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# Trading *N* and *O*. Part 2: Exploiting aziridinium intermediates for the synthesis of β-hydroxy-α-amino acids

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ABSTRACT

The β-hydroxy-α-amino acids (*S*,*S*)-*allo*-threonine, (*S*,*S*)-β-hydroxyleucine and a range of aryl substituted (*S*,*S*)-β-hydroxyphenylalanines were prepared from the corresponding enantiopure *anti*-α-hydroxy-β-amino esters via a rearrangement protocol, which proceeds via the intermediacy of the corresponding aziridinium ions. The starting *anti*-α-hydroxy-β-amino esters were prepared in >99:1 dr using our diastereoselective aminohydroxylation procedure, whereby conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to an α,β-unsaturated ester is followed by oxidation of the resultant enolate with (−)-camphorsulfonyloxaziridine. Subsequent activation of the hydroxyl group within the *anti*-α-hydroxy-β-amino esters promoted aziridinium ion formation [which proceeds with inversion of configuration at C(2)], and regioselective ring-opening of the intermediate aziridinium ions with $H_2O$ [which proceeds with inversion of configuration at C(3)] gave the corresponding *anti*-β-hydroxy-α-amino esters as single diastereoisomers (>99:1 dr). Deprotection of these substrates via sequential hydrogenolysis and ester hydrolysis gave the corresponding β-hydroxy-α-amino acids in good yield and high diastereoisomeric and enantiomeric purity.



## 1. Introduction

β-Hydroxy-α-amino acids are an important class of compounds because they occur naturally (e.g., serine, threonine and 3-hydroxyproline) and are also present as components within an array of more complex, biologically active natural products, such as antibiotics (e.g., vancomycin) and immunosuppressants (e.g., ciclosporin).[1] As a result of the impressive biological activity which this class of compounds displays, a number of elegant strategies for their synthesis in enantiopure form have been developed,[2] including several different aldol protocols,[3] enzymatic methods,[4] oxy-Michael reactions,[5] organocatalytic systems,[6] and dynamic kinetic resolution processes,[7] amongst other approaches.[8]

We have recently described asymmetric syntheses of (*S*,*S*)-2-amino-3-hydroxybutanoic acid [(*S*,*S*)-*allo*-threonine] **10** and (2*S*,3*R*)-2-amino-3-hydroxy-3-phenylpropanoic acid [(*S*,*S*)-β-hydroxyphenylalanine] **13**, and the corresponding C(2)-epimers in both cases.[9] Our synthetic strategy involved conversion of α-hydroxy-β-amino esters **5** and **6** (which were obtained in >99:1 dr upon aminohydroxylation of α,β-unsaturated esters **1** and **2** using our established lithium amide conjugate addition methodology)[10–13] to the corresponding *N*-Boc protected aziridines **7** and **8**, respectively, followed by regioselective ring-opening at the C(3)-position. Aziridines **7** and **8** were therefore produced from α-hydroxy-β-amino esters **5** and **6** via a three-step reaction sequence of: (i) hydrogenolysis and in situ *N*-Boc protection; (ii) OH-activation; and (iii) base-promoted aziridine formation. Subsequent regioselective ring-opening of the C(3)-methyl substituted aziridine **7** with $Cl_3CCO_2H$ proceeded with inversion of configuration at the C(3)-position to give the corresponding 2-amino-3-trichloroacetate ester **9**, whereas the analogous reaction with the C(3)-phenyl substituted aziridine **8** resulted in rearrangement to the corresponding oxazolidin-2-one **11** with retention of configuration at the C(3)-position. In each case, hydrolysis of the products from these ring-opening reactions produced the corresponding enantiopure β-hydroxy-α-amino acids **10** and **13** in high diastereoisomeric purity (Scheme 1). The analogous series of reactions was then conducted in the epimeric series following C(2)-epimerisation of *anti*-α-hydroxy-β-amino esters **5** and **6** via a sequential oxidation/diastereoselective reduction protocol.

Herein we report an extension of this methodology in which OH-activation of α-hydroxy-β-amino esters **14** promotes migration of the amino group to the C(2)-position via the intermediacy of the corresponding aziridinium species **15**,[14] followed by deprotection of the resultant β-hydroxy-α-amino esters **16**

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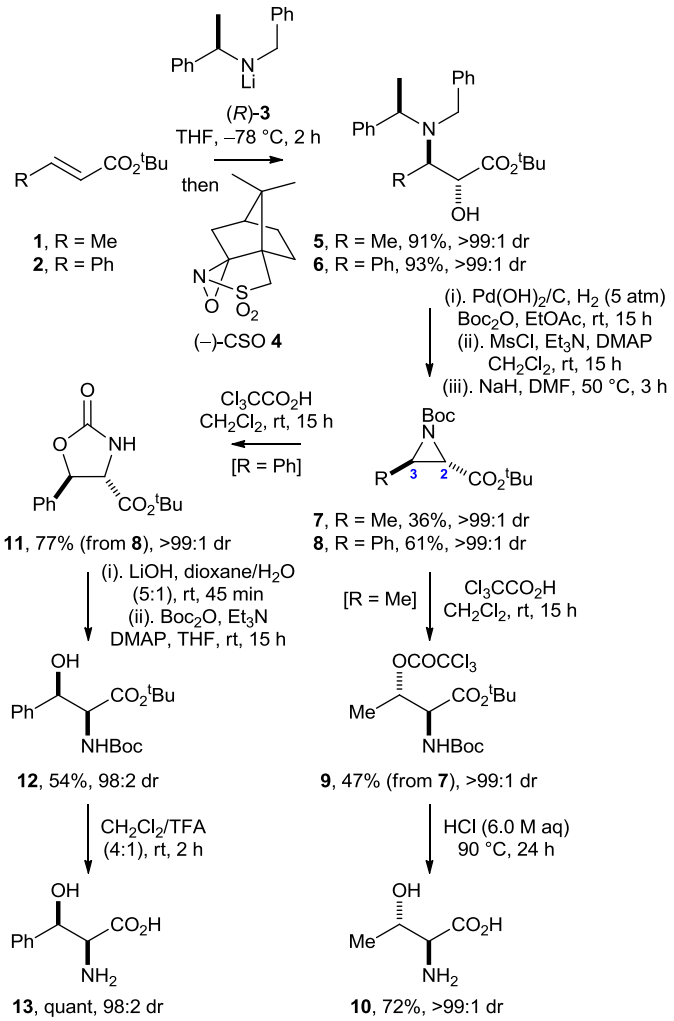


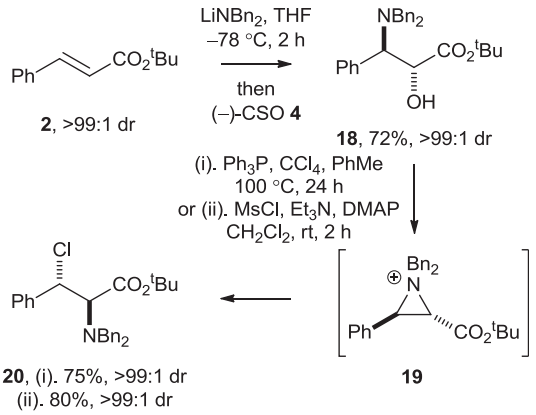

**Scheme 1.**

a reduction in the number of reaction steps and increased overall atom economy.

## 2. Results and discussion

### 2.1. Asymmetric synthesis of β-aryl-β-hydroxy-α-amino acids

Racemic α-hydroxy-β-amino ester **18** was selected as a model system to investigate this rearrangement process and optimise procedures for the synthesis of β-hydroxy-α-amino esters. α-Hydroxy-β-amino ester **18** was prepared as a single diastereoisomer (>99:1 dr) upon conjugate addition of lithium *N*,*N*-dibenzylamide to α,β-unsaturated ester **2**, followed by oxidation of the intermediate lithium (*Z*)-β-amino enolate[15] with (−)-CSO **4**.[16] Subsequent activation of the hydroxyl group within **18** under either Appel[17] or mesylation[14b] conditions gave β-chloro-α-amino ester **20** as the sole reaction product in 75 or 80% yield, respectively (Scheme 2). The relative *anti*-configuration within β-chloro-α-amino ester **20** was determined unambiguously via single crystal X-ray diffraction analysis (Fig. 2).[18] This stereochemical outcome is




**Scheme 2.**

(X=OH) to give β-hydroxy-α-amino acids **17**. The stereochemical outcome of this process would therefore constitute overall inversion of configuration, as inversion of configuration occurs at C(2) during the formation of aziridinium intermediate **15** and inversion of configuration occurs at C(3) upon ring-opening of **15** (Fig. 1). This approach would therefore provide significant advantages over our first generation approach in terms of both

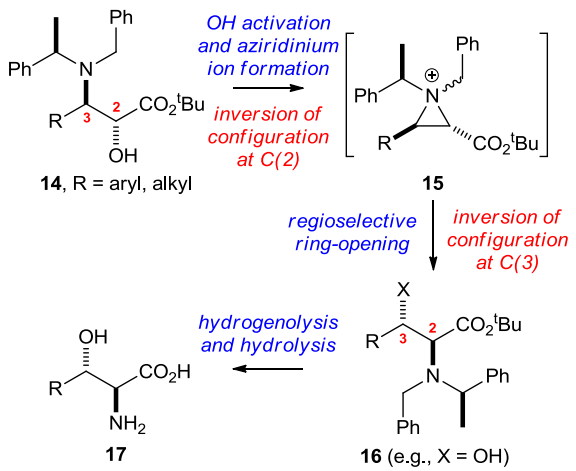



**Fig. 1.** Proposed second-generation synthesis of β-hydroxy-α-amino acids **17**.

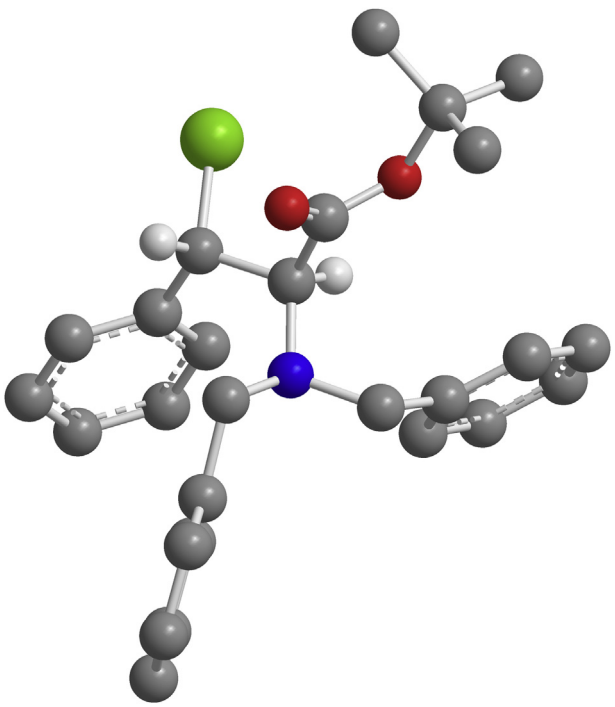
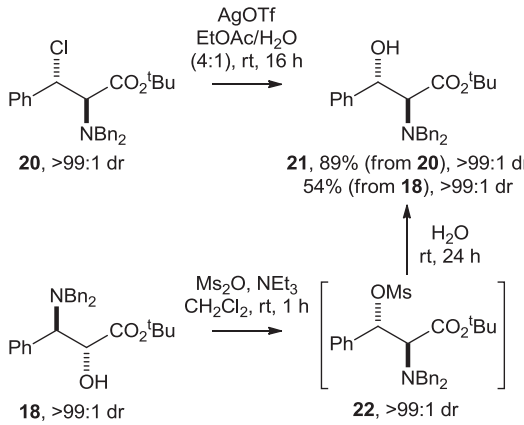


**Fig. 2.** X-ray crystal structure of (*RS*,*SR*)-**20** (selected H atoms are omitted for clarity).

entirely consistent with our proposed strategy, involving inversion of configuration at C(2) during the formation of aziridinium intermediate **19** and inversion of configuration at C(3) upon ring-opening of **19** with chloride.

β-Chloro-α-amino ester **20** was then treated with AgOTf in a 4:1 mixture of EtOAc/$H_2O$, which promoted substitution of the chloro group to give β-hydroxy-α-amino ester **21** in 89% yield and >99:1 dr (Scheme 3). The relative *anti*-configuration within **21** was determined unambiguously via single crystal X-ray diffraction analysis (Fig. 3),[18] establishing that the stereochemical outcome of this reaction (i.e., retention of configuration) is consistent with an $S_N1$-type neighbouring group participation process proceeding again via the intermediacy of aziridinium **19**. However, it was also found that β-hydroxy-α-amino ester **21** could be obtained directly from α-hydroxy-β-amino ester **18** upon treatment with $Ms_2O$ and $Et_3N$ in $CH_2Cl_2$, followed by the addition of $H_2O$ after 1 h; after a further 24 h stirring at rt, **21** was isolated in 54% yield as a single diastereoisomer (>99:1 dr). When this reaction was repeated, an aliquot was removed and worked-up 1 h after the $H_2O$ was added and revealed the presence of only β-mesylate **22** (>99:1 dr). The atom connectivity within **22** was established by $^1H/^{13}C$ NMR HMBC analysis, confirming that this reaction must proceed via the intermediacy of aziridinium **19**, followed by regioselective ring-opening with mesylate (reversibly in the first instance) then ring-opening of aziridinium **19** with $H_2O$ (Scheme 3).




**Scheme 3.**

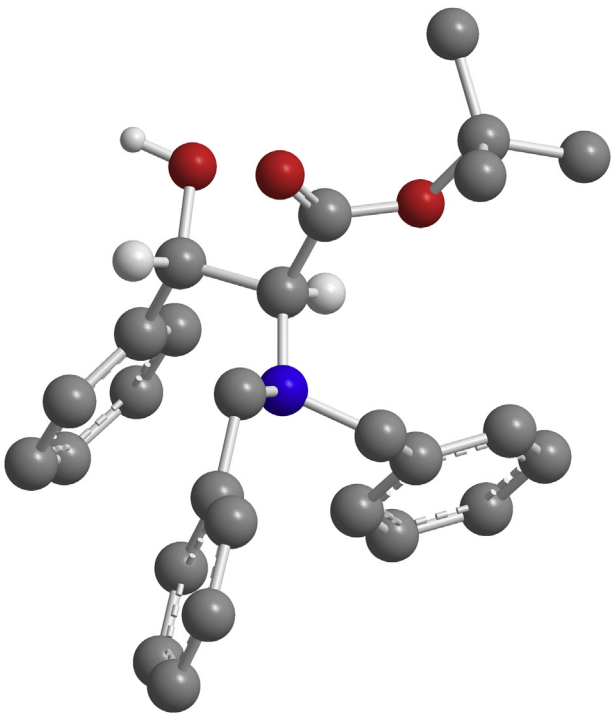
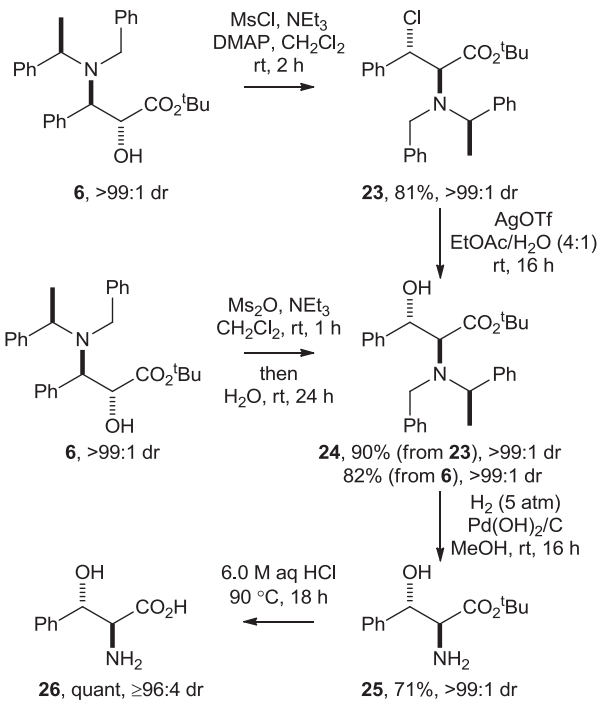


**Fig. 3.** X-ray crystal structure of (*RS*,*RS*)-**21** (selected H atoms are omitted for clarity).

The optimised procedures for rearrangement of the racemic model system were next applied to enantiopure α-hydroxy-β-amino ester **6**,[9] both via the corresponding β-chloro-α-amino ester **23** and directly from **6**.[19] Activation of the hydroxyl group within **6** with MsCl gave **23** as a single diastereoisomer (>99:1 dr) in 81% isolated yield (Scheme 4). The relative configuration within **23** was determined unambiguously via single crystal X-ray diffraction analysis, and the absolute (2*R*,3*S*,α*R*)-configuration within **23** was assigned by reference to the known (*R*)-configuration of the α-methylbenzyl fragment (Fig. 4).[18] Subsequent treatment of **23** with AgOTf in EtOAc/$H_2O$ (4:1) gave β-hydroxy-α-amino ester **24** in 90% yield and >99:1 dr, and the relative *anti*-configuration within **24** was assigned by analogy to that within **21**. However, a superior yield of β-hydroxy-α-amino ester **24** was obtained directly from α-hydroxy-β-amino ester **6**, giving **24** in 82% yield and >99:1 dr. Hydrogenolytic deprotection of **24** gave **25** in 71% yield and >99:1 dr, which was followed by hydrolysis of **25** to give β-hydroxyphenylalanine **26** {mp 183–188 °C (dec); $[\alpha]_D^{20}$ +1.9 (*c* 1.0, $H_2O$); lit.[8a] mp 174 °C (dec); lit.[20] $[\alpha]_D^{20}$ −4.3 (*c* 1.1, $H_2O$)} in quantitative yield and ≥96:4 dr, thereby confirming the assigned configurations within **24** and **25** (Scheme 4).




