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Trading *N* and *O*. Part 4: Asymmetric synthesis of *syn*-β-substituted-α-amino acids

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ABSTRACT

A total of nine enantiopure *syn*-β-substituted-α-amino acids have been synthesised, comprising both *syn*-β-hydroxy-α-amino acids and *syn*-β-fluoro-α-amino acids. The key step in the synthetic strategy towards these *syn*-β-substituted-α-amino acids involves a stereospecific rearrangement, which proceeds via the intermediacy of the corresponding aziridinium ions. The requisite enantiopure *syn*-α-hydroxy-β-amino esters were prepared via asymmetric aminohydroxylation of the corresponding α,β-unsaturated esters followed by epimerisation of the resultant *anti*-α-hydroxy-β-amino esters at the C(2)-position. Subsequent activation of the α-hydroxy moiety as a leaving group followed by displacement by the β-amino substituent gave the corresponding aziridinium species. Regioselective in situ ring-opening of the aziridinium intermediates with either water or fluoride gave the corresponding *syn*-β-hydroxy-α-amino ester or *syn*-β-fluoro-α-amino ester, respectively, and *N*-deprotection and ester hydrolysis afforded the target *syn*-β-substituted-α-amino acids as single diastereoisomers in good overall yield.

1. Introduction

β-Hydroxy-α-amino acids are constituents of naturally occurring peptides[1] and other natural products,[2] and are also useful synthetic building blocks and chiral auxiliaries.[3] As such, various strategies have been developed for their preparation, including asymmetric aminohydroxylation,[4] stereoselective hydrogenation,[5] stereoselective aldol reactions,[6] dynamic kinetic resolution protocols,[7] enzymatic methods,[8] and others.[9] β-Fluoro-α-amino acids,[10] the deoxyfluoro analogues of β-hydroxy-α-amino acids, have been shown to exhibit biological activity including antibacterial, antihypertensive, and antitumor properties, acting as metabolic antagonists to naturally occurring α-amino acids,[11] competitive inhibitors of enzymes,[12] and suicide substrates.[13] Several methods for the preparation of β-fluoro-α-amino acids have been devised, including fluorodehydroxylation of β-hydroxy-α-amino acids,[14] ring-opening of aziridines,[15] reductive amination of β-fluoro-α-keto acids,[16] sulfinimine mediated asymmetric Strecker synthesis,[17] and others.[18]

We have reported procedures for the conversion of enantiopure *anti*-α-hydroxy-β-amino esters into *anti*-β-hydroxy-α-amino acids[19] and *anti*-β-fluoro-α-amino acids,[20] in addition to the corresponding 1,2,3,4-tetrahydroquinolines.[21] The key mechanistic step in each of these procedures involves conversion of the *anti*-α-hydroxy-β-amino ester into the corresponding aziridinium intermediate upon activation of the α-hydroxy group as a leaving group.[22] For example, *O*-triflation of *anti*-α-hydroxy-β-amino esters bearing aliphatic substituents at the β-position, such as **1** (R = Me) or **2** (R = ^{i}Pr), upon treatment with Tf_2O and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) promotes displacement by the β-amino substituent to give the corresponding aziridinium species, **4** (R = Me) and **5** (R = ^{i}Pr). Subsequent regioselective ring-opening of aziridinium intermediates **4** and **5** with water [at the C(3)-position] gave the corresponding *anti*-β-hydroxy-α-amino esters **7** (R = Me) and **8** (R = ^{i}Pr), which underwent hydrogenolytic *N*-deprotection and ester hydrolysis to give *anti*-β-hydroxy-α-amino acids **10** (R = Me) and **11** (R = ^{i}Pr). For substrates bearing aromatic substituents at the β-position, such as **3** (R = Ph), treatment with Ms_2O and Et_3N promotes formation of aziridinium ion **6** (R = Ph) and regioselective ring-opening of **6** with water gave *anti*-β-hydroxy-α-amino ester **9** (R = Ph), with deprotection of **9** giving *anti*-β-hydroxy-α-amino acid **12** (R = Ph). Alternatively, reaction of **3** (R = Ph) with XtalFluor-E® promotes activation of the α-hydroxy group and regioselective ring-opening of the corresponding aziridinium

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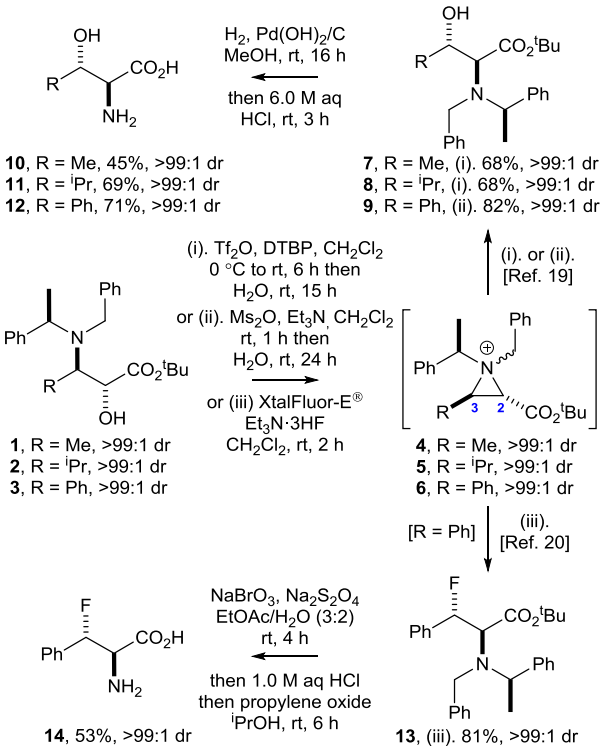
species **6** (R = Ph) with fluoride to give *anti*-β-fluoro-α-amino ester **13**. In this case, oxidative *N*-deprotection and ester hydrolysis provided access to *anti*-β-fluoro-α-amino acid **14** (Scheme 1).

In order to access all possible stereoisomers of these β-substituted-α-amino acids, we sought to effect similar transformations with the epimeric *syn*-substrates. It was envisaged that the requisite *syn*-α-hydroxy-β-amino esters could be accessed from their *anti*-epimers upon oxidation of the C(2)-hydroxyl group followed by diastereoselective reduction of the resultant ketones.[23] Our full results within this area are described below, which culminate in the synthesis of nine enantiopure *syn*-β-substituted-α-amino acids, including both *syn*-β-hydroxy-α-amino acids and *syn*-β-fluoro-α-amino acids.

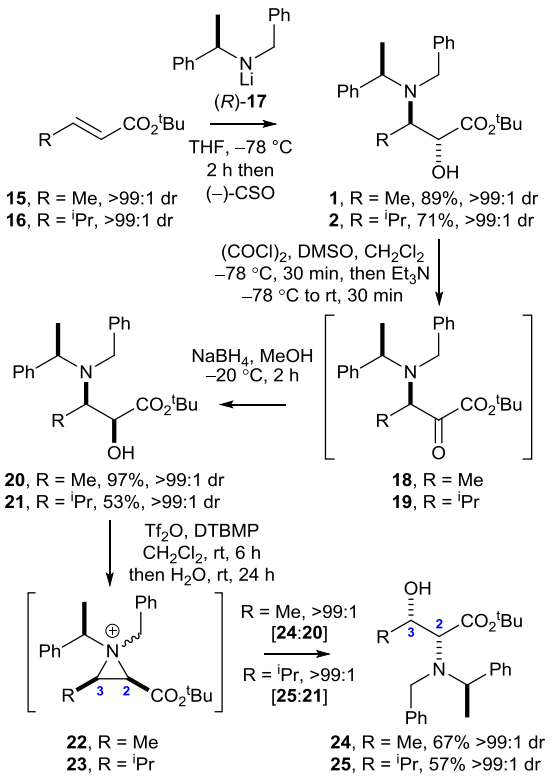
2. Results and discussion

syn-α-Hydroxy-β-amino esters **20** (R = Me) and **21** (R = ^{i}Pr) were prepared following our established procedures.[22,24] Conjugate addition of enantiopure lithium amide (*R*)-**17** to α,β-unsaturated esters **15** and **16** followed by oxidation of the intermediate lithium (*Z*)-β-amino enolates[25] with (−)-camphorsulfonyloxaziridine [(−)-CSO] gave *anti*-α-hydroxy-β-amino esters **1** and **2** in 89 and 71% yield, respectively, as single diastereoisomers (>99:1 dr) in each case. *syn*-α-Hydroxy-β-amino ester **20** (R = Me) was prepared from its epimer *anti*-**1** upon oxidation followed by diastereoselective reduction: [23] Swern oxidation of **1** promoted quantitative conversion to the intermediate ketone **18**, and reduction of **18** with $NaBH_4$ in MeOH at −20 °C gave *syn*-**20** exclusively; after chromatographic purification of the crude reaction mixture, **20** was isolated in 97% yield and >99:1 dr. Upon attempted epimerisation of *anti*-**2** (R = ^{i}Pr), using the same conditions employed for *anti*-**1** (R = Me),[22] it was found that the concentration of the reaction mixture had a significant effect upon the diastereoselectivity of the reduction step: at a concentration of 0.5 M a 35:65 mixture of *syn*-**21** and *anti*-**2**, respectively, was produced and the percentage of the *syn*-diastereoisomer **21** was then found to increase as the concentration of the reaction mixture was decreased. Under the optimised conditions, reaction at a concentration of 0.01 M gave a 69:31 mixture of *syn*-**21** and *anti*-**2**, respectively, from which *syn*-**21** was isolated as a single diastereoisomer (>99:1 dr) in 53% yield; in this case, the corresponding *anti*-α-hydroxy-β-amino ester **2** was also isolated in 25% yield and >99:1 dr, and this sample could then be recycled in subsequent runs of the epimerisation procedure. Following our established procedure for exchange of the hydroxyl and amino moieties within *anti*-α-hydroxy-β-amino esters,[19] treatment of *syn*-α-hydroxy-β-amino esters **20** and **21** with Tf_2O and DTBMP in CH_2Cl_2, followed by the addition of H_2O after 6 h, gave *syn*-β-hydroxy-α-amino esters **24** and **25**, which were isolated in 67 and 57% yield, respectively, as single diastereoisomers (>99:1 dr) in each case (Scheme 2). Comparison of the ^{1}H and ^{13}C NMR spectroscopic data for *syn*-β-hydroxy-α-amino esters **24** and **25** with those for the known *anti*-α-hydroxy-β-amino esters **1** and **2**, *syn*-α-hydroxy-β-amino esters **20** and **21**,[19] and the corresponding *anti*-β-hydroxy-α-amino esters **7** and **8**,[19] confirmed the assigned stereo- and regiochemistry of **24** and **25** [assuming that the possibility of epimerisation at *both* C(2) and C(3) can be excluded]. This reaction outcome is therefore consistent with a stereospecific reaction mechanism whereby activation of the α-hydroxy group as the corresponding triflate is followed by displacement by the β-amino group [with inversion of configuration at C(2)] to produce aziridinium ions **22** and **23** (of undetermined configuration at the nitrogen stereogenic centre). Subsequent regioselective ring-opening of aziridinium species **22** and **23** with H_2O [with inversion of configuration at C(3)] then gives *syn*-β-hydroxy-α-amino esters **24** and **25**, respectively, as the sole reaction products.

Three more *syn*-α-hydroxy-β-amino ester substrates **34**–**36**, all bearing β-aryl substituents, were next selected to probe the



Scheme 1.



Scheme 2.

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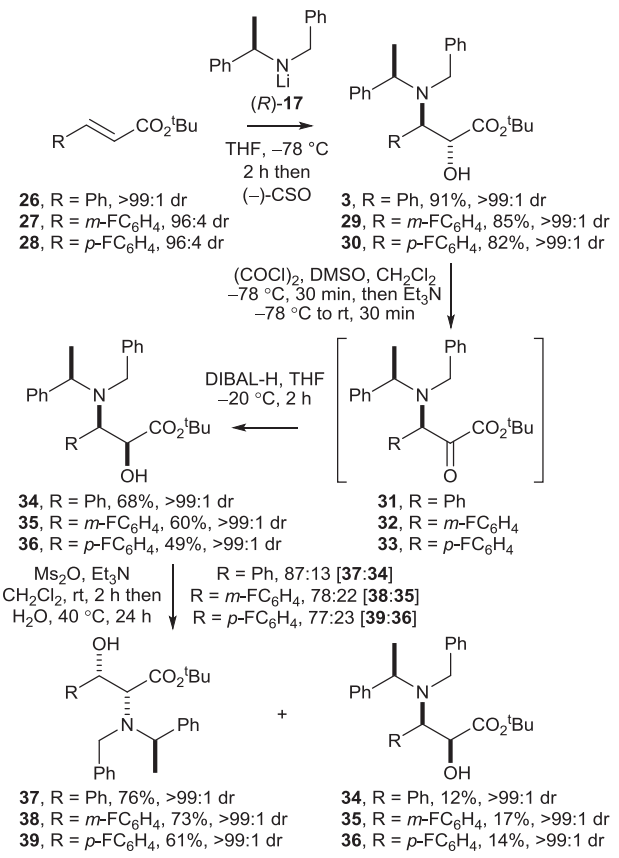
substrate scope of this reaction manifold, as samples of the corresponding *anti*-α-hydroxy-β-amino esters and *anti*-β-hydroxy-α-amino esters had previously been prepared in each case.[19] *anti*-α-Hydroxy-β-amino esters **3** (R = Ph), **29** (R = *m*-FC_6H_4) and **30** (R = *p*-FC_6H_4) were prepared as single diastereoisomers (>99:1 dr) in 82–91% yield upon aminohydroxylation[24] of the corresponding α,β-unsaturated esters **26**–**28**. Epimerisation of **3**, **29** and **30** at the C(2)-position was again achieved via oxidation and subsequent diastereoselective reduction. Employing the alternative procedure for the epimerisation of *anti*-α-hydroxy-β-amino esters bearing β-aryl substituents,[22] whereby the intermediate ketones **31**–**33** were reduced with DIBAL-H at −20 °C, gave *syn*-α-hydroxy-β-amino esters **34**–**36** in 49–68% isolated yield as single diastereoisomers (>99:1 dr). Treatment of **34** (R = Ph) with Ms_2O and Et_3N, under the established conditions for the rearrangement of *anti*-substrates bearing β-aryl substituents,[19,26] gave an 87:13 mixture of *syn*-β-hydroxy-α-amino ester **37** and *syn*-α-hydroxy-β-amino ester **34**, respectively, from which **37** was isolated in 76% yield and >99:1 dr, and **34** was isolated in 12% yield and >99:1 dr. Similarly, treatment of **35** (R = *m*-FC_6H_4) and **36** (R = *p*-FC_6H_4) under identical conditions gave mixtures of regioisomeric products: upon reaction of **35** (R = *m*-FC_6H_4) a 78:22 mixture of **38** and **35**, respectively, was produced and reaction of **36** (R = *p*-FC_6H_4) gave a 77:23 mixture of **39** and **36**. Following purification of the crude reaction mixtures, *syn*-β-hydroxy-α-amino esters **38** (R = *m*-FC_6H_4) and **39** (R = *p*-FC_6H_4) were isolated in 73 and 61% yield, respectively, and >99:1 dr in each case; in addition the regioisomeric *syn*-α-hydroxy-β-amino esters **35** (R = *m*-FC_6H_4) and **36** (R = *p*-FC_6H_4) were isolated as single diastereoisomers in 17 and 14% yield, respectively (Scheme 3).

