Aziridines and Aziridinium Intermediates in the Asymmetric Synthesis of β-Substituted-α-amino acids and 1,2,3,4-Tetrahydroisoquinolines

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for the degree of Doctor of Philosophy

by

Aileen Bernadette Frost

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For my big sister, Kristína

The work described in this thesis was carried out in the Chemistry Research Laboratory, University of Oxford from September 2011 until March 2015, under the supervision of Professor Stephen G. Davies. All of the work is my own unless otherwise stated and has not been submitted previously for any other degree at this or any other university.

Aileen Bernadette Frost

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This thesis is concerned with the development of methodology for the regioselective ring-opening of aziridines and aziridinium intermediates and its subsequent application to the asymmetric synthesis of β-substituted-α-amino acids and 1,2,3,4-tetrahydroisoquinolines.

Chapter 1 introduces methods for the formation of aziridines and aziridinium ions and focusses on their utility as intermediates in synthesis.

Chapter 2 describes studies into the synthesis of aziridines from enantiopure α-hydroxy-β-amino esters and their subsequent conversion to the corresponding β-hydroxy-α-amino acids via either a regioselective ring-opening with Cl_3CCO_2H, or a rearrangement promoted by Cl_3CCO_2H. Application of this procedure to both *syn*- and *anti*-configured substrates enabled the syntheses of (*S*,*S*)-*allo*-threonine, (2*R*,3*S*)-threonine, (*R*,*R*)-3-hydroxyphenylalanine and (2*S*,3*R*)-3-hydroxyphenylalanine.

Chapter 3 details attempts to truncate the synthesis described in Chapter 2 by investigating the synthesis of enantiopure *anti*-β-hydroxy-α-amino acids via the intermediacy of aziridinium ions. These studies culminated in the development of a regioselective and stereospecific one-pot aziridinium formation and ring-opening protocol, leading to the synthesis of a range of C(3)-aryl and C(3)-alkyl substituted *anti*-β-hydroxy-α-amino acids.

Chapter 4 discusses the conversion of enantiopure *anti*-α-hydroxy-β-amino esters to *anti*-β-fluoro-α-amino esters via the regioselective and stereospecific ring-opening of an aziridinium intermediates *in situ*. The subsequent development of a one-pot deprotection strategy leads to a concise and expedient synthesis of *anti*-β-fluorophenylalanines. The extension of this methodology to access a representative *anti*-α,β-diamino acid is also demonstrated.

Chapter 5 describes the development of a one-pot diastereoselective rearrangement of enantiopure α-hydroxy-β-amino esters to 1,2,3,4-tetrahydroisoquinolines. The substrate scope of this reaction manifold is examined and application to the asymmetric synthesis of enantiopure 1,2,3,4-tetrahydroisoquinolines also discussed.

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

Firstly I must thank my supervisor Professor Steve Davies. I am very grateful for the opportunities you have given me over these past 4 years, from enabling me to pursue my DPhil studies in your research group to the interest you have shown in my future career, and the (much needed!) encouragement you have given me. I have benefitted greatly from your guidance.

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alloc	Allyloxycarbonyl
app	Apparent
aq	Aqueous
Ar	Aryl
Atm	Atmosphere
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
br	Broad
Bu	Butyl
Bus	*tert*-Butyl sulfonyl
Bz	Benzoyl
c	Concentration
C	Celsius
^{13}C	Carbon
ca.	Circa
CAN	Ceric ammonium nitrate
cat.	Catalytic
Cbz	Carboxylbenzyl
CDI	1,1'-Carbonyldiimidazole
cm	Centimetres
cm^{-1}	Wavenumber
conc	Concentrated
COSY	Correlated spectroscopy
CSA	Camphorsulfonic acid
CSI	Camphorsulfonimine
CSO	Camphorsulfonyloxaziridine
d	Doublet
DAST	(Diethylamino)sulfur trifluoride
dba	Dibenzylideneacetone
DCC	Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DEAD	Diethyl azodicarboxylate
dec	Decomposes
deg	Degrees
DIBAL-H	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DMBA	1,3-Dimethylbarbituric acid
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
dr	Diastereoisomeric ratio
δ_H	Proton (^1H) NMR chemical shift
δ_C	Carbon (^{13}C) NMR chemical shift
(*E*)	Entgegen
EDCI	*N*-(3-Dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride
EDG	Electron donating group
ee	Enantiomeric excess
er	Enantiomer ratio
ent	Enantiomer

equiv	Equivalent(s)
ESI	Electrospray ionisation
Et	Ethyl
EWG	Electron withdrawing group
FGI	Functional group interconversion
FI	Field ionisation
Fmoc	Fluorenylmethoxycarbonyl
FT	Fourier transform
GCT, GCToF	Gas chromatography time of flight
h	Hour(s)
^{1}H	Proton
HFIP	1,1,1,3,3,3-Hexafluoro-2-propanol
HMBC	Heteronuclear multiple bond correlation
HMDS	Hexamethyldisilazide
HRMS	High resolution mass spectrometry
HOBt	1-Hydroxybenzotriazole
HSQC	Hetereonuclear single quantum correlation
Hz	Hertz
i	Ipso
^{i}Pr	Isopropyl
IR	Infrared
J	Coupling constant
K	Kelvin
L	Litres
LDA	Lithium diisopropylamide
lit.	Literature
LiTMP	Lithium tetramethylpiperidine
m	Meta
m	Multiplet
M	Molar
$[M]^{+}$	Molecular ion
m-CPBA	*meta*-Chloroperbenzoic acid
Me	Methyl
MeOH-d_4	Deuterated methanol
mg	Milligrams
MHz	Megahertz
min	Minutes
µL	Microlitres
mL	Millilitres
µmol	Micromoles
mmol	Millimoles
mp	Melting point
Ms	Methanesulfonyl
MS	Mass spectrometry
MTBE	Methyl *tert*-butyl ether
m/z	Mass to charge ratio
nm	Nanometre
Nu	Nucleophile
NMO	*N*-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
Ns	Nosyl

o	Ortho
p	Para
PCC	Pyridinium chlorochromate
Ph	Phenyl
PMP	*para*-Methoxyphenyl
ppm	Parts per million
Pr	Propyl
q	Quartet
quant	Quantitative
R	Alkyl
(*R*)	Rectus
rt	Room temperature
s	Singlet
(*S*)	Sinister
Satd	Saturated
S_N1	Substitution, nucleophilic, unimolecular
S_N2	Substitution, nucleophilic, bimolecular
^{t}Bu	*tert*-Butyl
tert	Tertiary
t	Triplet
T	Temperature
TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TBHP	*tert*-Butyl hydroperoxide
TEMPO	2,2,6,6-Tetramethylpiperidine 1-oxyl
Tf	Trifluoromethanesulfonate
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMS	Trimethyl silyl
ToF	Time of flight
TPAP	Tetrapropylammonium perruthenate
Tr	triphenylmethyl
Ts	*para*-Toluenesulfonyl
UHP	Urea-hydrogen pexoxide
UV	Ultra-violet
ν_{max}	Infra-red absorption maximum
(*Z*)	Zusammen

Abstract

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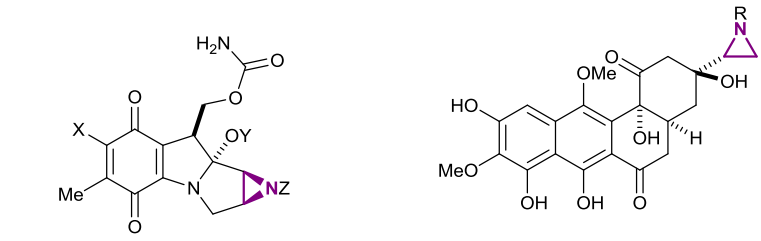
Chapter 1: Introduction

1.1 Aziridines and aziridinium ions in asymmetric synthesis

Aziridines are nitrogen containing three-membered rings and are the aza-analogue of epoxides. Many naturally occurring compounds containing the aziridine motif are known to exhibit desirable biological properties.[1] For example, the mitomycins (**1**–**4**), which are a family of natural products first isolated from *Streptomyces caespitosus* found in soil samples in 1956,[2] exhibit potent antitumor activity, with mitomycin C **3** widely prescribed as a chemotherapeutic agent.[3] The observed biological activity is thought to stem from their ability to cross link DNA via alkylation at the aziridine and carbamoyloxy electrophilic sites.[4] Azicemicins A and B (**5** and **6**) are antibiotics isolated from *Kibdelosporangium* sp. MJ126-NF4, which show activity against Gram-positive bacteria and mycobacteria.[5] The pentapeptide miraziridine A **7** was isolated from the marine sponge *Theonella aff. mirabilis* in 2000 and is a cathepsine B inhibitor.[6] This biological activity is expected to result from the ring-opening of the aziridine moiety by a cysteine residue[7] (Figure 1).



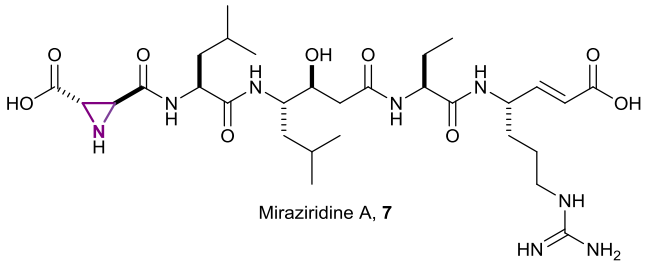


Figure 1. Biologically active compounds that contain an aziridine unit.

In addition to their own biological utility, aziridines are also valuable as building blocks in organic synthesis. Their inherent ring strain makes them potent electrophiles, which can undergo stereospecific ring-opening under S_N2-type conditions with high regioselectivity often observed. Due to their reliable and predictable mode of reactivity, aziridine intermediates are often included in strategies for the synthesis of chiral nitrogen containing natural products and other targets of interest to the pharmaceutical industry.[8] Aziridinium

ions, the quaternary salts of aziridines, have received increasing attention as reactive intermediates: quaternisation of an aziridine to the corresponding aziridinium ion is a strategy which can be employed to activate aziridines to nucleophilic attack.[9] These intermediates may also be generated and ring-opened regioselectively and stereospecifically *in situ*,[10] offering a highly efficient and atom economic alternative to traditional aziridine chemistry. This chapter will explore the use of both aziridines and aziridinium ions as intermediates in synthesis.

1.2 Aziridines in asymmetric synthesis

1.2.1. Synthesis of aziridines

Extensive research into the synthesis of enantioenriched aziridines has been undertaken since their discovery in 1888,[11] with many methods now at the disposal of the modern synthetic chemist.[12] Inducing an intramolecular S_N2-type reaction of chiral amino alcohols,[13] and related compounds,[14] provides a stereospecific route to chiral aziridines (route a). Aziridine formation can also be achieved from the introduction of a "carbon equivalent" to an imine, through reaction of an imine with either a carbene[15] or diazo compound.[16] In this case, high levels of stereoselectivity can be achieved by using chiral ligands in conjunction with a borate reagent as a Lewis acid (route b) or a metal carbenoid (route c). The asymmetric aza-Darzens reaction is another important method for making aziridines,[17] which relies on stereoinduction from a chiral auxiliary, attached to either the imine or anion reagent (route d). The asymmetric synthesis of aziridines via the addition of a nitrogen equivalent to an olefin can be achieved upon reaction with metal nitrenes[18] in the presence of a chiral ligand (route e) or by asymmetric organocatalytic aziridination (route f),[19] amongst other approaches[20] (Figure 2).

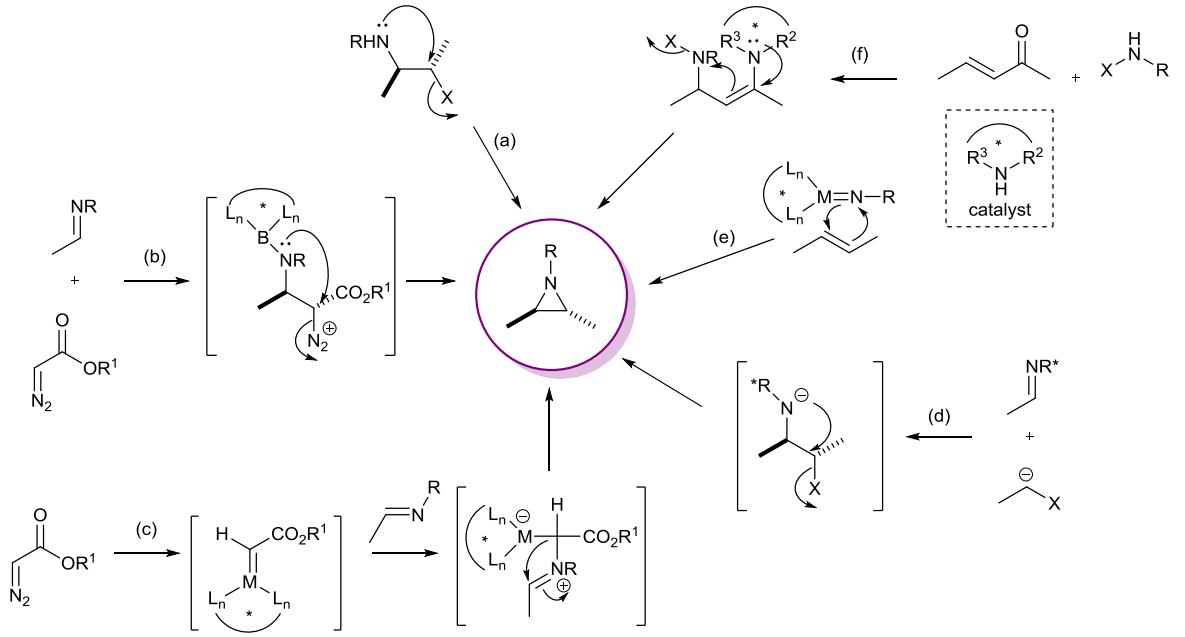


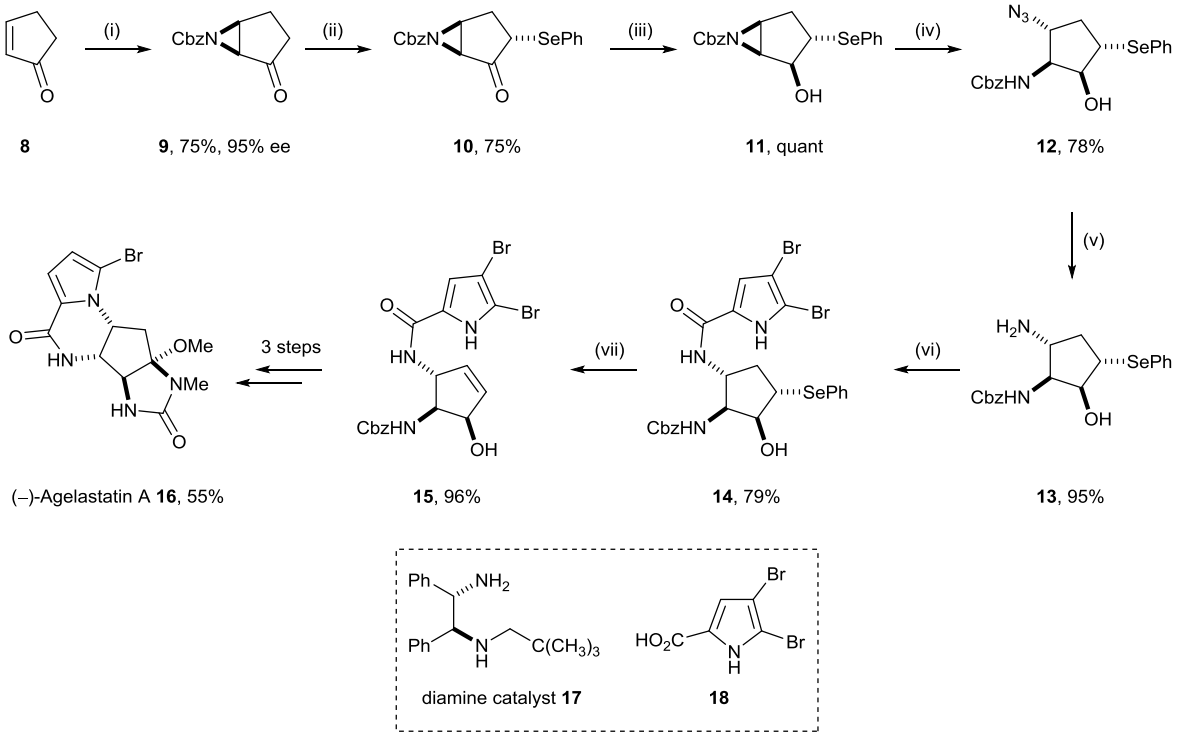
Figure 2. Methods for the formation of aziridines.

1.2.2. Regioselective aziridine ring-opening as a strategy in synthesis

Strategies involving the ring-opening of aziridines have been used extensively in natural product and drug target synthesis, and also as a means of accessing both natural amino acids and interesting unnatural analogues. Representative examples are discussed in more detail below.

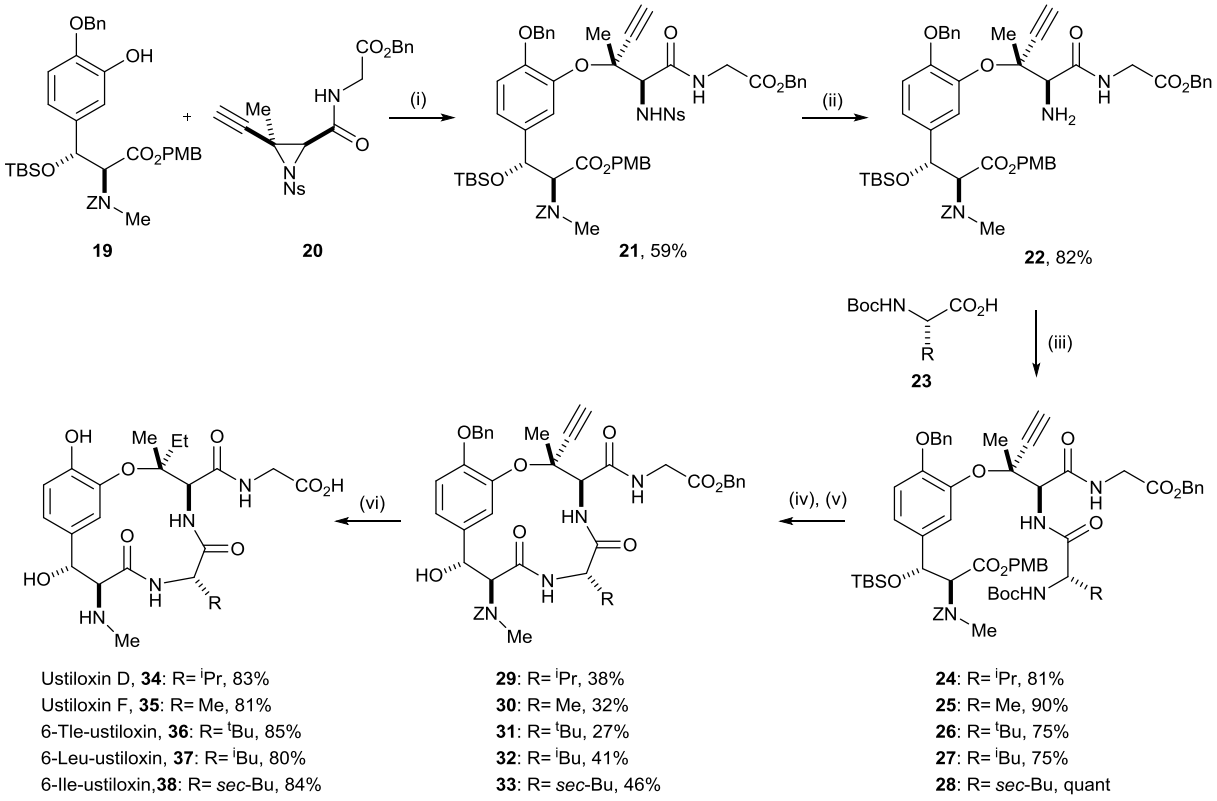
1.2.2.1. Synthesis of the natural products (−)-agelastatin A and the ustiloxins

Alkaloid natural products are often desirable targets in organic synthesis due to their potent biological activity.[21] The alkaloid (−)-agelastatin A **16** was isolated from the deep water marine sponge *Agelas dendromorpha*,[22] and has been shown to inhibit human tumor cell lines.[23] Hamada and co-workers have used the asymmetric aziridination of cyclic enone **8**, and the regioselective ring-opening of aziridine **11** with azide, as key steps in their formal synthesis of this natural product.[24] Aziridination of **8** was achieved by using chiral enamine catalysis: reaction of **8** with *p*-TsONHCbz in the presence of diamine catalyst **17** gave aziridine **9** in 75% yield and 95% ee. Phenylselenylation of **9** followed by diastereoselective reduction of the resultant ketone **10** gave **11**, which underwent regioselective ring-opening upon treatment with azide to give **12** in 78% yield. Sequential reduction of the azide moiety, amide coupling and oxidative elimination of the phenylselenyl group gave **15**, an intermediate in Ichikawa's synthesis of **16**,[25] thus completing this formal synthesis (Scheme 1).



Scheme 1. *Reagents and Conditions*: (i) diamine catalyst **17**, *p*-TsONHCbz, $PhCO_2H$, $NaHCO_3$, $CHCl_3$, rt, 40 h; (ii) *N*,*O*-bis(trimethylsilyl)acetamine, DBU, PhMe, rt, 16 h, then PhSeCl, −78 °C, 30 min; (iii) $NaBH_4$, THF/H_2O, −78 °C, 30 min; (iv) NaN_3, AcOH, MeOH/H_2O, rt, 7 days; (v) $NaBH_4$, $NiCl_2 \cdot 6H_2O$, MeOH, −20 °C, 1 h; (vi) **18**, EDCI, HOBt, DMAP, CH_2Cl_2, rt, 24 h; (vii) 30% H_2O_2, pyridine, THF, rt, 1 h.

The ustiloxin natural products are antimitotic agents that are known to inhibit the polymerisation of brain tubulin,[26] with tubulin being an established cancer chemotherapeutic target. Joullie *et al*. developed a route to access ustiloxins D and F and eight analogues which involved a regioselective aziridine ring-opening reaction as a key step.[27] Nucleophilic attack of aziridine **20** by phenol **19** occurred with complete regioselectivity, giving **21** as a single isomer which was isolated in 59% yield. Subsequent *N*-nosyl deprotection gave **22**, which underwent amide coupling with a range of α-amino acids **23**, giving amides **24**–**28** in 75% to quantitative yield. Macrolactamisation of **24**–**28** was followed by global hydrogenolysis to give natural products **34** and **35**, as well as synthetic analogues **36**–**38** (Scheme 2). A further three ustiloxin analogues were obtained in the analogous ring-opening of **20** with *ent*-**19**.

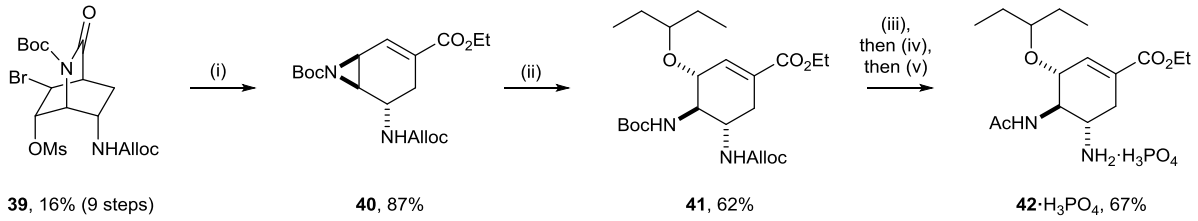


Scheme 2. *Reagents and Conditions*: (i) CuOAc, DBU, PhMe, rt, 2 h; (ii) PhSH, Cs_2CO_3, DMF, rt, 6 h; (iii) **23**, EDCl, HOBt, $NaHCO_3$, DMF, rt, 36 h; (iv) TFA, Et_3SiH, rt, 2 h; (v) EDCl, HOBt, $NaHCO_3$, DMF, rt, 36 h; (vi) H_2 (1 atm), Pd black, THF/H_2O, rt, overnight.

1.2.2.2. Aziridine ring-openings in the synthesis of Tamiflu and DMP 323

Fukuyama and co-workers have published an asymmetric synthesis of (−)-oseltamivir phosphate **42**·H_3PO_4 (Tamiflu) from pyridine,[28] in which aziridine formation and regioselective ring-opening are key steps. Intermediate **39** was synthesised from pyridine in 16% yield over 9 steps. Upon treatment of **39** with NaOEt, aziridine **40** was formed in 87% yield. Ring-opening of **40** with 3-pentanol occurred regioselectively in the presence of

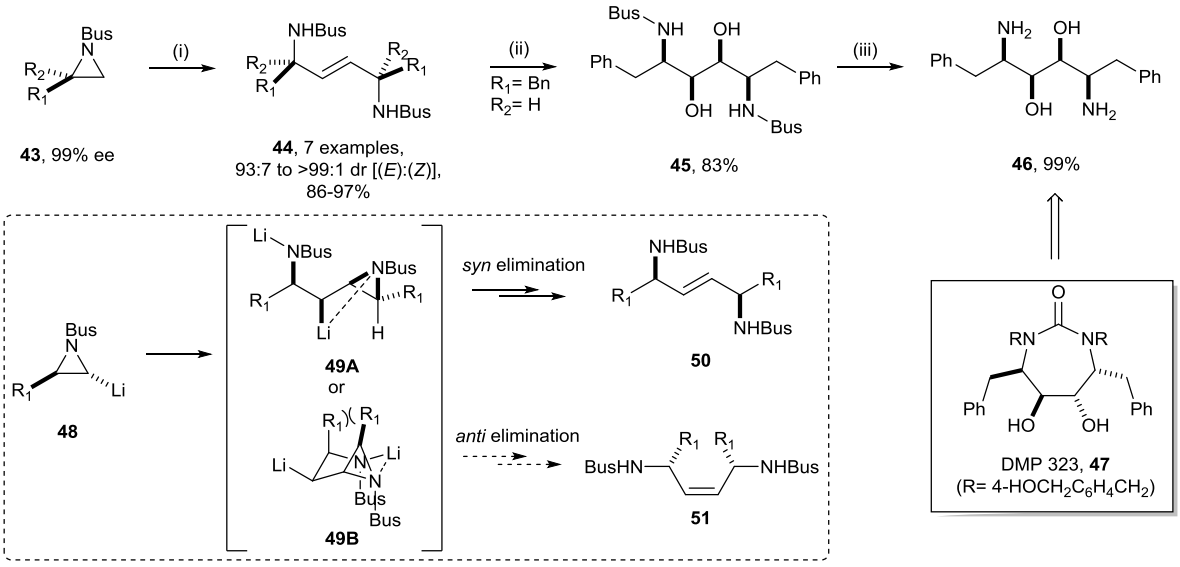
$BF_3{\cdot}Et_2O$, giving **41** in 62% yield, with subsequent elaboration of **41** giving **42**$\cdot H_3PO_3$ in 67% yield over 3 steps (Scheme 3).



39, 16% (9 steps) **40**, 87% **41**, 62% **42**$\cdot H_3PO_4$, 67%

Scheme 3. *Reagents and Conditions*: (i) NaOEt, EtOH, 0 °C, monitored by TLC until conversion; (ii) $BF_3{\cdot}Et_2O$, 3-pentanol, −20 °C, 30 min; (iii) TFA, CH_2Cl_2, 0 °C to rt, 3 h; (iv) Ac_2O, pyridine, rt, 1 h; (v) Pd/C, PPh_3, 1,3-dimethyl-barbituric acid, EtOH, reflux, 40 min then H_3PO_4.

The synthesis of 1,4-diamino-2,3-diol **46**, a precursor of the HIV protease inhibitor DMP 323 **47**, [29] has been achieved upon application of methodology developed by Hodgson *et al.*[30] Dimerization of enantiopure terminal *N*-Bus aziridines **43** was shown to give (*E*)-2-ene-1,4-diamines **44** in high diastereoselectivity (93:7 to >99:1 dr). It was rationalised that this stereochemical outcome was the result of a *syn*-elimination pathway, which it was proposed was significantly more favourable than the corresponding *anti*-elimination due to increased steric hindrance in transition state **49B** versus **49A** (Scheme 4).

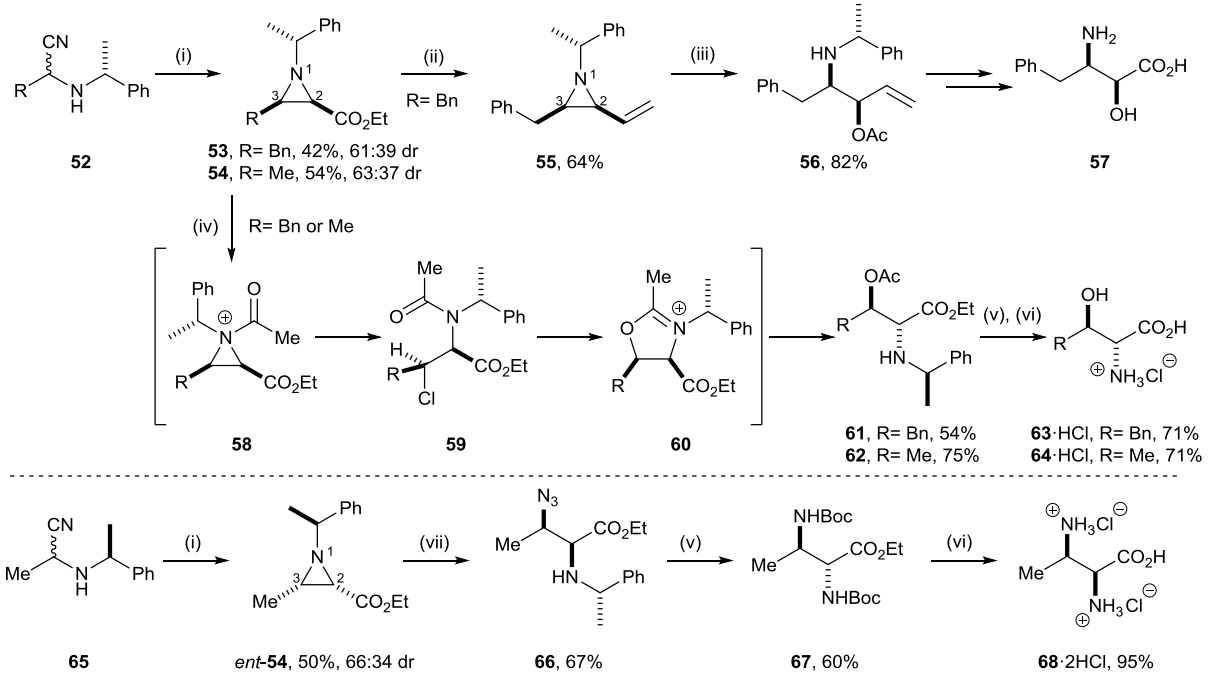


Scheme 4. *Reagents and Conditions*: (i) LiTMP, THF/hexanes, −78 to 0 °C, 80 min; (ii) OsO_4, NMO, THF/H_2O, rt, 2 days; (iii) F_3CSO_3H, anisole, 0 °C to rt, 16 h.

1.2.2.3. The synthesis of amino acids and related compounds by aziridine ring-opening

Nucleophilic ring-opening of aziridine-carboxylates and related analogues is a common strategy for the synthesis of amino acids.[31] Lee *et al.* have accessed β-hydroxy-α-amino, α-hydroxy-β-amino and α,β-diamino acids by regioselectively ring-opening aziridine-carboxylates.[32] *N*-α-Methylbenzyl-substituted aziridines were made via the reaction of α-amino nitrile **52** and ethyl diazoacetate in the presence of a Lewis acid catalyst: following this approach, (*R*)-*N*-α-methylbenzyl-substituted aziridines **53** and **54** were obtained in 42 and

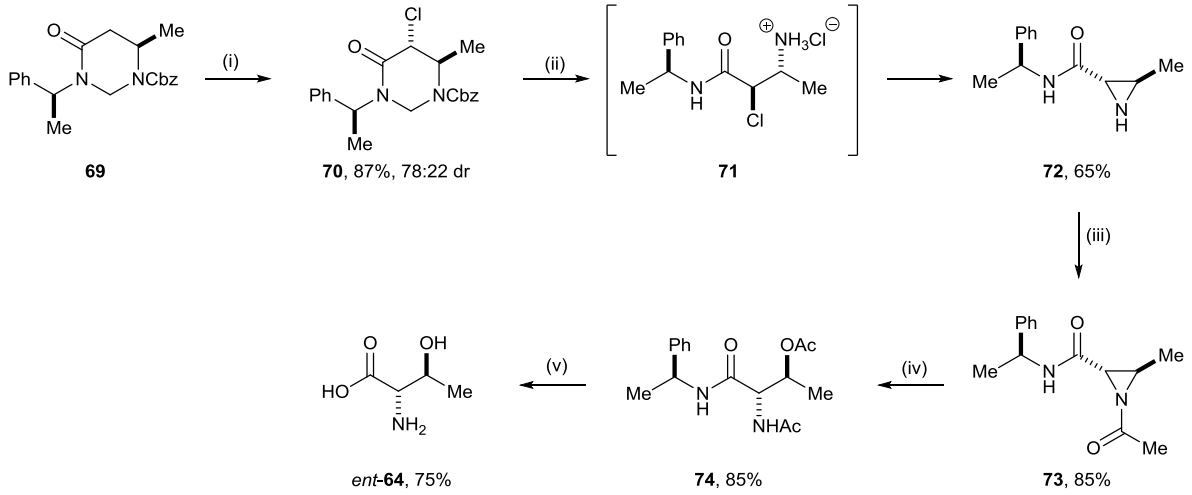
54% yield and 61:39 and 63:37 dr, respectively, whilst (*S*)-*N*-α-methylbenzyl-substituted aziridine *ent*-**54** was isolated in 50% yield and 66:34 dr. The major product of each of these aziridine forming reactions was taken on for the synthesis of amino acids, although the yields for the separation of the aziridine diastereoisomers were not reported. It was found that aziridine **53** could be regioselectively ring-opened with acetate at either the C(2) or C(3)-position by applying different reaction conditions. Reduction of **53** with DIBAL-H followed by *in situ* Wittig reaction gave **55** in 64% yield, which upon treatment with AcOH was found to open regioselectively at the C(2)-position, giving **56** in 82% yield. It was envisaged by the authors that this intermediate **56** could be oxidised to α-hydroxy-β-amino acid **57**, utilising a procedure developed by Sata *et al.*[33] Formal ring-opening by acetate at the C(3)-position of aziridines **53** and **54** was achieved by reaction of **53** and **54** with AcCl in the presence of $TiCl_4$, which promoted *N*-acylation and subsequent ring-opening by chloride. Rearrangement through **60** followed, giving **61** and **62** in 54 and 75% yield, respectively. Hydrogenolytic *N*-deprotection and global hydrolysis afforded β-hydroxy-α-amino acids **63**·HCl and **64**·HCl both in 71% yield. Ring-opening of aziridine *ent*-**54** with azide was achieved regioselectively in the presence of $BF_3{\cdot}Et_2O$, giving **66** in 67% yield. The authors referred to an electronic effect to explain this regioselectivity:[34] co-ordination of the Lewis acid to the aziridine nitrogen atom causes more significant weakening of the N(1)−C(3) bond, as C(3) is better able to accommodate developing positive charge. Deprotection of **66** via hydrogenolysis, then hydrolysis of **67** gave α,β-diamino acid **68**·2HCl in 57% yield over two steps (Scheme 5).



Scheme 5. *Reagents and Conditions*: (i) $SnCl_4$, N_2CHCO_2Et, CH_2Cl_2, rt, 8 h; (ii) CH_3PPh_3Br, BuLi, DIBAL-H, THF, −78 °C, 6 h; (iii) AcOH, CH_2Cl_2, rt; (iv) $TiCl_4$, AcCl, CH_2Cl_2, rt, 8 h; (v) Boc_2O, Pd/C, H_2 (1 atm), rt, 20 h; (vi) 6.0 M aq HCl, reflux, 6 h; (vii) $BF_3{\cdot}Et_2O$, $TMSN_3$, CH_2Cl_2, rt, 18 h.

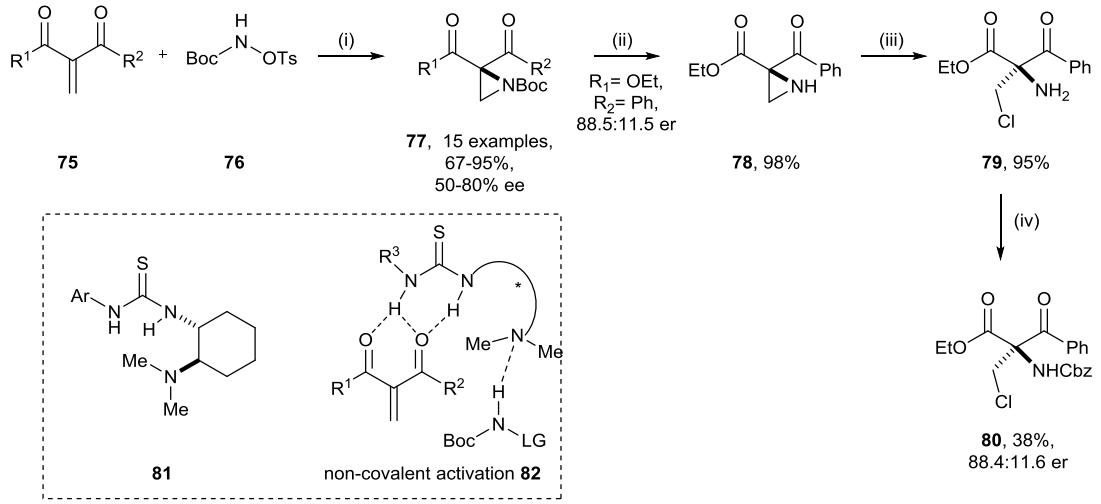
Cardillo *et al.* have employed an aziridine ring-opening strategy to access D-threonine and L-*allo*-threonine.[14(e)] Chlorination of 6-methylperhydropyrimidin-4-one **69** gave **70** in 87% yield and 78:22 dr. Acidic conditions facilitated ring-opening of the pyrimidinone motif to give **71**, which upon treatment with NaOH closed to the corresponding aziridine **72** in 65% yield.

N-Acyl protection of the aziridine **72** occurred in 85% yield, and was followed by regioselective ring-opening with acetate, giving **74** in 85% yield. Deprotection to *allo*-threonine *ent*-**64** was achieved by treatment of **74** with acid, followed by purification on cation exchange resin (Scheme 6).



Scheme 6. *Reagents and Conditions*: (i) LiHMDS, THF, 0 °C, 1 h, then TsCl, −30 °C to rt, 16 h; (ii) 11.0 M HCl/EtOH 1:1, reflux, 2 h, then 5.0 M aq NaOH; (iii) Ac_2O, pyridine, DMAP, CH_2Cl_2, 1 h; (iv) Ac_2O, pyridine, reflux, 1 h; (vi) 11.0 M HCl/EtOH 10:1, then cation exchange resin, 0.5 M aq NaOH.

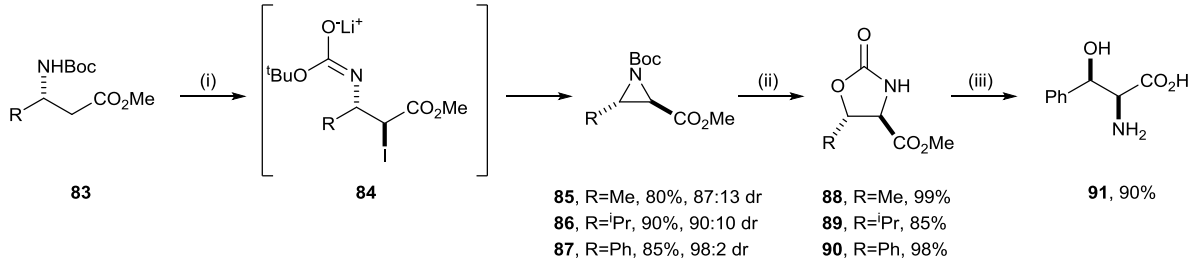
Lattanzi and co-workers have demonstrated the synthesis of β-chloro-α-amino esters **80** from the ring-opening of enantiopure aziridines **78**,[35] which were made via an aza-Michael initiated ring-closure. Good enantioselectivity in this reaction may be achieved via non-covalent activation of the requisite α-acyl acrylate **75** and *N*-tosyloxy *tert*-butyl carbamate **76** with Takemoto's thiourea catalyst **81**.[36] Hydrogen bonding interactions between the thiourea group and α-acyl acrylate, and the amine and nucleophile, would lead to a pre-organised, non-covalent transition state, such as **82**, from which ring-closure to an enantiomerically enriched aziridine was achieved. Application of this protocol to a range of α-acyl acrylates **75** was shown to result in good to excellent levels of enantioselectivity (50–80% ee), enabling asymmetric syntheses of 15 terminal aziridines **77** in 67–95% yield. Regioselective ring-opening of **78** by chloride at the terminal position resulted in α-amino ester **79** in 95% yield (Scheme 7).



Scheme 7. *Reagents and Conditions*: (i) **81**, K_2CO_3, PhMe, 0 °C, 3.5-29 h; (ii) TBAF, THF, 60 °C, 2 h; (iii) $HCl{\cdot}Et_2O$, THF, 0 °C, 2 h; (iv) $(Cbz)_2O$, THF, 0 °C, 2 h.

1.2.3 Aziridine rearrangements in organic synthesis

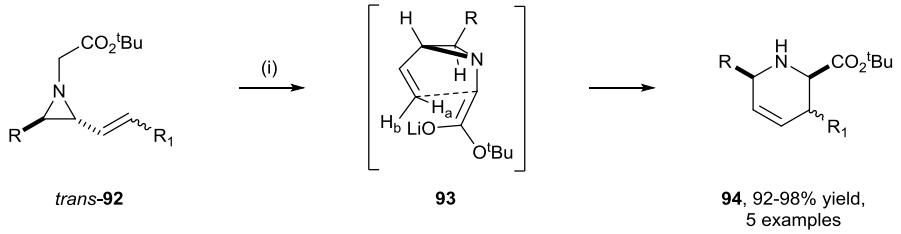
Stereoselective and stereospecific rearrangements of aziridines have also been used to good effect in organic synthesis. Tomasini and Vecchione have demonstrated that β-hydroxy-α-amino acids can be obtained from aziridines upon Lewis acid promoted rearrangement to the corresponding oxazolidinones.[37] Enolisation of **83**, followed by reaction with I_2, enabled ring-closure to aziridines **85**–**87** in ≥87:13 dr and ≥80% yield. Any erosion in diastereoselectivity of this step was attributed to a competitive Finkelstein reaction of intermediate **84**. Subsequent rearrangement was found to occur with retention of configuration, giving oxazolidinones **88**–**90** in 85 to 99% yield. Finally, hydrolysis of **90** gave phenylserine **91** in 90% yield (Scheme 8).



Scheme 8. *Reagents and Conditions*: (i) LiHMDS, THF, −60 °C, 1 h then I_2, −60 °C, 30 min; (ii) $Cu(OTf)_2$, CH_2Cl_2, rt, 40–70 h; (iii) LiOH, H_2O, rt, 2 h.

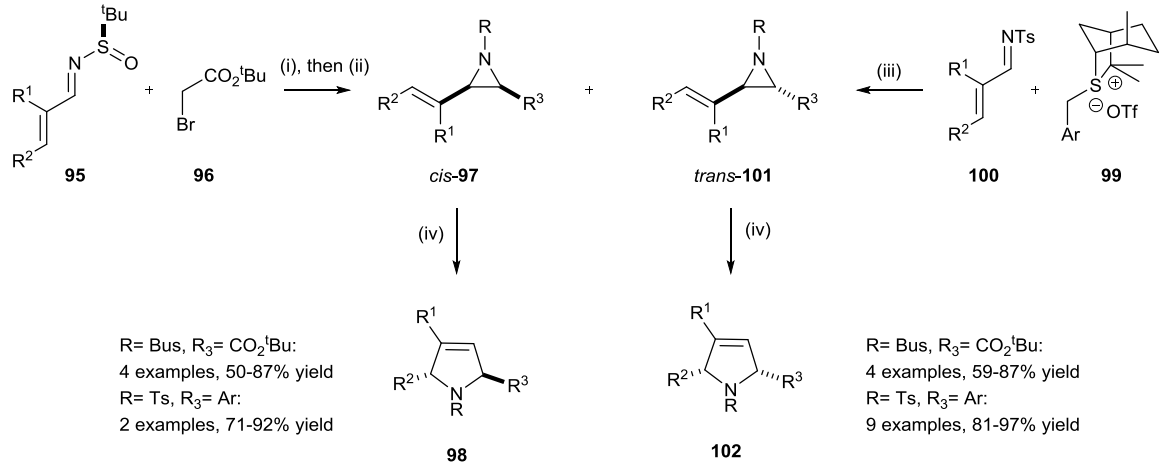
Somafai and Åhman found that vinyl aziridines **92** could be converted to tetrahydropyridines **94** via an aza-[2,3]-Wittig rearrangement.[38] Aziridines were obtained via the opening of enantiopure epoxides[39] with azide,[40] followed by reductive cyclisation.[41] Upon treatment with LDA, aziridines **92** were found to undergo rapid rearrangement to the corresponding tetrahydropyridines **94** as single diastereoisomers. The authors suggested that transition state **93**, which was based on the calculated transition structures for the [2,3]-Wittig rearrangement[42] and homodienyl-[1,5]-hydrogen shift,[43] was responsible for the observed

diastereoselectivity. To facilitate bond formation the ester and alkene groups are *cis* to one another in transition state **93**, with the enolate placed so that steric interactions with the aziridine ring substituents are minimised (Scheme 9).



Scheme 9. *Reagents and Conditions*: (i) LDA, THF, −78 °C, 5 min.

Dihydropyrroles **98** and **102** have been made by Njardarson and co-workers via the stereospecific ring-expansion of vinyl aziridines **97** and **101**.[44] *N*-Bus protected aziridines were obtained via Darzens reaction between bromoacetate **96** and chiral *N*-sulfinimine **95**,[45] giving *N*-*tert*-butyl sulfinamide protected aziridines between 67:33 and 80:20 dr. Subsequent oxidation was necessary to oxidise *N*-*tert*-butyl sulfinamide to the corresponding *N*-*tert*-butyl sulphonamide **97**, as *N*-sulfinamide protected vinyl aziridines were found not to undergo ring-expansion. Chiral *N*-Ts protected aziridines **101** were synthesised utilising **99**[46] in ≥85:15 dr. Subsequent treatment of aziridines **97** or **101** with $Cu(hfacac)_2$ facilitated stereospecific ring-expansion to the corresponding *cis*- or *trans*- dihydropyrroles, which were obtained in 50–92 and 59–97% yield, respectively (Scheme 10).

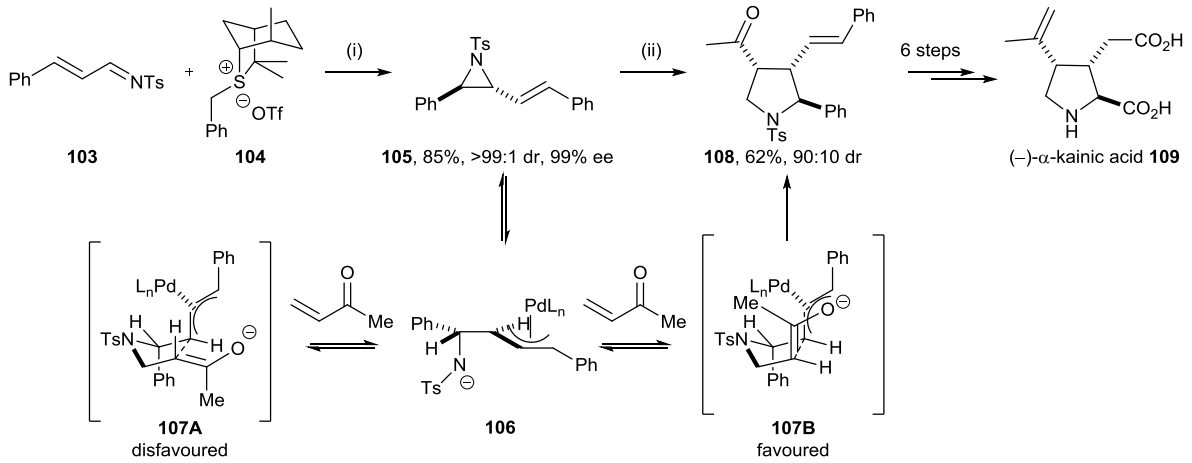


Scheme 10. *Reagents and Conditions*: (i) LiHMDS, THF, −78 °C to rt, overnight; (ii) *m*CPBA, CH_2Cl_2, rt, 15 min; (iii) K_2CO_3, MeCN, rt, overnight; (iv) 5 mol % $Cu(hfacac)_2$, PhMe, 150 °C, 5 h.

1.2.4. Palladium-mediated annulations of vinyl aziridines

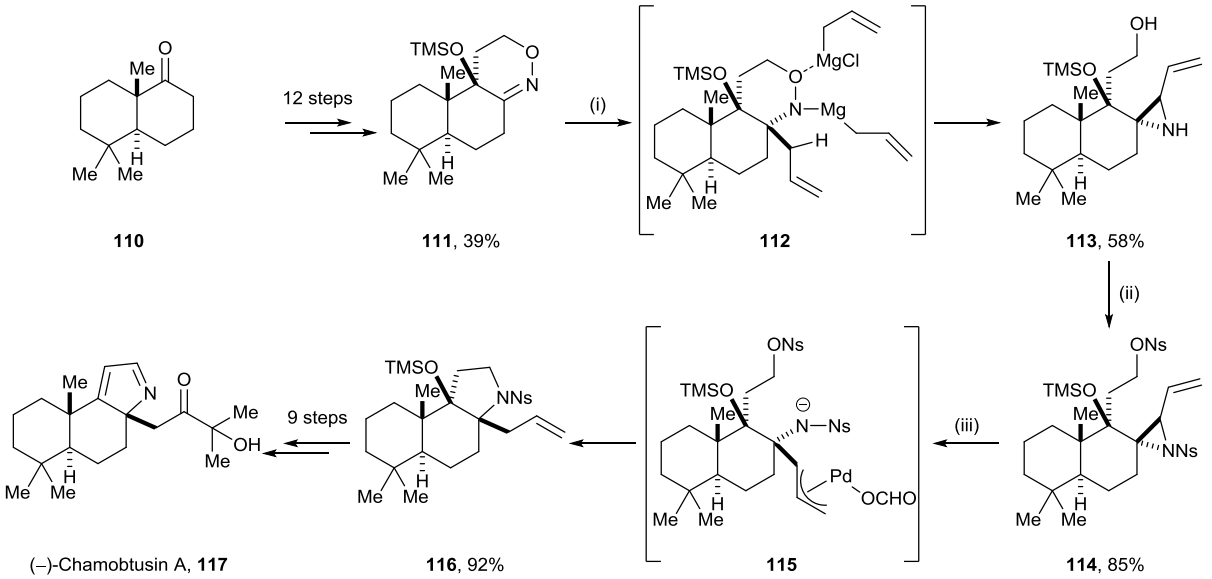
The palladium-mediated annulation of vinyl-aziridines has been used as a key step in the synthesis of the natural products, with Aggarwal *et al.* employing this strategy in their synthesis of (−)-α-kainic acid **109**. [47] Aziridine intermediate **105** was made via the enantio- and diastereoselective aziridination of imine **103** in the presence of sulfonium salt **104**, giving

vinyl aziridine **105** in 85% yield, >99:1 dr and 99% ee.[48] Subsequent palladium catalysed annulation gave pyrrolidine **108** in 62% yield and 90:10 dr. This outcome is rationalised by the proposed transition states **107A** and **107B**, in which the phenyl group adopts a pseudoaxial position in order to minimise steric interactions with the PdL_n group.[49] The authors cite attractive interactions between the electron rich π system of the enolate and electron poor π system of the π-allyl palladium complex as the origin of diastereoselectivity, causing **107B** to be favoured over **107A**. Elaboration of key intermediate **108** gave (−)-α-kainic acid **109** in a total of 8 steps from **103** (Scheme 11).



Scheme 11. *Reagents and Conditions*: (i) $NaHCO_3$, MeCN, rt, overnight; (ii) methyl vinyl ketone, $[Pd_2(dba)_3{\cdot}CHCl_3]$, Bu_4NCl, P(*o*-tolyl)$_3$, pentane, 24 h.

In their first enantioselective synthesis of (−)-chamobtusin A **117**, Suzuki and Aoyagi have also employed a palladium-mediated annulation strategy.[50] Starting from the known ketone **110**,[51] 1,2-oxazine **111** was synthesised in 39% yield over 12 steps. Upon attempted alkylation with allylmagnesium chloride, spirocyclic aziridine **113** was formed instead, and was isolated in 58% yield. It was suggested that abstraction of an allylic hydrogen by a proximal *N*-allyl component had followed the alkylation of oxime **111**, allowing aziridinium ring-formation with concomitant N−O bond cleavage to occur *in situ*.[52] *N*,*O*-Dinosyl protection of aziridine **113** gave **114** in 85% yield. Elaboration of **114** to the tricyclic framework of **117** employed the use of a palladium-mediated ring-expansion, via π-allyl palladium intermediate **115**, enabling formation of **116** in 92% isolated yield. The synthesis of (−)-chamobtusin A **117** was then completed in 9 further steps (Scheme 12).



Scheme 12. *Reagents and Conditions*: (i) allylMgCl, THF, 0 °C, 3 h, overnight; (ii) NsCl, pyridine, CH_2Cl_2, 0 °C to rt, 24 h; (iii) $[Pd_2(dba)_3{\cdot}CHCl_3]$, PPh_3, HCO_2H, Et_3N, THF, rt, 20 h.

1.3. Aziridinium ions in asymmetric synthesis

1.3.1. Formation of aziridinium ions

The formation of aziridinium ions typically occurs either from the quaternisation of the corresponding aziridine (route a), or from activation of the hydroxyl functionality within a vicinal amino alcohol (route b) (Figure 3). A discussion of the regioselectivity in the ring-opening reactions of aziridinium ions, and representative examples of the use of aziridinium ions as intermediates in synthesis, are detailed below.

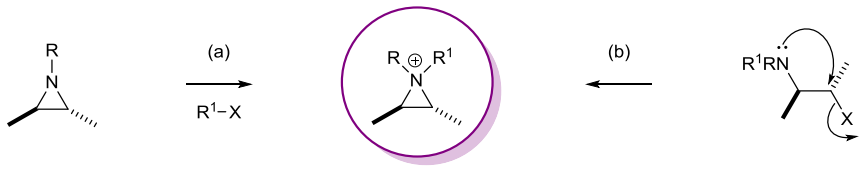
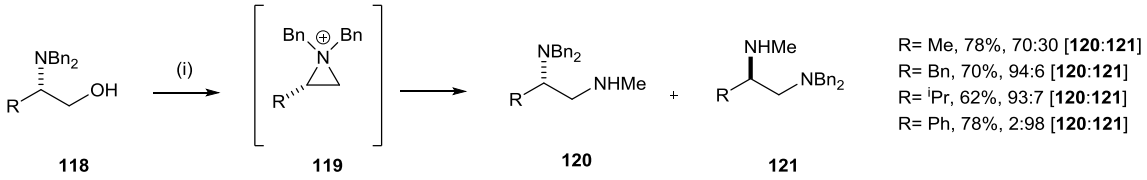


Figure 3. Methods for formation of aziridinium ions.

1.3.2. Studies into the regioselectivity of aziridinium ring-opening

The regioselectivity of aziridinium ring-opening has been studied by many research groups, with both substituent and nucleophile effects examined. O'Brien and Towers have undertaken their studies on C-monosubstituted aziridiniums **119**, varying the substituent "R" to see what impact this had on reaction regioselectivity.[53] Aziridiniums **119** were generated *in situ* by reaction of amino alcohols **118** with MsCl, followed by addition of NH_2Me. When R = Me, a 70:30 ratio of **120** and **121** was recovered, indicating a modest preference for ring-opening at the least hindered position. For bulkier alkyl groups (i.e., R = Bn and ^{i}Pr), this preference was enhanced giving a 94:6 and 93:7 ratio of products **120** and **121** respectively. However when R = Ph, high selectivity for the opposite regioisomer was observed, resulting in a 98:2 mixture of **121** and **120**. The ability of an aryl group to induce regioselective aziridinium ring-opening

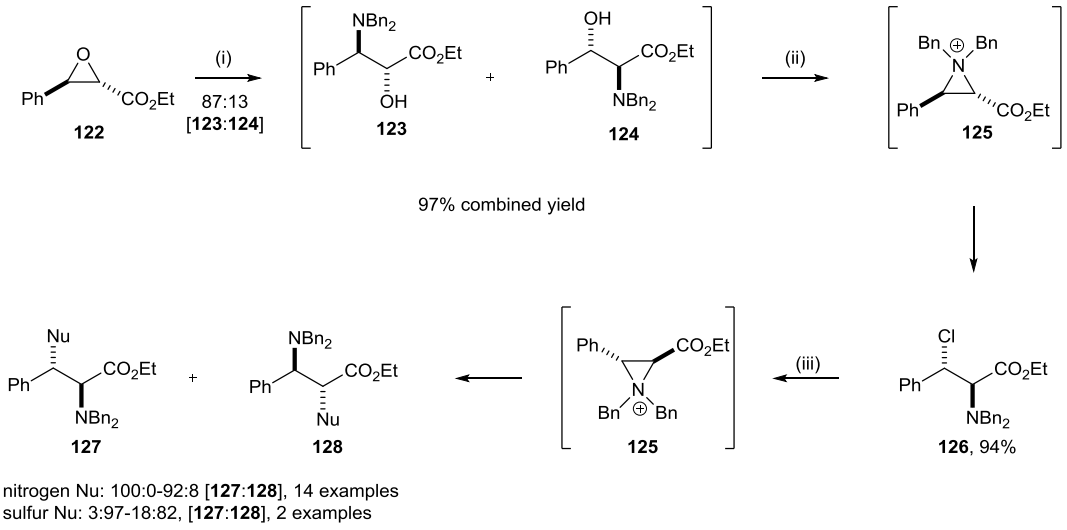
is well precedented in the literature,[54] and this is usually attributed to the ability of the aryl system to stabilise developing positive charge in the transition state through π-conjugation (Scheme 13).



118 **119** **120** **121**

Scheme 13. *Reagents and Conditions*: (i) MsCl, Et_3N, CH_2Cl_2, 0 °C, 30 min, then Et_3N, $MeNH_2$, H_2O, rt, 16 h.

Sharpless and Chuang have investigated the regioselectivity of ring-opening of C(3)-phenyl substituted aziridinium **125**, which was generated *in situ* from β-chloro-α-amino ester **126**, upon treatment with a range of nitrogen and sulfur nucleophiles.[55] Ring-opening of epoxide **122** with dibenzylamine gave an 87:13 ratio of regioisomeric products **123** and **124**, which upon treatment with MsCl resulted in *in situ* rearrangement to give β-chloro-α-amino ester **126**, which the authors postulated was the result of regioselective ring-opening of aziridinium **125** at the benzylic position with chloride. Heating **126** in MeCN in the presence of a nitrogen nucleophile resulted in formation of regioisomers **127** and **128**, in between 100:0 to 92:8 ratio, respectively. This is consistent with a reaction pathway in which aziridinium **125** undergoes ring-opening with high regioselectivity for the benzylic position. When sulfur based nucelophiles thiophenol or *tert*-butyl thiol were used however, the opposite regioselectivity was observed, giving a 97:3 or 82:18 ratio of **128** and **127**, respectively (Scheme 14).

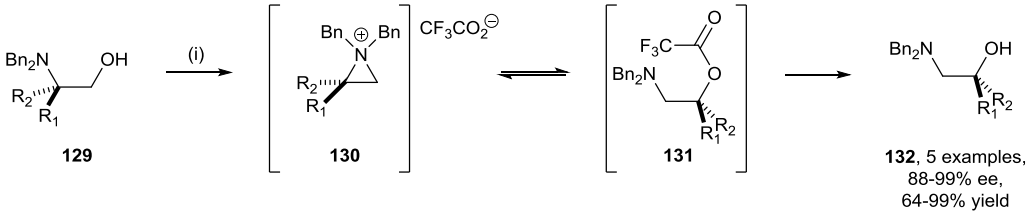


122 **123** **124** **125** **127** **128** **125** **126**, 94%

Scheme 14. *Reagents and Conditions*: (i) $NHBn_2$, EtOH, reflux, 12 h; (ii) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 3 h; (iii) nucleophile, K_2CO_3, MeCN, 60 °C, 12 h.

The stereospecific rearrangement of β-amino alcohols **129** via aziridinium intermediate **130** has been demonstrated by Cossy *et al*.[56] Both α-branched and bis-α-branched amines were formed in high enantiomeric excess, giving **132** in 88–99% ee and 64–99% yield. This

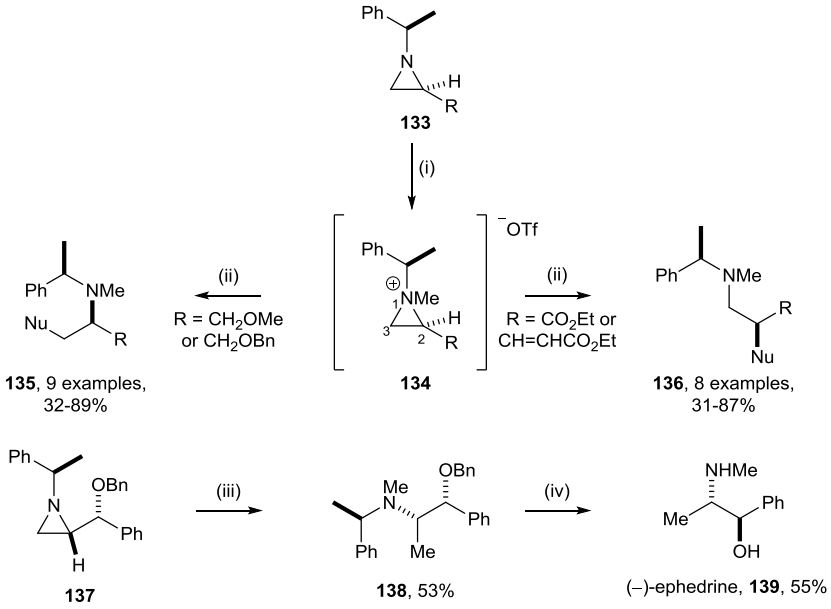
selectivity was explained by reversible ring-opening of the intermediate aziridinium ion **130** resulting in the formation of trifluoroacetate ester **131**, which it was suggested was the thermodynamic product,[57] with *in situ* hydrolysis giving 1,2-amino alcohols **132** (Scheme 15).



Scheme 15. *Reagents and Conditions*: (i) TFAA, Et_3N, THF, 100 °C, 2 h, MW, then 3.75 M aq NaOH, rt, 2 h.

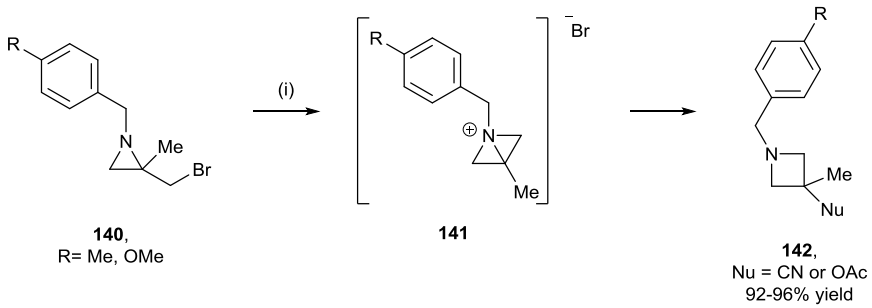
1.3.3. Aziridinium intermediates in synthesis: quaternisation of aziridines

Aziridines can be activated by quaternisation to the corresponding aziridinium ion, through reaction with either an external or internal electrophile, with these intermediates undergoing subsequent nucleophilic attack or intramolecular rearrangement. Ha and Lee have reacted aziridines **133** with MeOTf to form the corresponding terminal aziridinium triflates **134** *in situ*,[58] which were then ring-opened regioselectively by a range of nucleophiles. The regioselectivity was found to be dependent on the nature of substituent "R" at C(2): C(2)-alkoxymethyl substituents resulted in regioselective ring-opening at the distal C(3)-position, whereas C(2)-acyl or vinyl substituents showed a preference for regioselective ring-opening at the C(2)-position itself. This latter observation was attributed to the ability of the acyl or vinyl substituents to activate the position α- to themselves.[59] This methodology was applied to the synthesis of (–)-ephedrine **139**, via the reductive ring-opening of **137** with $NaCNBH_3$ (Scheme 16).



Scheme 16. *Reagents and Conditions*: (i) MeOTf, MeCN, rt, 10 min; (ii) Nu (NaN_3, NaOAc, morpholine, NH_2Bn, NaCN, or $NaCNBH_3$), rt, 1 h; (iii) MeOTf, ethylene glycol dimethyl ether, 0 °C, 10 min, then $NaCNBH_3$, 0 °C, 1 h; (iv) $Pd(OH)_2/C$, H_2 (3.5 atm), EtOH, rt.

An interesting rearrangement of 2-bromomethyl aziridines **140** to the corresponding azetidines **142** was reported by D'hooghe, De Kimpe and co-workers,[60] which was expected to proceed via bicyclic aziridinium intermediate **141**. Full conversion to substituted azetidine **142** was observed when **140** was reacted with either potassium cyanide or sodium acetate at reflux in MeCN. This was found to be solvent dependent, as in DMF direct substitution of the bromo moiety occurred instead, resulting in the corresponding substituted aziridines. This was explained by the stronger co-ordination of MeCN to the requisite nucleophile, hampering the direct S_N2 substitution pathway and facilitating formation of aziridinium intermediate **141** under S_N1-type conditions (Scheme 17).



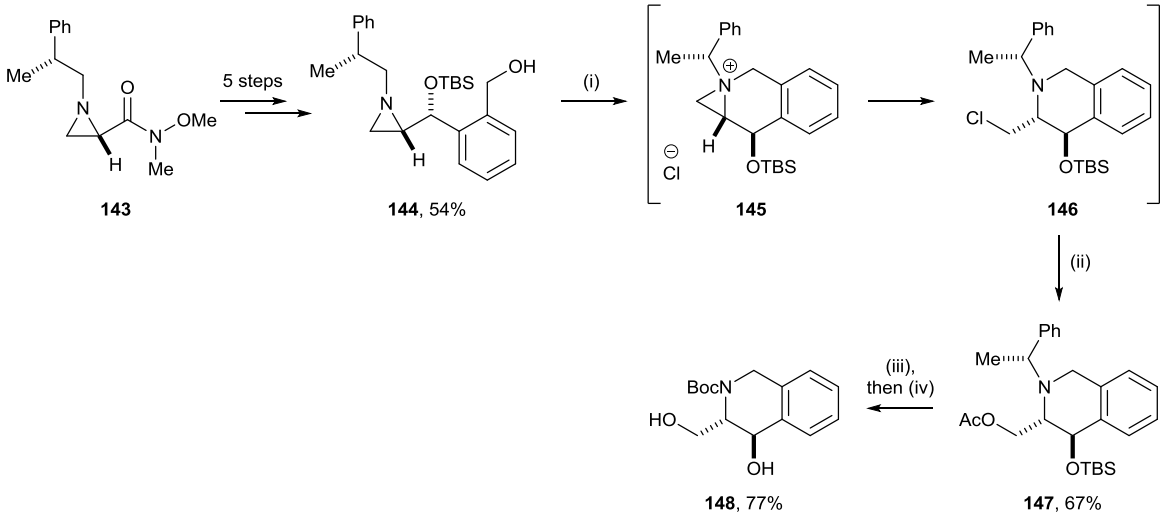
140, R= Me, OMe

141

142, Nu = CN or OAc, 92-96% yield

Scheme 17. *Reagents and Conditions*: (i) KCN or NaOAc, MeCN, reflux, 26 h.

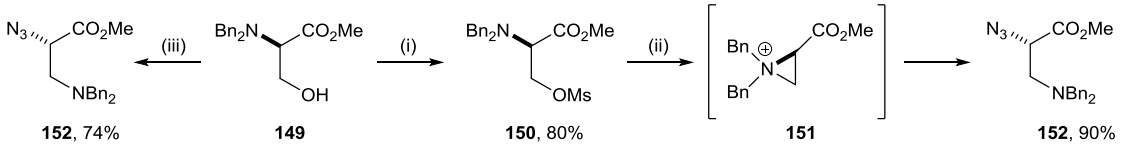
Lee *et al*. have developed a synthesis of substituted 1,2,3,4-tetrahydroisoquinolin-4-ol **148** from a chiral aziridine precursor **144** via aziridinium intermediate **145**, which was formed via another intramolecular quaternisation.[61] Manipulation of Weinreb amide **143** gave **144** in 54% yield over 5 steps. Subsequent treatment of **144** with MsCl facilitated rearrangement via aziridinium ion **145**, which was generated from displacement of mesylate by the aziridine nitrogen atom. Subsequent ring-opening of **145** by the chloride counter-ion then gave **146**. Displacement of the chloride moiety within **146** was also achieved *in situ* by adding KOAc to the reaction mixture after 5 min, then heating to 45 °C for 4 h, forming **147** as a single product, which was isolated in 67% yield. Subsequent hydrolysis and tandem hydrogenolysis/*N*-Boc protection gave **148** in 77% yield over the two steps (Scheme 18).



Scheme 18. *Reagents and Conditions*: (i) MsCl, Et_3N, MeCN, rt, 5 min, then KOAc, 4 h, 45 °C; (ii) LiOH, $EtOH/H_2O$ (2:1), reflux, 8 h; (iii) $Pd(OH)_2/C$, Boc_2O, H_2 (1 atm), MeOH, rt, 4 h.

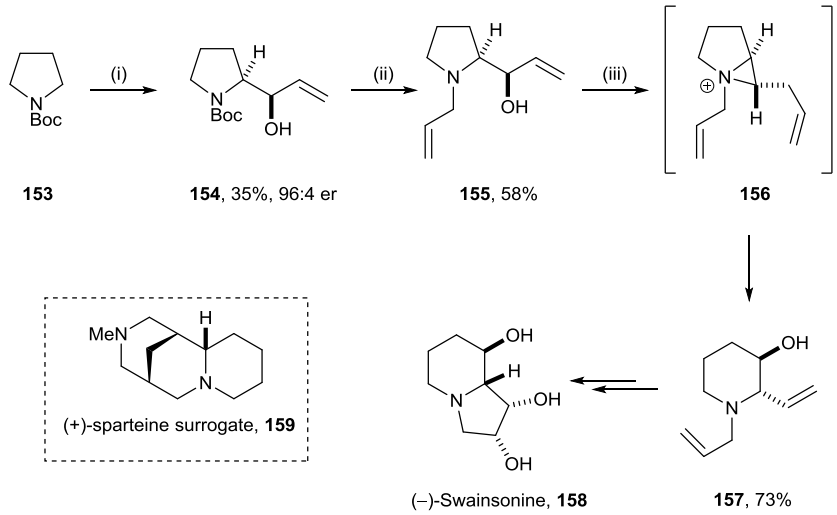
1.3.4. Aziridinium intermediates in synthesis: activation of amino alcohols

Formation of aziridinium ions from vicinal amino alcohols has been put to good effect as a strategy in synthesis. Zhu and co-workers have made α-substituted-β-amino ester **152** from D-serine via the regioselective ring-opening of the corresponding aziridinium intermediate **151**.[62] *N*,*N*-Dibenzyl-D-serine **149** was treated with MsCl, giving mesylate **150**,[63] which was then heated in MeCN in the presence NaN_3 giving **152** exclusively, which was isolated in 90% yield. A one pot conversion of *N*,*N*-dibenzyl-D-serine **149** into **152** was also developed, employing Ms_2O as the activating agent (Scheme 19).



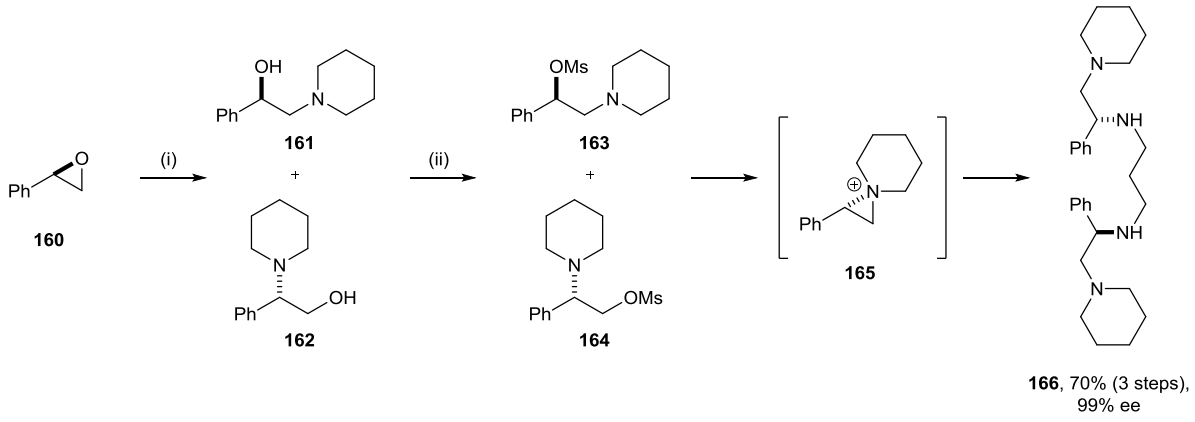
Scheme 19. *Reagents and Conditions*: (i) MsCl, Et_3N, CH_2Cl_2, rt, 4 h; (ii) NaN_3, MeCN, 60 °C, 2-3 h; (iii) Ms_2O, Et_3N, MeCN, then NaN_3, 60 °C, 2-3 h.

O'Brien *et al.* have completed a formal synthesis of (–)-swainsonine **158**, which involves the ring-expansion of a pyrrolidine to a piperidine via an aziridinium intermediate as a key step.[64,65] Asymmetric lithiation of *N*-Boc pyrrolidine and subsequent trapping with acrolein gave **154** in 50:50 dr, from which **154** was isolated in 35% yield and 96:4 er. *N*-Boc deprotection and allylation gave **155** in 58% yield, which upon treatment with TFAA underwent ring-expansion to piperidine **157**, an intermediate in Cossy's total synthesis of (–)-swainsonine **158**[66] (Scheme 20).



Scheme 20. *Reagents and Conditions*: (i) *s*-BuLi, (+)-sparteine surrogate **159**, Et_2O, –78 °C, 3 h, then acrolein; (ii) TFA, CH_2Cl_2, rt, 20 h, then K_2CO_3, allyl bromide, MeOH, rt, 12 h; (iii) TFAA, Et_3N, CH_2Cl_2, –78 °C, 1 h, then NaOH, rt, 2 h.

The stereospecific nature of reactions involving aziridinium intermediates, as well as the atom economy and efficiency of generating such an intermediate *in situ*, make them attractive for use in industry. Moniz and co-workers have achieved a one-pot synthesis of chiral base **166** on a kilogramme scale, by employing a regioselective and stereospecific aziridinium ring-opening as the key step.[67] Non-regioselective ring-opening of (*R*)-styrene oxide **160** with piperidine gave a mixture of regioisomers **161** and **162**. Subsequent treatment of this mixture with MsCl gave the corresponding mesylates **163** and **164**, which collapsed to common aziridinium intermediate **165** upon warming to 20 °C. *In situ* opening of **165** with 1,3-diaminopropane occurred regioselectively, giving **166** in 70% yield over the three step sequence (Scheme 21).



Scheme 21. *Reagents and Conditions*: (i) piperidine, EtOH, 80 °C, 5 h; (ii) MsCl, Et_3N, MTBE, –10 °C, 30 min, then 1,3-diaminopropane, H_2O, 20 °C, 18 h.

1.4. Thesis aims

The initial aim of this project was to develop methodology for the conversion of α-hydroxy-β-amino esters **167** into β-substituted-α-amino acids **170**. In the first instance a route involving an aziridine as an intermediate would be investigated, with protecting group manipulation and subsequent ring-closure transforming **167** to the corresponding aziridines **168**. It was proposed that stereospecific ring-opening of **168** at the C(3)-position may be achieved to give β-substituted-α-amino esters **169**, which upon deprotection would complete the route to β-substituted-α-amino acids **170**. An alternative strategy via an aziridinium intermediate **171** was also envisaged: activation of the hydroxyl group within **167** may promote ring-closure through the amino functionality, generating aziridinium ions **171** *in situ*. Subsequent regioselective and stereospecific ring-opening would give rise to β-substituted-α-amino esters **172**, which upon deprotection would yield β-substituted-α-amino acids **170** (Figure 4).

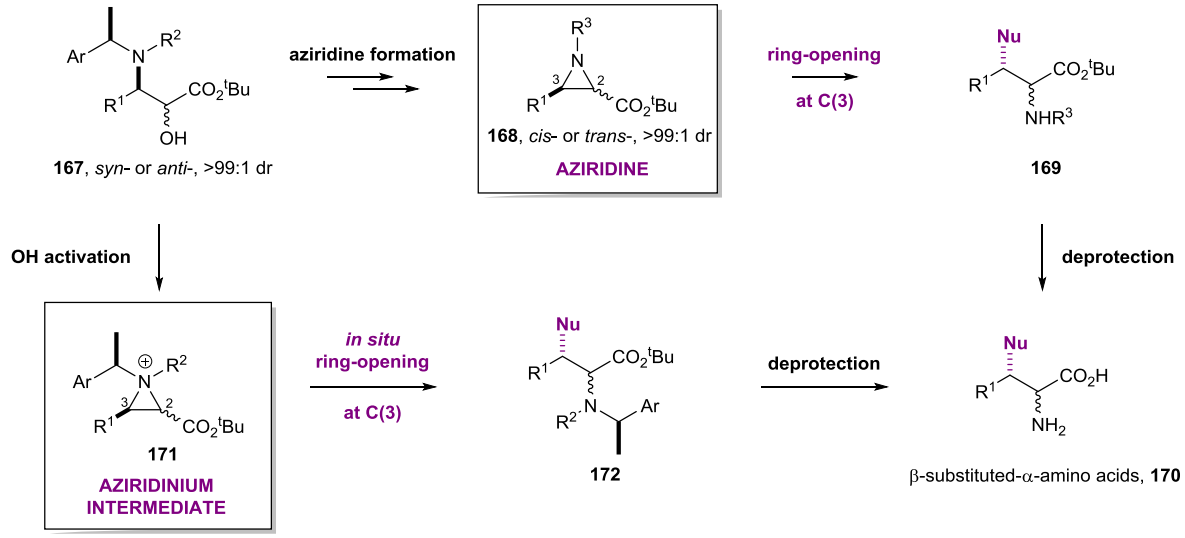


Figure 4. β-Hydroxy-α-amino acids from α-hydroxy-β-amino esters via aziridine or aziridinium intermediates.

1.5. References and notes

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Chapter 2: β-Hydroxy-α-amino acids via aziridines

This chapter describes the conversion of α-hydroxy-β-amino esters **173** into β-hydroxy-α-amino acids **175** via the regioselective ring-opening of the corresponding aziridines **174** (Figure 5).

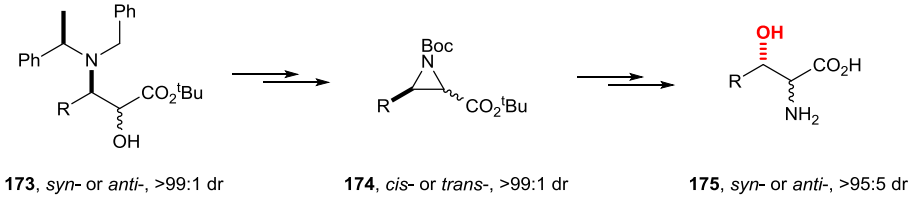


Figure 5. β-Hydroxy-α-amino acids from α- hydroxy-β-amino esters via aziridine intermediates.

2.1. Existing synthetic approaches to β-hydroxy-α-amino acids

Much synthetic interest in β-hydroxy-α-amino acids exists due to their utility as components of biologically significant peptides, such as the glycolpeptide antibiotics,[1] and other natural products including the proteasome inhibitors (+)-lactacystin **176** and (−)-salinosporamide A **177**[2] (Figure 6).

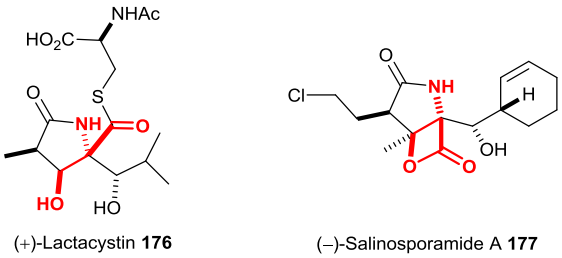
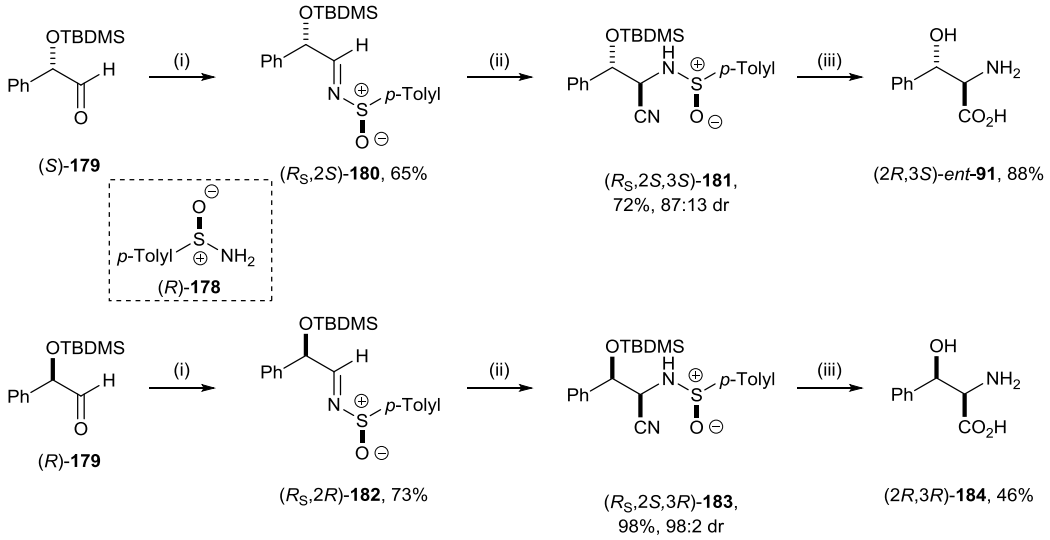


Figure 6. Naturally occurring proteasome inhibitors, (+)-lactacystin **176** and (−)-salinosporamide A **177**.

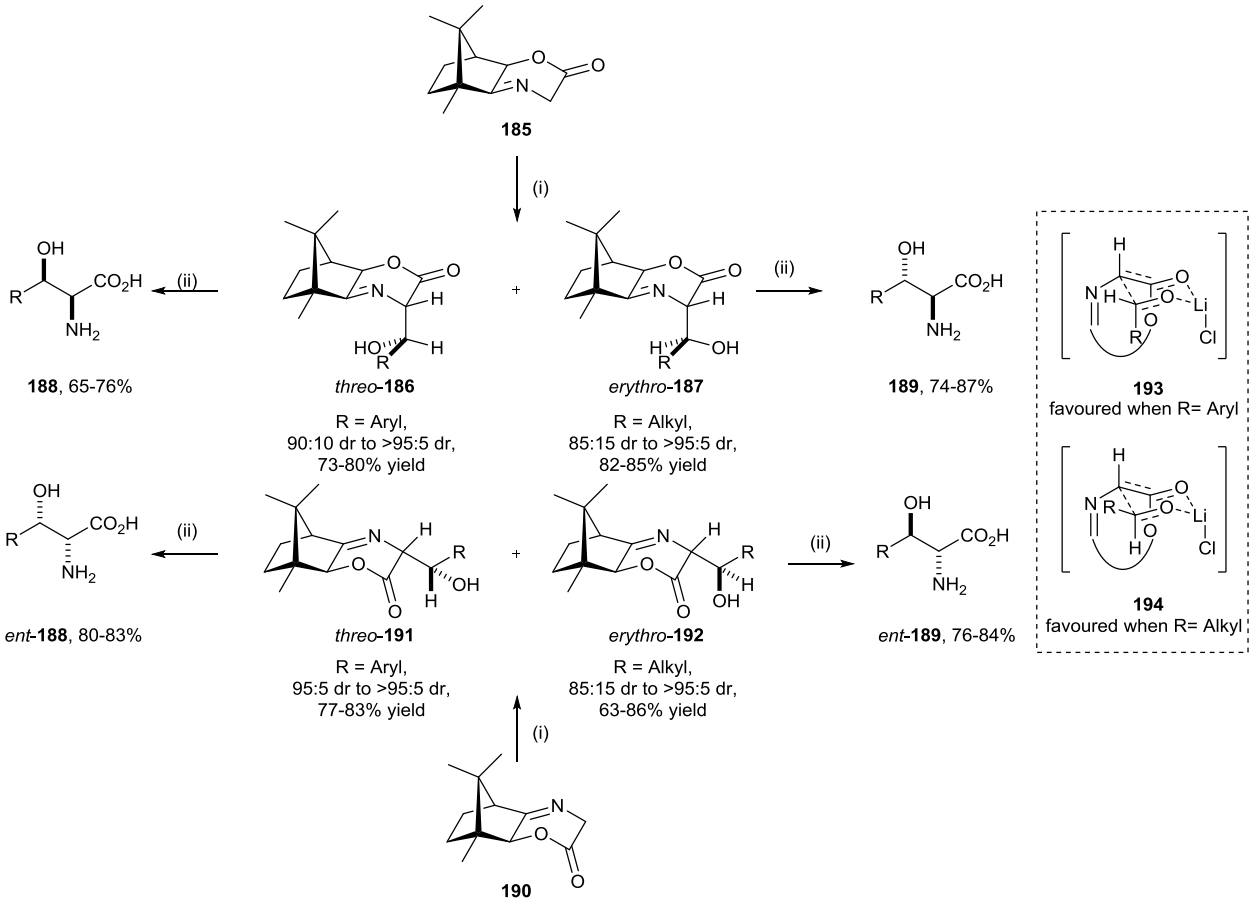
Published asymmetric syntheses of both natural β-hydroxy-α-amino acids and unnatural analogues have been achieved via numerous approaches, including Sharpless epoxidation,[3] dihydroxylation[4] and aminohydroxylation,[5] aldol condensation,[6] hydrolysis of aziridines,[7] dynamic kinetic resolution,[8] and via oxazolidinone intermediates,[9] amongst others.[10] Davis *et al.* have applied their sulfinimide mediated asymmetric Strecker reaction[11] to the synthesis of a range of β-substituted-α-amino acids, including β-hydroxy-α-amino acids.[12] Reaction of sulfinamine (*R*)-**178** with the enantiomeric aldehydes (*S*)-**179** and (*R*)-**179** gave the corresponding sulfinimines **180** and **182** in 65 and 73% yield, respectively. Subsequent treatment with EtAl(O^{i}Pr)CN (generated *in situ* from Et_2AlCN and ^{i}PrOH) resulted in addition of cyanide to sulfinimines **180** and **182**, giving **181** and **183** in 87:13 and 98:2 dr, respectively. The authors suggested that the sulfinyl moiety was the dominant stereocontrolling element in both of these cases, with the *O*-TBDMS bearing stereocentre within **182** augmenting this preference to give **183** in 98:2 dr, and the epimer opposing it

giving **181** in a reduced 87:13 dr. Hydrolysis of **181** and **183** gave β-hydroxy-α-amino acids *ent*-**91** and **184**, respectively, which were isolated in 88 and 46% yield. All stereoisomers of phenylserine were accessed using this methodology, with **91** and *ent*-**184** synthesised via the same method, using (*S*)-**178** (Scheme 22).



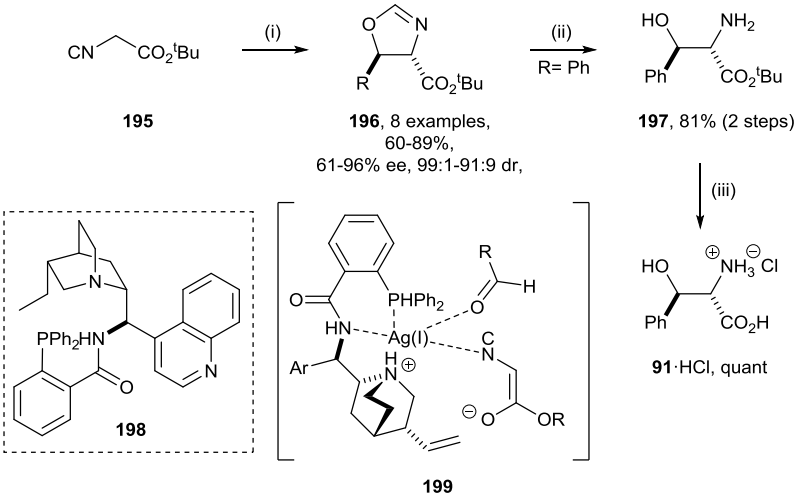
Scheme 22. *Reagents and Conditions:* (i) (*R*)-**178**, $Ti(OEt)_4$, CH_2Cl_2, rt, 2 h; (ii) Et_2AlCN, ^iPrOH, −78 °C to rt, 8 h; (iii) 3.0 M aq. HCl, reflux, 4 h, then DOWEX-50W8X ion-exchange resin.

Xu *et al*. have developed an asymmetric aldol reaction using pseudoenantiomeric tricyclic iminolactones **185** and **190** as the nucleophilic components,[13] enabling access to all stereoisomers of β-hydroxy-α-amino acids. Reaction of **185** and **190** with aromatic aldehydes was found to favour formation of *threo*-**186** and *threo*-**191**, whereas good diastereoselectivity for *erythro*-**187** and *erythro*-**192** was observed for reaction with aliphatic aldehydes. This was rationalised by invoking Zimmerman-Traxler transition states[14] **193** and **194**; when R = alkyl the substituent sits pseudoequatorial, however when R = aryl, placing the substituent in the pseudoaxial position is beneficial due to a π-π interaction between the aromatic ring and π-system of the iminolactone, leading to *threo*-**186** and *threo*-**191** as the preferred products. Subsequent hydrolysis released the β-hydroxy-α-amino acid products **188**, **189**, *ent*-**188** and *ent*-**189** (Scheme 23).



Scheme 23. *Reagents and Conditions:* (i) LDA, LiCl, RCHO, THF, −78 °C, 1–12 h (until conversion by TLC); (ii) 6.0 M aq. HCl, 80 °C, 3 h, then propylene oxide, ^{i}PrOH, rt, 30 min.

Dixon *et al*. have utilised a co-operative catalysis approach in their enantioselective synthesis of oxazolines, which were readily hydrolysed to give β-hydroxy-α-amino acids.[15] Treatment of isocyanate **195** with an aldehyde in the presence of pre-catalyst **198** and Ag_2O promoted an aldol reaction, which was found to occur with good enantio- (61 up to 96% ee) and diastereoselectivity (91:9 up to 99:1 dr) for both aromatic and α-branched aliphatic aldehydes. The stereocontrol was rationalised by reference to a proposed highly organised transition structure **199**, involving multi component complexation to the silver ion (Scheme 24).



Scheme 24. *Reagents and Conditions:* (i) **198**, Ag_2O, RCHO, EtOAc, 4Å MS, −20 °C, 24–36 h; (ii) $SOCl_2$, MeOH, 0 °C, 105 min; (iii) 6.0 M aq. HCl, rt, 4 h.

2.2. Results and discussion

2.2.1. Synthetic strategy

It was proposed that enantiopure β-hydroxy-α-amino acids **175** could be synthesised via the regio- and stereoselective ring opening of aziridine intermediates **174**. Access to the requisite aziridines **174** could be achieved from enantiopure α-hydroxy-β-amino esters **173** by intramolecular nucleophilic attack of nitrogen upon activation of the α-hydroxyl functionality as a good leaving group. The Davies diastereoselective aminohydroxylation protocol gives efficient access to α-hydroxy-β-amino esters with a high and predictable sense of diastereocontrol:[16] conjugate addition of an enantiopure lithium amide reagent (*R*)-**201** to an α,β-unsaturated ester **200**, with *in situ* oxidation of the intermediate lithium (*Z*)-β-amino enolate[17] with (−)-camphorsulfonyloxaziridine **202** (CSO), is known to give *anti*-α-hydroxy-β-amino esters as single diastereoisomers (>99:1 dr). Furthermore, the corresponding *syn*-α-hydroxy-β-amino esters are accessible from *anti*-α-hydroxy-β-amino esters via a sequential oxidation/diastereoselective reduction protocol.[18] Tandem hydrogenolysis and *N*-Boc protection of *syn*- or *anti*-**173** would be followed by activation of the α-hydroxy functionality to promote intramolecular attack by nitrogen to give *cis*- or *trans*-aziridines **174**, respectively. Subsequent regioselective ring-opening of the resultant aziridines **174** with an oxygen nucleophile was anticipated to occur at C(3), distal to the electron withdrawing ester substituent,[19] to give β-hydroxy-α-amino esters **204**, which could be deprotected to give the target β-hydroxy-α-amino acids **175** (Figure 7).

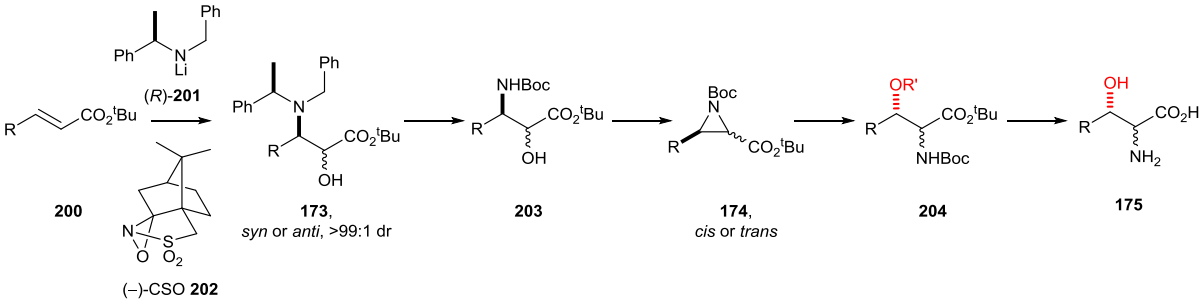
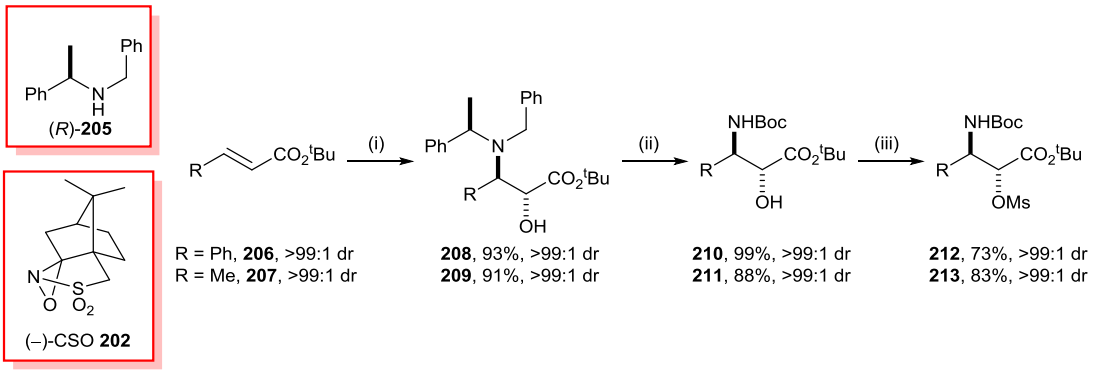


Figure 7. Strategy for the asymmetric synthesis of β-hydroxy-α-amino acids **175**.

Utilising lithium amide conjugate addition methodology in this work has two key advantages. Firstly, it is a reliable source of highly diastereoisomerically pure α-hydroxy-β-amino ester starting material and also access to all stereoisomers of β-hydroxy-α-amino acids using this methodology is possible: synthesis of both enantiomers of *anti*-α-hydroxy-β-amino esters can be achieved through the use of either antipode of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **201**. Studies into the development of this methodology were undertaken on representative aryl (R = Ph) and alkyl (R = Me) substrates.

2.2.2. Preparation of *trans*-aziridine precursors

Preparation of *N*-Boc protected *anti*-α-hydroxy-β-amino esters **210** and **211** and the corresponding mesylates **212** and **213** was undertaken to provide suitable precursors for the aziridine formation step. A reliable and scalable route was identified which would give **210**–**213** in multigram quantities. (*R*)-*N*-Benzyl-*N*-(α-methylbenzyl)amine **205** was synthesised (on ~100 g scale) by reductive amination of (*R*)-α-methylbenzylamine with benzaldehyde.[20] (−)-Camphorsulfonyloxaziridine [(–)-CSO] **202** was synthesised from (–)-camphorsulfonic acid (on ~200 g scale) following a known three step sequence.[21] α,β-Unsaturated ester **206** (R = Ph) was produced in 70% yield according to a modified Wadsworth-Emmons reaction[22] and α,β-unsaturated ester **207** (R = Me) was synthesised in 47% yield by esterification of crotonic acid with isobutylene. Conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **201** to α,β-unsaturated esters **206** and **207** followed by *in situ* enolate oxidation with (−)-CSO **202** gave the known[23] *anti*-α-hydroxy-β-amino esters **208** and **209** in 93 and 91% yield, respectively, and >99:1 dr in both cases. Hydrogenolysis of **208** and **209** in the presence of Boc_2O gave *N*-Boc protected derivatives **210** and **211**[24] in 99 and 88% yield, respectively, and subsequent treatment with MsCl gave mesylates **212** and **213**[24] in 73 and 83% yield, and >99:1 dr in each case (Scheme 25).



Scheme 25. *Reagents and Conditions*:(i) (*R*)-**205**, BuLi, THF, −78 °C, 2 h, then (−)-CSO **202**, −78 °C to rt, 18 h; (ii) Boc_2O, $Pd(OH)_2/C$, H_2 (5 atm), EtOAc, rt, 15 h; (iii) MsCl, Et_3N, DMAP, CH_2Cl_2, rt, 15 h.

The relative and absolute configurations within **210**–**213** were assigned from the known configurations of precursors **208** and **209**. Furthermore, the ^{1}H NMR ^3J coupling constants observed between the C(2)*H* and C(3)*H* protons within this class of *anti*-α-hydroxy-β-amino esters are known to be diagnostic of either *anti* ($^3J_{2,3}$ = 2–4 Hz)[25] or *syn* ($^3J_{2,3}$ = 8–9 Hz)[26] relative configurations. These assignments were then confirmed by single crystal X-ray diffraction analyses of **210** and **212**, and the determination of a Flack *x* parameter[27] of 0.00(6) for the crystal structure of **212** was also consistent with its assigned absolute (2*R*,3*R*)-configuration (Figure 8).[28]

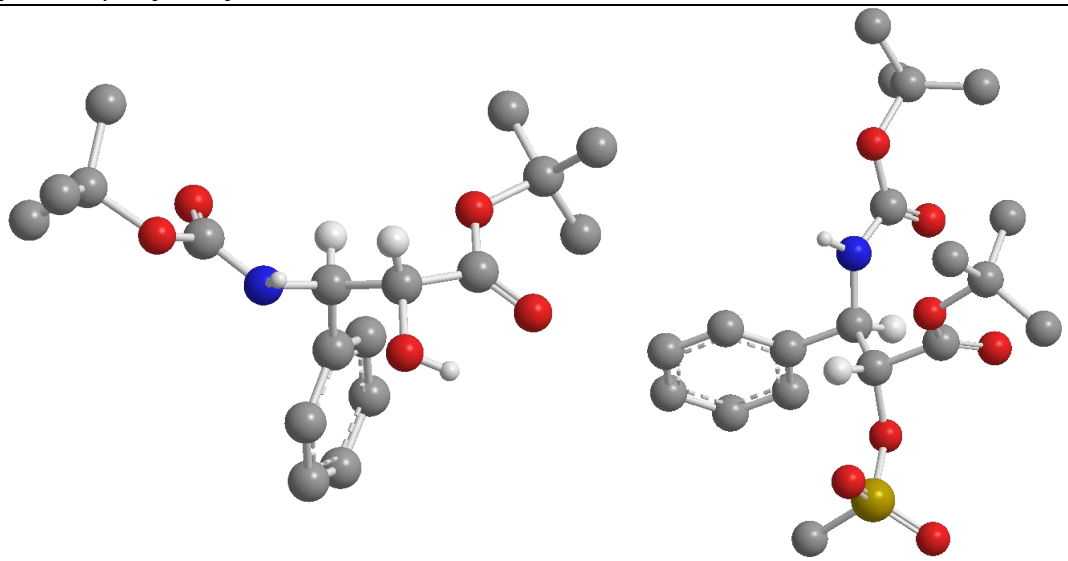
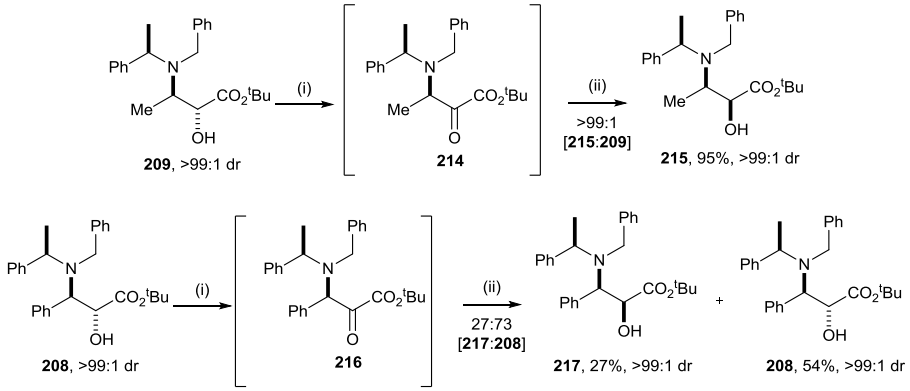


Figure 8. X-ray crystal structure of (*R*,*R*)-**210** [*left*] and (*R*,*R*)-**212** [*right*] (selected H atoms are omitted for clarity).

2.2.3. Preparation of *cis*-aziridine precursors

So that access to all diastereoisomers of β-hydroxy-α-amino acids could be achieved, it was necessary to make also the corresponding C(2)-epimers of *anti*-α-hydroxy-β-amino esters **208** and **209**. Precedent for the conversion of *anti*-α-hydroxy-β-amino esters to *syn*-α-hydroxy-β-amino esters via a sequential oxidation/diastereoselective reduction protocol was known from studies by Davies *et al.*[18] Thus, Swern oxidation of **209** and **208** gave β-amino-α-keto esters **214** and **216**. Subsequent reduction of **214** with $NaBH_4$ at −20 °C for 2 h occurred with complete diastereoselectively (>99:1 dr) to give *syn*-β-amino-α-hydroxy ester **215**, which was isolated in 95% yield. However, reduction of **216** under the same conditions proved to be moderately selective for the formation of the *anti*-diastereoisomer, **208** (73:27 dr), and thus the minor diastereoisomer *syn*-**217** could only be isolated in 27% yield (>99:1 dr) from this reaction (Scheme 26).



Scheme 26. *Reagents and Conditions*: (i) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 30 min, then Et_3N, −78 °C→rt, 30 min; (ii) $NaBH_4$, MeOH, −20 °C, 2 h.

The ^{1}H NMR ^3J coupling constants within both **215** and **217** were in good agreement with the values expected for a relative *syn*-configuration ($^3J_{2,3}$ = 8–9 Hz). For **217**, single crystal X-ray diffraction analysis confirmed this assignment, with the absolute (2*S*,3*R*,α*R*)-configuration

within **217** being assigned relative to the known (*R*)-configuration of the *N*-α-methylbenzyl fragment (Figure 9).[28]

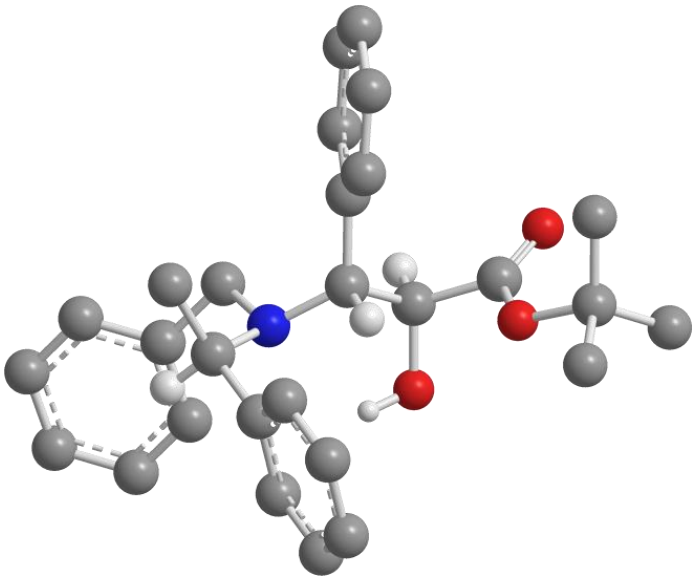
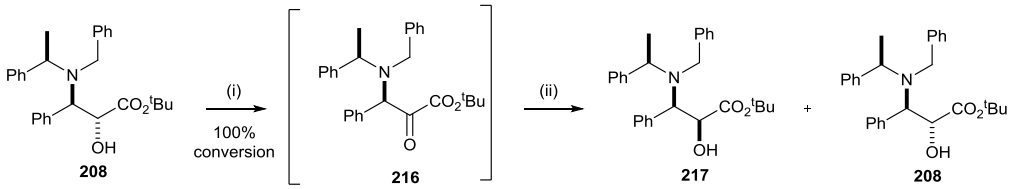


Figure 9. X-ray crystal structure of (2*S*,3*R*,α*R*)-**217** (selected H atoms are omitted for clarity).

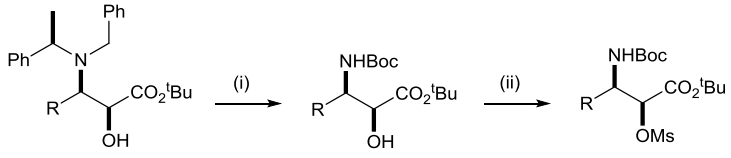
Investigations into alternative reduction protocols for the conversion of β-amino-α-keto ester **216** into *syn*-**217** were undertaken, with literature precedent indicating that the interplay of factors such as sterics, electronics and chelation can often result in highly substrate dependent reactions.[29] Initially, optimisation of the reduction with $NaBH_4$ was attempted by changing the reaction temperature and solvent. Cooling the reaction down increased the diastereoselectivity with respect to *anti*-**208** (up to 95:5 dr at −78 °C) whilst reaction in THF gave 76:24 dr at −20 °C and 94:6 dr at −78 °C, almost identical to the results obtained when MeOH was used as the solvent. A wider range of reducing agents was trialled next in THF at either −20 °C or −78 °C. At −20 °C, both $LiBH_4$ and Red-Al® were moderately selective for the formation of *anti*-**208** (79:21 dr and 76:24 dr, respectively). $LiAlH(O^tBu)_3$ and L-selectride® gave *anti*-**208** as the major product at both −20 °C and −78 °C, showing similar levels of diastereoselectivity to those observed when $NaBH_4$ was used as the reducing agent. The only reducing agent to show a preference for the formation of the *syn*-epimer was DIBAL-H, which proved to be completely diastereoselective (>99:1 dr) in THF at −20 °C, giving *syn*-**217** in 75% yield and >99:1 dr after purification (Scheme 27).



starting dr [208:217]	reducing agent	solvent	temperature (°C)	time	crude dr [217:208]
>99:1	$NaBH_4$	MeOH	–20	2 h	27:73
>99:1	$NaBH_4$	MeOH	–40	2 h	7:93
>99:1	$NaBH_4$	MeOH	–60	2 h	6:94
>99:1	$NaBH_4$	MeOH	–78	2 h	5:95
73:27	$NaBH_4$	THF	–20	2 h	24:76
>99:1	$NaBH_4$	THF	–78	2 h	6:94
73:27	$LiAlH_4$	THF	–20	2 h	8:92
73:27	$LiBH_4$	THF	–20	2 h	21:79
73:27	Red-Al	THF	–20	2 h	24:76
73:27	$LiAlH(O^tBu)_3$	THF	–20	2 h	29:71
>99:1	$LiAlH(O^tBu)_3$	THF	–78	2 h	7:93
73:27	L-Selectride	THF	–20	2 h	22:78
>99:1	L-Selectride	THF	–78	2 h	7:93
73:27	DIBAL-H	THF	–20	2 h	>99:1

Scheme 27. Optimisation of *syn*-selective oxidation reduction protocol.

With optimised routes to both *syn*-α-hydroxy-β-amino esters **217** and **215** now in hand, elaboration of **217** and **215** to the *N*-Boc protected derivatives **218** and **219**, and the corresponding mesylates **220** and **221**, was undertaken. Tandem hydrogenolysis and *N*-Boc protection of **217** and **215** gave **218** and **219** in 68 and 70% yield, respectively, and subsequent mesylation was achieved upon treatment with MsCl to give **220** and **221** in 95 and 92% yield (Scheme 28). Single crystal X-ray diffraction analyses confirmed the assigned relative configurations within **218**, **220** and **221** (Figure 10).[28]



R = Ph, **217**, >99:1 dr
R = Me, **215**, >99:1 dr

218, 68%, >99:1 dr
219, 70%, >99:1 dr

220, 95%, >99:1 dr
221, 92%, >99:1 dr

Scheme 28. *Reagents and Conditions*: (i) Boc_2O, $Pd(OH)_2/C$, H_2 (5 atm), EtOAc, rt, 15 h; (ii) MsCl, Et_3N, DMAP, CH_2Cl_2, rt, 15 h.

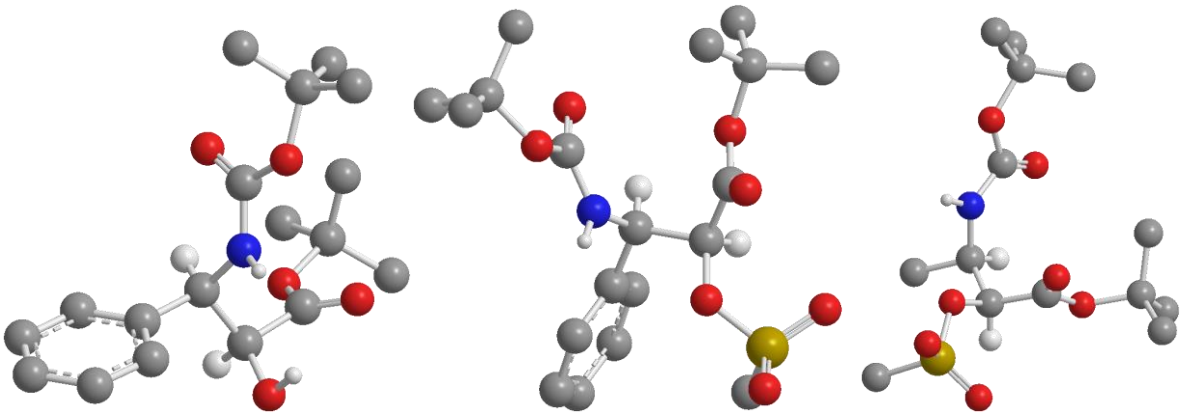


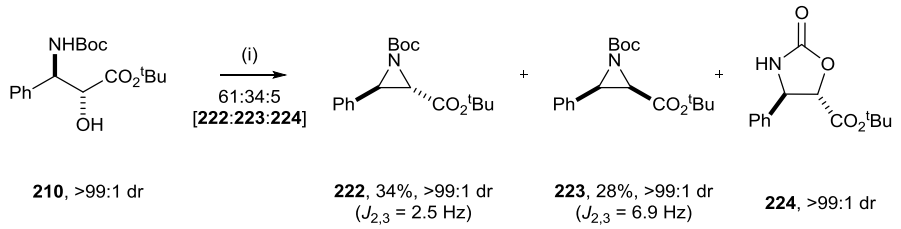
Figure 10. X-ray crystal structures of (2*S*,3*R*)-**218** [*left*], (2*S*,3*R*)-**220** [*middle*] and (2*S*,3*R*)-**221** [*right*] (selected H atoms are omitted for clarity).

With a robust and reliable route to the *N*-Boc protected alcohols **210**, **211**, **218** and **219** and their corresponding mesylates **212**, **213**, **220** and **221** now developed, attention turned to investigating the formation of the corresponding *cis*- and *trans*-aziridines.

2.2.4. Aziridine formation

2.2.4.1. Optimisation for the formation of *trans*-aziridines

A method for the formation of aziridines from *N*-Boc protected amino alcohols, which was published by Wessig *et al.*,[30] involves *in situ* activation of the hydroxyl group with TsCl in the presence of KOH. On application of these literature conditions to **210**, three products were observed: *trans*-aziridine **222**, *cis*-aziridine **223** and an oxazolidinone side product **224**, in a 61:34:5 ratio from which only **222** and **223** were isolated in 34 and 28% yield, respectively, and >99:1 dr in each case (Scheme 29). In the first instance, the relative configurations within aziridines **222** and **223** were assigned by ^{1}H NMR ^{3}J coupling constant analyses, as the coupling constants observed between the the C(2)*H* and C(3)*H* protons are diagnostic of either a *trans* ($^{3}J_{2,3}$ = 2–3 Hz) or *cis* ($^{3}J_{2,3}$ = 6–7 Hz) relative configuration.[31] These assignments were later confirmed unambiguously by single crystal X-ray diffraction analyses of both **222** and **223** (Figure 11).[28]



Scheme 29. *Reagents and conditions*: (i) KOH, TsCl, Et_2O, 40 °C, 15 h.

