The synthesis of novel heterocyclic substituted α-amino acids; further exploitation of α-amino acid alkynyl ketones as reactive substrates

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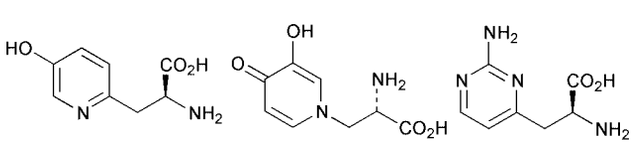
A series of novel non-proteinogenic heterocyclic substituted α-amino acids derived from L-aspartic acid have been synthesised using the alkynyl ketone functionality as a versatile building block. Condensation of (*S*)-2-*tert*-butoxycarbonylamino-4-oxohex-5-ynoic acid *tert*-butyl ester **4** with enamines **5**, **6**, phenylhydrazine, hydroxylamine and phenyl azide has led to the generation of pyridines **9**, **10**, pyrazolines **11a/b**, isoxazoles **12a/b**, and triazole **13**, respectively in moderate to excellent yields. Acid deprotection of the initial adducts afforded the desired heterocyclic substituted α-amino acids as their TFA salts or in the form of the zwitterions themselves after ion-exchange chromatography. The enantiomeric purity of a representative selection of these products were greater than 98% ee as verified by derivatisation to the corresponding Mosher's amides and subsequent ^{19}F NMR spectroscopy.

Introduction

There has recently been an increasing interest in the development of novel α-amino acids due to their diverse range of biological and toxicological properties. Their importance is exemplified not only by their role as constituents of peptides, proteins, and peptidoglycans in bacterial cell-walls but also as mediators of neuronal signal transduction.[1] In particular the heterocyclic α-amino acids azatyrosine **1**,[2] mimosine **2**, and lathyrine **3** have been observed to display antibiotic, antitumor, wool growth and pollen growth inhibition activities (Fig. 1).[3]

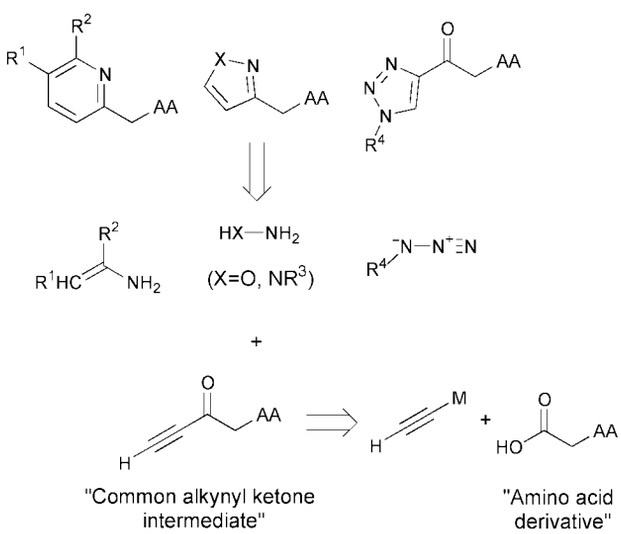
As part of an on going research program which focuses on the harnessing of new reactive cores using a parallel synthesis approach, we have developed a novel route to potentially biologically active α-amino acid substrates.[4,5] Through a retrosynthetic analysis we identified that pyridinyl, triazolyl, isoxazolyl and pyrazolyl heterocycles could all be derived from a common alkynyl ketone precursor,[5b] thus by application of a parallel synthesis strategy we envisaged that these core structures could all be accessed readily subsequent to the generation of the common reactive species. A disconnection of these heterocycles by our method led to three simple components comprised of a dinucleophilic amphiphile, an acetylene and a carboxylic acid (Scheme 1). The obvious advantage of utilising this strategy is that many variants of such α-amino acid heterocycles could be easily accessible, by selecting the appropriately substituted fragments, leading to the rapid generation of structurally related compound libraries in a controlled manner.

Herein we fully describe a versatile stereoselective synthetic route to a wide range of heterocyclic α-amino acids by involvement of a highly reactive alkynyl ketone intermediate and its cyclocondensation reactions with selected bifunctional nucleophiles.



L-Azatyrosine **1** L-Mimosine **2** L-Lathyrine **3**

Fig. 1



Scheme 1

Results and discussion

Initially (*S*)-2-*tert*-butoxycarbonylamino-4-oxohex-5-ynoic acid *tert*-butyl ester **4** was synthesised from the corresponding Weinreb amide as described previously.[4]

Bohlmann and Rahtz reported that cyclocondensations between alkynyl ketones and suitable enamines allowed the generation of functionalised pyridines in excellent yields.[6] From this evidence we believed that by reacting **4** with the appropriate enamines we would be able to access pyridine substituted α-amino acids, which would bear relation to the naturally occurring amino acid L-azatyrosine. The stabilised enamines methyl (*Z*)-3-aminobut-2-enoate **5** and (*Z*)-4-aminopent-3-en-2-one **6** were thus prepared by condensation of ammonia with methyl acetoacetate and acetoacetone respectively, in an attempt to investigate this possibility.[7,8] Trial reactions were

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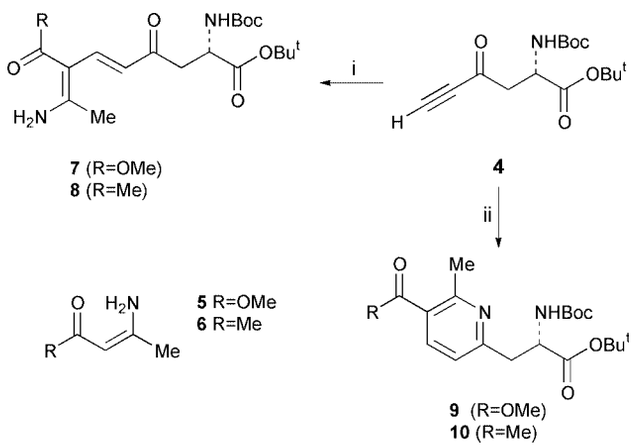
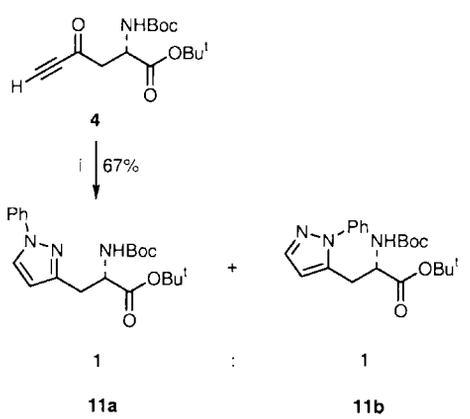
carried out on **4** with either **5** or **6** in ethanol at room temperature leading to the formation of single products. Proton NMR spectroscopy of these products revealed that instead of the expected cyclocondensations occurring to afford the desired pyridines, the disubstituted *trans*-alkenes **7** and **8** had been formed (olefinic $^3J = 15.5$, 16 Hz compared to *ca.* 8.0 Hz for pyridines) by means of singular Michael additions to the alkynyl ketone. The observation of *trans* addition to the triple bond of the alkynyl ketone was consistent with that reported by Bromidge,[9] with the *Z*-geometry of the enamine double bond expected due to the possibility of hydrogen bonding. Bohlmann and Rahtz[6] had however carried out their cyclocondensations at elevated temperatures and it was subsequently found that by stirring an ethanolic solution of **4** with either enamine **5** or **6** at reflux, a high conversion to the pyridin-6-yl substituted, protected amino acids **9** and **10** was observed (Scheme 2).



