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FREE-RADICAL ADDITION TO DI- AND TRIPEPTIDES CONTAINING DEHYDROALANINE RESIDUES

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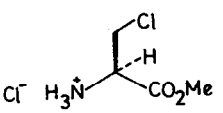
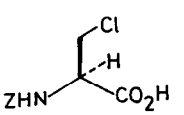
Abstract: Radical addition, by the alkylmercury halide/sodium borohydride method, to di-and tripeptides containing a dehydroalanine residue proceeds smoothly with good chemical yield, but low diastereoselectivity, to saturated di- and tripeptides.

The development of new synthetic methodology for the preparation of α-amino acids is currently an area of much activity and interest[1]. Although largely the domain of polar mechanisms and intermediates α-amino synthesis has not been exempt from the recent proliferation[2] of synthetic methods based on free-radical mechanisms; the amenability of various derivatives of side chain functionalised amino acids to modification by radical methods having been demonstrated[3] by several groups. More recently Baldwin has extended this chemistry to glycinyl radical equivalents[4] and further possibilities are opened up by the work[5] of Easton on the regioselective halogenation of alanine and valine derivatives. We[6], and independantly Orlinski[7], on the other hand have concentrated our efforts on radical addition to dehydroalanine derivatives, a class of compounds from which α-amino acids have also been prepared by catalytic hydrogenation[8] and by conjugate addition of a variety of nucleophiles[9].

In this paper we report the extension of our method[6] to the preparation of di- and tripeptides by radical addition to the appropriate dehydroalanine containing peptides. Thus a variety of *C*-terminal β-chloroalanine containing dipeptides (3) → (7) were prepared by coupling *N*-benzyloxycarbonyl protected L-amino acids with β-chloro-L-alanine methyl ester hydrochloride[10] (1) by the isobutylchloroformate route[11] (Table 1, Entries 1-5). The *N*-terminal β-chloroalanine containing dipeptides (8) and (9) were obtained by coupling *N*-Z-β-chloro-L-alanine[12] (2) with the methyl esters of L-valine and L-proline by the mixed anhydride route and the pentafluorophenyl ester route[13] respectively (Table 1, Entries 6 and 7).



(1)



(2)

Z-X-L-ClAla-OMe

(3) X = L-Val
(4) X = L-Phe
(5) X = L-Cys(Z)
(6) X = L-Ser(OH)
(7) X = L-Pro

Z = $PhCH_2OCO$

Z-L-ClAla-X-OMe

(8) X = L-Val
(9) X = L-Pro

Table 1

Entry	Product	Coupling Method	% Yield
1	(3)	A	56
2	(4)	A	92
3	(5)	A	98
4	(6)	A	a
5	(7)	A	69
6	(8)	A	76
7	(9)	B	73

a, not isolated; A, isobutylchloroformate; B, pentafluorophenol.

On treatment with either triethylamine in ethyl acetate or diazabicyclooctane (DABCO) in dichloromethane according to Olsen[14] the dipeptides (3) → (9) underwent elimination of HCl to give the *C* and *N* terminal dehydroalanine dipeptides (10) → (16) in good yield (Table 2) with the exception of (12) and (13) (Table 2, Entries 3 and 4) which were susceptible to polymerisation.

Z-X-ΔAla-OMe

(10) X = L-Val
(11) X = L-Phe
(12) X = L-Cys(Z)
(13) X = L-Ser (OH)
(14) X = L-Pro

Z-ΔAla-X-OMe

(15) X = L-Val
(16) X = L-Pro

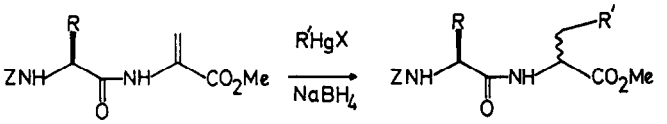
Table 2

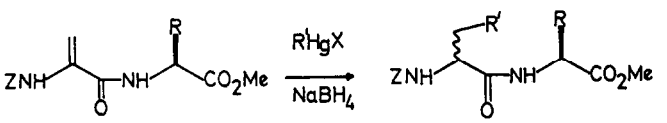
Entry	Product	Base	% Yield
1	(10)	Et_3N	92
2	(11)	Et_3N	93
3	(12)	Et_3N	43[a]
4	(13)	Et_3N	21[a]
5	(14)	Et_3N	97
6	(15)	DABCO	95
7	(16)	Et_3N	86

a, polymerise on standing

Attempts at radical addition to the dehydroalanine (17) with radicals generated by the *O*-acyl-thiohydroxamate method[15] had previously failed[6], presumably due to the reluctance of capto-dative radicals[16] to propagate such chain reactions. Likewise the tributyltin hydride method[17] had proven[6] to be incompatible with (17) owing to competing hydrostannylation. Thus it was decided that given the ready availability[18] of alkylmercury halides, their extensive free-radical chemistry[19] and their compatibility[6] with the dehydroalanine (17) to apply the Giese alkylmercury hydride methodology.[20]

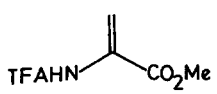
The radical reactions (eq. 1 and 2) were carried out, as in the case[6] of (17), by dropwise addition of aqueous sodium borohydride to a stirred solution of the dehydroalanine and an excess of the alkylmercury halide in dichloromethane under a nitrogen atmosphere at room temperature.





In the case of addition to the *C*-terminal dehydroalanines (10) → (14) yields, with the exception of Z-Ser-ΔAla-OMe (13), were generally good (Table 3, Entries 1 → 5). The diastereoselectivities at the newly formed chiral centre, estimated by normal phase HPLC analysis on an aliquot removed after aqueous workup but before chromatographic purification, were negligible. As such no attempt was made to determine the sense of induction. Treatment of (10), and (11), with cyclohexylmercury chloride in ethanol and subsequently with sodium borohydride again provided dipeptides (22), and (23), but with no improvement in diastereoselectivity and in substantially lower yield.

