A General Method for the Synthesis of (Carbamoylmethylene)amino Pseudopeptides

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Received February 25, 1994[⊗]

A general procedure for the preparation of (carbamoylmethylene)amino pseudopeptides from the corresponding (cyanomethylenene)amino analogues, compatible with peptide bonds and with the usual amino and carboxyl protecting groups, is described. This procedure involves the oxidative hydration of (cyanomethylene)amino pseudopeptides with basic hydrogen peroxide under phase-transfer conditions, using *n*-tetrabutylammonium hydrogen sulfate as catalyst. In the basic medium of this reaction the methyl esters of (carbamoylmethylene)amino pseudodipeptides cyclized to 2,6-dioxopiperazine analogues.

Introduction

The reduced peptide bond Ψ[CH_2NH][1] has been successfully used in the design of metabolically stable agonists[2]/antagonists[3] of bioactive peptides and peptidase inhibitors.[4] However, this surrogate causes an increase in the flexibility of the peptide backbone and a decrease in the H-bonding properties by loss of the H-bonding acceptor amide carbonyl group.[5,6] Semiempirical quantum mechanic calculations for the [CH(CN)NH] and [CH_2NH] groups showed that the first one could be a better mimic of the peptide bond and of the tetrahedral transition state involved in peptidase action than the second one.[7] On the basis of these calculations, and assuming that the replacement of one methylenic hydrogen atom of the reduced peptide bond with an H-bonding acceptor group could counteract, in part, the above-mentioned effects, we studied the solution-[7,8] and solid-phase[9] synthesis of (cyanomethylene)amino pseudopeptides. The preliminary biological data resulting from the application of this peptide backbone modification to the search of aminopeptidase inhibitors[10] and neurotensin analogues[11] support this assumption. A similar hypothesis was used for the synthesis of the ValΨ[(*S*)CH($CONH_2$)NH]His pseudodipeptide as Val-His surrogate, reported by Mohan *et al.*,[12] which was incorporated into angiotensin II analogues. The synthesis of this pseudodipeptide involved the cyanohydration of a 1:2 (*R*)- and (*S*)-epimeric mixture of the corresponding Boc-protected Ψ[CH(CN)NH] analogue with concentrated sulfuric acid. Due to this strong acidic reaction medium, the removal of the Boc-protecting group took place simultaneously with the cyanohydration. Therefore, it was necessary to reintroduce this protecting group in order to continue the peptide synthesis (17% overall yield). On the other hand, the strong acidic medium is not compatible with the presence of peptide bonds. This hampers the extension of this method to other pseudopeptides higher than pseudodipeptides. In order to avoid these drawbacks we described herein a general procedure for the preparation of (carbamoylmethylene)-amino pseudopeptides from the corresponding (cyanomethylene)amino analogues *via* cyanohydration in basic medium.

Results and Discussion

The starting R^1-PheΨ[CH(CN)NH]Xaa-OR^3 pseudodipeptides **1a** and **1b** and pseudotripeptides **1c-f** (Scheme 1) were obtained following our previously described method,[8] which involved the reaction of *N*-Boc-L-phenylalaninal with the appropriate amino acid or dipeptide derivative and trimethylsilyl cyanide (TMSCN) in the presence of $ZnCl_2$. In each case the epimeric pair at the [CH(CN)NH] chiral center was obtained in ≈1:1 *R*:*S* ratio. These epimers were separated by flash chromatography in the case of pseudopeptides **1b** and **1e**, while the epimeric mixtures **1a**, **1c**, **1d**, and **1f** could not be resolved using this technique or preparative reversed-phase HPLC, and were used as such for the following cyanohydration reaction.

