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An Expeditious Asymmetric Synthesis of Allophenylnorstatine

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Abstract: Allophenylnorstatine [APNS; (2*S*,3*S*)-3-amino-2-hydroxy-4-phenylbutanoic acid], a novel amino acid found in the kynostatin class of HIV-1 protease inhibitors, has been prepared in 39% overall yield *via* a tandem conjugate addition-electrophilic hydroxylation protocol using lithium (*S*)-(α-methylbenzyl)benzylamide and (+)-(camphorsulfonyl)oxaziridine. An unprecedented level of molecular recognition between a homochiral β-amino enolate and a homochiral oxaziridine is identified and the importance of enolate geometry upon hydroxylation stereoselectivity is also addressed.

β-Amino-α-hydroxy acids are becoming increasingly prevalent as components of compounds with exciting therapeutic potential. Many pseudopeptidic protease inhibitors, both designed and naturally occurring, derive their efficacy from the ability of the β-amino-α-hydroxy acid motif to act as a transition state mimic of peptide hydrolysis. Thus, consideration of the proposed intermediate for amide hydrolysis by, for example, an aspartic protease (such as human renin) suggests that the β-amino-α-hydroxy acid moiety may prevent peptide scission by acting as a hydroxymethylcarbonyl (HMC) isostere (Figure 1).[1] In light of the intimate interaction between such an isostere and the protease active site, one might expect that the configuration of the α- and β-stereogenic centres would have a marked effect upon inhibitory activity and this hypothesis has been validated by numerous experimental observations. Consequently, the efficient asymmetric synthesis of β-amino-α-hydroxy acid derivatives of defined absolute and relative stereochemistry for incorporation into such inhibitors is particularly desirable.

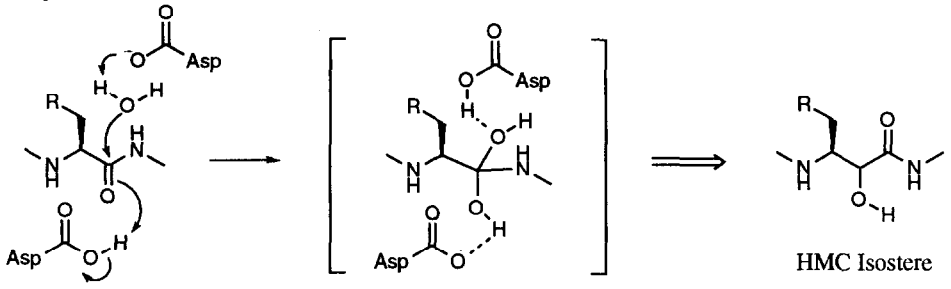
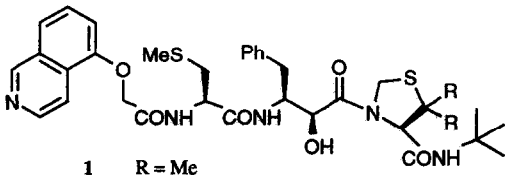
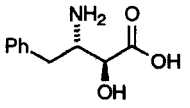


Figure 1

The human immunodeficiency virus HIV-1 codes for an aspartic protease essential for viral replication and maturation. Consequently, selective inhibitors of HIV-1 protease offer promise as anti-AIDS drugs and are attracting increasing interest.[2] A number of HIV-1 protease inhibitors[3] have been discovered and amongst the most potent are the kynostatins (KNI)-227 **1** and (KNI)-272 **2** designed by Kiso and co-workers.[4]



1 R = Me
2 R = H



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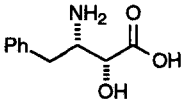

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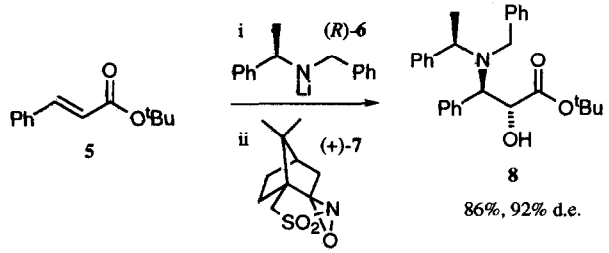
The unusual amino acid allophenylnorstatine (APNS) **3** has been identified as the most effective HMC isostere in the kynostatin inhibitors; it has been demonstrated that replacement of **3** with its α-epimer phenylnorstatine **4** leads to a dramatic reduction in activity.[1,4,5] Interestingly, this stereochemical preference is different to that observed for a variety of renin inhibitors[6] and the well-known immunological response modifier bestatin.[7] Evidently, an efficient asymmetric synthesis of APNS would be of particular benefit in the synthesis and development of the kynostatins and related inhibitors[8] as medicinally useful anti-AIDS drugs. We describe herein full details of the first convenient and highly stereoselective synthesis of APNS **3**.[9,10]

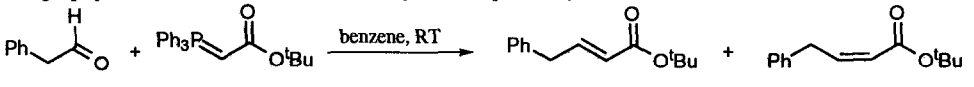
The propensity for the homochiral lithium amides derived from (*R*)- or (*S*)-(α-methylbenzyl)benzylamine to undergo highly diastereoselective conjugate additions to a variety of enoate substrates has been developed into a general protocol for the synthesis of homochiral β-amino acids.[11,12] Furthermore, we have demonstrated that *in situ* hydroxylation of the resultant β-amino enolates can occur with excellent levels of 1,2-asymmetric induction to afford the *anti* diastereoisomer of the corresponding β-amino-α-hydroxy acid derivative.[13,14] For example, during our early studies related to the synthesis of the taxol side chain,[13] we discovered that the tandem addition-hydroxylation of *tert*-butyl cinnamate **5** using lithium (*R*)-(α-methylbenzyl)benzylamine (*R*)-**6** and (+)-(camphorsulfonyl)oxaziridine (+)-**7** afforded **8** with excellent diastereoselectivity (92% d.e.) (Scheme 1).



5 8 86%, 92% d.e.

