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# SYNTHESIS OF KETOMETHYLENE DIPEPTIDES CONTAINING BASIC AMINO ACID ANALOGUES AT C-TERMINUS

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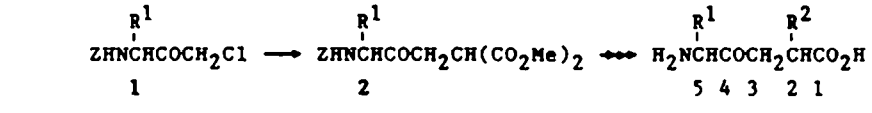
**Abstract.**-The four ketomethylene dipeptides Phe $\Psi(COCH_2)$(RS)Orn (6a) and Trp $\Psi(COCH_2)$(RS)X X-(RS)Orn (6b), (RS)Arg (8b) and (RS)Lys (12b) have been synthesised by a route involving two successive principal reactions: a malonic ester alkylation with the corresponding Z-protected amino acid iodomethyl ketone, and, the introduction of a cyanoethyl or cyanopropyl moiety in the resulting 4-ketodiesters 2a,b to give the 2-(cyanoalkyl)-4-ketodiesters 3a,b or 9b. The best way of obtaining 3a,b consisted of adding 2a,b to acrylonitrile, while 9b was prepared by alkylation of 2b with 4-iodobutyronitrile. Saponification of 3a,b and 9b, followed by decarboxylation and selective hydrogenation of the cyano group provided Z-Phe $\Psi(COCH_2)$(RS)Orn (5a), Z-Trp $\Psi(COCH_2)$(RS)Orn (5b) and Z-Trp $\Psi(COCH_2)$(RS)Lys (7b), which upon removal of the Z groups by hydrogenolysis afforded 6a, 6b and 12b, respectively. Compound 8b was obtained by guanidylation of 5b and subsequent cleavage of the Z group.

Replacement of peptide amide -CONH- bonds by ketomethylene $-COCH_2-$ groups[1] is being successfully used to prepare metabolism-resistant pseudopeptides[2] and enzyme inhibitors[3]. Additionally, the first naturally occurring carba analogues of peptides, namely Arg $\Psi(COCH_2)$Phe and Arg $\Psi(COCH_2)$Tyr (Arphamenines A and B) are aminopeptidase B inhibitors which also enhance immune responses[4].

In a previous communication[5], we reported a simple procedure for the synthesis of ketomethylene dipeptide analogues involving reaction of the 4-ketodiesters 2, easily obtained from amino acid halomethyl ketones 1 and dimethyl malonate, with appropiate alkylating agents, followed by hydrolysis, decarboxylation and removal of the Z-protecting group.




By application of the above general procedure ketomethylene dipeptides containing aliphatic (Ala), aromatic (Phe, Trp) and acidic (Asp) amino acid residues at the C-terminus were prepared. In order to confirm the versatility of this new method, we have extended it to the preparation of pseudodipeptides with basic amino acid analogues as C-terminal residues. Because of the lack of a convenient method, the synthesis of this type of compounds has not previously been described. Thus, as a modified Dakin-West reaction[6,7] as the use of Grignard reagents[7,9], the two previously reported methods affording ketomethylene dipeptides, might present difficulties in the preparation of these pseudodipeptides containing chemically labile side chains.

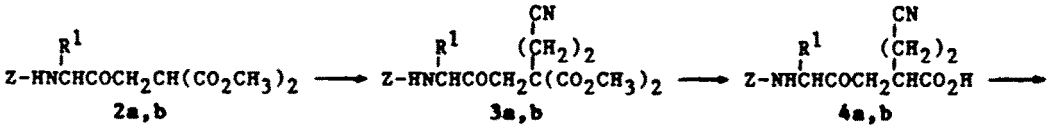
An additional advantage of this general route to ketomethylene dipeptides, outlined in Scheme I, is the use of the easily removable benzyloxycarbonyl (Z)-protecting group. In contrast, several problems have been found in the removal of the phthaloyl and benzoyl groups, used as protection in the routes involving Grignard reagents and a modified Dakin-West reaction respectively[10,11]. In amino acids gave the corresponding 5-oxazolones, these derivatives fail to produce ketomethylene dipeptides[11,12].

