Enantiopure Lithium Amides in Asymmetric Synthesis

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for the degree of Master of Science by Research

by

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For my Dad and Mum

致我亲爱的爸爸妈妈

The work described in this thesis was carried out in the Chemistry Research Laboratory, University of Oxford from September 2009 until February 2013, under the supervision of Professor Stephen G. Davies. All of the work is my own unless otherwise stated and has not been submitted previously for any other degree at this or any other university.

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Abstract

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This thesis is concerned with the application of the conjugate addition of enantiopure secondary lithium amides to α,β-unsaturated esters for the asymmetric synthesis of fluorinated β-amino acids, (–)-(*R*)-sitagliptin, and amino sugars.

Chapter 1 focuses on the asymmetric synthesis of compounds containing halogens, chalcogens and pnictogens *via* conjugate addition of enantiomerically pure lithium amides. The projective can be, achieved in two ways: incorporation of halogens, chalcogens and pnictogens in the α,β-unsaturated ester substrates (Class I), and electrophilic enolate functionalisation (Class II).

Chapter 2 details a full investigation into the conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to a range of β-fluoroaryl-α,β-unsaturated esters giving the corresponding β-fluoroaryl-β-amino esters. Subsequent efficient global *N*-deprotection was facilitated by hydrogenolysis without formation of products arising from defluorination being observed. Finally, hydrolysis of the resultant primary β-fluoroaryl-β-amino esters gave a range of β-fluoroaryl-β-amino acids in excellent yield. The power and generality of this conjugate addition methodology developed by Davies *at al.* to produce fluorinated β-amino acids was demonstrated well.

Chapter 3 describes two successful, efficient and concise asymmetric syntheses of (–)-(*R*)-sitagliptin, which is an effective treatment for type 2 diabetes, employing lithium amide conjugate addition methodology as the key stereodefining step.

Chapter 4 describes the successful and concise asymmetric syntheses of 5- or 6-membered ring amino sugars *via* cyclization of "alkene-masked" ω-aldehyde β-amino esters or "acetal-masked" ω-aldehyde β-amino esters derived from lithium amide conjugate addition methodology to the corresponding α,β-unsaturated ester.

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

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Abbreviations

The following abbreviations are used throughout this thesis:

Ac	Acetyl
aq	Aqueous
Ar	Aryl
atm	Atmosphere
ATR	Attenuated total reflectance
$[\alpha]_D$	Specific rotation
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
bp	Boiling point
br	Broad
Bu	Butyl
^{t}Bu	Tertiary Butyl
c	Concentration
C	Celsius
CAN	Cerium Ammonium Nitrate
cm^{-1}	Wavenumber
conc	Concentrated
CSO	(Camphorsulfonyl) oxaziridine
d	Doublet
DAST	Diethylaminosulfur trifluoride
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
dd	Double doublet
DEAD	Diethyl azodicarboxylate
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Diisobutylaluminium hydride
DIEPA	*N*,*N*-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DME	Dimethyl ether
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DPP-4	Dipeptidyl peptidase 4
dr	Diastereoisomeric ratio
δ_H	Proton (^{1}H) NMR chemical shift
δ_C	Carbon (^{13}C) NMR chemical shift
E	Stereoselectivity factor
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	Enatiomeric excess
ent	Enantiomer
equiv	Equivalents
ESI	Electrospray ionisation
Et	Ethyl

Fmoc-OSuc	*N*-(9-Fluorenylmethoxycarbonyloxy)succinimide
FT	Fourier transform
g	Grams
GLP-1	Glucagon-like peptide 1
^{1}H	Proton
h	Hours
HOBt	Hydroxybenzotriazole
Hoveyda-Grubbs II	(1,3-Bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(*o*-isopropoxyphenylmethylene)ruthenium
HRMS	High resolution mass spectrometry
HWE	Horner-Wadsworth-Emmons
Hz	Hertz
i	Ipso
IBX	2-Iodoxybenzoic acid
IPA	Isopropyl alcohol
IR	Infra-red
J	Coupling constant
K	Kelvin
lit.	Literature
LDA	Lithium diisopropylamide
m	Meta
m	Metres
m	Milli
m	Multiplet
M	Molar
M^{+}	Molecular ion
$M+H^{+}$	Protonated molecular ion
m-CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
mg	Milligrams
MHz	Megahertz
min	Minutes
mL	Millilitres
mm	Millimoles
mol	Moles
mp	Melting point
m/z	Mass to charge ratio
µ	Micro
NFSI	*N*-Fluorobenzenesulfonimide
nm	nanometre
NMM	*N*-Methylmorpholine
NMO	*N*-Methylmorpholine-*N*-Oxide
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
o	Ortho
p	Para

Ph	Phenyl
PMP	*p*-Methoxyphenyl
PPA	Polyphosphoric acid
ppm	Parts per million
Pr	Propyl
^{i}Pr	Isopropyl
q	Quartet
quant	Quantitative
R	Alkyl
ref.	Reference
rt	Room temperature
s	Singlet
sat	Saturated
tert	Tertiary
t	Triplet
T	Temperature
TBAF	Tetra-*n*-butylammonium fluoride
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TPAP	Tetrapropylammonium Perruthenate
Ts	Tosyl
UHP	Urea-hydrogen peroxide
UK	United Kingdom
V	Volume
v/v	Volume to volume ratio
ν_{max}	Infra red absorption
w/v	Weight to volume ratio (g per 100 mL)
w/w	Mass to mass ratio
X	Unspecified substitutent

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Abstract

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Chapter 1: Introduction

1.1 The conjugate addition of enantiomerically pure lithium amides

Lots of examples show the phenomenon of direct nucleophilic addition to a carbonyl group. This is defined as 1,2-nucleophilic addition or "ordinary" nucleophilic addition.[1] However, if the carbonyl group is conjugated with a C=C double bond, as in α,β-unsaturated carbonyl compounds, the β-position of the alkene becomes very electrophilic and readily reacts with nucleophiles. This type of reaction is defined as 1,4-addition, Michael addition or conjugate addition (Figure 1).[2]

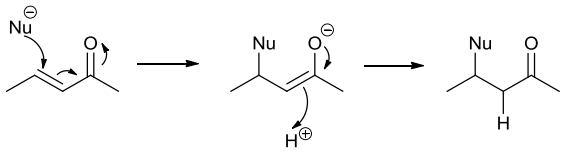
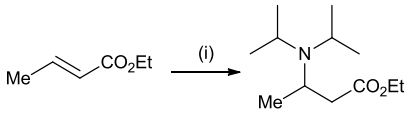


Figure 1. The conjugate addition reaction.

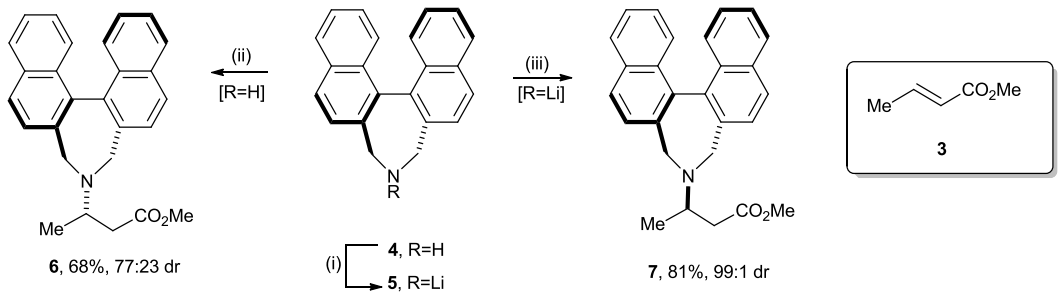
In 1973, Schlessinger et al. reported using one of the most well known lithium amides, LDA, as a nucleophile to carry out conjugate addition to ethyl crotonate **1**, which gave **2** in quantitative yield (Scheme 1).[3]



1 **2**, Quant.

Scheme 1. *Reagents and conditions*: (i) LDA, THF, –78 °C, 10 min.

In 1986, Hawkins et al. developed the conjugate addition of enantiopure lithium amides. Using binaphthyl derived lithium amide **5** as a nucleophile to carry out conjugate addition to methyl crotonate **3** gave **7** in 81% yield and 99:1 dr. The stereoselectivity was better than the result produced by thermal conjugate addition of amine **4** to methyl crotonate **3**, which gave the epimer **6** in 77:23 dr and 68% combined yield (Scheme 2).[4]



Scheme 2. *Reagents and conditions*: (i) BuLi, THF, −78 °C, 25 min; (ii) neat **3**, 68 °C, 21 h; (iii) **3**, THF, −78 °C, 30 min.

From 1991, investigations principally by Davies *et al*. have demonstrated the generality of the conjugate addition of a wide range of enantiopure lithium amides **8**−**24**, derived from commercially available enantiopure α-methylbenzylamines, to a range of structurally diverse α,β-unsaturated esters which proceed with high diastereoselectivity (Figure 2).[5]

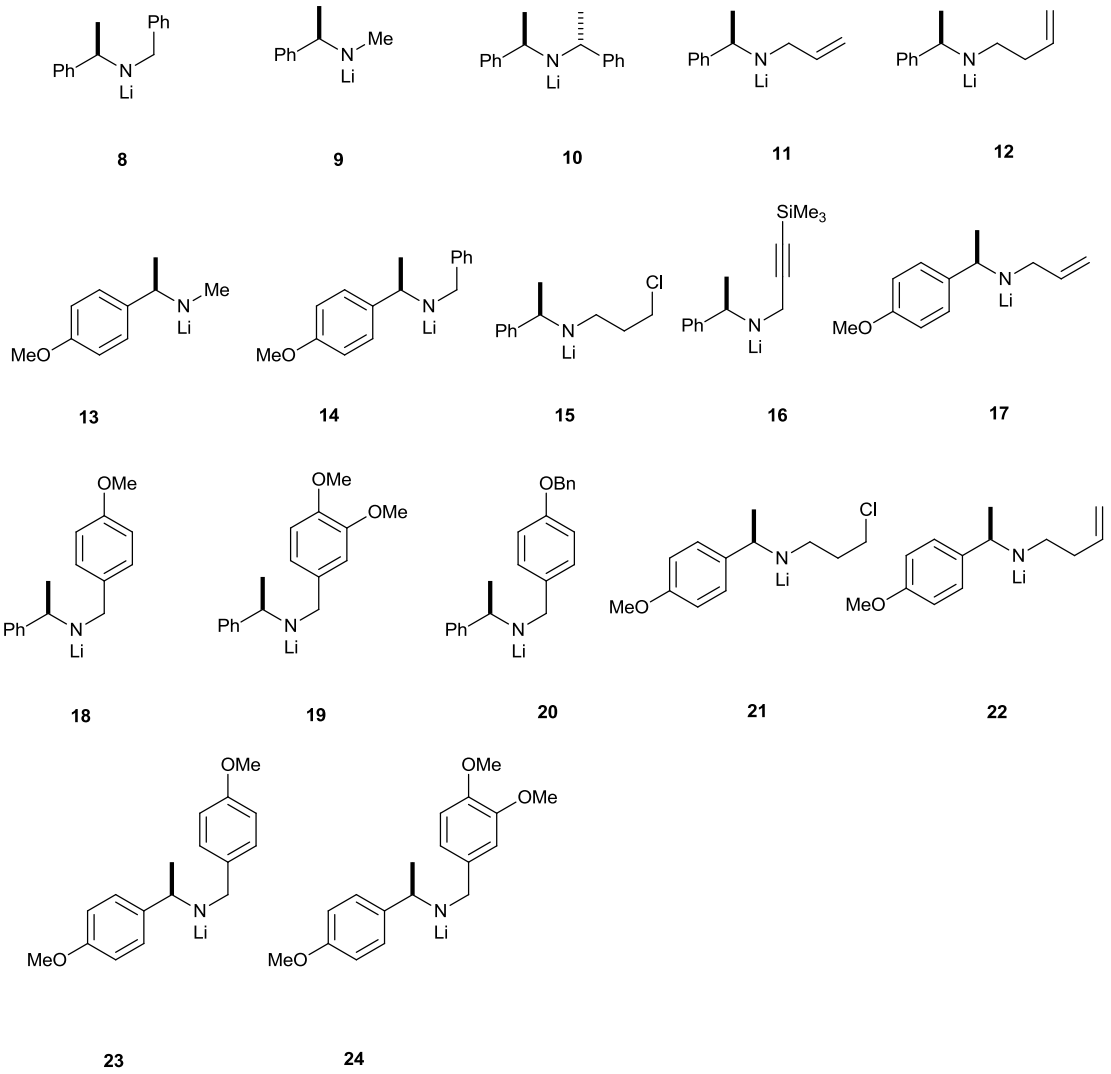
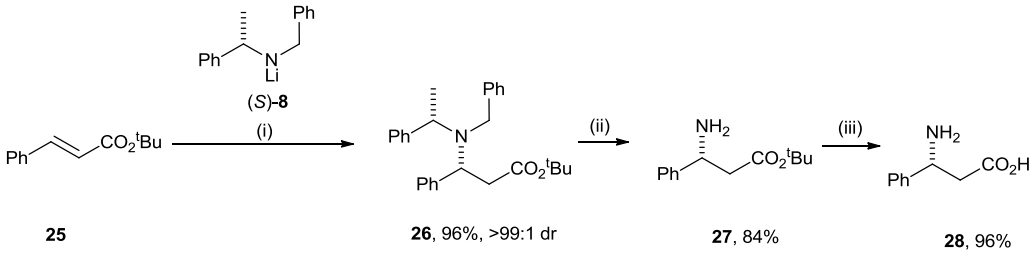


Figure 2. Enantiopure lithium amides **8**−**24** derived from α-methylbenzylamines**.**

Conjugate addition of enantiomerically pure lithium amides has been proven to be a very powerful and useful synthetic methodology for the asymmetric synthesis of a wide range of β-amino acids.[5] For example, conjugate addition of lithium amide (*S*)-**8** to *tert*-butyl cinnamate **25** gave β-amino ester **26** in 96% yield and >99:1 dr. High pressure hydrogenolysis using $Pd(OH)_2/C$ as catalyst gave primary β-amino ester **27** in 84% yield. Treatment of **27** with TFA gave β-amino acid **28** in 96% yield (Scheme 3).[6]



Scheme 3. *Reagents and conditions*: (i) (*S*)-**8**, THF, −78 °C, 2 h; (ii) H_2, $Pd(OH)_2/C$; (iii) TFA/CH_2Cl_2, rt, 15 h.

This methodology is also widely employed in the asymmetric synthesis of natural products and non-natural biologically important targets, in which a nitrogen atom is directly attached to a stereogenic centre. Examples include sperabillin C **29**,[7] (+)-negamycin **30**,[8] (+)-cisapride **31**[9] and (−)-absouline **32**[10] (Figure 3).

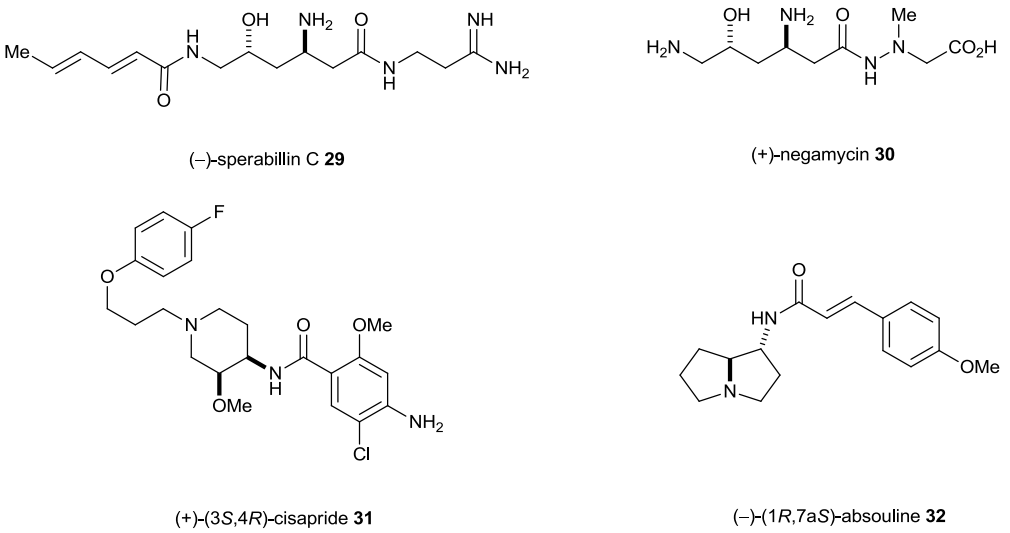


Figure 3. Natural products **29**–**32** prepared using the conjugate addition of lithium amides.

Davies *et al*. have published two comprehensive reviews concerning this methodology, in 2005 and 2012.[5,11] Compared with these two reviews, this chapter focus only on the asymmetric synthesis of compounds containing halogens, chalcogens and pnictogens *via* conjugate addition of enantiomerically pure lithium amides, which can be achieved by two ways: incorporation of halogens, chalcogens and pnictogens in the α,β-unsaturated ester substrates (Class I), and electrophilic enolate functionalisation (Class II) (Figure 4).

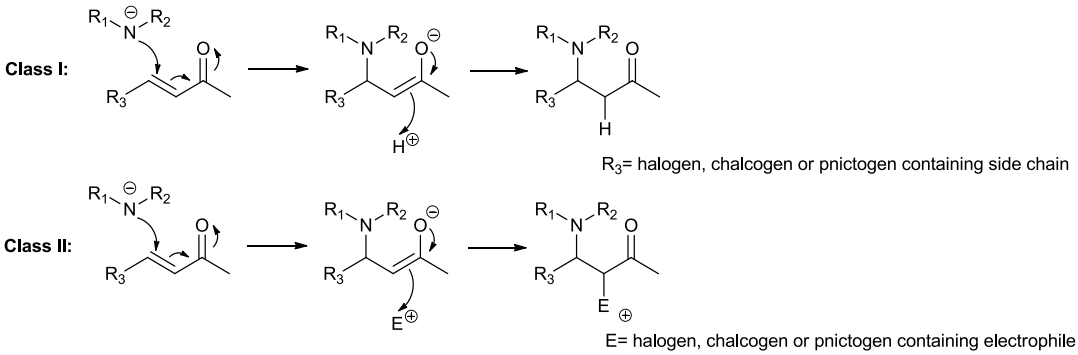


Figure 4. Class I & II asymmetric synthesis of compounds containing halogens, chalcogens and pnictogens *via* conjugate addition of enantiomerically pure lithium amides.

1.2 Asymmetric syntheses of compounds containing halogens *via* conjugate addition of enantiomerically pure lithium amides

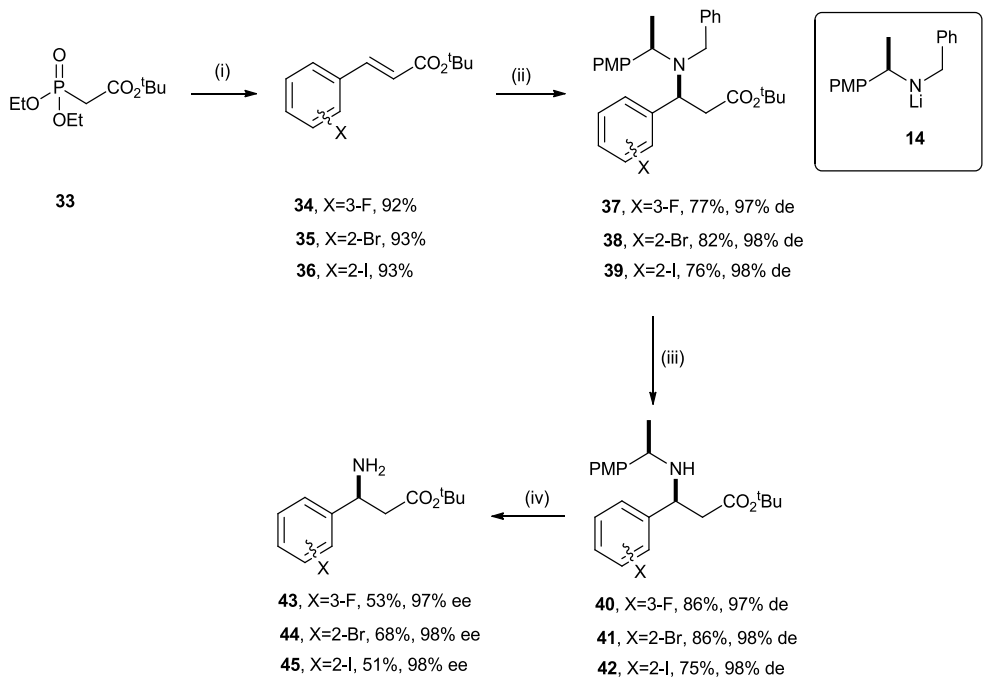
1.2.1 The importance of halogens in medicinal chemistry

A drug containing a halogen atom was first used in 1820.[12] From that time to 1945, halogen-containing drugs experienced an explosive development.[12] Presently, about one third of drugs contain halogen atoms.[12] Halogen atoms have many special properties and incorporation of halogen atoms into drug molecules may have a significant effect on their physicochemical and conformational properties, and metabolic stability.[12] For example, due to the steric effect of halogen atoms, especially chlorine and bromine which have a similar size to sulphur, halogen substitution can impose or disfavor certain conformations.[12] Another effect is due to the inductive effect of halogen atoms, which influences the potency of the drug.[13] Incorporation of halogen atoms into drug molecules also make them more lipophilic and less water soluble. This property helps

drugs to penetrate lipid membranes.[13] All these benefits encourage scientists to explore halogen-containing drugs tirelessly.

1.2.2 Asymmetric syntheses of β-haloaryl-β-amino acid derivatives (Class I)

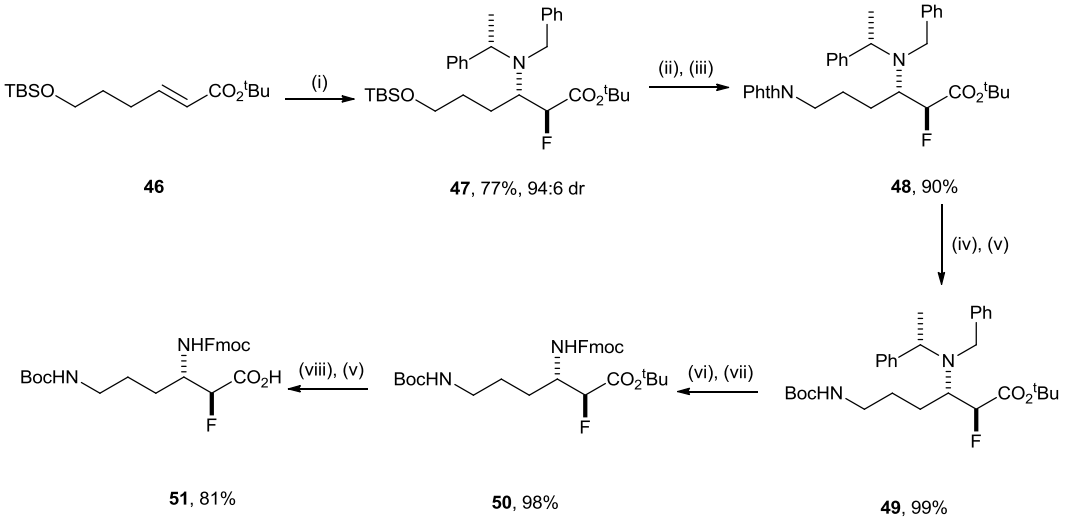
β-Haloaryl-β-amino acids are medicinally important compounds.[14] Some efficient synthetic strategies such as the enzymatic resolution of β-haloaryl-β-amino esters using (lipase Amano PS),[15] and cycloaddition between β-haloaryl imines and ketenes[16] have been published. However, the generality of these methods are limited. In 2001, Davies et al. reported a synthetic strategy for the synthesis of a wide range of β-haloaryl-β-amino acids *via* conjugate addition of lithium *N*-benzyl-*N*-(α-methyl-4-methoxybenzyl)amide to α,β-unsaturated-β-haloaryl esters followed by oxidative deprotection with CAN.[17] The paper listed a wide range of examples including fluorine, chlorine, bromine and iodine in *ortho*, *meta* and *para* positions. Three representative examples have been chosen to illustrate this methodology. The synthetic strategy started from preparation of a range of β-haloaryl-α,β-unsaturated esters **34**−**36** from the corresponding 3-fluoro-, 2-bromo- and 2-iodo-substituted aldehydes, using a Horner-Wadsworth-Emmons reaction, in 92–93% yield as single diastereoisomers. Conjugate addition of lithium *N*-benzyl-*N*-(α-methyl-4-methoxybenzyl)amide **14** to α,β-unsaturated esters **34**–**36** generated the β-amino esters **37**–**39** in 76–82% yield with high levels of diastereoselectivity. Davies and co-workers found that treatment of β-amino esters **37**–**39** with CAN (2.1 equiv) removed the unbranched *N*-benzyl protecting group firstly, allowing orthogonal deprotection of the nitrogen centre to generate *N*-α-methyl-4-methoxybenzyl protected β-amino esters **40**–**42** in 75–86% yield. Further treatment with CAN (4.0 equiv) successfully removed the remaining *N*-4-methoxy-α-methylbenzyl protecting group to give the corresponding β-amino esters **43**–**45** in 51–68% yield (Scheme 4).[17]



Scheme 4. *Reagents and conditions:* (i) **33**, BuLi, THF, −78 °C, then RCHO, −78 °C to rt; (ii) **14**, THF, −78 °C, 2 h; (iii) CAN (2.1 equiv), MeCN/ H_2O (v/v 5:1), rt, 2 h; (iv) CAN (4.0 equiv), MeCN/ H_2O (v/v 5:1), rt, 16 h.

1.2.3 Asymmetric syntheses of α-fluoro-β-amino acid derivatives (Class II)

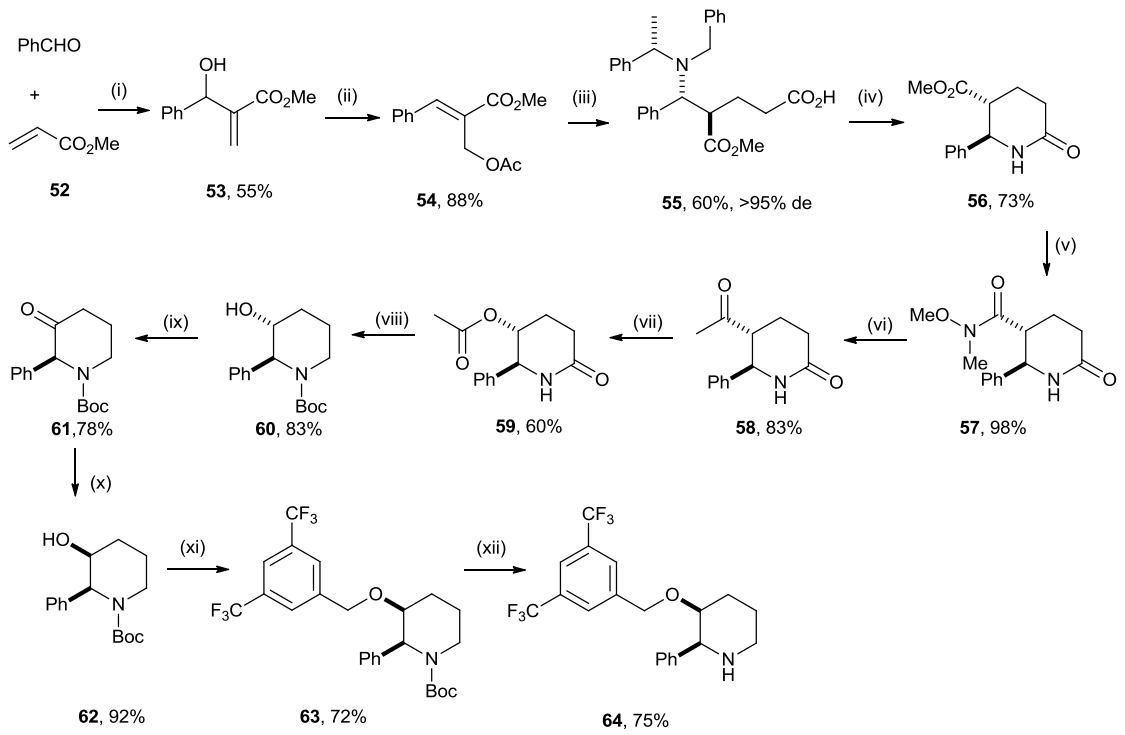
Beside β-haloaryl-β-amino acids which contain a fluorine atom in the aromatic ring, α-fluoro-β-amino acids are another type of β-amino acids which have proved pharmaceutically important.[18] In order to stereoselectively fluorinate the α-position of the β-amino ester enolate which is generated from conjugate addition, in 2010, Duggan et al. reported an elegant protocol involving lithium amide conjugate addition /fluorination occurring in a tandem manner to synthesize a range of *anti*-α-fluoro-β-amino esters in relatively high diastereoselectivity. Duggan et al. used lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide and $(PhSO_2)_2NF$ (NFSI) as an electrophilic fluorine source. The main advantage of this methodology was that it gave good generality to synthesize a range of enantiopure α-fluoro-β-amino acids. One application of this methodology was the synthesis of orthogonally protected (2*S*,3*S*)-α-fluoro-β-lysine **51** from *anti*-α-fluoro-β-amino ester **47**. This occurred with deprotection of the silyl ether followed by Mitsunobu reaction to generate phthalimide **48**, cleavage of the phthalimide **48** followed by *N*-Boc protection, debenzylation by hydrogenolysis followed by *N*-Fmoc protection, *tert*-butyl ester hydrolysis and *N*-Boc reprotection (Scheme 5).[18]



Scheme 5. *Reagents and conditions:* (i) (*S*)-**8**, THF, −78 °C, 2.5 h, then NFSI, −78 °C, 2 h; (ii) TBAF, AcOH, THF; (iii) phthalimide, Ph_3P, DIAD, THF; (iv) $MeNH_2$, EtOH; (v) Boc_2O, Na_2CO_3, THF/H_2O; (vi) $Pd(OH)_2$/C, H_2, AcOH, MeOH; (vii) Fmoc-OSuc, Na_2CO_3, THF/H_2O; (viii) TFA, CH_2Cl_2.

1.2.4 Other synthetic targets containing halogens

In 2009, Garrido and co-workers reported a concise asymmetric synthesis of (+)-L-733,060 **64** (which was proved to cure migraine and rheumatoid arthritis effectively) over 12 steps in 3.3% yield. This pharmaceutically important compound contains trifluoromethyl groups. The synthesis started from treatment of Baylis–Hillman adduct **53** with Ac_2O and pyridine. The right configuration of **55** was achieved *via* stereoselective Ireland–Claisen rearrangement and asymmetric lithium amide conjugate addition to **54**. Catalytic hydrogenolysis followed by lactamization generated **56**, which was then converted to methyl ketone **58**. Baeyer–Villiger oxidation, reduction by $LiAlH_4$ followed by *N*-Boc protection gave **60**. Inversion of the configuration of the hydroxy group was achieved by Swern oxidation and stereoselevtive reduction. Subsequent benzylation of **62** with 3,5-bis(trifluoromethyl)benzyl bromide followed by *N*-Boc deprotection furnished **64** (Scheme 6).[19]



Scheme 6. *Reagents and conditions:* (i) DBU; (ii) Ac_2O–pyridine; (iii) **8**, *n*-BuLi; (iv) H_2, Pd/C, AcOH; (v) Me-ONHMe·HCl, BuLi, THF; (vi) MeMgBr, THF; (vii) UHP, CH_2Cl_2, TFAA, Na_2HPO_4; (viii) $LiAlH_4$, THF, then Boc_2O, THF; (ix) NMO, TPAP; (x) $CeCl_3$, $NaBH_4$; (xi) 3,5-bis(trifluoromethyl)-benzyl bromide, NaH, DMF; (xii) TFA, CH_2Cl_2.

1.3 Asymmetric syntheses of compounds containing pnictogens *via* conjugate addition of enantiomerically pure lithium amides

1.3.1 Syntheses of β-pyridyl-β-amino acid derivatives (Class I)

β-Pyridyl-β-amino acid derivatives are another type of β-amino acids which are proved medically important.[20] For example, 3-(3'-pyridyl)propionic acid is a key component of elarofiban **65** which is an orally active GP IIb/IIIa antagonist (Figure 5).[21] Their biological activity encouraged scientists to develop different synthetic protocols *via* lithium amide conjugate addition towards them.

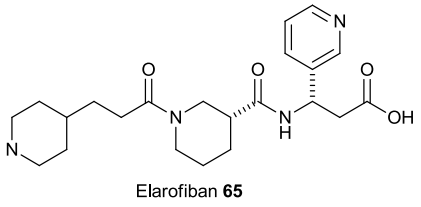
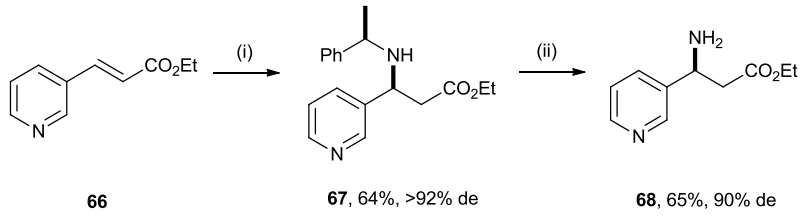


Figure 5. The structure of Elarofiban **65**.

In 1993, Bovy and co-workers reported the asymmetric synthesis of β-pyridyl-β-amino acid derivative **68** in 42% yield and 90% ee *via* conjugate addition of lithium (*R*)-*N*-(α-

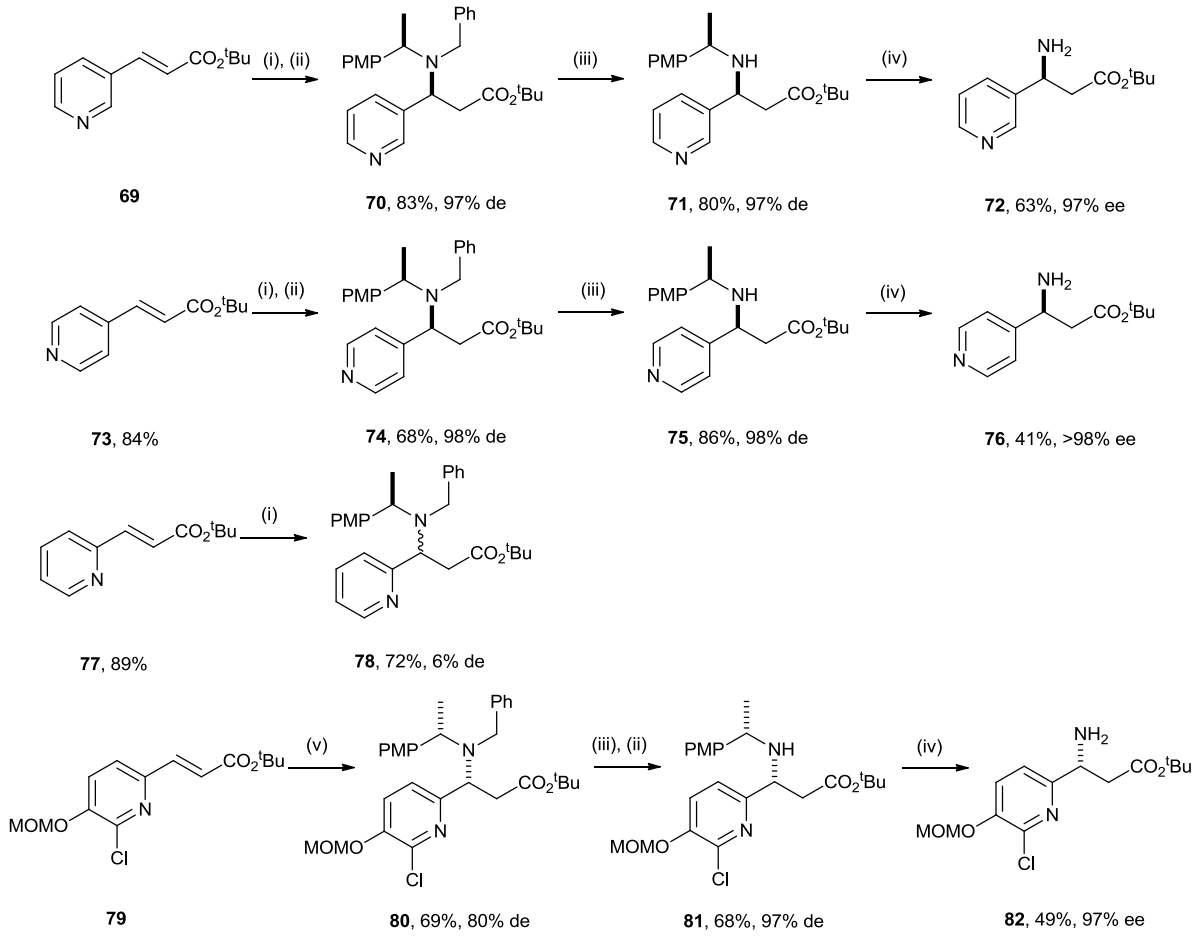
methylbenzyl)-*N*-(trimethylsilyl)amide to the 3-(3'-pyridyl)-α,β-unsaturated ester **66** followed by deprotection upon transfer hydrogenation conditions (Scheme 7).[22]



66 **67**, 64%, >92% de **68**, 65%, 90% de

Scheme 7. *Reagents and conditions:* (i) lithium (*R*)-*N*-(α-methylbenzyl)-*N*-(trimethylsilyl)amide, −78°C, THF; (ii) Pd/C, cyclohexa-1,3-diene, AcOH.

In 2002, Davies and co-workers reported the synthesis of (*S*)-3-(3'-pyridyl)- and (*S*)-3-(4'-pyridyl)-β-amino acid derivatives **72** and **76** in 97% ee and 98% ee respectively, *via* conjugate additions of lithium amide **14** to **69** and **73**, followed by recrystallisation and oxidative *N*-deprotection. However, the investigation of this method towards the synthesis of (2-pyridyl)-β-amino acid derivatives **78** resulted in very poor distereoselectivity (~ 6% de). Interestingly, when the scientists tried to synthesize the protected β-amino ester of kedarcidin *via* conjugate addition of lithium amide **14** to **79**, the stereoselectivity was good (80% de). A reasonable explanation may be the incorporation of a chloro-substituent on the pyridyl ring minimises chelation of the pyridyl nitrogen to the lithium amide (Scheme 8).[23]

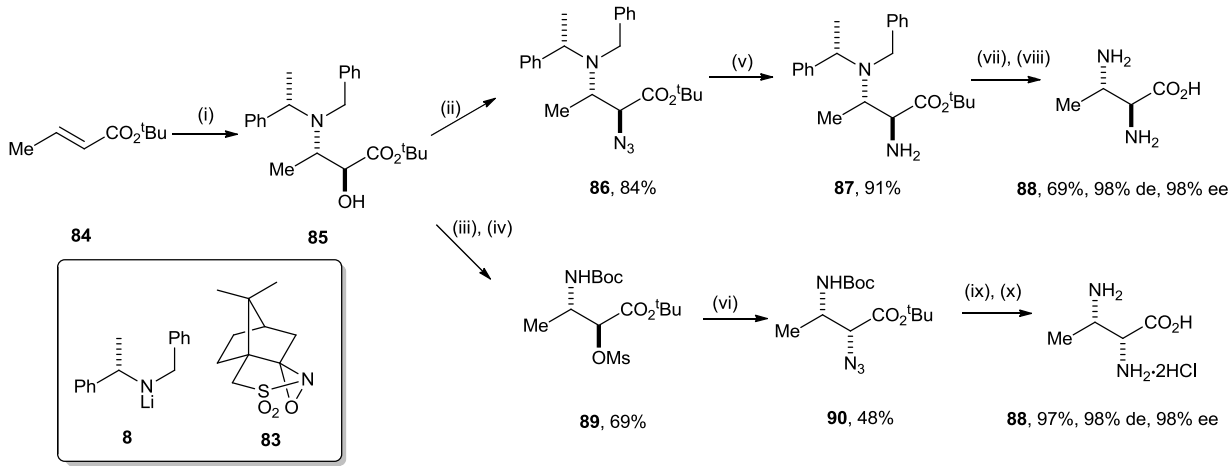


Scheme 8. *Reagents and conditions:* (i) (*R*)-**14**, −78°C, THF; (ii) recrystallisation; (iii) CAN (2.1 equiv), MeCN/ H_2O (v/v 5:1), rt; (iv) CAN (4.0 equiv), MeCN/ H_2O (v/v 5:1), rt; (v) (*S*)-**14**, THF, −78°C.

1.3.2 Asymmetric syntheses of 2,3-diamino acids (Class II)

2,3-Diamino acids are fragments of peptide antibiotics.[24] In 2003, Davies and co-workers reported two concise asymmetric syntheses of *anti*-(2*S*,3*S*)-diaminobutanoic acid **88** and *syn*-(2*R*,3*S*)-diaminobutanoic acid **88**.[25] The preparation of **88** started from *anti*-β-amino-α-hydroxy ester **85**, which was generated by conjugate addition of lithium amide **8** to *tert*-butyl crotonate **84** and enolate oxidation with (+)-CSO **83**. For the synthesis of *anti*-(2*S*,3*S*)-diaminobutanoic acid **88**, **85** was then transformed to *anti*-α-azido-β-aminoester **86** in 84% yield *via* aziridinium ion formation and regioselective ring-opening with azide ion. After Staudinger reduction, hydrogenolysis and ester hydrolysis, *anti*-(2*S*,3*S*)-diaminobutanoic acid **88** was successfully synthesised in 98% de and 98% ee. For the synthesis of *syn*-(2*R*,3*S*)-diaminobutanoic acid **88**, **85** was then transformed to *N*-Boc-3-amino mesylate **89** in 69% yield, followed by S_N2-type

methylate displacement using azide and subsequent deprotection. *syn*-(2*R*,3*S*)-Diaminobutanoic acid **88** was successfully synthesised in 98% de and 98% ee (Scheme 9).[25]

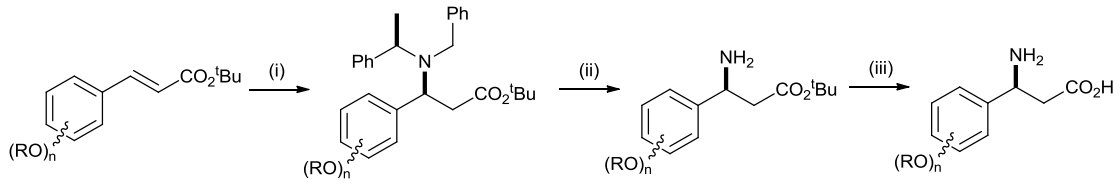


Scheme 9. *Reagents and conditions:* (i) (*S*)-**8**, THF, −78°C, 2 h, then (+)-CSO **83**, −78 °C to rt, 12 h; (ii) hydrazoic acid, PPh_3, DEAD, benzene, rt; (iii) $Pd(OH)_2/C$, H_2 (5atm), Boc_2O, EtOAc, rt; (iv) $MeSO_2Cl$, NEt_3, CH_2Cl_2, 0 ˚C to rt; (v) PPh_3,THF/H_2O, rt; (vi) NaN_3, DMF, 55 ˚C; (vii) $Pd(OH)_2/C$, MeOH, H_2(5 atm); (viii) TFA, rt then 1M HCl then Dowex 50X8-200; (ix) Pd/C, H_2 (5 atm), EtOAc, rt; (x) TFA, rt overnight then 1 M HCl, rt.

1.4 Asymmetric syntheses of compounds containing chalcogens *via* conjugate addition of enantiomerically pure lithium amides

1.4.1 Asymmetric syntheses of β-oxyaryl-β-amino acid derivatives (Class I)

β-Oxyaryl-β-amino acid derivatives are medicinally important compounds.[26] In 2007, Davies *et al*. reported a synthetic strategy for the synthesis of a wide range of β-oxyaryl-β-amino acids in 85–99% yield *via* conjugate addition of lithium amide **8** to α,β-unsaturated β-aryl acceptors followed by palladium catalytic deprotection and acid hydrolysis (Scheme 10).[6]

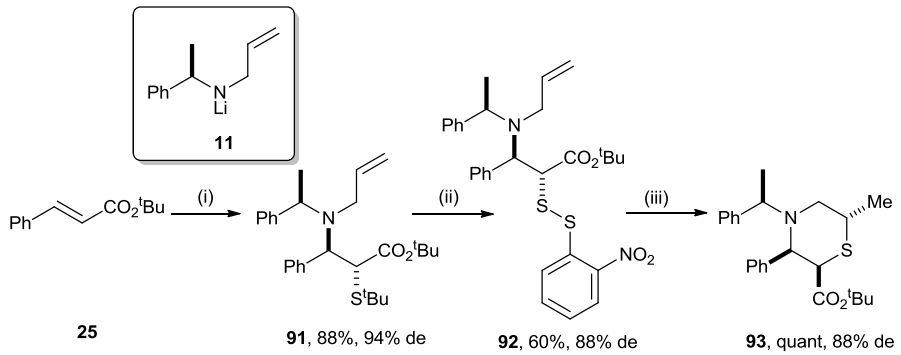


$(RO)_n$=*p*-MeO, *o*-MeO, *m*-MeO, *m*-OH or *p*-OH etc.

Scheme 10. *Reagents and conditions:* (i) (*R*)-**8**, THF, −78°C, 2 h; (ii) H_2 (1 atm), $Pd(OH)_2/C$, MeOH, H_2O, AcOH, rt, 15 h; (iii) TFA, CH_2Cl_2, rt, 15 h.

1.4.2 Asymmetric syntheses of α-thio-β-amino acid derivatives (Class II)

α-Thio-β-amino acid derivatives have potent biological activity such as inhibition of aminopeptidase A.[27] In order to prepare α-thioalkyl-β-amino esters, in 2006, Davies *et al*. reported an elegant protocol that was lithium amide conjugate addition to *tert*-butyl cinnamate/enolate trapping with electrophilic sources of sulphur occurring in a tandem manner. A few electrophilic sources of sulphur including *N*-phenylthio-ε-caprolactam, TsSBn, TsS^{t}Bu and S_8 were tested. One application of this methodology was the synthesis of thiomorpholine **93**. The conjugate addition of lithium (*R*)-*N*-allyl-*N*-(α-methylbenzyl)amide **11** to *tert*-butyl cinnamate **25** and enolate trapping with TsS^{t}Bu generated **91** in 88% and 94% de after purification. Treatment of **91** with 2-nitrobenzenesulphenyl chloride gave disulphide **92** in 60% yield and 88% de. Subsequent reduction of **92** with Lalancette's reagent in EtOH gave thiomorpholine **93** in quantitive yield and 88% de (Scheme 11).[28]



Scheme 11. *Reagents and conditions:* (i) **11**, THF, −78 °C, 2 h, then TsS^{t}Bu, −78 °C, 1 h; (ii) 2-nitrobenzenesulphenyl chloride, AcOH, rt, 2 h; (iii) $NaBH_2S_3$, EtOH, 0 °C to rt, 12 h.

1.4.3 Asymmetric syntheses of α-hydroxy-β-amino acid derivatives (Class II)

In order to synthesize α-hydroxy-β-amino acid derivatives, Davies *et al*. reported an elegant protocol involved lithium amide conjugate addition to a wide range of α-β-unsaturated esters followed by diastereoselective enolate oxidation with (−)-CSO **83** or (+)-CSO **83** to generate the corresponding *anti*-α-hydroxy-β-amino esters (Figure 6).[5]

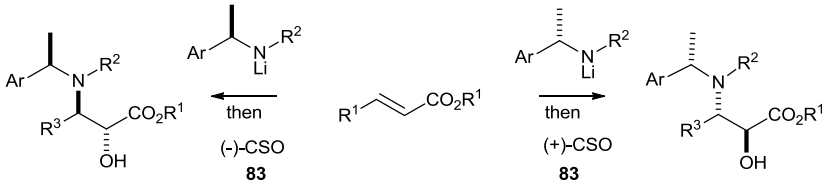
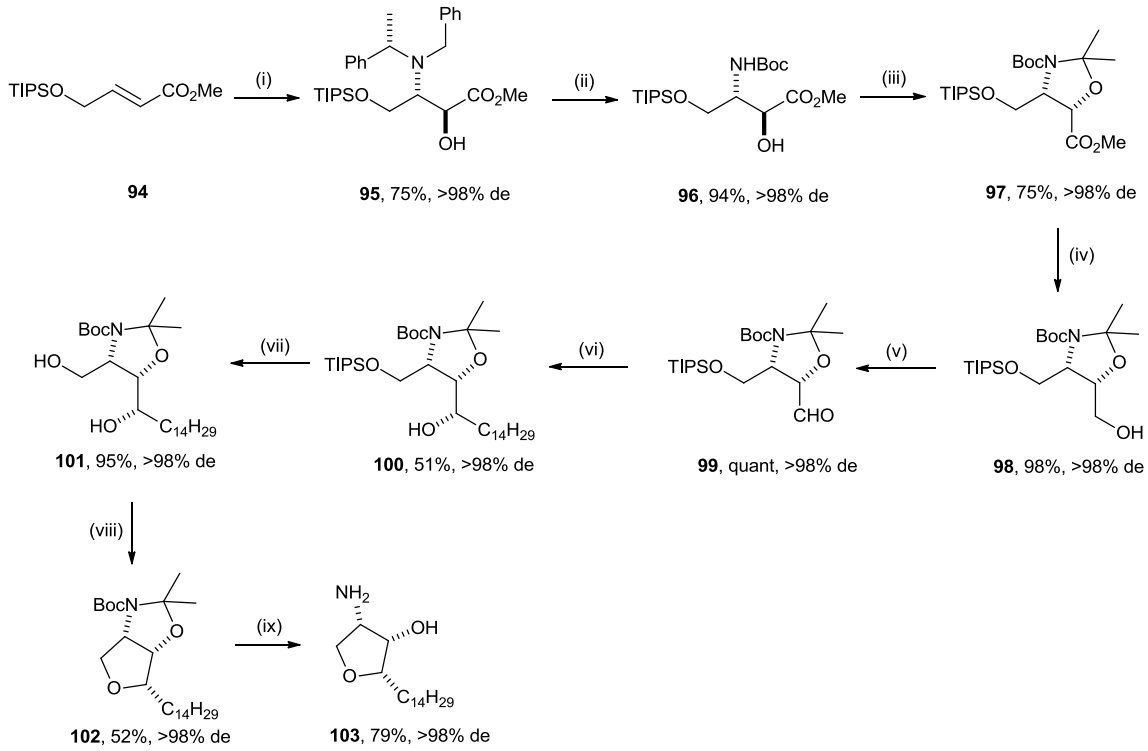


Figure 6. Asymmetric synthesis of α-hydroxy-β-amino acid derivatives.

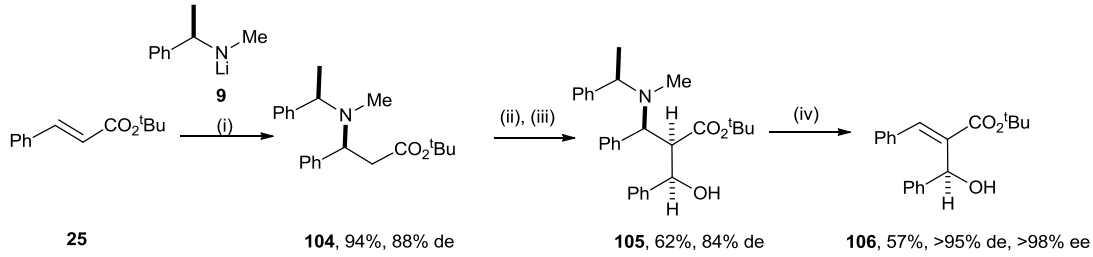
One application of this methodology was the synthesis of jaspine B **103**. Conjugate addition of lithium amide **8** to **94** and enolate oxidation with (+)-CSO **83** gave **95** in 75% yield and >98% de. Hydrogenolysis of **95** in the presence of Boc_2O gave **96** in 94% yield. Treatment of **96** with 2,2-dimethoxypropane and $BF_3{\cdot}Et_2O$ generated oxazolidine **97** in 75% yield. Reduction of **97** with DIBAL-H gave alcohol **98** in 98% yield, with subsequent oxidation with IBX giving aldehyde **99** in quantitative yield. Treatment of aldehyde **99** with tetradecylmagnesium bromide gave **100** in 51% yield and >98% de. Desilylation of **100** using TBAF gave diol **101** in 95% yield. Treatment of **101** with tosyl chloride gave **102** in 52% yield and >98% de. Final deprotection of **102** gave jaspine B **103** in 79% yield and >98% de (Scheme 12).[29]



Scheme 12. *Reagents and conditions:* (i) (*S*)-**8**, THF, −78 °C, 2 h, then (+)-CSO **83**, −78 °C to rt, 12 h; (ii) H_2 (5 atm), $Pd(OH)_2/C$, Boc_2O, EtOAc, rt, 12 h; (iii) 2,2-dimethoxypropane, $BF_3{\cdot}Et_2O$, acetone, reflux, 12 h; (iv) DIBAL-H, CH_2Cl_2, 0 °C, 6 h; (v) IBX, DMSO, rt, 12 h; (vi) $C_{14}H_{29}MgBr$, THF, 0 °C to rt, 6 h; (vii)TBAF, THF, rt, 12 h; (viii) TsCl, DMAP, pyridine, reflux, 8 h; (ix) HCl, MeOH, 50 °C, 6 h, then KOH.

1.4.4 Asymmetric syntheses of Baylis-Hillman products (Class II)

Baylis-Hillman products are useful synthetic intermediates.[30] In 2000, Davies *et al*. reported that conjugate addition of lithium amide **9** to *tert*-butyl cinnamate **25** gave **104** in 94% yield and 88% de. Subsequent asymmetric aldol reaction with benzaldehyde gave **105** in 62% yield and 84% de. Treatment of **105** with *m*-CPBA resulted in *N*-oxidation/Cope elimination to generate Baylis-Hillman product **106** in 57% yield, >95% de and >98% ee (Scheme 13).[31]



Scheme 13. *Reagents and Conditions*: (i**) 9**, −78 °C, THF, 2 h; (ii) LDA, −78 °C to 0˚C; (iii) $B(OMe)_3$, −78 °C then PhCHO; (iv) *m*-CPBA, $CHCl_3$.

1.5 Aims of this thesis

This thesis is concerned with the demonstration of the generality and utility of methodology involved conjugate addition of enantiopure secondary lithium amides to α,β-unsaturated esters for the asymmetric synthesis of fluorinated β-amino acids, (–)-(*R*)-sitagliptin, and amino sugars (Figure 7).

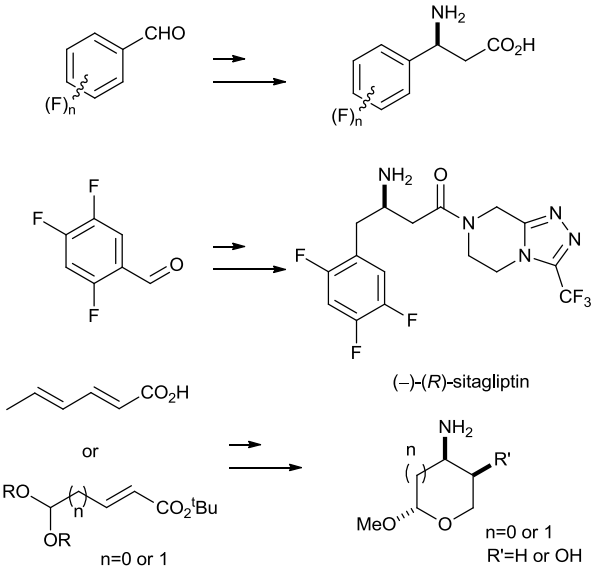


Figure 7. Asymmetric synthesis of fluorinated β-amino acids, (–)-(*R*)-sitagliptin and amino sugars.

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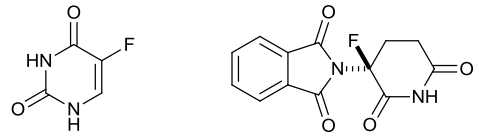
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Chapter 2: Asymmetric Syntheses of Fluorinated β-Amino Acids

2.1 Introduction

2.1.1 Fluorine in medicinal chemistry

Fluorine is one of the most abundant elements (13th most abundant in the Earth's crust) and has many special properties such as small size, high electronegativity, and high carbon-fluorine bond strength.[1] The incorporation of fluorine atom(s) into medicinally important molecules may have a remarkable effect on their physicochemical and conformational properties, and metabolic stability.[1] For example, the high electronegativity of fluorine has a strong effect on pKa of neighboring groups and the value of the pKa of a molecule can significantly affect the binding affinity of a pharmaceutical agent. All these effects mean that fluorinated compounds play an important role in therapeutic applications, and have stimulated the development of methodology for the intensive synthesis of fluorine-containing β-amino acids.[1] Examples include antineoplastic agent 5-fluorouracil **107**[2] and (*S*)-fluorothalidomide **108**[3] (Figure 8).



5-fluorouracil **107** (*S*)-fluorothalidomide **108**

Figure 8. The structure of 5-fluorouracil **107** and (*S*)-fluorothalidomide **108**.

2.1.2 The importance of β-amino acids and their syntheses

β-Amino acids, in free form or as constituents of more complex structures, are products of primary or secondary metabolism of animals, plants and micro-organisms.[4,5,6] They are an important class of compounds in medicinal chemistry due to their biological and pharmacological actions, such as antitumor, antibiotic and antidepressant.[4,5,6] For example, Lavendomycin **109**, which incorporates an α,β-diamino butyric acid fragment, an important antibiotic agent isolated from *Streptomyces lavendulae* (Figure 9).[7] Taxol

110, which incorporates an α-hydroxy-β-phenylalanine fragment, has potent anti-leukaemia and anti-tumour properties, and is used in the treatment of breast and ovarian cancer (Figure 9).[8]

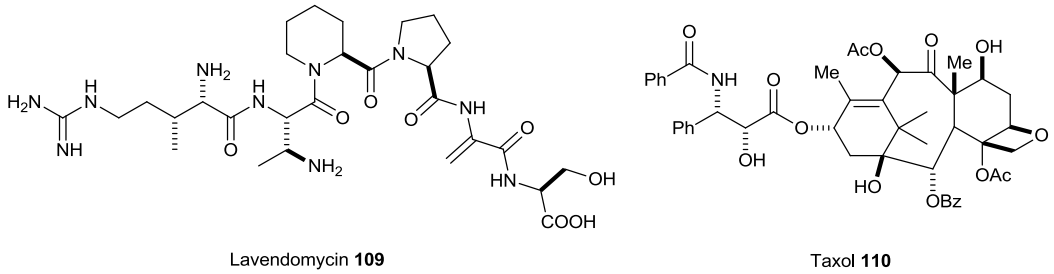


Figure 9. The structure of Lavendomycin **109** and Taxol **110**.

In the laboratory, four main asymmetric routes to β-amino acids have been developed and reported in the last few decades: asymmetric reduction of enamines **111**, conjugate addition of nitrogen nucleophiles (e.g. amines, azide or lithium amides) to α,β-unsaturated esters **112**, addition of an enolate to an imine **113** and functionalisation of an appropriate member of the chiral pool **114** (Figure 10).[9]

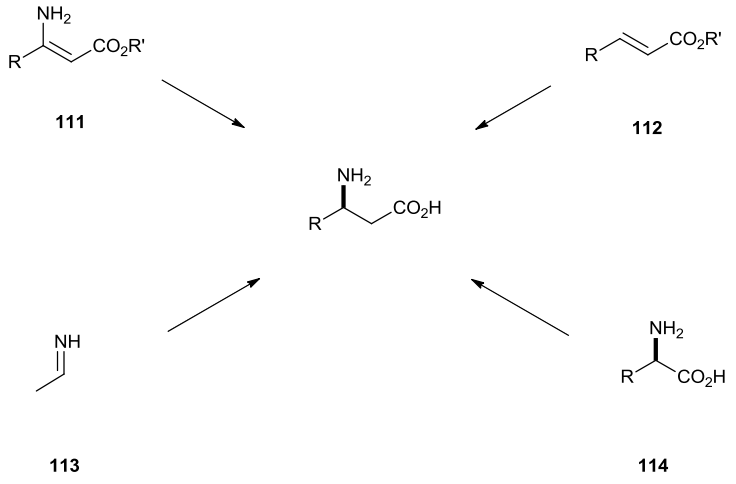
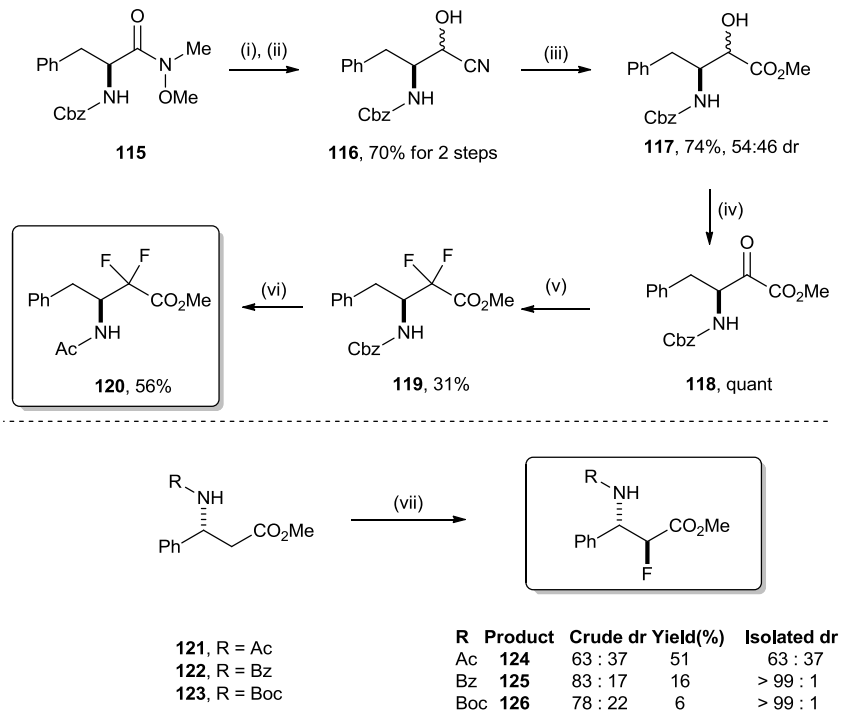


Figure 10. The main asymmetric routes to β-amino acids.

