Synthesis of β-substituted alanines *via* Michael addition of nucleophiles to dehydroalanine derivatives

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Several β-substituted alanines are synthesised in high yields by a Michael addition of nucleophiles to *N*-acyl-*N*-(*tert*-butoxycarbonyl)dehydroalanine methyl ester, using mild reaction conditions and simple work-up procedures. The same method can be applied to dipeptides containing dehydroalanine.

Introduction

In recent years a large number of non-proteinogenic amino acids have been isolated from plant and bacterial sources. Among these are a group of β-substituted alanines, some of which exhibit important biological activities, such as β-(pyrazol-1-yl)alanine which has hypoglycaemic properties,[1] and quisqualic acid, which possesses potent neuroexcitatory activities.[2,3] These compounds are isolated from pressed juice of watermelon (*Citrullus vulgaris*) and from Rangoon Creeper (*Quisqualis indica*), respectively.[4] Another heterocyclic β-substituted alanine, *viz.* β-(1,2,4-triazol-1-yl)alanine, is known as an important metabolite (in plants) of the fungicide myclobutanil.[5]

As far back as 1965, Zahn reported a 96.5% yield in a synthesis of a β-substituted alanine by the addition of N^{α}-acetyl-L-lysine to *N*-acetyldehydroalanine ethyl ester in the presence of sodium hydroxide.[6] Later, a 64% yield in a Michael addition of benzylamine to Boc-ΔAla-OMe † in the absence of inorganic base was obtained.[7] Recently, other Michael additions of nitrogen nucleophiles to dehydroalanine derivatives have been reported, either in $FeCl_3$-catalysed reactions to give various β-substituted alanine derivatives in yields varying within the range 13–98%[8] or in the presence of inorganic base to give two such compounds, *viz.* β-(pyrazol-1-yl)alanine and β-(1,2,4-triazol-1-yl)alanine, in fair yields (54 and 78%, respectively).[9] In the latter case, a solid-phase strategy was used to circumvent difficulties met in attempted solution syntheses, namely difficult purification of the products due to similarity of their solubility to that of the corresponding starting materials. Thus, *N*-acetyldehydroalanine was anchored to a Wang resin and treated with nucleophiles in the presence of potassium carbonate under forcing conditions (6 to 15 equiv. of nucleophile were used in 2-day reactions at temperatures within the range 50–60 °C).

Our recently reported high-yield synthesis of *N*-acyl-*N*-(*tert*-butoxycarbonyl)dehydroalanine (ΔAla) derivatives[10,11] made these compounds available in large amounts, ready for further applications. Indeed we were able to use these compounds with success as substrates for the Michael reaction, which seemed to be assisted by the second substituent on the nitrogen atom.[12] We now report the results obtained in the synthesis of amino acid and peptide derivatives of several β-substituted alanines by this procedure.

† ΔAla means dehydroalanine.

Results and discussion

The methyl ester of *N*,*N*-bis(*tert*-butoxycarbonyl)dehydroalanine [Boc-ΔAla(*N*-Boc)-OMe **1**][11] was treated at room temperature with one mole equivalent of a nucleophile (pyrazole, 1,2,4-triazole or imidazole) in acetonitrile with six mole equivalents of potassium carbonate to give compounds **1a**, **1b** and **1c** in excellent yields (Scheme 1 and Table 1 entries 1, 2 and 3, respectively).

Comparison of entries 1 and 2 in Table 1 with the corresponding results of Barbaste *et al.*[9], shows that the presence of two substituents on the nitrogen atom greatly increases the reactivity of the β-carbon atom of ΔAla towards nucleophilic attack. This was confirmed when Boc-ΔAla-OMe was substituted for Boc-ΔAla(*N*-Boc)-OMe, as in this case no reaction with pyrazole was detected under the same conditions. This enhanced reactivity allows the reactions to proceed to completion without the need for an excess of nucleophile, thus greatly simplifying the work-up procedures.

The scope of this reaction was further investigated with respect to other nitrogen nucleophiles such as pyrrole, indole and carbazole, but much lower yields were obtained, which may be related to a lower acidity of these compounds as compared with the previous ones. In fact, while no product had been isolated in the attempted reaction with pyrrole, the reaction with 2-formylpyrrole was quantitative and a yield of 82% was obtained with 2-acetylpyrrole, even when only one mole equivalent of nucleophile was used (Table 1, entries 4–6, compounds **1d**–**1f**, respectively). In the case of indole, the NMR spectrum of the reaction mixture of a 3-day reaction with 1 equiv. of nucleophile showed a 1:1 ratio of addition product to unchanged dehydroamino acid. However, this ratio could be improved to 5:1 when an excess of indole (3 equiv.) was used under identical conditions, and work-up of the reaction mixture gave a 49% yield of pure **1g** after recrystallisation (Table 1, entry 7). Much improved results were also obtained when these heterocycles were activated with an electron-withdrawing substituent (Table 1 entries 8, 10–12 and 14–16), but not when an electron-releasing group was placed at the same position (Table 1 entry 9). A broad correlation could be observed between reaction yields and the chemical shift of the nitrogen protons of the heterocyclic nucleophiles; in fact, from the data in Table 1 one may infer that whenever the chemical shift of the nucleophile NH proton used is equal to or higher than 11.68 ppm, as measured in DMSO, no more than 1 equiv. of nucleophile is required for a high yielding reaction.

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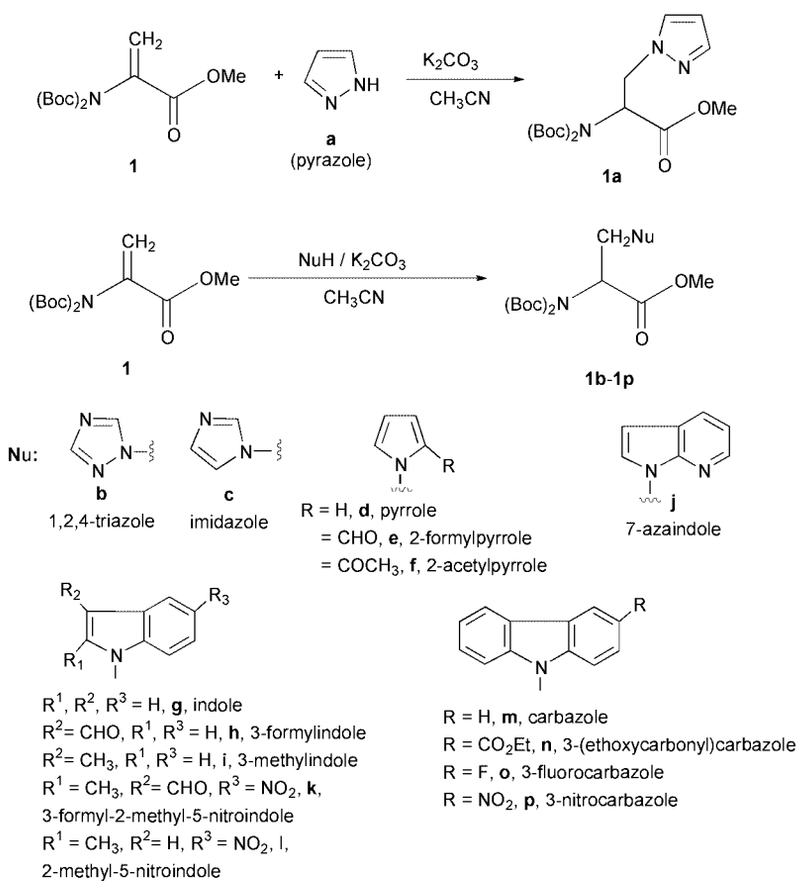
Table 1 Results obtained in the synthesis of heterocyclic β-substituted alanine derivatives by addition of a nucleophile to Boc-ΔAla(*N*-Boc)-OMe **1**