Scheme 1

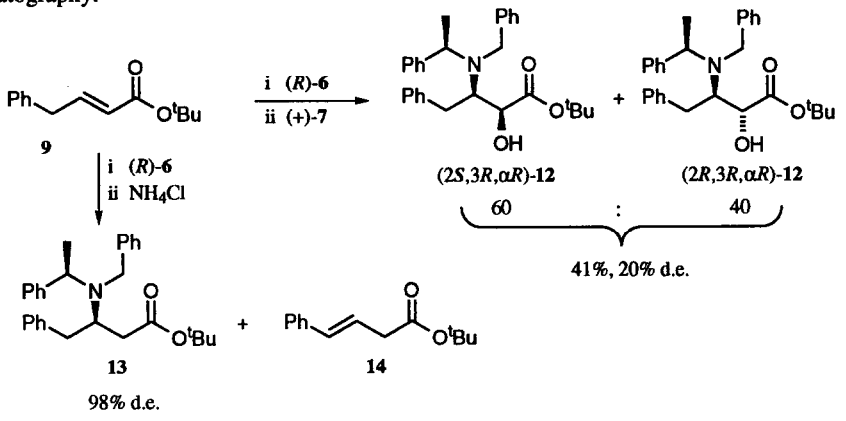
Encouraged by the above result, we anticipated that the corresponding tandem addition-hydroxylation of the homologous ester **9** would proceed in an analogous fashion to give rise to the *anti* relative stereochemistry necessary for a direct synthesis of APNS (either *enantiomeric* series being available through the appropriate choice of homochiral lithium amide). Firstly, the apparently unreported enoate **9** was prepared in good selectivity (8:1 *E*:*Z*) by a standard Wittig reaction using the readily available phosphorane[15] **10** and phenylacetaldehyde (Scheme 2). The *E* and *Z* stereoisomers **9** and **11** were readily separable by flash chromatography and recovered in 59% and 6% yields respectively.



10 9 59% 8:1 *E*:*Z* 11 6%

Scheme 2

The conjugate addition-hydroxylation reaction using **9** was attempted under identical conditions to those previously employed for the preparation of **8** but the product **12** was secured with only poor α-centre stereoselectivity (20% d.e.) (Scheme 3); furthermore, these diastereoisomers were found to be inseparable by flash chromatography.



Scheme 3

The stereochemical integrity of the β-stereogenic centre was confirmed by a standard lithium amide addition followed by protic work-up (Scheme 3). As expected the β-amino ester adduct **13** was formed with excellent diastereoselectivity (98% d.e.), however the crude ^{1}H nmr spectrum also indicated the generation of a by-product (*ca.* 20%) which was later confirmed as the rearranged starting material **14**. Unfortunately, this by-product could not be separated from **13** by flash chromatography. The formation of **14** is evidently the result of competing γ-proton abstraction of the relatively acidic benzylic protons in the enoate **9** by the lithium amide. The observation that conjugate addition of the lithium amide was still the favoured reaction pathway, even when presented with such acidic γ-protons, is consistent with a six-membered chelated addition to the enoate in an *s-cis* conformation[16] (Figure 2): the restraint of chelation would appear to render the γ-protons too remote for abstraction.

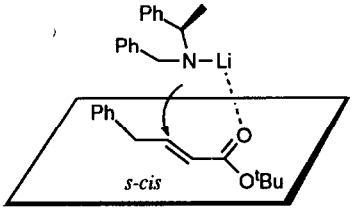
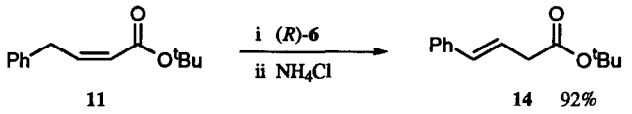


Figure 2

In contrast to the *E* stereoisomer **9**, it was anticipated that the γ-methylene protons in **11** would be ideally situated for abstraction by such a chelated lithium amide. Thus, treatment of **11** with the lithium amide (*R*)-**6**, and protic work-up, was attempted under conditions analogous to those employed previously for the addition to **9**. Analysis of the crude ^{1}H nmr spectrum for this reaction indicated the *exclusive* formation of the rearranged starting material **14**: no evidence of any addition products could be observed. The product **14** was readily isolated in 92% yield by flash chromatography.

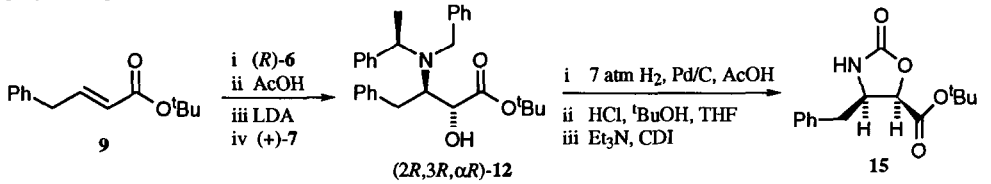


11 14 92%

Scheme 4

We have recently reported[17] that the homochiral *magnesium* amide (R_2NMgBr) analogous to (*R*)-**6** also undergoes highly diastereoselective conjugate additions to enoate acceptors and it was of interest to ascertain whether the utilisation of this reagent would circumvent γ-deprotonation of the substrate **9**. Unfortunately, although the addition of the magnesium amide to **9** afforded **13** with excellent diastereoselectivity (>90% d.e.), the proportion of the by-product **14** was approximately the same (*ca. 22%*) as previously observed with the alternative lithium amide and the reaction was not pursued.

With the stereochemical integrity of the β-stereogenic centre in **12** assured, attention was directed to factors affecting the π-facial selectivity of hydroxylation of the intermediate β-amino enolate. We have previously reported that deprotonation of preformed β-amino esters related to **13** results in formation of the enolate of opposite geometry to that obtained in the tandem process.[12] Thus, the enolate derived from the deprotonation of **13** might be expected to undergo hydroxylation with a different level of α-centre stereoselectivity to that secured in the aforementioned tandem procedure. In order to avoid the problematic isolation of the conjugate adduct **13**, a 'one-pot' stepwise hydroxylation procedure was devised. Hence, the enolate formed by the initial addition of (*R*)-**6** to **9** was quenched with acetic acid to afford the β-amino ester **13**, which was then deprotonated *in situ* with LDA and quenched with (+)-**7** (Scheme 5). Remarkably, this stepwise protocol resulted in excellent control of the α-centre stereoselectivity to afford (2*R*,3*R*,α*R*)-**12** as a single diastereoisomer (≥95% d.e.) which was readily isolated by flash chromatography in 49% yield (Scheme 5). Interestingly, this material was seen to be the 'minor' diastereoisomer obtained in the alternative tandem protocol described above (Scheme 3) and it thus appears that the configuration of the intermediate β-amino enolate plays a major rôle in determining α-centre selectivity in this system.[18]



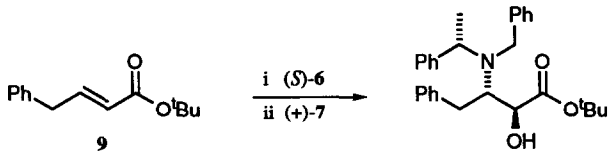
9 (2*R*,3*R*,α*R*)-**12** 49%, ≥95% d.e. **15** 23% J_{HH} = 8.6 Hz

Scheme 5

The *anti* stereochemistry of **12** was confirmed by catalytic debenzylation and conversion to the oxazolidinone **15** using carbonyl diimidazole (CDI). Analysis of the coupling constant for the ring protons in **15** (J = 8.6 Hz) was indicative of the *cis* stereochemistry[19] and this follows directly from the *anti* arrangement in (2*R*,3*R*,α*R*)-**12** (Scheme 5).