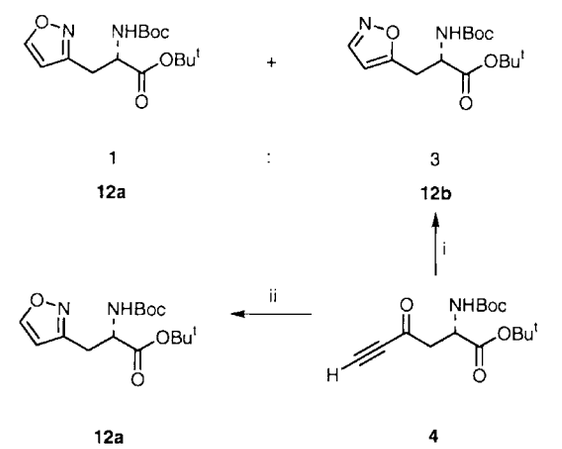
Scheme 2 *Reagents and conditions*: i, **5** or **6**, EtOH, RT, 89% (**7**), 91% (**8**); ii, **5** or **6**, EtOH, reflux, 81% (**9**), 91% (**10**).

Literature evidence also suggested that cyclocondensation of **4** with hydrazines and hydroxylamine should allow access to both pyrazole and isoxazole substituted amino acids.[10,11] Therefore the reaction of (*S*)-2-*tert*-butoxycarbonylamino-4-oxohex-5-ynoic acid *tert*-butyl ester **4** with hydrazines was investigated by refluxing an ethanolic solution of **4** and phenylhydrazine hydrochloride in the presence of solid sodium carbonate. This has encouragingly allowed the desired pyrazolyl substituted protected α-amino acids **11a/b** to be isolated in satisfactory yield, as an inseparable 1:1 mixture of regioisomers (Scheme 3).



Scheme 3 *Reagents and conditions*: i, H_2N-NHPh·HCl, Na_2CO_3, H_2O, EtOH, reflux, 67%.

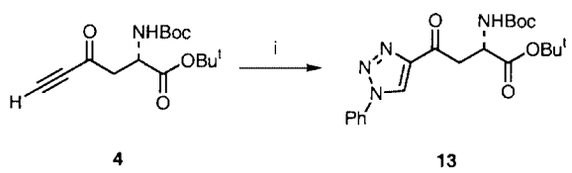
Isoxazoles were the next class of compounds to be targeted using our strategy since it is known that certain non-protein α-amino acids such as ibotenic acid behave effectively as conformationally restricted glutamic acid analogues.[12,13] Initially reaction of **4** with hydroxylamine hydrochloride in an ethanolic solution with solid sodium carbonate[10] allowed isolation of the isoxazole **12a** in poor yield (13%) as the only isoxazole isomer. Variation of the solvent and base employed, to ethanol and 1.2 equivalents of pyridine,[11] subsequently allowed the regioisomeric isoxazoles **12a/b** to be obtained in a moderate yield (51%), as a 1:3 separable mixture of regioisomers.[14] A literature search however revealed that Giacomelli and co-workers had reported a successful cyclocondensation of hydroxylamine upon an enamino ketone, albeit in low yield, by a simple reaction with the hydrochloride salt in refluxing methanol.[15] We therefore investigated the possibility of cyclocondensations under these conditions. Refluxing **4** with hydroxylamine hydrochloride in ethanol gratifyingly led to the formation of isoxazole **12a** exclusively in a respectable yield (62%) (Scheme 4). Assignment of the two regioisomers **12a/b** were made by



Scheme 4 *Reagents and conditions*: i, H_2N-OH·HCl, EtOH, pyridine, reflux, 51%; ii, H_2N-OH·HCl, EtOH, reflux, 62%.

comparison of their ^{1}H and ^{13}C NMR whereby the ^{1}H and ^{13}C chemical shifts for C_5(H) of **12a** were shown to occur at a characteristically lower field[16] than the corresponding C_3(H) resonances for **12b**.

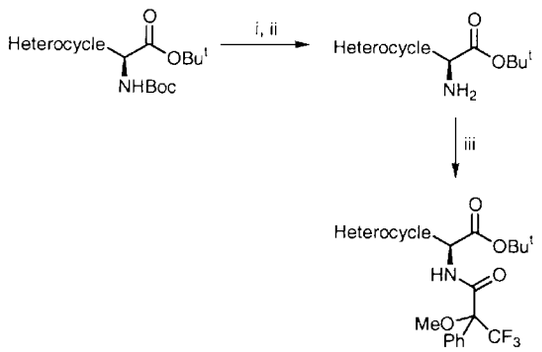
To diversify the scope of our compound library even further, it was next decided to attempt the formation of a 1,2,3-triazolyl substituted α-amino acid by a cycloaddition of **4** with an azide. Furthermore, it had been shown that reaction of azides with alkynyl ketones had led to exclusive addition at the acetylene.[17] Thus reaction of **4** with phenyl azide was carried out in refluxing diethyl ether[17] to generate the triazol-4-yl, protected amino acid **13**, in high yield (91%) (Scheme 5). Proton NMR spectroscopy (CD_3OD) indicated that only a single regioisomer **13** was generated with a high chemical shift value (δ_H 9.11 ppm) for the C-5 aromatic proton. Assignment of the structure to the 1,4-disubstituted regioisomer **13** is consistent with the preferred mode of azide addition to acetylenic ketones as demonstrated by Vereshchagin *et al.*[17] This regiochemistry also accounts for the ^{1}H NMR spectrum of **13** in which the phenyl substituent interacts with the triazole ring splitting the *ortho* protons with respect to the *meta-para* protons. A singlet would have been more likely expected if the phenyl substituent were in the more sterically hindered position adjacent to the carbonyl group,[18] *i.e.* 1,5-disubstituted adduct.



Scheme 5 *Reagents and conditions*: i, Ph-N_3, Et_2O, reflux, 91%.

