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Imidazolines as Amide Bond Replacements

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Abstract: This work describes the use of a 2,5,5-trisubstituted imidazoline as an amide bond replacement. The replacement is incorporated into dipeptide derivatives of Phe, Trp, Lys and Nle and also into the CCK-4 analogue Trp-Nle-Asp-Phe-NH_2 and the pentagastrin analogue Gly-Trp-Nle-Asp-Phe-NH_2. The amide bond replacement is synthesised in enantiomerically and diastereomerically pure form.

INTRODUCTION

There is considerable current interest in the design of drugs which modulate the actions of endogenous peptides.[3] Two important areas where peptides have been used as chemical leads for drug discovery programmes are in the inhibition of proteolytic enzymes (such as renin, angiotensin converting enzyme and HIV protease) and as agonists and antagonists at peptide receptors (such as the opioid and cholecystokinin receptors). However, the peptidic amide bond is metabolically labile to hydrolysis and this limits the therapeutic utility of peptides. A lot of work has gone into modifying the peptide bond so that it is no longer susceptible to hydrolysis, but contains the relevant features required for molecular recognition at either the proteolytic enzyme or the peptide receptor.[4]

The amide bond possesses a number of structural features that may be important to mimic when designing an amide bond replacement; for example the presence of two heteroatoms, multiple bonds, polarity, lipophilicity, steric size, geometry and hydrogen bonding. When designing an amide bond replacement, the relative importance of each of these features will vary depending on the particular biological target.

There have been a number of attempts at designing amide bond replacements.[5] Replacements of the peptidic amide bond (CONH) include the ketomethylene ($COCH_2$), the methyleneamino (CH_2NH), the reversed amide (NHCO) and the hydroxyethylene ($CHOHCH_2$). Such strategies have been employed in the development of a number of pharmaceutically active compounds such the angiotensin converting enzyme inhibitors,[6] captopril and enalapril, the HIV proteinase inhibitor[7] Ro 31-8959 and the cholecystokinin anatagonist[8] CI-988.

The above replacements mimic only a few features of the amide bond. The objective of this study was to develop the imidazoline as an amide bond replacement (Figure 1). The imidazoline contains an amidine that

has similar resonance structures to those of the parent amide bond and as such mimics many of the features of the amide bond. The similarities include the presence of two heteroatoms, similar configuration of double bonds, similar hydrogen bonding possibilities and similar steric properties. On the other hand the basicity of an amidine is greater than that of an amide, a property that retards hydrolysis under the conditions likely to prevail in biological systems.[9]

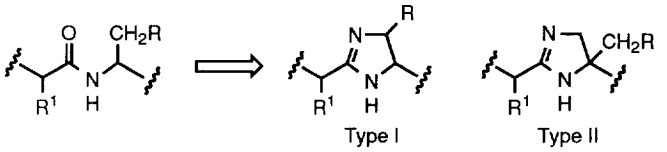
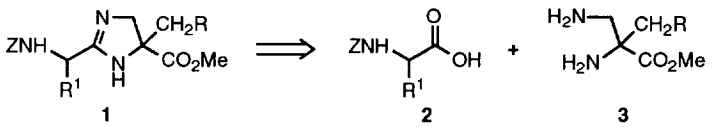


Figure 1

There has been a previous report of the imidazoline type I as an amide bond replacement.[10] In this imidazoline the amino acid side chain is directly attached to the imidazoline ring. In the present study we decided to synthesise imidazolines of type II. In imidazolines of type II the amino acid side chain R is no longer directly attached to the imidazoline ring, and hence is not so conformationally constrained. Imidazolines of type II may therefore be a better mimic of the parent peptide than imidazolines of type I. Some of this work has been previously reported in communications.[11] In this paper we describe for the first time in detail, a stereocontrolled route to the imidazoline, biological activities of our compounds and full experimental data.

INCORPORATION OF THE AMIDE REPLACEMENT IN DIPEPTIDES

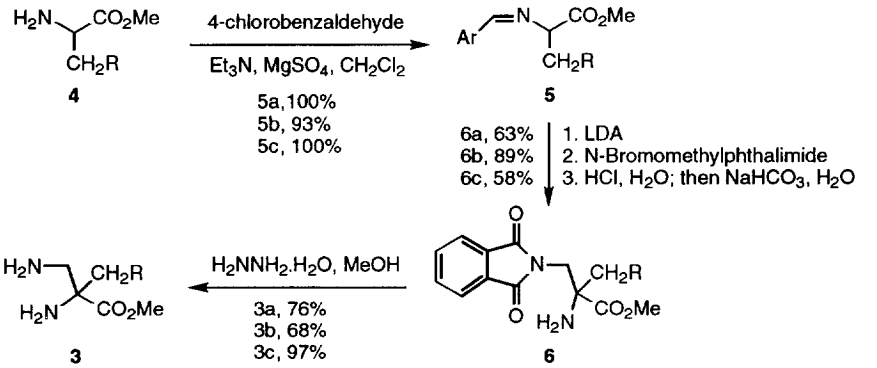
Initially we decided to establish our methodology by synthesising a variety of dipeptide isosteres **1**. The retrosynthetic strategy is shown in Scheme 1. We proposed to synthesise the imidazoline isostere by condensation of the N-protected amino acid **2** with the diamino compound **3**. To carry out the condensation the carboxylate group of amino acid **2** was activated by one of the methods of Jones and Ward.[10] To give the most general synthesis the diamino compound **3** was also synthesised from an amino acid.



Scheme 1

The synthesis of the diamino compound **3** in racemic form is shown in Scheme 2. The appropriate amino acid methyl ester **4** was condensed with 4-chlorobenzaldehyde to give the Schiff base **5**. This was then deprotonated with lithium diisopropylamide at low temperature and alkylated[12] at the α-position with N-bromomethylphthalimide. The resulting imine was hydrolysed on work up to give the mono-protected diamino compound **6**. Removal of the phthalimide protecting group with hydrazine gave the diamino compound **3** in good yield (76-97%).

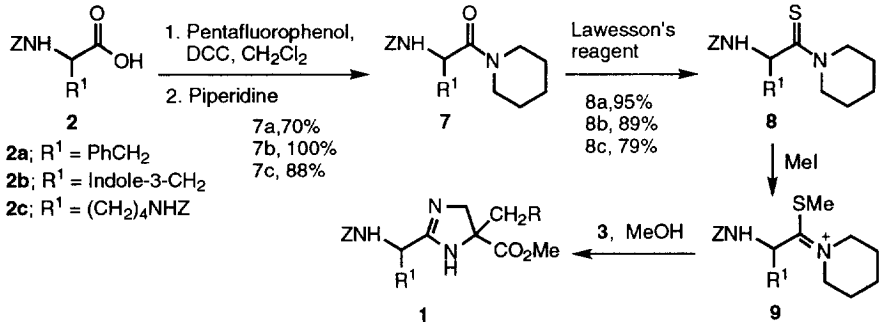
The N-protected amino acid **2** was activated by converting it to the S-methylthioimidate salt using the method of Jones and Ward.[10] This is shown in Scheme 3. The N-benzyloxycarbonyl protected amino acid was



a, R = Ph; **b**, R = $(CH_2)_2CH_3$; **c**, R = $(CH_2)_3NHZ$ [Z = $PhCH_2OC(O)$]

Scheme 2

converted to the piperidine amide **7** via the pentafluorophenol ester. Treatment of compound **7** with Lawesson's reagent gave the thioamide **8**, which was converted to the S-methylthioimidate salt **9** by treatment with methyl iodide. This salt was not isolated but immediately condensed with the diamino compound **3** to give the dipeptide isosteres **1** in good yield. By this methodology we incorporated our amide replacement into the dipeptides Phe-Phe, Trp-Phe, Lys-Lys and Trp-Nle, thus establishing the generality of our methodology. The stereochemistry of these dipeptides will be discussed later.



2a; R^1 = $PhCH_2$
2b; R^1 = Indole-3-CH_2
2c; R^1 = $(CH_2)_4NHZ$

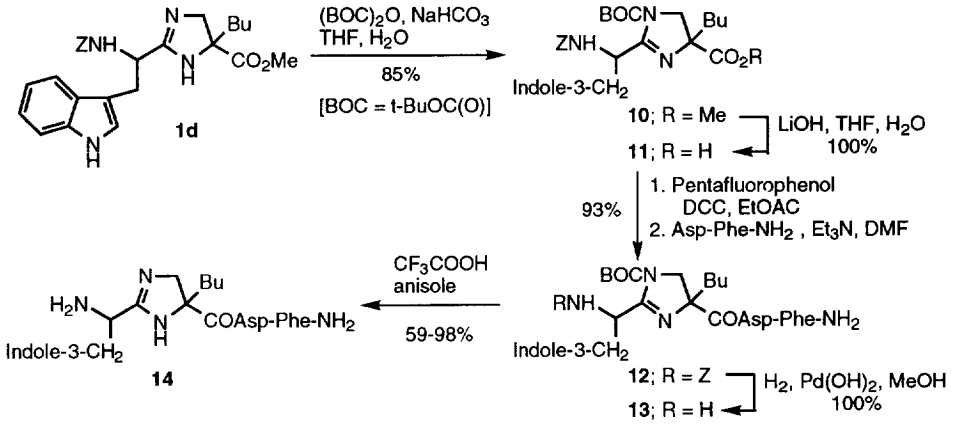
1a; R^1 = $PhCH_2$; R = Ph (87%)
1b; R^1 = Indole-3-CH_2; R = Ph (77%)
1c; R^1 = $(CH_2)_4NHZ$; R = $(CH_2)_3NHZ$ (42%)
1d; R^1 = Indole-3-CH_2; R = $(CH_2)_2CH_3$ (91%)

Scheme 3

INCORPORATION OF THE AMIDE REPLACEMEMENT INTO PEPTIDES

We sought to extend our methodology by incorporating our amide replacement into longer chain peptides by either N-terminal or C-terminal extension of the dipeptide isosteres **1**. Initially we planned to incorporate our amide replacement into an analogue of CCK-4, the C-terminal tetrapeptide (residues 30-33) of cholecystokinin. The structure of CCK-4 is Trp-Met-Asp-Phe-NH_2. Since methionine can be replaced by norleucine with little effect on the biological activity,[13] it was decided to incorporate our amide bond replacement between tryptophan and norleucine in the CCK-4 analogue Trp-Nle-Asp-Phe-NH_2.

The starting point was the Trp-Nle dipeptide isostere **1d** (Scheme 4). To incorporate the amide bond replacement between Trp and Nle in the CCK-4 analogue, requires deprotection of the Trp-Nle dipeptide isostere at the C-terminus and chain extension by Asp and Phe. Before attempting to deprotect at the C-terminal end, it was decided to protect the amidine functionality of the imidazoline as this is nucleophilic and was known to interfere with subsequent peptide coupling reactions.[14] The imidazoline functionality was protected as the *tert*-butyl carbamate to give compound **10**; this is a different protecting group to that on the amino terminus and should allow selective deprotection of either. The *tert*-butyloxycarbonyl protecting group derivatised just one of the imidazoline nitrogen atoms as shown by NMR spectroscopic examination (see also later). On steric grounds we assign this as being N-1 as shown in Scheme 4 for compound **10**, although a definitive structure must await, for example, long range coupling studies by NMR spectroscopy.

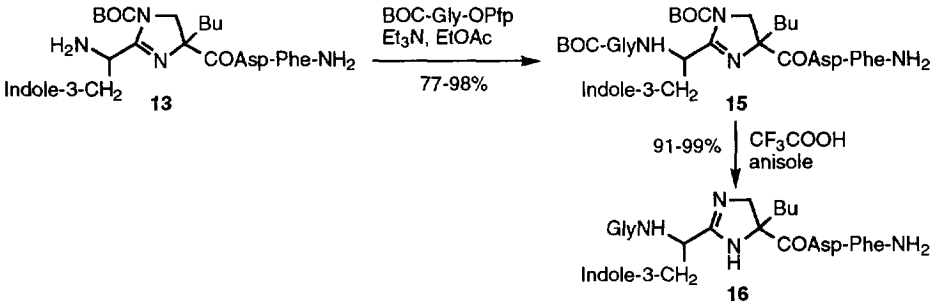


Scheme 4

The *tert*-butyloxycarbonyl protected dipeptide **10** was then deprotected at the C-terminus by ester hydrolysis to give the carboxylic acid **11** which was then activated as the pentafluorophenol ester and then coupled with Asp-Phe-NH_2 to give the diprotected tetrapetide isostere **12**. To complete the synthesis, the tetrapeptide was deprotected in two steps; firstly the benzyloxycarbonyl protecting group was removed by hydrogenolysis using Pearlman's catalyst to give **13** and then the *tert*-butyloxycarbonyl protecting group was removed with trifluoroacetic acid in the presence of anisole to give the target molecule **14**, as its trifluoroacetate salt.

The objective of C-terminal extension of the dipeptide isostere had now been achieved. The next objective was N-terminal extension. N-Terminal extension of the tetrapeptide **14** with glycine would afford a modified version of the analogue of pentagastrin, or residues 29-33 of CCK (Gly-Trp-Nle-Asp-Phe-NH_2), with the imidazoline amide replacement between tryptophan and norleucine.

