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Michael addition of thiols, carbon nucleophiles and amines to dehydroamino acid and dehydropeptide derivatives†

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Michael additions of nitrogen heterocycles, thiols, carbon nucleophiles and amines to dehydroalanine derivatives, including a glycyldehydroalanine peptide, are performed in fair to good yields. Didehydroaminobutyric acid derivatives react only with the stronger nucleophiles but in considerably lower yields and often no reaction is observed with the corresponding didehydrophenylalanine derivatives. When a tosyl group is bonded to the nitrogen atom of the dehydroamino acid, in some cases the addition product undergoes elimination of this group and yields the corresponding β-substituted derivative of the α,β-didehydroamino acid. Addition of some β-dicarbonyl compounds leads to formation of products to which the structure of α,α-disubstituted cyclic amino acid derivatives is assigned.

Introduction

Although being one of the most important and widely used synthetic tools for the construction of quaternary carbon atoms, there are few reports on the use of the Michael addition of nucleophiles to α,β-didehydroamino acids.[1–6] Difficulties met with reactions in solution were overcome by carrying them out in the solid phase.[5] In a recent publication[6] good yields were reported for the addition of heterocyclic nucleophiles to methyl 2-acetamidoacrylate in solution, by carrying out the reactions at 60 °C to yield the corresponding *N*-acetyl-β-substituted alanine salts. The limited use of α,β-didehydroamino acids in Michael additions can be assigned mainly to the fact that these compounds are poor Michael acceptors. Nevertheless, we were able to circumvent this difficulty[7] by double acylation of the acceptor at its amine group, which greatly enhances the reactivity of these compounds, thus avoiding the need for unwanted heating. Using several nitrogen heterocycles and thiols in combination with various *N*,*N*-diacyldehydroalanine derivatives we were able to synthesise several β-substituted alanines in high yields.[7,8] Unexpectedly, by substituting tosyl for one of the acyl groups we were able to prepare several β-substituted dehydroamino acid derivatives in high yield, which resulted from spontaneous elimination of toluenesulfinic acid.[9] In view of these results, we decided to extend our investigation to additional nucleophiles and other dehydroamino acids in order to investigate the scope and limitations of this reaction, having also in mind to further investigate the unexpected behaviour of tosyl derivatives.

Results and discussion

We have previously reported[8] the addition of thiophenol (**a**) and methyl mercaptoacetate (**b**) to *N*,*N*-bis-(*tert*-butoxycarbonyl)didehydroalanine methyl ester[10] [Boc-ΔAla(*N*-Boc)-OMe, **1**]. With substrates having Boc replaced by another acyl group such as benzyloxycarbonyl (Z, **2a** and **2b**), *p*-nitrobenzyloxycarbonyl [Z(NO_2), **3a** and **3b**], benzoyl (Bz, **4a** and **4b**) and *p*-nitrobenzoyl [Bz(NO_2), **5a** and **5b**] addition occurred in high yields and no cleavage of the acyl groups was observed (Scheme 1, Table 1). This differed from what had been observed when compounds having one of these groups combined with Boc were allowed to react with nitrogen nucleophiles such as pyrazole (**m**).[8,11] The two acyl groups being preserved in the final products allow selective cleavage of one of them for further synthetic use. Furthermore, thiophenol (**a**) and methyl mercaptoacetate (**b**) could also be added to a dipeptide derivative [Tos-Gly(*N*-Boc)-ΔAla(*N*-Boc)-OMe,[8] **7**] to give the addition products in yields of 87 and 90%, respectively. As shown before with nitrogen heterocycles,[9] in the case of reaction of the above thiols with the substrate having one of the Boc groups replaced by tosyl, addition also occurred. Subsequently, the product underwent spontaneous elimination of toluenesulfinic acid to give the corresponding β-substituted dehydroamino acid derivative in high yield. Thus, with thiophenol (**a**), an overnight reaction gave the expected addition product (**6a**) in a yield of 83%, but when the reaction mixture was kept for 10 days an identical yield of the detosylated product (**8a**) was obtained. This was a 4 : 1 mixture of the *E* and *Z* isomers of the corresponding dehydroamino acid derivative, both being obtained pure by chromatography through silica gel. With methyl mercaptoacetate (**b**), detosylation was faster than in the case of the other nucleophiles, which was shown by the formation of a mixture of the addition product with the detosylated one as soon as the reagents were mixed. Thus, only the latter (**8b**) could be isolated (86%), as its *E* isomer, the reaction taking 72 hours to completion. An identical behaviour was observed with octane-1-thiol (**c**), which gave the *E* isomer of the corresponding β-substituted dehydroamino acid (**8c**) in a yield of 78%. We have previously reported[9] the reaction of Tos-ΔAla(*N*-Boc)-OMe **6** with nitrogen heterocycles to give the corresponding β-substituted dehydroamino acids as above. However, by using chloroform instead of acetonitrile as the reaction solvent we were able to decrease the rate of detosylation, thus making it possible to isolate the corresponding saturated *N*-Tos-*N*-Boc-amino acid derivatives **6k**, **6l**, **6m** and **6n**. As shown in Table 1, in the case of the two latter compounds the reactions were nearly quantitative. Unfortunately, some thiols showed too much reactivity to allow isolation of the saturated intermediates even when chloroform was used as solvent.

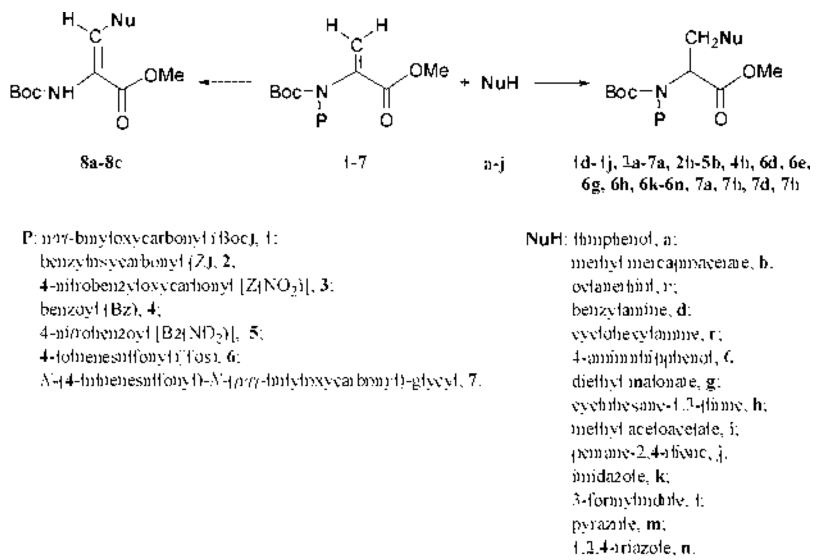
With aliphatic amines the reactions could be carried out in the absence of inorganic base but they required reaction times much longer than those for the other nucleophiles even when

