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A New Approach to the Synthesis of Di- and Tripeptides with Unnatural Amino Acids using Organozinc Chemistry†

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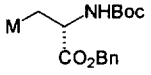
Abstract: Di- and tripeptides which incorporate an iodoalanine unit at the C-terminus can be converted into the corresponding organozinc reagents upon treatment with activated zinc. These C-terminal di- and tripeptide organozinc reagents react with electrophiles either under palladium catalysis, or by prior transmetallation to a zinc/copper reagent, to give di- and tripeptides incorporating non-proteinogenic amino acids without loss of stereochemical purity. © 1997 Elsevier Science Ltd.

It is only relatively recently that unconventional approaches to the synthesis of peptides, specifically including the modification of an amino acid moiety within a peptide, have been explored. Amongst the most notable examples of peptide modification by carbon-carbon bond forming reactions are those from the Seebach group, who have succeeded in generating polylithiated peptide derivatives which can be selectively alkylated.[1,2] Seebach has also extended his self-reproduction of chirality concept to dipeptide synthesis,[3] and a related approach using β-lactam esters has been described.[4] Other approaches to the modification of peptides have included radical addition to dehydroalanine residues[5] and introduction of allylic side chains by palladium-catalysed rearrangement.[6] Cycloaddition chemistry has been used to construct unnatural dipeptides by carbon-carbon bond formation.[7,8] Peptides have also been prepared by diastereoselective hydrogenation of didehydropeptides.[9] The majority of these methods have not permitted complete control of stereochemistry, since they generally rely on diastereoselective processes. However, Barton has demonstrated that simple dipeptides, with a C-terminal glutamic acid residue, can be converted without loss of stereochemical integrity into the corresponding homoalanine derivative by photolysis of the *N*-hydroxy-2-thiopyridone ester in the presence of *t*-butyl thiol.[10] It is likely that use of other radical traps may also be viable, and Baldwin has exploited such a strategy in the synthesis of the natural cyclic tetrapeptide, chlamydocin.[11]

In a series of papers, we have shown that amino acid-derived organozinc reagents can be prepared, and then subsequently treated with a range of electrophiles to give enantiomerically pure unnatural (and natural) amino acids in a direct manner. For example, the serine-derived organozinc reagent **1** is an effective reagent for the preparation of enantiomerically pure α-amino acids, either using palladium catalysis[12] or by transmetallation to the zinc/copper reagent **2** followed by reaction with electrophiles.[13] These results have established that a carbon-zinc bond at the β-position of an amino acid is kinetically stable to a significant extent both to protonolysis by the acidic NH group and to β-elimination with loss of the carbamate anion. It was partly Seebach's unconventional approach to the synthesis of unnatural peptides which encouraged us to explore

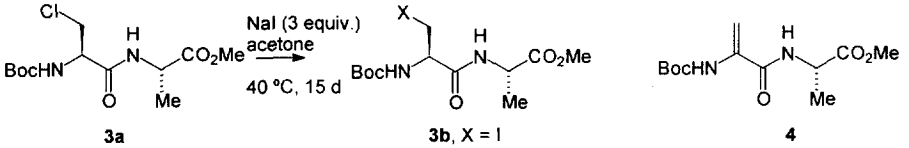
† Dedicated to Professor Dieter Seebach on the occasion of his 60th Birthday.

organozinc chemistry in the preparation of peptides incorporating unnatural amino acids. We recently reported our preliminary findings concerning the viability of this approach in the case of dipeptides.[14] We now report our findings in full, and include an additional example which indicates that it is also possible to prepare tripeptides by the same strategy.



1, M = IZn
2, M = IZn(NC)Cu

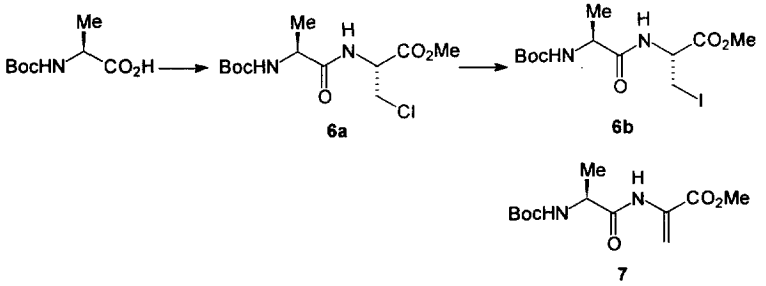
Our initial study centred on the potential application of the *N*-terminal zinc reagent **3c**. The starting material we chose to prepare was the dipeptide **3b**, incorporating a β-iodoalanine unit at the N-terminus. The immediate precursor to dipeptide **3b** (60 %), the chloro-derivative **3a**, was prepared by coupling N-Boc β-chloroalanine with alanine methyl ester using dicyclohexylcarbodiimide and 1-hydroxybenzotriazole in dichloromethane (90%). Treatment of the dipeptide **3a** with sodium iodide in acetone proceeded slowly at 40 °C to give the required iodide **3b**. Use of more vigorous conditions (acetone at reflux) lead to significant amounts of the didehydropeptide **4** (Scheme 1). While we did not optimise the elimination reaction, this process may provide a general approach to the synthesis of other dehydroalanine-containing peptides.[15] As we reported in our preliminary communication, reaction of the iodide **3b** with activated zinc,[16] followed by addition of electrophiles gave very poor yields of the desired products **5**.



3a **3b**, X = I; **3c**, X = IZn; **5**, X = E **4**

Scheme 1

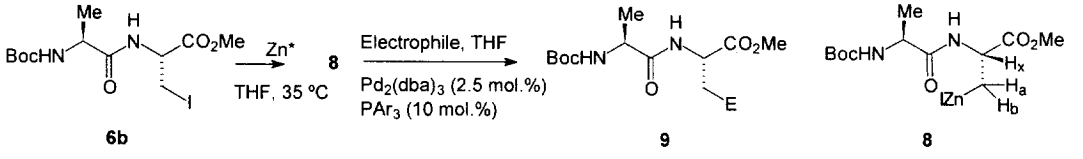
We therefore turned our attention to the C-terminal iodide **6b**, isomeric with iodide **3b**. The necessary precursor, the chloride **6a**, was prepared by coupling of N-Boc protected alanine with β-chloroalanine methyl ester (70 %).[5,17] Transformation of **6a** into **6b** by treatment with sodium iodide in acetone proceeded slowly (15 days) at 35 °C (75 %). As we had already observed during the preparation of **3b**, use of more vigorous conditions led to the formation of the dehydropeptide **7** (Scheme 2).



