Synthesis of fluorescent enone derived α-amino acids†

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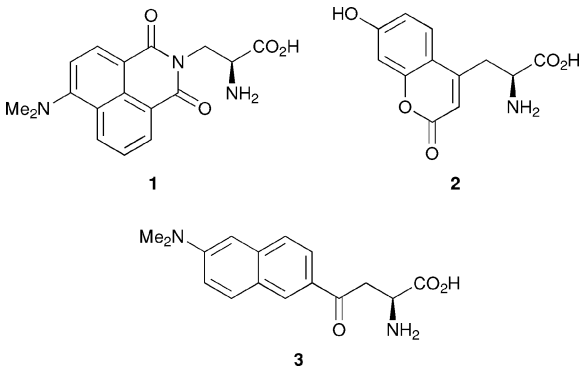
The development of a facile and general method for the preparation of enone derived α-amino acids is described. The key step involves a Horner–Wadsworth–Emmons reaction between an aspartic acid derived β-keto phosphonate ester and a range of aldehydes resulting in the formation of highly functionalised α-amino acids in good yields. An efficient two-stage deprotection process using mild conditions was developed to give the parent α-amino acids. Application of this methodology has produced a novel fluorescent α-amino acid that has potential as a biological marker.

Introduction

The importance of α-amino acids in virtually all disciplines of biology, medicine, biochemistry and chemistry is well established. α-Amino acids not only serve as the building blocks for structural proteins and enzymes but are important in signal induction pathways and play a key role in many enzymatic reactions.[1] Recent developments in the biosciences have renewed interest in the preparation of optically active α-amino acids and in particular non-proteinogenic analogues.[2] These compounds are of significant interest owing to their remarkable pharmacological and biological activities and also for their role as probes for bioactive conformations of peptides, protein–protein interactions and the mechanisms of enzyme reactions.[3]

More recently, attention has focused on the development of unnatural α-amino acids that possess solvatochromic fluorophores as the side chain group.[4] These fluorescent α-amino acids, many of which are of similar size to tryptophan, have been incorporated into biologically active peptides and proteins and used for studying biological structure and function and for visualising intracellular processes.[5] For example, Imperiali and co-workers have prepared a range of dimethylaminophthalimidoalanines such as **1** for investigating dynamic protein interactions.[6] A number of groups have reported the preparation of coumarin-bearing fluorescent α-amino acids (*e.g.* **2**),[7] while Cohen *et al.* used α-amino acid **3** with a dimethylaminonaphthalene derived side chain to study protein electrostatics.[8]

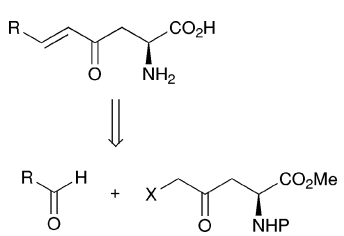
We recently began a programme of research focused on the efficient synthesis of enone derived α-amino acids for use as synthetic intermediates in organic synthesis. Enone derived α-amino acids are relatively rare in the literature, but a small number of protected derivatives have been prepared using various approaches.[9–12] These highly functionalized intermediates have been used for the preparation of azabicyclo[*X*.*Y*.0]alkane amino acids,[10] a C-linked glycoamino acid[11] and pipecolic acid analogues.[12] Herein,



we report a general and facile synthesis of enone derived α-amino acids using a Horner–Wadsworth–Emmons reaction between an aspartic acid derived β-keto phosphonate ester and a range of aldehydes. We also report for the first time, synthesis of the deprotected enone-derived α-amino acids using a two-stage process under mild conditions and demonstrate the use of this methodology for the preparation of a novel fluorescent α-amino acid.

Results and discussion

As shown in Scheme 1, our strategy for the general preparation of enone derived α-amino acids involved an alkene forming reaction between a suitably functionalised aspartic acid derived ketone and readily available aldehydes. In particular, we proposed to utilize an *N*-trityl protected aspartic acid derived β-keto phosphonate ester in a Horner–Wadsworth–Emmons reaction for the general synthesis of the desired α-amino acids.



Scheme 1 Retrosynthesis of enone derived amino acids.

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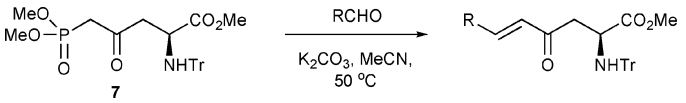
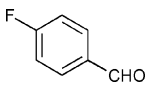
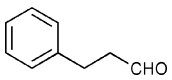
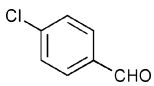
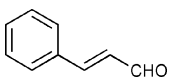
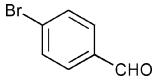
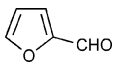
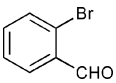
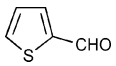
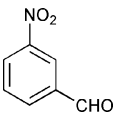
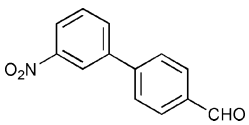
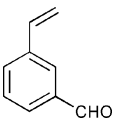
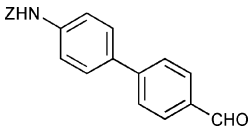
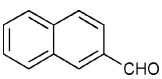
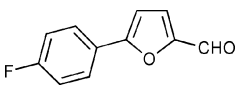
† Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data for compounds **5**–**7**. ^{1}H and ^{13}C NMR spectra for all new compounds. See DOI: 10.1039/b912782h

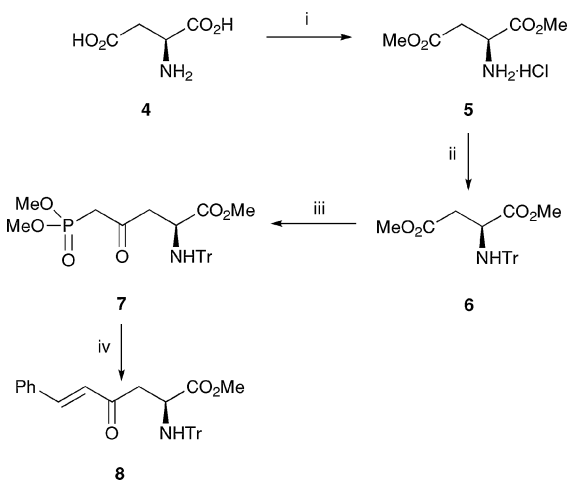
Table 1 Scope of the Horner–Wadsworth–Emmons reaction



Entry	RCHO	Product (Yield, %)[a]	Entry	RCHO	Product (Yield, %)[a]
1		**9** (69)	8		**16** (93)
2		**10** (77)	9		**17** (42)
3		**11** (96)	10		**18** (81)
4		**12** (78)	11		**19** (71)
5		**13** (56)	12		**20** (59)
6		**14** (56)	13		**21** (63)
7		**15** (80)	14		**22** (73)

[a] Isolated yield after flash chromatography.

Initially, an efficient synthesis of β-keto phosphonate ester **7** was developed (Scheme 2). L-Aspartic acid **4** was converted to *N*-trityl L-aspartate dimethyl ester **6** in quantitative yield using standard conditions.[13] After optimisation, it was found that reaction of **6** with 2.2 equivalents of the lithium anion of dimethyl methylphosphonate in THF gave **7** in a reproducible yield of 80%. With **7** in hand, conditions for the key Horner–Wadsworth–Emmons reaction using benzaldehyde as a model-coupling partner were then examined. Initially, Masamune–Roush conditions of the Horner–Wadsworth–Emmons reaction were attempted,[14] but this gave phenyl substituted enone **8** in only modest yield (42%). Switching to potassium carbonate as the base and heating the reaction mixture to 50 °C gave the desired product **8** in an improved 80% yield. It should be noted that only the *E*-alkene was isolated from these reactions.

