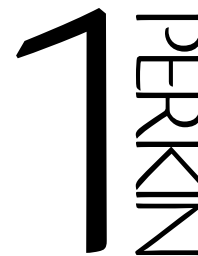


Synthesis of β -substituted alanines *via* Michael addition of nucleophiles to dehydroalanine derivatives



Paula M. T. Ferreira, Hernâni L. S. Maia,* Luís S. Monteiro, Joana Sacramento and Joana Sebastião

Department of Chemistry, University of Minho, Gualtar, P-4700-320 Braga, Portugal

Received (in Cambridge, UK) 26th April 2000, Accepted 10th July 2000

First published as an Advance Article on the web 13th September 2000

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- Δ Ala-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 FeCl₃-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 (Δ Ala) 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.

Results and discussion

The methyl ester of *N,N*-bis(*tert*-butoxycarbonyl)dehydroalanine [Boc- Δ Ala(*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 Δ Ala towards nucleophilic attack. This was confirmed when Boc- Δ Ala-OMe was substituted for Boc- Δ Ala(*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.

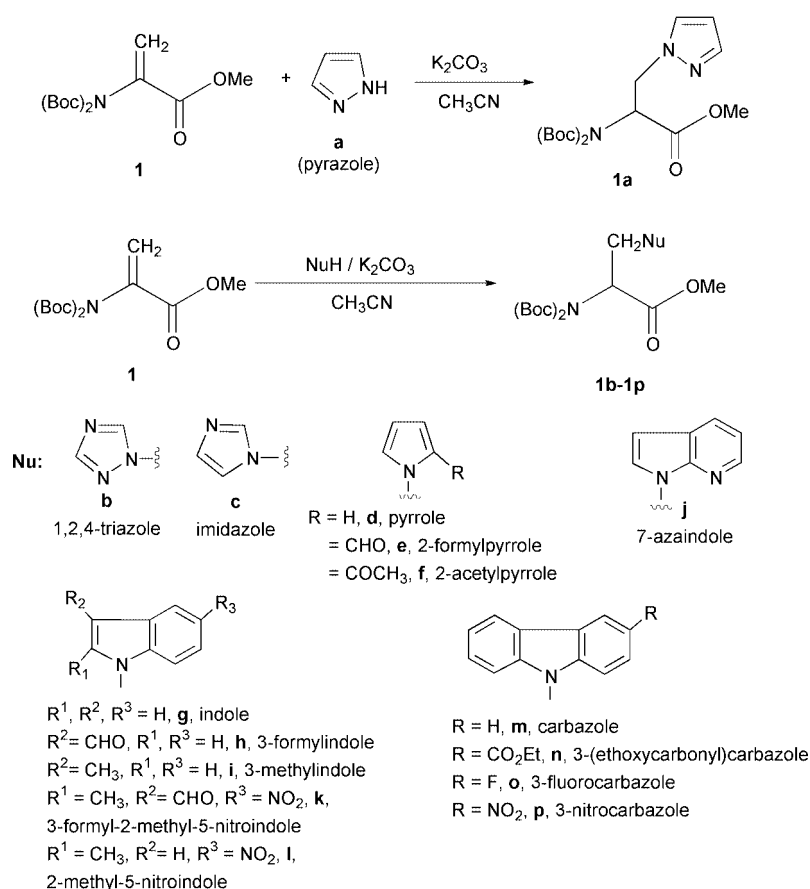
The scope of this reaction was further investigated with respect to other nitrogen nucleophiles such as pyrrole, indole and carbazole, but much lower yields were obtained, which may be related to a lower acidity of these compounds as compared with the previous ones. In fact, while no product had been 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.

[†] Δ Ala means dehydroalanine.

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

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

^a Pure non-recrystallised material. ^b For the NH proton of NuH (300 MHz; DMSO; Me₄Si). ^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 isosters 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- Δ Ala-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-workers¹³ 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

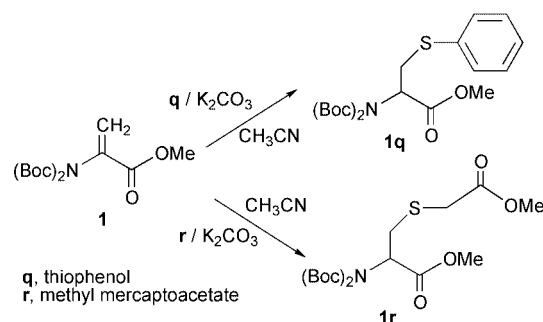
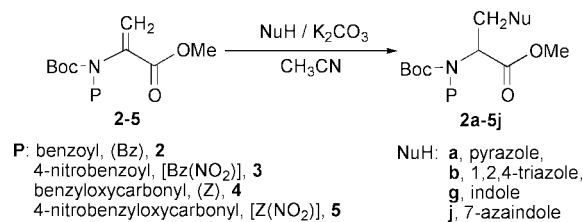
Table 2 Results obtained in the synthesis of heterocyclic β -substituted alanine derivatives by addition to P- Δ Ala(*N*-Boc)-OMe (2–5)

