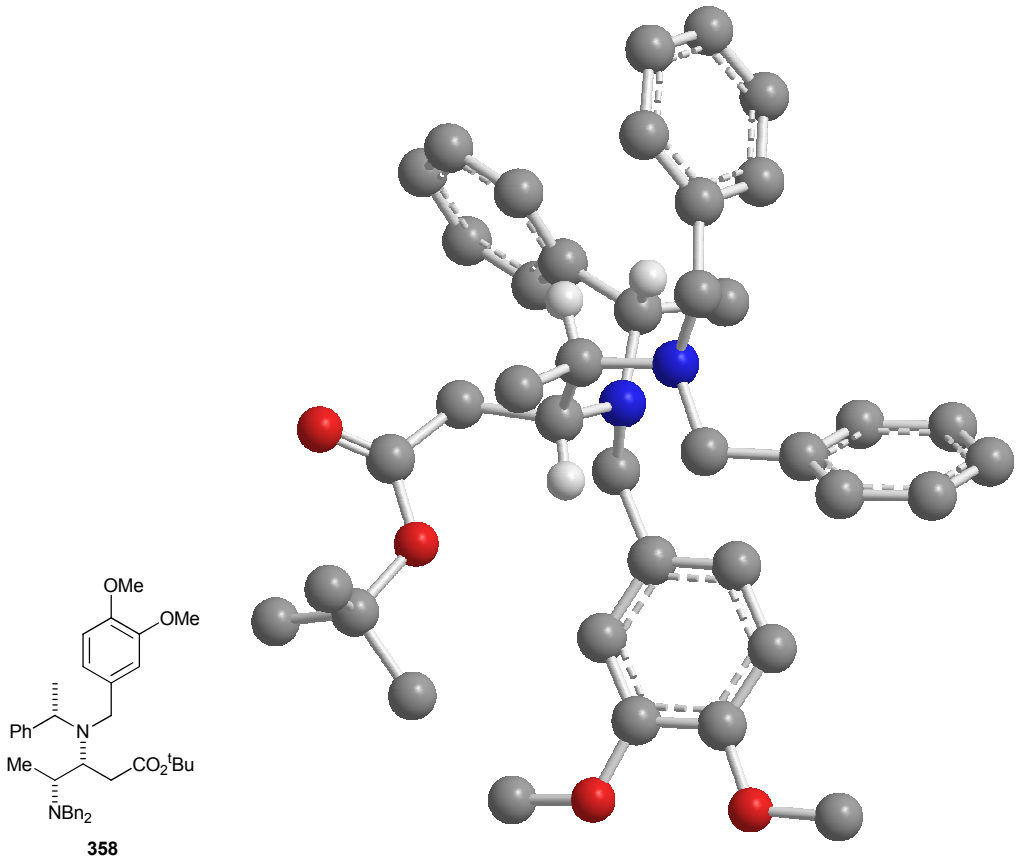


Fig. 42. X-ray crystal structure of (3*R*,4*R*,α*S*)-**358** (selected H atoms are omitted for clarity).

With a range of enantiopure β,γ-diamino esters in hand, their derivatization to 4-aminopyrrolidin-2-ones was next investigated.

4.8. Synthetic application: 4-aminopyrrolidin-2-ones

The synthesis of substituted enantiopure 4-aminopyrrolidin-2-ones has attracted considerable attention, due to their vast utilities as peptidomimetics,[7a] as precursors of γ-lactam bridged dipeptides,[7b] as fragments of renin-inhibiting peptides[7c] and as sub-units of natural products.[7d] In addition, 4-aminopyrrolidin-2-ones provide an entry into β,γ-diaminoacids, which have attracted growing interest due to their biological importance.[22] For instance, when (*S*,*S*)-3-deoxyaminostatine **363** is incorporated into rennin inhibitor peptides, an enhancement of biological activity is induced, compared with those derived from statine. Furthermore, 4-aminopyrrolidin-2-ones also serve as synthetic intermediates for the preparation of 3-aminopyrrolidines, which are sub-units found in natural products[23] and a diverse number of biologically active compounds, such as the highly active antipsychotic agent nemonapride **364** (Fig. 43).[24]

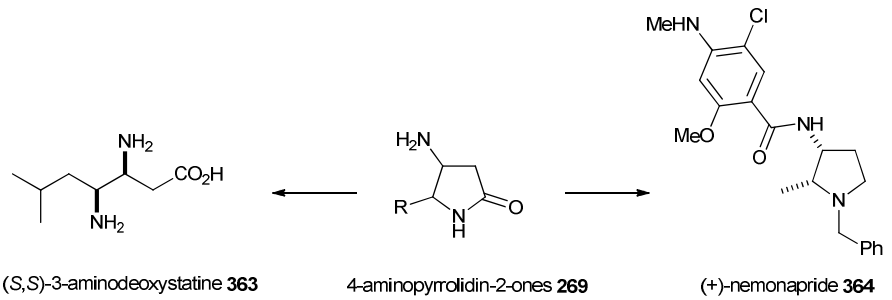
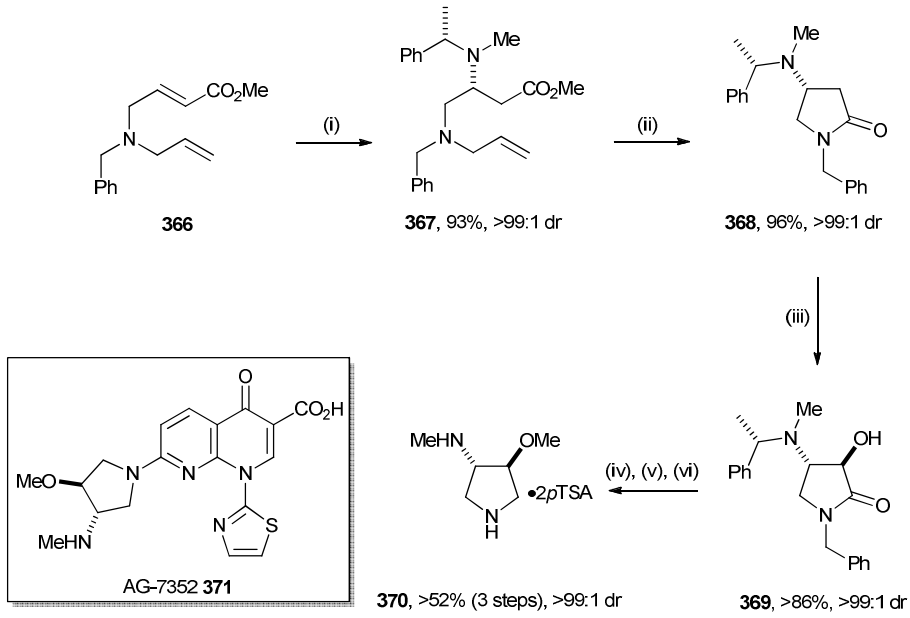


Fig. 43. 4-Aminopyrrolidin-2-ones **269** and biologically active compounds, (*S*,*S*)-3-aminodeoxystatine **363** and (+)-nemonapride **364**.

Typical synthetic routes to 4-aminopyrrolidin-2-ones include radical addition-cyclization of oxime ethers,[25] the Beckmann rearrangement of oximes,[26] the intramolecular rearrangement of β-lactams,[27] conjugate addition to bicyclic pyrrolidin-2-ones[28] and reductive amination of tetramic acids.[29] Davies and co-workers have demonstrated that conjugate addition of lithium (*S*)-*N*-methyl-*N*-(α-methylbenzyl)amide **365** to methyl 4-(*N*-benzyl-*N*-allylamino)but-2-enoate **366** followed by chemoselective *N*-deprotection and concomitant cyclisation furnished 4-aminopyrrolidinone **368** in 96% yield and >99:1 dr. Subsequent enolate functionalisation, *O*-methylation, $LiAlH_4$ reduction and hydrogenolysis allowed the preparation of pyrrolidine **370** (as its di-*p*-toluenesulfonic acid salt), which is an important fragment of the quinolone antitumour agent AG-7352 **371** (Scheme 85).[30]



Scheme 85. *Reagents and conditions:* (i) lithium (*S*)-*N*-methyl-*N*-(α-methylbenzyl)amide **365**, THF, –78 °C, 2 h; (ii) $Pd(PPh_3)_4$, 1,3-DMBA, CH_2Cl_2, rt, 16 h; (iii) LiTMP, THF, –78 °C, 2 h, then (+)-CSO, THF, –78 °C to rt, 16 h; (iv) NaH, THF, 0 °C, 1 h, then MeI, rt, 12 h; (v) $LiAlH_4$, THF, reflux, 12 h; (vi) H_2 (5 atm), $Pd(OH)_2$/C, MeOH, 48 h, then *p*TSA.

It was envisaged that the β,γ-diamino esters **372** (derived from PKR) could be elaborated to the corresponding 5-substituted-4-aminopyrrolidin-2-ones **269** via sequential *N*-deprotection and cyclisation (Fig. 44).

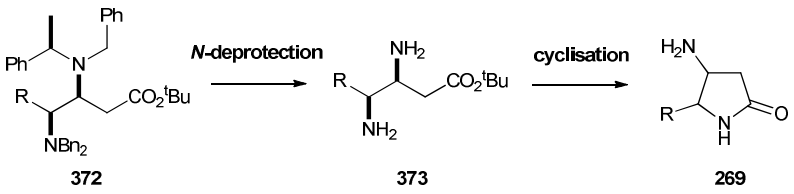
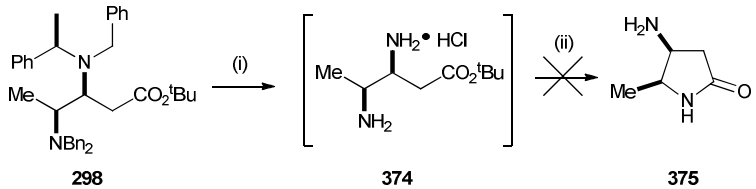


Fig. 44. Proposed elaboration of β,γ-diamino esters **372** to 5-substituted-4-aminopyrrolidin-2-ones **269**.

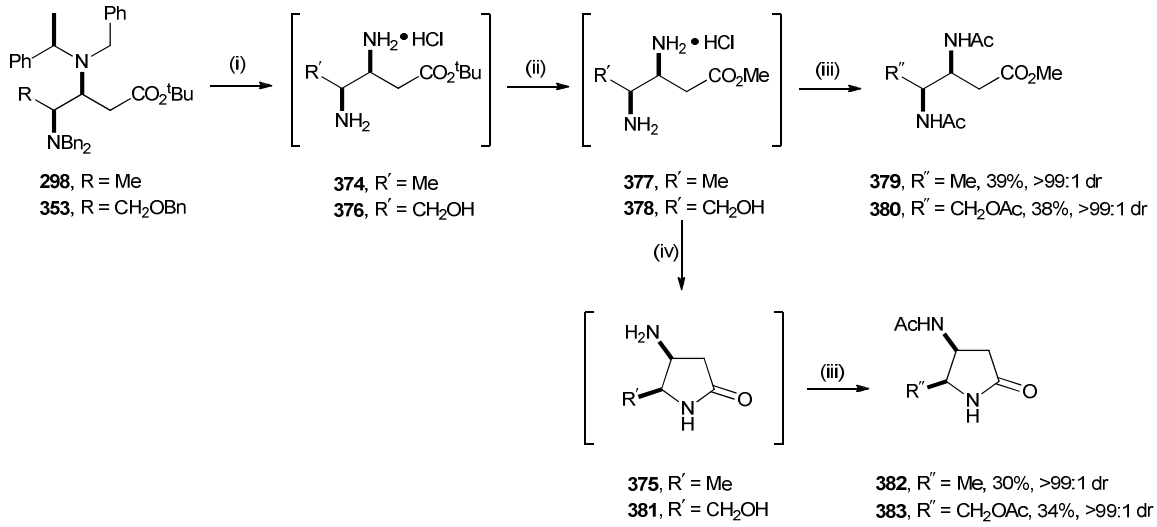
4.8.1. Initial route towards synthesis of 4-aminopyrrolidin-2-ones

N-Debenzylation of β,γ-diamino ester **298** using Pearlman's catalyst in MeOH under hydrogen (1 atm) was first attempted. However, completion of the *N*-debenzylation could not be achieved, even after 6 days reaction time. Therefore, a number of alternative hydrogenolysis conditions were examined, including changing the solvent, the pressure of hydrogen, presence of acid, and reaction time. It was found that treatment with Pearlman's catalyst in 1.25 M HCl/MeOH under pressure of hydrogen (5 atm) gave the debenzylated β,γ-diamino ester as the hydrochloride salt **374**. Although the ^{1}H NMR spectrum of the crude reaction mixture was somewhat broad and complex, both mass spectrometry and ^{1}H NMR spectroscopic analysis suggested the substantial existence of the *tert*-butyl ester functionality. With the debenzylated β,γ-diamino ester hydrochloride salt **374** in hand, cyclisation was next attempted. Upon refluxing **374** with K_2CO_3 in toluene, a complex mixture was obtained with no evidence of the desired 4-aminopyrrolidin-2-one **375** by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. It was postulated that the failure of this cyclisation may be due to the steric hindrance presented by the *tert*-butyl group and, therefore, that changing the *tert*-butyl group to a less sterically demanding group would facilitate the desired cyclisation (Scheme 86).



Scheme 86. *Reagents and conditions:* (i) H_2 (5 atm), $Pd(OH)_2$/C, 1.25 M HCl/MeOH, 48 h; (ii) K_2CO_3, toluene, reflux, 18 h.

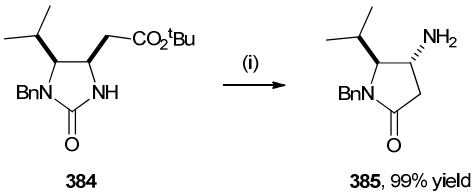
The thermal cyclisation of γ-amino methyl esters to form pyrrolidinones has been documented in the literature.[31] Therefore, **374** was converted to the corresponding methyl ester hydrochloride salt **377** by treatment of the crude mixture containing **374** with methanolic HCl. Formation of the methyl ester **377** was confirmed by isolation of the diacetate derivative **379** in 39% overall yield. Conversion of the methyl ester **377** to the corresponding 5-substituted 4-aminopyrrolidin-2-one **375** was achieved by refluxing **377** with K_2CO_3 in toluene. Subsequent acetylation of **375** gave the acetate derivative **382** in 30% yield over the four steps. An analogous sequence of reactions applied to β,γ-diamino ester **353** (derived from PKR of γ-amino-α,β-unsaturated ester **325**) gave 5-substituted 4-aminopyrrolidin-2-one as its diacetate derivative **383** in 34% overall yield (Scheme 87).



Scheme 87. *Reagents and conditions:* (i) H_2 (5 atm), $Pd(OH)_2/C$, 1.25 M HCl/MeOH, 48 h; (ii) 1.25 M HCl/MeOH, reflux, 18 h; (iii) Ac_2O, pyridine, rt, 18 h; (iv) K_2CO_3, toluene, reflux, 18 h.

4.8.2. Improved route towards the synthesis of 4-amino-pyrrolidin-2-ones

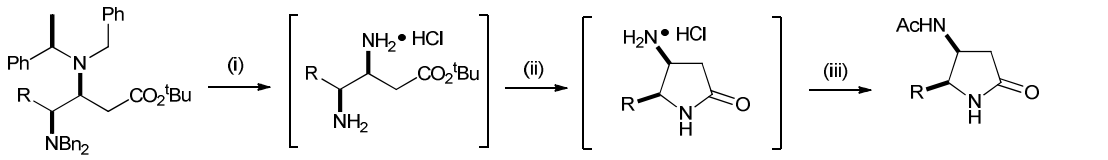
Although the β,γ-diamino esters **298** and **353** could be elaborated to the corresponding 5-substituted 4-aminopyrrolidin-2-ones **382** and **383**, the overall yield was low (30-34%), and therefore an alternative approach was sought. Hoang *et al*. have shown that treatment of imidazolidinone **384** with 3.0 M aq HCl at 90 °C afforded 4-aminopyrrolidin-2-one **385** in 99% yield. This reaction presumably proceeds via hydrolysis of the imidazolidinone ring and ester functionalities, and acid-promoted cyclisation of the resultant β,γ-diamino acid (Scheme 88).[32]



384 **385**, 99% yield

Scheme 88. *Reagents and conditions:* (i) 3.0 M aq HCl, 90 °C, 12 h.

Application of these conditions to *N*-debenzylated β,γ-diamino esters **298**, **350**, **351** and **352** gave the corresponding 5-substituted 4-aminopyrrolidin-2-ones **375**, **389**, **390** and **391**, which were isolated as their acetate derivatives **382**, **392**, **393** and **394** in 70-78% yield over the three steps (Scheme 89).



298, R = Me
350, R = Et
351, R = Bn
352, R = ^{i}Bu

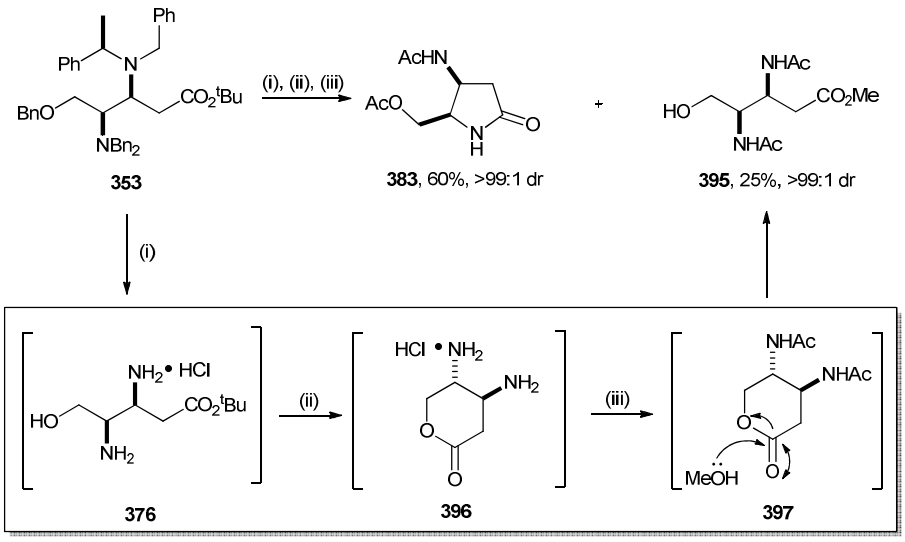
374, R = Me
386, R = Et
387, R = Bn
388, R = ^{i}Bu

375, R = Me
389, R = Et
390, R = Bn
391, R = ^{i}Bu

382, R = Me, 72%, >99:1 dr
392, R = Et, 70%, >99:1 dr
393, R = Bn, 76%, >99:1 dr
394, R = ^{i}Bu, 78%, >99:1 dr

Scheme 89. *Reagents and conditions:* (i) H_2 (5 atm), $Pd(OH)_2$/C, 1.25 M HCl/MeOH, 48 h; (ii) 3.0 M aq HCl, 90 °C, 18 h; (iii) Ac_2O, pyridine, rt, 18 h, then MeOH, 0 °C to rt, 30 min.

Upon application of this sequence of transformations to β,γ-diamino ester **353**, the 4-aminopyrrolidin-2-one diacetate derivative **383** was isolated in 60% yield along with by-product **395** in 25% yield. Presumably, **395** was derived from competing lactonisation of **376** to give **396**, which after subsequent *N*,*N*'-diacetylation undergoes ring opening upon attack of methanol at the lactone carbonyl during the work-up of the acetylation step (Scheme 90).



Scheme 90. *Reagents and conditions:* (i) H_2 (5 atm), $Pd(OH)_2$/C, 1.25 M HCl/MeOH, 48 h; (ii) 3.0 M aq HCl, 90 °C, 18 h; (iii) Ac_2O, pyridine, rt, 18 h, then MeOH, 0 °C to rt, 30 min.

The absolute configurations within **382**, **383**, **392**, **393** and **394** were initially assigned from the known absolute configurations of the precursor β,γ-diamino esters **298**, **350**, **351**, **352** and **353**. In support of these assignments, ^{1}H NMR NOE analyses of **382**, **383**, **392**, **393** and **394** were indicative of a relative 4,5-*syn*-configuration. Irradiation of C(4)*H* showed an enhancement to the signal corresponding to C(5)*H*, and did not show any enhancement to the protons of the C(5)-methyl or methylene group [i.e., C(5)CH_2R', where R' = H, Me, Ph, ^{i}Pr and OAc). Irradiation of C(5)*H* showed an enhancement to the signal corresponding to C(4)*H*. Irradiation of C(5)CH_2R' gave an enhancement to the signal corresponding to CO*Me* (Fig. 45).

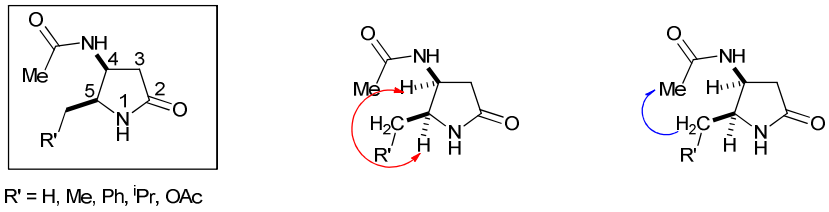
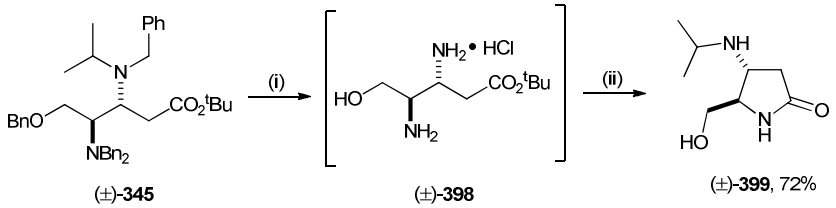


Fig. **45**. Representations of the ^{1}H NMR NOE enhancements observed within substituted 4-aminopyrrolidin-2-one acetate derivatives **382**, **383**, **392**, **393** and **394**. ["↔" represents reciprocal irradiation].

4.8.3. Chemical correlations for systems derived from *O*-benzyl serine

The results of the studies on γ-amino-α,β-unsaturated ester (±)-**325** [derived from (±)-*O*-benzyl serine **305**] demonstrate that conjugate addition of lithium *N*-benzyl-*N*-isopropylamide **107** proceeds with modest levels of substrate control (88:12 dr), whilst MKR and PKR of α,β-unsaturated ester (±)-**325** show very high levels of

diastereoselectivity (>99:1 dr), respectively. The stereochemistry of the products in this system was assigned by analogy to those of the other γ-amino-α,β-unsaturated esters (±)-**283** and (±)-**322**-**324**, and although supported by ^{1}H NMR NOE analysis of the 5-substituted 4-aminopyrrolidin-2-one **383**, no confirmation of the stereochemistry of these products was achieved by single crystal X-ray diffraction analysis. In order to verify that the stereochemical outcome observed upon substrate-directed addition of lithium *N*-benzyl-*N*-isopropylamide **107** to γ-amino-α,β-unsaturated ester (±)-**325** was identical to that observed in the PKR of (±)-**325** with a pseudoenantiomeric mixture of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **13** and lithium (*S*)-*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amide **270**, correlation of addition products (±)-**341**, (±)-**345** and **353** was next undertaken by elaboration to the corresponding 4-aminopyrrolidin-2-ones. Hydrogenolytic *N*-debenzylation of the minor diastereoisomeric product (±)-**345** derived from addition of lithium *N*-benzyl-*N*-isopropylamide **107** to (±)-**325** and subsequent cyclisation afforded the corresponding *N*-isopropyl substituted 4-aminopyrrolidin-2-one (±)-**399**. This compound was obtained in 72% overall yield after purification on ion-exchange resin (Scheme 91).



(±)-**345** (±)-**398** (±)-**399**, 72%

Scheme 91. *Reagents and conditions:* (i) H_2 (5 atm), $Pd(OH)_2$/C, 1.25 M HCl/MeOH, 48 h; (ii) 3.0 M aq HCl, 90 °C, 18 h, then Dowex 50WX4-200.

The relative 4,5-*anti*-configuration within (±)-**399** was unambiguously established by single crystal X-ray diffraction analysis[12] and, hence, the relative 3,4-*anti*-configuration within (±)-**345** could be assigned. Moreover, the relative 3,4-*syn*-configuration within the major diastereoisomeric product (±)-**341** (derived from conjugate addition of lithium *N*-benzyl-*N*-isopropylamide **107** to **325**) could also be assigned (Fig. 46).

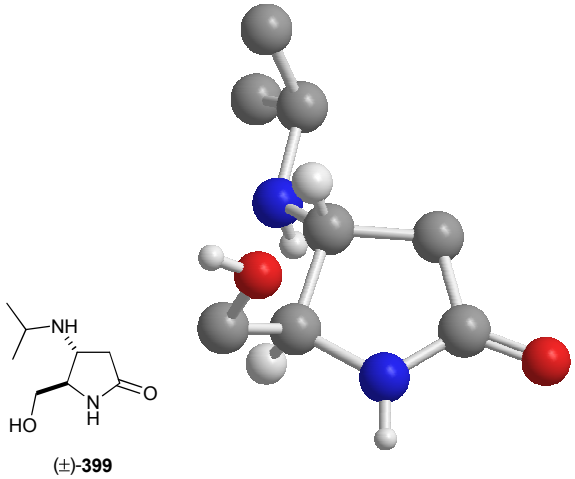
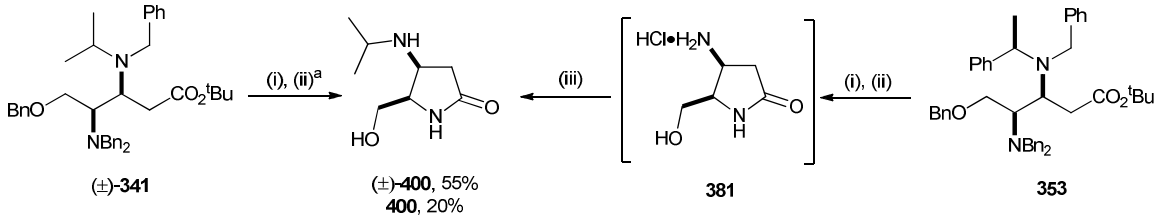


Fig. 46. X-ray crystal structure of (±)-**399** (selected H atoms are omitted for clarity).

An analogous sequence of transformations applied to the major diastereoisomeric product (±)-**341** [derived from substrate-directed addition of lithium *N*-benzyl-*N*-isopropylamide **107** to (±)-**325**], gave the corresponding *N*-isopropyl substituted 4-aminopyrrolidin-2-one (±)-**400** in 55% overall yield, of known relative 4,5-*syn*-configuration. Further application of this sequence of reactions to **353** [derived from PKR of γ-amino-α,β-unsaturated ester (±)-**325**], gave 4-aminopyrrolidin-2-one hydrochloride salt **381**, which was subjected to a reductive amination procedure to give *N*-isopropyl substituted 4-aminopyrrolidin-2-one **400** in 20% overall yield. The ^{1}H and ^{13}C NMR spectra of both samples of *N*-isopropyl substituted 4-aminopyrrolidin-2-one **400** prepared in this manner were identical, and showed distinct differences to the ^{1}H and ^{13}C NMR spectra of (±)-**399**, arising from the minor diastereoisomeric product (±)-**345**, providing unequivocal evidence of the same sense of stereoinduction of the substrate in MKR and PKR [using lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **13** and lithium (*S*)-*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amide **270**] and substrate-directed addition of lithium *N*-benzyl-*N*-isopropylamide **107** (Scheme 92).



Scheme 92. *Reagents and conditions:* (i) H_2 (5 atm), $Pd(OH)_2$/C, 1.25 M HCl/MeOH, 48 h; (ii) 3.0 M aq HCl, 90 °C, 18 h; (iii) $NaBH_4$, acetone, MeOH, 0 °C to rt, 18 h. [[a] then Dowex 50WX4-200]

4.9. Synthetic application: pyrrolizidines

It was anticipated that application of the synthetic protocol for preparation of 5-substituted 4-aminopyrrolidin-2-ones could be extended to the products of MKR of γ-amino-α,β-unsaturated ester (±)-**331** [derived from (±)-proline] to give the cyclised derivative 1-aminopyrrolizidin-3-one (±)-**401**. The pyrrolizidinone motif should allow for further application in synthesis through appropriate modification of the bicyclic ring. It was proposed that 1-aminopyrrolizidin-3-one (±)-**401** would be an ideal candidate for the synthesis of 1-aminopyrrolizidine (±)-**402**, which constitutes the heterocyclic core of a number of biologically active compounds, such as potent and selective 5-HT_3 antagonist **403** for serotonine receptors[33] and the alkaloids laburnamine **404**[34] and (+)-absouline **405**[35] (Fig. 47).

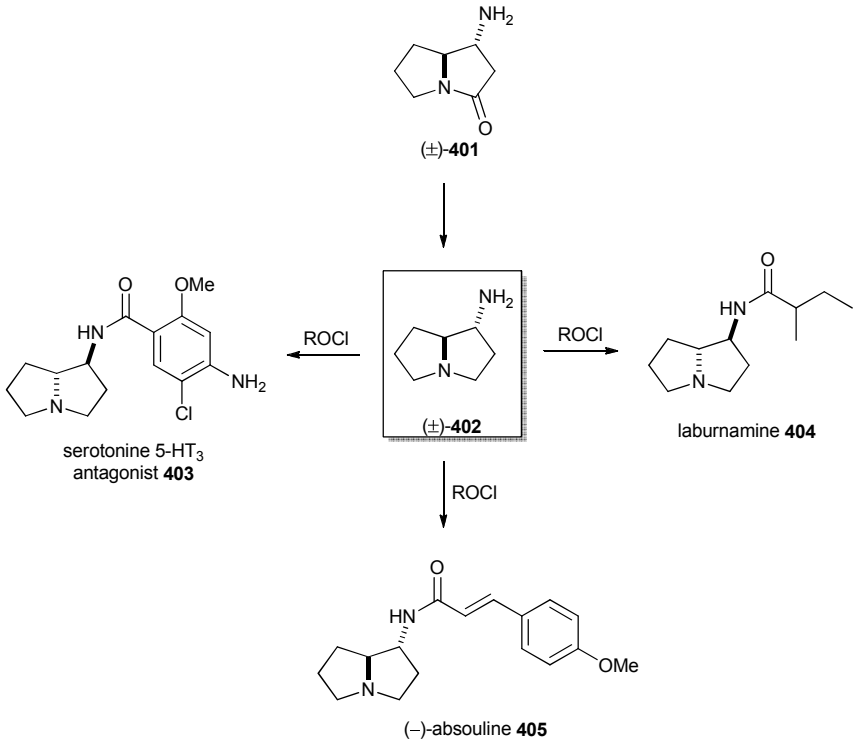
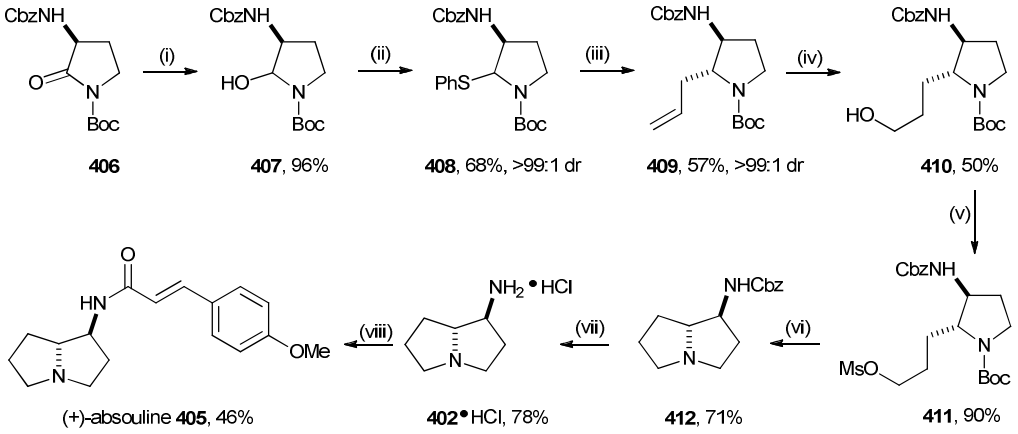


Fig. 47. Transformation of pyrrolizidinone (±)-**401** to 1-amino-pyrrolizidine (±)-**402** would facilitate the synthesis of biologically active compounds, such as serotonine 5-HT_3 antagonist **403**, laburnamine **404**, and (+)-absouline **405**.

4.9.1. Previous syntheses of absouline

The natural product (+)-absouline **405**, as well as its (*Z*)-stereoisomer (+)-isoabsouline and their *N*-oxide derivatives, were isolated from the New Caledonian plants *Hugonia oreogena* and *Hugonia penicillanthemum*, and were shown to possess modest antiviral activity. Since then, several synthetic routes have been reported. Potier and co-workers described the first synthesis of (±)-absouline through a pyrrolizidin-1-one intermediate.[36] The enantiomers of

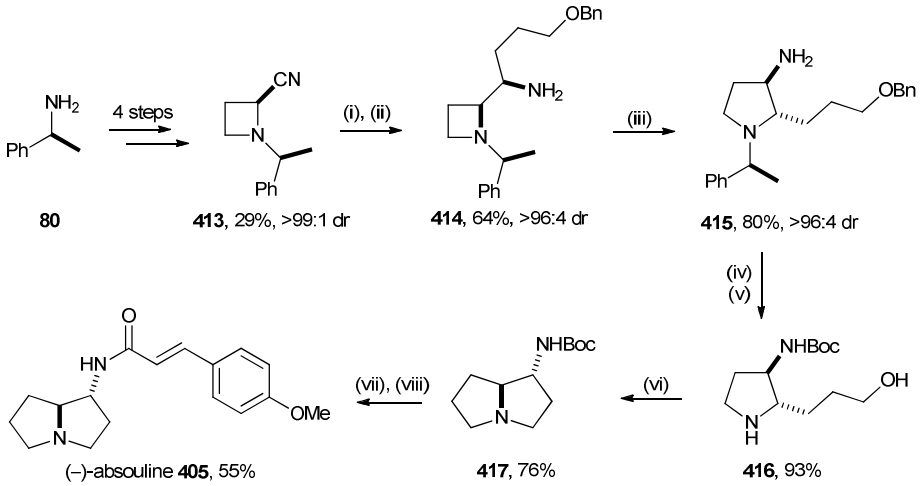
absouline were separated by resolution on a preparative chiral column. Then, Muñiz *et al.* reported another racemic synthesis of absouline **405**, which used a new diamination protocol to prepare a 2,3-diamino acid derivative, which was further converted to absouline through 1-aminopyrrolizidine **402**·HCl.[37] Recently, Huang and co-workers described the asymmetric synthesis of (+)-absouline **405** from 3-amino-2-pyrrolidinone **406**. Chemoselective reduction of **406** and subsequent treatment with thiophenol gave phenyl sulphide **408** as a single diastereoisomer (of unknown stereochemistry), which was converted to **409** by treatment with BuLi, lithium naphthalenide and allyl iodide. A sequence of hydroboration, mesylation and cyclisation reactions afforded the protected 1-aminopyrrolizidine **412**. Hydrogenolytic *N*-deprotection gave 1-aminopyrrolizidine hydrochloride salt **402**·HCl, which was coupled with (*E*)-*p*-methoxycinnamic acid using DCC as a coupling agent to afford (+)-absouline **405** in 4% yield over 8 steps (Scheme 93).[38]



Scheme 93. *Reagents and conditions:* (i) $NaBH_4$, MeOH; (ii) PhSH, TsOH, PPTS, CH_2Cl_2; (iii) BuLi, lithium naphthalenide, allyl iodide, THF, −78 °C; (iv) $BH_3{\cdot}SMe_2$, hexane, EtOH, NaOH, H_2O_2; (v) MsCl, Et_3N, CH_2Cl_2; (vi) 3.0 M HCl, dioxane, rt, 12 h; (vii) H_2, Pd/C, then 6.0 M HCl; (viii) (*E*)-*p*-methoxycinnamic acid, DCC, DMAP, 0 °C to rt.

The asymmetric synthesis of (−)-absouline **405** was reported by Couty and co-workers.[39] This synthesis started with cyanoazetidine **413**, which was prepared from (*S*)-α-methylbenzylamine **80** in 29% yield over 4 steps.[40] Addition of 3-benzyloxypropyllithium to **413** provided diamine **414**, which underwent rearrangement in the presence of boron trifluoride to give 3-aminopyrrolidine **415**. Then, protection of the exocyclic amine in **415** and removal of both *N*- and *O*-benzyl protecting groups by hydrogenolysis afforded the cyclisation precursor **416**. Appel's hydroxyl activation protocol effected formation of the 1-aminopyrrolizidine core **417**. Finally, *N*-Boc deprotection and subsequent DCC/DMAP-

mediated coupling with (*E*)-*p*-methoxycinnamic acid gave (–)-absouline **405** in 6% yield over 12 steps (Scheme 94).



Scheme 94. *Reagents and conditions:* (i) $Li(CH_2)_3OBn$, Et_2O/toluene, rt; (ii) $NaBH_4$, MeOH, rt; (iii) $BF_3{\cdot}OEt_2$, CH_3CN, reflux; (iv) Boc_2O, AcOEt, rt; (v) H_2, Pd/C, MeOH; (vi) PPh_3, CCl_4, Et_3N, DMF, rt; (vii) CF_3CO_2H, CH_2Cl_2, 0 °C; (viii) (*E*)-*para*-methoxycinnamic acid, DCC, DMAP, CH_2Cl_2, 0 °C.

4.9.2. Synthesis of 1-aminopyrrolizidin-3-ones

It was envisaged that the β,γ-diamino esters **418** (derived from MKR of γ-amino-α,β-unsaturated ester (±)-**331**) could be elaborated to the corresponding 1-aminopyrrolizidin-3-ones **420** via sequential *N*-deprotection and cyclisation. The resultant 1-aminopyrrolizidin-3-one **420** may be further converted to the natural product absouline **405** via reduction of the amide functionality and coupling with the requisite acylating agent (Fig. 48).

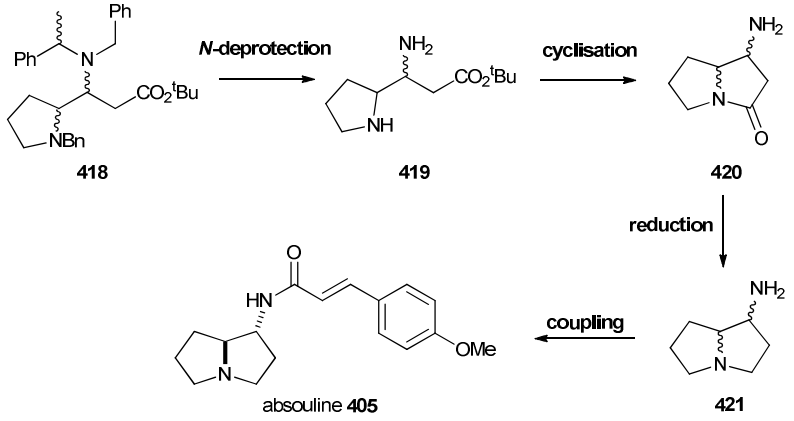
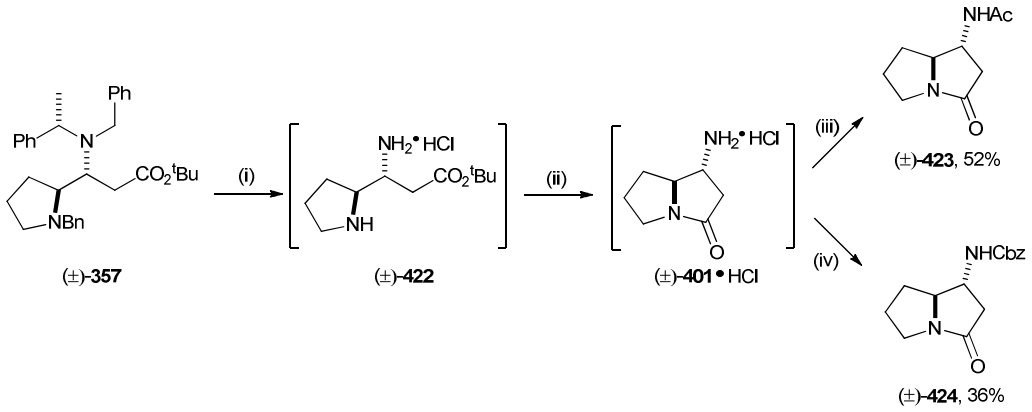


Fig. 48. Proposed elaboration of β,γ-diamino esters **418** to 1-aminopyrrolizidin-3-ones **420** and absouline **405**.

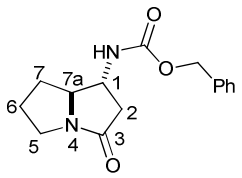
Under the optimised conditions employed for 4-aminopyrrolidin-2-one formation (*vide supra*), hydrogenolytic *N*-debenzylation of the major diastereoisomeric product (±)-**357**

(arising from MKR of γ-amino-α,β-unsaturated ester (±)-**331**) and concomitant cyclisation under strongly acidic conditions afforded the corresponding 1-aminopyrrolizidin-3-one (±)-**401**·HCl. Further acetylation of 1-aminopyrrolizidin-3-one (±)-**401**·HCl afforded its acetate derivative (±)-**423** in 52% overall yield. [41] In this case, the corresponding 1-aminopyrrolizidin-3-one carbamate derivative (±)-**424** was also prepared via treatment of 1-aminopyrrolizidin-3-one (±)-**401**·HCl with Cbz-Cl to give (±)-**424** in 36% overall yield (Scheme 95).



Scheme 95. *Reagents and conditions:* (i) H_2 (5 atm), $Pd(OH)_2/C$, 1.25 M HCl/MeOH, 48 h; (ii) 3.0 M aq HCl, 90 °C, 18 h; (iii) Ac_2O, pyridine, rt, 18 h, then MeOH, 0 °C to rt, 30 min; (iv) Cbz-Cl, K_2CO_3, THF, rt, 16 h.

The ^1H and ^{13}C NMR spectra of the 1-aminopyrrolizidin-3-one carbamate derivative (±)-**424** prepared in this manner were in agreement with those reported for the 1,7a-*anti*-diastereoisomer in the literature, with the exception of the signal for *C*(2). The reason for this discrepancy is unclear (Fig. 49).[42]



424

^{1}H NMR data for compound 424			
Petrini[59] (200 MHz)		**Davies (400 MHz)**	
Attribution	Chem. Shift	Chem. Shift	
C(1)H	3.95-4.15 (m)	3.95-4.15 (m)	
$C(2)H_A$	2.63 (dd, *J* 14.1, 10.6)	2.62 (dd, *J* 15.9, 10.6)	
$C(2)H_B$	2.78 (dd, *J* 14.1, 8.4)	2.78 (dd, *J* 15.9, 8.3)	
$C(5)H_A$	2.98-3.15 (m)	2.98-3.08 (m)	
$C(5)H_B$	3.45-3.77 (m)	3.46-3.61 (m)	
$C(6)H_2$	1.80-2.20 (m)	1.90-2.24 (m)	
$C(7)H_A$	1.80-2.20 (m)	1.52-1.68 (m)	
$C(7)H_B$	1.80-2.20 (m)	1.90-2.24 (m)	
C(7a)H	3.45-3.77 (m)	3.61-3.75 (m)	
OCH_2	5.08 (s)	5.10 (AB system, J_{AB} 12.0)	
Ph	7.29-7.37 (m)	7.29-7.37 (m)	

^{13}C NMR data for compound 424			
Petrini[59] (75 MHz)		**Davies (100 MHz)**	
Attribution	Chem. Shift	Chem. Shift	Δδ(P–D)
C1	53.5	53.3	+0.2
C2	62.2	41.6	+20.6
C3	171.9	171.6	+0.3
C5	41.7	41.5	+0.2
C6	26.8	26.6	+0.2
C7	30.9	30.7	+0.2
C7a	68.5	68.3	+0.2
CO	156.1	155.8	+0.3
OCH_2	67.2	67.0	+0.2
Ph	128.4	128.2	+0.2
Ph	128.5	128.3	+0.2
Ph	128.8	128.6	+0.2
i-Ph	136.4	136.1	+0.3

Fig. 49. ^{1}H and ^{13}C spectral data of the pyrrolizidinone carbamate derivative **424** compared to reported data in literature. [Chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. P = "Petrini's synthesis"; D = "Davies's synthesis"]

In light of this discrepancy, ^{1}H NMR NOE experiments were undertaken to further confirm the configurations within (±)-**423** and (±)-**424**. Irradiation of C(1)*H* showed an enhancement to the signal corresponding to C(7)H_B. Critically, no enhancement was observed to the signal corresponding to C(7a)*H*. Reciprocal irradiation of C(7)H_B showed an enhancement to

signals corresponding to C(1)*H* and C(5)H_B. Irradiation of C(7a)*H* showed an enhancement to the signal corresponding to C(7)H_A, and irradiation of C(7)H_A showed a reciprocal enhancement to C(7a)*H*. This analysis allows the relative 1,7a-*anti* configurations within the 1-aminopyrrolizidin-3-one carbamate derivative (±)-**424**, 1-aminopyrrolizidin-3-one acetate derivative (±)-**423** and 1-aminopyrrolizidin-3-one (±)-**401** to be confidently assigned. Hence, the relative 3,4-*anti*-configuration within the major diastereoisomeric product (±)-**357** was assigned. Based on this study, the assignment of the relative 3,4-*syn*-configuration within the minor diastereoisomeric product (±)-**356** was achieved (Fig. 50).

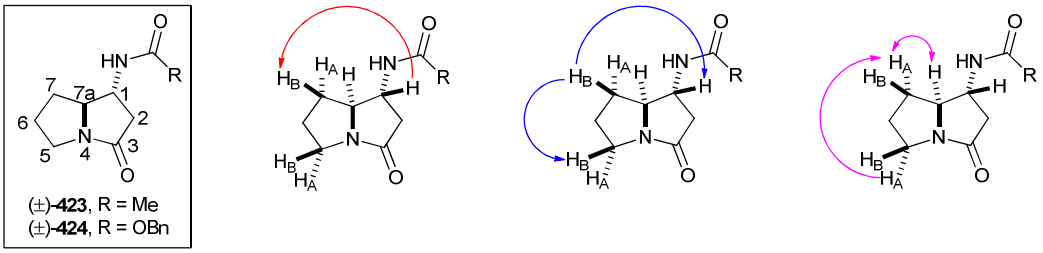
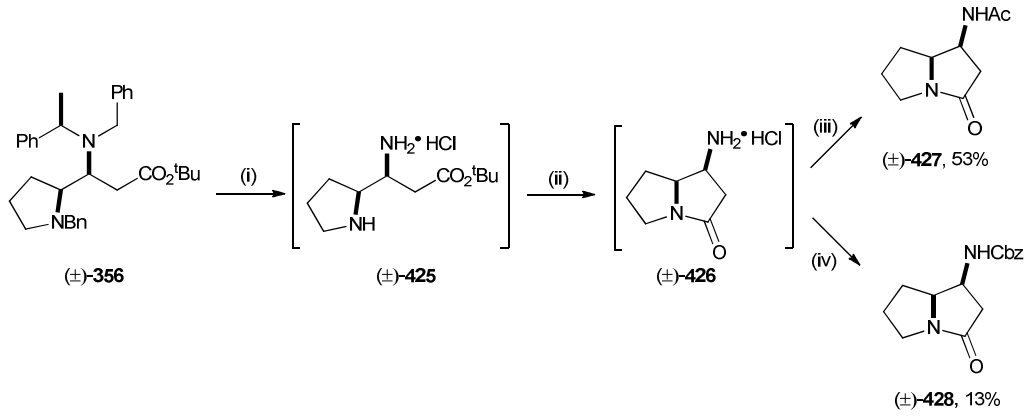


Fig. 50. Representations of the ^{1}H NMR NOE enhancements observed within pyrrolizidinone derivatives (±)-**423** and (±)-**424**. ["↔" represents reciprocal irradiation]

An analogous sequence of transformations was next applied to the minor diastereoisomeric product (±)-**356** [derived from MKR of γ-amino-α,β-unsaturated ester (±)-**331**]. In this case, 1,7a-*syn*-pyrrolizidinone hydrochloride salt (±)-**426** has been reported in the literature.[32] However, the ^{1}H and ^{13}C NMR spectra of neither the 1-aminopyrrolizidin-3-one hydrochloride salt (±)-**426** nor (±)-**401**·HCl prepared in this manner matched those for the 1,7a-*syn*-pyrrolizidinone hydrochloride salt (±)-**426** reported in the literature. Therefore, 1-aminopyrrolizidin-3-one hydrochloride salt (±)-**426** was converted into 1-aminopyrrolizidin-3-one acetate derivative (±)-**427** in 53% overall yield[43] and 1-aminopyrrolizidin-3-one carbamate derivative (±)-**428** in 13% yield, over three steps, respectively. The ^{1}H and ^{13}C NMR spectra of both samples of acetate derivative (±)-**427** and carbamate derivative (±)-**428** prepared in this manner showed distinctive differences to the ^{1}H and ^{13}C NMR spectra of (±)-**423** and (±)-**424**, arising from the major diastereoisomeric product (±)-**357**. Thus, the assignment of the relative 3,4-*syn*-configuration within the minor diastereoisomeric product (±)-**356** was confirmed (Scheme 96).



Scheme 96. *Reagents and conditions:* (i) H_2 (5 atm), $Pd(OH)_2/C$, 1.25 M HCl/MeOH, 48 h; (ii) 3.0 M aq HCl, 90 °C, 18 h; (iii) Ac_2O, pyridine, rt, 18 h, then MeOH, 0 °C to rt, 30 min; (iv) Cbz-Cl, K_2CO_3, THF, rt, 16 h.

^{1}H NMR NOE experiments were undertaken to further confirm the 1,7a-*syn*-configurations within (±)-**427** and (±)-**428**. Irradiation of N*H* showed an enhancement to signals corresponding to C(2)H_A and C(7)H_A. No enhancement was observed to the signal corresponding to C(7a)*H*. Crucially, irradiation of C(1)*H* showed an enhancement to the signals corresponding to C(2)H_B and C(7a)*H*. Moreover, irradiation of C(7a)*H* showed an enhancement to the signals corresponding to C(1)*H* and C(7)H_B (Fig. 51).

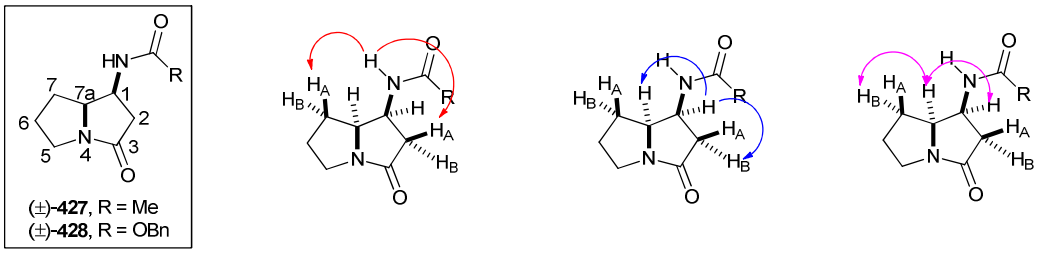
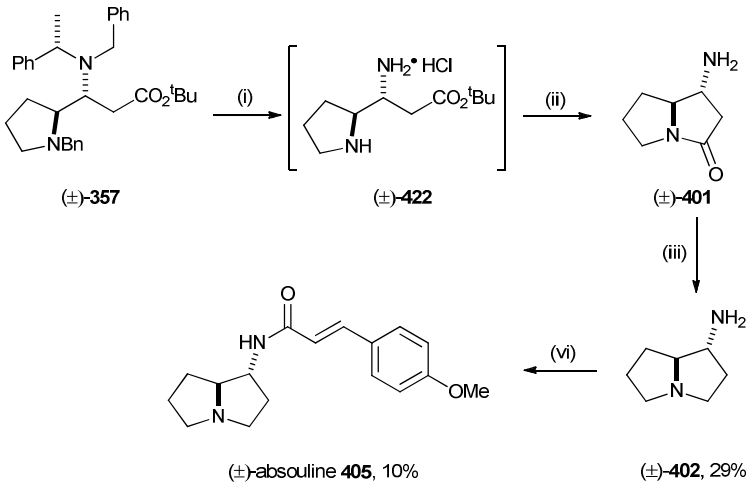


Fig. 51. Representations of the ^{1}H NMR NOE enhancements observed within pyrrolizidinone derivatives (±)-**427** and (±)-**428**. ["↔" represents reciprocal irradiation]

4.9.3. Synthesis of absouline 405

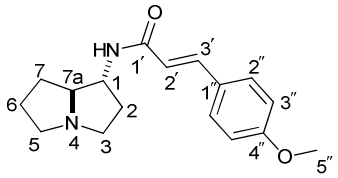
With 1,7a-*anti*-pyrrolizidinone (±)-**401** in hand, it was anticipated that absouline could be accessed in two more steps. Since the $LiAlH_4$ reduction of pyrrolidinones to pyrrolidines has been documented in the literature, [44] the same conditions were applied to 1-aminopyrrolizidin-3-one (±)-**401**. However, treatment of 1-aminopyrrolizidin-3-one (±)-**401** with $LiAlH_4$ in refluxing THF did not provide the reduced product, but a complex mixture from which no products could be identified. This elaboration was instead accomplished by employing the mild reduction conditions developed by Collas *et al.* [45] Thus, 1-aminopyrrolizidin-3-one (±)-**401** was converted into the corresponding 1-aminopyrrolizidine

(±)-**402** by treatment of (±)-**401** with borane-dimethyl sulphide complex in THF at rt, albeit in only modest 29% isolated yield. Finally, DCC/DMAP-mediated coupling of the amine with (*E*)-*p*-methoxycinnamic acid gave (±)-absouline **405** in 10% (unoptimised) yield. Overall (±)-absouline **405** was synthesised in 8 steps and 0.5% overall yield from commercially available proline **176** (Scheme 97).



Scheme 97. *Reagents and conditions:* (i) H_2 (5 atm), $Pd(OH)_2/C$, 1.25 M HCl/MeOH, 48 h; (ii) 3.0 M aq HCl, 90 °C, 18 h, then Dowex 50WX4-200; (iii) $BH_3{\cdot}SMe_2$, THF, rt, 18 h; (iv) (*E*)-*p*-methoxycinnamic acid, DCC, DMAP, CH_2Cl_2, 0 °C, 1 h.

The spectroscopic data of the synthetic sample of (±)-absouline **405** were in agreement with those reported for the sample isolated from the natural source by Poupat *et al.*,[35] and other synthetic samples (Fig. 52).[36,38,39] Moreover, the successful synthesis of absouline **405** provides further corroboration for the stereochemical outcome of the mutual kinetic resolution of γ-amino-α,β-unsaturated ester (±)-**331** with lithium amide (*RS*)-**13**, and hence the relative stereochemistry within **401**, **402** and **423**-**428**.



(±)-absouline **405**

^{1}H NMR data for Absouline 405							
Poupat[52] (400 MHz)		**Poupat[53] (300 MHz)**		**Couty[57] (300 MHz)**		**Davies (500 MHz)**	
Attribution	Chem. Shift	Chem. Shift		Chem. Shift		Chem. Shift	
C(1)H	4.22 (m)	4.33 (m)		4.25 (app quint J 6.7))		4.35-4.42 (m)	
C(2)H_A	1.75 (m)	1.92 (m)		1.56-1.91 (m)		1.91-2.01 (m)	
C(2)H_B	2.25 (m)	2.28 (m)		2.20-2.31 (m)		2.26-2.34 (m)	
C(3)H_A	2.60 (m)	2.72 (m)		2.59-2.69 (m)		2.71-2.81 (m)	
C(3)H_B	3.20 (m)	3.45 (m)		3.20-3.24 (m)		3.45-3.53 (m)	
C(5)H_A	2.62 (m)	2.72 (m)		2.59-2.69 (m)		2.71-2.81 (m)	
C(5)H_B	2.98 (m)	3.19 (m)		2.98-3.06 (m)		3.22-3.29 (m)	
C(6)H_A	1.73 (m)	1.77 (m)		1.56-1.91 (m)		1.81-1.91 (m)	
C(6)H_B	1.83 (m)	1.92 (m)		1.56-1.91 (m)		1.91-2.01 (m)	
C(7)H_A	1.67 (m)	1.77 (m)		1.56-1.91 (m)		1.70-1.78 (m)	
C(7)H_B	1.98 (m)	2.08 (m)		1.97-2.17 (m)		2.10-2.18 (m)	
C(7a)H	3.24 (m)	3.58 (m)		3.20-3.24 (m)		3.55-3.63 (m)	
C(2′)H	6.23 (d, *J* 16)	6.40 (d, *J* 16)		6.29 (d, *J* 15.6)		6.32 (d, *J* 15.6)	
C(3′)H	7.55 (d, *J* 16)	7.59 (d, *J* 16)		7.57 (d, *J* 15.6)		7.59 (d, *J* 15.6)	
C(2″)H	7.41 (d, *J* 9)	7.45 (d, *J* 9)		7.44 (d, *J* 8.6)		7.47 (d, *J* 8.5)	
C(3″)H	6.86 (d, *J* 9)	6.87 (d, *J* 9)		6.87 (d, *J* 8.7)		6.89 (d, *J* 8.5)	
O*Me*	3.80 (s)	3.80 (s)		3.82 (s)		3.83 (s)	

^{13}C NMR data for Absouline 405							
Poupat[52] (50.3 MHz)		**Poupat[53] (75 MHz)**		**Couty[57] (75 MHz)**		**Davies (125 MHz)**	
Attribution	Chem. Shift	Chem. Shift	Δδ(N–S)	Chem. Shift	Δδ(N–S)	Chem. Shift	Δδ(N–S)
C1	55.3	54.5	+0.8	55.2	+0.1	54.6	+0.7
C2	33.1	31.9	+1.2	33.0	+0.1	32.2	+0.9
C3	55.3	54.9	+0.4	55.37	–0.07	55.2	+0.1
C5	53.4	53.0	+0.4	53.4	0	53.3	+0.1
C6	25.5	25.0	+0.5	25.4	+0.1	25.4	+0.1
C7	30.7	30.1	+0.6	30.7	0	30.2	+0.5
C7a	71.1	70.8	+0.3	71.0	+0.1	71.5	–0.4
C1′	166.3	166.0	+0.3	166.2	+0.1	166.2	+0.1
C2′	118.9	118.1	+0.8	118.2	+0.7	118.1	+0.8
C3′	140.4	140.2	+0.2	140.7	–0.3	140.9	–0.5
C1″	127.9	127.3	+0.6	127.6	+0.3	127.5	+0.4
C2″	129.3	129.0	+0.3	129.4	–0.1	129.4	–0.1
C3″	114.4	113.8	+0.6	114.2	+0.2	114.2	+0.2
C4″	161.0	160.5	+0.5	160.9	+0.1	160.9	+0.1
O*Me*	55.7	55.0	+0.7	55.43	+0.27	55.3	+0.4

Fig. 52. ^{1}H and ^{13}C spectral data of (±)-absouline **405** compared to reported data in literatures. [Chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. N = Isolated natural product (+)-absouline; S = Synthetic absouline]

4.10. Conclusions

In conclusion, conjugate addition of a 50:50 pseudoenantiomeric mixture of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide and lithium (*S*)-*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amide to a range of racemic acyclic γ-amino-α,β-unsaturated esters (derived from the corresponding α-amino acids) effects their efficient parallel kinetic resolution, allowing the preparation of enantiopure β,γ-diamino esters. The β,γ-diamino ester products of these reactions are readily converted into the corresponding substituted 4-aminopyrrolidin-2-ones via *N*-debenzylation and cyclisation. Moreover, the addition product obained from mutual kinetic resolution of proline derived substrate is amenable of further transformations, as demonstrated by the synthesis of 1-aminopyrrolizidine (±)-**402**, leading ultimately to the racemic synthesis of the natural product absouline **405**.

4.11. Future work

Future work will focus on the development of an efficient asymmetric synthesis of the 1-aminopyrrolizidine building block **402**. It is anticipated that doubly diastereoselective conjugate addition of the antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **13** to enantiopure γ-amino-α,β-unsaturated ester **331** (derived from enantiopure proline) could be employed to prepare enantiopure β,γ-diamino ester **357**. Improved stereoselectivity might be derived from the "matched" pair, as double asymmetric induction in this system could give rise to increased levels of diastereoselectivity. The addition product having the relative 3,4-*anti*-configuration would be taken for *N*-deprotection and cyclisation to form 1,7a-*anti*-pyrrolizidinone **401**. Although successful reduction of pyrrolizidinone **401** to 1-aminopyrrolizidine **402** and coupling of the reduction product with acid have been developed, the yields of the two steps for small scaled reactions were low. Thus, improving the yields of reduction and coupling steps would be another area to investigate. In addition, once the synthetic route leading to asymmetric synthesis of 1-aminopyrrolizidine **402** has been established, synthesis of a number of biologically active compounds containing this core structure would be achieved by coupling with the requisite acylating agents (Fig 53).

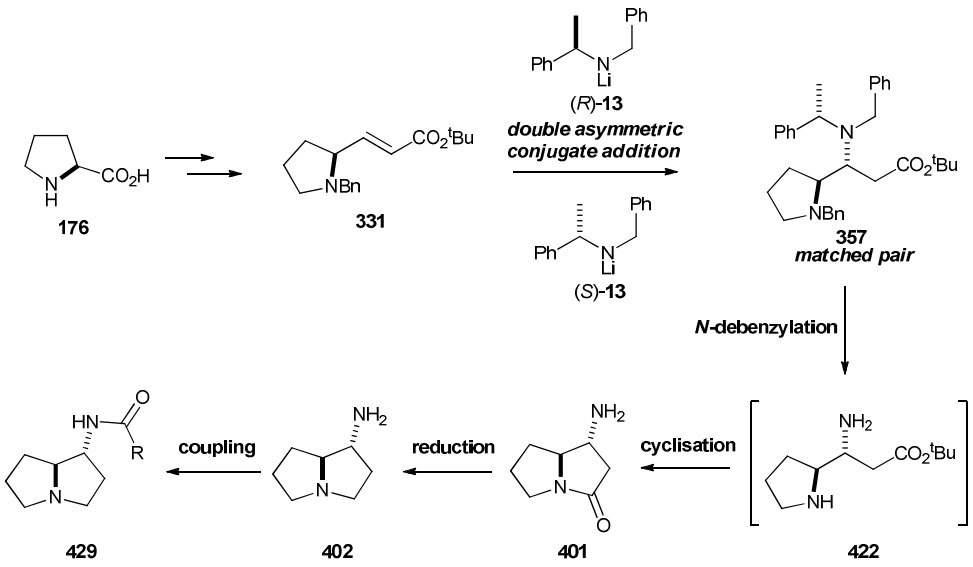


Fig. 53. Future work involving double asymmetric induction.

4.12. References and notes

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[13] Comparison with the substrate control elicited in the MKR of (±)-**283**, (±)-**322**, (±)-**323**, (±)-**324** and (±)-**325** with lithium amide (±)-**13**, as well as in the PKR of (±)-**283**, (±)-**322**, (±)-**323**, (±)-**324** and (±)-**325** with lithium amides (*R*)-**13** and (*S*)-**270**, allows these configurational assignments to be made confidently.

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CHAPTER 5
Experimental

5.1 General Experimental

Reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. BuLi was purchased from Sigma-Aldrich (as a solution in hexanes) and titrated against diphenylacetic acid before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[1] Water was purified by an Elix® UV-10 system. All other reagents were used as supplied without prior purification. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, 1% aq. $KMnO_4$, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica or on a Biotage SP4 automated flash column chromatography platform.

Elemental analyses were recorded by the microanalysis service of the London Metropolitan University, U.K. Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer as either a thin film on NaCl plates, a KBr disc, or on an ATR module. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated. Spectra were recorded at rt. The field was locked by external referencing to the relevant deuteron resonance. Low-resolution mass spectra were recorded on either a VG MassLab 20-250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF internally calibrated with polyalanine, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m × 0.25 mm) using amyl acetate as a lock mass.

5.2 General Experimental Procedures

***General Procedure 1*: Conjugate addition of lithium amide (including MKR and PKR)**

BuLi (1.60 equiv) was added to a solution of the requisite amine(s) (2.00 equiv) in THF at –78 °C. After 30 min, a solution of the requisite substrate (1.00 equiv) in THF at –78 °C was added dropwise *via* cannula. After a further 2 h, satd aq NH_4Cl was added and the reaction mixture was allowed to warm to rt before being concentrated *in vacuo*. The residue was suspended in 10% aq citric acid solution and extracted with three portions of CH_2Cl_2. The combined organic extracts were washed with satd aq $NaHCO_3$ and brine, then dried and concentrated *in vacuo*.

***General Procedure 2:* Deprotection with TFA**

TFA was added to a solution of the requisite substrate in CH_2Cl_2 at 0 °C. The reaction mixture was then allowed to warm to rt over 2 h then concentrated *in vacuo*.[1]

***General Procedure 3*: *N/O*-Acylation of a chiral auxiliary with a carboxylic acid derivative**

A solution of the requisite carboxylic acid (1.00-2.50 equiv) in CH_2Cl_2 at 0 °C was treated with $(COCl)_2$ (1.00-5.00 equiv) and DMF (1 drop). The reaction mixture was allowed to warm to rt over 1 h then concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 and the resultant mixture was added to a solution of the requisite chiral auxiliary (1.00 equiv) in CH_2Cl_2 at 0 °C. The reaction mixture was then allowed to warm to rt and stirred for 18 h. Satd aq $NaHCO_3$ was then added and the resultant mixture was extracted with three portions of CH_2Cl_2. The combined organic extracts were washed with brine, then dried and concentrated *in vacuo*.

***General Procedure 4*: Hydrogenolysis with Pearlman's catalyst**

$Pd(OH)_2/C$ (20% by weight as supplied, load 25-50% by weight of substrate for reaction) was added to a vigorously stirred solution of the requisite substrate in either (i) degassed EtOAc; (ii) degassed MeOH; or (iii) degassed MeOH:AcOH (v/v 40:1); or (iv) degassed HCl/MeOH (1.25 M), at rt. The resultant suspension was stirred under hydrogen at either: (i) 1 atm or (ii) 5 atm, as stated, for 18-72 h. The reaction mixture was filtered through Celite® [eluent either (i) EtOAc or (ii) MeOH] and concentrated *in vacuo*. For reactions which

[1] Tertiary amino acids were subjected to a further work-up with aqueous $NaHCO_3$.

required AcOH, the residue was dissolved in CH_2Cl_2 and the resultant solution was washed with satd aq $NaHCO_3$ and brine, then dried and concentrated *in vacuo.*

***General Procedure 5*: *N*-Benzylation of primary or secondary amines**

K_2CO_3 (10.0 equiv) was added to a stirred solution of the requisite amine (1.0 equiv) in BnBr (10.0 equiv). The resultant mixture was heated at 100 °C for 7 h then allowed to cool to rt and partitioned between satd aq $NaHCO_3$ and CH_2Cl_2. The aqueous layer was extracted with three portions of CH_2Cl_2 and the combined organic extracts were then dried and concentrated *in vacuo*.

***General Procedure 6*: Reductive amination with $NaBH_3CN$**

Acetone (2.0 equiv) and $NaBH_3CN$ (4.0 equiv) were added sequentially to a solution of the requisite primary amine (1.0 equiv) in MeOH at rt. The resultant mixture was stirred at rt for 18 h then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with three portions of CH_2Cl_2. The combined organic extracts were then dried and concentrated *in vacuo*.

***General Procedure 7*: *N*-Acylation of a SuperQuat auxiliary with a carboxylic acid derivative**

A solution of the requisite carboxylic acid (1.50 equiv) in CH_2Cl_2 at 0 °C was treated with $(COCl)_2$ or $(COBr)_2$ (3.50 equiv) and DMF (1 drop). The reaction mixture was allowed to warm to rt over 1 h then concentrated in vacuo.

BuLi (1.10 equiv) was added to a solution of the requisite auxiliary (1.00 equiv) in THF at –78 °C. After 10 min, a solution of the carboxylic acid derivative (1.50 equiv) in THF was added dropwise *via* cannula. After a further 2 h, satd aq NH_4Cl was added and the resultant mixture was extracted with three portions of EtOAc. The combined organic extracts were washed with brine, then dried and concentrated *in vacuo*.

***General Procedure 8*: *N*-Alkylation of 4-(benzylamino)butan-2-one**

4-(Benzylamino)butan-2-one (1.50 equiv), DIPEA (2.50 equiv) and NaI (0.40 equiv) were added sequentially to a solution of the requisite substrate (1.00 equiv) in acetone at 0 °C. The resultant mixture was stirred at rt for 3 h then concentrated *in vacuo*. The residue was partitioned between EtOAc and H_2O and the aqueous layer was extracted with three portions of EtOAc. The combined organic extracts were then dried and concentrated *in vacuo*.

***General Procedure 9*: Intramolecular organocatalytic Michael additions**

The catalyst (100 mol%) was added to a solution of the requisite substrate (1.00 equiv) in THF. After the designated reaction time the reaction mixture was concentrated *in vacuo*.

***General Procedure 10*: Auxiliary cleavage by LiOEt**

LiOEt (2.50 equiv) was added to a solution of the requisite adduct (1.00 equiv) in EtOH at 0 °C. The reaction mixture was allowed to warm to rt over 1 h. 10% aq citric acid was added and the resultant mixture was extracted with three portions of CH_2Cl_2. The combined organic extracts were washed with satd aq $NaHCO_3$ and brine, then dried and concentrated *in vacuo*.