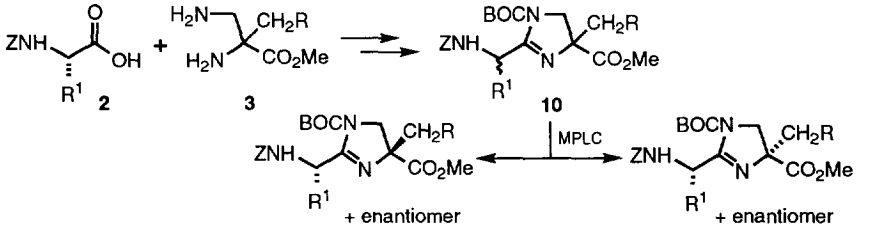
The starting point was the protected tetrapeptide **13** (Scheme 5); the imidazoline functionality was still protected as the *tert*-butyl carbamate. Compound **13** was coupled with N-*tert*-butyloxycarbonyl glycine activated as the pentafluorophenol ester to give the diprotected pentapeptide **15**. The BOC protecting groups were then both removed with trifluoroacetic acid in the presence of anisole to give the target pentapeptide isostere **16**, again as its trifluoroacetate salt.



Scheme 5

STEREOCHEMISTRY

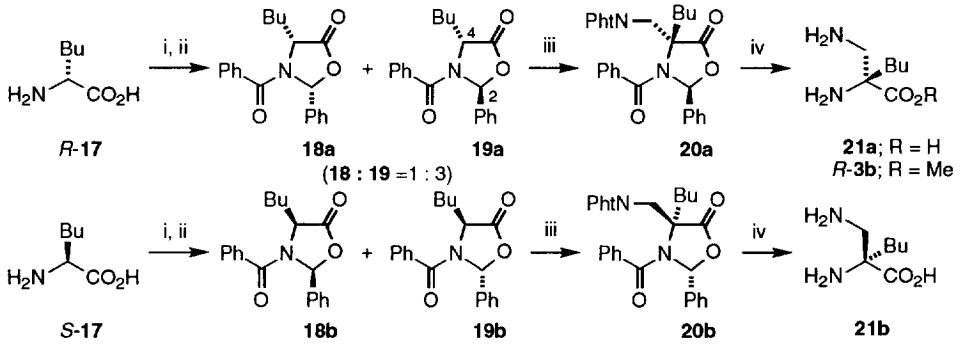
In the work described above, the dipeptide isosteres were synthesised as racemic mixtures of diastereoisomers. There are two stereocentres in the dipeptide isosteres, one derived from the N-protected amino acid moiety **2** and the other derived from the diamino moiety **3** (Scheme 6). By the method of Scheme 2, the diamino moiety **3** was synthesised as a racemic mixture. We found that when using enantiomerically pure N-protected amino acid moiety **2**, the stereocentre derived from the acid **2** was epimerised on condensation with the diamino compound **3**.[10] The epimerisation can be seen by examining the optical rotation data for compounds **7b**, **1** and **10** and from the NMR data for compound **10**; epimerisation occurs under the influence of the basic nature of the cyclic amidine.[15] However, after protection of the amidine as the *tert*-butyloxy carbamate the basicity is quenched and the mixture of diastereoisomers **10** could be separated into pairs of enantiomers by MPLC (Scheme 6). The imidazoline C-2(α) centre was found to retain stereochemical integrity whilst the amidine was protected as a carbamate or whilst protonated. Hence using enantiomerically pure diamino compound **3** would allow synthesis of enantiomerically and diastereomerically pure imidazolines.



Scheme 6

We therefore set about the synthesis of enantiomerically pure diamino compound **3**. The strategy selected was that used in the racemic synthesis (Scheme 2), namely the alkylation of an amino acid α-nucleophile synthon with a C^+N electrophile; the modification required was use of a homochiral amino acid α-nucleophile synthon.[16] Prior to our work, there was only one report of the use of such nucleophiles in α,β-diamino acid preparation,[17] for the special case of proline with a very reactive iminium electrophile, $CH_2{=}N^+Me_2$. Our preparation reported herein of the α,β-diamino acid precursor of ester **3b**, as either pure enantiomer, is generally applicable.

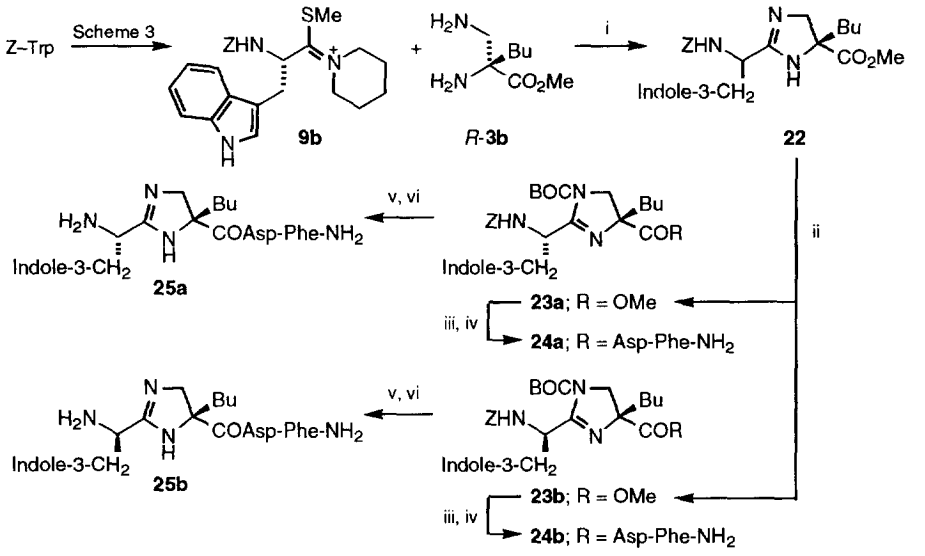
We chose to use the oxazolidinone approach (Scheme 7). Thus (*R*)-norleucine ***R*-17** was treated with benzaldehyde in aqueous sodium hydroxide to form the imine, which on N-benzoylation at –20°C afforded the oxazolidinone as a mixture of two diastereoisomers **18a** and **19a** in a ratio of 1:3 by ^{1}H n.m.r. spectroscopic examination. Under these conditions of oxazolidinone assembly,[18,19] the major product is the *anti*-isomer **19a** which was isolated pure in 56% yield on recrystallisation of the mixture. The *anti* relative configuration of **19a** was confirmed by observation in the ^{1}H n.m.r. spectrum of n.O.e. enhancements of methylene signals on irradiation of the signal from C-2(H), and of the C-4(H) signal on irradiation of the aromatic protons. The pure enantiomeric oxazolidinone **19b** was similarly prepared from (*S*)-norleucine *S*-**17** *via* the imine, acylation and crystallisation from the 3:1 mixture with its epimer **18b**. Alkylation of the oxazolidinones was achieved by deprotonation using lithium hexamethyldisilazide at low temperature, and N-bromomethylphthalimide as electrophile. Thus oxazolidinone **19a** afforded 4,4-disubstituted derivative **20a**, whilst **19b** gave **20b**; both **20a** and **20b** were isolated as single diastereoisomers. Alkylation occurs *anti* to the 2-phenyl substituent,[18] as confirmed by observation in the ^{1}H n.m.r. spectrum of, *inter alia*, an n.O.e. enhancement of the signals for the CH_2-phthaloyl protons on irradiation of the C-2(H) signal, and *vice versa*. Thus aminoalkylation of the original norleucine residue was accomplished with overall inversion. The α,α-disubstituted α,β-diamino acid was liberated in one step by an acidic hydrolysis with hydrobromic acid that cleaved the heterocyclic ring and the N-benzoyl and N-phthaloyl protecting groups to give *R*-enantiomer **21a** from **20a**, and *S*-enantiomer **21b** from **20b**. The pure *R*-enantiomer **21a** was converted into the methyl ester hydrochloride salt by 2-3 successive treatments with acetyl chloride in methanol at reflux, and thence by basification into the free diamino ester *R*-**3b**.



Scheme 7

Reagents: [Pht = phthaloyl]; i, PhCHO, aq. NaOH, EtOH (95-99%); ii, PhCOCl, CH_2Cl_2, –20°C (75-76%); crystallis-ation to separate **18** and **19** (56%); iii, lithium hexamethyldisilazide, THF, –78°C to –65°C, N-bromomethylphthalimide (88-89%); iv, 40% aq. HBr, reflux (86%).

The application of the optically pure diamino acid was illustrated by the conversion of *R*-enantiomer **21a** of the diamino acid into optically active isomers of the pseudotetrapeptide analogue **14** of CCK-4, using the methods of Schemes 3 and 4. Thus the S-methylthioimidate salt **9b** derived (Scheme 3) from N^{α}-benzyloxy-carbonyl-(*S*)-tryptophan was treated directly with homochiral *R*-diamino ester **3b** (Scheme 8) to give the protected pseudodipeptide **22** (cf. **1d**, Scheme 4) as an inseparable 1:1 mixture of diastereoisomers, epimeric at the α-carbon centre of the tryptophan residue as expected.[10,15] After protection of the amidine ring as the *tert*-butyloxycarbonyl amide, thus removing its basic properties, chromatographic separation of the two homo-



Scheme 8

Reagents: i, MeOH, reflux (80%); ii Boc_2O, $NaHCO_3$, aq. THF; column chromatography to separate **23a** and **23b** (41 & 43%); iii, 0.1M LiOH aq.-THF (100% each series); iv, pentafluorophenol, DCC, EtOAc (86% each series); then H-Asp-Phe-NH_2 Et_3N, DMF (97 & 62%); v, H_2, 50 psi, $Pd(OH)_2$ on C, MeOH (98% each series); vi, TFA, thioanisole & ethanedithiol, 0°C → 25°C (84% each series).

chiral diastereoisomers **23a** and **23b** was achieved (although it has not yet proved possible to determine the absolute configurations at the tryptophan α-carbon centre), and they were thereafter taken forward separately (Scheme 8).[20] Basic hydrolysis at the C-terminus followed by activation as the pentafluorophenyl ester and coupling with Asp-Phe-NH_2 afforded the separate protected pseudotetrapeptide diastereoisomers **24a** and **24b**. Deprotection as before by hydrogenolysis and trifluoroacetic acid treatment in the presence of cation scavengers, afforded the separate pseudotetrapeptide isomers **25a** and **25b** as trifluoroacetate salts (cf. **14**). Whilst the imidazolines **25** were kept as salts, no epimerisation was observed at the tryptophan α-carbon centre.

BIOLOGICAL ACTIVITY

The compounds were tested for their in vitro receptor binding affinity to the rodent CCK-A and CCK-B receptors (peripheral cholecystokinin receptor and central nervous system cholecystokinin receptor, respectively) by a previously described procedure.[8,21] The results shown in Table 1 are an average of at least three determinations.[8,22,23]

The biological data show that all the imidazoline replacements have higher binding to the CCK-B receptor than to the CCK-A receptor. This is expected as CCK-4 is the minimum peptide fragment needed for binding to CCK-B and is selective for CCK-B. The fully protected imidazoline isostere **15** of pentagastrin shows higher binding to both receptors than the deprotected isostere **16**. This may be due to the basic nature of the imidazoline lowering binding. In the *tert*-butyloxycarbonyl protected imidazoline the ring is not basic.

compound	IC_{50} CCK-A (nM)	IC_{50} CCK-B (nM)	comment
$AspTyr(SO_3H)MetGlyTrpMetAspPheNH_2$	0.5	2.5	endogenous peptide
$TrpMetAspPheNH_2$	$<10^5$	3.1	CCK-4
$GlyTrpMetAspPheNH_2$	600	0.8	pentagastrin
12	1920	749	protected CCK-4 analogue
14	14800	376	CCK-4 analogue
15	15100	3530	protected pentagastrin analogue
16	19000	6500	pentagastrin analogue

Table 1

EXPERIMENTAL

General: Melting points were determined with a Reichert Thermovar or a Kofler hot-stage apparatus and are uncorrected. All ^1H NMR spectra were recorded on a Bruker AM300 spectrometer; ^{13}C NMR spectra were recorded on Bruker AM400 or Jeol JNM-EX270 spectrometers as indicated. Chemical shifts were recorded in parts per million downfield from tetramethylsilane. IR spectra were recorded with compound (neat) on a sodium chloride disc, unless otherwise stated, with Perkin-Elmer 1750 or 1720X FT spectrometers, or a Pye-Unicam SP3-100 spectrometer. Optical rotations were determined on Perkin-Elmer 241, Optical Activity AA-10 or Jasco DIP-370 polarimeters. Silica gel for chromatography was Kieselgel 60 (230-400 mesh); reverse-phase silica gel was Lichroprep RP-18 (230-400 mesh). Both were supplied by E. Merck AG, Darmstadt, Germany. Elemental analyses were determined by CHN Analyses Limited, Leicester, U.K. Mass Spectra were recorded with Finnegan 4500, AEI MS 902, or VG 7070E spectrometers, or by the SERC Mass Spectrometry Centre, Swansea, U.K. All solvents were dried and distilled before use, and all experiments using moisture sensitive reagents were performed under a nitrogen atmosphere.