**Scheme 4.**

The substrate scope of this methodology was demonstrated by preparing a range of aryl substituted β-hydroxyphenylalanines **52**–**56**, incorporating both electron-donating and electron-withdrawing groups. The requisite α-hydroxy-β-amino ester substrates **32**–**36** were prepared, in 67–85% yield, and >99:1 dr in each case, upon conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **3** to α,β-unsaturated esters **27**–**31**,[21] followed by reaction of the resultant lithium (*Z*)-β-amino enolates[15] with

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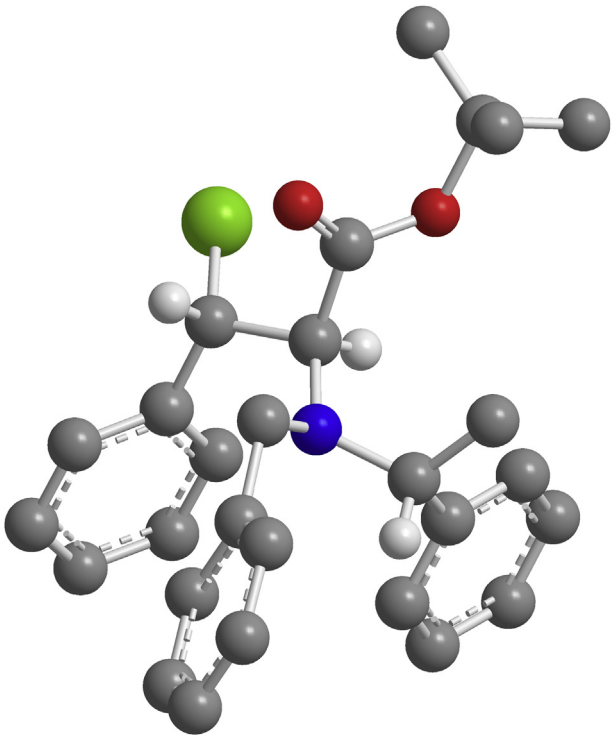
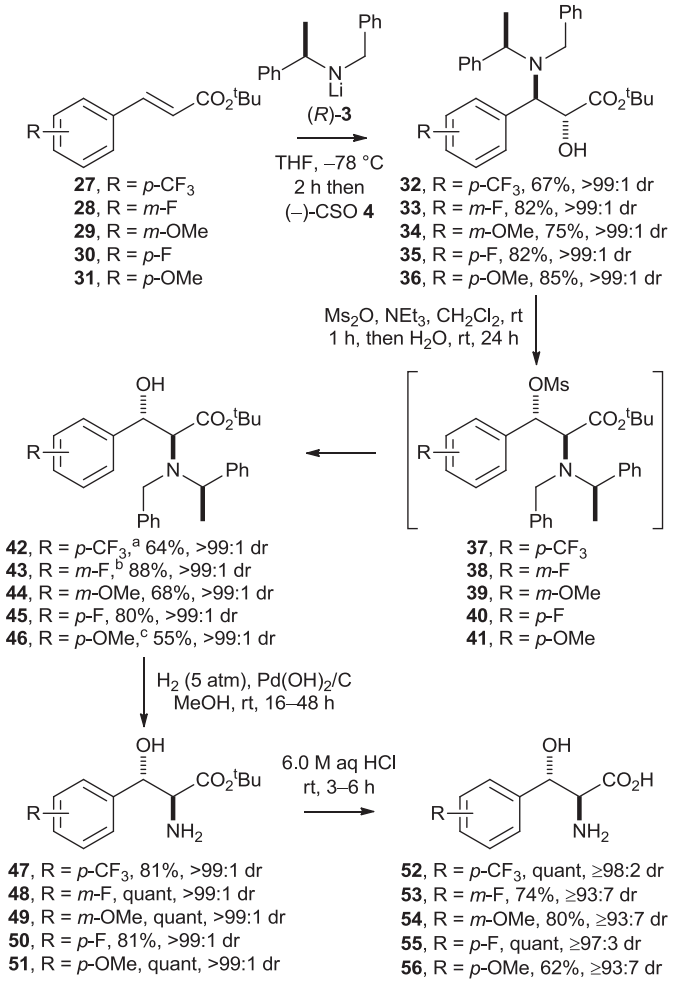


**Fig. 4.** X-ray crystal structure of (2*R*,3*S*,α*R*)-**23** (selected H atoms are omitted for clarity).




**Scheme 5.** [a]After $H_2O$ was added the reaction mixture was heated at 40 °C for 48 h. [b]After $H_2O$ was added the reaction mixture was heated at 40 °C for 24 h. [c]$H_2O$ was added after only 1 min then the reaction mixture was stirred at rt for 24 h.

(−)-CSO **4**. Under optimised conditions, treatment of this range of substrates **32**–**36** with $Ms_2O$ and $Et_3N$ in $CH_2Cl_2$ promoted rearrangement to mesylates **37**–**41**,[22] which were then stirred with $H_2O$ to give β-hydroxy-α-amino esters **42**–**46** as single diastereoisomers (>99:1 dr) in 55–88% yield (Scheme 5). Single crystal X-ray diffraction analysis of the *p*-fluoro substituted β-hydroxy-α-amino ester **45** allowed the relative configuration within **45** to be determined unambiguously (Fig. 5);[18] the absolute (2*S*,3*S*,α*R*)-configuration within **45** was then assigned by reference to the known (*R*)-configuration of the α-methylbenzyl fragment, and the configurations within **42**–**44** and **46** were assigned by analogy.[23] Deprotection of **42**–**46** via hydrogenolysis in the presence of Pearlman's catalyst [$Pd(OH)_2$/C] followed by hydrolysis of **47**–**51**, gave aryl substituted β-hydroxyphenylalanines **52**–**56** in good overall yield and ≥93:7 dr in each case (Scheme 5).[24]

## 2.2. Asymmetric synthesis of β-alkyl-β-hydroxy-α-amino acids

The compatibility of this protocol with substrates bearing β-alkyl substituents was examined next, and racemic α-hydroxy-β-amino alcohols **58** (R=Me) and **59** (R=$^i$Pr) were evaluated as model systems in the first instance. Conjugate addition of lithium *N*,*N*-dibenzylamide to α,β-unsaturated esters **1** and **57**, followed by oxidation of the intermediate lithium (*Z*)-β-amino enolate[15] with (−)-CSO **4**, gave **58** and **59** in 50 and 52% yield, respectively, and >99:1 dr in each case.[25] Activation of the hydroxyl groups within both **58** and **59**, under our standard conditions, gave the corresponding β-mesylates **60** and **61** (as determined by $^1H/^{13}C$ NMR HMBC spectroscopic analysis of the crude reaction mixtures), in 90 and 60% conversion from **58** and **59**, respectively. In an effort to promote the hydrolysis of these mesylates, subsequent addition of MeCN/$H_2O$ (2:1) to **60** and heating the resultant mixture at 50 °C produced a 41:59 mixture of α-hydroxy-β-amino ester **58** and β-hydroxy-α-amino ester **62**, and treatment of **59** under identical conditions produced a 24:76 mixture of α-hydroxy-β-amino ester **59** and β-hydroxy-α-amino ester **63**, as single diastereoisomers (>99:1 dr) in each case. These reaction outcomes are consistent with poor regioselectivity upon ring-opening of the corresponding aziridinium intermediates with $H_2O$.[26] Alternative reaction conditions were therefore examined whereby $Tf_2O$ was used instead of $Ms_2O$ and, after 3 h, $H_2O$ was added and the reaction mixture was then allowed to stir at rt for 24 h. After work-up a 34:66 mixture of α-hydroxy-β-amino ester **58** (>99:1 dr) and β-hydroxy-α-amino ester **62** (>99:1 dr) was isolated. However, repeating this reaction substituting 2,6-di-*tert*-butyl-4-methylpyridine **64** as the base was found to produce β-hydroxy-α-amino ester **62** exclusively, which was then isolated in 54% yield and >99:1 dr after chromatographic purification (Scheme 6).

These optimised conditions were next applied to enantiopure substrates **5** (R=Me) and **65** (R=$^i$Pr). α-Hydroxy-β-amino esters **5** and **65** were prepared in 91 and 56% yield, respectively, and in >99:1 dr in each case, using our standard aminohydroxylation procedure.[10–13] Treatment of either **5** or **65** with $Tf_2O$ and 2,6-di-*tert*-butyl-4-methylpyridine **64** followed, after 4–6 h, by the addition of $H_2O$ gave β-hydroxy-α-amino esters **68** and **69**, respectively, in 68% yield and >99:1 dr in both cases (Scheme 7). The relative configuration within **69** (R=$^i$Pr) was determined unambiguously via single crystal X-ray diffraction analysis (Fig. 6),[18] and the absolute (2*S*,3*S*,α*R*)-configuration within **69** was assigned by reference to the known (*R*)-configuration of the α-methylbenzyl

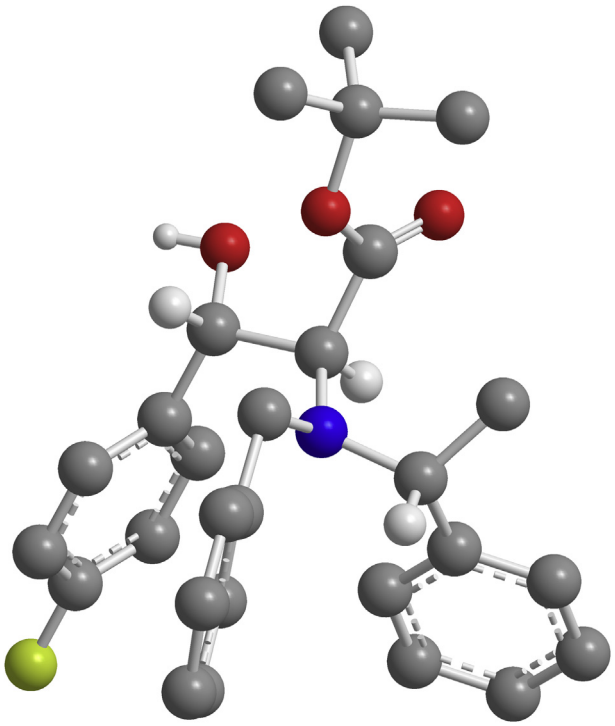
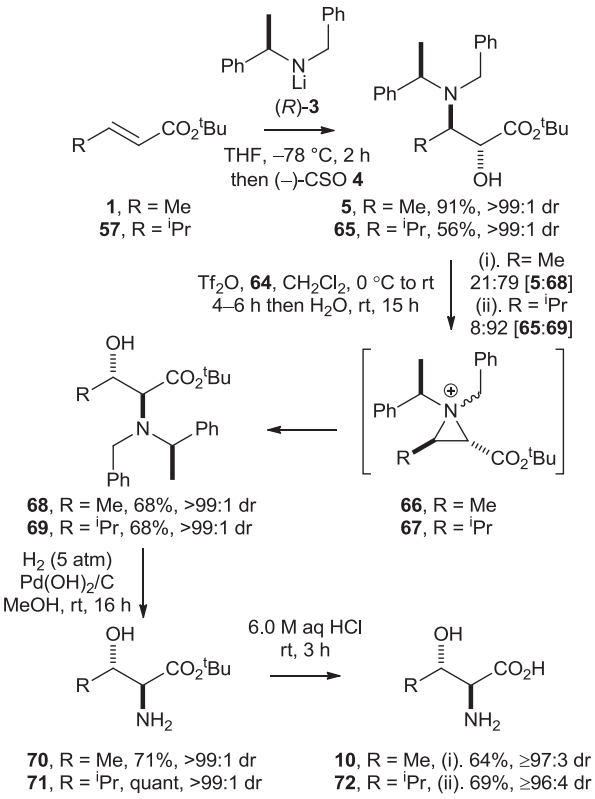
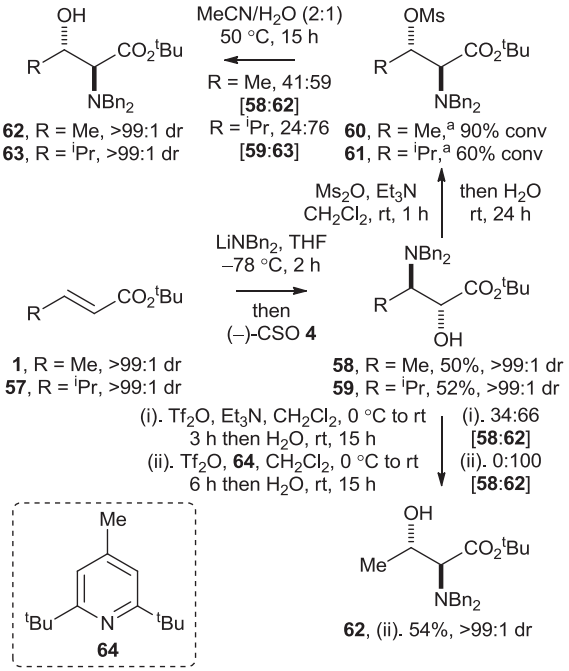


**Fig. 5.** X-ray crystal structure of (2*S*,3*S*,α*R*)-**45** (selected H atoms are omitted for clarity).




**Scheme 7.**




**Scheme 6.** [a]Produced as single diastereoisomers (>99:1 dr).

fragment; the configuration within **68** was then assigned by analogy. Subsequent deprotection of both **68** and **69** via hydrogenolysis in the presence of Pearlman's catalyst gave **70** and **71** in 71% and quantitative yield, respectively, as single diastereoisomers (>99:1 dr). Finally, hydrolysis of **70** and **71** in 6.0 M aq HCl gave (*S*,*S*)-*allo*-threonine **10** in 64% yield and ≥97:3 dr, and (*S*,*S*)-β-hydroxyleucine **72** in 69% yield and ≥96:4 dr, respectively (Scheme 7). The spectroscopic data, including specific rotations, for the samples of

