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SYNTHESIS OF CYCLIC KETOMETHYLENE DIPEPTIDE DERIVATIVES

M. J. Domínguez, R. González-Muñiz* and M. T. García-López

Instituto de Química Médica, Juan de la Cierva, 3. 28006 Madrid, Spain

Abstract.—Methyl 6-aralkyl-2,5-diketopiperidine-3-carboxylates derived from L-Phe and L-Trp, and their 3-substituted analogues in which the 3-substituent is the side chain of Phe, Asp and Ala have been synthesized. *Cycle*[Trpψ($COCH_2$)Gly] and *cycle*[Pheψ($COCH_2$)-ξ-Phe] have been also prepared.

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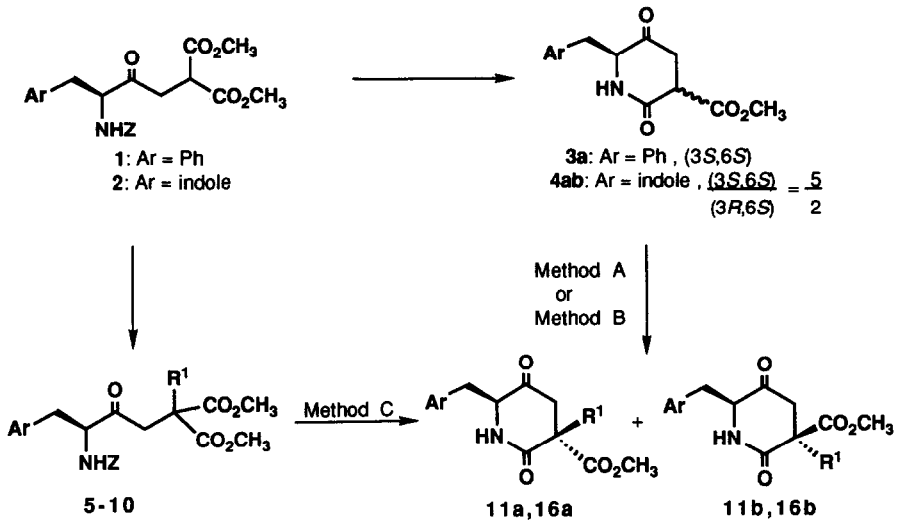
INTRODUCTION

Substitution of the amide bond -CONH- by the isosteric ketomethylene -$COCH_2$- group has been used to prepare metabolically stable peptides and various enzyme inhibitors.[1-3] However, this modification, which provides enzymatic resistance, causes a loss of the amide bond rigidity and, therefore, it increases conformational mobility. The lactam restriction of peptide conformation, originally introduced by Freidinger,[4] has aroused considerable interest in recent years as effective structural tools for probing the active conformation of bioactive peptides. [5,6] In a number of instances, locking bioactive peptides into active conformers by lactam backbone modification has led to increases in their potency.[7,8] The incorporation of 2-ketopiperazines into certain peptide neurotransmitter generates analogues with important biological activity,[9] while 3-amino-2-ketopiperidine-6-carboxylic acid stabilizes β-turns of peptides.[10] All these facts focused our attention on 2,5-diketopiperidines as conformationally restricted analogues of ketomethylene dipeptides.

In a previous communication,[11] we have reported the synthesis of the methyl 6-aralkyl-2,5-diketopiperidine-3-carboxylates **3a** and **4ab**. We now describe the synthesis of the 3-substituted derivatives **11ab-16ab** in which the new substituent at C-3 of the diketopiperidine ring is the side chain of the second amino acid residue (Phe, Asp, Ala). The corresponding 2,5-diketopiperidine-3-carboxylic acids could be incorporated into higher peptides or could provide the cyclic ketomethylene dipeptide analogues. In order to demonstrate this latter possibility, the syntheses of *cycle*[Trpψ($COCH_2$)Gly] (**19**) and cycle[Pheψ($COCH_2$)-ξ-Phe] (**20ab**) are also described. With the aim of determining the absolute configuration at C-3 of the diketopiperidines here reported, a conformational study of compounds **3a, 4ab** and their 3-substituted analogues is also included.