***General Procedure 11*: Perbenzylation and subsequent reduction of α-amino acids[2]**

A solution of the requisite amino acid (1.00 equiv) in DMF/H_2O was treated with K_2CO_3 (3.00 equiv) and allyl bromide/BnBr (3.00 equiv). The reaction mixture was heated at reflux for 3 h then allowed to cool to rt and extracted with three portions of Et_2O. The combined organic extracts were washed with brine, then dried and concentrated *in vacuo*. The residue was dissolved in THF and added to a suspension of $LiAlH_4$ (2.00 equiv) in THF at 0 °C. The reaction mixture was heated at reflux for 1 h then allowed to cool to 0 °C and cautiously treated with 2.0 M aq NaOH. The resultant suspension was filtered through Celite® (eluent Et_2O) and concentrated *in vacuo*. The residual BnOH was removed by distillation (bp 68-70 °C/2 mmHg).

***General Procedure 12*: One-pot Swern/Wittig reaction[3]**

A solution of $(COCl)_2$ (1.20 equiv) in CH_2Cl_2 at −78 °C was treated with DMSO (1.30 equiv) in CH_2Cl_2. After stirring for 10 min, a solution of the requisite alcohol (1.00 equiv) in CH_2Cl_2 was added. The reaction mixture was stirred for 1 h before the addition of Et_3N (2.00 equiv) and subsequent warming to rt. $Ph_3P{=}CHCO_2{}^tBu$ (1.00 equiv) was added and the mixture was stirred for 18 h. Satd aq Na_2CO_3 was then added and the resultant mixture was extracted with three portions of CH_2Cl_2. The combined organic extracts were washed with brine, then dried and concentrated *in vacuo*.

***General Procedure 13*: Transesterification**

A solution of the requisite *tert*-butyl ester in HCl/MeOH (1.25 M) was heated at reflux for 18 h then allowed to cool to rt and concentrated *in vacuo*.

***General Procedure 14*: Cyclisation of methyl esters**

A solution of the requisite methyl ester (1.00 equiv) in toluene was treated with K_2CO_3 (4.00 equiv). The reaction mixture was heated at reflux for 18 h then allowed to cool to rt. The resultant suspension was filtered [eluent toluene:MeOH (v:v 3:1)] and concentrated *in vacuo*.

***General Procedure 15*: Cyclisation of *tert*-butyl esters[4]**

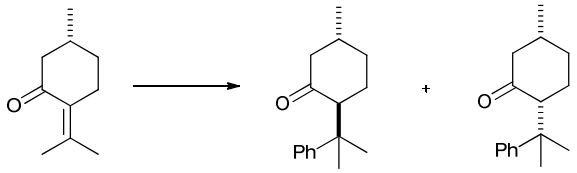
A solution of the requisite *tert*-butyl ester was dissolved in 3.0 M aq HCl and heated at 90 °C for 18 h, then allowed to cool to rt and concentrated *in vacuo*.

***General Procedure 16*: Acytylation[5]**

The requisite substrate (1.00 equiv) was dissolved in pyridine (28.0 equiv) and acetic anhydride (3.00-5.00 equiv) at rt for 18 h. The reaction mixture was cooled to 0 °C and MeOH was added. After stirring for 30 min, the reaction mixture was concentrated *in vacuo*.

5.3 Experimental for Chapter 2

(2*S*,5*R*)-2-(2'-Phenylpropan-2'-yl)-5-methylcyclohexanone 91 and (*R*,*R*)-2-(2'-phenylpropan-2'-yl)-5-methylcyclohexanone 92[6]



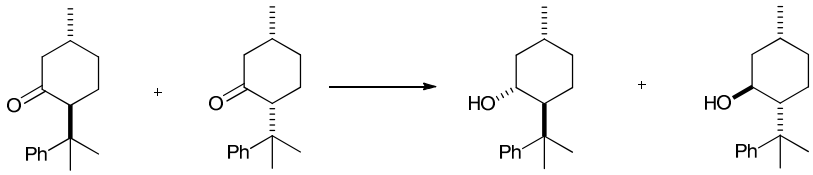
90 **91** **92**

Step 1: PhMgBr (3.0 M in Et_2O, 26.4 mL, 78.8 mmol) was added dropwise to a stirred solution of copper(I) bromide (1.12 g, 7.82 mmol) in Et_2O (20 mL) at –20 °C. After 30 min, a solution of (*R*)-(+)-pulegone **90** (10.0 g, 65.7 mmol) in Et_2O (13 mL) was added over a period of 15 min and the resultant mixture was stirred at –20 °C for 16 h. The reaction mixture was then added to 2.0 M aq HCl (80 mL) at 0 °C, and the aqueous layer was saturated with NH_4Cl and extracted with Et_2O (3 × 80 mL). The combined organic extracts were washed with satd aq $NaHCO_3$ (80 mL) and brine (80 mL), then dried and concentrated *in vacuo* to give a 60:40 mixture of **91** and **92** as a yellow oil (14.0 g, 93%).

Step 2: KOH (17.5 g, 300 mmol) was added to a stirred solution of **91** and **92** (14.0 g, 60.8 mmol) in EtOH (150 mL) and H_2O (20 mL). The resultant mixture was heated at reflux for 3 h and concentrated *in vacuo* to a volume of 50 mL. H_2O (125 mL) was then added, and the resultant mixture was saturated with NaCl and extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with brine (80 mL), then dried and concentrated *in*

vacuo to give an 85:15 mixture of **91** and **92** as a pale yellow oil (13.0 g, 93%). Data for **91**: δ_H (400 MHz, $CDCl_3$) 0.80-2.71 (8H, m, C(2)*H*, C(3)H_2, C(4)H_2, C(5)*H*, C(6)H_2), 0.98 (3H, d, *J* 6.1, C(5)*Me*), 1.41 (3H, s, C(1')H_3), 1.47 (3H, s, C(3')H_3), 7.15-7.63 (5H, m, *Ph*). Data for **92**: δ_H (400 MHz, $CDCl_3$) 0.80-2.71 (8H, m, C(2)*H*, C(3)H_2, C(4)H_2, C(5)*H*, C(6)H_2), 0.91 (3H, d, *J* 6.1, C(5)*Me*), 1.43 (3H, s, C(1')H_3), 1.47 (3H, s, C(3')H_3), 7.15-7.63 (5H, m, *Ph*).

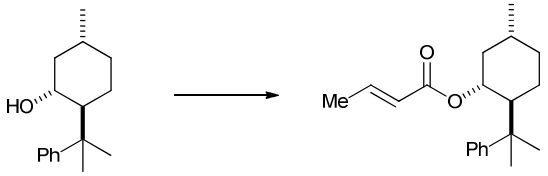
(1*R*,2*S*,5*R*)-2-(2'-Phenylpropan-2'-yl)-5-methylcyclohexanol 59 and (1*S*,2*R*,5*R*)-2-(2'-phenylpropan-2'-yl)-5-methylcyclohexanol 93



91 **92** **59** **93**

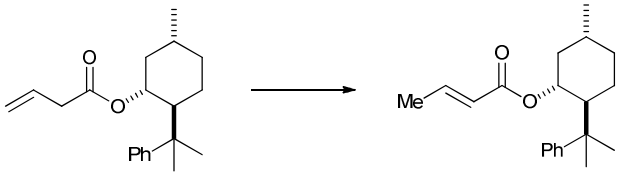
A mixture of Na (3.82 g, 164 mmol) in dry toluene (54 mL) was heated to reflux. A solution of **91** and **92** (13.0 g, 56.4 mmol) in freshly distilled ^{i}PrOH (12.6 mL) was then added dropwise at a rate as to keep the reaction at a gentle reflux. Once the addition was complete, the mixture was heated at reflux for 8 h and then cooled to 0 ºC. The mixture was diluted with Et_2O (60 mL) and poured into water (70 mL) at 0 ºC. The aqueous layer was saturated with NaCl and extracted with with Et_2O (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave **59** as a colourless oil (5.50 g, 42%, >99:1 dr); $[\alpha]_D^{22}$ −26.5 (*c* 1.0 in EtOH); {lit.[7] for enantiomer $[\alpha]_D^{20}$ +26.3 (*c* 2.02 in EtOH)}; δ_H (400 MHz, $CDCl_3$) 0.87 (3H, d, *J* 6.5, C(5)*Me*), 0.85-1.20 (3H, m, CH_2, C*H*), 1.29 (3H, s, C(1')H_3), 1.42 (3H, s, C(3')H_3), 1.43-1.78 (4H, m, 2 × CH_2), 1.81-1.89 (1H, m, C*H*), 3.48 (1H, app td, *J* 10.6, 4.4, C(1)*H*), 7.15-7.47 (5H, m, *Ph*). Further elution gave a 75:25 mixture of **59** and **93** as a colourless oil (3.93 g, 30%). Data for **93**: δ_H (400 MHz, $CDCl_3$) 0.93 (3H, d, *J* 6.5, C(5)*Me*), 0.87-1.30 (3H, m, CH_2, C*H*), 1.32 (3H, s, C(1')H_3), 1.44 (3H, s, C(3')H_3), 1.37-1.78 (4H, m, 2 × CH_2), 1.97-2.07 (1H, m, C*H*), 3.78 (1H, app td, *J* 10.6, 4.4, C(1)*H*), 7.16-7.45 (5H, m, *Ph*).

(1'*R*,2'*S*,5'*R*)-2'-(2''-Phenylpropan-2''-yl)-5'-methylcyclohexyl (*E*)-but-2-enoate 79[8]



59 **79**

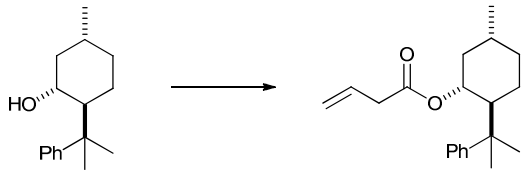
Method A: DMAP (315 mg, 2.58 mmol) was added in one portion to a stirred solution of crotonoyl chloride (247 mg, 2.37 mmol) in THF (16 mL) at 0 °C. An immediate precipitate was observed and the resulting inhomogeneous solution was stirred for 15 min before a solution of **59** (500 mg, 2.15 mmol) in CH_2Cl_2 (4 mL) was added. The resultant solution was allowed to warm to rt and stirred for 16 h. The reaction mixture was then partitioned between satd aq $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were washed with brine (10 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 1%→20% Et_2O in 30-40 °C petrol) gave **79** as a colourless oil (194 mg, 30%); $[\alpha]_D^{25}$ –10.0 (*c* 1.1 in hexane); {lit.[9] $[\alpha]_D^{25}$ –9.83 (*c* 13.1 in hexane)}; δ_H (400 MHz, $CDCl_3$) 0.91 (3H, d, *J* 6.5, C(5')*Me*), 0.95-1.27 (3H, m, CH_2, C*H*), 1.26 (3H, s, C(1'')H_3), 1.35 (3H, s, C(3'')H_3), 1.49-2.01 (4H, m, 2 × CH_2), 1.78 (3H, dd, *J* 7.2, 1.7, C(4)H_3), 2.04-2.16 (1H, m, C*H*), 4.88 (1H, app td, *J* 10.6, 4.4, C(1')*H*), 5.38 (1H, dd, *J* 15.7, 1.7, C(2)*H*), 6.50 (1H, dd, *J* 15.7, 7.2, C(3)*H*), 7.14-7.48 (5H, m, *Ph*).



96 **79**

Method B: DBU (5.00 mL, 33.6 mmol) was added to a stirred solution of **96** (3.36 g, 11.2 mmol) in THF (35 mL) at rt and the resultant solution was stirred at rt for 16 h. The reaction mixture was then partitioned between 2.0 M aq HCl (30 mL) and CH_2Cl_2 (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic extracts were washed with brine (30 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 1%→20% Et_2O in 30-40 °C petrol) gave **79** as a colourless oil (2.20 g, 65%); $[\alpha]_D^{25}$ –9.98 (*c* 1.0 in hexane); {lit.[9] $[\alpha]_D^{25}$ –9.83 (*c* 13.1 in hexane)}.

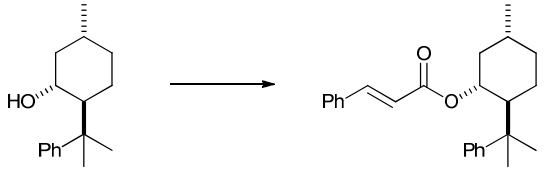
(1'*R*,2'*S*,5'*R*)-2'-(2''-Phenylpropan-2''-yl)-5'-methylcyclohexyl but-3-enoate 96



59 **96**

Crotonoyl chloride (2.40 mL, 25.0 mmol) and $^{i}Pr_2NEt$ (4.20 mL, 25.0 mmol) was added to a stirred solution of **59** (2.90 g, 12.5 mmol) in THF (30 mL) at 0 °C. The resultant solution was allowed to warm to rt and stirred for 16 h. The reaction mixture was partitioned between satd aq $NaHCO_3$ (30 mL) and CH_2Cl_2 (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with brine (30 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 1%→20% Et_2O in 30-40 °C petrol) gave **96** as a colourless oil (3.38 g, 90%); $[\alpha]_D^{25}$ +10.5 (*c* 1.0 in $CHCl_3$); ν_{max} 2955, 2924 (C–H), 1730 (C=O), 1643 (C=C); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, d, *J* 6.3, C(5')*Me*), 0.90-1.20 (3H, m, CH_2, C*H*), 1.23 (3H, s, C(1'')H_3), 1.33 (3H, s, C(3'')H_3), 1.42-2.10 (5H, m, 2 × CH_2, C*H*), 2.43 (1H, dd, *J* 16.7, 6.8, C(2)H_A), 2.48 (1H, dd, *J* 16.7, 6.8, C(2)H_B), 4.85 (1H, app td, *J* 10.6, 4.4, C(1')*H*), 5.02 (1H, dd, *J* 16.7, 1.3, C(4)H_A), 5.08 (1H, dd, *J* 10.1, 1.3, C(4)H_B), 5.64-5.77 (1H, m, C(3)*H*), 7.10-7.35 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 22.2 (C(5')*Me*), 24.9 (*C*(3'')), 26.9 (*C*H_2), 28.9 (*C*(1'')), 31.7 (*C*H), 35.0 (*C*H_2), 39.4 (*C*(2'')), 40.0 (*C*H_2), 42.1 (*C*(2)), 50.7 (*C*H), 74.6 (*C*(1')), 118.0 (*C*(4)), 125.0 (*C*(3)), 125.4, 127.9, 130.5 (*o*,*m*,*p*-*Ph*), 151.7 (*i*-*Ph*), 170.8 (*C*(1)); *m/z* (ESI$^+$) 323 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{28}NNaO_2^+$ ([M+Na]$^+$) requires 323.1982; found 323.1978.

(1'*R*,2'*S*,5'*R*)-2'-(2''-Phenylpropan-2''-yl)-5'-methylcyclohexyl (*E*)-3-phenylpropenoate 94



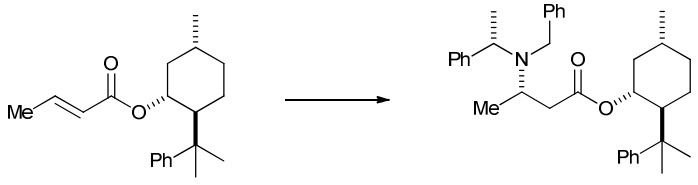
59 **94**

Method A: DMAP (289 mg, 2.37 mmol) was added in one portion to a stirred solution of cinnamoyl chloride (358 mg, 2.15 mmol) in THF (16 mL) at 0 °C. An immediate precipitate was observed and the resultant inhomogeneous solution was stirred for 15 min before a solution of **59** (500 mg, 2.15 mmol) in CH_2Cl_2 (4 mL) was added. The resultant mixture was

allowed to warm to rt and stirred for 16 h. The reaction mixture was then partitioned between satd aq $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were washed with brine (10 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 1%→20% Et_2O in 30-40 °C petrol) gave **94** as a colourless oil (436 mg, 56%); $[\alpha]_D^{25}$ +10.2 (*c* 2.2 in $CHCl_3$); {lit.[10] $[\alpha]_D^{25}$ +9.9 (*c* 2.23 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 0.94 (3H, d, *J* 6.5, C(5')*Me*), 0.96-1.27 (3H, m, CH_2, C*H*), 1.29 (3H, s, C(1")H_3), 1.38 (3H, s, C(3")H_3), 1.52-2.03 (4H, m, 2 × CH_2), 2.13-2.22 (1H, m, C*H*), 4.96 (1H, app td, *J* 10.6, 4.4, C(1')*H*), 5.81 (1H, d, *J* 16.0, C(2)*H*), 7.11-7.48 (11H, m, C(3)*H*, *Ph*).

Method B: Cinnamoyl chloride (358 mg, 2.15 mmol) and $^iPr_2NEt$ (289 mg, 2.37 mmol) was added to a stirred solution of **59** (500 mg, 2.15 mmol) in THF (16 mL) at 0 °C. The resultant solution was allowed to warm to rt and stirred for 16 h. The reaction mixture was partitioned between satd aq $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 1%→20% Et_2O in 30-40 °C petrol) gave **94** as a colourless oil (436 mg, 56%); $[\alpha]_D^{25}$ +10.0 (*c* 1.0 in $CHCl_3$); {lit.[10] $[\alpha]_D^{25}$ +9.9 (*c* 2.23 in $CHCl_3$)}.

(1'*R*,2'*S*,5'*R*)-2'-(2''-Phenylpropan-2''-yl)-5'-methylcyclohexyl (*S*,*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]butanoate 98

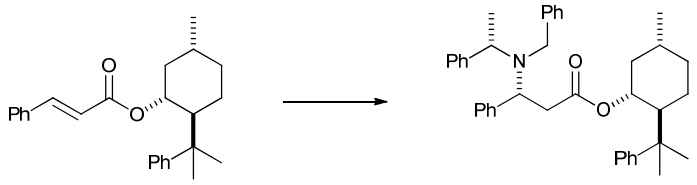


79 **98**

Following *General Procedure 1*, a solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (0.20 mL, 0.96 mmol) in THF (2 mL) at –78 °C was treated with BuLi (1.6 M in hexanes, 0.48 mL, 0.77 mmol) and **79** (143 mg, 0.48 mmol) in THF (2 mL) to give **98** in 98:2 dr. Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave **98** as a colorless oil that crystallised upon standing (175 mg, 71%, >99:1 dr); $C_{35}H_{45}NO_2$ requires C, 82.2; H, 8.9; N, 2.7%; found C, 82.3; H, 8.9; N, 2.7%; mp 72-74 °C; $[\alpha]_D^{20}$ +6.4 (*c* 0.5 in $CHCl_3$); ν_{max} 2959, 2924 (C–H), 1723 (C=O); δ_H (500 MHz, $CDCl_3$) 0.79-1.12 (3H, m, CH_2, C*H*), 0.88 (3H, d, *J* 6.3, C(5')*Me*), 1.07 (3H, d, *J* 6.6, C(4)H_3), 1.19

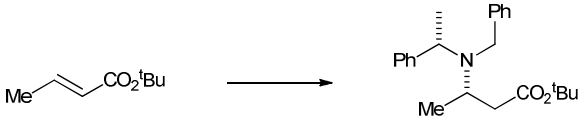
(3H, s, C(1'')H_3), 1.25 (3H, s, C(3'')H_3), 1.31 (3H, d, *J* 6.9, C(α)*Me*), 1.38-1.67 (4H, m, 2 × CH_2), 1.76-1.82 (1H, m, C(2)H_A), 1.87 (1H, dd, *J* 14.5, 4.1, C(2)H_B), 1.91-1.98 (1H, m, C*H*), 3.22-3.31 (1H, m, C(3)*H*), 3.61 (2H, AB system, J_{AB} 14.8, NCH_2Ph), 3.78 (1H, q, *J* 6.9, C(α)*H*), 4.72 (1H, app td, *J* 10.6, 4.3, C(1')*H*), 7.10-7.40 (15H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 18.5 (*C*(4)), 19.1 (C(α)*Me*), 21.8 (C(5')*Me*), 25.5 (*C*(3'')), 26.6 (*C*(1'')), 27.5 (*C*H_2), 31.2 (*C*H), 34.5 (*C*H_2), 39.0 (*C*(2)), 39.7 (*C*(2'')), 41.5 (*C*H_2), 49.7 (*C*H), 49.9 (N*C*H_2Ph), 50.3 (*C*(3)), 58.4 (*C*(α)), 73.9 (*C*(1')), 125.0, 125.5, 126.4, 126.7, 127.6, 128.0, 128.2 (*o*,*m*,*p*-*Ph*), 142.1, 144.5, 151.6 (*i*-*Ph*), 171.8 (*C*(1)); *m/z* (ESI^+) 512 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{35}H_{46}NO_2^+$ ($[M+H]^+$) requires 512.3523; found 512.3520.

(1'*R*,2'*S*,5'*R*)-2'-(2''-Phenylpropan-2''-yl)-5'-methylcyclohexyl (3*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 99



Following *General Procedure 1*, a solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (0.10 mL, 0.50 mmol) in THF (1 mL) at –78 °C was treated with BuLi (1.6 M in hexanes, 0.25 mL, 0.40 mmol) and **94** (90 mg, 0.25 mmol) in THF (1 mL) to give **99** in 95:5 dr. Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave **99** as a colourless oil (89 mg, 62%, >99:1 dr); $[\alpha]_D^{20}$ –10.3 (*c* 1.0 in $CHCl_3$); ν_{max} 2963, 2924 (C–H), 1725 (C=O); δ_H (500 MHz, $CDCl_3$) 0.57-1.03 (3H, m, CH_2, C*H*), 0.79 (3H, d, *J* 6.3, C(5')*Me*), 1.13 (3H, s, C(1'')H_3), 1.19 (3H, s, C(3'')H_3), 1.21 (3H, d, *J* 6.9, C(α)*Me*), 1.25-1.61 (4H, m, 2 × CH_2), 1.84-1.92 (1H, m, C*H*), 2.26 (1H, dd, *J* 15.3, 5.4, C(2)H_A), 2.11 (1H, dd, *J* 15.3, 9.8, C(2)H_B), 3.64 (2H, app s, NCH_2Ph), 3.94 (1H, q, *J* 6.9, C(α)*H*), 4.25 (1H, dd, *J* 9.8, 5.4, C(3)*H*), 4.62 (1H, app td, *J* 10.6, 4.3, C(1')*H*), 7.13-7.45 (20H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 16.1 (C(α)*Me*), 21.7 (C(5')*Me*), 26.1 (*C*(3'')), 26.7 (*C*(1'')), 26.8 (*C*H_2), 31.1 (*C*H), 34.5 (*C*H_2), 37.7 (*C*(2)), 39.7 (*C*(2'')), 41.2 (*C*H_2), 50.2 (N*C*H_2Ph), 50.6 (*C*H), 56.9 (*C*(α)), 59.3 (*C*(3)), 74.4 (*C*(1')), 125.1, 125.5, 126.4, 126.7, 127.1, 127.9, 128.0, 128.3 (*o*,*m*,*p*-*Ph*), 141.5, 141.7, 144.4, 151.4 (*i*-*Ph*), 170.9 (*C*(1)); *m/z* (ESI^+) 574 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{40}H_{48}NO_2^+$ ($[M+H]^+$) requires 574.3680; found 574.3680.

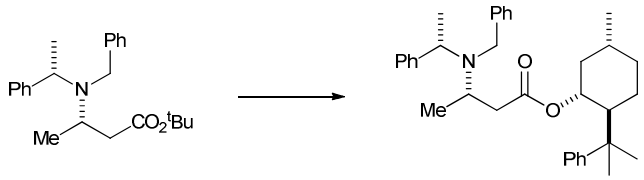
***tert*-Butyl (*S*,*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]butanoate 102**[11]



100 (*S*,*S*)-**102**

Following *General Procedure 1*, a solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (2.38 g, 11.3 mmol) in THF (20 mL) at –78 °C was treated with BuLi (2.5 M, 5.10 mL, 10.9 mmol) and **100** (1.00 g, 7.03 mmol) to give (*S*,*S*)-**102** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 1%→20% Et_2O in 30-40 °C petrol) gave (*S*,*S*)-**102** as a pale yellow oil (2.18 g, 88%, >99:1 dr); $[\alpha]_D^{24}$ +3.62 (*c* 1.0 in $CHCl_3$); {lit.[11] $[\alpha]_D^{24}$ +3.60 (*c* 0.8 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.12 (3H, d, *J* 6.5, C(4)H_3), 1.34 (3H, d, *J* 7.0, C(α)*Me*), 1.39 (9H, s, CMe_3), 2.02 (1H, dd, *J* 14.1, 9.0, C(2)H_A), 2.26 (1H, dd, *J* 14.1, 4.8, C(2)H_B), 3.39-3.48 (1H, m, C(3)*H*), 3.69 (2H, AB system, J_{AB} 15.0, NCH_2Ph), 3.89 (1H, q, *J* 7.0, C(α)*H*), 7.19-7.42 (10H, m, *Ph*).

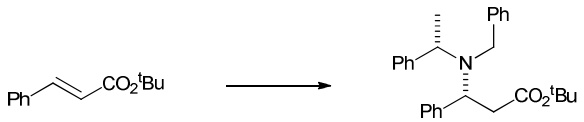
(1'*R*,2'*S*,5'*R*)-2'-(2''-Phenylpropan-2''-yl)-5'-methylcyclohexyl (*S*,*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]butanoate 98



(*S*,*S*)-**102** **98**

Following *General Procedure 2*, a solution of (*S*,*S*)-**102** (1.75 g, 4.95 mmol) in CH_2Cl_2 (17.0 mL) was treated with TFA (17.0 mL) to give a white foam (1.32 g). Then, following *General Procedure 3*, a solution of the residue (131 mg, 0.44 mmol) in CH_2Cl_2 (2 mL) was reacted with $(COCl)_2$ (40 μL, 0.46 mmol) and a solution of **59** (50 mg, 0.22 mmol) in CH_2Cl_2 (1 mL). Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave **98** as a colorless oil that crystallised upon standing (76 mg, 68%, >99:1 dr); mp 72-74 °C; $[\alpha]_D^{21}$ +6.45 (*c* 1.0 in $CHCl_3$).

***tert*-Butyl (3*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 103**[12]

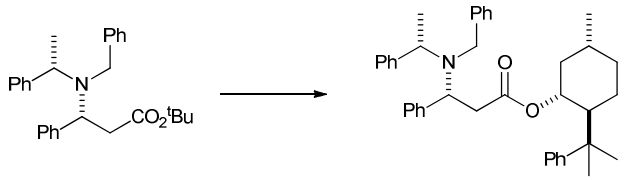


101 (3*R*,α*S*)-**103**

Following *General Procedure 1*, a solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (1.66 g, 7.84 mmol) in THF (20 mL) at –78 °C was treated with BuLi (2.5 M, 3.00 mL, 7.60

mmol) and **101** (1.00 g, 4.90 mmol) to give (3*R*,α*S*)-**103** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 1%→20% Et_2O in 30-40 °C petrol) gave (3*R*,α*S*)-**103** as a pale yellow oil (1.67 g, 84%, >99:1 dr); $[\alpha]_D^{24}$ –4.2 (c 1.0 in $CHCl_3$); {lit.[12] $[\alpha]_D^{23}$ – 4.0 (c 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.22 (9H, s, C*Me*$_3$), 1.26 (3H, d, *J* 6.9, C(α)*Me*), 2.48-2.56 (2H, m, C(2)*H*$_2$), 3.68 (2H, app s, NC*H*$_2$Ph), 4.00 (1H, q, *J* 6.9, C(α)*H*), 4.40 (1H, dd, *J* 9.9, 5.4, C(3)*H*), 7.18-7.43 (15H, m, *Ph*).

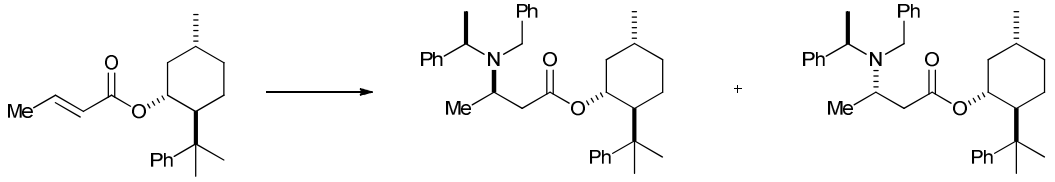
(1'*R*,2'*S*,5'*R*)-2'-(2''-Phenylpropan-2''-yl)-5'-methylcyclohexyl (3*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 99



(3*R*,α*S*)-**103** **99**

Following *General Procedure 2*, a solution of (3*R*,α*S*)-**103** (1.66 g, 3.99 mmol) in CH_2Cl_2 (16.0 mL) was treated with TFA (16.0 mL) to give a white foam (1.32 g). Then, following *General Procedure 3*, a solution of the residue (475 mg, 1.32 mmol) in CH_2Cl_2 (5 mL) was reacted with $(COCl)_2$ (0.11 mL, 1.39 mmol) and a solution of **59** (154 mg, 0.66 mmol) in CH_2Cl_2 (2 mL). Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave **99** as a colorless oil (227 mg, 60%, >99:1 dr); $[\alpha]_D^{22}$ −10.5 (*c* 1.1 in $CHCl_3$).

(1'*R*,2'*S*,5'*R*)-2'-(2''-Phenylpropan-2''-yl)-5'-methylcyclohexyl (*R*,*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]butanoate 104

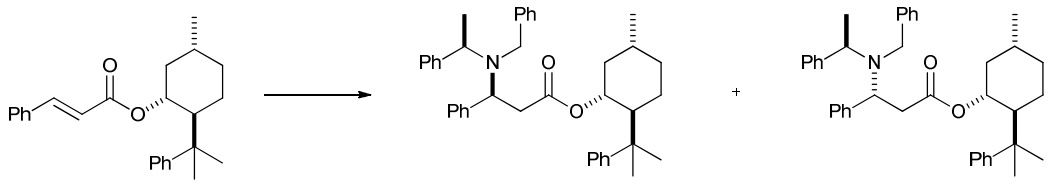


79 **104** (3S,1'*R*,2'*S*,5'*R*,α*R*)

Following *General Procedure 1*, a solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (212 mg, 1.00 mmol) in THF (2 mL) at –78 °C was treated with BuLi (2.5 M in hexanes, 0.32 mL, 0.80 mmol) and **79** (150 mg, 0.50 mmol) in THF (2 mL) to give **104** in 88:12 dr. Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave **104** as a colorless oil (51 mg, 20%, >99:1 dr); $[\alpha]_D^{20}$ +11.3 (*c* 1.0 in $CHCl_3$); ν_{max} 2965, 2925 (C–H), 1723 (C=O); δ_H (500 MHz, $CDCl_3$) 0.79-1.14 (3H, m, C*H*$_2$, C*H*), 0.86 (3H, d, *J* 6.3, C(5')*Me*), 0.98 (3H, d, *J* 6.6, C(4)*H*$_3$), 1.18 (3H, s, C(1'')*H*$_3$), 1.23 (3H, s,

C(3")H_3), 1.31 (3H, d, *J* 6.9, C(α)*Me*), 1.38-1.69 (4H, m, 2 × CH_2), 1.53 (1H, dd, *J* 14.6, 9.8, C(2)H_A), 1.90 (1H, dd, *J* 14.6, 4.4, C(2)H_B), 1.93-1.99 (1H, m, C*H*), 3.22-3.30 (1H, m, C(3)*H*), 3.58 (2H, AB system, J_{AB} 15.1, NCH_2Ph), 3.82 (1H, q, *J* 6.9, C(α)*H*), 4.71 (1H, app td, *J* 10.6, 4.3, C(1')*H*), 7.09-7.40 (15H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 18.4 (*C*(4)), 19.1 (C(α)*Me*), 21.8 (C(5')*Me*), 25.1 (*C*(3")), 26.5 (*C*(1")), 27.7 (*C*H_2), 31.2 (*C*H), 34.6 (*C*H_2), 39.2 (*C*(2)), 39.6 (*C*(2")), 41.7 (*C*H_2), 49.7 (*C*H), 49.9 (N*C*H_2Ph), 50.3 (*C*(3)), 58.4 (*C*(α)), 74.1 (*C*(1')), 124.9, 125.3, 126.5, 126.7, 127.7, 127.9, 128.1 (*o*,*m*,*p*-*Ph*), 142.0, 144.3, 151.7 (*i*-*Ph*), 171.8 (*C*(1)). Further elution gave an 85:15 mixture of **104** and its C(3)-epimer as colorless oil (128 mg, 50%). Data for the mixture: ν_{max} 2965, 2925 (C–H), 1723 (C=O); *m/z* (ESI$^+$) 512 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{35}H_{46}NO_2^+$ ([M+H]$^+$) requires 512.3523; found 512.3522. Data for the (3*S*,1'*R*,2'*S*,5'*R*,α*R*)-diastereoisomer: δ_H (500 MHz, $CDCl_3$) 0.79-1.14 (3H, m, CH_2 and C*H*), 0.72 (3H, d, *J* 6.3, C(5')*Me*), 0.90 (3H, d, *J* 6.6, C(4)H_3), 1.18 (3H, s, C(1")H_3), 1.21 (3H, s, C(3")H_3), 1.31 (3H, d, *J* 6.9, C(α)*Me*), 1.38-1.69 (4H, m, 2 × CH_2), 2.17-2.22 (1H, m, C(2)H_A), 2.25-2.32 (1H, m, C(2)H_B), 1.93-1.99 (1H, m, C*H*), 3.33-3.43 (1H, m, C(3)*H*), 3.66 (2H, AB system, J_{AB} 15.1, NCH_2Ph), 3.87 (1H, q, *J* 6.9, C(α)*H*), 4.81 (1H, app td, *J* 10.6, 4.3, C(1')*H*), 7.09-7.40 (15H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 18.7 (*C*(4)), 19.4 (C(α)*Me*), 22.0 (C(5')*Me*), 25.2 (*C*(3")), 27.1 (*C*(1")), 27.8 (*C*H_2), 31.2 (*C*H), 34.6 (*C*H_2), 39.3 (*C*(2)), 39.7 (*C*(2")), 41.9 (*C*H_2), 49.5 (*C*H), 49.9 (N*C*H_2Ph), 51.0 (*C*(3)), 58.7 (*C*(α)), 74.0 (*C*(1')), 124.9, 125.9, 126.5, 126.7, 127.7, 127.9, 128.3 (*o*,*m*,*p*-*Ph*), 141.8, 143.8, 149.9 (*i*-*Ph*), 171.9 (*C*(1)).

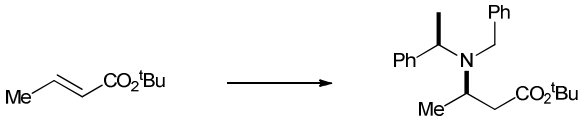
(1'*R*,2'*S*,5'*R*)-2'-(2"-Phenylpropan-2"-yl)-5'-methylcyclohexyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 105



Following *General Procedure 1*, a solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (350 mg, 1.66 mmol) in THF (3 mL) at –78 °C was treated with BuLi (2.5 M in hexanes, 0.53 mL, 1.33 mmol) and **94** (300 mg, 0.83 mmol) in THF (3 mL) to give **105** in 83:17 dr. Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave an 83:17 mixture of **105** and its C(3)-epimer as a colourless oil (334 mg, 70%).

Data for the mixture: ν_{max} 2964, 2924 (C–H), 1722 (C=O); *m/z* (ESI$^+$) 574 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{40}H_{48}NO_2^+$ ([M+H]$^+$) requires 574.3680; found 574.3680. Data for the (3*R*,1'*R*,2'*S*,5'*R*,α*R*)-diastereoisomer: δ_H (500 MHz, $CDCl_3$) 0.57-1.06 (3H, m, CH_2, C*H*), 0.76 (3H, d, *J* 6.3, C(5')*Me*), 1.19 (3H, s, C(1'')H_3), 1.23 (3H, s, C(3'')H_3), 1.26 (3H, d, *J* 6.9, C(α)*Me*), 1.29-1.66 (4H, m, 2 × CH_2), 1.81-1.89 (1H, m, C*H*), 2.42 (2H, app d, *J* 7.8, C(2)H_2), 3.65 (2H, AB system, J_{AB} 15.1, NCH_2Ph), 3.92 (1H, q, *J* 6.9, C(α)*H*), 4.22 (1H, app t, *J* 7.8, C(3)*H*), 4.64 (1H, app td, *J* 10.6, 4.3, C(1')*H*), 7.00-7.47 (20H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 19.3 (C(α)*Me*), 21.8 (C(5')*Me*), 25.9 (*C*(3")), 26.6 (*C*(1")), 27.0 (*C*H_2), 31.1 (*C*H), 34.5 (*C*H_2), 37.9 (*C*(2)), 39.7 (*C*(2")), 41.2 (*C*H_2), 50.2 (N*C*H_2Ph), 50.9 (*C*H), 58.2 (*C*(α)), 59.3 (*C*(3)), 74.3 (*C*(1')), 125.0, 125.3, 125.4, 126.5, 126.9, 127.1, 127.8, 127.9, 128.0, 128.1 (*o,m,p-Ph*), 140.4, 142.4, 144.6, 151.4 (*i-Ph*), 170.9 (*C*(1)). Further elution gave **105** as a colourless oil (86 mg, 18%, >99:1 dr); $[\alpha]_D^{24}$ +87.8 (*c* 1.2 in $CHCl_3$); ν_{max} 2964, 2924 (C–H), 1722 (C=O); δ_H (500 MHz, $CDCl_3$) 0.51-1.06 (3H, m, CH_2, C*H*), 0.76 (3H, d, *J* 6.3, C(5')*Me*), 1.14 (3H, s, C(1'')H_3), 1.16 (3H, s, C(3'')H_3), 1.26 (3H, d, *J* 6.9, C(α)*Me*), 1.29-1.66 (4H, m, 2 × CH_2), 1.81-1.89 (1H, m, C*H*), 2.02 (1H, dd, *J* 14.8, 10.8, C(2)H_A), 2.11 (1H, dd, *J* 14.8, 3.8, C(2)H_B), 3.61 (2H, AB system, J_{AB} 15.1, NCH_2Ph), 3.92 (1H, q, *J* 6.9, C(α)*H*), 4.33 (1H, dd, *J* 10.8, 3.8, C(3)*H*), 4.59 (1H, app td, *J* 10.6, 4.3, C(1')*H*), 7.00-7.47 (20H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 16.4 (C(α)*Me*), 21.7 (C(5')*Me*), 24.8 (*C*(3")), 26.5 (*C*(1")), 27.7 (*C*H_2), 31.1 (*C*H), 34.5 (*C*H_2), 37.0 (*C*(2)), 39.5 (*C*(2")), 41.1 (*C*H_2), 50.3 (N*C*H_2Ph), 50.9 (*C*H), 57.0 (*C*(α)), 59.2 (*C*(3)), 74.1 (*C*(1')), 125.0, 125.3, 125.4, 126.5, 126.9, 127.1, 127.8, 127.9, 128.0, 128.1 (*o,m,p-Ph*), 141.6, 141.8, 143.9, 151.5 (*i-Ph*), 171.2 (*C*(1)).

***tert*-Butyl (*R*,*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]butanoate 102**[11]

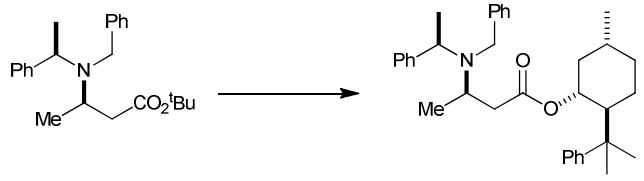


100 (*R*,*R*)-**102**

Following *General Procedure 1*, a solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (5.94 g, 28.1 mmol) in THF (40 mL) at –78 °C was treated with BuLi (2.5 M, 10.9 mL, 27.3 mmol) and **100** (2.50 g, 17.6 mmol) to give (*R*,*R*)-**102** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 1%→20% Et_2O in 30-40 °C petrol) gave (*R*,*R*)-**102** as a pale yellow oil (5.60 g, 90%, >99:1 dr); $[\alpha]_D^{25}$ –3.91 (*c* 1.0 in CH_2Cl_2); {lit.[11] $[\alpha]_D^{20}$

–3.70 (*c* 1.1 in CH_2Cl_2)}; δ_H (400 MHz, $CDCl_3$) 1.12 (3H, d, *J* 6.5, C(4)H_3), 1.34 (3H, d, *J* 7.0, C(α)*Me*), 1.39 (9H, s, CMe_3), 2.02 (1H, dd, *J* 14.1, 9.0, C(2)H_A), 2.26 (1H, dd, *J* 14.1, 4.8, C(2)H_B), 3.39-3.48 (1H, m, C(3)*H*), 3.69 (2H, AB system, J_{AB} 15.0, NCH_2Ph), 3.89 (1H, q, *J* 7.0, C(α)*H*), 7.19-7.42 (10H, m, *Ph*).

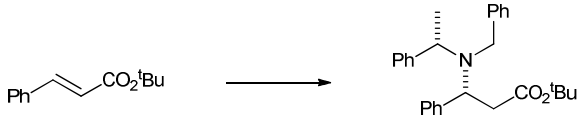
(1'*R*,2'*S*,5'*R*)-2'-(2''-Phenylpropan-2''-yl)-5'-methylcyclohexyl (*R*,*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]butanoate 104



(*R*,*R*)-**102** **104**

Following *General Procedure 2*, a solution of (*R*,*R*)-**102** (1.67 g, 4.72 mmol) in CH_2Cl_2 (16.0 mL) was treated with TFA (16.0 mL) to give a white foam (1.36 g). Then, following *General Procedure 3*, a solution of the residue (131 mg, 0.44 mmol) in CH_2Cl_2 (2 mL) was reacted with $(COCl)_2$ (40 μL, 0.46 mmol) and a solution of **59** (50 mg, 0.22 mmol) in CH_2Cl_2 (1 mL). Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave **104** as a colorless oil (52 mg, 47%, >99:1 dr); $[\alpha]_D^{22}$ +11.5 (*c* 1.1 in $CHCl_3$).

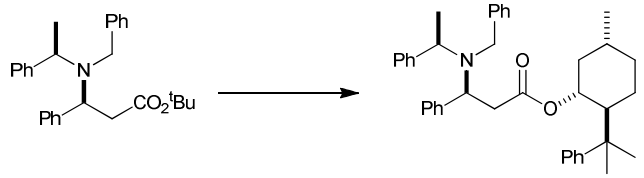
***tert*-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 103**[12]



101 (3*S*,α*R*)-**103**

Following *General Procedure 1*, a solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (6.62 g, 31.3 mmol) in THF (80 mL) at –78 °C was treated with BuLi (2.5 M, 12.0 mL, 30.4 mmol) and **101** (4.00 g, 19.6 mmol) to give (3*S*,α*R*)-**103** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 1%→20% Et_2O in 30-40 °C petrol) gave (3*S*,α*R*)-**103** as a pale yellow oil (6.70 g, 83%, >99:1 dr); $[\alpha]_D^{25}$ +4.1 (*c* 1.0 in $CHCl_3$); {lit.[12] for enantiomer $[\alpha]_D^{23}$ –4.0 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.22 (9H, s, CMe_3), 1.26 (3H, d, *J* 6.9, C(α)*Me*), 2.48-2.56 (2H, m, C(2)H_2), 3.68 (2H, app s, NCH_2Ph), 4.00 (1H, q, *J* 6.9, C(α)*H*), 4.40 (1H, dd, *J* 9.9, 5.4, C(3)*H*), 7.18-7.43 (15H, m, *Ph*).

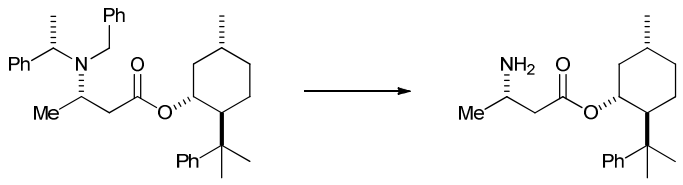
(1'*R*,2'*S*,5'*R*)-2'-(2''-Phenylpropan-2''-yl)-5'-methylcyclohexyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 105



(3*S*,α*R*)-**103** **105**

Following *General Procedure 2*, a solution of (3*S*,α*R*)-**103** (1.72 g, 4.14 mmol) in CH_2Cl_2 (17.0 mL) was treated with TFA (17.0 mL) to give a white foam (1.41 g). Then, following *General Procedure 3*, a solution of the residue (378 mg, 1.05 mmol) in CH_2Cl_2 (4 mL) was reacted with $(COCl)_2$ (93 μL, 1.10 mmol) and a solution of **59** (122 mg, 0.53 mmol) in CH_2Cl_2 (2 mL). Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave **105** as a colorless oil (176 mg, 58%, >99:1 dr); $[\alpha]_D^{25}$ +88.0 (*c* 1.0 in $CHCl_3$).

(1'*R*,2'*S*,5'*R*)-2'-(2''-Phenylpropan-2''-yl)-5'-methylcyclohexyl (*S*)-3-aminobutanoate 108

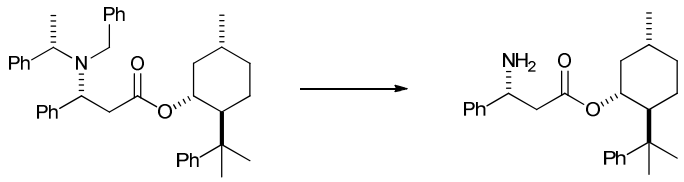


98 **108**

Following *General Procedure 4*, reacting **98** (410 mg, 0.80 mmol) and $Pd(OH)_2/C$ (205 mg) in EtOAc (5 mL) under H_2 (5 atm) for 18 h gave, after purification *via* flash column chromatography (eluent 30-40 ºC petrol (1% Et_3N)/Et_2O, 3:1, increased to 1:3), **108** as a pale yellow oil (192 mg, 76%, >99:1 dr); $[\alpha]_D^{25}$ +12.9 (c 2.0 in $CHCl_3$); ν_{max} 3374 (N–H), 2959, 2924 (C–H), 1723 (C=O); δ_H (500 MHz, $CDCl_3$) 0.87-1.22 (3H, m, CH_2, C*H*), 0.91 (3H, d, *J* 6.6, C(5')*Me*), 1.03 (3H, d, *J* 6.3, C(4)H_3), 1.24 (3H, s, C(1'')H_3), 1.35 (3H, s, C(3'')H_3), 1.46-1.92 (4H, m, 2 × CH_2), 1.65-1.73 (2H, m, NH_2), 1.74-1.82 (2H, m, C(2)H_2), 2.04-2.11 (1H, m, C*H*), 3.10-3.19 (1H, m, C(3)*H*), 4.87 (1H, app td, *J* 10.6, 4.3, C(1')*H*), 7.14-7.35 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 21.8 (C(5')*Me*), 23.2 (*C*(4)), 24.2 (*C*(3'')), 26.4 (*C*H_2), 28.6 (*C*(1'')), 31.3 (*C*H), 34.5 (*C*H_2), 39.5 (*C*(2'')), 41.8 (*C*H_2), 43.7 (*C*H), 43.9 (*C*(2)), 50.2 (*C*(3)), 73.9 (*C*(1')), 124.9, 125.4, 127.9 (*o*,*m*,*p*-*Ph*), 151.7 (*i*-*Ph*), 171.8 (*C*(1));

m/z (ESI$^+$) 318 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{32}NO_2^+$ ([M+H]$^+$) requires 318.2428; found 318.2428.

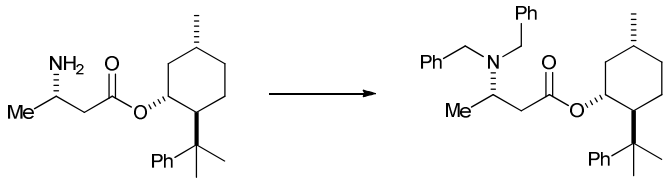
(1'*R*,2'*S*,5'*R*)-2'-(2''-Phenylpropan-2''-yl)-5'-methylcyclohexyl (*R*)-3-amino-3-phenylpropanoate 109



99 **109**

Following *General Procedure 4*, reacting **99** (168 mg, 0.29 mmol) and $Pd(OH)_2/C$ (85 mg) in MeOH/AcOH (v:v 40:1, 4.1 mL) under H_2 (5 atm) for 18 h gave, after purification *via* flash column chromatography (eluent 30-40 ºC petrol (1% Et_3N)/Et_2O, 3:1, increased to 1:3), **109** as a colourless oil (67 mg, 61%, >99:1 dr); $[\alpha]_D^{25}$ +42.8 (*c* 0.5 in $CHCl_3$); ν_{max} 3385 (N–H), 2955, 2923 (C–H), 1722 (C=O); δ_H (500 MHz, $CDCl_3$) 0.82-1.16 (3H, m, CH_2, C*H*), 0.86 (3H, d, *J* 6.3, C(5')*Me*), 1.18 (3H, s, C(1'')H_3), 1.28 (3H, s, C(3'')H_3), 1.39-1.83 (4H, m, 2 × CH_2), 1.73 (2H, br s, NH_2), 1.97-2.04 (1H, m, C*H*), 1.99 (1H, dd, *J* 16.1, 4.4, C(2)H_A), 2.15 (1H, dd, *J* 16.1, 9.5, C(2)H_B), 4.15 (1H, dd, *J* 9.5, 4.4, C(3)*H*), 4.82 (1H, app td, *J* 10.7, 4.4, C(1')*H*), 7.05-7.35 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 21.8 (C(5')*Me*), 24.6 (*C*(3'')), 26.5 (*C*H_2), 28.3 (*C*(1'')), 31.3 (*C*H), 34.5 (*C*H_2), 39.7 (*C*(2'')), 41.6 (*C*H_2), 43.8 (*C*(2)), 50.3 (*C*H), 52.2 (*C*(3)), 74.2 (*C*(1')), 125.1, 125.4, 126.3, 127.2, 128.0, 128.4 (*o,m,p-Ph*), 144.6, 151.5 (*i-Ph*), 171.4 (*C*(1)); *m/z* (ESI$^+$) 380 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{34}NO_2^+$ ([M+H]$^+$) requires 380.2584; found 380.2581.

(1'*R*,2'*S*,5'*R*)-2'-(2''-Phenylpropan-2''-yl)-5'-methylcyclohexyl (*S*)-3-(*N*,*N*-dibenzylamino)butanoate 112

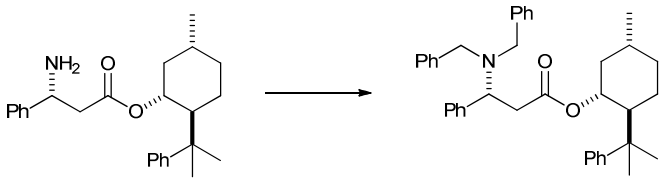


108 **112**

Following *General Procedure 5*, **108** (100 mg, 0.31 mmol) was reacted with K_2CO_3 (435 mg, 3.15 mmol) in BnBr (0.37 mL, 3.15 mmol). Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave **112** as a white solid (147 mg, 95%, >99:1 dr); $C_{34}H_{43}NO_2$ requires C, 82.05; H, 8.7; N, 2.8%; found C,

82.2; H, 8.8; N, 2.7%; mp 71-72 °C; $[\alpha]_D^{25}$ +12.8 (*c* 0.5 in $CHCl_3$); ν_{max} 2961, 2925 (C–H), 1725 (C=O); δ_H (500 MHz, $CDCl_3$) 0.81-1.14 (3H, m, C*H*$_2$, C*H*), 0.88 (3H, d, *J* 6.6, C(5')*Me*), 1.03 (3H, d, *J* 6.9, C(4)*H*$_3$), 1.20 (3H, s, C(1")*H*$_3$), 1.28 (3H, s, C(3")*H*$_3$), 1.42-1.71 (3H, m, C*H*$_2$, C*H*), 1.74 (1H, dd, *J* 14.5, 8.5, C(2)*H*$_A$), 2.09 (1H, dd, *J* 14.5, 5.7, C(2)*H*$_B$), 1.85-2.03 (2H, m, C*H*$_2$), 3.08-3.16 (1H, m, C(3)*H*), 3.46 (4H, AB system, J_{AB} 13.9, N(C*H*$_2$Ph)$_2$), 4.76 (1H, app td, *J* 10.6, 4.3, C(1')*H*), 7.11-7.38 (15H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 15.1 (*C*(4)), 21.8 (C(5')*Me*), 25.0 (*C*(3")), 26.5 (*C*H$_2$), 27.8 (*C*(1")), 31.3 (*C*H), 34.5 (*C*H$_2$), 38.0 (*C*H$_2$), 39.7 (*C*(2")), 41.6 (*C*H), 50.3 (*C*(2)), 50.5 (*C*(3)), 53.5 (N(*C*H$_2$Ph)$_2$), 74.0 (*C*(1')), 124.9, 125.4, 126.7, 128.0, 128.1, 128.7 (*o*,*m*,*p*-*Ph*), 140.1, 151.7 (*i*-*Ph*), 171.7 (*C*(1)); *m/z* (ESI$^+$) 498 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{34}H_{44}NO_2^+$ ([M+H]$^+$) requires 498.3367; found 498.3368.

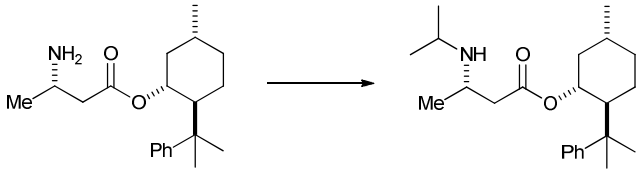
(1'*R*,2'*S*,5'*R*)-2'-(2"-Phenylpropan-2"-yl)-5'-methylcyclohexyl (*R*)-3-(*N*,*N*-dibenzylamino)-3-phenylpropanoate 113



109 **113**

Following *General Procedure 5*, **109** (55 mg, 0.15 mmol) was reacted with K_2CO_3 (200 mg, 1.45 mmol) in BnBr (0.17 mL, 1.45 mmol). Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave **113** as a colourless oil containing trace amounts of an unidentified impurity (71 mg, 88%, >99:1 dr); ν_{max} 2954, 2924 (C–H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 0.75-1.15 (3H, m, C*H*$_2$, C*H*), 0.88 (3H, d, *J* 6.3, C(5')*Me*), 1.22 (3H, s, C(1")*H*$_3$), 1.30 (3H, s, C(3")*H*$_3$), 1.37-1.80 (4H, m, 2 × C*H*$_2$), 1.96-2.05 (1H, m, C*H*), 2.39-2.54 (2H, m, C(2)*H*$_2$), 3.45 (4H, AB system, J_{AB} 13.6, N(C*H*$_2$Ph)$_2$), 4.19 (1H, app t, *J* 7.6, C(3)*H*), 4.76 (1H, app td, *J* 10.6, 4.3, C(1')*H*), 7.12-7.45 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.9 (C(5')*Me*), 25.4 (*C*(3")), 26.6 (*C*H$_2$), 27.7 (*C*(1")), 31.2 (*C*H), 34.6 (*C*H$_2$), 36.3 (*C*(2)), 39.7 (*C*(2")), 41.5 (*C*H$_2$), 50.3 (*C*H), 53.8 (N(*C*H$_2$Ph)$_2$), 58.7 (*C*(3)), 74.5 (*C*(1')), 125.0, 125.5, 126.9, 127.3, 128.0, 128.2, 128.4, 128.6, 128.7, 128.8 (*o*,*m*,*p*-*Ph*), 138.1, 139.8, 151.7 (*i*-*Ph*), 171.0 (*C*(1)); *m/z* (ESI$^+$) 560 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{39}H_{46}NO_2^+$ ([M+H]$^+$) requires 560.3523; found 560.3523.

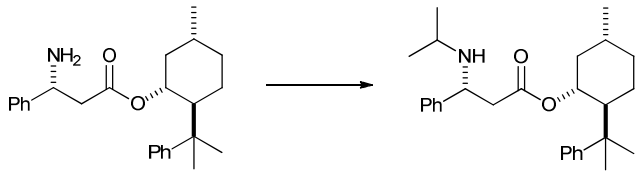
(1'*R*,2'*S*,5'*R*)-2'-(2''-Phenylpropan-2''-yl)-5'-methylcyclohexyl (*S*)-3-(*N*-isopropylamino)butanoate 116



108 **116**

Following *General Procedure 6*, **108** (76 mg, 0.24 mmol), acetone (35 μL, 0.48 mmol) and $NaBH_3CN$ (60 mg, 0.96 mmol) were reacted in MeOH (2 mL). Purification *via* flash column chromatography (gradient elution, 1%→50% Et_2O in 30-40 °C petrol) gave **116** as a colourless oil (63 mg, 73%, >99:1 dr); $[\alpha]_D^{25}$ –2.2 (c 0.5 in $CHCl_3$); ν_{max} 3321 (N–H), 2962, 2925 (C–H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 0.87 (3H, d, *J* 6.3, C(5')*Me*), 0.90-1.18 (3H, m, CH_2, C*H*), 0.98 (3H, d, *J* 6.6, C(4)H_3), 1.01 (3H, d, *J* 6.3, NCHMe_A), 1.03 (3H, d, *J* 6.3, NCHMe_B), 1.20 (3H, s, C(1'')H_3), 1.31 (3H, s, C(3'')H_3), 1.39-1.89 (4H, m, 2 × CH_2), 1.42-1.45 (1H, m, N*H*), 1.70 (1H, dd, *J* 15.4, 6.3, C(2)H_A), 1.93 (1H, dd, *J* 15.4, 6.3, C(2)H_B), 1.97-2.07 (1H, m, C*H*), 2.80 (1H, sept, *J* 6.3, C*H*Me_2), 2.94-3.03 (1H, m, C(3)*H*), 4.82 (1H, app td, *J* 10.6, 4.3, C(1')*H*), 7.08-7.32 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.6 (*C*(4)), 21.8 (C(5')*Me*), 22.8, 23.3 (NCHMe_2), 24.7 (*C*(3'')), 26.6 (*C*H_2), 28.1 (*C*(1'')), 29.7 (*C*H_2), 31.3 (*C*H), 34.6 (*C*H_2), 39.7 (*C*(2'')), 41.7 (*C*(2)), 45.3 (*C*H), 47.0 (*C*HMe_2), 50.2 (*C*(3)), 74.1 (*C*(1')), 125.0, 125.3, 128.0 (*o*,*m*,*p*-*Ph*), 150.6 (*i*-*Ph*), 171.6 (*C*(1)); *m/z* (ESI^+) 360 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{23}H_{38}NO_2^+$ ($[M+H]^+$) requires 360.2897; found 360.2897.

(1'*R*,2'*S*,5'*R*)-2'-(2''-Phenylpropan-2''-yl)-5'-methylcyclohexyl (*R*)-3-(isopropylamino)-3-phenylpropanoate 117

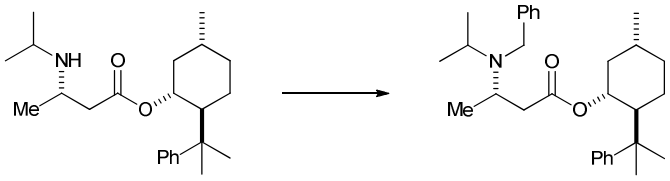


109 **117**

Following *General Procedure 6*, **109** (125 mg, 0.33 mmol), acetone (48 μL, 0.66 mmol) and $NaBH_3CN$ (83 mg, 1.32 mmol) were reacted in MeOH (3 mL). Purification *via* flash column chromatography (gradient elution, 1%→50% Et_2O in 30-40 °C petrol) gave **117** as a colourless oil (86 mg, 62%, >99:1 dr); $[\alpha]_D^{25}$ +26.8 (c 0.5 in $CHCl_3$); ν_{max} 3407 (N–H), 2959, 2924 (C–H), 1725 (C=O); δ_H (500 MHz, $CDCl_3$) 0.80-1.15 (3H, m, CH_2, C*H*), 0.88 (3H, d, *J*

6.6, C(5')*Me*), 0.98 (3H, d, *J* 6.3, NCH*Me*$_A$), 1.06 (3H, d, *J* 6.3, NCH*Me*$_B$), 1.19 (3H, s, C(1'')H_3), 1.27 (3H, s, C(3'')H_3), 1.39-1.72 (4H, m, 2 × CH_2), 1.72-1.80 (1H, m, N*H*), 1.96-2.04 (1H, m, C*H*), 2.07 (1H, dd, *J* 15.7, 6.1, C(2)H_A), 2.23 (1H, dd, *J* 15.7, 8.2, C(2)H_B), 2.52-2.62 (1H, m, C*H*Me$_2$), 4.01 (1H, dd, *J* 8.2, 6.1, C(3)*H*), 4.80 (1H, app td, *J* 10.6, 4.3, C(1')*H*), 7.08-7.38 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 21.7 (C(5')*Me*), 21.9, 24.2 (NCH*Me*$_2$), 25.1 (*C*(3'')), 26.5 (*C*H$_2$), 27.5 (*C*(1'')), 31.2 (*C*H), 34.5 (*C*H$_2$), 39.6 (*C*(2'')), 41.6 (*C*H$_2$), 43.1 (*C*(2)), 45.5 (*C*H), 50.3 (*C*HMe$_2$), 56.5 (*C*(3)), 74.4 (*C*(1')), 125.1, 125.4, 127.1, 127.8, 128.4 (*o,m,p-Ph*), 143.1, 151.5 (*i-Ph*), 171.1 (*C*(1)); *m/z* (ESI$^+$) 422 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{40}NO_2^+$ ([M+H]$^+$) requires 422.3054; found 422.3054.

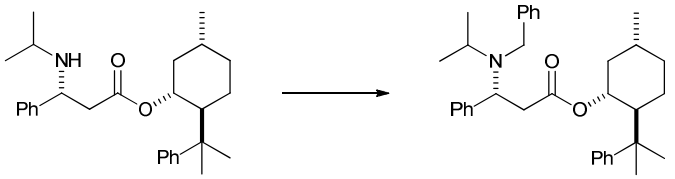
(1'*R*,2'*S*,5'*R*)-2'-(2''-Phenylpropan-2''-yl)-5'-methylcyclohexyl (*S*)-3-(*N*-isopropyl-*N*-benzylamino)butanoate 120



116 120

Following *General Procedure 5*, **116** (62 mg, 0.17 mmol) was reacted with K_2CO_3 (238 mg, 1.72 mmol) in BnBr (0.21 mL, 1.72 mmol). Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave **120** as a colourless oil containing trace amounts of an unidentified impurity (70 mg, 90%, >99:1 dr); ν_{max} 2963, 2926 (C–H), 1725 (C=O); δ_H (500 MHz, $CDCl_3$) 0.73-1.20 (3H, m, CH_2, C*H*), 0.93 (3H, d, *J* 6.6, C(5')*Me*), 0.99 (3H, d, *J* 6.6, C(4)H_3), 1.04 (3H, d, *J* 6.6, NCH*Me*$_A$), 1.06 (3H, d, *J* 6.6, NCH*Me*$_B$), 1.25 (3H, s, C(1'')H_3), 1.34 (3H, s, C(3'')H_3), 1.37-1.80 (4H, m, 2 × CH_2), 1.72 (1H, dd, *J* 14.7, 7.6, C(2)H_A), 1.99 (1H, dd, *J* 14.7, 7.8, C(2)H_B), 2.02-2.06 (1H, m, C*H*), 2.86 (1H, sept, *J* 6.6, C*H*Me$_2$), 3.28-3.38 (1H, m, C(3)*H*), 3.57 (2H, s, NCH_2Ph), 4.85 (1H, app td, *J* 10.6, 4.3, C(1')*H*), 7.12-7.42 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 18.7 (*C*(4)), 20.1, 21.6 (NCH*Me*$_2$), 22.3 (C(5')*Me*), 25.6 (*C*(3'')), 27.0 (*C*H$_2$), 28.3 (*C*(1'')), 30.2 (*C*(2)), 31.7 (*C*H), 35.0 (*C*H$_2$), 40.1 (*C*H$_2$), 41.2 (*C*(2'')), 48.8 (*C*H), 49.3 (*C*H$_2$N), 49.4 (*C*HMe$_2$), 50.7 (*C*(3)), 74.4 (*C*(1')), 125.4, 125.8, 128.3, 128.6 (*o,m,p-Ph*), 142.5, 152.1 (*i-Ph*), 172.5 (*C*(1)); *m/z* (ESI$^+$) 450 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{44}NO_2^+$ ([M+H]$^+$) requires 450.3367; found 450.3362.

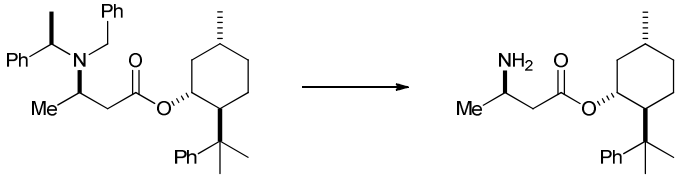
(1'*R*,2'*S*,5'*R*)-2'-(2''-Phenylpropan-2''-yl)-5'-methylcyclohexyl (*R*)-3-(*N*-isopropyl-*N*-benzylamino)-3-phenylpropanoate 121



117 **121**

Following *General Procedure 5*, **117** (67 mg, 0.16 mmol) was reacted with K_2CO_3 (221 mg, 1.59 mmol) in BnBr (0.19 mL, 1.59 mmol). Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave **121** as a colourless oil containing trace amounts of an unidentified impurity (68 mg, 83%, >99:1 dr); ν_{max} 2961, 2925 (C–H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 0.66-1.09 (3H, m, CH_2, C*H*), 0.79 (3H, d, *J* 6.3, C(5')*Me*), 0.81 (3H, d, *J* 6.6, NCHMe_A), 0.99 (3H, d, *J* 6.6, NCHMe_B), 1.14 (3H, s, C(1'')H_3), 1.21 (3H, s, C(3'')H_3), 1.30-1.65 (4H, m, 2 × CH_2), 1.90-1.99 (1H, m, C*H*), 2.25-2.39 (2H, m, C(2)H_2), 2.97 (1H, sept, *J* 6.6, C*H*Me$_2$), 3.63 (2H, AB system, J_{AB} 15.4, NCH_2Ph), 4.11 (1H, dd, *J* 8.8, 6.3, C(3)*H*), 4.67 (1H, app td, *J* 10.6, 4.3, C(1')*H*), 7.13-7.44 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.7, 21.2 (NCH*Me*$_2$), 21.8 (C(5')*Me*), 25.5 (*C*(3'')), 26.6 (*C*H$_2$), 27.4 (*C*(1'')), 31.1 (*C*H), 34.5 (*C*(2)), 38.8 (*C*H$_2$), 39.6 (*C*(2'')), 41.4 (*C*H$_2$), 48.1 (*C*H), 49.2 (N*C*H$_2$Ph), 50.3 (*C*HMe$_2$), 59.9 (*C*(3)), 74.4 (*C*(1')), 125.1, 125.5, 126.5, 127.0, 127.9, 128.0, 128.3, 128.6, 128.7 (*o*,*m*,*p*-*Ph*), 141.6, 142.2, 151.6 (*i*-*Ph*), 171.2 (*C*(1)); *m/z* (ESI$^+$) 512 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{35}H_{46}NO_2^+$ ([M+H]$^+$) requires 512.3523; found 512.3525.

(1'*R*,2'*S*,5'*R*)-2'-(2''-Phenylpropan-2''-yl)-5'-methylcyclohexyl (*R*)-3-aminobutanoate 110

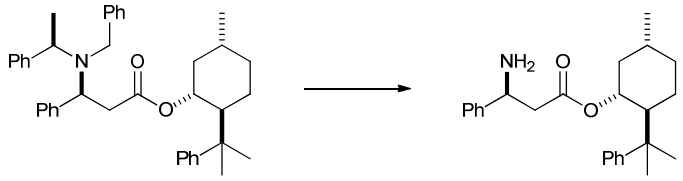


104 **110**

Following *General Procedure 4*, reacting **104** (160 mg, 0.31 mmol) and $Pd(OH)_2$/C (80 mg) in EtOAc (4 mL) under H_2 (5 atm) for 18 h gave **110** as a colourless oil (97 mg, 98%, >99:1 dr); $[\alpha]_D^{25}$ –25.0 (*c* 0.5 in $CHCl_3$); ν_{max} 3378 (N–H), 2957, 2924 (C–H), 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 0.82-1.17 (3H, m, CH_2, C*H*), 0.85 (3H, d, *J* 6.6, C(5')*Me*), 0.94 (3H, d, *J* 6.3,

C(4)H_3), 1.18 (3H, s, C(1'')H_3), 1.30 (3H, s, C(3'')H_3), 1.32-1.78 (4H, m, 2 × CH_2), 1.61-1.73 (2H, m, NH_2), 1.79-1.90 (2H, m, C(2)H_2), 1.95-2.08 (1H, m, C*H*), 2.97-3.10 (1H, m, C(3)*H*), 4.80 (1H, app td, *J* 10.6, 4.3, C(1')*H*), 7.09-7.31 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.7 (C(5')*Me*), 23.2 (*C*(4)), 24.4 (*C*(3'')), 26.5 (*C*H_2), 28.4 (*C*(1'')), 31.5 (*C*H), 34.5 (*C*H_2), 39.7 (*C*(2'')), 41.3 (*C*H_2), 43.7 (*C*H), 44.3 (*C*(2)), 50.2 (*C*(3)), 74.5 (*C*(1')), 125.1, 125.5, 128.0 (*o*,*m*,*p-Ph*), 151.8 (*i-Ph*), 171.2 (*C*(1)); *m/z* (ESI^+) 318 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{32}NO_2^+$ ($[M+H]^+$) requires 318.2428; found 318.2427.