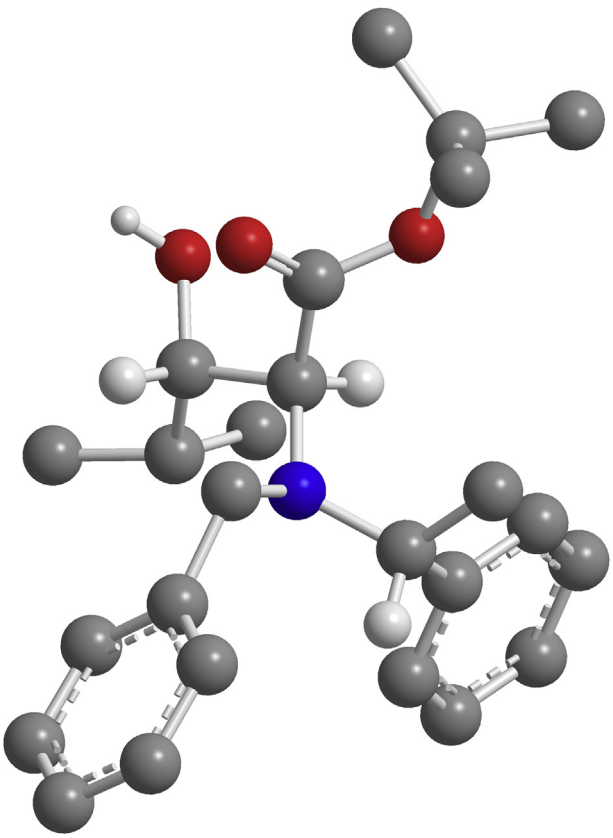


**Fig. 6.** X-ray crystal structure of (2*S*,3*S*,α*R*)-**69** (selected H atoms are omitted for clarity).

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(*S*,*S*)-**10** {mp 215–225 °C (dec); $[\alpha]_D^{20}$+7.6 (*c* 1.0, $H_2O$); lit.[3e] mp 264–266 °C (dec); lit.[3e] $[\alpha]_D^{20}$ +8 (*c* 1.1, $H_2O$)} and (*S*,*S*)-**72** {mp 220–226 °C (dec); $[\alpha]_D^{20}$ +17.6 (*c* 1.0, $H_2O$); lit.[3e] mp 187 °C (dec); lit.[3e] $[\alpha]_D^{25}$ +20 (*c* 1.1, $H_2O$)} were in good agreement with literature values, thereby confirming the assigned configurations within **68**–**71**.

## 3. Conclusion

In conclusion, a range of enantiopure *anti*-α-hydroxy-β-amino esters were prepared in >99:1 dr using our diastereoselective aminohydroxylation procedure. In each case, activation of the hydroxyl group within these substrates promoted aziridinium formation, and subsequent regioselective ring-opening of the intermediate aziridiniums with $H_2O$ gave the corresponding *anti*-β-hydroxy-α-amino esters as single diastereoisomers (>99:1 dr). The stereochemical outcomes of these reactions (i.e., overall inversion of configuration) are entirely consistent with this proposed mechanism. Following deprotection of the *anti*-β-hydroxy-α-amino esters, (*S*,*S*)-*allo*-threonine, (*S*,*S*)-β-hydroxyleucine and a range of six (*S*,*S*)-β-hydroxyphenylalanines were prepared in good overall yield and high diastereoisomeric purity.

## 4. Experimental

### 4.1. General experimental

Reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. BuLi was purchased from Sigma–Aldrich (as a solution in hexanes) and titrated against diphenylacetic acid before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[27] Water was purified by an Elix® UV-10 system. All other reagents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$ or $NaSO_4$. 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.

Melting points were recorded on a Gallenkamp Hot Stage apparatus. 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 using an ATR module. Selected characteristic peaks are reported in $cm^{-1}$. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated. Spectra were recorded at rt. The field was locked by external referencing to the relevant deuteron resonance. $^1H-^1H$ COSY, $^1H-^{13}C$ HMQC, and $^1H-^{13}C$ HMBC analyses were used to establish atom connectivity. Low-resolution mass spectra were recorded on either a 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.

### 4.2. General procedure for the diastereoselective aminohydroxylation of α,β-unsaturated esters

BuLi (1.55 equiv) was added dropwise to a stirred solution of the requisite amine (1.60 equiv) in THF at −78 °C and the resultant solution was stirred at −78 °C for 30 min. A solution of the requisite α,β-unsaturated ester (1.0 equiv) in THF was then added via cannula and the resultant mixture was stirred at −78 °C for 2 h. (−)-CSO **4** (1.60 equiv) was then added and the reaction mixture was allowed to warm to rt over 14 h. Satd aq $NH_4Cl$ was then added and the reaction mixture was stirred at rt for 5 min, then concentrated in vacuo. The residue was partitioned between $CH_2Cl_2$ and 10% aq citric acid and the aqueous layer was extracted with three portions of $CH_2Cl_2$. The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ and brine, then dried and concentrated in vacuo. The residue was then dissolved in $Et_2O$ and the resultant solution was filtered, then concentrated in vacuo.

### 4.3. *tert*-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]butanoate 5

Following the *general procedure*, BuLi (2.4 M in hexanes, 4.54 mL, 10.9 mmol) and (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (2.39 g, 11.3 mmol, >99:1 er) were reacted with **1** (1.00 g, 7.03 mmol, >99:1 dr) and **4** (2.74 g, 12.0 mmol) in THF (120 mL) at −78 °C to give **5** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/$Et_2O$, 10:1) gave **5** as a yellow solid (2.29 g, 91%, >99:1 dr);[9,28] mp 89–94 °C; {lit.[28] mp 88–89 °C}; $[\alpha]_D^{23}$ −35.5 (*c* 1.0, $CHCl_3$); {lit.[28] $[\alpha]_D^{25}$ −35.2 (*c* 1.0, $CHCl_3$)}; $\delta_H$ (400 MHz, $CDCl_3$) 1.08 (3H, d, *J* 7.0, C(4)$H_3$), 1.32 (3H, d, *J* 6.8, C(α)*Me*), 1.36 (9H, s, C$Me_3$), 2.92 (1H, d, *J* 6.5, O*H*), 3.25 (1H, qd, *J* 7.0, 2.6, C(3)*H*), 3.87 (1H, d, *J* 14.7, NC$H_AH_B$Ph), 3.97–4.04 (3H, m, C(2)*H*, C(α)*H*, NC$H_AH_B$Ph), 7.18–7.50 (10H, m, *Ph*).

### 4.4. *tert*-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 6

Following the *general procedure*, BuLi (2.5 M in hexanes, 15.2 mL, 38.01 mmol) and (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (8.26 g, 39.1 mmol, >99:1 er) were reacted with **2** (5.00 g, 24.5 mmol, >99:1 dr) and **4** (9.55 g, 41.7 mmol) in THF (200 mL) at −78 °C to give **6** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/$Et_2O$, 15:1) gave **6** as a pale yellow solid (9.77 g, 93%, >99:1 dr);[29] mp 85–88 °C; {lit.[28] mp 87–88 °C}; $[\alpha]_D^{23}$ −26.7 (*c* 1.0, $CHCl_3$); {lit.[28] $[\alpha]_D^{25}$ −27.2 (*c* 1.0, $CHCl_3$)}; $\delta_H$ (400 MHz, $CDCl_3$) 1.20 (9H, s, C$Me_3$), 1.18–1.22 (3H, obsc d, C(α)*Me*), 2.91 (1H, br s, O*H*), 3.92 (1H, d, *J* 14.9, NC$H_AH_B$Ph), 4.22 (1H, d, *J* 14.9, NC$H_AH_B$Ph), 4.27–4.33 (2H, m, C(α)*H*, C(3)*H*), 4.49 (1H, d, *J* 3.0, C(2)*H*), 7.21–7.61 (15H, m, *Ph*).

### 4.5. (*S*,*S*)-2-Amino-3-hydroxybutanoic acid [(*S*,*S*)-*allo*-threonine] 10

A solution of **70** (21 mg, 0.12 mmol, >99:1 dr) in 6.0 M aq HCl (1 mL) was stirred at rt for 3 h, then concentrated in vacuo. $H_2O$ (4 mL) and $CHCl_3$ (3 mL) were added and the aqueous layer was washed with $CHCl_3$ (2×3 mL) then concentrated in vacuo. Purification via ion exchange chromatography (DOWEX 50WX8-200, eluent 1.0 M aq $NH_4OH$) gave **10** as a white solid (9 mg, 64%, 97:3 dr);[9] mp 215–225 °C (dec); {lit.[3e] mp 264–266 °C}; $[\alpha]_D^{20}$ +7.6 (*c* 1.0, $H_2O$); {lit.[3e] $[\alpha]_D^{25}$ +8.0 (*c* 1.1, $H_2O$)}; $\delta_H$ (500 MHz, $D_2O$) 1.11 (3H, d, *J* 6.6, C(4)$H_3$), 3.75 (1H, d, *J* 4.0, C(2)*H*), 4.27 (1H, dq, *J* 6.6, 4.0, C(3)*H*).

### 4.6. *tert*-Butyl (*RS*,*RS*)-2-hydroxy-3-(*N*,*N*-dibenzylamino)-3-phenylpropanoate 18

Following the *general procedure*, BuLi (2.2 M in hexanes, 6.9 mL, 15.2 mmol) and $Bn_2NH$ (3.01 mL, 15.7 mmol) were reacted with **2** (2.00 g, 9.79 mmol, >99:1 dr) and **4** (3.82 g, 16.6 mmol) in THF (80 mL) at −78 °C to give **18** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 20:1) gave **18** as a white solid (2.94 g, 72%, >99:1 dr); mp 79–81 °C; $\nu_{max}$ (ATR) 3501 (O–H), 1724 (C=O); $\delta_H$ (400 MHz, $CDCl_3$) 1.30 (9H, s, C$Me_3$),

2.85 (1H, br s, O*H*), 3.46 (2H, d, *J* 13.9, N(C$H_A$H$_B$Ph)$_2$), 3.98 (2H, d, *J* 13.9, N(CH$_A$$H_B$Ph)$_2$), 4.11 (1H, d, *J* 4.3, C(3)*H*), 4.74–4.81 (1H, m, C(2)*H*), 7.19–7.42 (15H, m, *Ph*); $\delta_C$ (100 MHz, $CDCl_3$) 27.8 (C*Me*$_3$), 54.8 (N(*C*H$_2$Ph)$_2$), 64.5 (*C*(3)), 72.7 (*C*(2)), 82.6 (*C*Me$_3$), 126.9, 127.6, 128.0, 128.2, 128.8, 130.0 (*o*,*m*,*p*-*Ph*), 135.9, 139.8 (*i*-*Ph*), 173.0 (*C*(1)); *m*/*z* (ESI$^+$) 418 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{32}NO_3^+$ ([M+H]$^+$) requires 418.2377; found 418.2379.

### 4.7. *tert*-Butyl (*RS*,*SR*)-2-(*N*,*N*-dibenzylamino)-3-chloro-3-phenylpropanoate 20

*Method A*: MsCl (0.28 mL, 3.60 mmol), $Et_3N$ (1.10 mL, 8.27 mmol), and DMAP (5 mg) were added to a solution of **18** (300 mg, 0.719 mmol, >99:1 dr) in $CH_2Cl_2$ (20 mL) and the resultant mixture was stirred at rt for 2 h. $H_2O$ (10 mL) was then added, the aqueous layer was extracted with $CH_2Cl_2$ (3×10 mL) and the combined organic extracts were washed sequentially with 1.0 M aq HCl (20 mL), satd aq $NaHCO_3$ (20 mL) and brine (20 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/$Et_2O$, 10:1) gave **20** as a white solid (251 mg, 80%, >99:1 dr); mp 98–110 °C; $\nu_{max}$ (ATR) 1723 (C=O); $\delta_H$ (400 MHz, $CDCl_3$) 1.66 (9H, s, C*Me*$_3$), 3.35 (2H, d, *J* 13.4, N(C$H_A$H$_B$Ph)$_2$), 3.72–3.86 (3H, m, C(2)*H*, N(CH$_A$$H_B$Ph)$_2$), 5.24 (1H, d, *J* 11.1, C(3)*H*), 6.86–7.47 (15H, m, *Ph*); $\delta_C$ (400 MHz, $CDCl_3$) 28.5 (C*Me*$_3$), 54.5 (N(*C*H$_2$Ph)$_2$), 60.1 (*C*(3)), 66.9 (*C*(2)), 82.2 (*C*Me$_3$), 127.2, 128.0, 128.3, 128.6, 128.7, 129.1 (*o*,*m*,*p*-*Ph*), 138.2, 138.2 (*i*-*Ph*), 168.6 (*C*(1)); *m*/*z* (ESI$^+$) 460 ([M($^{37}$Cl)+Na]$^+$, 30%), 458 ([M($^{35}$Cl)+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{30}{}^{35}ClNNaO_2^+$ ([M($^{35}$Cl)+Na]$^+$) requires 458.1857; found 458.1865.

*Method B*: $CCl_4$ (1.74 mL, 18.0 mmol) was added to a solution of **18** (500 mg, 1.20 mmol, >99:1 dr), $PPh_3$ (630 mg, 2.40 mmol) in PhMe (4 mL) and the resultant mixture was heated at 100 °C for 2 h. The reaction mixture was allowed to cool to rt and filtered, then concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/$Et_2O$, 40:1) gave **20** as a white solid (389 mg, 75%, >99:1 dr).

### 4.8. *tert*-Butyl (*RS*,*RS*)-2-(*N*,*N*-dibenzylamino)-3-hydroxy-3-phenylpropanoate 21

*Method A (from **20**)*: AgOTf (12 mg, 0.046 mmol) was added to a solution of **20** (20 mg, 0.046 mmol, >99:1 dr) in EtOAc/$H_2O$ (0.5 mL, 4:1) and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then filtered through alumina (eluent EtOAc) and concentrated in vacuo to give **21** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/$Et_2O$, 5:1) gave **21** as a white solid (17 mg, 89%, >99:1 dr); mp 133–136 °C; $\nu_{max}$ (ATR) 3465 (O–H), 1722 (C=O); $\delta_H$ (500 MHz, $CDCl_3$) 1.65 (9H, s, C*Me*$_3$), 2.74 (1H, d, *J* 4.1, O*H*), 3.43–3.54 (3H, m, C(2)*H*, N(C$H_A$H$_B$Ph)$_2$), 3.90 (2H, d, *J* 13.9, N(CH$_A$$H_B$Ph)$_2$), 5.05 (1H, dd, *J* 9.4, 3.8, C(3)*H*), 6.94–7.41 (15H, m, *Ph*); $\delta_C$ (125 MHz, $CDCl_3$) 28.6 (C*Me*$_3$), 55.0 (N(*C*H$_2$Ph)$_2$), 66.5 (*C*(2)), 73.0 (*C*(3)), 82.2 (*C*Me$_3$), 126.9, 127.8, 127.9, 128.1, 128.1, 128.8 (*o*,*m*,*p*-*Ph*), 138.6, 140.9 (*i*-*Ph*), 171.6 (*C*(1)); *m*/*z* (ESI$^+$) 418 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{32}NO_3^+$ ([M+H]$^+$) requires 418.2377; found 418.2382.

*Method B (from **18**)*: $Ms_2O$ (125 mg, 0.719 mmol) was added to a solution of **18** (100 mg, 0.240 mmol >99:1 dr) and $Et_3N$ (0.14 mL, 1.1 mmol) in $CH_2Cl_2$ (1 mL) and the resultant solution was stirred at rt for 1 h. $H_2O$ (26 μL, 7.2 mmol) was added and the resultant mixture was stirred at rt for 24 h. $H_2O$ (1 mL) was then added and the resultant mixture was extracted with $CH_2Cl_2$ (3×2 mL). The combined organic extracts were washed sequentially with 1.0 M aq HCl (3 mL), satd aq $NaHCO_3$ (3 mL) and brine (3 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/$Et_2O$, 5:1) gave **21** as a white solid (54 mg, 54%, >99:1 dr).