The present paper describes the synthesis of Phe ψ(COCH$_2$)(RS)Orn (6a) and Trp ψ(COCH$_2$)X X=(RS)Orn (6b), (RS)Arg (8b), (RS)Lys (12b) . Due to our interest in dipeptides with one aromatic amino acid and the other basic[13], phenylalanine and tryptophan have been used as N-terminal amino acids.

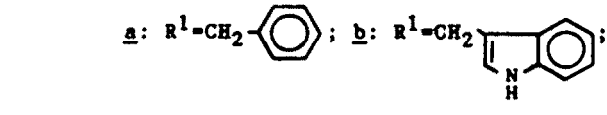
## RESULTS AND DISCUSSION

In a similar way to the Phe-containing ketodiester 2a[5], the Trp-containing analogue 2b was prepared by conversion of Z-tryptophan chloromethyl ketone (1b) to the corresponding iodomethyl ketone *in situ*, followed by reaction with the sodium derivative of dimethyl malonate. Compound 1b was prepared by adding 2.5 N HCl/EtOH to a solution (THF) of the corresponding diazoketone, which was obtained from Z-Trp and isobutyl chloroformate in THF followed by treatment with diazomethane in Et$_2$O.

The key step in the synthetic route to the target compounds 6a,b, 8b and 12b is the introduction of a suitably functionalized substituent in position 2 of the ketodiester 2 to give the 2-substituted derivative, in which the C-1 C-3 portion is the precursor of the C-terminal amino acid. In the case of the previously reported ketomethylene dipeptides, this step was achieved using appropiate alkyl halides[5]. According to this, 3-iodopropionitrile, generated, *in situ*, by transhalogenation of the 3-bromo derivative, was initially selected for the alkylation of 2a,b and the subsequent transformation of the cyanoethyl moiety of the alkylated compounds 3a,b into the 3-aminopropyl chain of the Orn-containing pseudodipeptides 6a,b. Attempts to carry out the alkylation in THF at room temperature, using 1 equiv of NaH as base, gave, after 24 h, only traces of 3a,b. When the reaction was carried out 70°C, in the presence of an excess of base (2 equiv), compounds 3a,b were obtained in ~40% yield. However, we found that the most efficient way of obtaining the cyanoethylated intermediates 3a,b was to add 2a,b to acrylonitrile in the presence of sodium methoxide. In this manner, compounds 3a,b were obtained within 90 min in ~80% yield (Scheme II).




HCl.Z-Phe ψ(COCH$_2$)(RS)Orn (5a) → 2HCl.Phe ψ(COCH$_2$)(RS)Orn (6a)
HCl.Z-Trp ψ(COCH$_2$)(RS)Orn (5b) → 2HCl.Trp ψ(COCH$_2$)(RS)Orn (6b)

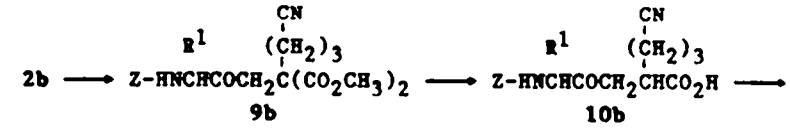


Saponification of 3a,b, followed by decarboxylation in dioxane, afforded the 2-substituted-4-ketoacids 4a,b. Selective hydrogenation of the cyano group of 4a,b in methanolic ammonia, in the presence of Raney nickel, gave the Z-protected ketomethylene dipeptides 5a,b. Removal of the Z group by hydrogenolysis in 6N HCl/MeOH (1:20), using 10% Pd/C as catalyst, afforded the desired pseudodipeptides 6a,b.