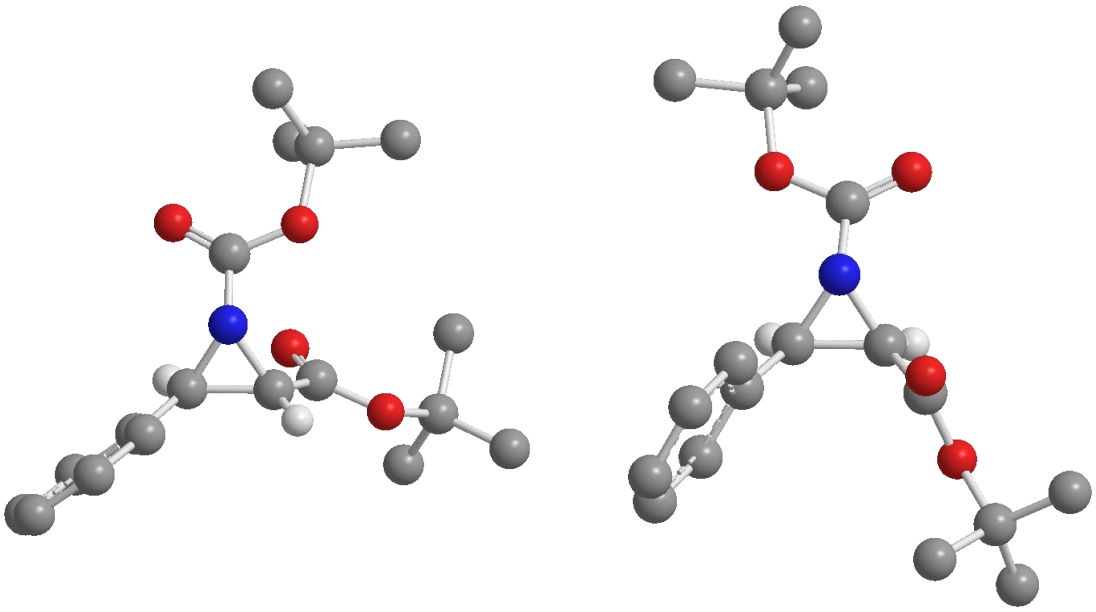
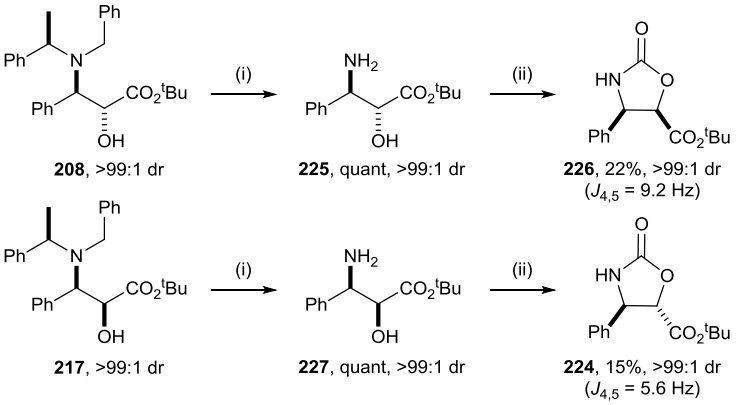


Figure 11. X-ray crystal structure of (2*S*,3*R*)-**222** [*left*] and (*R*,*R*)-**223** [*right*] (selected H atoms are omitted for clarity).

The synthesis of authentic samples of both *cis*-oxazolidinone **226** and *trans*-oxazolidinone **224** was undertaken to confirm the identity of and configuration within oxazolidinone **224**. Hydrogenolysis of *anti*-**208** gave **225** in quantitative yield and subsequent reaction with CDI gave *cis*-oxazolidinone **226**, which was isolated in 22% yield and >99:1 dr. Similarly, hydrogenolysis of *syn*-**217** gave **227** in quantitative yield, and treatment of **227** with CDI gave *trans*-oxazolidinone **224** in 15% yield and >99:1 dr (Scheme 30). The ^{1}H NMR spectroscopic data for *trans*-oxazolidinone **224** were found to be identical to those for the sample of **224** prepared from **210** upon attempted aziridine formation, and markedly different to those of *cis*-oxazolidinone **226**. Furthermore, the ^{1}H NMR ^3J coupling constants observed between the C(4)*H* and C(5)*H* protons within oxazolidin-2-ones are also diagnostic of either a *trans* ($^3J_{4,5}$ = 4–6 Hz) or *cis* ($^3J_{4,5}$ = 8–9 Hz) relative configuration[32] and this assignment was subsequently confirmed unambiguously by single crystal X-ray diffraction analysis of **224** (Figure 12).[28] The formation of oxazolidinone **224** as a side product upon attempted aziridine formation from **210** is consistent with a mechanistic pathway in which the tosylate group is displaced by the O atom of the carbonyl group within the carbamate functionality. This inverts the configuration at C(2), and is followed by concomitant loss of the *tert*-butyl group to give *trans*-**224**. The lack of stereospecifity in the aziridine formation reaction from *anti*-**210** suggests that the reaction mechanism does not follow a simple S_N2 pathway. Resubjection of pure samples of *trans*-**222** and *cis*-**223** to the reaction conditions gave returned starting material only, ruling out the possibility that *cis*-**223** is formed from epimerisation of *trans*-**222**. The observation of *cis*-**223** as a product in this reaction could be due to a competing S_N1 pathway, although this would rely on the formation of a carbocation α to the electron withdrawing ester group. Alternatively, enolisation of the ester may result in epimerisation at the α-position, with subsequent S_N2 reaction resulting in a mixture of diastereoisomeric aziridines.



Scheme 30. *Reagents and conditions*: (i) H_2 (5 atm), $Pd(OH)_2$/C, MeOH, rt, 15 h; (ii) CDI, DMAP, THF, rt, 12 h.

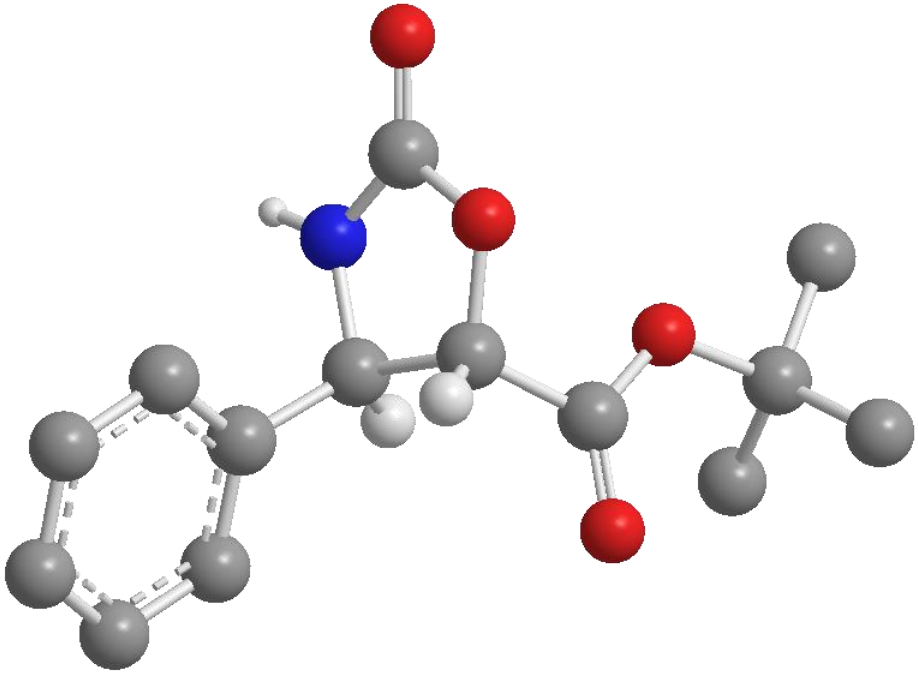
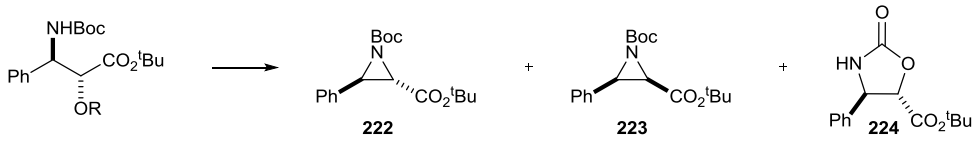


Figure 12. X-ray crystal structure of (4*R*,5*S*)- **224** (selected H atoms are omitted for clarity).

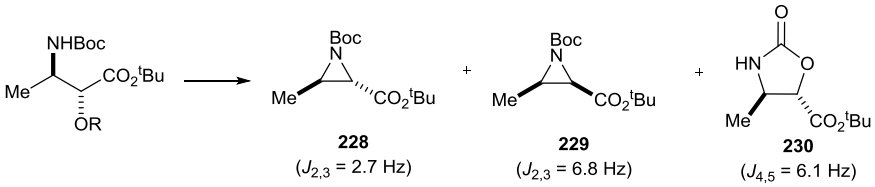
A range of condition sets were then screened to optimise the formation of *trans*-aziridine **222** from **210**. Treatment of alcohol **210** with MsCl in the presence of DIPEA failed to effect direct conversion to aziridine **222**, resulting in full conversion to oxazolidinone **224**. Attempts at aziridine formation from **210** via a Mitsonubu reaction were also unsuccessful; therefore studies into aziridine formation from mesylate **212** were undertaken next. Treatment of **212** with a variety of bases under various reaction conditions identified DMF to be the best solvent for this transformation, with the use of both Cs_2CO_3 and NaH as bases giving high selectivity for formation of *trans*-aziridine **222**. Reaction with Cs_2CO_3 in DMF gave an 81:10:9 ratio of **222**, **223** and **224**, respectively, whist this was improved to 98:2:0 when NaH was used as the base, enabling the isolation of **222** in 72% yield and >99:1 dr. Reaction with NaH was tested again in the presence of 15-crown-5, to assess the possible impact of the Na^+ counterion. In DMF, little difference was seen, with a slight reduction in selectivity, giving a 90:4:6 mixture of **222**, **223** and **224**, respectively. However, in THF a marked improvement in selectivity was observed, from a 58:41:1 mixture to a 90:7:3 mixture of **222**, **223** and **224**, respectively (Scheme 31).



R	base (equiv)	reagents	temperature (°C)	time (h)	crude ratio 212:222:223:224	yield (%) 222:223:224
H	DIPEA (5)	MsCl, $CH_3CH_2Cl_2$	–78 then 85	3 then 24	0:0:0:100	0:0:74
H	none	PPh_3, DEAD, THF	0	3	complex mixture	-
Ms	TBAF (5)	THF	rt	15	0:42:32:26	
Ms	Et_3N (5)	THF	rt	15	53:13:0:34	0:0:25
Ms	MeMgBr (1.05)	THF	–78 to rt	15	95:0:0:5	-
Ms	^tBuOK (1.05)	THF	rt	15	0:51:49:0	30:27:0
Ms	NaH (1.2)	THF	rt	15	0:58:41:1	28:14:0
Ms	NaH (0.5)	THF	rt	15	67:21:11:1	-
Ms	Cs_2CO_3 (3)	DMF	50	3	0:81:10:9	51:10:0
Ms	NaH (1.2)	DMF	50	3	0:98:2:0	72:0:0
Ms	none	DMF	50	3	80:0:0:20	-
Ms	NaH (1.2)	15-crown-5, DMF	50	3	0:90:4:6	62:2:0
Ms	NaH (1.2)	15-crown-5, THF	rt	15	0:90:7:3	56:6:0

Scheme 31. Optimisation of aziridine formation reaction.

Similarly, studies into the selective formation of *trans*-**228** were also undertaken. Reaction of **213** with Cs_2CO_3 in DMF gave a 66:14:20 ratio of **228**, **229** and **230**, respectively, which were isolated in 23, 8 and 20% yield, respectively. Under optimised conditions, treatment of mesylate **213** with NaH in DMF gave high selectivity for the formation of **228** (i.e., a 93:7 ratio of **228** and **230**, respectively), from which **228** was isolated in 48% yield and >99:1 dr. The addition of 15-crown-5 was successful in preventing formation of oxazolidinone **230**, but saw a reduction in diastereoselectivity (95:5 dr) (Scheme 32). The configurations within *trans*-aziridine **228**, *cis*-aziridine **229** and *trans*-oxazolidinone **230** were initially assigned by ^{1}H NMR ^3J coupling constant analyses, and these assignments were then unambiguously verified by single crystal X-ray diffraction analyses in each case (Figure 13).[28]



R	base (equiv)	reagents	temperature (°C)	time (h)	conversion (%)	crude ratio 228:229:230	yield (%) 228:229:230
H	KOH (4.0)	TsCl, Et_2O	40	15	92	66:6:20	43:0:0
H	none	PPh_3, DEAD, THF	0	3		complex mixture	-
Ms	Et_3N (5.0)	THF	rt	15	68	0:0:68	-
Ms	MeMgBr (1.05)	THF	–78 to rt	15	10	0:0:10	-
Ms	^tBuOK (1.05)	THF	rt	15	100	50:50:0	12:9:0
Ms	NaH (1.2)	THF	rt	15		complex mixture	-
Ms	Cs_2CO_3 (3)	DMF	50	3	100	66:14:20	23:8:20
Ms	NaH (1.2)	DMF	50	3	100	93:0:7	48:0:0
Ms	none	DMF	50	3	56	0:0:56	-
Ms	NaH (1.2)	15-crown-5, DMF	50	3	100	95:5:0	45:0:0
Ms	NaH (1.2)	15-crown-5, THF	rt	15	100	96:4:0	5[a]:0:0

Scheme 32. Optimisation of aziridine formation reaction [[a]an 84:16 mixture of **228** and **229** was also isolated in 20% combined yield].

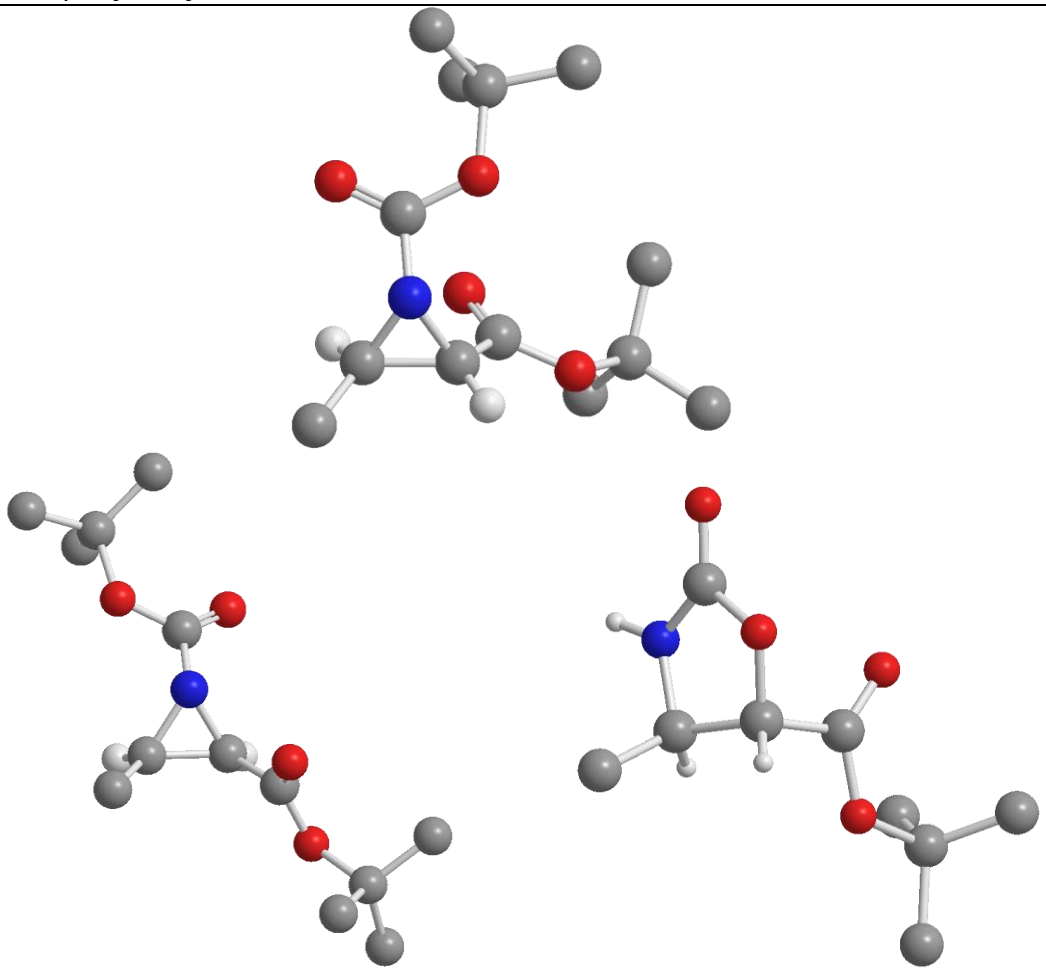
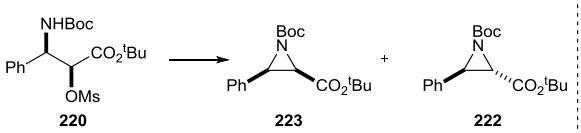


Figure 13. X-ray crystal structure of (2*S*,3*R*)-**228** [*top*], (*R*,*R*)-**229** [*left*] and (4*R*,5*S*)-**230** [*right*] (selected H atoms are omitted for clarity).

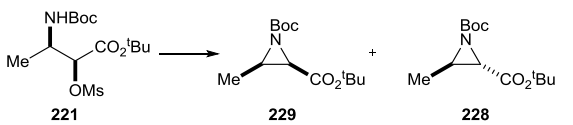
2.2.4.2. Optimisation for the formation of *cis*-aziridines

Attention was next turned to selective formation of *cis*-aziridines **223** and **229** from *syn*-**220** and *syn*-**221**. The most promising condition sets, as identified by studies into the formation of *trans*-aziridines, were tried first. Treatment of both **220** and **221** with Cs_2CO_3 in DMF gave completely selective formation of *cis*-aziridines **223** and **229** which were isolated in 99 and 73% yield, respectively, and >99:1 dr in each case. Reaction of **220** or **221** with NaH also gave rise to *cis*-aziridines **223** and **229** with high selectivity in both cases: **223** was formed in 93:7 dr, whilst **229** was formed in >99:1 dr. Addition of 15-crown-5 resulted in a reduction in diastereoselectivity in both cases (Scheme 33).



220 **223** **222**

base (equiv)	reagents	temperature (°C)	time (h)	crude ratio 223:222	Yield
Cs_2CO_3 (3)	DMF	50	3	>99:1	99%
NaH (1.2)	DMF	50	3	93:7	-
NaH (1.2)	15-crown-5, DMF	50	3	76:24	-



221 **229** **228**

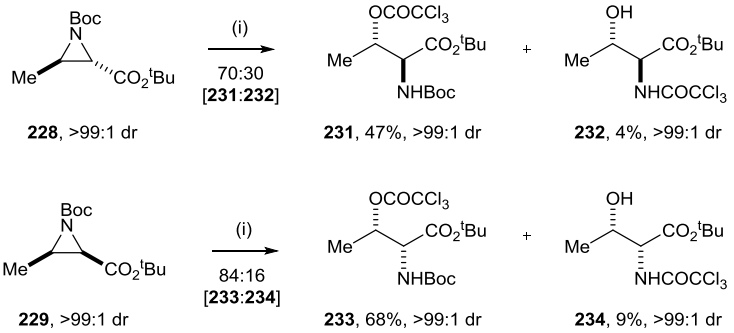
base (equiv)	reagents	temperature (°C)	time (h)	crude ratio 229:228	Yield
Cs_2CO_3 (3)	DMF	50	3	>99:1	73%
NaH (1.2)	DMF	50	3	>99:1	32%
NaH (1.2)	15-crown-5, DMF	50	3	83:17	-

Scheme 33. Formation of *cis*-aziridines.

With optimised routes through to aziridines **222**, **223**, **228** and **229** achieved, studies could progress to address their regioselective ring-opening and subsequent elaboration to β-hydroxy-α-amino acids.

2.2.5. Attempted aziridine ring-opening reactions

Investigations into the regioselective ring-opening of aziridines **222**, **223**, **228** and **229** with an oxygen based nucleophile began using Cl_3CCO_2H. Precedent for the regioselective ring-opening of epoxides with Cl_3CCO_2H was known from studies by Davies *et al.*[19] and so a similar approach was employed to see if aziridines could also be ring-opened in a regioselective fashion. Furthermore, the choice of trichloroacetate as a nucleophile would simplify the subsequent deprotection step, as the trichloroacetate group should also be labile under the acidic conditions required for ester hydrolysis. Treatment of C(3)-methyl substituted *trans*-aziridine **228** with Cl_3CCO_2H resulted in regioselective ring-opening at the C(3) position to give a 70:30 mixture of **231** and **232**, respectively, from which **231** was isolated in 47% yield and >99:1 dr, and **232** was isolated in 4% yield and >99:1 dr. Similarly, reaction of C(3)-methyl substituted *cis*-aziridine **229** with Cl_3CCO_2H also occurred regioselectively, giving an 84:16 ratio of **233** and **234**, respectively, from which **233** was isolated in 68% yield and >99:1 dr, and **234** was isolated in 9% yield and >99:1 dr (Scheme 34). ^{1}H NMR COSY and ^{1}H-^{13}C HMBC analyses were employed to assign the regiochemistries within **231**–**234**. Furthermore, single crystal X-ray diffraction analyses of **231** and **234** enabled unambiguous confirmation of their relative configurations, and the determination of Flack *x* parameters[27] of –0.017(15) and –0.023(13) for the crystal structures of **231** and **234**, respectively, allowed the assigned absolute (*S*,*S*)-configuration within **231** and (2*R*,3*S*)-configuration within **234** to be confirmed unambiguously (Figure 14).[28] The formation of **231** and **233** is consistent with a mechanism in which aziridines **228** and **229** undergo regioselective S_N2-type ring-opening at the C(3) position by the trichloroacetate ion, which occurs with inversion of configuration. Subsequent *N*-Boc hydrolysis may occur under the acidic reaction conditions, with *O* to *N* transfer of the trichloroacetyl group giving rise to products **232** and **234**. It was found that resubjecting **231** to the reaction conditions gave a 59:41 mixture of **231** and **232**, respectively, which is consistent with this mechanistic proposal.



Scheme 34. *Reagents and conditions*: (i) Cl_3CCO_2H, CH_2Cl_2, rt, 15 h.

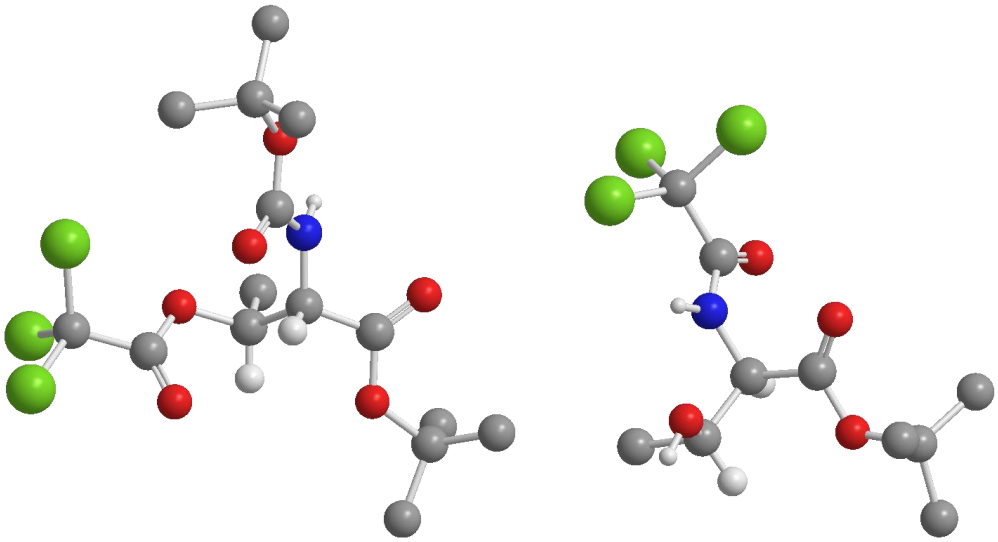
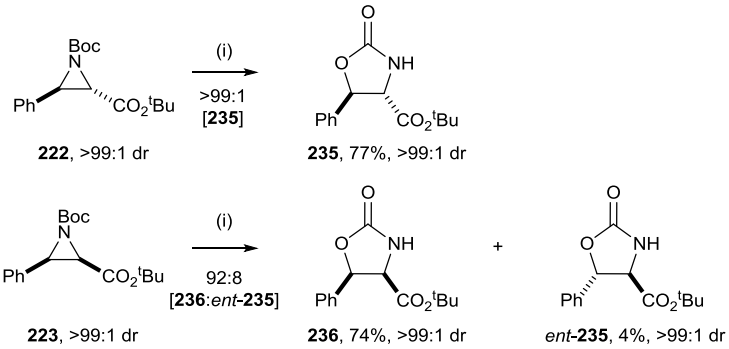


Figure 14. X-ray crystal structures of (*S*,*S*)-**231** [*left*] and (2*R*,3*S*)-**234** [*right*] (selected H atoms are omitted for clarity).

Upon treatment of the C(3)-phenyl substituted aziridines **222** and **223** with Cl_3CCO_2H, however, direct ring-opening products were not observed. Instead, reaction of **222** with Cl_3CCO_2H gave oxazolidinone **235** in >99:1 dr, which was isolated in 77% yield. Under the same reaction conditions, **223** was transformed to a 92:8 mixture of **236** and *ent*-**235**. Purification of the crude reaction mixture enabled isolation of *cis*-**236** in 74% yield and >99:1 dr, and *ent*-**235** was isolated in 4% yield and >99:1 dr (Scheme 35). For both **235** and **236**, single crystal X-ray diffraction analyses enabled unambiguous assignment of their relative configurations. Furthermore, the determination of Flack *x* parameters[27] of –0.03(19) and –0.08(16) for the crystal structures of **236** and **235**, respectively, allowed the absolute (*R*,*R*)- and (4*S*,5*R*)-configurations within **236** and **235** to be unambiguously assigned (Figure 15).[28]



Scheme 35. *Reagents and conditions*: (i) Cl_3CCO_2H, CH_2Cl_2, rt, 15 h.

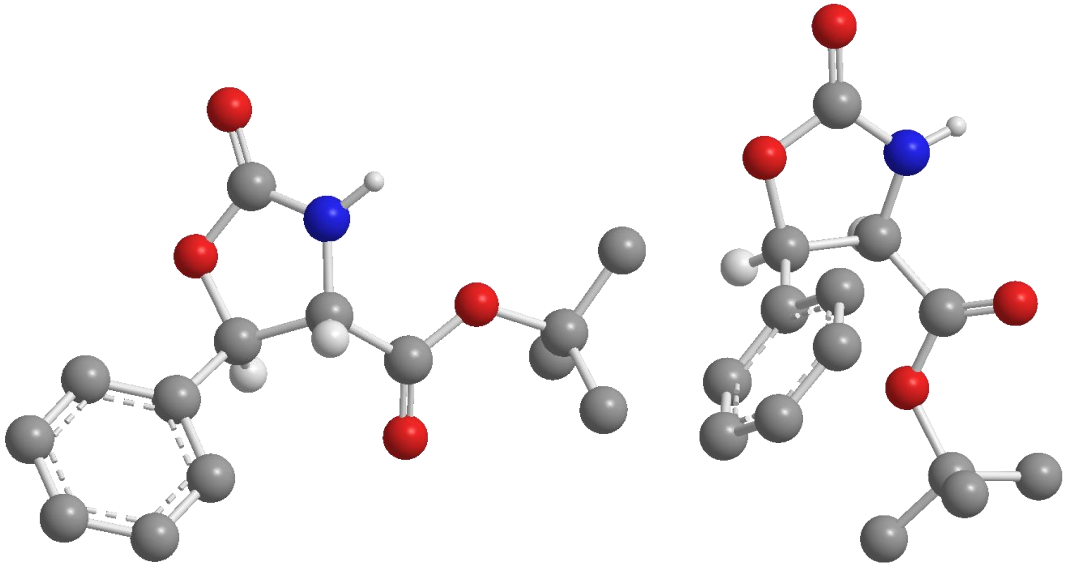


Figure 15. X-ray crystal structure of (4*S*,5*R*)-**235** [*left*] and (*R*,*R*)-**236** [*right*] (selected H atoms are omitted for clarity).

This experimental outcome is consistent with reports of the rearrangement of *N*-Boc aziridines to oxazolidinones in the literature, which are promoted by a Lewis acid.[33] The observed stereochemical result is retention of configuration, which is consistent with a mechanism in which acid promoted S_N1-type aziridine ring-opening occurs at the benzylic C(3)-position, where the resultant carbocation can be stabilised through conjugation with the aromatic ring. Subsequent ring-closure through the carbamate functionality, with concomitant loss of the *tert*-butyl group, leads to the observed oxazolidinone. For these substrates, this alternative reactivity is presumably observed due to the greater stability of the benzylic carbocation versus the corresponding 2° alkyl carbocation that would be formed from *cis*-**228** and *trans*-**229**. For **223**, the reduction in diastereoselectivity may be explained by competitive rotation around the C−C bond, presumably to minimise an unfavourable steric interaction between the phenyl and ester substituents (Figure 16).

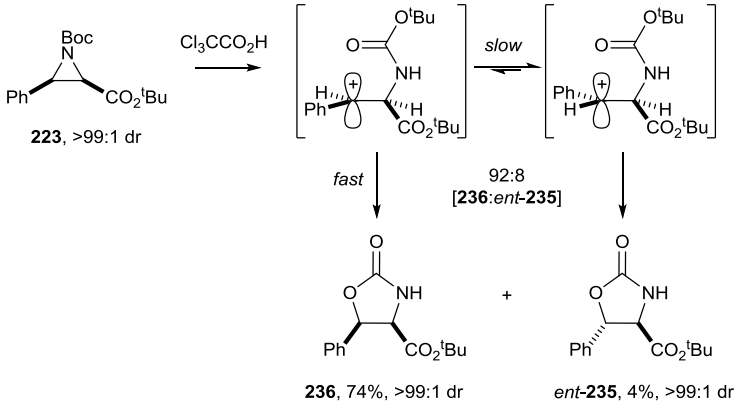
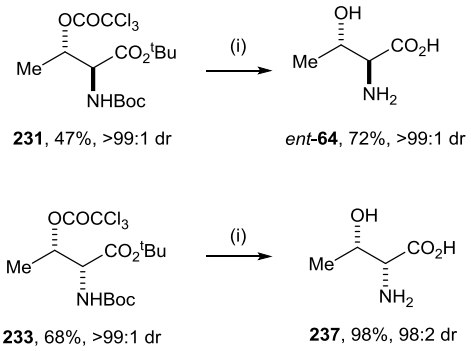


Figure 16. Possible rationalisation for reduction in diastereoselectivity of Cl_3CCO_2H facilitated rearrangement.

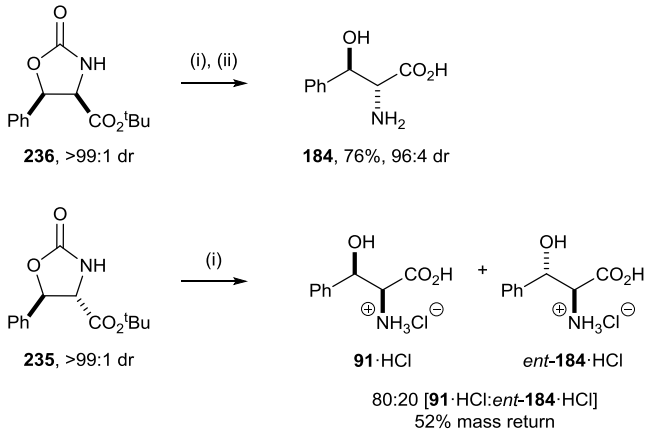
2.2.6. Deprotection to β-hydroxy-α-amino acids

The final transformation required to access the target β-hydroxy-α-amino acids *ent*-**64** and **237** from **231** and **233** was global deprotection of the *tert*-butyl ester, *N*-Boc and *O*-trichloroacetate groups. It was found that upon reflux in 6.0 M aq HCl for 24 h, both **231** and **233** were fully deprotected to give (*S*,*S*)-*allo*-threonine *ent*-**64** and (2*R*,3*S*)-threonine **237**, respectively, which were isolated in 72% yield and >99:1 dr, and 97% yield and 98:2 dr, after purification on DOWEX-50WX8 ion exchange resin (Scheme 36). The spectroscopic data, including specific rotations, for the samples of (*S*,*S*)-*ent*-**64** {mp 240–250 °C (dec.); $[\alpha]_D^{20}$ +7.5 (*c* 1.0 in H_2O); lit.[13] mp 264–266 °C; lit.[13] $[\alpha]_D^{20}$ +8 (*c* 1.1 in H_2O)} and (2*R*,3*S*)-**237** {mp 250–260 °C (dec.); $[\alpha]_D^{20}$ +23.2 (*c* 1.0 in H_2O); lit.[34] mp 264 °C; lit.[35] $[\alpha]_D$ +26.1 (*c* 1.0 in H_2O)} were in excellent agreement with literature values.



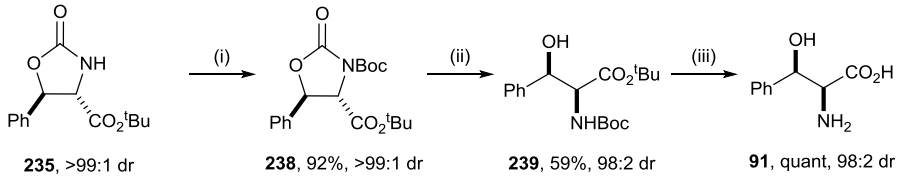
Scheme 36. *Reagents and conditions*: (i) 6.0 M aq HCl, 90 °C, 24 h, then DOWEX-50WX8 ion-exchange resin.

It was envisaged that acid catalysed hydrolysis of oxazolidinones **236** and **235** would cleave the carbamate functionality and deprotect the *tert*-butyl ester moiety to give the target β-hydroxy-α-amino acids **184** and **91**. Thus, treatment of **236** with 6.0 M aq HCl at reflux for 24 h gave **184**·HCl in 96:4 dr, which after purification on DOWEX-50WX8 ion exchange resin enabled isolation of **184** in 76% yield. However, significant epimerisation was observed during the hydrolysis of **235**, giving **91**·HCl in only 80:20 dr (Scheme 37).



Scheme 37. *Reagents and conditions*: (i) 6.0 M aq HCl, 90 °C, 24 h; (ii) DOWEX-50WX8 ion-exchange resin.

Attempted basic hydrolysis of **235** proved difficult; presumably deprotonation of the N(3)*H* proton occurred first,[36] retarding subsequent hydrolysis. An alternative pathway was found,[37] which involved initial protection of the carbamate functionality within **235**. Thus, *N*-Boc protection of **235** gave **238** in 92% yield. Hydrolysis of **238** with LiOH in dioxane/H_2O (5:1) successfully removed the carbamate functionality, giving **239** in 59% yield. The relative configuration within **239** was established unambiguously via single crystal X-ray diffraction analysis, and the determination of a Flack *x* parameter[27] of –0.06(14) for the crystal structure of **239** allowed the assigned absolute (2*S*,3*R*)-configuration within **239** to be confirmed (Figure 17).[28] Subsequent hydrolysis of **239** in TFA affected hydrolysis of both the *tert*-butyl ester moiety and *N*-Boc protecting group. Formation of the corresponding HCl salt and purification on DOWEX-50WX8 ion exchange resin gave **91** in quantitative yield and 98:2 dr (Scheme 38).



Scheme 38. *Reagents and conditions*: (i) Boc_2O, Et_3N, DMAP THF, rt, 15 h; (ii) LiOH, dioxane/H_2O (5:1), rt, 45 min; (iii) CH_2Cl_2/TFA (4:1), rt, 2 h, then 6.0 M aq HCl, then DOWEX-50WX8 ion-exchange resin.

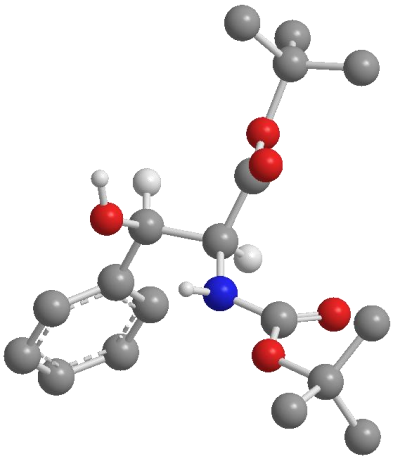


Figure 17. X-ray crystal structure of (2*S*,3*R*)-**239** (selected H atoms are omitted for clarity).

The spectroscopic data, including specific rotations, for both samples of (*R*,*R*)-**184** {mp 189–192 °C (dec.); $[\alpha]_D^{20}$ –2.4 (*c* 1.0 in H_2O); lit.[38] mp 174 °C (dec.); lit.[39] $[\alpha]_D$ –4.3 (*c* 1.1 in H_2O)} and (2*S*,3*R*)-**91** {mp 201–202 °C; $[\alpha]_D^{20}$ –28.9 (*c* 1.0 in H_2O); lit.[40] mp 192–195 °C; lit.[13] $[\alpha]_D^{20}$ –30 (*c* 1.0 in H_2O)} were in excellent agreement with literature values.

2.3. Conclusion

The work described in this chapter demonstrates that the amine and oxygen functionalities within α-hydroxy-β-amino esters can be "swapped" giving a route to both β-alkyl and β-aryl substituted β-hydroxy-α-amino acids. This has involved manipulation of the protecting groups on both *N* and *O*, the development of both diastereoselective aziridine formation and regioselective ring-opening methodologies and investigation into suitable deprotection strategies to access β-hydroxy-α-amino acids **91**, **184**, **237** and *ent*-**64** whilst maintaining high levels of diastereoselectivity (>95:5 dr). Overall, the asymmetric syntheses of **91** and **184** were achieved in 24% yield in 8 steps from **206**, and 25% yield in 7 steps from **206**, respectively. Furthermore, **237** was synthesised in 27% yield over 7 steps from **207**, and *ent*-**64** was synthesised in 11% yield over 6 steps from **207** (Figure 18). The next chapter describes attempts to truncate this process, by *in situ* formation and ring-opening of aziridinium intermediates.

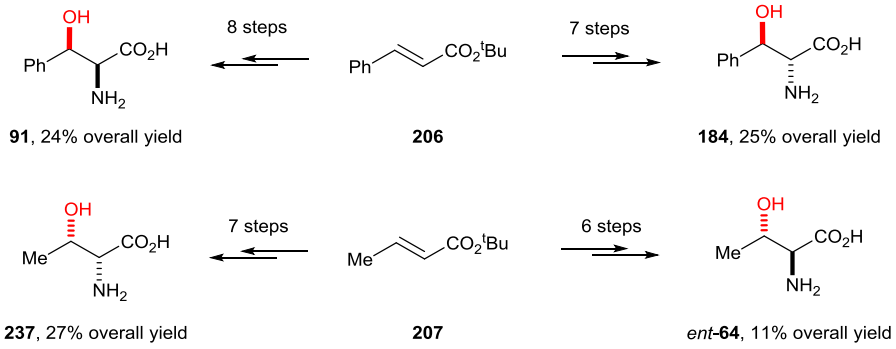


Figure 18. Asymmetric synthesis of β-hydroxy-α-amino acids from commercially available starting materials.

2.4. References and notes

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Chapter 3: β-Hydroxy-α-amino acids via aziridinium intermediates

This chapter describes studies concerning the conversion of α-hydroxy-β-amino esters **240** into β-hydroxy-α-amino acids **189** via the formation and *in situ* ring-opening of aziridinium intermediates **241** (Figure 19).

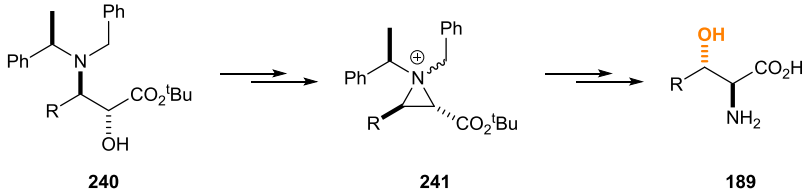


Figure 19. β-Hydroxy-α-amino acids **189** from α-hydroxy-β-amino esters **240** via aziridinium intermediates **241**.

3.1. Results and discussion

3.1.1. Synthetic strategy

In the previous chapter, methodology concerning the transformation of α-hydroxy-β-amino esters to β-hydroxy-α-amino acids was developed, which utilised either a stereospecific and regioselective ring-opening, or a stereoselective rearrangement of an aziridine as the key step. An alternative, streamlined strategy was proposed in which the synthesis of β-hydroxy-α-amino acids **189** from α-hydroxy-β-amino esters **240** could be achieved via the *in situ* formation, and subsequent stereospecific ring-opening, of aziridinium intermediates **241**. Activation of the α-hydroxyl group within **240** would promote displacement by the β-amino functionality, giving rise to aziridinium intermediate **241**, which would occur with inversion of configuration at C(2). Literature precedent suggested that ring-opening of aziridinium ion **241** would occur at the C(3)-position with inversion of configuration.[1] By employing H_2O (or an alternative oxygen based nucleophile) in this process, it was anticipated that β-hydroxy-α-amino esters **243** may be accessed, which could then be deprotected via hydrogenolytic *N*-debenzylation and subsequent ester hydrolysis to give the corresponding β-hydroxy-α-amino acids **189**. This approach would offer many advantages over the previous strategy discussed in Chapter 2: employing a reactive aziridinium intermediate rather than isolating an aziridine would limit the amount of protecting group manipulation necessary, thus resulting in a reduced step count and improved overall atom economy (Figure 20).

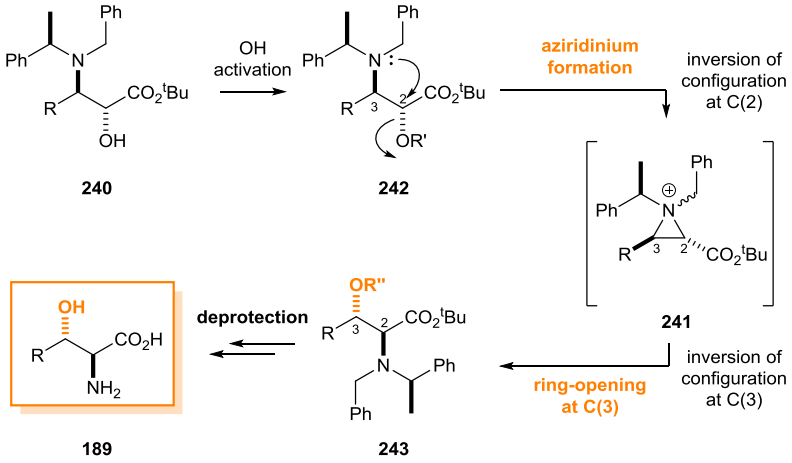


Figure 20. Proposed strategy for the synthesis of β-hydroxy-α-amino acids **189** from α-hydroxy-β-amino esters **240** via aziridinium intermediates **241**.

3.1.2. Model studies

Studies into aziridinium formation from α-hydroxy-β-amino esters began by using *N*,*N*-dibenzyl protected substrates **244**: if it proved possible to isolate or observe these reactive intermediates by NMR spectroscopy, it was thought advantageous to use a substrate which had two identical *N*-protecting groups, which would not give rise to a stereogenic centre at nitrogen upon aziridinium formation. Substrates with two different amine protecting groups, such as those with *N*-benzyl-*N*-(α-methylbenzyl) protection **240**, would give rise to diastereoisomeric aziridinium ions **246** and **247**, and thus bring added complexity to the interpretation of NMR spectra in preliminary studies. Representative β-aryl (R = Ph) and β-alkyl (R = Me, ^{i}Pr) substrates were chosen to undertake initial investigations (Figure 21).

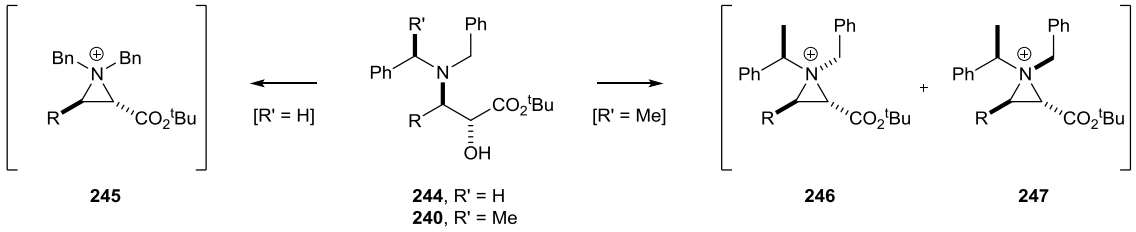
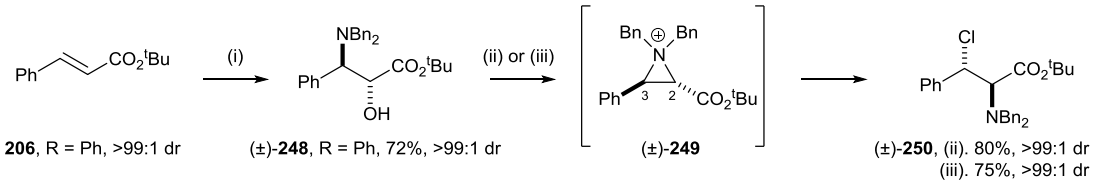


Figure 21. Potential diastereosiomeric mixtures of aziridinium ions **246** and **247** arising from **240**, versus the single aziridinium ion **245** arising from **244**.

3.1.2.1 Investigations into rearrangements via C(3)-aryl and C(3)-alkyl substituted aziridinium ions

Racemic *N*,*N*-dibenzyl α-hydroxy-β-amino ester (±)-**248** was made via conjugate addition of lithium *N*,*N*-dibenzylamide to *tert*-butyl cinnamate **206**, with *in situ* oxidation of the corresponding intermediate (*Z*)-β-amino enolate[2] with (−)-CSO **202**. The relative *anti*-stereochemistry within (±)-**248** was confidently assigned based on $^{3}J_{2,3}$ coupling constant analysis: the magnitude of the $^{3}J_{2,3}$ coupling constant ($^{3}J_{2,3}$ = 4.3 Hz) was within the expected range for *anti*-configured α-hydroxy-β-amino esters ($^{3}J_{2,3}$ = 2–4.5 Hz).[3] Previous literature in this area reports that treatment of vicinal amino alcohols with MsCl can often result in

rearrangement to chlorides, which is proposed to proceed via the corresponding aziridinium intermediate.[4] Thus, application of a mesylation procedure to (±)-**248** was investigated first. Reaction of α-hydroxy-β-amino ester (±)-**248** with MsCl was found to proceed cleanly, giving β-chloro-α-amino ester (±)-**250** as the sole product, which was isolated in 80% yield and >99:1 dr. Furthermore, reacting (±)-**248** with PPh_3 and CCl_4 under Appel[5] conditions was also found to facilitate rearrangement to give β-chloro-α-amino ester (±)-**250** exclusively, which was isolated in 75% yield and >99:1 dr. The regiochemistry within (±)-**250** was confidently assigned via ^1H-^{13}C HMBC analysis, and this assignment was later confirmed via single crystal X-ray diffraction analysis (Figure 22).[6] This also established the relative *anti*-configuration within (±)-**250**, and is consistent with the reaction proceeding via aziridinium intermediate (±)-**249**, where formation of the aziridinium ion occurs with inversion of configuration at C(2) and ring-opening with chloride occurs with inversion of configuration at C(3). The high regioselectivity associated with this process is precedented,[7] and is consistent with the stabilising effect of the π-aromatic system on the developing carbocationic character within the transition state, which directs ring-opening at C(3) to give the kinetic product. However, the possibility that this observation is the result of thermodynamic control (reversible ring-opening and formation of (±)-**249** to give the most stable product) cannot be excluded from the data available (Scheme 39).



Scheme 39. *Reagents and Conditions*: (i) $NHBn_2$, BuLi, THF, −78 °C, 2 h, then (−)-CSO **202**, −78 °C to rt, 18 h; (ii) MsCl, Et_3N, DMAP, CH_2Cl_2, rt, 2 h; (iii) PPh_3, CCl_4, PhMe, 100 °C, 2 h.

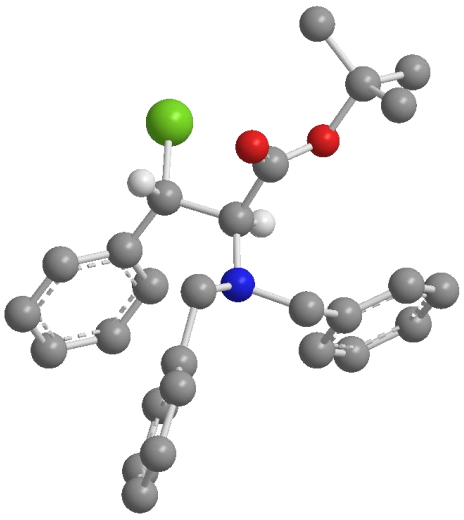
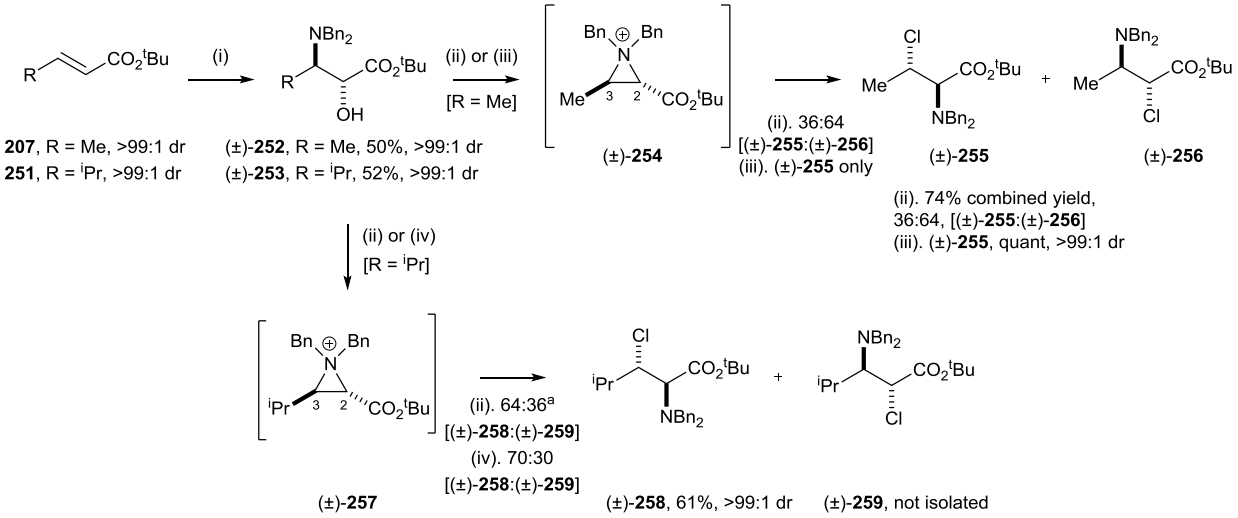


Figure 22. X-ray crystal structure of (*RS*,*SR*)-**250** (selected H atoms are omitted for clarity).

The corresponding mesylation and Appel reactions of β-alkyl substituted α-hydroxy-β-amino esters (±)-**252** and (±)-**253** were investigated next. Racemic *N*,*N*-dibenzyl α-hydroxy-β-amino esters (±)-**252** and (±)-**253** were made via conjugate addition of lithium *N*,*N*-dibenzylamide to α,β-unsaturated esters **207** and **251**, respectively, with *in situ* oxidation of the corresponding intermediate (*Z*)-β-amino enolates[2] with (−)-CSO **202**. Again, $^{3}J_{2,3}$ coupling constant analysis established the relative *anti*-configurations within (±)-**252** and (±)-**253**: for (±)-**252** (R = Me) a value of $^{3}J_{2,3}$ = 2.3 Hz was observed and for (±)-**253** (R = ^{i}Pr), $^{3}J_{2,3}$ = 3.2 Hz, both consistent with the diagnostic values.[3] Subsequent treatment of (±)-**252** (R = Me) with MsCl promoted rearrangement to a 36:64 mixture of β-chloro-α-amino ester (±)-**255** and α-chloro-β-amino ester (±)-**256**, respectively, which were not separable by column chromatography and were therefore isolated in 74% combined yield. Reaction of (±)-**253** (R = ^{i}Pr) with MsCl under identical conditions only proceeded to 66% conversion, to a 64:36 mixture of β-chloro-α-amino ester (±)-**258** and α-chloro-β-amino ester (±)-**259**, respectively. The regiochemistries within (±)-**255**, (±)-**256**, (±)-**258** and (±)-**259** were confidently assigned via ^{1}H-^{13}C COSY and HMBC analyses. It was subsequently found that formation of β-chloro-α-amino ester (±)-**255** as a single regioisomer could be achieved upon reaction of (±)-**252** (R = Me) under Appel conditions: reacting (±)-**252** with PPh_3 and CCl_4 at reflux for 24 h enabled full conversion to β-chloro-α-amino ester (±)-**255**. Shorter reaction times resulted in mixtures of α-chloro and β-chloro substituted products, which is consistent with equilibration occurring under the reaction conditions. Attempts to isolate (±)-**255** by column chromatography were unsuccessful, returning mixtures of β-chloro (±)-**255** and α-chloro (±)-**256**, again suggesting that the regioisomers could equilibrate, this time during the purification process. Appel reaction of (±)-**253** (R = ^{i}Pr) resulted in full conversion to a 70:30 mixture of β-chloro-α-amino ester (±)-**258** and α-chloro-β-amino ester (±)-**259**, enabling isolation of (±)-**258** in 61% yield and >99:1 dr. The relative *anti*-configuration within (±)-**258** was confirmed unambiguously via subsequent single crystal X-ray diffraction analysis (Figure 23).[6] The relative *anti*-configurations within (±)-**255**, (±)-**256** and (±)-**259** were tentatively assigned by analogy to the stereochemical outcome observed upon reaction of (±)-**248** (R = Ph) and (±)-**253** (R = ^{i}Pr) (Scheme 40).



Scheme 40. *Reagents and Conditions*: (i) $NHBn_2$, BuLi, THF, −78 °C, 2 h, then (−)-CSO **202**, −78 °C to rt, 18 h; (ii) MsCl, Et_3N, DMAP, CH_2Cl_2, rt, 2 h; (iii) PPh_3, CCl_4, PhMe, 100 °C, 24 h; (iv) PPh_3, CCl_4, PhMe, 100 °C, 2 h. [a] 66% conversion.

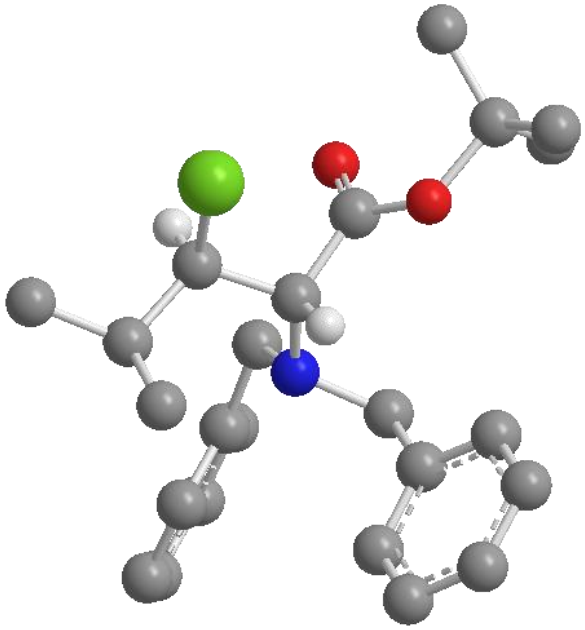
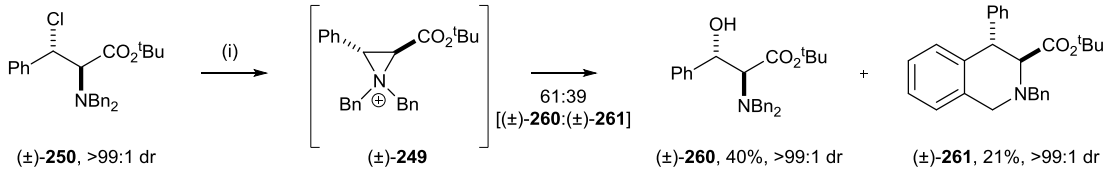


Figure 23. X-ray crystal structure of (*RS*,*SR*)-**258** (selected H atoms are omitted for clarity).

Examples in the literature have described the formation and characterisation of aziridinium intermediates upon treatment of vicinal amino chlorides with Ag(I) salts.[8] Thus, it was proposed that aziridinium intermediate (±)-**249** may potentially be observed by NMR spectroscopy upon the treatment of β-chloro-α-amino ester (±)-**250** with AgOTf, in the absence of a nucleophile that could affect its ring-opening. However, under these conditions full conversion to two products was observed instead: β-hydroxy-α-amino ester (±)-**260** and 1,2,3,4-tetrahydroisoquinoline[9] (±)-**261** were produced in a 61:39 ratio, respectively, from which (±)-**260** was isolated in 40% yield and (±)-**261** was isolated in 21% yield, as single diastereoisomers (>99:1 dr) in each case (Scheme 41).



Scheme 41. *Reagents and Conditions*: (i) AgOTf, EtOAc, rt, 1 h.

Regiochemical assignment of β-hydroxy-α-amino ester (±)-**260** was achieved by ^{1}H-^{13}C HMBC analysis, and both the structure and relative *anti*-configuration within (±)-**260** were subsequently confirmed unambiguously via subsequent single crystal X-ray diffraction analysis (Figure 25).[6] This is consistent with the reaction proceeding via aziridinium intermediate (±)-**249**, with subsequent ring-opening by adventitious water occurring regioselectively at C(3), with inversion of configuration. The structure of tetrahydroisoquinoline (±)-**261** was similarly elucidated with the aid of NMR spectroscopy[10] (including ^{1}H-^{13}C HMBC analysis), and this assignment was also confirmed by single crystal X-ray diffraction analysis,[6] from which the relative *anti*-configuration within (±)-**261** was also established unambiguously. Formation of tetrahydroisoquinoline (±)-**261** is consistent with reaction via a carbocationic intermediate (±)-**262**, which is trapped by one of the *N*-benzyl groups in an intramolecular Friedel-Crafts type process (Figure 24). This reaction had interesting implications for the development of this work as both (±)-**260** and (±)-**261** were formed upon activation of (±)-**250** with AgOTf, seemingly via a common aziridinium intermediate. Ring-opening of aziridinium ion (±)-**249** by an external nucleophile (i.e., H_2O) resulted in the formation of (±)-**260** as a single distereoisomer, whereas it was postulated that formation of tetrahydroisoquinoline (±)-**261** had occurred via the attack of an internal nucleophile, a process which had also occurred with high diastereoselectivity. With this result as precedent that these two structurally diverse product classes could be accessed from a common precursor, investigations into optimising both the selective ring-opening of aziridinium intermediates by external nucleophiles, and the development of a stereoselective cyclisation procedure to access tetrahydroisoquinolines were undertaken. The remainder of this chapter focusses on optimisation of a protocol leading to β-hydroxy-α-amino acids by regioselective opening of aziridinium ions with H_2O, whilst the optimisation of a one-pot synthesis of substituted tetrahydroisoquinolines, plus an investigation into the origin of the diastereoselectivity of this process, will be discussed in Chapter 5.

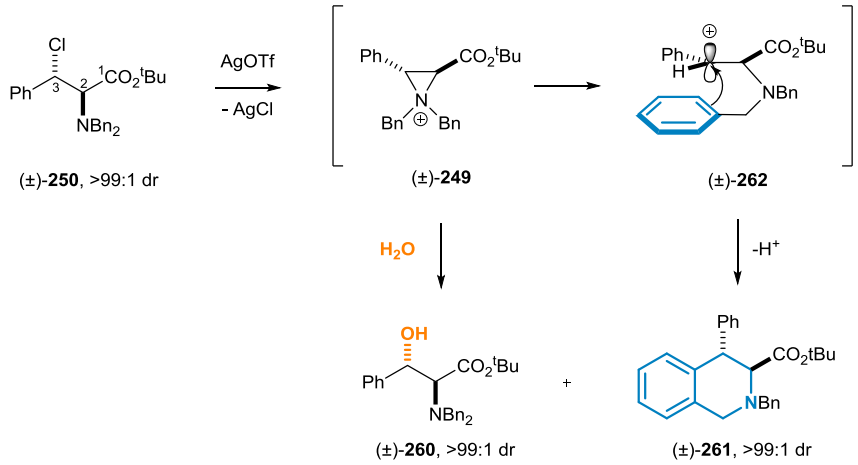


Figure 24. Proposed mechanistic pathway leading to the formation of β-hydroxy-α-amino ester (±)-**260** and tetrahydroisoquinoline (±)-**261**.

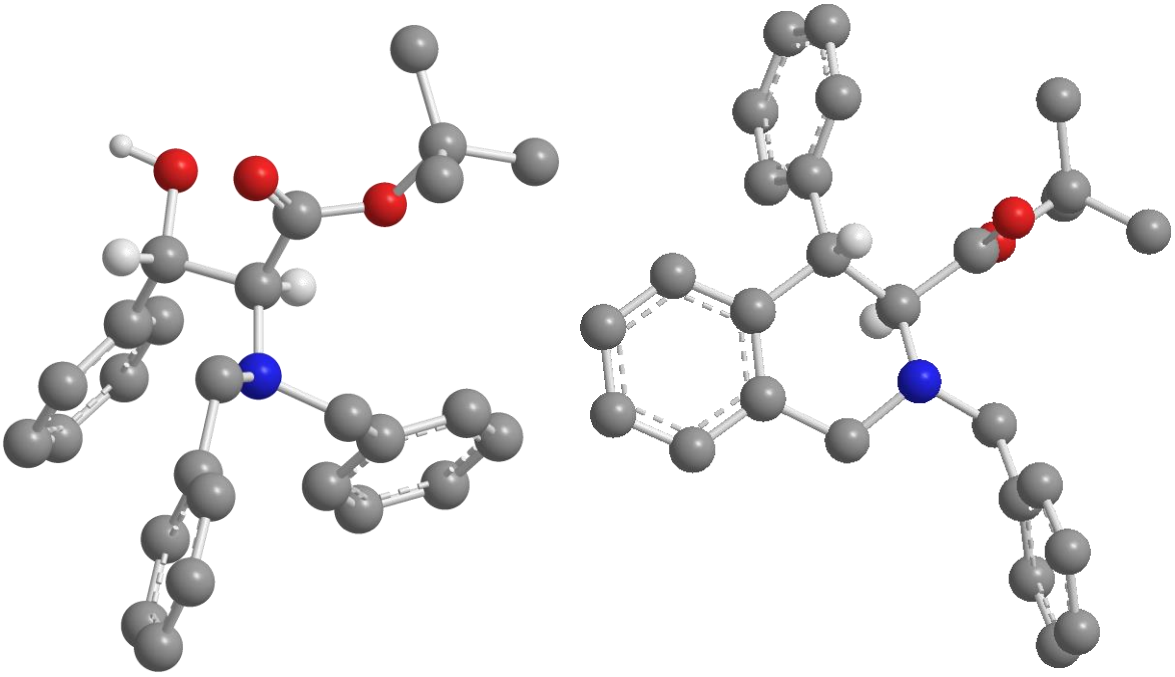
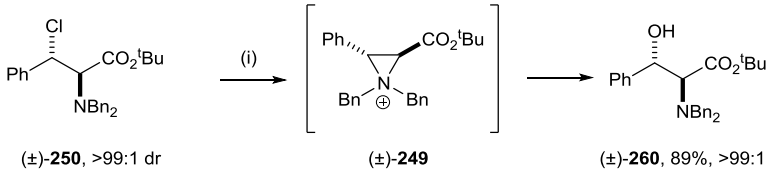


Figure 25. X-ray crystal structures of (*SR*,*SR*)-**260** [*left*] and (*SR*,*SR*)-**261** [*right*] (selected H atoms are omitted for clarity).

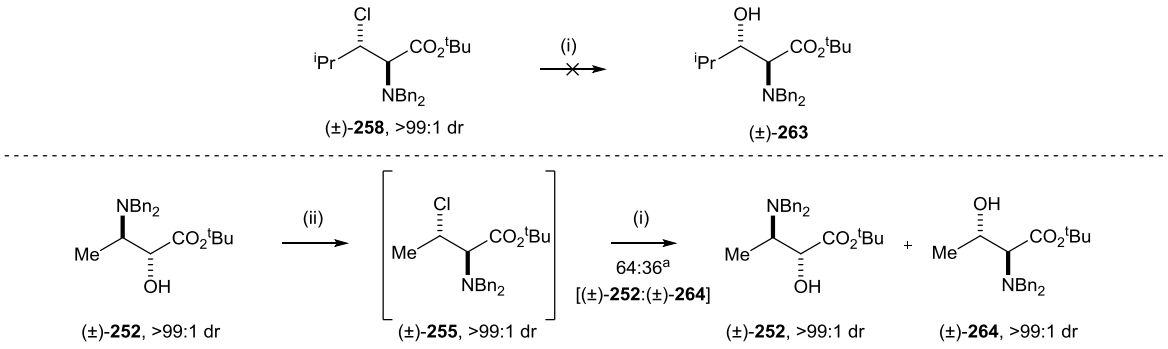
In support of the mechanistic origin of β-hydroxy-α-amino ester (±)-**260**, full conversion of β-chloro-α-amino ester (±)-**250** (>99:1 dr) to β-hydroxy-α-amino ester (±)-**260** was achieved by running the reaction in a mixed EtOAc/H_2O solvent system, which gave (±)-**260** in 89% yield and >99:1 dr (Scheme 42).



Scheme 42. *Reagents and Conditions*: (i) AgOTf, EtOAc/H_2O (4:1), rt, 16 h.

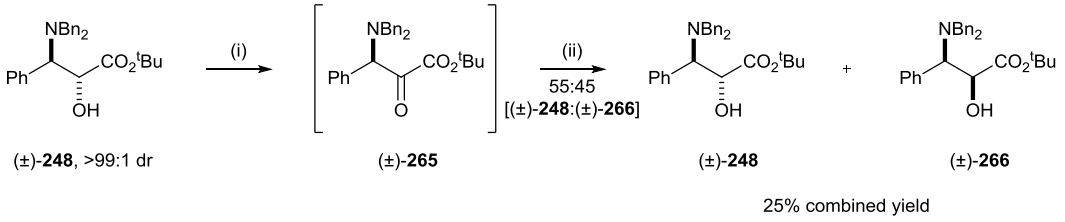
This optimised procedure was subsequently applied to the C(3)-alkyl substituted β-chloro-α-amino esters (±)-**258** and (±)-**255**. Reaction of C(3)-isopropyl substituted β-chloro-α-amino ester (±)-**258** with AgOTf in EtOAc/H_2O gave only returned starting material. β-Chloro-α-

amino ester (±)-**255** was prepared as a single regioisomer via Appel reaction of (±)-**252** and then used immediately, as it was known to rearrange upon standing. Treatment of (±)-**255** with AgOTf in EtOAc/H_2O gave 64% conversion to a 64:36 mixture of α-hydroxy-β-amino ester (±)-**252** and β-hydroxy-α-amino ester (±)-**264**, respectively. As ring-opening is likely to be irreversible under these conditions, this suggests that aziridinium ring-opening is not regioselective with H_2O as the nucleophile. This is likely to be due to decreased stabilisation of the developing positive charge at the C(3)-position in the transition state (relative to the C(3)-phenyl substituted substrate), which leads to competitive attack of the aziridinium intermediate by the nucleophile at the C(2)-position, which would be activated by the adjacent carbonyl group[11] (Scheme 43).



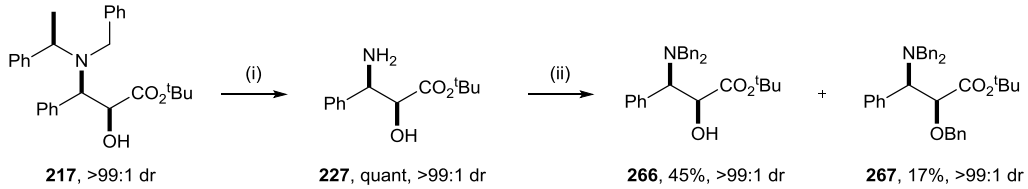
Scheme 43. *Reagents and Conditions*: (i) AgOTf, EtOAc/H_2O (4:1), rt 16 h; (ii) PPh_3, CCl_4, PhMe, 100 °C, 24 h. [a] 64% conversion.

Investigations into the ring-opening reactions of the corresponding *cis*-aziridinium ion in the C(3)-phenyl series were undertaken next, in an effort to confirm that the developed transformation was indeed a stereospecific rather than a stereoselective process. Attempts to synthesise *syn*-**266** began by following the optimised epimerisation procedure developed in Chapter 2: Swern oxidation of (±)-**248** gave α-keto ester (±)-**265**, for which reduction with DIBAL-H proved essentially non-stereoselective, giving an inseparable 55:45 mixture of (±)-*anti*-**248** and (±)-*syn*-**266**, respectively, in 25% combined yield (Scheme 44).



Scheme 44. *Reagents and Conditions*: (i) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 30 min, then Et_3N, −78 °C to rt, 1 h; (ii) DIBAL-H, THF, −20 °C, 2 h.

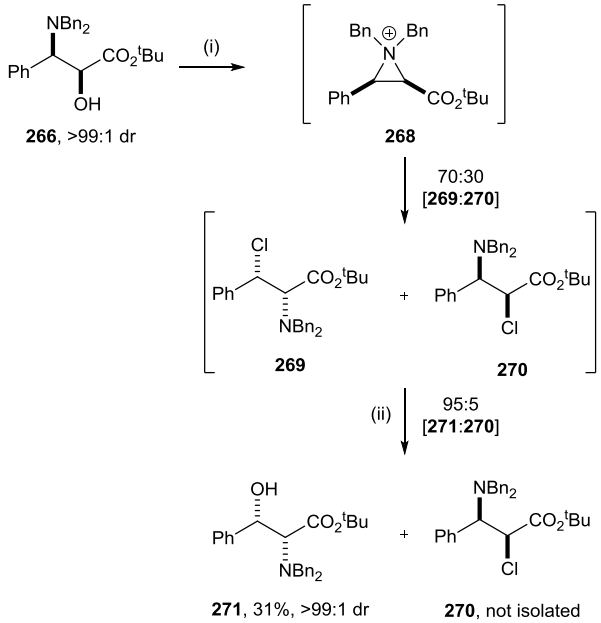
In order to access some material to perform test reactions, *N*,*N*-dibenzyl substituted α-hydroxy-β-amino ester **266** was synthesised from the corresponding enantiopure *N*-benzyl-*N*-(α-methylbenzyl)-substituted analogue **217**. Hydrogenolytic *N*-debenzylation resulted in the formation of **227** in quantitative yield, with subsequent treatment of **227** with BnBr and K_2CO_3 giving *syn*-**266** in 45% yield and >99:1 dr, in addition to **267** in 17% yield and >99:1 dr (Scheme 45).



217, >99:1 dr **227**, quant, >99:1 dr **266**, 45%, >99:1 dr **267**, 17%, >99:1 dr

Scheme 45. *Reagents and Conditions*: (i) $Pd(OH)_2/C$, H_2 (5 atm), MeOH, rt, 24 h; (ii) BnBr, K_2CO_3, MeCN, 80 °C, 24 h.

With a sample of *syn*-**266** in hand, investigations into reaction via the corresponding *cis*-aziridinium ion **268** were undertaken. Reaction of **266** under Appel conditions gave a 70:30 mixture of β-chloro-α-amino ester **269** and α-chloro-β-amino ester **270**. Upon treatment of this mixture with AgOTf in EtOAc/H_2O, a 95:5 mixture of β-hydroxy-α-amino ester **271** and α-chloro-β-amino ester **270** was obtained, from which only **271** was isolated in 31% yield. The regiochemistries of **269**, **270** and **271** were assigned via ^{1}H-^{13}C HMBC analyses and the relative *syn*-configurations within **269** and **271** were tentatively assigned based on ^{1}H NMR spectroscopic analysis, as these data were distinct from those of the corresponding *anti*-β-chloro-α-amino ester **250** and *anti*-β-hydroxy-α-amino ester **260** made previously (Scheme 46). In the case of **271** this assignment was unambiguously confirmed via single crystal X-ray diffraction analysis (Figure 26).[6]



266, >99:1 dr **268** **269** **270** **271**, 31%, >99:1 dr **270**, not isolated

Scheme 46. *Reagents and Conditions*: (i) PPh_3, CCl_4, PhMe, 100 °C, 24 h; (ii) AgOTf, EtOAc/H_2O (4:1), rt, 16 h.

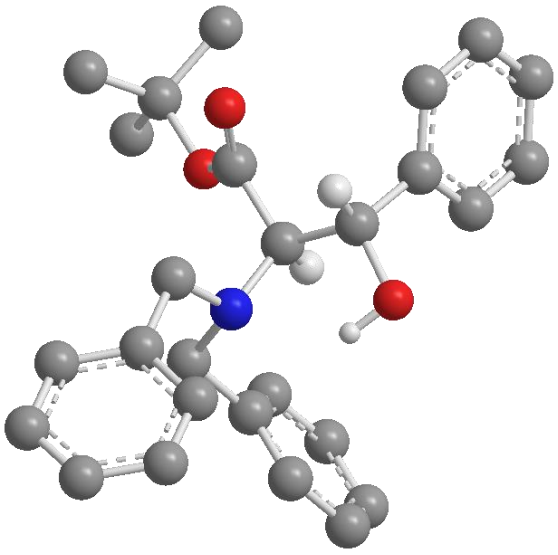
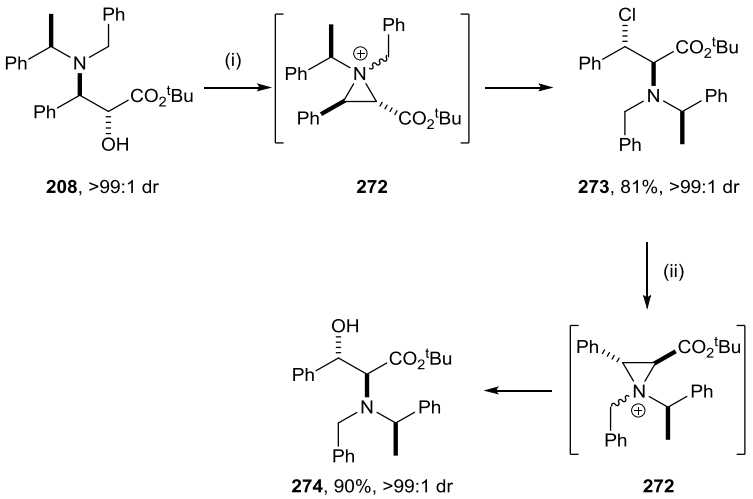


Figure 26. X-ray crystal structure of (2*R*,3*S*)-**271** (selected H atoms are omitted for clarity).

The stereospecific formation of (±)-*anti*-**260** from (±)-**250** and *syn*-**271** from **269** and **270**, as single diastereoisomers in both cases, adds further credence to the proposed involvement of aziridinium intermediates in both the Appel reaction, and in the subsequent reaction of the mixture of β-chloro-α-amino ester **269** and α-chloro-β-amino ester **270** with AgOTf. Furthermore, and significantly, the ring-openings of both (±)-*trans*-**249** and *cis*-**268** with H_2O proceed with complete regioselectivity, rendering this transformation synthetically valuable.

3.1.3. Rearrangement of enantiopure C(3)-aryl substituted α-hydroxy-β-amino esters

With a stereospecific and highly regioselective strategy developed on the model β-phenyl substituted racemic system, work on the corresponding enantiopure substrate began. Reaction of enantiopure α-hydroxy-β-amino ester **208** (>99:1 dr) with MsCl gave β-chloro-α-amino ester **273** as the sole product, which was isolated in 81% yield and >99:1 dr. The regiochemistry was assigned via ^{1}H-^{13}C HMBC analysis and the relative configuration within **273** was unambiguously assigned via single crystal X-ray diffraction analysis, with the absolute (2*R*,3*S*,α*R*)-configuration within **273** assigned relative to the known (*R*)-configuration of the α-methylbenzyl fragment (Figure 27).[6] This provided solid evidence that inversion of configuration at both C(2) and C(3) was involved during the conversion of **208** to **273**. Subsequent activation of **273** with AgOTf in EtOAc/H_2O (4:1) gave conversion to β-hydroxy-α-amino ester **274** exclusively, which was then isolated in 90% yield (>99:1 dr). The stereochemistry within **274** was subsequently established by chemical correlation (*vide infra*) (Scheme 47).



Scheme 47. *Reagents and Conditions*: (i) MsCl, Et_3N, DMAP, CH_2Cl_2, rt, 2 h; (ii) AgOTf, EtOAc/H_2O (4:1), rt, 16 h.

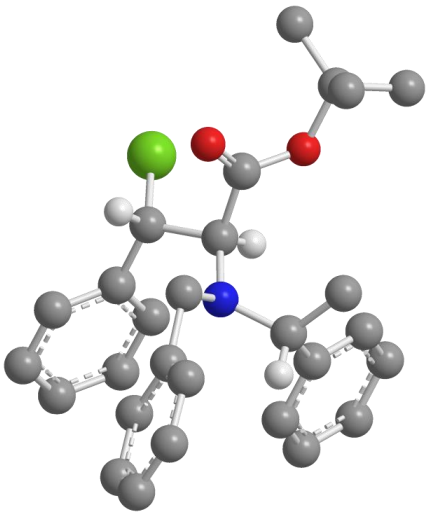


Figure 27. X-ray crystal structure of (2*R*,3*S*,α*R*)-**273** (selected H atoms are omitted for clarity).

3.1.4. Direct conversion of α-hydroxy-β-amino esters to β-hydroxy-α-amino esters

The methodology developed thus far successfully converts C(3)-phenyl substituted α-hydroxy-β-amino esters **208** to β-hydroxy-α-amino esters **274** stereospecifically, and has removed the need for additional protecting group manipulation, when compared to the first generation approach developed in Chapter 2. However, as the transformation was still dependent on the formation and isolation of intermediate β-chloro-α-amino ester **273**, efforts were turned next to improving the efficiency of this overall process by developing a third generation one-pot protocol in which α-hydroxy-β-amino ester **208** could be directly converted to β-hydroxy-α-amino ester **274** (Figure 28).

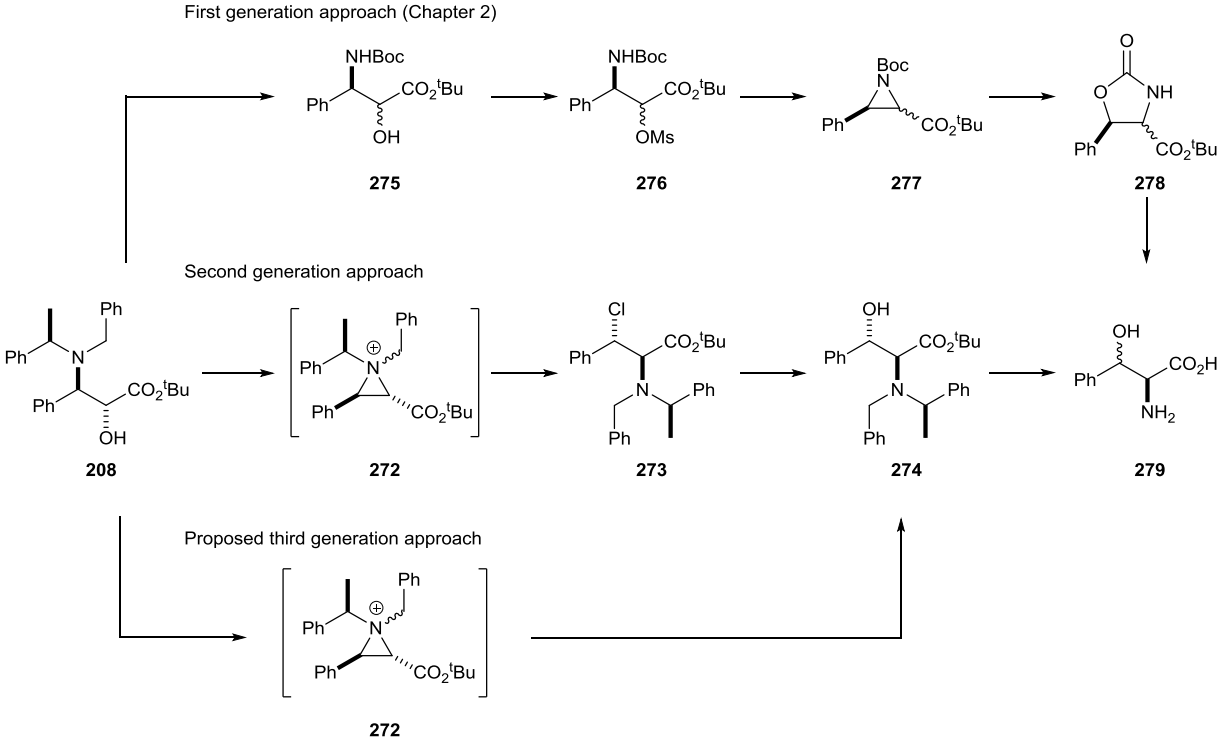
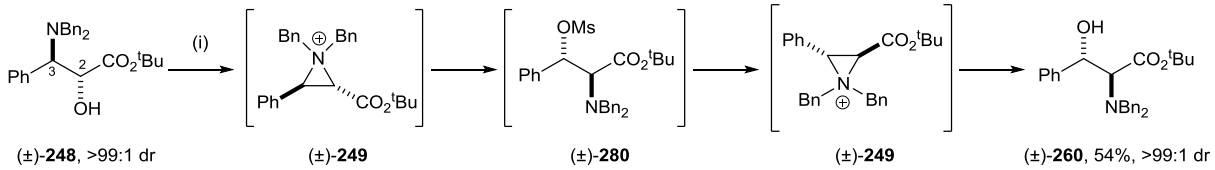


Figure 28. Comparison of current strategy with that developed in Chapter 2 and the proposed one-pot conversion of β-amino-α-hydroxy esters **208** to β-hydroxy-α-amino esters **279**.

Initial investigations with MsCl had indicated that activation of the α-hydroxyl moiety upon mesylation promoted ring-closure through nitrogen to form an aziridinium ion. However, in these cases the chloride counter-ion proved sufficiently nucleophilic to open this intermediate. It was envisaged that Ms_2O may be a suitable reagent to improve the developed methodology, as the mesylate counter ion is known to be less nucleophilic than chloride, thus potentially allowing the development of a procedure in which aziridinium intermediates could be opened *in situ* by alternative nucleophiles. Thus, *N*,*N*-dibenzyl substituted α-hydroxy-β-amino ester (±)-**248** was reacted with Ms_2O and Et_3N in CH_2Cl_2 at rt. After 1 h, H_2O was added, and after a further 1 h the reaction was subjected to work-up and analysed by ^{1}H and ^{13}C NMR

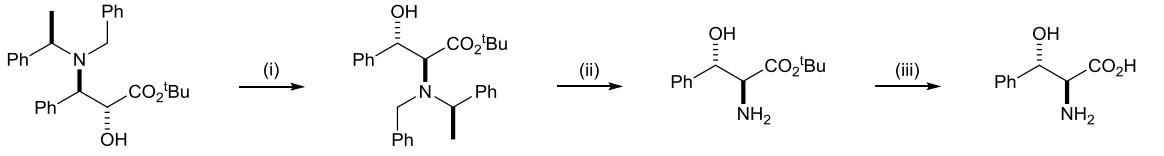
spectroscopy: the sole product observed was β-mesylate (±)-**280**, with the connectivity within (±)-**280** being established by ^{1}H-^{13}C HMBC analysis. Upon subsequent optimisation, it was found that on prolonged stirring of (±)-**280** in the presence of H_2O, it turned over to give β-hydroxy-α-amino ester (±)-**260**, reaching full conversion after a period of 24 h[12] and enabling isolation of (±)-**260** in 54% yield and in >99:1 dr. The spectroscopic data for (±)-**260** from this reaction were in complete agreement with the sample prepared from β-chloro-α-amino ester (±)-**250**, consistent with reaction via aziridinium intermediate (±)-**249** to give overall inversion of configuration at both C(2) and C(3) (Scheme 48).



(±)-**248**, >99:1 dr (±)-**249** (±)-**280** (±)-**249** (±)-**260**, 54%, >99:1 dr

Scheme 48. *Reagents and Conditions*: (i) Ms_2O, Et_3N, CH_2Cl_2, rt, 1 h, then H_2O, rt, 24 h.

Application of this one-pot procedure to enantiopure α-hydroxy-β-amino ester **208** resulted in the exclusive formation of β-hydroxy-α-amino ester **274**, which was isolated in 82% yield and >99:1 dr. This saw an improved efficiency over the two step approach via β-chloro-α-amino ester **273**, and also an improvement in yield from 73% over the two steps, to 82% for this single step. Deprotection of β-hydroxy-α-amino ester **274** was achieved in a two-step sequence under standard conditions: hydrogenolysis of **274** gave **281** in 71% yield and >99:1 dr, with subsequent hydrolysis of **281** affording (+)-(*S*,*S*)-β-hydroxyphenylalanine *ent*-**184** {mp 183–188 °C (dec.); $[\alpha]_D^{20}$ +1.9 (*c* 1.0 in H_2O); lit.[13] mp 174 °C (dec.); lit.[14] $[\alpha]_D^{20}$ −4.3 (*c* 1.1 in H_2O)} in quantitative yield and 96:4 dr, thereby confirming the assigned configurations within **274** and **281** (Scheme 49).



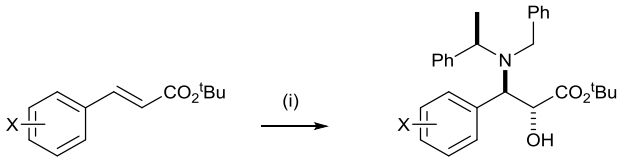
208, >99:1 dr **274**, 82%, >99:1 dr **281**, 71%, >99:1 dr *ent*-**184**, quant, 96:4 dr

Scheme 49. *Reagents and Conditions*: (i) Ms_2O, Et_3N, CH_2Cl_2, rt, 1 h, then H_2O, rt 24 h; (ii) H_2 (5 atm), $Pd(OH)_2$/C, MeOH, rt, 18 h; (iii) 6.0 M aq HCl, 90 °C, 18 h, , then DOWEX-50WX8 ion-exchange resin.

3.1.5. α-Hydroxy-β-amino esters to β-hydroxy-α-amino esters: substrate scope

Attention turned to probing the substrate scope of this methodology, with a particular emphasis on varying the substitutents around the C(3)-aryl ring to evaluate the impact of electronic perturbations on the reactivity of the aziridinium intermediate. This was achieved by selecting a series of aryl-substituted *tert*-butyl cinnamates **282**–**286**[15] with substitution patterns that ranged from highly electron withdrawing (e.g. X = *p*-CF_3) to highly electron

donating (e.g. X = *p*-OMe), with this parameter quantified by the Brown-Okamoto constant, σ^+, which is based on the solvolysis rates of the corresponding substituted *tert*-cumyl chlorides. [16] Thus, conjugate addition of lithium amide (*R*)-**201** to α,β-unsaturated esters **282**–**286**, with *in situ* oxidation of the intermediate lithium (*Z*)-β-amino enolates[2] with (−)-CSO **202**, gave α-hydroxy-β-amino esters **287**–**291** in 67–85% yield and >99:1 dr in each case. The 2,3-*anti*-configurations within **287**–**291** were assigned based on the established stereochemical outcome of the aminohydroxylation reaction.[17] These assignments were supported by $^3J_{2,3}$ coupling constant analysis, with the magnitude of the $^3J_{2,3}$ coupling constants falling within the expected range for *anti*-configured α-hydroxy-β-amino esters ($^3J_{2,3}$ = 2–4.5 Hz)[3] in all cases (Scheme 50).



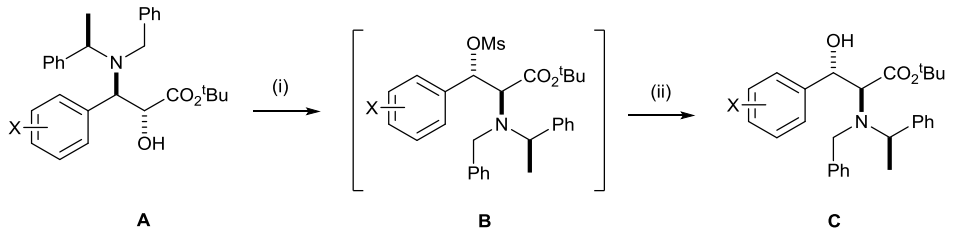
282-286, >99:1 dr **287-291**, >99:1 dr

	X	σ^+	dr		yield
282	*p*-CF_3	+0.61	>99:1	**287**	67%
283	*m*-F	+0.35	>99:1	**288**	82%
284	*m*-OMe	+0.05	>99:1	**289**	75%
285	*p*-F	-0.07	>99:1	**290**	82%
286	*p*-OMe	-0.78	>99:1	**291**	85%

Scheme 50. *Reagents and Conditions*: (i) (*R*)-**205**, BuLi, THF, −78 °C, 2 h, then **202**, −78 °C to rt, 18 h.

The application of the optimised one-pot rearrangement procedure was undertaken next. Under standard reaction conditions both the moderately electron poor substrate **289** (X = *m*-OMe) and the moderately electron rich substrate **290** (X = *p*-F) gave complete conversion to β-hydroxy-α-amino esters **298** and **299**, respectively, which were isolated in 64 and 80% yield, and >99:1 dr in both cases. For the more electron poor substrate **288** (X = *m*-F) and highly electron poor substrate **287** (X = *p*-CF_3), complete conversion of the intermediate mesylates **293** and **292** to the corresponding β-hydroxy-α-amino esters **297** and **296** was not observed after stirring in the presence of H_2O for 24 h. Instead, a 77:23 mixture of **297** and **293**, respectively, was recovered from the reaction of **288** (X = *m*-F) and a 31:69 mixture of **296** and **292** was observed upon reaction of **287** (X = *p*-CF_3). Heating the reaction mixture at reflux for 24 h after the addition of H_2O resulted in complete conversion of **293** to **297**, which was isolated in 88% yield and >99:1 dr; however, application of this alternative protocol to **287** (X = *p*-CF_3) gave only an 85:15 ratio of **296** and **292**, respectively. Full

conversion to **296** was finally achieved upon heating the reaction mixture at reflux for 48 h, after which **296** was isolated in 64% yield and in >99:1 dr (Scheme 51).



A **B** **C**

X	A	time (i)	temperature (ii)	time (ii)	B	C	product ratio B:C	yield
		1 h	rt	24 h			69:31	-
p-CF_3	**287**	1 h	40 °C	24 h	**292**	**296**	15:85	61%
		1 h	40 °C	48 h			0:100	64%
m-F	**288**	1 h	rt	24 h	**293**	**297**	23:77	-
		1 h	40 °C	24 h			0:100	88%
m-OMe	**289**	1 h	rt	24 h	**294**	**298**	0:100	69%
p-F	**290**	1 h	rt	24 h	**295**	**299**	0:100	80%

Scheme 51. *Reagents and Conditions*: (i) Ms_2O, Et_3N, CH_2Cl_2, rt, time: see table, then (ii) H_2O, temperature and time: see table.

Single crystal X-ray diffraction analysis of the *p*-fluorophenyl substituted β-hydroxy-α-amino ester **299** allowed the relative configuration within **299** to be determined unambiguously (Figure 29);[6] the absolute (2*S*,3*S*,α*R*)-configuration within **299** was then assigned by reference to the known (*R*)-configuration of the α-methylbenzyl fragment, and the configurations within **296**–**298** were assigned by analogy. The confirmation that formation of **299** from **290** had occurred with inversion of configuration at both the C(2) and C(3) stereogenic centres again provided strong evidence for the involvement of an aziridinium intermediate in this reaction.

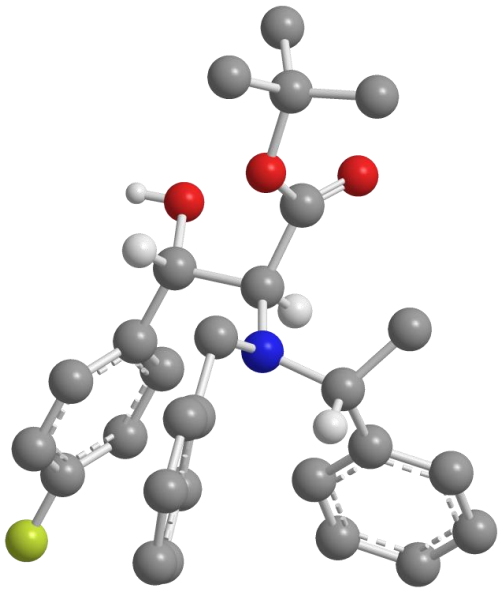
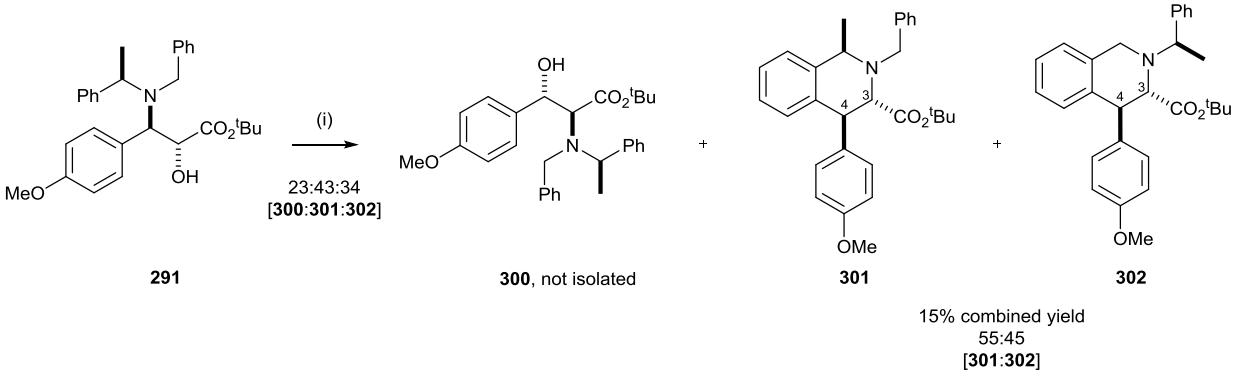


Figure 29. X-ray crystal structure of (2*S*,3*S*,α*R*)-**299** (selected H atoms are omitted for clarity).

The introduction of a highly electron donating substituent (X = *p*-OMe) had a dramatically different effect on the rearrangement reaction. Under standard reaction conditions, **291** was converted to a 23:43:34 mixture of β-hydroxy-α-amino ester **300** and the regioisomeric tetrahydroisoquinolines **301** and **302**, respectively. The relative 3,4-*anti*-configurations within tetrahydroisoquinolines **301** and **302** were assigned based on ^{1}H NMR ^{3}J coupling constant analyses:[10] for 3,4-*anti*-tetrahydroisoquinolines, $^{3}J_{2,3}$ = 1.5–4 Hz is usually observed, whereas $^{3}J_{2,3}$ = 5.5–6 Hz is indicative of 3,4-*syn*-tetrahydroisoquinolines. With $^{3}J_{2,3}$ = 3.7 Hz and $^{3}J_{2,3}$ = 2.4 Hz for **301** and **302**, respectively, a relative 3,4-*anti*-configuration within each was tentatively assigned (Scheme 52).



Scheme 52. *Reagents and Conditions*: (i) Ms_2O, Et_3N, CH_2Cl_2, rt, 1 h, then H_2O, rt, 24 h.

It was postulated that the formation of tetrahydroisoquinolines **301** and **302** was the result of reaction through a carbocationic intermediate **304**, analogous to the outcome observed upon treatment of β-chloro-α-amino ester **250** with AgOTf (*vide supra*). Cyclisation through either the *N*-(α-methylbenzyl) or the *N*-benzyl fragment would give rise to **301** or **302**, respectively. It was proposed that this competing side reaction is significant for **291** (X = *p*-OMe) because the mesomerically electron donating influence of the *p*-OMe group is able to assist with the ring-opening of aziridinium **303**, sufficiently stabilising the resultant carbocation **304** under these reaction conditions (Figure 30).

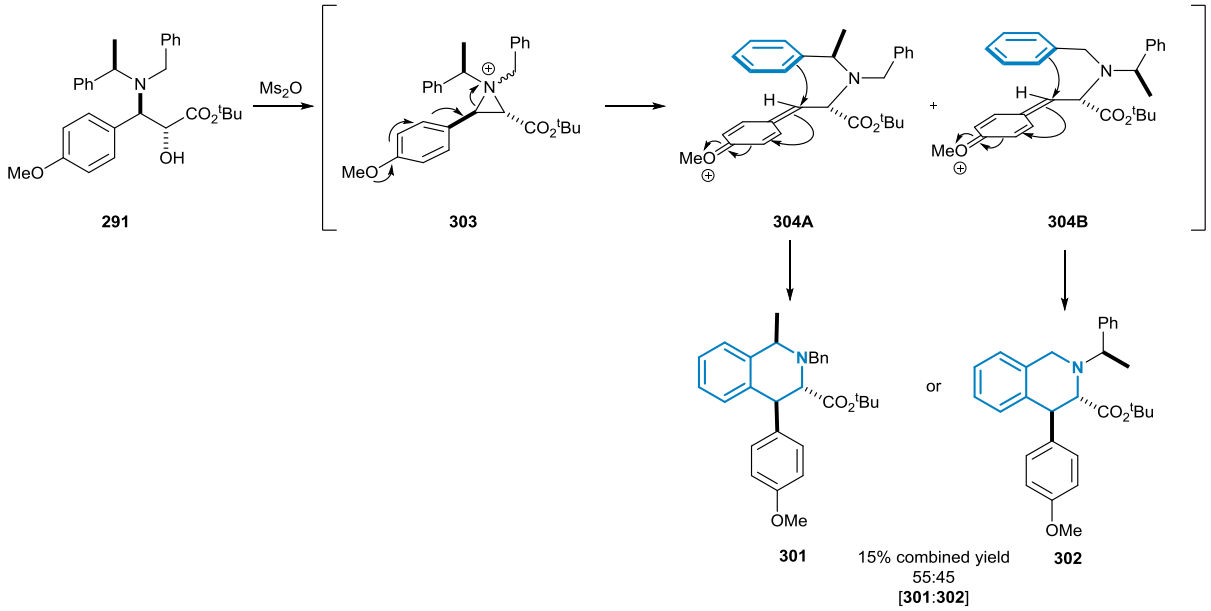
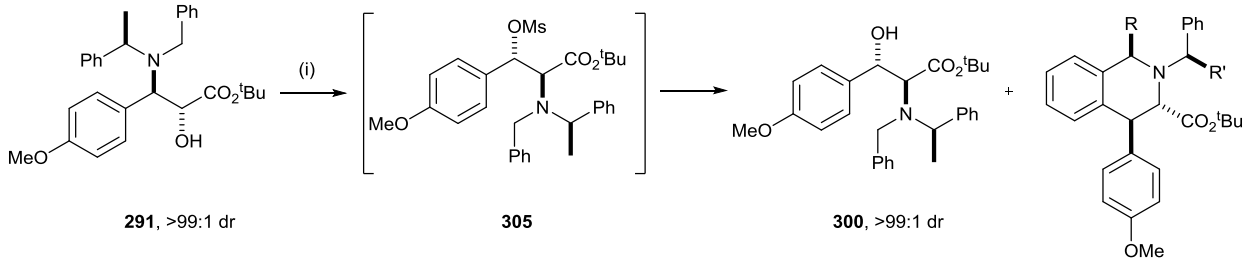


Figure 30. Proposed origin of the tetrahydroisoquinoline side products **301** and **302**.

Studies into improving the ratio of β-hydroxy-α-amino ester **300** to tetrahydroisoquinolines **301** and **302** formed in this reaction were next undertaken. It was found that reducing the time between additions of Ms_2O and H_2O successfully reduced the proportion of tetrahydroisoquinoline products: if H_2O was added after 1 min, and followed by stirring for 24 h, a 7:83:10 mixture of β-mesylate-α-amino ester **305**, β-hydroxy-α-amino ester **300** and tetrahydroisoquinolines [**301** + **302**] was recovered, from which **300** was isolated in 55% yield and >99:1 dr (Scheme 53).

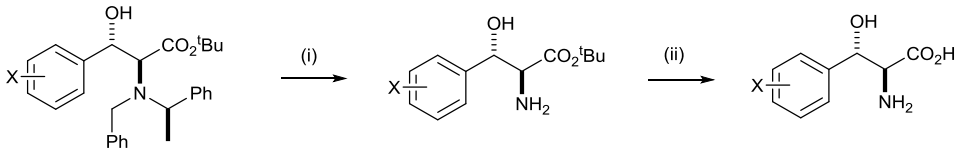


time	product ratio 305:300:[301+302]	yield 300
1 h	0:23:77	-
30 min	6:64:30	-
5 min	7:78:15	40%
1 min	7:83:10	55%

Scheme 53. *Reagents and Conditions*: (i) Ms_2O, Et_3N, CH_2Cl_2, rt, time: see table, then H_2O, rt, 24 h.

With optimised routes to a range of C(3)-aryl β-hydroxy-α-amino esters **296**–**300** in hand, deprotection to their corresponding amino acids **311**–**315** was undertaken next. Under optimised conditions hydrogenolytic *N*-debenzylation of **296**–**300** gave **306**–**310** in 80% to quantitative yield and subsequent hydrolysis afforded β-hydroxy-α-amino acids **311**–**315** in 62% to quantitative yield and ≥92:8 dr. The syntheses of these unnatural amino acids were achieved in 4 steps from commercially available starting materials, with overall yields ranging

from 29–53%. This has demonstrated the capability to access a wide range of C(3)-aryl substituted β-hydroxy-α-amino acids via this route, which shows good tolerance to differing substitution patterns and extremes of electron density (Scheme 54).



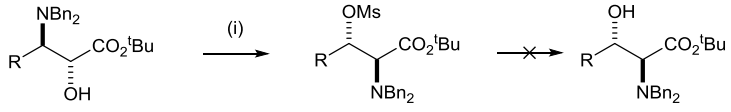
296-300, >99:1 dr **306-310**, >99:1 dr **311-315**

X	time (i)	product	yield	time (ii)	product	yield	dr	overall yield
p-CF_3 [**296**]	24 h	**306**	80%	6 h	**311**	quant	92:8	34%
m-F [**297**]	48 h	**307**	quant	3 h	**312**	74%	93:7	53%
m-OMe [**298**]	24 h	**308**	quant	3 h	**313**	80%	93:7	41%
p-F [**299**]	24 h	**309**	81%	6 h	**314**	quant	97:3	53%
p-OMe [**300**]	24 h	**310**	quant	3 h	**315**	62%	93:7	29%

Scheme 54. *Reagents and Conditions*: (i) H_2 (5 atm), $Pd(OH)_2/C$, rt, time: see table; (ii) 6.0 M aq HCl, rt, time: see table, then DOWEX-50WX8 ion-exchange resin.

3.1.6. Synthesis of C(3)-alkyl substituted β-hydroxy-α-amino acids

With the successful application of the developed methodology to the synthesis of a range of C(3)-aryl substituted β-hydroxy-α-amino acids, attention was next turned to the C(3)-alkyl substituted analogues. The racemic model system was first revisited to test the one-pot protocol: α-hydroxy-β-amino esters (±)-**252** (R = Me) and (±)-**253** (R = ^{i}Pr) were reacted with Ms_2O for 1 h, H_2O was then added and the resultant mixture was stirred for an additional 24 h. This procedure failed to yield β-hydroxy-α-amino esters (±)-**264** or (±)-**263**, instead resulting in 90% conversion to β-mesylate-α-amino ester (±)-**316** (R = Me) and 60% conversion to β-mesylate-α-amino ester (±)-**317** (R = ^{i}Pr), respectively. The regiochemistries within (±)-**316** and (±)-**317** were assigned via ^{1}H-^{13}C HMBC analyses, and the relative *anti*-stereochemistry within each was tentatively assigned based on assumption of reaction via an aziridinium intermediate, as had been observed in previous studies (Scheme 55).

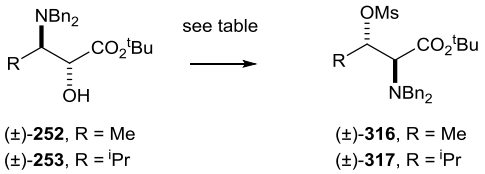


(±)-**252**, R = Me, >99:1 dr
(±)-**253**, R = ^{i}Pr, >99:1 dr
(±)-**316**, 90% conversion
(±)-**317**, 60% conversion
(±)-**264**
(±)-**263**

Scheme 55. *Reagents and Conditions*: (i) Ms_2O, Et_3N, CH_2Cl_2, rt, 1 h, then H_2O, rt, 24 h.

In the first instance, steps were taken to improve conversion to β-mesylate-α-amino esters (±)-**316** and (±)-**317**. For (±)-**252** (R = Me) reaction with Ms_2O for 2 h, followed by addition

of water and stirring for an additional 24 h, resulted in an improved 92% conversion to (±)-**316**, which was isolated in 38% yield and >99:1 dr. For (±)-**253** (R = ^{i}Pr), increasing the equivalents of Ms_2O and Et_3N to 6.0 and 9.0, respectively, gave 88% conversion to β-mesylate-α-amino ester (±)-**317**, enabling isolation of (±)-**317** in 22% yield. The relatively low yields of (±)-**316** and (±)-**317** were attributed to poor stability to column chromatography (Scheme 56).



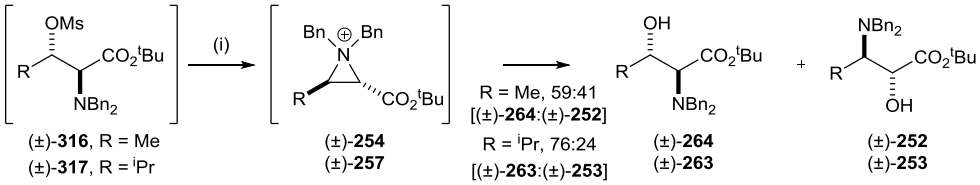
(±)-**252**, R = Me
(±)-**253**, R = ^{i}Pr

(±)-**316**, R = Me
(±)-**317**, R = ^{i}Pr

R	equiv Ms_2O	equiv Et_3N	temperature	time	conversion	yield mesylate
Me	3	4.5	rt	2 h, then 24 h	92%	38%
^{i}Pr	3	4.5	rt	1 h, then 24 h	60%	-
	6	9	rt	1 h, then 24 h	88%	22%

Scheme 56. *Reagents and Conditions*: (i) Ms_2O, Et_3N, CH_2Cl_2, rt, time: see table, then H_2O, rt, 24 h.

Attempts were made to convert β-mesylate-α-amino esters (±)-**316** and (±)-**317** into β-hydroxy-α-amino esters (±)-**264** and (±)-**263** by heating in H_2O/MeCN (1:1); however, a 59:41 ratio of β-hydroxy-α-amino ester (±)-**264** and α-hydroxy-β-amino ester (±)-**252**, respectively, and a 76:24 ratio of β-hydroxy-α-amino ester (±)-**263** and α-hydroxy-β-amino ester (±)-**253** was recovered. These results are consistent with reaction via the corresponding aziridinium intermediate, which undergoes ring-opening with poor regioselectivity (Scheme 57).



(±)-**316**, R = Me
(±)-**317**, R = ^{i}Pr

(±)-**254**
(±)-**257**

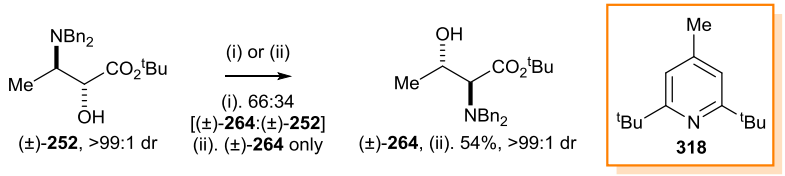
R = Me, 59:41 [(±)-**264**:(±)-**252**]
R = ^{i}Pr, 76:24 [(±)-**263**:(±)-**253**]

(±)-**264**
(±)-**263**

(±)-**252**
(±)-**253**

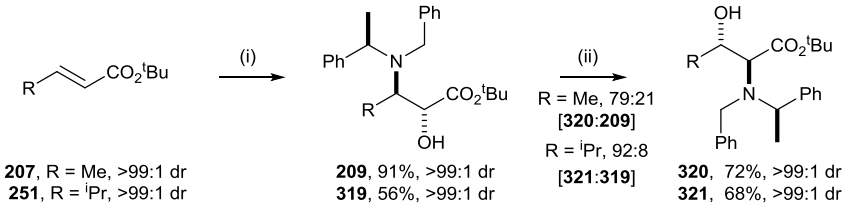
Scheme 57. *Reagents and Conditions*: (i) H_2O/MeCN (1:1), 50 °C, 15 h.

Tf_2O was next trialled as an alternative activating agent. Upon reaction with (±)-**252** in the presence of Et_3N, a 66:34 regioisomeric mixture of β-hydroxy-α-amino ester (±)-**264** and α-hydroxy-β-amino ester (±)-**252** was recovered, again consistent with poor regioselectivity of the aziridinium ring-opening reaction. This result was drastically improved when 2,6-di-*tert*-butyl-4-methylpyridine **318** was used as the base,[18] giving full conversion to (±)-**264**, which was isolated in 54% yield and >99:1 dr (Scheme 58).



Scheme 58. *Reagents and Conditions*: (i) Tf_2O, Et_3N, CH_2Cl_2, 0 °C to rt, 3 h, then H_2O, rt, 24 h; (ii) Tf_2O, **318**, CH_2Cl_2, 0 °C to rt, 6 h, then H_2O, rt, 24 h.

Reaction of Tf_2O and **318** with enantiopure α-hydroxy-β-amino esters **209** (R = Me) and **319** (R = ^{i}Pr) was tried next. Preparation of **209** and **319** was achieved via conjugate addition of lithium amide (*R*)-**201** to **207** and **251**, with *in situ* oxidation of the intermediate lithium (*Z*)-β-amino enolates[2] by (–)-CSO **202**. Subsequent treatment of **209** (R = Me) with Tf_2O gave a 79:21 ratio of β-hydroxy-α-amino ester **320** and α-hydroxy-β-amino ester **209**, from which **320** was isolated in 72% yield and >99:1 dr. For **319** (R = ^{i}Pr), a 92:8 ratio of β-hydroxy-α-amino ester **321** and α-hydroxy-β-amino ester **319** resulted, enabling isolation of **321** in 68% yield and >99:1 dr (Scheme 59). The relative configuration within **321** (R = ^{i}Pr) was determined unambiguously via single crystal X-ray diffraction analysis (Figure 31),[6] and the absolute (2*S*,3*S*,α*R*)-configuration within **321** was assigned by reference to the known (*R*)-configuration of the α-methylbenzyl fragment; the configuration within **320** (R = Me) was then assigned by analogy.



Scheme 59. *Reagents and Conditions*: (i) (*R*)-**205**, BuLi, THF, −78 °C, 2 h, then (−)-CSO **202**, −78 °C to rt, 18 h; (ii) Tf_2O, **318**, CH_2Cl_2, 0 °C to rt, 6 h, then H_2O, rt, 24 h.

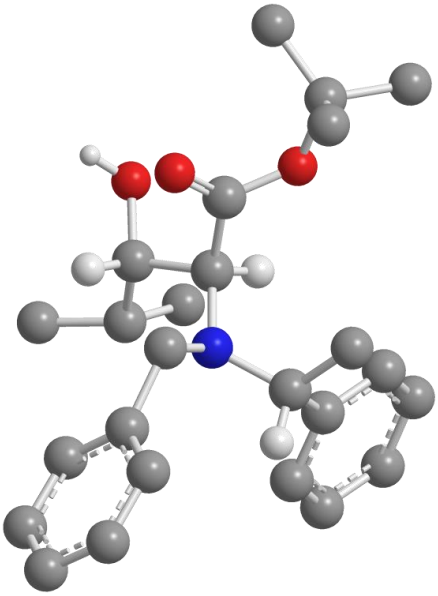
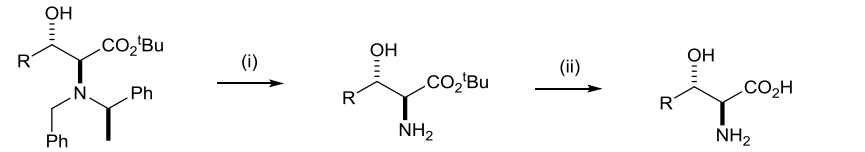


Figure 31. X-ray crystal structure of (2*S*,3*S*,α*R*)-**321** (selected H atoms are omitted for clarity).

Subsequent deprotection of both **320** and **321** via hydrogenolysis gave **322** and **323** in 71% and quantitative yield, respectively, as single diastereoisomers (>99:1 dr) in each case. Hydrolysis of **322** and **323** resulted in (+)-(*S*,*S*)-*allo*-threonine *ent*-**64** in 64% yield and 97:3 dr, and (+)-(*S*,*S*)-β-hydroxyleucine **324** in 69% yield and 96:4 dr, respectively (Scheme 60). The spectroscopic data, including specific rotations, for the samples of (*S*,*S*)-*ent*-**64** {mp 215–225 °C (dec.); $[\alpha]_D^{20}$+7.6 (*c* 1.0 in H_2O); lit.[19] mp 264–266 °C (dec.); lit.[19] $[\alpha]_D^{20}$ +8 (*c* 1.1 in H_2O)} and (*S*,*S*)-**324** {mp 220–226 °C (dec.); $[\alpha]_D^{20}$+17.6 (*c* 1.0 in H_2O); lit.[19] mp 187 °C (dec.); lit.[19] $[\alpha]_D^{25}$ +20 (*c* 1.1 in H_2O)} were in good agreement with literature values, thereby confirming the assigned configurations within **322**–**320**.



320, R = Me, >99:1 dr
321, R = ^{i}Pr, >99:1 dr

322, R = Me, 71%, >99:1 dr
323, R = ^{i}Pr, quant, >99:1 dr

ent-**64**, R = Me, 64%, 97:3 dr
324, R = ^{i}Pr, 69%, 94:6 dr

Scheme 60. *Reagents and Conditions*: (i) H_2 (5 atm), $Pd(OH)_2$/C, rt, 24 h; (ii) 6.0 M aq HCl, rt, 3 h, then DOWEX-50WX8 ion-exchange resin.