Sodium borohydride mediated addition of isopropylmercury chloride to the *N*-terminal dehydroalanine dipeptide (15) gave a good yield of the adduct (27) but once again with negligible diastereoselectivity (Table 3, Entry 6). However addition of the isopropyl radical to Z-ΔAla-Pro-OMe (16) provided the diastereoisomeric dipeptides (28) in 74% yield and with a d.e. of 28% (Table 3, Entry 7). An authentic sample of Z-L-Leu-L-Pro-OMe prepared by coupling Z-L-Leu with L-Pro-OMe by the pentafluorophenyl ester method was used to establish the major diastereoisomer of (28) as Z-L-Leu-L-Pro-OMe. Addition of other bulky radicals to (16) gave again good isolated yields of dipeptides but with lower diastereoselectivities (Table 3, Entries 8 and 9).



(17)

R-Hg-X

(18) R = cC_6H_{11}, X = Cl
(19) R = ^iPr, X = Cl
(20) R = $CH_2{}^tBu$, X = Br
(21) R = ^tBu, X = Cl

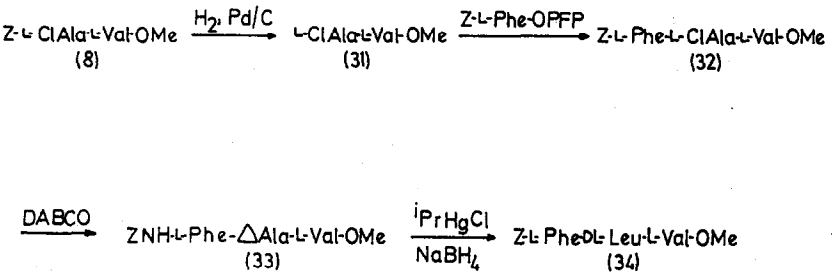
Z-X-Y-OMe

(22) X = L-Val, Y = DL-C_6H_{11}Ala
(23) X = L-Phe, Y = DL-C_6H_{11}Ala
(24) X = L-Cys(Z), Y = DL-C_6H_{11}Ala
(25) X = L-Ser(OH), Y = DL-C_6H_{11}Ala
(26) X = L-Pro, Y = DL-Leu
(27) X = DL-Leu, Y = L-Val
(28) X = DL-Leu, Y = L-Pro
(29) X = DL-^{t}BuCH$_2$Ala, Y = L-Pro
(30) X = DL-^{t}BuAla, Y = L-Pro

Table 3

Entry	Substrate	RHgX	Product	% Yield	% d.e.
1	(10)	(18)	(22)	71	11[a]
2	(11)	(18)	(23)	64	5[a]
3	(12)	(18)	(24)	70	6[a]
4	(13)	(18)	(25)	42	1[a]
5	(14)	(19)	(26)	98	1[a]
6	(15)	(19)	(27)	74	7[a]
7	(16)	(19)	(28)	74	28[b]
8	(16)	(20)	(29)	71	20[b]
9	(16)	(21)	(30)	87	12[b]

a, Determined by HPLC; b, Determined by ^{1}H-NMR (insufficient resolution on HPLC).

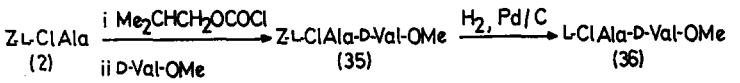


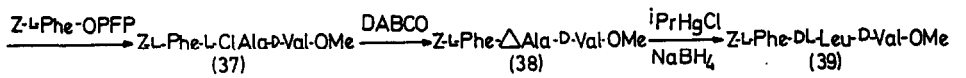
Scheme 1

We next turned our attention to tripeptides containing a dehydroalanine moiety. Thus hydrogenolysis of Z-L-βClAla-L-Val-OMe (8) over 5% palladium on charcoal gave the free amine which was immediately coupled with the pentafluorophenyl ester of Z-L-Phe to give an 83% isolated yield of the tripeptide (32). Dehydrochlorination with DABCO provided (90%) the dehydroalanine tripeptide (33) which was subjected to treatment, in a two phase dichlormethane-water system, with isopropylmercury chloride and sodium

borohydride giving an 88% yield of a diastereoisomeric mixture of tripeptides (34) with a d.e. of 15% (Scheme 1).

A second, diasteriosomeric tripeptide (38) was synthesized in an analogous manner (Scheme 2) by coupling (2) with D-Val-OMe, giving (35), followed by hydrogenolysis to (36) and coupling with Z-L-Phe-OPFP to (37). Dehydrochlorination of (37) gave (38) which was reacted with isopropylmercury chloride/sodium borohydride in the usual manner to give an 87% isolated yield of the tripeptides (39) with a d.e. only of 3%.





Scheme 2

It is interesting to note that radical addition to tripeptide (33) resulted in a d.e. of 15%, whilst addition to the diastereoisomer (38) gave only 3% d.e. suggesting that the two L-amino acid residues in (33) were reinforcing each other whilst the L and D residues of (38) had opposite directing effects which largely cancelled each other out.[21]

In conclusion our previous work on radical addition to dehydroalanine derivatives has been successfully extended to encompass di- and tripeptides containing dehydroalanine residues. The diastereoselectivities observed in the hydrogen atom transfer step were however disappointingly low; intermolecular diastereoselective hydrogen atom transfer remains an elusive process.[22]

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Experimental

General: Melting points are uncorrected and were determined with a Kofler hot stage apparatus. Optical rotations were measured in chloroform with an Optical Activity AA-10 polarimeter. IR spectra were recorded as chloroform solutions with a Perkin Elmer 983 spectrophotometer; ^{1}H-NMR spectra were obtained on Varian XL 400, XL 200 and Jeol PMX 60 spectrometers in deuteriochloroform solutions. Chemical shifts (δ) are in p.p.m. downfield from tetramethylsilane as internal standard. All solvents were

purified and dried by standard techniques. Normal phase analytical HPLC was carried out with a Lichrosorb 5 μm, silica column using either 1% ethanol in 40-60 petroleum ether or 35% chloroform in 40-60 petroleum ether as eluant.