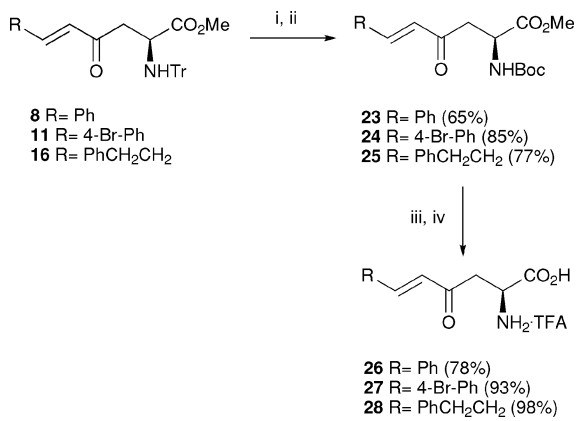


Scheme 2 *Reagents and conditions*: i. $SOCl_2$, MeOH, Δ, 100%; ii. TrCl, Et_3N, CH_2Cl_2, 100%; iii. $(MeO)_2POMe$, *n*-BuLi, THF, −78 °C, 80%; iv. PhCHO, LiCl, DBU, MeCN, 42% or PhCHO, K_2CO_3, MeCN, 50 °C, 80%.

On optimization of the Horner–Wadsworth–Emmons reaction, the scope of the reaction for the general synthesis of enone derived α-amino acids was explored (Table 1). Several points arise from this study. The Horner–Wadsworth–Emmons reaction of **7** is relatively slow and thus, extended reaction times are required (on average 48 h). However, the *N*-trityl protected enone derived α-amino acids are stable under these conditions and most products were obtained in high yield. The primary aim of this investigation was to produce highly conjugated enone derived α-amino acids

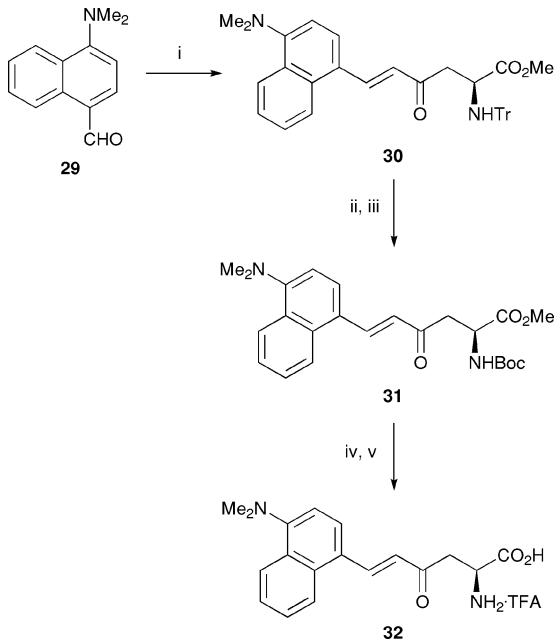
for a variety of applications and thus, most of the aldehydes used contained aromatic or heteroaromatic side chains. Nevertheless, the high yield obtained for product **16** (entry 8) shows that this procedure can be used effectively for enone derived α-amino acids with non-conjugated alkyl side chains. A number of products such as **11** (entry 3) were synthesized with the aim of using these in Pd(0)-mediated coupling reactions for the preparation of further substituted enone derived α-amino acids. While compound **11** can undergo Suzuki–Miyaura reactions, the coupled products are isolated in poor yields. A more effective strategy involved reversing the order of the coupling reactions. Thus, reaction of 4-bromobenzaldehyde or 5-bromo-2-furaldehyde with various boronic acids under standard Suzuki–Miyaura reaction conditions gave the highly functionalised aldehydes as shown in Table 1 (entries 12–14).[15] Subsequent HWE reaction using the optimized conditions gave enone derived α-amino acids **20–22** in good yields.

As mentioned above, a number of protected enone derived α-amino acids have been prepared before, however, none of these compounds has been deprotected to the parent α-amino acid.[9–12] Our initial attempt to achieve this goal involved a one-pot deprotection of both the amino and carboxylic acid groups by heating in 6 M hydrochloric acid. Our strategy was to isolate the amine salts to prevent any possible side reactions. Heating **8** in 6 M hydrochloric acid did give the HCl salt of **26** but in only 32% yield after purification. The next approach involved hydrolysis of the α-methyl ester followed by acid mediated removal of the trityl-protecting group. Due to the steric bulk of the trityl protecting group, the hydrolysis of α-esters of *N*-trityl α-amino acids is known to be difficult, requiring forcing conditions.[16] As expected, reaction of **8** with various bases (LiOH, NaOH, Cs_2CO_3) at room temperature returned only starting material, while at higher temperatures significant decomposition was observed. Our final strategy involved replacing the bulky trityl protecting group which is necessary for the efficient formation of the β-keto phosphonate ester **7** and high yields of the Horner–Wadsworth–Emmons reaction, with a protecting group that would allow hydrolysis of the α-methyl ester. Thus, the trityl group was replaced with the Boc-protecting group in two steps by treatment of **8** with TFA followed by reaction with di-*tert*-butyl dicarbonate in the presence of triethylamine. This gave Boc-analogue **23** in 65% yield over the two steps (Scheme 3). The methyl ester of **23** was smoothly hydrolysed at room temperature with caesium carbonate and the subsequent intermediate was then treated with TFA to remove the Boc-group to give the fully deprotected enone derived α-amino acid **26** in 78% yield over the two steps. This two-stage approach for the synthesis of the parent enone derived α-amino acids is general, as shown by the efficient synthesis of analogues **27** and **28** (79% and 75% overall yield over the four steps, respectively).



Scheme 3 *Reagents and conditions*: i. TFA, CH_2Cl_2; ii. Boc_2O, Et_3N, CH_2Cl_2; iii. Cs_2CO_3, MeOH, H_2O; iv. TFA, CH_2Cl_2.

Having developed a general approach for the synthesis of enone derived α-amino acids, it was proposed that this route could be used for the preparation of various biological probes and in particular, fluorescent analogues. Dimethylaminonaphthalene derivatives often show fluorescent properties[4,6,8] and thus, commercially available 4-dimethylamino-1-naphthaldehyde **29** was used in a Horner–Wadsworth–Emmons reaction with β-keto phosphonate ester **7** to give enone analogue **30** in 72% yield (Scheme 4). Compound **30** was converted to Boc-analogue **31** as described above in 61% yield over the two steps. Hydrolysis of the methyl ester and TFA mediated removal of the Boc-group then gave the α-amino acid **32**.



Scheme 4 *Reagents and conditions*: i. **7**, K_2CO_3, MeCN, 50 °C, 72%; ii. TFA, CH_2Cl_2; iii. Boc_2O, Et_3N, CH_2Cl_2, 61% (over two steps); iv. Cs_2CO_3, MeOH, H_2O; v. TFA, CH_2Cl_2, 46% (over two steps).