3.2. Conclusion

An efficient, one-pot method for the conversion of β-amino-α-hydroxy esters to β-hydroxy-α-amino esters has been developed which proceeds via the regioselective and stereospecific ring-opening of an aziridinium intermediate. Application of the methodology to synthesis of a wide range of β-hydroxy-α-amino acids has been undertaken, including those with both aryl and alkyl substitution (Figure 32).

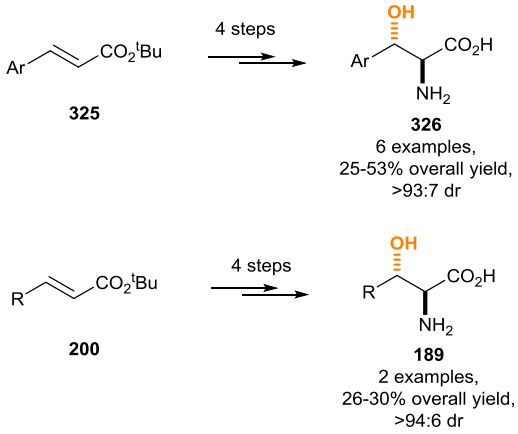


Figure 32. Asymmetric synthesis of β-hydroxy-α-amino acids from commercially available starting materials.

3.3. References and notes

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[9] From here on in this thesis "tetrahydroisoquinoline" will refer to "1,2,3,4-tetrahydroisoquinoline".
[10] For *anti*-tetrahydroisoquinolines, ^3J = 1.5–4 is usually observed whereas ^3J = 5.5–6 is indicative of *syn*-tetrahydroisoquinolines: (a) Brozda, D.; Koroniak, L.; Rozwadowska, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 3017. (b) Chen, W.; Cui, J.; Zhu, Y.; Hu, X.; Mo, W. *J. Org. Chem.* **2012**, *77*, 1585. (c) Hammad, S. F.; Smith, F. T. *J. Heterocyclic Chem.* **2013**, *50*, 114.
[11] See 1 (a) and 4 (d).
[12] The analogous reaction was also attempted using MsCl as the activating agent: α-hydroxy-β-amino ester **248** was reacted with MsCl in the presence of Et_3N and DMAP in CH_2Cl_2 at rt for 2 h. H_2O was then added and the resultant mixture was stirred at rt for 24 h, which upon work up yielded β-chloro-α-amino ester **250** exclusively.
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Chapter 4: β-Fluoro-α-amino acids via aziridinium intermediates

This chapter describes studies concerning the conversion of α-hydroxy-β-amino esters **240** into β-fluoro-α-amino acids **327** via ring-opening of an aziridinium intermediate **241** (Figure 33). Extension of the methodology to effect regioselective aziridinium ring-opening with azide and acetate nucleophiles will also be discussed.

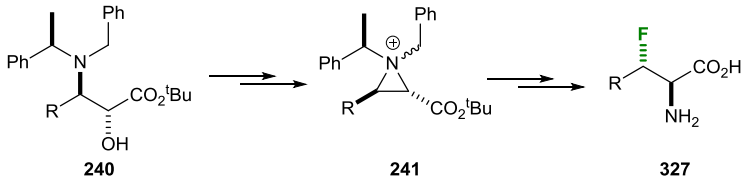
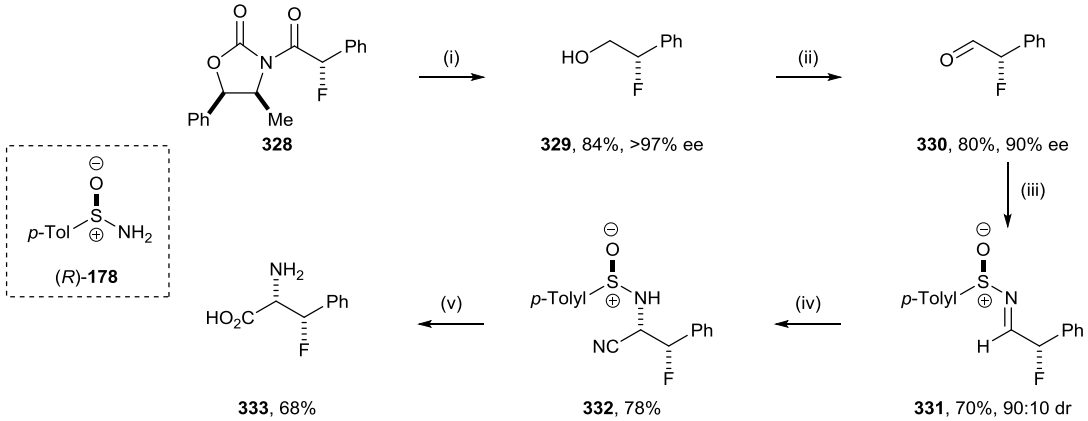


Figure 33. β-Fluoro-α-amino acids **327** from α-hydroxy-β-amino esters **240** via an aziridinium intermediate **241**.

4.1. Fluorinated amino acids

The incorporation of fluorine is known to dramatically alter the biological properties of organic molecules in many cases, and fluorination has become an established strategy for modifying lead compounds in medicinal chemistry.[1] Fluorinated amino acids have attracted significant attention in recent years, with many studies focussing on their incorporation into synthetic proteins and the resulting impact this may have on stability and secondary structure.[2] This has justified numerous synthetic efforts targeting fluorinated amino acids,[3] with approaches ranging from aziridine ring-opening by fluoride[4] to metal catalysed cross couplings.[5] For example, Davis *et al.* have made both diastereoisomers of fluorophenylalanine using a sulfinimine-mediated asymmetric Strecker reaction.[6] Coupling chiral sulfinamide (*R*)-**178** with α-fluoro aldehyde **330** (90% ee) gave sulfinimine **331** in 70% yield and 90:10 dr. Addition of cyanide to **331** gave **332** in 78% yield, and subsequent hydrolysis gave (*S*,*S*)-*syn*-β-fluorophenylalanine **333** in 68% yield (Scheme 61). The corresponding *anti*-diastereoisomer was accessed from *ent*-**330**.



Scheme 61. *Reagents and Conditions:* (i) $LiBH_4$, THF, 0 °C, 3 h; (ii) Dess-Martin periodine, CH_2Cl_2, rt, 7 min; (iii) (*R*)-**178**, 4 Å MS, CH_2Cl_2, rt, 8 h; (iv) Et_2AlCN, ^iPrOH, THF, −78 °C to rt, 12 h; (v) 6.0 M aq. HCl, reflux, 5 h then ^iPrOH, propylene oxide, rt, 6 h.

Deoxofluorinating reagents provide a convenient method of converting an alcohol to a fluoride moiety (Figure 34). These reagents have found application in the synthesis of fluorinated amino acids, both in direct substitution of alcohols and via rearrangements of amino alcohols.

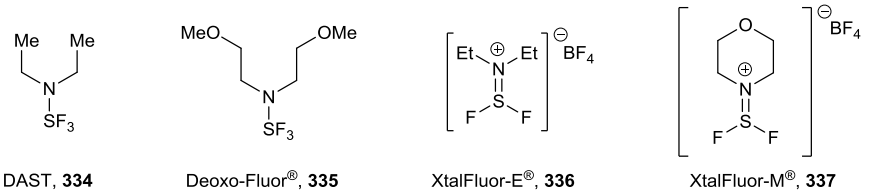
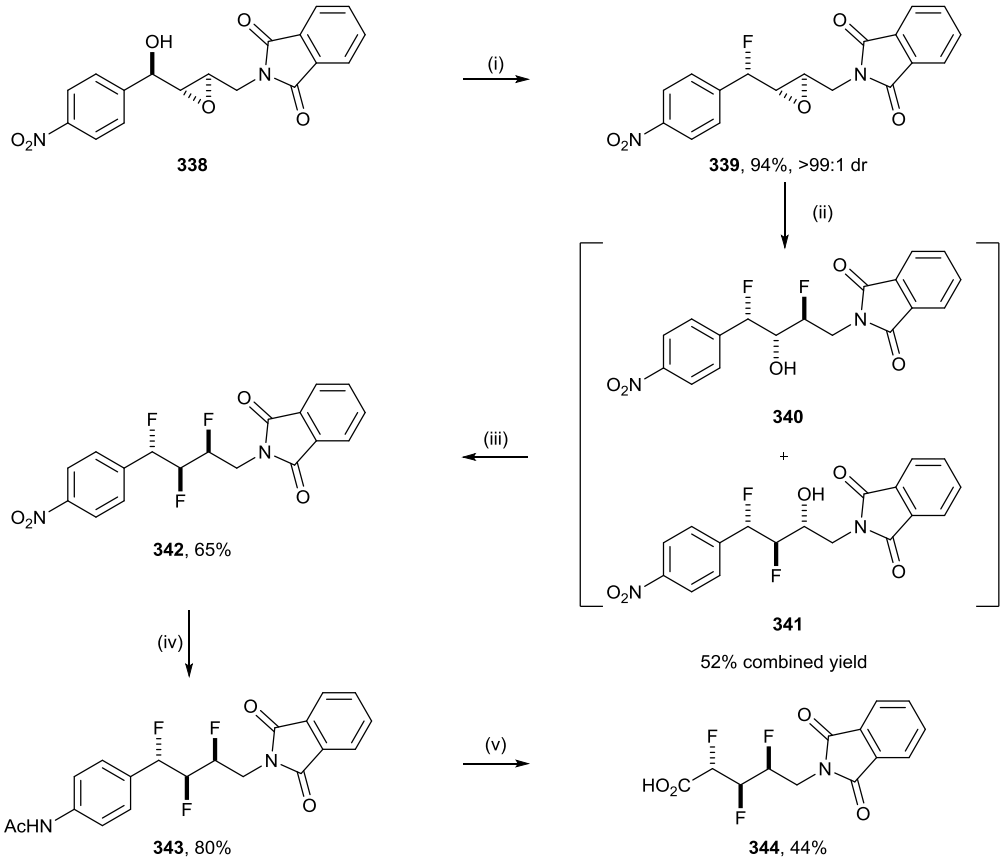


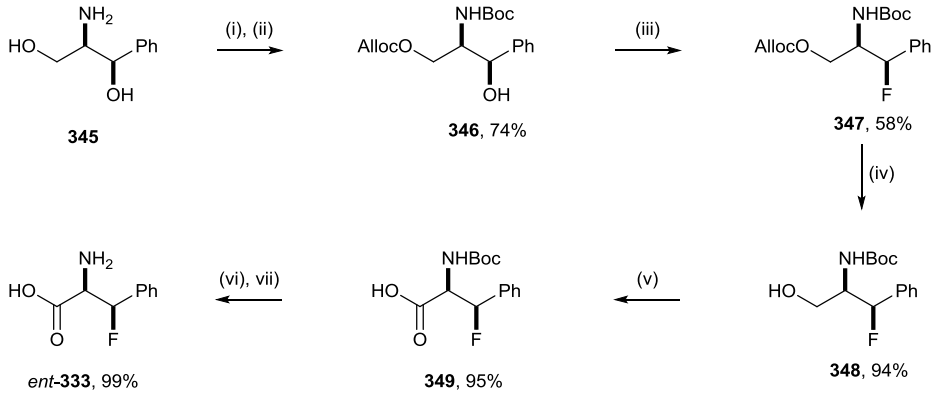
Figure 34. Commercially available deoxofluorinating agents **334**–**337**.

Hunter and co-workers have reported a synthesis of a protected α,β,γ-trifluoro-δ-aminopentanoic acid **344**, in which the three contiguous fluoride substituents are introduced stereospecifically.[7] Treatment of alcohol **338** with Deoxo-Fluor® **335** gave **339** as a single diastereoisomer which was isolated in 94% yield. Subsequent epoxide ring-opening with $Et_3N{\cdot}3HF$ gave a mixture of regioisomers **340** and **341**, which were isolated in 52% combined yield. Treatment of the regioisomeric mixture with neat Deoxo-Fluor® **335** caused both isomers to converge on a single product, giving **342** in 65% yield. Subsequent hydrogenolytic reduction of **342** in the presence of Ac_2O and oxidation of the aryl moiety within **343** gave **344** in 35% yield over the two steps (Scheme 62).



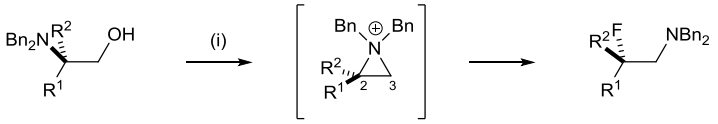
Scheme 62. *Reagents and Conditions*: (i) Deoxo-Fluor® **335**, TMS-morpholine, CH_2Cl_2, reflux, 19 h; (ii) $Et_3N{\cdot}3HF$, microwave, 150 °C, 15 min; (iii) Deoxo-Fluor® **335**, 70 °C, 19 h; (iv) H_2 (1 atm), Pd/C, Ac_2O, rt, 5 h; (v) $NaIO_4$, $RuCl_3$, H_2O, CH_2Cl_2, MeCN, rt, 5 days.

Okuda *et al.* have reported a synthesis of (*R*,*R*)-*syn*-β-fluorophenylalanine *ent*-**333** from commercially available amino diol **345** which uses DAST **334** to install the β-fluoro moiety.[8] The key fluorination step was found to be highly sensitive to the protecting groups used: combinations involving protection of the terminal hydroxyl with *O*-TBDMS, *O*-TBDPS or *O*-Tr and the amine with *N*-Boc, *N*-trifluoroacetyl, *N*-formyl or *N*,*N*-dibenzyl groups were found to give diastereoisomeric mixtures of fluorinated products. The combination of *N*-Boc and *O*-Alloc protection, however, was found to give **347** as a single diastereoisomer. It was postulated that this may be due to the participation of the carbonate functionality (i.e., *O*-Alloc), as only this protecting group led to high stereocontrol. Subsequent deprotection and oxidation of the primary hydroxyl group gave β-fluoro-α-amino acid *ent*-**333** in 38% yield over 7 steps from **345** (Scheme 63).



Scheme 63. *Reagents and Conditions*: (i) Boc_2O, MeOH, rt, 13 h; (ii) AllocCl, pyridine, CH_2Cl_2, rt, 20 min; (iii) DAST **334**, $^{i}Pr_2EtN$, CH_2Cl_2, −78 °C, 1 h, then −78 °C to rt, 18 h; (iv) $Pd(PPh_3)_4$, morpholine, THF, rt, 1 h; (v) NaOCl aq, TEMPO, Bu_4NBr, $NaHCO_3$, 30 min, 0 °C; (vi) 12% aq HCl, 1,4-dioxane, rt, 3.5 h; (vii) propylene oxide, $^{i}PrOH$, 3.5 h.

The use of deoxofluorinating agents to promote rearrangement via an aziridinium ion is also precedented: Cossy *et al.* have employed a deoxofluorination approach to facilitate the rearrangement of β-amino alcohols **350** and **351** to β-fluoroamines **352** and **353** with high regioselectivity.[9] Treatment of either **350** or **351** with DAST **334** activates the hydroxyl moiety, promoting ring-closure to aziridinium intermediate **130**. Attack of this intermediate by fluoride occurs regioselectivity at the more substituted C(2)-position, in a stereospecific ring-opening reaction (Scheme 64).



350, R^1 = Bn, R^2 = Me, >99% ee
351, R^1 = Me, R^2 = ^{i}Pr, >99% ee

130

352, R^1 = Bn, R^2 = Me, 91%, >99% ee
353, R^1 = Me, R^2 = ^{i}Pr, 90%, >99% ee

Scheme 64. *Reagents and Conditions*: (i) DAST **334**, THF, 0 °C, 1 h, then 1 h, rt.

4.2. Results and discussion

4.2.1. Synthetic strategy

In the previous chapter it was found that β-hydroxy-α-amino acids **189** could be made efficiently from α-hydroxy-β-amino esters **240** via the ring-opening of the corresponding aziridinium intermediates **241** with water. It was proposed that a similar approach could be employed to access β-fluoro-α-amino acids **327** upon ring-opening of the same aziridinium intermediates **241** with a source of fluoride. Thus, it was envisaged that a deoxofluorinating reagent may be used to activate the hydroxyl moiety within α-hydroxy-β-amino esters **240**. If intramolecular attack by the nitrogen atom within **240** occurs faster than substitution of the activated hydroxyl group with the latent fluoride source, then aziridinium intermediate **241** would be formed. Subsequent ring-opening of **241** at the C(3)-position *in situ* by the fluoride source would afford β-fluoro-α-amino esters **355**, which upon deprotection would complete an efficient synthesis to β-fluoro-α-amino acids **327** (Figure 35).

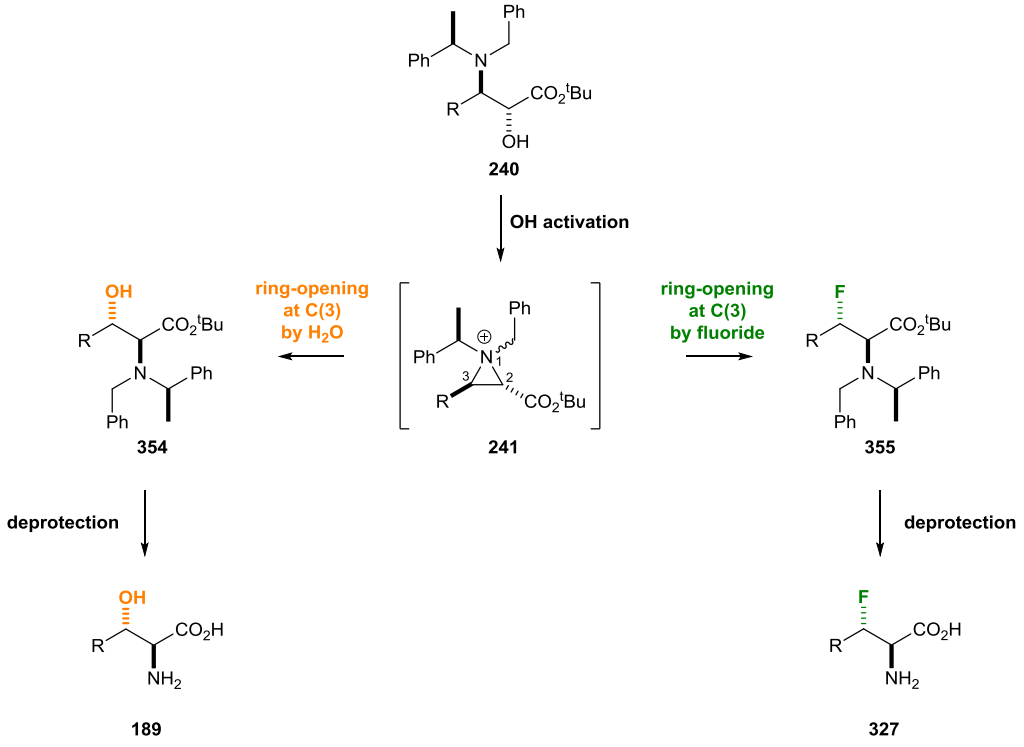


Figure 35. Strategy for the asymmetric synthesis of β-fluoro-α-amino acids **327** from α-hydroxy-β-amino esters **240**.

4.2.2. Deoxofluorination of racemic β-aryl *anti*-α-hydroxy-β-amino esters

C(3)-Phenyl substituted *N*,*N*-dibenzyl protected α-hydroxy-β-amino ester (±)-**248** was chosen for the initial studies. Thus, (±)-**248** was reacted with DAST **334** according to the procedure reported by Cossy *et al.*,[9] to give a 31:69 mixture of fluorinated products, which upon ^{1}H-^{13}C NMR HMBC analysis were identified as β-fluoro-α-amino ester (±)-**356** and α-fluoro-β-amino ester (±)-**357**, respectively. In the case of α-fluoro-β-amino ester (±)-**357**

($^3J_{2,3}$ = 4.1 Hz), the relative *anti*-configuration was assigned by ^{1}H NMR $^3J_{2,3}$ coupling constant analysis: reported coupling constants of $^3J_{2,3}$ = 3 Hz and $^3J_{2,3}$ = 8 Hz are known to be indicative of either an *anti*- or *syn*-configuration, respectively.[10] Reaction of (±)-**248** with XtalFluor-E® **336**[11,12] and $Et_3N{\cdot}3HF$ according to a literature protocol for deoxofluorination[12] proceeded with high regioselectivity, giving a 98:2 mixture of (±)-**356** and (±)-**357**, respectively, from which (±)-**356** was isolated in 94% yield and >99:1 dr. The relative *anti*-configuration within (±)-**356** was established unambiguously via single crystal X-ray diffraction analysis (Figure 36).[13] So that the relative regiochemical preferences of the two deoxofluorinating agents DAST **334** and XtalFluor-E® **336** could be compared, the reaction of (±)-**248** with DAST **334** was repeated in CH_2Cl_2. This resulted in a reversal of selectivity compared to the analogous reaction in THF, giving an 80:20 mixture of β-fluoro-α-amino ester (±)-**356** and α-fluoro-β-amino ester (±)-**357**, respectively (Scheme 65). The relative *anti*-configurations within (±)-**356** and (±)-**357** are consistent with a stereospecific reaction pathway which proceeds via an aziridinium intermediate. Activation of the hydroxyl group within (±)-**248** by either deoxofluorinating agent **334** or **336** invokes intramolecular attack by the amino group to give aziridinium intermediate (±)-**249** with inversion of configuration at C(2). This is followed by ring-opening of (±)-**249** by the fluoride source at either C(2) or C(3), which also occurs with inversion of configuration.



(±)-**248**, >99:1 dr (±)-**249** (±)-**356**, >99:1 dr (±)-**357**, >99:1 dr

reagents	solvent	temperature	time	product ratio (±)-356:(±)-357	yield (±)-356
DAST **334**	THF	0 °C, then rt	1 h, then 1 h	31:69	-
DAST **334**	CH_2Cl_2	0 °C, then rt	1 h, then 1 h	80:20	-
XtalFluor-E® **336**, $Et_3N{\cdot}3HF$	CH_2Cl_2	rt	2 h	98:2	94%

Scheme 65. *Reagents and Conditions*: see table.

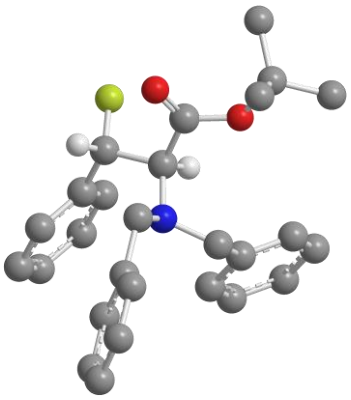
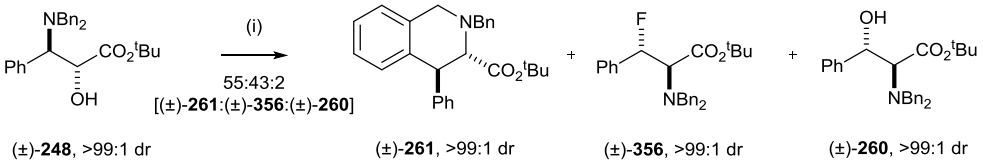


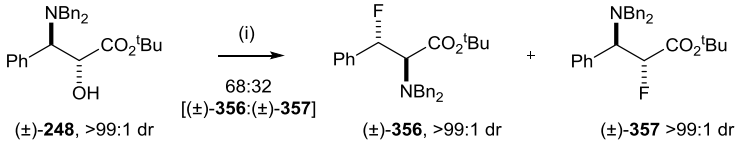
Figure 36. X-ray crystal structure of (*RS,SR*)-**356** (selected H atoms are omitted for clarity).

The superior regioselectivity observed upon reaction of (±)-**248** with XtalFluor-E® and $Et_3N{\cdot}3HF$ prompted studies to establish whether this result was entirely dependent on the XtalFluor-E®/$Et_3N{\cdot}3HF$ reagent combination, or if either **336** or $Et_3N{\cdot}3HF$ alone were capable of invoking similar levels of regiocontrol. Reaction of (±)-**248** with only XtalFluor-E® **336** was insufficient to effect full conversion to β-fluoro-α-amino ester (±)-**356**, giving a 55:43:2 ratio of tetrahydroisoquinoline (±)-**261**, (±)-**356** and β-hydroxy-α-amino ester (±)-**260**, respectively, but did deliver β-fluoro-α-amino ester (±)-**356** as a single regioisomer, indicating that this reagent exerted regiocontrol for fluorination (Scheme 66).



Scheme 66. *Reagents and Conditions*: (i) XtalFluor-E® **336**, CH_2Cl_2, rt, 2 h.

As XtalFluor-E® **336** alone proved to be a poor source of fluoride, it was considered that $Et_3N{\cdot}3HF$ must be necessary to effect full fluorination of α-hydroxy-β-amino esters. Reaction of (±)-**248** with $Et_3N{\cdot}3HF$ in the presence of an alternative activating agent was undertaken next, to establish whether use of **336** was indeed necessary to achieve high levels of regioselectivity. Activation of (±)-**248** with Ms_2O in presence of $Et_3N{\cdot}3HF$ resulted in a 68:32 ratio of (±)-**356** and (±)-**357**, respectively. This indicates that whilst $Et_3N{\cdot}3HF$ exhibits moderate regioselectivity for fluorination at the C(3)-position, the $Et_3N{\cdot}3HF$/XtalFluor-E® combination is required to achieve high levels of regioselectivity (Scheme 67).

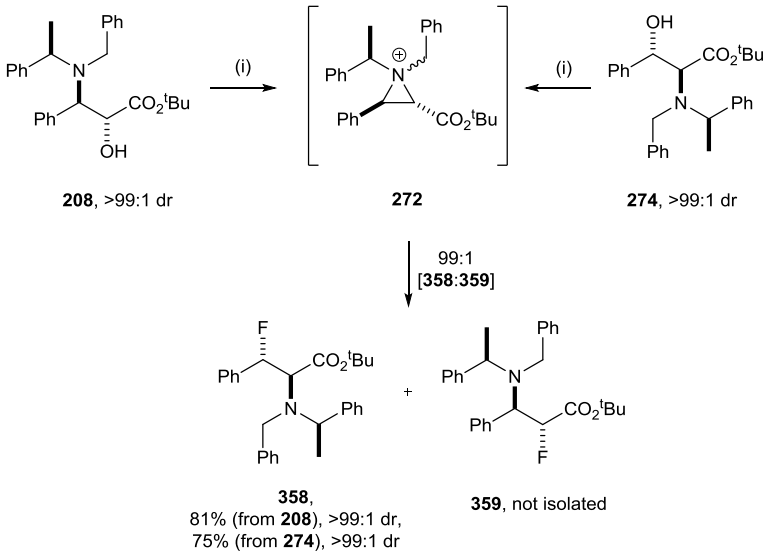


Scheme 67. *Reagents and Conditions*: (i) Ms_2O, $Et_3N{\cdot}3HF$, CH_2Cl_2, rt, 24 h.

4.2.3. Application to enantiopure β-aryl *anti*-α-hydroxy-β-amino esters

Reaction of XtalFluor-E® **336** and $Et_3N{\cdot}3HF$ with enantiopure α-hydroxy-β-amino ester **208** also proceeded with excellent regioselectivity, resulting in a 99:1 mixture of β-fluoro-α-amino ester **358** and α-fluoro-β-amino ester **359**, respectively, from which **358** was isolated in 81% yield and >99:1 dr. Additionally, reaction of β-hydroxy-α-amino ester **274** under the same reaction conditions was found to give an identical product ratio (Scheme 68). The relative *anti*-configuration within **358** was established unambiguously via single crystal X-ray diffraction analysis, with the absolute (2*R*,3*S*,α*R*)-configuration within **358** being assigned by reference to the known configuration of the (*R*)-α-methylbenzyl fragment; this assignment

was confirmed by the determination of a Flack *x* parameter[14] of −0.11(11) for this structure (Figure 37).[13] The ^{1}H and ^{13}C NMR data for α-fluoro-β-amino ester **359** were entirely consistent with the literature data for the known e*nt*-**359**[10] and distinct to those reported for the *syn*-diastereoisomer.[10] Reaction of both α-hydroxy-β-amino ester **208** and β-hydroxy-α-amino ester **274** with **336** and $Et_3N{\cdot}3HF$ gave an identical product distribution, with the major product β-fluoro-α-amino ester **358** resulting from overall inversion of configuration of **208** and overall retention of configuration of **274**, providing strong support for reaction via the same aziridinium intermediate **272** in both cases.



Scheme 68. *Reagents and Conditions*: (i) XtalFluor-E® **336**, $Et_3N{\cdot}3HF$, CH_2Cl_2, rt, 2 h.

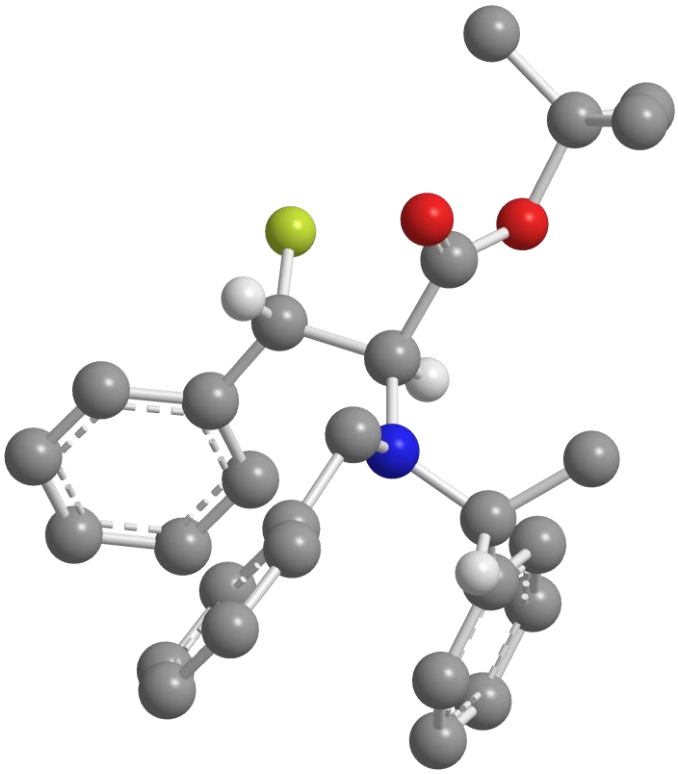
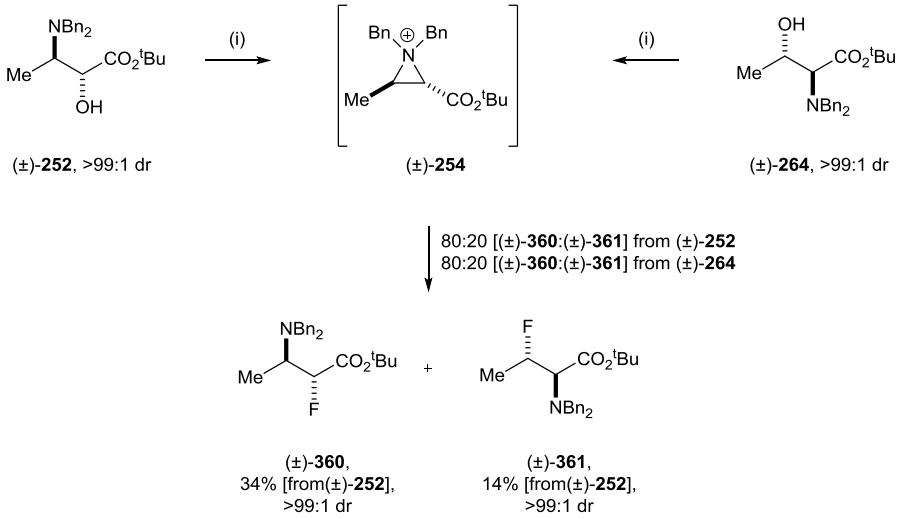


Figure 37. X-ray crystal structures of (2*R*,3*S*,α*R*)-**358** (selected H atoms are omitted for clarity).

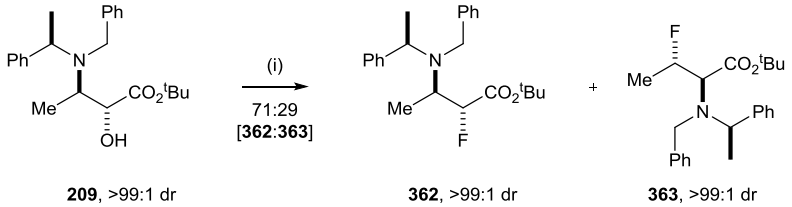
4.2.4. Deoxofluorination of β-alkyl α-hydroxy-β-amino esters

Deoxofluorination of C(3)-methyl substituted α-hydroxy-β-amino ester (±)-**252** was investigated next. Reaction of (±)-**252** with XtalFluor-E® **336** and $Et_3N{\cdot}3HF$ gave an 80:20 mixture of α-fluoro-β-amino ester (±)-**360** and β-fluoro-α-amino ester (±)-**361**, respectively. Reaction of β-hydroxy-α-amino ester (±)-**264** under the same conditions gave an identical 80:20 mixture of (±)-**360** and (±)-**361**, respectively. The regiochemistries within (±)-**360** and (±)-**361** were assigned on the basis of ^{1}H-^{1}H COSY and ^2J ^{1}H-^{19}F NMR coupling constant analyses and the relative *anti*-configuration of the α-fluoro-β-amino ester (±)-**360** was based on $^3J_{2,3}$ ^{1}H NMR coupling constant analysis: the observed multiplet splittings ($^3J_{2,3}$ = 2.4 Hz) were in good agreement with those reported to be indicative of C(3)-alkyl substituted *anti*-α-fluoro-β-amino esters ($^3J_{2,3}$= ~2 Hz).[10] Reaction of both α-hydroxy-β-amino ester (±)-**252** and β-hydroxy-α-amino ester (±)-**264** with XtalFluor-E® **336** and $Et_3N{\cdot}3HF$ gave an identical product distribution, supporting the proposal that these reactions had occurred via a common aziridinium intermediate (±)-**254**, and thus enabling tentative stereochemical assignment of (±)-*anti*-**361** on this basis (Scheme 69).



Scheme 69. *Reagents and Conditions*: (i) XtalFluor-E® **336**, $Et_3N{\cdot}3HF$, CH_2Cl_2, rt, 2 h.

Reacting enantiopure α-hydroxy-β-amino ester **209** under identical conditions gave a 71:29 mixture of α-fluoro-β-amino ester **362** and β-fluoro-α-amino ester **363**, respectively. The ^{1}H NMR data for **362** were entirely consistent with those reported for *ent*-**362**,[10] and distinct from those of the corresponding *syn*-diastereoisomer,[10] enabling the relative *anti*-configuration within **362** to be established. Regiochemical assignment of β-fluoro-α-amino ester **363** was based on ^{1}H-^{1}H COSY and ^2J ^{1}H-^{19}F NMR coupling constant analyses, with the relative *anti*-configuration assigned based on the proposed reaction mechanism (Scheme 70).



Scheme 70. *Reagents and Conditions*: (i) XtalFluor-E® **336**, $Et_3N{\cdot}3HF$, CH_2Cl_2, rt, 2 h.

These preliminary studies indicated that reaction of C(3)-phenyl substituted α-hydroxy-β-amino esters gave β-fluoro-α-amino esters with high regioselectivity, whereas moderate levels of regioselectivity were observed for the corresponding C(3)-methyl substituted analogues. These results may be due to the effect of the π-aromatic system of C(3)-aryl compounds, which is expected to stabilise developing carbocationic character at C(3) within the transition state.[15] The absence of this effect in the case of the C(3)-methyl substituted analogues may account for the reduced regioselectivity observed, with the activation of the C(2)-position by the adjacent carbonyl group[16] perhaps explaining the formation of α-fluoro-β-amino esters as the major regioisomers.

4.2.5. Alternative β-substitution

XtalFluor-E® **336** has previously been used in conjunction with nucleophiles other than fluoride in the substitution reactions of prolinols,[17] which are reported to proceed via an aziridinium intermediate: aziridinium formation is promoted by XtalFluor-E® **336**, with subsequent ring-opening by azide, for example, occurring *in situ*.[17] This prompted an investigation into the ring-opening of aziridinium intermediates **241** by other nucleophiles, to assess this route as a means of accessing alternative β-substituted-α-amino acids **365**. It was proposed that activation of α-hydroxy-β-amino esters **240** with XtalFluor-E® **336** would give aziridinium ions **241**. Carrying out this reaction in the presence of an alternative nucleophile (e.g., TMS-N_3, TMS-OAc, etc.) may lead to subsequent ring-opening of **241** *in situ*, giving β-substituted-α-amino esters **364**. Subsequent deprotection of **364** would then give access to β-substituted-α-amino acids **365** (Figure 38).

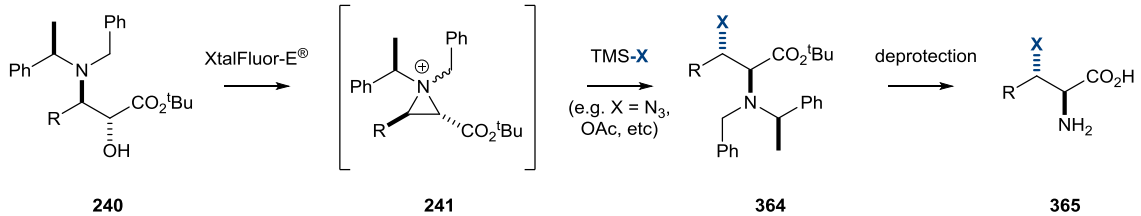
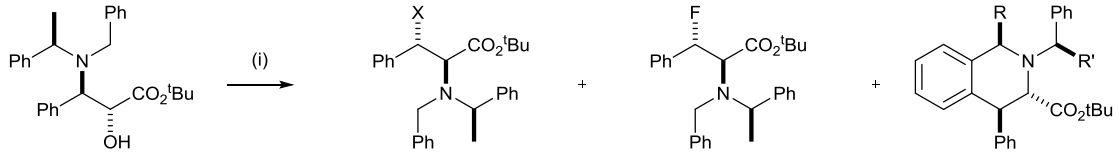


Figure 38. Strategy for the asymmetric synthesis of β-substituted-α-amino acids **365** from α-hydroxy-β-amino esters **240**.

Thus, **208** was treated with XtalFluor-E® **336** in the presence of TMS-N_3, TMS-OAc or TMS-CN. Upon reaction with TMS-N_3, an 80:12:8 mixture of β-azido-α-amino ester **368**, and

the regioisomeric tetrahydroisoquinolines **366** and **367**, respectively, was recovered, from which **368** was isolated in 58% yield and >99:1 dr. When TMS-OAc was used, fluorination was competitive, giving a 76:24 mixture of β-acetoxy-α-amino ester **369** and β-fluoro-α-amino ester **358**, from which **369** was isolated in 41% yield and >99:1 dr. The analogous reactions in the presence of either 3.0 or 1.1 equiv of TMS-CN proved unsuccessful, giving only complex mixtures of products (Scheme 71).



208, >99:1 dr | **A** | **358** | **366**, R = Me, R' = H; **367**, R = H, R' = Me

X	equiv TMS-X	A	product ratio A:358:[366+367]	yield A
N_3	3.0	**368**	80:0:20	58%
OAc	3.0	**369**	76:24:0	41%
CN	3.0	**370**	complex mixture	-
	1.1		complex mixture	-

Scheme 71. *Reagents and Conditions*: (i) XtalFluor-E® **336**, TMS-X (see table), CH_2Cl_2, rt, 2 h.

The relative *anti*-configurations within **368** and **369** were established unambiguously via single crystal X-ray diffraction analyses, with the absolute (2*S*,3*S*,α*R*)- and (2*S*,3*S*,α*R*)-configurations within **368** and **369**, respectively, assigned by reference to the known configuration of the (*R*)-α-methylbenzyl fragment. These assignments were also confirmed by the determination of Flack *x* parameters[14] of –0.1(2) and –0.12(15) for the structures of **368** and **369**, respectively (Figure 39).[13] This stereochemical outcome is also consistent with these reactions following a mechanistic pathway which proceeds via an aziridinium intermediate, whereby aziridinium formation occurs with inversion of configuration at the C(2)-position, with subsequent ring-opening at the C(3)-position also occurring with inversion of configuration.

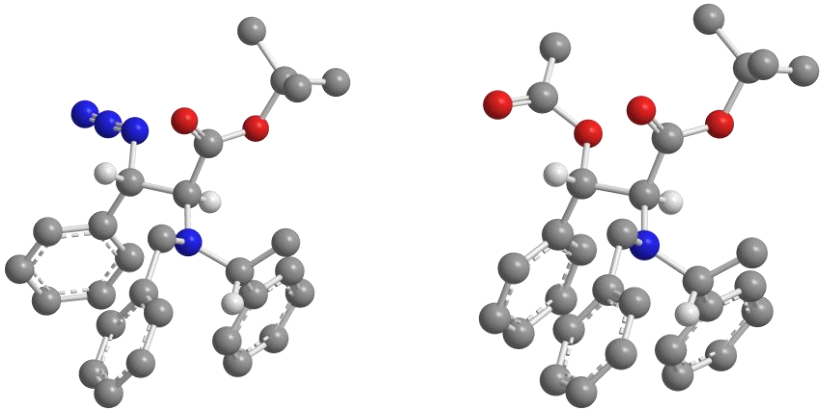
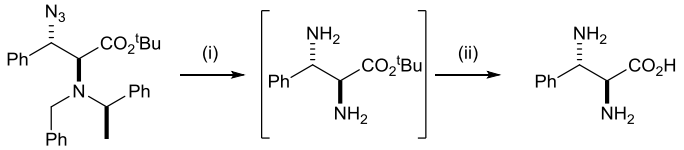


Figure 39. X-ray crystal structures of (2*S*,3*S*,α*R*)-**368** [*left*] and (2*S*,3*S*,α*R*)-**369** [*right*] (selected H atoms are omitted for clarity).

Elaboration of β-acetoxy-α-amino ester **369** to the corresponding β-hydroxy-α-amino acid *ent*-**184** was not pursued, as an effective method for the synthesis of *ent*-**184** had already been developed, which delivered *ent*-**184** in a yield higher than that possible from this alternative route (*vide supra*). β-Azido-α-amino ester **368** was, however, deprotected to the corresponding α,β-diamino acid **372**: hydrogenolysis of **368** with $Pd(OH)_2/C$ catalyst (25% w/w) at 5 atm H_2 pressure for 48 h gave α,β-diamino ester **371**, which was treated with 1.0 M aq HCl, then purified via ion exchange chromatography on DOWEX-50WX8 resin to give α,β-diamino acid **372** in >99:1 dr and in 82% yield over the two steps (Scheme 72).



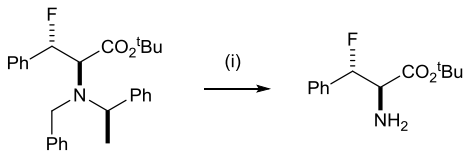
368, >99:1 dr **371** **372**, 82%, >99:1 dr

Scheme 72. *Reagents and Conditions*: (i) H_2 (5 atm), $Pd(OH)_2/C$, MeOH, rt, 48 h; (ii) 1.0 M HCl, then DOWEX-50WX8 ion-exchange resin.

4.2.6. β-Fluoro-α-amino acids from α-hydroxy-β-amino esters: deprotection

4.2.6.1. Attempted deprotection via hydrogenolysis

Studies into the effective deprotection of β-fluoro-α-amino ester **358** to the corresponding β-fluoro-α-amino acid were undertaken next. It was anticipated that effecting *N*-debenzylation without accompanying reduction of the labile benzylic fluoride moiety[18] may be difficult. Mild hydrogenolysis conditions were attempted in the first instance: samples of **358** were stirred under hydrogen at atmospheric pressure in the presence of 10% Pd/C catalyst (15% w/w loading). After 2 h there was no conversion of starting material, so the reaction was repeated and monitored by both TLC and mass spectrometry. Analysis by mass spectrometry showed the first signs of defluorination after 4 h, but starting material was still present by both mass spectrometry and TLC analysis. The reaction was stopped after 15 h, by which point consumption of starting material had been achieved, but only a complex mixture of over-reduction products was recovered (Scheme 73).



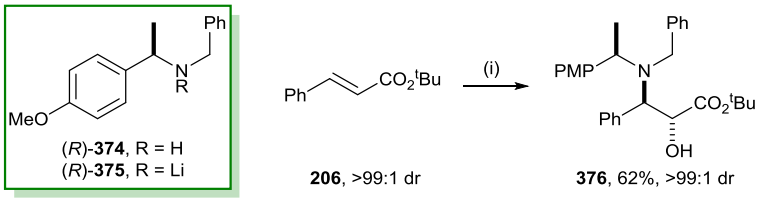
358, >99:1 dr **373**, >99:1 dr

solvent	time	result
EtOH	2 h	returned **358**
MeOH	2 h	returned **358**
MeOH	15 h	complex mixture

Scheme 73. *Reagents and Conditions*: (i) 10% Pd/C (15% w/w), rt, see table.

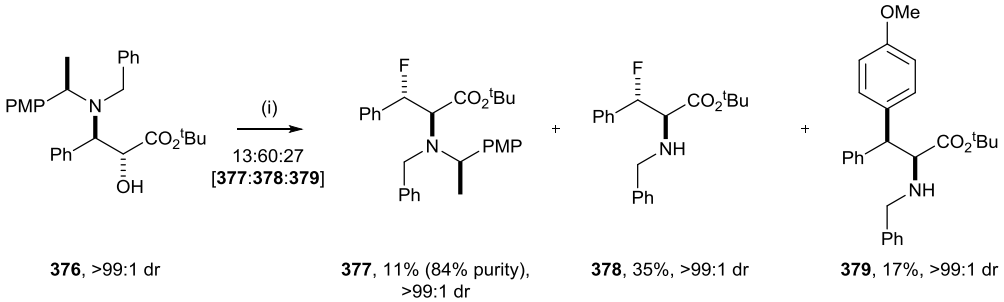
4.2.6.2. Exploring alternative protecting group strategies

As reductive *N*-debenzylation via hydrogenolysis had resulted in competitive defluorination, it was considered that *N*-deprotection via oxidative methods should be investigated next. Benzyl groups with a *p*-OMe substituent can be deprotected under either oxidative[19] or acidic[20] conditions, thus it was proposed that an *N*-(α-methyl-*p*-methoxybenzyl) protecting group should be used instead of an *N*-(α-methylbenzyl) group in order to explore these alternative deprotection methods. Therefore, lithium *N*-benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amide **375**[21] was added to *tert*-butyl cinnamate **206**, with *in situ* oxidation of the intermediate lithium (*Z*)-β-amino enolate[22] with (−)-CSO **202** giving α-hydroxy-β-amino ester **376** in 62% yield and >99:1 dr (Scheme 74). The configuration within **376** was assigned based on the established stereochemical outcome of the aminohydroxylation reaction,[23] and this assignment was supported by ^{1}H NMR $^3J_{2,3}$ coupling constant analysis: the magnitude of the $^3J_{2,3}$ coupling constant within **376** ($^3J_{2,3}$ = 3.0) was found to be within the expected range for *anti*-configured α-hydroxy-β-amino esters ($^3J_{2,3}$ = 2–4.5 Hz).[24]



Scheme 74. *Reagents and Conditions*: (i) (*R*)-**374**, BuLi, THF, −78 °C, 2 h, then **202**, −78 °C to rt, 18 h.

Treatment of **376** with XtalFluor-E® **336** and $Et_3N{\cdot}3HF$ gave a 13:60:27 mixture of β-fluoro-α-amino ester **377**, the corresponding secondary amine **378**, in which deprotection of the *N*-(α-methyl-*p*-methoxybenzyl) group had occurred *in situ*, and β,β-diaryl-α-amino ester **379**, respectively, which were isolated in 11,[25] 35 and 17% yield, respectively (Scheme 75).



Scheme 75. *Reagents and Conditions*: (i) XtalFluor-E® **336**, $Et_3N{\cdot}3HF$, CH_2Cl_2, rt, 2 h.

The formation of β,β-diaryl-α-amino ester **379** is consistent with a mechanism in which activation of **376** by **336** gives rise to aziridinium ion **380**, which can ring-open to give benzylic carbocation intermediate **381**. Subsequent attack of **381** by the electron rich *p*-OMe phenyl ring would give spirocyclic intermediate **382**, which may undergo fragmentation to

iminium intermediate **383**, with subsequent hydrolysis resulting in the formation of **379**[26] (Figure 40).

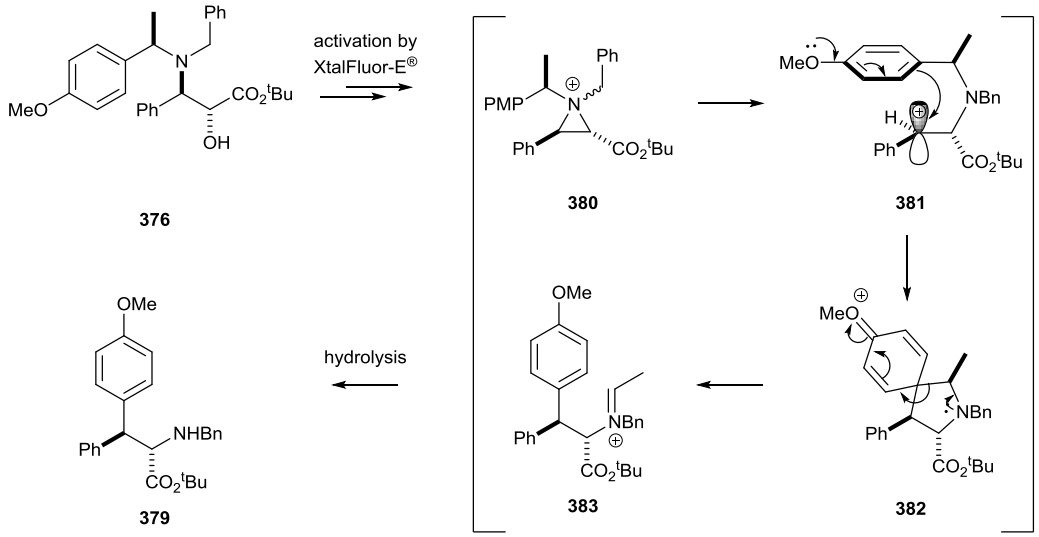


Figure 40. Mechanistic proposal for the formation of **379**.

To avoid further complications arising from the side reaction involved in the formation of **379**, an alternative protecting group strategy was required and attention returned to developing alternative deprotection methods for the *N*-(α-methylbenzyl) group. It was proposed that removal of the *N*-(α-methylbenzyl) protecting group may be achieved by a tandem oxidative elimination procedure: *N*-oxidation of **384** would give the corresponding *N*-oxide **385**, which may undergo Cope elimination to give hydroxylamine **386**, expelling styrene. Reduction of **386** would give the corresponding secondary amine **387**. In the case where R = allyl, it was envisaged that this this secondary amine could be readily deprotected under Tsuji-Trost conditions,[27] which it was hoped would not affect the benzylic fluoride moiety (Figure 41).

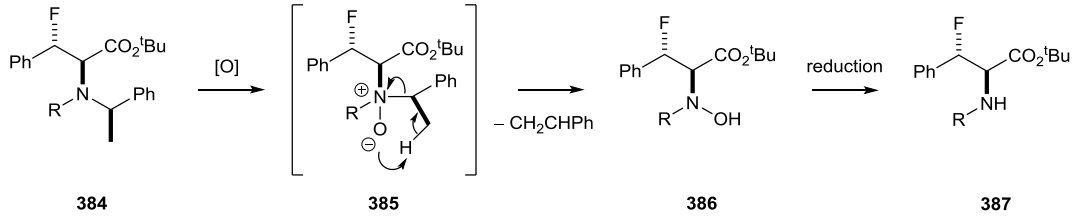
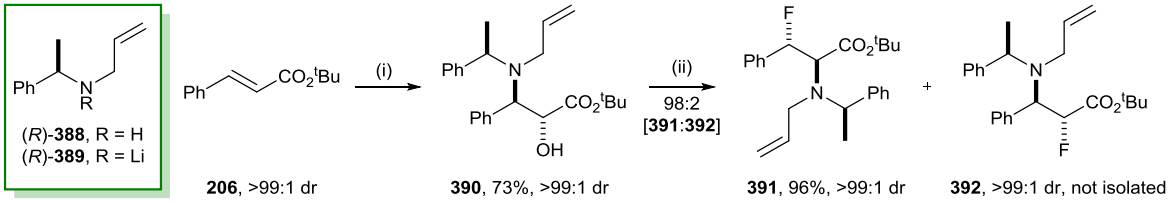


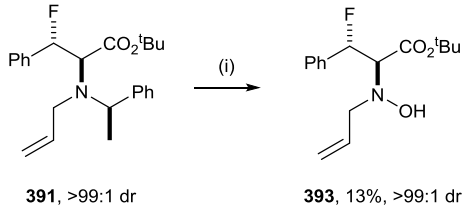
Figure 41. Proposed oxidative removal of an *N*-(α-methylbenzyl) group.

Conjugate addition of lithium (*R*)-*N*-allyl-*N*-(α-methylbenzyl)amide **389** to *tert*-butyl cinnamate **206**, with *in situ* oxidation of the intermediate lithium (*Z*)-β-amino enolate[22] with **202**, gave the known α-hydroxy-β-amino ester **390**[28] in 73% yield and >99:1 dr. Subsequent reaction of **390** with XtalFluor-E® **336** and $Et_3N{\cdot}3HF$ proved to be highly regioselective, giving a 98:2 mixture of β-fluoro-α-amino ester **391** and α-fluoro-β-amino ester **392**, from which **391** was isolated in 96% yield and >99:1 dr (Scheme 76).



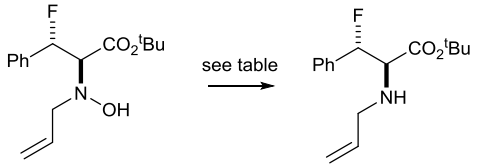
Scheme 76. *Reagents and Conditions*: (i) (*R*)-**388**, BuLi, THF, −78 °C, 2 h then (−)-CSO **202**, −78 °C to rt, 18 h; (ii) XtalFluor-E® **336**, $Et_3N{\cdot}3HF$, CH_2Cl_2, rt, 2 h.

Under optimised conditions, it was found that reaction of **391** with *m*-CPBA in the presence of a phosphate buffer facilitated removal of the *N*-(α-methylbenzyl) group in 15 min to give hydroxylamine **393**, which was isolated in 13% yield and >99:1 dr. The low isolated yield of **393** was attributed to poor stability to column chromatography (Scheme 77).



Scheme 77. *Reagents and Conditions*: (i) *m*-CPBA, CH_2Cl_2/HFIP, phosphate buffer, rt, 15 min.

Attempts were made to reduce hydroxylamine **393** to the corresponding secondary amine **394**, with reaction of both crude and purified samples of hydroxylamine **393** giving the same results in each case: reduction with Zn[29] resulted in a complex mixture of products, whilst reaction with either CS_2[30] or In powder[31] failed to cause any conversion of starting material (Scheme 78).

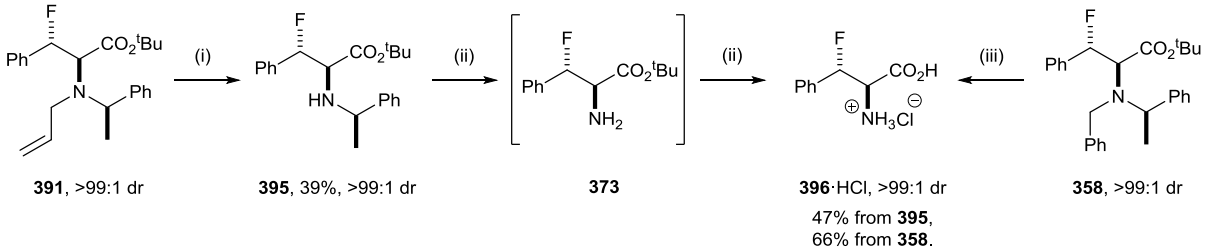


reagents	solvent	temperature	time	result
Zn	AcOH/THF/H_2O (3:3:1)	70 °C	2 h	complex mixture
CS_2	MeCN	rt	20 h	returned **393**
In powder	EtOH/satd aq NH_4Cl (2:1)	83 °C	18 h	returned **393**

Scheme 78. *Reagents and Conditions*: see table.

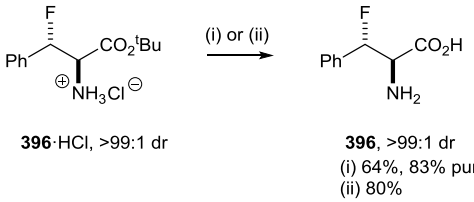
With poor yields for the formation of hydroxylamine **393** and the subsequent reduction being unsuccessful, investigations into alternative oxidative *N*-debenzylation methods were undertaken. The use of $NaBrO_3$ and $Na_2S_2O_4$ to effect *O*-debenzylation in fluorine containing sugars has been reported by O'Hagan *et al.*[32] and thus application of this strategy for the removal of an *N*-(α-methylbenzyl) group was investigated. *N*-Deallylation of **391** under Tsuji-Trost conditions[27] gave secondary amine **395**, which was isolated in 39% yield and >99:1 dr. Subsequent treatment of **395** with $NaBrO_3$ and $Na_2S_2O_4$ for 1 h resulted in complete removal

of the *N*-(α-methylbenzyl) group, giving a 77:23 mixture of β-fluoro-α-amino ester **373** and the corresponding β-fluoro-α-amino acid **396** respectively. This mixture was redissolved in $CHCl_3$ and extracted with 1.0 M aq HCl, giving **396**·HCl in 47% yield and >99:1 dr. This protocol was next attempted on the *N*-benzyl-*N*-(α-methylbenzyl) substituted analogue **358**, to see if the tertiary amine **358** could be completely deprotected to the corresponding primary amine **373** without compromising the β-fluoro moiety. Reaction of **358** with $NaBrO_3$ and $Na_2S_2O_4$ gave 82% conversion of starting material after 1 h, with a reaction time of 4 h found necessary to achieve full conversion. Extraction of the crude reaction mixture with 1.0 M aq HCl gave **396**·HCl in 66% yield and >99:1 dr (Scheme 79).



Scheme 79. *Reagents and Conditions*: (i) DMBA, $Pd(PPh_3)_4$, CH_2Cl_2, rt, 18 h; (ii) $NaBrO_3$, $Na_2S_2O_4$, H_2O/EtOAc (2:1), rt, 1 h, then 1.0 M aq HCl; (iii) $NaBrO_3$, $Na_2S_2O_4$, EtOAc/H_2O, rt, 4 h, then 1.0 M aq HCl.

Attempted conversion of hydrochloride salt **396**·HCl to the corresponding β-fluoro-α-amino acid **396** via treatment with DOWEX-50WX8 ion-exchange resin was unsuccessful, as **396** was recovered in ~83% purity.[33] However, it has previously been reported that treatment of **396**·HCl with propylene oxide in ^{i}PrOH gave access to **396**[6] in good yield. Application of this literature procedure to **396**·HCl gave **396** in 80% yield and >99:1 dr, completing the synthesis of (2*R*,3*S*)-*anti*-fluorophenylalanine **396** in 40% yield over four steps (Scheme 80).

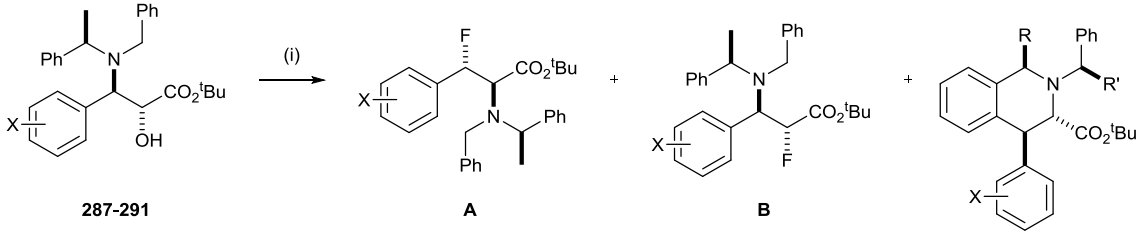


Scheme 80. *Reagents and Conditions*: (i) DOWEX 50WX8 ion exchange resin; (ii) propylene oxide, ^{i}PrOH, rt, 6 h.

4.2.7. β-Fluoro-α-amino esters from α-hydroxy-β-amino esters: substrate scope

Investigations into the substrate scope of the developed fluorination methodology were undertaken next on the same range of α-hydroxy-β-amino esters **287**–**291** as had been used for the synthesis of β-hydroxy-α-amino acids (*vide supra*). For the most electron poor substrate **287** (X = *p*-CF_3), a 91:9 mixture of β-fluoro-α-amino ester **397** and α-fluoro-β-amino ester **402**, respectively, was recovered, from which **397** was isolated in 85% yield, and **402** was isolated in 8% yield, as single diasteroisomers in both cases (>99:1 dr). For **288**

(X = *m*-F) and **289** (X = *m*-OMe), fluorination proceeded with higher regioselectivity, giving 95:5 and 98:2 mixtures of β-fluoro-α-amino esters and α-fluoro-β-amino esters, respectively, from which **398** and **399** were isolated in 92 and 78% yield, and >99:1 dr in both cases. For both **290** (X = *p*-F) and **291** (X = *p*-OMe), reaction under standard conditions resulted in the formation of mixtures of regioisomeric tetrahydroisoquinolines[34] as side products. Reaction of **290** (X = *p*-F) with XtalFluor-E® **336** and 2.0 equiv of $Et_3N{\cdot}3HF$ gave an 82:12:6 mixture of β-fluoro-α-amino ester **400**, and tetrahydroisoquinolines **410** and **414**, respectively, which was slightly improved to an 89:7:4 mixture upon addition of 3.0 equiv of $Et_3N{\cdot}3HF$, enabling isolation of **400** in 72% yield and >99:1 dr. Reaction of **291** (X = *p*-OMe) with **336** and 2.0 equiv of $Et_3N{\cdot}3HF$ gave a 37:37:26 mixture of β-fluoro-α-amino ester **401**, and tetrahydroisoquinolines **301** and **302**, respectively. A marked improvement was observed upon repetition of this reaction using 3.0 equiv of of $Et_3N{\cdot}3HF$, giving an 80:12:8 mixture of **401**, **301** and **302**, respectively, from which **401** was isolated in 44% yield and >99:1 dr (Scheme 81).



X		σ+	equiv $Et_3N{\cdot}3HF$	A	B	C	D	product ratio A:B:C:D	yield A	yield B
p-CF_3	**287**	+0.61	2	**397**	**402**	**407**	**411**	91:9:0:0	85%	8%
m-F	**288**	+0.35	2	**398**	**403**	**408**	**412**	95:5:0:0	92%	-
m-OMe	**289**	+0.05	2	**399**	**404**	**409**	**413**	98:2:0:0	78%	-
p-F	**290**	-0.07	2	**400**	**405**	**410**	**414**	82:0:12:6	-	-
			3					89:0:7:4	72%	-
p-OMe	**291**	-0.78	2	**401**	**406**	**301**	**302**	37:0:37:26	-	-
			3					80:0:12:8	44%	-

Scheme 81. *Reagents and Conditions*: (i) XtalFluor-E® **336**, $Et_3N{\cdot}3HF$, CH_2Cl_2, rt, 2 h.

The relative configurations within **398** (X = *m*-F) and **400** (X = *p*-F) were unambiguously assigned via single crystal X-ray diffraction analyses, with the absolute (2*R*,3*S*,α*R*)-configuration within **398** and the (2*R*,3*S*,α*R*)-configuration within **400** being assigned relative to the known (*R*)-configuration of the α-methylbenzyl fragment within both **398** or **400** (Figure 42).[13] The configurations within **397**, **399** and **401** were assigned by analogy.

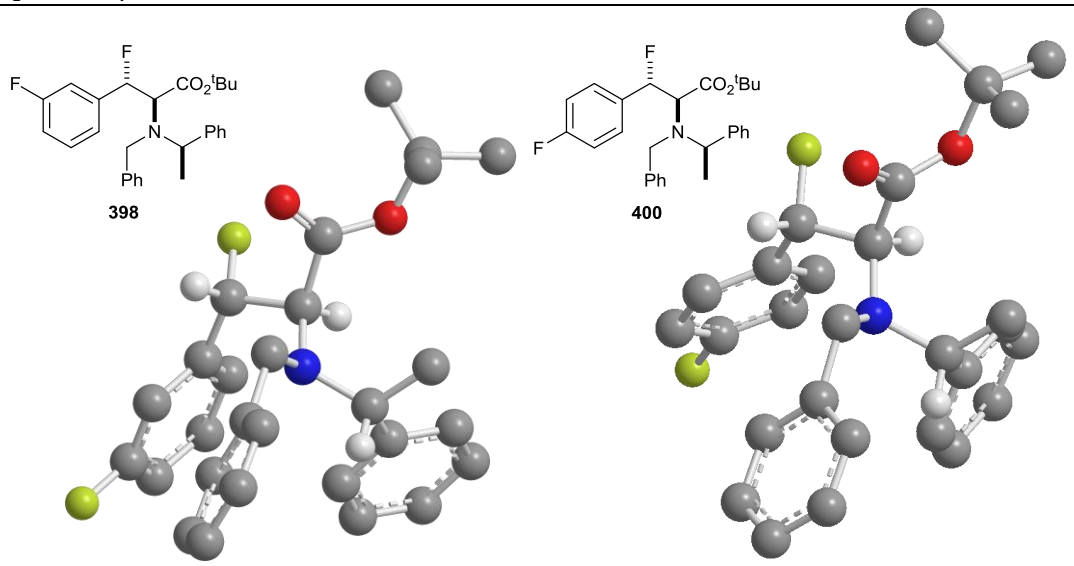


Figure 42. X-ray crystal structures of (2*R*,3*S*,α*R*)-**398** [*left*] and (2*R*,3*S*,α*R*)-**400** [*right*] (selected H atoms are omitted for clarity).

The observed differences in reactivity across the series **287**–**291** can be rationalised by considering the relative electron density of the C(3)-aryl ring within each substrate, and the likely impact this may have on the aziridinium intermediate **416** (or the resultant benzylic carbonium ion if ring-opening of **416** occurs readily). The more electron poor the aryl group is, the more destabilised any partial positive charge build-up at the C(3)-position within the transition state will be, and thus nucleophilic attack at the C(2)-position of **416** becomes a competitive process. For the most electron poor substrate in this series (X = *p*-CF_3), 9% conversion to α-fluoro-β-amino ester **402** is observed. The proportion of α-fluoro-β-amino ester **418** relative to β-fluoro-α-amino ester **417** present in the crude reaction mixture is seen to decrease as the electron density of the C(3)-aromatic ring increases, supporting this hypothesis (Figure 43).

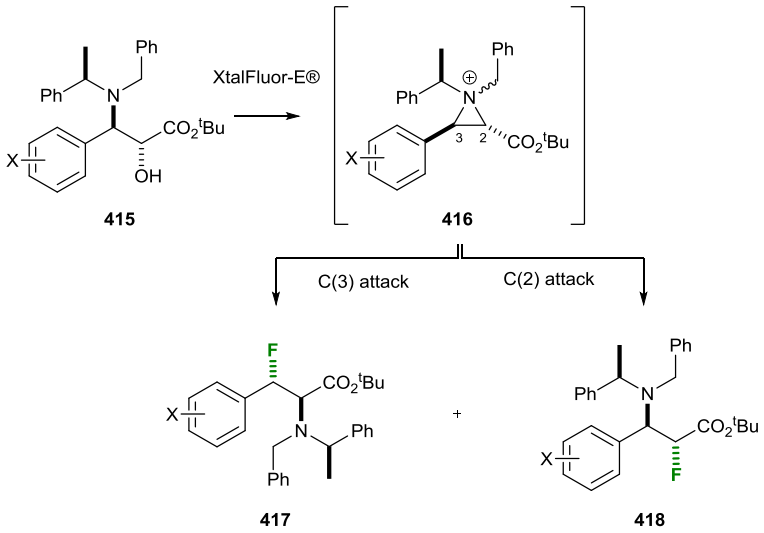


Figure 43. Proposed explanation of observance of α-fluoro-β-amino ester **418** when R= EWG.

As the electron density of the C(3)-aryl ring increases beyond that of a phenyl group (σ^+ = 0.00),[35] regioisomeric tetrahydroisoquinolines are also observed as side products. Reaction of **290** (X = *p*-F) and **291** (X = *p*-OMe) with XtalFluor-E® **336** and just 2.0 equiv of $Et_3N{\cdot}3HF$ leads to 18 and 63% conversion to tetrahydroisoquinolines, respectively, which is then reduced to 11 and 21% conversion when 3.0 equiv of $Et_3N{\cdot}3HF$ are used. The formation of these tetrahydroisoquinolines is consistent with a mechanistic pathway in which aziridinium ion **416** ring-opens to the corresponding carbocationic intermediate **419**, which is subsequently trapped by either the *N*-(α-methylbenzyl) (**419A**) or *N*-benzyl (**419B**) fragment, giving **420** and **421**, respectively. Presumably, this competing process occurs due to the increased electron density of the substituted aryl ring when X = *p*-F or *p*-OMe, which facilitates aziridinium ring-opening to the corresponding carbocation (Figure 44).

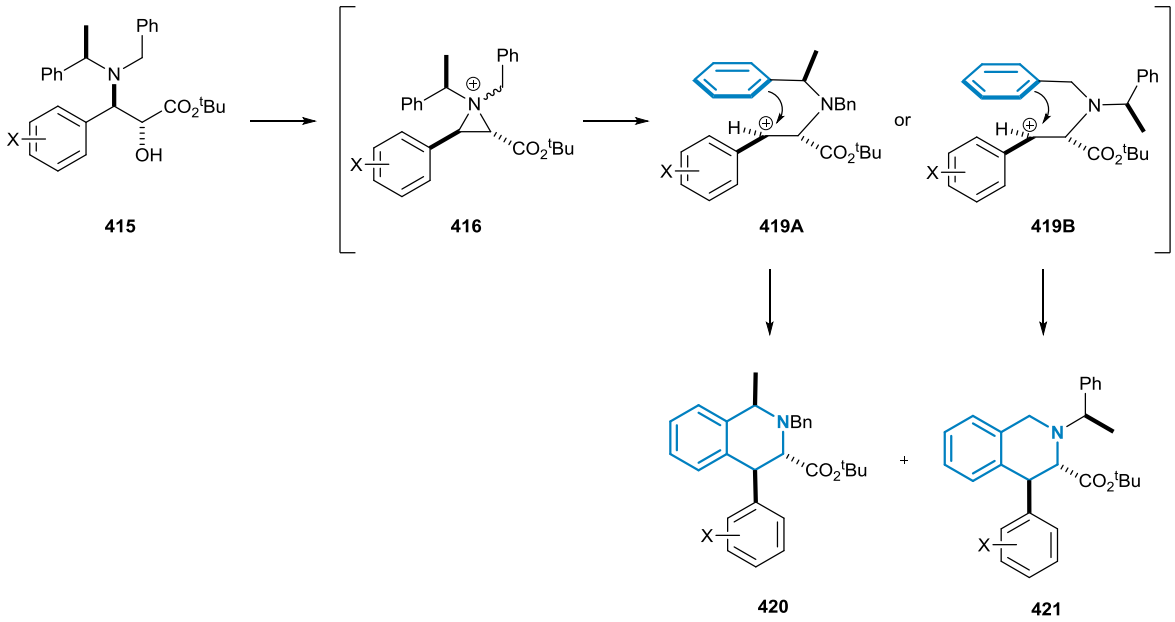
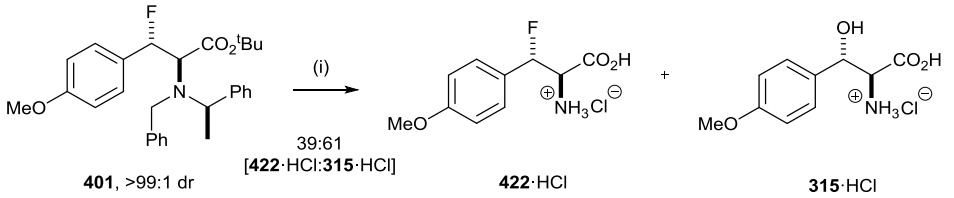


Figure 44. Proposed explaination of observance of regioisomeric tetrahydroisoquinolines **420** and **421** when R= EDG.

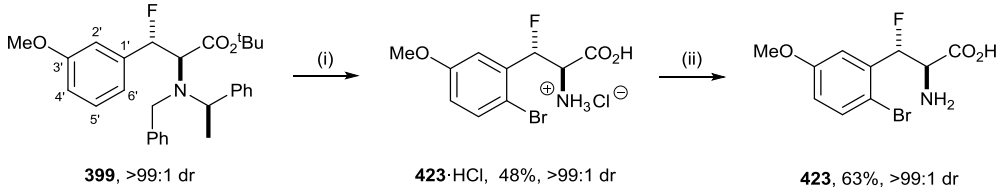
4.2.8. Deprotection to β-fluoro-α-amino acids

Deprotection of the range of β-fluoro-α-amino esters **397**–**401** was attempted next, employing the optimised one-pot *N*-debenzylation and ester hydrolysis method used for deprotection of **358** (*vide supra*). Attempted deprotection of **401** (X = *p*-OMe) with $NaBrO_3$ and $Na_2S_2O_4$ was unsuccessful, resulting in a complex mixture of products. Peaks consistent with **422**·HCl and **315**·HCl existing in a 39:61 ratio were observed in the ^{1}H NMR spectrum of the crude reaction mixture. The presence of **315**·HCl is consistent with the loss of fluoride from **422**, assisted by neighbouring group participation of the *p*-OMe group. This intermediate may then be attacked by water *in situ*, resulting in the formation of β-hydroxy-α-amino acid **315** (Scheme 82).



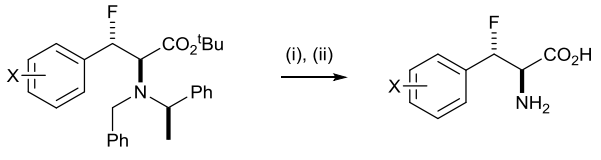
Scheme 82. *Reagents and Conditions*: (i) $NaBrO_3$, $Na_2S_2O_4$, H_2O/EtOAc (2:1), rt, 4 h.

Deprotection of **399** was attempted next, however, this process was accompanied by bromination of the aryl ring at the C(6')-position,[36] giving **423**·HCl in 48% yield. It was found that this mode of reactivity was not unique to **423** as reaction of anisole under identical conditions gave the known 4-bromo derivative[37] in quantitative yield. Subsequent treatment of **423**·HCl with propylene oxide in ^{i}PrOH gave **423** in 63% yield and >99:1 dr, and in 19% overall yield from **284** (Scheme 83).



Scheme 83. *Reagents and Conditions*: (i) $NaBrO_3$, $Na_2S_2O_4$, H_2O/EtOAc (2:1), rt, 4 h; (ii) propylene oxide, ^{i}PrOH, rt, 6 h.

Deprotection of β-fluoro-α-amino esters **397** (X = *p*-CF_3), **398** (X = *m*-F) and **400** (X = *p*-F) with $NaBrO_3$ and $Na_2S_2O_4$ proceeded successfully to give **424**·HCl (X = *p*-CF_3), **425**·HCl (X = *m*-F) and **426**·HCl (X = *p*-F), respectively. Subsequent treatment of **424**·HCl, **425**·HCl and **426**·HCl with propylene oxide in ^{i}PrOH gave **424**, **425** and **426** in 57, 69 and 65% yield over the two step sequence, and in 32, 52 and 38% overall yield from the corresponding substituted *tert*-butyl cinnamates **282**, **283** and **285** (Scheme 84).



X	product	yield	dr
p-CF_3 [**397**]	**424**	57%	>99:1
m-F [**398**]	**425**	69%	>99:1
p-F [**400**]	**426**	65%	>99:1

Scheme 84. *Reagents and Conditions*: (i) $NaBrO_3$, $Na_2S_2O_4$, EtOAc/H_2O, rt, 4 h then 1.0 M aq HCl; (ii) propylene oxide, ^{i}PrOH, rt, 6 h.

4.3. Conclusion

Methodology for the regioselective ring-opening of aziridinium intermediates by sources of fluoride, azide and acetate has been developed, enabling the direct conversion of α-hydroxy-β-amino esters to β-substituted-α-amino esters. Application of this methodology in the asymmetric syntheses of C(3)-aryl substituted β-fluoro-α-amino acids and a representative α,β-diamino acid has been demonstrated. This has required investigations into *N*-debenzylation methods which are compatible with a sensitive benzylic fluoride moiety and has culminated in the development of a one-pot protocol for the deprotection of β-fluoro-α-amino esters to the corresponding β-fluoro-α-amino acids (Figure 45).

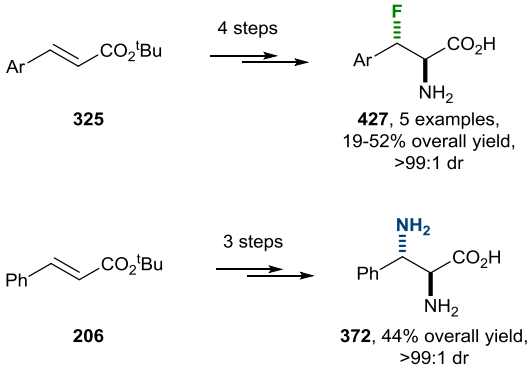


Figure 45. Asymmetric synthesis of β-substituted-α-amino acids from commercially available starting materials.

4.4. References and notes

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[25] **377** was isolated with a 16% impurity of an unknown fluorine-containing species.

[26] An analogous rearrangement was observed when a substrate with *p*-methoxybenzyl groups was used in an attempt to form a tetrahydroisoquinoline from a α-hydroxy-β-amino ester; see Kennedy, M. S. *Part II Thesis*, University of Oxford, **2014**.

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[33] **396** was isolated with ~17% of an unknown, non-fluorinated impurity.

[34] The relative 3,4-*anti*-configurations within tetrahydroisoquinolines **301** and **302** were assigned by ^{1}H NMR ^{3}J coupling constant analyses: for *anti*-tetrahydroisoquinolines, $^{3}J_{3,4}$ = 1.5–4.0 is usually observed whereas $^{3}J_{3,4}$ = 5.5–6.0 is indicative of *syn*-tetrahydroisoquinolines, see: (a) Brozda, D.; Koroniak, L.; Rozwadowska, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 3017. (b) Chen, W.; Cui, J.; Zhu, Y.; Hu, X.; Mo, W. *J. Org. Chem.* **2012**, *77*, 1585. (c) Hammad, S. F.; Smith, F. T. *J. Heterocyclic Chem.* **2013**, *50*, 114.

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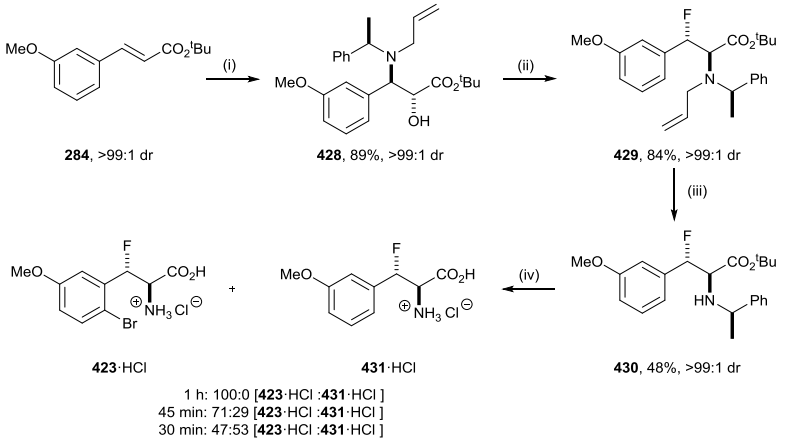
[36] Studies were undertaken to ascertain whether deprotection of a single *N*-(α-methylbenzyl) group would occur faster than bromination of a *m*-OMe substituted aryl ring. *N*-(α-Methylbenzyl) protected β-fluoro-α-amino ester **430** was prepared from **284** via aminohydroxylation, fluorination and deallylation. Reaction of **430** with $NaBrO_3$ and $Na_2S_2O_4$ at rt for 1 h effectively removed the *N*-(α-methylbenzyl) group, but also resulted in bromination, giving full conversion to **423**·HCl. Repeating the reaction for 45 min also showed full conversion of starting material, giving a 71:29 ratio of **423**·HCl and **431**·HCl. After 30 min, a 47:53 ratio of **423**·HCl and **431**·HCl was recovered, however decreasing the reaction time further was found insufficient to promote debenzylation. It was concluded that selective formation of **431**·HCl was not possible via this method (Scheme 85).



Scheme 85. *Reagents and Conditions*: (i) (*R*)-**388**, BuLi, THF, −78 °C, 2 h, then (−)-CSO **202**, −78 °C to rt, 18 h; (ii) XtalFluor-E® **336**, $Et_3N{\cdot}3HF$, CH_2Cl_2, rt, 2 h; (iii) DMBA, $Pd(PPh_3)_4$, CH_2Cl_2,rt, 18 h; (iv) $NaBrO_3$, $Na_2S_2O_4$, H_2O/EtOAc (2:1), rt, time: see scheme.

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Chapter 5: 1,2,3,4-Tetrahydroisoquinolines via aziridinium intermediates

This chapter describes studies concerning the conversion of α-hydroxy-β-amino esters **432** into tetrahydroisoquinolines[1] **435** via a stereoselective rearrangement (Figure 46).

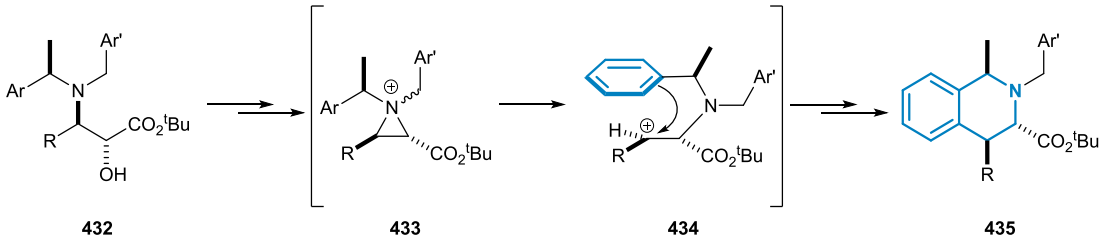


Figure 46. Tetrahydroisoquinolines **435** from α-hydroxy-β-amino esters **432** via an aziridinium ion **433**.

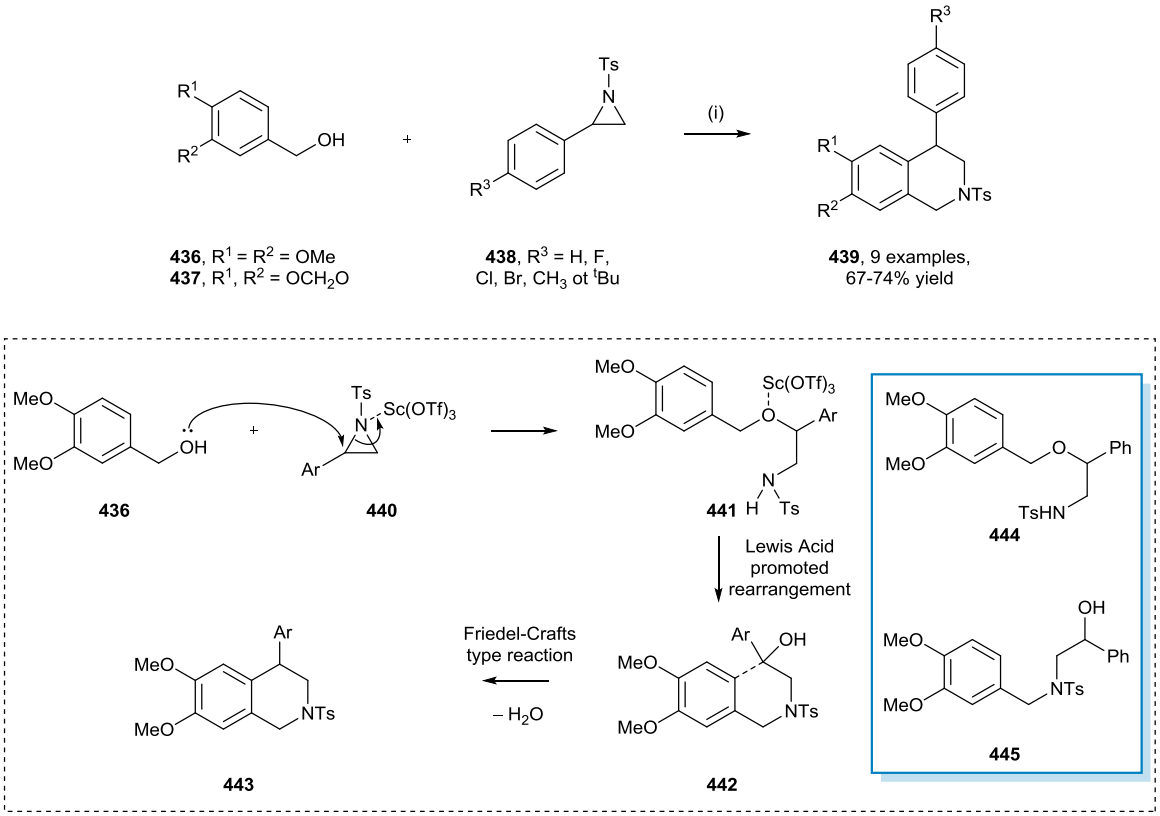
5.1. Existing syntheses of tetrahydroisoquinolines

The tetrahydroisoquinoline motif is highly prevalent in many alkaloid natural products and drug candidates, which often exhibit significant biological activity.[2] Classic synthetic methods to access these important molecular scaffolds include the Bischler-Napieralski synthesis[3] and Pictet-Spengler reaction,[4] but substantial efforts into the development of new methods for tetrahydroisoquinoline formation have been reported in recent years, including C−H activation strategies,[5] acid-catalysed cyclisations[6] and via Lewis acid promoted Friedel-Crafts type reactions,[7] amongst others.[8] Representative examples of recently reported syntheses of tetrahydroisoquinolines are discussed below.

5.1.1. Tetrahydroisoquinolines from aziridines

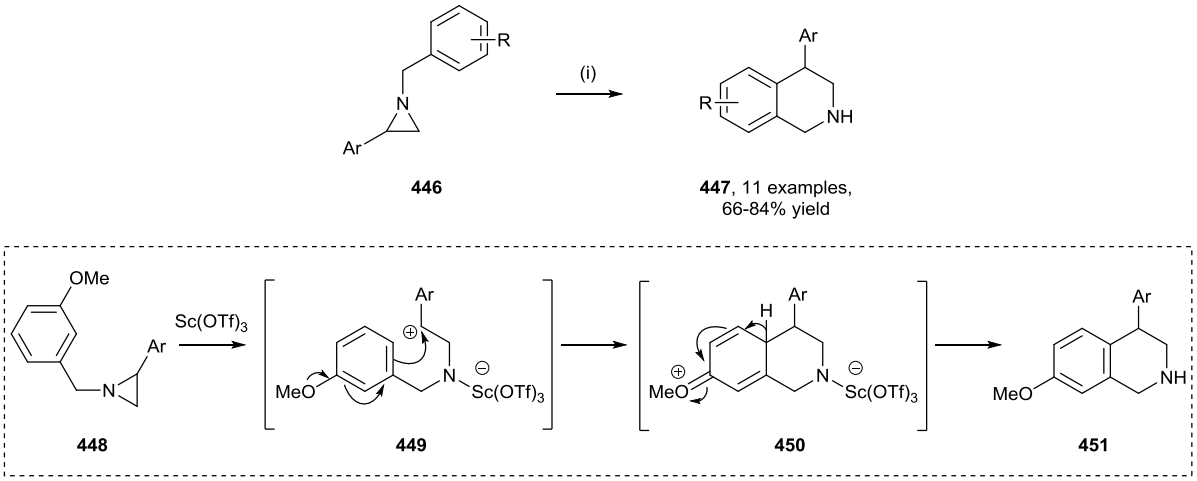
Wang and co-workers have developed a [3+3] annulation process for the synthesis of tetrahydroisoquinolines **439** from benzylic alcohols **436** or **437** and *N*-tosyl aziridines **438**.[9] Treatment of aziridines **438** with $Sc(OTf)_3$ in the presence of alcohols **436** or **437** gave tetrahydroisoquinolines **439** in 67–74% yield. A mechanism was proposed for this reaction based on the isolation of two intermediates, **444** and **445**, which were obtained by stopping the reaction after 3 and 6 h, respectively: the $Sc(OTf)_3$ Lewis acid activates aziridine **440**, enabling nucleophilic attack by **436**. Subsequent Lewis acid-promoted rearrangement is followed by Friedel-Crafts type attack by the substituted aromatic ring, giving 4-aryl tetrahydroisoquinolines **443**. The authors stated that the aryl substituent on the aziridine was crucial to the success of this reaction, postulating that this substituent may facilitate ring-opening of the aziridine. Additionally, this methodology was limited to benzyl alcohols in which R^1 and R^2 were electron donating groups; reaction with benzyl alcohol under identical

conditions halted at the 2° amine intermediate, implying that an electron rich arene was necessary to promote subsequent rearrangement (Scheme 86).



Scheme 86. *Reagents and Conditions*: (i) $Sc(OTf)_3$ (5 mol %), DCE, reflux, 15 h.

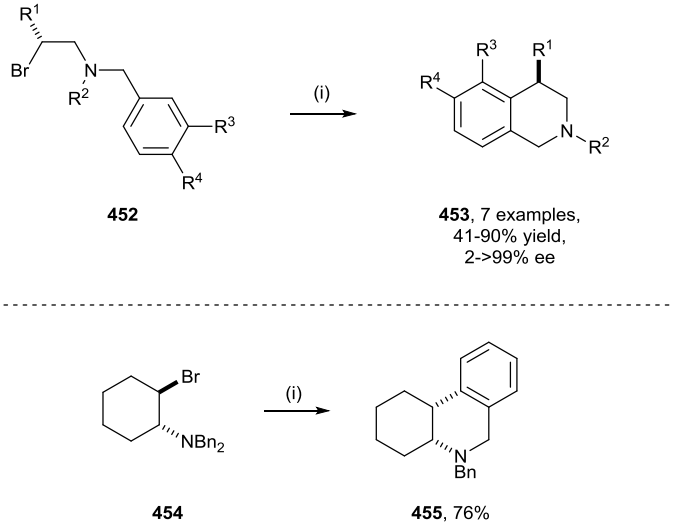
Tummanapalli *et al*. have reported an intramolecular ring-expansion of aziridines **446** which gave tetrahydroisoquinolines **447**, in which $Sc(OTf)_3$ is used as a Lewis acid.[10] Electron donating groups at the *meta*-position of the *N*-benzyl group were found to be necessary to promote the cyclisation reaction, consistent with the reaction mechanism proposed by the authors in which carbenium ion **449** is trapped by the *N*-(3-methoxy)benzyl moiety (Scheme 87).



Scheme 87. *Reagents and Conditions*: (i) $Sc(OTf)_3$ (1.2 equiv.), DCE, 90 °C, 2 h.

5.1.2. Tetrahydroisoquinolines from β-bromoamines

Chong and Chen have reported a Friedel-Crafts type rearrangement of β-bromoamines **452** to tetrahydroisoquinolines **453**.[11] *N*-Benzyl substituted tetrahydroisoquinolines were obtained in good to high enantiomeric excesses, with retention of configuration at the C(4) position. Studies into the nature of the non-cyclising group on N saw a decrease in ee when R^2 = allyl or methyl, which the authors speculated may be due to a reduced π-π stacking interaction, relative to the corresponding *N*,*N*-dibenzyl substrates.[12] In a more recent publication by the same authors, rearrangement of cyclic bromoamine **454** is reported to occur with overall inversion of configuration, giving *cis*-fused tetrahydroisoquinoline **455**[13] (Scheme 88).



Scheme 88. *Reagents and Conditions*: (i) $AlCl_3$, PhMe or DCE, −20 °C, 0 °C, or reflux, 2 h.

5.2. Results and discussion

5.2.1. Synthetic strategy

As described previously in this thesis, tetrahydroisoquinolines have been observed as side products in reactions which proceed via aziridinium intermediates. The first such instance was upon activation of β-chloro-α-amino ester (±)-**250** with AgOTf, which gave 39% conversion to tetrahydroisoquinoline (±)-**261** as a single diastereoisomer (>99:1 dr), which was subsequently isolated in 21% yield. Furthermore, direct conversion of *p*-methoxy substituted α-hydroxy-β-amino ester **291** to a regioisomeric mixture of tetrahydroisoquinolines **301** and **302** was observed when **291** was reacted with either Ms_2O or XtalFluorE® **336**. In all three cases, these results were attributed to a reaction pathway, in which rupture of the N−C(3) bond within the aziridinium intermediate gave rise to the corresponding carbocationic intermediate, which was subsequently trapped by an *N*-benzyl protecting group in a Friedel-Crafts type reaction. This precedent showed it was possible to access the tetrahydroisoquinoline motif in a two-step sequence from α-hydroxy-β-amino esters (via the

β-chloro-α-amino ester) and that it may also be possible to achieve this same transformation in a one-pot protocol upon direct activation of α-hydroxy-β-amino esters (Figure 47).

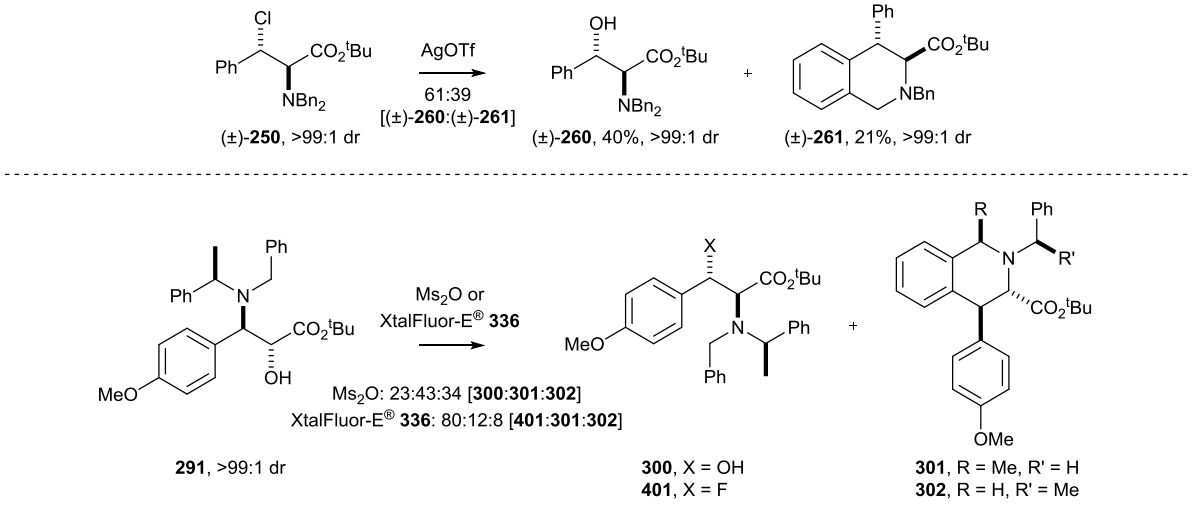


Figure 47. Tetrahydroisoquinoline side products observed during studies into regioselective aziridinium ring-opening.

Thus, it was envisaged that a general method for the synthesis of tetrahydroisoquinolines **459** from α-hydroxy-β-amino esters **456** could be developed. As already demonstrated, aziridinium formation from α-hydroxy-β-amino esters **456** could be achieved by direct activation or via the corresponding β-chloro-α-amino esters. Conditions which allowed ring-opening of aziridinium intermediates **457** to the corresponding carbocations **458** were to be sought, with subsequent cyclisation of an *N*-benzyl group resulting in tetrahydroisoquinolines **459**. Challenges in this work included managing to prevent *in situ* attack of either intermediate **457** or **458** by external nucleophiles, such as adventitious water, and effecting regioselective cyclisation from α-hydroxy-β-amino esters in which the nitrogen protecting groups were not identical, so that the Davies aminohydroxylation methodology may be used to access enantiopure α-hydroxy-β-amino ester cyclisation precursors (Figure 48).

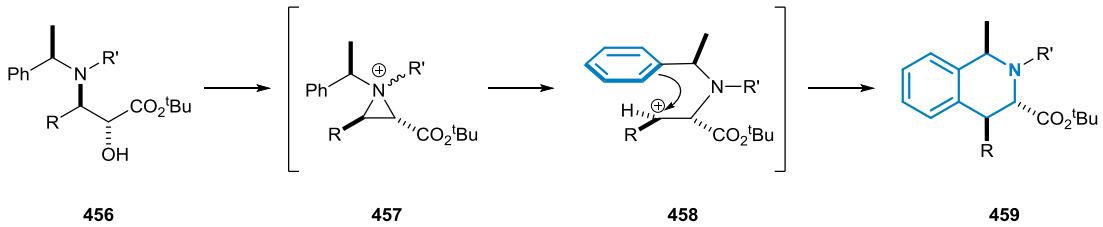


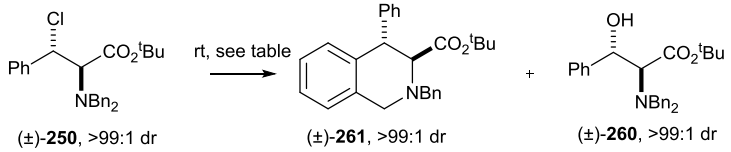
Figure 48. Proposed strategy for the synthesis of tetrahydroisoquinolines **459** from α-hydroxy-β-amino esters **456** via aziridinium intermediates **457**.

5.2.2. Model studies

Studies began on racemic *N*,*N*-dibenzyl protected α-hydroxy-β-amino esters, so that a tetrahydroisoquinoline formation reaction could be optimised without the added complexity of competitive cyclisation of the *N*-benzyl and *N*-(α-methylbenzyl) groups in the corresponding enantiopure series, which would give rise to regioisomeric products.

5.2.2.1. Reaction optimisation

In the first instance, the transformation of β-chloro-α-amino ester (±)-**250** to tetrahydroisoquinoline (±)-**261** was investigated to see if a condition set could be identified in which conversion to (±)-**261** would be favoured over formation of β-hydroxy-α-amino ester (±)-**260**. Building on the lead result in which β-chloro-α-amino ester (±)-**250** was treated with AgOTf, $AgBF_4$ was trialled as an alternative activating agent, but resulted in a 17:83 ratio of (±)-**261** and (±)-**260**, respectively. Solvents were next screened, with both PhMe and CH_2Cl_2 showing the highest levels of conversion to tetrahydroisoquinoline (±)-**261**, giving a 100:0 (PhMe) and a 94:6 (CH_2Cl_2) mixture of (±)-**261** and (±)-**260**, respectively. Isolation of (±)-**261** in was achieved in 68% yield for the reaction in CH_2Cl_2, but in only 9% yield[14] for the corresponding reaction in PhMe. Very high diastereoselectivity was observed in all cases, with (±)-**261** being formed in >99:1 dr (Scheme 89).



(±)-**250**, >99:1 dr (±)-**261**, >99:1 dr (±)-**260**, >99:1 dr

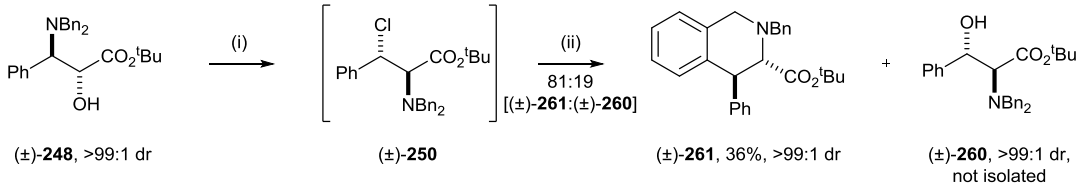
reagent	solvent	time	product ratio (±)-**261**:(±)-**260**:(±)-**250**	yield (±)-**261**
AgOTf	EtOAc	1 h	39:61:0	21%
$AgBF_4$	EtOAc	18 h	17:83:0	-
AgOTf	THF	18 h	32:68:0	-
AgOTf	MeCN	18 h	42:47:11	-
AgOTf	PhMe	18 h	100:0:0	9%
AgOTf	CH_2Cl_2	18 h	94:6:0	68%

Scheme 89. Optimisation of the formation of tetrahydroisoquinoline (±)-**261** from β-chloro-α-amino ester (±)-**250**.

5.2.2.2. Development of a one-pot protocol

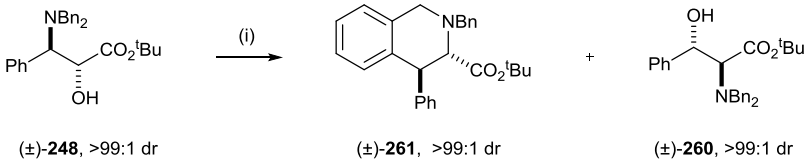
Attention was turned next to investigating a one-pot method to synthesise tetrahydroisoquinolines directly from α-hydroxy-β-amino esters. As the formation of tetrahydroisoquinoline (±)-**261** from β-chloro-α-amino ester (±)-**250** was known to proceed with high levels of conversion in PhMe, it was envisaged that a one-pot Appel reaction/rearrangement process may be possible. Therefore α-hydroxy-β-amino ester (±)-**248** was reacted with PPh_3 and CCl_4 at 100 °C in PhMe for 2 h which gave β-chloro-α-amino ester (±)-**250**. The reaction mixture was filtered through neutral alumina to remove $Ph_3P{=}O$ and AgOTf was then added, after which the reaction mixture was stirred at rt for 18 h. This resulted in an 81:19 ratio of (±)-**261** and (±)-**260**, respectively, from which tetrahydroisoquinoline (±)-**261** was isolated in 36% yield and >99:1 dr. This first generation

approach showed that it was possible to access tetrahydroisoquinolines directly from α-hydroxy-β-amino esters, however operational difficulty in not being able to filter the reaction mixture under strictly anhydrous conditions meant that β-hydroxy-α-amino ester (±)-**260** was always observed as a side product. Furthermore, the reaction was low yielding and proved somewhat unreliable, necessitating the development of a new strategy (Scheme 90).

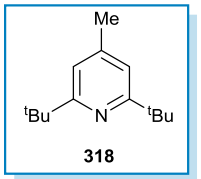


Scheme 90. *Reagents and Conditions*: (i) PPh_3, CCl_4, PhMe, 100 °C, 2 h, then alumina; (ii) AgOTf, rt, 18 h, then neutral alumina.

It was proposed that Tf_2O may be a suitable reagent for this transformation; the triflate anion is a very good leaving group with the added benefit that it is a relatively poor nucleophile. Furthermore previous work (Chapter 3) had identified this as a reagent capable of facilitating the rearrangement of β-alkyl-α-hydroxy-β-amino esters to β-alkyl-β-hydroxy-α-amino esters and the conversion of β-chloro-α-amino (±)-**250** to the corresponding tetrahydroisoquinoline was known to work well in the presence of a triflate anion, from studies involving AgOTf. Thus, (±)-**248** was reacted with 3.0 equiv of Tf_2O in the presence of Et_3N (6.0 equiv), to give a complex mixture from which tetrahydroisoquinoline (±)-**261** was isolated in 37% yield and >99:1 dr. The use of the bulky base 2,6-di-*tert*-butyl-4-methylpyridine **318** was tried next, as this base is often used alongside Tf_2O,[15] and in polymerisation reactions as its steric bulk prevents it from reacting with carbocationic intermediates.[16] Reaction of (±)-**248** with 3.0 equiv of Tf_2O and 6.0 equiv of **318** enabled the isolation of (±)-**261** in 58% yield and >99:1 dr. However, optimised conditions were found by decreasing the equivalents of Tf_2O and base used to 1.5 and 3.0, respectively: this resulted in the exclusive formation of (±)-**261** as a single diastereoisomer (>99:1 dr), which was isolated in 76% yield (Scheme 91).



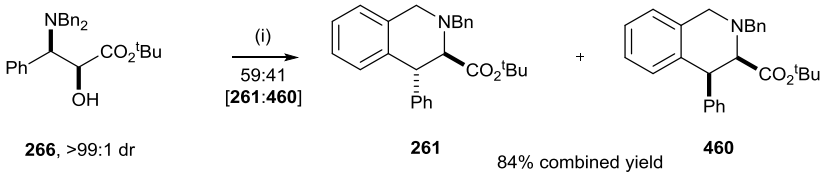
equiv Tf_2O	base	equiv base	yield (±)-**261**
3	Et_3N	6	37%
3	**318**	6	58%
1.5	**318**	3	76%



Scheme 91. *Reagents and Conditions*: (i) Tf_2O, base (see table), CH_2Cl_2, 0 °C, then rt, 6 h.

5.2.2.3. Mechanistic considerations

During investigations into the formation of tetrahydroisoquinoline (±)-**261**, only one diastereoisomer was ever observed upon reaction of *anti*-(±)-**248**, so it was proposed that attempted tetrahydroisoquinoline formation from *syn*-**266** should also be investigated. A sample of *syn*-**266**, which was prepared as discussed in Chapter 3, was reacted with Tf_2O and **318** under the optimised reaction conditions for tetrahydroisoquinoline formation. In this case the reaction did not proceed with high diastereoselectivity, resulting in a 59:41 mixture of *anti*-**261** and *syn*-**460**, respectively. The relative configuration within 3,4-*syn*-**460** ($^3J_{3,4}$ = 5.5 Hz) was assigned based on ^{1}H NMR ^3J coupling constant analysis as 3,4-*syn*-tetrahydroisoquinolines are known to display diagnostic values ($^3J_{3,4}$ = 5.5–6.0 Hz)[17] (Scheme 92).



Scheme 92. *Reagents and Conditions*: (i) Tf_2O, **318**, CH_2Cl_2, 0 °C, then rt, 6 h.

The observation of a mixture of epimers as a result of this reaction, with *trans*-**261** as the major product, gives credence to the proposal that this reaction proceeds via a carbocationic intermediate. Upon activation of *anti*-**248**, *trans*-aziridinium **249** is formed, followed by ring-opening to the corresponding carbocation in conformation **262A**, which undergoes rapid ring-closure to *trans*-**261** (in >99:1 dr). For *syn*-**266** however, treatment with Tf_2O results in formation of *cis*-aziridinium **268**. In this case, the corresponding carbocation is formed in conformation **262B**, which is presumably higher in energy than **262A** as the phenyl and ester substituents can experience unfavourable steric interactions. Collapse of conformer **262B** to tetrahydroisoquinoline **460** would be accompanied by an increase in steric strain, so ring-closure in this case is presumably slower than for ring-closure of conformer **262A**. This may allow rotation around the central C(2)–C(3) bond to occur at a competitive rate, alleviating this steric strain and giving rise to conformer **262A**, for which trapping with an *N*-benzyl group is rapid. Thus, cyclisation of **262A** presumably occurs faster than C–C bond rotation, and high diastereoselectivity is therefore observed in this case (Figure 49).

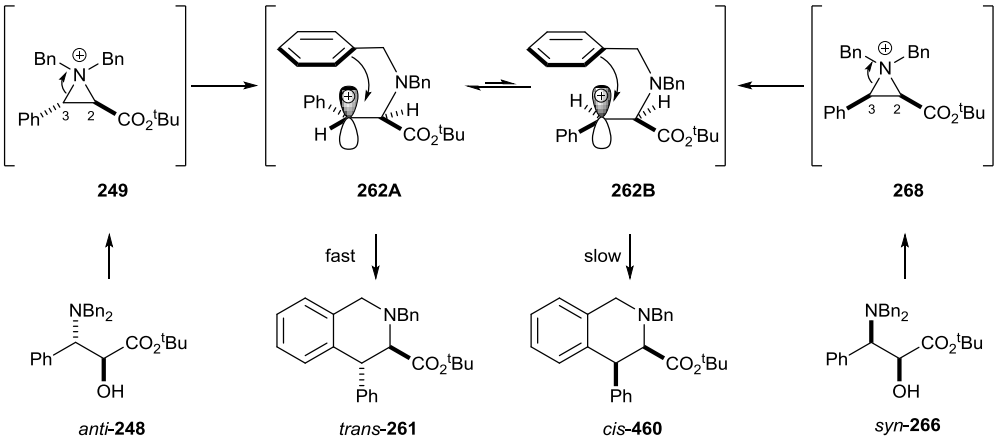
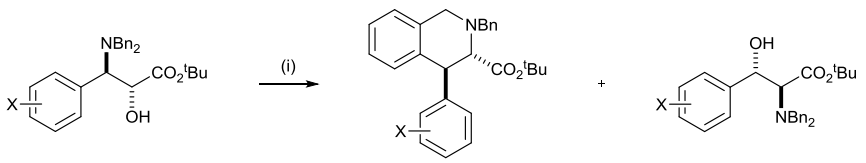


Figure 49. Proposed mechanistic explanation of the diastereoselectivities observed upon reaction of *anti*-**248** versus *syn*-**266** with Tf_2O.

5.2.2.4. Substrate scope

Investigations into the substrate scope of this methodology were undertaken in conjunction with Mr M. S. Kennedy.[18] In these studies, the substituents around the aryl ring were varied in order to evaluate the impact of electronic perturbations upon this reaction, and to see if these results may corroborate the proposed reaction mechanism. It was found that increasing the electron withdrawing ability of the substituent on the C(3)-aryl ring resulted in competitive formation of a β-hydroxy-α-amino ester side product. For α-hydroxy-β-amino ester (±)-**461** (X = *p*-CF_3), full conversion to β-hydroxy-α-amino ester (±)-**471** was observed upon reaction with Tf_2O and **318** at rt for 6 h, however upon heating the reaction mixture at reflux for 6 h an 80:20 mixture of tetrahydroisoquinoline (±)-**466** and β-hydroxy-α-amino ester (±)-**471** was recovered, from which (±)-**466** was isolated in 62% yield (>99:1 dr). Reaction of (±)-**462** (X = *m*-F) under the standard reaction conditions gave a 73:27 mixture of tetrahydroisoquinoline (±)-**467** and β-hydroxy-α-amino ester (±)-**472**, with isolation of (±)-**467** achieved in 58% yield, and in >99:1 dr. Full conversion to tetrahydroisoquinoline products (±)-**468** and (±)-**469** was achieved under standard reaction conditions for α-hydroxy-β-amino esters (±)-**463** (X = *m*-OMe) and (±)-**464** (X = *p*-F), enabling the isolation of (±)-**468** and (±)-**469** in 57 and 73% yield, respectively, and in >99:1 dr in both cases. Increasing the electron density of the C(3)-aryl ring further caused a reduction in diastereoselectivity: reaction of (±)-**465** (X = *p*-OMe) with Tf_2O and **318** at rt for 6 h gave tetrahydroisoquinoline (±)-**470** in 75:25 dr, although cooling the reaction mixture to –20 °C and reducing the reaction time to 2.5 h gave (±)-**470** in an improved 85:15 dr, from which (±)-**470** was isolated in 66% yield and 85:15 dr. In all cases the ^{1}H NMR $^3J_{3,4}$ coupling constant values of the major tetrahydroisoquinoline products were within the diagnostic range for 3,4-*anti*-tetrahydroisoquinolines ($^3J_{2,3}$ = 1.5–4 Hz)[17] (Scheme 93).



A, >99:1 dr **B** **C**

X	A	σ^+	temp	time	B	C	crude ratio A:B	crude dr of B	yield B	isolated dr of B
p-CF_3	(±)-**461**	+0.61	rt	6 h	(±)-**466**	(±)-**471**	0:100	>99:1	-	>99:1
			40 °C	6 h			80:20	>99:1	62%	>99:1
m-F	(±)-**462**	+0.35	rt	6 h	(±)-**467**	(±)-**472**	73:27	>99:1	58%	>99:1
m-OMe	(±)-**463**	+0.05	rt	6 h	(±)-**468**	(±)-**473**	100:0	>99:1	57%	>99:1
p-F	(±)-**464**	-0.07	rt	6 h	(±)-**469**	(±)-**474**	100:0	>99:1	73%	>99:1
p-OMe	(±)-**465**	-0.78	rt	6 h	(±)-**470**	(±)-**475**	100:0	75:25	34%	75:25
			–20 °C	2.5 h			100:0	85:15	66%	85:15

Scheme 93. *Reagents and Conditions*: (i) Tf_2O, **318**, CH_2Cl_2 temperature and time: see table.

The observation of β-hydroxy-α-amino esters when an electron withdrawing substituent is placed on the C(3)-aryl ring, and of diastereoisomeric mixtures of products when a highly electron donating substituent is present, is consistent with the proposed reaction mechanism. Activation of **476** with Tf_2O gives rise to aziridinium intermediate **477**. If X is an electron withdrawing group, then ring-opening to the corresponding carbocation **478A** may be disfavoured, and the aziridinium intermediate may instead be preferentially opened by either adventitious water or upon work up, to give β-hydroxy-α-amino ester **479**. Good levels of conversion to tetrahydroisoquinoline products can be achieved upon heating, perhaps enabling the energetic barrier for rupture of the C(3)–N bond and carbocation formation to be overcome. The reduction in diastereoselectivity observed when X is an electron donating group is consistent with reaction via carbocationic intermediate **478A**: stabilisation of this proposed intermediate by the electron-rich aryl group may occur to the extent that the rate of C(2)–C(3) bond rotation becomes competitive with the rate of cyclisation (Figure 50).

