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The efficient, enantioselective synthesis of quinoxaline, pyrazine and 1,2,4-triazine substituted α-amino acids from vicinal tricarbonyls

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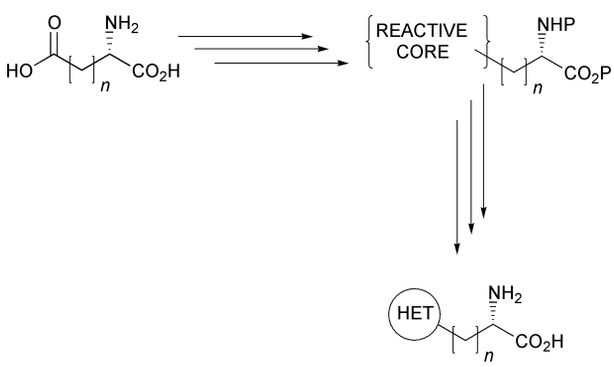
The reaction of diamines and amidrazones with α-amino acid vicinal tricarbonyls has been shown to be a versatile route towards novel heterocyclic α-amino acids. This route is also applicable to parallel synthesis and has allowed the formation of a range of heterocyclic amino acid systems.

Introduction

α-Amino acids play an important role in the synthesis of novel pharmaceuticals, which has led to their enantioselective synthesis being an active field of research.[1–3] Non-proteinogenic and unnatural amino acids are however becoming increasingly important with, in particular, heterocyclic substituted non-proteinogenic α-amino acids displaying a diverse range of structures and biological activities, for example azatyrosine, mimosine, ibotenic acid and lathyrine.[4–6] Heterocyclic amino acids of this type have therefore received significant attention, however the majority of these syntheses rely upon formation of the desired amino acids by manipulations with the required heterocycle already in place.[7] The formation of such compounds by the introduction of the heterocycle onto a pre-existing amino acid side chain has received considerably less attention and we have therefore investigated such routes, which due to the ever increasing demand for potentially biologically active compounds are applicable to parallel and/or combinatorial syntheses.[8–11] We have recently shown that access to a diverse range of products is possible by formation of a reactive substrate, capable of efficient construction of a range of heterocycles. This was carried out by the introduction of alkynyl ketone moieties into the side chains of L-aspartic and L-glutamic acids. By the generation of these suitable reactive building blocks for heterocyclic construction we then demonstrated that a range of heterocyclic substituted α-amino acids could be efficiently constructed including a whole family of pyrimidin-4-yl α-amino acids.[8–10]

Many other groups however have the potential to be suitable reactive cores for introduction into an amino acid side chain. Bidentate acceptors such as 1,3-diketones, α-bromoketones, α,β-unsaturated ketones and glyoxals, as well as α-alkynyl ketones, are particularly applicable as they all allow the synthesis of a whole range of heterocyclic structures (Scheme 1).[12]

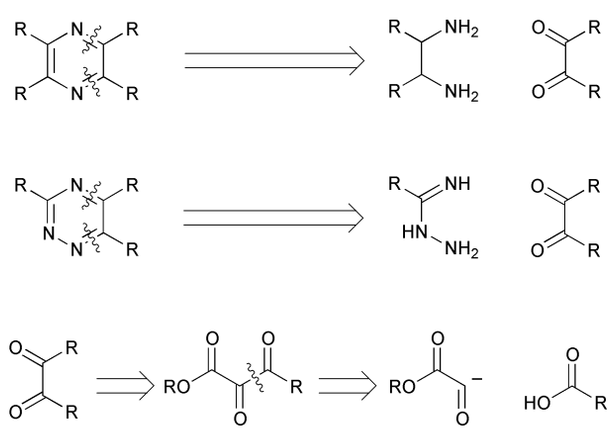
In order to allow efficient generation of further heterocyclic non-proteinogenic α-amino acids, it was therefore decided to attempt the formation of new amino acid reactive substrates by incorporation of a different reactive group into our aspartate and glutamate side chains. It was decided to direct our investigations towards pyrazines, quinoxalines and 1,2,4-triazines, compounds of which have often been shown to exhibit diverse biological activities.[13,14] These heterocycles were therefore seen as interesting bioactive cores for introduction into α-amino acid side chains and would hopefully allow the formation of compounds which are predisposed to bioactivity.



Scheme 1

Literature investigation indicated that the most common methods of generating both 'pyrazine' and 1,2,4-triazine cores involve cyclocondensation of nitrogen nucleophiles onto simple α-dicarbonyl systems.[13–15] It was believed this bis-acceptor synthon could be represented in the form of a vicinal tricarbonyl, containing a highly electrophilic central carbonyl, which could then be further disconnected to give an activated carboxylate core and some form of masked dicarbonyl system (Scheme 2).

If we consider this with respect to our previous syntheses it can be seen that the activated carboxylate synthon is identical and could therefore take the form of our previously protected



Scheme 2

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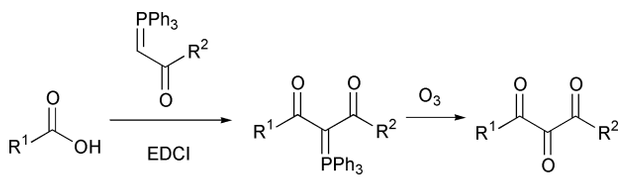
α-amino acids, *N-tert*-butoxycarbonyl-L-aspartic acid and *N-tert*-butoxycarbonyl-L-glutamic acid α-*tert*-butyl esters **1** and **2**. It can also be seen that the cyclocondensation di-nucleophiles of the required type are readily available with diverse functionality.

The vicinal tricarbonyl is a bis-acceptor, reactive building block, which behaves as a potent electrophile. It can be used in the synthesis of several different heterocyclic structures and therefore, over the last decade or so, it has received a great deal of synthetic attention, with Wasserman being instrumental in this field.[16] Examples of these heterocycles include substituted furans,[17] carbazoles,[18] substituted indoles,[19] imidazoles,[20,21] quinoxalines,[22] and 1,2,4-triazines.[23] They have also allowed the formation of cyclic non-proteinogenic α-amino acid derivatives,[24,25] and have been applied to the synthesis of various alkaloids.[16]

Owing to the general applicability of the vicinal tricarbonyls in functionalised heterocyclic synthesis several versatile approaches have been developed. One such route (Scheme 3),

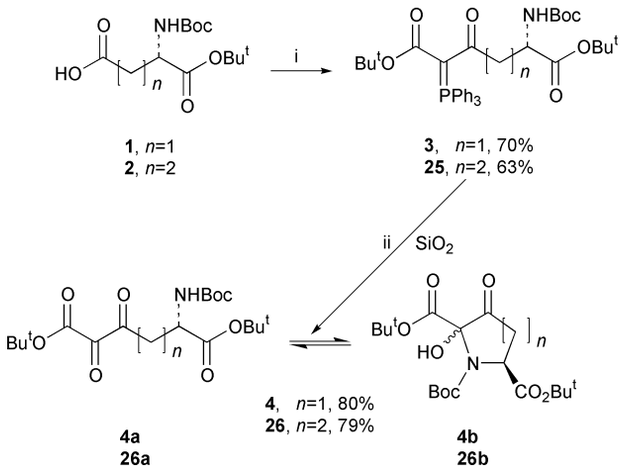


Scheme 3

developed by Wasserman,[16] involves conversion of carboxylic acids, using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) coupling reagent, or their acid chlorides into ketophosphoranes. The respective tricarbonyl units are then readily prepared by ozonolysis oxidation. This route has found the widest application in the formation of a range of tricarbonyl functionalised compounds, however other syntheses have also been documented.[22,26]

Results and discussion

In order to attempt the formation of pyrazine, quinoxaline and 1,2,4-triazine substituted non-proteinogenic α-amino acids our initial task was activation of the side chain carboxylic acid, followed by introduction of the vicinal tricarbonyl reactive core. Our strategy indicates that the selectively protected L-aspartate **1** and L-glutamate **2** would be suitable starting materials for this approach. Considering this, vicinal tricarbonyl formation appeared to be best achieved by conversion of the carboxylic acid functionality into a ketophosphorane, followed by ozonolysis oxidation of the carbon–phosphorus bond, as reported by Wasserman.[16] Starting from our selectively protected L-aspartate **1**, activation of the free β-side chain carboxylic acid to the ketophosphorane **3** was therefore carried out. Reactions of **1** under EDCI–DMAP coupling conditions with (*tert*-butoxycarbonylmethylene)triphenylphosphine in DCM initially allowed the desired phosphorane **3** to be isolated in low to reasonable yields (19–46%). In an effort to improve on this reaction optimal conditions were however found to be an analogous reaction using DCC as the coupling agent. This change allowed generally improved yields of **3** to be obtained, up to an optimum 70% conversion, which was believed to be due to easier separation of the crude product from the urea residue (Scheme 4). The ketophosphorane **3** then underwent ozonolysis, on bubbling ozone through a cooled, −78 °C, solution in DCM, with TLC analysis indicating a rapid consumption of starting material coupled with the formation of triphenylphosphine oxide and two products. Silica chromatography, however, initially proved perplexing, with the two widely different polarity products appearing to be eluted from the column simultaneously. Analysis of this residue, by ^{1}H and



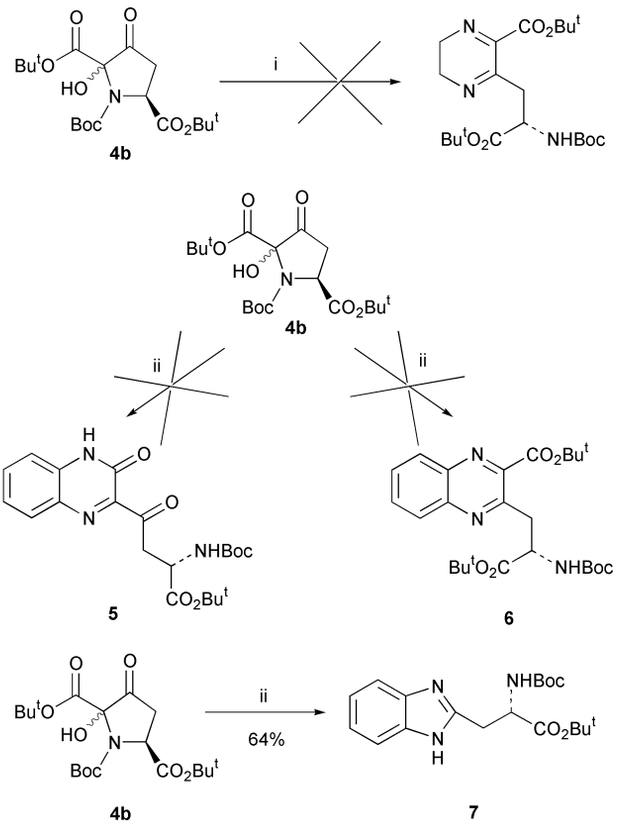
Scheme 4 *Reagents and conditions*: i, (*tert*-butoxycarbonylmethylene)-triphenylphosphine, DCC, DMAP, DCM, 0 °C; ii, O_3, DCM, −78 °C.

^{13}C NMR, indicated that the resulting product existed as an unequal mixture of 2 equilibrium species. It was likely that the vicinal tricarbonyl species **4a** was existing in an equilibrium with the 5-membered ring closed form **4b** as the major species, which resulted from the coupling of the α-amino group with the highly electrophilic central carbonyl (Scheme 4). This observation was not particularly surprising in light of the fact that the central carbonyl of the tricarbonyl group is usually found to exist in association with one molecule of water, as the gem diol.[16,26]

In order to further investigate this proposed equilibrium, variable temperature ^{1}H NMR analysis was carried out in d_8-toluene. At 25 °C the existence of two species was clearly indicated by a complicated spectrum, *i.e.* the presence of a five peak envelope corresponding to the *tert*-butyl ester groups and all other protons being represented by complex multiplets. When the temperature was raised to 90 °C, however, the ^{1}H spectrum was significantly simplified. The multiplets observed at lower temperature collapsed to give a spectrum corresponding to what appeared to be a single cyclic species, **4b**, consistent with the distinctive geminal coupling of the CH_2 protons.

Despite the equilibrium existence of **4** trial cyclocondensations with a range of bis-nucleophiles were carried out. Initially a cyclocondensation of **4** with ethylenediamine was attempted in order to generate a dihydropyrazine system. This however proved to be unsuccessful at a range of temperatures in both ethanol and toluene, with rapid consumption of starting material and formation of complex unidentifiable products (Scheme 5).