N-(4-Chlorobenzylidene)-(RS)-phenylalanine methyl ester **5a**. To a suspension of (*RS*)-phenylalanine methyl ester hydrochloride **4a** (5.0 g, 23 mmol) in dry dichloromethane (50 cm^3) were added dry triethylamine (4.5 cm^3, 3.3 g, 32 mmol), 4-chlorobenzaldehyde (3.6 g, 25 mmol) and excess magnesium sulphate. The mixture was stirred in a stoppered flask for 72 h, filtered and the filtrate washed with water (150 cm^3). The organic phase was dried over magnesium sulphate and the solvent removed under reduced pressure to yield a clear oil of essentially pure imine **5a** (7.1 g, 100%). A sample recrystallised from hexane gave the pure imine **5a**, m.p. 59-67°C (Found: C, 67.73; H, 5.33; N, 4.54; Cl, 11.67. $C_{17}H_{16}ClNO_2$ requires C, 67.66; H, 5.34; N, 4.64, Cl, 11.75%); υ_{max} 1741 (C=O), 1641 (C=N), 1595, 1575 and 1490 cm^{-1} (Ar); δ_H (300 MHz; $CDCl_3$) 7.83 (1H, s, HC=N), 7.60 and 7.34 (each 2H, d, *J* 8 Hz, Ar-H), 7.22-7.12 (5H, m, Ph), 4.16 (1H, dd, J_{AX} 9 Hz, J_{BX} 5 Hz, C*H*CO_2Me), 3.74 (3H, s, OMe), 3.36 (1H, dd, J_{AB} 13.6 Hz, J_{BX} 5.0 Hz, $PhCH_AH_B$), 3.13 (1H, dd, J_{AB} 13.5 Hz, J_{AX} 9 Hz, $PhCH_AH_B$); *m/z* (EI) 301 (M^+, 2%), 242 (M^+–CO_2Me, 33), 210 (M^+–$PhCH_2$, 100).

*N-(4-Chlorobenzylidene)-(*RS*)-norleucine methyl ester* **5b**. Imine **5b** was prepared from (*RS*)-norleucine methyl ester hydrochloride **4b** (4.71 g, 33.5 mmol) using the same method as for imine **5a**, to give imine **5b** as a mobile oil (8.3 g, 93%) (Found: C, 62.54; H, 6.87; Cl, 13.42. $C_{14}H_{18}ClNO_2$ requires C, 62.80; H, 6.78; Cl, 13.24; N, 5.23%); υ_{max} (neat) 2957 (C–H), 2861 (C–H), 1747 (C=O), 1645 (C=N), 1596 (Ar), 1573 (Ar) and 1490 cm^{-1} (Ar); δ_H (300 MHz; $CDCl_3$) 8.23 (1H, s, HC=N), 7.72 and 7.38 (each 2H, d, *J* 8.5 Hz, ArH), 3.97 (1H, dd, *J* 8.2 and 5.5 Hz, C*H*CO_2Me), 3.74 (3H, s, OMe), 2.01-1.86 (2H, m, CH_2CH), 1.39-1.22 (4H, m, 2 x CH_2), 0.89 (3H, t, *J* 7 Hz, CH_3); *m/z* (EI) 268 (*M*$^+$+H, 6%) and 208 (*M*$^+$–CO_2Me, 100).

N$^{\alpha}$-(4-Chlorobenzylidene)-N$^{\varepsilon}$-benzyloxycarbonyl-(RS)*-lysine methyl ester* **5c**. Imine **5c** was prepared from N$^{\omega}$–benzyloxycarbonyl-(*RS*)-lysine methyl ester hydrochloride **4c** (5.10 g, 15.4 mmol) using the same method as for imine **5a** to give an essentially pure viscous oil (6.7 g, 100%). A sample was purified by flash chromatography using ethyl acetate–hexane (25→100% v/v) containing triethylamine (2% v/v) to give pure imine **5c** (Found: C, 63.14; H, 5.93; Cl, 8.38; N, 6.54. $C_{22}H_{25}ClN_2O_4$ requires C, 63.38; H, 6.04; Cl, 8.50; N, 6.72%); υ_{max} (neat) 3340 (N–H), 2949 (C–H), 1723 (C=O), 1642 (C=N) and 1595 cm^{-1} (Ar); δ_H (300 MHz; $CDCl_3$) 8.22 (1H, s, *H*C=N), 7.70 (2H, d, *J* 8.4 Hz, ArH), 7.39-7.28 (7H, m, Ph and 2 x ArH), 5.29 (2H, s, PhCH_2O), 4.73 (1H, br s, NH), 3.96 (1H, br t, *J* 6 Hz, NC*H*CO_2Me), 3.73 (3H, s, OMe), 3.18 (2H, t, *J* 6.5 Hz, CH_2NHZ), 2.02-1.89, 1.59-1.49 and 1.38-1.30 (each 2H, m, CH_2); *m/z* (CI) 417 (*M*$^+$, 20%) and 91 (100).

*Methyl (*RS*)-2-amino-3-phenyl-2-phthalimidomethylpropanoate* **6a**. To a solution of dry diisopropylamine (2.4 cm^3, 1.7 g, 17 mmol) in dry THF (35 cm^3) at –78°C under nitrogen was added butyl-lithium (10.6 cm^3 of a 1.6M solution in hexanes, 17 mmol). The mixture was warmed to 0°C, stirred for 5 min, and cooled to –78°C. The imine **5a** (4.3 g, 14 mmol) was added dropwise in dry THF (20 cm^3) over 30 min, keeping the temperature below –50°C during the addition. After stirring the mixture for 1 h at –78°C, N-bromomethylphthalimide (4.1 g, 17 mmol) was added dropwise in dry THF (25 cm^3) over 10 min at –70°C. The reaction was stirred at –70°C for 40 min and then warmed to room temperature. After stirring for 20 h at room temperature, the reaction was quenched with water and the solvent evaporated under reduced pressure. The residue was suspended in methanol (75 cm^3) and 1M HCl (25 cm^3) was added at 0°C. The suspension was stirred for 20 min at 0°C and 30 min at room temperature. The solvent was removed under reduced pressure and the residue partitioned between water (100 cm^3) and ether (100 cm^3). The ethereal layer was further extracted with water (100 cm^3), and the combined aqueous layers were washed with ether (100 cm^3) and neutralised with solid sodium hydrogen carbonate. Salt was added to the aqueous layer which was then extracted with dichloromethane (3 x 200 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvents removed under reduced pressure. The residue was recrystallized from toluene–light petroleum (b.p. 80-100°C) (3:1 v/v) to yield the amine **6a** (3.0 g, 63%). A sample recrystallized from 2-propanol had m.p. 153-155.5°C (Found: C, 67.27; H, 5.37; N, 8.22. $C_{19}H_{18}N_2O_4$ requires C, 67.45; H, 5.36; N, 8.28%); υ_{max} (neat) 1770 and 1715 (C=O), 1609 and 1495 cm^{-1} (Ar); δ_H (300 MHz; $CDCl_3$) 7.88-7.83 and 7.75-7.70 (each 2H, m, phthalimide-H), 7.30-7.17 (5H, m, Ph), 4.09 and 4.00 (each 1H, d, J_{AB} 14 Hz, NCH_AH_B), 3.75 (3H, s, OMe), 3.37 and 2.84 (each 1H, d, J_{AB} 13.2 Hz, PhCH_AH_B); *m/z* (EI) 339 (*M*$^+$+1, 3%), 279 (*M*$^+$–CO_2Me, 19), 178 (*M*$^+$–(phthalimide-CH_2), 100) and 162 (phthalimide-CH_2^+, 75).

*Methyl (*RS*)-2-amino-2-phthalimidomethylhexanoate* **6b**. The amine **6b** was made from imine **5b** (8.0 g, 29.9 mmol) using the same method as for amine **6a** except that the product was purified by flash chromatography using diethyl ether–dichloromethane (40→100% v/v) to give amine **6b** as a white solid (8.0

g, 89%), m.p. 80-82°C (Found C, 63.02; H, 6.75; N, 9.09. $C_{16}H_{20}N_2O_4$ requires C, 63.14; H, 6.62; N, 9.20%); υ_{max} (neat) 3373 (N–H), 1740 and 1708 cm^{-1} (C=O); δ_H (300 MHz; $CDCl_3$) 7.85 and 7.72 (each 2H, m, phthalimide-H), 3.94 (2H, m, CH_2NPhth), 3.76 (3H, s, OMe), 1.80 (2H, br s, NH_2), 2.0-1.7 and 1.60 (each 1H, m, CHHC), 1.5-1.0 (4H, m, 2 x CH_2), 0.89 (3H, t, *J* 8 Hz, CH_2CH_3); *m/z* (CI) 305 (M^++H, 80%), 245 (M^+–CO_2Me, 66) and 144 (M^+–phthalimide, 100).

*Methyl (*RS*)-2-amino-6-benzyloxycarbonylamino-2-phthalimidomethylhexanoate* **6c**. The amine **6c** was prepared from imine **5c** (3.18 g, 7.62 mmol) using the same method as for amine **6a** except that **6c** was purified by flash chromatography using a gradient of ethyl acetate–hexane (80% v/v) to methanol–ethyl acetate (15% v/v) to give pure amine **6c** as a glass (2.0 g, 58%) (Found: C, 63.57, H, 6.05; N, 8.98. $C_{24}H_{27}N_3O_6$ requires C, 63.57; H, 6.00; N, 9.27%); υ_{max} (neat) 2950 (C–H) and 1740 cm^{-1} (C=O); δ_H (300 MHz; $CDCl_3$) 7.83 and 7.73 (each 2H, m, phthalimide-H), 7.36-7.24 (5H, m, Ph), 5.08 (2H, s, PhCH_2O), 4.86 (1H, br s, CONH), 3.94 (1H, d, J_{AB} 14.0 Hz, CH_AH$_B$N), 3.86 (1H, d, J_{AB} 14.0 Hz, CH$_A$$H_B$N), 3.76 (3H, s, OMe), 3.21-3.13 (2H, m, CH_2NHZ), 1.94-1.85 (1H, m), 1.68-1.38 (4H, m), 1.33-1.17 (1H, m); *m/z* (CI) 454 (M^++1, 2%), 185 (11), 108 (68), 107 (48) and 91 (100).

*Methyl (*RS*)-2-amino-3-phenyl-2-aminomethylpropanoate* **3a**. A mixture of the phthalimide **6a** (1.30 g, 3.9 mmol) and hydrazine (0.30 cm^3, 0.31 g, 6.2 mmol) was heated under reflux in dry methanol (14 cm^3) under nitrogen for 100 min. The white precipitate which had formed was removed by filtration and discarded. The methanol was removed under reduced pressure and the residue suspended in chloroform (50 cm^3). The organic phase was washed with water (3 x 50 cm^3), each aqueous layer being back-extracted with chloroform (25 cm^3). The combined organic layers were extracted with 1M HCl (75 cm^3) and the organic phase discarded. The aqueous phase was neutralised with solid sodium hydrogen carbonate and extracted with chloroform (3 x 75 cm^3). The combined organic layers were dried (magnesium sulphate) and the solvent removed to give pure diamine **3a** (0.61 g, 76%), m.p. 57-58°C (Found: C, 63.28; H, 7.91; N, 13.25. $C_{11}H_{16}N_2O_2$ requires C, 63.44; H, 7.74; N, 13.45%); υ_{max} (neat) 3367 (N–H), 1733 (C=O), 1603 and 1496 cm^{-1} (Ar); δ_H (300 MHz; $CDCl_3$) 7.31-7.09 (5H, m, Ph), 3.70 (3H, s, OMe), 3.19 (1H, d, J_{AB} 12.9 Hz), 3.08 (1H, d, J_{CD} 13.2 Hz), 2.73 (2H, 2 x d, J_{AB} 12.9Hz, J_{CD} 13.2 Hz); *m/z* (EI) 209 (M^++H, 2%) and 179 (M^+–H_2C=NH, 100).

*Methyl (*RS*)-2-amino-2-aminomethylhexanoate* **3b**. Diamine **3b** was prepared from amine **6b** (1.97 g, 6.47 mmol) using the same method as for diamine **3a** and isolated as an oil (0.77 g, 68%), b.p. 125°C (0.3 mmHg) (Found: M^++H 175.1447 (CI). $C_8H_{18}N_2O_2$ requires *M*+H 175.1447); υ_{max} (neat) 3401 (N–H) and 1729 cm^{-1} (C=O); δ_H (300 MHz; $CDCl_3$) 3.73 (3H, s, OMe), 3.06 and 2.62 (each 1H, d, J_{AB} 13 Hz, C$H_A$$H_BNH_2$), 1.7-1.1 (10H, m, 3 x CH_2, 2 x NH_2), 0.89 (3H, t, *J* 8 Hz, Me); *m/z* (EI) 175 (M^++H, 30%), 145 (M^+-OCH_3, 30) 115 (M^+-CO_2Me, 25) and 84 (100).