RESULTS AND DISCUSSION

As shown in Scheme 1, the 3-disubstituted-2,5-diketopiperidine derivatives **11ab**-**16ab** were prepared by two alternative routes, using the γ-ketodiesters **1**[12] and **2**[13] as common starting compounds. In the first synthetic route, the appropriate amino acid side chain at C-3 position was introduced by direct alkylation of the 2,5-diketopiperidine-3-carboxylate derivatives **3a** and **4ab**,[11] following Methods A and B. Thus, alkylation of **3a** or **4ab** with benzyl bromide and ethyl bromoacetate in 1,2-dimethoxyethane, using sodium methoxide as base (Method A) afforded the 3-disubstituted derivatives **11ab** or **12ab**, and **13ab** or **14ab**, respectively (Table 1). A similar alkylation using methyl iodide resulted in poor yield of compounds **16ab**, while formation of the 6-benzyl analogues **15ab** was not observed. However, 30-40% yield of these 3-methyl substituted derivatives were obtained, after six days, by alkylation with methyl iodide in a two phase reaction using NaOH as base and tetrabutylhydrogen sulfate as phase-transfer catalyst[14,15] (Method B). Under these conditions, the starting 3-monosubstituted compounds were recovered in 25-30%, while hydrolysis of the methyl ester took place when prolonged reaction times were used.



5,11ab : Ar = Ph, R^1 = CH_2Ph
6,12ab : Ar = indole, R^1=CH_2Ph
7,13ab : Ar = Ph, R^1 = CH_2COOEt
8,14ab : Ar = indole, R^1=CH_2COOEt
9,15ab : Ar = Ph, R^1 = CH_3
10,16ab : Ar = indole, R^1=CH_3

Scheme 1 . Method A : NaOMe/R^1CH_2X; Method B : $HSO_4N^tBu_4$/KOH/IMe; Method C : H_2/Pd-C

In order to improve the yield of the desired 3-disubstituted derivatives **11ab-16ab**, the reverse sequence route involving alkylation of ketodiesters **1** and **2** and subsequent cyclization was investigated. Thus, reaction of **1** and **2** with benzyl bromide, ethyl bromoacetate and methyl iodide in the presence of sodium methoxide afforded the disubstituted malonate derivatives **5-10** in high yield (> 82%). In a similar way to that described for the preparation of **3a** and **4ab**,[11] removal of the Z group and lactamization took place in one pot reaction when the ketodiesters **5-16** were hydrogenated at room temperature and 25 psi, using Pd/C as catalyst (Method C). Comparing both synthetic routes in each other starting from **1** and **2**, that involving catalytic hydrogenation and subsequent cyclization of the disubstituted malonates **5-10** (Method C) resulted in higher overall yields (50-60%) than direct alkylation of the diketopiperidine ring, previously formed, (17-34%, Method A and B).

Table 1.—Characterization data of compounds **11ab-16ab**

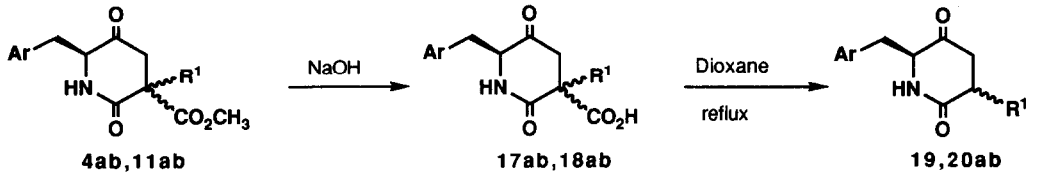
Compd.	Yield (%)	Chromatography EtOAc:hexane	Diastereomeric ratio **a/b**[d]	Mol. Formula	Found (Required) C	H	N	MS (M^+)
11ab	57[a]	1:3	2:1	$C_{21}H_{21}NO_4.H_2O$	68.02	6.16	3.95	351
	68[c]		2:1		(68.27)	(6.28)	(3.79)	
12ab	17[a]	1:1	2:1	$C_{23}H_{22}N_2O_4$	70.52	5.90	6.89	390
	67[c]		2:1		(70.75)	(5.68)	(7.17)	
13ab	54[a]	1:2	3:1	$C_{18}H_{21}NO_6$	62.01	5.97	4.20	347
	50[c]		3:1		(62.24)	(6.09)	(4.03)	
14ab	55[a]	1:1	2:1	$C_{20}H_{22}N_2O_6$	62.08	6.00	7.50	386
	67[c]		2:1		(62.17)	(5.74)	(7.25)	
15ab	31[b]	1:2	2:1	$C_{15}H_{17}NO_4.{}^1/_2H_2O$	63.17	6.34	4.97	275
	70[c]		2:1		(63.37)	(6.38)	(4.93)	
16ab	16[a]	2:1	2:1	$C_{17}H_{18}N_2O_4$	64.79	6.08	8.88	314
	41[b]		2:1		(64.96)	(5.77)	(8.91)	
	61[c]		2:1					