† Electronic supplementary information (ESI) available: experimental data for compounds **1**–**15**. See http://www.rsc.org/suppdata/p1/b1/b106487h/

Table 1 Results obtained in the addition of nucleophiles to P-ΔAla(*N*-Boc)-OMe **1**–**7**

Entry	P	NuH	Product (compound no.)	Yield/%[a]
1	**1**	**d**	Boc-Ala(*N*-Boc,β-benzylamino)-OMe **1d**	79
2	**1**	**e**	Boc-Ala(*N*-Boc,β-cyclohexylamino)-OMe **1e**	72
3	**1**	**f**	Boc-Ala[*N*-Boc,β-(4-aminophenylsulfanyl)]-OMe **1f**	87
4	**1**	**g**	Boc-Ala[*N*-Boc,β-bis(ethoxycarbonyl)methyl]-OMe **1g**	83
5	**1**	**h**	Boc-Ala[*N*-Boc,β-(2,6-dioxocyclohexyl)]-OMe **1h**	80
6	**1**	**i**	Boc-Ala{*N*-Boc,β-[acetyl(methoxycarbonyl)methyl]}-OMe **1i**	94
7	**1**	**j**	Boc-Ala(*N*-Boc,β-diacetylmethyl)-OMe **1j**	83
8	**2**	**a**	Z-Ala(*N*-Boc,β-phenylsulfanyl)-OMe **2a**	94
9	**2**	**b**	Z-Ala(*N*-Boc,β-methoxycarbonylmethylsulfanyl)-OMe **2b**	93
10	**3**	**a**	Z(NO_2)-Ala(*N*-Boc,β-phenylsulfanyl)-OMe **3a**	95
11	**3**	**b**	Z(NO_2)-Ala(*N*-Boc,β-methoxycarbonylmethylsulfanyl)-OMe **3b**	90
12	**4**	**a**	Bz-Ala(*N*-Boc,β-phenylsulfanyl)-OMe **4a**	96
13	**4**	**b**	Bz-Ala(*N*-Boc,β-methoxycarbonylmethylsulfanyl)-OMe **4b**	96
14	**4**	**h**	Bz-Ala[*N*-Boc,β-(2,6-dioxocyclohexyl)]-OMe **4h**	33
15	**5**	**a**	Bz(NO_2)-Ala(*N*-Boc,β-phenylsulfanyl)-OMe **5a**	87
16	**5**	**b**	Bz(NO_2)-Ala(*N*-Boc,β-methoxycarbonylmethylsulfanyl)-OMe **5b**	98
17	**6**	**a**	Tos-Ala(*N*-Boc,β-phenylsulfanyl)-OMe **6a**	83
18	**6**	**a**	Boc-ΔAla(β-phenylsulfanyl)-OMe **8a**	83
19	**6**	**b**	Boc-ΔAla(β-methoxycarbonylmethylsulfanyl)-OMe **8b**	86
20	**6**	**c**	Boc-ΔAla(β-octylsulfanyl)-OMe **8c**	78
21	**6**	**d**	Tos-Ala(*N*-Boc,β-benzylamino)-OMe **6d**	81
22	**6**	**e**	Tos-Ala(*N*-Boc,β-cyclohexylamino)-OMe **6e**	83
23	**6**	**g**	Tos-Ala[*N*-Boc,β-bis(ethoxycarbonyl)methyl]-OMe **6g**	72
24	**6**	**h**	Tos-Ala[*N*-Boc,β-(2,6-dioxocyclohexyl)]-OMe **6h**	84
25	**6**	**i**	2-(*tert*-butoxycarbonylamino)-2,4-bis(methoxycarbonyl)-5-methyl-2,3-dihydrofuran **9i**	86
26	**6**	**j**	4-acetyl-2-(*tert*-butoxycarbonylamino)-2-methoxycarbonyl-5-methyl-2,3-dihydrofuran **9j**	88
27	**6**	**k**	Tos-Ala(*N*-Boc,β-imidazol-1-yl)-OMe[9] **6k**	72
28	**6**	**l**	Tos-Ala[*N*-Boc,β-(3-formylindol-1-yl)]-OMe **6l**	41
29	**6**	**m**	Tos-Ala(*N*-Boc,β-pyrazol-1-yl)-OMe[9] **6m**	96
30	**6**	**n**	Tos-Ala[*N*-Boc,β-(1,2,4-triazol-1-yl)]-OMe[9] **6n**	95
31	**7**	**a**	Tos-Gly(*N*-Boc)-Ala(*N*-Boc,β-phenylsulfanyl)-OMe **7a**	87
32	**7**	**b**	Tos-Gly(*N*-Boc-)Ala(*N*-Boc,β-methoxycarbonylmethylsulfanyl)-OMe **7b**	90
33	**7**	**d**	Tos-Gly(*N*-Boc)-Ala(*N*-Boc,β-benzylamino)-OMe **7d**	53
34	**7**	**h**	Tos-Gly(*N*-Boc)-Ala[*N*-Boc,β-(2,6-dioxocyclohexyl)]-OMe **7h**	60

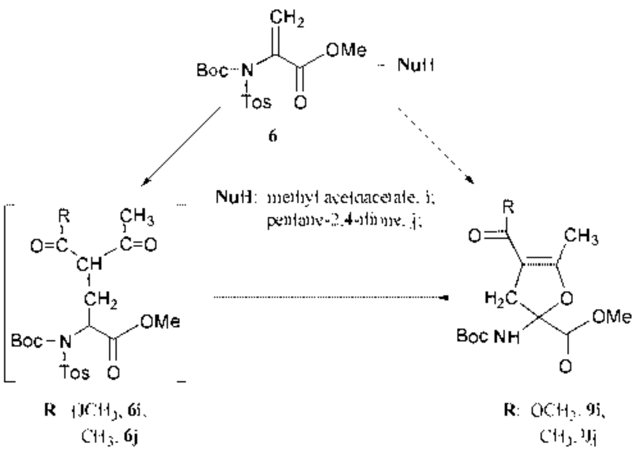
[a] Pure non-recrystallised material.