*Methyl (*RS*)-2-amino-6-benzyloxycarbonylamino-2-aminomethylhexanoate* **3c**. Diamine **3c** was prepared from amine **6c** (0.46 g, 1.0 mmol) using the same method as for diamine **3a** & isolated as an oil (0.32 g, 97%) (Found: M^++H 324.1923 (CI). $C_{16}H_{26}N_3O_4$ requires *M*+H 324.1917); υ_{max} (neat) 3368 (N–H), 2949 (C–H) and 1719 cm^{-1} (C=O); δ_H (300MHz; $CDCl_3$) 7.34 (5H, m, Ph), 5.09 (2H, s, PhCH_2), 4.81 (1H, br s, CONH), 3.71 (3H, s, OMe), 3.18 (2H, m, CH_2NHZ), 3.04 and 2.61 (each 1H, d, J_{AB} 13 Hz, C$H_A$$H_BNH_2$), 1.72-1.62 (1H, m), 1.6-1.3 (8H, m, 2 x CH_2, 2 x NH_2), 1.1-1.2 (1H, m); *m/z* (CI) 324 (M^++H, 95%) and 216 (100).

N-Benzyloxycarbonyl-(S)-phenylalanine piperidine amide **7a**. To N-benzyloxycarbonyl-(*S*)-phenylalanine **2a** (4.9 g, 16.7 mmol) and pentafluorophenol (3.68 g, 20.0 mmol) in dry dichloromethane (30 cm^3) under nitrogen at 0°C was added dicyclohexylcarbodiimide (5.16 g, 25.0 mmol). The mixture was slowly warmed to room temperature. After 40 min the mixture was cooled to 0°C, piperidine (5.0 cm^3, 4.3 g, 51 mmol) was added and the reaction stirred overnight at room temperature. Water (5 cm^3) was added and the mixture stirred for 5 h, then filtered to remove dicyclohexylurea. The filtrate was diluted with ethyl acetate (200 cm^3) and washed successively with 1M HCl (2 x 100 cm^3), 2M NaOH (2 x 100 cm^3), 1M HCl (100 cm^3) and 2M NaOH (100 cm^3), and then dried ($MgSO_4$). The solvent was removed under reduced pressure, the residue purified by flash chromatography using ether–hexane (40→100% v/v), and the product purified from excess pentafluorophenol by recrystallisation from toluene to afford pure amide **7a** (4.21 g, 70%), m.p. 113-115°C (Found: C, 72.05; H, 7.26; N, 7.83. $C_{22}H_{26}N_2O_3$ requires C, 72.11; H, 7.15; N, 7.64%); υ_{max} (neat) 3264 (N–H), 3025, 2937 and 2857 (C–H), 1714 (urethane C=O) and 1626 cm^{-1} (amide C=O); δ_H (300 MHz; $CDCl_3$) 7.37-7.15 (10H, m, 2 x Ph), 5.74 (1H, br d, *J* 8 Hz, NH), 5.10 and 5.05 (each 1H, d, J_{AB} 12 Hz, PhCH_AH_BO), 4.91 (1H, br q, *J* 8 Hz, NCHCO), 3.47 (2H, t, *J* 5 Hz), 3.2 (1H, br m), 3.0 (3H, m, including δ 2.98 (2H, d, *J* 7 Hz)), 1.72 (1H, m), 1.55-1.37 (4H, m, piperidine CH_2), 1.06-1.00 (1H, m); *m/z* (CI) 367 (M^++H, 16%) and 259 (100).

N-Benzyloxycarbonyl-(S)-tryptophan piperidine amide **7b**. The amide **7b** was prepared from N-benzyloxycarbonyl-(*S*)-tryptophan **2b** (4.99 g, 14.7 mmol) using the same method as for amide **7a**. The residue was purified by flash chromatography using triethylamine–ether–hexane (15:80:20 v/v/v) to triethylamine–ethyl acetate (15:100 v/v) to give essentially pure amide **7b** as a foam (6.1 g, 100%). A small portion was purified by flash chromatography using ethyl acetate–dichloromethane (10→50% v/v) to give a white foam, m.p. 50-52°C (Found: C, 70.89; H, 6.81; N, 10.12. $C_{24}H_{27}N_3O_3$ requires C, 71.09; H, 6.71; N, 10.36%); $[\alpha]_D^{22}$ +21.9 (*c* 0.0127 g cm^{-3} in EtOAc); υ_{max} 3282 (N–H), 1708 (urethane C=O) and 1626 cm^{-1} (amide C=O); δ_H (300 MHz, $CDCl_3$) 8.15 (1H, s, indole NH), 7.62 (1H, d *J* 7.7 Hz, indole 5-H), 7.4-6.95 (9H, m), 5.82 (1H, d, *J* 8 Hz, CONH), 5.10 (2H, s, PhCH_2), 5.01 (1H, m, NCHCO), 3.40 (2H, m), 3.2-2.8 (4H, m), and 1.7-0.6 (6H, m, 3 x CH_2); *m/z* (CI) 406 (M^++H, 17%), 254 (100), 130 (57), 91 (81) and 86 (42).

N^{α},N^{ε}-bis(Benzyloxycarbonyl)-(S)-lysine piperidine amide **7c**. The amide **7c** was prepared from N^{α},N^{ε}-bis(benzyloxycarbonyl)-(*S*)-lysine **2c** (4.96 g, 12.0 mmol) using the same method as for amide **7a**. The residue was purified by flash chromatography using triethylamine–ethyl acetate–hexane (5:40:60 v/v/v) to triethylamine–ethyl acetate–hexane (5:80:20 v/v/v) to give essentially pure amide **7c** (5.1 g, 88%) as an oil. A sample was recrystallised from toluene–light petroleum (b.p. 80-100°C) to give analytically pure amide **7c**, m.p. 82-86°C (Found: C, 67.34; H, 7.24; N, 8.67. $C_{27}H_{35}N_3O_5$ requires C, 67.34; H, 7.33; N, 8.73%); υ_{max} (neat) 3311 (N–H), 2940 and 2860 (C–H), 1718 (urethane C=O) and 1631 cm^{-1} (amide C=O); δ_H (300 MHz; $CDCl_3$) 7.33-7.29 (10 H, m, Ph), 5.82 (1H, d, *J* 9 Hz, NH), 5.08 (4H, s, PhCH_2O), 4.90 (1H, br s, NH), 4.68-4.62 (1H, m, NCHCO), 3.63-3.16 (6H, m, CH_2NHZ, CH_2NCH_2), 1.74-1.36 (12H, m, 6 x CH_2); *m/z* (FAB) 482 (M^++H, 100%), 374 (20) and 348 (73).

N-Benzyloxycarbonyl-(S)-phenylalanine piperidine thioamide **8a**. A mixture of the amide **7a** (3.15 g, 8.6 mmol) and Lawesson's reagent (2.25 g, 5.6 mmol) in dry toluene (25 cm^3) was heated at 100-120°C for 1.5 h under nitrogen. The reaction mixture was directly chromatographed using dichloromethane to give pure thioamide **8a** (3.11 g, 95%), m.p. 87-88°C (cyclohexane) (Found: C, 68.94; H, 6.96; N, 7.19; S, 8.32.

$C_{22}H_{26}N_2O_2S$ requires C, 69.08; H, 6.85; N, 7.32; S, 8.38%); υ_{max} 3350 (N–H), 3027 and 2938 (C–H), 1718 (urethane C=O) and 1494 cm^{-1} (SCN); δ_H (300 MHz; $CDCl_3$) 7.34-7.08 (10H, m, Ph), 6.22 (1H, br d, *J* 8.8 Hz, NH), 5.18 (1H, br q, *J* 8.7 Hz, CHCS), 5.12 and 5.04 (each 1H, d, J_{AB} 12.3 Hz, PhCH_AH_BO), 4.19-4.02 (2H, m), 3.51-3.45 (1H, m), 3.18-3.04 (3H, m), 1.57-1.43 (5H, m), 0.89-0.87 (1H, m); *m/z* (EI) 382 (M^+, 6%), 129 (23) and 91 (100).

N-Benzyloxycarbonyl-(S)-tryptophan piperidine thioamide **8b**. Thioamide **8b** was prepared from amide **7b** (3.2 g, 8.0 mmol) using the same method as for thioamide **8a**. The thioamide **8b** was purified by flash chromatography using diethyl ether–dichloromethane (0→100% v/v) to give essentially pure material (3.00 g, 89%). A sample purified by flash chromatography using ethyl acetate–hexane (40-60% v/v) gave pure thioamide **8b**, m.p. 42-6°C (Found: C, 68.20; H, 6.47; N, 9.91; S, 7.31. $C_{24}H_{27}N_3O_2S$ requires C, 68.38; H, 6.46; N, 9.97; S, 7.61%); $[\alpha]_D^{22}$ +100.6 (*c* 0.011 g cm^{-3} in EtOAc); υ_{max} 3343 (N–H) and 1704 cm^{-1} (C=O); δ_H (300 MHz; $CDCl_3$) 8.00 (1H, br s, indole NH), 7.73 (1H, d, *J* 8 Hz, 5-H), 7.4-7.0 (9H, m), 6.32 (1H, d, *J* 9 Hz, CONH), 5.35 (1H, m, CHCS), 5.10 (2H, m, PhCH_2), 4.05 (2H, m), 3.45-3.30 (4H, m), 1.65-0.5 (6H, m); *m/z* 422 (M^++H, 12%), 421 (23), 293 (43), 292 (100), 270 (64), 130 (67) and 91 (96).

N^{α},N^{ε}-bis(Benzyloxycarbonyl)-(S)-lysine piperidine thioamide **8c**. Thioamide **8c** was prepared from amide **7c** (1.00 g, 2.1 mmol) using the same method as for thioamide **8a**. The thioamide **8c** was isolated by flash chromatography using dichloromethane and then diethyl ether, to give **8c** as an oil (0.82 g, 79%) (Found: C, 65.11; H, 7.03; N, 8.41; S, 6.28. $C_{27}H_{35}N_3O_4S$ requires C, 65.17; H, 7.09; N, 8.44; S, 6.44%); υ_{max} (neat) 3342 (N–H), 2940 (C–H) and 1713 cm^{-1} (C=O); δ_H (300 MHz; $CDCl_3$) 7.35-7.28 (10H, m, Ph), 6.23 (1H, br d, *J* 9 Hz, NH), 5.29-5.03 (4H, m, 2 x PhCH_2), 4.89-4.84 (2H, m), 4.40-4.35 (1H, m), 4.12 (1H, m), 3.80-3.72 (2H, m), 3.18-3.16 (2H, m), 1.72-1.40 (12H, m); *m/z* (FAB) 498 (M^++H, 100%) and 218 (22).

Methyl 4(5)-benzyl-2-(1-benzyloxycarbonylamino-2-phenylethyl)-4,5-dihydroimidazole-4(5)-carboxylate **1a**. The thioamide **8a** (1.12 g, 2.93 mmol) was heated under reflux in methyl iodide (6.5 cm^3) under argon for 5.5 h. A yellow solid separated. The solvent was removed under reduced pressure and the residue azeotroped with dry methanol (2 x 5 cm^3). The diamine **3a** (0.61 g, 2.93 mmol) was added in dry methanol (13 cm^3) and the mixture heated at reflux for 1.5 h under nitrogen, left at room temperature overnight and then refluxed for 1 h. The solvent was removed and the residue purified by flash chromatography using ethyl acetate–hexane (50% v/v) to methanol–ethyl acetate (10% v/v) to give pure compound **1a** as a mixture of diastereoisomers (1.20 g, 87%), m.p. 127-130°C from toluene–light petroleum (b.p. 80-100°C) (1:1 v/v) (Found: C, 71.37; H, 6.21; N, 8.77. $C_{28}H_{29}N_3O_4$ requires C, 71.32; H, 6.20; N, 8.91%); υ_{max} (neat) 3326 (N–H), 3029 (C–H), 1733 (ester C=O), 1698 (urethane C=O), 1626 (amidine) and 1552 cm^{-1} (amidine); δ_H (300MHz; CD_3OD) 7.32-7.13 (15H, m, Ph), 5.03 (2H, m, PhCH_2O), 4.54-4.49 (1H, m, CHC=N), 3.93-3.87 (1H, m), 3.73-3.59 (4H, m, including OMe), 3.13-2.85 (4H, m); *m/z* (CI) 472 (M^++1, 5%), 108 (20), 93 (22) 92 (28) and 91 (100).

Methyl 4(5)-benzyl-2-[1-benzyloxycarbonylamino-2-(3-indolyl)ethyl]-4,5-dihydroimidazole-4(5)-carboxylate **1b**. Compound **1b** was prepared using the same method as for compound **1a**, from thioamide **8b** (212 mg, 0.50 mmol) which was heated under reflux with methyl iodide (6 cm^3) for 18 h and then treated with diamine **3a** (99 mg, 0.47 mmol). The residue after reaction was purified by flash chromatography using ethyl acetate–hexane (80% v/v) to methanol–ethyl acetate (50% v/v), then methanol–dichloromethane (10% v/v) to give compound **1b** as a mixture of diastereoisomers (198 mg, 77%), m.p. 64-7°C (Found: M^++H 511.2345

(CI). $C_{30}H_{30}N_4O_4$ requires *M*+H 511.2338); υ_{max} (neat) 3367 (N–H), 2951 (C–H), 1713 (C=O) and 1621 cm^{-1} (amidine); δ_H (300 MHz; CD_3OD) 7.63 (1H, d, *J* 8 Hz, indole NH), 7.4-7.0 (15H, m, 2 x Ph, indole-H), 5.08 (2H, m, PhCH_2O), 4.61 (1H, m, CHC=N), 3.90 (1H, m, C*H*HN=C), 3.72 and 3.71 (3H, 2 x s, OMe), 3.65 (1H, m, CH*H*N=C), 3.25-2.85 (4H, m, PhCH_2, CH_2-indole); *m/z* (CI) 511 (M^++H, 10%), 403 (100) and 130 (12).