The extent of racemisation during the syntheses of these compounds was then determined by the formation of their diastereomeric Mosher's amides. This was achieved by selective Boc-deprotection involving azeotropic distillation of the fully protected products with $TsOH{\cdot}H_2O$–toluene, which gave the corresponding free amines after a sodium bicarbonate wash. The *N*-deprotected form were thereafter converted into both Mosher's amides by coupling with both (*R*)- and (*S*)-Mosher's acid chlorides in dichloromethane with pyridine and catalytic DMAP (Scheme 6). Fluorine NMR analysis of these amides then proved the enantiomeric purity to be greater than 98% ee in a representative range of cases.[19]

Facile deprotection of the amino acids **10**, **11a/b**, **12a/b** and **13** was readily performed by their dissolution in TFA–anisole, whereas full deprotection of **9** had to be carried out by refluxing in 1 M HCl. The free amino acids **14** (80%) and **15** (85%) were then obtained, by ion-exchange chromatography, as solids in high yields and the amino acids **16a/b** (98%), **17a/b** (96%) and **18** (100%) were isolated as their TFA salts, after diethyl ether trituration, due to their low solubilities (Scheme 7).



Scheme 6 *Reagents and conditions*: i, $TsOH{\cdot}H_2O$ (1 equiv.), toluene, azeotropic distillation; ii, $NaHCO_3$ (aq), EtOAc; iii, (*R*)- or (*S*)-2-methoxy-2-(trifluoromethyl)phenylacetyl chloride (1 equiv.), pyridine (excess), DMAP (cat.), DCM.

Conclusions

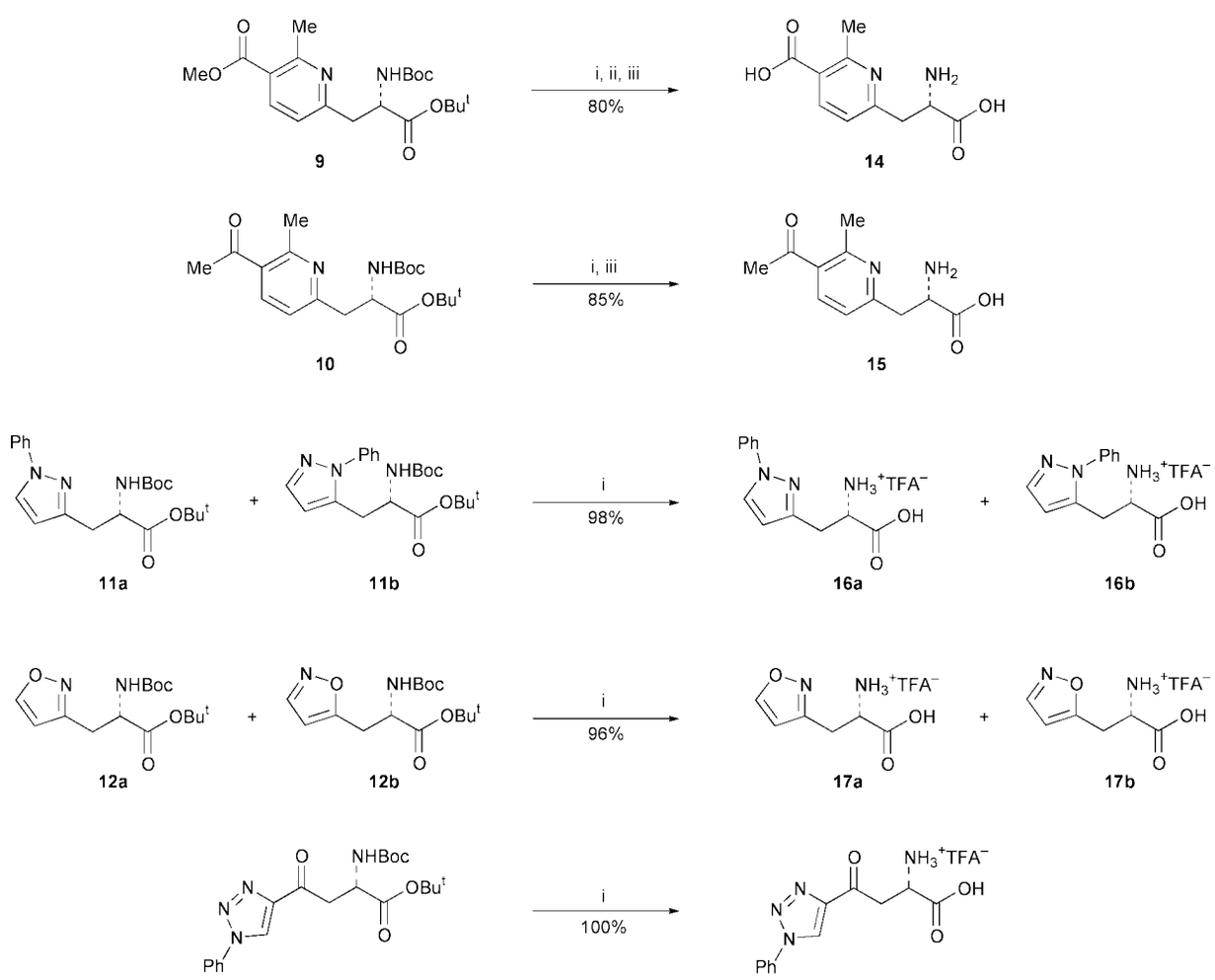
In conclusion we have shown that our methodology[4a,b] can be readily expanded to other novel heterocyclic systems using a parallel synthesis strategy. Further exploitation of the alkynyl ketone reactive group has allowed rapid and efficient construction of a range of representative heterocyclic non-proteinogenic amino acids including analogues of the natural product L-azatyrosine. This has further highlighted the flexibility and power of our approach with pyridinyl, pyrazolyl, isoxazolyl and 1,2,3-triazolyl substituted amino acids being generated in approximately 30% yield from L-aspartic acid. Further routes to novel heterocyclic non-protein amino acids, will be reported in due course.

Experimental

Standard general procedures and techniques as described previously[4b] were employed.