Following literature precedent, in order to generate the quinoxaline core, **4** was next reacted with 1,2-phenylenediamine in refluxing ethanol.[22] These reactions, however, all proceeded uncleanly, with only one compound consistently being successfully isolated. The presence of only two *tert*-butyl ester singlets in the ^{1}H NMR spectra suggested that an unexpected cyclocondensation of the diamine, onto the central and adjacent *tert*-butyl ester carbonyls, had occurred, with elimination of Bu^tOH to give the quinoxaline **5** and not the expected quinoxaline **6** (Scheme 5). Mass spectral analysis under a variety of mild (chemical ionisation and electrospray) conditions, however, indicated the product had a mass of 361 and not 417 (corresponding to **5**). High resolution mass spectroscopic analysis indicated a molecular formula of $C_{19}H_{27}N_3O_4$, as opposed to $C_{21}H_{27}N_3O_6$. This difference required a significantly different structure from the proposed product **5**. It became apparent that the benzimidazole substituted, protected amino acid **7** had been isolated (Scheme 5); formation of **7** must have occurred by a condensation of 1,2-phenylenediamine with **4** coupled with the elimination of the two carbon fragment introduced by ketophosphorane formation. Reinforcing



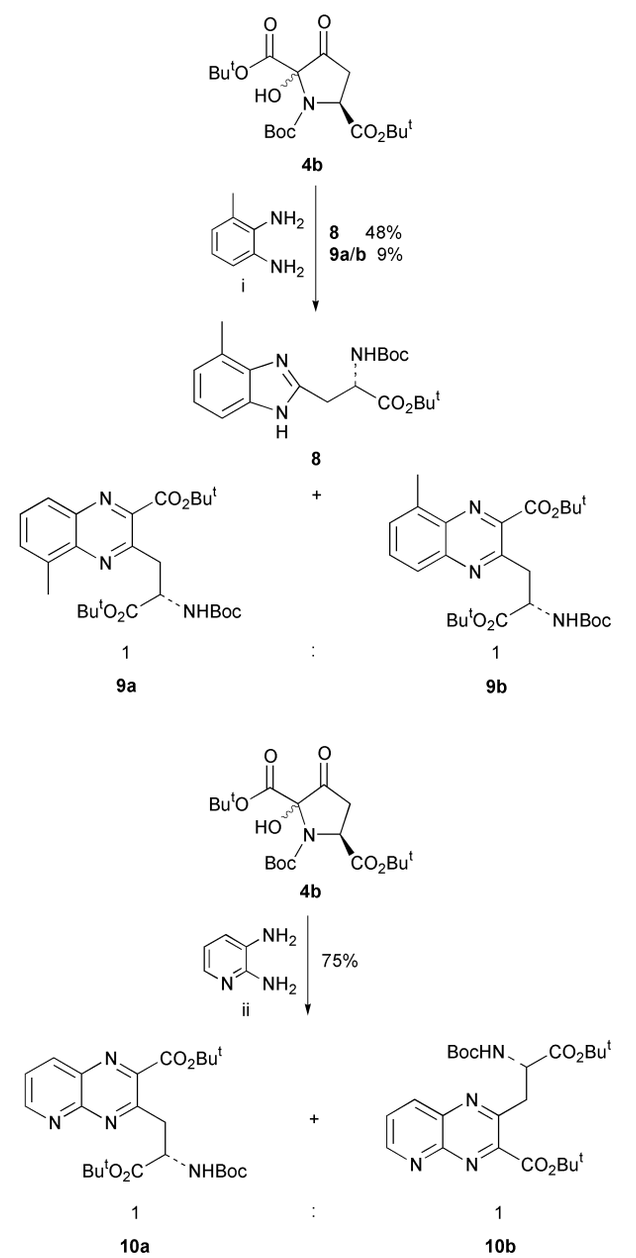
Scheme 5 *Reagents and conditions*: i, $H_2NCH_2CH_2NH_2$, EtOH, Δ; ii, *o*-$C_6H_4(NH_2)_2$, EtOH, reflux.

evidence for benzimidazole formation was also present in the ^{1}H NMR spectrum of **7** with the common broadening of the aromatic protons in this class of compounds being observed.[27,28]

Investigation into amino acid products of this type indicated some interesting activities, *e.g.* 3-(benzimidazol-2-yl)alanine, (*S*)-β-(benzimidazol-2-yl)-α-aminopropanoic acid (the deprotected form of our unexpected product **7**), and other analogues having been used for incorporation into novel polypeptide hormone analogues.[29]

In order to investigate the generality of the condensation of aromatic diamines with our reactive intermediate **4**, further reactions were carried out. Initially a condensation with toluene-2,3-diamine was attempted and as above an unclean reaction was observed. Purification of the reaction mixture allowed the benzimidazole **8** to be isolated in 48% yield, along with a 9% yield of the originally expected quinoxaline products **9a**,**b** (Scheme 6). In order to significantly alter the electronic nature and nucleophilicity of the diamine, the reaction of **4** with pyridine-2,3-diamine was next carried out. The reaction now appeared much cleaner than those above and allowed the formation of the expected quinoxaline products **10a**,**b**, as an inseparable mixture of regioisomers in 75% yield with no evidence of analogous benzimidazole type products (Scheme 6).

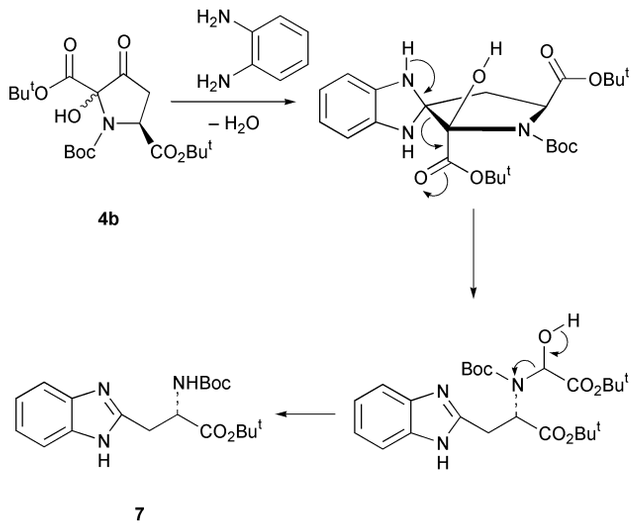
Different diamines had therefore been shown to react with the reactive substrate **4** in different ways. It was believed that this was chiefly a consequence of the equilibrium existence of **4** coupled with the variation in *N*-nucleophilicity of the diamines. The lack of any isolable products from the reaction of **4** with ethylenediamine, when compared with the aromatic diamines, was therefore attributed to its comparably high *N*-nucleophilicity. A fast and indiscriminate attack upon either equilibrium species **4a**,**b** followed by an almost equally rapid secondary attack (intra- or intermolecularly) could lead to complicated and polymeric products. The aromatic diamines,



Scheme 6 *Reagents and conditions*: i, EtOH, reflux; ii, EtOH, reflux.

however, have considerably reduced *N*-nucleophilicity, owing to delocalisation of the nitrogen lone pairs into the adjacent π-system, and it is believed that this selectivity allows isolable condensation products to be formed. In the condensation of phenylene- and toluenediamines the major benzimidazolyl product is believed to be formed by a rapid condensation of the diamine upon the ketonic carbonyl of the cyclic species **4b**. This reaction is encouraged by the high reactivity of 5-membered cyclic ketones towards nucleophilic attack, in order to alleviate ring strain. Aromatisation to the benzimidazole then causes ring opening with subsequent elimination of oxoacetic acid *tert*-butyl ester to generate the observed products (Scheme 7).

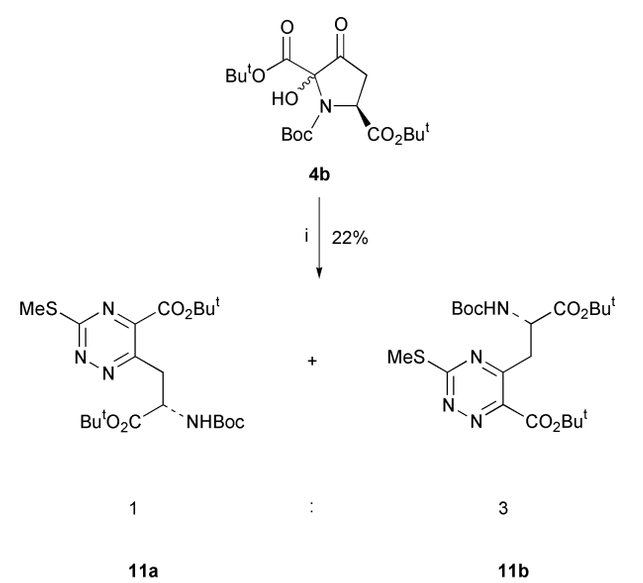
Reaction of pyridine-2,3-diamine with **4** had however allowed the desired 'pyrazine' cyclocondensation product to be obtained. We postulated that this may be a combination of two factors, the first being the significantly reduced *N*-nucleophilicity of the 2-amino group. This would dramatically lower the rate of secondary condensation with respect to our other diamines, allowing the equilibrium ring opening mechanism to factor more predominantly. It was also believed that this



Scheme 7

pyridinediamine may have a more direct effect on the equilibrium ring opening. 2-Amino- and 2-hydroxypyridines are known to catalyse the ring opening of sugars to bring about mutarotation.[30] It was therefore proposed that our reactant pyridine-2,3-diamine may also be behaving as a catalyst for the ring opening of our reactive species **4b**. This would allow the expected cyclocondensation to take place and a combination of both factors may explain the observed mixture of regioisomers.

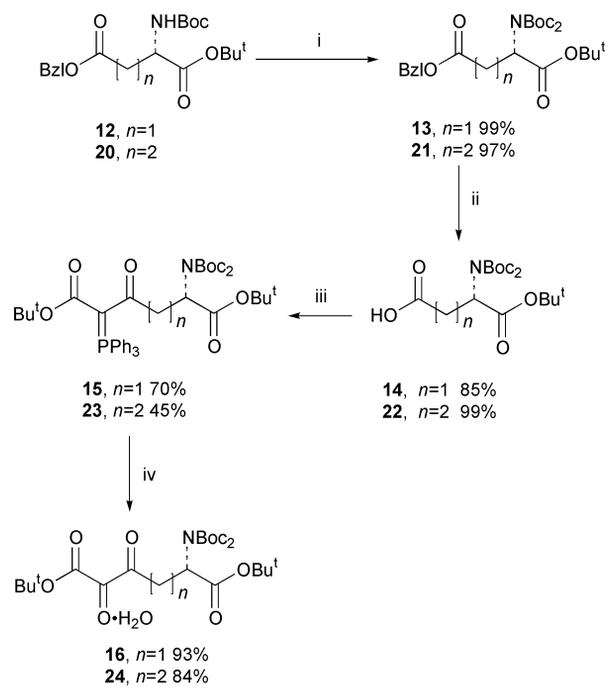
The reaction of diamines upon our reactive substrate **4** had therefore proved to be an unpredictable route to our desired pyrazine and quinoxaline substituted amino acids. Before addressing this problem, however, we decided to attempt 1,2,4-triazine formation by a cyclocondensation of **4** with *S*-methylisothiosemicarbazide hydrogen iodide salt in DCM with diisopropylethylamine. As with the diamine cyclocondensations this reaction also proved problematic, the desired regioisomeric triazines **11a**,**b** being isolated in a 1 : 3 ratio in only a 22% total yield, with a majority of unidentifiable/polymeric products being generated (Scheme 8).



Scheme 8 *Reagents and conditions*: i, $H_2NHN(CSMe)NH{\cdot}HI$, Pr^i_2NEt, DCM, reflux.

In order to overcome the problems we had encountered with the substrate **4** we decided to prevent the formation of the equilibrium species **4b**. It was believed that if we could protect the α-amino group with a second Boc group the ring closed species would be unable to form. This would therefore bias the ring opened vicinal tricarbonyl species to exist, for subsequent nucleophilic attack and expected heterocyclic formation.

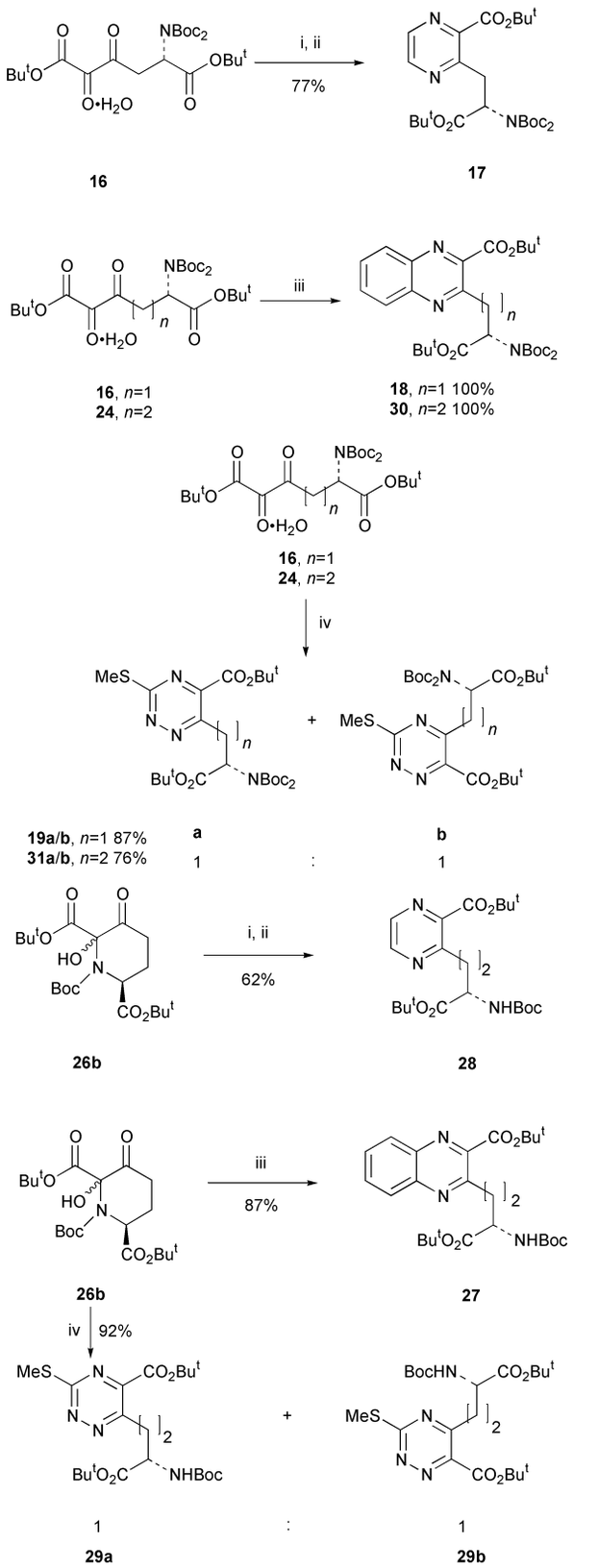
N-Di-Boc protection of amino acids can be carried out upon either the free amine or mono-Boc protected species as reported by Ragnarsson.[31,32] The reaction of a concentrated solution of the orthogonally protected aspartate **12** in acetonitrile with an excess of di-*tert*-butyl dicarbonate and DMAP thus generated **13** in almost quantitative yield (99%). The β-benzyl ester was then removed by hydrogenation over Pd/C to yield modified starting material **14**. An analogous conversion of the β-carboxylic acid to the ketophosphorane was then carried out to generate **15**, followed by ozonolysis oxidation to the vicinal tricarbonyl reactive substrate **16**, as previously described, in good overall yield (Scheme 9).



Scheme 9 *Reagents and conditions*: i, Boc_2O, DMAP, MeCN; ii, H_2, (10%) Pd–C, EtOH (95%); iii, (*tert*-butoxycarbonylmethylene)-triphenylphosphine, DCC, DMAP, DCM, 0 °C; iv, O_3, DCM, −78 °C.