The absorption and fluorescence spectra for α-amino acid **32** were initially measured using methanol as the solvent. The solution (concentration $= 1 \times 10^{-5}$ M) showed a strong absorption with a maximum at 393 nm and an extinction coefficient of 11 504 cm^{-1} M^{-1}. Excitation at 390 nm showed strong fluorescence with a maximum at 540 nm (Fig. 1). Strong fluorescence was also observed in other solvents (DMSO, ethyl acetate and toluene) and to a lesser extent in water. As expected, a shift in the emission maxima was generally observed depending on the polarity of the solvent.[8] For example, a solution in toluene gave a fluorescence maximum at 506 nm compared to 552 nm in water. The absorption and emission maxima for the naturally occurring α-amino acids, tryptophan ($\lambda_{Abs} = 278$ nm, $\lambda_{Em} = 352$ nm) and tyrosine ($\lambda_{Abs} = 274$ nm, $\lambda_{Em} = 303$ nm) occur at much lower wavelengths than α-amino acid **32**.[17] Hence, this should allow the effective use of **32**

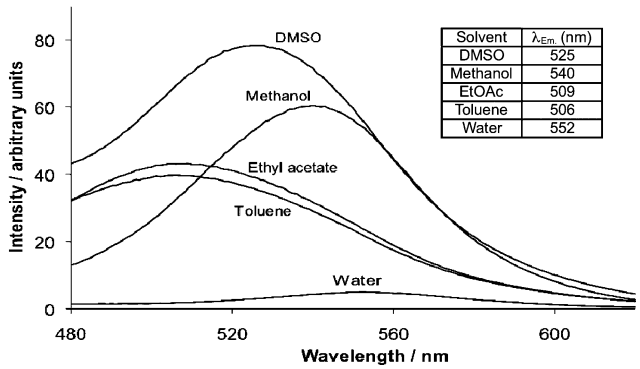


Fig. 1 Fluorescence spectra of α-amino acid **32** in various solvents after excitation at 390 nm. The concentration of each solution was 1×10^{-5} M and spectra were recorded using a 1 cm optical path length.

as a fluorescent marker when incorporated into biologically active proteins and peptides.

Conclusions

In summary, we have developed a general approach for the preparation of enone derived α-amino acids using a Horner–Wadsworth–Emmons reaction between an aspartic acid derived β-keto phosphonate ester and a range of aldehydes as the key step. The protected enone derived α-amino acids have for the first time been deprotected to the parent α-amino acids using a two-stage process under mild conditions. While this two-stage process does involve four steps, these are generally high yielding and the penultimate step produces Boc-protected α-amino acids that have the potential to be incorporated into proteins and peptides. Overall, our synthesis represents a useful tool for the preparation of highly functionalized α-amino acids that have potential as biological probes. This has been exemplified by the synthesis of a new fluorescent α-amino acid that shows favourable spectroscopic properties, suggesting it may find application as a fluorescent biomarker. Further work investigating the synthetic and biological uses of enone derived α-amino acids is currently underway.

Experimental

Dry solvents were purified using a PureSolv 500 MD solvent purification system. Flash column chromatography was carried out using Fisher matrix silica 60. Macherey-Nagel aluminium-backed plates pre-coated with silica gel 60 (UV_{254}) were used for thin layer chromatography and were visualised by staining with $KMnO_4$. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer with chemical shift values in ppm relative to TMS (δ_H 0.00 and δ_C 0.0) or residual chloroform (δ_H 7.28 and δ_C 77.2) as standard. Proton and carbon assignments are based on two-dimensional COSY and DEPT experiments, respectively. Mass spectra were obtained using a JEOL JMS-700 spectrometer. Infrared spectra were obtained using a JASCO FTIR 410 spectrometer. Optical rotations were determined as solutions irradiating with the sodium D line ($\lambda = 589$ nm) using an Autopol V polarimeter. $[\alpha]_D$ values are given in units 10^{-1} deg cm^2 g^{-1}.

General procedure for the Horner–Wadsworth–Emmons reaction

Methyl (2*S*)-5-(dimethoxyphosphoryl)-4-oxo-2-(tritylamino)-pentanoate **7** (0.20 g, 0.40 mmol) was dissolved in acetonitrile (4 mL) at room temperature under argon. Anhydrous potassium carbonate (0.06 g, 0.42 mmol) was added to the solution, which was then stirred for 0.5 h. An aldehyde (0.80 mmol) was added to the suspension and heated at 50 °C until the reaction was complete by TLC. The reaction mixture was allowed to cool to room temperature and then concentrated *in vacuo*. The resultant residue was dissolved in ethyl acetate (30 mL) and washed with water (20 mL), brine (30 mL) then dried ($MgSO_4$) and concentrated *in vacuo*. The products were purified by column chromatography on silica eluting with 20–40% diethyl ether in petroleum ether.

Methyl (2*S*,5*E*)-4-oxo-6-phenyl-2-(tritylamino)hex-5-enoate 8. Using the general procedure above gave **8** after 36 h as a yellow oil (0.15 g, 80%). ν_{max}/cm^{-1} (NaCl) 3023 (NH), 2950 (CH), 1737 (CO), 1657 (C=C), 1608, 1205; $[\alpha]_D^{25}$ +111.0 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.80 (1H, dd, *J* 15.2, 7.0 Hz, 3-*H*H), 2.88–2.97 (2H, m, 3-H*H* and NH), 3.28 (3H, s, OMe), 3.79–3.89 (1H, m, 2-H), 6.69 (1H, d, *J* 16.2 Hz, 5-H), 7.14–7.29 (10H, m, ArH and 6-H), 7.37–7.41 (3H, m, ArH), 7.44–7.53 (8H, m, ArH); δ_C (100 MHz, $CDCl_3$) 43.6 (CH_2), 50.0 (CH_3), 51.7 (CH), 69.2 (C), 124.5 (CH), 125.7 (CH), 126.1 (CH), 126.3 (CH), 127.4 (CH), 127.8 (CH), 128.6 (CH), 133.0 (C), 141.3 (C), 143.7 (CH), 172.4 (C), 195.5 (C); *m*/*z* (FAB) 476.2231 (MH^+. $C_{32}H_{30}NO_3$ requires 476.2226), 398 (15%), 259 (6), 243 (100), 232 (25), 166 (23), 132 (24).

Methyl (2*S*,5*E*)-6-(4-fluorophenyl)-4-oxo-2-(tritylamino)hex-5-enoate 9. Using the general procedure above gave **9** after 3 days as a yellow oil (0.14 g, 69%). ν_{max}/cm^{-1} (NaCl) 3057 (NH), 2950 (CH), 1738 (CO), 1612, 1598, 1233; $[\alpha]_D^{25}$ +128.8 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.78 (1H, dd, *J* 15.2, 7.0 Hz, 3-*H*H), 2.87–2.95 (2H, m, 3-H*H* and NH), 3.28 (3H, s, OMe), 3.78–3.85 (1H, m, 2-H), 6.61 (1H, d, *J* 16.1 Hz, 5-H), 7.05–7.11 (2H, m, ArH), 7.15–7.19 (3H, m, ArH), 7.21–7.29 (7H, m, ArH), 7.44 (1H, d, *J* 16.1 Hz, 6-H), 7.47–7.53 (7H, m, ArH); δ_C (100 MHz, $CDCl_3$) 44.9 (CH_2), 51.1 (CH_3), 52.9 (CH), 70.4 (C), 115.3 (d, $J_{C\text{-}C\text{-}F}$ 22.1 Hz, CH), 125.1 (CH), 127.0 (CH), 127.2 (CH), 128.2 (CH), 129.4 (CH), 129.7 (C), 141.1 (CH), 144.8 (C), 163.2 (d, $J_{C\text{-}F}$ 251.5 Hz, C), 173.6 (C), 196.4 (C); *m*/*z* (FAB) 494.2128 (MH^+. $C_{32}H_{29}FNO_3$ requires 494.2131), 416 (31%), 258 (6), 243 (100), 166 (34), 150 (35).