Entry	NuH (mol. equiv.)		Product (compound no.)	Yield (%)[a]	δ_H (ppm)[b]
1	**a**	1	Boc-Ala[*N*-Boc-β-(pyrazol-1-yl)]-OMe **1a**	98	
2	**b**	1	Boc-Ala[*N*-Boc-β-(1,2,4-triazol-1-yl)]-OMe **1b**	99	
3	**c**	1	Boc-Ala[*N*-Boc-β-(imidazol-1-yl)]-OMe **1c**	98	
4	**d**	3	Boc-Ala[*N*-Boc-β-(pyrrol-1-yl)]-OMe **1d**	[c]	10.75
5	**e**	1	Boc-Ala[*N*-Boc-β-(2-formylpyrrol-1-yl)]-OMe **1e**	99	12.08
6	**f**	1	Boc-Ala[*N*-Boc-β-(2-acetylpyrrol-1-yl)]-OMe **1f**	82	11.76
7	**g**	3	Boc-Ala[*N*-Boc-β-(indol-1-yl)]-OMe **1g**	49[d]	11.12
8	**h**	1	Boc-Ala[*N*-Boc-β-(3-formylindol-1-yl)]-OMe **1h**	99	12.12
9	**i**	3	Boc-Ala[*N*-Boc-β-(3-methylindol-1-yl)]-OMe **1i**	[c]	10.75
10	**j**	1.1	Boc-Ala[*N*-Boc-β-(7-azaindol-1-yl)]-OMe **1j**	93	11.68
11	**k**	1	Boc-Ala[*N*-Boc-β-(3-formyl-2-methyl-5-nitroindol-1-yl)]-OMe **1k**	87	12.53
12	**l**	1	Boc-Ala[*N*-Boc-β-(2-methyl-5-nitroindol-1-yl)]-OMe **1l**	93	11.71
13	**m**	3	Boc-Ala[*N*-Boc-β-(carbazol-9-yl)]-OMe **1m**	53[d]	11.29
14	**n**	1	Boc-Ala{*N*-Boc-β-[3-(ethoxycarbonyl)carbazol-9-yl]}-OMe **1n**	93	11.71
15	**o**	1	Boc-Ala[*N*-Boc-β-(3-fluorocarbazol-9-yl)]-OMe **1o**	80	11.71
16	**p**	1	Boc-Ala[*N*-Boc-β-(3-nitrocarbazol-9-yl)]-OMe **1p**	93	12.06
17	**q**	1	Boc-Ala[*N*-Boc-β-phenylthio]-OMe **1q**	81	
18	**r**	1	Boc-Ala[*N*-Boc-β-methoxycarbonylmethylthio]-OMe **1r**	91	

[a] Pure non-recrystallised material. [b] For the NH proton of NuH (300 MHz; DMSO; Me_4Si). [c] No reaction was detected. [d] Pure recrystallised material.



Scheme 1

The products **1c**, **1g** and **1j** of the reactions with imidazole, indole and 7-azaindole are isosteres of the corresponding histidine, tryptophan and 7-azatryptophan derivatives, respectively; 7-azatryptophan is used as a fluorescent probe in peptide labelling.[9]

This method was extended successfully to the addition of sulfur nucleophiles, namely thiophenol and methyl mercaptoacetate (Scheme 2, Table 1, entries 17 and 18).

This reaction was also investigated with several dehydroalanine derivatives having unsymmetrical double substitution at their nitrogen atom (Scheme 3, Table 2). In many cases a large amount of Boc-ΔAla-OMe was detected in the reaction mixture. We believe that this might have resulted from competitive nucleophilic cleavage of the substituents at the nitrogen atom of the dehydroalanine derivative in a manner similar to that described by Ragnarsson and co-workers[13] for cleavage of the acyl group from *N*-acyl-*N*-Boc-amines with nitrogen nucleophiles such as tetramethylguanidine and 2-(diethylamino)-ethylamine. This competition seems to occur in connection with the 4-nitrobenzoyl group (Table 2, entries 4–6), which can be easily cleaved by nucleophiles, and also with weak nucleophiles such as pyrazole (Table 2, entries 1, 4, 7 and 10). In fact, in the

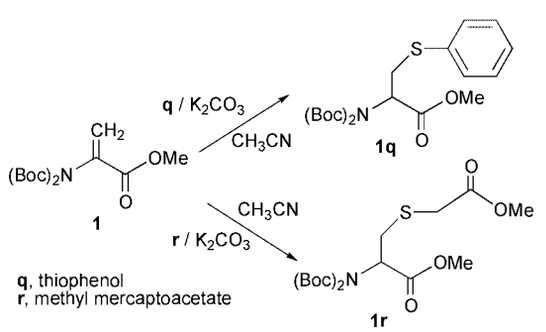
Table 2 Results obtained in the synthesis of heterocyclic β-substituted alanine derivatives by addition to P-ΔAla(*N*-Boc)-OMe (**2**–**5**)

Entry	P	NuH	Product (compound no.)	Yield (%)[a]
1	**2**	**a**	Bz-Ala[*N*-Boc-β-(pyrazol-1-yl)]-OMe **2a**	53[b]
2	**2**	**b**	Bz-Ala[*N*-Boc-β-(1,2,4-triazol-1-yl)]-OMe **2b**	98
3	**2**	**j**	Bz-Ala[*N*-Boc-β-(7-azaindol-1-yl)]-OMe **2j**	92
4	**3**	**a**	$Bz(NO_2)$-Ala[*N*-Boc-β-(pyrazol-1-yl)]-OMe[c] **3a**	[d]
5	**3**	**b**	$Bz(NO_2)$-Ala[*N*-Boc-β-(1,2,4-triazol-1-yl)]-OMe **3b**	67[e]
6	**3**	**j**	$Bz(NO_2)$-Ala[*N*-Boc-β-(7-azaindol-1-yl)]-OMe **3j**	54[f]
7	**4**	**a**	Z-Ala[*N*-Boc-β-(pyrazol-1-yl)]-OMe **4a**	48[g]
8	**4**	**b**	Z-Ala[*N*-Boc-β-(1,2,4-triazol-1-yl)]-OMe **4b**	98
9	**4**	**j**	Z-Ala[*N*-Boc-β-(7-azaindol-1-yl)]-OMe **4j**	99
10	**5**	**a**	$Z(NO_2)$-Ala[*N*-Boc-β-(pyrazol-1-yl)]-OMe **5a**[c]	37[h]
11	**5**	**b**	$Z(NO_2)$-Ala[*N*-Boc-β-(1,2,4-triazol-1-yl)]-OMe **5b**	98
12	**5**	**g**	$Z(NO_2)$-Ala[*N*-Boc-β-(indol-1-yl)]-OMe **5g**	46
13	**5**	**j**	$Z(NO_2)$-Ala[*N*-Boc-β-(7-azaindol-1-yl)]-OMe **5j**	87

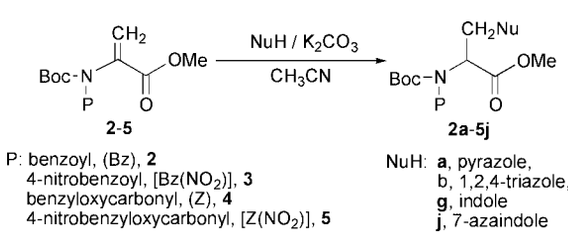
[a] Pure non-recrystallised material. [b] Boc-ΔAla-OMe was also isolated, in 22% yield. [c] $Bz(NO_2)$ = 4-nitrobenzoyl, $Z(NO_2)$ = 4-nitrobenzyloxycarbonyl. [d] Only Boc-ΔAla-OMe was isolated, in 82% yield. [e] Boc-ΔAla-OMe was also isolated, in 28% yield. [f] Boc-ΔAla-OMe was also isolated, in 42% yield. [g] Boc-ΔAla-OMe was also isolated, in 30% yield. [h] Boc-ΔAla-OMe was also isolated, in 45% yield.

Table 3 Yields in the selective cleavage of heterocyclic β-substituted alanine derivatives

Reactant	Deprotection reactant	Product	Yield (%)
1b	TFA	H-Ala[β-(1,2,4-triazol-1-yl)]-OMe·2TFA **6b**	80
1j	TFA	H-Ala[β-(7-azaindol-1-yl)]-OMe·TFA **6j**	85
1m	TFA	H-Ala[β-(carbazol-9-yl)]-OMe·TFA **6m**	91
2b	DEAEA	Boc-Ala[β-(1,2,4-triazol-1-yl)]-OMe **7b**	78
5b	Al/Hg	Boc-Ala[β-(1,2,4-triazol-1-yl)]-OMe **7b**	86
1a	NaOH	Boc-Ala[*N*-Boc-β-(pyrazol-1-yl)]-OH **8a**	91
1b	NaOH	Boc-Ala[*N*-Boc-β-(1,2,4-triazol-1-yl)]-OH **8b**	86
1h	NaOH	Boc-Ala[*N*-Boc-β-(3-formylindol-1-yl)]-OH **8h**	89
1j	NaOH	Boc-Ala[*N*-Boc-β-(7-azaindol-1-yl)]-OH **8j**	94



Scheme 2



Scheme 3

case of the strong nucleophile 1,2,4-triazole all reactions were almost quantitative except for that with the 4-nitrobenzoyl derivative (Table 2, entries 2, 5, 8 and 11), thus showing that competitive cleavage may be overcome when the nucleophile is sufficiently strong to provide fast addition. Slightly lower yields were obtained in the corresponding reactions with the weaker nucleophile 7-azaindole (Table 2, entries 3, 6, 9 and 13).