When comparing the analogous reactions of *syn*-α-hydroxy-β-amino esters **20**, **21** and **34**–**36** with those of the corresponding *anti*-epimers **1**–**3**, **29** and **30**,[19] it can be seen that the opposite trend in regioselectivity for aziridinium ring-opening with water is observed for the substrates bearing C(3)-alkyl versus C(3)-aryl substitution. For the C(3)-alkyl substrates, superior regioselectivity was observed upon reaction of the *syn*-epimers, whereas for the C(3)-aryl substrates higher levels of regioselectivity were apparent upon reaction of the *anti*-epimers. Reaction of *anti*-**1** (R = Me) gave an 83:17 mixture of **7** and **1**, and reaction of *anti*-**2** (R = ^{i}Pr) gave a 90:10 mixture of **8** and **2**, respectively, whereas reaction of the corresponding *syn*-α-hydroxy-β-amino esters **20** (R = Me) and **21** (R = ^{i}Pr) under the same conditions produced only the corresponding *syn*-β-hydroxy-α-amino esters **24** and **25**. The reactions of the C(3)-aryl substrates, for example *syn*-**34** (R = Ph) and *anti*-**3** (R = Ph), displayed the opposite trend in regioselectivity for aziridinium ring-opening: reaction of *anti*-**3** (R = Ph) gave **9** exclusively,[27] and reaction of *syn*-**34** (R = Ph) under identical conditions gave an 87:13 mixture of **37** and **34**, respectively. Presumably, a delicate interplay between steric and stereoelectronic factors is responsible for these trends upon ring-opening of the reactive tetrasubstituted aziridinium intermediates. In all cases, aziridinium ring-opening is favoured at the C(3)-position, distal to the inductively electron withdrawing ester group, giving the corresponding β-hydroxy-α-amino ester as the major product. As the transition state for ring-opening will be positively charged overall (the leaving group carries a positive charge and the nucleophile is neutral) these electronic effects therefore appear to be dominant in determining the overall sense of regioselectivity, and for the C(3)-alkyl bearing substrates this effect is amplified by the presence of an inductively electron donating alkyl substituent at the C(3)-position. For ring-opening of *syn*-aziridinium species **22** (R = Me) and **23** (R = ^{i}Pr) the steric compression experienced between the C(3)-alkyl substituent and the C(2)-ester group enforces a conformation whereby the π-system of the ester moiety is essentially orthogonal to the C(2)–N σ-bond; [28] however, no such steric interaction is present within *anti*-aziridinium species **4** (R = Me) and **5** (R = ^{i}Pr) so the π*-orbitals of the ester may overlap with the C(2)–N σ*-orbital and therefore lower the energy of the transition state for ring-opening at the C(2)-position,[28] thereby slightly increasing the proportion of *anti*-α-hydroxy-β-amino ester product formed in the latter cases. For the C(3)-aryl bearing substrates this trend is reversed. For *syn*-aziridinium **40** (R = Ph) neither the C(3)-phenyl nor C(2)-ester groups are able to adopt a conformation in which ring-opening is activated by the π-systems and so it is likely that the level of regioselectivity is principally governed by inductive effects in this case,[28] although the phenyl group will be moderately inductively electron withdrawing so poorer regioselectivity may be expected relative to ring-opening of the corresponding C(3)-alkyl substituted *syn*-aziridinium species **22** (R = Me) and **23** (R = ^{i}Pr), as observed experimentally. For ring-opening of the corresponding *anti*-aziridinium ion **6** (R = Ph), the combination of inductive and stereoelectronic control results in highly regioselective ring-opening at the C(3)-position as the phenyl group is now free to adopt a conformation in which the π-system can accelerate ring-opening at the benzylic position (Scheme 4).[28,29]

The deprotection of *syn*-β-hydroxy-α-amino esters **24**, **25** and **37**–**39** to the corresponding *syn*-β-hydroxy-α-amino acids **41**–**45** was undertaken next. Hydrogenolysis of **24** (R = Me) and **37** (R = Ph), in the presence of Pearlman's catalyst [$Pd(OH)_2$/C], and hydrolysis of the resultant β-hydroxy-α-amino esters with 6.0 M aq HCl gave, after purification via ion exchange chromatography on Dowex 50WX8 resin, the known *syn*-β-hydroxy-α-amino amino acids (2R,3*S*)-threonine **41** (R = Me) and (2R,3*S*)-β-hydroxyphenylalanine **43** (R = Ph) in 89 and 63% yield, respectively, as single diastereoisomers (>95:5 dr). The spectroscopic data, melting



Scheme 3.

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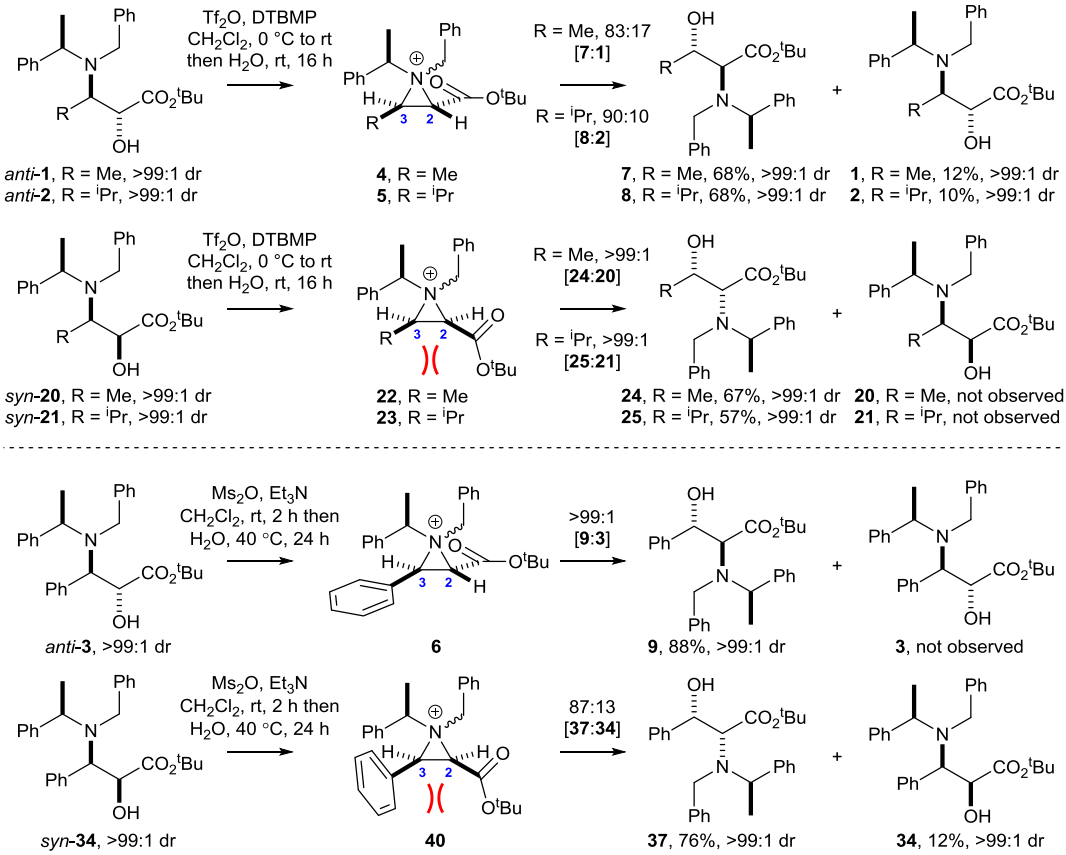
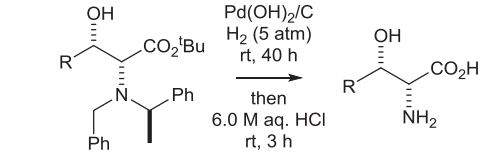


Scheme 4.

points, and specific rotations for these samples of **41** (R = Me) and **43** (R = Ph) were all in accord with literature values {for **41** (R = Me): mp 258–261 °C; lit.[30] mp 258.5–259 °C; $[\alpha]_D^{25}$ +28.1 (*c* 3.2 in H_2O); lit.[30] $[\alpha]_D^{25}$ +28.0 (*c* 3.2 in H_2O); for **43** (R = Ph): mp 196–198 °C; lit.[6b] mp 196–197 °C; $[\alpha]_D^{25}$ + 30.4 (*c* 0.6 in H_2O); lit.[6b] $[\alpha]_D^{25}$ + 30.2 (*c* 0.6 in H_2O)}, thereby confirming the assigned configurations of the synthetic precursors **24** and **37**. Hydrogenolysis and hydrolysis of **25** (R = ^{i}Pr), **38** (R = *m*-FC_6H_4) and **39** (R = *p*-FC_6H_4) under identical conditions gave **42**, **44** and **45** in 70–97% yield and >99:1 dr after purification via ion exchange chromatography (Scheme 5). The configurations of **42**, **44** and **45** (and therefore also the configurations of the synthetic precursors **25**, **38** and **39**) were assigned by analogy to those of **41** (R = Me) and **43** (R = Ph).

Targeting the analogous *syn*-β-fluoro-α-amino acids, the range of five *syn*-α-hydroxy-β-amino esters was subjected to our



24, R = Me, >99:1 dr
25, R = ^{i}Pr, >99:1 dr
37, R = Ph, >99:1 dr
38, R = *m*-FC_6H_4, >99:1 dr
39, R = *p*-FC_6H_4, >99:1 dr

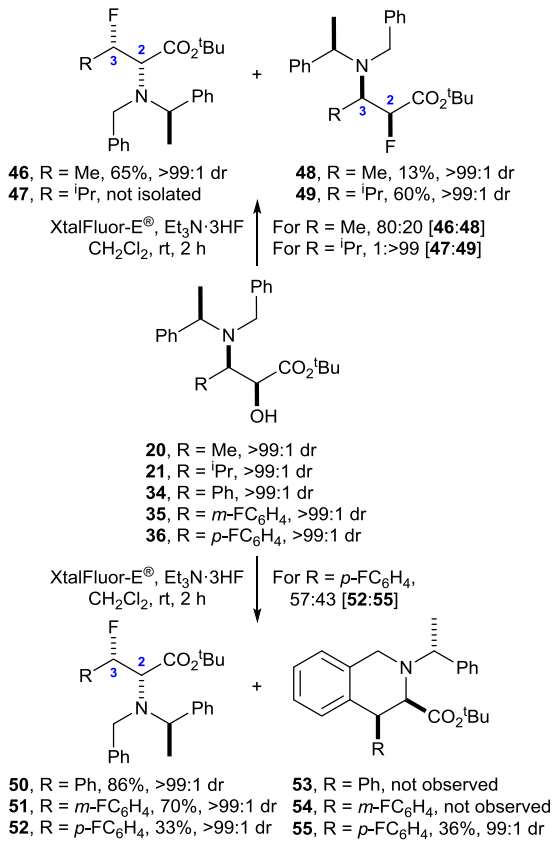
41, R = Me, 89%, >98:2 dr
42, R = ^{i}Pr, 70%, >99:1 dr
43, R = Ph, 63%, >95:5 dr
44, R = *m*-FC_6H_4, 71%, >99:1 dr
45, R = *p*-FC_6H_4, 97%, >99:1 dr

Scheme 5.