Although the above 'one-pot' stepwise procedure could be applied to a synthesis of APNS, a tandem procedure would evidently be much more convenient. We have previously noted that the excellent *anti* diastereoselectivity procured in the tandem addition-hydroxylation of *tert*-butyl cinnamate **5** using (*R*)-**6** and (+)-**7** (Scheme 1) could be further enhanced if the complementary pairing of homochiral reagents was employed.[13] Consequently, the tandem addition-hydroxylation of **9** described above (Scheme 3) was repeated using the alternative enantiomer of the lithium amide, whilst maintaining the oxaziridine configuration. Thus, **9** was

treated with (*S*)-**6** and the resultant β-amino enolate hydroxylated with (+)-**7** under otherwise identical conditions to those previously employed. Analysis of the crude product by ^{1}H nmr spectroscopy now indicated a *22:1 diastereoselectivity (91% d.e.) in favour of the anti diastereoisomer* (2*S*,3*S*,α*S*)-**12** (Scheme 6). Flash chromatography afforded the mixture of diastereoisomers in 63% yield.



(2*S*,3*S*,α*S*)-**12**
63%, 91% d.e.

Scheme 6

Evidently, the poor selectivity observed in the previous tandem procedure was a consequence of using the 'mismatched' pairing of homochiral reagents. Although the 'matched' pair of reagents in the tandem addition-hydroxylations of both **5** and **9** were thus the same, the degree of molecular recognition in the latter case is manifestly more significant. This unprecedented level of molecular recognition in the hydroxylation of a homochiral β-amino enolate with a homochiral oxaziridine was particularly surprising in light of our earlier studies[11] and a report from the Davis laboratory that the diastereoselectivity of hydroxylation using a related β-amino enolate was not influenced by the oxaziridine configuration.[20] Furthermore, the oxaziridine **7** has been found to exhibit only moderate enantiofacial differentiation in the hydroxylation of *achiral* ester enolates.[21]

The above observations suggest that the inherent diastereofacial bias of the β-amino enolates derived from the lithium amide addition to **9** is much lower than that obtained from the addition to **5** and the majority of other enoates investigated.[14] Indeed, in the 'mismatched' reaction described previously (Scheme 3), it appears that the oxaziridine exerted the overriding stereodirecting influence. Molecular modelling studies[22] on the purported chelated intermediate enolate resulting from the addition of (*S*)-**6** to (+)-**7** offer an insight into the possible origin of this effect. These studies suggest that the lowest energy conformation of the enolate situates the γ-phenyl group antiperiplanar to the nitrogen atom at the β-centre, as depicted below (Figure 3). Such a conformation allows the phenyl group to shield the lower face of the enolate from electrophilic attack, and consequently the usual preference for formation of the *anti* diastereoisomer would be attenuated. Under such circumstances the diastereofacial preference of the chiral reagent would be expected to become significant and any molecular recognition would thus be magnified. Indeed, **9** appears to be an exceptional substrate in this regard since replacement of the benzyl moiety with a phenyl (i.e. cinnamate) or methyl (i.e. crotonate) group, for example, would not allow such a shielding effect to come into operation. Although this model readily accounts for the attenuation of the *anti* stereodirecting effect of the substrate, it would not be straightforward to rationalise the diastereofacial preference for the chiral oxaziridine in such a system and consequently any *a priori* prediction of the preferred oxaziridine configuration would not be straightforward.

With the 'matched' pairing of reagents identified in the tandem procedure, a convenient and direct synthesis of APNS was now possible. Thus, the 22:1 mixture of diastereoisomers was debenzylated under standard conditions and the resultant free β-amino ester **16** was isolated by recrystallisation from hexane as a single diastereoisomer in 62% yield (Scheme 7). Treatment of **16** with trifluoroacetic acid (TFA) successfully removed the *tert*-butyl group to furnish the trifluoroacetate salt **17** in 90% isolated yield. The absolute and

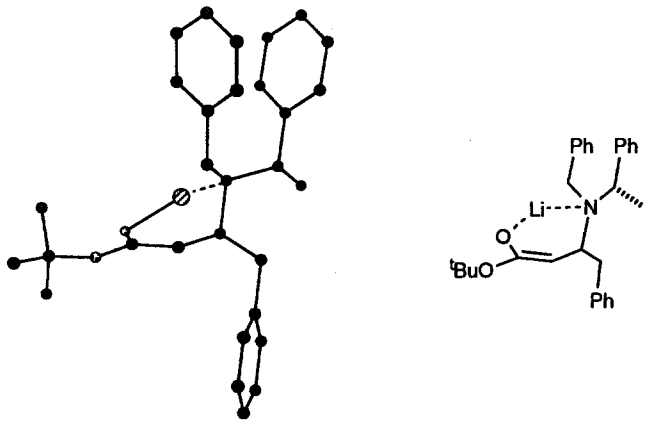
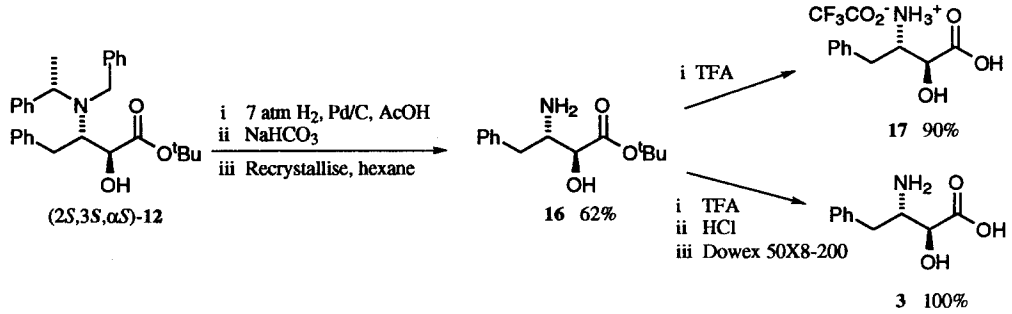


Figure 3: Proposed Model of β-Amino Enolate Intermediate in 'Matched Pair' Reaction

relative configuration within (2*S*,3*S*,α*S*)-**12** could now be confirmed by comparison of the specific rotation of **17** with the literature value: $[\alpha]_D^{20}$ -2.5 (*c* 0.59, 1N HCl) {lit.,[23] $[\alpha]_D^{24}$ -2.2 (*c* 0.67, 1N HCl)}.