As shown in Table 3, the Boc groups can be easily removed from the *N*,*N*-bis(*tert*-butoxycarbonyl) β-substituted alanine methyl esters by treatment with TFA, as exemplified in the preparation of compounds **6b**, **6j** and **6m**. Although in most cases the use of a combination of two different substituents at the α-amine nitrogen atom does not improve the yields of addition product, it allows selective cleavage of one of these substituents to yield an N-protected product. Thus, 2-(diethylamino)ethylamine (DEAEA)[13] was used to cleave benzoyl from **2b**, while 4-nitrobenzyloxycarbonyl was cleaved from **5b** by reduction with mercury-activated aluminium.[14] In both cases Boc-Ala[β-(1,2,4-triazol-1-yl)]-OMe **7b** was obtained in good yields as shown in Table 3. Saponification of the *N*,*N*-bis(*tert*-butoxycarbonyl) amino acid methyl esters gives the corresponding *N*,*N*-bis(*tert*-butoxycarbonyl) amino acids, as exemplified in the preparation of compounds **8a**, **8b**, **8h** and **8j** (Table 3). Any of these N-protected compounds can be readily used for peptide-chain elongation. Thus, by using standard dicyclohexylcarbodiimide (DCC) couplings, compounds **8a** and **8j** (Table 3) were treated with H-L-Phe-OEt to yield Boc-DL-Ala[*N*-Boc-β-(pyrazol-1-yl)]-L-Phe-OEt **9a** and Boc-DL-Ala[*N*-Boc-β-(7-azaindol-1-yl)]-L-Phe-OEt **9j** in yields of 80 and 86%, respectively. HPLC analysis of the reaction products indicated 1:1 mixtures of diastereomers, which shows that, as expected, the addition reaction gives rise to a racemic mixture with regard to the chiral centre generated within the β-substituted alanine residue.

The method described above can also be applied for direct reaction of nitrogen nucleophiles with dipeptides containing dehydroalanine. Table 4 shows the results obtained in the addition of various heterocyclic nucleophiles to either Tos-Gly(*N*-Boc)-ΔAla(*N*-Boc)-OMe or Boc-Ala(*N*-Boc)-ΔAla(*N*-Boc)-OMe.

Our results show that *N*,*N*-disubstituted dehydroamino acid residues are good substrates for nucleophilic attack in a Michael reaction, which allows the synthesis of a variety of β-substituted alanine derivatives under mild conditions and using very simple work-up procedures; in most cases the products are obtained in quantitative yields. Boc-ΔAla(*N*-Boc)-OMe proved to be an excellent substrate for nucleophilic attack, although other combinations of *N*-acyl groups can also be used, which increases the versatility of the method.

Table 4 Results obtained in the synthesis of heterocyclic β-substituted alanine peptides by addition of a nucleophile to Tos-Gly(*N*-Boc)-ΔAla(*N*-Boc)-OMe or Boc-Ala(*N*-Boc)-ΔAla(*N*-Boc)-OMe

Entry	NuH	Product (compound no.)	Yield (%)
1	**a**	Tos-Gly(*N*-Boc)-Ala[*N*-Boc-β-(pyrazol-1-yl)]-OMe **10a**	76
2	**b**	Tos-Gly(*N*-Boc)-Ala[*N*-Boc-β-(1,2,4-triazol-1-yl)]-OMe **10b**	99
3	**c**	Tos-Gly(*N*-Boc)-Ala[*N*-Boc-β-(imidazol-1-yl)]-OMe **10c**	75
4	**h**	Tos-Gly(*N*-Boc)-Ala[*N*-Boc-β-(3-formylindol-1-yl)]- OMe **10h**	74
5	**j**	Tos-Gly(*N*-Boc)-Ala[*N*-Boc-β-(7-azaindol-1-yl)]-OMe **10j**	90
6	**b**	Boc-Ala(*N*-Boc)-Ala[*N*-Boc-β-(1,2,4-triazol-1-yl)]-OMe **11b**	98

Experimental

General methods

All mps were determined on a Gallenkamp melting point apparatus and are uncorrected. TLC analyses were carried out on 0.25 mm thick precoated silica plates (Merck Fertigplatten Kieselgel $60F_{254}$) and spots were visualised under UV or by exposure to vaporised iodine. Preparative chromatography was carried out on Merck Kieselgel 60 (230–400 mesh). ^{1}H NMR spectra were recorded on a Varian 300 spectrometer for samples in ≈5% $CDCl_3$ solution at 25 °C, when not otherwise stated. All shifts are given in δ ppm using δ_H $Me_4Si = 0$ as reference. *J*-Values are given in Hz. Assignments were made by comparison of chemical shifts, peak multiplicities and *J*-values. ^{13}C NMR spectra were determined in the same instrument at 75.4 MHz using the solvent peak as internal reference. Elemental analyses of crystalline derivatives and some oils were carried out on a Leco CHNS 932 instrument. Analysis of diastereomers by HPLC experiments was run on a Shimadzu instrument, type 6A, connected to a Merck prepacked column, type Hibar RT 250-4, filled with LiChrospher 100 CH-18/2 (5 μm) and the eluent was a mixture of acetonitrile and water. The peaks were measured with a Shimadzu integrator, type C-R6A Chromatopack.

Preparation of dehydroalanine derivatives

Synthesis of Boc-ΔAla(*N*-Boc)-OMe 1, Bz-ΔAla(*N*-Boc)-OMe 2, Z-ΔAla(*N*-Boc)-OMe 4 and Z(NO_2)-ΔAla(*N*-Boc)-OMe 5. These compounds have been described elsewhere.[11]

Synthesis of Bz(NO_2)-ΔAla(*N*-Boc)-OMe 3. The same procedure as above was used in a 5-mmolar scale to synthesise this compound in 71% yield, mp 104–104.5 °C (from ethyl acetate–diethyl ether) (Found: C, 54.9; H, 5.2; N, 7.95. Calc. for $C_{16}H_{18}N_2O_7$: C, 54.9; H, 5.2; N, 8.0%); δ_H 1.29 (9 H, s, Boc), 3.86 (3 H, s, OMe), 5.91 (1 H, s, βCH_2), 6.60 (1 H, s, βCH_2), 7.85 [2 H, d, *J* 8.7, Bz(NO_2)], 8.31 [2 H, d, *J* 8.7, Bz(NO_2)]; δ_C 27.50, 52.85, 84.90, 98.55, 123.46, 126.91, 128.65, 135.10, 142.07, 149.22, 150.94, 163.41.

Synthesis of Boc-Ala(*N*-Boc)-ΔAla(*N*-Boc)-OMe 11. This compound has been described previously.[11]

Synthesis of Tos-Gly(*N*-Boc)-ΔAla(*N*-Boc)-OMe 10. The same procedure as above was used in a 5-mmolar scale to synthesise this compound in 96% yield, mp 60.5–62.5 °C (from diethyl ether–*n*-hexane) (Found: C, 54.2; H, 6.3; N, 5.3; S, 6.3. Calc. for $C_{23}H_{32}N_2O_9S$: C, 53.9; H, 6.3; N, 5.5; S, 6.2%); δ_H 1.24 (9 H, s, Boc), 1.49 (9 H, s, Boc), 2.43 (3 H, s, CH_3 Tos), 3.80 (3 H, s, OMe), 5.22 (2 H, s, CH_2 Gly), 5.74 (1 H, d, *J* 0.6, βCH_2 ΔAla), 6.52 (1 H, d, *J* 0.6, βCH_2 ΔAla), 7.29 (2 H, d, *J* 8.4, ArH T), 7.93 (2 H, d, *J* 8.4, ArH T); δ_C 21.62, 27.76, 27.79, 51.10, 52.48, 84.58, 84.63, 126.78, 128.72, 129.00, 134.47, 136.77, 144.17, 150.52, 151.19, 163.29, 170.36.

Michael addition to *N*,*N*-bis(*tert*-butoxycarbonyl)dehydroalanine methyl ester

General method. As described elsewhere,[12] to a solution of 1 mmol of Boc-ΔAla(*N*-Boc)-OMe in acetonitrile (10 cm^3) was added K_2CO_3 (6 equiv.), followed by the nucleophile (1 equiv.) with rapid stirring at room temperature. The reaction was monitored by TLC and when no starting material was detected, the solution was filtered and evaporated at reduced pressure to give the required product.