analogous deoxofluorination/rearrangement[20] protocol. Treatment of **34** (R = Ph) with Xtal-Fluor-E® and $Et_3N{\cdot}3HF$, following our optimised conditions for reaction of the *anti*-epimer **3**,[20] gave *syn*-β-fluoro-α-amino ester **50** in 86% isolated yield and >99:1 dr. Confirmation of this regiochemical assignment was gained from ^{1}H NMR and ^{1}H–^{13}C NMR HMBC spectroscopic analysis. Comparison of the ^{1}H and ^{13}C NMR spectroscopic data for **50** with those for the known[20] *anti*-β-fluoro-α-amino ester **13** then confirmed the assigned configuration of **50**. This stereospecific reaction outcome is again entirely consistent with the intermediacy of the corresponding aziridinium intermediate. Similarly, reaction of **35** (R = *m*-FC_6H_4) gave *syn*-β-fluoro-α-amino ester **51**, which was isolated in 70% yield as a single diastereoisomer (>99:1 dr). However, reaction of **36** (R = *p*-FC_6H_4) under identical conditions gave a 57:43 mixture of *syn*-β-fluoro-α-amino ester **52** and *syn*-1,2,3,4-tetrahydroisoquinoline **55**,[21] respectively. Following chromatographic purification, **52** was isolated in 33% yield and >99:1 dr, and **55** was isolated in 36% yield and >99:1 dr. The 3,4-*syn*-configuration within 1,2,3,4-tetrahydroisoquinoline **55** was assigned from the diagnostic value of the ^{1}H NMR ^3J coupling constant between the C(3)*H* and C(4)*H* protons ($^3J_{3,4}$ = 6.2 Hz).[31] None of the 1,2,3,4-tetrahydroisoquinoline resulting from competitive cyclisation via the *N*-α-methylbenzyl group was observed in the ^{1}H NMR spectrum of the crude reaction mixture, nor were the epimeric *anti*-β-fluoro-α-amino ester[20] and *anti*-1,2,3,4-tetrahydroisoquinoline products. This result is unusual in that we have previously observed regioisomeric mixtures resulting from competitive cyclisation via either the *N*-α-methylbenzyl or *N*-benzyl groups upon reaction of α-hydroxy-β-amino esters bearing an electron rich aryl group at the β-position,[19,20] as well as substantial epimerisation at the C(4)-

position (1,2,3,4-tetrahydroisoquinoline numbering convention) upon formation of a 1,2,3,4-tetrahydroisoquinoline from a *syn*-α-hydroxy-β-amino ester.[21] This result may therefore be indicative of an alternative mechanism for 1,2,3,4-tetrahydroisoquinoline formation. Subjection of *syn*-**20** (R = Me) to the same conditions gave a separable 80:20 mixture of regioisomers **46** and **48**; following chromatographic purification of the crude reaction mixture, *syn*-β-fluoro-α-amino ester **46** was isolated in 65% yield and >99:1 dr, and *syn*-α-fluoro-β-amino ester **48** was isolated in 13% yield and >99:1 dr. The corresponding reaction of **21** (R = ^{i}Pr) gave only *syn*-α-fluoro-β-amino ester **49**, which was isolated as a single diastereoisomer in 60% yield (Scheme 6). Confirmation of the regiochemical assignments for **46**, **48** and **49** was gained from ^{1}H–^{1}H and ^{1}H–^{19}F NMR coupling constant analyses. The configuration of **46** (R = Me) was assigned by comparison to the corresponding *anti*-β-fluoro-α-amino ester,[32] and the configurations of **48** (R = Me) and **49** (R = ^{i}Pr) were assigned by comparison to the corresponding *anti*-α-fluoro-β-amino esters,[33,34] assuming that stereospecific reactions occur via the intermediacy of the corresponding aziridinium ions give the products as single diastereoisomers (as observed experimentally). The configurations of **51** (R = *m*-FC_6H_4) and **52** (R = *p*-FC_6H_4) were assigned by analogy to that of **50** (R = Ph).

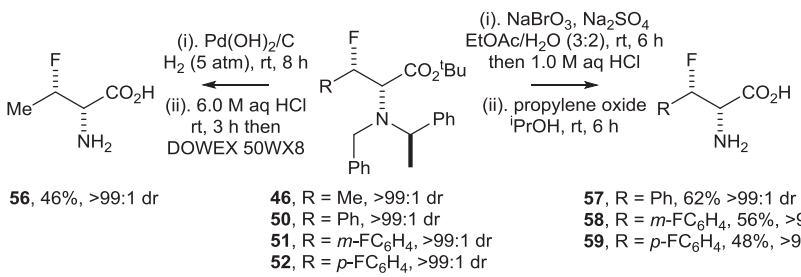
Deprotection of **46** (R = Me) was achieved via standard hydrogenolysis conditions followed by hydrolysis of the resultant β-fluoro-α-amino ester with 6.0 M aq HCl, which gave **56** in 46% yield and >99:1 dr after purification via ion exchange chromatography on Dowex 50WX8 resin. The spectroscopic data, melting point and specific rotation of this sample of **56** were in good agreement with literature values for the antipode {mp 192–194 °C; lit.[14a] mp for *ent*-**56**: 193–194 °C; $[\alpha]_D^{25}$ +16.4 (*c* 1.0 in 1 N HCl); lit.[14a] for *ent*-**56**: $[\alpha]_D$ −16.2 (*c* 1.0 in 1 N HCl)}, which confirmed the assigned configuration of **56** and thereby also the configuration of the precursor *syn*-β-fluoro-α-amino ester **46**. As protected *anti*-β-fluorophenylalanines are prone to defluorination under hydrogenolytic conditions, alternative oxidative conditions[20] were employed for the deprotection of **50**–**52**. Treatment of **50** (R = Ph) with $NaBrO_3$ and Na_2SO_4 in EtOAc followed by sequential treatment with 1.0 M aq HCl then propylene oxide in ^{i}PrOH gave **57** in 62% yield and >99:1 dr. The spectroscopic data, melting point and specific rotation of this sample of **57** were in good agreement with literature values {mp 151–161 °C; lit.[17] mp 149–150 °C; $[\alpha]_D^{25}$ −13.1 (*c* 0.4 in MeOH); lit.[17] $[\alpha]_D^{23}$ −14.5 (*c* 0.4 in MeOH)}, thereby confirming both the assigned configuration of **57** and its synthetic precursor **50**. Deprotection of **51** (R = *m*-FC_6H_4) and **52** (R = *p*-FC_6H_4) under identical conditions gave *syn*-β-fluoro-α-amino acids **58** and **59** in 56 and 48% yield, and >99:1 dr in each case, after purification via ion exchange chromatography, and their configurations were assigned by analogy to that of **57** (Scheme 7).



Scheme 6.

3. Conclusion

In conclusion, a range of enantiopure *syn*-α-hydroxy-β-amino esters were isolated as single diastereoisomers (>99:1 dr) following epimerisation of the corresponding *anti*-α-hydroxy-β-amino esters via an oxidation/diastereoselective reduction procedure. These *syn*-α-hydroxy-β-amino esters were then converted into the corresponding *syn*-β-hydroxy-α-amino esters and *syn*-β-fluoro-α-amino esters via stereospecific transformations involving activation of the α-hydroxy group as a leaving group, displacement by the β-amino substituent and regioselective ring-opening of the intermediate aziridinium species at the C(3)-position with either water or fluoride. Subsequent *N*-deprotection of these *syn*-β-substituted-α-amino esters followed by ester hydrolysis gave the corresponding *syn*-β-hydroxy-α-amino acids (5 examples) and *syn*-β-fluoro-α-amino esters (4 examples) as single diastereoisomers in good overall yield.



Scheme 7.

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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 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.[35] 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. tert-Butyl (E)-but-2-enoate [tert-butyl crotonate] **15**

Isobutylene (324 mL, 5.77 mol) was condensed at −78 °C and the resultant liquid was added to a stirred solution of crotonic acid (50.0 g, 0.580 mol) and conc H_2SO_4 (5 mL) in CH_2Cl_2 (500 mL) at 0 °C. The resultant mixture was stirred at 0 °C for 1 h, then allowed to warm to rt and stirred at rt for 48 h. Satd aq $NaHCO_3$ was added (3 × 150 mL) at 0 °C until pH > 7 was achieved. The organic layer was then dried and concentrated in vacuo to give **15** as a pale yellow oil (46.5 g, 56%, >99:1 dr [(*E*):(*Z*)]);[36] δ_H (400 MHz, $CDCl_3$) 1.45 (9H, s, CMe_3), 1.83 (3H, dd, *J* 6.9, 1.7, C(4)H_3), 5.74 (1H, dq, *J* 15.4, 1.7, C(2)*H*), 6.85 (1H, dq, *J* 15.4, 6.9, C(3)*H*).

4.3. tert-Butyl (E)-4-methylpent-2-enoate **16**

Isobutyraldehyde (10.0 g, 139 mmol) was added to a stirred solution of $Ph_3P=CHCO_2^tBu$ (57.6 g, 153 mmol) in CH_2Cl_2 (500 mL) and the resultant mixture was stirred at rt for 16 h, then concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 15:1) gave **16** as a colourless oil (15.5 g, 65%, >99:1 dr [(*E*):(*Z*)]);[37] δ_H (400 MHz, $CDCl_3$) 1.05 (6H, d, *J* 6.9, C(4)Me_2), 1.49 (9H, s, CMe_3), 2.43 (1H, app d septet, *J* 6.9, 1.5, C(4)*H*), 5.69 (1H, dd, *J* 15.7, 1.5, C(2)*H*), 6.85 (1H, dd, *J* 15.7, 6.6, C(3)*H*).

4.4. tert-Butyl (R,R,R)-2-hydroxy-3-[N-benzyl-N-(α-methylbenzyl) amino]butanoate **1**

BuLi (2.5 M in hexanes, 22.7 mL, 56.8 mmol) was added dropwise to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl) amine (12.0 g, 56.5 mmol, >99:1 er) in THF (60 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 30 min. A solution of **15** (5.00 g, 35.3 mmol, >99:1 dr [(*E*):(*Z*)]) in THF (60 mL) was then added dropwise via cannula and the resultant mixture was stirred at −78 °C for 2 h (−)-CSO (13.0 g, 58.8 mmol) was then added and the resultant mixture was allowed to warm to rt and stirred at rt for 16 h, then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (100 mL) and 10% aq citric acid (100 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (100 mL) and brine (100 mL), then dried and concentrated in vacuo. The residue was dissolved in Et_2O (100 mL) and filtered, and the filter cake was washed with Et_2O (2 × 100 mL), then the combined organic extracts were concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **1** as a white solid (11.6 g, 89%, >99:1 dr); [22] mp 90–93 °C; {lit.[22] mp 89–94 °C}; $[\alpha]_D^{25}$ −36.8 (*c* 1.0 in $CHCl_3$); {lit.[22] $[\alpha]_D^{23}$ −35.5 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.08 (3H, d, *J* 7.0, C(4)H_3), 1.32 (3H, d, *J* 6.8, C(α)*Me*), 1.36 (9H, s, CMe_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, NCH_AH_BPh), 3.97–4.04 (3H, m, C(2)*H*, C(α)*H*, NCH_AH_BPh), 7.18–7.50 (10H, m, *Ph*).

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

BuLi (2.2 M in hexanes, 20.7 mL, 45.6 mmol) was added dropwise to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl) amine (9.95 g, 47.0 mmol, >99:1 er) in THF (100 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 30 min. A solution of **16** (5.00 g, 29.4 mmol, >99:1 dr [(*E*):(*Z*)]) in THF (100 mL) was then added dropwise via cannula and the resultant mixture was stirred at −78 °C for 2 h (−)-CSO (13.5 g, 58.8 mmol) was then added and the resultant mixture was allowed to warm to rt and stirred at rt for 16 h, then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (100 mL) and 10% aq citric acid (100 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (100 mL) and brine (100 mL), then dried and concentrated in vacuo. The residue was dissolved in Et_2O (100 mL) and filtered, and the filter cake was washed with Et_2O (2 × 100 mL), then the combined organic extracts were concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **2** as a pale yellow solid (8.26 g, 71%, >99:1 dr); [19] mp 78–83 °C; {lit.[19] mp 82–86 °C}; $[\alpha]_D^{25}$ −28.1 (*c* 1.0 in $CHCl_3$); {lit.[19] $[\alpha]_D^{23}$ −32.2 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 0.77 (3H, d, *J* 6.6, C(4)Me_A), 1.15 (3H, d, *J* 6.6, C(4)Me_B), 1.35 (3H, d, *J* 7.1, C(α)*Me*), 1.52 (9H, s, CMe_3), 2.07 (1H, d septet, *J* 9.8, 6.6, C(4)*H*), 2.91 (1H, d, *J* 2.7, O*H*), 3.18 (1H, app d, *J* 9.8, C(3)*H*), 3.61 (1H, d, *J* 14.9, NCH_AH_BPh), 3.68 (1H, app d, *J* 2.7, C(2)*H*), 3.92 (1H, q, *J* 7.1, C(α)*H*), 4.33 (1H, d, *J* 14.9, NCH_AH_BPh) 7.21–7.53 (10H, m, *Ph*).

4.6. tert-Butyl (2S,3R,αR)-2-hydroxy-3-[N-benzyl-N-(α-methylbenzyl)amino]butanoate **20**

Step 1: DMSO (0.42 mL, 5.4 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (0.23 mL, 2.7 mmol) in CH_2Cl_2 (5 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 20 min. A solution of **1** (500 mg, 1.35 mmol, >99:1 dr) in CH_2Cl_2 (2.5 mL) was added via cannula and the resultant mixture was stirred at −78 °C for 30 min Et_3N (1.13 mL, 8.12 mmol) was added then the reaction mixture was allowed to warm to rt and stirred at rt for 30 min H_2O (20 mL) was then added, the reaction mixture was

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extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were dried and concentrated in vacuo.