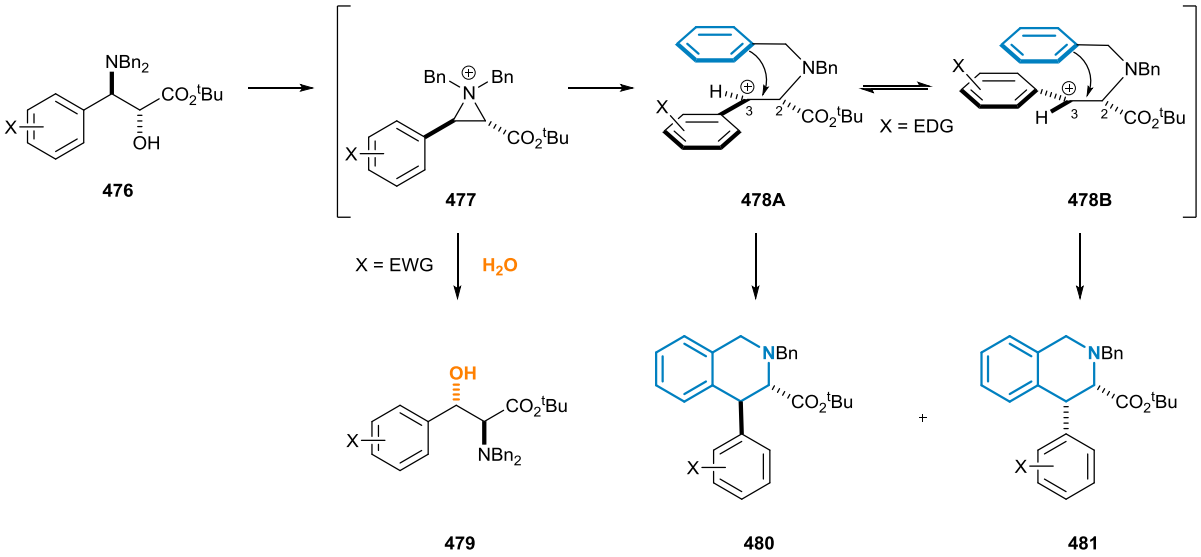
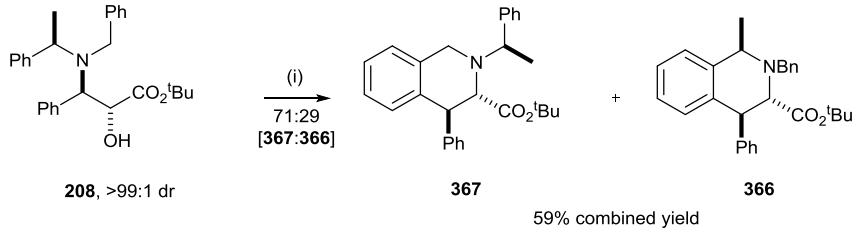


Figure 50. Proposed explanation of effect of X = EWG and X = EDG.

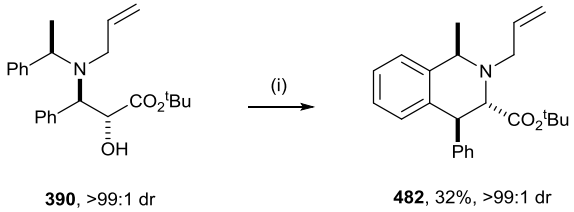
5.2.3. Asymmetric synthesis of enantiopure tetrahydroisoquinolines

With an optimised procedure for the one-pot, diastereoselective synthesis of racemic tetrahydroisoquinolines from α-hydroxy-β-amino esters developed, attention was turned next towards applying this methodology in the synthesis of enantiopure tetrahydroisoquinolines. As expected, reaction of enantiopure α-hydroxy-β-amino ester **208** with Tf_2O and **318** in CH_2Cl_2 gave a 71:29 mixture of regioisomers **367** and **366**, respectively, which were inseparable by chromatography and isolated in a 59% combined yield (Scheme 94).



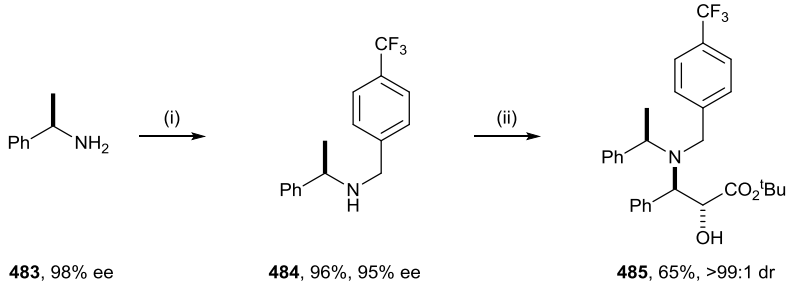
Scheme 94. *Reagents and Conditions*: (i) Tf_2O, **318**, CH_2Cl_2 0 °C, then rt, 6 h.

It was envisaged that changing the nitrogen protecting groups within the α-hydroxy-β-amino ester, such that only one of the protecting groups would be able to cyclise, may solve these regioselectivity issues. Thus *N*-allyl-*N*-α-methylbenzyl substituted α-hydroxy-β-amino ester **390** (prepared as described in Chapter 4) was reacted with Tf_2O under the standard reaction conditions, to give tetrahydroisoquinoline **482**, which was isolated in 32% yield and >99:1 dr. Attempts to improve this yield by alternative isolation and deprotection methods were unsuccessful[19] (Scheme 95).



Scheme 95. *Reagents and Conditions*: (i) Tf_2O, **318**, CH_2Cl_2 0 °C, then rt, 6 h.

As higher yields and cleaner conversion to tetrahydroisoquinoline products had been observed when both protecting groups on nitrogen were *N*-benzyl groups, investigations focussed next on trying to bias cyclisation of one benzyl group over another. Increasing the electron density of one ring (i.e., by adding a *p*-OMe group) to promote cyclisation through that ring lead to β,β-di-aryl products[19] (c.f. Chapter 4, *vide supra*), and any attempts to optimise this process were abandoned as this would limit the methodology by only allowing the synthesis of methoxy-substituted tetrahydroisoquinolines. Instead it was envisaged that regioselective cyclisation may be achieved by adding an electron withdrawing group to one of the aryl rings, thus retarding cyclisation through this electron poor group, in favour of cyclisation via the unsubstituted benzyl group. To test this proposal, a lithium amide reagent, incorporating a *p*-CF_3 group on one of the aryl rings, was synthesised: reductive alkylation of (*R*)-α-methylbenzylamine **483** with *p*-CF_3 substituted benzaldehyde gave (*R*)-*N*-[4-(trifluoromethyl)benzyl]-*N*-(α-methylbenzyl)amine **484** in 96% yield and 95% ee.[20] Conjugate addition of the lithium amide reagent derived from **484** to α,β-unsaturated ester **206**, with *in situ* oxidation of the intermediate lithium (*Z*)-β-amino enolate[21] with (−)-CSO **202**, proceeded with complete diastereoselectivity, giving **485** in 65% yield and >99:1 dr. The relative *anti*-configuration within **485** was assigned by analogy to the established stereochemical outcome of the aminohydroxylation reaction[22] and was supported by ^{1}H NMR $^3J_{2,3}$ coupling constant analysis, with a value of $^3J_{2,3}$ = 3.1 Hz for **485** within the expected range for *anti*-configured α-hydroxy-β-amino esters ($^3J_{2,3}$ = 2.0–4.5 Hz)[23] (Scheme 96).

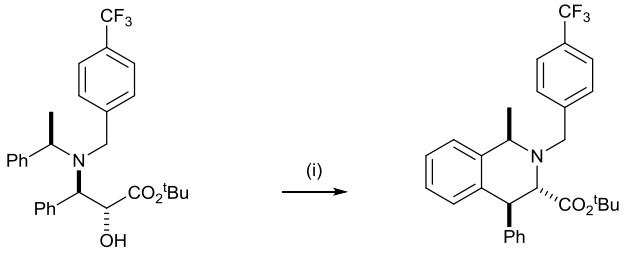


483, 98% ee **484**, 96%, 95% ee **485**, 65%, >99:1 dr

Scheme 96. *Reagents and Conditions*: (i) 4-$CF_3C_6H_5CHO$, EtOH, reflux, 3 h, then $NaBH_4$, 0 °C to rt, 20 h; (ii) **206**, BuLi, THF, –78 °C, 2 h, then **202**, –78 °C to rt, 18 h.

Attempted tetrahydroisoquinoline formation from **485** was investigated next, to assess whether the *p*-CF_3 substituent on the aryl ring was sufficiently electron withdrawing to result in regioselective cyclisation of the *N*-(α-methylbenzyl) group. Reaction of α-hydroxy-β-amino ester **485** with Tf_2O and **318** gave exclusive conversion to *N*-(*p*-trifluoromethyl)benzyl substituted tetrahydroisoquinoline **486** in 72% isolated yield and >99:1 dr, with the regiochemistry of **486** confidently assigned via ^{1}H-^{13}C HMBC analysis. This reaction shows

completely diastereoselective formation of tetrahydroisoquinoline **486**,[24] in a much improved yield when compared with the corresponding *N*-allyl-*N*-(α-methylbenzyl) protected substrate **390**. In this case the *N*-(α-methylbenzyl) chiral auxiliary is retained in the tetrahydroisoquinoline product, making this an efficient route to C(1)-methyl substituted tetrahydroisoquinolines (Scheme 97).

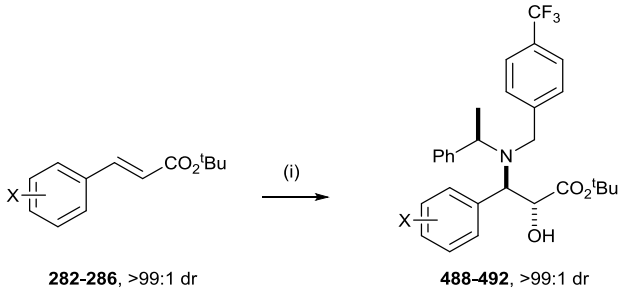


485, >99:1 dr **486**, 72%, >99:1 dr

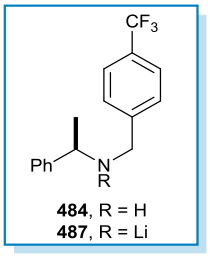
Scheme 97. *Reagents and Conditions*: (i) Tf_2O, **318**, CH_2Cl_2, 0 °C, then rt, 6 h.

5.2.4. Substrate scope

The optimised conditions for tetrahydroisoquinoline formation were next applied to the range of substituted α-hydroxy-β-amino esters **488**–**492**. The synthesis of **488**–**492** was achieved by conjugate addition of lithium amide (*R*)-**487** to α,β-unsaturated esters **282**–**286**, with *in situ* oxidation of the intermediate lithium (*Z*)-β-amino enolates[21] with (−)-CSO **202**, giving β-amino-α-hydroxy esters **488**–**492** in 67–95% yield and >99:1 dr in each case. The 2,3-*anti*-configurations within **488**–**492** were assigned based on the established stereochemical outcome of the aminohydroxylation reaction,[22] and these assignments were supported by ^{1}H NMR $^3J_{2,3}$ coupling constant analyses, with the magnitude of the ^{1}H NMR $^3J_{2,3}$ coupling constants falling within the expected range for *anti*-configured α-hydroxy-β-amino esters ($^3J_{2,3}$ = 2.0–4.5 Hz)[23] in all cases (Scheme 98).



282-286, >99:1 dr **488-492**, >99:1 dr

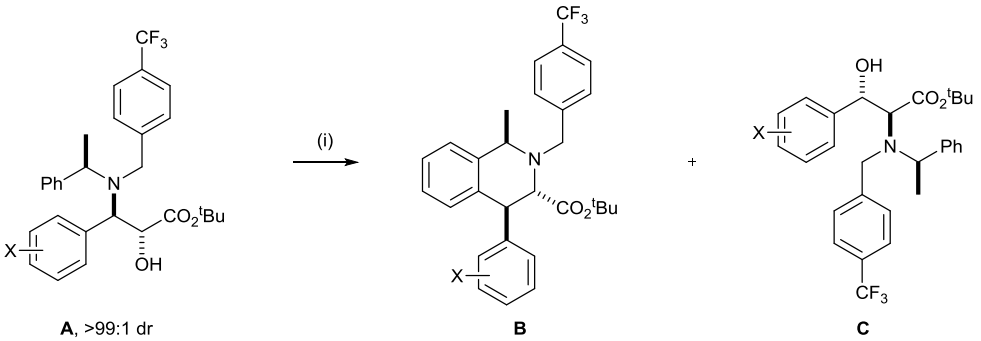


484, R = H
487, R = Li

	X	σ+	dr		yield
282	*p*-CF_3	+0.61	>99:1	**488**	71%
283	*m*-F	+0.35	>99:1	**489**	67%
284	*m*-OMe	+0.05	>99:1	**490**	95%
285	*p*-F	-0.07	>99:1	**491**	85%
286	*p*-OMe	-0.78	>99:1	**492**	81%

Scheme 98. *Reagents and Conditions*: (i) (*R*)-**484**, BuLi, THF, −78 °C, 2 h, then **202**, −78 °C to rt, 18 h.

With α-hydroxy-β-amino esters **488**–**492** in hand, attention was turned to the synthesis of enantiopure tetrahydroisoquinolines from these substrates. Reaction of **488**–**492** proceeded similarly to their *N*,*N*-dibenzyl α-hydroxy-β-amino ester analogues (*vide supra*). For α-hydroxy-β-amino esters **488** (X = *p*-CF_3) and **489** (X = *m*-F), it was necessary to heat the reaction mixture at reflux for 6 h to achieve full conversion: reaction of **488** (X = *p*-CF_3) gave a 93:7 mixture of tetrahydroisoquinoline **493** and β-hydroxy-α-amino ester **497**, respectively, from which **493** was isolated in 66% yield and >99:1 dr. For **489** (X = *m*-F) a 96:4 mixture of tetrahydroisoquinoline **494** and β-hydroxy-α-amino ester **498** was recovered, from which **494** was isolated in 75% yield and >99:1 dr. The relatively electronically neutral α-hydroxy-β-amino esters **490** (X = *m*-OMe) and **491** (X = *p*-F) were found to react cleanly under standard reaction conditions (i.e., rt, 6 h) to give full conversion to tetrahydroisoquinolines **495** and **496**, respectively, which were isolated in 81 and 89% yield and in >99:1 dr in both cases. The regiochemistries of **493**–**496** were assigned via ^{1}H-^{13}C HMBC analyses, and the relative 3,4-*anti*-configurations within **493**–**496** were assigned from ^{1}H NMR ^{3}J coupling constant analyses,[17] with $^{3}J_{3,4}$ values consistent with those usually observed for 3,4-*anti*-tetrahydroisoquinolines ($^{3}J_{3,4}$ = 1.5–4.0 Hz) in all cases (Scheme 99).



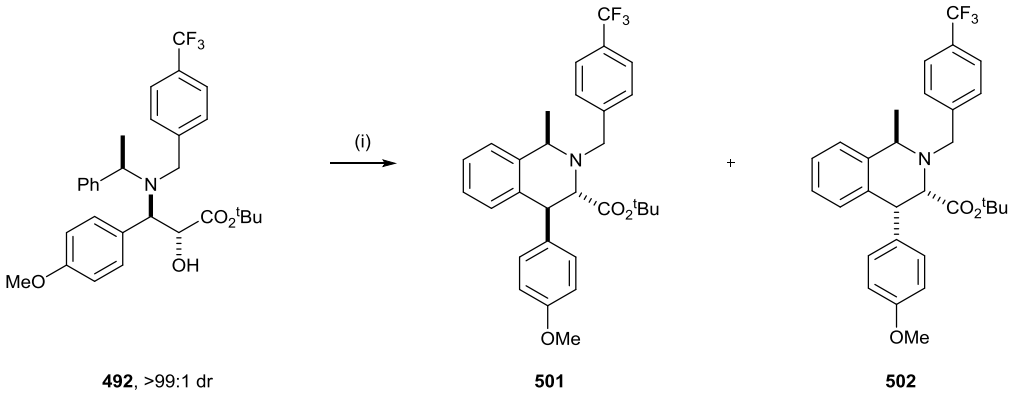
A, >99:1 dr **B** **C**

X	A	temp	time	B	C	crude ratio B: C	crude dr	yield B
p-CF_3	**488**	40 °C	6 h	**493**	**497**	93:7	>99:1	66%
m-F	**489**	40 °C	6 h	**494**	**498**	96:4	>99:1	75%
m-OMe	**490**	rt	6 h	**495**	**499**	100:0	>99:1	81%
p-F	**491**	rt	6 h	**496**	**500**	100:0	>99:1	89%

Scheme 99. *Reagents and Conditions*: (i) Tf_2O, **318**, CH_2Cl_2, temperature and time: see table.

However, when an electron rich *p*-OMe group was placed on the β-aromatic ring, a reduction in diastereoselectivity was observed, with reaction of α-hydroxy-β-amino ester **492** (X = *p*-OMe), giving tetrahydroisoquinoline **501** in 80:20 dr. Efforts to improve the diastereoselectivity of this reaction were undertaken, however reducing the temperature necessitated longer reaction times and did not improve the diastereoisomeric ratio of the crude

reaction mixture. The first condition set attempted proved the most successful: reacting α-hydroxy-β-amino ester **492** with Tf_2O and **318** at –20 °C for 2.5 h gave an 80:20 mixture of **501** and **502**, from which **501** was isolated in 39% yield and >99:1 dr, and **502** in 13% and >99:1 dr, respectively. The regiochemistries of **501** and **502** were assigned via ^{1}H-^{13}C HMBC analyses, and the relative configurations within 3,4-*anti*-**501** and 3,4-*syn*-**502** were assigned based on ^{1}H NMR ^{3}J coupling constant analyses. For **501**, $^{3}J_{3,4}$ = 3.8 Hz which is consistent with that of a 3,4-*anti*-tetrahydroisoquinoline ($^{3}J_{3,4}$ = 1.5–4.0 Hz) whereas for **502**, $^{3}J_{3,4}$ = 5.5 Hz, indicative of a 3,4-*syn*-configuration ($^{3}J_{3,4}$ = 5.5–6.0 Hz)[17] (Scheme 100).



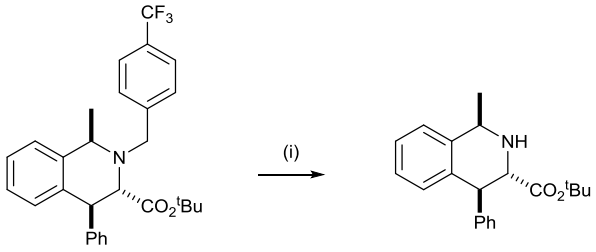
492, >99:1 dr **501** **502**

temp	time	conversion	crude dr	yield 501	yield 502
–20 °C	2.5 h	100%	80:20	39%	13%
–40 °C	6 h	100%	77:23	-	-
–60 °C	10 h	100%	77:23	-	-
–78 °C	10 h	0%	N/A	-	-

Scheme 100. *Reagents and Conditions*: (i) Tf_2O, **318**, CH_2Cl_2, temperature and time: see table.

5.2.5. *N*-Deprotection of tetrahydroisoquinolines

Studies into the hydrogenolytic removal of the *N*(2)-[4-(trifluoromethyl)benzyl] protecting group within tetrahydroisoquinolines **486**, **493**–**496** and **501** began with **486**. Reaction of **486** under H_2 pressure (5 atm) in the presence of $Pd(OH)_2/C$ (40% w/w) at rt for 24 h gave only 80% conversion to **503**. Full conversion to **503** was observed after 48 h, enabling isolation of **503** in 59% yield and >99:1 dr (Scheme 101).

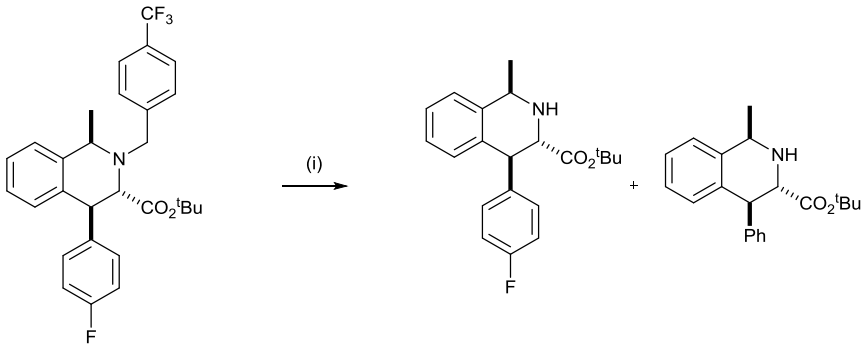


486 **503**

catalyst loading	time	product ratio	yield
40%	24 h	80:20	-
40%	48 h	100:0	59%

Scheme 101. *Reagents and Conditions*: (i) $Pd(OH)_2/C$, H_2 (5 atm), MeOH, rt, time: see table.

However, when **496** (X = *p*-F) was reacted under this optimised protocol, *N*-debenzylation was accompanied by complete defluorination, giving **503** as the sole product. Dropping the catalyst loading from 40% w/w to 25% w/w gave 69% conversion to **504** after 48 h. Full conversion to **504** was observed upon reaction of **496** with 25% w/w $Pd(OH)_2/C$ under H_2 pressure (5 atm) for 5 days, giving **504** in 72% yield and >99:1 dr (Scheme 102).

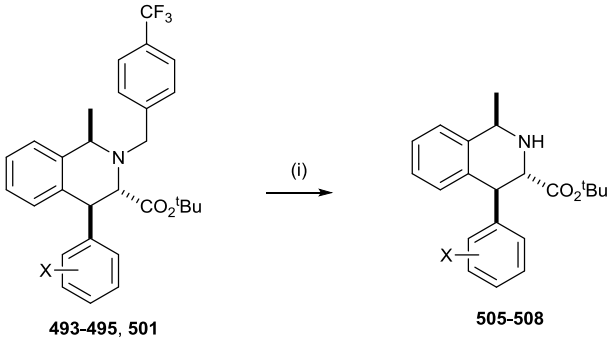


496 **504** **503**

catalyst loading	time	product ratio 496:504:503	yield 504
40%	48 h	0:0:100	-
25%	48 h	31:69:0	-
25%	5 days	0:100:0	72%

Scheme 102. *Reagents and Conditions*: (i) $Pd(OH)_2/C$, H_2 (5 atm), MeOH, rt, time: see table.

Deprotection of the remaining tetrahydrosioquinolines **493** (X = *p*-CF_3), **494** (X = *m*-F), **495** (X = *m*-OMe) and **501** (X = *p*-OMe) was undertaken next. For the fluorine containing substrates **493** and **494**, the protocol found effective for deprotection of **496** (X = *p*-F) was used, giving **505** (X = *p*-CF_3) and **506** (X = *m*-F) in 43 and 37% yield, respectively. Reaction of **495** (X = *m*-OMe) and **501** (X = *p*-OMe) under H_2 pressure (5 atm) in the presence of $Pd(OH)_2/C$ (40% w/w) for 48 h gave **507** (X = *m*-OMe) and **508** (X = *p*-OMe) in 74 and 61% yield, respectively (Scheme 103).



493-495, 501 **505-508**

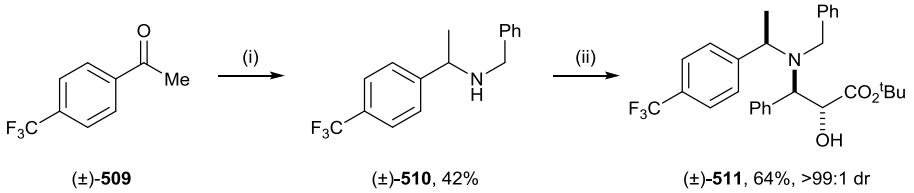
X	catalyst loading	time	product	yield
p-CF_3	25%	5 days	**505**	43%
m-F	25%	5 days	**506**	37%
m-OMe	40%	48 h	**507**	74%
p-OMe	40%	48 h	**508**	61%

Scheme 103. *Reagents and Conditions*: (i) $Pd(OH)_2/C$, H_2 (5 atm), MeOH, rt, time: see table.

5.2.6. Synthesis of enantiopure *N*(2)-[α-methyl-(*p*-trifluoromethyl)benzyl] substituted tetrahydroisoquinolines

5.2.6.1. Model studies: tetrahydroisoquinoline formation

The synthesis of enantiopure *N*(2)-[α-methyl-(*p*-trifluoromethyl)benzyl] substituted tetrahydroisoquinolines would rely on the selective cyclisation of the *N*-benzyl fragment within the α-hydroxy-β-amino ester, and thus would require a strategy to synthesise enantiomerically pure *N*-benzyl-*N*-[α-methyl-(4-trifluoromethyl)benzyl]amine reagent **510**. Initial studies into this selective cyclisation protocol, and the subsequent deprotection of the resultant tetrahydroisoquinoline, were undertaken on the corresponding racemic substrates due to the relative ease of accessing (±)-**510** on scale. Therefore (±)-**510** was synthesised by the reductive alkylation of benzylamine with *p*-CF_3 substituted ketone **509**, giving (±)-**510** in 42% yield. Subsequent conjugate addition of the lithium amide derived from (±)-**510** to *tert*-butyl cinnamate **206**, with *in situ* oxidation of the intermediate lithium (*Z*)-β-amino enolate[21] with (–)-CSO **202**, gave (±)-**511** in 64% yield and in >99:1 dr (Scheme 104). The relative configuration within (±)-**511** was assigned based on the established stereochemical outcome of the aminohydroxylation reaction,[22] and this assignment was supported by ^{1}H NMR $^3J_{2,3}$ coupling constant analysis, with the magnitude of the $^3J_{2,3}$ coupling constant falling within the expected range for *anti*-configured α-hydroxy-β-amino esters ($^3J_{2,3}$ = 2.0–4.5 Hz).[23]

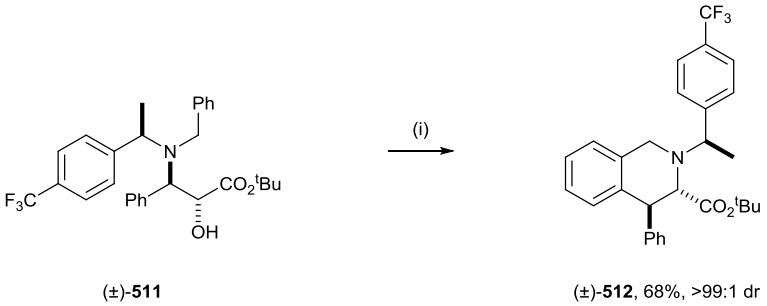


(±)-**509** (±)-**510**, 42% (±)-**511**, 64%, >99:1 dr

Scheme 104. *Reagents and Conditions*: (i) $BnNH_2$, EtOH, reflux, 3 h, then $NaBH_4$, 0 °C to rt, 20 h; (ii) **206**, BuLi, THF, –78 °C, 2 h, then **202**, –78 °C to rt, 18 h.

Reaction of (±)-**511** with Tf_2O and **318** at rt for 6 h resulted in full conversion to a single tetrahydroisoquinoline product (±)-**512**, which was the result of exclusive cyclisation through the unsubstituted phenyl ring, and (±)-**512** was isolated in 68% yield and >99:1 dr. The regiochemistry of (±)-**512** was assigned via ^{1}H-^{13}C HMBC analysis and the relative 3,4-*anti*-configuration within tetrahydroisoquinoline (±)-**512** was initially assigned based on ^{1}H NMR ^3J coupling constant analyses:[17] for 3,4-*anti*-tetrahydroisoquinolines, $^3J_{2,3}$ = 1.5–4.0 Hz is usually observed, whereas $^3J_{2,3}$ = 5.5–6.0 Hz is indicative of 3,4-*syn*-tetrahydroisoquinolines. With $^3J_{2,3}$ = 1.6 Hz for (±)-**512**, a relative 3,4-*anti*-configuration was tentatively assigned (Scheme 105). This assignment was subsequently confirmed by single crystal X-ray

diffraction analysis, which established the relative (3*SR*,4*SR*,α*RS*)-configuration within (±)-**512** (Figure 51).



(±)-**511** (±)-**512**, 68%, >99:1 dr

Scheme 105. *Reagents and Conditions*: (i) Tf_2O, **318**, CH_2Cl_2 0 °C, then rt, 6 h.

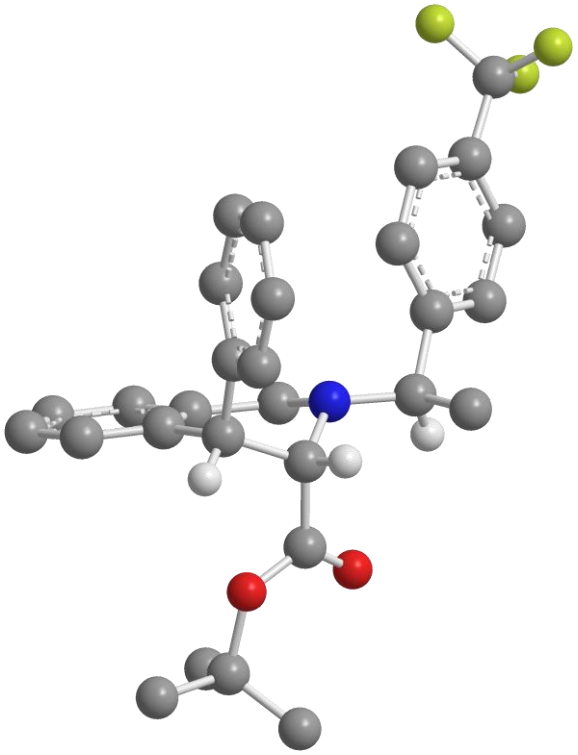
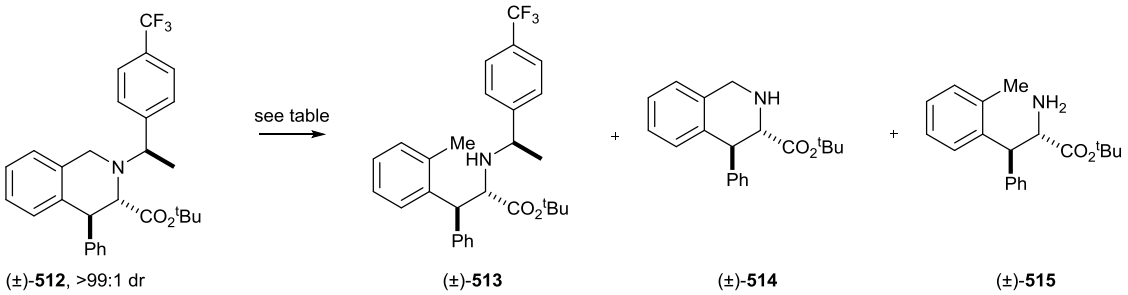


Figure 51. X-ray crystal structure of (3*RS*,4*SR*,α*SR*)-**512** (selected H atoms are omitted for clarity).

5.2.6.2. Model studies: deprotection

Investigations into an effective strategy to deprotect the *N*(2)-[α-methyl-4-(trifluoromethyl)benzyl] group within (±)-**512** were undertaken next. In the first instance (±)-**512** was reacted under standard hydrogenolysis conditions: stirring (±)-**512** under H_2 pressure (5 atm) in the presence of $Pd(OH)_2/C$ (25% w/w) at rt for 24 h gave a 90:10 mixture of starting material (±)-**512** and β,β-diaryl-α-amino ester (±)-**513**, resulting from hydrogenolytic cleavage of the C(1)−N(2) bond within (±)-**512**. Reaction of (±)-**512** under the same reaction conditions for 48 h gave a 55:20:22:3 mixture of (±)-**512**, (±)-**513**, tetrahydroisoquinoline (±)-**514** and the over-reduction product β,β-diaryl-α-amino ester (±)-**515**. Increasing the catalyst loading to 40% w/w resulted in a 26:28:28:18 mixture of (±)-**512**, (±)-**513**, (±)-**514** and (±)-**515** after 24 h, with full conversion of starting material being observed after 48 h, giving a 60:40 mixture of (±)-**514** and (±)-**515**. Hydrogenolysis in

the presence of AcOH was also attempted: reaction of (±)-**512** under 5 atm of H_2 in the presence of $Pd(OH)_2/C$ (25% w/w) in MeOH/AcOH at rt for 24 h gave a 35:24:35:6 mixture of (±)-**512**, (±)-**513**, (±)-**514** and (±)-**515**. Repeating the reaction for 48 h resulted in an 11:22:55:12 mixture of (±)-**512**, (±)-**513**, (±)-**514** and (±)-**515** (Scheme 106).

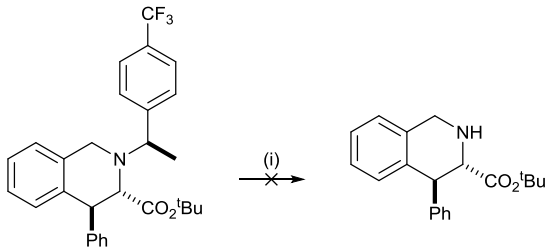


(±)-**512**, >99:1 dr (±)-**513** (±)-**514** (±)-**515**

catalyst loading	solvent	time	product ratio (±)-**512**:(±)-**513**:(±)-**514**:(±)-**515**
25%	MeOH	24 h	90:10:0:0
25%	MeOH	48 h	55:20:22:3
40%	MeOH	24 h	26:28:28:18
40%	MeOH	48 h	0:0:60:40
25%	MeOH/AcOH (20:1)	24 h	35:24:35:6
25%	MeOH/AcOH (20:1)	48 h	11:22:55:12

Scheme 106. *Reagents and Conditions*: (i) H_2 (5 atm), $Pd(OH)_2/C$, solvent: see table, rt, time: see table.

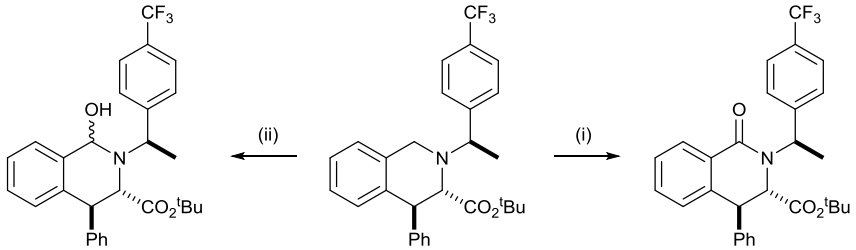
Investigations into alternative debenzylation strategies were undertaken, in the hope that a protocol may be found that would favour removal of the *N*(2)-[α-methyl-(*p*-trifluoromethyl)benzyl] group over cleavage of the C(1)−N(2) bond. However, treatment of (±)-**512** with Na in NH_3 at −78 °C for 30 min gave returned starting material (Scheme 107).



(±)-**512**, >99:1 dr (±)-**514**

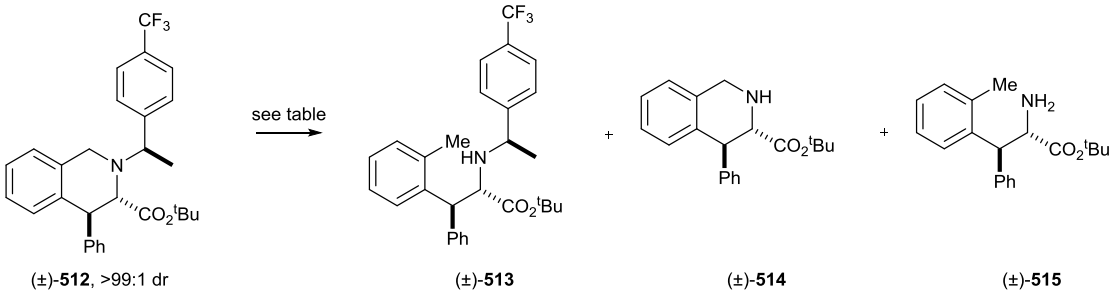
Scheme 107. *Reagents and Conditions*: (i) Na, NH_3, THF, −78 °C, 30 min.

Removal of the *N*(2)-[α-methyl-4-(trifluoromethyl)benzyl] group within (±)-**512** under oxidative methods was attempted next. Reaction of (±)-**512** with $NaBrO_3$ and $Na_2S_2O_4$ resulted in oxidation at the C(1) position, giving (±)-**516** in 82% yield, with treatment of (±)-**512** with CAN also leading to oxidation at C(1), giving (±)-**517** as a single diastereoisomer [of unknown configuration at C(1)] in 94% yield (Scheme 108).



Scheme 108. *Reagents and Conditions*: (i) $NaBrO_3$, $Na_2S_2O_3$, H_2O/EtOAc (2:1), rt, 4 h; (ii) CAN, MeCN/H_2O (2:1), rt, 24 h.

Reduction of (±)-**512** under transfer hydrogenolysis conditions was attempted next. Reaction of (±)-**512** with HCO_2NH_4 in the presence of Pd/C gave a 3:70:27 mixture of (±)-**513**, (±)-**514** and (±)-**515** after 8 h. Optimisation of this result was undertaken in an effort to maximise conversion to (±)-**514**. It was found that 3 h was sufficient to achieve full conversion of starting material, giving a 3:77:20 mixture of (±)-**513**, (±)-**514** and (±)-**515**, from which (±)-**514** was isolated in 59% yield and >99:1 dr (Scheme 109).



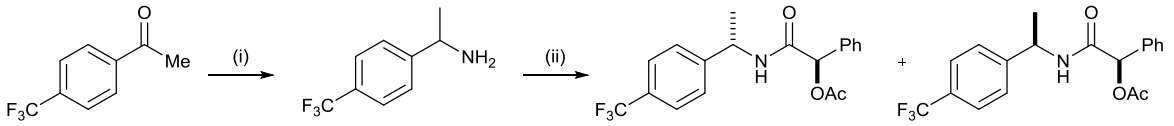
time	product ratio (±)-**512**:(±)-**513**:(±)-**514**:(±)-**515**	yield of (±)-**514**
1 h	21:9:63:7	-
2 h	10:9:72:9	-
3 h	0:3:77:20	59%
8 h	0:3:70:27	-

Scheme 109. *Reagents and Conditions*: (i) Pd/C, HCO_2NH_4, MeOH, 65 °C, time: see table.

5.2.6.3. Synthesis of enantiopure *N*-benzyl-*N*-[α-methyl-(4-trifluoromethyl)benzyl]amine

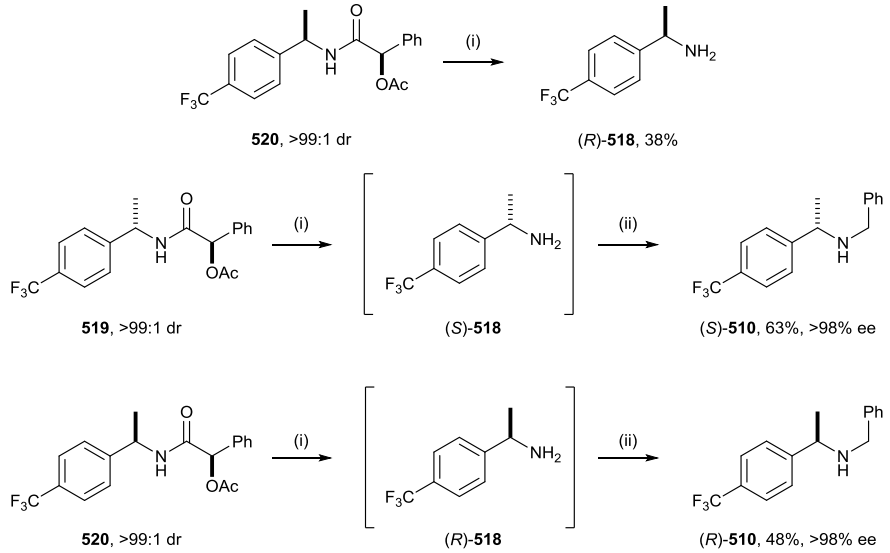
With a selective cyclisation pathway identified, and subsequent deprotection optimised, work could begin on the corresponding enantiopure system. The synthesis of the required enantiopure *N*-benzyl-*N*-[α-methyl-(4-trifluoromethyl)benzyl]amine reagent **510** would be achieved via reductive amination of enantiopure *N*-[α-methyl-(4-trifluoromethyl)benzyl]amine, which would be accessed by coupling the racemate with a chiral carboxylic acid and separating the resultant diastereoisomers, following a known procedure.[25] Thus, racemic α-methyl-[4-(trifluoromethyl)benzyl]amine (±)-**518** was synthesised from the reductive amination 4'-(trifluoromethyl)acetopheneone **509** with ammonia, which gave (±)-**518** in 68% yield.[26] Subsequent amide coupling of (±)-**518** with (*R*)-*O*-acetyl mandelic acid gave a mixture of enantiopure diastereoisomers **519** and **520**,

which were separated by column chromatography and isolated in 36 and 33% yield, respectively, and >99:1 dr in both cases. The absolute (2*R*,α*S*)- and (*R*,*R*)-configurations within **519** and **520** respectively were subsequently assigned via chemical correlation (*vide infra*) (Scheme 110).



Scheme 110. *Reagents and Conditions*: (i) NH_3 (2.0 M in EtOH), $Ti(O^iPr)_4$, then $NaBH_4$, rt, 3 h; (ii) (*R*)-*O*-acetyl mandelic acid, DCC, DMAP, CH_2Cl_2, rt, 16 h.

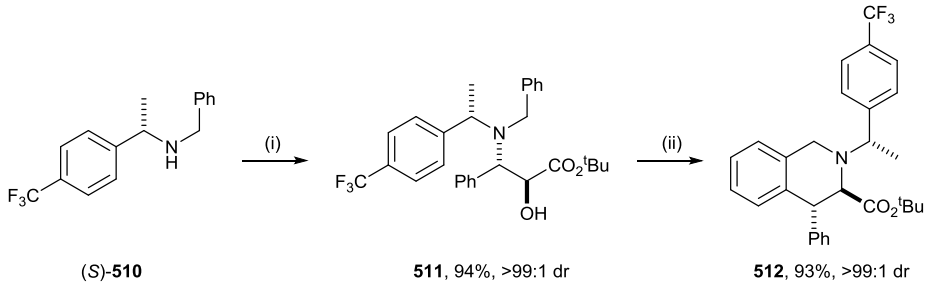
With diastereoisomerically pure samples of **519** and **520** in hand, subsequent hydrolysis was required to liberate the enantiomerically pure α-methyl-4-(trifluoromethyl)benzylamines (*R*)-**518** and (*S*)-**518**, respectively. Refluxing **520** in HBr for 24 h was found to effectively cleave the amide bond, but purification of (*R*)-**518** by acid/base extraction gave (*R*)-**518** in only 38% yield. However, comparison of the specific rotation value of (*R*)-**518** $[\alpha]_D^{20}$ = +22.0 (*c* 1.0 in MeOH) with that reported in the literature[27] $[\alpha]_D^{20}$ = +20.0 (*c* 1.0 in MeOH) enabled assignment of the absolute configurations within both (*R*)-**518** and (*S*)-**518**. Attempts to improve the isolated yield of either (*R*)-**518** or (*S*)-**518** by purification on either ion exchange chromatography on DOWEX-50WX8 resin or an SCX amine scavenging column was not possible. However, it was found that subjection of the crude reaction mixture of (*R*)-**518** or (*S*)-**518** to reductive alkylation with benzaldehyde, in the presence of 1.0 equiv of K_2CO_3, gave (*R*)-**510** or (*S*)-**510** in 48 and 63% yield, respectively, over the two steps and in >98% ee in each case[28] (Scheme 111).



Scheme 111. *Reagents and Conditions*: (i) 4.5 M aq HBr, reflux, 24 h; (ii) PhCHO, K_2CO_3, EtOH, reflux, 3 h, then $NaBH_4$, 0 °C to rt, 20 h.

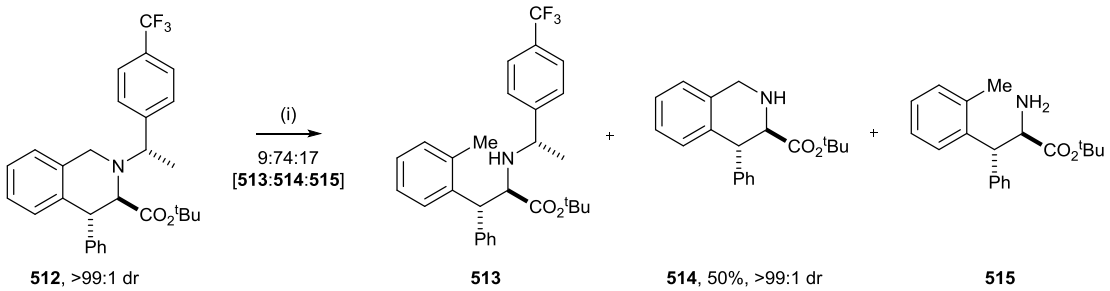
5.2.6.4. Enantiopure *N*(2)-[α-methyl-(*p*-trifluoromethyl)benzyl] substituted tetrahydroisoquinolines

With both antipodes of *N*-benzyl-*N*-[α-methyl-4-(trifluoromethyl)benzyl]amine **510** in hand, work towards the synthesis of the corresponding enantiopure *N*(2)-[α-methyl-(*p*-trifluoromethyl)benzyl] substituted tetrahydroisoquinoline **512** was undertaken. Conjugate addition of the lithium amide derived from (*S*)-**510** to α,β-unsaturated ester **206**, with *in situ* oxidation of the intermediate lithium (*Z*)-β-amino enolate[21] with (+)-CSO **202**,[29] gave α-hydroxy-β-amino ester **511** in 94% yield and >99:1 dr. The ^{1}H and ^{13}C NMR spectroscopic data for this sample of **511** were entirely consistent with the racemic sample prepared previously (*vide supra*). Subsequent treatment of **511** with Tf_2O in the presence of **318** afforded tetrahydroisoquinoline **512** as the sole product, which was isolated in 93% yield and >99:1 dr (Scheme 112).



Scheme 112. *Reagents and Conditions*: (i) **206**, BuLi, THF, –78 °C, 2 h, then (+)-CSO **202**, –78 °C to rt, 18 h; (ii) Tf_2O, **318**, CH_2Cl_2, 0 °C, then rt, 6 h.

Application of the previously optimised deprotection conditions to **512** gave a 9:74:17 mixture of **513**, **514** and **515**, repectively, from which enantiomerically pure **514** was isolated in 50% yield and >99:1 dr (Scheme 113).



Scheme 113. *Reagents and Conditions*: (i) Pd/C, HCO_2NH_4, MeOH, 65 °C, 3 h.

5.3. Conclusion

The development of highly effective methodology, which enables the one-pot conversion of α-hydroxy-β-amino esters to tetrahydroisoquinolines, has been achieved. Investigations carried out thus far are consistent with a mechanism which involves rearrangement via an aziridinium intermediate, with subsequent ring-opening and trapping of the resultant carbocation in a diastereoselective manner giving 3,4-*anti*-tetrahydroisoquinolines in

>99:1 dr. Furthermore, this methodology has been applied to the synthesis of enantiopure tetrahydroisoquinolines **522** and **523** via the development of a regioselective cylisation protocol, which has necessitated the synthesis and application of two new lithium amide reagents (Figure 52).

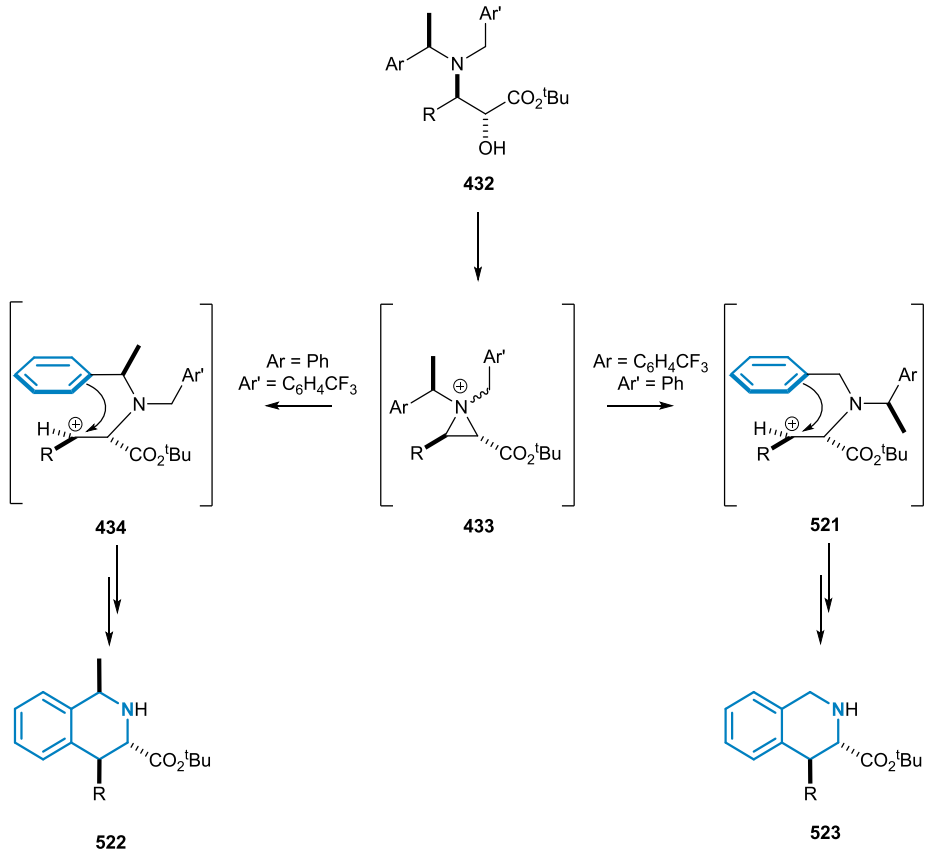


Figure 52. Tetrahydroisoquinolines **522** and **523** from α-hydroxy-β-amino esters **432** via an aziridinium intermediate **433**.

5.4. Future work

Further studies into a more robust and efficient deprotection of *N*(2)-[α-methyl-(*p*-trifluoromethyl)benzyl] substituted tetrahydroisoquinolines would enable the application of this procedure to the synthesis of a range of substituted tetrahydroisoquinolines. The utility of this methodology in the total synthesis of tetrahydroisoquinoline containing natural products and/or drug targets, such as dihydrexidine **527**, may also be pursued (Figure 53).

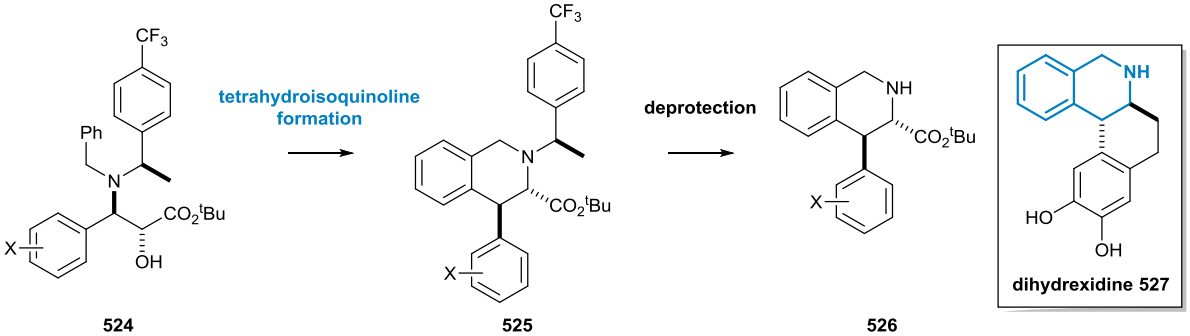


Figure 53. Application of the developed methodology to a range of substituted tetrahydroisoquinolines and to the synthesis of dihydrexidine **527**.

5.5. Summary

This thesis has demonstrated the use of aziridines and aziridinium intermediates in the asymmetric synthesis of a range of β-substituted-α-amino acids, 1,3,4-trisubstituted tetrahydroisoquinolines and 3,4-disubstituted tetrahydroisoquinolines. Using enantiopure α-hydroxy-β-amino esters **528** as precursors, formation of aziridines **174** and subsequent ring-opening was achieved to give access to *syn*- and *anti*-β-hydroxy-α-amino acids **175** (Chapter 2). Subsequent studies lead to the *in situ* formation of aziridinium intermediates **529** upon activation of *anti*-α-hydroxy-β-amino esters **528**, with the development of regioselective ring-opening methodology by a range of external nucleophiles allowing access to *anti*-β-hydroxy-α-amino esters **354** (Chapter 3), *anti*-β-fluoro-α-amino esters **530** (Chapter 4) and *anti*-β-azido-α-amino ester **398** (Chapter 4), which were successfully deprotected to the corresponding β-substituted-α-amino acids **189**, **427** and **372**, respectively, in each case. In the case of β-fluoro-α-amino esters **530**, the labile nature of the benzylic fluoride moiety necessitated investigations into an alternative strategy, which culminated in the development of a one-pot *N*-debenzylation/ester hydrolysis protocol, enabling efficient access to the corresponding *anti*-β-fluorophenylalanines **427**. A serendipitous observation inspired investigations into the synthesis of tetrahydroisoquinolines, leading ultimately to the discovery of a robust and reliable one-pot protocol for the diastereoselective synthesis of this product class from α-hydroxy-β-amino esters **528**. Furthermore, a pathway has been identified which enables the application of this developed protocol to the asymmetric synthesis of representative enantiopure 1,3,4-trisubstituted tetrahydroisoquinolines **532** and 3,4-disubstituted tetrahydroisoquinolines **533** (Figure 54).

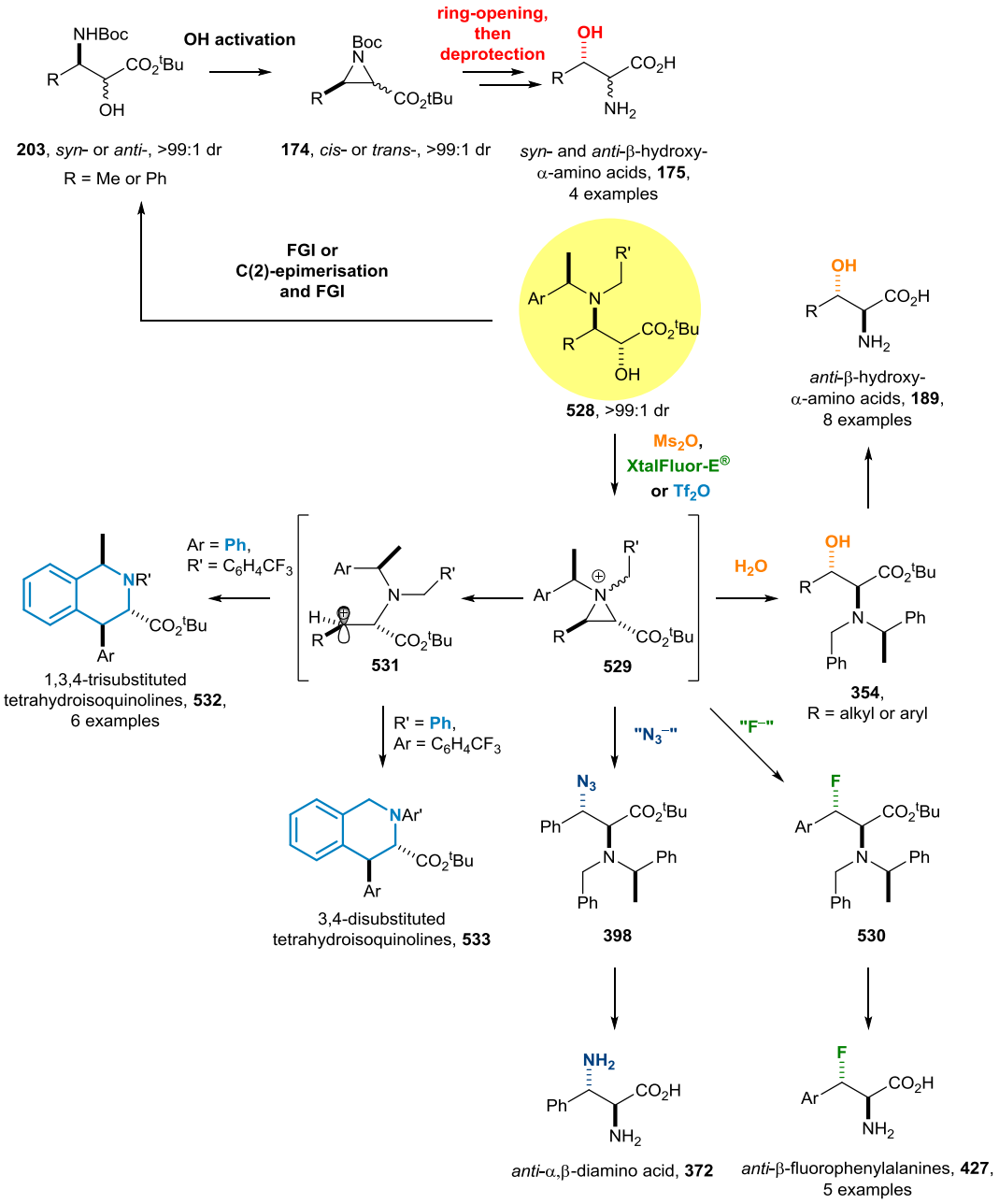


Figure 54. Aziridines and aziridinium intermediates in the asymmetric synthesis of β-substituted-α-amino acids and tetrahydroisoquinolines.

5.6. References and notes

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[28] (*R*)-**510** and (*S*)-**510** were assessed to be >98% ee by 400MHz ^{1}H NMR spectroscopic analysis in the presence of (*R*)-O-acteylmandelic acid in $CDCl_3$, and in comparison with that of an authentic racemic smaple.
[29] A sample of (+)-CSO **202** was generously donated by Mr M. S. Kennedy.

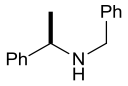
Chapter 6: Experimental

6.1 General experimental

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs *et al.*[1] Water was purified by an Elix® UV-10 system. BuLi was supplied as a solution in hexanes and titrated against Ph_2CHCO_2H before use. All other solvents and reagents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), 1% aq $KMnO_4$, or Dragendorff's reagent. Flash column chromatography was performed on Kieselgel 60 silica. Elemental analyses were recorded by the microanalysis service of the London Metropolitan University, U.K. Melting points were recorded on a Gallenkamp Hot Stage or Leica Gallen III apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 or 341 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded on Bruker Tensor 27 FT-IR spectrometer as either a thin film on NaCl plates (film), a KBr disc (KBr) or on a diamond ATR module (ATR), as stated. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated and at rt unless otherwise specified. The field was locked by external referencing to the relevant deuteron resonance. Chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. When the diastereotopic methyl groups of acetonide and isopropyl functionalities could not be unambiguously assigned, the descriptors *Me*CMe and *Me*CHMe were employed, respectively. In the ^{1}H and ^{13}C NMR spectra, these descriptors are intended to convey neither that the resonances are attributable to methyl groups that reside on the same, nor on different carbon atoms. Low-resolution mass spectra were recorded on either a Micromass LCT Premier or Agilent Quadrupole 6120 LC/MS spectrometer. Accurate mass measurements were run on a Bruker MicroToF internally calibrated with polyalanine.

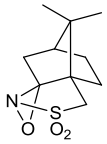
6.2. Experimental for Chapter 2

(*R*)-*N*-Benzyl-*N*-(α-methylbenzyl)amine 205



Benzaldehyde (83.8 mL, 826 mmol) was added to a stirred solution of (*R*)-*N*-(α-methylbenzyl)amine (100 mL, 786 mmol, 99% ee) in EtOH (500 mL) and the resultant solution was heated at reflux for 3 h, then allowed to cool to rt and then cooled to 0 °C. $NaBH_4$ (29.7 g, 786 mmol) was added portionwise, maintaining the reaction temperature below 15 °C, and the resultant suspension was stirred for 42 h at rt, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (500 mL) and H_2O (500 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL) and the combined organic extracts were dried and concentrated *in vacuo*. The residue was slowly added to a stirred mixture of Et_2O (300 mL) and 10 M aq HCl (10 mL), to give a white precipitate which was isolated by filtration and recrystallised (CH_2Cl_2/pentane) to give **205**·HCl as a white solid (127.0 g, 65%). The free amine **205** was then regenerated quantitatively as required by treatment with 2.0 M aq NaOH followed by extraction into CH_2Cl_2. The combined organic extracts were then dried and concentrated *in vacuo* to give (*R*)-**205** as a colourless oil (99% ee);[2,3] $[\alpha]_D^{25}$ +52.4 (*c* 1.0 in $CHCl_3$); {lit.[2] $[\alpha]_D^{25}$ +46.4 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.38 (3H, d, *J* 6.7, C(α)*Me*), 1.60 (1H, br s, N*H*), 3.60 (1H, d, *J* 13.1, NCH_AH_BPh), 3.67 (1H, d, *J* 13.1, NCH_AH_BPh), 3.83 (1H, q, *J* 6.7, C(α)*H*), 7.22–7.41 (10H, m, *Ph*).

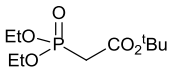
(−)-Camphorsulfonyloxazridine 202 [(−)-CSO]



Step 1: $SOCl_2$ (252 mL, 3.44 mol) was added dropwise to a stirred solution of (*R*)-10-camphorsulphonic acid (200 g, 86 mmol) in $CHCl_3$ (1.0 L) and the resultant mixture was heated at reflux for 12 h, then concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (1.0 L) and the resultant solution was added dropwise to a stirred solution of 35% aq NH_3 (2.0 L) at 0 °C, then stirred at 0 °C for 4 h. The layers were separated, the aqueous layer extracted with CH_2Cl_2 (2 × 800 mL), and the combined organic extracts dried and concentrated *in vacuo*. The residue was dissolved in PhMe (1.0 L) and Amberlyst 15 (wet) ion-exchange resin (12.0 g) was added. A Dean-Stark apparatus was fitted to the reaction vessel and the reaction

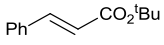
mixture heated at reflux for 12 h, then allowed to cool to rt and filtered through Celite® (eluent $CHCl_3$) and then concentrated *in vacuo* to give a pale yellow solid (171.6g); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, s, *Me*), 1.09 (3H, s, *Me*), 1.44–1.54 (1H, m), 1.72–1.86 (1H, m), 2.01–2.13 (2H, m), 2.24–2.29 (1H, m), 2.35–2.43 (1H, m), 2.74–2.83 (1H, m), 2.98 (1H, d, *J* 13.3, $CH_AH_BSO_2$), 3.19 (1H, d, *J* 13.3, $CH_AH_BSO_2$). The residue was dissolved in CH_2Cl_2 (1.5 L) and the resultant solution was cooled to 0 °C and Aliquat 336 (17.0 g) was added. 2.0 M aq K_2CO_3 (750 mL, 1.38 mol) was added via a dropping funnel at such a rate as to maintain the reaction temperature below 5 °C. A solution of peracetic acid (32% in AcOH, 315 mL) was then added dropwise, whilst maintaining the reaction temperature below 5 °C and the resultant mixture was allowed to warm to rt over 8 h. Na_2SO_3 (208 g, 1.64 mol) and 1.0 M aq NaOH (800 mL) were added and the aqueous layer was extracted with CH_2Cl_2 (3 × 800 mL). The combined organic extracts were washed sequentially with H_2O (500 mL) and satd aq $NaHCO_3$ (500 mL), then dried and concentrated *in vacuo*. Purification via recrystallisation (CH_2Cl_2/40–60 °C petrol) gave (−)-Camphorsulfonyloxazridine **202** [(−)-CSO] as a white solid (158.8 g, 96%);[4] mp 146–153 °C; {lit. mp[4] 165–167 °C}; $[\alpha]_D^{25}$ −50.4 (*c* 0.8 in $CHCl_3$); {lit.[4] $[\alpha]_D^{25}$ −43.6 (*c* 2.16 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.04 (3H, s, *Me*), 1.19 (3H, s, *Me*), 1.48–1.56 (1H, m), 1.79 (1H, d, *J* 15.5), 1.91–2.16 (4H, m), 2.61–2.68 (1H, m), 3.11 (1H, d, *J* 13.9, $CH_AH_BSO_2$), 3.28 (1H, d, *J* 13.9, $CH_AH_BSO_2$).

tert-Butyl (diethylphosphono)acetate



A stirred mixture of *tert*-butyl bromoacetate (57.5 mL, 389 mmol) and $P(OEt)_3$ (63.9 mL, 373 mmol) was heated at 50 °C for 48 h, then concentrated *in vacuo* to give *tert*-butyl (diethylphosphono)acetate as a colourless oil (82.0 g, 84%);[5] δ_H (400 MHz, $CDCl_3$) 1.34 (6H, t, *J* 7.1, $P(OCH_2CH_3)_2$), 1.46 (9H, s, CMe_3), 2.88 (2H, d, *J* 21.3, PCH_2), 4.09–4.21 (4H, m, $P(OCH_2CH_3)_2$).

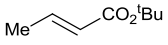
tert-Butyl cinnamate 206



MeMgBr (3.0 M in Et_2O, 33.1 mL, 99.3 mmol) was added dropwise to a stirred solution of *tert*-butyl (diethylphosphono)acetate (23.3 mL, 99.1 mmol) in THF (225 mL) at rt and the resultant mixture was stirred at rt for 15 min. A solution of PhCHO (11.1 mL, 109.4 mmol) in

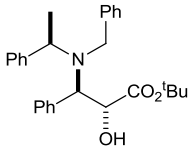
THF (225 mL) was added via cannula and the resultant mixture was heated at reflux for 2.5 h and then allowed to cool to rt. Satd aq NH_4Cl (350 mL) was added and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with brine (600 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 ºC petrol/EtOAc, 20:1) gave **206** as pale yellow oil (14.10 g, 70%, >99:1 dr);[6] δ_H (400 MHz, $CDCl_3$) 1.54 (9H, s, C*Me*$_3$), 6.38 (1H, d, *J* 16.0, C(2)*H*), 7.35–7.40 (3H, m, *Ph*), 7.49–7.55 (2H, m, *Ph*), 7.50 (1H, d, *J* 16.0, C(3)*H*).

tert-Butyl crotonate 207



Isobutylene (324 mL, 5.8 mol) was condensed at −78 °C and the resultant liquid was added to a stirred solution of crotonic acid (50 g, 0.58 mol) and conc H_2SO_4 (5 mL) in CH_2Cl_2 (500 mL) at 0 °C. The resultant mixture was stirred for 1 h, then allowed to warm to rt over 48 h. NaOH was added at 0 ºC until a pH >7 was achieved. The organic layer was dried and concentrated *in vacuo* to give **207** as a pale yellow oil (39.0 g, 47%, >99:1 dr);[7] δ_H (400 MHz, $CDCl_3$) 1.47 (9H, s, C*Me*$_3$), 1.85 (3H, dd, *J* 6.9, 1.7, C(4)*H*$_3$), 5.77 (1H, dq, *J* 15.4, 1.7, C(2)*H*), 6.86 (1H, dq, *J* 15.4, 6.9, C(3)*H*).

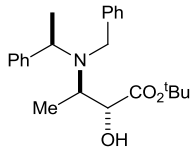
tert-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 208



BuLi (2.5 M in hexanes, 15.2 mL, 38.0 mmol) was added dropwise to a stirred solution of (*R*)-**205**[43] (8.26 g, 39.1 mmol, 99% ee) in THF (100 mL) at −78 °C and stirring was continued at –78 °C for 30 min. A solution of **206** (5.00 g, 24.5 mmol, >99:1 dr) in THF (100 mL) was then added via cannula and the resultant mixture was stirred at −78 °C for 2 h. (−)-**202** (8.97 g, 39.1 mmol) was then added and stirring was continued as the reaction mixture was allowed to warm to rt over 15 h. Satd aq NH_4Cl (5 mL) was added and the reaction mixture was stirred at rt for 5 min then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (100 mL) and 10% aq citric acid (100 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (100 mL) and brine (100 mL), then dried and concentrated *in vacuo*. The residue was dissolved in

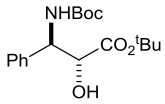
Et_2O (100 mL), the insoluble CSO residues were filtered off, and the filter cake was washed with Et_2O (2 × 50 mL). The filtrate was concentrated *in vacuo* and the process was repeated. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 15:1) gave **208** as a pale yellow solid (9.77 g, 93%, >99:1 dr);[8] mp 85–88 °C; {lit.[9] mp 87–88 °C}; $[\alpha]_D^{23}$ −26.7 (*c* 1.0 in $CHCl_3$); {lit.[9] $[\alpha]_D^{25}$ −27.2 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.26–1.29 (12H, m, C(α)*Me*, C*Me*$_3$), 2.91 (1H, br s, O*H*), 3.92 (1H, d, *J* 14.9, NC*H*$_A$H$_B$Ph), 4.22 (1H, d, *J* 14.9, NCH$_A$*H*$_B$Ph), 4.27–4.33 (2H, m, C(α)*H*, C(3)*H*), 4.49 (1H, d, *J* 3.0, C(2)*H*), 7.21–7.61 (15H, m, *Ph*).

tert-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]butanoate 209



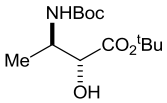
BuLi (2.4 M in hexanes, 4.54 mL, 10.9 mmol) was added dropwise to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine[43] (2.39 g, 11.3 mmol, 99% ee) in THF (60 mL) at −78 °C and stirring was continued at −78 °C for 30 min. A solution of **207** (1.00 g, 7.03 mmol, >99:1 dr) in THF (60 mL) was then added via cannula and the resultant mixture was stirred at −78 °C for 2 h. (−)-**202** (2.59 g, 11.3 mmol) was then added and stirring was continued as the reaction mixture was allowed to warm to rt over 15 h. Satd aq NH_4Cl (5 mL) was added and the reaction mixture was stirred at rt for 5 min then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (100 mL) and 10% aq citric acid (100 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (100 mL) and brine (100 mL), then dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (100 mL), the insoluble CSO residues were filtered off, and the filter cake was washed with Et_2O (2 × 50 mL). The filtrate was concentrated *in vacuo* and the process was repeated. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **209** as a yellow soild (2.29 g, 91%, >99:1 dr);[9] mp 89–94 °C; {lit.[9] mp 88–89 °C}; $[\alpha]_D^{23}$ −35.5 (*c* 1.0 in $CHCl_3$); {lit.[9] $[\alpha]_D^{25}$ −35.2 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.08 (3H, d, *J* 7.0, C(4)*H*$_3$), 1.32 (3H, d, *J* 6.8, C(α)*Me*), 1.36 (9H, s, C*Me*$_3$), 2.92 (1H, app d, *J* 6.5, O*H*), 3.25 (1H, qd, *J* 7.0, 2.6, C(3)*H*), 3.87 (1H, d, *J* 14.7, NC*H*$_A$H$_B$Ph), 3.97–4.04 (3H, m, C(2)*H*, C(α)*H*, NCH$_A$*H*$_B$Ph), 7.18–7.50 (10H, m, *Ph*).

tert-Butyl (_R_,_R_)-2-hydroxy-3-[_N_-(_tert_-butoxycarbonyl)amino]-3-phenylpropanoate 210



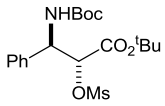
$Pd(OH)_2/C$ (500 mg, 25% w/w) was added to a degassed solution of **208** (2.00 g, 4.64 mmol, >99:1 dr) and Boc_2O (1.11 g, 7.66 mmol) in EtOAc (40 mL) and the resultant mixture was stirred under H_2 (5 atm) at rt for 15 h. The reaction mixture was then filtered through Celite® (eluent EtOAc) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **210** as a white solid (1.54 g, 99%, >99:1 dr); mp 75–79 °C; $[\alpha]_D^{23}$ −25.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3400 (N−H), 3292 (O−H), 2976, 2933 (C−H), 1707, 1687 (2 × C=O); δ_H (400 MHz, $CDCl_3$) 1.36 (9H, s, C*Me*$_3$), 1.43 (9H, s, C*Me*$_3$), 1.57 (1H, br s, O*H*), 4.44–4.51 (1H, m, C(2)*H*), 5.06 (1H, dd, *J* 8.9, 3.3, C(3)*H*), 5.60 (1H, d, *J* 8.9, N*H*), 7.26–7.36 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.9, 28.4 (2 × C*Me*$_3$), 56.3 (*C*(3)), 73.0 (*C*(2)), 79.8, 83.6 (2 × *C*Me$_3$), 127.9, 128.1, 128.2 (*o,m,p-Ph*), 137.2 (*i-Ph*), 155.0 (N*C*O), 171.0 (*C*(1)); *m*/*z* (ESI$^+$) 360 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{27}NNaO_5^+$ ([M+Na]$^+$) requires 360.1781; found 360.1767.

tert-Butyl (_R_,_R_)-2-hydroxy-3-[_N_-(_tert_-butoxycarbonyl)amino]butanoate 211



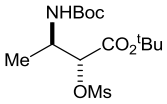
$Pd(OH)_2/C$ (1.00 g, 25% w/w) was added to a degassed solution of **209** (4.00 g, 10.8 mmol, >99:1 dr) and Boc_2O (2.60 g, 11.9 mmol) in EtOAc (50 mL) and the resultant mixture was stirred under H_2 (5 atm) at rt for 15 h. The reaction mixture was then filtered through Celite® (eluent EtOAc) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave **211** as a colourless oil (2.62 g, 88%, >99:1 dr);[10] $[\alpha]_D^{23}$ −10.4 (*c* 1.0 in $CHCl_3$); {lit.[10] for *ent*-**211**: $[\alpha]_D^{23}$ +10.8 (*c* 2.4 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.02 (3H, d, *J* 6.7, C(4)*H*$_3$), 1.45 (9H, s, C*Me*$_3$), 1.50 (9H, s, C*Me*$_3$), 3.04 (1H, d, *J* 5.5, O*H*), 4.05–4.15 (1H, m, C(3)*H*), 4.21 (1H, m, C(2)*H*), 4.90 (1H, d, *J* 8.9, N*H*).

tert-Butyl (*R*,*R*)-2-methanesulfonyloxy-3-[*N*-(_tert_-butoxycarbonyl)amino]-3-phenylpropanoate 212



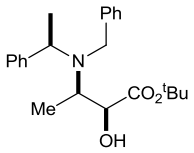
MsCl (1.37 mL, 17.8 mmol), Et_3N (5.90 mL, 44.5 mmol) and DMAP (5 mg, cat.) were added to a stirred solution of **210** (3.00 g, 8.89 mmol, >99:1 dr) in CH_2Cl_2 (270 mL) and the resultant solution was stirred at rt for 15 h. H_2O (180 mL) was then added and the aqueous layer was extracted with CH_2Cl_2 (2 × 90 mL). The combined organic extracts were washed sequentially with 1.0 M aq HCl (200 mL), satd aq $NaHCO_3$ (200 mL) and brine (200 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:1) gave **212** as a yellow solid (3.16 g, 86%, >99:1 dr); mp 113–116 °C; $[\alpha]_D^{23}$ −17.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3381 (N−H), 3064, 3034, 2974, 2936, 2872 (C−H), 1740, 1695 (2 × C=O); δ_H (400 MHz, $CDCl_3$) 1.32 (9H, s, C*Me*$_3$), 1.45 (9H, s, C*Me*$_3$), 3.15 (3H, s, SO_2*Me*), 5.22–5.32 (2H, m, C(3)*H*, N*H*), 5.41–5.46 (1H, m, C(2)*H*), 7.31–7.39 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.7, 28.3 (2 × C*Me*$_3$), 39.1 (SO_2*Me*), 55.2 (*C*(3)), 79.0 (*C*(2)), 80.4, 83.9 (2 × *C*Me$_3$), 128.1, 128.6, 128.6 (*o*,*m*,*p*-*Ph*), 135.8 (*i*-*Ph*), 154.8 (N*C*O), 165.5 (*C*(1)); *m*/*z* (ESI^+) 438 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{19}H_{29}NNaO_7S^+$ ($[M+Na]^+$) requires 438.1557; found 438.1574.

tert-Butyl (*R*,*R*)-2-methanesulfonyloxy-3-[*N*-(_tert_-butoxycarbonyl)amino]butanoate 213



MsCl (0.56 mL, 7.26 mmol), Et_3N (2.41 mL, 18.2 mmol) and DMAP (3 mg, cat.) were added to a stirred solution of **211** (1.00 g, 3.63 mmol, >99:1 dr) in CH_2Cl_2 (110 mL) and the resultant solution was stirred at rt for 15 h. H_2O (60 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic extracts were washed sequentially with 1.0 M aq HCl (100 mL), satd aq $NaHCO_3$ (100 mL) and brine (100 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **213** a pale yellow oil (1.10 g, 85%, >99:1 dr);[10] $[\alpha]_D^{23}$ +35.5 (*c* 1.0 in $CHCl_3$); {lit.[10] for *ent*-**213**: $[\alpha]_D^{25}$ –38.4 (*c* 1.05 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.13 (3H, d, *J* 7.0, C(4)H_3), 1.45 (9H, s, C*Me*$_3$), 1.51 (9H, s, C*Me*$_3$), 3.17 (3H, s, SO_2*Me*), 4.23–4.34 (1H, m, C(3)*H*), 4.75 (1H, d, *J* 8.7, N*H*), 5.20 (1H, d, *J* 2.7, C(2)*H*).

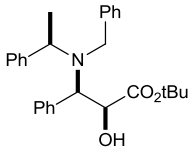
tert-Butyl (2*S*,3*R*,α*R*)-2-hydroxy-3-[*N*-benzyl-*N*(α-methylbenzyl)amino]butanoate 215



Step 1: DMSO (0.58 mL, 8.13 mmol) was added to a stirred solution of $(COCl)_2$ (0.69 mL, 8.13 mmol) in CH_2Cl_2 (50 mL) at −78 °C and the resultant mixture was stirred at –78 °C for 5 min. A solution of **209** (1.50 g, 4.06 mmol, >99:1 dr) in CH_2Cl_2 (50 mL) was added via cannula and the resultant mixture was stirred at −78 °C for 30 min. Et_3N (2.18 mL, 16.2 mmol) was added and the reaction mixture was allowed to warm to rt. H_2O (80 mL) was then added, the reaction mixture was extracted with CH_2Cl_2 (3 ×50 mL), and combined organic extracts were dried and concentrated *in vacuo* to give **214** as a yellow oil (1.49 g, >99:1 dr).

Step 2: $NaBH_4$ (154 mg, 4.06 mmol) was added to a stirred solution of **214** (1.49 g, >99:1 dr) in MeOH (105 mL) at −20 °C and the resultant solution was stirred at −20 °C for 2 h, then allowed to warm to rt and concentrated *in vacuo*. The reaction mixture was then partitioned between Et_2O (50 mL) and H_2O (30 mL) and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give **215** as a colourless oil (1.42 g, 95%, >99:1 dr); $[\alpha]_D^{23}$ −68.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3501 (O−H), 3086, 3062, 3028, 2975, 2935, 2881 (C−H), 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.17 (3H, d, *J* 6.8, C(4)H_3), 1.43 (9H, s, CMe_3), 1.47 (3H, d, *J* 6.9, C(α)*Me*), 3.07 (1H, dq, *J* 8.3, 6.8 C(3)*H*), 3.65–3.72 (2H, m, C(2)*H*, NCH_AH_BPh), 3.78 (1H, br s, O*H*), 3.81 (1H, d, *J* 13.6, NCH_AH_BPh), 4.06 (1H, q, *J* 6.9, C(α)*H*), 7.19–7.39 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.6 (*C*(4)), 14.4 (C(α)*Me*), 27.9 (CMe_3), 49.6 (N*C*H_2Ph), 54.9 (*C*(3)), 57.1 (*C*(α)), 73.5 (*C*(2)), 81.3 (*C*Me_3), 127.3, 127.3, 127.7, 128.4, 128.5, 129.1 (*o*,*m*,*p*-*Ph*), 139.8, 143.0 (*i*-*Ph*), 172.2 (*C*(1)); *m*/*z* (ESI^+) 370 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{23}H_{32}NO_3^+$ ($[M+H]^+$) requires 370.2377; found 370.2364.

tert-Butyl (2*S*,3*R*,α*R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 217



Step 1: DMSO (0.17 mL, 2.32 mmol) was added to a stirred solution of $(COCl)_2$ (0.20 mL, 2.32 mmol) in CH_2Cl_2 (15 mL) at −78 °C and the resultant mixture was stirred at –78 °C for 5 min. A solution of **208** (500 mg, 1.16 mmol, >99:1 dr) in CH_2Cl_2 (15 mL) was added via

cannula and the resultant mixture was stirred at −78 °C for 30 min. Et_3N (0.62 mL, 4.64 mmol) was added and the reaction mixture was allowed to warm to rt. H_2O (20 mL) was then added, the reaction mixture was extracted with CH_2Cl_2 (3 ×10 mL), and the combined organic extracts were dried and concentrated *in vacuo* to give **216** as a yellow oil (498 mg, >99:1 dr).

Step 2:

Method A: $NaBH_4$ (44 mg, 1.16 mmol) was added to a stirred solution of **216** (1.16 mmol) in MeOH (15 mL) at −20 °C and the resultant mixture was stirred at −20 °C for 2 h, then allowed to warm to rt and concentrated *in vacuo*. The reaction mixture was partitioned beween Et_2O (10 mL) and H_2O (10 mL) and the aqueous layer was extracted with Et_2O (2 × 5 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give a 73:27 mixture of **208** and **217**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **208** as a white solid (270 mg, 54%). Further elution gave **217** as a white solid (135 mg, 27%, >99:1 dr); mp 110.0–114.5 °C; $[\alpha]_D^{23}$ −25.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3492 (O−H), 3085, 3062, 3028, 2976, 2934, 2879, 2842 (C−H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.08 (9H, s, C*Me*$_3$), 1.10 (3H, d, *J* 6.9, C(α)*Me*), 3.66 (1H, *J* 13.3, C*H*$_A$H$_B$Ph), 3.84 (1H, br s, O*H*), 3.90 (1H, d, *J* 9.9, C(3)*H*), 4.07 (1H, d, *J* 13.3, CH$_A$*H*$_B$Ph), 4.21 (1H, q, *J* 6.9, C(α)*H*), 4.47 (1H, d, *J* 9.9, C(2)*H*), 7.24–7.42 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.7 (C(α)*Me*), 27.4 (C*Me*$_3$), 50.4 (*C*H$_2$Ph), 56.0 (*C*(α)), 64.4 (*C*(3)), 71.0 (*C*(2)), 81.0 (*C*Me$_3$), 127.3, 127.4, 127.9, 128.1, 128.2, 128.6, 128.7, 129.1, 130.0 (*o*, *m*, *p*-*Ph*), 136.7, 139.3, 143.2 (*i*-*Ph*), 171.2 (*C*(1)); *m*/*z* (ESI$^+$) 432 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{34}NO_3^+$ ([M+H]$^+$) requires 432.2533; found 432.2518.

Method B: $NaBH_4$ (4 mg, 0.116 mmol) was added to a stirred solution of **216** (0.116 mmol) in MeOH (1.2 mL) at −40 °C and the resultant mixture was stirred at −40 °C for 2 h, then allowed to warm to rt and concentrated *in vacuo*. The reaction mixture was partitioned beween Et_2O (2 mL) and H_2O (2 mL) and the aqueous layer was extracted with Et_2O (2 × 2 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give a 93:7 mixture of **208** and **217**, respectively.

Method C: $NaBH_4$ (4 mg, 0.116 mmol) was added to a stirred solution of **216** (0.116 mmol) in MeOH (1.2 mL) at −60 °C and the resultant mixture was stirred at −60 °C for 2 h, then allowed to warm to rt and concentrated *in vacuo*. The reaction mixture was partitioned beween Et_2O (2 mL) and H_2O (2 mL) and the aqueous layer was extracted with Et_2O (2 × 2

mL). The combined organic extracts were then dried and concentrated *in vacuo* to give a 94:6 mixture of **208** and **217**, respectively.

Method D: $NaBH_4$ (4 mg, 0.116 mmol) was added to a stirred solution of **216** (0.116 mmol) in MeOH (1.2 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 2 h, then allowed to warm to rt and concentrated *in vacuo*. The reaction mixture was partitioned beween Et_2O (2 mL) and H_2O (2 mL) and the aqueous layer was extracted with Et_2O (2 × 2 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give a 95:5 mixture of **208** and **217**, respectively.

Method E: $NaBH_4$ (4 mg, 0.116 mmol) was added to a stirred solution of **216** (0.116 mmol) in THF (1.2 mL) at −20 °C and the resultant mixture was stirred at −20 °C for 2 h, then allowed to warm to rt and concentrated *in vacuo*. The reaction mixture was partitioned beween Et_2O (2 mL) and H_2O (2 mL) and the aqueous layer was extracted with Et_2O (2 × 2 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give a 76:24 mixture of **208** and **217**, respectively.

Method F: $NaBH_4$ (4 mg, 0.116 mmol) was added to a stirred solution of **216** (0.116 mmol) in THF (1.2 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 2 h, then allowed to warm to rt and concentrated *in vacuo*. The reaction mixture was partitioned beween Et_2O (2 mL) and H_2O (2 mL) and the aqueous layer was extracted with Et_2O (2 × 2 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give a 94:6 mixture of **208** and **217**, respectively.

Method G: $LiAlH_4$ (1.0 M in THF, 0.567 mL, 0.567 mmol) was added to a stirred solution of **216** (0.567 mmol) in THF (6 mL) at −20 °C and the resultant mixture was stirred at −20 °C for 2 h. MeOH (1 mL) was added and the resultant mixture was allowed to warm to rt, then concentrated *in vacuo*. The reaction mixture was partitioned beween Et_2O (10 mL) and H_2O (10 mL), the aqueous layer extracted with Et_2O (2 × 5 mL), and the combined organic extracts were then dried and concentrated *in vacuo*. The residue was loaded onto Celite® and passed through a short plug of silica (eluent 30–40 °C petrol/Et_2O, 5:1), then concentrated *in vacuo* to give a 92:8 mixture of **208** and **217**, respectively.

Method H: $LiBH_4$ (2.0 M in THF, 0.284 mL, 0.567 mmol) was added to to a stirred solution of **216** (0.567 mmol) in THF (6 mL) at −20 °C and the resultant mixture was stirred at −20 °C for 2 h. MeOH (1 mL) was added and the resultant mixture was allowed to warm to rt, then concentrated *in vacuo*. The reaction mixture was partitioned beween Et_2O (10 mL) and H_2O

(10 mL), the aqueous layer extracted with Et_2O (2 × 5 mL), and the combined organic extracts were then dried and concentrated *in vacuo*. The residue was loaded onto Celite® and passed through a short plug of silica (eluent 30–40 °C petrol/Et_2O, 5:1), then concentrated *in vacuo* to give a 79:21 mixture of **208** and **217**, respectively.

Method I: Red-Al (0.171 mL, 0.567 mmol) was added to to a stirred solution of **216** (0.567 mmol) in THF (6 mL) at −20 °C and the resultant mixture was stirred at −20 °C for 2 h. MeOH (1 mL) was added and the resultant mixture was allowed to warm to rt, then concentrated *in vacuo*. The reaction mixture was partitioned beween Et_2O (10 mL) and H_2O (10 mL), the aqueous layer was extracted with Et_2O (2 × 5 mL), and the combined organic extracts were then dried and concentrated *in vacuo*. The residue was loaded onto Celite® and passed through a short plug of silica (eluent 30–40 °C petrol/Et_2O, 5:1), then concentrated *in vacuo* to give a 76:24 mixture of **208** and **217**, respectively.

Method J: $LiAlH(O^tBu)_3$ (144 mg, 0.567 mmol) was added to to a stirred solution of **216** (0.567 mmol) in THF (6 mL) at −20 °C and the resultant mixture was stirred at −20 °C for 2 h. MeOH (1 mL) was added and the resultant mixture was allowed to warm to rt, then concentrated *in vacuo*. The reaction mixture was partitioned beween Et_2O (10 mL) and H_2O (10 mL), the aqueous layer was extracted with Et_2O (2 × 5 mL), and the combined organic extracts were then dried and concentrated *in vacuo*. The residue was loaded onto Celite® and passed through a short plug of silica (eluent 30–40 °C petrol/Et_2O, 5:1), then concentrated *in vacuo* to give a 71:29 mixture of **208** and **217**, respectively.

Method K: $LiAlH(O^tBu)_3$ (29 mg, 0.116 mmol) was added to to a stirred solution of **216** (0.16 mmol) in THF (2 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 2 h. MeOH (0.5 mL) was added and the resultant mixture was allowed to warm to rt, then concentrated *in vacuo*. The reaction mixture was partitioned beween Et_2O (5 mL) and H_2O (4 mL), the aqueous layer extracted with Et_2O (2 × 3 mL), and the combined organic extracts were then dried and concentrated *in vacuo*. The residue was loaded onto Celite® and passed through a short plug of silica (eluent 30–40 °C petrol/Et_2O, 5:1), then concentrated *in vacuo* to give a 93:7 mixture of **208** and **217**, respectively.

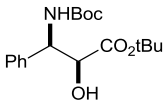
Method L: L-Selectride (1.0 M in THF, 0.567 mL, 0.567 mmol) was added to to a stirred solution of **216** (0.567 mmol) in THF (6 mL) at −20 °C and the resultant mixture was stirred at −20 °C for 2 h. MeOH (1 mL) was added and the resultant mixture was allowed to warm to rt, then concentrated *in vacuo*. The reaction mixture was partitioned beween Et_2O (10 mL)

and H_2O (10 mL), the aqueous layer was extracted with Et_2O (2 × 5 mL), and the combined organic extracts were then dried and concentrated *in vacuo*. The residue was loaded onto Celite® and passed through a short plug of silica (eluent 30–40 °C petrol/Et_2O, 5:1), then concentrated *in vacuo* to give a 78:22 mixture of **208** and **217**, respectively.

Method M: L-Selectride (1.0 M in THF, 0.116 mL, 0.116 mmol) was added to to a stirred solution of **216** (0.116 mmol) in THF (2 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 2 h. MeOH (0.5 mL) was added and the resultant mixture was allowed to warm to rt, then concentrated *in vacuo*. The reaction mixture was partitioned beween Et_2O (5 mL) and H_2O (4 mL), the aqueous layer extracted with Et_2O (2 × 3 mL) and the combined organic extracts were then dried and concentrated *in vacuo*. The residue was loaded onto Celite® and passed through a short plug of silica (eluent 30–40 °C petrol/Et_2O, 5:1), then concentrated *in vacuo* to give a 93:7 mixture of **208** and **217**, respectively.

Method N: DIBAL-H (1.0 M in THF, 1.16 mL, 1.16 mmol) was added to a stirred solution of **216** (498 mg, >99:1 dr) in THF (13 mL) at −20 °C and the resultant mixture was stirred at −20 °C for 2 h. MeOH (1 mL) was added and the reaction mixture was then allowed to warm to rt. Satd aq Rochelle salt (1 mL) was added and the resultant suspension was stirred at rt for 15 h, then filtered through Celite® (eluent MeOH) and concentrated *in vacuo* to give **217** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 7:1) gave **217** as a white solid (375 mg, 75%, >99:1 dr).

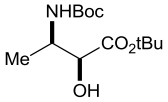
tert-Butyl (2*S*,3*R*)-2-hydroxy-3-[*N*-(*tert*-butoxycarbonyl)amino]-3-phenylpropanoate 218



$Pd(OH)_2/C$ (150 mg, 40% w/w) was added to a degassed solution of **217** (375 mg, 0.870 mmol, >99:1 dr) and Boc_2O (189 mg, 0.870 mmol) in EtOAc (10 mL) and the resultant mixture was stirred under H_2 (5 atm) at rt for 15 h. The reaction mixture was then filtered through Celite® (eluent EtOAc) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **218** as a white solid (163 mg, 68%, >99:1 dr);[11] mp 106–107 °C; $[\alpha]_D^{23}$ −9.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3447 (N−H), 3392 (O−H), 3091, 3065, 3032, 2978, 2933 (C−H), 1716 (2 × C=O); δ_H (400 MHz, $CDCl_3$) 1.42 (9H, s, C*Me*$_3$), 1.52 (9H, s, C*Me*$_3$), 3.27 (1H, br s, O*H*), 4.31–4.39 (1H, m, C(2)*H*), 5.20–5.26 (1H, m, C(3)*H*), 5.41–5.49 (1H, m, N*H*), 7.22–7.43 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.9,

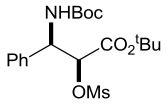
28.3 (2 × C*Me*$_3$), 55.7 (*C*(3)), 73.7 (*C*(2)), 79.6, 83.7 (2 × *C*Me$_3$), 126.7, 127.5, 128.5 (*o,m,p-Ph*), 139.7 (*i-Ph*), 155.0 (N*C*O), 172.1 (*C*(1)); *m*/*z* (ESI$^+$) 360 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{27}NNaO_5^+$ ([M+Na]$^+$) requires 360.1781; found 360.1769.

tert-Butyl (2*S*,3*R*)-2-hydroxy-3-[*N*-(_tert_-butoxycarbonly)amino]butanoate 219



Pd(OH)$_2$/C (78 mg, 25% w/w) was added to a degassed solution of **215** (313 mg, 0.847 mmol, >99:1 dr) and Boc$_2$O (203 mg, 0.932 mmol) in EtOAc (10 mL) and the resultant mixture was stirred under H_2 (5 atm) at rt for 15 h. The reaction mixture was then filtered through Celite® (eluent EtOAc) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et$_2$O, 5:1) gave **219** as a yellow solid (164 mg, 70%, >99:1 dr); mp 65–80 °C; $[\alpha]_D^{23}$ +17.7 (*c* 1.0 in CHCl$_3$); ν_{max} (ATR) 3449 (N−H), 3391 (O−H), 2978, 2934 (C−H), 1714 (2 × C=O); δ_H (400 MHz, CDCl$_3$) 1.24 (3H, d, *J* 7.1, C(4)*H*$_3$), 1.40 (9H, s, C*Me*$_3$), 1.49 (9H, s, C*Me*$_3$), 3.12–3.26 (1H, m, O*H*), 3.98 (1H, app br s, C(2)*H*), 4.13–4.24 (1H, m, C(3)*H*), 4.70–4.79 (1H, m, N*H*); δ_C (100 MHz, CDCl$_3$) 18.5 (*C*(4)), 27.8, 28.3 (2 × C*Me*$_3$), 48.3 (*C*(3)), 73.4 (*C*(2)), 79.1, 83.3 (2 × *C*Me$_3$), 154.9 (N*C*O), 172.6 (*C*(1)); *m*/*z* (ESI$^+$) 298 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{25}NNaO_5^+$ ([M+Na]$^+$) requires 298.1625; found 298.1626.

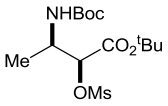
tert-Butyl (2*S*,3*R*)-2-methanesulfonyloxy-3-[*N*-(_tert_-butoxycarbonyl)amino]-3-phenylpropanoate 220



MsCl (34 μL, 0.45 mmol), Et$_3$N (0.14 mL, 1.0 mmol) and DMAP (1 mg, cat.) were added to a solution of **218** (30 mg, 0.09 mmol, >99:1 dr) in CH$_2$Cl$_2$ (3 mL) and the resultant solution was stirred at rt for 15 h. H$_2$O (1.5 mL) was added and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 × 5 mL). The combined organic extracts were washed sequentially with 1.0 M aq HCl (3 mL), satd aq NaHCO$_3$ (3 mL) and brine (3 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et$_2$O, 3:1 then increased to 1:1) gave **220** as a colourless oil (35 mg, 95%, >99:1 dr); $[\alpha]_D^{23}$ −5.8 (*c* 1.0 in CHCl$_3$); ν_{max} (ATR) 3065, 2980, 2936 (C−H), 1749, 1717 (2 × C=O); δ_H (400 MHz, CDCl$_3$) 1.42, (9H, s, C*Me*$_3$), 1.51 (9H, s, C*Me*$_3$), 2.72 (3H, s, SO$_2$*Me*), 5.05–5.14 (1H, m, C(2)*H*),

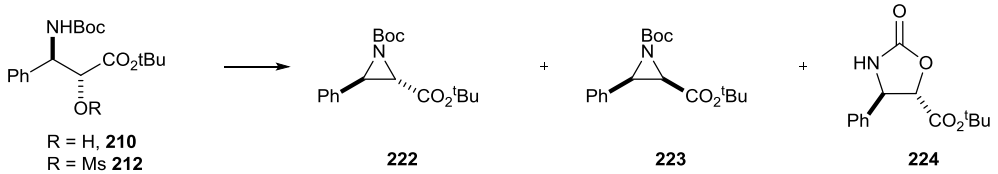
5.35–5.44 (1H, m, N*H*), 5.46–5.53 (1H, m, C(3)*H*), 7.28–7.42 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.8, 28.2 (2 × C*Me*$_3$), 38.6 (SO_2*Me*), 55.1 (*C*(3)), 81.5 (*C*(2)), 84.2 (2 × *C*Me$_3$), 126.4, 128.2, 128.8 (*o,m,p-Ph*), 137.7 (*i-Ph*), 154.6 (N*C*O), 165.6 (*C*(1)); *m*/*z* (ESI$^+$) 438 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{29}NNaO_7S^+$ ([M+Na]$^+$) requires 438.1557; found 438.1544.

tert-Butyl (2*S*,3*R*)-2-methanesulfonyloxy-3-[(_tert_-butoxycarbonyl)amino]butanoate 221



MsCl (0.26 mL, 3.31 mmol), Et_3N (1.10 mL, 8.30 mmol) and DMAP (3 mg, cat.) were added to a stirred solution of **219** (456 mg, 1.66 mmol, >99:1 dr) in CH_2Cl_2 (50 mL) and the resultant solution was stirred at rt for 16 h. H_2O (40 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extracts were washed sequentially with 1.0 M aq HCl (50 mL), satd aq $NaHCO_3$ (50 mL) and brine (50 mL), then dried and concentrated *in vacuo* to give **221** as a yellow solid (473 mg, 92%, >99:1); mp 97–106 °C; $[\alpha]_D^{20}$ +4.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3388 (N−H), 2981, 2966, 2935, 2866 (C−H), 1750, 1722 (2 × C=O); δ_H (400 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6.8, C(4)*H*$_3$), 1.42 (9H, s, C*Me*$_3$), 1.49 (9H, s, C*Me*$_3$), 3.19 (3H, s, SO_2*Me*), 4.39–4.50 (1H, m, C(3)*H*), 4.65–4.75 (1H, m, C(2)*H*), 4.88 (1H, d, *J* 2.3, N*H*); δ_C (100 MHz, $CDCl_3$) 18.3 (*C*(4)), 27.8, 28.3 (2 × C*Me*$_3$), 39.3 (SO_2*Me*), 47.6 (*C*(3)), 81.0 (*C*(2)), 79.7, 83.9 (2 × *C*Me$_3$), 154.6 (N*C*O), 166.2 (*C*(1)); *m*/*z* (ESI$^+$) 376 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{27}NNaO_7S^+$ ([M+Na]$^+$) requires 376.1400; found 376.1384.

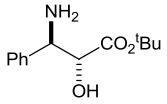
Di-_tert_-butyl (2*S*,3*R*)-3-phenylaziridine-*N*(1),2-dicarboxylate 222



KOH (266 mg, 4.74 mmol) and TsCl (273 mg, 1.43 mmol) were added to a solution of **210** (400 mg, 1.19 mmol, >99:1 dr) in Et_2O (20 mL) and the resultant mixture was heated at reflux for 16 h. The reaction mixture was then allowed to cool to rt, H_2O (12 mL) was added and the aqueous layer was extracted with Et_2O (3 × 4 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give a 61:34:5 mixture of **222**, **223** and **224**, respectively.

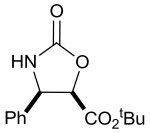
Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 15:1) gave **222** as a white solid (130 mg, 34%, >99:1 dr); mp 120–128 °C; $[\alpha]_D^{23}$ +69.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3064, 3036, 2986, 2967, 2933 (C−H), 1729, 1717 (2 × C=O); δ_H (500 MHz, $CDCl_3$) 1.48 (9H, s, C*Me*$_3$), 1.52 (9H, s, C*Me*$_3$), 3.01 (1H, d, *J* 2.5, C(2)*H*), 3.74 (1H, d, *J* 2.5, C(3)*H*), 7.27–7.37 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 27.9, 28.1 (2 × C*Me*$_3$), 44.5 (*C*(3)), 45.1 (*C*(2)), 82.0, 82.7 (2 × *C*Me$_3$), 126.5, 128.2, 128.5 (*o,m,p-Ph*), 135.7 (*i-Ph*), 158.6 (N*C*O), 166.4 (*C*O_2^{t}Bu); *m*/*z* (ESI$^+$) 342 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{25}NNaO_4^+$ ([M+Na]$^+$) requires 342.1676; found 342.1674. Further elution gave **223** as a white solid (107 mg, 28%, >99:1 dr); mp 120.5-124.5 °C; $[\alpha]_D^{25}$−18.3 (*c* 1.0 in $CHCl_3$); ν_{max} 3065, 3034, 3007, 2976, 2959, 2926, 2853 (C−H), 1736 (C=O ester), 1724 (C=O carbamate); δ_H (500 MHz, $CDCl_3$); 1.16 (9H, s, C*Me*$_3$), 1.49 (9H, s, C*Me*$_3$), 3.33 (1H, d, *J* 6.9, C(2)*H*), 3.77 (1H, d, *J* 6.9, C(3)*H*), 7.25-7.45 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 27.8, 27.9 (2 × C*Me*$_3$), 43.3 (*C*(2)), 44.2 (*C*(3)), 81.9, 82.2 (2 × *C*Me$_3$), 127.6, 127.9, 128.5 (*o,m,p-Ph*), 133.4 (*i-Ph*), 160.8 (N*C*O), 165.1 (*C*(1)); *m*/*z* (ESI$^+$) 342 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{25}NNaO_4^+$ ([M+Na]$^+$) requires 342.1676; found 342.1661.

tert-Butyl (*R,R*)-2-hydroxy-3-amino-3-phenylproanoate 225



$Pd(OH)_2$/C (27 mg, 25 % w/w) was added to a degassed solution of **208** (108 mg, 0.292 mmol, >99:1 dr) in MeOH (5 mL) and the resultant mixture was stirred under H_2 (5 atm) at rt for 15 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated *in vacuo* to give **225** as a colourless oil (55 mg, quant, >99:1 dr);[12] $[\alpha]_D^{23}$ −27.7 (*c* 1.0 in $CHCl_3$); {lit.[12] $[\alpha]_D^{23}$ −29.0 (*c* 0.5 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.33 (9H, s, C*Me*$_3$), 3.42–3.47 (3H, br s, N*H*$_2$, O*H*), 4.33–4.38 (2H, m, C(2)*H*, C(3)*H*), 7.21–7.36 (5H, m, *Ph*).

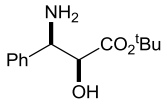
(*R,R*)-4-Phenyl-5-(*tert*-butoxycarbonyl)oxazolidin-2-one 226



CDI (205 mg, 1.26 mmol) and DMAP (3 mg, cat.) were added to a stirred solution of **225** (200 mg, 0.843 mmol, >99:1 dr) in THF (7 mL) and the resultant mixture was stirred at rt for

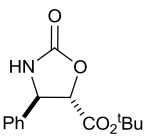
12 h. Satd aq NH_4Cl (5 mL) was added and the reaction mixture was extracted with EtOAc (3 × 3 mL). The combined organic extracts were washed with brine (5 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1) gave **226** as a white solid (49 mg, 22%, >99:1 dr); mp 163–168 °C; $[\alpha]_D^{25}$ −63.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3288 (N−H), 3067, 3036, 2980, 2934 (C−H), 1735 (2 × C=O); δ_H (400 MHz, $CDCl_3$) 1.04 (9H, s, C*Me*$_3$), 5.16 (1H, d, *J* 9.2 C(5)*H*), 5.20 (1H, d, *J* 9.2, C(4)*H*), 6.53 (1H, br s, N*H*), 7.23–7.39 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.3 (C*Me*$_3$), 58.4 (*C*(4)), 77.9 (*C*(5)), 83.0 (*C*Me$_3$), 127.5, 128.7, 129.2 (*o*,*m*,*p*-*Ph*), 135.8 (*i*-*Ph*), 158.6 (*C*(2)), 165.0 (*C*$O_2{}^t$Bu); *m*/*z* (ESI^+) 286 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{14}H_{17}NNaO_4^+$ ($[M+Na]^+$) requires 286.1050; found 286.1039.

tert-Butyl (2*S*,3*R*)-2-hydroxy-3-amino-3-phenylproanoate 227



$Pd(OH)_2$/C (35 mg, 25% w/w) was added to a degassed solution of **217** (139 mg, 0.322 mmol, >99:1 dr) in MeOH (5 mL) and the resultant mixture was stirred under H_2 (5 atm) at rt for 15 h. The reaction mixture was filtered through Celite® (eluent MeOH) and concentrated *in vacuo* to give **227** as a colourless oil (77 mg, quant, >99:1 dr); $[\alpha]_D^{23}$ +11.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3363, 3298 (N−H), 3165 (O−H), 3086, 3063, 3030, 3003, 2978, 2932 (C−H), 1727 (C=O); δ_H (400 MHz, $CDCl_3$) 1.41 (9H, s, C*Me*$_3$), 2.59 (3H, br s, N*H*$_2$, O*H*), 4.15–4.20 (2H, m, C(2)*H*, C(3)*H*), 7.21–7.41 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.9 (C*Me*$_3$), 58.5, 75.3 (*C*(2), *C*(3)), 82.5 (*C*Me$_3$), 127.0, 127.5, 128.4 (*o*,*m*,*p*-*Ph*), 142.2 (*i*-*Ph*), 172.6 (*C*(1)); *m*/*z* (ESI^+) 260 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{13}H_{19}NNaO_3^+$ ($[M+Na]^+$) requires 260.1257; found 260.1250.

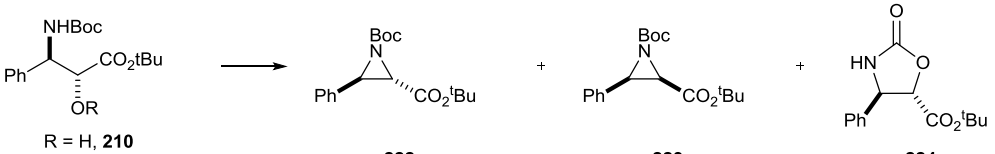
(4*R*,5*S*)-4-Phenyl-5-(*tert*-butoxycarbonyl)oxazolidin-2-one 224



CDI (73 mg, 0.449 mmol) and DMAP (3 mg, cat.) were added to a stirred solution of **227** (77 mg, 0.299 mmol, >99:1 dr) in THF (2.5 mL) and the resultant mixture was stirred at rt for 12 h. Satd aq NH_4Cl (2 mL) was added and the reaction mixture was extracted with EtOAc (3 × 2 mL). The combined organic extracts were washed with brine (5 mL), then dried and

concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1) gave **224** as a white solid (12 mg, 15%, >99:1 dr); mp 145–150 °C; $[\alpha]_D^{25}$ +30.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3287 (N−H), 3037, 3004, 2981, 2932 (C−H), 1760, 1734 (2 × C=O); δ_H (500 MHz, $CDCl_3$) 1.54 (9H, s, C*Me*$_3$), 4.64 (1H, d, *J* 5.6, C(5)*H*), 4.93 (1H, d, *J* 5.6, C(4)*H*), 5.78 (1H, br s, N*H*), 7.36–7.46 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 28.0 (C*Me*$_3$), 59.2 (*C*(4)), 80.8 (*C*(5)), 83.8 (*C*Me$_3$), 126.0, 129.1, 129.3 (*o,m,p-Ph*), 139.0 (*i-Ph*), 157.7 (*C*(2)), 167.1 (*C*O_2^tBu); *m*/*z* (ESI$^+$) 286 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{17}NNaO_4^+$ ([M+Na]$^+$) requires 286.1050; found 286.1041.

Representative experimental procedures for Scheme 31



Method A: MsCl (23 μL, 0.296 mmol) and DIPEA (0.129 mL, 0.740 mmol) were added to a stirred solution of **210** (50 mg, 0.148 mmol) in CH_2Cl_2 (0.2 mL) at −78 °C and the resultant solution was stirred at −78 °C for 3 h, then at reflux for 24 h, then allowed to warm to rt, and concentrated *in vacuo*. The reaction mixture was partitioned between EtOAc (5 mL) and H_2O (3 mL) and the aqueous layer was extracted with EtOAc (3 × 2 mL). The combined organic extracts were washed with brine (7 mL) then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1) gave **224** (29 mg, 74%).

Method B: DEAD (82 μL, 0.480 mmol) was added to a stirred solution of **210** (65 mg, 0.192 mmol) and PPh_3 (126 mg, 0.480 mmol) in THF (5 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 12 h, then allowed to warm, to rt and concentrated *in vacuo* to give a complex mixture of products.

Method C: TBAF (1.0 M in THF, 0.60 mL, 0.60 mmol) was added to a solution of **212** (50 mg, 0.12 mmol, >99:1 dr) in THF (3 mL) and the resultant solution was stirred at rt for 16 h. Et_2O (5 mL) was added and the resultant mixture was washed with H_2O (5 mL), then dried and concentrated *in vacuo* to give a 42:32:26 mixture of **222**, **223** and **224**, respectively.

Method D: Et_3N (84 μL, 0.600 mmol) was added to a stirred solution of **212** (56 mg, 0.135 mmol, >99:1 dr) in THF (3 mL) and the resultant solution was heated at reflux for 16 h. H_2O (2 mL) was added and the aqueous layer was extracted with EtOAc (2 × 1.5 mL). The combined organic extracts were washed sequentially with 1.0 M HCl (4 mL), satd aq

$NaHCO_3$ (4 mL) and brine (4 mL), then dried and concentrated *in vacuo* to give a 53:34:13 mixture of **212**, **224** and **222**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 5:1) gave **224** as a yellow solid (32 mg, 25%).

Method E: MeMgBr (37 μL, 0.089 mmol) was added to a stirred solution of **212** (20 mg, 0.059 mmol) in THF (1.5 mL) at −78 °C and the resultant mixture was warmed to rt over 16 h. Satd aq NH_4Cl (2 mL) was added and the aqueous layer was extracted with EtOAc (3 × 2 mL). The combined organic extracts were washed with brine (3 mL), then dried and concentrated *in vacuo* to give a 95:5 mixture of **212** and **224**, respectively.

Method F: ^tBuOK (519 mg, 4.62 mmol) was added to a stirred solution of **212** (1.5 g, 4.44 mmol) in THF (200 mL) and the resultant solution was stirred for 1 h at rt. H_2O (200 mL) and EtOAc (250 mL) were added and the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic extracts were washed with brine (300 mL), then dried and concentrated *in vacuo* to give a 51:49 mixture of **222** and **223**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O 15:1) gave **222** as a white solid (430 mg, 30%). Further elution gave **223** as a white solid (385 mg, 27%).

Method G: NaH (60% dispersion in mineral oil, 92 mg, 2.31 mmol) was added to a stirred solution of **212** (800 mg, 1.93 mmol, >99:1 dr) in THF (50 mL) at 0 °C and the resultant suspension was allowed to warm to rt over 16 h. MeOH (10 mL) was added and the resultant solution was concentrated *in vacuo*. The reaction mixture was partitioned between EtOAc (20 mL) and H_2O (15 mL) and the aqueous layer was extracted with EtOAc (2 ×10 mL). The combined organic extracts were washed with brine (30 mL), then dried and concentrated *in vacuo* to give a 58:41:1 mixture of **222**, **223** and **224**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 15:1) gave **222** as a white solid (175 mg, 28%, >99:1 dr). Further elution gave **223** as a white solid (84 mg, 14%, >99:1 dr).

Method H: NaH (60% dispersion in mineral oil, 15 mg, 0.060 mmol) was added to a stirred solution of **212** (50 mg, 0.120 mmol, >99:1 dr) in THF (3 mL) at 0 °C and the resultant suspension was allowed to warm to rt over 16 h. MeOH (0.5 mL) was added and the resultant solution was concentrated *in vacuo*. The reaction mixture was partitioned between EtOAc (5 mL) and H_2O (5 mL), and the aqueous layer was extracted with EtOAc (2 × 3 mL). The combined organic extracts were washed with brine (5 mL), then dried and concentrated *in vacuo* to give a 67:21:11:1 mixture of **212**, **222**, **223** and **224**, respectively.

Method I: Cs_2CO_3 (9.98 g, 10.4 mmol) was added to a stirred solution of **212** (3.47 g, 10.2 mmol, >99:1 dr) in DMF (200 mL) and the resultant mixture was heated at 50 °C for 3 h. Et_2O (80 mL) was added and the resultant mixture was washed with H_2O (4 × 150 mL), then dried and concentrated *in vacuo* to give a 81:10:9 mixture of **222**, **223** and **224**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 15:1) gave **222** as a white solid (1.68 g, 51%, >99:1 dr). Further elution gave **223** as a white solid (340 mg, 10%, >99:1 dr).

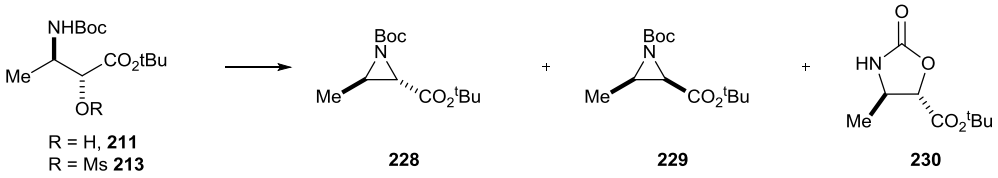
Method J: NaH (60% dispersion in mineral oil, 323 mg, 8.09 mmol) was added to a stirred solution of **212** (2.8 g, 6.74 mmol) in DMF (100 mL) at rt and the resultant solution was heated at 50 °C for 3 h. Et_2O (60 mL) was added and the resultant mixture was washed with H_2O (4 × 40 mL), then dried and concentrated *in vacuo* to give a 98:2 mixture of **222** and **223**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **222** as a white solid (1.55 g, 72%, >99:1 dr).

Method K: A solution of **212** (20 mg, 0.059 mmol, >99:1 dr) in DMF (0.5 mL) and was heated at 50 °C for 3 h. Et_2O (2mL) was added and the resultant mixture was washed with H_2O (4 × 1 mL), then dried and concentrated *in vacuo* to give a 80:20 mixture of **212** and **224**, respectively.

Method L: 15-crown-5 (0.237 mL, 1.20 mmol) was added to a stirred solution of **212** (500 mg, 1.20 mmol) in DMF (15 mL) at rt. NaH (60% dispersion in mineral oil, 58 mg, 1.45 mmol) was added and the resultant solution was heated at 50 °C for 3 h. Et_2O (10 mL) was added and the resultant mixture was washed with H_2O (4 × 5 mL), then dried and concentrated *in vacuo* to give a 90:4:6 mixture of **222**, **223** and **224**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 15:1) gave **222** as a white solid (240 mg, 62%). Further elution gave **223** as a white solid (8 mg, 2%).

Method M: 15-crown-5 (0.2374 mL, 1.20 mmol) was added to a stirred solution of **212** (500 mg, 1.20 mmol) in THF (15 mL) at rt. NaH (60% dispersion in mineral oil, 58 mg, 1.45 mmol) was added and the resultant solution was stirred at rt for 16 h. Brine (10 mL) was added and the resultant mixture was extracted with Et_2O (3 × 5 mL). The combined organic extracts were dried and concentrated *in vacuo* to give a 90:7:3 mixture of **222**, **223** and **224**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 15:1) gave **222** as a white solid (215 mg, 56%). Further elution gave **223** as a white solid (22 mg, 6%).