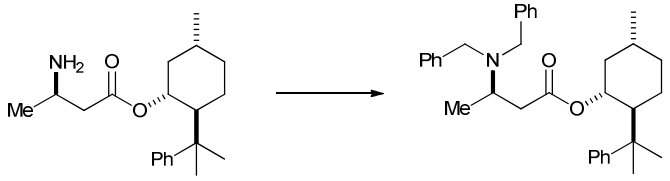
(1'*R*,2'*S*,5'*R*)-2'-(2''-Phenylpropan-2''-yl)-5'-methylcyclohexyl (*S*)-3-amino-3-phenylpropanoate 111



105 **111**

Following *General Procedure 4*, reacting **105** (189 mg, 0.33 mmol) and $Pd(OH)_2$/C (95 mg) in MeOH/AcOH (v:v 40:1, 4.1 mL) under H_2 (5 atm) for 18 h gave, after purification *via* flash column chromatography (eluent 30-40 ºC petrol (1% Et_3N)/Et_2O, 3:1, increased to 1:3), **111** as a colourless oil (81 mg, 65%, >99:1 dr); $[\alpha]_D^{21}$ +4.20 (*c* 2.1 in $CHCl_3$); ν_{max} 3385 (N–H), 2955, 2923 (C–H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 0.80-1.17 (3H, m, CH_2, C*H*), 0.86 (3H, d, *J* 6.3, C(5')*Me*), 1.21 (3H, s, C(1'')H_3), 1.32 (3H, s, C(3'')H_3), 1.38-1.83 (4H, m, 2 × CH_2), 1.60-1.77 (2H, m, NH_2), 1.97-2.04 (1H, m, C*H*), 2.04-2.13 (2H, m, C(2)H_2), 4.11 (1H, dd, *J* 8.3, 5.1, C(3)*H*), 4.82 (1H, app td, *J* 10.9, 4.6, C(1')*H*), 7.13-7.45 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.8 (C(5')*Me*), 24.6 (*C*(3'')), 26.5 (*C*H_2), 28.3 (*C*(1'')), 31.3 (*C*H), 34.5 (*C*H_2), 39.7 (*C*(2'')), 41.6 (*C*H_2), 44.2 (*C*(2)), 50.2 (*C*H), 52.4 (*C*(3)), 74.4 (*C*(1')), 125.1, 125.4, 126.3, 127.2, 128.0, 128.4 (*o*,*m*,*p-Ph*), 144.7, 151.7 (*i-Ph*), 171.2 (*C*(1)); *m/z* (ESI^+) 380 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{25}H_{34}NO_2^+$ ($[M+H]^+$) requires 380.2584; found 380.2581.

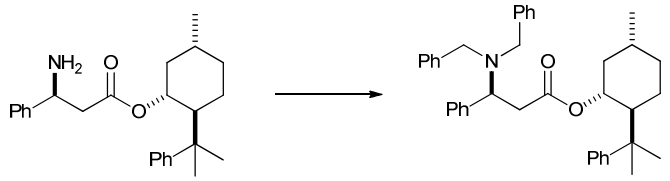
(1'*R*,2'*S*,5'*R*)-2'-(2''-Phenylpropan-2''-yl)-5'-methylcyclohexyl (*R*)-3-(*N*,*N*-dibenzylamino)butanoate 114



110 114

Following *General Procedure 5*, **110** (86 mg, 0.27 mmol) was reacted with K_2CO_3 (375 mg, 2.71 mmol) in BnBr (0.32 mL, 2.71 mmol). Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave **114** as a colourless oil containing trace amounts of an unidentified impurity (116 mg, 86%, >99:1 dr); ν_{max} 2961, 2925 (C–H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 0.86-1.22 (3H, m, CH_2, C*H*), 0.94 (3H, d, *J* 6.6, C(5')*Me*), 1.00 (3H, d, *J* 6.9, C(4)H_3), 1.24 (3H, s, C(1'')H_3), 1.32 (3H, s, C(3'')H_3), 1.45-1.80 (3H, m, CH_2, C*H*), 1.67 (1H, dd, *J* 14.5, 8.5, C(2)H_A), 2.24 (1H, dd, *J* 14.5, 5.7, C(2)H_B), 1.91-2.06 (2H, m, CH_2), 3.02-3.31 (1H, m, C(3)*H*), 3.53 (4H, AB system, J_{AB} 13.9, N(CH_2Ph)$_2$), 4.80 (1H, app td, *J* 10.6, 4.3, C(1')*H*), 7.14-7.46 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.7 (*C*(4)), 21.9 (C(5')*Me*), 24.6 (*C*(3'')), 26.5 (*C*H_2), 28.4 (*C*(1'')), 31.3 (*C*H), 34.7 (*C*H_2), 38.6 (*C*H_2), 39.6 (*C*(2'')), 41.6 (*C*H), 50.2 (*C*(2)), 50.5 (*C*(3)), 53.5 (N(*C*H_2Ph)$_2$), 74.2 (*C*(1')), 124.9, 125.4, 126.8, 128.0, 128.2, 128.4, 128.6, 128.8 (*o,m,p-Ph*), 140.1, 151.9 (*i-Ph*), 171.7 (*C*(1)); *m/z* (ESI$^+$) 498 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{34}H_{44}NO_2^+$ ([M+H]$^+$) requires 498.3367; found 498.3368.

(1'*R*,2'*S*,5'*R*)-2'-(2''-Phenylpropan-2''-yl)-5'-methylcyclohexyl (*S*)-3-(*N*,*N*-dibenzylamino)-3-phenylpropanoate 115

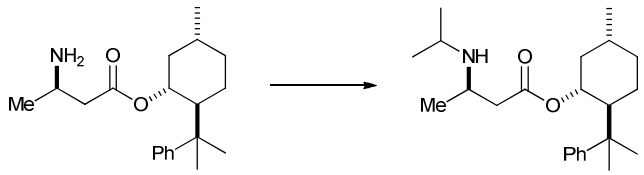


111 115

Following *General Procedure 5*, **111** (60 mg, 0.16 mmol) was reacted with K_2CO_3 (218 mg, 1.58 mmol) in BnBr (0.19 mL, 1.58 mmol). Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave **115** as a colourless oil containing trace amounts of an unidentified impurity (80 mg, 90%, >99:1 dr); ν_{max} 2954, 2924 (C–H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 0.72-1.15 (3H, m, CH_2, C*H*), 0.85 (3H, d, *J* 6.3, C(5')*Me*), 1.20 (3H, s, C(1'')H_3), 1.27 (3H, s, C(3'')H_3), 1.33-1.76 (4H, m, 2 × CH_2), 1.93-

2.02 (1H, m, C*H*), 2.26 (1H, dd, *J* 14.9, 9.2, C(2)H_A), 2.55 (1H, dd, *J* 14.9, 6.2, C(2)H_B), 3.45 (4H, AB system, J_{AB} 13.6, N(CH_2Ph)$_2$), 4.09 (1H, dd, *J* 9.2, 6.2, C(3)*H*), 4.72 (1H, app td, *J* 10.6, 4.3, C(1')*H*), 7.10-7.42 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.8 (C(5')*Me*), 24.6 (*C*(3")), 26.5 (*C*H$_2$), 28.2 (*C*(1")), 31.2 (*C*H), 34.6 (*C*H$_2$), 35.9 (*C*(2)), 39.6 (*C*(2")), 41.4 (*C*H$_2$), 50.2 (*C*H), 53.8 (N(*C*H$_2$Ph)$_2$), 58.7 (*C*(3)), 74.3 (*C*(1')), 125.0, 125.4, 126.9, 127.2, 127.9, 128.2, 128.4, 128.6, 128.8 (*o,m,p-Ph*), 138.3, 139.8, 151.8 (*i-Ph*), 171.0 (*C*(1)); *m/z* (ESI$^+$) 560 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{39}H_{46}NO_2^+$ ([M+H]$^+$) requires 560.3523; found 560.3523.

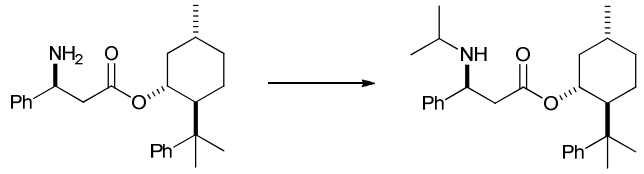
(1'*R*,2'*S*,5'*R*)-2'-(2"-Phenylpropan-2"-yl)-5'-methylcyclohexyl (*R*)-3-(*N*-isopropylamino)butanoate 118



110 **118**

Following *General Procedure 6*, **110** (96 mg, 0.32 mmol), acetone (47 μL, 0.64 mmol) and $NaBH_3CN$ (80 mg, 1.26 mmol) were reacted in MeOH (2 mL). Purification *via* flash column chromatography (gradient elution, 1%→50% Et_2O in 30-40 °C petrol) gave **118** as a colourless oil (95 mg, 83%, >99:1 dr); $[\alpha]_D^{25}$ +6.0 (*c* 0.5 in $CHCl_3$); ν_{max} 3320 (N–H), 2960, 2924 (C–H), 1725 (C=O); δ_H (500 MHz, $CDCl_3$) 0.88 (3H, d, *J* 6.3, C(5')*Me*), 0.90-1.18 (3H, m, CH_2, C*H*), 0.97 (3H, d, *J* 6.6, C(4)H_3), 1.00 (3H, d, *J* 6.3, NCH*Me*$_A$), 1.02 (3H, d, *J* 6.3, NCH*Me*$_B$), 1.22 (3H, s, C(1")H_3), 1.31 (3H, s, C(3")H_3), 1.39-1.89 (4H, m, 2 × CH_2), 1.42-1.45 (1H, m, N*H*), 1.71 (1H, dd, *J* 15.4, 6.3, C(2)H_A), 2.00 (1H, dd, *J* 15.4, 6.3, C(2)H_B), 1.97-2.07 (1H, m, C*H*), 2.79 (1H, sept, *J* 6.3, C*H*Me$_2$), 2.88-2.95 (1H, m, C(3)*H*), 4.80 (1H, app td, *J* 10.6, 4.3, C(1')*H*), 7.08-7.32 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 20.1 (*C*(4)), 21.8 (C(5')*Me*), 22.2, 22.8 (NCH*Me*$_2$), 25.2 (*C*(3")), 26.6 (*C*H$_2$), 27.8 (*C*(1")), 31.0 (*C*H$_2$), 31.3 (*C*H), 34.5 (*C*H$_2$), 39.7 (*C*(2")), 41.8 (*C*(2)), 45.6 (*C*H), 47.2 (*C*HMe$_2$), 50.3 (*C*(3)), 74.6 (*C*(1')), 125.1, 125.4, 127.9 (*o,m,p-Ph*), 151.5 (*i-Ph*), 171.4 (*C*(1)); *m/z* (ESI$^+$) 360 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{38}NO_2^+$ ([M+H]$^+$) requires 360.2897; found 360.2897.

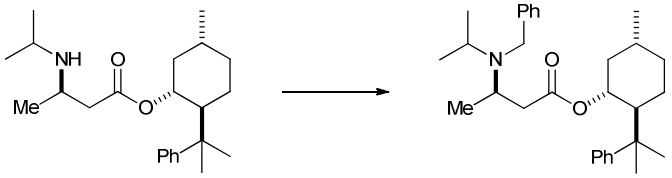
(1'*R*,2'*S*,5'*R*)-2'-(2''-Phenylpropan-2''-yl)-5'-methylcyclohexyl (*S*)-3-(*N*-isopropylamino)-3-phenylpropanoate 119



111 **119**

Following *General Procedure 6*, **111** (85 mg, 0.22 mmol), acetone (38 μL, 0.52 mmol) and $NaBH_3CN$ (65 mg, 1.04 mmol) were reacted in MeOH (2 mL). Purification *via* flash column chromatography (gradient elution, 1%→50% Et_2O in 30-40 °C petrol) gave **119** as a colourless oil (82 mg, 75%, >99:1 dr); $[\alpha]_D^{25}$ –11.6 (c 1.0 in $CHCl_3$); ν_{max} 3426 (N–H), 2970, 2927 (C–H), 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 0.73-1.14 (3H, m, CH_2, C*H*), 0.84 (3H, d, *J* 6.6, C(5')*Me*), 0.96 (3H, d, *J* 6.3, NCH*Me*$_A$), 1.00 (3H, d, *J* 6.3, NCH*Me*$_B$), 1.21 (3H, s, C(1'')H_3), 1.30 (3H, s, C(3'')H_3), 1.34-1.72 (4H, m, 2 × CH_2), 1.59-1.66 (1H, m, N*H*), 1.93-2.01 (1H, m, C*H*), 2.04 (1H, dd, *J* 15.2, 5.8, C(2)H_A), 2.15 (1H, dd, *J* 15.2, 8.6, C(2)H_B), 2.54 (1H, sept, *J* 6.3, C*H*Me$_2$), 3.94 (1H, dd, *J* 8.6, 5.8, C(3)*H*), 4.76 (1H, app td, *J* 10.6, 4.3, C(1')*H*), 7.09-7.34 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.7 (C(5')*Me*), 21.9, 24.2 (NCH*Me*$_2$), 25.0 (*C*(3'')), 26.5 (*C*H$_2$), 27.9 (*C*(1'')), 31.2 (*C*H), 34.5 (*C*H$_2$), 39.7 (*C*(2'')), 41.5 (*C*H$_2$), 43.5 (*C*(2)), 45.4 (*C*H), 50.3 (*C*HMe$_2$), 56.7 (*C*(3)), 74.3 (*C*(1')), 125.1, 125.4, 127.0, 127.9, 128.3 (*o*,*m*,*p*-*Ph*), 143.3, 151.6 (*i*-*Ph*), 171.1 (*C*(1)); *m/z* (ESI$^+$) 422 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{40}NO_2^+$ ([M+H]$^+$) requires 422.3054; found 422.3054.

(1'*R*,2'*S*,5'*R*)-2'-(2''-Phenylpropan-2''-yl)-5'-methylcyclohexyl (*R*)-3-(*N*-isopropyl-*N*-benzylamino)butanoate 122

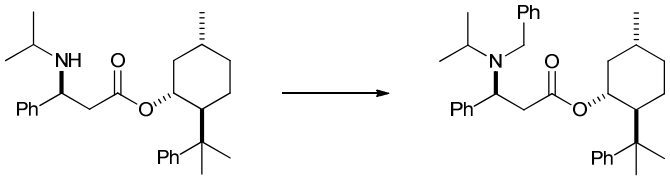


118 **122**

Following *General Procedure 5*, **118** (76 mg, 0.21 mmol) was reacted with K_2CO_3 (292 mg, 2.11 mmol) in BnBr (0.25 mL, 2.11 mmol). Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave **122** as a colourless oil containing trace amounts of an unidentified impurity (71 mg, 75%, >99:1 dr); ν_{max} 2963, 2926 (C–H), 1725 (C=O); δ_H (500 MHz, $CDCl_3$) 0.83-1.18 (3H, m, CH_2, C*H*), 0.88 (3H, d, *J* 6.6, C(5')*Me*), 0.96 (3H, d, *J* 6.6, C(4)H_3), 0.99 (3H, d, *J* 6.6, NCH*Me*$_A$), 1.00 (3H, d, *J* 6.6,

NCH*Me*$_B$), 1.21 (3H, s, C(1'')*H*$_3$), 1.30 (3H, s, C(3'')*H*$_3$), 1.44-1.75 (3H, m, C*H*$_2$, C*H*), 1.88-2.06 (2H, m, C*H*$_2$), 1.60 (1H, dd, *J* 14.5, 8.2, C(2)*H*$_A$), 2.09 (1H, dd, *J* 14.5, 6.0, C(2)*H*$_B$), 2.87 (1H, sept, *J* 6.6, C*H*Me$_2$), 3.09-3.16 (1H, m, C(3)*H*), 3.56 (2H, AB system, J_{AB} 14.8, NC*H*$_2$Ph), 4.78 (1H, app td, *J* 10.6, 4.3, C(1')*H*), 7.10-7.35 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 18.1 (*C*(4)), 20.1, 21.0 (NCH*Me*$_2$), 21.8 (C(5')*Me*), 24.5 (*C*(3'')), 26.5 (*C*H$_2$), 28.3 (*C*(1'')), 31.3 (*C*(2)), 34.6 (*C*H), 39.6 (*C*H$_2$), 40.9 (*C*H$_2$), 41.7 (*C*(2'')), 48.5 (*C*H), 48.8 (NC*H*$_2$Ph), 49.3 (*C*HMe$_2$), 50.3 (*C*(3)), 74.1 (*C*(1')), 124.9, 125.3, 126.3, 127.8, 128.0, 128.1 (*o*,*m*,*p*-*Ph*), 142.1, 151.9 (*i*-*Ph*), 171.9 (*C*(1)); *m/z* (ESI$^+$) 450 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{44}NO_2^+$ ([M+H]$^+$) requires 450.3367; found 450.3362.

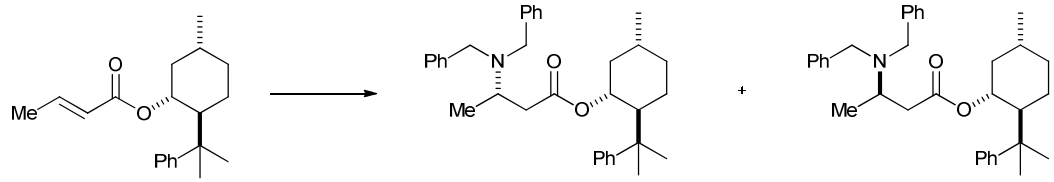
(1'*R*,2'*S*,5'*R*)-2'-(2''-Phenylpropan-2''-yl)-5'-methylcyclohexyl (*S*)-3-(*N*-isopropyl-*N*-benzylamino)-3-phenylpropanoate 123



119 **123**

Following *General Procedure 5*, **119** (60 mg, 0.14 mmol) was reacted with K_2CO_3 (196 mg, 1.42 mmol) in BnBr (0.17 mL, 1.42 mmol). Purification *via* flash column chromatography (gradient elution, 1%→10% Et$_2$O in 30-40 °C petrol) gave **123** as a colourless oil containing trace amounts of an unidentified impurity (58 mg, 80%, >99:1 dr); ν_{max} 2961, 2925 (C–H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 0.51-1.12 (3H, m, C*H*$_2$, C*H*), 0.78 (3H, d, *J* 6.3, C(5')*Me*), 0.86 (3H, d, *J* 6.6, NCH*Me*$_A$), 1.03 (3H, d, *J* 6.6, NCH*Me*$_B$), 1.18 (3H, s, C(1'')*H*$_3$), 1.24 (3H, s, C(3'')*H*$_3$), 1.27-1.73 (4H, m, 2 × C*H*$_2$), 1.87-1.95 (1H, m, C*H*), 2.03 (1H, dd, *J* 14.4, 10.4, C(2)*H*$_A$), 2.33 (1H, dd, *J* 14.4, 4.8, C(2)*H*$_B$), 2.96 (1H, sept, *J* 6.6, C*H*Me$_2$), 3.66 (2H, AB system, J_{AB} 15.4, NC*H*$_2$Ph), 4.14 (1H, dd, *J* 10.4, 4.8, C(3)*H*), 4.65 (1H, app td, *J* 10.6, 4.3, C(1')*H*), 7.00-7.44 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.8, 20.9 (NCH*Me*$_2$), 21.7 (C(5')*Me*), 24.2 (*C*(3'')), 26.4 (*C*H$_2$), 28.3 (*C*(1'')), 31.1 (*C*H), 34.5 (*C*(2)), 38.4 (*C*H$_2$), 39.5 (*C*(2'')), 41.2 (*C*H$_2$), 48.2 (*C*H), 49.4 (NC*H*$_2$Ph), 50.3 (*C*HMe$_2$), 60.4 (*C*(3)), 74.9 (*C*(1')), 125.1, 125.5, 126.5, 126.9, 127.8, 128.0, 128.2, 128.6, 128.8 (*o*,*m*,*p*-*Ph*), 141.8, 142.2, 151.6 (*i*-*Ph*), 171.4 (*C*(1)); *m/z* (ESI$^+$) 512 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{35}H_{46}NO_2^+$ ([M+H]$^+$) requires 512.3523; found 512.3525.

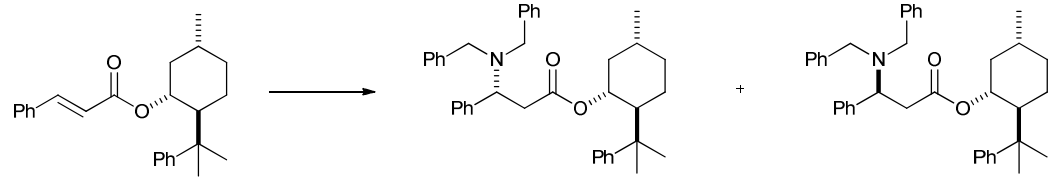
(1'*R*,2'*S*,5'*R*)-2'-(2''-Phenylpropan-2''-yl)-5'-methylcyclohexyl (*S*)-3-(*N*,*N*-dibenzylamino)butanoate 112 and (1'*R*,2'*S*,5'*R*)-2'-(2''-phenylpropan-2''-yl)-5'-methylcyclohexyl (*R*)-3-(*N*,*N*-dibenzylamino)butanoate 114



79 112 114

Following *General Procedure 1*, a solution of dibenzylamine (0.64 mL, 3.33 mmol) in THF (5 mL) at –78 °C was treated with BuLi (2.5 M in hexanes, 1.07 mL, 2.67 mmol) and **79** (500 mg, 1.67 mmol) in THF (5 mL) to give a 78:22 mixture of **112** and **114**. Purification *via* flash column chromatography (gradient elution, 1%→5% Et_2O in 30-40 °C petrol) gave a 37:63 mixture of **112** and **114** as a colourless oil (83mg, 10%). Further elution gave **112** as a colourless oil that crystallised upon standing (208 mg, 25%, >99:1 dr); mp 71-72 °C; $[\alpha]_D^{24}$ +12.6 (*c* 1.0 in $CHCl_3$).

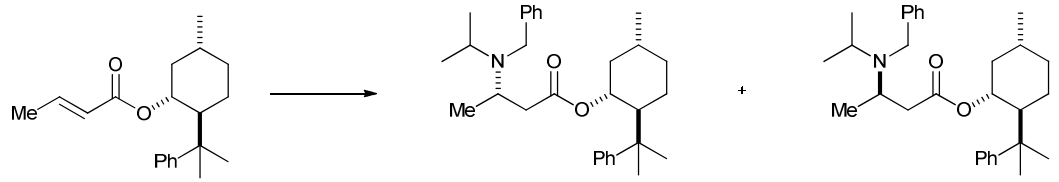
(1'*R*,2'*S*,5'*R*)-2'-(2''-Phenylpropan-2''-yl)-5'-methylcyclohexyl (*R*)-3-(*N*,*N*-dibenzylamino)-3-phenylpropanoate 113 and (1'*R*,2'*S*,5'*R*)-2'-(2''-phenylpropan-2''-yl)-5'-methylcyclohexyl (*S*)-3-(*N*,*N*-dibenzylamino)-3-phenylpropanoate 115



94 113 115

Following *General Procedure 1*, a solution of dibenzylamine (0.32 mL, 1.66 mmol) in THF (3 mL) at –78 °C was treated with BuLi (2.5 M in hexanes, 0.53 mL, 1.33 mmol) and **94** (300 mg, 0.83 mmol) in THF (3 mL) to give a 65:35 mixture of **113** and **115**. Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave a 65:35 mixture of **113** and **115** as a colourless oil (394 mg, 85%).

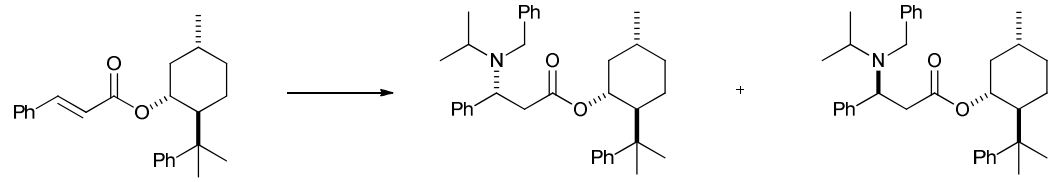
(1'*R*,2'*S*,5'*R*)-2'-(2''-Phenylpropan-2''-yl)-5'-methylcyclohexyl (*S*)-3-(*N*-isopropyl-*N*-benzylamino)butanoate 120 and (1'*R*,2'*S*,5'*R*)-2'-(2''-phenylpropan-2''-yl)-5'-methylcyclohexyl (*R*)-3-(*N*-isopropyl-*N*-benzylamino)butanoate 122



79 120 122

Following *General Procedure 1*, a solution of *N*-benzyl-*N*-isopropylamine (0.56 mL, 3.33 mmol) in THF (5 mL) at –78 °C was treated with BuLi (2.5 M in hexanes, 1.07 mL, 2.67 mmol) and **79** (500 mg, 1.67 mmol) in THF (5 mL) to give a 72:28 mixture of **120** and **122**. Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave an 83:17 mixture of **120** and **122** as a colorless oil (300 mg, 40%). Further elution gave **120** as a colorless oil (68 mg, 9%, >99:1 dr); $[\alpha]_D^{25}$ +22.2 (*c* 0.5 in $CHCl_3$).

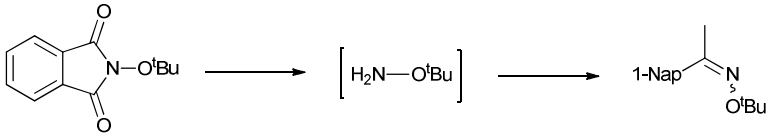
(1'*R*,2'*S*,5'*R*)-2'-(2''-Phenylpropan-2''-yl)-5'-methylcyclohexyl (*R*)-3-(*N*-isopropyl-*N*-benzylamino)-3-phenylpropanoate 121 and (1'*R*,2'*S*,5'*R*)-2'-(2''-phenylpropan-2''-yl)-5'-methylcyclohexyl (*S*)-3-(*N*-isopropyl-*N*-benzylamino)-3-phenylpropanoate 123



94 121 123

Following *General Procedure 1*, a solution of *N*-benzyl-*N*-isopropylamine (0.10 mL, 0.56 mmol) in THF (1 mL) at –78 °C was treated with BuLi (2.5 M in hexanes, 0.17 mL, 0.44 mmol) and **94** (100 mg, 0.28 mmol) in THF (1 mL) to give a 80:20 mixture of **121** and **123**. Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave a 80:20 mixture of **121** and **123** as a colorless oil (112 mg, 78%).

1-Acetylnaphthalene-*O*-*tert*-butyl oxime 149[13]

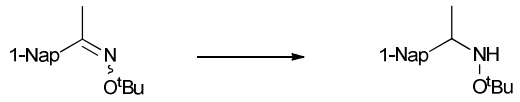


147 148 149

Methylhydrazine (8.83 g, 192 mmol) was added to a solution of *N*-*tert*-butoxyphthalimide **147** (42.0 g, 192 mmol) in CH_2Cl_2 (200 mL). A white precipitate quickly formed. The mixture was stirred at rt for 12 h. A solution of 1-acetylnaphthalene in EtOH (55 mL) and

AcOH (11.5 g, 192 mmol) were added sequentially and the resultant mixture was then heated at reflux for 12 h. The reaction mixture was then allowed to cool to rt and partitioned between 1.0 M aq HCl (200 mL) and CH_2Cl_2 (200 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic extracts were washed with satd aq $NaHCO_3$ (100 mL) and brine (100 mL), then dried and concentrated *in vacuo*. The residue was redissolved in 30-40 °C petrol/Et_2O (v/v 5:1, 100 mL), and filtered through a short plug of silica gel (eluent 30-40 °C petrol/Et_2O). The filtrate was concentrated *in vacuo* to give a 15:1 mixture of **149** (~5:1 mixture of geometrical isomers) and unreacted 1-acetylnaphthalene as a colourless oil (46.3 g). Data for major isomer: δ_H (400 MHz, $CDCl_3$) 1.52 (9H, s, C*Me*$_3$), 2.44 (3H, s, N=C*Me*), 7.52-7.64 (4H, m, *Ar*), 7.86-8.09 (2H, m, *Ar*), 8.25-8.31 (1H, m, *Ar*). Data for minor isomer: δ_H (400 MHz, $CDCl_3$) 1.29 (9H, s, C*Me*$_3$), 2.38 (3H, s, N=C*Me*), 7.52-7.64 (4H, m, *Ar*), 7.86-8.09 (2H, m, *Ar*), 8.25-8.31 (1H, m, *Ar*).

(*RS*)-*N*-[1-(1'-Naphthyl)ethyl]-*O*-*tert*-butylhydroxylamine 60



149 **60**

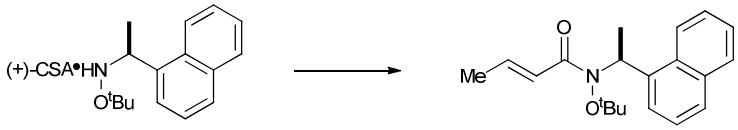
Borane-pyridine complex (*ca.* 8 M in pyridine, 67 mL, 535 mmol) was added dropwise to a solution of **149** (46.3 g) in EtOH (100 mL) at 0 °C. 20% HCl in EtOH (644 mL) was then added dropwise over 1 h, then the resultant mixture was allowed to warm to rt and stirred for a further 1 h. The reaction mixture was made basic by the cautious addition of satd aq K_2CO_3 (100 mL), and the resultant mixture was extracted with CH_2Cl_2 (4 × 100 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give (*RS*)-**60** as a yellow oil (40.3 g); δ_H (400 MHz, $CDCl_3$) 1.22 (9H, s, C*Me*$_3$), 1.57 (3H, d, *J* 6.6, NCH*Me*), 4.89 (1H, q, *J* 6.6, NC*H*Me), 5.16 (1H, br s, N*H*), 7.44-7.56 (3H, m, *Ar*), 7.61 (1H, d, *J* 6.5, *Ar*), 7.78 (1H, d, *J* 8.1, *Ar*), 7.88 (1H, d, *J* 8.5, *Ar*), 8.26 (1H, d, *J* 8.3, *Ar*).

Resolution of (*RS*)-*N*-1-(1'-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine 60

(*RS*)-**60** (40.3 g) was dissolved in acetone (380 mL), (+)-CSA (19.0 g, 81.8 mmol) was added, and the flask was swirled to ensure complete dissolution. The solution was placed under a nitrogen atmosphere, and left at −30 °C over 12 h (seed crystals may be added if available). The resulting fine white needles were collected by rapid filtration under a nitrogen atmosphere, washed with pentane (2 × 30 mL) and dried under high vacuum to give (*S*)-**60**•(+)-CSA (22.0 g). An aliquot of (*S*)-**60**•(+)-CSA was partitioned between 1.0 M aq

NaOH and Et_2O, and the organic layer was then dried and concentrated *in vacuo* to give (*S*)-**60** as a pale yellow oil (90% ee). The bulk material (*S*)-**60**•(+)-CSA was dissolved in boiling acetone (280 mL), placed under a nitrogen atmosphere and left at −30 °C over 12 h. The resulting fine white needles were collected to give (*S*)-**60**•(+)-CSA (19.0 g, 23% from **147**, >98% ee); $[\alpha]_D^{25}$ +65.0 (*c* 1.0 in $CHCl_3$); {lit.[13] $[\alpha]_D^{23}$ +63.2 (*c* 1.1 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, s, *Me*$_A$CMe$_B$), 1.17 (12H, s, C*Me*$_3$, Me$_A$C*Me*$_B$), 1.42-1.23 (1H, m), 1.76-1.68 (1H, m), 1.89 (1H, d, *J* 18.2), 2.01 (3H, d, *J* 6.9, C(1)*Me*), 2.01-2.10 (2H, m), 2.36 (1H, app dt, *J* 18.2, 3.8), 2.73-2.85 (1H, m), 2.85 (1H, d, *J* 14.8, C*H*$_A$S), 3.37 (1H, d, *J* 14.8, C*H*$_B$S), 5.62 (1H, q, *J* 6.9, C(1)*H*), 7.49-7.59 (3H, m, *Ar*), 7.88 (2H, app d, *J* 8.0, *Ar*), 8.04 (1H, d, *J* 7.2, *Ar*), 8.18 (1H, d, *J* 8.4, *Ar*). The mother liquors and washings from this crystallization were concentrated *in vacuo* and the residue was partitioned between 1.0 M aq NaOH (250 mL) and Et_2O (100 mL). The aqueous layer was extracted with Et_2O (2 × 100 mL) and the combined organic extracts were then dried and concentrated *in vacuo*. The resulting yellow oil was dissolved in acetone (380 mL), (−)-CSA (19.0 g, 81.8 mmol) was added, and the flask was swirled to ensure complete dissolution. Crystallisation as described above gave (*R*)-**60**•(−)-CSA (23.2 g, 97% ee). Recrystallisation from boiling acetone (280 mL) gave (*R*)-**60**•(−)-CSA (22.8 g, 28% from **147**, >98% ee); $[\alpha]_D^{25}$ –64.8 (*c* 1.0 in $CHCl_3$); {lit.[13] $[\alpha]_D^{24}$ –63.0 (*c* 1.1 in $CHCl_3$)}; Basification of the mother liquors with 1.0 M aq NaOH and extraction with Et_2O gave a yellow oil (20.0 g). A further crystallisation with (+)-CSA (6.75 g, 29.1 mmol) in acetone (130 mL), and recrystallisation gave a second crop of (*S*)-**60**•(+)-CSA (1.53 g, 2% from **147**, >98% ee). Similarly, a second crop of (*R*)-**60**•(−)-CSA was obtained (1.62 g, 2% from **147**, >98% ee).

(*S*)-*N*-*tert*-Butoxy-*N*-1'-(1''-naphthyl)ethyl (*E*)-but-2-enamide 150

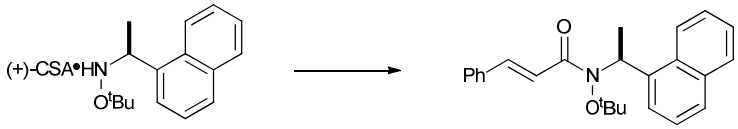


(*S*)-**60**•(+)-CSA **150**

K_2CO_3 (5.80 g, 42.0 mmol) and crotonoyl chloride (1.00 mL, 10.5 mmol) were added sequentiallly to a stirred solution of (*S*)-**60**•(+)-CSA (2.00 g, 4.20 mmol) in CH_2Cl_2 (40 mL) at rt. The resultant mixture was stirred at rt for 12 h then quenched with H_2O (40 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL) and the combined organic extracts were washed with brine (40 mL), then dried and concentrated *in vacuo*. Purification *via*

flash column chromatography (gradient elution, 1%→20% Et_2O in 30-40 °C petrol) gave **150** as a colourless oil that crystallised upon standing (1.15g, 88%); $C_{20}H_{25}NO_2$ requires C, 77.1; H, 8.1; N, 4.5%; found C, 77.0; H, 8.2; N, 4.4%; mp 68-70 °C; $[\alpha]_D^{24}$ –87.6 (*c* 1.0 in $CHCl_3$); ν_{max} 2979, 2937, 2913 (C–H), 1657 (C=O), 1624 (C=C); δ_H (250 MHz, PhMe-d_8, 343 K) 0.69 (9H, s, C*Me*$_3$), 1.55 (3H, dd, *J* 6.7, 1.5, C(4)*H*$_3$), 1.68 (3H, d, *J* 7.0, C(1')*Me*), 6.35-6.56 (1H, br m, C(1')*H*), 6.63 (1H, dq, *J* 15.2, 1.5, C(2)*H*), 7.03-7.29 (3H, m, C(3)*H*, *Ar*), 7.31-7.42 (1H, m, *Ar*), 7.48-7.66 (3H, m, *Ar*), 8.48-8.72 (1H, br m, *Ar*); δ_C (100 MHz, $CDCl_3$) 16.2 (C(1')*Me*), 18.4 (*C*(4)), 27.8 (C*Me*$_3$), 55.4 (*C*(1')), 82.6 (*C*Me$_3$), 123.3 (*C*(3)), 126.5 (*C*(2)), 124.1, 124.2, 124.4, 124.9, 125.6, 126.0, 128.6, 133.6, 136.4, 142.9 (*Ar*), 173.7 (*C*(1)); *m/z* (ESI$^+$) 334 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{25}NNaO_2^+$ ([M+Na]$^+$) requires 334.1778; found 334.1780.

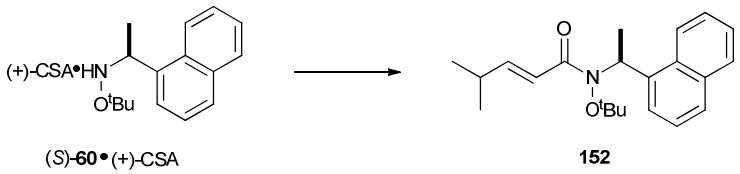
(*S*)-*N*-*tert*-Butoxy-*N*-1'-(1''-naphthyl)ethyl (*E*)-3-phenylpropanamide 151



(*S*)-**60**•(+)-CSA **151**

K_2CO_3 (5.80 g, 42.0 mmol) and cinnamoyl chloride (1.76 g, 10.5 mmol) were added sequentiallly to a stirred solution of (*S*)-**60**•(+)-CSA (2.00 g, 4.20 mmol) in CH_2Cl_2 (40 mL) at rt. The resultant mixture was stirred at rt for 12 h then quenched with H_2O (40 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL) and the combined organic extracts were washed with brine (40 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 1%→20% Et_2O in 30-40 °C petrol) gave **151** as a colourless oil that crystallised upon standing (1.47g, 94%); mp 85-86 °C; $[\alpha]_D^{17}$ –44.5 (*c* 1.0 in $CHCl_3$); ν_{max} 2975, 2932 (C–H), 1648 (C=O), 1623 (C=C); δ_H (250 MHz, PhMe-d_8, 343 K) 0.73 (9H, s, C*Me*$_3$), 1.73 (3H, d, *J* 6.7, C(1')*Me*), 6.47-6.64 (1H, br m, C(1')*H*), 7.05-7.15 (2H, m, *Ar*), 7.18-7.45 (7H, m, C(2)*H*, *Ar*), 7.53-7.66 (3H, m, *Ar*), 7.92 (1H, d, *J* 15.8, C(3)*H*), 8.56-8.76 (1H, br m, *Ar*); δ_C (100 MHz, $CDCl_3$) 16.4 (C(1')*Me*), 27.8 (C*Me*$_3$), 55.6 (*C*(1')), 83.1 (*C*Me$_3$), 118.8 (*C*(3)), 126.6 (*C*(2)), 124.5, 124.9, 125.7, 126.1, 128.0, 128.6, 128.9, 129.9, 133.7, 135.4, 143.3 (*Ar*), 173.8 (*C*(1)); *m/z* (ESI$^+$) 396 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{27}NNaO_2^+$ ([M+Na]$^+$) requires 396.1934; found 396.1932.

(*S*)-*N*-*tert*-Butoxy-*N*-1'-(1''-naphthyl)ethyl (*E*)-4-methyl-pent-2-enamide 152

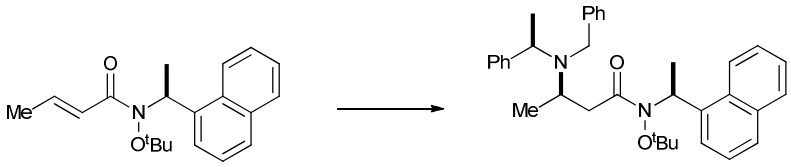


(*S*)-**60**•(+)-CSA **152**

Step 1: MeMgBr (3.0 M in Et_2O, 30.7 mL, 92.2 mmol) was added dropwise to a stirred solution of isobutyraldehyde (23.3 g, 92.2 mmol) in THF (500 mL) at 0 °C and the resultant mixture was stirred for 30 min. Freshly distilled isobutyraldehyde (9.26 mL, 101 mmol) was then added dropwise and the reaction mixture was heated at reflux for 2.5 h. The reaction mixture was then cooled to 0 °C, quenched with satd aq NH_4Cl (100 mL) and extracted with Et_2O (3 × 200 mL). The combined organic extracts were washed with brine (200 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 1%→5% Et_2O in 30-40 °C petrol) gave **156** as a clourless oil (14.1g, 90%);[14] δ_H (400 MHz, $CDCl_3$) 1.06 (6H, d, *J* 6.8, CH*Me*$_2$), 1.49 (9H, s, C*Me*$_3$), 2.38-2.50 (1H, m, C(4)*H*), 5.69 (1H, dd, *J* 15.7, 1.4, C(2)*H*), 6.85 (1H, dd, *J* 15.7, 6.5, C(3)*H*).

Step 2: Following *General Procedure 2*, a solution of **156** (3.00 g, 17.6 mmol) in CH_2Cl_2 (30 mL) was treated with TFA (30 mL) to give a pale yellow oil (1.68 g). Then, following *General Procedure 3*, a solution of the residue (380 mg, 3.33 mmol) in CH_2Cl_2 (4 mL) was reacted with $(COCl)_2$ (0.28 mL, 3.33 mmol) and a mixture of (*S*)-**60**•(+)-CSA (1.59 g, 3.33 mmol) and K_2CO_3 (4.60 g, 33.3 mmol) in CH_2Cl_2 (30 mL). Purification *via* flash column chromatography (gradient elution, 1%→20% Et_2O in 30-40 °C petrol) gave **152** as a colourless oil (1.26g, 63%); $[\alpha]_D^{25}$ –92.3 (*c* 1.0 in $CHCl_3$); ν_{max} 2970, 2871 (C–H), 1660 (C=O), 1631 (C=C); δ_H (250 MHz, PhMe-d_8, 363 K) 0.73 (9H, s, C*Me*$_3$), 0.89 (6H, d, *J* 6.7, C(4)*Me*$_2$), 1.69 (3H, d, *J* 7.0, C(1')*Me*), 2.20-2.26 (1H, m, C(4)*H*), 6.45 (1H, q, *J* 7.0, C(1')*H*), 6.62 (1H, dd, *J* 15.5, 1.5, C(2)*H*), 7.11-7.26 (3H, m, C(3)*H*, *Ar*), 7.30-7.40 (1H, m, *Ar*), 7.51-7.63 (3H, m, *Ar*), 8.52-8.63 (1H, br m, *Ar*); δ_C (100 MHz, $CDCl_3$) 16.1 (C(1')*Me*), 21.4 (C(4)*Me*$_2$), 27.7 (C*Me*$_3$), 31.2 (*C*(4)), 55.2 (*C*(1')), 82.7 (*C*Me$_3$), 119.0 (*C*(3)), 124.4, 124.8, 125.6, 126.5, 128.5, 129.2, 142.9 (*Ar*), 153.9 (*C*(2)), 174.1 (*C*(1)); *m/z* (ESI$^+$) 362 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{29}NNaO_2^+$ ([M+Na]$^+$) requires 362.2091; found 362.2090.

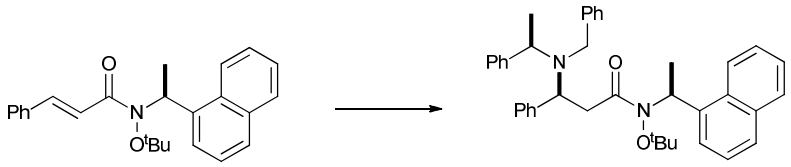
(*S*)-*N*-*tert*-Butoxy-*N*-1'-(1''-naphthyl)ethyl (*R*,*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]butanamide 153



150 153

Following *General Procedure 1*, a solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (101 mg, 0.48 mmol) in THF (1 mL) at –78 °C was treated with BuLi (2.5 M in hexanes, 0.15 mL, 0.39 mmol) and **150** (75 mg, 0.24 mmol) in THF (1 mL) to give **153** in >95:5 dr. Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave **153** as a colorless oil that crystallised upon standing (102 mg, 81%, >99:1 dr); $C_{35}H_{42}N_2O_2$ requires C, 80.4; H, 8.1; N, 5.4%; found C, 80.5; H, 8.2; N, 5.3%; mp 155-158 °C; $[\alpha]_D^{25}$ +33.8 (*c* 0.5 in $CHCl_3$); ν_{max} 2972, 2928 (C–H), 1660 (C=O); δ_H (250 MHz, PhMe-d_8, 343 K) 0.67 (9H, s, C*Me*$_3$), 1.23 (3H, d, *J* 6.4, C(1')*Me*), 1.29 (3H, d, *J* 6.9, C(α)*Me*), 1.59 (3H, d, *J* 7.0, C(4)H_3), 2.30-2.43 (1H, br m, C(2)H_A), 2.48-2.60 (1H, br m, C(2)H_B), 3.66 (2H, AB system, J_{AB} 14.6, NCH_2Ph), 3.88 (1H, q, *J* 6.9, C(α)*H*), 3.80-3.90 (1H, m, C(3)*H*), 6.12-6.26 (1H, br m, C(1')*H*), 6.92-7.40 (13H, m, *Ar*, *Ph*), 7.50-7.63 (3H, m, *Ar*, *Ph*), 8.25-8.39 (1H, br m, *Ar*); δ_C (100 MHz, $CDCl_3$) 14.2 (C(1')*Me*), 18.9 (C(α)*Me*), 19.4 (*C*(4)), 27.8 (C*Me*$_3$), 29.8 (*C*(2)), 39.4 (*C*(α)), 49.7 (*C*(3)), 50.1 (N*C*H$_2$Ph), 58.8 (*C*(1')), 82.3 (*C*Me$_3$), 124.9, 125.5, 126.1, 126.4, 126.5, 126.7, 127.7, 128.2, 128.6, 133.6, 142.4, 144.4 (*Ar*, *Ph*), 186.0 (*C*(1)); *m/z* (ESI$^+$) 523 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{35}H_{43}N_2O_2^+$ ([M+H]$^+$) requires 523.3319; found 523.3320.

(*S*)-*N*-*tert*-Butoxy-*N*-1'-(1''-naphthyl)ethyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanamide 154

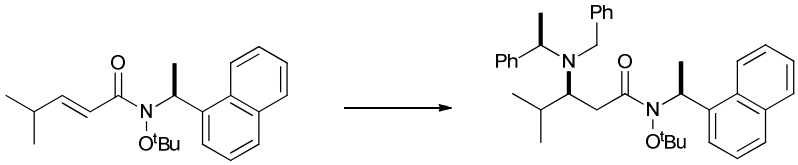


151 154

Following *General Procedure 1*, a solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (114 mg, 0.54 mmol) in THF (1 mL) at –78 °C was treated with BuLi (2.5 M in hexanes, 0.17 mL, 0.43 mmol) and **151** (100 mg, 0.27 mmol) in THF (1 mL) to give **154** in >95:5 dr. Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave **154** as a colorless oil (126 mg, 80%, >95:5 dr); $[\alpha]_D^{25}$ +47.5 (*c* 1.0 in $CHCl_3$);

ν_{max} 3060, 2965, 2934 (C–H), 1659 (C=O); δ_H (500 MHz, PhMe-d_8, 343 K) 0.68 (9H, s, CMe_3), 1.29 (3H, d, *J* 6.9, C(1')*Me*), 1.47 (3H, d, *J* 6.9, C(α)*Me*), 2.71 (1H, br m, C(2)H_A), 3.12 (1H, br m, C(2)H_B), 3.74 (2H, AB system, J_{AB} 14.8, NCH_2Ph), 4.06 (1H, q, *J* 6.9, C(α)*H*), 4.93 (1H, dd, *J* 10.1, 3.8, C(3)*H*), 5.82-6.01 (1H, br m, C(1')*H*), 7.05-7.68 (21H, m, *Ar*, *Ph*), 7.91-8.05 (1H, br m, *Ar*); δ_C (100 MHz, $CDCl_3$) 27.3 (CMe_3), 27.8 (C(1')*Me*), 30.9 (C(α)*Me*), 38.0 (*C*(2)), 51.1 (N*C*H_2Ph), 53.4 (*C*(α)), 56.7 (*C*(3)), 61.6 (*C*(1')), 82.2 (*C*Me$_3$), 125.3, 125.9, 126.2, 126.4, 126.7, 127.0, 127.8, 128.1, 128.6, 133.5, 125.3, 142.7, 144.3 (*Ar*, *Ph*), 176.9 (*C*(1)); *m/z* (ESI$^+$) 585 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{40}H_{45}N_2O_2^+$ ([M+H]$^+$) requires 585.3476; found 585.3481.

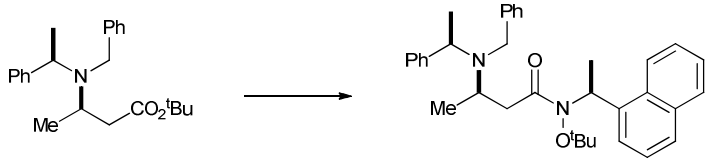
(*S*)-*N*-*tert*-Butoxy-*N*-1'-(1''-naphthyl)ethyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-methyl-pentanamide 155



152 **155**

Following *General Procedure 1*, a solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (187 mg, 0.88 mmol) in THF (2 mL) at –78 °C was treated with BuLi (2.5 M in hexanes, 0.28 mL, 0.70 mmol) and **152** (150 mg, 0.44 mmol) in THF (2 mL) to give **155** in >95:5 dr. Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave **155** as a colorless oil (158 mg, 65%, >95:5 dr); $[\alpha]_D^{25}$ +43.4 (*c* 1.0 in $CHCl_3$); ν_{max} 2974, 2934 (C–H), 1664 (C=O); δ_H (250 MHz, PhMe-d_8, 363 K) 0.73 (9H, s, CMe_3), 1.00 (3H, d, *J* 6.7, C(4)Me_A), 1.17 (3H, d, *J* 6.7, C(4)Me_B), 1.39 (3H, d, *J* 7.3, C(α)*Me*), 1.67 (3H, d, *J* 7.0, C(1')*Me*), 1.66-1.78 (1H, m, C(4)*H*), 2.10-2.17 (1H, br m, C(2)H_A), 2.50 (1H, dd, *J* 17.7, 8.5, C(2)H_B), 3.69 (2H, AB system, J_{AB} 14.9, NCH_2Ph), 3.74-3.87 (2H, m, C(3)*H*, C(α)*H*), 6.11 (1H, q, *J* 7.0, C(1')*H*), 6.93-7.38 (13H, m, *Ar*, *Ph*), 7.39-7.49 (3H, m, *Ar*, *Ph*), 8.20 (1H, d, *J* 8.2, *Ar*); δ_C (100 MHz, $CDCl_3$) 20.2, 20.8 (C(4)Me_2), 25.6 (C(α)*Me*), 27.9 (CMe_3), 32.7 (*C*(4)), 32.9 (C(1')*Me*), 35.0 (*C*(2)), 51.6 (N*C*H_2Ph), 53.5 (*C*(α)), 56.2 (*C*(1')), 57.9 (*C*(3)), 82.1 (*C*Me$_3$), 125.4, 126.0, 126.3, 126.6, 126.9, 128.0, 128.3, 133.6, 141.6 (*Ar*, *Ph*); *m/z* (ESI$^+$) 551 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{37}H_{47}N_2O_2^+$ ([M+H]$^+$) requires 551.3632; found 551.3632.

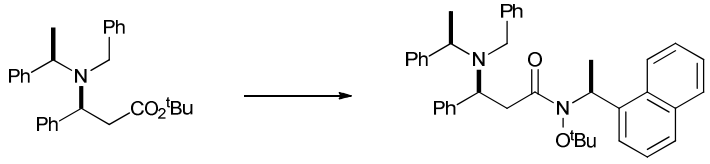
(*S*)-*N*-*tert*-Butoxy-*N*-1'-(1''-naphthyl)ethyl (*R*,*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]butanamide 153



(*R*,*R*)-**102** **153**

Following *General Procedure 2*, a solution of (*R*,*R*)-**102** (1.67 g, 4.72 mmol) in CH_2Cl_2 (16.0 mL) was treated with TFA (16.0 mL) to give a white foam (1.36 g). Then, following *General Procedure 3*, a solution of the residue (156 mg, 0.52 mmol) in CH_2Cl_2 (2 mL) was reacted with $(COCl)_2$ (0.10 mL, 1.04 mmol) and a mixture of (*S*)-**60**•(+)-CSA (100 mg, 0.21 mmol) and K_2CO_3 (290 mg, 2.10 mmol) in CH_2Cl_2 (1 mL). Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave **153** as a colorless oil that crystallised upon standing (18 mg, 16%, >95:5 dr); mp 155-158 °C; $[\alpha]_D^{25}$ +33.9 (*c* 1.0 in $CHCl_3$).

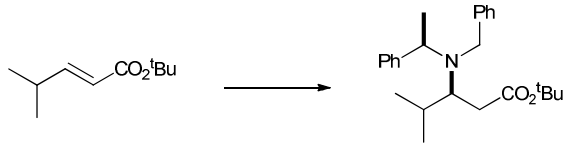
(*S*)-*N*-*tert*-Butoxy-*N*-1'-(1''-naphthyl)ethyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanamide 154



(3*S*,α*R*)-**103** **154**

Following *General Procedure 2*, a solution of (3*S*,α*R*)-**103** (1.72 g, 4.14 mmol) in CH_2Cl_2 (17.0 mL) was treated with TFA (17.0 mL) to give a white foam (1.41 g). Then, following *General Procedure 3*, a solution of the residue (170 mg, 0.47 mmol) in CH_2Cl_2 (2 mL) was reacted with $(COCl)_2$ (80 μL, 0.95 mmol) and a mixture of (*S*)-**60**•(+)-CSA (90 mg, 0.19 mmol) and K_2CO_3 (263 mg, 1.90 mmol) in CH_2Cl_2 (1 mL). Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave **154** as a colorless oil (11 mg, 10%, >95:5 dr); $[\alpha]_D^{23}$ +46.9 (*c* 1.1 in $CHCl_3$).

***tert*-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-methylpentanoate 157**[11]

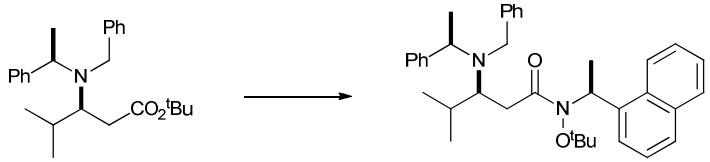


156 (3*S*,α*R*)-**157**

Following *General Procedure 1*, a solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (7.94 g, 37.6 mmol) in THF (80 mL) at –78 °C was treated with BuLi (2.5 M, 14.6 mL, 36.4

mmol) and **156** (4.00 g, 23.5 mmol) to give (3*S*,α*R*)-**157** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 1%→20% Et_2O in 30-40 °C petrol) gave (3*S*,α*R*)-**157** as a pale yellow oil (7.79 g, 87%, >99:1 dr); $[\alpha]_D^{25}$ –2.0 (*c* 1.0 in $CHCl_3$); {lit.[11] $[\alpha]_D^{24}$ –1.9 (*c* 1.4 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, d, *J* 6.9, C(4)*Me*$_A$), 1.11 (3H, d, *J* 6.9, C(4)*Me*$_B$), 1.39 (3H, d, *J* 7.2, C(α)*Me*), 1.41 (9H, s, C*Me*$_3$), 1.66-1.71 (1H, m, C(4)*H*), 1.78 (1H, dd, *J* 16.0, 2.1, C(2)*H*$_A$), 1.96 (1H, dd, *J* 16.0, 9.4, C(2)*H*$_B$), 3.23-3.28 (1H, m, C(3)*H*), 3.61 (2H, AB system, J_{AB} 15.1, NC*H*$_2$Ph), 3.76 (1H, q, *J* 7.2, C(α)*H*), 7.21-7.48 (10H, m, *Ph*).

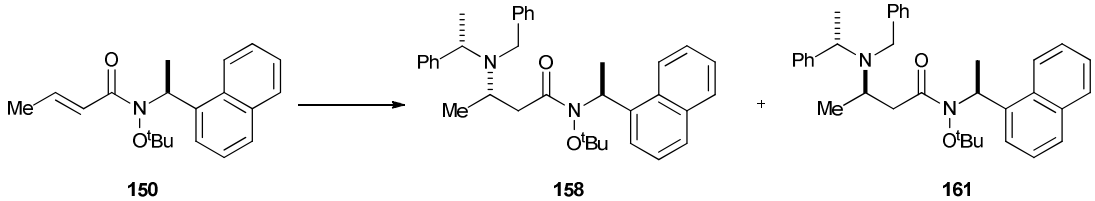
(*S*)-*N*-*tert*-Butoxy-*N*-1'-(1''-naphthyl)ethyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-methyl-pentanamide 155



(3*S*,α*R*)-**157** **155**

Following *General Procedure 2*, a solution of (3*S*,α*R*)-**157** (600 mg, 1.57 mmol) in CH_2Cl_2 (6.0 mL) was treated with TFA (6.0 mL) to give a white foam (512 mg). Then, following *General Procedure 3*, a solution of the residue (342 mg, 1.03 mmol) in CH_2Cl_2 (4 mL) was reacted with $(COCl)_2$ (0.18 mL, 2.06 mmol) and a solution of (*S*)-**60** (100 mg, 0.41 mmol) in CH_2Cl_2 (1 mL). Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave **155** as a colorless oil (22 mg, 10%, >95:5 dr); $[\alpha]_D^{23}$ +43.1 (*c* 1.0 in $CHCl_3$).

(*S*)-*N*-*tert*-Butoxy-*N*-1'-(1''-naphthyl)ethyl (*S*,*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]butanamide 158 and (*S*)-*N*-*tert*-butoxy-*N*-1'-(1''-naphthyl)ethyl (3*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]butanamide 161

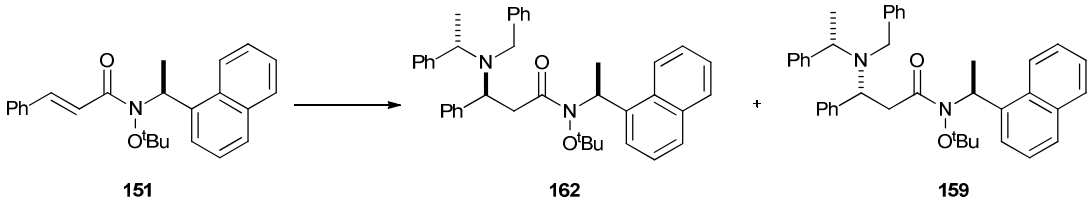


150 **158** **161**

Following *General Procedure 1*, a solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (101 mg, 0.48 mmol) in THF (1 mL) at –78 °C was treated with BuLi (2.5 M in hexanes, 0.15 mL, 0.39 mmol) and **150** (75 mg, 0.24 mmol) in THF (1 mL) to give a 75:25 mixture of **158** and **161**. Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave a 60:40 mixture of **158** and **161** as a colourless oil (38 mg, 30%). Data

for the mixture: ν_{max} 2974, 2932 (C–H), 1658 (C=O); *m/z* (ESI$^+$) 523 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{35}H_{43}N_2O_2^+$ ([M+H]$^+$) requires 523.3319; found 523.3316. Data for **158**: δ_H (250 MHz, PhMe-d_8, 343 K) 0.62 (9H, s, C*Me*$_3$), 1.15 (3H, d, *J* 6.4, C(1')*Me*), 1.33 (3H, d, *J* 7.0, C(α)*Me*), 1.59 (3H, d, *J* 6.7, C(4)*H*$_3$), 2.26-2.41 (1H, br m, C(2)*H*$_A$), 2.50-2.67 (1H, br m, C(2)*H*$_B$), 3.67 (2H, AB system, J_{AB} 14.9, NC*H*$_2$Ph), 3.89 (1H, q, *J* 7.0, C(α)*H*), 3.87-4.01 (1H, m, C(3)*H*), 6.15-6.35 (1H, br m, C(1')*H*), 6.95-7.46 (13H, m, *Ar*, *Ph*), 7.46-7.68 (3H, m, *Ar*, *Ph*), 8.35-8.50 (1H, br m, *Ar*); δ_C (125 MHz, $CDCl_3$) 17.4 (C(1')*Me*), 18.8 (C(α)*Me*), 19.1 (*C*(4)), 27.7 (C*Me*$_3$), 29.7 (*C*(2)), 38.9 (*C*(α)), 49.8 (*C*(3)), 50.1 (N*C*H$_2$Ph), 58.4 (*C*(1')), 82.3 (*C*Me$_3$), 124.8, 125.5, 126.1, 126.3, 126.5, 126.7, 127.7, 127.8, 128.1, 128.2, 128.6, 133.6, 136.2, 142.2, 144.1 (*Ar*, *Ph*), 179.5 (*C*(1)). Data for **161**: δ_H (250 MHz, PhMe-d_8, 343 K) 0.72 (9H, s, C*Me*$_3$), 0.98 (3H, d, *J* 6.4, C(1')*Me*), 1.31 (3H, d, *J* 7.0, C(α)*Me*), 1.68 (3H, d, *J* 6.7, C(4)*H*$_3$), 2.26-2.41 (1H, br m, C(2)*H*$_A$), 2.84-3.02 (1H, br m, C(2)*H*$_B$), 3.68 (2H, AB system, J_{AB} 14.9, NC*H*$_2$Ph), 3.89 (1H, q, *J* 7.0, C(α)*H*), 3.87-4.01 (1H, m, C(3)*H*), 6.15-6.35 (1H, br m, C(1')*H*), 6.95-7.46 (13H, m, *Ar*, *Ph*), 7.46-7.68 (3H, m, *Ar*, *Ph*), 8.35-8.50 (1H, br m, *Ar*); δ_C (125 MHz, $CDCl_3$) 17.4 (C(1')*Me*), 18.4 (C(α)*Me*), 19.1 (*C*(4)), 26.6 (C*Me*$_3$), 29.7 (*C*(2)), 38.9 (*C*(α)), 49.9 (*C*(3)), 50.1 (N*C*H$_2$Ph), 54.9 (*C*(1')), 82.4 (*C*Me$_3$), 124.8, 125.5, 126.1, 126.3, 126.5, 126.7, 127.7, 127.8, 128.1, 128.2, 128.6, 133.6, 136.2, 142.2, 144.1 (*Ar*, *Ph*), 179.5 (*C*(1)). Further elution gave a 90:10 mixture of **158** and **161** as a colourless oil (58 mg, 46%).

(*S*)-*N*-*tert*-Butoxy-*N*-1'-(1''-naphthyl)ethyl (*S*,*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanamide 162 and (*S*)-*N*-*tert*-butoxy-*N*-1'-(1''-naphthyl)ethyl (3*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanamide 159

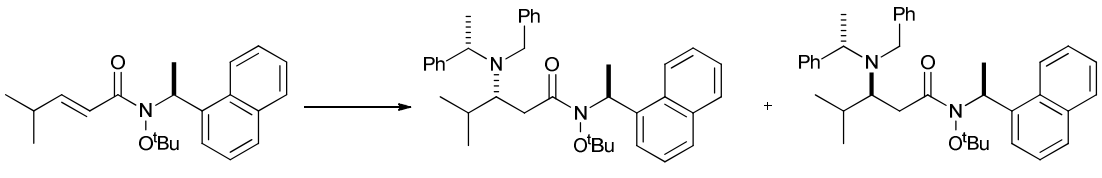


151 162 159

Following *General Procedure 1*, a solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (114 mg, 0.54 mmol) in THF (1 mL) at –78 °C was treated with BuLi (2.5 M in hexanes, 0.17 mL, 0.43 mmol) and **151** (100 mg, 0.27 mmol) in THF (1 mL) to give a 60:40 mixture of **162** and **159**. Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave an 85:15 mixture of **162** and **159** as a colorless oil (28 mg,

18%). Data for the mixture: ν_{max} 2974 (C–H), 1654 (C=O); *m/z* (ESI$^+$) 585 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{40}H_{45}N_2O_2^+$ ([M+H]$^+$) requires 585.3476; found 585.3481. Data for **162**: δ_H (250 MHz, PhMe-d_8, 343 K) 0.71 (9H, s, CMe_3), 1.27 (3H, d, *J* 6.7, C(1')*Me*), 1.48 (3H, d, *J* 7.0, C(α)*Me*), 2.91-3.09 (1H, br m, C(2)H_A), 3.10-3.29 (1H, br m, C(2)H_B), 3.74 (2H, AB system, J_{AB} 15.2, NCH_2Ph), 4.07 (1H, q, *J* 7.0, C(α)*H*), 4.91 (1H, dd, *J* 9.1, 4.9, C(3)*H*), 5.84-6.09 (1H, br m, C(1')*H*), 7.04-7.71 (21H, m, *Ar*, *Ph*), 7.91-8.12 (1H, br m, *Ar*); δ_C (125 MHz, $CDCl_3$) 18.7 (C(1')*Me*), 27.5 (CMe_3), 31.0 (C(α)*Me*), 38.0 (*C*(2)), 50.4 (N*C*H$_2$Ph), 51.2 (*C*(α)), 56.4 (*C*(1')), 57.8 (*C*(3)), 82.4 (*C*Me$_3$), 125.3, 125.9, 126.2, 126.4, 126.7, 127.0, 127.7, 127.8, 128.0, 128.1, 128.2, 128.6, 128.8, 133.5, 141.8, 142.8, 143.9 (*Ar*, *Ph*). Data for **159**: δ_H (250 MHz, PhMe-d_8, 343 K) 0.44 (9H, s, CMe_3), 1.19 (3H, d, *J* 6.7, C(1')*Me*), 1.33 (3H, d, *J* 7.0, C(α)*Me*), 2.40-2.51 (1H, br m, C(2)H_A), 3.25-3.40 (1H, br m, C(2)H_B), 3.70 (2H, AB system, J_{AB} 14.9, NCH_2Ph), 4.03 (1H, q, *J* 7.0, C(α)*H*), 4.95 (1H, dd, *J* 11.2, 3.1, C(3)*H*), 6.26 (1H, q, *J* 7.0, C(1')*H*), 7.04-7.62 (21H, m, *Ar*, *Ph*), 8.51 (1H, d, *J* 8.2, Ar); δ_C (125 MHz, $CDCl_3$) 15.2 (C(1')*Me*), 27.5 (CMe_3), 27.8 (C(α)*Me*), 37.8 (*C*(2)), 51.2 (N*C*H$_2$Ph), 54.0 (*C*(α)), 56.4 (*C*(3)), 61.6 (*C*(1')), 82.3 (*C*Me$_3$), 124.4, 124.7, 125.6, 126.0, 126.3, 126.4, 126.7, 127.1, 127.7, 128.0, 128.1, 128.2, 128.4, 128.6, 128.9, 129.9, 132.4, 133.5, 136.3, 142.5, 144.0 (*Ar*, *Ph*). Further elution gave a 50:50 mixture of **162** and **159** as a colourless oil (63 mg, 40%).

(*S*)-*N*-*tert*-Butoxy-*N*-1'-(1''-naphthyl)ethyl (3*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-methyl-pentanamide 160 and (*S*)-*N*-*tert*-Butoxy-*N*-1'-(1''-naphthyl)ethyl (*S*,*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-methyl-pentanamide 163

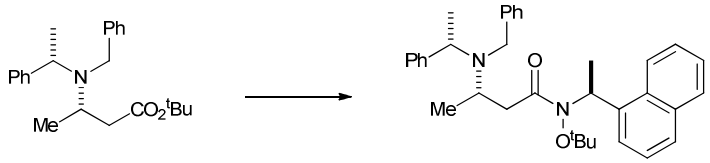


152 160 163

Following *General Procedure 1*, a solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (187 mg, 0.88 mmol) in THF (2 mL) at –78 °C was treated with BuLi (2.5 M in hexanes, 0.28 mL, 0.70 mmol) and **152** (150 mg, 0.44 mmol) in THF (2 mL) to give a 65:35 mixture of **160** and **163**. Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave **160** as a colorless oil (40 mg, 17%, >95:5 dr); $[\alpha]_D^{25}$ +14.6 (*c* 0.5 in $CHCl_3$); ν_{max} 2972, 2874 (C–H), 1661 (C=O); δ_H (250 MHz, PhMe-d_8, 363 K) 0.56

(9H, s, C*Me*$_3$), 0.84 (3H, d, *J* 6.7, C(4)*Me*$_A$), 1.15 (3H, d, *J* 6.7, C(4)*Me*$_B$), 1.46 (3H, d, *J* 7.3, C(α)*Me*), 1.61 (3H, d, *J* 7.0, C(1')*Me*), 1.58-1.69 (1H, m, C(4)*H*), 1.86 (1H, dd, *J* 17.1, 1.2, C(2)*H*$_A$), 2.62 (1H, dd, *J* 17.1, 9.1, C(2)*H*$_B$), 3.68 (2H, AB system, J_{AB} 14.6, NC*H*$_2$Ph), 3.78-3.91 (2H, m, C(3)*H*, C(α)*H*), 6.33 (1H, q, *J* 7.0, C(1')*H*), 6.94-7.42 (13H, m, *Ar*, *Ph*), 7.43-7.66 (3H, m, *Ar*, *Ph*), 8.52 (1H, d, *J* 8.5, *Ar*); δ_C (125 MHz, $CDCl_3$) 15.4, 19.7 (C(4)*Me*$_2$), 20.9 (C(α)*Me*), 27.8 (C*Me*$_3$), 30.9 (*C*(4)), 32.6 (C(1')*Me*), 34.8 (*C*(2)), 51.4 (N*C*H$_2$Ph), 54.3 (*C*(α)), 56.2 (*C*(1')), 56.8 (*C*(3)), 82.3 (*C*Me$_3$), 125.6, 126.2, 126.7, 127.9, 128.3, 129.0, 132.6, 133.6, 136.4, 141.4 (*Ar*, *Ph*), 179.3 (*C*(1)). Further elution gave a 68:32 mixture of **160** and **163** (61 mg, 25%). Data for the mixture: ν_{max} 2972, 2874 (C–H), 1661 (C=O); *m/z* (ESI$^+$) 551 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{37}H_{47}N_2O_2^+$ ([M+H]$^+$) requires 551.3632; found 551.3637. Data for **163**: δ_H (250 MHz, PhMe-d_8, 363 K) 0.89 (9H, s, C*Me*$_3$), 0.81 (3H, d, *J* 6.7, C(4)*Me*$_A$), 0.87 (3H, d, *J* 6.7, C(4)*Me*$_B$), 1.22 (3H, d, *J* 7.3, C(α)*Me*), 1.74 (3H, d, *J* 7.0, C(1')*Me*), 1.50-1.64 (1H, m, C(4)*H*), 2.58 (1H, dd, *J* 17.1, 7.0, C(2)*H*$_A$), 2.82 (1H, dd, *J* 17.1, 2.4, C(2)*H*$_B$), 3.65 (2H, AB system, J_{AB} 14.0, NC*H*$_2$Ph), 3.56-3.67 (1H, m, C(3)*H*), 3.89 (1H, q, *J* 7.3, C(α)*H*), 6.21 (1H, q, *J* 7.0, C(1')*H*), 6.94-7.38 (13H, m, *Ar*, *Ph*), 7.43-7.73 (3H, m, *Ar*, *Ph*), 8.30 (1H, d, *J* 8.5, *Ar*); δ_C (125 MHz, $CDCl_3$) 15.4, 19.5 (C(4)*Me*$_2$), 20.4 (C(α)*Me*), 28.0 (C*Me*$_3$), 29.4 (*C*(4)), 32.8 (C(1')*Me*), 35.7 (*C*(2)), 51.7 (N*C*H$_2$Ph), 54.3 (*C*(α)), 56.2 (*C*(1')), 56.8 (*C*(3)), 82.4 (*C*Me$_3$), 125.6, 126.3, 126.7, 127.8, 128.4, 129.0, 132.7, 133.6, 136.4, 141.4 (*Ar*, *Ph*), 179.4 (*C*(1)).