Scheme 7

Finally, treatment of **16** with TFA, conversion to the hydrochloride salt, and subsequent ion exchange chromatography afforded the desired free amino acid homochiral APNS **3** in quantitative yield (Scheme 7) (39% overall from **9**): $[\alpha]_D^{20}$ -5.4 (*c* 0.51, 1N HCl).[24] The availability of such a direct and highly diastereoselective approach to allophenylnorstatine should be of benefit in the synthesis and development of the kynostatins and related protease inhibitors.

EXPERIMENTAL

General. Melting points were determined using either Gallenkamp or Koffler hot stage apparatus and are uncorrected. Specific rotations were recorded using a Perkin-Elmer 241 Polarimeter with a thermally jacketed 10 cm cell. IR spectra were obtained on a Perkin-Elmer 781 or Perkin-Elmer 1750 spectrophotometer with solution spectra generally being recorded in chloroform using 0.1 mm or 1.0 mm NaCl cells. Nmr spectra were generally recorded in deuteriochloroform and referenced with respect to residual protio solvent as internal standard. All chemical shifts are quoted in parts per million relative to tetramethylsilane (δ0.00 ppm), and coupling constants (*J*) are measured in Hertz. ^{1}H nmr spectra were recorded using Bruker WH300 or AM500 spectrometers and ^{13}C nmr spectra were recorded with DEPT editing as necessary using either the latter instrument or a Varian Gemini 200. Mass spectra were recorded on a VG MASSLAB VG 20-250 instrument

using the chemical ionisation (CI) technique. Elemental analyses were performed by the Dyson Perrins Laboratory analytical department. Flash column chromatography was undertaken on silica gel (kieselgel 60). Tetrahydrofuran was distilled from sodium benzophenone ketyl under an atmosphere of dry nitrogen. Petrol refers to that fraction of petroleum ether which boils in the range 40-60°C and was redistilled before use. Reactions involving lithium amides were performed under an atmosphere of dry nitrogen and reaction diastereoselectivities were determined by integration of the appropriate peaks in the ^{1}H nmr spectrum of the crude reaction product.

Preparation of (E)- *and* (Z)-tert-*Butyl* 4-*phenyl*-2-*butenoate* **9** *and* **11**. A stirred solution of the phosphorane **10** (4.87 g, 12.8 mmol) in benzene (20 cm^3) was treated with phenylacetaldehyde (1.43 cm^3, 12.2 mmol) and the resultant mixture stirred overnight. The solvent was evaporated under reduced pressure to afford an oily solid residue containing the title compound as a mixture of stereoisomers (8:1 *E*:*Z*). Purification of the residue by flash chromatography on silica gel (4% diethyl ether in petrol) afforded the minor *Z* stereoisomer **11** as a colourless oil (167 mg, 6%) and the more polar *E* stereoisomer **9**, also as a colourless oil (1.57 g, 59%); **9**: $\nu_{max}(CH_2Cl_2)$/cm^{-1} 1708vs (C=O), 1653s (C=C); δ_H (300 MHz; $CDCl_3$) 7.32-7.17 (5H, m, Ph), 7.00 (1H, dt, *J* 15.5, 6.8, CH_2CH=$CHCO_2$), 5.73 (1H, d, *J* 15.5, CH_2CH=$CHCO_2$), 3.50 (2H, d, *J* 6.8, CH_2CH=$CHCO_2$), 1.47 [9H, s, $CO_2C(CH_3)_3$]; δ_C (50 MHz; $CDCl_3$) 166.2 (CO_2), 146.3 (CH=$CHCO_2$), 138.2 (Ph:C_{ipso}), 129.1, 128.9 (Ph:C_{ortho}, C_{meta}), 126.8 (Ph:C_{para}), 124.3 (CH=$CHCO_2$), 80.3 [$CO_2C(CH_3)_3$], 38.3 ($PhCH_2$), 28.0 [$CO_2C(CH_3)_3$]; *m/z* (CI) 236 (MNH_4^+, 100%), 219 (MH^+, 67), 180 (70); (Found: C, 77.27; H, 8.46. $C_{14}H_{18}O_2$ requires C, 77.03; H, 8.31%); **11**: $\nu_{max}(CH_2Cl_2)$/cm^{-1} 1712vs (C=O), 1641m (C=C); δ_H (300 MHz; $CDCl_3$) 7.33-7.19 (5H, m, Ph), 6.26 (1H, dt, *J* 11.4, 7.5, CH_2CH=$CHCO_2$), 5.78 (1H, d, *J* 11.4, CH_2CH=$CHCO_2$), 3.99 (2H, d, *J* 7.5, CH_2CH=$CHCO_2$), 1.52 [9H, s, $CO_2C(CH_3)_3$]; δ_C (50 MHz; $CDCl_3$) 166.2 (CO_2), 146.6 (CH=$CHCO_2$), 139.9 (Ph:C_{ipso}), 128.8 (Ph:C_{ortho}, C_{meta}), 126.4 (Ph:C_{para}), 122.0 (CH=$CHCO_2$), 80.4 [$CO_2C(CH_3)_3$], 34.9 ($PhCH_2$), 28.1 [$CO_2C(CH_3)_3$]; *m/z* (CI) 236 (MNH_4^+, 87%), 219 (MH^+, 41), 180 (100), 162 (28), 144 (38); (Found: C, 76.76; H, 8.54. $C_{14}H_{18}O_2$ requires C, 77.03; H, 8.31%).