Step 2: $NaBH_4$ (51 mg, 1.4 mmol) was added to a stirred solution of the residue from the previous step in MeOH (5 mL) at −20 °C and the resultant mixture was stirred at −20 °C for 2 h, then allowed to warm to rt and concentrated in vacuo. The reaction mixture was then partitioned between CH_2Cl_2 (20 mL) and H_2O (20 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were then dried and concentrated in vacuo to give **20** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 8:1) gave **20** as a colourless oil (490 mg, 97%, >99:1 dr); [22,23c] $[\alpha]_D^{25}$ −68.5 (*c* 1.0 in $CHCl_3$); {lit.[22] $[\alpha]_D^{23}$ −68.0 (*c* 1.0 in $CHCl_3$); lit.[23c] for *ent*-**20**: $[\alpha]_D^{25}$ +68.3 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.17 (3H, d, *J* 6.8, C(4)H_3), 1.43 (9H, s, CMe_3), 1.47 (3H, d, *J* 6.9, C(α)*Me*), 3.07 (1H, dq, *J* 8.3, 6.8, C(3)*H*), 3.65–3.72 (2H, m, C(2)*H*, NCH_AH_BPh), 3.78 (1H, br s, OH), 3.81 (1H, d, *J* 13.6, NCH_AH_BPh), 4.06 (1H, q, *J* 6.9, C(α)*H*), 7.19–7.39 (10H, m, *Ph*).

4.7. *tert*-Butyl (2*S*,3*R*,α*R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-methylpentanoate **21**

Step 1: DMSO (0.54 mL, 7.6 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (0.65 mL, 7.6 mmol) in CH_2Cl_2 (8 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 20 min. A solution of **2** (1.50 g, 3.77 mmol, >99:1 dr) in CH_2Cl_2 (8 mL) was added via cannula and the resultant mixture was stirred at −78 °C for 30 min Et_3N (2.09 mL, 15.1 mmol) was added then the reaction mixture was allowed to warm to rt and stirred at rt for 30 min H_2O (50 mL) was then added, the reaction mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic extracts were dried and concentrated in vacuo.

Step 2: $NaBH_4$ (133 mg, 7.55 mmol) was added to a stirred solution of the residue from the previous step in MeOH (352 mL) at −20 °C and the resultant mixture was stirred at −20 °C for 2 h, then allowed to warm to rt and concentrated in vacuo. The reaction mixture was then partitioned between CH_2Cl_2 (60 mL) and H_2O (60 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were then dried and concentrated in vacuo to give a 69:31 mixture of *syn*-**21** and *anti*-**2**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **2** as a white solid (380 mg, 25% from **2**, >99:1 dr). Further elution gave **21** as a colourless oil (785 mg, 53% from **2**, >99:1 dr); $[\alpha]_D^{25}$ +1.8 (*c* 1.0 in $CHCl_3$); ν_{max} 3502 (O–H), 1717 (C=O); δ_H (400 MHz, $CDCl_3$) 0.92 (3H, d, *J* 6.9, C(4)Me_A), 1.00 (3H, d, *J* 6.9, C(4)Me_B), 1.43 (3H, d, *J* 7.1, C(α)*Me*), 1.47 (9H, s, CMe_3), 2.10 (1H, d septet, *J* 6.9, 6.0, C(4)*H*), 3.04 (1H, app t, *J* 6.0, C(3)*H*), 3.23 (1H, d, *J* 5.1, O*H*), 3.94 (1H, d, *J* 14.8, NCH_AH_BPh), 3.94 (1H, app d, *J* 5.1, C(2)*H*), 3.99 (1H, d, *J* 14.8, NCH_AH_BPh), 4.07 (1H, q, *J* 7.1, C(α)*H*), 7.20–7.37 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.0 (C(α)*Me*), 20.3 21.8 (C(4)Me_2), 28.0 (CMe_3), 28.6 (*C*(4)), 51.1 (NCH_2Ph), 59.9 (*C*(α)), 65.0 (*C*(3)), 71.6 (*C*(2)), 81.8 (*C*Me_3), 126.7127.5, 128.0128.2128.3128.5 (*o*,*m*,*p*-*Ph*), 141.3143.6 (*i*-*Ph*), 173.6 (*C*(1)); *m*/*z* (ESI^+) 398 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{25}H_{36}NO_3^+$ ($[M+H]^+$) requires 398.2690; found 398.2685.

4.8. *tert*-Butyl (2*R*,3*S*,α*R*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-hydroxybutanoate **24**

Tf_2O (72 μL, 0.42 mmol) was added to a stirred solution of **20** (100 mg, 0.270 mmol, >99:1 dr) and DMTBP (174 mg, 0.847 mmol) in CH_2Cl_2 (1.2 mL) at 0 °C and the resultant mixture was allowed to warm to rt and stirred at rt for 6 h H_2O (50 μL, 7.2 mmol) was then added and the resultant mixture was stirred at rt for 24 h H_2O (2 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 4 mL). The combined organic extracts were then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **24** as a colourless oil (67 mg, 67%, >99:1 dr); $[\alpha]_D^{25}$ −7.5 (*c* 1.0 in $CHCl_3$); ν_{max} 3428 (O–H), 2975 (C–H), 1721 (C=O); δ_H (400 MHz, $CDCl_3$) 1.06 (3H, d, *J* 6.1, C(4)H_3), 1.30 (3H, obsc d, C(α)*Me*), 1.31 (9H, s, CMe_3), 3.12 (1H, d, *J* 9.5, C(2)*H*), 3.62 (1H, br s, O*H*), 3.70–3.76 (2H, m, C(3)*H*, NCH_AH_BPh), 4.01 (1H, q, *J* 7.0, C(α)*H*), 4.2 (1H, d, *J* 15.3, NCH_AH_BPh), 7.18–7.31 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(4)), 22.4 (C(α)*Me*), 28.1 (CMe_3), 51.5 (NCH_2Ph), 60.2 (*C*(α)), 64.6 (*C*(2)), 68.1 (*C*(3)), 81.5 (*C*Me_3), 127.0, 127.5 (*p*-*Ph*), 128.2, 128.3, 128.5, 128.6 (*o*,*m*-*Ph*), 140.7, 142.4 (*i*-*Ph*), 170.5 (*C*(1)); *m*/*z* (ESI^+) 370 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{23}H_{32}NO_3^+$ ($[M+H]^+$) requires 370.2377; found 370.2382.

4.9. *tert*-Butyl (2*R*,3*S*,α*R*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-hydroxy-4-methylpentanoate **25**

Tf_2O (0.12 mL, 0.75 mmol) was added to a stirred solution of **21** (200 mg, 0.504 mmol, >99:1 dr) and DMTBP (308 mg, 1.58 mmol) in CH_2Cl_2 (2.4 mL) at 0 °C and the resultant mixture was allowed to warm to rt and stirred at rt for 6 h H_2O (0.90 mL, 50 mmol) was then added and the resultant mixture was stirred at 40 °C for 24 h H_2O (2 mL) was then added and the resultant mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 15:1) gave **25** as a colourless oil (113 mg, 57%, >99:1 dr); $[\alpha]_D^{25}$ +74.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3432 (O–H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 0.71 (3H, d, *J* 6.9, C(4)Me_A), 1.00 (3H, d, *J* 6.9, C(4)Me_B), 1.37 (3H, d, *J* 6.9, C(α)*Me*), 1.38 (9H, s, CMe_3), 1.58 (1H, d septet, *J* 6.9, 1.7, C(4)*H*), 3.41 (1H, d, *J* 9.8, C(2)*H*), 3.64 (1H, dd, *J* 9.8, 1.7, C(3)*H*) 3.73 (1H, br s, O*H*), 3.75 (1H, d, *J* 15.2, NCH_AH_BPh), 4.07 (1H, q, *J* 6.9, C(α)*H*), 4.28 (1H, d, *J* 15.2, NCH_AH_BPh), 7.23–7.39 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.2, 20.8 (C(4)Me_2), 21.2 (C(α)*Me*), 28.1 (CMe_3), 29.7 (*C*(4)), 52.2 (NCH_2Ph), 60.2 (*C*(α)), 63.3 (*C*(2)), 71.6 (*C*(3)), 81.3 (*C*Me_3) 127.0, 127.4, 128.1, 128.4, 128.5, 128.6 (*o*,*m*,*p*-*Ph*), 140.4, 142,6 (*i*-*Ph*), 170.4 (*C*(1)); *m*/*z* (ESI^+) 398 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{25}H_{36}NO_3^+$ ($[M+H]^+$) requires 398.2690; found 398.2688.

4.10. *tert*-Butyl (*E*)-3-phenylpropenoate [*tert*-butyl cinnamate] **26**

MeMgBr (3.0 M in Et_2O, 42.6 mL, 128 mmol) was added dropwise to a stirred solution of $(EtO)_2P(O)CHCO_2^tBu$ (30.0 mL, 128 mmol) in THF (300 mL) at rt and the resultant mixture was stirred at rt for 15 min. A solution of PhCHO (14.3 mL, 141 mmol) in THF (225 mL) was added via cannula and the resultant mixture was heated at 67 °C for 2.5 h, then allowed to cool to rt. Satd aq NH_4Cl (450 mL) was added and the aqueous layer was extracted with Et_2O (3 × 150 mL). The combined organic extracts were washed with brine (800 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 20:1) gave **26** as pale yellow oil (12.8 g, 52%, >99:1 dr [(*E*):(*Z*)]);[37] δ_H (400 MHz, $CDCl_3$) 1.41 (9H, s, CMe_3), 6.24 (1H, d, *J* 16.0, C(2)*H*), 7.20–7.22 (3H, m, *Ph*), 7.28–7.41 (2H, m, *Ph*), 7.50 (1H, d, *J* 16.0, C(3)*H*).

4.11. *tert*-Butyl (*E*)-3-(3′-fluorophenyl)propenoate **27**

3-Fluorobenzaldehyde (10.0 g, 45.0 mmol) was added to a stirred solution of $Ph_3P=CHCO_2^tBu$ (18.6 g, 49.5 mmol) in CH_2Cl_2 (500 mL) and the resultant mixture was stirred at rt for 16 h, then concentrated in vacuo. Purification via flash column

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chromatography (eluent 30–40 °C petrol/Et_2O, 15:1) gave **27** as a colourless oil (17.7 g, quant, 96:4 dr [(*E*):(*Z*)]);[38,39] δ_H (400 MHz, $CDCl_3$) 1.54 (9H, s, CMe_3), 6.37 (1H, d, *J* 15.9, C(2)*H*), 7.07–7.10 (1H, m, *Ar*), 7.18–7.23 (1H, m, *Ar*), 7.26–7.38 (2H, m, *Ar*), 7.54 (1H, d, *J* 15.9, C(3)*H*).

4.12. tert-Butyl (E)-3-(3-fluorophenyl)propenoate 28

4-Fluorobenzaldehyde (10.0 g, 45.0 mmol) was added to a stirred solution of $Ph_3P{=}CHCO_2^tBu$ (18.6 g, 49.5 mmol) in CH_2Cl_2 (500 mL) and the resultant mixture was stirred at rt for 16 h, then concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 15:1) gave **28** as a colourless oil (18.1 g, quant, 96:4 dr [(*E*):(*Z*)]);[39] δ_H (400 MHz, $CDCl_3$) 1.54 (9H, s, CMe_3), 6.30 (1H, d, *J* 15.9, C(2)*H*), 7.07–7.10 (2H, m, *Ar*), 7.47–7.53 (2H, m, *Ar*), 7.55 (1H, d, *J* 15.9, C(3)*H*).

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

BuLi (2.5 M in hexanes, 15.5 mL, 38.8 mmol) was added dropwise to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl) amine (8.25 g, 39.2 mmol, >99:1 er) in THF (60 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 30 min. A solution of **26** (5.00 g, 24.5 mmol, >99:1 dr [(*E*):(*Z*)]) in THF (60 mL) was then added dropwise via cannula and the resultant mixture was stirred at −78 °C for 2 h (−)-CSO (9.00 g, 39.3 mmol) was then added and the resultant mixture was allowed to warm to rt and stirred at rt for 16 h, then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (100 mL) and 10% aq citric acid (100 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (100 mL) and brine (100 mL), then dried and concentrated in vacuo. The residue was dissolved in Et_2O (100 mL) and filtered, and the filter cake was washed with Et_2O (2 × 100 mL), then the combined organic extracts were concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **3** as a white solid (9.04 g, 91%, >99:1 dr); [22] mp 86–90 °C; {lit.[22] mp 85–88 °C}; $[\alpha]_D^{25}$ −24.8 (*c* 1.0 in $CHCl_3$); {lit.[22] $[\alpha]_D^{23}$ −26.7 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.26 (3H, d, *J* 6.9, C(α)*Me*), 1.28 (9H, s, CMe_3), 2.91 (1H, br s, O*H*), 3.92 (1H, d, *J* 14.9, NCH_AH_BPh), 4.22 (1H, d, *J* 14.9, NCH_AH_BPh), 4.27–4.33 (2H, m, C(3)*H*, C(α)*H*), 4.49 (1H, d, *J* 3.0, C(2)*H*), 7.21–7.61 (15H, m, *Ph*).