Methyl 4(5)-(4-benzyloxycarbonylaminobutyl)-2-[1,5-bis(benzyloxycarbonylamino)pentyl]-4,5-dihydroimidazole-4(5)-carboxylate **1c**. Compound **1c** was made using the same method as for compound **1a**, from thioamide **8c** (81 mg, 0.18 mmol) which was heated at reflux with methyl iodide (8 cm^3) for 18 h and then treated with diamine **3c** (63 mg, 0.19 mmol). The residue after reaction was purified by flash chromatography using methanol–dichloromethane (10% v/v) to give compound **1c** as a mixture of diastereoisomers as a wax (54 mg, 42%) (Found: C, 64.90; H, 9.69; N, 9.83. $C_{38}H_{47}N_5O_8$ requires C, 65.03; H, 6.75; N, 9.98%); υ_{max} (neat) 3337 (N–H), 2944 (C–H), 1703 (C=O) and 1531 cm^{-1} (amidine); δ_H (300 MHz; CD_3OD) 7.40-7.25 (15H, m, Ar-H), 5.0 and 5.06 (6H, 2 x s, 3 x PhCH_2), 4.25 (1H, m, NCHC=N), 3.92 (1H, m, C*H*HN=C), 3.70 and 3.69 (3H, 2 x s, CO_2Me), 3.50 (1H, m, CH*H*N=C), 3.10 (4H, m, 2 x CH_2NHZ), 1.90-1.15 (12H, m, 6 x CH_2); *m/z* (FAB) 702 (M^++H, 38%), 217 (100) and 215 (27).

Methyl 2-[1-benzyloxycarbonylamino-2-(3-indolyl)ethyl]-4(5)-butyl-4,5-dihydroimidazole-4(5)-carboxylate **1d**. The thioamide **8b** (2.44 g, 5.8 mmol) was heated to reflux in methyl iodide (15 cm^3) for 8 h under nitrogen, after which the solvent was removed under reduced pressure. Residual methyl iodide was removed by azeotroping with dry methanol (2 x 10 cm^3). To the residue was added the diamine **3b** (1.27 g, 7.3 mmol) in dry methanol (10 cm^3). The mixture was refluxed for 2.5 h under nitrogen. The solvent was removed under reduced pressure and the residue purified by flash chromatography using ethyl acetate to give compound **1d** as a mixture of diastereoisomers (2.53 g, 91%), m.p. 53-56°C (Found: M^++H 477.2502 (CI). $C_{27}H_{32}N_4O_4$ requires *M*+H 477.2502); $[\alpha]_D^{20}$ +0.3 (*c* 0.011 g cm^{-3} in EtOAc); υ_{max} (neat) 3353 (N–H), 3063, 2955 and 2872 (C–H), 1714 (C=O) and 1621 cm^{-1} (amidine); δ_H [300 MHz; $(CD_3)_2SO$] 10.86 (1H, br s, indole NH), 7.60-7.45 (2H, m, indole 4-H, 7-H), 7.40-7.2 (5H, m, Ph), 7.16 (1H, m, indole 2-H), 7.07 (1H, m, indole 6-H), 6.99 (1H, m, indole 5-H), 4.98 (2H, s, PhCH_2O), 4.55 (1H, m, CHC=N), 3.89 (1H, m, C*H*HN=C), 3.69 and 3.66 (3H, 2 x s, CO_2Me), 3.52 (1H, m, CH*H*N=C), 3.3-3.0 (2H, m, CH_2-indole), 1.71-1.45 (2H, m, CH_2), 1.3-0.95 (4H, m, 2 x CH_2), 0.85 (3H, m, CH_2*Me*); *m/z* (CI) 477 (M^++H, 40%), 369 (100) and 130 (20).

*Methyl 2-[1-benzyloxycarbonylamino-2-(3-indolyl)ethyl]-4(5)-butyl-1(3)-*tert*-butyloxycarbonyl-4,5-dihydroimidazole-4(5)-carboxylate* **10**. To a solution of the amidine **1d** (0.78 g, 1.63 mmol) in THF–H_2O (1:1 v/v, 10 cm^3) was added sodium hydrogen carbonate (0.24 g, 3.0 mmol) and di-*tert*-butyldicarbonate (0.79 g, 3.6 mmol) in THF (5 cm^3). The reaction was stirred at room temperature for 1.5 h before more sodium hydrogen carbonate (0.04 g, 0.5 mmol) and di-*tert*-butyldicarbonate (0.25 g, 1.1 mmol) were added and the mixture was stirred for a further 30 min at room temperature. The solvent was evaporated and the mixture purified by flash chromatography using diethyl ether–hexane (60→100%) to give compound **10** (0.80 g, 85%) as a mixture of diastereoisomers; δ_H (300 MHz; CD_3OD) 7.55-6.95 (10H, m, Ar-H), 5.63 (1H, m, CHC=N), 5.10 (2H, m, PhCH_2), 4.09 (1H, m, C*H*HN), 3.68 (3H, s, CO_2Me), 3.55 (1H, m, CH*H*N), 3.3-3.1 (2H, m, CH_2-indole), 1.6-0.8 (9H, m, Bu-H), 1.62 and 1.56 (9H, 2 x s, CMe_3).

The mixture of diastereomers (1:1) was separated by medium pressure chromatography using diethyl ether–cyclohexane (60% v/v): Isomer 1 had R_f 0.34 (diethyl ether–cyclohexane; 70% v/v), m.p. 43-8°C

(Found: C, 66.72; H, 7.10; N, 9.48. $C_{32}H_{40}N_4O_6$ requires C, 66.65; H, 6.99; N, 9.72%); $[\alpha]_D^{20}$ +0.1 (*c* 0.010 g cm^{-3} in EtOAc); υ_{max} (neat) 3405 (N–H), 3035, 2955 and 2863 (C–H), 1723 (C=O) and 1631 cm^{-1} (amidine); δ_H (300 MHz; CD_3OD) 7.51 (1H, d, *J* 8 Hz), 7.36-7.34 (6H, m), 7.13-7.09 (2H, m), 7.04-6.99 (1H, m), 5.64 (1H, t, *J* 5.6 Hz, CHC=N), 5.11 (2H, s, PhC*H*$_2$), 4.18 (1H, d, *J* 11 Hz, C*H*HN), 3.68 (3H, s, CO_2Me), 3.45 (1H, d, *J* 11 Hz, CH*H*N), 3.34 (2H, m, C*H*$_2$-indole), 1.62 (9H, s, CMe_3), 1.5-0.9 (6H, m, 3 x CH_2), 0.85 (3H, t, *J* 7 Hz, Me); *m/z* (CI) 577 (M^++H, 22%), 477 (55), 369 (100) and 130 (42). Isomer 2 had R_f 0.25 (diethyl ether–cyclohexane; 70% v/v), m.p. 137-139°C (Found: C, 66.60; H, 7.10; N, 9.48. $C_{32}H_{40}N_4O_6$ requires C, 66.65; H, 6.99; N, 9.72%); υ_{max} (neat) 3404 (N–H), 2955 (C–H), 1723 (C=O) and 1632 cm^{-1} (amidine); δ_H (300 MHz; CD_3OD) 7.53 (1H, d, *J* 8 Hz), 7.35-7.34 (6H, m), 7.13-7.07 (2H, m), 7.01-6.97 (1H, m), 5.65 (1H, m, CHC=N), 5.10 (2H, s, PhC*H*$_2$), 4.04 (1H, d, J_{AB} 11Hz, C*H*HN), 3.68 (4H, including 3H, s, CO_2Me, and 1H, d, CH*H*N), 3.34-3.19 (2H, m, C*H*$_2$-indole), 1.56 (9H, s, CMe_3), 1.4-1.1 (6H, m, 3 x CH_2), 0.88 (3H, t, *J* 7.3 Hz, Me); *m/z* (CI) 577 (M^++H, 22%), 477 (55), 369 (100) and 130 (45).

*2-[1-Benzyloxycarbonylamino-2-(3-indolyl)ethyl]-4(5)-butyl-1(3)-*tert*-butyloxycarbonyl-4,5-dihydro-imidazole-4(5)-carboxylic acid* **11**. To a solution of a mixture of diastereoisomers of the ester **10** (255 mg, 0.44 mmol) in THF (15 cm^3) was added lithium hydroxide (5 cm^3 of a 0.10M aqueous solution, 0.50 mmol). The reaction was stirred at room temperature for 1 h before more lithium hydroxide solution (5 cm^3, 0.50 mmol) was added and the mixture stirred for a further 3.5 h, and then concentrated under reduced pressure. The residue was partitioned between ethyl acetate (100 cm^3) and 0.5M HCl (100 cm^3). The organic phase was washed with 0.5M HCl (50 cm^3). The combined organic phases were dried ($MgSO_4$) and the solvents removed to give a quantitative yield of crude acid **11** as a mixture of diastereoisomers; δ_H (300 MHz; d_6-DMSO) 10.85 (1H, m, indole NH), 7.7-6.9 (10H, m, Ar-H), 5.45 (1H, m, CHC=N), 5.05-4.85 (2H, m, PhC*H*$_2$), 4.3-2.9 (6H, m, C*H*$_2$-indole, NCH_2CCOOH, NH), 1.75-0.9 (6H, m, 3 x CH_2), 0.80 (3H, m, Me), 1.51 and 1.45 (9H, 2 x s, CMe_3). This material was used directly in the next step.

To the pure diastereoisomer Isomer 1 of the ester **10** (0.49 g, 0.85 mmol) in THF (30 cm^3) was added lithium hydroxide (22 cm^3 of a 0.12M aqueous solution, 2.5 mmol). The reaction was stirred at room temperature for 2.5 h and then evaporated to dryness with ethanol. The residue was suspended in ethyl acetate (100 cm^3), washed with 0.5M HCl (100 cm^3), and the aqueous phase re-extracted with ethyl acetate (100 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The acid **11** was purified by flash chromatography using dichloromethane containing acetic acid (1% v/v) and methanol (5% v/v) to give pure Isomer 1 of acid **11** (0.48 g, 100%), m.p. 125-127°C (Found: C, 65.98; H, 6.80; N, 9.69. $C_{31}H_{38}N_4O_6$ requires C, 66.17; H, 6.81; N, 9.96%); υ_{max} (neat) 3330 (N–H), 2927 (C–H), 1720 (C=O) and 1621 cm^{-1} (amidine); δ_H (300 MHz; d_6-DMSO) 10.84 (1H, s, COOH), 7.64 (1H, d, *J* 7.5 Hz), 7.40-7.26 (7H, m), 7.17 (1H, br s), 7.08 (1H, dd, *J* 7.5 Hz), 6.98 (1H, dd, *J* 7.5 Hz), 5.37 (1H, m, CHC=N), 5.06 and 4.99 (each 1H, d, J_{AB} 13 Hz, PhC*H*$_2$), 4.14 and 3.51 (each 1H, d, J_{CD} 11 Hz, CH_2N), 3.35-3.0 (2H, m, C*H*$_2$-indole), 1.54 (9H, s, CMe_3), 1.46, 1.24-1.19 and 1.13-1.06 (each 2H, m, CH_2), 0.85 (3H, t, *J* 7 Hz, Me); *m/z* (FAB) 563 (M^++H, 16%) 463 (52), 130 (62), 91 (100) and 57 (52).

The reaction was repeated using the pure diastereoisomer Isomer 2 of the ester **10** (0.53 g, 0.92 mmol) to give the pure Isomer 2 of acid **11** (0.44 g, 84%), m.p. 78-81°C (Found: M^++H 563.2870 (FAB). $C_{31}H_{39}N_4O_6$ requires *M*+H 563.2860); υ_{max} (neat) 3435 (N–H), 2947 (C–H), 1722 (C=O) and 1621 cm^{-1} (amidine); δ_H (300 MHz; d_6-DMSO) 10.8 (1H, s, COOH), 7.72 (1H, d, *J* 7.5 Hz), 7.53 (1H, d, *J* 8.6 Hz), 7.32-7.28 (6H, m),

7.16 (1H, br s), 7.04 (1H, dd, *J* 7.3 Hz), 6.94 (1H, dd, *J* 7.3 Hz), 5.29 (1H, m, CHC=N), 5.05 and 4.88 (each 1H, d, J_{AB} 13 Hz, PhCH_2), 4.04 and 3.61 (each 1H, d, J_{CD} 11 Hz, CH_2N), 3.17-3.14 and 2.91-2.83 (each 1H, m, CH_2-indole), 1.8-1.6 (2H, m, CH_2) 1.46 (9H, s, CMe_3), 1.3-1.1 (4H, m, 2 x CH_2), 0.82 (3H, t, *J* 7 Hz, Me); *m/z* (FAB) 563 (M^++H, 48%), 464 (100), 130 (100), 91 (100) and 57 (39).