Synthesis of 1a, 1b, 1c, 1g, 1h, 1j and 1n. These compounds have been synthesised as described elsewhere.[12]

Synthesis of 1e. The above general method was used with 2-formylpyrrole to prepare this compound as a crystalline material (99%), mp 73–74 °C (from diethyl ether–*n*-hexane) (Found: C, 57.6; H, 7.1; N, 7.0. Calc. for $C_{19}H_{28}N_2O_7$: C, 57.6; H, 7.1; N, 7.1%); δ_H 1.41 (18 H, s, Boc), 3.78 (3 H, s, OMe), 4.54 (1 H, dd, *J* 10.2 and 13.8, βCH_2), 5.25 (1 H, dd, *J* 4.5 and 13.8, βCH_2), 5.48 (1 H, dd, *J* 4.5 and 10.2, αCH), 6.21 (1 H, dd, *J* 2.7 and 4.1, 4-H pyr.), 6.81 (1 H, m, 3-H pyr.), 6.93 (1 H, dd, *J* 1.5 and 4.1, 5-H pyr.), 9.53 (1 H, s, CHO); δ_C 27.82, 48.45, 52.35, 57.95, 83.34, 109.80, 120.86, 131.64, 132.22, 151.44, 169.03, 179.30.

Synthesis of 1f. The above general method was used with 2-acetylpyrrole to prepare this compound as an oil which failed to crystallise (82%); δ_H 1.40 (18 H, s, Boc), 2.42 (3H, s, CH_3CO), 3.78 (3 H, s, OMe), 4.47 (1 H, dd, *J* 10.2 and 12.0, βCH_2), 5.29 (1 H, dd, *J* 13.8 and 9.0, βCH_2), 5.54 (1 H, dd, *J* 10.2 and 7.4, αCH), 6.12 (1 H, dd, *J* 3.9 and 3.2, 4-H pyr.), 6.71 (1 H, m, 3-H pyr.), 6.94 (1 H, dd, *J* 4.2 and 3, 5-H, pyr.); δ_C 26.99, 27.83, 49.15, 52.30, 58.10, 83.14, 108.33, 120.38, 130.61, 131.18, 151.53, 169.25, 188.31.

Synthesis of 1k. The above general method was used with 3-formyl-2-methyl-5-nitroindole to prepare this compound as a crystalline material (87%), mp 161–162 °C (from diethyl ether–*n*-hexane) (Found: C, 56.9; H, 6.1; N, 8.3. Calc. for $C_{24}H_{31}N_3O_9$: C, 57.0; H, 6.2; N, 8.3%); δ_H 1.28 (18 H, s, Boc), 2.78 (3 H, s, 2-CH_3 ind.), 3.83 (3 H, s, OMe), 4.81–4.98 (2 H, complex signal, βCH_2), 5.36 (1 H, dd, *J* 4.5 and 10.2, αCH), 7.42 (1 H, d, *J* 9.3, 7-H ind.), 8.16 (1 H, dd, *J* 2.1 and 9.3, 6-H ind.), 9.17 (1 H, d, *J* 2.1, 4-H ind.), 10.22 (1 H, s, 3-CHO); δ_C 10.54, 27.63, 43.57, 52.77, 56.83, 84.32, 109.65, 115.82, 117.57, 118.71, 125.25, 139.85, 143.95, 150.56, 151.81, 168.33, 183.86.

Synthesis of 1l. The above general method was used with 2-methyl-5-nitroindole to prepare this compound as a crystalline material (93%), mp 110–111 °C (from diethyl ether–*n*-hexane) (Found: C, 57.7; H, 6.5; N, 8.8. Calc. for $C_{23}H_{31}N_3O_8$: C, 57.85; H, 6.5; N, 8.8%); δ_H 1.28 (18 H, s, Boc), 2.46 (3 H, s, 2-CH_3 ind.), 3.82 (3 H, s, OMe), 4.77 (12 H, dd, *J* 4.5 and 15.3, βCH_2), 4.87 (1 H, dd, *J* 9.9 and 15.3, βCH_2), 5.29 (1 H, dd, *J* 4.5 and 9.9, αCH), 6.43 (1 H, s, 3-H ind.), 7.30 (1 H, d, *J* 9.0, 7-H ind.), 8.02 (1H, dd, *J* 2.4 and 9.0, 6-H ind.), 8.44 (1 H, d, *J* 2.4, 4-H ind.); δ_C 12.61, 27.61, 43.39, 52.56, 57.69, 83.77, 103.17, 108.76, 116.39, 116.53, 127.48, 140.33, 141.58, 151.68, 168.77.

Synthesis of 1m. The above general method was used with carbazole to prepare this compound as an oily material, which

was crystallised from diethyl ether–*n*-hexane to give a pure crystalline product (53%), mp 120–121 °C (from diethyl ether–*n*-hexane) (Found: C, 66.9; H, 7.0; N, 5.9. Calc. for $C_{26}H_{32}N_2O_6$: C, 66.65; H, 6.9; N, 6.0%); δ_H 1.18 (18 H, s, Boc), 3.83 (3 H, s, OMe), 4.90 (2 H, comp. signal, βCH_2), 5.46 (1H, dd, *J* 4.2 and 10.2, αCH), 7.22–8.07 (8 H, complex signal, ArH carb.); δ_C 27.45, 42.87, 52.44, 57.40, 83.21, 108.55, 119.21, 120.16, 123.08, 125.75, 140.41, 151.42, 169.43.

Synthesis of 1o. The above general method was used with 3-fluorocarbazole to prepare this compound as a crystalline material (80%), mp 131.5–133 °C (from diethyl ether–*n*-hexane) (Found: C, 64.0; H, 6.6; N, 5.9. Calc. for $C_{26}H_{31}FN_2O_6$: C, 64.2; H, 6.4; N, 5.8%); δ_H 1.19 (18 H, s, Boc), 3.83 (3 H, s, OMe), 4.97 (1H, dd, *J* 4.6 and 15.4, βCH_2), 5.06 (1 H, dd, *J* 9.2 and 15.4, βCH_2), 5.42 (1 H, dd, *J* 4.6 and 9.2, αCH), 7.13–7.48 (5 H, complex signal, 1-H, 2-H, 6-H, 7-H, 8-H carb.), 7.70 (1 H, dd, *J* 2.4 and 8.9, 5-H carb.), 8.00 (1 H, d, *J* 7.9, 4-H carb.); δ_C 27.52, 43.35, 52.65, 56.96, 83.64, 108.49, 109.61, 117.02, 120.85, 121.16, 121.62, 122.86, 122.90, 127.57, 140.94, 141.63, 143.76, 151.62, 168.96.

Synthesis of 1p. The above general method was used with 3-nitrocarbazole to prepare this compound as a crystalline material (93%), mp 142.5–143 °C (from diethyl ether–*n*-hexane) (Found: C, 60.7; H, 6.1; N, 8.1. Calc. for $C_{26}H_{31}N_3O_8$: C, 60.8; H, 6.1; N, 8.2%); δ_H 1.20 (18 H, s, Boc), 3.84 (3 H, s, OMe), 5.03 (1 H, dd, *J* 4.8 and 15.2, βCH_2), 5.13 (1 H, dd, *J* 9.6 and 15.2, βCH_2), 5.46 (1 H, dd, *J* 4.8 and 9.6, αCH), 7.27–7.59 (4 H, complex signal, 1-, 6-, 7- and 8-H carb.), 8.13 (1 H, d, *J* 8.1, 2-H carb.), 8.37 (1 H, dd, *J* 2.4 and 9.0, 5-H carb.), 8.99 (1 H, d, *J* 2.1, 4-H carb.); δ_C 27.53, 43.37, 52.68, 56.96, 83.69, 108.50, 109.61, 117.07, 120.89, 121.19, 121.67, 122.86, 122.93, 127.53, 141.10, 142.02, 145.05, 151.62, 169.03.

Synthesis of 1q. The above general method was used with thiophenol to prepare this compound as a crystalline material (81%), mp 68–70 °C (from diethyl ether–*n*-hexane) (Found: C, 58.2; H, 7.1; N, 3.65; S, 7.7. Calc. for $C_{20}H_{29}NO_6S$: C, 58.4; H, 7.1; N, 3.4; S, 7.8%); δ_H 1.47 (18 H, s, Boc), 3.49 (1 H, dd, *J* 9.9 and 14.6, βCH_2), 3.73 (3 H, s, OMe), 3.76 (1 H, dd, *J* 4.8 and 14.6, βCH_2), 5.12 (1 H, dd, *J* 4.8 and 9.9, αCH), 7.20–7.54 (5 H, m, ArH); δ_C 27.86, 34.76, 52.38, 57.78, 83.24, 126.40, 128.94, 129.68, 135.59, 151.76, 170.16.