Analysis of **16** by ^1H and ^{13}C NMR indicated, by simple spectra, that introduction of a second Boc group had indeed led to the formation of a masked vicinal tricarbonyl reactive substrate only. This was exemplified by the presence of two peaks in the ^1H NMR spectrum, at 5.00 and 5.08 ppm, corresponding to associated water at the central carbonyl, *i.e.* the gem diol, which as previously mentioned is commonly observed in these systems.[16,26]

The 'ring-opened' vicinal tricarbonyl **16** was then reacted with ethylenediamine in ethanol, which resulted in rapid consumption of starting material, coupled with the appearance of a single product, expected to be the dihydropyrazine system. Palladium on carbon (10%) was subsequently added and the reaction heated to reflux, to affect oxidation, and this resulted in the formation of the desired pyrazine **17** in 77% yield (Scheme 10). With the success of this diamine condensation, which had previously proved the most problematic, a reaction between **16** and 1,2-phenylenediamine was then carried out in refluxing ethanol. The desired quinoxaline substituted protected amino acid **18** was thus generated in quantitative yield (Scheme 10). Finally our reactive substrate **16** underwent a cyclocondensation reaction with *S*-methylisothiosemicarbazide as previously. This resulted in the formation of the 1,2,4-triazines **19a** and **19b** in a very high yield (87%), as a partially separable 1 : 1 mixture of regioisomers (Scheme 10).



Scheme 10 *Reagents and conditions*: i, $H_2NCH_2CH_2NH_2$, EtOH, RT; ii, (10%) Pd/C, EtOH, reflux; iii, *o*-$C_6H_4(NH_2)_2$, EtOH, reflux; iv, $H_2NHN(CSMe)NH{\cdot}HI$, Pr^i_2NEt, DCM, reflux.

With the interesting results observed in the above cyclocondensations upon *N*-mono- and *N*-di-*tert*-butoxycarbonyl protected reactive substrates **4** and **16** respectively it was next decided to expand to the glutamate system. This would not only allow us to generate different heterocyclic amino acid families and highlight the flexibility of our strategy but also investigate the nature and reactivity of the resulting, reactive substrates with each other and their 'aspartate' homologues.

Starting from *N*-*tert*-butoxycarbonyl-L-glutamic acid γ-benzyl α-*tert*-butyl diester **20** di-Boc protection, to give **21**, followed by removal of the γ-benzyl ester *via* hydrogenolysis to generate **22** was carried out, as for **12**, in excellent overall yield (Scheme 9). Both the di-Boc and mono-Boc-glutamates **22** and **2** then underwent DCC–DMAP coupling reactions with (*tert*-butoxycarbonylmethylene)triphenylphosphine to generate the ketophosphoranes **23** and **25** in average to satisfactory yields (45 and 63% respectively). Ozonolyses of these phosphoranes were then carried out and the reactive substrates **24** and **26** isolated in high yields. As with the analogous 'aspartate' system the mono-Boc reactive substrate **26** was found to exist as an equilibrium mixture between the ring opened vicinal tricarbonyl **26a** and the cyclic ketone species **26b**. The di-Boc reactive substrate **24**, as expected, existed as only the masked vicinal tricarbonyl species, with associated water again evident in the ^1H spectrum (Schemes 9 and 4).

In order to compare the reactivity of **26** with its 'aspartate' homologue **4** an analogous cyclocondensation with phenylenediamine was attempted. This, however, now resulted in the formation of the desired quinoxaline **27** in a very high yield (87%) with no benzimidazole product being observed (Scheme 10). With the success of this reaction condensations between **26** and ethylenediamine and *S*-methylisothiosemicarbazide were also carried out, as previously described. The desired pyrazine **28** was thus isolated, in satisfactory yield (62%), after condensation and aerial oxidation, as were the 1,2,4-triazines **29a**,**b** which were generated in excellent total yield (92%), once again as a partially separable 1 : 1 mixture of regioisomers (Scheme 10).

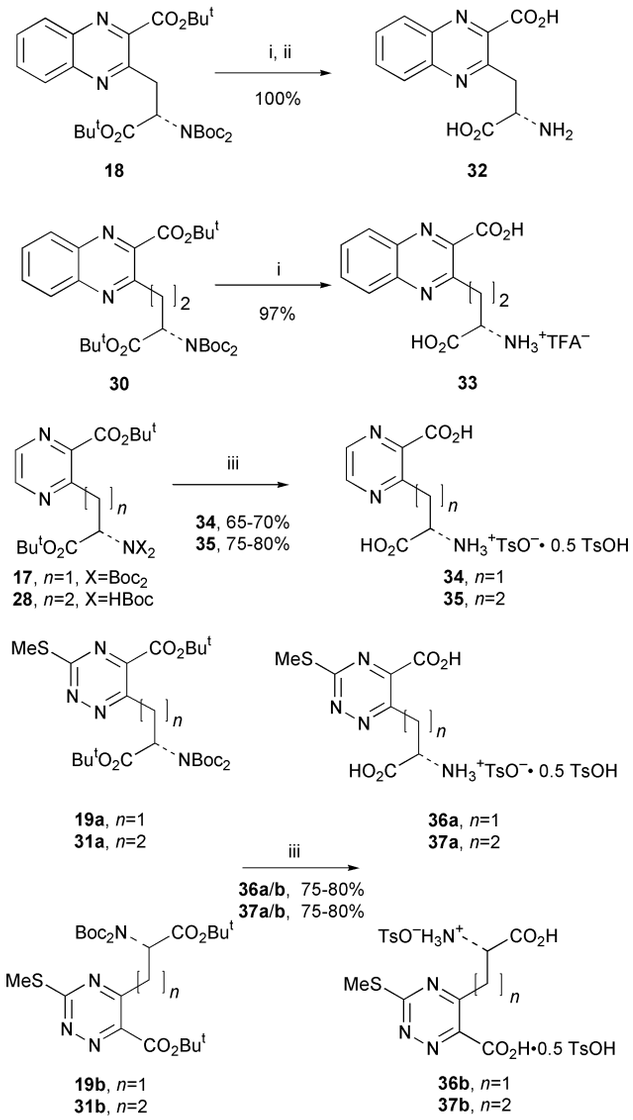
The existence of the reactive substrates **26** as an equilibrium mixture of ring closed and opened species had therefore had little effect upon its expected reactivity.

Finally, in order to contrast the reactivities of the glutamate reactive substrates **24** and **26**, cyclocondensations of 1,2-phenylenediamine and *S*-methylisothiosemicarbazide were carried out upon di-*N*-Boc-**24**. These reactions resulted in the formation of the desired quinoxaline **30** in quantitative yield and the 1,2,4-triazines **31a**,**b** in high yield, in accord with results obtained from the di-*N*-Boc-**16** (Scheme 10).

With the formation of our desired target materials, the enantioselectivity of the route was investigated. Selective Boc deprotections of the representative compounds **18**, **19** and **28** were therefore carried out followed by Mosher's amide formation, as previously.[33] Analysis of the resulting diastereoisomers by ^{19}F NMR then proved their enantiomeric purity to be greater than 98% ee.[33]

Deprotection of the protected amino acids **17**–**19a**,**b** and **27**–**29a**,**b** generated above was then attempted using the standard TFA–anisole conditions. Facile Boc and *tert*-butyl ester deprotection of the quinoxalines **18** and **30** was found to occur to generate compounds **32** and **33**. Subsequently **32** was purified by ion-exchange chromatography, the free amino acid being obtained in excellent yield, whilst **33** was isolated, after trituration with diethyl ether, as the TFA salt in high yield (Scheme 11).

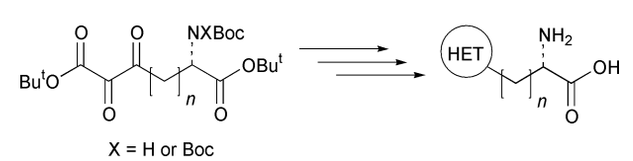
Attempted TFA–anisole deprotection of the pyrazines and triazines **17**, **28** and **19a**,**b**, **29a**,**b** however proved less successful with various conditions leading to at least partially decomposed products. Considering the mild/selective deprotection procedure we had utilised in Mosher's amide formation, these deprotections were therefore carried out by azeotropic distillation with 1.5 equivalents of $TsOH{\cdot}H_2O$–PhMe. The deprotected pyrazine and 1,2,4-triazine functionalised amino acids **34**, **35**, **36a**,**b** and **37a**,**b** were thus obtained as their tosylate salts in high yields as sensitive species (Scheme 11). Owing to the sensitive nature of these deprotected amino acids, however, full characterisation proved very difficult.



Scheme 11 *Reagents and conditions*: i, TFA, anisole; ii, Dowex® 50X8-100 ion-exchange resin; iii, $TsOH{\cdot}H_2O$ (1.5 equiv.), toluene, azeotropic distillation.

Conclusions

The vicinal tricarbonyl reactive core has thus allowed access to a range of novel heterocyclic substituted amino acids, along with some interesting and unexpected chemistry. This reactive group could be efficiently introduced into the side chain of our amino acids, allowing the construction of a range of heterocyclic substituted α-amino acid systems (Scheme 12). The existence of **4** as an equilibrium mixture of ring opened and ring closed forms highlighted the reactivity of this species and allowed an interesting route to protected benzimidazolyl substituted β-alanines. The problems encountered from the equilibrium existence of **4** in the generation of the desired quinoxaline, pyrazine and 1,2,4-triazine systems were then shown to be easily circumvented, by simple addition of a further *N*-Boc protecting group.



Scheme 12

Experimental

Standard general procedures and techniques as described previously were employed.[9] Petroleum ether refers to the fraction boiling at 40–60 °C. *J* values are given in Hz.

Preparation of *N*,*N*-bis(*tert*-butoxycarbonyl)-L-aspartic acid β-benzyl α-*tert*-butyl diester and *N*,*N*-bis(*tert*-butoxycarbonyl)-L-glutamic acid γ-benzyl α-*tert*-butyl diester

Typically, to a stirred, concentrated, solution of the orthogonally protected L-amino acid in acetonitrile was added excess di-*tert*-butyl dicarbonate followed by catalytic DMAP. The reaction was stirred at RT overnight, concentrated *in vacuo* and taken into diethyl ether before being washed with 1 M $KHSO_4$, saturated aqueous bicarbonate and brine. The organic residue was then dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude product.

***N*,*N*-Bis(*tert*-butoxycarbonyl)-L-aspartic acid β-benzyl α-*tert*-butyl diester 13.** This compound was prepared from **12** (4.93 g, 13.0 mmol), di-*tert*-butyl dicarbonate (7.2 g, 33 mmol), DMAP (159 mg, 1.3 mmol), acetonitrile (6 ml), 1 M $KHSO_4$ (3 × 40 ml), saturated aqueous bicarbonate (3 × 40 ml) and brine (3 × 40 ml). A 300 mg portion, from 6.23 g crude weight, was purified by flash column chromatography (SiO_2, 1 : 4 Et_2O–petroleum ether) to yield **13** (297 mg, 99%) as a colourless oil; $[\alpha]_D^{22}$ −30.6 (*c* 1.0 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2980m, 2936w (CH), 1740s, 1701m (C=O), 1457w, 1368s, 1258m, 1157s, 849w; δ_H (200 MHz, $CDCl_3$) 1.44 (9H, s, $C(CH_3)_3$), 1.48 (9H, s, $C(CH_3)_3$), 1.50 (9H, s, $C(CH_3)_3$), 2.74 (1H, dd, *J* 6.5, 16.5, C*H*(H)), 3.29 (1H, dd, *J* 7.0, 16.5, C*H*(H)), 5.15 (2H, ABq, *J* 9.0, OCH_2), 5.38 (1H, br t, *J* 7, C*H*), 7.36 (5H, s, Ar*H*); δ_C (50.3 MHz, $CDCl_3$) 27.69 ($C(CH_3)_3$), 27.82 ($C(CH_3)_3$), 35.49 (CH_2), 55.51 (*C*H), 66.50 (OCH_2), 81.86 ($C(CH_3)_3$), 83.11 ($C(CH_3)_3$), 128.09, 128.43 (3 × Ar-*C*H), 135.95 (Ar-*C*, *ipso*), 152.22, 168.86, 170.97 (3 × *C*=O); *m*/*z* (APCI+) 480 (MH^+, 2%), 424 [$MH^+ - (C_4H_8)$, 5], 380 [60], 285 [100]; HRMS found MH^+ 480.2597; $C_{25}H_{38}NO_8$ requires 480.2597.

***N*,*N*-Bis(*tert*-butoxycarbonyl)-L-glutamic acid γ-benzyl α-*tert*-butyl diester 21.** This compound was prepared from **20** (1.18 g, 3.00 mmol), di-*tert*-butyl dicarbonate (1.64 g, 7.5 mmol), DMAP (36.7 mg, 0.3 mmol), acetonitrile (4 ml), 1 M $KHSO_4$ (3 × 20 ml), saturated aqueous bicarbonate (3 × 20 ml) and brine (3 × 20 ml). Purification by flash column chromatography (SiO_2, 1 : 4 Et_2O–petroleum ether) yielded **21** (1.43 g, 97%) as a colourless oil; $[\alpha]_D^{22}$ −23.2 (*c* 1.1 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2980s, 2935m (CH), 1740s, 1700s (C=O), 1456m, 1368s, 1257s, 1141s, 850m; δ_H (200 MHz, $CDCl_3$) 1.44 (9H, s, $C(CH_3)_3$), 1.48 (18H, s, 2 × $C(CH_3)_3$), 2.13–2.45 (2H, br m, CH_2), 2.42–2.44 (2H, m, CH_2), 4.76–4.83 (1H, m, C*H*), 5.11 (2H, s, OCH_2), 7.33 (5H, s, Ar*H*); δ_C (125.8 MHz, $CDCl_3$) 24.47 (CH_2), 27.84 ($C(CH_3)_3$), 27.90 ($C(CH_3)_3$), 30.92 (CH_2), 58.02 (*C*H), 66.18 (OCH_2), 81.29 ($C(CH_3)_3$), 82.85 ($C(CH_3)_3$), 128.09, 128.43 (3 × Ar-*C*H), 135.85 (Ar-*C*, *ipso*), 152.24, 169.18, 172.55 (3 × *C*=O); *m*/*z* (APCI+) 494 (MH^+, 5%), 438 [60], 282 [100]; HRMS found MH^+ 494.2763. $C_{26}H_{40}NO_8$ requires 494.2754.