{2-[1-Benzyloxycarbonylamino-2-(3-indolyl)ethyl]-4(5)-butyl-1(3)-tert-*butyloxycarbonyl-4,5-dihydro-imidazol-4(5)-oyl}-(*S*)-aspartyl-(*S*)-phenylalanine amide* **12**. The acid **11** (249 g, 0.44 mmol), as a mixture of diastereoisomers, and pentafluorophenol (127 mg, 0.69 mmol) were dissolved in dry ethyl acetate (7 cm^3) under nitrogen and treated with dicychohexylcarbodiimide (0.27 g, 1.3 mmol) in dry ethyl acetate (5 cm^3) at room temperature for 2 h. The mixture was filtered and the filtrate chromatographed on silica gel using diethyl ether-hexane (20→100%) to give an oil which was dissolved in dry N,N-dimethylformamide (5 cm^3). Dry triethylamine (0.15 cm^3, 1.1 mmol) and (*S*)-aspartyl-(*S*)-phenylalanine amide (supplied by Bachem) (128 mg, 0.46 mmol) were added. After stirring at room temperature for 1 h under nitrogen the solvent was removed under reduced pressure. Chromatography of the residue on silica gel using acetic acid–methanol–dichloromethane (1:5:95 followed by 1:5:9 then 1:15:85) gave the peptide **12** (199 mg, 0.24 mmol, 36%) as a 1:1:1:1 mixture of four diastereoisomers; υ_{max} (neat) 1723 and 1657cm^{-1} (C=O); δ_H (300 MHz; CD_3OD) 7.9-7.1 (15H, m, Ar-H), 5.75 (1H, m, CHC=N), 5.4-5.15 (2H, m, PhCH_2O), 4.95-4.65 (2H, m, 2 x NCHCO), 4.2-2.5 (8H, m, CH_2-indole, PhCH_2, CH_2CO_2H and NCH_2CCO), 1.58 and 1.57 (9H, 2 x s, CMe_3), 2.0-1.1 (6H, m, 3 x CH_2), 1.00 (3H, m, Me); *m/z* (FAB) 824 (M^++H, 5%), 692 (55), 676 (95), 391 (80) and 266 (100).

Using the same procedure the racemic pure diastereomer Isomer 1 of acid **11** (373 mg, 0.66 mmol) was converted to the peptide **12** which was isolated as a mixture of two diastereoisomers (510 mg, 93%) (the two diastereoisomers could be separated by TLC using dichloromethane containing acetic acid (1% v/v) and methanol (10% v/v)); δ_H (300 MHz, CD_3OD) 7.54 (1H, d, *J* 8 Hz), 7.36-6.98 (14H, m), 5.69-5.49 (1H, m, CHC=N), 5.22-5.04 (2H, m), 4.62-4.57 (2H, m), 3.96-3.87 (1H, m), 3.45-3.42 (1H, m), 3.16-3.13 (1H, m), 2.99-2.87 (1H, m), 2.67-2.50 (2H, m), 1.61 and 1.58 (9H, 2 x s, CMe_3), 1.4-0.8 (9H, m, Bu-H); also some impurity of other diastereoisomer pair δ 1.53 (s) and 1.49 (s), ratio of peaks δ 1.61:1.58:1.53:1.49 = 15:14:7:5.

{2-[1-Amino-2-(3-indolyl)ethyl]-4(5)-butyl-1(3)-tert-*butyloxycarbonyl-4,5-dihydroimidazol-4(5)-oyl}-(*S*)-aspartyl-(*S*)-phenylalanine amide* **13**. The benzyl carbamate **12** (126 mg, 0.153 mmol), as a mixture of four diastereoisomers, in methanol (70 cm^3) was shaken with 20% palladium hydroxide on carbon (Pearlman's catalyst) (17 mg) under an atmosphere of hydrogen gas (50 psi) for 4 h at room temperature. The mixture was filtered and concentrated under reduced pressure to give the amine **13** (106 mg, 0.153 mmol, 100%) as a 1:1:1:1 mixture of four diastereoisomers (three spots by TLC using dichloromethane containing acetic acid (1.5% v/v) and methanol (15% v/v)) (Found: M^++H 690.3661 (FAB). $C_{36}H_{48}N_7O_7$ requires *M*+H 690.3604); δ_H (300 MHz; CD_3OD) 7.7-6.9 (10H, m, Ar-H), 4.7-4.35 (3H, m, 2 x NCHCO and CHC=N), 3.9-2.35 (8H, m, CH_2-indole, CH_2COOH, PhCH_2 and NCH_2CCO), 1.63, 1.61, 1.59 and 1.57 (9H, 4 x s, CMe_3), 1.7-0.65 (9H, m, Bu-H); *m/z* (FAB) 690 (M^++H, 25%) and 590 (100).

The procedure was repeated using the mixture of two isomers of compound **12** (prepared from Isomer 1 of acid **11**, see above) (240 mg, 0.29 mmol). The product was purified by reverse phase chromatography using methanol–water (3:1 v/v) to give compound **13** (162 mg, 81%) as a mixture of two diastereoisomers (two spots by TLC using dichloromethane containing acetic acid (1% v/v) and methanol (10% v/v)); δ_H (300 MHz;

CD_3OD) 7.59-7.56 (1H, m), 7.40-7.36 (1H, m), 7.28-7.03 (8H, m), 4.95-4.85 (1H, m, CHC=N), 4.58-4.51 (2H, m, 2 x NCHCO), 4.97 (1H, t, *J* 12 Hz), 3.65 (1H, q, *J* 7 Hz), 3.47 (1H, dd, *J* 11, 4 Hz), 3.40-3.88, 3.25-3.17 and 3.02-2.91 (each 1H, m), 2.59-2.58 (2H, m), 1.64 and 1.62 (9H, 2 x s, CMe_3), 1.5-0.8 (9H, m, Bu-H).

*{2-[1-Amino-2-(3-indolyl)ethyl]-4(5)-butyl-4,5-dihydroimidazol-4(5)-oyl}-(*S*)-aspartyl-(*S*)-phenylalanine amide* **14**. The *tert*-butyl carbamate **13** (28 mg, 0.041 mmol), as a mixture of four diastereoisomers, was stirred at 0°C under nitrogen in trifluoroacetic acid (5 cm^3) containing anisole (0.4 cm^3). The mixture was allowed to warm to room temperature and after 2.5 h was concentrated under reduced pressure to give an oil, which after trituration with diethyl ether gave the trifluoroacetate salt of peptide **14** (20 mg, 0.024 mmol, 59%) as a mixture of four diastereoisomers; (Found: M^++H 590.3091 (FAB). $C_{31}H_{39}N_7O_5$ requires *M*+H 590.3091); δ_H (300 MHz; CD_3OD), 7.7-7.05 (10H, m, Ar-H), 4.8-4.5 (3H, m, 2 x NCHCO and CHC=N), 4.2-2.6 (8H, m, CH_2-indole, CH_2COOH, $PhCH_2$ and NCH_2CCO), 1.8-0.75 (9H, m, Bu-H); *m/z* (FAB) 590 (M^++H, 55%) and 266 (100). The procedure was repeated using compound **13** (40 mg, 0.06 mmol) as a mixture of two diastereoisomers (prepared, *via* compound **12**, from Isomer 1 of acid **11**, see above) to give compound **14** (117 mg, 98%) as a mixture of two diastereoisomers.

*{2-[1-(Benzyloxycarbonylglycylamino)-2-(3-indolyl)ethyl]-4(5)-butyl-1(3)-*tert*-butyloxycarbonyl-4,5-dihydroimidazol-4(5)-oyl}-(*S*)-aspartyl-(*S*)-phenylalanine amide* **15**. To a suspension of compound **13** (75 mg, 0.11 mmol), as a mixture of four diastereoisomers, in dry ethyl acetate (12 cm^3) under nitrogen was added triethylamine (0.09 cm^3, 0.07 g, 0.65 mmol) and N-*tert*-butyloxycarbonylglycine pentafluorophenyl ester (0.079 g, 0.23 mmol). The reaction was stirred at room temperature for 1.5 h, the mixture evaporated to dryness under reduced pressure, and the residue purified by flash chromatography using acetic acid–ethyl acetate (1% v/v) and then dichloromethane containing acetic acid (1% v/v) and methanol (5→10% v/v) to yield compound **15** (71 mg, 77%) as a mixture of diastereoisomers; δ_H (300 MHz; CD_3OD) 7.59-7.04 (10H, m, Ar-H), 5.71 (1H, m, CHC=N), 4.63-4.54 (2H, m, 2 x NCHCO), 4.0-2.5 (10H, m, NCH_2CN, NCH_2CO, CH_2CO_2H, $PhCH_2$ and CH_2-indole), 1.7-0.8 (9H, m, Bu-H), 1.66 and 1.62 (9H, 2 x s, CMe_3), 1.49 (9H, s, CMe_3); *m/z* (FAB) 874 (M^++H, 17%), 154 (100), 130 (100), 91 (100) and 77 (100). The same procedure was repeated using compound **13** (97 mg, 0.14 mmol) as a mixture of two diastereoisomers (prepared, *via* compound **12**, from Isomer 1 of acid **11**, see above) to give compound **15** (117 mg, 98%) as a mixture of two diastereoisomers.

*{4(5)-Butyl-1(3)-*tert*-butyloxycarbonyl-2-[1-(Glycylamino)-2-(3-indolyl)ethyl]-4,5-dihydroimidazol-4(5)-oyl}-(*S*)-aspartyl-(*S*)-phenylalanine amide* **16**. The di-*tert*-butyloxycarbonyl protected peptide **15** (54 mg, 0.064 mmol), as a mixture of four diastereoisomers, was stirred at 0°C under nitrogen for 2 h in trifluoroacetic acid (5 cm^3) containing anisole (0.3 cm^3). The mixture was evaporated to dryness under reduced pressure and triturated with diethyl ether. The resultant gum was washed with diethyl ether to give the peptide **16** as the trifluoroacetate salt (53 mg, 91%) (Found: M^++H 647.3306 (FAB). $C_{33}H_{43}N_8O_6$ requires *M*+H 647.3296); δ_H (300 MHz; CD_3OD) 7.60-7.11 (10H, m, Ar-H), 4.8-4.5 (2H, m, 2 x NCHCO), 4.1-2.7 (10H, m, NCH_2CO, NCH_2CN, CH_2CO_2H and $PhCH_2C$), 1.6-0.8 (9H, m, Bu-H); *m/z* (FAB) 647 (M^++H, 4%), 154 (90) and 130 (100). The procedure was repeated using compound **15** (65 mg, 0.076 mmol) as a mixture of two diastereoisomers (prepared, *via* compounds **12** and **13**, from Isomer 1 of acid **11**, see above) to give compound **16** (66 mg, 99%) as a mixture of two diastereoisomers.

(2S,4R)-3-Benzoyl-4-butyl-2-phenyloxazolidin-5-one **19a**. To (*R*)-norleucine *R*-**17** (1.31 g, 10 mmol) was added sodium hydroxide (1M, 10 cm^3, 10 mmol); addition of ethanol and warming was required to afford solution. Evaporation was then carried out under reduced pressure until precipitation began to occur, when benzaldehyde (1.59 g, 15 mmol) was added and evaporation continued. Further ethanol was added and the mixture azeotroped to dryness. The product was isolated by filtration and thoroughly washed using diethyl ether. After further drying *in vacuo* over phosphorus pentoxide the imine was isolated as a white solid (2.37 g, 98%); υ_{max} (neat) 1643 (C=N) and 1593 cm^{-1}. Benzoyl chloride (0.87 cm^3, 1.014g) was added to a stirred suspension of freshly prepared imine (1.16 g, 4.8 mmol) in dichloromethane (10 cm^3) at –20°C. The mixture was stirred at –20°C for 30 min. before being stored at –20°C for 3 days. The turbid mixture was washed successively with water, aqueous sodium hydrogen carbonate (5% w/v) and sodium hydrogen sulphite (5% w/v) solutions, and water. The organic layer was dried and the solvent evaporated under reduced pressure to afford the crude product. Recrystallisation from ether–dichloromethane (3:1 v/v) gave exclusively the *trans* oxazolidinone **19a** as white crystals, m.p. 148-149°C (0.87g, 56%) (Found: C, 74.31; H, 6.68; N, 4.39. $C_{20}H_{21}NO_3$ requires C, 74.26; H, 6.56; N, 4.33%); $[\alpha]_D^{25}$ –201.36 (*c* 0.0117 g cm^{-3} in $CHCl_3$); υ_{max} (neat) 1796 (lactone C=O), 1656 cm^{-1} (amide C=O); δ_H (300 MHz; $CDCl_3$, 60°C) 7.2-7.7 (10H, m, Ar-H), 6.9 (1H, s, C(2)-H), 5.1 (1H, t, C(4)-H), 1.75 (2H, br, CH_2), 1.1-1.5 (4H, br, 2 x CH_2), 0.7 (3H, t, Me); δ_C (67.8 MHz; $CDCl_3$) 171.8 (COO), 169.3 (CON), 136.5 and 135.1 (ArC), 131.2, 129.8, 128.6, 126.8 and 126.6 (ArCH), 90.9 (C-2), 57.1 (C-4), 30.3, 25.6 and 22.0 (CH_2), 13.7 (Me).