[a] From method A. [b] From method B. [c] From method C. [d] Estimated by ^{1}H-NMR.

Independently of the Method, compounds **11ab**, **12ab**, **14ab-16ab** were obtained as 2:1 mixtures of diastereoisomers while a 3:1 ratio was obtained for **13ab** (Table 1), as determined by ^{1}H-NMR spectroscopy. At this point, it is interesting to note that the degree of stereoselectivity found in the lactamization of **1** and **2** to the 2,5-diketopiperidine-3-carboxylates **3a** and **4ab** was strongly dependent on the starting amino acid derivative.[11] Nevertheless in the case of the disubstituted malonates **5-10**,

neither this starting derivatives nor the R^1 substituent influenced the stereoselectivity of the lactamization. Similarly, neither the alkylating agent nor the nature of the starting 2,5-diketopiperidine (Ar and stereochemistry at C-3) affected, in general, the stereoselectivity of the alkylation. In all cases, the 3-substituted-6-aralkyl-2,5-diketopiperidine-3-carboxylates **11a-16a** having a *cis* disposition between the 3-alkyl substituent and the 6-aralkyl group were obtained as the major diastereoisomers.

Finally, compounds **4ab** and **11ab** were saponified to provide the corresponding 3-carboxylic acid derivatives **17ab** and **18ab**, which upon decarboxylation, led to the cyclic ketomethylene dipeptides *cycle*[Trpψ(COCH$_2$)Gly] (**19**) and *cycle*[Pheψ(COCH$_2$)-ξ-Phe] (**20ab**), respectively (Scheme 2). Although there is no reason why the decarboxylation step should be stereoselective, compound **20ab** was obtained as a 2:1 mixture of diastereoisomers.



4ab,11ab **17ab,18ab** **19,20ab**

17ab, 19 : Ar=indole, R^1= H
18ab,20ab : Ar=Ph, R^1=CH_2Ph

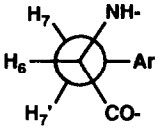
Scheme 2

The absolute configuration at C-3 of all the 2,5-diketopiperidines here reported was deduced from a conformational study by ^{1}H-RMN of the 3-monosubstituted derivatives **3a** and **4ab** and the 3-disubstituted analogues **11ab, 12ab, 13a, 14ab, 15ab** and **16ab**.

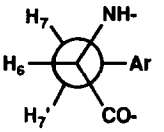
It is known that in 2,5-diketopiperazines derived from one aromatic amino acid, the preferred conformation is one in which the arylmethylene side chain folds over the diketopiperazine ring (Conformation A).[16-18] In order to study whether the diketopiperidine analogues **3a**, **4ab** and their C-3 alkyl derivatives also show this preference, the percentage of the three staggered conformers around the C_6-C_7 bond (Conformations A, B and C) were calculated in $CDCl_3$ and DMSO.[19] Since it was not possible to determine experimentally the coupling constants for each rotamer, they were calculated using the generalized Karplus equation parametrized for three substituents (Table 2).[19] As indicated in the Table, the conformation equilibrium is clearly dependent on the solvent. Thus, the 6-aralkyl side chain adopts predominantly the folded conformation A in DMSO while in $CDCl_3$ one of the unfolded forms, B or C, is the most populated. According to this, and due to the aromatic ring current,[20] the H-3 proton in the 3-monosubstituted compounds **3a** and **4a** is more shielded than in

compounds **4b** (Table 3) indicating that this proton in diketopiperidines **3a** and **4a** is *cis* to the 6-aralkyl moiety. The lower shielding effect observed for the H-3 in the *cis* diastereoisomers in $CDCl_3$ ($\Delta\delta_{DMSO}$=0.87 ppm, $\Delta\delta_{CDCl_3}$=0.21 ppm) is in agreement with the lower percentage of the folded conformation in this solvent. As the absolute configuration at C-6 is *S*, since the synthesis started with L-phenylalanine and L-tryptophan derivatives, the absolute configuration at C-3 is *S* in compounds **3a** and **4a**, and *R* in the diastereoisomer **4b**.