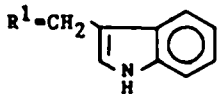
The Arg-containing pseudodipeptide 8b was prepared by guanidylation of the analogue 5b, using 1-amidino-3,5-dimethylpyrazole nitrate by a method similar to that reported by Klausner et al.[14], and subsequent hydrogenolysis of the Z-group (Scheme III).

5b ⟶ HCl.Z-Trp ψ($COCH_2$)(RS)Arg (7b) ⟶ 2HCl.Trp ψ($COCH_2$)(RS)Arg (8b)

Finally, for the synthesis of the Lys-containing pseudodipeptide 12b (Scheme IV), the ketodiester 2b was alkylated with 4-iodobutyronitrile, generated in situ from 4-bromobutyronitrile and NaI, using NaH as base, to give the cyanopropyl substituted derivative 9b in 67% yield. Compound 9b was converted to 12b following a similar route to that indicated for the synthesis of the ornithine analogues 6a,b. Thus, the 2-(cyanopropyl)-4-ketoacid 10b, obtained by successive saponification and decarboxylation of 9b, was selectively reduced to give the protected pseudodipeptide 11b which, by removal of the Z protecting group, provided 12b.




HCl.Z-Trp ψ($COCH_2$)(RS)Lys (11b) ⟶ 2HCl.Trp ψ($COCH_2$)(RS)Lys (12b)




While the asymmetric centre of the starting amino acid derivatives is not affected in this synthetic route, there is no reason why the decarboxylation step should be stereoselective. Therefore, the configurations at C-5 and C-2 were assigned as S and R S, respectively, for all the ketomethylene dipeptides here reported. Accordingly, the 300-MHz $^1H$ NMR spectra of 6a,b, 8b and 12b showed, in each case, the presence of a mixture of two diastereomeric pseudodipeptides, but, they did not show detectable peaks attributable to two additional stereoisomers. Separation of the S R and S S diastereomers was not observed in any of our chromatography experiments. Therefore, our biochemical and biological studies, to be reported elsewhere, is done using mixtures of both diastereomeric ketomethylene dipeptides.

The Z-protected pseudodipeptides, obtained by this procedure, could be incorporated into larger peptides by standard coupling techniques, or, could be converted to the corresponding pseudodipeptide halomethyl ketones to afford additional ketomethylene linkages. In the case of N-terminal protected pseudodipeptides having chemically labile side chains, such as 5a,b, 8b and 12b, convenient precursors, such as 4a,b and 10b, could be used for these purposes.

## EXPERIMENTAL

Melting points were measured with a Kofler hot-stage apparatus and are uncorrected. $^1$H NMR spectra were recorded with a Varian EM-390 or a Varian XL-300 spectrometer operating at 90 or 300 MHz, respectively, using $Me_4Si$ as internal standard. Analytical TLC was performed on aluminium sheets coated with a 0.2-mm layer of silica gel 60 $F_{254}$ (Merck). Silica gel 60 (230-400 mesh) (Merck) was used for column chromatography. Compounds were detected with UV light (254 nm) and ninhydrin spray. All final products showed one spot on TLC.

All the amino acids used were of the L configurations. N -Z-tryptophan was synthesized as described in the literature[15].