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

^a Pure non-recrystallised material. ^b Boc- Δ Ala-OMe was also isolated, in 22% yield. ^c Bz(NO₂) = 4-nitrobenzoyl, Z(NO₂) = 4-nitrobenzyloxy-carbonyl. ^d Only Boc- Δ Ala-OMe was isolated, in 82% yield. ^e Boc- Δ Ala-OMe was also isolated, in 28% yield. ^f Boc- Δ Ala-OMe was also isolated, in 42% yield. ^g Boc- Δ Ala-OMe was also isolated, in 30% yield. ^h Boc- Δ Ala-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[<i>N</i> -Boc- β -(pyrazol-1-yl)]-OH 8a	91
1b	NaOH	Boc-Ala[<i>N</i> -Boc- β -(1,2,4-triazol-1-yl)]-OH 8b	86
1h	NaOH	Boc-Ala[<i>N</i> -Boc- β -(3-formylindol-1-yl)]-OH 8h	89
1j	NaOH	Boc-Ala[<i>N</i> -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)- Δ Ala(*N*-Boc)-OMe or Boc-Ala(*N*-Boc)- Δ Ala(*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- Δ Ala(*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)- Δ Ala(*N*-Boc)-OMe or Boc-Ala(*N*-Boc)- Δ Ala(*N*-Boc)-OMe

Entry	NuH	Product (compound no.)	Yield (%)
1	a	Tos-Gly(<i>N</i> -Boc)-Ala[<i>N</i> -Boc- β -(pyrazol-1-yl)]-OMe 10a	76
2	b	Tos-Gly(<i>N</i> -Boc)-Ala[<i>N</i> -Boc- β -(1,2,4-triazol-1-yl)]-OMe 10b	99
3	c	Tos-Gly(<i>N</i> -Boc)-Ala[<i>N</i> -Boc- β -(imidazol-1-yl)]-OMe 10c	75
4	h	Tos-Gly(<i>N</i> -Boc)-Ala[<i>N</i> -Boc- β -(3-formylindol-1-yl)]-OMe 10h	74
5	j	Tos-Gly(<i>N</i> -Boc)-Ala[<i>N</i> -Boc- β -(7-azaindol-1-yl)]-OMe 10j	90
6	b	Boc-Ala(<i>N</i> -Boc)-Ala[<i>N</i> -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 60F₂₅₄) and spots were visualised under UV or by exposure to vapourised iodine. Preparative chromatography was carried out on Merck Kieselgel 60 (230–400 mesh). ¹H NMR spectra were recorded on a Varian 300 spectrometer for samples in \approx 5% CDCl₃ solution at 25 °C, when not otherwise stated. All shifts are given in δ ppm using δ_{H} Me₄Si = 0 as reference. *J*-Values are given in Hz. Assignments were made by comparison of chemical shifts, peak multiplicities and *J*-values. ¹³C 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 μ m) 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- Δ Ala(*N*-Boc)-OMe 1, Bz- Δ Ala(*N*-Boc)-OMe 2, Z- Δ Ala(*N*-Boc)-OMe 4 and Z(NO₂)- Δ Ala(*N*-Boc)-OMe 5. These compounds have been described elsewhere.¹¹

Synthesis of Bz(NO₂)- Δ Ala(*N*-Boc)-OMe 3. The same procedure as above was used in a 5-mmol 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 C₁₆H₁₈N₂O₇: 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, β CH₂), 6.60 (1 H, s, β CH₂), 7.85 [2 H, d, *J* 8.7, Bz(NO₂)], 8.31 [2 H, d, *J* 8.7, Bz(NO₂)]; 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)- Δ Ala(*N*-Boc)-OMe 11. This compound has been described previously.¹¹