Preparation of Z-L-Val-L-βClAla-OMe (3) by the mixed Anhydride Method: Typical Procedure. Isobutyl chloroformate (0.56 ml, 4.3 mmol) was added dropwise, *via* a syringe to a stirred solution of Z-L-Val (1.0 g, 3.9 mmol) and triethylamine (0.55 ml, 3.9 mmol) in THF (20 ml) cooled to -15 °C under an atmosphere of nitrogen. After stirring for 15 min. at -15 °C an ice-cooled, preformed solution of L-β-ClAla-OMe.HCl[10] (1) (0.67 g, 3.9 mmol) and triethylamine (0.55 ml, 3.9 mmol) in DMF (2 ml) was added and the reaction stirred at -15 °C for 2 hrs. and then a further 1 hr. at ambient temperature. After filtration and concentration *in vacuo* the crude product was taken up in ethyl acetate (30 ml) and washed successively with 2M HCl (3 x 20 ml), 5% $NaHCO_3$ (3 x 20 ml) and brine (3 x 10 ml). The organic phase was dried on $MgSO_4$ and reduced *in vacuo* to a solid, which was recrystallised from ethyl acetate -40-60 petroleum ether 1:10 to give a white solid (51%) with mp 155 °C, lit.[14] mp 151-152 °C and δ (200 MHz): 0.95 (3H, d, J = 6.8Hz), 1.01 (3H, d, J = 6.8Hz), 2.19 (1H, sept.), 3.81 (3H, s, O*Me*), 3.89 (1H, m, CH_2-Cl), 3.98 (1H, m, CH_2-Cl), 4.17 (1H, m, Val α*H*), 4.97 (1H, m, βClAla α*H*), 5.14 (2H, d, CH_2Ph), 5.39 (1H, d, J = 7.3 Hz, N*H*), 6.38 (1H, d, J = 7.3 Hz, N*H*), 7.36 (5H, m).

Z-L-Phe-L-βClAla-OMe (4) was prepared in 92% yield analogously to (3) and had m.p. 128-130 °C, lit[14] mp 127-129 °C and δ (60 MHz): 3.1 (2H, m, CH_2Ph), 3.5 (3H, s, O*Me*), 3.8 (2H, d, J = 4.8 Hz, CH_2Cl), 4.8 (1H, m, βClAla α*H*), 5.0 (2H, s, CH_2Ph), 4.5 (1H, m, Val α*H*), 7.2 (10H, m), 7.4 (1H, s, N*H*), 8.40 (1H, S, N*H*).

Z-L-Cys(Z)-L-βClAla-OMe (5) was prepared in 98% yield analogously to (3) and had mp. 141 °C; δ (200 MHz): 3.30 (2H, m, CH_2S), 3.80 (3H, s), 3.80-4.02 (2H, m, CH_2Cl), 4.60 (1H, m, Cys α*H*), 4.95 (1H, m, βClAla α*H*), 5.15 (2H, s, CH_2Ph), 5.23 (2H, s, CH_2Ph), 5.80 (1H, d, N*H*), 5.27 (1H, m, N*H*), 7.36 (10H, m); $\bar{\nu}_{max}$: 3412, 2931, 1718, 1601, 1498 cm^{-1}; *m/z*: 395, 337, 213, 108, 91. (Found: C, 54.20; H, 4.95; N, 5.61; S, 6.67 calc. for $C_{23}H_{25}ClN_2O_7S$: C, 54.28; H, 4.95; N, 5.50; S, 6.30%).

Z-L-Pro-L-βClAla-OMe (7) which was a viscous oil, prepared in 69% yield analogously to (3) with purification by chromatography on silica gel (eluant ethyl acetate -40-60 petroleum ether 1:1) had δ (200 MHz): 1.6-2.4 (4H,m), 3.50 (2H, m), 3.82 (3H, s), 3.95 (2H, m, CH_2Cl), 4.55 (1H, m, Pro α*H*), 4.91 (1H, m, βClAla α*H*), 5.20 (2H, s, CH_2Ph), 7.36 (5H, m), 7.63 (1H, m, N*H*); $\bar{\nu}_{max}$: 3680, 3413, 1748, 1685, 1601, 1408 cm^{-1}; *m/z*: 332, 233, 160, 91, 65. (Found: C, 55.02; H, 5.62; N, 7.45 calc. for $C_{17}H_{21}ClN_2O_5$: C, 55.36; H, 5.74; N, 7.60%).

N-Benzyloxycarbonyl-L-β-chloroalanine Pentafluorophenyl Ester. Pentafluorophenol (0.78g, 4.2 mmol) in dichloromethane (10 ml) was added to a solution of dicyclohexylcarbodiimide (1.25 g, 6 mmol) stirred in dichloromethane (20 ml) at 0 °C. After 5 mins Z-L-β-βClAla[12] (2) (1g, 3.9 mmol) was added and the

solution stirred for 2 hrs. After filtration of the precipitated dicyclohexylurea the solvent was removed *in vacuo* and the residual oil taken up in a minimum of ethyl acetate. On cooling further dicyclohexylurea precipitated and was removed by filtration. This cycle was repeated 4 times before the filtrate was washed with 2M HCl (2 x 10 ml), 5% $NaHCO_3$ (2 x 10ml) and brine (2 x 10 ml). Drying over $MgSO_4$, filtration and concentration gave an oil which was crystallised from ethyl acetate -40-60 petroleum ether 1:20 to give the title compound (1.33g) 75% as a white solid with mp 108-109 °C; $[\alpha]_D^{20}$ = -29, (c = 5 in MeOH); δ (200 MHz): 3.99 (1H, dd, J = 11.7 and 3.5 Hz, C*H*$_2$Cl), 4.14 (1H, dd, J = 11.7 and 3.5 Hz, C*H*$_2$Cl), 5.17 (2H, s, C*H*$_2$Ph), 5.21 (1H, m, α*H*), 5.80 (1H, d, J = 8Hz, N*H*), 7.37 (5H, m); $\tilde{\nu}_{max}$: 3425, 2931, 1795, 1721, 1651, 1494, 1334 cm^{-1}; *m/z*: 423.0247 (M^+, $C_{17}H_{11}F_5ClNO_4$ requires: 423.0294), 240, 212, 184, 164, 91, 79. (Found: C, 48.43; H, 2.71; N, 3.27 calc. for $C_{17}H_{11}ClF_5NO_4$: C, 48.19; H, 2.62; N, 3.31%).