Representative experimental procedures for Scheme 32



Method A: KOH (407 mg, 7.26 mmol, >99:1 dr) and TsCl (416 mg, 2.18 mmol) were added to a stirred solution of **211** (500 mg, 1.82 mmol) in Et_2O (30 mL) and the resultant mixture was heated at reflux for 16 h. The reaction mixture was then allowed to cool to rt, H_2O (15 mL) was added and the aqueous layer was extracted with Et_2O (3 × 8 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give a 66:6:20:8 mixture of **228**, **229**, **230** and **211** respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 20:1 then increased to 10:1) gave **228** as a white solid (200 mg, 43%); mp 69.0–71.0 °C; $[\alpha]_D^{25}$ −1.7 (*c* 1.0 in $CHCl_3$); ν_{max} 3007, 2980, 2933, 2872 (C−H), 1728 (C=O ester) 1718 (C=O carbamate); δ_H (500 MHz, $CDCl_3$) 1.31 (3H, d, *J* 5.5, C(3)*Me*), 1.46 (9H, s, C*Me*$_3$), 1.49 (9H, s, C*Me*$_3$), 2.68 (1H, d, *J* 2.7 C(2)*H*), 2.75 (1H, dq, *J* 5.5, 2.7, C(3)*H*); δ_C (125 MHz, $CDCl_3$) 16.5 (C(3)*Me*), 28.0, 28.0 (2 × C*Me*$_3$), 38.9 (*C*(3)), 42.4 (*C*(2)), 81.5, 82.3 (2 × *C*Me$_3$), 159.3 (N*C*O), 167.4 (*C*O$_2$^{t}Bu); *m*/*z* (ESI$^+$) 280 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{23}NNaO_4^+$ ([M+Na]$^+$) requires 280.1519; found 280.1518.

Method B: DEAD (248 μL, 1.45 mmol) was added to a stirred solution of **211** (200 mg, 0.726 mmol) and PPh_3 (381 mg, 1.45 mmol) in THF (25 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 12 h, then allowed to warm to rt, and concentrated *in vacuo* to give a complex mixture of products.

Method C: Et_3N (0.10 mL, 0.705 mmol) was added to a stirred solution of **213** (50 mg, 0.141 mmol, >99:1 dr) in THF (3 mL) and the resultant solution was heated at reflux for 16 h. H_2O (2 mL) was then added and the aqueous layer was extracted with EtOAc (2 × 1.5 mL). The combined organic extracts were washed sequentially with 1.0 M HCl (4 mL), satd aq $NaHCO_3$ (4 mL) and brine (4 mL), then dried and concentrated *in vacuo* to give a 68:32 mixture of **230** and **213**, respectively.

Method D: MeMgBr (28 μL, 0.067 mmol) was added to **213** (20 mg, 0.064 mmol) in THF (1.5 mL) at −78 °C and the resultant mixture was warmed to rt over 16 h. Satd aq NH_4Cl (2 mL) was added and the aqueous layer was extracted with EtOAc (3 × 2 mL). The combined organic extracts were washed with brine (3 mL), then dried and concentrated *in vacuo* to give a 90:10 mixture of **213** and **230**, respectively.

Method E: ^{t}BuOK (1.18 g, 3.62 mmol) was added to a stirred solution of **213** (1.23 g, 3.48 mmol) in THF (70 mL) and the resultant solution was stirred for 1 h at rt. H_2O (50 mL) and EtOAc (50 mL) were added and the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with brine (80 mL), then dried and concentrated *in vacuo* to give a 50:50 mixture of **228** and **229**, respectively. Purification via flash column chromatography (eluent PhMe/Et_2O, 80:1) gave **228** as a white solid (117 mg, 12%, >99:1 dr). Further elution gave **229** as a white solid (90 mg, 9%, >99:1 dr). A 61:39 mixture of **229** and **228** was also isolated (229 mg, 24%).

Method F: NaH (60% dispersion in mineral oil, 136 mg, 3.39 mmol) was added to a stirred solution of **213** (1.0 g, 2.83 mmol, >99:1 dr) in THF (34 mL) at 0 °C and the resultant suspension was allowed to warm to rt over 16 h. MeOH (15 mL) was added and the resultant solution was concentrated *in vacuo*. The reaction mixture was partitioned between EtOAc (20 mL) and H_2O (15 mL) and the aqueous layer was extracted with EtOAc (2 ×10 mL). The combined organic extracts were washed with brine (30 mL), then dried and concentrated *in vacuo* to give a complex mixture of products.

Method G: Cs_2CO_3 (4.85 g, 17.0 mmol) was added to a stirred solution of **213** (1.76 g, 5.66 mmol, >99:1 dr) in DMF (110 mL) and the resultant mixture was heated at 50 °C for 3 h. Et_2O (50 mL) was added and the resultant mixture was washed with H_2O (4 × 70 mL), then dried and concentrated *in vacuo* to give a 66:14:20 mixture of **228**, **229** and **230**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 30:1) gave **228** as a white solid (342 mg, 23%, >99:1 dr). Further elution gave **229** as a white solid (88 mg, 8%, >99:1 dr); mp 60.5–63.5 °C; $[\alpha]_D^{25}$ +68.0 (*c* 1.0 in $CHCl_3$); ν_{max} 3041, 2998, 2977, 2933, 2873, 2851 (C−H), 1740 (C=O ester), 1712 (C=O carbamate) 1678 (C−N); δ_H (500 MHz, $CDCl_3$) 1.31 (3H, d, *J* 5.6, C(3)*Me*), 1.44 (9H, s, C*Me*$_3$), 1.47 (9H, s, C*Me*$_3$), 2.62-2.69 (1H, m, C(3)*H*), 3.00 (1H, d, *J* 6.8, C(2)*H*); δ_C (125 MHz, $CDCl_3$) 12.7 (C(3)*Me*), 27.8, 28.1 (2 × C*Me*$_3$), 38.5 (*C*(3)), 40.5 (*C*(2)), 81.7, 82.0 (2 × *C*Me$_3$), 161.0 (N*C*O), 166.5 (*C*(1)); *m*/*z* (ESI$^+$) 280 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{23}NNaO_4^+$ ([M+Na]$^+$) requires 280.1519; found 280.1519. Further elution gave **230** as a white solid (227 mg, 20%, >99:1 dr);[10] mp 113–122 °C; $[\alpha]_D^{25}$ +27.3 (*c* 1.0 in $CHCl_3$); {lit.[10] for *ent*-**230** $[\alpha]_D^{25}$ −22.6 (*c* 0.5 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.40 (3H, d, *J* 6.1, C(4)*Me*), 1.49 (9H, s, C*Me*$_3$), 3.88–3.96 (1H, m, C(4)*H*), 4.39 (1H, d, *J* 5.8, C(5)*H*), 6.49–6.59 (1H, m, N*H*).

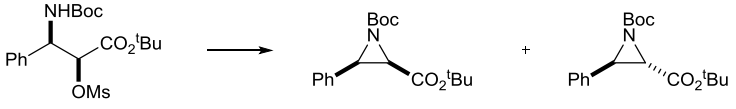
Method H: NaH (60% dispersion in mineral oil, 68 mg, 1.69 mmol) was added to a stirred solution of **213** (459 mg, 1.41 mmol, >99:1 dr) in DMF (15 mL) and the resultant mixture was heated at 50 °C for 3 h. Et_2O (15 mL) was then added and the resultant mixture was washed with H_2O (4 × 10 mL), then dried and concentrated *in vacuo* to give a 93:7 mixture of **228** and **230**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 15:1) gave **228** as a white solid (185 mg, 48%, >99:1 dr);

Method I: A solution of **213** (20 mg, 0.059 mmol, >99:1 dr) in DMF (0.5 mL) was heated at 50 °C for 3 h. Et_2O (2mL) was added and the resultant mixture was washed with H_2O (4 × 1 mL), then dried and concentrated *in vacuo* to give a 44:56 mixture of **213** and **230**, respectively.

Method J: 15-Crown-5 (0.127 mL, 0.642 mmol) was added to a solution of **213** (200 mg, 0.642 mmol) in DMF (10 mL) at rt. NaH (60% dispersion in mineral oil, 31 mg, 0.771 mmol) was added and the resultant solution was heated at 50 °C for 3 h. Et_2O (15 mL) was added and the resultant mixture was washed with H_2O (4 × 10 mL), then dried and concentrated *in vacuo* to give a 95:5 mixture of **228** and **229**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 50:3) gave **228** as a white solid (79 mg, 45%, >99:1 dr).

Method K: 15-Crown-5 (0.310 mL, 1.56 mmol) was added to a stirred solution of **213** (487 mg, 1.56 mmol) in THF (15 mL) at rt. NaH (60% dispersion in mineral oil, 75 mg, 1.87 mmol) was added and the resultant solution was stirred at rt for 16 h. Brine (8 mL) was added and the resultant mixture was extracted with Et_2O (3 × 8 mL). The combined organic extracts were dried and concentrated *in vacuo* to give a 96:4 of **228** and **229**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 15:1) gave **228** as a white solid (21 mg, 5%, >99:1 dr). A 84:16 mixture of **228** and **229** was also isolated (80 mg, 20%).

Representative experimental procedures for Scheme 33

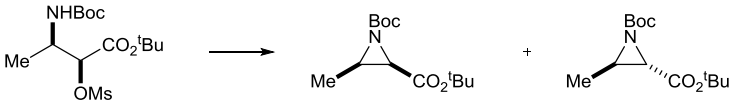


220 **223** **222**

Method A: Cs_2CO_3 (299 mg, 0.918 mmol) was added to a stirred solution of **220** (127 mg, 0.306 mmol, >99:1 dr) in DMF (6.2 mL) at rt and the resultant mixture was heated at 50 °C for 3 h. Et_2O (5 mL) was added and the resultant mixture was washed with H_2O (4 × 3 mL), then dried and concentrated *in vacuo* to give **223** as a white solid (97 mg, 99%, >99:1 dr).

Method B: NaH (60% dispersion in mineral oil, 3 mg, 0.056 mmol) was added to a stirred solution of **220** (20 mg, 0.048 mmol) in DMF (0.5 mL) at rt and the resultant solution was heated at 50 °C for 3 h. Et_2O (2 mL) was added and the resultant mixture was washed with H_2O (4 × 2 mL), then dried and concentrated *in vacuo* to give a 93:7 mixture of **223** and **222**, respectively.

Method C: 15-crown-5 (0.095 mL, 0.048 mmol) was added to **220** (20 mg, 0.048 mmol) in DMF (0.5 mL) at rt. NaH (60% dispersion in mineral oil, 3 mg, 0.056 mmol) was added and the resultant solution was heated at 50 °C for 3 h. Et_2O (2 mL) was added and the resultant mixture was washed with H_2O (4 × 2 mL), then dried and concentrated *in vacuo* to give a 76:24 mixture of **223** and **222**, respectively.



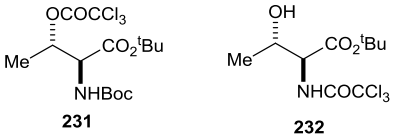
221 **229** **228**

Method A: Cs_2CO_3 (974 mg, 2.99 mmol) was added to a stirred solution of **221** (352 mg, 0.997 mmol, >99:1 dr) in DMF (9 mL) at rt and the resultant mixture was heated at 50 °C for 3 h. Et_2O (15 mL) was added and the resultant mixture was washed with H_2O (4 × 10 mL), then dried and concentrated *in vacuo* to give **229** in >99:1 dr. Purification via flash column chromatography (eluent PhMe/Et_2O, 80:1) gave **229** as a white solid (187 mg, 73%); $[\alpha]_D^{25}$ + 47.3 (*c* 1.0 in $CHCl_3$).

Method B: NaH (60% dispersion in mineral oil, 7 mg, 0.142 mmol) was added to a stirred solution of **221** (50 mg, 0.142 mmol) in DMF (1.5 mL) at rt and the resultant mixture was heated at 50 °C for 3 h. Et_2O (5 mL) was added and the resultant mixture was washed with H_2O (4 × 5 mL), then dried and concentrated *in vacuo* to give **229** in >99:1 dr. Purification via flash column chromatography (eluent PhMe/Et_2O, 80:1) gave **229** as a white solid (12 mg, 32%).

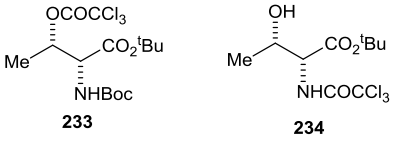
Method C: 15-Crown-5 (0.022 mL, 0.113 mmol) was added to a stirred solution of **221** (40 mg, 0.113 mmol) in DMF (1.0 mL) at rt. NaH (60% dispersion in mineral oil, 5 mg, 0.136 mmol) was added and the resultant solution was stirred at rt for 16 h. Brine (2 mL) was added and the resultant mixture was extracted with Et_2O (3 × 2 mL). The combined organic extracts were dried and concentrated *in vacuo* to give a 83:17 mixture of **229** and **228**, respectively.

tert-Butyl (_S_,_S_)-2-[_N_-(_tert_-butoxycarbonyl)amino]-3-(trichloroacetoxy)butanoate 231 and _tert_-butyl (_S_,_S_)-2-(trichloroacetamido)-3-hydroxybutanoate 232



Cl_3CCO_2H (1.19 g, 7.26 mmol) was added to a stirred solution of **228** (400 mg, 1.45 mmol, >99:1 dr) in CH_2Cl_2 (9 mL) and the resultant mixture was stirred at rt for 15 h. Satd aq $NaHCO_3$ (5 mL) was then added, the aqueous layer was extracted with CH_2Cl_2 (2 × 4 mL), and the combined organic extracts were dried and concentrated *in vacuo* to give a 70:30 mixture of **231** and **232**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **231** as a white solid (287 mg, 47%, >99:1 dr); mp 61–63 °C; $[\alpha]_D^{25}$ +36.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3440 (N−H), 2979, 2935 (C−H), 1763, 1743, 1707 (3 × C=O); δ_H (400 MHz, C_6D_6) 1.17 (3H, d, *J* 6.6 C(4)*H*$_3$), 1.31 (9H, s, C*Me*$_3$), 1.47 (9H, s, C*Me*$_3$), 4.77–4.84 (1H, m, C(2)*H*), 5.39–5.47 (1H, m, C(3)*H*), 5.48–5.55 (1H, m, N*H*); δ_C (100 MHz, C_6D_6) 15.3 (*C*(4)), 27.7, 28.2 (2 × C*Me*$_3$), 57.1 (*C*(2)), 77.0 (*C*(3)), 80.0, 82.7 (2 × *C*Me$_3$), 90.5 (*C*Cl$_3$), 155.2 (N*C*O), 161.4 (*C*OCCl$_3$), 167.6 (*C*(1)); *m/z* (FI^+) 419 ($[M(^{35}Cl_3)]^+$, 100%); HRMS (FI^+) $C_{15}H_{24}{}^{35}Cl_3NO_6^+$ ($[M(^{35}Cl_3)]^+$) requires 419.0664; found 419.0698. Further elution gave **232** as a colourless oil (14 mg, 4%, >99:1 dr); $[\alpha]_D^{25}$ +4.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3413 (O−H), 2979, 2936 (C−H), 1713 (2 × C=O); δ_H (400 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6.6, C(4)*H*$_3$), 1.52 (9H, s, C*Me*$_3$), 2.76 (1H, br s, O*H*), 4.20–4.26 (1H, m, C(3)*H*), 4.48 (1H, dd, *J* 7.3, 3.5, C(2)*H*), 7.56–7.63 (1H, m, N*H*); δ_C (100 MHz, $CDCl_3$) 18.9 (*C*(4)), 28.0 (C*Me*$_3$), 60.0 (*C*(2)), 68.9 (*C*(3)), 84.0 (*C*Me$_3$), 92.1 (*C*Cl$_3$), 162.3 (*C*OCCl$_3$), 168.0 (*C*(1)); *m/z* (ESI^+) 342 ($[M(^{35}Cl_3)+Na]^+$, 100%); HRMS (ESI^+) $C_{10}H_{16}{}^{35}Cl_3NNaO_4^+$ ($[M(^{35}Cl_3)+Na]^+$) requires 342.0037; found 342.0028.

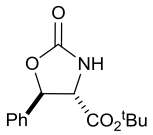
tert-Butyl (2_R_,3_S_)-2-[_N_-(_tert_-butoxycarbonyl)amino]-3-(trichloroacetoxy)butanoate 233 and _tert_-butyl (2_R_,3_S_)-2-(trichloroacetamido)-3-hydroxybutanoate 234



Cl_3CCO_2H (682 mg, 4.18 mmol) was added to a stirred solution of **229** (230 mg, 0.835 mmol, >99:1 dr) in CH_2Cl_2 (5 mL) and the resultant solution was stirred at rt for 15 h. Satd aq $NaHCO_3$ (4 mL) was then added, the aqueous layer was extracted with CH_2Cl_2 (2 × 3 mL), and the combined organic extracts were dried and concentrated *in vacuo* to give an 84:16 mixture of **233** and **234**, respectively. Purification via flash column chromatography (eluent

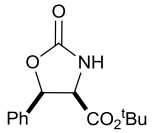
30–40 °C petrol/Et_2O, 5:1) gave **233** as a yellow oil (239 mg, 68%, >99:1 dr); $[\alpha]_D^{25}$ −17.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3441 (N−H), 2981, 2936 (C−H), 1767, 1741, 1717 (3 × C=O); δ_H (400 MHz, $CDCl_3$) 1.42 (3H, d, *J* 6.5, C(4)*H*$_3$), 1.46 (9H, s, C*Me*$_3$), 1.49 (9H, s, C*Me*$_3$), 4.47 (1H, dd, *J* 9.4, 2.2, C(2)*H*), 5.19 (1H, d, *J* 9.4, N*H*), 5.58 (1H, qd, *J* 6.5, 2.2, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 16.0 (*C*(4)), 27.9, 28.2 (2 × C*Me*$_3$), 57.2 (*C*(2)), 76.7 (*C*(3)), 80.4, 83.2 (2 × *C*Me$_3$), 89.6 (*C*Cl$_3$), 155.9 (N*C*O), 160.8, 168.0 (*C*(1), *C*OCCl$_3$); *m/z* (FI^+) 419 ($[M(^{35}Cl_3)]^+$, 100%); HRMS (FI^+) $C_{15}H_{24}{}^{35}Cl_3NO_6^+$ ($[M(^{35}Cl_3)]^+$) requires 419.0664; found 419.0678. Further elution gave **234** as a brown solid (24 mg, 9%, >99:1 dr); mp 91–111 °C; $[\alpha]_D^{25}$ +3.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3401 (O−H), 3420 (N−H), 2976, 2925, 2852 (C−H), 1737, 1698 (2 × C=O); δ_H (400 MHz, C_6D_6) 1.02 (3H, d, *J* 6.3, C(4)*H*$_3$), 1.40 (9H, s, C*Me*$_3$), 2.32 (1H, br s, O*H*), 4.19 (1H, qd, *J* 6.3, 2.3, C(3)*H*), 4.48 (1H, dd, *J* 8.6, 2.3, C(2)*H*), 7.54–7.60 (1H, m, N*H*); δ_C (100 MHz, C_6D_6) 20.0 (*C*(4)), 28.2 (C*Me*$_3$), 59.5 (*C*(2)), 68.0 (*C*(3)), 82.5 (*C*Me$_3$), 93.0 (*C*Cl$_3$), 162.3 (*C*OCCl$_3$), 168.8 (*C*(1)); *m/z* (ESI^+) 342 ($[M(^{35}Cl_3)+Na]^+$, 100%); HRMS (ESI^+) $C_{10}H_{16}{}^{35}Cl_3NNaO_4^+$ ($[M(^{35}Cl_3)+Na]^+$) requires 342.0037; found 342.0026.

(4*S*,5*R*)-5-Phenyl-4-(*tert*-butoxycarbonyl)oxazolidin-2-one 235



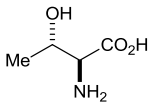
Cl_3CCO_2H (2.14 g, 13.1 mmol) was added to a stirred solution of **222** (839 mg, 2.63 mmol, >99:1 dr) in CH_2Cl_2 (15 mL) and the resultant mixture was stirred at rt for 15 h. Satd aq $NaHCO_3$ (8 mL) was added, the aqueous layer was extracted with CH_2Cl_2 (2 × 6 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 3:1) gave **235** (531 mg, 77%, >99:1 dr); mp 109–116 °C; $[\alpha]_D^{25}$ +39.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3279 (N−H), 3067, 3036, 2980, 2934 (C−H), 1764 (2 × C=O); δ_H (400 MHz, $CDCl_3$) 1.52 (9H, s, C*Me*$_3$), 4.18 (1H, d, *J* 5.3, C(4)*H*), 5.58 (1H, d, *J* 5.3, C(5)*H*), 6.89 (1H, br s, N*H*), 7.33–7.45 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.9 (C*Me*$_3$), 62.1 (*C*(4)), 79.6 (*C*(5)), 83.7 (*C*Me$_3$), 125.4, 128.9, 129.0 (*o*,*m*,*p*-*Ph*), 138.4 (*i*-*Ph*), 158.6 (*C*(2)), 168.7 (*C*O$_2$^{t}Bu); *m/z* (ESI^+) 286 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{14}H_{17}NNaO_4^+$ ($[M+Na]^+$) requires 286.1050; found 286.1048.

(*R*,*R*)-5-Phenyl-4-(*tert*-butoxycarbonyl)oxazolidin-2-one 236



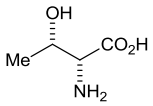
Cl_3CCO_2H (826 mg, 5.08 mmol) was added to a stirred solution of **223** (323 mg, 1.01 mmol, >99:1 dr) in CH_2Cl_2 (6.5 mL) and the resultant mixture was stirred at rt for 18 h. Satd aq $NaHCO_3$ (5 mL) was added, the aqueous layer was extracted with CH_2Cl_2 (2 × 3 mL), and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:1) gave *ent*-**235** as a white solid (10 mg, 4%, >99:1 dr); mp 113–127 °C; $[\alpha]_D^{25}$ −33.9 (*c* 1.0 in $CHCl_3$); Further elution gave (*R*,*R*)-**236** as a white solid (197 mg, 74%, >99:1 dr); mp 239–242 °C (dec.); $[\alpha]_D^{25}$ −79.0 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 3355 (N−H), 2989, 2937 (C−H), 1772, 1745 (2 × C=O); δ_H (400 MHz, $CDCl_3$) 1.01 (9H, s, C*Me*$_3$), 4.61 (1H, d, *J* 9.2, C(4)*H*), 5.80 (1H, d, *J* 9.2, C(5)*H*), 6.14 (1H, br s, N*H*), 7.30–7.43 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.3 (C*Me*$_3$), 59.9 (*C*(4)), 79.2 (*C*(5)), 82.9 (*C*Me$_3$), 126.8, 128.5, 129.2 (*o*,*m*,*p*-*Ph*), 134.5 (*i*-*Ph*), 158.9 (*C*(2)), 167.3 (*C*O_2^tBu); *m*/*z* (ESI^+) 286 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{14}H_{17}NNaO_4^+$ ($[M+Na]^+$) requires 286.1050; found 286.1047.

(*S*,*S*)-2-Amino-3-hydroxybutanoic acid [(*S*,*S*)-*allo*-threonine] *ent*-64



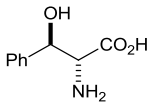
A stirred solution of **231** (212 mg, 0.506 mmol, >99:1 dr) in 6.0 M aq HCl (5.7 mL) was heated at 90 °C for 24 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. Purification via ion exchange chromatography on Dowex-50WX8 resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) gave *ent*-**64** as a white solid (43 mg, 72%, >99:1 dr);[13] mp 240–250 °C (dec.); {lit.[13] mp 264–266 °C}; $[\alpha]_D^{20}$ +7.5 (*c* 1.0 in H_2O); {lit.[13] $[\alpha]_D^{20}$ +8.0 (*c* 1.1 in H_2O)}; δ_H (400 MHz, D_2O) 1.11 (3H, d, *J* 6.6, C(4)*H*$_3$), 3.75 (1H, d, *J* 4.1, C(2)*H*), 4.27 (1H, qd, *J* 6.6, 4.1, C(3)*H*); δ_C (100 MHz, D_2O) 16.2 (*C*(4)), 59.7 (*C*(2)), 65.3 (*C*(3)), 171.8 (*C*(1)).

(2*R*,3*S*)-2-Amino-3-hydroxybutanoic acid [(2*R*,3*S*)-threonine] 237



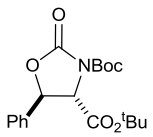
A stirred solution of **233** (160 mg, 0.382 mmol, >99:1 dr) in 6.0 M aq HCl (4.8 mL) was heated at 90 °C for 24 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. Purification via ion exchange chromatography on Dowex-50WX8 resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) gave **237** as a white solid (44 mg, 98%, 98:2 dr);[14] mp 250–260 °C (dec.); {lit.[15] mp 264 °C (dec.)}; $[\alpha]_D^{25}$ +23.2 (*c* 1.0 in H_2O); {lit.[16] $[\alpha]_D^{20}$ +26.1 (*c* 1.0 in H_2O)}; δ_H (400 MHz, D_2O) 1.21 (3H, d, *J* 6.6, C(4)*H*$_3$), 3.47 (1H, d, *J* 5.0, C(2)*H*), 4.13 (1H, qd, *J* 6.6, 5.0, C(3)*H*); δ_C (100 MHz, D_2O) 19.4 (*C*(4)), 60.4 (*C*(2)), 65.8 (*C*(3)), 172.8 (*C*(1)).

(*R*,*R*)-2-Amino-3-hydroxy-3-phenylpropanoic acid 184



A stirred solution of **236** (50 mg, 0.190 mmol, >99:1 dr) in 6.0 M aq HCl (4 mL) was heated at 90 °C for 24 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. Purification via ion exchange chromatography on Dowex-50WX8 resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) gave **184** as a white solid (26 mg, 76%, 96:4 dr);[17] mp 189–192 °C (dec.); {lit.[18] mp 174 °C (dec.)}; $[\alpha]_D^{20}$ −2.4 (*c* 1.0 in H_2O); {lit.[17] $[\alpha]_D^{20}$ −4.3 (*c* 1.1 in H_2O)}; δ_H (400 MHz, D_2O) 4.00 (1H, d, *J* 4.3, C(2)*H*), 5.28 (1H, d, *J* 4.3, C(3)*H*), 7.28–7.41 (5H, m, *Ph*); δ_C (100 MHz, D_2O) 60.4 (*C*(2)), 71.1 (*C*(3)), 126.3, 128.8, 128.8 (*o*,*m*,*p*-*Ph*), 136.8 (*i*-*Ph*), 171.1 (*C*(1)).

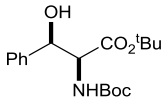
(4*S*,5*R*)-5-Phenyl-4-(*tert*-butoxycarbonyl)-*N*(3)-(*tert*-butoxycarbonyl)oxazolidin-2-one 238



Et_3N (0.143 mL, 1.08 mmol), Boc_2O (542 mg, 2.49 mmol) and DMAP (20 mg, cat.) were added to a stirred solution of **235** (142 mg, 0.540 mmol, >99:1 dr) in THF (7 mL) and the resultant mixture was stirred at rt for 15 h, then concentrated *in vacuo*. The residue was partitioned between $CHCl_3$ (10 mL) and $NaHCO_3$ (10 mL) and the organic layer was washed with brine (10 mL), then dried over Na_2SO_4 and concentrated *in vacuo*. Purification via flash

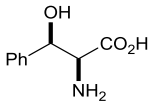
column chromatography (eluent 30–40 °C petrol/Et_2O, 3:1) gave **238** as a white solid (180 mg, 92%, >99:1 dr); mp 102–104 °C; $[\alpha]_D^{25}$ +15.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2981, 2935 (C−H), 1827, 1747, 1730 (3 × C=O); δ_H (400 MHz, $CDCl_3$) 1.43 (9H, s, C*Me*$_3$), 1.47 (9H, s, C*Me*$_3$), 4.42 (1H, d, *J* 4.1, C(5)*H*), 5.26 (1H, d, *J* 4.1, C(4)*H*), 7.28–7.40 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.8, 27.9 (C*Me*$_3$), 64.3 (*C*(4)), 76.1 (*C*(5)), 83.8, 84.5 (*C*Me$_3$), 124.9, 129.2, 129.3 (*o*,*m*,*p*-*Ph*), 137.5 (*i*-*Ph*), 148.5, 151.0 (*C*(2), N*C*O), 167.5 (*C*O_2^tBu); *m*/*z* (ESI^+) 386 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{19}H_{25}NNaO_6^+$ ($[M+Na]^+$) requires 386.1574; found 386.1578.

tert-Butyl (2*S*,3*R*)-2-[(_tert_-butoxycarbonyl)amino]-3-hydroxy-3-phenylpropanoate 239



2.0 M aq LiOH (1.4 mL) was added to a stirred solution of **238** (100 mg, 0.275 mmol, >99:1 dr) in 1,4-dioxane (7 mL) and the resultant mixture was stirred at rt for 45 min, then concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (15 mL) and the resultant solution was filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1) gave **239** as a white solid (55 mg, 59%, 98:2 dr); mp 120–125 °C; $[\alpha]_D^{25}$ −8.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3457 (O−H), 2979 (N−H), 1721, 1695 (2 × C=O); δ_H (400 MHz, $CDCl_3$) 1.27 (9H, s, C*Me*$_3$), 1.34 (9H, s, C*Me*$_3$), 3.00–3.18 (1H, m, O*H*), 4.28–4.39 (1H, m, C(2)*H*), 4.99–5.04 (1H, m, C(3)*H*), 5.19-5.30 (1H, m, N*H*), 7.16–7.32 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.9, 28.2 (2 × C*Me*$_3$), 59.9 (*C*(2)), 74.6 (*C*(3)), 79.9, 82.5 (2 × *C*Me$_3$), 126.3, 127.9, 128.3 (*o*,*m*,*p*-*Ph*), 140.1 (*i*-*Ph*), 155.8 (N*C*O), 169.9 (*C*(1)); *m*/*z* (ESI^+) 360 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{18}H_{27}NNaO_5^+$ ($[M+Na]^+$) requires 360.1781; found 360.1785.

(2*S*,3*R*)-2-Amino-3-hydroxy-3-phenylpropanoic acid 91

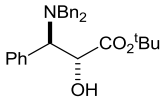


*Method A (from **235**):* A stirred solution of **235** (90 mg, 0.342 mmol, >99:1 dr) in 6.0 M aq HCl (1.7 mL) was heated at 90 °C for 24 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo* to give **91**·HCl (39 mg, 52%, 80:20 dr). Purification via ion exchange chromatography on Dowex-50WX8 resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) gave **91** as a white solid (31 mg, 50%, 80:20 dr).

*Method B (from **239**):* A solution of **239** (51 mg, 0.151 mmol, 98:2 dr) in CH_2Cl_2/TFA (4:1, 4 mL) was stirred at rt for 2 h, then concentrated *in vacuo*. 6.0 M aq HCl (2 mL) was then added and the resultant solution was concentrated *in vacuo*. Purification via ion exchange chromatography on Dowex-50WX8 resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) gave **91** as a white solid (20 mg, quant, 98:2 dr);[13,19] mp 201–202 °C; {lit.[19] mp 192–195 °C}; $[\alpha]_D^{20}$ −28.9 (*c* 1.0 in H_2O); {lit.[13] $[\alpha]_D^{20}$ −30.0 (*c* 1.0 in H_2O)}; δ_H (500 MHz, D_2O) 3.83 (1H, d, *J* 4.1, C(2)*H*), 5.22 (1H, d, *J* 4.1, C(3)*H*), 7.28–7.45 (5H, m, *Ph*); δ_C (125 MHz, D_2O) 60.9 (*C*(2)), 71.3 (*C*(3)), 125.8, 128.5, 128.9 (*o*,*m*,*p*-*Ph*), 139.1 (*i*-*Ph*), 172.0 (*C*(1)).

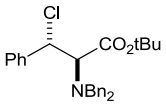
6.4. Experimental for Chapter 3

tert-Butyl (*RS*,*RS*)-2-hydroxy-3-[*N*-*N*-dibenzylamino]-3-phenylpropanoate 248



BuLi (2.2 M in hexanes, 6.9 mL, 15.2 mmol) was added dropwise to a stirred solution of Bn_2NH (3.01 mL, 15.7 mmol) in THF (40 mL) at −78 °C and stirring was continued at –78 °C for 30 min. A solution of **206** (2.00 g, 9.79 mmol, >99:1 dr) in THF (40 mL) was then added via cannula and the resultant mixture was stirred at −78 °C for 2 h. (−)-**202** (3.82 g, 16.6 mmol) was then added and stirring was continued as the reaction mixture was allowed to warm to rt over 15 h. Satd aq NH_4Cl (5 mL) was added and the reaction mixture was stirred at rt for 5 min then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (50 mL) and 10% aq citric acid (50 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (100 mL) and brine (100 mL), then dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (60 mL), the insoluble CSO residues were filtered off, and the filter cake was washed with Et_2O (2 × 50 mL). The filtrate was concentrated *in vacuo* and the process was repeated. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 20:1) gave **248** as a white soild (2.94 g, 72%, >99:1 dr); mp 79–81 °C; ν_{max} (ATR) 3501 (O−H), 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.30 (9H, s, C*Me*$_3$), 2.85 (1H, br s, O*H*), 3.46 (2H, d, *J* 13.9, N(CH_AH_BPh)$_2$), 3.98 (2H, d, *J* 13.9, N(CH_AH_BPh)$_2$), 4.11 (1H, d, *J* 4.3, C(3)*H*), 4.74–4.81 (1H, m, C(2)*H*), 7.19–7.42 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.8 (C*Me*$_3$), 54.8 (N(*C*H$_2$Ph)$_2$), 64.5 (*C*(3)), 72.7 (*C*(2)), 82.6 (*C*Me$_3$), 126.9, 127.6, 128.0, 128.2, 128.8, 130.0 (*o*,*m*,*p*-*Ph*), 135.9, 139.8 (*i*-*Ph*), 173.0 (*C*(1)); *m*/*z* (ESI$^+$) 418 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{32}NO_3^+$ ([M+H]$^+$) requires 418.2377; found 418.2379.

tert-Butyl (*RS*,*SR*)-2-dibenzylamino-3-chloro-3-phenylpropanoate 250

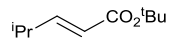


Method A: MsCl (0.28 mL, 3.60 mmol), Et_3N (1.10 mL, 8.27 mmol) and DMAP (5 mg, cat.) were added to a stirred solution of **248** (300 mg, 0.719 mmol, >99:1 dr) in CH_2Cl_2 (20 mL) and the resultant mixture was stirred at rt for 2 h. H_2O (10 mL) was then added, the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were washed sequentially with 1.0 M aq HCl (20 mL), satd aq $NaHCO_3$ (20 mL) and brine (20 mL), then

dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **250** as a white solid (251 mg, 80%, >99:1 dr); mp 98–110 °C; ν_{max} (ATR) 1723 (C=O); δ_H (400 MHz, $CDCl_3$) 1.66 (9H, s, C*Me*$_3$), 3.35 (2H, d, *J* 13.4, N(C*H*$_A$H$_B$Ph)$_2$), 3.72–3.86 (3H, m, C(2)*H*, N(CH$_A$*H*$_B$Ph)$_2$), 5.24 (1H, d, *J* 11.1, C(3)*H*), 6.86–7.47 (15H, m, *Ph*); δ_C (400 MHz, $CDCl_3$) 28.5 (C*Me*$_3$), 54.5 (N(*C*H$_2$Ph)$_2$), 60.1 (*C*(3)), 66.9 (*C*(2)), 82.2 (*C*Me$_3$), 127.2, 128.0, 128.3, 128.6, 128.7, 129.1 (*o,m,p-Ph*), 138.2, 138.2 (*i-Ph*), 168.6 (*C*(1)); *m*/*z* (ESI$^+$) 460 ([M(^{37}Cl)+Na]$^+$, 30%), 458 ([M(^{35}Cl)+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{30}{}^{37}ClNNaO_2{}^+$ ([M(^{37}Cl)+Na]$^+$) requires 460.1830; found 460.1852; HRMS (ESI$^+$) $C_{27}H_{30}{}^{35}ClNNaO_2{}^+$ ([M(^{35}Cl)+Na]$^+$) requires 458.1857; found 458.1865.

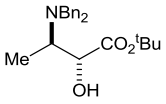
Method B: CCl_4 (1.74 mL, 18.0 mmol) was added to a stirred solution of **248** (500 mg, 1.20 mmol, >99:1 dr) and PPh_3 (630 mg, 2.40 mmol) in PhMe (4 mL) and the resultant mixture was heated at 100 °C for 2 h. The reaction mixture was allowed to cool to rt and filtered, then concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 40:1) gave **250** as a white solid (389 mg, 75%, >99:1 dr).

tert-Butyl (*E*)-4-methylpent-2-enoate 251



MeMgBr (2.4 M in Et_2O, 33.0 mL, 79.3 mmol) was added dropwise to a stirred solution of *tert*-butyl (diethylphosphono)acetate (20 g, 79.3 mmol) in THF (80 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 15 min. A solution of ^{i}PrCHO (7.92 mL, 87.2 mmol) in THF (80 mL) was added via cannula at 0 °C and the resultant mixture was heated at 67 °C for 2.5 h, then allowed to cool to rt. Satd aq NH_4Cl (100 mL) was added and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine (100 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 30:1) gave **251** as a colourless oil (11.8 g, 88%, >99:1 dr);[20] δ_H (400 MHz, $CDCl_3$) 1.02 (6H, d, *J* 6.7, C(4)*Me*$_2$), 1.46 (9H, s, C*Me*$_3$), 2.36–2.45 (1H, m, C(4)*H*), 5.66 (1H, d, *J* 15.7, C(2)*H*), 6.81 (1H, dd, *J* 15.7, 6.7, C(3)*H*).

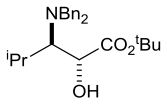
tert-Butyl (*RS*,*RS*)-2-hydroxy-3-(*N*,*N*-dibenzylamino)butanoate 252



BuLi (2.2 M in hexanes, 9.9 mL, 21.9 mmol) was added dropwise to a stirred solution of Bn_2NH (4.44 g, 22.5 mmol) in THF (40 mL) at −78 °C and stirring was continued at –78 °C

for 30 min. A solution of **207** (2.00 g, 14.1 mmol, >99:1 dr) in THF (40 mL) was then added via cannula and the resultant mixture was stirred at −78 °C for 2 h. (−)-**202** (5.50 g, 2.40 mmol) was then added and stirring was continued as the reaction mixture was allowed to warm to rt over 15 h. Satd aq NH_4Cl (5 mL) was added and the reaction mixture was stirred at rt for 5 min then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (50 mL) and 10% aq citric acid (50 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (100 mL) and brine (100 mL), then dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (60 mL), the insoluble CSO residues were filtered off, and the filter cake was washed with Et_2O (2 × 50 mL). The filtrate was concentrated *in vacuo* and the process was repeated. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1 then increased to 8:1) gave **252** as a white soild (2.51 g, 50%, >99:1 dr); mp 73–77 °C; ν_{max} (ATR) 3468 (O−H), 1720 (C=O); δ_H (400 MHz, $CDCl_3$) 1.04 (3H, d, *J* 7.0, C(4)H_3), 1.38 (9H, s, CMe_3), 2.97 (1H, br s, O*H*), 3.15 (1H, qd, *J* 7.0, 2.3, C(3)*H*), 3.66 (2H, d, *J* 14.0, N(CH_AH$_B$Ph)$_2$), 3.75 (2H, d, *J* 14.0, N(CH_AH$_B$Ph)$_2$), 4.40 (1H, d, *J* 2.3, C(2)*H*), 7.18–7.41 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 10.1 (*C*(4)), 28.0 (CMe_3), 54.5 (N(*C*H$_2$Ph)$_2$), 55.5 (*C*(3)), 71.4 (*C*(2)), 82.3 (*C*Me$_3$), 126.9, 128.2, 128.9 (*o,m,p-Ph*), 140.3 (*i-Ph*), 174.3 (*C*(1)); *m*/*z* (ESI$^+$) 356 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{30}NO_3^+$ ([M+H]$^+$) requires 356.2220; found 356.2216.

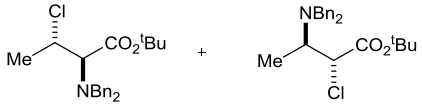
tert-Butyl (*RS*,*RS*)-2-hydroxy-3-[*N*-*N*-dibenzylamino]-4-methylpentanoate 253



BuLi (2.2 M in hexanes, 8.3 mL, 18.2 mmol) was added dropwise to a stirred solution of Bn_2NH (3.61 g, 18.8 mmol) in THF (40 mL) at −78 °C and stirring was continued at –78 °C for 30 min. A solution of **251** (2.00 g, 11.8 mmol, >99:1 dr) in THF (40 mL) was then added via cannula and the resultant mixture was stirred at −78 °C for 2 h. (−)-**202** (4.60 g, 20.1 mmol) was then added and stirring was continued as the reaction mixture was allowed to warm to rt over 15 h. Satd aq NH_4Cl (5 mL) was added and the reaction mixture was stirred at rt for 5 min then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (50 mL) and 10% aq citric acid (50 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (100

mL) and brine (100 mL), then dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (60 mL), the insoluble CSO residues were filtered off, and the filter cake was washed with Et_2O (2 × 50 mL). The filtrate was concentrated *in vacuo* and the process was repeated. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **253** as a white soild (2.32 g, 52%, >99:1 dr); mp 119.0–123.5 °C; ν_{max} (ATR) 3468 (O−H), 1720 (C=O); δ_H (400 MHz, $CDCl_3$) 0.70 (3H, d, *J* 6.6, C(4)*Me*$_A$), 1.00 (3H, d, *J* 6.6, C(4)*Me*$_B$), 1.42 (9H, s, C*Me*$_3$), 2.23 (1H, d septet, *J* 10.4, 6.6, C(4)*H*), 2.71 (1H, app d, *J* 10.4, C(3)*H*), 3.12 (1H, d, *J* 3.2, O*H*), 3.34 (2H, d, *J* 13.9, N(C*H*$_A$H$_B$Ph)$_2$), 3.99 (2H, d, *J* 13.9, N(CH$_A$*H*$_B$Ph)$_2$), 4.48 (1H, app d, *J* 3.2, C(2)*H*), 7.16–7.44 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.0, 21.4 (C(4)*Me*$_2$), 26.2 (*C*(4)), 28.0 (C*Me*$_3$), 54.7 (N(CH$_A$*H*$_B$Ph)$_2$), 66.1 (*C*(3)), 67.3 (*C*(2)), 82.9 (*C*Me$_3$), 126.8, 128.1, 128.3 (*o,m,p-Ph*), 140.1 (*i-Ph*), 175.9 (*C*(1)); *m*/*z* (ESI$^+$) 384 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{34}NO_3^+$ ([M+H]$^+$) requires 384.2533; found 384.2539.

tert-Butyl (2*RS*,3*SR*)-2-(*N*,*N*-dibenzylamino)-3-chloro-butanoate 255 and *tert*-Butyl (2*RS*,3*RS*)-2-chloro-3-(*N*,*N*-dibenzylamino)-butanoate 256



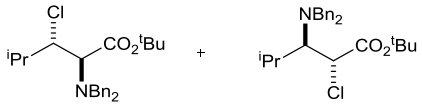
255 **256**

Method A: MsCl (0.108 mL, 1.40 mmol), Et_3N (0.429 mL, 3.23 mmol) and DMAP (2 mg) were added to a stirred solution of **252** (100 mg, 0.281 mmol, >99:1 dr) in CH_2Cl_2 (8 mL) and the resultant mixture was stirred at rt for 2 h. H_2O (5 mL) was then added, the aqueous layer was extracted with CH_2Cl_2 (3 × 4 mL) and the combined organic extracts were washed sequentially with 1.0 M aq HCl (10 mL), satd aq $NaHCO_3$ (10 mL) and brine (10 mL), then dried and concentrated *in vacuo* to give a 36:64 mixture of **255** and **256**, respectively. Selected data for **255**: δ_H (500 MHz, $CDCl_3$) 1.57 (3H, d, *J* 6.6, C(4)*H*$_3$), 1.64 (9H, s, C*Me*$_3$), 3.26 (1H, d, *J* 10.7, C(2)*H*), 3.46 (2H, d, *J* 13.7, N(C*H*$_A$H$_B$Ph)$_2$), 3.97 (2H, d, *J* 13.7, N(CH$_A$*H*$_B$Ph)$_2$), 4.39 (1H, dq, *J* 10.7, 6.6, C(3)*H*), 7.26–7.42 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 21.8 (*C*(4)), 28.5 (C*Me*$_3$), 54.9 (*C*(3)), 55.1 (N(*C*H$_2$Ph)$_2$), 68.4 (*C*(2)), 81.9 (*C*Me$_3$), 127.3, 128.4, 128.9 (*o,m,p-Ph*), 138.6 (*i-Ph*), 168.6 (*C*(1)). Selected data for **256**: δ_H (500 MHz, $CDCl_3$) 1.21 (3H, d, *J* 6.6, C(4)*H*$_3$), 1.51 (9H, s, C*Me*$_3$), 3.11–3.17 (1H, m, C(3)*H*), 3.56 (2H, d, *J* 13.9, N(C*H*$_A$H$_B$Ph)$_2$), 3.75 (2H, d, *J* 13.9, N(CH$_A$*H*$_B$Ph)$_2$), 4.22 (1H, d, *J* 8.8, C(2)*H*), 7.26–7.42 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 10.3 (*C*(4)), 27.8 (C*Me*$_3$), 54.2

(N(CH_2Ph)$_2$), 56.7 (*C*(2)), 60.5 (*C*(3)), 82.0 (*C*Me$_3$), 127.1 128.2, 129.2 (*o,m,p-Ph*), 138.9 (*i-Ph*), 168.3 (*C*(1)).

Method B: CCl_4 (0.204 mL, 2.12 mmol) was added to a stirred solution of **252** (30 mg, 0.141 mmol, >99:1 dr) and PPh_3 (74 mg, 0.281 mmol) in PhMe (0.4 mL) and the resultant mixture was heated at 100 °C for 24 h. The reaction mixture was allowed to cool to rt and filtered, then concentrated *in vacuo* to give a 100:0 mixture of **255** and **256**, respectively.

tert-Butyl (*RS*,*SR*)-2-dibenzylamino-3-chloro-4-methylpentanoate 258

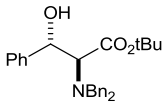


258 **259**

Method A: MsCl (46 μL, 0.60 mmol), Et_3N (182 μL, 1.38 mmol) and DMAP (2 mg, cat.) were added to a stirred solution of **253** (50 mg, 0.120 mmol, >99:1 dr) in CH_2Cl_2 (3 mL) and the resultant mixture was stirred at rt for 2 h. H_2O (5 mL) was then added, the aqueous layer was extracted with CH_2Cl_2 (3 × 4 mL) and the combined organic extracts were washed sequentially with 1.0 M aq HCl (10 mL), satd aq $NaHCO_3$ (10 mL) and brine (10 mL), then dried and concentrated *in vacuo* to give a 34:42:24 mixture of **253**, **258** and **259**, respectively.

Method B: CCl_4 (188 μL, 1.95 mmol) was added to a stirred solution of **253** (50 mg, 0.120 mmol, >99:1 dr) and PPh_3 (68 mg, 0.260 mmol) in PhMe (0.4 mL) and the resultant mixture was heated at 100 °C for 2 h. The reaction mixture was allowed to cool to rt and filtered, then concentrated *in vacuo* to give a 70:30 mixture of **258** and **259**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 40:1) gave **258** as a white solid (32 mg, 61%, >99:1 dr). mp 122.5–125.0 °C; ν_{max} (ATR) 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 0.32 (3H, d, *J* 6.7, C(4)*Me*$_A$), 0.89 (3H, d, *J* 6.7, C(4)*Me*$_B$), 1.54 (9H, s, C*Me*$_3$), 2.43 (1H, app septet, *J* 16.7, C(4)*H*), 3.27–3.34 (3H, m, N(CH_AH$_B$Ph)$_2$, C(2)*H*), 3.82 (2H, d, *J* 13.6, N(CH_AH$_B$Ph)$_2$), 4.21 (1H, app d, *J* 10.9, C(3)*H*), 7.16–7.30 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1, 20.8 (C(4)*Me*$_2$), 27.7 (*C*(4)), 28.5 (C*Me*$_3$), 55.0 (N(CH$_A$*H*$_B$Ph)$_2$), 65.1 (*C*(2)), 67.2 (*C*(3)), 81.9 (*C*Me$_3$), 127.3, 128.3, 129.3 (*o,m,p-Ph*), 138.7 (*i-Ph*), 168.6 (*C*(1)); *m/z* (ESI$^+$) 404 ([M(^{37}Cl)+H]$^+$, 30%); 402 ([M(^{35}Cl)+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{33}{}^{37}C\,NO_2{}^+$ ([M(^{37}Cl)+H]$^+$) requires 404.2165; found 402.2166; HRMS (ESI$^+$) $C_{24}H_{33}{}^{35}ClNO_2{}^+$ ([M(^{35}Cl)+H]$^+$) requires 402.2194; found 402.2195.

tert-Butyl (*RS*,*RS*)-2-dibenzylamino-3-hydroxy-3-phenylpropanoate 260



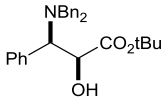
*Method A (from **250**):* AgOTf (30 mg, 0.115 mmol) was added to a stirred solution of **250** (50 mg, 0.115 mmol) in EtOAc (1.12 mL) and the resultant mixture was stirred at rt for 1 h, then filtered through alumina (eluent EtOAc) and concentrated *in vacuo* to give a 61:39 mixture of **260** and **261**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 30:1 then increased to 5:1) gave **261** as a pale yellow solid (8 mg, 21%, >99:1 dr); mp 63.0–70.5 °C; ν_{max} (ATR) 1723 (C=O); δ_H (500 MHz, $CDCl_3$) 1.38 (9H, s, C*Me*$_3$), 3.58 (1H, d, *J* 3.0, C(3)*H*)), 3.86 (1H, d, *J* 13.4, NC(1')H_AH_BPh), 3.92 (1H, d, *J* 14.9, C(1)H_AH_BPh), 3.96 (1H, d, *J* 13.4, NC(1')H_AH_BPh), 4.06 (1H, d, *J* 14.9, C(1)H_AH_BPh), 4.50 (1H, d, *J* 3.0, C(4)*H*), 6.90–7.42 (14H, m, *Ph*, *Ar*); δ_C (125 MHz, $CDCl_3$) 28.2 (C*Me*$_3$), 47.9 (*C*(4)), 51.0 (*C*(1)), 59.5 (N*C*(1'))|, 67.0 (*C*(3)), 81.3 (*C*Me$_3$), 126.0, 126.1, 126.2, 126.3 (*C*(5), *C*(6), *C*(7), *C*(8)), 126.9, 127.8, 128.1, 128.6, 129.1, 129.7 (*o*,*m*,*p*-*Ph*), 134.7 (*C*(8a)), 135.2 (*C*(4a)), 138.6, 144.7 (*i*-*Ph*), 171.4 (*C*=O); *m*/*z* (ESI$^+$) 400 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{30}NO_2^+$ ([M+H]$^+$) requires 400.2271; found 400.2273. Further elution gave **260** as a white solid (19 mg, 40%, >99:1 dr); mp 132.5–136.5 °C; ν_{max} (ATR) 3465 (O−H), 1722 (C=O); δ_H (500 MHz, $CDCl_3$) 1.65 (9H, s, C*Me*$_3$), 2.74 (1H, d, *J* 4.0, O*H*), 3.43–3.54 (3H, m, N(CH_AH_BPh)$_2$, C(2)*H*), 3.90 (2H, d, *J* 13.9, N(CH$_A$$H_B$Ph)$_2$), 5.05 (1H, dd, *J* 9.4, 4.0, C(3)*H*), 6.94–7.41 (15H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 28.6 (C*Me*$_3$), 55.0 (N(*C*H_2Ph)$_2$), 66.5 (*C*(2)), 73.0 (*C*(3)), 82.2 (*C*Me$_3$), 126.9, 127.8, 127.9, 128.1, 128.1, 128.8 (*o*,*m*,*p*-*Ph*), 138.6, 140.9 (*i*-*Ph*), 171.6 (*C*(1)); *m*/*z* (ESI$^+$) 418 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{32}NO_3^+$ ([M+H]$^+$) requires 418.2377; found 418.2382.

*Method B (from **250**):* AgOTf (12 mg, 0.046 mmol) was added to a stirred solution of **250** (20 mg, 0.046 mmol, >99:1 dr) in EtOAc/H_2O (0.5 mL, 4:1) and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then filtered through alumina (eluent EtOAc) and concentrated *in vacuo* to give **260** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave **260** as a white solid (17 mg, 89%, >99:1 dr).

*Method C (from **248**):* Ms_2O (125 mg, 0.719 mmol) was added to a stirred solution of **248** (100 mg, 0.240 mmol >99:1 dr) and Et_3N (0.14 mL, 1.1 mmol) in CH_2Cl_2 (1 mL) and the resultant solution was stirred at rt for 1 h. H_2O (26 μL, 7.2 mmol) was added and the resultant mixture was stirred at rt for 24 h. H_2O (1 mL) was then added and the resultant mixture was

extracted with CH_2Cl_2 (3 × 2 mL). The combined organic extracts were washed sequentially with 1.0 M aq HCl (3 mL), satd aq $NaHCO_3$ (3 mL) and brine (3 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave **260** as a white solid (54 mg, 54%, >99:1 dr).

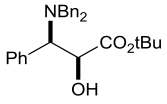
tert-Butyl (2*SR*,3*RS*)-2-hydroxy-3- dibenzylamino-3-phenylpropanoate 266



Step 1: DMSO (68 μL, 0.959 mmol) was added to a stirred solution of $(COCl)_2$ (81 μL, 0.959 mmol) in CH_2Cl_2 (6 mL) at −78 °C and the resultant mixture was stirred for 5 min. A solution of **248** (200 mg, 0.479 mmol, >99:1 dr) in CH_2Cl_2 (6 mL) was added via cannula and the resultant mixture was stirred at −78 °C for 30 min. Et_3N (254 μL, 1.92 mmol) was added and the reaction mixture was allowed to warm to rt. H_2O (5 mL) was then added, the reaction mixture was extracted with CH_2Cl_2 (3 × 4 mL) and combined organic extracts were dried and concentrated *in vacuo* to give **265** which was used without purification.

Step 2: DIBAL-H (1.0 M in THF, 0.479 mL, 0.479 mmol) was added to a stirred solution of **265** (0.479 mmol, >99:1 dr) in THF (12 mL) at −20 °C and the resultant mixture was stirred at −20 °C for 2 h. MeOH (2 mL) was added and the reaction mixture was then allowed to warm to rt. Satd aq Rochelle's salt (2 mL) was added and the resultant suspension was stirred at rt for 15 h, then filtered through Celite® (eluent MeOH) and concentrated *in vacuo* to give a 55:45 mixture of **248** and **266**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave a 55:45 mixture of **248** and **266** (50 mg, 25%), respectively.

tert-Butyl (2*S*,3*R*)-2-hydroxy-3-dibenzylamino-3-phenylpropanoate 266



BnBr (0.100 mL, 0.843 mmol) and K_2CO_3 (291 mg, 2.11 mmol) were added to a stirred solution of **227** (100 mg, 0.421 mmol) in MeCN (2.5 mL) and the resultant mixture was heated at reflux for 24 h, the cooled to rt. The reaction mixture was filtered, the filter cake washed with EtOAc (3 mL) and the combined filtrates concentrated *in vacuo* to give a 71:29 mixture of **266** and **267**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **267** as a colourless oil (37 mg, 17%, >99:1 dr); ν_{max} (ATR)

1738 (C=O); $[\alpha]_D^{23}$ −49.4 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.09 (9H, s, C*Me*$_3$), 3.22 (2H, d, *J* 13.8, N(C*H*$_A$H$_B$Ph)$_2$), 3.94 (2H, d, *J* 13.8, N(CH$_A$*H*$_B$Ph)$_2$), 4.12 (1H, d, *J* 8.2, C(3)*H*), 4.32 (1H, d, *J* 8.2, C(2)*H*), 4.38 (1H, d, *J* 11.5, O(C*H*$_A$H$_B$Ph)), 4.63 (1H, d, *J* 11.5, O(CH$_A$*H*$_B$Ph)), 7.09–7.36 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.6 (C*Me*$_3$), 54.7 (N(*C*H$_2$Ph)$_2$), 64.2 (*C*(3)), 72.3 (O(*C*H$_2$Ph)), 81.2 (*C*(2)), 81.3 (*C*Me$_3$), 126.7, 127.6, 127.7, 127.8, 128.1, 128.1, 128.3 129.0, 130.2 (*o,m,p-Ph*), 135.5, 137.9, 140.0 (*i-Ph*), 170.2 (*C*(1)); *m*/*z* (ESI$^+$) 508 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{34}H_{38}NO_3^+$ ([M+H]$^+$) requires 508.2846; found 508.2848. Further elution gave **266** as a colourless oil (78 mg, 45%, >99:1 dr); ν_{max} (ATR) 3464 (O−H), 1724 (C=O); $[\alpha]_D^{23}$ −32.4 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.00 (9H, s, C*Me*$_3$), 308 (2H, d, *J* 13.4, N(C*H*$_A$H$_B$Ph)$_2$), 3.81 (1H, d, *J* 9.8, C(3)*H*), 3.91 (2H, d, *J* 13.4, N(CH$_A$*H*$_B$Ph)$_2$), 4.14 (1H, br s, O*H*), 4.55 (1H, d, *J* 9.8, C(2)*H*), 7.15–7.39 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.5 (C*Me*$_3$), 53.8 (N(*C*H$_2$Ph)$_2$), 65.6 (*C*(3)), 70.4 (*C*(2)), 81.3 (*C*Me$_3$), 127.4, 128.1, 128.3, 128.7, 129.1, 130.5 (*o,m,p-Ph*), 133.1, 138.5 (*i-Ph*), 171.3 (*C*(1)); *m*/*z* (ESI$^+$) 418 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{32}NO_3^+$ ([M+H]$^+$) requires 418.2377; found 418.2374.

tert-Butyl (2*S*,3*S*)-2-*N*,*N*-dibenzylamino-3-chloro-3-phenylpropanoate 269 and *tert*-Butyl (2*S*,3*R*)-2-chloro-3-*N*,*N*-dibenzylamino-3-phenylpropanoate 270

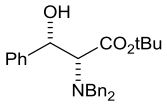


269 **270**

CCl_4 (0.156 mL, 1.72 mmol) was added to a stirred solution of **266** (45 mg, 0.108 mmol, >99:1 dr) and PPh_3 (57 mg, 0.216 mmol) in PhMe (0.3 mL) and the resultant mixture was heated at 100 °C for 2 h. The reaction mixture was allowed to cool to rt and filtered, then concentrated *in vacuo* to give a 70:30 mixture of **269** and **270** (47 mg, quant), respectively. Selected data for **269**: δ_H (500 MHz, $CDCl_3$) 1.21 (9H, s, C*Me*$_3$), 3.53 (2H, d, *J* 13.8, N(C*H*$_A$H$_B$Ph)$_2$), 3.76 (1H, d, *J* 11.0, C(2)*H*), 4.16 (2H, d, *J* 13.8, N(CH$_A$*H*$_B$Ph)$_2$), 5.20 (1H, d, *J* 11.0, C(3)*H*), 7.20–7.43 (15H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 27.9 (C*Me*$_3$), 54.6 (N(*C*H$_2$Ph)$_2$), 60.7 (*C*(3)), 67.9 (*C*(2)), 81.7 (*C*Me$_3$), 128.2, 128.5, 128.6, 129.1, 132.0, 132.1 (*o,m,p-Ph*), 138.5, 138.9 (*i-Ph*), 168.1 (*C*(1)). Selected data for **270**: δ_H (500 MHz, $CDCl_3$) 1.05 (9H, s, C*Me*$_3$), 3.12 (2H, d, *J* 13.6, N(C*H*$_A$H$_B$Ph)$_2$), 3.93 (2H, d, *J* 13.6, N(CH$_A$*H*$_B$Ph)$_2$), 4.14 (1H, d, *J* 11.2, C(3)*H*), 4.84 (1H, d, *J* 11.2, C(2)*H*), 7.20–7.43 (15H, m, *Ph*); δ_C (125

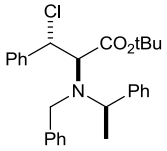
MHz, $CDCl_3$) 27.1 (C*Me*$_3$), 53.8 (N(*C*H$_2$Ph)$_2$), 58.3 (*C*(3)), 64.8 (*C*(2)), 82.2 (*C*Me$_3$), 127.1, 128.4, 129.0, 131.9, 132.0, 132.9 (*o*,*m*,*p*-*Ph*), 138.2, 139.0 (*i*-*Ph*), 167.5 (*C*(1)).

tert-Butyl (2*R*,3*S*)-2-dibenzylamino-3-hydroxy-3-phenylpropanoate 271



AgOTf (57 mg, 0.216 mmol) was added to a stirred solution of **269** and **270** (0.108 mmol, >99:1 dr) in EtOAc/H_2O (0.5 mL, 4:1) and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then filtered through alumina (eluent EtOAc) and concentrated *in vacuo* to give a 95:5 mixture of **271** and **270**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave **271** as a colourless oil (14 mg, 31%, >99:1 dr);[21] ν_{max} (ATR) 3468 (O−H), 1722 (C=O); $[\alpha]_D^{23}$ +97.8 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.37 (9H, s, C*Me*$_3$),), 3.30 (1H, d, *J* 10.0, C(2)*H*), 3.51 (2H, d, *J* 13.4, N(C*H*$_A$H$_B$Ph)$_2$), 4.17 (2H, d, *J* 13.4, N(CH$_A$*H*$_B$Ph)$_2$), 4.91 (1H, d, *J* 9.0, C(3)*H*), 7.13–7.41 (15H, m, *Ph*); *m*/*z* (ESI$^+$) 418 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{32}NO_3^+$ ([M+H]$^+$) requires 418.2377; found 418.2376.

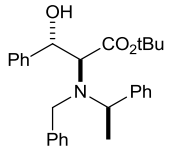
tert-Butyl (2*R*,3S,α*R*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-chloro-3-phenylpropanoate 273



MsCl (0.179 mL, 2.32 mmol), Et_3N (0.709 mL, 5.34 mmol) and DMAP (5 mg, cat.) were added to a stirred solution of **208** (200 mg, 0.464 mmol, >99:1 dr) in CH_2Cl_2 (13 mL) and the resultant mixture was stirred at rt for 2 h. H_2O (10 mL) was then added and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed sequentially with 1.0 M aq HCl (25 mL), satd aq $NaHCO_3$ (25 mL) and brine (25 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **273** as a white solid (170 mg, 81%, >99:1 dr); mp 90–93 °C; $[\alpha]_D^{23}$ +27.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1723 (C=O); δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, *J* 7.0, C(α)*Me*), 1.55 (9H, s, C*Me*$_3$), 3.70–3.82 (3H, m, C(2)*H*, C(α)*H*, NC*H*$_A$H$_B$Ph), 4.01 (1H, d, *J* 14.3, NCH$_A$*H*$_B$Ph), 5.06 (1H, d, *J* 11.0, C(3)*H*), 7.24–7.42 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.3 (C(α)*Me*), 28.2 (C*Me*$_3$), 50.7 (N*C*H$_2$Ph), 55.8 (*C*(α)), 61.5 (*C*(3)), 64.5 (*C*(2)),

82.0 (*C*Me$_3$), 127.0, 127.1, 128.2, 128.4, 128.4, 128.6, 128.7, 129.0 (*o,m,p-Ph*), 138.4, 139.3, 141.9 (*i-Ph*), 171.7 (*C*(1)); *m*/*z* (ESI$^+$) 474 ([M(^{37}Cl)+Na]$^+$, 30%), 472 ([M(^{35}Cl)+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{32}{}^{37}ClNNaO_2{}^+$ ([M(^{37}Cl)+Na]$^+$) requires 474.1987; found 474.2008; HRMS (ESI$^+$) $C_{28}H_{32}{}^{35}ClNNaO_2{}^+$ ([M(^{35}Cl)+Na]$^+$) requires 472.2014; found 472.2024.

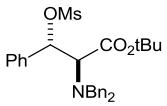
tert-Butyl (2*S*,3*S*,α*R*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-hydroxy-3-phenylpropanoate 274



*Method A (from **273**):* AgOTf (61 mg, 0.229 mmol) was added to a stirred solution of **273** (100 mg, 0.23 mmol, >99:1 dr) in EtOAc/H_2O (2.62 mL, 4:1) and the resultant mixture was stirred at rt for 16 h, then filtered through alumina (eluent EtOAc) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave **274** as a white solid (89 mg, 90%, >99:1 dr); mp 78–85 °C; $[\alpha]_D^{23}$ −22.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3496 (C−O), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.39 (3H, d, *J* 6.9, C(α)*Me*), 1.58 (9H, s, C*Me*$_3$), 2.59 (1H, br s, O*H*), 3.60 (1H, d, *J* 8.0, C(2)*H*), 3.94 (1H, d, *J* 14.2, NCH_AH_BPh), 4.01 (1H, q, *J* 6.9, C(α)*H*), 4.19 (1H, d, *J* 14.2, NCH_AH_BPh), 4.92 (1H, dd, *J* 8.0, 4.7, C(3)*H*), 6.86–7.39 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.4 (C(α)*Me*), 28.2 (C*Me*$_3$), 51.7 (N*C*H$_2$Ph), 56.2 (*C*(α)), 64.6 (*C*(2)), 74.6 (*C*(3)), 81.7 (*C*Me$_3$), 126.7, 126.9, 127.5, 127.7, 127.9, 128.1, 128.1, 128.1, 129.0 (*o,m,p-Ph*), 139.9, 141.2, 143.0 (*i-Ph*), 173.5 (*C*(1)); *m*/*z* (ESI$^+$) 432 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{33}NNaO_3{}^+$ ([M+Na]$^+$) requires 454.2353; found 454.2362.

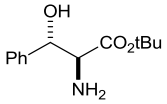
*Method B (from **208**):* Ms_2O (121 mg, 0.695 mmol) was added to a stirred solution of **208** (100 mg, 0.23 mmol, >99:1 dr) and Et_3N (0.139 mL, 1.04 mmol) in CH_2Cl_2 (1 mL) and the resultant mixture was stirred at rt for 1 h, then H_2O (0.125 mL, 6.96 mmol) was added and the reaction mixture was stirred at rt for 24 h. H_2O (1 mL) was then added and the resultant mixture was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic extracts were washed sequentially with 1.0 M aq HCl (3 mL), satd aq $NaHCO_3$ (3 mL) and brine (3 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 4:1) gave **274** as a white solid (82 mg, 82%, >99:1 dr).

tert-Butyl (*RS*,*RS*)-2-(*N*,*N*-dibenzylamino)-3-(methanesulfonyloxy)-3-phenylpropanoate 280



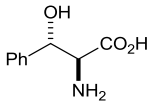
Ms_2O (25 mg, 0.144 mmol) was added to a stirred solution of **248** (20 mg, 48 μmol, >99:1 dr) and Et_3N (29 μL, 0.216 mmol) in CH_2Cl_2 (0.2 mL) and the resultant mixture was stirred at rt for 1 h. H_2O (0.026 mL, 7.2 mmol) was then added and the reaction mixture was stirred at rt for 1 h. H_2O (1 mL) was then added and the resultant mixture was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic extracts were washed sequentially with 1.0 M aq HCl (3 mL), satd aq $NaHCO_3$ (3 mL) and brine (3 mL), then dried and concentrated *in vacuo* to give **280** as yellow oil (17 mg, >99:1 dr); δ_H (500 MHz, $CDCl_3$) 1.67 (9H, s, C*Me*$_3$), 2.55 (3H, s, SO_2*Me*), 3.41 (2H, d, *J* 13.6, N(C*H*$_A$H$_B$Ph)$_2$), 3.75 (1H, d, *J* 10.7, C(2)*H*), 3.84 (2H, d, *J* 13.6, N(CH$_A$*H*$_B$Ph)$_2$), 5.89 (1H, d, *J* 10.7, C(3)*H*), 6.88–7.52 (15H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 28.4 (C*Me*$_3$), 39.2 (SO_2*Me*), 54.8 (N(*C*H$_2$Ph)$_2$), 64.2 (*C*(2)), 82.6 (*C*(3)), 82.7 (*C*Me$_3$), 127.2, 128.1, 128.5, 128.7, 129.1, 129.5 (*o*,*m*,*p*-*Ph*), 135.3, 137.9 (*i*-*Ph*), 168.3 (*C*(1)).

tert-Butyl (*S*,*S*)-2-amino-3-hydroxy-3-phenylpropanoate 281



$Pd(OH)_2$/C (22 mg, 25% w/w) was added to a degassed solution of **274** (89 mg, 0.21 mmol, >99:1 dr) in MeOH (1 mL) and the resultant mixture was placed under an atmosphere of H_2 (5 atm) and stirred at rt for 16 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated *in vacuo* to give **281** as a white solid (35 mg, 71%, >99:1 dr); mp 151–154 °C; $[\alpha]_D^{20}$ +44.7 (*c* 1.0 in MeOH); ν_{max} (ATR) 3446 (O−H), 1732 (C=O); δ_H (400 MHz, $CDCl_3$) 1.22 (9H, s, C*Me*$_3$), 4.07–4.15 (1H, m, C(2)*H*), 5.13–5.17 (1H, m, C(3)*H*), 7.19–7.36 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 26.8 (C*Me*$_3$), 60.5 (*C*(2)), 74.6 (*C*(3)), 81.6 (*C*Me$_3$), 126.4, 127.5, 127.8 (*o*,*m*,*p*-*Ph*), 140.3 (*i*-*Ph*), 171.1 (*C*(1)); *m*/*z* (ESI$^+$) 260 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{19}NNaO_3^+$ ([M+Na]$^+$) requires 260.1257; found 260.1270.

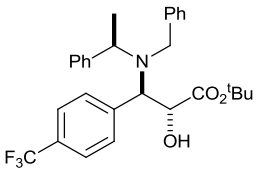
(*S*,*S*)-2-Amino-3-hydroxy-3-phenylpropanoic acid *ent*-184



A stirred solution of **281** (27 mg, 0.114 mmol) in 6.0 M aq HCl (2 mL) was heated at 90 °C for 18 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*.

Purification via ion exchange chromatography (DOWEX 50WX8-200, eluent 1.0 M aq NH_4OH) gave *ent*-**184** as a white solid (21 mg, quant, 96:4 dr);[22] mp 183.0–188.5 °C; {lit.[23] mp 185–187 °C}; $[\alpha]_D^{20}$ +1.9 (*c* 1.0 in H_2O); {lit.[22] *for enantiomer* $[\alpha]_D^{20}$ −2.4 (*c* 1.0 in H_2O); ν_{max} (ATR) 3135 (O−H, N−H), 1604 (C=O); δ_H (500 MHz, D_2O) 4.01 (1H, d, *J* 4.1, C(2)*H*), 5.28 (1H, d, *J* 4.1, C(3)*H*), 7.28-7.39 (5H, m, *Ph*); δ_C (125 MHz, D_2O) 60.4 (*C*(2)), 71.1 (*C*(3)), 126.3, 128.8, 128.8 (*o*,*m*,*p*-*Ph*), 136.8 (*i*-*Ph*), 171.1 (*C*(1)); *m*/*z* (ESI^+) 204 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_9H_{11}NNaO_3^+$ ($[M+Na]^+$) requires 204.0631; found 204.0634.

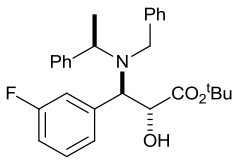
tert-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-[4'-(trifluoromethyl)phenyl]propanoate 287



BuLi (2.3 M in hexanes, 1.73 mL, 3.98 mmol) was added dropwise to a stirred solution of (*R*)-**205**[43] (993 mg, 4.11 mmol, 99% ee) in THF (10 mL) at −78 °C and stirring was continued at –78 °C for 30 min. A solution of **282** (700 mg, 2.57 mmol, >99:1 dr) in THF (10 mL) was then added via cannula and the resultant mixture was stirred at −78 °C for 2 h. (−)-CSO **202** (1.00 g, 4.37 mmol) was then added and stirring was continued as the reaction mixture was allowed to warm to rt over 15 h. Satd aq NH_4Cl (1 mL) was added and the reaction mixture was stirred at rt for 5 min then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and 10% aq citric acid (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 8 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (20 mL) and brine (20 mL), then dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (10 mL), the insoluble CSO residues were filtered off, and the filter cake was washed with Et_2O (2 × 10 mL). The filtrate was concentrated *in vacuo* and the process was repeated. Purification via flash column chromatography (eluent 30-40 ºC petrol/Et_2O, 10:1) gave **287** as a pale yellow oil (865 mg, 67%, >99:1 dr); $[\alpha]_D^{23}$ –27.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3496 (O−H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.38 (9H, s, C*Me*$_3$), 1.36–1.44 (3H, obscured d, C(α)*Me*), 3.24 (1H, br s, O*H*), 4.16 (1H, d, *J* 14.8, NC*H*$_A$H$_B$Ph), 4.36 (1H, d, *J* 14.8, NCH$_A$*H*$_B$Ph), 4.40–4.48 (1H, m, C(α)*H*), 4.54–4.59 (1H, m, C(3)*H*), 4.64–4.72 (1H, m, C(2)*H*), 7.34–7.89 (14H, m, *Ar*, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.5 (C(α)*Me*), 27.7 (C*Me*$_3$), 52.4 (NCH_2Ph), 57.9 (*C*(α)), 64.4 (*C*(3)), 73.2 (*C*(2)), 82.6 (*C*Me$_3$), 124.5 (q, *J* 272.2, *C*F$_3$), 124.9 (q, *J* 4.0, *C*(3'), *C*(5')), 126.9, 127.2, 128.1, 128.1, 128.4, 128.5 (*o*,*m*,*p*-*Ph*), 129.7 (q, *J*

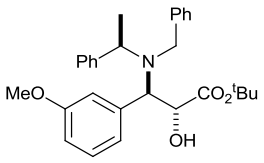
34.4, *C*(4')), 130.3 (*C*(2'), *C*(6')), 143.1, 143.7 (*i-Ph*), 143.9 (*C*(1')), 172.4 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −62.2 (CF_3); *m*/*z* (ESI$^+$) 500 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{33}F_3NO_3^+$ ([M+H]$^+$) requires; 500.2407 found 500.2400.

tert-Butyl (*R,R,R*)-2-hydroxy-3-[*N*-benzyl-*N*(α-methylbenzyl)amino]-3-(3'-fluorophenyl)propanoate 288



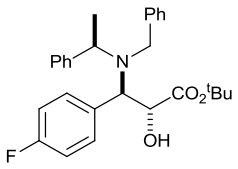
BuLi (2.3 M in hexanes, 2.12 mL, 4.88 mmol) was added dropwise to a stirred solution of (*R*)-**205**[43] (1.22 g, 5.04 mmol, 99% ee) in THF (10 mL) at −78 °C and stirring was continued at –78 °C for 30 min. A solution of **283** (700 mg, 3.15 mmol, >99:1 dr) in THF (10 mL) was then added via cannula and the resultant mixture was stirred at −78 °C for 2 h. (−)-CSO **202** (1.23 g, 5.36 mmol) was then added and stirring was continued as the reaction mixture was allowed to warm to rt over 15 h. Satd aq NH_4Cl (1 mL) was added and the reaction mixture was stirred at rt for 5 min then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and 10% aq citric acid (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 8 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (20 mL) and brine (20 mL), then dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (10 mL), the insoluble CSO residues were filtered off, and the filter cake was washed with Et_2O (2 × 10 mL). The filtrate was concentrated *in vacuo* and the process was repeated. Purification via flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 10:1) gave **288** as a pale yellow solid (1.16 g, 82%, >99:1 dr); mp 72.5–79.0 °C; $[\alpha]_D^{20}$ –34.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3485 (O−H), 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.39 (9H, s, CMe_3), 1.32–1.50 (3H, obscured d, C(α)*Me*), 3.20 (1H, br s, O*H*), 4.13 (1H, d, *J* 15.0, NCH_AH_BPh), 4.37 (1H, d, *J* 15.0, NCH_AH_BPh), 4.41–4.50 (2H, m, C(3)*H*, C(α)*H*), 4.61–4.70 (1H, m, C(2)*H*), 7.09-7.75 (14H, m, *Ar*, *Ph*); δ_C (125 MHz, $CDCl_3$) 14.6 (C(α)*Me*) 27.7 (C*Me*$_3$) 52.2 (N*C*H$_2$Ph), 57.4 (*C*(α)Me), 64.6 (*C*(3)), 73.3 (*C*(2)), 82.5 (*C*Me$_3$), 114.4, 116.8 (2 × d, *J* 21.5, *C*(2'), *C*(4')), 125.5 (d, *J* 2.9, *C*(6')), 126.7, 127.0, 128.0, 128.0, 128.2, 128.3 (*o,m,p-Ph*), 129.4 (d, *J* 7.6, *C*(5')), 141.1 (d, *J* 6.7, *C*(1')), 143.9, 141.6 (*i-Ph*), 162.5 (d *J* 245.1, *C*(3')), 172.1 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −112.9 (C(3')*F*); *m*/*z* (ESI$^+$) 450 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{33}FNO_3^+$ ([M+H]$^+$) requires 450.2439; found 450.2439.

tert-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-benzyl-*N*(α-methylbenzyl)amino]-3-(3'-methoxy)phenylpropanoate 289



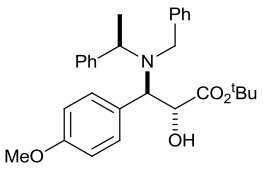
BuLi (2.3 M in hexanes, 2.02 mL, 4.63 mmol) was added dropwise to a stirred solution of (*R*)-**205**[43] (1.15 g, 4.78 mmol, 99% ee) in THF (10 mL) at −78 °C and stirring was continued at –78 °C for 30 min. A solution of **284** (700 mg, 2.99 mmol, >99:1 dr) in THF (10 mL) was then added via cannula and the resultant mixture was stirred at −78 °C for 2 h. (−)-CSO **202** (1.17 g, 5.09 mmol) was then added and stirring was continued as the reaction mixture was allowed to warm to rt over 15 h. Satd aq NH_4Cl (1 mL) was added and the reaction mixture was stirred at rt for 5 min then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and 10% aq citric acid (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 8 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (20 mL) and brine (20 mL), then dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (10 mL), the insoluble CSO residues were filtered off, and the filter cake was washed with Et_2O (2 × 10 mL). The filtrate was concentrated *in vacuo* and the process was repeated. Purification via flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 10:1) gave **289** as a pale yellow oil (1.04 g, 75%, >99:1 dr); $[\alpha]_D^{20}$ –30.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3958 (O−H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.23 (9H, s, CMe_3), 1.17–1.26 (3H, obscured d, C(α)*Me*), 2.72 (1H, br s, O*H*), 3.79 (3H, s, OMe), 3.86 (1H, d, *J* 15.0, CH_AH_BPh), 4.12 (1H, d, *J* 15.0, CH_AH_BPh), 4.19 (1H, d, *J* 3.1, C(3)*H*), 4.22 (1H, q, *J* 6.8, C(α)*H*), 4.37 (1H, d, *J*, 3.1, C(2)*H*), 6.77–7.57 (14H, m, *Ar*, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.6 (C(α)*Me*) 27.8 (C*Me*$_3$) 52.4 (NCH_2Ph), 55.2 (O*Me*), 57.4 (*C*(α)Me), 65.4 (*C*(3)), 73.5 (*C*(2)), 82.2 (*C*Me_3), 112.9, 115.8, 122.4, 126.9 (*Ar*), 126.7, 128.1, 128.1, 128.2, 128.3, 129.0 (*o*,*m*,*p*-*Ph*), 140.0 (*C*(1')), 141.9, 144.2 (*i*-*Ph*), 159.4 (C(3')), 172.3 (*C*(1)); *m*/*z* (ESI^+) 462 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{29}H_{36}NO_3^+$ ($[M+H]^+$) requires 462.2639; found 462.2636.

tert-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-benzyl-*N*(α-methylbenzyl)amino]-3-(4'-fluorophenyl)propanoate 290



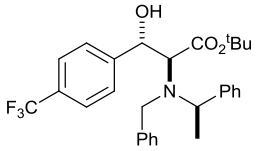
BuLi (2.3 M in hexanes, 2.12 mL, 4.88 mmol) was added dropwise to a stirred solution of (*R*)-**205**[43] (1.22 g, 5.04 mmol, 99% ee) in THF (10 mL) at −78 °C and stirring was continued at –78 °C for 30 min. A solution of **285** (493 mg, 2.22 mmol, >99:1 dr) in THF (10 mL) was then added via cannula and the resultant mixture was stirred at −78 °C for 2 h. (−)-CSO **202** (865 mg, 3.77 mmol) was then added and stirring was continued as the reaction mixture was allowed to warm to rt over 15 h. Satd aq NH_4Cl (1 mL) was added and the reaction mixture was stirred at rt for 5 min then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and 10% aq citric acid (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 8 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (20 mL) and brine (20 mL), then dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (10 mL), the insoluble CSO residues were filtered off, and the filter cake was washed with Et_2O (2 × 10 mL). The filtrate was concentrated *in vacuo* and the process was repeated. Purification via flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 10:1) gave **290** as a pale yellow oil (819 mg, 82%, >99:1 dr); $[\alpha]_D^{20}$ –26.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3499 (O−H), 1723 (C=O); δ_H (400 MHz, $CDCl_3$) 1.23 (9H, s, C*Me*$_3$), 1.19–1.31 (3H, obscured d, C(α)*Me*), 2.77 (1H, br s, O*H*), 3.85 (1H, d, *J* 15.0, C*H*$_A$H$_B$Ph), 4.11 (1H, d, *J* 15.0, CH$_A$*H*$_B$Ph), 4.16–4.25 (2H, m, C(3)*H*, C(α)*H*), 4.40–4.44 (1H, m, C(2)*H*), 7.01 (2H, t, *J* 8.0, C(3')*H*, C(5')*H*), 7.38 (2H, t, *J* 8.0, (C(2')*H*, C(6')*H*), 7.20–7.52 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 14.7 (C(α)*Me*) 27.8 (C*Me*$_3$) 52.2 (N*C*H$_2$Ph), 57.5 (*C*(α)Me), 64.7 (*C*(3)), 73.3 (*C*(2)), 82.4 (*C*Me$_3$), 114.9 (d, *J* 21.5, *C*(3'), *C*(5')), 126.8, 127.0, 128.0, 128.0, 128.3, 128.4, (*o*,*m*,*p*-*Ph*), 131.6 (d, *J* 7.2, *C*(2'), *C*(6')), 134.3 (*C*(1')), 141.9, 144.1 (*i*-*Ph*), 162.3 (d, *J* 246.4, *C*(4')), 172.2 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −114.7 (C(4')*F*); *m*/*z* (ESI$^+$) 450 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{33}FNO_3^+$ ([M+H]$^+$) requires 450.2439; found 450.2435.

tert-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-benzyl-*N*(α-methylbenzyl)amino]-3-(4'-methoxyphenyl)propanoate 291



BuLi (2.3 M in hexanes, 2.02 mL, 4.63 mmol) was added dropwise to a stirred solution of (*R*)-**205**[43] (1.15 g, 4.78 mmol, 99% ee) in THF (10 mL) at −78 °C and stirring was continued at –78 °C for 30 min. A solution of **284** (700 mg, 2.99 mmol, >99:1 dr) in THF (10 mL) was then added via cannula and the resultant mixture was stirred at −78 °C for 2 h. (−)-CSO **202** (1.17 g, 5.09 mmol) was then added and stirring was continued as the reaction mixture was allowed to warm to rt over 15 h. Satd aq NH_4Cl (1 mL) was added and the reaction mixture was stirred at rt for 5 min then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and 10% aq citric acid (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 8 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (20 mL) and brine (20 mL), then dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (10 mL), the insoluble CSO residues were filtered off, and the filter cake was washed with Et_2O (2 × 10 mL). The filtrate was concentrated *in vacuo* and the process was repeated. Purification via flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 10:1) gave **291** as a yellow oil (1.18 g, 85%, >99:1 dr); $[\alpha]_D^{20}$ –24.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3497 (O−H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.26 (9H, s, C*Me*$_3$) 1.22–1.37 (3H, obscured d, C(α)*Me*), 3.16 (1H, br s, O*H*), 3.83 (3H, s, O*Me*), 3.97 (1H, d, *J* 15.0, NC*H*$_A$H$_B$Ph), 4.26 (1H, d, *J* 15.0, NCH$_A$*H*$_B$Ph), 4.30–4.41 (2H, m, C(3)*H*, C(α)*H*), 4.52-4.57 (1H, m, C(2)*H*), 6.96 (2H, d, *J* 7.8, C(3')*H*, C(5')*H*), 7.45 (2H, d, *J* 7.8, C(2')*H*, C(6')*H*), 7.25–7.64 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.6 (C(α)*Me*) 27.8 (C*Me*$_3$) 52.3 (N*C*H$_2$Ph), 55.2 (O*Me*), 57.5 (*C*(α)Me), 64.8 (*C*(3)), 73.7 (*C*(2)), 82.0 (*C*Me$_3$), 113.5 (*C*(3'), *C*(5')), 128.2 (*C*(2'), *C*(6')), 126.7, 126.9, 128.2, 128.2, 128.3, 131.2 (*o,m,p-Ph*), 130.5 (C(1')), 142.1, 144.5, (*i-Ph*), 159.1 (C(4')), 172.4 (*C*(1)); *m*/*z* (ESI$^+$) 462 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{36}NO_4^+$ ([M+H]$^+$) requires 462.2639; found 462.2628.

tert-Butyl (*R*,*R*,*R*)-2-[*N*-benzyl-*N*(α-methylbenzyl)amino]-3-hydroxy-3-[4'-(trifluoromethyl)]phenylpropanoate 296



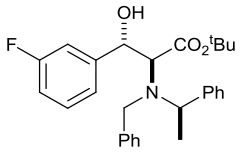
Method A: Ms_2O (52 mg, 0.30 mmol) was added to a stirred solution of **287** (50 mg, 0.10 mmol, >99:1 dr) and Et_3N (0.06 mL, 0.45 mmol) in CH_2Cl_2 (0.43 mL) and the resultant solution was stirred at rt for 1 h, then H_2O (0.054 mL, 3.00 mmol) was added and the resultant mixture was stirred at rt for 24 h. H_2O (1 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 2 mL) and the combined organic washed with 1M HCl (3 mL), satd aq $NaHCO_3$ (3 mL) and brine (3 mL), then dried and concentrated *in vacuo* to give a 69:31 mixture of **292** and **296**, respectively

Method B: Ms_2O (104 mg, 0.60 mmol) was added to a stirred solution of **287** (100 mg, 0.20 mmol, >99:1 dr) and Et_3N (0.12 mL, 0.90 mmol) in CH_2Cl_2 (0.86 mL) and the resultant solution was stirred at rt for 1 h, then H_2O (0.11 mL, 6.00 mmol) was added and the resultant mixture was stirred at 40 °C for 24 h. H_2O (2 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 3 mL) and the combined organic washed with 1M HCl (4 mL), satd aq $NaHCO_3$ (4 mL) and brine (4 mL), then dried and concentrated *in vacuo* to give a 85:15 mixture of **296** and **292**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave **296** as a pale yellow oil (61 mg, 61%, >99:1 dr); $[\alpha]_D^{23}$ −30.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3498 (O−H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.39 (3H, d, *J* 6.9, C(α)*Me*), 1.59 (9H, s C*Me*$_3$), 3.01 (1H, br s, O*H*), 3.60 (1H, d, *J* 8.3, C(2)*H*), 3.92 (1H, d, *J* 14.3, NCH_AH_BPh), 4.02 (1H, q, *J* 6.9, C(α)*H*), 4.14 (1H, d, *J* 14.3, NCH_AH_BPh), 4.90 (1H, d, *J* 8.3 C(3)*H*), 6.88 (2H, d, *J* 8.1, C(2')*H*, C(6')*H*), 6.90–7.22 (10H, m, *Ph*) 7.32 (2H, d, *J* 8.1, C(3')*H*, C(5')*H*); δ_C (125 MHz, $CDCl_3$) 12.5 (C(α)*Me*), 27.1 (C*Me*$_3$), 50.9 (N*C*H_2Ph), 55.3 (*C*(α)H), 63.8 (*C*(2)), 72.9 (*C*(3)), 81.1 (*C*Me$_3$), 123.2 (q, *J* 271.8, *C*F_3), 123.8 (q, *J* 3.8, *C*(3'), *C*(5')), 125.8, 126.1, 126.6, 126.9, 127.0, 127.9 (*o,m,p-Ph*), 127.2 (*C*(2'), *C*(6')), 128.7 (q, *J* 32.4, *C*(4')), 138.4, 141.8 (*i-Ph*), 144.3 (*C*(1')), 172.0 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −62.4 (C*F*$_3$); *m/z* (ESI$^+$) 500 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{32}F_3NNaO_3^+$ ([M+Na]$^+$) requires; 522.2226 found 522.2223.

Method C: Ms_2O (52 mg, 0.30 mmol) was added to a stirred solution of **287** (50 mg, 0.10 mmol, >99:1 dr) and Et_3N (0.06 mL, 0.45 mmol) in CH_2Cl_2 (0.43 mL) and the resultant solution was stirred at rt for 1 h, then H_2O (54 μL, 3.00 mmol) was added and the resultant

mixture was stirred at 40 °C for 48 h. H_2O (1 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic extracts were washed sequentially with 1M HCl (3 mL), satd aq $NaHCO_3$ (3 mL) and brine (3 mL), then dried and concentrated *in vacuo* to give a 100:0 mixture of **296** and **292**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave **296** as a pale yellow oil (32 mg, 64%, >99:1 dr).

tert-Butyl (2*S*,3*S*,α*R*)-2-[*N*-benzyl-*N*(α-methylbenzyl)amino]-3-hydroxy-3-(3'-fluorophenyl)propanoate 297

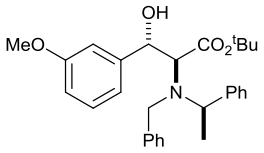


Method A: Ms_2O (58 mg, 0.333 mmol) was added to a stirred solution of **288** (50 mg, 0.111 mmol, >99:1 dr) and Et_3N (66 µL, 0.50 mmol) in CH_2Cl_2 (0.45 mL) and the resultant solution was stirred at rt for 1 h, then H_2O (60 µL, 3.33 mmol) was added and the resultant mixture was stirred at rt for 24 h. H_2O (1 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic extracts were washed sequentially with 1.0 M aq HCl (3 mL), satd aq $NaHCO_3$ (3 mL) and brine (3 mL), then dried and concentrated *in vacuo* to give a 77:23 mixture of **297** and **293**, respectively.

Method B: Ms_2O (58 mg, 0.333 mmol) was added to a stirred solution of **288** (50 mg, 0.111 mmol, >99:1 dr) and Et_3N (66 µL, 0.50 mmol) in CH_2Cl_2 (0.45 mL) and the resultant solution was stirred at rt for 1 h, then H_2O (60 µL, 3.33 mmol) was added and the resultant mixture was stirred at 40 °C for 24 h. H_2O (1 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic extracts were washed with 1.0 M aq HCl (3 mL), satd aq $NaHCO_3$ (3 mL) and brine (3 mL), then dried and concentrated *in vacuo* to give a 100:0 mixture of **297** and **293**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave **297** as a pale yellow oil (44 mg, 88%, >99:1 dr); $[\alpha]_D^{20}$ −29.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3498 (O−H), 1721 (C=O); δ_H (400 MHz, $CDCl_3$) 1.39 (3H, d, *J* 6.9, C(α)*Me*), 1.58 (9H, s, C*Me*$_3$), 2.86 (1H, br s, O*H*), 3.56 (1H, d, *J* 8.0, C(2)*H*), 3.94 (1H, d, *J* 14.3, NC*H*$_A$H$_B$Ph), 4.04 (1H, q, *J* 6.9, C(α)*H*), 4.14 (1H, d, *J* 14.3, NCH$_A$*H*$_B$Ph), 4.87 (1H, d, *J* 8.0, C(3)*H*), 6.53–7.34 (14H, m, *Ar*, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.5 (C(α)*Me*), 28.2 (C*Me*$_3$), 51.9 (N*C*H$_2$Ph), 56.3 (*C*(α)), 64.7 (*C*(2)), 74.1 (*C*(3)), 82.0 (*C*Me$_3$), 114.1, 114.6 (2 × d, *J* 21.5, *C*(2'), *C*(4')), 123.1 (d, *J* 2.4, *C*(6')), 126.9, 127.1, 128.0,

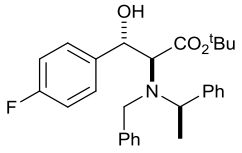
128.0, 128.2, 128.9 (*o,m,p-Ph*), 129.4 (d, *J* 8.0, *C*(5')), 140.0, 142.9 (*i-Ph*), 143.9 (d, *J* 7.2, *C*(1')), 162.7 (d, *J* 245.6, *C*(3')), 173.2 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −113.3 (C(3')*F*); *m*/*z* (ESI^+) 472 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{28}H_{32}FNNaO_3^+$ ($[M+Na]^+$) requires 472.2258; found 472.2247.

tert-Butyl (2*S*,3*S*,α*R*)-2-[*N*-benzyl-*N*(α-methylbenzyl)amino]-3-hydroxy-3-(3'-methoxyphenyl)propanoate 298



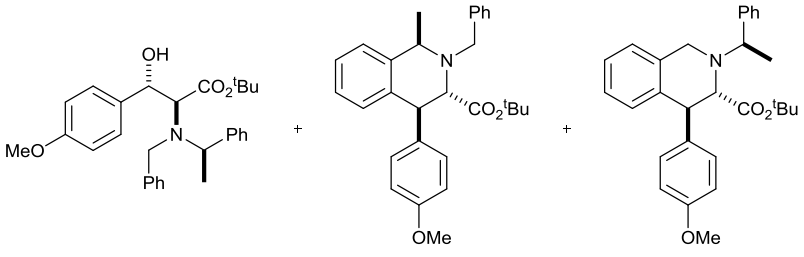
Ms_2O (227 mg, 1.30 mmol) was added to a stirred solution of **289** (200 mg, 0.433 mmol, >99:1 dr) and Et_3N (0.257 mL, 1.94 mmol) in CH_2Cl_2 (1.72 mL) and the resultant solution was stirred at rt for 1 h, then H_2O (0.240 mL, 13.3 mmol) was added and the resultant mixture was stirred at rt for 24 h. H_2O (3 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic extracts were washed sequentially with 1.0 M aq HCl (4 mL), satd aq $NaHCO_3$ (4 mL) and brine (4 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 4:1) gave **298** as a yellow oil (137 mg, 69%, >99:1 dr); $[\alpha]_D^{20}$ −34.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3502 (O−H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.38 (3H, d, *J* 6.9, C(α)*Me*), 1.58 (9H, s, C*Me*$_3$), 2.77 (1H, br s, O*H*), 3.57 (1H, d, *J* 8.1, C(2)*H*), 3.66 (3H, s, O*Me*), 3.95 (1H, d, *J* 14.3, NC*H*$_A$H$_B$Ph), 4.02 (1H, q, *J* 6.9, C(α)*H*), 4.17 (1H, d, *J* 14.3, NCH$_A$*H*$_B$Ph), 4.89 (1H, d, *J* 8.1, C(3)*H*), 6.37–6.40 (1H, m, C(2')*H*), 6.49 (1H, d, *J* 8.0, C(6')*H*), 6.74 (1H, app dd, *J* 8.0, 2.5, C(4')*H*), 7.05 (1H, t, *J* 8.0, C(5')*H*), 6.95-7.22 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.4 (C(α)*Me*) 28.2 (C*Me*$_3$) 51.8 (NCH_2Ph), 55.1 (O*Me*), 56.2 (*C*(α)), 64.9 (*C*(2)), 74.6 (*C*(3)), 81.7 (*C*Me$_3$), 111.7 (*C*(2')), 114.3 (*C*(4')), 119.9 (*C*(6')), 129.0 (*C*(5')), 126.7, 126.9, 127.9, 128.1, 128.2, 129.0 (*o,m,p-Ph*), 139.9 (*C*(1')), 143.9, 143.1 (*i-Ph*), 159.4 (C(3')), 173.4 (*C*(1)); *m*/*z* (ESI^+) 462 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{29}H_{36}NO_4^+$ ($[M+H]^+$) requires 462.2639; found 462.2640.

tert-Butyl (2*S*,3*S*,α*R*)-2-[*N*-benzyl-*N*(α-methylbenzyl)amino]-3-hydroxy-3-(4'-fluorophenyl)propanoate 299



Method A: Ms_2O (58 mg, 0.333 mmol) was added to a stirred solution of **290** (50 mg, 0.111 mmol, >99:1 dr) and Et_3N (66 μL, 0.50 mmol) in CH_2Cl_2 (0.45 mL) and the resultant solution was stirred at rt for 1 h, then H_2O (0.060 mL, 3.33 mmol) was added and the resultant mixture was stirred at rt for 24 h. H_2O (1 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic extracts were washed sequentially with 1.0 M aq HCl (3 mL), satd aq $NaHCO_3$ (3 mL) and brine (3 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave **299** as a pale yellow oil (40 mg, 80%, >99:1 dr); $[\alpha]_D^{20}$ −30.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3496 (O−H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.39 (3H, d, *J* 6.9, C(α)*Me*), 1.59 (9H, s, C*Me*$_3$), 2.70 (1H, br s, O*H*), 3.56 (1H, d, *J* 8.4, C(2)H), 3.92 (1H, d, *J* 14.2, NC*H*$_A$H$_B$Ph), 4.01 (1H, q, *J* 6.9, C(α)*H*), 4.11 (1H, d, *J* 14.2, NCH$_A$*H*$_B$Ph), 4.87 (1H, d, *J* 8.4, C(3)*H*), 6.72–6.82 (4H, m, *Ar*), 6.92–7.22 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.5 (C(α)*Me*) 28.2 (C*Me*$_3$) 51.7 (N*C*H$_2$Ph), 56.3 (*C*(α)Me), 64.7 (C(2)), 73.8 (C(3)), 81.9 (*C*Me$_3$), 114.9 (d, *J* 20.7, *C*(3'), *C*(5')), 126.8, 127.0, 128.0, 128.1, 128.2, 129.0, (*o*,*m*.*p*-*Ph*), 129.1 (d, *J* 8.0, *C*(2'), *C*(6')), 137.0 (d, *J* 2.4, *C*(1')), 143.0, 139.7 (*i*-*Ph*), 162.3 (d, *J* 244.8, *C*(4')), 173.4 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −114.9 (C(4')*F*); *m*/*z* (ESI$^+$) 450 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{33}FNO_3^+$ ([M+H]$^+$) requires 450.2439; found 450.2442.

tert-Butyl (2*S*,3*S*,α*R*)-2-[*N*-benzyl-*N*(α-methylbenzyl)amino]-3-hydroxy-3-(4'-methoxyphenyl)propanoate 300, (1*R*,3*S*,4*S*)-1-methyl-2-benzyl-3-*tert*-butoxycarbonyl-4-(4'-methoxy)phenyl-1,2,3,4-tetrahydroisoquinoline 301 and (3*S*,4*S*,α*R*)-2-*N*-(α-methyl)benzyl-3-*tert*-butoxycarbonyl-4-(4'-methoxy)phenyl-1,2,3,4-tetrahydroisoquinoline 302



300 **301** **302**

Method A: Ms_2O (57 mg, 0.325 mmol) was added to a stirred solution of **291** (50 mg, 0.108 mmol, >99:1 dr) and Et_3N (0.065 mL, 0.486 mmol) in CH_2Cl_2 (0.43 mL) and the resultant

solution was stirred at rt for 1 h, then H_2O (0.060 mL, 3.33 mmol) was added and the resultant mixture was stirred at rt for 24 h. H_2O (1 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 2 mL) and the combined organic extracts washed with 1M HCl (3 mL), satd aq $NaHCO_3$ (3 mL) and brine (3 mL), then dried and concentrated *in vacuo* to give 23:43:34 mixture of **300**, **301** and **302**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave a 55:45 mixture of **301** and **302**, respectively, as a red oil (7 mg, 15%); ν_{max} (ATR) 1724 (C=O), 1150 (C−F); *m*/*z* (ESI^+) 444 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{29}H_{34}NO_3^+$ ($[M+H]^+$) requires 444.2533; found 444.2533. Data for **301**: δ_H (500 MHz, $CDCl_3$) 1.29 (9H, s, C*Me*$_3$), 1.47 (3H, d, *J* 6.6, C(1)*Me*), 3.72 (1H, d, *J* 3.7, C(3)*H*), 3.73 (O*Me*), 3.94 (1H, d, *J* 15.0, NCH_AH_BPh), 3.98 (1H, d, *J* 15.0, CH_AH_BPh), 4.35 (1H, q, *J* 6.6, C(1)*H*), 4.45 (1H, d, *J* 3.7, C(4)*H*), 6.75–7.30 (13H, m, *Ar*, *Ph*); δ_C (125 MHz, $CDCl_3$) 23.2 (C(1)*Me*), 27.9 (C*Me*$_3$), 46.8 (*C*(4)), 54.9 (N*C*H_2Ph), 55.3 (O*Me*), 55.6 (*C*(1)), 64.3 (*C*(3)), 80.9 (*C*Me$_3$), 113.2 (*C*(3'), *C*(5')), 125.9 (*C*(6)), 126.5 (*C*(8)), 127.0 (*p-Ph*), 128.0, 128.0 (*o-*,*m-Ph*), 128.3 (*C*(7)), 129.7 (*C*(5)), 129.9 (*C*(2'), *C*(6')), 134.3 (*C*(4a)), 136.1 (*C*(1')), 139.9 (*C*(1")), 140.9 (*C*(8a)), 158.0 (*C*(4')), 172.1 (*C*O_2^tBu). Data for **302**: δ_H (500 MHz, $CDCl_3$) 1.18 (3H, d, *J* 6.6, C(α)*Me*), 1.40 (9H, s, C*Me*$_3$), 3.69 (1H, app s, C(1)H_AH_B), 3.73 (O*Me*), 3.77 (1H, app s, C(1)H_AH_B), 3.92 (1H, q, *J* 6.6, C(α)*H*), 3.94 (1H, d, *J* 2.4, C(3)*H*), 4.44 (1H, d, *J* 2.4, C(4)*H*), 6.75-7.30 (13H, m, *Ar*); δ_C (125 MHz, $CDCl_3$) 20.9 (C(α)*Me*), 28.1 (C*Me*$_3$), 47.1 (*C*(4)), 49.5 (*C*(1)), 55.2 (O*Me*), 61.9 (*C*(α)), 62.9 (*C*(3)), 81.1 (*C*Me$_3$), 113.2 (*C*(3'), *C*(5')), 125.9, 126.0, 126.0, 126.6, 126.7, 127.2, 128.2, 129.5 (*Ar*, *Ph*), 135.0, 135.3, 137.6, 146.2 (*Ar*, *i-Ph*), 158.1 (*C*(4')), 172.0 (*C*O_2^tBu).

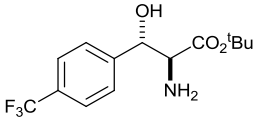
Method B: Ms_2O (57 mg, 0.325 mmol) was added to a stirred solution of **291** (50 mg, 0.108 mmol) and Et_3N (0.065 mL, 0.486 mmol) in CH_2Cl_2 (0.43 mL) and the resultant solution was stirred at rt for 30 min, then H_2O (0.060 mL, 3.33 mmol) was added and the resultant mixture was stirred at rt for 24 h. H_2O (1 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 2 mL) and the combined organic extracts washed with 1M HCl (3 mL), satd aq $NaHCO_3$ (3 mL) and brine (3 mL), then dried and concentrated *in vacuo* to give 64:30:6 mixture of **300**, [**301** + **302**] and **305**, respectively.

Method C: Ms_2O (57 mg, 0.325 mmol) was added to a stirred solution of **291** (50 mg, 0.108 mmol, >99:1 dr) and Et_3N (0.065 mL, 0.486 mmol) in CH_2Cl_2 (0.43 mL) and the resultant solution was stirred at rt for 5 min, then H_2O (0.060 mL, 3.33 mmol) was added and the resultant mixture was stirred at rt for 24 h. H_2O (1 mL) was added and the mixture was

extracted with CH_2Cl_2 (3 × 2 mL) and the combined organics washed with 1M HCl (3 mL), satd aq $NaHCO_3$ (3 mL) and brine (3 mL), then dried and concentrated *in vacuo* to give 78:15:7 mixture of **300**, [**301** + **302**] and **305**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 4:1) gave **300** as a pale yellow oil (21 mg, 40%, >99:1 dr); $[\alpha]_D^{20}$ −5.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3504 (O−H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.38 (3H, d, J 7.0, C(α)*Me*), 1.59 (9H, s, C*Me*$_3$), 2.52 (1H, br s, O*H*), 3.55 (1H, d, *J* 8.5, C(2)H), 3.84 (3H, s, O*Me*), 3.92 (1H, d, *J* 14.3, NC*H*$_A$H$_B$Ph), 3.98 (1H, q, *J* 7.0, C(α)*H*), 4.11 (1H, d, *J* 14.3, NCH$_A$*H*$_B$Ph), 4.87 (1H, d, *J* 8.5, C(3)*H*), 6.66 (2H, d, *J* 8.6, C(3')*H*, C(5')*H*), 6.75 (2H, d, *J* 8.6, C(2')*H*, C(6')*H*), 6.92-7.21 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.3 (C(α)*Me*) 28.2 (C*Me*$_3$) 51.6 (N*C*H$_2$Ph), 55.4 (O*Me*), 56.2 (*C*(α)Me), 64.5 (*C*(2)), 74.0 (*C*(3)), 81.6 (*C*Me$_3$), 113.5 (*C*(3'), *C*(5')), 128.1 (*C*(2'), *C*(6')), 126.7, 127.0, 127.9, 128.2, 128.7, 129.0 (*o,m,p-Ph*), 133.5 (*C*(1'), 139.9, 143.0 (*i-Ph*), 159.2 (*C*(4')), 173.7 (*C*(1)); *m*/*z* (ESI$^+$) 462 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{36}NO_4^+$ ([M+H]$^+$) requires 462.2639; found 462.2643.

Method D: Ms_2O (114 mg, 0.650 mmol) was added to a stirred solution of **291** (100 mg, 0.218 mmol, >99:1 dr) and Et_3N (0.130 mL, 0.972 mmol) in CH_2Cl_2 (0.86 mL) and the resultant solution was stirred at rt for 1 min, then H_2O (0.12 mL, 6.66 mmol) was added and the resultant mixture was stirred at rt for 24 h. H_2O (2 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 4 mL) and the combined organic extracts washed with 1M HCl (6 mL), satd aq $NaHCO_3$ (6 mL) and brine (6 mL), then dried and concentrated *in vacuo* to give 83:10:7 mixture of **300**, [**301** + **302**] and **305**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 4:1) gave **300** as a pale yellow oil (55 mg, 55%, >99:1 dr).

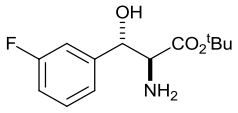
tert-Butyl (*S*,*S*)-2-amino-3-hydroxy-3-[4'-(trifluoromethyl)phenyl]propanoate 306



$Pd(OH)_2$/C (12 mg, 20% w/w) was added to a degassed mixture of **296** (60 mg, 0.120 mmol, >99:1 dr) in MeOH (1 mL) and the resultant mixture was placed under an atmosphere of H_2 (5 atm) and stirred at rt for 24 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated *in vacuo* to give **306** as an orange solid (30 mg, 80%, >99:1 dr); mp 163.5–172.0 °C; $[\alpha]_D^{20}$ +45.8 (*c* 1.0 in MeOH); ν_{max} (ATR) 3409 (O−H, N−H), 1734

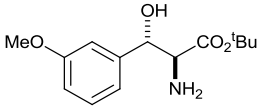
(C=O); δ_H (700 MHz, MeOD) 1.18 (9H, s, CMe_3), 4.07 (1H, br s, C(2)*H*), 5.15 (1H, br s, C(3)*H*), 7.60 (2H, d, *J* 8.3, C(2')*H*, C(6')*H*), 7.55 (2H, d, *J* 8.3, C(3')*H*, C(5')*H*); δ_C (176 MHz, MeOD) 26.6 (C*Me*$_3$), 58.9 (*C*(2)), 71.4 (*C*(3)), 83.1 (*C*Me$_3$), 124.3 (q, *J* 270.8, *C*F_3), 124.8 (q, *J* 3.8, *C*(3'), *C*(5')), 126.6 (*C*(2'), *C*(6')), 129.7 (q, *J* 31.8, *C*(4')), 144.5 (*C*(1')), 166.7 (*C*(1)); *m*/*z* (ESI$^+$) 306 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{18}F_3NNaO_3^+$ ([M+Na]$^+$) requires 328.1131; found 328.1131.

tert-Butyl (*S*,*S*)-2-amino-3-hydroxy-3-(3'-fluorophenyl)propanoate 307



Pd(OH)$_2$/C (15 mg, 20% w/w) was added to a degassed mixture of **297** (75 mg, 0.167 mmol, >99:1 dr) in MeOH (1 mL) and the resultant mixture was placed under an atmosphere of H_2 (5 atm) and stirred at rt for 48 h. the reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated *in vacuo* to give **307** as an orange oil (43 mg, quant, >99:1 dr); $[\alpha]_D^{20}$ +32.7 (*c* 1.0 in MeOH); ν_{max} (ATR) 3432 (O−H, N−H), 1734 (C=O); δ_H (500 MHz, MeOD) 1.22 (9H, s, C*Me*$_3$), 3.98 (1H, br s, C(2)*H*), 5.06 (1H, br s, C(3)*H*), 7.07 (1H, dt, *J* 8.5, 2.4, C(4')*H*), 7.20–7.25 (1H, m, C(2')*H*), 7.25–7.30 (1H, m, C(6')*H*), 7.39–7.45 (1H, m, C(5')*H*); δ_C (125 MHz, MeOD) 26.7 (C*Me*$_3$), 59.0 (*C*(2)), 71.2 (*C*(3)), 83.1 (*C*Me$_3$), 112.9 (d, *J* 22.0, *C*(2')), 114.2 (d, *J* 22.0, *C*(4')), 121.8 (d, *J* 2.9, *C*(6')), 129.8 (d, *J* 7.6, *C*(5')), 142.6 (*C*(1')), 162.9 (d, *J* 244.1, *C*(3')), 166.6 (*C*(1)); *m*/*z* (ESI$^+$) 256 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{18}FNNaO_3^+$ ([M+Na]$^+$) requires 278.1163; found 278.1166.

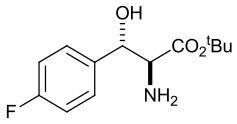
tert-Butyl (*S*,*S*)-2-amino-3-hydroxy-3-(3'-methoxyphenyl)propanoate 308



Pd(OH)$_2$/C (22 mg, 20% w/w) was added to a degassed mixture of **298** (58 mg, 0.126 mmol, >99:1 dr) in MeOH (1 mL) and the resultant mixture was placed under an atmosphere of H_2 (5 atm) and stirred at rt for 24 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated *in vacuo* to give **308** as a colourless oil (36 mg, quant, >99:1 dr); $[\alpha]_D^{20}$ +21.4 (*c* 0.5 in MeOH); ν_{max} (ATR) 3273 (O−H, N−H), 1733 (C=O); δ_H (400 MHz, MeOD) 1.22 (9H, s, CMe_3), 3.71 (3H, s, O*Me*), 3.98 (1H, br s, C(2)*H*), 5.06 (1H, br s, C(3)*H*), 6.78 (1H, dd, *J* 8.1, 2.2, C(5')*H*), 6.87–6.94 (2H, m, *Ar*), 7.19 (1H, t, *J* 8.1, C(4')*H*);

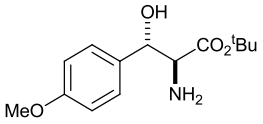
δ_C (100 MHz, MeOD) 26.7 (C*Me*$_3$), 54.4 (O*Me*), 58.9 (*C*(2)), 71.1 (*C*(3)), 83.3 (*C*Me$_3$), 111.8 (*Ar*), 113.0 (*C*(5')), 118.2 (*Ar*), 129.1 (*C*(4')), 140.6 (*C*(1')), 159.9 (*C*(3')), 165.9 (*C*(1)); *m*/*z* (ESI$^+$) 268 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{21}NNaO_4^+$ ([M+Na]$^+$) requires 290.1363; found 290.1366.

tert-Butyl (*S*,*S*)-2-amino-3-hydroxy-3-(4'-fluorophenyl)propanoate 309



Pd(OH)$_2$/C (13 mg, 25% w/w) was added to a degassed mixture of **299** (65 mg, 0.145 mmol, >99:1 dr) in MeOH/EtOAc (3 mL, 2:1) and the resultant mixture was placed under an atmosphere of H_2 (5 atm) and stirred at rt for 24 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated *in vacuo* to give **309** as a colourless oil (30 mg, 81%, >99:1 dr); $[\alpha]_D^{20}$ +21.2 (*c* 1.0 in MeOH); ν_{max} (ATR) 3281, 2980 (O−H, N−H), 1732 (C=O); δ_H (400 MHz, MeOD) 1.26 (9H, s, CMe$_3$), 3.52 (1H, d, *J* 4.7, C(2)*H*), 4.77–4.81 (1H, m, C(3)*H*), 6.97 (2H, t, *J* 8.7, C(3')*H*, C(5')*H*), 7.29 (2H, dd, *J* 8.7, 5.3, C(2')*H*, C(6')*H*); δ_C (100 MHz, MeOD) 26.8 (C*Me*$_3$), 60.6 (*C*(2)), 74.2 (*C*(3)), 81.3 (*C*Me$_3$), 114.3 (d, *J* 21.5, *C*(3'), *C*(5')), 128.3 (d, *J* 7.8, *C*(2'), *C*(6')), 136.7 (*C*(1')), 162.5 (d, *J* 244.8, *C*(4')), 171.4 (*C*(1)); *m*/*z* (ESI$^+$) 256 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{18}FNNaO_3^+$ ([M+Na]$^+$) requires 278.1163; found 278.1167.