Scheme 1

they were carried out in the presence of K_2CO_3. Thus, 3-day reactions of Boc-ΔAla(*N*-Boc)-OMe **1** with benzylamine (**d**) and cyclohexylamine (**e**) gave compounds **1d** and **1e** in yields of 79 and 72%, respectively (Scheme 1, Table 1). An attempt was made to attain reaction of benzylamine (**d**) with Bz-ΔAla-(*N*-Boc)-OMe **4**; although 7 days later the starting dehydroamino acid derivative had been consumed, the only product obtained by column chromatography of the material collected from the reaction mixture was Boc-ΔAla-OMe. This resulted from aminolysis of the benzoyl group as mentioned with some nitrogen heterocycles,[8] which in the case of amines was facilitated by their low reactivity as compared with thiols. Thus, we were able to take advantage of this feature to carry out the selective addition of the thiol function of 4-aminothiophenol (**f**) to Boc-ΔAla(*N*-Boc)-OMe to prepare Boc-Ala[*N*-Boc,β-(4-aminophenylsulfanyl)]-OMe **1f** in 87% yield. With Tos-Gly(*N*-Boc)-ΔAla(*N*-Boc)-OMe, the product of addition of benzylamine (**7d**) was obtained in fair yield (53%). The reaction of Tos-ΔAla(*N*-Boc)-OMe **6** with benzylamine (**d**) and cyclohexylamine (**e**) gave the addition products **6d** and **6e** in slightly higher yields (81 and 83%, respectively) than those reported above for the substrate having two Boc groups. These addition products did not undergo detosylation even when the reaction was extended for several days.

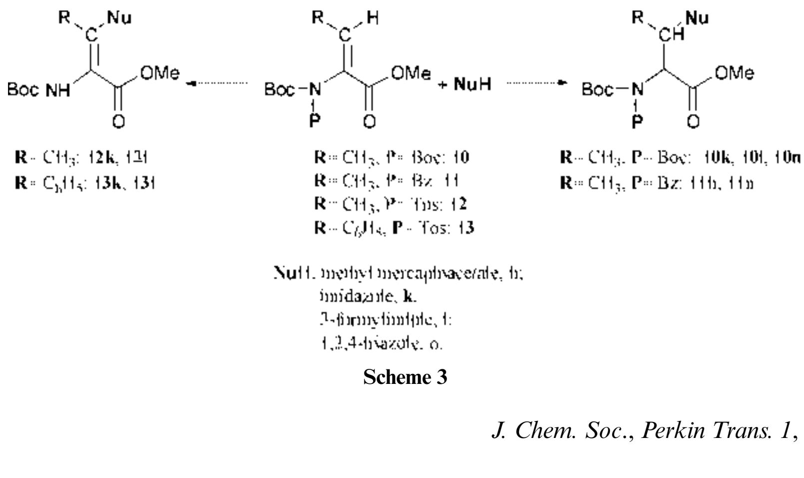
Addition of carbon nucleophiles of the β-dicarbonyl type was also performed; diethyl malonate (**g**), cyclohexane-1,3-dione (**h**), methyl acetoacetate (**i**) and pentane-2,4-dione (**j**) were used for this purpose. When the substrate was Boc-ΔAla-(*N*-Boc)-OMe the expected addition products (**1g**, **1h**) were obtained in yields of around 80% (Scheme 1, Table 1). With Tos-Gly(*N*-Boc)-ΔAla(*N*-Boc)-OMe as substrate, a yield of 60% for the product **7h** of addition of cyclohexane-1,3-dione (**h**) was obtained. As observed with amines, when one of the Boc groups was replaced by Tos the reactions with diethyl malonate (**g**) and cyclohexane-1,3-dione (**h**) gave the addition products (**6g** and **6h**) in yields of 72 and 84%, respectively. However, with methyl acetoacetate (**i**) and pentane-2,4-dione (**j**), which have at least one methyl group bonded to a carbonyl group, NMR spectroscopy revealed in both cases that the products (**9i** and **9j**) had a CH_2 group. In fact, the ^1H spectrum showed for both compounds a well resolved AB quartet centred at δ 3.16 ($-J$ = 15.9 Hz) and 3.23 ($-J$ = 15.7 Hz), respectively, integrating for two protons, which is typical of the β-CH_2 group of amino acids having no α-proton.[12] In addition, ^{13}C 'distortionless enhancement by polarisation transfer' (DEPT 135) spectra of these compounds showed a methylene group at δ_C 39.74 and 40.23, respectively. With this evidence, we propose for these compounds the structure resulting from spontaneous detosylation of the Michael adducts **6i** and **6j** followed by a rearrangement of the detosylated β-substituted alanine derivative *via* enolisation with attack of the enolic oxygen atom to the amino acid α-carbon, as shown in Scheme 2. These cyclic amino acids were obtained in yields of 86 and 88%, respectively.



Scheme 2

Addition of the nucleophiles mentioned above to Boc-ΔAbu(*N*-Boc)-OMe **10** and Bz-ΔAbu(*N*-Boc)-OMe **11** under conditions identical to those described for reaction with the corresponding dehydroalanine derivatives was attempted (Scheme 3, Table 2). In the case of the heterocyclic nitrogen compounds only the strong nucleophiles imidazole (**k**), 3-formylindole (**l**) and 1,2,4-triazole (**n**) underwent reaction with substrate **10**, to give **10k**, **10l** and **10n** in yields of 43, 47 and 65%, respectively, but required longer reaction times when compared with the equivalent reactions in the dehydroalanine series. The products were obtained as 1 : 1 diastereomeric mixtures, which could be separated by column chromatography. With weaker nucleophiles such as pyrazole and 7-azaindole no reaction was detected. In the addition of methyl mercaptoacetate (**b**) to the same substrate NMR spectroscopy indicated the formation of a small amount of **10b**; however, isolation of the product was not possible. No reaction was detected with either benzylamine (**d**) or cyclohexane-1,3-dione (**h**). The reaction of methyl mercaptoacetate (**b**) and 1,2,4-triazole (**n**) with compound **11** gave compounds **11b** and **11n** as diastereomeric mixtures in yields of 68 and 50%, respectively, which could be separated by column chromatography. In the latter case, also Boc-Abu[β-(1,2,4-triazol-1-yl)]-OMe (30%) and a small amount of Boc-ΔAbu-OMe[10] were obtained resulting from simultaneous and competitive cleavage of the Bz group. These slightly better overall yields for the addition product show that compounds having a Bz group are more reactive than those with only Boc groups. This may be due, on the one hand, to further conjugation through the phenyl ring of the former and, on the other hand, to a decreased reactivity of the latter due to the electron-donating mesomeric effect of the *tert*-butoxy group. No addition product was obtained in reactions with the even weaker nucleophiles benzylamine (**d**) and cyclohexane-1,3-dione; with benzylamine the benzoyl group was quantitatively cleaved to give Boc-ΔAbu-OMe. Reaction of Tos-ΔAbu-(*N*-Boc)-OMe **12** with imidazole (**k**) and 3-formylindole (**l**) gave the β-substituted didehydroaminobutyric acid derivatives **12k** and **12l** in yields of 48 and 89%. Didehydrophenylalanine derivatives showed an even lower reactivity than that found with those of didehydroaminobutyric acid. Thus, no addition product could be obtained with any of the test nucleophiles in conjunction with either Boc-ΔPhe(*N*-Boc)-OMe or even Bz-ΔPhe(*N*-Boc)-OMe; in an attempted reaction of the latter with methyl mercaptoacetate (**b**) no product was formed even 10 days after the reactants had been mixed. However, the reaction of Tos-ΔPhe(*N*-Boc)-OMe **13** with imidazole (**k**) and 3-formylindole (**l**) gave the expected products, **13k** and **13l**, as *E*/*Z* mixtures in yields of 69 and 85%, respectively.