The [CH(CN)NH] configuration in the separated epimers of **1b** and **1e** was assigned on the basis of the $J_{4,5}$ value in the ^1H NMR spectra of the 2-oxoimidazolidines (*S*)-**5b** and (*S*)-**5e**, obtained from the *N*-deprotected pseudopeptides (*S*)-**3b,e**, after reaction with bis(trichloromethyl) carbonate. Thus, these 2-oxoimidazolidines showed a $J_{4,5}$ value of 8 Hz, consistent with a H_4,H_5 *cis* disposition.[8] This assignment was confirmed by NOE experiments on the 2-oxoimidazolidines (*S*)-**5b,e**.

⊗ Abstract published in *Advance ACS Abstracts*, June 1, 1994.

(1) The general accepted nomenclature for pseudopeptides, indicated in ref 5, is used.

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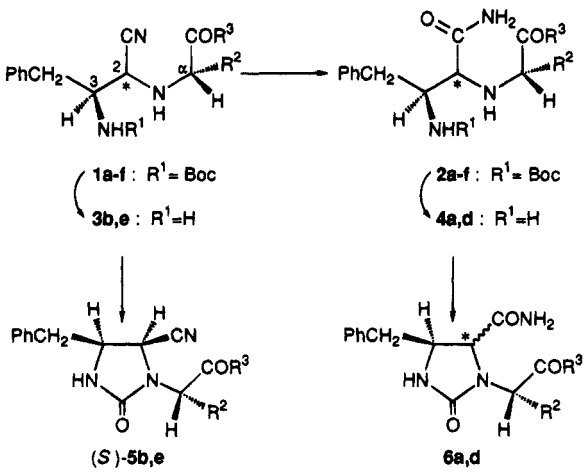
Scheme 1



a : $R^2 = CH_2CH(CH_3)_2$; R^3 = OMe
b : $R^2 = CH_2CH(CH_3)_2$; $R^3 = NH_2$
c : $R^2 = CH_2CH(CH_3)_2$; R^3 = Ala-OH
d : $R^2 = CH_2CH(CH_3)_2$; R^3 = Ala-OMe
e : $R^2 = CH_2CH(CH_3)_2$; R^3 = Ala-NH_2
f : $R^2 = CH_3$; R^3 = Pro-OMe

The oxidative hydration of separated (*R*)- and (*S*)-epimers of the Ψ[CH(CN)NH] pseudopeptides **1b,e** and of the epimeric mixtures **1a,c,d,f** with basic hydrogen peroxide under phase-transfer conditions,[13,14] using *n*-tetrabutylammonium hydrogen sulfate as catalyst, led to the corresponding Ψ[CH($CONH_2$)NH] analogues **2a-f** (Scheme 1) in good yield (60–85%). The *C*-terminal amides of the Ψ[CH($CONH_2$)NH] pseudopeptides (*R*)- and (*S*)-**2b** and (*R*)- and (*S*)-**2e**, as well as the epimeric mixture of the sodium salt of the acid **2c**, precipitated from the reaction mixture and were isolated by filtration. The epimeric mixture **2d**, which could not be resolved in the starting cyano analogues **1d**, was separated by flash chromatography. However, the epimeric mixtures (*R,S*)-**2c** and **-2f** could not be resolved in this reaction step.

As we have previously reported,[8] the starting (cyanomethylene)amino pseudopeptides **1a-f** were not stable in the basic medium (NaOH) used in the cyanohydration, due to the scission of the peptide bond surrogate releasing HCN. However, the study of this reaction by HPLC showed that after 4 h of reaction the cleavage of the peptide bond surrogate was minimal (<10%), while the conversion of the cyano group into the corresponding carboxamide took place almost completely.

In the oxidative hydration of the (*R,S*)-epimeric mixture of methyl esters of the pseudodipeptides **1a**, only the (*S*)-epimer of the corresponding (carbamoylmethylene)amino analogue (*S*)-**2a** could be isolated from the reaction mixture in low yield (20%), along with the (*R*)- and (*S*)-epimers of the 2,6-dioxopiperazine **7a**. These conformationally constrained dipeptide analogues resulted from the easy intramolecular reaction of the intermediate 4-carbamoyl esters **2a** in the basic medium required for the cyanohydration.[15] In the (*R*)-epimer, this cyclization was so fast that the intermediate (*R*)-**2a** could not be detected.