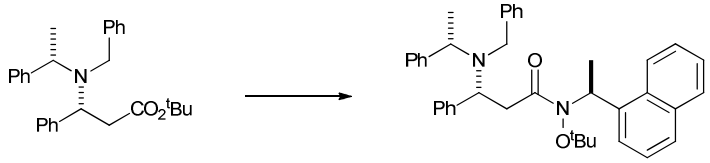
(*S*)-*N*-*tert*-Butoxy-*N*-1'-(1''-naphthyl)ethyl (*S*,*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]butanamide 158



(*S*,*S*)-**102** **158**

Following *General Procedure 2*, a solution of (*S*,*S*)-**102** (1.75 g, 4.95 mmol) in CH_2Cl_2 (17.0 mL) was treated with TFA (17.0 mL) to give a white foam (1.32 g). Then, following *General Procedure 3*, a solution of the residue (156 mg, 0.52 mmol) in CH_2Cl_2 (2 mL) was reacted with $(COCl)_2$ (0.10 mL, 1.04 mmol) and a mixture of (*S*)-**60**•(+)-CSA (100 mg, 0.21 mmol) and K_2CO_3 (290 mg, 2.10 mmol) in CH_2Cl_2 (1 mL). Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave **158** as a colorless oil (16 mg, 15%, >95:5 dr); $[\alpha]_D^{25}$ −51.2 (*c* 0.5 in $CHCl_3$).

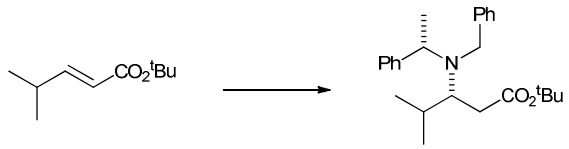
(*S*)-*N*-*tert*-butoxy-*N*-1'-(1''-naphthyl)ethyl (3*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanamide 159



(3*R*,α*S*)-**103** **159**

Following *General Procedure 2*, a solution of (3*R*,α*S*)-**103** (1.66 g, 3.99 mmol) in CH_2Cl_2 (16.0 mL) was treated with TFA (16.0 mL) to give a white foam (1.32 g). Then, following *General Procedure 3*, a solution of the residue (187 mg, 0.52 mmol) in CH_2Cl_2 (2 mL) was reacted with $(COCl)_2$ (0.10 mL, 1.04 mmol) and a mixture of (*S*)-**60**•(+)-CSA (100 mg, 0.21 mmol) and K_2CO_3 (290 mg, 2.10 mmol) in CH_2Cl_2 (1 mL). Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave **159** as a colorless oil containing trace amounts of impurity (15 mg, 12%, >95:5 dr).

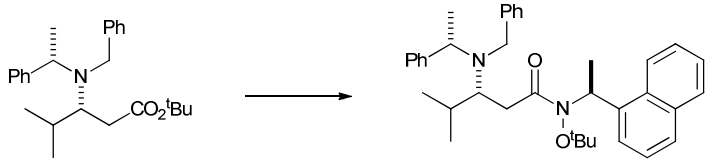
***tert*-Butyl (3*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-methylpentanoate 157**[11]



156 (3*R*,α*S*)-**157**

Following *General Procedure 1*, a solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (1.99 g, 9.40 mmol) in THF (20 mL) at –78 °C was treated with BuLi (2.35 M, 3.87 mL, 9.10 mmol) and **156** (1.00 g, 5.87 mmol) to give (3*R*,α*S*)-**157** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 1%→20% Et_2O in 30-40 °C petrol) gave (3*R*,α*S*)-**157** as a pale yellow oil (1.93 g, 86%, >99:1 dr); $[\alpha]_D^{25}$ +1.92 (*c* 1.0 in $CHCl_3$); {lit.[11] $[\alpha]_D^{24}$ +1.9 (*c* 1.1 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, d, *J* 6.9, C(4)*Me*$_A$), 1.11 (3H, d, *J* 6.9, C(4)*Me*$_B$), 1.39 (3H, d, *J* 7.2, C(α)*Me*), 1.41 (9H, s, C*Me*$_3$), 1.66-1.71 (1H, m, C(4)*H*), 1.78 (1H, dd, *J* 16.0, 2.1, C(2)*H*$_A$), 1.96 (1H, dd, *J* 16.0, 9.4, C(2)*H*$_B$), 3.23-3.28 (1H, m, C(3)*H*), 3.61 (2H, AB system, J_{AB} 15.1, NC*H*$_2$Ph), 3.76 (1H, q, *J* 7.2, C(α)*H*), 7.21-7.48 (10H, m, *Ph*).

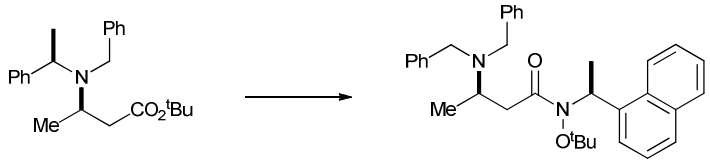
(*S*)-*N*-*tert*-Butoxy-*N*-1'-(1''-naphthyl)ethyl (3*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-methyl-pentanamide 160



(3*R*,α*S*)-**157** **160**

Following *General Procedure 2*, a solution of (3*R*,α*S*)-**157** (1.85 g, 4.85 mmol) in CH_2Cl_2 (19.0 mL) was treated with TFA (19.0 mL) to give a white foam (1.58 g). Then, following *General Procedure 3*, a solution of the residue (342 mg, 1.03 mmol) in CH_2Cl_2 (4 mL) was reacted with $(COCl)_2$ (0.18 mL, 2.06 mmol) and a solution of (*S*)-**60** (100 mg, 0.41 mmol) in CH_2Cl_2 (1 mL). Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave **160** as a colorless oil (27 mg, 12%, >95:5 dr); $[\alpha]_D^{23}$ +14.5 (*c* 1.0 in $CHCl_3$).

(*S*)-*N*-*tert*-Butoxy-*N*-1'-(1''-naphthyl)ethyl (*R*)-3-(*N*,*N*-dibenzylamino)butanamide 164



(*R*,*R*)-**102** **164**

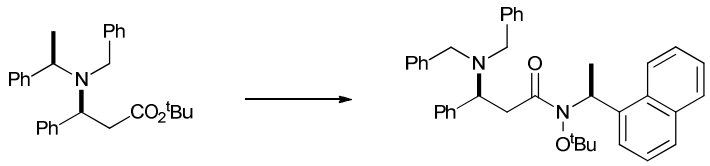
Step 1: Following *General Procedure 4*, reacting (*R*,*R*)-**102** (5.27 g, 14.9 mmol) and $Pd(OH)_2/C$ (1.32 g) in MeOH (50 mL) under H_2 (5 atm) for 36 h gave *tert*-butyl (*R*)-3-aminobutanoate as a colourless oil (1.48 g, 62%); $[\alpha]_D^{23}$ −22.0 (*c* 1.0 in $CHCl_3$); {lit.[15] $[\alpha]_D^{25}$ −22.2 (*c* 0.5 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.13 (3H, d, *J* 6.5, C(4)H_3), 1.46 (9H, s, CMe_3), 1.85 (2H, br s, NH_2), 2.23 (1H, dd, *J* 15.4, 8.2, C(2)H_A), 2.34 (1H, dd, *J* 15.4, 4.8, C(2)H_B), 3.31-3.40 (1H, m, C(3)*H*).

Step 2: Following *General Procedure 5*, *tert*-butyl (*R*)-3-aminobutanoate (740 mg, 4.65 mmol) was reacted with K_2CO_3 (6.43 g, 46.5 mmol) in BnBr (5.50 mL, 46.5 mmol). Purification *via* flash column chromatography (gradient elution, 1%→20% Et_2O in 30-40 °C petrol) gave *tert*-butyl (*R*)-3-(*N*,*N*-dibenzylamino)butanoate as a colourless oil that crystallised upon standing (1.02 g, 64%); mp 42-45 °C; $[\alpha]_D^{25}$ −12.3 (*c* 1.0 in $CHCl_3$); ν_{max} 2974, 2933 (C–H), 1727 (C=O); δ_H (400 MHz, $CDCl_3$) 1.20 (3H, d, *J* 6.8, C(4)H_3), 1.54 (9H, s, CMe_3), 2.29 (1H, dd, *J* 13.9, 7.8, C(2)H_A), 2.70 (1H, dd, *J* 13.9, 6.6, C(2)H_B), 3.37-3.47 (1H, m, C(3)*H*), 3.66 (4H, AB system, J_{AB} 13.6, N(CH_2Ph)$_2$), 7.25-7.58 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.8 (*C*(4)), 28.3 (CMe_3), 40.1 (*C*(2)), 51.1 (*C*(3)), 53.6, 69.8

(N(CH_2Ph)$_2$), 80.1 (CMe_3), 126.9, 128.2, 128.4, 128.7, 128.9, 135.4 (*o,m,p-Ph*), 140.2, 155.1 (*i-Ph*), 171.9 (*C*(1)); *m/z* (ESI$^+$) 340 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{30}NO_2^+$ ([M+H]$^+$) requires 340.2271; found 340.2270.

Step 3: Following *General Procedure 2*, a solution of *tert*-butyl (*R*)-3-(*N*,*N*-dibenzylamino)butanoate (600 mg, 1.77 mmol) in CH_2Cl_2 (6.0 mL) was treated with TFA (6.0 mL) to give a white foam (501 mg). Then, following *General Procedure 3*, a solution of the residue (298 mg, 1.05 mmol) in CH_2Cl_2 (3 mL) was reacted with $(COCl)_2$ (0.18 mL, 2.10 mmol) and a mixture of (*S*)-**60**•(+)-CSA (200 mg, 0.42 mmol) and K_2CO_3 (580 mg, 4.20 mmol) in CH_2Cl_2 (2 mL). Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave **164** as a colorless oil containing trace amounts of impurity (24 mg, 11%, >95:5 dr); ν_{max} 2973, 2928 (C–H), 1660 (C=O); δ_H (500 MHz, PhMe-d_8, 343 K) 0.78 (9H, s, CMe_3), 1.15 (3H, d, *J* 6.6, C(1')*Me*), 1.64 (3H, d, *J* 6.6, C(4)H_3), 2.43 (1H, dd, *J* 15.1, 9.1, C(2)H_A), 3.00 (1H, dd, *J* 15.1, 3.5, C(2)H_B), 3.53 (4H, AB system, J_{AB} 13.9, N(CH_2Ph)$_2$), 3.59-3.65 (1H, m, C(3)*H*), 6.19 (1H, q, *J* 6.6, C(1')*H*), 6.89-7.36 (13H, m, *Ar*, *Ph*), 7.47-7.63 (3H, m, *Ar*, *Ph*), 8.28-8.39 (1H, br m, *Ar*); δ_C (125 MHz, $CDCl_3$) 14.4 (C(1')*Me*), 15.7 (*C*(4)), 27.7 (CMe_3), 29.8 (*C*(2)), 38.1 (*C*(3)), 50.5 (*C*(1')), 53.7 (N(CH_2Ph)$_2$), 82.4 (CMe_3), 124.1, 125.5, 126.2, 126.4, 126.7, 128.2, 128.5, 128.7, 129.0, 133.6, 140.3 (*Ar*, *Ph*), 179.4 (*C*(1)); *m/z* (ESI$^+$) 509 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{34}H_{41}N_2O_2^+$ ([M+H]$^+$) requires 509.3163; found 509.3164.

(*S*)-*N*-*tert*-Butoxy-*N*-1'-(1''-naphthyl)ethyl (*S*)-3-(*N*,*N*-dibenzylamino)-3-phenylpropanamide 165



(3*S*,α*R*)-**103** **165**

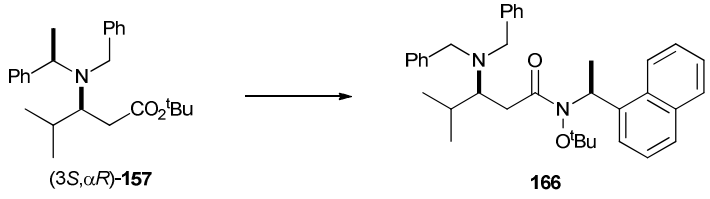
Step 1: Following *General Procedure 4*, reacting (3*S*,α*R*)-**103** (6.70 g, 16.1 mmol) and $Pd(OH)_2$/C (1.70 g) in MeOH (65 mL) under H_2 (5 atm) for 36 h gave *tert*-butyl (*S*)-3-amino-3-phenylpropanoate as a colourless oil (2.48 g, 72%); $[\alpha]_D^{23}$ −22.0 (*c* 1.0 in $CHCl_3$); {lit.[16] $[\alpha]_D^{20}$ −21.0 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.43 (9H, s, CMe_3), 1.71 (2H, br s, NH_2), 2.59 (2H, d, *J* 7.2, C(2)H_2), 4.38 (1H, app t, *J* 6.8, C(3)*H*), 7.24-7.40 (5H, m, *Ph*).

Step 2: Following *General Procedure 5*, *tert*-butyl (*S*)-3-amino-3-phenylpropanoate (1.20 g, 5.42 mmol) was reacted with K_2CO_3 (7.50 g, 54.2 mmol) in BnBr (6.46 mL, 54.2 mmol).

Purification *via* flash column chromatography (gradient elution, 1%→20% Et_2O in 30-40 °C petrol) gave *tert*-butyl (*S*)-3-(*N*,*N*-dibenzylamino)-3-phenylpropanoate as a white solid (1.54 g, 71%); mp 64-67 °C; {lit.[17] mp 64-66 °C}; $[\alpha]_D^{25}$ −78.4 (*c* 2.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.34 (9H, s, C*Me*$_3$), 2.72 (1H, dd, *J* 14.3, 8.5, C(2)*H*$_A$), 3.00 (1H, dd, *J* 14.3, 6.8, C(2)*H*$_B$), 3.50 (4H, AB system, J_{AB} 13.7, N(C*H*$_2$Ph)$_2$), 4.28 (1H, app t, *J* 7.2, C(3)*H*), 7.18-7.40 (15H, m, *Ph*).

Step 3: Following *General Procedure 2*, a solution of *tert*-butyl (*S*)-3-(*N*,*N*-dibenzylamino)-3-phenylpropanoate (938 mg, 2.34 mmol) in CH_2Cl_2 (10.0 mL) was treated with TFA (10.0 mL) to give a white foam (703 mg). Then, following *General Procedure 3*, a solution of the residue (363 mg, 1.05 mmol) in CH_2Cl_2 (4 mL) was reacted with $(COCl)_2$ (0.18 mL, 2.10 mmol) and a mixture of (*S*)-**60**•(+)-CSA (200 mg, 0.42 mmol) and K_2CO_3 (580 mg, 4.20 mmol) in CH_2Cl_2 (2 mL). Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave **165** as a colorless oil containing trace amounts of impurity (26 mg, 10%, >95:5 dr); ν_{max} 2977 (C–H), 1659 (C=O); δ_H (250 MHz, PhMe-d_8, 343 K) 0.75 (9H, s, C*Me*$_3$), 1.54 (3H, d, *J* 7.0, C(1')*Me*), 3.12-3.28 (2H, br m, C(2)*H*$_2$), 3.56 (4H, AB system, J_{AB} 14.0, N(C*H*$_2$Ph)$_2$), 4.78 (1H, app t, *J* 7.3, C(3)*H*), 5.98-6.19 (1H, br m, C(1')*H*), 7.10-7.68 (21H, m, *Ar*, *Ph*), 8.05-8.22 (1H, br m, *Ar*); δ_C (100 MHz, $CDCl_3$) 28.0 (C*Me*$_3$), 36.0 (C(1')*Me*), 53.5 (*C*(1')), 54.5 (*C*(2)), 54.7(N(*C*H$_2$Ph)$_2$), 54.8 (*C*(3)), 82.3 (*C*Me$_3$), 125.5, 126.1, 126.4, 127.0, 127.2, 128.0, 128.3, 128.4, 128.8, 128.9, 133.6, 139.3, 140.1, 140.3 (*Ar*, *Ph*); *m/z* (ESI$^+$) 571 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{39}H_{43}N_2O_2^+$ ([M+H]$^+$) requires 571.3319; found 571.3316.

(*S*)-*N*-*tert*-Butoxy-*N*-1'-(1''-naphthyl)ethyl (*S*)-3-(*N*,*N*-dibenzylamino)pentanamide 166



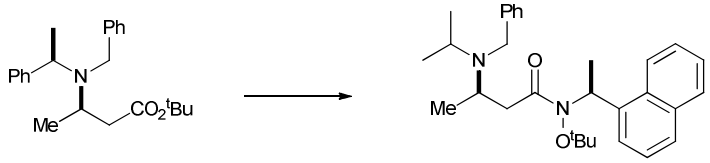
Step 1: Following *General Procedure 4*, reacting (3*S*,α*R*)-**157** (7.20 g, 18.9 mmol) and $Pd(OH)_2$/C (1.80 g) in MeOH (72 mL) under H_2 (5 atm) for 36 h gave *tert*-butyl (*S*)-3-amino-4-methylpentanoate as a colourless oil (2.82 g, 80%); $[\alpha]_D^{23}$ −26.2 (*c* 1.0 in $CHCl_3$); {lit.[11] $[\alpha]_D^{20}$ −25.8 (*c* 3.4 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 0.91 (3H, d, *J* 4.1, C(4)*Me*$_A$), 0.92 (3H, d, *J* 4.1, C(4)*Me*$_B$), 1.30 (2H, br s, N*H*$_2$), 1.46 (9H, s, C*Me*$_3$), 1.57-1.66(1H, m,

C(4)*H*), 2.15 (1H, dd, *J* 15.7, 9.9, C(2)H_A), 2.39 (1H, dd, *J* 15.7, 3.8, C(2)H_B), 2.96-3.02 (1H, m, C(3)*H*).

Step 2: Following *General Procedure 5*, *tert*-butyl (*S*)-3-amino-4-methylpentanoate (1.35 g, 7.21 mmol) was reacted with K_2CO_3 (9.96 g, 72.1 mmol) in BnBr (8.60 mL, 72.1 mmol). Purification *via* flash column chromatography (gradient elution, 1%→20% Et_2O in 30-40 °C petrol) gave *tert*-butyl (*S*)-3-(*N*,*N*-dibenzylamino)-4-methylpentanoate as a white solid (2.39 g, 91%); mp 63-64 °C; $[\alpha]_D^{25}$ +10.0 (*c* 1.0 in $CHCl_3$); ν_{max} 2977, 2932 (C–H), 1727 (C=O); δ_H (400 MHz, $CDCl_3$) 0.91 (3H, d, *J* 6.8, C(4)*Me*$_A$), 1.07 (3H, d, *J* 6.8, C(4)*Me*$_B$), 1.53 (9H, s, C*Me*$_3$), 1.86-1.96 (1H, m, C(4)*H*), 2.27 (1H, dd, *J* 14.9, 8.0, C(2)H_A), 2.73 (1H, dd, *J* 14.9, 3.6, C(2)H_B), 2.87-2.93 (1H, m, C(3)*H*), 3.62 (4H, AB system, J_{AB} 13.6, N(CH_2Ph)$_2$), 7.26-7.48 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.0, 21.2 (C(4)*Me*$_2$), 28.1 (C*Me*$_3$), 31.6 (*C*(4)), 34.2 (*C*(2)), 54.3 (N(*C*H_2Ph)$_2$), 61.5 (*C*(3)), 80.2 (*C*Me$_3$), 126.9, 128.2, 129.2 (*o*,*m*,*p*-*Ph*), 140.1 (*i*-*Ph*), 172.9 (*C*(1)); *m/z* (ESI$^+$) 368 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{34}NO_2^+$ ([M+H]$^+$) requires 368.2584; found 368.2583.

Step 3: Following *General Procedure 2*, a solution of *tert*-butyl (*S*)-3-(*N*,*N*-dibenzylamino)-4-methylpentanoate (1.00 g, 2.72 mmol) in CH_2Cl_2 (10.0 mL) was treated with TFA (10.0 mL) to give a white foam (840 mg). Then, following *General Procedure 3*, a solution of the residue (320 mg, 1.03 mmol) in CH_2Cl_2 (4 mL) was reacted with $(COCl)_2$ (0.18 mL, 2.06 mmol) and a solution of (*S*)-**60** (100 mg, 0.41 mmol) in CH_2Cl_2 (1 mL). Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave **166** as a colorless oil (19 mg, 9%, >95:5 dr); $[\alpha]_D^{25}$ +45.6 (*c* 0.5 in $CHCl_3$); ν_{max} 2975, 2935 (C–H), 1664 (C=O); δ_H (250 MHz, PhMe-d_8, 363 K) 0.86 (3H, d, *J* 6.7, C(4)*Me*$_A$), 0.88 (9H, s, C*Me*$_3$), 1.03 (3H, d, *J* 6.7, C(4)*Me*$_B$), 1.75 (3H, d, *J* 7.0, C(1')*Me*), 1.70-1.78 (1H, m, C(4)*H*), 2.47 (1H, dd, *J* 17.1, 6.4, C(2)H_A), 2.85 (1H, dd, *J* 17.1, 4.3, C(2)H_B), 3.46 (4H, AB system, J_{AB} 14.6, N(CH_2Ph)$_2$), 3.32-3.41 (1H, m, C(3)*H*), 6.22 (1H, q, *J* 7.0, C(1')*H*), 6.92-7.43 (13H, m, *Ar*, *Ph*), 7.51-7.71 (3H, m, *Ar*, *Ph*), 8.35 (1H, d, *J* 8.8, *Ar*); δ_C (125 MHz, $CDCl_3$) 16.2 (C(1')*Me*), 20.3, 20.8 (C(4)*Me*$_2$), 28.0 (C*Me*$_3$), 31.9 (*C*(4)), 32.3 (*C*(2)), 54.6 (N(*C*H_2Ph)$_2$), 55.3 (*C*(3)), 60.3 (*C*(1')), 82.5 (*C*Me$_3$), 124.9, 126.3, 126.7, 127.8, 128.1, 128.7, 129.2, 129.4, 132.4, 133.7, 136.2, 140.1 (*Ar*, *Ph*), 179.3 (*C*(1)); *m/z* (ESI$^+$) 537 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{36}H_{45}N_2O_2^+$ ([M+H]$^+$) requires 537.3476; found 537.3477.

(*S*)-*N*-*tert*-Butoxy-*N*-1'-(1''-naphthyl)ethyl (*R*)-3-(*N*-isopropyl-*N*-benzylamino)butanamide 167



(*R*,*R*)-**102** **167**

Step 1: Following *General Procedure 4*, reacting (*R*,*R*)-**102** (5.27 g, 14.9 mmol) and $Pd(OH)_2/C$ (1.32 g) in MeOH (50 mL) under H_2 (5 atm) for 36 h gave *tert*-butyl (*R*)-3-aminobutanoate as a colourless oil (1.50 g, 63%); $[\alpha]_D^{23}$ −22.4 (*c* 1.5 in $CHCl_3$); {lit.[15] $[\alpha]_D^{25}$ −22.2 (*c* 0.5 in $CHCl_3$)}.

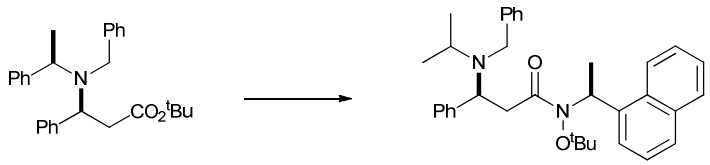
Step 2: Following *General Procedure 6*, *tert*-butyl (*R*)-3-aminobutanoate (1.40 g, 8.79 mmol), acetone (1.29 mL, 17.6 mmol) and $NaBH_3CN$ (2.21 g, 35.2 mmol) were reacted in MeOH (40 mL). Purification *via* flash column chromatography (gradient elution, 1%→30% Et_2O in 30-40 °C petrol) gave *tert*-butyl (*R*)-3-(*N*-isopropylamino)butanoate as a colourless oil (1.33 g, 75%);[18] $[\alpha]_D^{23}$ −20.1 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.41 (3H, d, *J* 6.5, C(4)H_3), 1.46 (3H, d, *J* 6.5, NCHMe_A), 1.47 (9H, s, CMe_3), 1.48 (3H, d, *J* 6.5, NCHMe_B), 2.70 (1H, dd, *J* 17.1, 6.8, C(2)H_A), 2.97 (1H, dd, *J* 17.1, 6.1, C(2)H_B), 3.33-3.44 (1H, m, NC*H*Me_2), 3.53-3.62 (1H, m, C(3)*H*).

Step 3: Following *General Procedure 5*, *tert*-butyl (*R*)-3-(*N*-isopropylamino)butanoate (850 mg, 4.22 mmol) was reacted with K_2CO_3 (5.83 g, 42.2 mmol) in BnBr (5.00 mL, 42.2 mmol). Purification *via* flash column chromatography (gradient elution, 1%→20% Et_2O in 30-40 °C petrol) gave *tert*-butyl (*R*)-3-(*N*-isopropyl-*N*-benzylamino)butanoate as a colourless oil (849 mg, 69%); $[\alpha]_D^{25}$ −36.7 (*c* 1.0 in $CHCl_3$); ν_{max} 2970, 2932 (C–H), 1729 (C=O); δ_H (400 MHz, $CDCl_3$) 1.08 (3H, d, *J* 6.6, NCHMe_A), 1.10 (3H, d, *J* 6.6, NCHMe_B), 1.16 (3H, d, *J* 6.8, C(4)H_3), 1.53 (9H, s, CMe_3), 2.21 (1H, dd, *J* 13.9, 6.8, C(2)H_A), 2.54 (1H, dd, *J* 13.9, 7.3, C(2)H_B), 2.93-3.04 (1H, m, NC*H*Me_2), 3.48-3.54 (1H, m, C(3)*H*), 3.70 (2H, AB system, J_{AB} 14.7, NCH_2Ph), 7.22-7.48 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.1, 19.5 (NCHMe_2), 21.3 (*C*(4)), 28.2 (CMe_3), 42.2 (*C*(2)), 48.6 (N*C*HMe_2), 49.0 (N*C*H_2Ph), 49.6 (*C*(3)), 79.9 (*C*Me_3), 127.8, 128.0, 128.3 (*o*,*m*,*p*-*Ph*), 142.0 (*i*-*Ph*), 172.1 (*C*(1)); *m/z* (ESI^+) 292 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{18}H_{30}NO_2^+$ ($[M+H]^+$) requires 292.2271; found 292.2270.

Step 4: Following *General Procedure 2*, a solution of *tert*-butyl (*R*)-3-(*N*-isopropyl-*N*-

benzylamino)butanoate (849 mg, 2.91 mmol) in CH_2Cl_2 (9.0 mL) was treated with TFA (9.0 mL) to give a white foam (516 mg). Then, following *General Procedure 3*, a solution of the residue (396 mg, 0.84 mmol) in CH_2Cl_2 (4 mL) was reacted with $(COCl)_2$ (0.14 mL, 1.68 mmol) and a mixture of (*S*)-**60**•(+)-CSA (160 mg, 0.34 mmol) and K_2CO_3 (470 mg, 3.40 mmol) in CH_2Cl_2 (4 mL). Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave **167** as a colorless oil containing trace amounts of impurity (14 mg, 9%, >95:5 dr); ν_{max} 2972 (C–H), 1660 (C=O); δ_H (250 MHz, PhMe-d_8, 343 K) 0.73 (9H, s, CMe_3), 0.97 (3H, d, *J* 6.6, NCHMe_A), 0.99 (3H, d, *J* 6.6, NCHMe_B), 1.17 (3H, d, *J* 6.6, C(1')*Me*), 1.68 (3H, d, *J* 6.9, C(4)H_3), 2.39 (1H, dd, *J* 15.5, 8.8, C(2)H_A), 2.87 (1H, dd, *J* 15.5, 4.0, C(2)H_B), 2.91-2.97 (1H, m, C*H*Me$_2$), 3.59 (2H, AB system, J_{AB} 14.8, NCH_2Ph), 3.67-3.76 (1H, m, C(3)*H*), 6.19-6.36 (1H, br m, C(1')*H*), 6.90-7.63 (11H, m, *Ar*, *Ph*), 8.32-8.49 (1H, br m, *Ar*); δ_C (125MHz, $CDCl_3$) 18.4, 18.6 (NCHMe_2), 19.8 (C(1')*Me*), 21.0 (*C*(4)), 27.9 (CMe_3), 29.7 (*C*(2)), 40.7 (*C*HMe$_2$), 47.2 (*C*(3)), 49.3 (N*C*H$_2$Ph), 54.7 (*C*(1')), 82.3 (*C*Me$_3$), 123.2, 124.9, 125.5, 126.1, 126.3, 126.5, 128.0, 128.2, 128.6, 133.6, 142.3 (*Ar*, *Ph*), 179.7 (*C*(1)); *m/z* (ESI$^+$) 461 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{41}N_2O_2^+$ ([M+H]$^+$) requires 461.3163; found 461.3158.

(*S*)-*N*-*tert*-Butoxy-*N*-1'-(1''-naphthyl)ethyl (*S*)-3-(*N*-isopropyl-*N*-benzylamino)-3-phenylpropanamide 168



(3*S*,α*R*)-**103** **168**

Step 1: Following *General Procedure 4*, reacting (3*S*,α*R*)-**103** (6.70 g, 16.1 mmol) and $Pd(OH)_2$/C (1.70 g) in MeOH (65 mL) under H_2 (5 atm) for 36 h gave *tert*-butyl (*S*)-3-amino-3-phenylpropanoate as a colourless oil (2.48 g, 72%); $[\alpha]_D^{23}$ −22.0 (*c* 1.0 in $CHCl_3$); {lit.[16] $[\alpha]_D^{20}$ −21.0 (*c* 1.0 in $CHCl_3$)}.

Step 2: Following *General Procedure 6*, *tert*-butyl (*S*)-3-amino-3-phenylpropanoate (1.00 g, 4.50 mmol), acetone (0.66 mL, 9.00 mmol) and $NaBH_3CN$ (1.13 g, 18.0 mmol) were reacted in MeOH (30 mL). Purification *via* flash column chromatography (gradient elution, 1%→30% Et_2O in 30-40 °C petrol) gave *tert*-butyl (*S*)-3-(*N*-isopropylamino)-3-phenylpropanoate as a colourless oil (1.12 g, 94%); $[\alpha]_D^{25}$ –23.1 (c 1.0 in $CHCl_3$); ν_{max} 3328 (N–H), 2968, 2932 (C–H), 1727 (C=O); δ_H (400 MHz, $CDCl_3$) 0.98 (3H, d, *J* 6.3,

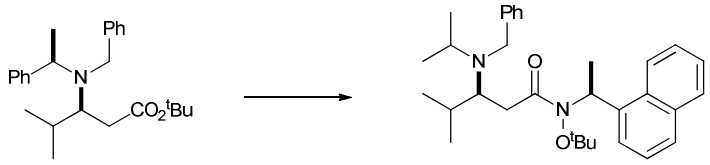
NCH*Me*$_A$), 1.04 (3H, d, *J* 6.3, NCH*Me*$_B$), 1.38 (9H, s, C*Me*$_3$), 1.86 (1H, br s, N*H*), 2.51 (1H, dd, *J* 15.2, 6.1, C(2)*H*$_A$), 2.61 (1H, dd, *J* 15.2, 8.3, C(2)*H*$_B$), 2.56-2.65 (1H, m, NC*H*Me$_2$), 4.15 (1H, dd, *J* 8.3, 6.1, C(3)*H*), 7.20-7.38 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.9, 24.2 (NCH*Me*$_2$), 28.0 (C*Me*$_3$), 44.7 (*C*(2)), 45.6 (N*C*HMe$_2$), 57.0 (*C*(3)), 80.6 (*C*Me$_3$), 127.1, 127.2, 128.4 (*o*,*m*,*p*-*Ph*), 143.1 (*i*-*Ph*), 171.0 (*C*(1)); *m/z* (ESI$^+$) 264 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{26}NO_2^+$ ([M+H]$^+$) requires 264.1958; found 264.1956.

Step 3: Following *General Procedure 5*, *tert*-butyl (*S*)-3-(*N*-isopropylamino)-3-phenylpropanoate (1.12 g, 4.18 mmol) was reacted with K_2CO_3 (5.25 g, 41.8 mmol) in BnBr (4.50 mL, 41.8 mmol). Purification *via* flash column chromatography (gradient elution, 1%→20% Et_2O in 30-40 °C petrol) gave *tert*-butyl (*S*)-3-(*N*-isopropyl-*N*-benzylamino)-3-phenylpropanoate as a colourless oil (1.22 g, 83%); $[\alpha]_D^{25}$ –17.0 (*c* 0.5 in $CHCl_3$); ν_{max} 2972, 2932 (C–H), 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 0.86 (3H, d, *J* 6.6, NCH*Me*$_A$), 1.07 (3H, d, *J* 6.6, NCH*Me*$_B$), 1.28 (9H, s, C*Me*$_3$), 2.56 (1H, dd, *J* 14.2, 9.5, C(2)*H*$_A$), 2.81 (1H, dd, *J* 14.2, 5.9, C(2)*H*$_B$), 3.02-3.11 (1H, m, NC*H*Me$_2$), 3.71 (2H, AB system, J_{AB} 15.1, NC*H*$_2$Ph), 4.29 (1H, dd, *J* 9.5, 5.9, C(3)*H*), 7.21-7.43 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.5, 21.1 (NCH*Me*$_2$), 27.9 (C*Me*$_3$), 40.1 (*C*(2)), 48.2 (N*C*HMe$_2$), 49.4 (N*C*H$_2$Ph), 60.5 (*C*(3)), 80.1 (*C*Me$_3$), 126.4, 126.9, 128.0, 128.1, 128.3, 128.8 (*o*,*m*,*p*-*Ph*), 141.8, 142.2 (*i*-*Ph*), 171.3 (*C*(1)); *m/z* (ESI$^+$) 354 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{32}NO_2^+$ ([M+H]$^+$) requires 354.2428; found 354.2427.

Step 4: Following *General Procedure 2*, a solution of *tert*-butyl (*S*)-3-(*N*-isopropyl-*N*-benzylamino)-3-phenylpropanoate (1.13 g, 4.14 mmol) in CH_2Cl_2 (12.0 mL) was treated with TFA (12.0 mL) to give a white foam (1.00 g). Then, following *General Procedure 3*, a solution of the residue (312 mg, 1.05 mmol) in CH_2Cl_2 (4 mL) was reacted with $(COCl)_2$ (0.18 mL, 2.10 mmol) and a mixture of (*S*)-**60**•(+)-CSA (200 mg, 0.42 mmol) and K_2CO_3 (580 mg, 4.20 mmol) in CH_2Cl_2 (2 mL). Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave **168** as a colorless oil containing trace amounts of impurity (19 mg, 8%, >95:5 dr); ν_{max} 2973, 2930 (C–H), 1655 (C=O); δ_H (500 MHz, PhMe-d_8, 343 K) 0.67 (9H, s, C*Me*$_3$), 0.86 (3H, d, *J* 6.6, NCH*Me*$_A$), 0.97 (3H, d, *J* 6.4, NCH*Me*$_B$), 1.49 (3H, d, *J* 7.0, C(1')*Me*), 2.90-3.10 (2H, br m, C(2)*H*$_2$), 3.07-3.11 (1H, m, C*H*Me$_2$), 3.66 (2H, AB system, J_{AB} 15.2, NC*H*$_2$Ph), 4.79 (1H, app t, *J* 6.7, C(3)*H*), 5.88-6.12 (1H, br m, C(1')*H*), 7.04-7.67 (16H, m, *Ar*, *Ph*), 8.57-8.75 (1H, br m, *Ar*); δ_C (125

MHz, $CDCl_3$) 17.3, 19.5 (NCH*Me*$_2$), 21.3 (C(1')*Me*), 22.7 (*C*(2)), 27.6 (C*Me*$_3$), 36.1 (*C*HMe$_2$), 39.0 (*C*(1')), 48.7 (N*C*H$_2$Ph), 54.1 (*C*(3)), 82.3 (*C*Me$_3$), 124.5, 124.9, 125.7, 126.3, 126.5, 126.8, 127.9, 128.2, 128.6, 128.8, 130.0, 133.6, 135.4, 143.1 (*Ar*, *Ph*), 179.3 (*C*(1)); *m/z* (ESI$^+$) 523 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{35}H_{43}N_2O_2^+$ ([M+H]$^+$) requires 523.3319; found 523.3319.

(*S*)-*N*-*tert*-Butoxy-*N*-1'-(1''-naphthyl)ethyl (*S*)-3-(*N*-isopropyl-*N*-benzylamino)-4-methyl-pentanamide 169



(3*S*,α*R*)-**157** **169**

Step 1: Following *General Procedure 4*, reacting (3*S*,α*R*)-**157** (7.20 g, 18.9 mmol) and Pd(OH)$_2$/C (1.80 g) in MeOH (72 mL) under H_2 (5 atm) for 36 h gave *tert*-butyl (*S*)-3-amino-4-methylpentanoate as a colourless oil (2.82 g, 80%); $[\alpha]_D^{23}$ −26.2 (*c* 1.0 in $CHCl_3$); {lit.[11] $[\alpha]_D^{20}$ −25.8 (*c* 3.4 in $CHCl_3$)}.

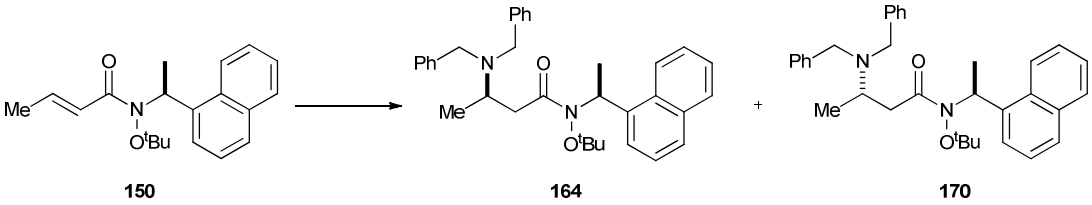
Step 2: Following *General Procedure 6*, *tert*-butyl (*S*)-3-amino-4-methylpentanoate (1.20 g, 6.41 mmol), acetone (0.94 mL, 12.8 mmol) and $NaBH_3CN$ (1.63 g, 25.7 mmol) were reacted in MeOH (35 mL). Purification *via* flash column chromatography (gradient elution, 1%→30% Et_2O in 30-40 °C petrol) gave *tert*-butyl (*S*)-3-(*N*-isopropylamino)-4-methylpentanoate as a colourless oil (1.10 g, 75%); $[\alpha]_D^{25}$ –2.8 (*c* 1.0 in $CHCl_3$); ν_{max} 3334 (N–H), 2963, 2933 (C–H), 1729 (C=O); δ_H (400 MHz, $CDCl_3$) 0.84 (3H, d, *J* 6.8, C(4)*Me*$_A$), 0.87 (3H, d, *J* 6.8, C(4)*Me*$_B$), 0.99 (3H, d, *J* 5.9, NCH*Me*$_A$), 1.00 (3H, d, *J* 5.9, NCH*Me*$_B$), 1.43 (9H, s, C*Me*$_3$), 1.71-1.79 (1H, m, C(4)*H*), 2.13 (1H, dd, *J* 14.7, 7.6, C(2)*H*$_A$), 2.27 (1H, dd, *J* 14.7, 5.1, C(2)*H*$_B$), 2.78-2.85 (1H, m, NC*H*Me$_2$), 2.80-2.87 (1H, m, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 17.5, 18.8 (C(4)*Me*$_2$), 23.4, 23.5 (NCH*Me*$_2$), 28.0 (C*Me*$_3$), 30.9 (*C*(4)), 38.0 (*C*(2)), 45.8 (N*C*HMe$_2$), 57.3 (*C*(3)), 80.1 (*C*Me$_3$), 172.6 (*C*(1)); *m/z* (ESI$^+$) 230 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{28}NO_2^+$ ([M+H]$^+$) requires 230.2115; found 230.2115.

Step 3: Following *General Procedure 5*, *tert*-butyl (*S*)-3-(*N*-isopropylamino)-4-methylpentanoate (1.00 g, 4.36 mmol) was reacted with K_2CO_3 (6.00 g, 43.6 mmol) in BnBr (5.20 mL, 43.6 mmol). Purification *via* flash column chromatography (gradient elution, 1%→20% Et_2O in 30-40 °C petrol) gave *tert*-butyl (*S*)-3-(*N*-isopropyl-*N*-benzylamino)-4-methylpentanoate as a colourless oil (1.19 g, 86%); $[\alpha]_D^{25}$ +10.3 (*c* 1.0 in $CHCl_3$); ν_{max} 2966,

2934 (C–H), 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 0.93 (3H, d, *J* 6.8, NCH*Me*$_A$), 1.05 (3H, d, *J* 6.6, C(4)*Me*$_A$), 1.06 (3H, d, *J* 6.6, C(4)*Me*$_B$), 1.12 (3H, d, *J* 6.8, NCH*Me*$_B$), 1.51 (9H, s, C*Me*$_3$), 1.69-1.80 (1H, m, C(4)*H*), 2.30 (1H, dd, *J* 15.4, 8.3, C(2)*H*$_A$), 2.64 (1H, dd, *J* 15.4, 3.0, C(2)*H*$_B$), 2.96 (1H, sept, *J* 6.8, NC*H*Me$_2$), 3.01-3.06 (1H, m, C(3)*H*), 3.68 (2H, AB system, J_{AB} 14.7, NC*H*$_2$Ph), 7.21-7.44 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.2 (NCH*Me*$_A$), 19.8 (C(4)*Me*$_A$), 21.1 (C(4)*Me*$_B$), 22.2 (NCH*Me*$_B$), 28.1 (C*Me*$_3$), 32.8 (*C*(4)), 37.5 (*C*(2)), 48.8 (N*C*HMe$_2$), 50.6 (N*C*H$_2$Ph), 58.7 (*C*(3)), 80.1 (*C*Me$_3$), 126.4, 128.1, 128.4 (*o*,*m*,*p-Ph*), 141.8 (*i-Ph*), 173.0 (*C*(1)); *m/z* (ESI$^+$) 320 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{34}NO_2^+$ ([M+H]$^+$) requires 320.2584; found 320.2583.

Step 4: Following *General Procedure 2*, a solution of *tert*-butyl (*S*)-3-(*N*-isopropyl-*N*-benzylamino)-4-methylpentanoate (1.00 g, 3.13 mmol) in CH_2Cl_2 (10.0 mL) was treated with TFA (10.0 mL) to give a white foam (818 mg). Then, following *General Procedure 3*, a solution of the residue (271 mg, 1.03 mmol) in CH_2Cl_2 (3 mL) was reacted with $(COCl)_2$ (0.18 mL, 2.06 mmol) and a solution of (*S*)-**60** (100 mg, 0.41 mmol) in CH_2Cl_2 (1 mL). Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave **169** as a colorless oil (20 mg, 10%, >95:5 dr); $[\alpha]_D^{25}$ +21.2 (*c* 1.0 in $CHCl_3$); ν_{max} 2969, 2872 (C–H), 1665 (C=O); δ_H (250 MHz, PhMe-d_8, 363 K) 0.87 (9H, s, C*Me*$_3$), 0.88 (3H, d, *J* 6.7, NCH*Me*$_A$), 0.97 (3H, d, *J* 6.7, NCH*Me*$_B$), 1.04 (3H, d, *J* 6.7, C(4)*Me*$_A$), 1.08 (3H, d, *J* 6.7, C(4)*Me*$_B$), 1.71 (3H, d, *J* 7.0, C(1')*Me*), 1.61-1.76 (1H, m, C(4)*H*), 2.56 (1H, dd, *J* 17.7, 7.3, C(2)*H*$_A$), 2.82 (1H, dd, *J* 17.7, 4.6, C(2)*H*$_B$), 2.83-2.96 (1H, m, NC*H*Me$_2$), 3.58 (2H, AB system, J_{AB} 14.6, NC*H*$_2$Ph), 3.46-3.57 (1H, m, C(3)*H*), 6.24 (1H, q, *J* 7.0, C(1')*H*), 6.93-7.40 (8H, m, *Ar*, *Ph*), 7.50-7.69 (3H, m, *Ar*, *Ph*), 8.32 (1H, d, *J* 8.8, *Ar*); δ_C (125 MHz, $CDCl_3$) 16.3 (C(1')*Me*), 20.0, 20.5 (NCH*Me*$_2$), 22.1 (C(4)*Me*$_A$), 25.6 (*C*(4)), 28.0 (C*Me*$_3$), 32.9 (C(4)*Me*$_B$), 35.9 (*C*(2)), 49.2 (N*C*HMe$_2$), 51.1 (N*C*H$_2$Ph), 53.4 (*C*(3)), 56.5 (*C*(1')), 82.3 (*C*Me$_3$), 124.8, 125.5, 126.3, 128.2, 128.7, 132.4, 133.6, 136.4, 142.0 (*Ar*, *Ph*), 180.0 (*C*(1)); *m/z* (ESI$^+$) 489 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{45}N_2O_2^+$ ([M+H]$^+$) requires 489.3476; found 489.3475.

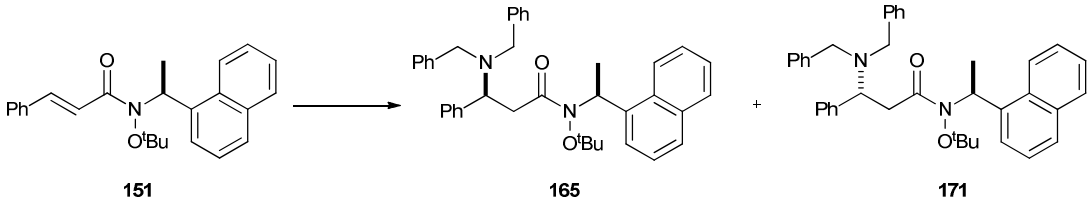
(*S*)-*N*-*tert*-Butoxy-*N*-1'-(1''-naphthyl)ethyl (*R*)-3-(*N*,*N*-dibenzylamino)butanamide 164 and (*S*)-*N*-*tert*-butoxy-*N*-1'-(1''-naphthyl)ethyl (*S*)-3-(*N*,*N*-dibenzylamino)butanamide 170



150 **164** **170**

Following *General Procedure 1*, a solution of dibenzylamine (0.14 mL, 0.71 mmol) in THF (1 mL) at –78 °C was treated with BuLi (1.2 M in hexanes, 0.47 mL, 0.57 mmol) and **150** (110 mg, 0.35 mmol) in THF (1 mL) to give a 80:20 mixture of **164** and **170**. Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave an 80:20 mixture of **164** and **170** as a colourless oil (119 mg, 66%). Data for the mixture: ν_{max} 2973, 2928 (C–H), 1660 (C=O); *m/z* (ESI^+) 509 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{34}H_{41}N_2O_2^+$ ($[M+H]^+$) requires 509.3163; found 509.3164. Data for **170**: δ_H (500 MHz, PhMe-d_8, 343 K) 0.72 (9H, s, CMe_3), 1.09 (3H, d, *J* 6.6, C(1')*Me*), 1.62 (3H, d, *J* 6.6, C(4)H_3), 2.61 (1H, dd, *J* 15.1, 9.1, C(2)H_A), 2.85-2.90 (1H, br m, C(2)H_B), 3.52 (4H, AB system, J_{AB} 13.9, N(CH_2Ph)$_2$), 3.65-3.71 (1H, m, C(3)*H*), 6.19 (1H, q, *J* 6.6, C(1')*H*), 6.89-7.36 (13H, m, *Ar*, *Ph*), 7.47-7.63 (3H, m, *Ar*, *Ph*), 8.28-8.39 (1H, br m, *Ar*); δ_C (125 MHz, $CDCl_3$) 14.4 (C(1')*Me*), 18.1 (*C*(4)), 27.7 (CMe_3), 31.8 (*C*(2)), 38.1 (*C*(3)), 50.5 (*C*(1')), 55.0 (N(*C*H_2Ph)$_2$), 82.4 (*C*Me_3), 124.1, 125.5, 126.2, 126.4, 126.7, 128.2, 128.5, 128.7, 129.0, 133.6, 140.3 (*Ar*, *Ph*), 179.4 (*C*(1)).

(*S*)-*N*-*tert*-Butoxy-*N*-1'-(1''-naphthyl)ethyl (*S*)-3-(*N*,*N*-dibenzylamino)-3-phenylpropanamide 165 and (*S*)-*N*-*tert*-butoxy-*N*-1'-(1''-naphthyl)ethyl (*R*)-3-(*N*,*N*-dibenzylamino)-3-phenylpropanamide 171

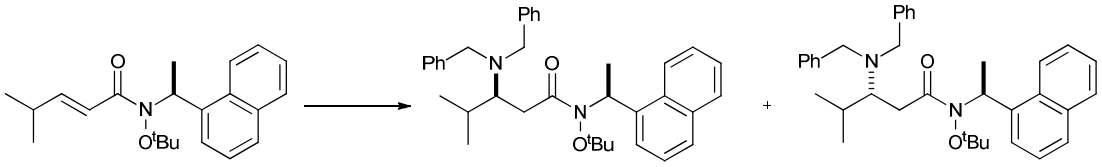


151 **165** **171**

Following *General Procedure 1*, a solution of dibenzylamine (77 μL, 0.40 mmol) in THF (1 mL) at –78 °C was treated with BuLi (2.5 M in hexanes, 0.13 mL, 0.32 mmol) and **151** (75 mg, 0.20 mmol) in THF (1 mL) to give a 70:30 mixture of **165** and **171**. Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave a 70:30 mixture of **165** and **171** as a colorless oil (71 mg, 62%). Data for the mixture: ν_{max}

2977 (C–H), 1659 (C=O); *m/z* (ESI$^+$) 571 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{39}H_{43}N_2O_2^+$ ([M+H]$^+$) requires 571.3319; found 571.3316. Data for **171**: δ_H (250 MHz, PhMe-d_8, 343 K) 0.62 (9H, s, CMe_3), 1.29 (3H, d, *J* 7.0, C(1')*Me*), 2.85-2.97 (2H, br m, C(2)H_2), 3.58 (4H, AB system, J_{AB} 13.7, N(CH_2Ph)$_2$), 4.77 (1H, app t, *J* 4.6, C(3)*H*), 6.26 (1H, q, *J* 7.0, C(1')*H*), 7.10-7.68 (21H, m, *Ar*, *Ph*), 8.48 (1H, d, *J* 8.8, *Ar*); δ_C (100 MHz, $CDCl_3$) 29.8 (CMe_3), 36.0 (C(1')*Me*), 53.5 (*C*(1')), 54.5 (*C*(2)), 54.7 (N(*C*H$_2$Ph)$_2$), 54.8 (*C*(3)), 82.3 (*C*Me$_3$), 125.5, 126.1, 126.4, 127.0, 127.2, 128.0, 128.3, 128.4, 128.8, 128.9, 133.6, 139.3, 140.1, 140.3 (*Ar*, *Ph*).

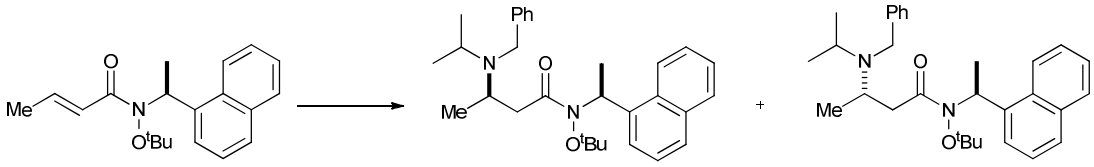
(*S*)-*N*-*tert*-Butoxy-*N*-1'-(1''-naphthyl)ethyl (*S*)-3-(*N*,*N*-dibenzylamino)-4-methyl-pentanamide 166 and (*S*)-*N*-*tert*-butoxy-*N*-1'-(1''-naphthyl)ethyl (*R*)-3-(*N*,*N*-dibenzylamino)-4-methyl-pentanamide 172



152 **166** **172**

Following *General Procedure 1*, a solution of dibenzylamine (0.11 mL, 0.59 mmol) in THF (1 mL) at –78 °C was treated with BuLi (2.5 M in hexanes, 0.19 mL, 0.47 mmol) and **152** (100 mg, 0.29 mmol) in THF (1 mL) to give an 80:20 mixture of **166** and **172**. Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave an 88:12 mixture of **166** and **172** as a colorless oil (94 mg, 60%). Data for the mixture: ν_{max} 2975, 2935 (C–H), 1664 (C=O); *m/z* (ESI$^+$) 537 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{36}H_{45}N_2O_2^+$ ([M+H]$^+$) requires 537.3476; found 537.3477. Data for **172**: δ_H (250 MHz, PhMe-d_8, 363 K) 0.75 (3H, d, *J* 6.7, C(4)Me_A), 0.85 (9H, s, CMe_3), 1.02 (3H, d, *J* 6.7, C(4)Me_B), 1.67 (3H, d, *J* 7.0, C(1')*Me*), 1.78-1.86 (1H, m, C(4)*H*), 2.56-2.74 (2H, m, C(2)H_2), 3.58 (4H, AB system, J_{AB} 14.6, N(CH_2Ph)$_2$), 3.32-3.41 (1H, m, C(3)*H*), 6.34 (1H, q, *J* 7.0, C(1')*H*), 6.92-7.43 (13H, m, *Ar*, *Ph*), 7.51-7.71 (3H, m, *Ar*, *Ph*), 8.50 (1H, d, *J* 8.8, *Ar*); δ_C (125 MHz, $CDCl_3$) 16.2 (C(1')*Me*), 19.9, 20.5 (C(4)Me_2), 28.0 (CMe_3), 31.8 (*C*(4)), 32.3 (*C*(2)), 54.8 (N(*C*H$_2$Ph)$_2$), 55.3 (*C*(3)), 60.3 (*C*(1')), 82.5 (*C*Me$_3$), 124.9, 125.5, 126.7, 127.8, 128.7, 129.2, 132.4, 136.2, 140.2 (*Ar*, *Ph*), 179.3 (*C*(1)).

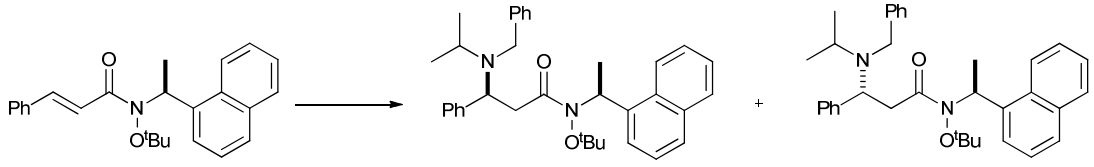
(*S*)-*N*-*tert*-Butoxy-*N*-1'-(1''-naphthyl)ethyl (*R*)-3-(*N*-isopropyl-*N*-benzylamino)butanamide 167 and (*S*)-*N*-*tert*-butoxy-*N*-1'-(1''-naphthyl)ethyl (*S*)-3-(*N*-isopropyl-*N*-benzylamino)butanamide 173



150 **167** **173**

Following *General Procedure 1*, a solution of *N*-benzyl-*N*-isopropylamine (0.13 mL, 0.77 mmol) in THF (1 mL) at –78 °C was treated with BuLi (1.2 M in hexanes, 0.51 mL, 0.62 mmol) and **150** (120 mg, 0.39 mmol) in THF (1 mL) to give an 80:20 mixture of **167** and **173**. Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave an 80:20 mixture of **167** and **173** as a colorless oil (124 mg, 70%). Data for the mixture: ν_{max} 2972 (C–H), 1660 (C=O); *m/z* (ESI$^+$) 461 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{41}N_2O_2^+$ ([M+H]$^+$) requires 461.3163; found 461.3158. Data for **173**: δ_H (250 MHz, PhMe-d_8, 343 K) 0.70 (9H, s, C*Me*$_3$), 0.99 (3H, d, *J* 6.6, NCH*Me*$_A$), 1.01 (3H, d, *J* 6.6, NCH*Me*$_B$), 1.12 (3H, d, *J* 6.6, C(1')*Me*), 1.65 (3H, d, *J* 6.9, C(4)*H*$_3$), 2.62-2.71 (2H, m, C(2)*H*$_2$), 2.93-2.99 (1H, m, C*H*Me$_2$), 3.62 (2H, AB system, J_{AB} 14.8, NC*H*$_2$Ph), 3.75-3.80 (1H, m, C(3)*H*), 6.38-6.48 (1H, br m, C(1')*H*), 6.90-7.63 (11H, m, *Ar*, *Ph*), 8.52-8.64 (1H, br m, *Ar*); δ_C (125 MHz, $CDCl_3$) 18.5, 18.6 (NCH*Me*$_2$), 19.8 (C(1')*Me*), 21.6 (*C*(4)), 27.6 (C*Me*$_3$), 29.7 (*C*(2)), 40.7 (*C*HMe$_2$), 47.2 (*C*(3)), 49.0 (N*C*H$_2$Ph), 54.7 (*C*(1')), 82.4 (*C*Me$_3$), 123.2, 124.9, 125.5, 126.1, 126.3, 126.5, 128.0, 128.2, 128.6, 133.6, 142.3 (*Ar*, *Ph*), 179.7 (*C*(1)).

(*S*)-*N*-*tert*-Butoxy-*N*-1'-(1''-naphthyl)ethyl (*S*)-3-(*N*-isopropyl-*N*-benzylamino)-3-phenylpropanamide 168 and (*S*)-*N*-*tert*-butoxy-*N*-1'-(1''-naphthyl)ethyl (*R*)-3-(*N*-isopropyl-*N*-benzylamino)-3-phenylpropanamide 174

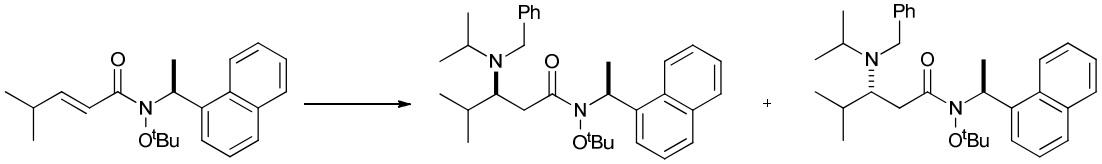


151 **168** **174**

Following *General Procedure 1*, a solution of *N*-benzyl-*N*-isopropylamine (67 μL, 0.40 mmol) in THF (1 mL) at –78 °C was treated with BuLi (2.5 M in hexanes, 0.13 mL, 0.32 mmol) and **151** (75 mg, 0.20 mmol) in THF (1 mL) to give an 80:20 mixture of **168** and **174**. Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-

40 °C petrol) gave an 80:20 mixture of **168** and **174** as a colorless oil (63 mg, 60%). Data for the mixture: ν_{max} 2973, 2930 (C–H), 1655 (C=O); *m/z* (ESI$^+$) 523 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{35}H_{43}N_2O_2^+$ ([M+H]$^+$) requires 523.3319; found 523.3319. Data for **174**: δ_H (500 MHz, PhMe-d_8, 343 K) 0.49 (9H, s, C*Me*$_3$), 0.88 (3H, d, *J* 6.6, NCH*Me*$_A$), 0.98 (3H, d, *J* 6.4, NCH*Me*$_B$), 1.49 (3H, d, *J* 7.0, C(1')*Me*), 2.70-2.79 (1H, br m, C(2)*H*$_A$), 3.35-3.43 (1H, br m, C(2)*H*$_B$), 3.07-3.11 (1H, m, C*H*Me$_2$), 3.66 (2H, AB system, J_{AB} 15.2, NC*H*$_2$Ph), 4.74 (1H, app t, *J* 6.7, C(3)*H*), 6.27 (1H, q, *J* 7.0, C(1')*H*), 7.04-7.67 (16H, m, *Ar*, *Ph*), 8.51 (1H, d, *J* 8.2, *Ar*); δ_C (125 MHz, $CDCl_3$) 15.2, 18.8 (NCH*Me*$_2$), 21.1 (C(1')*Me*), 27.7 (C*Me*$_3$), 29.1 (*C*(2)), 33.7 (*C*HMe$_2$), 41.4 (*C*(1')), 49.6 (N*C*H$_2$Ph), 62.7 (*C*(3)), 82.3 (*C*Me$_3$), 124.5, 124.9, 125.7, 126.3, 126.5, 126.8, 127.9, 128.2, 128.6, 128.8, 130.0, 133.6, 135.4, 143.1 (*Ar*, *Ph*), 179.3 (*C*(1)).

(*S*)-*N*-*tert*-Butoxy-*N*-1'-(1''-naphthyl)ethyl (*S*)-3-(*N*-isopropyl-*N*-benzylamino)-4-methyl-pentanamide 169 and (*S*)-*N*-*tert*-butoxy-*N*-1'-(1''-naphthyl)ethyl (*R*)-3-(*N*-isopropyl-*N*-benzylamino)-4-methyl-pentanamide 175



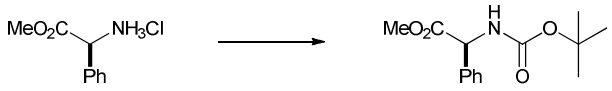
152 **169** **175**

Following *General Procedure 1*, a solution of *N*-benzyl-*N*-isopropylamine (100 μL, 0.59 mmol) in THF (1 mL) at –78 °C was treated with BuLi (2.5 M in hexanes, 0.19 mL, 0.47 mmol) and **152** (100 mg, 0.29 mmol) in THF (1 mL) to give an 85:15 mixture of **169** and **175**. Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave a 90:10 mixture of **169** and **175** as a colorless oil (68 mg, 48%). Data for the mixture: ν_{max} 2969, 2872 (C–H), 1665 (C=O); *m/z* (ESI$^+$) 489 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{45}N_2O_2^+$ ([M+H]$^+$) requires 489.3476; found 489.3475. Data for **175**: δ_H (250 MHz, PhMe-d_8, 363 K) 0.82 (9H, s, C*Me*$_3$), 0.83 (3H, d, *J* 6.7, NCH*Me*$_A$), 0.96 (3H, d, *J* 6.7, NCH*Me*$_B$), 1.03 (3H, d, *J* 6.7, C(4)*Me*$_A$), 1.09 (3H, d, *J* 6.7, C(4)*Me*$_B$), 1.69 (3H, d, *J* 7.0, C(1')*Me*), 1.81-1.86 (1H, m, C(4)*H*), 2.64-2.80 (2H, br m, C(2)*H*$_2$), 2.93-3.02 (1H, m, NC*H*Me$_2$), 3.60 (2H, AB system, J_{AB} 14.6, NC*H*$_2$Ph), 3.81-3.96 (1H, m, C(3)*H*), 6.33 (1H, q, *J* 7.0, C(1')*H*), 6.93-7.40 (8H, m, *Ar*, *Ph*), 7.50-7.69 (3H, m, *Ar*, *Ph*), 8.48 (1H, d, *J* 8.8, *Ar*); δ_C (125 MHz, $CDCl_3$) 14.2 (C(1')*Me*), 19.8, 20.2 (NCH*Me*$_2$), 22.3 (C(4)*Me*$_A$), 28.0 (C*Me*$_3$), 29.7 (*C*(4)), 32.8 (C(4)*Me*$_B$), 35.7 (*C*(2)), 49.3 (N*C*HMe$_2$), 51.3 (N*C*H$_2$Ph), 60.3

(*C*(3)), 55.1 (*C*(1')), 82.5 (*C*Me$_3$), 124.8, 125.5, 126.1, 128.0, 128.2, 132.4, 133.6, 136.4, 142.0 (*Ar*, *Ph*), 180.0 (*C*(1)).

5.4 Experimental for Chapter 3

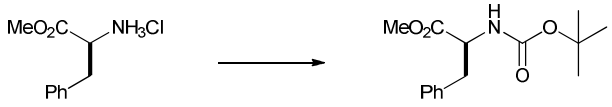
(*S*)-Methyl 2-(*tert*-butoxycarbonylamino)-2-phenylacetate 217



214 **217**

$NaHCO_3$ (125 g, 1.48 mol) was added in one portion to a stirred solution of **214** (100 g, 496 mmol) in EtOH (350 mL) at 0 °C, immediately followed by the addition of di-*tert*-butyldicarbonate (114 g, 521 mmol) in one portion. The mixture was allowed to warm to rt and stirred for 48 h, after which the reaction mixture was filtered through Celite® (eluent: EtOH) and concentrated *in vacuo*. The residue was partitioned between Et_2O (1.0 L) and satd aq $NaHCO_3$ (1.0 L) and the aqueous layer was extracted with Et_2O (3 × 1.0 L). The combined organic extracts were washed with brine (1.0 L), then dried and concentrated *in vacuo* to give the crude product **217** as a colourless oil (132 g);[19] δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s, C*Me*$_3$), 3.73 (3H, s, O*Me*), 5.33 (1H, d, *J* 7.5, C(2)*H*), 5.56 (1H, br s, N*H*), 7.30-7.39 (5H, m, *Ph*).

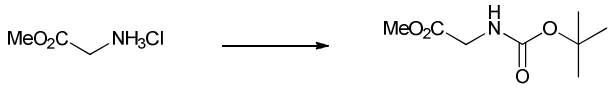
(*S*)-Methyl 2-(*tert*-butoxycarbonylamino)-3-phenylpropanoate 218



215 **218**

$NaHCO_3$ (11.1 g, 132 mmol) was added in one portion to a stirred solution of **215** (9.51 g, 44.0 mmol) in EtOH (35 mL) at 0 °C, immediately followed by the addition of di-*tert*-butyldicarbonate (10.1 g, 46.2 mmol) in one portion. The mixture was allowed to warm to rt and stirred for 48 h, after which the reaction mixture was filtered through Celite® (eluent: EtOH) and concentrated *in vacuo*. The residue was partitioned between EtOAc (50 mL) and satd aq $NaHCO_3$ (50 mL) and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), then dried and concentrated *in vacuo* to give the crude product **218** as a yellow oil (12.7 g);[19] δ_H (400 MHz, $CDCl_3$) 1.43 (9H, s, C*Me*$_3$), 3.03-3.15 (2H, m, C(3)*H*$_2$), 3.72 (3H, s, O*Me*), 4.60 (1H, dd, *J* 14.0, 6.1, C(2)*H*), 4.98 (1H, br s, N*H*), 7.13-7.31 (5H, m, *Ph*).

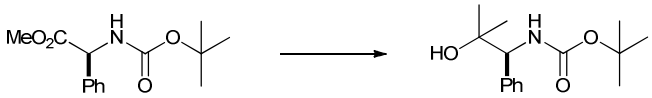
Methyl 2-(*tert*-butoxycarbonylamino)acetate 219



216 **219**

$NaHCO_3$ (201 g, 2.39 mol) was added in one portion to a stirred solution of **216** (100 g, 796 mmol) in EtOH (350 mL) at 0 °C, immediately followed by the addition of di-*tert*-butyldicarbonate (183 g, 836 mmol) in one portion. The mixture was allowed to warm to rt and stirred for 48 h, after which the reaction mixture was filtered through Celite® (eluent: EtOH) and concentrated *in vacuo*. The residue was partitioned between Et_2O (1.0 L) and satd aq $NaHCO_3$ (1.0 L) and the aqueous layer was extracted with Et_2O (3 × 1.0 L). The combined organic extracts were washed with brine (1.0 L), then dried and concentrated *in vacuo* to give the crude product **219** as a colourless oil (150 g);[19] δ_H (400 MHz, $CDCl_3$) 1.46 (9H, s, C*Me*$_3$), 3.76 (3H, s, O*Me*), 3.93 (2H, d, *J* 5.8, C(2)*H*$_2$), 5.01 (1H, br s, N*H*).

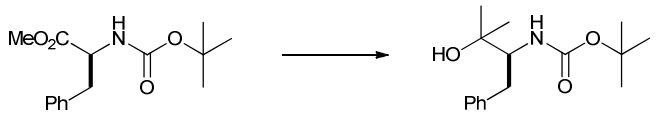
(*S*)-*tert*-Butyl 2-hydroxy-2-methyl-1-phenylpropylcarbamate 220



217 **220**

Mg (48.2 g, 1.98 mol) was stirred in Et_2O (1.1 L) and a small volume of MeI added dropwise followed by catalytic amount of I_2, with gentle heating to initiate formation of the Grignard reagent. Once an exothermic reaction had commenced, Et_2O (560 mL) was added to the residual MeI (282 g, 1.98 mol) and addition of the resulting solution was maintained at a rate as to keep the reaction at gentle reflux. Once addition was complete, the reaction was allowed to stir at rt for 1 h. A solution of **217** (132 g, 496 mmol) in Et_2O (560 mL) was then added dropwise over 15 min at 0 °C. The reaction mixture was stirred at rt for 48 h. After cooling to 0 °C, satd aq NH_4Cl (600 mL) and 2.0 M aq HCl (500 mL) were added and the resultant mixture was extracted with Et_2O (3 × 1.0 L). The combined organic extracts were washed with brine (1.0 L), dried and concentrated *in vacuo* to give the crude product **220** as a white solid (103 g);[19] δ_H (400 MHz, $CDCl_3$) 1.07 (3H, s, C(2)*Me*$_A$), 1.34 (3H, s, C(2)*Me*$_B$), 1.41 (9H, s, C*Me*$_3$), 4.53 (1H, d, *J* 7.9, C(1)*H*), 5.52 (1H, br s, N*H*), 7.24-7.37 (5H, m, *Ph*).