Preparation of (2R,3R,αR)- *and* (2S,3R,αR)-tert-*Butyl* 3-(N-*benzyl*-N-α-*methylbenzyl*)*amino*-2-*hydroxy*-4-*phenylbutanoate* **12** via *'Mismatched Pair'*. A solution of (*R*)-(α-methylbenzyl)benzylamine (0.774 g, 3.67 mmol) in anhydrous THF (20 cm^3) was cooled to -78°C and 1.60M butyllithium (2.15 cm^3, 3.44 mmol) was added dropwise *via* syringe. The resultant pink lithium amide solution was stirred for 45 min whereupon *tert*-butyl 4-phenyl-2-butenoate **9** (500 mg, 2.29 mmol) was added as a solution in anhydrous THF (3 cm^3). The resultant deep yellow enolate solution was stitrred for a further 2 h before solid (+)-(camphorsulfonyl)oxaziridine (+)-**7** (1.05 g, 4.59 mmol) was added. After stirring for 1 h at -78°C, the mixture was warmed to 0°C for 20 min and quenched by the addition of saturated aqueous ammonium chloride. The THF was removed under reduced pressure and the residue was diluted with water (20 cm^3) and extracted with dichloromethane (3 x 30 cm^3). The combined organic extracts were dried (magnesium sulfate), filtered, and the solvent evaporated under reduced pressure. Analysis of the crude material by ^{1}H nmr spectroscopy indicated a 60:40 mixture of products in favour of the *syn* diastereoisomer (2*S*,3*R*,α*R*)-**12**. Purification by flash chromatography on silica gel [petrol/diethyl ether (5:1)] afforded an inseparable mixture of the title compounds as a colourless oil (421 mg, 41%). The minor diastereoisomer (2*R*,3*R*,α*R*)-**12** was later prepared independently (*vide infra*) and the major diasteroisomer (2*S*,3*R*,α*R*)-**12** could consequently be unambiguously assigned from the mixture which was also fully characterised; (2*S*,3*R*,α*R*)-**12**: $\nu_{max}(CHCl_3)$/cm^{-1} 1719s

(C=O); δ_H (300 MHz; $CDCl_3$) 7.45-7.13 (15H, m, Ph), 4.21 (1H, q, *J* 7.0, NC<u>H</u>CH_3), 4.12, 3.91 (2H, AB system, J_{AB} 14.7, NC<u>H</u>$_2$Ph), 3.86 [1H, m, C<u>H</u>(OH)], 3.51 [1H, m, CH(OH)C<u>H</u>N], 2.98, 2.74 (2H, ABX system, J_{AB} 13.0, J_{AX} 10.3, J_{BX} 4.2, PhC<u>H</u>$_2$CHN), 1.41 [9H, s, $CO_2C(C\underline{H}_3)_3$], 1.35 (3H, d, *J* 7.0, NCHC<u>H</u>$_3$); δ_C (50 MHz; $CDCl_3$) 173.8 (<u>C</u>O_2), 143.7, 142.0, 140.1 (Ph:C_{ipso}), 129.7-128.0 (Ph:C_{ortho}, C_{meta}), 127.4, 126.9, 126.4 (Ph:C_{para}), 82.2 [$CO_2\underline{C}(CH_3)_3$], 72.8 [<u>C</u>H(OH)], 63.1 [CH(OH)<u>C</u>HN], 61.3 (N<u>C</u>HCH_3), 50.5 (N<u>C</u>H$_2$Ph), 33.9 (PhC<u>H</u>$_2$CHN), 27.9 [$CO_2C(\underline{C}H_3)_3$], 18.7 (NCH<u>C</u>H$_3$); *m/z* (CI) 446 ($MH^+$, 100%), 314 (63), 210 (48), 105 (42), 91 (69); (Found: C, 78.03; H, 7.94; N, 2.88. $C_{29}H_{35}NO_3$ requires C, 78.17; H, 7.92; N, 3.14%).

Preparation of (3R,αR)-tert-*Butyl* 3-(N-*benzyl*-N-*α-methylbenzyl*)*amino*-4-*phenylbutanoate* **13**. A solution of (*R*)-(α-methylbenzyl)benzylamine (1.18 g, 5.58 mmol) in anhydrous THF (20 cm^3) was cooled to -78°C and treated with 1.40M butyllithium (3.74 cm^3, 5.24 mmol). The resultant pink solution was stirred at -78°C for 30 min whereupon **9** (760 mg, 3.49 mmol) in anhydrous THF (3 cm^3) was added. After stirring for a further 3 h, the reaction was quenched by the addition of saturated aqueous ammonium chloride (5 cm^3), warmed to room temperature, and the solvent evaporated under reduced pressure. The residue was diluted with water (30 cm^3) and extracted with diethyl ether (3 x 40 cm^3). The combined organic extracts were then dried (magnesium sulfate), filtered, and the solvent evaporated under reduced pressure. Analysis of the crude product by ^1H nmr spectroscopy indicated the presence of the rearranged starting material **14** (*ca.* 20%) together with the desired title compound [98% d.e. by ^1H nmr spectroscopy (500 MHz)]. Purification of the residue by flash chromatography on silica gel [petrol/diethyl ether (19:1)] afforded the title compound contaminated with **14** as a colourless oil (1.04 g, 69%). Analysis of this material by TLC with a variety of eluents did not result in separation of the components. Removal of **14** was also attempted by the partitioning of the product between aqueous hydrochloric acid and diethyl ether. Unfortunately, this did not aid purification on account of the extraordinary solubility of the hydrochloride salt of **13** in organic solvents.

A sample of **9** could be prepared for characterisation by the selective hydroxylation of **14**. We have found that *tert*-butyl ester adducts analogous to **13** are not readily enolised using the bulky base lithium hexamethyldisilazide (LHMDS).[14] Thus, a THF solution of an impure sample (400 mg) of **13** (*ca.* 355 mg, 0.828 mmol **13**) was treated with an excess of 1.0M LHMDS (1.34 cm^3, 1.34 mmol) at 0°C (30 min), cooled to -78°C, and hydroxylated using (+)-**7** (530 mg, 2.31 mmol) in the manner described above. Analysis of the crude reaction product by ^1H nmr spectroscopy indicated that, although **13** remained unreacted under the experimental conditions, the impurity **14** was completely consumed. Consequently, the residue was subjected to flash chromatography on silica gel [petrol/diethyl ethyl (19:1)] to afford the purified title compound as a colourless oil (284 mg, 80%); $[\alpha]_D^{21}$ -6.74 (*c* 0.97, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1714vs (C=O); δ_H (300 MHz; $CDCl_3$) 7.38-7.15 (15H, m, Ph), 3.92, 3.62 (2H, AB system, J_{AB} 14.9, NC<u>H</u>$_2$Ph), 3.82 (1H, q, *J* 7.0, NC<u>H</u>CH_3), 3.70 (1H, m, CH_2C<u>H</u>N), 2.75, 2.64 (2H, ABX system, J_{AB} 13.5, J_{AX} 8.2, J_{BX} 5.9, PhC<u>H</u>$_2$CHN), 2.04, 1.97 (2H, ABX system, J_{AB} 15.2, J_{AX} 8.1, J_{BX} 5.1, CHC<u>H</u>$_2CO_2$), 1.41 [9H, s, $CO_2C(C\underline{H}_3)_3$], 1.10 (3H, d, *J* 7.0, NCHC<u>H</u>$_3$); δ_C (125 MHz; $CDCl_3$) 171.8 (<u>C</u>O_2), 143.1, 141.4, 140.3 (Ph:C_{ipso}), 129.6, 128.3, 128.2, 128.0, 127.9 (Ph:C_{ortho},C_{meta}), 126.8, 126.6, 125.9 (Ph:C_{para}), 80.1 [$CO_2\underline{C}(CH_3)_3$], 58.2, 56.6 (N<u>C</u>HCH_3, CH_2<u>C</u>HN), 50.1 (N<u>C</u>H$_2$Ph), 39.7, 37.8 (Ph<u>C</u>H$_2$CHN, CH<u>C</u>H$_2CO_2$), 28.1 [$CO_2C(\underline{C}H_3)_3$], 19.6 (NCH<u>C</u>H$_3$); *m/z* (CI) 430 ($MH^+$, 100%), 338 (30), 178 (54), 105 (40), 91 (59); (Found: C, 80.91; H, 8.50; N, 3.49. $C_{29}H_{35}NO_2$ requires C, 81.08; H, 8.21; N, 3.26%).