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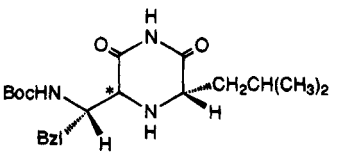
The structural assignment of the new compounds **1–6** was based on their analytical and ^1H- and ^{13}C-NMR spectral data (Tables 1–4). As in the case of the aforementioned Ψ[CH(CN)NH] pseudopeptides **1b,e**, the assignment of the [CH($CONH_2$)NH] configuration in the separated epimers (*S*)-**2a** and (*R*)- and (*S*)-**2d** was established on the basis of the $J_{4,5}$ value in the ^1H NMR spectra of the corresponding 2-oxoimidazolidines **6a,d**. The saponification[8] of the methyl ester in the pseudotripeptide derivative (*S*)-**2d** with NaOH led to the sodium salt of its acid (*S*)-**2c**, identical by HPLC and ^1H NMR to one of the isomers of the epimeric mixture **2c**. This result allowed the ^1H NMR assignment of both epimers (*R*)- and (*S*)-**2c**. On the other hand, the NaOH treatment, under phase-transfer conditions, of the Ψ[CH($CONH_2$)NH] pseudodipeptide (*S*)-**2a** yielded the corresponding 2,6-dioxopiperazine (*S*)-**7a**, identical to one epimer of the 2,6-dioxopiperazines **7a** obtained in the cyanohydration of **1a**, allowing the unequivocal assignment of both isomers.



7a

In conclusion, the methodology described here permits the preparation of Ψ[CH($CONH_2$)NH] pseudopeptides in good yield. This method is compatible with the presence of peptide bonds and the usual amino and carboxyl protecting groups.

Experimental Section

General. All reagents were of commercial quality. Solvents were dried and purified by standard methods. Amino acid derivatives were obtained from Bachem Feinchemikalien AG. Analytical TLC was performed on aluminum 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 flash chromatography. Melting points were taken on a micro hot stage apparatus and are uncorrected. NMR spectra were recorded at 200 or 300 MHz, using TMS as reference, except for the spectra recorded in D_2O, where this solvent was the reference. Reversed-phase HPLC analyses were performed on a μ-Bondapak C18 (10-μm) stainless steel, Waters, column (3.0 × 300 mm), with a flow rate of 1 mL/min, and μsing a tunable UV detector set at 214 nm. Mixtures of 0.05 % TFA in H_2O (solvent A) and CH_3CN (solvent B) were used as mobile phase. Preparative reversed-phase HPLC was performed on a μ-Bondapak C18 (10 μm) stainless steel, Waters, column (7.7 × 300 mm).

Synthesis of the Ψ[CH(CN)NH] Pseudopeptides 1a-f. These compounds were prepared following the method described in ref 8, and their analytical and spectroscopic data are summarized in Table 1.

General Procedure for the Synthesis of Ψ[CH($CONH_2$)-NH] Pseudopeptides 2a-f. *n*-Tetrabutylammonium hydrogen sulfate (136 mg, 0.4 mmol) and 30% hydrogen peroxide (0.41 mL, 3.6 mmol) were added to a solution of the corresponding starting (cyanomethylene)amino pseudopeptide **1a-f** (1 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred at 0 °C, and 24% aqueous sodium hydroxide (0.4 mL, 2.4 mmol) was added dropwise. After 4 h of stirring at 0 °C, the reaction mixture was diluted with H_2O (5 mL) and CH_2Cl_2 (5 mL). (Carbamoylmethylene)amino pseudopeptides **2b**, **2c**, and **2e** precipitated from the reaction mixture and were purified by filtration, washing the precipitate with CH_2Cl_2 (3 × 5 mL), and recrystallization (**2b**, from acetone–hexane; **2c**, from 2-propanol; and **2e**, from *n*-butanol). Starting from (cyanomethylene)amino pseudopeptides **1a**, **1d**, and **1f**, the organic layer