4.14. tert-Butyl (R,R,R)-2-hydroxy-3-[N-benzyl-N-(α-methylbenzyl) amino]-3-(3′-fluorophenyl)propanoate 29

BuLi (2.2 M in hexanes, 15.9 mL, 34.9 mmol) was added dropwise to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl) amine (7.61 g, 36.0 mmol, >99:1 er) in THF (100 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 30 min. A solution of **27** (5.00 g, 22.5 mmol, 96:4 dr [(*E*):(*Z*)]) in THF (100 mL) was then added dropwise via cannula and the resultant mixture was stirred at −78 °C for 2 h (−)-CSO (10.3 g, 45.0 mmol) was then added and the resultant mixture was allowed to warm to rt and stirred at rt for 16 h, then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (100 mL) and 10% aq citric acid (100 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (100 mL) and brine (100 mL), then dried and concentrated in vacuo. The residue was dissolved in Et_2O (100 mL) and filtered, and the filter cake was washed with Et_2O (2 × 100 mL), then the combined organic extracts were concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **29** as a pale yellow oil (6.23 g, 85%, >99:1 dr); [19] $[\alpha]_D^{25}$ −19.4 (*c* 1.0 in $CHCl_3$); {lit.[19] $[\alpha]_D^{20}$ −34.6 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.22 (9H, s, CMe_3), 1.19–1.22 (3H, obsc d, C(α)*Me*), 2.75 (1H, d, *J* 2.4, O*H*), 3.86 (1H, d, *J* 14.9, NCH_AH_BPh), 4.13 (1H, d, *J* 14.9, NCH_AH_BPh), 4.16–4.23 (2H, m, C(3)*H*, C(α)*H*), 4.39 (1H, dd, *J* 3.9, 2.4, C(2)*H*), 6.93–7.00 (1H, m, *Ar*) 7.17–7.39 (11H, m, *Ar*, *Ph*), 7.46–7.48 (2H, m, *Ar*).

4.15. tert-Butyl (R,R,R)-2-hydroxy-3-[N-benzyl-N-(α-methylbenzyl) amino]-3-(4′-fluorophenyl)propanoate 30

BuLi (2.2 M in hexanes, 15.9 mL, 34.9 mmol) was added dropwise to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl) amine (7.61 g, 36.0 mmol, >99:1 er) in THF (100 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 30 min. A solution of **28** (5.00 g, 22.5 mmol, 96:4 dr [(*E*):(*Z*)]) in THF (100 mL) was then added dropwise via cannula and the resultant mixture was stirred at −78 °C for 2 h (−)-CSO (10.3 g, 45.0 mmol) was then added and the resultant mixture was allowed to warm to rt and stirred at rt for 16 h, then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (100 mL) and 10% aq citric acid (100 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (100 mL) and brine (100 mL), then dried and concentrated in vacuo. The residue was dissolved in Et_2O (100 mL) and filtered, and the filter cake was washed with Et_2O (2 × 100 mL), then the combined organic extracts were concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **30** as a pale yellow oil (6.03 g, 82%, >99:1 dr); [19] $[\alpha]_D^{25}$ −27.0 (*c* 1.0 in $CHCl_3$); {lit.[19] $[\alpha]_D^{20}$ −26.7 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.20 (9H, s, CMe_3), 1.19–1.22 (3H, obsc d, *J* 6.9, C(α)*Me*), 2.75 (1H, br s, O*H*), 3.82 (1H, d, *J* 15.2, NCH_AH_BPh), 4.10 (1H, d, *J* 15.2, NCH_AH_BPh), 4.13–4.22 (2H, m, C(3)*H*, C(α)*H*), 4.40 (1H, d, *J* 2.7, C(2)*H*), 6.99 (2H, app t, *J* 8.6, C(3′)*H*, C(5′)*H*), 7.16–7.49 (10H, m, *Ph*), 7.36 (2H, app t, *J* 7.3, C(2′)*H*, C(6′)*H*).

4.16. tert-Butyl (2S,3R,αR)-2-hydroxy-3-[N-benzyl-N-(α-methylbenzyl)amino]-3-phenylpropanoate 34

Step 1: DMSO (0.33 mL, 4.64 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (0.20 mL, 2.32 mmol) in CH_2Cl_2 (2.5 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 20 min. A solution of **3** (500 mg, 1.16 mmol, >99:1 dr) in CH_2Cl_2 (2.5 mL) was added via cannula and the resultant mixture was stirred at −78 °C for 30 min Et_3N (0.62 mL, 4.64 mmol) was added then the reaction mixture was allowed to warm to rt and stirred at rt for 30 min H_2O (20 mL) was then added, the reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were dried and concentrated in vacuo.

Step 2: DIBAL-H (1.0 M in THF, 1.16 mL, 1.16 mmol) was added to a stirred solution of the residue from the previous step in THF (5 mL) at −20 °C and the resultant mixture was stirred at −20 °C for 2 h. MeOH (1 mL) was added and the resultant mixture was allowed to warm to rt. Satd aq Rochelle's salt was added (1 mL) and the resultant mixture was stirred at rt for 16 h, then filtered through Celite® (eluent MeOH) and concentrated in vacuo 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 white solid (339 mg, 68%, >99:1 dr); [22] mp 111–116 °C; {lit.[22] mp 110–114 °C}; $[\alpha]_D^{25}$ −24.9 (*c* 1.0 in $CHCl_3$); {lit.[22] $[\alpha]_D^{23}$ −25.9 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.08 (9H, s, CMe_3), 1.10 (3H, d, *J* 6.9, C(α)*Me*), 3.66 (1H, *J* 13.3, NCH_AH_BPh), 3.84 (1H, br s, O*H*), 3.90 (1H, d, *J* 9.9, C(3)*H*), 4.07 (1H, d, *J* 13.3, NCH_AH_BPh), 4.21 (1H, q, *J* 6.9, C(α)*H*), 4.47 (1H, d, *J* 9.9, C(2)*H*), 7.24–7.42 (15H, m, *Ph*).

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

Step 1: DMSO (2.14 mL, 30.3 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (1.28 mL, 15.1 mmol) in CH_2Cl_2 (20 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 20 min. A solution of **29** (3.40 g, 7.56 mmol, >99:1 dr) in CH_2Cl_2 (20 mL) was added via cannula and the resultant mixture was stirred at −78 °C for 30 min Et_3N (6.32 mL, 45.4 mmol) was added then the reaction mixture was allowed to warm to rt and stirred at rt for 30 min H_2O (30 mL) was then added, the reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic extracts were dried and concentrated in vacuo.

Step 2: DIBAL-H (1.0 M in THF, 9.82 mL, 9.82 mmol) was added to a stirred solution of the residue from the previous step in THF (40 mL) at −20 °C and the resultant mixture was stirred at −20 °C for 2 h. MeOH (5 mL) was added and the resultant mixture was allowed to warm to rt. Satd aq Rochelle's salt was added (20 mL) and the resultant mixture was stirred at rt for 16 h, then filtered through Celite® (eluent EtOAc) and concentrated in vacuo to give an 87:13 mixture of *syn*-**35** and *anti*-**29**, respectively. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 10:1) gave **29** as a colourless oil (153 mg, 5% from **29**, >99:1 dr). Further elution gave **35** as a pale orange solid (2.04 g, 60% from **29**, >99:1 dr); mp 76–79 °C; $[\alpha]_D^{25}$ −71.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3449 (O–H), 1740 (C=O); δ_H (500 MHz, $CDCl_3$) 1.09 (9H, s, C*Me*$_3$), 1.10 (3H, obsc d, C(α)*Me*), 3.65–3.71 (2H, m, NC*H*$_A$H$_B$Ph, O*H*), 3.91 (1H, d, *J* 9.8, C(3)*H*), 4.06 (1H, d, *J* 13.6, NCH$_A$*H*$_B$Ph), 4.20 (1H, q, *J* 7.0, C(α)*H*), 4.41 (1H, d, *J* 9.8, C(2)*H*), 7.03–7.15 (3H, m, C(2′)*H*, C(4′)*H*, C(6′)*H*), 7.25–7.40 (11H, m, C(5′)*H*, *Ph*); δ_C (125 MHz, $CDCl_3$) 13.9 (C(α)*Me*), 27.5 (C*Me*$_3$), 50.4 (N*C*H$_2$Ph), 56.2 (*C*(α)), 63.9 (*C*(3)), 71.1 (*C*(2)), 81.4 (*C*Me$_3$), 115.0 (d, *J* 20.8, *C*(4′)), 116.7 (d, *J* 22.4, *C*(2′)), 125.7 (d, *J* 3.4, *C*(6′)), 127.4, 127.5 (*p-Ph*), 127.8, 128.6, 128.7, 129.0 (*o,m-Ph*), 129.7 (d, *J* 8.4, *C*(5′)), 139.1 (*i-Ph*), 139.7 (d, *J* 6.5, *C*(1′)), 142.9 (*i-Ph*), 162.6 (d, *J* 245.7, *C*(3′)), 171.0 (*C*(1)); δ_F (472 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 450.2428.

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

Step 1: DMSO (2.53 mL, 35.6 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (1.51 mL, 17.8 mmol) in CH_2Cl_2 (22 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 20 min. A solution of **30** (4.00 g, 8.90 mmol, >99:1 dr) in CH_2Cl_2 (22 mL) was added via cannula and the resultant mixture was stirred at −78 °C for 30 min Et_3N (7.44 mL, 53.4 mmol) was added then the reaction mixture was allowed to warm to rt and stirred at rt for 30 min H_2O (30 mL) was then added, the reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic extracts were dried and concentrated in vacuo.

Step 2: DIBAL-H (1.0 M in THF, 11.57 mL, 11.57 mmol) was added to a stirred solution of the residue from the previous step in THF (45 mL) at −20 °C and the resultant mixture was stirred at −20 °C for 2 h. MeOH (5 mL) was added and the resultant mixture was allowed to warm to rt. Satd aq Rochelle's salt was added (20 mL) and the resultant mixture was stirred at rt for 16 h, then filtered through Celite® (eluent EtOAc) and concentrated in vacuo to give a 90:10 mixture of *syn*-**36** and *anti*-**30**, respectively. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 10:1) gave **30** as a colourless oil (97 mg, 2% from **30**, >99:1 dr). Further elution gave **36** as a pale orange solid (1.95 g, 49% from **30**, >99:1 dr); mp 83–85 °C; $[\alpha]_D^{25}$ −85.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3452 (O–H), 1740 (C=O); δ_H (500 MHz, $CDCl_3$) 1.10 (9H, s, C*Me*$_3$), 1.11 (3H, obsc d, C(α)*Me*), 3.64 (1H, *J* 13.6, NC*H*$_A$H$_B$Ph), 3.75 (1H, br s, O*H*), 3.92 (1H, d, *J* 9.9, C(3)*H*), 4.03 (1H, d, *J* 13.6, NCH$_A$*H*$_B$Ph), 4.19 (1H, q, *J* 6.8, C(α)*H*), 4.40 (1H, d, *J* 9.9, C(2)*H*), 7.08 (1H, app t, *J* 8.6, C(3′)*H*, C(5′)*H*), 7.23–7.40 (12H, m, C(2′)*H*, C(6′)*H*, *Ph*); δ_C (125 MHz, $CDCl_3$) 13.9 (C(α)*Me*), 27.5 (C*Me*$_3$), 50.3 (N*C*H$_2$Ph), 56.1 (*C*(α)), 63.6 (*C*(3)), 71.2 (*C*(2)), 81.3 (*C*Me$_3$), 115.1 (d, *J* 22.0, *C*(3′), *C*(5′)), 127.4, 127.5 (*p-Ph*), 127.9, 128.6, 128.7, 129.0 (*o,m-Ph*), 131.5 (d, *J* 8.0, *C*(2′), *C*(6′)), 132.7 (d, *J* 3.6, *C*(1′)), 139.1, 143.0 (*i-Ph*), 162.6 (d, *J* 247.1, *C*(4′)), 171.1 (*C*(1)); δ_F (472 MHz, $CDCl_3$) −113.9 (C(4′)*F*); *m/z* (ESI$^+$) 450 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{33}FNO_3^+$ ([M+H]$^+$) requires 450.2439; found 450.2433.

4.19. tert-Butyl (2R,3S,αR)-2-[N-benzyl-N-(α-methylbenzyl)amino]-3-hydroxy-3-phenylpropanoate ***37***

Ms_2O (258 mg, 1.48 mmol) was added to a stirred solution of **34** (213 mg, 0.494 mmol, >99:1 dr) and Et_3N (0.31 mL, 2.22 mmol) in CH_2Cl_2 (2.1 mL) at rt, and the resultant mixture was stirred at rt for 1 h H_2O (2.67 mL, 148 mmol) was then added and the resultant mixture was stirred at 40 °C for 24 h then allowed to cool to rt. The aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL) and 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 an 87:13 mixture of **37** and **34**, respectively. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 10:1) gave **37** as a colourless viscous oil (161 mg, 76%, >99:1 dr); $[\alpha]_D^{25}$ +48.2 (*c* 1.0 in $CHCl_3$); ν_{max} 3428 (O–H), 2976 (C–H), 1721 (C=O); δ_H (400 MHz, $CDCl_3$) 1.00 (9H, s, C*Me*$_3$), 1.40 (3H, d, *J* 7.1, C(α)*Me*), 3.50 (1H, d, *J* 9.7, C(2)*H*), 3.74 (1H, d, *J* 14.9, NC*H*$_A$H$_B$Ph), 4.06 (1H, q, *J* 7.1, C(α)*H*), 4.24 (1H, br s, O*H*), 4.35 (1H, d, *J* 14.9, NCH$_A$*H*$_B$Ph), 4.57 (1H, d, *J* 9.7, C(3)*H*), 7.13–7.35 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.8 (C(α)*Me*), 27.7 (C*Me*$_3$), 51.7 (N*C*H$_2$Ph), 60.1 (*C*(α)), 67.9 (*C*(2)), 71.4 (*C*(3)), 81.3 (*C*Me$_3$), 127.2, 127.6, 128.0 (*p-Ph*), 127.9, 128.1, 128.3, 128.6, 128.6, 128.7 (*o,m-Ph*), 140.3, 140.3, 142.3 (*i-Ph*), 169.5 (*C*(1)); *m/z* (ESI$^+$) 432 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{34}NO_3^+$ ([M+H]$^+$) requires 432.2533; found 432.2526. Further elution gave **34** as a white solid (26 mg, 12%, >99:1 dr).