### 4.9. *tert*-Butyl (*RS*,*RS*)-2-(*N*,*N*-dibenzylamino)-3-(methanesulfonyloxy)-3-phenylpropanoate 22

$Ms_2O$ (25 mg, 0.144 mmol) was added to a solution of **18** (20 mg, 48 μmol, >99:1 dr) and $Et_3N$ (29 μL, 0.216 mmol) in $CH_2Cl_2$ (0.2 mL) and the resultant mixture was stirred at rt for 1 h. $H_2O$ (0.026 mL, 7.2 mmol) was then added and the reaction mixture was stirred at rt for 1 h. $H_2O$ (1 mL) was then added and the resultant mixture was extracted with $CH_2Cl_2$ (3×2 mL). The combined organic extracts were washed sequentially with 1.0 M aq HCl (3 mL), satd aq $NaHCO_3$ (3 mL) and brine (3 mL), then dried and concentrated in vacuo to give **22** as yellow oil (17 mg, >99:1 dr); $\delta_H$ (500 MHz, $CDCl_3$) 1.67 (9H, s, C*Me*$_3$), 2.55 (3H, s, $SO_2$*Me*), 3.41 (2H, d, *J* 13.6, N(C$H_A$H$_B$Ph)$_2$), 3.75 (1H, d, *J* 10.7, C(2)*H*), 3.84 (2H, d, *J* 13.6, N(CH$_A$$H_B$Ph)$_2$), 5.89 (1H, d, *J* 10.7, C(3)*H*), 6.88–7.52 (15H, m, *Ph*); $\delta_C$ (125 MHz, $CDCl_3$) 28.4 (C*Me*$_3$), 39.2 ($SO_2$*Me*), 54.8 (N(*C*H$_2$Ph)$_2$), 64.2 (*C*(2)), 82.6 (*C*(3)), 82.7 (*C*Me$_3$), 127.2, 128.1, 128.5, 128.7, 129.1, 129.5 (*o*,*m*,*p*-*Ph*), 135.3, 137.9 (*i*-*Ph*), 168.3 (*C*(1)).

### 4.10. *tert*-Butyl (2*R*,3S,α*R*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-3-chloro-3-phenylpropanoate 23

MsCl (0.179 mL, 2.32 mmol), $Et_3N$ (0.709 mL, 5.34 mmol) and DMAP (5 mg) were added to a solution of **6** (200 mg, 0.464 mmol, >99:1 dr) in $CH_2Cl_2$ (13 mL) and the resultant mixture was stirred at rt for 2 h. $H_2O$ (10 mL) was then added and the aqueous layer was extracted with $CH_2Cl_2$ (3×10 mL). The combined organic extracts were washed sequentially with 1.0 M aq HCl (25 mL), satd aq $NaHCO_3$ (25 mL) and brine (25 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/$Et_2O$, 20:1) gave **23** as a white solid (170 mg, 81%, >99:1 dr); mp 90–93 °C; $[\alpha]_D^{23}$ +27.0 (*c* 1.0, $CHCl_3$); $\nu_{max}$ (ATR) 1723 (C=O); $\delta_H$ (400 MHz, $CDCl_3$) 1.27 (3H, d, *J* 7.0, C(α)*Me*), 1.55 (9H, s, C*Me*$_3$), 3.70–3.82 (3H, m, C(2)*H*, C(α)*H*, NC$H_A$H$_B$Ph), 4.01 (1H, d, *J* 14.3, NCH$_A$$H_B$Ph), 5.06 (1H, d, *J* 11.0, C(3)*H*), 7.24–7.42 (15H, m, *Ph*); $\delta_C$ (100 MHz, $CDCl_3$) 12.3 (C(α)*Me*), 28.2 (C*Me*$_3$), 50.7 (N*C*H$_2$Ph), 55.8 (*C*(α)), 61.5 (*C*(3)), 64.5 (*C*(2)), 82.0 (*C*Me$_3$), 127.0, 127.1, 128.2, 128.4, 128.4, 128.6, 128.7, 129.0 (*o*,*m*,*p*-*Ph*), 138.4, 139.3, 141.9 (*i*-*Ph*), 171.7 (*C*(1)); *m*/*z* (ESI$^+$) 474 ([M($^{37}$Cl)+Na]$^+$, 30%), 472 ([M($^{35}$Cl)+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{32}{}^{35}ClNNaO_2^+$ ([M($^{35}$Cl)+Na]$^+$) requires 472.2014; found 472.2024.

### 4.11. *tert*-Butyl (2*S*,3S,α*R*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-3-hydroxy-3-phenylpropanoate 24

*Method A (from **23**)*: AgOTf (61 mg, 0.229 mmol) was added to a solution of **23** (100 mg, 0.23 mmol, >99:1 dr) in EtOAc/$H_2O$ (2.62 mL, v/v 4:1) and the resultant mixture was stirred at rt for 16 h, then filtered through alumina (eluent EtOAc) and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/$Et_2O$, 5:1) gave **24** as a white solid (89 mg, 90%, >99:1 dr); mp 78–85 °C; $[\alpha]_D^{23}$ −22.7 (*c* 1.0, $CHCl_3$); $\nu_{max}$ (ATR) 3496 (C–O), 1722 (C=O); $\delta_H$ (400 MHz, $CDCl_3$) 1.39 (3H, d, *J* 6.9, C(α)*Me*), 1.58 (9H, s, C*Me*$_3$), 2.59 (1H, br s, O*H*), 3.60 (1H, d, *J* 8.0, C(2)*H*), 3.94 (1H, d, *J* 14.2, NC$H_A$H$_B$Ph), 4.01 (1H, q, *J* 6.9, C(α)*H*), 4.19 (1H, d, *J* 14.2, NC$H_A$H$_B$Ph), 4.92 (1H, dd, *J* 8.0, 4.7, C(3)*H*), 6.86–7.39 (15H, m, *Ph*); $\delta_C$ (100 MHz, $CDCl_3$) 13.4 (C(α)*Me*), 28.2 (C*Me*$_3$), 51.7 (N*C*H$_2$Ph), 56.2 (*C*(α)), 64.6 (*C*(2)), 74.6 (*C*(3)), 81.7 (*C*Me$_3$), 126.7, 126.9, 127.5, 127.7, 127.9, 128.1, 128.1, 128.1, 129.0 (*o*,*m*,*p*-*Ph*), 139.9, 141.2, 143.0 (*i*-*Ph*), 173.5 (*C*(1)); *m*/*z* (ESI$^+$) 432 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{33}NNaO_3^+$ ([M+Na]$^+$) requires 454.2353; found 454.2362.

*Method B (from **6**)*: $Ms_2O$ (121 mg, 0.695 mmol) was added to a solution of **6** (100 mg, 0.23 mmol, >99:1 dr) and $Et_3N$ (0.139 mL, 1.04 mmol) in $CH_2Cl_2$ (1 mL) and the resultant mixture was stirred at rt for 1 h, then $H_2O$ (0.125 mL, 6.96 mmol) was added and the

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reaction mixture was stirred at rt for 24 h. $H_2O$ (1 mL) was then added and the resultant mixture was extracted with $CH_2Cl_2$ (3×2 mL). The combined organic extracts were washed sequentially with 1.0 M aq HCl (3 mL), satd aq $NaHCO_3$ (3 mL) and brine (3 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/$Et_2O$, 4:1) gave **24** as a white solid (82 mg, 82%, >99:1 dr).

### 4.12. *tert*-Butyl (*S*,*S*)-2-amino-3-hydroxy-3-phenylpropanoate 25

$Pd(OH)_2$/C (22 mg, 25% w/w) was added to a degassed solution of **24** (89 mg, 0.21 mmol, >99:1 dr) in MeOH (1 mL) and the resultant mixture was placed under an atmosphere of $H_2$ (5 atm) and stirred at rt for 16 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated in vacuo to give **25** as a white solid (35 mg, 71%, >99:1 dr); mp 151–154 °C; $[\alpha]_D^{20}$ +44.7 (*c* 1.0, MeOH); $\nu_{max}$ (ATR) 3446 (O–H), 1732 (C=O); $\delta_H$ (400 MHz, $CDCl_3$) 1.22 (9H, s, C*Me*$_3$), 4.07–4.15 (1H, m, C(2)*H*), 5.13–5.17 (1H, m, C(3)*H*), 7.19–7.36 (5H, m, *Ph*); $\delta_C$ (125 MHz, $CDCl_3$) 26.8 (C*Me*$_3$), 60.5 (*C*(2)), 74.6 (*C*(3)), 81.6 (*C*Me$_3$), 126.4, 127.5, 127.8 (*o*,*m*,*p*-*Ph*), 140.3 (*i*-*Ph*), 171.1 (*C*(1)); *m*/*z* (ESI$^+$) 260 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{19}NNaO_3^+$ ([M+Na]$^+$) requires 260.1257; found 260.1270.

### 4.13. (*S*,*S*)-2-Amino-3-hydroxy-3-phenyl propanoic acid 26

A solution of **25** (27 mg, 0.114 mmol, >99:1 dr) in 6.0 M aq HCl (2 mL) was heated at 90 °C for 18 h. The reaction mixture was then allowed to cool to rt and concentrated in vacuo. Purification via ion exchange chromatography (DOWEX 50WX8-200, eluent 1.0 M aq $NH_4OH$) gave **26** as a white solid (21 mg, quant, 96:4 dr);[9] mp 183–188 °C; {lit.[30] mp 185–187 °C}; $[\alpha]_D^{20}$ +1.9 (*c* 1.0, $H_2O$); {lit.[9] for *ent*-**26** $[\alpha]_D^{20}$ −2.4 (*c* 1.0, $H_2O$); $\nu_{max}$ (ATR) 3135 (O–H, N–H), 1604 (C=O); $\delta_H$ (500 MHz, $D_2O$) 4.01 (1H, d, *J* 4.1, C(2)*H*), 5.28 (1H, d, *J* 4.1, C(3)*H*), 7.28–7.39 (5H, m, *Ph*).

### 4.14. *tert*-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(4′-trifluoromethylphenyl)propanoate 32

Following the *general procedure*, BuLi (2.5 M in hexanes, 1.73 mL, 3.98 mmol) and (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (993 mg, 4.11 mmol, >99:1 er) were reacted with **27** (700 mg, 2.57 mmol, >99:1 dr) and **4** (1.00 g, 4.37 mmol) in THF (20 mL) at −78 °C to give **32** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/$Et_2O$, 10:1) gave **32** as a pale yellow oil (865 mg, 67%, >99:1 dr); $[\alpha]_D^{23}$ −27.5 (*c* 1.0, $CHCl_3$); $\nu_{max}$ (ATR) 3496 (O–H), 1722 (C=O); $\delta_H$ (400 MHz, $CDCl_3$) 1.38 (9H, s, C*Me*$_3$), 1.36–1.44 (3H, obsc d, C(α)*Me*), 3.24 (1H, br s, O*H*), 4.16 (1H, d, *J* 14.8, NC*H*$_A$H$_B$Ph), 4.36 (1H, d, *J* 14.8, NCH$_A$*H*$_B$Ph), 4.40–4.48 (1H, m, C(α)*H*), 4.54–4.59 (1H, m, C(3)*H*), 4.64–4.72 (1H, m, C(2)*H*), 7.34–7.89 (14H, m, *Ar*, *Ph*); $\delta_C$ (100 MHz, $CDCl_3$) 15.5 (C(α)*Me*), 27.7 (C*Me*$_3$), 52.4 (NC$H_2$Ph), 57.9 (*C*(α)), 64.4 (*C*(3)), 73.2 (*C*(2)), 82.6 (*C*Me$_3$), 124.5 (q, *J* 272.2, *C*F$_3$), 124.9 (q, *J* 4.0, *C*(3′), *C*(5′)), 126.9, 127.2, 128.1, 128.1, 128.4, 128.5 (*o*,*m*,*p*-*Ph*), 129.7 (q, *J* 34.4, *C*(4′)), 130.3 (*C*(2′), *C*(6′)), 143.1, 143.7 (*i*-*Ph*), 143.9 (*C*(1′)), 172.4 (*C*(1)); $\delta_F$ (377 MHz, $CDCl_3$) −62.2 (C*F*$_3$); *m*/*z* (ESI$^+$) 500 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{33}F_3NO_3^+$ ([M+H]$^+$) requires 500.2407; found 500.2400.

### 4.15. *tert*-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(3′-fluorophenyl)propanoate 33

Following the *general procedure*, BuLi (2.3 M in hexanes, 2.12 mL, 4.88 mmol) and (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (1.22 g, 5.04 mmol, >99:1 er) were reacted with **28** (700 mg, 3.15 mmol, >99:1 dr) and **4** (1.23 g, 5.36 mmol) in THF (20 mL) at −78 °C to give **33** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/$Et_2O$, 10:1) gave **33** as a pale yellow solid (1.16 g, 82%, >99:1 dr); mp 73–79 °C; $[\alpha]_D^{20}$ −34.6 (*c* 1.0, $CHCl_3$); $\nu_{max}$ (ATR) 3485 (O–H), 1724 (C=O); $\delta_H$ (400 MHz, $CDCl_3$) 1.39 (9H, s, C*Me*$_3$), 1.32–1.50 (3H, obsc d, C(α)*Me*), 3.20 (1H, br s, O*H*), 4.13 (1H, d, *J* 15.0, NC*H*$_A$H$_B$Ph), 4.37 (1H, d, *J* 15.0, NCH$_A$*H*$_B$Ph), 4.41–4.50 (2H, m, C(3)*H*, C(α)*H*), 4.61–4.70 (1H, m, C(2)*H*), 7.09–7.75 (14H, m, *Ar*, *Ph*); $\delta_C$ (100 MHz, $CDCl_3$) 14.8 (C(α)*Me*) 27.4 (C*Me*$_3$) 52.0 (NC$H_2$Ph), 57.3 (*C*(α)), 64.0 (*C*(3)), 73.1 (*C*(2)), 82.1 (*C*Me$_3$), 114.4, 116.8 (2×d, *J* 21.5, *C*(2′), *C*(4′)), 125.5 (d, *J* 2.9, *C*(6′)), 126.7, 127.0, 128.0, 128.0, 128.2, 128.3 (*o*,*m*,*p*-*Ph*), 129.4 (d, *J* 7.6, *C*(5′)), 141.1 (d, *J* 6.7, *C*(1′)), 143.9, 141.6 (*i*-*Ph*), 162.5 (d, *J* 245.1, *C*(3′)), 172.0 (*C*(1)); $\delta_F$ (377 MHz, $CDCl_3$) −112.9 (C(3′)*F*); *m*/*z* (ESI$^+$) 450 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{33}FNO_3^+$ ([M+H]$^+$) requires 450.2439; found 450.2439.