Table 1. Analytical and Significant Spectroscopic Data for the Boc-Phe ψ[CH(CN)NH]Xaa-R³ Pseudopeptides 1a-f

compd	yield (%)	t_R (A:B)[a]	formula	found (%) (calcd) C	H	N	^{13}C NMR C≡N	^{1}H NMR (δ, ppm)[b] Phe 2-H	3-H	4-H	4′-H	Xaa NH	α-H
(*R*)-**1a**[c]		16.45						3.73	4.10	2.83	3.10	1.90	3.30
+	95	(60:40)	$C_{22}H_{33}N_3O_4$	65.60	8.40	10.60	117.99; 118.46						
(*S*)-**1a**		15.10		(65.48)	(8.24)	(10.41)		3.77	4.23	2.96		2.00	3.50
(*R*)-**1b**	48	16.18	$C_{21}H_{32}N_4O_3$	64.97	8.40	14.70	119.54	3.81	4.07	2.88	3.18	2.58	3.32
		(45:55)		(64.94)	(8.25)	(14.43)							
(*S*)-**1b**	36	14.15	$C_{21}H_{32}N_4O_3$	64.79	8.35	14.53	119.37	3.79	4.14	2.87	3.22	2.65	3.36
				(64.94)	(8.25)	(14.43)							
(*R*)-**1c**		25.68						3.80	4.20	2.81	3.10		3.35
+	70	(40:60)	$C_{24}H_{35}N_4O_5$	62.43	7.81	11.98	*d*						
(*S*)-**1c**		24.30		(62.74)	(7.62)	(12.20)		3.87	4.20	2.81	3.19		3.35
(*R*)-**1d**		23.16						3.65	3.89	2.84	3.11	1.97	3.11
+	75	(50:50)	$C_{25}H_{38}N_4O_5$	63.25	8.32	11.74	*d*						
(*S*)-**1d**		22.68		(63.29)	(8.02)	(11.81)		3.89	4.35	2.84		2.15	3.32
(*R*)-**1e**	41	20.91	$C_{24}H_{37}N_5O_4$	62.51	7.97	14.98	119.29	3.89	4.05	2.90	3.16	2.63	3.38
		(40:60)		(62.74)	(8.06)	(15.25)							
(*S*)-**1e**	39	19.98	$C_{24}H_{37}N_5O_4$	62.58	8.31	15.06	*d*	3.85	4.22	2.89	3.23	2.72	3.39
				(62.51)	(8.06)	(15.25)							
(*R*)-**1f**		21.37						3.70	4.07	2.86	3.13	2.69	3.70
+	60	(40:60)	$C_{24}H_{34}N_4O_5$	62.65	7.39	11.99	118.42; 118.15						
(*S*)-**1f**		18.10		(62.88)	(7.42)	(12.23)		3.80	4.07	2.84		2.69	3.70

[a] A = 0.05% TFA in H_2O; B = CH_3CN. [b] **1a**, **1d** in $CDCl_3$; **1b**, **1c**, **1e**, and **1f** in $(CD_3)_2CO$. [c] Described in ref 8. [d] Not registered.

Table 2. Analytical and Significant Spectroscopic Data for the Boc-Phe ψ[CH(CONH₂)NH]Xaa-R³ Pesudopeptides 2a–f