Preparation of Z-L-βClAla-L-Val-OMe (8) by the Pentafluorophenyl Ester Method: Typical Procedure. L-Val-OMe HCl (0.42 g, 2.5 mmol) in DMF (2 ml) and then ethyldiisopropyl amine (0.44 ml, 2.5 mmol) were added to a stirred solution of Z-L-βClAla-OPFP (1.07 g, 2.5 mmol) in dichloromethane (15 ml) at 0 °C. After 2 hrs. concentration gave a gum which was diluted with ethyl acetate and washed with 2M HCl (3 x 10 ml), 10% NaOH (10 ml) and brine (2 x 10 ml). Drying on $MgSO_4$, filtration and evaporation gave an oil which solidified on cooling. Recrystallisation from ethyl acetate -40-60 petroleum ether gave the title compound (0.70 g) 76% with mp 121-123 °C; $[\alpha]_D^{20}$ = -20.6 (c = 2.5 in MeOH); δ (200 MHz): 0.90 (6H, 2d, $CHMe_2$), 2.10 (1H, m, C*H*Me$_2$), 3.73 (4H, m, O*Me* + Val α*H*), 3.96 (1H, dd, J = 4.52 and 11.61 Hz, C*H*$_2$Cl), 4.56 (1H, dd, J = 8.88 and 4.52 Hz, C*H*$_2$Cl), 4.63 (1H, m, βClAla α*H*), 5.16 (2H, s, C*H*$_2$Ph), 5.84 (1H, d, J = 8.3Hz, N*H*), 6.98 (1H, d, J = 8.2Hz, N*H*), 7.36 (5H, m): $\tilde{\nu}_{max}$: 3680, 3419, 1732, 1685, 1601, 1495 cm^{-1}; *m/z*: 370 (M^+), 311, 263, 220, 130, 108, 91, 79, 77, 59, 55. (Found: C, 55.27; H, 6.27; N, 7.60 calc. for $C_{17}H_{23}ClN_2O_5$: C, 55.06; H, 6.25; N, 7.55%).

Z-L-βClAla-L-Pro-OMe (9) a clear oil was prepared in 73% yield analogously to (8) and was isolated by chromatography on silica gel (eluant: ethyl acetate -40-60 petroleum ether 2:3). It had $[\alpha]_D^{19}$ = -25 (c = 1.6 in MeOH) δ (400 MHz): 1.80-2.35 (4H, m), 3.65-3.85 (7H, m, O*Me* + *CH*$_2$N + *CH*$_2$Cl), 4.51 (1H, m, Pro α*H*), 4.83 (1H, m, βClAla α*H*), 5.10 (2H, s, C*H*$_2$Ph), 5.61 (1H, bs, N*H*), 7.23 (5H, m); $\tilde{\nu}_{max}$: 3540, 3432, 2985, 1728, 1638, 1394, 1334 cm^{-1}; *m/z* 368.1108 (M^+, $C_{17}H_{21}ClN_2O_5$ requires 368.1138), 241, 193, 165, 128, 96, 91, 79, 68, 41.

Preparation of Z-L-Val-ΔAla-OMe (10). A solution of Z-L-Val-βClAla-OMe (3) (1.61 g, 4.35 mmol) in ethyl acetate (50 ml) was stirred at room temperature with triethylamine (0.66 ml, 4.8 mmol) overnight. The reaction mixture was filtered and the filtrate washed with 2M HCl (2 x 20 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product which was crystallised from ethyl acetate -40-60 petroleum ether to give pure (10) (1.34 g) 92% with mp 117-119 °C lit.[14] mp 118 °C and δ (200 MHz): 0.94 (3H, d, J = 6.9Hz, *Me*), 0.99 (3H, d, J = 6.7Hz, *Me*), 2.15 (1H, m), 3.84 (3H, s, O*Me*), 4.15 (1H, m, Val α*H*), 5.12 (2H, s, C*H*$_2$Ph), 5.42 (1H, d, J = 8.0Hz, N*H*), 5.93 (1H, s, =C*H*$_2$), 6.62 (1H, s, =C*H*$_2$), 7.35

(5H, s), 8.15 (1H, s, N*H*).

Z-L-Phe-ΔAla-OMe (11)[14] an oil was prepared in 93% analogously to (10) and had δ (200 MHz): 3.02 (2H, d, J = 6.9Hz, CH_2Ph), 3.78 (3H, s, O*Me*), 4.50 (1H, d, J = 8.0Hz, Phe α*H*), 5.10 (2H, s, CH_2Ph) 5.32 (1H, d, J = 8.0Hz, N*H*), 5.90 (1H, d, J = 1.3Hz =CH_2), 6.60 (1H, s, =CH_2), 6.90-7.60 (10H, m), 8.05 (1H, s, N*H*).

Z-L-Cys(Z)-ΔAla-OMe (12) an oil which polymerised on standing was prepared in 43% yield analogously to (10) followed by chromatography on silica gel (eluant: ethyl acetate -40-60 petroleum ether 1:2). It had δ (200 MHz): 3.34 (2H, m, CH_2S), 3.80 (3H, s, O*Me*), 4.67 (1H, m, Cys α*H*), 5.13 (2H, s, CH_2Ph), 5.21 (2H, s, CH_2Ph), 5.92 (2H, m, N*H* + =CH_2), 6.58 (1H, s, =CH_2), 7.33 (10H, m), 8.65 (1H, s, N*H*); $\tilde{\nu}_{max}$: 3379, 2795, 1722, 1498, 1151 cm^{-1}; *m/z*: 461 (M + H$^+$), 337, 300, 256, 91, 79.