2.1.3 Previous syntheses of fluorinated β-amino acids

Compared to fluorinated α-amino acids, there are only a few previous reports concerning the syntheses of fluorinated β-amino acids. It has been reported that α-fluorinated-β-amino acid derivatives **120** and **124**–**126** are inhibitors of the α-

chymotrypsin enzyme.[10,11] Two syntheses of these compounds have been reported, both relied on homologation of the corresponding α-amino acids with subsequent fluorination. Ohba *et al.* reported **115** was firstly reduced with $LiAlH_4$ and treated with KCN to generate **116** in 70% yield.[10] Subsequent transformation to methyl ester **117** and oxidation gave **118** in 74% yield over 2 steps. Treatment with DAST (as a fluorine source) gave **119** in 31% yield. The final product **120** was synthesized in 56% yield via manipulation of the protecting group. In 2010, the syntheses of **124**–**126** were reported by Abell and co-workers. Treatment of **121**–**123** with LDA and NFSI (as a fluorine source) generated mixtures of *anti*- and *syn*-α-fluoro-β-amino esters **124**–**126**. Purification gave *anti*-**125** and *anti*-**126** in 16 and 6% yield, respectively, as single diastereoisomers (Scheme 13).[11]



Scheme 13. *Reagents and conditions*: (i) $LiAlH_4$, THF, 0 °C; (ii) KCN, THF/H_2O, rt; (iii) HCl, 1,4-dioxane, MeOH, 5 °C then H_2O; (iv) Dess-Martin periodinane, TFA, CH_2Cl_2, rt; (v) DAST, DME, rt; (vi) NH_4CO_2H, 10% Pd/C, DMF, rt then Ac_2O, pyridine, rt; (vii) LDA, THF, –78 °C, 1 h then NFSI, THF, –78 °C, 2.5 h.

2.2 Chapter aims

By far one of the most elegant approaches to the asymmetric synthesis of β-amino acids is the conjugate addition of enantiopure lithium amides to α,β-unsaturated esters as

developed by Davies and co-workers.[12,13,14] Using lithium amides such as lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **8** and lithium (*R*)-*N*-benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amide **14** for conjugate addition to α,β-unsaturated esters has several advantages: they undergo conjugate addition to a wide range of α,β-unsaturated esters with high yield and predictable diastereoselectivity, and the *N*-protecting groups are easy to remove by catalytic hydrogenolysis or oxidation.[13] This chapter aims to demonstrate the generality of this conjugate addition methodology for the synthesis of a range of fluorinated β-amino acids. The synthetic strategy involved the preparation of a range of *tert*-butyl β-fluoroaryl-α,β-unsaturated esters **128**[15] from the corresponding aldehydes **127** using a modified Wadsworth-Emmons reaction. The conjugate addition of lithium amides **8** or **14** would then be followed by hydrogenolytic or oxidative *N*-deprotection of the β-amino esters **129** and **130**, respectively. Hydrolysis of the resultant primary β-amino esters **131** with HCl would complete the asymmetric synthesis of a collection of β-fluoroaryl-β-amino acids **132** (Figure 11).

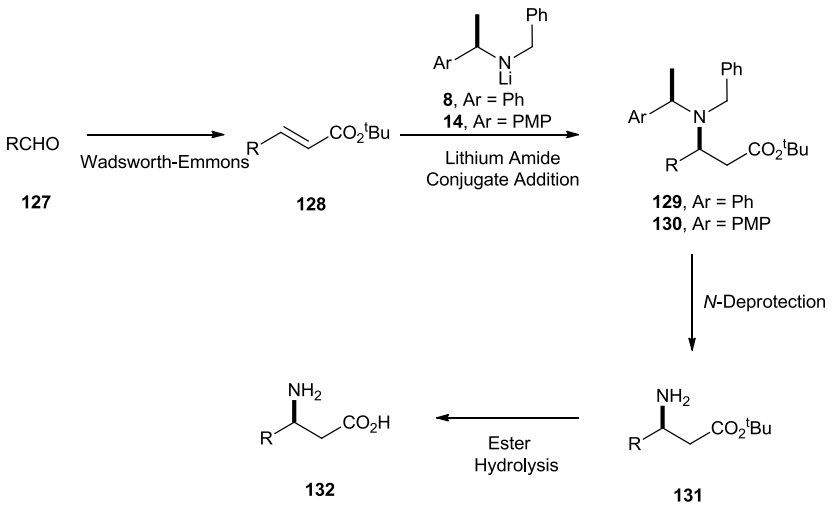


Figure 11. Strategy for the synthesis of an array of enantiopure β-fluoroaryl-β-amino acids.

2.3 Syntheses of α,β-unsaturated esters

2.3.1 The choice of protocol

As part of the investigations concerned with the synthesis of a range of fluorinated β-amino acids, a simple and reliable protocol for the preparation of (*E*)-β-fluoroaryl-α,β-unsaturated esters needed to be chosen. Many methodologies to achieve this goal have

been reported such as Wittig[16,17] and Julia[18] olefinations, and variants. The Wadsworth-Emmons reaction, a modification of the Wittig reaction, has proved useful for the synthesis of (*E*)-alkenes from the reaction of an aldehyde with the anion of a phosphonate ester.[19,20] A range of factors such as the nature of the solvent, base and substrates, and the reaction temperature dictate the diastereoselectivity of the reaction. Of these, the nature of alkali metal bases such as BuLi, NaH or KH used to generate the reactive metalated phosphonate intermediate is found to have a more significant influence on diastereoselectivity.[21] Protocols employing either lithium or magnesium halides and a tertiary amine base were reported to generate alkenes with good diastereoselectivity by Masamune *et al.*[22] and Rathke *et al.*[23] An experimentally simple protocol by Davies and co-workers was reported for highly (*E*)-selective Wadsworth-Emmons reactions using MeMgBr as a base.[15] This protocol was chosen for the preparation of the range of (*E*)-β-fluoroaryl-β-unsaturated esters.

2.3.2 Syntheses of a range of (*E*)-β-fluoroaryl-β-unsaturated esters

The range of fluorinated aryl aldehydes chosen incorporated all possible isomers of fluorobenzaldehyde and difluorobenzaldehyde, as well as one representative trifluorobenzaldehyde, and pentafluorobenzaldehyde. A small range of other substituted monofluorobenzaldehydes was also investigated (Table 1).

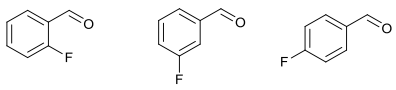
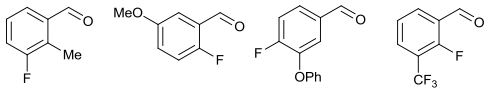
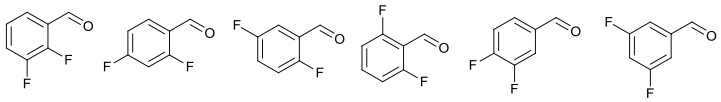
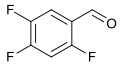
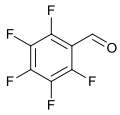
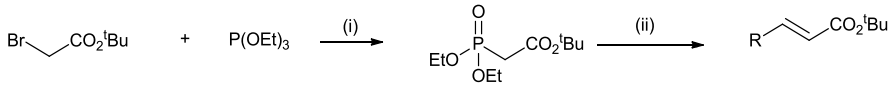
Aldehyde Classification	Structure of selected fluorinated aryl aldehydes
mono-F	
di-substituted mono-F	
di-F	
tri-F	
penta-F	

Table 1. Selected fluorobenzyl aldehydes.

tert-Butyl diethylphosphonoacetate **33** was synthesised in 99% yield *via* the Arbusov reaction of *tert*-butyl bromoacetate **133** and triethylphosphite (Scheme 14). Following the literature procedure,[24] deprotonation of *tert*-butyl diethylphosphonoacetate **33** (1.2 equiv) with MeMgBr at rt followed by addition of the requisite fluorobenzyl aldehydes (1.0 equiv) and heating the resultant mixtures at reflux for 15 h gave complete conversion to the corresponding (*E*)-β-fluoroaryl-β-unsaturated esters **134**–**148** in 79–90% yield and >99:1 dr (Scheme 14). In each case, the configurations of the newly formed carbon-carbon double bonds within **134**–**148** were assigned from the values of the C(2)*H* to C(3)*H* ^3J ^{1}H NMR coupling constants observed for these compounds (^3J ~16 Hz).



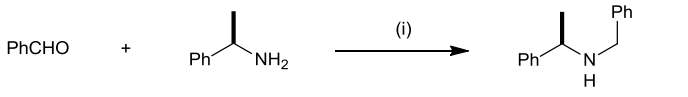
133 **33**, 99% **134-148**

Subtituent Classification	R	Product	dr (*E*):(*Z*)	Yield (%)	$J_{2,3}$ Value (Hz)
mono-F	(C_6H_4)(2-F)	**134**	> 99 : 1	80	16.1
	(C_6H_4)(3-F)	**135**	> 99 : 1	79	15.9
	(C_6H_4)(4-F)	**136**	> 99 : 1	88	15.9
mono-F di-substituted	(C_6H_3)(3-F-2-Me)	**137**	> 99 : 1	79	15.7
	(C_6H_3)(2-F-5-OMe)	**138**	> 99 : 1	80	16.2
	(C_6H_3)(4-F-3-OPh)	**139**	> 99 : 1	82	15.9
	(C_6H_3)(2-F-3-CF_3)	**140**	> 99 : 1	87	16.4
di-F	(C_6H_3)(2,3-F)	**141**	> 99 : 1	88	16.2
	(C_6H_3)(2,4-F)	**142**	> 99 : 1	89	16.2
	(C_6H_3)(2,5-F)	**143**	> 99 : 1	87	16.2
	(C_6H_3)(2,6-F)	**144**	> 99 : 1	88	16.2
	(C_6H_3)(3,4-F)	**145**	> 99 : 1	90	16.0
	(C_6H_3)(3,5-F)	**146**	> 99 : 1	89	16.0
tri-F	(C_6H_2)(2,4,5-F)	**147**	> 99 : 1	88	16.1
penta-F	(C_6)(penta-F)	**148**	> 99 : 1	84	16.4

Scheme 14. *Reagents and conditions:* (i) 50 °C, 2 h; (ii) MeMgBr, THF, rt, 15 min, then RCHO, reflux, 15 h.

2.4 Conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide 8 to β-fluoroaryl-α,β-unsaturated esters: preparation of β-fluoroaryl-β-amino esters

Reductive alkylation of primary amine **149** with benzaldehyde and $NaBH_4$ in EtOH gave secondary amine **150** in 85% yield (Scheme 15). After recrystallization of the hydrochloride salt, ^{1}H NMR spectroscopic analysis in the presence of the chiral solvating agent (*S*)-*O*-acetyl mandelic acid revealed the enantiopurity of the amine (*R*)-**150** to be >98% ee, by comparison with an authentic racemic standard.[25]

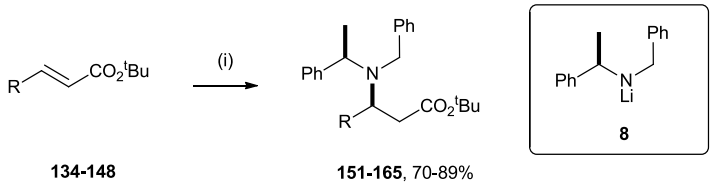


149 **150**, 85%, >98% ee

Scheme 15. *Reagents and conditions:* (i) $NaBH_4$, EtOH, rt, 3 days.

With amine **150** and α,β-unsaturated esters **134**–**148** in hand, lithium amide conjugate addition reactions were performed. Following the previously reported procedure,[12,13] addition of BuLi to a solution of amine **150** in THF at −78 °C generated the lithium amide **8**. The β-fluoroaryl-α,β-unsaturated esters **134**–**148** were added to solutions of lithium amide **8** gave β-amino esters **151**–**165**. The diastereoisomeric purity of each β-amino ester was determined from the ^{1}H NMR spectrum of the crude reaction mixture by integration of the signals arising from the diastereotopic C(2)H_2 protons (around δ_H

~2 ppm). The diastereoselectivities of the reactions were all high (≥89:11 dr). Purification by chromatography on silica generated the 15 pure β-amino esters **151**–**165** in 70–89% yield (Scheme 16).



134-148 **151-165**, 70-89%

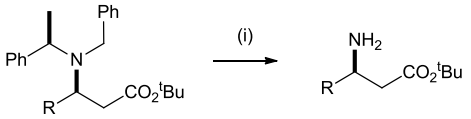
Subtituent Classification	R	Product	dr	Yield (%)
mono-F	(C_6H_4)(2-F)	**151**	98 : 2	89
	(C_6H_4)(3-F)	**152**	98 : 2	83
	(C_6H_4)(4-F)	**153**	98 : 2	88
mono-F di-substituted	(C_6H_3)(3-F-2-Me)	**154**	98 : 2	73
	(C_6H_3)(2-F-5-OMe)	**155**	95 : 5	70
	(C_6H_3)(4-F-3-OPh)	**156**	98 : 2	76
	(C_6H_3)(2-F-3-CF_3)	**157**	89 : 11	80
di-F	(C_6H_3)(2,3-F)	**158**	96 : 4	84
	(C_6H_3)(2,4-F)	**159**	>99 : 1	82
	(C_6H_3)(2,5-F)	**160**	96 : 4	87
	(C_6H_3)(2,6-F)	**161**	97 : 3	86
	(C_6H_3)(3,4-F)	**162**	96 : 4	82
	(C_6H_3)(3,5-F)	**163**	98 : 2	80
tri-F	(C_6H_2)(2,4,5-F)	**164**	97 : 3	88
penta-F	(C_6)(penta-F)	**165**	94 : 6	72

Scheme 16. *Reagents and conditions:* (i) **8**, THF, −78 °C, 2 h.

2.5 Hydrogenolysis of β-fluoroaryl-β-amino esters

The standard procedure previously applied for hydrogenolytic *N*-debenzylation of a range of β-amino esters employs $Pd(OH)_2/C$ under a hydrogen pressure of 1 atmosphere in MeOH/H_2O/AcOH (v/v/v 40:4:1) for 72 h.[13] However, all of the *N*-benzyl-*N*-(α-methylbenzyl)-protected β-fluoroaryl-β-amino esters **151**–**165** did not dissolve in this solvent system, therefore all reactions were performed using MeOH as a solvent instead, in which **151**–**165** proved freely soluble. Unfortunately, competitive *N*-debenzylation and dehalogenation occurred in all cases under these conditions. Varying the reaction time from 1 h to 72 h for substrates **151**–**157** and monitoring by ^{1}H NMR spectroscopy and mass spectrometry gave the optimal reaction time for each substrate at which *N*-debenzylation finished but with no significant loss of the fluorine substituent. Thus the corresponding primary β-monofluoroaryl-β-amino esters **166**–**172** were synthesized in 91–96% yield (Scheme 17). The catalytic hydrogenation of β-multi-

fluoroaryl-β-amino esters **158**–**165** was also investigated although in this case the defluorination remained problematic and the reaction could not be optimal to enable the isolating of the corresponding primary β-multi-fluoroaryl-β-amino esters.



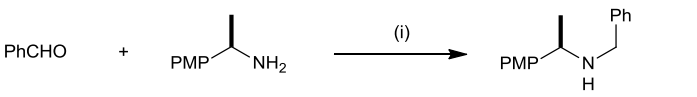
151-157 **166-172** , 91-96%

Subtituent Classification	R	Product	Reaction time /h	Yield (%)
mono-F	(C_6H_4)(2-F)	**166**	36	95
	(C_6H_4)(3-F)	**167**	9	91
	(C_6H_4)(4-F)	**168**	48	93
mono-F di-substituted	(C_6H_3)(3-F-2-Me)	**169**	15	96
	(C_6H_3)(2-F-5-OMe)	**170**	5	94
	(C_6H_3)(4-F-3-OPh)	**171**	4	96
	(C_6H_3)(2-F-3-CF_3)	**172**	15	95

Scheme 17. *Reagents and conditions:* (i) H_2 (1atm), $Pd(OH)_2$/C (50% w/w), MeOH, rt.

2.6 Conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methyl-*p*-methoxybenzyl)-amide 14 to β-fluoroaryl-α,β-unsaturated esters: preparation of β-fluoroaryl-β-amino esters

Due to the competitive defluorination for the multi-fluoro substrates **158**–**165**, another method, involving the conjugate addition of lithium amide **14** followed by oxidative *N*-deprotection of the corresponding β-amino esters, was attempted. Secondary (*R*)-*N*-benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amine **174** was prepared by reductive alkylation of primary amine **173** with benzaldehyde and $NaBH_4$ in EtOH in 87% yield (Scheme 18). After recrystallization of the hydrochloride salt, ^{1}H NMR spectroscopic analysis in the presence of the chiral solvating agent (*S*)-*O*-acetyl mandelic acid revealed the enantiopurity of the amine **174** to be >98% ee, by comparison with an authentic racemic standard.[25]

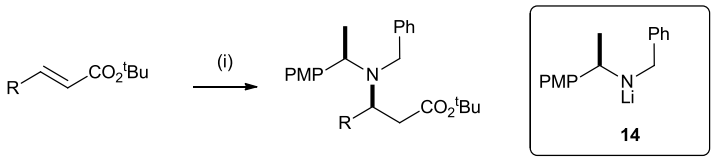


173 **174**, 87%, >98% ee

Scheme 18. *Reagents and conditions:* (i) $NaBH_4$, EtOH, rt, 3 days.

Following the same procedure as the synthesis of β-fluoroaryl-β-amino esters **158**–**165**,

addition of BuLi to a solution of amine **174** in THF at −78 °C generated the lithium amide **14**. The β-multifluoroaryl-α,β-unsaturated esters **141**–**148** were added to solutions of the lithium amide **14** gave β-amino esters **175**–**182**. The diastereoisomeric purity of each β-amino ester was again determined from the ^{1}H NMR spectrum of the crude reaction mixture by integration of the signals arising from the diastereotopic C(2)H_2 protons (around δ_H ~2 ppm). The diastereoselectivities of the reactions were all ≥97:3 dr. Purification by chromatography on silica generated the 8 pure β-amino esters **175**–**182** in 80–86% yield (Scheme 19).



141-148 **175-182**, 80-86%

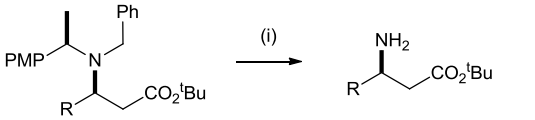
Subtituent Classification	R	Product	dr	Yield (%)
di-F	(C_6H_3)(2,3-F)	**175**	97 : 3	82
	(C_6H_3)(2,4-F)	**176**	97 : 3	86
	(C_6H_3)(2,5-F)	**177**	>99 : 1	85
	(C_6H_3)(2,6-F)	**178**	97 : 3	84
	(C_6H_3)(3,4-F)	**179**	>99 : 1	86
	(C_6H_3)(3,5-F)	**180**	98 : 2	83
tri-F	(C_6H_2)(2,4,5-F)	**181**	99 : 1	80
penta-F	(C_6)(penta-F)	**182**	98 : 2	80

Scheme 19. *Reagents and conditions:* (i) **14**, THF, −78 °C, 2 h.

2.7 CAN Promoted oxidative *N*-debenzylation

Davies and co-workers have found that treatment of haloaryl-β-amino esters with CAN (2.1 equiv) removed the unbranched *N*-benzyl protecting group first, allowing orthogonal deprotection of the nitrogen centre. The range of examples reported included one containing two fluorine substituents on the same ring.[26] Further treatment with CAN (4.0 equiv) successfully removed the remaining *N*-4-methoxy-α-methylbenzyl protecting group to give the corresponding β-amino ester **131**.[26] This oxidative *N*-deprotection strategy with CAN allowed *N*-debenzylation of both *N*-protecting groups by treatment of β-multifluoroaryl-β-amino esters **175**–**182** with excess CAN (6.0 equiv) in one pot, giving the corresponding primary β-amino esters **183**–**190** in 73–79% yield

(Scheme 20). However, the purities of primary β-amino esters **183**–**190** were not good. They were all contaminated with some unknown brown species (~10%).



175-182 **183-190** , 73-79%[a]

Subtituent Classification	R	Product	Yield (%)
di-F	(C_6H_3)(2,3-F)	**183**	78 [a]
	(C_6H_3)(2,4-F)	**184**	73 [a]
	(C_6H_3)(2,5-F)	**185**	79 [a]
	(C_6H_3)(2,6-F)	**186**	75 [a]
	(C_6H_3)(3,4-F)	**187**	73 [a]
	(C_6H_3)(3,5-F)	**188**	73 [a]
tri-F	(C_6H_2)(2,4,5-F)	**189**	79 [a]
penta-F	(C_6)(penta-F)	**190**	76 [a]

Scheme 20. *Reagents and conditions:* (i) CAN (6.0 equiv), MeCN/ H_2O (v/v 5:1), rt, 16 h. [[a] contaminated with some unknown brown impurities].

2.8 Hydrogenolysis of β-fluoroaryl-β-amino esters

Liu and co-workers reported *N*-debenzylation of a similar substrate without defluorination by using 6% w/w $Pd(OH)_2/C$ under 5 atm hydrogen environment.[27] Using these conditions, hydrogenolysis of β-fluoroaryl-β-amino esters **151**–**153** and **158**–**165** gave the corresponding primary β-amino esters **166**–**168** and **183**–**190** which were isolated in 90–95% yield. The only exception was pentafluorophenyl substituted **165**. The catalyst loading for this substrate needed to be increased to 26% w/w to generate the corresponding primary β-pentafluoroaryl-β-amino ester **190** in 94% yield, otherwise the reaction gave back starting material only (Scheme 21).



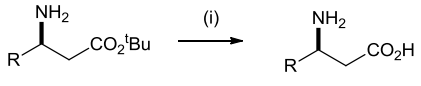
151-153, **158-165** **166-168** , **183-190**, 90-95%

Subtituent Classification	R	Product	Yield (%)
mono-F	(C_6H_4)(2-F)	**166**	92
	(C_6H_4)(3-F)	**167**	93
	(C_6H_4)(4-F)	**168**	95
di-F	(C_6H_3)(2,3-F)	**183**	94
	(C_6H_3)(2,4-F)	**184**	93
	(C_6H_3)(2,5-F)	**185**	95
	(C_6H_3)(2,6-F)	**186**	93
	(C_6H_3)(3,4-F)	**187**	91
	(C_6H_3)(3,5-F)	**188**	90
tri-F	(C_6H_2)(2,4,5-F)	**189**	93
penta-F	(C_6)(penta-F)	**190**	94[a]

Scheme 21. *Reagents and conditions*: (i) $Pd(OH)_2/C$ (6 % w/w), H_2 (5 atm), MeOH, rt, 24 h. [[a] $Pd(OH)_2/C$ (26 % w/w)].

2.9 Syntheses of β-fluoroaryl-β-amino acids

Hydrolysis of primary β-amino esters with trifluoroacetic acid, their conversion to HCl salts and subsequent ion-exchange chromatography was used to yield the free amino acids. However, the complete removal of trifluoroacetic acid from the final product using this procedure was unsuccessful. Hydrolysis employing HCl instead of trifluoroacetic acid solved this problem. Treatment of β-fluoroaryl-β-amino esters **166**–**172** and **183**–**190** with 2.0 M aq HCl at reflux and subsequent ion-exchange chromatography on Dowex 50WX8-100 resin gave the corresponding β-fluoroaryl-β-amino acids **191**–**205** in 90–97% yield (Scheme 22). The ^1H and ^{13}C NMR spectroscopic data, melting points and specific rotations of the known β-fluoroaryl-β-amino acids **191**–**193**, **197**, **202** and **205** showed excellent agreement with those reported previously in the literature (Table 2).



166-172, **183-190** **191-205**, 90-97%

Subtituent Classification	R	Product	Yield (%)
mono-F	(C_6H_4)(2-F)	**191**	96
	(C_6H_4)(3-F)	**192**	97
	(C_6H_4)(4-F)	**193**	96
mono-F di-substituted	(C_6H_3)(3-F-2-Me)	**194**	95
	(C_6H_3)(2-F-5-OMe)	**195**	94

	(C_6H_3)(4-F-3-OPh)	**196**	97
	(C_6H_3)(2-F-3-CF_3)	**197**	95
di-F	(C_6H_3)(2,3-F)	**198**	96
	(C_6H_3)(2,4-F)	**199**	92
	(C_6H_3)(2,5-F)	**200**	93
	(C_6H_3)(2,6-F)	**201**	95
	(C_6H_3)(3,4-F)	**202**	90
	(C_6H_3)(3,5-F)	**203**	90
tri-F	(C_6H_2)(2,4,5-F)	**204**	93
penta-F	(C_6)(penta-F)	**205**	97

Scheme 22. *Reagents and conditions:* (i) HCl (2.0 M aq), reflux, 6 h, and then Dowex 50WX8-100.

R	Product	mp (°C)	specific rotation	ref	lit. mp (°C)	lit. specific rotation
(C_6H_4)(2-F)	**191**	239–240	$[\alpha]^{25}$ –2.7 (*c* 0.3 in H_2O)	28	247[a]	$[\alpha]^{22}$ +3.0 (*c* 0.3 in H_2O) lit. data for the antipode
(C_6H_4)(3-F)	**192**	220–223	$[\alpha]^{25}$ –2.0 (*c* 0.4 in H_2O)	29	226–229	$[\alpha]^{25}$ –1.8 (*c* 0.4 in H_2O)
(C_6H_4)(4-F)	**193**	220–221	$[\alpha]^{25}$ –5.6 (*c* 0.5 in H_2O)	28	220–222	$[\alpha]^{22}$ –4.0 (*c* 0.5 in H_2O)
(C_6H_3)(3-F-2-Me)	**194**	228–230	$[\alpha]^{25}$ –2.7 (*c* 0.3 in H_2O)			
(C_6H_3)(2-F-5-OMe)	**195**	189–191	$[\alpha]^{25}$ –2.7 (*c* 0.3 in H_2O)			
(C_6H_3)(4-F-3-OPh)	**196**	>370	$[\alpha]^{25}$ –2.7 (*c* 0.3 in H_2O)			
(C_6H_3)(2-F-3-CF_3)	**197**	207–208	$[\alpha]^{25}$ –2.7 (*c* 0.3 in H_2O)	30	206	
(C_6H_3)(2,3-F)	**198**	200–202	$[\alpha]^{25}$ –2.5 (*c* 0.5 in H_2O)			
(C_6H_3)(2,4-F)	**199**	207–209	$[\alpha]^{25}$ –4.9 (*c* 0.5 in H_2O)			
(C_6H_3)(2,5-F)	**200**	207–209	$[\alpha]^{25}$ –3.2 (*c* 0.5 in H_2O)			
(C_6H_3)(2,6-F)	**201**	198–200	$[\alpha]^{25}$ –4.8 (*c* 0.5 in H_2O)			
(C_6H_3)(3,4-F)	**202**	225–227	$[\alpha]^{25}$ –3.9 (*c* 1.0 in H_2O)	31	226–230	$[\alpha]^{23}$ –3.2 (*c* 1.0 in H_2O)
(C_6H_3)(3,5-F)	**203**	206–208	$[\alpha]^{25}$ –4.5 (*c* 0.5 in H_2O)			
(C_6H_2)(2,4,5-F)	**204**	219–221	$[\alpha]^{25}$ –7.2 (*c* 0.5 in H_2O)			
(C_6)(penta-F)	**205**	188–190	$[\alpha]^{25}$ +27.3 (*c* 2.5 in H_2O)	32		$[\alpha]^{22}$ +24 (*c* 2.5 in D_2O)

Table 2. Measured and literature melting point & specific rotation of β-fluoroaryl-β-amino acids **191**–**205** [[a] lit. data for the antipode].

2.10 Conclusions

In conclusion, the conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to a range of β-fluoroaryl-α,β-unsaturated esters gave the corresponding β-fluoroaryl-β-amino esters in high diastereoselectivities and with good isolated yields. Subsequent efficient *N*-deprotection was facilitated by hydrogenolysis without the formation of the products arising from defluorination being observed. Finally, hydrolysis of the resultant

primary β-fluoroaryl-β-amino esters gave a range of β-fluoroaryl-β-amino acids in excellent yield. The power and generality of this conjugate addition methodology derived by Davies *at al.* to produce fluorinated β-amino acids was demonstrated well.

With this methodology in hand, one application of this methodology remained to be developed, that of the synthesis of sitagliptin (the active ingredient in approved preparations for the treatment of type 2 diabetes) and this will be discussed in chapter 3.

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Chapter 3: Asymmetric Synthesis of (–)-(*R*)-Sitagliptin

3.1 Introduction

Many pharmaceutically important molecules such as analogues of the most widely used cancer chemotherapy drugs Taxol (paclitaxel) **206** and Taxotere (docetaxel) **207** incorporate fluorinated β-amino acid motifs.[1] Merck developed (–)-(*R*)-sitagliptin (JANUVIA™), (2*R*)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,-4,5-trifluoro-phenyl)butan-2-amine (**208**),[2] as an inhibitor of dipeptidyl peptidase IV (DPP-4) enzymes which led to its approval as an effective treatment for type 2 diabetes (Figure 12).[3,4] In contrast to Type 1 diabetes that is characterized by an absolute insulin deficiency caused by devastation of islet cells existing in the pancreas, type 2 diabetes, as a metabolic disorder, is characterized by relative insulin deficiency or insulin resistance, in which both endogenous insulin levels and blood glucose are high. Type 2 diabetes has become one of the most common public health problems in the past 25 years, affecting approximately 285 million people worldwide in 2010 (compared to around 30 million in 1985), and makes up about 90% of cases of diabetes. Type 2 diabetes, characterized by long-term high blood glucose, can cause serious vascular complications, decreased eyesight, heart disease, strokes, and death. Current effective type 2 diabetes therapies mainly aim to increase the concentration of circulating insulin, however, undesirable side effects such as increased weight and hypoglycaemia occur at the same time. Based on this situation, a more safe and effective therapy was required. DPP-4 inhibitors, stimulating insulin secretion indirectly, were a solution. The process is as follows: ingestion of food releases glucagon-like peptide 1 (GLP-1); GLP-1 functions as a stimulator of insulin biosynthesis and secretion; DPP-4 makes GLP-1 degrade rapidly by cleaving a dipeptide from the *N*-terminus; DPP-4 inhibitors increase the half-life of GLP-1. Because GLP-1 stimulates insulin in a strictly glucose-dependent manner, this therapy has no risk of hypoglycemia.

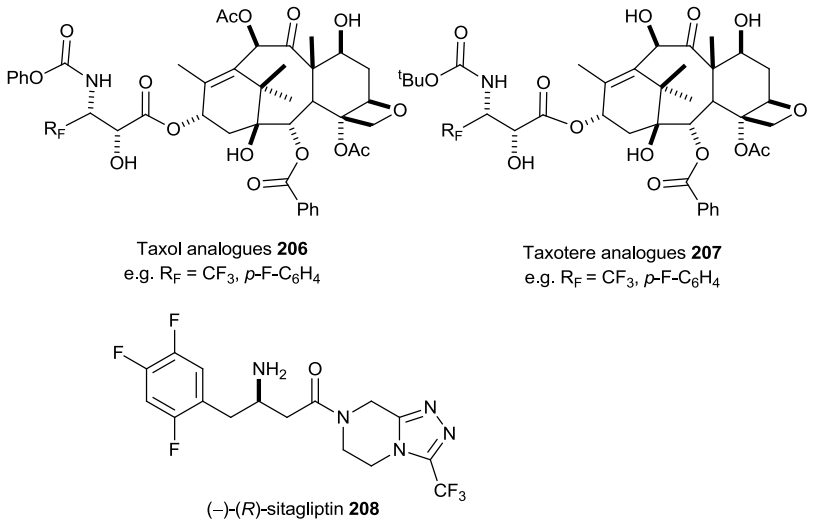
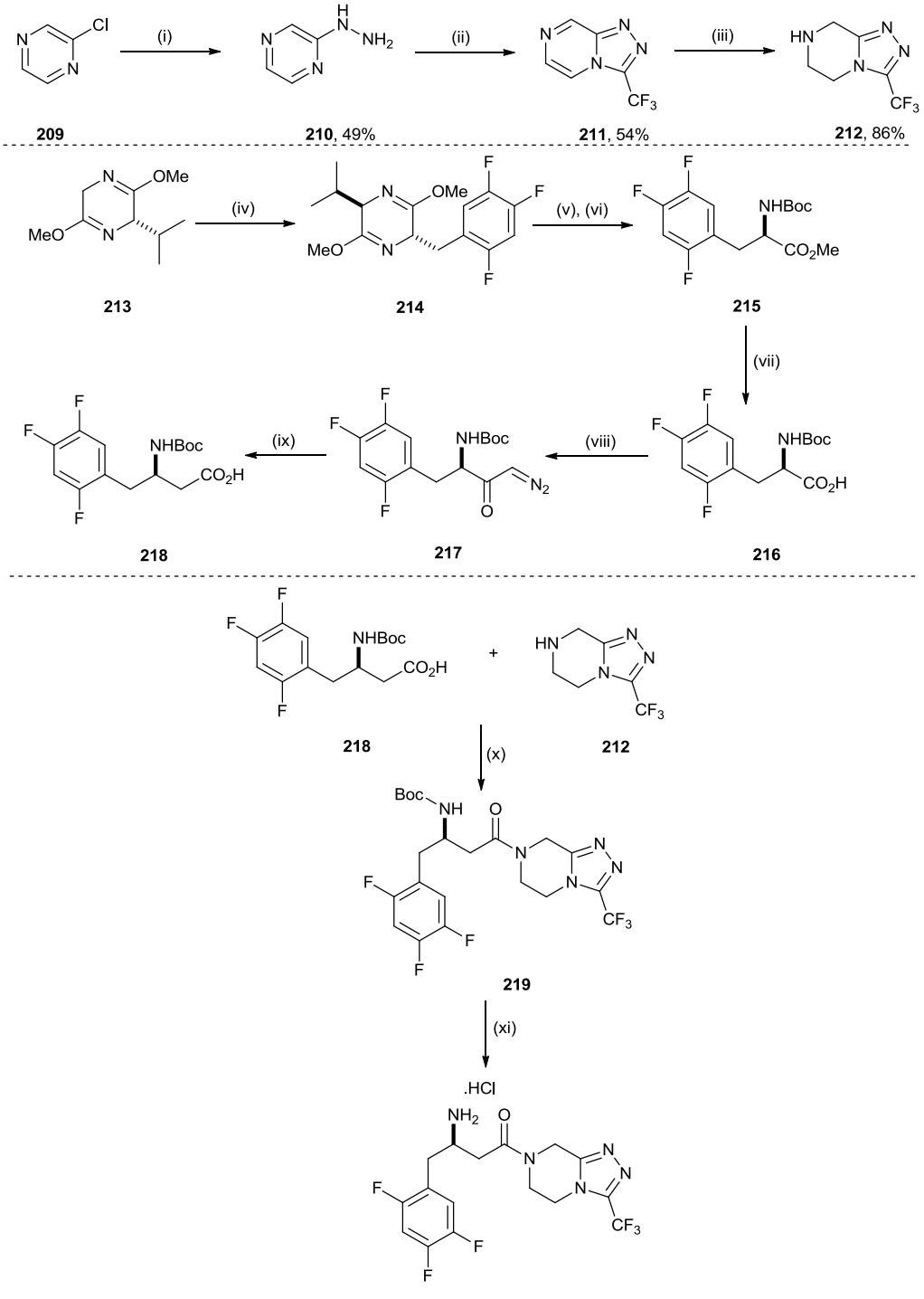


Figure 12. Fluorinated analogues of Taxol **206** and Taxotere **207**, and the structure of (–)-(*R*)-sitagliptin **208**.

3.2 Previous syntheses

3.2.1 Merck's original laboratory scale route

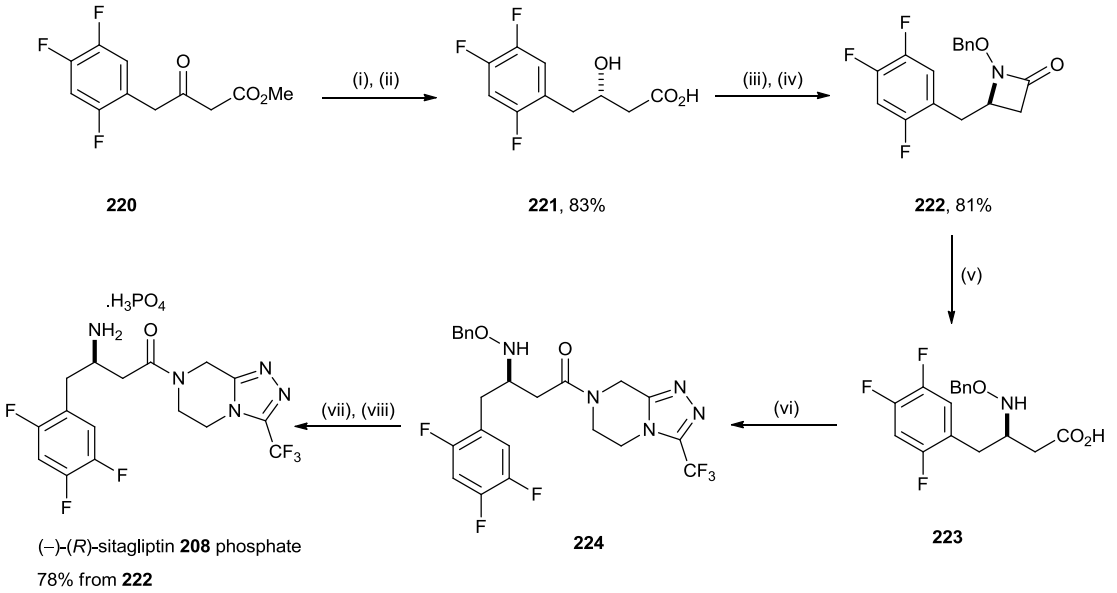
In 2005, Merck's scientists first reported the synthesis of sitagliptin **208** by peptide coupling of β-amino acid **218** with triazole **212** followed by removal of the Boc-protecting group in 28% overall yield for the 8 step procedure. Triazole **212** was prepared from chloropyrazine **209**: treatment of **209** with hydrazine hydrate gave **210** which was reacted with trifluoroacetic anhydride followed by heating with polyphosphoric acid to give triazolopyrazine **211**. Hydrogenation of **211** then afforded triazole **212**. Enantiopure β-amino acid **218** was prepared from the commercial available Schollkopf reagent (*S*)-**213**. Alkylation of **213** with 2,4,5-trifluorobenzyl bromide gave **214**. Acidic hydrolysis of **214** gave α-amino acid, and this α-amino acid was then transformed to **216** by *N*-Boc protection and ester hydrolysis. Treatment of **216** with isopropyl chloroformate and diazomethane gave diazo ketone **217** which was transformed to β-amino acid **218** by sonicating with silver benzoate. Subsequent coupling of β-amino acid **218** and triazole **212** followed by *N*-Boc deprotection gave sitagliptin **208** (Scheme 23).[3]



Scheme 23. *Reagents and conditions*: (i) $NH_2NH_2 \cdot H_2O$, EtOH, reflux, 5 h; (ii) $(CF_3CO)_2O$, 0 °C to rt, 2 h, and then PPA, 140 °C, 18 h; (iii) H_2 (1atm), Pd/C (20% w/w), EtOH, rt, 18 h; (vi) BuLi, THF, –78 °C, 20 min, and then 2,4,5-trifluorobenzyl bromide, THF; (v) HCl, CH_3CN, rt, 16 h, and then MeOH; (vi) $(Boc)_2O$, Et_3N, CH_2Cl_2; (vii) LiOH, THF/H_2O (1:1), rt, 16 h; (viii) Et_2O, Et_3N, isobutyl chloroformate, –30 °C, diazomethane; (ix) silver benzoate, 1,4-dioxane/H_2O (5:1), sonication, rt; (x) HOBt, EDC, DIPEA, DMF, rt, 18 h; (xi) satd HCl/MeOH.

3.2.2 Merck's first generation large scale route

In the first generation large scale synthesis of **208**, installation of the correct configuration for (–)-(*R*)-sitagliptin **208** was achieved by sequential asymmetric hydrogenation of β-ketoester **220** (employing a chiral ruthenium catalyst), an EDC coupling and Mitsunobu reaction. Hydrolysis of lactam **222** gave protected amino acid **223**. Direct coupling to triazole **212**, prepared as before,[3] after removal of *N*-benzyloxy group and salt formation gave (–)-(*R*)-sitagliptin **208** in 52% overall yield over 8 steps (Scheme 24).[5]

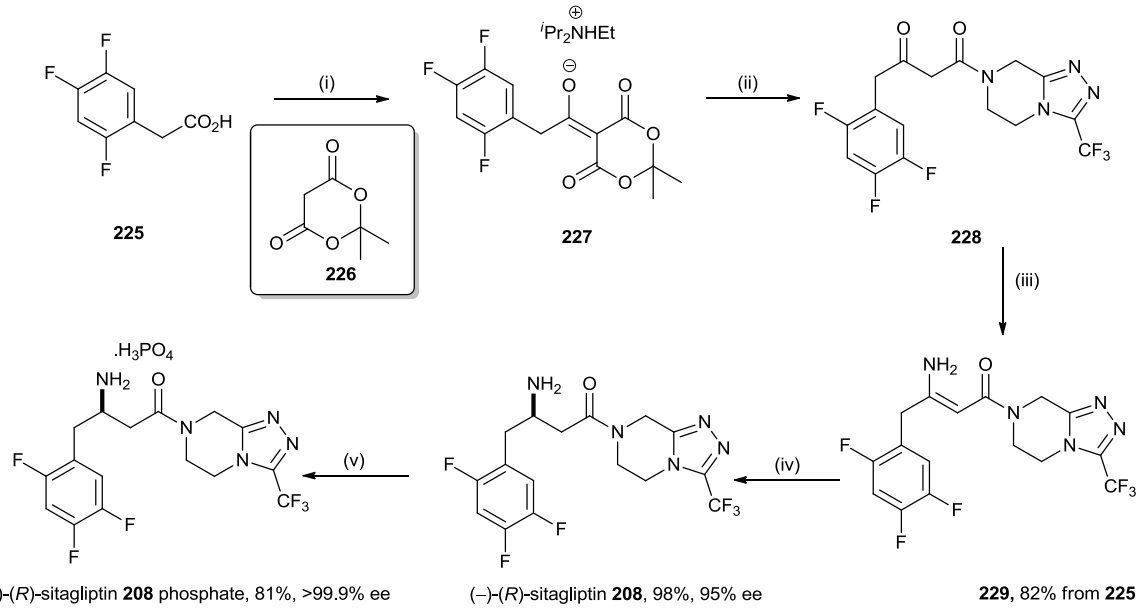


Scheme 24. *Reagents and conditions*: (i) (*S*)-BINAPRuCl$_2$, HBr, MeOH, 80 °C, 10 h; (ii) NaOH, MeOH/H$_2$O; (iii) BnONH$_2$·HCl, EDC, LiOH, THF/H$_2$O (1:1); (iv) DIAD, PPh$_3$, THF; (v) LiOH·H$_2$O, THF, H$_2$O; (vi) EDC, NMM, ACN, 0 °C; (vii) H$_2$ (40 psi), Pd/C, MeOH, 50 °C, 18 h; (viii) H$_3$PO$_4$, EtOH.

3.2.3 Merck's second generation route

Although the first generation synthesis was a suitable method to prepare the sitagliptin in large scale and good overall yield, poor atom efficiency and large amounts of waste at the EDC coupling/Mitsunobu reaction sequence remained the challenge. In 2009, Merck's scientists reported a second generation process. Treatment of 2,4,5-trifluorophenyl acetic acid **225** with pivaloyl chloride gave a mixed anhydride. Addition of Meldrum's acid **226**, ^{i}Pr$_2$NEt, and DMAP in MeCN afforded Meldrum's adduct **227**. Treatment of **227** with triazole **212** and trifluoroacetic acid gave β-keto amide **228**.

Without work-up, addition of NH_4OAc and MeOH to the crude reaction mixture furnished dehydrositagliptin **229**, which incorpotated the entire backbone of sitagliptin. The process described above was carried out in one pot in 82% overall yield, with minimal waste output. Successful installation of the correct configuration for (–)-(*R*)-sitagliptin **208** was achieved by a rhodium-catalysed asymmetric hydrogenation of enamine **229** under high pressure. The overall process gave (–)-(*R*)-sitagliptin **208** in 65% overall isolated yield (Scheme 25).[6]



Scheme 25. *Reagents and conditions*: (i) **226**, DMAP, $^{i}Pr_2NEt$, $^{t}BuCOCl$, MeCN, 50 °C, 3 h; (ii) **212** hydrochloride, CF_3CO_2H, 50 °C, 6 h; (iii) NH_4OAc, MeCN/MeOH, 45 °C to 0 °C; (iv) $[(COD)RhCl]_2$, NH_4Cl, ^{t}Bu-josiphos, H_2 (250 psi), MeOH, 50 °C, 18 h; (v) H_3PO_4, $H_2O/^{i}PrOH$.

3.2.4 Merck's third generation route

In order to reduce the significant cost of the high-pressure hydrogenation equipment and removal of the transition metal catalyst after reaction in second generation process, employing a recyclable biocatalyst became the key feature of the third generation process. Asymmetric reductive amination of β-keto amide **228** to **208** was achieved by transaminase biocatalyst to give enantiopure (–)-(*R*)-sitagliptin **208** in 92% yield (Figure 13).[7]

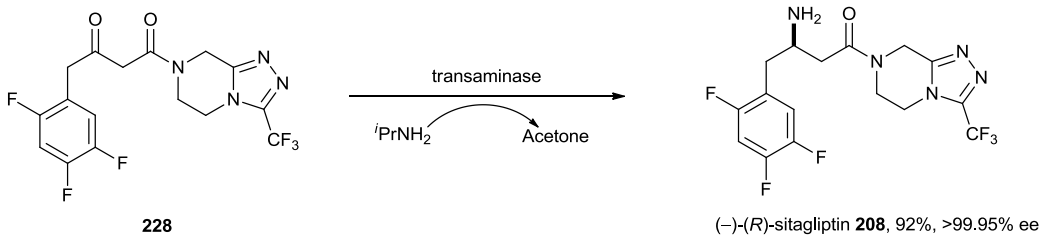


Figure 13. Third generation synthesis of (–)-(*R*)-sitagliptin **208**.

3.3 Chapter aims

The methodology described in Chapter 2, that is the conjugate addition of enantiopure secondary lithium amide to an α,β-unsaturated ester, has been widely applied in natural product syntheses. (–)-(*R*)-Sitagliptin **208** was selected as an ideal example to demonstrate the utility of this methodology. This chapter describes the synthesis of (–)-(*R*)-sitagliptin **208** employing this lithium amide conjugate addition methodology as the stereodefining step (Figure 14).

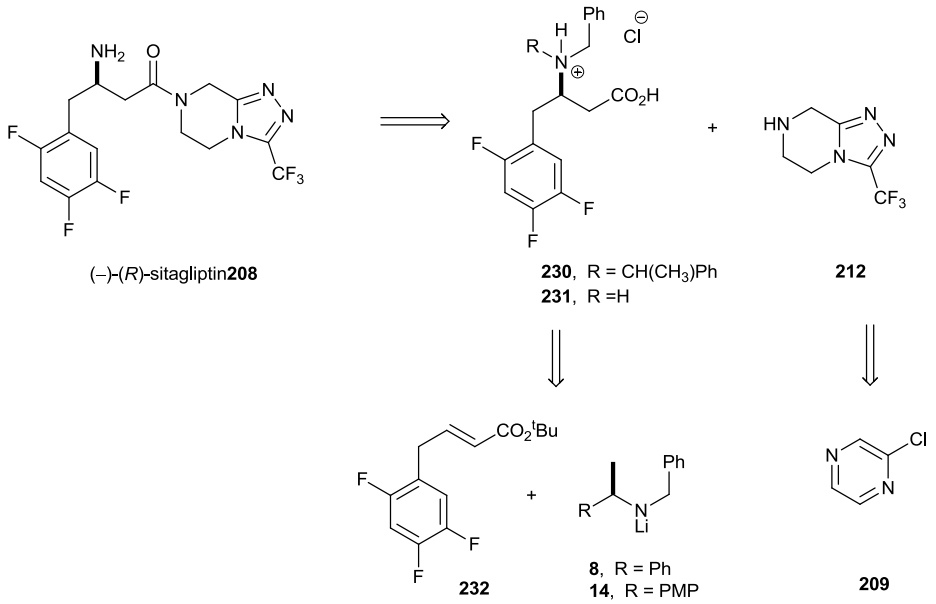
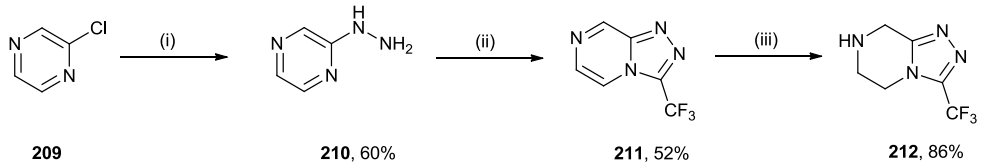


Figure 14. Retrosynthesis of (–)-(*R*)-sitagliptin **208**.

3.4 Conjugate addition of enantiopure lithium amides route

Initial synthetic efforts focused on the preparation of triazole **212** following the literature protocol.[3] Treatment of chloropyrazine **209** with hydrazine hydrate gave **210** which was then reacted with trifluoroacetic anhydride followed by heating with

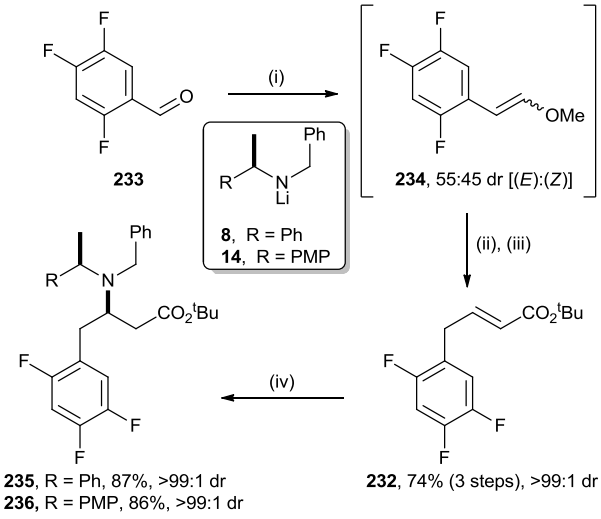
polyphosphoric acid to give triazolopyrazine **211**. Hydrogenation of **211** afforded triazole **212** in 27% overall yield (Scheme 26).



209 **210**, 60% **211**, 52% **212**, 86%

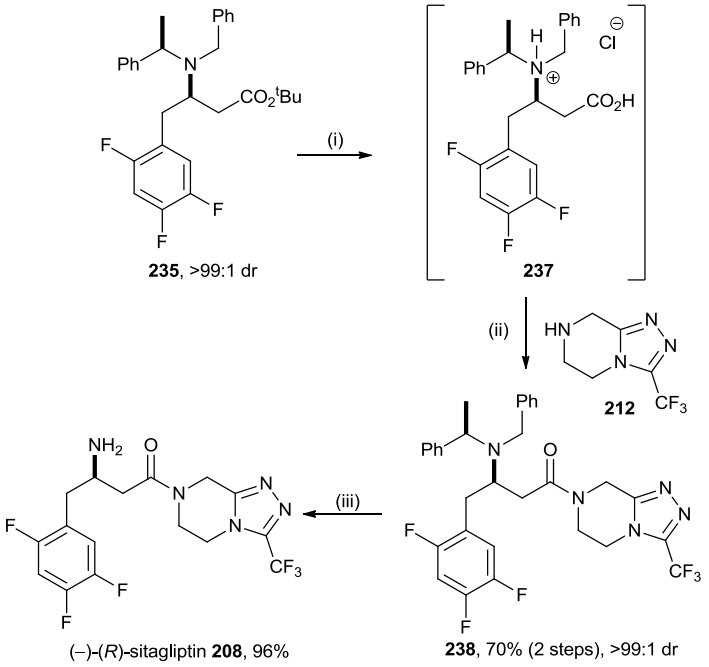
Scheme 26. *Reagents and conditions*: (i) $NH_2NH_2{\cdot}H_2O$, EtOH, reflux, 5 h; (ii) $(CF_3CO)_2O$, 0 °C to rt, 2 h, and then PPA, 140 °C, 18 h; (iii) H_2 (1atm), Pd/C (20% w/w), EtOH, rt, 18 h.

Commercially available 2,4,5-trifluorobenzaldehyde **233** was reacted with ^{t}BuOK activated $[MeOCH_2PPh_3]^+[Cl]^-$ *via* a Wittig reaction to give a 55:45 [(*E*):(*Z*)] mixture of enol ether **234**. Treatment of **234** with 4.0 M HCl in 1,4-dioxane for 6 h and subsequent treatment of the resultant aldehyde with *tert*-butyl diethylphosphonoacetate **33** *via* a modified Wadsworth-Emmons reaction (promoted by MeMgBr)[8] gave α,β-unsaturated ester **232** in 74% isolated yield (from **233**) and >99:1 dr. Two *N*-protecting group strategies were investigated: conjugate additions of (*R*)-**8** or (*R*)-**14** to α,β-unsaturated ester **232**, for investigation of their compatibility with the 2',4',5'-trifluorophenyl group. Treatment of **232** with either (*R*)-**8** or (*R*)-**14** gave the corresponding β-amino esters **235** and **236** in 87 and 86% isolated yield, respectively, and >99:1 dr in each case (Scheme 27).



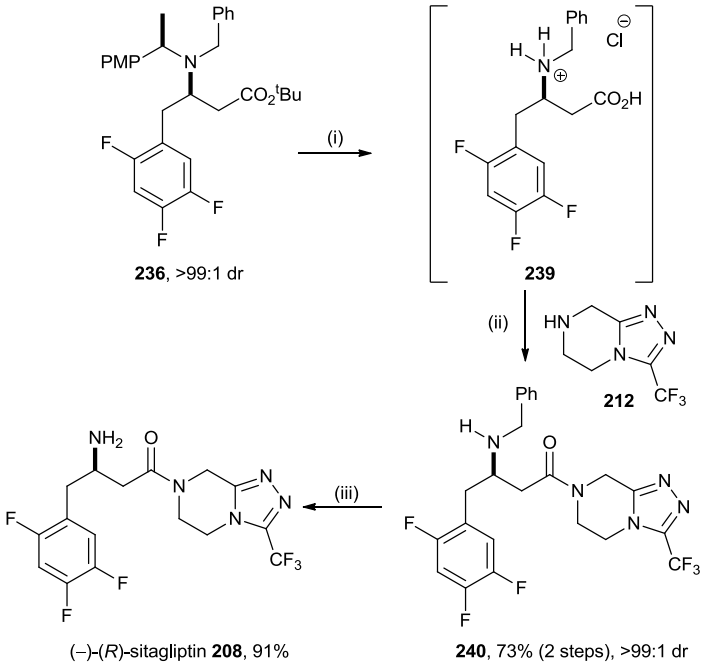
Scheme 27. *Reagents and conditions*: (i) $[MeOCH_2PPh_3]^+[Cl]^-$, ^tBuOK, THF, rt, 48 h; (ii) 4.0 M HCl in 1,4-dioxane, rt, 6 h; (iii) MeMgBr, *tert*-butyl diethylphosphonoacetate, THF, reflux, 15 h; (iv) (*R*)-**8** or (*R*)-**14**, THF, –78 °C, 2 h. [PMP = *p*-Methoxyphenyl].

The corresponding carboxylic acid hydrochloride salt **237** was generated by reacting *N*-benzyl-*N*-α-methylbenzyl protected β-amino ester **235** with 2.0 M aq HCl at reflux. Subsequent preparation of **238** was achieved by HOBt/EDC mediated amide coupling of **237** with triazole **212**. The combined yield over 2 steps was 70%. Finally, *N*-deprotection by hydrogenolysis using $Pd(OH)_2/C$ gave (–)-(*R*)-sitagliptin **208** in 96% yield (Scheme 28). There was no defluorination observed under these conditions, and the spectroscopic data obtained for this sample of (–)-(*R*)-sitagliptin **208** were in excellent agreement with literature data {$[\alpha]_D^{25}$ −23.3 (*c* 1.0 in $CHCl_3$); lit.[9] $[\alpha]_D^{26}$ −22.8 (*c* 1.0 in $CHCl_3$)}.



Scheme 28. *Reagents and conditions*: (i) HCl (2.0 M, aq), reflux, 6 h; (ii) HOBt, EDC·HCl, DIPEA, $CHCl_3$, rt, 16 h; (iii) H_2 (5 atm), $Pd(OH)_2/C$ (30% w/w), MeOH, rt, 24 h.

Similarly, treatment of *N*-benzyl-*N*-α-methyl-*p*-methoxybenzyl protected β-amino ester **236** with 2.0 M aq HCl gave the corresponding carboxylic acid hydrochloride salt **239**. Interestingly, the acid-labile α-methyl-*p*-methoxybenzyl group was also cleaved during this reaction. Subsequent preparation of **240** was achieved by HOBt/EDC mediated amide coupling of **239** with triazole **212**. The combined yield over 2 steps was 73%. Finally, *N*-deprotection by hydrogenolysis under higher pressure hydrogen using $Pd(OH)_2/C$ gave (–)-(*R*)-sitagliptin **208** in 91% yield (Scheme 29). The spectroscopic data obtained for this (–)-(*R*)-sitagliptin **208** were also in excellent agreement with literature data {$[\alpha]_D^{25}$ −22.0 (*c* 1.0 in $CHCl_3$); lit.[9] $[\alpha]_D^{26}$ −22.8 (*c* 1.0 in $CHCl_3$)}. This sample of (–)-(*R*)-sitagliptin **208** was then converted into its phosphate salt **208**·H_3PO_4 and recrystallised from ^{i}PrOH. The spectroscopic data for this sample were also in excellent agreement with literature data {$[\alpha]_D^{25}$ −75.8 (*c* 1.0 in H_2O); lit.[9] $[\alpha]_D^{20}$ −72.9 (*c* 1.0 in H_2O); lit.[10] $[\alpha]_D$ −74.4 (*c* 1.0 in H_2O)}.



Scheme 29. *Reagents and conditions*: (i) HCl (2.0 M, aq), reflux, 6 h; (ii) HOBt, EDC·HCl, DIPEA, $CHCl_3$, rt, 16 h; (iii) H_2 (5 atm), $Pd(OH)_2/C$ (20% w/w), MeOH, rt, 24 h. [PMP = *p*-Methoxyphenyl].

3.5 Conclusions

In conclusion, two successful, efficient and concise asymmetric syntheses of (–)-(*R*)-sitagliptin **208**, in 7 steps, demonstrated the utility of Davies' conjugate addition methodology. One employed *N*-α-methylbenzyl protection and gave (–)-(*R*)-sitagliptin **208** in 43% overall yield while the other one employed *N*-α-methyl-*p*-methoxybenzyl protection and gave (–)-(*R*)-sitagliptin **208** in 42% overall yield.

3.6 References and notes for chapter 3

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Chapter 4: Asymmetric Syntheses of Amino Sugars

4.1 Introduction

Amino sugars occur widely in Nature. Compounds incorporating an amino sugar scaffold include mucoproteins, nucleotides, teichoic acids, glycolipids, bacterial capsular polysaccharides, structural polysaccharides and a number of antibiotics.[1,2] They are important components of the mucopolysaccharides of connective skeletal tissues of invertebrates, mammals, and plants.[3] They are also found as body movement lubricants and in chemical signalling process.[4] Examples include the chemotherapy agents daunorubicin **241**[5] and doxorubicin **242**,[6] which were first isolated and developed in the 1960's.[7] Their structure comprises a typical amino sugar fragment, L-daunosamine **243** (Figure 15).

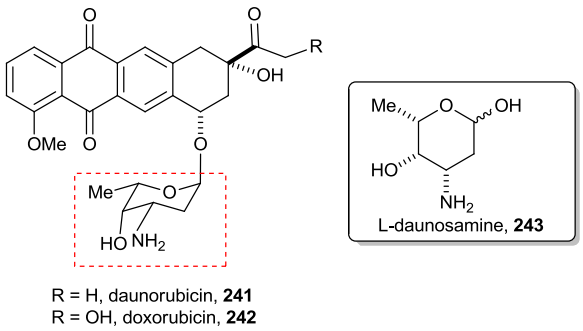


Figure 15. Structures of daunorubicin **241** and doxorubicin **242**.