(2R,4S)-3-Benzoyl-4-butyl-2-phenyloxazolidin-5-one **19b**. The oxazolidinone **19b** was prepared from (*S*)-norleucine *S*-**17** (1.31 g, 10 mmol) using the same method as for the enantiomer **19a**, to give the *S*-imine (2.40 g, 99%). This *S*-imine (2.41 g, 10 mmol) afforded the oxazolidinone **19b** (1.8 g, 56%); $[\alpha]_D^{20}$ +201.37 (*c* 0.0102 g cm^{-3} in $CHCl_3$); δ_H (300 MHz; $CDCl_3$, 82°C) 7.25-7.6 (10H, m, Ar-H), 6.88 (1H, s, C(2)-H), 5.15 (1H, t, C(4)-H), 1.7 (2H, br, CH_2), 1.1-1.5 (4H, br, 2 x CH_2), 0.8 (3H, t, Me).

(2S,4R)-3-Benzoyl-4-butyl-2-phenyl-4-phthalimidomethyloxazolidin-5-one **20a**. To a stirred solution of the oxazolidinone **19a** (485 mg, 1.5 mmol) in THF (10 cm^3) at –78°C was added lithium hexamethyldisilazide (1.65 cm^3 of a 1M solution in THF, 1.65 mmol). The solution was stirred for 40 min at –78°C before N-bromomethylphthalimide (576 mg, 2.4 mmol) was added in THF (3 cm^3). The mixture was stirred for a further 1 h at –78°C before being allowed to warm to –10°C over the next 2 h. The reaction was quenched at –50°C with acetic acid (4.5 cm^3) before aqueous work up and extraction into dichloromethane. The organic phase was washed once with water before being dried and the solvent removed under reduced pressure. The crude product was recrystallised from dichloromethane–methanol to obtain pure oxazolidinone **20a** as a white crystalline solid (640 mg, 89%), m.p. 179-180°C (Found: C, 71.75; H, 5.57; N, 6.00. $C_{29}H_{26}N_2O_5$. 0.1 H_2O requires C, 71.90; H, 5.41; N, 5.79%); $[\alpha]_D^{23}$ –174.8 (*c* 0.010 g cm^{-3} in $CHCl_3$); υ_{max} (neat) 1796 (lactone C=O), 1719 (phthalimide C=O), 1660 cm^{-1} (amide C=O); δ_H (300 MHz; $CDCl_3$) 7.77 and 7.9 (each 2H, m, phthaloyl-H), 7.72 (8H, m, Ph-H), 6.95 (2H, d, Ph-H), 6.43 (1H, s, C(2)-H), 4.3-4.65 (2H, dd, NCH_2), 2.81 and 2.39 (each 1H, m, CH_2C), 1.72 (1H, m), 1.5 (3H, m), 1.05 (3H, m, Me); δ_C (67.8 MHz; $CDCl_3$) 171.1 (COO), 169.7 (amide CO), 168.0 (phthalimide CO), 136.4 and 135.4 (ArC), 134.3 and 134.2 (ArCH), 131.5 (ArC), 129.4, 129.3, 128.1, 127.7, 127.5, 125.8 and 123.6 (ArCH), 90.0 (C-2), 77.4 (C-4), 41.7 (NCH_2), 35.3, 27.5 and 22.5 (CH_2), 13.75 (Me); *m/z* (EI) 483 (M^++H, 50%), 377 (73) and 333 (100).

(2R,4S)-3-Benzoyl-4-butyl-2-phenyl-4-phthalimidomethyloxazolidin-5-one **20b**. The oxazolidinone **20b** was prepared from oxazolidinone **19b** (125 mg, 0.4 mmol) using the same method as for the enantiomer **20a**, to give the oxazolidinone **20b** (164 mg, 88%), m.p. 179-181°C ; $[\alpha]_D^{25}$ +174.9 (*c* 0.0055 g cm^{-3} in $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 7.75 and 7.91 (each 2H, m, phthaloyl-H), 7-7.25 (8H, m, Ph-H), 6.93 (2H, d, Ph-H), 6.42 (1H, s, C(2)-H), 4.3-4.7 (2H, dd, NCH_2), 2.81 and 2.41 (each 1H, m, CH_2C), 1.71 (1H, m), 1.5 (3H, m), 1.01 (3H, m, Me).

(R)-2-Amino-2-aminomethylhexanoic acid **21a**. To a stirred suspension of the oxazolidinone **20a** (1.11 g, 2.3 mmol) in water (3 cm^3) was added hydrobromic acid (48% w/v, 14 cm^3) and the mixture heated at reflux for 3 h. The solvent was then removed under reduced pressure. Water (10 cm^3) was added to the residue before it was loaded onto an Amberlite IR 120(H) ion-exchange column (ca. 70 cm^3). The column was flushed with water until no trace of HBr remained and then eluted with aqueous ammonia (8% w/v, 1 l). The solvent was removed under reduced pressure before further water (200 cm^3) was added and then evaporated to remove any ammonia. The diamino acid **21a** was isolated pure after freeze-drying (0.31 g, 86%) (Found: M^++H 161.1306. $C_7H_{16}N_2O_2$ requires *M*+H 161.1320); $[\alpha]_D^{25}$ +5.9 (*c* 0.0101 g cm^{-3} in H_2O); υ_{max} (neat) 3185, 3112, 3063, 2959, 1592 cm^{-1}; δ_H (250 MHz; D_2O) 3.0-3.3 (2H, dd NCH_2), 1.65-2.0 (2H, m, CH_2), 1.25-1.6 (4H, m, 2 x CH_2), 0.99 (3H, t, Me); δ_C (67.8 MHz; $CDCl_3$) 179.6 (COOH), 65.6 (C-2), 48.5 (NCH_2), 37.6, 27.8 and 24.8 (CH_2), 15.7 (Me); *m/z* (EI) 161 (M^++H, 100%), 144 (*M*+H–NH_2, 14) and 115 (24).

(S)-2-Amino-2-aminomethylhexanoic acid **21b**. The diamino acid **21b** was prepared from oxazolidinone **20b** (1.11 g, 2.3 mmol) using the same method as for the enantiomer **21a**, to give the diamino acid **21b** (0.31 g, 86%); $[\alpha]_D^{27}$ –5.7 (*c* 0.0028 g cm^{-3} in H_2O); δ_H (300 MHz; D_2O) 2.95-3.3 (2H, dd NCH_2), 1.84 and 1.66 (each 1H, m, CH_2), 1.3-1.5 (4H, m, 2 x CH_2), 0.97 (3H, t, Me).

Methyl (R)-2-aminomethylhexanoate R-**3b**. Acetyl chloride (13 cm^3) was added dropwise to stirred dry methanol (25 cm^3) at 0°C. The acid **21a** (529 mg, 3.3 mmol) was then added and the mixture heated to reflux for 16 h. The solvent was removed under reduced pressure and the residue dried before the treatment with acetyl chloride in methanol was repeated until the reaction was complete by tlc (butanol–acetic acid–water 4:1:1 v/v/v). The hydrochloride salt was then taken up in the minimum brine and the solution basified with sodium hydrogen carbonate. The free diamino ester was extracted with dichloromethane (3 x 20 cm^3), the organic layers were combined, dried and evaporated under reduced pressure to yield the diamino ester *R*-**3b** as a pale oil (430 mg, 75%); υ_{max} (neat) 3303 (N–H), 2957, 1732 (C=O) and 1699 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 3.75 (3H, s, OMe), 3.06 and 2.62 (each 1H, d, *J* 13 Hz, NCH_2), 1.75-2.12 (2H, m, CH_2), 1.35-1.7 (4H, m, 2 x CH_2), 1.1 (3H, t, Me); δ_C (67.8 MHz; $CDCl_3$) 176.8 (COOH), 62.8 (C-2), 51.9 (OMe), 50.0 (CH_2N), 37.4, 25.7 and 22.7 (CH_2), 13.7 (Me).

Methyl [4(5)R]-2-[(1RS)-1-benzyloxycarbonylamino-2-(3-indolyl)ethyl]-4(5)-butyl-4,5-dihydroimidazole-4(5)-carboxylate **22**. Imidazoline **22** was made using the same method as for the racemic counterpart **1d**, from thioamide **8b** (0.25 g, 0.6 mmol) which was heated at reflux with methyl iodide (6 cm^3) for 16 h to form thioimidate **9b**, and then treated with the diamino ester *R*-**3b** (0.13 g, 0.75 mmol) at reflux in methanol for 4 h. The residue after evaporation was purified by flash chromatography using ethyl acetate–triethylamine (95:5 v/v) to give imidazoline **22**, a mixture of two diastereoisomers, as a white powder (0.225 g, 80%)

(Found: M^++H (FAB) 477. $C_{27}H_{32}N_4O_4$ requires M+H 477); υ_{max} (neat) 3355 (N–H), 2955 (C–H), 1716 (urethane C=O) 1621 cm^{-1} (C=N); δ_H (300 MHz; $CDCl_3$) 8.65 (1H, br s, indole NH), 7.6 (1H, m, indole 4-H), 7.25 (6H, s, Ar-H, indole 7-H), 7.15 (1H, t, indole 2-H), 7.05 (1H, t, indole 6-H), 6.9 (1H, d, indole 5-H), 5.9 (1H, br s, NH), 5.05 (2H, s, PhC*H*$_2$), 4.65 (1H, m, CHC=N), 3.9 (1H, m, C*H*HN=C), 3.66 and 3.67 (3H, 2 x s, OMe), 3.45 (1H, m, CH*H*N=C), 3.2 (2H, m, C*H*$_2$-indole), 1.65, 1.2 and 1.05 (each 2H, m, CH_2), 0.85 (3H, t, Me); δ_C (100 MHz; $CDCl_3$) 175.0 (CO ester), 166.6 (C=N), 156.1 (CO urethane), 136.4, 136.3 and 136.1 (ArC), 128.5, 128.1 and 128.0 (ArCH), 127.6 (ArC), 123.3, 123.1, 122.2, 119.7, 119.6 and 118.9 (ArCH), 111.3 (CH), 110.7 (CH_2), 71.8 (C), 66.8 and 57.8 (CH_2), 52.4 (OMe), 50.6 (CH), 38.4, 29.4, 26.2 and 22.6 (CH_2), 13.8 (Me); *m/z* (FAB) 499 (M^++Na, 6%), 477 (M^++H, 100), 347 (8), 326 (15), 221 (26), 207 (30), 147 (69) and 130 (46).

*Methyl [4(5)R]-2-[(1RS)-1-benzyloxycarbonylamino-2-(3-indolyl)ethyl]-4(5)-butyl-1(3)-*tert*-butyloxycarbonyl-4,5-dihydroimidazole-4(5)-carboxylates* **23**. To a solution of the amidine **22** (530 mg, 1.11 mmol) in THF–H_2O (1:1 v/v, 14 cm^3) were added sodium bicarbonate (165 mg, 2 mmol) and di-*tert*-butyl dicarbonate (543 mg, 2.5 mmol) in THF (2 cm^3). The reaction was stirred at room temperature and monitored by TLC. After a further 3 h, the THF layer was separated and the aqueous layer washed with dichloromethane (2 x 10 cm^3). The organic layers were combined, dried and the solvents removed under reduced pressure. The residue was purified by flash chromatography using diethyl ether–hexane (7:3 v/v) to obtain the imidazolines **23** (total 535 mg, 84%) as two separated diastereoisomers **23a** and **23b** (Isomer 1: 262 mg, 41%; Isomer 2: 273 mg 43%) (Found: M^++H 577.3051. $C_{32}H_{40}N_4O_6$ requires M+H 577.3026); υ_{max} (neat) 3408 (N–H), 2956 (C–H), 1732 (urethane C=O), 1633 cm^{-1} (C=N). **Isomer 1** had $[\alpha]_D^{22}$ +2.4 ($CHCl_3$); δ_H (300MHz; $CDCl_3$) 8.7 (1H, br s, indole NH), 7.42 (1H, d, indole 4-H), 7.3 (6H, s, Ar-H & indole 7-H), 7.0-7.2 (2H, m, indole 6-H &2-H), 6.95 (1H,s, indole 5-H), 6.05 (1H, d, NH), 5.55 (1H, m, CHC=N), 5.05 (2H, d, PhC*H*$_2$), 4.15 (1H, d, C*H*HN=C), 3.65 (3H, s, OMe), 3.35 (3H, m, CC*H*$_2$CH & CH*H*N=C), 1.58 (9H, s, CMe_3), 1.2, 1.05 and 0.85 (each 2H, m, CH_2), 0.8 (3H, t, Me); δ_C (67.8 MHz; $CDCl_3$) 173.0 (CO ester), 159.5 (C=N), 155.4 and 149.9 (CO urethane), 136.6 and 135.9 (ArC), 128.4, 128.0, 127.9, 123.2, 121.8, 119.3 and 118.3 (ArCH), 111.2 (CH), 109.9 (CH_2), 83.0 and 74.0 (C), 66.5 and 54.2 (CH_2), 52.5 (Me), 50.8 (CH), 38.1 and 29.7 (CH_2), 28.2 (Me), 25.4 and 22.5 (CH_2), 13.8 (Me). **Isomer 2** had $[\alpha]_D^{22}$ –63.0 ($CHCl_3$); δ_H (300MHz; $CDCl_3$) 8.2 (1H, br s, indole NH), 7.45 (1H, d, indole 4-H), 7.25 (6H, s, Ar-H & indole 7-H), 7.1 (1H, t, indole 2-H), 7.05 (1H, t, indole 6-H.), 6.9 (1H, d, indole 5-H), 5.9 (1H, br s, NH), 5.6 (1H, m, CHC=N), 5.05 (2H, d, PhC*H*$_2$), 4.05 (1H, d, C*H*HN=C), 3.65 (4H, m, OMe & CH*H*N=C), 3.25 (2H, ddd, CC*H*$_2$CH), 1.7 (1H, br s), 1.53 (9H, s, CMe_3), 1.35 (1H, d), 1.05 and 1.2 (each 2H, m, CH_2), 0.85 (3H, t, Me); δ_C (67.8 MHz; $CDCl_3$) 172.9 (CO ester), 160.8 (C=N), 155.5 and 149.8 (CO urethane), 136.6 and 135.9 (ArC), 128.3, 127.8, 123.5, 121.6, 119.3 and 118.3 (ArCH), 111.1 (CH), 109.7 (CH_2), 83.0 and 74.0 (C), 66.5 and 53.9 (CH_2), 52.5 (Me), 50.6 (CH), 38.6 and 29.6 (CH_2), 28.7 (Me), 25.4 and 22.6 (CH_2), 13.8 (Me); *m/z* (FAB) 599 (M^++Na, 4%), 577 (M^++H, 19), 477 (M^++H–BOC, 100), 391 (19), 348 (6), 212 (10), 130 (21).