4.20. tert-Butyl (2R,3S,αR)-2-[N-benzyl-N-(α-methylbenzyl)amino]-3-hydroxy-3-(3′-fluorophenyl)propanoate ***38***

Ms_2O (116 mg, 0.667 mmol) was added to a stirred solution of **35** (100 mg, 0.222 mmol, >99:1 dr) and Et_3N (0.14 mL, 1.00 mmol) in CH_2Cl_2 (1.0 mL) at rt, and the resultant mixture was stirred at rt for 1 h H_2O (1.20 mL, 66.6 mmol) was then added and the resultant mixture was stirred at 40 °C for 24 h then allowed to cool to rt. The aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL) and 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 78:22 mixture of **38** and **35**, respectively. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 10:1) gave **38** as a colourless oil (73 mg, 73%, >99:1 dr); $[\alpha]_D^{25}$ +59.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3422 (O–H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.18 (9H, s, C*Me*$_3$), 1.50 (3H, d, *J* 7.0, C(α)*Me*), 3.53 (1H, d, *J* 9.9, C(2)*H*), 3.85 (1H, d, *J* 15.0, NC*H*$_A$H$_B$Ph), 4.17 (1H, q, *J* 7.0, C(α)*H*), 4.40 (1H, d, *J* 15.0, NCH$_A$*H*$_B$Ph), 4.43 (1H, br s, O*H*), 4.67 (1H, d, *J* 9.9, C(3)*H*), 6.93–6.98 (2H, m, C(2′)*H*, C(4′)*H*), 7.02 (1H, d, *J* 7.6, C(6′)*H*), 7.20–7.27 (1H, m, C(5′)*H*), 7.29–7.36 (2H, m, *Ph*), 7.37–7.44 (8H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.9 (C(α)*Me*), 27.9 (C*Me*$_3$), 51.9 (N*C*H$_2$Ph), 60.3 (*C*(α)), 68.0 (*C*(2)), 70.8 (*C*(3)), 81.6 (*C*Me$_3$), 114.5 (d, *J* 22.2, *C*(2′)), 114.8 (d, *J* 20.7, *C*(4′)), 123.5 (d, *J* 2.8, *C*(6′)), 127.3, 127.7, 128.2, 128.6, 128.8 (*o,m,p-Ph*), 129.5 (d, *J* 8.1, *C*(5′)), 140.0, 142.3 (*i-Ph*), 143.4 (d, *J* 7.0, *C*(1′)), 162.7

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(d, *J* 245.4, *C*(3′)), 169.4 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −113.6 (C(3′)*F*); *m/z* (ESI$^+$) 450 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{33}FNO_3^+$ ([M+H]$^+$) requires 450.2439; found 450.2431. Further elution gave **35** as a colourless oil (17 mg, 17%, >99:1 dr).

4.21. tert-Butyl (2R,3S,αR)-2-[N-benzyl-N-(α-methylbenzyl) amino]-3-hydroxy-3-(4′-fluorophenyl)propanoate **39**

Ms_2O (232 mg, 1.33 mmol) was added to a stirred solution of **36** (200 mg, 0.445 mmol, >99:1 dr) and Et_3N (0.28 mL, 2.00 mmol) in CH_2Cl_2 (2.0 mL) at rt, and the resultant mixture was stirred at rt for 1 h H_2O (2.40 mL, 133 mmol) was then added and the resultant mixture was stirred at 40 °C for 24 h then allowed to cool to rt. The aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL) and the combined organic extracts were washed sequentially with 1.0 M aq HCl (3 mL), satd aq $NaHCO_3$ (3 mL) and brine (3 mL), then dried and concentrated in vacuo to give a 77:23 mixture of **39** and **36**, respectively. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 10:1) gave **39** as a colourless oil (123 mg, 61%, >99:1 dr); $[\alpha]_D^{25}$ +70.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3433 (O–H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.15 (9H, s, C*Me*$_3$), 1.49 (3H, d, *J* 7.0, C(α)*Me*), 3.52 (1H, d, *J* 9.7, C(2)*H*), 3.84 (1H, d, *J* 14.8, NC*H*$_A$H$_B$Ph), 4.16 (1H, q, *J* 7.0, C(α)*H*), 4.37 (1H, br s, O*H*), 4.40 (1H, d, *J* 14.8, NCH$_A$*H*$_B$Ph), 4.66 (1H, d, *J* 9.7, C(3)*H*), 6.97 (2H, app t, *J* 8.4, C(3′)*H*, C(5′)*H*), 7.17–7.28 (2H, m, C(2′)*H*, C(6′)*H*), 7.29–7.36 (2H, m, *Ph*), 7.37–7.43 (8H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.9 (C(α)*Me*), 27.8 (C*Me*$_3$), 51.8 (N*C*H$_2$Ph), 60.3 (*C*(α)), 68.1 (*C*(2)), 70.7 (*C*(3)), 81.5 (*C*Me$_3$), 115.0 (d, *J* 22.2, *C*(3′), *C*(5′)), 127.3, 127.6 (*p-Ph*), 128.2, 128.6, 128.6, 128.7 (*o,m-Ph*), 129.5 (d, *J* 8.1, *C*(2′), *C*(6′)), 136.3 (d, *J* 3.6, *C*(1′)), 140.2, 142.3 (*i-Ph*), 162.6 (d, *J* 245.7, *C*(4′)), 169.4 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −114.5 (C(4′)*F*); *m/z* (ESI$^+$) 450 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{33}FNO_3^+$ ([M+H]$^+$) requires 450.2439; found 450.2445. Further elution gave **36** as a colourless oil (27 mg, 14%, >99:1 dr).

4.22. (2R,3S)-2-Amino-3-hydroxybutanoic acid [(+)-threonine] **41**

Step 1: Pd(OH)$_2$/C (100 mg, 25% w/w) was added to a stirred, degassed solution of **24** (400 mg, 1.08 mmol, >99:1 dr) in MeOH (2 mL) at rt and the resultant mixture was placed under at atmosphere of H_2 (5 atm) and stirred at rt for 40 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated in vacuo.

Step 2: The residue from the previous step was dissolved in 6.0 M aq HCl (7.2 mL) and the resultant mixture was stirred at rt for 3 h, then concentrated in vacuo. Purification via ion exchange chromatography (Dowex 50WX8 resin hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) gave **41** as a white solid (115 mg, 89% from **24**, >98:2 dr); [22] mp 258–261 °C; {lit.[40] mp 264 °C (dec.)}; $[\alpha]_D^{25}$ +28.1 (*c* 3.2 in H_2O); {lit.[41] $[\alpha]_D^{20}$ +26.1 (*c* 1.0 in H_2O)}; ν_{max} (ATR) 2976 (C–H), 1620 (C=O); δ_H (400 MHz, D_2O) 1.27 (3H, d, *J* 6.6, C(4)*H*$_3$), 3.54 (1H, d, *J* 4.9, C(2)*H*), 4.20 (1H, m, C(3)*H*); δ_C (400 MHz, D_2O) 19.5 (*C*(4)), 60.4 (*C*(2)), 65.9 (*C*(3)), 172.8 (*C*(1)); *m/z* (ESI$^+$) 120 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_4H_{10}NO_3^+$ ([M+H]$^+$) requires 120.0655; found 120.0658.

4.23. (2R,3S)-2-Amino-3-hydroxy-4-methylpentanoic acid [(+)-β-hydroxyleucine] **42**

Step 1: Pd(OH)$_2$/C (24 mg, 20% w/w) was added to a stirred, degassed solution of **25** (120 mg, 302 μmol, >99:1 dr) in MeOH (3 mL) at rt and the resultant mixture was placed under at atmosphere of H_2 (5 atm) and stirred at rt for 40 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated in vacuo.

Step 2: The residue from the previous step was dissolved in 6.0 M aq HCl (3 mL) and the resultant mixture was stirred at rt for 3 h, then concentrated in vacuo. Purification via ion exchange chromatography (Dowex 50WX8 resin hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) gave **42** as a white solid (31 mg, 70% from **25**, >99:1 dr); [42] mp 215 °C (dec.); {lit.[43] mp 212–213 °C (dec.)}; $[\alpha]_D^{25}$ +2.1 (*c* 1.0 in H_2O); {lit.[43] $[\alpha]_D^{20}$ +2.7 (*c* 0.8 in H_2O)}; ν_{max} (ATR) 3471, 3260 (N–H, O–H), 2968 (C–H), 1636 (C=O); δ_H (400 MHz, D_2O) 0.90 (3H, d, *J* 6.6, C(4)*Me*$_A$), 0.95 (3H, d, *J* 6.9, C(4)*Me*$_B$), 1.63 (1H, m, C(4)*H*), 3.71 (1H, dd, *J* 7.8, 3.9, C(3)*H*), 3.77 (1H, d, *J* 3.9, C(2)*H*); δ_C (400 MHz, D_2O) 17.4 (C(4)*Me*$_B$), 18.4 (C(4)*Me*$_A$), 30.2 (*C*(4)), 56.9 (*C*(2)), 75.1 (*C*(3)), 173.4 (*C*(1)); *m/z* (ESI$^-$) 146 ([M−H]$^-$, 100%); HRMS (ESI$^+$) $C_6H_{14}NO_3^+$ ([M+H]$^+$) requires 148.0968; found 148.0967.

4.24. (2R,3S)-2-Amino-3-hydroxy-3-phenylpropanoic acid [(2R,3S)-β-hydroxyphenylalanine] **43**

Step 1: Pd(OH)$_2$/C (100 mg, 20% w/w) was added to a stirred, degassed solution of **37** (400 mg, 0.94 mmol, >99:1 dr) in MeOH (2 mL) at rt and the resultant mixture was placed under at atmosphere of H_2 (5 atm) and stirred at rt for 40 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated in vacuo.

Step 2: The residue from the previous step was dissolved in 6.0 M aq HCl (8.9 mL) and the resultant mixture was stirred at rt for 3 h, then concentrated in vacuo. Purification via ion exchange chromatography (Dowex 50WX8 resin hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) gave **43** as a white solid (119 mg, 63% from **37**, >95:5 dr); [6b] mp 196–198 °C; {lit.[6b] mp 196–197 °C}; $[\alpha]_D^{20}$ +30.4 (*c* 0.6 in H_2O); {lit.[6b] $[\alpha]_D^{20}$ +31 (*c* 1.28 in H_2O)}; ν_{max} (ATR) 2976 (C–H), 1653 (C=O); δ_H (500 MHz, D_2O) 3.91 (1H, d, *J* 4.3, C(2)*H*), 5.29 (1H, d, *J* 4.3, C(3)*H*), 7.38–7.48 (5H, m, *Ph*); δ_C (125 MHz, D_2O) 60.9 (*C*(2)), 71.4 (*C*(3)), 126.0, 129.1, 129.2 (*o,m,p-Ph*), 139.2 (*i-Ph*), 172.0 (*C*(1)); *m/z* (ESI$^+$) 182 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_9H_{12}NO_3^+$ ([M+H]$^+$) requires 182.0812; found 182.0821.

4.25. (2R,3S)-2-Amino-3-hydroxy-3-(3′-fluorophenyl)propanoic acid **44**

Step 1: Pd(OH)$_2$/C (32 mg, 20% w/w) was added to a stirred, degassed solution of **38** (160 mg, 0.356 mmol, >99:1 dr) in MeOH (2 mL) at rt and the resultant mixture was placed under at atmosphere of H_2 (5 atm) and stirred at rt for 40 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated in vacuo.

Step 2: The residue from the previous step was dissolved in 6.0 M aq HCl (2 mL) and the resultant mixture was stirred at rt for 3 h, then concentrated in vacuo. Purification via ion exchange chromatography (Dowex 50WX8 resin hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) gave **44** as a white solid (50 mg, 71% from **38**, >99:1 dr); mp 208–210 °C; $[\alpha]_D^{25}$ +18.1 (*c* 1.0 in H_2O); ν_{max} (ATR) 3328 (O–H, N–H) 1637 (C=O); δ_H (400 MHz, D_2O) 3.89 (1H, d, *J* 4.2, C(2)*H*), 5.29 (1H, d, *J* 4.2, C(3)*H*), 7.11 (1H, td, *J* 8.6, 2.5, C(4′)*H*), 7.18–7.26 (2H, m, C(2′)*H*, C(6′)*H*), 7.40–7.47 (1H, m, C(5′)*H*); δ_C (100 MHz, D_2O) 60.6 (*C*(2)), 70.7 (*C*(3)), 112.7 (d, *J* 22.7, *C*(2′)), 115.2 (d, *J* 21.1, *C*(4′)), 121.7 (d, *J* 2.5, *C*(6′)), 130.7 (d, *J* 8.5, *C*(5′)), 141.9 (d, *J* 7.1, *C*(1′)), 162.8 (d, *J* 244.5, *C*(3′)), 171.8 (*C*(1)); δ_F (377 MHz, D_2O) −112.9 (C(3′)*F*); *m/z* (ESI$^-$) 198 ([M−H]$^-$, 100%); HRMS (ESI$^+$) $C_9H_{11}FNO_3^+$ ([M+H]$^+$) requires 200.0717; found 200.0719.

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4.26. (2R,3S)-2-Amino-3-hydroxy-3-(4′-fluorophenyl)propanoic acid **45**

Step 1: $Pd(OH)_2/C$ (24 mg, 20% w/w) was added to a stirred, degassed solution of **39** (121 mg, 0.27 mmol, >99:1 dr) in MeOH (2 mL) at rt and the resultant mixture was placed under at atmosphere of H_2 (5 atm) and stirred at rt for 40 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated in vacuo.