Methyl (2*S*,5*E*)-6-(4-chlorophenyl)-4-oxo-2-(tritylamino)hex-5-enoate 10. Using the general procedure above gave **10** after 2 days as a colourless solid (0.16 g, 77%). Mp 121–122 °C; ν_{max}/cm^{-1} (NaCl) 3020 (NH), 2950 (CH), 1737 (CO), 1658 (C=C), 1608, 1205; $[\alpha]_D^{25}$ +144.8 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.77 (1H, dd, *J* 15.2, 6.9 Hz, 3-*H*H), 2.86–2.93 (2H, m, 3-H*H* and NH), 3.29 (3H, s, OMe), 3.75–3.82 (1H, m, 2-H), 6.65 (1H, d, *J* 16.2 Hz, 5-H), 7.15–7.21 (3H, m, ArH), 7.22–7.27 (7H, m, ArH and 6-H), 7.36–7.41 (2H, m, ArH), 7.43–7.51 (8H, m, ArH); δ_C (100 MHz, $CDCl_3$) 44.7 (CH_2), 50.9 (CH_3), 52.6 (CH), 70.2 (C), 125.4 (CH), 125.6 (CH), 127.0 (CH), 128.0 (CH), 128.4 (CH), 128.7 (CH), 132.2 (C), 135.4 (C), 140.6 (C), 144.9 (CH), 173.3 (C), 196.2 (C); *m*/*z* (FAB) 510.1847 (MH^+. $C_{32}H_{29}{}^{35}ClNO_3$ requires 510.1836), 432 (11%), 267 (17), 243 (100), 166 (19).

Methyl (2*S*,5*E*)-6-(4-bromophenyl)-4-oxo-2-(tritylamino)hex-5-enoate 11. Using the general procedure above gave **11** after 2 days as a colourless solid (0.21 g, 96%). Mp 134–135 °C; ν_{max}/cm^{-1} (NaCl) 3021 (NH), 2950 (CH), 1737 (CO), 1659 (C=C), 1608, 1488; $[\alpha]_D^{27}$ +64.6 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.77 (1H, dd, *J* 15.2, 7.0 Hz, 3-*H*H), 2.86–2.95 (2H, m, 3-H*H* and NH), 3.29 (3H, s, OMe), 3.75–3.83 (1H, m, 2-H), 6.66 (1H, d, *J* 16.2 Hz, 5-H), 7.14–7.21 (3H, m, ArH), 7.22–7.27 (7H, m, ArH and 6-H), 7.37–7.43 (2H, m, ArH), 7.46–7.57 (8H, m, ArH); δ_C (100 MHz, $CDCl_3$) 45.8 (CH_2), 51.9 (CH_3), 53.7 (CH), 71.2 (C), 124.9 (C), 126.2 (CH), 126.5 (CH), 127.9 (CH), 129.0 (CH), 129.7 (CH), 132.2 (CH), 133.3 (C), 141.7 (C), 145.7 (CH), 174.3 (C), 197.2 (C); *m*/*z* (FAB) 554.1332 (MH^+. $C_{32}H_{29}{}^{79}BrNO_3$ requires 554.1331), 478 (16%), 378 (3), 312 (13), 243 (100), 209 (16), 166 (43).

Methyl (2*S*,5*E*)-6-(2-bromophenyl)-4-oxo-2-(tritylamino)hex-5-enoate 12. Using the general procedure above gave **12** after 24 h as a colourless oil (0.2 g, 78%). ν_{max}/cm^{-1} (NaCl) 3021 (NH), 2950 (CH), 1737 (CO), 1437, 1204, 1027; $[\alpha]_D^{25}$ +48.6 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.82 (1H, dd, *J* 15.4, 6.8 Hz, 3-*H*H), 2.88–2.97 (2H, m, NH and 3-H*H*), 3.30 (3H, s, OMe), 3.78–3.83 (1H, m, 2-H), 6.60 (1H, d, *J* 16.2 Hz, 5-H), 7.13–7.33 (11H, m, ArH), 7.48–7.53 (6H, m, ArH), 7.59 (2H, td, *J* 8.0, 1.1 Hz, ArH), 7.85 (1H, d, *J* 16.2 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 45.3 (CH_2), 52.1 (CH), 53.8 (CH_3), 71.3 (C), 125.9 (C), 126.6 (CH), 127.8 (CH), 127.9 (CH), 128.0 (CH), 128.9 (CH), 129.1 (CH), 131.6 (CH), 133.6 (CH), 134.4 (C), 141.7 (CH), 145.8 (C), 174.4 (C), 197.5 (C); *m*/*z* (FAB) 554.1322 (MH^+. $C_{32}H_{29}{}^{79}BrNO_3$ requires 554.1331), 478 (7%), 312 (13), 243 (100), 209 (7), 165 (19).

Methyl (2*S*,5*E*)-6-(3-nitrophenyl)-4-oxo-2-(tritylamino)hex-5-enoate 13. Using the general procedure above gave **13** after 5 days as a yellow oil (0.12 g, 56%). ν_{max}/cm^{-1} (NaCl) 3022 (NH), 2951 (CH), 1737 (CO), 1613, 1530, 1352; $[\alpha]_D^{27}$ +49.3 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.79 (1H, dd, *J* 15.4, 7.0 Hz, 3-*H*H), 2.88–2.98 (2H, m, 3-H*H* and NH), 3.32 (3H, s, OMe), 3.77–3.85 (1H, m, 2-H), 6.79 (1H, d, *J* 16.2 Hz, 5-H), 7.16–7.21 (3H, m, ArH), 7.23–7.29 (6H, m, ArH), 7.46–7.52 (7H, m, ArH and 6-H), 7.57 (1H, t, *J* 8.0 Hz, ArH), 7.81 (1H, d, *J* 8.0 Hz, ArH), 8.24 (1H, d, *J* 8.0 Hz, ArH), 8.37 (1H, br s, ArH); δ_C (100 MHz, $CDCl_3$) 46.2 (CH_2), 52.1 (CH_3), 53.8 (CH), 71.3 (C), 122.6 (CH), 124.8 (CH), 126.9 (CH), 127.8 (CH), 128.6 (CH), 128.8 (CH), 130.1 (CH), 133.9 (CH), 136.2 (C), 140.1 (CH), 145.7 (C), 148.8 (C), 174.3 (C), 196.9 (C); *m*/*z* (FAB) 521.2074 (MH^+. $C_{32}H_{29}N_2O_5$ requires 521.2076), 443 (63%), 277 (31), 243 (100), 184 (44), 166 (79).

Methyl (2*S*,5*E*)-4-oxo-2-(tritylamino)-6-(3-vinylphenyl)hex-5-enoate 14. Using the general procedure above gave **14** after 4 days as a yellow oil (0.12 g, 56%). ν_{max}/cm^{-1} (NaCl) 3019 (NH), 2950 (CH), 1737 (CO), 1658 (C=C), 1609, 1490, 1447, 1215, 1172; $[\alpha]_D^{27}$ +52.0 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.79 (1H, dd, *J* 15.1, 7.0 Hz, 3-*H*H), 2.89–2.96 (2H, m, 3-H*H* and NH), 3.27 (3H, s, OMe), 3.76–3.85 (1H, m, 2-H), 5.31 (1H, d, *J* 10.9 Hz, 2′-*H*H), 5.79 (1H, d, *J* 17.6 Hz, 2′-H*H*), 6.66–6.76 (2H, m, 1′-H and 5-H), 7.13–7.28 (9H, m, ArH), 7.31–7.55 (11H, m, ArH and 6-H); δ_C (100 MHz, $CDCl_3$) 45.8 (CH_2), 52.0 (CH_3), 53.9 (CH), 71.3 (C), 115.1 (CH_2), 126.3 (CH), 126.7 (CH), 126.8 (CH), 127.8 (CH), 128.2 (CH), 128.4 (CH), 129.1 (CH), 129.2 (CH), 134.7 (C), 136.1 (CH), 138.4 (C), 143.2 (CH), 145.8 (C), 174.5 (C), 197.5 (C); *m*/*z* (FAB) 502.2388 (MH^+. $C_{34}H_{32}NO_3$ requires 502.2382), 424 (45%), 258 (72), 243 (100), 166 (83), 158 (77).