Confirming and extending what had been previously demonstrated concerning the Michael addition to *N*-acyl-*N*-Boc-didehydroalanine methyl esters,[8] the results presented above show that not only strong nucleophiles such as thiols and nitrogen heterocycles but also aliphatic amines and β-dicarbonyl compounds are suitable reagents leading to good yields in the addition products. The lability to nitrogen nucleophiles typical of all acyl groups but Boc[8,11] was revealed in the case of the slow reactions involving the weaker nucleophiles. In this case, extensive cleavage was observed, which resulted in deactivation of the substrate and, thus, in very low yields or even in no formation of the required products. This low reactivity of aliphatic amines made it possible to add selectively the thiol function of 4-aminothiophenol (**f**) with a yield as good as 87%



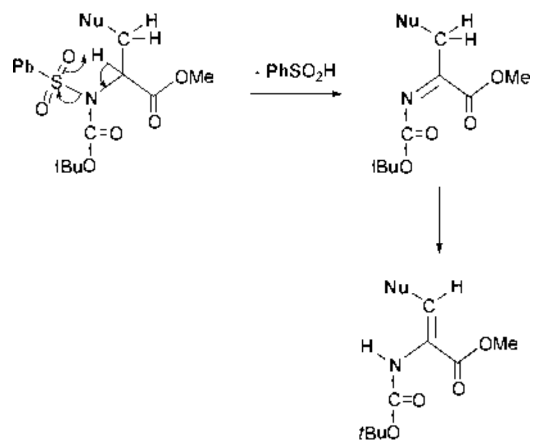
Scheme 3

Table 2 Results obtained in the addition of nucleophiles to P-ΔAbu(*N*-Boc)-OMe and P-ΔPhe(*N*-Boc)-OMe (P = Boc, Bz, Tos)

Entry	P	NuH	Product (compound no.)	Yield/%[a]
1	Boc	**k**	Boc-Abu[*N*-Boc,β-(imidazol-1-yl)]-OMe **10k**	43
2	Boc	**l**	Boc-Abu[*N*-Boc,β-(3-formylindol-1-yl)]-OMe **10l**	47
3	Boc	**n**	Boc-Abu[*N*-Boc,β-(1,2,4-triazol-1-yl)]-OMe **10n**	65
4	Bz	**b**	Bz-Abu(*N*-Boc,β-methoxycarbonylmethylsulfanyl)-OMe **11b**	68
5	Bz	**n**	Bz-Abu[*N*-Boc,β-(1,2,4-triazol-1-yl)]-OMe **11n**	50
6	Tos	**k**	Boc-ΔAbu[β-(imidazol-1-yl)]-OMe **12k**	48
7	Tos	**l**	Boc-ΔAbu[β-(3-formylindol-1-yl)]-OMe **12l**	89
8	Tos	**k**	Boc-ΔPhe[β-(imidazol-1-yl)]-OMe **13k**	69
9	Tos	**l**	Boc-ΔPhe[β-(3-formylindol-1-yl)]-OMe **13l**	85

[a] Pure non-recrystallised material.

(for **1f**). With the stronger nucleophiles all reactions were sufficiently fast to allow good yields in the expected product and this was also the case of the addition of thiols to a dipeptide derivative. In the *N*-acyl-*N*-Boc-didehydroaminobutyric acid methyl ester series only with the stronger nucleophiles was it possible to obtain an addition product, but the yields were moderate. The products were diastereomeric mixtures that could be resolved by column chromatography. In the *N*-acyl-*N*-Boc-didehydrophenylalanine methyl ester series no addition product could be obtained with any nucleophile tested. The low reactivity of the ΔAbu and ΔPhe substrates is interpreted in terms of deactivation caused by the electron-releasing contribution of the methyl and the conjugation effect related to phenyl, respectively, the latter being more effective in stabilising such substrates. Showing good reactivity, *N*-Tos-*N*-Boc-didehydroamino acid esters do not undergo nucleophilic cleavage under the reaction conditions, which leads to good yields in the addition reactions even in the case of the ΔAbu and ΔPhe substrates. With the stronger nucleophiles (nitrogen heterocycles and thiols) the addition products undergo detosylation to yield the corresponding β-substituted dehydroamino acid derivatives in very good yields, which confirms the results previously reported.[9] With some nucleophiles detosylation was slower than addition and, thus, it was possible to isolate the addition product prior to elimination. This was most evident in the case of thiophenol (**a**), which allowed obtention of the addition and the elimination products (**6a** and **8a**) both with a yield of 83%, only by controlling the reaction time. This tendency to detosylate may be due to steric pressure within the product side chain, associated with some electron-releasing effect exerted by the nucleophile moiety. Based on this hypothesis, in Scheme 4



Scheme 4

we propose a possible mechanism for this elimination. Usually, with the didehydroalanine derivative **6** only the *E* isomer was produced, or this was obtained in large excess with regard to the *Z* isomer. However, with *N*-Tos-*N*-Boc-didehydroaminobutyric acid and *N*-Tos-*N*-Boc-didehydrophenylalanine derivatives mixtures of the *E* and *Z* isomers were obtained, but these could be separated by column chromatography. Aliphatic amines and carbon nucleophiles reacted with *N*-Tos-*N*-Boc-didehydroalanine methyl ester but not with the corresponding ΔAbu and ΔPhe substrates. In the reaction of amines with the ΔAla derivative only the addition product was isolated in good yields. The products of addition of β-dicarbonyl compounds behaved in two different ways according to the structure of the nucleophile. The derivatives of diethyl malonate (**g**) and cyclohexane-1,3-dione (**h**) behaved much in the same way as those of aliphatic amines, but evidence was collected to support the idea that the derivatives of methyl acetoacetate (**i**) and pentane-2,4-dione (**f**) undergo cyclisation to give a furan derivative, which certainly releases some steric pressure within the side chain. The need for a methyl group bonded to a carbonyl group suggests that this process takes place through enolisation. However, as this rearrangement of structure seems to occur after detosylation, it is not clear to us why some of the compounds undergo detosylation and others do not; thus, we are now setting up to further investigate the behaviour of various tosyl substrates. We are also applying the results presented above to make side-chain-to-side-chain bonds within amino acids.

Experimental

General procedures

All melting points were measured on a Gallenkamp melting-point apparatus and are uncorrected. TLC analyses were carried out on 0.25 mm thick precoated silica gel plates (Merck Fertigplatten Kieselgel $60F_{254}$) and spots were visualised under UV light or by exposure to vaporised iodine. Preparative chromatography was carried out on Merck Kieselgel 60 (230–400 mesh). ^{1}H NMR spectra were recorded at 25 °C in ≈5% $CDCl_3$ solution on a Varian 300 spectrometer. 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 recorded with the same instrument at 75.4 MHz and using the solvent peak as internal reference. Elemental analyses of crystalline derivatives were carried out on a Leco CHNS 932 instrument. Petroleum ether refers to the fraction with distillation range 40–60 °C.