Preparation of *N*,*N*-bis(*tert*-butoxycarbonyl)-L-aspartic acid α-*tert*-butyl ester and *N*,*N*-bis(*tert*-butoxycarbonyl)-L-glutamic acid α-*tert*-butyl ester

Typically, to a solution of *N*-*tert*-butoxycarbonyl-L-amino acid benzyl α-*tert*-butyl diester in 95% ethanol was added palladium on carbon (10% Pd/C). The reaction vessel was evacuated and flushed with hydrogen several times and the reaction mixture stirred under a hydrogen atmosphere overnight at room temperature. The reaction mixture was then filtered through Celite and concentrated *in vacuo* to yield

N,*N*-bis(*tert*-butoxycarbonyl)-L-aspartic acid α-*tert*-butyl ester **14** and *N*,*N*-bis(*tert*-butoxycarbonyl)-L-glutamic acid α-*tert*-butyl ester **22**.

***N*,*N*-Bis(*tert*-butoxycarbonyl)-L-aspartic acid α-*tert*-butyl ester 14.** This compound was prepared from **13** (7.09 g, 14.8 mmol), 95% ethanol (150 ml) and 10% Pd/C (415 mg). Purification by flash column chromatography (SiO_2, 1 : 1 Et_2O–petroleum ether) yielded **14** (4.89 g, 85%) as a white solid; mp 77–79 °C; $[\alpha]_D^{22}$ −50.5 (*c* 1.0 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3400–2900br w (OH), 2981m, 2936w (CH), 1739br s (C=O), 1459w, 1369s, 1252m, 1145s, 848w; δ_H (200 MHz, $CDCl_3$) 1.44 (9H, s, C(CH_3)$_3$), 1.50 (18H, s, 2 × C(CH_3)$_3$), 2.73 (1H, dd, *J* 6.5, 17.0, C*H*(H)), 3.26 (1H, dd, *J* 7.0, 17.0, CH(*H*)), 5.21–5.42 (1H, br t, *J* 6.5, C*H*), 9.29 (1H, br s, O*H*); δ_C (50.3 MHz, $CDCl_3$) 27.67 (C(*C*H$_3$)$_3$), 27.79 (C(*C*H$_3$)$_3$), 35.30 (*C*H$_2$), 55.28 (*C*H), 82.14 (*C*(CH$_3$)$_3$), 83.28 (*C*(CH$_3$)$_3$), 152.18, 168.78, 177.45 (3 × C=O); *m*/*z* (ES−) 388 [(M − H)$^-$, 100%].

***N*,*N*-Bis(*tert*-butoxycarbonyl)-L-glutamic acid α-*tert*-butyl ester 22.** This compound was prepared from **21** (1.20 g, 2.43 mmol), 95% ethanol (24 ml) and 10% Pd/C (67 mg). This afforded **22** (967 mg, 99%) as a white crystalline solid; mp 73–76 °C; $[\alpha]_D^{22}$ −22.6 (*c* 1.1 in $CHCl_3$) (Found: C, 56.48; H, 8.19; N, 3.52. $C_{19}H_{33}NO_8$ requires C, 56.56; H, 8.24; N, 3.47%); ν_{max} (thin film)/cm^{-1} 3400–2900br w (OH), 2981m, 2936m (CH), 1740s, 1713s (C=O), 1479w, 1368s, 1256s, 1143s, 850m; δ_H (200 MHz, $CDCl_3$) 1.42 (9H, s, C(CH_3)$_3$), 1.47 (18H, s, 2 × C(CH_3)$_3$), 2.11–2.44 (2H, br m, CH_2), 2.41–2.43 (2H, m, CH_2), 4.73–4.80 (1H, m, C*H*); δ_C (125.8 MHz, $CDCl_3$) 24.07 (*C*H$_2$), 27.77 (C(*C*H$_3$)$_3$), 30.65 (*C*H$_2$), 58.05 (*C*H), 81.45 (*C*(CH$_3$)$_3$), 83.05 (*C*(CH$_3$)$_3$), 152.24, 169.49, 179.11 (3 × *C*=O); *m*/*z* (ES−) 402 [(M − H)$^-$, 100].

General procedure for ketophosphorane formation

Typically, to a cooled, 0 °C, stirred solution of the acid in DCM was added (*tert*-butoxycarbonylmethylene)triphenylphosphine followed by DCC and catalytic DMAP. After 30 minutes the reaction mixture was allowed to warm to room temperature and stirred overnight. Et_2O was then added, the resulting emulsion filtered through a sinter funnel under vacuum and the filtrate concentrated *in vacuo* to afford the crude ketophosphorane.

(*S*)-5-*tert*-Butoxycarbonylamino-2-(triphenylphosphoranylidene)-3-oxohexanedioic acid di-*tert*-butyl ester 3. This compound was prepared from **1**[9] (578 mg, 2.00 mmol), (*tert*-butoxycarbonylmethylene)triphenylphosphine (753 mg, 2.00 mmol), DCM (15 ml) and DCC (413 mg, 2.00 mmol). Purification by flash column chromatography (SiO_2, 1 : 2 EtOAc–petroleum ether) yielded **3** (906 mg, 70%) as a white crystalline solid; mp 171–174 °C; $[\alpha]_D^{22}$ +0.6 (*c* 1.0 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3428br w (NH), 2977m, 2931w (CH), 1738m, 1715s (C=O), 1666s, 1456w, 1366s, 1254m, 1164s, 1087s, 850w; δ_H (200 MHz, $CDCl_3$) 1.05 (9H, s, C(CH_3)$_3$), 1.26 (9H, s, C(CH_3)$_3$), 1.41 (9H, s, C(CH_3)$_3$), 3.09 (1H, dd, *J* 4.0, 16.0, C*H*(H)), 3.67 (1H, dd, *J* 6.0, 16.0, CH(*H*)), 4.29–4.35 (1H, m, C*H*), 5.68 (1H, d, *J* 9.0, N*H*), 7.37–7.52 (9H, m, Ar*H*), 7.60–7.70 (6H, m, Ar*H*); δ_C (50.3 MHz, $CDCl_3$) 27.75 (C(*C*H$_3$)$_3$), 28.01 (C(*C*H$_3$)$_3$), 28.35 (C(*C*H$_3$)$_3$), 41.86 (d, $J_{^{31}P-^{13}C}$ 7, *C*H$_2$), 51.48 (*C*H), 78.66 (*C*(CH$_3$)$_3$), 78.88 (*C*(CH$_3$)$_3$), 80.43 (*C*(CH$_3$)$_3$), 126.91 (Ar-*C*, *ipso*, $J_{^{31}P-^{13}C}$ 120), 128.69 (Ar-*C*, $J_{^{31}P-^{13}C}$ 13), 131.75 (Ar-*C*), 133.25 (Ar-*C*, $J_{^{31}P-^{13}C}$ 10), 156.26 (*C*=O), 167.67 (d, $J_{^{31}P-^{13}C}$ 13, *C*=P), 171.95, 194.08 (2 × *C*=O); *m*/*z* (APCI+) 648 (MH^+, 100%), 548 [MH^+ − (CO_2 + C_4H_8), 20]; HRMS found MH^+ 648.3090; $C_{37}H_{47}NO_7P$ requires 648.3090.

(*S*)-5-Bis(*tert*-butoxycarbonyl)amino-2-(triphenylphosphoranylidene)-3-oxohexanedioic acid di-*tert*-butyl ester 15. This compound was prepared from **14** (778 mg, 2.00 mmol), (*tert*-butoxycarbonylmethylene)triphenylphosphine (753 mg, 2.00 mmol), DCM (15 ml) and DCC (413 mg, 2.00 mmol). Purification by flash column chromatography (SiO_2, 1 : 2 EtOAc–petroleum ether) yielded **15** (1.05 g, 70%) as a white crystalline solid; mp 71–75 °C; $[\alpha]_D^{22}$ −20.5 (*c* 2.1 in $CHCl_3$) (Found: C, 67.52; H, 7.49; N, 2.15. $C_{42}H_{54}NO_9P$ requires C, 67.47; H, 7.23; N, 1.87%); ν_{max} (thin film)/cm^{-1} 2978m, 2930w (CH), 1786w, 1740br s (C=O), 1664m, 1560m, 1366s, 1298s, 1142s, 1082m, 998w; δ_H (200 MHz, $CDCl_3$) 1.06 (9H, s, C(CH_3)$_3$), 1.40 (9H, s, C(CH_3)$_3$), 1.47 (18H, s, C(CH_3)$_3$), 3.03 (1H, dd, *J* 5.0, 17.0, C*H*(H)), 3.97 (1H, dd, *J* 7.5, 17.0, CH(*H*)), 5.53–5.60 (1H, m, C*H*), 7.37–7.51 (9H, m, Ar*H*), 7.65–7.75 (6H, m, Ar*H*); δ_C (50.3 MHz, $CDCl_3$) 27.89 (C(*C*H$_3$)$_3$), 28.07 (C(*C*H$_3$)$_3$), 41.10 (d, $J_{^{31}P-^{13}C}$ 7.5, *C*H$_2$), 55.82 (*C*H), 78.32 (*C*(CH$_3$)$_3$), 80.40 (*C*(CH$_3$)$_3$), 82.23 (*C*(CH$_3$)$_3$), 127.42 (Ar-*C*, *ipso*, $J_{^{31}P-^{13}C}$ 94), 128.58 (Ar-*C*, $J_{^{31}P-^{13}C}$ 12), 131.40 (Ar-*C*), 133.28 (Ar-*C*, $J_{^{31}P-^{13}C}$ 10), 152.42 (HN*C*=O), 167.35 (d, $J_{^{31}P-^{13}C}$ 13, *C*=P), 170.25 (*C*=O), 193.47 (d, $J_{^{31}P-^{13}C}$ 5, *C*=O); *m*/*z* (APCI+) 748 (MH^+, 100%), 648 [MH^+ − (CO_2 + C_4H_8), 15], 548 [MH^+ − 2 × (CO_2 + C_4H_8), 5]; HRMS found MH^+ 748.3650; $C_{42}H_{55}NO_9P$ requires 748.3600.

(*S*)-6-Bis(*tert*-butoxycarbonyl)amino-2-(triphenylphosphoranylidene)-3-oxoheptanedioic acid di-*tert*-butyl ester 23. This compound was prepared from **22** (605 mg, 1.50 mmol), (*tert*-butoxycarbonylmethylene)triphenylphosphine (565 mg, 1.50 mmol), DCM (15 ml) and DCC (310 mg, 1.50 mmol). Purification by flash column chromatography (SiO_2, 1 : 2 EtOAc–petroleum ether) yielded **23** (514 mg, 45%) as a white crystalline solid; mp 57–61 °C; $[\alpha]_D^{22}$ −18.6 (*c* 1.0 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3059w, 2979s, 2933m (CH), 1788w, 1738s, 1699s (C=O), 1666s, 1556s, 1367s, 1141s, 852m; δ_H (200 MHz, $CDCl_3$) 1.07 (9H, s, C(CH_3)$_3$), 1.42 (9H, s, C(CH_3)$_3$), 1.48 (18H, s, 2 × C(CH_3)$_3$), 2.00–2.15 (1H, m, C*H*(H)), 2.31–2.47 (1H, m, CH(*H*)), 2.74–2.89 (1H, m, C*H*(H)C=O), 2.96–3.08 (1H, m, CH(*H*)C=O), 4.81 (1H, q, *J* 5, C*H*), 7.37–7.53 (9H, m, Ar*H*), 7.63–7.73 (6H, m, Ar*H*); δ_C (125.8 MHz, $CDCl_3$) 24.95 (*C*H$_2$), 27.95 (C(*C*H$_3$)$_3$), 28.00 (C(*C*H$_3$)$_3$), 28.13 (C(*C*H$_3$)$_3$), 37.04 (*C*H$_2$), 59.21 (*C*H), 80.61 (*C*(CH$_3$)$_3$), 82.24 (*C*(CH$_3$)$_3$), 127.25 (Ar-*C*, *ipso*, $J_{^{31}P-^{13}C}$ 93), 128.39 (Ar-*C*, $J_{^{31}P-^{13}C}$ 12), 131.24 (Ar-*C*), 132.95 (Ar-*C*, $J_{^{31}P-^{13}C}$ 10), 156.46 (C=O), 167.50 (d, $J_{^{31}P-^{13}C}$ 13, *C*=P), 169.94, 196.02 (2 × *C*=O); *m*/*z* (APCI+) 762 (MH^+, 100%), 662 [MH^+ − (CO_2 + C_4H_8), 30], 562 [MH^+ − 2 × (CO_2 + C_4H_8), 20]; HRMS found MH^+ 762.3770; $C_{43}H_{57}NO_9P$ requires 762.3771.

(*S*)-6-*tert*-Butoxycarbonylamino-2-(triphenylphosphoranylidene)-3-oxoheptanedioic acid di-*tert*-butyl ester 25. This compound was prepared from **2** (303 mg, 1.00 mmol), (*tert*-butoxycarbonylmethylene)triphenylphosphine (376 mg, 1.00 mmol), DCM (10 ml) and DCC (206 mg, 1.00 mmol). Purification by flash column chromatography (SiO_2, from 1 : 2 to 1 : 1 EtOAc–petroleum ether) yielded **25** (416 mg, 63%) as a white crystalline solid; mp 105–108 °C; $[\alpha]_D^{22}$ +1.5 (*c* 1.1 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3334w (NH), 2977s, 2931m (CH), 1712s (C=O), 1664s, 1439m, 1366s, 1170s, 848w; δ_H (200 MHz, $CDCl_3$) 1.02 (9H, s, C(CH_3)$_3$), 1.43 (18H, s, 2 × C(CH_3)$_3$), 1.90–2.06 (2H, br m, CH_2), 2.93 (2H, br t, *J* 7.5, CH_2), 4.00–4.13 (1H, br m, C*H*), 5.60 (1H, d, *J* 8.0, N*H*), 7.37–7.49 (6H, m, Ar*H*), 7.60–7.70 (9H, m, Ar*H*); δ_C (125.8 MHz, $CDCl_3$) 27.89 (C(*C*H$_3$)$_3$), 27.99 (C(*C*H$_3$)$_3$), 28.28 (C(*C*H$_3$)$_3$), 33.82 (*C*H$_2$), 36.50 (d, $J_{^{31}P-^{13}C}$ 7.5, *C*H$_2$), 54.47 (*C*H), 78.69 (*C*(CH$_3$)$_3$), 78.92 (*C*(CH$_3$)$_3$), 81.05 (*C*(CH$_3$)$_3$), 127.18 (Ar-*C*, *ipso*, $J_{^{31}P-^{13}C}$ 93), 128.71 (Ar-*C*, $J_{^{31}P-^{13}C}$ 12), 131.66 (Ar-*C*), 133.15 (Ar-*C*, $J_{^{31}P-^{13}C}$ 10), 156.00 (*C*=O), 167.56 (d, $J_{^{31}P-^{13}C}$ 13.0, *C*=P), 172.56 (*C*=O), 196.55 (d, $J_{^{31}P-^{13}C}$ 4.5, *C*=O); *m*/*z* (APCI+) 662 (MH^+, 100%), 562 [MH^+ − (CO_2 + C_4H_8), 70], 506 [MH^+ − (CO_2 + 2 × C_4H_8), 15]; HRMS found MH^+ 662.3250. $C_{38}H_{49}NO_7P$ requires 662.3247.