Methyl (2*S*,5*E*)-6-(naphthalen-2-yl)-4-oxo-2-(tritylamino)hex-5-enoate 15. Using the general procedure above gave **15** after 2 days as a yellow solid (0.16 g, 80%). Mp 62–63 °C; ν_{max}/cm^{-1} (NaCl) 3055 (NH), 2982 (CH), 1734 (CO), 1655 (C=C), 1604, 1593, 1489, 1172; $[\alpha]_D^{24}$ +64.1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.84 (1H, dd, *J* 15.1, 7.0 Hz, 3-*H*H), 2.92–3.00 (2H, m, 3-H*H* and NH), 3.29 (3H, s, OMe), 3.79–3.86 (1H, m, 2-H), 6.80 (1H, d, *J* 16.2 Hz, 5-H), 7.15–7.30 (9H, m, ArH), 7.50–7.55 (8H, m, ArH), 7.62–7.69 (2H, m, 6-H and ArH), 7.84–7.89 (3H, m, ArH), 7.94 (1H, br s, ArH); δ_C (100 MHz, $CDCl_3$) 45.9 (CH_2), 52.1 (CH), 54.0 (CH_3), 71.4 (C), 123.6 (CH), 126.6 (CH), 126.6 (CH), 126.9 (CH), 127.6 (CH), 128.0 (CH), 128.0 (CH), 128.2 (CH), 128.7 (CH), 128.9 (CH), 130.7 (CH), 132.0 (C), 133.4 (C), 134.5 (C), 143.5 (CH), 145.9 (C), 174.6 (C), 197.6 (C); *m*/*z* (FAB) 526.2388 (MH^+. $C_{36}H_{32}NO_3$ requires 526.2382), 448 (7%), 273 (8), 243 (100), 181 (19), 165 (24).

Methyl (2*S*,5*E*)-4-oxo-8-phenyl-2-(tritylamino)oct-5-enoate 16. Using the general procedure above gave **16** after 2 days as a yellow oil (0.15 g, 93%). ν_{max}/cm^{-1} (NaCl) 3027 (NH), 2948 (CH), 1738 (CO), 1667 (C=C), 1626, 1492, 1448, 1205; $[\alpha]_D^{27}$ +26.6 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.50 (2H, q, *J* 7.1 Hz, 7-H_2), 2.63 (1H, dd, *J* 15.3, 7.0 Hz, 3-*H*H), 2.70–2.80 (3H, m, 3-H*H* and 8-H_2), 2.85 (1H, br s, NH), 3.25 (3H, s, OMe), 3.67–3.74 (1H, m, 2-H), 6.06 (1H, d, *J* 15.9 Hz, 5-H), 6.76 (1H, dt, *J* 15.9, 7.1 Hz, 6-H), 7.12–7.30 (14H, m, ArH), 7.45–7.50 (6H, m, ArH); δ_C (100 MHz, $CDCl_3$) 32.4 (CH_2), 32.6 (CH_2), 43.2 (CH_2), 50.1 (CH_3), 51.9 (CH), 69.5 (C), 124.5 (CH), 125.0 (CH), 126.1 (CH), 126.6 (CH), 126.7 (CH), 127.0 (CH), 129.2 (CH), 138.9 (C), 144.0 (C), 145.3 (CH), 172.7 (C), 195.8 (C); *m*/*z* (FAB) 504.2534 (MH^+. $C_{34}H_{34}NO_3$ requires 504.2539), 426 (69%), 252 (78), 243 (100), 166 (78), 160 (38).

Methyl (2*S*,5*E*,7*E*)-4-oxo-8-phenyl-2-(tritylamino)octa-5,7-dienoate 17. Using the general procedure above gave **17** after 5 days as a yellow solid (0.08 g, 42%). Mp 66–67 °C; ν_{max}/cm^{-1} (NaCl) 3024 (NH), 2950 (CH), 1737 (CO), 1619, 1586, 1448; $[\alpha]_D^{27}$ +64.2 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.72 (1H, dd, *J* 15.0, 7.0 Hz, 3-*H*H), 2.83–2.93 (2H, m, 3-H*H* and NH), 3.26 (3H, s, OMe), 3.74–3.79 (1H, m, 2-H), 6.22 (1H, d, *J* 15.4 Hz, 7-H), 6.82–6.96 (1H, m, 5-H), 7.14–7.39 (13H, m, ArH and 6-H), 7.45–7.52 (9H, m, ArH and 8-H); δ_C (100 MHz, $CDCl_3$) 45.6 (CH_2), 52.0 (CH_3), 53.9 (CH), 71.3 (C), 126.5 (CH), 126.7 (CH), 127.3 (CH), 127.9 (CH), 128.8 (CH), 128.9 (CH), 129.4 (CH), 129.8 (CH), 136.0 (C), 141.8 (CH), 143.5 (CH), 145.8 (C), 174.5 (C), 197.6 (C); *m*/*z* (FAB) 502.2387 (MH^+. $C_{34}H_{32}NO_3$ requires 502.2382), 424 (21%), 258 (22), 243 (100), 194 (17), 166 (91), 158 (55).

Methyl (2*S*,5*E*)-6-(furan-2-yl)-4-oxo-2-(tritylamino)hex-5-enoate 18. Using the general procedure above gave **18** after 4 days as a light brown solid (0.14 g, 81%). Mp 97–98 °C; ν_{max}/cm^{-1} (NaCl) 3058 (NH), 2951 (CH), 1737 (CO), 1607; $[\alpha]_D^{23}$ +42.9 (*c* 0.3, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.72 (1H, dd, *J* 15.1, 7.0 Hz, 3-*H*H), 2.82–2.94 (2H, m, 3-H*H* and NH), 3.27 (3H, s, OMe), 3.74–3.81 (1H, m, 2-H), 6.47–6.50 (1H, m, 4′-H), 6.59 (1H, d, *J* 15.8 Hz, 5-H), 6.66 (1H, d, *J* 3.3 Hz, 3′-H), 7.14–7.30 (11H, m, 6-H, 5′-H and ArH), 7.46–7.52 (6H, m, ArH); δ_C (100 MHz,

$CDCl_3$) 46.2 (CH_2), 52.0 (CH_3), 53.9 (CH), 71.3 (C), 112.7 (CH), 116.2 (CH), 123.6 (CH), 126.6 (CH), 128.0 (CH), 128.6 (CH), 129.8 (CH), 145.2 (CH), 145.8 (C), 151.0 (C), 174.5 (C), 197.1 (C); *m/z* (FAB) 488.1833 (MNa^+. $C_{30}H_{27}NO_4Na$ requires 488.1838), 388 (7%), 352 (3), 243 (100), 166 (18).