Synthesis of 1r. The above general method was used with methyl mercaptoacetate to prepare this compound as a crystalline material (91%), mp 50.5–52 °C (from diethyl ether–*n*-hexane) (Found: C, 50.4; H, 7.3; N, 3.55. Calc. for $C_{17}H_{29}NO_8S$: C, 50.1; H, 7.2; N, 3.4%); δ_H 1.48 (18 H, s, Boc), 3.07–3.44 (4 H, m, βCH_2 + CH_2 thiol), 3.71 (6 H, s, CH_3 thiol + OMe), 5.11 (1 H, dd, *J* 5.4 and 9.5, αCH); δ_C 27.04, 32.74, 33.11, 52.31, 52.36, 57.12, 83.39, 151.86, 169.96, 170.48.

Michael addition to *N*-acyl-*N*-(*tert*-butyloxycarbonyl)dehydroalanine methyl ester

General method. The method described above for addition of nucleophiles to Boc-ΔAla(*N*-Boc)-OMe was used, yielding in most cases an oil; this was then purified by chromatography through a silica column and using diethyl ether–*n*-hexane as the eluent.

Synthesis of 2a. The above general method was used with Bz-ΔAla(*N*-Boc)-OMe and pyrazole to prepare this compound as a crystalline material (53%), mp 50.0–51.5 °C (from diethyl ether–*n*-hexane) (Found: C, 61.0; H, 6.3; N, 11.2. Calc. for $C_{19}H_{23}N_3O_5$: C, 61.1; H, 6.2; N, 11.25%); δ_H 1.09 (9 H, s, Boc), 3.81 (3 H, s, OMe), 4.94 (2 H, m, βCH_2), 5.70 (1 H, dd, *J* 6.0 and 8.9, αCH), 6.23 (1 H, t, *J* 2.4, 4-H pyr.), 7.34–7.51 (7 H, m, Bz + 3-H + 5-H pyr.); δ_C 27.19, 50.86, 52.70, 57.93, 83.93, 105.71, 127.70, 127.88, 130.23, 131.26, 136.90, 140.14, 152.36, 168.88, 172.81.

Synthesis of 2b. The above general method was used with Bz-ΔAla(*N*-Boc)-OMe and 1,2,4-triazole to prepare this compound; in this case the crude product was crystalline and did not require further purification (98%), mp 84.0–85.5 °C (from diethyl ether–*n*-hexane) (Found: C, 58.0; H, 6.1; N, 15.2. Calc. for $C_{18}H_{22}N_4O_5$: C, 57.75; H, 5.9; N, 15.0%); δ_H 1.08 (9 H, s, Boc), 3.82 (3 H, s, OMe), 4.98 (2 H, d, *J* 7.5, βCH_2), 5.66 (1 H, t, *J* 7.5, αCH), 7.40 (5 H, m, Bz), 7.94 (1 H, s, 3- or 5-H triaz.), 8.13 (1 H, s, 5- or 3-H triaz.); δ_C 27.10, 48.49, 52.90, 57.14, 84.43, 127.58, 128.07, 131.57, 136.54, 143.18, 144.19, 152.41, 168.40, 172.79.

Synthesis of 2j. The above general method was used with Bz-ΔAla(*N*-Boc)-OMe and 7-azaindole to prepare this compound; in this case the crude product was crystalline and did not require further purification (92%), mp 91.5–92.0 °C (from diethyl ether–*n*-hexane) (Found: C, 65.2; H, 6.1; N, 9.9. Calc. for $C_{23}H_{25}N_3O_5$: C, 65.2; H, 5.95; N, 9.9%); δ_H 0.98 (9 H, s, Boc), 3.84 (3 H, s, OMe), 5.11 (2 H, m, βCH_2), 5.82 (1 H, dd, *J* 5.7 and 9.6, αCH), 6.43 (1 H, d, *J* 3.6, 3-H ind.), 7.04 (1 H, dd, *J* 4.8 and 7.9, 5-H ind.), 7.21–7.40 (6 H, m, Bz + 2H ind.), 7.85 (1 H, dd, *J* 1.5 and 7.9, 4-H ind.), 8.31 (1 H, dd, *J* 1.5 and 4.8, 6-H ind.); δ_C 27.05, 44.09, 52.63, 57.50, 83.67, 100.01, 115.97, 120.66, 127.47, 127.78, 128.64, 128.70, 131.07, 136.80, 143.00, 147.61, 152.18, 169.16, 172.87.

Synthesis of 3b. The above general method was used with Bz(NO_2)-ΔAla(*N*-Boc)-OMe and 1,2,4-triazole to prepare this compound as an oil which failed to crystallise (67%); δ_H 1.12 (9 H, s, Boc), 3.83 (3 H, s, OMe), 4.98 (2 H, m, βCH_2), 5.66 (1 H, dd, *J* 6.6 and 8.3, αCH), 7.57 [2H, d, *J* 8.7, Bz(NO_2)], 7.93 (1 H, s, 3- or 5-H triaz.), 8.16 (1 H, s, 5- or 3-H triaz.), 8.25 [2H, d, *J* 8.7, Bz(NO_2)]; δ_C 27.24, 48.13, 53.10, 57.13, 85.64, 123.34, 128.21, 142.29, 144.15, 149.03, 151.33, 152.46, 167.88, 170.73.

Synthesis of 3j. The above general method was used with Bz(NO_2)-ΔAla(*N*-Boc)-OMe and 7-azaindole to prepare this compound as an oil which failed to crystallise (54%); δ_H 1.07 (9 H, s, Boc), 3.86 (3 H, s, OMe), 5.04 (1 H, dd, *J* 5.1 and 14.6, βCH_2), 5.17 (1 H, dd, *J* 10.5 and 14.6, βCH_2), 5.85 (1 H, dd, *J* 5.1 and 10.5, αCH), 6.47 (1 H, d, *J* 3.6, 3-H ind.), 7.06–7.21 [4 H, m, Bz(NO_2) + 2- + 5-H ind.], 7.88 (1 H, dd, *J* 1.5 and 7.8, 4-H ind.), 8.10 [2 H, d, *J* 9.0, Bz(NO_2)], 8.30 (1 H, dd, *J* 1.5 and 4.5, 6-H ind.); δ_C 27.17, 43.78, 52.79, 57.38, 84.89, 100.38, 116.19, 120.56, 123.04, 127.87, 128.34, 128.94, 142.50, 143.09, 147.66, 148.66, 151.26, 168.68, 170.74.

Synthesis of 4a. The above general method was used with Z-ΔAla(*N*-Boc)-OMe and pyrazole to prepare this compound as an oil which failed to crystallise (48%) (Found: C, 59.5; H, 6.25; N, 10.4. Calc. for $C_{20}H_{25}N_3O_6$: C, 59.5; H, 6.1; N, 10.3%); δ_H 1.41 (9 H, s, Boc), 3.70 (3 H, s, OMe), 4.64 (1 H, dd, *J* 9.3 and 14.4, βCH_2), 4.89 (1 H, dd, *J* 4.5 and 14.4, βCH_2), 5.16 (2 H, s, CH_2 Z), 5.48 (1 H, dd, *J* 4.5 and 9.3, αCH), 6.18 (1 H, t, *J* 2.1, 4-H pyr.), 7.27 (1 H, d, *J* 2.1, 3- or 5-H pyr.), 7.37 (5 H, m, ArH Z), 7.47 (1 H, d, *J* 2.1, 5- or 3-H pyr.); δ_C 27.69, 51.14, 52.43, 58.59, 68.85, 84.08, 105.60, 128.32, 128.36, 128.40, 130.07, 134.89, 139.99, 150.77, 152.96, 168.65.

Synthesis of 4b. The above general method was used with Z-ΔAla(*N*-Boc)-OMe and 1,2,4-triazole to prepare this compound as an oil which failed to crystallise (98%); δ_H 1.30 (9 H, s, Boc), 3.60 (3 H, s, OMe), 4.59 (1 H, dd, *J* 8.7 and 14.4, βCH_2), 4.81 (1 H, dd, *J* 5.1 and 14.4, βCH_2), 5.08 (2 H, s, CH_2 Z), 5.38

(1 H, dd, *J* 8.7 and 5.1, αCH), 7.27 (5 H, m, ArH Z), 7.77 (1 H, s, 3- or 5-H triaz.), 7.89 (1 H, s, 5- or 3-H triaz.); δ_C 27.73, 51.18, 52.47, 58.63, 68.89, 84.13, 105.64, 128.36, 128.44, 130.11, 134.92, 140.05, 150.79, 152.99, 168.69.