compd	yield (%)	t_R (A:B)[a]	mp (°C)	formula[b]	MS MH^+ (*m/e*)	$CONH_2$ and COR²	solvent	^{1}H NMR (δ, ppm) Phe 2-H	3-H	4-H	4′-H	$CONH_2$	Xaa NH	α-H
(*S*)-**2a**	20	7.80 (52:48)	108–109	$C_{22}H_{35}N_3O_5$	422	175.45; 174.59	$CDCl_3$	3.16	4.15	2.80	3.00	5.70; 7.20	2.70	3.16
(*R*)-**2b**	65	6.60 (45:55)	218–220	$C_{21}H_{34}N_4O_4$	407	176.65; 174.46	DMSO-d_6	2.96	3.85	2.65	2.79	6.96; 7.26; 7.29; 7.35	2.38	2.86
(*S*)-**2b**	68	6.30 (45:55)	197–198	$C_{21}H_{34}N_4O_4$	407	176.34; 174.14	DMSO-d_6	3.00	3.85	2.60	2.79	6.99; 7.23; 7.37; 7.43	2.29	2.99
(*R*)-**2c**		8.50						3.00	3.90	2.62	2.75	6.95; 7.85	2.20	2.75
+	73	(40:60)		$C_{24}H_{36}N_4O_6$-Na	*c*	175.13; 174.55; 173.18	DMSO-d_6							
(*S*)-**2c**		7.90						3.20	3.70	2.75		7.23; 7.30	2.40	2.80
(*R*)-**2d**	36	9.20 (70:30)	foam	$C_{25}H_{40}N_4O_6$	493	175.06; 174.47; 173.76	$CDCl_3$	3.21	4.03	2.79		5.68; 6.67	2.30	3.26
(*S*)-**2d**	37	9.20 (70:30)	foam	$C_{25}H_{40}N_4O_6$	493	174.54; 174.24; 173.70	$CDCl_3$	3.44	4.12	2.85		5.68; 6.67	2.40	3.10
(*R*)-**2e**	83	8.00 (40:60)	263–264	$C_{24}H_{39}N_5O_5$	478	174.45; 174.35; 173.94	DMSO-d_6	3.06	3.87	2.66	2.77	6.93; 7.06; 7.27; 7.40	2.28	3.06
(*R*)-**2f**		7.50				175.58; 173.49; 172.53		3.08	4.15	2.72	2.88	5.61; 7.18	2.52	3.33
+	66	(40:60)	foam	$C_{24}H_{36}N_4O_6$	477		$CDCl_3$							
(*S*)-**2f**		7.53				175.13; 173.45; 172.43		3.11	4.18	2.74	2.90	5.58; 5.69	2.50	3.34

[a] A = 0.05% TFA in H_2O; B = CH_3CN. [b] Satisfactory analyses for C, H, N. [c] Not registered.

Table 3. Analytical and Significant Spectroscopic Data for the H₂N-Phe ψ[CH(R)NH]Xaa-R³ Pseudopeptides 3 and 4

compd[a]	R	formula	found (%) (calcd) C	H	N	solvent	^{1}H NMR (δ, ppm) Phe 2-H	3-H	4-H	4′-H	Xaa α-H
(*S*)-**3b**	CN	$C_{16}H_{24}N_3O$·2($C_2HF_3O_2$)	46.90 (46.52)	5.40 (5.07)	10.39 (10.85)	D_2O	3.96	3.77	2.94	3.06	3.50
(*S*)-**3e**	CN	$C_{19}H_{29}N_5O_2$·2($C_2HF_3O_2$)	47.14 (46.99)	5.32 (5.28)	12.02 (11.92)	D_2O	3.86	3.86	3.02	3.13	3.40
(*S*)-**4a**	$CONH_2$	$C_{17}H_{27}N_3O_3$·$C_2HF_3O_2$	52.49 (52.41)	6.71 (6.43)	9.83 (9.65)	$CDCl_3$ + D_2O	3.07	3.40	2.52	2.88	3.29
(*R*)-**4d**	$CONH_2$	$C_{20}H_{32}H_4O_4$·$C_2HF_3O_2$	52.37 (52.15)	6.58 (6.52)	11.07 (11.06)	$CDCl_3$ + D_2O	3.98	4.14	3.00		3.53

[a] Hygroscopic solids, it was not possible to determine mp.

was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed successively with water (10 mL), 1 N HCl (10 mL), and brine (10 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography, using hexane–ethyl acetate mixtures as eluants. The analytical and spectroscopic data of pseudopeptides **2a-f** are summarized in Table 2.