**Z-Trp-$CH_2$Cl (1b).** N-Methylmorpholine (6.5 mL, 59 mmol) and isobutyl chloroformate (8.1 mL, 70 mmol) were added to a cooled solution (-20°C) of Z-tryptophan (20 g, 59 mmol) in dry THF (100 mL). The mixture was stirred at that temperature for 30 min and then filtered. An ethereal solution of diazomethane, prepared from nitrosomethylurea (7.2 g, 70 mmol), was added to the filtrate and the reaction mixture was stirred for 15 min at 0°C, concentrated to a small volume and then 2.5 N ethanolic HCl was added at room temperature until nitrogen evolution ceased. Solvents were removed by evaporation and the residue purified by column chromatography eluting with EtOAc-hexane (1:3) to provide 1b which was recrystallized from EtOAc-hexane (12 g, 59%): m.p. 134-136°C; $^1$H NMR ($CDCl_3$) δ 3.23 (d, 2H, Trpβ$CH_2$), 4.00 (d, 2H, $CH_2Cl$), 4.86 (m, 1H, Trpα$CH$), 5.03 (s, 2H, benzyl $CH_2$), 5.43 (m, 1H, NH-α), 7,26 (s, 5H, benzyl, $C_6H_5$), 6.83-7.76 (m, 5H, indole), 8.16 (s, 1H, NH-indole). Anal. Calcd. for $C_{20}H_{19}ClN_2O_3$: C, 64.78; H, 5.16; Cl, 9.56; N, 7.55. Found: C, 64.77; H, 5.12; Cl, 9.58; N, 7.55.

**Methyl 5(S)-N-(benzyloxycarbonyl)amino-6-(indol-3-yl)-2-methoxycarbonyl-4-oxohexanoate (2b).** A mixture of 1b (7.4 g, 20 mmol) and sodium iodide (3 g, 20 mmol) in 1,2-dimethoxyethane (60 mL) was stirred at room temperature for 15 min, followed by the addition of the sodium salt of dimethyl malonate (3.43 g, 22 mmol), freshly prepared from the corresponding diester and sodium methoxide, in 1,2-dimethoxyethane (20 mL). Stirring was continued at that temperature for 1 h, the solvents were removed, and the residue was extracted with chloroform (100 mL) and washed with water (100 mL). The organic extract was dried ($Na_2SO_4$) and evaporated leaving a residue which was purified on a silica gel column with EtOAc-hexane (1:2) to provide 2b as a syrup (8.6 g, 92%): $^1$H NMR ($CDCl_3$) δ 2.90-3.36 (m, 4H, H-3, H-6), 3.73 (s, 6H, $2CO_2CH_3$), 3.86 (t, 1H, H-2), 4.70 (m, 1H, H-5), 5.06 (s, 2H, benzyl $CH_2$), 5.46 (m, 1H, NH-5), 7.30 (s, 5H, benzyl $C_6H_5$), 6.96-7.60 (m, 5H, indole), 8.20 (s, 1H, NH- indole). Anal. Calcd. for $C_{25}H_{26}N_2O_7$: C, 64.37; H, 5.62; N, 6.00. Found: C, 64.26; H, 5.91; N, 6.38.

**General procedure for the reaction of 2 with acrylonitrile.** A stirred solution of 2 (5.3 mmol) and freshly prepared sodium methoxide (5.8 mmol) in methanol (40 mL) was treated with acrylonitrile (5.8 mmol). After 3 h of stirring at room temperature, the mixture was neutralized with acetic acid and the solvents were evaporated to give a residue which was purified and identified as specified in each case.

**Methyl 5(S)-N-(benzyloxycarbonyl)amino-2-(2-cyanoethyl)-6-phenyl-2-methoxycarbonyl-4-oxohexanoate (3a).** This compound was purified on a silica gel column using EtOAc-hexane (1:3): 83% yield; homogeneous syrup; $^1$H NMR ($CDCl_3$) δ 2.30 (m, 4H, $CH_2CH_2CN$), 2.90-3.30 (m, 4H, H-3, H-6), 3,66 (s, 6H, $2CO_2CH_3$), 4.50 (m, 1H, H-5), 5.03 (s, 2H, benzyl $CH_2$), 5.30 (m, 1H, NH-5), 7.00-7.40 (m, 10H, benzyl $C_6H_5$,

$C_6H_5$). Anal. Calcd. for $C_{26}H_{28}N_2O_7$: C, 64.99; H, 5.87; N, 5.83. Found: C, 65.24; H, 6.15; N, 5.84.