6a **6b** **7**

Scheme 2

Treatment of iodide **6b** with activated zinc led to efficient formation of the corresponding zinc reagent **8**, which was characterised in d_8-THF by ^{1}H NMR spectroscopy, and appeared to be significantly more stable than the isomeric zinc reagent **3c**. One significant feature of the spectrum is the substantial difference in the coupling constants between the two protons adjacent to zinc, and the proton at the α-carbon (J_{AX} = 12.0 Hz and J_{BX} = 5.5 Hz). This suggests that there is a substantial conformational preference, perhaps due to internal co-ordination of the zinc by either the ester carbonyl, the amide carbonyl, or both. Reaction of the zinc reagent **8** with a range of electrophiles under palladium catalysis, gave the corresponding dipeptides **9a-9f** (Scheme 3). The incompatibility of aliphatic acid chlorides with THF in the presence of zinc salts[18] restricted the electrophiles that could be employed to aromatic acid chlorides [for which we used the catalyst derived from *tris*(dibenzylideneacetone)-*di*-palladium(0) and triphenylphosphine] and to aromatic iodides [for which we used the catalyst derived from *tris*(dibenzylideneacetone)-*di*-palladium(0) and tri-*o*-tolylphosphine]. Our results are detailed in the Table. In all cases, the products were isolated as pure diastereoisomers, indicating that no epimerisation had occurred during the process.



6b **9** **8**

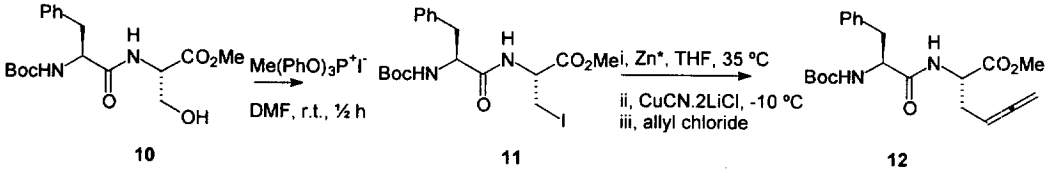
Scheme 3

Table. Preparation of C-terminal Modified Dipeptides from **6b**

Electrophile	Catalyst	Temp °C	Time/h	Product	E	Yield, %
PhCOCl	A	20	1	**9a**	PhCO	31
2-FuroylCOCl	A	20	1	**9b**	2-FuroylCO	51
PhI	B	50	2	**9c**	Ph	15
4-$O_2NC_6H_4I$	B	50	2	**9d**	4-$O_2NC_6H_4$	63
4-BrC_6H_4I	B	65	2	**9e**	BrC_6H_4	20
1-iodonaphthalene	B	65	2	**9f**	1-naphthyl	41

Catalyst A: $[Pd_2(dba)_3]/PPh_3$
Catalyst B: $[Pd_2(dba)_3]/P(o\text{-tol})_3$

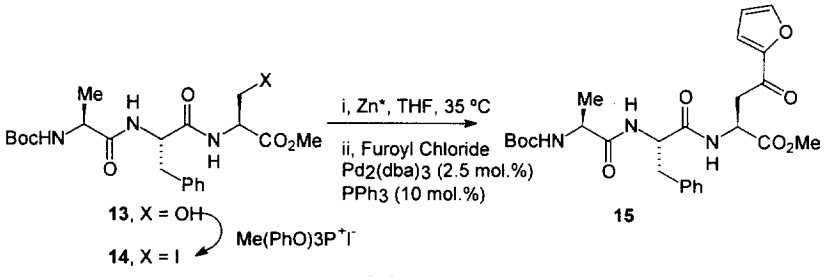
Although the yields of coupled products **9** were not high, the main drawback to this approach was the extended reaction times required for the preparation of the iodide **6**. We therefore explored an alternative method for the preparation of dipeptides containing iodoalanine residues, namely the direct conversion of the corresponding serine-containing dipeptide into the corresponding iodide using $Me(PhO)_3P^+I^-$.[19] Thus, Boc-Phe-Ala(β-I)-OMe **11** was prepared directly (44 %) from Boc-Phe-Ser-OMe **10** using $Me(PhO)_3P^+I^-$. This transformation was complete within ½ h, which represents a very significant improvement over our previous method. Treatment of iodide **11** with zinc in dimethylacetamide (DMA) gave the corresponding zinc reagent, which was then treated sequentially with CuCN.2LiCl (as a solution in DMA) followed by addition of propargyl chloride to give the adduct **12** (43%), thus demonstrating that it is also possible to prepare a zinc/copper reagent from dipeptide derivatives (Scheme 4).



10 11 12

Scheme 4

Having established that dipeptide-derived organozinc reagents are viable, we then turned our attention to the preparation of a tripeptide derivative, and selected Boc-Ala-Phe-Ala(β-I)-OMe **14** as a suitable target. This compound was prepared from Boc-Ala-Phe-Ser-OMe **13**, again using $Me(PhO)_3P^+I^-$. The tripeptide **13** was prepared by standard coupling techniques from Boc-Ala-Phe-OH and Ser-OMe. Using the same general techniques as we had employed for the preparation of the dipeptide derivatives **9**, we could convert **14** into the corresponding zinc reagent, and then couple it under palladium catalysis with furoyl chloride to give the tripeptide **15** in reasonable yield (43%) (Scheme 5).



Scheme 5

Although, at this stage, we have only carried out a brief survey of the application of organozinc chemistry in the preparation of di- and tripeptides containing unnatural amino acids, our results are sufficiently encouraging that future developments in this area may be forthcoming. The key issues relate to stability of these organometallic reagents, and recent results suggest that careful choice of solvent can have a substantial beneficial effect on stability.[20] Further efforts in this area are ongoing.