***N*-Boc-Deprotection of Pseudopeptides 1b,e and 2a,d.** TFA (4 mL) was added to a solution of the appropriate *N*-Boc-protected pseudopeptide **1b,e** or **2a,d** (0.5 mmol) in dry CH_2Cl_2 (8 mL), and the resulting solution was stirred at rt for 4 h. Evaporation of the solvent, and subsequent lyophilization of the residue dissolved in H_2O, yielded quantitatively the corresponding *N*-deprotected compounds **3b,e** or **4a,d** as

Table 4. Analytical and Significant Spectroscopic Data for the 2-Oxoimidazolidines 5 and 6

			found (%) (calcd)			^{1}H NMR [$(CD_3)_2CO$, δ, ppm]				
						Phe				Xaa
compd	yield (%)	formula	C	H	N	5-H	4-H	$J_{4,5}$ (Hz)	NH	α-H
(*S*)-**5b**	60	$C_{17}H_{22}N_4O_2$	65.42 (64.95)	6.43 (7.05)	18.12 (17.85)	4.92	4.32	8	6.21	4.51
(*S*)-**5e**	50	$C_{20}H_{27}N_5O_3$	62.35 (62.33)	7.12 (7.01)	18.40 (18.18)	4.85	4.32	8	6.31	4.45
(*S*)-**6a**	58	$C_{18}H_{25}N_3O_4$	62.48 (62.24)	7.32 (7.20)	12.27 (12.10)	4.91	4.32	8	6.10	4.51
(*R*)-**6d**	55	$C_{21}H_{30}N_4O_5$	60.32 (60.29)	7.45 (7.18)	13.32 (13.40)	4.12	3.85	4	6.04	4.02

trifluoroacetates, whose analytical and spectroscopic data are summarized in Table 3.

Synthesis of the 2-Oxoimidazolidines 5b,e and 6a,d. Triethylamine (0.14 mL, 1 mmol) was added to a suspension of the corresponding *N*-deprotected pseudopeptide **3b,e** or **4a,d** (0.5 mmol) in dry CH_2Cl_2 (10 mL), and the mixture was stirred at rt for 15 min. Then, bis(trichloromethyl) carbonate (59 mg, 0.2 mmol) and triethylamine (0.17 mL, 1.2 mmol) were added at 0 °C, and the stirring was continued at this temperature for 5 h. Afterwards, the reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with water (10 mL) and brine (10 mL), and dried over Na_2SO_4. Removal of the solvent and flash chromatography of the residue, using hexane–ethyl acetate mixtures as eluants, gave the 2-oxoimidazolidines **5b,e** and **6a,d**, whose analytical and spectroscopic data are summarized in Table 4.

Synthesis of 3-[1′-[(*tert*-Butyloxycarbonyl)amino]-2′-phenylethyl]-5-isobutyl-2,6-dioxopiperazines (7a). Following the general procedure for the preparation of carbamoylmethyleneamino pseudopeptides **2**, starting from the methyl ester of the pseudodipeptide **1a**, the flash chromatography of the crude reaction mixture gave, along with the corresponding pseudodipeptide (*S*)-**2a** (20%), two higher R_f compounds which were identified as the 2,6-dioxopiperazines (*R*)-**7a** (30%) and (*S*)-**7a** (15%).

