The synthesis of pyrimidin-4-yl substituted α-amino acids. A versatile approach from alkynyl ketones

Robert M. Adlington, Jack E. Baldwin,* David Catterick and Gareth J. Pritchard

The Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford, UK OX1 3QY. E-mail: jack.baldwin@dpl.ox.ac.uk

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The reaction of amidines with α-amino acid alkynyl ketones is shown to be a versatile route to pyrimidin-4-yl substituted α-amino acids. This route is also applicable to a parallel synthesis approach and has allowed the formation of a range of pyrimidin-4-yl substituted α-amino acids, including the naturally occurring α-amino acid L-lathyrine **4**.

Introduction

In recent years the stereoselective synthesis of proteinogenic and non-proteinogenic α-amino acids has proved to be an active field of research.[1] The interest in non-proteinogenic amino acids has arisen due to the biological and toxicological properties displayed by many of these compounds.[2] The non-proteinogenic amino acids are a diverse range of compounds and in particular heterocyclic substituted non-proteinogenic α-amino acids display a wide range of biological activities. Examples of these include azatyrosine **1**,[3] mimosine **2**,[4] discadenine **3**[5] and lathyrine **4**[6,7]whose activities include antibiotic, antitumor and wool growth inhibition. Many non-proteinogenic amino acids are also found in a range of γ-glutamyl-linked peptides, cyclic and other peptides such as NK374200 **5**, which contains a novel peptidyl adenine nucleus and displays insecticidal activity (Fig. 1).[8]

In view of the diverse activities displayed we wished to develop a versatile synthetic route to these types of compounds. Due, however, to the ever increasing demand being placed upon synthetic organic chemistry to provide potentially biologically active compounds we also wished to develop synthetic routes that may be applicable to parallel and/or combinatorial syntheses. In order to access a diverse range of products we chose to generate a reactive group within a molecule that would allow efficient construction of a range of heterocycles. It was decided to attempt this initially by the introduction of a reactive moiety into the side chain of α-amino acids. These species could then be subsequently reacted with a whole range of different substrates, allowing families of related compounds to be generated quickly, in appreciable quantities and with family members of known composition (Scheme 1).

It was decided to direct our initial investigations towards a range of pyrimidine substituted α-amino acids, with the naturally occuring amino acid L-lathyrine **4** as a specific target compound. L-Lathyrine is a structurally simple pyrimidine substituted α-amino acid which displays a diverse range of bioactivities, including pollen growth inhibition, antitumor properties and hypoglycaemic activity.[6,7] Our initial target was therefore the synthesis of a reactive group capable of pyrimidine formation. One simple retrosynthesis of the pyrimidine core is illustrated below; this required initially a 1,3-dinitrogen amidine type synthon along with an alkynyl ketone synthon. This can then be further disconnected to functionalised acetylene and activated carboxylate synthons. If an analogous analysis is therefore carried out on L-lathyrine **4** the synthons could be represented by L-aspartic acid, acetylene and guanidine (Fig. 2).

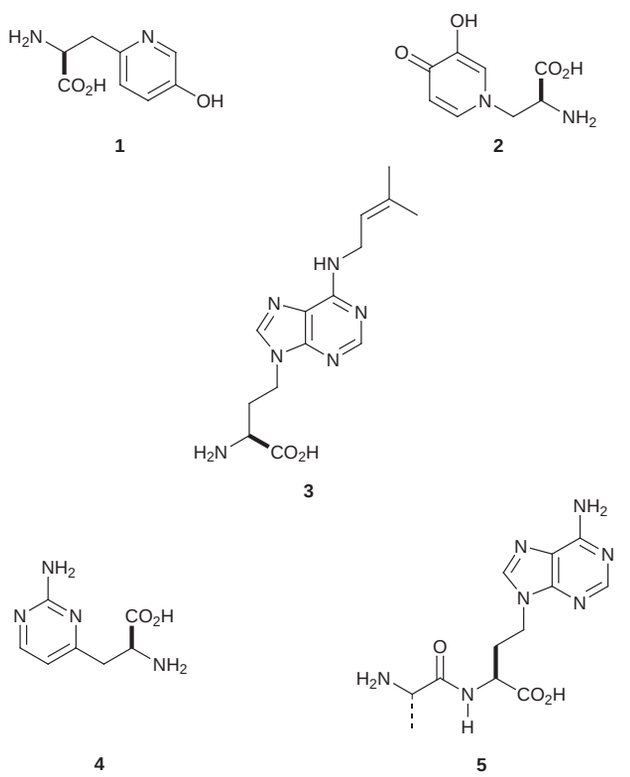
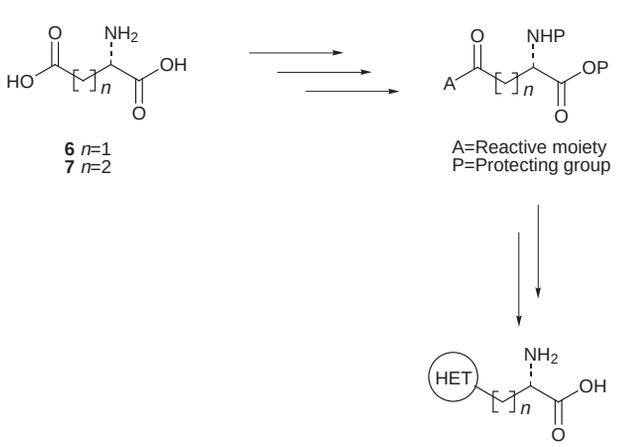


Fig. 1



Scheme 1

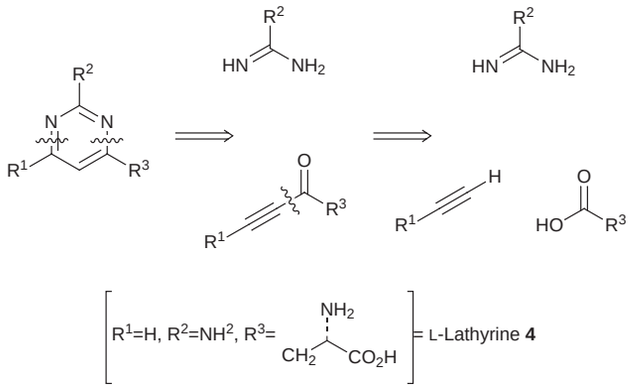
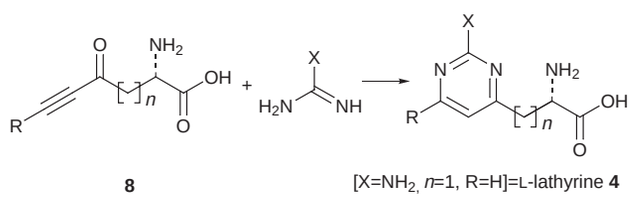


Fig. 2

We observed that alkynyl ketones have been used in the formation of a range of heterocyclic systems including a single literature precedent for the condensation of alkynyl ketones with guanidine to generate 2-amino substituted pyrimidines.[9] Most recently they have been used in pyrimidine synthesis *via* a condensation with amidines.[10,11] Due to the large number of amidines available the alkynyl ketone moiety therefore appeared most attractive as a potential reactive group for a parallel synthesis. Introduction of the alkynyl ketone functionality into the side chain of different α-amino acids offered the possibility of three different groups on the heterocyclic ring and therefore a large number of structurally related families would be readily accessible (Scheme 2).



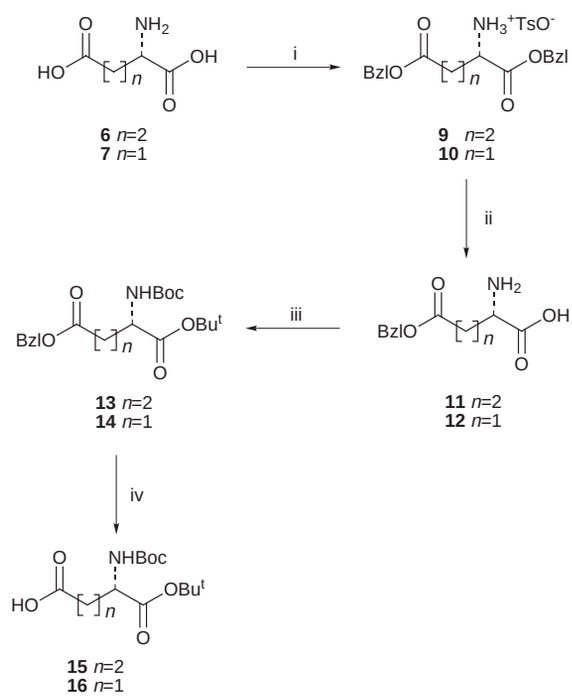
Scheme 2

Herein we fully describe a versatile stereoselective synthetic route to pyrimidin-4-yl substituted α-amino acids which has not only allowed the total synthesis of the natural product L-lathyrine **4** but is also applicable to the parallel synthesis of families of substituted amino acid compounds.[11]

Results and discussion

Methodologies which exist for alkynyl ketone synthesis include coupling of acid chlorides with an organocopper alkynyl derivative or an alkynyllithium in the presence of zinc chloride,[12,13] the cross coupling of an acid chloride with a tributylstannyl alkynyl derivative in the presence of a palladium(0) catalyst,[14] the addition of alkynyllithium to aldehydes followed by oxidation of the resulting acetylenic alcohol,[15] and nucleophilic substitution of 'Weinreb' amides with metalloacetylide reagents.[16]

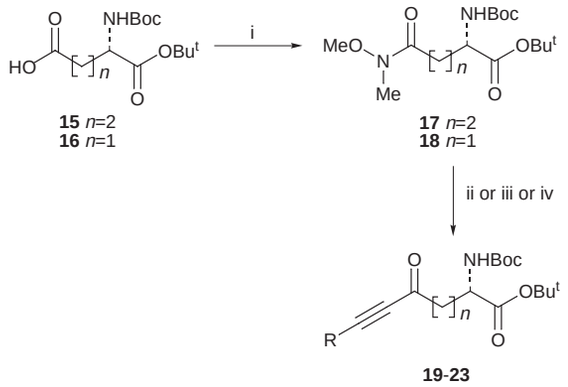
From our retrosynthesis it was considered that the side chain carboxylic acid groups in L-glutamic acid **6** and L-aspartic acid **7** would be a suitable precursor to a reactive group alkynyl ketone **8**. Introduction of the alkynyl ketone functionality could be carried out by side chain activation and reaction with a metallo acetylide. The activation chosen was conversion of the side chain acid into the 'Weinreb' amide,[16] which has been used to synthesise α′-amino-α,β-ynones and aryl ketone amino acids.[17,18] L-Glutamic acid was thus selectively protected at the α-amine and α-carboxylic acid functionalities following a four step literature procedure. Initially the dibenzyl ester tosylate salt **9** was prepared in good yield (72%) by treatment of **6** with benzyl alcohol and toluene-*p*-sulfonic acid monohydrate in refluxing benzene, as reported by Olsen.[19] The resulting salt then underwent a pH dependant, copper chelated mono deprotection as reported by Prestidge, to generate after EDTA decomplexation the desired mono γ-benzyl protected amino acid **11**.[20] The free α-carboxylic acid was then protected as a *tert*-butyl ester by reaction with isobutylene and concentrated sulfuric acid in 1,4-dioxane, followed by Boc protection of the α-amine by treatment with di-*tert*-butyl dicarbonate and triethylamine to give **13**.[19] Catalytic hydrogenation of the triprotected glutamate **13**, removed the γ-benzyl ester and thus generated α-*tert*-butyl *N*-*tert*-butoxycarbonylglutamate **15**, as required for side chain activation, in satisfactory overall yield (33%) (Scheme 3).



Scheme 3 *Reagents and conditions*: i, $TsOH\cdot H_2O$, C_6H_6, $PhCH_2OH$, reflux, 72% (**9**), 76% (**10**); ii, EtOH, $CuSO_4\cdot 5H_2O$, H_2O, pH 8 (60 minutes) to pH 3, 32 °C then EDTA–H_2O, 100 °C, 56% (**11**), 100% (**12**); iii, 1,4-dioxane, H_2SO_4 (conc.), $(Me)_2C{=}CH_2$, RT then NEt_3, H_2O, $(Boc)_2O$, 0 °C, 81% (**13**), 48% (**14**); iv, H_2, Pd/C (10%), EtOH (95%), 100% (**15**), 100% (**16**).

With the selectively protected amino acid **15** in hand, side chain activation by conversion to the 'Weinreb' amide was carried out. Reaction with *N*,*O*-dimethylhydroxylamine *via* a mixed anhydride thus generated **17** in good yield (74%).[18] Subsequent reaction of this amide **17** with a five fold excess of lithium phenylacetylide or lithium pentylacetylide at −78 °C in THF or ethynylmagnesium bromide at −78 °C in diethyl ether thus afforded the alkynyl ketones **19**, **20** and **21** in good yields (Scheme 4 and Table 1). We had therefore successfully generated a range of reactive groups, containing aryl, alkyl and hydrogen functionalities, which could in turn allow control and variation of the resulting pyrimidine functionality.

Trial cyclocondensations between **19** (R = Ph) and benzamidine hydrochloride were then attempted in order to optimise conditions for the formation of the desired pyrimidinyl substituted amino acid **24** (R = Ph, X = Ph). Initially **24** was isolated in low yield (16%) by their reaction in ethanol with one equivalent of sodium ethoxide. The yield was then improved (70%) by reaction in a butanone solution with solid K_2CO_3 and a catalytic amount of water at reflux. Optimal conditions were eventually found to be stirring an MeCN or EtOAc solution of the alkynyl ketone with benzamidine hydrochloride and solid Na_2CO_3 with a catalytic amount of water at reflux (87%). A range of hetero, aryl, alkyl and hydrogen functionalised amidines were then selected in order to investigate not only the



Scheme 4 *Reagents and conditions*: i, NMM, Bu^{t}OCOCl, THF, −15 °C; HN(OMe)Me·HCl, NEt_3, DMF, 74% (**17**), 76% (**18**); ii, PhC≡CLi (5 equiv.), THF, −78 °C; iii, HCCMgBr (5 equiv.), Et_2O, −78 °C; iv, PrCCLi (5 equiv.), THF, −78 °C.

Table 1 Protected α-amino acid alkynyl ketones from the reaction of 'metallo-acetylides' with Weinreb amides

Compound	*n*	R	Yield (%)
19	2	Ph	79
20	2	H	61
21	2	Pr	95
22	1	Ph	62
23	1	H	78

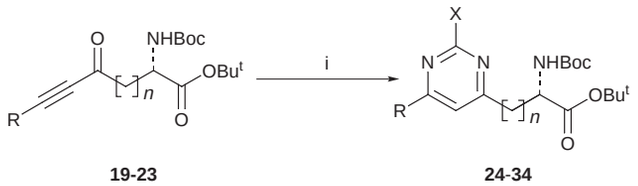
effect of varying substitution on the cyclocondensations with **19**, **20** and **21** but also to highlight the generality and overall flexibility of the procedure.[21] Pyrimidines **24**–**31** were thus generated, in generally excellent yields, the variation in the amidine functionalisation allowing control of the resulting pyrimidine 2 position (Scheme 5 and Table 2).