Synthesis of Tos-Gly(*N*-Boc)- Δ Ala(*N*-Boc)-OMe 10. The same procedure as above was used in a 5-mmol 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 C₂₃H₃₂N₂O₉S: 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, CH₃ Tos), 3.80 (3 H, s, OMe), 5.22 (2 H, s, CH₂ Gly), 5.74 (1 H, d, *J* 0.6, β CH₂ Δ Ala), 6.52 (1 H, d, *J* 0.6, β CH₂ Δ Ala), 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- Δ Ala(*N*-Boc)-OMe in acetonitrile (10 cm³) was added K₂CO₃ (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 C₁₉H₂₈N₂O₇: 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, β CH₂), 5.25 (1 H, dd, *J* 4.5 and 13.8, β CH₂), 5.48 (1 H, dd, *J* 4.5 and 10.2, α CH), 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, CH₃CO), 3.78 (3 H, s, OMe), 4.47 (1 H, dd, *J* 10.2 and 12.0, β CH₂), 5.29 (1 H, dd, *J* 13.8 and 9.0, β CH₂), 5.54 (1 H, dd, *J* 10.2 and 7.4, α CH), 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 C₂₄H₃₁N₃O₉: C, 57.0; H, 6.2; N, 8.3%; δ_{H} 1.28 (18 H, s, Boc), 2.78 (3 H, s, 2-CH₃ ind.), 3.83 (3 H, s, OMe), 4.81–4.98 (2 H, complex signal, β CH₂), 5.36 (1 H, dd, *J* 4.5 and 10.2, α CH), 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 C₂₃H₃₁N₃O₈: C, 57.85; H, 6.5; N, 8.8%; δ_{H} 1.28 (18 H, s, Boc), 2.46 (3 H, s, 2-CH₃ ind.), 3.82 (3 H, s, OMe), 4.77 (12 H, dd, *J* 4.5 and 15.3, β CH₂), 4.87 (1 H, dd, *J* 9.9 and 15.3, β CH₂), 5.29 (1 H, dd, *J* 4.5 and 9.9, α CH), 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 C₂₆H₃₂N₂O₆: 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, βCH₂), 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 C₂₆H₃₁FN₂O₆: 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, βCH₂), 5.06 (1 H, dd, *J* 9.2 and 15.4, βCH₂), 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 C₂₆H₃₁N₃O₈: 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, βCH₂), 5.13 (1 H, dd, *J* 9.6 and 15.2, βCH₂), 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 C₂₀H₂₉NO₆S: 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, βCH₂), 3.73 (3 H, s, OMe), 3.76 (1 H, dd, *J* 4.8 and 14.6, βCH₂), 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 C₁₇H₂₉NO₈S: C, 50.1; H, 7.2; N, 3.4%); δ_H 1.48 (18 H, s, Boc), 3.07–3.44 (4 H, m, βCH₂ + CH₂ thiol), 3.71 (6 H, s, CH₃ 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 C₁₉H₂₃N₃O₅: 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, βCH₂), 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 C₁₈H₂₂N₄O₅: 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, βCH₂), 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 C₂₃H₂₅N₃O₅: 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, βCH₂), 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(NO₂)-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, βCH₂), 5.66 (1 H, dd, *J* 6.6 and 8.3, αCH), 7.57 [2H, d, *J* 8.7, Bz(NO₂)], 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(NO₂)]; 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(NO₂)-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, βCH₂), 5.17 (1 H, dd, *J* 10.5 and 14.6, βCH₂), 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(NO₂) + 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(NO₂)], 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 C₂₀H₂₅N₃O₆: 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, βCH₂), 4.89 (1 H, dd, *J* 4.5 and 14.4, βCH₂), 5.16 (2 H, s, CH₂ 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, βCH₂), 4.81 (1 H, dd, *J* 5.1 and 14.4, βCH₂), 5.08 (2 H, s, CH₂ Z), 5.38

(1 H, dd, J 8.7 and 5.1, α CH), 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- Δ Ala(*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, β CH₂), 4.96–5.11 (3 H, m, β CH₂ + CH₂ Z), 5.54 (1 H, dd, J 4.5 and 9.6, α CH), 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(NO₂)- Δ Ala(*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 C₂₀H₂₄N₄O₈: 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, β CH₂), 4.90 (1 H, dd, J 4.8 and 14.4, β CH₂), 5.26 [2H, s, CH₂ Z(NO₂)], 5.51 (1 H, dd, J 4.8 and 9.6, α CH), 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(NO₂)], 7.63 (1 H, d, J 1.8, 5- or 3-H pyr.), 8.23 [2 H, d, J 9.0, ArH Z(NO₂)]; 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(NO₂)- Δ Ala(*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 C₁₉H₂₃N₅O₈: 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, β CH₂), 4.94 (1 H, dd, J 5.4 and 14.4, β CH₂), 5.29 [2H, s, CH₂ Z(NO₂)], 5.49 (1 H, dd, J 5.4 and 8.8, α CH), 7.55 [2 H, d, J 8.7, ArH Z(NO₂)], 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(NO₂)]; 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(NO₂)- Δ Ala(*N*-Boc)-OMe and indole but on a 5-mmol 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, β CH₂), 4.89 (1 H, dd, J 4.8 and 15.0, β CH₂), 5.00 [2 H, 2d, J 13.5, CH₂ Z(NO₂)], 5.38 (1 H, dd, J 4.8 and 9.6, α CH), 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(NO₂)], 7.60 (1 H, d, J 8.1, 4-H ind.), 8.16 [2 H, d, J 9.0, ArH Z(NO₂)]; 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(NO₂)- Δ Ala(*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, β CH₂), 4.87–5.15 [3 H, m, β CH₂ + CH₂ Z(NO₂)], 5.56 (1 H, dd, J 9.9 and 4.5, α CH), 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(NO₂)], 7.85 (1 H, dd, J 1.5 and 7.5, 4-H ind.), 8.17 [2 H, d, J 8.4, ArH Z(NO₂)], 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 cm³ 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 cm³) were added 3 cm³ of NaOH (1 mol dm⁻³). The solution was stirred at room temperature for 2 h, acidified to pH 2–3 with KHSO₄ (1 mol dm⁻³) and then extracted with ethyl acetate. The organic layer was dried over MgSO₄ 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 C₁₀H₁₂F₆N₄O₆: C, 30.2; H, 3.0; N, 14.1%); δ_H 3.74 (3 H, s, OMe), 4.65 (3 H, m, β CH₂ + α CH), 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, NH₃); 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 C₁₃H₁₄F₃N₃O₄: C, 46.85; H, 4.2; N, 12.6%); δ_H (DMSO) 3.70 (3 H, s, OMe), 4.86 (3 H, m, β CH₂ + α CH), 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 C₁₈H₁₇F₃N₂O₄: 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, β CH₂), 4.81 (1H, d, J 7.2, α CH), 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, NH₃); 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-workers¹³ 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 C₁₁H₁₈N₄O₄: 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, α CH + β CH₂), 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 cm³) 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