(*S*,5*E*,7*Z*)-8-Amino-2-(*tert*-butoxycarbonylamino)-4-oxo-7-methoxycarbonylnona-5,7-dienoic acid *tert*-butyl ester 7

To a stirred solution of **4** (130 mg, 0.44 mmol) in ethanol (5 ml), (*Z*)-methyl 3-aminobut-2-enoate **5** (51 mg, 0.44 mmol) was



Scheme 7 *Reagents and conditions*: i, TFA, anisole, DCM; ii, 1 M HCl, reflux; iii, Dowex 50X8-100 ion-exchange resin.

added and the mixture was stirred at room temperature for 48 hours. The solvent was then concentrated *in vacuo* and the residue was subjected to purification by flash chromatography (SiO_2, EtOAc–petroleum ether (PE) 40–60; 1:1) to afford the title compound **7** (160 mg, 89%) as a pale yellow oil (Found: C, 58.24; H, 7.82; N, 6.79. $C_{20}H_{32}N_2O_7$ requires C, 58.09; H, 8.00; N, 6.57%) (R_f 0.2, EtOAc–PE 40–60; 1:1); $[\alpha]_D^{22}$ +66.0 (*c* 0.98 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 3371br (N–H str), 3220w, 2979m (C–H str), 2934w, 1717s (C=O str), 1670m (C=O str), 1624m, 1560s, 1496s, 1457m, 1438m, 1393m, 1368s, 1319m, 1287s, 1252m, 1211s, 1156s; δ_H (200 MHz; $CDCl_3$) 1.44 (9H, s, C(CH_3)$_3$), 1.46 (9H, s, C(CH_3)$_3$), 2.31 (3H, s, 8-CH_3), 2.99 (1H, dd, *J* 4.0 and 17.5 Hz, 3-C(*H*)H), 3.25 (1H, dd, *J* 4.0 and 17.5 Hz, 3-C(H)*H*), 3.82 (3H, s, CH_3O), 4.40–4.47 (1H, m, 2-C*H*), 5.62 (1H, d, *J* 9.0 Hz, N*H*), 6.52 (1H, d, *J* 15.5 Hz, CH=C*H*), 7.64 (1H, d, *J* 15.5 Hz, C*H*=CH), 9.6–9.8 (1H, br, NH); δ_C (50.31 MHz; $CDCl_3$) 22.03 (*C*H$_3$), 27.75 (C(*C*H$_3$)$_3$), 28.18 (C(*C*H$_3$)$_3$), 42.77 (3-*C*H$_2$), 50.57 (2-*C*H), 50.83 (*C*H$_3$O), 79.54 (*C*(CH$_3$)$_3$), 81.72 (*C*(CH$_3$)$_3$), 94.23 (C=*C*), 118.82, 140.14 (*C*H = *C*H), 156.02 (N*C*=O), 167.49 (*C*=C), 170.23, 171.29, 198.04 (3 × *C*=O); *m*/*z* (APCI, CI$^+$) 395 [MH$^+$ − H_2O, 100%], 340 [31], 296 [38], 295 [91] and 239 [26].

(*S*,5*E*,7*Z*)-7-Acetyl-8-amino-2-(*tert*-butoxycarbonylamino)-4-oxonona-5,7-dienoic acid *tert*-butyl ester 8

To a solution of **4** (0.120 g, 0.40 mmol) in ethanol (5 ml) was added (*Z*)-4-aminopent-3-en-2-one **6** (0.040 g, 0.40 mmol) and the resulting mixture was stirred for 48 hours at RT. Flash chromatography (SiO_2, EtOAc–PE 40–60; 1:1) of the residue left after removal of the solvent *in vacuo* yielded the title compound **8** (0.145 g, 91%) as a pale yellow oil (Found: C, 60.59; H, 8.13; N, 7.07. $C_{20}H_{32}N_2O_6$ requires C, 60.44; H, 8.29; N, 7.01%) (R_f 0.25, EtOAc–PE 40–60; 1:1); $[\alpha]_D^{22}$ +52.0 (*c* 0.95 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 3339br (N–H str), 2979m (C–H str), 1715s (C=O str), 1558s, 1368s, 1280m, 1155s, 1107m, 1027w, 983m, 733w; δ_H (200 MHz; $CDCl_3$) 1.42 (9H, s, C(CH_3)$_3$), 1.44 (9H, s, C(CH_3)$_3$), 2.25 (3H, s, CH_3), 2.33 (3H, s, CH_3), 2.98 (1H, dd, *J* 4.5 and 17.5 Hz, 3-C(*H*)H), 3.23 (1H, dd, *J* 4.5 and 17.5 Hz, 3-C(H)*H*), 4.38–4.46 (1H, m, 2-C*H*), 5.57 (1H, d, *J* 9.0 Hz, N*H*), 5.98 (1H, d, *J* 16.0 Hz, CH=C*H*), 7.74 (1H, d, *J* 16.0 Hz, C*H*=CH); δ_C (50.31 MHz; $CDCl_3$) 23.13 (*C*H$_3$), 27.78 (C(*C*H$_3$)$_3$), 28.21 (C(*C*H$_3$)$_3$), 29.86 (*C*H$_3$), 42.65 (3-*C*H$_2$), 50.53 (2-*C*H), 79.64 (*C*(CH$_3$)$_3$), 81.77 (C(*C*H$_3$)$_3$), 104.98 (C=*C*), 120.83 (=*C*H), 142.65 (=*C*H), 156.00 (N*C*=O), 167.07 (*C*=C), 171.08, 197.13, 198.11 (3 × *C*=O); *m*/*z* (APCI, CI$^+$) 379 [MH$^+$ − H_2O, 100%], 324 [45], 279 [15], 267 [17] and 223 [12].

(*S*)-2-*tert*-Butoxycarbonylamino-3-(5-methoxycarbonyl-6-methylpyridin-2-yl)propanoic acid *tert*-butyl ester 9

To a stirred solution of **4** (160 mg, 0.54 mmol) in ethanol (10 ml) was added methyl (*Z*)-3-aminobut-2-enoate **5** (62 mg, 0.54 mmol). The reaction was set to reflux and stirred for 16 hours before the solvent was concentrated *in vacuo* to afford a yellow oil. The residue was taken up into ethyl acetate, washed with saturated aqueous sodium bicarbonate (2 × 20 ml) and brine (2 × 20 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product. Purification by flash column chromatography (SiO_2, 2:3; Et_2O–PE 40–60) yielded the title compound **9** as a yellow oil (173 mg, 81%) (R_f 0.25, Et_2O–PE 40–60; 2:3); $[\alpha]_D^{23}$ +26.13 (*c* 0.75 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 2978 (C–H str), 1726s (C=O str), 1591m (C=C str), 1497m, 1393m, 1367s, 1278s, 1154s, 1085s, 849w; δ_H (200 MHz; $CDCl_3$) 1.35 (9H, s, C(CH_3)$_3$), 1.40 (9H, s, C(CH_3)$_3$), 2.77 (3H, s, ArCH_3), 3.15–3.37 (2H, m, 3-CH_2), 3.88 (3H, s, OCH_3), 4.50–4.60 (1H, m, 2-C*H*), 5.75 (1H, d, *J* 8.5 Hz, N*H*), 7.04 (1H, d, *J* 8.0 Hz, Ar-C*H*), 8.09 (1H, d, *J* 8.0 Hz, Ar-C*H*); δ_C (50.31 MHz; $CDCl_3$) 24.78 (Ar*C*H$_3$), 27.85, 28.28 (2 × C(*C*H$_3$)$_3$), 39.46 (3-*C*H$_2$), 52.12 (O*C*H$_3$), 53.03 (2-*C*H), 79.48, 81.60 (2 × *C*(CH$_3$)$_3$), 120.89 (Ar-*C*H), 132.50 (Ar-*C*), 138.77 (Ar-*C*H), 155.50 (Ar-*C*), 159.42, 160.33, (2 × *C*=O), 166.50 (Ar-*C*), 170.62 (*C*=O); *m*/*z* (APCI, CI$^+$) 417 [MNa$^+$, 5%], 283 [100], 239 [90] and 193 [23] (Found: MH$^+$ 395.2187, $C_{20}H_{31}N_2O_6$ requires 395.2182) (Found: C, 60.90; H, 7.84; N, 7.20. $C_{20}H_{30}N_2O_6$ requires C, 60.90; H, 7.67; N, 7.10%).