Synthesis of 4j. The above general method was used with Z-ΔAla(*N*-Boc)-OMe and 7-azaindole to prepare this compound as an oil which failed to crystallise (99%); δ_H 1.22 (9 H, s, Boc), 3.72 (3 H, s, OMe), 4.76 (1 H, dd, *J* 9.6 and 14.6, βCH_2), 4.96–5.11 (3 H, m, βCH_2 + CH_2 Z), 5.54 (1 H, dd, *J* 4.5 and 9.6, αCH), 6.39 (1 H, d, *J* 3.6, 3-H ind.), 7.01 (1 H, d, *J* 3.6, 2-H ind.), 7.04 (1 H, dd, *J* 4.7 and 7.8, 5-H ind.), 7.23–7.35 (5 H, m, ArH Z), 7.86 (1 H, dd, *J* 1.8 and 7.8, 4-H ind.), 8.26 (1 H, dd, *J* 1.8 and 4.7, 6-H ind.); δ_C 27.45, 43.96, 52.38, 58.17, 68.65, 83.78, 99.97, 115.91, 120.55, 128.23, 128.29, 128.38, 128.50, 128.63, 134.91, 142.86, 147.45, 150.49, 152.91, 168.87.

Synthesis of 5a. The above general method was used with Z(NO_2)-ΔAla(*N*-Boc)-OMe and pyrazole to prepare this compound as a crystalline material (37%), mp 83–84 °C (from diethyl ether–*n*-hexane) (Found: C, 53.5; H, 5.35; N, 12.8. Calc. for $C_{20}H_{24}N_4O_8$: C, 53.6; H, 5.4; N, 12.5%); δ_H 1.45 (9 H, s, Boc), 3.75 (3 H, s, OMe), 4.67 (1 H, dd, *J* 9.6 and 14.4, βCH_2), 4.90 (1 H, dd, *J* 4.8 and 14.4, βCH_2), 5.26 [2H, s, CH_2 Z(NO_2)], 5.51 (1 H, dd, *J* 4.8 and 9.6, αCH), 6.20 (1 H, t, *J* 2.1, 4-H pyr.), 7.32 (1 H, d, *J* 2.4, 3- or 5-H pyr.), 7.53 [2 H, d, *J* 9.0, ArH Z(NO_2)], 7.63 (1 H, d, *J* 1.8, 5- or 3-H pyr.), 8.23 [2 H, d, *J* 9.0, ArH Z(NO_2)]; δ_C 27.78, 51.07, 52.65, 58.86, 67.26, 84.61, 105.78, 123.69, 123.95, 128.16, 130.12, 140.12, 142.33, 150.29, 153.09, 168.50.

Synthesis of 5b. The above general method was used with Z(NO_2)-ΔAla(*N*-Boc)-OMe and 1,2,4-triazole to prepare this compound as a crystalline material (98%), mp 124–125 °C (from ethyl acetate–diethyl ether) (Found: C, 50.55; H, 5.1; N, 15.6. Calc. for $C_{19}H_{23}N_5O_8$: C, 50.8; H, 5.2; N, 15.6%); δ_H 1.45 (9 H, s, Boc), 3.77 (3 H, s, OMe), 4.73 (1 H, dd, *J* 8.8 and 14.4, βCH_2), 4.94 (1 H, dd, *J* 5.4 and 14.4, βCH_2), 5.29 [2H, s, CH_2 Z(NO_2)], 5.49 (1 H, dd, *J* 5.4 and 8.8, αCH), 7.55 [2 H, d, *J* 8.7, ArH Z(NO_2)], 7.90 (1 H, s, 3- or 5-H triaz.), 8.06 (1 H, s, 5- or 3-H triaz.), 8.26 [2 H, d, *J* 8.7, ArH Z(NO_2)]; δ_C 27.77, 48.69, 52.86, 58.03, 67.57, 85.10, 123.78, 128.26, 142.03, 144.09, 147.83, 150.33, 152.34, 153.21, 168.12.

Synthesis of 5g. The above general method was used with Z(NO_2)-ΔAla(*N*-Boc)-OMe and indole but on a 5-mmolar scale to prepare this compound as an oil which failed to crystallise (46%); δ_H 1.32 (9 H, s, Boc), 3.79 (3 H, s, OMe), 4.74 (1 H, dd, *J* 9.6 and 15.0, βCH_2), 4.89 (1 H, dd, *J* 4.8 and 15.0, βCH_2), 5.00 [2 H, 2d, *J* 13.5, CH_2 Z(NO_2)], 5.38 (1 H, dd, *J* 4.8 and 9.6, αCH), 6.47 (1 H, dd, *J* 0.9 and 3.2, 3-H ind.), 7.00 (1 H, d, *J* 3.2, 2-H ind.), 7.08–7.31 [5 H, m, 5-, 6- and 7-H ind. + ArH Z(NO_2)], 7.60 (1 H, d, *J* 8.1, 4-H ind.), 8.16 [2 H, d, *J* 9.0, ArH Z(NO_2)]; δ_C 27.58, 45.53, 52.66, 58.69, 67.18, 84.61, 102.20, 108.90, 119.70, 121.07, 121.84, 123.62, 128.13, 128.58, 128.64, 136.07, 142.04, 147.93, 150.33, 153.00, 168.62.

Synthesis of 5j. The above general method was used with Z(NO_2)-ΔAla(*N*-Boc)-OMe and 7-azaindole to prepare this compound as an oil which failed to crystallise (87%); δ_H 1.30 (9 H, s, Boc), 3.78 (3 H, s, OMe), 4.83 (1 H, dd, *J* 9.9 and 14.6, βCH_2), 4.87–5.15 [3 H, m, βCH_2 + CH_2 Z(NO_2)], 5.56 (1 H, dd, *J* 9.9 and 4.5, αCH), 6.40 (1 H, d, *J* 3.3, 3-H ind.), 7.01–7.08 (2 H, m, 2- + 5-H ind.), 7.34 [2 H, d, *J* 8.4, ArH Z(NO_2)], 7.85 (1 H, dd, *J* 1.5 and 7.5, 4-H ind.), 8.17 [2 H, d, *J* 8.4, ArH Z(NO_2)], 8.24 (1 H, dd, *J* 1.5 and 4.8, 6-H ind.); δ_C 27.57, 43.96, 52.58, 58.52, 67.02, 84.33, 100.15, 116.02, 120.52, 123.64, 128.00, 128.42, 128.72, 128.89, 142.31, 142.94, 147.53, 150.12, 153.03, 168.72.

Deprotection of β-substituted *N*-acyl-*N*-(*tert*-butyloxycarbonyl)-alanine methyl esters

General method of acidolysis. To the fully protected amino acid (1 mmol) were added 3 cm^3 of TFA at room temperature and the solution was left for 1 h. Excess of TFA was removed by evaporation at reduced pressure to give the required Boc-free amino acid.

General method of saponification. To the fully protected amino acid (1 mmol) in 1,4-dioxane (5 cm^3) were added 3 cm^3 of NaOH (1 mol dm^{-3}). The solution was stirred at room temperature for 2 h, acidified to pH 2–3 with $KHSO_4$ (1 mol dm^{-3}) and then extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and evaporated at reduced pressure to give the corresponding acid as required.

Acidolysis of 1b. The above general method of acidolysis was used to give **6b** in 80% yield, mp 115.5–116.5 °C (from ethyl acetate–*n*-hexane) (Found: C, 30.7; H, 3.3; N, 13.8. Calc. for $C_{10}H_{12}F_6N_4O_6$: C, 30.2; H, 3.0; N, 14.1%); δ_H 3.74 (3 H, s, OMe), 4.65 (3 H, m, βCH_2 + αCH), 8.05 (1 H, s, 3- or 5-H triaz.), 8.51 (1 H, s, 5- or 3-H triaz.), 8.65 (3 H, broad signal, s, NH_3); δ_C (DMSO) 47.72, 51.54, 53.20, 145.46, 152.21, 167.53.

Acidolysis of 1j. The above general method of acidolysis was used to give **6j** in 85% yield, mp 132–133 °C (from ethyl acetate–*n*-hexane) (Found: C, 46.7; H, 4.35; N, 12.8. Calc. for $C_{13}H_{14}F_3N_3O_4$: C, 46.85; H, 4.2; N, 12.6%); δ_H (DMSO) 3.70 (3 H, s, OMe), 4.86 (3 H, m, βCH_2 + αCH), 6.52 (1 H, d, *J* 3.6, 3-H ind.), 7.17 (2 H, m, 5- + 2-H ind.), 8.01 (1 H, dd, *J* 1.5 and 8.1, 4-H ind.), 8.27 (1 H, dd, *J* 1.5 and 4.8, 6-H ind.); δ_C (DMSO) 44.08, 52.02, 52.94, 100.39, 116.24, 120.49, 128.99, 129.69, 142.45, 147.43, 168.15.