General procedure for 1,2,3-tricarbonyl formation

Typically, through a cooled, −78 °C, stirred solution of the ketophosphorane in DCM was bubbled a stream of ozone; after consumption of the starting material, as indicated by TLC analysis, the supply of ozone was replaced by nitrogen for 20 minutes before the resulting solution was concentrated *in vacuo* to yield the crude 1,2,3-tricarbonyl.

(*S*)-5-*tert*-Butoxycarbonylamino-2,3-dioxohexanedioic acid di-*tert*-butyl ester 4. This compound was prepared from **3** (485 mg, 0.75 mmol) and DCM (10 ml). Purification by flash column chromatography (SiO_2, 1 : 19; DCM–Et_2O) yielded **4** (240 mg, 80%) as a white crystalline solid; mp 121–123 °C; $[\alpha]_D^{22}$ −11.6 (*c* 1.0 in $CHCl_3$) (Found: C, 56.85; H, 7.80; N, 3.44. $C_{19}H_{31}NO_8$ requires C, 56.85; H, 7.78; N, 3.49%); ν_{max} (thin film)/cm^{-1} 3475br w (NH, OH), 2980m, 2935w (CH), 1780m, 1746s, 1716s (C=O), 1478w, 1369s, 1259m, 1147s, 847w; δ_H (major species only) (200 MHz, $CDCl_3$) 1.46 (27H, s, 3 × C(C*H*$_3$)$_3$), 2.63–2.73 (1H, br m, C*H*(H)), 2.93–3.11 (1H, br m, CH(*H*)), 4.59 (1H, td, *J* 3.0, 10.0, C*H*), 4.70 (1H, d, *J* 14.5, N*H*); δ_H (major species only) (500 MHz, $C_6D_5CD_3$, 25 °C) 1.25–1.38 (27H, envelope, 3 × C(C*H*$_3$)$_3$), 2.42–2.60 (2H, m, C*H*$_2$), 4.34–4.51 (1H, m, C*H*), 4.82–4.95 (1H, m, N*H*/O*H*); δ_H (500 MHz, $C_6D_5CD_3$, 90 °C) 1.30 (9H, s, C(C*H*$_3$)$_3$), 1.34 (9H, s, C(C*H*$_3$)$_3$), 1.38 (9H, s, C(C*H*$_3$)$_3$), 2.46 (1H, dd, *J* 3.5, 18.5, C*H*(H)), 2.61 (1H, dd, *J* 9.5, 18.5, CH(*H*)), 4.43 (1H, dd, *J* 3.5, 9.5, C*H*), 4.54 (1H, s, N*H*); δ_C (50.3 MHz, $CDCl_3$) 27.51, 27.65, 27.92 (3 × C(*C*H$_3$)$_3$), 38.17, 38.44 (2 × *C*H$_2$), 54.98, 55.22 (2 × *C*H), 82.22, 82.51, 82.62, 84.09, 84.47, 84.64 (6 × *C*(CH$_3$)$_3$), 152.85, 152.96, 166.57, 166.76, 170.28, 170.58 (6 × *C*=O); *m*/*z* (APCI+) 419 (MNH_4^+, 30%), 190 [MH^+ − (CO_2 + 3 × C_4H_8), 50], 172 (100).

(*S*)-5-Bis(*tert*-butoxycarbonyl)amino-2,3-dioxohexanedioic acid di-*tert*-butyl ester hydrate 16. Compound **16** was prepared from **15** (598 mg, 0.80 mmol) and DCM (20 ml). Purification by flash column chromatography (SiO_2, 1 : 2 EtOAc–petroleum ether) yielded **16** (385 mg, 93%) as a white crystalline solid; $[\alpha]_D^{22}$ −31.9 (*c* 2.0 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3452br m (OH), 2981s, 2936m (CH), 1791w, 1732br s, 1720s (C=O), 1480m, 1387s, 1258s, 1147s, 1050w, 846m; δ_H (200 MHz, $CDCl_3$) 1.41 (9H, s, C(C*H*$_3$)$_3$), 1.48 (9H, s, C(C*H*$_3$)$_3$), 1.49 (18H, s, 2 × C(C*H*$_3$)$_3$), 2.96 (1H, dd, *J* 6.0, 18.5, C*H*(H)), 3.57 (1H, dd, *J* 6.5, 18.5, CH(*H*)), 5.00 (1H, s, O*H*), 5.08 (1H, s, O*H*), 5.41 (1H, br t, *J* 6.5, C*H*); δ_C (50.3 MHz, $CDCl_3$) 27.45 (C(*C*H$_3$)$_3$), 27.68 (C(*C*H$_3$)$_3$), 27.86 (2 × C(*C*H$_3$)$_3$), 36.98 (*C*H$_2$), 54.64 (*C*H), 82.23 (*C*(CH$_3$)$_3$), 83.32 (*C*(CH$_3$)$_3$), 85.06 (*C*(CH$_3$)$_3$), 92.85 (*C*(OH)$_2$), 152.26, 168.04, 169.03 (3 × C=O).

(*S*)-6-Bis(*tert*-butoxycarbonyl)amino-2,3-dioxoheptanedioic acid di-*tert*-butyl ester hydrate 24. Compound **24** was prepared from **23** (380 mg, 0.50 mmol) and DCM (15 ml). Purification by flash column chromatography (SiO_2, 1 : 2 EtOAc–petroleum ether) yielded **24** (224 mg, 84%) as a white crystalline solid; $[\alpha]_D^{22}$ −30.2 (*c* 0.2 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3441br w (OH), 2981m, 2936w (CH), 1737s, 1702m (C=O), 1478w, 1369s, 1258m, 1145s, 847w; δ_H (200 MHz, $CDCl_3$) 1.44 (9H, s, C(C*H*$_3$)$_3$), 1.50 (18H, s, 2 × C(C*H*$_3$)$_3$), 1.56 (9H, s, C(C*H*$_3$)$_3$), 2.09–2.25 (1H, m, C*H*(H)), 2.39–2.55 (1H, m, CH(*H*)), 2.72–3.02 (2H, m, C*H*$_2$), 4.70–4.78 (1H, m, C*H*), 4.90 (1H, m, O*H*), 4.97 (1H, m, O*H*); δ_C (Two species present) (50.3 MHz, $CDCl_3$) 22.13, 23.34, 27.48, 27.82, 32.44, 33.47, 57.73, 57.94, 81.50, 81.57, 83.10, 83.18, 85.86, 152.55, 169.30, 197.24 (5 × *C*=O); *m*/*z* (APCI+) 538 (MNa^+, 3%), 348 (25), 292 (45), 186 (100).

(*S*)-6-*tert*-Butoxycarbonylamino-2,3-dioxoheptanedioic acid di-*tert*-butyl ester 26. This compound was prepared from **25** (250 mg, 0.38 mmol) and DCM (10 ml). Purification by flash column chromatography (SiO_2, 1 : 2 EtOAc–petroleum ether) yielded **26** (125 mg, 79%) as a white crystalline solid; mp 94–97 °C; $[\alpha]_D^{22}$ −7.8 (*c* 0.5 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3452br w (NH/OH), 2980s, 2935m (CH), 1720br s (C=O), 1457w, 1369s, 1257m, 1156s, 1087w, 847w; δ_H (200 MHz, $CDCl_3$) 1.41–1.58 (27H, envelope, 3 × C(C*H*$_3$)$_3$), 2.20–2.39 (2H, m, C*H*$_2$), 2.43–2.71 (2H, m, C*H*$_2$), 4.30–5.12 (2H, m, C*H* and N*H*/O*H*); δ_C (50.3 MHz, $CDCl_3$) 21.65, 23.19 (2 × CH$_2$), 27.46, 27.78, 27.93 (3 × C(CH$_3$)$_3$), 31.24, 33.07 (2 × CH$_2$), 54.99, 55.18 (2 × CH), 81.72–83.73 (envelope, C(CH$_3$)$_3$), 153.99, 154.44, 167.30, 170.38, 170.88, 171.36, 198.48 (7 × C=O); *m*/*z* (FAB+) 438 (MNa^+, 10%), 398 (15), 298 (20), 186 (100).

General procedure for the formation of fused pyrazine substituted amino acids

Typically, to a stirred solution of the 1,2,3-tricarbonyl in ethanol was added the aromatic diamine. The reaction mixture was then heated to reflux and stirred for 2–4 hours, before being concentrated *in vacuo.* The organic residue was then taken into ethyl acetate, washed with saturated aqueous bicarbonate solution and brine, dried over $MgSO_4$ and concentrated *in vacuo*, to afford the crude pyrazine product.

(*S*)-α-*tert*-Butoxycarbonylamino-β-(benzimidazol-2-yl)propanoic acid α-*tert*-butyl ester 7. This compound was prepared from **4** (105 mg, 0.26 mmol), 1,2-phenylenediamine (28 mg, 0.26 mmol), EtOH (2 ml), saturated aqueous bicarbonate solution (2 × 10 ml) and brine (2 × 10 ml). Purification by flash column chromatography (SiO_2, 5 : 6 EtOAc–petroleum ether) yielded **7** (60 mg, 64%) as a pale yellow solid; mp 150–153 °C; $[\alpha]_D^{22}$ −1.6 (*c* 0.3 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3306br w (NH), 2979m, 2932w (CH), 1718br s (C=O), 1508m, 1368s, 1273m, 1154s, 854w; δ_H (200 MHz, $CDCl_3$) 1.42 (18H, s, 2 × C(CH$_3$)$_3$), 3.30–3.54 (2H, m, CH$_2$), 4.61–4.72 (1H, m, CH), 5.69 (1H, d, *J* 8.5, NH), 7.18–7.27 (2H, m, Ar*H*), 7.56 (2H, br s, Ar*H*); δ_H (200 MHz, CD_3OD) 1.28 (9H, s, C(C*H*$_3$)$_3$), 1.37 (9H, s, C(C*H*$_3$)$_3$), 3.21–3.37 (2H, m, C*H*$_2$), 4.50 (1H, br t, *J* 7.5, C*H*), 7.16–7.21 (2H, m, Ar*H*), 7.47–7.51 (2H, br m, Ar*H*); δ_C (125.8 MHz, $CDCl_3$) 27.81 (C(*C*H$_3$)$_3$), 28.22 (C(*C*H$_3$)$_3$), 33.18 (*C*H$_2$), 52.36 (*C*H), 80.62 (*C*(CH$_3$)$_3$), 82.94 (*C*(CH$_3$)$_3$), 122.28 (Ar-*C*H), 150.61, 156.15, 170.50 (Ar-*C*, *ipso*; 2 × *C*=O); *m*/*z* (APCI+) 362 (MH^+, 100%), 306 [MH^+ − (C_4H_8), 40], 250 [MH^+ − 2 × (C_4H_8), 20]; HRMS found MH^+ 362.2080; $C_{19}H_{28}N_3O_4$ requires 362.2080.

(*S*)-α-*tert*-Butoxycarbonylamino-β-(4-methylbenzimidazol-2-yl)propanoic acid α-*tert*-butyl ester 8 and (*S*)-α-*tert*-butoxycarbonylamino-β-(2-*tert*-butoxycarbonyl-5-methylquinoxalin-3-yl)propanoic acid α-*tert*-butyl ester 9a, (*S*)-α-*tert*-butoxycarbonylamino-β-(2-*tert*-butoxycarbonyl-8-methylquinoxalin-3-yl)propanoic acid α-*tert*-butyl ester 9b. These compounds were prepared from **4** (100 mg, 0.25 mmol), toluene-2,3-diamine (30.5 mg, 0.25 mmol), EtOH (2 ml), saturated aqueous bicarbonate solution (2 × 10 ml) and brine (2 × 10 ml). Purification by flash column chromatography (SiO_2, 1 : 2 EtOAc–petroleum ether) yielded **8** and **9a**,**b**. Compound **8** was obtained (45 mg, 48%) as a pale yellow oil; $[\alpha]_D^{22}$ −3.6 (*c* 1.2 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3400br w (NH), 2978m (CH), 1699br s (C=O), 1502m, 1367s, 1253m, 1154s, 1054w, 846w; δ_H (500 MHz, $CDCl_3$) 1.42 (18H, s, 2 × C(C*H*$_3$)$_3$), 2.57 (3H, br s, C*H*$_3$), 3.35–3.41 (1H, br m, C*H*(H)), 3.51 (1H, dd, *J* 4.5, 16.0, CH(*H*)), 4.69 (1H, br s, C*H*), 5.76 (1H, br s, N*H*Boc), 7.01–7.14 (2H, m, Ar*H*), 7.37–7.39 (1H, m, Ar*H*); δ_H (200 MHz, CD_3OD) 1.28 (9H, s, C(C*H*$_3$)$_3$), 1.38 (9H, s, C(C*H*$_3$)$_3$), 2.53 (3H, s, C*H*$_3$), 3.15–3.38 (2H, m, C*H*$_2$), 4.52 (1H, br t, *J* 7.5, C*H*), 6.97–7.13 (2H, m, Ar*H*), 7.31–7.35 (1H, m, Ar*H*); δ_C (125.8 MHz, $CDCl_3$) 16.85 (*C*H$_3$), 27.82 (C(*C*H$_3$)$_3$), 28.22 (C(*C*H$_3$)$_3$), 33.25 (*C*H$_2$), 52.31 (*C*H), 80.67 (*C*(CH$_3$)$_3$), 82.94 (*C*(CH$_3$)$_3$), 122.29, 122.71 (2 × Ar-*C*H), 150.02, 156.31, 170.52 (Ar-*C*, *ipso*; 2 × *C*=O); *m*/*z* (APCI+) 376 (MH^+, 8%), 320 [MH^+ − (C_4H_8), 12], 264

[$MH^+ - 2 \times (C_4H_8)$, 100]; HRMS found MH^+ 376.2236; $C_{20}H_{30}N_3O_4$ requires 376.2236.