Preparation of (E)-tert-*Butyl 4-phenyl-3-butenoate* **14**. A solution of (*R*)-(α-methylbenzyl)benzylamine (155 mg, 0.735 mmol) in anhydrous THF (10 cm^3) was cooled to -78°C and treated with 1.60M butyllithium (0.43 cm^3, 0.688 mmol). The resultant pink solution was stirred at -78°C for 45 min whereupon **11** (100 mg, 0.459 mmol) in anhydrous THF (2 cm^3) was added. After stirring for a further 2 h, the reaction was quenched by the addition of saturated aqueous ammonium chloride (5 cm^3), warmed to room temperature, and the solvent evaporated under reduced pressure. The residue was diluted with water (30 cm^3) and extracted with dichloromethane (3 x 30 cm^3). The combined organic extracts were then dried (magnesium sulfate), filtered, and the solvent evaporated under reduced pressure. Analysis of the crude product by ^1H nmr spectroscopy indicated that complete rearrangement to the title compound had occurred: no lithium amide addition products were observed. Purification of the residue by flash chromatography on silica gel [petrol/diethyl ether (19:1)] afforded the title compound as a colourless oil (92 mg, 92%); ν_{max}(thin film)/cm^{-1} 1730s (C=O); δ_H (300 MHz; $CDCl_3$) 7.40-7.21 (5H, m, Ph), 6.48 (1H, d, *J* 16.0, C<u>H</u>=CHCH$_2$), 6.30 (1H, dt, *J* 16.0, 7.0, CH=C<u>H</u>CH$_2$), 3.17 (2H, d, *J* 7.0, CH=CHC<u>H</u>$_2$), 1.49 [9H, s, $CO_2C(C\underline{H}_3)_3$]; δ_C (50 MHz; $CDCl_3$) 171.3 (<u>C</u>O$_2$), 137.3 (Ph:C_{ipso}), 133.2 (<u>C</u>H=CHCH$_2$), 128.7, 126.5 (Ph:C_{ortho}, C_{meta}), 127.6 (Ph:C_{para}), 122.7 (CH=<u>C</u>HCH$_2$), 80.8 [$CO_2\underline{C}(CH_3)_3$], 39.6 (CH=CH<u>C</u>H$_2$), 28.0 [$CO_2C(\underline{C}H_3)_3$]; *m/z* (CI) 236 ($MNH_4^+$, 14%), 219 ($MH^+$, 4), 180 (100); (Found: C, 76.76; H, 8.41. $C_{14}H_{18}O_2$ requires C, 77.03; H, 8.31%).

Preparation of (2R,3R,αR)-tert-*Butyl* 3-(N-*benzyl*-N-*α-methylbenzyl*)*amino*-2-*hydroxy*-4-*phenyl butanoate* **12** via *'One-pot' Stepwise Procedure.* A solution of (*R*)-(α-methylbenzyl)benzylamine (929 mg, 4.40 mmol) in anhydrous THF (20 cm^3) was cooled to -78°C and treated with 1.49M butyllithium (2.77 cm^3, 4.13 mmol). The resultant pink solution was stirred at -78°C for 30 min whereupon **9** (600 mg, 2.75 mmol) in anhydrous THF (3 cm^3) was added. After stirring for a further 3 h, the intermediate enolate was quenched by the addition of a solution of acetic acid (330 mg, 5.50 mmol) in THF (2 cm^3). The resultant colourless solution was warmed to 0°C, stirred for 40 min, and then recooled to -78°C. A freshly prepared solution of LDA [diisopropylamine (612 mg, 6.06 mmol); 1.49M butyllithium (3.88 cm^3, 5.78 mmol); 0°C for 20 min] was cooled to -78°C and added *via* cannula to the β-amino ester. The resultant deep orange solution was stirred at -78°C for 45 min whereupon solid oxaziridine (+)-**7** (1.26 g, 5.50 mmol) was added. After stirring for a further 2 h, the mixture was warmed to 0°C over 15 min, and quenched by the addition of saturated aqueous ammonium chloride (5 cm^3). The solvent was evaporated *in vacuo* and the residue diluted with water (20 cm^3) and extracted with dichloromethane (3 x 40 cm^3). The combined organic extracts were dried (magnesium sulfate), filtered, and the solvent evaporated under reduced pressure. Purification of the residue by flash chromatography on silica gel [petrol/diethyl ether (9:1)] afforded the single diastereoisomer (2*R*,3*R*,α*R*)-**12** as a colourless oil (604 mg, 49%); $[\alpha]_D^{21}$ -39.1 (*c* 1.05, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1719s (C=O); δ_H (300 MHz; $CDCl_3$) 7.45-7.13 (15H, m, Ph), 4.37, 3.82 (2H, AB system, J_{AB} 15.5, NC<u>H</u>$_2$Ph), 3.96 (1H, q, *J* 7.0, NC<u>H</u>CH$_3$), 3.92 [1H, m, C<u>H</u>(OH)], 3.65 [1H, m, CH(OH)C<u>H</u>N], 2.99 [1H, br d, *J* 5.3, CH(O<u>H</u>)], 2.93, 2.73 (2H, ABX system, J_{AB} 14.0, J_{AX} 7.8, J_{BX} 6.2, PhC<u>H</u>$_2$CHN), 1.39 [9H, s, $CO_2C(C\underline{H}_3)_3$], 1.14 (3H, d, *J* 7.0, NCHC<u>H</u>$_3$); D_2O shake: selected δ_H (300 MHz; $CDCl_3$) 3.92 [1H, d, *J* 1.3, C<u>H</u>(OH)]; δ_C (125 MHz; $CDCl_3$) 174.0 (<u>C</u>O$_2$), 143.5, 142.0, 139.9 (Ph:C_{ipso}), 129.7, 128.2, 128.1, 128.0 (Ph:C_{ortho},C_{meta}), 126.9, 126.4, 126.0 (Ph:C_{para}), 82.5 [$CO_2\underline{C}(CH_3)_3$], 71.6 [<u>C</u>H(OH)], 61.1 [CH(OH)<u>C</u>HN], 58.2 (N<u>C</u>HCH$_3$), 51.1 (N<u>C</u>H$_2$Ph), 34.2 (PhC<u>H</u>$_2$CHN), 28.0 [$CO_2C(\underline{C}H_3)_3$], 18.7 (NCH<u>C</u>H$_3$); *m/z* (CI) 446 ($MH^+$, 100%), 314 (59), 210 (43), 105 (28), 91 (40); (Found: C, 78.46; H, 8.22; N, 3.14. $C_{29}H_{35}NO_3$ requires C, 78.17; H, 7.92; N, 3.14%).