Because amino sugars play an important role in therapeutic applications due to their biological and pharmacological actions, they are becoming popular synthetic targets which have stimulated the development of synthetic methodology. A variety of methodologies have been reported in the past 20 years such as manipulation of carbohydrate[8] and non-carbohydrate[9] chiral pool starting materials, and asymmetric syntheses[10]. In 2010, Davies *et al.* reported a concise and highly selective asymmetric synthesis of L-acosamine from sorbic acid in 7 steps and 15% overall yield. The key steps involve conjugate addition of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **8** to methyl sorbate **244**, chemo- and diastereoselective olefinic oxidation of the resultant β-

amino ester **245** under direction of the ammonium group, regioselective epoxide opening to furnish diol **247**, subsequent lactonisation giving **248**, reduction and *N*-deprotection to generate L-acosamine (Figure16).[11]

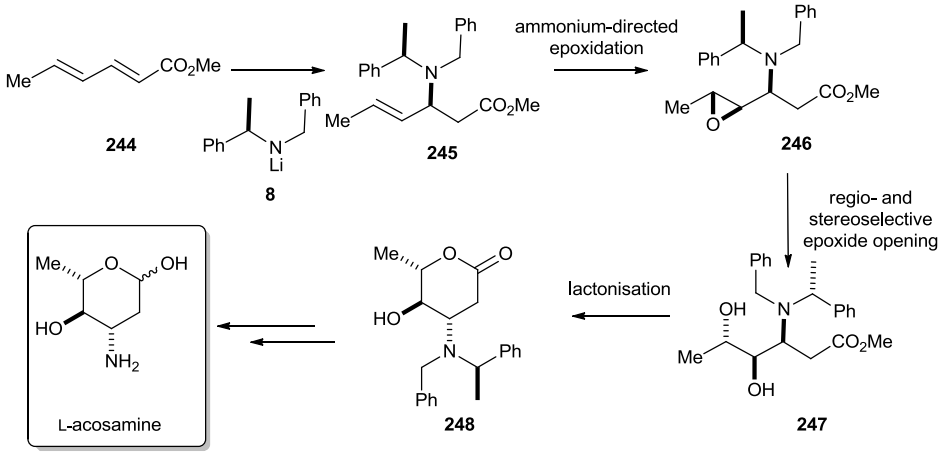


Figure 16. Key steps in the synthesis of L-acosamine **243**.

4.2 Chapter aims

This chapter describes the synthesis of 5- or 6-membered ring amino sugars *via* cyclization of "alkene-masked" aldehyde β-amino esters or "acetal-masked" aldehyde β-amino esters. The key steps involve conjugate addition of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **8** to **244** or acetal containing α,β-unsaturated ester **249** [with C(2) functionalisation being achieved by diastereoselective enolate oxidation with (−)-CSO **83**], reduction of the resultant β-amino esters **245**/**246** or **250**/**251** using $LiAlH_4$, unmasking the aldehyde **254**/**255** *via* alkene ozonolysis of **247**/**248** or *via* acid catalyzed acetal deprotection of **252**/**253**, subsequent cyclization giving **256**/**257**, and *N*-deprotection to generate amino sugar **258**/**259** (Figure 17).

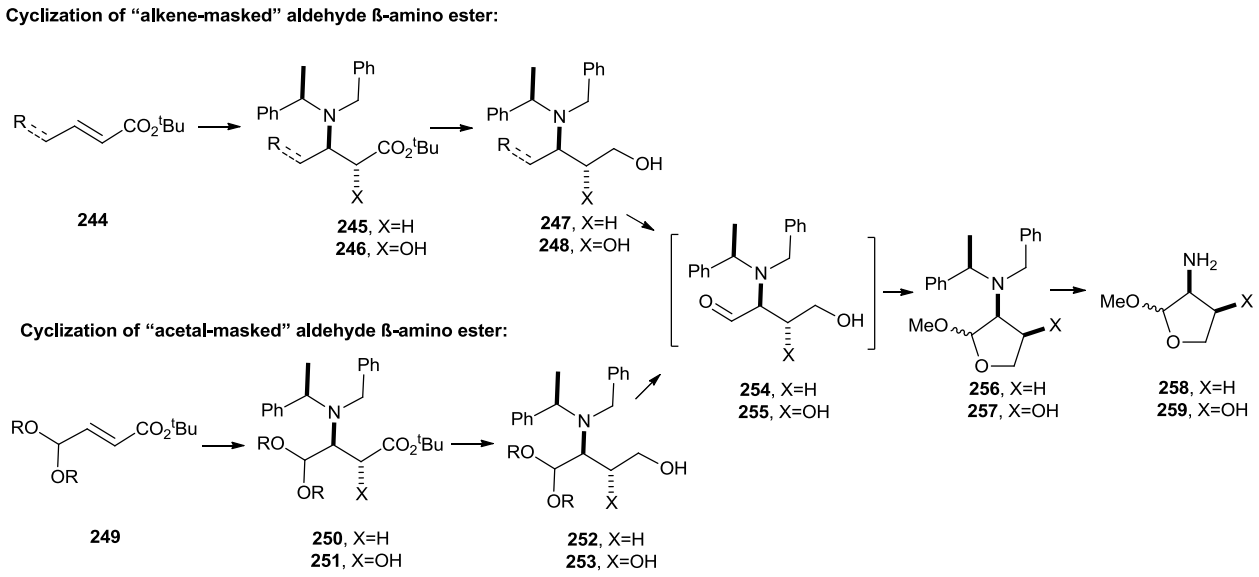


Figure 17. Key steps in the synthesis of 5- or 6-membered ring amino sugars *via* "alkene-masked" aldehyde β-amino ester or "acetal-masked" aldehyde β-amino ester.

4.3 Asymmetric syntheses of 5-membered ring amino sugars

4.3.1 Bis-addition attempt

For the synthesis of 5-membered ring amino sugars, the first proposed synthetic route started from the conjugate addition of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **8** to bis-*tert* butyl ester **261**, reduction of the resultant bis-β-amino ester **262** using $LiAlH_4$, ozonolysis of **263** and subsequent cyclization of **264** and *N*-deprotection to generate amino sugar **258** (Figure 18).

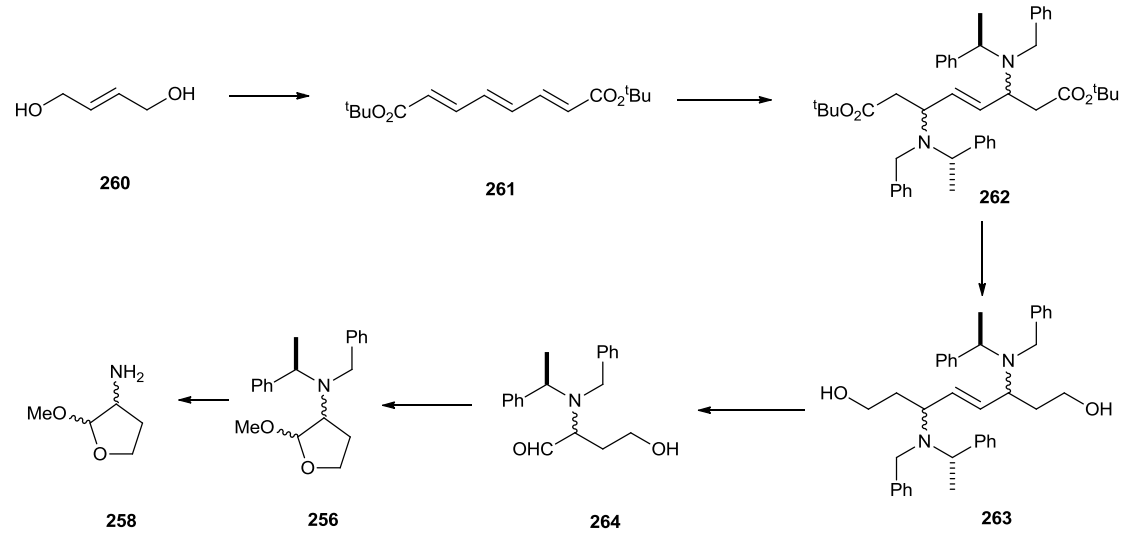
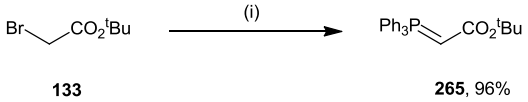


Figure 18. Proposed synthesis of 5-membered ring amino sugar **258**.

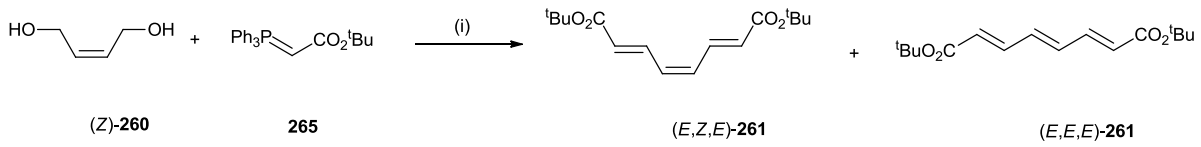
4.3.1.1 Attempted of synthesis of bis-β-amino ester 262

Initial work focused on the synthesis of (*E*,*E*,*E*)-**261**. Ylide **265** was prepared in 96% yield *via* the reaction of *tert*-butyl bromoacetate **133** and triphenylphosphine followed by deprotonation with NaOH (Scheme 30).



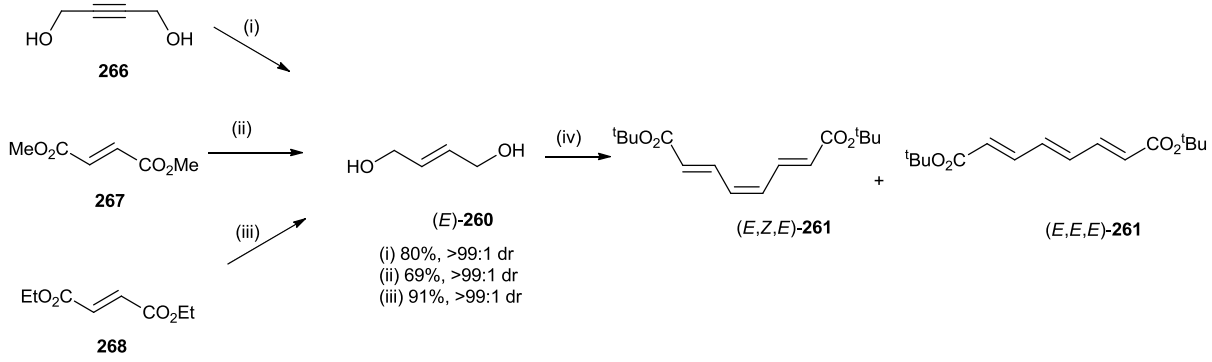
Scheme 30. *Reagents and conditions:* (i) rt, 12 h; (ii) NaOH (2.0 M, aq), 0 °C, 5 min.

In order to evaluate the feasibility of the approach, commercially available (*Z*)-diol **260** (1.0 equiv) was treated with **265** (2.4 equiv) and activated MnO_2 (20 equiv) in CH_2Cl_2 to give a 55:45 mixture of (*E*,Z,*E*)-**261** and (*E*,*E*,*E*)-**261**, respectively, after purification by chromatography on silica (Scheme 31).



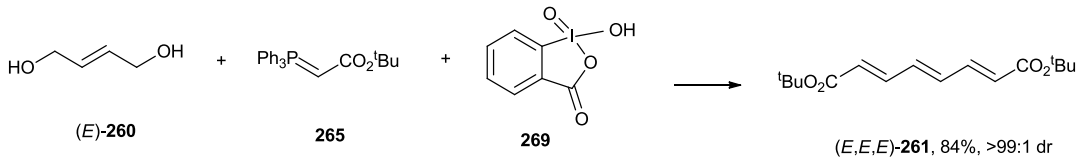
Scheme 31. *Reagents and conditions:* (i) activated MnO_2, rt, 48 h.

Studies next focused on synthesis of (*E*)-diol **260**. Reduction of **266**, **267** or **268** generated (*E*)-diol **260** in 80%, 69% and 91% yield, respectively.[12] However, treatment of (*E*)-diol **260** (1.0 equiv) with **265** (2.4 equiv) and activated MnO_2 (20 equiv) gave a 48:52 mixture of (*E*,Z,*E*)-**261** and (*E*,*E*,*E*)-**261**, respectively, after purification (Scheme 32).



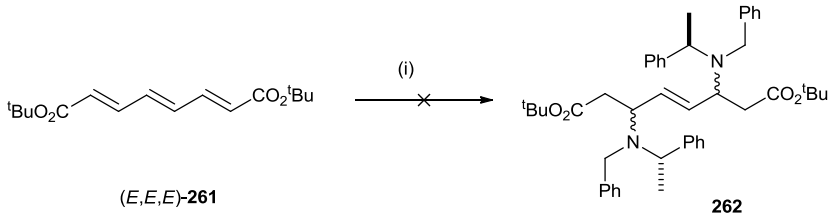
Scheme 32. *Reagents and conditions:* (i) $LiAlH_4$, THF rt, 16 h; (ii) DIBAL-H, toluene, −78°C to rt , 6 h; (iii) DIBAL-H, toluene, −78°C to rt, 6 h; (iv) **265**, activated MnO_2, CH_2Cl_2, rt, 48 h.

Treatment of (*E*)-diol **260** (1.0 equiv) with **265** (2.0 equiv) and iodoxybenzoic acid **269** (2.0 equiv) in DMSO gave bis-ester (*E*,*E*,*E*)-**261** in 84% yield and >99:1 dr (Scheme 33).[13]



Scheme 33. *Reagents and conditions:* (i) rt, 16 h.

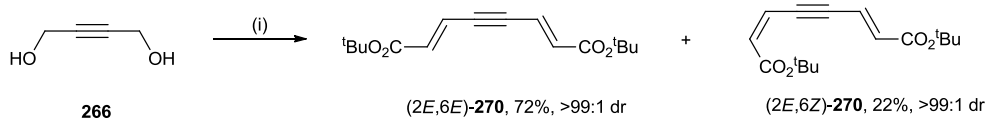
Conjugate addition of (*R*)-**8** (3.0 equiv) to (*E*,*E*,*E*)-**261** (1.0 equiv) according to the procedure outlined by Davies *et al*.[14] was performed. There was no starting material, mono-addition product or bi-addition product observed by analysis of the mass spectrum and ^{1}H NMR spectrum of the crude reaction mixture. A similar reaction using (*R*)-**8** (10 equiv) was investigated as well. This gave an analogous result (Scheme 34).



Scheme 34. *Reagents and conditions:* (i) (*R*)-**8**, THF, −78°C, 2 h.

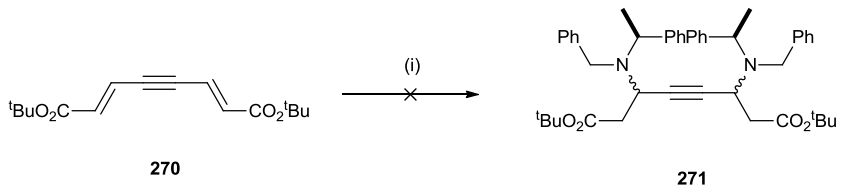
4.3.1.2 Attempted of synthesis of bis-β-amino ester 271

A synthetic route to bis-β-amino ester **271** was also investigated. Treatment of commercially available alkyne diol **266** (1.0 equiv) with **265** (2.4 equiv) and activated MnO_2 (20 equiv) in CH_2Cl_2 gave a 76:24 mixture of (2*E*,6*E*)-**270** and (2*E*,6Z)-**270**, respectively, which were separated by chromatography on silica and isolated in 72% and 22% yield (Scheme 35).



Scheme 35. *Reagents and conditions:* (i) activated MnO_2, **265**, CH_2Cl_2, rt, 48 h.

With ester **270** in hand, lithium amide conjugate addition of (*R*)-**8** (3.0 equiv) to (2*E*,6*E*)-**270** (1.0 equiv) was performed. However, there was no staring material, mono-addition product or bis-addition product observed by analysis of the mass spectrum and ^{1}H NMR spectrum of the crude reaction mixture. The similar reaction by using (*R*)-**8** (10 equiv) gave the same result (Scheme 36).

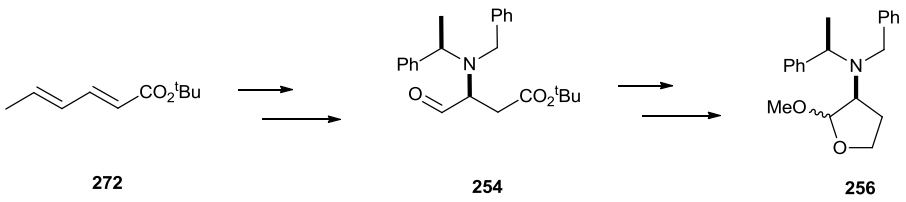


270 **271**

Scheme 36. *Reagents and conditions:* (i) (*R*)-**8**, THF, −78°C, 2 h.

4.3.2 Synthesis of 5-membered ring amino cyclization product 256 from sorbic acid *via* ozonolysis

Due to the unsuccessful syntheses of bi-β-amino esters **262** and **271**, an alternative route from *tert*-butyl sorbate **272** was considered (Figure 19).

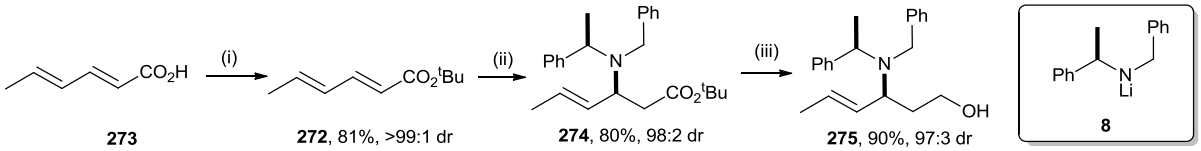


272 **254** **256**

Figure 19. Synthesis of **256** from prepared *tert*-butyl sorbate .

4.3.2.1 Synthesis of β-amino alcohol 275

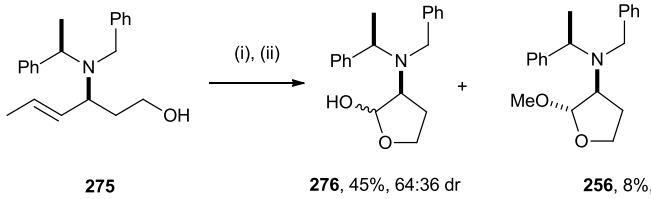
tert-Butyl sorbate **272** was prepared from sorbic acid **273** under the reported reaction conditions in 81% yield. Treatment of **272** with lithium amide **8** according to the procedure outlined by Davies and co-workers[14] gave β-amino ester **274** in 80% yield and 98:2 dr. The diastereoisomeric purity of β-amino ester **274** was determined from analysis of the ^{1}H NMR spectrum of the crude reaction mixture, by integration of the signals arising from the diastereotopic C(2)H_2 protons (around δ_H ~2 ppm) associated with both diastereoisomers. Reduction of β-amino ester **274** with $LiAlH_4$ gave the corresponding β-amino alcohol **275** in 90% yield and 97:3 dr (Scheme 37).



Scheme 37. *Reagents and conditions:* (i) $H_2C{=}C(CH_3)_2$, H_2SO_4, CH_2Cl_2, 0 °C to rt, 48 h; (ii) **8**, THF, −78°C, 2 h; (iii) $LiAlH_4$, THF, 0 °C to rt, 16 h.

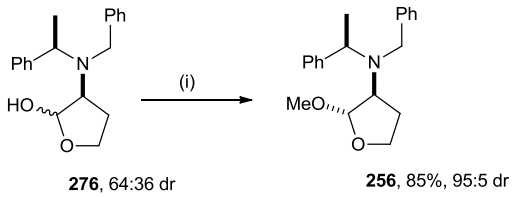
4.3.2.2 Cyclization of "alkene-masked" aldehyde β-amino ester 275

With β-amino alcohol **275** in hand, ozonolysis was performed. HCl (2.0 M in Et_2O) was added to **275**, and the resultant solution was concentrated in *vacuo* to yield the HCl salt of **275** (to prevent oxidation of the N atom upon ozonolysis), which was dissolved in 1:1 CH_2Cl_2/MeOH. Ozonolysis followed by use of Me_2S as a reducing agent gave a 84:16 mixture of **276** and **256**, respectively. Purification by chromatography on silica gave a mixture of **276** in a ratio of 64:36, respectively, in 45% combined yield. Purification also gave **256** in 8% yield and 95:5 dr. The relative configuration of the stereocentres around the THF ring within **256** was established by ^{1}H NMR NOE analysis (Scheme 38).



Scheme 38. *Reagents and conditions:* (i) HCl, Et_2O; (ii) O_3, CH_2Cl_2/MeOH (1:1), −78 °C then Me_2S, −78 °C to rt, 16 h.

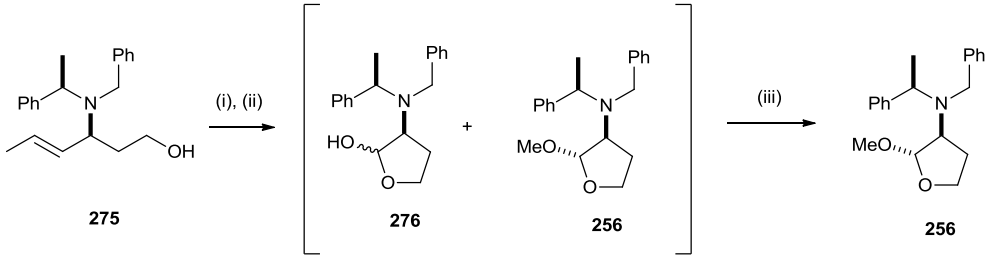
Conversion of **276** (64:36 dr) to **256** (95:5 dr) was achieved by heating the mixture in MeOH in the presence of HCl (Scheme 39).



Scheme 39. *Reagents and conditions:* (i) HCl, MeOH, 50 °C, 16 h.

In order to improve the yield of **256**, a combination of these two reactions was tried. HCl (2.0 M in Et_2O) was added to **275**, and the resultant solution was concentrated *in vacuo* to yield the HCl salt of **275**, which was dissolved in MeOH. Ozonolysis of **275**

followed by adding Me_2S, and heating the resultant mixture with HCl at 50 °C for another 16 h gave **256** in 80% yield and 92:8 dr. The same reaction performed in 1:1 CH_2Cl_2:MeOH gave **256** in 50% yield and 91:9 dr (Scheme 40).



Solvent	dr of **256**	Yield of **256** (%)
CH_2Cl_2/MeOH (1:1)	91:9	50
MeOH	92:8	80

Scheme 40. *Reagents and conditions:* (i) HCl, Et_2O; (ii) O_3, CH_2Cl_2/MeOH (1:1) or MeOH, −78 °C then Me_2S, −78 °C to rt, 16 h; (iii) HCl, MeOH, 50 °C, 16 h.

To understand effect of the reducing agent on the yield of **256**, two reactions with different reducing agents (i.e. Me_2S and $PPh_{3)}$ were performed. The reaction with Me_2S gave 93% yield, whereas reaction with PPh_3 gave 81% yield (Table 3).

Reducing Agent	dr of **256**	Yield of **256** (%)
Me_2S	89:11	93
PPh_3	88:12	81

Table 3. Effect of reducing agent on yield of **256**.

4.3.3 Synthesis of 5-membered ring amino cyclization product 256 from acetal substrate

A different synthetic route to **256** from an acetal containing substrate was tried as well (Figure 20).

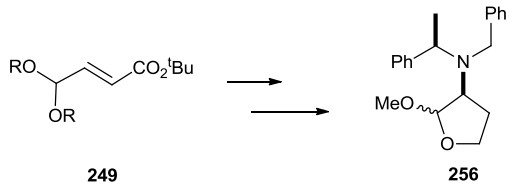
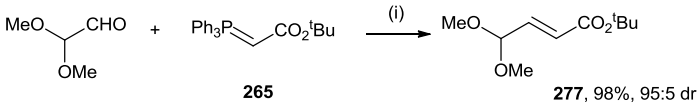


Figure 20. Synthesis of **256** from acetal substrate .

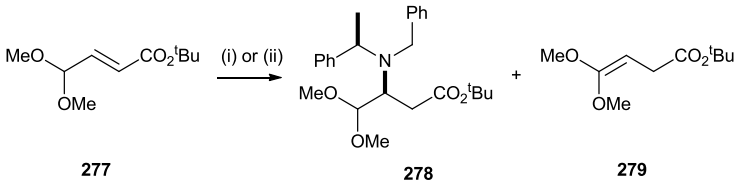
4.3.3.1 Attempt of synthesis of 256 from 2,2-dimethoxyacetaldehyde

Reaction of K_2CO_3 (1.8 equiv), ylide **265** (1.0 equiv) and commercially available 2,2-dimethoxyacetaldehyde (60% wt in H_2O, 2.5 equiv) in cyclohexane with heating gave the corresponding acetal ester **277** in 98% yield and 95:5 dr (Scheme 41).[15]



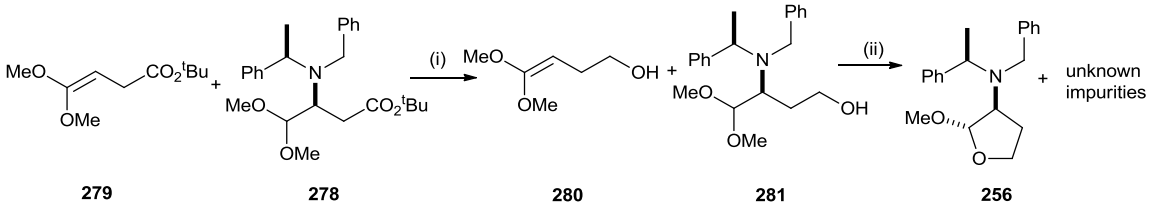
Scheme 41. *Reagents and conditions:* (i) K_2CO_3, cyclohexane, 60°C, 3 h.

Treatment of **277** with lithium amide **8**, according to the standard procedure outlined by Davies and co-workers,[14] in THF at −78 °C after 2 h gave an 87:13 inseparable mixture of conjugate addition product **278** (>99:1 dr) and γ-deprotonation side product **279**, respectively. An attempt at the same reaction in Et_2O at −20 °C[16] after 5 h still gave an inseparable 85:15 mixture of **278** (>99:1 dr):**279** (Scheme 42).



Scheme 42. *Reagents and conditions:* (i) **8**, THF, −78 °C, 2 h; (ii) **8**, Et_2O, −20 °C, 5 h.

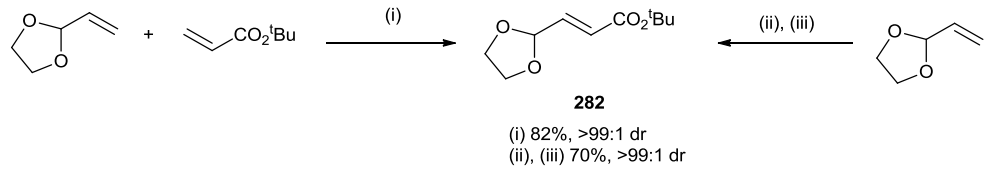
Reduction of an 87:13 mixture of **278** and **279** by $LiAlH_4$ gave an 87:13 mixture of the corresponding alcohols **281** and **280**, respectively. Heating a mixture of **280** and **281** in MeOH in the presence of HCl gave **256** and an unknown impurity (Scheme 43).



Scheme 43. *Reagents and conditions:* (i) $LiAlH_4$, THF, 0 °C to rt, 16 h; (ii) HCl, MeOH, 50 °C, 16 h.

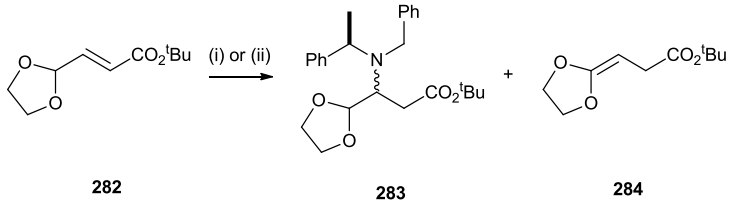
4.3.3.2 Attempt of synthesis of 256 from 2-vinyl-1,3-dioxolane acrylate

Due to the γ-deprotonation problem during the conjugate addition step of the dimethyl acetal substrate, another acetal starting material, 2-vinyl-1,3-dioxolane acrylate, was tried. Reaction of 2-vinyl-1,3-dioxolane acrylate with and *tert*-butyl acrylate following two different reaction mechanisms, either a cross metathesis or ozonolysis-Wittig reaction, gave the cyclic acetal ester **282**, in 82% and 70% yield, respectively (Scheme 44).



Scheme 44. *Reagents and conditions:* (i) Hoveyda-Grubbs II, CH_2Cl_2, reflux, 22 h; (ii) O_3, CH_2Cl_2, −78 °C then Me_2S, −78 °C to rt, 16 h; (iii) **265**, rt, 16 h.

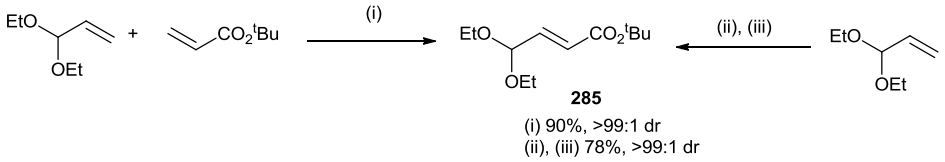
Treatment of **282** with lithium amide **8** under two different conditions, in THF at −78°C for 2 h or in Et_2O at −20 °C for 5 h, both gave an inseparable mixture of conjugate addition product **283** (54:46 dr) and γ-deprotonation side product **284** in the same 82:18 ratio (Scheme 45).



Scheme 45. *Reagents and conditions:* (i) **8**, THF, −78 °C, 2 h; (ii) **8**, Et_2O, −20 °C, 5 h.

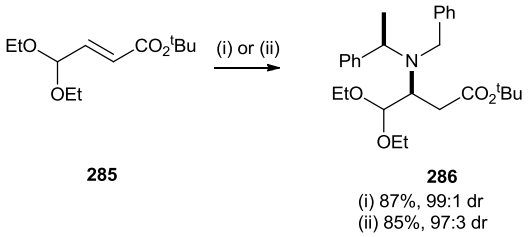
4.3.3.3 Synthesis of 256 from acrolein diethyl acetal

In order to solve the γ-deprotonation problem at the conjugate addition step, one more acetal, acrolein diethyl acetal, was investigated. Reaction of acrolein diethyl acetal with *tert*-butyl acrylate *via* cross metathesis, or *via* ozonolysis-Wittig reaction gave the corresponding ethyl acetal α,β-unsaturated ester **285** in 90% and 78% yield, respectively (Scheme 46).



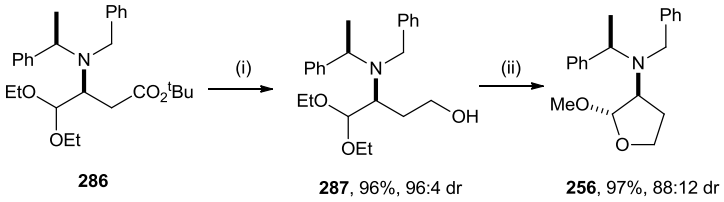
Scheme 46. *Reagents and conditions:* (i) Hoveyda-Grubbs II, CH_2Cl_2, reflux, 22 h; (ii) O_3, CH_2Cl_2, −78 °C then Me_2S, −78 °C to rt, 16 h; (iii) **265**, rt, 16 h.

Treatment of **285** with lithium amide **8**, according to the standard procedure outlined by Davies and co-workers,[14] in THF at −78 °C for 2 h gave **286** in 87% yield and 99:1 dr. The same reaction in Et_2O at −20 °C for 5 h gave **286** in 85% yield and 97:3 dr. There was no γ-deprotonation side product observed in either case (Scheme 47).



Scheme 47. *Reagents and conditions:* (i) **8**, THF, −78 °C, 2 h; (ii) **8**, Et_2O, −20 °C, 5 h.

Reduction of β-amino ester **286** with $LiAlH_4$ gave the corresponding β-amino alcohol **287** in 96% yield and 96:4 dr. Heating **287** in MeOH with HCl gave **256** in 97% yield and 88:12 dr (Scheme 48).



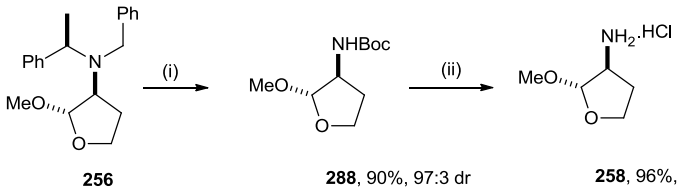
Scheme 48. *Reagents and conditions:* (i) $LiAlH_4$, THF, 0 °C to rt, 16 h; (ii) HCl, MeOH, 80 °C, 16 h.

5-Membered ring amino cyclization product **256** was synthesized from sorbic acid in 54% yield over 4 steps; whereas it was synthesized from acrolein diethyl acetal in 73% yield over 4 steps.

4.3.4 *N*-Deprotection

Attempting hydrogenolysis of **256** followed by filtration through Celite® gave low mass return. A two-step procedure was therefore implemented. Thus, treatment of **256** with

Boc_2O and $Pd(OH)_2/C$ under H_2 (5 atm) in MeOH gave **288** in 90% yield and 97:3 dr. Finally, treatment of **288** with methanolic HCl yielded **258** in 96% yield and 82:18 dr (Scheme 49).



256 **288**, 90%, 97:3 dr **258**, 96%, 82:18 dr

Scheme 49. *Reagents and conditions:* (i) $Pd(OH)_2/C$, Boc_2O, H_2 (5 atm), MeOH, 24 h, rt; (ii) HCl, MeOH, rt, 16 h.

4.4 Asymmetric syntheses of more functionalised 5-membered ring amino sugars

Two different synthetic routes to **259** either from *tert*-butyl sorbate **272** or from acetal containing α,β-unsaturated ester **285** were investigated (Figure 21).

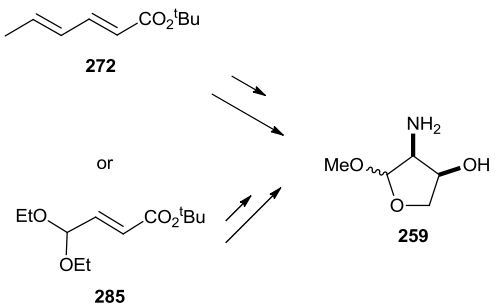
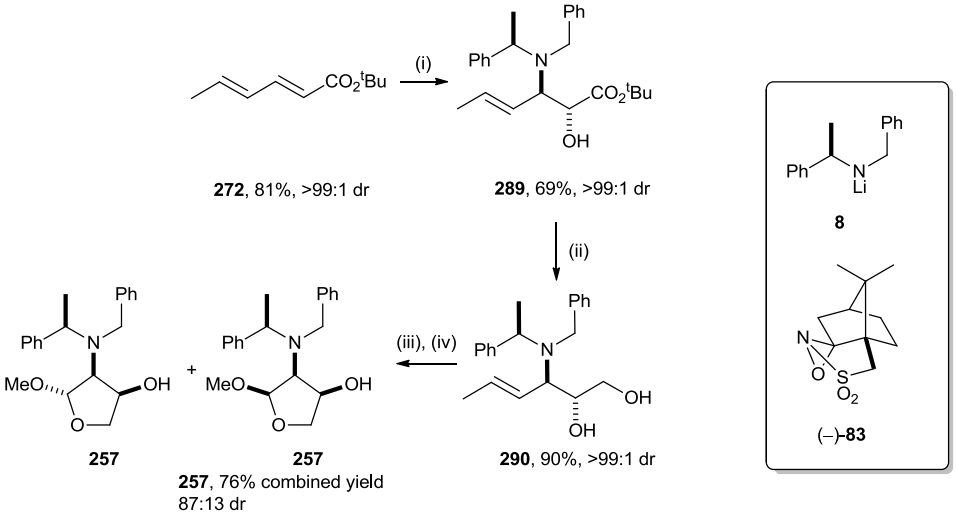


Figure 21. Synthesis of **259** from *tert*-butyl sorbate **272** or acetal containing α,β-unsaturated ester **285**.

4.4.1 Asymmetric synthesis of more functionalised 5-membered ring cyclization product 257 from *tert*-butyl sorbate 272 *via* ozonolysis

Treatment of *tert*-butyl sorbate **272** with the lithium amide **8** followed by the addition of (−)-CSO **83**, according to the procedure outlined by Davies and co-workers,[14] gave *anti*-α-hydroxy-β-amino ester **289** in 69% yield and as a single diastereoisomer (>99:1 dr), as determined by ^1H NMR spectroscopic analysis. Reduction of *anti*-α-hydroxy-β-amino ester **289** with $LiAlH_4$ gave the corresponding β-amino alcohol **290** in 90% yield and >99:1 dr (Scheme 50). With β-amino alcohol **290** in hand, ozonolysis was performed using the optimal conditions developed for the synthesis of the 5-membered ring amino sugar **258**. HCl (2.0 M in Et_2O) in Et_2O was added to **290** to yield the HCl salt of **290**, which was dissolved in MeOH. Ozonolysis followed by reflux with

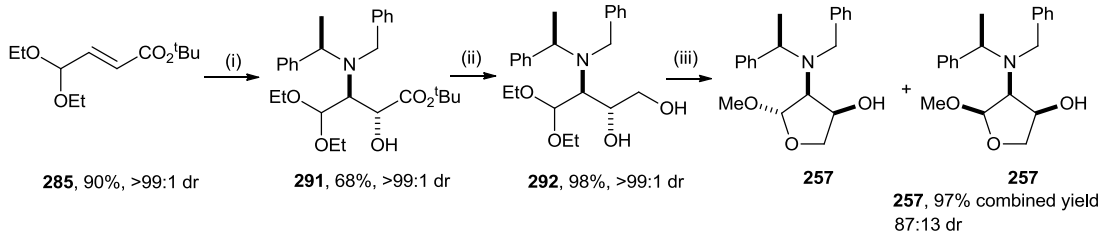
methanolic HCl gave the crude reaction mixture. Purification via flash column chromatography gave **257** in 76% yield and 87:13 dr, within both of which the relative stereochemistry around the THF ring was established by ^{1}H NMR NOE analysis (Scheme 50).



Scheme 50. *Reagents and conditions:* (i) **8**, THF, −78 °C, 2 h, then (−)-CSO **83**, −78 °C to rt, 12 h (ii) $LiAlH_4$, THF, 0 °C to rt, 16 h; (iii) O_3, MeOH, −78 °C then Me_2S, −78 °C to rt, 16 h; (iv) HCl, MeOH, 50 °C, 16 h.

4.4.2 Synthesis of 257 from acrolein diethyl acetal

Treatment of **285** with lithium amide **8** followed by the addition of (−)-CSO **83**, according to the procedure outlined by Davies and co-workers,[14] gave diethyl acetal *anti*-α-hydroxy-β-amino ester **291** in 68% yield and as a single diastereoisomer (>99:1 dr). The absolute (2*R*,3*R*,α*R*)-configuration within **291** was assigned by analogy to the stereochemical outcome of this diastereoselective aminohydroxylation reaction which has been applied to a range of substrates.[14] Reduction of **291** with $LiAlH_4$ gave **292** in 98% yield and >99:1 dr, then heating **292** in MeOH in the presence of HCl gave **257** in 97% yield and 83:17 dr (Scheme 51).

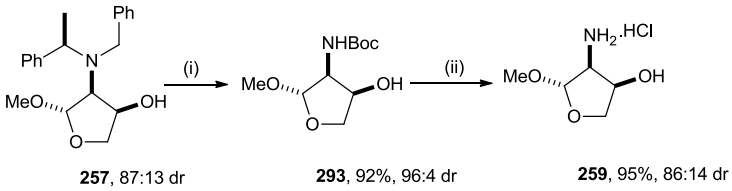


Scheme 51. *Reagents and conditions:* (i) **8**, THF, −78 °C, 2 h, then (−)-CSO **83**, −78 °C to rt, 12 h; (ii) $LiAlH_4$, THF, 0 °C to rt, 16 h; (iii) HCl, MeOH, 80 °C, 16 h.

Functionalised 5-membered ring amino cyclization product **257** was synthesized from sorbic acid in 38% overall yield in 4 steps, whereas it was synthesized from acrolein diethyl acetal in 58% overall yield in 4 steps.

4.4.3 *N*-Deprotection

N-Deprotection of **257** was achieved by the two-step protocol developed for 5-membered ring amino sugar **258**. Thus, treatment of **257** with Boc_2O and $Pd(OH)_2/C$ under H_2 (5 atm) in MeOH gave **293** in 92% yield and 96:4 dr. Finally, treatment of **293** with methanolic HCl yielded **259** in 95% yield and 86:14 dr (Scheme 52).



Scheme 52. *Reagents and conditions:* (i) $Pd(OH)_2/C$, Boc_2O, H_2 (5 atm), MeOH, 24 h, rt; (ii) HCl, MeOH, rt, 16 h.

4.5 Asymmetric synthesis of 6-membered ring amino sugar

With successful experience of the synthesis of 5-membered ring amino sugars, the investigation of a synthetic route to 6-membered ring amino sugar **295** from acetal containing substrate **294** was carried out (Figure 22).

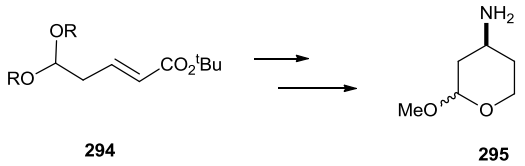
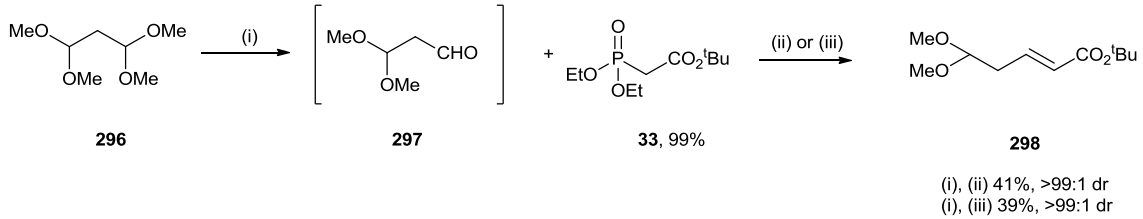


Figure 22. Synthesis of **295** from an acetal substrate .

4.5.1 Attempted of synthesis of 6-membered ring amino sugar 295 from 1,1,3,3-tetramethoxypropane 296

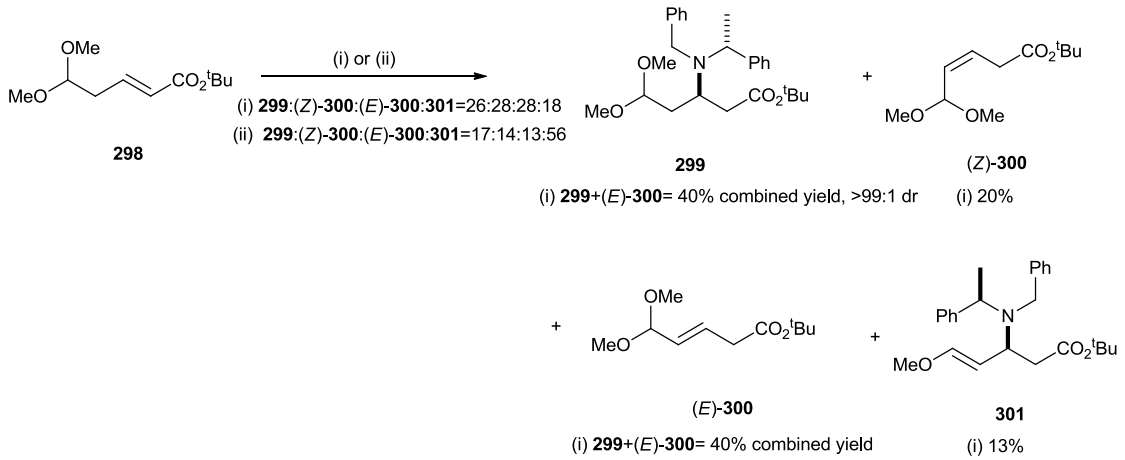
Preparation of **295** started from a synthesis of the dimethoxy acetal ester **298**. Aldehyde **297** was synthesized by adding 30% aq orthophosphoric acid to commercially available 1,1,3,3-tetramethoxypropane **296**,[17] and then subsequent reaction according to a

modified HWE protocol using either ^{t}BuOK or MeMgBr[18] as the base gave α,β-unsaturated ester **298** in 41 and 39% yield, respectively (Scheme 53).



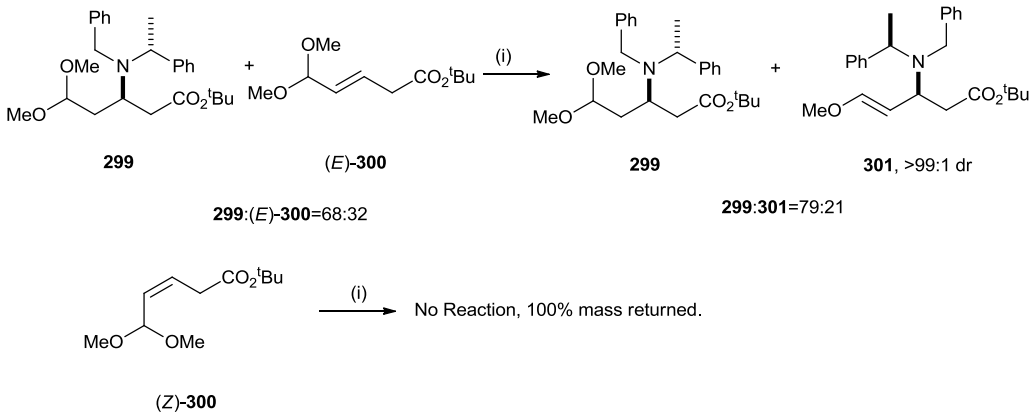
Scheme 53. *Reagents and conditions:* (i) 30% aq orthophosphoric acid, rt, 16 h; (ii) ^{t}BuOK, MeOH, 0 °C, 15 min, then 0 °C to rt, 4 h; (iii) MeMgBr, THF, rt, 15 min, then reflux, 15 h.

Treatment of **298** with lithium amide **8**, according to the standard procedure outlined by Davies and co-workers,[14] in THF at −78 °C after 2 h gave a mixture of four compounds, identified as a direct conjugate addition product **299**, the *cis*-isomer of γ-deprotonation side product **300**, the *trans*-isomer of γ-deprotonation side product **300** and mono-methoxy addition product **301**. Purification gave (*Z*)-**300** in 20% yield, **301** in 13% yield and a 68:32 mixture of **299** and (*E*)-**300**, respectively, in approximate 40% combined yield. The same reaction in Et_2O at −20 °C after 5 h[16] gave a similar result (Scheme 54).



Scheme 54. *Reagents and conditions:* (i) **8**, THF, −78 °C, 2 h; (ii) **8**, Et_2O, −20 °C, 5 h.

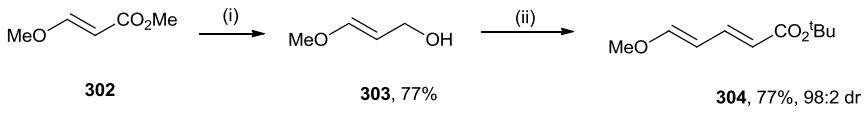
Resubjection of a 68:32 mixture of **299** and (*E*)-**300** to the reaction conditions gave a 79:21 mixture of **299** and **301**. However, resubjection of (*Z*)-**300** to the reaction crudes gave no reaction. This result suggested that **301** was derived from (*E*)-**300** (Scheme 55).



Scheme 55. *Reagents and conditions:* (i) **8**, Et_2O, −20 °C, 5 h.

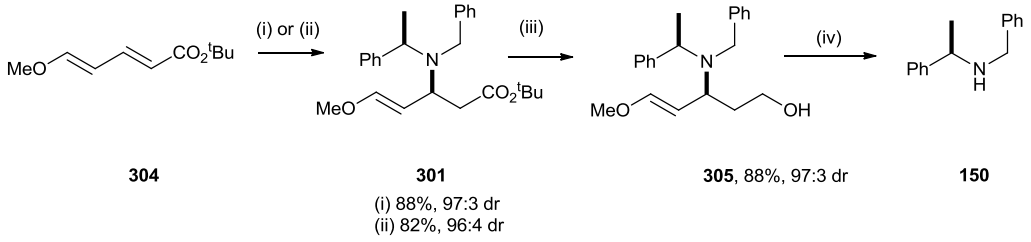
4.5.2 Attempted formation of 295 from (*E*)-methyl-3-methoxyacrylate 302

In order to investigate this sequence further, the synthesis of **301** was the next target. Reduction of commercially available **302** with DIBAL-H gave the corresponding alcohol **303** in 77% yield. Treatment of **303** (1.0 equiv) with **265** (1.0 equiv) activated MnO_2 (20 equiv) in CH_2Cl_2 generated α,β,γ,δ-diunsaturated ester **304** in 77% yield and 98:2 dr (Scheme 56).



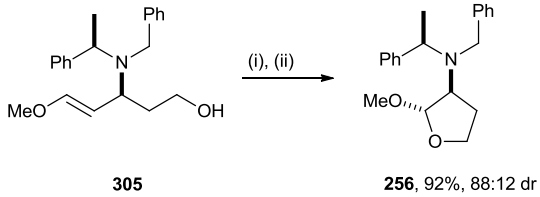
Scheme 56. *Reagents and conditions:* (i) DIBAL-H, toluene, −78 °C, 6 h; (ii) activated MnO_2, **265**, CH_2Cl_2, rt, 48 h.

Reaction of **304** with lithium amide **8** in THF at −78 °C for 2 h gave **301** in 88% yield and 97:3 dr. The same reaction in Et_2O at −20 °C after 5 h[16] gave for **301** in 82% yield and 96:4 dr. With a single major product in hand, elaboration to the amino sugar was examined. Reduction of **301** with $LiAlH_4$ gave the corresponding alcohol **305** in 88% yield and 97:3 dr. However, treatment of **305** in MeOH in the presence of HCl generated amine **150** rather than 6-membered ring cyclization product (Scheme 57).



Scheme 57. *Reagents and conditions:* (i) **8**, THF, −78 °C, 2 h; (ii) **8**, Et_2O, −20 °C, 5 h; (iii) $LiAlH_4$, THF, 0 °C to rt, 16 h; (iv) HCl, MeOH, 0 °C, 16 h.

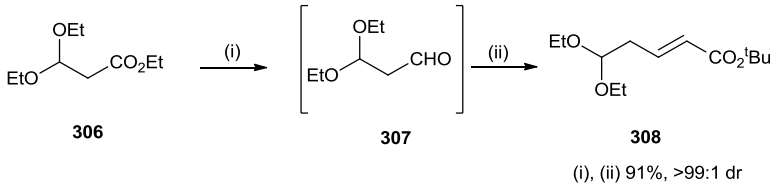
Although reaction of **305** gave 6-membered ring amino sugar **295** unsuccessfully, it was suitable to make 5-membered ring amino sugar **258**. With β-amino alcohol **305** in hand, ozonolysis, followed by heating in methanolic HCl gave 5-membered ring cyclization product **256** in 92% yield and 88:12 dr (Scheme 58).



Scheme 58. *Reagents and conditions:* (i) O_3, MeOH, −78 °C then Me_2S, −78 °C to rt, 16 h; (ii) HCl, MeOH, 50 °C, 16 h.

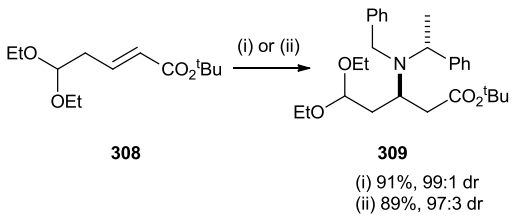
4.5.3 Synthesis of 295 from 3,3-diethoxypropanoate 306

In order to investigate the γ-deprotonation problem during the conjugate addition step, one more acetal, 3,3-diethoxypropanoate **306**, was investigated. Reduction of **306** with DIBAL-H gave the corresponding aldehyde **307**. Treatment of crude aldehyde **307** with **265** in CH_2Cl_2 generated ester **308** in 91% yield and >99:1 dr (Scheme 59).



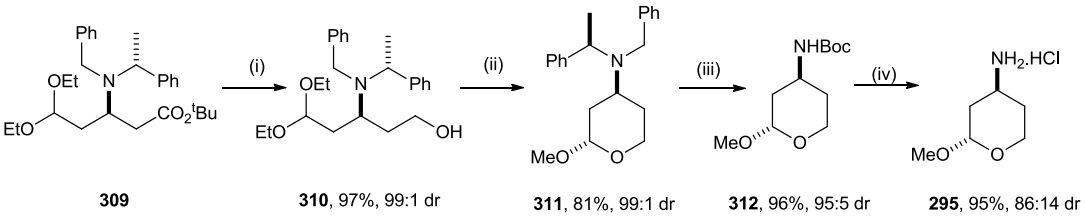
Scheme 59. *Reagents and conditions:* (i) DIBAL-H, CH_2Cl_2, −78 °C, 50 min; (ii) **265**, rt, 16 h.

Unlike addition to dimethyl acetal containing α,β-unsaturated ester **298**, treatment of **308** with lithium amide **8** in THF at −78 °C after 2 h gave **309** as a single product, which was isolated in 91% yield and 99:1 dr. The same reaction in Et_2O at −20 °C after 5 h gave **309** in 89% yield and 97:3 dr. There was no γ-deprotonation side product observed in either case (Scheme 60).



Scheme 60. *Reagents and conditions:* (i) **8**, THF, −78 °C, 2 h; (ii) **8**, Et_2O, −20 °C, 5 h.

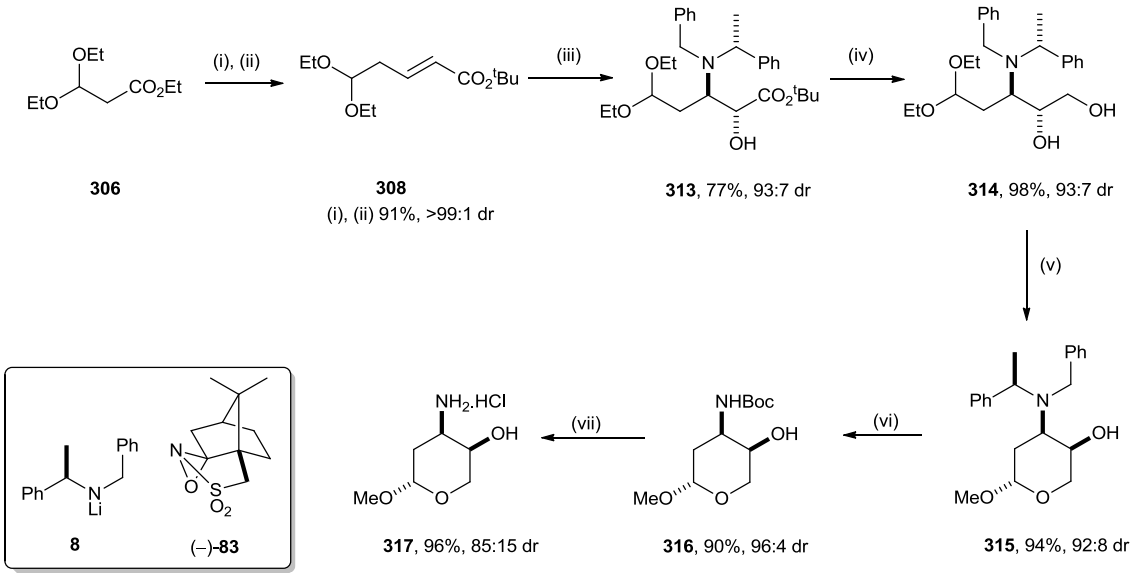
Reduction of β-amino ester **309** with $LiAlH_4$ gave β-amino alcohol **310** in 97% yield and 99:1 dr. Heating **310** in MeOH in the presence of HCl gave 6-membered ring amino cyclization product **311** in 81% yield and 99:1 dr. *N*-Deprotection by treatment of **311** with Boc_2O and $Pd(OH)_2/C$ under H_2 (5 atm) in MeOH gave **312** in 96% yield and 95:5 dr. Finally, treatment of **312** with methanolic HCl yielded **295** in 95% yield and 86:14 dr (Scheme 61).



Scheme 61. *Reagents and conditions:* (i) $LiAlH_4$, THF, 0 °C to rt, 16 h; (ii) HCl, MeOH, 80 °C, 16 h; (iii) $Pd(OH)_2/C$, Boc_2O, H_2 (5 atm), MeOH, 24 h, rt; (iv) HCl, MeOH, rt, 16 h.

4.6 Asymmetric synthesis of more functionalised 6-membered ring amino sugar

Treatment of **308** with lithium amide **8** followed by the addition of (−)-CSO **83** in THF at −78 °C after 2 h gave diethyl acetal *anti*-α-hydroxy-β-amino ester **313** in 77% yield and 93:7 dr. The absolute (2*R*,3*R*,α*R*)-configuration within **313** was assigned by analogy to the stereochemical outcome of this diastereoselective aminohydroxylation reaction which has been successfully applied to a range of substrates.[14] Reduction of **313** with $LiAlH_4$ gave **314** in 98% yield and 93:7 dr. Heating **314** in MeOH in the presence of HCl gave the more heavily functionalised 6-membered ring amino cyclization product **315** in 94% yield and 92:8 dr. *N*-Deprotection by treatment of **315** with Boc_2O and $Pd(OH)_2/C$ under H_2 (5 atm) in MeOH gave **316** in 90% yield and 96:4 dr. Finally, treatment of **316** with methanolic HCl yielded **317** in 96% yield and 85:15 dr (Scheme 62).



Scheme 62. *Reagents and conditions:* (i) DIBAL-H, CH_2Cl_2, −78 °C, 50 min; (ii) **265**, rt, 16 h; (iii) **8**, THF, −78 °C, 2h, then (−)-CSO **83**, −78 °C to rt, 12 h; (iv) $LiAlH_4$, THF, 0 °C to rt, 16 h; (v) HCl, MeOH, 80 °C, 16 h; (vi) $Pd(OH)_2/C$, Boc_2O, H_2 (5 atm), MeOH, 24 h, rt; (vii) HCl, MeOH, rt, 16 h.

4.7 Conclusions and future work

In conclusion, successful and concise asymmetric syntheses of 5- or 6-membered ring amino sugars *via* cyclization of "alkene-masked" aldehyde β-amino esters or "acetal-masked" aldehyde β-amino esters demonstrated the utility of the Davies' conjugate addition methodology. 5-Membered ring amino sugar **258** has been synthesized successfully *via* 3 different routes. The first route was from sorbic acid **273** over 6 steps to give **258** in 47% yield. The second route was from acrolein diethyl acetal over 6 steps to give **258** in 63% yield. The third route was from (*E*)-methyl-3-methoxyacrylate **302** over 7 steps to give **258** in 36% yield. The acetal route is the best one due to the higher yield and shorter procedure. More functionalised 5-membered ring amino sugar **259** has been synthesized successfully *via* 2 different routes. The first route was from sorbic acid **273** over 6 steps to give **259** in 33% yield. The second route was from acrolein diethyl acetal over 6 steps to give **259** in 51% yield. The acetal route is the best one due to the higher yield and shorter procedures involved.

Both 6-membered ring amino sugar **295** and more functionalised 6-membered ring amino sugar **317** have been synthesized successfully from 3,3-diethoxypropanoate **306** over 6 steps, in 59% yield and 56% yield, respectively.

In future, further investigations can be tried. One possible suggestion is to functionalize the double bond of **301** to synthesize more functionalized amino sugars. One more possible suggestion is to expand the stereochemistry of the amino sugars synthesized already by investigating the synthesis of the diastereoisomers, for example, **317**. Finally, elaboration of previously synthesized amino sugar **259** to jaspine B analogue **103**[19] can also be attempted (Figure 23).

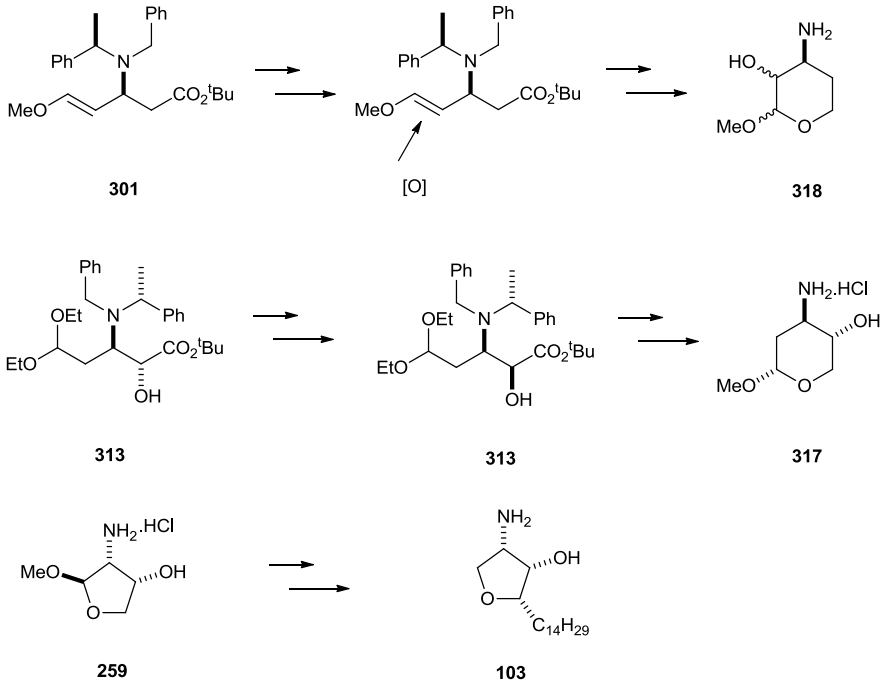


Figure 23. Proposed future work.

4.8 References and notes for chapter 4

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Chapter 5: Experimental

5.1 General experimental

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers. Water was purified by an Elix® UV-10 system. BuLi was used as a solution in hexanes and titrated against diphenylacetic acid. 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), iodine, 1% aq $KMnO_4$, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica on a glass column, or on a Biotage SP4 flash column chromatography platform. Elemental analyses were recorded by the microanalysis service of the London Metropolitan University, UK. Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer as either a thin film on NaCl plates (film) or a KBr disc (KBr), as stated. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated. The field was locked by external referencing to the relevant deuteron resonance. Chemical shifts (δ) are reported in ppm and coupling constants (J) in Hz. Low-resolution mass spectra were recorded on either a VG MassLab 20-250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF internally calibrated with polyalanine, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m × 0.25 mm) using amyl acetate

as a lock mass, by the mass spectrometry department of the Chemistry Research Laboratory, University of Oxford, UK.