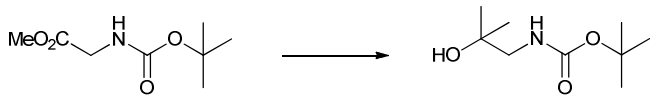
(*S*)-*tert*-Butyl 3-hydroxy-3-methyl-1-phenylbutan-2-ylcarbamate 221



218 221

MeMgBr (3.0 M in Et_2O, 153 mL, 458 mmol) was added to a solution of **218** (31.9 g, 114 mmol) in Et_2O (100 mL) at 0 °C. The reaction mixture was stirred at rt for 30 h. After cooling to 0 °C, satd aq NH_4Cl (125 mL) and 1.0 M aq HCl (125 mL) were added and the resultant mixture was extracted with EtOAc (3 × 300 mL). The combined organic extracts were washed with brine (100 mL), dried and concentrated *in vacuo* to give the crude product **221** as a white solid (32.6 g);[19] δ_H (400 MHz, $CDCl_3$) 1.31 (15H, s, C*Me*$_2$, C*Me*$_3$), 2.40 (1H, bs, O*H*), 2.61 (1H, m, C(1)H_A), 3.09 (1H, dd, *J* 14.2, 3.6, C(1)H_B), 3.63-3.72 (1H, m, C(2)*H*), 4.53 (1H, d, *J* 8.9, N*H*), 7.19-7.32 (5H, m, *Ph*).

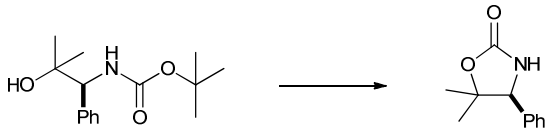
***tert*-Butyl 2-hydroxy-2-methylpropylcarbamate 222**



219 222

Mg (77.5 g, 3.19 mol) was stirred in Et_2O (1.0 L) and a small volume of MeI added dropwise followed by catalytic amount of I_2, with gentle heating to initiate formation of the Grignard reagent. Once an exothermic reaction had commenced, Et_2O (600 mL) was added to the residual MeI (452 g, 3.19 mol) and addition of the resulting solution was maintained at a rate as to keep the reaction at gentle reflux. Once addition was complete, the reaction was allowed to stir at rt for 1 h. A solution of **219** (150 g, 796 mmol) in Et_2O (560 mL) was then added dropwise over 15 min at 0 °C. The reaction mixture was stirred at rt for 48 h. After cooling to 0 °C, satd aq NH_4Cl (600 mL) and 2.0 M aq HCl (500 mL) were added and the resultant mixture was extracted with Et_2O (3 × 1.0 L). The combined organic extracts were washed with brine (1.0 L), dried and concentrated *in vacuo* to give the crude product **222** as a white solid (93.1 g);[19] δ_H (400 MHz, $CDCl_3$) 1.22 (6H, s, C(2)*Me*$_2$), 1.45 (9H, s, C*Me*$_3$), 3.12 (2H, d, *J* 6.1, C(1)H_2), 4.96 (1H, br s, N*H*).

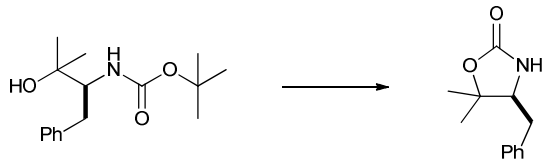
(*S*)-4-Phenyl-5,5-dimethyloxazolidin-2-one 220



220 **212**

KO^{t}Bu (52.1 g, 465 mmol) was added to a solution of **220** (103 g, 387 mmol) in THF (1.50 L) at 0 °C. Then the reaction mixture was stirred at rt for 16 h. Satd aq NH_4Cl (600 mL) was added and the resultant mixture was extracted with EtOAc (3 × 1.0 L). The combined organic extracts were washed with brine (1.0 L), then dried and concentrated *in vacuo* to give a white solid, which was recrystallised from hexanes/EtOAc to give the SuperQuat **212** as a white solid (70 g, 94%);[20] mp 47-48 °C (lit.,[20] mp 49 °C); $[\alpha]_D^{25}$ +80.1 (*c* 0.6 in $CHCl_3$) {lit.,[20] $[\alpha]_D^{23}$ +79.0 (*c* 0.5 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 0.96 (3H, s, C(5)*Me*$_A$), 1.63 (3H, s, C(5)*Me*$_B$), 4.67 (1H, s, C(4)*H*), 5.29 (1H, br s, N*H*), 7.24-7.43 (5H, m, *Ph*).

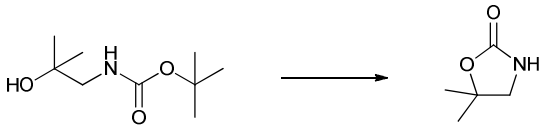
(*S*)-4-Benzyl-5,5-dimethyloxazolidin-2-one 223



221 **223**

KO^{t}Bu (31.4 g, 140 mmol) was added to a solution of **221** (32.6 g, 117 mmol) in THF (400 mL) at 0 °C. Then the reaction mixture was stirred at rt for 16 h. Satd aq NH_4Cl (150 mL) was added and the resultant mixture was extracted with EtOAc (3 × 200 mL). The combined organic extracts were washed with brine (200 mL), then dried and concentrated *in vacuo* to give a yellow solid, which was recrystallised from hexanes/EtOAc to give the SuperQuat **223** as a light yellow solid (20.1 g, 84%);[20] mp 59-60 °C (lit.,[20] mp 59 °C); $[\alpha]_D^{25}$ −104.7 (*c* 0.6 in $CHCl_3$) {lit.,[20] $[\alpha]_D^{25}$ −103.5 (*c* 0.6 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.47 (3H, s, C(5)*Me*$_A$), 1.50 (3H, s, C(5)*Me*$_B$), 2.67 (1H, dd, *J* 13.3, 10.9, C(4)C*H*$_A$), 3.09 (1H, dd, *J* 13.3, 3.6, C(4)C*H*$_B$), 3.69 (1H, dd, *J* 10.9, 3.6, C(4)*H*), 4.75 (1H, s, N*H*), 7.18-7.37 (5H, m, *Ph*).

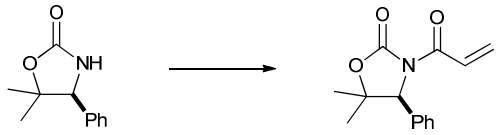
5,5-Dimethyloxazolidin-2-one 224



222 **224**

KO^{t}Bu (66.3 g, 591 mmol) was added to a solution of **222** (93.1 g, 493 mmol) in THF (1.50 L) at 0 °C. Then the reaction mixture was stirred at rt for 16 h. Satd aq NH_4Cl (600 mL) was added and the resultant mixture was extracted with EtOAc (3 × 1.0 L). The combined organic extracts were washed with brine (1.0 L), then dried and concentrated *in vacuo* to give a white solid, which was recrystallised from hexanes/EtOAc to give the SuperQuat **224** as a white solid (42 g, 75%);[21] mp 78-79 °C (lit.,[21] mp 80 °C); δ_H (400 MHz, $CDCl_3$) 1.49 (6H, s, C(5)Me_2), 3.36(2H, d, *J* 0.7, C(4)H_2), 5.55 (1H, br s, N*H*).

(*S*)-3-Acryloyl-4-phenyl-5,5-dimethyloxazolidin-2-one 228



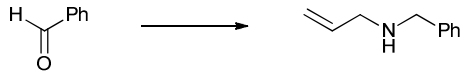
212 **228**

Acryloyl chloride (0.54 mL, 6.63 mmol) and Et_3N (0.92 mL, 6.63 mmol) were added to a solution of acrylic acid (0.50 mL, 6.63 mmol) in Et_2O (25 mL) at 0 °C. The resultant mixture was stirred at 0 °C for 2 h and concentrated *in vacuo*.

A solution of **212** (1.00 g, 5.30 mmol) in THF (2 mL) at rt was treated with a solution of the above residue in THF (2 mL), LiCl (280 mg, 6.63 mmol) and Et_3N (0.92 mL, 6.63 mmol). The resultant mixture was stirred at rt for 4 h and concentrated *in vacuo*. The residue was partitioned between EtOAc (50 mL) and 1.0 M aq HCl (20 mL) and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 10%→20% EtOAc in 30-40 °C petrol) gave **228** as a white solid (983 mg, 76%); mp 55-56 °C; $[\alpha]_D^{25}$ +96.7 (*c* 1.0 in $CHCl_3$); ν_{max} 1775 (C=O), 1692 (C=O), 1620 (C=C); δ_H (400 MHz, $CDCl_3$) 1.02 (3H, s, C(5)Me_A), 1.63 (3H, s, C(5)Me_B), 5.14 (1H, s, C(4)*H*), 5.90 (1H, dd, *J* 10.6, 1.9, C(3')H_A), 6.49 (1H, dd, *J* 17.0, 1.9, C(3')H_B), 7.16-7.40 (5H, m, *Ph*), 7.60 (1H, dd, *J* 17.0, 10.6, C(2')*H*); δ_C (100 MHz, $CDCl_3$) 23.7 (C(5)Me_A), 28.9 (C(5)Me_B), 67.1 (*C*(4)), 82.6 (*C*(5)), 126.4 (*C*(3')), 127.4, 128.7, 128.9 (*o*,*m*,*p*-*Ph*), 132.1 (*i*-*Ph*), 136.1 (*C*(2')), 153.1 (*C*(2)), 164.7 (*C*(1')); *m/z* (ESI$^+$) 513

([2M+Na]$^+$, 100%), 246 ([M+H]$^+$, 15%); HRMS (ESI$^+$) $C_{14}H_{15}NNaO_3$ ([M+Na]$^+$) requires 268.0944; found 268.0943.

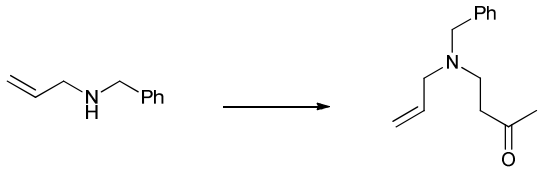
_N_-Benzylprop-2-en-1-amine 227



229 **227**

Allyl amine (5.00 mL, 66.6 mmol) and benzaldehyde **229** (7.11 mL, 70.0 mmol) in EtOH (30 mL) were heated at reflux for 3 h. Upon cooling to 0 °C, $NaBH_4$ (2.52 g, 66.6 mmol) was added. The reaction mixture was allowed to warm to rt and stirred for 72 h then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (200 mL) and H_2O (200 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were washed with brine (150 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 10%→50% EtOAc in 30-40 °C petrol) gave **227** as a yellow oil (7.96 g, 81%);[22] δ_H (400 MHz, $CDCl_3$) 3.26-3.31 (2H, m, C(1)H_2), 3.81 (2H, s, NCH_2Ph), 5.11-5.24 (2H, m, C(3)H_2), 5.90-6.00 (1H, m, C(1)*H*), 7.24-7.38 (5H, m, *Ph*).

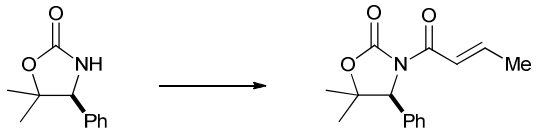
4-(_N_-Allyl-_N_-benzylamino)butan-2-one 226



227 **226**

Methyl vinyl ketone (0.64 mL, 7.90 mmol) was added to a solution of **227** (1.00 g, 6.80 mmol) in CH_2Cl_2 (85 mL). The resultant mixture was stirred at rt for 18 h then concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 20%→50% EtOAc in 30-40 °C petrol) gave **226** as a colourless oil (1.34 g, 91%);[23] δ_H (400 MHz, $CDCl_3$) 2.10 (3H, s, C(1)H_3), 2.59 (2H, t, *J* 7.0, C(3)H_2), 2.78 (2H, t, *J* 7.0, C(4)H_2), 3.07 (2H, app d, *J* 6.5, C(1')H_2), 3.57 (2H, s, NCH_2Ph), 5.14-5.22 (2H, m, C(3')H_2), 5.81-5.91 (1H, m, C(2')*H*), 7.23-7.39 (5H, m, *Ph*).

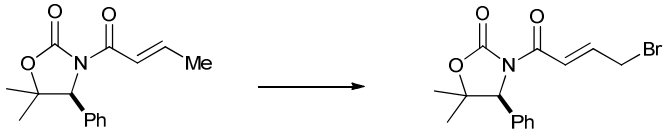
(*S,E*)-3-(But-2'-enoyl)-4-phenyl-5,5-dimethyloxazolidin-2-one 209



212 **209**

BuLi (1.00 M in hexanes, 5.75 mL, 5.75 mmol) and crotonyl chloride (0.71 mL, 6.63 mmol) was added to a solution of **212** (1.00 g, 5.30 mmol) in THF (16 mL) at −78 °C. The reaction mixture was then allowed to warm to rt and stirred for 2 h. Satd aq NH_4Cl (30 mL) was then added and the resultant mixture was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 10%→20% EtOAc in 30-40 °C petrol) gave **209** as a white solid (811 mg, 66%);[20] mp 102-103 °C (lit.,[20] mp 104 °C); $[\alpha]_D^{23}$ +62.9 (*c* 1.0 in $CHCl_3$) {lit.,[20] $[\alpha]_D^{23}$ +84.2 (*c* 1.1 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 0.99 (3H, s, C(5)Me_A), 1.60 (3H, s, C(5)Me_B), 1.93 (3H, app d, *J* 5.4, C(4')H_3), 5.13 (1H, s, C(4)*H*), 7.02-7.40 (7H, m, C(2')*H*, C(3')*H*, *Ph*).

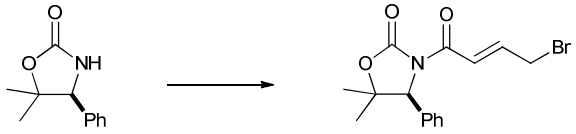
(*S,E*)-3-(4'-Bromobut-2'-enoyl)-4-phenyl-5,5-dimethyloxazolidin-2-one 234



209 **234**

Method A: NBS (137 mg, 0.77 mmol) and benzoyl peroxide (2.0 mg, 0.08 mmol) were added to a solution of **209** (100 mg, 0.39 mmol) in CCl_4 (4 mL). The mixture was heated at reflux for 1.5 h. After cooling to 0 °C, 5% aq $NaHCO_3$ (20 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 10%→20% EtOAc in 30-40 °C petrol) gave **234** as a light yellow solid (94 mg, 72%); $C_{15}H_{16}BrNO_3$ requires C, 53.3; H, 4.8; N, 4.1%; found C, 53.4; H, 4.7; N, 4.1%; mp 78-79 °C; $[\alpha]_D^{23}$ +69.2 (*c* 1.0 in $CHCl_3$); ν_{max} 1773 (C=O), 1695 (C=O), 1637 (C=C); δ_H (400 MHz, $CDCl_3$) 1.02 (3H, s, C(5)Me_A), 1.63 (3H, s, C(5)Me_B), 4.05-4.08 (2H, m, C(4')H_2), 5.13 (1H, s, C(4)*H*), 7.06-7.10 (1H, m, C(2')*H*), 7.15-7.40 (5H, m, *Ph*), 7.54-7.58 (1H, m, C(3')*H*); δ_C (100 MHz, $CDCl_3$) 23.7 (C(5)Me_A), 28.9 (C(5)Me_B), 29.4 (*C*(4')), 67.2 (*C*(4)), 82.8 (*C*(5)), 123.3 (*C*(3')), 126.3, 128.7, 128.9 (*o,m,p-Ph*), 135.9 (*i-Ph*), 143.5 (*C*(2')), 153.1 (*C*(2)), 163.8 (*C*(1')); *m/z* (ESI^+) 699 ($[2M+Na]^+$, 100%), 338

([M+H]$^+$, 20%); HRMS (ESI$^+$) $C_{15}H_{16}{}^{79}BrNNaO_3$ ([M+Na]$^+$) requires 360.0206; found 360.0197.

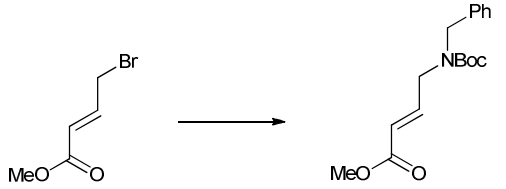


212 **234**

Method B: Following *General Procedure 7*, a solution of acid **243** (200 mg, 1.21 mmol) in CH_2Cl_2 (1 mL) was reacted with $(COBr)_2$ (2.0 M in CH_2Cl_2, 1.30 mL, 2.60 mmol).

BuLi (1.37 M in hexanes, 0.65 mL, 0.89 mmol) and a solution of the above residue in THF (2 mL) was added to a solution of **212** (154 mg, 0.81 mmol) in THF (2 mL) at −78 °C. Purification *via* flash column chromatography (gradient elution, 20%→50% EtOAc in 30-40 °C petrol) gave **234** as a light yellow solid (120 mg, 44%); mp 78-79 °C; $[\alpha]_D^{25}$ +69.0 (*c* 1.2 in $CHCl_3$).

(*E*)-Methyl 4-[*N*-benzyl-*N*-(*tert*-butoxycarbonyl)amino]but-2-enoate 238

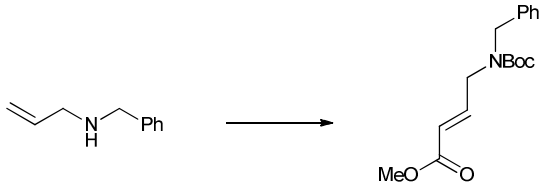


239 **238**

Method A: *Step 1*: Benzyl amine **81** (6.60 mL, 61.2 mmol) and DIPEA (17.7 mL, 102 mmol) were added to a solution of **239** (6.0 mL, 51.0 mmol) in CH_2Cl_2 (75 mL) at 0 °C. The resultant mixture was stirred at rt for 3 h then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (100 mL) and H_2O (100 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), then dried and concentrated *in vacuo* to give **240** as a yellow oil (11.0 g).

Step 2: Di-*tert*-butyldicarbonate (11.8 g, 54.0 mmol) and DIPEA (12 mL, 463 mmol) were added to a solution of **240** (11.0 g, 51.0 mmol) in dioxane (60 mL) and water (18 mL). The resultant mixture was stirred at rt for 2 h then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (200 mL) and 10% aq citric acid (200 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic extracts were washed with brine (200 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 10%→20% EtOAc in 30-40 °C petrol) gave **238** as a clourless oil (5.95 g, 40%); $C_{17}H_{23}NO_4$ requires C, 66.9; H, 7.6; N, 4.6%; found C, 67.0; H,

7.5; N, 4.6%; ν_{max} 1697 (C=O), 1663 (C=C); δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, C*Me*$_3$), 3.74 (3H, s, O*Me*), 3.91-4.03 (2H, br m, C(4)*H*$_2$), 4.40-4.44 (2H, br m, NC*H*$_2$Ph), 5.83-5.87 (1H, m, C(2)*H*), 6.82-6.86 (1H, m, C(3)*H*), 7.21-7.35 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 28.4 (C*Me*$_3$), 46.7(*C*(4)), 50.3 (N*C*H$_2$Ph), 51.6 (O*Me*), 80.4 (*C*Me$_3$), 121.7 (*C*(3)), 127.3, 127.5, 128.6 (*o*,*m*,*p*-*Ph*), 138.2 (*i*-*Ph*), 144.0 (*C*(2)), 159.2 (*C*O$_2$^{t}Bu), 166.5 (*C*(1)); *m/z* (ESI$^+$) 328 ([M+Na]$^+$, 30%); HRMS (ESI$^+$) $C_{17}H_{23}NNaO_4^+$ ([M+Na]$^+$) requires 328.1519; found 328.1517.

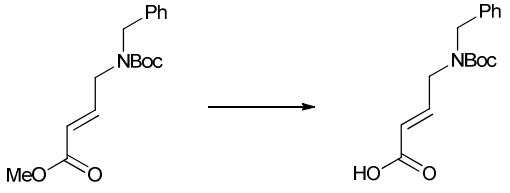


227 **238**

Method B: *Step 1*: $NaHCO_3$ (1.17 g, 13.9 mmol) was added in one portion to a stirred solution of **227** (1.00 g, 6.80 mmol) in EtOH (10 mL) at 0 °C, immediately followed by the addition of di-*tert*-butyldicarbonate (1.56 g, 7.14 mmol) in one portion. The mixture was allowed to warm to rt and stirred for 48 h, after which the reaction mixture was filtered through Celite® (eluent: EtOH) and concentrated *in vacuo*. The residue was partitioned between EtOAc (50 mL) and satd aq $NaHCO_3$ (50 mL) and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), then dried and concentrated *in vacuo* to give *tert*-butyl allyl(benzyl)carbamate as a colourless oil (1.68 g).

Step 2: Methyl acrylate (109 μL, 1.20 mmol) and Grubbs II catalyst **231** (34 mg, 0.04 mmol) were added to a solution of *tert*-butyl allyl(benzyl)carbamate (100 mg, 0.40 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was heated at reflux for 16 h and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 10%→20% EtOAc in 30-40 °C petrol) gave **238** as a clourless oil (86 mg, 70%, >99:1 dr).

4-[*N*-Benzyl-*N*-(*tert*-butoxycarbonyl)amino]but-2-enoic acid 237

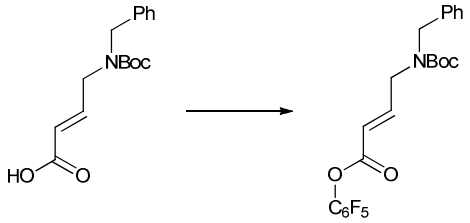


238 **237**

2.0 M aq NaOH (200 mL) was added to a solution of **238** (5.95 g, 19.5 mmol) in THF (200 mL). The reaction mixture was stirred at rt for 16 h and concentrated *in vacuo*. The residue

was partitioned between EtOAc (200 mL) and H_2O (100 mL). The aqueous layer was acidified to pH~4 by addition of 1.0 M aq HCl (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), then dried and concentrated *in vacuo* to give **237** as a colourless oil (5.68 g, quant); ν_{max} 1698 (C=O), 1660 (C=C); δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, C*Me*$_3$), 3.90-4.02 (2H, br m, C(4)*H*$_2$), 4.40-4.45 (2H, br m, NC*H*$_2$Ph), 5.82-5.87 (1H, m, C(2)*H*), 6.92-6.96 (1H, m, C(3)*H*), 7.17-7.39 (5H, m, *Ph*), 10.50 (1H, br s, CO_2H); δ_C (100 MHz, $CDCl_3$) 28.4 (C*Me*$_3$), 46.7(*C*(4)), 50.0 (N*C*H$_2$Ph), 80.6 (*C*Me$_3$), 121.2 (*C*(3)), 127.5, 127.9, 180.0 (*o*,*m*,*p*-*Ph*), 137.5 (*i*-*Ph*), 146.5 (*C*(2)), 171.2 (*C*O$_2^t$Bu), 177.7 (*C*(1)); *m/z* (ESI$^+$) 290 ([M-H$^+$]$^-$, 100%); HRMS (ESI$^+$) $C_{16}H_{21}NNaO_4^+$ ([M+Na]$^+$) requires 314.1363; found 314.1357.

(*E*)-Perfluorophenyl 4-[*N*-benzyl-*N*-(*tert*-butoxycarbonyl)amino]but-2-enoate 241[24]

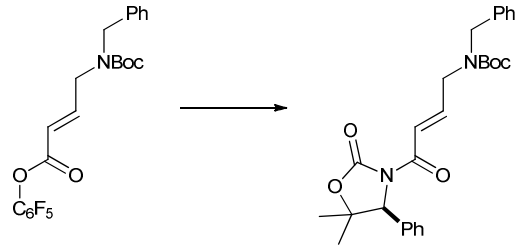


237 **241**

A solution of pentafluorophenol (3.19 g, 17.3 mmol) in EtOAc (30 mL) and DCC (3.57 g, 17.3 mmol) were added to a solution of **237** (4.2 g, 14.4 mmol) in EtOAc (70 mL). The reaction mixture was stirred at rt for 24 h, filtered and concentrated *in vacuo*.

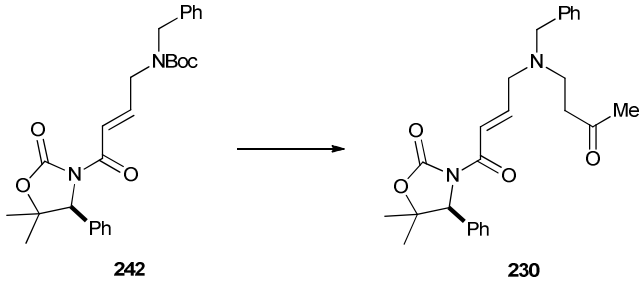
The residue was partitioned between EtOAc (100 mL) and H_2O (100 mL). The aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 20%→30% EtOAc in 30-40 °C petrol) gave **241** as a colourless oil (4.48 g, 68%); ν_{max} 1766 (C=O), 1643 (C=C); δ_H (400 MHz, $CDCl_3$) 1.51 (9H, s, C*Me*$_3$), 4.02-4.05 (2H, br m, C(4)*H*$_2$), 4.50 (2H, s, NC*H*$_2$Ph), 6.03-6.07 (1H, m, C(2)*H*), 7.11-7.15 (1H, m, C(3)*H*), 7.21-7.39 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 28.4 (C*Me*$_3$), 47.4(*C*(4)), 50.8 (N*C*H$_2$Ph), 80.8 (*C*Me$_3$), 118.1 (*C*(3)), 127.4, 127.7, 128.7 (*o*,*m*,*p*-Ph), 137.3 (*i*-Ph), 136.6, 138.4, 139.1, 140.0, 140.7, 141.1 (m, *C*$_6$F$_5$), 149.6 (*C*(2)), 155.4 (*C*O$_2^t$Bu), 161.6 (*C*(1)); δ_F (100 MHz, $CDCl_3$) -162.3 (2F, dd, *J* 41.3, 20.7, *m*-C$_6$*F*$_5$), -158.0 (1F, m, *p*-C$_6$*F*$_5$), -152.5 (2F, dd, *J* 108.9, 19.5, *o*-C$_6$*F*$_5$), *m/z* (ESI$^+$) 480 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{20}F_5NNaO_4^+$ ([M+Na]$^+$) requires 480.1205; found 480.1206.

(*S*,*E*)-3-{4'-[*N*-Benzyl-*N*-(*tert*-butoxycarbonyl)amino]but-2'-enoyl}-4-phenyl-5,5-dimethyloxazolidin-2-one 242



BuLi (1.60 M in hexanes, 3.59 mL, 5.75 mmol) and a solution of **212** (2.40 g, 5.23 mmol) in THF (2 mL) was added to a solution of **241** (1.00 g, 5.23 mmol) in THF (20 mL) at −78 °C. After a further 2 h, satd aq NH_4Cl (30 mL) was added and the reaction mixture was allowed to warm to rt before being concentrated *in vacuo*. The aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with satd aq $NaHCO_3$ (30 mL) and brine (100 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 20%→30% EtOAc in 30-40 °C petrol) gave **242** as a light yellow oil (1.55 g, 60%); $[\alpha]_D^{25}$ +30.4 (*c* 1.0 in $CHCl_3$); ν_{max} 1775 (C=O), 1688 (C=O), 1641 (C=C); δ_H (400 MHz, $CDCl_3$) 1.01 (3H, s, C(5)*Me*$_A$), 1.62 (3H, s, C(5)*Me*$_B$), 1.49 (9H, s, C*Me*$_3$), 3.39-3.93 (1H, m, C(4')*H*$_A$), 4.03-4.07 (1H, m, C(4')*H*$_B$), 4.45 (2H, s, NC*H*$_2$Ph), 5.12 (1H, s, C(4)*H*), 6.83-6.98 (1H, m, C(2')*H*), 7.14-7.18 (1H, m, C(3')*H*), 7.19-7.44 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 23.7 (C(5)*Me*$_A$), 28.4 (C*Me*$_3$), 29.0 (C(5)*Me*$_B$), 47.4(*C*(4')), 50.1 (N*C*H$_2$Ph), 67.2 (*C*(4)), 80.5 (*C*Me$_3$), 82.5 (*C*(5)), 128.0 (*C*(3')), 126.3, 127.4, 128.6, 128.7, 128.9, 136.2 (*o*,*m*,*p*-*Ph*), 137.8 (*i*-*Ph*), 145.8 (*C*(2')), 153.0 (*i*-*Ph*), 155.5 (*C*(2)), 164.3 (*C*O$_2$^{t}Bu), 171.2 (*C*(1')); *m/z* (ESI$^+$) 487 ([M+Na]$^+$, 85%); HRMS (ESI$^+$) $C_{27}H_{32}N_2NaO_5^+$ ([M+Na]$^+$) requires 487.2203; found 487.2195.

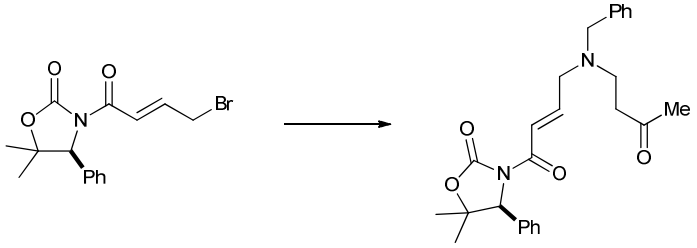
(*S*,*E*)-3-{4'-[*N*-Benzyl-*N*-(3''-oxobutyl)amino]but-2'-enoyl}-4-phenyl-5,5-dimethyloxazolidin-2-one 230



Method A: TFA (1.00 mL, 13.5 mmol) was added to a solution of **242** (300 mg, 0.65 mmol) in CH_2Cl_2 (3 mL) at 0 °C. The resultant mixture was allowed to warm to rt over 2 h and

concentrated *in vacuo* to give **235** as a brown oil (260 mg).

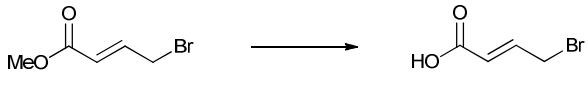
Methyl vinyl ketone (1.00 mL, 12.3 mmol) and Et_3N (1.00 mL, 7.10 mmol) were added to a solution of **235** (260 mg, 0.65 mmol) in CH_2Cl_2 (2 mL). The resultant mixture was stirred at rt for 1h. Then H_2O (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 10%→50% EtOAc in 30-40 °C petrol) gave **230** as a colourless oil (84 mg, 30%); $[\alpha]_D^{25}$ +48.2 (*c* 1.0 in $CHCl_3$); ν_{max} 1771, 1720, 1686 (C=O), 1638 (C=C); δ_H (400 MHz, $CDCl_3$) 1.01 (3H, s, C(5)*Me*$_A$), 1.62 (3H, s, C(5)*Me*$_B$), 2.11 (3H, s, CO*Me*), 2.62 (2H, app t, *J* 7.1, C(2'')*H*$_2$), 2.79 (2H, app t, *J* 7.1, C(1'')*H*$_2$), 3.27 (2H, dd, *J* 5.8, 1.6, C(4')*H*$_2$), 3.59 (2H, s, NC*H*$_2$Ph), 5.13 (1H, s, C(4)*H*), 7.03-7.07 (1H, m, C(2')*H*), 7.21-7.42 (10H, m, *Ph*), 7.50-7.54 (1H, m, C(3')*H*); δ_C (100 MHz, $CDCl_3$) 23.9 (C(5)*Me*$_A$), 29.0 (C(5)*Me*$_B$), 30.1 (CO*Me*), 42.0 (*C*((2'')), 48.8 (*C*((1'')), 55.1 (*C*(4')), 58.8 (N*C*H$_2$Ph), 67.2 (*C*(4)), 82.5 (*C*(5)), 121.8 (*C*(3´)), 126.5, 127.2, 127.5, 128.4, 128.7, 128.8 (*o*,*m*,*p*-*Ph*), 136.2, 138.7 (*i*-*Ph*), 148.4 (*C*(2´)), 153.2 (*C*(2)), 164.1 (*C*(1')), 208.7 (*C*(3″)); *m/z* (ESI$^+$) 435 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{31}N_2O_4^+$ ([M+H]$^+$) requires 435.2278; found 435.2275.



234 **230**

Method B: Following *General Procedure 8*, **234** (4.58 g, 13.6 mmol), 4-(benzylamino)butan-2-one **244** (3.61 g, 20.4 mmol), DIPEA (5.92 mL, 34.0 mmol) and NaI (815 mg, 5.44 mmol) were reacted in acetone (50 mL). Purification *via* flash column chromatography (gradient elution, 40%→60% EtOAc in 30-40 °C petrol) gave **230** as a colourless oil (2.98 g, 52%); $[\alpha]_D^{25}$ +48.0 (*c* 1.0 in $CHCl_3$).

(*E*)-4-Bromobut-2-enoic acid 243



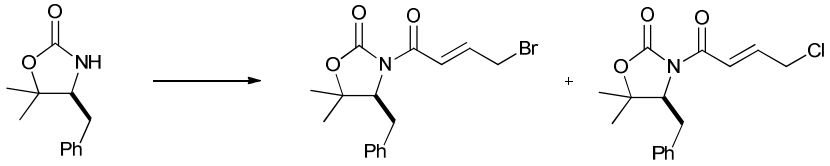
239 **243**

Method A:[25] **239** (3.00 g, 16.8 mmol) was added to a solution of bis(tributyltin) oxide (17.0 mL, 33.5 mmol) in toluene (30 mL). The reaction mixture was heated at reflux for 6 h and concentrated *in vacuo*. The residue was partitioned between EtOAc (100 mL) and 5% aq

$NaHCO_3$ (100 mL). The aqueous layer was acidified to pH 4-5 by addition of 1.0 M aq HCl (30 mL) and extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), then dried and concentrated *in vacuo* to give **243** as a white solid (2.77 g, 40%); mp 71-73 °C (lit.,[26] mp 74 °C); δ_H (400 MHz, $CDCl_3$) 4.04 (2H, dd, *J* 7.2, 1.2, C(4)H_2), 6.04-6.08 (1H, m, C(2)*H*), 7.11-7.15 (1H, m, C(3)*H*).

Method B:[26] $Ba(OH)_2$ (7.90 g, 25.0 mmol) was added portionwise to a solution of **239** (8.95 g, 50.0 mmol) in EtOH (16 mL) and water (45 mL) at −11 °C. Cooling and vigorous stirring was continued for 16 h. Then the reaction mixture was extracted with Et_2O (50 mL). The aqueous layer was treated with concentrated H_2SO_4 (1.34 mL, 25.0 mmol) and extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried and concentrated in *vacuo*. The residue was recrystallised from heptane to give **243** as a white solid (1.67 g, 20%); mp 72-73°C (lit.,[26] mp 74 °C).

(*S*,*E*)-3-(4'-Bromobut-2'-enoyl)-4-benzyl-5,5-dimethyloxazolidin-2-one 245 and (*S*,*E*)-3-(4'-chlorobut-2'-enoyl)-4-benzyl-5,5-dimethyloxazolidin-2-one 247



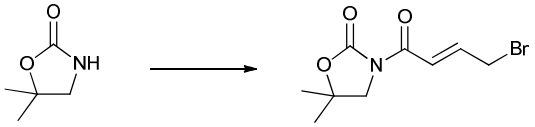
223 **245** **247**

Following *General Procedure 7*, a solution of acid **243** (5.30 g, 32.1 mmol) in CH_2Cl_2 (50 mL) was reacted with $(COCl)_2$ (5.44 mL, 64.3 mmol).

BuLi (1.50 M in hexanes, 18.8 mL, 28.3 mmol) and a solution of the above residue in THF (10 mL) was added to a solution of **223** (5.27 g, 25.7 mmol) in THF (100 mL) at −78 °C. Purification *via* flash column chromatography (gradient elution, 20%→50% EtOAc in 30-40 °C petrol) gave an 84:16 mixture of **245** and **247** as a light yellow oil (2.26 g). Data for the mixture: ν_{max} 2955 (C–H), 1713, 1670 (C=O), 1638 (C=C). Data for **245**: δ_H (400 MHz, $CDCl_3$) 1.37 (3H, s, C(5)Me_A), 1.39 (3H, s, C(5)Me_B), 2.89 (1H, dd, *J* 14.4, 9.6, C(4)CH_A), 3.22 (1H, dd, *J* 14.4, 3.8, C(4)CH_B), 4.08 (2H, d, *J* 7.6, C(4')H_2), 4.56 (1H, dd, *J* 9.6, 3.8, C(4)*H*), 7.11-7.15 (1H, m, C(2')*H*), 7.21-7.34 (5H, m, *Ph*), 7.44-7.48 (1H, m, C(3')*H*); δ_C (100 MHz, $CDCl_3$) 22.3, 28.6 (C(5)Me_2), 29.5 (*C*(4')), 35.2 (C(4)CH_2), 63.8 (*C*(4)), 82.5 (*C*(5)), 123.6 (*C*(3')), 126.9, 128.7, 129.0 (*o,m,p-Ph*), 136.8 (*i-Ph*), 143.0 (*C*(2')), 152.5 (*C*(2)), 164.2 (*C*(1')); Data for **247** [selected peaks]: δ_H (400 MHz, $CDCl_3$) 4.22 (2H, d, *J* 7.6, C(4')H_2), 7.05-7.09 (1H, m, C(2')*H*), 7.49-7.53 (1H, m, C(3')*H*); δ_C (100 MHz, $CDCl_3$)

42.8 (C(4)*C*H_2), 164.3 (*C*(1')).

(*E*)-3-(4'-Bromobut-2'-enoyl)-5,5-dimethyloxazolidin-2-one 246

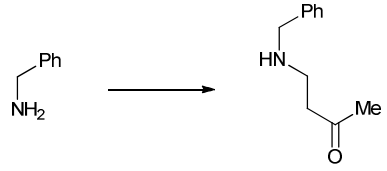


224 **246**

Following *General Procedure 7*, a solution of acid **243** (1.94 g, 11.8 mmol) in CH_2Cl_2 (10 mL) was reacted with $(COBr)_2$ (2.0 M in CH_2Cl_2, 13.0 mL, 26.0 mmol).

BuLi (1.37 M in hexanes, 6.30 mL, 8.62 mmol) and a solution of the above residue in THF (9 mL) was added to a solution of **224** (900 mg, 7.82 mmol) in THF (9 mL) at −78 °C. Purification *via* flash column chromatography (gradient elution, 20%→50% EtOAc in 30-40 °C petrol) gave **246** as a yellow solid (1.02 g, 50%); mp 51-52 °C; ν_{max} 1773 (C=O), 1692 (C=O), 1639 (C=C); δ_H (400 MHz, $CDCl_3$) 1.51 (6H, s, C(5)*Me*$_2$), 3.78 (2H, s, C(4)*H*$_2$), 4.07 (2H, dd, *J* 7.1, 1.3, C(4')*H*$_2$), 7.12-7.16 (1H, m, C(2')*H*), 7.43-7.47 (1H, m, C(3')*H*); δ_C (100 MHz, $CDCl_3$) 27.3 (C(5)*Me*$_2$), 29.5 (*C*(4')), 54.5 (*C*(4)), 78.8 (*C*(5)), 123.3 (*C*(3')), 142.9 (*C*(2')), 152.4 (*C*(2)), 164.4 (*C*(1')); *m/z* (ESI^+) 547 ($[2M+Na]^+$, 100%); HRMS (ESI^+) $C_9H_{12}{}^{79}BrNNaO_3^+$ ($[M+Na]^+$) requires 283.9893; found 283.9892.

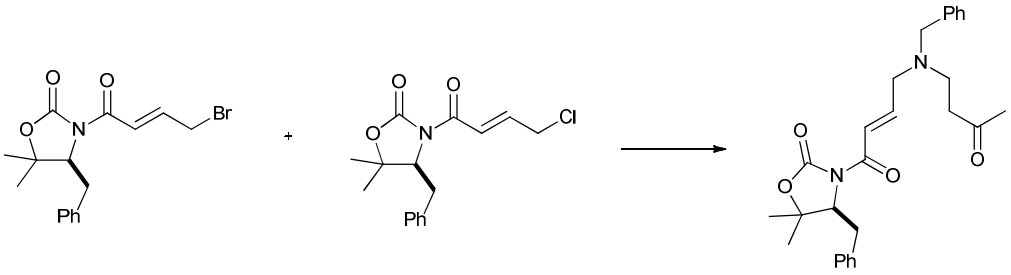
4-(*N*-Benzylamino)butan-2-one 244



81 **244**

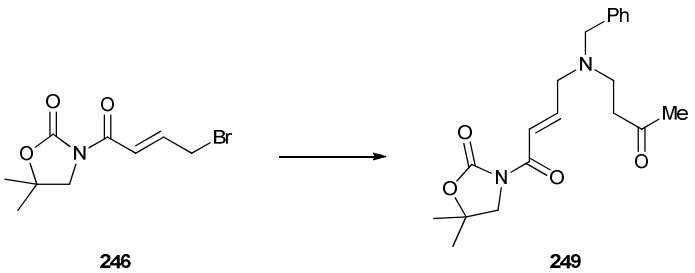
Methyl vinyl ketone (0.42 mL, 5.14 mmol) was added to a solution of benzylamine **81** (0.51 mL, 4.67 mmol) in CH_2Cl_2 (3 mL). The resultant mixture was stirred at rt for 18 h then concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 20%→75% EtOAc in 30-40 °C petrol) gave **244** as a colourless oil (579 mg, 70%);[23] δ_H (400 MHz, $CDCl_3$) 2.16 (3H, s, CO*Me*), 2.67 (2H, t, *J* 6.1, C(3)*H*$_2$), 2.86 (2H, t, *J* 6.1, C(4)*H*$_2$), 3.79 (2H, s, NC*H*$_2$Ph), 7.23-7.36 (5H, m, *Ph*).

(*S*,*E*)-3-{4'-[*N*-Benzyl-*N*-(3''-oxobutyl)amino]but-2'-enoyl}-4-benzyl-5,5-dimethyloxazolidin-2-one 248



Following *General Procedure 8*, an 86:14 mixture of **245** and **247** (2.16 g, 6.13 mmol), 4-(benzylamino)butan-2-one **244** (1.63 g, 9.20 mmol), DIPEA (2.60 mL, 15.3 mmol) and NaI (368 mg, 2.45 mmol) were reacted in acetone (35 mL). Purification *via* flash column chromatography (gradient elution, 40%→60% EtOAc in 30-40 °C petrol) gave **248** as a colourless oil (1.51 g, 55%); $[\alpha]_D^{24}$ −26.0 (*c* 0.8 in $CHCl_3$); ν_{max} 2965 (C–H), 1769 (C=O), 1712 (C=O), 1681 (C=O), 1637 (C=C); δ_H (400 MHz, $CDCl_3$) 1.37 (3H, s, C(5)*Me*$_A$), 1.39 (3H, s, C(5)*Me*$_B$), 2.12 (3H, s, CO*Me*), 2.65 (2H, app t, *J* 7.1, C(2'')H_2), 2.82 (2H, app t, *J* 7.1, C(1'')H_2), 2.90 (1H, dd, *J* 15.4, 10.9, C(4)CH_APh), 3.24 (1H, dd, *J* 15.4, 3.5, C(4)CH_BPh), 3.29 (2H, d, *J* 6.1, C(4')H_2), 3.62 (2H, s, NCH_2Ph), 4.57 (1H, dd, *J* 10.9, 3.5, C(4)*H*), 7.09-7.13 (1H, m, C(2')*H*), 7.19-7.37 (10H, m, *Ph*), 7.40-7.48 (1H, m, C(3')*H*); δ_C (100 MHz, $CDCl_3$) 22.4 (C(5)*Me*$_A$), 28.6 (C(5)*Me*$_B$), 30.1 (CO*Me*), 35.2 (C(4)*C*H_2Ph), 41.9 (*C*(2'')), 48.8 (*C*(1'')), 55.0 (*C*(4')), 58.7 (N*C*H_2Ph), 63.7 (*C*(4)), 82.2 (*C*(5)), 122.3 (*C*(3´)), 126.8, 127.2, 128.4, 128.7, 128.8, 129.1 (*o*,*m*,*p*-*Ph*), 137.0, 138.7 (*i*-*Ph*), 147.8 (*C*(2´)), 152.6 (*C*(2)), 164.9 (*C*(1')), 208.1 (*C*(3″)); *m/z* (ESI$^+$) 471 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{32}N_2NaO_4^+$ ([M+Na]$^+$) requires 471.2254; found 471.2249.

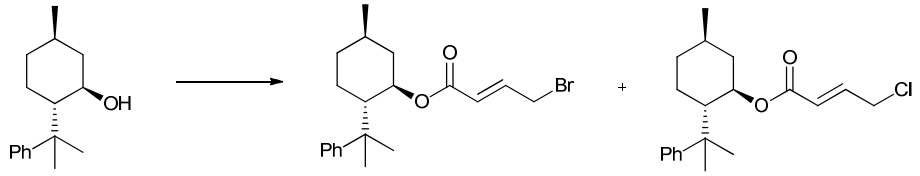
(*E*)-3-{4'-[*N*-Benzyl-*N*-(3''-oxobutyl)amino]but-2'-enoyl}-5,5-dimethyloxazolidin-2-one 249



Following *General Procedure 8*, **246** (920 mg, 3.51 mmol), 4-(benzylamino)butan-2-one **244** (1.24 g, 7.02 mmol), DIPEA (1.50 mL, 17.6 mmol) and NaI (210 mg, 1.40 mmol) were reacted in acetone (10 mL). Purification *via* flash column chromatography (gradient elution,

40%→60% EtOAc in 30-40 °C petrol) gave **249** as a yellow oil (626 mg, 50%); ν_{max} 1773 (C=O), 1695 (C=O), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 1.51 (6H, s, C(5)Me_2), 2.11 (3H, s, CO*Me*), 2.63 (2H, t, *J* 7.1, C(2'')H_2), 2.79 (2H, t, *J* 7.1, C(1'')H_2), 3.27 (2H, dd, *J* 5.8, 1.5, C(4')H_2), 3.60 (2H, s, NCH_2Ph), 3.79 (2H, s, C(4)H_2), 7.10-7.14 (1H, m, C(2')*H*), 7.20-7.35 (5H, m, *Ph*), 7.42-7.46 (1H, m, C(3')*H*); δ_C (100 MHz, $CDCl_3$) 27.1 (C(5)Me_2), 30.0 (CO*Me*), 41.7 (*C*(2'')), 48.6 (*C*(1'')), 54.5 (*C*(4')), 55.2 (*C*(4)), 58.8 (N*C*H_2Ph), 78.5 (*C*(5)), 121.8 (*C*(3´)), 126.8, 127.4, 128.8 (*o*,*m*,*p*-*Ph*), 138.9 (*i*-*Ph*), 147.7 (*C*(2´)), 152.8 (*C*(2)), 165.1 (*C*(1')), 208.1 (*C*(3″)); *m/z* (ESI^+) 359 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{27}N_2O_4^+$ ($[M+H]^+$) requires 359.1965; found 359.1966.

(1'*R*,2'*S*,5'*R*)-2'-(2''-Phenylpropan-2''-yl)-5'-methylcyclohexyl (*E*)-4-bromobut-2-enoate 250 and (1'*R*,2'*S*,5'*R*)-2'-(2''-phenylpropan-2''-yl)-5'-methylcyclohexyl (*E*)-4-chlorobut-2-enoate 251



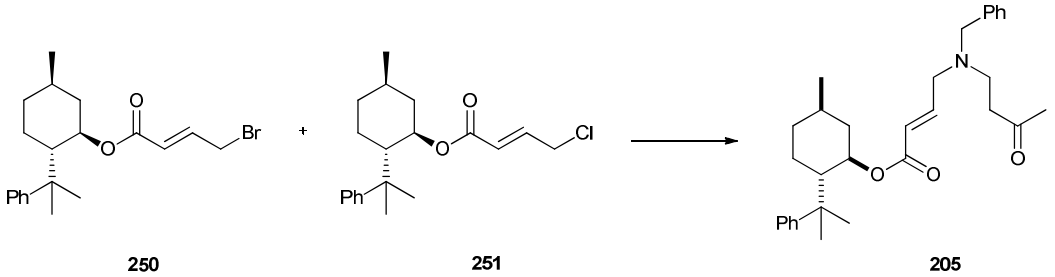
59 **250** **251**

Following *General Procedure 7*, a solution of acid **243** (2.16 g, 13.1 mmol) in CH_2Cl_2 (15 mL) was reacted with $(COCl)_2$ (2.20 mL, 26.2 mmol).

A solution of **59** (1.52 g, 6.54 mmol) in THF (15 mL) at 0 °C was treated with a solution of acid chloride in THF (10 mL) and DIPEA (1.14 mL, 6.54 mmol). After stirring at rt for 18 h, the resultant mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 20%→50% EtOAc in 30-40 °C petrol) gave an 86:14 mixture of **250** and **251** as a light yellow oil (2.27 g); Data for the mixture: ν_{max} 2955 (C–H), 1727 (C=O), 1629 (C=C). Data for **250**: δ_H (400 MHz, $CDCl_3$) 0.84-1.20 (3H, m, CH_2, C*H*), 0.89 (3H, d, *J* 6.6, C(5')*Me*), 1.22 (3H, s, C(1″)H_3), 1.32 (3H, s, C(3″)H_3), 1.40-2.12 (5H, m, 2 × CH_2, C*H*), 2.53 (1H, app td, *J* 18.7, 8.6, C(4)H_A), 2.64-2.78 (1H, m, C(4)H_B), 4.86 (1H, app td, *J* 10.9, 4.6, C(1')*H*), 5.74 (1H, app q, *J* 8.6, C(2)*H*), 6.06-6.09 (1H, m, C(3)*H*), 7.11-7.34 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.8 (C(5')*Me*), 23.9 (*C*(3″)), 26.4 (*C*H_2), 28.9 (*C*(1″)), 31.3 (*C*H), 34.5 (*C*H_2), 35.3 (*C*(4)), 39.6 (*C*(2″)), 41.7 (*C*H_2), 50.3 (*C*H), 74.6 (*C*(1')), 110.0 (*C*(2)), 120.3 (*C*(3)), 124.0, 125.2, 127.8 (*o*,*m*,*p*-*Ph*), 151.6 (*i*-*Ph*), 169.6 (*C*(1)); Data for **251** [selected peaks]: δ_H (400 MHz, $CDCl_3$) 6.07-6.10 (1H, m,

C(2)*H*), 6.24 (1H, app d, *J* 7.1, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 32.6 (*C*(4)), 169.8 (*C*(1)).

(1''*R*,2''*S*,5''*R*)-2''-(2'''-Phenylpropan-2'''-yl)-5''-methylcyclohexyl 4-[*N*-Benzyl-*N*-(3'-oxobutyl)amino]but-2-enoate 205



250 **251** **205**

Following *General Procedure 8*, an 86:14 mixture of **250** and **251** (1.13 g, 2.98 mmol), 4-(benzylamino)butan-2-one **244** (792 g, 4.47 mmol), DIPEA (1.30 mL, 7.45 mmol) and NaI (178 mg, 1.19 mmol) were reacted in acetone (12 mL). Purification *via* flash column chromatography (gradient elution, 40%→60% EtOAc in 30-40 °C petrol) gave **205** as a light yellow oil (854 mg, 60%); $[\alpha]_D^{24}$ −3.9 (*c* 0.9 in $CHCl_3$); ν_{max} 2953 (C–H), 1709 (C=O), 1656 (C=C); δ_H (400 MHz, $CDCl_3$) 0.82-1.19 (3H, m, CH_2, C*H*), 0.89 (3H, d, *J* 6.6, C(5″)*Me*), 1.22 (3H, s, C(1'')H_3), 1.31 (3H, s, C(3''')H_3), 1.43-2.10 (5H, m, 2 × CH_2, C*H*), 2.11 (3H, s, CO*Me*), 2.59 (2H, app t, *J* 6.5, C(2')H_2), 2.75 (2H, app t, *J* 6.5, C(1')H_2), 3.00-3.13 (2H, m, C(4)H_2), 3.54 (2H, AB system, J_{AB} 13.9, NCH_2Ph), 4.87 (1H, app td, *J* 10.9, 4.6, C(1″)*H*), 5.47 (1H, d, *J* 13.9, C(2)*H*), 6.43-6.54 (1H, m, C(3)*H*), 7.00-7.39 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.8 (C(5″)*Me*), 25.0 (*C*(3''')), 26.6 (*C*H_2), 27.9 (*C*(1''')), 30.0 (*C*H), 31.3 (CO*Me*), 34.6 (*C*H_2), 39.7 (*C*(2''')), 41.7 (*C*(2')), 41.9 (*C*H_2), 48.7 (*C*(1')), 50.5 (*C*H), 54.6 (*C*(4)), 58.6 (N*C*H_2), 74.3 (*C*(1″)), 123.3 (*C*(2)), 124.8, 125.4, 127.2, 127.9, 128.3, 128.8 (*o,m,p-Ph*), 138.8, 151.6 (*i-Ph*), 145.1 (*C*(3)), 165.3 (*C*(1)), 207.9 (*C*(3')); *m/z* (ESI^+) 476 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{31}H_{42}NO_3^+$ ($[M+H]^+$) requires 476.3159; found 476.3153.

(*S*,*S*)-3-[2'-(1''-Benzyl-4''-acetylpyrrolidin-3''-yl)acetyl]-5,5-dimethyloxazolidin-2-one 254

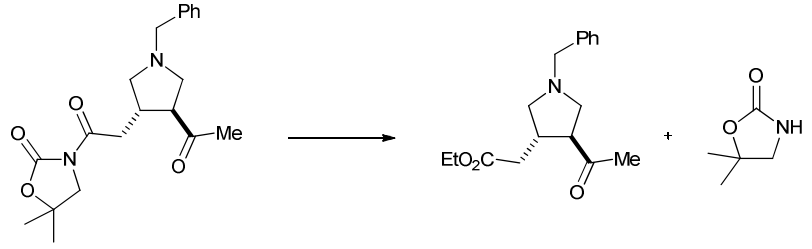
249 (*S*,*S*)-**254**

Method A: Following *General Procedure 9*, **249** (100 mg, 0.28 mmol) was reacted with (*S*)-

α-methylbenzylamine **80** (34 mg, 0.28 mmol) in THF (1.00 mL) for 24 h. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave (*S*,*S*)-**254** as a colourless oil (38 mg, 38%, 40% ee[27]); ν_{max} 1750 (C=O), 1712 (C=O); δ_H (400 MHz, $CDCl_3$) 1.46 (3H, s, C(5)*Me*$_A$), 1.47 (3H, s, C(5)*Me*$_B$), 2.15 (3H, s, CO*Me*), 2.36 (1H, dd, *J* 8.8, 5.1, C(2')*H*$_A$), 2.54-2.59 (1H, m, C(2″)*H*$_A$), 2.78-3.02 (5H, m, C(2')*H*$_B$, C(2″)*H*$_B$, C(3″)*H*, C(4″)*H*, C(5″)*H*$_A$), 3.17 (1H, dd, *J* 16.2, 6.3, C(5″)*H*$_B$), 3.57 (2H, app d, *J* 4.0, C(4)*H*$_2$), 3.65 (2H, app s, NC*H*$_2$Ph), 7.18-7.33 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.3 (C(5)*Me*$_2$), 28.7 (CO*Me*), 35.7 (*C*(4″)), 40.6 (*C*(5″)), 54.1 (N*C*H$_2$Ph), 56.1 (*C*(2″)), 56.7 (*C*(3″)), 59.7 (*C*(2')), 59.8 (*C*(4)), 78.8 (*C*(5)), 127.0, 128.3, 128.6 (*o*,*m*,*p*-*Ph*), 138.6 (*i*-*Ph*), 152.7 (*C*(2)), 172.4 (*C*(1')), 208.5 (*C*OMe); *m/z* (ESI$^+$) 359 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{27}N_2O_4^+$ ([M+H]$^+$) requires 359.1965; found 359.1966.

Method B: Following *General Procedure 9*, **249** (28 mg, 0.08 mmol) was reacted with (*S*)-**80**·HOAc (14 mg, 0.08 mmol) in THF (0.28 mL) for 24 h. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave (*S*,*S*)-**254** as a colourless oil (17 mg, 61%, 30% ee[27]).

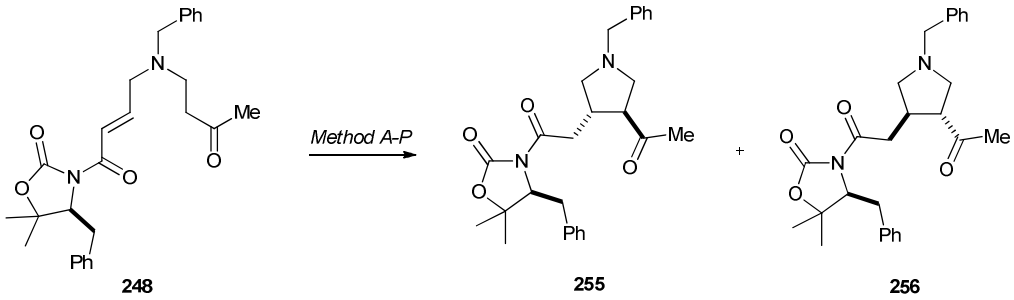
(*S*,*S*)-Ethyl-2-(1'-benzyl-4'-acetylpyrrolidin-3'-yl)acetate 198 and 5,5-dimethyloxazolidin-2-one 234



(*S*,*S*)-**254** (*S*,*S*)-**198** **234**

Following *General Procedure 10*, (*S*,*S*)-**254** (100 mg, 0.28 mmol, 10% ee) was reacted with LiOEt (1.0 M in EtOH, 0.70 mL, 0.70 mmol) in EtOH (1.0 mL). Purification *via* flash column chromatography (gradient elution, 50%→100% EtOAc in 30-40 °C petrol) gave (*S*,*S*)-**198** as a colourless oil (54 mg, 72%, 10% ee[28]); $[\alpha]_D^{23}$ −1.2 (*c* 0.50 in $CHCl_3$); {lit.[23] $[\alpha]_D^{22}$ −5.1 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.24 (3H, t, *J* 7.3, CH_2CH_3), 2.19 (3H, s, CO*Me*), 2.37-2.40 (1H, m, C(3')*H*), 2.47-2.49 (2H, m, C(2)*H*$_2$), 2.58-2.61 (1H, m, C(4')*H*), 2.79-2.90 (4H, m, C(2')*H*$_2$, C(5')*H*$_2$), 3.62 (1H, AB system, J_{AB} 13.0, NC*H*$_2$Ph), 4.11 (2H, q, *J* 7.3, CH_2CH_3), 7.23-7.34 (5H, m, *Ph*). Further elution gave **234** as a white solid (22 mg, 70%); mp 79-80 °C (lit.[21] mp 80 °C).

(*S*,*S*,*S*)-3-[2'-(1''-Benzyl-4''-acetylpyrrolidin-3''-yl)acetyl]-4-benzyl-5,5-dimethyloxazolidin-2-one 255 and (4*S*,3''*R*,4''*R*)-3-[2'-(1''-benzyl-4''-acetylpyrrolidin-3''-yl)acetyl]-4-benzyl-5,5-dimethyloxazolidin-2-one 256



248 255 256

Method A: Following *General Procedure 9*, **248** (25 mg, 0.06 mmol) was reacted with benzylamine **81** (6 mg, 0.06 mmol) in THF (0.25 mL) for 24 h to give a 60:40 mixture of **255** and **256**. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave a 60:40 mixture of **255** and **256** as a colourless oil (3 mg, 10%); Data for the mixture: ν_{max} 1755 (C=O), 1708 (C=O), 1700 (C=O); *m/z* (ESI$^+$) 471 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{32}N_2NaO_4^+$ ([M+Na]$^+$) requires 471.2254; found 471.2249. Data for **255**: δ_H (400 MHz, $CDCl_3$) 1.36 (3H, s, C(5)*Me*$_A$), 1.37 (3H, s, C(5)*Me*$_B$), 2.17 (3H, s, CO*Me*), 2.30 (1H, dd, *J* 9.1, 5.3, C(2')*H*$_A$), 2.55-2.61 (1H, m, C(2″)*H*$_A$), 2.78-2.95 (6H, m, C(4)C*H*$_A$, C(2')*H*$_B$, C(2″)*H*$_B$, C(3″)*H*, C(5″)*H*$_2$), 3.04-3.14 (2H, m, C(4)C*H*$_B$, C(4″)*H*), 3.60 (2H, AB system, J_{AB} 13.1, NC*H*$_2$Ph), 4.49 (1H, dd, *J* 9.4, 4.6, C(4)*H*), 7.14-7.36 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 22.3, 28.5 (C(5)*Me*$_2$), 28.7 (CO*Me*), 35.3 (*C*(4″)), 35.7 (*C*(5″)), 40.9 (C(4)C*H*$_2$), 56.1 (*C*(2″)), 56.8 (*C*(3″)), 59.7 (*C*(2')), 59.8 (NC*H*$_2$Ph), 63.3 (*C*(4)), 82.3 (*C*(5)), 126.8, 127.1, 128.3, 128.7, 128.9, 129.0 (*o*,*m*,*p*-*Ph*), 136.9, 138.8 (*i*-*Ph*), 152.8 (*C*(2)), 172.1 (*C*(1')), 208.5 (*C*OMe). Data for **256** [selected peaks]: δ_H (400 MHz, $CDCl_3$) 1.46 (3H, s, C(5)*Me*$_A$), 1.48 (3H, s, C(5)*Me*$_B$), 2.15 (3H, s, CO*Me*), 2.38 (1H, dd, *J* 9.1, 5.3, C(2')*H*$_A$); δ_C (100 MHz, $CDCl_3$) 22.7, 29.0 (C(5)*Me*$_2$), 29.7 (CO*Me*), 35.4 (*C*(4″)), 37.1 (*C*(5″)), 56.2 (*C*(2″)), 56.6 (*C*(3″)), 63.0 (*C*(4)), 82.1 (*C*(5)).

Method B: Following *General Procedure 9*, **248** (25 mg, 0.06 mmol) was reacted with **81**·HOAc (9 mg, 0.06 mmol) in THF (0.25 mL) for 24 h to give a 63:37 mixture of **255** and **256**. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave a 63:37 mixture of **255** and **256** as a colourless oil (16 mg, 64%).

Method C: Following *General Procedure 9*, **248** (25 mg, 0.06 mmol) was reacted with isopropylamine **257** (3 mg, 0.06 mmol) in THF (0.25 mL) for 24 h to give a 68:32 mixture

of **255** and **256**. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave a 68:32 mixture of **255** and **256** as a colourless oil (3 mg, 10%).

Method D: Following *General Procedure 9*, **248** (25 mg, 0.06 mmol) was reacted with **257**·HOAc (7 mg, 0.06 mmol) in THF (0.25 mL) for 24 h to give a 68:32 mixture of **255** and **256**. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave a 68:32 mixture of **255** and **256** as a colourless oil (19 mg, 75%).

Method E: Following *General Procedure 9*, **248** (25 mg, 0.06 mmol) was reacted with (*S*)-α-methylbenzylamine **80** (7.0 mg, 0.06 mmol) in THF (0.25 mL) for 24 h to give a 73:27 mixture of **255** and **256**. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave a 73:27 mixture of **255** and **256** as a colourless oil (11 mg, 38%).

Method F: Following *General Procedure 9*, **248** (30 mg, 0.07 mmol) was reacted with (*S*)-**80**·HOAc (12 mg, 0.07 mmol) in THF (0.30 mL) for 24 h to give an 80:20 mixture of **255** and **256**. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave an 80:20 mixture of **255** and **256** as a colourless oil (24 mg, 80%).

Method G: Following *General Procedure 9*, **248** (25 mg, 0.06 mmol) was reacted with (*S*)-α-ethylbenzylamine **252** (8 mg, 0.06 mmol) in THF (0.25 mL) for 24 h to give an 80:20 mixture of **255** and **256**. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave an 80:20 mixture of **255** and **256** as a colourless oil (8 mg, 30%).

Method H: Following *General Procedure 9*, **248** (25 mg, 0.06 mmol) was reacted with (*S*)-**252**·HOAc (11 mg, 0.06 mmol) in THF (0.25 mL) for 24 h to give an 80:20 mixture of **255** and **256**. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave an 80:20 mixture of **255** and **256** as a colourless oil (22 mg, 86%).

Method I: Following *General Procedure 9*, **248** (25 mg, 0.06 mmol) was reacted with (*S*)-1-(1'-naphthyl)ethylamine **253** (10 mg, 0.06 mmol) in THF (0.25 mL) for 5 d to give an 80:20 mixture of **255** and **256**. Purification *via* flash column chromatography (gradient elution,

20%→100% EtOAc in 30-40 °C petrol) gave an 80:20 mixture of **255** and **256** as a colourless oil (13 mg, 50%).

Method J: Following *General Procedure 9*, **248** (25 mg, 0.06 mmol) was reacted with (*S*)-**253**·HOAc (14 mg, 0.06 mmol) in THF (0.25 mL) for 24 h to give an 80:20 mixture of **255** and **256**. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave an 80:20 mixture of **255** and **256** as a colourless oil (20 mg, 80%).

Method K: Following *General Procedure 9*, **248** (25 mg, 0.06 mmol) was reacted with (*R*)-α-methylbenzylamine **80** (7.0 mg, 0.06 mmol) in THF (0.25 mL) for 24 h to give a 58:42 mixture of **255** and **256**. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave a 58:42 mixture of **255** and **256** as a colourless oil (8 mg, 30%).

Method L: Following *General Procedure 9*, **248** (30 mg, 0.07 mmol) was reacted with (*R*)-**80**·HOAc (12 mg, 0.07 mmol) in THF (0.30 mL) for 24 h to give a 58:42 mixture of **255** and **256**. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave a 58:42 mixture of **255** and **256** as a colourless oil (26 mg, 85%).

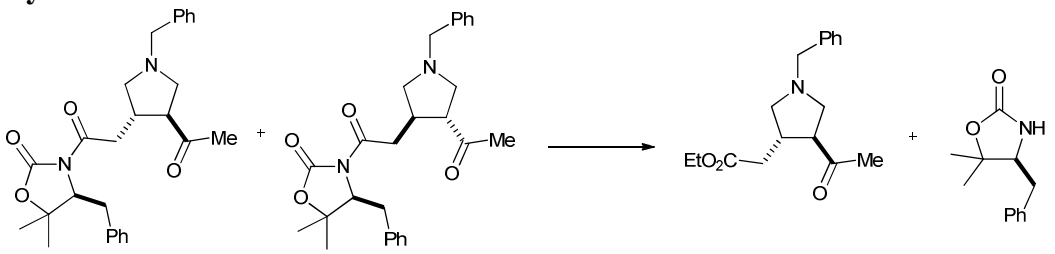
Method M: Following *General Procedure 9*, **248** (25 mg, 0.06 mmol) was reacted with (*R*)-α-ethylbenzylamine **252** (8 mg, 0.06 mmol) in THF (0.25 mL) for 24 h to give a 50:50 mixture of **255** and **256**. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave a 50:50 mixture of **255** and **256** as a colourless oil (5 mg, 20%).

Method N: Following *General Procedure 9*, **248** (25 mg, 0.06 mmol) was reacted with (*R*)-**252**·HOAc (11 mg, 0.06 mmol) in THF (0.25 mL) for 24 h to give a 56:44 mixture of **255** and **256**. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave a 56:44 mixture of **255** and **256** as a colourless oil (20 mg, 80%).

Method O: Following *General Procedure 9*, **248** (25 mg, 0.06 mmol) was reacted with (*R*)-1-(1'-naphthyl)ethylamine **253** (10 mg, 0.06 mmol) in THF (0.25 mL) for 5 d to give a 50:50 mixture of **255** and **256**. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave a 50:50 mixture of **255** and **256** as a colourless oil (11 mg, 45%).

Method P: Following *General Procedure 9*, **248** (25 mg, 0.06 mmol) was reacted with (*R*)-**253**·HOAc (14 mg, 0.06 mmol) in THF (0.25 mL) for 24 h to give a 50:50 mixture of **255** and **256**. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave a 50:50 mixture of **255** and **256** as a colourless oil (21 mg, 84%).

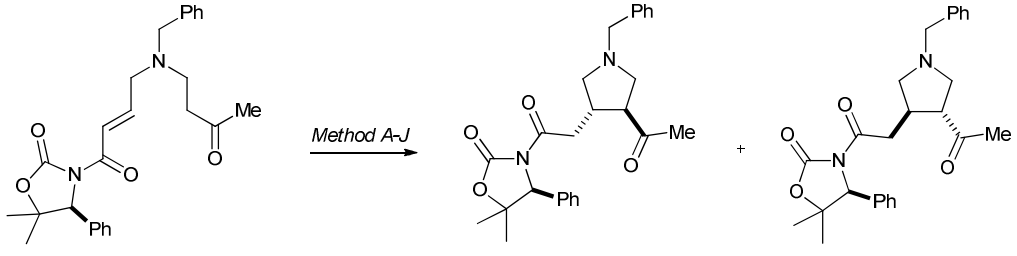
(*S*,*S*)-Ethyl-2-(1'-benzyl-4'-acetylpyrrolidin-3'-yl)acetate 198 and (*S*)-4-benzyl-5,5-dimethyloxazolidin-2-one 223



255 **256** (*S*,*S*)-**198** **223**

Following *General Procedure 10*, a 73:27 mixture of **255** and **256** (80 mg, 0.18 mmol) was reacted with LiOEt (1.0 M in EtOH, 0.45 mL, 0.45 mmol) in EtOH (0.5 mL). Purification *via* flash column chromatography (gradient elution, 50%→100% EtOAc in 30-40 °C petrol) gave (*S*,*S*)-**198** as a colourless oil (32 mg, 65%, 46% ee[28]); $[\alpha]_D^{23}$ −5.7 (*c* 0.80 in $CHCl_3$); {lit.[23] $[\alpha]_D^{22}$ −5.1 (*c* 1.0 in $CHCl_3$)}. Further elution gave **223** as a white solid (30 mg, 73%); mp 59-60 °C (lit.[20] mp 59 °C); $[\alpha]_D^{25}$ −104.6 (*c* 0.6 in $CHCl_3$); {lit.[20] $[\alpha]_D^{25}$ −103.5 (*c* 0.6 in $CHCl_3$).