Experimental

General experimental procedures and instrumentation are as previously described.[12,13] *J* values are given in Hz. Light petroleum refers to that fraction with boiling point 40-60 °C. All organic extracts were dried over anhydrous $MgSO_4$, and solvent was removed using a rotary evaporator.

Methyl 2-(*R*)-amino-3-chloropropionate hydrochloride (L-(β-Cl)Ala-OMe).[21]

Dry hydrogen chloride gas was bubbled through ice-cold acetyl chloride (400 cm^3) for 5min., with stirring. Methyl-2-(*R*)-amino-3-hydroxypropionate hydrochloride (50 g, 0.32 mol) was then dissolved in the liquid and the passage of gas curtailed. Phosphorous pentachloride (75 g, 0.36 mol) was introduced portionwise to the solution over a period of 20 min during which time the product was formed as a white precipitate (vigorous stirring is recommended). On reaching room temperature the reaction mixture was stirred for a further 45 min. At this point, petrol (300 cm^3, 100-120 °C boiling range) was introduced into the flask in 50 cm^3 portions over 30 min. The contents of the flask were collected in a large sinter, washed twice by suspension in petrol (2 ×

400cm^3, 100-120 ^oC boiling range), filtered, washed again by suspension in petrol (400 cm^3, 40-60 ^oC boiling range) and finally filtered. Removal of residual petrol under reduced pressure gave pure methyl 2-(*R*)-amino-3-chloropropionate hydrochloride as a white solid. (44.6047g, 256 mmol, 80%); (mp 142-144^oC, decomposes); (Found: C 27.13, H 5.11, N 7.91. $C_4H_9NO_2Cl_2$ requires C 27.61, H 5.21, N 8.05%); (Found: MH^+ 137.0249. $C_4H_9NO_2Cl_2$ requires 137.0244); $[\alpha]_D$ -6.1 (c 0.95 in H_2O); υ_{max} (cap. film) 3 015, 1 751, 1 518 cm^{-1}; δ_H (200 MHz; D_2O) 3.89 (3H, s, OC**H**$_3$), 4.07 (1H, dd, *J* 3.5 and 13, C(3)**H**), 4.21 (1H, dd, *J* 4.5 and 13, C(3)**H**), 4.69 (1H, dd, *J* 3.5 and 4.5, C(2)**H**); *m/z* (e.i.) 137 (M^+ 1.6%).

Boc-L-ala-L-(β-Cl)ala OMe 6a

Isobutyl chloroformate (3.76 cm^3, 29.0 mmol) was added dropwise to a stirred solution of Boc-L-alanine (5.0 g, 26.4 mmol) and triethylamine (3.68 cm^3, 26.4 mmol) in tetrahydrofuran (100 cm^3) cooled to -15^oC, under nitrogen. After stirring for 15min an ice-cooled, preformed solution of methyl 2-(*R*)-amino-3-chloropropionate hydrochloride (4.59 g, 26.4 mmol) and triethylamine (3.68 cm^3, 26.4 mmol) in dimethylformamide (20 cm^3) was added and the reaction mixture stirred at -15^oC for a further 1.5h and then at room temperature for 48h. Filtration and concentration gave a solid which was dissolved in ethyl acetate (150 cm^3), washed with hydrochloric acid (300 cm^3, 2M), sodium hydrogen carbonate (300 cm^3, 5%), brine (150 cm^3), dried, and concentrated under reduced pressure to give a crude product. Recrystallisation from petrol-ethyl acetate afforded Boc-L-ala-L-(β-Cl)ala OMe **6a** as a white solid. (5.4281g, 18.0 mmol, 68%); (mp 120-122^oC);(Found: C 46.48, H 6.66, N 8.68. $C_{12}H_{21}N_2O_5Cl$ requires C 46.68, H 6.86, N 9.07%); $[\alpha]_D$ +5.9 (c 0.95 in CH_2Cl_2); υ_{max} (cap. film) 3 391, 1 750, 1 670, 1 505, 1 219 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 1.37 (3H, d, *J* 7.1, C**H**$_3$), 1.44 (9H, s, OC(C**H**$_3$)$_3$), 3.79 (3H, s, C**H**$_3$O), 3.88 (1H, dd, *J* 3.5 and 11.5, C(3)**H**), 3.96 (1H, dd, *J* 3 and 11.5, C(3)**H**), 4.18-4.28 (1H, m, C(2)**H**), 4.92-4.99 (1H, m, C(2)**H**), 5.04 (1H, d, *J* 7, N**H**), 7.05 (1H, br, N**H**); *m/z* (e.i.) 235 (M^+ - $(CH_3)_2C{=}CH_2$ - CH_4-H 23.9%).

Boc-L-ala-L-(β-I)ala OMe 6b

Solid sodium iodide (15.51 g, 103.5 mmol) was introduced at room temperature into a stirred solution of Boc-L-ala-L-(β-Cl)ala OMe (3.168 g, 10.35 mmol) in dry acetone, (90 cm^3) under nitrogen. On stirring at 30^oC for 15 days n.m.r analysis indicated complete conversion (>95%) of the chloride starting material. The resulting sodium chloride was removed by filtration and the filtrate thus produced concentrated to give a crude, coloured solid. This material was dissolved in chloroform (150 cm^3), washed with distilled water (2 × 75cm^3), sodium thiosulphate (75 cm^3), distilled water (3 × 75cm^3), dried, and the solvent removed to afford Boc-L-ala-L-(β-I)ala OMe as a white solid. (3.4167 g, 8.5 mmol, 75%); (mp 88-90^oC); (Found: C 36.6, H 5.18, N 6.83. $C_{12}H_{21}N_2O_5I$ requires C 36.04, H 5.23, N 7.00%); $[\alpha]_D$ +6.9 (c 0.95 in CH_2Cl_2); υ_{max} (cap. film) 3 395, 1 752, 1 701, 1 655, 1 505, 1 219 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 1.37 (3H, d, *J* 7 C**H**$_3$), 1.45 (9H, s, OC(C**H**$_3$)$_3$), 3.55 (1H, dd, *J* 4 and 10.5, C(3)**H**), 3.61 (1H, dd, *J* 4 and 10.5, C(3)**H**), 3.79 (3H, s, C**H**$_3$O), 4.15-4.22 (1H, m, C(2)**H**), 4.70-4.75 (1H, m, C(2)**H**), 4.93 (1H, br, N**H**), 6.97 (1H, br, N**H**); *m/z* (e.i.) 344 (M^+ - $(CH_3)_2C{=}CH_2$ 6.0 %).