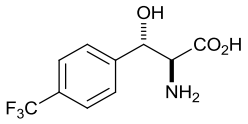
tert-Butyl (*S*,*S*)-2-amino-3-hydroxy-3-(4'-methoxyphenyl)propanoate 310



Pd(OH)$_2$/C (15 mg, 20% w/w) was added to a degassed mixture of **300** (75 mg, 0.162 mmol, >99:1 dr) in MeOH (1 mL) and the resultant mixture was placed under an atmosphere of H_2 (5 atm) and stirred at rt for 24 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated *in vacuo* to give **310** as a colourless oil (43 mg, quant, >99:1 dr); $[\alpha]_D^{20}$ −4.0 (*c* 0.5 in MeOH); ν_{max} (ATR) 3401 (O−H, N−H), 1728 (C=O); δ_H (400 MHz, MeOD) 1.28 (9H, s, CMe$_3$), 3.63–3.72 (1H, m, C(2)*H*), 3.68 (3H, s, O*Me*), 4.84–4.92 (1H, m, C(3)*H*), 6.81 (2H, d, *J* 8.7, C(3')*H*, C(5')*H*), 7.21 (2H, d, *J* 8.5, C(2')*H*, C(6')*H*); δ_C (100 MHz, MeOD) 26.8 (C*Me*$_3$), 54.4 (O*Me*), 60.0 (*C*(2)), 73.1 (*C*(3)), 82.1 (*C*Me$_3$), 113.3(*C*(3'), *C*(5')),

127.5 (*C*(2'), *C*(6')), 131.7 (*C*(1')), 159.6 (*C*(4')), 169.5 (*C*(1)); *m*/*z* (ESI^+) 268 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{14}H_{21}NNaO_4^+$ ($[M+Na]^+$) requires 290.1363; found 290.1364.

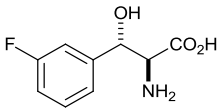
(*S*,*S*)-2-Amino-3-hydroxy-3-[4'-(trifluoromethyl)phenyl]propanoic acid 311



Method A: A stirred solution of **306** (30 mg, 0.098 mmol, >99:1 dr) in 6.0 M aq HCl (0.6 mL) was heated at 90 °C for 24 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. Purification via ion exchange chromatography (DOWEX 50WX8-200, eluent 1.0 M aq NH_4OH) gave **311** as a white solid (17 mg, 71%, 99:1 dr).

Method B: A stirred solution of **306** (20 mg, 0.066 mmol, >99:1 dr) in 6.0 M aq HCl (0.6 mL) was stirred at rt for 6 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. Purification via ion exchange chromatography (DOWEX 50WX8-200, eluent 1.0 M aq NH_4OH) gave **311** as a white solid (17 mg, quant, 92:8 dr); mp 171.5–180.0 °C dec.; $[\alpha]_D^{20}$ +14.4 (*c* 0.5 in H_2O); ν_{max} (ATR) 3508, 3364 (O−H, N−H), 1579 (C=O); δ_H (500 MHz, D_2O) 4.04 (1H, d, *J* 4.0, C(2)*H*), 5.33 (1H, d, *J* 4.0, C(3)*H*), 7.46 (2H, d, *J* 8.2, C(2')*H*, C(6')*H*), 7.65 (2H, d, *J* 8.2, C(3')*H*, C(5')*H*); δ_C (125 MHz, D_2O) 60.3 (*C*(2)), 70.6 (*C*(3)), 124.0 (q, *J* 271.8, *C*F_3), 125.6 (q, *J* 3.8, *C*(3'), *C*(5')), 126.8 (*C*(2'), *C*(6')), 130.0 (q, *J* 31.8, *C*(4')), 141.4 (*C*(1')), 170.6 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −62.4 (C*F*$_3$); *m*/*z* (ESI^+) 250 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{10}H_{10}F_3NNaO_3^+$ ($[M+Na]^+$) requires 272.0505; found 272.0507.

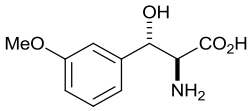
(*S*,*S*)-2-αmino-3-hydroxy-3-(3'-fluorophenyl)propanoic acid 312



A solution of **307** (44 mg, 0.172 mmol, >99:1 dr) in 6.0 M aq HCl (1 mL) was stirred at rt for 3 h, then concentrated *in vacuo*. H_2O (4 mL) and $CHCl_3$ (3 mL) were added, the layers separated and the aqueous layer washed with $CHCl_3$ (2 × 3 mL), then concentrated *in vacuo*. Purification via ion exchange chromatography (DOWEX 50WX8-200, eluent 1.0 M aq NH_4OH) gave **312** as a white solid (25 mg, 74%, 93:7 dr); mp 197.0–199.0 °C dec.; $[\alpha]_D^{20}$ +17.6 (*c* 0.5 in H_2O); ν_{max} (ATR) 3059 (O−H, N−H), 1591 (C=O); δ_H (500 MHz, D_2O) 4.00 (1H, d, *J* 3.9, C(2)*H*), 5.28 (1H, d, *J* 3.9, C(3)*H*), 7.02-7.13 (3H, m, *Ar*), 7.32-7.37 (1H, m, C(5')*H*); δ_C (125 MHz, D_2O) 60.3 (*C*(2)), 70.5 (*C*(3)), 113.1 (d, *J* 22.5, *C*(2')), 115.5 (d, *J* 22.5, *C*(4')), 122.1 (d, *J* 2.9, *C*(6')), 130.5 (d, *J* 8.6, *C*(5')), 140.0 (d, *J* 6.7, *C*(1')), 162.6 (d, *J*

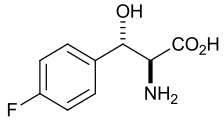
244.1, *C*(3')), 170.9 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −113.0 (C(3')*F*); *m*/*z* (ESI^+) 200 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_9H_{10}FNNaO_3^+$ ($[M+Na]^+$) requires 222.0537; found 222.0542.

(*S*,*S*)-2-Amino-3-hydroxy-3-(3'-methoxyphenyl)propanoic acid 313



A solution of **308** (45 mg, 0.168 mmol, >99:1 dr) in 6.0 M aq HCl (1 mL) was stirred at rt for 3 h, then concentrated *in vacuo*. H_2O (4 mL) and $CHCl_3$ (3 mL) were added, the layers separated and the aqueous layer washed with $CHCl_3$ (2 × 3 mL), then concentrated *in vacuo*. Purification via ion exchange chromatography (DOWEX 50WX8-200, eluent 1.0 M aq NH_4OH) gave **313** as a white solid (28 mg, 80%, 93:7 dr); mp 161.5–170.0 °C dec.; $[\alpha]_D^{20}$ +5.0 (*c* 1.0 in H_2O); ν_{max} (ATR) 3137 (O−H, N−H), 1598 (C=O); δ_H (500 MHz, D_2O) 3.76 (3H, s, O*Me*), 4.04 (1H, d, *J* 4.1, C(2)*H*), 5.27 (1H, d, *J* 4.1, C(3)*H*), 6.85–6.95 (3H, m, *Ar*) 7.31 (1H, app t, *J* 8.0, C(4')*H*); δ_C (125 MHz, D_2O) 55.4 (O*Me*), 60.3 (*C*(2)), 70.9 (*C*(3)), 111.8 (*Ar*), 114.4 (*C*(5')), 119.0 (*Ar*), 130.1 (*C*(4')), 138.7 (*C*(1')), 159.0 (*C*(3')), 170.0 (*C*(1)); *m*/*z* (ESI^+) 212 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{10}H_{13}NNaO_4^+$ ($[M+Na]^+$) requires 234.0737; found 234.0740.

(*S*,*S*)-2-Amino-3-hydroxy-3-(4'-fluorophenyl)propanoic acid 314

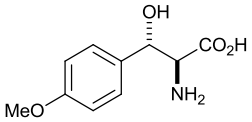


Method A: A stirred solution of **309** (30 mg, 0.178 mmol, >99:1 dr) in 6 M HCl (1 mL) was heated at 90 °C for 24 h, then concentrated *in vacuo*. H_2O (4 mL) and $CHCl_3$ (3 mL) were added, the layers separated and the aqueous layer washed with $CHCl_3$ (2 × 3 mL), then concentrated *in vacuo*. Purification via ion exchange chromatography (DOWEX 50WX8-200, eluent 1.0 M aq NH_4OH) gave **314** as a white solid (13 mg, 57%, 96:4 dr).

Method B: A solution of **309** (8 mg, 0.031 mmol, >99:1 dr) in 6 M HCl (0.5 mL) was stirred at rt for 6 h, then concentrated *in vacuo*. H_2O (2 mL) and $CHCl_3$ (3 mL) were added, the layers separated and the aqueous layer washed with $CHCl_3$ (2 × 3 mL), then concentrated *in vacuo*. Purification via ion exchange chromatography (DOWEX 50WX8-200, eluent 1.0 M aq NH_4OH) gave **314** as a white solid (7 mg, quant, 97:3 dr); mp 160.5–168.5 °C dec.; $[\alpha]_D^{20}$ +9.0 (*c* 0.5 in H_2O); ν_{max} (ATR) 3066 (O−H, N−H), 1602 (C=O); δ_H (500 MHz, D_2O) 3.99

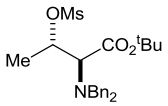
(1H, d, *J* 4.1, C(2)*H*), 5.27 (1H, d, *J* 4.1, C(3)*H*), 7.08 (2H, t, *J* 8.7, C(3')*H*, C(5')*H*), 7.31 (2H, dd, *J* 8.7, 5.5, C(2')*H*, C(6')*H*); δ_C (125 MHz, D_2O) 60.3 (*C*(2)), 70.5 (*C*(3)), 115.5 (d, *J* 21.9, *C*(3'), *C*(5')), 128.2 (d, *J* 8.6, *C*(2'), *C*(6')), 132.8 (*C*(1')), 162.5 (d, *J* 244.1, *C*(4')), 171.0 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −114.1 (C(4')*F*); *m*/*z* (ESI^+) 200 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_9H_{10}FNNaO_3^+$ ($[M+Na]^+$) requires 222.0537; found 222.0537.

(*S*,*S*)-2-Amino-3-hydroxy-3-(4'-methoxyphenyl)propanoic acid 315



A solution of **310** (43 mg, 0.161 mmol, >99:1 dr) in 6.0 M aq HCl (1 mL) was stirred at rt for 3 h, then concentrated *in vacuo*. H_2O (4 mL) and $CHCl_3$ (3 mL) were added, the layers separated and the aqueous layer washed with $CHCl_3$ (2 × 3 mL), then concentrated *in vacuo*. Purification via ion exchange chromatography (DOWEX 50WX8-200, eluent 1.0 M aq NH_4OH) gave **315** as a white solid (21 mg, 62%, 93:7 dr); mp 176.0–181.0 °C dec.; $[\alpha]_D^{20}$ +8.0 (*c* 1.0 in H_2O); $[\alpha]_D^{20}$ −2.4 (*c* 0.5, H_2O/MeOH, 1:1); {lit.[24] $[\alpha]_D^{20}$ –2.73 (*c* 0.586, H_2O/MeOH, 1:1)}; ν_{max} (ATR) 3503, 3238 (O−H, N−H), 1513 (C=O); δ_H (500 MHz, D_2O) 3.75 (3H, s, O*Me*), 3.97 (1H, d, *J* 4.1, C(2)*H*), 5.22 (1H, d, *J* 4.1, C(3)*H*), 6.94 (2H, d, *J* 8.7, C(3')*H*, C(5')*H*), 7.25 (2H, d, *J* 8.7, C(2')*H*, C(6')*H*); δ_C (125 MHz, D_2O) 55.3 (O*Me*) 60.4 (*C*(2)), 71.1 (*C*(3)), 114.2 (*C*(3'), *C*(5')), 127.7 (*C*(2'), *C*(6')), 129.3 (*C*(1')), 159.1 (*C*(4')), 171.1 (*C*(1)); *m*/*z* (ESI^+) 212 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{10}H_{13}NNaO_4^+$ ($[M+Na]^+$) requires 234.0737; found 234.0737.

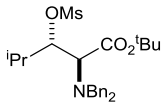
***tert*-Butyl (*RS*,*RS*)-2-dibenzylamino-3-(methanesulfonyloxy)butanoate 316**



Method A: Ms_2O (74 mg, 0.422 mmol) was added to a stirred solution of **252** (50 mg, 0.141 mmol, >99:1 dr) and Et_3N (0.084 mL, 0.635 mmol) in CH_2Cl_2 (0.6 mL) and the resultant solution was stirred at rt for 1 h. H_2O (76 μL, 4.23 mmol) was then added and the resultant mixture was stirred at rt for 24 h. H_2O (1 mL) was then added and the resultant mixture was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic extracts were washed sequentially with 1.0 M aq HCl (3 mL), satd aq $NaHCO_3$ (3 mL) and brine (3 mL), then dried and concentrated *in vacuo* to give a 90:10 mixture of **316** and **252**, respectively.

Method B: Ms_2O (74 mg, 0.422 mmol) was added to a stirred solution of **252** (50 mg, 0.141 mmol, >99:1 dr) and Et_3N (0.084 mL, 0.635 mmol) in CH_2Cl_2 (0.6 mL) and the resultant solution was stirred at rt for 2 h, then H_2O (0.076 mL, 4.23 mmol) was added and the resultant mixture was stirred at rt for 24 h. H_2O (1 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 2 mL) and the combined organic extracts washed with 1.0 M aq HCl (3 mL), satd aq $NaHCO_3$ (3 mL) and brine (3 mL), then dried and concentrated *in vacuo* to give a 92:8 mixture of **316** and **252**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1 then increased to 5:1) gave **316** as a brown oil (23 mg, 38%, >99:1 dr); δ_H (400 MHz, $CDCl_3$) 1.47, (3H, d, *J* 6.3, C(4)H_3), 1.63 (9H, s, CMe_3), 2.96 (3H, s, SO_2Me), 3.24 (1H, d, *J* 10.4, C(2)*H*), 3.43 (2H, d, *J* 13.4, N(C$H_AH_BPh)_2$), 3.92 (2H, d, *J* 13.4, N(C$H_AH_BPh)_2$), 5.05 (1H, dq, *J* 10.1, 6.3, C(3)*H*), 7.22–7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.1 (*C*(4)), 28.5 (CMe_3), 38.3 (SO_2Me), 55.3 (N($CH_2Ph)_2$), 64.4 (*C*(2)), 78.2 (*C*(3)), 82.3 (*C*Me_3), 127.5, 128.4, 129.0 (*o,m,p-Ph*), 138.1 (i-*Ph*), 169.0 (*C*=O).

tert-Butyl (*RS,RS*)-2-dibenzylamino-3-methanesulfonyloxy-4-methylpentanoate 317

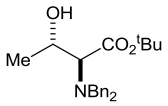


Method A: Ms_2O (68 mg, 0.39 mmol) was added to a stirred solution of **253** (50 mg, 0.130 mmol, >99:1 dr) and Et_3N (77 µL, 0.585 mmol) in CH_2Cl_2 (0.55 mL) and the resultant solution was stirred at rt for 1 h. H_2O (70 µL, 3.90 mmol) was then added and the resultant mixture was stirred at rt for 24 h. H_2O (1 mL) was then added and the resultant mixture was extracted with CH_2Cl_2 (3 × 2 mL) and the combined organic extracts were washed with 1.0 M aq HCl (3 mL), satd aq $NaHCO_3$ (3 mL) and brine (3 mL), then dried and concentrated *in vacuo* to give a 60:40 mixture of **317** and **253**, respectively.

Method B: Ms_2O (136 mg, 0.780 mmol) was added to a stirred solution of **253** (50 mg, 0.130 mmol, >99:1 dr) and Et_3N (0.154 mL, 1.17 mmol) in CH_2Cl_2 (0.55 mL) and the resultant solution was stirred at rt for 1 h. H_2O (70 µL, 3.90 mmol) was then added and the resultant mixture was stirred at rt for 24 h. H_2O (1 mL) was then added and the mixture was extracted with CH_2Cl_2 (3 × 2 mL) and the combined organic extracts washed with 1.0 M aq HCl (3 mL), satd aq $NaHCO_3$ (3 mL) and brine (3 mL), then dried and concentrated *in vacuo* to give a 88:12 mixture of **317** and **253**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1 then increased to 5:1) gave **253** as a white solid (2 mg,

4%, >99:1 dr). Further elution gave **317** as a brown oil (13 mg, 22%, >99:1 dr); δ_H (400 MHz, $CDCl_3$) 0.35 (3H, d, *J* 6.8, C(4)*Me*$_A$), 1.07 (3H, d, *J* 7.3, C(4)*Me*$_B$), 1.68 (9H, s, C*Me*$_3$), 2.40 (1H, app septet, *J* 6.9, C(4)*H*), 3.00 (3H, s, SO_2*Me*), 3.39–3.49 (3H, m, C(2)*H*, N(C*H*$_A$H$_B$Ph)$_2$), 3.94 (2H, d, *J* 13.4, N(CH$_A$*H*$_B$Ph)$_2$), 5.03 (1H, d, *J* 10.6, C(3)*H*), 7.22–7.46 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.0, 20.4 (C(4)*Me*$_2$), 27.5 (*C*(4)), 28.7 (C*Me*$_3$), 38.9 (SO_2*Me*), 55.2 (N(*C*H$_2$Ph)$_2$), 61.5 (*C*(2)), 82.4 (*C*Me$_3$), 85.6 (*C*(3)), 127.5, 128.4, 129.3 (*o*,*m*,*p*-*Ph*), 138.3 (i-*Ph*), 169.0 (*C*(1)).

tert-Butyl (*RS*,*RS*)-2-dibenzylamino-3-hydroxybutanoate 264



Method A – Step 1: CCl_4 (0.204 mL, 2.12 mmol) was added to a stirred solution of **252** (30 mg, 0.141 mmol, >99:1 dr) and PPh_3 (74 mg, 0.281 mmol) in PhMe (0.4 mL) and the resultant mixture was heated at 100 °C for 24 h. The reaction mixture was allowed to cool to rt and filtered, then concentrated *in vacuo* to give a 100:0 mixture of **255** and **256**, respectively.

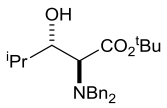
Method A – Step 2: AgOTf (68 mg, 0.126 mmol) was added to a stirred solution of **255** (0.141 mmol, >99:1 dr) in EtOAc/H_2O (1.0 mL, 4:1) and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then filtered through alumina (eluent EtOAc) and concentrated *in vacuo* to give a 41:23:36 mixture of **252**, **264** and **255**, respectively.

Method B: Ms_2O (74 mg, 0.422 mmol) was added to a stirred solution of **252** (50 mg, 0.141 mmol, >99:1 dr) and Et_3N (84 μL, 0.635 mmol) in CH_2Cl_2 (0.6 mL) and the resultant solution was stirred at rt for 3 h, then H_2O (0.076 mL, 4.23 mmol) was added and the resultant mixture was stirred at rt for 24 h. H_2O (1 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 2 mL) and the combined organic extracts washed with 1.0 M aq HCl (3 mL), satd aq $NaHCO_3$ (3 mL) and brine (3 mL), then dried and concentrated *in vacuo* to give a 92:8 mixture of **316** and **252**, respectively. H_2O (0.5 mL) and MeCN (0.5 mL) were added and the resultant mixture was heated at 50 °C for 15 h, then allowed to cool to rt and concentrated *in vacuo*. The reaction mixture was partitioned between CH_2Cl_2 (3 mL) and H_2O (3 mL), the aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give a 59:41 mixture of **264** and **252**, respectively.

Method C: Tf_2O (71 μL, 0.211 mmol) was added to a stirred solution of **252** (50 mg, 0.141 mmol, >99:1 dr) and Et_3N (84 μL, 0.635 mmol) in CH_2Cl_2 (0.6 mL) at 0 °C and the resultant solution was stirred at rt for 6 h. H_2O (26 μL, 7.2 mmol) was then added and the resultant mixture was stirred at rt for 24 h. H_2O (1 mL) was then added and the resultant mixture was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic extracts were then dried and concentrated *in vacuo*. Et_2O (10 mL) was added and the resultant mixture was filtered and the filtrate was concentrated *in vacuo* to give 66:34 mixture of **264** and **252**, respectively.

Method D: Tf_2O (35 μL, 0.211 mmol) was added to a stirred solution of **252** (50 mg, 0.141 mmol, >99:1 dr) and 2,6-di-*tert*-butyl-4-methyl pyridine (87 mg, 0.423 mmol) in CH_2Cl_2 (1.75 mL) at 0 °C and the resultant solution was stirred at rt for 3 h. H_2O (26 μL, 7.2 mmol) was then added and the resultant mixture was stirred at rt for 24 h. H_2O (1 mL) was then added and the resultant mixture was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic extracts were then dried and concentrated *in vacuo*. Et_2O (10 mL) was added and the resultant mixture was filtered and the filtrate was concentrated *in vacuo* to give **264**. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 3:1) gave **264** as a white solid (27 mg, 54%, >99:1 dr);[25] mp 97.5–101 °C; ν_{max} (ATR) 3461 (O−H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.11 (3H, d, *J* 6.4, C(4)H_3), 1.55 (9H, s, CMe_3), 2.49 (1H, br s, O*H*), 2.94 (1H, d, *J* 9.1, C(2)*H*), 3.45 (2H, d, *J* 13.4 N(CH_AH_BPh)$_2$), 3.83 (2H, d, *J* 13.4, N(CH_AH_BPh)$_2$), 4.01–4.11 (1H, m, C(3)*H*), 7.10–7.33 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.0 (*C*(4)), 28.7 (C*Me*$_3$), 55.6 (N(*C*H$_2$Ph)$_2$), 66.2 (*C*(2)), 67.2 (*C*(3)), 82.1 (*C*Me$_3$), 127.2, 128.3, 129.1 (*o*,*m*,*p*-*Ph*), 139.0 (*i*-*Ph*), 172.2 (*C*(1)); *m*/*z* (ESI^+) 378 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{22}H_{29}NNaO_3^+$ ($[M+H]^+$) requires 378.2040; found 378.2038.

tert-Butyl (*RS*,*RS*)-2-dibenzylamino-3-hydroxy-4-methylpentanoate 263

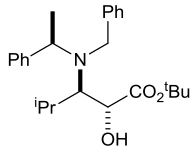


*Method A (From **258**):* AgOTf (21 mg, 0.082 mmol) was added to a stirred solution of **258** (30 mg, 0.078 mmol, >99:1 dr) in EtOAc/H_2O (0.73 mL, 4:1) and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then filtered through alumina (eluent EtOAc) and concentrated *in vacuo* to give **258**.

*Method B (From **253**):* Ms_2O (136 mg, 0.780 mmol) was added to a stirred solution of **253** (50 mg, 0.130 mmol, >99:1 dr) and Et_3N (0.154 mL, 1.17 mmol) in CH_2Cl_2 (0.55 mL) and the

resultant solution was stirred at rt for 1 h. H_2O (70 μL, 3.90 mmol) was then added and the resultant mixture was stirred at rt for 24 h. H_2O (1 mL) was then added and the mixture was extracted with CH_2Cl_2 (3 × 2 mL) and the combined organics washed with 1.0 M aq HCl (3 mL), satd aq $NaHCO_3$ (3 mL) and brine (3 mL), then dried and concentrated in vacuo to give a 88:12 mixture of **317** and **253**, respectively. H_2O (0.5 mL) and MeCN (0.5 mL) were added and the resultant mixture was heated at 50 °C for 15 h, then allowed to cool to rt and concentrated *in vacuo*. The reaction mixture was partitioned between CH_2Cl_2 (3 mL) and H_2O (3 mL), the aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give a 76:24 mixture of **263** and **253**, respectively. Selected data for **263**: δ_H (400 MHz, $CDCl_3$) 0.36 (3H, d, *J* 7.0, C(4)*Me*$_A$), 0.95 (3H, d, *J* 7.0, C(4)*Me*$_B$), 1.65 (9H, s, C*Me*$_3$), 2.16 (1H, septet d, *J* 7.0, 2.1, C(4)*H*), 3.23 (1H, d, *J* 9.2, C(2)*H*), 3.52 (2H, d, *J* 13.4, N(CH$_A$*H*$_B$Ph)$_2$), 3.84 (1H, dd, *J* 9.2, 2.1, C(3)*H*), 3.93 (2H, d, *J* 13.4, N(C*H*$_A$H$_B$Ph)$_2$), 7.23–7.44 (10H, m, *Ph*).

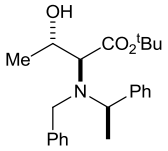
tert-Butyl (*R,R,R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-methylpentanoate 319



BuLi (2.3 M in hexanes, 1.98 mL, 4.56 mmol) was added dropwise to a stirred solution of (*R*)-**205**[43] (1.14 g, 4.70 mmol, 99% ee) in THF (10 mL) at −78 °C and stirring was continued at –78 °C for 30 min. A solution of **251** (500 mg, 2.94 mmol, >99:1 dr) in THF (10 mL) was then added via cannula and the resultant mixture was stirred at −78 °C for 2 h. (−)-**202** (1.15 g, 5.00 mmol) was then added and stirring was continued as the reaction mixture was allowed to warm to rt over 15 h. Satd aq NH_4Cl (1 mL) was added and the reaction mixture was stirred at rt for 5 min then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and 10% aq citric acid (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 8 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (20 mL) and brine (20 mL), then dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (10 mL), the insoluble CSO residues were filtered off, and the filter cake was washed with Et_2O (2 × 10 mL). The filtrate was concentrated *in vacuo* and the process was repeated. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **319** as a white soild (658 mg, 56%, >99:1 dr); mp 81.5–86.0 °C; $[\alpha]_D^{23}$ –32.2 (*c* 1.0 in $CHCl_3$);

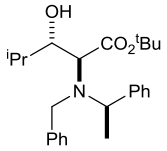
ν_{max} (ATR) 3498 (O−H), 1716 (C=O); δ_H (400 MHz, $CDCl_3$) 0.77 (3H, d, *J* 6.7, C(4)*Me*$_A$), 1.14 (3H, d, *J* 6.7, C(4)*Me*$_B$), 1.35 (3H, d, *J* 7.0, C(α)*Me*), 1.52 (9H, s, C*Me*$_3$), 2.07 (1H, d septet, *J* 9.8, 6.7, C(4)*H*), 2.91 (1H, app d, *J* 2.9, O*H*), 3.18 (1H, app d, *J* 9.8, C(3)*H*), 3.60 (1H, d, *J* 15.7, NC*H*$_A$H$_B$Ph), 3.68 (1H, app d, *J* 2.9 C(2)*H*), 3.91 (1H, q, *J* 7.0, C(α)*H*), 4.32 (1H, d, *J* 15.7, NCH$_A$*H*$_B$Ph), 7.18–7.57 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.0 (C(4)*Me*$_A$), 20.9 (C(α)*Me*), 22.3 (C(4)*Me*$_B$), 27.8 (*C*(4)), 28.1 (C*Me*$_3$), 52.0 (N*C*H$_2$Ph), 58.1 (*C*(α)), 64.1 (*C*(3)), 70.9 (*C*(2)), 82.8 (*C*Me$_3$), 126.4, 127.1, 128.0, 128.4, 128.4, 128.6 (*o,m,p-Ph*), 142.5, 142.5 (*i-Ph*), 175.4 (*C*(1)); *m*/*z* (ESI$^+$) 398 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{35}NNaO_3^+$ ([M+Na]$^+$) requires 420.2509; found 420.2513.

tert-Butyl (2*S*,3*S*, α*R*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-hydroxybutanoate 320



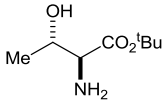
Tf_2O (94 μL, 0.564 mmol) was added to a stirred solution of **209** (100 mg, 0.282 mmol, >99:1 dr) and 2,6-di-*tert*-butyl-4-methyl pyridine (232 mg, 1.13 mmol) in CH_2Cl_2 (0.6 mL) at 0 °C and the resultant solution was stirred at rt for 6 h. H_2O (52 μL, 1.8 mmol) was then added and the resultant mixture was stirred at rt for 24 h. H_2O (2 mL) was then added and the resultant mixture was extracted with CH_2Cl_2 (3 × 4 mL). The combined organic extracts were then dried and concentrated *in vacuo*. Et_2O (20 mL) was added and the resultant mixture was filtered and the filtrate was concentrated *in vacuo* to give 79:21 mixture of **320** and **209**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave **209** as a white solid (21 mg, 21%, >99:1 dr). Further elution gave **320** as a colourless oil (72 mg, 72%, >99:1 dr); $[\alpha]_D^{23}$ −52.6 (*c* 1.0 in MeOH); ν_{max} (ATR) 3475 (O−H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 0.97 (3H, d, *J* 6.4, C(4)*H*$_3$), 1.38, (3H, d, *J* 6.9, C(α)*Me*), 1.53 (9H, s, C*Me*$_3$), 2.25 (1H, br s, O*H*), 3.06 (1H, d, *J* 8.6, C(2)*H*), 3.82 (1H, d, *J* 14.2, NC*H*$_A$H$_B$Ph), 3.85–3.94 (1H, m, C(3)*H*), 4.99 (1H, d, *J* 14.2, NC*H*$_A$H$_B$Ph), 4.04 (1H, q, *J* 6.9, C(α)*H*), 7.14–7.31 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.3 (C(α)*Me*), 20.3 (*C*(4)), 28.3 (C*Me*$_3$), 52.3 (N*C*H$_2$Ph), 57.1 (*C*(α)), 65.7 (*C*(2)), 67.4 (*C*(3)), 81.6 (*C*Me$_3$), 127.0, 127.0, 128.1, 128.1, 128.3, 129.1 (*o,m,p-Ph*), 140.2, 143.7 (*i-Ph*), 173.6 (*C*(1)); *m*/*z* (ESI$^+$) 370 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{31}NNaO_3^+$ ([M+Na]$^+$) requires 392.2196; found 392.2197.

tert-Butyl (2*S*,3*S*,α*R*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-hydroxy-4-methylpentanoate 321



Tf_2O (32 μL, 0.189 mmol) was added to a stirred solution of **319** (50 mg, 0.126 mmol, >99:1 dr) and 2,6-di-*tert*-butyl-4-methyl pyridine (78 mg, 0.378 mmol) in CH_2Cl_2 (0.6 mL) at 0 °C and the resultant solution was stirred at rt for 6 h. H_2O (26 μL, 7.2 mmol) was then added and the resultant mixture was stirred at rt for 24 h. H_2O (1 mL) was then added and the resultant mixture was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic extracts were dried and concentrated *in vacuo*. Et_2O (10 mL) was added and the resultant mixture was filtered and the filtrate was concentrated *in vacuo* to give a 92:8 mixture of **321** and **319**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave **321** as a colourless oil (34 mg, 68%, >99:1 dr); $[\alpha]_D^{23}$ –38.3 (*c* 1.0 in MeOH); ν_{max} (ATR) 3540 (O−H), 1707 (C=O); δ_H (700 MHz, $CDCl_3$) 0.18 (3H, d, *J* 7.0, C(4)*Me*$_A$), 0.71 (3H, d, *J* 7.0, C(4)*Me*$_B$), 1.35 (3H, d, *J* 6.9, C(α)*Me*), 1.50 (9H, s, C*Me*$_3$), 1.84 (1H, d septet, *J* 7.0, 2.6, C(4)*H*), 1.90 (1H, app d, *J* 6.0, O*H*), 3.17 (1H, d, *J* 8.6, C(2)*H*), 3.53–3.58 (1H, m, C(3)*H*) 3.79, (1H, d, *J* 14.2, NC*H*$_A$H$_B$Ph), 4.01 (1H, q, *J* 6.9, C(α)*H*), 4.05 (1H, d, *J* 14.2, NCH$_A$*H*$_B$Ph), 7.11–7.27 (10H, m, *Ph*); δ_C (176 MHz, $CDCl_3$) 12.6 (C(α)Me), 12.9, 19.2 (C(4)*Me*$_2$), 27.2 (C*Me*$_3$), 27.3 (*C*(4)), 50.9 (N*C*H$_2$Ph), 55.9 (*C*(α)Me), 60.4 (*C*(2)), 74.6 (*C*(3)), 80.4 (*C*Me$_3$), 125.9, 125.9, 127.0, 127.2, 127.2, 128.1 (*o*,*m*,*p*-*Ph*), 139.4, 142.5 (*i*-*Ph*), 172.8 (*C*(1)); *m*/*z* (ESI$^+$) 398 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{35}NNaO_3^+$ ([M+Na]$^+$) requires 420.2509; found 420.2516.

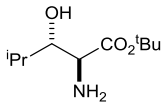
tert-Butyl (*S*,*S*)-2-amino-3-hydroxybutanoate 322



$Pd(OH)_2$/C (12 mg, 20% w/w) was added to a degassed mixture of **320** (60 mg, 0.162 mmol, >99:1 dr) in MeOH (1 mL) and the resultant mixture was placed under at atmosphere of H_2 (5 atm) and stirred at rt for 24 h, then filtered through Celite® (eluent MeOH) and concentrated *in vacuo* to give **322** as a colourless oil (20 mg, 71%, >99:1 dr);[26] $[\alpha]_D^{20}$ +7.1 (*c* 1.0 in $CHCl_3$); lit.[26] $[\alpha]_D^{28}$ +8.7 (*c* 0.18 in $CHCl_3$, 99% ee); ν_{max} (ATR) 3368 (O−H, N−H), 1728 (C=O); δ_H (400 MHz, MeOD) 1.03 (3H, d, *J* 6.4, C(4)*H*$_3$), 1.38 (9H, s, C*Me*$_3$), 3.28 (1H, d, *J* 4.2,

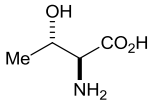
C(2)*H*), 3.88 (1H, qd, *J* 6.4, 4.2, C(3)*H*); δ_C (100 MHz, MeOD) 16.8 (*C*(4)), 26.7 (C*Me*$_3$), 60.0 (*C*(2)), 68.4 (*C*(3)), 81.2 (*C*Me$_3$), 174.6 (*C*(1)); *m*/*z* (ESI$^+$) 176 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_8H_8NO_3^+$ ([M+H]$^+$) requires 176.1281; found 176.1285

. ***tert*-Butyl (*S*,*S*)-2-amino-3-hydroxy-4-methylpentanoate 323**



$Pd(OH)_2$/C (9 mg, 20% w/w) was added to a degassed mixture of **321** (43 mg, 0.108 mmol, >99:1 dr) in MeOH (1 mL) and the resultant mixture was placed under an atmosphere of H_2 (5 atm) and stirred at rt for 24 h, then filtered through Celite® (eluent MeOH) and concentrated *in vacuo* to give **323** as a colourless oil (22 mg, quant, >99:1 dr); mp 68.0–73.5 °C; $[\alpha]_D^{23}$+14.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3361 (O−H, N−H), 1729 (C=O); δ_H (500 MHz, $CDCl_3$) 0.97 (3H, d, *J* 6.7, C(4)*Me*$_A$), 0.99 (3H, d, *J* 6.7, C(4)*Me*$_B$), 1.49 (9H, s, C*Me*$_3$), 1.80 (1H, septet, *J* 6.7, C(4)*H*), 2.62 (3H, br s, N*H*$_2$, O*H*), 3.38–3.46 (1H, m, C(3)*H*), 3.49–3.59 (1H, m, C(2)*H*); δ_C (125 MHz, $CDCl_3$) 18.7, 19.9 (C(4)*Me*$_2$), 28.5 (C*Me*$_3$), 31.3 (*C*(4)), 57.5 (*C*(2)), 78.9 (*C*(3)), 82.5 (*C*Me$_3$), 173.7 (*C*(1)); *m*/*z* (ESI$^+$) 204 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{10}H_{21}NNaO_3^+$ ([M+Na]$^+$) requires 226.1414; found 226.1420.

(*S*,*S*)-2-amino-3-hydroxybutanoic acid *ent*-64

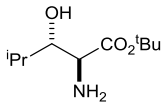


Method A: A stirred solution of **322** (20 mg, 0.114 mmol, >99:1 dr) in 6.0 M aq HCl (1 mL) was heated at 90 °C for 24 h, then concentrated *in vacuo*. H_2O (4 mL) and $CHCl_3$ (3 mL) were added, the layers separated and the aqueous layer was washed with $CHCl_3$ (2 × 3 mL) then concentrated *in vacuo*. Purification via ion exchange chromatography (DOWEX 50WX8-200, eluent 1.0 M aq NH_4OH) gave *ent*-**64** as a white solid (8 mg, 57%, 97:3 dr).

Method B: A solution of **322** (21 mg, 0.120 mmol, >99:1 dr) in 6.0 M aq HCl (1 mL) was stirred at rt for 3 h, then concentrated *in vacuo*. H_2O (4 mL) and $CHCl_3$ (3 mL) were added, the layers separated and the aqueous layer was washed with $CHCl_3$ (2 × 3 mL) then concentrated *in vacuo*. Purification via ion exchange chromatography (DOWEX 50WX8-200, eluent 1.0 M aq NH_4OH) gave *ent*-**64** as a white solid (9 mg, 64%, 97:3 dr);[27] mp 215–225 °C dec.; $[\alpha]_D^{20}$ +7.6 (*c* 1.0 in H_2O); {lit.[27] $[\alpha]_D^{25}$ +8.0 (*c* 1.1 in H_2O)}; ν_{max} (ATR) 3091 (O−H, N−H), 1626 (C=O); δ_H (500 MHz, D_2O) 1.11 (3H, d, *J* 6.6, C(4)*H*$_3$), 3.75 (1H, d, *J* 4.0,

C(2)*H*), 4.27 (1H, qd, *J* 6.6, 4.0, C(3)*H*); δ_C (125 MHz, D_2O) 16.6 (*C*(4)), 59.7 (*C*(2)), 65.3 (*C*(3)), 171.8 (*C*(1)); *m*/*z* (ESI^+) 212 ($[M+H]^+$, 100%); HRMS 120 (ESI^+) $C_4H_9NNaO_3^+$ ($[M+Na]^+$) requires 142.0475; found 142.0473.

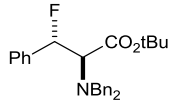
(*S*,*S*)-2-amino-3-hydroxy-4-methylpentanoic acid 324



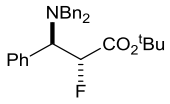
A solution of **323** (22 mg, 0.114 mmol, >99:1 dr) in 6.0 M aq HCl (1 mL) was stirred at rt for 3 h, then concentrated *in vacuo*. H_2O (4 mL) and $CHCl_3$ (3 mL) were added, and the aqueous layer was washed with $CHCl_3$ (2 × 3 mL), then concentrated *in vacuo*. Purification via ion exchange chromatography (DOWEX 50WX8-200, eluent 1.0 M aq NH_4OH) gave **324** as a white solid (11 mg, 69%, 94:6 dr);[27] mp 220–226 °C dec.; $[\alpha]_D^{20}$ +17.6 (*c* 1.0 in H_2O); {lit.[27] $[\alpha]_D^{25}$ +20 (*c* 1.1 in H_2O)}; ν_{max} (ATR) 3449, 3058 (O−H, N−H), 1627 (C=O); δ_H (500 MHz, D_2O) 0.89 (3H, d, *J* 6.7, C(4)*Me*$_A$), 0.90 (3H, d, *J* 6.7, C(4)*Me*$_B$), 1.87 (1H, d septet, *J* 9.1, 6.7, C(4)*H*), 3.46 (1H, dd, *J* 9.1, 3.2, C(3)*H*), 3.84 (1H, d, *J* 3.2, C(2)*H*); δ_C (125 MHz, $CDCl_3$) 18.5, 18.5 (C(4)*Me*$_2$), 30.2 (*C*(4)), 57.1 (*C*(2)), 76.1 (*C*(3)), 171.7 (*C*(1)); *m*/*z* (ESI^+) 148 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_6H_{13}NNaO_3^+$ ($[M+Na]^+$) requires 170.0788; found 170.0788.

6.4. Experimental for Chapter 4

tert-Butyl (*RS,SR*)-2-dibenzylamino-3-fluoro-3-phenylpropanoate 356 and *tert*-Butyl (*RS,SR*)-2-fluoro-3-dibenzylamino-3-phenylpropanoate 357



356



357

Method A: DAST **334** (7 μmL, 0.053 mmol) was added to a stirred solution of **248** (20 mg, 0.048 mmol, >99:1 dr) in THF (0.96 mL) at 0 °C and the resultant solution was stirred at 0 °C for 1h, then stirred at rt for 1 h and then cooled to −78 °C. MeOH (0.1 mL) was added and the resultant solution was allowed to warm to rt. H_2O (2 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (2 × 3 mL), dried and concentrated *in vacuo* to give a 69:31 mixture of **357** and **356**, respectively (25 mg, quant). Selected data for **357**: δ_H (400MHz, $CDCl_3$) 1.28 (9H, s, C*Me*$_3$), 3.50 (2H, d, *J* 13.7, N(C*H*$_A$H$_B$Ph)$_2$), 3.85 (2H, d, *J* 13.7, N(CH$_A$*H*$_B$Ph)$_2$), 4.25 (1H, dd, *J* 30.4, 4.1, C(3)*H*), 5.48 (1H, dd, *J* 49.5, 4.1, C(2)*H*), 6.95–7.46 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.7 (C*Me*$_3$), 54.8 (2 × *C*H$_2$Ph), 62.7 (d, *J* 19.1, *C*(3)), 82.6 (*C*Me$_3$), 90.0 (d, J, 192.6, *C*(2)), 127.0, 128.3, 128.8, 128.2, 128.9, 129.6 (*o,m,p-Ph*), 134.8, 139.4, (*i-Ph*), 167.7 (d, *J* 22.9, *C*(1)).

Method B: DAST **334** (7 μmL, 0.053 mmol) was added to a stirred solution of **248** (20 mg, 0.048 mmol, >99:1 dr) in CH_2Cl_2 (0.96 mL) at 0 °C and the resultant solution was stirred at 0 °C for 1h, then stirred at rt for 1 h and then cooled to −78 °C. MeOH (0.1 mL) was added and the resultant solution was allowed to warm to rt. H_2O (2 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (2 × 3 mL), dried and concentrated *in vacuo* to give a 80:20 mixture of **356** and **357**, respectively (24 mg, quant).

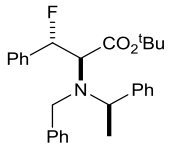
Method C: $Et_3N{\cdot}3HF$ (78 μL, 0.48 mmol) was added to a stirred solution of **248** (100 mg, 0.240 mmol, >99:1 dr) and XtalFluor-E® **336** (82 mg, 0.360 mmol) in CH_2Cl_2 (0.57 mL) at rt and the resultant solution was stirred at rt for 2 h. 5% aq $NaHCO_3$ solution (0.5 mL) was added and the resultant mixture was stirred at rt for 15 min, then extracted with CH_2Cl_2 (2 × 2 mL). The combined organic extracts were dried, then filtered through a pad of silica and concentrated *in vacuo* to give **356** as a white solid (95 mg, 94%, >99:1 dr); mp 70.0–74.5 °C; ν_{max} (ATR) 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.55 (9H, s, C*Me*$_3$), 3.39 (2H, d, *J* 13.9, N(C*H*$_A$H$_B$Ph)$_2$), 3.59 (1H, dd, *J* 11.0, 9.6, C(2)*H*), 3.78 (2H, d, *J* 13.9, N(CH$_A$*H*$_B$Ph)$_2$), 5.69 (1H, dd, *J* 45.6, 9.6, C(3)*H*), 6.83–7.38 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.5 (C*Me*$_3$), 54.0 (N(*C*H$_2$Ph)$_2$), 63.8 (d, *J* 33.4, *C*(2)), 81.1 (*C*Me$_3$), 91.7 (d, *J* 168.8, *C*(3)), 126.1, 127.1,

127.9 (*o,m,p-Ph*), 126.8 (d, *J* 5.7, *C*(2'), *C*(6')), 127.1 (*C*(3'), *C*(5')), 128.0 (*C*(4')), 135.7 (d, *J* 18.1, *C*(1')), 137.4 (*i-Ph*), 168.1 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −175.2 (C(3)*F*); *m*/*z* (ESI^+) 442 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{27}H_{30}FNNaO_2^+$ ($[M+Na]^+$) requires 442.2153; found 442.2141.

Method D: XtalFluor-E® **336** (41 mg, 0.180 mmol) was added to **248** (50 mg, 0.120 mmol, >99:1 dr) in CH_2Cl_2 (0.275 mL) at rt and the resultant solution was stirred at rt for 2 h. 5% aq $NaHCO_3$ solution (0.3 mL) was added and the resultant mixture was stirred for 15 min, then extracted with CH_2Cl_2 (2 × 1 mL). The combined organic extracts were dried, then filtered through a pad of silica and concentrated *in vacuo* to give a 55:43:2 mixture of **261**, **356** and **260**, respectively.

Method E: Ms_2O (25 mg, 0.144 mmol) was added to a stirred solution of **248** (20 mg, 0.048 mmol, >99:1 dr), and Et_3N (29 μL, 0.216 mmol) in CH_2Cl_2 (0.18 mL) and the resultant solution was stirred at rt for 1 h. $Et_3N{\cdot}3HF$ (24 μL, 0.144 mmol) was added and the resultant solution was stirred at rt for 24 h. 5% aq $NaHCO_3$ solution (0.25 mL) was added and the resultant mixture was stirred at rt for 15 min, then extracted with CH_2Cl_2 (2 × 2 mL). The combined organic extracts were washed sequentially with 1.0 M aq HCl (3 mL), satd aq $NaHCO_3$ (3 mL) and brine (3 mL), then dried and concentrated *in vacuo* to give a 68:32 mixture of **356** and **357**, respectively (28 mg, quant).

tert-Butyl (2*R*,3*S*,α*R*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-fluoro-3-phenylpropanoate 358

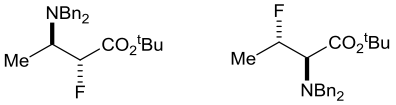


Method A (From **208**): $Et_3N{\cdot}3HF$ (304 μL, 1.85 mmol) was added to a stirred solution of **208** (400 mg, 0.927 mmol, >99:1 dr) and XtalFluor-E® **336** (318 mg, 1.39 mmol) in CH_2Cl_2 (0.615 mL) at rt and the resultant solution was stirred at rt for 2 h. 5% aq $NaHCO_3$ solution (1 mL) was added and the resultant mixture was stirred at rt for 15 min, then extracted with CH_2Cl_2 (2 × 3 mL). The combined organic extracts were dried, then filtered through a pad of silica and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 40:1) gave **358** as a white solid (326 mg, 81%, >99:1 dr); mp 65.0–71.0 °C; ν_{max} (ATR) 1726 (C=O); $[\alpha]_D^{20}$ −11.1 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.41 (3H, d, *J* 6.9, C(α)*Me*), 1.59 (9H, s, C*Me*$_3$), 3.75 (1H, dd, *J* 11.2, 9.0, C(2)*H*), 3.94 (1H, q, *J* 6.9,

C(α)*H*), 4.04 (1H, d, *J* 14.7, NC*H*$_A$H$_B$Ph), 4.27 (1H, d, *J* 14.7, NCH$_A$*H*$_B$Ph), 5.67 (1H, dd, *J* 45.7, 9.0, C(3)*H*), 6.94–7.40 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.6 (α*Me*), 28.1 (C*Me*$_3$), 51.6 (N*C*H$_2$Ph), 56.0 (*C*(α)), 62.9 (d, *J* 32.4, *C*(2)), 81.6 (*C*Me$_3$), 94.1 (d, *J* 170.7, *C*(3)), 126.7, 127.0, (*p-Ph*), 127.7 (d, *J* 5.7, *C*(2'), *C*(6')), 127.9, 128.1, 128.1, 128.2, 128.8, 128.9 (*C*(3'), *C*(4'), *C*(5'), *o,m-Ph*), 137.8 (d, *J* 18.1, *C*(1')), 139.7, 142.4 (*i-Ph*), 171.7 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −175.6 (C(3)*F*); *m*/*z* (ESI$^+$) 456 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{32}FNNaO_2^+$ ([M+Na]$^+$) requires 456.2309; found 456.2305.

Method B (From **274**): $Et_3N{\cdot}3HF$ (47 μL, 0.292 mmol) was added to a stirred solution of **274** (63 mg, 0.146 mmol, >99:1 dr) and XtalFluor-E® **336** (50 mg, 0.219 mmol) in CH_2Cl_2 (0.250 mL) at rt and the resultant solution was stirred at rt for 2 h. 5% aq $NaHCO_3$ solution (0.5 mL) was added and the resultant mixture was stirred at rt for 15 min, then extracted with CH_2Cl_2 (2 × 1.5 mL). The combined organic extracts were dried, then filtered through a pad of silica and concentrated *in vacuo* to give **358** as a white solid (47 mg, 75%, >99:1 dr).

tert-Butyl (*RS*,*RS*)-2-fluoro-3-dibenzylamino-butanoate 360 and *tert*-Butyl (*RS*,*SR*)-2-dibenzylamino-3-fluoro-butanoate 361



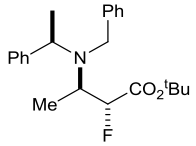
360 **361**

Method A: $Et_3N{\cdot}3HF$ (46 μL, 0.23 mmol) was added to a stirred solution of **252** (50 mg, 0.141 mmol, >99:1 dr) and XtalFluor-E® **336** (48 mg, 0.211 mmol) in CH_2Cl_2 (0.330 mL) at rt and the resultant solution was stirred at rt for 2 h. 5% aq $NaHCO_3$ solution (0.5 mL) was added and the resultant mixture was stirred at rt for 15 min, then extracted with CH_2Cl_2 (2 × 2 mL). The combined organic extracts were dried, then filtered through a pad of silica and concentrated *in vacuo* to give an 80:20 mixture of **360** and **361**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 30:1) gave **361** as a colourless oil (7 mg, 14%, >99:1 dr); ν_{max} (ATR) 1752 (C=O); δ_H (400 MHz, $CDCl_3$) 1.37 (3H, dd, *J* 24.8, 6.3, C(4)*H*$_3$), 1.60 (9H, s, C*Me*$_3$), 3.20 (1H, dd, *J* 10.6, 8.7, C(2)*H*), 3.52 (2H, d, *J* 13.7, N(C*H*$_A$H$_B$Ph)$_2$), 3.92 (2H, d, *J* 13.7, N(CH$_A$*H*$_B$Ph)$_2$), 5.03 (1H, ddq, 46.7, 8.7, 6.3, C(3)*H*), 7.23–7.39 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.6 (d, *J* 21.9, *C*(4)), 28.5 (C*Me*$_3$), 55.4 (N(*C*H$_2$Ph)$_2$), 65.6 (d, *J* 27.7, *C*(2)), 81.8 (*C*Me$_3$), 89.0 (d, *J* 165.9, *C*(3)), 127.3, 128.4, 128.9 (*o,m,p-Ph*), 138.9 (*i-Ph*), 169.3 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −181.7 (C(2)*F*); *m*/*z* (ESI$^+$) 358 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{29}FNO_2^+$ ([M+H]$^+$) requires 358.2177; found 358.2172.

Further elution gave **360** as a colourless oil (18 mg, 34%, >99:1 dr); ν_{max} (ATR) 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 1.16 (3H, dd, *J* 7.1, 7.0, C(4)H_3), 1.40 (9H, s, CMe_3), 3.27 (1H, ddq, *J* 26.5, 6.9, 2.4, C(3)*H*), 3.62 (2H, d, *J* 14.0, N(C$H_A$$H_B$Ph)$_2$), 3.77 (2H, d, *J* 14.0, N($H_A$$H_B$Ph)$_2$), 5.14 (1H, dd, 50.8, 2.4, C(2)*H*), 7.21–7.39 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 9.0 (d, *J* 5.2, *C*(4)), 26.9 (CMe_3), 53.3 (N(*C*H_2Ph)$_2$), 53.6 (d, *J* 19.1, *C*(3)), 81.3 (*C*Me_3), 88.7 (d, *J* 188.8, *C*(2)), 125.9, 127.2, 127.7 (*o*,*m*,*p*-*Ph*), 138.7 (*i*-*Ph*), 167.4 (d, *J* 24.8, *C*(1)); δ_F (377 MHz, $CDCl_3$) −200.5 (C(3)*F*); *m*/*z* (ESI$^+$) 358 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{29}FNO_2^+$ ([M+H]$^+$) requires 358.2177; found 358.2170. A 93:7 mixture of **360** and **361**, respectively, was also isolated (13 mg, 26%).

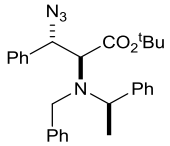
Method B: $Et_3N{\cdot}3HF$ (47 μL, 0.29 mmol) was added to a stirred solution of **264** (52 mg, 0.146 mmol, >99:1 dr) and XtalFluor-E® **336** (50 mg, 0.219 mmol) in CH_2Cl_2 (0.330 mL) at rt and the resultant solution was stirred at rt for 2 h. 5% aq $NaHCO_3$ solution (0.5 mL) was added and the resultant mixture was stirred at rt for 15 min, then extracted with CH_2Cl_2 (2 × 2 mL). The combined organic extracts were dried, then filtered through a pad of silica and concentrated *in vacuo* to give an 80:20 mixture of **360** and **361**, respectively (56 mg, quant).

tert-Butyl (2*R*,3*R*,α*R*)-2-fluoro-3-[*N*-benzyl-*N*(α-methylbenzyl)amino]-butanoate 362



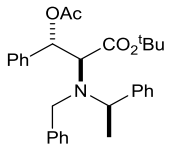
$Et_3N{\cdot}3HF$ (45 μL, 0.274 mmol) was added to a stirred solution of **209** (50 mg, 0.137 mmol, >99:1 dr) and XtalFluor-E® **336** (47 mg, 0.205 mmol) in CH_2Cl_2 (0.300 mL) at rt and the resultant solution was stirred at rt for 2 h. 5% aq $NaHCO_3$ solution (0.5 mL) was added and the resultant mixture was stirred at rt for 15 min, then extracted with CH_2Cl_2 (2 × 2 mL). The combined organic extracts were dried, then filtered through a pad of silica and concentrated *in vacuo* to give a 80:29 mixture of **362** and **363**, respectively (54 mg, quant). Selected data for **362**: δ_H (400 MHz, $CDCl_3$) 1.17 (3H, d, *J* 7.0, C(4)H_3), 1.35 (3H, d, *J* 6.9, C(α)*Me*), 1.40 (9H, s, CMe_3), 3.41 (1H, app dq, *J* 30.4, 7.0, C(3)*H*), 3.86 (1H, d, *J* 15.0, NC$H_A$$H_B$Ph), 3.96–4.03 (2H, m, NC$H_A$$H_B$Ph, C(α)*H*), 4.67 (1H, app d, 50.8, C(2)*H*), 7.21–7.49 (10H, m, *Ph*).[28]

tert-Butyl (2*S*,3*S*,α*R*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-azido-3-phenylpropanoate 368



XtalFluor-E® **336** (80 mg, 0.348 mmol) was added to a stirred solution of **208** (100 mg, 0.232 mmol, >99:1 dr) and TMS-N_3 (113 μL, 0.696 mmol) in CH_2Cl_2 (0.550 mL) at rt and the resultant mixture was stirred at rt for 2 h. 5% aq $NaHCO_3$ (1 mL) was added and the reaction mixture was stirred for 15 min, then extracted with CH_2Cl_2 (2 × 2 mL). The combined organic extracts were dried, then filtered through a pad of silica and concentrated *in vacuo* to give an 80:12:8 mixture of **358**, **366** and **367**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 40:1) gave **368** as a white solid (61 mg, 58%, >99:1 dr); mp 92.5–98.5 °C; $[\alpha]_D^{20}$ +60.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2102 ($N^-=N^+=N-$); 1722 (C=O); δ_H (500 MHz, $CDCl_3$) 1.38 (3H, d, *J* 6.7, *Me*), 1.65 (9H, s, C*Me*$_3$), 3.59 (1H, d, *J* 10.8, C(2)*H*), 3.87 (1H, d, *J* 14.3, NC*H*$_A$H$_B$Ph), 3.89 (1H, q, *J* 6.7, C(α)*H*), 4.13 (1H, d, *J* 14.3, NCH$_A$*H*$_B$Ph), 4.79 (1H, d, *J* 10.8, C(3)*H*), 6.76–7.41 (15H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 13.3 (C(α)*Me*), 28.2 (C*Me*$_3$), 50.8 (N*C*H$_2$Ph), 55.7 (*C*(α)), 62.3 (d, *C*(2)), 66.5 (*C*(3)), 81.9 (*C*Me$_3$), 126.8, 127.0 (*p-Ph*), 127.9, 128.1, 128.4, 128.5 (*o,m-Ph*), 128.5 (*p-Ph*), 128.7, 129.0 (*o,m-Ph*), 136.2, 139.3, 142.1 (*i-Ph*), 172.3 (*C*(1)); *m/z* (ESI$^+$) 457 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{33}N_4O_2^+$ ([M+Na]$^+$) requires 457.2598; found 457.25850.

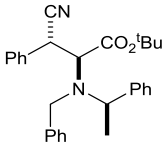
tert-Butyl (2*S*,3*S*,α*R*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-acetoxy-3-phenylpropanoate 369



XtalFluor-E® **336** (80 mg, 0.348 mmol) was added to a stirred solution of **208** (100 mg, 0.232 mmol, >99:1 dr) and TMS-OAc (87 μL, 0.580 mmol) in CH_2Cl_2 (0.550 mL) at rt and the resultant mixture was stirred at rt for 2 h. 5% aq $NaHCO_3$ (1 mL) was added and the reaction mixture was stirred for 15 min, then extracted with CH_2Cl_2 (2 × 2 mL). The combined organic extracts were dried, then filtered through a pad of silica and concentrated *in vacuo* to give a 76:24 mixture of **369** and **358**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 7:1) gave **358** as a white solid (18 mg, 18%, >99:1 dr). Futher elution gave **369** as a white solid (45 mg, 41%, >99:1 dr); mp 101.5–106.0 °C; $[\alpha]_D^{20}$ +8.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1744, 1725 (C=O); δ_H (500 MHz, $CDCl_3$) 1.29 (3H, d, *J* 6.9,

C(α)*Me*), 1.49 (9H, s, C*Me*$_3$), 1.82 (3H, s, *Me*), 3.67 (1H, d, *J* 10.4, C(2)*H*), 3.83 (1H, d, *J* 14.3, NC*H*$_A$H$_B$Ph), 3.84 (1H, q, *J* 6.9, C(α)*H*), 4.12 (1H, d, *J* 14.3, NCH$_A$*H*$_B$Ph), 5.99 (1H, d, *J* 10.4, C(3)*H*), 6.82–7.20 (15H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 12.4 (C(α)*Me*), 21.0 (*Me*), 28.1 (C*Me*$_3$), 51.1 (NC*H*$_2$Ph), 55.5 (*C*(α)), 62.6 (*C*(2)), 74.8 (*C*(3)), 81.3 (*C*Me$_3$), 125.3, 126.7, 127.0 (*p-Ph*), 127.9, 128.0, 128.1, 128.2, 128.8, 129.0 (*o,m-Ph*), 137.2, 139.4, 142.3 (*i-Ph*), 169.3 (*C*=O), 171.9 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −175.6 (C(3)*F*); *m*/*z* (ESI$^+$) 474 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{36}NO_4^+$ ([M+H]$^+$) requires 474.2639; found 474.2639.

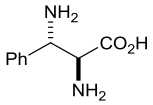
tert-Butyl (*S*,*S*,α*R*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-cyano-3-phenylpropanoate 370



Method A: XtalFluor-E® **336** (159 mg, 0.695 mmol) was added to a stirred solution of **208** (200 mg, 0.463 mmol, >99:1 dr) and TMS-CN (173 μL, 1.39 mmol) in CH_2Cl_2 (1.10 mL) at rt and the resultant mixture was stirred at rt for 2 h. 5% aq $NaHCO_3$ (1 mL) was added and the reaction mixture was stirred for 15 min, then extracted with CH_2Cl_2 (2 × 2 mL). The combined organic extracts were dried, then filtered through a pad of silica and concentrated *in vacuo* to give a complex mixture of products.

Method B: XtalFluor-E® **336** (159 mg, 0.695 mmol) was added to a stirred solution of **208** (200 mg, 0.463 mmol, >99:1 dr) and TMS-CN (93 μL, 0.741 mmol) in CH_2Cl_2 (1.10 mL) at rt and the resultant mixture was stirred at rt for 2 h. 5% aq $NaHCO_3$ (1 mL) was added and the reaction mixture was stirred for 15 min, then extracted with CH_2Cl_2 (2 × 2 mL). The combined organic extracts were dried, then filtered through a pad of silica and concentrated *in vacuo* to give a complex mixture of products.

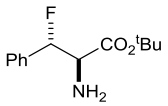
(*S*,*S*)-2,3-Diamino-3-phenylpropanoic acid 372



$Pd(OH)_2$/C (14 mg, 25% w/w) was added to a degassed mixture of **368** (70 mg, 0.153 mmol, >99:1 dr) in MeOH (1 mL) and the resultant mixture was placed under an atmosphere of H_2 (5 atm) and stirred at rt for 48 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was redissolved in $CHCl_3$ (4 mL) and extracted with 1.0 M aq HCl (4 × 3 mL), then concentrated *in vacuo*. Purification via ion

exchange chromatography (DOWEX 50WX8-200, eluent 1.0 M aq NH_4OH) gave **372** as a white solid (22 mg, 82%, >99:1 dr);[29] mp 205–213 °C; {lit.[29] mp 192–193 °C}; $[\alpha]_D^{20}$ +6.0 (*c* 0.3 in H_2O); $[\alpha]_D^{20}$ −7.2 (*c* 0.42 in 6N HCl); {lit.[29,30] $[\alpha]_D^{23}$ for *ent*-**372** –8.0 (*c* 0.65, 6N HCl)}; ν_{max} (ATR) 1604 (C=O); δ_H (500 MHz, D_2O) 3.79 (1H, d, *J* 6.9, C(2)*H*), 4.42 (1H, d, *J* 6.9, C(3)*H*), 7.31–7.44 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 56.1 (*C*(2)), 58.3 (*C*(3)), 127.3 (*p*-*Ph*), 129.2, 129.9 (*o*,*m*-*Ph*), 135.3 (*i*-*Ph*), 175.0 (*C*(1)); *m*/*z* (ESI^+) 181 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_9H_{13}N_2O_2^+$ ($[M+Na]^+$) requires 181.0972; found 181.0973.

tert-Butyl (2*R*,3*S*)-2-amino-3-fluoro-3-phenylpropanoate 373

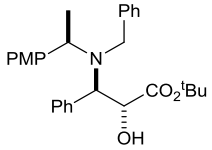


Method A: 10% Pd/C (4 mg, 15% w/w) was added to a degassed mixture of **358** (25 mg, 0.06 mmol, >99:1 dr) in EtOH (0.2 mL) at rt. The reaction mixture was saturated with H_2 (1 atm) then stirred under H_2 pressure at rt for 2 h. The reaction mixture was filtered through Celite® (eluent MeOH) and concentrated *in vacuo* to give starting material **358**.

Method B: 10% Pd/C (5 mg, 15% w/w) was added to a degassed mixture of **358** (31 mg, 0.07 mmol, >99:1 dr) in MeOH (0.5 mL) at rt. The reaction mixture was saturated with H_2 (1 atm) then stirred under H_2 pressure at rt for 2 h. The reaction mixture was filtered through Celite® (eluent MeOH) and concentrated *in vacuo* to give starting material **358**.

Method C: 10% Pd/C (5 mg, 15% w/w) was added to a degassed mixture of **358** (31 mg, 0.07 mmol, >99:1 dr) in MeOH (0.5 mL) at rt. The reaction mixture was saturated with H_2 (1 atm) then stirred under H_2 pressure at rt for 15 h. The reaction mixture was filtered through Celite® (eluent MeOH) and concentrated *in vacuo* to give a complex mixture of products.

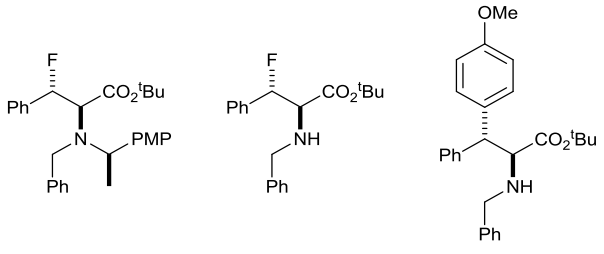
tert-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methyl-4''-methoxybenzyl)amino]-3-phenylpropanoate 376



BuLi (2.3 M in hexanes, 3.26 mL, 7.50 mmol) was added dropwise to a stirred solution of (*R*)-**374** (1.89 g, 7.83 mmol, 99% ee)[31] in THF (20 mL) at −78 °C and stirring was continued at –78 °C for 30 min. A solution of **206** (1.00 g, 4.90 mmol, >99:1 dr) in THF (20 mL) was then added via cannula and the resultant mixture was stirred at −78 °C for 2 h. (−)-CSO **202**

(1.89 g, 8.23 mmol) was then added and stirring was continued as the reaction mixture was allowed to warm to rt over 15 h. Satd aq NH_4Cl (2 mL) was added and the reaction mixture was stirred at rt for 5 min then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and 10% aq citric acid (20 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (40 mL) and brine (40 mL), then dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (10 mL), the insoluble CSO residues were filtered off, and the filter cake was washed with Et_2O (2 × 20 mL). The filtrate was concentrated *in vacuo* and the process was repeated. Purification via flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 10:1) gave **376** as a yellow oil (1.38 g, 62%, >99:1 dr); ν_{max} (ATR) 3495 (O−H), 1722 (C=O); $[\alpha]_D^{20}$ +13.9 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.21 (3H, d, *J* 6.7, C(α)*Me*), 1.23 (9H, s, C*Me*$_3$), 2.77 (1H, br s, O*H*), 3.80 (1H, d, *J* 15.2, NC*H*$_A$H$_B$Ph), 3.83 (3H, s, O*Me*), 4.14 (1H, d, *J* 15.2, NCH$_A$*H*$_B$Ph), 4.17 (1H, q, *J* 6.7, C(α)*H*), 4.23 (1H, d, *J* 3.0, C(3)*H*), 4.39 (1H, d, *J*, 3.0, C(2)*H*), 6.86–7.57 (14H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.0 (C(α)*Me*), 27.7 (C*Me*$_3$), 52.2 (N*C*H$_2$Ph), 53.3 (O*Me*), 56.6 (*C*(α)), 65.8 (*C*(3)), 73.4 (*C*(2)), 82.2 (*C*Me$_3$), 113.5 (C(3"), C(5")), 126.7, 127.6, 128.0, 128.0, 128.3, 129.1, 129.9 (C(2"), C(6"), *o,m,p-Ph*), 136.1 (*C*(1")), 138.4, 141.9 (*i-Ph*), 158.5 (C(4")), 172.1 (*C*(1)); *m/z* (ESI$^+$) 462 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{36}NO_3^+$ ([M+H]$^+$) requires 462.2639; found 462.2624.

tert-Butyl (2*R*,3*S*,α*R*)-2-[*N*-benzyl-*N*(α-methyl-4''-methoxybenzyl)amino]-3-fluoro-3-phenylpropanoate 377 and _tert_-Butyl (2*R*,3*S*)-2-*N*-benzyl-3-fluoro-3-phenylpropanoate 378 and _tert_-Butyl (2*RS*,3*R*)-2-*N*-benzyl-3-fluoro-3-(4''-methoxy)phenyl-3-phenylpropanoate 379

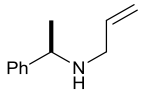


377 **378** **379**

$Et_3N{\cdot}3HF$ (141 μL, 0.866 mmol) was added to a stirred solution of **376** (200 mg, 0.433 mmol) and XtalFluor-E® **336** (149 mg, 0.650 mmol) in CH_2Cl_2 (1.4 mL) at rt and the resultant solution was stirred at rt for 2 h. 5% aq $NaHCO_3$ solution (1 mL) was added and the resultant mixture was stirred at rt for 15 min, then extracted with CH_2Cl_2 (2 × 2 mL). The combined organic extracts were dried, then filtered through a pad of silica and concentrated *in vacuo* to give a 13:60:27 mixture of **377**, **378** and **379**, respectively. Purification via flash column

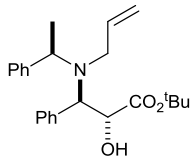
chromatography (eluent 30–40 °C petrol/Et_2O, 15:1) gave **377** as a colourless oil (22 mg, 11%, 84% purity); ν_{max} (ATR) 1725 (C=O); $[\alpha]_D^{20}$ −2.6 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.36 (3H, d, *J* 6.8, C(α)*Me*), 1.57 (9H, s, C*Me*$_3$), 3.73 (1H, dd, *J* 10.7, 9.0, C(2)*H*), 3.82 (3H, s, O*Me*), 3.85 (1H, q, *J* 6.8, C(α)*H*), 3.98 (1H, d, *J* 14.6, NC*H*$_A$H$_B$Ph), 4.24 (1H, d, *J* 14.6, NCH$_A$*H*$_B$Ph), 5.63 (1H, dd, *J* 45.6, 9.0, C(3)*H*), 6.71 (2H, d, *J* 8.7, C(3")*H*, C(5")*H*), 6.88 (2H, d, *J* 8.7, C(2")*H*, C(6")*H*), 6.97 (2H, d, *J* 7.9, C(2')*H*, C(6')*H*), 7.10-7.40 (8H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 11.5 (C(α)*Me*), 27.1 (C*Me*$_3$), 50.4 (N*C*H$_2$Ph), 54.3 (O*Me*), 59.6 (*C*(α)), 61.7 (d, *J* 31.5, *C*(2)), 80.5 (*C*Me$_3$), 93.0 (d, *J*, 169.8, *C*(3)), 112.2 (*C*(3"), *C*(5")), 126.7 (d, *J* 5.7, *C*(2'), *C*(6')), 128.1 (*C*(2"), *C*(6")), 125.9, 127.0, 127.2, 127.8, 127.8 (*C*(3'), *C*(4'), *C*(5'), *o,m,p-Ph*), 133.4 (*C*(1")), 135.8 (d, *J* 19.1, *C*(1')), 138.8 (*i-Ph*), 157.3 (*C*(4")), 170.8 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −175.2 (C(3)*F*); *m*/*z* (ESI$^+$) 486 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{34}FNNaO_3^+$ ([M+Na]$^+$) requires 486.2415; found 486.2409. Further elution gave **378** as a colourless oil (49 mg, 35%); ν_{max} (ATR) 1728 (C=O); $[\alpha]_D^{20}$ −10.9 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.41 (9H, s, C*Me*$_3$), 3.58 (1H, dd, *J* 16.1, 5.8 C(2)*H*), 3.68 (1H, d, *J* 13.2, NC*H*$_A$H$_B$Ph), 3.86 (1H, d, *J* 13.2, NCH$_A$*H*$_B$Ph), 5.62 (1H, dd, *J* 45.9, 5.8 C(3)*H*), 7.21–7.41 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 28.0 (C*Me*$_3$), 52.0 (N*C*H$_2$Ph), 65.7 (d, *J* 24.8, *C*(2)), 82.0 (*C*Me$_3$), 94.2 (d, *J*, 177.4, *C*(3)), 126.2 (d, *J* 7.6, *C*(2'), *C*(6')), 127.1, 128.2, 128.2, 128.4, 128.5 (*C*(3'), *C*(4'), *C*(5'), *o,m,p-Ph*), 136.9 (d, *J* 20.0, *C*(1')), 139.4 (*i-Ph*), 170.9 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −186.0 (C(3)*F*); *m*/*z* (ESI$^+$) 330 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{25}FNO_2^+$ ([M+H]$^+$) requires 330.1864; found 330.1859. Further elution gave **379** as a yellow oil (31 mg, 17%); ν_{max} (ATR) 1722 (C=O); $[\alpha]_D^{20}$ −10.7 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.21 (9H, s, C*Me*$_3$), 1.78 (1H, br s, N*H*), 3.63 (1H, d, *J* 13.3, NC*H*$_A$H$_B$Ph), 3.78 (3H, s, O*Me*), 3.84 (1H, d, *J* 9.7 C(2)*H*), 3.86 (1H, d, *J* 13.3, NCH$_A$*H*$_B$Ph), 4.10 (1H, d, *J* 9.7, C(3)*H*), 6.80 (2H, d, *J* 8.7, C(3")*H*, C(5")*H*), 7.15 (2H, d, *J* 8.7, C(2")*H*, C(6")*H*), 7.13–7.33 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 26.7 (C*Me*$_3$), 51.0 (N*C*H$_2$Ph), 53.1 (*C*(3)), 54.2 (O*Me*), 63.8 (*C*(2)), 82.0 (*C*Me$_3$), 112.8 (C(3"), C(5")), 127.2, 127.2 (*C*(2'), *C*(6'), *C*(2"), *C*(6")), 125.5, 126.0, 127.5, 127.5, 128.4 (*C*(3'), *C*(5'), *o,m,p-Ph*), 132.4 (*C*(1")), 138.6 (*i-Ph*), 140.9 (*C*(1')), 157.2 (C(4")), 172.3 (*C*(1)); *m*/*z* (ESI$^+$) 418 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{32}NO_3^+$ ([M+H]$^+$) requires 418.2377; found 418.2367.

(*R*)-*N*-Allyl-*N*-(α-methylbenzyl)amine 388



BuLi (2.2 M in hexanes, 198 mL, 0.436 mol) was added dropwise to a stirred solution of (*R*)-*N*-(α-methylbenzyl)amine (58.0 mL, 0.456 mol, 99% ee) in THF (800 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 1 h. Allyl bromide (38.9 mL, 0.447 mol) was added dropwise over 30 min and the resultant mixture was stirred at 0 °C for 2 h. Satd aq NH_4Cl (200 mL) and brine (200 mL) were then added, the aqueous layer was extracted with EtOAc (3 × 200 mL), and the combined organic extracts were dried and concentrated *in vacuo*. Purification by flash column chromatography (eluent Et_2O/30–40 °C petrol, 7:3) gave **388** as a pale yellow oil (45.6 g, 62%, 99% ee);[32,33] $[\alpha]_D^{22}$ +64.3 (*c* 1.0 in $CHCl_3$); {lit.[32] $[\alpha]_D^{22}$ +63.0 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.40 (3H, d, *J* 6.6, C(α)*Me*), 1.52 (1H, br s, N*H*), 3.13 (2H, app d, *J* 5.7, C(1)H_2), 3.84 (1H, q, *J* 6.6, C(α)*H*), 5.10 (1H, dd, *J* 10.2, 1.5 C(3)H_A), 5.16 (1H, dd, *J* 17.1, 1.5, C(3)H_B), 5.92 (1H, dddd, *J* 17.1, 10.2, 6.1, 5.7, C(2)*H*), 7.25–7.39 (5H, m, *Ph*).

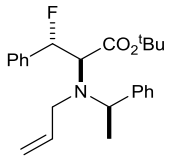
***tert*-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-allyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 390**



BuLi (2.3 M in hexanes, 4.95 mL, 11.4 mmol) was added dropwise to a stirred solution of (*R*)-**388** (1.89 g, 11.8 mmol, 99% ee)[34] in THF (30 mL) at −78 °C and stirring was continued at –78 °C for 30 min. A solution of **206** (1.50 g, 7.34 mmol, >99:1 dr) in THF (30 mL) was then added via cannula and the resultant mixture was stirred at −78 °C for 2 h. (−)-CSO **202** (2.86 g, 12.5 mmol) was then added and stirring was continued as the reaction mixture was allowed to warm to rt over 15 h. Satd aq NH_4Cl (5 mL) was added and the reaction mixture was stirred at rt for 5 min then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (30 mL) and 10% aq citric acid (30 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (40 mL) and brine (40 mL), then dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (10 mL), the insoluble CSO residues were filtered off, and the filter cake was washed with Et_2O (2 × 20 mL). The filtrate was concentrated *in vacuo* and the process was repeated. Purification via flash column chromatography (eluent 30–40 ºC petrol/Et_2O,

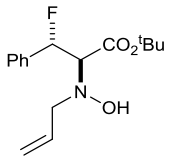
10:1) gave **390** as a pale yellow oil (2.03 g, 73%, >99:1 dr); ν_{max} (ATR) 3498 (O−H), 1723 (C=O); $[\alpha]_D^{20}$ +4.5 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.18 (3H, d, *J* 6.8, C(α)*Me*), 1.26 (9H, s, C*Me*$_3$), 2.96 (1H, br s, O*H*), 3.23 (1H, dd, *J* 15.6, 7.2, C(1')H_A), 3.44 (1H, dd, *J* 15.6, 5.3, C(1')H_B), 4.11 (1H, q, *J* 6.8, C(α)*H*), 4.21 (1H, d, *J* 3.5, C(3)*H*), 4.51 (1H, d, *J* 3.5, C(2)*H*), 5.01 (1H, dd, *J* 10.2, 1.3, C(3')H_A), 5.10 (1H, dd, *J* 17.2, 1.3, C(3')H_B), 5.87 (1H, dddd, *J* 17.2, 10.2, 7.2, 5.3, C(2')*H*), 7.16–7.50 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.9 (C(α)*Me*), 27.9 (C*Me*$_3$), 50.7 (*C*(1')), 56.7 (*C*(α)), 66.0 (*C*(3)), 72.5 (*C*(2)), 82.2 (*C*Me$_3$), 115.8 (*C*(3')), 126.7, 127.8, 127.8, 128.1, 128.2, 129.7 (*o,m,p-Ph*), 139.0 (*C*(2')), 137.9, 144.3 (*i-Ph*), 172.1 (*C*(1)); *m*/*z* (ESI^+) 382 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{24}H_{32}NO_3^+$ ($[M+H]^+$) requires 382.2377; found 382.2365.

tert-Butyl (2*R*,3*S*,*αR*)-2-[*N*-allyl-*N*-(α-methylbenzyl)amino]-3-fluoro-3-phenylpropanoate 391



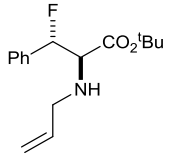
$Et_3N{\cdot}3HF$ (256 μL, 1.57 mmol) was added to a stirred solution of **390** (300 mg, 0.786 mmol, >99:1 dr) and XtalFluor-E® **366** (270 mg, 1.18 mmol) in CH_2Cl_2 (1.6 mL) at rt and the resultant solution was stirred at rt for 2 h. 5% aq $NaHCO_3$ solution (1 mL) was added and the resultant mixture was stirred for 15 min, then extracted with CH_2Cl_2 (2 × 3 mL). The combined organic extracts were dried, then filtered through a pad of silica and concentrated *in vacuo* to give a 98:2 mixture of **391** and **392**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 40:1) gave **391** as a pale yellow oil (289 mg, 96%, >99:1 dr); ν_{max} (ATR) 1726 (C=O), 1143 (C−F); $[\alpha]_D^{20}$ +46.7 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.33 (3H, d, *J* 6.8, C(α)*Me*), 1.54 (9H, s, C*Me*$_3$), 3.42 (1H, dd, *J* 15.0, 8.0, C(1')H_A), 3.63 (1H, dd, *J* 9.9, 9.0, C(2)*H*), 3.69 (1H, dd, *J* 15.0, 4.6, C(1')H_B), 4.05 (1H, q, *J* 6.8, C(α)*H*), 5.10 (1H, dd, *J* 10.1, 1.0, C(3')H_A), 5.16 (1H, dd, *J* 17.2, 1.0, C(3')H_B), 5.59 (1H, dd, *J* 45.4, 9.0, C(3)*H*), 5.66 (1H, dddd, *J* 17.2, 10.1, 8.0, 4.6, C(2')*H*), 6.86–7.35 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.2 (C(α)*Me*), 28.1 (C*Me*$_3$), 50.8 (*C*(1')), 56.6 (*C*(α)), 63.6 (d, *J* 32.4, *C*(2)), 81.5 (*C*Me$_3$), 93.6 (d, *J* 171.7, *C*(3)), 117.2 (*C*(3')), 126.4, 127.7, 127.9, 128.0, 128.5 (*C*(3''), *C*(4''), *C*(5''), *o,m,p-Ph*), 127.2 (d, *J* 6.7, *C*(2''), *C*(6'')), 137.4 (*C*(2')), 137.4 (d, *J* 19.0, *C*(1'')), 142.9 (*i-Ph*), 172.1 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −178.9 (C(3)*F*); *m*/*z* (FI^+) 383 ($[M]^+$, 100%); HRMS (ESI^+) $C_{24}H_{30}FNO_2^+$ ($[M]^+$) requires 383.2255; found 383.2263.

tert-Butyl (2*R*,3*S*)-2-[*N*-allyl-*N*-hydroxyamino]-3-fluoro-3-phenylpropanoate 393



Phosphate buffer (13 μL) added to a stirred solution of **391** (50 mg, 0.130 mmol, >99:1 dr) and mCPBA (52%, 54 mg, 0.163 mmol) in CH_2Cl_2/HFIP (v/v, 1:1, 1.3 mL) at rt and the resultant solution was stirred at rt for 15 min. Satd aq Na_2SO_3 (0.5 mL) was then added and the resultant mixture was extracted with $CHCl_3$ (2 × 2 mL). The combined organic extracts were washed with 0.1% $NaHCO_3$ (2 mL), the aqueous layer was extracted with CH_2Cl_2 (2 × 2 mL) and the combined extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 3:1 then increased to 1:1) gave **393** as a pale yellow oil (5 mg, 13%, >99:1 dr); ν_{max} (ATR) 3423 (O−H), 1736 (C=O), 1152 (N−O); $[\alpha]_D^{20}$ +26.4 (*c* 0.33 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.51 (9H, s, C*Me*$_3$), 3.45 (1H, dd, *J* 13.6, 6.9, C(1')*H*$_A$), 3.56 (1H, dd, *J* 13.6, 6.0, C(1')*H*$_B$), 3.75 (1H, dd, *J* 12.0, 7.4, C(2)*H*), 5.15–5.21 (2H, m, C(3')*H*$_2$), 5.77 (1H, dddd, *J* 17.0, 10.2, 6.9, 6.0, C(2')*H*), 5.84 (1H, br s, NO*H*), 5.96 (1H, dd, *J* 45.9, 7.4, C(3)*H*), 7.33–7.45 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 27.1 (C*Me*$_3$), 60.1 (*C*(1')), 70.8 (d, *J* 28.6, *C*(2)), 82.0 (*C*Me$_3$), 90.9 (d, *J* 172.6, *C*(3)), 118.0 (C(3')), 125.4 (d, *J* 6.7, *C*(2''), *C*(6'')), 127.7, 128.3 (*C*(3''), *C*(4''), *C*(5'')), 132.1 (*C*(2')), 136.5 (d, *J* 19.1, *C*(1'')), 168.3 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −184.4 (C(3)*F*); *m*/*z* (ESI^+) 318 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{16}H_{22}FNNaO_3^+$ ($[M+Na]^+$) requires 318.1476; found 318.1475.

tert-Butyl (2*R*,3*S*)-2-[*N*-allyl-amino]-3-fluoro-3-phenylpropanoate 394



Method A – Step 1: Phosphate buffer (10 μL) was added to a stirred solution of **391** (40 mg, 0.104 mmol, >99:1 dr) and *m*CPBA (52%, 43 mg, 0.130 mmol) in CH_2Cl_2/HFIP (1:1, 1 mL) at rt and the resultant solution was stirred at rt for 15 min. Satd aq Na_2SO_3 (0.5 mL) was then added and the resultant mixture was extracted with $CHCl_3$ (2 × 2 mL). The combined organic extracts were washed with 0.1% $NaHCO_3$ (2 mL), the aqueous layer was extracted with CH_2Cl_2 (2 × 2 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **393**.

Method A – Step 2: Zn (272 mg, 4.16 mmol) was added to a stirred solution of **393** in AcOH/THF/H_2O (3:1:1, 8 mL) at rt and the resultant mixture was heated at 70 °C for 2 h. Satd aq $NaHCO_3$ (3 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 3 mL). The combined organics were washed with brine, then dried over Na_2SO_4 and concentrated *in vacuo* to give a complex mixture of products.

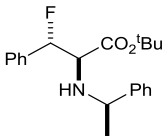
Method B – Step 1: Phosphate buffer (13 μL) was added to a stirred solution of **391** (50 mg, 0.130 mmol, >99:1 dr) and *m*CPBA (52%, 54 mg, 0.163 mmol) in CH_2Cl_2/HFIP (1:1, 1.3 mL) at rt and the resultant solution was stirred at rt for 15 min. Satd aq Na_2SO_3 (0.5 mL) was then added and the resultant mixture was extracted with $CHCl_3$ (2 × 2 mL). The combined organic extracts were washed with 0.1% $NaHCO_3$ (2 mL), the aqueous layer was extracted with CH_2Cl_2 (2 × 2 mL) and the combined extracts were dried and concentrated *in vacuo* to give **393**.

Method B – Step 2: CS_2 (0.15 mL, 2.49 mmol) was added to a stirred solution of **393** in MeCN (0.5 mL) at rt and the resultant mixture was stirred at rt for 20 h, then concentrated *in vacuo* to give returned starting material **393**.

Method C – Step 1: Phosphate buffer (15 μL) was added to a stirred solution of **391** (51 mg, 0.116 mmol, >99:1 dr) and *m*CPBA (52%, 48 mg, 0.145 mmol) in CH_2Cl_2/HFIP (1:1, 1.2 mL) at rt and the resultant solution was stirred at rt for 15 min. Satd aq Na_2SO_3 (0.5 mL) was then added and the resultant mixture was extracted with $CHCl_3$ (2 × 2 mL). The combined organic extracts were washed with 0.1% $NaHCO_3$ (2 mL), the aqueous layer was extracted with CH_2Cl_2 (2 × 2 mL) and the combined extracts were dried and concentrated *in vacuo* to give **393**.

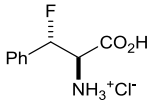
Method C – Step 2: In powder (16 mg, 0.145 mmol) was added to a stirred solution of **393** in EtOH/satd aq NH_4Cl (2:1, 0.70 mL) at rt and the resultant mixture was heated at 83 °C for 18 h. The reaction mixture was filtered throught Celite® (eluent EtOH) and concentrated *in vacuo*. The residue was partitioned between satd aq Na_2CO_3 (2 mL) and EtOAc (2 mL), the aqueous layer extracted with EtOAc (2 × 2 mL) and the combines organic extracts dried over Na_2SO_4 and concentrated *in vacuo* to give returned starting material **393**.

tert-Butyl (2*R*,3*S*,α*R*)-2-[*N*-(α-methylbenzyl)amino]-3-fluoro-3-phenylpropanoate 395



N,*N*-Dimethylbarbituric acid (100 mg, 0.782 mmol) was added to a stirred solution of **391** (93 mg, 0.261 mmol, >99:1 dr) in CH_2Cl_2 (2.3 mL) and the resultant solution was degassed with N_2. $Pd(PPh_3)_4$ (3 mg, 3 mmol, 1 mol%) was then added and the resultant mixture was stirred at rt for 18 h in the dark, befor being concentrated *in vacuo*. The residue was dissolved in Et_2O (3 mL) and washed with satd aq K_2CO_3 (2 × 2 mL). The aqueous layer was extracted with Et_2O (5 mL) and the combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 8:1, 1% Et_3N) gave **395** as an orange oil (35 mg, 39%, >99:1 dr); ν_{max} (ATR) 3372 (N−H), 1729 (C=O); $[\alpha]_D^{20}$ +46.7 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.19 (3H, d, *J* 6.6, C(α)*Me*), 1.22 (9H, s, C*Me*$_3$), 2.03 (1H, br s, N*H*), 3.50 (1H, dd, *J* 15.4, 5.7, C(2)*H*), 3.65 (1H, q, *J* 6.6, C(α)*H*), 5.52 (1H, dd, *J* 45.9, 5.7, C(3)*H*), 7.12–7.31 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 23.2 (C(α)*Me*), 27.9 (C*Me*$_3$), 56.5 (*C*(α)), 64.1 (d, *J* 25.7, *C*(2)), 81.7 (*C*Me$_3$), 94.3 (d, *J* 178.2, *C*(3)), 126.3 (d, *J* 7.3, *C*(2'), *C*(6')), 126.8, 127.2, 128.1, 128.5 (C(4'), *o*,*m*,*p*-*Ph*), 128.4 (d, *J* 1.5, *C*(3'), *C*(5')), 137.2 (d, *J*, 19.8, *C*(1')), 145.2 (*i*-*Ph*), 170.8 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −185.7 (C(3)*F*); *m*/*z* (ESI$^+$) 344 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{27}FNO_2^+$ ([M+H]$^+$) requires 344.2020; found 344.2015.

(2*R*,3*S*)-2-Amino-3-fluoro-3-phenylpropanoic acid hydrochloride 396·HCl

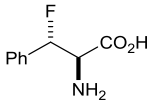


Method A: A solution of $NaBrO_3$ (40 mg, 0.262 mmol) in H_2O (0.870 mL) was added to a stirred solution of **395** (30 mg, 87 μmol, >99:1 dr) in EtOAc (1.2 mL) at rt and the resultant mixture was stirred at rt for 10 min. A solution of $Na_2S_2O_4$ (38 mg, 0.218 mmol) in H_2O (1.6 mL) was added dropwise at rt over 5 min and the resultant mixture was stirred at rt for 1 h. EtOAc (4 mL) was added and the resultant mixture was washed with satd aq $Na_2S_2O_3$ (4 mL). The aqueous layer was extracted with EtOAc (2 × 3 mL) and the combined organic extracts were washed with brine (5 mL), then dried over Na_2SO_3 and concentrated *in vacuo*. The residue was redissolved in CH_2Cl_2 (5 mL) and the resultant solution was washed with 1.0 M aq HCl (3 × 4 mL). The combined aqueous layers were concentrated *in vacuo* to give

396·HCl as a white solid (9 mg, 47%, >99:1 dr); mp 329 °C dec.; ν_{max} (ATR) 1738 (C=O), 1219 (C−F); $[\alpha]_D^{20}$ +2.6 (*c* 0.5 in H_2O); δ_H (400 MHz, MeOD) 4.60 (1H, dd, *J* 18.6, 3.3, C(2)*H*), 6.10 (1H, dd, *J* 44.3, 3.3, C(3)*H*), 7.29–7.39 (5H, m, *Ph*); δ_C (100 MHz, MeOD) 57.2 (d, *J* 24.9, *C*(2)), 90.6 (d, *J* 180.5, *C*(3)), 125.2 (d, *J* 8.1, *C*(2'), *C*(6')), 129.2 (*C*(3'), *C*(5')), 128.5 (*C*(4')), 133.5 (d, *J* 21.3, *C*(1')), 166.1 (d, *J* 8.1, *C*(1)); δ_F (377 MHz, MeOD) −191.6 (C(3)*F*); *m*/*z* (ESI^+) 184 ($[M-Cl]^+$, 100%); HRMS (ESI^+) $C_9H_{11}FNO_2^+$ ($[M-Cl]^+$) requires 184.0768; found 184.0770.

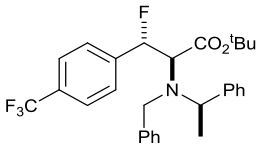
Method B: A solution of $NaBrO_3$ (157 mg, 1.04 mmol) in H_2O (3.47 mL) was added to a stirred solution of **358** (150 mg, 0.346 mmol, >99:1 dr) in EtOAc (4.8 mL) at rt and the resultant mixture was stirred at rt for 10 min. A solution of $Na_2S_2O_4$ (151 mg, 0.865 mmol) in H_2O (6.34 mL) was added dropwise at rt over 15 min and the resultant mixture was stirred at rt for 4 h. EtOAc (8 mL) was added and the resultant mixture was washed with satd aq $Na_2S_2O_3$ (5 mL). The aqueous layer was extracted with EtOAc (2 × 4 mL) and the combined organic extracts were washed with brine (10 mL), then dried over Na_2SO_3 and concentrated *in vacuo*. The residue was redissolved in CH_2Cl_2 (10 mL) and the resultant solution was washed with 1.0 M aq HCl (3 × 8 mL). The combined aqueous layers were concentrated *in vacuo* to give **396**·HCl as a white solid (50 mg, 66%, >99:1 dr).

(2*R*,3*S*)-2-Amino-3-fluoro-3-phenylpropanoic acid 396

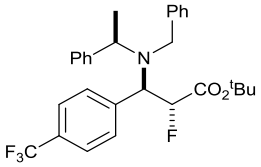


Propylene oxide (30 μL, 0.546 mmol) was added to a stirred solution of **396**·HCl (30 mg, 0.137 mmol, >99:1 dr) in ^{i}PrOH (0.685 mL) and the resultant mixture was stirred at rt for 6 h, then concentrated *in vacuo* to give **396** as a white solid (20 mg, 80%, >99:1 dr); mp 171.7–174.0 °C; {lit.[35] mp 170–171 °C}; ν_{max} (ATR) 1608 (C=O), 1030 (C−F); $[\alpha]_D^{20}$ +14.4 (*c* 0.5 in H_2O), −13.3 (c 0.3 in MeOH); {lit.[36,37] $[\alpha]_D^{23}$ for *ent*-**396** −14.5 (*c* 0.4, MeOH)}; δ_H (500 MHz, D_2O) 4.31 (1H, dd, *J* 16.2, 3.3, C(2)*H*), 6.13 (1H, dd, *J* 43.7, 3.3, C(3)*H*), 7.29–7.39 (5H, m, *Ph*); δ_C (100 MHz, D_2O) 59.1 (d, *J* 21.9, *C*(2)), 91.5 (d, *J* 178.3, *C*(3)), 125.3 (d, *J* 8.6, *C*(2'), *C*(6')), 128.9 (*C*(3'), *C*(5')), 129.5 (*C*(4')), 133.2 (d, *J* 21.0, *C*(1')), 169.3 (d, *J* 9.5, *C*(1)); δ_F (377 MHz, D_2O) −188.3 (C(3)*F*); *m*/*z* (ESI^+) 184 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_9H_{11}FNO_2^+$ ($[M+H]^+$) requires 184.0768; found 184.0767.

tert-Butyl (2*R*,3*S*,α*R*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-fluoro-3-[4'-(trifluoromethyl)phenyl]propanoate 397 and _tert_-Butyl (*R*,*R*,*R*)-2-fluoro-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-[4'-(trifluoromethyl)phenyl]propanoate 402



397

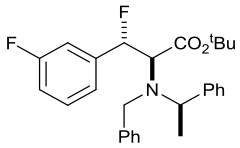


402

$Et_3N{\cdot}3HF$ (39 μL, 0.240 mmol) was added to a stirred solution of **287** (60 mg, 0.120 mmol, >99:1 dr) and XtalFluor-E® **336** (41 mg, 0.180 mmol) in CH_2Cl_2 (0.360 mL) at rt and the resultant solution was stirred at rt for 2 h. 5% aq $NaHCO_3$ solution (0.5 mL) was added and the resultant mixture was stirred at rt for 15 min, then extracted with CH_2Cl_2 (2 × 2 mL). The combined organic extracts were dried, then filtered through a pad of silica and concentrated *in vacuo* to give 91:9 mixture of **397** and **402**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 40:1) gave **397** as a colourless oil (51 mg, 85%, >99:1 dr); ν_{max} (ATR) 1728 (C=O), 1325 (CF_3), 1128 (C−F); $[\alpha]_D^{20}$ −7.6 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.41 (3H, d, *J* 6.9, C(α)*Me*), 1.59 (9H, s, C*Me*$_3$), 3.74 (1H, dd, *J* 11.0, 8.8, C(2)*H*), 3.96 (1H, q, *J* 6.9, C(α)*H*), 4.01 (1H, d, *J* 14.5, NCH_AH_BPh), 4.31 (1H, d, *J* 14.5, NCH_AH_BPh), 5.67 (1H, dd, *J* 45.6, 8.8, C(3)*H*), 6.95–7.48 (14H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 11.5 (C(α)*Me*), 27.0 (C*Me*$_3$), 50.8 (N*C*H_2Ph), 55.1 (*C*(α)), 62.2 (d, *J* 31.5, *C*(2)), 80.9 (*C*Me$_3$), 92.0 (d, *J* 173.6, *C*(3)), 123.0 (q, *J* 272.1, *C*F_3), 123.9 (q, *J* 3.8, *C*(3'), *C*(5')), 125.8, 126.2 (*p-Ph*), 126.6 (d, *J* 6.7, *C*(2'), *C*(6')), 126.9, 127.0, 127.3, 127.8 (*o,m-Ph*), 129.6 (q, *J* 32.4, *C*(4')), 138.3 (*i-Ph*), 139.9 (d, *J* 19.1, *C*(1')), 141.1 (*i-Ph*), 169.9 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −178.7 (C(3)*F*), −62.6 (C*F*$_3$); *m*/*z* (ESI^+) 502 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{29}H_{32}F_4NO_2^+$ ($[M+H]^+$) requires 502.2364; found 502.2355. Further elution gave **402** as a colourless oil (5 mg, 8%, >99:1 dr); ν_{max} (ATR) 1754 (C=O), 1326 (CF_3), 1126 (C−F); $[\alpha]_D^{20}$ −8.6 (*c* 0.5 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.21 (9H, s, C*Me*$_3$), 1.24 (3H, d, *J* 6.8, C(α)*Me*), 3.88 (1H, d, *J* 14.9, NCH_AH_BPh), 3.95 (1H, d, *J* 14.9, NCH_AH_BPh), 4.16 (1H, q, *J* 6.8, C(α)*H*), 4.45 (1H, dd, *J* 32.3, 2.6, C(3)*H*), 5.00 (1H, dd, *J* 49.3, 2.8, C(2)*H*), 7.19–7.62 (14H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 15.5 (C(α)*Me*), 26.6 (C*Me*$_3$), 51.0 (N*C*H_2Ph), 57.0 (*C*(α)), 61.8 (d, *J* 18.1, *C*(3)), 81.7 (*C*Me$_3$), 89.1 (d, *J* 196.5, *C*(2)), 123.1 (q, *J* 272.1, *C*F_3), 124.0 (q, *J* 3.8, *C*(3'), *C*(5')), 125.8, 126.3, 126.7, 126.9, 127.2, 127.4 (*o,m,p-Ph*), 128.8 (q, *J* 32.4, *C*(4')), 129.9 (d, *J* 2.8, *C*(2'), *C*(6')), 139.9 (*i-Ph*), 140.5 (*C*(1')), 142.3 (*i-Ph*), 166.3 (d, *J*

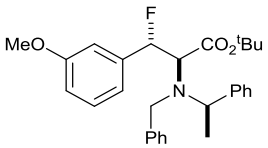
22.9, *C*(1)); δ_F (377 MHz, $CDCl_3$) −198.6 (C(2)*F*), −62.6 (CF_3); *m*/*z* (ESI^+) 502 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{29}H_{32}F_4NO_2^+$ ($[M+H]^+$) requires 502.2364; found 502.2359.

tert-Butyl (2*R*,3*S*,α*R*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-fluoro-3-(3'-fluorophenyl)propanoate 398



$Et_3N{\cdot}3HF$ (42 μL, 0.266 mmol) was added to a stirred solution of **288** (60 mg, 0.133 mmol, >99:1 dr) and XtalFluor-E® **336** (45 mg, 0.200 mmol) in CH_2Cl_2 (0.360 mL) at rt and the resultant solution was stirred at rt for 2 h. 5% aq $NaHCO_3$ solution (0.5 mL) was added and the resultant mixture was stirred at rt for 15 min, then extracted with CH_2Cl_2 (2 × 2 mL). The combined organic extracts were dried, then filtered through a pad of silica and concentrated *in vacuo* to give a 95:5 mixture of **398** and **403**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 40:1) gave **398** as a white solid (55 mg, 92%, >99:1 dr); mp 55.0–57.5 °C; ν_{max} (ATR) 1727 (C=O), 1144 (C−F); $[\alpha]_D^{20}$ −16.6 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.38 (3H, d, *J* 6.9, C(α)*Me*), 1.55 (9H, s, C*Me*$_3$), 3.66 (1H, dd, *J* 11.6, 8.7, C(2)*H*), 3.93 (1H, q, *J* 6.9, C(α)*H*), 3.99 (1H, d, *J* 14.5, NCH_AH_BPh), 4.25 (1H, d, *J* 14.5, NCH_AH_BPh), 5.59 (1H, dd, *J* 45.6, 8.7, C(3)*H*), 6.53 (1H, d, *J* 8.5, C(2')*H*), 6.74 (1H, d, *J* 8.5 C(6')*H*), 6.98–7.05 (3H, m, *Ar*, *Ph*), 7.16-7.31 (9H, m, *Ar*, *Ph*); δ_C (125 MHz, $CDCl_3$) 11.6 (C(α)*Me*), 27.0 (C*Me*$_3$), 50.7 (N*C*H_2Ph), 55.0 (*C*(α)), 62.0 (d, *J* 31.5, *C*(2)), 80.7 (*C*Me_3), 92.2 (d, *J* 173.6, *C*(3)), 113.2 (dd, *J* 22.5, 6.0, *C*(2')), 114.6 (dd, *J* 21.0, 1.9, *C*(4')), 122.4 (dd, *J* 5.7, 2.9, *C*(6')), 125.9, 126.1, 126.9, 126.9, 127.3, 127.8 (*o*,*m*,*p*-*Ph*), 128.5 (d, *J* 8.6, *C*(5')), 138.4 (dd, *J* 19.1, 7.6, *C*(1')), 138.5, 141.2 (*i*-*Ph*), 161.4 (d, *J* 246.1, *C*(3')), 170.2 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −177.2 (C(3)*F*), −112.9 (C(3')*F*); *m*/*z* (ESI^+) 452 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{28}H_{32}F_2NO_2^+$ ($[M+H]^+$) requires 452.2396; found 452.2390.

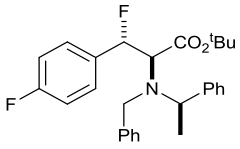
tert-Butyl (2*R*,3*S*,α*R*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-fluoro-3-(3'-methoxyphenyl)propanoate 399



$Et_3N{\cdot}3HF$ (42 μL, 0.260 mmol) was added to a stirred solution of **289** (60 mg, 0.130 mmol, >99:1 dr) and XtalFluor-E® **366** (45 mg, 0.195 mmol) in CH_2Cl_2 (0.360 mL) at rt and the resultant solution was stirred at rt for 2 h. 5% aq $NaHCO_3$ solution (0.5 mL) was added and

the resultant mixture was stirred at rt for 15 min, then extracted with CH_2Cl_2 (2 × 2 mL). The combined organic extracts were dried, then filtered through a pad of silica and concentrated *in vacuo* to give a 98:2 mixture of **399** and **404**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 40:1) gave **399** as a colourless oil (47 mg, 78%, >99:1 dr); ν_{max} (ATR) 1726 (C=O), 1143 (C−F); $[\alpha]_D^{20}$ −18.9 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.40 (3H, d, *J* 6.9, C(α)*Me*), 1.58 (9H, s, C*Me*$_3$), 3.67 (3H, s, O*Me*), 3.69 (1H, dd, *J* 19.7, 8.7, C(2)*H*), 3.95 (1H, q, *J* 6.9, C(α)*H*), 4.03 (1H, d, *J* 14.7, NC*H*$_A$H$_B$Ph), 4.30 (1H, d, *J* 14.7, NCH$_A$*H*$_B$Ph), 5.63 (1H, dd, *J* 45.6, 8.7, C(3)*H*), 6.45-6.49 (1H, m, *Ar*), 6.60 (1H, d, *J* 7.4, C(6')*H*), 6.91 (1H, d, *J* 8.4, C(4')*H*), 6.99-7.04 (2H, m, *Ar*, *Ph*), 7.15–7.32 (10H, m, *Ar*, *Ph*); δ_C (125 MHz, $CDCl_3$) 11.6 (C(α)*Me*), 27.1 (C*Me*$_3$), 50.6 (N*C*H$_2$Ph), 54.1 (O*Me*), 54.9 (*C*(α)), 62.4 (d, *J* 31.5, *C*(2)), 80.5 (*C*Me$_3$), 93.0 (d, *J* 171.7, *C*(3)), 110.6 (d, *J* 5.7, *C*(2')), 114.3 (d, *J* 2.9, *C*(4')), 118.9 (d, *J* 5.7, *C*(6')), 125.6, 126.0, 126.8, 127.0, 127.2, 127.8 (*o*,*m*,*p*-*Ph*), 128.0 (*C*(5')), 137.4 (d, *J* 19.1, *C*(1')), 138.7, 141.4 (*i*-*Ph*), 158.3 (*C*(3')), 170.5 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −177.2 (C(3)*F*); *m*/*z* (ESI$^+$) 464 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{35}FNO_3^+$ ([M+H]$^+$) requires 464.2595; found 464.2585.

tert-Butyl (2*R*,3*S*,α*R*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-fluoro-3-(4'-fluorophenyl)propanoate 400

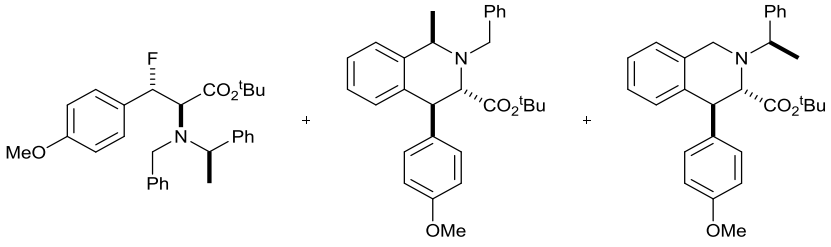


Method A: $Et_3N{\cdot}3HF$ (42 μL, 0.266 mmol) was added to a stirred solution of **290** (60 mg, 0.133 mmol, >99:1 dr) and XtalFluor-E® **336** (45 mg, 0.200 mmol) in CH_2Cl_2 (0.360 mL) at rt and the resultant solution was stirred at rt for 2 h. 5% aq $NaHCO_3$ solution (0.5 mL) was added and the resultant mixture was stirred at rt for 15 min, then extracted with CH_2Cl_2 (2 × 2 mL). The combined organic extracts were dried, then filtered through a pad of silica and concentrated *in vacuo* to give a 82:12:6 mixture of **400**, **410** and **414**, respectively.

Method B: $Et_3N{\cdot}3HF$ (42 μL, 0.266 mmol) was added to a stirred solution of **290** (60 mg, 0.133 mmol, >99:1 dr) and XtalFluor-E® **336** (45 mg, 0.200 mmol) in CH_2Cl_2 (0.360 mL) at rt and the resultant solution was stirred at rt for 2 h. 5% aq $NaHCO_3$ solution (0.5 mL) was added and the resultant mixture was stirred at rt for 15 min, then extracted with CH_2Cl_2 (2 × 2 mL). The combined organic extracts were dried, then filtered through a pad of silica and concentrated *in vacuo* to give an 89:7:4 mixture of **400**, **410** and **414**, respectively.

Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **400** as a white solid (43 mg, 72%, >99:1 dr); mp 56.5–61.0 °C; ν_{max} (ATR) 1727 (C=O), 1146 (C−F); $[\alpha]_D^{20}$ −3.6 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.39 (3H, d, *J* 6.9, C(α)*Me*), 1.59 (9H, s, C*Me*$_3$), 3.70 (1H, dd, *J* 9.9, 9.2, C(2)*H*), 3.92 (1H, q, *J* 6.9, C(α)*H*), 3.97 (1H, d, *J* 14.5, NC*H*$_A$H$_B$Ph), 4.22 (1H, d, *J* 14.5, NCH$_A$*H*$_B$Ph), 5.59 (1H, dd, *J* 45.4, 9.2, C(3)*H*), 6.83-6.93 (4H, m, *Ph*), 6.99 (2H, d, *J* 6.9, *C*(2'), *C*(6')), 7.12 (2H, d, *J* 6.9, C(3')*H*, C(5')*H*), 7.17-7.30 (6H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 11.5 (C(α)*Me*), 27.1 (C*Me*$_3$), 50.5 (N*C*H$_2$Ph), 55.0 (*C*(α)), 61.7 (d, *J* 33.4, *C*(2)), 80.7 (*C*Me$_3$), 92.2 (d, *J* 170.7, *C*(3)), 113.9 (d, *J* 21.9, *C*(3'), *C*(5')), 125.8, 126.1, 126.9, 127.1, 127.3, 127.8 (*o*,*m*,*p*-*Ph*), 128.5 (dd, *J* 8.1, 5.2, *C*(2'), *C*(6')), 131.6 (dd, *J* 19.1, 2.9, *C*(1')), 138.5, 141.2 (*i*-*Ph*), 162.1 (d, *J* 244.1, *C*(4')), 170.2 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −173.4 (C(3)*F*), −112.9 (C(4')*F*); *m*/*z* (ESI^+) 452 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{28}H_{32}F_2NO_2^+$ ($[M+H]^+$) requires 452.2396; found 452.2391.

tert-Butyl (2*R*,3*S*,α*R*)-2-[*N*-benzyl-*N*(α-methylbenzyl)amino]-3-fluoro-3-(4'-methoxyphenyl)propanoate 401, (1*R*,3*S*,4*S*)-1-methyl-2-benzyl-3-*tert*-butoxycarbonyl-4-(4'-methoxy)phenyl-1,2,3,4-tetrahydroisoquinoline 301 and (3*S*,4S,α*R*)-2-*N*-(α-methylbenzyl)-3-*tert*-butoxycarbonyl-4-(4'-methoxy)phenyl-1,2,3,4-tetrahydroisoquinoline 302



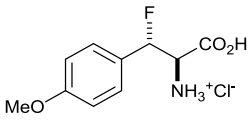
401 **301** **302**

Method A: $Et_3N{\cdot}3HF$ (42 μL, 0.260 mmol) was added to a stirred solution of **291** (60 mg, 0.130 mmol, >99:1 dr) and XtalFluor-E® (45 mg, 0.195 mmol) in CH_2Cl_2 (0.360 mL) at rt and the resultant solution was stirred at rt for 2 h. 5% aq $NaHCO_3$ solution (0.5 mL) was added and the resultant mixture was stirred at rt for 15 min, then extracted with CH_2Cl_2 (2 × 2 mL). The combined organic extracts were dried, then filtered through a pad of silica and concentrated *in vacuo* to give a 37:37:26 mixture of **401**, **301** and **302**, respectively.

Method B: $Et_3N{\cdot}3HF$ (64 μL, 0.531 mmol) was added to a stirred solution of **291** (500 mg, 1.08 mmol, >99:1 dr) and XtalFluor-E® (372 mg, 1.62 mmol) in CH_2Cl_2 (3 mL) at rt and the resultant solution was stirred at rt for 2 h. 5% aq $NaHCO_3$ solution (1.5 mL) was added and the resultant mixture was stirred at rt for 15 min, then extracted with CH_2Cl_2 (2 × 2 mL). The combined organic extracts were dried, then concentrated *in vacuo* to give a 80:12:8 mixture of

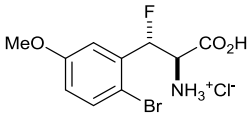
401, **301** and **302**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave an 68:32 mixture of **301** and **302**, respectively, as a brown oil (37 mg, 8%); ν_{max} (ATR) 1724 (C=O), 1150 (C−F); *m*/*z* (ESI^+) 444 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{29}H_{34}NO_3^+$ ($[M+H]^+$) requires 444.2533; found 444.2533. Data for **301**: δ_H (500 MHz, $CDCl_3$) 1.29 (9H, s, C*Me*$_3$), 1.47 (3H, d, *J* 6.6, C(1)*Me*), 3.72 (1H, d, *J* 3.7, C(3)*H*), 3.73 (O*Me*), 3.94 (1H, d, *J* 15.0, NC*H*$_A$H$_B$Ph), 3.98 (1H, d, *J* 15.0, NCH$_A$*H*$_B$Ph), 4.35 (1H, q, *J* 6.6, C(1)*H*), 4.45 (1H, d, *J* 3.7, C(4)*H*), 6.75–7.30 (13H, m, *Ar*, *Ph*); δ_C (125 MHz, $CDCl_3$) 23.2 (C(1)*Me*), 27.9 (C*Me*$_3$), 46.8 (*C*(4)), 54.9 (N*C*H$_2$Ph), 55.3 (O*Me*), 55.6 (*C*(1)), 64.3 (*C*(3)), 80.9 (*C*Me$_3$), 113.2 (*C*(3'), *C*(5')), 125.9 (*C*(6)), 126.5 (*C*(8)), 127.0 (*p-Ph*), 128.0, 128.0 (*o,m-Ph*), 128.3 (*C*(7)), 129.7 (*C*(5)), 129.9 (*C*(2'), *C*(6')), 134.3 (*C*(4a)), 136.1 (*C*(1')), 139.9 (*C*(1")), 140.9 (*C*(8a)), 158.0 (*C*(4')), 172.1 (*C*O$_2$^{t}Bu). Data for **302**: δ_H (500 MHz, $CDCl_3$) 1.18 (3H, d, *J* 6.6, C(α)*Me*), 1.40 (9H, s, C*Me*$_3$), 3.69 (1H, app s, C(1)*H*$_A$H$_B$), 3.73 (O*Me*), 3.77 (1H, app s, C(1)H$_A$*H*$_B$), 3.92 (1H, q, *J* 6.6, C(α)*H*), 3.94 (1H, d, *J* 2.4, C(3)*H*), 4.44 (1H, d, *J* 2.4, C(4)*H*), 6.75-7.30 (13H, m, *Ar*); δ_C (125 MHz, $CDCl_3$) 20.9 (C(α)*Me*), 28.1 (C*Me*$_3$), 47.1 (*C*(4)), 49.5 (*C*(1)), 55.2 (O*Me*), 61.9 (*C*(α)), 62.9 (*C*(3)), 81.1 (*C*Me$_3$), 113.2 (*C*(3'), *C*(5')), 125.9, 126.0, 126.0, 126.6, 126.7, 127.2, 128.2, 129.5 (*Ar*, *Ph*), 135.0, 135.3, 137.6, 146.2 (*Ar*, *i-Ph*), 158.1 (*C*(4')), 172.0 (*C*O$_2$^{t}Bu). Further elution gave **401** as a colourless oil (222 mg, 44%, >99:1 dr); ν_{max} (ATR) 1726 (C=O), 1144 (C−F); $[\alpha]_D^{20}$ + 9.3 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.39 (3H, d, *J* 6.9, C(α)*Me*), 1.59 (9H, s, C*Me*$_3$), 3.71 (1H, app t, *J* 9.5, C(2)*H*), 3.86 (3H, s, O*Me*), 3.90 (1H, q, *J* 6.9, C(α)*H*), 3.97 (1H, d, *J* 14.5, NC*H*$_A$H$_B$Ph), 4.20 (1H, d, *J* 14.5, NCH$_A$*H*$_B$Ph), 5.59 (1H, dd, *J* 45.6, 9.3, C(3)*H*), 6.76 (2H, d, *J* 6.7, C(3')*H*, C(5')*H*), 6.84 76 (2H, d, *J* 7.1, C(2')*H*, C(6')*H*), 6.99 (2H, d, *J* 7.0, *Ph*), 7.11 (2H, d, *J* 6.7, *Ph*), 7.16–7.28 (6H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 12.5 (C(α)*Me*), 28.1 (C*Me*$_3$), 51.4 (N*C*H$_2$Ph), 55.4 (O*Me*), 56.0 (*C*(α)), 62.6 (d, *J* 33.4, *C*(2)), 81.5 (*C*Me$_3$), 93.6 (d, *J* 167.9, *C*(3)), 113.5 (*C*(3'), *C*(5')), 126.8, 127.0 (*p-Ph*), 127.9 (*m-Ph*), 128.2, 128.2 (*o-Ph*), 128.9 (*m-Ph*), 128.9 (d, *J* 19.1, *C*(1')), 129.4 (d, *J* 5.7, *C*(2'), *C*(6')), 139.7, 142.3 (*i-Ph*), 160.1 (*C*(4')), 172.0 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −170.7 (C(3)*F*); *m*/*z* (ESI^+) 464 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{29}H_{35}FNO_3^+$ ($[M+H]^+$) requires 464.2596; found 464.2587.