Methyl (2*S*,5*E*)-4-oxo-6-(thiophen-2-yl)-2-(tritylamino)hex-5-enoate 19. Using the general procedure above gave **19** after 7 days as a light brown oil (0.14 g, 71%). ν_{max}/cm^{-1} (NaCl) 3058 (NH), 2949 (CH), 1737 (CO), 1595; $[\alpha]_D^{25}$ +52.6 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.65 (1H, dd, *J* 15.0, 6.9 Hz, 3-*H*H), 2.77 (1H, dd, *J* 15.0, 5.3 Hz, 3-H*H*), 2.83 (1H, br s, NH), 3.19 (3H, s, OMe), 3.65–3.73 (1H, m, 2-H), 6.42 (1H, d, *J* 15.8 Hz, 5-H), 6.96 (1H, dd, *J* 5.1, 3.7 Hz, 4′-H), 7.05–7.11 (3H, m, ArH), 7.13–7.19 (7H, m, 3′-H and ArH), 7.29 (1H, d, *J* 5.1 Hz, 5′-H), 7.38–7.43 (6H, m, ArH), 7.51 (1H, d, *J* 15.8 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 44.7 (CH_2), 50.8 (CH_3), 52.7 (CH), 70.1 (C), 123.9 (CH), 125.5 (CH), 127.0 (CH), 127.2 (CH), 127.6 (CH), 127.9 (CH), 130.7 (CH), 134.5 (CH), 138.6 (C), 144.6 (C), 173.2 (C), 195.8 (C); *m/z* (FAB) 482.1793 (MH^+. $C_{30}H_{28}NO_3S$ requires 482.1790), 404 (12%), 307 (8), 289 (11), 243 (100), 165 (53), 155 (32), 107 (23).

Methyl (2*S*,5*E*)-6-(3′-nitrobiphen-4-yl)-4-oxo-2-(tritylamino)-hex-5-enoate 20. Using the general procedure above gave **20** after 3 days as a yellow foam (0.19 g, 59%). ν_{max}/cm^{-1} (neat) 3030 (NH), 1736 (CO), 1657 (C=C), 1603, 1530, 1514, 1348; $[\alpha]_D^{23}$ +61.7 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.82 (1H, dd, *J* 15.2, 6.9 Hz, 3-*H*H), 2.90–3.02 (2H, m, 3-H*H* and NH), 3.30 (3H, s, OMe), 3.77–3.88 (1H, m, 2-H), 6.75 (1H, d, *J* 16.2 Hz, 5-H), 7.12–7.32 (9H, m, ArH), 7.45–7.73 (12H, m, ArH and 6-H), 7.93 (1H, d, *J* 7.9 Hz, ArH), 8.23 (1H, d, *J* 7.9 Hz, ArH), 8.48 (1H, s, ArH); δ_C (100 MHz, $CDCl_3$) 45.9 (CH_2), 52.1 (CH_3), 53.8 (CH), 71.3 (C), 121.9 (CH), 122.7 (CH), 126.6 (CH), 127.0 (CH), 127.7 (CH), 128.0 (CH), 128.9 (CH), 129.2 (CH), 130.0 (CH), 132.9 (CH), 134.7 (C), 140.6 (C), 141.7 (C), 142.2 (CH), 145.8 (C), 148.8 (C), 174.5 (C), 197.4 (C); *m/z* (FAB) 597.2384 (MH^+. $C_{38}H_{33}N_2O_5$ requires 597.2389), 519 (23%), 419 (5), 353 (32), 243 (100), 194 (9), 166 (54).

Methyl (2*S*,5*E*)-6-(4′-benzyloxycarbonylaminobiphen-4-yl)-4-oxo-2-(tritylamino)hex-5-enoate 21. Using the general procedure above gave **21** after 2 days as yellow foam (0.06 g, 63%). ν_{max}/cm^{-1} (NaCl) 3333 (NH), 3030, 1734 (CO), 1654 (C=C), 1595, 1534, 1499, 1217; $[\alpha]_D^{24}$ +62.3 (*c* 0.6, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.79 (1H, dd, *J* 15.2, 7.2 Hz, 3-*H*H), 2.88–3.00 (2H, m, 3-H*H* and NH), 3.29 (3H, s, OMe), 3.75–3.86 (1H, m, 2-H), 5.23 (2H, s, PhCH_2), 6.66–6.78 (2H, m, 5-H and NH), 7.11–7.65 (29H, m, ArH and 6-H); δ_C (100 MHz, $CDCl_3$) 45.7 (CH_2), 52.0 (CH_3), 53.9 (CH), 67.2 (CH_2), 71.3 (C), 119.0 (CH), 126.1 (CH), 126.6 (CH), 127.2 (CH), 127.7 (CH), 128.0 (CH), 128.4 (CH), 128.5 (CH), 128.7 (CH), 128.8 (CH), 129.0 (CH), 133.1 (C), 135.1 (C), 136.0 (C), 137.9 (C), 142.7 (C), 143.0 (CH), 145.8 (C), 153.3 (C), 174.6 (C), 197.6 (C); *m/z* (FAB) 701.3018 (MH^+. $C_{46}H_{41}N_2O_5$ requires 701.3015), 623 (4%), 530 (3), 457 (5), 356 (8), 243 (100), 166 (9).

Methyl (2*S*,5*E*)-6-[5-(4′-fluorophenyl)furan-2-yl]-4-oxo-2-(tritylamino)hex-5-enoate 22. Using the general procedure above gave **22** after 24 h as a yellow foam (0.16 g, 73%). ν_{max}/cm^{-1} (NaCl) 3324 (NH), 3021, 2950 (CH), 1737 (CO), 1652 (C=C), 1601, 1486, 1448, 1369; $[\alpha]_D^{23}$ +63.6 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.77 (1H, dd, *J* 14.9, 7.0 Hz, 3-*H*H), 2.85–2.99 (2H, m, 3-H*H* and NH), 3.27 (3H, s, OMe), 3.72–3.86 (1H, m, 2-H), 6.63–6.79 (3H, m, 5-H, 3′-H and 4′-H), 7.02–7.62 (18H, m, ArH and 6-H), 7.67–7.76 (2H, m, ArH); δ_C (100 MHz, $CDCl_3$) 46.3 (CH_2), 52.0 (CH_3), 54.0 (CH), 71.3 (C), 107.9 (CH), 116.1 (d, J_{C-C-F} 22.1 Hz, CH), 118.8 (CH), 123.1 (CH), 126.3 (C), 126.4 (CH), 126.6 (CH), 128.0 (CH), 128.9 (CH), 129.0 (CH), 145.8 (C), 150.4 (C), 155.7 (C), 162.9 (d, J_{C-F} 249.6 Hz, C), 174.5 (C), 196.9 (C); *m/z* (FAB) 560.2233 (MH^+. $C_{36}H_{31}FNO_4$ requires 560.2237), 482 (24%), 419 (4), 378 (3), 316 (98), 243 (100), 216 (96), 166 (71), 124 (35).

Methyl (2*S*,5*E*)-6-(4-dimethylaminonaphthalen-1-yl)-4-oxo-2-(tritylamino)hex-5-enoate 30. Using the general procedure above gave **30** after 4 days as an orange oil (0.24 g, 72%). ν_{max}/cm^{-1} (NaCl) 3448 (NH), 3019, 2947 (CH), 1737 (CO), 1651 (C=C), 1569, 1449, 1390; $[\alpha]_D^{18}$ +73.7 (*c* 0.4, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.83 (1H, dd, *J* 14.8, 6.8 Hz, 3-*H*H), 2.88–3.04 (8H, m, 3-H*H*, NH and NMe_2), 3.30 (3H, s, OMe), 3.78–3.88 (1H, m, 2-H), 6.71 (1H, d, *J* 15.7 Hz, 5-H), 7.04 (1H, d, *J* 8.0 Hz, ArH), 7.14–7.29 (9H, m, ArH), 7.49–7.60 (8H, m, ArH), 7.74 (1H, d, *J* 8.0 Hz, ArH), 8.13–8.26 (2H, m, ArH), 8.30 (1H, d, *J* 15.7 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 44.9 (CH_3), 45.8 (CH_2), 52.0 (CH_3), 54.0 (CH), 71.3 (C), 113.4 (CH), 123.6 (CH), 125.2 (CH), 125.3 (CH), 125.4 (C), 125.8 (CH), 126.5 (CH), 126.6 (CH), 126.9 (CH), 127.9 (CH), 128.4 (C), 128.9 (CH), 133.1 (C), 140.2 (CH), 145.9 (C), 153.8 (C), 174.7 (C), 197.4 (C); *m/z* (FAB) 569.2799 (MH^+. $C_{38}H_{37}N_2O_3$ requires 569.2804), 491 (3%), 460 (4), 325 (52), 243 (100), 224 (19), 85 (56).