**Methyl 5(S)-N-(benzyloxycarbonyl)amino-2-(2-cyanoethyl)-6-(indol-3-yl)-2-methoxycarbonyl-4-oxohexanoate (3b).** This compound was purified on a silica gel column using EtOAc-hexane (1:2): 74% yield; homogeneous syrup; $^1$H NMR ($CDCl_3$) δ 2.16 (m, 4H, $CH_2CH_2CN$), 3.00-3.26 (m, 4H, H-3, H-6), 3.66 (s, 6H, $2CO_2CH_3$), 4.60 (m, 1H, H-5), 5.06 (2s, 2H, benzyl $CH_2$), 5.43 (m, 1H, NH-5), 6.90-7.63 (m, 5H, indole), 7,30 (s, 5H, benzyl $C_6H_5$), 8.36 (s, 1H, NH- indole). Anal. Calcd. for $C_{28}H_{29}N_3O_7$: C, 64.73; H, 5.63; N, 8.09. Found: C, 64.65; H, 5.71; N, 7.85.

**Methyl 5(S)-N-(benzyloxycarbonyl)amino-2-(3-cyanopropyl)-2-methoxycarbonyl-6-(indol-3-yl)-4-oxohexanoate (9b).** A mixture of 2b (4 g, 8.5 mol) and NaH (2 equiv) in dry THF (60 mL) was stirred at room temperature for 15 min, followed by the addition of 4-bromobutyronitrile (0.99 mL, 10 mmol) and sodium iodide (1.5 g, 10 mmol). Stirring was continued at that temperature for 24 h, water (40 mL) was added and the aqueous mixture was extracted with EtOAc (2x40 mL). The organic extracts were dried ($Na_2SO_4$) and evaporated to yield crude 9b which was purified on a silica gel column using EtOAc-hexane (1:3) : 67% yield; homogeneous syrup; $^1$H NMR ($CDCl_3$) δ 1.20-1.66 (m, 2H, $CH_2CH_2CH_2CN$), 1.73-2.30 (m, 4H, $CH_2CH_2CH_2CN$), 3.03-3.30 (m, 4H, H-3, H-6), 3.70 (s, 6H, $2CO_2CH_3$), 4.70 (m, 1H, H-5), 5.10 (s, 2H, benzyl $CH_2$), 5,43 (m, 1H, NH-5), 6.93-7.70 (m, 5H, indole), 7.23 (s, 5H, benzyl $C_6H_5$), 8.30 (s, 1H, NH-indole). Anal. Calcd. for $C_{29}H_{31}N_3O_7$: C, 65.29; H, 5.85; N,7.87. Found: C, 65.15; H, 5.76; N, 7.65.

**General procedure for saponification and decarboxylation.** A solution of the 2-substituted diester (4 mmol) in methanol (40 mL) was treated with 6N NaOH (2 mL) and the mixture was stirred at room temperature for 3 h. After evaporation of the methanol, the remaining aqueous mixture was diluted with water (30 mL), acidified with concentrated HCl to pH 3, and extracted with EtOAc (100 mL). The extract was dried ($Na_2SO_4$) and evaporated. The residue was dissolved in dioxane (30 mL) and heated under reflux for 4 h. Removal of the solvent left a syrup which was purified as specified in each case.

**5(S)-N-(Benzyloxycarbonyl)amino-2(RS)-(2-cyanoethyl)-6-phenyl-4-oxohexanoic Acid (4a).** This compound was purified on a silica gel column using $CHCl_3$-MeOH (10:1). 79% yield: m.p. 100-102 °C; $^1$H NMR (DMSO+TFA) δ 1.75 (m, 2H, $CH_2CH_2CN$), 2.41-3.12 (m, 6H, $CH_2CH_2CN$, H-3, H-6), 3.15 (m, 1H, H-2), 4.26 (m, 1H, H-5), 4.97 (s, 2H, benzyl $CH_2$), 7.27 (m, 10H, benzyl $C_6H_5$, $C_6H_5$), 7.73 (m, 1H, NH-5). Anal. Calcd. for $C_{23}H_{24}N_2O_5$: C, 67.64; H, 5.92; N, 6.86. Found: C, 67.46; H, 5.79; N, 6.61.