### 4.16. *tert*-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(3′-methoxyphenyl)propanoate 34

Following the *general procedure*, BuLi (2.3 M in hexanes, 2.02 mL, 4.63 mmol) and (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (1.15 g, 4.78 mmol, >99:1 er) were reacted with **29** (700 mg, 2.99 mmol, >99:1 dr) and **4** (1.17 g, 5.09 mmol) in THF (20 mL) at −78 °C to give **34** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/$Et_2O$, 10:1) gave **34** as a pale yellow oil (1.04 g, 75%, >99:1 dr); $[\alpha]_D^{20}$ −30.8 (*c* 1.0, $CHCl_3$); $\nu_{max}$ (ATR) 3958 (O–H), 1722 (C=O); $\delta_H$ (400 MHz, $CDCl_3$) 1.23 (9H, s, C*Me*$_3$), 1.17–1.26 (3H, obsc d, C(α)*Me*), 2.72 (1H, br s, O*H*), 3.79 (3H, s, O*Me*), 3.86 (1H, d, *J* 15.0, NC*H*$_A$H$_B$Ph), 4.12 (1H, d, *J* 15.0, NCH$_A$*H*$_B$Ph), 4.19 (1H, d, *J* 3.1, C(3)*H*), 4.22 (1H, q, *J* 6.8, C(α)*H*), 4.37 (1H, d, *J*, 3.1, C(2)*H*), 6.77–7.57 (14H, m, *Ar*, *Ph*); $\delta_C$ (100 MHz, $CDCl_3$) 14.6 (C(α)*Me*), 27.8 (C*Me*$_3$), 52.4 (NC$H_2$Ph), 55.2 (O*Me*), 57.4 (*C*(α)), 65.4 (*C*(3)), 73.5 (*C*(2)), 82.2 (*C*Me$_3$), 112.9, 115.8, 122.4, 126.7 (*C*(2′), *C*(4′), *C*(5′), *C*(6′)), 126.7, 128.1, 128.1, 128.2, 128.3, 129.0 (*o*,*m*,*p*-*Ph*), 140.0 (*C*(1′)), 141.9, 144.2 (*i*-*Ph*), 159.4 (*C*(3′)), 172.3 (*C*(1)); *m*/*z* (ESI$^+$) 462 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{36}NO_4^+$ ([M+H]$^+$) requires 462.2639; found 462.2636.

### 4.17. *tert*-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(4′-fluorophenyl)propanoate 35

Following the *general procedure*, BuLi (2.3 M in hexanes, 2.12 mL, 4.88 mmol) and (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (1.22 g, 5.04 mmol, >99:1 er) were reacted with **30** (493 mg, 2.22 mmol, >99:1 dr) and **4** (865 mg, 3.77 mmol) in THF (20 mL) at −78 °C to give **35** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/$Et_2O$, 10:1) gave **35** as a pale yellow oil (819 mg, 82%, >99:1 dr); $[\alpha]_D^{20}$ −26.7 (*c* 1.0, $CHCl_3$); $\nu_{max}$ (ATR) 3499 (O–H), 1723 (C=O); $\delta_H$ (400 MHz, $CDCl_3$) 1.23 (9H, s, C*Me*$_3$), 1.19–1.31 (3H, obsc d, C(α)*Me*), 2.77 (1H, br s, O*H*), 3.85 (1H, d, *J* 15.0, NC*H*$_A$H$_B$Ph), 4.11 (1H, d, *J* 15.0, NCH$_A$*H*$_B$Ph), 4.16–4.25 (2H, m, C(3)*H*, C(α)*H*), 4.40–4.44 (1H, m, C(2)*H*), 7.01 (2H, app t, *J* 8.0, C(3′)*H*, C(5′)*H*), 7.38 (2H, app t, *J* 8.0, C(2′)*H*, C(6′)*H*), 7.20–7.52 (10H, m, *Ph*); $\delta_C$ (125 MHz, $CDCl_3$) 14.7 (C(α)*Me*) 27.8 (C*Me*$_3$) 52.2 (NC$H_2$Ph), 57.5 (*C*(α)), 64.7 (*C*(3)), 73.3 (*C*(2)), 82.4 (*C*Me$_3$), 114.9 (d, *J* 21.5, *C*(3′), *C*(5′)), 126.8, 127.0, 128.0, 128.0, 128.3, 128.4 (*o*,*m*,*p*-*Ph*), 131.6 (d, *J* 7.2, *C*(2′), *C*(6′)), 134.3 (*C*(1′)), 141.9, 144.1 (*i*-*Ph*), 162.3 (d, *J* 246.4, *C*(4′)), 172.2 (*C*(1)); $\delta_F$ (377 MHz, $CDCl_3$) −114.7 (C(4′)*F*); *m*/*z* (ESI$^+$) 450 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{33}FNO_3^+$ ([M+H]$^+$) requires 450.2439; found 450.2435.

### 4.18. *tert*-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(4′-methoxyphenyl)propanoate 36

Following the *general procedure*, BuLi (2.3 M in hexanes, 2.02 mL, 4.63 mmol) and (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (1.15 g,

4.78 mmol, >99:1 er) were reacted with **31** (700 mg, 2.99 mmol, >99:1 dr) and **4** (1.17 g, 5.08 mmol) in THF (20 mL) at −78 °C to give **36** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/$Et_2O$, 10:1) gave **36** as a yellow oil (1.18 g, 85%, >99:1 dr); $[\alpha]_D^{20}$ −24.5 (*c* 1.0, $CHCl_3$); $\nu_{max}$ (ATR) 3497 (O—H), 1722 (C═O); $\delta_H$ (400 MHz, $CDCl_3$) 1.26 (9H, s, C*Me*$_3$), 1.22–1.37 (3H, obsc d, C(α)*Me*), 3.16 (1H, br s, O*H*), 3.83 (3H, s, O*Me*), 3.97 (1H, d, *J* 15.0, NC*H*$_A$H$_B$Ph), 4.26 (1H, d, *J* 15.0, NCH$_A$*H*$_B$Ph), 4.30–4.41 (2H, m, C(3)*H*, C(α)*H*), 4.52–4.57 (1H, m, C(2)*H*), 6.96 (2H, d, *J* 7.8, C(3′)*H*, C(5′)*H*), 7.45 (2H, d, *J* 7.8, C(2′)*H*, C(6′)*H*), 7.25–7.64 (10H, m, *Ph*); $\delta_C$ (100 MHz, $CDCl_3$) 14.6 (C(α)*Me*), 27.8 (C*Me*$_3$), 52.3 (NC$H_2$Ph), 55.2 (O*Me*), 57.5 (*C*(α)), 64.8 (*C*(3)), 73.7 (*C*(2)), 82.0 (*C*Me$_3$), 113.5 (*C*(3′), *C*(5′)), 128.2 (*C*(2′), *C*(6′)), 126.7, 126.9, 128.2, 128.2, 128.3, 131.2 (*o*,*m*,*p*-*Ph*), 130.5 (*C*(1′)), 142.1, 144.5 (*i*-*Ph*), 159.1 (*C*(4′)), 172.4 (*C*(1)); *m*/*z* (ESI$^+$) 462 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{36}NO_4^+$ ([M+H]$^+$) requires 462.2639; found 462.2628.

### 4.19. *tert*-Butyl (2*S*,3*S*,α*R*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-3-hydroxy-3-(4′-trifluoromethylphenyl)propanoate 42

$Ms_2O$ (52 mg, 0.30 mmol) was added to a solution of **32** (50 mg, 0.10 mmol, >99:1 dr) and $Et_3N$ (0.06 mL, 0.45 mmol) in $CH_2Cl_2$ (0.43 mL) and the resultant solution was stirred at rt for 1 h, then $H_2O$ (0.054 mL, 3.00 mmol) was added and the resultant mixture was stirred at 40 °C for 48 h. $H_2O$ (1 mL) was added and the mixture was extracted with $CH_2Cl_2$ (3×2 mL) and the combined organic washed with 1.0 M aq HCl (3 mL), satd aq $NaHCO_3$ (3 mL) and brine (3 mL), then dried and concentrated in vacuo to give **42** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/$Et_2O$, 5:1) gave **42** as a pale yellow oil (32 mg, 64%, >99:1 dr); $[\alpha]_D^{23}$ −30.5 (*c* 1.0, $CHCl_3$); $\nu_{max}$ (ATR) 3498 (O—H), 1722 (C═O); $\delta_H$ (400 MHz, $CDCl_3$) 1.39 (3H, d, *J* 6.9, C(α)*Me*), 1.59 (9H, s C*Me*$_3$), 3.01 (1H, br s, O*H*), 3.60 (1H, d, *J* 8.3, C(2)*H*), 3.92 (1H, d, *J* 14.3, NC*H*$_A$H$_B$Ph), 4.02 (1H, q, *J* 6.9, C(α)*H*), 4.14 (1H, d, *J* 14.3, NCH$_A$*H*$_B$Ph), 4.90 (1H, d, *J* 8.3, C(3)*H*), 6.88 (2H, d, *J* 8.1, C(2′)*H*, C(6′)*H*), 6.90–7.22 (10H, m, *Ph*), 7.32 (2H, d, *J* 8.1, C(3′)*H*, C(5′)*H*); $\delta_C$ (100 MHz, $CDCl_3$) 13.5 (C(α)*Me*), 28.1 (C*Me*$_3$), 51.9 (NC$H_2$Ph), 53.6 (*C*(α)), 64.8 (*C*(2)), 73.9 (*C*(3)), 82.1 (*C*Me$_3$), 123.2 (q, *J* 271.8, *C*F$_3$), 123.8 (q, *J* 3.8, *C*(3′), *C*(5′)), 125.8, 126.1, 126.6, 126.9, 127.0, 127.9 (*o*,*m*,*pPh*), 127.2 (*C*(2′), *C*(6′)), 128.7 (q, *J* 32.4, C(4′)), 138.4, 141.8 (*i*-*Ph*), 144.3 (*C*(1′)), 173.1 (*C*(1)); $\delta_F$ (377 MHz, $CDCl_3$) −62.4 (C*F*$_3$); *m*/*z* (ESI$^+$) 500 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{32}F_3NNaO_3^+$ ([M+Na]$^+$) requires 522.2226; found 522.2223.

### 4.20. *tert*-Butyl (2*S*,3*S*,α*R*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-3-hydroxy-3-(3′-fluorophenyl)propanoate 43

$Ms_2O$ (58 mg, 0.333 mmol) was added to a solution of **33** (50 mg, 0.111 mmol, >99:1 dr) and $Et_3N$ (66 μL, 0.50 mmol) in $CH_2Cl_2$ (0.45 mL) and the resultant solution was stirred at rt for 1 h, then $H_2O$ (60 μL, 3.3 mmol) was added and the resultant mixture was stirred at 40 °C for 24 h. $H_2O$ (1 mL) was added and the resultant mixture was extracted with $CH_2Cl_2$ (3×2 mL). The combined organic extracts were washed sequentially with 1.0 M aq HCl (3 mL), satd aq $NaHCO_3$ (3 mL) and brine (3 mL), then dried and concentrated in vacuo to give **43** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/$Et_2O$, 5:1) gave **43** as a pale yellow oil (44 mg, 88%, >99:1 dr); $[\alpha]_D^{20}$ −29.0 (*c* 1.0, $CHCl_3$); $\nu_{max}$ (ATR) 3498 (O—H), 1721 (C═O); $\delta_H$ (400 MHz, $CDCl_3$) 1.39 (3H, d, *J* 6.8, C(α)*Me*), 1.58 (9H, s, C*Me*$_3$), 2.86 (1H, br s, O*H*), 3.56 (1H, d, *J* 8.0, C(2)*H*), 3.94 (1H, d, *J* 14.3, NC*H*$_A$H$_B$Ph), 4.04 (1H, q, *J* 6.8, C(α)*H*), 4.14 (1H, d, *J* 14.3, NCH$_A$*H*$_B$Ph), 4.87 (1H, d, *J* 8.0, C(3)*H*), 6.53–7.34 (14H, m, *Ar*, *Ph*); $\delta_C$ (100 MHz, $CDCl_3$) 13.5 (C(α)*Me*), 28.2 (C*Me*$_3$), 51.9 (NC$H_2$Ph), 56.3 (*C*(α)), 64.7 (*C*(2)), 74.1 (*C*(3)), 82.0 (*C*Me$_3$), 114.1 (2×d, *J* 21.5, *Ar*), 114.6 (2×d, *J* 21.5, *Ar*), 123.1 (d, *J* 2.4, *C*(6′)), 126.9, 127.1, 128.0, 128.2, 128.9 (*o*,*m*,*p*-*Ph*), 129.4 (d, *J* 8.0, *C*(5′)), 140.0, 142.9 (*i*-*Ph*), 143.9 (d, *J* 7.2, *C*(1′)), 162.7 (d *J* 245.6, *C*(3′)), 173.2 (*C*(1)); $\delta_F$ (377 MHz, $CDCl_3$) −113.3 (C(3′)*F*); *m*/*z* (ESI$^+$) 472 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{32}FNNaO_3^+$ ([M+Na]$^+$) requires 472.2258; found 472.2247.

### 4.21. *tert*-Butyl (2*S*,3*S*,α*R*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-3-hydroxy-3-(3′-methoxyphenyl)propanoate 44

$Ms_2O$ (227 mg, 1.30 mmol) was added to a solution of **34** (200 mg, 0.433 mmol, >99:1 dr) and $Et_3N$ (0.257 mL, 1.94 mmol) in $CH_2Cl_2$ (1.72 mL) and the resultant mixture was stirred at rt for 1 h, then $H_2O$ (0.240 mL, 13.3 mmol) was added and the resultant mixture was stirred at rt for 24 h. $H_2O$ (3 mL) was then added and the resultant mixture was extracted with $CH_2Cl_2$ (3×3 mL). The combined organic extracts were washed sequentially with 1.0 M aq HCl (4 mL), satd aq $NaHCO_3$ (4 mL) and brine (4 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/$Et_2O$, 4:1) gave **44** as a yellow oil (137 mg, 68%, >99:1 dr); $[\alpha]_D^{20}$ −34.4 (*c* 1.0, $CHCl_3$); $\nu_{max}$ (ATR) 3502 (O—H), 1722 (C═O); $\delta_H$ (400 MHz, $CDCl_3$) 1.38 (3H, d, *J* 6.9, C(α)*Me*), 1.58 (9H, s, C*Me*$_3$), 2.77 (1H, br s, O*H*), 3.57 (1H, d, *J* 8.1, C(2)*H*), 3.66 (3H, s, O*Me*), 3.95 (1H, d, *J* 14.3, NC*H*$_A$H$_B$Ph), 4.02 (1H, q, *J* 6.9, C(α)*H*), 4.17 (1H, d, *J* 14.3, NCH$_A$*H*$_B$Ph), 4.89 (1H, d, *J* 8.1, C(3)*H*), 6.37–6.40 (1H, m, C(2′)*H*), 6.49 (1H, d, *J* 8.0, C(6′)*H*), 6.74 (1H, app dd, *J* 8.0, 2.5, C(4′)*H*), 7.05 (1H, t, *J* 8.0, C(5′)*H*), 6.95–7.22 (10H, m, Ph); $\delta_C$ (100 MHz, $CDCl_3$) 13.4 (C(α)*Me*), 28.2 (C*Me*$_3$), 51.8 (NC$H_2$Ph), 55.1 (O*Me*), 56.2 (*C*(α)), 64.9 (*C*(2)), 74.6 (*C*(3)), 81.7 (*C*Me$_3$), 111.7 (*C*(2′)), 114.3 (*C*(4′)), 119.9 (*C*(6′)), 129.0 (*C*(5′)), 126.7, 126.9, 127.9, 128.1, 128.2, 129.0 (*o*,*m*,*p*-*Ph*), 139.9 (*C*(1′)), 143.9, 143.1 (*i*-*Ph*), 159.4 (*C*(3′)), 173.4 (*C*(1)); *m*/*z* (ESI$^+$) 462 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{36}NO_4^+$ ([M+H]$^+$) requires 462.2639; found 462.2640.