General procedure for the synthesis of Boc-protected analogues

To a solution of the trityl protected amino acid (2.1 mmol) in dichloromethane (15 mL) at room temperature under argon was added trifluoroacetic acid (21.0 mmol) and the reaction mixture was allowed to stir for 2 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in water (20 mL) and washed with diethyl ether (2 × 20 mL). The aqueous layer was concentrated *in vacuo*, azeotroping with ethyl acetate–chloroform to give the TFA salts. These were dissolved in dichloromethane (5 mL) under argon and cooled to 0 °C. To the solution was added triethylamine (4.2 mmol) and di-*tert*-butyl dicarbonate (4.2 mmol) and the reaction mixture was allowed to warm to room temperature and stirred for 6 h. The reaction mixture was diluted with dichloromethane (10 mL) then washed with water (2 × 10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude products were purified by column chromatography on silica eluting with 20–40% diethyl ether in petroleum ether.

Methyl (2*S*,5*E*)-4-oxo-6-phenyl-2-(*tert*-butoxycarbonylamino)-hex-5-enoate 23. Using the general procedure above gave **23** as a colourless oil (0.07 g, 65%). ν_{max}/cm^{-1} (NaCl) 3368 (NH), 2979 (CH), 1747 (CO), 1713 (CO), 1663 (C=C), 1496, 1367, 1168; $[\alpha]_D^{17}$ +56.9 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s, O^{t}Bu), 3.33 (1H, dd, *J* 17.8, 4.3 Hz, 3-*H*H), 3.44 (1H, dd, *J* 17.8, 4.1 Hz, 3-H*H*), 3.75 (3H, s, OMe), 4.62 (1H, ddd, *J* 8.5, 4.3, 4.1 Hz, 2-H), 5.60 (1H, d, *J* 8.5 Hz, NH), 6.71 (1H, d, *J* 16.1 Hz, 5-H), 7.38–7.42 (3H, m, ArH), 7.52–7.55 (2H, m, ArH), 7.57 (1H, d, *J* 16.1 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 28.3 (CH_3), 42.4 (CH_2), 49.6 (CH), 52.6 (CH_3), 79.9 (C), 125.6 (CH), 128.4 (CH), 129.2 (CH), 130.9 (CH), 134.1 (C), 143.9 (CH), 155.6 (C), 172.0 (C), 197.6 (C); *m/z*

(CI) 334.1653 (MH^+. $C_{18}H_{24}NO_5$ requires 334.1654), 320 (4%), 278 (100), 234 (13).

Methyl (2*S*,5*E*)-6-(4-bromophenyl)-4-oxo-2-(*tert*-butoxycarbonylamino)hex-5-enoate 24. Using the general procedure above gave **24** as a white solid (0.07 g, 85%). Mp 78–79 °C; ν_{max}/cm^{-1} (NaCl) 3437 (NH), 3370, 2978 (CH), 1747 (CO), 1712 (CO), 1666 (C=C), 1611, 1488, 1168; $[\alpha]_D^{20}$ +42.4 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s, O^{t}Bu), 3.22 (1H, d, *J* 17.8 Hz, 3-*H*H), 3.41 (1H, d, *J* 17.8 Hz, 3-H*H*), 3.75 (3H, s, OMe), 4.58–4.64 (1H, m, 2-H), 5.56 (1H, d, *J* 8.0 Hz, NH), 6.69 (1H, d, *J* 16.0 Hz, 5-H), 7.40 (2H, d, *J* 8.0 Hz, ArH), 7.46–7.56 (3H, m, 6-H and ArH); δ_C (100 MHz, $CDCl_3$) 28.3 (CH_3), 42.6 (CH_2), 49.6 (CH), 52.7 (CH_3), 80.0 (C), 125.2 (C), 126.0 (CH), 129.8 (CH), 132.3 (CH), 133.0 (C), 142.5 (CH), 155.6 (C), 172.0 (C), 197.5 (C); *m*/*z* (FAB) 412.0755 (MH^+. $C_{18}H_{23}{}^{79}BrNO_5$ requires 412.0760), 358 (100%), 356 (89), 314 (23), 278 (22), 234 (7).

Methyl (2*S*,5*E*)-4-oxo-8-phenyl-2-(*tert*-butoxycarbonylamino)-oct-5-enoate 25. Using the general procedure above gave **25** as a colourless oil (0.09 g, 77%). ν_{max}/cm^{-1} (NaCl) 3439 (NH), 3371, 2978 (CH), 1749 (CO), 1714 (CO), 1630 (C=C), 1487, 1367, 1167; $[\alpha]_D^{19}$ +47.4 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s, O^{t}Bu), 2.51–2.58 (2H, m, 7-H_2), 2.76–2.81 (2H, m, 8-H_2), 3.06 (1H, dd, *J* 18.0, 4.0 Hz, 3-*H*H), 3.30 (1H, dd, *J* 18.0, 4.0 Hz, 3-H*H*), 3.73 (3H, s, OMe), 4.54 (1H, dt, *J* 8.8, 4.0 Hz, 2-H), 5.53 (1H, d, *J* 8.8 Hz, NH), 6.10 (1H, dt, *J* 16.0, 1.4 Hz, 5-H), 6.88 (1H, dt, *J* 16.0, 6.8 Hz, 6-H), 7.16–7.24 (2H, m, ArH), 7.28–7.34 (3H, m, ArH); δ_C (100 MHz, $CDCl_3$) 28.3 (CH_3), 34.2 (CH_2), 34.3 (CH_2), 41.8 (CH_2), 49.5 (CH), 52.6 (CH_3), 79.9 (C), 126.3 (CH), 128.3 (CH), 128.6 (CH), 130.3 (CH), 140.5 (C), 147.8 (CH), 155.6 (C), 172.0 (C), 197.7 (C); *m*/*z* (FAB) 362.1974 (MH^+. $C_{20}H_{28}NO_5$ requires 362.1967), 306 (94%), 262 (100), 203 (11), 176 (14), 160 (34).

Methyl (2*S*,5*E*)-6-(4-dimethylaminonaphthalen-1-yl)-4-oxo-2-(*tert*-butoxycarbonylamino)hex-5-enoate 31. Using the general procedure above gave **31** as a yellow oil (0.09 g, 61%). ν_{max}/cm^{-1} (NaCl) 3438 (NH), 3362, 2978 (CH), 1747 (CO), 1709 (CO), 1580, 1599, 1512; $[\alpha]_D^{23}$ +49.3 (*c* 0.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.45 (9H, s, O^{t}Bu), 2.96 (6H, s, NMe_2), 3.29 (1H, dd, *J* 17.7, 3.7 Hz, 3-*H*H), 3.53 (1H, dd, *J* 17.7, 3.7 Hz, 3-H*H*), 3.77 (3H, s, OMe), 4.61–4.70 (1H, m, 2-H), 5.64 (1H, d, *J* 8.7 Hz, NH), 6.75 (1H, d, *J* 15.8 Hz, 5-H), 7.04 (1H, d, *J* 8.0 Hz, ArH), 7.46–7.62 (2H, m, ArH), 7.76 (1H, d, *J* 8.0 Hz, ArH), 8.17 (1H, d, *J* 8.2 Hz, ArH), 8.23 (1H, d, *J* 8.2 Hz, ArH), 8.41 (1H, d, *J* 15.8 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 28.4 (CH_3), 42.7 (CH_2), 44.9 (CH_3), 49.7 (CH), 52.6 (CH_3), 80.0 (C), 113.3 (CH), 123.5 (CH), 125.0 (C), 125.2 (CH), 125.3 (CH), 125.4 (CH), 126.0 (CH), 126.9 (CH), 128.3 (C), 133.1 (C), 140.8 (CH), 154.0 (C), 155.6 (C), 172.2 (C), 197.5 (C); *m*/*z* (CI) 427.2239 (MH^+. $C_{24}H_{31}N_2O_5$ requires 427.2233), 353 (6%), 312 (6), 240 (12), 172 (12), 134 (10), 113 (26).