(*S*)-2-*tert*-Butoxycarbonylamino-3-(5-acetyl-6-methylpyridin-2-yl)propanoic acid *tert*-butyl ester 10

To a stirred solution of **4** (185 mg, 0.62 mmol) in ethanol (10 ml) was added (*Z*)-4-aminopent-3-en-2-one **6** (61.7 mg, 0.62 mmol). The reaction was set to reflux and stirred for 16 hours before the solvent was concentrated *in vacuo* to afford a yellow oil. The residue was taken up into ethyl acetate, washed with saturated aqueous sodium bicarbonate (2 × 20 ml) and brine (2 × 20 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product. Purification by flash column chromatography (SiO_2, 3:2; Et_2O–PE 40–60) yielded the title compound **10** as a yellow oil (215 mg, 91%) (R_f 0.3, Et_2O–PE 40–60; 3:2); $[\alpha]_D^{23}$ +27.65 (*c* 1.15 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 3360br (N–H str), 2978m (C–H str), 1715s (C=O str), 1689s (C=O), 1586s (C=C str), 1497s, 1392m, 1367s, 1257s, 1155s, 1057w, 848w; δ_H (200 MHz; $CDCl_3$) 1.30 (9H, s, C(CH_3)$_3$), 1.34 (9H, s, C(CH_3)$_3$), 2.49 (3H, s, ArCH_3), 2.63 (3H, s, COCH_3), 3.10–3.33 (2H, m, 3-CH_2), 4.45–4.55 (1H, m, 2-C*H*), 5.71 (1H, d, *J* 8.0 Hz, N*H*), 7.02 (1H, d, *J* 8.0 Hz, Ar-C*H*), 7.85 (1H, d, *J* 8.0 Hz, Ar-C*H*); δ_C (50.31 MHz; $CDCl_3$) 24.63 (Ar*C*H$_3$), 27.67, 28.10 (2 × C(*C*H$_3$)$_3$), 29.05 (CO*C*H$_3$), 39.27 (3-*C*H$_2$), 52.98 (2-*C*H), 79.39, 81.55 (2 × *C*(CH$_3$)$_3$), 120.88 (Ar-H), 130.58 (Ar-*C*, *ipso*), 137.51 (Ar-*C*H), 155.60, 157.98, 159.94 (2 × Ar-C, NH*C*O$_2$), 170.84 (CO$_2$); *m*/*z* (APCI, CI$^+$) 401 [MNa$^+$, 5%], 267 [100], 245 [18] and 223 [44] (Found: MH$^+$ 379.2218, $C_{20}H_{31}N_2O_5$ requires 379.2233) (Found: C, 63.71; H, 8.01; N, 7.22. $C_{20}H_{30}N_2O_5$ requires C, 63.47; H, 7.99; N, 7.40%).

(*S*)-2-*tert*-Butoxycarbonylamino-3-(1-phenylpyrazol-3-yl)-propanoic acid *tert*-butyl ester 11a and (*S*)-2-*tert*-butoxycarbonylamino-3-(2-phenylpyrazol-3-yl)propanoic acid *tert*-butyl ester 11b

To a stirred solution of **4** (148.5 mg, 0.50 mmol) in ethanol (3 ml) was added water (18 μl), phenyl hydrazine hydrochloride (72.3 mg, 0.50 mmol) and sodium carbonate (64 mg, 0.60 mmol). The reaction was then heated to reflux and stirred for four hours before being concentrated *in vacuo*. The residue was taken into ethyl acetate, washed with saturated aqueous sodium bicarbonate (2 × 20 ml) and brine (2 × 20 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give a crude product. Purification by flash column chromatography (SiO_2, from 3:1 to 2:1; Et_2O–PE 40–60) yielded the title compounds **11a** and **11b** (overall 130 mg, 67%, as a 1:1 inseparable mixture of regioisomers) as a brown oil; ν_{max} (thin film)/cm^{-1} 3438w, 3281w (NH), 2978s, 2933w (CH), 1715br s (C=O), 1603s, 1505s, 1367s, 1253s, 1155s, 1056m, 847w; δ_H (200 MHz; $CDCl_3$, both regioisomers corresponding to 58H) 1.42 (18H, s, 2 × C(CH_3)$_3$), 1.43 (18H, s, 2 × C(CH_3)$_3$), 2.8–3.0 (2H, m, CH_2), 3.19 (2H, br d, *J* 5.0, CH_2), 4.45–4.60 (2H, br m, 2 × C*H*), 5.38 (1H, br d, *J* 8.5 Hz, N*H*), 5.46 (1H, br d, *J* 8.5 Hz, N*H*), 6.29 (1H, d, *J* 2.5 Hz, Ar*H*), 6.85–6.92 (1H, m, Ar*H*), 7.02–7.06 (2H, m, Ar*H*), 7.22–7.30 (3H, m, Ar*H*), 7.39–7.46 (3H, m, Ar*H*), 7.6–7.7 (2H, m, Ar*H*), 7.83 (1H, d, *J* 2.5 Hz, Ar*H*), 8.39 (1H, br s, Ar*H*); δ_C (125.8 MHz; $CDCl_3$ both regioisomers) 27.93 (C(*C*H$_3$)$_3$), 28.30 (C(*C*H$_3$)$_3$), 31.04 (*C*H$_2$), 38.04 (*C*H$_2$), 51.85 (*C*H), 53.32 (*C*H), 79.47 (*C*(CH$_3$)$_3$), 79.64 (*C*(CH$_3$)$_3$), 81.69 (*C*(CH$_3$)$_3$), 81.98 (*C*(CH$_3$)$_3$), 107.56, 113.01, 118.72, 120.74 (4 × Ar-*C*H), 121.55 (Ar-*C*, *ipso*), 126.08, 127.25, 129.25, 129.32 (4 × Ar-*C*H), 139.90, 143.20, 151.00 (3 × Ar-*C*, *ipso*), 155.27, 170.54, 170.84 (3 × *C*=O); *m*/*z* (APCI+) 388 (MH$^+$, 35%), 332 [MH$^+$ − (C_4H_8), 30] and 276 [MH$^+$ − 2 × (C_4H_8), 100]; HRMS found MH$^+$ 388.2236; $C_{21}H_{30}N_3O_4$ requires 388.2236.