Step 2: The residue from the previous step was dissolved in 6.0 M aq HCl (2 mL) and the resultant mixture was stirred at rt for 3 h, then concentrated in vacuo. Purification via ion exchange chromatography (Dowex 50WX8 resin hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) gave **45** as a white solid (52 mg, 97% from **39**, >99:1 dr); [44] mp 232–234 °C; {lit.[44] mp 207–208 °C (dec.)}; $[\alpha]_D^{25}$ +17.9 (*c* 1.0 in H_2O); {lit.[44] $[\alpha]_D^{25}$ +20.5 (*c* 0.21 in H_2O)}; ν_{max} (ATR) 3271 (O–H, N–H), 1611 (C=O); δ_H (400 MHz, D_2O) 3.88 (1H, d, *J* 4.6, C(2)*H*), 5.26 (1H, d, *J* 4.6, C(3)*H*), 7.18 (2H, app t, *J* 9.0, C(3′)*H*, C(5′)*H*), 7.43–7.47 (2H, m, C(2′)*H*, C(6′)*H*); δ_C (100 MHz, D_2O) 60.8 (*C*(2)), 70.8 (*C*(3)), 115.6 (d, *J* 21.4, *C*(3′), *C*(5′)), 127.8 (d, *J* 8.8, *C*(2′), *C*(6′)), 135.0 (d, *J* 3.4, *C*(1′)), 162.4 (d, *J* 244.7, *C*(4′)), 171.9 (*C*(1)); δ_F (377 MHz, D_2O) −114.5 (C(4′)*F*); *m/z* (ESI^-) 198 ($[M-H]^-$, 100%); HRMS (ESI^+) $C_9H_{11}FNO_3^+$ ($[M+H]^+$) requires 200.0717; found 200.0718.

4.27. tert-Butyl (2S,3S,αR)-2-[N-benzyl-N-(α-methylbenzyl) amino]-3-fluorobutanoate **46** and tert-butyl (2S,3R,αR)-2-fluoro-3-[N-benzyl-N-(α-methylbenzyl)amino]butanoate **48**

$Et_3N{\cdot}3HF$ (304 μL, 1.85 mmol) was added to a stirred solution of **20** (400 mg, 1.08 mmol, >99:1 dr) and XtalFluor-E® (318 mg, 1.39 mmol) in CH_2Cl_2 (0.62 mL) at rt, and the resultant mixture was stirred at rt for 2 h. 5% aq $NaHCO_3$ (1 mL) was added and the resultant mixture was stirred at rt for 15 min, then extracted with CH_2Cl_2 (2 × 3 mL). The combined organic extracts were dried, then filtered through a pad of silica (eluent CH_2Cl_2) and concentrated in vacuo to give an 80:20 mixture of **46** and **48**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 40:1) gave **46** as a colourless oil (261 mg, 65%, >99:1 dr); $[\alpha]_D^{25}$ +49.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1719 (C=O), δ_H (500 MHz, $CDCl_3$) 1.15 (3H, d, *J* 6.9, C(α)*Me*), 1.22 (3H, dd, *J* 24.0, 6.3, C(4)H_3), 1.28 (9H, s, CMe_3), 3.29 (1H, dd, *J* 19.6, 6.8, C(2)*H*), 3.92 (1H, d, *J* 16.1, NCH_AH$_B$Ph), 3.98 (1H, q, *J* 6.9, C(α)*H*), 4.19 (1H, d, *J* 16.1, NCH$_A$$H_B$Ph), 4.79–4.85 (1H, m, C(3)*H*), 7.09–7.40 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 18.4 (d, *J* 21.9, *C*(4)), 21.0 (C(α)*Me*), 28.1 (CMe_3), 52.7 (NCH_2Ph), 60.4 (*C*(α)), 66.1 (d, *J* 20.0, *C*(2)), 81.4 (CMe_3), 89.7 (d, *J* 172.6, *C*(3)), 126.4, 127.0, 127.8, 127.8, 128.2, 128.3 (*o*,*m*,*p*-*Ph*), 142.5, 144.1 (*i*-*Ph*), 170.4 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −180.1 (C(3)*F*); *m/z* (ESI^+) 372 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{23}H_{31}FNO_2^+$ ($[M+H]^+$) requires 372.2333; found 372.2337. Further elution gave **48** as a colourless oil (51 mg, 13%, >99:1 dr); [33] $[\alpha]_D^{25}$ −31.0 (*c* 0.1 in $CHCl_3$); ν_{max} (ATR) 1753 (C=O), 1160 (C–F); δ_H (500 MHz, $CDCl_3$) 1.10 (3H, *J* 6.8, C(4)H_3), 1.26 (3H, d, *J* 6.8, C(α)*Me*), 1.37 (9H, s, CMe_3), 3.28–3.38 (1H, m, C(3)*H*), 3.70 (1H, d, *J* 14.7, NCH_AH$_B$Ph), 3.84 (1H, d, *J* 14.7, NCH$_A$$H_B$Ph), 4.06 (1H, q, *J* 6.8, C(α)*H*), 4.52 (1H, dd, *J* 49.2, 5.7, C(2)*H*) 7.11–7.34 (10H, m, *Ph*); δ_F (377 MHz, $CDCl_3$) −192.1 (C(2)*F*); *m/z* (ESI^+) 372 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{23}H_{31}FNO_2^+$ ($[M+H]^+$) requires 372.2333; found 372.2337.

4.28. tert-Butyl (2S,3R,αR)-2-fluoro-3-[N-benzyl-N-(α-methylbenzyl)amino]-4-methylpentanoate **49**

$Et_3N{\cdot}3HF$ (82 μL, 503 μmol) was added to a stirred solution of **21** (100 mg, 251 μmol, >99:1 dr) and XtalFluor-E® (86 mg, 38 μmol) in CH_2Cl_2 (170 μL) at rt, and the resultant mixture was stirred at rt for 2 h. 5% aq $NaHCO_3$ (1 mL) was added and the resultant mixture was stirred at rt for 15 min, then extracted with CH_2Cl_2 (2 × 1 mL). The combined organic extracts were dried, then filtered through a pad of silica (eluent CH_2Cl_2) and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 50:1) gave a **49** as a colourless oil (60 mg, 60%, >99:1 dr); $[\alpha]_D^{25}$ −4.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1732 (C=O); δ_H (400 MHz, $CDCl_3$) 0.94 (3H, d, *J* 6.6, C(4)Me_A), 0.95 (3H, d, *J* 6.6, C(4)Me_B), 1.27 (3H, d, *J* 6.9, C(α)*Me*), 1.52 (9H, s, CMe_3), 1.94 (1H, septet, *J* 6.9, C(4)*H*) 3.09 (1H, ddd, *J* 26.4, 6.9, 3.8, C(3)*H*), 4.00 (1H, d, *J* 15.7, NCH_AH$_B$Ph), 4.08–4.16 (2H, m, C(α)*H*, NCH_AH$_B$Ph), 4.82 (1H, dd, 47.7, 3.8, C(2)*H*), 7.17–7.46 (10H, m, *Ph*); *m/z* (ESI^+) 400 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{25}H_{35}FNO_2^+$ ($[M+H]^+$) requires 400.2646; found 400.2642.

4.29. tert-Butyl (2S,3S,αR)-2-[N-benzyl-N-(α-methylbenzyl) amino]-3-fluoro-3-phenylpropanoate **50**

$Et_3N{\cdot}3HF$ (304 μL, 1.85 mmol) was added to a stirred solution of **34** (400 mg, 0.93 mmol, >99:1 dr) and XtalFluor-E® (318 mg, 1.39 mmol) in CH_2Cl_2 (0.62 mL) at rt, and the resultant mixture was stirred at rt for 2 h. 5% aq $NaHCO_3$ (1 mL) was added and the resultant mixture was stirred at rt for 15 min, then extracted with CH_2Cl_2 (2 × 3 mL). The combined organic extracts were dried, then filtered through a pad of silica (eluent CH_2Cl_2) and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 40:1) gave **50** as a colourless oil (346 mg, 86%, >99:1 dr); $[\alpha]_D^{25}$ +51.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1720 (C=O), 1146 (C–F); δ_H (500 MHz, $CDCl_3$) 1.11 (9H, s, CMe_3), 1.30 (3H, d, *J* 6.9, C(α)*Me*), 3.85 (1H, dd, *J* 15.5, 8.7, C(2)*H*), 4.00 (1H, d, *J* 15.8, NCH_AH$_B$Ph), 4.12 (1H, q, *J* 6.9, C(α)*H*), 4.45 (1H, d, *J* 15.8, NCH$_A$$H_B$Ph), 5.62 (1H, dd, *J* 47.8, 8.7, C(3)*H*), 7.18–7.43 (15H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 20.4 (C(α)*Me*), 28.1 (CMe_3), 51.8 (NCH_2Ph), 59.9 (*C*(α)), 66.6 (d, *J* 22.8, *C*(2)), 81.2 (CMe_3)$_3$, 92.9 (d, *J* 178.3, *C*(3)), 126.5, 127.0, 127.2 (*p*-*Ph*), 127.3, 127.9, 128.2, 128.3, 128.3, 128.4 (*o*,*m*-*Ph*), 137.0, 142.1, 144.0 (*i*-*Ph*), 169.3 (*C*(1)); δ_F (377 MHz, $CDCl_3$) −178.7 (C(3)*F*); *m/z* (ESI^+) 434 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{28}H_{33}FNO_2^+$ ($[M+H]^+$) requires 434.2490; found 434.2492.

4.30. tert-Butyl (2S,3S,αR)-2-[N-benzyl-N-(α-methylbenzyl) amino]-3-fluoro-3-(3′-fluorophenyl)propanoate **51**

$Et_3N{\cdot}3HF$ (0.15 mL, 0.89 mmol) was added to a stirred solution of **35** (200 mg, 0.445 mmol, >99:1 dr) and Xtal-FluorE® (153 mg, 0.667 mmol) in CH_2Cl_2 (1.2 mL) at rt, and the resultant mixture was stirred at rt for 2 h. 5% aq $NaHCO_3$ (3 mL) was added and the resultant mixture was stirred at rt for 15 min, then extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried, then filtered through a pad of silica (eluent CH_2Cl_2) and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 30:1 to 10:1) gave **51** as a pale yellow oil (142 mg, 70%, >99:1 dr); $[\alpha]_D^{25}$ +69.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1720 (C=O), 1147 (C–F); δ_H (500 MHz, $CDCl_3$) 1.21 (9H, s, CMe_3), 1.31 (3H, d, *J* 6.9, C(α)*Me*), 3.81 (1H, dd, *J* 16.6, 8.2, C(2)*H*), 4.05 (1H, d, *J* 15.9, NCH_AH$_B$Ph), 4.15 (1H, q, *J* 6.9, C(α)*H*), 4.43 (1H, d, *J* 15.9, NCH$_A$$H_B$Ph), 5.66 (1H, dd, *J* 47.3, 8.2, C(3)*H*), 6.92 (1H, d, *J* 10.2, C(2′)*H*), 6.97–7.04 (2H, m, C(4′)*H*, C(6′)*H*), 7.22–7.29 (3H, m, C(5′)*H*, *Ph*), 7.31–7.37 (6H, m, *Ph*), 7.42 (2H, d, *J* 7.5, *Ph*); δ_C (125 MHz, $CDCl_3$) 20.4 (C(α)*Me*), 27.8 (CMe_3), 52.0 (NCH_2Ph), 60.1 (*C*(α)), 66.5 (d, *J* 23.9, *C*(2)), 81.6 (CMe_3), 92.3 (dd, *J* 178.9, 1.9, *C*(3)), 114.1 (dd, *J* 22.6, 6.7, *C*(2′)), 115.5 (d, *J* 21.2, *C*(4′)), 122.7 (dd, *J* 6.6, 2.9, *C*(6′)), 126.6, 127.1, 127.9, 127.9, 128.2, 128.3 (*o*,*m*,*p*-*Ph*), 129.8 (d, *J* 7.6, *C*(5′)), 139.7 (dd, *J* 20.3, 7.3, *C*(1′)), 162.6 (d, *J* 246.0, *C*(3′)), 169.2 (d, *J* 10.5, *C*(1)); δ_F (472 MHz, $CDCl_3$) −181.2 (C(3)*F*), −113.0 (C(3′)*F*); *m/z* (ESI^+) 452

([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{32}F_2NO_2^+$ ([M+H]$^+$) requires 452.2396; found 452.2390.