Z-L-Ser(OH)-ΔAla-OMe (13) Z-L-Ser was coupled with L-βClAla-OMe.HCl by the isobutylchloroformate method giving crude (6) which was immediately subjected to dehydrochlorination with triethylamine in ethyl acetate as described for (10) above. The crude product was purified by chromatography on silica gel (eluant: ethyl acetate -40-60 petreleum spirit) giving pure (13) in 21% overall yield as an oil which was susceptible to polymerisation and which had δ (200 MHz): 3.70 (3H, s, O*Me*), 4.00 (3H, m, Ser α*H* + CH_2OH), 4.37 (1H, s, O*H*), 5.10 (2H, s, CH_2Ph), 5.90 (1H, s, =CH_2), 6.20 (1H, d, J= 8.0Hz, N*H*), 6.55 (1H, s, =CH_2), 7.30 (5H, s), 8.90 (1H, s, N*H*); $\tilde{\nu}_{max}$: 3626, 3413, 2945, 2832, 1722, 1685, 1495, 1321, 1014 cm^{-1}; *m/z*: 320 (M$^+$), 292, 263, 238, 231, 213, 150, 108, 91, 79. (Found: C, 56.13; H, 5.56; N, 8.26 calc. for $C_{15}H_{16}N_2O_6$: C, 55.89; H, 5.63; N, 8.69%).

Z-L-Pro-ΔAla-OMe (14) was prepared analogously to (10) in 97% yield and was a clear oil which was susceptible to polymerisation and had δ (200 MHz): 1.5-2.5 (4H, m), 3.50 (2H, m), 3.82 (3H, s, O*Me*), 4.55 (1H, m, Pro α*H*), 5.20 (2H, s, CH_2Ph), 5.90 (1H, s, =CH_2), 6.59 (1H, s, =CH_2), 7.30 (5H, m).

Z-ΔAla-L-Val-OMe (15) was prepared by treatment of (8) (0.72 g, 1.94 mmol) with DABCO (0.33g, 2.1 mmol) in chloroform (5 ml) overnight at room temperature. After filtration the reaction mixture was washed with 2M HCl (2 x 10 ml) and brine (2 x 10 ml), dried on $MgSO_4$ filtered and evaporated to give (15) (0.62 g) 95% as a colourless oil with δ (200 MHz): 0.92 (3H, d, J = 6.9Hz, *Me*), 0.95 (3H, d, J = 6.9Hz, *Me*), 2.18 (1H m), 3.75 (3H, s, O*Me*), 4.59 (1H, dd, J = 5.1 and 8.7Hz, Val α*H*), 5.15 (2H, s, CH_2Ph), 5.25 (1H, d, J = 2.0 =CH_2), 6.13 (1H, d, J = 2.0 =CH_2), 6.70 (1H, d, J = 8.7Hz, N*H*), 7.36 (5H, m), 7.55 (1H, s, NH); $\tilde{\nu}_{max}$: 3386, 2945, 1735, 1668, 1631, 1495 cm^{-1}; *m/z*: 334 (M$^+$), 275, 243, 167, 91, 72. (Found: C, 60.57; H, 6.66; N, 8.17 calc. for $C_{17}H_{22}N_2O_5$: C, 61.07; H, 6.63; N, 8.38%).

Z-L-Val-DL-β-CyclohexylAla-OMe (22): Standard Method for Radical Addition to Di- and Tripeptides with Dehydroalanine Residues. Sodium borohydride (0.34 g, 9 mmol) suspended in water (7 ml) was added dropwise over 20 min to a vigorously stirred solution of cyclohexylmercury chloride (18)[18] (0.72g, 2.2

mmol) and Z-L-Val-ΔAla-OMe (10) (0.30 g, 0.89 mmol) in dichloromethane (3 ml) at room temperature under a nitrogen atmosphere. Stirring was continued for a further 1hr. before the reaction mixture was filtered on celite and concentrated to dryness giving a solid residue which was subject to chromatography on silical gel (eluant: ethyl acetate - 40-60 petroleum ether 2:1) giving finally (22) (264 mg) 71% as a mixture of diastereoisomers with mp 120 °C; δ (400 MHz): 0.80-1.90 (19H, m), 2.15 (1H, m), 3.70 (major) + 3.73 (3H, 2s, O*Me*), 4.15 (1H, m, Val α*H*), 4.65 (1H, m, CyclAla α*H*), 5.10 (2H, m, CH_2Ph), 5.68 (1H, m, N*H*), 6.72 + 6.90 (1H, 2d, N*H*) 7.35 (5H, m); $\tilde{\nu}_{max}$: 3422, 2925, 2845, 1726, 1673, 1495 cm^{-1}; *m/z*: 418.2435 (M$^+$, calc. for $C_{23}H_{34}N_2O_5$ 418.2468), 322, 251, 206, 162, 91, 55.

Z-L-Phe-DL-β-CyclohexylAla-OMe (23) was prepared in 64% by addition cyclohexylmercury chloride to (11). It was an oil with δ (400 MHz): 0.75-1.74 (13H, m), 3.10 (2H, m, CH_2Ph), 3.67 (major) + 3.69 (minor) (3H, 2s, O*Me*), 4.43 (1H, m, Phe α*H*), 4.53 (1H, m, CyclAla α*H*), 5.09 (2H, 2s, CH_2Ph), 5.33 (1H, m, N*H*), 6.13 (1H, m, N*H*), 7.0- 7.4 (10H, m); $\tilde{\nu}_{max}$: 3419, 2925, 2845, 1728, 1678, 1601, 1495 cm^{-1}; *m/z*: 466.2504 (M$^+$ calc. for $C_{27}H_{34}N_2O_5$ 466.2468, 370, 210, 131, 91. (Found: C, 69.48, H, 7.40; N, 6.17 calc. for $C_{27}H_{34}N_2O_5$: C, 69.51; H, 7.34; N, 6.00%).