General method A. Synthesis of didehydroamino acid derivatives

The general procedure described elsewhere[10] was used.

General method B. Addition of nucleophiles to didehydroamino acid derivatives

As described elsewhere,[7] to a solution of 1 mmol of the methyl ester of an *N*,*N*-diacyl or *N*-tosyl-*N*-acyl-didehydroamino acid in acetonitrile (10 cm^3), K_2CO_3 (6 eq.) was added, followed by the nucleophile (1 eq.) 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 Boc-ΔAla(*N*-Boc)-OMe 1, Z-ΔAla(*N*-Boc)-OMe 2, Z(NO_2)-ΔAla(*N*-Boc)-OMe 3, Bz-ΔAla(*N*-Boc)-OMe 4, Bz(NO_2)-ΔAla(*N*-Boc)-OMe 5, Tos-ΔAla(*N*-Boc)-OMe 6, Tos-Gly(*N*-Boc)-ΔAla(*N*-Boc)-OMe 7 and Boc-ΔAbu(*N*-Boc)-OMe 10 and Tos-ΔAbu(*N*-Boc)-OMe 12. The synthesis of these compounds has been described elsewhere.[10,13]

Synthesis of didehydroamino acid derivatives by general method A

Synthesis of Bz-ΔAbu(*N*-Boc)-OMe 11. Bz-Thr-OMe gave a crystalline material (97%), mp 52–54 °C (from *n*-hexane) (Found: C, 64.1; H, 6.5; N, 4.5. Calc. for $C_{17}H_{21}NO_5$: C, 63.95; H, 6.6; N, 4.4%).

Synthesis of Tos-ΔPhe(*N*-Boc)-OMe 13. Tos-Phe(β-OH)-OMe gave a crystalline material (94%), mp 97.5–98 °C (from ethyl acetate–*n*-hexane) (Found: C, 61.3; H, 5.9; N, 3.1; S, 7.4. Calc. for $C_{22}H_{25}NO_6S$: C, 61.2; H, 5.8; N, 3.25; S, 7.4%).

Synthesis of Boc-ΔPhe(*N*-Boc)-OMe 14. Boc-Phe(β-OH)-OMe gave a solid product (98%), mp 55–56 °C (from *n*-hexane) (Found: C, 63.8; H, 7.2; N, 3.9. Calc. for $C_{20}H_{27}NO_6$: C, 63.65; H, 7.2; N, 3.7%).

Synthesis of Bz-ΔPhe(*N*-Boc)-OMe 15. Bz-Phe(β-OH)-OMe gave a solid product (98%), mp 99.5–101 °C (from diethyl ether–*n*-hexane) (Found: C, 69.3; H, 6.1; N, 3.8. Calc. for $C_{22}H_{23}NO_5$: C, 69.3; H, 6.1; N, 3.7%).

Addition of nucleophiles by general method B

Addition of sulfur nucleophiles to *N*-acyl-*N*-(*tert*-butoxycarbonyl)didehydroalanine methyl esters. *Synthesis of Z-Ala(N-Boc,β-phenylsulfanyl)-OMe* ***2a***. Z-ΔAla(*N*-Boc)-OMe and thiophenol gave an oil, which solidified on storage (94%) (Found: C, 62.1; H, 6.2; N, 3.2; S, 7.6. Calc. for $C_{23}H_{27}NO_6S$: C, 62.0; H, 6.1; N, 3.1; S, 7.2%).

Synthesis of Z-Ala(N-Boc,β-methoxycarbonylmethylsulfanyl)-OMe ***2b***. Z-ΔAla(*N*-Boc)-OMe and methyl mercaptoacetate gave an oil failing all attempts to crystallise (93%).

Synthesis of Z(NO$_2$)-Ala(N-Boc,β-phenylsulfanyl)-OMe ***3a***. Z(NO_2)-ΔAla(*N*-Boc)-OMe and thiophenol gave a crystalline material (95%), mp 84–85 °C (from *n*-hexane) (Found: C, 56.6; H, 5.4; N, 5.8; S, 6.5. Calc. for $C_{23}H_{26}N_2O_8S$: C, 56.3; H, 5.3; N, 5.7; S, 6.5%).

Synthesis of Z(NO$_2$)-Ala(N-Boc,β-methoxycarbonylmethylsulfanyl)-OMe ***3b***. Z(NO_2)-ΔAla(*N*-Boc)-OMe and methyl mercaptoacetate gave an oil failing all attempts to crystallise (90%).

Synthesis of Bz-Ala(N-Boc,β-phenylsulfanyl)-OMe ***4a***. Bz-ΔAla(*N*-Boc)-OMe and thiophenol gave a crystalline material (96%), mp 73–74 °C (from diethyl ether–*n*-hexane) (Found: C, 63.9; H, 6.1; N, 3.5; S, 7.6. Calc. for $C_{22}H_{25}NO_5S$: C, 63.6; H, 6.1; N, 3.4; S, 7.7%).

Synthesis of Bz-Ala(N-Boc,β-methoxycarbonylmethylsulfanyl)-OMe ***4b***. Bz-ΔAla(*N*-Boc)-OMe and methyl mercaptoacetate gave a crystalline material (96%), mp 60–62 °C (from diethyl ether–*n*-hexane) (Found: C, 55.6; H, 6.15; N, 3.5; S, 7.6. Calc. for $C_{19}H_{25}NO_7S$: C, 55.5; H, 6.1; N, 3.4; S, 7.8%).

Synthesis of Bz(NO$_2$)-Ala(N-Boc,β-phenylsulfanyl)-OMe ***5a***. Bz(NO_2)-ΔAla(*N*-Boc)-OMe and thiophenol gave a crystalline material (87%), mp 61–63 °C (from diethyl ether–*n*-hexane) (Found: C, 57.7; H, 5.3; N, 6.1; S, 6.9. Calc. for $C_{22}H_{24}N_2O_7S$: C, 57.4; H, 5.25; N, 6.1; S, 7.0%).

Synthesis of Bz(NO$_2$)-Ala(N-Boc,β-methoxycarbonylmethylsulfanyl)-OMe ***5b***. Bz(NO_2)-ΔAla(*N*-Boc)-OMe and methyl mercaptoacetate gave a crystalline material (98%), mp 70–71 °C (from diethyl ether–*n*-hexane) (Found: C, 50.35; H, 5.4; N, 6.1; S, 6.9. Calc. for $C_{19}H_{24}N_2O_9S$: C, 50.0; H, 5.3; N, 6.1; S, 7.0%).