Organozinc couplings; preparation of dipeptides 9.

Zinc dust (0.3 g, 4.5 mmol), 1,2-dibromoethane (0.042 g, 20 µl, 0.023 mmol) and dry tetrahydrofuran (0.34 cm^3) were introduced to a dry, nitrogen-purged flask. This mixture was heated to 65^oC, with stirring, for 5 min with accompanying effervescence. At room temperature trimethylchlorosilane (6 µl, 0.05 mmol) was added and the entire flask contents were sonicated for 30 min. After heating to 35^oC, a solution of the iodide **6b** (0.300g 0.75 mmol) in dry tetrahydrofuran (0.75 cm^3) was syringed into the flask and the reactants were held at this temperature for 30 min until no starting material remained (t.l.c analysis, 2:1 / petrol-ethyl acetate).

Immediately on removal from the warming bath, dry tetrahydrofuran (5 cm^3) was added and, after the solids had settled, the solution was carefully transferred from the residue *via* syringe into a dry, nitrogen-purged flask.
(a). For palladium mediated acyl chloride reactions:
At room temperature *tris*(dibenzylideneacetone)-*di*-palladium(0) (0.018 g, 0.02 mmol), triphenylphosphine (0.021 g, 0.08 mmol), and the electrophile (1.0 mmol) were added sequentially. After stirring for 1h the reaction mixture was cooled to ambient temperature, diluted with ethyl acetate (50 cm^3), washed with aqueous hydrochloric acid (25 cm^3, 0.1 M), water (3 × 25 cm^3), dried, and solvent removed to give a crude sample. Column chromatography over silica gel (petrol-ethyl acetate) yielded the pure dipeptide **9**.

Boc-L-Ala-L-(β-Benzoyl)Ala-OMe 9a
(0.087g, 0.23 mmol, 31%); (mp 122-124°C); (Found: M^+- $(CH_3)_2C{=}CH_2$ 322.1154. $C_{15}H_{18}N_2O_6$ requires 322.1165); $[\alpha]_D$ +41.8 (c 1.1 in CH_2Cl_2); υ_{max} (cap. film) 3 303, 1 748, 1 547, 1 217 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 1.37 (3H, d, *J* 7, CH_3), 1.39 (9H, s, $OC(CH_3)_3$), 3.38 (1H, dd, *J* 4 and 18, C(3)**H**), 3.74 (3H, s, OCH_3), 3.77 (1H, dd, *J* 4 and 18, C(3)**H**), 4.10-4.20 (1H, m, C(2)**H**), 4.92-5.00 (1H, m, C(2)**H**), 5.04 (1H, brd, *J* 7.3, N**H**), 7.10 (1H, brd, *J* 8, N**H**), 7.42-7.64 (3H, m, **Ph**), 7.90-7.96 (2H, m, **Ph**); *m/z* (e.i.) 322 (M^+ - $(CH_3)_2C{=}CH_2$ 16%).

Boc-L-Ala-L-(β-Furoyl)Ala-OMe 9b
(0.1409 g, 0.38 mmol, 51%); (mp 132-134°C); (Found: C 55.79, H 6.80, N 7.27. $C_{17}H_{24}N_2O_7$ requires C 55.43, H 6.57, N 7.60 %); (Found: M^+- $(CH_3)_2C{=}CH_2$ 312.1154. $C_{13}H_{16}N_2O_7$ requires 312.0958); $[\alpha]_D$ +31.8 (c 1.05 in CH_2Cl_2); υ_{max} (cap. film) 3 291, 1 748, 1 551, 1 219 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 1.33 (3H, d, *J* 7.1, CH_3), 1.37 (9H, s, $OC(CH_3)_3$), 3.38 (1H, dd, *J* 4.5 and 18, C(3)**H**), 3.56 (1H, dd, *J* 4.5 and 18, C(3)**H**), 3.71 (3H, s, OCH_3), 4.06-4.17 (1H, m, C(2)**H**), 4.85-4.93 (1H, m, C(2)**H**), 5.04 (1H, brd, *J* 7, N**H**), 6.52 (1H, dd, *J* 1.7 and 3.5, **Furoyl**), 7.07 (1H, brd, *J* 8, N**H**), 7.19 (1H, dd, *J* 0.7 and 3.5, **Furoyl**), 7.57 (1H, dd, *J* 1.7 and 0.7, **Furoyl**); *m/z* (e.i.) 313 (MH^+ - $(CH_3)_2C{=}CH_2$ 20%).

(b). For palladium mediated aryl iodide reactions, *either*:
(i) On warming to 50°C, *tris*(dibenzylideneacetone)-*di*-palladium(0) (0.018 g, 0.02 mmol), tri-*o*-tolylphosphine (0.024 g, 0.08 mmol), and the electrophile (1.0 mmol) were added sequentially. After stirring for 2h the reaction mixture was cooled to ambient temperature, diluted with ethyl acetate (50 cm^3), washed with aqueous hydrochloric acid (25 cm^3, 0.1 M), water (3 × 25 cm^3), dried, and the solvent removed to give a crude sample. Column chromatography over silica gel (petrol-ethyl acetate) yielded the pure dipeptide.