(1′*S*,3*R*,5*S*)-3-[1′-[(*tert*-Butyloxycarbonyl)amino]-2′-phenylethyl]-5-isobutyl-2,6-dioxopiperazine [(*R*)-7a]. Foam: t_R=13.40 min (A:B = 48:52); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.85 and 0.90 [2d, 6H, J = 7 Hz, CH_3(*i*-Bu)], 1.32 (s, 9H, Boc), 1.52 and 1.87 [2m, 2H, CH_2(*i*-Bu)], 1.64 [m, 1H, CH(*i*-Bu)], 2.05 (s, 1H, 4-NH), 2.91 (m, 2H, C*H*$_2$-Ph), 3.30 (dd, 1H, J = 3.5 and 10 Hz, 5-H), 3.49 (d, 1H, J = 3 Hz, 3-H), 4.39 (m, 1H, 1′-H), 5.20 (d, 1H, J = 9 Hz, NH-Boc), 7.20 (m, 5H, Ph), 7.90 (s, 1H, 1-NH); ^{13}C NMR (200 MHz, $CDCl_3$) δ (ppm) 21.10 and 23.32 [CH_3(*i*-Bu)], 24.26 [CH(*i*-Bu)], 28.19 [CH_3(Boc)], 37.38 (*C*H$_2$Ph), 38.71 [CH_2(*i*-Bu)], 52.34, 56.42, and 60.94 (1′-C, 3-C, and 5-C), 78.78 [*C*(CH_3)$_3$], 126.77, 128.65, 129.05 and 137.37 (aromatics), 155.17 [CO(Boc)], 171.83 and 172.78 [2CO, 2,6-dioxopiperazine); MS (*m/e*) MH^+ 390. Anal. Calcd for $C_{21}H_{31}N_3O_4$: C, 64.78; H, 7.97; N, 10.80. Found: C, 64.62; H, 8.18; N, 10.65.

(1′*S*,3*S*,5*S*)-3-[1′-[(*tert*-Butyloxycarbonyl)amino]-2′-phenylethyl]-5-isobutyl-2,6-dioxopiperazine [(*S*)-7a]. This compound was also obtained quantitatively from the (carbamoylmethylene)amino pseudodipeptide (*S*)-**2a** (42 mg, 0.1 mmol) in CH_2Cl_2 (10 mL), after treatment with 24% NaOH (0.01 mL, 0.6 mmol) and *n*-tetrabutylammonium hydrogen sulfate (13 mg, 0.04 mmol) for 1 h. White solid: mp 153–155 °C ($CHCl_3$–hexane); t_R=9.85 (A:B = 52:48); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.90 and 0.92 [2d, 6H, J = 7 Hz, CH_3(*i*-Bu)], 1.30 (s, 9H, Boc), 1.32 [m, 2H, CH_2(*i*-Bu)], 1.49 [m, 1H, CH(*i*-Bu)], 1.90 (s, 1H, 4-NH), 3.06 (m, 2H, CH_2Ph), 3.62 (d, 1H, J = 4 Hz, 3-H), 3.70 (dd, 1H, J = 5 and 10 Hz, 5-H), 4.35 (m, 1H, 1′-H), 4.77 (d, 1H, J = 9 Hz, NH-Boc), 7.28 (m, 5H, Ph), 8.0 (s, 1H, 1-NH); ^{13}C NMR (200 MHz, $CDCl_3$) δ (ppm) 20.10 and 23.32 [CH_3(*i*-Bu)], 24.00 [CH(*i*-Bu)], 27.90 [CH_3(Boc)], 37.82 (CH_2Ph), 38.40 [CH_2(*i*-Bu)], 52.95, 53.69, and 55.45 (1′-C, 3-C, and 5-C), 79.82 [*C*(CH_3)$_3$], 127.35, 129.16, 129.31, 129.63, 129.80, and 137.73 (aromatics), 156.37 [CO(Boc)], 172.79 and 174.95 [2CO, 2,6-dioxopiperazine); MS (*m/e*) MH^+ 390. Anal. Cald for $C_{21}H_{31}N_3O_4$: C, 64.78; H, 7.97; N, 10.80. Found: C, 64.56; H, 8.24; N, 10.60.

Acknowledgment. We thank the Comisión Interministerial de Ciencia y Tecnología (FAR-91-1120-CO2-01) and Comunidad Autónoma de Madrid (C-167/91) for financial support. We also thank Mr. F. Caballero for the preparation of the manuscript.