Acidolysis of 1m. The above general method of acidolysis was used to give **6m** in a 91% yield, mp 186–186.5 °C (from ethyl acetate–*n*-hexane) (Found: C, 56.4; H, 4.75; N, 7.1. Calc. for $C_{18}H_{17}F_3N_2O_4$: C, 56.55; H, 4.5; N, 7.3%); δ_H (DMSO) 3.32 (3 H, s, OMe), 4.45 (2 H, t, *J* 7.2, βCH_2), 4.81 (1H, d, *J* 7.2, αCH), 7.25 (2 H, t, *J* 8.1, 1- and 8-H carb.), 7.49 (4 H, m, 2-, 3-, 6- and 7-H carb.), 8.18 (2 H, d, *J* 7.5, 4- and 5-H carb.), 8.71 (3 H, broad signal, NH_3); δ_C (DMSO) 42.51, 50.44, 52.69, 108.92, 119.57, 120.45, 122.60, 125.98, 139.97, 168.64.

Aminolysis of 2b. DEAEA-induced aminolysis of **2b** was carried out according to the procedure described by Ragnarsson and co-workers[13] to give **7b** (78%), mp 76–78 °C (from diethyl ether-*n*-hexane) (Found: C, 49.0; H, 6.5; N, 20.8. Calc. for $C_{11}H_{18}N_4O_4$: C, 48.9; H, 6.7; N, 20.7%); δ_H 1.44 (9 H, s, Boc), 3.80 (3 H, s, OMe), 4.67 (3 H, broad signal, αCH + βCH_2), 5.38 (1 H, broad signal, NH), 7.94 (1 H, s, 3- or 5-H triaz.), 8.02 (1 H, s, 5- or 3-H triaz.); δ_C 28.17, 50.07, 53.10, 53.41, 80.66, 144.16, 152.46, 155.03, 169.61.

Al(Hg)-Mediated cleavage of 5b. Finely cut aluminium foil (10 mmol) was stirred with a few drops of mercury for 30 min under a stream of nitrogen; a solution of **5b** (0.5 mmol) in THF (5 cm^3) with 1% water was then added. After 2 h, when most of the Al had dissolved and TLC indicated only minor amounts of starting material, more Al(Hg) (5 mmol) was added and left to react for 2 h. The greyish solid material was then filtered off by suction and rinsed thoroughly with ethyl acetate. Evaporation of the filtrate gave an oil which was chromatographed by column chromatography through silica with ethyl acetate–diethyl ether 1 : 1 as eluent to give **7b** (86%).

Saponification of 1a. The above general method of saponification was used to give **8a** (91%), mp 149–150 °C (from ethyl acetate–*n*-hexane) (Found: C, 54.2; H, 7.1; N, 11.9. Calc. for

$C_{16}H_{25}N_3O_6$: C, 54.1; H, 7.1; N, 11.8%); δ_H (DMSO) 1.48 (18 H, s, Boc), 4.67 (1 H, dd, *J* 8.7 and 14.5, βCH_2), 5.06 (1 H, dd, *J* 4.8 and 14.5, βCH_2), 5.47 (1 H, dd, *J* 4.8 and 8.7, αCH), 6.28 (1 H, t, *J* 2.4, 4-H pyr.), 7.39 (1 H, d, *J* 2.4, 3- or 5-H pyr.), 7.58 (1 H, d, *J* 1.8, 5- or 3-H pyr.); δ_C (DMSO) 27.48, 50.74, 58.21, 82.40, 105.22, 130.52, 139.01, 150.94, 169.86.

Saponification of 1b. The above general method of saponification was used to give **8b** (86%), mp 129–129.5 °C (from ethyl acetate–*n*-hexane) (Found: C, 50.7; H, 7.0; N, 15.2. Calc. for $C_{15}H_{24}N_4O_6$: C, 50.55; H, 6.8; N, 15.7%); δ_H (DMSO) 1.47 (18 H, s, Boc), 4.70 (1 H, dd, βCH_2), 4.96 (1 H, dd, βCH_2), 5.44 (1 H, dd, αCH), 7.97 (1 H, s, 3- or 5-H triaz.), 8.23 (1 H, s, 5- or 3-H triaz.); δ_C (DMSO) 27.43, 48.23, 57.73, 82.65, 144.78, 150.90, 151.47, 169.51.

Saponification of 1h. The above general method of saponification was used to give **8h** (89%), mp 155–156 °C (from ethyl acetate–*n*-hexane) (Found: C, 61.05; H, 6.6; N, 6.5. Calc. for $C_{22}H_{28}N_2O_7$: C, 61.1; H, 6.5; N, 6.5%); δ_H (DMSO) 1.32 (18 H, s, Boc), 4.81 (1H, dd, *J* 9.3 and 14.7, βCH_2), 4.93 (1 H, dd, *J* 4.8 and 14.7, βCH_2), 5.44 (1 H, dd, *J* 4.8 and 9.3, αCH), 7.27–7.44 (3 H, complex signal, 5-, 6- and 7-H ind.), 7.75 (1 H, s, 2-H ind.), 8.30 (1 H, d, *J* 5.4, 4-H ind.), 9.99 (1 H, s, CHO); δ_C (DMSO) 27.17, 46.03, 57.84, 82.65, 110.70, 117.76, 120.99, 122.45, 123.55, 124.64, 137.44, 141.27, 151.07, 169.61, 184.64.

Saponification of 1j. The above general method of saponification was used to give **8j** (94%), mp 156–156.5 °C (from ethyl acetate–*n*-hexane) (Found: C, 59.3; H, 6.8; N, 10.0. Calc. for $C_{20}H_{27}N_3O_6$: C, 59.25; H, 6.7; N, 10.4%); δ_H (DMSO) 1.30 (18 H, s, Boc), 4.67 (1 H, dd, *J* 10.2 and 14.7, αCH), 5.45 (2H, m, βCH_2), 6.51 (1H, d, *J* 3.3, 3-H ind.), 7.13 (1 H, d, *J* 3.3, 2-H ind.), 7.21 (1 H, dd, *J* 4.8 and 7.8, 5-H ind.), 8.04 (1 H, d, *J* 7.8, 4-H ind.), 8.42 (1 H, d, *J* 4.8, 6-H ind.); δ_C (DMSO) 27.74, 44.12, 58.33, 82.65, 99.91, 116.17, 120.64, 128.85, 129.79, 142.79, 147.76, 151.19, 170.51.

Coupling reactions of β-substituted alanine derivatives

Synthesis of Boc-DL-Ala[*N*-Boc-β-(pyrazol-1-yl)]-L-Phe-OEt 9a. Compound **8a** was treated on a 1-mmolar scale with H-Phe-OEt·HCl in ethyl acetate by using the standard DCC–1-hydroxybenzotriazole(HOBt) procedure to give Boc-Ala-[*N*-Boc-β-(pyrazol-1-yl)]-L-Phe-OEt as a pure oil that solidified on storage (80%) (Found: C, 61.0; H, 7.3; N, 10.45. Calc. for $C_{27}H_{38}N_4O_7$: C, 61.1; H, 7.2; N, 10.6%).

Synthesis of Boc-DL-Ala[*N*-Boc-β-(7-azaindol-1-yl)]-L-Phe-OEt 9j. Compound **8j** was treated on a 1-mmolar scale as above to give Boc-Ala[*N*-Boc-β-(7-azaindol-1-yl)]-L-Phe-OEt as a pure oil that solidified on storage (86%) (Found: C, 64.05; H, 7.1; N, 9.7. Calc. for $C_{31}H_{40}N_4O_7$: C, 64.1; H, 6.9; N, 9.65%).

Michael addition to dehydroalanine dipeptides

General method. To a solution of 0.25 mmol of the fully protected dehydro dipeptide in acetonitrile, *viz.* Tos-Gly(*N*-Boc)-ΔAla(*N*-Boc)-OMe **10** or Boc-Ala(*N*-Boc)-ΔAla(*N*-Boc)-OMe **11** (2.5 cm^3) was added K_2CO_3 (6 equiv.), followed by 1 equiv. of pyrazole with rapid stirring at room temperature. The reaction was monitored by TLC and when no starting material was detected the solution was filtered, and evaporated at reduced pressure to give the corresponding addition product.