(*S*,*S*,*S*)-3-[2'-(1''-Benzyl-4''-acetylpyrrolidin-3''-yl)acetyl]-4-phenyl-5,5-dimethyloxazolidin-2-one 258 and (4*S*,3''*R*,4''*R*)-3-[2'-(1''-benzyl-4''-acetylpyrrolidin-3''-yl)acetyl]-4-phenyl-5,5-dimethyloxazolidin-2-one 259



230 **258** **259**

Method A: Following *General Procedure 9*, **230** (50 mg, 0.12 mmol) was reacted with benzylamine **81** (12 mg, 0.12 mmol) in THF (0.50 mL) for 24 h to give a 50:50 mixture of **258** and **259**. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave a 50:50 mixture of **258** and **259** as a colourless oil (8 mg, 15%); Data for the mixture: ν_{max} 1775 (C=O), 1706 (C=O); *m/z* (ESI$^+$) 435 ([M+H]$^+$, 100%);

HRMS (ESI$^+$) $C_{26}H_{31}N_2O_4^+$ ([M+H]$^+$) requires 435.2278; found 435.2275. Data for **258**: δ_H (500 MHz, $CDCl_3$) 0.97 (3H, s, C(5)*Me*$_A$), 1.60 (3H, s, C(5)*Me*$_B$), 2.11 (3H, s, CO*Me*), 2.32-2.37 (1H, m, C(2´)*H*$_A$), 2.53-2.58 (1H, m, C(2")*H*$_A$), 2.76-2.85 (2H, m, C(2´)*H*$_B$, C(3")*H*), 2.86-2.93 (2H, m, C(2")*H*$_B$, C(4")*H*), 3.17-3.21 (2H, m, C(5")*H*$_2$), 3.58 (2H, AB system, J_{AB} 12.9, NC*H*$_2$Ph), 5.04 (1H, s, C(4)*H*), 7.06-7.40 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 23.7 (C(5)*Me*$_A$), 28.6 (C(5)*Me*$_B$), 29.0 (CO*Me*), 35.8 (*C*(4")), 40.9 (*C*(5")), 55.9 (*C*(2")), 56.6 (*C*(3")), 59.6 (N*C*H$_2$Ph), 66.9 (*C*(4)), 82.6 (*C*(5)), 127.1, 128.3, 128.6, 128.7, 128.8, 128.9 (*o*, *m*, *p-Ph*), 136.1, 136.8 (*i-Ph*), 153.2 (*C*(2)), 171.7 (*C*(1')), 208.5 (*C*OMe). Data for **259** [selected peaks]: δ_H (500 MHz, $CDCl_3$) 0.99 (3H, s, C(5)*Me*$_A$), 1.62 (3H, s, C(5)*Me*$_B$), 2.04 (3H, s, CO*Me*), 2.38-2.45 (1H, m, C(2´)*H*$_A$), 5.01 (1H, s, C(4)*H*); δ_C (125 MHz, $CDCl_3$) 26.0 (C(5)*Me*$_A$), 28.1 (C(5)*Me*$_B$), 29.7 (CO*Me*), 41.1 (*C*(5")), 56.1 (*C*(2")), 65.9 (*C*(4)), 84.5 (*C*(5)), 208.3 (*C*OMe).

Method B: Following *General Procedure 9*, **230** (25 mg, 0.06 mmol) was reacted with **81**·HOAc (10 mg, 0.06 mmol) in THF (0.25 mL) for 24 h to give a 55:45 mixture of **258** and **259**. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave a 55:45 mixture of **258** and **259** as a colourless oil (14 mg, 55%).

Method C: Following *General Procedure 9*, **230** (25 mg, 0.06 mmol) was reacted with isopropylamine **257** (4 mg, 0.06 mmol) in THF (0.25 mL) for 24 h to give a 55:45 mixture of **258** and **259**. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave a 55:45 mixture of **258** and **259** as a colourless oil (9 mg, 36%).

Method D: Following *General Procedure 9*, **230** (25 mg, 0.06 mmol) was reacted with **257**·HOAc (8 mg, 0.06 mmol) in THF (0.25 mL) for 24 h to give a 55:45 mixture of **258** and **259**. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave a 55:45 mixture of **258** and **259** as a colourless oil (15 mg, 60%).

Method E: Following *General Procedure 9*, **230** (25 mg, 0.06 mmol) was reacted with (*S*)-α-methylbenzylamine **80** (7.0 mg, 0.06 mmol) in THF (0.25 mL) for 24 h to give a 73:27 mixture of **258** and **259**. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave a 73:27 mixture of **258** and **259** as a colourless oil (6.0 mg, 25%). Further elution gave **260** as a colourless oil (11 mg, 60%, 75:25 dr); Data for the mixture: ν_{max} 1673 (C=O); *m/z* (ESI$^+$) 295 ([M+H]$^+$, 50%), 589 ([2M+H]$^+$, 100%);

HRMS (ESI$^+$) $C_{19}H_{23}N_2O^+$ ([M+H]$^+$) requires 295.1805; found 295.1806. Data for the major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 1.34 (3H, d, *J* 6.6, C(α)*Me*), 2.34 (1H, dd, *J* 16.7, 6.8, C(3)H_A), 2.64 (1H, dd, *J* 16.7, 7.1, C(3)H_B), 2.91 (1H, dd, *J* 9.6, 4.6, C(4)*H*), 3.29 (2H, m, C(5)H_2), 3.78 (1H, q, *J* 6.8, C(α)*H*), 4.45 (2H, AB system, J_{AB} 13.4, NCH_2Ph), 7.16-7.39 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 24.6 (C(α)*Me*), 38.8 (*C*(3)), 46.4 (*C*(5)), 49.0 (*C*(4)), 53.4 (N*C*H_2Ph), 56.3 (*C*(α)), 126.5, 127.3, 127.6, 128.2, 128.6, 128.7 (*o*,*m*,*p*-*Ph*), 136.7, 144.8 (*i*-*Ph*), 173.2 (*C*(2)).

Method F: Following *General Procedure 9*, **230** (25 mg, 0.06 mmol) was reacted with (*S*)-**80**·HOAc (11 mg, 0.06 mmol) in THF (0.25 mL) for 24 h to give a 73:27 mixture of **258** and **259**. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave a 73:27 mixture of **258** and **259** as a colourless oil (19 mg, 75%).

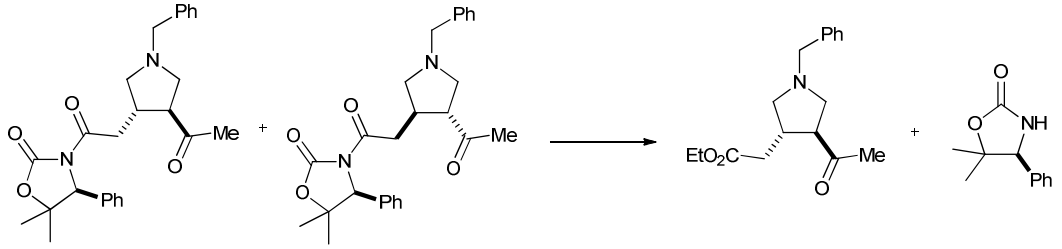
Method G: Following *General Procedure 9*, **230** (25 mg, 0.06 mmol) was reacted with (*S*)-**80**·HOAc (11 mg, 0.06 mmol) in THF (0.25 mL) and H_2O (13 μL) for 7 h to give a 77:23 mixture of **258** and **259**. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave a 77:23 mixture of **258** and **259** as a colourless oil (16 mg, 64%).

Method H: Following *General Procedure 9*, **230** (25 mg, 0.06 mmol) was reacted with (*R*)-α-methylbenzylamine **80** (7.0 mg, 0.06 mmol) in THF (0.25 mL) for 24 h to give a 49:51 mixture of **258** and **259**. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave a 49:51 mixture of **258** and **259** as a colourless oil (4.0 mg, 14%). Further elution gave **260** as a colourless oil (11 mg, 63%, 49:51 dr).

Method I: Following *General Procedure 9*, **230** (25 mg, 0.06 mmol) was reacted with (*R*)-**80**·HOAc (11 mg, 0.06 mmol) in THF (0.25 mL) for 24 h to give a 45:55 mixture of **258** and **259**. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave a 45:55 mixture of **258** and **259** as a colourless oil (19.3 mg, 77%).

Method J: Following *General Procedure 9*, **230** (25 mg, 0.06 mmol) was reacted with (*R*)-**80**·HOAc (11 mg, 0.06 mmol) in THF (0.25 mL) and H_2O (13 μL) for 7 h to give a 45:55 mixture of **258** and **259**. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave a 45:55 mixture of **258** and **259** as a colourless oil (17 mg, 66%).

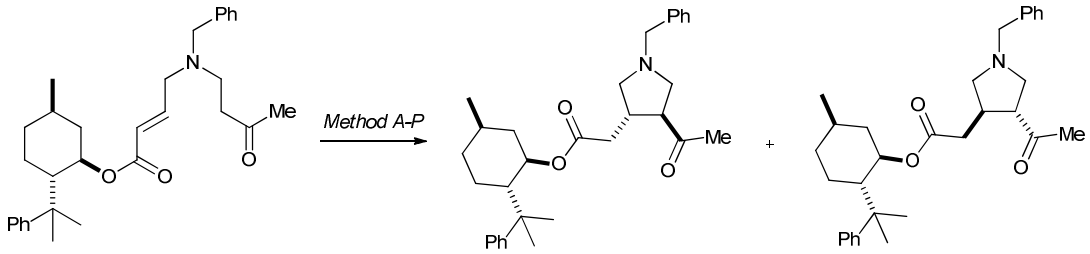
(*S*,*S*)-Ethyl-2-(1'-benzyl-4'-acetylpyrrolidin-3'-yl)acetate 198 and (*S*)-4-phenyl-5,5-dimethyloxazolidin-2-one 212



258 **259** (*S*,*S*)-**198** **212**

Following *General Procedure 10*, a 60:40 mixture of **258** and **259** (200 mg, 0.46 mmol) was reacted with LiOEt (1.0 M in EtOH, 1.15 mL, 1.15 mmol) in EtOH (1 mL). Purification *via* flash column chromatography (gradient elution, 50%→100% EtOAc in 30-40 °C petrol) gave (*S*,*S*)-**198** as a colourless oil (93 mg, 70%, 20% ee[28]); $[\alpha]_D^{23}$ −2.5 (*c* 0.85 in $CHCl_3$); {lit.[23] $[\alpha]_D^{22}$ −5.1 (*c* 1.0 in $CHCl_3$)}. Further elution gave **212** as a white solid (66 mg, 75%); mp 47-48 °C (lit.[20] mp 49 °C); $[\alpha]_D^{23}$ +80.0 (*c* 0.6 in $CHCl_3$); {lit.[20] $[\alpha]_D^{23}$ +79.0 (*c* 0.5 in $CHCl_3$)}.

(1''*R*,2''*S*,5''*R*)-2''-(2'''-Phenylpropan-2'''-yl)-5''-methylcyclohexyl (*S*,*S*)-2-(1'-benzyl-4'-acetylpyrrolidin-3'-yl)acetate 263 and (1''*R*,2''*S*,5''*R*)-2''-(2'''-phenylpropan-2'''-yl)-5''-methylcyclohexyl (*R*,*R*)-2-(1'-benzyl-4'-acetylpyrrolidin-3'-yl)acetate 264



205 **263** **264**

Method A: Following *General Procedure 9*, **205** (25 mg, 0.05 mmol) was reacted with benzylamine **81** (6 mg, 0.05 mmol) in THF (0.25 mL) for 14 days to give a 63:37 mixture of **263** and **264**. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave a 63:37 mixture of **263** and **264** as a colourless oil (19 mg, 75%); Data for the mixture: ν_{max} 2922 (C–H), 1717 (C=O); *m/z* (ESI^+) 476 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{31}H_{42}NO_3^+$ ($[M+H]^+$) requires 476.3159; found 476.3153. Data for **263**: δ_H (400 MHz, $CDCl_3$) 0.81-1.16 (3H, m, CH_2, C*H*), 0.86 (3H, d, *J* 6.6, C(5″)*Me*), 1.18 (3H, s, C(1''')H_3), 1.28 (3H, s, C(3''')H_3), 1.38-1.76 (5H, m, 2 × CH_2, C*H*), 1.77-2.05 (3H, m, C(4')*H*, C(5')H_2), 2.15 (3H, s, CO*Me*), 2.18-2.83 (5H, m, C(2)H_2, C(2')H_2, C(3')*H*), 3.51-3.65 (2H, m,

NC*H*$_2$Ph), 4.77 (1H, app td, *J* 10.9, 4.6, C(1″)*H*), 7.07-7.35 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.7 (C(5″)*Me*), 24.2 (*C*(3‴)), 26.4 (*C*H$_2$), 28.5 (*C*(1‴)), 28.8 (*C*H), 31.2 (CO*Me*), 34.5 (*C*H$_2$), 36.2 (*C*(4')), 39.1 (*C*(2‴)), 39.6 (*C*(5')), 41.7 (*C*H$_2$), 50.2 (*C*H), 55.9 (*C*(2')), 56.5 (*C*(3')), 59.4 (*C*(2)), 59.6 (N*C*H$_2$Ph), 74.1 (*C*(1″)), 125.0, 125.3, 127.1, 127.9, 128.3, 128.6 (*o*,*m*,*p*-*Ph*), 138.6, 151.8 (*i*-*Ph*), 171.5 (*C*(1)), 208.3 (*C*OMe). Data for **264**: δ_H (400 MHz, $CDCl_3$) 1.20 (3H, s, C(1‴)*H*$_3$), 1.29 (3H, s, C(3‴)*H*$_3$), 2.13 (3H, s, CO*Me*); δ_C (100 MHz, $CDCl_3$) 31.1 (CO*Me*), 55.8 (*C*(2')), 59.5 (*C*(2)), 74.2 (*C*(1″)),171.4 (*C*(1)).

Method B: Following *General Procedure 9*, **205** (25 mg, 0.05 mmol) was reacted with **81**·HOAc (9 mg, 0.05 mmol) in THF (0.25 mL) for 14 days to give a 63:37 mixture of **263** and **264**. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave a 63:37 mixture of **263** and **264** as a colourless oil (21 mg, 84%).

Method C: Following *General Procedure 9*, **205** (25 mg, 0.05 mmol) was reacted with isopropylamine **257** (3 mg, 0.05 mmol) in THF (0.25 mL) for 14 days to give a 65:35 mixture of **263** and **264**. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave a 65:35 mixture of **263** and **264** as a colourless oil (20 mg, 80%).

Method D: Following *General Procedure 9*, **205** (25 mg, 0.05 mmol) was reacted with **257**·HOAc (6 mg, 0.05 mmol) in THF (0.25 mL) for 14 days to give a 67:33 mixture of **263** and **264**. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave a 67:33 mixture of **263** and **264** as a colourless oil (21 mg, 84%).

Method E: Following *General Procedure 9*, **205** (25 mg, 0.05 mmol) was reacted with (*S*)-α-methylbenzylamine **80** (6.0 mg, 0.05 mmol) in THF (0.25 mL) for 7 days to give a 79:21 mixture of **263** and **264**. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave a 79:21 mixture of **263** and **264** as a colourless oil (17 mg, 38%).

Method F: Following *General Procedure 9*, **205** (25 mg, 0.05 mmol) was reacted with (*S*)-**80**·HOAc (10 mg, 0.05 mmol) in THF (0.25 mL) for 7 days to give a 68:32 mixture of **263** and **264**. Purification *via* flash column chromatography (gradient elution, 20%→100%

EtOAc in 30-40 °C petrol) gave a 68:32 mixture of **263** and **264** as a colourless oil (20 mg, 80%).

Method G: Following *General Procedure 9*, **205** (25 mg, 0.05 mmol) was reacted with (*S*)-α-ethylbenzylamine **252** (7 mg, 0.05 mmol) in THF (0.25 mL) for 7 days to give a 73:27 mixture of **263** and **264**. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave a 73:27 mixture of **263** and **264** as a colourless oil (20 mg, 80%).

Method H: Following *General Procedure 9*, **205** (25 mg, 0.05 mmol) was reacted with (*S*)-**252**·HOAc (10 mg, 0.05 mmol) in THF (0.25 mL) for 12 days to give a 65:35 mixture of **263** and **264**. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave a 65:35 mixture of **263** and **264** as a colourless oil (21 mg, 85%).

Method I: Following *General Procedure 9*, **205** (25 mg, 0.05 mmol) was reacted with (*S*)-1-(1'-naphthyl)ethylamine **253** (10 mg, 0.05 mmol) in THF (0.25 mL) for 5 days to give an 85:15 mixture of **263** and **264**. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave an 85:15 mixture of **263** and **264** as a colourless oil (18 mg, 72%).

Method J: Following *General Procedure 9*, **205** (25 mg, 0.05 mmol) was reacted with (*S*)-**253**·HOAc (13 mg, 0.05 mmol) in THF (0.25 mL) for 6 days to give a 60:40 mixture of **263** and **264**. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave a 60:40 mixture of **263** and **264** as a colourless oil (19 mg, 75%).

Method K: Following *General Procedure 9*, **205** (25 mg, 0.05 mmol) was reacted with (*R*)-α-methylbenzylamine **80** (6.0 mg, 0.05 mmol) in THF (0.25 mL) for 7 days to give a 64:36 mixture of **263** and **264**. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave a 64:36 mixture of **263** and **264** as a colourless oil (14 mg, 56%).

Method L: Following *General Procedure 9*, **205** (25 mg, 0.05 mmol) was reacted with (*R*)-**80**·HOAc (10 mg, 0.05 mmol) in THF (0.25 mL) for 7 days to give a 60:40 mixture of **263** and **264**. Purification *via* flash column chromatography (gradient elution, 20%→100%

EtOAc in 30-40 °C petrol) gave a 60:40 mixture of **263** and **264** as a colourless oil (19 mg, 75%).

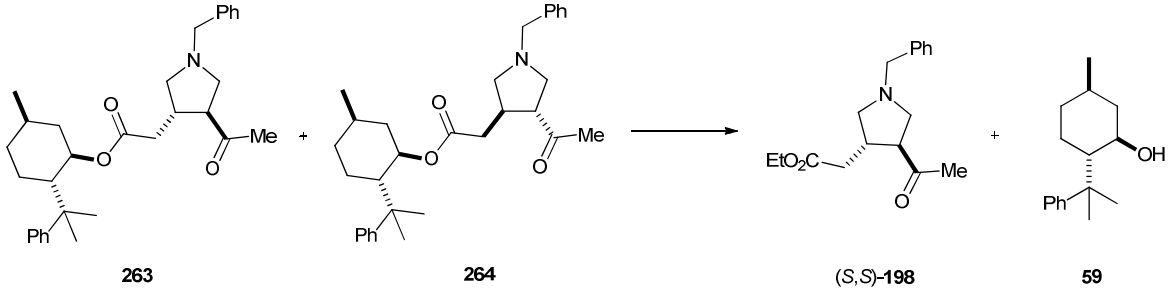
Method M: Following *General Procedure 9*, **205** (25 mg, 0.05 mmol) was reacted with (*R*)-α-ethylbenzylamine **252** (7 mg, 0.05 mmol) in THF (0.25 mL) for 7 days to give a 67:33 mixture of **263** and **264**. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave a 67:33 mixture of **263** and **264** as a colourless oil (19 mg, 75%).

Method N: Following *General Procedure 9*, **205** (25 mg, 0.05 mmol) was reacted with (*R*)-**252**·HOAc (10 mg, 0.05 mmol) in THF (0.25 mL) for 12 days to give a 60:40 mixture of **263** and **264**. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave a 60:40 mixture of **263** and **264** as a colourless oil (20 mg, 80%).

Method O: Following *General Procedure 9*, **205** (25 mg, 0.05 mmol) was reacted with (*R*)-1-(1'-naphthyl)ethylamine **253** (10 mg, 0.05 mmol) in THF (0.25 mL) for 5 days to give a 55:45 mixture of **263** and **264**. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave a 55:45 mixture of **263** and **264** as a colourless oil (20 mg, 80%).

Method P: Following *General Procedure 9*, **205** (25 mg, 0.05 mmol) was reacted with (*R*)-**253**·HOAc (13 mg, 0.05 mmol) in THF (0.25 mL) for 6 days to give a 55:45 mixture of **263** and **264**. Purification *via* flash column chromatography (gradient elution, 20%→100% EtOAc in 30-40 °C petrol) gave a 55:45 mixture of **263** and **264** as a colourless oil (18 mg, 72%).

(*S*,*S*)-Ethyl-2-(1'-benzyl-4'-acetylpyrrolidin-3'-yl)acetate 198 and (1*R*,2*S*,5*R*)-2-(2'-phenylpropan-2'-yl)-5-methylcyclohexanol 59

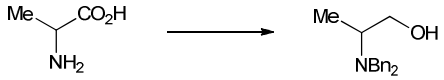


Following *General Procedure 10*, a 67:33 mixture of **263** and **264** (60 mg, 0.13 mmol) was reacted with LiOEt (1.0 M in EtOH, 0.32 mL, 0.32 mmol) in EtOH (0.5 mL). Purification

via flash column chromatography (gradient elution, 50%→100% EtOAc in 30-40 °C petrol) gave (*S*,*S*)-**198** as a colourless oil (33 mg, 55%, 34% ee[28]); $[\alpha]_D^{23}$ −4.2 (*c* 1.10 in $CHCl_3$); {lit.[23] $[\alpha]_D^{22}$ −5.1 (*c* 1.0 in $CHCl_3$)}. Further elution gave **59** as a colourless oil (29 mg, 60%); $[\alpha]_D^{22}$ −26.4 (*c* 1.1 in EtOH); {lit.[7] for enantiomer $[\alpha]_D^{20}$ +26.3 (*c* 2.02 in EtOH).

5.5 Experimental for Chapter 4

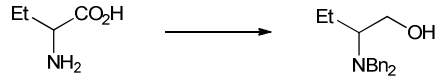
(*RS*)-2-(*N*,*N*-Dibenzylamino)propan-1-ol 315



301 **315**

Following *General Procedure 11*, a solution of (*RS*)-alanine **301** (5.00 g, 56.0 mmol) in H_2O (100 mL) was treated with K_2CO_3 (23.2 g, 168 mmol) and BnBr (20.0 mL, 168 mmol) to give **308** as a pale yellow oil (19.2 g). A solution of the residue (19.2 g) in THF (19 mL) was reacted with $LiAlH_4$ (3.90 g, 104 mmol) in THF (60 mL). Purification *via* flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 20:1, increased to 10:1) gave **315** as a colourless oil (9.00 g, 63%);[29] δ_H (400 MHz, $CDCl_3$) 0.98 (3H, d, *J* 6.7, C(3)H_3), 2.95-3.05 (1H, m, C(2)*H*), 3.16 (1H, br s, O*H*), 3.31-3.38 (1H, m, C(1)H_A), 3.47 (1H, t, *J* 10.5, C(1)H_B), 3.60 (4H, AB system, J_{AB} 13.4, N(CH_2Ph)$_2$), 7.23-7.40 (10H, m, *Ph*).

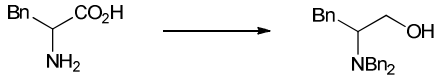
(*RS*)-2-(*N*,*N*-Dibenzylamino)butan-1-ol 316



302 **316**

Following *General Procedure 11*, a solution of (*RS*)-2-aminobutyric acid **302** (10.0 g, 97.0 mmol) in H_2O (200 mL) was treated with K_2CO_3 (40.2 g, 291 mmol) and BnBr (34.6 mL, 291 mmol) to give **309** as a pale yellow oil (35.0 g). A solution of the residue (35.0 g) in THF (35 mL) was reacted with $LiAlH_4$ (7.36 g, 194 mmol) in THF (80 mL). Purification *via* flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 20:1, increased to 10:1) gave **316** as a colourless oil (18.3 g, 70%);[30] δ_H (400 MHz, $CDCl_3$) 0.93 (3H, t, *J* 7.5, C(4)H_3), 1.19-1.31 (1H, m, C(3)H_A), 1.77-1.88 (1H, m, C(3)H_B), 2.69-2.78 (1H, m, C(2)*H*), 3.21 (1H, app d, *J* 9.6, O*H*), 3.42 (1H, app t, *J* 10.5, C(1)H_A), 3.51-3.58 (1H, m, C(1)H_B), 3.64 (4H, AB system, J_{AB} 13.3, N(CH_2Ph)$_2$), 7.23-7.40 (10H, m, *Ph*).

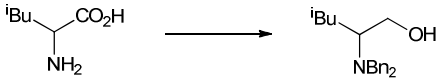
(*RS*)-2-(*N*,*N*-Dibenzylamino)-3-phenylpropan-1-ol 317



303 **317**

Following *General Procedure 11*, a solution of (*RS*)-phenylalanine **303** (5.00 g, 30.3 mmol) in H_2O (100 mL) was treated with K_2CO_3 (12.6 g, 90.9 mmol) and BnBr (10.8 mL, 90.9 mmol) to give **310** as a pale yellow oil (12.8 g). A solution of the residue (12.8 g) in THF (13 mL) was reacted with $LiAlH_4$ (2.23 g, 58.8 mmol) in THF (35 mL). Purification *via* flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 20:1, increased to 10:1) gave **317** as a colourless oil (7.84 g, 78%);[31] δ_H (400 MHz, $CDCl_3$) 2.45 (1H, dd, *J* 13.3, 9.6, C(3)H_A), 3.03 (1H, br s, O*H*), 3.04-3.14 (2H, m, C(1)H_A, C(3)H_B), 3.30-3.39 (1H, m, C(2)*H*), 3.52 (1H, app t, *J* 10.2, C(1)H_B), 3.72 (4H, AB system, J_{AB} 13.3, N(CH_2Ph)$_2$), 7.08-7.37 (15H, m, *Ph*).

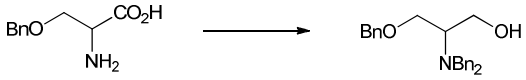
(*RS*)-2-(*N*,*N*-Dibenzylamino)-4-methylpentan-1-ol 318



304 **318**

Following *General Procedure 11*, a solution of (*RS*)-leucine **304** (5.00 g, 38.1 mmol) in H_2O (100 mL) was treated with K_2CO_3 (15.8 g, 114 mmol) and BnBr (13.6 g, 114 mmol) to give **311** as a pale yellow oil (7.49 g). A solution of the residue (7.40 g) in THF (7 mL) was reacted with $LiAlH_4$ (1.40 g, 36.9 mmol) in THF (30 mL). Purification *via* flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 20:1, increased to 10:1) gave **318** as a colourless oil (5.12 g, 45%);[29] δ_H (400 MHz, $CDCl_3$) 0.86 (3H, d, *J* 6.1, C(4)Me_A), 0.93 (3H, d, *J* 6.1, C(4)Me_B), 1.12-1.22 (1H, m, C(4)*H*), 1.46-1.60 (2H, m, C(3)H_2), 2.85 (1H, app tdd, *J* 10.2, 5.0, 2.6, C(2)*H*), 3.24 (1H, br s, O*H*), 3.43 (1H, app d, *J* 10.2, C(1)H_A), 3.49 (1H, dd, *J* 10.2, 5.0, C(1)H_B), 3.59 (4H, AB system, J_{AB} 13.3, N(CH_2Ph)$_2$), 7.22-7.36 (10H, m, *Ph*).

(*RS*)-2-(*N*,*N*-Dibenzylamino)-3-(benzyloxy)propan-1-ol 319

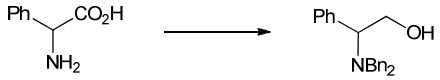


305 **319**

Following *General Procedure 11*, a solution of *O*-benzyl-(*RS*)-serine **305** (15.0 g, 76.8 mmol) in H_2O (200 mL) was treated with K_2CO_3 (31.9 g, 231 mmol) and BnBr (27.4 mL, 231 mmol) to give **312** as a pale yellow oil (40.4 g). A solution of the residue (40.4 g) in THF (40 mL) was reacted with $LiAlH_4$ (5.83 g, 154 mmol) in THF (80 mL). Purification *via* flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 20:1, increased to 10:1) gave

319 as a colourless oil (25.0 g, 90%);[32] δ_H (400 MHz, $CDCl_3$) 2.94 (1H, br s, O*H*), 3.12-3.20 (1H, m, C(2)*H*), 3.51-3.78 (4H, m, C(1)H_2, C(3)H_2), 3.79 (4H, AB system, J_{AB} 13.3, N(CH_2Ph)$_2$), 4.54 (2H, AB system, J_{AB} 12.3, OCH_2Ph), 7.23-7.42 (15H, m, *Ph*).

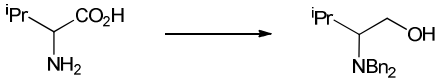
(*RS*)-2-(*N*,*N*-Dibenzylamino)-2-phenylethan-1-ol 320



306 **320**

Following *General Procedure 11*, a solution of (*RS*)-phenylglycine **306** (5.00 g, 33.0 mmol) in H_2O (100 mL) was treated with K_2CO_3 (13.7 g, 99 mmol) and BnBr (12.0 mL, 99 mmol) to give **313** as a pale yellow oil (13.9 g). A solution of the residue (13.0 g) in THF (13 mL) was reacted with $LiAlH_4$ (2.34 g, 61.7 mmol) in THF (30 mL). Purification *via* flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 20:1, increased to 10:1) gave **320** as a colourless oil (7.10 g, 68%);[31] δ_H (400 MHz, $CDCl_3$) 3.06 (1H, br s, O*H*), 3.55 (4H, AB system, J_{AB} 13.5, N(CH_2Ph)$_2$), 3.57-3.66 (1H, m, C(2)*H*), 3.95 (1H, app d, *J* 10.6, C(1)H_A), 4.16 (1H, app t, *J* 10.6, C(1)H_B), 7.24-7.47 (15H, m, *Ph*).

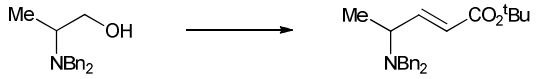
(*RS*)-2-(*N*,*N*-Dibenzylamino)-3-methylbutan-1-ol 321



307 **321**

Following *General Procedure 11*, a solution of (*RS*)-valine **307** (5.00 g, 42.7 mmol) in H_2O (100 mL) was treated with K_2CO_3 (17.7 g, 128 mmol) and BnBr (15.2 mL, 128 mmol) to give **314** as a pale yellow oil (15.1 g). A solution of the residue (15.1 g) in THF (15 mL) was reacted with $LiAlH_4$ (2.94 g, 77.4 mmol) in THF (35 mL). Purification *via* flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 20:1, increased to 10:1) gave **321** as a colourless oil (6.76 g, 55%);[29] δ_H (400 MHz, $CDCl_3$) 0.90 (3H, d, *J* 6.7, C(3)Me_A), 1.16 (3H, d, *J* 6.7, C(3)Me_B), 2.02-2.14 (1H, m, C(3)*H*), 2.55 (1H, ddd, *J* 9.9, 7.9, 4.6, C(2)*H*), 3.02 (1H, br s, O*H*), 3.44 (1H, app t, *J* 10.4, C(1)H_A), 3.58 (1H, dd, *J* 10.4, 4.6, C(1)H_B), 3.79 (4H, AB system, J_{AB} 13.0, N(CH_2Ph)$_2$), 7.22-7.35 (10H, m, *Ph*).

***tert*-Butyl (*RS*,*E*)-4-(*N*,*N*-dibenzylamino)pent-2-enoate 283**

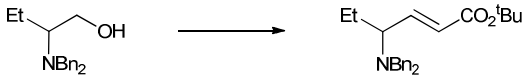


315 **283**

Following *General Procedure 12*, a solution of $(COCl)_2$ (2.95 mL, 34.9 mmol) in CH_2Cl_2 (100 mL) was treated with DMSO (2.69 mL, 37.8 mmol) in CH_2Cl_2 (10 mL) and a solution

of **315** (7.42 g, 29.1 mmol) in CH_2Cl_2 (10 mL). Then Et_3N (8.11 mL, 58.2 mmol) and $Ph_3P{=}CHCO_2{}^tBu$ (11.0 g, 29.1 mmol) was added to the reaction mixture. Purification *via* flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 20:1, increased to 10:1) gave **283** as a white solid (8.18 g, 80%); m.p. 56-57 °C; ν_{max} 2973 (C–H), 1706 (C=O), 1648 (C=C); δ_H (400 MHz, $CDCl_3$) 1.24 (3H, d, *J* 6.8, C(5)H_3), 1.53 (9H, s, CMe_3), 3.48 (1H, app quintet, *J* 6.8, C(4)*H*), 3.63 (4H, AB system, J_{AB} 14.9, N(CH_2Ph)$_2$), 5.85 (1H, d, *J* 15.9, C(2)*H*), 7.02 (1H, dd, *J* 15.9, 5.8, C(3)*H*), 7.24-7.41 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.2 (*C*(5)), 28.2 (CMe_3), 53.7 (N(*C*H_2Ph)$_2$), 53.8 (*C*(4)), 80.4 (*C*Me$_3$), 123.6 (*C*(2)), 126.9, 128.3, 128.5 (*o*,*m*,*p*-*Ph*), 140.0 (*i*-*Ph*), 149.1 (*C*(3)), 165.9 (*C*(1)); *m/z* (ESI$^+$) 352 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{30}NO_2^+$ ([M+H]$^+$) requires 352.2271; found 352.2271.

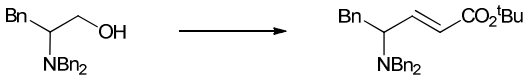
***tert*-Butyl (*RS*,*E*)-4-(*N*,*N*-dibenzylamino)hex-2-enoate 322**



316 **322**

Following *General Procedure 12*, a solution of $(COCl)_2$ (1.88 mL, 22.3 mmol) in CH_2Cl_2 (100 mL) was treated with DMSO (1.72 mL, 24.2 mmol) in CH_2Cl_2 (10 mL) and a solution of **316** (5.00 g, 18.6 mmol) in CH_2Cl_2 (10 mL). Then Et_3N (5.18 mL, 37.2 mmol) and $Ph_3P{=}CHCO_2{}^tBu$ (7.00 g, 18.6 mmol) was added to the reaction mixture. Purification *via* flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 20:1, increased to 10:1) gave **322** as a colourless oil (3.81 g, 56%); ν_{max} 2975 (C–H), 1711 (C=O), 1647 (C=C); δ_H (400 MHz, $CDCl_3$) 0.95 (3H, t, *J* 7.5, C(6)H_3), 1.51-1.60 (1H, m, C(5)H_A), 1.57 (9H, s, CMe_3), 1.75-1.86 (1H, m, C(5)H_B), 3.11 (1H, app q, *J* 8.6, C(4)*H*), 3.67 (4H, AB system, J_{AB} 13.9, N(CH_2Ph)$_2$), 5.81 (1H, d, *J* 15.7, C(2)*H*), 6.95 (1H, dd, *J* 15.7, 8.6, C(3)*H*), 7.23-7.45 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.2 (*C*(6)), 24.4 (*C*(5)), 28.2 (CMe_3), 53.7 (N(*C*H_2Ph)$_2$), 60.7 (*C*(4)), 80.5 (*C*Me$_3$), 125.2 (*C*(2)), 126.9, 128.3, 128.7 (*o*,*m*,*p*-*Ph*), 140.0 (*i*-*Ph*), 145.9 (*C*(3)), 165.8 (*C*(1)); *m/z* (ESI$^+$) 366 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{32}NO_2^+$ ([M+H]$^+$) requires 366.2428; found 366.2419.

***tert*-Butyl (*RS*,*E*)-4-(*N*,*N*-dibenzylamino)-5-phenylpent-2-enoate 323**

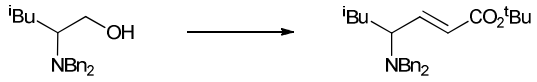


317 **323**

Following *General Procedure 12*, a solution of $(COCl)_2$ (1.23 mL, 14.5 mmol) in CH_2Cl_2 (90 mL) was treated with DMSO (1.11 mL, 15.7 mmol) in CH_2Cl_2 (10 mL) and a solution of

317 (4.00 g, 12.1 mmol) in CH_2Cl_2 (10 mL). Then Et_3N (3.36 mL, 24.1 mmol) and $Ph_3P{=}CHCO_2{}^tBu$ (4.54 g, 12.1 mmol) was added to the reaction mixture. Purification *via* flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 20:1, increased to 10:1) gave **323** as a colourless oil (3.49 g, 68%); $C_{29}H_{33}NO_2$ requires C, 81.5; H, 7.8; N, 3.3%; found C, 81.6; H, 7.7; N, 3.3%; ν_{max} 2978 (C–H), 1711 (C=O), 1647 (C=C); δ_H (400 MHz, $CDCl_3$) 1.57 (9H, s, CMe_3), 2.85 (1H, dd, *J* 13.8, 7.5, C(5)H_A), 3.13 (1H, dd, *J* 13.8, 7.5, C(5)H_B), 3.61 (1H, app q, *J* 7.5, C(4)*H*), 3.74 (4H, AB system, J_{AB} 13.9, N(CH_2Ph)$_2$), 5.87 (1H, d, *J* 15.7, C(2)*H*), 7.02 (1H, dd, *J* 15.7, 7.5, C(3)*H*), 7.06-7.35 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 28.2 (CMe_3), 37.3 (*C*(5)), 53.6 (N(*C*H_2Ph)$_2$), 60.2 (*C*(4)), 80.5 (*C*Me$_3$), 125.3 (*C*(2)), 126.2, 126.9, 128.2, 128.3, 128.6, 129.5 (*o,m,p-Ph*), 138.8, 139.5 (*i-Ph*), 145.3 (*C*(3)), 165.7 (*C*(1)); *m/z* (ESI$^+$) 428 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{34}NO_2{}^+$ ([M+H]$^+$) requires 428.2584; found 428.2573.

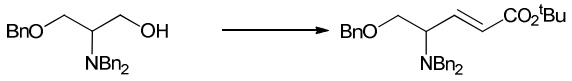
***tert*-Butyl (*RS*,*E*)-4-(*N*,*N*-dibenzylamino)-6-methylhept-2-enoate 324**



318 **324**

Following *General Procedure 12*, a solution of $(COCl)_2$ (0.85 mL, 10.1 mmol) in CH_2Cl_2 (60 mL) was treated with DMSO (0.78 mL, 10.9 mmol) in CH_2Cl_2 (6 mL) and a solution of **318** (2.50 g, 8.41 mmol) in CH_2Cl_2 (6 mL). Then Et_3N (2.34 mL, 16.8 mmol) and $Ph_3P{=}CHCO_2{}^tBu$ (3.16 g, 8.41 mmol) was added to the reaction mixture. Purification *via* flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 20:1, increased to 10:1) gave **324** as a colourless oil (2.58 g, 78%); $C_{26}H_{35}NO_2$ requires C, 79.4; H, 9.0; N, 3.6%; found C, 79.5; H, 9.1; N, 3.5%; ν_{max} 2955 (C–H), 1712 (C=O), 1647 (C=C); δ_H (400 MHz, $CDCl_3$) 0.72 (3H, d, *J* 6.6, C(6)Me_A), 0.83 (3H, d, *J* 6.6, C(6)Me_B), 1.30-1.38 (1H, m, C(5)H_A), 1.58 (9H, s, CMe_3), 1.63-1.74 (1H, m, C(5)H_B), 1.80 (1H, app sept, *J* 6.6, C(6)*H*), 3.30 (1H, app q, *J* 7.4, C(4)*H*), 3.66 (4H, AB system, J_{AB} 13.9, N(CH_2Ph)$_2$), 5.83 (1H, d, *J* 15.7, C(2)*H*), 6.97 (1H, dd, *J* 15.7, 8.3, C(3)*H*), 7.24-7.44 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 22.4, 22.9 (C(6)Me_2), 24.4 (*C*(6)), 28.2 (CMe_3), 40.7 (*C*(5)), 53.8 (N(*C*H_2Ph)$_2$), 56.6 (*C*(4)), 80.5 (*C*Me$_3$), 124.9 (*C*(2)), 126.9, 128.3, 128.8 (*o,m,p-Ph*), 140.0 (*i-Ph*), 146.3 (*C*(3)), 165.8 (*C*(1)); *m/z* (ESI$^+$) 394 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{36}NO_2{}^+$ ([M+H]$^+$) requires 394.2741; found 394.2740.

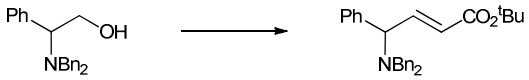
***tert*-Butyl (*RS*,*E*)-4-(*N*,*N*-dibenzylamino)-5-(benzyloxy)pent-2-enoate 325**



319 **325**

Following *General Procedure 12*, a solution of $(COCl)_2$ (1.97 mL, 23.2 mmol) in CH_2Cl_2 (100 mL) was treated with DMSO (1.79 mL, 25.2 mmol) in CH_2Cl_2 (10 mL) and a solution of **319** (7.00 g, 19.4 mmol) in CH_2Cl_2 (10 mL). Then Et_3N (5.41 mL, 38.8 mmol) and $Ph_3P{=}CHCO_2{}^tBu$ (7.30 g, 19.4 mmol) was added to the reaction mixture. Purification *via* flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 20:1, increased to 10:1) gave **325** as a white solid (5.59 g, 63%); mp 56-57 °C; ν_{max} 2962 (C–H), 1706 (C=O), 1644 (C=C); δ_H (400 MHz, $CDCl_3$) 1.55 (9H, s, C*Me*$_3$), 3.58-3.71 (2H, m, C(4)*H*, C(5)H_A), 3.74 (4H, AB system, J_{AB} 14.7, N(CH_2Ph)$_2$), 3.78-3.84 (1H, m, C(5)H_B), 4.51 (2H, s, OCH_2Ph), 5.98 (1H, d, *J* 15.9, C(2)*H*), 6.98 (1H, dd, *J* 15.9, 6.8, C(3)*H*), 7.22-7.44 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 28.2 (C*Me*$_3$), 54.6 (N(*C*H$_2$Ph)$_2$), 58.2 (*C*(4)), 70.3 (*C*(5)), 73.1 (O*C*H$_2$Ph), 80.5 (*C*Me$_3$), 125.6 (*C*(2)), 127.0, 127.5, 127.6, 128.3, 128.4, 128.6 (*o*,*m*,*p*-*Ph*), 138.2, 139.8 (*i*-*Ph*), 144.5 (*C*(3)), 165.7 (*C*(1)); *m/z* (ESI$^+$) 458 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{36}NO_3{}^+$ ([M+H]$^+$) requires 458.2609; found 458.2693.

***tert*-Butyl (*RS*,*E*)-4-(*N*,*N*-dibenzylamino)-4-phenylbut-2-enoate 326**

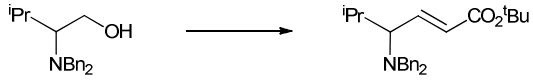


320 **326**

Following *General Procedure 12*, a solution of $(COCl)_2$ (0.85 mL, 10.0 mmol) in CH_2Cl_2 (65 mL) was treated with DMSO (0.77 mL, 10.9 mmol) in CH_2Cl_2 (6 mL) and a solution of **320** (2.65 g, 8.35 mmol) in CH_2Cl_2 (10 mL). Then Et_3N (2.33 mL, 16.7 mmol) and $Ph_3P{=}CHCO_2{}^tBu$ (3.14 g, 8.35 mmol) was added to the reaction mixture. Purification *via* flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 20:1, increased to 10:1) gave **326** as a white solid (1.38 g, 40%); $C_{28}H_{31}NO_2$ requires C, 81.3; H, 7.6; N, 3.4%; found C, 81.4; H, 7.5; N, 3.3%; mp 144-146 °C; ν_{max} 2973 (C–H), 1705 (C=O), 1650 (C=C); δ_H (400 MHz, $CDCl_3$) 1.57 (9H, s, C*Me*$_3$), 3.67 (4H, AB system, J_{AB} 13.9, N(CH_2Ph)$_2$), 4.48 (1H, d, *J* 8.2, C(4)*H*), 5.98 (1H, dd, *J* 15.8, 1.0, C(2)*H*), 7.20 (1H, dd, *J* 15.8, 8.2, C(3)*H*), 7.26-7.49 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 28.2 (C*Me*$_3$), 53.9 (N(*C*H$_2$Ph)$_2$), 63.8 (*C*(4)), 80.6 (*C*Me$_3$), 126.3 (*C*(2)), 127.0, 127.5, 128.4, 128.5, 128.7 (*o*,*m*,*p*-*Ph*), 139.5 (*i*-*Ph*), 145.5 (*C*(3)), 165.5 (*C*(1)); *m/z* (ESI$^+$) 414 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{32}NO_2{}^+$ ([M+H]$^+$)

requires 414.2428; found 414.2422.

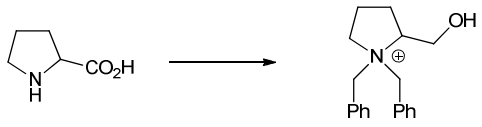
***tert*-Butyl (*RS*,*E*)-4-(*N*,*N*-dibenzylamino)-5-methylhex-2-enoate 327**



321 **327**

Following *General Procedure 12*, a solution of $(COCl)_2$ (1.08 mL, 12.7 mmol) in CH_2Cl_2 (80 mL) was treated with DMSO (0.98 mL, 13.8 mmol) in CH_2Cl_2 (8 mL) and a solution of **321** (3.00 g, 10.6 mmol) in CH_2Cl_2 (8 mL). Then Et_3N (2.95 mL, 21.2 mmol) and $Ph_3P{=}CHCO_2{}^tBu$ (3.99 g, 10.6 mmol) was added to the reaction mixture. Purification *via* flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 20:1, increased to 10:1) gave **327** as a colourless oil (1.27 g, 32%); $C_{25}H_{33}NO_2$ requires C, 79.1; H, 8.8; N, 3.7%; found C, 79.2; H, 8.8; N, 3.6%; ν_{max} 2977 (C–H), 1712 (C=O), 1647 (C=C); δ_H (400 MHz, $CDCl_3$) 0.80 (3H, d, *J* 6.6, C(5)Me_A), 1.16 (3H, d, *J* 6.6, C(5)Me_B), 1.62 (9H, s, CMe_3), 2.02 (1H, dsept, *J* 10.1, 6.6, C(5)*H*), 2.69 (1H, app t, *J* 10.1, C(4)*H*), 3.68 (4H, AB system, J_{AB} 13.9, N(CH_2Ph)$_2$), 5.78 (1H, d, *J* 15.7, C(2)*H*), 6.88 (1H, dd, *J* 15.7, 10.1, C(3)*H*), 7.26-7.49 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.3, 20.8 (C(5)Me_2), 28.3 (CMe_3), 29.0 (*C*(5)), 53.8 (N(*C*H$_2$Ph)$_2$), 66.2 (*C*(4)), 80.5 (*C*Me$_3$), 126.7 (*C*(2)), 126.9, 128.3, 128.8 (*o*,*m*,*p*-*Ph*), 139.9 (*i*-*Ph*), 144.8 (*C*(3)), 165.5 (*C*(1)); *m/z* (ESI$^+$) 402 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{33}NNaO_2{}^+$ ([M+Na]$^+$) requires 402.2404; found 402.2399.

(*RS*)-1,1-Dibenzyl-2-(hydroxymethyl)pyrrolidin-1-ium 328

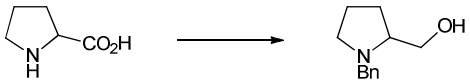


176 **328**

Following *General Procedure 11*, a solution of (*RS*)-proline **176** (5.00 g, 43.4 mmol) in H_2O (100 mL) was treated with K_2CO_3 (12.0 g, 86.9 mmol) and BnBr (10.3 mL, 86.9 mmol) to give a pale yellow oil (10.3 g). A solution of the residue (10.3 g) in THF (10 mL) was reacted with $LiAlH_4$ (2.65 g, 69.7 mmol) in THF (30 mL). Purification *via* flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 20:1, increased to 10:1) gave **328** as a colourless oil (2.50 g, 30%); ν_{max} 3542 (O–H), 2973 (C–H); δ_H (400 MHz, $CDCl_3$) 1.68-2.00 (4H, m, C(3)H_2 and C(4)H_2), 2.63-2.72 (1H, m, C(5)H_A), 2.83 (2H, s, NCH_2Ph), 3.03-3.10 (1H, m, C(5)H_B), 3.38-3.49 (1H, m, C(2)*H*), 3.50-3.58 (2H, m, CH_2OH), 3.90 (2H, AB system, J_{AB} 10.4, NCH_2Ph), 7.22-7.45 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.4 (*C*(4)), 30.3 (*C*(3)), 37.2 (N*C*H$_2$Ph), 51.0 (*C*(5)), 52.1 (N*C*H$_2$Ph), 63.3 (*C*H$_2$OH), 67.3 (*C*(2)), 126.7,

127.1, 128.3, 128.7, 129.1, 130.4 (*o,m,p-Ph*), 138.0, 139.8 (*i-Ph*); *m/z* (ESI$^+$) 282 ([M]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{24}NO^+$ ([M]$^+$) requires 282.1852; found 282.1852.

(*RS*)-(1'-Benzylpyrrolidin-2'-yl)methanol 330

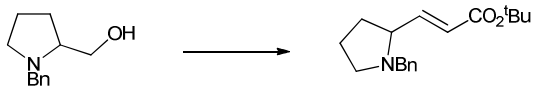


176 330

Step 1: (*RS*)-Proline **176** (10.0 g, 86.9 mmol) was added to a stirred solution of NaOH (3.48 g, 87.0 mmol) in H_2O (150 mL) at 0 °C. Benzoyl chloride (10.1 mL, 86.9 mmol) and a solution of NaOH (3.48 g, 87.0 mmol) in H_2O (10 mL) were added simultaneously. The reaction mixture was stirred at 0 °C for 2 h and washed with Et_2O (2 × 50 mL). The aqueous layer was acidified with cold 6.0 M aq HCl (pH=2), extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine, then dried and concentrated *in vacuo* give **329** as a colourless oil (17.7 g).

Step 2: A solution of the residue (17.3 g) in THF (17 mL) was reacted with $LiAlH_4$ (6.00 g, 158 mmol) in THF (200 mL). Purification *via* flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 20:1, increased to 10:1) gave **330** as a colourless oil (13.2 g, 81%);[33] δ_H (400 MHz, $CDCl_3$) 1.65-2.00 (4H, m, C(3')H_2 and C(4')H_2), 2.26-2.34 (1H, m, C(5')H_A), 2.71-2.78 (1H, m, C(5')H_B), 2.79 (1H, br s, O*H*), 2.95-3.02 (1H, m, C(2')*H*), 3.44 (1H, dd, *J* 10.6, 2.1, C(1)H_A), 3.67 (1H, dd, *J* 10.6, 3.4, C(1)H_B), 3.68 (2H, AB system, J_{AB} 13.0, NCH_2Ph), 7.24-7.39 (5H, m, *Ph*).

***tert*-Butyl (*RS*,*E*)-3-(1'-benzylpyrrolidin-2'-yl)acrylate 331**

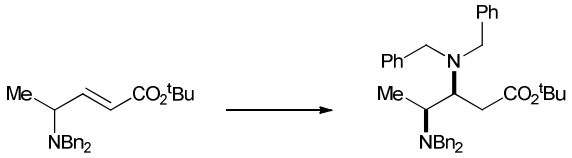


330 331

Following *General Procedure 12*, a solution of $(COCl)_2$ (4.25 mL, 50.2 mmol) in CH_2Cl_2 (250 mL) was treated with DMSO (3.86 mL, 54.4 mmol) in CH_2Cl_2 (50 mL) and a solution of **330** (8.00 g, 41.8 mmol) in CH_2Cl_2 (50 mL). Then Et_3N (11.7 mL, 83.7 mmol) and $Ph_3P{=}CHCO_2{}^tBu$ (15.8 g, 41.8 mmol) was added to the reaction mixture. Purification *via* flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 20:1, increased to 10:1) gave **331** as a colourless oil (5.05 g, 42%); ν_{max} 2974 (C–H), 1710 (C=O), 1655 (C=C); δ_H (400 MHz, $CDCl_3$) 1.51 (9H, s, CMe_3), 1.65-1.88 (3H, m, C(3')H_A and C(4')H_2), 1.95-2.06 (1H, m, C(3')H_B), 2.18 (1H, dd, *J* 17.2, 8.3, C(5')H_A), 2.95-3.06 (2H, m, C(2')*H* and C(5')H_B), 3.88 (2H, AB system, J_{AB} 12.9, NCH_2Ph), 5.92 (1H, d, *J* 15.7, C(2)*H*), 6.81 (1H, dd, *J* 15.7,

8.1, C(3)*H*), 7.21-7.35 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 22.5 (*C*(4')), 28.2 (C*Me*$_3$), 31.5 (*C*(3')), 53.5 (*C*(5')), 58.6 (N*C*H$_2$Ph), 65.9 (*C*(2')), 80.2 (*C*Me$_3$), 123.8 (*C*(2)), 126.9, 128.2, 128.8 (*o*,*m*,*p*-*Ph*), 139.2 (*i*-*Ph*), 149.3 (*C*(3)), 165.8 (*C*(1)); *m/z* (ESI$^+$) 288 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{26}NO_2^+$ ([M+H]$^+$) requires 288.1958; found 288.1950.

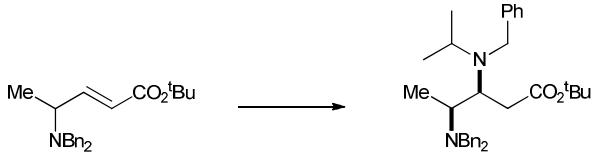
***tert*-Butyl (3*RS*,4*RS*)-3-(*N*,*N*-dibenzylamino)-4-(*N*,*N*-dibenzylamino)pentanoate 288**



283 (±)-**288**

Following *General Procedure 1*, a solution of dibenzylamine (0.16 mL, 0.85 mmol) in THF (2 mL) at –78 °C was treated with BuLi (2.5 M in hexanes, 0.27 mL, 0.68 mmol) and **283** (150 mg, 0.43 mmol) in THF (2 mL) to give (±)-**288** in 92:8 dr. Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave (±)-**288** as a colourless oil (170 mg, 72%, >99:1 dr);[34] δ_H (400 MHz, $CDCl_3$) 1.08 (3H, d, *J* 6.8, C(5)*H*$_3$), 1.49 (9H, s, C*Me*$_3$), 2.15 (1H, dd, *J* 15.3, 7.2, C(2)*H*$_A$), 2.59 (1H, dd, *J* 15.3, 4.7, C(2)*H*$_B$), 3.14 (1H, app quintet, *J* 6.8, C(4)*H*), 3.38 (4H, AB system, J_{AB} 13.7, N(C*H*$_2$Ph)$_2$), 3.55 (1H, ddd, *J* 7.1, 6.9, 4.7, C(3)*H*), 3.67 (4H, AB system, J_{AB} 13.7, N(C*H*$_2$Ph)$_2$), 7.28-7.36 (20H, m, *Ph*).

***tert*-Butyl (*RS*,*RS*)-3-(*N*-isopropyl-*N*-benzylamino)-4-(*N*,*N*-dibenzylamino)pentanoate 336**

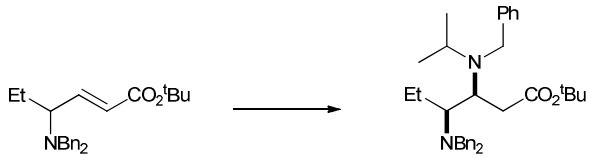


283 (±)-**336**

Following *General Procedure 1*, a solution of *N*-benzyl-*N*-isopropylamine (95 μL, 0.57 mmol) in THF (1 mL) at –78 °C was treated with BuLi (2.5 M in hexanes, 0.18 mL, 0.46 mmol) and **283** (100 mg, 0.29 mmol) in THF (1 mL) to give (±)-**336** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave (±)-**336** as a colourless oil (123 mg, 86%, >99:1 dr); $C_{33}H_{44}N_2O_2$ requires C, 79.2; H, 8.9; N, 5.6%; found C, 79.3; H, 8.9; N, 5.5%; ν_{max} 2974 (C–H), 1723 (C=O); δ_H (400 MHz, $CDCl_3$) 0.92 (3H, d, *J* 6.6, CH*Me*$_A$), 1.05 (3H, d, *J* 6.6, CH*Me*$_B$), 1.06 (3H, d, *J* 6.8, C(5)*H*$_3$), 1.46 (9H, s, C*Me*$_3$), 2.34 (1H, dd, *J* 15.7, 7.1, C(2)*H*$_A$), 2.57 (1H, dd, *J* 15.7, 4.6, C(2)*H*$_B$), 2.90 (1H, app sept, *J* 6.6, C*H*Me$_2$), 2.97 (1H, app quintet, *J* 6.8, C(4)*H*), 3.46-

3.54 (1H, m, C(3)*H*), 3.55 (4H, AB system, J_{AB} 13.9, N(CH_2Ph)$_2$), 3.56 (2H, AB system, J_{AB} 14.9, NCH_2Ph), 7.15-7.38 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 10.5 (*C*(5)), 18.6, 22.1 (CH*Me*$_2$), 28.1 (C*Me*$_3$), 36.7 (*C*(2)), 48.4 (C*H*Me$_2$), 49.9 (N*C*H$_2$Ph), 54.1 (N(*C*H$_2$Ph)$_2$), 56.0 (*C*(4)), 57.4 (*C*(3)), 80.2 (*C*Me$_3$), 126.2, 126.6, 127.8, 128.0, 128.5, 128.9 (*o*,*m*,*p*-*Ph*), 140.3, 141.3 (*i*-*Ph*), 172.7 (*C*(1)); *m/z* (ESI$^+$) 501 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{33}H_{45}N_2O_2^+$ ([M+H]$^+$) requires 501.3476; found 501.3476.

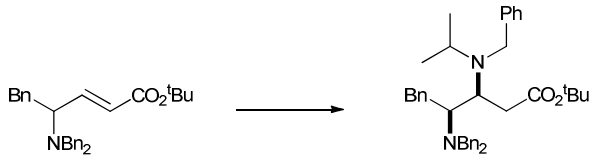
***tert*-Butyl (*RS*,*RS*)-3-(*N*-isopropyl-*N*-benzylamino)-4-(*N*,*N*-dibenzylamino)hexanoate 338**



322 (±)-**338**

Following *General Procedure 1*, a solution of *N*-benzyl-*N*-isopropylamine (0.18 mL, 1.10 mmol) in THF (2 mL) at –78 °C was treated with BuLi (2.5 M in hexanes, 0.35 mL, 0.88 mmol) and **322** (200 mg, 0.55 mmol) in THF (2 mL) to give (±)-**338** in 94:6 dr. Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave (±)-**338** as a colourless oil (190 mg, 67%, >99:1 dr); ν_{max} 2964 (C–H), 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 0.97 (3H, d, *J* 6.6, CH*Me*$_A$), 1.00 (3H, d, *J* 7.3, C(6)*H*$_3$), 1.10 (3H, d, *J* 6.6, CH*Me*$_B$), 1.48 (9H, s, C*Me*$_3$), 1.55-1.65 (2H, m, C(5)*H*$_2$), 2.50-2.62 (2H, m, C(2)*H*$_2$), 2.65 (1H, app td, *J* 6.6, 3.0, C(4)*H*), 3.00 (1H, app sept, *J* 6.6, C*H*Me$_2$), 3.53-3.58 (1H, m, C(3)*H*), 3.63 (4H, AB system, J_{AB} 14.4, N(CH_2Ph)$_2$), 3.65 (2H, AB system, J_{AB} 15.7, NCH_2Ph), 7.13-7.35 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.9 (*C*(6)), 18.1, 22.2 (CH*Me*$_2$), 19.6 (*C*(5)), 28.2 (C*Me*$_3$), 35.7 (*C*(2)), 49.4 (*C*HMe$_2$), 50.5 (N*C*H$_2$Ph), 54.2 (*C*(3)), 54.6 (N(*C*H$_2$Ph)$_2$), 63.4 (*C*(4)), 80.2 (*C*Me$_3$), 126.0, 126.5, 127.8, 128.0, 128.7 (*o*,*m*,*p*-*Ph*), 140.3, 141.3 (*i*-*Ph*), 172.5 (*C*(1)); *m/z* (ESI$^+$) 515 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{34}H_{47}N_2O_2^+$ ([M+H]$^+$) requires 515.3632; found 515.3623.

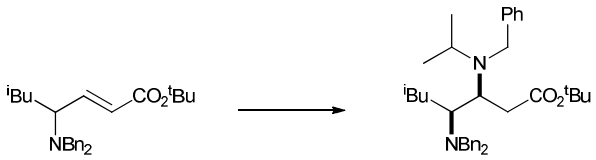
tert-Butyl (*RS*,*RS*)-3-(*N*-isopropyl-*N*-benzylamino)-4-(*N*,*N*-dibenzylamino)-5-phenylpentanoate 339



323 (±)-**339**

Following *General Procedure 1*, a solution of *N*-benzyl-*N*-isopropylamine (0.16 mL, 0.94 mmol) in THF (2 mL) at –78 °C was treated with BuLi (2.5 M in hexanes, 0.30 mL, 0.75 mmol) and **323** (200 mg, 0.47 mmol) in THF (2 mL) to give (±)-**339** in 97:3 dr. Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave (±)-**339** as a colourless oil (213 mg, 78%, 97:3 dr); $C_{39}H_{48}N_2O_2$ requires C, 81.2; H, 8.4; N, 4.9%; found C, 81.1; H, 8.3; N, 4.8%; ν_{max} 2973 (C–H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.01 (3H, d, *J* 6.6, CHMe_A), 1.10 (3H, d, *J* 6.6, CHMe_B), 1.58 (9H, s, CMe_3), 2.59-2.72 (2H, m, C(2)H_2), 2.90-3.03 (3H, m, C(5)H_2, C*H*Me_2), 3.35 (1H, ddd, *J* 8.8, 6.1, 3.3, C(4)*H*), 3.68 (2H, AB system, J_{AB} 15.4, NCH_2Ph), 3.74 (4H, AB system, J_{AB} 14.4, N(CH_2Ph)$_2$), 3.76-3.80 (1H, m, C(3)*H*), 7.17-7.40 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.1, 21.9 (CHMe_2), 28.3 (CMe_3), 33.7 (*C*(5)), 36.0 (*C*(2)), 49.9 (*C*HMe_2), 50.2 (N*C*H_2Ph), 54.4 (N(*C*H_2Ph)$_2$), 56.6 (*C*(3)), 63.1 (*C*(4)), 80.5 (*C*Me_3), 125.9, 126.3, 126.6, 128.0, 128.2, 128.3, 128.4, 128.6, 129.6 (*o*,*m*,*p*-*Ph*), 140.1, 141.1, 141.8 (*i*-*Ph*), 172.5 (*C*(1)); *m/z* (ESI^+) 577 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{39}H_{49}N_2O_2^+$ ($[M+H]^+$) requires 577.3789; found 577.3787.

tert-Butyl (*RS*,*RS*)-3-(*N*-isopropyl-*N*-benzylamino)-4-(*N*,*N*-dibenzylamino)-6-methylheptanoate 340

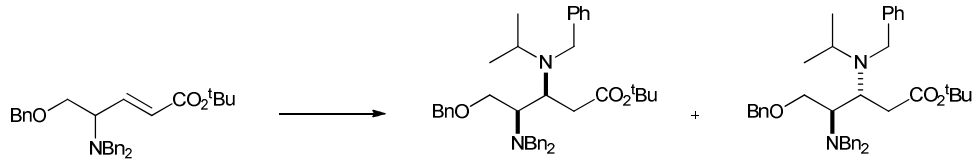


324 (±)-**340**

Following *General Procedure 1*, a solution of *N*-benzyl-*N*-isopropylamine (0.17 mL, 1.02 mmol) in THF (2 mL) at –78 °C was treated with BuLi (2.5 M in hexanes, 0.33 mL, 0.82 mmol) and **324** (200 mg, 0.51 mmol) in THF (2 mL) to give (±)-**340** in 98:2 dr. Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave (±)-**340** as a colourless oil (199 mg, 72%, 98:2 dr); ν_{max} 2961 (C–H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 0.87 (3H, d, *J* 6.6, C(6)Me_A), 0.99 (6H, d, *J* 6.6, C(6)Me_B, CHMe_A), 1.17

(3H, d, *J* 6.6, CH*Me*$_B$), 1.46 (9H, s, C*Me*$_3$), 1.51-1.63 (2H, m, C(5)*H*$_2$), 1.89 (1H, app sept, C(6)*H*), 2.54 (1H, dd, *J* 16.4, 4.0, C(2)*H*$_A$), 2.66 (1H, dd, *J* 16.4, 7.3, C(2)*H*$_B$), 2.70-2.76 (1H, m, C(4)*H*), 2.99 (1H, sept, *J* 6.6, C*H*Me$_2$), 3.53-3.59 (1H, m, C(3)*H*), 3.62 (4H, AB system, J_{AB} 14.2, N(C*H*$_2$Ph)$_2$), 3.73 (2H, AB system, J_{AB} 15.7, NC*H*$_2$Ph), 7.12-7.46 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.3, 22.3 (CH*Me*$_2$), 22.9, 23.3 (C(6)*Me*$_2$), 25.2 (*C*(6)), 28.1 (C*Me*$_3$), 35.3 (*C*(2)), 35.6 (*C*(5)), 49.9 (*C*HMe$_2$), 50.9 (N*C*H$_2$Ph), 53.7 (*C*(3)), 55.1 (N(*C*H$_2$Ph)$_2$), 59.6 (*C*(4)), 80.1 (*C*Me$_3$), 126.0, 126.5, 127.7, 127.8, 128.0, 128.3, 128.6, 128.8 (*o,m,p-Ph*), 140.5, 141.1 (*i-Ph*), 172.4 (*C*(1)); *m/z* (ESI$^+$) 543 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{36}H_{51}N_2O_2^+$ ([M+H]$^+$) requires 543.3945; found 543.3945.

***tert*-Butyl (*RS*,*SR*)-3-(*N*-isopropyl-*N*-benzylamino)-4-(*N*,*N*-dibenzylamino)-5-benzyloxypentanoate 341 and *tert*-butyl (*RS*,*RS*)-3-(*N*-isopropyl-*N*-benzylamino)-4-(*N*,*N*-dibenzylamino)-5-benzyloxypentanoate 345**

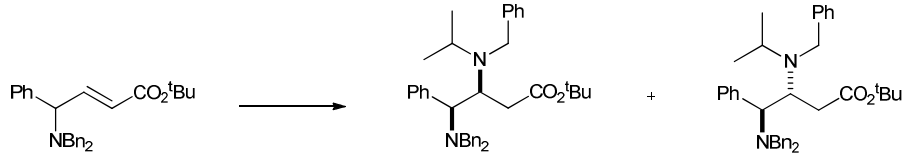


325 (±)-**341** (±)-**345**

Following *General Procedure 1*, a solution of *N*-benzyl-*N*-isopropylamine (4.39 mL, 26.2 mmol) in THF (60 mL) at –78 °C was treated with BuLi (2.5 M in hexanes, 8.40 mL, 21.0 mmol) and **325** (6.00 g, 13.1 mmol) in THF (60 mL) to give a 88:12 mixture of (±)-**341** and (±)-**345**. Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave (±)-**345** as a colourless oil (398 mg, 5%, >99:1 dr); ν_{max} 2965 (C–H), 1720 (C=O); δ_H (500 MHz, $CDCl_3$) 0.94 (3H, d, *J* 6.6, CH*Me*$_A$), 0.98 (3H, d, *J* 6.6, CH*Me*$_B$), 1.46 (9H, s, C*Me*$_3$), 2.21 (1H, dd, *J* 17.0, 6.6, C(2)*H*$_A$), 2.74 (1H, app sept, *J* 6.6, C*H*Me$_2$), 2.83 (1H, ddd, *J* 11.0, 8.5, 2.8, C(4)*H*), 3.18 (1H, dd, *J* 17.0, 3.2, C(2)*H*$_B$), 3.37 (2H, AB system, J_{AB} 16.0, NC*H*$_2$Ph), 3.49-3.59 (1H, m, C(3)*H*), 3.60-3.79 (1H, br m, C(5)*H*$_A$), 3.82 (4H, AB system, J_{AB} 14.3, N(C*H*$_2$Ph)$_2$), 3.96-4.05 (1H, m, C(5)*H*$_B$), 4.54 (2H, AB system, J_{AB} 12.0, OC*H*$_2$Ph), 7.12-7.47 (20H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 18.1, 22.2 (CH*Me*$_2$), 28.1 (C*Me*$_3$), 34.5 (*C*(2)), 48.8 (*C*HMe$_2$), 50.1 (N*C*H$_2$Ph), 53.4 (*C*(3)), 54.8 (N(*C*H$_2$Ph)$_2$), 58.7 (*C*(4)), 70.1 (*C*(5)), 73.2 (O*C*H$_2$Ph), 126.4, 126.6, 127.3, 127.4, 127.9, 128.0, 128.3, 128.6, 129.4 (*o,m,p-Ph*), 139.1, 140.3, 141.3 (*i-Ph*), 173.8 (*C*(1)); *m/z* (ESI$^+$) 607 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{40}H_{51}N_2O_3^+$ ([M+H]$^+$) requires 607.3894; found 607.3898. Further elution gave a 68:32 mixture of (±)-**341** and (±)-**345** as a colourless oil (1.34 g, 17%).