Boc-L-Ala-L-Phe-OMe 9c
(0.1208 g, 0.38 mmol, 51%); (mp 83-84°C, lit. mp 82-84 °C);[22] (Found: M^+ - $(CH_3)_2C{=}CH_2$ 294.1219. $C_{14}H_{18}N_2O_5$ requires 294.1215); $[\alpha]_D$ + 24.2 (c 1.11 in CH_2Cl_2), lit. $[\alpha]_D$ +23 (c 0.61 in $CHCl_3$)[22]; υ_{max} (cap. film) 3 327, 1 738, 1 692, 1 655, 1 533, 1 171 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 1.31 (3H, d, *J* 7, CH_3), 1.44 (9H, s, $OC(CH_3)_3$), 3.07 (1H, dd, *J* 6 and 14, C(3)**H**), 3.17 (1H, dd, *J* 6 and 14, C(3)**H**), 3.72 (3H, s, OCH_3), 4.10-4.16 (1H, m, C(2)**H**), 4.82-5.00 (1H, m, C(2)**H**, N**H**), 6.52 (1H, brd, *J* 8, N**H**), 7.07-7.12 (2H, m, **Ph**), 7.23-7.33 (3H, m, **Ph**); *m/z* (e.i.) 294 (M^+ - $(CH_3)_2C{=}CH_2$ 32.4%).

Boc-L-Ala-L-(4-Nitro)Phe-OMe 9d
(0.1838 g, 0.46 mmol, 63%); (mp 126-127 °C; lit. mp 139-141 °C)[23] (Found: C 54.65, H 6.91, N 10.50. $C_{18}H_{25}N_3O_7$ requires C 54.68, H 6.37, N 10.63%); (Found: M^+ - ^tBuO 322.1024. $C_{14}H_{16}N_3O_6$ requires 322.1039); $[\alpha]_D$ +10.7 (c 1.05 in CH_2Cl_2); υ_{max} (cap. film) 3 334, 1 738, 1 675, 1 666, 1 523, 1 251 cm^{-1}; δ_H

(200 MHz; $CDCl_3$) 1.32 (3H, d, *J* 7, CH_3), 1.44 (9H, s, $OC(CH_3)_3$), 3.16 (1H, dd, *J* 6.2 and *J* 13.8, CH_2Ar), 3.51 (1H, dd, *J* 5.6 and *J* 13.8, CH_2Ar), 3.75 (3H, s, OCH_3), 4.09-4.16 (1H, m, C(2)**H**), 4.83-4.96 (2H, m, C(2)**H**, N**H**), 6.76 (1H, brd, *J* 7.5, N**H**), 7.32 (2H, d, *J* 8.5, **Ar**), 8.15 (2H, d, *J* 8.5, **Ar**); *m/z* (e.i.) 322 (M^+ - $(CH_3)_2C=CH_2$ - CH_4 - H 1.8%).

(ii) *or;*

While warming to reflux temperature, *tris*(dibenzylideneacetone)-*di*-palladium(0) (0.018 g, 0.02 mmol), tri-*o*-tolylphosphine (0.024 g, 0.08 mmol), and the electrophile (1.0 mmol) were added sequentially. After stirring the reaction mixture at reflux for 2h the flask contents were cooled to ambient temperature, and worked up as above.

Boc-L-Ala-L-(4-Bromo)Phe-OMe 9e

(0.0659 g, 0.15 mmol, 20%).%); (Found: M^+- $(CH_3)_2C=CH_2$ 372.0322. $C_{14}H_{17}N_2O_5Br$ requires 372.0321); υ_{max} (cap. film) 3 315, 1 746, 1 712, 1 670, 1 520, 1 169 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 1.31 (3H, d, *J* 7, CH_3), 1.43 (9H, s, $OC(CH_3)_3$), 3.02 (1H, dd, *J* 6 and *J* 14, CH_2Ar), 3.14 (1H, dd, *J* 5.5 and *J* 14, CH_2Ar), 3.72 (3H, s, OCH_3), 4.06-4.1 (1H, m, C(2)**H**), 4.77-4.98 (2H, m, N**H** and C(2)**H**), 6.66 (1H, brd, *J* 7.5, N**H**), 6.98 (2H, d, *J* 8, **Ar**), 7.40 (2H, d, *J* 8, **Ar**); *m/z* (e.i.) 372 (M^+ - $(CH_3)_2C=CH_2$ 4.8%).

Boc-L-Ala-L-(β-Naphthyl)Ala-OMe 9f

(0.1253 g, 0.31 mmol, 41%); (mp 115-116°C); (Found: C 64.83, H 7.24, N 7.02. $C_{22}H_{28}N_2O_5$ requires C 65.98, H 7.05, N 7.00%); (Found: M^+ 400.2006. $C_{22}H_{28}N_2O_5$ requires 400.1998); $[\alpha]_D$ -8.1 (c 1.1 in CH_2Cl_2); υ_{max} (cap. film) 3 353, 1 742, 1 679, 1 672, 1 522, 1 167 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 1.27 (3H, d, *J* 7, CH_3), 1.42 (9H, s, $OC(CH_3)_3$), 3.50 - 3.65 (2H, m, CH_2Ar), 3.61 (3H, s, OCH_3), 4.06-4.17 (1H, m, C(2)**H**), 4.87-5.02 (2H, m, N**H** and C(2)**H**), 6.71 (1H, brd, *J* 7, N**H**), 7.22-7.58 (4H, m, **Ar**), 7.74-7.87 (2H, m, **Ar**), 8.09 (1H, d, *J* 9.0, **Ar**); *m/z* (e.i.) 400 (M^+ 2.4%).

Preparation of Boc-L-Ala-L-(β-Iodozinc)Ala-OMe. NMR Experiment.

Zinc dust (0.15 g, 2.25 mmol), 1,2-dibromoethane (9.7μl, 11 mmol) and dry, d_8 tetrahydrofuran (0.17 cm^3) were placed in a dry, argon-purged n.m.r tube fitted with a Young valve and a 3-way tap. This mixture was heated to 65°C for 5 min. On cooling, trimethylchlorosilane (3μl, 0.025 mmol) was added and the tube sonicated for 30 min. A solution of Boc-L-ala-L-(β-iodo)ala-OMe (0.148 g, 0.37 mmol) in dry D_8 tetrahydrofuran (0.37 cm^3) was introduced and the tube contents were sonicated for a further 30 min until proton n.m.r analysis indicated complete consumption of iodide. δ_H (200 MHz; d_8 THF) 0.25 (1H, m, J_{AX} 12.0, and J_{AB} 12.0, C(3)**H**), 0.56 (1H, m, J_{BX} 5.5, and J_{AB} 12.0, C(3)**H**), 1.27 (3H, d, *J* 7.2, CH_3) 1.36 (9H, s, $OC(CH_3)_3$), 3.62 (3H, s, OCH_3), 4.04-4.29 (2H, m, 2C(2)**H**), 6.55 (1H, br, N**H**), 7.96 (1H, br, N**H**). The spectrum also contained some evidence for the presence of Boc-L-Ala-L-Ala-OMe, presumably formed by protonolysis of Boc-L-Ala-L-(β-Iodozinc)Ala-OMe.