Synthesis of Tos-Ala(N-Boc,β-phenylsulfanyl)-OMe ***6a***. Tos-ΔAla(*N*-Boc)-OMe and thiophenol gave a crystalline material (83%), mp 67–69 °C (from diethyl ether–*n*-hexane) (Found: C, 57.0; H, 5.8; N, 3.1; S, 13.4. Calc. for $C_{22}H_{27}NO_6S_2$: C, 56.75; H, 5.8; N, 3.0; S, 13.8%).

Synthesis of Boc-ΔAla(β-phenylsulfanyl)-OMe ***8a***. In a 10-day reaction, Tos-ΔAla(*N*-Boc)-OMe and thiophenol gave a 4 : 1 *E*/*Z* mixture (83%). These were separated by chromatographing the product through silica gel using diethyl ether–*n*-hexane 4 : 1 as eluent; *E*-isomer, mp 108–109 °C (from diethyl ether–*n*-hexane) (Found: C, 58.3; H, 6.25; N, 4.5; S, 10.25. Calc. for $C_{15}H_{19}NO_4S$: C, 58.2; H, 6.2; N, 4.5; N, 10.4%); *Z*-isomer, oil.

Synthesis of Boc-ΔAla(β-methoxycarbonylsulfanyl)-OMe ***8b***. By letting the reaction proceed for 72 hours, Tos-ΔAla(*N*-Boc)-OMe and methyl mercaptoacetate gave the *E* isomer as a crystalline material (86%), mp 66–67 °C (from diethyl ether–*n*-hexane) (Found: C, 47.0; H, 6.3; N, 4.5; S, 10.3. Calc. for $C_{12}H_{19}NO_6S$: C, 47.2; H, 6.3; N, 4.6; S, 10.5%).

Synthesis of Boc-ΔAla(β-octylsulfanyl)-OMe ***8c***. By letting the reaction proceed for 72 hours, Tos-ΔAla(*N*-Boc)-OMe and octane-1-thiol gave the *E* isomer as a crystalline material (78%), mp 49.5–51 °C (from diethyl ether–*n*-hexane) (Found: C, 59.1; H, 8.9; N, 4.0; S, 9.5. Calc. for $C_{17}H_{31}NO_4S$: C, 59.1; H, 9.0; N, 4.05; S, 9.3%).

Addition of nitrogen heterocycles to *N*-tosyl-*N*-(*tert*-butoxycarbonyl)didehydroalanine methyl ester. *Synthesis of Tos-Ala(N-Boc,β-imidazol-1-yl)-OMe*[9] ***6k***. Using chloroform as solvent, Tos-ΔAla(*N*-Boc)-OMe and imidazole gave an oil failing all attempts to crystallise (72%).

Synthesis of Tos-Ala[N-Boc,β-(3-formylindol-1-yl)]-OMe ***6l***. Using chloroform as solvent, Tos-ΔAla(*N*-Boc)-OMe and 3-formylindole gave a product which was chromatographed through silica gel using diethyl ether–*n*-hexane 2 : 1 as eluent to yield a crystalline material (41%), mp 165–167 °C (from diethyl ether–*n*-hexane) (Found: C, 60.05; H, 5.8; N, 5.6; S, 6.3. Calc. for $C_{25}H_{28}N_2O_7S$: C, 60.0; H, 5.6; N, 5.6; S, 6.4%).

Synthesis of Tos-Ala(N-Boc,β-pyrazol-1-yl)-OMe[9] ***6m***. Using chloroform as solvent, Tos-ΔAla(*N*-Boc)-OMe and pyrazole gave a crystalline material (96%), mp 113.5–115.5 °C (from diethyl ether–*n*-hexane) (Found: C, 54.0; H, 5.9; N, 9.55; S, 7.6. Calc. for $C_{19}H_{25}N_3O_6S$: C, 53.9; H, 5.95; N, 9.9; S, 7.6%).

Synthesis of Tos-Ala[N-Boc,β-(1,2,4-triazol-1-yl)]-OMe[9] ***6n***. Using chloroform as solvent, Tos-ΔAla(*N*-Boc)-OMe and 1,2,4-triazole gave a crystalline material (95%), mp 114–115 °C (from ethyl acetate–diethyl ether) (Found: C, 50.8; H, 5.65; N, 13.2; S, 7.9. Calc. for $C_{18}H_{24}N_4O_6S$: C, 50.9; H, 5.7; N, 13.2; S, 7.55%).

Addition of amines to *N*-acyl-*N*-(*tert*-butoxycarbonyl)didehydroalanine methyl esters. *Synthesis of Boc-Ala(N-Boc,β-benzylamino)-OMe* ***1d***. Boc-ΔAla(*N*-Boc)-OMe and benzylamine gave an oil failing all attempts to crystallise (79%).

Synthesis of Boc-Ala(N-Boc,β-cyclohexylamino)-OMe ***1e***. Boc-ΔAla(*N*-Boc)-OMe and cyclohexylamine gave an oil that eventually crystallised (72%), mp 59.0–60.5 °C (Found: C, 59.9; H, 9.1; N, 6.85. Calc. for $C_{20}H_{36}N_2O_6$: C, 60.0; H, 9.1; N, 7.0%).

Synthesis of Boc-Ala[N-Boc,β-(4-aminophenylsulfanyl)]-OMe ***1f***. Boc-ΔAla(*N*-Boc)-OMe and 4-aminothiophenol gave a crystalline material (87%), mp 63–64.5 °C (from diethyl ether–*n*-hexane) (Found: C, 56.3; H, 7.1; N, 6.6; S, 7.4. Calc. for $C_{20}H_{30}N_2O_6S$: C, 56.3; H, 7.1; N, 6.6; S, 7.5%).

Synthesis of Tos-Ala(N-Boc,β-benzylamino)-OMe ***6d***. Tos-ΔAla(*N*-Boc)-OMe and benzylamine gave an oil failing all attempts to crystallise (81%).

Synthesis of Tos-Ala(N-Boc,β-cyclohexylamino)-OMe ***6e***. Tos-ΔAla(*N*-Boc)-OMe and cyclohexylamine gave an oil failing all attempts to crystallise (83%).

Attempt to synthesise Bz-Ala(N-Boc,β-benzylamino)-OMe ***4d***. Seven days after Bz-ΔAla(*N*-Boc)-OMe and benzylamine had been mixed, ^{1}H NMR indicated that the reactants had been consumed. The crude material obtained was chromatographed through silica gel using diethyl ether–petroleum ether as eluent to give Boc-ΔAla-OMe (44%) and a benzylamine salt.

Addition of carbon nucleophiles to *N*-acyl-*N*-(*tert*-butoxycarbonyl)didehydroalanine methyl esters. *Synthesis of Boc-Ala[N-Boc,β-bis(ethoxycarbonyl)methyl]-OMe* ***1g***. Boc-ΔAla(*N*-Boc)-OMe and diethyl malonate gave an oil failing all attempts to crystallise (83%).