5.2 General procedures

General Procedure 1 for Horner-Wadsworth-Emmons Reactions

MeMgBr (1.20 equiv.) was added dropwise to a stirred solution of the requisite phosphonate (1.20 equiv.) in anhydrous THF at rt under a nitrogen atmosphere and stirred for 15 min. The requisite aldehyde (1.00 equiv.) was added dropwise via syringe and the reaction mixture refluxed for 15 h at 85 ^{o}C. The reaction was quenched with sat aq NH_4Cl and extracted with EtOAc. The combined organic layers were then washed with brine, dried and concentrated *in vacuo*.

General Procedure 2a, 2b, 2c and 2d for Lithium Amide Conjugate Additions

BuLi [(a) 1.55 equiv., (b) 3.00 equiv., (c) 10.00 equiv. or (d) 1.94 equiv.] was added dropwise via syringe to a stirred solution of the requisite amine [(a) 1.60 equiv., (b) 3.00 equiv., (c) 10.00 equiv. or (d) 2.00 equiv.] in THF at −78 °C under nitrogen. After stirring for thirty minutes, a solution of the α,β-unsaturated ester (1.00 equiv.) in THF at −78 °C was added dropwise *via* cannula. After stirring for a further two hours at −78 °C the reaction mixture was quenched with sat aq NH_4Cl solution. After warming to rt over 15 min the reaction mixture was concentrated *in vacuo*. The phases were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried, filtered, and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 and washed sequentially with 10% aq citric acid solution and sat aq $NaHCO_3$, dried, filtered, and concentrated *in vacuo*.

General Procedure 3 for Hydrogenolysis of Benzyl Groups

A stirred solution of the requisite amine in the stated solvent was purged with nitrogen for 15 min. After this time, Pd $(OH)_2$/C (the stated amount) was added and the reaction was placed under an atmosphere of H_2 (the stated pressure). Stirring under H_2 continued for the stated reaction time, after which time, the suspension was filtered by passage through Celite® (stated eluent) and the collected organics were concentrated *in vacuo*.

General Procedure 4 for CAN Promoted Oxidative *N*-Debenzylation

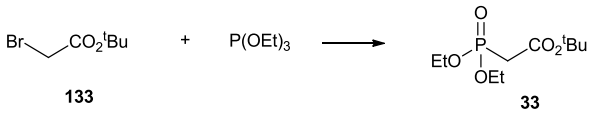
CAN (6.0 equiv.) was added to a solution of the amine (1.0 equiv.) in 5:1 MeCN/H_2O and the solution stirred for 16 h at rt. The reaction was quenched by addition of sat aq $NaHCO_3$ and partitioned between brine and Et_2O. The phases were separated and the combined organic extracts were dried and concentrated *in vacuo*.

General Procedure 5 for Cleavage of Esters with aq. HCl

2M aq HCl was added dropwise to a stirred solution of the requisite *tert*-butyl ester at rt and the reaction mixture was refluxed for 6 h. After this time the reaction mixture was concentrated *in vacuo* to give the crude reaction mixture. The residue was subjected to ion-exchange chromatography (Dowex 50WX8-100, eluent 1M aq NH_4OH) to yield the free amino acid.

5.3 Experimental for chapter 2

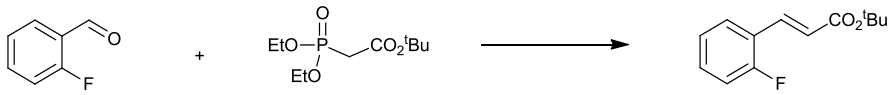
tert-Butyl diethylphosphonoacetate 33



133 **33**

A mixture of *tert*-butyl bromoacetate **133** (50.7 g, 260 mmol) and triethylphosphite (43.2 g, 260 mmol) was heated at 50 ºC for 2 h. Volatiles were then removed *in vacuo* to give **33** as a colourless oil (67.5 g, 99%);[2] δ_H (400 MHz, $CDCl_3$) 1.23 (6H, t, *J* 7.2, $P(OCH_2C\mathit{H}_3)_2$), 1.35 (9H, s, $C\mathit{Me}_3$), 2.77 (2H, d, *J* 21.5, $PC\mathit{H}_2$), 4.17 (4H, app quintet, *J* 7.2, $P(OC\mathit{H}_2CH_3)_2$).

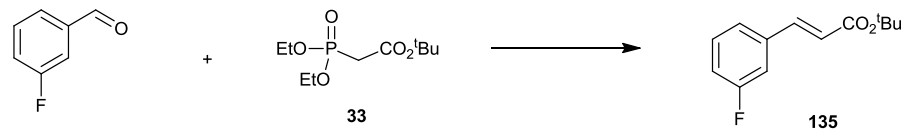
tert-Butyl (*E*)-3-(2'-fluorophenyl)prop-2-enoate 134



33 **134**

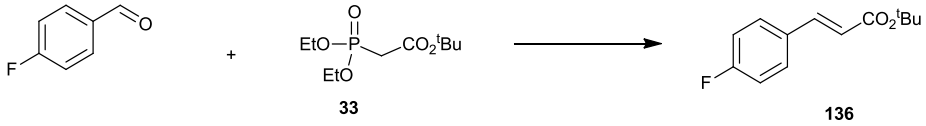
Following *General Procedure 1*, **33** (7.57 g, 30.0 mmol), MeMgBr (2.5 M in Et_2O, 12.0 mL, 30.0 mmol) and 2-fluorobenzaldehyde (3.10 g, 25.0 mmol) in THF (300 mL) gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 40:1) gave **134** as a colourless oil (4.44 g, 80%, >99:1 dr);[3] ν_{max} (ATR) 3044 (C–H), 1710 (C=O), 1638 (C=C); δ_H (400 MHz, $CDCl_3$) 1.54 (9H, s, $C\mathit{Me}_3$), 6.46 (1H, d, *J* 16.1, C(2)*H*), 7.08–7.51 (4H, m, *Ar*), 7.72 (1H, d, *J* 16.1, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 28.1 ($C\mathit{Me}_3$), 80.7 ($\mathit{C}Me_3$), 122.7 (*C*(2)), 116.1, 124.4, 128.8, 131.3 (*C*(3′), *C*(4′), *C*(5′), *C*(6′)), 136.0 (*C*(3)), 161.2 (*C*(2′)), 166.1 (*C*(1)); *m/z* (ESI^+) 467 ($[2M+Na]^+$, 100%), 245 ($[M+Na]^+$, 82%); HRMS (ESI^+) $C_{13}H_{15}FNaO_2^+$ ($[M+Na]^+$) requires 245.0948; found 245.0952.

tert-Butyl (*E*)-3-(3'-fluorophenyl)prop-2-enoate 135



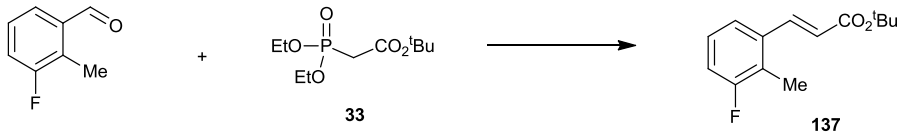
Following *General Procedure 1*, **33** (6.05 g, 24.0 mmol), MeMgBr (2.7 M in Et_2O, 8.89 mL, 24.0 mmol) and 3-fluorobenzaldehyde (2.48 g, 20.0 mmol) in THF (240 mL) gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 40:1) gave **135** as a pale yellow oil (3.51 g, 79%, >99:1 dr);[4] δ_H (400 MHz, $CDCl_3$) 1.54 (9H, s, C*Me*$_3$), 6.37 (1H, d, *J* 15.9, C(2)*H*), 7.03–7.37 (4H, m, *Ar*), 7.54 (1H, d, *J* 15.9, C(3)*H*).

tert-Butyl (*E*)-3-(4'-fluorophenyl)prop-2-enoate 136



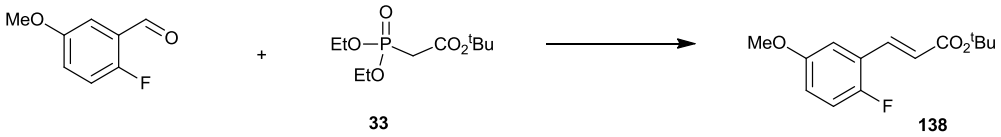
Following *General Procedure 1*, **33** (6.05 g, 24.0 mmol), MeMgBr (2.7 M in Et_2O, 8.89 mL, 24.0 mmol) and 4-fluorobenzaldehyde (2.15 mL, 20.0 mmol) in THF (240 mL) gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 40:1) gave **136** as a white crystalline solid (3.91 g, 88%, >99:1 dr);[5] mp 46–47 ºC; {lit.[5] mp 47.5–48.5 ºC}; δ_H (400 MHz, $CDCl_3$) 1.54 (9H, s, C*Me*$_3$), 6.30 (1H, d, *J* 15.9, C(2)*H*), 7.05–7.09 (2H, m, C(2′)*H*, C(6′)*H*), 7.48–7.53 (2H, m, C(3′)*H*, C(5′)*H*), 7.55 (1H, d, *J* 15.9, C(3)*H*).

***tert*-Butyl (*E*)-3-(3'-fluoro-2'-methylphenyl)prop-2-enoate 137**



Following *General Procedure 1*, **33** (6.57 g, 26.1 mmol), MeMgBr (2.6 M in Et_2O, 10.0 mL, 26.1 mmol) and 3-fluoro-2-methylbenzaldehyde (3.00 g, 21.7 mmol) in THF (300 mL) gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 40:1) gave **137** as a colourless oil (4.05 g, 79%, >99:1 dr); ν_{max} (ATR) 3004 (C–H), 1711 (C=O), 1637 (C=C); δ_H (400 MHz, $CDCl_3$) 1.56 (9H, s, C*Me*$_3$), 2.32 (3H, s, C(2′)*Me*), 6.30 (1H, d, *J* 15.7, C(2)*H*), 7.01–7.03 (1H, m, C(6′)*H*), 7.15 (1H, td, *J* 7.8, 5.8, C(5′)*H*), 7.32 (1H, d, *J* 7.8, C(4′)*H*), 7.84 (1H, d, *J* 15.7, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 10.6 (C(2′)*Me*), 28.1 (C*Me*$_3$), 80.7 (*C*Me$_3$), 116.0 (*C*(6′)), 122.0 (*C*(4′)), 122.6 (*C*(2)), 124.4, 135.9 (*C*(2′), *C*(1′)), 126.8 (*C*(5′)), 140.1 (*C*(3)), 161.3 (*C*(3′)), 166.0 (*C*(1)); *m/z* (ESI$^+$) 495 ([2M+Na]$^+$, 100%), 259 ([M+Na]$^+$, 69%); HRMS (ESI$^+$) $C_{14}H_{17}FNaO_2^+$ ([M+Na]$^+$) requires 259.1105; found 259.1106.

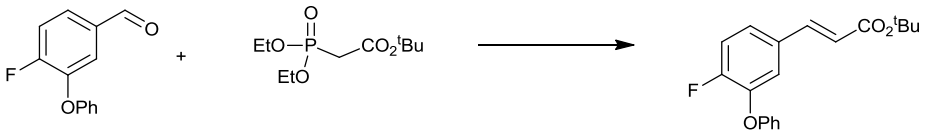
***tert*-Butyl (*E*)-3-(2'-fluoro-5'-methoxyphenyl)prop-2-enoate 138**



Following *General Procedure 1*, **33** (5.45 g, 21.6 mmol), MeMgBr (2.7 M in Et_2O, 8.00 mL, 21.6 mmol) and 2-fluoro-5-methoxybenzaldehyde (2.77 g, 18.0 mmol) in THF (220 mL) gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 30:1) gave **138** as a white crystalline solid (3.63 g, 80%, >99:1 dr); $C_{14}H_{17}FO_3$ requires C, 66.7; H, 6.8%; found C, 66.6; H, 6.8%; mp 34–35 ºC; ν_{max} (ATR) 3072 (C–H), 1708 (C=O), 1638 (C=C); δ_H (400 MHz, $CDCl_3$) 1.54 (9H, s C*Me*$_3$), 3.81 (3H, s, O*Me*), 6.44 (1H, d, *J* 16.2, C(2)*H*), 6.85–7.04 (3H, m, *Ar*), 7.69 (1H, d, *J* 16.2, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 28.1 (C*Me*$_3$), 55.8

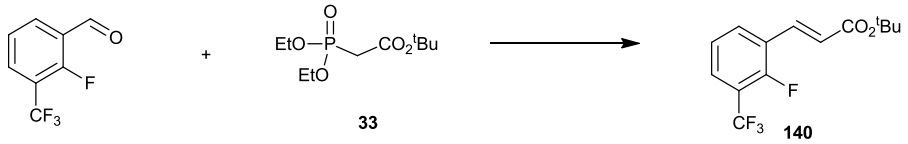
(O*Me*), 80.7 (*C*Me$_3$), 112.5, 116.7, 117.1 (*C*(3′), *C*(4′), *C*(6′)), 122.7 (*C*(2)), 122.9 (*C*(1′)), 136.1 (*C*(3)), 155.8, 157.0 (*C*(2′), *C*(5′)), 166.0 (*C*(1)); *m/z* (ESI$^+$) 527 ([2M+Na]$^+$, 100%), 275 ([M+Na]$^+$, 89%); HRMS (ESI$^+$) $C_{14}H_{17}FNaO_3^+$ ([M+Na]$^+$) requires 275.1054; found 275.1057.

tert-Butyl (_E_)-3-(4'-fluoro-3'-phenoxyphenyl)prop-2-enoate 139



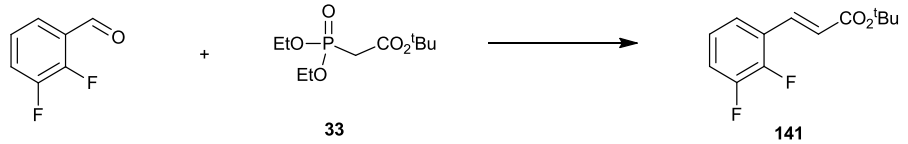
Following *General Procedure 1*, **33** (2.39 g, 9.48 mmol), MeMgBr (2.4 M in Et_2O, 3.95 mL, 9.48 mmol) and 4-fluoro-3-phenoxybenzaldehyde (1.41 mL, 7.90 mmol) in THF (100 mL) gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 40:1) gave **139** as a white crystalline solid (2.04 g, 82%, >99:1 dr); $C_{19}H_{19}FO_3$ requires C, 72.6; H, 6.1%; found C, 72.75; H, 6.15%; mp 88–90 ºC; ν_{max} (ATR) 3063 (C–H), 1707 (C=O), 1639 (C=C); δ_H (400 MHz, $CDCl_3$) 1.52 (9H, s, C*Me*$_3$), 6.21 (1H, d, *J* 15.9, C(2)*H*), 7.01–7.36 (8H, m, *Ar*), 7.46 (1H, d, *J* 15.9, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 28.1 (C*Me*$_3$), 80.7 (*C*Me$_3$), 117.4, 117.6, 120.3, 120.7, 124.5, 129.8 (*C*(2′), *C*(5′), *C*(6′), *o,m,p-Ph*), 123.6 (*C*(2)), 131.8 (*C*(1′)), 141.7 (*C*(3)), 143.0, 153.8, 156.8 (*C*(3′), (*C*(4′), *i-Ph*), 165.9 (*C*(1)); *m/z* (ESI$^+$) 965 ([3M+Na]$^+$, 100%), 651 ([2M+Na]$^+$, 100%), 337 ([M+Na]$^+$, 49%); HRMS (ESI$^+$) $C_{19}H_{19}FNaO_3^+$ ([M+Na]$^+$) requires 337.1210; found 337.1209.

***tert*-Butyl (*E*)-3-(2'-fluoro-3'-(trifluoromethyl)phenyl)prop-2-enoate 140**



Following *General Procedure 1*, **33** (7.88 g, 31.2 mmol), MeMgBr (2.6 M in Et_2O, 12.0 mL, 31.2 mmol) and 2-fluoro-3-trifluoromethylbenzaldehyde (5.00 g, 26.0 mmol) in THF (320 mL) gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 40:1) gave **140** as a colourless oil (6.56 g, 87%, >99:1 dr); ν_{max} (ATR) 1713 (C=O), 1643 (C=C); δ_H (400 MHz, $CDCl_3$) 1.54 (9H, s, C*Me*$_3$), 6.49 (1H, d, *J* 16.4, C(2)*H*), 7.23–7.27 (1H, m, C(5′)*H*), 7.57–7.60 (1H, m, C(6′)*H*), 7.70–7.73 (1H, m, C(4′)*H*), 7.71 (1H, d, *J* 16.4, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 28.1 (C*Me*$_3$), 81.0 (*C*Me$_3$), 119.4 (*C*F$_3$), 121.0, 123.7 (*C*(1′), *C*(3′)), 124.1 (*C*(5′)), 124.5 (*C*(2)), 128.0 (*C*(6′)), 132.3, 134.1 (*C*(4′), *C*(2)), 157.7 (*C*(2′)), 165.4 (*C*(1)); *m/z* (ESI$^+$) 603 ([2M+Na]$^+$, 97%), 313 ([M+Na]$^+$, 61%); HRMS (ESI$^+$) $C_{14}H_{14}F_4NaO_2^+$ ([M+Na]$^+$) requires 313.0822; found 313.0823.

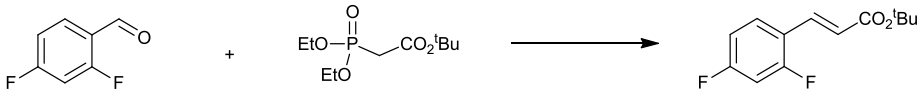
***tert*-Butyl (*E*)-3-(2',3'-difluorophenyl)prop-2-enoate 141**



Following *General Procedure 1*, **33** (4.26 g, 16.9 mmol), MeMgBr (3.0 M in Et_2O, 5.63 mL, 16.9 mmol) and 2,3-difluorobenzaldehyde (2.00 g, 14.1 mmol) in THF (180 mL) gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 50:1), **141** as a colourless crystalline solid (2.98 g, 88%, >99:1 dr); $C_{13}H_{14}F_2O_2$ requires C, 65.0; H, 5.9%; found C, 64.6; H, 5.7%; mp 25–26 ºC; ν_{max} (ATR) 2980, 2934 (C–H), 1708 (C=O), 1639 (C=C); δ_H (400 MHz, $CDCl_3$) 1.52 (9H, s, C*Me*$_3$), 6.45 (1H, d, *J* 16.2, C(2)*H*), 7.03–7.26 (3H, m, *Ar*), 7.65 (1H, d, *J* 16.2, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 28.0 (C*Me*$_3$), 80.8 (*C*Me$_3$), 118.2, 123.5, 124.0 (*C*(4′), *C*(5′),

C(6′)), 124.1 (*C*(2)), 124.9 (*C*(1′)), 134.8 (*C*(3)), 148.7, 151.5 (*C*(2′), *C*(3′)), 165.6 (*C*(1)); *m/z* (ESI$^+$) 503 ([2M+Na]$^+$, 74%), 263 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{14}F_2NaO_2^+$ ([M+Na]$^+$) requires 263.0854; found 263.0851.

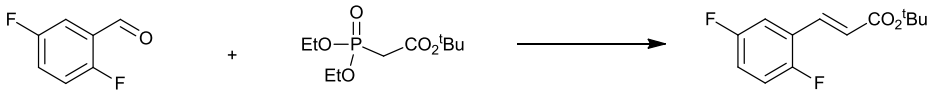
tert-Butyl (*E*)-3-(2',4'-difluorophenyl)prop-2-enoate 142



33 **142**

Following *General Procedure 1*, **33** (4.26 g, 16.9 mmol), MeMgBr (3.0 M in Et_2O, 5.63 mL, 16.9 mmol) and 2,4-difluorobenzaldehyde (2.00 g, 14.1 mmol) in THF (180 mL) gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 50:1) gave **142** as a white solid (3.01 g, 89%, >99:1 dr);[6] mp 42–43 ºC; {lit.[6] mp 43 ºC}; δ_H (400 MHz, $CDCl_3$) 1.52 (9H, s, C*Me*$_3$), 6.39 (1H, d, *J* 16.2, C(2)*H*), 6.80–6.90 (2H, m, *Ar*), 7.46–7.52 (1H, m, *Ar*), 7.63 (1H, d, *J* 16.2, C(3)*H*).

tert-Butyl (*E*)-3-(2',5'-difluorophenyl)prop-2-enoate 143

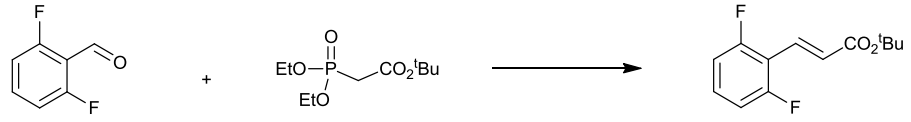


33 **143**

Following *General Procedure 1*, **33** (4.26 g, 16.9 mmol), MeMgBr (3.0 M in Et_2O, 5.63 mL, 16.9 mmol) and 2,5-difluorobenzaldehyde (2.00 g, 14.1 mmol) in THF (180 mL) gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 50:1) gave **143** as a white solid (2.94 g, 87%, >99:1 dr); $C_{13}H_{14}F_2O_2$ requires C, 65.0; H, 5.9%; found C, 64.9; H, 5.8%; mp 52–53 ºC; ν_{max} (ATR) 2980, 2934 (C–H), 1708 (C=O), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 1.54 (9H, s, C*Me*$_3$), 6.43 (1H, d, *J* 16.2, C(2)*H*), 7.01–7.23 (3H, m, *Ar*), 7.65 (1H, d, *J* 16.2, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 28.2 (C*Me*$_3$), 80.8 (*C*Me$_3$), 114.4, 117.2, 117.8 (*C*(3′), *C*(4′),

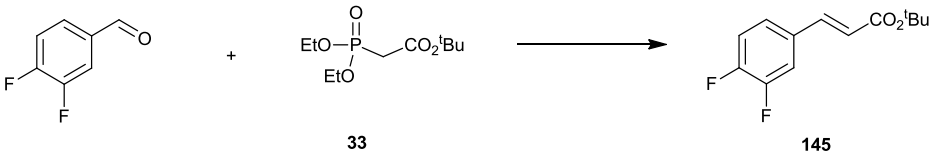
C(6′)), 123.9 (*C*(2)), 124.0 (*C*(1′)), 134.8 (*C*(3)), 156.7, 159.2 (*C*(2′), *C*(5′)), 165.6 (*C*(1)); *m/z* (ESI$^+$) 503 ([2M+Na]$^+$, 100%), 263 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{14}F_2NaO_2^+$ ([M+Na]$^+$) requires 263.0854; found 263.0853.

tert-Butyl (*E*)-3-(2',6'-difluorophenyl)prop-2-enoate 144



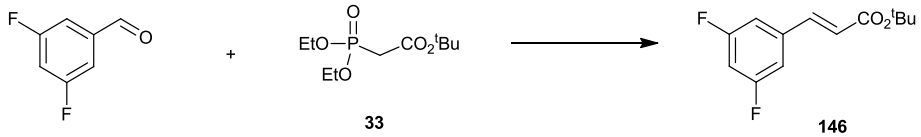
Following *General Procedure 1*, **33** (4.26 g, 16.9 mmol), MeMgBr (3.0 M in Et_2O, 5.63 mL, 16.9 mmol) and 2,6-difluorobenzaldehyde (2.00 g, 14.1 mmol) in THF (180 mL) gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 50:1) gave **144** as a white solid (2.98 g, 88%, >99:1 dr);[7] mp 56–57 ºC; {lit.[7] mp 55–56 ºC};δ_H (400 MHz, $CDCl_3$) 1.54 (9H, s, C*Me*$_3$), 6.43 (1H, d, *J* 16.2, C(2)*H*), 6.90–6.94 (2H, m, *Ar*), 7.24–7.31 (1H, m, *Ar*), 7.68 (1H, d, *J* 16.2, C(3)*H*).

tert-Butyl (*E*)-3-(3',4'-difluorophenyl)prop-2-enoate 145



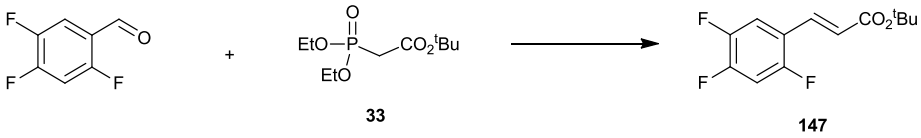
Following *General Procedure 1*, **33** (4.26 g, 16.9 mmol), MeMgBr (3.0 M in Et_2O, 5.63 mL, 16.9 mmol) and 3,4-difluorobenzaldehyde (2.00 g, 14.1 mmol) in THF (180 mL) gave the crude reaction mixture. Purification via flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 50:1) gave **145** as a white solid (3.04 g, 90%, >99:1 dr);[8] mp 60–61 ºC; {lit.[8] mp 61 ºC}; δ_H (400 MHz, $CDCl_3$) 1.51 (9H, s, C*Me*$_3$), 6.26 (1H, d, *J* 16.0, C(2)*H*), 7.06–7.34 (3H, m, *Ar*), 7.46 (1H, d, *J* 16.0, C(3)*H*).

tert-Butyl (*E*)-3-(3',5'-difluorophenyl)prop-2-enoate 146



Following *General Procedure 1*, **33** (4.26 g, 16.9 mmol), MeMgBr (3.0 M in Et_2O, 5.63 mL, 16.9 mmol) and 3,5-difluorobenzaldehyde (2.00 g, 14.1 mmol) in THF (180 mL) gave the crude reaction mixture. Purification via flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 50:1) gave **146** as a white crystalline solid (3.01 g, 89%, >99:1 dr); $C_{13}H_{14}F_2O_2$ requires C, 65.0; H, 5.9%; found C, 50.8; H, 4.1%; mp 68–69 ºC; ν_{max} (ATR) 2980, 2934 (C–H), 1708 (C=O), 1644 (C=C); δ_H (400 MHz, $CDCl_3$) 1.54 (9H, s, C*Me*$_3$), 6.35 (1H, d, *J* 16.0, C(2)*H*), 6.79–6.83 (1H, m, *Ar*), 7.00–7.03 (2H, m, *Ar*), 7.47 (1H, d, *J* 16.0, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 28.2 (C*Me*$_3$), 81.2 (*C*Me$_3$), 105.0, 110.4, 110.6 (*C*(2′), *C*(4′), *C*(6′)), 122.9 (*C*(2)), 138.0 (*C*(1′)), 140.9 (*C*(3)), 161.8, 164.3 (*C*(2′), *C*(5′)), 165.4 (*C*(1)); *m/z* (ESI$^+$) 503 ([2M+Na]$^+$, 15%), 263 ([M+Na]$^+$, 50%); HRMS (ESI$^+$) $C_{13}H_{14}F_2NaO_2^+$ ([M+Na]$^+$) requires 263.0854; found 263.0854.

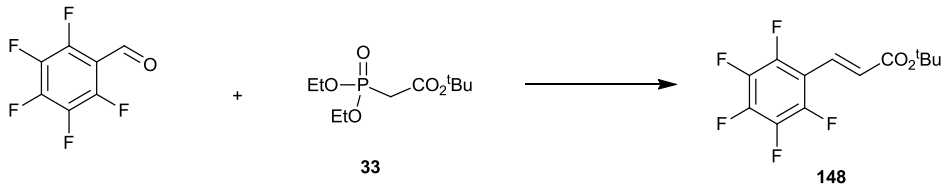
tert-Butyl (*E*)-3-(2',4',5'-trifluorophenyl)prop-2-enoate 147



Following *General Procedure 1*, **33** (4.26 g, 16.9 mmol), MeMgBr (3.0 M in Et_2O, 5.63 mL, 16.9 mmol) and 2,4,5-trifluorobenzaldehyde (2.25 g, 14.1 mmol) in THF (180 mL) gave the crude reaction mixture. Purification via flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 50:1) gave **147** as a white crystalline solid (3.20 g, 88%, >99:1 dr); $C_{13}H_{13}F_3O_2$ requires C, 60.5; H, 5.1%; found C, 60.4; H, 5.0%; mp 86–87 ºC; ν_{max} (ATR) 2973, 2938 (C–H), 1695 (C=O), 1634 (C=C); δ_H (400 MHz, $CDCl_3$) 1.54 (9H, s, C*Me*$_3$), 6.37 (1H, d, *J* 16.2, C(2)*H*), 6.93–7.00 (1H, m, *Ar*), 7.30–7.37 (1H, m, *Ar*), 7.60 (1H, d, *J* 16.0, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 28.2 (C*Me*$_3$), 81.1 (*C*Me$_3$), 106.1, 115.9

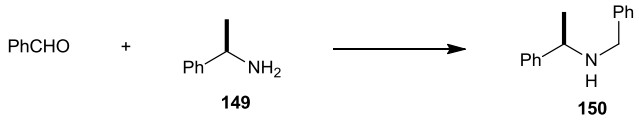
(*C*(3′), *C*(6′)), 119.3 (*C*(1′)), 123.6 (*C*(2)), 133.7 (*C*(3)), 149.6, 152.0, 155.2 (*C*(2′), *C*(4′), *C*(5′)), 165.4 (*C*(1)); *m/z* (ESI^+) 539 ($[2M+Na]^+$, 62%), 281 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{13}H_{13}F_3NaO_2^+$ ($[M+Na]^+$) requires 281.0760; found 281.0758.

tert-Butyl (_E_)-3-(pentafluorophenyl)prop-2-enoate 148



Following *General Procedure 1*, **33** (3.03 g, 12.0 mmol), MeMgBr (2.4 M in Et_2O, 5.00 mL, 12.0 mmol) and pentafluorobenzaldehyde (1.96 g, 10.0 mmol) in THF (120 mL) gave the crude reaction mixture. Purification via flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 30:1) gave **148** as a white crystalline solid (2.47 g, 84%, >99:1 dr);[6] mp 37–38 ºC; δ_H (400 MHz, $CDCl_3$) 1.54 (9H, s, C*Me*$_3$), 6.67 (1H, d, *J* 16.4, C(2)*H*), 7.55 (1H, d, *J* 16.4, C(3)*H*).

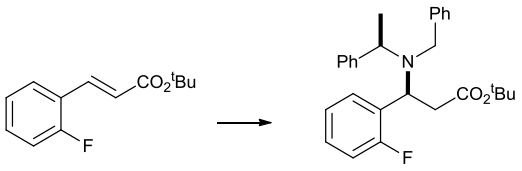
(*R*)-*N*-Benzyl-*N*-(α-methylbenzyl)amine 150



Benzaldehyde (42.8 mL, 418 mmol) was added to a solution of (*R*)-α-methylbenzylamine **149** (53.2 mL, 412 mmol) in EtOH (250 mL) at rt and the reaction mixture was then heated at reflux for 3 h. The reaction mixture was allowed to cool to rt and was then further cooled to 0 ºC. $NaBH_4$ (15.6 g, 412 mmol) was added portionwise and the resultant suspension was stirred for 3 d at rt. The reaction mixture was concentrated *in vacuo* and then resultant residue was partitioned between H_2O (150 mL) and CH_2Cl_2 (200 mL). The organic layer was dried and concentrated *in vacuo*. The residue was slowly added to a solution of Et_2O (300 mL) and 10.0 M aq HCl to give a white solid, which was isolated by filtration and recrystallised to homogeneity

(CH_2Cl_2/pentane). The free amine was then regenerated by treatment of the hydrochloride salt with 2.0 M aq NaOH and subsequent extraction with CH_2Cl_2. The combined organic extracts were dried and concentrated in *vacuo* to give **150** as a colourless oil (73.8 g, 85%);[9] $[\alpha]_D^{25}$ +53.4 (*c* 3.9 in EtOH); {lit.[9] $[\alpha]_D^{22}$ +54.4 (*c* 3.9 in EtOH)}; δ_H (400 MHz, $CDCl_3$) 1.39 (3H, d, *J* 6.5, C(α)*Me*), 1.66 (1H, br s, N*H*), 3.61 (1H, d, *J* 13.0, NCH_A), 3.68 (1H, d, *J* 13.0, NCH_B), 3.84 (1H, q, *J* 6.5, C(α)*H*), 7.23–7.40 (10H, m, *Ph*).

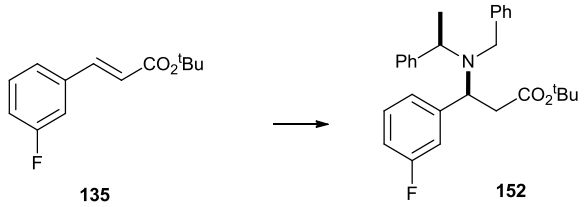
tert-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(2'-fluorophenyl)-propanoate 151



134 **151**

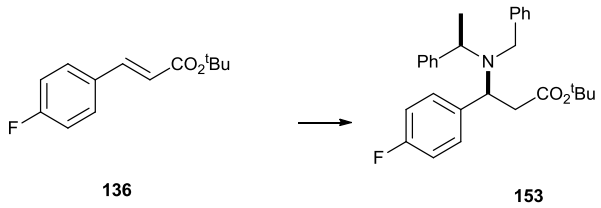
Following *General Procedure 2a*, BuLi (2.6 M in hexanes, 5.96 mL, 15.5 mmol) and **150** (3.38 g, 16.0 mmol) in THF (65 mL) at −78 °C, and **134** (2.22 g, 10.0 mmol) in THF (50 mL) at −78 °C gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 30:1) gave **151** as a colourless oil (3.85 g, 89%, 98:2 dr); $[\alpha]_D^{25}$ +7.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2977 (C−H), 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 1.22 (9H, s, C*Me*$_3$), 1.28 (3H, d, *J* 6.8, C(α)*Me*), 2.49 (2H, d, *J* 7.9, C(2)H_2), 3.74 (2H, app q, J_{AB} 14.9, NCH_AH_B), 4.06 (1H, q, *J* 6.8, C(α)*H*), 4.75 (1H, t, *J* 7.9, C(3)*H*), 7.06−7.47 (14H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 14.6 (C(α)*Me*), 27.7 (C*Me*$_3$), 39.3 (*C*(2)), 50.8 (N*C*H$_2$), 53.8 (*C*(3)), 56.7 (*C*(α)Me), 80.2 (*C*Me$_3$), 115.5, 115.8, 123.8, 126.5, 126.8, 127.9, 128.0, 128.1, 128.8, 129.6 (*C*(3′), *C*(4′), *C*(5′), *C*(6′), *o,m,p-Ph*), 128.5 (*C*(1′)), 141.5, 143.9 (*i-Ph*), 161.4 (d, *J* 246.1, *C*(2′)), 171.2 (*C*(1)); *m/z* (ESI$^+$) 456 ([M+Na]$^+$, 91%), 434 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{33}FNO_2^+$ ([M+H]$^+$) requires 434.2490; found 434.2490.

***tert*-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(3'-fluorophenyl)-propanoate 152**



Following *General Procedure 2a*, BuLi (2.3 M in hexanes, 9.11 mL, 20.9 mmol) and **150** (4.57 g, 21.6 mmol) in THF (75 mL) at −78 °C, and **135** (3.00 g, 13.5 mmol) in THF (65 mL) at −78 °C gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 25:1) gave **152** as a colourless oil (4.85 g, 83%, 98:2 dr); $[\alpha]_D^{25}$ +3.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2976 (C–H), 1727 (C=O); δ_H (400 MHz, $CDCl_3$) 1.27 (9H, s, C*Me*$_3$), 1.31 (3H, d, *J* 7.0, C(α)*Me*), 2.45−2.54 (2H, m, C(2)*H*$_2$), 3.69 (2H, s, NC*H*$_2$), 4.00 (1H, q, *J* 7.0, C(α)*H*), 4.43 (1H, app dd, *J* 9.6, 5.6, C(3)*H*), 6.93−7.45 (14H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 16.9 (C(α)*Me*), 27.8 (C*Me*$_3$), 37.9 (*C*(2)), 50.9 (N*C*H$_2$), 57.3 (*C*(α)Me), 59.0 (*C*(3)), 80.4 (*C*Me$_3$), 113.9, 115.2, 123.7, 126.7, 127.0, 127.8, 128.0, 128.2, 129.5, 129.6 (*C*(2′), *C*(4′), *C*(5′), *C*(6′), *o,m,p-Ph*), 141.3, 143.7 (*i-Ph*), 144.9 (*C*(1′)), 161.4 (*C*(3′)), 171.2 (*C*(1)); *m/z* (ESI$^+$) 456 ([M+Na]$^+$, 94%), 434 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{33}FNO_2^+$ ([M+H]$^+$) requires 434.2490; found 434.2490.

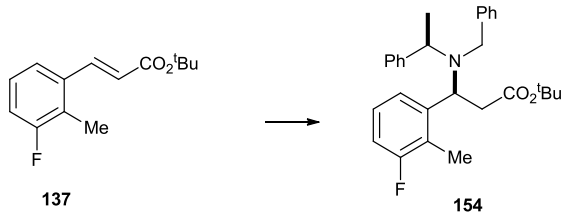
***tert*-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(4'-fluorophenyl)-propanoate 153**



Following *General Procedure 2a*, BuLi (2.3 M in hexanes, 6.07 mL, 13.9 mmol) and **150** (3.04 g, 14.4 mmol) in THF (50 mL) at −78 °C, and **136** (2.00 g, 9.00 mmol) in THF (45 mL) at −78 °C gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 30:1) gave **153** as a colourless oil (3.43

g, 88%, 98:2 dr); $[\alpha]_D^{25}$ +4.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2976 (C−H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.25 (9H, s, C*Me*$_3$), 1.29 (3H, d, *J* 7.0, C(α)*Me*), 2.45−2.56 (2H, m, C(2) *H*$_2$), 3.68 (2H, s, NC*H*$_2$), 3.98 (1H, q, *J* 7.0, C(α)*H*), 4.40 (1H, dd, *J* 10.4, 4.8, C(3)*H*), 7.18−7.43 (14H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 16.7 (C(α)*Me*), 27.8 (C*Me*$_3$), 38.2 (*C*(2)), 50.8 (N*C*H$_2$), 57.3 (*C*(α)Me), 59.0 (*C*(3)), 80.3 (*C*Me$_3$), 114.8, 115.0, 126.6, 126.9, 127.8, 127.9, 128.2, 129.8 (*C*(2′), *C*(3′), *C*(5′), *C*(6′), *o,m,p-Ph*), 137.7 (*C*(1′)), 141.6, 143.9 (*i-Ph*), 161.2 (*C*(4′)), 171.0 (*C*(1)); *m/z* (ESI^+) 456 ($[M+Na]^+$, 97%), 434 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{28}H_{33}FNO_2^+$ ($[M+H]^+$) requires 434.2490; found 434.2479.

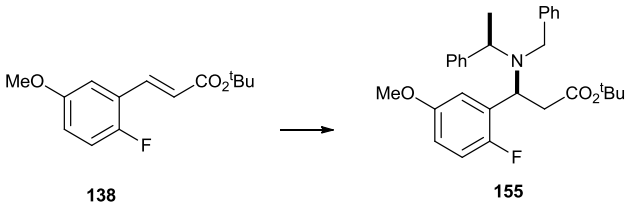
tert-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(3'-fluoro-2'-methylphen-yl)propanoate 154



Following *General Procedure 2a*, BuLi (2.5 M in hexanes, 7.88 mL, 19.7 mmol) and **150** (4.30 g, 20.3 mmol) in THF (75 mL) at −78 °C, and **137** (3.00 g, 12.7 mmol) in THF (60 mL) at −78 °C gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 20:1) gave **154** as a white crystalline solid (4.14 g, 73%, 98:2 dr); $C_{29}H_{34}FNO_2$ requires C, 77.8; H, 7.7; N, 3.1%; found C, 78.0; H, 7.7; N, 3.1%; mp 69−72 ºC; $[\alpha]_D^{25}$ +51.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2976 (C−H), 1723 (C=O); δ_H (400 MHz, $CDCl_3$) 1.13 (9H, s, C*Me*$_3$), 1.35 (3H, d, *J* 6.8, C(α)*Me*), 2.26 (3H, s, C(2′) *Me*), 2.32−2.38 (1H, m, C(2)*H*$_A$H$_B$), 2.66−2.70 (1H, m, C(2)H$_A$*H*$_B$), 3.72−3.82 (2H, m, NC*H*$_2$), 3.96 (1H, q, *J* 6.8, C(α)*H*), 4.58 (1H, dd, *J* 10.9, 5.0, C(3)*H*), 6.90−7.41 (13H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 10.5 (C(2′) *Me*), 14.2 (C(α)*Me*), 27.6 (C*Me*$_3$), 40.0 (*C*(2)), 51.0 (N*C*H$_2$), 57.2 (*C*(α)Me), 58.5 (*C*(3)), 80.2 (*C*Me$_3$), 113.4, 113.7, 123.8, 126.3, 126.4, 127.6, 127.9, 128.0, 128.1 (*C*(4′), *C*(5′),

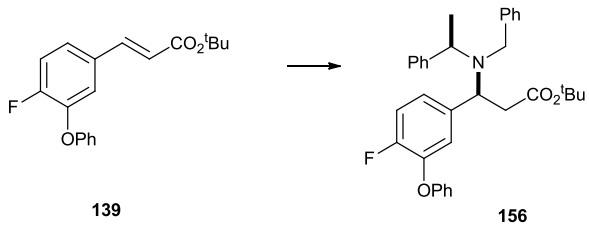
C(6′), *o,m,p-Ph*), 124.7, 142.6 ((*C*(1′)), *C*(2′)), 142.3, 143.9 (*i-Ph*), 162.9 (*C*(3′)), 170.9 (*C*(1)); *m/z* (ESI$^+$) 470 ([M+Na]$^+$, 92%), 448 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{35}FNO_2^+$ ([M+H]$^+$) requires 448.2646; found 448.2645.

tert-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(2'-fluoro-5'-methoxyphenyl)propanoate 155



Following *General Procedure 2a*, BuLi (2.6 M in hexanes, 5.91 mL, 15.4 mmol) and **150** (3.35 g, 15.9 mmol) in THF (50 mL) at −78 °C, and **138** (2.50 g, 9.92 mmol) in THF (50 mL) at −78 °C gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 15:1) gave **155** as a light yellow crystalline solid (3.22 g, 70%, 95:5 dr); $C_{29}H_{34}FNO_3$ requires C, 75.1; H, 7.4; N, 3.0%; found C, 75.3; H, 7.4; N, 2.9%; mp 61−63 ºC; $[\alpha]_D^{25}$ +11.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2976 (C−H), 1727 (C=O); δ_H (400 MHz, $CDCl_3$) 1.23 (9H, s, C*Me*$_3$), 1.29 (3H, d, *J* 6.8, C(α)*Me*), 2.58−2.61 (2H, m, C(2)*H*$_2$), 3.67−3.77 (2H, m, NC*H*$_2$), 3.78 (3H, s, O*Me*), 4.06 (1H, q, *J* 6.8, C(α)*H*), 4.68 (1H, dd, *J* 9.4, 6.3, C(3)*H*), 6.74−7.45 (13H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 14.6 (C(α)*Me*), 27.7 (C*Me*$_3$), 39.4 (*C*(2)), 50.8 (N*C*H$_2$), 54.1 (*C*(3)), 55.7 (O*Me*), 56.8 (*C*(α)Me), 80.2 (*C*Me$_3$), 113.4, 113.5, 114.8, 115.9, 116.2, 126.5, 126.8, 127.9, 128.0 (*C*(3′), *C*(4′), *C*(6′), *o,m,p-Ph*), 129.2 (*C*(1′)), 141.5, 143.9 (*i-Ph*), 155.4 (*C*(5′)), 155.7 (*C*(2′)), 171.2 (*C*(1)); *m/z* (ESI$^+$) 486 ([M+Na]$^+$, 95%), 464 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{35}FNO_3^+$ ([M+H]$^+$) requires 464.2595; found 464.2596.

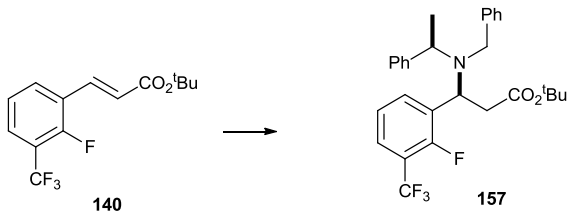
***tert*-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(4'-fluoro-3'-phenoxy-phenyl)propanoate 156**



139 **156**

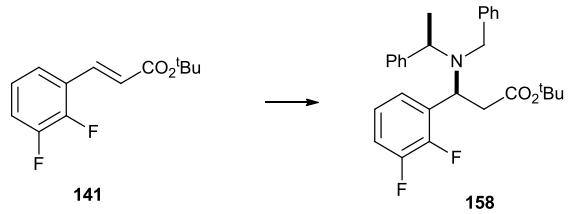
Following *General Procedure 2a*, BuLi (2.5 M in hexanes, 5.92 mL, 14.8 mmol) and **150** (3.23 g, 15.3 mmol) in THF (50 mL) at −78 °C, and **139** (3.00 g, 9.55 mmol) in THF (50 mL) at −78 °C gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol /Et_2O, 20:1) gave **156** as a colourless oil (3.81 g, 76%, 98:2 dr); $C_{34}H_{36}FNO_3$ requires C, 77.7; H, 6.9; N, 2.7%; found C, 77.7; H, 6.8; N, 2.6%; $[\alpha]_D^{25}$ +5.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2976 (C−H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.25 (9H, s, C*Me*$_3$), 1.24−1.34 (3H, m, C(α)*Me*), 2.39−2.52 (2H, m, C(2)*H*$_2$), 3.59−3.67 (2H, m, NC*H*$_2$), 3.93 (1H, q, *J* 6.8, C(α)*H*), 4.68 (1H, dd, *J* 10.1, 4.6, C(3)*H*), 6.99−7.38 (18H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 17.3 (C(α)*Me*), 27.8 (C*Me*$_3$), 37.4 (*C*(2)), 50.8 (N*C*H$_2$), 57.6 (*C*(α)Me), 58.6 (*C*(3)), 80.4 (*C*Me$_3$), 116.2, 116.4, 117.6, 121.6, 123.2, 123.9, 126.6, 127.0, 127.7, 127.8, 128.2, 129.7 (*C*(2′), *C*(5′), *C*(6′), *o,m,p-Ph*), 139.7 (*C*(1′)), 143.0, 153.8, 157.3 ((*C*(3′), *i-Ph*O, *C*(4′)), 141.5, 143.9 (*i-Ph*), 170.9 (*C*(1)); *m/z* (ESI^+) 548 ($[M+Na]^+$, 52%), 464 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{34}H_{37}FNO_3^+$ ($[M+H]^+$) requires 526.2752; found 526.2750.

tert-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(2'-fluoro-3'-(trifluorom-ethyl)phenyl)propanoate 157



Following *General Procedure 2a*, BuLi (2.0 M in hexanes, 8.02 mL, 16.0 mmol) and **150** (3.50 g, 16.5 mmol) in THF (60 mL) at −78 °C, and **140** (3.00 g, 10.3 mmol) in THF (50 mL) at −78 °C gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 20:1) gave **157** as a colourless oil (4.14 g, 80%, 89:11 dr); $[\alpha]_D^{25}$ +5.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2978 (C−H), 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 1.20 (9H, s, C*Me*$_3$), 1.32 (3H, d, *J* 6.8, C(α)*Me*), 2.61 (2H, d, *J* 7.8, C(2)*H*$_2$), 3.67 (1H, d, *J* 14.9, NC*H*$_A$H$_B$), 3.77 (1H, d, *J* 14.9, NCH$_A$*H*$_B$), 4.01 (1H, q, *J* 6.8, C(α)*H*), 4.78−4.82 (1H, m, C(3)*H*), 7.18−7.63 (13H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 14.9 (C(α)*Me*), 27.6 (C*Me*$_3$), 38.9 (*C*(2)), 50.8 (N*C*H$_2$), 53.4 (*C*(3)), 57.2 (*C*(α)Me), 80.6 (*C*Me$_3$), 118.9 (*C*F$_3$), 123.6, 126.0, 126.7, 127.0, 127.8, 127.9, 128.1, 128.2, 133.4 (*C*(4′), *C*(5′), *C*(6′), *o,m,p-Ph*), 124.1 (*C*(3′)), 130.6 (*C*(1′)), 141.1, 143.3 (*i-Ph*), 157.0 (*C*(2′)), 170.1 (*C*(1)); *m/z* (ESI$^+$) 524 ([M+Na]$^+$, 94%), 502 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{32}F_4NO_2^+$ ([M+H]$^+$) requires 502.2364; found 502.2364.

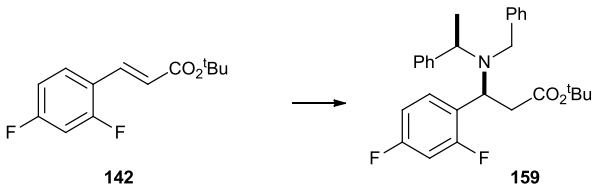
tert-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(2',3'-difluorophenyl)-propanoate 158



Following *General Procedure 2a*, BuLi (2.5 M in hexanes, 7.75 mL, 19.4 mmol) and **150** (4.23 g, 20.0 mmol) in THF (50 mL) at −78 °C, and **141** (3.00 g, 12.5 mmol) in

THF (50 mL) at −78 °C gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 25:1) gave **158** as a colourless oil (4.74 g, 84%, 96:4 dr); $C_{28}H_{31}F_2NO_2$ requires C, 74.5; H, 6.9; N, 3.1%; found C, 74.4; H, 6.9; N, 3.0%; $[\alpha]_D^{25}$ +16.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2977 (C−H), 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.24 (9H, s, C*Me*$_3$), 1.32 (3H, d, *J* 6.8, C(α)*Me*), 2.61−2.64 (2H, m, C(2)*H*$_2$), 3.75 (2H, app q, J_{AB} 14.9, NC*H*$_2$), 4.05 (1H, q, *J* 6.8, C(α)*H*), 4.76−4.80 (1H, m, C(3)*H*), 7.06−7.47 (13H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 15.0 (C(α)*Me*), 27.7 (C*Me*$_3$), 38.9 (*C*(2)), 50.7 (N*C*H$_2$), 53.4 (*C*(3)), 57.0 (*C*(α)Me), 80.4 (*C*Me$_3$), 115.9, 116.1, 123.6, 124.0, 126.7, 126.9, 127.9, 128.1, 128.2 (*C*(4′), *C*(5′), *C*(6′), *o,m,p-Ph*), 131.3 (*C*(1′)), 141.2, 143.5 (*i-Ph*), 148.8, 150.9 (*C*(2′), *C*(3′)), 170.3 (*C*(1)); *m/z* (ESI^+) 474 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{28}H_{31}F_2NNaO_2^+$ ($[M+Na]^+$) requires 474.2215; found 474.2207.

tert-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(2',4'-difluorophenyl)-propanoate 159

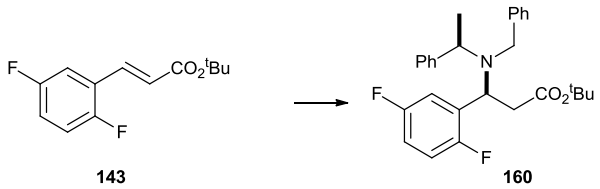


142 **159**

Following *General Procedure 2a*, BuLi (2.5 M in hexanes, 7.75 mL, 19.4 mmol) and **150** (4.23 g, 20.0 mmol) in THF (50 mL) at −78 °C, and **142** (3.00 g, 12.5 mmol) in THF (50 mL) at −78 °C gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 25:1) gave **159** as a colourless oil (4.62 g, 82%, >99:1 dr); $C_{28}H_{31}F_2NO_2$ requires C, 74.5; H, 6.9; N, 3.1%; found C, 74.4; H, 6.7; N, 2.9%; $[\alpha]_D^{25}$ +18.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2978 (C−H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.27 (9H, s, C*Me*$_3$), 1.35 (3H, d, *J* 6.8, C(α)*Me*), 2.64−2.66 (2H, m, C(2)*H*$_2$), 3.77 (2H, app q, J_{AB} 14.7, NC*H*$_2$), 4.08 (1H, q, *J* 6.8, C(α)*H*), 4.75−4.79 (1H, m, C(3)*H*), 6.85−7.49 (13H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 15.0 (C(α)*Me*), 27.7 (C*Me*$_3$), 38.9 (*C*(2)), 50.7 (N*C*H$_2$), 53.4 (*C*(3)), 57.0 (*C*(α)Me), 80.4 (*C*Me$_3$), 104.0, 110.9,

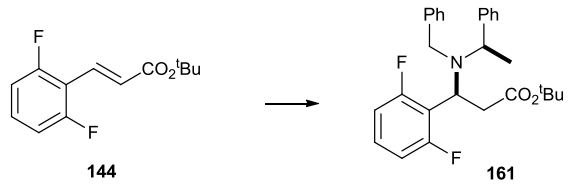
111.0, 126.6, 126.9, 127.9, 128.1, 128.2, 130.3 (*C*(3′), *C*(5′), *C*(6′), *o,m,p-Ph*), 124.7 (*C*(1′)), 141.3, 143.6 (*i-Ph*), 160.4, 163.0 (*C*(2′), *C*(4′)), 170.3 (*C*(1)); *m/z* (ESI^+) 474 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{28}H_{31}F_2NNaO_2^+$ ($[M+Na]^+$) requires 474.2215; found 474.2213.

tert-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(2',5'-difluorophenyl)-propanoate 160



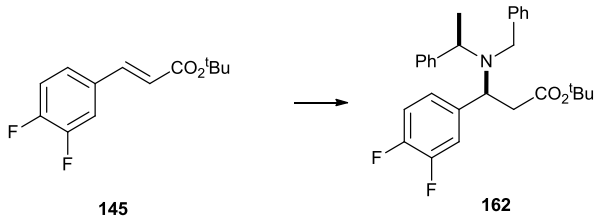
Following *General Procedure 2a*, BuLi (2.5 M in hexanes, 7.75 mL, 19.4 mmol) and **150** (4.23 g, 20.0 mmol) in THF (50 mL) at −78 °C, and **143** (3.00 g, 12.5 mmol) in THF (50 mL) at −78 °C gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 25:1) gave **160** as a colourless solid (4.90 g, 87%, 96:4 dr); $C_{28}H_{31}F_2NO_2$ requires C, 74.5; H, 6.9; N, 3.1%; found C, 74.3; H, 7.0; N, 2.9%; mp 59−60 ºC; $[\alpha]_D^{25}$ +17.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2977 (C−H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.25 (9H, s, C*Me*$_3$), 1.32 (3H, d, *J* 6.8, C(α)*Me*), 2.57−2.60 (2H, m, C(2)*H*$_2$), 3.74 (2H, app q, J_{AB} 14.7, NC*H*$_2$), 4.04 (1H, q, *J* 6.8, C(α)*H*), 4.72−4.76 (1H, m, C(3)*H*), 6.92−7.46 (13H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 14.9 (C(α)*Me*), 27.7 (C*Me*$_3$), 38.9 (*C*(2)), 50.8 (N*C*H$_2$), 53.6 (*C*(3)), 57.0 (*C*(α)Me), 80.5 (*C*Me$_3$), 115.1, 115.8, 116.6, 126.7, 126.9, 127.9, 128.0, 128.1, 128.2 (*C*(3′), *C*(4′), *C*(6′), *o,m,p-Ph*), 130.6 (*C*(1′)), 141.1, 143.6 (*i-Ph*), 156.7, 159.1 (*C*(2′), *C*(5′)), 170.2 (*C*(1)); *m/z* (ESI^+) 474 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{28}H_{31}F_2NNaO_2^+$ ($[M+Na]^+$) requires 474.2215; found 474.2212.

tert-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(2',6'-difluorophenyl)-propanoate 161



Following *General Procedure 2a*, BuLi (2.5 M in hexanes, 7.75 mL, 19.4 mmol) and **150** (4.23 g, 20.0 mmol) in THF (50 mL) at −78 °C, and **144** (3.00 g, 12.5 mmol) in THF (50 mL) at −78 °C gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 25:1) gave **161** as a colourless solid (4.85 g, 86%, 97:3 dr); $C_{28}H_{31}F_2NO_2$ requires C, 74.5; H, 6.9; N, 3.1%; found C, 73.2; H, 5.6; N, 2.6%; mp 52−53 ºC; $[\alpha]_D^{25}$ +16.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2977 (C−H), 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 1.25 (9H, s, C*Me*$_3$), 1.31 (3H, d, *J* 6.8, C(α)*Me*), 2.74 (1H, dd, *J* 14.9, 5.8, C(2)*H*$_A$H$_B$), 2.94−3.01 (1H, m, C(2)H$_A$*H*$_B$), 3.79 (2H, app q, J_{AB} 14.9, NC*H*$_2$), 4.23 (1H, q, *J* 6.8, C(α)*H*), 4.83−4.87 (1H, m, C(3)*H*), 6.90−7.51 (13H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 13.7 (C(α)*Me*), 27.7 (C*Me*$_3$), 39.3 (*C*(2)), 51.0 (N*C*H$_2$), 51.7 (*C*(3)), 56.4 (*C*(α)Me), 80.2 (*C*Me$_3$), 111.6, 111.9, 126.5, 126.7, 127.9, 128.0, 128.1, 129.1 (*C*(3′), *C*(4′), *C*(5′), *o,m,p-Ph*), 117.4 (*C*(1′)), 141.3, 143.8 (*i-Ph*), 160.8, 163.3 (*C*(2′), *C*(6′)), 170.5 (*C*(1)); *m/z* (ESI$^+$) 474 ([M+Na]$^+$, 91%); HRMS (ESI$^+$) $C_{28}H_{31}F_2NNaO_2^+$ ([M+Na]$^+$) requires 474.2215; found 474.2210.

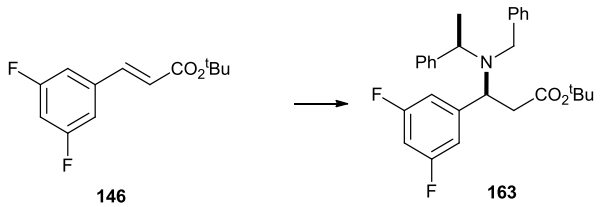
tert-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(3',4'-difluorophenyl)-propanoate 162



Following *General Procedure 2a*, BuLi (2.5 M in hexanes, 7.75 mL, 19.4 mmol) and **150** (4.23 g, 20.0 mmol) in THF (50 mL) at −78 °C, and **145** (3.00 g, 12.5 mmol) in

THF (50 mL) at −78 °C gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 35:1) gave **162** as a colourless oil (4.62 g, 82%, 96:4 dr); $C_{28}H_{31}F_2NO_2$ requires C, 74.5; H, 6.9; N, 3.1%; found C, 79.3; H, 5.8; N, 2.6%; $[\alpha]_D^{25}$ +19.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2977 (C−H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.32 (9H, s, C*Me*$_3$), 1.35 (3H, d, *J* 6.8, C(α)*Me*), 2.45−2.57 (2H, m, C(2)*H*$_2$), 3.71 (2H, app q, J_{AB} 14.9, NC*H*$_2$), 4.0 (1H, q, *J* 6.8, C(α)*H*), 4.42−4.45 (1H, m, C(3)*H*), 7.11−7.45 (13H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 17.4 (C(α)*Me*), 27.9 (C*Me*$_3$), 37.5 (*C*(2)), 50.9 (N*C*H$_2$), 57.6 (*C*(α)Me), 58.4 (*C*(3)), 80.6 (*C*Me$_3$), 116.7, 117.1, 123.9, 126.8, 127.1, 127.8, 127.9, 128.3, 128.4 (*C*(2′), *C*(4′), *C*(6′), *o,m,p-Ph*), 139.5 (*C*(1′)), 141.1, 143.6 (*i-Ph*), 148.6, 150.9 (*C*(3′), *C*(4′)), 170.8 (*C*(1)); *m/z* (ESI^+) 474 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{28}H_{31}F_2NNaO_2^+$ ($[M+Na]^+$) requires 474.2215; found 474.2209.