C₁₆H₂₅N₃O₆: 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 C₁₅H₂₄N₄O₆: 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 C₂₂H₂₈N₂O₇: C, 61.1; H, 6.5; N, 6.5%; δ_{H} (DMSO) 1.32 (18 H, s, Boc), 4.81 (1 H, 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 C₂₂H₂₇N₃O₆: 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-mmol 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 C₂₇H₃₈N₄O₇: 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-mmol 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 C₃₁H₄₀N₄O₇: 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)- Δ Ala(*N*-Boc)-OMe **10** or Boc-Ala(*N*-Boc)- Δ Ala(*N*-Boc)-OMe **11** (2.5 cm³) was added K₂CO₃ (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 10a. 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 C₂₆H₃₆N₄O₉S: 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, CH₃ 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, CH₂ 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 C₂₅H₃₅N₅O₉S: 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, CH₃ 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, CH₂ 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 C₂₆H₃₆N₄O₉S: 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, CH₃ 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, CH₂ 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 C₃₂H₃₉N₃O₁₀S: 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, CH₃ 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, CH₂ 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 C₃₀H₃₈N₄O₉S: 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, CH₃ 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, CH₂ 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 C₂₄H₃₉N₅O₉: C, 53.2; H, 7.3; N, 12.9%).

References

- 1 P. M. Dunnill and L. Fowde, *Phytochemistry*, 1965, **4**, 935.
- 2 H. Shinozaki and S. Konishi, *Neuropharmacology*, 1974, **13**, 665.
- 3 R. H. Evans, A. A. Francis, K. Hunt, M. R. Martin and J. C. Watkins, *J. Pharm. Pharmac.*, 1978, **30**, 364.
- 4 F. Ikegami and I. Murakoshi, *Phytochemistry*, 1994, **35**, 1089.
- 5 F. Ikegami, Y. Komada, M. Kobori, D. R. Hawkins and I. Murakoshi, *Phytochemistry*, 1990, **29**, 2507.
- 6 T. Okuda and H. Zahn, *Chem. Ber.*, 1965, **98**, 1164.
- 7 R. Labia and C. Morin, *J. Org. Chem.*, 1986, **51**, 249.
- 8 M. Pérez and R. Pleixats, *Tetrahedron*, 1995, **51**, 8355.
- 9 M. Barbaste, V. Rolland-Fulcrand, M. L. Roumestant, P. Viallefont and J. Martinez, *Tetrahedron Lett.*, 1998, **39**, 6287.
- 10 P. M. T. Ferreira, H. L. S. Maia and L. S. Monteiro, *Tetrahedron Lett.*, 1998, **39**, 9575.
- 11 P. M. T. Ferreira, H. L. S. Maia, L. S. Monteiro and J. Sacramento, *J. Chem. Soc., Perkin Trans. 1*, 1999, 3697.
- 12 P. M. T. Ferreira, H. L. S. Maia and L. S. Monteiro, *Tetrahedron Lett.*, 1999, **40**, 4099.
- 13 L. Grehn, K. Gunnarsson and U. Ragnarsson, *Acta Chem. Scand., Ser. B*, 1987, **41**, 18.
- 14 B. Nyassé, L. Grehn, H. L. S. Maia, L. S. Monteiro and U. Ragnarsson, *J. Org. Chem.*, 1999, **64**, 7135.