### 4.22. *tert*-Butyl (2*S*,3*S*,α*R*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-3-hydroxy-3-(3′-fluorophenyl)propanoate 45

$Ms_2O$ (58 mg, 0.333 mmol) was added to a solution of **35** (50 mg, 0.11 mmol, >99:1 dr) and $Et_3N$ (66 μL, 0.50 mmol) in $CH_2Cl_2$ (0.45 mL) and the resultant mixture was stirred at rt for 1 h, then $H_2O$ (60 μL, 3.3 mmol) was added and the resultant mixture was stirred at rt for 24 h. $H_2O$ (1 mL) was then added and the resultant mixture was extracted with $CH_2Cl_2$ (3×2 mL). The combined organic extracts were washed sequentially with 1.0 M aq HCl (3 mL), satd aq $NaHCO_3$ (3 mL) and brine (3 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/$Et_2O$, 5:1) gave **45** as a pale yellow oil (40 mg, 80%, >99:1 dr); $[\alpha]_D^{20}$ −30.2 (*c* 1.0, $CHCl_3$); $\nu_{max}$ (ATR) 3496 (O—H), 1722 (C═O); $\delta_H$ (400 MHz, $CDCl_3$) 1.39 (3H, d, *J* 6.9, C(α)*Me*), 1.59 (9H, s, C*Me*$_3$), 2.70 (1H, br s, O*H*), 3.56 (1H, d, *J* 8.4, C(2)*H*), 3.92 (1H, d, *J* 14.2, NC*H*$_A$H$_B$Ph), 4.01 (1H, q, *J* 6.9, C(α)*H*), 4.11 (1H, d, *J* 14.2, NCH$_A$*H*$_B$Ph), 4.87 (1H, d, *J* 8.4, C(3)*H*), 6.72–6.82 (4H, m, *Ar*), 6.92–7.22 (10H, m, *Ph*); $\delta_C$ (100 MHz, $CDCl_3$) 13.5 (C(α)*Me*), 28.2 (C*Me*$_3$), 51.7 (NC$H_2$Ph), 56.3 (*C*(α)), 64.7 (*C*(2)), 73.8 (*C*(3)), 81.9 (*C*Me$_3$), 114.9 (d, *J* 20.7, *C*(3′), *C*(5′)), 126.8, 127.0, 128.0, 128.1, 128.2, 129.0 (*o*,*m*,*p*-*Ph*), 129.1 (d, *J* 8.0, *C*(2′), *C*(6′)), 137.0 (d, *J* 2.4, *C*(1′)), 143.0, 139.7 (*i*-*Ph*), 162.3 (d, *J* 244.8, *C*(4′)), 173.4 (*C*(1)); $\delta_F$ (377 MHz, $CDCl_3$) −114.9 (C(4′)*F*); *m*/*z* (ESI$^+$) 450 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{33}FNO_3^+$ ([M+H]$^+$) requires 450.2439; found 450.2442.

### 4.23. *tert*-Butyl (2*S*,3*S*,α*R*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-3-hydroxy-3-(4′-methoxyphenyl)propanoate 46

$Ms_2O$ (114 mg, 0.65 mmol) was added to a solution of **36** (100 mg, 0.22 mmol, >99:1 dr) and $Et_3N$ (0.13 mL, 0.97 mmol) in

$CH_2Cl_2$ (0.86 mL) and the resultant solution was stirred at rt for 1 min, then $H_2O$ (0.12 mL, 6.66 mmol) was added and the resultant mixture was stirred at rt for 24 h. $H_2O$ (2 mL) was then added and the mixture was extracted with $CH_2Cl_2$ (3×4 mL). The combined organic extracts were washed sequentially with 1.0 M aq HCl (6 mL), satd aq $NaHCO_3$ (6 mL) and brine (6 mL), then dried and concentrated in vacuo to give **46** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/$Et_2O$, 4:1) gave **46** as a pale yellow oil (55 mg, 55%, >99:1 dr); $[\alpha]_D^{20}$ −5.5 (*c* 1.0, $CHCl_3$); $\nu_{max}$ (ATR) 3504 (O–H), 1722 (C=O); $\delta_H$ (400 MHz, $CDCl_3$) 1.38 (3H, d, *J* 7.0, C(α)*Me*), 1.59 (9H, s, C*Me*$_3$), 2.52 (1H, br s, O*H*), 3.55 (1H, d, *J* 8.5, C(2)*H*), 3.84 (3H, s, O*Me*), 3.92 (1H, d, *J* 14.3, NC*H*$_A$H$_B$Ph), 3.98 (1H, q, *J* 7.0, C(α)*H*), 4.11 (1H, d, *J* 14.3, NCH$_A$*H*$_B$Ph), 4.87 (1H, d, *J* 8.5, C(3)*H*), 6.66 (2H, d, *J* 8.6, C(3′)*H*, C(5′)*H*), 6.75 (2H, d, *J* 8.6, C(2′)*H*, C(6′)*H*), 6.92–7.21 (10H, m, *Ph*); $\delta_C$ (100 MHz, $CDCl_3$) 13.3 (C(α)*Me*), 28.2 (C*Me*$_3$), 51.6 ($NCH_2Ph$), 55.4 (O*Me*), 56.2 (*C*(α)), 64.5 (*C*(2)), 74.0 (*C*(3)), 81.6 (*C*Me$_3$), 113.5 (*C*(3′), *C*(5′)), 128.1 (*C*(2′), *C*(6′)), 126.7, 127.0, 127.9, 128.2, 128.7, 129.0 (*o*,*m*,*p*-*Ph*), 133.5 (*C*(1′)), 139.9, 143.0 (*i*-*Ph*), 159.2 (*C*(4′)), 173.7 (*C*(1)); *m*/*z* (ESI$^+$) 462 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{36}NO_4^+$ ([M+H]$^+$) requires 462.2639; found 462.2643.

### 4.24. *tert*-Butyl (*S*,*S*)-2-amino-3-hydroxy-3-(4′-trifluoromethylphenyl)propanoate 47

$Pd(OH)_2$/C (12 mg, 20% w/w) was added to a degassed solution of **42** (60 mg, 0.12 mmol, >99:1 dr) in MeOH (1 mL) and the resultant mixture was placed under an atmosphere of $H_2$ (5 atm) and stirred at rt for 24 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated in vacuo to give **47** as an orange solid (30 mg, 81%, >99:1 dr); mp 164–172 °C; $[\alpha]_D^{20}$ +45.8 (*c* 1.0, MeOH); $\nu_{max}$ (ATR) 3409 (O–H, N–H), 1734 (C=O); $\delta_H$ (700 MHz, MeOH-$d_4$) 1.18 (9H, s, C*Me*$_3$), 4.07 (1H, br s, C(2)*H*), 5.15 (1H, br s, C(3)*H*), 7.60 (2H, d, *J* 8.3, C(2′)*H*, C(6′)*H*), 7.55 (2H, d, *J* 8.3, C(3′)*H*, C(5′)*H*); $\delta_C$ (176 MHz, MeOH-$d_4$) 26.6 (C*Me*$_3$), 58.9 (*C*(2)), 71.4 (*C*(3)), 83.1 (*C*Me$_3$), 124.3 (q, *J* 270.8, *C*F$_3$), 124.8 (q, *J* 3.8, *C*(3′), *C*(5′)), 126.6 (*C*(2′), *C*(6′)), 129.7 (q, *J* 31.8, *C*(4′)), 144.5 (*C*(1′)), 166.7 (*C*(1)); *m*/*z* (ESI$^+$) 306 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{18}F_3NNaO_3^+$ ([M+Na]$^+$) requires 328.1131; found 328.1131.

### 4.25. *tert*-Butyl (*S*,*S*)-2-amino-3-hydroxy-3-(3′-fluorophenyl)propanoate 48

$Pd(OH)_2$/C (15 mg, 20% w/w) was added to a degassed solution of **43** (75 mg, 0.17 mmol, >99:1 dr) in MeOH (1 mL) and the resultant mixture was placed under an atmosphere of $H_2$ (5 atm) and stirred at rt for 48 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated in vacuo to give **48** as an orange oil (43 mg, quant, >99:1 dr); $[\alpha]_D^{20}$ +32.7 (*c* 1.0, MeOH); $\nu_{max}$ (ATR) 3432 (O–H, N–H), 1734 (C=O); $\delta_H$ (500 MHz, MeOH-$d_4$) 1.22 (9H, s, C*Me*$_3$), 3.98 (1H, br s, C(2)*H*), 5.06 (1H, br s, C(3)*H*), 7.07 (1H, dt, *J* 8.5, 2.4, C(4′)*H*), 7.20–7.25 (1H, m, C(2′)*H*), 7.25–7.30 (1H, m, C(6′)*H*), 7.39–7.45 (1H, m, C(5′)*H*); $\delta_C$ (125 MHz, MeOH-$d_4$) 26.7 (C*Me*$_3$), 59.0 (*C*(2)), 71.2 (*C*(3)), 83.1 (*C*Me$_3$), 112.9 (d, *J* 22.0, *C*(2′)), 114.2 (d, *J* 22.0, *C*(4′)), 121.8 (d, *J* 2.9, *C*(6′)), 129.8 (d, *J* 7.6, *C*(5′)), 142.6 (*C*(1′)), 162.9 (d, *J* 244.1, *C*(3′)), 166.6 (*C*(1)); *m*/*z* (ESI$^+$) 256 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{18}FNNaO_3^+$ ([M+Na]$^+$) requires 278.1163; found 278.1166.

### 4.26. *tert*-Butyl (*S*,*S*)-2-amino-3-hydroxy-3-(3′-methoxyphenyl)propanoate 49

$Pd(OH)_2$/C (22 mg, 20% w/w) was added to a degassed solution of **44** (58 mg, 0.13 mmol, >99:1 dr) in MeOH (1 mL) and the resultant mixture was placed under an atmosphere of $H_2$ (5 atm) and stirred at rt for 24 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated in vacuo to give **49** as a colourless oil (36 mg, quant, >99:1 dr); $[\alpha]_D^{20}$ +21.4 (*c* 0.5, MeOH); $\nu_{max}$ (ATR) 3273 (O–H, N–H), 1733 (C=O); $\delta_H$ (400 MHz, MeOH-$d_4$) 1.22 (9H, s, C*Me*$_3$), 3.71 (3H, s, O*Me*), 3.98 (1H, br s, C(2)*H*), 5.06 (1H, br s, C(3)*H*), 6.78 (1H, dd, *J* 8.1, 2.2, C(5′)*H*), 6.87–6.94 (2H, m, C(2′)*H*, C(6′)*H*), 7.19 (1H, t, *J* 8.1, C(4′)*H*); $\delta_C$ (100 MHz, MeOH-$d_4$) 26.7 (C*Me*$_3$), 54.4 (O*Me*), 58.9 (*C*(2)), 71.1 (*C*(3)), 83.3 (*C*Me$_3$), 111.8, 118.2 (*C*(2′), *C*(6′)), 113.0 (*C*(5′)), 129.1 (*C*(4′)), 140.6 (*C*(1′)), 159.9 (*C*(3′)), 165.9 (*C*(1)); *m*/*z* (ESI$^+$) 268 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{21}NNaO_4^+$ ([M+Na]$^+$) requires 290.1363; found 290.1366.

### 4.27. *tert*-Butyl (*S*,*S*)-2-amino-3-hydroxy-3-(4′-fluorophenyl)propanoate 50

$Pd(OH)_2$/C (13 mg, 25% w/w) was added to a degassed solution of **45** (65 mg, 0.15 mmol, >99:1 dr) in MeOH (3 mL) and the resultant mixture was placed under an atmosphere of $H_2$ (5 atm) and stirred at rt for 16 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated in vacuo to give **50** as a colourless oil (30 mg, 81%, >99:1 dr); $[\alpha]_D^{20}$ +21.2 (*c* 1.0, MeOH); $\nu_{max}$ (ATR) 3281, 2980 (O–H, N–H), 1732 (C=O); $\delta_H$ (400 MHz, MeOH-$d_4$) 1.26 (9H, s, C*Me*$_3$), 3.52 (1H, d, *J* 4.7, C(2)*H*), 4.77–4.81 (1H, m, C(3)*H*), 6.97 (2H, app t, *J* 8.7, C(3′)*H*, C(5′)*H*), 7.29 (2H, dd, *J* 8.7, 5.3, C(2′)*H*, C(6′)*H*); $\delta_C$ (100 MHz, MeOH-$d_4$) 26.8 (C*Me*$_3$), 60.6 (*C*(2)), 74.2 (*C*(3)), 81.3 (*C*Me$_3$), 114.3 (d, *J* 21.5, *C*(3′), *C*(5′)), 128.3 (d, *J* 7.8, *C*(2′), *C*(6′)), 136.7 (*C*(1′)), 162.5 (d, *J* 244.8, *C*(4′)), 171.4 (*C*(1)); *m*/*z* (ESI$^+$) 256 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{18}FNNaO_3^+$ ([M+Na]$^+$) requires 278.1163; found 278.1167.

### 4.28. *tert*-Butyl (*S*,*S*)-2-amino-3-hydroxy-3-(4′-methoxyphenyl)propanoate 51

$Pd(OH)_2$/C (15 mg, 20% w/w) was added to a degassed solution of **46** (75 mg, 0.16 mmol, >99:1 dr) in MeOH (1 mL) and the resultant mixture was placed under an atmosphere of $H_2$ (5 atm) and stirred at rt for 24 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated in vacuo to give **51** as a colourless oil (43 mg, quant, >99:1 dr); $[\alpha]_D^{20}$ −4.0 (*c* 0.5, MeOH); $\nu_{max}$ (ATR) 3401 (O–H, N–H), 1728 (C=O); $\delta_H$ (400 MHz, MeOH-$d_4$) 1.28 (9H, s, C*Me*$_3$), 3.68 (3H, s, O*Me*), 3.63–3.72 (1H, m, C(2)*H*), 4.84–4.92 (1H, m, C(3)*H*), 6.81 (2H, d, *J* 8.7, C(3′)*H*, C(5′)*H*), 7.21 (2H, d, *J* 8.5, C(2′)*H*, C(6′)*H*); $\delta_C$ (100 MHz, MeOH-$d_4$) 26.8 (C*Me*$_3$), 54.4 (O*Me*), 60.0 (*C*(2)), 73.1 (*C*(3)), 82.1 (*C*Me$_3$), 113.3 (*C*(3′), *C*(5′)), 127.5 (*C*(2′), *C*(6′)), 131.7 (*C*(1′)), 159.6 (*C*(4′)), 169.5 (*C*(1)); *m*/*z* (ESI$^+$) 268 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{21}NNaO_4^+$ ([M+Na]$^+$) requires 290.1363; found 290.1364.

### 4.29. (*S*,*S*)-2-Amino-3-hydroxy-3-(4′-trifluoromethylphenyl)propanoic acid 52

A solution of **47** (20 mg, 66 μmol, >99:1 dr) in 6.0 M aq HCl (0.6 mL) was stirred at rt for 6 h. The reaction mixture was then allowed to cool to rt and concentrated in vacuo. Purification via ion exchange chromatography (DOWEX 50WX8-200, eluent 1.0 M aq $NH_4OH$) gave **52** as a white solid (17 mg, quant, 98:2 dr); mp 172–180 °C (dec); $[\alpha]_D^{20}$ +14.4 (*c* 0.5, $H_2O$); $\nu_{max}$ (ATR) 3508, 3364 (O–H, N–H), 1579 (C=O); $\delta_H$ (500 MHz, $D_2O$) 4.04 (1H, d, *J* 4.0, C(2)*H*), 5.33 (1H, d, *J* 4.0, C(3)*H*), 7.46 (2H, d, *J* 8.2, C(2′)*H*, C(6′)*H*), 7.65 (2H, d, *J* 8.2, C(3′)*H*, C(5′)*H*); $\delta_C$ (125 MHz, $D_2O$) 60.3 (*C*(2)), 70.6 (*C*(3)), 124.0 (q, *J* 271.8, *C*F$_3$), 125.6 (q, *J* 3.8, *C*(3′), *C*(5′)), 126.8 (*C*(2′), *C*(6′)), 130.0 (q, *J* 31.8, *C*(4′)), 141.4 (*C*(1′)), 170.6 (*C*(1)); $\delta_F$ (377 MHz, $CDCl_3$) −62.4 (*C*F$_3$); *m*/*z* (ESI$^+$) 250 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{10}H_{10}F_3NNaO_3^+$ ([M+Na]$^+$) requires 272.0505; found 272.0507.