Two cyclocondensations however, with formamidine and guanidine, were of much lower yield than those for other amidines. The low yield observed in the condensation with formamidine (40%) was attributed to the low boiling point of the formamidine with respect to the reaction conditions. The optimal reaction conditions were therefore adjusted to 40 °C with 10 equivalents of the formamidine. The low yield observed with guanidine (28%) was attributed to its three nucleophilic sites thus leading to the possible formation of undesirable polymeric products. The yield however compared favourably to that reported for the condensation of guanidine with phenyl ethynyl ketone (25%).[9]

Cyclocondensations with urea were also attempted, however these proved unsuccessful with no reaction being observed. This lack of reactivity towards the alkynyl ketone functionality compared to the amidines was attributed to urea's lower nitrogen nucleophilicity.

In order to determine whether any racemisation of the amino acid α centre had occured it was next decided to carry out Mosher's amide formation. Selective Boc-deprotection by azeotropic distillaton with TsOH·H_2O–PhMe was therefore carried out and the free amine released by washing with saturated aqueous sodium bicarbonate solution. The *N*-deprotected forms were then converted into both Mosher's amides by coupling with both (*R*)- and (*S*)-Mosher's acid chlorides in dichloromethane with pyridine and catalytic DMAP. ^{19}F NMR analysis of the resulting diastereoisomers then proved the enantiomeric purity to be greater than 98% ee.[22]

We had thus shown that from a key precursor **17** a large family of diverse structures can be quickly built which incorporate hydrogen, alkyl, aryl and hetero functionalities. Control of the resulting substituted pyrimidines being possible at the 6 position by the choice of the acetylide used and at the 2 position by the amidine chosen.



Scheme 5 *Reagents and conditions*: i, HN(CX)NH_2·HCl or 0.5 H_2SO_4, EtOAc or CH_3CN, Na_2CO_3, H_2O (cat.), reflux (or 40 °C for X = H and for all *n* = 1).

Table 2 (Pyrimidin-4-yl) substituted protected α-amino acids from the cyclocondensations of ethynyl ketones with amidines

Compound	*n*	R	X	Yield (%)
24	2	Ph	Ph	87
25	2	Ph	Me	90
26	2	Ph	H	40
27	2	Ph	SMe	79
28	2	H	SMe	82
29	2	H	NH_2	28
30	2	Pr	SMe	95
31	2	Pr	Me	83
32	1	Ph	SMe	91
33	1	Ph	4-Cl-C_6H_4	89
34	1	H	SMe	87

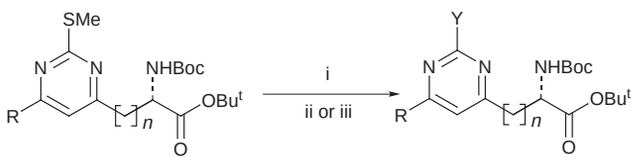
In order to diversify the methodology by varying the substitution at the pyrimidine 4 position, the above chemistry was expanded to L-aspartic acid **7**. The α-*tert*-butyl *N*-(*tert*-Boc)-aspartate **16** was prepared and converted to the 'Weinreb' amide **18**, as previously for **17**, in 28% over five steps. The acetylenic ketones **22** and **23** were then formed by reaction of **18** with, a five fold excess of, lithium phenylacetylide and ethynylmagnesium bromide respectively (Scheme 4 and Table 1). These ketones, **22** and **23**, then underwent high yielding cyclocondensations with amidines to produce the pyrimidines **32**, **33** and **34** (Scheme 5 and Table 2).

An analogous investigation into the enantiomeric purity of these pyrimidine substituted compounds by Mosher's amide formation, however, showed up to 5% racemisation. Subsequent Mosher's amide formation of the precursors indicated that the observed racemisation that occurred was taking place in the cyclocondensation step. By carrying out these condensations at temperatures below reflux however, it was discovered that the degree of racemisation was reduced. Cyclocondensations, under analogous conditions, at 40 °C thus afforded enantiomeric purity greater than 98% ee.

One of the compounds generated of particular note is **29** which is a homologue of the naturally occurring amino acid L-lathyrine **4**.[6,7] This had been generated by the condensation of **21** with guanidine which as previously noted had been in a disappointingly low yield. In order to attempt the synthesis of L-lathyrine itself as well as analogues and to further diversify the functionality at the pyrimidine 2 position it was decided to undertake 'nucleophilic' substitutions of a suitable leaving group. It was expected that the existing methylthio functionality, derived from cyclisations of alkynyl ketones with 2-methyl-2-thiopseudourea, if oxidised to the corresponding sulfone, would be susceptible to substitution by nucleophiles. It has been documented that the sulfonyl group when at the 2-positon of pyrimidine rings is readily susceptible to 'nucleophilic displacement' type chemistry, even more so than their 2-chloro analogues.[23] Reaction of the pyrimidines **28**, **30**, **32** and **34** with 2 equivalents of MCPBA in dichloromethane at room temperature thus resulted in the formation of the corresponding sulfones **35**– **38** in excellent yields (76–100%).

In order to access 2-aminopyrimidines we required substitution of the methylsulfonyl group with ammonia. Similar literature substitutions with primary amines and hyrazine were carried out at reflux in ethanol for up to four hours; conditions

which were unsuitable for our needs. Substitution of the methyl sulfonyl group was therefore attempted using ammonia saturated THF solutions at room temperature and THF–liquid ammonia at −33 °C, however these conditions proved unsuccessful. Substitution was eventually achieved by reaction of a concentrated THF solution of the sulfone with an excess of liquid ammonia at room temperature in a sealed vessel. Good yields of the corresponding pyrimidines **39**–**41** were thus achieved, **41** (R = H, Y = H) being protected L-lathyrine (Scheme 6 and Table 3).



28 *n*=2, R=H **32** *n*=1, R=Ph
30 *n*=2, R=Pr **34** *n*=1, R=H

35-41

Scheme 6 *Reagents and conditions*: i, MCPBA (2 equiv.), DCM, RT; ii, 1,4-dioxane, 1 M NaOH, RT; iii, NH_3(l), THF, RT.

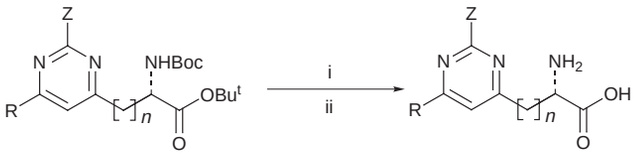
Table 3 Results for oxidation of **28**, **30**, **32** and **34** and subsequent nucleophilic substitutions

Compound	*n*	R	Y	Yield (%)
Oxidation				
35	2	H	SO_2Me	86
36	2	Pr	SO_2Me	88
37	1	Ph	SO_2Me	76
38	1	H	SO_2Me	100
Substitution				
39	2	Pr	NH_2	75
40	1	Ph	NH_2	87
41	1	H	NH_2	93

Substitutions of the sulfonyl group with sodium hydroxide had also been reported allowing access to 2-hydroxypyrimidines/pyrimidones.[23] 1 M Sodium hydroxide was therefore used in the substitution reaction with **35**, followed by mild acidic work up (KH_2PO_4–H_2O) and it was noted that as well as hydroxide substitution, Boc and Bu^t ester deprotecton also occured. By concentration *in vacuo* and purification by ion-exchange chromatography, the pyrimidone **57** was thus obtained in 71% yield (Scheme 7 and Table 4).

Finally deprotection of the protected pyrimidin-4-yl amino acids was achieved by dissolution in TFA–anisole. The free amino acids **42**–**44**, **46**–**50**, **52**–**59** and **4** were obtained by ion-exchange chromatography as solids in high yields. A lower yield was observed for the deprotection/purification of **45** due to the low solubility of its TFA salt, whilst **51** was preferably isolated as its TFA salt and **56** was obtained as a highly sensitive species (Scheme 7 and Table 4). The optical rotation of **4**, synthetic L-lathyrine, had a value of $[\alpha]_D^{22}$ −55.4 (*c* = 1.2, H_2O), consistent with that reported for the naturally occurring amino acid [lit.,[7] $[\alpha]_D^{25}$ −55.9 (*c* 1.2, H_2O)].[24]

In conclusion we have developed a versatile approach, applicable to parallel synthesis, to a family of pyrimidin-4-yl substituted α-amino acids, the chemistry allowing diversification by facile control of the substituents at the 2, 4 and 6 positions of the pyrimidine. This route allows the total synthesis of non-proteinogenic amino acids in approximately 10–25% overall yield from aspartic or glutamic acids. The novel pyrimidin-4-yl substituted α-amino acids generated are currently under investigation for potential bioactivity and have been produced in a partially protected form capable of incorporation into novel di-, tri- or polypeptides. Further routes to other families of natural product derivatives will be reported in due course.



24-41 **42-59** and **4**

Scheme 7 *Reagents and conditions*: i, TFA, anisole; ii, Dowex® 50X8-100 ion-exchange resin.

Table 4 Deprotection of protected pyrimidin-4-yl α-amino acids

Compound	*n*	R	Z	Yield (%)
42	2	Ph	Ph	97
43	2	Ph	Me	93
44	2	Ph	H	91
45	2	Ph	SMe	51[a]
46	2	H	SMe	74
47	2	H	NH_2	94
48	2	Pr	SMe	100
49	2	Pr	Me	99
50	1	Ph	SMe	87
51	1	Ph	4-ClC_6H_4	78[b]
52	1	H	SMe	100
53	2	H	SO_2Me	100
54	2	Pr	SO_2Me	99
55	1	Ph	SO_2Me	98
56	1	H	SO_2Me	99[c]
57	2	H	OH	71[d]
58	2	Pr	NH_2	90
59	1	Ph	NH_2	96
4	1	H	NH_2	99

[a] Low yield observed due to the low solubility of the TFA salt. [b] Purified as the TFA salt. [c] Crude yield of labile species. [d] Yield over two steps; nucleophilic substitution and deprotection.

Experimental

General

All solvents and reagents were purified by standard techniques[25] or used as supplied from commercial sources as appropriate. 40–60 Petroleum ether (PE) refers to the fraction of light petroleum ether which boils in the range 40–60 °C. DCM, Et_2O and MeOH refer to dichloromethane, diethyl ether and methanol respectively. Solvents were removed under reduced pressure using a Büchi R110.

Melting and decomposition points were obtained using a Buchi 510 capillary apparatus and are uncorrected.

Specific optical rotations were recorded using a Perkin-Elmer 241 automatic polarimeter with a cell of path length 1 dm. Concentrations are given in g per 100 ml.

Infrared spectra were recorded using either a Perkin-Elmer 1750 Fourier transform spectrometer or a Perkin-Elmer Paragon 1000 Fourier transform spectrometer with major absorbances only being quoted. The following abbreviations are used: w, weak; m, medium; s, strong; br, broad.

^{1}H NMR spectra were recorded at 200 and 500 MHz using Varian Gemini 200, Bruker AC200 and Bruker AM500 instruments. For ^{1}H spectra recorded in $CDCl_3$ or D_2O, chemical shifts are quoted in parts per million (ppm) and are referenced to the residual solvent peak. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

^{13}C NMR spectra were recorded at 50.3 and 125.8 MHz using Varian Gemini 200 and Bruker AM500 instruments with DEPT[26] editing to assist assignment. Chemical shifts are quoted in ppm and are referenced to $CDCl_3$ and 1,4-dioxane (for spectra run in D_2O).

Low resolution mass spectra were recorded on V. G. Micromass ZAB 1F, V. G. Masslab20-250 and V. G. Bio-Q instruments as appropriate, with modes of ionisation being indicated

as DCI, CI, APCI, EI, FAB or ES and with only molecular ion, molecular ion fragments and major peaks being reported.

High resolution mass spectrometry was performed by the EPSRC Mass Spectrometry Service Centre, Department of Chemistry, University of Wales, Swansea and was recorded on a VG ZAB-E instrument.

Flash chromatography was carried out using Sorbsil™ C60 (40–63 mm, 230–40 mesh) silica gel and Prolabo Silica Gel 60 (35–75 mm, 200–400 mesh) as stationary phase. Thin layer chromatography was carried out on glass backed plates pre-coated with Merck silica gel 60 F_{254} which were visualised by quenching of UV fluorescence or by staining with 10% w/v ammonium molybdate in 2 M sulfuric acid (followed by heat) as appropriate.

L-Glutamic and L-aspartic acid dibenzyl ester toluene-*p*-sulfonate salts[18]

L-Glutamic acid dibenzyl ester toluene-*p*-sulfonate salt 9. Prepared from L-glutamic acid **6**, following a literature procedure,[18] as a white crystalline solid in 72% yield; mp 139–143 °C (lit.,[27] 144–145 °C); $[\alpha]_D^{22}$ +7.0 (*c* 1.0 in MeOH) [lit.,[27] $[\alpha]_D^{22}$ +7.6 (*c* 1.5 in MeOH)]; HRMS found M^+ 328.1549. $C_{19}H_{22}NO_4$ requires 328.1549.

L-Aspartic acid dibenzyl ester toluene-*p*-sulfonate salt 10. Prepared from L-aspartic acid **7**, following a literature procedure,[18] as a white crystalline solid in 76% yield; mp 156–158 °C (lit.,[27] 158–160 °C); $[\alpha]_D^{22}$ +0.8 (*c* 1.0 in MeOH) [lit.,[27] $[\alpha]_D^{25}$ +1.0 (*c* 1.5 in MeOH)]; HRMS found M^+ 314.1392. $C_{18}H_{20}NO_4$ requires 314.1392.

L-Glutamic acid γ-benzyl ester and L-aspartic acid β-benzyl esters[19]

L-Glutamic acid γ-benzyl ester 11. Prepared from **9**, following a literature procedure,[19] as a white crystalline solid in 56% yield; mp 169–170 °C (lit.,[19] 169–170 °C); $[\alpha]_D^{22}$ +19.6 (*c* 5.49 in acetic acid) [lit.,[19] $[\alpha]_D^{25}$ +19.2 (*c* 5.49 in acetic acid)]; HRMS found MH^+ 238.1079. $C_{12}H_{16}NO_4$ requires 238.1079.

L-Aspartic acid β-benzyl ester 12. Prepared from **10**, following a literature procedure,[19] as a white crystalline solid in 100% yield; mp 219–221 °C (lit.,[19] 220–222 °C); $[\alpha]_D^{24}$ +10.5 (*c* 0.089 in acetic acid); HRMS found MH^+ 224.0923. $C_{11}H_{14}NO_4$ requires 224.0923.