Boc-L-Phe-L-Ser-OMe 10

Gaseous ammonia was bubbled for 30 min through a suspension of serine methyl ester hydrochloride (3.516g, 22.6mmol) in diethyl ether (100cm^3) cooled to 0°C. Careful evaporation of the ether yielded serine methyl ester (1.4615g, 12.3mmol). A solution of dicyclohexylcarbodiimide (2.7855g, 13.5mmol) in dichloromethane (10cm^3) was added dropwise to a stirred mixture of the Boc-Phe-OH (2.328g, 12.3mmol), and serine methyl ester (1.4615g, 12.3mmol), and 1-hydroxybenzotriazole (1.8241g, 13.5mmol) dissolved in dichloromethane (20cm^3), cooled in an ice bath. Stirring was continued overnight during which time the flask contents reached

ambient temperature. On removal of the white precipitate by filtration, the filtrate was diluted with dichloromethane (170cm^3), washed with sodium hydrogen carbonate (100cm^3, 10%), citric acid (100cm^3, 10%), dried, and concentrated under reduced pressure to yield a foam. Recrystallisation afforded Boc-L-Phe-L-Ser-OMe **10** as a white solid. (3.62 g, 9.9 mmol, 87%); (mp 59-60^{o}C, lit. mp 88-89 ^{o}C);[24] (Found: MH^+ 367.1872. $C_{18}H_{27}N_2O_6$ requires 367.1869); $[\alpha]_D$ +12.1 (c 1.02 in CH_2Cl_2); υ_{max} (cap. film) 3 321, 1 745, 1 663, 1 526, 1 251 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 1.39 (9H, s, OC(**CH**$_3$)$_3$), 1.89 (1H, br, **OH**), 2.97-3.18 (2H, m, **CH**$_2$Ph), 3.75 (3H, s, O**CH**$_3$), 3.85-3.95 (2H, br, **CH**$_2$OH), 4.30-4.40 (1H, m, C(2)**H**), 4.56-4.63 (1H, m, C(2)**H**), 5.14 (1H, d, *J* 7.5 N**H**), 6.94 (1H, bd, *J* 7.5 N**H**), 7.19-7.35 (5H, m, **Ph**); *m/z* (e.i.) 367 (MH^+ 3.2%).

Boc-L-Phe-L-(β-Iodo)Ala-OMe 11

Freshly recrystallised triphenoxyphosphonium methiodide (18.0892g, 40mmol) was added in one portion to a stirred solution of Boc-L-Phe-L-Ser-OMe (7.3349g, 20mmol) in dry dimethylformamide (80cm^3) at room temperature, under nitrogen in the absence of light. On stirring for 45min, the reaction mixture was diluted with ether (400cm^3), washed with distilled water (2 × 200cm^3), sodium thiosulphate (200cm^3, 1*M*), distilled water (3 × 200cm^3), dried, and the solvent removed to give a crude reaction mixture. Purification using flash chromatography (10 : 1, petrol : ethyl acetate) afforded Boc-L-Phe-L-(β-Iodo)Ala-OMe **11** as a white solid. (3.77 g, 8.0 mmol, 44%); (mp 86-87^{o}C); (Found: M^+ - $(CH_3)_2C{=}CH_2$ 420.0190. $C_{14}H_{17}N_2O_5I$ requires 420.0184); $[\alpha]_D$ +19.2 (c 1.14 in CH_2Cl_2); υ_{max} (cap. film) 3 333, 1 740, 1 687, 1 521, 1 169 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 1.43 (9H, s, OC(**CH**$_3$)$_3$), 3.11 (2H, d, *J* 6.5, **CH**$_2$Ph), 3.50-3.63 (2H, m, **CH**$_2$I), 3.78 (3H, s, O**CH**$_3$), 4.40-4.43 (1H, m, C(2)**H**), 4.67-4.74 (1H, m, C(2)**H**), 4.93 (1H, br, N**H**), 6.81 (1H, brd, *J* 7, N**H**), 7.19-7.36 (5H, m, **Ar**); *m/z* (e.i.) 420 (MH^+ - $(CH_3)_2C{=}CH_2$ 10.2%).