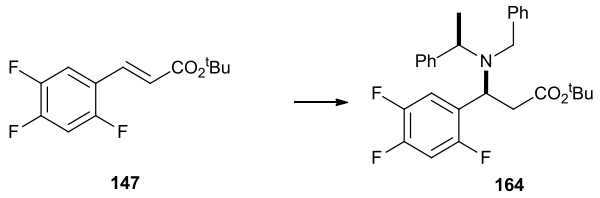
tert-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(3',5'-difluorophenyl)-propanoate 163



Following *General Procedure 2a*, BuLi (2.5 M in hexanes, 7.75 mL, 19.4 mmol) and **150** (4.23 g, 20.0 mmol) in THF (50 mL) at −78 °C, and **146** (3.00 g, 12.5 mmol) in THF (50 mL) at −78 °C gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 30:1) gave **163** as a colourless oil (4.51 g, 80%, 98:2 dr); $C_{28}H_{31}F_2NO_2$ requires C, 74.5; H, 6.9; N, 3.1%; found C, 69.4; H, 4.4; N, 2.5%; $[\alpha]_D^{25}$ +22.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2978 (C−H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.34 (9H, s, C*Me*$_3$), 1.36 (3H, d, *J* 6.8, C(α)*Me*), 2.48−2.51 (2H, m, C(2)*H*$_2$), 3.71 (2H, app q, J_{AB} 14.7, NC*H*$_2$), 4.00 (1H, q, *J* 6.8, C(α)*H*), 4.44−4.48 (1H, m, C(3)*H*), 6.70−7.45 (13H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 17.5 (C(α)*Me*), 27.9 (C*Me*$_3$),

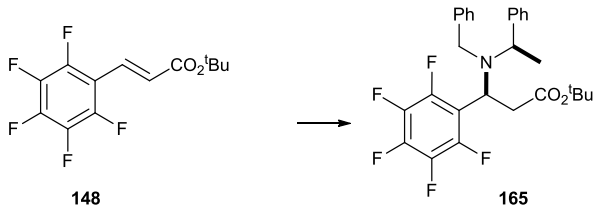
37.3 (*C*(2)), 51.1 (N*C*H_2), 57.6 (*C*(α)Me), 58.5 (*C*(3)), 80.7 (*C*Me_3), 102.4, 110.8, 111.1, 126.9, 127.2, 127.7, 128.0, 128.3, 128.4 (*C*(2′), *C*(4′), *C*(6′), *o,m,p-Ph*), 140.9, 143.3 (*i-Ph*), 146.9 (*C*(1′)), 161.7, 164.1 (*C*(3′), *C*(4′)), 170.7 (*C*(1)); *m/z* (ESI^+) 474 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{28}H_{31}F_2NNaO_2^+$ ($[M+Na]^+$) requires 474.2215; found 474.2216.

tert-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(2',4',5'-trifluorophenyl)propanoate 164



Following *General Procedure 2b*, BuLi (2.5 M in hexanes, 14.0 mL, 34.9 mmol) and **150** (7.37 g, 34.9 mmol) in THF (100 mL) at −78 °C, and **147** (3.00 g, 11.6 mmol) in THF (50 mL) at −78 °C gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 30:1) gave **164** as a colourless oil (4.79 g, 88%, 97:3 dr); $[\alpha]_D^{25}$ +22.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2977 (C−H), 1727 (C=O); δ_H (400 MHz, $CDCl_3$) 1.25 (9H, s, C*Me*$_3$), 1.32 (3H, d, *J* 6.8, C(α)*Me*), 2.48−2.59 (2H, m, C(2)*H*$_2$), 3.70 (2H, app q, J_{AB} 14.9, N*C*H_2), 4.00 (1H, q, *J* 6.8, C(α)*H*), 4.66−4.70 (1H, m, C(3)*H*), 6.90−7.42 (12H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 15.2 (C(α)*Me*), 27.8 (C*Me*$_3$), 38.6 (*C*(2)), 50.7 (N*C*H_2), 53.2 (*C*(α)Me), 57.2 (*C*(3)), 80.6 (*C*Me_3), 105.4, 106.0, 117.2, 126.8, 127.1, 127.9, 128.2, 128.3 (*C*(3′), *C*(6′), *o,m,p-Ph*), 125.6 (*C*(1′)), 141.0, 143.2 (*i-Ph*), 146.6, 150.2, 156.2 (*C*(2′), *C*(4′), *C*(5′)), 170.0 (*C*(1)); *m/z* (ESI^+) 492 ($[M+Na]^+$, 100%), 470 ($[M+H]^+$, 43%); HRMS (ESI^+) $C_{28}H_{30}F_3NNaO_2^+$ ($[M+Na]^+$) requires 492.2121; found 492.2113.

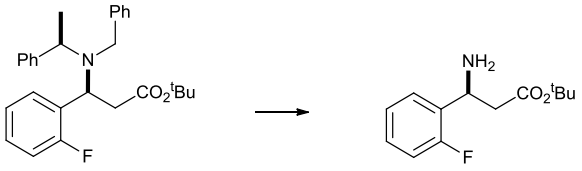
tert-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(pentaphenyl)-propanoate 165



148 165

Following *General Procedure 2a*, BuLi (2.3 M in hexanes, 6.88 mL, 15.8 mmol) and **150** (3.45 g, 16.3 mmol) in THF (80 mL) at −78 °C, and **148** (3.00 g, 10.2 mmol) in THF (50 mL) at −78 °C gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 55:1) gave **165** as a light yellow oil (3.71 g, 72%, 94:6 dr); $[\alpha]_D^{25}$ +35.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2979 (C−H), 1730 (C=O); δ_H (400 MHz, $CDCl_3$) 1.29 (9H, s, C*Me*$_3$), 1.31 (3H, d, *J* 6.8, C(α)*Me*), 2.70 (1H, dd, *J* 15.4, 5.6, C(2)*H*$_A$H$_B$), 2.95 (1H, dd, *J* 15.4, 10.4, C(2)H$_A$*H*$_B$), 3.68−3.86 (2H, m, NC*H*$_2$), 4.14 (1H, q, *J* 6.8, C(α)*H*), 4.79 (1H, dd, *J* 10.4, 5.6, C(3)*H*), 7.12−7.44 (10H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 14.8 (C(α)*Me*), 27.8 (C*Me*$_3$), 38.2 (*C*(2)), 50.9 (N*C*H$_2$), 51.7 (*C*(α)Me), 56.9 (*C*(3)), 80.8 (*C*Me$_3$), 126.8, 127.1, 127.7, 127.8, 128.1, 128.2 (*o,m,p-Ph*), 140.3, 142.9 (*i-Ph*), 170.0 (*C*(1)); *m/z* (ESI$^+$) 528 ([M+Na]$^+$, 98%), 506 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{29}F_5NO_2^+$ ([M+H]$^+$) requires 506.2113; found 506.2107.

tert-Butyl (*S*)-3-amino-3-(2'-fluorophenyl)propanoate 166



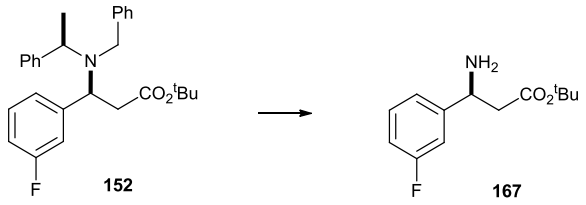
151 166

Method 1: Following *General Procedure 3*, **151** (433 mg, 1.00 mmol), $Pd(OH)_2$/C (50% w/w, 217 mg) and H_2 (1 atm) in MeOH (9 mL) after 36 h gave **166** as a pale yellow oil (227 mg, 95%); $[\alpha]_D^{25}$ −9.3 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 3384 (N–H), 1726 (C=O); δ_H

(500 MHz, $CDCl_3$) 1.40 (9H, s, C*Me*$_3$), 1.99 (2H, br s, N*H*$_2$), 2.60–2.69 (2H, m, C(2)*H*$_2$), 4.60–4.63 (1H, m, C(3)*H*), 7.00–7.04 (1H, m, *Ar*), 7.10–7.13 (1H, m, *Ar*), 7.21–7.25 (1H, m, *Ar*), 7.41–7.43 (1H, m, *Ar*); δ_C (125 MHz, $CDCl_3$) 28.0 (C*Me*$_3$), 43.6 (*C*(2)), 47.0 (*C*(3)), 80.7 (*C*Me$_3$), 115.5, 124.2, 127.6, 128.7 (*C*(3′), *C*(4′), *C*(5′), *C*(6′)), 131.3 (*C*(1′)), 160.3 (*C*(2′)), 171.0 (*C*(1)); *m/z* (ESI^+) 262 ($[M+Na]^+$, 90%), 240 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{13}H_{19}FNO_2^+$ ($[M+H]^+$) requires 240.1394; found 240.1394.

Method 2: Following *General Procedure 3*, **151** (433 mg, 1.00 mmol), $Pd(OH)_2/C$ (6% w/w, 26 mg) and H_2 (5 atm) in MeOH (9 mL) after 24 h gave **166** as a pale yellow oil (220 mg, 92%).

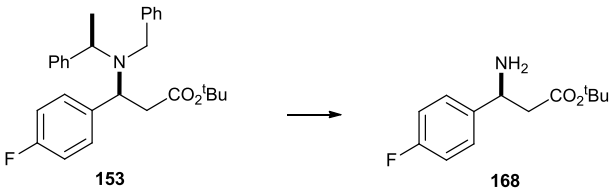
tert-Butyl (*S*)-3-amino-3-(3'-fluorophenyl)propanoate 167



Method 1: Following *General Procedure 3*, **152** (433 mg, 1.00 mmol), $Pd(OH)_2/C$ (50% w/w, 217 mg) and H_2 (1 atm) in MeOH (9 mL) after 9 h gave **167** as a pale yellow oil (217 mg, 91%);[8] $[\alpha]_D^{25}$ –14.0 (*c* 1.0 in $CHCl_3$); {lit. *ent*.[8] $[\alpha]_D^{20}$ +11.6 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.41 (9H, s, C*Me*$_3$), 1.93 (2H, br s, N*H*$_2$), 2.56 (2H, d, *J* 6.8, C(2)*H*$_2$), 4.35–4.39 (1H, m, C(3)*H*), 6.91–7.37 (4H, m, *Ar*);

Method 2: Following *General Procedure 3*, **152** (433 mg, 1.00 mmol), $Pd(OH)_2/C$ (6% w/w, 26 mg) and H_2 (5 atm) in MeOH (9 mL) after 24 h gave **167** as a pale yellow oil (222 mg, 93%).

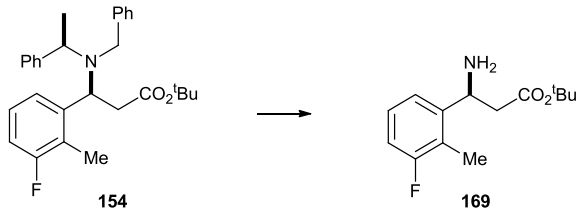
***tert*-Butyl (*S*)-3-amino-3-(4'-fluorophenyl)propanoate 168**



Method 1: Following *General Procedure 3*, **153** (433 mg, 1.00 mmol), $Pd(OH)_2/C$ (50% w/w, 217 mg) and H_2 (1 atm) in MeOH (9 mL) after 48 h gave **168** as a pale yellow oil (222 mg, 93%);[10] $[\alpha]_D^{25}$ –7.9 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 3382 (N–H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.42 (9H, s, C*Me*$_3$), 1.87 (2H, br s, N*H*$_2$), 2.56–2.58 (2H, m, C(2)*H*$_2$), 4.38 (1H, br s, C(3)*H*), 7.00–7.04 (2H, m, C(2′)*H*, C(6′)*H*), 7.32–7.36 (2H, m, C(3′)*H*, C(5′)*H*); δ_C (125 MHz, $CDCl_3$) 28.0 (C*Me*$_3$), 44.8 (*C*(2)), 52.0 (*C*(3)), 80.9 (*C*Me$_3$), 115.3 (*C*(2′), *C*(6′)), 128.0 (*C*(3′), *C*(5′)), 139.5 (*C*(1′)), 162.0 (*C*(4′)), 170.9 (*C*(1)); *m/z* (ESI^+) 262 ($[M+Na]^+$, 61%), 240 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{13}H_{19}FNO_2^+$ ($[M+H]^+$) requires 240.1394; found 240.1395;

Method 2: Following *General Procedure 3*, **153** (433 mg, 1.00 mmol), $Pd(OH)_2/C$ (6% w/w, 26 mg) and H_2 (5 atm) in MeOH (9 mL) after 24 h gave **168** as a pale yellow oil (227 mg, 95%).

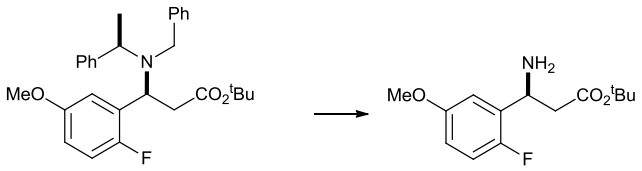
***tert*-Butyl (*S*)-3-amino-3-(3'-fluoro-2'-methylphenyl)propanoate 169**



Following *General Procedure 3*, **154** (447 mg, 1.00 mmol), $Pd(OH)_2/C$ (50% w/w, 224 mg) and H_2 (1 atm) in EtOAc (9 mL) after 15 h gave **169** as a pale yellow oil (243 mg, 96%); $[\alpha]_D^{25}$ –14.4 (*c* 0.50 in $CHCl_3$); ν_{max} (ATR) 3383 (N–H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.43 (9H, s, C*Me*$_3$), 1.75 (2H, br s, N*H*$_2$), 2.28 (3H, s, C(2′)*Me*), 2.52–2.54 (2H, m, C(2)*H*$_2$), 4.59–4.63 (1H, m, C(3)*H*), 6.89–6.94 (1H, m, C(6′)*H*), 7.15

(1H, dd, *J* 7.8, 5.8, C(5′)*H*), 7.24 (1H, d, *J* 7.8, C(4′)*H*); δ_C (100 MHz, $CDCl_3$) 9.9 (C(2′)*Me*), 28.0 (C*Me*$_3$), 44.2 (*C*(2)), 48.2 (*C*(3)), 80.9 (*C*Me$_3$), 113.5 (*C*(6′)), 120.7 (*C*(4′)), 122.0, 145.0 (*C*(1′), *C*(2′)), 127.0 (*C*(5′)), 161.0 (*C*(3′)), 171.3 (*C*(1)); *m/z* (ESI^+) 276 ($[M+Na]^+$, 46%), 254 ($[M+H]^+$, 87%); HRMS (ESI^+) $C_{14}H_{21}FNO_2^+$ ($[M+H]^+$) requires 254.1551; found 254.1551.

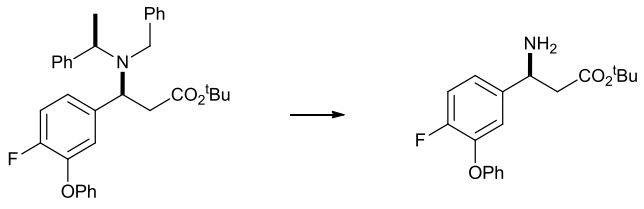
tert-Butyl (*S*)-3-amino-3-(2'-fluoro-5'-methoxyphenyl)propanoate 170



155 **170**

Following *General Procedure 3*, **155** (463 mg, 1.00 mmol), $Pd(OH)_2/C$ (50% w/w, 232 mg) and H_2 (1 atm) in MeOH (9 mL) after 5 h gave **170** as a pale yellow oil (253 mg, 94%); $[\alpha]_D^{25}$ –5.7 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 3384 (N–H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.41 (9H, s, C*Me*$_3$), 2.14 (2H, br s, N*H*$_2$), 2.57–2.68 (2H, m, C(2)*H*$_2$), 3.78 (3H, s, O*Me*), 4.61 (1H, dd, *J* 8.6, 5.1, C(3)*H*), 6.70–6.97 (3H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 28.0 (C*Me*$_3$), 43.5 (*C*(2)), 47.1 (*C*(3)), 55.7 (O*Me*), 80.9 (*C*Me$_3$), 112.5, 113.4, 116.0 (*C*(3′), *C*(4′), *C*(6′)), 132.0 (*C*(1′)), 153.4 (*C*(5′)), 155.8 (*C*(2′)), 171.0 (*C*(1)); *m/z* (ESI^+) 292 ($[M+Na]^+$, 19%), 270 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{14}H_{21}FNO_3^+$ ($[M+H]^+$) requires 270.1500; found 270.1500.

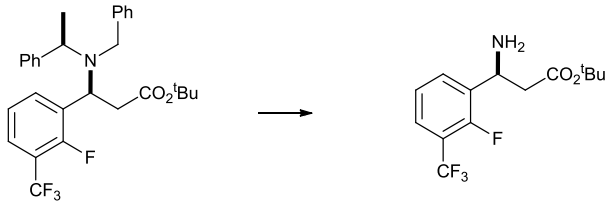
***tert*-Butyl (*S*)-3-amino-3-(4'-fluoro-3'-phenoxyphenyl)propanoate171**



156 **171**

Following *General Procedure 3*, **156** (525 mg, 1.00 mmol), $Pd(OH)_2/C$ (50% w/w, 263 mg) and H_2 (1 atm) in MeOH (11 mL) after 4 h gave **171** as a white powder (318 mg, 96%); mp 42–44 ºC; $[\alpha]_D^{25}$ –18.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3425 (N–H), 1721 (C=O); δ_H (400 MHz, $CDCl_3$) 1.41 (9H, s, C*Me*$_3$), 2.53 (2H, br s, N*H*$_2$), 2.52 (2H, d, *J* 6.8, C(2)*H*$_2$), 4.32 (1H, t, *J* 6.8, C(3)*H*), 7.01–7.36 (8H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 28.1 (C*Me*$_3$), 45.3 (*C*(2)), 52.1 (*C*(3)), 80.9 (*C*Me$_3$), 117.0, 117.2, 119.8, 122.5, 123.1, 129.7 (*C*(2′), *C*(5′), *C*(6′), *o*,*m*,*p*-*Ph*), 141.7, 143.5, 157.3 (*C*(1′), (*C*(3′), *i*-*Ph*), 153.4 (*C*(4′)), 171.0 (*C*(1)); *m/z* (ESI^+) 354 ($[M+Na]^+$, 29%), 332 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{19}H_{23}FNO_3^+$ ($[M+H]^+$) requires 332.1656; found 332.1644.

***tert*-Butyl (*S*)-3-amino-3-(2'-fluoro-3'-(trifluoromethyl)phenyl)propanoate 172**

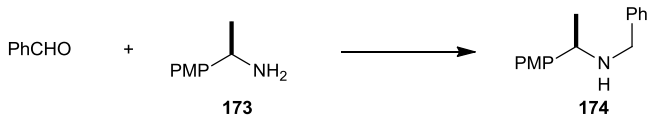


157 **172**

Following *General Procedure 3*, **157** (501 mg, 1.00 mmol), $Pd(OH)_2/C$ (50% w/w, 251 mg) and H_2 (1 atm) in MeOH (10 mL) after 15 h gave **172** as a pale yellow oil (292 mg, 95%); $[\alpha]_D^{25}$ –8.1 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 3385 (N–H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.41 (9H, s, C*Me*$_3$), 1.80 (2H, br s, N*H*$_2$), 2.59–2.70 (2H, m, C(2)*H*$_2$), 4.27 (1H, dd, *J* 8.3, 5.3, C(3)*H*), 7.22–7.26 (1H, m, C(5′)*H*), 7.50–7.53 (1H, m, C(6′)*H*), 7.68–7.71 (1H, m, C(4′)*H*); δ_C (125 MHz, $CDCl_3$) 28.0 (C*Me*$_3$), 43.4 (*C*(2)), 46.4 (*C*(3)), 81.1 (*C*Me$_3$), 118.4 (*C*F$_3$), 121.5, 133.1 (*C*(1′), *C*(3′)), 124.1 (*C*(5′)), 125.9

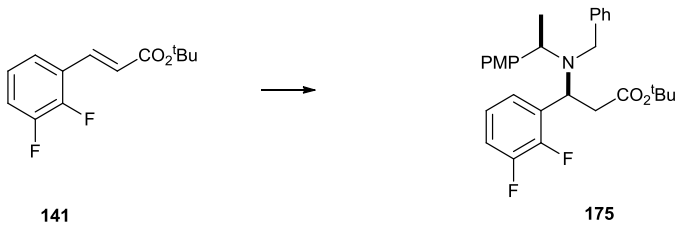
(*C*(6′)), 131.8 (*C*(4′)), 157.0 (*C*(2′)), 170.5 (*C*(1)); *m/z* (ESI$^+$) 330 ([M+Na]$^+$, 12%), 308 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{18}F_4NO_2^+$ ([M+H]$^+$) requires 308.1268; found 308.1267.

(*R*)-*N*-Benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amine 174



Benzaldehyde (14.7 mL, 139 mmol) was added to a solution of (*R*)-α-methyl-*p*-methoxybenzylamine **173** (20.0 mL, 132 mmol) in EtOH (100 mL) at rt and the reaction mixture was then heated at reflux for 3 h. The reaction mixture was allowed to cool to rt and was then further cooled to 0 ºC. $NaBH_4$ (5.03 g, 132 mmol) was added portionwise and the resultant suspension was stirred for 3 d at rt. The reaction mixture was then concentrated *in vacuo* and then resultant residue was partitioned between H_2O (50 mL) and CH_2Cl_2 (80 mL). The organic layer was dried and concentrated *in vacuo*. The residue was slowly added to a solution of Et_2O (100 mL) and 10.0 M aq HCl to give a white solid, which was isolated by filtration and recrystallised to homogeneity (CH_2Cl_2/pentane). The free amine was then regenerated by treatment of the hydrochloride salt with 2.0 M aq NaOH and subsequent extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated in *vacuo* to give **174** as a colorless oil (26.9 g, 85%);[11] $[\alpha]_D^{20}$ +50.6 (*c* 1.3 in $CHCl_3$); {lit.[11] $[\alpha]_D^{22}$ +46.9 (c 1.3 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.36 (3H, d, *J* 6.7, C(α)*Me*), 1.61 (1H, s, N*H*), 3.63 (1H, d, *J* 13.3, NCH_A), 3.71 (1H, d, *J* 13.3, NCH_B), 3.82 (1H, q, *J* 6.7, C(α)*H*), 3.83 (3H, s, O*Me*), 6.88–6.92 (2H, m, C(3)*H*, C(5)*H*), 7.23–7.34 (7H, m, C(2)*H*, C(6)*H*, *Ph*).

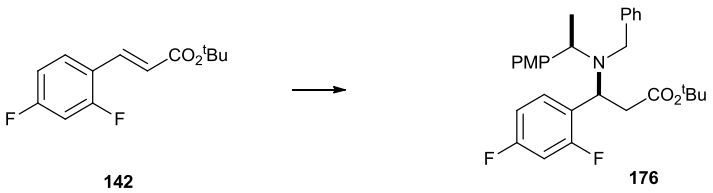
tert-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amino]-3-(2',3'-difluoro-phenyl)propanoate 175



141 **175**

Following *General Procedure 2a*, BuLi (2.5 M in hexanes, 7.75 mL, 19.4 mmol) and **174** (4.83 g, 20.0 mmol) in THF (50 mL) at −78 °C, and **141** (3.00 g, 12.5 mmol) in THF (50 mL) at −78 °C gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 12:1) gave **175** as a colourless oil (4.93 g, 82%, 97:3 dr); $C_{29}H_{33}F_2NO_3$ requires C, 72.3; H, 6.9; N, 2.9%; found C, 72.4; H, 6.8; N, 2.8%; $[\alpha]_D^{25}$ +16.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2977 (C−H), 1723 (C=O), 1511 (OMe bend), 1247 (Ph−O); δ_H (400 MHz, $CDCl_3$) 1.22 (9H, s, C*Me*$_3$), 1.28 (3H, d, *J* 6.8, C(α)*Me*), 2.59−2.61 (2H, m, C(2)*H*$_2$), 3.71 (2H, app q, J_{AB} 14.9, NC*H*$_2$), 3.80 (3H, s, O*Me*), 3.98 (1H, q, *J* 6.8, C(α)*H*), 4.74−4.78 (1H, m, C(3)*H*), 6.86−7.35 (12H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 15.1 (C(α)*Me*), 27.7 (C*Me*$_3$), 38.9 (*C*(2)), 50.7 (N*C*H$_2$), 53.4 (*C*(3)), 55.2 (O*Me*), 56.3 (*C*(α)Me), 80.4 (*C*Me$_3$), 113.4, 115.9, 123.6, 124.0, 126.6, 127.9, 128.1, 128.9 (*C*(4′), *C*(5′), *C*(6′), *C*(2″), *C*(3″), *C*(5″), *C*(6″), *o,m,p-Ph*), 131.5 (*C*(1′)), 135.5, 141.3 (*i-Ph*, *C*(1″)), 148.7, 150.8 (*C*(2′), *C*(3′)), 158.5 (*C*(4″)), 170.3 (*C*(1)); *m/z* (ESI^+) 504 ($[M+Na]^+$, 75%), 482 ($[M+H]^+$, 74%); HRMS (ESI^+) $C_{29}H_{34}F_2NO_3^+$ ($[M+H]^+$) requires 482.2501; found 482.2503.

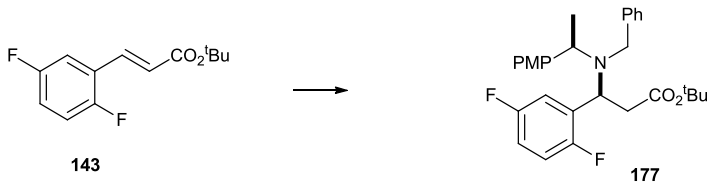
tert-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amino]-3-(2',4'-difluoro-phenyl)propanoate 176



142 176

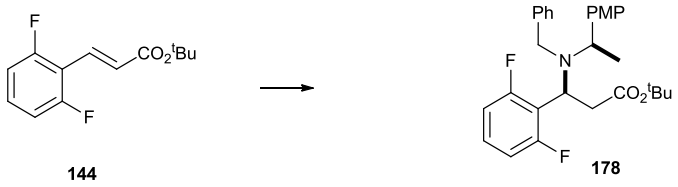
Following *General Procedure 2a*, BuLi (2.5 M in hexanes, 7.75 mL, 19.4 mmol) and **174** (4.83 g, 20.0 mmol) in THF (50 mL) at −78 °C, and **142** (3.00 g, 12.5 mmol) in THF (50 mL) at −78 °C gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 15:1) gave **176** as a colourless oil (5.17 g, 86%, 97:3 dr); $[\alpha]_D^{25}$ +18.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2977 (C−H), 1724 (C=O), 1510 (OMe bend), 1248 (Ph−O); δ_H (400 MHz, $CDCl_3$) 1.22 (9H, s, C*Me*$_3$), 1.27 (3H, d, *J* 6.8, C(α)*Me*), 2.56−2.59 (2H, m, C(2)*H*$_2$), 3.69 (2H, app q, J_{AB} 14.9, NC*H*$_2$), 3.80 (3H, s, O*Me*), 3.96 (1H, q, *J* 6.8, C(α)*H*), 4.67−4.71 (1H, m, C(3)*H*), 6.80−7.39 (12H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 15.0 (C(α)*Me*), 27.7 (C*Me*$_3$), 38.9 (*C*(2)), 50.5 (N*C*H$_2$), 53.4 (*C*(3)), 55.2 (O*Me*), 56.3 (*C*(α)Me), 80.4 (*C*Me$_3$), 103.9, 110.8, 113.4, 126.5, 127.8, 128.1, 128.9, 130.2 (*C*(3′), *C*(5′), *C*(6′), *C*(2″), *C*(3″), *C*(5″), *C*(6″), *o,m,p-Ph*), 124.8 (*C*(1′)), 135.7, 141.5 (*i-Ph*, *C*(1″)), 160.5, 162.8 (*C*(2′), *C*(4′)), 158.5 (*C*(4″)), 170.3 (*C*(1)); *m/z* (ESI^+) 504 ($[M+Na]^+$, 78%), 482 ($[M+H]^+$, 77%); HRMS (ESI^+) $C_{29}H_{34}F_2NO_3^+$ ($[M+H]^+$) requires 482.2501; found 482.2517.

tert-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amino]-3-(2',5'-difluoro-phenyl)propanoate 177



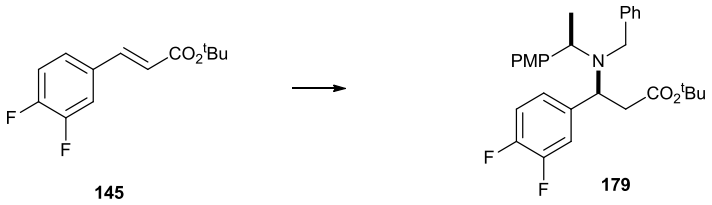
Following *General Procedure 2a*, BuLi (2.5 M in hexanes, 7.75 mL, 19.4 mmol) and **174** (4.83 g, 20.0 mmol) in THF (50 mL) at −78 °C, and **143** (3.00 g, 12.5 mmol) in THF (50 mL) at −78 °C gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 15:1) gave **177** as a yellow oil (5.11 g, 85%, >99:1 dr); $C_{29}H_{33}F_2NO_3$ requires C, 72.3; H, 6.9; N, 2.9%; found C, 68.6; H, 6.0; N, 2.7%; $[\alpha]_D^{25}$ +19.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2977 (C−H), 1724 (C=O), 1511 (OMe bend), 1247 (Ph−O); δ_H (400 MHz, $CDCl_3$) 1.24 (9H, s, C*Me*$_3$), 1.29 (3H, d, *J* 6.8, C(α)*Me*), 2.54−2.58 (2H, m, C(2)*H*$_2$), 3.71 (2H, app q, J_{AB} 14.9, NC*H*$_2$), 3.81 (3H, s, O*Me*), 3.97 (1H, q, *J* 6.8, C(α)*H*), 4.69−4.73 (1H, m, C(3)*H*), 6.86−7.35 (12H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 15.0 (C(α)*Me*), 27.7 (C*Me*$_3$), 38.9 (*C*(2)), 50.5 (N*C*H$_2$), 53.4 (*C*(3)), 55.2 (O*Me*), 56.3 (*C*(α)Me), 80.4 (*C*Me$_3$), 113.4, 115.0, 115.8, 116.6, 126.6, 127.9, 128.1, 128.9 (*C*(3′), *C*(4′), *C*(6′), *C*(2″), *C*(3″), *C*(5″), *C*(6″), *o,m,p-Ph*), 130.6 (*C*(1′)), 135.5, 141.3 (*i-Ph*, *C*(1″)), 156.7, 159.2 (*C*(2′), *C*(5′)), 158.5 (*C*(4″)), 170.3 (*C*(1)); *m/z* (ESI^+) 504 ($[M+Na]^+$, 87%), 482 ($[M+H]^+$, 86%); HRMS (ESI^+) $C_{29}H_{34}F_2NO_3^+$ ($[M+H]^+$) requires 482.2501; found 482.2511.

***tert*-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amino]-3-(2',6'-difluoro-phenyl)propanoate 178**



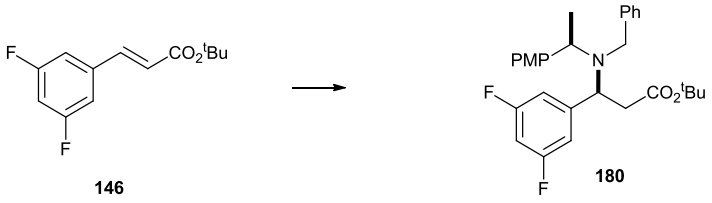
Following *General Procedure 2a*, BuLi (2.5 M in hexanes, 7.75 mL, 19.4 mmol) and **174** (4.83 g, 20.0 mmol) in THF (50 mL) at −78 °C, and **144** (3.00 g, 12.5 mmol) in THF (50 mL) at −78 °C gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 15:1) gave **178** as a colourless oil (5.05 g, 84%, 97:3 dr); $C_{29}H_{33}F_2NO_3$ requires C, 72.3; H, 6.9; N, 2.9%; found C, 72.4; H, 6.7; N, 2.9%; $[\alpha]_D^{25}$ +13.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2977 (C−H), 1725 (C=O), 1511 (OMe bend), 1248 (Ph−O); δ_H (400 MHz, $CDCl_3$) 1.24 (9H, s, C*Me*$_3$), 1.27 (3H, d, *J* 6.8, C(α)*Me*), 2.71 (1H, dd, *J* 14.9, 5.8, C(2)*H*$_A$H$_B$), 2.91−2.97 (1H, m, C(2)H$_A$*H*$_B$), 3.75 (2H, app q, J_{AB} 14.9, NC*H*$_2$), 3.80 (3H, s, O*Me*), 4.14 (1H, q, *J* 6.8, C(α)*H*), 4.80−4.84 (1H, m, C(3)*H*), 6.86−7.40 (12H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 13.7 (C(α)*Me*), 27.7 (C*Me*$_3$), 39.4 (*C*(2)), 50.9 (N*C*H$_2$), 51.6 (*C*(3)), 55.2 (O*Me*), 55.8 (*C*(α)Me), 80.2 (*C*Me$_3$), 111.6, 111.9, 113.3, 126.4, 128.0, 129.0 (*C*(3′), *C*(4′), *C*(5′), *C*(2″), *C*(3″), *C*(5″), *C*(6″), *o,m,p-Ph*), 117.5 (*C*(1′)), 135.9, 141.4 (*i-Ph*, *C*(1″)), 158.3 (*C*(4″)), 160.8, 163.3 (*C*(2′), *C*(6′)), 170.6 (*C*(1)); *m/z* (ESI$^+$) 504 ([M+Na]$^+$, 100%), 482 ([M+H]$^+$, 93%); HRMS (ESI$^+$) $C_{29}H_{34}F_2NO_3^+$ ([M+H]$^+$) requires 482.2501; found 482.2502.

***tert*-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amino]-3-(3',4'-difluoro-phenyl)propanoate 179**



Following *General Procedure 2a*, BuLi (2.5 M in hexanes, 7.75 mL, 19.4 mmol) and **174** (4.83 g, 20.0 mmol) in THF (50 mL) at −78 °C, and **145** (3.00 g, 12.5 mmol) in THF (50 mL) at −78 °C gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 15:1) gave **179** as a white solid (5.17 g, 86%, >99:1 dr);[8] mp 85−86 ºC; {lit.[8] mp 84−86 ºC}; $[\alpha]_D^{25}$ +15.7 (*c* 1.0 in $CHCl_3$); {lit.[8] $[\alpha]_D^{26}$ +13.9 (c 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.25 (9H, s, C*Me*$_3$), 1.29 (3H, d, *J* 6.8, C(α)*Me*), 2.44−2.48 (2H, m, C(2)*H*$_2$), 3.65 (2H, app q, J_{AB} 14.9, NC*H*$_2$), 3.82 (3H, s, O*Me*), 3.92 (1H, q, *J* 6.8, C(α)*H*), 4.37−4.41 (1H, m, C(3)*H*), 6.88−7.31 (12H, m, *Ar*).

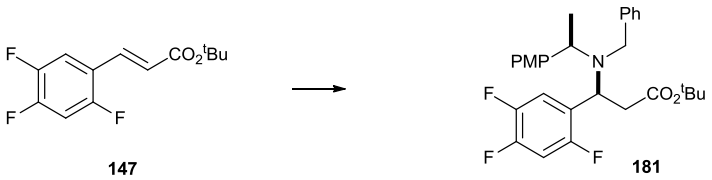
***tert*-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amino]-3-(3',5'-difluoro-phenyl)propanoate 180**



Following *General Procedure 2a*, BuLi (2.5 M in hexanes, 7.75 mL, 19.4 mmol) and **174** (4.83 g, 20.0 mmol) in THF (50 mL) at −78 °C, and **146** (3.00 g, 12.5 mmol) in THF (50 mL) at −78 °C gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 15:1) gave **180** as a colourless oil (4.99 g, 83%, 98:2 dr); $[\alpha]_D^{25}$ +17.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2976 (C−H), 1724 (C=O), 1511 (OMe bend), 1246 (Ph−O); δ_H (400 MHz, $CDCl_3$) 1.31 (9H, s, C*Me*$_3$), 1.31 (3H, d,

J 6.8, C(α)*Me*), 2.44−2.47 (2H, m, C(2)H_2), 3.65 (2H, s, NCH_2), 3.82 (3H, s, O*Me*), 3.92 (1H, q, *J* 6.8, C(α)*H*), 4.40−4.43 (1H, m, C(3)*H*), 6.86−7.35 (12H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 17.5 (C(α)*Me*), 27.9 (C*Me*$_3$), 37.3 (*C*(2)), 50.9 (N*C*H$_2$), 55.2 (O*Me*), 56.7 (*C*(α)Me), 58.3 (*C*(3)), 80.6 (*C*Me$_3$), 102.4, 110.8, 111.1, 113.6, 126.8, 127.9, 128.3, 128.8 (*C*(2′), *C*(4′), *C*(6′), *C*(2″), *C*(3″), *C*(5″), *C*(6″), *o,m,p-Ph*), 146.9 (*C*(1′)), 135.3, 141.1 (*i-Ph*, *C*(1″)), 158.7 (*C*(4″)), 161.6, 164.1 (*C*(3′), *C*(5′)), 170.8 (*C*(1)); *m/z* (ESI$^+$) 504 ([M+Na]$^+$, 91%), 482 ([M+H]$^+$, 79%); HRMS (ESI$^+$) $C_{29}H_{34}F_2NO_3^+$ ([M+H]$^+$) requires 482.2501; found 482.2500.

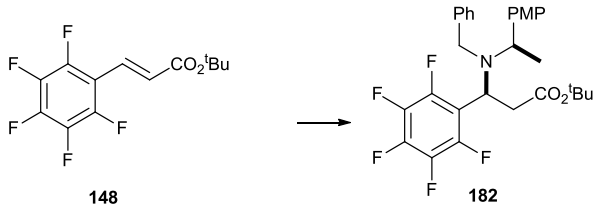
tert-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amino]-3-(2',4',5'-trifluo-rophenyl)propanoate 181



Following *General Procedure 2b*, BuLi (2.5 M in hexanes, 15.0 mL, 37.6 mmol) and **174** (9.06 g, 37.6 mmol) in THF (50 mL) at −78 °C, and **147** (3.23 g, 12.5 mmol) in THF (50 mL) at −78 °C gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 15:1) gave **181** as a yellow solid (4.99 g, 80%, 99:1 dr); $C_{29}H_{32}F_3NO_3$ requires C, 69.7; H, 6.5; N, 2.8%; found C, 70.0; H, 6.5; N, 2.9%; mp 92−93 ºC; $[\alpha]_D^{25}$ +19.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2977 (C−H), 1724 (C=O), 1510 (OMe bend), 1247 (Ph−O); δ_H (400 MHz, $CDCl_3$) 1.31 (9H, s, C*Me*$_3$), 1.35 (3H, d, *J* 6.8, C(α)*Me*), 2.58−2.63 (2H, m, C(2)H_2), 3.74 (2H, app q, J_{AB} 14.9, NCH_2), 3.83 (3H, s, O*Me*), 4.01 (1H, q, *J* 6.8, C(α)*H*), 4.72−4.77 (1H, m, C(3)*H*), 6.92−7.39 (11H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 15.4 (C(α)*Me*), 27.8 (C*Me*$_3$), 38.6 (*C*(2)), 50.6 (N*C*H$_2$), 53.1 (*C*(3)), 55.2 (O*Me*), 56.6 (*C*(α)Me), 80.6 (*C*Me$_3$), 105.6, 113.5, 117.1, 126.7, 127.9, 128.2, 128.9 (*C*(3′), *C*(6′), *C*(2″), *C*(3″), *C*(5″), *C*(6″), *o,m,p-Ph*), 125.5 (*C*(1′)), 135.3, 141.1 (*i-Ph*, *C*(1″)), 146.6, 150.5, 156.2 (*C*(2′), *C*(4′), *C*(5′)),

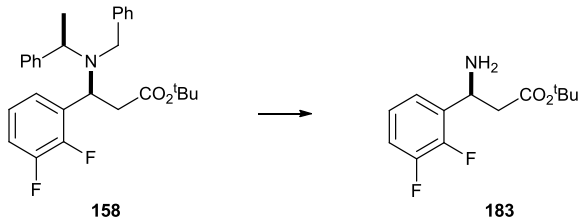
158.6 (*C*(4″)), 170.2 (*C*(1)); *m/z* (ESI$^+$) 522 ([M+Na]$^+$, 96%), 500 ([M+H]$^+$, 94%); HRMS (ESI$^+$) $C_{29}H_{32}F_3NNaO_3^+$ ([M+Na]$^+$) requires 522.2226; found 522.2233.

tert-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amino]-3-(pentaphen-yl)propanoate 182

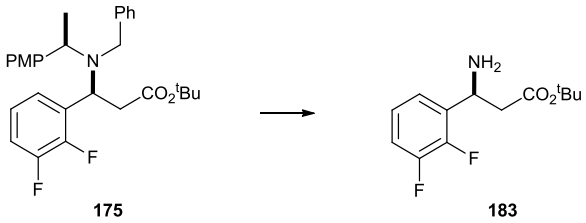


Following *General Procedure 2a*, BuLi (2.5 M in hexanes, 7.76 mL, 19.4 mmol) and **174** (4.83 g, 20.0 mmol) in THF (50 mL) at −78 °C, and **148** (3.68 g, 12.5 mmol) in THF (50 mL) at −78 °C gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 15:1) gave **182** as a yellow oil (5.35 g, 80%, 86:14 dr); $[\alpha]_D^{25}$ +22.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2978 (C−H), 1727 (C=O), 1511 (OMe bend), 1248 (Ph−O); δ_H (400 MHz, $CDCl_3$) 1.29 (9H, s, C*Me*$_3$), 1.30 (3H, d, *J* 6.8, C(α)*Me*), 2.70 (1H, dd, *J* 15.4, 5.6, C(2)*H*$_A$H$_B$), 2.92−2.99 (1H, m, C(2)H$_A$*H*$_B$), 3.66−3.86 (2H, m, NC*H*$_2$), 3.82 (3H, s, O*Me*), 4.09 (1H, q, *J* 6.8, C(α)*H*), 4.78−4.82 (1H, m, C(3)*H*), 6.82−7.36 (9H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 14.9 (C(α)*Me*), 27.8 (C*Me*$_3$), 38.1 (*C*(2)), 50.8 (N*C*H$_2$), 51.6 (*C*(3)), 55.2 (O*Me*), 56.2 (*C*(α)Me), 80.9 (*C*Me$_3$), 113.5, 126.7, 127.8, 128.1, 128.8 (*C*(2″), *C*(3″), *C*(5″), *C*(6″), *o*,*m*,*p*-*Ph*), 115.3 (*C*(1′)), 134.9, 140.4 (*i*-*Ph*, *C*(1″)), 137.3, 140.2, 145.6 (*C*(2′), *C*(3′), *C*(4′), *C*(5′), *C*(6′)), 158.6 (*C*(4″)), 170.0 (*C*(1)); *m/z* (ESI$^+$) 558 ([M+Na]$^+$, 100%), 536 ([M+H]$^+$, 66%); HRMS (ESI$^+$) $C_{29}H_{30}F_5NNaO_3^+$ ([M+Na]$^+$) requires 558.2038; found 558.2048.

***tert*-Butyl (*S*)-3-amino-3-(2',3'-difluorophenyl)propanoate 183**

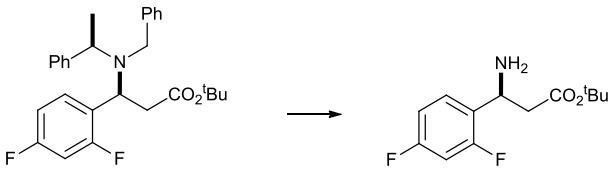


Method 1: Following *General Procedure 3*, **158** (451 mg, 1.00 mmol), $Pd(OH)_2/C$ (6% w/w, 27 mg) and H_2 (5 atm) in MeOH (8 mL) after 24 h gave **183** as a pale yellow oil (242 mg, 94%); $[\alpha]_D^{25}$ –22.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3312 (N–H), 1724 (C=O); δ_H (500 MHz, $CDCl_3$) 1.32 (9H, s, C*Me*$_3$), 1.82 (2H, br s, N*H*$_2$), 2.53–2.56 (2H, m, C(2)*H*$_2$), 4.55 (1H, br s, C(3)*H*), 6.94–7.11 (3H, m, *Ar*); δ_C (125 MHz, $CDCl_3$) 27.8 (C*Me*$_3$), 43.5 (*C*(2)), 46.7 (*C*(3)), 80.8 (*C*Me$_3$), 115.7, 122.2, 124.0 (*C*(4′), *C*(5′), *C*(6′)), 134.0 (*C*(1′)), 148.2, 150.5 (*C*(2′), *C*(3′)), 170.6 (*C*(1)); *m/z* (ESI^+) 280 ($[M+Na]^+$, 92%), 258 ($[M+H]^+$, 91%); HRMS (ESI^+) $C_{13}H_{18}F_2NO_2^+$ ($[M+H]^+$) requires 258.1300; found 258.1300.



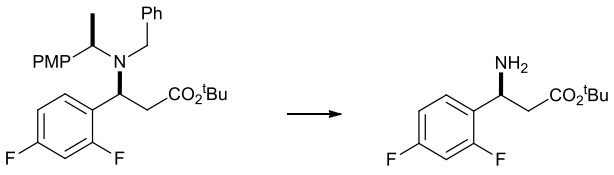
Method 2: Following *General Procedure 4*, **175** (481 mg, 1.00 mmol), CAN (3.29 g, 6.00 mmol) in $MeCN/H_2O$ (v/v, 5:1, 30 mL) after 16 h gave the crude reaction mixture. Purification via flash column chromatography (eluent hexane/Et_2O, 1:2) gave **183** (with 10% unknown impurities) as a pale yellow oil (200 mg, 78%).

***tert*-Butyl (*S*)-3-amino-3-(2',4'-difluorophenyl)propanoate 184**



159 **184**

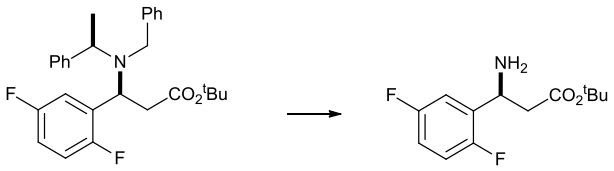
Method 1: Following *General Procedure 3*, **159** (451 mg, 1.00 mmol), $Pd(OH)_2/C$ (6% w/w, 27 mg) and H_2 (5 atm) in MeOH (8 mL) after 24 h gave **184** as a pale yellow oil (239 mg, 93%); $[\alpha]_D^{25}$ −13.0 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 3312 (N–H), 1724 (C=O); δ_H (500 MHz, $CDCl_3$) 1.42 (9H, s, C*Me*$_3$), 1.76 (2H, br s, N*H*$_2$), 2.60–2.62 (2H, m, C(2)*H*$_2$), 4.59 (1H, t, *J* 6.1, C(3)*H*), 6.76–6.80 (1H, m, *Ar*), 6.84–6.87 (1H, m, *Ar*), 7.38–7.43 (1H, m, *Ar*); δ_C (125 MHz, $CDCl_3$) 28.0 (C*Me*$_3$), 43.6 (*C*(2)), 46.6 (*C*(3)), 80.9 (*C*Me$_3$), 103.8, 111.4, 128.7 (*C*(3′), *C*(5′), *C*(6′)), 127.5 (*C*(1′)), 160.1, 162.1 (*C*(2′), *C*(4′)), 170.8 (*C*(1)); *m/z* (ESI^+) 280 ($[M+Na]^+$, 53%), 258 ($[M+H]^+$, 78%); HRMS (ESI^+) $C_{13}H_{18}F_2NO_2^+$ ($[M+H]^+$) requires 258.1300; found 258.1298.



176 **184**

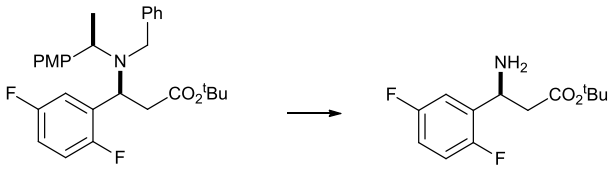
Method 2: Following *General Procedure 4*, **176** (481 mg, 1.00 mmol), CAN (3.29 g, 6.00 mmol) in MeCN/H_2O (v/v, 5:1, 30 mL) after 16 h gave the crude reaction mixture. Purification via flash column chromatography (eluent hexane/Et_2O, 1:2) gave **184** (with 15% unknown impurities) as a pale yellow oil (188 mg, 73%).

***tert*-Butyl (*S*)-3-amino-3-(2',5'-difluorophenyl)propanoate 185**



160 **185**

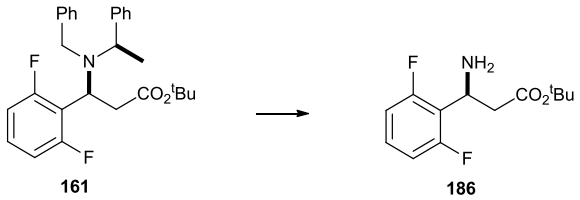
Method 1: Following *General Procedure 3*, **160** (451 mg, 1.00 mmol), $Pd(OH)_2/C$ (6% w/w, 27 mg) and H_2 (5 atm) in MeOH (8 mL) after 24 h gave **185** as a pale yellow oil (244 mg, 95%); $[\alpha]_D^{25}$ –13.6 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 3309 (N–H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.41 (9H, s, C*Me*$_3$), 2.34 (2H, br s, N*H*$_2$), 2.58–2.63 (2H, m, C(2)*H*$_2$), 4.58–4.61 (1H, m, C(3)*H*), 6.86–6.92 (1H, m, *Ar*), 6.95–7.00 (1H, m, *Ar*), 7.14–7.19 (1H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 28.0 (C*Me*$_3$), 43.4 (*C*(2)), 46.6 (*C*(3)), 81.0 (*C*Me$_3$), 114.3, 114.8, 116.5 (*C*(3′), *C*(4′), *C*(6′)), 128.3 (*C*(1′)), 157.4, 159.8 (*C*(2′), *C*(5′)), 170.7 (*C*(1)); *m/z* (ESI^+) 280 ($[M+Na]^+$, 51%), 258 ($[M+H]^+$, 66%); HRMS (ESI^+) $C_{13}H_{18}F_2NO_2^+$ ($[M+H]^+$) requires 258.1300; found 258.1301.



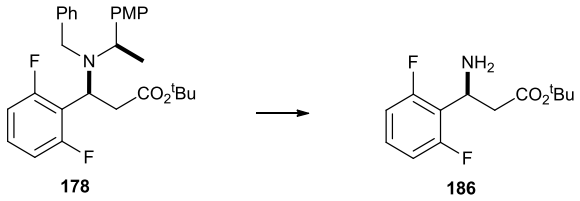
177 **185**

Method 2: Following *General Procedure 4*, **177** (481 mg, 1.00 mmol), CAN (3.29 g, 6.00 mmol) in $MeCN/H_2O$ (v/v, 5:1, 30 mL) after 16 h gave the crude reaction mixture. Purification via flash column chromatography (eluent hexane/Et_2O, 1:2) gave **185** (with 10% unknown impurities) as a pale yellow oil (203 mg, 79%).

***tert*-Butyl (*S*)-3-amino-3-(2',6'-difluorophenyl)propanoate 186**

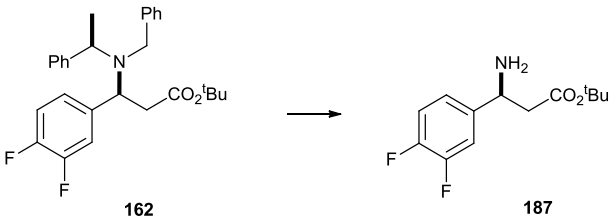


Method 1: Following *General Procedure 3*, **161** (451 mg, 1.00 mmol), $Pd(OH)_2/C$ (6% w/w, 27 mg) and H_2 (5 atm) in MeOH (8 mL) after 24 h gave **186** as a pale yellow oil (239 mg, 93%); $[\alpha]_D^{25}$ −14.2 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 3308 (N–H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.36 (9H, s, C*Me*$_3$), 2.16 (2H, br s, N*H*$_2$), 2.68 (1H, dd, *J* 15.4, 6.3, C(2)*H*$_A$H$_B$), 2.80–2.86 (1H, m, C(2)H$_A$*H*$_B$), 4.68–4.72 (1H, m, C(3)*H*), 6.82–6.86 (2H, m, *Ar*), 7.14–7.18 (1H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 28.0 (C*Me*$_3$), 43.3 (*C*(2)), 44.0 (*C*(3)), 80.8 (*C*Me$_3$), 111.7, 128.7 (*C*(3′), *C*(4′), *C*(5′)), 119.9 (*C*(1′)), 159.8, 162.2 (*C*(2′), *C*(6′)), 170.5 (*C*(1)); *m/z* (ESI^+) 280 ($[M+Na]^+$, 97%), 258 ($[M+H]^+$, 73%); HRMS (ESI^+) $C_{13}H_{18}F_2NO_2^+$ ($[M+H]^+$) requires 258.1300; found 258.1302.



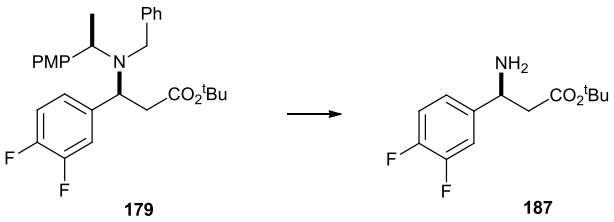
Method 2: Following *General Procedure 4*, **178** (481 mg, 1.00 mmol), CAN (3.29 g, 6.00 mmol) in MeCN/H_2O (v/v, 5:1, 30 mL) after 16 h gave the crude reaction mixture. Purification via flash column chromatography (eluent hexane/Et_2O, 1:2) gave **186** (with 15% unknown impurities) as a pale yellow oil (193 mg, 79%).

***tert*-Butyl (*S*)-3-amino-3-(3',4'-difluorophenyl)propanoate 187**



162 **187**

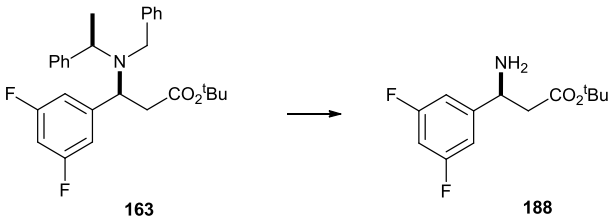
Method 1: Following *General Procedure 3*, **162** (451 mg, 1.00 mmol), $Pd(OH)_2/C$ (6% w/w, 27 mg) and H_2 (5 atm) in MeOH (8 mL) after 24 h gave **187** as a colourless solid (234 mg, 91%);[12] mp 31–33 °C; $[\alpha]_D^{25}$ −21.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3310 (N–H), 1717 (C=O); δ_H (400 MHz, $CDCl_3$) 1.35 (9H, s, C*Me*$_3$), 1.70 (2H, br s, N*H*$_2$), 2.44–2.46 (2H, m, C(2)*H*$_2$), 4.26–4.28 (1H, m, C(3)*H*), 6.97–7.19 (3H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 27.9 (C*Me*$_3$), 45.1 (*C*(2)), 51.8 (*C*(3)), 80.8 (*C*Me$_3$), 115.2, 116.8, 122.2 (*C*(2′), *C*(5′), *C*(6′)), 141.9 (*C*(1′)), 148.6, 150.9 (*C*(3′), *C*(4′)), 170.7 (*C*(1)); *m/z* (ESI^+) 280 ($[M+Na]^+$, 63%), 258 ($[M+H]^+$, 65%); HRMS (ESI^+) $C_{13}H_{18}F_2NO_2^+$ ($[M+H]^+$) requires 258.1300; found 258.1300.



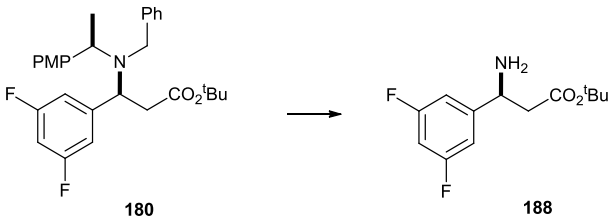
179 **187**

Method 2: Following *General Procedure 4*, **179** (481 mg, 1.00 mmol), CAN (3.29 g, 6.00 mmol) in $MeCN/H_2O$ (v/v, 5:1, 30 mL) after 16 h gave the crude reaction mixture. Purification via flash column chromatography (eluent hexane/Et_2O, 1:2) gave **187** (with 10% unknown impurities) as a colourless solid (188 mg, 73%).

***tert*-Butyl (*S*)-3-amino-3-(3',5'-difluorophenyl)propanoate 188**

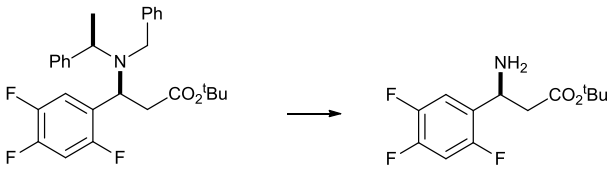


Method 1: Following *General Procedure 3*, **163** (451 mg, 1.00 mmol), $Pd(OH)_2/C$ (6% w/w, 27 mg) and H_2 (5 atm) in MeOH (8 mL) after 24 h gave **188** as a light yellow oil (231 mg, 90%); $[\alpha]_D^{25}$ −12.6 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 3314 (N–H), 1724 (C=O); δ_H (500 MHz, $CDCl_3$) 1.42 (9H, s, C*Me*$_3$), 1.73 (2H, br s, N*H*$_2$), 2.51–2.53 (2H, m, C(2)*H*$_2$), 4.33–4.35 (1H, m, C(3)*H*), 6.65–6.69 (1H, m, *Ar*), 6.89–6.91 (2H, m, *Ar*); δ_C (125 MHz, $CDCl_3$) 28.0 (C*Me*$_3$), 45.0 (*C*(2)), 52.2 (*C*(3)), 81.2 (*C*Me$_3$), 102.5, 109.1, 109.2 (*C*(2′), *C*(4′), *C*(6′)), 148.9 (*C*(1′)), 161.9, 164.1 (*C*(3′), *C*(5′)), 170.7 (*C*(1)); *m/z* (ESI^+) 280 ($[M+Na]^+$, 41%), 258 ($[M+H]^+$, 45%); HRMS (ESI^+) $C_{13}H_{18}F_2NO_2^+$ ($[M+H]^+$) requires 258.1300; found 258.1295.



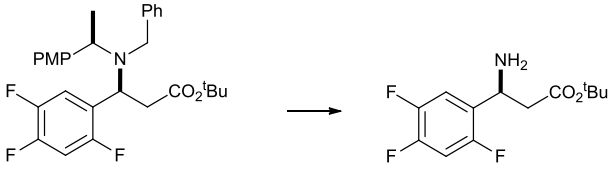
Method 2: Following *General Procedure 4*, **180** (481 mg, 1.00 mmol), CAN (3.29 g, 6.00 mmol) in MeCN/H_2O (v/v, 5:1, 30 mL) after 16 h gave the crude reaction mixture. Purification via flash column chromatography (eluent hexane/Et_2O, 1:2) gave **188** (with 15% unknown impurities) as a pale yellow oil (188 mg, 73%).

***tert*-Butyl (*S*)-3-amino-3-(2',4',5'-trifluorophenyl)propanoate 189**



164 **189**

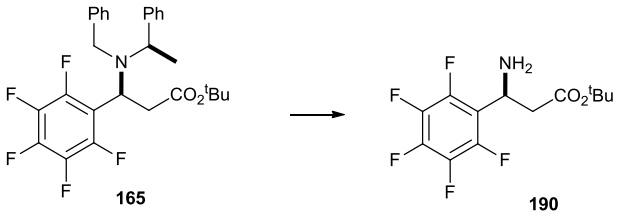
Method 1: Following *General Procedure 3*, **164** (469 mg, 1.00 mmol), $Pd(OH)_2/C$ (6% w/w, 28 mg) and H_2 (5 atm) in MeOH (9 mL) after 24 h gave **189** as a pale yellow solid (256 mg, 93%); mp 60–62 ºC; $[\alpha]_D^{25}$ –19.9 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 3358 (N–H), 1729 (C=O); δ_H (500 MHz, $CDCl_3$) 1.43 (9H, s, C*Me*$_3$), 1.75 (2H, br s, N*H*$_2$), 2.54 (1H, dd, *J* 15.9, 8.6, C(2)*H*$_A$H$_B$), 2.62 (1H, dd, *J* 15.9, 4.8, C(2)H$_A$*H*$_B$), 4.59 (1H, dd, *J* 8.6, 4.8, C(3)*H*), 6.87–6.92 (1H, m, *Ar*), 7.30–7.35 (1H, m, *Ar*); δ_C (125 MHz, $CDCl_3$) 27.9 (C*Me*$_3$), 43.5 (*C*(2)), 46.0 (*C*(3)), 81.1 (*C*Me$_3$), 105.5, 115.8 (*C*(3′), *C*(6′)), 128.1 (*C*(1′)), 146.8, 148.8, 154.8 (*C*(2′), *C*(4′), *C*(5′)), 170.7 (*C*(1)); *m/z* (ESI$^+$) 298 ([M+Na]$^+$, 55%), 276 ([M+H]$^+$, 36%); HRMS (ESI$^+$) $C_{13}H_{16}F_3NNaO_2^+$ ([M+Na]$^+$) requires 298.1025; found 298.1020.



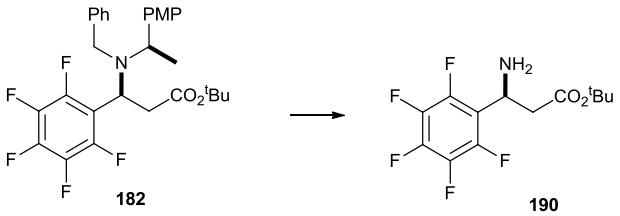
181 **189**

Method 2: Following *General Procedure 4*, **181** (499 mg, 1.00 mmol), CAN (3.29 g, 6.00 mmol) in MeCN/H_2O (v/v, 5:1, 30 mL) after 16 h gave the crude reaction mixture. Purification via flash column chromatography (eluent hexane/Et_2O, 1:2) gave **189** (with 15% unknown impurities) as a pale yellow solid (217 mg, 79%).

tert-Butyl (*S*)-3-amino-3-(pentafluorophenyl)propanoate 190

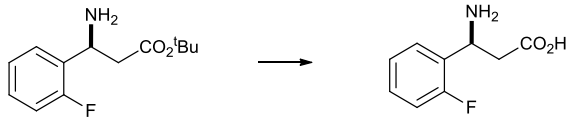


Method 1: Following *General Procedure 3*, **165** (505 mg, 1.00 mmol), $Pd(OH)_2/C$ (26% w/w, 131 mg) and H_2 (5 atm) in MeOH (9 mL) after 24 h gave **190** as a pale yellow oil (292 mg, 94%); $[\alpha]_D^{25}$ –26.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3356 (N–H), 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 1.41 (9H, s, C*Me*$_3$), 2.18 (2H, br s, N*H*$_2$), 2.70 (1H, dd, *J* 15.7, 6.6, C(2)*H*$_A$H$_B$), 2.82–2.88 (1H, m, C(2)H$_A$*H*$_B$), 4.69–4.73 (1H, m, C(3)*H*); δ_C (100 MHz, $CDCl_3$)[XX] 28.0 (C*Me*$_3$), 42.9 (*C*(2)), 44.3 (*C*(3)), 81.4 (*C*Me$_3$), 169.8 (*C*(1)); *m/z* (ESI^+) 334 ($[M+Na]^+$, 71%), 312 ($[M+H]^+$, 37%); HRMS (ESI^+) $C_{13}H_{15}F_5NO_2^+$ ($[M+H]^+$) requires 312.1017; found 312.1012.