N-*tert*-Butoxycarbonyl-L-glutamic acid γ-benzyl α-*tert*-butyl diester and *N*-*tert*-butoxycarbonyl-L-aspartic acid β-benzyl α-*tert*-butyl diester[18]

***N*-*tert*-Butoxycarbonyl-L-glutamic acid γ-benzyl α-*tert*-butyl diester 13.** Prepared from **11**, following a literature procedure,[18] as a white crystalline solid in 81% yield; mp 35–37 °C; $[\alpha]_D^{22}$ +9.0 (*c* 1.0 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3375br (NH), 2978s (CH), 2934m (CH), 1718s (C=O), 1500m, 1368s, 1254m, 1155s, 1028w; δ_H (200 MHz, $CDCl_3$) 1.39 (9H, s, $C(CH_3)_3$), 1.41 (9H, s, $C(CH_3)_3$), 1.83–2.23 (2H, m, CH_2), 2.36–2.45 (2H, m, CH_2), 4.16–4.19 (1H, m, C*H*), 5.07 (2H, s, OCH_2), 5.23 (1H, br d, *J* 8.0, N*H*), 7.29 (5H, s, Ar*H*); δ_C (50.3 MHz, $CDCl_3$) 27.27 (CH_2), 27.85 ($C(CH_3)_3$), 28.18 ($C(CH_3)_3$), 30.19 (CH_2), 53.33 (*C*H), 66.40 (OCH_2), 79.76 ($C(CH_3)_3$), 82.16 ($C(CH_3)_3$), 128.42, 128.61, 128.74 (3 × Ar-*C*H), 136.03 (Ar-*C*, *ipso*), 155.70, 171.67, 172.99 (3 × *C*=O); *m*/*z* (CI+) 394 (MH^+, 40%), 294 [$MH^+ - (CO_2+C_4H_8)$, 100]; HRMS found MH^+ 394.2230. $C_{21}H_{32}NO_6$ requires 394.2230.

***N*-*tert*-Butoxycarbonyl-L-aspartic acid β-benzyl α-*tert*-butyl diester 14.** Prepared from **12**, following a literature procedure,[18] as a white crystalline solid in 48% yield; mp 61–63 °C; $[\alpha]_D^{22}$ +19.6 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3438w (NH), 2979m (CH), 1723s (C=O), 1499m, 1457w, 1369m, 1156s, 1070w, 848w; δ_H (200 MHz, $CDCl_3$) 1.43 (9H, s, $C(CH_3)_3$), 1.46 (9H, s, $C(CH_3)_3$), 2.78–3.06 (2H, m, CH_2), 4.43–4.49 (1H, m, C*H*), 5.08–5.22 (2H, m, OCH_2), 5.45–5.49 (1H, d, *J* 7.0, N*H*), 7.37 (5H, s, Ar*H*); *m*/*z* (CI+) 380 (MH^+, 60%), 268 [$MH^+ - 2$ (C_4H_8), 100]; HRMS found MH^+ 380.2073. $C_{20}H_{30}NO_6$ requires 380.2073.

N-*tert*-Butoxycarbonyl-L-glutamic and -L-aspartic acid α-*tert*-butyl esters[18]

***N*-*tert*-Butoxycarbonyl-L-glutamic acid α-*tert*-butyl ester 15.** Prepared from **13**, following a literature procedure,[18] as a white crystalline solid in 100% yield; mp 108–111 °C (lit.,[28] 110–114 °C); $[\alpha]_D^{22}$ −27.5 (*c* 0.6 in MeOH) [lit.,[28] $[\alpha]_D^{25}$ −30.2 (*c* 1.0 in MeOH)]; HRMS found MH^+ 304.1760. $C_{14}H_{26}NO_6$ requires 304.1760.

***N*-*tert*-Butoxycarbonyl-L-aspartic acid α-*tert*-butyl ester 16.** Prepared from **14**, following a literature procedure,[18] as a white crystalline solid in 100% yield; mp 98–100 °C; $[\alpha]_D^{22}$ −22.3 (*c* 1.5 in MeOH); ν_{max} (KBr)/cm^{-1} 3354br s (NH, OH), 2980s (CH), 1734s (C=O), 1510s, 1456s, 1369s, 1060s, 1028m, 855w; δ_H (200 MHz, $CDCl_3$) 1.44 (18H, s, 2 × $C(CH_3)_3$), 2.73–3.02 (2H, m, CH_2), 4.40–4.46 (1H, m, C*H*), 5.47–5.51 (1H, d, *J* 7.5, N*H*), 8.04 (1H, br s, O*H*); *m*/*z* (CI+) 290 (MH^+, 60%), 195 [$MNH_4^+ - 2 \times (C_4H_8)$, 100]; HRMS found MH^+ 290.1604. $C_{13}H_{24}NO_6$ requires 290.1604.

General procedure for 'Weinreb' amide formation

Typically to a cooled, −15 °C, solution of the *N*-*tert*-butoxycarbonyl-L-amino acid α-*tert*-butyl ester (1.0 equiv.) in THF was added 4-methylmorpholine (1.0 equiv.) followed by isobutyl chloroformate (1.0 equiv.). A cooled, −15 °C, mixture of *N*,*O*-dimethylhydroxylamine hydrochloride (1.0 equiv.) and triethylamine (1.1 equiv.) in DMF was then added and the reaction mixture left to stir for 30 minutes before being warmed to room temperature and stirred for 12 hours. The solvents were then removed *in vacuo* and the residue was partitioned between ethyl acetate and 1 M orthophosphoric acid. The organic layer was washed with 1 M orthophosphoric acid and saturated aqueous sodium bicarbonate solution, dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude product.

***N*-*tert*-Butoxycarbonyl-L-glutamic acid α-*tert*-butyl ester γ-*N*-methoxy-*N*-methylamide 17.** Prepared from **15** (455 mg, 1.5 mmol), THF (10 ml), 4-methylmorpholine (165 μl, 1.5 mmol), isobutyl chloroformate (195 μl, 1.5 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (0.15 g, 1.5 mmol), triethylamine (0.23 ml, 1.65 mmol), DMF (10 ml), ethyl acetate (20 ml), 1 M orthophosphoric acid (2 × 10 ml) and saturated aqueous sodium bicarbonate solution (3 × 10 ml). Purification by flash column chromatography (SiO_2, 5:2 Et_2O–PE) yielded **17** (384 mg, 74%) as a colourless oil; $[\alpha]_D^{22}$ +6.6 (*c* 0.7 in $CHCl_3$) (Found: C, 55.47; H, 8.99; N, 8.00. $C_{16}H_{30}N_2O_6$ requires C, 55.47; H, 8.73; N, 8.09%); ν_{max} (thin film)/cm^{-1} 3336m (NH), 2978s (CH), 1714s (C=O), 1664s (C=O), 1515m, 1368s, 1155s, 1052w, 849w; δ_H (200 MHz, $CDCl_3$) 1.37 (9H, s, $C(CH_3)_3$), 1.40 (9H, s, $C(CH_3)_3$), 1.83–2.10 (2H, m, CH_2), 2.40–2.51 (2H, m, CH_2), 3.11 (3H, s, NCH_3), 3.61 (3H, s, OCH_3), 4.11–4.13 (1H, br m, C*H*), 5.21 (1H, br d, *J* 8.0, N*H*); δ_C (50.3 MHz, $CDCl_3$) 27.33 (CH_2), 27.79 ($C(CH_3)_3$), 28.14 ($C(CH_3)_3$; CH_2), 32.09 (NCH_3), 53.66 (*C*H), 61.12 (OCH_3), 79.47 ($C(CH_3)_3$), 81.82 ($C(CH_3)_3$), 155.71, 171.83, 173.78 (3 × *C*=O), *m*/*z* (CI+) 347 (MH^+, 100%), 291 [$MH^+ - (C_4H_8)$, 100].

***N*-*tert*-Butoxycarbonyl-L-aspartic acid α-*tert*-butyl ester β-*N*-methoxy-*N*-methylamide 18.** Prepared from **16** (3.47 g, 12.0 mmol), THF (50 ml), 4-methylmorpholine (1.32 ml, 12.0 mmol), isobutyl chloroformate (1.56 ml, 12.0 mmol), *N*,*O*-

dimethylhydroxylamine hydrochloride (1.17 g, 12.0 mmol), triethylamine (1.84 ml, 13.2 mmol), DMF (50 ml), ethyl acetate (40 ml), 1 M orthophosphoric acid (2 × 20 ml) and saturated aqueous sodium bicarbonate solution (3 × 20 ml). Purification by flash column chromatography (SiO_2, 5:2 Et_2O–PE) yielded **18** (3.03 g, 76%) as a colourless oil; $[a]_D^{22}$ +18.0 (*c* 1.01 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3434m, 3357m (NH), 2978s, 2936s (CH), 1718s (C=O), 1664s, 1496s, 1392s, 1368s, 1158s, 1055m; δ_H (200 MHz, $CDCl_3$) 1.38 (9H, s, $C(CH_3)_3$), 1.40 (9H, s, $C(CH_3)_3$), 2.81 (1H, dd, *J* 4.0, 17.0, C*H*(H)), 3.10 (1H, dd, *J* 4.0, 17.0, CH(*H*)), 3.15 (3H, s, NCH_3), 3.64 (3H, s, OCH_3), 4.36–4.44 (1H, m, C*H*), 5.63 (1H, d, *J* 8.5, N*H*); δ_C (50.3 MHz, $CDCl_3$) 27.74 ($C(CH_3)_3$), 28.18 ($C(CH_3)_3$), 31.83 (NCH_3), 34.56 (CH_2), 50.27 (*C*H), 61.16 (OCH_3), 79.47 ($C(CH_3)_3$), 81.72 ($C(CH_3)_3$), 155.97, 170.82, 172.03 (3 × *C*=O); *m*/*z* (APCI+) 333 (MH^+, 10%), 221 [$MH^+ - 2 \times (C_4H_8)$, 100]; HRMS found MH^+ 333.2026. $C_{15}H_{29}N_2O_6$ requires 333.2026.

General procedure for the formation of phenyl and propyl functionalised alkynyl ketones

Typically to a cooled, −78 °C, stirred solution of the alkyne (5.5 equiv.) in THF was added *n*-butyllithium (5.0 equiv.) dropwise and the mixture left for 30 minutes. This solution was then added to a cooled, −78 °C, stirred solution of the 'Weinreb' amide (1.0 equiv.) dissolved in THF and the reaction mixture left for 30 minutes before being allowed to warm to room temperature for two hours. The reaction mixture was then poured onto a vigorously stirred mixture of Et_2O, 1 M potassium dihydrogen orthophosphate and ice and the aqueous layer extracted with Et_2O. The combined organic extracts were washed with 1 M potassium dihydrogen orthophosphate, saturated aqueous sodium bicarbonate solution and brine and dried over $MgSO_4$ before concentrating *in vacuo* to give the crude product.

(*S*)-2-*tert*-Butoxycarbonylamino-5-oxo-7-phenylhept-6-ynoic acid *tert*-butyl ester 19. Prepared from phenyl acetylene (92 µl, 0.84 mmol), THF (2 × 5 ml), *n*-butyllithium (0.58 ml, 1.3 M solution in hexanes, 0.75 mmol), **17** (52 mg, 0.15 mmol), Et_2O (2 × 10 ml), 1 M potassium dihydrogen orthophosphate (2 × 25 ml), saturated aqueous sodium bicarbonate solution (2 × 15 ml) and brine (2 × 15 ml). Purification by flash column chromatography (SiO_2, 4:96 Et_2O–DCM) yielded **19** (46 mg, 79%) as a white solid; mp 73.5–75.5 °C; $[a]_D^{22}$ +6.2 (*c* 1.54 in $CHCl_3$) (Found: C, 68.39; H, 7.77; N, 3.49. $C_{22}H_{29}NO_5$ requires C, 68.20; H, 7.54; N, 3.61%); ν_{max} (thin film)/cm^{-1} 3372m (NH), 3061s, 2978m, 2933m (CH), 2204s (C≡C), 1718s (C=O), 1598w, 1368s, 1251m, 1054s; δ_H (200 MHz; $CDCl_3$) 1.41 (9H, s, $(C(CH_3)_3)$, 1.49 (9H, s, $(C(CH_3)_3)$, 2.00–2.24 (2H, m, CH_2), 2.69–2.80 (2H, m, CH_2), 4.19–4.22 (1H, br m, C*H*), 5.16 (1H, br d, *J* 8.0, N*H*), 7.29–7.43 (3H, m, Ar-*H*), 7.51–7.55 (2H, m, Ar-*H*); δ_C (50.3 MHz; $CDCl_3$) 26.85 (CH_2), 27.85 ($C(CH_3)_3$), 28.17 ($C(CH_3)_3$), 41.36 (CH_2), 53.25 (*C*H), 79.79 ($C(CH_3)_3$), 82.27 ($C(CH_3)_3$), 87.65, 91.25 (2 × C≡*C*), 119.94 (Ar-*C*, *ipso*), 128.82, 130.99, 133.25 (3 × Ar-*C*H), 155.66, 171.54, 186.73 (3 × *C*=O); *m*/*z* (CI+) 388 (MH^+, 10%), 332 [$MH^+ - (C_4H_8)$, 100].

(*S*)-2-*tert*-Butoxycarbonylamino-4-oxo-6-phenylhex-5-ynoic acid *tert*-butyl ester 22. Prepared from phenyl acetylene (0.91 ml, 8.25 mmol), THF (2 × 25 ml), *n*-butyllithium (3 ml, 2.5 M solution in hexanes, 7.5 mmol), **18** (0.50 g, 1.5 mmol), Et_2O (2 × 35 ml), 1 M potassium dihydrogen orthophosphate (2 × 75 ml), saturated aqueous sodium bicarbonate solution (2 × 50 ml) and brine (2 × 50 ml). Purification by flash column chromatography (SiO_2, 7:13 Et_2O–PE) yielded **22** (345 mg, 62%) as a pale yellow oil; $[a]_D^{22}$ +12.2 (*c* 0.15 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3791m, 3584m (NH), 3062s, 2979s, 2933s (CH), 2204s (C≡C), 1718s (C=O), 1673s (C=O), 1492s, 1368s, 1250s, 1156s, 847w; δ_H (200 MHz, $CDCl_3$) 1.44 (9H, s, $C(CH_3)_3$), 1.46 (9H, s, $C(CH_3)_3$), 3.18 (1H, dd, *J* 5.0, 18.0, C*H*(H)), 3.32 (1H, dd, *J* 5.0, 18.0, CH(*H*)), 4.46–4.53 (1H, m, C*H*), 5.44 (1H, d, *J* 8.0, N*H*), 7.34–7.60 (5H, m, Ar*H*); δ_C (50.3 MHz, $CDCl_3$) 27.73 ($C(CH_3)_3$), 28.18 ($C(CH_3)_3$), 47.47 (CH_2), 50.09 (*C*H), 79.91 ($C(CH_3)_3$), 82.51 ($C(CH_3)_3$), 87.46, 92.07 (2 × C≡*C*), 119.73 (Ar-*C*, *ipso*), 128.85, 131.18, 133.37 (3 × Ar-*C*H), 155.72, 170.15, 185.04 (3 × *C*=O); *m*/*z* (APCI+) 374 (MH^+, 20%), 218 [$MH^+ - (CO_2 + 2 \times C_4H_8)$, 100]; HRMS found MH^+ 374.1967. $C_{21}H_{28}NO_5$ requires 374.1967.