Boc-L-Phe-L-(β-Allenyl)Ala-OMe 12

Zinc dust (0.3 g, 4.5 mmol), 1,2-dibromoethane (0.042 g, 20 µl, 0.023 mmol) and dry dimethylacetamide (0.34 cm^3) were introduced to a dry, nitrogen-purged flask. This mixture was heated to 65^{o}C, with stirring, for 5 min with accompanying effervescence. At room temperature trimethylchlorosilane (6 µl, 0.05 mmol) was added and the entire flask contents were sonicated for 30 min. After heating to 35^{o}C, a solution of the iodide (0.75 mmol) in dry dimethylacetamide (0.75 cm^3) was syringed into the flask and the reactants were held at this temperature for 30 min until no starting material remained (t.l.c analysis, 2:1 / petrol-ethyl acetate). Immediately on removal from the warming bath, dry dimethylacetamide (5 cm^3) was added and, after the inorganics had settled, the solution was carefully removed from the residue *via* syringe into a dry, nitrogen-purged flask. The stirred flask contents were cooled to -10^{o}C, a solution of copper (I) cyanide-lithium chloride complex (CuCN.2LiCl) (0.75 mmol) in dry dimethylacetamide (2 cm^3) was introduced, and stirring was continued at 0^{o}C for 10 min. At -25^{o}C the electrophile (1.0 mmol) was added and the flask contents were stirred at 0^{o}C for 3 h. Once the flask had reached room temperature, the mixture was diluted with ethyl acetate (50 cm^3), washed with aqueous sodium hydrogen carbonate (25 cm^3, sat.), water (3 × 25 cm^3), dried and concentrated under reduced pressure to produce the crude compound. Flash chromatography over silica gel (petrol-ethyl acetate) afforded the pure dipeptide **12** as a white solid. (0.1223 g, 0.32 mmol, 43%); (mp 95-96^{o}C);); (Found: C 65.22, H 7.57, N 7.00. $C_{21}H_{28}N_2O_5$ requires C 64.93, H 7.26, N 7.21%); (Found: M^+ 388.2006. $C_{21}H_{28}N_2O_5$ requires 388.1998); $[\alpha]_D$ +18.6 (c 1.15 in CH_2Cl_2);); υ_{max} (cap. film) 3 337, 1 761, 1 736, 1 691, 1 658, 1 528, 1 171 cm^{-1} δ_H (200 MHz; $CDCl_3$) 1.42 (9H, s, OC(**CH**$_3$)$_3$), 2.40-2.54 (2H, m, C(3)**H**$_2$), 3.08 (2H, d, *J* 6.5, C(3)**H**$_2$), 3.72 (3H, s, O**CH**$_3$), 4.36-4.40 (1H, m, C(2)**H**), 4.58-4.68 (3H, m, C(2)**H**, C(6)**H**$_2$), 4.87 (1H, pentet, *J* 6.5, C(5)**H**), 4.98 (1H, brd, *J* 7, N**H**), 6.51 (1H, d, *J* 7.5, N**H**), 7.28 (5H, m, **Ph**); *m/z* (e.i.) 388 (M^+ 5.7 %).

Boc-L-Ala-L-Phe-OMe 9c

This compound was prepared on large scale according to the general method already described for Boc-L-Phe-L-Ser-OMe **10**. (9.171 g, 26.2 mmol, 97%). The compound was identical to that prepared by coupling of the zinc reagent **8** with iodobenzene.

Boc-L-Ala-L-Phe-OH

Sodium hydroxide (15cm^3, 1M) was introduced dropwise into a flask containing a stirred solution of Boc-L-Ala-L-Phe-OMe (4.2568g, 14.7mmol) in methanol (50cm^3) at room temperature. After 45min the methanol was removed and the resulting aqueous phase combined with ethyl acetate (80cm^3). This mixture was then acidified with hydrochloric acid (17.6cm^3, 1M), the organic portion separated, and the aqueous phase extracted with ethyl acetate (2 × 80cm^3). Concentration under reduced pressure gave Boc-L-Ala-L-Phe-OH as a white solid. (8.1271 g, 24.2 mmol, 94%); (mp 75-76^{o}C); (Found: C 61.13, H 7.39, N 8.58. $C_{17}H_{24}N_2O_5$ requires C 60.70, H 7.19, N 8.33%); (Found: M^+ - $(CH_3)_2C{=}CH_2$ 280.1055. $C_{13}H_{16}N_2O_5$ requires 280.1059); $[\alpha]_D$ +12.5 (c 1.16 in CH_2Cl_2); υ_{max} (cap. film) 3 320, 1 719, 1 664, 1 524, 1 249 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 1.28 (3H, d, *J* 7.0, C**H**$_3$), 1.43 (9H, s, OC(C**H**$_3$)$_3$), 3.04 (1H, dd, *J* 6.4 and *J* 14.0, C(3)**H**), 3.22 (1H, dd, *J* 5.2 and *J* 14.0, C(3)**H**), 4.20 (1H, m, C(2)**H**), 4.75-4.85 (1H, m, C(2)**H**), 5.16 (1H, br, N**H**), 5.33 (1H, br, COO**H**), 6.83 (1H, brd, *J* 7.5, N**H**), 7.12-7.33 (5H, m, **Ar**); *m/z* (e.i.) 280 (MH^+- $(CH_3)_2C{=}CH_2$ 14.0%).

Boc-L-Ala-L-Phe-L-Ser-OMe 13

This compound was prepared according to the general method already described for Boc-L-Phe-L-Ser-OMe **10**. (6.30 g, 14.4 mmol, 64%); (mp 157-158^{o}C); $[\alpha]_D$ -43.2 (c 1.005 in CH_2Cl_2); υ_{max} (cap. film) 3 299, 1 746, 1 693, 1 523, 1 219 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 1.27 (3H, d, *J* 7, C**H**$_3$), 1.39 (9H, s, OC(C**H**$_3$)$_3$), 1.87 (1H, br, O**H**), 3.12-3.15 (2H, m, C(3)**H**$_2$), 3.48-3.57 (1H, m, C**H**OH), 3.75 (3H, s, OC**H**$_3$), 3.86-3.91 (1H, m, C**H**OH), 4.03-4.13 (1H, m, C(2)**H**), 4.55-4.62 (1H, m, C(2)**H**), 4.77 (1H, q, *J* 7, C(2)**H**), 4.99 (1H, bd, *J* 6, N**H**), 6.76 (1H, brd, *J* 7.5, N**H**), 7.18-7.33 (6H, m, N**H**, **Ar**).

Boc-L-Ala-L-Phe-L-(β-Iodo)Ala-OMe 14

This compound was prepared according to the general method already described for Boc-L-Phe-L-(β-Iodo)Ala-OMe **11.** (2.29 g, 4.2 mmol, 58%); (mp 145-146^{o}C); (Found: C 46.53, H 5.02, N 7.28. $C_{21}H_{30}N_3O_6I$ requires C 46.08, H 5.52, N 7.68%); (Found: M^+- $(CH_3)_2C{=}CH_2$ 491.0563. $C_{17}H_{22}N_3O_6I$ requires 491.0555); $[\alpha]_D$ -22.2 (c 1.05 in CH_2Cl_2); υ_{max} (cap. film) 3 294, 1 734, 1 690, 1 549, 1 170 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 1.33 (3H, d, *J* 7, C**H**$_3$), 1.43 (9H, s, OC(C**H**$_3$)$_3$), 3.12 (2H, d, *J* 6.5, C(3)**H**$_2$), 3.45-3.59 (2H, m, C**H**$_2$I), 3.77 (3H, s, OC**H**$_3$), 4.10-4.17 (1H, m, C(2)**H**), 4.64-4.78 (2H, m, 2 × C(2)**H**), 4.91 (1H, bd, *J* 6.7, N**H**), 6.69 (1H, bd, *J* 8, N**H**), 6.84 (1H, br, N**H**), 7.19-7.35 (5H, m, **Ar**); *m/z* (e.i.) 491 (M^+ - $(CH_3)_2C{=}CH_2$ 2.1%).