Synthesis of Tos-Gly(*N*-Boc)-Ala[*N*-Boc-β-(pyrazol-1-yl)]-OMe. The above general method with pyrazole gave Tos-Gly(*N*-Boc)-Ala[*N*-Boc-β-(pyrazol-1-yl)]-OMe **10a** in 76% yield, mp 129.5–131 °C (from diethyl ether–*n*-hexane) (Found: C, 53.6; H, 6.25; N, 9.3; S, 5.7. Calc. for $C_{26}H_{36}N_4O_9S$: C, 53.8; H, 6.25; N, 9.65; S, 5.5%); δ_H 1.33 (9 H, s, Boc), 1.44 (9 H, s, Boc), 2.45 (3 H, s, CH_3 Tos), 3.76 (3 H, s, OMe), 4.59 (1 H, dd, *J* 9.6 and 14.4, βCH_2 Ala), 4.94 (1 H, dd, *J* 4.5 and 14.4, βCH_2 Ala), 5.10 (2 H, d, *J* 6.9, CH_2 Gly), 5.50 (1 H, dd, *J* 4.5 and 9.6, αCH Ala), 6.23 (1 H, t, *J* 2.1, 4-H pyr.), 7.30 (2 H, d, *J* 8.1, ArH Tos), 7.45 (1 H, d, *J* 2.1, 3- or 5-H pyr.), 7.53 (1 H, d, *J* 1.5, 5- or 3-H pyr.), 7.87 (2 H, d, *J* 8.1, ArH Tos); δ_C 21.62, 27.71, 27.76, 50.27, 51.54, 52.49, 57.70, 84.63, 85.43, 105.86, 128.69, 128.98, 130.45, 136.82, 140.14, 144.22, 150.54, 151.14, 168.30, 170.63.

Synthesis of Tos-Gly(*N*-Boc)-Ala[*N*-Boc-β-(1,2,4-triazol-1-yl)]-OMe. The above general method with 1,2,4-triazole gave Tos-Gly(*N*-Boc)-Ala[*N*-Boc-β-(1,2,4-triazol-1-yl)]-OMe **10b** in 99% yield, mp 130.5–132 °C (from diethyl ether–*n*-hexane) (Found: C, 51.8; H, 6.1; N, 11.85; S, 5.6. Calc. for $C_{25}H_{35}N_5O_9S$: C, 51.6; H, 6.1; N, 12.0; S, 5.5%); δ_H 1.33 (9 H, s, Boc), 1.45 (9 H, s, Boc), 2.46 (3 H, s, CH_3 Tos), 3.78 (3 H, s, OMe), 4.62 (1 H, dd, *J* 9.0 and 14.4, βCH_2 Ala), 4.94 (1 H, dd, *J* 4.5 and 14.4, βCH_2 Ala), 5.08 (2 H, s, CH_2 Gly), 5.46 (1 H, dd, *J* 4.5 and 9.0, αCH Ala), 7.32 (2 H, d, *J* 8.1, ArH Tos), 7.87 (2 H, d, *J* 8.1, ArH Tos), 7.95 (1 H, s, 3- or 5-H triaz.), 8.23 (1 H, s, 5- or 3-H triaz.); δ_C 21.61, 27.70, 27.75, 47.84, 51.53, 52.72, 57.01, 84.89, 85.95, 128.55, 129.05, 136.73, 144.34, 144.43, 150.56, 150.94, 152.36, 167.89, 170.85.

Synthesis of Tos-Gly(*N*-Boc)-Ala[*N*-Boc-β-(imidazol-1-yl)]-OMe. The above general method with imidazole gave Tos-Gly(*N*-Boc)-Ala[*N*-Boc-β-(imidazol-1-yl)]-OMe **10c** in 75% yield, mp 108–109.5 °C (from diethyl ether–*n*-hexane) (Found: C, 53.7; H, 6.2; N, 9.4; S, 5.4. Calc. for $C_{26}H_{36}N_4O_9S$: C, 53.8; H, 6.25; N, 9.65; S, 5.5%); δ_H 1.33 (9 H, s, Boc), 1.43 (9 H, s, Boc), 2.45 (3 H, s, CH_3 Tos), 3.77 (3 H, s, OMe), 4.38 (1 H, dd, *J* 8.4 and 14.9, βCH_2 Ala), 4.70 (1 H, dd, *J* 4.8 and 14.9, βCH_2 Ala), 5.11 (2 H, d, *J* 10.2, CH_2 Gly), 5.25 (1 H, dd, *J* 4.8 and 8.4, αCH Ala), 6.96 (1 H, t, *J* 1.2, 4- or 5-H imid.), 7.04 (1 H, s, 5- or 4-H imid.), 7.33 (2 H, d, *J* 8.4, ArH Tos), 7.54 (1 H, s, 2-H imid.), 7.87 (2 H, d, *J* 8.4, ArH Tos); δ_C 21.65, 27.69, 27.78, 45.58, 51.61, 52.71, 58.06, 84.92, 86.18, 119.62, 128.58, 129.09, 129.74, 136.75, 137.82, 144.39, 150.56, 150.96, 168.10, 170.76.

Synthesis of Tos-Gly(*N*-Boc)-Ala[*N*-Boc-β-(3-formylindol-1-yl)]-OMe. The above general method with 3-formylindole gave Tos-Gly(*N*-Boc)-Ala[*N*-Boc-β-(3-formylindol-1-yl)]-OMe **10h** in 74% yield, mp 117.0–119.0 °C (from diethyl ether–*n*-hexane) (Found: C, 58.6; H, 5.9; N, 6.65; S, 4.32. Calc. for $C_{32}H_{39}N_3O_{10}S$: C, 58.4; H, 5.9; N, 6.4; S, 4.86%); δ_H 1.06 (9 H, s, Boc), 1.35 (9 H, s, Boc), 2.47 (3 H, s, CH_3 Tos), 3.80 (3 H, s, OMe), 4.65 (1 H, dd, *J* 9.0 and 15.0, βCH_2 Ala), 5.00 (1 H, dd, *J* 4.8 and 15.0, βCH_2 Ala), 5.11 (2 H, d, *J* 5.7, CH_2 Gly), 5.33 (1 H, m, αCH Ala), 7.29–7.43 (5 H, m, 2-, 5- and 6-H ind. + ArH Tos), 7.87–7.92 (3 H, m, 7-H ind. + ArH Tos), 8.32 (1 H, dd, *J* 2.7 and 6.2, 4-H ind.), 9.98 (1 H, s, CH); δ_C 21.66, 27.16, 27.80, 45.52, 51.75, 52.78, 56.83, 85.06, 85.97, 109.57, 118.91, 122.65, 123.13, 124.36, 125.36, 128.46, 129.15, 136.86, 137.10, 140.24, 144.44, 150.69, 150.82, 168.11, 171.01, 184.99.

Synthesis of Tos-Gly(*N*-Boc)-Ala[*N*-Boc-β-(7-azaindol-1-yl)]-OMe. The above general method with 7-azaindole gave Tos-Gly(*N*-Boc)-Ala[*N*-Boc-β-(7-azaindol-1-yl)]-OMe **10j** in 90% yield, mp 141.5–143 °C (from diethyl ether-*n*-hexane) (Found: C, 57.0; H, 6.2; N, 8.7; S, 5.2. Calc. for $C_{30}H_{38}N_4O_9S$: C, 57.1; H, 6.1; N, 8.9; S, 5.1%); δ_H 1.05 (9 H, s, Boc), 1.34 (9 H, s, Boc), 2.45 (3 H, s, CH_3 Tos), 3.77 (3 H, s, OMe), 4.73 (1 H, dd, *J* 9.6 and 14.6, βCH_2 Ala), 5.13 (3 H, m, βCH_2 Ala, CH_2 Gly), 5.49 (1 H, dd, *J* 3.6 and 9.6, αCH Ala), 6.46 (1 H, d, *J* 5.1, 3-H ind.), 7.07 (1 H, dd, *J* 5.1 and 7.8, 5-H ind.), 7.27 (3 H, m, 2-H ind., ArH Tos), 7.88 (3 H, m, 4-H ind., ArH Tos), 8.35 (1 H, dd, *J* 1.5 and 5.1, 6-H ind.); δ_C 21.63, 27.20, 27.75, 51.21, 51.75, 52.37, 57.47, 84.50, 84.80, 105.68, 128.78, 128.91, 130.14, 136.93, 140.09, 142.94, 144.13, 151.15, 170.70, 168.45.

Synthesis of Boc-DL-Ala(*N*-Boc)-Ala[*N*-Boc-β-(1,2,4-triazol-1-yl)]-OMe. The above general method with 1,2,4-triazole gave Boc-Ala(*N*-Boc)-Ala[*N*-Boc-β-(1,2,4-triazol-1-yl)]-OMe **11b** in 98% yield (from diethyl ether–*n*-hexane) (Found: C, 52.9; H, 7.1; N, 12.9. Calc. for $C_{24}H_{39}N_5O_9$: C, 53.2; H, 7.3; N, 12.9%).

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