Z-L-Cys(Z)-DL-CyclAla-OMe (24), a white crystalline solid, prepared in 70% yield by addition of cyclohexylmercury chloride to (12), had mp 110 °C; δ (400 MHz): 0.80-1.80 (13H, m), 3.26 and 3.37 (2H, 2m, CH_2S), 3.72 (3H, s, O*Me*), 4.52 (1H, m, CyclAla α*H*), 4.62 (1H, m, Cys α*H*), 5.15 (2H, s, CH_2Ph), 5.25 (2H, s, CH_2Ph), 5.74 (1H, d, N*H*), 6.71 (1H, s, N*H*), 7.36 (10H, m); $\tilde{\nu}_{max}$: 3420, 2925, 1727, 1495, 1150 cm^{-1}; *m/z*: 557.2388 (MH$^+$ calc. for $C_{29}H_{37}N_2O_7S$: 557.2321), 513, 449, 389, 345, 311, 184, 91. (Found: C, 61.66; H, 6.35; N, 4.86; S, 6.03 calc. for $C_{29}H_{36}N_2O_7S$: C, 62.57; H, 6.52; N, 5.03; S, 5.76%).

Z-L-Ser(OH)-DL-CyclAla-OMe (25) an oil, prepared in 42% yield by addition of cylcohexylmercury chloride to (13), had δ (400 MHz): 0.88-1.77 (13H, m), 3.60-3.78 (2H, m, CH_2OH), 3.72 (major) and 3.74 (minor) (3H, 2s, O*Me*), 4.05 (1H, m, CyclAla α*H*), 4.30 (1H, s, O*H*), 4.61 (1H, m, Ser α*H*), 5.13 (2H, m, CH_2Ph), 5.87 and 5.98 (1H, 2d, N*H*), 6.95 (1H, m, N*H*), 7.36 (5H, m); $\tilde{\nu}_{max}$: 3419, 2925, 1725, 1675, 1601, 1495 cm^{-1}; *m/z*: 406.2136 (M$^+$ calc. for $C_{21}H_{30}N_2O_6$: 406.2104), 376, 126, 91, 79, 55. (Found: C, 61.64; H, 7.14; N, 6.79 calc. for $C_{21}H_{30}N_2O_6$: C, 62.05, H, 7.44; N, 6.89%).

Z-L-Pro-DL-Leu-OMe (26) an oil, prepared in 98% yield by addition of isopropylmercury chloride[25] to (14), had δ (400 MHz): 0.81-1.0 (6H, m), 1.4-2.3 (7H, m), 3.55 (2H, m, CH_2N), 3.69 (3H, s, O*Me*), 4.38 (1H, m, Leu α*H*), 4.56 (1H, m, α*H*), 5.18 (2H, m, CH_2Ph), 7.35 (6H, m, *Ph* + N*H*); $\tilde{\nu}_{max}$: 3673; 3419, 2945, 1738, 1682 cm^{-1}; *m/z*: 377.2077 (MH$^+$ calc. for $C_{20}H_{29}N_2O_5$: 377.2076).

Z-DL-Leu-L-Val-OMe (27) an oil, prepared in 74% yield by addition of isopropylmercury chloride to (15) had δ (400 MHz): 0.89-0.99 (12H, m), 1.56 (1H, m), 1.69 (2H, m), 2.18 (1H, m), 3.74 (3H, s, O*Me*), 4.27 (1H, m, Leu α*H*), 4.55 (1H, m, Val α*H*), 5.14 (2H, m, CH_2Ph), 5.31 (1H, m, N*H*) 6.57 + 6.67 (1H, 2d, N*H*), 7.36 (5H, m); $\tilde{\nu}_{max}$: 3426, 2952, 1732, 1678, 1601, 1501 cm^{-1}; *m/z*: 378.2155 (M$^+$ calc. for

$C_{20}H_{30}N_2O_5$: 378.2154), 220, 176, 130, 91, 72, 43. (Found: C, 63.00; H, 7.99; N, 7.40 calc. for $C_{20}H_{30}N_2O_5$: C, 63.47; H, 7.99; N, 7.40%).

Z-DL-Leu-L-Pro-OMe (28) an oil, prepared in 74% yield by addition of isopropylmercury chloride to (16), had δ (400 MHz, at 55 °C): 0.82-1.05 (6H, m), 1.60-2.30 (5H, m), 3.60 (2H, m, Leu β*H*), 3.71 (minor) and 3.72 (major) (3H, 2s, O*Me*), 3.81 (2H, m, CH_2N), 4.43-4.55 (2H, m, Leu α*H* + Pro α*H*), 5.11 (2H, m, CH_2Ph), 5.45 (1H, bs, N*H*), 7.34 (5H, m); $\tilde{\nu}_{max}$: 3421, 2945, 1725, 1641, 1501, 1438 cm^{-1}; *m/z*: 376.2047 ($M^{+\bullet}$ calc. for $C_{20}H_{28}N_2O_5$: 376.1998), 320, 220, 176, 128, 91, 70.

Z-DL-NeopentylAla-L-Pro-OMe (29) an oil, prepared in 71% yield by addition of neopentylmercury bromide[23] to (16), had δ (400 MHz at 55 °C): 0.97 (minor) and 1.01 (major) (9H, 2s, ^tBu), 2.70 (2H, m, C$H_2{}^t$Bu), 1.90-2.25 (4H, m), 3.61 (2H, m, ^{t}BuCH_2Ala β*H*), 3.70 (minor) and 3.72 (major) (3H, 2s, O*Me*), 3.80-3.95 (2H, M, CH_2N), 4.41-4.62 (2H, m, 2 α*H*), 5.10 (2H, m, CH_2Ph), 5.26 (1H, bs, N*H*), 7.35 (5H, m); $\tilde{\nu}_{max}$: 3419, 2945, 1725, 1641, 1498, 1438 cm^{-1}; *m/z*: 404.2311 ($M^{+\bullet}$ calc. for $C_{22}H_{32}N_2O_5$: 404.2375), 320, 248, 204, 149, 128, 91, 70, 57.