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### 4.30. (*S*,*S*)-2-Amino-3-hydroxy-3-(3′-fluorophenyl)propanoic acid 53

A solution of **48** (44 mg, 0.172 mmol, >99:1 dr) in 6.0 M aq HCl (1 mL) was stirred at rt for 3 h, then concentrated in vacuo. $H_2O$ (4 mL) and $CHCl_3$ (3 mL) were added and the aqueous layer was washed with $CHCl_3$ (2×3 mL) then concentrated in vacuo. Purification via ion exchange chromatography (DOWEX 50WX8-200, eluent 1.0 M aq $NH_4OH$) gave **53** as a white solid (25 mg, 74%, 93:7 dr); mp 197–199 °C (dec); $[\alpha]_D^{20}$ +17.6 (*c* 0.5, $H_2O$); $\nu_{max}$ (ATR) 3059 (O–H, N–H), 1591 (C=O); $\delta_H$ (500 MHz, $D_2O$) 4.00 (1H, d, *J* 3.9, C(2)*H*), 5.28 (1H, d, *J* 3.9, C(3)*H*), 7.02–7.13 (3H, m, C(2′)*H*, C(4′)*H*, C(6′)*H*), 7.32–7.37 (1H, m, C(5′)*H*); $\delta_C$ (125 MHz, $D_2O$) 60.3 (*C*(2)), 70.5 (*C*(3)), 113.1 (d, *J* 22.5, *C*(2′)), 115.5 (d, *J* 22.5, *C*(4′)), 122.1 (d, *J* 2.9, *C*(6′)), 130.5 (d, *J* 8.6, *C*(5′)), 140.0 (d, *J* 6.7, *C*(1′)), 162.6 (d, *J* 244.1, *C*(3′)), 170.9 (*C*(1)); $\delta_F$ (377 MHz, $CDCl_3$) −113.0 (C(3′)*F*); *m*/*z* ($ESI^+$) 200 ($[M+H]^+$, 100%); HRMS ($ESI^+$) $C_9H_{10}FNNaO_3^+$ ($[M+Na]^+$) requires 222.0537; found 222.0542.

### 4.31. (*S*,*S*)-2-Amino-3-hydroxy-3-(3-methoxy)phenylpropanoic acid 54

A solution of **49** (45 mg, 0.17 mmol, >99:1 dr) in 6.0 M aq HCl (1 mL) was stirred at rt for 3 h, then concentrated in vacuo. $H_2O$ (4 mL) and $CHCl_3$ (3 mL) were added and the aqueous layer was washed with $CHCl_3$ (2×3 mL) then concentrated in vacuo. Purification via ion exchange chromatography (DOWEX 50WX8-200, eluent 1.0 M aq $NH_4OH$) gave **54** as a white solid (28 mg, 80%, 93:7 dr); mp 162–170 °C (dec); $[\alpha]_D^{20}$ +5.0 (*c* 1.0, $H_2O$); $\nu_{max}$ (ATR) 3137 (O–H, N–H), 1598 (C=O); $\delta_H$ (500 MHz, $D_2O$) 3.76 (3H, s, O*Me*), 4.04 (1H, d, *J* 4.1, C(2)*H*), 5.27 (1H, d, *J* 4.1, C(3)*H*), 6.85–6.95 (3H, m, C(2′)*H*, C(4′)*H*, C(6′)*H*) 7.31 (1H, app t, *J* 8.0, C(5′)*H*); $\delta_C$ (125 MHz, $D_2O$) 55.4 (O*Me*), 60.3 (*C*(2)), 70.9 (*C*(3)), 111.8, 119.0 (*C*(2′), *C*(6′)), 114.4 (*C*(5′)), 130.1 (*C*(4′)), 138.7 (*C*(1′)), 159.0 (*C*(3′)), 170.0 (*C*(1)); *m*/*z* ($ESI^+$) 212 ($[M+H]^+$, 100%); HRMS ($ESI^+$) $C_{10}H_{13}NNaO_4^+$ ($[M+Na]^+$) requires 234.0737; found 234.0740.

### 4.32. (*S*,*S*)-2-Amino-3-hydroxy-3-(4′-fluorophenyl)propanoic acid 55

A solution of **50** (8 mg, 31 μmol, >99:1 dr) in 6.0 M aq HCl (1 mL) was stirred at rt for 6 h, then concentrated in vacuo. $H_2O$ (2 mL) and $CHCl_3$ (3 mL) were added and the aqueous layer washed with $CHCl_3$ (2×3 mL) then concentrated in vacuo. Purification via ion exchange chromatography (DOWEX 50WX8-200, eluent 1.0 M aq $NH_4OH$) gave **55** as a white solid (7 mg, quant, 97:3 dr); mp 161–168 °C (dec); $[\alpha]_D^{20}$ +9.0 (*c* 0.5, $H_2O$); $\nu_{max}$ (ATR) 3066 (O–H, N–H), 1602 (C=O); $\delta_H$ (500 MHz, $D_2O$) 3.99 (1H, d, *J* 4.1, C(2)*H*), 5.27 (1H, d, *J* 4.1, C(3)*H*), 7.08 (2H, app t, *J* 8.7, C(3′)*H*, C(5′)*H*), 7.31 (2H, dd, *J* 8.7, 5.5, C(2′)*H*, C(6′)*H*); $\delta_C$ (125 MHz, $D_2O$) 60.3 (*C*(2)), 70.5 (*C*(3)), 115.5 (d, *J* 21.9, *C*(3′), *C*(5′)), 128.2 (d, *J* 8.6, *C*(2′), *C*(6′)), 132.8 (*C*(1′)), 162.5 (d, *J* 244.1, *C*(4′)), 171.0 (*C*(1)); $\delta_F$ (377 MHz, $CDCl_3$) −114.1 (C(4′)*F*); *m*/*z* ($ESI^+$) 200 ($[M+H]^+$, 100%); HRMS ($ESI^+$) $C_9H_{10}FNNaO_3^+$ ($[M+Na]^+$) requires 222.0537; found 222.0537.

### 4.33. (*S*,*S*)-2-Amino-3-hydroxy-3-(4-methoxy)phenylpropanoic acid 56

A solution of **51** (43 mg, 0.16 mmol, >99:1 dr) in 6.0 M aq HCl (1 mL) was stirred at rt for 3 h, then concentrated in vacuo. $H_2O$ (4 mL) and $CHCl_3$ (3 mL) were added and the aqueous layer washed with $CHCl_3$ (2×3 mL) then concentrated in vacuo. Purification via ion exchange chromatography (DOWEX 50WX8-200, eluent 1.0 M aq $NH_4OH$) gave **56** as a white solid (21 mg, 62%, 93:7 dr); mp 176–181 °C (dec); $[\alpha]_D^{20}$ +8.0 (*c* 1.0, $H_2O$); $[\alpha]_D^{20}$ −2.4 (*c* 0.5, $H_2O$/MeOH 1:1); {lit.[24] $[\alpha]_D^{20}$ −2.73 (*c* 0.586, $H_2O$/MeOH 1:1)}; $\nu_{max}$ (ATR) 3503, 3238 (O–H, N–H), 1513 (C=O); $\delta_H$ (500 MHz, $D_2O$) 3.75 (3H, s, O*Me*), 3.97 (1H, d, *J* 4.1, C(2)*H*), 5.22 (1H, d, *J* 4.1, C(3)*H*), 6.94 (2H, d, *J* 8.7, C(3′)*H*, C(5′)*H*), 7.25 (2H, d, *J* 8.7, C(2′)*H*, C(6′)*H*); $\delta_C$ (125 MHz, $D_2O$) 55.3 (O*Me*), 60.4 (*C*(2)), 71.1 (*C*(3)), 114.2 (*C*(3′), *C*(5′)), 127.7 (*C*(2′), *C*(6′)), 129.3 (*C*(1′)), 159.1 (*C*(4′)), 171.1 (*C*(1)); *m*/*z* ($ESI^+$) 212 ($[M+H]^+$, 100%); HRMS ($ESI^+$) $C_{10}H_{13}NNaO_4^+$ ($[M+Na]^+$) requires 234.0737; found 234.0737.

### 4.34. *tert*-Butyl (*RS*,*RS*)-2-hydroxy-3-(*N*,*N*-dibenzylamino)-butanoate 58

Following the *general procedure*, BuLi (2.2 M in hexanes, 9.9 mL, 21.9 mmol) and $Bn_2NH$ (4.44 g, 22.5 mmol) were reacted with **1** (2.00 g, 14.1 mmol, >99:1 dr) and **4** (5.50 g, 2.40 mmol) in THF (80 mL) at −78 °C to give **58** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/$Et_2O$, 10:1→8:1) gave **58** as a white solid (2.51 g, 50%, >99:1 dr); mp 73–77 °C; $\nu_{max}$ (ATR) 3468 (O–H), 1720 (C=O); $\delta_H$ (400 MHz, $CDCl_3$) 1.04 (3H, d, *J* 7.0, C(4)$H_3$), 1.38 (9H, s, C$Me_3$), 2.97 (1H, br s, O*H*), 3.15 (1H, dq, *J* 7.0, 2.3, C(3)*H*), 3.66 (2H, d, *J* 14.0, N(C$H_A$$H_B$Ph)$_2$), 3.75 (2H, d, *J* 14.0, N(C$H_A$$H_B$Ph)$_2$), 4.40 (1H, d, *J* 2.3, C(2)*H*), 7.18–7.41 (10H, m, *Ph*); $\delta_C$ (100 MHz, $CDCl_3$) 10.1 (*C*(4)), 28.0 (C$Me_3$), 54.5 (N($CH_2$Ph)$_2$), 55.5 (*C*(3)), 71.4 (*C*(2)), 82.3 (C$Me_3$), 126.9, 128.2, 128.9 (*o*,*m*,*p*-*Ph*), 140.3 (*i*-*Ph*), 174.3 (*C*(1)); *m*/*z* ($ESI^+$) 356 ($[M+H]^+$, 100%); HRMS ($ESI^+$) $C_{22}H_{30}NO_3^+$ ($[M+H]^+$) requires 356.2220; found 356.2216.

### 4.35. *tert*-Butyl (*RS*,*RS*)-2-hydroxy-3-(*N*,*N*-dibenzylamino)-4-methylpentanoate 59

Following the *general procedure*, BuLi (2.2 M in hexanes, 8.3 mL, 18.2 mmol) and $Bn_2NH$ (3.61 g, 18.8 mmol) were reacted with **57** (2.00 g, 11.8 mmol, >99:1 dr) and **4** (4.60 g, 2.01 mmol) in THF (80 mL) at −78 °C to give **59** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/$Et_2O$, 20:1) gave **59** as a white solid (2.32 g, 52%, >99:1 dr); mp 119–123 °C; $\nu_{max}$ (ATR) 3468 (O–H), 1720 (C=O); $\delta_H$ (400 MHz, $CDCl_3$) 0.70 (3H, d, *J* 6.6, C(4)$Me_A$), 1.00 (3H, d, *J* 6.6, C(4)$Me_B$), 1.42 (9H, s, C$Me_3$), 2.23 (1H, d septet, *J* 10.4, 6.6, C(4)*H*), 2.71 (1H, app d, *J* 10.4, C(3)*H*), 3.12 (1H, d, *J* 3.1, O*H*), 3.34 (2H, d, *J* 13.9, N(C$H_A$$H_B$Ph)$_2$), 3.99 (2H, d, *J* 13.9, N(C$H_A$$H_B$Ph)$_2$), 4.48 (1H, app d, *J* 3.1, C(2)*H*), 7.16–7.44 (10H, m, *Ph*); $\delta_C$ (100 MHz, $CDCl_3$) 20.0, 21.4 (C(4)$Me_2$), 26.2 (*C*(4)), 28.0 (C$Me_3$), 54.7 (N($CH_2$Ph)$_2$), 66.1 (*C*(3)), 67.3 (*C*(2)), 82.9 (C$Me_3$), 126.8, 128.1, 128.3 (*o*,*m*,*p*-*Ph*), 140.1 (*i*-*Ph*), 175.9 (*C*(1)); *m*/*z* ($ESI^+$) 384 ($[M+H]^+$, 100%); HRMS ($ESI^+$) $C_{24}H_{34}NO_3^+$ ($[M+H]^+$) requires 384.2533; found 384.2539.

### 4.36. *tert*-Butyl (*RS*,*RS*)-2-(*N*,*N*-dibenzylamino)-3-(methanesulfonyloxy)butanoate 60

$Ms_2O$ (74 mg, 0.422 mmol) was added to a solution of **58** (50 mg, 0.141 mmol, >99:1 dr) and $Et_3N$ (84 μL, 0.64 mmol) in $CH_2Cl_2$ (0.6 mL) and the resultant solution was stirred at rt for 1 h, then $H_2O$ (76 μL, 4.2 mmol) was then added and the resultant mixture was stirred at rt for 24 h. $H_2O$ (1 mL) was then added and the resultant mixture was extracted with $CH_2Cl_2$ (3×2 mL). The combined organic extracts were washed sequentially with 1.0 M aq HCl (3 mL), satd aq $NaHCO_3$ (3 mL) and brine (3 mL), then dried and concentrated in vacuo to give a 90:10 mixture of **60** and **58**, respectively, as a colourless oil. Data for **60**: $\delta_H$ (400 MHz, $CDCl_3$) 1.47 (3H, d, *J* 6.3, C(4)$H_3$), 1.63 (9H, s, C$Me_3$), 2.96 (3H, s, $SO_2Me$), 3.24 (1H, d, *J* 10.4, C(2)*H*), 3.43 (2H, d, *J* 13.4, N(C$H_A$$H_B$Ph)$_2$), 3.92 (2H, d, *J* 13.4, N(C$H_A$$H_B$Ph)$_2$), 5.05 (1H, dq, *J* 10.1, 6.3, C(3)*H*), 7.22–7.40 (10H, m, *Ph*); $\delta_C$ (100 MHz, $CDCl_3$) 19.1 (*C*(4)), 28.5 (C$Me_3$), 38.3 ($SO_2Me$), 55.3 (N($CH_2$Ph)$_2$), 64.4 (*C*(2)), 78.2 (*C*(3)), 82.3 (C$Me_3$), 127.5, 128.4, 129.0 (*o*,*m*,*p*-*Ph*), 138.1 (*i*-*Ph*), 169.0 (*C*(1)).

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### 4.37. *tert*-Butyl (*RS*,*RS*)-2-(*N*,*N*-dibenzylamino)-3-(methanesulfonyloxy)-4-methylpentanoate 61

$Ms_2O$ (68 mg, 0.391 mmol) was added to a solution of **59** (50 mg, 0.130 mmol, >99:1 dr) and $Et_3N$ (77 μL, 0.59 mmol) in $CH_2Cl_2$ (0.55 mL) and the resultant solution was stirred at rt for 1 h. $H_2O$ (0.070 mL, 3.90 mmol) was then added and the resultant mixture was stirred at rt for 24 h. $H_2O$ (1 mL) was then added and the resultant mixture was extracted with $CH_2Cl_2$ (3×2 mL). The combined organic extracts were washed sequentially with 1.0 M aq HCl (3 mL), satd aq $NaHCO_3$ (3 mL) and brine (3 mL), then dried and concentrated in vacuo to give a 60:40 mixture of **61** and **59**, respectively, as a colourless oil. Data for **61**: $\delta_H$ (400 MHz, $CDCl_3$) 0.35 (3H, d, *J* 6.8, C(4)$Me_A$), 1.07 (3H, d, *J* 7.3, C(4)$Me_B$), 1.68 (9H, s, C$Me_3$), 2.40 (1H, app septet, *J* 6.9, C(4)*H*), 3.00 (3H, s, $SO_2Me$), 3.39–3.49 (3H, m, C(2)*H*, N(C$H_AH_B$Ph)$_2$), 3.94 (2H, d, *J* 13.4, N(C$H_AH_B$Ph)$_2$), 5.03 (1H, d, *J* 10.6, C(3)*H*), 7.22–7.46 (10H, m, *Ph*); $\delta_C$ (100 MHz, $CDCl_3$) 14.0, 20.4 (C(4)$Me_2$), 27.5 (*C*(4)), 28.7 (C$Me_3$), 38.9 ($SO_2Me$), 55.2 (N(*C*$H_2$Ph)$_2$), 61.5 (*C*(2)), 82.4 (*C*Me$_3$), 85.6 (*C*(3)), 127.5, 128.4, 129.3 (*o*,*m*,*p*-*Ph*), 138.3 (*i*-*Ph*), 169.0 (*C*(1)).