(*S*)-2-*tert*-Butoxycarbonylamino-5-oxodeca-6-ynoic acid *tert*-butyl ester 21. Prepared from pent-1-yne (149 µl, 1.51 mmol), THF (2 × 5 ml), *n*-butyllithium (0.69 ml, 2.0 M solution in hexanes, 1.38 mmol), **17** (95 mg, 0.27 mmol), Et_2O (2 × 20 ml), 1 M potassium dihydrogen orthophosphate (2 × 50 ml), saturated aqueous sodium bicarbonate solution (2 × 25 ml) and brine (2 × 25 ml). Purification by flash column chromatography (SiO_2, 1:4; Et_2O–PE) yielded **21** (91 mg, 95%) as a white solid; mp 62–64 °C; $[a]_D^{22}$ +11.8 (*c* 0.82 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3370w (NH), 2976m, 2936m (CH), 2212m (C≡C), 1716s, 1677s (C=O), 1506m, 1456w, 1368s, 1251m, 1048w, 848w; δ_H (200 MHz, $CDCl_3$) 0.98 (3H, t, *J* 7.0, CH_3), 1.43 (9H, s, $C(CH_3)_3$), 1.46 (9H, s, $C(CH_3)_3$), 1.60 (2H, q, *J* 7.0, CH_2), 1.90–2.20 (2H, m, CH_2), 2.33 (2H, t, *J* 7.0, CH_2), 2.57–2.68 (2H, m, CH_2), 4.16–4.18 (1H, br m, C*H*), 5.06 (1H, d, *J* 7.0, N*H*); δ_C (125.8 MHz, $CDCl_3$) 13.29 (CH_3), 20.69 (CH_2), 21.01 (CH_2), 26.82 (CH_2), 27.82 ($C(CH_3)_3$), 28.14 ($C(CH_3)_3$), 41.34 (CH_2), 53.22 (*C*H), 79.75 ($C(CH_3)_3$), 80.80 (Pr-*C*≡C), 82.20 ($C(CH_3)_3$), 94.85 (Pr-C≡*C*), 155.60, 171.57, 186.99 (3 × *C*=O); *m*/*z* (APCI, CI+) 354 (MH^+, 7%), 242 [$MH^+ - 2 \times (C_4H_8)$, 100]; HRMS found MH^+ 354.2280. $C_{19}H_{32}NO_5$ requires 354.2280.

General procedure for the formation of hydrogen functionalised alkynyl ketones

Typically to a cooled, −78 °C, stirred solution of the 'Weinreb' amide (1.0 equiv.) in Et_2O ethynyl magnesium bromide (5.0 equiv.) was added dropwise.[29] The reaction was stirred for one hour before being warmed to room temperature and stirred overnight. The reaction was then poured onto a vigorously stirred mixture of Et_2O, 1 M potassium dihydrogen orthophosphate and ice and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with 1 M potassium dihydrogen orthophosphate, saturated aqueous sodium bicarbonate solution and brine and dried over $MgSO_4$ before concentrating *in vacuo* to give the crude product.

(*S*)-2-*tert*-Butoxycarbonylamino-5-oxohept-6-ynoic acid *tert*-butyl ester 20. Prepared from **17** (173 mg, 0.5 mmol), Et_2O (3 × 20 ml), ethynylmagnesium bromide (5 ml of a 0.5 M solution in THF, 2.5 mmol), 1 M potassium dihydrogen orthophosphate (2 × 50 ml), saturated aqueous sodium bicarbonate solution (2 × 25 ml) and brine (2 × 25 ml). Purification by flash column chromatography (SiO_2, 1:1 Et_2O–PE) yielded **20** (95 mg, 61%) as a colourless oil; $[a]_D^{22}$ +14.0 (*c* 0.8 in $CHCl_3$) (Found: C, 61.78; H, 8.25; N, 4.40. $C_{16}H_{25}NO_5$ requires C, 61.72; H, 8.09; N, 4.50%); ν_{max} (thin film)/cm^{-1} 3362m (NH), 3249m (C≡CH), 2980s, 2935m (CH), 2093s (C≡C), 1713s (C=O), 1510s, 1393m, 1252s, 1157s, 1027m, 964w; δ_H (200 MHz; $CDCl_3$) 1.38 (9H, s, $(C(CH_3)_3)$, 1.41 (9H, s, $(C(CH_3)_3)$, 1.86–2.15 (2H, m, CH_2), 2.59–2.70 (2H, m, CH_2), 3.28 (1H, s, *H*-C≡C), 4.12–4.14 (1H, br m, C*H*), 5.11 (1H, br d, *J* 8.0, N*H*); δ_C (50.3 MHz; $CDCl_3$) 26.51 (CH_2), 27.82 ($C(CH_3)_3$), 28.14 ($C(CH_3)_3$), 41.31 (CH_2), 53.08 (*C*H), 79.16 (H-*C*≡C), 79.86 ($C(CH_3)_3$), 81.19 ($C(CH_3)_3$), 82.34 (H-C≡*C*), 155.60, 171.40, 186.14 (3 × *C*=O); *m*/*z* (CI+) 334 (MNa^+, 15%), 156 [$MH^+ - (CO_2 + 2 \times C_4H_8)$, 20], 138 (100).

(*S*)-2-*tert*-Butoxycarbonylamino-4-oxohex-5-ynoic acid *tert*-butyl ester 23. Prepared from **18** (33 mg, 0.1 mmol), Et_2O (3 × 5

ml), ethynylmagnesium bromide (1 ml of a 0.5 M solution in THF, 0.5 mmol), 1 M potassium dihydrogen orthophosphate (2 × 15 ml), saturated aqueous sodium bicarbonate solution (2 × 10 ml) and brine (2 × 10 ml). Purification by flash column chromatography (SiO_2, 1:1; Et_2O–PE) yielded **23** (23 mg, 78%) as a colourless oil; $[a]_D^{22}$ +15.0 (*c* 0.4 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3433m (NH), 3250m (C≡CH), 2980s, 2926m (CH), 2094m (C≡C), 1716s (C=O), 1687s (C=O), 1502m, 1368s, 1154s, 845w; δ_H (200 MHz, $CDCl_3$) 1.42 (18H, s, 2 × (C(CH_3)$_3$), 3.06 (1H, dd, *J* 5.0, 18.0, C*H*(H)), 3.26 (1H, dd, *J* 5.0, 18.0, CH(*H*)), 3.30 (1H, s, *H*–C≡C), 4.43–4.47 (1H, m, C*H*), 5.34–5.38 (1H, d, *J* 8.0, N*H*); δ_C (50.3 MHz, $CDCl_3$) 27.71 (C(*C*H_3)$_3$), 28.18 (C(*C*H_3)$_3$), 47.88 (*C*H_2), 49.88 (*C*H), 79.83 (*C*(CH$_3$)$_3$), 80.04, 80.92 (2 × C≡*C*), 82.74 (*C*(CH$_3$)$_3$), 155.65, 169.87, 184.52 (3 × *C*=O); *m*/*z* (CI+) 298 (MH^+, 20%), 186 [$MH^+ - 2 \times (C_4H_8)$, 100]; HRMS found MH^+ 298.1654. $C_{15}H_{24}NO_5$ requires 298.1654.

General procedure for pyrimidine formation

Typically to a stirred solution of an alkynyl ketone (1.0 equiv.) in ethyl acetate or acetonitrile and water the amidine acid salt (1.2 equiv.) and sodium carbonate (2.4 equiv.) were added. The reaction mixture was heated to reflux and stirred for two hours before being cooled to room temperature. It was then added to ethyl acetate and washed with saturated aqueous sodium bicarbonate solution and brine. The organic extract was then dried over $MgSO_4$ and concentrated *in vacuo* to generate the crude product.

(*S*)-α-*tert*-Butoxycarbonylamino-γ-(2,6-diphenylpyrimidin-4-yl)butyric acid α-*tert*-butyl ester 24. Prepared from **19** (194 mg, 0.5 mmol), acetonitrile (3 ml), water (18 μl), benzamidine hydrochloride hydrate (94 mg, 0.6 mmol) and sodium carbonate (127 mg, 1.2 mmol). Purification by flash column chromatography (SiO_2, 1:49 Et_2O–DCM) yielded **24** (213 mg, 87%) as a white solid; mp 52–54 °C; $[a]_D^{23}$ +22.0 (*c* 1.0 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3362br s(NH), 2978m (CH), 1714s (C=O), 1591m, 1573s, 1369s, 1154s, 1028w, 847w; δ_H (200 MHz, $CDCl_3$) 1.46 (9H, s, C(CH_3)$_3$), 1.51 (9H, s, C(CH_3)$_3$), 2.25–2.46 (2H, m, CH_2), 2.95–2.99 (2H, m, CH_2), 4.36–4.39 (1H, br m, C*H*), 5.40 (1H, d, *J* 8.0, N*H*), 7.50–7.57 (7H, m, Ar*H*), 8.22–8.27 (2H, m, Ar*H*), 8.62–8.67 (2H, m, Ar*H*); δ_C (125.8 MHz, $CDCl_3$) 27.98 (C(*C*H_3)$_3$), 28.28 (C(*C*H_3)$_3$), 31.42 (*C*H_2), 33.80 (*C*H_2), 53.76 (*C*H), 79.67 (*C*(CH$_3$)$_3$), 82.03 (*C*(CH$_3$)$_3$), 113.66, 127.19, 128.33, 128.38, 128.82, 130.49, 130.68 (7 × Ar-*C*H), 137.16, 137.96 (2 × Ar-*C*, *ipso*), 155.45, 163.90, 164.21, 169.95, 171.69 (3 × Ar-*C*, *ipso*; 2 × *C*=O); *m*/*z* (APCI+) 490 (MH^+, 100%), 434 [$MH^+ - (C_4H_8)$, 30]; HRMS found MH^+ 490.2706. $C_{29}H_{36}N_3O_4$ requires 490.2706.

(*S*)-α-*tert*-Butoxycarbonylamino-γ-(2-methyl-6-phenylpyrimidin-4-yl)butyric acid α-*tert*-butyl ester 25. Prepared from **19** (194 mg, 0.5 mmol), ethyl acetate (3 ml), water (18 μl), acetamidine hydrochloride hydrate (114 mg, 1.2 mmol) and sodium carbonate (254 mg, 2.4 mmol). Purification by flash column chromatography (SiO_2, 1:1 Et_2O–PE) yielded **25** (192 mg, 90%) as a pale yellow oil; $[a]_D^{22}$ +12.5 (*c* 1.03 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3351br w (NH), 2978br m (CH), 2933m (CH), 1714s (C=O), 1581s, 1542s, 1454m, 1154s, 1029w; δ_H (200 MHz, $CDCl_3$) 1.45 (9H, s, C(CH_3)$_3$), 1.48 (9H, s, C(CH_3)$_3$), 2.07–2.34 (2H, m, CH_2), 2.79 (3H, s, CH_3), 2.84–2.91 (2H, m, CH_2), 4.27–4.30 (1H, m, C*H*), 5.48 (1H, br d, *J* 7.5, N*H*), 7.40 (1H, s, Ar*H*), 7.49–7.52 (3H, m, Ar*H*), 8.04–8.09 (2H, m, Ar*H*); δ_C (50.3 MHz, $CDCl_3$) 26.04 (*C*H_3), 27.84 (C(*C*H_3)$_3$), 28.16 (C(*C*H_3)$_3$), 31.54 (*C*H_2), 33.76 (*C*H_2), 53.72 (*C*H), 79.62 (*C*(CH$_3$)$_3$), 81.97 (*C*(CH$_3$)$_3$), 113.16, 127.32, 128.99, 130.72 (4 × Ar-*C*H), 137.31 (Ar-*C*, *ipso*), 155.69, 164.49, 168.30, 169.93, 171.82 (3 × Ar-*C*, *ipso*; 2 × *C*=O); *m*/*z* (APCI+) 428 (MH^+, 100%), 372 ($MH^+ - (C_4H_8)$, 25); HRMS found MH^+ 428.2549. $C_{24}H_{34}N_3O_4$ requires 428.2549.

(*S*)-α-*tert*-Butoxycarbonylamino-γ-(6-phenylpyrimidin-4-yl)-butyric acid α-*tert*-butyl ester 26. Prepared from **19** (97 mg, 0.25 mmol), acetonitrile (2 ml), water (10 μl), formamidine hydrochloride hydrate (202 mg, 2.5 mmol) and sodium carbonate (530 mg, 5.0 mmol). Purification by flash column chromatography (SiO_2, 4:3 Et_2O–PE) yielded **26** (41 mg, 40%) as a white solid; mp 108–109 °C; $[a]_D^{22}$ +12.4 (*c* 0.25 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3338br s (NH), 2979m, 2933m (CH), 1715s (C=O), 1591m, 1454m, 1251m, 1155s, 1027w; δ_H (200 MHz, $CDCl_3$) 1.45 (9H, s, C(CH_3)$_3$), 1.49 (9H, s, C(CH_3)$_3$), 2.06–2.38 (2H, m, CH_2), 2.88–2.96 (2H, m, CH_2), 4.29–4.31 (1H, m, C*H*), 5.25 (1H, br d, *J* 8.0, N*H*), 7.51–7.55 (3H, m, Ar*H*), 7.63 (1H, s, Ar*H*), 8.08–8.12 (2H, m, Ar*H*), 9.19 (1H, s, Ar*H*); δ_C (50.3 MHz, $CDCl_3$) 27.89 (C(*C*H_3)$_3$), 28.20 (C(*C*H_3)$_3$), 31.67 (*C*H_2), 33.78 (*C*H_2), 53.65 (*C*H), 79.81 (*C*(CH$_3$)$_3$), 82.22 (*C*(CH$_3$)$_3$), 116.33, 127.36, 129.14, 131.08 (4 × Ar-*C*H), 136.94 (Ar-*C*, *ipso*), 155.80 (HN*C*=O), 159.10 (Ar-*C*H), 164.33, 170.13, 171.80 (2 × Ar-*C*, *ipso*; *C*=O); *m*/*z* (APCI+) 414 (MH^+, 100%), 358 [$MH^+ - (C_4H_8)$, 85]; HRMS found MH^+ 414.2393. $C_{23}H_{32}N_3O_4$ requires 414.2393.