Compounds **9a** and **9b** were obtained (overall 11 mg, 9%, as a 1 : 1 mixture of inseparable regioisomers) as a pale yellow oil; ν_{max} (thin film)/cm^{-1} 3480br w (NH), 2979m (CH), 1720s (C=O), 1477m, 1368s, 1249m, 1153s, 845w; δ_H (200 MHz, $CDCl_3$) 1.27 ($2 \times 9H$, s, $2 \times C(CH_3)_3$), 1.41 ($2 \times 9H$, s, $2 \times C(CH_3)_3$), 1.70 ($2 \times 9H$, s, $2 \times C(CH_3)_3$), 2.78 ($2 \times 3H$, br s, $2 \times CH_3$), 3.60–3.90 ($2 \times 2H$, m, $2 \times CH_2$), 4.77–4.84 ($2 \times 1H$, m, $2 \times CH$), 6.04 ($2 \times 1H$, br d, *J* 9.0, $2 \times NH$), 7.60–8.03 ($2 \times 3H$, m, Ar*H*); *m*/*z* (APCI+) 488 (MH^+, 100%), 432 [$MH^+ - (C_4H_8)$, 20]; HRMS found MH^+ 488.2760; $C_{26}H_{38}N_3O_6$ requires 488.2761.

(*S*)-α-*tert*-Butoxycarbonylamino-β-(2-*tert*-butoxycarbonylpyrido[2,3-*b*]pyrazin-3-yl)propanoic acid α-*tert*-butyl ester 10a and (*S*)-α-*tert*-butoxycarbonylamino-β-(3-*tert*-butoxycarbonylpyrido[2,3-*b*]pyrazin-2-yl)propanoic acid α-*tert*-butyl ester 10b. These compounds were prepared from **4** (100 mg, 0.25 mmol), pyridine-2,3-diamine (27 mg, 0.25 mmol), EtOH (2 ml), saturated aqueous bicarbonate solution (2×10 ml) and brine (2×10 ml). Purification by flash column chromatography (SiO_2, 4 : 5 EtOAc–petroleum ether) yielded **10a** and **10b** (overall 89 mg, 75% as a 1 : 1 mixture of regioisomers) as a colourless oil; ν_{max} (thin film)/cm^{-1} 3428br w (NH), 2979m, 2934w (CH), 1721s (C=O), 1501w, 1369m, 1250m, 1154s, 1084m, 846w; δ_H (200 MHz, $CDCl_3$) 1.32 (9H, s, $C(CH_3)_3$), 1.36 (9H, s, $C(CH_3)_3$), 1.38 (9H, s, $C(CH_3)_3$), 1.41 (9H, s, $C(CH_3)_3$), 1.70 (9H, s, $C(CH_3)_3$), 1.73 (9H, s, $C(CH_3)_3$), 3.66–3.78 (4H, m, $2 \times CH_2$), 4.79–4.85 (2H, br m, $2 \times CH$), 5.66 (1H, br d, *J* 8.0, N*H*), 5.81 (1H, br d, *J* 8.0, N*H*), 7.71–7.80 (2H, m, Ar*H*), 8.41 (1H, dd, *J* 2.0, 8.5, Ar*H*), 8.55 (1H, dd, *J* 2.0, 8.5, Ar*H*), 9.19–9.21 (2H, m, Ar*H*); δ_C (125.8 MHz, $CDCl_3$) 27.89, 28.08, 28.12, 28.19, 28.25 ($5 \times C(CH_3)_3$), 37.23, 38.17 ($2 \times CH_2$), 52.41, 52.70 ($2 \times CH$), 79.56, 79.76, 81.86, 82.02, 84.57, 84.77 ($6 \times C(CH_3)_3$), 125.36, 126.27, 135.30, 137.23, 137.49, 138.74 ($2 \times$ Ar-*C*H; $4 \times$ Ar-*C*, *ipso*), 147.50, 148.72, 154.37, 155.34, 164.19, 170.54 (Ar-*C*H; $2 \times$ Ar-*C*, *ipso*; $3 \times C$=O); *m*/*z* (APCI+) 475 (MH^+, 100%), 419 [$MH^+ - (C_4H_8)$, 20], 375 [$MH^+ - (CO_2 + C_4H_8)$, 30]; HRMS found MH^+ 475.2557; $C_{24}H_{35}N_4O_6$ requires 475.2557.

(*S*)-α-Bis(*tert*-butoxycarbonyl)amino-β-(2-*tert*-butoxycarbonylquinoxalin-3-yl)propanoic acid α-*tert*-butyl ester 18. This compound was prepared from **16** (105 mg, 0.20 mmol), 1,2-phenylenediamine (22 mg, 0.2 mmol), EtOH (2 ml), saturated aqueous bicarbonate solution (2×10 ml) and brine (2×10 ml). Purification by flash column chromatography (SiO_2, 1 : 2 Et_2O–petroleum ether) yielded **18** (114.5 mg, 100%) as a colourless oil; $[\alpha]_D^{22}$ −43.1 (*c* 1.3 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2980m, 2935w (CH), 1795w, 1738br s, 1700m (C=O), 1481w, 1368s, 1255m, 1160s, 1082m, 847w; δ_H (200 MHz, $CDCl_3$) 1.37 (18H, s, $2 \times C(CH_3)_3$), 1.41 (9H, s, $C(CH_3)_3$), 1.67 (9H, s, $C(CH_3)_3$), 3.57 (1H, dd, *J* 8.5, 15.0, C*H*(H)), 4.09 (1H, dd, *J* 5.5, 15.0, CH(*H*)), 5.69–5.76 (1H, dd, *J* 5.5, 8.5, C*H*), 7.66–7.77 (2H, m, Ar*H*), 7.96–8.00 (1H, m, Ar*H*), 8.10–8.15 (1H, m, Ar*H*); δ_C (50.3 MHz, $CDCl_3$) 27.78 ($2 \times C(CH_3)_3$), 27.96 ($C(CH_3)_3$), 35.53 (CH_2), 57.59 (*C*H), 81.46 ($C(CH_3)_3$), 82.70 ($C(CH_3)_3$), 83.95 ($C(CH_3)_3$), 129.03, 129.76, 129.90, 131.19 ($4 \times$ Ar-*C*H), 140.11, 142.32, 146.43 ($3 \times$ Ar-*C*, *ipso*), 152.24, 165.18, 169.39 (Ar-*C*, *ipso*; $2 \times C$=O); *m*/*z* (APCI+) 574 (MH^+, 100%), 474 [$MH^+ - (CO_2 + C_4H_8)$, 50], 362 [$MH^+ - (CO_2 + 3 \times C_4H_8)$, 60]; HRMS found MH^+ 574.3128; $C_{30}H_{44}N_3O_8$ requires 574.3128.

(*S*)-α-*tert*-Butoxycarbonylamino-γ-(2-*tert*-butoxycarbonylquinoxalin-3-yl)butyric acid α-*tert*-butyl ester 27. This compound was prepared from **26** (41.5 mg, 0.10 mmol), 1,2-phenylenediamine (11 mg, 0.10 mmol), EtOH (2 ml), saturated aqueous bicarbonate solution (2×5 ml) and brine (2×5 ml). Purification by flash column chromatography (SiO_2, 1 : 2 Et_2O–petroleum ether) yielded **27** (42.3 mg, 87%) as a colourless oil; $[\alpha]_D^{22}$ +50.6 (*c* 0.49 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3440br w (NH), 2990m, 2929m (CH), 1720s (C=O), 1501w, 1368m, 1251m, 1156s, 1082m, 700w; δ_H (500 MHz, $CDCl_3$) 1.44 (9H, s, $C(CH_3)_3$), 1.47 (9H, s, $C(CH_3)_3$), 1.71 (9H, s, $C(CH_3)_3$), 2.15–2.21 (1H, m, C*H*(H)), 2.38–2.47 (1H, m, CH(*H*)), 3.21–3.32 (2H, m, CH_2), 4.34–4.40 (1H, br m, C*H*), 5.38 (1H, br d, *J* 8.0, N*H*), 7.72–7.82 (2H, m, Ar*H*), 8.04–8.06 (1H, dd, *J* 1, 8.5, Ar*H*), 8.14–8.17 (1H, dd, *J* 1.5, 8, Ar*H*); δ_C (125.8 MHz, $CDCl_3$) 27.97 ($C(CH_3)_3$), 28.14 ($C(CH_3)_3$), 28.30 ($C(CH_3)_3$), 31.52 (CH_2), 31.95 (CH_2), 53.95 (*C*H), 79.56 ($C(CH_3)_3$), 81.92 ($C(CH_3)_3$), 84.06 ($C(CH_3)_3$), 128.59, 129.62, 129.76, 131.16 ($4 \times$ Ar-*C*H), 139.92, 142.16, 147.00 ($3 \times$ Ar-*C*, *ipso*), 153.76, 155.50, 165.22, 171.65 (Ar-*C*, *ipso*; $3 \times C$=O); *m*/*z* (APCI+) 488 (MH^+, 100%), 432 [$MH^+ - (C_4H_8)$, 20], 376 [$MH^+ - 2 \times (C_4H_8)$, 30], 320 ($MH^+ - 3 \times Bu^t$, 10); HRMS found MH^+ 488.2758; $C_{26}H_{38}N_3O_6$ requires 488.2761.

(*S*)-α-Bis(*tert*-butoxycarbonyl)amino-γ-(2-*tert*-butoxycarbonylquinoxalin-3-yl)butyric acid α-*tert*-butyl ester 30. This compound was prepared from **24** (53 mg, 0.1 mmol), 1,2-phenylenediamine (11 mg, 0.1 mmol), EtOH (2 ml), saturated aqueous bicarbonate solution (2×5 ml) and brine (2×5 ml). Purification by flash column chromatography (SiO_2, 2 : 5 Et_2O–petroleum ether) yielded **30** (59 mg, 100%) as a colourless oil; $[\alpha]_D^{22}$ +16.4 (*c* 1.3 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3065w, 2979m (CH), 1790m, 1732s (C=O), 1564w, 1453m, 1368s, 1257s, 1158s, 962w; δ_H (200 MHz, $CDCl_3$) 1.46 (9H, s, $C(CH_3)_3$), 1.47 (18H, s, $2 \times C(CH_3)_3$), 1.69 (9H, s, $C(CH_3)_3$), 2.37–2.53 (1H, m, C*H*(H)), 2.68–2.85 (1H, m, CH(*H*)), 3.10–3.36 (2H, m, CH_2), 4.96 (1H, dd, *J* 5, 10, C*H*), 7.68–7.82 (2H, m, Ar*H*), 8.02–8.17 (2H, m, Ar*H*); δ_C (125.8 MHz, $CDCl_3$) 27.56 (CH_2), 27.95 ($C(CH_3)_3$), 28.09 ($C(CH_3)_3$), 32.35 (CH_2), 58.53 (*C*H), 81.20 ($C(CH_3)_3$), 82.70 ($C(CH_3)_3$), 83.84 ($C(CH_3)_3$), 128.78, 129.51, 129.57, 130.90 ($4 \times$ Ar-*C*H), 139.79, 142.26, 146.53 ($3 \times$ Ar-*C*, *ipso*), 152.38, 153.75, 165.22, 169.55 (Ar-*C*, *ipso*; $3 \times C$=O); *m*/*z* (APCI+) 588 (MH^+, 70%), 488 [$MH^+ - (CO_2 + C_4H_8)$, 100], 432 [$MH^+ - (CO_2 + 2 \times C_4H_8)$, 100]; HRMS found MH^+ 588.3292; $C_{31}H_{46}N_3O_8$ requires 588.3285.

General procedure for formation of pyrazine substituted amino acids

Typically, to a solution of the 1,2,3-tricarbonyl in ethanol was added ethylenediamine. The reaction mixture was stirred at RT for up to 2 hours, or until the tricarbonyl had disappeared as shown by TLC, before the addition of catalytic Pd/C and subsequent heating of the reaction mixture to reflux. The reaction mixture was then stirred overnight after which it was concentrated *in vacuo*, taken into ethyl acetate, washed with saturated aqueous bicarbonate and brine solutions, dried over $MgSO_4$ and reconcentrated *in vacuo* to yield the crude product.

(*S*)-α-Bis(*tert*-butoxycarbonyl)amino-β-(2-*tert*-butoxycarbonylpyrazin-3-yl)propanoic acid α-*tert*-butyl ester 17. This compound was prepared from **16** (89 mg, 0.17 mmol), 1,2-ethylenediamine (12 μl, 0.18 mmol), 10% Pd/C (10 mg) and EtOH (3 ml). Purification by flash column chromatography (SiO_2, 1 : 3 Et_2O–petroleum ether) yielded **17** (69 mg, 77%) as a colourless oil; $[\alpha]_D^{22}$ −0.3 (*c* 2.0 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2980m, 2935w (CH), 1796w, 1738br s (C=O), 1480w, 1368s, 1251m, 1136s, 848w; δ_H (200 MHz, $CDCl_3$) 1.42 (9H, s, $C(CH_3)_3$), 1.44 (18H, s, $2 \times C(CH_3)_3$), 1.63 (9H, s, $C(CH_3)_3$), 3.48 (1H, dd, *J* 8.5, 15.0, C*H*(H)), 4.00 (1H, dd, *J* 5.5, 15.0, CH(*H*)), 5.56–5.63 (1H, dd, *J* 5.5, 8.5, C*H*), 8.48 (1H, d, *J* 2.5, Ar*H*), 8.56 (1H, d, *J* 2.5, Ar*H*); δ_C (125.8 MHz, $CDCl_3$) 27.87, 27.94, 28.01 ($3 \times C(CH_3)_3$), 35.08 (CH_2), 57.80 (*C*H), 81.41 ($C(CH_3)_3$), 82.69 ($C(CH_3)_3$), 83.41 ($C(CH_3)_3$), 141.32,

144.97 (2 × Ar-*C*H), 145.40, 151.87 (2 × Ar-*C*, *ipso*), 154.11, 164.47, 169.01 (4 × *C*=O); *m*/*z* (APCI+) 524 (MH^+, 10%), 368 [$MH^+ - (CO_2 + 2 \times C_4H_8)$, 15], 256 [$MH^+ - (CO_2 + 4 \times C_4H_8)$, 100]; HRMS found MH^+ 524.2972; $C_{26}H_{42}N_3O_8$ requires 524.2972.