General procedure for the deprotection of Boc-compounds

To a solution of Boc-protected amino methyl ester (0.16 mmol) in 1 : 1 methanol–water (4 mL) was added caesium carbonate (0.21 mmol). The resultant suspension was stirred at room temperature for 48 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in water (10 mL) and acidified to pH 1 with hydrochloric acid (1 M). The aqueous layer was washed with dichloromethane (3 × 20 mL) and the combined organic layers were concentrated *in vacuo*. To a solution of the resulting residue (0.16 mmol) in dichloromethane (2 mL) was added trifluoroacetic acid (0.80 mmol) and the reaction mixture was stirred at room temperature under argon for 3 h. The reaction mixture was concentrated *in vacuo* to give the TFA salts, which were purified by recrystallisation from chloroform and methanol.

(2*S*,5*E*)-2-Amino-4-oxo-6-phenylhex-5-enoic acid 26. Using the general procedure above gave **26** as a white solid (0.04 g, 78%). Mp 112–114 °C (decomposition); ν_{max}/cm^{-1} (neat) 3028 (NH), 2914 (CH), 1738 (CO), 1655 (C=C), 1495, 1184, 1134; $[\alpha]_D^{19}$ +23.3 (*c* 1.0, MeOH); δ_H (400 MHz, CD_3OD) 3.43 (1H, dd, *J* 18.5, 6.1 Hz, 3-*H*H), 3.48–3.56 (1H, m, 3-H*H*), 4.22–4.28 (1H, m, 2-H), 6.92 (1H, d, *J* 16.2 Hz, 5-H), 7.40–7.48 (3H, m, ArH), 7.62–7.69 (2H, m, ArH), 7.74 (1H, d, *J* 16.2, 6-H); δ_C (100 MHz, CD_3OD) 40.9 (CH_2), 50.2 (CH), 126.1 (CH), 129.7 (CH), 130.2 (CH), 132.1 (CH), 135.6 (C), 146.0 (CH), 171.8 (C), 198.0 (C); *m*/*z* (FAB) 220.0973 (MH^+. $C_{12}H_{14}NO_3$ requires 220.0974), 175 (7%), 148 (16), 132 (12).

(2*S*,5*E*)-2-Amino-6-(4-bromophenyl)-4-oxohex-5-enoic acid 27. Using the general procedure above gave **27** as a white solid (0.14 g, 93%). Mp 151–152 °C (decomposition); ν_{max}/cm^{-1} (neat) 3364 (NH), 3061, 1684 (CO), 1607 (C=C), 1547, 1487, 1397, 1339; $[\alpha]_D^{18}$ +55.0 (*c* 0.3, MeOH); δ_H (400 MHz, CD_3OD) 3.23 (1H, dd, *J* 18.8, 9.3 Hz, 3-*H*H), 3.46 (1H, dd, *J* 18.8, 3.4 Hz, 3-H*H*), 3.95 (1H, dd, *J* 9.3, 3.4 Hz, 2-H), 6.91 (1H, d, *J* 16.3 Hz, 5-H), 7.56–7.62 (4H, m, ArH), 7.67 (1H, d, *J* 16.3 Hz, 6-H); δ_C (100 MHz, CD_3OD) 40.9 (CH_2), 50.2 (CH), 126.2 (C), 126.7 (CH), 131.3 (CH), 133.4 (CH), 134.8 (C), 144.6 (CH), 171.5 (C), 197.7 (C); *m*/*z* (FAB) 298.0067 (MH^+. $C_{12}H_{13}{}^{79}BrNO_3$ requires 298.0079), 292 (16%), 254 (12), 243 (21), 209 (18), 155 (29), 138 (15).

(2*S*,5*E*)-2-Amino-4-oxo-8-phenyloct-5-enoic acid 28. Using the general procedure above gave **28** as a white solid (0.03 g, 98%). Mp 94–96 °C (decomposition); ν_{max}/cm^{-1} (neat) 3161 (NH), 3030, 2918 (CH), 1736 (CO), 1661 (C=C), 1640, 1497, 1180; $[\alpha]_D^{18}$ +10.2 (*c* 0.3, MeOH); δ_H (400 MHz, CD_3OD) 2.54–2.63 (2H, m, 7-H_2), 2.82 (2H, t, *J* 7.4 Hz, 8-H_2), 3.20 (1H, dd, *J* 18.8, 8.0 Hz, 3-*H*H), 3.28–3.37 (1H, m, 3-H*H*), 4.11 (1H, dd, *J* 8.0, 3.6 Hz, 2-H), 6.17 (1H, dt, *J* 16.0, 1.4 Hz, 5-H), 7.03 (1H, dt, *J* 16.0, 6.9 Hz, 6-H), 7.12–7.31 (5H, m, ArH); δ_C (100 MHz, CD_3OD) 35.3 (CH_2), 35.5 (CH_2), 40.4 (CH_2), 50.5 (CH) 127.3 (CH), 129.5 (CH), 129.6 (CH), 130.8 (CH), 142.1 (C), 150.5 (CH), 172.5 (C), 198.1 (C); *m*/*z* (FAB) 248.1289 (MH^+. $C_{14}H_{18}NO_3$ requires 248.1287), 203 (8%), 146 (12), 160 (8), 132 (4).

(2*S*,5*E*)-2-Amino-6-(4-dimethylaminonaphthalen-1-yl)-4-oxohex-5-enoic acid 32. Using the general procedure above gave **32** as an orange solid (0.04 g, 46%). Mp 78–80 °C (decomposition); ν_{max}/cm^{-1} (neat) 3009 (NH), 2930 (CH), 1738 (CO), 1667 (C=C), 1609, 1566, 1180; $[\alpha]_D^{17}$ +42.5 (*c* 0.8, MeOH); δ_H (400 MHz, CD_3OD) 3.00 (6H, s, NMe_2), 3.47–3.62 (2H, m, 3-H_2), 4.39 (1H, dd, *J* 6.0, 4.4 Hz, 2-H), 6.95 (1H, d, *J* 15.9 Hz, 5-H), 7.21 (1H, d, *J* 8.1 Hz, ArH), 7.52–7.69 (2H, m, ArH), 7.94 (1H, d, *J* 8.1 Hz, ArH), 8.21–8.32 (2H, m, ArH), 8.57 (1H, d, *J* 15.9 Hz, 6-H); δ_C (100 MHz, CD_3OD) 41.0 (CH_2), 45.7 (CH_3), 50.0 (CH), 115.5 (CH), 124.7 (CH), 125.4 (CH), 126.6 (CH), 127.1 (CH), 127.2 (CH), 128.1 (C), 128.4 (CH), 129.0 (C), 134.5 (C), 142.3 (CH), 152.8 (C), 171.3 (C), 197.5 (C); *m*/*z* (FAB) 313.1551

(MH^+. $C_{18}H_{21}N_2O_3$ requires 313.1552), 291 (4%), 268 (3), 241 (8), 224 (18), 198 (8), 185 (11).

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