Preparation of (4R,5R)-5-(tert-*Butoxycarbonyl*)-4-(*phenylmethyl*)-2-*oxazolidinone* **15**. β-Amino ester (2*R*,3*R*,α*R*)-**12** (146 mg, 0.328 mmol) was dissolved in acetic acid (5 cm^3) and treated with 10% palladium on activated carbon (60 mg). The mixture was then stirred at room temperature overnight under 7 atm of hydrogen. After removal of the catalyst by filtration, the solvent was evaporated under reduced pressure to afford the acetate salt of the debenzylated β-amino ester. This salt was then dissolved in a saturated solution of HCl(g) in *tert*-butanol and THF (1:1), stirred for 5 min, and the solvent subsequently evaporated under reduced pressure. The crude HCl salt was then treated with dichloromethane (5 cm^3) and triethylamine (166 mg, 1.64 mmol) was added. After the mixture had been stirred for 30 min at room temperature, solid carbonyldiimidazole (80 mg, 0.494 mmol) was added and stirring continued overnight. The solution was subsequently diluted with dichloromethane (30 cm^3) and washed successively with 0.5M hydrochloric acid (2 x 20 cm^3), saturated aqueous sodium bicarbonate (10 cm^3), and brine (10 cm^3). The organic layer was then dried (magnesium sulfate) and the solvent evaporated under reduced pressure. Purification of the residue by silica gel chromatography [diethyl ether/petrol (4:1)] afforded the title compound as a colourless oil (20 mg, 22%) which solidified on standing and was recrystallised from dichloromethane; m.p. 78-80°C; $[\alpha]_D^{22}$ +96.8 (*c* 0.70, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3449w (N-H), 1774vs (oxazolidinone C=O), 1727m (ester C=O); δ_H (300 MHz; $CDCl_3$) 7.39-7.18 (5H, m, Ph), 5.03 (1H, d, *J* 8.6, $CHCHCO_2$), 4.94 (1H, br s, CONH), 4.26 (1H, ddd, *J* 11.7, 8.6, 3.0, $CHCHCO_2$), 3.00, 2.62 (2H, ABX system, J_{AB} 13.2, J_{AX} 3.0, J_{BX} 11.7, $CH_2CHCHCO_2$), 1.57 [9H, s, $CO_2C(CH_3)_3$]; δ_C (125 MHz; $CDCl_3$) 166.0 (CO_2), 157.1 (CONH), 136.1 (Ph:C_{ipso}), 129.3, 128.9 (Ph:C_{ortho}, C_{meta}), 127.5 (Ph:C_{para}), 84.0 [$CO_2C(CH_3)_3$], 76.5 ($CHCHCO_2$), 55.6 ($CHCHCO_2$), 37.2 ($CH_2CHCHCO_2$), 28.1 [$CO_2C(CH_3)_3$]; *m/z* (CI) 295 (MNH_4^+, 98%), 278 (MH^+, 100), 239 (27); (Found: C, 64.74; H, 6.80; N, 5.01. $C_{15}H_{19}NO_4$ requires C, 64.97 H, 6.91; N, 5.05%).

Preparation of (2S,3S,αS)-tert-*Butyl* 3-(N-*benzyl*-N-α-*methylbenzyl*)*amino*-2-*hydroxy*-4-*phenylbutanoate* **12** via *'Matched Pair'*. A solution of (*R*)-(α-methylbenzyl)benzylamine (0.929 g, 4.40 mmol) in anhydrous THF (20 cm^3) was cooled to -78°C and 1.67M butyllithium (2.47 cm^3, 4.13 mmol) was added dropwise *via* syringe. The resultant pink lithium amide solution was stirred for 45 min whereupon *tert*-butyl 4-phenyl-2-butenoate **9** (600 mg, 2.75 mmol) was added as a solution in anhydrous THF (3 cm^3). The resultant deep yellow enolate solution was stitrred for a further 2 h before solid (+)-(camphorsulfonyl)oxaziridine (+)-**7** (1.01 g, 4.41 mmol) was added. After stirring for 1 h at -78°C, the mixture was warmed to 0°C for 15 min and quenched by the addition of saturated aqueous ammonium chloride. The THF was removed under reduced pressure and the residue was diluted with water (20 cm^3) and extracted with dichloromethane (3 x 30 cm^3). The combined organic extracts were dried (magnesium sulfate), filtered, and the solvent evaporated under reduced pressure. Analysis of the crude product by ^1H nmr spectroscopy indicated a 22:1 (91% d.e.) mixture of α-epimeric products in favour of the desired *anti* diastereoisomer (2*S*,3*S*,α*S*)-**12**. Purification of the residue by flash chromatography on silica gel [petrol/diethyl ether (9:1)] afforded the title compound (91% d.e.) as a colourless oil (777 mg, 63%). The spectroscopic data matched that obtained for the enantiomer (2*R*,3*R*,α*R*)-**12** previously prepared using the stepwise hydroxylation protocol (*vide supra*); (2*S*,3*S*,α*S*)-**12** (91% d.e.): $[\alpha]_D^{20}$ +43.6 (*c* 1.05, $CHCl_3$).