(*S*)-α-*tert*-Butoxycarbonylamino-γ-(2-*tert*-butoxycarbonylpyrazin-3-yl)butyric acid α-*tert*-butyl ester 28. This compound was prepared from **26** (85 mg, 0.20 mmol), 1,2-ethylenediamine (13.5 μl, 0.2 mmol), 10% Pd/C (11 mg) and EtOH (4 ml). Purification by flash column chromatography (SiO_2, 2 : 1 Et_2O–petroleum ether) yielded **28** (54 mg, 62%) as a colourless oil; $[\alpha]_D^{22}$ +21.6 (*c* 0.3 in $CHCl_3$) (Found: C, 58.25; H, 8.42; N, 9.35. $C_{22}H_{35}N_3O_6(+H_2O)$ requires C, 58.02; H, 8.13; N, 9.23%); ν_{max} (thin film)/cm^{-1} 3370br w (NH), 2979m, 2934w (CH), 1716s (C=O), 1504w, 1368s, 1252m, 1155s, 1026w; δ_H (500 MHz, $CDCl_3$) 1.44 (9H, s, C(CH_3)$_3$), 1.46 (9H, s, C(CH_3)$_3$), 1.65 (9H, s, C(CH_3)$_3$), 2.02–2.09 (1H, m, C*H*(H)), 2.24–2.30 (1H, m, CH(*H*)), 3.08–3.15 (2H, m, CH_2), 4.26–4.31 (1H, m, C*H*), 5.25 (1H, br d, *J* 8.5, N*H*), 8.48 (1H, d, *J* 2.5, Ar*H*), 8.58 (1H, d, *J* 2.5, Ar*H*); δ_C (125.8 MHz, $CDCl_3$) 27.95 (C(*C*H$_3$)$_3$), 28.07 (C(*C*H$_3$)$_3$), 28.30 (C(*C*H$_3$)$_3$), 31.44 (*C*H$_2$), 31.96 (*C*H$_2$), 53.86 (*C*H), 79.56 (*C*(CH$_3$)$_3$), 81.93 (*C*(CH$_3$)$_3$), 83.61 (*C*(CH$_3$)$_3$), 141.47, 145.23 (2 × Ar-*C*H), 145.35, 155.46, 155.78, 164.77, 171.55 (2 × Ar-*C*, *ipso*, 3 × *C*=O); *m*/*z* (APCI+) 438 (MH^+, 30%), 326 [$MH^+ - 2 \times (C_4H_8)$, 75], 270 [$MH^+ - 3 \times (C_4H_8)$, 100]; HRMS found MH^+ 438.2604; $C_{22}H_{36}N_3O_6$ requires 438.2604.

General procedure for formation of 1,2,4-triazine substituted amino acids

Typically, to a solution of the 1,2,3-tricarbonyl in DCM was added *S*-methylisothiosemicarbazide hydroiodide followed by *N*,*N*-diisopropylethylamine. The reaction mixture was then heated to reflux and left to stir for 4 hours before being concentrated *in vacuo*. The resulting organic residue was then taken into ethyl acetate, washed with saturated aqueous bicarbonate and brine solutions, dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude product.

(*S*)-α-*tert*-Butoxycarbonylamino-β-(5-*tert*-butoxycarbonyl-3-methylthio-1,2,4-triazin-6-yl)propanoic acid α-*tert*-butyl ester 11a and (*S*)-α-*tert*-butoxycarbonylamino-β-(6-*tert*-butoxycarbonyl-3-methylthio-1,2,4-triazin-5-yl)propanoic acid α-*tert*-butyl ester 11b. These compounds were prepared from **4** (76 mg, 0.19 mmol), *S*-methylisothiosemicarbazide hydroiodide (44 mg, 0.19 mmol), *N*-ethyldiisopropylamine (32.5 μl, 0.19 mmol), DCM (2 ml), saturated aqueous bicarbonate (2 × 10 ml) and brine (2 × 10 ml). Purification by flash column chromatography (SiO_2, 1 : 2 Et_2O–petroleum ether) yielded **11a** and **11b** (overall 19.7 mg, 22%, as a 3 : 1 mixture of partially separable regioisomers). Compound **11a** (5.4 mg, 6%) was isolated as a pale yellow oil; $[\alpha]_D^{22}$ +21.6 (*c* 0.1 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3392w (NH), 2979m, 2933w (CH), 1720s (C=O), 1499m, 1368s, 1252m, 1156s, 1043w, 844w; δ_H (500 MHz, $CDCl_3$) 1.42 (9H, s, C(CH_3)$_3$), 1.49 (9H, s, C(CH_3)$_3$), 1.70 (9H, s, C(CH_3)$_3$), 2.73 (3H, s, SCH_3), 3.54–3.67 (2H, m, CH_2), 4.72–4.77 (1H, br m, C*H*), 5.53 (1H, br d, *J* 8.5, N*H*); δ_C (125.8 MHz, $CDCl_3$) 13.85 (S*C*H$_3$), 27.88, 27.98, 28.19 (3 × C(*C*H$_3$)$_3$), 35.31 (*C*H$_2$), 52.69 (*C*H), 79.76, 82.38, 85.44 (3 × *C*(CH$_3$)$_3$), 148.34, 150.76 (2 × Ar-*C*, *ipso*), 155.26, 162.59, 170.21, 172.32 (Ar-*C*, *ipso*; 3 × *C*=O); *m*/*z* (APCI+) 471 (MH^+, 100%), 415 [$MH^+ - (C_4H_8)$, 20]; HRMS found MH^+ 471.2277; $C_{21}H_{35}N_4O_6S$ requires 471.2277.

Compound **11b** was obtained, inseparable from **11a** (14.3 mg, as a 1 : 2 mixture of regioisomers) as a yellow oil; δ_H (500 MHz, $CDCl_3$) 1.44 (9H, s, C(CH_3)$_3$), 1.46 (9H, s, C(CH_3)$_3$), 1.70 (9H, s, C(CH_3)$_3$), 2.75 (3H, s, SCH_3), 3.54–3.67 (2H, m, CH_2), 4.72–4.77 (1H, br m, C*H*), 5.45 (1H, br d, *J* 8.5, N*H*); δ_C (125.8 MHz, $CDCl_3$) 13.90 (S*C*H$_3$), 27.86, 28.06, 28.24 (3 × C(*C*H$_3$)$_3$), 36.89 (*C*H$_2$), 51.70 (*C*H), 79.95, 82.32, 85.30 (3 × *C*(CH$_3$)$_3$), 147.45, 150.76 (2 × Ar-*C*, *ipso*), 158.52, 162.93, 170.16, 174.03 (Ar-*C*, *ipso*; 3 × *C*=O).

(*S*)-α-Bis(*tert*-butoxycarbonyl)amino-β-(5-*tert*-butoxycarbonyl-3-methylthio-1,2,4-triazin-6-yl)propanoic acid α-*tert*-butyl ester 19a and (*S*)-α-bis(*tert*-butoxycarbonyl)amino-β-(6-*tert*-butoxycarbonyl-3-methylthio-1,2,4-triazin-5-yl)propanoic acid α-*tert*-butyl ester 19b. These compounds were prepared from **16** (130 mg, 0.25 mmol), *S*-methylisothiosemicarbazide hydroiodide (58 mg, 0.25 mmol), *N*-ethyldiisopropylamine (43 μl, 0.25 mmol), DCM (3 ml), saturated aqueous bicarbonate (2 × 10 ml) and brine (2 × 10 ml). Purification by flash column chromatography (SiO_2, 1 : 6 : 18; DCM–Et_2O–petroleum ether) yielded **19a** and **19b** (overall 124 mg, 87%, as a 1 : 1 mixture of partially separable regioisomers). Compound **19a** (45.6 mg, 32%) was isolated as a yellow oil; $[\alpha]_D^{22}$ −57.9 (*c* 1.4 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2980m, 2934w (CH), 1738s, 1699m (C=O), 1479w, 1368s, 1253m, 1159s, 1116s, 1036w, 846w; δ_H (500 MHz, $CDCl_3$) 1.44 (27H, s, 3 × C(CH_3)$_3$), 1.62 (9H, s, C(CH_3)$_3$), 2.65 (3H, s, SCH_3), 3.59 (1H, dd, *J* 9.0, 14.5, C*H*(H)), 3.96 (1H, dd, *J* 5.0, 14.5, CH(*H*)), 5.43–5.47 (1H, dd, *J* 5.0, 9.0, C*H*); δ_C (125.8 MHz, $CDCl_3$) 14.28 (S*C*H$_3$), 28.34 (C(*C*H$_3$)$_3$), 28.36 (C(*C*H$_3$)$_3$), 28.40 (C(*C*H$_3$)$_3$), 33.20 (*C*H$_2$), 58.31 (*C*H), 82.24 (*C*(CH$_3$)$_3$), 83.49 (*C*(CH$_3$)$_3$), 85.59 (*C*(CH$_3$)$_3$), 148.62, 152.31, 152.40, 163.12, 169.02, 172.30 (3 × Ar-*C*, *ipso*; 3 × *C*=O); *m*/*z* (APCI+) 571 (MH^+, 22%), 471 [$MH^+ - (CO_2 + C_4H_8)$, 100], 415 [$MH^+ - (CO_2 + 2 \times C_4H_8)$, 37]; HRMS found MH^+ 571.2802; $C_{26}H_{43}N_4O_8S$ requires 571.2802.

Compound **19b** was obtained, inseparable from **19a**, (78.4 mg, as a 2 : 1 mixture of regioisomers) as a yellow oil; δ_H (500 MHz, $CDCl_3$) 1.42 (9H, s, C(CH_3)$_3$), 1.44 (9H, s, C(CH_3)$_3$), 1.45 (9H, s, C(CH_3)$_3$), 1.63 (9H, s, C(CH_3)$_3$), 2.63 (3H, s, SCH_3), 3.35 (1H, dd, *J* 8.5, 15.0, C*H*(H)), 3.94 (1H, dd, *J* 5.5, 15.0, CH(*H*)), 5.53–5.57 (1H, dd, *J* 5.5, 8.5, C*H*); δ_C (125.8 MHz, $CDCl_3$) 13.75 (S*C*H$_3$), 27.85 (C(*C*H$_3$)$_3$), 27.87 (C(*C*H$_3$)$_3$), 27.92 (C(*C*H$_3$)$_3$), 28.02 (C(*C*H$_3$)$_3$), 34.88 (*C*H$_2$), 56.73 (*C*H), 81.87 (*C*(CH$_3$)$_3$), 83.16 (*C*(CH$_3$)$_3$), 84.00 (*C*(CH$_3$)$_3$), 147.47, 151.81, 159.15, 162.92, 168.42, 174.13 (3 × Ar-*C*, *ipso*; 3 × *C*=O).

(*S*)-α-*tert*-Butoxycarbonylamino-γ-(5-*tert*-butoxycarbonyl-3-methylthio-1,2,4-triazin-6-yl)butyric acid α-*tert*-butyl ester 29a and (*S*)-α-*tert*-butoxycarbonylamino-γ-(6-*tert*-butoxycarbonyl-3-methylthio-1,2,4-triazin-5-yl)butyric acid α-*tert*-butyl ester 29b. These compounds were prepared from **26** (85 mg, 0.20 mmol), *S*-methylisothiosemicarbazide hydroiodide (46.6 mg, 0.20 mmol), *N*-ethyldiisopropylamine (34.5 μl, 0.20 mmol), DCM (3 ml), saturated aqueous bicarbonate (2 × 10 ml) and brine (2 × 10 ml). Purification by flash column chromatography (SiO_2, 1 : 2 Et_2O–petroleum ether) yielded **29a** and **29b** (overall 89 mg, 92%, as a 1 : 1 mixture of partially separable regioisomers). **29a** (8.7 mg, 9%), isolated as a yellow oil; $[\alpha]_D^{22}$ +25.8 (*c* 0.3 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3370br w (NH), 2979m, 2933w (CH), 1716br s (C=O), 1501m, 1368s, 1156s, 1052w, 847w; δ_H (200 MHz, $CDCl_3$) 1.45 (9H, s, C(CH_3)$_3$), 1.47 (9H, s, C(CH_3)$_3$), 1.64 (9H, s, C(CH_3)$_3$), 2.04–2.13 (1H, m, C*H*(H)), 2.30–2.39 (1H, m, CH(*H*)), 2.69 (3H, s, SCH_3), 3.08–3.21 (2H, m, CH_2), 4.30–4.35 (1H, br m, C*H*), 5.19 (1H, br d, *J* 8.0, N*H*); δ_C (125.8 MHz, $CDCl_3$) 13.93 (S*C*H$_3$), 27.97 (C(*C*H$_3$)$_3$), 27.99 (C(*C*H$_3$)$_3$), 28.31 (C(*C*H$_3$)$_3$), 28.82 (*C*H$_2$), 31.91 (*C*H$_2$), 53.71 (*C*H), 79.74 (*C*(CH$_3$)$_3$), 82.25 (*C*(CH$_3$)$_3$), 85.37 (*C*(CH$_3$)$_3$), 148.21, 153.33, 155.44, 162.80, 171.31, 171.86 (3 × Ar-*C*, *ipso*; 3 × *C*=O); *m*/*z* (APCI+) 485 (MH^+, 75%), 429 [$MH^+ - (C_4H_8)$, 100], 373 [$MH^+ - 2 \times (C_4H_8)$, 100]; HRMS found MH^+ 485.2433. $C_{22}H_{37}N_4O_6S$ requires 485.2434.

Compound **29b** was obtained, inseparable from **29a**, (80.3 mg, 83% as a 5 : 4 mixture of regioisomers) as a yellow oil; δ_H (200 MHz, $CDCl_3$) 1.44 (9H, s, C(CH_3)$_3$), 1.46 (9H, s, C(CH_3)$_3$), 1.63 (9H, s, C(CH_3)$_3$), 2.03–2.13 (1H, m, C*H*(H)),

2.30–2.38 (1H, m, CH(*H*)), 2.68 (3H, s, SCH_3), 3.03–3.19 (2H, m, CH_2), 4.29–4.34 (1H, br m, C*H*), 5.19 (1H, br d, *J* 8.0, N*H*); δ_C (125.8 MHz, $CDCl_3$) 13.89 (S*C*H_3), 27.93 (C(*C*H_3)$_3$), 27.95 (C(*C*H_3)$_3$), 28.02 (C(*C*H_3)$_3$), 30.20 (*C*H_2), 30.74 (*C*H_2), 53.43 (*C*H), 79.70 (*C*(CH$_3$)$_3$), 82.21 (*C*(CH$_3$)$_3$), 84.05 (*C*(CH$_3$)$_3$), 147.28, 155.39, 160.87, 162.75, 171.81, 174.25 (3 × Ar-*C*, *ipso*; 3 × *C*=O).