(*S*)-α-*tert*-Butoxycarbonylamino-γ-(2-methylthio-6-phenylpyrimidin-4-yl)butyric acid α-*tert*-butyl ester 27. Prepared from **19** (194 mg, 0.5 mmol), ethyl acetate (3 ml), water (18 μl), 2-methyl-2-thiopseudourea sulfate (167 mg, 0.6 mmol) and sodium carbonate (254 mg, 2.4 mmol). Purification by flash column chromatography (SiO_2, 1:2 Et_2O–PE) yielded **27** (181 mg, 79%) as a colourless oil; $[a]_D^{22}$ +15.3 (*c* 1.25 in $CHCl_3$) (Found C, 63.11; H, 7.39; N, 9.41. $C_{24}H_{33}N_3O_4S$ requires C, 62.72; H, 7.23; N, 9.14%); ν_{max} (thin film)/cm^{-1} 3361br w (NH), 3063m, 2978w, 2930m (CH), 1713s (C=O), 1573s, 1392m, 1257s, 1152s, 1052w; δ_H (200 MHz, $CDCl_3$) 1.44 (9H, s, C(CH_3)$_3$), 1.47 (9H, s, C(CH_3)$_3$), 2.05–2.31 (2H, m, CH_2), 2.64 (3H, s, SCH_3), 2.78–2.86 (2H, m, CH_2), 4.26–4.29 (1H, m, C*H*), 5.27 (1H, br d, *J* 8.0, N*H*), 7.24 (1H, s, Ar*H*), 7.44–7.51 (3H, m, Ar*H*), 8.05–8.10 (2H, m, Ar*H*); δ_C (50.3 MHz, $CDCl_3$) 14.05 (S*C*H$_3$), 27.89 (C(*C*H_3)$_3$), 28.22 (C(*C*H_3)$_3$), 31.31 (*C*H_2), 33.57 (*C*H_2), 53.69 (*C*H), 79.71 (*C*(CH$_3$)$_3$), 82.05 (*C*(CH$_3$)$_3$), 111.27, 127.36, 128.99, 131.10 (4 × Ar-*C*H), 136.78 (Ar-*C*, *ipso*), 155.72, 164.15, 170.39, 171.89, 172.63 (3 × Ar-*C*, *ipso*; 2 × *C*=O); *m*/*z* (APCI+) 460 (MH^+, 100%), 404 [$MH^+ - (C_4H_8)$, 40]; HRMS found MH^+ 460.2270. $C_{24}H_{34}N_3O_4S$ requires 460.2270.

(*S*)-α-*tert*-Butoxycarbonylamino-γ-(2-methylthiopyrimidin-4-yl)butyric acid α-*tert*-butyl ester 28. Prepared from **20** (156 mg, 0.5 mmol), ethyl acetate (3 ml), water (18 μl), 2-methyl-2-thiopseudourea sulfate (167 mg, 0.6 mmol) and sodium carbonate (254 mg, 2.4 mmol). Purification by flash column chromatography (SiO_2, 5:7 Et_2O–PE) yielded **28** (157 mg, 82%) as a colourless oil; $[a]_D^{22}$ +22.4 (*c* 0.59 in $CHCl_3$) (Found C, 56.08; H, 7.86; N, 11.34. $C_{18}H_{29}N_3O_4S$ requires C, 56.37; H, 7.62; N, 10.96%); ν_{max} (thin film)/cm^{-1} 3356m (NH), 2978s, 2931s (CH), 1714s (C=O), 1568s, 1545s, 1367s, 1155s, 1027m, 847m; δ_H (200 MHz, $CDCl_3$) 1.46 (9H, s, C(CH_3)$_3$), 1.48 (9H, s, C(CH_3)$_3$), 1.98–2.29 (2H, m, CH_2), 2.58 (3H, s, SCH_3), 2.61–2.82 (2H, m, CH_2), 4.24–4.28 (1H, m, C*H*), 5.21 (1H, d, *J* 8.0, N*H*), 6.85 (1H, d, *J* 5.0, Ar*H*), 8.41 (1H, d, *J* 5.0 Hz, Ar*H*); δ_C (50.3 MHz, $CDCl_3$) 13.88 (S*C*H$_3$), 27.85 (C(*C*H_3)$_3$), 28.18 (C(*C*H_3)$_3$), 31.12 (*C*H_2), 33.25 (*C*H_2), 53.57 (*C*H), 79.74 (*C*(CH$_3$)$_3$), 82.12 (*C*(CH$_3$)$_3$), 115.64 (Ar-*C*H), 155.64 (HN*C*=O), 157.21 (Ar-*C*H), 169.90, 171.79, 172.67 (2 × Ar-*C*, *ipso*; *C*=O); *m*/*z* (APCI+) 384 (MH^+, 17%), 272 [$MH^+ - 2 \times (C_4H_8)$, 100]; HRMS found MH^+ 384.1957. $C_{18}H_{30}N_3O_4S$ requires 384.1957.

(*S*)-α-*tert*-Butoxycarbonylamino-γ-(2-aminopyrimidin-4-yl)butyric acid α-*tert*-butyl ester 29. Prepared from **20** (104 mg, 0.33 mmol), acetonitrile (3 ml), water (12 μl), guanidine hydrochloride (38.2 mg, 0.4 mmol) and sodium carbonate (85 mg, 0.8 mmol). Purification by flash column chromatography (neutral

alumina, 1:1:18 Et_2O–MeOH–PE) yielded **29** (33 mg, 28%) as a yellow solid; ν_{max} (thin film)/cm^{-1} 3360s (NH), 2927s (CH), 1716s (C=O), 1456m, 1260m, 1155m, 801m; δ_H (200 MHz, $CDCl_3$) 1.44 (9H, s, $C(CH_3)_3$), 1.47 (9H, s, $C(CH_3)_3$), 1.93–2.19 (2H, m, CH_2), 2.60–2.68 (2H, m, CH_2), 4.21–4.25 (1H, m, CH), 5.08 (2H, br s, NH_2), 5.40 (1H, d, *J* 7.5, NH), 6.50 (1H, d, *J* 5.0, ArH), 8.17 (1H, d, *J* 5.0, ArH); δ_C (500 MHz, $CDCl_3$) 27.98 ($C(CH_3)_3$), 28.30 ($C(CH_3)_3$), 31.37 (CH_2), 33.42 (CH_2), 53.75 (CH), 79.61 ($C(CH_3)_3$), 81.98 ($C(CH_3)_3$), 110.52 (Ar-CH), 155.44 (HNC=O), 157.98 (Ar-CH), 162.86, 170.74, 171.59 (2 × Ar-*C*, *ipso*; *C*=O); *m*/*z* (APCI+) 353 (MH^+, 100%), 297 [$MH^+ - (C_4H_8)$, 25].

(*S*)-α-*tert*-Butoxycarbonylamino-γ-(2-methylthio-6-propylpyrimidin-4-yl)butyric acid α-*tert*-butyl ester 30. Prepared from **21** (88 mg, 0.25 mmol), ethyl acetate (1.5 ml), water (9 μl), 2-methyl-2-thiopseudourea sulfate (104 mg, 0.37 mmol) and sodium carbonate (159 mg, 1.50 mmol). Purification by flash column chromatography (SiO_2, 5:2 Et_2O–PE) yielded **30** (101 mg, 95%) as a colourless oil; $[\alpha]_D^{22}$ +17.3 (*c* 0.48 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3368w (NH), 2975m, 2931m, 2874w (CH), 1714s (C=O), 1577s, 1534s, 1259m, 1154s, 849w; δ_H (200 MHz, $CDCl_3$) 0.95 (3H, t, *J* 7.0, CH_3), 1.43 (9H, s, $C(CH_3)_3$), 1.46 (9H, s, $C(CH_3)_3$), 1.62–1.81 (2H, m, CH_2), 1.99–2.25 (2H, m, CH_2), 2.55 (3H, s, SCH_3), 2.60 (2H, t, *J* 7.0, CH_2), 2.66–2.75 (2H, m, CH_2), 4.22–4.25 (1H, br m, CH), 5.22 (1H, d, *J* 8.0, NH), 6.68 (1H, s, ArH); δ_C (125.8 MHz, $CDCl_3$) 13.66, 13.89 (2 × CH_3), 21.81 (CH_2), 27.86 ($C(CH_3)_3$), 28.18 ($C(CH_3)_3$), 31.20 (CH_2), 33.16 (CH_2), 39.50 (CH_2), 53.68 (CH), 79.72 ($C(CH_3)_3$), 82.05 ($C(CH_3)_3$), 114.59 (Ar-CH), 155.64, 169.40, 171.15, 171.88, 172.03 (3 × Ar-*C*, *ipso*; 2 × *C*=O); *m*/*z* (APCI+) 426 (MH^+, 100%), 370 [$MH^+ - (C_4H_8)$, 97]; HRMS found MH^+ 426.2427. $C_{21}H_{36}N_3O_4S$ requires 426.2426.

(*S*)-α-*tert*-Butoxycarbonylamino-γ-(2-methyl-6-propylpyrimidin-4-yl)butyric acid α-*tert*-butyl ester 31. Prepared from **21** (100 mg, 0.28 mmol), ethyl acetate (1.5 ml), water (10 μl), acetamidine hydrochloride (40 mg, 0.42 mmol) and sodium carbonate (178 mg, 1.7 mmol). Purification by flash column chromatography (SiO_2, 3:1 Et_2O–PE) yielded **31** (91 mg, 83%) as a colourless oil; $[\alpha]_D^{22}$ +9.8 (*c* 0.53 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3350w (NH), 2975m, 2933m, 2874w (CH), 1714s (C=O), 1588s, 1547m, 1454w, 1397m, 1250m, 1155s, 849w; δ_H (200 MHz, $CDCl_3$) 0.96 (3H, t, *J* 7.0, CH_3), 1.43 (9H, s, $C(CH_3)_3$), 1.45 (9H, s, $C(CH_3)_3$), 1.62–1.80 (2H, m, CH_2), 1.94–2.28 (2H, m, CH_2), 2.66 (3H, s, CH_3), 2.60–2.78 (4H, m, 2 × CH_2), 4.16–4.26 (1H, br m, CH), 5.47 (1H, d, *J* 8.0, NH), 6.82 (1H, s, ArH); δ_C (125.8 MHz, $CDCl_3$) 13.67 (CH_3), 22.21 (CH_2), 25.85 (CH_3), 27.85 ($C(CH_3)_3$), 28.17 ($C(CH_3)_3$), 31.42 (CH_2), 33.44 (CH_2), 39.73 (CH_2), 53.76 (CH), 79.58 ($C(CH_3)_3$), 81.94 ($C(CH_3)_3$), 116.11 (Ar-CH), 155.70, 167.76, 169.16, 170.92, 171.87 (3 × Ar-*C*, *ipso*; 2 × *C*=O); *m*/*z* (APCI+) 394 (MH^+, 100%), 338 [$MH^+ - (C_4H_8)$, 30]; HRMS found MH^+ 394.2706. $C_{21}H_{36}N_3O_4$ requires 394.2706.

(*S*)-α-*tert*-Butoxycarbonylamino-β-(2-methylthio-6-phenylpyrimidin-4-yl)propanoic acid α-*tert*-butyl ester 32. Prepared from **22** (162 mg, 0.43 mmol), ethyl acetate (2 ml), water (16 μl), 2-methyl-2-thiopseudourea sulfate (167 mg, 0.60 mmol) and sodium carbonate (254 mg, 2.40 mmol). Purification by flash column chromatography (SiO_2, 2:3 Et_2O–PE) yielded **32** (175 mg, 91%) as a pale yellow oil; $[\alpha]_D^{22}$ +26.8 (*c* 1.66 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3370w (NH), 2978m, 2930w (CH), 1715s (C=O), 1574s, 1496s, 1225s, 1154s, 1026w; δ_H (200 MHz, $CDCl_3$) 1.39 (9H, s, $C(CH_3)_3$), 1.43 (9H, s, $C(CH_3)_3$), 2.64 (3H, s, SCH_3), 3.15–3.39 (2H, m, CH_2), 4.11–4.65 (1H, m, CH), 5.75 (1H, d, *J* 8.5, NH), 7.26 (1H, s, ArH), 7.47–7.51 (3H, m, ArH), 8.06–8.11 (2H, m, ArH); δ_C (50.3 MHz, $CDCl_3$) 14.06 (SCH_3), 27.81 ($C(CH_3)_3$), 28.21 ($C(CH_3)_3$), 39.17 (CH_2), 52.57 (CH), 79.75 ($C(CH_3)_3$), 82.16 ($C(CH_3)_3$), 111.86, 127.38, 129.04, 131.25 (4 × Ar-CH), 136.56 (Ar-*C*, *ipso*), 155.71, 164.19, 167.31, 170.72, 172.67 (3 × Ar-*C*, *ipso*; 2 × *C*=O); *m*/*z* (APCI+), 446 (MH^+, 100%), 390 [$MH^+ - (C_4H_8)$, 60); HRMS found MH^+ 446.2114. $C_{23}H_{32}N_3O_4S$ requires 446.2114.

(*S*)-α-*tert*-Butoxycarbonylamino-β-(2-*p*-chlorophenyl-6-phenylpyrimidin-4-yl)propanoic acid α-*tert*-butyl ester 33. Prepared from **22** (163 mg, 0.44 mmol), ethyl acetate (2 ml), water (16 μl), 4-chlorobenzamidine hydroiodide (170 mg, 0.60 mmol) and sodium carbonate (127 mg, 1.20 mmol). Purification by flash column chromatography (SiO_2, 1:1 Et_2O–PE) yielded **33** (198 mg, 89%) as pale yellow oil; $[\alpha]_D^{22}$ +26.9 (*c* 0.28 in $CHCl_3$) (Found C, 65.97; H, 6.37; N, 8.23. $C_{28}H_{32}ClN_3O_4$ requires C, 65.94; H, 6.32; N, 8.24%); ν_{max} (thin film)/cm^{-1} 3436w, 3361w (NH), 2979m, 2932w (CH), 1714s (C=O), 1590s, 1495s, 1369s, 1252m, 1155s, 1015m; δ_H (200 MHz, $CDCl_3$) 1.35 (9H, s, $C(CH_3)_3$), 1.43 (9H, s, $C(CH_3)_3$), 3.36 (1H, dd, *J* 5.0, 16.0, CH(H)), 3.45 (1H, dd, *J* 5.0, 16.0, CH(H)), 4.70–4.74 (1H, m, CH), 5.81 (1H, d, *J* 7.0, NH), 7.39–7.62 (6H, m, Ar-H), 8.17–8.21 (2H, m, Ar-H), 8.54 (2H, d, *J* 8.5, Ar-H); δ_C (50.3 MHz, $CDCl_3$) 27.84 ($C(CH_3)_3$), 28.24 ($C(CH_3)_3$), 39.24 (CH_2), 52.27 (CH), 79.83 ($C(CH_3)_3$), 82.04 ($C(CH_3)_3$), 114.54, 127.39, 128.87, 129.14, 130.05, 131.22 (6 × Ar-CH), 136.39, 136.99, 137.15 (3 × Ar-*C*, *ipso*), 155.79, 163.30, 164.34, 167.31, 171.00 (3 × Ar-*C*, *ipso*; 2 × *C*=O); *m*/*z* (APCI+) 512 (^{37}MH, 50%), 510 ($^{35}MH^+$, 100).