Z-DL-*t*-ButylAla-L-Pro-OMe (30) an oil, prepared in 87% yield by addition of *t*-butylmercury chloride[23] to (14), had δ (400 MHz at 55 °C): 0.87 (minor) and 0.89 (major) (9H, s, ^{t}Bu), 1.71-2.30 (4H, m), 3.60 (2H, C$H_2{}^t$Bu), 3.70-3.85 (2H, m, CH_2N), 3.73 (3H, s, O*Me*), 4.42-4.58 (2H, m, 2 α*H*), 5.10 (2H, m, CH_2Ph), 5.47 (1H, bs, N*H*), 7.35 (5H, m): $\tilde{\nu}_{max}$: 3426, 2945, 1725, 1641, 1501, 1438 cm^{-1}; *m/z*: 390.2155 ($M^{+\bullet}$ calc. for $C_{21}H_{30}N_2O_5$: 390.2116), 234, 190, 128, 91, 70, 57.

Preparation of an Authentic Sample of Z-L-Leu-L-Pro-OMe. An authentic sample of Z-L-Leu-L-Pro-OMe was prepared in 93% yield by coupling Z-L-Leu with L-Pro-OMe.HCl by the pentafluorophenyl ester method. The intermediate Z-L-Leu-OPFP ester was not isolated in this case. The title compound was a clear oil with $[\alpha]_D^{19}$ = -49 (c = 1.3 in $CHCl_3$); δ (200 MHz), 0.92 (3H, d, J = 6.6 Hz), 0.95 (3H, d, J = 6.5 Hz), 1.53-2.20 (5H, m), 3.69 (3H, s, O*Me*), 3.60-3.70 (2H, m), 4.52 (2H, 2 α*H*), 5.05 (2H, s, CH_2Ph), 5.46 (1H, d, J = 9Hz, N*H*), 7.31 (5H, m).

Z-L-Phe-OPFP was prepared in 90% yield according to the method described above for Z-L-βClAla-OPFP. It had mp 94-95 °C; $[\alpha]_D$ = -27 (c = 5 in $CHCl_3$); δ (200 MHz): 3.29 (2H, m, CH_2Ph), 5.02 (1H, m, α*H*), 5.12 (2H, s, CH_2Ph), 5.27 (1H, d, J = 8.1Hz, N*H*), 7.25 (10H, m); $\tilde{\nu}_{max}$: 3432, 1788, 1722, 1502, 1006 cm^{-1}; *m/z*: 466 ($M^{+\bullet}$), 422, 320, 254, 181, 91, 65. (Found: C, 59.24; H, 3.54; N, 3.05 calc. for $C_{23}H_{16}F_5NO_4$: C, 59.36; H, 3.47; N, 3.01%).

Z-L-Phe-L-βClAla-L-Val-OMe (32) . Hydrogenolysis of Z-L-βClAla-L-Val-OMe (8) (0.5 g, 1.35 mmol) over 10% palladium/charcoal in absolute ethanol (4 ml) for 2 hrs. gave after filtration and evaporation crude L-ClAla-L-Val-OMe (31) (HCl salt mp 231 °C, dec.) which was immediately coupled with Z-L-Phe-OPFP according to the method described for (8) above giving the title compound (32) in 83% yield as a

crystalline solid with mp 156 °C; $[\alpha]_D^{19}$ = -11 (c = 5 in MeOH); δ (400 MHz): 0.89 (3H, d, J = 6.9Hz), 0.92 (3H, d, J = 6.9Hz), 2.17 (1H, m), 3.11 (2H, m, C*H*$_2$Ph), 3.63 (1H, m, C*H*$_2$Cl), 3.72 (3H, s), 3.91 (1H, m, C*H*$_2$Cl), 4.49 (2H, m, Val α*H* + Phe α*H*), 4.84 (1H, m, βClAla α*H*), 5.07 (2H, s, C*H*$_2$Ph), 5.44 (1H, d, N*H*), 6.96 (1H, d, N*H*), 7.06 (1H, d, N*H*), 7.2-7.4 (10H, m); $\tilde{\nu}_{max}$: 3413, 2945, 1728, 1678, 1491 cm^{-1}; *m/z*: 481 (M-HCl$^{+\bullet}$), 390, 331, 173, 91. (Found: C, 60.35; H, 6.32; N, 8.11 calc. for $C_{26}H_{32}ClN_3O_6$: C, 60.29; H, 6.23; N, 8.11%).

Z-L-Phe-ΔAla-L-Val-OMe (33) was prepared by elimination of HCl from (32) with DABCO in chloroform as described for (15) above. After purification by filtration on silica gel (eluant: ethyl acetate -40-60 petroleum ether 1:2) (33) was obtained in 90% yield as a white crystalline solid with mp 122 °C; $[\alpha]_D^{19}$ = -31 (c = 2.5 in MeOH), δ (200 MHz): 0.93 (3H, d, J = 6.8Hz), 0.94 (3H, d, J = 6.8Hz), 2.15 (1H, m), 3.09 (2H, m, C*H*$_2$Ph), 3.75 (3H, s), 4.55 (2H, m, 2 α*H*), 5.05 (2H, d, C*H*$_2$Ph), 5.37 (1H, s, =C*H*$_2$), 5.5 (1H, d, N*H*), 6.46 (1H, d, J = 1.7Hz, =C*H*$_2$), 6.81 (1H, d, N*H*), 7.10-7.40 (10H, m), 8.48 (1H, s, N*H*); $\tilde{\nu}_{max}$: 3419, 2932, 1728, 1631, 1491, 1224 cm^{-1}; *m/z*: 481 (M$^{+\bullet}$), 390, 330, 323, 314, 91, 72. (Found: C, 64.89; H, 6.43; N, 8.71 calc. for $C_{26}H_{31}N_3O_6$: C, 64.85; H, 6.49; N, 8.73%).