(*S*)-α-Bis(*tert*-butoxycarbonyl)amino-γ-(5-*tert*-butoxycarbonyl-3-methylthio-1,2,4-triazin-6-yl)butyric acid α-*tert*-butyl ester 31a and (*S*)-α-bis(*tert*-butoxycarbonyl)amino-γ-(6-*tert*-butoxycarbonyl-3-methylthio-1,2,4-triazin-5-yl)butyric acid α-*tert*-butyl ester 31b. These compounds were prepared from **24** (107 mg, 0.2 mmol), *S*-methylisothiosemicarbazide hydroiodide (46.6 mg, 0.2 mmol), *N*-ethyldiisopropylamine (34.5 μl, 0.2 mmol), DCM (2 ml), saturated aqueous bicarbonate (2 × 10 ml) and brine (2 × 10 ml). Purification by flash column chromatography (SiO_2, 1 : 2 Et_2O–petroleum ether) yielded **31a** and **31b** (overall 88.8 mg, 76%, as a 1 : 1 mixture of partially separable regioisomers). Compound **31a** (21 mg, 18%) was isolated as a yellow oil; $[\alpha]_D^{22}$ −2.9 (*c* 0.8 in $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2980m, 2934w (CH), 1737s, 1702m (C=O), 1479w, 1368s, 1254s, 1158s, 1034w, 848m; δ_H (200 MHz, $CDCl_3$) 1.44 (9H, s, C(CH_3)$_3$), 1.49 (18H, s, C(CH_3)$_3$), 1.62 (9H, s, C(CH_3)$_3$), 2.29–2.45 (1H, m, C*H*(H)), 2.55–2.74 (1H, m, CH(*H*)), 2.68 (3H, s, SCH_3), 3.09–3.19 (2H, m, CH_2), 4.84–4.91 (1H, dd, *J* 5.0, 9.0, C*H*); δ_C (125.8 MHz, $CDCl_3$) 13.89 (S*C*H_3), 27.93 (C(*C*H_3)$_3$), 27.96 (C(*C*H_3)$_3$), 29.48 (*C*H_2), 58.33 (*C*H), 81.38 (*C*(CH$_3$)$_3$), 82.88 (*C*(CH$_3$)$_3$), 85.17 (*C*(CH$_3$)$_3$), 148.29, 152.30, 153.34, 162.78, 169.17, 171.58 (3 × Ar-*C*, *ipso*; 3 × *C*=O); *m*/*z* (APCI+) 585 (MH^+, 5%), 485 [$MH^+ - (CO_2 + C_4H_8)$, 100]; HRMS found MH^+ 585.2958; $C_{27}H_{45}N_4O_8S$ requires 585.2958.

Compound **31b** was obtained, inseparable from **31a**, (67.8 mg, as a 2 : 1 mixture of regioisomers) as a yellow oil; δ_H (200 MHz, $CDCl_3$) 1.44 (9H, s, C(CH_3)$_3$), 1.48 (18H, s, C(CH_3)$_3$), 1.63 (9H, s, C(CH_3)$_3$), 2.20–2.40 (1H, m, C*H*(H)), 2.55–2.71 (1H, m, CH(*H*)), 2.66 (3H, s, SCH_3), 3.02–3.19 (2H, m, CH_2), 4.81–4.90 (1H, br m, C*H*); δ_C (125.8 MHz, $CDCl_3$) 13.79 (S*C*H_3), 26.28 (*C*H_2), 27.90 (C(*C*H_3)$_3$), 28.24 (C(*C*H_3)$_3$), 31.46 (*C*H_2), 58.23 (*C*H), 81.42 (*C*(CH$_3$)$_3$), 82.95 (*C*(CH$_3$)$_3$), 83.89 (*C*(CH$_3$)$_3$), 147.42, 152.31, 161.00, 163.06, 169.23, 174.24 (3 × Ar-*C*, *ipso*; 3 × *C*=O).

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® 50 × 8-100 ion-exchange resin. The crude TFA salts were loaded in aqueous solution and eluted using 2 M aqueous ammonia solution.

(*S*)-β-(2-Carboxyquinoxalin-3-yl)-α-aminopropanoic acid 32. This compound was prepared from **18** (51.6 mg, 0.09 mmol), TFA (2 ml) and anisole (50 μl). Purification by ion-exchange chromatography yielded **32** (23 mg, 100%) as a dark brown solid; mp 161–178 °C (decomp.); ν_{max} (KBr)/cm^{-1} 3500–2500br s (NH/OH, CH), 1634s (C=O), 1590s, 1519m, 1398s, 1341m, 1127m, 927w, 668m; δ_H (200 MHz, D_2O) 3.40–3.63 (2H, m, CH_2), 4.11–4.17 (1H, m, C*H*), 7.60–7.65 (2H, m, Ar*H*), 7.77–7.87 (2H, m, Ar*H*); δ_C (125.8 MHz, D_2O) 34.38 (*C*H_2), 52.89 (*C*H), 127.77, 127.97, 130.81, 131.04 (4 × Ar-*C*H), 139.09, 140.56, 149.24, 151.26, (4 × Ar-*C*, *ipso*), 172.38, 173.65 (2 × *C*=O); *m*/*z* (APCI+) 262 (MH^+, 4%), 218 (100).

(*S*)-γ-(2-Carboxyquinoxalin-3-yl)-α-aminobutyric acid trifluoroacetate 33. This compound was prepared from **30** (29.5 mg, 0.05 mmol), TFA (0.5 ml), anisole (50 μl), DCM (2 ml) without purification to yield the TFA salt **33** (19 mg, 97%) as a pale brown hygroscopic solid; ν_{max} (KBr)/cm^{-1} 3520–2400br s (NH, OH), 2981s (CH), 1736s, 1677s (C=O), 1618s, 1371m, 1250w, 1157s, 1083w, 840w; δ_H (500 MHz, D_2O) 2.32–2.45 (2H, m, CH_2), 3.23–3.31 (2H, m, CH_2), 4.09 (1H, t, *J* 6, C*H*), 7.76–7.80 (2H, m, ArC*H*), 7.82–7.91 (2H, br m, ArC*H*); δ_C (125.8 MHz, D_2O) 28.99 (*C*H_2), 30.77 (*C*H_2), 52.81 (*C*H), 127.20 (1 × Ar-*C*H), 128.35 (2 × Ar-*C*, *ipso*), 131.03, 132.36, 139.10 (3 × Ar-*C*H), 135.21, 153.10 (2 × Ar-*C*, *ipso*), 169.20, 172.13 (2 × *C*=O); *m*/*z* (APCI+) 276 (MH^+, 100%), 184 (20).

General procedure for toluene-*p*-sulfonic acid amino acid deprotection

Typically, to a solution of the protected amino acid (1 eq.), in toluene, was added toluene-*p*-sulfonic acid monohydrate (1.5 eq.). The toluene was then gradually removed *in vacuo*. To the residue was added toluene and the process repeated until no starting material was present by ^{1}H NMR analysis, to afford the crude product.

(*S*)-β-(2-Carboxypyrazin-3-yl)-α-aminopropanoic acid toluene-4-sulfonic acid salt·0.5 toluene-4-sulfonic acid 34. This compound was prepared from **17** (26.2 mg, 0.05 mmol), TsOH·H_2O (14.3 mg, 0.075 mmol) and toluene (20 ml) without purification to yield the TsOH salt **34** (17 mg, 67%) as a brown oil; ν_{max} (KBr)/cm^{-1} 3520–2500br s (CH, OH, NH), 1735m (C=O), 1498w, 1163s, 1125s, 1010s, 818w, 689s; δ_H (500 MHz, D_2O) 2.23 (4.5H, s, CH_3), 3.75 (1H, dd, *J* 7, 17, C*H*(H)), 3.81 (1H, dd, *J* 5, 17, CH(*H*)), 4.46–4.48 (1H, m, C*H*), 7.20 (3H, d, *J* 8.0, Ar*H*), 7.53 (3H, d, *J* 8.0, Ar*H*), 8.49 (1H, d, *J* 2.0, Ar*H*), 8.61 (1H, d, *J* 2.0, Ar*H*); δ_C (125.8 MHz, D_2O) 20.36 (*C*H_3), 34.08 (*C*H_2), 51.13 (*C*H), 125.22 (Ar*C*H), 129.32 (Ar*C*H), 139.26, 142.08, 142.35, 146.51, 152.25 (2 × Ar-*C*H, 3 × Ar-*C*, *ipso*), 166.90, 171.22 (2 × *C*=O).

(*S*)-γ-(2-Carboxypyrazin-3-yl)-α-aminobutyric acid toluene-4-sulfonic acid salt·0.5 toluene-4-sulfonic acid 35. This compound was prepared from **28** (15 mg, 0.034 mmol), TsOH·H_2O (9.8 mg, 0.05 mmol) and toluene (20 ml) without purification to yield the TsOH salt **35** (13 mg, 79%) as a brown oil; ν_{max} (KBr)/cm^{-1} 3530–2450br m (CH, OH, NH), 2926m (CH), 1734m (C=O), 1624w, 1497w, 1453w, 1164s, 1124s, 1035s, 817w; δ_H (500 MHz, D_2O) 2.24–2.42 (2H, m, CH_2), 2.29 (4.5H, s, CH_3), 3.18–3.51 (2H, m, CH_2), 4.10 (1H, t, *J* 6.0, C*H*), 7.26 (3H, d, *J* 8.0, Ar*H*), 7.59 (3H, d, *J* 8.0, Ar*H*), 8.52 (1H, s, Ar*H*), 8.65 (1H, s, Ar*H*); δ_C (125.8 MHz, D_2O) 20.43 (*C*H_3), 28.78 (*C*H_2), 30.14 (*C*H_2), 52.33 (*C*H), 125.31 (Ar*C*H), 129.37 (Ar*C*H), 139.41, 142.01, 142.39, 146.61, 155.60 (2 × Ar-*C*H, 3 × Ar-*C*, *ipso*), 167.50, 171.51 (*C*=O); *m*/*z* (APCI+) 226 (MH^+, 100%), 102 (65).

(*S*)-β-(3-Methylthio-5-carboxy-1,2,4-triazin-6-yl)-α-aminopropanoic acid toluene-4-sulfonic acid salt·0.5 toluene-4-sulfonic acid 36a and (*S*)-β-(3-methylthio-6-carboxy-1,2,4-triazin-5-yl)-α-aminopropanoic acid toluene-4-sulfonic acid salt·0.5 toluene-4-sulfonic acid 36b. These compounds were prepared from **19a**,**b** (as a 1 : 1 mixture of regioisomers) (20 mg, 0.035 mmol), TsOH·H_2O (10 mg, 0.053 mmol) and toluene (20 μl) without purification to yield the TsOH salt **36a**,**b** (14 mg, 77%) as a brown oil; ν_{max} (KBr)/cm^{-1} 3530–2350br s (CH, OH, NH), 1700m (C=O), 1653m, 1540w, 1457w, 1171m, 1124m, 1035m, 817w; δ_H (500 MHz, DMSO-d_6) 2.31 (4.5H, s, CH_3), 2.69 (3H, s, SCH_3), 3.64 (1H, dd, *J* 7.5, 16.0, C*H*(H)), 3.83 (1H, dd, *J* 6.0, 16.0, CH(*H*)), 4.49–4.54 (1H, m, C*H*), 7.13 (3H, d, *J* 8.0, Ar*H*), 7.49 (3H, d, *J* 8.0, Ar*H*); δ_C (125.8 MHz, DMSO-d_6) 13.59 (S*C*H_3), 20.99 (*C*H_3), 32.72 (*C*H_2), 50.72 (*C*H), 125.69, 128.28 (2 × Ar-*C*H), 137.86, 145.83, 147.90, 150.90, 164.95, 170.20, 171.68 (5 × Ar-*C*, *ipso*, 2 × *C*=O).

(*S*)-γ-(3-Methylthio-5-carboxy-1,2,4-triazin-6-yl)-α-aminobutyric acid toluene-4-sulfonic acid salt·0.5 toluene-4-sulfonic acid 37a and (*S*)-γ-(3-methylthio-6-carboxy-1,2,4-triazin-5-yl)-α-aminobutyric acid toluene-4-sulfonic acid salt·0.5 toluene-4-sulfonic acid 37b. These compounds were prepared from **31a**,**b** (as a 1 : 1 mixture of regioisomers) (23.5 mg, 0.04 mmol), $TsOH·H_2O$ (11.4 mg, 0.06 mmol) and toluene (20 μl) without purification to yield the TsOH salt **37a**,**b** (17 mg, 80%) as a brown oil; ν_{max} (KBr)/cm^{-1} 3500–2500br m (CH, OH, NH), 1718m (C=O), 1617w, 1168s, 1124s, 1010s, 817w, 685s; δ_H (500 MHz, DMSO-d_6) 2.37–2.63 (2H, m, CH_2), 2.50 (4.5H, s, CH_3), 2.87 (3H, s, SCH_3), 3.37–3.43 (1H, m, C*H*(H)), 3.48–3.54 (1H, m, CH(*H*)), 4.25–4.27 (1H, m, C*H*), 7.34 (3H, d, *J* 8.0, Ar*H*), 7.70 (3H, d, *J* 8.0, Ar*H*); δ_C (125.8 MHz, DMSO-d_6) 13.54 (S*C*H$_3$), 21.03 (*C*H$_3$), 26.37 (*C*H$_2$), 29.80 (*C*H$_2$), 51.52 (*C*H), 125.73, 128.39 (2 × Ar-*C*H), 138.17, 145.46, 147.10, 161.20, 165.25, 171.35, 173.80 (5 × Ar-*C*, *ipso*, 2 × *C*=O); *m*/*z* (APCI+) 273 (MH$^+$, 3%), 229 (100), 139 (30).

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

Typically, to a solution of the protected amino acid (1 eq.), in toluene, was added toluene-*p*-sulfonic acid monohydrate (1 eq.). The toluene was then gradually removed *in vacuo*. To the residue was added toluene and the process was 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 eq.), 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.

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