4.31. *tert*-Butyl (2*S*,3*S*,α*R*)-2-[*N*-benzyl-*N*-(α-methylbenzyl) amino]-3-fluoro-3-(4′-fluorophenyl)propanoate **52** and (3*R*,4*S*,α*R*)-*N*(2)-(α-methylbenzyl)-3-(*tert*-butoxycarbonyl)-4-(4′-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline **55**

$Et_3N\cdot 3HF$ (0.44 mL, 2.67 mmol) was added to a stirred solution of **36** (400 mg, 0.890 mmol, >99:1 dr) and Xtal-FluorE® (307 mg, 1.34 mmol) in CH_2Cl_2 (2.4 mL) at rt, and the resultant mixture was stirred at rt for 2 h. 5% aq $NaHCO_3$ (3 mL) was added and the resultant mixture was stirred at rt for 15 min, then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried, then filtered through a pad of silica (eluent CH_2Cl_2) and concentrated in vacuo to give a 57:43 mixture of **52** and **55**, respectively. Purification via flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O/1.0 M aq NH_4OH, 100:3:1) gave **52** as a pale yellow oil (132 mg, 33%, >99:1 dr); $[\alpha]_D^{25}$ +62.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1720 (C=O), 1140 (C–F); δ_H (400 MHz, $CDCl_3$) 1.18 (9H, s, C*Me*$_3$), 1.32 (3H, d, *J* 6.8, C(α)*Me*), 3.82 (1H, dd, *J* 15.0, 8.7, C(2)*H*), 4.01 (1H, d, *J* 15.8, NC*H*$_A$H$_B$Ph), 4.15 (1H, q, *J* 6.8, C(α)*H*), 4.44 (1H, d, *J* 15.8, NCH$_A$*H*$_B$Ph), 5.62 (1H, dd, *J* 47.3, 8.7, C(3)*H*), 6.99 (2H, app t, *J* 8.5, C(3′)*H*, C(5′)*H*), 7.15–7.41 (10H, m, *Ar*), 7.45 (2H, d, *J* 7.7, *Ar*); δ_C (100 MHz, $CDCl_3$) 20.4 (C(α)*Me*), 27.7 (C*Me*$_3$), 51.7 (NCH_2Ph), 60.0 (*C*(α)), 66.6 (d, *J* 24.3, *C*(2)), 81.4 (*C*Me$_3$), 92.1 (d, *J* 178.2, *C*(3)), 115.1 (d, *J* 21.6, *C*(3′), *C*(5′)), 126.5, 127.0, 127.9, 127.9, 128.1, 128.2 (*o*,*m*,*p*-*Ph*), 129.0 (dd, *J* 8.3, 5.9, *C*(2′), *C*(6′)), 141.9, 143.9 (*i*-*Ph*), 162.9 (d, *J* 247.5, *C*(4′)), 169.2 (d, *J* 11.4, *C*(1)); δ_F (377 MHz, $CDCl_3$) −177.8 (C(3)*F*), −113.0 (C(4′)*F*); *m*/*z* (ESI$^+$) 452 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{32}F_2NO_2^+$ ([M+H]$^+$) requires 452.2396; found 452.2389. Further elution gave **55** as a white solid (119 mg, 36%, >99:1 dr); mp 111–114 °C; $[\alpha]_D^{25}$ +19.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1729 (C=O); δ_H (400 MHz, $CDCl_3$) 1.22 (9H, s, C*Me*$_3$), 1.50 (3H, d, *J* 6.6, C(α)*Me*), 3.61 (1H, d, *J* 6.2, C(3)*H*), 3.81 (1H, q, *J* 6.6, C(α)*H*), 4.26 (2H, app s, C(1)H_2), 4.46 (1H, d, *J* 6.2, C(4)*H*), 6.88–7.44 (13H, m, *Ar*, *Ph*); δ_C (100 MHz, $CDCl_3$) 22.0 (C(α)*Me*), 28.0 (C*Me*$_3$), 47.6 (*C*(4)), 48.0 (*C*(1)), 62.3 (*C*(α)), 64.2 (*C*(3)), 80.7 (*C*Me$_3$), 114.8 (d, *J* 21.1, *C*(3′), *C*(5′)), 125.7, 125.9, 126.2, 127.1, 128.0, 128.4 (*o*,*m*,*p*-*Ph*, *C*(5)–*C*(8)), 132.0 (d, *J* 7.9, *C*(2′), *C*(6′)), 134.9 (*C*(4a)), 135.6 (*C*(8a)), 135.6 (d, *J* 3.2, *C*(1′)), 145.0 (*i*-*Ph*) 161.8 (d, *J* 244.9, *C*(4′)), 169.2 (*C*O$_2^t$Bu); δ_F (377 MHz, $CDCl_3$) −116.1 (C(4′)*F*); *m*/*z* (ESI$^+$) 432 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{31}FNO_2^+$ ([M+H]$^+$) requires 432.2333; found 432.2335.

4.32. (*S*,*S*)-2-Amino-3-fluorobutanoic acid **56**

Step 1: $Pd(OH)_2$/C (22 mg, 25% w/w) was added to a stirred, degassed solution of **46** (89 mg, 0.21 mmol, >99:1 dr) in MeOH (1 mL) at rt and the resultant mixture was placed under an atmosphere of H_2 (5 atm) and stirred at rt for 8 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated in vacuo.

Step 2: The residue from the previous step was dissolved in 6.0 M aq HCl (1 mL) and the resultant solution was stirred at rt for 3 h, then concentrated in vacuo. Purification via ion exchange chromatography (Dowex 50WX8 resin hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) gave **56** as a white solid (13 mg, 46% from **46**, >99:1 dr); [14a] mp 192–194 °C; {lit.[14a] for *ent*-**56** mp 193–194 °C}; $[\alpha]_D^{25}$ +16.4 (*c* 1.0 in 1 N HCl); {lit.[14a] for *ent*-**56**: $[\alpha]_D^{23}$ −16.2 (*c* 1.0 in 1 N HCl)}; ν_{max} (ATR) 1602 (C=O); δ_H (500 MHz, MeOH-d_4) 1.46 (3H, dd, *J* 25.1, 6.6, C(4)H_3), 3.80 (1H, dd, *J* 25.4, 4.4, C(2)*H*), 5.10–5.24 (1H, m, C(3)*H*); δ_C (125 MHz, MeOH-d_4) 17.1 (d, *J* 21.9, *C*(4)), 58.7 (d, *J* 21.0, *C*(2)), 90.0 (d, *J* 170.7, *C*(3)), 170.1 (d, *J* 4.8, *C*(1)); δ_F (377 MHz, MeOH-d_4) −183.7 (C(3)*F*); *m*/*z* (ESI$^+$) 122 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_4H_9FNO_2^+$ ([M+H]$^+$) requires 122.0612; found 122.0613.

4.33. (*S*,*S*)-2-Amino-3-fluoro-3-phenylpropanoic acid [(*S*,*S*)-β-fluorophenylalanine] **57**

Step 1: A solution of $NaBrO_3$ (157 mg, 1.04 mmol) in H_2O (3.5 mL) was added to a stirred solution of **50** (150 mg, 0.35 mmol, >99:1 dr) in EtOAc (4.8 mL) at rt, and the resultant mixture was stirred at rt for 10 min. A solution of $Na_2S_2O_4$ (151 mg, 0.87 mmol) in H_2O (6.3 mL) was added dropwise at rt over 15 min and the resultant mixture was stirred at rt for 4 h. EtOAc (8 mL) was added and the resultant mixture was washed with satd aq $Na_2S_2O_3$ (5 mL). The aqueous layer was extracted with EtOAc (2 × 4 mL) and the combined organic extracts were washed with brine (10 mL), then dried and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (10 mL) and the resultant mixture was extracted with 1.0 M aq HCl (3 × 8 mL), then the combined aqueous extracts were concentrated in vacuo.

Step 2: The residue from the previous step was dissolved in ^{i}PrOH (0.69 mL). Propylene oxide (30 μL, 0.546 mmol) was added and the resultant mixture was stirred at rt for 6 h, then concentrated in vacuo to give **57** as a white solid (14 mg, 62% from **50**, >99:1 dr); [17] mp 151–161 °C; {lit.[17] mp 149–150 °C}; $[\alpha]_D^{25}$ −13.1 (*c* 0.4 in MeOH); {lit.[17] $[\alpha]_D^{23}$ −14.5 (*c* 0.4 in MeOH)}; ν_{max} (ATR) 1618 (C=O); δ_H (400 MHz, MeOH-d_4) 3.90 (1H, dd, *J* 27.0, 3.9, C(2)*H*), 6.03 (1H, dd, *J* 44.9, 3.9, C(3)*H*), 7.31–7.40 (5H, m, *Ph*); δ_C (100 MHz, MeOH-d_4) 65.4 (*C*(2)), 97.8 (d, *J* 178.4, *C*(3)), 126.1, 129.0, 129.0 (*o*,*m*,*p*-*Ph*), 129.2 (*i*-*Ph*), 174.8 (*C*(1)); δ_F (377 MHz, MeOH-d_4) −194.3 (C(3)*F*); *m*/*z* (ESI$^+$) 184 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_9H_{11}FNO_2^+$ ([M+H]$^+$) requires 184.0768; found 184.0770.

4.34. (*S*,*S*)-2-Amino-3-fluoro-3-(3′-fluorophenyl)propanoic acid **58**

Step 1: A solution of $NaBrO_3$ (124 mg, 0.824 mmol) in H_2O (2.8 mL) was added to a stirred solution of **51** (124 mg, 0.275 mmol, >99:1 dr) in EtOAc (3.7 mL) at rt, and the resultant mixture was stirred at rt for 10 min. A solution of $Na_2S_2O_4$ (120 mg, 0.69 mmol) in H_2O (5 mL) was added dropwise over 5 min and the resultant mixture was stirred at rt for 4 h. EtOAc (5 mL) was then added and the organic layer was washed with satd aq $Na_2S_2O_3$ (5 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL) and the combined organic extracts were washed with brine (10 mL), then dried and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (5 mL) and washed with 1.0 M aq HCl (5 × 5 mL) then the combined aqueous layers were concentrated in vacuo.

Step 2: The residue from the previous step was dissolved in ^{i}PrOH (1.4 mL). Propylene oxide (0.08 mL, 1.10 mmol) was added and the resultant mixture was stirred at rt for 6 h, then concentrated in vacuo to give **58** as a white solid (31 mg, 56% from **51**, >99:1 dr); mp 148–150 °C (dec.); $[\alpha]_D^{25}$ +16.8 (*c* 1.0 in H_2O); ν_{max} (ATR) 3374 (O–H, N–H), 1636 (C=O), 1150 (C–F); δ_H (400 MHz, D_2O) 4.19 (1H, dd, *J* 21.8, 4.0, C(2)*H*), 6.18 (1H, dd, *J* 44.5, 4.0, C(3)*H*), 7.17–7.27 (3H, m, C(2′)*H*, C(4′)*H*, C(6′)*H*), 7.46–7.55 (1H, m, C(5′)*H*); δ_C (125 MHz, D_2O) 59.2 (d, *J* 23.2, *C*(2)), 91.2 (dd, *J* 178.1, 1.4, *C*(3)), 112.3 (dd, *J* 23.8, 9.5, *C*(2′)), 116.3 (d, *J* 20.6, *C*(4′)), 121.1 (dd, *J* 8.5, 2.9, *C*(6′)), 131.1 (d, *J* 8.6, *C*(5′)), 136.9 (dd, *J* 21.5, 7.6, *C*(1′)), 162.8 (d, *J* 245.7, *C*(3′)), 169.9 (d, *J* 4.0, *C*(1)); δ_F (377 MHz, D_2O) −192.9 (C(3)F), −112.3 (C(3′)*F*); *m*/*z* (ESI$^-$) 200 ([M−H]$^-$, 100%); HRMS (ESI$^-$) $C_9H_{10}F_2NO_2^+$ ([M+H]$^+$) requires 202.0674; found 202.0675.

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4.35. (S,S)-2-Amino-3-fluoro-3-(4′-fluorophenyl)propanoic acid **59**

Step 1: A solution of $NaBrO_3$ (132 mg, 0.877 mmol) in H_2O (2.9 mL) was added to a stirred solution of **52** (132 mg, 0.292 mmol, >99:1 dr) in EtOAc (3.9 mL) at rt, and the resultant mixture was stirred at rt for 10 min. A solution of $Na_2S_2O_4$ (125 mg, 0.731 mmol) in H_2O (5.3 mL) was then added dropwise over 5 min at rt and the resultant mixture was stirred at rt for 4 h, then EtOAc (10 mL) was added. The organic layer was washed with satd aq $Na_2S_2O_3$ (10 mL), the aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were washed with brine (25 mL), then dried and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (5 mL) and washed with 1.0 M aq HCl (5 × 5 mL), then the combined aqueous layers were concentrated in vacuo.

Step 2: The residue from the previous step was dissolved in ^{i}PrOH (1.5 mL) and propylene oxide (0.08 mL, 1.2 mmol) was added at rt and the resultant mixture was stirred at rt for 6 h then concentrated in vacuo to give **59** as a pale yellow solid (28 mg, 48% from **52**, >99:1 dr); mp 190–194 °C; $[\alpha]_D^{25}$ +22.1 (*c* 1.0 in H_2O); ν_{max} (ATR) 3217 (N–H), 1611 (C=O), 1103 (C–F); δ_H (400 MHz, D_2O) 4.19 (1H, dd, *J* 26.0, 4.7, C(2)*H*), 6.13 (1H, dd, *J* 44.7, 4.7, C(3)*H*), 7.25 (1H, app t, *J* 8.6, C(3′)*H*, C(5′)*H*), 7.48 (2H, dd, *J* 8.6, 5.3, C(2′)*H*, C(6′)*H*); δ_C (125 MHz, $CDCl_3$) 59.4 (d, *J* 23.0, *C*(2)), 91.5 (d, *J* 176.9, *C*(3)), 115.9 (d, *J* 22.2, *C*(3′), *C*(5′)), 127.5 (app t, *J* 8.4, *C*(2′), *C*(6′)), 130.4 (dd, *J* 20.9, 2.9, *C*(1′)), 163.0 (d, *J* 246.0, *C*(4′)), 170.0 (d, *J* 4.6, *C*(1)); δ_F (377 MHz, D_2O) −189.6 (C(3)*F*), −112.7 (C(4′)*F*); *m/z* (ESI$^-$) 200 ([M−H]$^-$, 100%); HRMS (ESI$^-$) $C_9H_8F_2NO_2^-$ ([M−H]$^-$) requires 200.0529; found 200.0528.

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