(2*R*,3*S*)-2-Amino-3-fluoro-3-(4'-methoxyphenyl)propanoic acid 422·HCl



A solution of $NaBrO_3$ (98 mg, 0.647 mmol) in H_2O (2.17 mL) was added to a stirred solution of **401** (100 mg, 0.216 mmol, >99:1 dr) in EtOAc (2.9 mL) at rt and the resultant mixture was stirred at rt for 10 min. A solution of $Na_2S_2O_4$ (94 mg, 0.540 mmol) in H_2O (3.80 mL) was added dropwise at rt over 5 min and the resultant mixture was stirred at rt for 4 h. EtOAc (4 mL) was added and the resultant mixture was washed with satd aq $Na_2S_2O_3$ (4 mL). The aqueous layer was extracted with EtOAc (2 × 3 mL) and the combined organic extracts were washed with brine (5 mL), then dried over Na_2SO_3 and concentrated *in vacuo*. The residue was redissolved in CH_2Cl_2 (5 mL) and the resultant solution was washed with 1.0 M aq HCl (3 × 4 mL). The combined aqueous layers were concentrated *in vacuo* to give a 61:39 mixture of **315**·HCl and **422**·HCl, respectively. Selected data for **422**·HCl: δ_H (400 MHz, MeOD) 3.91 (3H, s, O*Me*), 4.67 (1H, dd, *J* 18.1, 3.4, C(2)*H*), 6.13 (1H, dd, *J* 43.8, 3.4, C(3)*H*), 6.95–7.62 (4H, m, *Ar*).

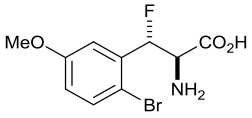
(2*R*,3*S*)-2-Amino-3-fluoro-3-(3'-methoxy-6'-bromophenyl)propanoic acid hydrochloride 423·HCl



A solution of $NaBrO_3$ (118 mg, 0.783 mmol) in H_2O (2.6 mL) was added to **399** (121 mg, 0.261 mmol, >99:1 dr) in EtOAc (3.4 mL) at rt and the resultant mixture was stirred at rt for 10 min. A solution of $Na_2S_2O_4$ (114 mg, 0.653 mmol) in H_2O (4.8 mL) was added dropwise at rt over 5 min and the resultant mixture was stirred at rt for 4 h. EtOAc (4 mL) was added and the resultant mixture was washed with satd aq $Na_2S_2O_3$ (4 mL). The aqueous layer was extracted with EtOAc (2 × 3 mL) and the combined organic extracts were washed with brine (8 mL), then dried over Na_2SO_3 and concentrated *in vacuo*. The residue was redissolved in CH_2Cl_2 (5 mL) and the resultant solution was washed with 1.0 M aq HCl (3 × 4 mL). The combined aqueous layers were concentrated *in vacuo* to give **423**·HCl as a white solid (31 mg, 48%, >99:1 dr); mp 161.5–163.5 °C; ν_{max} (ATR) 3016 (N−H), 1703 (C=O), 1237 (C−F); $[\alpha]_D^{20}$ +8.2 (*c* 1.0 in MeOH); δ_H (500 MHz, D_2O) 3.76 (3H, s, O*Me*), 4.26 (1H, dd, *J* 30.3, 2.3, C(2)*H*), 6.10 (1H, dd, *J* 46.2, 2.3, C(3)*H*), 6.88 (1H, dd, *J* 8.8, 3.0, C(4')*H*), 6.98 (1H, d, *J* 3.0, C(2')*H*), 7.50 (1H, d, *J* 8.8, C(5')*H*); δ_C (125 MHz, D_2O) 55.6 (O*Me*), 56.9 (d, *J* 23.8, *C*(2)),

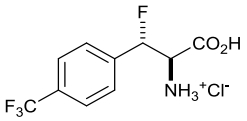
91.0 (d, *J* 180.2, *C*(3)), 110.2 (d, *J* 5.7, *C*(6')), 113.0 (d, *J* 13.4, *C*(2')), 116.9 (*C*(4')), 131.6 (*C*(5')), 134.9 (d, *J* 21.0, *C*(1')), 158.5 (*C*(3')), 168.5 (d, *J* 1.9, *C*(1)); δ_F (377 MHz, D_2O) −195.8 (C(3)*F*); *m*/*z* (ESI^+) 293 ([M(^{81}Br)–Cl^-]$^+$, 100%), 291 ([M(^{79}Br)–Cl^-]$^+$, 100%); HRMS (ESI^+) $C_{10}H_{11}{}^{81}BrFNO_3{}^+$ ([M(^{81}Br)–Cl^-]$^+$) requires 293.9958; found 293.9959; HRMS (ESI^+) $C_{10}H_{11}{}^{79}BrFNO_3{}^+$ ([M(^{79}Br)–Cl^-]$^+$) requires 291.9979; found 291.9979.

tert-Butyl (2*R*,3*S*)-2-amino-3-fluoro-3-(3'-methoxy-6'-bromo)phenylpropanoic acid 423



Propylene oxide (10 μL, 0.144 mmol) was added to **423**·HCl (9 mg, 0.036 mmol, >99:1 dr) in ^{i}PrOH (0.180 mL) and the resultant mixture was stirred at rt for 6 h, then concentrated in vacuo to give **423** as a white solid (5 mg, 63%, >99:1 dr); mp 236–242 °C dec; ν_{max} (ATR) 2931 (N−H), 1597 (C=O), 1324 (C−F); $[\alpha]_D^{20}$ +6.0 (*c* 0.1, MeOH); δ_H (500 MHz, D_2O) 3.71 (3H, s, O*Me*), 4.01 (1H, dd, *J* 29.5, 1.7, C(2)*H*), 5.96 (1H, dd, *J* 46.5, 1.7, C(3)*H*), 6.77 (1H, dd, *J* 8.8, 3.0, C(4')*H*), 7.00 (1H, d, *J* 2.8, C(2')*H*), 7.37 (1H, d, *J* 8.8, C(5')*H*); δ_C (125 MHz, D_2O) 54.6 (O*Me*), 57.0 (d, *J* 23.8, *C*(2)), 91.4 (d, *J* 179.3, *C*(3)), 111.0 (d, *J* 5.7, *C*(6')), 113.4 (d, *J* 12.4, *C*(2')), 116.4 (*C*(4')), 132.9 (*C*(5')), 135.6 (d, *J* 21.0, *C*(1')), 158.5 (*C*(3')), 169.2 (d, *J* 1.9, *C*(1)); δ_F (377 MHz, D_2O) −195.6 (C(3)*F*); *m*/*z* (ESI^+) 293 ([M(^{81}Br)+H]$^+$, 100%), 291 ([M(^{79}Br)+H]$^+$, 100%); HRMS (ESI^+) $C_{10}H_{11}{}^{81}BrFNO_3{}^+$ ([M(^{81}Br)+H]$^+$) requires 293.9958; found 293.9952; HRMS (ESI^+) $C_{10}H_{11}{}^{79}BrFNO_3{}^+$ ([M(^{79}Br)+H]$^+$) requires 291.9979; found 291.9972.

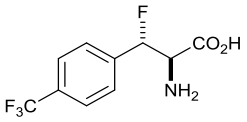
(2*R*,3*S*)-2-Amino-3-fluoro-3-[4'-(trifluoromethyl)phenyl]propanoic acid hydrochloride 424·HCl



A solution of $NaBrO_3$ (175 mg, 1.16 mmol) in H_2O (3.9 mL) was added to a stirred solution of **397** (194 mg, 0.387 mmol, >99:1 dr) in EtOAc (5.2 mL) at rt and the resultant mixture was stirred at rt for 10 min. A solution of $Na_2S_2O_4$ (168 mg, 0.968 mmol) in H_2O (7 mL) was added dropwise at rt over 5 min then the resultant mixture was stirred at rt for 4 h. EtOAc (6 mL) was added and the resultant mixture was washed with satd aq $Na_2S_2O_3$ (5 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL) and the combined organic extracts were washed with brine (10 mL), then dried over Na_2SO_3 and concentrated *in vacuo*. The residue

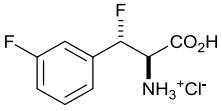
was redissolved in CH_2Cl_2 (5 mL) and the resultant solution was washed with 1.0 M aq HCl (3 × 4 mL). The combined aqueous layers were concentrated *in vacuo* to give **424**·HCl as a white solid (74 mg, 67%, >99:1 dr); mp 170.0–172.5 °C dec.; ν_{max} (ATR) 2979 (N−H), 1733 (C=O), 1327 (C−F); $[\alpha]_D^{20}$ +26.7 (*c* 0.26 in MeOH); δ_H (500 MHz, MeOD) 4.77 (1H, app d, *J* 22.4, C(2)*H*), 6.33 (1H, app d, *J* 44.9, C(3)*H*), 7.66 (2H, d, *J* 8.0, C(2')*H*, C(6')*H*), 7.78 (2H, d, *J* 8.0, C(3')*H*, C(5')*H*); δ_C (125 MHz, MeOD) 57.2 (d, *J* 21.0, *C*(2)), 90.3 (d, *J* 182.2, *C*(3)), 124.0 (q, *J* 270.8, *C*F_3), 125.3 (d, *J* 3.8, *C*(3'), *C*(5')), 125.8 (d, *J* 9.5, *C*(2'), *C*(6')), 130.9 (q, *J* 32.4 *C*(4')), 138.3 (d, *J* 21.0, *C*(1')), 165.9 (*C*(1)); δ_F (377 MHz, MeOD) −64.3 (C*F*$_3$), −191.6 (C(3)*F*); *m*/*z* (ESI$^+$) 1252 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{10}H_{10}F_4NO_2^+$ ([M+H]$^+$) requires 252.0642; found 252.0638.

(2*R*,3*S*)-2-Amino-3-fluoro-3-(4'-trifluoromethyl)phenylpropanoic acid 424



Propylene oxide (37 μL, 0.528 mmol) was added to a stirred solution of **424**·HCl (38 mg, 0.132 mmol, >99:1 dr) in ^{i}PrOH (0.663 mL) at rt and the resultant mixture was stirred at rt for 6 h, then concentrated *in vacuo* to give **424** as a white solid (30 mg, 85%, >99:1 dr); mp 185.0–187.5 °C dec.; ν_{max} (ATR) 3276 (N−H), 1607 (C=O), 1324 (C−F); $[\alpha]_D^{20}$ −5.0 (*c* 0.20 in MeOH); δ_H (500 MHz, D_2O) 4.34 (1H, dd, *J* 18.3, 3.0, C(2)*H*), 6.20 (1H, dd, *J* 44.1, 3.0, C(3)*H*), 7.46 (2H, d, *J* 8.0, C(2')*H*, C(6')*H*), 7.72 (2H, d, *J* 8.0, C(3')*H*, C(5')*H*); δ_C (125 MHz, D_2O) 59.0 (d, *J* 21.0, *C*(2)), 91.0 (d, *J* 180.2, *C*(3)), 123.8 (q, *J* 271.8, *C*F_3), 125.7 (app s, *C*(3'), *C*(5')), 125.8 (app s, *C*(2'), *C*(6')), 130.6 (q, *J* 32.4 *C*(4')), 137.6 (d, *J* 21.0, *C*(1')), 168.8 (*C*(1)); δ_F (377 MHz, DMSO-d_6) −62.0 (C*F*$_3$), −185.4 (C(3)*F*); *m*/*z* (ESI$^+$) 252 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{10}H_{10}F_4NO_2^+$ ([M+H]$^+$) requires 252.0642; found 252.0637.

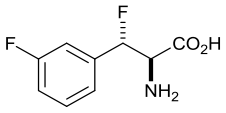
(2*R*,3*S*)-2-Amino-3-fluoro-3-(3'-fluorophenyl)propanoic acid hydrochloride 425·HCl



A solution of $NaBrO_3$ (249 mg, 1.65 mmol) in H_2O (5.5 mL) was added to a stirred solution of **398** (248 mg, 0.549 mmol, >99:1 dr) in EtOAc (7.4 mL) at rt and the resultant mixture was stirred at rt for 10 min. A solution of $Na_2S_2O_4$ (239 mg, 1.37 mmol) in H_2O (10.0 mL) was added dropwise at rt over 5 min and the resultant mixture was stirred at rt for 4 h. EtOAc (5

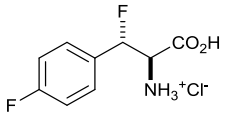
mL) was added and the resultant mixture was washed with satd aq $Na_2S_2O_3$ (8 mL). The aqueous layer was extracted with EtOAc (2 × 4 mL) and the combined organic extracts were washed with brine (10 mL), then dried over Na_2SO_3 and concentrated *in vacuo*. The residue was redissolved in CH_2Cl_2 (5 mL) and the resultant solution was washed with 1.0 M aq HCl (3 × 4 mL). The combined aqueous layers were concentrated *in vacuo* to give **425**·HCl as a white solid (90 mg, 69%, 87% purity); δ_H (500 MHz, D_2O) 4.53 (1H, dd, *J* 18.3, 3.2, C(2)*H*), 6.18 (1H, dd, *J* 43.8, 3.2, C(3)*H*), 7.05–7.43 (4H, m, *Ar*); δ_C (125 MHz, D_2O) 58.1 (d, *J* 22.9, *C*(2)), 90.3 (d, *J* 180.2, *C*(3)), 112.3 (dd, *J* 23.8, 9.5 *C*(2')), 116.4 (d, *J* 21.0, *C*(4')), 121.1 (dd, *J* 8.6, 2.9 *C*(6')), 131.0 (d, *J* 8.6, *C*(5')), 135.4 (dd, *J* 21.9, 7.6, *C*(1')), 162.7 (dd, *J* 245.1, 1.9, *C*(3')), 168.1 (d, *J* 8.6, *C*(1)).

(2*R*,3*S*)-2-Amino-3-fluoro-3-(3'-fluorophenyl)propanoic acid 425



Propylene oxide (22 μL, 0.320 mmol) was added to a stirred solution of **425**·HCl (19 mg, 0.080 mmol) in ^{i}PrOH (0.400 mL) at rt and the resultant mixture was stirred at rt for 6 h, then concentrated *in vacuo* to give **425** as a white solid (17 mg, quant, >99:1 dr); mp 180.5–184 °C dec.; ν_{max} (ATR) 3065 (N−H), 1617 (C=O), 1146 (C−F); $[\alpha]_D^{20}$ −8.0 (*c* 0.25 in MeOH); δ_H (500 MHz, D_2O) 4.32 (1H, dd, *J* 17.3, 3.2, C(2)*H*), 6.14 (1H, dd, *J* 44.0, 3.2, C(3)*H*), 7.03–7.43 (4H, m, *Ar*); δ_C (125 MHz, D_2O) 59.0 (d, *J* 21.9, *C*(2)), 90.8 (dd, *J* 179.3, 1.9, *C*(3)), 112.4 (dd, *J* 22.9, 9.5 *C*(2')), 116.2 (d, *J* 21.9, *C*(4')), 121.1 (dd, *J* 8.6, 2.8, *C*(6')), 130.9 (d, *J* 8.6, *C*(5')), 135.8 (dd, *J* 21.9, 7.6, *C*(1')), 162.6 (dd, *J* 245.1, 1.9, *C*(3')), 169.0 (d, *J* 7.6, *C*(1)); δ_F (377 MHz, D_2O) −112.5.3 (C(3')*F*), −189.2 (C(3)*F*); *m*/*z* (ESI^+) 202 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_9H_{10}F_2NO_2^+$ ($[M+H]^+$) requires 202.0674; found 202.0672.

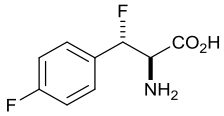
(2*R*,3*S*)-2-Amino-3-fluoro-3-(4'-fluorophenyl)propanoic acid hydrochloride 426·HCl



A solution of $NaBrO_3$ (88 mg, 0.585 mmol) in H_2O (1.95 mL) was added to a stirred solution of **400** (89 mg, 0.195 mmol, >99:1 dr) in EtOAc (2.6 mL) at rt and the resultant mixture was stirred at rt for 10 min. A solution of $Na_2S_2O_4$ (85 mg, 0.488 mmol) in H_2O (3.54 mL) was added dropwise at rt over 5 min and the resultant mixture was stirred at rt for 4 h. EtOAc (4

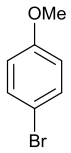
mL) was added and the resultant mixture was washed with satd aq $Na_2S_2O_3$ (4 mL). The aqueous layer was extracted with EtOAc (2 × 3 mL) and the combined organic extracts were washed with brine (5 mL), then dried over Na_2SO_3 and concentrated *in vacuo*. The residue was redissolved in CH_2Cl_2 (5 mL) and the resultant solution was washed with 1.0 M aq HCl (3 × 4 mL). The combined aqueous layers were concentrated *in vacuo* to give **426**·HCl as a white solid (30 mg, 65%, >99:1 dr); mp 152.5–157.5 °C dec.; ν_{max} (ATR) 2976 (N−H), 1731 (C=O), 1222 (C−F); $[\alpha]_D^{20}$ +16.8 (*c* 0.5 in MeOH); δ_H (500 MHz, D_2O) 4.58 (1H, dd, *J* 17.5, 3.3, C(2)*H*), 6.16 (1H, dd, *J* 43.4, 3.3, C(3)*H*), 7.13 (2H, app t, *J* 8.8, C(3')*H*, C(5')*H*), 7.32 (2H, dd, *J* 8.8, 5.2, C(2')*H*, C(6')*H*); δ_C (125 MHz, D_2O) 57.7 (d, *J* 24.8, *C*(2)), 90.3 (d, *J* 179.3, *C*(3)), 115.9 (d, *J* 21.9, *C*(3'), *C*(5')), 127.5 (app t, *J* 8.6, *C*(2'), *C*(6')), 128.7 (dd, *J* 21.9, 3.8, *C*(1')), 163.1 (d, *J* 246.1, *C*(4')), 167.8 (d, *J* 9.5, *C*(1)); δ_F (377 MHz, MeOD) −114.6 (C(4')*F*), −188.5 (C(3)*F*); *m*/*z* (ESI^+) 202 ($[M–Cl^–]^+$, 100%); HRMS (ESI^+) $C_9H_{10}F_2NO_2^+$ ($[M−Cl^–]^+$) requires 202.0674; found 202.0674.

(2*R*,3*S*)-2-Amino-3-fluoro-3-(4'-fluorophenyl)propanoic acid 426



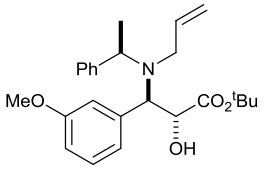
Propylene oxide (62 μL, 0.858 mmol) was added to a stirred solution of **426**·HCl (51 mg, 0.215 mmol, >99:1 dr) in ^{i}PrOH (1.08 mL) at rt and the resultant mixture was stirred at rt for 6 h, then concentrated *in vacuo* to give **426** as a white solid (43 mg, quant, >99:1 dr); mp 164.5–167.5 °C; ν_{max} (ATR) 3292 (N−H), 1605 (C=O), 1227 (C−F); $[\alpha]_D^{20}$ −19.7 (*c* 0.142 in MeOH); δ_H (500 MHz, D_2O) 4.29 (1H, dd, *J* 16.4, 3.3, C(2)*H*), 6.12 (1H, dd, *J* 43.5, 3.3, C(3)*H*), 7.13 (2H, app t, *J* 8.8, C(3')*H*, C(5')*H*), 7.30 (2H, dd, *J* 8.8, 5.4, C(2')*H*, C(6')*H*); δ_C (125 MHz, D_2O) 59.1 (d, *J* 21.9, *C*(2)), 91.0 (d, *J* 178.3, *C*(3)), 115.8 (d, *J* 21.9, *C*(3'), *C*(5')), 127.5 (app t, *J* 8.6, *C*(2'), *C*(6')), 129.2 (dd, *J* 21.9, 2.9, *C*(1')), 163.0 (d, *J* 246.1, *C*(4')), 169.1 (d, *J* 9.5, *C*(1)); δ_F (377 MHz, D_2O) −112.9 (C(4')*F*), −187.4 (C(3)*F*); *m*/*z* (ESI^+) 202 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_9H_{10}F_2NO_2^+$ ($[M+H]^+$) requires 202.0674; found 202.0673.

1-Methoxy-4-bromobenzene



A solution of $NaBrO_3$ (419 mg, 2.77 mmol) in H_2O (9.3 mL) was added to a stirred solution of anisole (0.101 mL, 0.925 mmol) in EtOAc (12.5 mL) at rt and the resultant mixture was stirred at rt for 10 min. A stirred solution of $Na_2S_2O_4$ (403 mg, 2.31 mmol) in H_2O (16.3 mL) was added dropwise at rt over 5 min and the resultant mixture was stirred at rt for 1 h. EtOAc (10 mL) was added and the resultant mixture was washed with satd aq $Na_2S_2O_3$ (10 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL) and the combined organic extracts were washed with brine (20 mL), then dried over Na_2SO_3 and concentrated *in vacuo* to give 1-methoxy-4-bromobenzene as a yellow oil (175 mg, quant.);[38] δ_H (400 MHz, $CDCl_3$) 3.67 (3H, s, O*Me*), 6.67 (2H, d, *J* 8.9, *Ar*), 7.27 (2H, d, *J* 8.9, *Ar*); δ_C (100 MHz, $CDCl_3$) 55.4 (O*Me*), 112.8 (*C*(4)), 115.8 (*Ar*), 132.3 (*Ar*), 158.7 (*C*(1)).

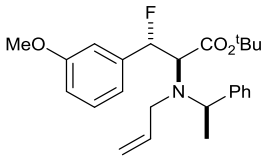
***tert*-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-allyl-*N*(α-methylbenzyl)amino]-3-(3''-methoxyphenyl)propanoate 428**[39]



BuLi (2.2 M in hexanes, 1.50 mL, 3.30 mmol) was added dropwise to a stirred solution of (*R*)-**388** (551 mg, 3.41 mmol, 99% ee)[40] in THF (9 mL) at −78 °C and stirring was continued at –78 °C for 30 min. A solution of **284** (500 mg, 2.13 mmol, >99:1 dr) in THF (9 mL) was then added via cannula and the resultant mixture was stirred at −78 °C for 2 h. (−)-CSO **202** (830 mg, 3.62 mmol) was then added and stirring was continued as the reaction mixture was allowed to warm to rt over 15 h. Satd aq NH_4Cl (2 mL) was added and the reaction mixture was stirred at rt for 5 min then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and 10% aq citric acid (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 8 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (15 mL) and brine (15 mL), then dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (10 mL), the insoluble CSO residues were filtered off, and the filter cake was washed with Et_2O (2 × 10 mL). The filtrate was concentrated *in vacuo* and the process was repeated. Purification via flash column chromatography (eluent 30–40 ºC petrol/Et_2O,

5:1) gave **428** as a pale yellow oil (780 mg, 89%, >99:1 dr); ν_{max} (ATR) 3495 (N−H), 1722 (C=O); $[\alpha]_D^{23}$ +2.4 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.23 (3H, d, *J* 6.8, C(α)*Me*), 1.32 (9H, s, C*Me*$_3$), 2.98 (1H, br s, O*H*), 3.28 (1H, dd, *J* 15.7, 7.1, C(1')H_A), 3.47 (1H, dd, *J* 15.7, 5.5, C(1')H_B), 3.81 (3H, s, O*Me*), 4.15 (1H, q, *J* 6.8, C(α)*H*), 4.21 (1H, d, *J* 3.7, C(2)*H*), 4.51 (1H, d, *J* 3.7, C(3)*H*), 5.04 (1H dd, *J* 10.0, 1.4, C(3')H_A), 5.13 (1H dd, *J* 17.4, 1.4, C(3')H_B), 5.91 (1H, dddd, *J* 17.4, 10.0, 7.1, 5.5, C(2')*H*), 6.80–6.84 (1H, m, C(2")*H*), 7.02–7.08 (2H, m, C(4")*H*, C(6")*H*), 7.20–7.25 (2H, m, *p-Ph*, C(5")*H*), 7.33–7.49 (4H, m, *o,m-Ph*); δ_C (100 MHz, $CDCl_3$) 14.0 (C(α)*Me*) 27.9 (C*Me*$_3$) 50.6 (*C*(1')), 55.2 (O*Me*), 55.7 (*C*(α)), 65.8 (*C*(2)), 72.4 (*C*(3)), 82.3 (*C*Me$_3$), 113.0 (*C*(2")), 115.4 (*C*(4")), 115.6 (*C*(3')), 121.9 (*C*(6")), 126.6 (*p-Ph*), 128.1, 127.8 (*o,m-Ph*), 129.0 (*C*(5")), 139.0 (*C*(2')), 139.5 (*C*(1")), 144.3 (*i-Ph*), 159.4 (C(3")), 172.1 (*C*(1)); *m/z* (ESI$^+$) 412 ($[M+H]^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{34}NO_4^+$ ($[M+H]^+$) requires 412.2482; found 412.2482.

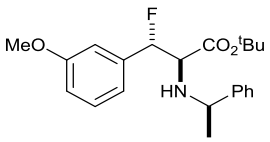
tert-Butyl (2*R*,3*S*,α*R*)-2-[*N*-allyl-*N*-(α-methylbenzyl)amino]-3-fluoro-3-(3''-methoxyphenyl)propanoate 429



$NEt_3 \cdot 3HF$ (79 μL, 0.486 mmol) was added to a stirred solution of **428** (100 mg, 0.243 mmol) and XtalFluor-E® (83 mg, 0.364 mmol) in CH_2Cl_2 (0.60 mL) at rt and the resultant solution was stirred at rt for 2 h. 5% aq $NaHCO_3$ solution (0.5 mL) was added and the resultant mixture was stirred at rt for 15 min, then extracted with CH_2Cl_2 (2 × 2 mL). The combined organic extracts were dried, then filtered through a pad of silica and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 40:1) gave **429** as a pale yellow oil (84 mg, 84%, >99:1 dr); ν_{max} (ATR) 1724 (C=O), 1148 (C−F); $[\alpha]_D^{20}$ −32.5 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.35 (3H, d, *J* 6.9, C(α)*Me*), 1.56 (9H, s, C*Me*$_3$), 3.44 (1H, dd, *J* 15.0, 8.4, C(1')H_A), 3.59 (1H app t, *J* 9.3, C(2)*H*), 3.69 (3H, s, O*Me*), 3.70–3.76 (1H, m, C(1') H_B), 4.06 (1H, q, *J* 6.9, C(α)*H*), 5.13 (1H, app d, *J* 10.1, C(3')H_A), 5.20 (1H, app d, *J* 17.2, C(3') H_B), 5.57 (1H, dd, *J* 45.4, 9.3, C(3)*H*), 6.54–6.57 (1H, m, C(2")*H*), 6.69–6.72 (1H, m, C(6")*H*), 6.86–7.22 (7H, m, *Ar*); δ_C (125 MHz, $CDCl_3$) 12.9 (C(α)*Me*), 27.0 (C*Me*$_3$), 47.1 (*C*(1')), 54.0 (O*Me*), 55.3 (*C*(α)), 62.7 (d, *J* 32.4, *C*(2)), 80.4 (*C*Me$_3$), 92.4 (d, *J* 171.7, *C*(3)), 110.4 (d, *J* 6.7, *C*(2")), 113.9 (d, *J* 1.9, *C*(4")), 116.2 (*C*(3')), 118.7 (d, *J* 6.7, *C*(6")), 125.3 (*p-Ph*), 126.7, 126.7 (*o,m-Ph*), 127.8 (*C*(5")), 136.4 (*C*(2')),

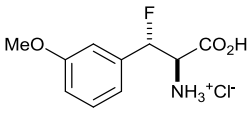
137.9 (d, *J* 19.1, *C*(1")), 141.8 *(i-Ph*), 158.3 (*C*(3")), 170.5 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −179.7 (C(3)*F*); *m*/*z* (ESI^+) 414 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{25}H_{33}FNO_3^+$ ($[M+H]^+$) requires 414.2439; found 414.2429.

tert-Butyl (2*R*,3*S*,α*R*)-2-[*N*-allyl-*N*(α-methylbenzyl)amino]-3-fluoro-3-(3'-methoxy)phenyl propanoate 430



N,*N*-Dimethylbarbituric acid (646 mg, 3.63 mmol) was added to a stirred solution of **429** (500 mg, 1.21 mmol) in CH_2Cl_2 (27 mL) at rt and the resultant solution was degassed with N_2. $Pd(PPh_3)_4$ (14 mg, 0.012 mmol, 1 mol%) was added and the resultant mixtures was stirred at rt for 18 h in the dark, before being concentrated *in vacuo*. The residue was dissolved in Et_2O (8 mL) and washed with satd aq K_2CO_3 (2 × 5 mL). The aqueous layer was extracted with Et_2O (10 mL) and the combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 8:1, 1% Et_3N) gave **430** as an orange oil (215 mg, 48%); ν_{max} (ATR) 3348 (N−H), 1728 (C=O), 1150 (C−F); $[\alpha]_D^{20}$ +45.0 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6.6, C(α)*Me*), 1.31 (9H, s, C*Me*$_3$), 2.10 (1H, br s, N*H*), 3.57 (1H, dd, *J* 15.4, 5.6, C(2)*H*), 3.74 (1H, q, *J* 6.6, C(α)*H*), 3.80 (3H, s, O*Me*), 5.57 (1H, dd, *J* 51.6, 5.6, C(3)*H*), 6.85–7.32 (9H, m, *Ar*, *Ph*); δ_C (100 MHz, $CDCl_3$) 23.2 (C(α)*Me*), 27.9 (C*Me*$_3$), 55.3 (O*Me*), 56.5 (*C*(α)), 64.1 (d , *J* 25.4, *C*(2)), 81.7 (*C*Me$_3$), 94.1 (d, *J* 178.8, *C*(3)), 110.4 (d, *J* 8.0, *C*(2')), 114.2 (*C*(4')), 118.6 (d, *J* 8.0, *C*(6')), 126.8, 127.2 128.5 (*o*,*m-Ph*), 129.1 (*C*(5')), 138.7 (d, *J* 20.7, *C*(1')), 145.2 *(i-Ph*), 159.5 (*C*(3')), 170.7 (d, *J* 4.8, *C*(1)); δ_F (377 MHz, $CDCl_3$) −185.2 (C(3)*F*); *m*/*z* (ESI^+) 374 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{22}H_{29}FNO_3^+$ ($[M+H]^+$) requires 374.2126; found 374.2127.

tert-Butyl (2*R*,3*S*)-2-amino-3-fluoro-3-phenylpropanoate·HCl 431·HCl



Method A: A solution of $NaBrO_3$ (61 mg, 0.402 mmol) in H_2O (1.35 mL) was added to a stirred solution of **430** (50 mg, 0.134 mmol) in EtOAc (1.8 mL) at rt and the resultant mixture was stirred at rt for 10 min. A solution of $Na_2S_2O_4$ (58 mg, 0.335 mmol) in H_2O (2.34 mL) was added dropwise at rt over 5 min and the resultant mixture was stirred at rt for 1 h. EtOAc (4 mL) was added and the resultant mixture was washed with satd aq $Na_2S_2O_3$ (4 mL). The

aqueous layer was extracted with EtOAc (2 × 3 mL) and the combined organic extracts were washed with brine (5 mL), then dried over Na_2SO_3 and concentrated *in vacuo*. The residue was redissolved in CH_2Cl_2 (5 mL) and the resultant solution was washed with 1.0 M aq HCl (3 × 4 mL). The combined aqueous layers were concentrated *in vacuo* to give **423**·HCl as a white solid (17 mg, 39%).

Method B: A solution of $NaBrO_3$ (36 mg, 0.241 mmol) in H_2O (0.809 mL) was added to a stirred solution of **430** (30 mg, 0.080 mmol) in EtOAc (1 mL) at rt and the resultant mixture was stirred at rt for 10 min. A solution of $Na_2S_2O_4$ (35 mg, 0.200 mmol) in H_2O (1.40 mL) was added dropwise at rt over 5 min and the resultant mixture was stirred at rt for 45 min. EtOAc (3 mL) was added and the resultant mixture was washed with satd aq $Na_2S_2O_3$ (3 mL). The aqueous layer was extracted with EtOAc (2 × 2 mL) and the combined organic extracts were washed with brine (5 mL), then dried over Na_2SO_3 and concentrated *in vacuo*. The residue was redissolved in CH_2Cl_2 (5 mL) and the resultant solution was washed with 1.0 M aq HCl (3 × 4 mL). The combined aqueous layers were concentrated *in vacuo* to give a 71:29 mixture of **423**·HCl and **431**·HCl, respectively.

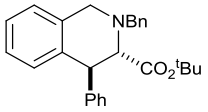
Method C: A solution of $NaBrO_3$ (36 mg, 0.241 mmol) in H_2O (0.809 mL) was added to a stirred solution of **430** (30 mg, 0.080 mmol) in EtOAc (1 mL) at rt and the resultant mixture was stirred at rt for 10 min. A solution of $Na_2S_2O_4$ (35 mg, 0.200 mmol) in H_2O (1.40 mL) was added dropwise at rt over 5 min and the resultant mixture was stirred at rt for 30 min. EtOAc (3 mL) was added and the resultant mixture was washed with satd aq $Na_2S_2O_3$ (3 mL). The aqueous layer was extracted with EtOAc (2 × 2 mL) and the combined organic extracts were washed with brine (5 mL), then dried over Na_2SO_3 and concentrated *in vacuo*. The residue was redissolved in CH_2Cl_2 (5 mL) and the resultant solution was washed with 1.0 M aq HCl (3 × 4 mL). The combined aqueous layers were concentrated *in vacuo* to give a 47:53 mixture of **423**·HCl and **431**·HCl, respectively.

Method D: A solution of $NaBrO_3$ (36 mg, 0.241 mmol) in H_2O (0.809 mL) was added to a stirred solution of **430** (30 mg, 0.080 mmol) in EtOAc (1 mL) at rt and the resultant mixture was stirred at rt for 10 min. A solution of $Na_2S_2O_4$ (35 mg, 0.200 mmol) in H_2O (1.40 mL) was added dropwise at rt over 5 min and the resultant mixture was stirred at rt for 15 min. EtOAc (3 mL) was added and the resultant mixture was washed with satd aq $Na_2S_2O_3$ (3 mL). The aqueous layer was extracted with EtOAc (2 × 2 mL) and the combined organic extracts

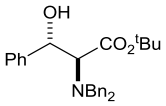
were washed with brine (5 mL), then dried over Na_2SO_3 and concentrated *in vacuo* to give **430**.

6.5. Experimental for Chapter 5

(*RS*,*RS*)-2-*N*-Benzyl-3-*tert*-butoxycarbonyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline 261 and *tert*-Butyl (*RS*,*RS*)-2-dibenzylamino-3-hydroxy-3-phenylpropanoate 260



261



260

Method A: AgOTf (30 mg, 0.115 mmol) was added to a stirred solution of **250** (50 mg, 0.115 mmol, >99:1 dr) in EtOAc (1.12 mL) and the resultant mixture was stirred at rt for 1 h, then filtered through alumina (eluent EtOAc) and concentrated *in vacuo* to give a 61:39 mixture of **260** and **261**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 30:1 then increased to 5:1) gave **261** as a pale yellow solid (8 mg, 21%, >99:1 dr); mp 63.0–70.5 °C; ν_{max} (ATR) 1723 (C=O); δ_H (500 MHz, $CDCl_3$) 1.38 (9H, s, C*Me*$_3$), 3.58 (1H, d, *J* 3.0, C(3)*H*), 3.86 (1H, d, *J* 13.4, NC(1')H_AH_BPh), 3.92 (1H, d, *J* 15.0, C(1)H_A), 3.96 (1H, d, *J* 13.4, NC(1')H_AH_BPh), 4.06 (1H, d, *J* 15.0, C(1) H_B), 4.50 (1H, d, *J* 3.0, C(4)*H*), 6.90–7.42 (14H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 28.2 (C*Me*$_3$), 47.9 (*C*(4)), 51.0 (*C*(1)), 59.5 (*C*(1')), 67.0 (*C*(3)), 81.3 (*C*Me$_3$), 126.0, 126.1, 126.2, 126.3 (*C*(5), *C*(6), *C*(7), *C*(8)), 126.9, 127.8, 128.1, 128.6, 129.1, 129.7 (*o*,*m*,*p*-*Ph*), 134.7 (*C*(8a)), 135.2 (*C*(4a)), 138.6, 144.7 (*i*-*Ph*), 171.4 (*C*O_2^{t}Bu); *m*/*z* (ESI$^+$) 400 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{30}NO_2^+$ ([M+H]$^+$) requires 400.2271; found 400.2273. Further elution gave **260** as a white solid (19 mg, 40%, >99:1 dr); mp 132.5–136.5 °C; ν_{max} (ATR) 3465 (O−H), 1722 (C=O); δ_H (500 MHz, $CDCl_3$) 1.65 (9H, s, C*Me*$_3$), 2.74 (1H, d, *J* 4.0, O*H*), 3.43–3.54 (3H, m, N(CH_AH_BPh)$_2$, C(2)*H*), 3.90 (2H, d, *J* 13.9, N(CH_AH_BPh)$_2$), 5.05 (1H, dd, *J* 9.4, 4.0, C(3)*H*), 6.94–7.41 (15H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 28.6 (C*Me*$_3$), 55.0 (N(*C*H_2Ph)$_2$), 66.5 (*C*(2)), 73.0 (*C*(3)), 82.2 (*C*Me$_3$), 126.9, 127.8, 127.9, 128.1, 128.1, 128.8 (*o*,*m*,*p*-*Ph*), 138.6, 140.9 (*i*-*Ph*), 171.6 (*C*(1)); *m*/*z* (ESI$^+$) 418 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{32}NO_3^+$ ([M+H]$^+$) requires 418.2377; found 418.2382.

Method B: $AgBF_4$ (27 mg, 0.138 mmol) was added to a stirred solution of **250** (50 mg, 0.115 mmol, >99:1 dr) in EtOAc (1.12 mL) and the resultant mixture was stirred at rt for 18 h, then filtered through alumina (eluent EtOAc) and concentrated *in vacuo* to give a 83:17 mixture of **260** and **261**, respectively.

Method C: AgOTf (30 mg, 0.115 mmol) was added to a stirred solution of **250** (50 mg, 0.115 mmol, >99:1 dr) in THF (1.12 mL) and the resultant mixture was stirred at rt for 18 h, then

filtered through alumina (eluent EtOAc) and concentrated *in vacuo* to give a 68:32 mixture of **260** and **261**, respectively.

Method D: AgOTf (12 mg, 0.050 mmol) was added to a stirred solution of **250** (20 mg, 0.050 mmol, >99:1 dr) in MeCN (1.12 mL) and the resultant mixture was stirred at rt for 18 h, then filtered through alumina (eluent MeCN) and concentrated *in vacuo* to give a 47:42:11 mixture of **260**, **261** and **250**, respectively.

Method E: AgOTf (122 mg, 0.498 mmol) was added to a stirred solution of **250** (276 mg, 0.634 mmol, >99:1 dr) in CH_2Cl_2 (4.5 mL) and the resultant mixture was stirred at rt for 18 h, then filtered through alumina (eluent CH_2Cl_2) and concentrated *in vacuo* to give a 94:6 mixture of **261** and **260**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **261** as a pale yellow solid (93 mg, 68%).

Method F: AgOTf (30 mg, 0.115 mmol) was added to a stirred solution of **250** (50 mg, 0.115 mmol, >99:1 dr) in PhMe (1.12 mL) and the resultant mixture was stirred at rt for 18 h, then filtered through alumina (eluent PhMe) and concentrated *in vacuo* to give a 100:0 mixture of **261** and **260**, respectively (4 mg, 9%).

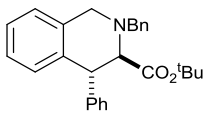
Method G: CCl_4 (867 μL, 8.99 mmol) was added to a stirred solution of **248** (250 mg, 0.599 mmol, >99:1 dr) and PPh_3 (314 mg, 1.20 mmol) in PhMe (1.8 mL) and the resultant mixture was heated at 100 °C for 2 h, then cooled to rt and filtered through alumina (eluent PhMe, 1 mL). AgOTf (175 mg, 0.659 mmol) was added to the filtrate and the resultant mixture was stirred at rt for 18 h, then filtered through alumina (eluent PhMe) and concentrated *in vacuo* to give a 81:19 mixture of **261** and **260**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **261** as a pale yellow solid (87 mg, 36%).

Method H: Tf_2O (24 μL, 0.144 mmol) was added to a stirred solution of **248** (20 mg, 0.048 mmol, >99:1 dr) and Et_3N (38 μL, 0.288 mmol) in CH_2Cl_2 (0.6 mL) at 0 °C and the resultant mixture was stirred at rt for 6 h. H_2O (1 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 1 mL), and the combined organic extracts were washed sequentially with 1.0 M aq HCl (2 mL), satd aq $NaHCO_3$ (2 mL) and brine (2 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1 then increased to 10:1) gave **261** as a pale yellow solid (7 mg, 37%). A 51:49 mixture of **248** and **260**, respectively, was also recovered (3 mg, 7%).

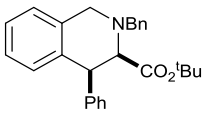
Method I: Tf_2O (61 μL, 0.360 mmol) was added to a stirred solution of **248** (50 mg, 0.120 mmol, >99:1 dr) and 2,6,-di-*tert*-butyl-4-methylpyridine **318** (148 mg, 0.720 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C and the resultant mixture was stirred at rt for 6 h. H_2O (5 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 4 mL), and the combined organic extracts were dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (10 mL), the resultant suspension filtered, and the filtrate concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **261** as a pale yellow solid (28 mg, 58%).

Method J: Tf_2O (181 μL, 1.08 mmol) was added to a stirred solution of **248** (300 mg, 0.719 mmol, >99:1 dr) and **318** (443 mg, 2.16 mmol) in CH_2Cl_2 (9 mL) at 0 °C and the resultant mixture was stirred at rt for 6 h. H_2O (5 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 4 mL), and the combined organic extracts were dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (10 mL), the resultant suspension filtered, and the filtrate concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **261** as a pale yellow solid (219 mg, 76%).

(*RS*,*RS*)-2-*N*-Benzyl-3-*tert*-butoxycarbonyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline 261 and (*RS*,*SR*)-2-*N*-benzyl-3-*tert*-butoxycarbonyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline 460



261

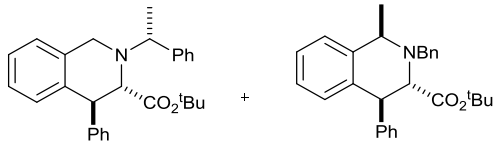


460

Tf_2O (15 μL, 0.090 mmol) was added to a stirred solution of **266** (25 mg, 0.060 mmol, >99:1 dr) and **318** (36 mg, 0.180 mmol) in CH_2Cl_2 (0.6 mL) at 0 °C and the resultant mixture was stirred at rt for 6 h. H_2O (1 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 1 mL), and the combined organic extracts were dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (3 mL), the resultant suspension filtered, and the filtrate concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave a 59:41 mixture of **261** and **460**, respectively, as a pale yellow oil (20 mg, 84%); Selected data for **460**: δ_H (500 MHz, $CDCl_3$) 1.21 (9H, s, C*Me*$_3$), 3.77 (1H, d, *J* 13.4, NC(1')*H*$_A$H$_B$Ph), 3.79 (1H, d, *J* 6.1, C(3)*H*), 3.85 (1H, d, *J* 15.3, C(1)*H*$_A$), 3.86 (1H, d, *J* 13.4, NC(1')H$_A$*H*$_B$Ph), 4.16 (1H, d, *J* 15.3, C(1)*H*$_B$), 4.57 (1H, d, *J* 6.1, C(4)*H*), 6.95–7.48 (14H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 28.0 (C*Me*$_3$), 48.2 (*C*(4)), 52.0 (*C*(1)), 60.0 (*C*(1')), 66.6

(*C*(3)), 80.9 (*C*Me$_3$), 125.8, 125.8, 125.9 (*C*(6), *C*(7), *C*(8)), 126.9, 127.2 (*p-Ph*), 127.9, 128.0, 128.3, 128.4 (*o,m-Ph*), 129.0 (*C*(5)), 135.0, 138.3, 140.3, 140.6 (*C*(4a), *C*(8a), *i-Ph*), 169.2 (*C*O$_2$^{t}Bu).

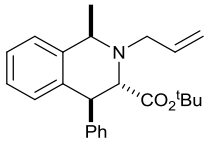
(3*S*,4*S*,α*R*)-*N*(2)-[α-Methylbenzyl]-3-*tert*-butoxycarbonyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline 367 and (1*R*,3*S*,4*S*)-1-methyl-2-benzyl-3-*tert*-butoxycarbonyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline 366



367 **366**

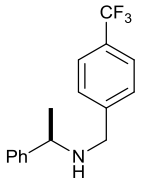
Tf_2O (58 μL, 0.348 mmol) was added to a stirred solution of **208** (100 mg, 0.232 mmol, >99:1 dr) and **318** (143 mg, 0.696 mmol) in CH_2Cl_2 (3.3 mL) at 0 °C and the resultant mixture was stirred at rt for 6 h. H_2O (2 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 2 mL), and the combined organic extracts were dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (5 mL), the resultant suspension filtered, and the filtrate concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave a 71:29 mixture of **367** and **366**, respectively, as a pale yellow oil (57 mg, 59%); ν_{max} (ATR) 1723 (C=O), 1149 (C−F); *m*/*z* (ESI$^+$) 414 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{32}NO_2^+$ ([M+H]$^+$) requires 414.2428; found 414.2440. Data for **367**: δ_H (500 MHz, $CDCl_3$) 1.16 (3H, d, *J* 6.8, C(α)*Me*), 1.39 (9H, s, C*Me*$_3$), 3.77 (1H, d, *J* 15.8, C(1)*H*$_A$), 3.86 (1H, d, *J* 15.8, C(1)*H*$_B$), 4.01 (1H, q, *J* 6.8, C(α)*H*), 4.08 (1H, d, *J* 3.3, C(3)*H*), 4.59 (1H, d, *J* 3.3, C(4)*H*), 6.85–7.34 (14H, m, *Ph*, *Ar*); δ_C (125 MHz, $CDCl_3$) 21.0 (C(α)*Me*), 28.1 (C*Me*$_3$), 47.9 (*C*(4)), 49.6 (*C*(1)), 62.0 (*C*(α)), 62.8 (*C*(3)), 81.2 (*C*Me$_3$), 125.9 (*C*(8)), 126.0, 126.0 (*C*(6), *C*(7)), 126.0, 126.3 (*p-Ph*), 127.1, 127.8, 128.3, 129.0 (*o,m-Ph*), 129.6 (*C*(5)), 134.9 (*C*(4a)), 135.2 (*C*(8a)), 145.3, 146.3 (*i-Ph*), 171.9 (*C*O$_2$^{t}Bu). Data for **366**: δ_H (500 MHz, $CDCl_3$) 1.28 (9H, s, C*Me*$_3$), 1.47 (3H, d, *J* 6.4, C(1)*Me*), 3.75 (1H, d, *J* 3.8, C(3)*H*), 3.94 (1H, d, *J* 14.8, NC*H*$_A$H$_B$Ph), 3.98 (1H, d, *J* 14.8, CH$_A$*H*$_B$Ph), 4.37 (1H, q, *J* 6.4, C(1)*H*), 4.50 (1H, d, *J* 3.8, C(4)*H*), 6.75–7.30 (14H, m, *Ar*, *Ph*); δ_C (125 MHz, $CDCl_3$) 23.2 (C(1)*Me*), 27.9 (C*Me*$_3$), 47.6 (*C*(4)), 55.0 (N*C*H$_2$Ph), 55.7 (*C*(1)), 64.7 (*C*(3)), 81.0 (*C*Me$_3$), 126.0, 126.5, 126.7 (*C*(6), *C*(7), *C*(8)), 126.8, 127.0 (*p-Ph*), 127.8, 127.9, 128.0, 129.0 (*o-*,*m-Ph*), 129.7 (*C*(5)), 133.9 (*C*(4a)), 139.8 (*i-Ph*), 141.0 (*C*(8a)), 143.8 (*i-Ph*), 172.0 (*C*O$_2$^{t}Bu).

(1*R*,3*S*,4*S*)-1-Methyl-*N*(2)-allyl-3-*tert*-butoxycarbonyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline 482



Tf_2O (53 μL, 0.314 mmol) was added to a stirred solution of **390** (100 mg, 0.262 mmol, >99:1 dr) and **318** (129 mg, 0.629 mmol) in CH_2Cl_2 (3.3 mL) at 0 °C and the resultant mixture was stirred at rt for 6 h. H_2O (2 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 2 mL), and the combined organic extracts were dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (5 mL), the resultant suspension filtered, and the filtrate concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **482** as a red oil (30 mg, 32%, >99:1 dr); ν_{max} (ATR) 1728 (C=O), 1149 (C=C); $[\alpha]_D^{20}$ +80.0 (*c* 0.5 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.28 (9H, s, C*Me*$_3$), 1.43 (3H, d, *J* 6.6, C(1)*Me*), 3.33–3.39 (1H, m, C(1')*H*$_A$), 3.43 (1H, dd, *J* 14.8, 6.9, C(1')*H*$_B$), 3.91 (1H, d, *J* 4.5, C(3)*H*), 4.28 (1H, q, *J* 6.6, C(1)*H*), 4.64 (1H, d, *J* 4.5, C(4)*H*), 4.91–4.98 (2H, m, C(3')*H*$_2$), 5.63 (1H, dddd, *J* 17.0, 10.7, 6.9, 5.0 C(2')*H*), 6.96–7.29 (9H, m, *Ar*, *Ph*); δ_C (125 MHz, $CDCl_3$) 22.6 (C(1)*Me*), 27.9 (C*Me*$_3$), 47.3 (*C*(4)), 53.9 (*C*(1')), 55.4 (*C*(1)), 64.8 (*C*(3)), 80.9 (*C*Me$_3$), 116.3 (*C*(3')), 125.9 (*C*(8)), 126.2, 126.5 (*C*(6), *C*(7)), 126.9 (*p-Ph*), 127.9, 129.0 (*o-*,*m-Ph*), 129.6 (*C*(5)), 134.3 (*C*(4a)), 136.3 (*C*(2')), 140.7 (*C*(8a)), 143.8 (*i-Ph*), 172.1 (*C*O$_2$^{t}Bu); *m*/*z* (ESI$^+$) 364 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{31}NO_2^+$ ([M+H]$^+$) requires 364.2271; found 364.2276.

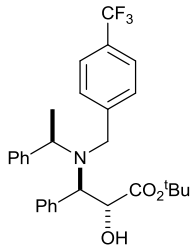
(*R*)-*N*-(4-Trifluoromethyl)benzyl-*N*-(α-methylbenzyl)amine 484



4-(Trifluoromethyl)benzaldehyde (8.62 g, 49.5 mmol) was added to a solution of (*R*)-*N*-(α-methylbenzyl)amine **483** (6 mL, 47.2 mmol) in EtOH (30 mL) and the resultant solution was heated at reflux for 3 h, then allowed to cool to rt and then cooled to 0 °C. $NaBH_4$ (1.78 g, 47.2 mmol) was added portionwise, maintaining the reaction temperature below 15 °C, and the resultant suspension was stirred for 20 h at rt, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (500 mL) and H_2O (500 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL) and the combined organic extracts were dried and concentrated *in*

vacuo to give (*R*)-**484** as a yellow oil (12.6 g, 96 %, 95% ee);[41] ν_{max} (ATR) 3467 (N−H), 1325 (C−F); $[\alpha]_D^{25}$ +39.4 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.30 (3H, d, *J* 6.6, C(α)*Me*), 1.55 (1H, br s, N*H*), 3.57 (1H, d, *J* 13.7, NCH_AH_BAr), 3.62 (1H, d, *J* 13.7, NCH_AH_BAr), 3.71 (1H, q, *J* 6.6, C(α)*H*), 7.16–7.29 (5H, m, *Ph*), 7.32 (2H, d, *J* 8.0, *Ar*), 7.48 (2H, d, *J* 8.0, *Ar*); δ_C (125 MHz, $CDCl_3$) 24.5 (C(α)*Me*), 51.1 (*C*H_2Ar), 57.6 (*C*(α)), 124.3 (q, *J* 271.8, *C*F_3), 125.3 (q, *J* 3.8, *C*(3), *C*(5)), 126.7 (*m-Ph*), 127.1 (*p-Ph*)), 128.3 (*o-Ph*), 128.6 (*C*(2), *C*(6)), 129.1 (q, *J* 32,4, *C*(4)), 144.8 (*C*(1)), 145.3 (*i-Ph*); δ_F (377 MHz, $CDCl_3$) −62.3 (C*F*$_3$); *m*/*z* (ESI^+) 280 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{16}H_{17}F_3N^+$ ($[M+H]^+$) requires 280.1308; found 280.1303.

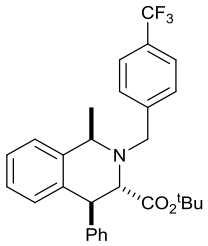
tert-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-(4''-trifluoromethyl)benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 485



BuLi (2.2 M in hexanes, 3.45 mL, 7.6 mmol) was added to (*R*)-**484** (2.19 g, 7.83 mmol, 95% ee) in THF (20 mL) at −78 °C and the resultant solution was stirred at −78 °C for 30 min. A solution of **206** (1.00 g, 4.90 mmol, >99:1 dr) in THF (20 mL) was added at −78 °C via cannula and the resultant solution was stirred at −78 °C for 2 h. (−)-CSO **202** (1.91 g, 4.90 mmol) was then added and stirring was continued as the reaction mixture was allowed to warm to rt over 14 h. Satd aq NH_4Cl (5 mL) was added and the reaction mixture was stirred at rt for 5 min then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and 10% aq citric acid (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (15 mL) and brine (15 mL), then dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (20 mL) and filtered, and the filtrate was concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 5:1) gave **485** as a colourless oil (1.59 g, 65%, >99:1 dr); ν_{max} (ATR) 3494 (O−H), 1724 (C=O), 1325 (C−F); $[\alpha]_D^{25}$ −25.6 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.20 (9H, s, C*Me*$_3$), 1.21 (3H, d, *J* 6.9, C(α)*Me*), 2.79 (1H, br s, O*H*), 4.02 (1H, d, *J* 15.6, NCH_AH_BAr), 4.17 (1H, d, *J* 15.6, NCH_AH_BAr), 4.21 (1H, q, *J* 6.9, C(α)*H*), 4.22 (1H, d, *J* 3.0, C(3)*H*), 4.45 (1H, d, *J* 3.0, C(2)*H*), 7.24–7.52 (14H, m, *Ph*, *Ar*); δ_C (125 MHz, $CDCl_3$) 15.5 (C(α)*Me*), 27.7 (C*Me*$_3$), 51.9 (*C*H_2Ar), 58.2 (*C*(α)), 65.1 (*C*(3)), 73.1 (*C*(2)), 82.5 (*C*Me$_3$), 124.3 (q, *J* 271.8, *C*F_3), 125.0 (q, *J* 3.0, *C*(3''), *C*(5'')), 127.9 (*C*(2''),

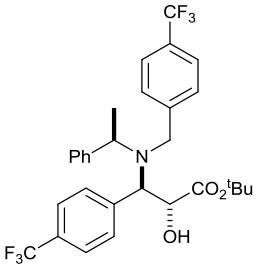
C(6")), 127.1, 127.7 (*p-Ph*), 128.0, 128.1, 128.2, 129.8 (*o-*,*m-Ph*), 128.7 (q, *J* 32.0, *C*(4")), 138.1, 143.9 (*i-Ph*), 146.6 (*C*(1")), 172.4 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −62.2 (CF_3); *m*/*z* (ESI^+) 500 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{29}H_{33}F_3NO_3^+$ ($[M+H]^+$) requires 500.2407; found 500.2401.

(1*R*,3*S*,4*S*)-1-Methyl-*N*(2)-[4'-(trifluoromethyl)benzyl]-3-*tert*-butoxycarbonyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline 486



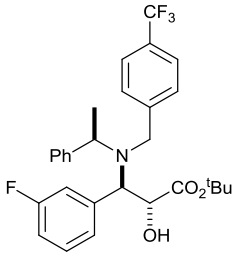
Tf_2O (151 μL, 0.901 mmol) was added to a stirred solution of **485** (300 mg, 0.601 mmol, >99:1 dr) and **318** (370 mg, 1.80 mmol) in CH_2Cl_2 (8 mL) at 0 °C and the resultant mixture was stirred at rt for 6 h. H_2O (4 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 4 mL), and the combined organic extracts were dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (5 mL), the resultant suspension filtered, and the filtrate concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **486** as a pale yellow oil (208 mg, 72%, >99:1 dr); ν_{max} (ATR) 1724 (C=O), 1323 (C−F); $[\alpha]_D^{20}$ +6.2 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.26 (9H, s, C*Me*$_3$), 1.44 (3H, d, *J* 6.4, C(1)*Me*), 3.67 (1H, d, *J* 3.5, C(3)*H*), 3.97 (1H, d, *J* 15.8, NCH_AH_BAr), 4.03 (1H, d, *J* 15.8, NCH_AH_BAr), 4.38 (1H, q, *J* 6.4, C(1)*H*), 4.51 (1H, d, *J* 3.5, C(4)*H*), 6.88 (2H, d, *J* 8.1, C(2")*H*, C(6")*H*), 6.99–7.06 (3H, m, *Ar*, *Ph*), 7.12–7.31 (8H, m, *Ar*, *Ph*); δ_C (125 MHz, $CDCl_3$) 23.3 (C(1)*Me*), 27.9 (C*Me*$_3$), 47.8, (*C*(4)), 55.0 (NCH_2Ar), 55.9 (*C*(1)), 65.4 (*C*(3)), 81.2 (*C*Me_3), 124.3 (q, *J* 272.8, *C*F_3), 124.9 (q, *J* 3.8, *C*(3'), *C*(5')), 126.1 (*p-Ph*), 126.2 (*C*(8)), 126.8, 127.0 (*C*(6), *C*(7)), 127.9, 127.9 (*C*(2'), *C*(6'), *m-Ph*), 128.7 (q, *J* 32.4, *C*(4')), 129.0 (*o-Ph*), 129.8 (*C*(5)), 133.5 (*C*(4a)), 140.8 (*C*(8a)), 143.8 (*i-Ph*), 144.4 (*C*(1')), 171.7 (*C*O_2^{t}Bu); δ_F (377 MHz, $CDCl_3$) –62.2 (CF_3); *m*/*z* (ESI^+) 482 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{29}H_{31}F_3NO_2^+$ ($[M+H]^+$) requires 482.2301; found 482.2290.

tert-Butyl (_R_,_R_,_R_)-2-hydroxy-3-[_N_-(4''-trifluoromethyl)benzyl-_N_(α-methylbenzyl)amino]-3-(4'-trifluoromethyl)phenylpropanoate 488



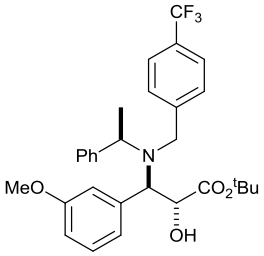
BuLi (2.2 M in hexanes, 1.30 mL, 2.85 mmol) was added to (*R*)-**484** (821 mg, 2.94 mmol, 95% ee) in THF (7.5 mL) at −78 °C and the resultant solution was stirred at −78 °C for 30 min. A solution of **282** (500 mg, 1.84 mmol, >99:1 dr) in THF (7.5 mL) was added at −78 °C via cannula and the resultant solution was stirred at −78 °C for 2 h. (−)-CSO **202** (717 mg, 3.13 mmol) was then added and stirring was continued as the reaction mixture was allowed to warm to rt over 18 h. Satd aq NH_4Cl (2 mL) was added and the reaction mixture was stirred at rt for 5 min then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and 10% aq citric acid (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 4 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (10 mL) and brine (10 mL), then dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (10 mL) and filtered, and the filtrate concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 7:1) gave **488** as a pale yellow oil (737 mg, 71%, >99:1 dr); ν_{max} (ATR) 3481 (O−H), 1724 (C=O), 1325 (C−F); $[\alpha]_D^{25}$ −31.2 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.26 (9H, s, C*Me*$_3$), 1.26 (3H, d, *J* 6.9, C(α)*Me*), 2.97 (1H, br s, O*H*), 4.09 (1H, d, *J* 15.8, NC*H*$_A$H$_B$Ar), 4.22 (1H, d, *J* 15.8, NCH$_A$*H*$_B$Ar), 4.22 (1H, q, *J* 6.9, C(α)*H*), 4.35 (1H, d, *J* 2.7, C(3)*H*), 4.48–4.53 (1H, m, C(2)*H*), 7.26–7.64 (13H, m, *Ph*, *Ar*); δ_C (125 MHz, $CDCl_3$) 16.1 (C(α)*Me*), 27.7 (C*Me*$_3$), 51.9 (N*C*H$_2$Ar), 58.5 (*C*(α)), 64.3 (*C*(3)), 72.7 (*C*(2)), 83.0 (*C*Me$_3$), 124.0, 124.3 (q, *J* 271.8, 2 × *C*F$_3$), 124.9, 125.1 (q, *J* 3.5, *C*(3'), *C*(5'), *C*(3''), *C*(5'')), 127.3 (*p-Ph*), 127.8, 130.0 (*o*,*m-Ph*), 128.0 (*C*(2''), *C*(6'')), 128.4 (*C*(2'), *C*(6')), 128.9, 129.8 (q, *J* 32.5, *C*(4'), *C*(4'')), 142.5 (*C*(1')), 143.4 (*i-Ph*), 146.2 (*C*(1'')), 172.2 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −62.3, −62.5 (2 × C*F*$_3$); *m*/*z* (ESI^+) 500 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{30}H_{32}F_6NO_3^+$ ($[M+H]^+$) requires 568.2281; found 568.2274.

tert-Butyl (_R_,_R_,_R_)-2-hydroxy-3-[_N_-(4''-trifluoromethyl)benzyl-_N_(α-methylbenzyl)amino]-3-(3'-fluoro)phenylpropanoate 489



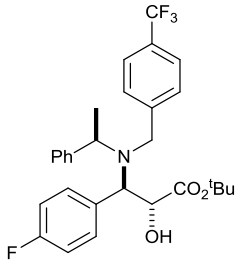
BuLi (2.2 M in hexanes, 1.59 mL, 3.49 mmol) was added to (*R*)-**484** (1.00 g, 3.60 mmol, 95% ee) in THF (9 mL) at −78 °C and the resultant solution was stirred at −78 °C for 30 min. **283** (500 mg, 2.25 mmol, >99:1 dr) in THF (9 mL) was added at −78 °C via cannula and the resultant solution was stirred at −78 °C for 2 h. (−)-CSO **202** (877 mg, 3.83 mmol) was then added and stirring was continued as the reaction mixture was allowed to warm to rt over 18 h. Satd aq NH_4Cl (2 mL) was added and the reaction mixture was stirred at rt for 5 min then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and 10% aq citric acid (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 4 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (10 mL) and brine (10 mL), then dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (10 mL) and filtered, and the filtrate was concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 7:1) gave **489** as a pale yellow oil (775 mg, 67%, >99:1 dr); ν_{max} (ATR) 3482 (O−H), 1724 (C=O), 1325 (C−F); $[\alpha]_D^{25}$ −30.9 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.22 (3H, d, *J* 6.9, C(α)*Me*), 1.24 (9H, s, C*Me*$_3$), 2.94 (1H, br s, O*H*), 4.05 (1H, d, *J* 15.6, NC*H*$_A$H$_B$Ar), 4.17–4.25 (3H, m, NCH$_A$*H*$_B$Ar, C(α)*H*, C(3)*H*), 4.46 (1H, app s, C(2)*H*), 6.95–7.55 (13H, m, *Ph*, *Ar*); δ_C (125 MHz, $CDCl_3$) 15.8 (C(α)*Me*), 27.7 (C*Me*$_3$), 51.9 (NCH_2Ar), 58.3 (*C*(α)), 64.2 (*C*(3)), 72.9 (*C*(2)), 82.9 (*C*Me$_3$), 114.6 (d, *J* 21.0, *C*(4')), 116.7 (d, *J* 21.9, *C*(2')), 124.2 (q, *J* 271.8, *C*F$_3$), 125.1 (q, *J* 3.8, *C*(3''), *C*(5'')), 125.4 (*C*(6')), 127.9 (*C*(2''), *C*(6'')), 127.2 (*p-Ph*), 128.1, 128.3 (*o,m-Ph*), 128.8 (q, *J* 32.4, *C*(4'')), 129.5 (d, *J* 8.6, *C*(5')), 140.8 (d, *J* 4.8, *C*(1')), 143.6 (i-*Ph*), 146.3 (*C*(1'')), 162.6 (d, *J* 246.1, *C*(3')), 172.4 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −62.2, (C*F*$_3$), −113.1 (C(3')*F*); *m*/*z* (ESI^+) 518 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{29}H_{32}F_4NO_3^+$ ($[M+H]^+$) requires 518.2313; found 518.2305.

tert-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-(4''-trifluoromethyl)benzyl-*N*(α-methylbenzyl)amino]-3-(3'-methoxy)phenylpropanoate 490



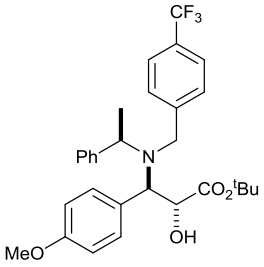
BuLi (2.2 M in hexanes, 1.41 mL, 3.10 mmol) was added to (*R*)-**484** (954 mg, 3.41 mmol, 95% ee) in THF (8 mL) at −78 °C and the resultant solution was stirred at −78 °C for 30 min. **284** (500 mg, 2.00 mmol, >99:1 dr) in THF (8 mL) was added at −78 °C via cannula and the resultant solution was stirred at −78 °C for 2 h. (−)-CSO **202** (779 mg, 3.40 mmol) was then added and stirring was continued as the reaction mixture was allowed to warm to rt over 18 h. Satd aq NH_4Cl (2 mL) was added and the reaction mixture was stirred at rt for 5 min then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and 10% aq citric acid (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 4 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (10 mL) and brine (10 mL), then dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (10 mL) and filtered, and the filtrate was concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 5:1) gave **490** as a pale yellow oil (1.01 g, 95%, >99:1 dr); ν_{max} (ATR) 3487 (O−H), 1725 (C=O), 1325 (C−F); $[\alpha]_D^{25}$ −29.0 (*c* 1.0, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.21–1.27 (3H, obscured d, *J* 6.9, C(α)*Me*), 1.24 (9H, s, C*Me*$_3$), 2.91 (1H, br s, O*H*), 3.79 (3H, s, O*Me*), 4.04 (1H, d, *J* 15.6, NCH_AH_BAr), 4.17 (1H, d, *J* 15.6, NCH_AH_BAr), 4.21 (1H, d, *J* 2.9, C(3)*H*), 4.24 (1H, q, *J* 6.9, C(α)*H*), 4.42–4.45 (1H, m, C(2)*H*), 6.82 (1H, d, *J* 8.2, C(4')*H*), 7.00–7.08 (2H, m, C(2")*H*, C(6")*H*), 7.20–7.54 (10H, m, *Ph*, *Ar*); δ_C (125 MHz, $CDCl_3$) 15.7 (C(α)*Me*), 27.7 (C*Me*$_3$), 51.9 (NCH_2Ar), 55.2 (O*Me*), 58.2 (*C*(α)), 64.9 (*C*(3)), 73.0 (*C*(2)), 82.6 (*C*Me$_3$), 112.8 (*C*(4')), 115.8 (*C*(2')), 122.2 (*C*(6')), 124.5 (q, *J* 271.8, *C*F_3), 125.0 (q, *J* 3.5, *C*(3"), *C*(5")), 127.1 (*p-Ph*), 127.9 (*C*(2"), *C*(6")), 128.1, 128.2 (*o,m-Ph*), 128.7 (q, *J* 32.1, *C*(4")), 129.0 (*C*(5')), 139.6 (*C*(1')), 143.8 (*i-Ph*), 146.6 (*C*(1")), 159.3 (*C*(3')), 172.4 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −62.2 (C*F*$_3$); *m*/*z* (ESI^+) 530 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{30}H_{35}F_3NO_4^+$ ($[M+H]^+$) requires 530.2513; found 530.2507.

tert-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-(4''-trifluoromethyl)benzyl-*N*-(α-methylbenzyl)amino]-3-(4'-fluoro)phenylpropanoate 491



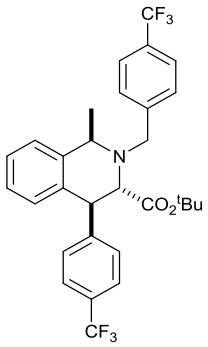
BuLi (2.2 M in hexanes, 1.59 mL, 3.49 mmol) was added to (*R*)-**484** (1.00 g, 3.60 mmol, 95% ee) in THF (9 mL) at −78 °C and the resultant solution was stirred at −78 °C for 30 min. **285** (500 mg, 2.25 mmol, >99:1 dr) in THF (9 mL) was added at −78 °C via cannula and the resultant solution was stirred at −78 °C for 2 h. (−)-CSO **202** (877 mg, 3.83 mmol) was then added and stirring was continued as the reaction mixture was allowed to warm to rt over 18 h. Satd aq NH_4Cl (2 mL) was added and the reaction mixture was stirred at rt for 5 min then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and 10% aq citric acid (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 4 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (10 mL) and brine (10 mL), then dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (10 mL) and filtered, and the filtrate was concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 5:1) gave **491** as a pale yellow oil (985 mg, 85%, >99:1 dr); ν_{max} (ATR) 3490 (O−H), 1724 (C=O), 1325 (C−F); $[\alpha]_D^{25}$ −25.6 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.23–1.26 (3H, obscured d, *J* 6.9, C(α)*Me*), 1.24 (9H, s, C*Me*$_3$), 2.94 (1H, br s, O*H*), 4.05 (1H, d, *J* 15.6, NC*H*$_A$H$_B$Ar), 4.18 (1H, d, *J* 15.6, NCH$_A$*H*$_B$Ar), 4.23 (1H, q, *J* 6.9, C(α)*H*) 4.25 (1H, app s, C(3)*H*), 4.48–4.51 (1H, m, C(2)*H*), 6.00–7.56 (13H, m, *Ph*, *Ar*); δ_C (125 MHz, $CDCl_3$) 15.8 (C(α)*Me*), 27.6 (C*Me*$_3$), 51.7 (N*C*H$_2$Ph), 58.3 (*C*(α)), 64.0 (*C*(3)), 72.8 (*C*(2)), 82.6 (*C*Me$_3$), 114.9 (d, *J* 21.0, *C*(3'), *C*(5')), 124.3 (q, *J* 271.8, *C*F$_3$), 125.0 (q, *J* 3.8, *C*(3''), *C*(5'')), 127.1 (*p-Ph*), 127.9 (*C*(2''), *C*(6'')), 127.8 128.3 (*o,m-Ph*), 129.7 (q, *J* 32.4, *C*(4'')), 132.4 (d, *J* 7.6, *C*(2'), *C*(6')), 135.0 (*C*(1')), 144.7 (*i-Ph*), 147.5 (*C*(1'')), 163.1 (d, *J* 247.0, *C*(4')), 173.2 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −62.2, (C*F*$_3$), −114.5 (C(3')*F*); *m*/*z* (ESI$^+$) 540 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{31}F_4NNaO_3^+$ ([M+Na]$^+$) requires 540.2132; found 540.2124.

tert-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-(4''-trifluoromethyl)benzyl-*N*(α-methylbenzyl)amino]-3-(4'-methoxy)phenylpropanoate 492



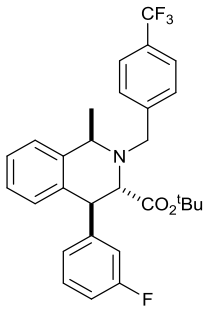
BuLi (2.2 M in hexanes, 1.41 mL, 3.10 mmol) was added to (*R*)-**484** (954 mg, 3.41 mmol, 95% ee) in THF (8 mL) at −78 °C and the resultant solution was stirred at −78 °C for 30 min. **286** (500 mg, 2.00 mmol, >99:1 dr) in THF (8 mL) was added at −78 °C via cannula and the resultant solution was stirred at −78 °C for 2 h. (−)-CSO **202** (779 mg, 3.40 mmol) was then added and stirring was continued as the reaction mixture was allowed to warm to rt over 18 h. Satd aq NH_4Cl (2 mL) was added and the reaction mixture was stirred at rt for 5 min then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and 10% aq citric acid (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 4 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (10 mL) and brine (10 mL), then dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (10 mL) and filtered, and the filtrate was concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 5:1) gave **492** as a pale yellow oil (859 mg, 81%, >99:1 dr); ν_{max} (ATR) 3486 (O−H), 1724 (C=O), 1325 (C−F); $[\alpha]_D^{25}$ −26.7 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.20–1.23 (3H, obscured d, *J* 6.6, C(α)*Me*), 1.22 (9H, s, C*Me*$_3$), 2.88 (1H, br s, O*H*), 3.79 (3H, s, O*Me*), 3.98 (1H, d, *J* 15.6, NC*H*$_A$H$_B$Ar), 4.14 (1H, d, *J* 15.6, NCH$_A$*H*$_B$Ar), 4.15–4.17 (1H, m, C(3)*H*), 4.20 (1H, q, *J* 6.6, C(α)*H*), 4.42–4.45 (1H, m, C(2)*H*), 6.83 (2H, d, *J* 8.2, C(3')*H*, C(5')*H*), 7.23–7.42 (7H, m, *Ph*, *Ar*), 7.64 (2H, d, *J* 7.4, *o-Ph*), 7.50 (2H, d, *J* 7.7, C(2")*H*, C(6")*H*); δ_C (125 MHz, $CDCl_3$) 15.5 (C(α)*Me*), 27.7 (C*Me*$_3$), 51.8 (NCH_2Ar), 55.2 (O*Me*), 58.1 (*C*(α)), 64.6 (*C*(3)), 73.2 (*C*(2)), 82.4 (*C*Me$_3$), 113.4 (*C*(3'), *C*(5')), 124.4 (q, *J* 271.8, *C*F_3), 125.0 (q, *J* 3.8, *C*(3"), *C*(5")), 127.0 (*p-Ph*), 127.9 (*C*(2"), *C*(6")), 128.1, 128.2 (*o,m-Ph*), 128.6 (q, *J* 32.4, *C*(4")), 130.0 (*C*(1')), 130.9 (*C*(2'), *C*(6')), 144.0 (*i-Ph*), 146.7 (*C*(1")), 159.0 (*C*(4')), 172.4 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −62.2 (C*F*$_3$); *m*/*z* (ESI$^+$) 530 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{35}F_3NO_4^+$ ([M+H]$^+$) requires 530.2513; found 530.2504.

(1*R*,3*S*,4*S*)-1-Methyl-*N*(2)-[4''-(trifluoromethyl)benzyl]-3-*tert*-butoxycarbonyl-4-[4'-(trifluoromethyl)]phenyl-1,2,3,4-tetrahydroisoquinoline 493



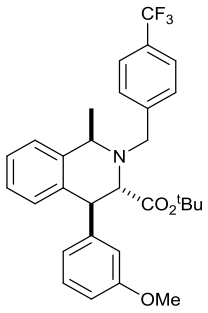
Tf_2O (89 μL, 0.529 mmol) was added to a stirred solution of **488** (200 mg, 0.352 mmol, >99:1 dr) and **318** (217 mg, 1.06 mmol) in CH_2Cl_2 (5 mL) at 0 °C and the resultant mixture was stirred at 40 °C for 6 h. H_2O (3 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 3 mL), and the combined organic extracts were dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (5 mL), the resultant suspension filtered, and the filtrate concentrated *in vacuo* to give a 93:7 mixture of **493** and **497**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 30:1) gave **493** as a red oil (127 mg, 66%, >99:1 dr); ν_{max} (ATR) 1726 (C=O), 1326 (C−F); $[\alpha]_D^{20}$ +14.4 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.27 (9H, s, C*Me*$_3$), 1.46 (3H, d, *J* 6.5, C(1)*Me*), 3.60 (1H, d, *J* 3.2, C(3)*H*), 3.98 (2H, app s, NC*H*$_2$Ar), 4.41 (1H, q, *J* 6.5, C(1)*H*), 4.55 (1H, d, *J* 3.2, C(4)*H*), 6.85 (2H, d, *J* 8.0, C(2'')*H*, C(6'')*H*), 6.99 (1H, d, *J* 7.6 C(5)*H*), 7.12 (2H, d, *J* 8.1, C(2')*H*, C(6')*H*), 7.14–7.31 (5H, m, *Ar*), 7.49 (2H, d, *J* 8.1, C(3')*H*, C(5')*H*); δ_C (125 MHz, $CDCl_3$) 23.3 (C(1)*Me*), 27.9 (C*Me*$_3$), 47.7, (*C*(4)), 54.7 (N*C*H$_2$Ar), 55.7 (*C*(1)), 65.0 (*C*(3)), 81.6 (*C*Me$_3$), 124.3 (q, *J* 271.8, C(4'')*C*F$_3$), 124.4 (q, *J* 271.8, C(4')*C*F$_3$), 124.7 (q, *J* 3.8, *C*(3'), *C*(5')), 124.8 (q, *J* 3.8, *C*(3''), *C*(5'')), 126.4 (*C*(8)), 127.2 (*C*(6)), 127.3 (*C*(7)), 128.0 (*C*(2''), *C*(6'')), 128.6 (q, *J* 32.4, *C*(4')), 128.9 (q, *J* 32.4, *C*(4'')), 129.2 (*C*(2'), *C*(6')), 129.7 (*C*(5)), 132.6 (*C*(4a)), 140.8 (*C*(8a)), 144.0 (*C*(1'')), 148.0 (*C*(1')), 171.2 (*C*O$_2$^{t}Bu); δ_F (377 MHz, $CDCl_3$) –62.5, –62.3 (2 × C*F*$_3$); *m*/*z* (ESI$^+$) 550 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{30}F_6NO_2^+$ ([M+H]$^+$) requires 550.2175; found 550.2166.

(1*R*,3*S*,4*S*)-1-Methyl-*N*(2)-[4''-(trifluoromethyl)benzyl]-3-*tert*-butoxycarbonyl-4-(3'-fluoro)phenyl-1,2,3,4-tetrahydroisoquinoline 494



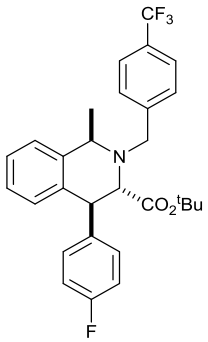
Tf_2O (98 μL, 0.580 mmol) was added to a stirred solution of **489** (200 mg, 0.386 mmol, >99:1 dr) and **318** (238 mg, 1.16 mmol) in CH_2Cl_2 (5.5 mL) at 0 °C and the resultant mixture was stirred at 40 °C for 6 h. H_2O (3 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 3 mL), and the combined organic extracts were dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (5 mL), the resultant suspension filtered, and the filtrate concentrated *in vacuo* to give a 96:4 mixture of **494** and **498**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 30:1) gave **494** as a red oil (145 mg, 75%, >99:1 dr); ν_{max} (ATR) 1726 (C=O), 1325 (C−F); $[\alpha]_D^{20}$ +10.2 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.29 (9H, s, C*Me*$_3$), 1.47 (3H, d, *J* 6.5, C(1)*Me*), 3.67 (1H, d, *J* 3.4, (C(3)*H*), 4.03 (2H, app t, *J* 17.7, NC*H*$_2$Ar), 4.41 (1H, q, *J* 6.5, C(1)*H*), 4.51 (1H, d, *J* 3.4, C(4)*H*), 6.71–6.76 (1H, m, C(2')*H*), 6.85 (1H, d, *J* 7.7, C(6')*H*), 6.95–6.99 (3H, m, *Ar*), 7.02 (1H, d, *J* 7.4, C(5)*H*), 7.16–7.31 (4H, m, *Ar*), 7.38 (2H, d, *J* 8.0, C(3")*H*, C(5")*H*); δ_C (125 MHz, $CDCl_3$) 23.3 (C(1)*Me*), 27.9 (C*Me*$_3$), 47.5, (*C*(4)), 54.8 (NC*H*$_2$Ar), 55.8 (*C*(1)), 64.9 (*C*(3)), 81.4 (*C*Me$_3$), 113.0 (d, *J* 21.9, *C*(4')), 116.0 (d, *J* 21.0, *C*(2')), 124.2 (q, *J* 271.8, *C*F$_3$), 124.5 (d, *J* 2.9, *C*(6')), 124.9 (q, *J* 3.8, *C*(3"), *C*(5")), 126.3 (*C*(8)), 127.1, 127.1 (*C*(6), *C*(7)), 128.0 (*C*(2"), *C*(6")), 128.9 (q, *J* 32.4, *C*(4")), 129.2 (d, *J* 7.6, *C*(5')), 129.7 (*C*(5)), 132.9 (*C*(4a)), 140.7 (*C*(8a)), 144.2 (*C*(1")), 146.5 (d, *J* 6.7, *C*(1')), 162.6 (d, *J* 246.1, *C*(3')), 171.4 (*C*O$_2$^{t}Bu); δ_F (377 MHz, $CDCl_3$) –113.9 (C(3')*F*), –62.3 (C*F*$_3$); *m*/*z* (ESI^+) 500 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{29}H_{30}F_4NO_2^+$ ($[M+H]^+$) requires 500.2207; found 500.2195.

(1*R*,3*S*,4*S*)-1-Methyl-*N*(2)-[4''-(trifluoromethyl)benzyl]-3-*tert*-butoxycarbonyl-4-(3'-methoxy)phenyl-1,2,3,4-tetrahydroisoquinoline 495



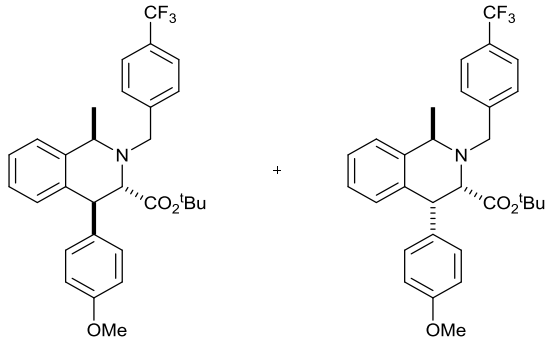
Tf_2O (95 μL, 0.567 mmol) was added to a stirred solution of **490** (200 mg, 0.378 mmol, >99:1 dr) and **318** (233 mg, 1.13 mmol) in CH_2Cl_2 (5.4 mL) at 0 °C and the resultant mixture was stirred at rt for 6 h. H_2O (3 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 3 mL), and the combined organic extracts were dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (5 mL), the resultant suspension filtered, and the filtrate concentrated *in vacuo* to give a 100:0 mixture of **495** and **499**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 30:1) gave **495** as a red oil (156 mg, 81%, >99:1 dr); ν_{max} (ATR) 1725 (C=O), 1325 (C−F); $[\alpha]_D^{20}$ +2.4 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.30 (9H, s, C*Me*$_3$), 1.48 (3H, d, *J* 6.5, C(1)*Me*), 3.70 (1H, d, *J* 3.4, (C(3)*H*), 3.72 (3H, s, O*Me*), 4.02 (1H, d, *J* 15.7, NC*H*$_A$H$_B$Ar), 4.06 (1H, d, *J* 15.7, NCH$_A$*H*$_B$Ar), 4.42 (1H, q, *J* 6.5, C(1)*H*), 4.51 (1H, d, *J* 3.4, C(4)*H*), 6.59–6.69 (1H, m, C(2')*H*), 6.64 (1H, d, *J* 7.6, C(6')*H*), 6.82–6.86 (1H, m, C(4')*H*), 6.96 (2H, d, *J* 8.0, C(2")*H*, C(6")*H*), 7.06 (1H, d, *J* 7.6, C(5)*H*), 7.15–7.30 (4H, m, *Ar*), 7.34 (2H, d, *J* 8.0, C(3")*H*, C(5")*H*); δ_C (125 MHz, $CDCl_3$) 23.3 (C(1)*Me*), 27.9 (C*Me*$_3$), 47.9, (*C*(4)), 54.8 (N*C*H$_2$Ar), 55.0 (O*Me*), 55.8 (*C*(1)), 65.2 (*C*(3)), 81.2 (*C*Me$_3$), 111.5 (*C*(4')), 114.7 (*C*(2')), 121.5 (*C*(6')), 124.3 (q, *J* 271.8, *C*F$_3$), 124.8 (q, *J* 3.8, *C*(3"), *C*(5")), 126.1 (*C*(8)), 126.9, 126.9 (*C*(6), *C*(7)), 128.1 (*C*(2"), *C*(6")), 128.7 (*C*(5')), 128.7 (q, *J* 32.4, *C*(4")), 129.8 (*C*(5)), 133.3 (*C*(4a)), 140.8 (*C*(8a)), 144.4 (*C*(1"), 145.4 (*C*(1')), 159.3 (*C*(3')), 171.7 (*C*O$_2$^{t}Bu); δ_F (377 MHz, $CDCl_3$) –62.3 (C*F*$_3$); *m*/*z* (ESI$^+$) 512 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{33}F_3NO_3^+$ ([M+H]$^+$) requires 512.2407; found 512.2397.

(1*R*,3*S*,4*S*)-1-Methyl-*N*(2)-[4''-(trifluoromethyl)benzyl]-3-*tert*-butoxycarbonyl-4-(4'-fluoro)phenyl-1,2,3,4-tetrahydroisoquinoline 496



Tf_2O (98 μL, 0.580 mmol) was added to a stirred solution of **491** (200 mg, 0.386 mmol, >99:1 dr) and **318** (238 mg, 1.16 mmol) in CH_2Cl_2 (5.5 mL) at 0 °C and the resultant mixture was stirred at rt for 6 h. H_2O (3 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 3 mL), and the combined organic extracts were dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (5 mL), the resultant suspension filtered, and the filtrate concentrated *in vacuo* to give a 100:0 mixture of **496** and **500**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 30:1) gave **496** as a red oil (171 mg, 89%, >99:1 dr); ν_{max} (ATR) 1726 (C=O), 1325 (C−F); $[\alpha]_D^{20}$ +10.9 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.30 (9H, s, C*Me*$_3$), 1.48 (3H, d, *J* 6.5, C(1)*Me*), 3.65 (1H, d, *J* 3.6, C(3)*H*), 4.01 (1H, d, *J* 15.4, NCH_AH$_B$Ar), 4.05 (1H, d, *J* 15.4, NCH$_A$$H_B$Ar), 4.40 (1H, q, *J* 6.5, C(1)*H*), 4.51 (1H, d, *J* 3.6, C(4)*H*), 6.75–7.04 (7H, m, *Ar*), 7.15–7.30 (3H, m, *Ar*), 7.36 (2H, d, *J* 8.3, C(3'')*H*, C(5'')*H*); δ_C (125 MHz, $CDCl_3$) 23.3 (C(1)*Me*), 27.9 (C*Me*$_3$), 47.9, (*C*(4)), 54.8 (N*C*H$_2$Ar), 55.8 (*C*(1)), 65.1 (*C*(3)), 81.4 (*C*Me$_3$), 114.5 (d, *J* 21.9, *C*(3'), *C*(5')), 124.2 (q, *J* 271.8, *C*F$_3$), 124.9 (q, *J* 3.8, *C*(3''), *C*(5'')), 126.2 (*C*(8)), 127.0, 127.1 (*C*(6), *C*(7)), 128.0 (*C*(2''), *C*(6'')), 129.0 (q, *J* 32.4, *C*(4'')), 129.7 (*C*(5)), 130.3 (d, *J* 7.6, *C*(2'), *C*(6')), 133.4 (*C*(4a)), 139.5 (d, *J* 2.9, *C*(1')), 140.6 (*C*(8a)), 144.2 (*C*(1''), 161.5 (d, *J* 245.1, *C*(4')), 171.5 (*C*O$_2$^{t}Bu); δ_F (377 MHz, $CDCl_3$) –117.1 (C(4')*F*), –62.3 (C*F*$_3$); *m*/*z* (ESI$^+$) 500 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{30}F_4NO_2^+$ ([M+H]$^+$) requires 500.2207; found 500.2195.

(1*R*,3*S*,4*S*)-1-Methyl-*N*(2)-[4''-(trifluoromethyl)benzyl]-3-*tert*-butoxycarbonyl-4-(4'-methoxy)phenyl-1,2,3,4-tetrahydroisoquinoline 501 and (1*R*,3*S*,4*R*)-1-methyl-*N*(2)-[4''-(trifluoromethyl)benzyl]-3-*tert*-butoxycarbonyl-4-(4'-methoxy)phenyl-1,2,3,4-tetrahydroisoquinoline 502

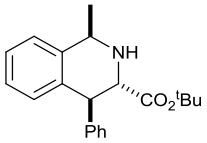


501 **502**

Tf_2O (74 μL, 0.440 mmol) was added to a stirred solution of **492** (155 mg, 0.293 mmol, >99:1 dr) and **318** (180 mg, 0.879 mmol) in CH_2Cl_2 (4.2 mL) at 0 °C and the resultant mixture was stirred at – 20 °C for 2.5 h. H_2O (3 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 3 mL), and the combined organic extracts were dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (5 mL), the resultant suspension filtered, and the filtrate concentrated *in vacuo* to give an 80:20 mixture of **501** and **502**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **501** as a red oil (59 mg, 39%, >99:1 dr); ν_{max} (ATR) 1726 (C=O), 1325 (C−F); $[\alpha]_D^{25}$ +31.3 (*c* 0.3 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.27 (9H, s, C*Me*$_3$), 1.45 (3H, d, *J* 6.5, C(1)*Me*), 3.64 (1H, d, *J* 3.8, C(3)*H*), 3.84 (3H, s, O*Me*), 3.98 (1H, d, *J* 15.7, NC*H*$_A$H$_B$Ar), 4.03 (1H, d, *J* 15.7, NCH$_A$*H*$_B$Ar), 4.36 (1H, q, *J* 6.5, C(1)*H*), 4.45 (1H, d, *J* 3.8, C(4)*H*), 6.79–6.99 (6H, m, *Ar*), 7.01 (1H, d, *J* 7.4, C(5)*H*), 7.13–7.27 (3H, m, *Ar*), 7.32 (2H, d, *J* 8.0, C(3'')*H*, C(5'')*H*); δ_C (125 MHz, $CDCl_3$) 23.3 (C(1)*Me*), 27.9 (C*Me*$_3$), 46.8, (*C*(4)), 54.8 (N*C*H$_2$Ar), 55.3 (O*Me*), 55.8 (*C*(1)), 65.3 (*C*(3)), 81.2 (*C*Me$_3$), 113.2 (*C*(3'), *C*(5')), 124.3 (q, *J* 271.8, *C*F$_3$), 124.8 (q, *J* 3.8, *C*(3''), *C*(5'')), 126.1 (*C*(8)), 126.7, 126.9 (*C*(6), *C*(7)), 128.0 (*C*(2''), *C*(6'')), 128.7 (q, *J* 32.4, *C*(4'')), 129.7 (*C*(5)), 130.0 (C(2'), C(6')), 134.0 (*C*(4a)), 135.9 (*C*(1')), 140.6 (*C*(8a)), 144.4 (*C*(1'')), 158.1 (*C*(4')), 171.8 (*C*O$_2$^{t}Bu); δ_F (377 MHz, $CDCl_3$) –62.3 (C*F*$_3$); *m*/*z* (ESI$^+$) 512 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{33}F_3NO_3^+$ ([M+H]$^+$) requires 512.2407; found 512.2405. Further elution gave **502** as a red oil (20 mg, 13%, >99:1 dr); ν_{max} (ATR) 1726 (C=O), 1325 (C−F); $[\alpha]_D^{25}$ −28.6 (*c* 0.5 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.26 (9H, s, C*Me*$_3$), 1.54 (3H, d, *J* 6.3, C(1)*Me*), 3.59 (1H, d, *J* 5.5, C(3)*H*), 3.64 (1H, d, *J* 14.8, NC*H*$_A$H$_B$Ar), 3.79 (3H, s, O*Me*), 4.18 (1H, d, *J* 14.8, NCH$_A$*H*$_B$Ar), 4.32 (1H, q, *J* 6.3, C(1)*H*), 4.46 (1H, d, *J* 5.5, C(4)*H*), 6.80 (2H, d, *J* 8.7, C(3')*H*, C(5')*H*), 6.91 (1H, d, *J* 7.7, C(5)*H*), 7.04–7.11 (3H, m, *Ar*),

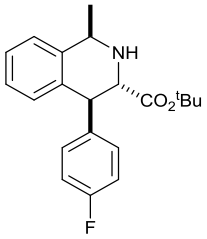
7.17–7.23 (2H, m, *Ar*), 7.54 (2H, d, *J* 8.2, C(3'')*H*, C(5'')*H*), 7.60 (2H, d, *J* 8.2, C(2'')*H*, C(6'')*H*); δ_C (125 MHz, $CDCl_3$) 23.3 (C(1)*Me*), 28.1 (C*Me*$_3$), 47.8, (*C*(4)), 55.1 (N*C*H$_2$Ar), 55.2 (O*Me*), 55.8 (*C*(1)), 64.2 (*C*(3)), 81.0 (*C*Me$_3$), 113.5 (*C*(3'), *C*(5')), 124.3 (q, *J* 271.8, *C*F$_3$), 125.3 (q, *J* 3.8, *C*(3''), *C*(5'')), 125.3 (*C*(8)), 126.0, 126.1 (*C*(6), *C*(7)), 127.8 (*C*(5)), 128.6 (*C*(2''), *C*(6'')), 129.3 (q, *J* 31.5, *C*(4'')), 131.3 (C(2'), C(6')), 131.9 (*C*(1')), 134.5 (*C*(4a)), 140.7 (*C*(8a)), 143.9 (*C*(1'')), 158.6 (*C*(4')), 170.4 (*C*O$_2$^{t}Bu); δ_F (377 MHz, $CDCl_3$) –62.3 (C*F*$_3$); *m*/*z* (ESI$^+$) 512 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{33}F_3NO_3^+$ ([M+H]$^+$) requires 512.2407; found 512.2404.

(1*R*,3*S*,4*S*)-1-Methyl-3-*tert*-butoxycarbonyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline 503



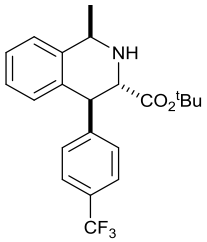
$Pd(OH)_2$/C (35 mg, 40% w/w) was added to a degassed solution of **486** (139 mg, 0.289 mmol, >99:1 dr) in MeOH (1 mL) and the resultant mixture was placed under H_2 pressure (5 atm) and stirred at rt for 48 h. The reaction mixture was filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1, 1% Et_3N) gave **503** as a pale yellow oil (55 mg, 59%, >99:1 dr); ν_{max} (ATR) 3290 (O–H), 1724 (C=O); $[\alpha]_D^{20}$ +87.7 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.30 (9H, s, C*Me*$_3$), 1.57 (3H, d, *J* 6.8, C(1)*Me*), 2.01 (1H, br s, N*H*), 3.85 (1H, d, *J* 7.1, C(3)*H*), 4.28 (1H, d, *J* 7.1, C(4)*H*), 4.37 (1H, q, *J* 6.8, C(1)*H*), 6.85 (1H, d, *J* 7.7, C(5)*H*), 7.05–7.10 (1H, m, *Ar*), 7.13–7.34 (7H, m, *Ar*, *Ph*); δ_C (125 MHz, $CDCl_3$) 23.9 (C(1)*Me*), 27.8 (C*Me*$_3$), 47.9 (*C*(4)), 49.6 (*C*(1)), 60.3 (*C*(3)), 81.2 (*C*Me$_3$), 125.9 (*C*(8)), 126.3, 126.3 (*C*(6), *C*(7)), 126.6 (*p*-*Ph*), 128.3, 129.3 (*o*,*m*-*Ph*), 129.8 (*C*(5)), 136.1 (*C*(4a)), 139.9 (*C*(8a)), 143.4 (*i*-*Ph*), 172.1 (*C*O$_2$^{t}Bu); *m*/*z* (ESI$^+$) 324 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{26}NO_2^+$ ([M+H]$^+$) requires 324.1958; found 324.1956.

(1*R*,3*S*,4*S*)-1-Methyl-3-*tert*-butoxycarbonyl-4-(4'-fluoro)phenyl-1,2,3,4-tetrahydroisoquinoline 504



$Pd(OH)_2$/C (29 mg, 25% w/w) was added to a degassed solution of **496** (115 mg, 0.230 mmol, >99:1 dr) in MeOH (1 mL) and the resultant mixture was placed under H_2 pressure (5 atm) and stirred at rt for 5 days. The reaction mixture was filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1, 1% Et_3N) gave **504** as a colourless oil (57 mg, 72%, >99:1 dr); ν_{max} (ATR) 3394 (N−H), 1726 (C=O), 1151 (C−F); $[\alpha]_D^{20}$ +55.3 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.31 (9H, s, C*Me*$_3$), 1.55 (3H, d, *J* 6.8, C(1)*Me*), 1.95 (1H, br s, N*H*), 3.79 (1H, d, *J* 6.8, C(3)*H*), 4.28 (1H, d, *J* 6.8, C(4)*H*), 4.35 (1H, q, *J* 6.8, C(1)*H*), 6.82 (1H, d, *J* 7.7, C(5)*H*), 6.97–7.02 (2H, m, C(3')*H*, C(5')*H*), 7.06–7.10 (1H, m, *Ar*), 7.11–7.21 (4H, m, *Ar*); δ_C (125 MHz, $CDCl_3$) 23.9 (C(1)*Me*), 27.9 (C*Me*$_3$), 47.0, (*C*(4)), 49.5 (*C*(1)), 60.4 (*C*(3)), 81.4 (*C*Me_3), 115.1 (d, *J* 21.0, *C*(3'), *C*(5')), 126.0 (*C*(8)), 126.4, 126.4 (*C*(6), *C*(7)), 129.7 (*C*(5)), 130.7 (d, *J* 7.6, *C*(2'), *C*(6')), 135.9 (*C*(4a)), 139.3 (d, *J* 3.8, *C*(1')), 139.8 (*C*(8a)), 161.8 (d, *J* 244.1, *C*(4')), 172.1 (*C*O_2^{t}Bu); δ_F (377 MHz, $CDCl_3$) –116.4 (C(4')*F*); *m*/*z* (ESI^+) 342 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{21}H_{25}FNO_2^+$ ($[M+H]^+$) requires 342.1864; found 342.1865.

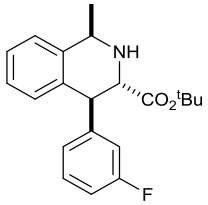
(1*R*,3*S*,4*S*)-1-Methyl-3-*tert*-butoxycarbonyl-4-[4'-(trifluoromethyl)]phenyl-1,2,3,4-tetrahydroisoquinoline 505



$Pd(OH)_2$/C (26 mg, 25% w/w) was added to a degassed solution of **493** (105 mg, 0.191 mmol, >99:1 dr) in MeOH (1 mL) and the resultant mixture was placed under H_2 pressure (5 atm) and stirred at rt for 5 days. The reaction mixture was filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1, 1% Et_3N) gave **505** as a colourless oil (32 mg, 43%, >99:1 dr); ν_{max} (ATR) 3322 (N−H), 1729 (C=O), 1369 (C−F); $[\alpha]_D^{20}$ +44.4 (*c* 0.5 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.31 (9H, s, C*Me*$_3$), 1.56 (3H, d, *J* 6.8, C(1)*Me*), 1.98 (1H, br s, N*H*), 3.81 (1H, d, *J* 6.3,

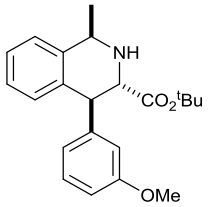
C(3)*H*), 4.38 (1H, q, *J* 6.8, C(1)*H*), 4.39 (1H, d, *J* 6.3, C(4)*H*), 6.81 (1H, d, *J* 7.7 C(5)*H*), 7.07–7.11 (1H, m, *Ar*), 7.17–7.23 (2H, m, Ar), 7.31 (2H, d, *J* 8.1, C(3')*H*, C(5')*H*), 7.57 (2H, d, *J* 8.1, C(2')*H*, C(6')*H*); δ_C (125 MHz, $CDCl_3$) 23.8 (C(1)*Me*), 27.8 (C*Me*$_3$), 47.4, (*C*(4)), 49.3 (*C*(1)), 60.3 (*C*(3)), 81.6 (*C*Me$_3$), 124.3 (q, *J* 271.8, *C*F$_3$), 125.2 (q, *J* 3.8, *C*(3'), *C*(5')), 126.1 (*C*(8)), 126.5, 126.7 (*C*(6), *C*(7)), 128.9 (q, *J* 32.4, *C*(4')), 129.6 (*C*(2'), *C*(6')), 129.8 (*C*(5)), 134.9 (*C*(4a)), 139.8 (*C*(8a)), 148.0 (*C*(1')), 171.8 (*C*O$_2$^{t}Bu); δ_F (377 MHz, $CDCl_3$) –62.4 (C*F*$_3$); *m*/*z* (ESI$^+$) 392 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{25}F_3NO_2^+$ ([M+H]$^+$) requires 392.1832; found 392.1831.

(1*R*,3*S*,4*S*)-1-Methyl-3-*tert*-butoxycarbonyl-4-(3'-fluoro)phenyl-1,2,3,4-tetrahydroisoquinoline 506



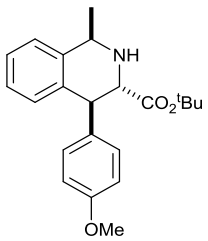
$Pd(OH)_2$/C (50 mg, 25% w/w) was added to a degassed solution of **494** (200 mg, 0.401 mmol, >99:1 dr) in MeOH (1 mL) and the resultant mixture was placed under H_2 pressure (5 atm) and stirred at rt for 5 days. The reaction mixture was filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1, 1% Et_3N) gave **506** as a colourless oil (51 mg, 37%, >99:1 dr); ν_{max} (ATR) 3402 (N−H), 1725 (C=O), 1152 (C−F); $[\alpha]_D^{20}$ +79.1 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.32 (9H, s, C*Me*$_3$), 1.55 (3H, d, *J* 6.6, C(1)*Me*), 2.03 (1H, br s, N*H*), 3.82 (1H, d, *J* 6.6, C(3)*H*), 4.30 (1H, d, *J* 6.6, C(4)*H*), 4.36 (1H, q, *J* 6.6, C(1)*H*), 6.85 (1H, d, *J* 7.7, C(5)*H*), 6.87–6.91 (1H, m, C(2')*H*), 6.92–6.97 (1H, m, C(4')*H*), 6.98 (1H, d, *J* 7.7, C(6')*H*), 7.07–7.11 (1H, m, *Ar*), 7.15–7.22 (2H, m, *Ar*), 7.24–7.30 (1H, m, C(5')*H*); δ_C (125 MHz, $CDCl_3$) 23.8 (C(1)*Me*), 27.8 (C*Me*$_3$), 47.4, (*C*(4)), 49.4 (*C*(1)), 60.3 (*C*(3)), 81.4 (*C*Me$_3$), 113.0 (d, *J* 21.0, *C*(4')), 116.2 (d, *J* 21.9, *C*(2')), 124.9 (d, *J* 2.9, *C*(6')), 126.0 (*C*(8)), 126.4, 126.6 (*C*(6), *C*(7)), 129.7 (d, *J* 8.6, *C*(5')), 129.8 (*C*(5)), 132.2 (*C*(4a)), 139.8 (*C*(8a)), 146.3 (d, *J* 6.7, *C*(1')), 162.9 (d, *J* 246.1, *C*(3')), 171.9 (*C*O$_2$^{t}Bu); δ_F (377 MHz, $CDCl_3$) –113.4 (C(3')*F*); *m*/*z* (ESI$^+$) 342 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{25}FNO_2^+$ ([M+H]$^+$) requires 342.1864; found 342.1862 .

(1*R*,3*S*,4*S*)-1-Methyl-3-*tert*-butoxycarbonyl-4-(3'-methoxy)phenyl-1,2,3,4-tetrahydroisoquinoline 507



$Pd(OH)_2$/C (40 mg, 40% w/w) was added to a degassed solution of **495** (100 mg, 0.196 mmol, >99:1 dr) in MeOH (1 mL) and the resultant mixture was placed under H_2 pressure (5 atm) and stirred at rt for 48 h. The reaction mixture was filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1, 1% Et_3N) gave **507** as a colourless oil (51 mg, 74%, >99:1 dr); ν_{max} (ATR) 3405 (N−H), 1725 (C=O); $[\alpha]_D^{20}$ +67.9 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.31 (9H, s, C*Me*$_3$), 1.55 (3H, d, *J* 6.8, C(1)*Me*), 1.95 (1H, br s, N*H*), 3.77 (3H, s, O*Me*), 3.85 (1H, d, *J* 6.7, C(3)*H*), 4.26 (1H, d, *J* 6.7, C(4)*H*), 4.36 (1H, q, *J* 6.8, C(1)*H*), 6.70–6.81 (3H, m, C(2')*H*, C(4')*H*, C(6')*H*), 6.88 (1H, d, *J* 7.7, C(5)*H*), 7.04–7.10 (1H, m, *Ar*), 7.13–7.25 (3H, m, *Ar*); δ_C (125 MHz, $CDCl_3$) 23.9 (C(1)*Me*), 27.8 (C*Me*$_3$), 47.8, (*C*(4)), 49.5 (*C*(1)), 55.1 (O*Me*), 60.3 (*C*(3)), 81.2 (*C*Me$_3$), 111.7 (*C*(4')), 115.4 (*C*(2')), 121.7 (*C*(6')), 125.9 (*C*(8)), 126.3, 126.4 (*C*(6), *C*(7)), 129.3 (*C*(5')), 129.8 (*C*(5)), 135.8 (*C*(4a)), 139.8 (*C*(8a)), 145.1 (*C*(1')), 159.5 (*C*(3')), 172.1 (*C*O$_2$^{t}Bu); *m*/*z* (ESI$^+$) 354 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{28}NO_3^+$ ([M+H]$^+$) requires 354.2064; found 354.2062.

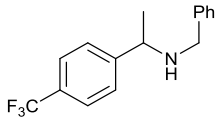
(1*R*,3*S*,4*S*)-1-Methyl-3-*tert*-butoxycarbonyl-4-(4'-methoxy)phenyl-1,2,3,4-tetrahydroisoquinoline 508



$Pd(OH)_2$/C (24 mg, 40% w/w) was added to a degassed solution of **501** (60 mg, 0.117 mmol, >99:1 dr) in MeOH (1 mL) and the resultant mixture was placed under H_2 pressure (5 atm) and stirred at rt for 48 h. The reaction mixture was filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1, 1% Et_3N) gave **508** as a colourless oil (25 mg, 61%, >99:1 dr); ν_{max} (ATR) 3378 (N−H), 1725 (C=O); $[\alpha]_D^{25}$ +72.0 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.31 (9H, s, C*Me*$_3$), 1.56 (3H, d, *J* 6.9, C(1)*Me*), 3.88 (3H, s, O*Me*), 3.81 (1H, d, *J* 7.1, C(3)*H*), 4.24 (1H,

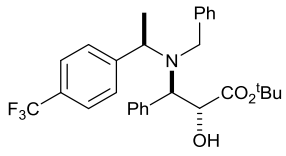
d, *J* 7.1, C(4)*H*), 4.38 (1H, q, *J* 6.9, C(1)*H*), 6.83–6.87 (3H, m, C(5)*H*, C(3')*H*, C(5')*H*), 7.05–7.10 (3H, m, *Ar*), 7.13–7.20 (2H, m, *Ar*); δ_C (125 MHz, $CDCl_3$) 23.8 (C(1)*Me*), 27.8 (C*Me*$_3$), 47.0 (*C*(4)), 49.6 (*C*(1)), 55.2 (O*Me*), 60.4 (*C*(3)), 81.3 (*C*Me$_3$), 113.7 (*C*(3'), *C*(5')), 125.9 (*C*(8)), 126.3, 126.3 (*C*(6), *C*(7)), 129.8 (*C*(5)), 130.2 (C(2'), C(6')), 135.4 (*C*(4a)), 136.3 (*C*(1')), 139.7 (*C*(8a)), 158.3 (*C*(4')), 172.1 (*C*O$_2$^{t}Bu); *m*/*z* (ESI$^+$) 354 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{28}NO_3^+$ ([M+H]$^+$) requires 354.2064; found 354.2064.

(*RS*)-*N*-Benzyl-*N*-[α-methyl-(4-trifluoromethyl)benzyl]amine 510



4'-(Trifluoromethyl)acetophenone **509** (2.00 g, 10.6 mmol) was added to a solution of benzylamine (1.10 mL, 10.1 mmol) in EtOH (6.5 mL) and the resultant solution was heated at reflux for 3 h, then allowed to cool to rt and then cooled to 0 °C. $NaBH_4$ (382 mg, 10.1 mmol) was added portionwise, maintaining the reaction temperature below 15 °C, and the resultant suspension was stirred for 20 h at rt, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 8 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give (*R*,*S*)-**510** as a pale yellow oil (1.25 g, 42%); ν_{max} (ATR) 3321 (N−H), 1323 (C−F); δ_H (400 MHz, $CDCl_3$) 1.35 (3H, d, *J* 6.6, C(α)*Me*), 1.70 (1H, br s, N*H*), 3.56 (1H, d, *J* 13.2, NC*H*$_A$H$_B$Ph), 3.63 (1H, d, *J* 13.2, NCH$_A$*H*$_B$Ph), 3.87 (1H, q, *J* 6.6, C(α)*H*), 6.20–7.34 (5H, m, *Ph*), 7.48 (2H, d, *J* 7.8, C(2)*H*, C(6)*H*), 7.59 (2H, d, *J* 7.8, C(3)*H*, C(5)*H*); δ_C (100 MHz, $CDCl_3$) 24.2 (C(α)*Me*), 51.3 (N*C*H$_2$Ph), 56.9 (*C*(α)), 124.0 (q, *J* 271.8, *C*F$_3$), 125.1 (q, *J* 4.0, *C*(3), *C*(5)), 126.7 (*p*-*Ph*), 126.7 (*C*(2), *C*(6)), 127.7, 128.1 (*o*,*m*-*Ph*), 128.9 (q, *J* 31.8, *C*(4)), 139.9, 149.4 (*i*-*Ph*, *C*(1)); δ_F (377 MHz, $CDCl_3$) −62.2 (C*F*$_3$); *m*/*z* (ESI$^+$) 280 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{17}F_3N^+$ ([M+H]$^+$) requires 280.1307; found 280.1305.

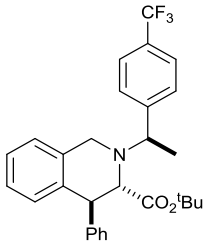
***tert*-Butyl (*RS*,*RS*,*RS*)-2-hydroxy-3-*N*-benzyl-*N*-[(α-methyl(4'-trifluoromethyl)benzyl]amino-3-phenylpropanoate 511**



BuLi (2.2 M in hexanes, 3.45 mL, 7.60 mmol) was added to (*RS*)-**510** (2.19 g, 7.84 mmol) in THF (20 mL) at −78 °C and the resultant solution was stirred at −78 °C for 30 min. **206** (1.00

g, 4.90 mmol) in THF (20 mL) was added at −78 °C via cannula and the resultant solution was stirred at −78 °C for 2 h. (−)-CSO **202** (1.91 g, 8.33 mmol) was then added and stirring was continued as the reaction mixture was allowed to warm to rt over 18 h. Satd aq NH_4Cl (10 mL) was added and the reaction mixture was stirred at rt for 5 min then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (15 mL) and 10% aq citric acid (15 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (25 mL) and brine (25 mL), then dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (40 mL) and filtered, and the filtrate was concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 5:1) gave **511** as a colourless oil (1.08 g, 64%, >99:1 dr); ν_{max} (ATR) 3491 (O−H), 1722 (C=O), 1325 (C−F); δ_H (400 MHz, $CDCl_3$) 1.16 (3H, d, *J* 6.9, C(α)*Me*), 1.18 (9H, s, C*Me*$_3$), 2.83 (1H, d, *J* 4.7, O*H*), 3.85 (1H, d, *J* 14.7, NC*H*$_A$H$_B$Ph), 4.14 (1H, d, *J* 3.1, C(3)*H*), 4.15 (1H, d, *J* 14.7, NCH$_A$*H*$_B$Ph), 4.32 (1H, q, *J* 6.9, C(α)*H*), 4.43 (1H, dd, *J* 4.7, 3.1, C(2)*H*), 7.19–7.35 (8H, m, *Ph*), 7.44–7.48 (2H, m, *Ph*), 7.59 (2H, d, *J* 8.8, C(3')*H*, C(5')*H*), 7.63 (2H, d, *J* 8.8, C(2')*H*, C(6')*H*); δ_C (100 MHz, $CDCl_3$) 14.0 (C(α)*Me*), 27.6 (C*Me*$_3$), 52.2 (*C*H$_2$Ph), 56.8 (*C*(α)), 64.8 (*C*(3)), 74.1 (*C*(2)), 82.4 (*C*Me$_3$)), 124.3 (q, *J* 271.8, *C*F$_3$), 124.9 (q, *J* 4.0, *C*(3'), *C*(5')), 126.8, 127.7 (*p-Ph*), 128.1, 128.1, 128.3, 129.8 (*o,m-Ph*), 128.2 (*C*(2'), *C*(6')), 129.0 (q, *J*, 32.6, *C*(4')), 137.9, 141.2, 148.7 (*C*(1'), *i-Ph*), 171.2 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −62.3 (C*F*$_3$); *m*/*z* (ESI$^+$) 500 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{33}F_3NO_3^+$ ([M+H]$^+$) requires 500.2407; found 500.2403.