(*S*)-α-*tert*-Butoxycarbonylamino-β-(2-methylthiopyrimidin-4-yl)propanoic acid α-*tert*-butyl ester 34. Prepared from **23** (45 mg, 0.15 mmol), ethyl acetate (1.5 ml), water (6 μl), 2-methyl-2-thiopseudourea sulfate (56 mg, 0.20 mmol) and sodium carbonate (85 mg, 0.80 mmol). Purification by flash column chromatography (SiO_2, 1:1 Et_2O–PE) yielded **34** (48 mg, 87%) as a colourless oil; $[\alpha]_D^{22}$ +20.7 (*c* 0.85 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3370br w (NH), 2978m, 2931w (CH), 1716s (C=O), 1568s, 1548m, 1496m, 1367s, 1154s, 1056w; δ_H (200 MHz, $CDCl_3$) 1.38 (9H, s, $C(CH_3)_3$), 1.44 (9H, s, $C(CH_3)_3$), 2.60 (3H, s, SCH_3), 3.13–3.29 (2H, m, CH_2), 4.57–4.61 (1H, m, CH), 5.68 (1H, d, *J* 8.0, NH), 6.84 (1H, d, *J* 5.0, ArH), 8.40 (1H, d, *J* 5.0, ArH); δ_C (50.3 MHz, $CDCl_3$) 13.88 (SCH_3), 27.76 ($C(CH_3)_3$), 28.18 ($C(CH_3)_3$), 38.97 (CH_2), 52.42 (CH), 79.77 ($C(CH_3)_3$), 82.13 ($C(CH_3)_3$), 116.30 (Ar-CH), 155.61 (HNC=O), 157.17 (Ar-CH), 166.94, 170.60, 172.76 (2 × Ar-*C*, *ipso*; *C*=O); *m*/*z* (APCI+) 370 (MH^+, 100%), 314 [$MH^+ - (C_4H_8)$, 40]; HRMS found MH^+ 370.1801. $C_{17}H_{28}N_3O_4S$ requires 370.1801.

General procedure for methylthio derivative oxidation

Typically to a stirred solution of the 2-thiomethyl pyrimidine functionalised amino acids in dichloromethane was added *m*-chloroperbenzoic acid (50%, 2 equiv.). The reaction mixture was stirred for two hours at room temperature and then washed with 1 M sodium thiosulfate solution before being taken into ethyl acetate. The organic extract was washed with saturated aqueous sodium bicarbonate solution and brine before being dried over $MgSO_4$ and concentrated *in vacuo* afforded the crude product.

(*S*)-α-*tert*-Butoxycarbonylamino-γ-(2-methylsulfonylpyrimidin-4-yl)butyric acid α-*tert*-butyl ester 35. Prepared from **28** (255 mg, 0.66 mmol), MCPBA (460 mg at 50%, 1.33 mmol) and DCM (3 ml). Purification by flash column chromatography (SiO_2, 3:17 ethyl acetate–DCM) yielded **35** (238 mg, 86%) as a colourless oil; $[\alpha]_D^{22}$ 13.5 (*c* 3.11 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3374w (NH), 2979m, 2934w (CH), 1711s (C=O), 1581s, 1534m, 1452w, 1368s, 1155s, 847w; δ_H (200 MHz, $CDCl_3$) 1.42 (9H, s, $C(CH_3)_3$), 1.45 (9H, s, $C(CH_3)_3$), 2.01–2.31 (2H, m, CH_2), 2.92–3.01 (2H, m, CH_2), 3.35 (3H, s, SO_2CH_3), 4.11–4.25 (1H, br m, CH), 5.15 (1H, d, *J* 8.0, NH), 7.43 (1H, d, *J* 5.0, ArH), 8.77 (1H, d, *J* 5.0, ArH); δ_C (125.8 MHz, $CDCl_3$) 27.81 ($C(CH_3)_3$),

28.11 (C(CH_3)$_3$), 31.23 (CH_2), 33.32 (CH_2), 38.97 (SO_2CH_3), 53.27 (*C*H), 79.91 (*C*(CH$_3$)$_3$), 82.46 (*C*(CH$_3$)$_3$), 123.29 (Ar-*C*H), 155.56 (HN*C*=O), 158.37 (Ar-*C*H), 166.08, 171.32, 172.57 (2 × Ar-*C*, *ipso*; *C*=O); *m*/*z* (CI+) 416 (MH^+, 15%), 304 [MH^+ − 2 × (C_4H_8), 100]; HRMS found MH^+ 416.1855. $C_{18}H_{30}N_3O_6S$ requires 416.1855.

(*S*)-α-*tert*-Butoxycarbonylamino-γ-(2-methylsulfonyl-6-propylpyrimidin-4-yl)butyric acid α-*tert*-butyl ester 36. Prepared from **30** (94 mg, 0.22 mmol), MCPBA (155 mg at 50%, 0.45 mmol) and DCM (2 ml). Purification by flash column chromatography (SiO_2, 3:37 ethyl acetate–DCM) yielded **36** (88 mg, 88%) as a colourless oil; $[\alpha]_D^{22}$ +12.6 (*c* 0.31 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3375m (NH), 2974s, 2933s, 2875m (CH), 1716br s (C=O), 1590s, 1520s, 1459m, 1368m, 1259m, 1026m; δ_H (200 MHz, $CDCl_3$) 0.98 (3H, t, *J* 7.5, CH_3), 1.43 (9H, s, C(CH_3)$_3$), 1.46 (9H, s, C(CH_3)$_3$), 1.79 (2H, q, *J* 7.5, CH_2), 2.02–2.30 (2H, m, CH_2), 2.81 (2H, t, *J* 7.5, CH_2), 2.86–2.95 (2H, m, CH_2), 3.35 (3H, s, SO_2CH_3), 4.16–4.29 (1H, br m, C*H*), 5.14 (1H, d, *J* 8.0, N*H*), 7.22 (1H, s, Ar*H*); δ_C (50.3 MHz, $CDCl_3$) 13.60 (*C*H$_3$), 21.82 (*C*H$_2$), 27.81 (C(*C*H$_3$)$_3$), 28.19 (C(*C*H$_3$)$_3$), 31.48 (*C*H$_2$), 33.24 (*C*H$_2$), 38.95 (SO_2CH_3), 39.41 (*C*H$_2$), 53.40 (*C*H), 79.98 (*C*(CH$_3$)$_3$), 82.53 (*C*(CH$_3$)$_3$), 122.02 (Ar-*C*H), 155.60, 165.98, 171.53, 171.81, 173.58 (3 × Ar-*C*, *ipso*; 2 × *C*=O); *m*/*z* (APCI+) 480 (MNa^+, 30%), 358 [MH^+ − (CO_2+C_4H_8), 100)]; HRMS found MH^+ 458.2325. $C_{21}H_{36}N_3O_6S$ requires 458.2325.

(*S*)-α-*tert*-Butoxycarbonylamino-β-(2-methylsulfonyl-6-phenylpyrimidin-4-yl)propanoic acid α-*tert*-butyl ester 37. Prepared from **32** (156 mg, 0.35 mmol), MCPBA (242 mg at 50%, 0.70 mmol) and DCM (3 ml). Purification by flash column chromatography (SiO_2, 3:17 ethyl acetate–DCM) yielded **37** (127 mg, 76%) as a colourless oil; $[\alpha]_D^{22}$ +24.3 (*c* 0.07 in $CHCl_3$) (Found C, 58.08; H, 6.65; N, 8.53. $C_{23}H_{31}N_3O_6S$ requires C, 57.84; H, 6.54; N, 8.80%); ν_{max} (thin film)/cm^{-1} 3374w (NH), 2976m, 2931w (CH), 1717s (C=O), 1590s, 1516m, 1368m, 1141s, 844w; δ_H (200 MHz, $CDCl_3$) 1.39 (9H, s, C(CH_3)$_3$), 1.43 (9H, s, C(CH_3)$_3$), 3.41 (3H, s, SO_2CH_3), 3.34–3.58 (2H, m, CH_2), 4.69–4.72 (1H, m, C*H*), 5.37–5.41 (1H, d, *J* 8.0, N*H*), 7.49–7.55 (4H, m, Ar*H*), 8.13–8.17 (2H, m, Ar*H*); δ_C (50.3 MHz, $CDCl_3$) 27.80 (C(*C*H$_3$)$_3$), 28.11 (C(*C*H$_3$)$_3$), 39.10 (SO_2CH_3), 39.64 (*C*H$_2$), 52.53 (*C*H), 80.12 (*C*(CH$_3$)$_3$), 82.82 (*C*(CH$_3$)$_3$), 118.82, 127.79, 128.38, 132.48 (4 × Ar-*C*H), 134.75 (Ar-*C*, *ipso*), 155.54, 165.97, 169.66, 170.37 (2 × Ar-*C*, *ipso*; 2 × C=O); *m*/*z* (APCI+) 478 (MH^+, 5), 422 [MH^+ − (C_4H_8), 85].

(*S*)-α-*tert*-Butoxycarbonylamino-β-(2-methylsulfonylphenyl-pyrimidin-4-yl)propanoic acid α-*tert*-butyl ester 38. Prepared from **34** (111 mg, 0.30 mmol); MCPBA (207 mg at 50%, 0.6 mmol); DCM (3 ml). Purification by flash column chromatography (SiO_2, 3:17 ethyl acetate–DCM) yielded **38** (122 mg, 100%) as a colourless oil; $[\alpha]_D^{22}$ +23.8 (*c* 1.51 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3374w (NH), 2980m, 2934w (CH), 1714s (C=O), 1582s, 1534m, 1368s, 1155s, 1054w, 840w; δ_H (200 MHz, $CDCl_3$) 1.41 (9H, s, C(CH_3)$_3$), 1.43 (9H, s, C(CH_3)$_3$), 3.36 (3H, s, SO_2CH_3), 3.31–3.56 (2H, m, CH_2), 4.65–4.68 (1H, m, C*H*), 5.35 (1H, d, *J* 7.0, N*H*), 7.46 (1H, d, *J* 5.0, Ar*H*), 8.83 (1H, d, *J* 5.0, Ar*H*); δ_C (50.3 MHz, $CDCl_3$) 27.77 (C(*C*H$_3$)$_3$), 28.10 (C(*C*H$_3$)$_3$), 39.13 (SO_2CH_3), 39.53 (*C*H$_2$), 52.49 (*C*H), 80.16 (*C*(CH$_3$)$_3$), 82.92 (*C*(CH$_3$)$_3$), 124.08 (Ar-*C*H), 155.43 (HN*C*=O), 158.45 (Ar-*C*H), 165.94, 169.54, 170.19 (2 × Ar-*C*, *ipso*; *C*=O); *m*/*z* (CI+) 419 (MNH_4^+, 60%), 307 [MNH_4^+ − 2 × (C_4H_8), 100]; HRMS found MNH_4^+ 419.1964. $C_{17}H_{31}N_4O_6S$ requires 419.1964.

General procedure for amino–sulfone nucleophilic substitution

Typically to a cooled, −78 °C, stirred solution of the 2-methylsulfonylpyrimidine functionalised amino acids, in a pressure vessel, was added 10–15 ml of liquid ammonia. The reaction vessel was then sealed, allowed to warm to room temperature and the reaction mixture stirred for three hours. After this time the vessel was opened and the crude product obtained by concentration *in vacuo.*

(*S*)-α-*tert*-Butoxycarbonylamino-γ-(2-amino-6-propyl-pyrimidin-4-yl)butyric acid α-*tert*-butyl ester 39. Prepared from **36** (40 mg, 0.09 mmol), THF (3 ml) and ammonia (10–15 ml). Purification by flash column chromatography (SiO_2, 3:2 ethyl acetate–DCM) yielded **39** (26 mg, 75%) as a white solid; mp 85–86 °C; $[\alpha]_D^{22}$ +20.0 (*c* 0.15 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3423m, 3340m (NH), 2973m, 2942m (CH), 1712s (C=O), 1582s, 1451m, 1368m, 1250m, 1154s; δ_H (200 MHz, $CDCl_3$) 0.96 (3H, t, *J* 7.0, CH_3), 1.44 (9H, s, C(CH_3)$_3$), 1.46 (9H, s, C(CH_3)$_3$), 1.61–1.78 (2H, m, CH_2), 1.93–2.20 (2H, m, CH_2), 2.46–2.65 (4H, m, 2 × CH_2), 4.21–4.23 (1H, br m, C*H*), 4.94 (2H, s, NH_2), 5.46 (1H, d, *J* 8.0, N*H*), 6.37 (1H, s, Ar*H*); δ_C (125.8 MHz, $CDCl_3$) 13.85 (*C*H$_3$), 22.03 (*C*H$_2$), 28.00 (C(*C*H$_3$)$_3$), 28.32 (C(*C*H$_3$)$_3$), 31.39 (*C*H$_2$), 33.35 (*C*H$_2$), 39.67 (*C*H$_2$), 53.84 (*C*H), 79.57 (*C*(CH$_3$)$_3$), 81.91 (*C*(CH$_3$)$_3$), 109.57 (Ar-*C*H), 155.45, 162.69, 170.20, 171.64, 171.98 (3 × Ar-*C*, *ipso*; 2 × *C*=O); *m*/*z* (APCI+) 395 (MH^+, 100%), 339 [MH^+ − (C_4H_8), 40]; HRMS found MH^+ 395.2658. $C_{20}H_{35}N_4O_4$ requires 395.2658.

(*S*)-α-*tert*-Butoxycarbonylamino-β-(2-amino-6-phenyl-pyrimidin-4-yl)propanoic acid α-*tert*-butyl ester 40. Prepared from **37** (38 mg, 0.08 mmol), THF (5 ml) and ammonia (10–15 ml). Purification by flash column chromatography (SiO_2, 1:4 ethyl acetate–DCM) yielded **40** (28.7 mg, 87%) as a white solid; mp 157–159 °C; $[\alpha]_D^{22}$ +25.9 (*c* 0.56 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3403m, 3202w (NH), 2978m, 2931w (CH), 1716s (C=O), 1576s, 1498m, 1392w, 1249w, 1154s, 1024w; δ_H (200 MHz, $CDCl_3$) 1.39 (9*H*, s, C(CH_3)$_3$), 1.43 (9H, s, C(CH_3)$_3$), 3.08 (1H, dd, *J* 5.5, 15, C*H*(H)), 3.22 (1H, dd, *J* 5.5, 15, CH(*H*)), 4.57–4.62 (1H, m, C*H*), 5.08 (2H, s, NH_2), 5.66 (1H, d, *J* 8.0, N*H*), 6.93 (1H, s, Ar*H*), 7.45–7.48 (3H, m, Ar*H*), 7.99–7.94 (2H, m, Ar*H*); δ_C (125.8 MHz, $CDCl_3$) 27.85 (C(*C*H$_3$)$_3$), 28.28 (C(*C*H$_3$)$_3$), 39.34 (*C*H$_2$), 52.55 (*C*H), 79.63 (*C*(CH$_3$)$_3$), 81.74 (*C*(CH$_3$)$_3$), 107.43, 126.99, 128.67, 130.43 (4 × Ar-*C*H), 137.24 (Ar-*C*, *ipso*), 155.40, 162.93, 165.45, 167.81, 170.65 (3 × Ar-*C*, *ipso*; 2 × *C*=O); *m*/*z* (APCI+) 415 (MH^+, 100%), 359 [MH^+ − (C_4H_8), 35]; HRMS found MH^+ 415.2345. $C_{22}H_{31}N_4O_4$ requires 415.2345.