Preparation of (2S,3S)-tert-*Butyl* 3-*amino*-2-*hydroxy*-4-*phenylbutanoate* **16**. β-Amino ester (2*S*,3*S*,α*S*)-**12** (91% d.e.) (706 mg, 1.59 mmol) was dissolved in acetic acid (8 cm^3) and treated with 10% palladium on activated carbon (400 mg). The mixture was then stirred at room temperature overnight under 7 atm of hydrogen. After removal of the catalyst by filtration, the solvent was evaporated under reduced pressure,

and the resultant acetate salt was partitioned between saturated aqueous sodium bicarbonate (30 cm^3) and dichloromethane (30 cm^3). After thorough mixing, the organic layer was separated and the aqueous layer extracted with further dichloromethane (2 x 30 cm^3). The combined organic layers were then dried (magnesium sulfate), filtered, and the solvent removed under reduced pressure. Recrystallisation of the resultant solid from hexane afforded colourless needles of the title compound as a single diastereoisomer (246 mg, 62%); m.p. 93-94°C; $[\alpha]_D^{21}$ +19.1 (*c* 1.02, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1723s (C=O); δ_H (300 MHz; $CDCl_3$) 7.35-7.19 (5H, m, Ph), 4.13 [1H, d, *J* 3.4, C<u>H</u>(OH)CHN], 3.30 (1H, m, $PhCH_2C\underline{H}N$), 2.80, 2.59 (2H, ABX system, J_{AB} 13.5, J_{AX} 4.0, J_{BX} 9.9, $PhC\underline{H}_2CHN$), 1.56 [9H, s, $CO_2C(C\underline{H}_3)_3$]; δ_C (50 MHz; $CDCl_3$) 173.0 ($\underline{C}O_2$), 139.1 ($Ph:C_{ipso}$), 129.5, 128.8 ($Ph:C_{ortho}$, C_{meta}), 126.7 ($Ph:C_{para}$), 82.9 [$CO_2\underline{C}(CH_3)_3$], 74.3 [<u>C</u>H(OH)], 56.0 [CH(OH)<u>C</u>HN], 38.7 ($Ph\underline{C}H_2$), 28.1 [$CO_2C(\underline{C}H_3)_3$]; *m/z* (CI) 252 ($MH^+$, 100%), 196 (85), 120 (89); (Found: C, 66.79; H, 8.28; N, 5.63. $C_{14}H_{21}NO_3$ requires C, 66.91; H, 8.42; N, 5.57%).

Preparation of (2S,3S)-3-*Amino*-2-*hydroxy*-4-*phenylbutanoic acid trifluoroacetate salt* **17**. β-Amino ester **16** (34 mg, 0.135 mmol) was treated with trifluoroacetic acid (2 cm^3) and the resultant solution stirred at room temperature overnight. The solvent was subsequently evaporated under reduced pressure and the residue washed with diethyl ether (5 cm^3). The resultant material was dried *in vacuo* overnight to afford the title compound as a white solid (38 mg, 90%); m.p. 157°C (dec.); $[\alpha]_D^{20}$ -2.5 (*c* 0.59, 1N HCl) {lit.,[23] $[\alpha]_D^{24}$ -2.2 (*c* 0.67, 1N HCl)}; $\nu_{max}(KBr)/cm^{-1}$ 3078br (OH), 1752s (acid C=O), 1666vs (carboxylate C=O); δ_H (500 MHz; D_2O) 7.33-7.21 (5H, m, Ph) 4.45 [1H, d, *J* 3.2, C<u>H</u>(OH)CHN], 3.92 (1H, m, $PhCH_2C\underline{H}N$), 2.93, 2.84 (2H, ABX system, J_{AB} 14.4, J_{AX} 5.8, J_{BX} 9.2, $PhC\underline{H}_2CHN$); δ_C (125 MHz; D_2O) 174.9 ($\underline{C}O_2$), 163.9 (q, J_{CCF} 35.5, $CF_3\underline{C}O_2$), 135.9 ($Ph:C_{ipso}$), 130.6, 130.1 ($Ph:C_{ortho}$, C_{meta}), 128.8 ($Ph:C_{para}$), 117.4 (q, J_{CF} 292.2, $\underline{C}F_3CO_2$), 70.6 [<u>C</u>H(OH)], 55.8 [CH(OH)<u>C</u>HN], 33.9 ($Ph\underline{C}H_2$); δ_F (235 MHz; D_2O) -76.3 ($C\underline{F}_3CO_2$); *m/z* (CI) 196 (M^+, 100%), 120 (27); (Found: C, 46.43; H, 4.53; N, 4.61. $C_{12}H_{14}NO_5F_3$ requires C, 46.61; H, 4.56; N, 4.53%).

Preparation of (2S,3S)-3-*Amino*-2-*hydroxy*-4-*phenylbutanoic acid: Allophenylnorstatine (APNS)* **3**. β-Amino ester **16** (106 mg, 0.422 mmol) was treated with trifluoroacetic acid (2 cm^3) and the resultant solution stirred at room temperature overnight. The solvent was subsequently evaporated *in vacuo* and the residue dissolved in 10% aqueous hydrochloric acid (5 cm^3). After stirring for 5 min, the solvent was removed *in vacuo* and the residue submitted to ion exchange chromatography (Dowex 50X8-200) which afforded the desired amino acid as a white solid. This material was dried *in vacuo* to afford the title compound as a white solid in quantitative yield (82 mg); m.p. 195°C (dec.); $[\alpha]_D^{20}$ -5.4 (*c* 0.51, 1N HCl), $[\alpha]_{578}^{20}$ -17.8 (*c* 0.51, 1N HCl) {lit.,[24] $[\alpha]_{578}^{20\text{-}25}$ -5.6 (1N HCl)}; $\nu_{max}(KBr)/cm^{-1}$ 1609vs (C=O); δ_H (500 MHz; D_2O) 7.33-7.30 (2H, m, Ph), 7.27-7.22 (3H, m, Ph), 4.16 [1H, d, *J* 3.6, C<u>H</u>(OH)CHN], 3.68 (1H, m, $PhCH_2C\underline{H}N$), 2.85, 2.73 (2H, ABX system, J_{AB} 14.5, J_{AX} 3.9, J_{BX} 10.8, $PhC\underline{H}_2CHN$); δ_C (125 MHz; D_2O) 177.2 ($\underline{C}O_2$), 136.7 ($Ph:C_{ipso}$), 130.2, 129.8 ($Ph:C_{ortho}$, C_{meta}), 128.2 ($Ph:C_{para}$), 72.6 [<u>C</u>H(OH)], 56.4 [CH(OH)<u>C</u>HN], 34.4 ($Ph\underline{C}H_2$); *m/z* (CI) 196 (MH^+, 100%), 120 (18); (Found: C, 61.76; H, 6.56; N, 7.27. $C_{10}H_{13}NO_3$ requires C, 61.53; H, 6.71; N, 7.17%).

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22. Full details of our molecular modelling studies will be be reported in due course.
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24. The literature rotation[7] for **3** {$[\alpha]_{578}^{20\text{-}25}$ -5.6 (1N HCl)} appears to have been recorded at the sodium D line and not as stated {our rotations: $[\alpha]_{578}^{20}$ -17.8 (*c* 0.51, 1N HCl) and $[\alpha]_{D}^{20}$ -5.4 (*c* 0.51, 1N HCl)}. However, our rotation for the TFA salt of **3** does concur with the literature value.

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