(*S*)-2-*tert*-Butoxycarbonylamino-3-(isoxazol-3-yl)propanoic acid *tert*-butyl ester 12a

To a stirred solution of **4** (59.4 mg, 0.20 mmol) in ethanol (2 ml) was added hydroxylamine hydrochloride (13.9 mg, 0.20 mmol). The reaction was then heated to reflux and stirred overnight before being concentrated *in vacuo*. The residue was taken into ethyl acetate, washed with saturated aqueous sodium bicarbonate (2 × 10 ml) and brine (2 × 10 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give a crude product. Purification by flash column chromatography (SiO_2, from 1 : 3; EtOAc–PE 40–60) yielded the title compound **12a** (38.5 mg, 62%) as a white solid; mp 95–98 °C; $[\alpha]_D^{26}$ +23.1 (*c* 0.5 in $CHCl_3$); ν_{max} (thin disc)/cm^{-1} 3362br w (NH), 2980m, 2934w (CH), 1715br s (C=O), 1503m, 1368s, 1251m, 1155s, 1054w, 848w; δ_H (200 MHz; $CDCl_3$) 1.43 (9H, s, C(C*H*$_3$)$_3$), 1.44 (9H, s, C(C*H*$_3$)$_3$), 3.20 (2H, br d, *J* 5.5 Hz, C*H*$_2$), 4.49–4.59 (1H, br m, C*H*), 5.30 (1H, br d, *J* 6.0 Hz, N*H*), 6.28 (1H, d, *J* 1.5 Hz, Ar*H*), 8.35 (1H, d, *J* 1.5 Hz, Ar*H*); δ_C (125.8 MHz; $CDCl_3$) 27.85 (C(*C*H$_3$)$_3$), 28.26 (C(*C*H$_3$)$_3$), 29.06 (*C*H$_2$), 52.54 (*C*H), 79.90 (*C*(CH$_3$)$_3$), 82.58 (*C*(CH$_3$)$_3$), 104.66 (Ar-*C*H), 155.00 (HN*C*=O), 158.34 (Ar-*C*H), 170.04 (*C*=O); *m*/*z* (APCI+) 313 (MH^+, 4%), 257 [$MH^+ - (C_4H_8)$, 10], 213 [$MH^+ - (CO_2 + C_4H_8)$, 70], 157 [$MH^+ - (CO_2 + 2 \times C_4H_8)$, 100]; HRMS found MH^+ 313.1761; $C_{15}H_{25}N_2O_5$ requires 313.1763.

(*S*)-2-*tert*-Butoxycarbonylamino-3-(isoxazol-3-yl)propanoic acid *tert*-butyl ester 12a and (*S*)-2-*tert*-butoxycarbonylamino-3-(isoxazol-5-yl)propanoic acid *tert*-butyl ester 12b

To a stirred solution of **4** (50.5 mg, 0.17 mmol) in ethanol (2 ml) was added hydroxylamine hydrochloride (11.8 mg, 0.17 mmol) and pyridine (19.5 µl, 0.24 mmol). The reaction was then heated to reflux and stirred overnight before being concentrated *in vacuo*. The residue was taken into ethyl acetate, washed with saturated aqueous sodium bicarbonate (2 × 10 ml) and brine (2 × 10 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give a crude product. Purification by flash column chromatography (SiO_2, from 2 : 7; EtOAc–PE 40–60) yielded the title compounds **12a** and **12b** (overall 27.1 mg, 51%, as an inseparable 1 : 3 mixture of regioisomers) as a white solid; data for **12b**, δ_H (200 MHz; $CDCl_3$) 1.42 (9H, s, C(C*H*$_3$)$_3$), 1.44 (9H, s, C(C*H*$_3$)$_3$), 3.28–3.34 (2H, br m, C*H*$_2$), 4.47–4.55 (1H, br m, C*H*), 5.24 (1H, br d, *J* 8.0 Hz, N*H*), 6.09 (1H, d, *J* 1.5 Hz, Ar*H*), 8.17 (1H, d, *J* 1.5 Hz, Ar*H*); δ_C (125.8 MHz; $CDCl_3$) 27.84 (C(*C*H$_3$)$_3$), 28.25 (C(*C*H$_3$)$_3$), 29.71 (*C*H$_2$), 52.46 (*C*H), 80.07 (*C*(CH$_3$)$_3$), 82.94 (*C*(CH$_3$)$_3$), 101.97, 150.21 (2 × Ar-*C*H), 155.01, 158.71, 169.58 (Ar-*C*, *ipso*; 2 × *C*=O).

(*S*)-2-*tert*-Butoxycarbonylamino-4-(1-phenyl-1,2,3-triazol-4-yl)-4-oxobutanoic acid *tert*-butyl ester 13

To a stirred solution of **4** (148.5 mg, 0.50 mmol) in Et_2O (5 ml) was added phenyl azide (59.5 mg, 0.5 mmol) and the reaction mixture heated to reflux for 24 hours. The solvent was then removed *in vacuo* to generate a crude product. Purification by flash column chromatography (SiO_2, 4 : 5; Et_2O–PE 40–60) yielded the title compound **13** (189 mg, 91%) as a white crystalline solid; mp 116–117 °C; $[\alpha]_D^{22}$ 32.9 (*c* 1.74 in $CHCl_3$) (Found: C, 60.43; H, 6.83; N, 13.35. $C_{21}H_{28}N_4O_5$ requires C, 60.57; H, 6.78; N, 13.45%); ν_{max} (thin disc)/cm^{-1} 3372br w (NH), 2979m (CH), 1708s (C=O), 1506s, 1368s, 1257m, 1155s, 1020m, 847w; δ_H (200 MHz; $CDCl_3$) 1.45 (18H, s, 2 × C(C*H*$_3$)$_3$), 3.66 (1H, dd, *J* 4.5 Hz, 18.0, C*H*(H)), 3.86 (1H, dd, *J* 4.5 and 18.0 Hz, CH(*H*)), 4.63–4.72 (1H, m, C*H*), 5.53 (1H, d, *J* 8.0 Hz, N*H*), 7.51–7.64 (3H, m, Ar*H*), 7.74–7.80 (2H, m, Ar*H*), 8.52 (1H, s, Ar*H*); δ_H (200 MHz; CD_3OD) 1.42 (18H, s, 2 × C(C*H*$_3$)$_3$), 3.42–3.68 (2H, m, C*H*$_2$), 4.61 (1H, t, *J* 6.0 Hz, C*H*), 7.51–7.63 (3H, m, Ar*H*), 7.86–7.91 (2H, m, Ar*H*), 9.11 (1H, s, Ar*H*); δ_C (50.3 MHz; $CDCl_3$) 27.74 (C(*C*H$_3$)$_3$), 28.18 (C(*C*H$_3$)$_3$), 42.00 (*C*H$_2$), 50.05 (*C*H), 79.75 (*C*(CH$_3$)$_3$), 82.14 (*C*(CH$_3$)$_3$), 120.95, 123.81, 129.83, 130.19 (4 × Ar-*C*H), 136.48, 147.97 (2 × Ar-*C*, *ipso*), 155.75, 170.71, 192.73 (3 × *C*=O); *m*/*z* (APCI+) 417 (MH^+, 7%), 361 [$MH^+ - (C_4H_8)$, 25] and 305 [$MH^+ - 2 \times (C_4H_8)$, 100); HRMS found MH^+ 417.2138; $C_{21}H_{29}N_4O_5$ requires 417.2138.