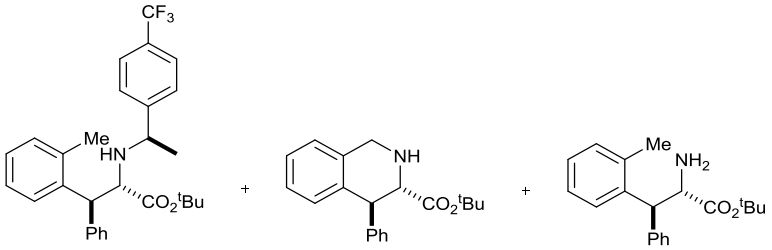
(3*SR*,4*SR*,α*RS*)- 2-*N*-[α-Methyl-(4'-trifluoromethyl)benzyl]-3-*tert*-butoxycarbonyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline 512



Tf_2O (253 μL, 1.50 mmol) was added to a stirred solution of **511** (500 mg, 1.00 mmol, >99:1 dr) and **318** (616 mg, 3.0 mmol) in CH_2Cl_2 (15 mL) at 0 °C and the resultant mixture was stirred at rt for 6 h. H_2O (5 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 4 mL), and the combined organic extracts were dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (10 mL), the resultant suspension filtered, and the filtrate concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C

petrol/Et_2O, 30:1) gave **512** as a white solid (328 mg, 68%, >99:1 dr); mp 118.0–125.0 °C; ν_{max} (ATR) 1724 (C=O), 1324 (C−F); δ_H (500 MHz, $CDCl_3$) 1.15 (3H, d, *J* 6.8, C(α)*Me*), 1.38 (9H, s, C*Me*$_3$), 3.71 (1H, d, *J* 15.8, C(1)H_A), 3.91 (1H, d, *J* 15.8, C(1)H_B), 4.03 (1H, q, *J* 6.8, C(α)*H*), 4.08 (1H, d, *J* 1.6, C(3)*H*), 4.62 (1H, d, *J* 1.6, C(4)*H*), 6.96 (1H, d, *J* 7.1, C(8)*H*), 7.04 (1H, d, *J* 7.3, C(5)*H*), 7.08–7.16 (2H, m, C(6)*H*, C(7)*H*), 7.16 (2H, d, *J* 7.1, *Ph*), 7.24 (2H, d, *J* 8.2, C(2')*H*, C(6')*H*), 7.25–7.35 (3H, m, *Ph*), 7.48 (2H, d, *J* 8.2, C(3')*H*, C(5')*H*); δ_C (125 MHz, $CDCl_3$) 21.0 (C(α)*Me*), 28.1 (C*Me*$_3$), 47.9, (*C*(4)), 49.9 (*C*(1)), 61.8 (*C*(α)), 62.7 (*C*(3)), 81.4 (*C*Me$_3$), 124.3 (q, *J* 262.3, *C*F_3), 125.3 (q, *J* 3.8, *C*(3'), *C*(5')), 126.0 (*C*(8)), 126.2, 126.2 (*C*(6), *C*(7)), 126.3 (*p-Ph*), 127.3 (*C*(2'), *C*(6')), 127.9, 128.9 (*o,m-Ph*), 129.0 (q, *J* 32.4, *C*(4')), 129.7 (*C*(5)), 134.6 (*C*(4a)), 134.9 (*C*(8a)), 145.1 (*i-Ph*), 150.6 (*C*(1')), 170.8 (*C*O_2^{t}Bu); δ_F (377 MHz, $CDCl_3$) –62.3 (CF_3); *m*/*z* (ESI$^+$) 482 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{30}F_3NO_2^+$ ([M+H]$^+$) requires 482.2301; found 482.2287.

tert-Butyl (2*RS*,3*SR*,α*RS*)-2-[*N*-α-methyl-(4''-trifluoromethyl)benzyl]amino-3-(2'-methyl)phenyl-3-phenylpropanoate 513, (3*SR*,4*SR*)-3-*tert*-butoxycarbonyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline 514 *tert*-butyl (2*SR*,3*SR*)-2-amino-3-(2'-methyl)phenyl-3-phenylpropanoate 515



513 **514** **515**

Method A: $Pd(OH)_2$/C (8 mg, 25% w/w) was added to a degassed solution of **512** (32 mg, 0.066 mmol, >99:1 dr) in MeOH (1 mL) and the resultant mixture was placed under H_2 pressure (5 atm) and stirred at rt for 24 h. The reaction mixture was filtered through Celite® (eluent MeOH) and concentrated *in vacuo* to give a 90:10 mixture of **512** and **513**, respectively.

Method B: $Pd(OH)_2$/C (14 mg, 25% w/w) was added to a degassed solution of **512** (56 mg, 0.104 mmol, >99:1 dr) in MeOH (1 mL) and the resultant mixture was placed under H_2 pressure (5 atm) and stirred at rt for 48 h. The reaction mixture was filtered through Celite® (eluent MeOH) and concentrated *in vacuo* to give a 55:20:22:3 mixture of **512**, **513**, **514** and **515**, respectively.

Method C: $Pd(OH)_2$/C (17 mg, 40% w/w) was added to a degassed solution of **512** (43 mg, 0.089 mmol, >99:1 dr) in MeOH (1 mL) and the resultant mixture was placed under H_2

pressure (5 atm) and stirred at rt for 24 h. The reaction mixture was filtered through Celite® (eluent MeOH) and concentrated *in vacuo* to give a 26:28:28:18 mixture of **512**, **513**, **514** and **515**, respectively.

Method D: $Pd(OH)_2/C$ (34 mg, 40% w/w) was added to a degassed solution of **512** (84 mg, 0.175 mmol, >99:1 dr) in MeOH (1 mL) and the resultant mixture was placed under H_2 pressure (5 atm) and stirred at rt for 48 h. The reaction mixture was filtered through Celite® (eluent MeOH) and concentrated *in vacuo* to give a 60:40 mixture of **514** and **515**, respectively.

Method E: $Pd(OH)_2/C$ (13 mg, 25% w/w) was added to a degassed solution of **512** (50 mg, 0.104 mmol, >99:1 dr) in MeOH/AcOH (20:1, 1 mL) and the resultant mixture was placed under H_2 pressure (5 atm) and stirred at rt for 24 h. The reaction mixture was filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was redissolved in CH_2Cl_2 (5 mL) and washed with satd aq $NaHCO_3$ (3 × 3 mL), then dried and concentrated *in vacuo* to give a 35:24:35:6 mixture of **512**, **513**, **514** and **515**, respectively.

Method F: $Pd(OH)_2/C$ (13 mg, 25% w/w) was added to a degassed solution of **512** (50 mg, 0.104 mmol, >99:1 dr) in MeOH/AcOH (20:1, 1 mL) and the resultant mixture was placed under H_2 pressure (5 atm) and stirred at rt for 48 h. The reaction mixture was filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was redissolved in CH_2Cl_2 (5 mL) and washed with satd aq $NaHCO_3$ (3 × 3 mL), then dried and concentrated *in vacuo* to give an 11:22:55:12 mixture of **512**, **513**, **514** and **515**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1, 1% Et_3N) gave **515** as a pale yellow solid (5 mg, 16%, >99:1 dr); mp 51.5–59.0 °C; ν_{max} (ATR) 1735 (C=O); δ_H (500 MHz, $CDCl_3$) 1.16 (9H, s, C*Me*$_3$), 2.00–2.10 (2H, br s, N*H*$_2$), 2.32 (3H, s, C(2')*Me*), 4.15 (1H, d, *J* 9.9, C(2)*H*), 4.33 (1H, d, *J* 9.9, C(3)*H*), 7.14 (2H, d, *J* 3.9, *Ph*), 7.16–7.28 (6H, m, *Ar*, *Ph*), 7.59 (1H, d, *J* 7.7, *Ar*); δ_C (125 MHz, $CDCl_3$) 28.7 (C*Me*$_3$), 31.9 (C(2')*Me*), 52.7, *C*(3)), 59.6 (*C*(2)), 81.1 (*C*Me$_3$), 125.0 (*p-Ph*), 126.3 (C(6')), 126.6, 126.6 (C(4'), C(5')), 128.3 (*m-Ph*), 129.0 (*o-Ph*), 131.0 (*C*(3')), 137.4 (*C*(2')), 139.3 (*C*(1')), 140.4 (*i-Ph*), 173.3 (*C*(1)); *m*/*z* (ESI^+) 312 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{26}NO_2^+$ ($[M+H]^+$) requires 312.1958; found 312.1960. Further elution gave **514** as a pale yellow solid (5 mg, 16%, >99:1 dr); mp 94.5–113.0 °C; ν_{max} (ATR) 1727 (C=O); δ_H (500 MHz, $CDCl_3$) 1.26 (9H, s, C*Me*$_3$), 1.78 (1H, br s, N*H*), 3.71 (1H, d, *J* 9.0, (C(3)), 4.16–4.26 (3H, m, C(1)*H*$_2$, C(4)*H*), 6.82 (1H, d, *J* 7.7, C(5)*H*), 7.04–7.09 (2H, m, *Ar*, *Ph*), 7.13–7.18 (3H, m, *Ar*, *Ph*), 7.22–7.33 (3H, m, *Ar*, *Ph*); δ_C (125

MHz, $CDCl_3$) 27.7 (C*Me*$_3$), 47.1 (*C*(1)), 48.3, (*C*(4)), 64.2 (*C*(3)), 81.3 (*C*Me$_3$), 125.5 (*C*(8)), 126.3, 126.4, 126.8 (*C*(6), *C*(7), *p-Ph*), 128.4 (*m-Ph*), 129.4 (*o-Ph*), 129.8 (*C*(5)), 135.0 (*C*(8a)), 137.3 (*C*(4a)), 142.6 (*i-Ph*), 171.9 (*C*O_2^{t}Bu); *m*/*z* (ESI$^+$) 310 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{24}NO_2^+$ ([M+H]$^+$) requires 310.1802; found 310.1801. A 71:29 mixture of **513** and **512** and a 90:10 mixture of **514** and **515**, respectively, were also recovered. Selected data for **513**: δ_H (500 MHz, $CDCl_3$) 0.97 (9H, s, C*Me*$_3$), 1.21 (3H, d, *J* 6.6, C(α)*Me*), 1.89 (1H, br s, N*H*), 2.28 (3H, s, C(2')*Me*), 3.60 (1H, q, *J* 6.6, C(α)*H*), 3.92 (1H, d, *J* 9.9, C(2)*H*), 4.36 (1H, d, *J* 9.9, C(3)*H*), 7.06–7.62 (13H, m, *Ar*, *Ph*); δ_C (125 MHz, $CDCl_3$) 20.0 (C(2')*Me*), 203.5 (C(α)*Me*), 27.4 (C*Me*$_3$), 50.6, (*C*(3)), 57.7 (*C*(α)), 64.9 (*C*(2)), 80.9 (*C*Me$_3$), 124.2 (q, *J* 271.8, *C*F_3), 125.2 (q, *J* 3.8, *C*(3''), *C*(5'')), 125.9 (*p-Ph*), 126.4 (C(6')), 126.5, 126.5 (C(4'), C(5')), 127.2, 128.2 (*m-Ph*, *C*(2''), *C*(6'')), 129.4 (*o-Ph*), 129.2 (q, *J* 32.4, *C*(4'')), 130.7 (*C*(3')), 137.2 (*C*(2')), 139.4 (*C*(1')), 140.0 (*i-Ph*), 149.8 (*C*(1'')), 173.3 (*C*(1)).

Method G: Pd/C (50 mg, 100% w/w) and HCO_2NH_4 (66 mg, 1.64 mmol) were added to a degassed solution of **512** (50 mg, 0.164 mmol, >99:1 dr) in MeOH (2.3 mL) and the resultant mixture was stirred at rt for 5 min, then at reflux for 8 h. The reaction mixture was filtered through Celite® (eluent MeOH) and concentrated *in vacuo* to give a 3:70:27 mixture of **513**, **514** and **515**, respectively.

Method H: Pd/C (20 mg, 100% w/w) and HCO_2NH_4 (26 mg, 0.420 mmol) were added to a degassed solution of **512** (20 mg, 0.042 mmol, >99:1 dr) in MeOH (0.59 mL) and the resultant mixture was stirred at rt for 5 min, then at reflux for 1 h. The reaction mixture was filtered through Celite® (eluent MeOH) and concentrated *in vacuo* to give a 21:9:63:7 mixture of **512**, **513**, **514** and **515**, respectively.

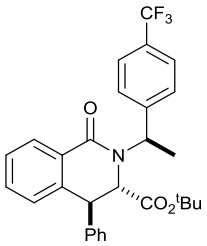
Method I: Pd/C (20 mg, 100% w/w) and HCO_2NH_4 (26 mg, 0.420 mmol) were added to a degassed solution of **512** (20 mg, 0.042 mmol, >99:1 dr) in MeOH (0.59 mL) and the resultant mixture was stirred at rt for 5 min, then at reflux for 2 h. The reaction mixture was filtered through Celite® (eluent MeOH) and concentrated *in vacuo* to give a 10:9:72:9 mixture of **512**, **513**, **514** and **515**, respectively.

Method J: Pd/C (100 mg, 100% w/w) and HCO_2NH_4 (132 mg, 3.28 mmol) were added to a degassed solution of **512** (100 mg, 0.328 mmol, >99:1 dr) in MeOH (4.6 mL) and the resultant mixture was stirred at rt for 5 min, then at reflux for 3 h. The reaction mixture was filtered through Celite® (eluent MeOH) and concentrated *in vacuo* to give a 3:77:20 mixture of **513**, **514** and **515**, respectively. Purification via flash column chromatography (eluent 30–

40 °C petrol/acetone, 10:1) gave **515** as a pale yellow solid (12 mg, 12%, >99:1 dr). Further elution gave **514** as a pale yellow solid (38 mg, 59%, >99:1 dr). A 55:45 mixture of **515** and **514**, respectively, was also recovered (3 mg).

Method K: Na (10 mg, 0.416 mmol) was added to a stirred solution of NH_3 (2 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 10 min. **512** (50 mg, 0.104 mmol, >99:1 dr) in THF (0.20 mL) was added and the resultant mixture was stirred at −78 °C for 30 min. Satd aq NH_4Cl (1 mL) was added and the resultant mixture was allowed to warm to rt. Et_2O (3 mL) and H_2O (3 mL) were added, the aqueous layer extracted with Et_2O (2 × 1.5 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **512** as a white solid.

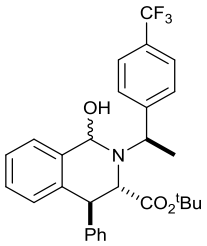
(3*SR*,4*SR*,*αRS*)-1-Oxo-*N*(2)-[*α*-methyl-(4'-trifluoromethyl)benzyl]-3-*tert*-butoxycarbonyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline 516



A solution of $NaBrO_3$ (56 mg, 0.374 mmol) in H_2O (1.25 mL) was added to a stirred solution of **512** (60 mg, 0.125 mmol, >99:1 dr) in EtOAc (1.64 mL) at rt and the resultant mixture was stirred at rt for 10 min. A solution of $Na_2S_2O_4$ (54 mg, 0.373 mmol) in H_2O (2.27 mL) was added dropwise at rt over 5 min and the resultant mixture was stirred at rt for 4 h. EtOAc (4 mL) was added and the resultant mixture was washed with satd aq $Na_2S_2O_3$ (4 mL). The aqueous layer was extracted with EtOAc (2 × 3 mL) and the combined organic extracts were washed with brine (5 mL), then dried over Na_2SO_3 and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (5 mL) and the resultant solution was washed with 1.0 M aq HCl (3 × 4 mL). The combined aqueous layers were concentrated *in vacuo* to give **516** as a yellow oil (49 mg, 82%, >99:1 dr); ν_{max} (ATR) 1726, 1653 (C=O); δ_H (500 MHz, $CDCl_3$) 1.24 (9H, s, C*Me*$_3$), 1.47 (3H, d, *J* 7.2, C(α)*Me*), 3.89 (1H, d, *J* 1.9, C(3)*H*), 4.41–4.44 (1H, m, C(4)*H*), 6.14 (1H, q, *J* 7.2, C(α)*H*), 6.57 (2H, d, *J* 7.6, *o-Ph*), 6.86 (2H, d, *J* 8.0, C(2')*H*, C(6')*H*), 6.98 (2H, app t, *J* 7.7, *m-Ph*), 7.04–7.14 (4H, m, *Ar*, *Ph*), 7.44–7.51 (2H, m, *Ar*, *Ph*), 8.26–8.29 (1H, m, C(8)*H*); δ_C (125 MHz, $CDCl_3$) 14.9 (C(α)*Me*), 27.5 (C*Me*$_3$), 46.8, (*C*(4)), 50.2 (*C*(α)), 61.6 (*C*(3)), 82.7 (*C*Me$_3$), 124.0 (q, *J* 271.8, *C*F$_3$), 124.9 (q, *J* 3.8, *C*(3'), *C*(5')), 127.1 (*p-Ph*), 127.3 (*C*(2'), *C*(6')), 127.6 (*o-Ph*), 128.0 (*C*(8)), 128.1, 128.8 (*C*(6), *C*(7)), 128.4 (*m-Ph*),

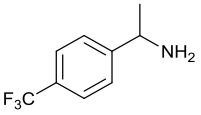
128.9 (q, *J* 32.4, *C*(4')), 130.8 (*C*(8a)), 132.3 (*C*(5)), 135.3 (*C*(4a)), 139.8 (*i-Ph*), 142.9 (*C*(1'), 164.2 (*C*(1)), 170.5 ($CO_2{}^tBu$); *m*/*z* (FI^+) 480 ($[M]^+$, 100%).

(1*RS,3*SR*,4*SR*,α*RS*)-1-Hydroxy-*N*(2)-[α-methyl-(4'-trifluoromethyl)benzyl]-3-*tert*-butoxycarbonyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline 517**



CAN (205 mg, 0.347 mmol) was added to a stirred solution of **512** (30 mg, 0.062 mmol, >99:1 dr) in MeCN/H_2O (2:1, 0.55 mL) and the resultant solution was stirred at rt for 24 h. Satd aq $NaHCO_3$ (0.5 mL) was added and the resultant mixture was stirred at rt for 10 min, then extracted with Et_2O (3 × 2 mL), dried and concentrated *in vacuo* to give **517** as a yellow oil (29 mg, 94%, >99:1 dr); ν_{max} (ATR) 3642 (O−H), 1713 (C=O); δ_H (500 MHz, $CDCl_3$) 1.34 (3H, d, *J* 6.9, C(α)*Me*), 1.41 (9H, s, C*Me*$_3$), 3.94 (1H, d, *J* 1.3, C(3)*H*), 4.37 (1H, app s, C(4)*H*), 4.56 (1H, q, *J* 6.9, C(α)*H*), 4.85 (1H, d, *J* 11.0, O*H*), 5.39 (1H, d, *J* 11.0, C(1)*H*), 6.80 (2H, d, *J* 6.6, *o-Ph*), 6.95–7.02 (3H, m, C(2')*H*, C(6')*H*, *p-Ph*), 7.12–7.33 (7H, m, *Ar*, *Ph*), 7.60 (1H, d, *J* 7.7, C(5)*H*); δ_C (125 MHz, $CDCl_3$) 19.4 (C(α)*Me*), 27.9 (C*Me*$_3$), 48.3, (*C*(4)), 56.9 (*C*(α)), 61.4 (*C*(3)), 79.9 (*C*(1)), 82.3 (*C*Me$_3$), 124.2 (q, *J* 271.8, *C*F_3), 124.7 (q, *J* 3.8, *C*(3'), *C*(5')), 126.6, 127.3 (*Ar*), 127.4 (*C*(2'), *C*(6')), 128.0 (*o-Ph*), 128.1 (*Ar*), 128.1 (*m-Ph*), 128.7 (q, *J* 32.4, *C*(4')), 128.8 (*p-Ph*), 128.8 (*C*(5)), 132.2 (*C*(4a)), 138.2 (*C*(8a)), 143.7 (*i-Ph*), 147.7 (*C*(1'), 175.8 ($CO_2{}^tBu$); *m*/*z* (ESI^+) 480 ($[M-H_2O]^+$, 100%); HRMS (ESI^+) $C_{29}H_{28}F_3NO_2{}^+$ ($[M-H_2O]^+$) requires 480.2145; found 480.2143.

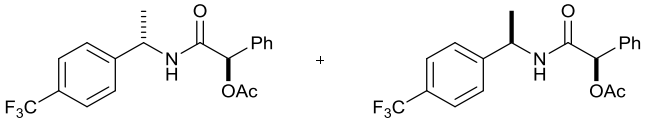
(*RS*)- *N*-[α-Methyl-(4-trifluoromethyl)benzyl]amine 518



Ti(O^iPr)$_4$ (31.5 mL, 106 mmol) was added to (4-trifluoromethyl)acetophenone **509** (10.0 g, 53.1 mmol) in NH_3 (2.0 M in EtOH, 133 mL) and the resultant mixture was stirred at rt for 6 h. $NaBH_4$ (3.01 g, 79.7 mmol) was added at 0 °C, and the resultant suspension was stirred at rt for 3 h, then poured into 2.0 M aq NH_4OH (200 mL). The resultant suspension was filtered (eluent EtOAc), the layers separated and the aqueous layer extracted with EtOAc (2 × 80 mL). The combined organic extracts were extracted with 1.0 M aq HCl (3 × 50 mL) and the

combined aqueous layers were washed with EtOAc (3 × 30 mL), then treated with 2.0 M aq NaOH until pH >8 was observed, then extracted with EtOAc (4 × 50 mL). The combined organic extracts were washed with brine (200 mL), then dried over Na_2SO_4 and concentrated *in vacuo* to give **518** as a pale yellow oil (6.84 g, 68%);[42] δ_H (400 MHz, $CDCl_3$) 1.40 (3H, d, *J* 6.6, C(α)*Me*), 1.59 (2H, br s, N*H*), 4.20 (1H, q, *J* 6.6, C(α)*H*), 7.48 (2H, d, *J* 7.8, C(2)*H*, C(6)*H*), 7.59 (2H, d, *J* 7.8, C(3)*H*, C(5)*H*).

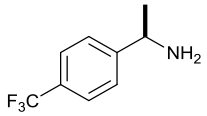
(*S*)-*N*-[α-Methyl-(4'-trifluoromethyl)benzyl] (*R*)-2-acetoxy-2-phenylethanamide 519 and (*R*)-*N*-[α-Methyl-(4'-trifluoromethyl)benzyl] (*R*)-2-acetoxy-2-phenylethanamide 520



DCC (2.35 g, 12.1 mmol) and DMAP (50 mg, cat.) were added to **518** (2.29 g, 12.1 mmol) and (*R*)-*O*-acetyl mandelic acid (2.35 g, 12.1 mmol) in CH_2Cl_2 (60 mL) at 0 °C and the resultant mixture was stirred at rt for 16 h. The reaction mixture was filtered and the filtrate was washed with 1.0 M aq HCl (40 mL), satd aq $NaHCO_3$ (40 mL) and brine (40 mL), then dried over Na_2SO_4 and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 2:1, 1% Et_3N) gave **519** as a white solid (1.58 g, 36%, >99:1 dr); mp 132.5–133.5 °C; ν_{max} (ATR) 3292 (N−H), 1742, 1662 (C=O), 1327 (C−F); $[\alpha]_D^{25}$ −153.0 (*c* 1.0 in MeOH); δ_H (500 MHz, $CDCl_3$) 1.40 (3H, d, *J* 7.0, C(α)*Me*), 2.13 (3H, s, C(O)*Me*) 5.00 (1H, q, *J* 7.0, C(α)*H*), 5.94 (1H, s, C(2)*H*), 7.33–7.39 (3H, m, *Ar*, *Ph*), 7.48–7.53 (4H, m, *Ph*), 7.58 (2H, d, *J* 8.2, C(3')*H*, C(5')*H*); δ_C (125 MHz, $CDCl_3$) 20.8 (C(O)*Me*), 22.1 (C(α)*Me*), 50.0 (*C*(α)), 77.2 (*C*(2)), 125.9 (q, *J* 269.9, *C*F_3), 126.4 (q, *J* 3.8, *C*(3'), *C*(5')), 127.9 (*C*(2'), *C*(6')), 128.7 (*o-Ph*), 129.8 (*m-Ph*), 130.2 (*p-Ph*), 130.3 (q, *J* 31.5, *C*(4')), 136.8 (*i-Ph*), 149.5 (*C*(1')), 171.0 (*C*(1)), 172.1 (*C*(O)Me); δ_F (377 MHz, $CDCl_3$) −63.9 (*C*F_3); *m*/*z* (ESI^+) 388 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{27}H_{18}F_3NNaO_3^+$ ($[M+Na]^+$) requires 388.1131; found 388.1122. Further elution gave **520** as a white solid (1.46 g, 33%, >99:1 dr); mp 118.0–120.0 °C; ν_{max} (ATR) 3291 (N−H), 1744, 1663 (C=O), 1327 (C−F); $[\alpha]_D^{25}$ −17.0 (*c* 1.0 in MeOH); δ_H (500 MHz, $CDCl_3$) 1.47 (3H, d, *J* 7.0, C(α)*Me*), 2.15 (3H, s, C(O)*Me*) 5.06 (1H, q, *J* 7.0, C(α)*H*), 5.94 (1H, s, C(2)*H*), 7.24 (2H, d, *J* 8.4, C(2')*H*, C(6')*H*), 7.34–7.38 (3H, m, *Ph*), 7.44–7.49 (4H, m, *Ar*, *Ph*); δ_C (125 MHz, $CDCl_3$) 20.8 (C(O)*Me*), 22.0 (C(α)*Me*), 50.0 *C*(α)), 77.1 (*C*(2)), 125.7 (q, *J* 270.8, *C*F_3), 126.4 (q, *J* 3.8, *C*(3'), *C*(5')), 127.6 (*C*(2'), *C*(6')), 128.8 (*o-Ph*), 129.8 (*m-Ph*), 130.2 (*p-Ph*), 130.3 (q, *J* 32.4, *C*(4')), 136.7 (*i-Ph*), 149.5 (*C*(1')),

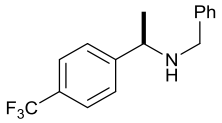
170.9 (*C*(1)), 172.1 (*C*(O)Me); δ_F (377 MHz, $CDCl_3$) −63.7 (*C*F_3); *m*/*z* (ESI$^+$) 388 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{18}F_3NNaO_3^+$ ([M+Na]$^+$) requires 388.1131; found 388.1120. A 57:43 mixture of **520** and **519**, respectively, was also recovered (812 mg, 18%).

(*R*)-*N*-Benzyl-*N*-[α-methyl-(4-trifluoromethyl)benzyl]amine 518



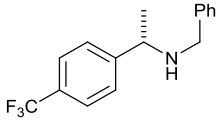
520 (100 mg, 0.274 mmol, >99:1 dr) in 4.5 M aq HBr (2 mL) was heated at reflux for 24 h, then concentrated *in vacuo*. The resultant residue was dissolved in CH_2Cl_2 (3 mL), and extracted with 1.0 M aq HCl (4 × 3 mL). The combined aqueous extracts were treated with 2.0 M NaOH until a pH > 8 was observed, and the resultant mixture was extracted with CH_2Cl_2 (4 × 5 mL), then dried and concentrated *in vacuo* to give (*R*)-**518** as a pale yellow oil (20 mg, 38%); $[\alpha]_D^{20}$ +22.0 (c 1.0 in MeOH); lit.[43] $[\alpha]_D^{20}$ = +20.0 (c 1.0 in MeOH).

(*R*)-*N*-Benzyl-*N*-[α-methyl-(4-trifluoromethyl)benzyl]amine 510



520 (1.52 g, 4.15 mmol, >99:1 dr) in 4.5 M aq HBr (10 mL) was heated at reflux for 24 h, then concentrated *in vacuo*, and the resultant residue was dissolved in EtOH (26 mL). PhCHO (461 μL, 4.56 mmol) and K_2CO_3 (630 mg, 4.56 mmol) were added and the resultant mixture was heated to reflux for 3 h, then cooled to 0 °C. $NaBH_4$ (157 mg, 4.15 mmol) was added and the resultant mixture was stirred at rt for 20 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 3:1, 1% Et_3N) gave (*R*)-**510** as a pale yellow oil (0.554 g, 48%, 98% ee);[44] $[\alpha]_D^{20}$ +47.8 (*c* 1.0 in MeOH).

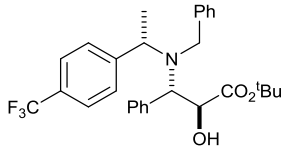
(*S*)-*N*-Benzyl-*N*-[α-methyl-(4-trifluoromethyl)benzyl]amine 510



519 (1.58 g, 4.33 mmol, >99:1 dr) in 4.5 M aq HBr (10 mL) was heated at reflux for 24 h, then concentrated *in vacuo*, and the resultant residue was dissolved in EtOH (27 mL). PhCHO

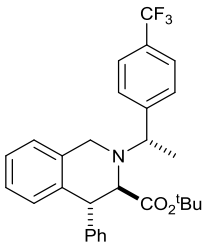
(481 μL, 4.76 mmol) and K_2CO_3 (598 mg, 4.37 mmol) were added and the resultant mixture was heated to reflux for 3 h, then cooled to 0 °C. $NaBH_4$ (163 mg, 4.33 mmol) was added and the resultant mixture was stirred at rt for 20 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 3:1, 1% Et_3N) gave (*S*)-**510** as a pale yellow oil (756 mg, 63%, >98% ee);[45] $[\alpha]_D^{20}$ −45.7 (*c* 1.0 in MeOH).

tert-Butyl (*S*,*S*,*S*)-2-hydroxy-3-*N*-benzyl-*N*-[(α-methyl(4'-trifluoromethyl)benzyl]amino-3-phenylpropanoate 511



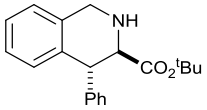
BuLi (2.2 M in hexanes, 1.20 mL, 2.65 mmol) was added to (*S*)-**510** (718 mg, 2.57 mmol, >98% ee) in THF (7 mL) at −78 °C and the resultant solution was stirred at −78 °C for 30 min. A solution of **206** (350 mg, 1.71 mmol, >99:1 dr) in THF (7 mL) was added at −78 °C via cannula and the resultant solution was stirred at −78 °C for 2 h. (+)-CSO **202**[46] (667 mg, 8.33 mmol) was then added and stirring was continued as the reaction mixture was allowed to warm to rt over 18 h. Satd aq NH_4Cl (10 mL) was added and the reaction mixture was stirred at rt for 5 min then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (15 mL) and 10% aq citric acid (15 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (25 mL) and brine (25 mL), then dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (40 mL) and filtered, and the filtrate was concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 5:1) gave **511** as a colourless oil (800 mg, 94%, >99:1 dr); $[\alpha]_D^{20}$ +27.8 (*c* 1.0 in $CHCl_3$).

(3*R*,4*R*,α*S*)-*N*(2)-[α-Methyl-(4'-trifluoromethyl)benzyl]-3-*tert*-butoxycarbonyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline 512



Tf_2O (252 μL, 1.50 mmol) was added to a stirred solution of **511** (500 mg, 1.00 mmol, >99:1 dr) and **318** (616 mg, 3.0 mmol) in CH_2Cl_2 (15 mL) at 0 °C and the resultant mixture was stirred at rt for 6 h. H_2O (5 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 4 mL), and the combined organic extracts were concentrated *in vacuo*. The residue was dissolved in Et_2O (10 mL), the resultant suspension filtered, and the filtrate concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 30:1) gave **512** as a white solid (449 mg, 93%, >99:1 dr); mp 92.0–97.5 °C; $[\alpha]_D^{20}$ +6.8 (*c* 1.0 in $CHCl_3$).

(3*R*,4*R*)-3-*tert*-Butoxycarbonyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline 514



Pd/C (100 mg, 100% w/w) and HCO_2NH_4 (132 mg, 3.28 mmol) were added to a degassed solution of **512** (100 mg, 0.328 mmol, >99:1 dr) in MeOH (4.6 mL) and the resultant mixture was stirred at rt for 5 min, then at reflux for 3 h. The reaction mixture was filtered through Celite® (eluent MeOH) and concentrated *in vacuo* to give a 9:74:17 mixture of **513**, **514** and **515**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/acetone, 10:1) gave **514** as a pale yellow solid (34 mg, 50%, >99:1 dr); mp 78.5–81.0 °C; $[\alpha]_D^{20}$ −30.8 (*c* 1.0 in $CHCl_3$).

6.6. References and notes

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[31] (*R*)-**374** was assessed to be 99% ee by 400MHz ^{1}H NMR spectroscopic analysis in the presence of (*R*)-*O*-acteylmandelic acid in $CDCl_3$, and in comparison with that of an authentic racemic smaple.
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[40] (*R*)-**388** was assessed to be 99% ee by 400MHz ^{1}H NMR spectroscopic analysis in the presence of (*R*)-*O*-acteylmandelic acid in $CDCl_3$, and in comparison with that of an authentic racemic smaple.
[41] (*R*)-**484** was assessed to be 95% ee by 400MHz ^{1}H NMR spectroscopic analysis in the presence of (*R*)-*O*-acteylmandelic acid in $CDCl_3$, and in comparison with that of an authentic racemic smaple.
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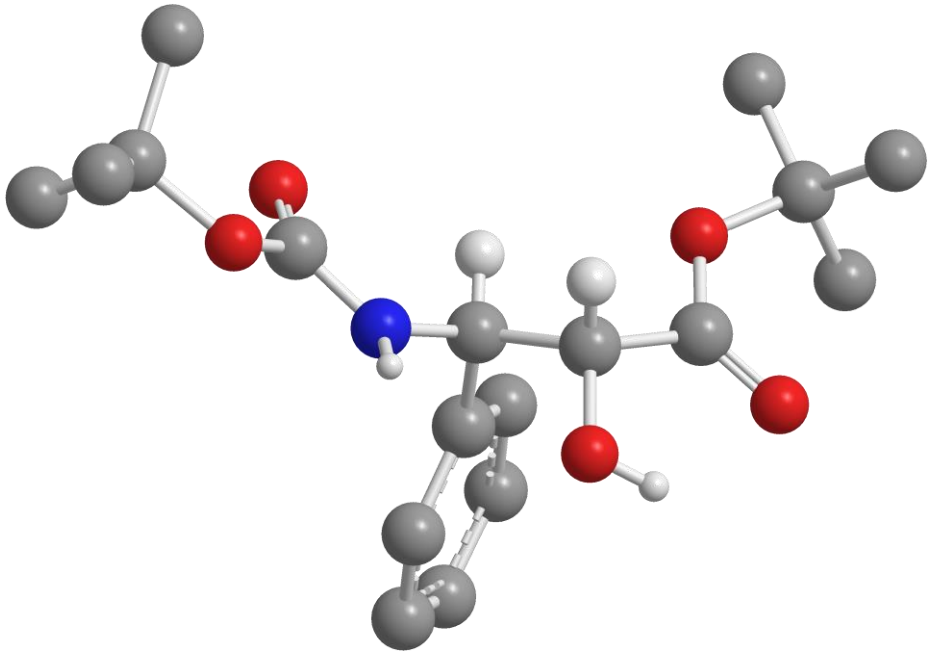
[45] (*S*)-**510** was assessed to be >98% ee by 400MHz ^{1}H NMR spectroscopic analysis in the presence of (*R*)-*O*-acteylmandelic acid in $CDCl_3$, and in comparison with that of an authentic racemic smaple.
[46] A sample of (+)-CSO **202** was generously donated by Mr M. S. Kennedy.

X-Ray crystal structure data for (*R*,*R*)-210

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 210

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 **210** [$C_{18}H_{27}NO_5$]: M = 337.42, triclinic, space group P –*1*, a = 9.1641(2) Å, b = 10.2600(3) Å, c = 11.3750(3) Å, α = 38.656(1)°, β = 67.9745(11)°, γ = 80.8588(15)°, V = 923.15(4) Å^3, Z = 2, μ = 0.088 mm^{-1}, colourless prism, crystal dimensions = 0.10 × 0.11 × 0.25 mm^3. A total of 4202 unique reflections were measured for $5 < \theta < 27$ and 4201 reflections were used in the refinement. The final parameters were wR_2 = 0.118 and R_1 = 0.071 [I>–3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

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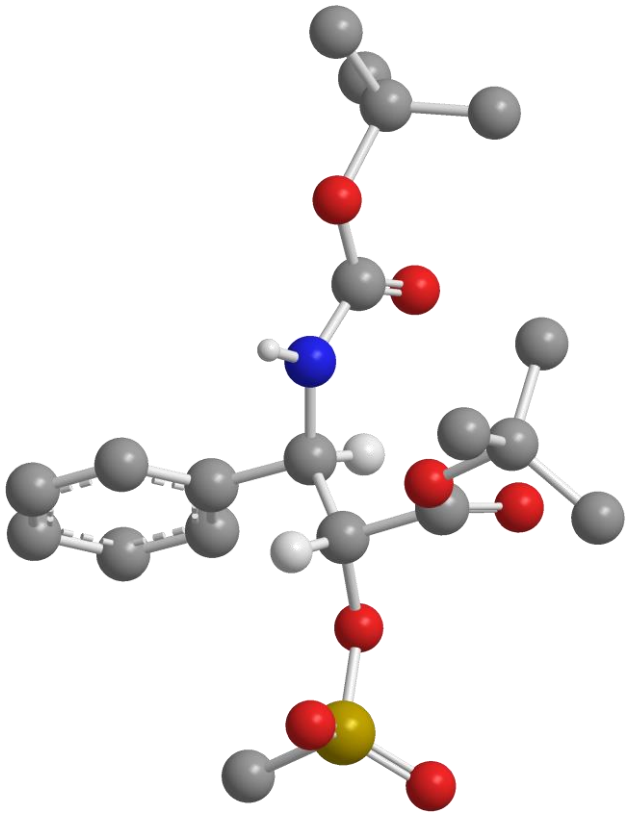
X-Ray crystal structure data for (*R*,*R*)-212

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 212

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 **212** [$C_{19}H_{29}NO_7S$]: M = 415.51, triclinic, space group *P 1*, a = 9.3006(4) Å, b = 11.6834(3) Å, c = 11.9350(4) Å, α = 118.6706(16)°, β = 92.7922(14)°, γ = 100.1202(17)°, V = 1106.81(7) Å^3, Z = 2, μ = 0.184 mm^{-1}, colourless block, crystal dimensions = 0.20 × 0.21 × 0.27 mm^3. A total of 4896 unique reflections were measured for $5 < \theta < 27$ and 7024 reflections were used in the refinement. The final parameters were wR_2 = 0.091 and R_1 = 0.046 [I>–3.0σ(I)], with Flack enantiopole = 0.00(6).[3] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

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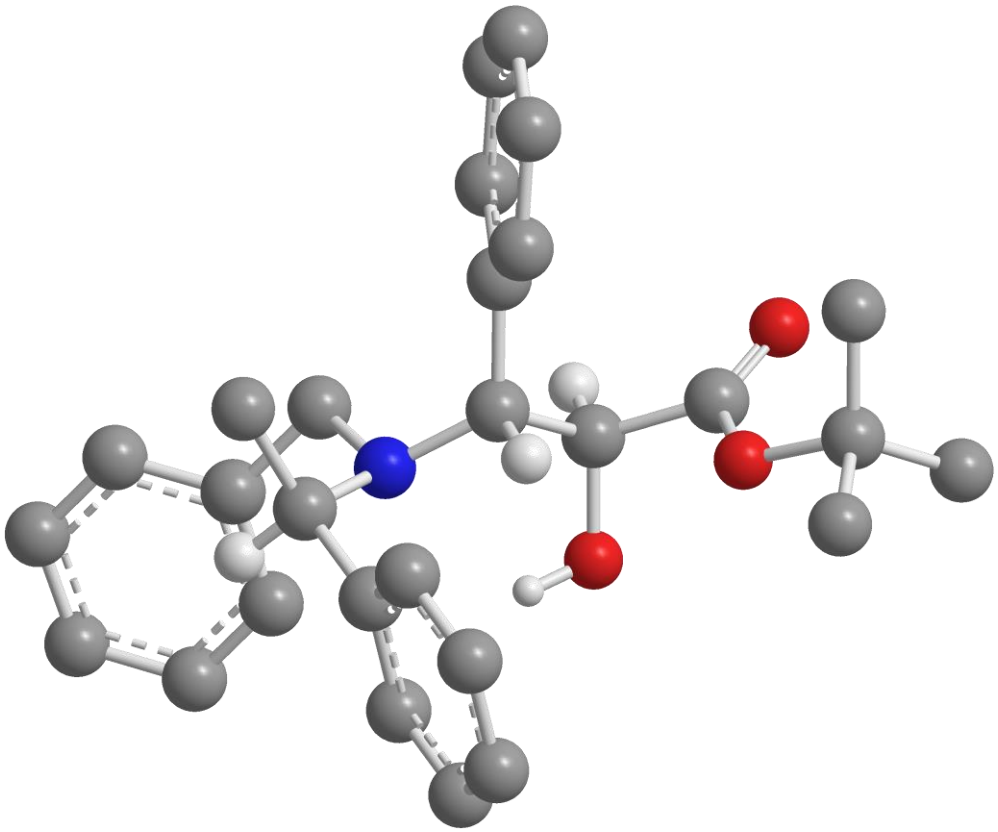
X-Ray crystal structure data for (2*S*,3*R*,α*R*)-217

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 217

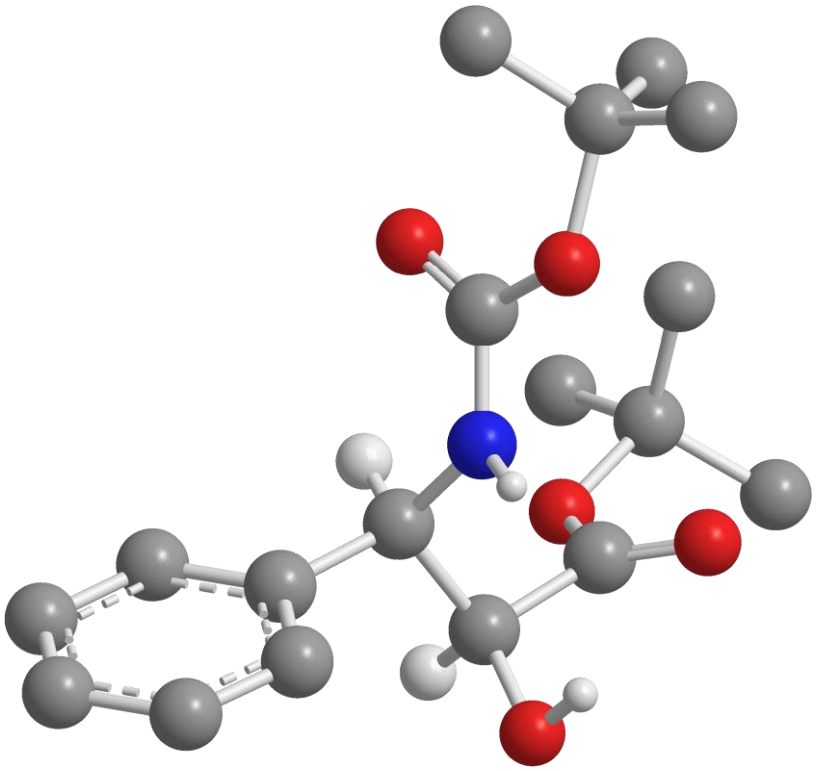
Data were collected using a an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[4]

X-ray crystal structure data for **217** [$C_{28}H_{33}NO_3$]: M = 431.57, trigonal, space group $P\ 3_2\ 2\ 1$, $a = b$ = 12.17738(16) Å, c = 56.9457(7) Å, V = 731306(17) Å^3, Z = 12, μ = 0.595 mm^{-1}, colourless block, crystal dimensions = 0.10 × 0.12 × 0.13 mm^3. A total of 10264 unique reflections were measured for $4 < \theta < 76$ and 10220 reflections were used in the refinement. The final parameters were wR_2 = 0.093 and R_1 = 0.039 [I>–3.0σ(I)], with Flack enantiopole = 0.03(15).[5] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

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

X-Ray crystal structure data for (2*S*,3*R*)-218

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 218

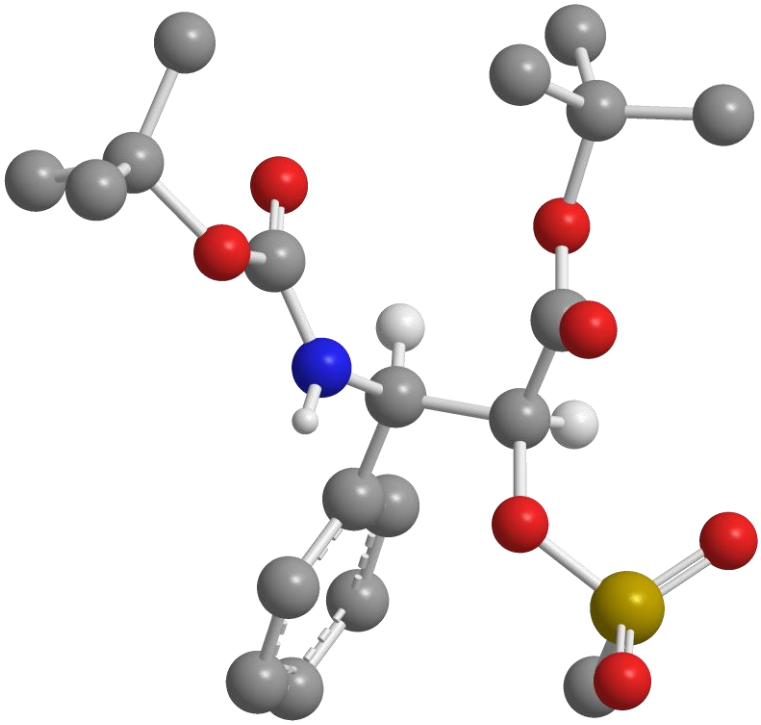
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[6]

X-ray crystal structure data for **218** [$C_{18}H_{27}NO_5$]: M = 337.42, monoclinic, space group $P\ 2_1$, a = 5.7223(3) Å, b = 17.9706(9) Å, c = 18.531(1) Å, β = 96.325(5)°, V = 1894.00(17) Å^3, Z = 4, μ = 0.703 mm^{-1}, colourless block, crystal dimensions = 0.09 × 0.12 × 0.27 mm^3. A total of 7857 unique reflections were measured for 3 < θ < 77 and 7827 reflections were used in the refinement. The final parameters were wR_2 = 0.140 and R_1 = 0.061 [I>–3.0σ(I)], with Flack enantiopole = 0.09(17).[7] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

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

X-Ray crystal structure data for (2*S*,3*R*)-220

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 220

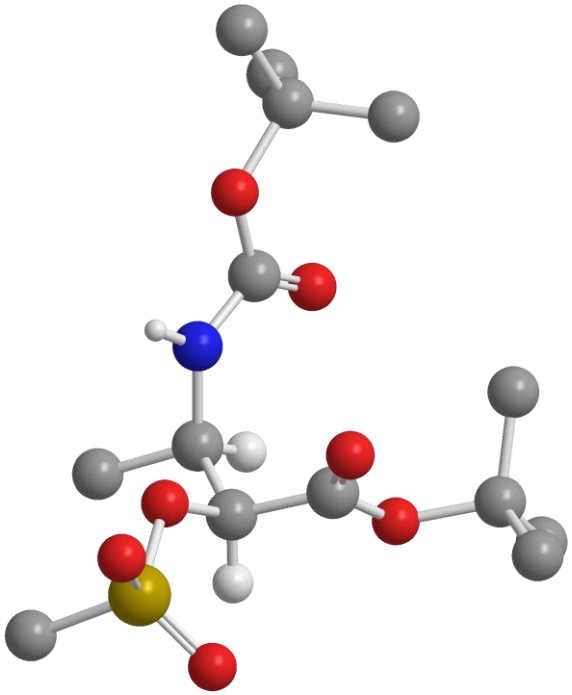
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[8]

X-ray crystal structure data for **220** [$C_{19}H_{29}NO_7S$]: M = 415.51, orthorhombic, space group $P\,2_1\,2_1\,2_1$, a = 9.6124(1) Å, b = 11.7698(1) Å, c = 19.5735(2) Å, V = 2214.47(4) Å^3, Z = 4, μ = 1.625 mm^{-1}, colourless prism, crystal dimensions = 0.06 × 0.06 × 0.23 mm^3. A total of 4609 unique reflections were measured for 4 < θ < 76 and 4043 reflections were used in the refinement. The final parameters were wR_2 = 0.067 and R_1 = 0.028 [I>–3.0σ(I)], with Flack enantiopole = –0.008(13).[9] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

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

X-Ray crystal structure data for (2*S*,3*R*)-221

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 221

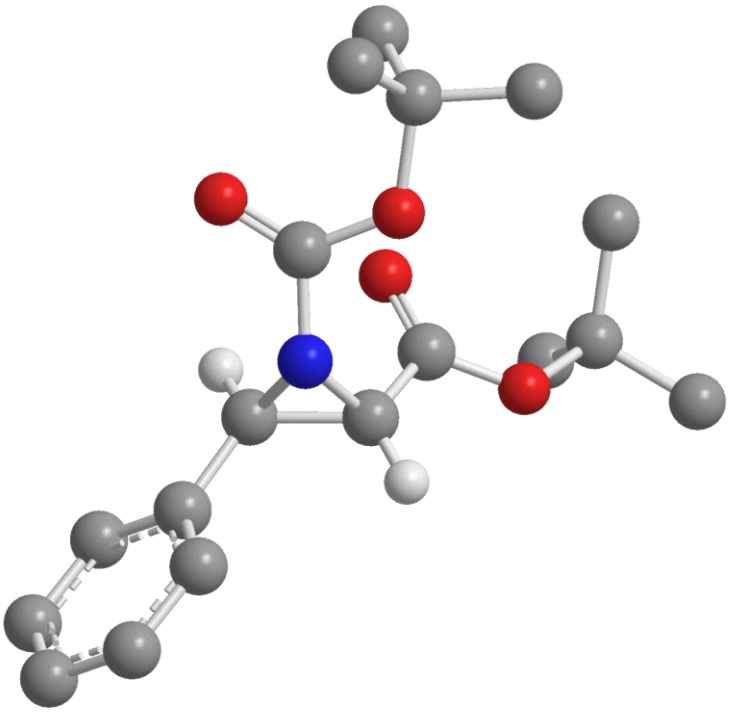
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[10]

X-ray crystal structure data for **221** [$C_{14}H_{24}NO_7S$]: M = 350.41, orthorhombic, space group $P\,2_1\,2_1\,2_1$, a = 9.0861(2) Å, b = 13.2496(4) Å, c = 16.0384(4) Å, V = 1930.82(9) Å^3, Z = 4, μ = 1.770 mm^{-1}, colourless prism, crystal dimensions = 0.11 × 0.13 × 0.27 mm^3. A total of 3998 unique reflections were measured for $4 < \theta < 77$ and 3983 reflections were used in the refinement. The final parameters were wR_2 = 0.105 and R_1 = 0.042 [I>–3.0σ(I)], with Flack enantiopole = –0.008(19).[11] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

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

X-Ray crystal structure data for (2*S*,3*R*)-222

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 222

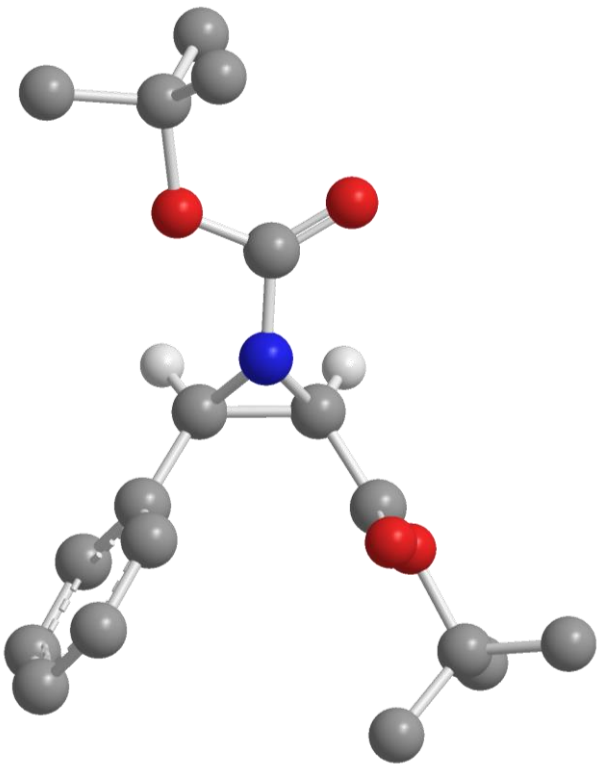
Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[12]

X-ray crystal structure data for **222** [$C_{18}H_{25}NO_4$]: M = 319.40, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 5.7496(1) Å, b = 17.4169(5) Å, c = 17.8979(5) Å, V = 1792.30(8) Å^3, Z = 4, μ = 0.083 mm^{-1}, colourless block, crystal dimensions = 0.17 × 0.21 × 0.23 mm^3. A total of 2369 unique reflections were measured for 5 < θ < 27 and 2059 reflections were used in the refinement. The final parameters were wR_2 = 0.095 and R_1 = 0.055 [I>−3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

[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 (*R*,*R*)-223

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 223

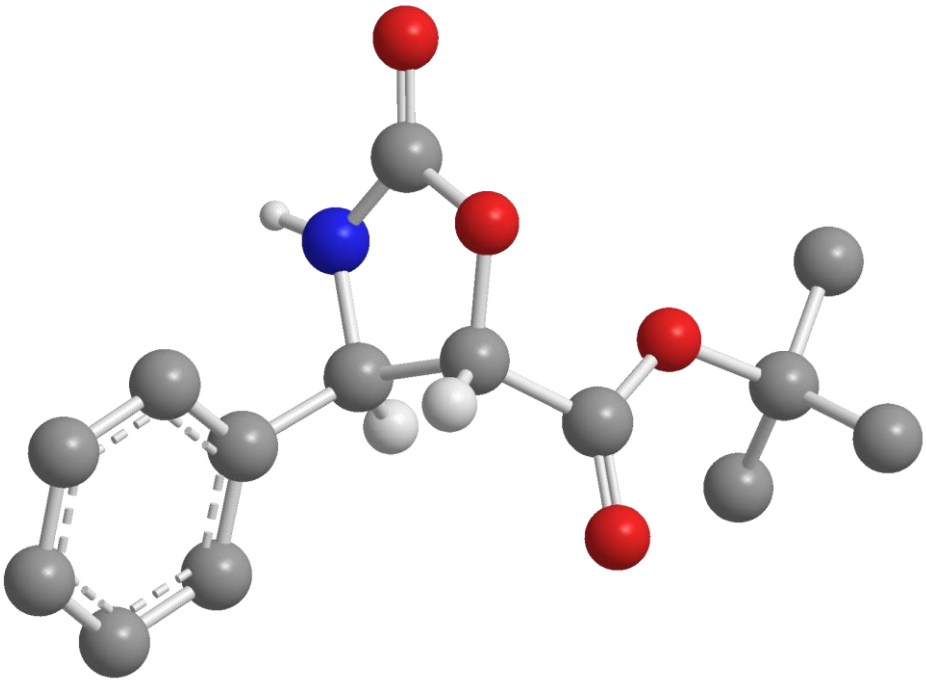
Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[13]

X-ray crystal structure data for **223** [$C_{18}H_{25}NO_4$]: M = 319.40, monoclinic, space group $P\ 2_1$, a = 5.6815(4) Å, b = 10.5198(7) Å, c = 15.2090(10) Å, β = 90.519(3)°, V = 908.98(11) Å^3, Z = 2, μ = 0.082 mm^{-1}, colourless plate, crystal dimensions = 0.11 × 0.24 × 0.25 mm^3. A total of 2088 unique reflections were measured for 5 < θ < 27 and 1780 reflections were used in the refinement. The final parameters were wR_2 = 0.120 and R_1 = 0.050 [I>−3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

[13] 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 (4*R*,5*S*)-224

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 224

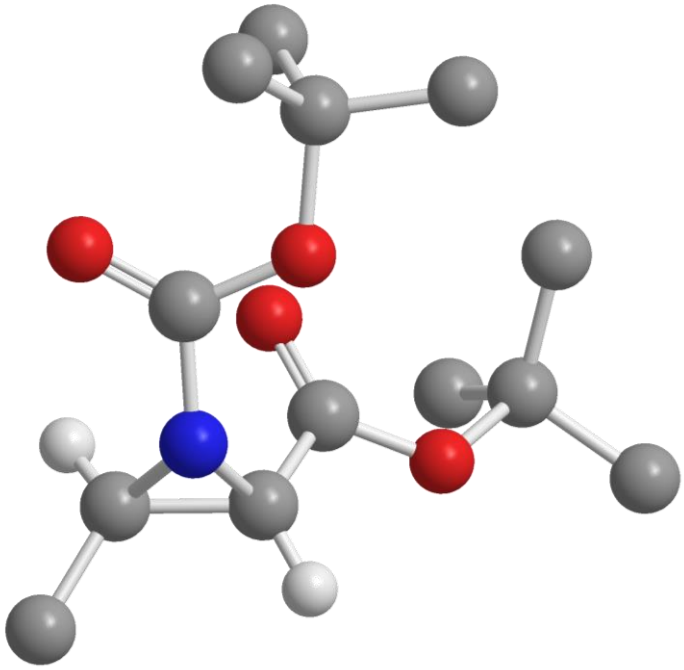
Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[14]

X-ray crystal structure data for **224** [$C_{14}H_{17}NO_4$]: M = 263.29, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 5.8164(1) Å, b = 8.1776(2) Å, c = 28.2005(7) Å, V = 1341.33(5) Å^3, Z = 4, μ = 0.096 mm^{-1}, colourless plate, crystal dimensions = 0.09 × 0.23 × 0.25 mm^3. A total of 1787 unique reflections were measured for $5 < \theta < 27$ and 1787 reflections were used in the refinement. The final parameters were wR_2 = 0.120 and R_1 = 0.071 [I>−3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

[14] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

X-Ray crystal structure data for (2*S*,3*R*)-228

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 228

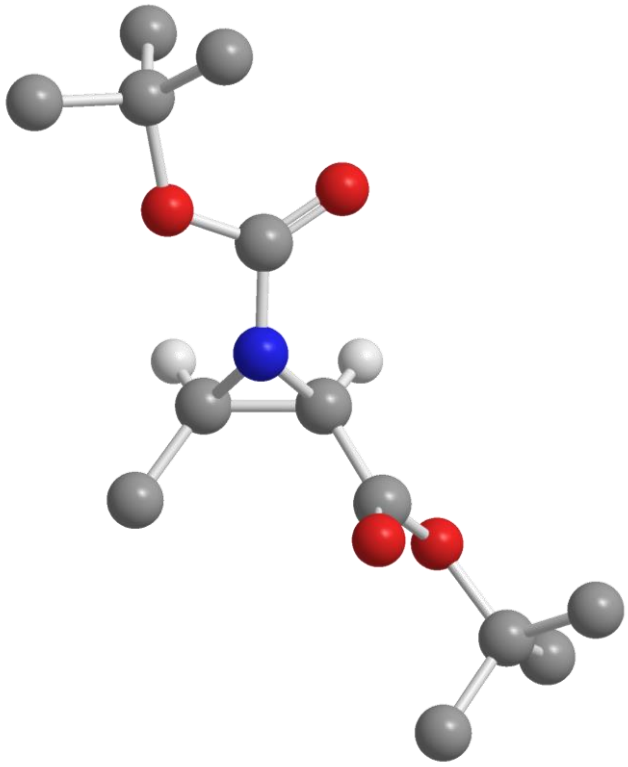
Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[15]

X-ray crystal structure data for **228** [$C_{13}H_{23}NO_4$]: M = 257.33, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 8.5428(2) Å, b = 10.3009(2) Å, c = 16.6744(4) Å, V = 1467.32(6) Å^3, Z = 4, μ = 0.085 mm^{-1}, colourless block, crystal dimensions = 0.21 × 0.37 × 0.41 mm^3. A total of 1916 unique reflections were measured for $5 < \theta < 27$ and 1916 reflections were used in the refinement. The final parameters were wR_2 = 0.086 and R_1 = 0.040 [$I > -3.0\sigma(I)$]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

[15] 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 (*R*,*R*)-229

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 229

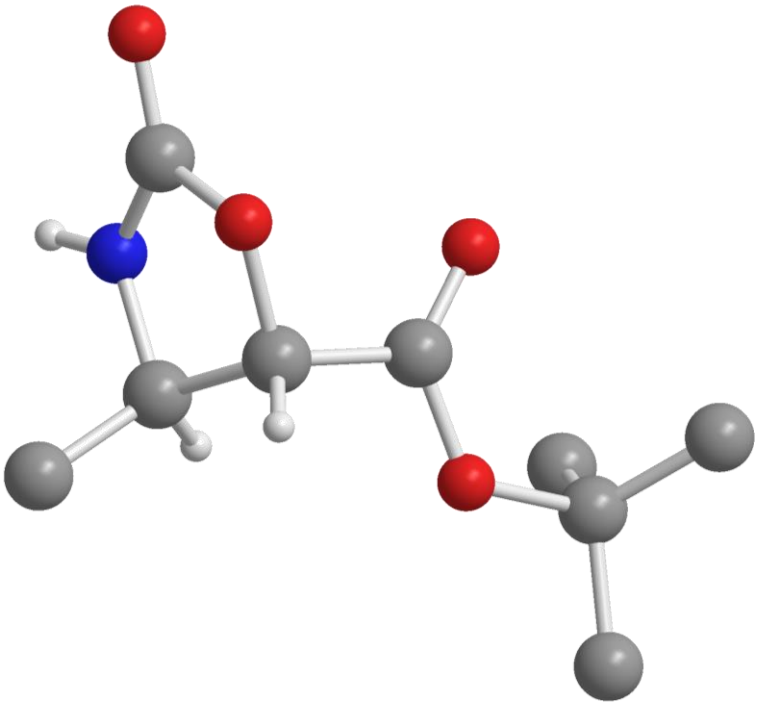
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[16]

X-ray crystal structure data for **229** [$C_{13}H_{23}NO_4$]: M = 257.33, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 5.90422(8) Å, b = 15.23535(18) Å, c = 16.76204(18) Å, V = 1507.79(3) Å^3, Z = 4, μ = 0.683 mm^{-1}, colourless plate, crystal dimensions = 0.08 × 0.16 × 0.18 mm^3. A total of 15404 unique reflections were measured for $5 < \theta < 77$ and 15373 reflections were used in the refinement. The final parameters were wR_2 = 0.077 and R_1 = 0.034 [$I > -3.0\sigma(I)$], with Flack enantiopole = −0.04(7).[17] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

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

X-Ray crystal structure data for (4*R*,5*S*)-230

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 230

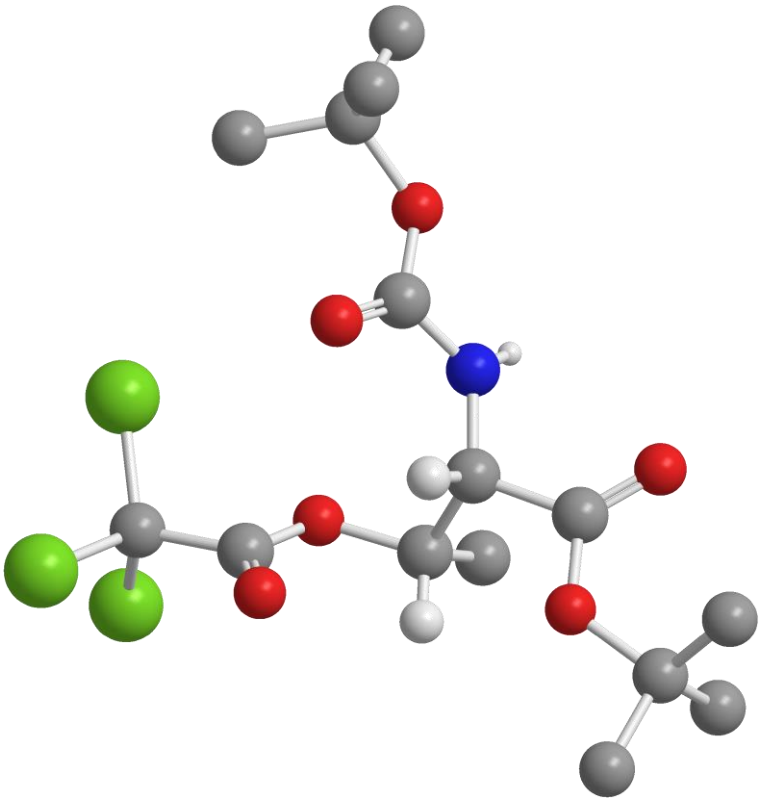
Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[18]

X-ray crystal structure data for **230** [$C_9H_{15}NO_4$]: M = 201.22, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 5.6511(2) Å, b = 9.7237(3) Å, c = 18.8148(6) Å, V = 1033.87(6) Å^3, Z = 4, μ = 0.102 mm^{-1}, colourless plate, crystal dimensions = 0.07 × 0.20 × 0.24 mm^3. A total of 1390 unique reflections were measured for $5 < \theta < 27$ and 1390 reflections were used in the refinement. The final parameters were wR_2 = 0.080 and R_1 = 0.054 [$I > -3.0\sigma(I)$]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

[18] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

X-Ray crystal structure data for (*S*,*S*)-231

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 231

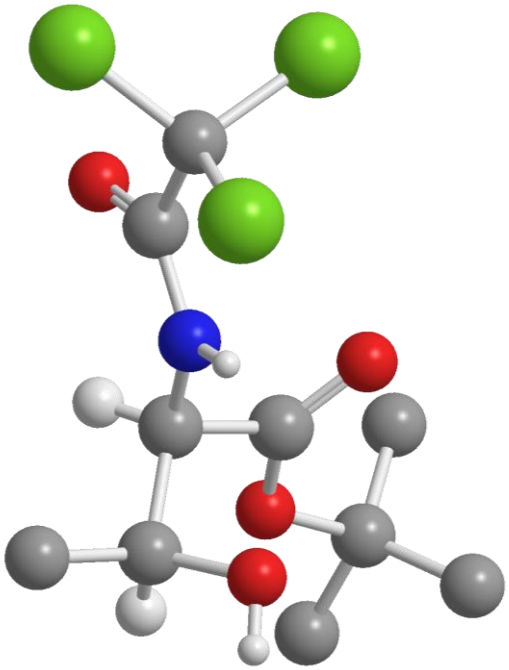
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[19]

X-ray crystal structure data for **231** [$C_{15}H_{24}Cl_3NO_6$]: M = 420.72, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 6.42264(10) Å, b = 9.76809(16) Å, c = 32.9146(6) Å, V = 2064.96(6) Å^3, Z = 4, μ = 4.277 mm^{-1}, colourless plate, crystal dimensions = 0.02 × 0.11 × 0.41 mm^3. A total of 2498 unique reflections were measured for 5 < θ < 76 and 2498 reflections were used in the refinement. The final parameters were wR_2 = 0.128 and R_1 = 0.054 [I>–3.0σ(I)], with Flack enantiopole = –0.017(15).[20] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

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

X-Ray crystal structure data for (2*R*,3*S*)-234

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 234

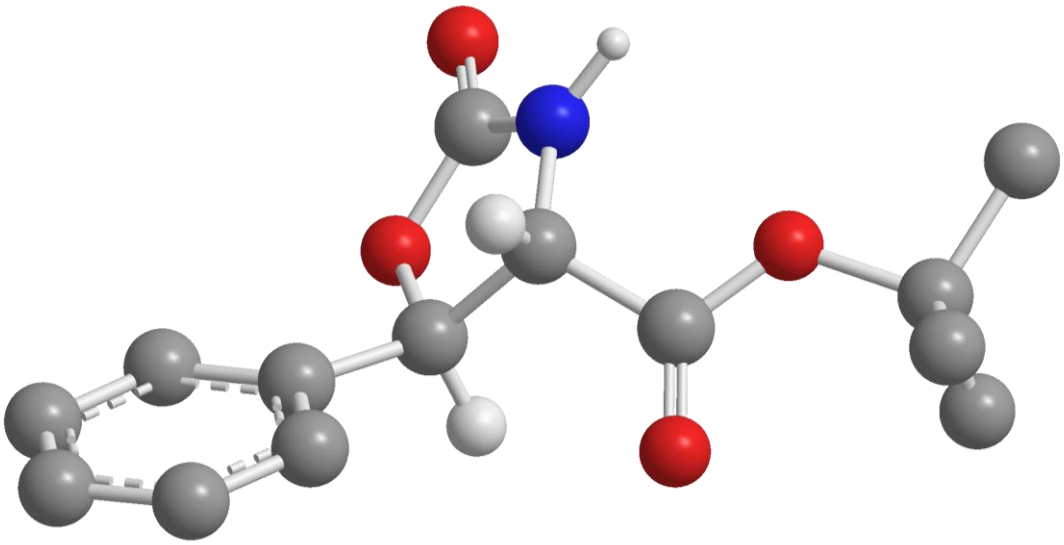
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[21]

X-ray crystal structure data for **234** [$C_{10}H_{16}Cl_3NO_4$]: M = 320.60, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 5.85350(14) Å, b = 15.2105(3) Å, c = 16.5251(4) Å, V = 1471.30(6) Å^3, Z = 4, μ = 5.714 mm^{-1}, colourless block, crystal dimensions = 0.06 × 0.16 × 0.24 mm^3. A total of 6601 unique reflections were measured for 5 < θ < 77 and 6578 reflections were used in the refinement. The final parameters were wR_2 = 0.110 and R_1 = 0.045 [I>−3.0σ(I)], with Flack enantiopole = −0.023(13).[22] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

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

X-Ray crystal structure data for (4*S*,5*R*)-235

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 235

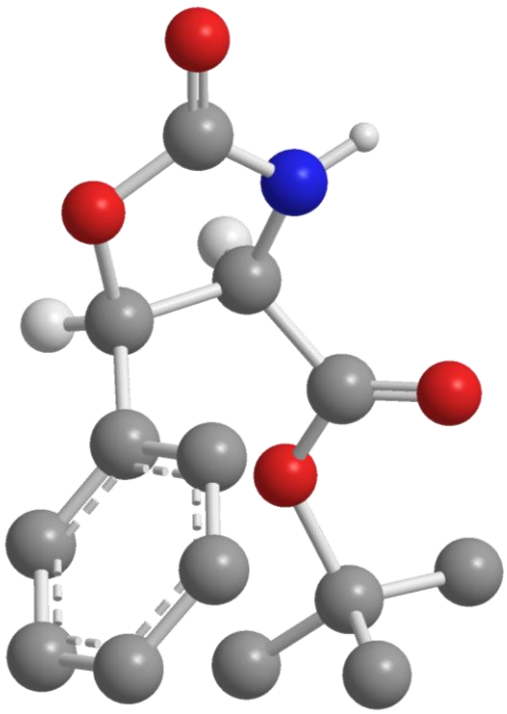
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[23]

X-ray crystal structure data for **235** [$C_{14}H_{17}NO_4$]: M = 263.29, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 5.63909(17) Å, b = 11.4642(3) Å, c = 20.4828(8) Å, V = 1324.17(8) Å^3, Z = 4, μ = 0.803 mm^{-1}, colourless block, crystal dimensions = 0.08 × 0.13 × 0.20 mm^3. A total of 6455 unique reflections were measured for 5 < θ < 76 and 6438 reflections were used in the refinement. The final parameters were wR_2 = 0.111 and R_1 = 0.046 [I>−3.0σ(I)], with Flack enantiopole = −0.08(16).[24] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

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

X-Ray crystal structure data for (*R*,*R*)-236

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 236

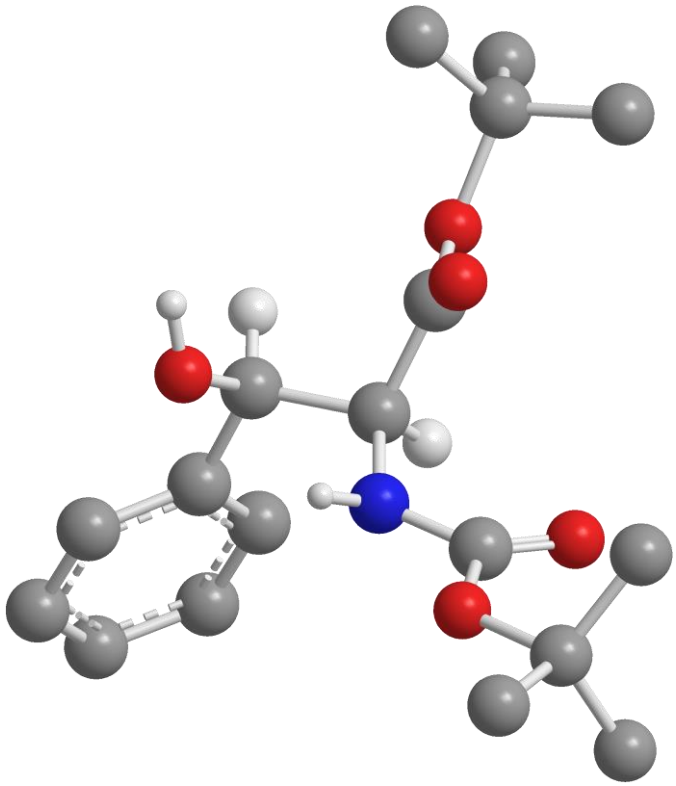
Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[25]

X-ray crystal structure data for **236** [$C_{14}H_{17}NO_4$]: M = 263.29, monoclinic, space group $P\ 2_1$, a = 9.9353(3) Å, b = 5.9307(2) Å, c = 11.2665(4) Å, β = 97.900(3)°, V = 657.56(4) Å^3, Z = 2, μ = 0.809 mm^{-1}, colourless block, crystal dimensions = 0.04 × 0.06 × 0.24 mm^3. A total of 2734 unique reflections were measured for 5 < θ < 27 and 2376 reflections were used in the refinement. The final parameters were wR_2 = 0.087 and R_1 = 0.036 [I>−3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

[25] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

X-Ray crystal structure data for (2*S*,3*R*)-239

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 239

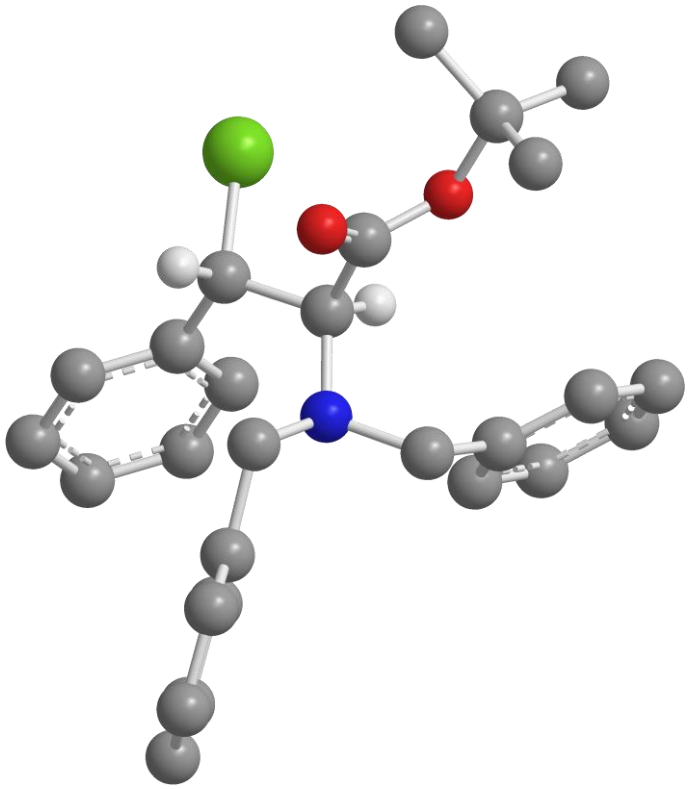
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[26]

X-ray crystal structure data for **239** [$C_{18}H_{27}NO_5$]: M = 337.42, monoclinic, space group $P\ 2_1$, a = 9.7162(4) Å, b = 9.8279(3) Å, c = 10.7947(4) Å, β = 110.898(4)°, V = 962.97(7) Å^3, Z = 2, μ = 0.691 mm^{-1}, colourless prism, crystal dimensions = 0.09 × 0.12 × 0.28 mm^3. A total of 3835 unique reflections were measured for $4 < \theta < 77$ and 3477 reflections were used in the refinement. The final parameters were wR_2 = 0.093 and R_1 = 0.035 [I>–3.0σ(I)], with Flack enantiopole = –0.06(14).[27] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

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

X-Ray crystal structure data for (*RS*,*SR*)-250

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 250

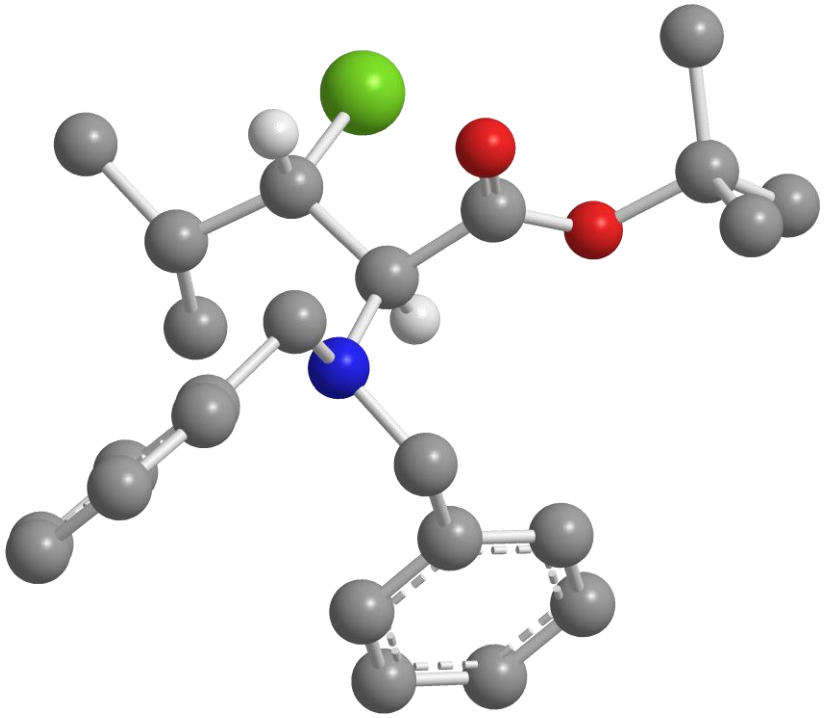
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[28]

X-ray crystal structure data for **250** [$C_{27}H_{30}ClNO_2$]: M = 435.99, triclinic, space group $P\,{-1}$, a = 9.4596(2) Å, b = 10.1502(3) Å, c = 13.2223(3) Å, α = 89.776(2)°, β = 81.880(2)°, γ = 76.852(3)°, V = 1223.36(5) Å^3, Z = 2, μ = 1.548 mm^{-1}, colourless block, crystal dimensions = 0.19 × 0.24 × 0.30 mm^3. A total of 9430 unique reflections were measured for $3 < \theta < 77$ and 9395 reflections were used in the refinement. The final parameters were wR_2 = 0.140 and R_1 = 0.053 [I>–3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

[28] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

X-Ray crystal structure data for (*RS*,*SR*)-258

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 258

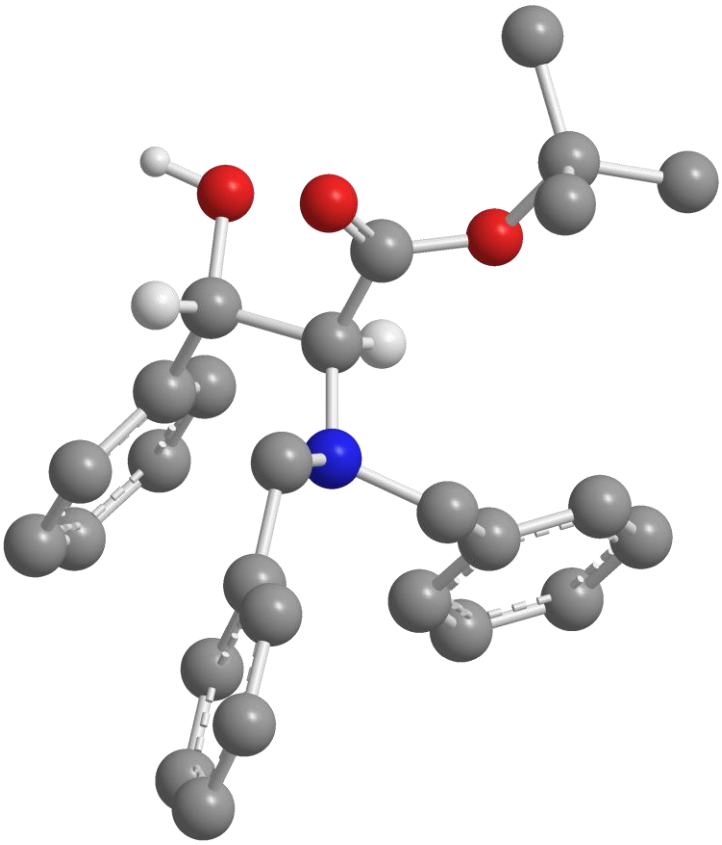
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[29]

X-ray crystal structure data for **258** [$C_{24}H_{32}ClNO_2$]: M = 401.98, triclinic, space group $P\,{-1}$, a = 10.2170(7) Å, b = 11.5497(8) Å, c = 11.6285(8) Å, α = 71.546(6)°, β = 68.144(6)°, γ = 66.373(7)°, V = 1143.99(15) Å^3, Z = 2, μ = 1.608 mm^{-1}, colourless block, crystal dimensions = 0.21 × 0.23 × 0.26 mm^3. A total of 4740 unique reflections were measured for $4 < \theta < 77$ and 4718 reflections were used in the refinement. The final parameters were wR_2 = 0.097 and R_1 = 0.040 [I>–3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

[29] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

X-Ray crystal structure data for (*SR*,*SR*)-260

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 260

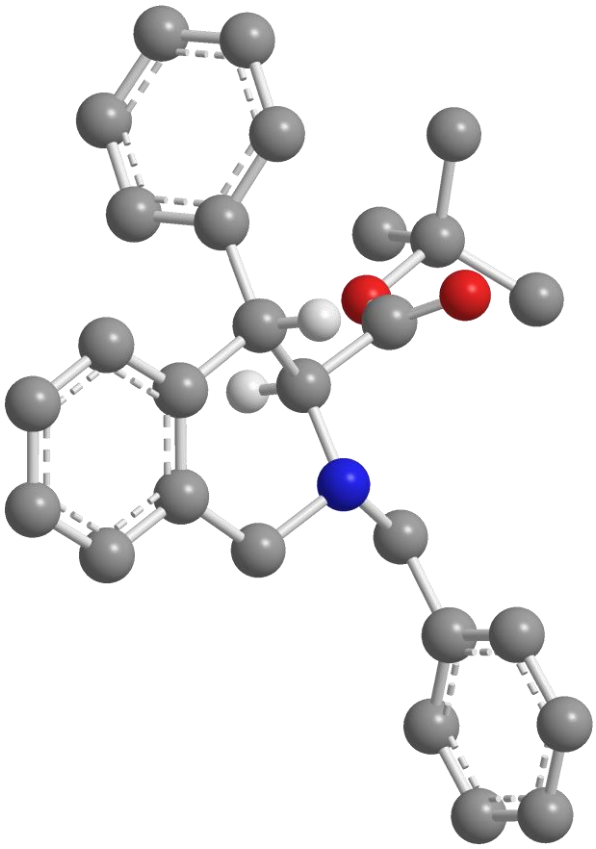
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[30]

X-ray crystal structure data for **260** [$C_{27}H_{31}NO_3$]: M = 417.55, triclinic, space group $P\ -1$, a = 8.9881(3) Å, b = 9.5258(5) Å, c = 15.1977(8) Å, α = 94.139(4)°, β = 109.126(4)°, γ = 109.126(4)°, V = 1172.90(11) Å^3, Z = 2, μ = 0.602 mm^{-1}, colourless block, crystal dimensions = 0.15 × 0.20 × 0.23 mm^3. A total of 4822 unique reflections were measured for $5 < \theta < 76$ and 4383 reflections were used in the refinement. The final parameters were wR_2 = 0.108 and R_1 = 0.048 [I>–3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

[30] 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 (*SR*,*SR*)-261

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 261

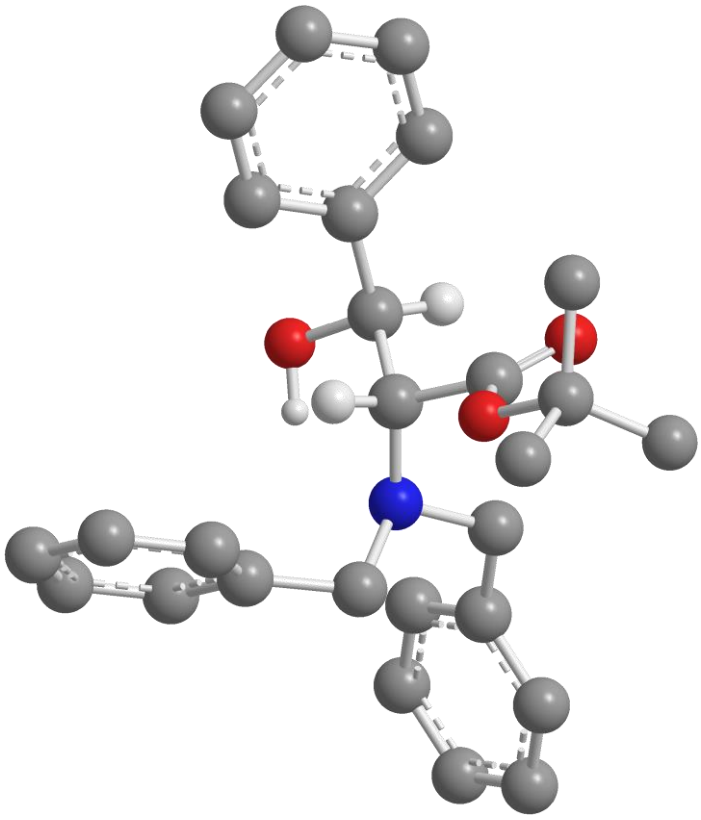
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[31]

X-ray crystal structure data for **261** [$C_{27}H_{29}NO_2$]: M = 399.53, monoclinic, space group $P\ 2_1/c$, a = 10.6596(2) Å, b = 16.4234(3) Å, c = 12.6659(3) Å, β = 93.632(2)°, V = 2212.93(8) Å^3, Z = 4, μ = 0.583 mm^{-1}, colourless block, crystal dimensions = 0.23 × 0.26 × 0.27 mm^3. A total of 4610 unique reflections were measured for 4 < θ < 77 and 4591 reflections were used in the refinement. The final parameters were wR_2 = 0.115 and R_1 = 0.050 [I>–3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

[31] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

X-Ray crystal structure data for (2*R*,3*S*)-271

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 271

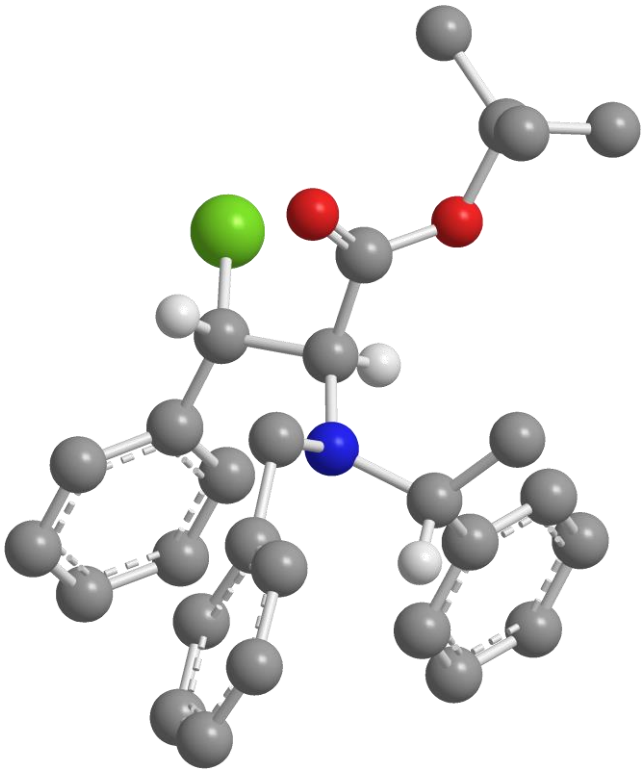
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[32]

X-ray crystal structure data for **271** [$C_{27}H_{31}NO_3$]: M = 417.55, triclinic, space group *P 1*, a = 7.7291(3) Å, b = 9.7886(5) Å, c = 9.8523(5) Å, β = 119.719(5)°, V = 605.28(6) Å^3, Z = 1, μ = 0.584 mm^{-1}, colourless plate, crystal dimensions = 0.09 × 0.21 × 0.22 mm^3. A total of 4523 unique reflections were measured for 5 < θ < 76 and 3880 reflections were used in the refinement. The final parameters were wR_2 = 0.104 and R_1 = 0.040 [I>–3.0σ(I)], with Flack enantiopole = –0.09(16).[33] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

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

X-Ray crystal structure data for (2*R*,3*S*,α*R*)-273

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 273

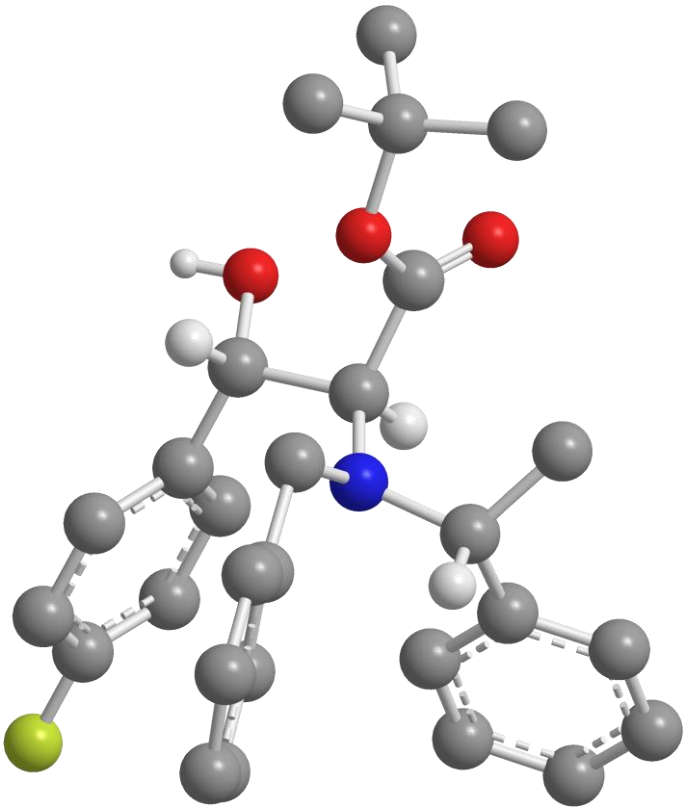
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[34]

X-ray crystal structure data for **273** [$C_{56}H_{64}Cl_2N_2O_4$]: M = 900.04, triclinic, space group $P\ 1$, a = 10.7282(3) Å, b = 11.1453(3) Å, c = 23.9398(5) Å, α = 95.3776(19)°, β = 97.858(2)°, γ = 113.467(2)°, V = 2566.24(13) Å^3, Z = 2, μ = 1.490 mm^{-1}, colourless block, crystal dimensions = 0.28 × 0.30 × 0.31 mm^3. A total of 19461 unique reflections were measured for $4 < \theta < 77$ and 19378 reflections were used in the refinement. The final parameters were wR_2 = 0.177 and R_1 = 0.062 [I>–3.0σ(I)], with Flack enantiopole = 0.056(11).[35] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

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

X-Ray crystal structure data for (2*S*,3*S*,α*R*)-299

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 299

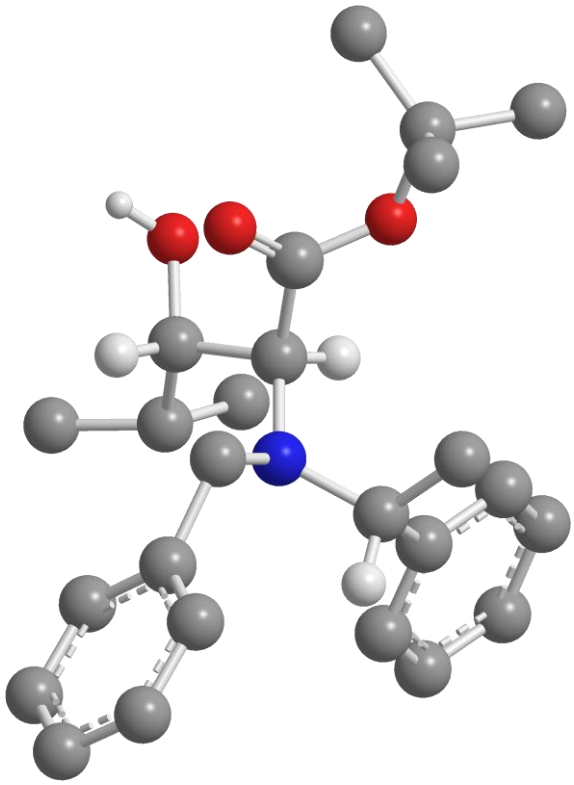
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[36]

X-ray crystal structure data for **299** [$C_{28}H_{32}FNO_3$]: M = 449.56, tetragonal, space group $I\,4$, $a = b$ = 19.9827(3) Å, c = 12.0780(3) Å, V = 4822.88(14) Å^3, Z = 8, μ = 0.684 mm^{-1}, colourless block, crystal dimensions = 0.23 × 0.24 × 0.26 mm^3. A total of 5023 unique reflections were measured for $3 < \theta < 77$ and 4274 reflections were used in the refinement. The final parameters were wR_2 = 0.078 and R_1 = 0.031 [I>–3.0σ(I)], with Flack enantiopole = –0.06(12).[37] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

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

X-Ray crystal structure data for (2*S*,3*S*,α*R*)-321

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 321

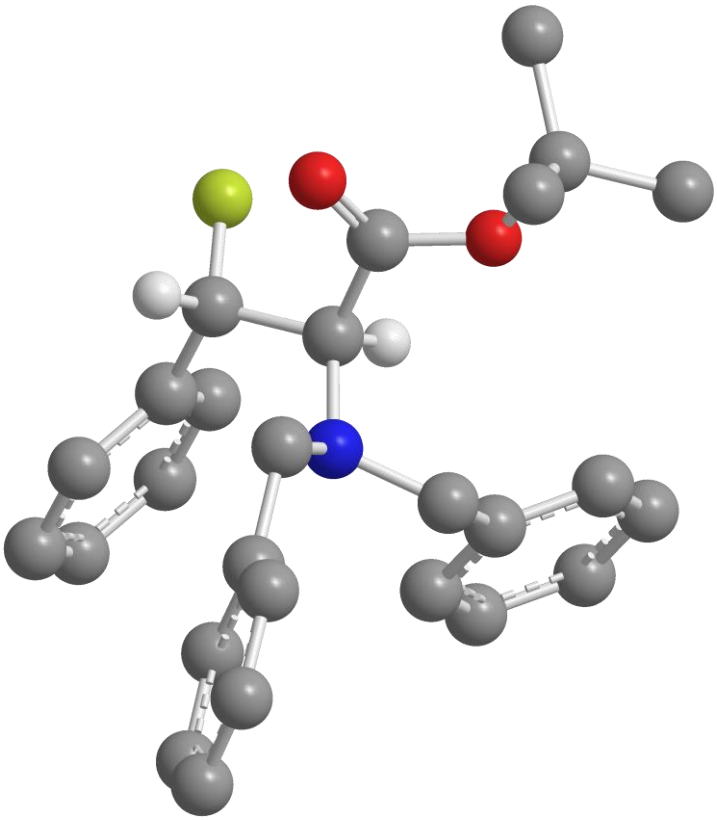
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[38]

X-ray crystal structure data for **321** [$C_{25}H_{35}NO_3$]: M = 397.56, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 12.53600(9) Å, b = 15.54905(12) Å, c = 24.26918(17) Å, V = 4730.62(6) Å^3, Z = 8, μ = 0.567 mm^{-1}, colourless prism, crystal dimensions = 0.06 × 0.08 × 0.21 mm^3. A total of 9859 unique reflections were measured for 3 < θ < 77 and 9819 reflections were used in the refinement. The final parameters were wR_2 = 0.095 and R_1 = 0.038 [I>–3.0σ(I)], with Flack enantiopole = 0.04(12).[39] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

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

X-Ray crystal structure data for (*RS*,*SR*)-356

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 356

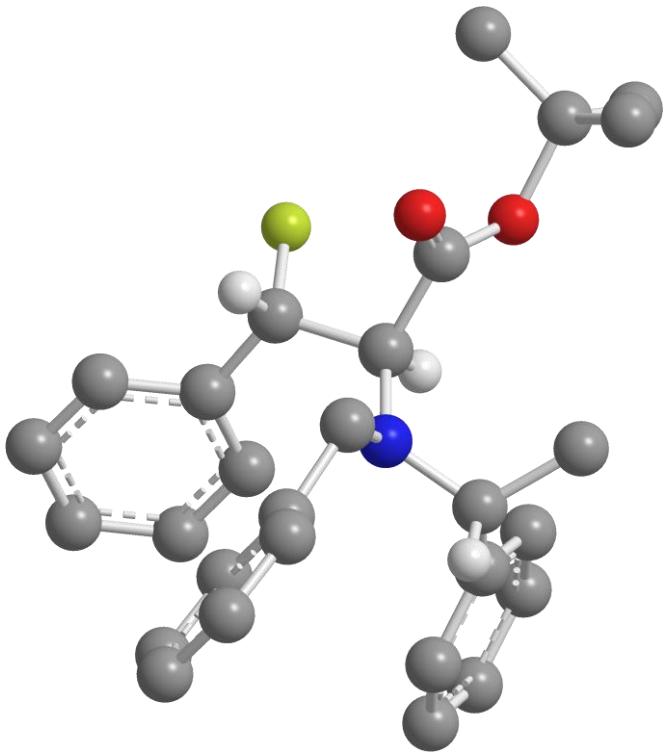
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[40]

X-ray crystal structure data for **356** [$C_{27}H_{30}FNO_2$]: M = 419.54, triclinic, space group P –*1*, a = 9.3088(4) Å, b = 9.5092(4) Å, c = 14.5742(7) Å, α = 92.724(4)°, β = 104.673(4)°, γ = 110.000(4)°, V = 1159.92(10) Å^3, Z = 2, μ = 0.642 mm^{-1}, colourless plate, crystal dimensions = 0.08 × 0.23 × 0.26 mm. A total of 4753 unique reflections were measured for $3 < \theta < 76$ and 4735 reflections were used in the refinement. The final parameters were wR_2 = 0.120 and R_1 = 0.049 [I>–3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

[40] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

X-Ray crystal structure data for (2*R*,3*S*,α*R*)-358

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 358

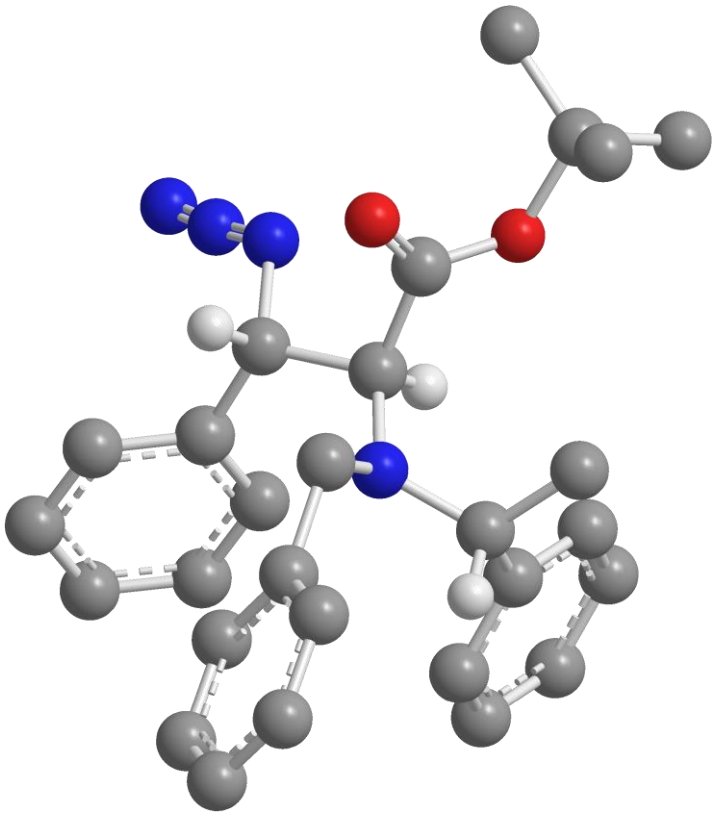
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[41]

X-ray crystal structure data for **358** [$C_{28}H_{32}FNO_2$]: M = 433.57, orthorhombic, space group $P\,2_1\,2_1\,2_1$, a = 8.03153(18) Å, b = 10.6860(2) Å, c = 28.3689(7) Å, V = 2434.77(10) Å^3, Z = 4, μ = 0.627 mm^{-1}, colourless block, crystal dimensions = 0.23 × 0.23 × 0.24 mm. A total of 5050 unique reflections were measured for 4 < θ < 76 and 5030 reflections were used in the refinement. The final parameters were wR_2 = 0.080 and R_1 = 0.033 [I>–3.0$\sigma(I)$], with Flack enantiopole = –0.11(11).[42] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

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

X-Ray crystal structure data for (2*S*,3*S*,α*R*)-368

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 368

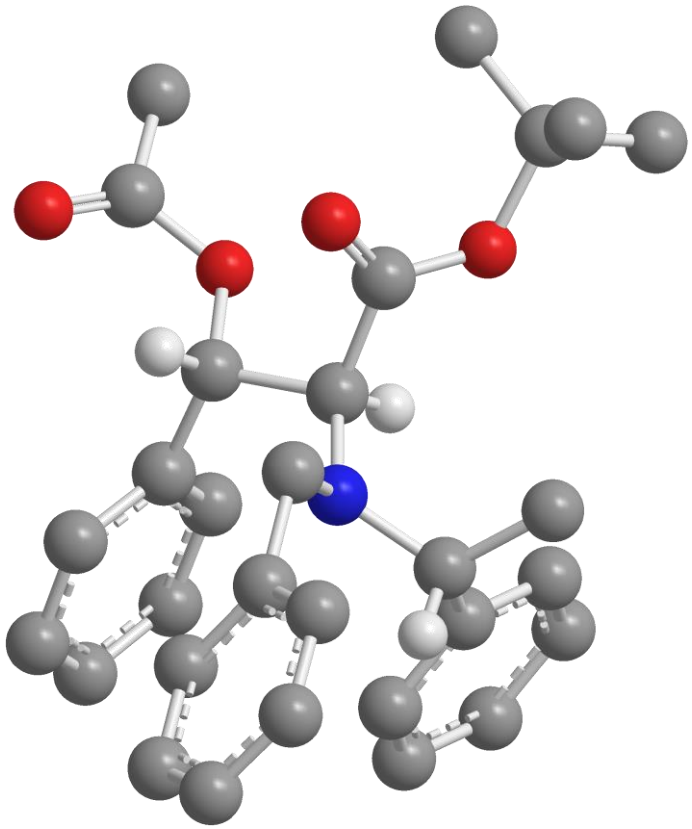
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[43]

X-ray crystal structure data for **368** [$C_{28}H_{32}N_4O_2$]: M = 456.59, trigonal, space group $P\,3_2\,2\,1$, $a = b$ = 11.32263(12) Å, c = 35.3830(4) Å, V = 3928.43(7) Å^3, Z = 6, μ = 0.586 mm^{-1}, colourless block, crystal dimensions = 0.17 × 0.18 × 0.20 mm. A total of 10847 unique reflections were measured for 5 < θ < 76 and 9252 reflections were used in the refinement. The final parameters were wR_2 = 0.137 and R_1 = 0.053 [I>−3.0σ(I)], with Flack enantiopole = –0.1(2).[44] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

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

X-Ray crystal structure data for (2*S*,3*S*,α*R*)-369

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 369

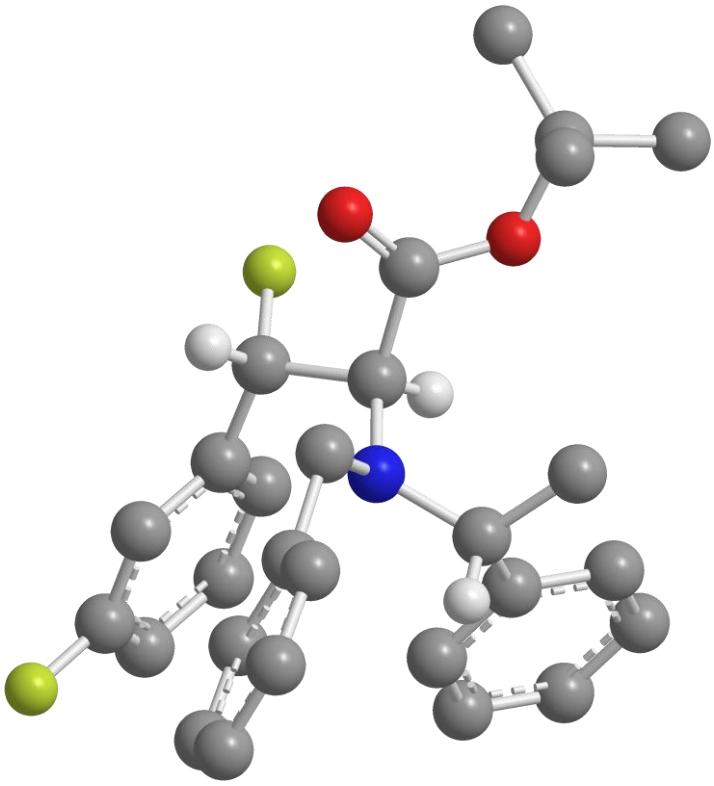
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[45]

X-ray crystal structure data for **369** [$C_{30}H_{35}NO_4$]: M = 473.61, triclinic, space group $P\ 1$, a = 9.7073(3) Å, b = 10.1680(3) Å, c = 14.0374(4) Å, α = 85.597(2)°, β = 85.998(2)°, γ = 82.306(2)°, V = 1366.53(7) Å^3, Z = 2, μ = 0.601 mm^{-1}, colourless plate, crystal dimensions = 0.15 × 0.22 × 0.23 mm. A total of 10245 unique reflections were measured for $3 < \theta < 76$ and 10206 reflections were used in the refinement. The final parameters were wR_2 = 0.143 and R_1 = 0.052 [$I>-3.0\sigma(I)$], with Flack enantiopole = –0.12(15).[46] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

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

X-Ray crystal structure data for (2*R*,3*S*,*αR*)-398

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 398

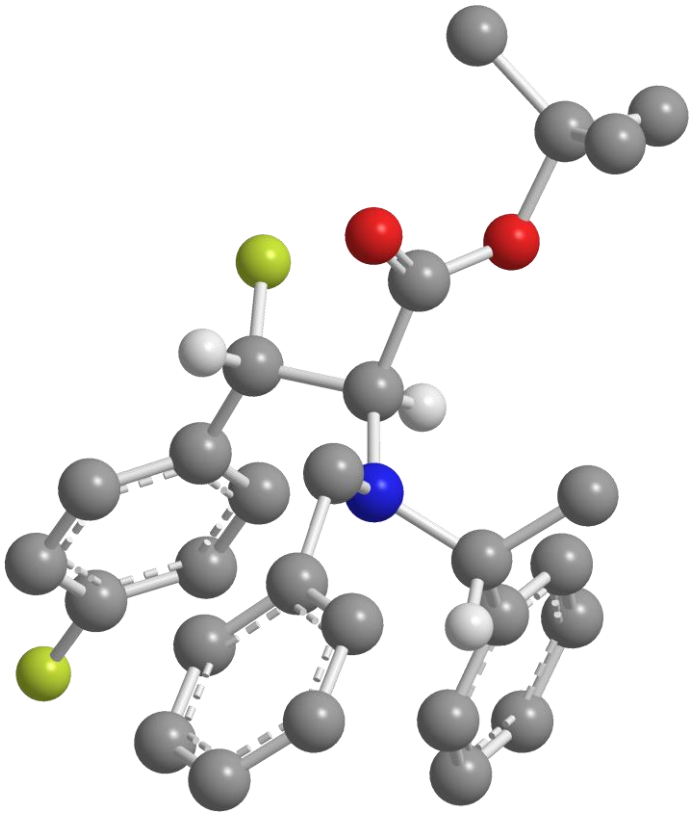
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[47]

X-ray crystal structure data for **398** [$C_{28}H_{31}F_2NO_2$]: M = 451.56, triclinic, space group $P\ 1$, a = 10.4764(5) Å, b = 10.6867(5) Å, c = 12.3768(4) Å, α = 85.757(3)°, β = 70.552(3)°, γ = 69.477(4)°, V = 1222.26(10) Å^3, Z = 2, μ = 0.706 mm^{-1}, colourless block, crystal dimensions = 0.25 × 0.27 × 0.30 mm. A total of 9190 unique reflections were measured for $4 < \theta < 77$ and 8421 reflections were used in the refinement. The final parameters were wR_2 = 0.156 and R_1 = 0.056 [$I>-3.0\sigma(I)$], with Flack enantiopole = 0.02(12).[48] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

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

X-Ray crystal structure data for (2*R*,3*S*,α*R*)-400

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 400

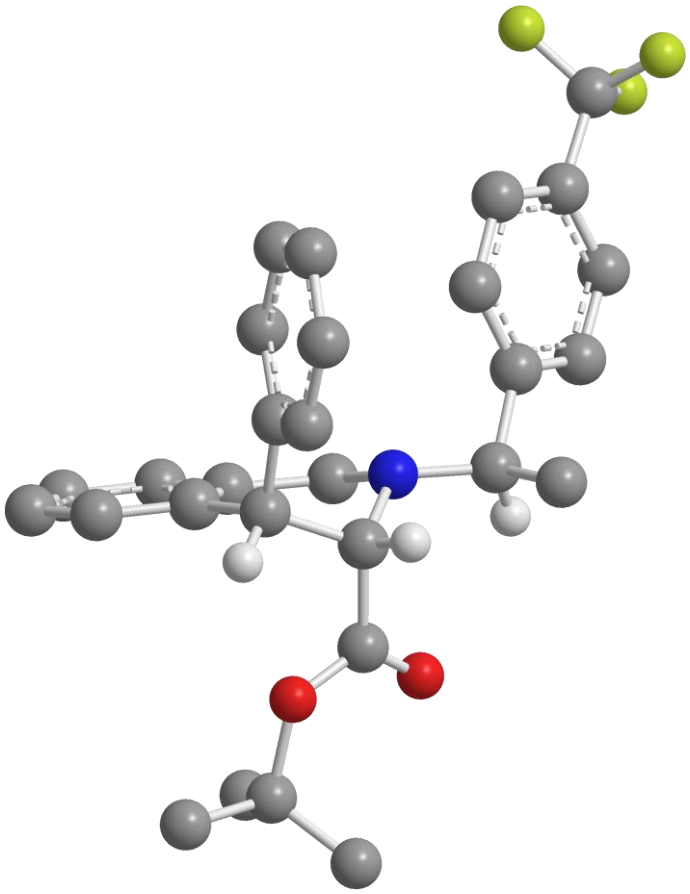
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[49]

X-ray crystal structure data for **400** [$C_{28}H_{31}F_2NO_2$]: M = 451.56, monoclinic, space group $P\ 2_1$, a = 7.09952(11) Å, b = 16.3522(3) Å, c = 9.53794(13) Å, β = 95.6737(13)°, V = 1227.58(3) Å^3, Z = 2, μ = 0.703 mm^{-1}, colourless prism, crystal dimensions = 0.15 × 0.26 × 0.29 mm. A total of 4754 unique reflections were measured for 5 < θ < 76 and 3951 reflections were used in the refinement. The final parameters were wR_2 = 0.072 and R_1 = 0.028 [I>−3.0σ(I)], with Flack enantiopole = –0.01(10).[50] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

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

X-Ray crystal structure data for (*RS*,*SR*,*SR*)-512

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 512

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.[51]

X-ray crystal structure data for **512** [$C_{29}H_{30}F_3NO_2$]: M = 481.56, monoclinic, space group $P\ 2_1/a$, a = 16.0919(3) Å, b = 18.7852(3) Å, c = 16.7140(3) Å, β = 94.1041(7)°, V = 5039.51(15) Å^3, Z = 8, μ = 0.094 mm^{-1}, colourless block, crystal dimensions = 0.25 × 0.26 × 0.30 mm^3. A total of 11461 unique reflections were measured for $5 < \theta < 27$ and 9132 reflections were used in the refinement. The final parameters were wR_2 = 0.146 and R_1 = 0.099 [I>–3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

[51] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.