### 4.38. *tert*-Butyl (*RS*,*RS*)-2-(*N*,*N*-dibenzylamino)-3-hydroxybutanoate 62

$Tf_2O$ (35 μL, 0.21 mmol) was added to a solution of **58** (50 mg, 0.141 mmol, >99:1 dr) and **64** (87 mg, 0.42 mmol) in $CH_2Cl_2$ (1.75 mL) at 0 °C and the resultant solution was stirred at rt for 6 h. $H_2O$ (26 μL, 7.2 mmol) was then added and the resultant mixture was stirred at rt for 15 h. $H_2O$ (1 mL) was then added and the resultant mixture was extracted with $CH_2Cl_2$ (3×2 mL). The combined organic extracts were then dried and concentrated in vacuo. The residue was dissolved in $Et_2O$ (10 mL), and the resultant solution was filtered and concentrated in vacuo to give **62** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/$Et_2O$, 3:1) gave **62** as a white solid (27 mg, 54%, >99:1 dr); mp 98–101 °C; $\nu_{max}$ (ATR) 3461 (O–H), 1722 (C=O); $\delta_H$ (400 MHz, $CDCl_3$) 1.11 (3H, d, *J* 6.4, C(4)$H_3$), 1.55 (9H, s, C$Me_3$), 2.49 (1H, br s, O*H*), 2.94 (1H, d, *J* 9.1, C(2)*H*), 3.45 (2H, d, *J* 13.4, N(C$H_AH_B$Ph)$_2$), 3.83 (2H, d, *J* 13.4, N(C$H_AH_B$Ph)$_2$), 4.01–4.11 (1H, m, C(3)*H*), 7.10–7.33 (10H, m, *Ph*); $\delta_C$ (100 MHz, $CDCl_3$) 20.0 (*C*(4)), 28.7 (C$Me_3$), 55.6 (N(*C*$H_2$Ph)$_2$), 66.2 (*C*(2)), 67.2 (*C*(3)), 82.1 (*C*Me$_3$), 127.2, 128.3, 129.1 (*o*,*m*,*p*-*Ph*), 139.0 (*i*-*Ph*), 172.2 (*C*(1)); *m*/*z* (ESI$^+$) 378 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{29}NNaO_3^+$ ([M+H]$^+$) requires 378.2040; found 378.2038.

### 4.39. *tert*-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-methylpentanoate 65

Following the *general procedure*, BuLi (2.3 M in hexanes, 1.98 mL, 4.56 mmol) and (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (1.14 g, 4.70 mmol, >99:1 er) were reacted with **57** (500 mg, 2.94 mmol, >99:1 dr) and **4** (1.15 mg, 5.00 mmol) in THF (20 mL) at −78 °C to give **65** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/$Et_2O$, 10:1) gave **65** as a white solid (658 mg, 56%, >99:1 dr);[28] mp 82–86 °C; $[\alpha]_D^{23}$ −32.2 (*c* 1.0, $CHCl_3$); $\nu_{max}$ (ATR) 3498 (O–H), 1716 (C=O); $\delta_H$ (400 MHz, $CDCl_3$) 0.77 (3H, d, *J* 6.7, C(4)$Me_A$), 1.14 (3H, d, *J* 6.7, C(4)$Me_B$), 1.35 (3H, d, *J* 7.0, C(α)*Me*), 1.52 (9H, s, C$Me_3$), 2.07 (1H, d septet, *J* 9.8, 6.7, C(4)*H*), 2.91 (1H, d, *J* 2.9, O*H*), 3.18 (1H, app d, *J* 9.8, C(3)*H*), 3.60 (1H, d, *J* 15.7, NC$H_AH_B$Ph), 3.68 (1H, app d, *J* 2.9, C(2)*H*), 3.91 (1H, q, *J* 7.0, C(α)*H*), 4.32 (1H, d, *J* 15.7, NCH$_A$*H*$_B$Ph), 7.18–7.57 (10H, m, *Ph*); $\delta_C$ (100 MHz, $CDCl_3$) 20.0, 22.3 (C(4)$Me_2$), 20.9 (C(α)*Me*), 27.8 (*C*(4)), 28.1 (C$Me_3$), 52.0 (N*C*H$_2$Ph), 58.1 (*C*(α)), 64.1 (*C*(3)), 70.9 (*C*(2)), 82.8 (*C*Me$_3$), 126.4, 127.1, 128.0, 128.4, 128.4, 128.6 (*o*,*m*,*p*-*Ph*), 142.5, 142.5 (*i*-*Ph*), 175.4 (*C*(1)); *m*/*z* (ESI$^+$) 398 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{35}NNaO_3^+$ ([M+Na]$^+$) requires 420.2509; found 420.2513.

### 4.40. *tert*-Butyl (2*S*,3*S*,α*R*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-3-hydroxybutanoate 68

$Tf_2O$ (36 μL, 0.21 mmol) added to a solution of **5** (50 mg, 0.14 mmol, >99:1 dr) and **64** (87 mg, 0.42 mmol) in $CH_2Cl_2$ (0.6 mL) at 0 °C and the resultant solution was stirred at rt for 6 h. $H_2O$ (0.026 mL, 7.2 mmol) was then added and the resultant mixture was stirred at rt for 24 h. $H_2O$ (1 mL) was then added and the resultant mixture was extracted with $CH_2Cl_2$ (3×2 mL). The combined organic extracts were then dried and concentrated in vacuo. The residue was dissolved in $Et_2O$ (10 mL), and the resultant solution was filtered and concentrated in vacuo to give a 79:21 mixture of **68** and **5**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/$Et_2O$, 5:1) gave **68** as a colourless oil (34 mg, 68%, >99:1 dr); $[\alpha]_D^{23}$ −52.6 (*c* 1.0, MeOH); $\nu_{max}$ (ATR) 3475 (O–H), 1722 (C=O); $\delta_H$ (400 MHz, $CDCl_3$) 0.97 (3H, d, *J* 6.4, C(4)$H_3$), 1.38 (3H, d, *J* 6.9, C(α)*Me*), 1.53 (9H, s, C$Me_3$), 2.25 (1H, br s, O*H*), 3.06 (1H, d, *J* 8.6, C(2)*H*), 3.82 (1H, d, *J* 14.2, NC$H_AH_B$Ph), 3.85–3.94 (1H, m, C(3)*H*), 4.99 (1H, d, *J* 14.2, NC$H_AH_B$Ph), 4.04 (1H, q, *J* 6.9, C(α)*H*), 7.14–7.31 (10H, m, *Ph*); $\delta_C$ (100 MHz, $CDCl_3$) 14.3 (C(α)*Me*), 20.3 (*C*(4)), 28.3 (C$Me_3$), 52.3 (N*C*H$_2$Ph), 57.1 (*C*(α)), 65.7 (*C*(2)), 67.4 (*C*(3)), 81.6 (*C*Me$_3$), 127.0, 127.0, 128.1, 128.1, 128.3, 129.1 (*o*,*m*,*p*-*Ph*), 140.2, 143.7 (*i*-*Ph*), 173.6 (*C*(1)); *m*/*z* (ESI$^+$) 370 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{31}NNaO_3^+$ ([M+Na]$^+$) requires 392.2196; found 392.2197.

### 4.41. *tert*-Butyl (2*S*,3*S*,α*R*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-3-hydroxy-4-methylpentanoate 69

$Tf_2O$ (32 μL, 0.19 mmol) was added to a solution of **65** (50 mg, 0.13 mmol, >99:1 dr) and **64** (78 mg, 0.38 mmol) in $CH_2Cl_2$ (0.6 mL) at 0 °C and the resultant solution was stirred at rt for 6 h. $H_2O$ (26 μL, 7.2 mmol) was then added and the resultant mixture was stirred at rt for 24 h. $H_2O$ (1 mL) was then added and the resultant mixture was extracted with $CH_2Cl_2$ (3×2 mL). The combined organic extracts were then dried and concentrated in vacuo. The residue was dissolved in $Et_2O$ (10 mL), and the resultant solution was filtered and concentrated in vacuo to give a 92:8 mixture of **65** and **69**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/$Et_2O$, 5:1) gave **69** as a colourless oil (34 mg, 68%, >99:1 dr); $[\alpha]_D^{23}$ −38.3 (*c* 1.0, MeOH); $\nu_{max}$ (ATR) 3540 (O–H), 1707 (C=O); $\delta_H$ (700 MHz, $CDCl_3$) 0.18 (3H, d, *J* 7.0, C(4)$Me_A$), 0.71 (3H, d, *J* 7.0, C(4)$Me_B$), 1.35 (3H, d, *J* 6.9, C(α)*Me*), 1.50 (9H, s, C$Me_3$), 1.84 (1H, d septet, *J* 7.0, 2.6, C(4)*H*), 1.90 (1H, d, *J* 6.0, O*H*), 3.17 (1H, d, *J* 8.6, C(2)*H*), 3.53–3.58 (1H, m, C(3)*H*), 3.79 (1H, d, *J* 14.2, NC$H_AH_B$Ph), 4.01 (1H, q, *J* 6.9, C(α)*H*), 4.05 (1H, d, *J* 14.2, NCH$_A$*H*$_B$Ph), 7.11–7.27 (10H, m, *Ph*); $\delta_C$ (176 MHz, $CDCl_3$) 12.6 (C(α)*Me*), 12.9, 19.2 (C(4)$Me_2$), 27.2 (C$Me_3$), 27.3 (*C*(4)), 50.9 (N*C*H$_2$Ph), 55.9 (*C*(α)), 60.4 (*C*(2)), 74.6 (*C*(3)), 80.4 (*C*Me$_3$), 125.9, 125.9, 127.0, 127.2, 127.2, 128.1 (*o*,*m*,*p*-*Ph*), 139.4, 142.5 (*i*-*Ph*), 172.8 (*C*(1)); *m*/*z* (ESI$^+$) 398 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{35}NNaO_3^+$ ([M+Na]$^+$) requires 420.2509; found 420.2516.

### 4.42. *tert*-Butyl (*S*,*S*)-2-amino-3-hydroxybutanoate 70

$Pd(OH)_2$/C (12 mg, 20% w/w) was added to a degassed solution of **68** (60 mg, 0.162 mmol, >99:1 dr) in MeOH (1 mL) and the resultant mixture was placed under an atmosphere of $H_2$ (5 atm) and stirred at rt for 16 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated in vacuo to give **70** as a colourless oil (20 mg, 71%, >99:1 dr);[9] $[\alpha]_D^{23}$ +7.1 (*c* 1.0, $CHCl_3$); $\nu_{max}$ (ATR) 3368 (O–H, N–H), 1728 (C=O); $\delta_H$ (400 MHz, MeOH-$d_4$) 1.03 (3H, d, *J* 6.4, C(4)$H_3$), 1.38 (9H, s, C$Me_3$), 3.28 (1H, d, *J* 4.2, C(2)*H*), 3.88 (1H, dq, *J* 6.4, 4.2, C(3)*H*); $\delta_C$ (100 MHz, MeOH-$d_4$) 16.8 (*C*(4)), 26.7 (C$Me_3$), 60.0 (*C*(2)), 68.4 (*C*(3)), 81.2 (*C*Me$_3$), 174.6 (*C*(1)); *m*/*z*

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(ESI$^+$) 176 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_8H_{18}NO_3^+$ ([M+H]$^+$) requires 176.1281; found 176.1285.

### 4.43. *tert*-Butyl (*S*,*S*)-2-amino-3-hydroxy-4-methylpentanoate 71

Pd(OH)$_2$/C (9 mg, 20% w/w) was added to a degassed solution of **69** (43 mg, 0.11 mmol, >99:1 dr) in MeOH (1 mL) and the resultant mixture was placed under an atmosphere of $H_2$ (5 atm) and stirred at rt for 16 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated in vacuo to give **71** as a colourless oil (22 mg, quant, >99:1 dr); mp 68–73 °C; $[\alpha]_D^{23}$ +14.0 (*c* 1.0, $CHCl_3$); $\nu_{max}$ (ATR) 3361 (O–H, N–H), 1729 (C=O); $\delta_H$ (500 MHz, $CDCl_3$) 0.97 (3H, d, *J* 6.7, C(4)*Me*$_A$), 0.99 (3H, d, *J* 6.7, C(4)*Me*$_B$), 1.49 (9H, s, C*Me*$_3$), 1.80 (1H, app septet, *J* 6.7, C(4)*H*), 2.62 (3H, br s, N*H*$_2$, O*H*), 3.38–3.46 (1H, m, C(3)*H*), 3.49–3.59 (1H, m, C(2)*H*); $\delta_C$ (125 MHz, $CDCl_3$) 18.7, 19.9 (C(4)*Me*$_2$), 28.5 (C*Me*$_3$), 31.3 (*C*(4)), 57.5 (*C*(2)), 78.9 (*C*(3)), 82.5 (*C*Me$_3$), 173.7 (*C*(1)); *m*/*z* (ESI$^+$) 204 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{10}H_{21}NNaO_3^+$ ([M+Na]$^+$) requires 226.1414; found 226.1420.

### 4.44. (*S*,*S*)-2-Amino-3-hydroxy-4-methylpentanoic acid [(*S*,*S*)-β-hydroxyleucine] 72

A solution of **71** (22 mg, 0.11 mmol, >99:1 dr) in 6.0 M aq HCl (1 mL) was stirred at rt for 3 h, then concentrated in vacuo. $H_2O$ (4 mL) and $CHCl_3$ (3 mL) were then added and the aqueous layer was washed with $CHCl_3$ (2×3 mL) then concentrated in vacuo. Purification via ion exchange chromatography (DOWEX 50WX8-200, eluent 1.0 M aq $NH_4OH$) gave **72** as a white solid (11 mg, 69%, 96:4 dr);[3e] mp 220–226 °C (dec); $[\alpha]_D^{20}$ +17.6 (*c* 1.0, $H_2O$); {lit.[3e] $[\alpha]_D^{25}$ +20 (*c* 1.1, $H_2O$)}; $\nu_{max}$ (ATR) 3449, 3058 (O–H, N–H), 1627 (C=O); $\delta_H$ (500 MHz, $D_2O$) 0.89 (3H, d, *J* 6.7, C(4)*Me*$_A$), 0.90 (3H, d, *J* 6.7, C(4)*Me*$_B$), 1.87 (1H, d septet, *J* 9.1, 6.7, C(4)*H*), 3.46 (1H, dd, *J* 9.1, 3.2, C(3)*H*), 3.84 (1H, d, *J* 3.2, C(2)*H*); $\delta_C$ (125 MHz, $CDCl_3$) 18.5, 18.5 (C(4)*Me*$_2$), 30.2 (*C*(4)), 57.1 (*C*(2)), 76.1 (*C*(3)), 171.7 (*C*(1)); *m*/*z* (ESI$^+$) 148 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_6H_{13}NNaO_3^+$ ([M+Na]$^+$) requires 170.0788; found 170.0788.

## Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.06.057.

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23. Longer reaction times (after the addition of water) may be required for substrates with strongly electron-withdrawing groups (i.e., *p*-$CF_3$ and *m*-F) due to slower $S_N1$-type hydrolysis of the mesylates, whilst for substrates with strongly electron-donating groups (i.e., *p*-OMe) the addition of water was required sooner, which may be to prevent other reaction pathways, proceeding via the benzylic carbonium ion, competing with the hydrolysis.
24. The specific rotation for **56** was in good agreement with the literature value {$[\alpha]_D^{20}$ −2.4 (*c* 0.5, $H_2O$/MeOH 1:1); lit. $[\alpha]_D^{20}$ −2.73 (*c* 0.586, $H_2O$/MeOH 1:1)}; see: Inoue, H.; Matsuki, K.; Oh-ishi, T. *Chem. Pharm. Bull.* **1993**, *41*, 1521.
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