(*S*)-α-*tert*-Butoxycarbonylamino-β-(2-aminopyrimidin-4-yl)-propanoic acid α-*tert*-butyl ester 41. Prepared from **38** (100 mg, 0.25 mmol), THF (2 ml) and ammonia (10–15 ml). Purification by flash column chromatography (SiO_2, 1:4 ethyl acetate–DCM) yielded **41** (79 mg, 93%) as a white solid; mp 115–118 °C; $[\alpha]_D^{22}$ +21.7 (*c* 0.71 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3352m, 3208w (NH), 2978m, 2938w (CH), 1712s (C=O), 1634m, 1568s, 1464m, 1367m, 1251m, 1052w; δ_H (200 MHz, $CDCl_3$) 1.39 (9H, s, C(CH_3)$_3$), 1.44 (9H, s, C(CH_3)$_3$), 3.01 (1H, dd, *J* 5.0, 15.0, C*H*(H)), 3.14 (1H, dd, *J* 5.0, 15.0, C*H*(H)), 4.51–4.58 (1H, m, C*H*), 5.10 (2H, s, NH_2), 5.68 (1H, d, *J* 9.0, N*H*), 6.49 (1H, d, *J* 5.0, Ar*H*), 8.17 (1H, d, *J* 5.0, Ar*H*); δ_C (125.8 MHz, $CDCl_3$) 27.82 (C(*C*H$_3$)$_3$), 28.26 (C(*C*H$_3$)$_3$), 39.15 (*C*H$_2$), 52.45 (*C*H), 79.58 (*C*(CH$_3$)$_3$), 81.75 (*C*(CH$_3$)$_3$), 111.20 (Ar-*C*H), 155.37 (HN*C*=O), 157.89 (Ar-*C*H), 162.63, 167.44, 170.59 (2 × Ar-*C*, *ipso*; *C*=O); *m*/*z* (APCI+) 339 (MH^+, 100%), 283 [MH^+ − (C_4H_8), 20]; HRMS found MH^+ 339.2032. $C_{16}H_{27}N_4O_4$ requires 339.2032.

General procedure for amino acid deprotection and purification

Typically to a stirred solution of the protected compounds in trifluoroacetic acid 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 the crude

TFA salt. This was then 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*)-β-(2-Aminopyrimidin-4-yl)-α-aminopropanoic acid (L-lathyrine) 4. Prepared from **41** (45 mg, 0.13 mmol), TFA (3 ml) and anisole (100 μl). Purification by ion-exchange chromatography yielded **4** (24 mg, 99%) as a white solid; mp 211–216 °C (decomp.); $[\alpha]_D^{22}$ −55.4 (*c* 1.2 in H_2O) [lit., $[\alpha]_D^{25}$ −55.9 (*c* 1.2 in H_2O)]; ν_{max} (KBr)/cm^{-1} 3389m, 3312m, 3193m, 3550–2500br m (NH_2/OH), 2928m (CH), 1642s (C=O), 1589s, 1564s, 1471s, 1349m, 1270w, 1076w; δ_H (500 MHz, D_2O) 3.13 (1H, dd, *J* 7.0, 16.0, C*H*(H)), 3.21 (1H, dd, *J* 4.0, 16.0, CH(*H*)), 4.07–4.09 (1H, m, C*H*), 6.67 (1H, d, *J* 5.0, Ar*H*), 8.17 (1H, d, *J* 5.0, Ar*H*); δ_C (125.8 MHz, D_2O) 36.23 (*C*H_2), 53.48 (*C*H), 111.45, 158.70 (2 × Ar-*C*H), 162.48, 167.67, 173.74 (2 × Ar-*C*, *ipso*; *C*=O); *m*/*z* (APCI+) 183 (MH^+, 100%); HRMS found MH^+ 183.0882. $C_7H_{11}N_4O_2$ requires 183.0882.

(*S*)-γ-(2,6-Diphenylpyrimidin-4-yl)-α-aminobutyric acid 42. Prepared from **24** (140 mg, 0.29 mmol), TFA (3 ml) and anisole (120 μl). Purification by ion-exchange chromatography yielded **42** (92 mg, 97%) as a white solid; mp 213–216 °C (decomp.); ν_{max} (KBr)/cm^{-1} 3409br m, 3550–2500br m (NH_2/OH), 3062m (CH), 1592s (C=O), 1574s, 1535s, 1498s, 1372m, 1074w; δ_H (200 MHz, CD_3OD) 2.44–2.51 (2H, m, CH_2), 3.05–3.12 (2H, m, CH_2), 3.75 (1H, t, *J* 8.0, C*H*), 7.52–7.56 (6H, m, Ar*H*), 7.88 (1H, s, Ar*H*), 8.31–8.34 (2H, m, Ar*H*), 8.51–8.55 (2H, m, Ar*H*); δ_C (125.8 MHz, CD_3OD) 31.19 (*C*H_2), 34.49 (*C*H_2), 55.82 (*C*H), 114.99, 128.36, 129.40, 129.52, 129.99, 131.74, 132.06 (7 × Ar-*C*H), 138.33, 139.29 (Ar-*C*, 2 × *ipso*), 165.60, 165.75, 171.41, 174.12 (3 × Ar-*C*, *ipso*; *C*=O); *m*/*z* (APCI+) 334 (MH^+, 100%); HRMS found MH^+ 334.1556. $C_{20}H_{20}N_3O_2$ requires 334.1555.

(*S*)-γ-(2-Methyl-6-phenylpyrimidin-4-yl)-α-aminobutyric acid 43. Prepared from **25** (98 mg, 0.23 mmol), TFA (3 ml) and anisole (120 μl). Purification by ion-exchange chromatography yielded **43** (58 mg, 93%) as a white solid; mp 218–220 °C (decomp.); ν_{max} (KBr)/cm^{-1} 3652–2600br s (NH_2/OH), 2935s (CH), 1662s (C=O), 1590s, 1537s, 1459m, 1396s, 1279s, 1075s, 857m; δ_H (500 MHz, CD_3OD) 2.22–2.36 (2H, m, CH_2), 2.72 (3H, s, CH_3), 2.97 (2H, br t, *J* 8.0, CH_2), 3.65 (1H, t, *J* 6.0, C*H*), 7.49–7.55 (3H, m, Ar*H*), 7.70 (1H, s, Ar*H*), 8.11–8.17 (2H, m, Ar*H*); δ_C (125.8 MHz, CD_3OD) 25.72 (*C*H_3), 31.06 (*C*H_2), 34.34 (*C*H_2), 55.76 (*C*H), 114.67, 128.47, 129.97, 132.05 (4 × Ar-*C*H), 138.09 (Ar-*C*, *ipso*), 166.30, 169.00, 171.08, 173.73 (3 × Ar-*C*, *ipso*; *C*=O); *m*/*z* (APCI+) 272 (MH^+, 100%); HRMS found MH^+ 272.1399. $C_{15}H_{18}N_3O_2$ requires 272.1399.

(*S*)-γ-(6-Phenylpyrimidin-4-yl)-α-aminobutyric acid 44. Prepared from **26** (60 mg, 0.14 mmol), TFA (3 ml) and anisole (100 μl). Purification by ion-exchange chromatography yielded **44** (34 mg, 91%) as a white solid; mp 158–170 °C (decomp.); ν_{max} (KBr)/cm^{-1} 3435w, 3325–2600br m (NH_2/OH), 2924m (CH), 1582s (C=O), 1525s, 1452m, 1320m, 1286s, 1078s; δ_H (500 MHz, D_2O) 2.05–2.12 (2H, m, CH_2), 2.65–2.77 (2H, m, CH_2), 3.68 (1H, t, *J* 6.0, C*H*), 7.31–7.40 (3H, m, Ar*H*), 7.48 (1H, s, Ar*H*), 7.63–7.64 (2H, m, Ar*H*), 8.68 (1H, s, Ar*H*); δ_C (125.8 MHz, D_2O) 29.15 (*C*H_2), 32.40 (*C*H_2), 54.14 (*C*H), 117.15, 127.05, 128.98, 131.36 (4 × Ar-*C*H), 135.15 (Ar-*C*, *ipso*), 157.17 (Ar-*C*H), 164.17, 169.11, 173.87 (2 × Ar-*C*, *ipso*; *C*=O); *m*/*z* (APCI+) 258 (MH^+, 100%); HRMS found MH^+ 258.1243. $C_{14}H_{16}N_3O_2$ requires 258.1242.

(*S*)-γ-(2-Methylthio-6-phenylpyrimidin-4-yl)-α-aminobutyric acid 45. Prepared from **27** (60 mg, 0.13 mmol), TFA (3 ml) and anisole (100 μl). Purification by ion-exchange chromatography yielded **45** (20 mg, 51%) as a white solid; mp 168–174 °C (decomp.); ν_{max} (KBr)/cm^{-1} 3418w, 3304–2600br m (NH_2/OH), 2925m (CH), 1574s (C=O), 1527s, 1496m, 1323w, 1252m, 837w; δ_H (200 MHz, CD_3OD) 2.25–2.40 (2H, m, CH_2), 2.61 (3H, s, SCH_3), 2.94 (2H, br t, *J* 8.0, CH_2), 3.91 (1H, t, *J* 6.0, C*H*), 7.45–7.51 (4H, m, Ar*H*), 8.10–8.15 (2H, m, Ar*H*); δ_C (125.8 MHz, CD_3OD) 14.21 (S*C*H$_3$), 31.01 (*C*H$_2$), 34.12 (*C*H$_2$), 55.52 (*C*H), 112.36, 128.34, 129.99, 132.32 (4 × Ar-*C*H), 137.66 (Ar-*C*, *ipso*), 165.63, 171.40, 173.63, 173.90 (3 × Ar-*C*, *ipso*; *C*=O); *m*/*z* (APCI+) 304 (MH^+, 100%); HRMS found MH^+ 304.1120. $C_{15}H_{18}N_3O_2S$ requires 304.1120.

(*S*)-γ-(2-Methylthiopyrimidin-4-yl)-α-aminobutyric acid 46. Prepared from **28** (96 mg, 0.25 mmol), TFA (3 ml) and anisole (120 μl). Purification by ion-exchange chromatography yielded **46** (42 mg, 74%) as a white solid; mp 190–198 °C (decomp.); ν_{max} (KBr)/cm^{-1} 3435br w (NH_2), 3310–2600br m (NH_2/OH), 2926m (CH), 1576s (C=O), 1544m, 1516m, 1405m, 1334m, 1074m, 961w; δ_H (200 MHz, CD_3OD) 2.23 (2H, br m, CH_2), 2.53 (3H, s, SCH_3), 2.86 (2H, br t, *J* 8.0, CH_2), 3.55–3.68 (1H, br m, C*H*), 7.02 (1H, d, *J* 5.0, Ar*H*), 8.41 (1H, d, *J* 5.0, Ar*H*); δ_C (125.8 MHz, D_2O) 13.74 (S*C*H$_3$), 29.45 (*C*H$_2$), 32.78 (*C*H$_2$), 54.64 (*C*H), 116.79, 158.01 (2 × Ar-*C*H), 170.28, 172.01, 174.43 (2 × Ar-*C*, *ipso*; *C*=O); *m*/*z* (APCI+) 228 (MH^+, 100%); HRMS found MH^+ 228.0807. $C_9H_{14}N_3O_2S$ requires 228.0806.

(*S*)-γ-(2-Aminopyrimidin-4-yl)-α-aminobutyric acid 47. Prepared from **29** (42 mg, 0.12 mmol), TFA (3 ml) and anisole (100 μl). Purification by ion-exchange chromatography yielded **47** (22 mg, 94%) as a yellow solid; mp 195–205 °C (decomp.); ν_{max} (KBr)/cm^{-1} 3362m, 3171m, 3500–2600br m (NH_2/OH), 2921m (CH), 1654s (C=O), 1586s, 1486m, 1349m, 1085w, 874w; δ_H (500 MHz, D_2O) 2.07–2.17 (2H, m, CH_2), 2.62–2.68 (2H, m, CH_2), 3.69 (1H, t, *J* 6.0, C*H*), 6.65 (1H, d, *J* 5.0, Ar*H*), 8.10 (1H, d, *J* 5.0, Ar*H*); δ_C (125.8 MHz, D_2O) 28.89 (*C*H$_2$), 32.33 (*C*H$_2$), 54.14 (*C*H), 110.60, 157.58 (2 × Ar-*C*H), 171.30, 174.03 (Ar-*C*, *ipso*; *C*=O); *m*/*z* (APCI+) 197 (MH^+, 100%); HRMS found MH^+ 197.1039. $C_8H_{13}N_4O_2$ requires 197.1038.

(*S*)-γ-(2-Methylthio-6-propylpyrimidin-4-yl)-α-aminobutyric acid 48. Prepared from **30** (55 mg, 0.13 mmol), TFA (3 ml) and anisole (100 μl). Purification by ion-exchange chromatography yielded **48** (35 mg, 100%) as a white solid; mp 167–173 °C (decomp.); ν_{max} (KBr)/cm^{-1} 3422m, 3298–2600br m (NH_2/OH), 2962m, 2929m, 2905w (CH), 1624m (C=O), 1582s, 1535s, 1451w, 1319w, 1133w; δ_H (500 MHz, D_2O) 0.86 (3H, t, *J* 7.0, CH_3), 1.62–1.66 (2H, m, CH_2), 2.15–2.28 (2H, br m, CH_2), 2.54 (3H, s, SCH_3), 2.60 (2H, t, *J* 7.0, CH_2), 2.78–2.80 (2H, m, CH_2), 3.78 (1H, t, *J* 6.0, C*H*), 6.99 (1H, s, Ar*H*); δ_C (125.8 MHz, CD_3OD) 12.80 (*C*H$_3$), 13.31 (S*C*H$_3$), 21.64 (*C*H$_2$), 29.05 (*C*H$_2$), 32.20 (*C*H$_2$), 38.41 (*C*H$_2$), 54.19 (*C*H), 115.50 (Ar-*C*H), 169.36, 171.01, 172.27, 173.93 (3 × Ar-*C*, *ipso*; *C*=O); *m*/*z* (APCI+) 270 (MH^+, 100%); HRMS found MH^+ 270.1276. $C_{12}H_{20}N_3O_2S$ requires 270.1276.

(*S*)-γ-(2-Methyl-6-propylpyrimidin-4-yl)-α-aminobutyric acid 49. Prepared from **31** (60 mg, 0.15 mmol), TFA (3 ml) and anisole (100 μl). Purification by ion-exchange chromatography yielded **49** (36 mg, 99%) as a white solid; mp 206–212 °C (decomp.); ν_{max} (KBr)/cm^{-1} 3630–2500br s (NH_2/CO_2H), 2962s, (CH), 1661s (C=O), 1594s, 1544s, 1518s, 1399s, 1279m, 1154m, 854w; δ_H (500 MHz, D_2O) 0.77 (3H, t, *J* 7.0, Me), 1.51–1.58 (2H, m, CH_2), 2.06–2.15 (2H, m, CH_2), 2.47 (3H, s, CH_3), 2.54 (2H, t, *J* 7.0, CH_2), 2.65–2.77 (2H, m, CH_2), 3.69 (1H, t, *J* 6.0, C*H*), 7.06 (1H, s, Ar*H*); δ_C (125.8 MHz, D_2O) 12.69 (CH_3), 21.90 (*C*H$_2$), 23.74 (*C*H$_3$), 29.51 (*C*H$_2$), 32.23 (*C*H$_2$), 38.39 (*C*H$_2$), 54.18 (*C*H), 116.88 (Ar-*C*H), 166.51, 168.58, 171.78, 173.93 (3 × Ar-*C*, *ipso*; *C*=O); *m*/*z* (APCI+) 238 (MH^+, 40%); HRMS found MH^+ 238.1555. $C_{12}H_{20}N_3O_2$ requires 238.1555.