Method 2: Following *General Procedure 4*, **182** (535 mg, 1.00 mmol), CAN (3.29 g, 6.00 mmol) in MeCN/H_2O (v/v, 5:1, 30 mL) after 16 h gave the crude reaction mixture. Purification via flash column chromatography (eluent hexane/Et_2O, 1:2) gave **190** (with 15% unknown impurities) as a pale yellow oil (236 mg, 76%).

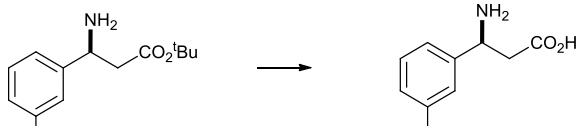
(*S*)-3-Amino-3-(2'-fluorophenyl)propanoic acid 191



166 **191**

Following *General Procedure 5*, 2 M HCl (15 mL) and **166** (184 mg, 0.77 mmol) refluxing 6 h gave the crude reaction mixture. Evaporation and purification via ion exchange chromatography (Dowex 50 WX8-100, eluent 1.0 M aq NH_4OH) gave **191** as a white powder (135 mg, 96%);[13] mp 239–240 ºC; {lit. *ent*.[14] mp 247 ºC};$[\alpha]_D^{25}$ –2.7 (*c* 0.30 in H_2O); {lit. *ent*.[14] $[\alpha]_D^{22}$ +3.0 (*c* 0.3 in H_2O)}; δ_H (400 MHz, D_2O) 2.77 (1H, dd, *J* 16.2, 6.8, C(2)H_AH_B), 2.87 (1H, dd, *J* 16.2, 8.1, C(2)H_AH_B), 4.80–4.84 (1H, m, C(3)*H*), 7.11–7.22 (2H, m, *Ar*), 7.35–7.42 (2H, m, *Ar*).

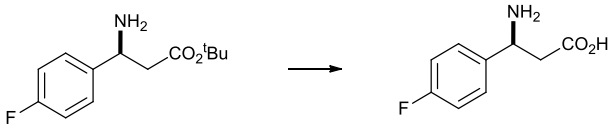
(*S*)-3-Amino-3-(3'-fluorophenyl)propanoic acid 192



167 **192**

Following *General Procedure 5*, 2 M HCl (15 mL) and **167** (184 mg, 0.77 mmol) refluxing 6 h gave the crude reaction mixture. Evaporation and purification via ion exchange chromatography (Dowex 50WX8-100, eluent 1.0 M aq NH_4OH) gave **192** as a white powder (137 mg, 97%);[14] mp 220–223 ºC; {lit.[15] mp 226–229 ºC}; $[\alpha]_D^{25}$ –2.0 (*c* 0.4 in H_2O); {lit.[15] $[\alpha]_D^{25}$ –1.8 (*c* 0.4 in H_2O)}; δ_H (400 MHz, D_2O) 2.72 (1H, dd, *J* 16.2, 6.8, C(2)H_AH_B), 2.80 (1H, dd, *J* 16.2, 7.8, C(2)H_AH_B), 4.55–4.58 (1H, m, C(3)*H*), 7.06–7.42 (4H, m, *Ar*).

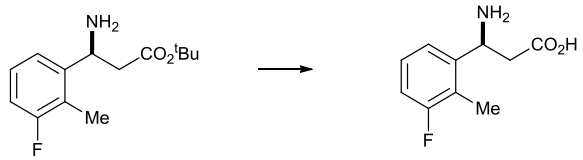
(*S*)-3-Amino-3-(4'-fluorophenyl)propanoic acid 193



168 **193**

Following *General Procedure 5*, 2 M HCl (15 mL) and **168** (184 mg, 0.77 mmol) refluxing 6 h gave the crude reaction mixture. Evaporation and purification via ion exchange chromatography (Dowex 50 WX8-100, eluent 1.0 M aq NH_4OH) gave **193** as a white powder (135 mg, 96%);[13] mp 220–221 ºC; {lit.[13] mp 220–222 ºC}; $[\alpha]_D^{25}$ –5.6 (*c* 0.5 in H_2O); {lit.[13] $[\alpha]_D^{22}$ –4.0 (*c* 0.5 in H_2O)}; δ_H (400 MHz, AcOH-d_4) 3.15–3.20 (1H, m, C(2)H_AH_B), 3.48–3.55 (1H, m, C(2)H_AH_B), 4.94 (1H, br s, C(3)*H*), 7.16–7.20 (2H, m, C(2′)*H*, C(6′)*H*), 7.66–7.67 (2H, m, C(3′)*H*, C(5′)*H*).

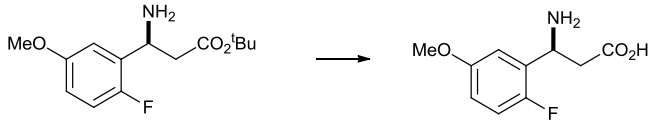
(*S*)-3-Amino-3-(3'-fluoro-2'-methylphenyl)propanoic acid 194



169 **194**

Following *General Procedure 5*, 2 M HCl (19 mL) and **169** (253 mg, 1.00 mmol) refluxing 6 h gave the crude reaction mixture. Evaporation and purification via ion exchange chromatography (Dowex 50 WX8-100, eluent 1.0 M aq NH_4OH) gave **194** as a beige powder (187 mg, 95%);[15] mp 228–230 ºC; $[\alpha]_D^{25}$ –15.6 (*c* 0.5 in H_2O); ν_{max} (ATR) 3418br (O–H, N–H), 1647 (C=O); δ_H (400 MHz, AcOH-d_4) 2.35 (3H, s, C(2′)*Me*), 2.87–3.00 (1H, m, C(2)H_AH_B), 3.08–3.39 (1H, m, C(2)H_AH_B), 5.17–5.68 (1H, m, C(3)*H*), 6.97–7.48 (3H, m, *Ar*); δ_C (100 MHz, AcOH-d_4) 9.5 (C(2′) *Me*), 38.2 (*C*(2)), 48.0 (*C*(3)), 115.9, 122.2, 128.2 (*C*(4′), *C*(5′), *C*(6′)), 124.3, 136.9 (*C*(1′), *C*(2′))), 162.0 (*C*(3′)), 175.9 (*C*(1)); *m/z* (ESI^+) 220 ($[M+Na]^+$, 92%), 198 ($[M+H]^+$, 83%); HRMS (ESI^+) $C_{10}H_{13}FNO_2^+$ ($[M+H]^+$) requires 198.0925; found 198.0925.

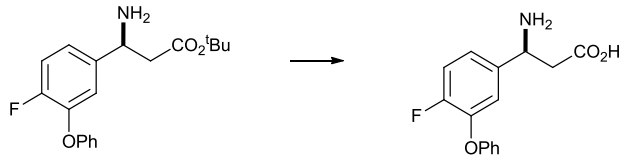
(*S*)-3-Amino-3-(2'-fluoro-5'-methoxyphenyl)propanoic acid 195



170 **195**

Following *General Procedure 5*, 2 M HCl (20 mL) and **170** (276 mg, 1.03 mmol) refluxing 6 h gave the crude reaction mixture. Evaporation and purification via ion exchange chromatography (Dowex 50 WX8-100, eluent 1.0 M aq NH_4OH) gave **195** as a light yellow powder (206 mg, 94%);[16] mp 189–191 ºC; $[\alpha]_D^{25}$ –3.8 (*c* 0.5 in H_2O); ν_{max} (ATR) 3425 br (O–H, N–H), 1641 (C=O); δ_H (400 MHz, D_2O) 2.85 (1H, dd, *J* 16.7, 6.8, C(2)H_AH_B), 2.96 (1H, dd, *J* 16.7, 7.8, C(2)H_AH_B), 3.73 (3H, s, O*Me*), 4.80–4.84 (1H, m, C(3)*H*), 6.93–7.l2 (3H, m, *Ar*); δ_C (125 MHz, D_2O) 38.0 (*C*(2)), 46.7 (*C*(3)), 56.0 (O*Me*), 113.4, 116.4, 117.0 (*C*(3′), *C*(4′), *C*(6′)), 123.0 (*C*(1′)), 154.6 (*C*(2′), 155.3 (*C*(5′)), 175.1 (*C*(1)); *m/z* (ESI^+) 236 ($[M+Na]^+$, 87%), 214 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{10}H_{13}FNO_3^+$ ($[M+H]^+$) requires 214.0874; found 214.0875.

(*S*)-3-Amino-3-(4'-fluoro-3'-phenoxyphenyl)propanoic acid 196

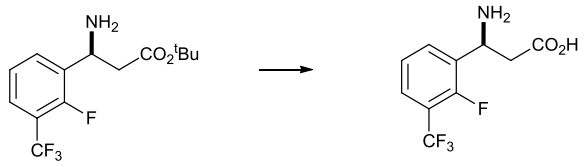


171 **196**

Following *General Procedure 5*, 2 M HCl (19 mL) and **171** (331 mg, 1.00 mmol) refluxing 6 h gave the crude reaction mixture. Evaporation and purification via ion exchange chromatography (Dowex 50 WX8-100, eluent 1.0 M aq NH_4OH) gave **196** as a white powder (267 mg, 97%);[17] mp >370 ºC; $[\alpha]_D^{25}$ –12.0 (*c* 0.5 in H_2O); ν_{max} (ATR) 3418 br (O–H, N–H), 1642 (C=O); δ_H (400 MHz, AcOH-d_4) 3.09 (1H, dd, *J* 17.4, 5.6, C(2)H_AH_B), 3.34 (1H, dd, *J* 17.4, 8.3, C(2)H_AH_B), 4.85–4.89 (1H, m, C(3)*H*), 7.00–7.38 (8H, m, *Ar*); δ_C (100 MHz, AcOH-d_4) 37.8 (*C*(2)), 51.8 (*C*(3)), 117.5, 117.9, 121.9, 123.8, 124.8, 130.2 (*C*(2′), *C*(5′), *C*(6′), *o,m,p-Ph*), 132.9, 143.0, 157.4 (*C*(1′), (*C*(3′), *i*-

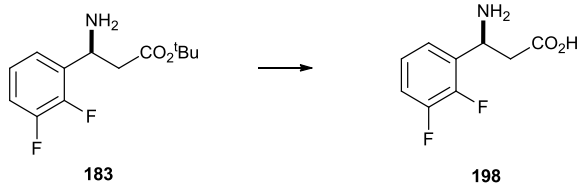
Ph), 154.6 (*C*(4′)), 174.9 (*C*(1)); *m/z* (ESI^+) 298 ($[M+Na]^+$, 79%), 276 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{15}H_{15}FNO_3^+$ ($[M+H]^+$) requires 276.1030; found 276.1032.

(*S*)-3-Amino-3-(2'-fluoro-3'-(trifluoromethyl)phenyl)propanoic acid 197



Following *General Procedure 5*, 2 M HCl (19 mL) and **172** (307 mg, 1.00 mmol) refluxing 6 h gave the crude reaction mixture. Evaporation and purification via ion exchange chromatography (Dowex 50WX8-100, eluent 1.0 M aq NH_4OH) gave **197** as a white solid (239 mg, 95%);[18] mp 207–208 ºC; {lit.[18] mp 206 ºC}; $[\alpha]_D^{25}$ –1.7 (*c* 0.5 in H_2O); δ_H (400 MHz, AcOH-d_4) 3.29 (1H, dd, *J* 17.6, 6.0, C(2)H_AH_B), 3.61 (1H, dd, *J* 17.6, 7.2, C(2)H_AH_B), 5.29–5.32 (1H, m, C(3)*H*), 7.48 (1H, t, *J* 7.2, *Ar*), 7.78 (1H, t, *J* 7.0, *Ar*), 8.17 (1H, br s, *Ar*).

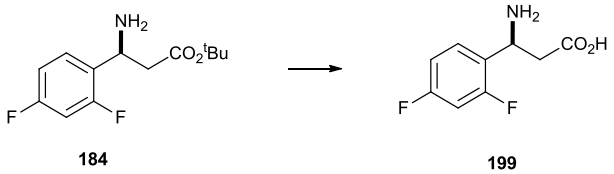
(*S*)-3-Amino-3-(2',3'-difluorophenyl)propanoic acid 198



Following *General Procedure 5*, 2 M HCl (15 mL) and **183** (198 mg, 0.77 mmol) refluxing 6 h gave the crude reaction mixture. Evaporation and purification via ion exchange chromatography (Dowex 50WX8-100, eluent 1.0 M aq NH_4OH) gave **198** as a beige powder (149 mg, 96%);[19] mp 200–202 ºC; $[\alpha]_D^{25}$ –2.5 (*c* 0.5 in H_2O); ν_{max} (ATR) 3429br (O–H, N–H), 1623 (C=O); δ_H (500 MHz, AcOH-d_4) 3.20 (1H, dd, *J* 17.7, 6.3, C(2)H_AH_B), 3.51 (1H, dd, *J* 17.7, 7.6, C(2)H_AH_B), 4.95–4.97 (1H, m, C(3)*H*), 7.31–7.63 (3H, m, *Ar*); δ_C (125 MHz, AcOH-d_4) 36.8 (*C*(2)), 45.7 (*C*(3)), 113.7(*C*(1′)), 118.2,

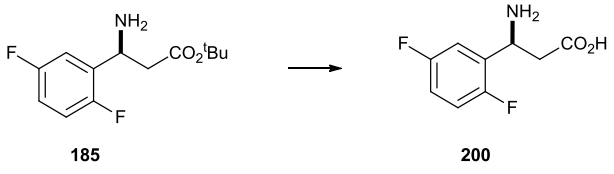
123.7, 125.1, (*C*(4′), *C*(5′), *C*(6′)), 132.5 (*C*(1′)), 148.5, 150.3 (*C*(2′), *C*(3′)), 174.1 (*C*(1)); *m/z* (ESI$^+$) 224 ([M+Na]$^+$, 19%), 202 ([M+H]$^+$, 13%); HRMS (ESI$^+$) $C_9H_{10}F_2NNaO_2^+$ ([M+Na]$^+$) requires 224.0494; found 224.0497.

(*S*)-3-Amino-3-(2',4'-difluorophenyl)propanoic acid 199



Following *General Procedure 5*, 2 M HCl (15 mL) and **184** (198 mg, 0.77 mmol) refluxing 6 h gave the crude reaction mixture. Evaporation and purification via ion exchange chromatography (Dowex 50WX8-100, eluent 1.0 M aq NH_4OH) gave **199** as a beige powder (142 mg, 92%);[19] mp 207–209 ºC; $[\alpha]_D^{25}$ –5.5 (*c* 0.5 in H_2O); ν_{max} (ATR) 3121br (O–H, N–H), 1658 (C=O); δ_H (400 MHz, AcOH-*d*$_4$) 3.10 (1H, dd, *J* 17.6, 5.6, C(2)*H*$_A$H$_B$), 3.40 (1H, dd, *J* 17.4, 6.6, C(2)H$_A$*H*$_B$), 5.25–5.28 (1H, m, C(3)*H*), 7.07–7.12 (2H, m, *Ar*), 7.48–7.55 (1H, m, *Ar*); δ_C (100 MHz, AcOH-*d*$_4$) 37.3 (*C*(2)), 46.1 (*C*(3)), 104.5, 112.3, 130.9 (*C*(3′), *C*(5′), *C*(6′)), 119.4 (*C*(1′)), 161.0, 163.9 (*C*(2′), *C*(4′)), 174.8 (*C*(1)); *m/z* (ESI$^+$) 224 ([M+Na]$^+$, 38%), 202 ([M+H]$^+$, 26%); HRMS (ESI$^+$) $C_9H_9F_2NNaO_2^+$ ([M+Na]$^+$) requires 224.0494; found 224.0489.

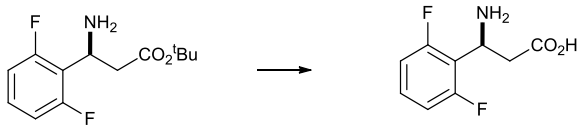
(*S*)-3-Amino-3-(2',5'-difluorophenyl)propanoic acid 200



Following *General Procedure 5*, 2 M HCl (15 mL) and **185** (198 mg, 0.77 mmol) refluxing 6 h gave the crude reaction mixture. Evaporation and purification via ion exchange chromatography (Dowex 50WX8-100, eluent 1.0 M aq NH_4OH) gave **200** as a beige powder (144 mg, 93%);[19] mp 207–209 ºC; $[\alpha]_D^{25}$ –3.2 (*c* 0.5 in H_2O); ν_{max} (ATR)

3043br (O–H, N–H), 1620 (C=O); δ_H (400 MHz, AcOH-d_4) 3.10 (1H, dd, *J* 17.7, 5.8, C(2)H_AH_B), 3.40 (1H, dd, *J* 17.4, 9.1,C(2)H_AH_B), 5.24–5.29 (1H, m, C(3)*H*), 7.06–7.10 (2H, m, *Ar*), 7.47–7.54 (1H, m, *Ar*); δ_C (100 MHz, AcOH-d_4) 37.3 (*C*(2)), 46.5 (*C*(3)), 115.9, 117.7, 118.1 (*C*(3′), *C*(4′), *C*(6′)), 124.7 (*C*(1′)), 156.7, 159.2 (*C*(2′), *C*(5′)), 174.9 (*C*(1)); *m/z* (ESI^+) 224 ($[M+Na]^+$, 75%), 202 ($[M+H]^+$, 75%); HRMS (ESI^+) $C_9H_9F_2NNaO_2^+$ ($[M+Na]^+$) requires 224.0494; found 224.0493.

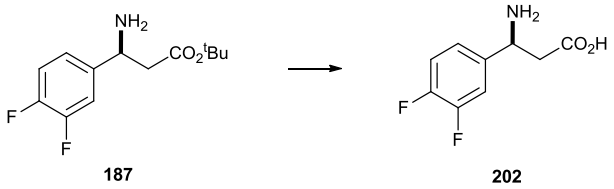
(*S*)-3-Amino-3-(2',6'-difluorophenyl)propanoic acid 201



186 **201**

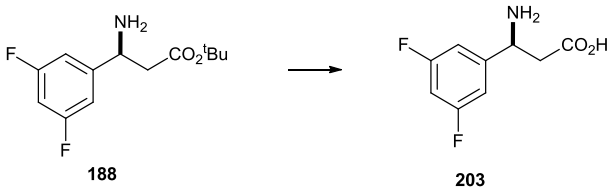
Following *General Procedure 5*, 2 M HCl (15 mL) and **186** (198 mg, 0.77 mmol) refluxing 6 h gave the crude reaction mixture. Evaporation and purification via ion exchange chromatography (Dowex 50WX8-100, eluent 1.0 M aq NH_4OH) gave **201** as a beige powder (147 mg, 95%);[19] mp 198–200 ºC; $[\alpha]_D^{25}$ –4.8 (*c* 0.5 in H_2O); ν_{max} (ATR) 2866br (O–H, N–H), 1625 (C=O); δ_H (400 MHz, AcOH-d_4) 3.10 (1H, dd, *J* 17.7, 5.8, C(2)H_AH_B), 3.40 (1H, dd, *J* 17.4, 8.8, C(2)H_AH_B), 5.24–5.28 (1H, m, C(3)*H*), 7.06–7.10 (2H, m, *Ar*), 7.46–7.53 (1H, m, *Ar*); δ_C (100 MHz, AcOH-d_4) 36.8 (*C*(2)), 43.4 (*C*(3)), 112.4, 132.4 (*C*(3′), *C*(4′), *C*(5′)), 111.9 (*C*(1′)), 160.1, 162.6 (*C*(2′), *C*(6′)), 174.8 (*C*(1)); *m/z* (ESI^+) 224 ($[M+Na]^+$, 98%), 202 ($[M+H]^+$, 74%); HRMS (ESI^+) $C_9H_9F_2NNaO_2^+$ ($[M+H]^+$) requires 224.0494; found 224.0498.

(*S*)-3-Amino-3-(3',4'-difluorophenyl)propanoic acid 202



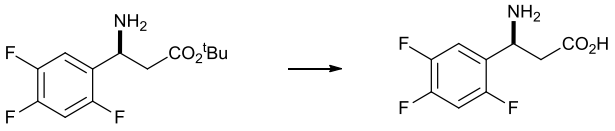
Following *General Procedure 5*, 2 M HCl (15 mL) and **187** (198 mg, 0.77 mmol) refluxing 6 h gave the crude reaction mixture. Evaporation and purification via ion exchange chromatography (Dowex 50WX8-100, eluent 1.0 M aq NH_4OH) gave **202** as a beige powder (139 mg, 90%);[8] mp 225–227 ºC; {lit.[8] mp 226–230 ºC}; $[\alpha]_D^{25}$ –3.9 (*c* 1.0 in H_2O); {lit.[8] $[\alpha]_D^{23}$ –3.2 (*c* 1.0 in H_2O)}; δ_H (400 MHz, AcOH-d_4) 3.19 (1H, dd, *J* 17.6, 6.1, C(2)H_AH_B), 3.51 (1H, dd, *J* 17.6, 7.3, C(2)H_AH_B), 4.96 (1H, br s, C(3)*H*), 7.30–7.36 (1H, m, *Ar*), 7.49–7.50 (1H, m, *Ar*), 7.58–7.63 (1H, m, *Ar*).

(*S*)-3-Amino-3-(3',5'-difluorophenyl)propanoic acid 203



Following *General Procedure 5*, 2 M HCl (15 mL) and **188** (184 mg, 0.77 mmol) refluxing 6 h gave the crude reaction mixture. Evaporation and purification via ion exchange chromatography (Dowex 50WX8-100, eluent 1.0 M aq NH_4OH) gave **203** as a beige powder (139 mg, 90%);[20] mp 206–208 ºC; $[\alpha]_D^{25}$ –4.5 (*c* 0.5 in H_2O); δ_H (400 MHz, AcOH-d_4) 3.07 (1H, dd, *J* 17.4, 5.1, C(2)H_AH_B), 3.28 (1H, dd, *J* 17.4, 9.1, C(2)H_AH_B), 4.89–4.92 (1H, m, C(3)*H*), 6.97–7.01 (1H, m, *Ar*), 7.21–7.22 (2H, m, *Ar*).

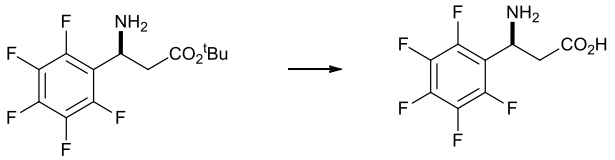
(*S*)-3-Amino-3-(2',4',5'-trifluorophenyl)propanoic acid 204



189 204

Following *General Procedure 5*, 2 M HCl (15 mL) and **189** (212 mg, 0.77 mmol) refluxing 6 h gave the crude reaction mixture. Evaporation and purification via ion exchange chromatography (Dowex 50WX8-100, eluent 1.0 M aq NH_4OH) gave **204** as a beige powder (157 mg, 93%);[19] mp 219–221 ºC; $[\alpha]_D^{25}$ –6.7 (*c* 0.5 in H_2O); ν_{max} (ATR) 3444br (O–H, N–H), 1628 (C=O); δ_H (400 MHz, AcOH-*d*$_4$) 3.22 (1H, dd, *J* 17.6, 6.5, C(2)H_AH_B), 3.53 (1H, dd, *J* 17.6, 7.3, C(2)H_AH_B), 5.18 (1H, t, *J* 6.8, C(3)*H*), 7.17–7.24 (1H, m, *Ar*), 7.77–7.84 (1H, m, *Ar*); δ_C (125 MHz, AcOH-*d*$_4$) 37.4 (*C*(2)), 46.3 (*C*(3)), 107.1, 118.9 (*C*(3′), *C*(6′)), 120.3 (*C*(1′)), 147.8, 151.7, 156.9 (*C*(2′), *C*(4′), *C*(5′)), 174.6 (*C*(1)); *m/z* (ESI^+) 242 ($[M+Na]^+$, 74%), 220 ($[M+H]^+$, 51%); HRMS (ESI^+) $C_9H_8F_3NNaO_2^+$ ($[M+Na]^+$) requires 242.0399; found 242.0404.

(*S*)-3-Amino-3-(pentafluorophenyl)propanoic acid 205

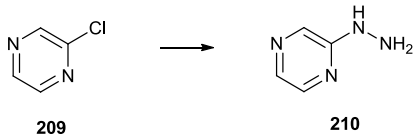


190 205

Following *General Procedure 5*, 2 M HCl (15 mL) and **190** (239 mg, 0.77 mmol) refluxing 6 h gave the crude reaction mixture. Evaporation and purification via ion exchange chromatography (Dowex 50WX8-100, eluent 1.0 M aq NH_4OH) gave **205** as a beige powder (190 mg, 97%);[21] mp 188–190 ºC; $[\alpha]_D^{25}$ +27.3 (*c* 2.5 in H_2O); {lit.[21] $[\alpha]_D^{20}$ +24 (*c* 2.5 in D_2O)}; δ_H (400 MHz, AcOH-*d*$_4$) 3.28–3.36 (1H, m, C(2)H_AH_B), 3.55–3.63 (1H, m, C(2)H_AH_B), 5.35 (1H, br s, C(3)*H*).

5.4 Experimental for chapter 3

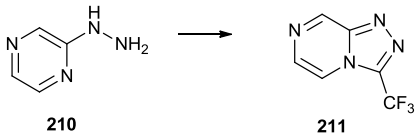
2-Hydrazinopyrazine 210



209 **210**

Compound **209** (23.0 mL, 262 mmol) and hydrazine hydrate (30.0 mL, 524 mmol) in absolute ethanol (600 mL) were heated at reflux for 5 h, then concentrated *in vacuo.* Purification via recrystallization (EtOH) gave **210** as cream needles (17.3 g, 60%);[22] mp 108–109 ºC; {lit.[22] mp 108–110 ºC}; δ_H (400 MHz, MeOH-d_4) 7.75 (1H, d, *J* 2.9, *Ar*), 8.01–8.02 (1H, m, *Ar*), 8.12 (1H, m, *Ar*).

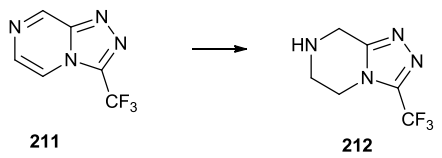
3-(Trifluoromethyl)-1,2,4-triazolo[4,3-α]pyrazine 211



210 **211**

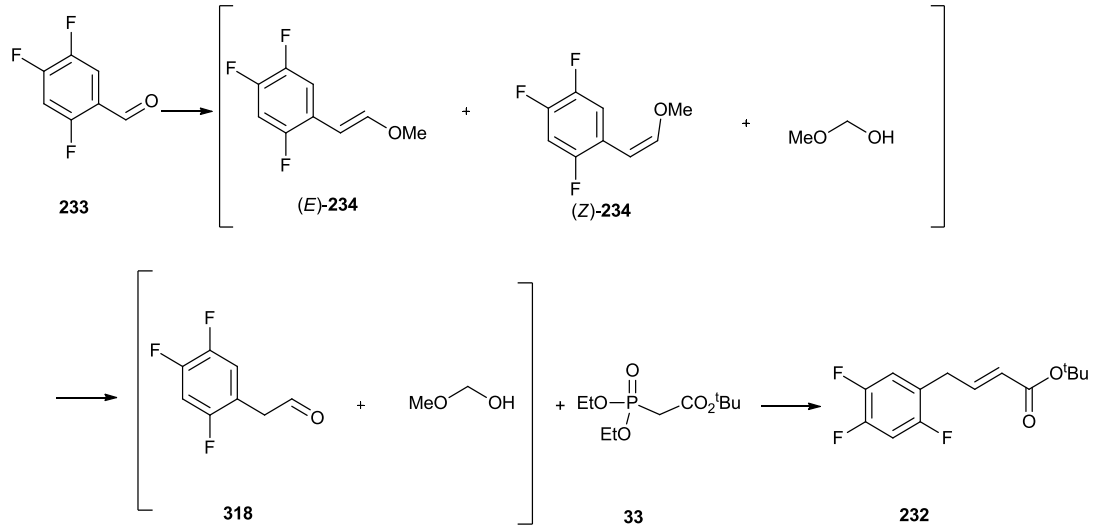
Trifluoroacetic anhydride (150 mL) was added dropwise to a **210** (17.5 g, 159 mmol) at 0 ºC, and the resultant solution was stirred at rt for 2 h, then concentrated *in vacuo* to give a brown solid. Polyphosphoric acid (200 mL) was added and the resultant solution was stirred at 140 ºC for 18 h, then poured over ice. NH_4OH was added until a pH of 7 was achieved and then the aqueous solution was extracted with EtOAc, washed with brine, and dried over $MgSO_4$ and concentrated *in vacuo*. Purification via flash column chromatography (eluent hexane/EtOAc, 1:1) gave **211** as a bright yellow solid (15.5 g, 52%);[22] mp 94–96 ºC; δ_H (400 MHz, $CDCl_3$) 8.16–8.19 (2H, m, *Ar*), 9.54–9.55 (1H, m, *Ar*).

3-(Trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-α]pyrazine 212



Pd/C (20% w/w, 400 mg) was added to a degassed solution of **211** (2.01 g, 11 mmol) in EtOH (20 mL) and the resultant mixture was stirred under H_2 (1atm) at rt for 18 h. The reaction mixture was filtered through Celite® and concentrated *in vacuo*. Purification via flash column chromatography (eluent CH_2Cl_2/MeOH, 1:1) gave **212** as a viscous oil (1.77 g, 86%);[22] δ_H (400 MHz, $CDCl_3$) 1.77 (1H, br s, N*H*), 3.30 (2H, t, *J* 5.5, CH_2), 4.12 (2H, t, *J* 5.5, CH_2), 4.28 (2H, s, CH_2).

***tert*-Butyl (*E*)-4-(2',4',5'-trifluorophenyl)but-2-enoate 232**



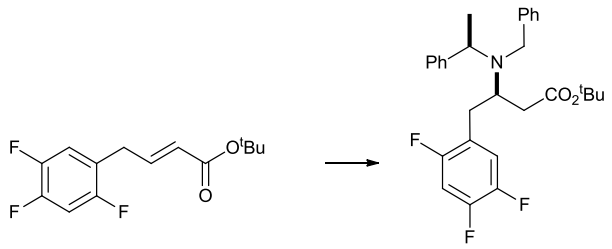
Step 1: KO^{t}Bu (17.5 g, 156 mmol) was added to methoxymethyltriphenylphosphonium chloride (53.5 g, 156 mmol) in THF (300 mL) at rt and the resultant mixture was stirred for 1 h. **233** (5.00 g, 31.2 mmol) was added dropwise at rt and stirring was continued at rt for 48 h. The suspension was filtered and the filter cake was washed with EtOAc (3 × 45 mL). The combined organics were sequentially washed with satd aq NH_4Cl (500 mL), brine (300 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent hexane/EtOAc, 20:1) gave a 1:1 mixture of **234** (55:45

dr) and a by-product (which was tentatively assigned as methoxymethanol) as a light yellow oil (7.19 g). Data for (*E*)-**234**: δ_H (400 MHz, $CDCl_3$) 3.72 (3H, s, O*Me*), 5.80 (1H, d, *J* 13.0, HC=C*H*), 6.92–6.96 (1H, m, *Ar*), 7.02–7.08 (1H, m, *Ar*), 7.15 (1H, d, *J* 13.0, HC=C*H*). Data for (*Z*)-**234**: δ_H (400 MHz, $CDCl_3$) 3.82 (3H, s, O*Me*), 5.44 (1H, d, *J* 7.0, HC=C*H*), 6.26 (1H, d, *J* 7.0, HC=C*H*), 7.02–7.08 (1H, m, *Ar*), 7.74–7.79 (1H, m, *Ar*). Data for methoxymethanol: δ_H (400 MHz, $CDCl_3$) 3.41 (3H, s, O*Me*), 4.46 (2H, s, CH_2).

Step 2: A 1:1 mixture of **234** (55:45 dr) and methoxymethanol (7.19 g) and HCl (4.0 M in dioxane, 36 mL, 144 mmol) was stirred for 6 h at rt, then diluted with Et_2O (72 mL). The reaction mixture was cooled to 0 ºC and satd aq $NaHCO_3$ (200 mL) was added. The organic layer was washed with brine (50 mL), then dried over Na_2SO_4, and concentrated *in vacuo* to give a 1:1 mixture of **318** and methoxymethanol as a yellow oil (6.53 g). **318**: δ_H (400 MHz, $CDCl_3$) 4.49 (2H, s, C(2)H_2), 7.31–7.35 (1H, m, *Ar*), 7.49–7.53 (1H, m, *Ar*), 10.30–10.38 (1H, m, C(1)*H*).

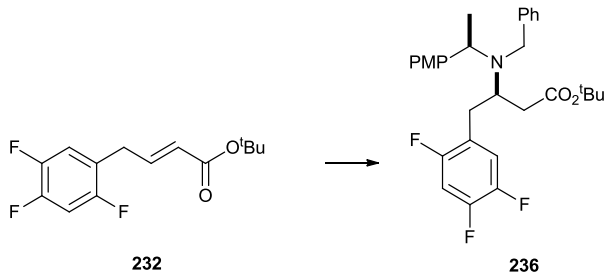
Step 3: Following *General Procedure 1*, **33** (8.27 g, 32.8 mmo), MeMgBr (3.0 M in Et_2O, 10.9 mL, 32.8 mmol) and 1:1 mixture of **318** and methoxymethanol (6.53 g) in THF (360 mL) gave, after purification via flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 50:1), **232** a colourless oil (6.31 g, 74% from **233**, >99:1 dr); ν_{max} (ATR) 2980, 2934 (C–H), 1711 (C=O), 1632 (C=C); δ_H (400 MHz, $CDCl_3$) 1.47 (9H, s, CMe_3), 3.45 (2H, d, *J* 6.6, C(4)H_2), 5.70 (1H, d, *J* 15.8, C(2)*H*), 6.85–7.02 (2H, m, *Ar*), overlapping 6.89 (1H, app d, *J* 15.8, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 27.9 (CMe_3), 30.6 (*C*(4)), 80.6 (*C*Me_3), 105.6 (dd, *J* 28, 20, *C*(3′)), 118.3 (dd, *J* 10, 6, *C*(6′)), 121.2 (d, *J* 18, *C*(1′)), 125.0 (*C*(2)), 142.9 (*C*(3)), 146.6 (ddd, *J* 209, 12, 4, *C*F), 149.0 (dd, *J* 224, 14, *C*F), 155.7 (ddd, *J* 243, 10, 3, *C*F) 165.4 (*C*(1)); *m/z* (ESI^-) 271 ($[M-H]^-$, 100%); HRMS (ESI^+) $C_{14}H_{15}F_3NaO_2^+$ ($[M+Na]^+$) requires 295.0916; found 295.0918.

tert-Butyl(3*R*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(2',4',5'-trifluorophenyl)bu-tanoate 235



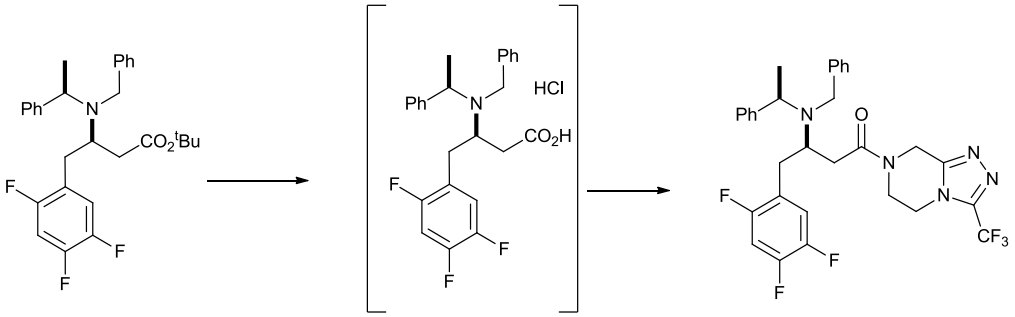
Following *General Procedure 2b*, BuLi (2.5 M in hexanes, 15.0 mL, 37.5 mmol) and **150** (7.92 g, 37.5 mmol) in THF (50 mL) at −78 °C, and **232** (3.40 g, 12.5 mmol) in THF (50 mL) at −78 °C gave the crude reaction mixture. Purification via flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 20:1) gave **235** as a colourless oil (5.25 g, 87%, >99:1 dr); $[\alpha]_D^{25}$ +10.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2976 (C−H), 1721 (C=O); δ_H (400 MHz, $CDCl_3$) 1.14 (3H, d, *J* 7.1, C(α)*Me*), 1.43 (9H, s, C*Me*$_3$), 1.98–2.00 (2H, m, C(2)*H*$_2$), 2.64 (1H, dd, *J* 12.8, 5.0, C(4)*H*$_A$), 2.76 (1H, dd, *J* 12.8, 9.1, C(4)*H*$_B$), 3.58 (1H, d, *J* 14.9, NC*H*$_A$CH$_B$Ph), 3.67–3.74 (1H, m, C(3)*H*), 3.81 (1H, q, *J* 7.1, C(α)*H*), 3.92 (1H, d, *J* 14.9, NCH$_A$C*H*$_B$Ph), 6.87–6.99 (2H, m, *Ar*), 7.22–7.37 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.6 (C(α)*Me*), 27.9 (C*Me*$_3$), 32.4 (*C*(2)), 37.5 (*C*(4)), 50.0 (N*C*H$_2$Ph), 54.4 (*C*(3)), 57.6 (*C*(α)), 80.4 (*C*Me$_3$), 104.8 (dd, *J* 28, 20, *C*(3′)), 119.4 (dd, *J* 19, 7, *C*(6′)), 123.6 (d, *J* 19, *C*(1′)), 126.8, 127.1, 127.9, 128.0, 128.2, 128.3 (*o,m,p-Ph*), 140.6, 142.1 (*i-Ph*), 146.1 (d, *J* 209, *C*F), 148.6 (d, *J* 203, *C*F), 153.9 (d, *J* 226, *C*F), 171.5 (*C*(1)); *m/z* (ESI$^+$) 506 ([M+Na]$^+$, 63%), 484 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{33}F_3NO_2^+$ ([M+H]$^+$) requires 484.2458; found 484.2458.

tert-Butyl(3*R*,α*R*)-3-[*N*-benzyl-*N*-(α-methy-*p*-methoxybenzyl)amino]-4-(2',4',5'-trifluor-ophenyl)butanoate 236



Following *General Procedure 2b*, BuLi (2.5 M in hexanes, 15.0 mL, 37.5 mmol) and **174** (9.05 g, 37.5 mmol) in THF (50 mL) at −78 °C, and **232** (3.40 g, 12.5 mmol) in THF (50 mL) at −78 °C gave the crude reaction mixture. Purification via flash column chromatography (eluent hexane/Et_2O, 30:1) gave **236** as a colourless oil (5.51 g, 86%, >99:1 dr); $[\alpha]_D^{25}$ +27.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2976 (C−H), 1721 (C=O); δ_H (400 MHz, $CDCl_3$) 1.12 (3H, d, *J* 6.8, C(α)*Me*), 1.43 (9H, s, C*Me*$_3$), 2.00 (2H, app d, *J* 6.6, C(2)*H*$_2$), 2.64 (1H, dd, *J* 14.1, 5.3, C(4)*H*$_A$), 2.76 (1H, dd, *J* 14.1, 9.1, C(4)*H*$_B$), 3.56 (1H, d, *J* 14.9, NC*H*$_A$CH$_B$Ph), 3.68–3.72 (1H, m, C(3)*H*), 3.77 (1H, q, *J* 6.8, C(α)*H*), 3.81 (3H, s, O*Me*), 3.91 (1H, d, *J* 14.9, CH$_A$C*H*$_B$Ph), 6.84 (2H, d, *J* 8.5, *Ar*), 6.85–6.98 (2H, m, *Ar*), 7.15 (2H, d, *J* 8.5, *Ar*), 7.25–7.36 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.7 (C(α)*Me*), 27.9 (C*Me*$_3$), 32.4 (*C*(2)), 37.6 (*C*(4)), 50.0 (N*C*H$_2$), 54.3 (*C*(3)), 55.2 (O*Me*), 56.7 (*C*(α)), 80.4 (*C*Me$_3$), 104.9 (dd, *J* 29, 20, *C*(3′)), 113.5 (*Ar*), 119.3 (dd, *J* 18, 7, *C*(6′)), 123.7 (d, *J* 18, *C*(1′)), 126.7, 128.1, 128.3, 128.9 (*Ar*, *Ph*), 134.2, 140.7 (*Ar*, *i-Ph*), 146.1 (d, *J* 209, *C*F), 148.5 (d, *J* 202, *C*F), 156.1 (d, *J* 244, *C*F), 158.7 (*Ar*), 171.7 (*C*(1)); *m/z* (ESI$^+$) 536 ([M+Na]$^+$, 96%), 514 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{35}F_3NO_3^+$ ([M+H]$^+$) requires 514.2564; found 514.2580.

(2*R*,α*R*)-1-(2',4',5'-Trifluorophenyl)-4-oxo-4-(3''-(trifluoromethyl)-5'',6''-dihydro-[1'',2'',4'']-triazolo[4,3-α]pyrazin-7''(8''*H*)-yl)butan-2- *N*-benzyl-*N*-(α-methylbenzyl)amine 238

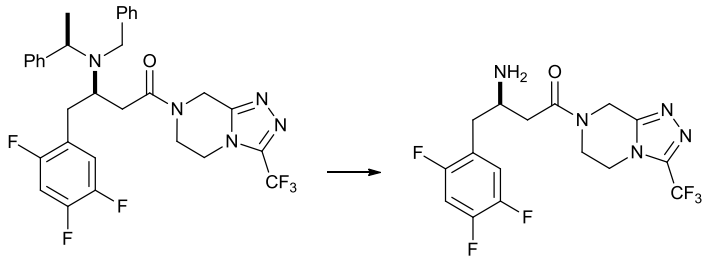


Step 1: Following *General Procedure 5*, 2.0 M HCl (19.0 mL) and **235** (483 mg, 1.00 mmol) were refluxed for 6 h to give **237** as a white powder (407 mg, 88%); mp 90–91 ºC; $[\alpha]_D^{25}$ −28.0 (*c* 1.0 in H_2O); ν_{max} (ATR) 1701 (C=O); δ_H (400 MHz, MeOH-d_4) 1.76–1.85 (3H, m, C(α)*Me*), 2.47–3.00 (2H, m, C(2)H_2), 3.15–3.63 (2H, m, C(4)H_2), 3.86–5.00 (4H, m, C(3)*H*, C(α)*H*, NCH_2Ph), 7.21–7.62 (12H, m, *Ar*, *Ph*); *m/z* (ESI^+) 450 ($[M+Na]^+$, 95%), 428 ($[M+H]^+$, 90%); HRMS (ESI^+) $C_{25}H_{25}F_3NO_2^+$ ($[M+H]^+$) requires 428.1832; found 428.1832.

Step 2: DIPEA (0.60 mL, 3.66 mmol), HOBt (94.0 mg, 0.70 mmol), EDC·HCl (134 mg, 0.70 mmol) and **237** (282 mg, 0.61 mmol) were added sequentially to a solution of **212** (117 mg, 0.61 mmol) in $CHCl_3$ (8 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then partitioned between 1.0 M aq HCl (10 mL) and $CHCl_3$ (10 mL). The organic layer was washed with satd aq $NaHCO_3$ (10 mL) and brine (10 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent hexane/EtOAc, 1:1) gave **238** as a white solid (293 mg, 80%); mp 80–82 ºC; $[\alpha]_D^{25}$ −26.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2972 (C−H), 1657 (C=O); δ_H (500 MHz, MeOH-d_4) 1.18–1.27 (3H, m, C(α)*Me*), 2.03–2.44 (2H, m, C(3)H_2), 2.69–2.73 (1H, m, C(1)H_A), 2.96–3.09 (1H, m, C(1)H_B), 3.39–4.15 (8H, m, C(2)*H*, C(α)*H*, NCH_2Ph, C(5′)H_2, C(6′)H_2), 4.39–4.52 (1H, m, C(8′)H_A), 4.75–4.84 (1H, m, C(8′)H_B), 7.00–7.44 (12H, m, *Ar*, *Ph*); δ_C (125 MHz, MeOH-d_4) 18.5, 19.3 (C(α)*Me*),

33.1, 33.4 (*C*(1)), 35.7, 35.9 (*C*(3)), 39.0, 42.8 (*C*(8′′)), 39.7, 42.2, 44.6, 50.9, 51.0 (*C*(5′′), *C*(6′′), N*C*H$_2$Ph), 55.2, 55.8, (*C*(2)), 57.7, 57.9 (*C*(α)), 106.1 (m, *C*(3′)), 119.7 (q, *J* 270, *C*F$_3$), 120.6 (d, *J* 26, *C*(6′)), 125.4 (m, *C*(1′)), 127.7, 127.8, 129.0, 129.1, 129.2, 129.3, 129.5, 129.6 (*o,m,p-Ph*), 142.1 (*i-Ph*), 144.1 (*C*(3′′)), 144.2, 144.5 (*C*(8a′′)), 144.6 (*i-Ph*), 147.8 (d, *J* 237, *C*F), 151.8 (d, *J* 206, *C*F), 157.8 (dd, *J* 235, 8, *C*F), 172.8 (*C*(4)); *m/z* (ESI$^+$) 624 ([M+Na]$^+$, 94%), 602 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{29}F_6N_5NaO^+$ ([M+Na]$^+$) requires 624.2169; found 624.2170.

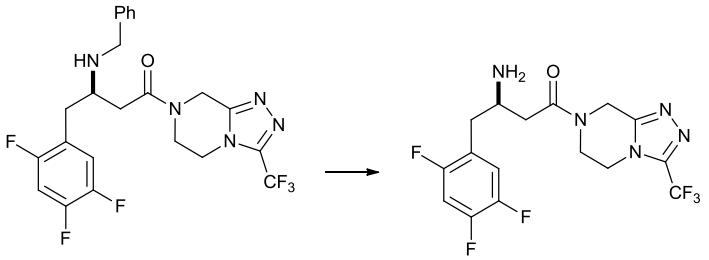
(*R*)-1-(2',4',5'-Trifluorophenyl)-4-oxo-4-(3''-(trifluoromethyl)-5'',6''-dihydro-[1'',2'',4'']-triazolo[4,3-α]pyrazin-7''(8''*H*)-yl)butan-2-amine 208, Sitagliptin



238 **208**

Method 1: Following *General Procedure 3*, **238** (451 mg, 1.00 mmol), Pd(OH)$_2$/C (30% w/w, 68 mg) and H$_2$ (5 atm) in MeOH (4 mL) after 24 h gave the crude mixture. Purification via flash column chromatography (eluent CH$_2$Cl$_2$/ MeOH, 10:1) gave **208** as a colorless oil (148 mg, 96%);[23] $[\alpha]_D^{25}$ –23.3 (*c* 1.0 in CHCl$_3$); {lit.,[23] $[\alpha]_D^{26}$ –22.8(*c* 1.0 in CHCl$_3$)}; ν_{max} (ATR) 3371 (N–H), 1651 (C=O); δ_H (500 MHz, CDCl$_3$) 2.44–2.56 (2H, m, C(3)*H*$_2$), 2.64–2.69 (1H, m, C(1)*H*$_A$), 2.75–2.80 (1H, m, C(1)*H*$_B$), 3.55 (1H, br s, C(2)*H*), 3.39–4.22 (4H, m, C(5′′)*H*$_2$, C(6′′)*H*$_2$), 4.87–5.09 (2H, m, C(8′′)*H*$_2$), 6.87–6.92 (1H, m, *Ar*), 7.04–7.09 (1H, m, *Ar*); δ_C (125 MHz, CDCl$_3$) 36.2 (*C*(1)), 37.9, 41.6, 43.2 (*C*(5′′), *C*(6′′)), 39.9, 40.0 (*C*(3)), 39.1, 42.3 (*C*(8′′)), 48.5 (*C*(2)), 105.5 (m, *C*(3′)), 118.1 (q, *J* 270, *C*F$_3$), 118.9 (dd, *J* 19, 6, *C*(6′)), 121.6 (d, *J* 19, *C*(1′)), 143.5 (quintet, *J* 40, *C*(3")), 146.5 (ddd, *J* 245, 13, 4, *C*F), 148.9 (dd, *J* 249, 14, *C*F), 156.0 (ddd, *J* 245, 9, 4, *C*F), 149.7, 150.4 (*C*(8"a)), 170.2, 170.5 (*C*(4)); *m/z* (ESI$^+$) 815

([2M+H]$^+$, 88%), 408 ([M+H]$^+$, 88%); HRMS (ESI$^+$) $C_{16}H_{16}F_6N_5O^+$ ([M+H]$^+$) requires 408.1254; found 408.1247.

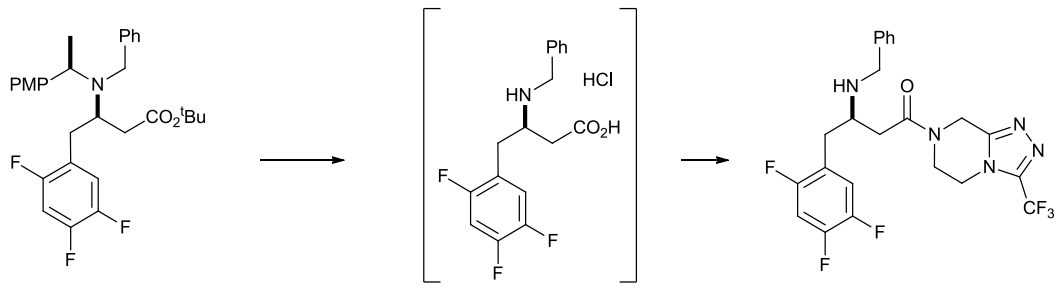


240 **208**

Method 2: A stirred solution of **240** (190 mg, 0.38 mmol) in MeOH (3 mL) was purged with nitrogen for 15 min. After this time, Pd/C (200% w/w, 380 mg) was added and the reaction was placed under an atmosphere of H_2 (3 atm). After Stirring under H_2 continued for 12 h, the suspension was filtered by passage through Celite® (stated eluent) and the collected organics were concentrated *in vacuo*. Purification via flash column chromatography (eluent CH_2Cl_2/ MeOH, 10:1) gave **208** as a colorless oil (139 mg, 90%);[23] $[\alpha]_D^{25}$ –20.9 (*c* 1.0 in $CHCl_3$).

Method 3: Following *General Procedure 3*, **240** (190 mg, 0.38 mmol), $Pd(OH)_2/C$ (20% w/w, 38 mg) and H_2 (5 atm) in MeOH (3 mL) after 24 h gave the crude mixture. Purification via flash column chromatography (eluent CH_2Cl_2/ MeOH, 10:1) gave **208** as a colorless oil (141 mg, 91%);[23] $[\alpha]_D^{25}$ –22.0 (*c* 1.0 in $CHCl_3$).

(*R*)-1-(2',4',5'-Trifluorophenyl)-4-oxo-4-(3''-(trifluoromethyl)-5'',6''-dihydro-[1'',2'',4'']-triazolo[4,3-α]pyrazin-7''(8''*H*)-yl)butan-2-*N*-benzylamine 240

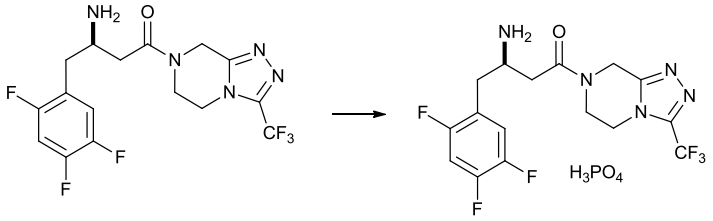


236 **239** **240**

Step1: Following *General Procedure 5*, 2.0 M HCl (19.0 mL) and **236** (513 mg, 1.00 mmol) were refluxed for 6 h to give **239** as a beige powder (359 mg, 90%); mp 213–215 ºC; $[\alpha]_D^{25}$ –40.0 (*c* 1.0 in H_2O); ν_{max} (ATR) 3039 (N–H), 1726 (C=O); δ_H (400 MHz, AcOH-*d*$_4$) δ_H (400 MHz, AcOH-*d*$_4$) 2.89–2.95 (1H, m, C(2)H_A), 3.08–3.14 (1H, m, C(2)H_B), 3.21-3.27 (1H, m, C(4)H_A), 3.47–3.50 (1H, m, C(4)H_B), 3.96–3.98 (1H, m, C(3)*H*), 4.43–4.53 (2H, m, NCH_2Ph), 7.05–7.12 (1H, m, *Ar*), 7.32–7.38 (1H, m, *Ar*), 7.44–7.55 (3H, m, *Ph*), 7.63–7.78 (2H, m, *Ph*); δ_C (100 MHz, AcOH-*d*$_4$) 29.9 (*C*(4)), 33.9 (*C*(2)), 49.7 (N*C*H$_2$), 54.6 (*C*(3)), 106.0, 120.3, 129.3, 129.9, 130.8 (*C*(3′), *C*(6′), *o,m,p-Ph*), 174.7 (*C*(1)); *m/z* (ESI$^+$) 346 ([M+Na]$^+$, 67%); HRMS (ESI$^+$) $C_{17}H_{16}F_3NNaO_2^+$ ([M+Na]$^+$) requires 346.1025; found 346.1022.

Step2: DIPEA (0.60 mL, 3.66 mmol), HOBt (94.0 mg, 0.70 mmol), EDC·HCl (134 mg, 0.70 mmol) and **239** (218 mg, 0.61 mmol) were added sequentially to a solution of **212** (117 mg, 0.61 mmol) in $CHCl_3$ (8 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then partitioned between 1.0 M aq HCl (10 mL) and $CHCl_3$ (10 mL). The organic layer was washed with satd aq $NaHCO_3$ (10 mL) and brine (10 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent hexane/EtOAc, 1:10) gave **240** as a white solid (246 mg, 81%); mp 107–108 ºC; $[\alpha]_D^{25}$ –35.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3325 (N–H), 1652 (C=O); δ_H (400 MHz, $CDCl_3$) 2.46–2.48 (2H, m, C(3)H_2), 2.73–2.78 (1H, m, C(1)H_A), 2.90–2.95 (1H, m, C(1)H_B), 3.26–3.35 (1H, m, C(2)*H*), 3.73–4.08 (6H, m, NCH_2Ph, C(5″)H_2, C(6″)H_2), 4.74–4.95 (2H, m, C(8″)H_2), 6.87–6.88 (1H, m, *Ar*), 7.02–7.04 (1H, m, *Ar*), 7.21–7.26 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 32.8, 33.0 (*C*(1)), 37.3, 39.1 (*C*(3)), 37.6, 37.9, 43.2, 43.4 (*C*(5″), *C*(6″)), 42.1 (*C*(8″)), 51.1 (N*C*H$_2$Ph), 54.3, 54.6 (*C*(2)), 105.3 (dd, *J* 29, 21, *C*(3′)), 119.1 (m, *C*(6′)), 121.3 (q, *J* 270, *C*F$_3$), 121.9 (m, *C*(1′)), 127.0, 128.0, 128.4 (*o,m,p-Ph*), 140.0 (*i-Ph*), 146.4 (m, *C*F), 149.5 (*C*(8"a)), 152.4 (m, *C*F), 170.1, 170.5 (*C*(4)); *m/z* (ESI$^+$) 498 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{22}F_6N_5O^+$ ([M+H]$^+$) requires 498.1723; found 498.1724.

(*R*)-1-(2',4',5'-Trifluorophenyl)-4-oxo-4-(3''-(trifluoromethyl)-5'',6''-dihydro-[1'',2'',4'']-triazolo[4,3-α]pyrazin-7''(8''*H*)-yl)butan-2-amine phosphate 208, Sitagliptin phosphate

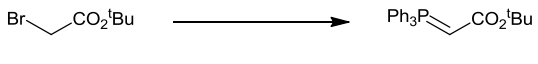


208 **208.H_3PO_4**

Phosphoric acid (85 wt%, 13.8 mg, 0.12 mmol) was added in one portion to a solution of **208** (50.0 mg, 0.12 mmol) in EtOH (0.70 mL) and the resultant mixture was heated at 80 ºC for 30 min. The reaction mixture was then allowed to cool to rt and filtered. The solid residue was then recrystallised (^{i}PrOH) to give **208**·H_3PO_4 as a white powder (58.0 mg, 95%); mp 214–216 ºC; {lit.[23] mp 213–216 ºC}; $[\alpha]_D^{25}$ –75.8 (*c* 1.0 in H_2O); {lit.[23] $[\alpha]_D^{20}$ –72.9 (*c* 1.0 in H_2O); lit.[24] $[\alpha]_D$ –74.4 (*c* 1.0 in H_2O)}; ν_{max} (ATR) 1653 (C=O); δ_H (500 MHz, D_2O) 2.78–2.95 (2H, m, C(3)H_2), 2.98–3.06 (2H, m, C(1)H_2), 3.91–4.02 (3H, m, C(2)*H*, NCH_2), 4.13–4.26 (2H, m, NCH_2), 4.81–4.91 (2H, m, C(8″)H_2), 7.00–7.08 (1H, m, *Ar*), 7.16–7.23 (1H, m, *Ar*); δ_C (125 MHz, D_2O) 30.9, 31.0 (*C*(1)), 33.7, 33.8 (*C*(3)), 41.2, 41.8, 43.1, 43.4, 48.3 (*C*(5″), *C*(6″), *C*(8″), *C*(2)), 105.8 (dd, *J* 28, 22, *C*(3′)), 117.0 (q, *J* 270, *C*F_3), 118.4, 119.1 (*C*(6′), *C*(1′)), 143.7 (m, *C*(3")), 146.5 (d, *J* 242, *C*F), 149.3 (d, *J* 249, *C*F), 150.6, 151.1 (*C*(8"a)), 156.3 (d, *J* 243, *C*F), 170.1, 170.2 (*C*(4)); *m/z* (ESI^+) 815 ($[2M+H]^+$, 75%), 408 ($[M+H]^+$, 87%); HRMS (ESI^+) $C_{16}H_{16}F_6N_5O^+$ ($[M+H]^+$) requires 408.1254; found 408.1247.

5.5 Experimental for chapter 4

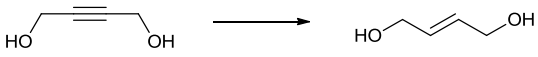
tert-Butyl (triphenylphosphoranylidene)acetate 265



133 **265**

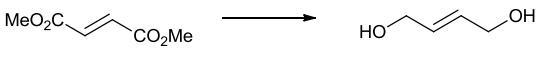
Triphenylphosphine (40.4 g, 154 mmol) was added to a stirred solution of **133** (30.0 g, 154 mmol) in EtOAc (200 mL). After 12 h the white precipitate was filtered off and washed with Et_2O (2 × 10 mL). The resultant solid was then added portionwise to stirred 2.0 M aq NaOH (200 mL) at 0 °C over a period of 5 min. After a further 5 min the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried, filtered and concentrated *in vacuo* to give **265** as an off-white solid (55.2 g, 96%);[25] mp 151–153 ºC; {lit.[25] mp 152–155 ºC}; δ_H (400MHz, $CDCl_3$) 1.20 (9H, br s, C*Me*$_3$), 2.70 (1H, br s, C(2)*H*), 7.45–7.68 (15H, m, *Ph*).

(*E*)-But-2-ene-1,4-diol 260



266 (*E*)-**260**

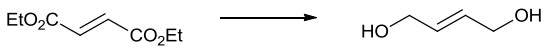
Method 1: $LiAlH_4$ (1.0 M in THF, 2.79 mL, 2.79 mmol) was added into a solution of **266** (200 mg, 2.32 mmol) in anhydrous THF (10 mL) at 0 °C under N_2, and the reaction mixture stirred at rt for 16 h. Lumps of ice were added into reaction mixture at 0 °C cautiously with vigorous stirring. The reaction mixture was stirred and allowed to warm to rt. Silica and H_2O (5 mL) were added, and the mixture stirred for 1h, before being dried, filtered and concentrated *in vacuo* to give (*E*)-**260** as a pale yellow oil (163 mg, 80%, >99:1 dr);[26] δ_H (400 MHz, $CDCl_3$) 1.52 (1H, br s, OH), 4.19 (4H, dd, *J* 2.5, 1.0, C(1)*H*$_2$, C(4)*H*$_2$), 5.91 (2H, m , C(2)*H*, C(3)*H*).



267 (*E*)-**260**

Method 2: DIBAL-H (1.0 M in toluene, 62.5 mL, 62.5 mmol) was added into a stirred solution of **267** (2.00 g, 13.9 mmol) in toluene (60 ml) at –78 °C dropwise. After

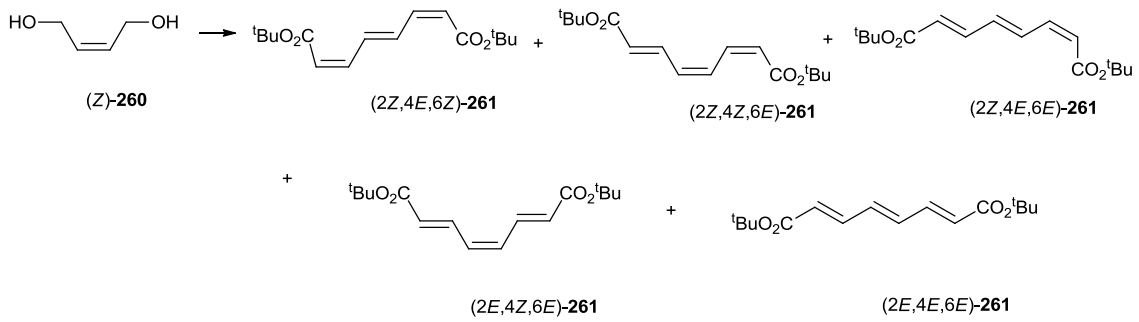
addition the reaction was stirred at rt for 6 h, before adding of MeOH (40 ml) with vigorous stirring. Celite® and H_2O (20 mL) were added, and the mixture stirred for 1h, before being dried, filtered and concentrated *in vacuo* to give (*E*)-**260** as a pale yellow oil (1.22 g, 69%, >99:1 dr).