**5(S)-N-(Benzyloxycarbonyl)amino-2(RS)-(2-cyanoethyl)-6-(indol-3-yl)-4-oxohexanoic Acid (4b).** This compound was purified on a silica gel column using $CHCl_3$-MeOH (15:1). 93% yield: foam; $^1$H NMR (DMSO+TFA) δ 1.74 (m, 2H, $CH_2CH_2CN$), 2.42-2.94 (m, 6H, $CH_2CH_2CN$, H-3, H-6), 3,17 (m, 1H, H-2), 4.31 (m, 1H, H-5), 4.99 (s, 2H, benzyl $CH_2$), 6.96-7.58 (m, 9H, benzyl $C_6H_5$, indole, H-2, H-5, H-6 and H-7), 7.75 and 7.72 (2d, 1H, intensity ratio 1:1, indole H-4), 10.80 (s, 1H, NH-indole). Anal. Calcd. for $C_{25}H_{25}N_3O_5$: C, 67.10; H, 5.63; N, 9.39. Found: C, 66.93; H, 5.89; N, 9.17.

**5(S)-N-(Benzyloxycarbonyl)amino-2(RS)-(3-cyanopropyl)-6-(indol-3-yl)-4-oxohexanoic Acid (10b).** This compound was purified on a silica gel column using $CHCl_3$-MeOH (12:1). 88% yield: foam; $^1$H NMR (DMSO+TFA) δ 1.52 (m, 4H, $CH_2CH_2CH_2CN$), 2.43-2.97 (m, 6H, $CH_2CH_2CH_2CN$, H-3, H-6), 3.14 (m, 1H, H-2), 4.30 (m, 1H, H-5), 4.98 (s, 2H, benzyl $CH_2$), 6.93-7.54 (m, 9H, benzyl $C_6H_5$, indole H-2, H-5, H-6 and H-7), 7.68

and 7.73 (2d, 1H, intensity ratio 1:1, indole H-4), 10.82 (s, 1H, NH-indole). Anal. Calcd. for $C_{26}H_{27}N_3O_5$: C, 67.66; H, 5.90; N, 9.10. Found: C, 67.45; H, 5.85; N, 9.11.

**General procedure for the reduction of the cyano group.** A solution of the 2-(cyanoalkyl)substituted ketoacid (2.9 mmol) in saturated methanolic ammonia (50 mL) was hydrogenated in a Parr apparatus in the presence of wet Raney nickel (0.94 g) at room temperature and 40 psi for 7 h. The insoluble material was discarded by filtration and the filtrate was evaporated. The resulting residue was dissolved in 2N HCl (30 mL) and washed with EtOAc. The aqueous layer was evaporated to a gum which was purified as specified in each case.

**HCl.Z-Phe ψ(COCH$_2$)(RS)Orn (5a).** This compound was purified on a silica gel column using $CHCl_3$-MeOH (4:1): 70% yield; foam; $^1$H NMR (DMSO+TFA) δ 1.48-1.56 (m, 4H, Orn β- and γ $CH_2$), 2.61-3.15 (m, 7H, $COCH_2$, Phe β $CH_2$, Orn αCH- and δ $CH_2$), 4.25 (m, 1H, Phe αCH), 4.98 (2, 2H, benzyl $CH_2$), 7.27 (m, 10H, benzyl $C_6H_5$, $C_6H_5$), 7.80 (m, 1H, NH). Anal. Calcd. for $C_{23}H_{29}ClN_2O_5$: C, 61.53; H, 6.51; Cl, 7.91; N, 6.24. Found: C, 61.45; H, 6.35; Cl, 7.95; N, 6.28.