General procedure for selective Boc deprotection and Mosher's amide formation

Typically, to a solution of the protected amino acid (1 equiv.), in toluene, was added toluene-*p*-sulfonic acid monohydrate (1 equiv.). The toluene was then gradually removed *in vacuo*. To the residue was added toluene and the process repeated approximately 10 further times. The resulting residue was taken into ethyl acetate before being washed with saturated aqueous sodium bicarbonate solution and brine, dried over $MgSO_4$ and concentrated *in vacuo*. To a solution of the resulting free amine in DCM was added either (*R*)- or (*S*)-2-methoxy-2-(trifluoromethyl)phenylacetyl chloride (1 equiv.), excess pyridine and catalytic DMAP. After being stirred overnight the reaction mixture was concentrated *in vacuo*, taken into ethyl acetate, washed with saturated aqueous sodium bicarbonate solution and brine, dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude product for ^{19}F NMR analysis.

(*S*)-3-(5-Methoxycarbonyl-6-methylpyridin-2-yl)-2-aminopropanoic acid *tert*-butyl ester. δ_H (200 MHz; $CDCl_3$) 1.39 (9H, s, C(C*H*$_3$)$_3$), 2.79 (3H, s, ArC*H*$_3$), 3.13 (1H, dd, *J* 7.5 and 15.0 Hz, 3-C(*H*)H), 3.31 (1H, dd, *J* 4.5 and 15.0 Hz, 3-C(H)*H*), 3.91 (3H, s, OC*H*$_3$), 4.01 (1H, dd, *J* 4.5 and 7.5 Hz, 2-C*H*), 7.08 (1H, d, *J* 8.0 Hz, Ar-C*H*), 8.13 (1H, d, *J* 8.0 Hz, Ar-C*H*).

δ_F of (*R*,*S*)-Mosher's amide using (*R*)-Mosher's acid chloride −71.03 ppm, δ_F of (*SS*)-Mosher's amide using (*S*)-Mosher's acid chloride −69.79 ppm.

(*S*)-3-(5-Acetyl-6-methylpyridin-2-yl)-2-aminopropanoic acid *tert*-butyl ester. δ_H (200 MHz; $CDCl_3$) 1.42 (9H, s, C(C*H*$_3$)$_3$), 2.58 (3H, s, ArC*H*$_3$), 2.72 (3H, s, COC*H*$_3$), 3.07 (1H, dd, *J* 7.5 and 14.5 Hz, 3-C(*H*)H), 3.27 (1H, dd, *J* 5.0 and 14.5 Hz, 3-C(H)*H*), 3.91 (1H, dd, *J* 5.0 and 7.5 Hz, 2-C*H*), 7.12 (1H, d, *J* 8.0 Hz, Ar-C*H*), 7.92 (1H, d, *J* 8.0 Hz, Ar-C*H*).

δ_F of (*RS*)-Mosher's amide using (*R*)-Mosher's acid chloride −71.01 ppm, δ_F of (*SS*)-Mosher's amide using (*S*)-Mosher's acid chloride −69.77 ppm.

(*S*)-4-(1-Phenyl-1,2,3-triazol-4-yl)-4-oxo-2-aminobutanoic acid *tert*-butyl ester, toluene-*p*-sulfonate salt. δ_H (200 MHz; $CDCl_3$) 1.31 (9H, s, C(C*H*$_3$)$_3$), 2.10 (3H, s, C*H*$_3$), 3.85–4.01 (2H, m, C*H*$_2$), 4.54–4.62 (1H, m, C*H*), 6.87 (2H, d, *J* 8.0 Hz, Ar*H*), 7.32–7.44 (3H, m, ArH), 7.58 (2H, d, *J* 8.0 Hz, Ar*H*), 7.65–7.70 (2H, m, Ar*H*), 8.21 (3H, br s, NH_3^+), 8.89 (1H, s, ArH).

δ_F of (*RS*)-Mosher's amide using (*R*)-Mosher's acid chloride −69.24 ppm, δ_F of (*SS*)-Mosher's amide using (*S*)-Mosher's acid chloride −69.74 ppm.

General procedure for the amino acid deprotection and purification

Typically, to a stirred solution of the protected compounds, in trifluoroacetic acid and dichloromethane was added anisole (*ca.* 3% v/v). The reaction mixture was stirred at room temperature overnight before being concentrated *in vacuo* and triturated with Et_2O to give a crude TFA salt. This could then be purified by ion-exchange chromatography using Dowex® 50X8-100 ion-exchange resin. The crude TFA salts were loaded in aqueous solution and eluted using 2 M aqueous ammonia solution.

(*S*)-3-(5-Carboxy-6-methylpyridin-2-yl)-2-aminopropanoic acid 14. When the usual procedure was operated on **9** (100 mg, 0.25 mmol), 52 mg of a (2 : 1; α-amino acid ester–amino-diacid) mixture was obtained. Thus the mixture was further subjected

to reflux in 1 M HCl (4 ml) aqueous solution for 24 hours to give 57 mg of the amino-diacid hydrochloride salt on evaporation of the solvent under vacuum. The free amino-diacid was liberated using ion-exchange chromatography to afford the title compound **14** as a white powder (45 mg, 80%); ν_{max}(thin disc)/cm^{-1} 3043br, 1588s (C=O str), 1398s, 1104m, 969w, 864w, 825w, 789w, 534w; δ_H (200 MHz; D_2O) 2.34 (3H, s, CH_3), 2.98 (1H, dd, *J* 8.0 and 15.0 Hz, 3-C(*H*)H), 3.17 (1H, dd, *J* 5.0 and 15.0 Hz, 3-C(H)*H*), 3.87 (1H, dd, *J* 5.0 Hz and 8.0 Hz, 2-C*H*), 7.01 (1H, d, *J* 8.0 Hz, Ar-C*H*), 7.55 (1H, d, *J* 8.0 Hz, Ar-C*H*); δ_C (50.31 MHz; D_2O) 21.65 (*C*H$_3$), 37.12 (3-*C*H$_2$), 54.80 (2-*C*H), 122.19 (Ar-*C*H), 134.31 (Ar-*C*), 137.29 (Ar-*C*H), 154.45, 154.77 (2 × Ar-*C*), 173.79 (*C*O$_2$H), 176.50 (*C*O$_2$H); *m*/*z* (APCI, CI$^+$) 225 [MH$^+$, 35%] and 152 [100].