D-Val-OMe.HCl. Thionyl chloride (3.36 ml) was added dropwise to methanol (8.3 ml) with stirring at -15 °C over 40 min. D-Valine (3.0 g, 25.6 mmol) was then added portionwise with vigorous stirring. The suspension was then allowed to warm to ambient temperature and was finally heated to 40 °C for 2 hrs. until all the solid had dissolved. The hot solution was filtered and the methanol removed *in vacuo*. The semisolid residue was treated with benzene and the benzene evaporated *in vacuo* giving D-Val-OMe.HCl (4.18 g) 98% with mp 169-171 °C, lit[24] mp 171 °C; $[\alpha]_D^{21}$ = -22° (c = 2, MeOH); δ (200 MHz): 0.95 (3H, d), 1.0 (3H, d), 2.20 (1H, m), 3.75 (3H, s), 3.80 (1H, d), 8.75 (2H, s).

Z-L-βClAla-D-Val-OMe (35) D-Val-OMe.HCl (0.96 g, 5.7 mmol) and ethyldiisopropylamine (0.99 ml) in a 1:10 mixture of DMF and ethyl acetate (10 ml) were added at 0 °C to a solution of Z-L-βClAla-OPFP prepared *in situ* from Z-L-βClAla (1.47 g, 5.7 mmol), pentafluorophenol (1.17 g) and dicyclohexylcarbodiimide (1.82 g) as described above. After a further 1 hr. at 0 °C the reaction mixture was filtered, diluted with ethyl acetate and refiltered - a process which was repeated 4 times. Finally the filtrate was washed with 2M HCl (3 x 20 ml), 5% NaOH (3 x 20 ml) and brine (3 x 20 ml). Drying over $MgSO_4$ filtration and concentration gave a crude solid which was recrystallised from ethyl acetate -40-60 petroleum ether to give the title compound (35) (1.49 g) 71% as a white crystalline solid with mp 140-142 °C; $[\alpha]_D^{19}$ = -17 (c = 0.3 in MeOH); δ (200 MHz): 0.86 (3H, d), 0.92 (3H, d), 2.10 (1H, m), 3.71 (3H, s), 3.74 (2H, m, C*H*$_2$Cl), 4.50 (2H, m, 2 α*H*), 5.13 (2H, s), 5.80 (1H, d, N*H*), 6.85 (1H, d, N*H*) 7.35 (5H, m); $\tilde{\nu}_{max}$: 3417, 2952, 1728, 1682, 1601, 1494 cm^{-1}; *m/z*: 370 (M$^{+\bullet}$), 311, 257, 212, 130, 122, 91, 72. (Found: C, 55.04; H, 6.26; N, 7.66 calc. for $C_{17}H_{23}ClN_2O_5$; C, 55.06; H, 6.25; N, 7.55%).

Z-L-Phe-L-βClAla-D-Val-OMe (37) was prepared from Z-L-βClAla-D-Val-OMe (35) and Z-L-Phe-OPFP in 88% yield analogously to (32) described above. It was a white crystalline solid with mp 140-1455 °C; δ (400

MHz): 0.87 (3H, d), 0.90 (3H, d), 2.09 (1H, m), 2.74 (1H, dd, CH_2Ph), 3.00 (1H, dd, CH_2Ph), 3.67 (3H, s), 3.78 (2H, d, CH_2Cl), 4.29 (1H, t, βClAla α*H*), 4.36 (1H, m, Phe α*H*), 4.84 (1H, m, Val α*H*), 4.95 (2H, s, CH_2Ph), 7.2-7.4 (10H, m), 7.89 (1H, d, N*H*), 8.39 (1H, d, N*H*), 8.61 (1H, d, N*H*). (Found: C, 60.05; H, 6.14; N, 8.19 calc. for $C_{26}H_{32}ClN_3O_6$: C, 60.29; H, 6.23; N, 8.11%).

Z-L-Phe-ΔAla-D-Val-OMe (38) was prepared in 80% yield by dehydrochlorination of (37) with DABCO. It was a white crystalline solid with mp 110 °C; $[\alpha]_D^{19}$ = -45 (c = 0.3 in MeOH); δ (200 MHz): 0.91 (3H, s), 0.94 (3H, s), 2.15 (1H, m), 3.13 (2H, m, CH_2Ph), 3.75 (3H, s), 4.56 (2H, m, 2α*H*), 5.05 (2H, d, CH_2Ph), 5.39 (1H, s, $=CH_2$), 5.57 91H, d, N*H*), 6.47 (1H, s, $=CH_2$), 6.77 (1H, d, N*H*), 7.05-7.50 (10H, m), 8.49 (1H, s, N*H*).

Z-L-Phe-DL-Leu-L-Val-OMe (34) was prepared in 88% yield by reaction of (33) with isopropylmercury chloride and sodium borohydride as described for (22) above followed by chromatography on silica gel (eluant: ethyl acetate -40-60 petroleum ether 2:3). It was a crystalline solid with mp 161-163 °C; δ (400 MHz): 0.83-2.15 (16H, m), 3.08 (2H, m, CH_2Ph), 3.66 (major) and 3.74 (3H, 2s, O*Me*), 4.53 (3H, m, 3α*H*), 5.06 (2H, m, CH_2Ph), 5.71 (1H, m, N*H*), 6.64 and 6.87 (1H, 2s, N*H*) 7.07 and 7.11 (1H, 2d, N*H*), 7.16-7.39 (10H, m); $\tilde{\nu}_{max}$: 3413, 2952, 1728, 1675, 1601, 1495 cm^{-1}; *m/z*: 525.2776 ($M^{+\bullet}$ calc. for $C_{29}H_{39}N_3O_6$: 525.2829), 429, 417, 395, 259, 217, 91, 72.

Z-L-Phe-DL-Leu-D-Val-OMe (39) was prepared (87%) from (38) analogously to (34) and was a white solid with mp 151-153 °C; δ (400 MHz): 0.79-2.15 (16H, m), 3.05 (2H, m), 3.69 (major) and 3.71 (3H, 2s, O*Me*), 4.45 (3H, m, 3α*H*), 5.08 (2H, m, CH_2Ph), 5.39 and 5.57 (1H, 2d, N*H*), 6.52 (1H, m, N*H*), 6.86 (1H, m, N*H*), 7.10-7.40 (10H, m).

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