**HCl.Z-Trp ψ(COCH$_2$)(RS)Orn (5b).** This compound was purified on a silica gel column using $CHCl_3$-MeOH (6:1): 70% yield; foam; $^1$H NMR (DMSO+TFA) δ 1.48-1.56 (m, 4H, Orn β- and γ $CH_2$), 2.45-3.00 (m, 6H, $COCH_2$, Trp β $CH_2$, Orn δ $CH_2$), 3.12 (m, 1H, Orn αCH), 4.27 (m, 1H, Trp αCH), 4.97 and 4.98 (2s, 2H, intensity ratio 1:1, benzyl $CH_2$), 6.97-7.54 (m, 9H, benzyl $C_6H_5$, indole H-2, H-5, H-6, H-7), 7.77 and 7.80 (2d, 1H, intensity ratio 1:1, indole H-4). Anal. Calcd. for $C_{25}H_{30}ClN_3O_5$: C, 61.53; H, 6.19; Cl, 7.28; N, 8.61. Found: C, 61.68; H, 5.90; Cl, 7.25; N, 8.45.

**HCl.Z-Trp ψ(COCH$_2$)(RS)Lys (11b).** This compound was purified on a silica gel column using $CHCl_3$-MeOH (6:1): 76% yield; foam; $^1$H NMR (DMSO+TFA) δ 1.10-1.55 (m, 6H, Lys β-, γ- and δ $CH_2$), 2.45-2.95 (m, 6H, $COCH_2$, Trp β $CH_2$, Lys ε $CH_2$), 3.15 (m, 1H, Lys αCH), 4.28 (m, 1H, Trp αCH), 4.94 and 4.97 (2s, 2H, intensity ratio 1:1, benzyl $CH_2$), 6.95-7.56 (m, 9H, benzyl $C_6H_5$, indole H-2, H-5, H-6, H-7), 7.73 (m, 1H, indole H-4). Anal. Calcd. for $C_{26}H_{32}ClN_3O_5$: C, 62.21; H, 6.42; Cl, 7.07; N, 8.37. Found: C, 61.98; H, 6.45; Cl, 6.95; N, 8.24.

**HCl.Z-Trp ψ(COCH$_2$)(RS)Arg (7b).** A solution of 5b (1.8 g, 3.6 mmol) in dry DMF (10 mL) was added to a solution of 1-amidino-3,5-dimethylpyrazole nitrate (0,72 g, 3,6 mmol) in dry DMF (10 mL), adjusted to pH 8-9 with triethylamine (0.5 mL), and the pH of the reaction mixture was brought to pH 8-9 with more triethylamine (1.0 mL). After 7 days at room temperature, the solvent was removed, the residue was dissolved in 2N HCl (20 mL) and washed with EtOAc. The aqueous phase was evaporated to dryness, and the residue was purified on a silica gel column, eluting with $CHCl_3$-MeOH (3:1), to give pure 7b (1.15 g, 63.5%): foam; $^1$H NMR (DMSO+TFA) δ 1.38-2.00 (m, 4H, Arg β- and γ $CH_2$), 2.38-3.24 (m, 7H, $COCH_2$, Trp β $CH_2$, Arg α- and δ $CH_2$), 4.28 (m, 1H, Trp αCH), 4.93 and 4.97 (2s, 2H, intensity ratio 1:1 benzyl $CH_2$), 6.91-7.51 (m, 9H, benzyl $C_6H_5$, indole H-2, H-5, H-6, H-7), 7.70 (m, 1H, indole H-4). Anal. Calcd. for $C_{26}H_{32}ClN_5O_5$: C, 58.92; H, 6.09; Cl, 6.70; N, 13.22. Found: C, 58.93; H, 6.36; Cl, 6.65; N, 12.97.

**General procedure for removing the Z protecting group:** A solution of the Z protected pseudodipeptide (1.1 mmol) in EtOH (50 mL) containing 6N HCl (0.2 mL) was hydrogenated at 30 psi and room temperature, in the presence of 10% Pd/C (0.62 g) for 8 h. The catalyst was removed by filtration, and the filtrate was evaporated to

dryness to leave the crude deprotected compound which was purified on a silica gel column using $CHCl_3$-MeOH (5:1).