Boc-L-Ala-L-Phe-L-(β-Furoyl)Ala-OMe 15

The iodide **14** (0.75 mmol) was converted into the corresponding zinc reagent in THF, which was then treated with furoyl chloride, using the same procedure as that employed for the preparation of **9b**. Purification by flash chromatography gave the tripeptide **15**. (0.1643 g, 0.32 mmol, 43%); (mp 87-88^{o}C); (Found: C 60.40, H 6.54, N 8.10. $C_{26}H_{33}N_3O_8$ requires C 60.57, H 6.45, N 8.15%); (Found: M^+ 515.2223. $C_{26}H_{33}N_3O_8$ requires 515.2268); $[\alpha]_D$ -12.5 (c 0.55 in CH_2Cl_2); υ_{max} (cap. film) 3 314, 1 738, 1 684, 1 524, 1 166 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 1.28 (3H, d, *J* 7, C**H**$_3$), 1.41 (9H, s, OC(C**H**$_3$)$_3$), 3.11 (2H, d, *J* 6.4, C(3)**H**$_2$), 3.33-3.56 (2H, m, C(3)**H**$_2$), 3.71 (3H, s, OC**H**$_3$), 4.06-4.17 (1H, m, C(2)**H**), 4.62-4.72 (1H, m, C(2)**H**), 4.83-4.92 (2H, m, C(2)**H**, N**H**), 6.55 (1H,dd, *J* 1.5, 3.5, **Furoyl**), 6.64 (1H, brd, *J* 8, N**H**), 6.94 (1H, brd, *J* 8, N**H**), 7.23 (6H, m, **Ph**, **Furoyl**), 7.80 (1H, d, *J* 1.5, **Furoyl**); *m/z* (e.i.) 515 (M^+ 2.2%).

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References

1. Seebach, D.; Bossler, H.; Gründler, H.; Shoda, S.-i.; Wenger, R. *Helv. Chim. Acta* **1991**, *74*, 197.
2. Bossler H.G.; Seebach, D. *Helv. Chim. Acta*, **1994**, *77*, 1124, and references cited therein.
3. Polt, R.; Seebach, D. *J. Am. Chem. Soc.*, **1989**, *111*, 2622.
4. Ojima, I.; Komata, T.; Qiu, X. *J. Am. Chem. Soc.*, **1990**, *112*, 770.
5. Crich D.; Davies, J.W. *Tetrahedron* **1989**, *45*, 5641.
6. Kazmaier, U. *J. Org. Chem.* **1994**, *59*, 6667.
7. Ritter A.R.; Miller, M.J. *Tetrahedron Lett.* **1994**, *35*, 9379.
8. Jäger, M.; Polborn K.; Steglich, W. *Tetrahedron Lett.* **1995**, *36*, 861.
9. Ojima, I.; Yoda, N.; Yatabe, M.; Tanaka, T.; Kogure, T. *Tetrahedron* **1984**, *40*, 1255; Takasaki, M.; Harada, K. *J. Chem. Soc., Chem. Commun.* **1987**, 571, and references cited therein.
10. Barton, D.H.R.; Hervé, Y.; Potier, P; Thierry, J. *Tetrahedron* **1988**, *44*, 5479.
11. Baldwin, J.E.; Adlington, R.M.; Godfrey, C.R.A.; Patel, V.K. *Tetrahedron* **1993**, *49*, 7837.
12. Jackson, R.F.W.; Wishart, N.; Wood, A.; James, K.; Wythes, M.J. *J. Org. Chem.*, **1992**, *57*, 3397.
13. Dunn, M.J.; Jackson, R.F.W.; Pietruszka, J.; Turner, D. *J. Org. Chem.* **1995**, *60*, 2210.
14. Dunn, M.J.; Gomez, S.; Jackson, R.F.W. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1639.
15. For existing methods, see: Sommerfeld, T.L.; Seebach, D. *Helv. Chim. Acta* **1993**, *76*, 1702, and references cited therein.
16. Knochel, P.; Yeh, M.C.P.; Berk, S.C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390; Duddu, R.; Eckhardt, M.; Furlong, M.; Knoess, H.P.; Berger, S.; Knochel, P. *Tetrahedron* **1994**, *50*, 2415; Knochel P.; Singer, R.D. *Chem. Rev.* **1993**, *93*, 2117.
17. Srinivasan, A.; Stephenson, R.W.; Olsen, R.K. *J. Org. Chem.* **1977**, *42*, 2253.
18. For a discussion, see; Fraser, J.L.; Jackson, R.F.W.; Porter, B. *Synlett* **1995**, 819.
19. Verheyden, J.P.H.; Moffatt, J.G.; *J. Org. Chem.*, **1970**, *35*, 2319.
20. Moore, R.J.; Dexter, C.S.; Jackson, R.F.W. unpublished results.
21. Fischer, E.; Raske, K. *Chem.Ber.* **1907**, *41*, 893; Brown, G.B.; du Vigneaud, V. *J. Biol.Chem.* **1941**, *137*, 611.
22. Beugelmans, R.; Neuville, L.; Bois-Choussy, M.; Chastanet, J.; Zhu, J. *Tetrahedron Lett.* **1995**, *36*, 3129.
23. Tokutake, S.; Imanishi, Y.; Sisido, M. *Mol. Cryst. Liq. Cryst.* **1989**, *170*, 245.
24. Schwyzer, R.; Karlaganis, G. *Liebigs Ann. Chem.* **1973**, 1298.

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