(*S*)-3-(5-Acetyl-6-methylpyridin-2-yl)-2-aminopropanoic acid 15. Carrying out the TFA–anisole procedure followed by ion exchange on **10** (100 mg, 0.26 mmol) afforded **15** (50 mg, 85%) as a yellow powdery solid; ν_{max}(thin disc)/cm^{-1} 3168br, 1684s (C=O str), 1587s (C=O str), 1500s, 1420s, 1360s, 1295m, 1264s, 1146m, 1097w, 1061m, 972m, 934w; δ_H (200 MHz; D_2O) 2.39 (6H, s, 2 × CH_3), 3.00–3.22 (2H, m, 3-CH_2), 3.90 (1H, dd, *J* 5.5 and 7.0 Hz, 2-C*H*), 7.08 (1H, d, *J* 8.0 Hz, Ar-C*H*), 7.92 (1H, d, *J* 8.0 Hz, Ar-C*H*); δ_C (50.31 MHz; D_2O) 23.46 (Ar*C*H$_3$), 29.40 (CO*C*H$_3$), 37.24 (3-*C*H$_2$), 54.64 (2-*C*H), 122.00 (Ar-*C*H), 132.17 (Ar-*C*), 139.60 (Ar-*C*H), 157.76, 158.61 (2 × Ar-*C*), 173.68 (*C*O$_2$H), 206.17 (*C*OCH$_3$); *m*/*z* (APCI, CI$^+$) 223 [MH$^+$, 57%], 177 [100] and 149 [82].

(*S*)-3-(1-Phenylpyrazol-3-yl)-2-aminopropanoic acid trifluoroacetate 16a and (*S*)-3-(2-phenylpyrazol-3-yl)-2-aminopropanoic acid trifluoroacetate 16b. Compounds **16a** and **16b** were prepared from **11a/b** (as a 1:1 mixture of regioisomers) (31 mg, 0.08 mmol), TFA (0.5 ml), anisole (50 µl) and DCM (2 ml), followed by ether tituration to yield the TFA salt **16a/b** (27 mg, 98%) as a dark brown solid; mp 75–81 °C (decomp.); ν_{max} (KBr)/cm^{-1} 3600–2400br m (NH/OH), 3060m (CH), 1676s (C=O), 1600s, 1501s, 1400w, 1319w, 1202s, 1054w, 800w; δ_H (500 MHz; D_2O, 20H for both **16a/b**) 3.21–3.31 (4H, s, CH_2(**16a** and **16b**)), 4.11–4.13 (2H, m, C*H*(**16a** and **16b**)), 6.40 (1H, d, *J* 2.5 Hz, Ar*H*), 7.28–7.59 (12H, m, Ar*H*), 8.03 (1H, d, *J* 2.5 Hz, Ar*H*); δ_C (125.8 MHz; D_2O), 28.59 (*C*H$_2$), 53.74 (*C*H), 107.57, 114.91, 119.65, 123.93, 125.53, 127.15, 129.39, 129.51, 129.60, 130.32, 139.20, 148.44, 172.65 (*C*=O); *m*/*z* (APCI+) 232 (MH$^+$, 80%), 197 (50) and 94 (100); HRMS found MH$^+$ 232.1084; $C_{12}H_{14}N_3O_2$ requires 232.1086.

(*S*)-3-(Isoxazol-3-yl)-2-aminopropanoic acid trifluoroacetate 17a and (2*S*)-3-(isoxazol-5-yl)-2-aminopropanoic acid trifluoroacetate 17b. Compounds **17a** and **17b** were prepared from **12a/b** (as a 1:3 mixture of regioisomers) (15.6 mg, 0.05 mmol), TFA (0.5 ml), anisole (50 µl) and DCM (2 ml), followed by ether tituration to yield the TFA salt **17a/b** (13 mg, 96%) as a white solid; mp 205–209 °C (decomp.); ν_{max} (KBr)/cm^{-1} 3540–2480br m, 3504m (*c* H, O H, NH), 1735s, 1690s (C=O), 1594m, 1454w, 1177m, 1053w, 818w; δ_H (500 MHz; D_2O **17a:17b** (1:3)) 3.20–3.30 (2H, m, CH_2(**17a**)), 3.32–3.42 (2H, m, CH_2(**17b**)), 4.01–4.03 (2H, m, C*H*(**17a** and **17b**)), 6.29 (1H, d, *J* 2.0 Hz, Ar*H*(**17a**)), 6.39 (1H, d, *J* 1.5 Hz, Ar*H*(**17b**)), 8.30 (1H, d, *J* 2.0 Hz, Ar*H*(**17a**)), 8.50 (1H, d, *J* 1.5 Hz, Ar*H*(**17b**)); δ_C (125.8 MHz; D_2O) 26.80, 27.38 (*C*H$_2$), 52.95, 53.09 (*C*H), 103.40, 104.92, 151.47 (3 × Ar-*C*H), 158.51 (Ar-*C, ipso*), 160.35 (Ar-*C*H), 166.79, 172.47, 172.75 (Ar-*C, ipso*, 2 × *C*=O); *m*/*z* (APCI+) 157 (MH$^+$, 20%) and 141 (100); HRMS found MH$^+$ 157.0617; $C_6H_9N_2O_3$ requires 157.0613.

(*S*)-4-(1-Phenyl-1,2,3-triazol-4-yl)-4-oxo-2-aminobutanoic acid trifluoroacetate 18. Compound **18** was prepared from **13** (25 mg, 0.06 mmol), TFA (0.5 ml), anisole (50 µl) and DCM (2 ml), followed by ether tituration to yield the TFA salt **18** (22.4 mg, 100%) as a white solid; mp 156–158 °C (decomp.); $[a]_D^{22}$ +7.3 (*c* 0.22 in 1 M NaOH); ν_{max} (KBr)/cm^{-1} 3520–2400br m (NH/OH), 2958m (CH), 1735s, 1697s (C=O), 1655s, 1538m, 1507s, 1393m, 1209s, 1183s, 1136s, 1024w, 850w; δ_H (500 MHz; D_2O) 3.75–3.85 (2H, m, CH_2), 4.43–4.45 (1H, m, C*H*), 7.48–7.54 (3H, m, Ar*H*), 7.68–7.69 (2H, m, Ar*H*), 8.99 (1H, s, Ar*H*); δ_C (125.8 MHz; D_2O), 39.01 (*C*H$_2$), 48.48 (*C*H), 121.29, 126.87, 129.93, 130.10 (4 × Ar-*C*H), 135.67, 145.66 (2 × Ar-*C, ipso*), 171.39, 191.24 (2 × *C*=O); *m*/*z* (APCI+) 261 (MH$^+$, 20%), 172 (70) and 102 (100).

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