Synthesis of Boc-Ala[N-Boc,β-(2,6-dioxocyclohexyl)]-OMe ***1h***. Boc-ΔAla(*N*-Boc)-OMe and cyclohexane-1,3-dione gave a crystalline material (80%), mp 144–145 °C (from diethyl ether–*n*-hexane) (Found: C, 57.8; H, 7.5; N, 3.4. Calc. for $C_{20}H_{31}NO_8$: C, 58.1; H, 7.6; N, 3.4%).

Synthesis of Boc-Ala{N-Boc,β-[(acetylmethoxycarbonyl)-methyl]}-OMe ***1i***. Boc-ΔAla(*N*-Boc)-OMe and methyl acetoacetate gave a crystalline material (94%), mp 94–95.5 °C (from *n*-hexane) (Found: C, 54.8; H, 7.5; N, 3.45. Calc. for $C_{19}H_{31}NO_9$: C, 54.7; H, 7.5; N, 3.4%).

Synthesis of Boc-Ala(N-Boc,β-(diacetylmethyl)-OMe ***1j***. Boc-ΔAla(*N*-Boc)-OMe and pentane-2,4-dione gave a crystalline material (83%), mp 107–108 °C (from diethyl ether–*n*-hexane) (Found: C, 56.8; H, 7.7; N, 3.6. Calc. for $C_{19}H_{31}NO_8$: C, 56.85; H, 7.8; N, 3.5%).

Synthesis of Bz-Ala[N-Boc,β-(2,6-dioxocyclohexyl)]-OMe ***4h***. Seven days after Bz-ΔAla(*N*-Boc)-OMe and cyclohexane-1,3-dione had been mixed, ^{1}H NMR indicated that the reactants had been consumed. The crude material was chromatographed through silica gel using diethyl ether–*n*-hexane as eluent to give **4h** as a crystalline material (33%); mp 149–150 °C (from diethyl ether–*n*-hexane) (Found: C, 63.4; H, 6.6; N, 3.4. Calc. for $C_{22}H_{27}NO_7$: C, 63.3; H, 6.5; N, 3.4%).

Synthesis of Tos-Ala[N-Boc,β-bis(ethoxycarbonyl)methyl]-OMe ***6g***. Tos-ΔAla(*N*-Boc)-OMe and diethyl malonate gave a crystalline material (72%), mp 102–103 °C (from diethyl ether–*n*-hexane) (Found: C, 53.7; H, 6.3; N, 2.85; S, 6.2. Calc. for $C_{23}H_{33}NO_{10}S$: C, 53.6; H, 6.45; N, 2.7; S, 6.2%).

Synthesis of Tos-Ala[N-Boc,β-(2,6-dioxocyclohexyl)]-OMe ***6h***. Tos-ΔAla(*N*-Boc)-OMe and cyclohexane-1,3-dione gave a crystalline material (84%), mp 165–167 °C (from diethyl ether) (Found: C, 56.3; H, 6.3; N, 3.0; S, 6.6. Calc. for $C_{22}H_{29}NO_8S$: C, 56.5; H, 6.25; N, 3.0; S, 6.9%).

Synthesis of 2-(tert-butoxycarbonylamino)-2,4-bis(methoxycarbonyl)-5-methyl-2,3-dihydrofuran ***9i***. Tos-ΔAla(*N*-Boc)-OMe and methyl acetoacetate gave a crystalline material (86%), mp 121.5–123 °C (from diethyl ether–*n*-hexane) (Found: C, 53.3; H, 6.6; N, 4.3. Calc. for $C_{14}H_{21}NO_7$: C, 53.3; H, 6.7; N, 4.4%).

Synthesis of 4-acetyl-2-(tert-butoxycarbonylamino)-2-methoxycarbonyl-5-methyl-2,3-dihydrofuran ***9j***. Tos-ΔAla(*N*-Boc)-OMe and pentane-2,4-dione gave a crystalline material (88%), mp 113.5–114.5 °C (from diethyl ether–*n*-hexane) (Found: C, 56.1; H, 7.1; N, 4.8. Calc. for $C_{14}H_{21}NO_6$: C, 56.2; H, 7.1; N, 4.7%).

Addition of thiophenol, methyl mercaptoacetate, cyclohexane-1,3-dione and benzylamine to Tos-Gly(*N*-Boc)-ΔAla(*N*-Boc)-OMe. *Synthesis of Tos-Gly(N-Boc)-Ala(N-Boc,β-phenylsulfanyl)-OMe* ***7a***. Tos-Gly(*N*-Boc)-ΔAla(*N*-Boc)-OMe and thiophenol gave a crystalline material (87%), mp 53–55 °C (from diethyl ether–*n*-hexane) (Found: C, 56.1; H, 6.1; N, 4.6; S, 10.0. Calc. for $C_{29}H_{38}N_2O_9S_2$: C, 55.9; H, 6.15; N, 4.5; S, 10.3%).

Synthesis of Tos-Gly(N-Boc)-Ala(N-Boc,β-methoxycarbonylmethylsulfanyl)-OMe ***7b***. Tos-Gly(*N*-Boc)-ΔAla(*N*-Boc)-OMe and methyl mercaptoacetate gave an oil failing all attempts to crystallise (90%).

Synthesis of Tos-Gly(N-Boc)-Ala(N-Boc,β-benzylamino)-OMe ***7d***. Tos-Gly(*N*-Boc)-ΔAla(*N*-Boc)-OMe and benzylamine gave a crystalline material (53%), mp 58.5–61 °C (from diethyl ether–*n*-hexane) (Found: C, 58.3; H, 6.55; N, 6.7; S, 5.5. Calc. for $C_{30}H_{41}N_3O_9S$: C, 58.1; H, 6.7; N, 6.8; S, 5.2%).

Synthesis of Tos-Gly(N-Boc)-Ala[N-Boc,β-(2,6-dioxocyclohexyl)]-OMe ***7h***. Tos-Gly(*N*-Boc)-ΔAla(*N*-Boc)-OMe and cyclohexane-1,3-dione gave a crystalline material (60%), mp 173–174 °C (from diethyl ether) (Found: C, 56.1; H, 6.6; N, 4.5; S, 5.0. Calc. for $C_{29}H_{40}N_2O_{11}S$: C, 55.8; H, 6.45; N, 4.5; S, 5.1%).

Addition to *N*-acyl,*N*-(*tert*-butoxycarbonyl)-didehydroaminobutyric acid and -didehydrophenylalanine methyl esters. *Synthesis of Boc-Abu[N-Boc,β-(imidazol-1-yl)]-OMe* ***10k***. Boc-ΔAbu(*N*-Boc)-OMe and imidazole gave a 1 : 1 mixture of diastereomers (43%). This was chromatographed through silica gel using ethyl acetate–diethyl ether 1 : 1 as eluent; mp 81.5–83.5 °C and 82.5–84.5 °C (from ethyl acetate–*n*-hexane) (Found: C, 56.5; H, 7.75; N, 10.6. Calc. for $C_{18}H_{29}N_3O_6$: C, 56.4; H, 7.6; N, 10.95%).