**2HCl.Phe ψ($COCH_2$)(RS)Orn (6a).** 78.5% Yield: foam; $^1H$ NMR ($D_2O$) δ 1.55-1.80 (m, 4H, Orn β- and γ $CH_2$), 2.70-3.20 (m, 6H, $COCH_2$, Orn αCH, Orn δ$CH_2$, Phe β CH'), 3.44 and 3.88 (2dd, 1H, intensity ratio 1:1, Phe β CH''), 4.57 (m, Phe α CH), 7.33-7.47 (m, 5H, Phe $C_6H_5$). Anal. Calcd. for $C_{15}H_{24}Cl_2N_2O_3$: C, 51.28; H, 6.89; Cl, 20.19; N, 7.98. Found: C, 51.55; H, 6.54; Cl, 19.89; N, 7.95.

**2HCl.Trp ψ($COCH_2$)(RS)Orn (6b).** 82% Yield; foam; $^1H$ NMR ($D_2O$) δ 1.40-1.80 (m, 4H, Orn β- and γ $CH_2$), 2.65-3.20 (m, 5H, $COCH_2$, Orn α CH, Orn δ$CH_2$), 3.31 and 3.40 (2dd, 1H, intensity ratio 1:1, Trp β CH'), 3.57 and 3.70 (2dd, 1H, intensity ratio 1:1, Trp βCH''), 4.66 (m, 1H, Trp α CH), 7.27-7.61 (m, 4H, indole H-2, H-5, H-6, H-7), 7.66 and 7.70 (2d, 1H, intensity ratio 1:1 indole H-4). Anal. Calcd. for $C_{17}H_{25}Cl_2N_3O_3$: C, 52.30; H, 6.46; Cl, 18.17; N, 10.76. Found: C, 52.10; H, 6.05; Cl, 18.12; N, 10.50.

**2HCl.Trp ψ($COCH_2$)(RS)Arg (8b).** 60% Yield; foam; $^1H$ NMR ($D_2O$) δ 1.40-1.75 (m, 4H, Arg β- and γ $CH_2$), 2.62-3.20 (m, 5H, $COCH_2$, Arg α CH, Arg δ$CH_2$), 3.32 and 3.40 (2dd, 1H, intensity ratio 1:1, Trp β CH'), 3.56 and 3.64 (2dd, 1H, intensity ratio 1:1, Trp βCH''), 4.63 (m, 1H, Trp αCH), 7.22-7.60 (m, 4H, indole H-2, H-5, H-6,H-7), 7.68 and 7.74 (2d, 1H, intensity ratio 1:1, indole H-4). Anal. Calcd. for $C_{18}H_{27}Cl_2N_5O_3$: C, 50.00; H, 6.29; Cl, 16.40; N, 16.20. Found: C, 50.10; H, 6.20; Cl, 16.58; N, 15.93.

**2HCl.Trp ψ($COCH_2$)(RS)Lys (12b).** 62.5% Yield; foam; $^1H$ NMR ($D_2O$)δ 1.10-1.80 (m, 6H, Lys β,-γ- and δ$CH_2$), 2.55-3.10 (m, 5H, $COCH_2$, Lys αCH, Lys ε $CH_2$), 3.30 and 3.38 (2dd, 1H, intensity ratio 1:1, Trp βCH'), 3.52 and 3.62 (2dd, 1H, intensity ratio 1:1, Trp βCH''), 4.63 (m, 1H, Trp α CH), 7.23-7.60 (m, 4H, indole H-2, H-5, H-6, H-7), 7.66 and 7.74 (2d, 1H, intensity ratio 1:1, indole H-4). Anal. Calcd. for $C_{18}H_{27}Cl_2N_3O_3$: C, 53.46; H, 6.73; Cl, 17.54; N, 10.39. Found: C, 53.37; H, 6.72; Cl, 17.85; N, 10.13.

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