(*S*)-β-(2-Methylthio-6-phenylpyrimidin-4-yl)-α-aminopropanoic acid 50. Prepared from **32** (80 mg, 0.18 mmol), TFA (3 ml) and anisole (100 μl). Purification by ion-exchange chromatography yielded **50** (45 mg, 87%) as a pale yellow solid; mp 180–182 °C (decomp.); ν_{max} (KBr)/cm^{-1} 3436m, 3315–2600br m (NH_2/CO_2H), 2924m (CH), 1624s (C=O), 1574s, 1530s, 1496w, 1268w, 1135w, 833w; δ_H (500 MHz, CD_3OD) 2.65 (3H, s, SCH_3), 3.20–3.33 (1H, masked, CH(H)), 3.48 (1H, dd, *J* 4.0, 16.0, CH(H)), 4.12–4.18 (1H, m, CH), 7.50–7.58 (4H, m, ArH), 8.14–8.19 (2H, m, ArH); δ_C (125.8 MHz, CD_3OD) 14.28 (SCH$_3$), 38.32 (CH$_2$), 54.51 (CH), 113.03, 128.40, 130.00, 132.41 (4 × Ar-CH), 137.53 (Ar-C, *ipso*), 165.74, 168.14, 173.07, 173.96 (3 × Ar-C, *ipso*; C=O); *m*/*z* (APCI+) 290 (MH$^+$, 100%); HRMS found MH$^+$ 290.0963. $C_{14}H_{16}N_3O_2S$ requires 290.0963.

(*S*)-β-(2-*p*-Chlorophenyl-6-phenylpyrimidin-4-yl)-α-aminopropanoic acid trifluoroacetate 51. Prepared from **33** (87 mg, 0.17 mmol), TFA (3 ml) and anisole (100 μl) without purification to yield the TFA salt **51** (62 mg, 78%) as a pale brown solid; mp 225–237 °C (decomp.); ν_{max} (KBr)/cm^{-1} 3427w, 3304–2600br m (NH_2/CO_2H), 3065m (CH), 1630s (C=O), 1592s, 1535s, 1494m, 1375s, 1276w, 1092m; δ_H (500 MHz, CD_3OD) 3.44–3.62 (2H, br m, CH_2), 4.25 (1H, br m, CH), 7.55–7.58 (5H, m, ArH), 7.83 (1H, s, ArH), 8.29–8.31 (2H, m, ArH), 8.58 (2H, d, *J* 8.0, ArH); δ_C (125.8 MHz, CD_3OD) 38.39 (CH$_2$), 50.21 (CH), 115.57, 128.44, 129.74, 130.04, 131.09, 132.30 (6 × Ar-CH), 137.76, 142.00, 157.30, 164.51, 166.30 (4 × Ar-C, *ipso*; C=O); *m*/*z* (APCI+) 354 (MH$^+$, 100%); HRMS found MH$^+$ 354.1009. $C_{19}H_{17}{}^{35}ClN_3O_2$ requires 354.1009.

(*S*)-β-(2-Methylthiopyrimidin-4-yl)-α-aminopropanoic acid 52. Prepared from **34** (60 mg, 0.16 mmol), TFA (3 ml) and anisole (100 μl). Purification by ion-exchange chromatography yielded **52** (35 mg, 100%) as a yellow solid; mp 167–180 °C (decomp.); ν_{max} (KBr)/cm^{-1} 3412w, 3348–2500br m (NH_2/CO_2H), 2926m (CH), 1610br s (C=O), 1569s, 1544s, 1411m, 1337m, 1233w, 833w; δ_H (500 MHz, D_2O) 2.47 (3H, s, SCH_3), 3.25 (1H, dd, *J* 5.0, 17.0, CH(H)), 3.31 (1H, dd, *J* 5.0, 17.0, CH(H)), 4.11–4.14 (1H, m, CH), 7.05 (1H, d, *J* 5.0, ArH), 8.37 (1H, d, *J* 5.0, ArH); δ_C (125.8 MHz, D_2O) 13.21 (SCH$_3$), 36.07 (CH$_2$), 52.83 (CH), 116.73, 157.40 (2 × Ar-CH), 166.31, 171.72, 173.07 (2 × Ar-C, *ipso*; C=O); *m*/*z* (APCI+) 214 (MH$^+$, 100%); HRMS found MH$^+$ 214.0650. $C_8H_{12}N_3O_2S$ requires 214.0650.

(*S*)-γ-(2-Methylsulfonylpyrimidin-4-yl)-α-aminobutyric acid 53. Prepared from **35** (62 mg, 0.15 mmol), TFA (3 ml) and anisole (100 μl). Purification by ion-exchange chromatography yielded **53** (39 mg, 100%) as a white solid; mp 136–141 °C (decomp.); ν_{max} (KBr)/cm^{-1} 3630–2600br m (NH_2/CO_2H), 2928m (CH), 1632s (C=O), 1582s, 1534m, 1448m, 1355m, 1132s, 966m; δ_H (500 MHz, D_2O) 2.30–2.34 (2H, m, CH_2), 3.02–3.13 (2H, m, CH_2), 3.41 (3H, s, SO_2CH_3), 3.81–3.83 (1H, m, CH), 7.71 (1H, d, *J* 5.5, ArH), 8.86 (1H, d, *J* 5.5, ArH); δ_C (125.8 MHz, D_2O) 28.53 (CH$_2$), 32.47 (CH$_2$), 39.17 (SO_2CH_3), 54.08 (CH), 124.44, 158.78, 163.56 (2 × Ar-CH, Ar-C, *ipso*), 172.27, 173.85 (Ar-C, *ipso*; C=O); *m*/*z* (APCI+) 260 (MH$^+$, 50), 136 (100).

(*S*)-γ-(2-Methylsulfonyl-6-propylpyrimidin-4-yl)-α-aminobutyric acid 54. Prepared from **36** (26 mg, 0.057 mmol), TFA (3 ml) and anisole (100 μl). Purification by ion-exchange chromatography yielded **54** (17 mg, 99%) as a white solid; mp 102–110 °C (decomp.); ν_{max} (KBr)/cm^{-1} 3423m, 3197m, 3600–2600br m (NH_2/CO_2H), 2964m (CH), 1628m (C=O), 1594s, 1516m, 1310m, 1136s, 1082s, 801w; δ_H (500 MHz, D_2O) 0.79 (3H, t, *J* 7.5, CH_3), 1.59–1.66 (2H, m, CH_2), 2.17–2.21 (2H, m, CH_2), 2.73 (2H, t, *J* 7.5, CH_2), 2.85–2.96 (2H, m, CH_2), 3.27 (3H, s, SO_2CH_3), 3.71 (1H, t, *J* 6.0, CH), 7.50 (1H, s, ArH); δ_C (125.8 MHz, D_2O) 12.62 (CH$_3$), 21.64 (CH$_2$), 28.63 (CH$_2$), 32.16 (CH$_2$), 38.46 (CH$_2$), 39.20 (SO_2CH_3), 53.96 (CH), 123.27 (Ar-CH), 163.18, 171.10, 173.81, 174.46 (3 × Ar-C, *ipso*; C=O); *m*/*z* (APCI+) 302 (MH$^+$, 100%), 240 (MNH$_4^+$ − SO_2Me, 25).

(*S*)-β-(2-Methylsulfonyl-6-phenylpyrimidin-4-yl)-α-aminopropanoic acid 55. Prepared from **37** (67 mg, 0.14 mmol), TFA (3 ml) and anisole (100 μl). Purification by ion-exchange chromatography yielded **55** (44 mg, 98%) as a pale yellow solid; mp 165–172 °C (decomp.); ν_{max} (KBr)/cm^{-1} 3500–2600br s (NH_2/CO_2H, CH), 1752br m, 1623s (C=O), 1590s, 1518m, 1498m, 1406s, 1308s, 1134m, 902w; δ_H (500 MHz, CD_3OD) 3.46 (3H, s, SO_2CH_3), 3.44–3.51 (1H, masked, CH(H)), 3.64 (1H, dd, *J* 4.0, 16.0, CH(H)), 4.17–4.19 (1H, m, CH), 7.50–7.62 (3H, m, ArH), 8.20 (1H, s, Ar-CH), 8.29 (2H, m, ArH); δ_C (125.8 MHz, CD_3OD) 38.77 (SO_2CH_3), 39.62 (CH$_2$), 53.00 (CH), 128.94, 130.32, 133.44 (3 × Ar-CH); *m*/*z* (APCI+) 322 (MH$^+$, 100%), 244 (25); HRMS found MH$^+$ 322.0860. $C_{14}H_{16}N_3O_4S$ requires 322.0861.

(*S*)-β-(2-Methylsulfonylpyrimidin-4-yl)-α-aminopropanoic acid 56. Prepared from **38** (58 mg, 0.145 mmol), TFA (3 ml) and anisole (100 μl). Purification by ion-exchange chromatography yielded **56** (35 mg, 99% crude) as an unstable pale yellow solid; δ_H (200 MHz, CD_3OD) 3.14–3.46 (2H, m, CH_2), 3.38 (3H, s, SO_2CH_3), 4.05–4.11 (1H, m, CH), 7.69 (1H, d, *J* 5.0, ArH), 8.90 (1H, d, *J* 5.0, ArH); *m*/*z* (APCI+) 246 (MH$^+$, 20), 198 (100), 183 (20).

(*S*)-γ-(2-Amino-6-propylpyrimidin-4-yl)-α-aminobutyric acid 58. Prepared from **39** (24 mg, 0.06 mmol), TFA (3 ml) and anisole (100 μl). Purification by ion-exchange chromatography yielded **58** (13 mg, 90%) as a white solid; mp 198–208 °C (decomp.); ν_{max} (KBr)/cm^{-1} 3337m, 3158m, 3638–2600br m (NH_2/CO_2H), 2963m (CH), 1618s (C=O), 1585s, 1459w, 1374w, 1080m, 802w; δ_H (500 MHz, D_2O) 0.79 (3H, t, *J* 7.0, CH_3), 1.51–1.58 (2H, m, CH_2), 2.01–2.15 (2H, m, CH_2), 2.43–2.46 (2H, m, CH_2), 2.55–2.65 (2H, m, CH_2), 3.68 (1H, t, *J* 6.0, CH), 6.50 (1H, s, ArH); δ_C (125.8 MHz, D_2O) 12.75 (CH$_3$), 21.59 (CH$_2$), 29.14 (CH$_2$), 32.17 (CH$_2$), 38.36 (CH$_2$), 54.21 (CH), 109.85 (Ar-CH), 162.10, 170.06, 173.17, 174.08 (3 × Ar-C, *ipso*; C=O); *m*/*z* (APCI+) 239 (MH$^+$, 100%); HRMS found MH$^+$ 239.1508. $C_{11}H_{19}N_4O_2$ requires 239.1508.

(*S*)-β-(2-Amino-6-phenylpyrimidin-4-yl)-α-aminopropanoic acid 59. Prepared from **40** (60 mg, 0.145 mmol), TFA (3 ml) and anisole (100 μl). Purification by ion-exchange chromatography yielded **59** (36 mg, 96%) as a pale yellow solid; mp 204–210 °C (decomp.); ν_{max} (KBr)/cm^{-1} 3676–2700br s (NH_2/CO_2H, CH), 1706–1600br s (C=O), 1580s, 1550s, 1446s, 1404s, 1154m, 1072m, 834w; δ_H (500 MHz, D_2O) 2.88–3.10 (2H, m, CH_2), 3.79–3.81 (1H, m, CH), 4.75 (2H, br s, NH_2), 7.03 (1H, s, ArH), 7.48–7.53 (3H, m, ArH), 7.84–7.85 (2H, m, ArH); δ_C (125.8 MHz, D_2O) 39.77 (CH$_2$), 54.89 (CH), 108.26, 127.28, 128.99, 131.06 (4 × Ar-CH), 136.46 (Ar-C, *ipso*), 162.89, 166.31, 168.80, 178.10 (3 × Ar-C, *ipso*; C=O); *m*/*z* (APCI+) 259 (MH$^+$, 100%).

Formation of (*S*)-γ-(2-hydroxypyrimidin-4-yl)-α-aminobutyric acid 57

To a stirred solution of (*S*)-α-*tert*-butoxycarbonylamino-γ-(2-methylsulfonylpyrimidin-4-yl)butyric acid α-*tert*-butyl ester **35** (104 mg, 0.25 mmol) in 1,4-dioxane (2 ml) was added 1 M sodium hydroxide solution (0.25 ml) and the reaction left at room temperature overnight. The reaction was then acidified by addition of 3 M potassium hydrogen sulfate solution (0.5 ml) and the reaction mixture concentrated *in vacuo*. The residue was then washed with boiling methanol, filtered and the filtrate

concentrated to give the crude deprotected product. Purification by ion-exchange chromatography yielded (*S*)-γ-(2-hydroxy-

Table 5 Representative examples of Mosher's amide ^{19}F NMR analysis

Protected amino acid for coupling	δ_F of *RS* Mosher's amide	δ_F of *SS* Mosher's amide
10	−69.21	—
24	−69.13	−69.40
27	−69.09	−69.44
32	−69.23	−69.61
38	−69.11	−69.59

pyrimidin-4-yl)-α-aminobutyric acid **57** (35 mg, 71%) as a yellow solid; mp 222–230 °C (decomp.); ν_{max} (KBr)/cm^{-1} 3421s, 3676–2600br s (NH_2/CO_2H, CH), 1654br s (C=O), 1474s, 1407s, 1146w, 826w; δ_H (500 MHz, D_2O) 2.01–2.11 (2H, m, CH_2), 2.69 (2H, t, *J* 8.0, CH_2), 3.55 (1H, t, *J* 6.0, C*H*), 6.55 (1H, d, *J* 6.0, Ar*H*), 8.04 (1H, d, *J* 6.0, Ar*H*); δ_C (125.8 MHz, D_2O) 30.54 (*C*H_2), 32.92 (*C*H_2), 54.99 (*C*H), 106.92, 154.17 (2 × Ar-C*H*), 161.27, 175.58, 177.57 (2 × Ar-*C*, *ipso*; *C*=O); *m*/*z* (APCI+) 198 (MH^+, 70%), 155 (100).

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 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*)-α-methoxy-α-(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 bicarbonate soluton and brine, dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude product for ^{19}F NMR analysis (Table 5).

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