Further elution gave a (±)-**341** as a colourless oil (4.76 g, 60%); ν_{max} 2971 (C–H), 1721 (C=O); δ_H (500 MHz, $CDCl_3$) 0.90 (3H, d, *J* 6.6, CH*Me*$_A$), 0.99 (3H, d, *J* 6.6, CH*Me*$_B$), 1.42 (9H, s, C*Me*$_3$), 2.50 (1H, dd, *J* 16.0, 5.0, C(2)*H*$_A$), 2.64 (1H, dd, *J* 16.0, 6.9, C(2)*H*$_B$), 2.88 (1H, app sept, *J* 6.6, C*H*Me$_2$), 3.05-3.10 (1H, m, C(4)*H*), 3.58 (1H, dt, *J* 6.9, 5.0, C(3)*H*), 3.60 (2H, AB system, J_{AB} 16.1, NC*H*$_2$Ph), 3.64-3.67 (1H, m, C(5)*H*$_A$), 3.68 (4H, AB system, J_{AB} 14.2, N(C*H*$_2$Ph)$_2$), 3.78 (1H, dd, *J* 9.8, 5.4, C(5)*H*$_B$), 4.50 (2H, AB system, J_{AB} 12.0, OC*H*$_2$Ph), 7.11-7.41 (20H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 17.9, 21.9 (CH*Me*$_2$), 28.2 (C*Me*$_3$), 35.4 (*C*(2)), 49.1 (*C*HMe$_2$), 50.4 (N*C*H$_2$Ph), 55.2 (N(*C*H$_2$Ph)$_2$), 55.6 (*C*(3)), 61.2 (*C*(4)), 68.4 (*C*(5)), 73.0 (O*C*H$_2$Ph), 80.1 (*C*Me$_3$), 126.0, 126.5, 127.4, 127.5, 127.8, 128.0, 128.3, 128.7 (*o*,*m*,*p*-*Ph*), 138.6, 140.1, 141.3 (*i*-*Ph*), 172.6 (*C*(1)); *m/z* (ESI$^+$) 607 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{40}H_{51}N_2O_3^+$ ([M+H]$^+$) requires 607.3894; found 607.3898.

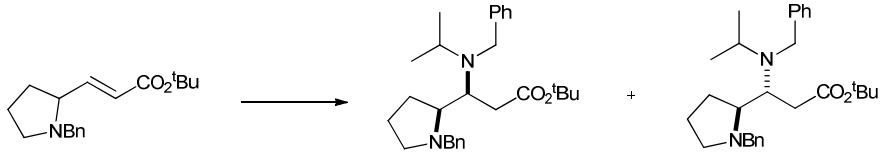
***tert*-Butyl (*RS*,*RS*)-3-(*N*-isopropyl-*N*-benzylamino)-4-(*N*,*N*-dibenzylamino)-4-phenylbutanoate 346 and *tert*-butyl (*RS*,*SR*)-3-(*N*-isopropyl-*N*-benzylamino)-4-(*N*,*N*-dibenzylamino)-4-phenylbutanoate 347**



Following *General Procedure 1*, a solution of *N*-benzyl-*N*-isopropylamine (81 μL, 0.48 mmol) in THF (1 mL) at –78 °C was treated with BuLi (2.5 M in hexanes, 0.15 mL, 0.39 mmol) and **326** (100 mg, 0.24 mmol) in THF (1 mL) to give a 73:27 mixture of (±)-**347** and (±)-**346**. Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave (±)-**347** as a white solid (66 mg, 48%, >99:1 dr); mp 125-127 °C; ν_{max} 2975 (C–H), 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 0.75 (3H, d, *J* 6.6, CH*Me*$_A$), 0.86 (3H, d, *J* 6.6, CH*Me*$_B$), 1.54 (9H, s, C*Me*$_3$), 2.53 (1H, dd, *J* 16.7, 6.3, C(2)*H*$_A$), 2.66 (1H, app sept, *J* 6.6, C*H*Me$_2$), 3.36-3.45 (1H, m, C(2)*H*$_B$), 3.42 (2H, AB system, J_{AB} 14.2, NC*H*$_2$Ph), 2.96 (2H, d, *J* 13.4, N(C*H*$_A$Ph)$_2$), 3.62 (1H, d, *J* 11.4, C(4)*H*), 3.94 (2H, br s, N(C*H*$_B$Ph)$_2$), 4.30 (1H, ddd, *J* 11.4, 6.3, 2.5, C(3)*H*), 6.70-6.76 (2H, m, *Ph*), 7.01-7.42 (18H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.2, 21.8 (CH*Me*$_2$), 28.2 (C*Me*$_3$), 35.4 (*C*(2)), 49.2 (C*H*Me$_2$), 49.6 (N*C*H$_2$Ph), 54.2 (N(*C*H$_2$Ph)$_2$), 54.5 (*C*(3)), 65.4 (*C*(4)), 80.5 (*C*Me$_3$), 126.2, 126.7, 126.8, 127.3, 127.7, 128.3, 128.6, 129.0, 130.7 (*o*,*m*,*p*-*Ph*), 138.9, 139.8, 140.9 (*i*-*Ph*), 173.8 (*C*(1)); *m/z* (ESI$^+$) 563 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{38}H_{47}N_2O_2^+$ ([M+H]$^+$) requires 563.3632;

found 563.3627. Further elution gave (±)-**346** as a colourless oil (20 mg, 15%, >99:1 dr); ν_{max} 2966 (C–H), 1723 (C=O); δ_H (500 MHz, $CDCl_3$) 0.97 (3H, d, *J* 6.6, CH*Me*$_A$), 1.23 (9H, s, C*Me*$_3$), 1.30 (3H, d, *J* 6.6, CH*Me*$_B$), 1.96 (1H, dd, *J* 16.4, 5.4, C(2)*H*$_A$), 2.48 (1H, dd, *J* 16.4, 4.4, C(2)*H*$_B$), 3.11 (1H, app sept, *J* 6.6, C*H*Me$_2$), 3.36 (4H, AB system, J_{AB} 13.6, N(C*H*$_2$Ph)$_2$), 3.60 (2H, AB system, J_{AB} 14.2, NC*H*$_2$Ph), 3.77 (1H, d, *J* 10.1, C(4)*H*), 4.13-4.19 (1H, m, C(3)*H*), 7.13-7.44 (20H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 18.5, 23.1 (CH*Me*$_2$), 28.0 (C*Me*$_3$), 37.8 (*C*(2)), 47.7 (C*H*Me$_2$), 49.2 (N*C*H$_2$Ph), 53.7 (N(*C*H$_2$Ph)$_2$), 54.4 (*C*(3)), 66.7 (*C*(4)), 79.9 (*C*Me$_3$), 126.4, 126.6, 127.3, 127.8, 127.9, 129.1, 130.6 (*o*,*m*,*p*-*Ph*), 135.8, 140.0, 141.2 (*i*-*Ph*), 172.1 (*C*(1)); *m/z* (ESI$^+$) 563 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{38}H_{47}N_2O_2^+$ ([M+H]$^+$) requires 563.3632; found 563.3627.

***tert*-Butyl (*RS*,*RS*)-3-(*N*-isopropyl-*N*-benzylamino)-3-(1'-benzylpyrrolidin-2'-yl)propanoate 348 and *tert*-butyl (*RS*,*SR*)-3-(*N*-isopropyl-*N*-benzylamino)-3-(1'-benzylpyrrolidin-2'-yl)propanoate 349**

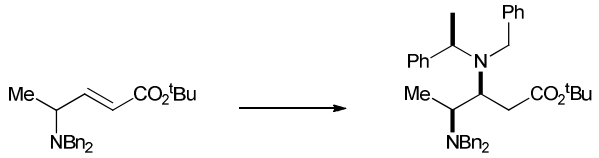


331 (±)-348 (±)-349

Following *General Procedure 1*, a solution of *N*-benzyl-*N*-isopropylamine (0.23 mL, 1.40 mmol) in THF (2 mL) at –78 °C was treated with BuLi (2.5 M in hexanes, 0.45 mL, 1.12 mmol) and **331** (200 mg, 0.70 mmol) in THF (2 mL) to give a 84:16 mixture of (±)-**349** and (±)-**348**. Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave (±)-**349** as a colourless oil (141 mg, 46%, >99:1 dr); ν_{max} 2965 (C–H), 1721 (C=O); δ_H (400 MHz, $CDCl_3$) 1.08 (3H, d, *J* 6.6, CH*Me*$_A$), 1.13 (3H, d, *J* 6.6, CH*Me*$_B$), 1.57 (9H, s, C*Me*$_3$), 1.64-1.89 (3H, m, C(3')*H*$_A$ and C(4')*H*$_2$), 2.01-2.10 (1H, m, C(3')*H*$_B$), 2.40-2.52 (3H, m, C(2)*H*$_2$ and C(5')*H*$_A$), 2.77-2.84 (1H, m, C(2')*H*), 2.84-2.90 (1H, m, C(5')*H*$_B$), 2.93 (1H, app sept, *J* 6.6, C*H*Me$_2$), 3.24 (1H, ddd, *J* 11.4, 7.8, 3.8, C(3)*H*), 3.62 (2H, AB system, J_{AB} 15.2, NC*H*$_2$Ph), 3.69 (2H, AB system, J_{AB} 12.9, N(1')C*H*$_2$Ph), 7.24-7.44 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.7, 22.4 (CH*Me*$_2$), 23.7 (*C*(4')), 27.7 (*C*(3')), 28.2 (C*Me*$_3$), 37.0 (*C*(2)), 49.5 (*C*HMe$_2$), 50.4 (N*C*H$_2$Ph), 53.0 (*C*(5')), 56.8 (*C*(3)), 62.3 (N(1')*C*H$_2$Ph), 67.6 (*C*(2')), 79.6 (*C*Me$_3$), 126.5, 126.8, 128.0, 128.1, 128.3, 129.4 (*o*,*m*,*p*-*Ph*), 140.2, 142.0 (*i*-*Ph*), 172.5 (*C*(1)); *m/z* (ESI$^+$) 437 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{41}N_2O_2^+$ ([M+H]$^+$) requires 437.3163; found 437.3158. Further elution gave an 80:20

mixture of (±)-**349** and (±)-**348** as a colourless oil (50 mg, 16%). Data for the mixture: ν_{max} 2965 (C–H), 1722 (C=O); *m/z* (ESI$^+$) 437 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{41}N_2O_2^+$ ([M+H]$^+$) requires 437.3163; found 437.3158. Data for minor (±)-**348** [selected peaks]: δ_H (400 MHz, $CDCl_3$) 1.13 (3H, d, *J* 6.6, CH*Me*$_A$), 1.16 (3H, d, *J* 6.6, CH*Me*$_B$), 2.07-2.16 (1H, m, C(3')*H*$_B$), 3.08 (1H, app sept, *J* 6.6, C*H*Me$_2$), 3.64 (2H, AB system, J_{AB} 12.9, N(1')C*H*$_2$Ph), 3.70 (2H, AB system, J_{AB} 14.7, NC*H*$_2$Ph); δ_C (100 MHz, $CDCl_3$) 20.4, 23.5 (CH*Me*$_2$), 26.6 (*C*(4')), 29.7 (*C*(3')), 30.3 (C*Me*$_3$), 34.4 (*C*(2)), 48.8 (*C*HMe$_2$), 50.4 (N*C*H$_2$Ph), 53.3 (*C*(5')), 55.2 (*C*(3)), 59.1 (N(1')*C*H$_2$Ph), 66.9 (*C*(2')), 79.9 (*C*Me$_3$), 126.6, 128.2, 128.9 (*o,m,p-Ph*), 154.5 (*i-Ph*), 173.2 (*C*(1)).

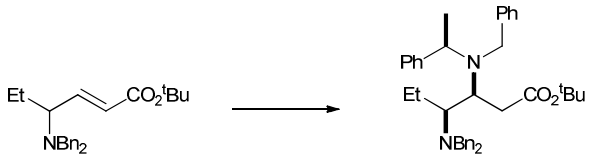
***tert*-Butyl (3*RS*,4*RS*,α*SR*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(*N*,*N*-dibenzylamino)pentanoate 298**



283 (±)-**298**

Following *General Procedure 1*, a solution of (*RS*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (241 mg, 1.14 mmol) in THF (2 mL) at –78 °C was treated with BuLi (2.5 M in hexanes, 0.36 mL, 0.91 mmol) and **283** (200 mg, 0.57 mmol) in THF (2 mL) to give (±)-**298** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave (±)-**298** as a colourless oil (266 mg, 83%, >99:1 dr); ν_{max} 2974 (C–H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.11 (3H, d, *J* 6.8, C(5)*H*$_3$), 1.43 (9H, s, C*Me*$_3$), 1.56 (3H, d, *J* 6.8, C(α)*Me*), 1.84-1.97 (2H, m, C(2)*H*$_2$), 3.09 (1H, app quintet, *J* 6.8, C(4)*H*), 3.55-3.61 (2H, m, C(3)*H*), 3.59 (4H, AB system, J_{AB} 13.9, N(C*H*$_2$Ph)$_2$), 3.73 (2H, AB system, J_{AB} 14.9, NC*H*$_2$Ph), 3.90 (1H, q, *J* 6.8, C(α)*H*), 7.04-7.51 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 9.6 (*C*(5)), 21.1 (C(α)*Me*), 28.1 (C*Me*$_3$), 35.7 (*C*(2)), 50.8 (N*C*H$_2$Ph), 54.0 (N(*C*H$_2$Ph)$_2$), 56.0 (*C*(4)), 56.9 (*C*(α)), 57.2 (*C*(3)), 80.0 (*C*Me$_3$), 126.3, 126.8, 127.9, 128.1, 128.5, 129.1 (*o,m,p-Ph*), 140.2, 140.8, 143.5 (*i-Ph*), 172.5 (*C*(1)); *m/z* (ESI$^+$) 563 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{38}H_{47}N_2O_2^+$ ([M+H]$^+$) requires 563.3632; found 563.3631.

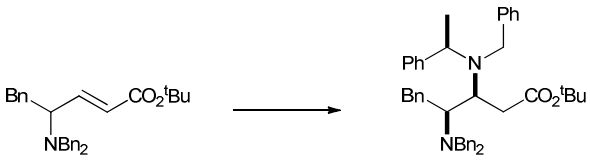
***tert*-Butyl (3*RS*,4*RS*,α*SR*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(*N*,*N*-dibenzylamino)hexanoate 350**



322 (±)-**350**

Following *General Procedure 1*, a solution of (*RS*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (231 mg, 1.10 mmol) in THF (2 mL) at –78 °C was treated with BuLi (2.5 M in hexanes, 0.35 mL, 0.88 mmol) and **322** (200 mg, 0.55 mmol) in THF (2 mL) to give (±)-**350** in 95:5 dr. Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave (±)-**350** as a colourless oil that crystallised to a colourless solid upon standing (222 mg, 70%, >99:1 dr); mp 122-124 °C; ν_{max} 2973 (C–H), 1723 (C=O); δ_H (400 MHz, $CDCl_3$) 1.10 (3H, t, *J* 7.3, C(6)H_3), 1.39 (9H, s, CMe_3), 1.52 (3H, d, *J* 6.8, C(α)*Me*), 1.70 (1H, dd, *J* 16.7, 2.9, C(2)H_A), 1.71-1.82 (2H, m, C(5)H_2), 2.41 (1H, dd, *J* 16.7, 8.7, C(2)H_B), 2.61-2.66 (1H, m, C(4)*H*), 3.67 (4H, AB system, J_{AB} 14.7, N(CH_2Ph)$_2$), 3.69 (1H, app dt, *J* 8.7, 2.9, C(3)*H*), 3.73 (2H, AB system, J_{AB} 15.9, NCH_2Ph), 3.87 (1H, q, *J* 6.8, C(α)*H*), 7.10-7.34 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.2 (*C*(6)), 18.6 (*C*(5)), 19.7 (C(α)*Me*), 28.1 (CMe_3), 34.0 (*C*(2)), 51.6 (NCH_2Ph), 53.2 (*C*(3)), 55.2 (N(CH_2Ph)$_2$), 57.8 (*C*(α)), 63.5 (*C*(4)), 79.8 (*C*Me$_3$), 126.0, 126.5, 127.0, 127.3, 127.9, 128.0, 128.3, 128.5 (*o*,*m*,*p*-*Ph*), 140.1, 140.6, 141.7 (*i*-*Ph*), 172.0 (*C*(1)); *m/z* (ESI$^+$) 599 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{39}H_{48}N_2NaO_2^+$ ([M+Na]$^+$) requires 599.3608; found 599.3604.

***tert*-Butyl (3*RS*,4*RS*,α*SR*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(*N*,*N*-dibenzylamino)-5-phenylpentanoate 351**

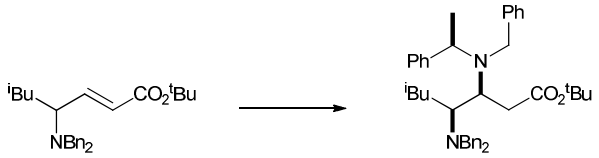


323 (±)-**351**

Following *General Procedure 1*, a solution of (*RS*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (198 mg, 0.94 mmol) in THF (2 mL) at –78 °C was treated with BuLi (2.5 M in hexanes, 0.30 mL, 0.75 mmol) and **323** (200 mg, 0.47 mmol) in THF (2 mL) to give (±)-**351** in 96:4 dr. Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave (±)-**351** as a colourless oil (40 mg, 13%, >99:1 dr). Further elution gave (±)-**351** as a colorless oil (210 mg, 70%, 95:5 dr); ν_{max} 2980 (C–H), 1720 (C=O); δ_H (400

MHz, $CDCl_3$) 1.42 (9H, s, C*Me*$_3$), 1.43 (3H, d, *J* 6.6, C(α)*Me*), 1.86 (1H, dd, *J* 16.7, 4.0, C(2)H_A), 2.39 (1H, dd, *J* 16.7, 8.1, C(2)H_B), 2.89 (1H, dd, *J* 14.7, 6.8, C(5)H_A), 3.07 (1H, dd, *J* 14.7, 6.8, C(5)H_B), 3.36 (1H, td, *J* 6.8, 3.5, C(4)*H*), 3.53 (2H, AB system, J_{AB} 15.7, NCH_2Ph), 3.70 (4H, AB system, J_{AB} 14.2, N(CH_2Ph)$_2$), 3.75 (1H, q, *J* 6.6, C(α)*H*), 3.78-3.84 (1H, m, C(3)*H*), 7.02-7.35 (25H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.6 (C(α)*Me*), 28.1 (C*Me*$_3$), 32.9 (*C*(5)), 34.6 (*C*(2)), 50.9 (N*C*H$_2$Ph), 54.7 (N(*C*H$_2$Ph)$_2$), 56.6 (*C*(3)), 58.3 (*C*(α)), 63.4 (*C*(4)), 80.2 (*C*Me$_3$), 125.9, 126.1, 126.6, 126.9, 127.7, 128.0, 128.3, 128.6, 129.5 (*o,m,p-Ph*), 140.0, 140.2, 141.1, 141.3, 142.3 (*i-Ph*), 172.1 (*C*(1)); *m/z* (ESI$^+$) 639 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{44}H_{51}N_2O_2^+$ ([M+H]$^+$) requires 639.3945; found 639.3944.

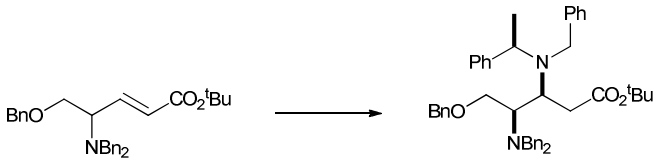
***tert*-Butyl (3*RS*,4*RS*,α*SR*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(*N*,*N*-dibenzylamino)-6-methylheptanoate 352**



324 (±)-**352**

Following *General Procedure 1*, a solution of (*RS*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (215 mg, 1.02 mmol) in THF (2 mL) at –78 °C was treated with BuLi (2.5 M in hexanes, 0.33 mL, 0.82 mmol) and **324** (200 mg, 0.51 mmol) in THF (2 mL) to give (±)-**352** in 99:1 dr. Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave (±)-**352** as a colourless oil that crystallised to a colourless solid upon standing (237 mg, 77%, >99:1 dr); mp 174-176 °C; ν_{max} 2977 (C–H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 0.99 (3H, d, *J* 6.6, C(6)*Me*$_A$), 1.03 (3H, d, *J* 6.6, C(6)*Me*$_B$), 1.28 (9H, s, C*Me*$_3$), 1.40-1.45 (1H, m, C(2)H_A), 1.45-1.49 (1H, m, C(5)H_A), 1.53 (3H, d, *J* 7.1, C(α)*Me*), 1.81-1.90 (1H, m, C(5)H_B), 1.90-1.97 (1H, m, C(6)*H*), 2.42 (1H, dd, *J* 17.2, 9.4, C(2)H_B), 2.54-2.60 (1H, m, C(4)*H*), 3.62 (4H, AB system, J_{AB} 14.7, N(CH_2Ph)$_2$), 3.62-3.67 (1H, m, C(3)*H*), 3.74 (2H, AB system, J_{AB} 16.4, NCH_2Ph), 3.84 (1H, q, *J* 7.1, C(α)*H*), 7.05-7.30 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.4 (C(α)*Me*), 22.7, 23.8 (C(6)*Me*$_2$), 25.5 (*C*(6)), 28.0 (C*Me*$_3$), 33.6 (*C*(2)), 34.3 (*C*(5)), 51.9 (N*C*H$_2$Ph), 52.5 (*C*(3)), 55.6 (N(*C*H$_2$Ph)$_2$), 57.7 (*C*(α)), 59.4 (*C*(4)), 79.7 (*C*Me$_3$), 125.8, 126.4, 126.9, 127.0, 127.9, 128.3 (*o,m,p-Ph*), 140.2, 140.3, 140.7 (*i-Ph*), 171.7 (*C*(1)); *m/z* (ESI$^+$) 605 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{41}H_{53}N_2O_2^+$ ([M+H]$^+$) requires 605.4102; found 605.4103.

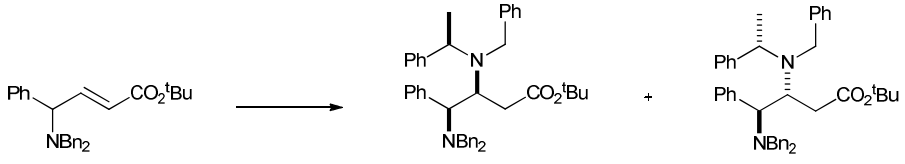
***tert*-Butyl (3*RS*,4*SR*,α*SR*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(*N*,*N*-dibenzylamino)-5-benzyloxypentanoate 353**



325 (±)-**353**

Following *General Procedure 1*, a solution of (*RS*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (185 mg, 0.88 mmol) in THF (2 mL) at –78 °C was treated with BuLi (2.5 M in hexanes, 0.32 mL, 0.70 mmol) and **325** (200 mg, 0.44 mmol) in THF (2 mL) to give (±)-**353** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30-40 °C petrol) gave (±)-**353** as a colourless oil (221 mg, 75%, >99:1 dr); ν_{max} 2974 (C–H), 1719 (C=O); δ_H (500 MHz, $CDCl_3$) 1.36 (9H, s, C*Me*$_3$), 1.44 (3H, d, *J* 6.9, C(α)*Me*), 1.75 (1H, dd, *J* 16.4, 2.2, C(2)H_A), 2.43 (1H, dd, *J* 16.4, 8.8, C(2)H_B), 3.12-3.18 (1H, m, C(4)*H*), 3.69 (2H, AB system, J_{AB} 15.5, NCH_2Ph), 3.71 (4H, AB system, J_{AB} 13.9, N(CH_2Ph)$_2$), 3.70-3.90 (4H, m, C(3)*H*, C(5)H_2, C(α)*H*), 4.56 (2H, AB system, J_{AB} 12.0, OCH_2Ph), 7.03-7.43 (25H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 20.3 (C(α)*Me*), 28.1 (C*Me*$_3$), 34.0 (*C*(2)), 51.3 (N*C*H$_2$Ph), 55.1 (N(*C*H$_2$Ph)$_2$), 55.2 (*C*(3)), 57.8 (*C*(α)), 61.4 (*C*(4)), 67.9 (*C*(5)), 73.0 (O*C*H$_2$Ph), 79.9 (*C*Me$_3$), 126.0, 126.5, 127.4, 127.5, 127.8, 128.0, 128.3, 128.7 (*o*,*m*,*p*-*Ph*), 138.6, 140.1, 141.3 (*i*-*Ph*), 172.3 (*C*(1)); *m/z* (ESI$^+$) 669 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{45}H_{53}N_2O_3^+$ ([M+H]$^+$) requires 669.4051; found 669.4050.

***tert*-Butyl (3*RS*,4*RS*,α*SR*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(*N*,*N*-dibenzylamino)-4-phenylbutanoate 354 and *tert*-butyl (3*RS*,4*SR*,α*SR*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(*N*,*N*-dibenzylamino)-4-phenylbutanoate 355**

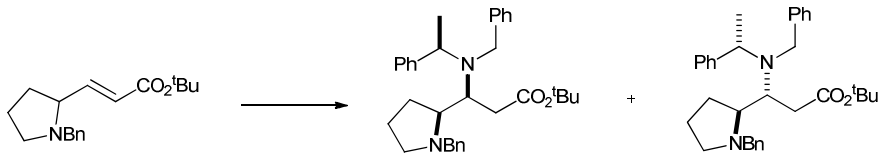


326 (±)-**354** (±)-**355**

Following *General Procedure 1*, a solution of (*RS*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (205 mg, 0.97 mmol) in THF (2 mL) at –78 °C was treated with BuLi (2.5 M in hexanes, 0.31 mL, 0.77 mmol) and **326** (200 mg, 0.48 mmol) in THF (2 mL) to give a 55:45 mixture of (±)-**355** and (±)-**354**. Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave (±)-**355** as a colourless oil (36 mg, 12%, >99:1 dr); ν_{max} 2970 (C–H), 1721 (C=O); δ_H (500 MHz, $CDCl_3$) 1.11 (3H, d, *J* 6.9, C(α)*Me*), 1.51 (9H,

s, C*Me*$_3$), 2.25 (1H, dd, *J* 17.0, 4.4, C(2)H_A), 2.90 (2H, d, *J* 13.6, N(CH_APh)$_2$), 3.00 (1H, dd, *J* 17.0, 4.4, C(2)H_B), 3.41 (2H, AB system, J_{AB} 15.8, NCH_2Ph), 3.64-3.70 (2H, m, C(4)*H*, C(α)*H*), 3.86 (2H, br s, N(CH_BPh)$_2$), 4.36 (1H, app dt, *J* 11.0, 4.4, C(3)*H*), 6.66-6.71 (2H, m, *Ph*), 6.96-7.46 (23H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 20.2 (C(α)*Me*), 28.3 (C*Me*$_3$), 34.9 (*C*(2)), 50.3 (N*C*H$_2$Ph), 54.2 (N(*C*H$_2$Ph)$_2$), 54.6 (*C*(3)), 59.8 (*C*(α)), 66.2 (*C*(4)), 80.3 (*C*Me$_3$), 126.2, 126.7, 126.8, 127.3, 127.7, 127.8, 128.2, 128.3, 129.1, 131.1 (*o,m,p-Ph*), 135.4, 139.7, 141.2, 143.5 (*i-Ph*), 173.3 (*C*(1)); *m/z* (ESI$^+$) 625 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{43}H_{49}N_2O_2^+$ ([M+H]$^+$) requires 625.3789; found 625.3786. Further elution gave a 58:42 mixture of (±)-**355** and (±)-**354** as a colourless oil (211 mg, 70%). Further elution gave (±)-**354** as a colourless oil (14 mg, 5%, >99:1 dr); ν_{max} 2966 (C–H), 1720 (C=O); δ_H (500 MHz, $CDCl_3$) 1.07 (9H, s, C*Me*$_3$), 1.40 (1H, dd, *J* 16.7, 6.9, C(2)H_A), 1.65 (3H, d, *J* 6.9, C(α)*Me*), 1.81 (1H, dd, *J* 16.7, 2.5, C(2)H_B), 3.37 (4H, AB system, J_{AB} 13.6, N(CH_2Ph)$_2$), 3.84 (2H, AB system, J_{AB} 14.2, NCH_2Ph), 3.90 (1H, d, *J* 10.4, C(4)*H*), 4.05-4.12 (1H, m, C(3)*H*), 4.23 (1H, q, *J* 6.9, C(α)*H*), 6.98-7.55 (25H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 22.2 (C(α)*Me*), 27.8 (C*Me*$_3$), 37.5 (*C*(2)), 50.1 (N*C*H$_2$Ph), 53.9 (N(*C*H$_2$Ph)$_2$), 54.4 (*C*(3)), 56.2 (*C*(α)), 66.5 (*C*(4)), 79.5 (*C*Me$_3$), 126.5, 126.7, 126.8, 127.3, 127.7, 127.8, 127.9, 128.0, 128.2, 129.2, 129.3, 130.8 (*o,m,p-Ph*), 135.0, 140.1, 140.8, 144.7 (*i-Ph*), 171.8 (*C*(1)); *m/z* (ESI$^+$) 625 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{43}H_{49}N_2O_2^+$ ([M+H]$^+$) requires 625.3789; found 625.3785.

***tert*-Butyl (3*RS*,2'*RS*,α*SR*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(1'-benzylpyrrolidin-2'-yl)propanoate 356 and *tert*-butyl (3*RS*,2'*SR*,α*SR*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(1'-benzylpyrrolidin-2'-yl)propanoate 357**

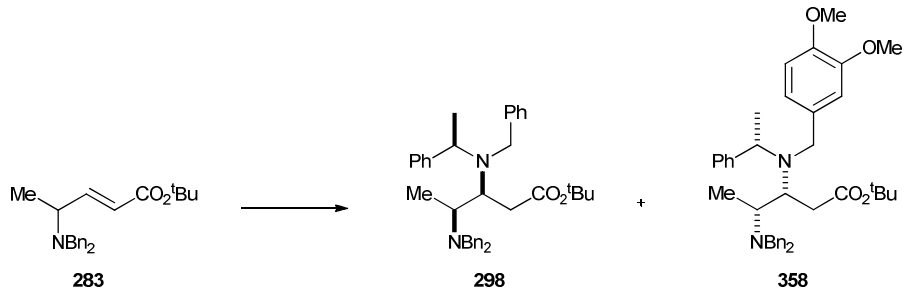


331 (±)-**356** (±)-**357**

Following *General Procedure 1*, a solution of (*RS*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (8.93 g, 42.2 mmol) in THF (90 mL) at –78 °C was treated with BuLi (2.5 M in hexanes, 13.5 mL, 33.8 mmol) and **331** (6.07 g, 21.1 mmol) in THF (60 mL) to give a 84:16 mixture of (±)-**357** and (±)-**356**. Purification *via* flash column chromatography (gradient elution, 1%→10% Et_2O in 30–40 °C petrol) gave (±)-**357** as a colourless oil (6.60 g, 63%, >99:1 dr); ν_{max} 2971 (C–H), 1720 (C=O); δ_H (400 MHz, $CDCl_3$) 1.42 (3H, d, *J* 7.1, C(α)*Me*), 1.51 (9H,

s, C*Me*$_3$), 1.66-1.76 (1H, m, C(4')H_A), 1.71 (1H, dd, *J* 15.8, 1.8, C(2)H_A), 1.77-1.95 (2H, m, C(3')H_A and C(4')H_B), 2.00 (1H, dd, *J* 15.8, 9.6, C(2)H_B), 2.12-2.19 (1H, m, C(3')H_B), 2.42-2.50 (1H, m, C(5')H_A), 2.78-2.88 (2H, m, C(2')*H* and C(5')H_B), 3.44 (1H, app td, *J* 9.6, 1.8, C(3)*H*), 3.56 (2H, AB system, J_{AB} 15.2, NCH_2Ph), 3.64 (2H, AB system, J_{AB} 12.8, N(1')CH_2Ph), 3.78 (1H, q, *J* 7.1, C(α)*H*), 7.21-7.49 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.2 (C(α)*Me*), 23.8 (*C*(4')), 27.7 (*C*(3')), 28.2 (C*Me*$_3$), 35.6 (*C*(2)), 50.7 (N*C*H$_2$Ph), 53.0 (*C*(5')), 56.3 (*C*(3)), 58.3 (*C*(α)), 62.5 (N(1')*C*H$_2$Ph), 67.4 (*C*(2')), 79.3 (*C*Me$_3$), 126.6, 126.8, 127.0, 127.9, 128.0, 128.1, 128.3, 129.6 (*o,m,p-Ph*), 140.0, 141.9, 142.0 (*i-Ph*), 171.9 (*C*(1)); *m/z* (ESI$^+$) 499 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{33}H_{43}N_2O_2^+$ ([M+H]$^+$) requires 499.3319; found 499.3317. Further elution gave (±)-**356** as a colourless oil (819 mg, 8%, >99:1 dr); ν_{max} 2972 (C–H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.42 (3H, d, *J* 6.8, C(α)*Me*), 1.48 (9H, s, C*Me*$_3$), 1.54-1.69 (2H, m, C(4')H_2), 1.69-1.94 (2H, m, C(3')H_2), 2.11 (1H, dd, *J* 16.4, 8.8， C(5')H_A), 2.23 (1H, dd, *J* 15.3, 7.3, C(2)H_A), 2.59 (1H, dd, *J* 15.3, 5.1, C(2)H_B), 2.74-2.82 (1H, m, C(5')H_B), 2.85-2.93 (1H, m, C(2')*H*), 3.52 (2H, AB system, J_{AB} 13.1, N(1')CH_2Ph), 3.74-3.80 (1H, m, C(3)*H*), 3.88 (2H, AB system, J_{AB} 15.4, NCH_2Ph), 4.07 (1H, q, *J* 6.8, C(α)*H*), 7.17-7.46 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.8 (C(α)*Me*), 23.7 (*C*(4')), 26.6 (*C*(3')), 28.2 (C*Me*$_3$), 33.7 (*C*(2)), 51.0 (N*C*H$_2$Ph), 53.4 (*C*(5')), 56.2 (*C*(3)), 59.0 (*C*(α)), 59.4 (N(1')*C*H$_2$Ph), 66.8 (*C*(2')), 79.8 (*C*Me$_3$), 126.4, 126.6, 126.8, 127.9, 128.0, 128.1, 128.9 (*o,m,p-Ph*), 140.2, 142.4, 144.1 (*i-Ph*), 172.8 (*C*(1)); *m/z* (ESI$^+$) 499 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{33}H_{43}N_2O_2^+$ ([M+H]$^+$) requires 499.3319; found 499.3317.

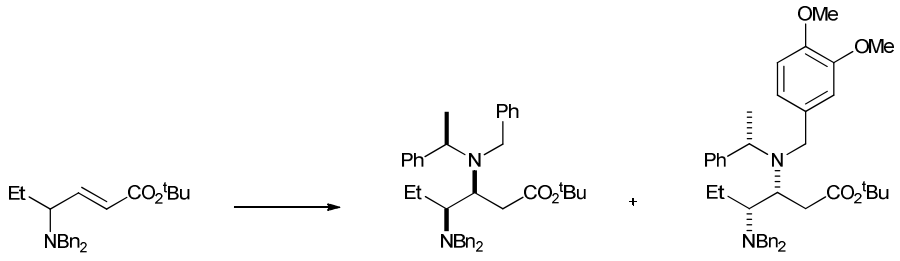
***tert*-Butyl (3*S*,4*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(*N*,*N*-dibenzylamino)pentanoate 298 and *tert*-butyl (3*R*,4*R*,α*S*)-3-[*N*-(3',4'-dimethoxybenzyl)-*N*-(α-methylbenzyl)amino]-4-(*N*,*N*-dibenzylamino)pentanoate 358**



Following *General Procedure 1*, a solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (3.61 g, 17.1 mmol) and (*S*)-*N*-(3,4-dimethoxybenzyl)-*N*-(α-methylbenzyl)amine (4.64 g, 17.1 mmol) in THF (80 mL) at –78 °C was treated with BuLi (2.5 M in hexanes, 13.2 mL, 32.9

mmol) and **283** (3.00 g, 8.54 mmol) in THF (30 mL) to give a 50:50 mixture of **298** in >99:1 dr and **358** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 1%→20% Et_2O in 30–40 °C petrol) gave **298** as a white solid (1.94 g, 40%, >99:1 dr); mp 60-61 °C; $[\alpha]_D^{24}$ +3.5 (*c* 3.2 in $CHCl_3$). Further elution gave **358** as a colourless oil that crystallised upon standing (2.29 g, 43%, >99:1 dr); $C_{40}H_{50}N_2O_4$ requires C, 77.1; H, 8.1; N, 4.5%; found C, 77.1; H, 8.0; N, 4.4%; mp 113-114 °C; $[\alpha]_D^{24}$ −6.4 (*c* 2.0 in $CHCl_3$); ν_{max} 2975 (C–H), 1703 (C=O); δ_H (500 MHz, $CDCl_3$) 1.01 (3H, d, *J* 6.6, C(5)H_3), 1.33 (9H, s, CMe_3), 1.52 (3H, d, *J* 6.9, C(α)*Me*), 1.71-1.84 (2H, m, C(2)H_2), 3.00 (1H, app quintet, *J* 6.6, C(4)*H*), 3.46 (1H, app td, *J* 7.6, 3.5, C(3)*H*), 3.51 (4H, AB system, J_{AB} 13.6, N(CH_2Ph)$_2$), 3.61 (3H, s, O*Me*), 3.64 (2H, AB system, J_{AB} 14.5, NCH_2Ar), 3.82 (3H, s, O*Me*), 3.88 (1H, q, *J* 6.9, C(α)*H*), 6.60-7.44 (18H, m, *Ar*, *Ph*); δ_C (125 MHz, $CDCl_3$) 9.58 (*C*(5)), 20.9 (C(α)*Me*), 27.9 (CMe_3), 35.6 (*C*(2)), 50.1 (N*C*H_2Ar), 53.9 (N(*C*H_2Ph)$_2$), 55.5 (O*Me*), 55.6 (*C*(4)), 55.8 (O*Me*), 56.4 (*C*(α)), 56.9 (*C*(3)), 79.8 (*C*Me$_3$), 110.5, 111.6, 120.7, 126.7, 128.0, 129.1, 133.1, 140.3, 143.6, 147.5, 148.5 (*Ar*, *Ph*), 172.5 (*C*(1)); *m/z* (ESI$^+$) 623 ($[M+H]^+$, 100%); HRMS (ESI$^+$) $C_{40}H_{51}N_2O_4^+$ ($[M+H]^+$) requires 623.3843; found 623.3838.

***tert*-Butyl (3*S*,4*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(*N*,*N*-dibenzylamino)hexanoate 350 and *tert*-butyl (3*R*,4*R*,α*S*)-3-[*N*-(3',4'-dimethoxybenzyl)-*N*-(α-methylbenzyl)amino]-4-(*N*,*N*-dibenzylamino)hexanoate 359**

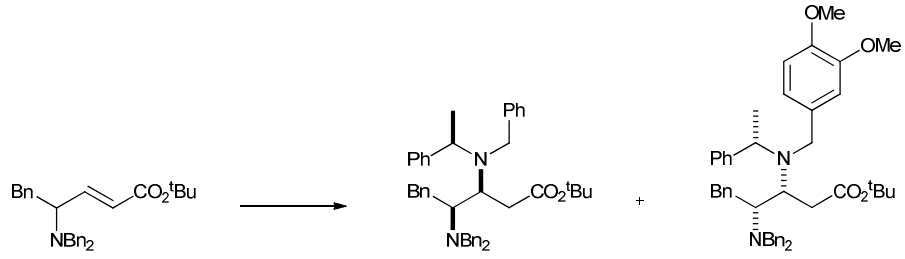


322 **350** **359**

Following *General Procedure 1*, a solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (3.47 g, 16.4 mmol) and (*S*)-*N*-(3,4-dimethoxybenzyl)-*N*-(α-methylbenzyl)amine (4.46 g, 16.4 mmol) in THF (80 mL) at –78 °C was treated with BuLi (2.5 M in hexanes, 12.6 mL, 31.6 mmol) and **322** (3.00 g, 8.21 mmol) in THF (30 mL) to give a 50:50 mixture of **350** in 95:5 dr and **359** in 95:5 dr. Purification *via* flash column chromatography (gradient elution, 1%→20% Et_2O in 30–40 °C petrol) gave **350** as a colourless oil (1.47 g, 31%, >99:1 dr); $[\alpha]_D^{24}$ −21.2 (*c* 1.0 in $CHCl_3$). Further elution gave **359** as a yellow oil (2.08 g, 40%, >99:1 dr); $[\alpha]_D^{24}$ +13.0 (*c* 2.7 in $CHCl_3$); ν_{max} 2972 (C–H), 1723 (C=O); δ_H (500 MHz, $CDCl_3$)

1.05 (3H, t, *J* 7.3, C(6)H_3), 1.35 (9H, s, CMe_3), 1.48 (3H, d, *J* 7.3, C(α)*Me*), 1.59-1.73 (3H, m, C(2)H_A, C(5)H_2), 2.35 (1H, dd, *J* 16.7, 8.2, C(2)H_B), 2.58-2.63 (1H, m, C(4)*H*), 3.63 (2H, AB system, J_{AB} 16.1, NCH_2Ar), 3.64 (1H, app dt, *J* 8.2, 3.5, C(3)*H*), 3.65 (4H, AB system, J_{AB} 14.5, N(CH_2Ph)$_2$), 3.71 (3H, s, O*Me*), 3.83 (1H, q, *J* 7.3, C(α)*H*), 3.84 (3H, s, O*Me*), 6.53 (1H, d, *J* 1.9, *Ar*), 6.68 (1H, d, *J* 8.2, *Ar*), 6.74 (1H, dd, *J* 8.2, 1.9, *Ar*), 7.12-7.30 (15H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 13.2 (*C*(6)), 18.5 (*C*(5)), 18.9 (C(α)*Me*), 28.1 (CMe_3), 34.0 (*C*(2)), 50.6 (NCH_2Ar), 53.3 (*C*(3)), 55.2 (N(CH_2Ph)$_2$), 55.5 (O*Me*), 55.9 (O*Me*), 57.7 (*C*(α)), 63.4 (*C*(4)), 80.0 (*C*Me$_3$), 110.6, 110.7, 119.0, 126.5, 126.9, 127.9, 128.0, 128.2, 128.5, 133.3, 140.1, 141.8, 147.2, 148.6 (*Ar*, *Ph*), 172.0 (*C*(1)); *m/z* (ESI$^+$) 637 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{41}H_{53}N_2O_4^+$ ([M+H]$^+$) requires 637.4000; found 637.4003.

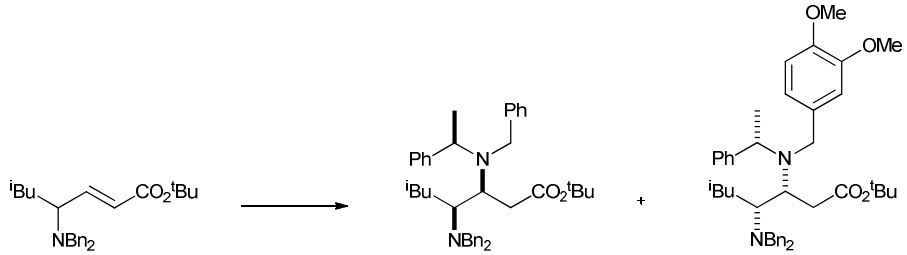
***tert*-Butyl (3*S*,4*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(*N*,*N*-dibenzylamino)-5-phenylpentanoate 351 and *tert*-butyl (3*R*,4*R*,α*S*)-3-[*N*-(3',4'-dimethoxybenzyl)-*N*-(α-methylbenzyl)amino]-4-(*N*,*N*-dibenzylamino)-5-phenylpentanoate 360**



Following *General Procedure 1*, a solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (2.44 g, 11.6 mmol) and (*S*)-*N*-(3,4-dimethoxybenzyl)-*N*-(α-methylbenzyl)amine (3.13 g, 11.6 mmol) in THF (60 mL) at –78 °C was treated with BuLi (2.5 M in hexanes, 8.90 mL, 22.2 mmol) and **323** (2.47 g, 5.78 mmol) in THF (30 mL) to give a 50:50 mixture of **351** in 96:4 dr and **360** in 96:4 dr. Purification *via* flash column chromatography (gradient elution, 1%→20% Et_2O in 30–40 °C petrol) gave **351** as a colourless oil (1.55 g, 42%, >99:1 dr); $[\alpha]_D^{24}$ +6.8 (*c* 2.3 in $CHCl_3$). Further elution gave **360** as a yellow oil (1.74 g, 43%, >99:1 dr); $[\alpha]_D^{24}$ −18.0 (*c* 1.0 in $CHCl_3$); ν_{max} 2974 (C–H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s, CMe_3), 1.45 (3H, d, *J* 7.1, C(α)*Me*), 1.98 (1H, dd, *J* 16.7, 5.3, C(2)H_A), 2.44 (1H, dd, *J* 16.7, 6.8, C(2)H_B), 2.88 (1H, dd, *J* 14.7, 5.8, C(5)H_A), 2.97 (1H, dd, *J* 14.7, 7.8, C(5)H_B), 3.37 (1H, ddd, *J* 7.8, 5.8, 3.3, C(4)*H*), 3.58 (2H, AB system, J_{AB} 15.7, NCH_2Ar), 3.69 (3H, s, O*Me*), 3.71 (4H, AB system, J_{AB} 14.4, N(CH_2Ph)$_2$), 3.77 (1H, q, *J* 7.1, C(α)*H*), 3.78-3.84 (1H, m, C(3)*H*), 3.86 (3H, s, O*Me*), 6.53 (1H, d, *J* 1.3, Ar), 6.69-6.75 (2H, m, Ar),

7.07-7.38 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.4 (C(α)*Me*), 28.2 (C*Me*$_3$), 33.1 (*C*(5)), 34.7 (*C*(2)), 49.9 (N*C*H$_2$Ar), 54.8 (N(*C*H$_2$Ph)$_2$), 55.6 (O*Me*), 55.9 (O*Me*), 56.5 (*C*(3)), 58.5 (*C*(α)), 63.1 (*C*(4)), 80.2 (*C*Me$_3$), 110.8, 111.0, 119.3, 125.9, 126.6, 126.8, 128.0, 128.2, 128.3, 128.5, 129.5, 134.0, 140.0, 141.2, 142.6, 147.4, 148.6 (*Ar*, *Ph*), 172.1 (*C*(1)); *m/z* (ESI$^+$) 721 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{46}H_{54}N_2NaO_4^+$ ([M+Na]$^+$) requires 721.3976; found 721.3976.

***tert*-Butyl (3*S*,4*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(*N*,*N*-dibenzylamino)-6-methylheptanoate 352 and *tert*-butyl (3*R*,4*R*,α*S*)-3-[*N*-(3',4'-dimethoxybenzyl)-*N*-(α-methylbenzyl)amino]-4-(*N*,*N*-dibenzylamino)-6-methylheptanoate 361**

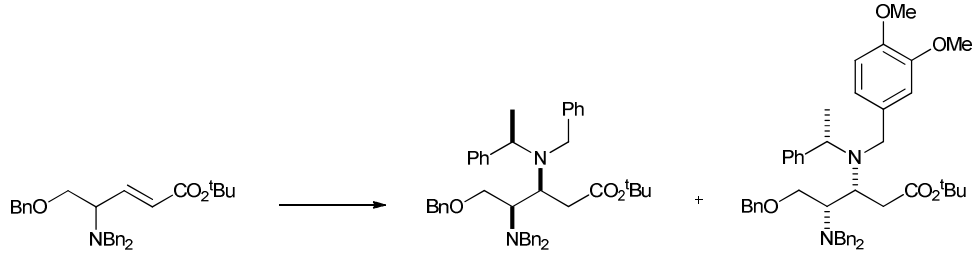


324 **352** **361**

Following *General Procedure 1*, a solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (3.10 g, 14.7 mmol) and (*S*)-*N*-(3,4-dimethoxybenzyl)-*N*-(α-methylbenzyl)amine (3.99 g, 14.7 mmol) in THF (70 mL) at –78 °C was treated with BuLi (2.5 M in hexanes, 11.3 mL, 28.3 mmol) and **324** (2.89 g, 7.34 mmol) in THF (30 mL) to give a 50:50 mixture of **352** in 98:2 dr and **361** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 1%→20% Et_2O in 30–40 °C petrol) gave **352** as a colourless oil (1.72 g, 39%, >99:1 dr); $[\alpha]_D^{24}$ +0.7 (*c* 2.9 in $CHCl_3$). Further elution gave **361** as a yellow oil (2.08 g, 43%, >99:1 dr); $[\alpha]_D^{24}$ –0.6 (*c* 2.0 in $CHCl_3$); ν_{max} 2955 (C–H), 1721 (C=O); δ_H (400 MHz, $CDCl_3$) 0.97 (3H, d, *J* 6.6, C(6)*Me*$_A$), 1.01 (3H, d, *J* 6.6, C(6)*Me*$_B$), 1.28 (9H, s, C*Me*$_3$), 1.38-1.43 (1H, m, C(5)*H*$_A$), 1.43-1.51 (1H, m, C(2)*H*$_A$), 1.52 (3H, d, *J* 7.1, C(α)*Me*), 1.75-1.85 (1H, m, C(5)*H*$_B$), 1.86-1.98 (1H, m, C(6)*H*), 2.42 (1H, dd, *J* 17.2, 8.8, C(2)*H*$_B$), 2.55-2.61 (1H, m, C(4)*H*), 3.62 (1H, app dt, *J* 8.8, 2.5, C(3)*H*), 3.64 (4H, AB system, J_{AB} 14.7, N(C*H*$_2$Ph)$_2$), 3.66 (2H, AB system, J_{AB} 16.4, NC*H*$_2$Ar), 3.75 (3H, s, O*Me*), 3.83-3.88 (1H, m, C(α)*H*), 3.85 (3H, s, O*Me*), 6.51 (1H, d, *J* 1.5, Ar), 6.71 (1H, d, *J* 8.3, Ar), 6.78 (1H, dd, *J* 8.3, 1.5, Ar), 7.10-7.31 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.0 (C(α)*Me*), 22.8, 23.7 (C(6)*Me*$_2$), 25.3 (*C*(6)), 28.0 (C*Me*$_3$), 33.6 (*C*(2)), 34.3 (*C*(5)), 51.1 (N*C*H$_2$Ar), 52.6 (*C*(3)), 55.6 (O*Me*), 55.7 (N(*C*H$_2$Ph)$_2$), 56.0 (O*Me*), 57.8 (*C*(α)), 59.2 (*C*(4)), 79.7 (*C*Me$_3$), 110.4, 110.9, 118.7,

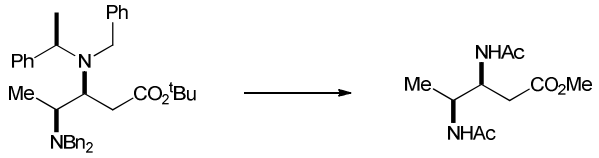
126.4, 126.9, 127.9, 128.0, 128.3, 133.1, 140.2, 140.9, 147.2, 148.6 (*Ar*, *Ph*), 171.7 (*C*(1)); *m/z* (ESI$^+$) 687 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{43}H_{56}N_2NaO_4^+$ ([M+Na]$^+$) requires 687.4132; found 687.4137.

***tert*-Butyl (3*S*,4*R*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(*N*,*N*-dibenzylamino)-5-benzyloxypentanoate 353 and *tert*-butyl (3*R*,4*S*,α*S*)-3-[*N*-(3',4'-dimethoxybenzyl)-*N*-(α-methylbenzyl)amino]-4-(*N*,*N*-dibenzylamino)-5-benzyloxypentanoate 362**



Following *General Procedure 1*, a solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (4.27 g, 20.2 mmol) and (*S*)-*N*-(3,4-dimethoxybenzyl)-*N*-(α-methylbenzyl)amine (5.48 g, 20.2 mmol) in THF (100 mL) at –78 °C was treated with BuLi (2.5 M in hexanes, 15.6 mL, 39.0 mmol) and **325** (4.63 g, 10.1 mmol) in THF (50 mL) to give a 50:50 mixture of **353** in >99:1 dr and **362** in >99:1 dr. Purification *via* flash column chromatography (gradient elution, 1%→20% Et_2O in 30–40 °C petrol) gave **353** as a colourless oil (2.48 g, 37%, >99:1 dr); $[\alpha]_D^{24}$ +11.3 (*c* 2.6 in $CHCl_3$). Further elution gave **362** as a yellow oil (2.95 g, 40%, >99:1 dr); $[\alpha]_D^{24}$ −12.4 (*c* 2.5 in $CHCl_3$); ν_{max} 2974 (C–H), 1721 (C=O); δ_H (500 MHz, $CDCl_3$) 1.33 (9H, s, C*Me*$_3$), 1.44 (3H, d, *J* 6.9, C(α)*Me*), 1.71 (1H, dd, *J* 16.7, 3.5, C(2)H_A), 2.35 (1H, dd, *J* 16.7, 8.2, C(2)H_B), 3.15 (1H, app q, *J* 5.6, C(4)*H*), 3.62 (2H, AB system, J_{AB} 15.5, NCH_2Ar), 3.69 (3H, s, O*Me*), 3.70-3.74 (2H, m, C(3)*H*, C(5)H_A), 3.72 (4H, AB system, J_{AB} 13.9, N(CH_2Ph)$_2$), 3.75-3.83 (2H, m, C(5)H_B, C(α)*H*), 3.84 (3H, s, O*Me*), 4.53 (2H, AB system, J_{AB} 12.0, OCH_2Ph), 6.61 (1H, s, *Ar*), 6.64-6.68 (2H, m, *Ar*), 7.09-7.43 (20H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 19.6 (C(α)*Me*), 28.1 (C*Me*$_3$), 34.1 (*C*(2)), 50.6 (N*C*H$_2$Ar), 54.7 (*C*(3)), 55.2 (N(*C*H$_2$Ph)$_2$), 55.6 (O*Me*), 55.9 (O*Me*), 57.5 (*C*(α)), 60.9 (*C*(4)), 68.3 (*C*(5)), 73.0 (O*C*H$_2$Ar), 79.8 (*C*Me$_3$), 110.6, 110.8, 119.6, 126.8, 127.6, 127.8, 128.0, 128.2, 128.9, 133.4, 138.6, 140.0, 140.3, 142.4, 147.3, 148.6 (*Ar*, *Ph*), 172.2 (*C*(1)); *m/z* (ESI$^+$) 729 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{47}H_{57}N_2O_5^+$ ([M+H]$^+$) requires 729.4262; found 729.4245.

(*S*,*S*)-Methyl 3,4-diacetamidopentanoate 379



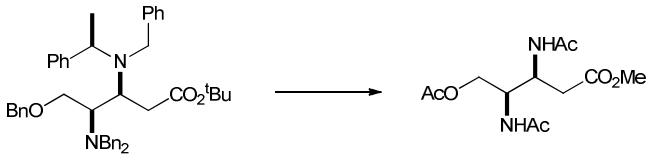
298 **379**

Step 1: Following *General Procedure 4*, reacting **298** (600 mg, 1.07 mmol) and $Pd(OH)_2/C$ (300 mg) in 1.25 M HCl/MeOH (5 mL) under H_2 (5 atm) for 48 h gave **374** as a colourless oil (246 mg).

Step 2: Following *General Procedure 13*, the residue (246 mg) in 1.25 M HCl/MeOH (5 mL) was heated at reflux for 18 h to give **377** as a yellow foam (196 mg).

Step 3: Following *General Procedure 16*, the residue (98 mg, 0.54 mmol) was reacted with pyridine (1.23 mL, 15.1 mmol) and Ac_2O (0.15 mL, 1.62 mmol) at rt for 18 h. Purification *via* flash column chromatography (eluent CH_2Cl_2/MeOH, 99:1, increased to 90:10) gave **379** as a colourless oil (48 mg, 39%); $[\alpha]_D^{24}$ −3.3 (*c* 2.0 in MeOH); ν_{max} 3349 (N–H), 2956 (C–H), 1713, 1635 (C=O); δ_H (500 MHz, MeOD) 1.14 (3H, d, *J* 7.3, C(5)H_3), 2.07 (6H, s, 2 × CO*Me*), 2.54 (1H, dd, *J* 16.4, 10.1, C(2)H_A), 2.61 (1H, dd, *J* 16.4, 4.1, C(2)H_B), 3.69 (3H, s, CO_2*Me*), 4.04-4.11 (1H, m, C(4)*H*), 4.39 (1H, app dt, *J* 9.8, 3.6, C(3)*H*); δ_C (125 MHz, MeOD) 13.8 (*C*(5)), 22.8 (2 × CO*Me*), 33.5 (*C*(2)), 49.9 (*C*(4)), 50.9 (*C*(3)), 52.6 (CO_2*Me*), 173.3, 173.8, 174.0 (3 × *C*=O); *m/z* (ESI^+) 253 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{10}H_{18}N_2NaO_4^+$ ($[M+Na]^+$) requires 253.1159; found 253.1158.

(3*S*,4*R*)-Methyl 3,4-diacetamido-5-acetoxypentanoate 380



353 **380**

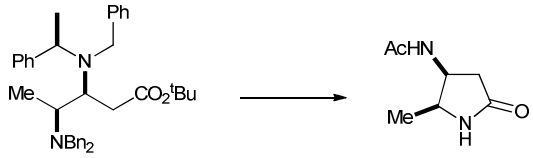
Step 1: Following *General Procedure 4*, reacting **353** (870 mg, 1.30 mmol) and $Pd(OH)_2/C$ (435 mg) in 1.25 M HCl/MeOH (5 mL) under H_2 (5 atm) for 48 h gave **376** as a colourless oil (316 mg).

Step 2: Following *General Procedure 13*, the residue (316 mg) in 1.25 M HCl/MeOH (6 mL) was heated at reflux for 18 h to give **378** as a yellow foam (250 mg).

Step 3: Following *General Procedure 16*, the residue (125 mg, 0.65 mmol) was reacted with pyridine (1.47 mL, 18.2 mmol) and Ac_2O (0.25 mL, 2.60 mmol) at rt for 18 h. Purification *via* flash column chromatography (eluent CH_2Cl_2/MeOH, 99:1, increased to 90:10) gave **380**

as a colourless oil (72 mg, 38%); $[\alpha]_D^{24}$ −45.1 (*c* 2.0 in MeOH); ν_{max} 3267 (N–H), 2955 (C–H), 1733, 1648 (C=O); δ_H (400 MHz, MeOD) 1.96 (3H, s, CO*Me*), 2.00 (3H, s, CO*Me*), 2.05 (3H, s, CO*Me*), 2.49 (1H, dd, *J* 16.3, 8.3, C(2)H_A), 2.63 (1H, dd, *J* 16.3, 5.8, C(2)H_B), 3.67 (3H, s, CO_2*Me*), 3.97 (1H, dd, *J* 11.4, 7.1, C(5)H_A), 4.17 (1H, dd, *J* 11.4, 5.3, C(5)H_B), 4.31-4.38 (1H, m, C(4)*H*), 4.48-4.55 (1H, m, C(3)*H*); δ_C (100 MHz, MeOD) 19.7, 21.7, 21.8 (3 × CO*Me*), 36.4 (*C*(2)), 47.2 (*C*(3)), 51.2 (CO_2*Me*), 51.3 (*C*(4)), 63.7 (*C*(5)), 171.4, 171.7, 172.1, 172.7 (4 × *C*=O); *m/z* (ESI^+) 311 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{12}H_{20}N_2NaO_6^+$ ($[M+Na]^+$) requires 311.1214; found 311.1206.

(*S*,*S*)-4-(*N*-Acetylamino)-5-methylpyrrolidin-2-one 382



298 **382**

Method A:

Step 1: Following *General Procedure 4*, reacting **298** (600 mg, 1.07 mmol) and $Pd(OH)_2/C$ (300 mg) in 1.25 M HCl/MeOH (5 mL) under H_2 (5 atm) for 48 h gave **374** as a colourless oil (246 mg).

Step 2: Following *General Procedure 13*, the residue (246 mg) in 1.25 M HCl/MeOH (5 mL) was heated at reflux for 18 h to give **377** as a yellow foam (196 mg).

Step 3: Following *General Procedure 14*, the residue (64 mg, 0.35 mmol) and K_2CO_3 (193 mg, 1.40 mmol) in toluene (10 mL) was heated at reflux for 18 h to gave **375** as a yellow oil (38 mg).

Step 4: Following *General Procedure 16*, the residue (38 mg, 0.35 mmol) was reacted with pyridine (0.79 mL, 9.80 mmol) and Ac_2O (0.10 mL, 1.05 mmol) at rt for 18 h. Purification *via* flash column chromatography (eluent CH_2Cl_2/MeOH, 99:1, increased to 90:10) gave **382** as a white foam (17 mg, 30%); $[\alpha]_D^{24}$ −68.1 (*c* 1.0 in MeOH); ν_{max} 3353 (N–H), 2981 (C–H), 1635 (C=O); δ_H (400 MHz, MeOD) 1.11 (3H, d, *J* 6.6, C(5)*Me*), 2.01 (3H, s, CO*Me*), 2.32 (1H, dd, *J* 17.1, 5.8, C(3)H_A), 2.67 (1H, dd, *J* 17.1, 8.6, C(3)H_B), 3.97 (1H, app quintet, *J* 6.6, C(5)*H*), 4.60-4.68 (1H, m, C(4)*H*); δ_C (125 MHz, MeOD) 15.7 (C(5)*Me*), 22.4 (CO*Me*), 37.0 (*C*(3)), 49.6 (*C*(4)), 54.5 (*C*(5)), 173.5 (*C*OMe), 177.6 (*C*(2)); *m/z* (ESI^+) 179 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_7H_{12}N_2NaO_2^+$ ($[M+Na]^+$) requires 179.0791; found 179.0790.

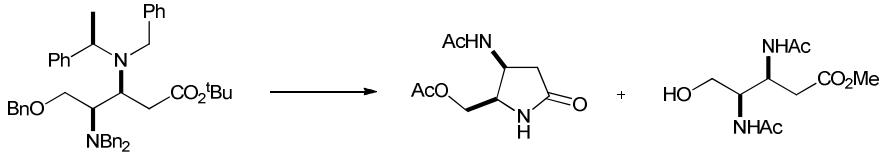
Method B:

Step 1: Following *General Procedure 4*, reacting **298** (623 mg, 1.11 mmol) and $Pd(OH)_2/C$ (312 mg) in 1.25 M HCl/MeOH (5 mL) under H_2 (5 atm) for 48 h gave **374** as a colourless oil (248 mg).

Step 2: Following *General Procedure 15*, the residue (124 mg) in 3.0 M aq HCl (12 mL) was heated at 90 °C for 18 h to give **375** as a yellow foam (80 mg).

Step 3: Following *General Procedure 16*, the residue (80 mg, 0.55 mmol) was reacted with pyridine (1.25 mL, 15.4 mmol) and Ac_2O (0.16 mL, 1.65 mmol) at rt for 18 h. Purification *via* flash column chromatography (eluent CH_2Cl_2/MeOH, 99:1, increased to 90:10) gave **382** as a white foam (62 mg, 72%); $[\alpha]_D^{24}$ −68.5 (*c* 1.2 in MeOH).

(4*S*,5*R*)-4-(*N*-Acetylamino)-5-(acetoxymethyl)pyrrolidin-2-one 383 and methyl (3*S*,4*R*)-3,4-diacetamido-5-hydroxypentanoate 395



Method A:

Step 1: Following *General Procedure 4*, reacting **353** (870 mg, 1.30 mmol) and $Pd(OH)_2/C$ (435 mg) in 1.25 M HCl/MeOH (5 mL) under H_2 (5 atm) for 48 h gave **376** as a colourless oil (316 mg).

Step 2: Following *General Procedure 13*, the residue (316 mg) in 1.25 M HCl/MeOH (6 mL) was heated at reflux for 18 h to give **378** as a yellow foam (250 mg).

Step 3: Following *General Procedure 14*, the residue (63 mg, 0.33 mmol) and K_2CO_3 (180 mg, 1.30 mmol) in toluene (10 mL) was heated at reflux for 18 h to gave **381** as a yellow oil (42 mg).

Step 4: Following *General Procedure 16*, the residue (42 mg, 0.33 mmol) was reacted with pyridine (0.75 mL, 9.24 mmol) and Ac_2O (0.12 mL, 1.30 mmol) at rt for 18 h. Purification *via* flash column chromatography (eluent CH_2Cl_2/MeOH, 99:1, increased to 90:10) gave **383** as a colourless oil (24 mg, 34%); $[\alpha]_D^{24}$ −99.3 (*c* 1.0 in MeOH); ν_{max} 3225, 3057 (N–H), 2977 (C–H), 1742, 1682, 1664 (C=O); δ_H (400 MHz, MeOD) 1.99 (3H, s, NCO*Me*), 2.08 (3H, s, OCO*Me*), 2.39 (1H, dd, *J* 16.9, 8.2, C(3)H_A), 2.62 (1H, dd, *J* 16.9, 8.9, C(3)H_B), 4.01 (1H, dd, *J* 11.3, 5.1, C(5)CH_A), 4.06-4.12 (1H, m, C(5)*H*), 4.18 (1H, dd, *J* 11.3, 3.8,

C(5)CH_B), 4.74 (1H, app q, *J* 8.2, C(4)*H*); δ_C (125 MHz, MeOD) 20.8 (OCO*Me*), 22.3 (NCO*Me*), 36.5 (*C*(3)), 48.2 (*C*(4)), 56.8 (*C*(5)), 64.2 (O*C*H_2), 172.4 (O*C*O), 173.7 (N*C*O), 177.4 (*C*(2)); *m/z* (ESI$^+$) 237 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_9H_{14}N_2NaO_4^+$ ([M+Na]$^+$) requires 237.0846; found 237.0853.

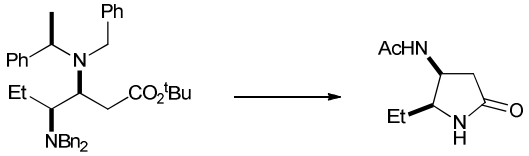
Method B:

Step 1: Following *General Procedure 4*, reacting **353** (975 mg, 1.46 mmol) and Pd(OH)$_2$/C (488 mg) in 1.25 M HCl/MeOH (5 mL) under H_2 (5 atm) for 48 h gave **376** as a colourless oil (348 mg).

Step 2: Following *General Procedure 15*, the residue (174 mg) in 3.0 M aq HCl (17 mL) was heated at 90 °C for 18 h to give **381** as a yellow foam (120 mg).

Step 3: Following *General Procedure 16*, the residue (120 mg, 0.73 mmol) was reacted with pyridine (1.66 mL, 20.4 mmol) and Ac_2O (0.28 mL, 2.92 mmol) at rt for 18 h. Purification *via* flash column chromatography (eluent CH_2Cl_2/MeOH, 99:1, increased to 90:10) gave **383** as a colourless oil (94 mg, 60%); $[\alpha]_D^{24}$ −99.0 (*c* 2.0 in MeOH). Further elution gave **395** as a colourless oil (45 mg, 25%); $[\alpha]_D^{24}$ −29.0 (*c* 2.0 in MeOH); ν_{max} 3258 (N–H), 2959 (C–H), 1714, 1636 (C=O); δ_H (400 MHz, MeOD) 2.05 (3H, s, CO*Me*), 2.08 (3H, s, CO*Me*), 2.56 (1H, dd, *J* 16.7, 9.9, C(2)H_A), 2.67 (1H, dd, *J* 16.7, 5.1, C(2)H_B), 3.58 (2H, d, *J* 6.6, C(5)H_2), 3.68 (3H, s, CO_2*Me*), 4.10 (1H, td, *J* 6.6, 3.3, C(4)*H*), 4.47-4.54 (1H, m, C(3)*H*), 8.30 (1H, d, *J* 8.6, N*H*), 8.52 (1H, d, *J* 8.6, N*H*); δ_C (100 MHz, MeOD) 21.8, 21.9 (2 × CO*Me*), 34.5 (*C*(2)), 47.6 (*C*(3)), 51.5 (CO_2*Me*), 54.0 (*C*(4)), 60.2 (*C*(5)), 172.1, 173.0, 173.3 (3 × *C*=O); *m/z* (ESI$^+$) 269 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{10}H_{18}N_2NaO_5^+$ ([M+Na]$^+$) requires 269.1108; found 269.1102.

(*S*,*S*)-4-(*N*-Acetylamino)-5-ethylpyrrolidin-2-one 392



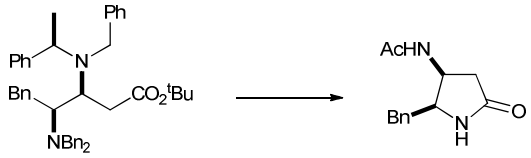
350 **392**

Step 1: Following *General Procedure 4*, reacting **350** (692 mg, 1.20 mmol) and Pd(OH)$_2$/C (346 mg) in 1.25 M HCl/MeOH (5 mL) under H_2 (5 atm) for 48 h gave **386** as a colourless oil (286 mg).

Step 2: Following *General Procedure 15*, the residue (286 mg) in 3.0 M aq HCl (28 mL) was heated at 90 °C for 18 h to give **389** as a yellow foam (196 mg).