268 (*E*)-**260**

Method 3: DIBAL-H (1.0 M in toluene, 52.3 mL, 52.3 mmol) was added into a stirred solution of **268** (2.00 g, 11.6 mmol) in toluene (60 ml) at –78 °C dropwise. After addition the reaction was stirred at rt for 6 h, before adding of MeOH (40 ml) with vigorous stirring. Celite® and H_2O (20 mL) were added, and the mixture stirred for 1h, before being dried, filtered and concentrated *in vacuo* to give (*E*)-**260** as a pale yellow oil (929 mg, 91%, >99:1 dr).

Di-*tert*-butyl octa-(2*Z*,4*E*,6*Z*)-triene-1,8-dioate 261, di-*tert*-butyl octa-(2*Z*,4*Z*,6*E*)-triene-1,8-dioate 261, di-*tert*-butyl octa-(2*Z*,4*E*,6*E*)-triene-1,8-dioate 261, di-*tert*-butyl octa-(2*E*,4*Z*,6*E*)-triene-1,8-dioate 261, di-*tert*-butyl octa-(2*E*,4*E*,6*E*)-triene-1,8-dioate 261



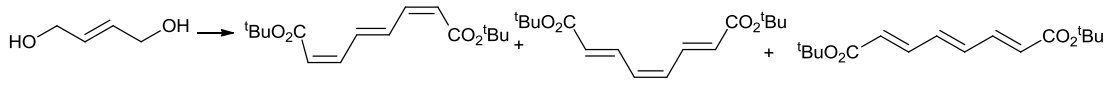
(*Z*)-**260** (2*Z*,4*E*,6*Z*)-**261** (2*Z*,4*Z*,6*E*)-**261** (2*Z*,4*E*,6*E*)-**261**

(2*E*,4*Z*,6*E*)-**261** (2*E*,4*E*,6*E*)-**261**

Method 1: Activated MnO_2 (19.7 g, 227 mmol) was added into a stirred solution of (*Z*)-**260** (1.00 g, 11.4 mmol) and **265** (10.2 g, 27.2 mmol) in CH_2Cl_2 (150 mL) at rt. After addition the reaction was stirred at rt for 48 h, before filtering by passage through a pad of Celite® (prewashed with 10% TEA in CH_2Cl_2) and the collected organics were concentrated *in vacuo to* give the crude reaction mixture. Purification via flash column

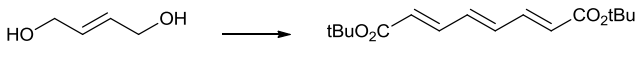
chromatography (eluent 30–40 ºC petrol/Et_2O, 20:1) gave (2*Z*,4*E*,6*Z*)-**261** as a white powdery solid (13.0 mg, 0.4%, >99:1 dr); mp 115–117 ºC; ν_{max} (ATR) 1704 (C=O), 1614 (C=C); δ_H (400 MHz, $CDCl_3$) 1.51 (18H, s, C*Me*$_3$), 5.72 (2H, d, *J* 11.4, C(2)*H*, C(7)*H*), 6.58–6.70 (2H, m, C(3)*H*, C(6)*H*), 7.68–7.77 (2H, m, C(4)*H*, C(5)*H*); δ_C (100 MHz, $CDCl_3$) 28.2 (C*Me*$_3$), 80.6 (*C*Me$_3$), 122.42 (*C*(2), *C*(7)), 135.5 (*C*(4), *C*(5)), 142.6 (*C*(3), *C*(6)), 165.6 (*C*O); *m/z* (ESI^+) 303 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{16}H_{24}NaO_4^+$ ($[M+Na]^+$) requires 303.1567; found 303.1561. Further elution gave (2*Z*,4*Z*,6*E*)-**261** as a white powdery solid (262 mg, 8%, >99:1 dr); mp 116–118 ºC; ν_{max} (ATR) 1698 (C=O), 1615 (C=C); δ_H (400 MHz, $CDCl_3$) 1.50 (18H, br s, C*Me*$_3$), 5.76 (1H, d, *J* 11.4, C(2)*H*), 5.94 (1H, d, *J* 14.9, C(7)*H*), 6.37 (1H, t, *J* 11.6, C(5)*H*), 7.06 (1H, t, *J* 11.6, C(3)*H*), 7.55 (1H, t, *J* 11.6, C(4)*H*), 7.68 (1H, dd, *J* 14.9, 11.6, C(6)*H*); δ_C (100 MHz, $CDCl_3$) 28.2 (C*Me*$_3$), 80.7 (*C*Me$_3$), 122.7 *C*(2), 126.5 *C*(7), 130.6 *C*(4), 132.9 *C*(5), 135.9 *C*(3), 136.2 *C*(6), 165.4, 166.0 (*C*O); *m/z* (ESI^+) 303 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{16}H_{24}NaO_4^+$ ($[M+Na]^+$) requires 303.1567; found 303.1564. Further elution gave (2*Z*,4*E*,6*E*)-**261** as a white powdery solid (265 mg, 8%, 90:10 dr); mp 85–87 ºC; ν_{max} (ATR) 1702 (C=O), 1624 (C=C); δ_H (400 MHz, $CDCl_3$) 1.49 (9H, s, C*Me*$_3$), 1.50 (9H, s, C*Me*$_3$), 5.72 (1H, d, *J* 11.4, C(2)*H*), 5.92 (1H, d, *J* 15.4, C(7)*H*), 6.49 (1H, dd, *J* 15.2, 11.4, C(5)*H*), 6.53 (1H, t, *J* 11.4, C(3)*H*), 7.28 (1H, dd, *J* 15.4, 11.4, C(6)*H*), 7.78 (1H, dd, *J* 15.2, 11.6, C(4)*H*); δ_C (100 MHz, $CDCl_3$) 28.2 (C*Me*$_3$), 80.7 (*C*Me$_3$), 122.5 *C*(2), 126.3 *C*(7), 134.8 *C*(4), 137.2 *C*(5), 141.7 *C*(3), 142.4 *C*(6), 165.5, 165.8 (*C*O); *m/z* (ESI^+) 303 ($[M+Na]^+$, 88%); HRMS (ESI^+) $C_{16}H_{24}NaO_4^+$ ($[M+Na]^+$) requires 303.1567; found 303.1562. Further elution gave a mixture of (2*E*,4*Z*,6*E*)-**261** : (2*E*,4*E*,6*E*)-**261** (55:45) as a white powdery solid (2.00 g, 63%); (2*E*,4*Z*,6*E*)-**261**: δ_H (400 MHz, $CDCl_3$) 1.50 (18H, m, C*Me*$_3$), 5.93 (2H, d, *J* 15.2, C(2)*H*, C(7)*H*), 6.30–6.37 (2H, m, C(4)*H*, C(5)*H*), 7.63–7.74 (2H, m, C(3)*H*, C(6)*H*); δ_C (100 MHz, $CDCl_3$) 28.1 (C*Me*$_3$), 80.7 (*C*Me$_3$), 126.8 (*C*(2), *C*(7)), 133.1 (*C*(3), *C*(5)), 136.6 (*C*(3), *C*(6)), 165.8 (*C*O); (2*E*,4*E*,6*E*)-**261**: δ_H (400 MHz, $CDCl_3$) 1.49 (18H, s, C*Me*$_3$), 5.94 (2H, d, *J* 15.2, C(2)*H*, C(7)*H*), 6.53–6.62 (2H, m, C(4)*H*, C(5)*H*),

7.15–7.27 (2H, m, C(3)*H*, C(6)*H*); δ_C (100 MHz, $CDCl_3$) 28.1 (C*Me*$_3$), 80.7 (*C*Me$_3$), 126.3 (*C*(2), *C*(7)), 136.7 (*C*(4), *C*(5)), 141.8 (*C*(3), *C*(6)), 165.8 (*C*O).



(E)-**260** (2*Z*,4*E*,6*Z*)-**261** (2*E*,4*Z*,6*E*)-**261** (2*E*,4*E*,6*E*)-**261**

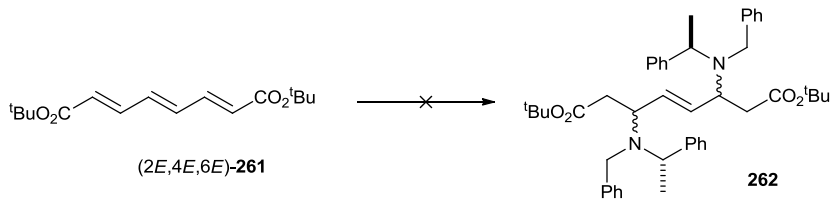
Method 2: Activated MnO_2 (9.87 g, 113 mmol) was added into a stirred solution of (*E*)-**260** (500 mg, 5.67 mmol) and **265** (5.12 g, 13.6 mmol) in CH_2Cl_2 (75 mL) at rt. After addition the reaction was stirred at rt for 48 h, before filtering by passage through a pad of Celite® (prewashed with 10% TEA in CH_2Cl_2) and the collected organics were concentrated *in vacuo to* give the crude reaction mixture. Purification via flash column chromatography (eluent 30-40 ºC petrol/Et_2O, 20:1) gave (2*Z*,4*E*,6*Z*)-**261** as a white powdery solid (191 mg, 12%, 90:10 dr) and a mixture of (2*E*,4*Z*,6*E*)-**261** : (2*E*,4*E*,6*E*)-**261** (48:52) as a white powdery solid (1.24g, 78%).



(E)-**260** (2*E*,4*E*,6*E*)-**261**

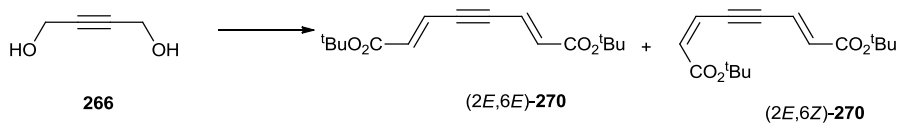
Method 3: A mixture of (*E*)-**260** (1.00 g, 11.4 mmol), **265** (8.55 g, 22.7 mmol), and iodoxybenzoic acid (6.36 g, 22.7 mmol) in dimethylsulfoxide (50 mL) was stirred at rt for 16 h. After that, water (100 mL) was added and stirred for another 5 min. Solid precipitate was filtered through a Celite® pad and filtrate was extracted with Et_2O (3 × 25 mL). The collected organics were concentrated *in vacuo to* give the crude reaction mixture. Purification via flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 10:1) gave (2*E*,4*E*,6*E*)-**261** as a white powder (2.67 g, 84%, >99:1 dr); mp 156–157 ºC; ν_{max} (ATR) 1696 (C=O), 1633 (C=C).

(*E*)-Di-*tert*-butyl 3-(benzyl[(*R*)-1-phenylethyl]amino)-6-{benzyl[(*S*) -1-phenylethyl]amino}oct-4-enedioate 262



Following *General Procedure 2c*, BuLi (2.5 M in hexanes, 0.72 mL, 1.80 mmol) and **150** (380 mg, 1.80 mmol) in THF (10 mL) at −78 °C, and (2*E,4E,6E*)-**261** (50 mg, 0.18 mmol) in THF (5 mL) at −78 °C gave the crude reaction mixture. There was no staring material, mono-addition product or bi-addition product observed by analysis of the mass spectrum and ^{1}H NMR spectrum of the crude reaction mixture.

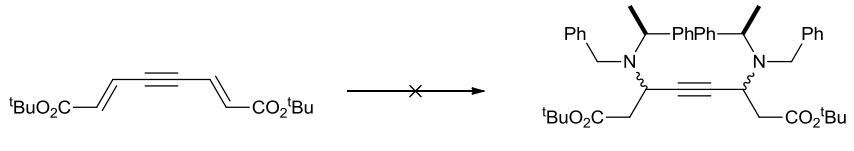
Di-*tert*-butyl octa-(2*E*,6*E*)-dien-4- ynedioate 270, di-*tert*-butyl -octa-(2*Z*,6*E*)-dien-4-ynedioate 270



Activated MnO_2 (60.6 g, 697 mmol) was added into a stirred solution of **266** (3.00 g, 34.9 mmol) and **265** (32.6 g, 83.6 mmol) in CH_2Cl_2 (500 mL) at rt. The reaction mixture was stirred at rt for 48 h, before filtering by passage through a pad of Celite® (prewashed with 10% TEA in CH_2Cl_2) and the collected organics were concentrated *in vacuo to* give the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 20:1) gave (2*E*,6*E*)-**270** as a white powder (6.98 g, 72%, >99:1 dr); mp 93−94 ºC; ν_{max} (ATR) 1624 (C=C); δ_H (400 MHz, $CDCl_3$) 1.50 (18H, s, C*Me*$_3$), 6.22 (2H, d, *J* 15.3, C(2)*H*, C(7)*H*), 6.79 (2H, d, *J* 15.3, C(3)*H*, C(6)*H*); δ_C (100 MHz, $CDCl_3$) 28.0 (C*Me*$_3$), 81.3 (*C*Me$_3$), 93.6 (*C*(4), *C*(5)), 122.9 (*C*(3), *C*(6)), 133.7 (*C*(2), *C*(7)), 164.7 (*C*O). Further elution gave (2*Z*,6*E*)-**270** as a pale yellow crystalline solid (2.13 g, 22%, >99:1 dr); mp 53−54 ºC; ν_{max} (ATR) 1620 (C=C); δ_H (400 MHz,

$CDCl_3$) 1.49 (9H, s, C*Me*$_3$), 1.51 (9H, s, C*Me*$_3$), 6.07 (1H, d, *J* 11.6, C(2)*H*), 6.21 (1H, dd, *J* 11.6, 2.0, C(3)*H*), 6.23 (1H, d, *J* 15.8, C(7)*H*), 6.86 (1H, dd, *J* 15.8, 2.5, C(6)*H*); δ_C (100 MHz, $CDCl_3$) 28.0 (C*Me*$_3$), 28.1 (C*Me*$_3$), 81.2 (*C*Me$_3$), 81.3 (*C*Me$_3$), 93.5, 96.5 (*C*(4), *C*(5)), 120.5 *C*(3), 123.4 *C*(6), 131.9 *C*(2), 133.2 *C*(7), 163.7, 164.8 (*C*O); *m/z* (ESI^+) 301 ($[M+Na]^+$, 95%); HRMS (ESI^+) $C_{16}H_{22}NaO_4^+$ ($[M+Na]^+$) requires 301.1410; found 301.1398.

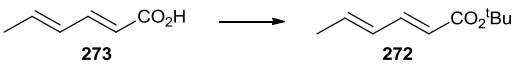
Di-*tert*-butyl 3-{benzyl[(*R*)-1-phenylethyl]amino}-6-{benzyl[(*S*)-1-phenylethyl]amino}oct-4-ynedioate 271



270 **271**

Following *General Procedure 2b*, BuLi (2.5 M in hexanes, 4.32 mL, 10.8 mmol) and **150** (2.28 g, 10.8 mmol) in THF (60 mL) at −78 °C, and **270** (1.00 g, 3.60 mmol) in THF (30 mL) at −78 °C gave the crude reaction mixture. There was no staring material, mono-addition product or bi-addition product observed by analysis of the mass spectrum and ^{1}H NMR spectrum of the crude reaction mixture.

(*E*,*E*)-*tert*-Butyl sorbate 272

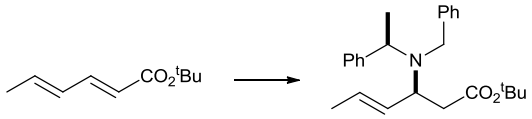


273 **272**

Condensed isobutylene (60 mL) at –78 °C was added to a stirred solution of **273** (10.0 g, 89.3 mmol) and concentrated H_2SO_4 (1.00 mL) in CH_2Cl_2 (200 mL) at 0 °C and stirred for 1 h. The reaction mixture was allowed to warm to rt and stirred for 48 h. The reaction mixture was washed with satd aq $NaHCO_3$ solution (5 × 100 mL) and the aq washing extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried, filtered and concentrated *in vacuo* to give **272** as a colourless oil (12.0 g, 81%) which required no further purification;[27] δ_H (400 MHz,

$CDCl_3$) 1.44 (9H, s, C*Me*$_3$), 1.80 (3H, d, *J* 6.0, C(6)*H*$_3$), 5.66 (1H, d, *J* 15.4, C(2)*H*), 6.01−6.16 (2H, m, C(4)*H*, C(5)*H*), 7.14 (1H, dd, *J* 15.4, 10.2, C(3)*H*).

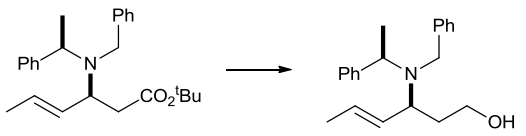
(3*S*,α*R*)-(*E*)-*tert*-Butyl 3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-enoate 274



272 **274**

Following *General Procedure 2a*, BuLi (2.5 M in hexanes, 15.0 mL, 37.5 mmol) and **150** (8.04 g, 38.1 mmol) in THF (120 mL) at −78 °C, and **272** (4.00 g, 23.8 mmol) in THF (80 mL) at −78 °C gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 20:1) gave **274** as a pale yellow oil (7.22 g, 80%, 98:2 dr);[27] $[\alpha]_D^{25}$ −22.2 (*c* 2.0 in $CHCl_3$); {lit.[27] $[\alpha]_D^{24}$ −23.3 (*c* 2.04 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$); 1.37 (9H, s, C*Me*$_3$), 1.38 (3H, partially obscured d, C(α)*Me*), 1.70 (3H, d, *J* 4.6, C(6)*H*$_3$), 2.22 (1H, dd, *J* 14.2, 9.2, C(2)H_AH_B), 2.35 (1H, dd, *J* 14.2, 5.5, C(2)H_AH_B), 3.66 (2H, s, NCH_2), 3.73−3.78 (1H, m, C(3)*H*), 4.01 (1H, q, *J* 6.8, C(α)*H*), 5.52−5.54 (2H, m, C(4)*H*, C(5)*H*), 7.17−7.39 (10H, m, *Ph*).

(3*S*,α*R*)-(*E*)-3-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]hex-4-en-1-ol 275

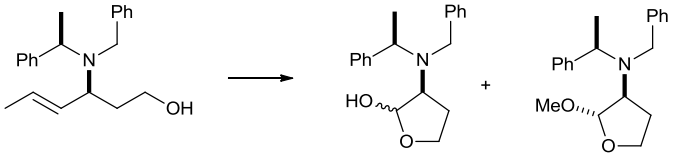


274 **275**

$LiAlH_4$ (1.0 M in THF, 7.65 mL, 7.65 mmol) was added into a solution of **274** (2.90 g, 7.65 mmol) in anhydrous THF (30 mL) at 0 °C under N_2, and the reaction mixture stirred at rt for 16 h. Lumps of ice and then 2.0 M aq NaOH solution (15 mL) were added into reaction mixture at 0 °C cautiously with vigorous stirring. The reaction mixture was stirred and allowed to warm to rt. EtOAc (90 mL) was added, and the mixture stirred for 30 min, before being filtered through Celite®, dried, filtered and

concentrated *in vacuo*. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 2:1) gave **275** as a colourless oil (2.14 g, 90%, 97:3 dr);[28] $[\alpha]_D^{25}$ −65.6 (*c* 2.7 in $CHCl_3$); {lit.[28] $[\alpha]_D^{24}$−62.3 (*c* 2.73 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.40−1.47 (1H, m, C(2)H_AH_B), 1.42 (3H, d, *J* 7.0, C(α)*Me*), 1.75 (3H, d, *J* 5.9, C(6)H_3), 1.81−1.90 (1H, m, C(2)H_AH_B), 2.73 (1H, br s, O*H*), 3.28−3.41 and 3.55−3.60 (3H, m, C(1)H_2, C(3)*H*), 3.64 (1H, d, *J* 13.7, NCH_AH_B), 3.90 (1H, d, *J* 13.7, NCH_AH_B), 4.06 (1H, q, *J* 7.0, C(α)*H*), 5.55 (1H, dq, *J* 15.0, 5.9, C(5)*H*), 5.67 (1H, dd, *J* 15.0, 9.1, C(4)*H*), 7.22−7.37 (10H, m, *Ph*).

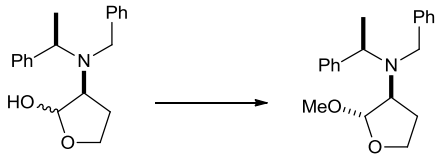
(3*S*)-3-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]tetrahydrofuran-2-ol 276, (2*S*,3*S*)-2-methoxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]tetrahydrofuran 256



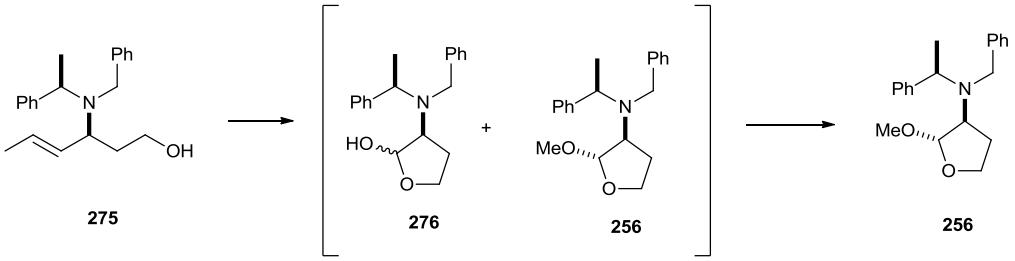
275 **276** **256**

Method 1: HCl (2.0 M in Et_2O, 6.50 mL, 13.0 mmol) was added to a solution of **275** (570 mg, 1.84 mmol) in Et_2O (14 mL). Solvent was removed *in vacuo* to yield the HCl salt of **276** which was dissolved in 1:1 CH_2Cl_2 : MeOH (80 mL). The solution was then cooled to –78˚C and ozone was bubbled through the solution until it was seen to turn blue. Oxygen was then bubbled through the solution until it was colourless, after which Me_2S (5 mL) was added dropwise. The reaction was allowed to warm to rt over 16 h. Volatiles were removed *in vacuo* and the residue dissolved in CH_2Cl_2 (50 mL), washed with satd aq $NaHCO_3$ solution (30 mL), dried and concentrated *in vacuo* to give a 84:16 mixture of **276**:**256**. Purification via flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 2:1) gave **276** as a coloreless oil (247 mg, 45%, 64:36 dr); ν_{max} (ATR) 3394 br (O–H), 1250 (C–N); δ_H (400 MHz, $CDCl_3$) 1.48 (3H, d, *J* 6.8, C(α)*Me*, major), 1.53 (3H, d, *J* 7.1, C(α)*Me*, minor), 1.59–1.77 (3H, m, C(4)H_A major, C(4)H_2 minor), 1.89–1.97 (1H, m, C(4)H_B major), 3.50–3.99 (11H, m, C(3)*H* both, C(5)H_2 both, NCH_2 both, C(α)*H* major), 4.17 (1H, q, *J* 7.1, C(α)*H*, minor), 5.37 (1H, d, *J* 4.3, C(2)*H*, minor), 5.51

(1H, d, *J* 1.8, C(2)*H*, major), 7.27–7.50 (20H, m, *Ph*, both); δ_C (100 MHz, $CDCl_3$) 13.5 (C(α)*Me*, minor), 15.9 (C(α)*Me*, major), 26.9 (*C*(4), minor), 29.1 (*C*(4), major), 50.8 (N*C*H_2, major), 52.9 (N*C*H_2, minor), 57.2 (*C*(α)Me, minor), 57.5 (*C*(α)Me, major), 63.1 (*C*(3), minor), 65.5 (*C*(3), major), 65.9(*C*(5), minor), 66.4(*C*(5), major), 96.5 (*C*(2), minor), 100.8 (*C*(2), major), 126.7, 126.8, 127.0, 127.2, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.5 (*o,m,p-Ph*, both), 140.6, 142.2 (*i-Ph*, minor), 141.3, 143.4 (*i-Ph*, major); *m/z* (ESI^+) 320 ($[M+Na]^+$, 92%), 298 ($[M+H]^+$, 69%); HRMS (ESI^+) $C_{19}H_{24}NO_2^+$ ($[M+H]^+$) requires 298.1802; found 298.1790. Further elution gave **256** as a colourless oil (46.0 mg, 8%, 95:5 dr); $[\alpha]_D^{25}$ −55.7 (*c* 2.0 in $CHCl_3$); ν_{max} (ATR) 1097, 1041 (C–O); δ_H (500 MHz, $CDCl_3$) 1.41 (3H, d, *J* 6.9, C(α)*Me*), 1.63–1.70 (1H, m, C(4)H_A), 1.84–1.90 (1H, m, C(4)H_B), 3.32 (3H, s, O*Me*), 3.47–3.51 (1H, m, C(3)*H*), 3.66–3.71 (1H, m, C(5)H_AH_B), 3.79 (2H, d, *J* 15.1, NCH_AH_B), 3.85–3.91 (2H, m, C(5)H_AH_B and C(α)*H*), 4.93 (1H, d, *J* 2.0, C(2)*H*), 7.21–7.44 (10H, m, *Ph*); δ_C (500 MHz, $CDCl_3$) 15.5 (C(α)*Me*), 29.2 (*C*(4)), 50.6 (N*C*H_2), 54.7 (O*Me*), 57.5 (*C*(α)Me), 64.6 (*C*(3)), 66.0 (*C*(5)), 107.2 (*C*(2)), 126.78, 126.79, 127.7, 128.0, 128.1, 128.2 (*o,m,p-Ph*), 141.4, 143.3 (*i-Ph*); *m/z* (ESI^+) 312 ($[M+H]^+$, 81%); HRMS (ESI^+) $C_{20}H_{26}NO_2^+$ ($[M+H]^+$) requires 312.1958; found 312.1955.



Method 2: HCl (1.25 M in MeOH, 2.00 mL, 2.50 mmol) was added to a solution of **276** (200 mg, 0.67 mmol) in MeOH (3 mL) at 50 °C under N_2, and the reaction mixture stirred at 50 °C for 16 h. Volatiles were removed *in vacuo* and the residue dissolved in CH_2Cl_2 (4 mL), washed with $NaHCO_3$ solution (4 mL), dried and concentrated *in vacuo* to give the crude reaction mixture. Purification via flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 15:1) gave **256** as a colourless oil (178 mg, 85%, 95:5 dr); $[\alpha]_D^{25}$ −56.7 (*c* 2.0 in $CHCl_3$).



Method 3: HCl (2.0 M in Et_2O, 3.40 mL, 6.80 mmol) was added to a solution of **275** (298 mg, 0.96 mmol) in Et_2O (10 mL). Solvent was removed *in vacuo* to yield the HCl salt of **275** which was dissolved in 1:1 CH_2Cl_2 : MeOH (40 mL). The solution was then cooled to −78˚C and ozone was bubbled through the solution until it was seen to turn blue. Oxygen was then bubbled through the solution until it was colourless, after which Me_2S (3 mL) was added dropwise. The reaction was allowed to warm to rt over 16 h. Volatiles were removed *in vacuo* and the residue dissolved in CH_2Cl_2 (25 mL), washed with satd aq $NaHCO_3$ solution (15 mL), dried and concentrated *in vacuo* to give a 85:15 mixture of **276**:**256** (179 mg). HCl (1.25 M in MeOH, 5.00 mL, 6.25 mmol) was added to a solution of a 85:15 mixture of **276**:**256** (179 mg) in MeOH (5 mL) at 50 °C under N_2, and the reaction mixture stirred at 50 °C for 16 h. Volatiles were removed *in vacuo* and the residue dissolved in CH_2Cl_2 (5 mL), washed with satd aq $NaHCO_3$ solution (5 mL), dried and concentrated *in vacuo* to give the crude reaction mixture. Purification via flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 15:1) gave **256** as a colourless oil (149 mg, 50%, 91:9 dr); $[\alpha]_D^{25}$ −56.4 (*c* 2.0 in $CHCl_3$).

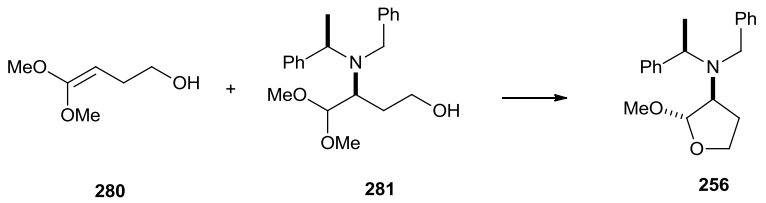
Method 4: HCl (2.0 M in Et_2O, 3.40 mL, 6.80 mmol) was added to a solution of **275** (298 mg, 0.96 mmol) in Et_2O (10 mL). Solvent was removed *in vacuo* to yield the HCl salt of **275** which was dissolved in MeOH (40 mL). The solution was then cooled to −78˚C and ozone was bubbled through the solution until it was seen to turn blue. Oxygen was then bubbled through the solution until it was colourless, after which Me_2S (3 mL) was added dropwise. The reaction was allowed to warm to rt over 16 h. Volatiles were removed *in vacuo* and the residue dissolved in CH_2Cl_2 (25 mL), washed with satd aq $NaHCO_3$ solution (15 mL), dried and concentrated *in vacuo* to give a 94:6 mixture of **276**:**256** (280 mg). HCl (1.25 M in MeOH, 5.00 mL, 6.25 mmol) was added to a

solution of a 94:6 mixture of **276**:**256** (280 mg) in MeOH (5 mL) at 50 °C under N_2, and the reaction mixture stirred at 50 °C for 16 h. Volatiles were removed *in vacuo* and the residue dissolved in CH_2Cl_2 (5 mL), washed with satd aq $NaHCO_3$ solution (5 mL), dried and concentrated *in vacuo* to give the crude reaction mixture. Purification via flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 15:1) gave **256** as a colourless oil (240 mg, 80%, 92:8 dr); $[\alpha]_D^{25}$ −56.9 (*c* 2.0 in $CHCl_3$).

Method 5: HCl (2.0 M in Et_2O, 3.40 mL, 6.80 mmol) was added to a solution of **275** (298 mg, 0.96 mmol) in Et_2O (10 mL). Solvent was removed *in vacuo* to yield the HCl salt of **275** which was dissolved in MeOH (40 mL). The solution was then cooled to –78˚C and ozone was bubbled through the solution until it was seen to turn blue. Oxygen was then bubbled through the solution until it was colourless, after which Me_2S (3 mL) was added dropwise. The reaction was allowed to warm to rt over 16 h. After this time, the reaction mixture is concentrated by rotary evaporation to 5 mL. HCl (1.25 M in MeOH, 5.00 mL, 6.25 mmol) was added to the reaction mixture at 50 °C under N_2, and the reaction mixture stirred at 50 °C for 16 h. Volatiles were removed *in vacuo* and the residue dissolved in CH_2Cl_2 (5 mL), washed with satd aq $NaHCO_3$ solution (5 mL), dried and concentrated *in vacuo* to give the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 15:1) gave **256** as a colourless oil (278 mg, 93%, 89:11 dr); $[\alpha]_D^{25}$ −60.0 (*c* 2.0 in $CHCl_3$).

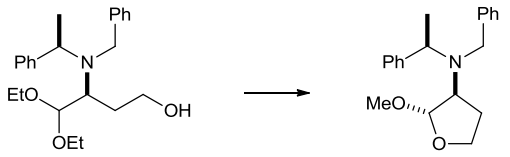
Method 6: HCl (2.0 M in Et_2O, 3.40 mL, 6.80 mmol) was added to a solution of **275** (298 mg, 0.96 mmol) in Et_2O (10 mL). Solvent was removed *in vacuo* to yield the HCl salt of **275** which was dissolved in MeOH (40 mL). The solution was then cooled to –78˚C and ozone was bubbled through the solution until it was seen to turn blue. Oxygen was then bubbled through the solution until it was colourless, after which PPh_3 (2.50 g, 9.60 mmol) was added potionwise. The reaction was allowed to warm to rt over 16 h. After this time, the reaction mixture is concentrated by rotary evaporation to 5 mL. HCl (1.25 M in MeOH, 5.00 mL, 6.25 mmol) was added to the reaction mixture at 50 °C

under N_2, and the reaction mixture stirred at 50 °C for 16 h. Volatiles were removed *in vacuo* and the residue dissolved in CH_2Cl_2 (5 mL), washed with satd aq $NaHCO_3$ solution (5 mL), dried and concentrated *in vacuo* to give the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 15:1) gave **256** as a colourless oil (242 mg, 81%, 88:12 dr); $[\alpha]_D^{25}$ −59.3 (*c* 2.0 in $CHCl_3$).



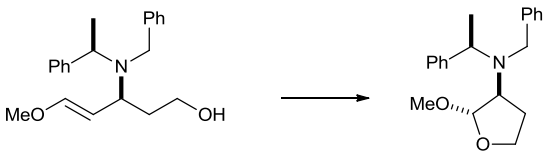
280 **281** **256**

Method 7: HCl (1.25 M in MeOH, 1.50 mL, 1.88 mmol) was added to a solution of a 87:13 inseparable mixture of **280**:**281** (150 mg) in MeOH (1.50 mL) at rt under N_2, and the reaction mixture stirred at 50 °C for 16 h. Volatiles were removed *in vacuo* and the residue dissolved in CH_2Cl_2 (3 mL), washed with satd aq $NaHCO_3$ solution (3 mL), dried and concentrated *in vacuo* to give **256 (**with 15% unknown impurities) as a colourless oil (126 mg, 72:28 dr).



287 **256**

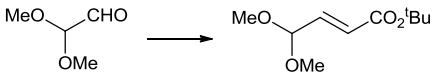
Method 8: HCl (1.25 M in MeOH, 0.26 mL, 0.32 mmol) was added to a solution of **287** (30.0 mg, 0.08 mmol) in MeOH (1.60 mL) at rt under N_2, and the reaction mixture stirred at 80 °C for 16 h. Volatiles were removed *in vacuo* and the residue dissolved in CH_2Cl_2 (3 mL), washed with satd aq $NaHCO_3$ solution (3 mL), dried and concentrated *in vacuo* to give **256** as a colourless oil (24 mg, 97%, 88:12 dr); $[\alpha]_D^{25}$ −58.9 (*c* 2.0 in $CHCl_3$).



305 **256**

Method 9: HCl (2.0 M in Et_2O, 3.40 mL, 6.80 mmol) was added to a solution of **305** (312 mg, 0.96 mmol) in Et_2O (10 mL). Solvent was removed *in vacuo* to yield the HCl salt of **305** which was dissolved in MeOH (40 mL). The solution was then cooled to –78˚C and ozone was bubbled through the solution until it was seen to turn blue. Oxygen was then bubbled through the solution until it was colourless, after which Me_2S (3 mL) was added dropwise. The reaction was allowed to warm to rt over 16 h. After this time, the reaction mixture is concentrated by rotary evaporation to 5 mL. HCl (1.25 M in MeOH, 5.00 mL, 6.25 mmol) was added to the reaction mixture at 50 °C under N_2, and the reaction mixture stirred at 50 °C for 16 h. Volatiles were removed *in vacuo* and the residue dissolved in CH_2Cl_2 (5 mL), washed with satd aq $NaHCO_3$ solution (5 mL), dried and concentrated *in vacuo* to give the crude reaction mixture. Purification via flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 15:1) gave **256** as a colourless oil (275 mg, 92%, 88:12 dr); $[\alpha]_D^{25}$ −59.0 (*c* 2.0 in $CHCl_3$).

(*E*)-*tert*-Butyl 4,4-dimethoxybut-2-enoate 277

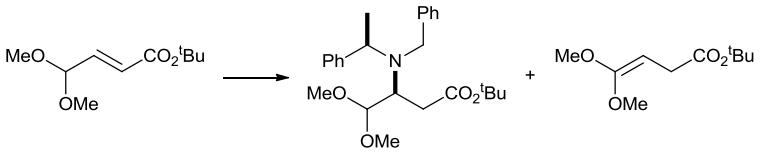


277

K_2CO_3 (7.89 g, 57.1 mmol) was added portionwise to a stirred solution of **265** (8.00 g, 31.7 mmol) in cyclohexane (48 mL) at 60 ˚C under nitrogen. After stirring for 2 h, 2,2-Dimethoxyacetaldehyde (60%wt in H_2O, 11.9 mL, 79.3 mmol) was added *via* syringe. After stirring for a further 3 h at 60 ˚C the reaction mixture was quenched with sat aq NH_4Cl solution. The phases were separated and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried, filtered, and concentrated *in vacuo* to give the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 20:1) gave **277** as a colourless oil (6.28

g, 98%, 95:5 dr);[29] δ_H (400 MHz, $CDCl_3$) 1.46−1.47 (9H, m, C*Me*$_3$), 3.31−3.32 (6H, m, C(O*Me*)$_2$), 4.89−4.90 (1H, m, *J* 4.4, C(4)*H*), 6.01−6.06 (1H, m, C(2)*H*), 6.61−6.67 (1H, m, C(3)*H*).

tert-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,4-dimethoxybutanoate 278, _tert_-Butyl 4,4-dimethoxybut-3-enoate 279

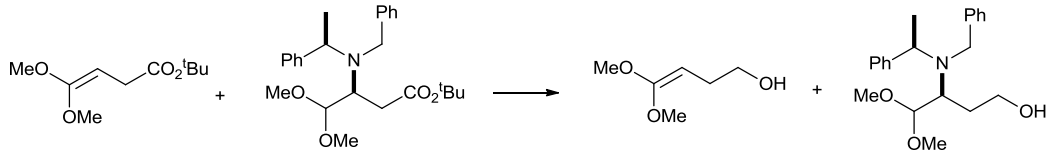


277 **278** **279**

Method 1: Following *General Procedure 2a*, BuLi (2.5 M in hexanes, 6.20 mL, 15.5 mmol) and **150** (3.38 g, 16.0 mmol) in THF (50 mL) at −78 °C, and **277** (2.02 g, 10.0 mmol) in THF (30 mL) at −78 °C gave the crude reaction mixture. Purification via flash column chromatography (eluent hexane/EtOAc, 10:1) gave a 87:13 inseparable mixture of **278**:**279** as a yellow oil (2.80 g). **278**: δ_H (400 MHz, $CDCl_3$) 1.38 (3H, d, *J* 7.0, C(α)*Me*), 1.43 (9H, s, C*Me*$_3$), 1.97 (1H, dd, *J* 15.2, 4.1, C(2)H_AH_B), 2.24 (1H, dd, *J* 15.4, 8.5, C(2)H_AH_B), 3.30 (3H, s, O*Me*), 3.35 (3H, s, O*Me*), 3.58 (1H, d, 14.9, NCH_AH_B), 3.69−3.74 (1H, m, C(3)*H*), 3.90 (1H, q, *J* 7.0, C(α)*H*), 3.93 (1H, d, 15.0, NCH_AH_B), 4.28 (1H, d, *J* 5.0, C(4)*H*), 7.21−7.43 (10H, m, *Ph*); **279**: δ_H (400 MHz, $CDCl_3$) 1.49 (9H, s, C*Me*$_3$), 2.47−2.49 (2H, m, C(2)H_2), 2.92 (3H, s, O*Me*), 3.26 (3H, s, O*Me*), 3.77 (1H, d 4.0, C(3)*H*).

Method 2: Following *General Procedure 2d*, BuLi (2.5 M in hexanes, 1.94 mL, 4.85 mmol) and **150** (1.06 g, 5.00 mmol) in Et_2O (10 mL) at −20 °C, and **277** (505 mg, 2.50 mmol) in Et_2O (5 mL) at −20 °C gave the crude reaction mixture. Purification via flash column chromatography (eluent hexane/EtOAc, 10:1) gave a 85:15 inseparable mixture of **278**:**279** as a yellow oil (693 mg).

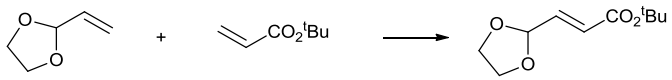
4,4-Dimethoxybut-3-en-1-ol 280 and (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-4,4-dimethoxybutan-1-ol 281



279 **278** **280** **281**

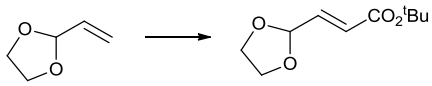
$LiAlH_4$ (1.0 M in THF, 1.13 mL, 1.13 mmol) was added into a solution of a 87:13 inseparable mixture of **278**:**279** (450 mg) in anhydrous THF (5 mL) at 0 °C under N_2, and the reaction mixture stirred at rt for 16 h. Lumps of ice and then 2.0 M aq NaOH solution (3.00 mL) were added into reaction mixture at 0 °C cautiously with vigorous stirring. The reaction mixture was stirred and allowed to warm to rt. EtOAc (13 mL) was added, and the mixture stirred for 30 min, before being filtered through Celite®, dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 1:1) gave a 87:13 inseparable mixture of **281**:**280** as a colourless oil (269 mg, 99:1 dr); ν_{max} (ATR) 3425br (O–H). **281**: δ_H (500 MHz, $CDCl_3$) 1.40 (3H, d, *J* 6.9, C(α)*Me*), 1.54−1.60 (1H, m, C(2)H_AH_B), 1.69−1.76 (1H, m, C(2)H_AH_B), 2.28 (1H, br s, O*H*), 3.02−3.06 (1H, m, C(3)*H*), 3.39 (3H, s, O*Me*), 3.42 (3H, s, O*Me*), 3.44−3.46 (2H, m, C(1)H_2), 3.88 (1H, d, *J* 14.2, NCH_AH_B), 3.93 (1H, d, *J* 14.2, NCH_AH_B), 4.06 (1H, q, *J* 6.9, C(α)*H*), 4.45 (1H, d, *J* 3.5, C(4)*H*), 7.24−7.46 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 17.7 (C(α)*Me*), 29.0 (*C*(2)), 50.9 (N*C*H_2), 55.4 (O*Me*), 55.6 (O*Me*), 56.4 (*C*(3)), 57.4 (*C*(α)Me), 61.3 (*C*(1)), 108.4 (*C*(4)), 126.7, 126.9, 127.8, 128.2, 128.3, 128.5 (*o,m,p-Ph*), 141.5, 143.1 (*i-Ph*); *m/z* (ESI^+) 366 ($[M+Na]^+$, 100%), 344 ($[M+H]^+$, 97%). **280**: δ_H (500 MHz, $CDCl_3$) 1.82−1.86 (2H, m, C(2)H_2), 3.02−3.06 (2H, m, C(1)H_2), 3.05 (3H, s, O*Me*), 3.30 (3H, s, O*Me*), 3.72−3.77 (1H, m, C(3)*H*); δ_C (500 MHz, $CDCl_3$) 29.5 (*C*(2)), 50.9 (*C*(1)), 55.5 (O*Me*), 56.7 (O*Me*), 61.9 (*C*(3)), 143.7 (*C*(4)).

(*E*)-*tert*-Butyl 3-(1,3-dioxolan-2-yl)acrylate 282



282

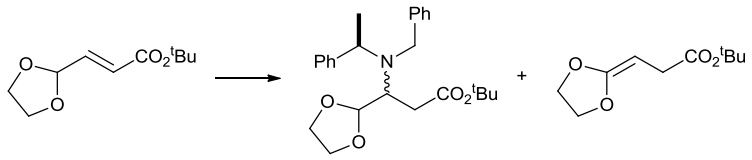
Method 1: Hoveyda-Grubbs II (625 mg, 1.00 mmol) was added to a degassed solution of 2-vinyl-1,3-dioxolane acrylate (1.00 g, 9.98 mmol) and *tert*-butyl acrylate (4.39 mL, 30.0 mmol) in CH_2Cl_2 (38 mL) and the resultant mixture was heated at reflux for 22 h. The reaction mixture was then concentrated *in vacuo* to give the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 35:1) gave **282** as a brown oil (1.64 g, 82%, >99:1 dr); ν_{max} (ATR) 1717 (C=O), 1663 (C=C), 1058 (C–O–C); δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, C*Me*$_3$), 3.92−4.02 (4H, m, OC*H*$_2$C*H*$_2$O), 5.43 (1H, dd, *J* 4.8, 1.0, C(4)*H*), 6.06 (1H, dd, *J* 15.7, 1.0, C(2)*H*), 6.66 (1H, dd, *J* 15.7, 4.8, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 27.9 (C*Me*$_3$), 65.0 (OCH_2CH_2O), 80.8 (*C*Me$_3$), 101.3 (*C*(4)), 126.3 (*C*(2)), 140.7 (*C*(3)), 164.9 (*C*O).



282

Method 2: A solution of 2-vinyl-1,3-dioxolane acrylate (2.50 g, 25.0 mmol) in CH_2Cl_2 (80 mL) was cooled to –78˚C and ozone was bubbled through the solution until it was seen to turn blue. Oxygen was then bubbled through the solution until it was colourless, after which Me_2S (5 mL) was added dropwise. The reaction was allowed to warm to rt over 16 h. **265** (9.40 g, 25.0 mmol) was added into this reaction mixture at rt. The reaction was then stirred at rt for 16 h and concentrated *in vacuo* to give a crude reaction mixture. Purification via flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 35:1) gave **282** as a brown oil (3.50 g, 70%, >99:1 dr).

***tert*-Butyl (α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(1,3-dioxolan-2-yl)-propanoate 283 and *tert*-butyl 3-(1',3'-dioxolan-2'-ylidene)propanoate 284**

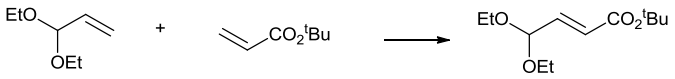


282 **283** **284**

Method 1: Following *General Procedure 2a*, BuLi (2.5 M in hexanes, 0.35 mL, 0.88 mmol) and **150** (191 mg, 0.90 mmol) in THF (15 mL) at −78 °C, and **282** (113 mg, 0.57 mmol) in THF (8 mL) at −78 °C gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 7:1) gave a 82:18 inseparable mixture of **283**:**284** as a light yellow oil (140 mg, **283**: 54:46 dr). **283**: δ_H (400 MHz, $CDCl_3$) 1.41 (3H, d, *J* 6.8, C(α)*Me*, minor), 1.42 (3H, d, *J* 7.1, C(α)*Me*, major), 1.44 (9H, s, C*Me*$_3$, minor), 1.50 (9H, s, C*Me*$_3$, major), 1.90 (1H, dd, *J* 14.9, 3.4, C(2)H_AH_B, major), 2.28 (1H, dd, *J* 14.9, 9.4, C(2)H_AH_B, major), 2.43−2.53 (2H, m, C(2)H_AH_B, minor), 3.58−4.04 (8H, m, NCH_2, C(3)*H*, C(α)*H*, both), 4.51 (1H, d, *J* 2.0, C(4)*H*, major), 5.07 (1H, d, *J* 3.3, C(4)*H*, minor), 7.23−7.47 (20H, m, *Ph*, both). **284**: δ_H (400 MHz, $CDCl_3$) 1.47 (9H, s, C*Me*$_3$), 2.17 (1H, dd, *J* 14.7, 6.6, C(2)H_AH_B), 2.40 (1H, dd, *J* 14.7, 6.1, C(2)H_AH_B), 3.58−4.04 (4H, m, OCH_2CH_2O), 4.87 (1H, d 3.5, C(3)*H*).

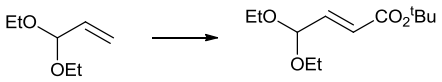
Method 2: Following *General Procedure 2d*, BuLi (2.5 M in hexanes, 0.78 mL, 1.94 mmol) and **150** (423 mg, 2.00 mmol) in Et_2O (20 mL) at −20 °C, and **282** (200 mg, 1.00 mmol) in Et_2O (10 mL) at −20 °C gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 7:1) gave a 82:18 inseparable mixture of **283**:**284** as a light yellow oil (235 mg, **283**: 52:48 dr).

(*E*)-*tert*-Butyl 4,4-diethoxybut-2-enoate 285



285

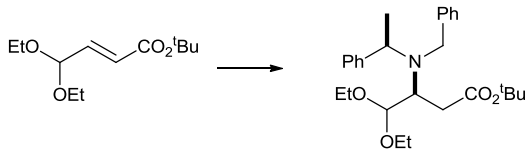
Method 1: Hoveyda-Grubbs II (482 mg, 0.77 mmol) was added to a degassed solution of acrolein diethyl acetal (1.00 g, 7.68 mmol) and *tert*-butyl acrylate (3.37 mL, 23.0 mmol) in CH_2Cl_2 (38 mL) and the resultant mixture was heated at reflux for 22 h. The reaction mixture was then concentrated *in vacuo* to give the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 35:1) gave **285** as a colourless oil (1.59 g, 90%, >99:1 dr); ν_{max} (ATR) 1716 (C=O), 1664 (C=C); δ_H (400 MHz, $CDCl_3$) 1.23 (6H, t, *J* 7.2, $O(CH_2\mathit{Me})_2$), 1.49 (9H, s, $C\mathit{Me}_3$), 3.49−3.56 and 3.62−3.69 (4H, m, $O(C\mathit{H}_2Me)_2$), 5.03 (1H, dd, *J* 4.4, 1.4, C(4)*H*), 6.05 (1H, dd, *J* 15.9, 1.4, C(2)*H*), 6.72 (1H, dd, *J* 15.9, 4.4, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 15.1 ($O(CH_2\mathit{Me})_2$), 27.9 ($C\mathit{Me}_3$), 61.2 ($O(\mathit{C}H_2Me)_2$), 80.6 ($\mathit{C}Me_3$), 99.2 (*C*(4)), 125.7 (*C*(2)), 142.2 (*C*(3)), 165.2 (*C*O); *m/z* (ESI^+) 253 ($[M+Na]^+$, 44%); HRMS (ESI^+) $C_{12}H_{22}NaO_4^+$ ($[M+Na]^+$) requires 253.1410; found 253.1401.



285

Method 2: A solution of acrolein diethyl acetal (2.50 g, 19.2 mmol) in CH_2Cl_2 (80 mL) was cooled to –78˚C and ozone was bubbled through the solution until it was seen to turn blue. Oxygen was then bubbled through the solution until it was colourless, after which Me_2S (5 mL) was added dropwise. The reaction was allowed to warm to rt over 16 h. **265** (7.23 g, 19.2 mmol) was added into this reaction mixture at rt. The reaction was then stirred at rt for 16 h and concentrated *in vacuo* to give a crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 35:1) gave **285** as a colourless oil (3.45 g, 78%, >99:1 dr).

tert-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,4-diethoxybutanoate 286

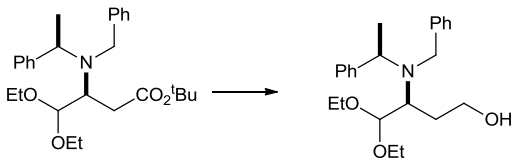


285 **286**

Method 1: Following *General Procedure 2a*, BuLi (2.5 M in hexanes, 0.35 mL, 0.86 mmol) and **150** (188 mg, 0.89 mmol) in THF (15 mL) at −78 °C, and **285** (128 mg, 0.56 mmol) in THF (10 mL) at −78 °C gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 15:1) gave **286** as a colourless oil (214 mg, 87%, 99:1 dr); $[\alpha]_D^{25}$ −33.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.12 (3H, t, *J* 7.1, $OCH_2\textit{Me}$), 1.22 (3H, t, *J* 7.1, $OCH_2\textit{Me}$), 1.41 (3H, d, *J* 7.1, C(α)*Me*), 1.46 (9H, s, C$\textit{Me}_3$), 1.99 (1H, dd, *J* 15.7, 4.3, C(2)$\textit{H}_A\text{H}_B$), 2.33 (1H, dd, *J* 15.7, 7.8, C(2)$\text{H}_A\textit{H}_B$), 3.42−3.58 (3H, m, OC$\textit{H}_2$Me and OC$\textit{H}_A\text{H}_B$Me), 3.63 (1H, d, 14.9, NC$\textit{H}_A\text{H}_B$), 3.72−3.80 (2H, m, C(3)*H* and $OCH_A\textit{H}_B$Me), 3.93 (1H, q, *J* 7.1, C(α)*H*), 3.99 (1H, d, 14.9, NC$\textit{H}_A\text{H}_B$), 4.45 (1H, d, *J* 4.8, C(4)*H*), 7.22−7.44 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.1, 15.4 ($O(CH_2\textit{Me})_2$), 19.9 (C(α)*Me*), 28.1 (C$\textit{Me}_3$), 33.5 (*C*(2)), 51.2 (N*C*H_2), 55.0 (*C*(3)), 58.6 (*C*(α)Me), 62.7, 63.8 ($O(\textit{C}H_2Me)_2$), 79.7 (*C*Me_3), 105.8 (*C*(4)), 126.4, 126.8, 127.9, 128.0, 128.1, 128.2 (*o,m,p-Ph*), 141.9, 143.2 (*i-Ph*), 171.8 (*C*O); *m/z* (ESI^+) 442 ($[M+H]^+$, 69%); HRMS (ESI^+) $C_{27}H_{40}NO_4^+$ ($[M+H]^+$) requires 442.2952; found 442.2948.

Method 2: Following *General Procedure 2d*, BuLi (2.5 M in hexanes, 0.78 mL, 1.94 mmol) and **150** (423 mg, 2.00 mmol) in Et_2O (20 mL) at −20 °C, and **285** (230 mg, 1.00 mmol) in Et_2O (10 mL) at −20 °C gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 15:1) gave **286** as a colourless oil (375 mg, 85%, 97:3 dr); $[\alpha]_D^{25}$ −32.7 (*c* 1.0 in $CHCl_3$).

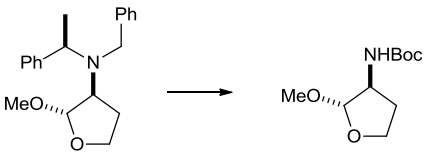
(3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,4-diethoxybutan-1-ol 287



286 **287**

$LiAlH_4$ (1.0 M in THF, 2.72 mL, 2.72 mmol) was added into a solution **286** (1.00 g, 2.27 mmol) in anhydrous THF (10 mL) at 0 °C under N_2, and the reaction mixture stirred at rt for 16 h. Lumps of ice and then 2.0 M aq NaOH solution (6.00 mL) were added into reaction mixture at 0 °C cautiously with vigorous stirring. The reaction mixture was stirred and allowed to warm to rt. EtOAc (30 mL) was added, and the mixture stirred for 30 min, before being filtered through Celite®, dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 2:1) gave **287** as a colourless oil (808 mg, 96%, 96:4 dr); $[\alpha]_D^{25}$ −28.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3427br (O–H), 1057 (C–O–C); δ_H (400 MHz, $CDCl_3$) 1.16 (3H, t, *J* 7.1, OCH_2*Me*), 1.24 (3H, t, *J* 7.1, OCH_2*Me*), 1.39 (3H, d, *J* 6.8, C(α)*Me*), 1.50−1.58 (1H, m, C(2)H_AH_B), 1.74−1.82 (1H, m, C(2)H_AH_B), 2.57 (1H, br s, O*H*), 2.99−3.03 (1H, m, C(3)*H*), 3.45−3.53 (2H, m, C(1)H_2), 3.61−3.68 (2H, m, OCH_2Me), 3.75−3.82 (2H, m, OCH_2Me), 3.86 (1H, d, *J* 14.6, NCH_AH_B), 3.98 (1H, d, *J* 14.6, NCH_AH_B), 4.03 (1H, q, *J* 6.8, C(α)*H*), 4.59(1H, d, *J* 3.5, C(4)*H*), 7.23−7.39 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.2, 15.4 (O(CH_2*Me*)$_2$), 18.2 (C(α)*Me*), 29.0 (*C*(2)), 51.0 (NCH_2), 57.3, 57.6 (*C*(3), *C*(α)Me), 61.6 (*C*(1)), 63.7, 63.9 (O(CH_2Me)$_2$), 106.3 (*C*(4)), 126.6, 126.9, 127.7, 128.20, 128.22, 128.4 (*o,m,p-Ph*), 141.8, 144.2 (*i-Ph*); *m/z* (ESI^+) 394 ($[M+Na]^+$, 16%), 372 ($[M+H]^+$, 83%); HRMS (ESI^+) $C_{23}H_{33}NaNO_3^+$ ($[M+Na]^+$) requires 394.2353; found 394.2350.

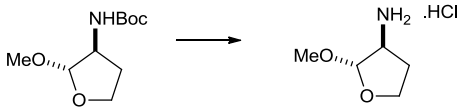
tert-Butyl [(2*S*,3*S*)-2-methoxytetrahydrofuran-3-yl]carbamate 288



256 **288**

Following *General Procedure 3*, **256** (200 mg, 0.64 mmol), Boc_2O (435 mg, 1.28 mmol), $Pd(OH)_2/C$ (50% w/w, 100 mg) and H_2 (5 atm) in MeOH (2 mL) after 24 h gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/EtOAc, 10:1) gave **288** as a colourless oil (125 mg, 90%, 97:3 dr); $[\alpha]_D^{25}$ −34.8 (*c* 2.1 in $CHCl_3$); ν_{max} (ATR) 3329 (N−H), 1690 (C=O); δ_H (500 MHz, $CDCl_3$) 1.44 (9H, s, C*Me*$_3$), 1.66−1.72 (1H, m, C(4)*H*$_A$), 2.32−2.39 (1H, m, C(4)*H*$_B$), 3.32 (3H, s, O*Me*), 3.90−4.00 (2H, m, C(5)*H*$_2$), 4.08 (1H, br s, C(3)*H*), 4.62 (1H, br s, N*H*), 4.78 (1H, m, C(2)*H*); δ_C (125 MHz, $CDCl_3$) 28.3 (C*Me*$_3$), 30.2 (*C*(4)), 54.4 (O*Me*), 55.8 (*C*(3)), 65.7 (*C*(5)), 79.6 (*C*Me$_3$), 107.8 (*C*(2)), 155.0 (*C*O); *m/z* (ESI^+) 240 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{10}H_{19}NNaO_4^+$ ($[M+Na]^+$) requires 240.1206; found 240.1214.

(2*S*,3*S*)-2-Methoxy-3-aminotetrahydrofuran hydrochloride salt 258

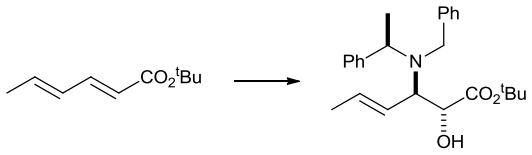


288 **258**

HCl (1.25 M in MeOH, 10.0 mL, 12.5 mmol) was added in **288** (100 mg, 0.46 mmol, 97:3 dr) at rt, and the reaction mixture stirred at rt for 16 h. Volatiles were removed *in vacuo* to give **258** as a coloreless oil (68.0 mg, 96%, 82:18 dr); $[\alpha]_D^{25}$ −46.7 (*c* 2.2 in $CHCl_3$); ν_{max} (ATR) 1451 (CH_2), 1388 (CH_3), 1097, 1041 (C–O); δ_H (500 MHz, D_2O) 1.91−1.98 (1H, m, C(4)*H*$_A$, major), 1.97−2.04 (1H, m, C(4)*H*$_A$, minor), 2.29−2.35 (1H, m, C(4)*H*$_B$, minor), 2.36−2.44 (1H, m, C(4)*H*$_B$, major), 3.31 (3H, s, O*Me*, major), 3.36 (3H, s, O*Me*, minor), 3.75 (1H, dd, *J* 7.6, 2.8, C(3)*H*, major), 3.78 (1H, dd, *J* 8.5, 4.7, C(3)*H*, minor), 3.84−3.90 (1H, m, C(5)*H*$_A$, minor), 3.94 (1H, ddd, *J* 18.0, 8.8, 6.6, C(5)*H*$_A$, major), 4.01 (1H, ddd, *J* 17.7, 8.8, 5.0, C(5)*H*$_B$, minor), 4.10 (1H, ddd, *J* 17.3,

8.5, 5.4, C(5)H_B, major), 5.06 (1H, d, *J* 4.7, C(2)*H*, minor), 5.08 (1H, s, C(2)*H*, major); δ_C (125 MHz, D_2O) 26.7 (*C*(4), minor), 27.5 (*C*(4), major), 51.4 (O*Me*, minor), 51.7 (*C*(3), minor), 54.6 (O*Me*, major), 55.2 (*C*(3), major), 65.4 (*C*(5), minor), 65.8 (*C*(5), major), 100.8 (*C*(2), minor), 105.0 (*C*(2), major).

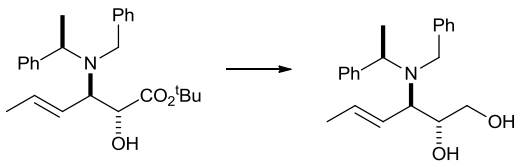
(2*R*,3*R*,α*R*)-(*E*)-*tert*-Butyl 3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-2-hydroxyhex-4-enoate 289



272 **289**

Following *General Procedure 2a*, **150** (5.03 g, 23.8 mmol) in THF (60 mL), BuLi (2.5 M in hexanes, 9.22 mL, 23.1 mmol), **272** (2.50 g, 14.9 mmol) in THF (30 mL) and (−)-CSO **83** (5.80 g, 25.3 mmol) at −78 °C gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 20:1) gave **289** as a pale yellow oil (4.06 g, 69%, >99:1 dr);[27] $[\alpha]_D^{25}$ −63.1 (*c* 1.0 in $CHCl_3$); {lit.[27] $[\alpha]_D^{25}$ −62.6 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$); 1.34 (9H, s, C*Me*$_3$), 1.37 (3H, d, *J* 6.8, C(α)*Me*), 1.71 (3H, d, *J* 6.3, C(6)H_3), 2.94 (1H, br s, O*H*), 3.54 (1H, dd, *J* 9.1, 2.6, C(3)*H*), 3.76 (1H, d, *J* 14.4, NCH_AH_B), 3.97 (1H, d, *J* 14.4, NCH_AH_B), 4.08 (1H, br s, C(2)*H*), 4.23 (1H, q, *J* 6.8, C(α)*H*), 5.55 (1H, dq, *J* 15.4, 6.3, C(5)*H*), 5.66−5.72 (1H, m, C(4)*H*), 7.19−7.42 (10H, m, *Ph*).