Synthesis of Boc-Abu[N-Boc,β-(3-formylindol-yl)]-OMe ***10l***. Boc-ΔAbu(*N*-Boc)-OMe and 3-formylindole gave a 1 : 1 mixture of diastereomers (47%). This was chromatographed through silica gel using diethyl ether–*n*-hexane 2 : 1 as eluent; mp 109–111 °C and 145–147 °C (from diethyl ether–*n*-hexane) (Found: C, 62.9; H, 7.0; N, 6.15. Calc. for $C_{24}H_{32}N_2O_7$: C, 62.6; H, 7.0; N, 6.1%).

Synthesis of Boc-Abu[N-Boc,β-(1,2,4-triazol-1-yl)]-OMe ***10n***. Boc-ΔAbu(*N*-Boc)-OMe and 1,2,4-triazole gave a 1 : 1 mixture of diastereomers (65%). This was chromatographed through silica gel using diethyl ether as eluent; mp 84–85 °C and 108–110 °C (from diethyl ether–*n*-hexane) (Found: C, 53.1; H, 7.4; N, 14.5. Calc. for $C_{17}H_{28}N_4O_6$: C, 53.1; H, 7.3; N, 14.6%).

Synthesis of Bz-Abu(N-Boc,β-methoxycarbonylmethylsulfanyl)-OMe ***11b***. Bz-ΔAbu(*N*-Boc)-OMe and methyl mercaptoacetate gave a 1 : 1 mixture of diastereomers (68%). This was chromatographed through silica gel using diethyl ether–petroleum ether 1 : 2 as eluent; mp 60–61 °C (from *n*-hexane) and an oil (Found: C, 56.5; H, 6.55; N, 3.3; S, 7.4. Calc. for $C_{20}H_{27}NO_7S$: C, 56.5; H, 6.4; N, 3.3; S, 7.5%).

Synthesis of Bz-Abu[N-Boc,β-(1,2,4-triazol-1-yl)]-OMe ***11n***. Bz-ΔAbu(N-Boc)-OMe and 1,2,4-triazole were mixed and left for 72 hours to give a mixture containing both diastereomers of the expected product and also Boc-Abu[β-(1,2,4-triazol-1-yl)]-OMe and some Boc-ΔAbu-OMe. The crude material obtained was chromatographed through silica gel using diethyl ether–*n*-hexane 2 : 1 as eluent to give **11n** as a 1 : 1 mixture of diastereomers (50%), *Boc-Abu[β-(1,2,4-triazol-1-yl)]-OMe* (30%) (Found: C, 51.05; H, 7.0; N, 19.5. Calc. for $C_{12}H_{20}N_4O_4$: C, 50.7; H, 7.1; N, 19.7%); and Boc-ΔAbu-OMe.[10] The diastereomeric mixture of **11n** was in turn separated by chromatography through silica gel using diethyl ether–*n*-hexane as eluent to give products with mp 108–109.5 °C and 79.5–81.5 °C (from ethyl acetate–*n*-hexane) (Found: C, 59.0; H, 6.1; N, 14.1. Calc. for $C_{19}H_{24}N_4O_5$: C, 58.75; H, 6.2; N, 14.4%).

Synthesis of Boc-ΔAbu[β-(imidazol-1-yl)]-OMe ***12k***. Tos-ΔAbu(*N*-Boc)-OMe and imidazole gave a 65 : 35 *E*/*Z* mixture (48%). These were chromatographed through silica gel using diethyl ether–*n*-hexane (1 : 1) and ethyl acetate–*n*-hexane (2 : 1) as eluents to give: *E*-isomer, mp 145–146 °C (from diethyl ether–*n*-hexane), and *Z*-isomer, mp 115.5–116.5 °C (from diethyl ether–*n*-hexane) (Found: C, 55.5; H, 6.7; N, 14.7. Calc. for $C_{13}H_{19}N_3O_4$: C, 55.5; H, 6.8; N, 14.9%).

Synthesis of Boc-ΔAbu[β-(3-formylindol-1-yl)]-OMe **12l**. Tos-ΔAbu(*N*-Boc)-OMe and 3-formylindole gave a 65 : 35 mixture (89%). These were chromatographed through silica gel using diethyl ether–*n*-hexane as eluent to give: *E*-isomer, mp 145.5–147 °C (from ethyl acetate–*n*-hexane), and *Z*-isomer, mp 170–171 °C (from ethyl acetate–*n*-hexane) (Found: C, 63.5; H, 6.2; N, 7.7. Calc. for $C_{19}H_{22}N_2O_5$: C, 63.7; H, 6.2; N, 7.8%).

Attempt to synthesise Bz-Abu(N-Boc,β-benzylamino)-OMe. Bz-ΔAbu(*N*-Boc)-OMe and benzylamine gave Boc-ΔAbu-OMe [10] (87%).

Synthesis of Boc-ΔPhe[β-(imidazol-1-yl)]-OMe **13k**. Tos-ΔPhe(*N*-Boc)-OMe and imidazole gave an 1 : 1 *E*/*Z* mixture (69%). This was chromatographed through silica gel using ethyl acetate–diethyl ether as eluent; mp 164–165.5 °C and 142–144 °C (from ethyl acetate–diethyl ether) (Found: C, 63.2; H, 6.4; N, 11.7. Calc. for $C_{18}H_{21}N_3O_4$: C, 63.0; H, 6.2; N, 12.2%).

Synthesis of Boc-ΔPhe[β-(3-formylindol-1-yl)]-OMe **13l**. Tos-ΔPhe(*N*-Boc)-OMe and 3-formylindole gave a 1 : 1 *E*/*Z* mixture (85%). This was chromatographed through silica gel using diethyl ether–*n*-hexane 2 : 1 as eluent; mp 168–170 °C and 193–195 °C (from diethyl ether–*n*-hexane) (Found: C, 68.25; H, 5.9; N, 6.5. Calc. for $C_{24}H_{24}N_2O_5$: C, 68.6; H, 5.75; N, 6.7%).

Attempt to synthesise Bz-Phe[β-(1,2,4-triazol-1-yl)]-OMe. Bz-ΔPhe(*N*-Boc)-OMe and 1,2,4-triazole were mixed and set aside for 72 hours; then, the solution was filtered and the solvent was evaporated at reduced pressure to give Boc-ΔPhe-OMe (84%), mp 80.5–81.5 °C (from diethyl ether–*n*-hexane) (Found: C, 65.0; H, 7.2; N, 5.1. Calc. for $C_{15}H_{19}NO_4$: C, 65.0; H, 6.9; N, 5.05%).

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