*{[4(5)R]-2-[(1RS)-1-Benzyloxycarbonylamino-2-(3-indolyl)ethyl]-4(5)-butyl-1(3)-*tert*-butyloxycarbonyl-4,5-dihydroimidazol-4(5)-oyl}-(S)-aspartyl-(S)-phenylalanine amides* **24**. The protected peptides **24a** and **24b** were made from esters **23a** and **23b**, respectively, using the same methods as for the racemic counterpart **12** from ester **10** *via* acid **11**. Thus each pure diastereoisomer of the ester (115 mg, 0.2 mmol) was

separately stirred with lithium hydroxide solution (0.1M) at room temperature for 5.5 h; work-up and purification by flash chromatography using dichloromethane–methanol–acetic acid (94:5:1 v/v/v) afforded the corresponding acids (110 mg, 98%) (Found: M^++H (FAB) 563. $C_{31}H_{38}N_4O_6$ requires M+H 563); υ_{max} (neat) 3306 (N–H), 2958 (C–H), 1723 (C=O), 1622 (C=N) cm^{-1}. The acid **Isomer 1**, formed from Isomer 1 of ester **23**, had $[\alpha]_D^{22}$ +2.1 (*c* 0.019 g cm^{-3} in $CHCl_3$); δ_H (300MHz; $CDCl_3$) 8.25 (1H, br s, indole NH), 7.45 (1H, d, indole 4-H), 7.25 (6H, s, Ar-H, indole 7-H), 7.0-7.2 (3H, m, indole 2-H, 5-H, 6-H), 6.1 (1H, br s, NH), 5.6 (1H, m, CHC=N), 5.05 (2H, m, PhCH_2), 4.1 and 3.4 (each 1H, d, *J* 11 Hz, CHHN=C), 3.35 (2H, m, CCH_2CH), 1.56 (9H, s, CMe_3), 0.85-1.4 (6H, m), 0 .75 (3H, t, Me); δ_C (67.8 MHz; $CDCl_3$) 174.1 (CO acid), 164.0 (C=N), 155.6 and 149.0 (CO urethane), 136.3 and 136.0 (ArC), 128.4, 127.9 and 127.7 (ArCH), 127.5 (ArC), 124.0, 121.7, 119.3 and 117.9 (ArCH), 111.6 (CH), 108.7 (CH_2), 84.4 and 72.7 (C), 66.7 and 55.0 (CH_2), 55.1 (CH), 38.0 and 29.6 (CH_2), 28.0 (Me), 25.3 and 22.4 (CH_2), 13.7 (Me). The acid **Isomer 2**, formed from Isomer 2 of ester **23**, had $[\alpha]_D^{24}$ –41.8 (*c* 0.01 g cm^{-3} in $CHCl_3$); δ_H (300MHz; $CDCl_3$) 10.8 (1H, s, CO_2H), 8.6 (1H, br s, indole NH), 7.7 (1H, d, indole 4-H), 7.45 (1H, s, indole 7-H), 7.25 (6H, m, Ar-H, indole 2-H), 7.0 (1H, t, indole 6-H), 6.9 (1H, t, indole 5-H), 5.35 (1H, m, CHC=N), 4.9 (2H, m, PhCH_2), 4.1 and 3.45 (each 1H, d, *J* 11 Hz, CHHN=C), 2.95 (2H, m, CCH_2CH), 1.65 (2H, m), 1.4 (9H, s, CMe_3), 1.2 (4H, m), 0 8 (3H, t, Me); *m/z* (FAB) 585 (M^++Na, 49%), 563 (M^++H, 30), 485 (M^++Na–BOC, 39), 463 (M^++H–BOC, 100), 417 (14), 333 (5), 130 (68).

Each pure diastereoisomer of the acid (75 mg, 0.13 mmol) was separately converted into the pentafluorophenyl ester, purified by chromatography using diethyl ether–hexane (3:7→1:1 v/v), and condensed with (*S*)-aspartyl-(*S*)-phenylalanine amide. Purification by chromatography using dichloromethane–methanol–acetic acid (95:5:0→89:10:1 v/v/v) afforded the corresponding protected peptides **24** (90 mg, 83%) (Found: M^++H 824.4015. $C_{44}H_{53}N_7O_9$ requires M+H 824.3983); υ_{max} (neat) 3300 (N–H), 2927 (C–H), 1722 and 1714 (C=O), 1660 (C=N), 1514 cm^{-1}. The protected peptide **Isomer 1**, formed from Isomer 1 of ester **23**, had $[\alpha]_D^{25}$ –1.0 (*c* 0.005 g cm^{-3} in MeOH); δ_H (300MHz; CD_3OD) 7.55 (1H, d, indole 4-H), 7.0-7.3 (13H, m, Ar-H), 6.95 (1H, t, indole 5-H), 5.65 (1H, br, NH), 5.6 (1H, br, Asp α-CH), 5.2 (2H, m, PhCH_2O), 4.5 (2H, br, Trp and Phe α-CH)3.9 and 3.42 (each 1H, d, *J* 11 Hz, NCHHC), 3.0-3.4 (2H, m, HO_2CCH_2CH), 2.95 (2H, m, indole-CH_2CH), 2.55 (2H, m, PhCH_2CH), 1.52 (9H, s, CMe_3), 1.3 (2H, m), 0 .6-1.2 (7H, m); δ_C (100 MHz; CD_3OD) 175.8 (CO_2H), 175.1, 171.4 and 170.4 (CONH), 160.6 (C=N), 155.7 and 150.0 (CO urethane), 136.4 and 136.0 (ArC), 129.2, 128.5, 128.4, 128.2 and 128.1 (ArCH), 127.6 (ArC), 126.9, 123.5, 122.0, 119.4and 118.3 (ArCH), 111.4 (CH), 109.9, 83.5 and 73.4 (C), 66.7 and 55.0 (CH_2), 54.6 (Me), 51.6, 50.6 and 49.2 (CH), 39.1, 36.7, 35.2, 29.7 (CH_2), 28.2 (Me), 25.1 and 22.5 (CH_2), 13.8 (Me). The protected peptide **Isomer 2**, formed from Isomer 2 of ester **23**, had δ_H (300MHz; CD_3OD) 8.0 (1H, s, indole NH), 7.65 (1H, d, indole 4-H), 7.0-7.45 (12H, m, Ar-H), 6.9 (1H, d, indole 5-H), 5.5 (1H, m, Asp α-CH), 5.03 (2H, m, PhCH_2O), 4.65 (2H, m, Trp and Phe α-CH), 3.65 and 3.9 (each 1H, d, *J* 11 Hz, NCHHC), 3.15-3.3 (2H, m, HO_2CCH_2CH), 2.8-3.0 (3H, m, indole-CH*H*CH and PhCH_2CH), 2.7 (1H, m, indole-C*H*HCH), 1.7 (1H, m), 1.58 (9H, s, CMe_3), 1.25 (4H, m), 1.1 (1H, m), 0.85 (3H, t, Me).

{[4(5)R]-2-[(1RS)-1-Amino-2-(3-indolyl)ethyl]-4(5)-butyl-4,5-dihydroimidazol-4(5)-oyl}-(S)-aspartyl-(S)-phenylalanine amides **25**. The peptides **25a** and **25b** were made from protected peptides **24a** and **24b**, respectively, using the same methods as for the racemic counterpart **14** from protected peptide **12** *via tert*-butyl carbamate **13**. Thus each pure diastereoisomer of the protected peptide (50 mg, 0.06 mmol) was

separately submitted to hydrogenolysis to afford the corresponding *tert*-butyl carbamate (41 mg, 98%); υ_{max} (neat) 3297 (N–H), 2957 (C–H), 1724 (C=O), 1686, 1659, 1567 cm^{-1}. The *tert*-butyl carbamate **Isomer 1**, formed from Isomer 1 of protected peptide **24**, had $[\alpha]_D^{26}$ –1.9 (*c* 0.005 g cm^{-3} in MeOH); δ_H (300MHz; CD_3OD) 7.65 (1H, d, indole 4-H), 7.35 (1H, d, indole 7-H), 7.25 (5H, m, Ar-H), 7.2 (1H, br, indole 2-H), 7.15 (1H, t, indole 6-H), 7.05 (1H, t, indole 5-H), 4.8 (1H, m, Asp α-CH), 4.55 (2H, m, Trp and Phe α-CH), 3.95 and 3.5 (each 1H, m, NCHHC), 2.9-3.4 (1H, m, 2H, m, HO_2CCH_2CH), 2.95 (1H, m, indole-CH_2CH), 2.6 (2H, m, $PhCH_2CH$), 1.6 (9H, s, CMe_3), 0.9-1.5 (6H, m), 0.8 (3H, t, Me). The *tert*-butyl carbamate **Isomer 2**, formed from Isomer 2 of protected peptide **24**, had δ_H (300MHz; CD_3OD) 7.75 (1H, d, indole 4-H), 6.98-7.35 (9H, m, Ar-H), 5.05 (1H, m, Asp α-CH), 4.55 (2H, m, Trp and Phe α-CH), 3.95 and 3.67 (each 1H, d, *J* 11 Hz, NCHHC), 3.3-3.5 (2H, m, HO_2CCH_2CH), 2.95 (2H, m, indole-CH_2CH), 2.65 (2H, d, $PhCH_2CH$), 1.6 (9H, s, CMe_3), 1.0 - 1.5 (6H, m), 0.9 (3H, t, Me).

Each pure diastereoisomer of the *tert*-butyl carbamate (34 mg, 0.05 mmol) was separately treated with trifluoroacetic acid (2 cm^3), thioanisole (0.05 cm^3) and ethane dithiol (0.02 cm^3) at 0°C. The mixture was stirred whilst being allowed to warm to room temperature, and after 3 h was concentrated under reduced pressure. The residue was then partioned between diethyl ether and water and the aqueous layer freeze-dried to afford the bis-trifluoroacetate salts of the corresponding peptides **25** as off-white solids (34 mg, 84%); υ_{max} (neat) 3297 (N–H), 2957 (C–H), 1724 and 1686 (C=O), 1659 (C=N), 1567 cm^{-1}. The peptide salt **Isomer 1**, formed from Isomer 1 of the protected peptide **24**, had δ_H (270MHz; CD_3OD) 7.7 (1H, d, indole 4-H), 7.45 (1H, d, indole 7-H), 7.15 - 7.45 (6H, m, Ar-H), 4.8, 4.65 and 4.5 (each 1H, m, α-CH), 3.95 and 3.65 (each 1H, d, *J* 12 Hz, NCHHC), 3.4 (2H, m, HO_2CCH_2CH), 3.2 and 3.0 (each 1H, m, indole-$CHHCH$), 2.8 (2H, ddd, $PhCH_2CH$), 1.0-1.7 (6H, m), 0.9 (3H, t, Me). The peptide salt **Isomer 2**, formed from Isomer 2 of the protected peptide **24**, had δ_H (300MHz; CD_3OD) 7.6 (1H, d, indole 4-H), 7.45 (1H, d, indole 7-H), 7.25-7.35 (5H, m, Ar-H), 7.05-7.25 (2H, m, indole 5-H, 6-H), 4.7 (1H, m, Asp α-CH), 4.55 (2H, m, Trp and Phe α-CH), 4.05 and 3.6 (each 1H, d, *J* 12 Hz, NCHHC), 3.5 (2H, m, HO_2CCH_2CH), 3.15 and 2.95 (each 1H, m, indole-$CHHCH$), 2.8 (2H, ddd, $PhCH_2CH$), 1.0-1.6 (6H, m), 0.85 (3H, t, Me).

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