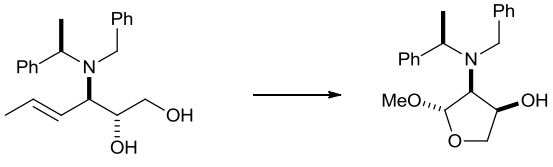
(2*R*,3*R*,*αR*)-(*E*)-2-Hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-en-1-ol 290



289 290

$LiAlH_4$ (1.0 M in THF, 3.80 mL, 3.80 mmol) was added into a solution of **289** (1.50 g, 3.80 mmol) in anhydrous THF (15 mL) at 0 °C under N_2, and the reaction mixture stirred at rt for 16 h. Lumps of ice and then 2.0 M aq NaOH solution (8.00 mL) were added into reaction mixture at 0 °C cautiously with vigorous stirring. The reaction mixture was stirred and allowed to warm to rt. EtOAc (45 mL) was added, and the mixture stirred for 30 min, before being filtered through Celite®, dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 2:1) gave **290** as a colourless oil (1.10 g, 90%, >99:1 dr);[30] $[\alpha]_D^{25}$ −49.4 (*c* 1.0 in $CHCl_3$); {lit.[30] $[\alpha]_D^{22}$ −48.7 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.42 (3H, d, *J* 6.7, C(α)*Me*), 1.83 (3H, d, *J* 4.8, C(6)H_3), 3.20 (1H, br s, C(3)*H*), 3.44 (2H, d, *J* 5.0, C(1)H_2OH), 3.62 (1H, br s, C(2)*H*OH), 3.70 (1H, d, *J* 13.7, NCH_AH_B), 3.93 (1H, d, *J* 13.7, NCH_AH_B), 4.04−4.13 (1H, m, C(α)*H*), 5.67−5.79 (2H, m, C(5)*H*, C(4)*H*), 7.26−7.36 (10H, m, *Ph*).

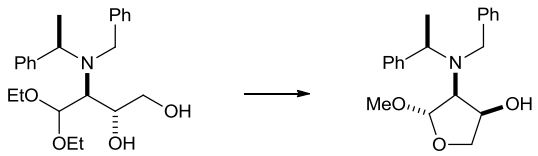
(2*S*,3*S*,*4R*)-2-Methoxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]tetrahydrofuran-4-ol 257



290 257

Method 1: HCl (2.0 M in Et_2O, 3.77 mL, 7.53 mmol) was added to a solution of **290** (350 mg, 1.08 mmol) in Et_2O (10 mL). Solvent was removed *in vacuo* to yield the HCl salt of **290** which was dissolved in MeOH (40 mL). The solution was then cooled to –

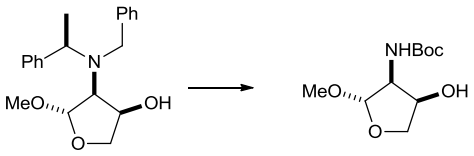
78˚C and ozone was bubbled through the solution until it was seen to turn blue. Oxygen was then bubbled through the solution until it was colourless, after which Me_2S (3 mL) was added dropwise. The reaction was allowed to warm to rt over 16 h. After this time, the reaction mixture is concentrated by rotary evaporation to 5 mL. HCl (1.25 M in MeOH, 6.00 mL, 7.50 mmol) was added to the reaction mixture at 50 °C under N_2, and the reaction mixture stirred at 50 °C for 16 h.Volatiles were removed *in vacuo* and the residue dissolved in CH_2Cl_2 (5 mL), washed with satd aq $NaHCO_3$ solution (5 mL), dried and concentrated *in vacuo* to give the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 4:1) gave **257** as a colourless oil (268 mg, 76%, 87:13 dr); $[\alpha]_D^{25}$ −56.8 (*c* 2.0 in $CHCl_3$); ν_{max} (ATR) 3440 (O−H), 1450 (CH_2), 1377 (CH_3), 1097, 1044 (C–O); δ_H (400 MHz, $CDCl_3$) 1.53 (3H, d, *J* 6.8, C(α)*Me*, major), 1.48 (3H, d, *J* 7.0, C(α)*Me*, minor), 3.00−3.02 (1H, m, C(3)*H*, minor), 3.17 (3H, s, O*Me*, minor), 3.30 (1H, dd, *J* 5.6, 2.1, C(3)*H*, major), 3.32 (3H, s, O*Me*, major), 3.83−3.97 (5H, m, C(5)H_AH_B, C(4)*H*OH, NCH_AH_B, both), 4.12 (1H, q, *J* 6.8, C(α)*H*, major), 4.43 (1H, q, *J* 7.0, C(α)*H*, minor), 4.81 (1H, d, *J* 3.9, C(2)*H*, minor), 5.12 (1H, d, *J* 2.2, C(2)*H*, major), 7.24−7.44 (10H, m, *Ph*, both); δ_C (100 MHz, $CDCl_3$) 12.7 (C(α)*Me*, major), 15.2 (C(α)*Me*, minor), 51.9 (N*C*H_2, major), 53.3 (N*C*H_2, minor), 54.8 (O*Me*, minor), 55.1 (O*Me*, major), 56.3 (*C*(α)Me, major), 57.6 (*C*(α)Me, minor), 66.6 (*C*(3), major), 68.7 (*C*(3), minor), 69.6, 75.3 (*C*(4), *C*(5), minor), 69.8, 73.1 (*C*(4), *C*(5), major), 103.7 (*C*(2), minor), 104.8 (*C*(2), major), 126.8, 127.1, 128.0, 128.2, 128.3 (*o,m,p-Ph*, minor), 127.3, 127.4, 127.8, 128.4, 128.7 (*o,m,p-Ph*, major), 139.6, 141.8 (*i-Ph*, major), 141.3, 142.0 (*i-Ph*, minor); *m/z* (ESI^+) 350 ($[M+Na]^+$, 100%), 328 ($[M+H]^+$, 94%); HRMS (ESI^+) $C_{20}H_{26}NO_3^+$ ($[M+H]^+$) requires 328.1907; found 328.1900.



292 **257**

Method 2: HCl (1.25 M in MeOH, 0.72 mL, 0.90 mmol) was added to a solution of **292** (87.0 mg, 0.22 mmol) in MeOH (4 mL) at rt under N_2, and the reaction mixture stirred at 80 °C for 16 h. Volatiles were removed *in vacuo* and the residue dissolved in CH_2Cl_2 (4 mL), washed with satd aq $NaHCO_3$ solution (3 mL), dried and concentrated *in vacuo* to give **257** as a colourless oil (70 mg, 97%, 83:17 dr); $[\alpha]_D^{25}$ −57.4 (*c* 2.0 in $CHCl_3$).

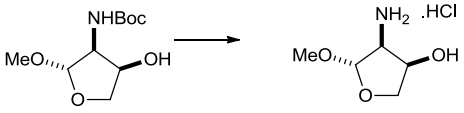
tert-Butyl [(2*S*,3*S*,4*R*)-4-hydroxy-2-methoxytetrahydrofuran-3-yl]carbamate 293



257 **293**

Following *General Procedure 3*, **257** (209 mg, 0.64 mmol), Boc_2O (435 mg, 1.28 mmol), $Pd(OH)_2/C$ (50% w/w, 105 mg) and H_2 (5 atm) in MeOH (2 mL) after 24 h gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/EtOAc, 10:1) gave **293** as a colourless oil (137 mg, 92%, 96:4 dr); $[\alpha]_D^{25}$ −31.8 (*c* 2.0 in $CHCl_3$); ν_{max} (ATR) 3442 (O−H), 3329 (N−H), 1688 (C=O); δ_H (500 MHz, $CDCl_3$) 1.39 (3H, d, *J* 6.8, C(α)*Me*), 3.51 (3H, s, O*Me*), 3.58 (1H, br s, O*H*), 3.59−4.22 (3H, m, C(5)H_AH_B, C(4)*H*OH), 4.33 (1H, dd, *J* 5.8, 2.3, C(3)*H*), 5.71 (1H, d, *J* 2.3, C(2)*H*), 8.01 (1H, br s, N*H*); δ_C (125 MHz, $CDCl_3$) 28.3 (C*Me*$_3$), 54.8 (O*Me*), 67.9 (*C*(3)), 69.0 (*C*(4)), 71.3 (*C*(5)), 79.6 (*C*Me$_3$), 114.2 (*C*(2)), 155.7 (*C*O); *m/z* (ESI^+) 256 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{10}H_{19}NNaO_5^+$ ($[M+Na]^+$) requires 256.1155; found 256.1158.

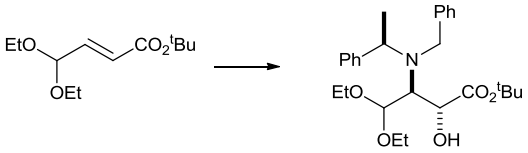
(2*S*,3*S*,4*R*)-4-hydroxy-2-methoxy-3-aminotetrahydrofuran hydrochloride salt 259



293 **259**

HCl (1.25 M in MeOH, 10.0 mL, 2.5 mmol) was added in **293** (107 mg, 0.46 mmol, 96:4 dr) at rt, and the reaction mixture stirred at rt for 16 h. Volatiles were removed *in vacuo* to give **259** as a colourless oil (73.9 mg, 95%, 86:14 dr); $[\alpha]_D^{25}$ −35.7 (*c* 2.1 in $CHCl_3$); ν_{max} (ATR) 3440 (O−H), 3328 (N−H), 1098, 1042 (C–O); δ_H (500 MHz, $CDCl_3$) 3.39 (1H, dd, *J* 5.7, 2.2, C(3)*H*), 3.51 (3H, s, O*Me*), 3.58 (1H, br s, O*H*), 3.61−4.10 (3H, m, C(5)H_AH_B, C(4)*H*OH), 5.12 (2H, br s, NH_2), 5.34 (1H, d, *J* 2.3, C(2)*H*); δ_C (125 MHz, $CDCl_3$) 55.2 (O*Me*), 58.7 (*C*(3)), 71.2 (*C*(5)), 71.9 (*C*(4)), 116.7 (*C*(2)).

***tert*-Butyl (2*R*,3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,4-diethoxy-2 -hydroxybutanoate 291**

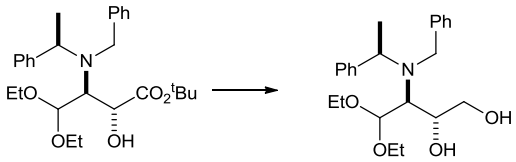


285 **291**

Following *General Procedure 2a*, **150** (524 mg, 2.48 mmol) in THF (10 mL), BuLi (2.5 M in hexanes, 0.96 mL, 2.40 mmol), **285** (357 mg, 1.55 mmol) in THF (8 mL) and (−)-CSO **83** (605 mg, 2.64 mmol) at −78 °C gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 20:1) gave **291** as a colourless solid (482 mg, 68%, >99:1 dr); mp 51−52 ºC; $[\alpha]_D^{25}$ −41.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.13 (3H, t, *J* 7.1, OCH_2*Me*), 1.35 (3H, t, *J* 7.1, OCH_2*Me*), 1.44 (3H, d, *J* 6.8, C(α)*Me*), 1.49 (9H, s, CMe_3), 3.12 (1H, d, *J* 4.0, CHO*H*), 3.47−3.77 (6H, m, (OCH_2Me)$_2$, C(2)*H*OH and C(3)*H*), 3.80 (1H, d, *J* 15.6, NCH_AH_B), 4.08 (1H, q, *J* 6.8, C(α)*H*), 4.37 (1H, d, 15.6, NCH_AH_B), 4.71 (1H, d, *J* 8.1, C(4)*H*), 7.22−7.53 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.1, 15.6 (O(CH_2*Me*)$_2$), 19.3

(C(α)*Me*), 28.0 (C*Me*$_3$), 51.7 (N*C*H$_2$), 57.6 (*C*(α)Me), 60.1(*C*(3)), 62.5, 65.1 (O(*C*H$_2$Me)$_2$), 71.5 (*C*(2)), 82.0 (*C*Me$_3$), 102.0 (*C*(4)), 126.4, 126.9, 127.9, 128.0, 128.1, 128.2 (*o,m,p-Ph*), 141.9, 142.5 (*i-Ph*), 173.7 (*C*O); *m/z* (ESI$^+$) 458 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{39}NNaO_5^+$ ([M+Na]$^+$) requires 480.2720; found 480.2728.

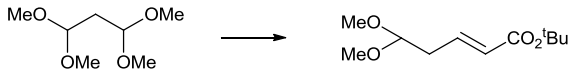
(2*R*,3*S*,α*R*)-3-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-4,4-diethoxybutan-1,2-diol 292



291 **292**

LiAlH$_4$ (1.0 M in THF, 0.36 mL, 0.36 mmol) was added into a solution **291** (164 mg, 0.36 mmol) in anhydrous THF (4 mL) at 0 °C under N$_2$, and the reaction mixture stirred at rt for 16 h. Lumps of ice and then 2.0 M aq NaOH solution (3.00 mL) were added into reaction mixture at 0 °C cautiously with vigorous stirring. The reaction mixture was stirred and allowed to warm to rt. EtOAc (10 mL) was added, and the mixture stirred for 30 min, before being filtered through Celite®, dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et$_2$O, 1:2) gave **292** as a colourless oil (137 mg, 98%, >99:1 dr); $[\alpha]_D^{25}$ −39.3 (*c* 1.0 in CHCl$_3$); ν_{max} (ATR) 3424 br (O−H); δ_H (400 MHz, CDCl$_3$) 1.12−1.18 (6H, m, (OCH$_2$*Me*)$_2$), 1.31 (3H, d, *J* 6.9, C(α)*Me*), 2.87 (1H, dd, *J* 7.6, 2.5, C(3)*H*), 3.22 (1H, dd, *J* 11.5, 6.1, C(1)*H*$_A$H$_B$), 3.39 (1H, dd, *J* 11.3, 3.7, C(1)H$_A$*H*$_B$), 3.44−3.83 (4H, m, (OC*H*$_2$Me)$_2$), 3.84−3.87 (1H, m, C(2)*H*), 3.90 (1H, d, *J* 14.4, NC*H*$_A$H$_B$), 3.98 (1H, d, *J* 14.4, NCH$_A$*H*$_B$), 4.02 (1H, q, *J* 6.9, C(α)*H*), 4.71 (1H, d, *J* 2.5, C(4)*H*), 7.14−7.29 (10H, m, *Ph*); δ_C (400 MHz, CDCl$_3$) 15.3, 15.4 (O(CH$_2$*Me*)$_2$), 16.7 (C(α)*Me*), 51.7 (N*C*H$_2$), 57.7 (*C*(α)Me), 59.1 (*C*(3)), 64.5, 64.6 (O(*C*H$_2$Me)$_2$), 65.1 (*C*(1)), 71.1 (*C*(2)), 106.1 (*C*(4)), 126.9, 127.2, 127.9, 128.3, 128.4, 128.6 (*o,m,p-Ph*), 141.2, 143.7 (*i-Ph*); *m/z* (ESI$^+$) 388 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{33}NNaO_4^+$ ([M+Na]$^+$) requires 410.2302; found 410.2295.

(*E*)-*tert*-Butyl 5,5-dimethoxypent-2-enoate 298



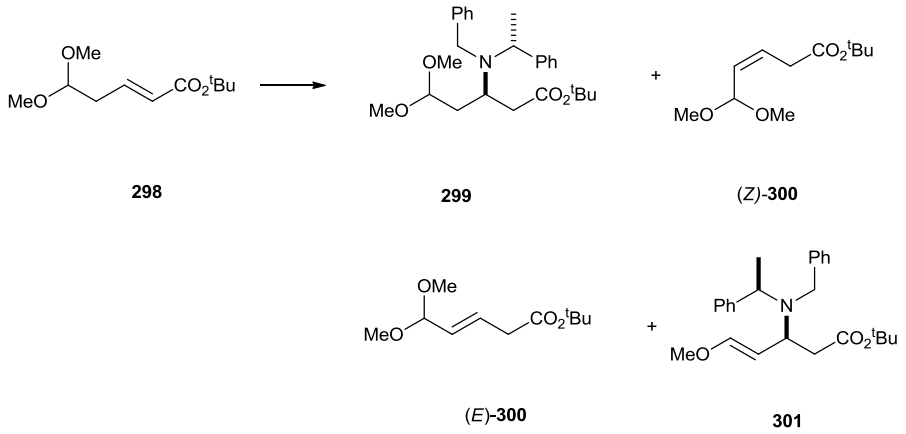
296 **298**

Method 1: 30% aq Orthophosphoric acid (20 mL) was added to a stirred **296** (20.1 mL, 122 mmol) at rt under N_2. After stirring for 16 h, Et_2O (300 mL) was added to the above mixture. And then the solution neutralized with Na_2CO_3 and filtered. The filtrate was concentrated *in vacuo* to give the crude reaction mixture (8.33 g). ^{t}BuOK (9.50 g, 84.5 mmol) was added dropwise to a stirred solution of **33** (21.3 g, 84.5 mmol) in MeOH (250 mL) at 0 ˚C under N_2 and stirred for 15 min. The crude reaction mixture (8.33 g) in MeOH (100 mL) was added via syringe at 0 ˚C and the reaction mixture stirred for 4 h at rt. The reaction mixture was concentrated in *vacuo* to yield a residue, to which Et_2O (200 mL) and satd aq $NaHCO_3$ (200 mL) were then added. The layers were separated, and the aq layer was further extracted with Et_2O (3 x 100 mL), and the combined organics were washed with brine (200 mL), dried, filtered, and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 10:1) gave **298** as a colourless oil (10.8 g, 41%, >99:1 dr);[31] δ_H (400 MHz, $CDCl_3$) 1.49 (9H, s, C*Me*$_3$), 2.48−2.52 (2H, m, C(4)*H*$_2$), 3.35 (6H, s, C(O*Me*)$_2$), 4.48 (1H, t, *J* 5.6, C(5)*H*), 5.81−5.85 (1H, m, C(2)*H*), 6.79 (1H, dt, *J* 15.2, 7.2, C(3)*H*).

Method 2: 30% aq Orthophosphoric acid (2 mL) was added to a stirred **296** (2.01 mL, 12.2 mmol) at rt under N_2. After stirring for 16 h, Et_2O (30 mL) was added to the above mixture. And then the solution neutralized with Na_2CO_3 and filtered. The filtrate was concentrated *in vacuo* to give the crude reaction mixture (830 mg). MeMgBr (3.0 M in Et_2O, 2.81 mL, 8.44 mmol) was added dropwise to a suspension of **33** (2.13 g, 8.44 mmol) in THF (50 mL) and the resultant mixture was stirred for 15 min. The crude reaction mixture (830 mg) was added dropwise and the reaction mixture was heated at reflux for 15 h. After being allowed to cool to rt, the reaction mixture was quenched with satd aq NH_4Cl (30 mL) and extracted with EtOAc (3 × 30 mL). The combined

organic extracts were washed with brine (20 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 10:1) gave **298** as a colourless oil (1.03 g, 39%, >99:1 dr).

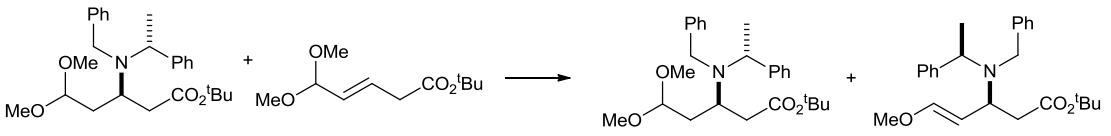
***tert*-Butyl (3*R*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5,5-dimethoxypentanoate 299, (*Z*)-*tert*-butyl 5,5-dimethoxypent-3-enoate 300, (*E*)-*tert*-butyl 5,5-dimethoxypent-3-enoate 300, (*E*)-*tert*-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-methoxypent-4-enoate 301**



Method 1: Following *General Procedure 2a*, BuLi (2.5 M in hexanes, 0.29 mL, 0.72 mmol) and **150** (157 mg, 0.74 mmol) in THF (10 mL) at −78 °C, and **298** (100 mg, 0.46 mmol) in THF (5 mL) at −78 °C gave the crude reaction mixture **299**:(*Z*)-**300**:(*E*)-**300**:**301=**26:28:28:18. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 5:1) gave **301** as a colourless oil (with 5% unknown impurities, 23.6 mg, 13%, >99:1 dr); $[\alpha]_D^{25}$ −37.8 (*c* 2.0 in $CHCl_3$); ν_{max} (ATR) 1723 (C=O), 1646 (C=C); δ_H (500 MHz, $CDCl_3$) 1.37 (9H, s, C*Me*$_3$), 1.41 (3H, d, *J* 6.9, C(α)*Me*), 2.25 (1H, dd, *J* 13.9, 9.0, C(2)H_AH_B), 2.45 (1H, dd, *J* 13.9, 5.4, C(2)H_AH_B), 3.52 (3H, s, O*Me*), 3.68 (2H, br s, NCH_2), 3.72 (1H, ddd, *J* 17.7, 9.0, 5.4, C(3)*H*), 4.06 (1H, q, *J* 6.9, C(α)*H*), 4.78 (1H, dd, *J* 12.6, 9.0, C(4)*H*), 6.34 (1H, d, *J* 12.9, C(5)*H*), 7.16−7.41 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 17.5 (C(α)*Me*), 28.0 (C*Me*$_3$), 41.1 (*C*(2)), 50.2 (N*C*H$_2$), 54.7 (*C*(3)), 55.9 (O*Me*), 57.1 (*C*(α)Me), 80.1 (*C*Me$_3$), 102.1 (*C*(4)), 126.4, 126.6, 127.7, 127.9, 128.0, 128.2 (*o,m,p-Ph*), 141.5, 144.5 (*i-Ph*), 149.1 (*C*(5)), 171.1 (*C*O); *m/z*

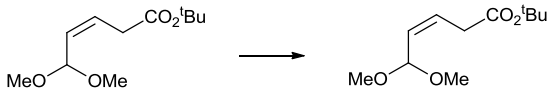
(ESI^+) 396 ($[M+H]^+$, 74%); HRMS (ESI^+) $C_{25}H_{34}NO_3^+$ ($[M+H]^+$) requires 396.2533; found 396.2526. Further elution gave (*Z*)-**300** as a colourless oil (with 5% unknown impurity, 20.0 mg, 20%); δ_H (500 MHz, $CDCl_3$) 1.46 (9H, s, C*Me*$_3$), 3.14 (1H, dd, *J* 7.3, 1.6, C(2)*H*$_2$), 3.31 (6H, s, O*Me*), 5.06 (1H, dd, *J* 5.7, 1.3, C(5)*H*), 5.57 (1H, ddt, *J* 11.0, 5.7, 1.6, C(4)*H*), 5.87 (1H, dtd, *J* 11.0, 7.3, 1.3, C(3)*H*); δ_C (125 MHz, $CDCl_3$) 28.0 (C*Me*$_3$), 34.9 (*C*(2)), 52.2 (O*Me*), 80.9 (*C*Me$_3$), 99.5 (*C*(5)), 127.1 (*C*(3)), 129.1 (*C*(4)), 170.5 (*C*O). Further elution gave a 54:46 inseparable mixture of (*E*)-**300**:**299** as a colourless oil (60.7 mg, 40% combined yield, >99:1 dr for **299**). **299**: δ_H (500 MHz, $CDCl_3$) 1.37 (3H, d, *J* 6.9, C(α)*Me*), 1.45 (9H, s, C*Me*$_3$), 1.66−1.72 (2H, m, C(4)*H*$_2$), 1.78 (1H, dd, *J* 14.5, 3.2, C(2)*H*$_A$H$_B$), 1.88 (1H, dd, *J* 14.8, 10.1, C(2)H$_A$*H*$_B$), 3.30 (3H, s, O*Me*), 3.31 (3H, s, O*Me*), 3.50 (1H, d, 14.8, NC*H*$_A$H$_B$), 3.56−3.61 (1H, m, C(3)*H*), 3.78 (1H, d, 16.1, NC*H*$_A$H$_B$), 3.80 (1H, q, *J* 6.9, C(α)*H*), 4.76−4.79 (1H, m, C(5)*H*), 7.24−7.42 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 19.8 (C(α)*Me*), 28.0 (C*Me*$_3$), 36.1 (*C*(4)), 37.5 (*C*(2)), 49.8, 50.0 (*C*(3), N*C*H$_2$), 52.2, 52.5 (O*Me*), 57.7 (*C*(α)Me), 80.1 (*C*Me$_3$), 102.3 (*C*(5)), 126.7, 127.0, 128.0, 128.1, 128.2, 128.3 (*o,m,p-Ph*), 141.2, 142.1 (*i-Ph*), 171.6 (*C*O); *m/z* (ESI^+) 427 ($[M+H]^+$, 12%). (*E*)-3**00**: δ_H (500 MHz, $CDCl_3$) 1.40 (9H, s, C*Me*$_3$), 3.14 (1H, dd, *J* 6.9, 0.6, C(2)*H*$_2$), 3.33 (6H, s, O*Me*), 4.76−4.79 (1H, m, C(5)*H*), 5.57 (1H, ddt, *J* 15.8, 5.0, 1.6, C(4)*H*), 5.94 (1H, dtd, *J* 15.8, 6.9, 1.3, C(3)*H*); δ_C (125 MHz, $CDCl_3$) 28.0 (C*Me*$_3$), 38.7 (*C*(2)), 52.7 (O*Me*), 80.8 (*C*Me$_3$), 102.8 (*C*(5)), 127.6 (*C*(3)), 129.9 (*C*(4)), 170.5 (*C*O).

Method 2: Following *General Procedure 2d*, BuLi (2.5 M in hexanes, 1.08 mL, 2.69 mmol) and **150** (587 mg, 2.78 mmol) in Et_2O (25 mL) at −20 °C, and **298** (300 mg, 1.39 mmol) in Et_2O (15 mL) at −20 °C gave the crude reaction mixture **299**:(*Z*)-**300**:(*E*)-**300**:**301** = 17:14:13:56.



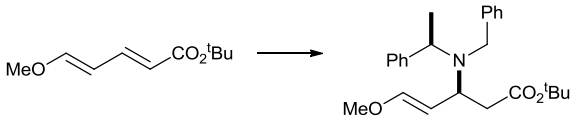
299 (*E*)-**300** **299** **301**

Method 3: Resubjection of a 68:32 mixture of **299** and (*E*)-**300** following *General Procedure 2a* gave a 79:21 mixture of **299** and **301**.



(*Z*)-**300** (*Z*)-**300**

Method 4: resubjection of (*Z*)-**300** following *General Procedure 2a* gave no reaction.

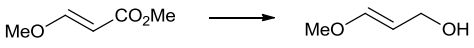


304 **301**

Method 5: Following *General Procedure 2a*, BuLi (2.5 M in hexanes, 0.84 mL, 2.11 mmol) and **150** (459 mg, 2.17 mmol) in THF (25 mL) at −78 °C, and **304** (250 mg, 1.36 mmol) in THF (10 mL) at −78 °C gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 15:1) gave **301** as as a colourless oil (473 mg, 88%, 97:3 dr); $[\alpha]_D^{25}$ −41.9 (*c* 2.0 in $CHCl_3$).

Method 6: Following *General Procedure 2d*, BuLi (2.5 M in hexanes, 1.06 mL, 2.64 mmol) and **150** (575 mg, 2.72 mmol) in Et_2O (25 mL) at –20 °C, and **304** (250 mg, 1.36 mmol) in Et_2O (10 mL) at –20 °C gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 15:1) gave **301** as as a colourless oil (440 mg, 82%, 96:4 dr); $[\alpha]_D^{25}$ −40.9 (*c* 2.0 in $CHCl_3$).

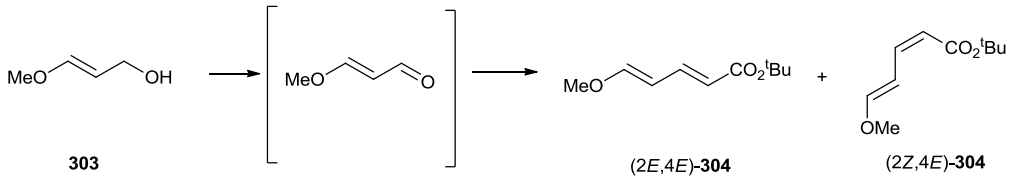
(*E*)-3-Methoxyprop-2-en-1-ol 303



302 **303**

DIBAL-H (1.0 M in toluene, 64.7 mL, 64.7 mmol) was added into a stirred solution of **302** (3.00 g, 25.9 mmol) in toluene (150 ml) at –78 °C dropwise. After addition the reaction was stirred at –78 °C for 6 h, before pouring onto ice-cold satd Rochelle's salt solution (150 ml) followed by the addition of EtOAc (150 ml). The biphasic mixture was vigorously stirred at 0 °C for 2 h before separating and extracting with EtOAc (150 ml). The organics were combined and washed with satd Rochelle salt solution (225 ml), dried over sodium sulfate, filtered and concentrated in vacuo to give **303** as a yellow oil (1.90 g, 77%);[32] δ_H (400 MHz, acetone-d_4) 3.42 (1H, t, *J* 5.5, O*H*), 3.51 (3H, s, O*Me*), 3.97 (2H, t, *J* 7.0, CH_2OH), 4.96 (1H, dt, *J* 12.6, 7.2, C(2)*H*), 6.53 (1H, d, *J* 12.6, C(3)*H*).

***tert*-Butyl (2*E*,4*E*)-5-methoxypenta-2,4-dienoate 304, *tert*-Butyl (2*Z*,4*E*)-5-methoxypenta-2,4-dienoate 304**

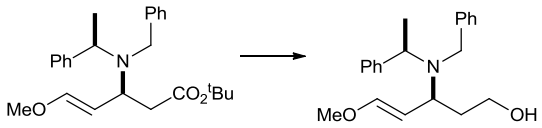


303 (2*E*,4*E*)-**304** (2*Z*,4*E*)-**304**

Method 3: Activated MnO_2 (3.95 g, 45.5 mmol), **265** (854 mg, 2.27 mmol) were added into a stirred solution of **303** (0.20 g, 2.27 mmol) in CH_2Cl_2 (40 mL) at rt. After addition the reaction was stirred at rt for 48 h, before filtering by passage through a pad of Celite® (prewashed with 10% TEA in CH_2Cl_2) and concentrating *in vacuo* to give a crude reaction mixture. Purification via flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 5:1) gave (2*Z*,4*E*)-**304** as a colourless oil (44 mg, 11%, 98:2 dr); δ_H (400 MHz, C_6D_6) 1.44 (9H, s, CMe_3), 3.11 (3H, s, O*Me*), 5.56 (1H, d, *J* 11.3, C(2)*H*), 6.08 (1H, t, *J* 11.3, C(3)*H*), 6.52 (1H, d, *J* 12.8, C(5)*H*), 7.30–7.32 (1H, m, C(4)*H*); δ_H (400 MHz, $CDCl_3$) 1.51 (9H, s, CMe_3), 3.72 (3H, s, O*Me*), 5.39 (1H, d, *J* 11.1, C(2)*H*), 6.41–

6.47 (1H, m, C(3)*H*), 6.90–6.92 (2H, m, C(4)*H*, C(5)*H*); δ_C (100 MHz, C_6D_6) 28.3 (C*Me*$_3$), 56.0 (O*Me*), 79.0 (*C*Me$_3$), 103.6 (*C*(4)), 114.1 (*C*(2)), 142.5 (*C*(3)), 159.0 (*C*(5)), 166.7 (*C*O). Further elution gave (2*E*,4*E*)-**304** as a colourless oil (323.45 mg, 77%, 98:2 dr); ν_{max} (ATR) 1701 (C=O), 1627 (C=C); δ_H (400 MHz, C_6D_6) 1.47 (9H, s, C*Me*$_3$), 2.85 (3H, s, O*Me*), 5.29–5.35 (1H, m, C(4)*H*), 5.86 (1H, t, *J* 15.2, C(2)*H*), 6.29 (1H, d, *J* 12.5, C(5)*H*), 7.39 (1H, dd, , *J* 15.2, 11.4, C(3)*H*); δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, C*Me*$_3$), 3.67 (3H, s, O*Me*), 5.59–5.68 (2H, m, C(2)*H*, C(4)*H*), 6.88 (1H, d, *J* 12.4, C(5)*H*), 7.15 (1H, dd, *J* 14.9, 11.4, C(3)*H*); δ_C (100 MHz, C_6D_6) 28.3 (C*Me*$_3$), 56.3 (O*Me*), 79.1 (*C*Me$_3$), 104.3 (*C*(4)), 118.3 (*C*(2)), 142.0 (*C*(3)), 157.8 (*C*(5)), 166.6 (*C*O); δ_C (400 MHz, $CDCl_3$) 28.2 (C*Me*$_3$), 57.0 (O*Me*), 80.1 (*C*Me$_3$), 104.0 (*C*(4)), 117.9 (*C*(2)), 141.6 (*C*(3)), 157.7 (*C*(5)), 166.9 (*C*O); *m/z* (ESI$^+$) 207 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{10}H_{16}NaO_3^+$ ([M+Na]$^+$) requires 207.0992; found 207.0987.

(3*S*,α*R*)-(*E*)-3-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-5-methoxypent-4-en-1-ol 305

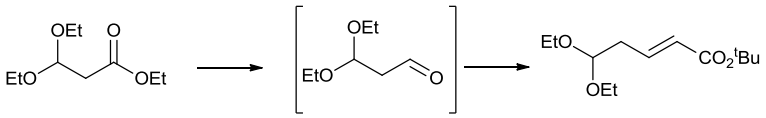


301 **305**

$LiAlH_4$ (1.0 M in THF, 0.81 mL, 0.81 mmol) was added into a solution of **301** (320 mg, 0.81 mmol) in anhydrous THF (4 mL) at 0 °C under N_2, and the reaction mixture stirred at rt for 16 h. Lumps of ice and then 2.0 M aq NaOH solution (2.00 mL) were added into reaction mixture at 0 °C cautiously with vigorous stirring. The reaction mixture was stirred and allowed to warm to rt. EtOAc (10 mL) was added, and the mixture stirred for 30 min, before being filtered through Celite®, dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 2:1) gave **305** as a yellow oil (232 mg, 88%, 97:3 dr); $[\alpha]_D^{25}$ −29.7 (*c* 2.0 in $CHCl_3$); ν_{max} (ATR) 3404 (O−H), 1644 (C=C); δ_H (400 MHz, $CDCl_3$) 1.42–1.51 (1H, m, C(2)H_AH_B), 1.46 (3H, d, *J* 6.8, C(α)*Me*), 1.87–1.96 (1H, m, C(2)H_AH_B), 3.33–3.40 (2H, m, C(1) H_AH_B, C(3)*H*), 3.57–3.61 (1H, m, C(1) H_AH_B), 3.58 (3H, s, O*Me*), 3.65 (1H, d, *J* 13.6,

NC*H*$_A$H$_B$), 3.88 (1H, d, *J* 13.9, NCH$_A$*H*$_B$), 4.10 (1H, q, *J* 6.8, C(α)*H*), 4.91 (1H, dd, *J* 12.6, 9.4, C(4)*H*), 6.36 (1H, d, *J* 12.6, C(5)*H*), 7.25–7.38 (10H, m, *Ph*); δ_C(400 MHz, $CDCl_3$) 15.1 (C(α)*Me*), 36.5 (*C*(2)), 50.2 (N*C*H$_2$), 54.5 (*C*(3)), 55.8 (O*Me*), 56.0 (*C*(α)Me), 61.4 (*C*(1)OH), 103.1 (*C*(4)), 126.8, 126.9, 127.9, 128.2, 128.4, 128.9 (*o,m,p-Ph*), 140.4, 144.1 (*i-Ph*), 148.7 (*C*(5)); *m/z* (ESI$^+$) 326 ([M+H]$^+$, 55%); HRMS (ESI$^+$) $C_{21}H_{27}NNaO_2^+$ ([M+Na]$^+$) requires 348.1934; found 348.1922.

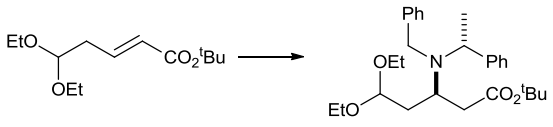
***tert*-Butyl (*E*)-5,5-diethoxypent-2-enoate 308**



306 **308**

DIBAL-H (1.0 M in toluene, 23.7 mL, 23.7 mmol) was added into a stirred solution of ethyl 3,3-diethoxypropanoate **306** (3.00 g, 15.8 mmol) in CH_2Cl_2 (160 ml) at –78 °C dropwise. After addition the reaction was stirred at –78 °C for 50 minutes. MeOH (40 mL) was added and the solution was allowed to warm to rt. Celite® and water were added and the mixture was stirred for 15 min. The mixture was then dried, filtered to get a clear solution. **265** (5.93 g, 15.8 mmol) was added into this stirred solution at rt. The reaction was stirred at rt for 16 h and concentrated *in vacuo* to give a crude reaction mixture. Purification via flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 7:1) gave **308** as a colourless oil (3.50 g, 91%, >99:1 dr); ν_{max} (ATR) 1714 (C=O), 1655 (C=C); δ_H (400 MHz, $CDCl_3$) 1.20 (6H, t, *J* 7.1, O(OCH$_2$C*H*$_3$)$_2$), 1.47 (9H, s, C*Me*$_3$), 2.48–2.52 (2H, m, C(4)*H*$_2$), 3.47–3.54 (2H, m, OC*H*$_2$CH$_3$), 3.61–3.69 (2H, m, OC*H*$_2$CH$_3$), 4.55–4.58 (1H, m, C(5)*H*), 5.82 (1H, d, *J* 15.7, C(2)*H*), 6.80 (1H, dt, *J* 15.7, 7.1, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 15.2 (O(CH$_2$*Me*)$_2$), 28.1 (C*Me*$_3$), 36.8 (*C*(4)), 61.2 (O(*C*H$_2$Me)$_2$), 80.1 (*C*Me$_3$), 101.4 (*C*(5)), 125.4 (*C*(2)), 142.2 (*C*(3)), 165.7 (*C*O); *m/z* (ESI$^+$) 267 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{24}NaO_4^+$ ([M+Na]$^+$) requires 267.1567; found 267.1570.

tert-Butyl (3*R*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5,5-diethoxypentanoate 309

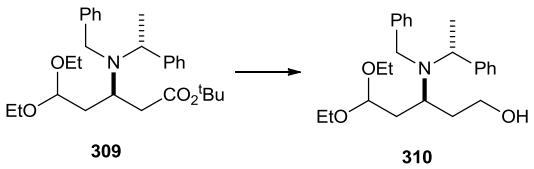


308 **309**

Method 1: Following *General Procedure 2a*, BuLi (2.5 M in hexanes, 1.90 mL, 4.82 mmol) and **150** (1.05 g, 4.98 mmol) in THF (25 mL) at −78 °C, and **308** (865 mg, 3.11 mmol) in THF (10 mL) at −78 °C gave the crude reaction mixture. Purification via flash column chromatography (eluent 30–40 ºC petrol/Et_2O, 10:1) gave **309** as a colourless oil (1.29 g, 91%, 99:1 dr); $[\alpha]_D^{25}$ −42.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.17–1.25 (6H, m, $(OCH_2\mathit{Me})_2$), 1.37 (3H, d, *J* 7.1, C(α)*Me*), 1.42 (9H, s, CMe_3), 1.64-1.70 (1H, m, C(4)H_AH$_B$), 1.73–1.79 (1H, m, C(4)H$_A\mathit{H}_B$), 1.89–1.91 (2H, m, C(2)H_2), 3.35–3.42 (1H, m, OCH_AH$_B$Me), 3.47–3.62 (4H, m, OCH_2Me, C(3)*H* and NCH_AH$_B$), 3.67–3.75 (1H, m, OCH$_A\mathit{H}_B$Me), 3.78–3.85 (2H, m, C(α)*H* and NCH$_A\mathit{H}_B$), 4.87 (1H, dd, *J* 8.1, 3.0, C(5)*H*), 7.23–7.44 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.2, 15.4 ($O(CH_2\mathit{Me})_2$), 19.9 (C(α)*Me*), 28.0 (CMe_3), 37.1 (*C*(4)), 37.8 (*C*(2)), 50.0 (N*C*H$_2$), 50.5 (*C*(3)), 58.0 (*C*(α)Me), 60.4, 61.0 ($O(\mathit{C}H_2Me)_2$), 80.1 (*C*Me$_3$), 100.9 (*C*(5)), 126.7, 127.0, 128.0, 128.1, 128.2, 128.3 (*o,m,p-Ph*), 141.5, 142.4 (*i-Ph*), 171.7 (*C*O); *m/z* (ESI$^+$) 456 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{41}NNaO_4^+$ ([M+Na]$^+$) requires 478.2928; found 478.2931.

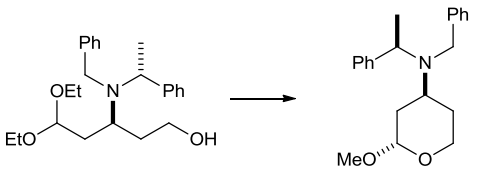
Method 2: Following *General Procedure 2d*, BuLi (2.5 M in hexanes, 0.78 mL, 1.94 mmol) and **150** (423 mg, 2.00 mmol) in Et_2O (20 mL) at −20 °C, and **308** (244 mg, 1.00 mmol) in Et_2O (10 mL) at −20 °C gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 10:1) gave **309** as a colourless oil (405 mg, 89%, 97:3 dr); $[\alpha]_D^{25}$ −41.7 (*c* 1.0 in $CHCl_3$).

(3*S*,α*R*)-3-[*N*- Benzyl-*N*-(α-methylbenzyl)amino]-5,5-diethoxypentane-1-ol 310



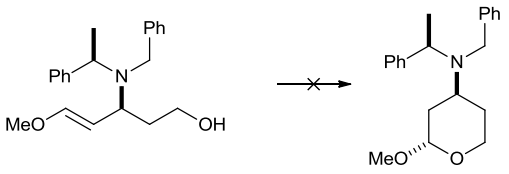
$LiAlH_4$ (1.0 M in THF, 2.20 mL, 2.20 mmol) was added into a solution **309** (1.00 g, 2.20 mmol) in anhydrous THF (13 mL) at 0 °C under N_2, and the reaction mixture stirred at rt for 16 h. Lumps of ice and then 2.0 M aq NaOH solution (6.00 mL) were added into reaction mixture at 0 °C cautiously with vigorous stirring. The reaction mixture was stirred and allowed to warm to rt. EtOAc (10 mL) was added, and the mixture stirred for 30 min, before being filtered through Celite®, dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 2:1) gave **310** as a colourless oil (822 mg, 97%, 99:1 dr); $[\alpha]_D^{25}$ −41.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3421 br (O–H); δ_H (500 MHz, $CDCl_3$) 1.20 (3H, t, *J* 6.9, OCH_2*Me*), 1.25 (3H, t, *J* 6.9, OCH_2*Me*), 1.43 (3H, d, *J* 6.9, C(α)*Me*), 1.38−1.43 (1H, m, C(2)H_AH_B), 1.58−1.66 (2H, m, C(2)H_AH_B, C(4)H_AH_B), 2.08 (1H, ddd, C(4)H_AH_B, *J* 13.6, 6.9, 3.8), 2.48 (1H, br s, O*H*), 3.05−3.10 (1H, m, C(3)*H*), 3.22−3.26 (1H, m, C(1)H_AH_B), 3.42−3.53 (3H, m, OCH_2Me, C(1)H_AH_B), 3.64−3.75 (3H, m, OCH_2Me, NCH_AH_B), 3.83 (1H, d, *J* 13.9, NCH_AH_B), 3.92 (1H, q, *J* 6.9, C(α)*H*), 4.53 (1H, d, *J* 6.9, 4.7, C(5)*H*), 7.22−7.42 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 15.0 (C(α)*Me*), 15.3, 15.4 (O(CH_2*Me*)$_2$), 34.2 (*C*(2)), 37.5 (*C*(4)), 50.0 (NCH_2), 50.7 (*C*(3)), 57.0 (*C*(α)Me), 61.4, 61.8 (O(CH_2Me)$_2$), 62.4 (*C*(1)), 102.5 (*C*(5)), 126.9, 127.0, 128.0, 128.3, 128.4, 128.9 (*o,m,p-Ph*), 140.6, 143.8 (*i-Ph*); *m/z* (ESI^+) 386 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{24}H_{36}NO_3^+$ ($[M+H]^+$) requires 386.2690; found 386.2689.

(4*S*,α*R*)-2-Methoxy-4-[*N*-benzyl-*N*-(α-methylbenzyl)amino]tetrahydro-2*H*-pyran 311



310 **311**

Method 1: HCl (1.25 M in MeOH, 1.60 mL, 1.97 mmol) was added to a solution of **310** (190 mg, 0.49 mmol) in MeOH (8 mL) at rt under N_2, and the reaction mixture stirred at 80 °C for 16 h. Volatiles were removed *in vacuo* and the residue dissolved in CH_2Cl_2 (5 mL), washed with satd aq $NaHCO_3$ solution (5 mL), dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 11:1) gave **311** as a colourless oil (129 mg, 81%, 99:1 dr); $[\alpha]_D^{25}$ −44.1 (*c* 2.0 in $CHCl_3$); ν_{max} (ATR) 1052 (C–O–C); δ_H (400 MHz, C_6D_6) 1.19−1.22 (1H, m, C(5)H_AH_B), 1.25 (3H, d, *J* 6.9, C(α)*Me*), 1.40−1.50 (1H, m, C(5)H_AH_B), 1.56 (1H, td, *J* 12.5, 3.7, C(3)H_AH_B), 1.84−1.88 (1H, m, C(3)H_AH_B), 3.09 (3H, s, O*Me*), 3.37−3.55 (3H, m, C(4)*H*, C(6)H_AH_B), 3.57 (2H, s, NCH_2), 3.86 (1H, q, *J* 6.9, C(α)*H*), 4.67 (1H, d, *J* 2.9, C(2)*H*), 7.04−7.38 (10H, m, *Ph*); δ_C (100 MHz, C_6D_6) 17.4 (C(α)*Me*), 30.6 (*C*(5)), 35.5 (*C*(3)), 48.9 (*C*(4)), 50.0 (N*C*H_2), 53.8 (O*Me*), 57.1 (*C*(α)Me), 59.2 (*C*(6)), 99.3 (*C*(2)), 126.5, 126.6, 127.4, 127.6, 128.0, 128.1 (*o,m,p-Ph*), 142.3, 144.6 (*i-Ph*); *m/z* (ESI^+) 326 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{21}H_{28}NO_2^+$ ($[M+H]^+$) requires 326.2115; found 326.2119.



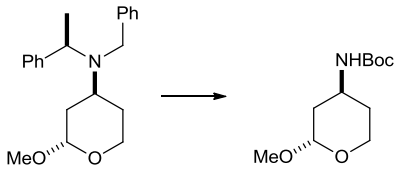
305 **311**

Method 2: HCl (1.25 M in MeOH, 0.10 mL, 0.13 mmol) was added to a solution of **305** (33.0 mg, 0.10 mmol) in MeOH (0.7 mL) at 50 °C under N_2, and the reaction mixture stirred at 50 °C for 16 h. Volatiles were removed *in vacuo* and the residue dissolved in

CH_2Cl_2 (2 mL), washed with satd aq $NaHCO_3$ solution (1 mL), dried and concentrated *in vacuo* to give **150**.

Method 3: HCl (1.25 M in MeOH, 0.10 mL, 0.13 mmol) was added to a solution of **305** (33.0 mg, 0.10 mmol) in MeOH (0.7 mL) at 0 °C under N_2, and the reaction mixture stirred at 0 °C for 10 h. Volatiles were removed *in vacuo* and the residue dissolved in CH_2Cl_2 (2 mL), washed with satd aq $NaHCO_3$ solution (1 mL), dried and concentrated *in vacuo* to give **150**.

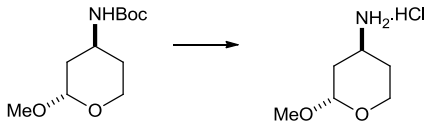
tert-Butyl [(2*S*,4*S*)-2-methoxytetrahydro-2*H*-pyran-4-yl]carbamate 312



311 **312**

Following *General Procedure 3*, **311** (208 mg, 0.64 mmol), Boc_2O (435 mg, 1.28 mmol), $Pd(OH)_2/C$ (50% w/w, 104 mg) and H_2 (5 atm) in MeOH (2 mL) after 24 h gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/EtOAc, 11:1) gave **312** as a colourless oil (142 mg, 96%, 95:5 dr); $[\alpha]_D^{25}$ −26.8 (*c* 2.0 in $CHCl_3$); ν_{max} (ATR) 3327 (N−H), 1691 (C=O); δ_H (500 MHz, $CDCl_3$) 1.40 (9H, s, C*Me*$_3$), 1.70−2.09 (4H, m, C(3)*H*$_2$, C(5)*H*$_2$), 3.51 (3H, s, O*Me*), 3.55−3.70 (3H, m, C(4)*H*, C(6)*H*$_2$), 4.93 (1H, m, C(2)*H*), 8.01 (1H, br s, N*H*); δ_C (125 MHz, $CDCl_3$) 28.3 (C*Me*$_3$), 38.4 (*C*(3)), 38.9 (*C*(5)), 51.7 (*C*(4)), 55.2 (O*Me*), 58.2 (*C*(6)), 79.5 (*C*Me$_3$), 112.0 (*C*(2)), 155.3 (*C*O); *m/z* (ESI$^+$) 254 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{11}H_{21}NNaO_4^+$ ([M+Na]$^+$) requires 254.1363; found 254.1364.

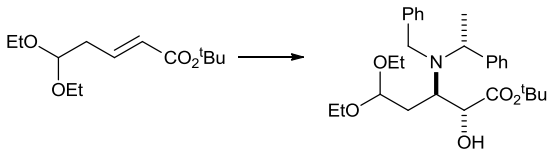
(2*S*,4*S*)-2-Methoxytetrahydro-2*H*-pyran-4-amine hydrochloride salt 295



312 **295**

HCl (1.25 M in MeOH, 10.0 mL, 12.5 mmol) was added in **312** (106 mg, 0.46 mmol, 99:1 dr) at rt, and the reaction mixture stirred at rt for 16 h. Volatiles were removed *in vacuo* to give **295** as a coloreless oil (73.0 mg, 95%, 86:14 dr);[XX] $[\alpha]_D^{25}$ −33.6 (*c* 1.8 in $CHCl_3$); ν_{max} (ATR) 3328 (N−H), 1098, 1042 (C–O); δ_H (500 MHz, $CDCl_3$) 1.83−2.08 (4H, m, C(3)H_2, C(5)H_2), 2.74 (1H, m, C(4)*H*), 3.51 (3H, s, O*Me*), 3.55−3.65 (2H, m, C(6)H_2), 4.96 (1H, s, C(2)*H*), 5.11 (1H, br s, NH_2); δ_C (125 MHz, $CDCl_3$) 39.7 (*C*(5)), 41.3 (*C*(3)), 43.9 (*C*(4)), 55.4 (O*Me*), 58.3 (*C*(6)), 112.1 (*C*(2)).

***tert*-Butyl (2*R*,3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5,5-diethoxy-2 -hydroxypentanoate 313**

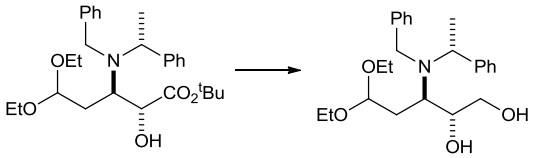


308 **313**

Following *General Procedure 2a*, **150** (4.26 g, 20.1 mmol) in THF (60 mL), BuLi (2.5 M in hexanes, 7.80 mL, 19.5 mmol), **308** (3.50 g, 12.6 mmol) in THF (50 mL) and (−)-CSO **83** (4.90 g, 21.4 mmol) at −78 °C gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 8:1) gave **313** as a colourless oil (4.57 g, 77%, 93:7 dr); $[\alpha]_D^{25}$ −33.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3495 br (O–H), 1719 (C=O); δ_H (400 MHz, $CDCl_3$) 1.05−1.12 (6H, m, $(OCH_2Me)_2$), 1.24 (3H, d, *J* 6.9, C(α)*Me*), 1.27−1.32 (1H, m, C(4)H_AH_B), 1.40 (9H, s, CMe_3), 1.76−1.83 (1H, m, C(4)H_AH_B), 2.88 (1H, d, *J* 5.6, CHO*H*), 3.21−3.50 (4H, m, OCH_2Me , OCH_AH_BMe and C(3)*H*), 3.58 (1H, d, *J* 15.7, NCH_AH_B), 3.62−3.70 (2H, m, OCH_AH_BMe, C(2)*H*),

3.84 (1H, q, *J* 6.9, C(α)*H*), 4.27 (1H, d, 15.7, NCH_AH_B), 4.75 (1H, dd, *J* 8.3, 2.5, C(4)*H*), 7.14−7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.4, 15.5 (O(CH_2*Me*)$_2$), 19.7 (C(α)*Me*), 27.9 (C*Me*$_3$), 32.3 (*C*(4)), 50.9 (N*C*H$_2$), 55.4 (*C*(3)), 58.3 (*C*(α)Me), 60.3, 62.3 (O(*C*H$_2$Me)$_2$), 71.1 (*C*(2)), 82.7 (*C*Me$_3$), 101.6 (*C*(5)), 126.5, 127.1, 128.0, 128.1, 128.2, 128.3 (*o,m,p-Ph*), 142.4, 142.6 (*i-Ph*), 174.3 (*C*O); *m/z* (ESI$^+$) 472 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{42}NO_5^+$ ([M+H]$^+$) requires 472.3057; found 472.3066.

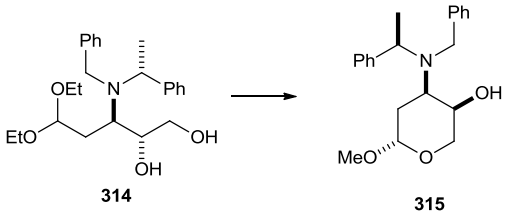
(2*R*,3*S*,*αR*)-3-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-5,5-diethoxypentane-1,2-diol 314



$LiAlH_4$ (1.0 M in THF, 1.78 mL, 1.78 mmol) was added into a solution **313** (840 mg, 1.78 mmol) in anhydrous THF (20 mL) at 0 °C under N_2, and the reaction mixture stirred at rt for 16 h. Lumps of ice and then 2.0 M aq NaOH (8.00 mL) were added into reaction mixture at 0 °C cautiously with vigorous stirring. The reaction mixture was stirred and allowed to warm to rt. EtOAc (30 mL) was added, and the mixture stirred for 30 min, before being filtered through Celite®, dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 1:2) gave **314** as a colourless oil (699 mg, 98%, 93:7 dr); $[\alpha]_D^{25}$ −41.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3417 br (O−H); δ_H (400 MHz, $CDCl_3$) 1.22 (3H, t, *J* 7.1, OCH$_2$*Me*), 1.27 (3H, t, *J* 7.1, OCH$_2$*Me*), 1.43 (3H, d, *J* 6.8, C(α)*Me*), 1.95−2.02 (1H, m, C(4)H_AH_B), 2.09−2.14 (1H, m, C(4)H$_A$*H*$_B$), 2.97 (1H, br s, C(3)*H*), 3.28 (1H, dd, *J* 10.9, 5.8, C(1)H_AH_B), 3.38 (1H, dd, *J* 11.1, 4.0, C(1)H$_A$*H*$_B$), 3.47−3.58 (3H, m, OC*H*$_2$Me, C(2)*H*), 3.69−3.93 (5H, m, NC*H*$_2$, C(α)*H* and OC*H*$_2$Me), 4.71−4.74 (1H, m, C(5)*H*), 7.25−7.41 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.0 (C(α)*Me*), 15.2, 15.4 (O(CH_2*Me*)$_2$), 34.2 (*C*(4)), 51.5 (N*C*H$_2$), 53.4 (*C*(3)), 57.3 (*C*(α)Me), 62.2, 63.1 (O(*C*H$_2$Me)$_2$), 65.2 (*C*(1)), 72.9 (*C*(2)), 102.9

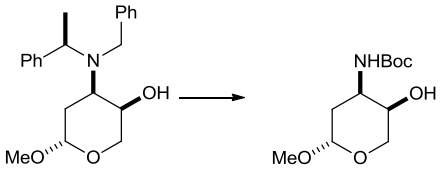
(*C*(5)), 127.1, 127.2, 128.2, 128.3, 128.4, 128.8 (*o,m,p-Ph*), 140.5, 143.6 (*i-Ph*); *m/z* (ESI$^+$) 402 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{36}NO_4^+$ ([M+H]$^+$) requires 402.2639; found 402.2641.

(2*S*,4*R*,5*R*,α*R*)-2-Methoxy-4-[*N*-benzyl-*N*-(α-methylbenzyl)amino]tetrahydro-2*H*-pyran-5-ol 315



HCl (1.25 M in MeOH, 8.78 mL, 11.0 mmol) was added to a solution of **314** (1.10 g, 2.74 mmol) in MeOH (30 mL) at rt under N_2, and the reaction mixture stirred at 80 °C for 16 h. Volatiles were removed *in vacuo* and the residue dissolved in CH_2Cl_2 (15 mL), washed with satd aq $NaHCO_3$ solution (10 mL), dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30−40 ºC petrol/Et_2O, 1:1) gave **315** as a coloreless oil (878 mg, 94%, 92:8 dr); $[\alpha]_D^{25}$ −37.8 (*c* 2.0 in $CHCl_3$); ν_{max} (ATR) 3419 br (O−H); δ_H (400 MHz, $CDCl_3$) 1.48 (3H, d, *J* 6.8, C(α)*Me*), 1.82 (1H, dd, *J* 12.6, 4.3, C(3)H_AH_B), 2.03 (1H, td, *J* 12.6, 3.5, C(3)H_AH_B), 2.64 (1H, br s, C(5)HO*H*), 3.25 (1H, dt, *J* 12.6, 3.8, C(4)*H*), 3.34 (3H, s, O*Me*), 3.51 (1H, br s, C(5)*H*), 3.60−3.70 (3H, m, C(6)H_2, NCH_AH_B), 3.91 (1H, d, *J* 15.4, NCH_AH_B), 4.26 (1H, q, *J* 6.8, C(α)*H*), 4.77 (1H, d, *J* 2.0, C(2)*H*), 7.17−7.48 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.9 (C(α)*Me*), 30.1 (*C*(3)), 51.8 (N*C*H_2), 54.8 (O*Me*), 54.9 (*C*(4)), 55.5 (*C*(α)Me), 62.3 (*C*(6)), 66.1 (*C*(5)), 98.3 (*C*(2)), 126.8, 127.0, 127.3, 128.0, 128.3, 128.4 (*o,m,p-Ph*), 142.3, 142.9 (*i-Ph*); *m/z* (ESI$^+$) 342 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{27}NO_3^+$ ([M+H]$^+$) requires 342.2064; found 342.2056.

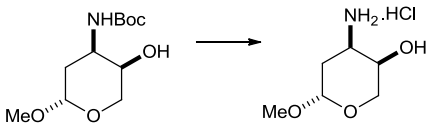
***tert*-Butyl [(2*S*,4*R*,5*R*)-5-hydroxy-2-methoxytetrahydro-2*H*-pyran-4-yl]carbamate 316**



315 **316**

Following *General Procedure 3*, **315** (218 mg, 0.64 mmol), Boc_2O (435 mg, 1.28 mmol), $Pd(OH)_2/C$ (50% w/w, 109 mg) and H_2 (5 atm) in MeOH (2 mL) after 24 h gave the crude reaction mixture. Purification via flash column chromatography (eluent 30−40 ºC petrol/EtOAc, 11:1) gave **316** as a colourless oil (142 mg, 90%, 96:4 dr); $[\alpha]_D^{25}$ −23.8 (*c* 2.0 in $CHCl_3$); ν_{max} (ATR) 3441 (O−H), 3328 (N−H), 1687 (C=O); δ_H (500 MHz, $CDCl_3$) 1.39 (3H, d, *J* 6.8, C(α)*Me*), 1.83−2.08 (3H, m, C(3)H_2), 3.51 (3H, s, O*Me*), 3.58−3.86 (5H, m, C(4)*H*, C(5)*H*OH, O*H*, C(6)H_2), 4.97 (1H, d, *J* 2.3, C(2)*H*), 8.01 (1H, br s, N*H*); δ_C (125 MHz, $CDCl_3$) 28.3 (CMe_3), 32.4 (*C*(3)), 53.2 (*C*(4)), 54.9 (O*Me*), 66.1 (*C*(5)), 67.5 (*C*(6)), 79.6 (*C*Me_3), 112.7 (*C*(2)), 155.7 (*C*O); *m/z* (ESI^+) 270 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{11}H_{21}NNaO_5^+$ ($[M+Na]^+$) requires 270.1312; found 270.1311.

(2*S*,4*R*,5*R*)-5-Hydroxytetrahydro-2*H*-pyran-4-amine hydrochloride salt 317



316 **317**

HCl (1.25 M in MeOH, 10.0 mL, 2.5 mmol) was added in **316** (114 mg, 0.46 mmol, 96:4 dr) at rt, and the reaction mixture stirred at rt for 16 h. Volatiles were removed *in vacuo* to give **317** as a coloreless oil (80.8 mg, 96%, 85:15 dr); $[\alpha]_D^{25}$ −45.7 (*c* 2.0 in $CHCl_3$); ν_{max} (ATR) 3439 (O−H), 3329 (N−H), 1098, 1041 (C–O); δ_H (500 MHz, $CDCl_3$) 1.84−2.09 (2H, m, C(3)H_2), 2.80−2.82 (1H, m, C(4)*H*), 3.51 (3H, s, O*Me*), 3.56−3.83 (4H, m, O*H*, C(6)H_2, C(4)*H*OH), 4.97 (1H, d, *J* 2.3, C(2)*H*), 5.12 (2H, br s,

N*H*$_2$); δ_C (125 MHz, $CDCl_3$) 35.2 (*C*(3)), 49.8 (*C*(4)), 55.3 (O*Me*), 67.4 (*C*(6)), 70.9 (*C*(5)), 112.4 (*C*(2)).

5.6 References and notes for chapter 5

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