Step 3: Following *General Procedure 16*, the residue (98 mg, 0.60 mmol) was reacted with pyridine (1.36 mL, 16.8 mmol) and Ac_2O (0.17 mL, 1.80 mmol) at rt for 18 h. Purification *via* flash column chromatography (eluent CH_2Cl_2/MeOH, 99:1, increased to 90:10) gave **392** as a white foam (72 mg, 70%); $[\alpha]_D^{24}$ −76.4 (*c* 2.0 in MeOH); ν_{max} 3356 (N–H), 2977 (C–H), 1634 (C=O); δ_H (400 MHz, MeOD) 0.96 (3H, t, *J* 7.5, CH_2*Me*), 1.39-1.58 (2H, m, CH_2Me), 2.00 (3H, s, CO*Me*), 2.29 (1H, dd, *J* 17.1, 6.1, C(3)H_A), 2.66 (1H, dd, *J* 17.1, 8.5, C(3)H_B), 3.68-3.76 (1H, m, C(5)*H*), 4.65-4.73 (1H, m, C(4)*H*), 8.10 (1H, s, N*H*), 8.53 (1H, d, *J* 8.2, N*H*)[35]; δ_C (125 MHz, MeOD) 10.7 (CH_2*Me*), 22.5 (CO*Me*), 24.1 (*C*H_2Me), 37.6 (*C*(3)), 48.5 (*C*(4)), 60.5 (*C*(5))[36]; *m/z* (ESI$^+$) 193 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_8H_{14}N_2NaO_2^+$ ([M+Na]$^+$) requires 193.0947; found 193.0940.

(*S*,*S*)-4-(*N*-Acetylamino)-5-benzylpyrrolidin-2-one 393



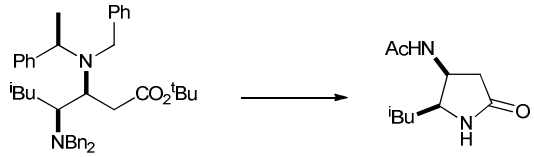
351 **393**

Step 1: Following *General Procedure 4*, reacting **351** (540 mg, 0.85 mmol) and $Pd(OH)_2$/C (270 mg) in 1.25 M HCl/MeOH (5 mL) under H_2 (5 atm) for 48 h gave **387** as a colourless oil (255 mg).

Step 2: Following *General Procedure 15*, the residue (128 mg) in 3.0 M aq HCl (13 mL) was heated at 90 °C for 18 h to give **390** as a yellow foam (96 mg).

Step 3: Following *General Procedure 16*, the residue (96 mg, 0.43 mmol) was reacted with pyridine (0.97 mL, 12.0 mmol) and Ac_2O (0.12 mL, 1.29 mmol) at rt for 18 h. Purification *via* flash column chromatography (eluent CH_2Cl_2/MeOH, 99:1, increased to 90:10) gave **393** as a white solid (76 mg, 76%); mp 195-197 °C; $[\alpha]_D^{24}$ −89.1 (*c* 1.0 in MeOH); ν_{max} 3305 (N–H), 2966 (C–H), 1639 (C=O); δ_H (400 MHz, MeOD) 1.97 (3H, s, CO*Me*), 2.40 (1H, dd, *J* 16.9, 7.1, C(3)H_A), 2.63 (1H, dd, *J* 16.9, 8.3, C(3)H_B), 2.70 (1H, dd, *J* 13.9, 8.8, CH_APh), 2.85 (1H, dd, *J* 13.9, 5.6, CH_BPh), 4.12-4.20 (1H, m, C(5)*H*), 4.65-4.73 (1H, m, C(4)*H*), 7.19-7.33 (5H, m, Ph), 7.73 (1H, s, N(1)*H*), 8.61 (1H, d, *J* 7.8, C(4)N*H*);[35] δ_C (100 MHz, MeOD) 21.5 (CO*Me*), 35.9 (*C*(3)), 36.3 (*C*H_2Ph), 48.4 (*C*(4)), 58.8 (*C*(5)), 126.6, 128.7, 129.2 (*o*,*m*,*p-Ph*), 138.0 (*i-Ph*);[36] *m/z* (ESI$^+$) 255 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{16}N_2NaO_2^+$ ([M+Na]$^+$) requires 255.1104; found 255.1103.

(*S*,*S*)-4-(*N*-Acetylamino)-5-isobutylpyrrolidin-2-one 394



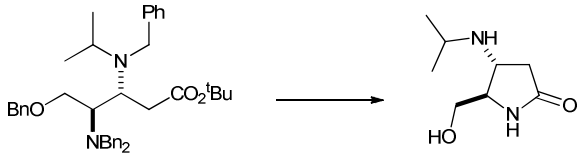
352 **394**

Step 1: Following *General Procedure 4*, reacting **352** (605 mg, 1.00 mmol) and $Pd(OH)_2/C$ (303 mg) in 1.25 M HCl/MeOH (5 mL) under H_2 (5 atm) for 48 h gave **388** as a colourless oil (265 mg).

Step 2: Following *General Procedure 15*, the residue (265 mg) in 3.0 M aq HCl (27 mL) was heated at 90 °C for 18 h to give **391** as a yellow foam (190 mg).

Step 3: Following *General Procedure 16*, the residue (190 mg, 1.00 mmol) was reacted with pyridine (2.30 mL, 28.0 mmol) and Ac_2O (0.28 mL, 3.00 mmol) at rt for 18 h. Purification *via* flash column chromatography (eluent CH_2Cl_2/MeOH, 99:1, increased to 90:10) gave **394** as a white solid (155 mg, 78%); mp 138-140 °C; $[\alpha]_D^{24}$ −88.8 (*c* 2.0 in MeOH); ν_{max} 3267, 3080 (N–H), 2956 (C–H), 1690, 1652 (C=O); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, d, *J* 6.6, CH*Me*$_A$), 0.92 (3H, d, *J* 6.6, CH*Me*$_B$), 1.30-1.37 (2H, m, C(5)C*H*$_2$), 1.63 (1H, app sept, *J* 6.6, C*H*Me$_2$), 1.98 (3H, s, CO*Me*), 2.15 (1H, dd, *J* 17.1, 3.0, C(3)*H*$_A$), 2.66 (1H, dd, *J* 17.1, 7.3, C(3)*H*$_B$), 3.79-3.86 (1H, m, C(5)*H*), 4.69-4.77 (1H, m, C(4)*H*), 7.22 (1H, d, *J* 9.1, C(4)N*H*), 7.34 (1H, br s, N(1)*H*); δ_C (100 MHz, $CDCl_3$) 22.0 (CH*Me*$_A$), 22.9 (CO*Me*), 23.4 (CH*Me*$_B$), 25.0 (*C*HMe$_2$), 38.1 (C(5)*C*H$_2$), 38.5 (*C*(3)), 48.3 (*C*(4)), 56.3 (*C*(5)), 170.1 (*C*OMe), 176.8 (*C*(2)); *m/z* (ESI$^+$) 221 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{10}H_{18}N_2NaO_2^+$ ([M+Na]$^+$) requires 221.1260; found 221.1262.

(*RS*,*RS*)-4-(*N*-Isopropylamino)-5-(hydroxymethyl)pyrrolidin-2-one 399



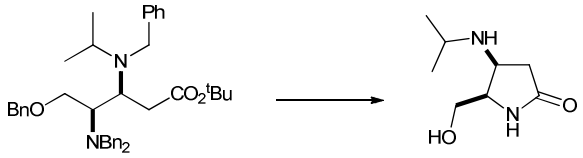
(±)-**345** (±)-**399**

Step 1: Following *General Procedure 4*, reacting (±)-**345** (350 mg, 0.58 mmol) and $Pd(OH)_2/C$ (175 mg) in 1.25 M HCl/MeOH (3 mL) under H_2 (5 atm) for 48 h gave (±)-**398** as a colourless oil (160 mg).

Step 2: Following *General Procedure 15*, the residue (160 mg) in 3.0 M aq HCl (16 mL) was heated at 90 °C for 18 h to give a yellow foam (85 mg) after purification *via* Dowex. Further purification *via* flash column chromatography (eluent CH_2Cl_2 (1% NH_4OH)/MeOH,

99:1, increased to 90:10) gave (±)-**399** as a white solid (72 mg, 72%); mp 148-150 °C; ν_{max} 3252 (N–H), 2959 (C–H), 1675 (C=O); δ_H (400 MHz, MeOD) 1.09 (3H, d, *J* 6.3, CH*Me*$_A$), 1.11 (3H, d, *J* 6.3, CH*Me*$_B$), 2.17 (1H, dd, *J* 17.3, 4.3, C(3)*H*$_A$), 2.68 (1H, dd, *J* 17.3, 8.1, C(3)*H*$_B$), 2.91 (1H, app sept, *J* 6.3, C*H*Me$_2$), 3.41-3.51 (2H, m, C(4)*H*, C(5)*H*), 3.56 (1H, dd, *J* 11.1, 4.6, C(5)C*H*$_A$), 3.64 (1H, dd, *J* 11.1, 4.2, C(5)C*H*$_B$); δ_C (100 MHz, MeOD) 21.4, 21.9 (CH*Me*$_2$), 37.8 (*C*(3)), 46.2 (*C*HMe$_2$), 52.8 (*C*(4)), 63.0 (*C*(5)), 63.4 (C(5)*C*H$_2$), 178.0 (*C*(2)); *m/z* (ESI$^+$) 195 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_8H_{16}N_2NaO_2^+$ ([M+Na]$^+$) requires 195.1104; found 195.1103.

(*RS*,*SR*)-4-(*N*-Isopropylamino)-5-(hydroxymethyl)pyrrolidin-2-one 400

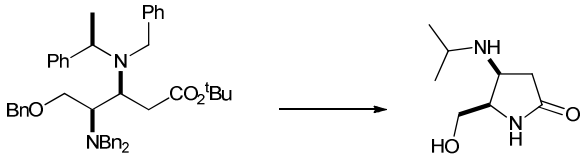


(±)-**341** (±)-**400**

Step 1: Following *General Procedure 4*, reacting (±)-**341** (800 mg, 1.32 mmol) and Pd(OH)$_2$/C (400 mg) in 1.25 M HCl/MeOH (5 mL) under H_2 (5 atm) for 48 h gave a colourless oil (370 mg).

Step 2: Following *General Procedure 15*, the residue (185 mg) in 3.0 M aq HCl (19 mL) was heated at 90 °C for 18 h to give a yellow foam (80 mg) after purification *via* Dowex. Further purification *via* flash column chromatography (eluent CH_2Cl_2 (1% NH_4OH)/MeOH, 99:1, increased to 90:10) gave (±)-**400** as a white solid (63 mg, 55%); mp 112-114 °C; ν_{max} 3119 (N–H), 2966 (C–H), 1679 (C=O); δ_H (400 MHz, MeOD) 1.10 (3H, d, *J* 6.3, CH*Me*$_A$), 1.12 (3H, d, *J* 6.3, CH*Me*$_B$), 2.29 (1H, dd, *J* 16.4, 12.1, C(3)*H*$_A$), 2.48 (1H, dd, *J* 16.4, 8.6, C(3)*H*$_B$), 2.91 (1H, app sept, *J* 6.3, C*H*Me$_2$), 3.64-3.79 (3H, m, C(5)*H*, C(5)C*H*$_2$), 3.79-3.87 (1H, m, C(4)*H*); δ_C (100 MHz, MeOD) 21.4, 22.2 (CH*Me*$_2$), 37.7 (*C*(3)), 47.1 (*C*HMe$_2$), 53.3 (*C*(4)), 58.1 (*C*(5)), 61.7 (C(5)*C*H$_2$), 178.0 (*C*(2)); *m/z* (ESI$^+$) 195 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_8H_{16}N_2NaO_2^+$ ([M+Na]$^+$) requires 195.1104; found 195.1103.

(4*S*,5*R*)-4-(*N*-Isopropylamino)-5-(hydroxymethyl)pyrrolidin-2-one 400

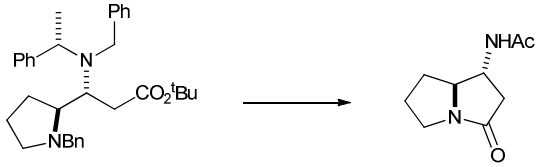


353 **400**

Step 1: Following *General Procedure 4*, reacting **353** (800 mg, 1.20 mmol) and $Pd(OH)_2/C$ (400 mg) in 1.25 M HCl/MeOH (5 mL) under H_2 (5 atm) for 48 h gave a colourless oil (285 mg).

Step 2: Following *General Procedure 15*, the residue (285 mg) in 3.0 M aq HCl (30 mL) was heated at 90 °C for 18 h to give a yellow foam (195 mg). The resultant foam (65 mg, 0.40 mmol), acetone (59 μL, 0.80 mmol) and $NaBH_4$ (76 mg, 2.00 mmol) were reacted in MeOH (3 mL). The reaction mixture was concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CH_2Cl_2 (1% NH_4OH)/MeOH, 99:1, increased to 90:10) gave **400** as a colourless oil (14 mg, 20%); $[\alpha]_D^{24}$ −7.0 (*c* 1.0 in MeOH).

(*RS*,*SR*)-1-Acetylaminopyrrolizin-3-one 423



(±)-**357** (±)-**423**

Method A:

Step 1: Following *General Procedure 4*, reacting (±)-**357** (194 mg, 0.39 mmol) and $Pd(OH)_2/C$ (97 mg) in MeOH/AcOH (v:v 40:1, 4.1 mL) under H_2 (1 atm) for 72 h gave (±)-**422** as a yellow solid (163 mg).

Step 2: Following *General Procedure 15*, the residue (163 mg) in 3.0 M aq HCl (16 mL) was heated at 90 °C for 18 h to give (±)-**401** as a yellow foam (68 mg).

Step 3: Following *General Procedure 16*, the residue (68 mg, 0.39 mmol) was reacted with pyridine (0.88 mL, 10.9 mmol) and Ac_2O (74 μL, 0.78 mmol) at rt for 18 h. Purification *via* flash column chromatography (eluent CH_2Cl_2/MeOH, 99:1, increased to 90:10) gave (±)-**423** as a colourless oil (39 mg, 55%); ν_{max} 3272 (N–H), 2976 (C–H), 1655 (C=O); δ_H (400 MHz, $CDCl_3$) 1.53-1.66 (1H, m, C(7)H_A), 1.99 (3H, s, CO*Me*), 1.91-2.21 (3H, m, C(7)H_B and C(6)H_2), 2.63 (1H, dd, *J* 16.2, 10.2, C(2)H_A), 2.77 (1H, dd, *J* 16.2, 8.2, C(2)H_B), 2.98-3.07 (1H, m, C(5)H_A), 3.50-3.59 (1H, m, C(5)H_B), 3.64 (1H, app q, *J* 8.2, C(7a)*H*), 4.29 (1H, app

quintet, *J* 8.2, C(1)*H*); δ_C (100 MHz, $CDCl_3$) 23.0 (CO*Me*), 26.5 (*C*(6)), 30.8 (*C*(7)), 41.2 (*C*(2)), 41.5 (*C*(5)), 51.4 (*C*(1)), 68.4 (*C*(7a)), 170.6 (N*C*O), 172.1 (*C*(3)); *m/z* (ESI^+) 205 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_9H_{14}N_2NaO_2^+$ ($[M+Na]^+$) requires 205.0947; found 205.0943.

Method B:

Step 1: Following *General Procedure 4*, reacting (±)-**357** (1.57 g, 3.15 mmol) and $Pd(OH)_2/C$ (785 mg) in 1.25 M HCl/MeOH (15 mL) under H_2 (1 atm) for 72 h gave (±)-**422** as a yellow solid (785 mg).

Step 2: Following *General Procedure 13*, the residue (500 mg) in 1.25 M HCl/MeOH (10 mL) was heated at reflux for 18 h to give a yellow foam (415 mg).

Step 3: Following *General Procedure 14*, the residue (415 mg, 2.00 mmol) and K_2CO_3 (1.10 g, 8.00 mmol) in toluene (25 mL) was heated at reflux for 18 h to gave (±)-**401** as a yellow foam (260 mg).

Step 4: Following *General Procedure 16*, the residue (56 mg, 0.40 mmol) was reacted with pyridine (0.91 mL, 11.2 mmol) and Ac_2O (0.11 mL, 1.20 mmol) at rt for 18 h. Purification *via* flash column chromatography (eluent CH_2Cl_2/MeOH, 99:1, increased to 90:10) gave (±)-**423** as a colourless oil (30 mg, 41%).

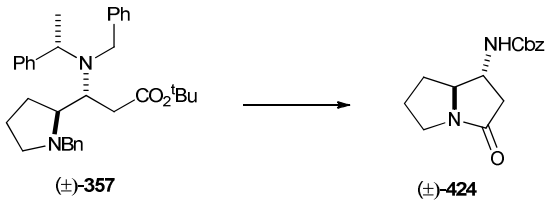
Method C:

Step 1: Following *General Procedure 4*, reacting (±)-**357** (600 mg, 1.20 mmol) and $Pd(OH)_2/C$ (300 mg) in 1.25 M HCl/MeOH (5 mL) under H_2 (5 atm) for 48 h gave (±)-**422** as a yellow solid (295 mg).

Step 2: Following *General Procedure 15*, the residue (295 mg) in 3.0 M aq HCl (30 mL) was heated at 90 °C for 18 h to give (±)-**401** as a yellow foam (210 mg).

Step 3: Following *General Procedure 16*, the residue (105 mg, 0.60 mmol) was reacted with pyridine (1.36 mL, 16.8 mmol) and Ac_2O (0.17 mL, 1.80 mmol) at rt for 18 h. Purification *via* flash column chromatography (eluent CH_2Cl_2/MeOH, 99:1, increased to 90:10) gave (±)-**423** as a colourless oil (57 mg, 52%).

(*RS*,*SR*)-1-(*N*-Carboxybenzylamino)pyrrolizin-3-one 424



(±)-**357** (±)-**424**

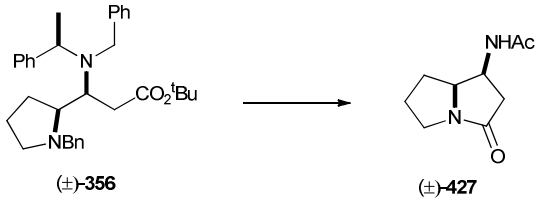
Step 1: Following *General Procedure 4*, reacting (±)-**357** (1.57 g, 3.15 mmol) and $Pd(OH)_2/C$ (785 mg) in 1.25 M HCl/MeOH (15 mL) under H_2 (1 atm) for 72 h gave (±)-**422** as a yellow solid (785 mg).

Step 2: Following *General Procedure 13*, the residue (500 mg) in 1.25 M HCl/MeOH (10 mL) was heated at reflux for 18 h to give a yellow foam (415 mg).

Step 3: Following *General Procedure 14*, the residue (415 mg, 2.00 mmol) and K_2CO_3 (1.10 g, 8.00 mmol) in toluene (25 mL) was heated at reflux for 18 h to give (±)-**401** as a yellow foam (260 mg).

Step 4: The residue (56 mg, 0.40 mmol) was reacted with benzyl chloroformate (63 μL, 0.44 mmol) and K_2CO_3 (83 mg, 0.60 mmol) in THF (1 mL) at rt for 18 h. The reaction mixture was concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CH_2Cl_2/MeOH, 99:1, increased to 90:10) gave (±)-**424** as a colourless oil (40 mg, 36%);[37] δ_H (400 MHz, $CDCl_3$) 1.52-1.68 (1H, m, C(7)H_A), 1.90-2.24 (3H, m, C(7)H_B, C(6)H_2), 2.62 (1H, dd, *J* 15.9, 10.6, C(2)H_A), 2.78 (1H, dd, *J* 15.9, 8.3, C(2)H_B), 2.98-3.08 (1H, m, C(5)H_A), 3.46-3.61 (1H, m, C(5)H_B), 3.61-3.75 (1H, m, C(7a)*H*), 3.95-4.15 (1H, m, C(1)*H*), 5.10 (2H, AB system, J_{AB} 12.0, OCH_2), 5.26 (1H, d, *J* 5.6, N*H*), 7.29-7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 26.6 (*C*(6)), 30.7 (*C*(7)), 41.5 (*C*(5)), 41.6 (*C*(2)), 53.3 (*C*(1)), 67.0 (O*C*H_2), 68.3 (*C*(7a)), 128.2, 128.3, 128.6 (*o*,*m*,*p*-*Ph*), 136.1 (*i*-*Ph*), 155.8 (O*C*O), 171.6 (*C*(3)); *m/z* (ESI^+) 297 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{15}H_{18}N_2NaO_3^+$ ($[M+Na]^+$) requires 297.1210; found 297.1208.

(*RS*,*RS*)-1-Acetylaminopyrrolizin-3-one 427



(±)-**356** (±)-**427**

Method A:

Step 1: Following *General Procedure 4*, reacting (±)-**356** (720 mg, 1.44 mmol) and $Pd(OH)_2/C$ (360 mg) in 1.25 M HCl/MeOH (5 mL) under H_2 (1 atm) for 72 h gave (±)-**425** as a yellow solid (358 mg).

Step 2: Following *General Procedure 13*, the residue (358 mg) in 1.25 M HCl/MeOH (7 mL) was heated at reflux for 18 h to give a yellow foam (295 mg).

Step 3: Following *General Procedure 14*, the residue (120 mg, 0.58 mmol) and K_2CO_3 (320 mg, 2.31 mmol) in toluene (10 mL) was heated at reflux for 18 h to gave (±)-**426** as a yellow oil (78 mg).

Step 4: Following *General Procedure 16*, the residue (78 mg, 0.58 mmol) was reacted with pyridine (1.31 mL, 16.2 mmol) and Ac_2O (0.16 mL, 1.74 mmol) at rt for 18 h. Purification *via* flash column chromatography (eluent CH_2Cl_2/MeOH, 99:1, increased to 90:10) gave (±)-**427** as a colourless oil (23 mg, 22%); ν_{max} 3271 (N–H), 2978 (C–H), 1649 (C=O); δ_H (500 MHz, $CDCl_3$) 1.53-1.63 (1H, m, C(7)H_A), 1.80-1.88 (1H, m, C(7)H_B), 2.02 (3H, s, CO*Me*), 2.04-2.17 (2H, m, C(6)H_2), 2.22 (1H, app d, *J* 16.7, C(2)H_A), 3.02-3.11 (2H, m, C(2)H_B and C(5)H_A), 3.37-3.45 (1H, m, C(5)H_B), 4.06-4.12 (1H, m, C(7a)*H*), 4.64 (1H, app q, *J* 6.9, C(1)*H*), 7.70-7.81 (1H, m, N*H*); δ_C (125 MHz, $CDCl_3$) 22.8 (CO*Me*), 24.8 (*C*(7)), 27.2 (*C*(6)), 41.1 (*C*(5)), 42.5 (*C*(2)), 47.7 (*C*(1)), 66.2 (*C*(7a)), 170.5 (N*C*O), 172.3 (*C*(3)); *m/z* (ESI$^+$) 205 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_9H_{14}N_2NaO_2^+$ ([M+Na]$^+$) requires 205.0947; found 205.0945.

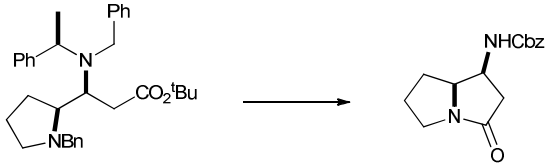
Method B:

Step 1: Following *General Procedure 4*, reacting (±)-**356** (250 mg, 0.50 mmol) and $Pd(OH)_2/C$ (125 mg) in 1.25 M HCl/MeOH (3 mL) under H_2 (5 atm) for 48 h gave (±)-**425** as a yellow solid (122 mg).

Step 2: Following *General Procedure 15*, the residue (122 mg) in 3.0 M aq HCl (12 mL) was heated at 90 °C for 18 h to give (±)-**426** as a yellow foam (70 mg) after purification *via* Dowex.

Step 3: Following *General Procedure 16*, the residue (35 mg, 0.25 mmol) was reacted with pyridine (0.57 mL, 7.00 mmol) and Ac_2O (70 μL, 0.75 mmol) at rt for 18 h. Purification *via* flash column chromatography (eluent CH_2Cl_2/MeOH, 99:1, increased to 90:10) gave (±)-**427** as a colourless oil (24 mg, 53%).

(*RS*,*RS*)-1-(*N*-Carboxybenzylamino)pyrrolizin-3-one 428



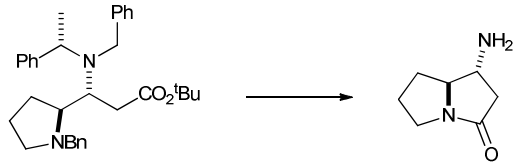
(±)-**356** (±)-**428**

Step 1: Following *General Procedure 4*, reacting (±)-**356** (250 mg, 0.50 mmol) and $Pd(OH)_2$/C (125 mg) in 1.25 M HCl/MeOH (3 mL) under H_2 (5 atm) for 48 h gave (±)-**425** as a yellow solid (122 mg).

Step 2: Following *General Procedure 15*, the residue (122 mg) in 3.0 M aq HCl (12 mL) was heated at 90 °C for 18 h to give (±)-**426** as a yellow foam (70 mg) after purification *via* Dowex.

Step 3: The residue (35 mg, 0.25 mmol) was reacted with benzyl chloroformate (40 μL, 0.28 mmol) and K_2CO_3 (52 mg, 0.38 mmol) in THF (1 mL) at rt for 18 h. The reaction mixture was concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CH_2Cl_2/MeOH, 99:1, increased to 90:10) gave (±)-**428** as a colourless oil (9 mg, 13%); ν_{max} 3281 (N–H), 2953 (C–H), 1673 (C=O); δ_H (500 MHz, $CDCl_3$) 1.52-1.62 (1H, m, C(7)H_A), 1.78-1.88 (1H, m, C(7)H_B), 2.00-2.12 (2H, m, C(6)H_2), 2.27 (1H, app d, *J* 17.0, C(2)H_A), 3.00-3.14 (2H, m, C(2)H_B and C(5)H_A), 3.44-3.52 (1H, m, C(5)H_B), 4.03-4.12 (1H, m, C(7a)*H*), 4.39-4.47 (1H, m, C(1)*H*), 5.11 (2H, AB system, J_{AB} 12.3, OCH_2), 5.41 (1H, br s, N*H*), 7.29-7.40 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 24.6 (*C*(7)), 27.0 (*C*(6)), 41.0 (*C*(5)), 42.4 (*C*(2)), 49.1 (*C*(1)), 65.9 (*C*(7a)), 67.0 (O*C*H_2), 128.1, 128.2, 128.5 (*o*,*m*,*p*-*Ph*), 136.2 (*i*-*Ph*), 155.9 (O*C*O), 171.5 (*C*(3)); *m/z* (ESI^+) 297 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{15}H_{18}N_2NaO_3^+$ ($[M+Na]^+$) requires 297.1210; found 297.1208.

(*RS*,*SR*)-1-Aminopyrrolizin-3-one 401

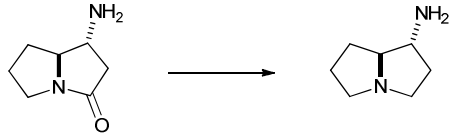


(±)-**357** (±)-**401**

Step 1: Following *General Procedure 4*, reacting (±)-**357** (347 mg, 0.70 mmol) and $Pd(OH)_2/C$ (174 mg) in 1.25 M HCl/MeOH (3 mL) under H_2 (5 atm) for 48 h gave (±)-**422** as a yellow solid (180 mg).

Step 2: Following *General Procedure 15*, the residue (180 mg) in 3.0 M aq HCl (18 mL) was heated at 90 °C for 18 h to give (±)-**401** as a yellow foam (80 mg, 82%) after purification *via* Dowex; ν_{max} 3351 (N–H), 2973 (C–H), 1656 (C=O); δ_H (500 MHz, MeOD) 1.50-1.62 (1H, m, C(7)H_A), 2.04-2.25 (3H, m, C(6)H_2, C(7)H_B), 2.67-2.80 (2H, m, C(2)H_2), 3.05-3.10 (1H, m, C(5)H_A), 3.47-3.57 (2H, m, C(1)*H*, C(5)H_B), 3.75-3.82 (1H, m, C(7a)*H*); δ_C (125 MHz, MeOD) 27.6 (*C*(6)), 30.9 (*C*(7)), 42.6 (*C*(5)), 43.9 (*C*(2)), 54.8 (*C*(1)), 70.0 (*C*(7a)), 174.4 (*C*(3)); *m/z* (ESI$^+$) 163 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_7H_{12}N_2NaO^+$ ([M+Na]$^+$) requires 163.0842; found 163.0837.

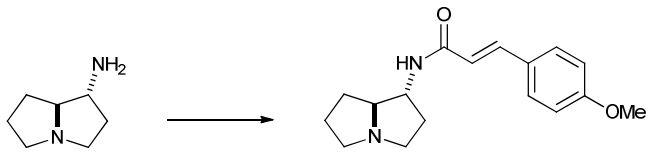
(*RS*,*SR*)-1-Aminopyrrolizidine 402



(±)-**401** (±)-**402**

(±)-**401** (80 mg, 0.57 mmol) was treated with $BH_3{\cdot}SMe_2$ (2.0 M in THF, 2.85 mL, 5.70 mmol). The reaction mixture was stirred at rt for 18 h. MeOH (0.54 mL) was added and the mixture was concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CH_2Cl_2/MeOH, 95:5, increased to 90:10) gave (±)-**402** as a brown oil (21 mg, 29%);[37,38] ν_{max} 3383 (N–H), 2943 (C–H); δ_H (500 MHz, MeOD) 1.76-2.02 (4H, m, C(2)H_A, C(6)H_A, C(7)H_2), 2.08-2.17 (2H, m, C(2)H_B, C(6)H_B), 2.91-3.01 (2H, m, C(3)H_A, C(5)H_A), 3.05-3.13 (2H, m, C(1)*H*, C(3)H_B), 3.25-3.31 (1H, m, C(7a)*H*), 3.33-3.40 (1H, m, C(5)H_B); δ_C (125 MHz, MeOD) 25.3 (*C*(7)), 31.1 (*C*(2)), 34.4 (*C*(6)), 59.3 (*C*(1)), 62.9 (*C*(5)), 65.4 (*C*(3)), 81.5 (*C*(7a)); *m/z* (ESI$^+$) 127 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_7H_{15}N_2^+$ ([M+H]$^+$) requires 127.1230; found 127.1233.

(±)-Absouline 405



(±)-**402** (±)-**405**

DMAP (10 mg, 0.09 mmol) and *trans*-4-methoxycinnamic acid (36 mg, 0.20 mmol) were added to a solution of (±)-**402** (21 mg, 0.17 mmol) in CH_2Cl_2 (4 mL). The mixture was cooled to 0 °C before adding DCC (70 mg, 0.34 mmol) in one portion. The resultant mixture was stirred at 0 °C for 15 min, slowly warmed to rt and stirred for 30 min. The precipitate was filtered and diluted with satd aq $NaHCO_3$ (1 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CH_2Cl_2/MeOH/NH_4OH, 90:10:1) gave (±)-**405** as a colourless oil (5 mg, 10%);[38a,39] ν_{max} 3249 (N–H), 2927 (C–H), 1660 (C=O), 1603 (C=C); δ_H (500 MHz, $CDCl_3$) 1.70-1.78 (1H, m, C(7)H_A), 1.81-1.91 (1H, m, C(6)H_A), 1.91-2.01 (2H, m, C(2)H_A, C(6)H_B), 2.10-2.18 (1H, m, C(7)H_B), 2.26-2.34 (1H, m, C(2)H_B), 2.71-2.81 (2H, m, C(3)H_A, C(5)H_A), 3.22-3.29 (1H, m, C(5)H_B), 3.45-3.53 (1H, m, C(3)H_B), 3.55-3.63 (1H, m, C(8)*H*), 3.83 (3H, s, O*Me*), 4.35-3.42 (1H, m, C(1)*H*), 6.32 (1H, d, *J* 15.6, C(2')*H*), 6.64 (1H, br d, N*H*), 6.89 (2H, d, *J* 8.5, 2 × C(3")*H*), 7.47 (2H, d, *J* 8.5, 2 × C(2")*H*), 7.59 (1H, d, *J* 15.6, C(3')*H*); δ_C (125 MHz, $CDCl_3$) 25.4 (*C*(6)), 30.2 (*C*(7)), 32.2 (*C*(2)), 53.3 (*C*(5)), 54.6 (*C*(1)), 55.2 (*C*(3)), 55.3 (O*Me*), 71.5 (*C*(8)), 114.2 (*C*(3")), 118.1 (*C*(2')), 127.5 (*C*(1")), 129.4 (*C*(2")), 140.9 (*C*(3')), 160.9 (*C*(4")), 166.2 (*C*(1')); *m/z* (ESI^+) 287 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{17}H_{23}N_2O_2^+$ ($[M+H]^+$) requires 287.1754; found 287.1753.

5.6 References and notes

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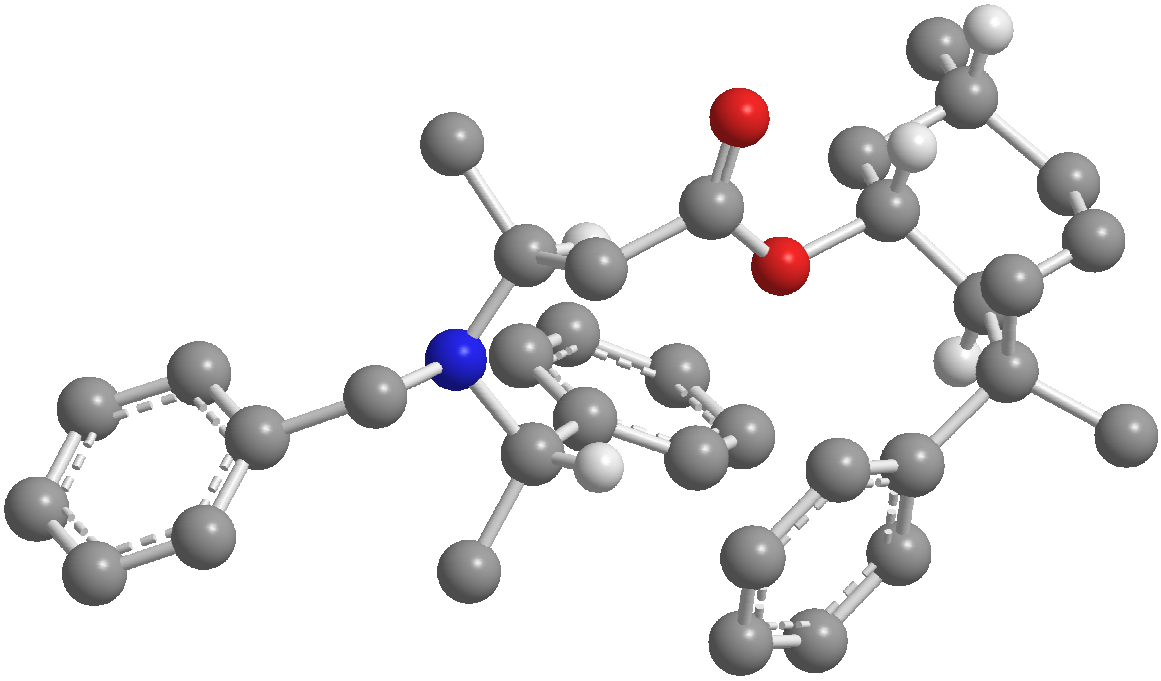
Appendix: X-Ray Crystal Structure Data

X-Ray crystal structure data for 98

(Some H atoms omitted for clarity)



X-ray crystal structure determination for 98

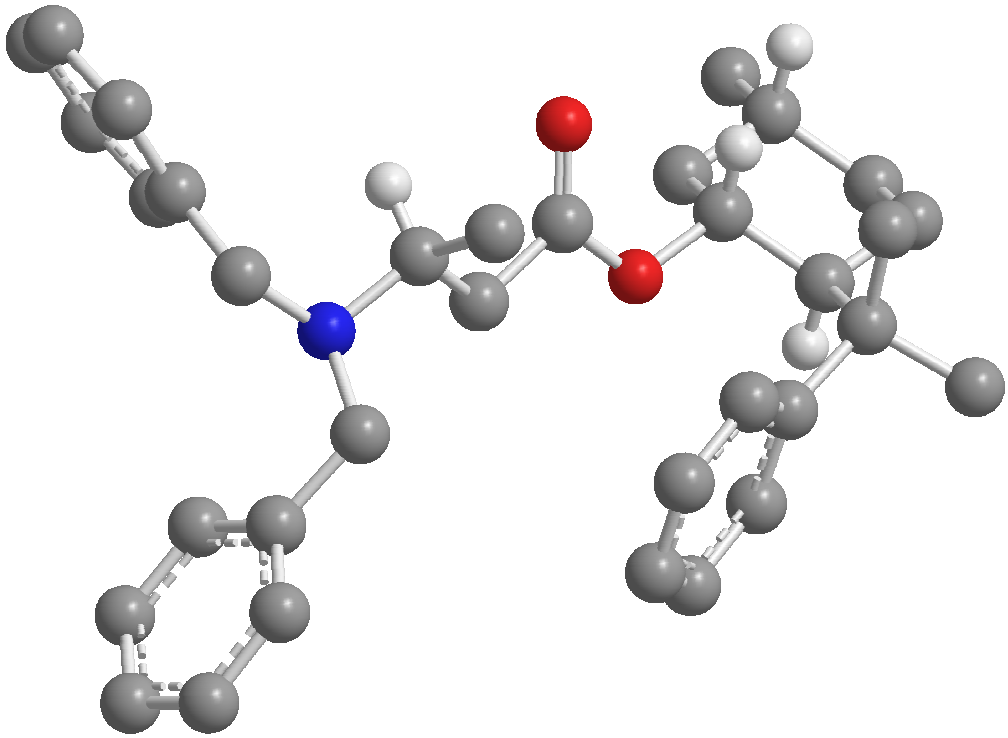
Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions.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

X-ray crystal structure data for **98** [$C_{35}H_{45}NO_2$]: M = 511.75, triclinic, space group $P\ 1$, a = 8.7141(2) Å, b = 9.8528(2) Å, c = 10.1472(2) Å, α = 98.8224(7)°, β = 111.4837(8)°, γ = 105.3920(9)°, V = 750.51(3) Å^3, Z = 1, μ = 0.069 mm^{-1}, colourless block, crystal dimensions = 0.17 × 0.21 × 0.24 mm^3. A total of 3396 unique reflections were measured for $5 < \theta < 27$ and 2765 reflections were used in the refinement. The final parameters were wR_2 = 0.067 and R_1 = 0.032 [$I > -3.0\sigma(I)$]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr 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 112

(Some H atoms omitted for clarity)



X-ray crystal structure determination for 112

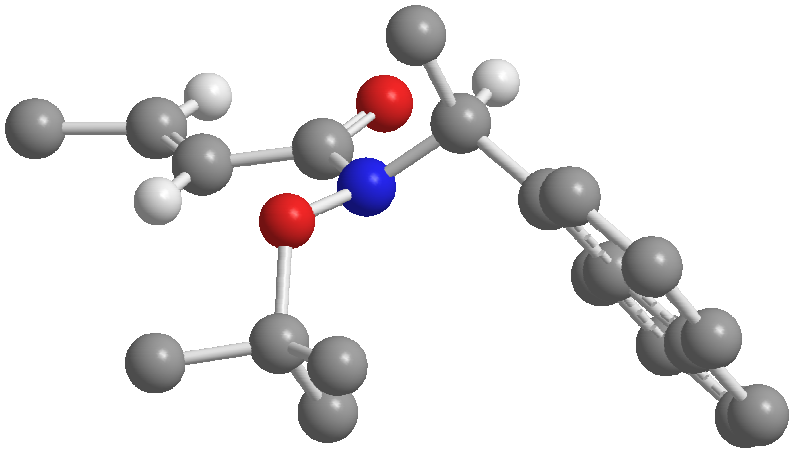
Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[2]

X-ray crystal structure data for **112** [$C_{34}H_{43}NO_2$]: M = 497.72, monoclinic, space group $P\ 2_1$, a = 6.2135(1) Å, b = 35.5431(5) Å, c = 13.2219(2) Å, β = 91.2327(5)°, V = 2919.34(8) Å^3, Z = 4, μ = 0.069 mm^{-1}, colourless block, crystal dimensions = 0.10 × 0.14 × 0.15 mm^3. A total of 6339 unique reflections were measured for $5 < \theta < 27$ and 4973 reflections were used in the refinement. The final parameters were wR_2 = 0.251 and R_1 = 0.090 [I>–3.0σ (I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

[2] 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 150

(Some H atoms omitted for clarity)



X-ray crystal structure determination for 150

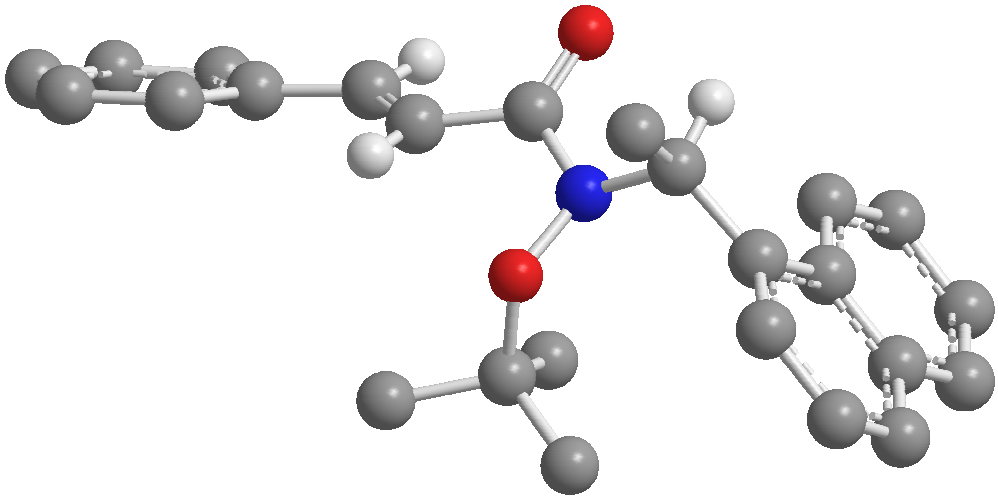
Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[3]

X-ray crystal structure data for **150** [$C_{20}H_{25}NO_2$]: M = 311.42, monoclinic, space group $P\ 2_1$, a = 13.1038(2) Å, b = 9.7412(2) Å, c = 14.4605(3) Å, β = 101.4490(9)°, V = 1809.11(6) Å^3, Z = 4, μ = 0.073 mm^{-1}, colourless block, crystal dimensions = 0.16 × 0.19 × 0.21 mm^3. A total of 4332 unique reflections were measured for $5 < \theta < 27$ and 4332 reflections were used in the refinement. The final parameters were wR_2 = 0.106 and R_1 = 0.051 [I>–3.0σ (I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

[3] 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 151

(Some H atoms omitted for clarity)



X-ray crystal structure determination for 151

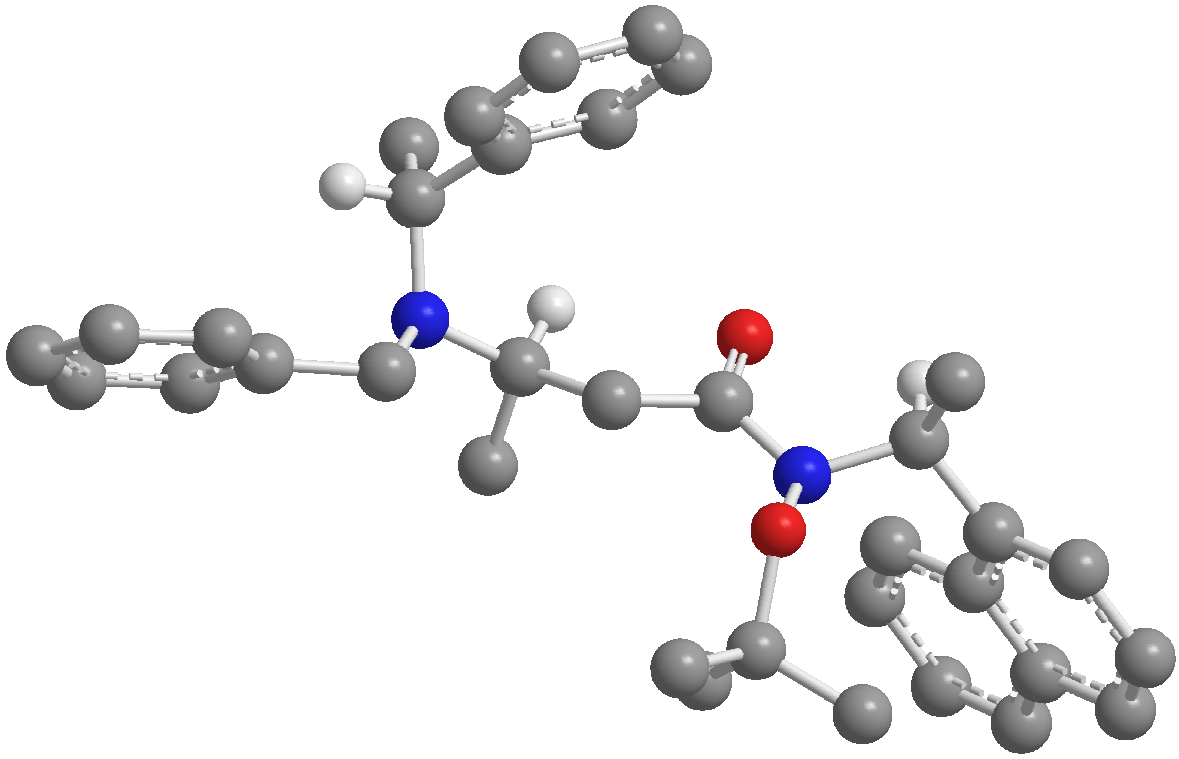
Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[4]

X-ray crystal structure data for **151** [$C_{25}H_{27}NO_2$]: M = 373.49, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 8.1118(1) Å, b = 26.0315(4) Å, c = 9.7014(2) Å, V = 2048.57(6) Å^3, Z = 4, μ = 0.076 mm^{-1}, colourless plate, crystal dimensions = 0.16 × 0.20 × 0.28 mm^3. A total of 2632 unique reflections were measured for $5 < \theta < 27$ and 2028 reflections were used in the refinement. The final parameters were wR_2 = 0.065 and R_1 = 0.031 [I>–3.0σ (I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr 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.

X-Ray crystal structure data for 153

(Some H atoms omitted for clarity)



X-ray crystal structure determination for 153

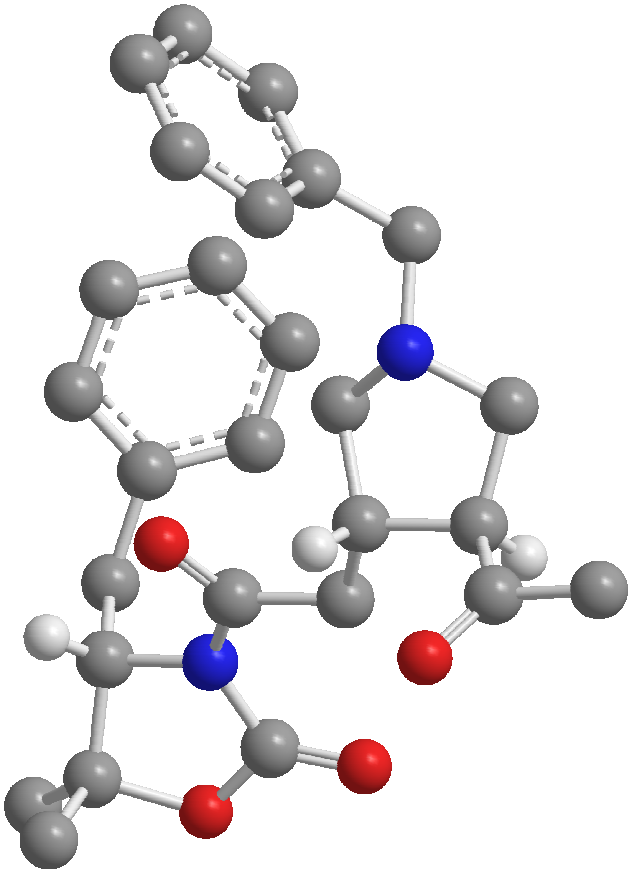
Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[5]

X-ray crystal structure data for **153** [$C_{35}H_{42}N_2O_2$]: M = 522.73, monoclinic, space group $P\ 2_1$, a = 11.6903(3) Å, b = 10.8507(3) Å, c = 12.1629(3) Å, β = 104.3593(14)°, V = 1494.64(7) Å^3, Z = 2, μ = 0.071 mm^{-1}, colourless plate, crystal dimensions = 0.11 × 0.13 × 0.24 mm^3. A total of 3557 unique reflections were measured for $5 < \theta < 27$ and 3120 reflections were used in the refinement. The final parameters were wR_2 = 0.079 and R_1 = 0.035 [$I > -3.0\sigma\ (I)$]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

[5] 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 255

(Some H atoms omitted for clarity)



X-ray crystal structure determination for 255

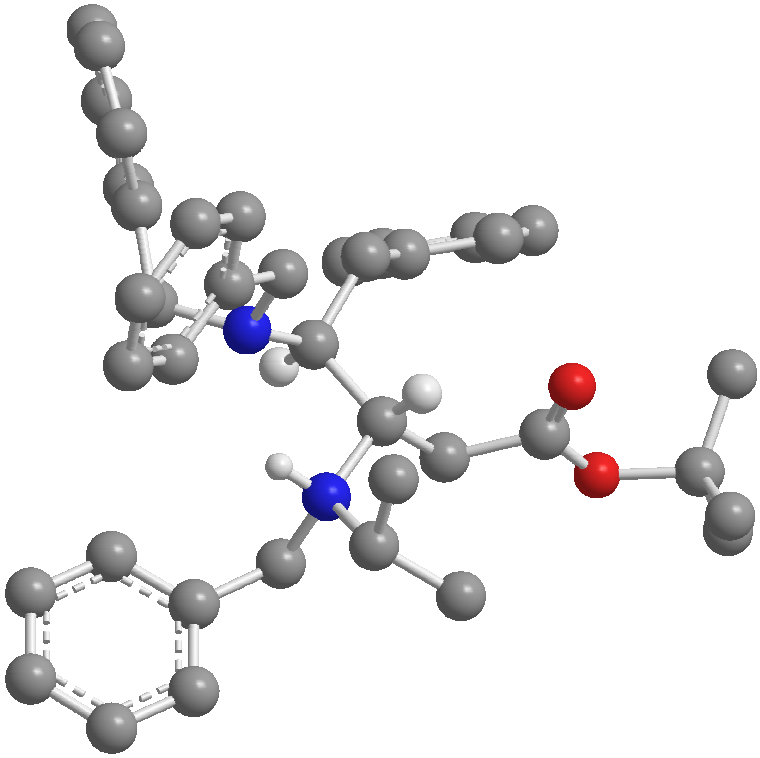
Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[6]

X-ray crystal structure data for **255** [$C_{27}H_{32}N_2O_4$]: M = 448.56, monoclinic, space group $P\,2_1$, a = 6.6765(2) Å, b = 22.6483(6) Å, c = 7.9874(2) Å, β = 97.6546(13)°, V = 1197.02(6) Å^3, Z = 2, μ = 0.083 mm^{-1}, colourless plate, crystal dimensions = 0.13 × 0.15 × 0.21 mm^3. A total of 2775 unique reflections were measured for 5 < θ < 27 and 2119 reflections were used in the refinement. The final parameters were wR_2 = 0.071 and R_1 = 0.040 [I>–3.0σ (I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

[6] 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 339

(Some H atoms omitted for clarity)



X-ray crystal structure determination for 339

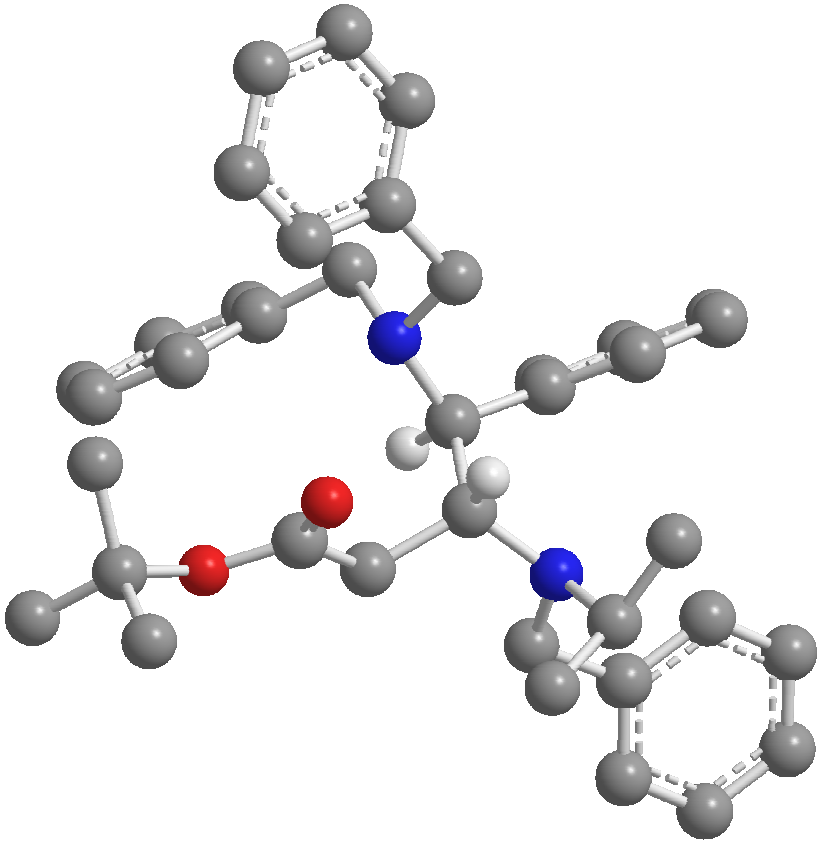
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[7]

X-ray crystal structure data for **339** [$C_{28}H_{38}Cl_{0.67}N_{1.33}O_2$]: M = 448.92, triclinic, space group $P\,{-1}$, a = 9.9186(3) Å, b = 13.6626(5) Å, c = 15.7674(5) Å, α = 109.510(3)°, β = 92.589(3)°, γ = 104.121(3)°, V = 1934.30(13) Å^3, Z = 3, μ = 1.17 mm^{-1}, colourless plate, crystal dimensions = 0.04 × 0.10 × 0.20 mm^3. A total of 8081 unique reflections were measured for $5 < \theta < 27$ and 8081 reflections were used in the refinement. The final parameters were wR_2 = 0.177 and R_1 = 0.065 [$I > -3.0\sigma(I)$]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

[7] 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 347

(Some H atoms omitted for clarity)



X-ray crystal structure determination for 347

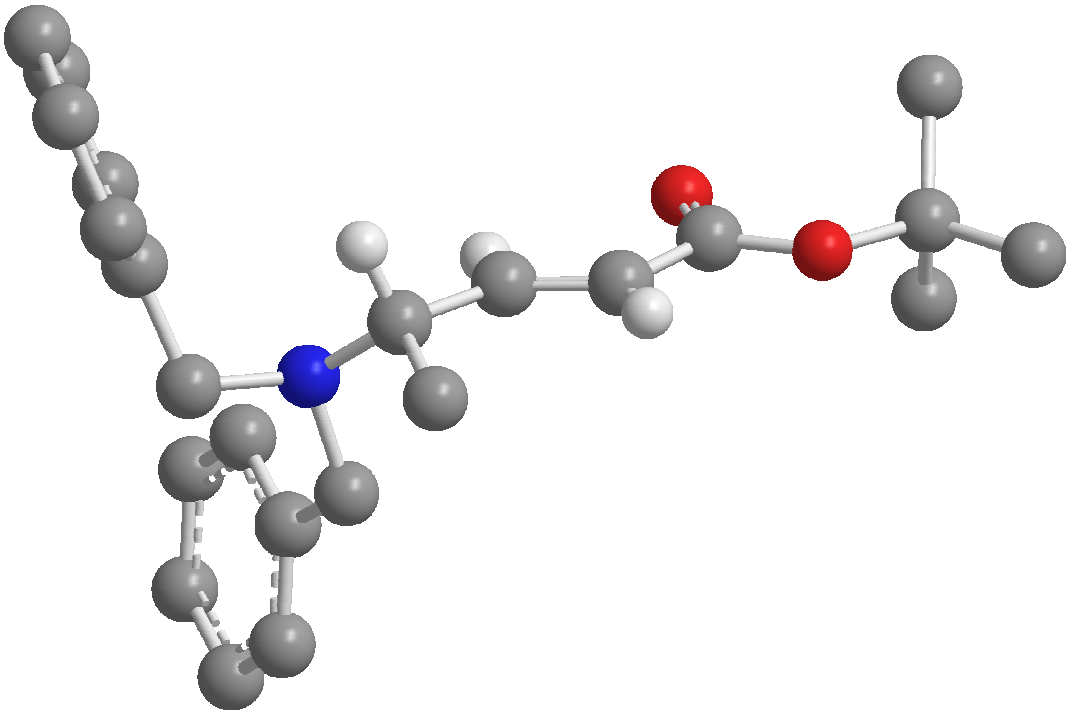
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[8]

X-ray crystal structure data for **347** [$C_{38}H_{46}N_2O_2$]: M = 562.80, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 11.68976(18) Å, b = 14.9507(2) Å, c = 18.3439(3) Å, V = 3205.97(8) Å^3, Z = 4, μ = 0.549 mm^{-1}, colourless block, crystal dimensions = 0.18 × 0.22 × 0.24 mm^3. A total of 9922 unique reflections were measured for $5 < \theta < 27$ and 9922 reflections were used in the refinement. The final parameters were wR_2 = 0.094 and R_1 = 0.040 [I>–3.0σ (I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr 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.

X-Ray crystal structure data for 283

(Some H atoms omitted for clarity)



X-ray crystal structure determination for 283

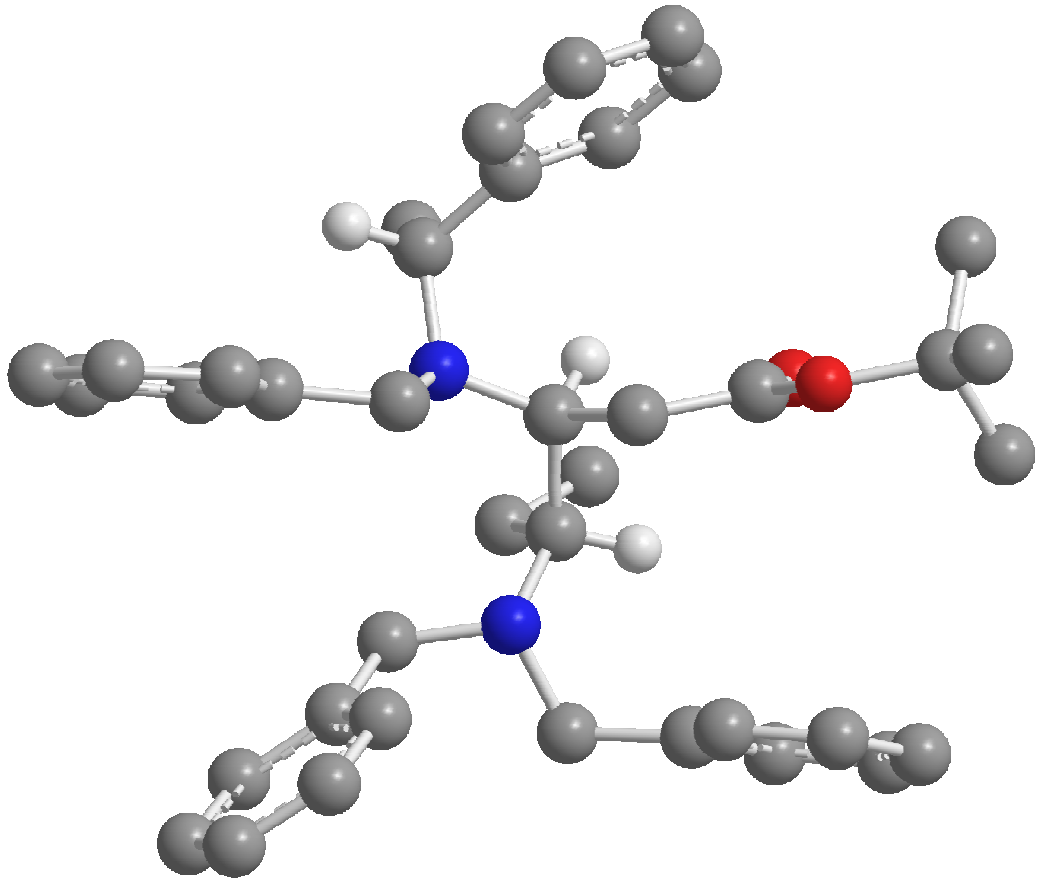
Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[9]

X-ray crystal structure data for **283** [$C_{23}H_{29}NO_2$]: M = 351.49, monoclinic, space group $P\ 2_1/n$, a = 5.8327(1) Å, b = 10.1818(2) Å, c = 33.8568(8) Å, β = 94.4233(8)°, V = 2004.68(7) Å^3, Z = 4, μ = 0.073 mm^{-1}, colourless plate, crystal dimensions = 0.09 × 0.18 × 0.20 mm^3. A total of 3055 unique reflections were measured for $5 < \theta < 27$ and 3055 reflections were used in the refinement. The final parameters were wR_2 = 0.148 and R_1 = 0.078 [$I > -3.0\sigma\ (I)$]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

[9] 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 350

(Some H atoms omitted for clarity)



X-ray crystal structure determination for 350

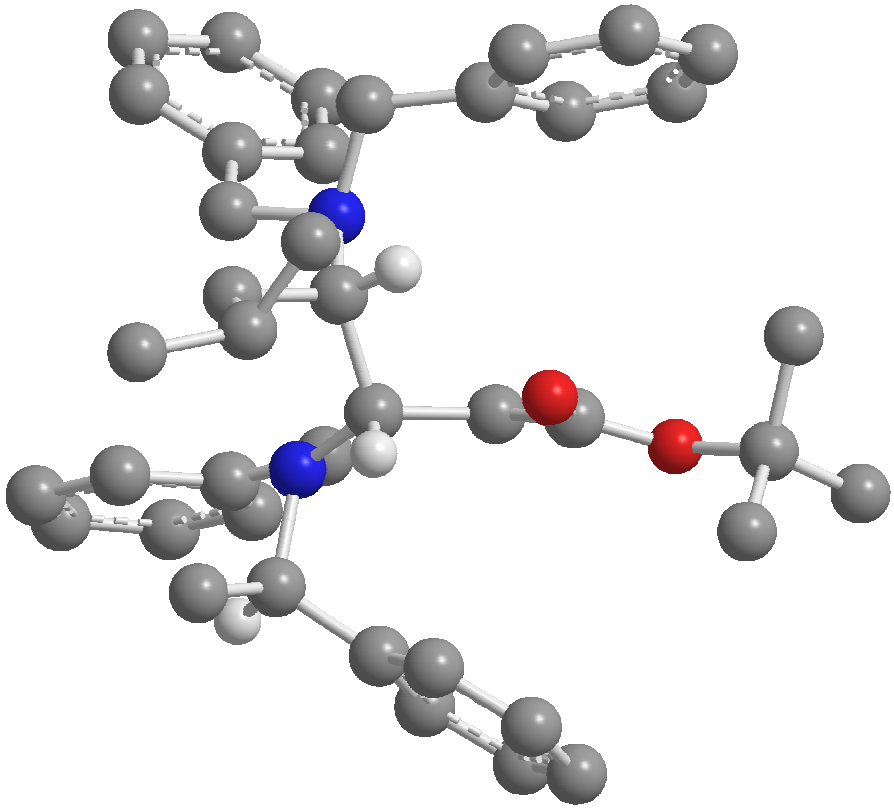
Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[10]

X-ray crystal structure data for **350** [$C_{39}H_{48}N_2O_2$]: M = 576.82, monoclinic, space group $P\ 2_1/n$, a = 17.6291(3) Å, b = 11.7882(2) Å, c = 18.3855(4) Å, β = 116.6367(9)°, V = 3415.28(11) Å^3, Z = 4, μ = 0.068 mm^{-1}, colourless block, crystal dimensions = 0.28 × 0.33 × 0.34 mm^3. A total of 7759 unique reflections were measured for $5 < \theta < 27$ and 5755 reflections were used in the refinement. The final parameters were wR_2 = 0.134 and R_1 = 0.072 [$I > -3.0\sigma\ (I)$]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr 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 352

(Some H atoms omitted for clarity)



X-ray crystal structure determination for 352

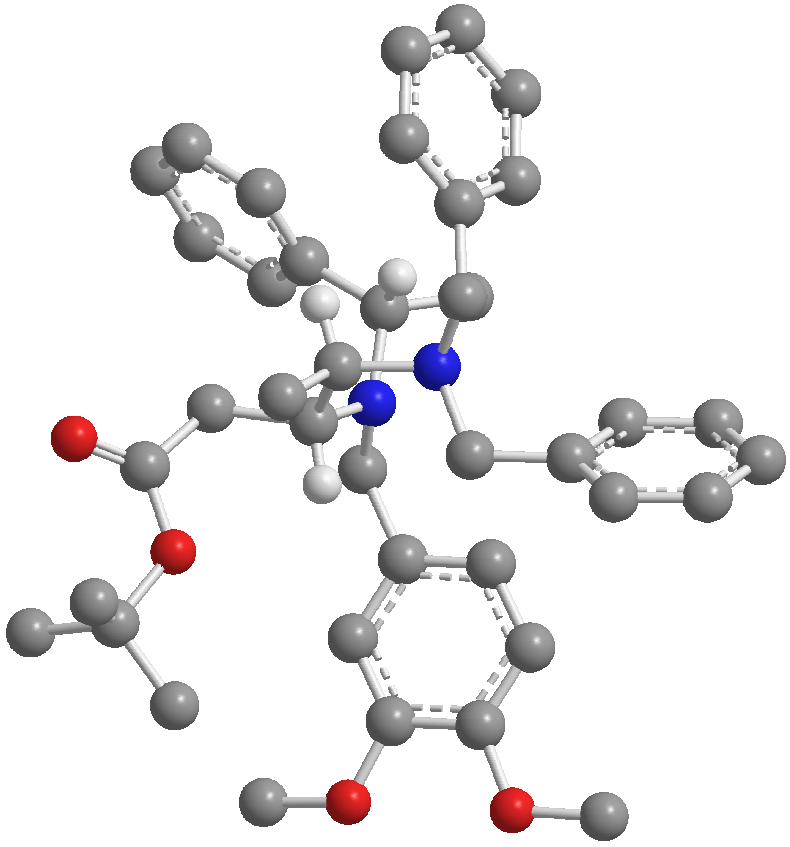
Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[11]

X-ray crystal structure data for **352** [$C_{41}H_{52}N_2O_2$]: M = 604.88, monoclinic, space group $P\ 2_1/n$, a = 17.7110(6) Å, b = 12.0009(4) Å, c = 18.5046(6) Å, β = 116.3099(14)°, V = 3525.7(2) Å^3, Z = 4, μ = 0.069 mm^{-1}, colourless block, crystal dimensions = 0.14 × 0.24 × 0.26 mm^3. A total of 7964 unique reflections were measured for $5 < \theta < 27$ and 3716 reflections were used in the refinement. The final parameters were wR_2 = 0.063 and R_1 = 0.063 [I>2.0σ (I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

[11] 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 358

(Some H atoms omitted for clarity)



X-ray crystal structure determination for 358

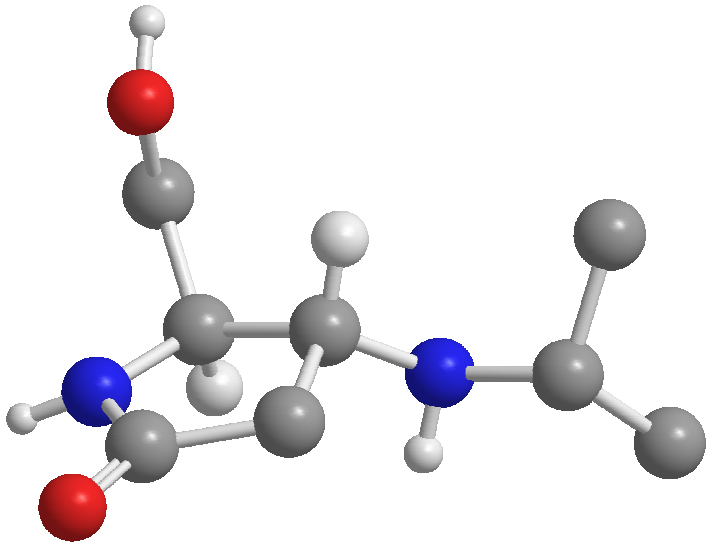
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[12]

X-ray crystal structure data for **358** [$C_{40}H_{50}N_2O_4$]: M = 622.85, monoclinic, space group $P\ 2_1$, a = 10.26594(7) Å, b = 9.75883(8) Å, c = 17.96995(14) Å, β = 98.0805(7)°, V = 1782.42(2) Å^3, Z = 2, μ = 0.582 mm^{-1}, colourless block, crystal dimensions = 0.07 × 0.09 × 0.33 mm^3. A total of 3967 unique reflections were measured for $5 < \theta < 27$ and 3966 reflections were used in the refinement. The final parameters were wR_2 = 0.134 and R_1 = 0.046 [$I > -3.0\sigma\ (I)$]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

[12] 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 399

(Some H atoms omitted for clarity)



X-ray crystal structure determination for 399

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 **399** [$C_{7.11}H_{14.22}N_{1.78}O_{1.78}$]: M = 153.09, orthorhombic, space group $P\ b\ c\ a$, a = 13.5392(6) Å, b = 6.7124(4) Å, c = 20.4694(10) Å, V = 1860.26(16) Å^3, Z = 9, μ = 0.724 mm^{-1}, colourless plate, crystal dimensions = 0.04 × 0.16 × 0.19 mm^3. A total of 1911 unique reflections were measured for $5 < \theta < 27$ and 1661 reflections were used in the refinement. The final parameters were wR_2 = 0.056 and R_1 = 0.069 [I>–3.0σ (I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, 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.