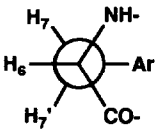
Table 2.—Calculated percentages of rotameric states around C_6-C_7 bond for the 2,5-diketopiperidines **3, 4, 11-16**[a]



A



B



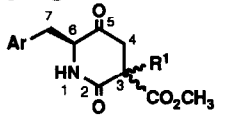
C

Comp.	Solvent	% A_I	%B_I	% C_I	%A_{II}	%B_{II}	% C_{II}
3a	DMSO	51	20	29	56	26	22
4a	DMSO	57	17	26	53	23	24
4a	$CDCl_3$	25	2	73	30	70	0
4b	DMSO	50	18	32	50	30	20
4b	$CDCl_3$	18	7	75	23	74	3
11a	DMSO	67	11	22	67	18	15
11a	$CDCl_3$	12	8	80	18	79	3
11b	DMSO	62	13	25	63	20	17
11b	$CDCl_3$	12	2	86	14	84	2
12a	DMSO	60	18	22	60	18	22
12a	$CDCl_3$	12	5	83	18	82	0
12b	DMSO	44	14	42	46	40	14
13a	$CDCl_3$	7	8	85	14	85	1
14a	DMSO	59	24	17	57	15	28
14a	$CDCl_3$	5	8	87	11	87	2
15a	DMSO	60	11	29	61	25	14
15b	DMSO	52	16	32	53	29	18
16a	DMSO	52	16	32	55	26	19
16a	$CDCl_3$	8	9	83	15	82	3
16b	DMSO	47	21	32	47	30	23

J_A^{60}=3.39; J_A^{300}=2.65; J_B^{60}=3.62; J_B^{180}=11.8; J_C^{180}=11.8; J_C^{300}=2.87.

[a] Because the H-7 and H-7' resonances can not be assigned individually, the percentages of rotamers A, B and C were calculated for the two possible solutions (I and II).

Table 3.—Significant ^{1}H-NMR chemical shifts and coupling constants of 2,5-diketopiperidine derivatives **3, 4, 11-16** (300 MHz)



Compd.	Ar	R^1	Solvent	δ (ppm)[a] 1-H	3-H	4-H	4'-H	6-H	7-H	7'-H	CO_2CH_3	R^1	Coupling constants (Hz) $J_{1,6}$	$J_{6,7}$	$J_{6,7'}$
3a	Ph	H	DMSO-d_6	8.26	3.01	2.79	2.31	4.15	3.10	2.89	3.61	—	2.0	4.9	5.5
4a	Indole	H	DMSO-d_6	8.22	3.03	2.76	2.30	4.12	3.27	3.03	3.60	—	2.0	4.7	5.2
4a	Indole	H	$CDCl_3$	6.04	3.52	2.92	2.68	4.27	3.45	2.98	3.77	—	0.0	3.2	9.3
4b	Indole	H	DMSO-d_6	7.99	3.90	2.64	2.39	4.19	3.12	3.02	3.59	—	0.0	4.7	5.8
4b	Indole	H	$CDCl_3$	5.97	3.73	3.05	2.88	4.16	3.58	2.92	3.81	—	0.9	3.6	9.6
11a	Ph	CH_2Ph	DMSO-d_6	8.32	—	2.38	1.77	4.11	2.94	2.81	3.65	3.22[b] 3.06[b]	0.0	4.2	4.8
11a	Ph	CH_2Ph	$CDCl_3$	5.74	—	2.78	2.34	4.09	3.25	2.55	3.77	3.46[b] 3.26[b]	0.0	3.7	10.0
11b	Ph	CH_2Ph	DMSO-d_6	8.19	—	2.70	2.40	3.82	2.81	2.65	3.47	3.18[b] 3.08[b]	2.4	4.4	5.0
11b	Ph	CH_2Ph	$CDCl_3$	5.70	—	2.92	2.67	3.57	3.34	2.59	3.83	3.60[b] 3.16[b]	0.8	3.1	10.5
12a	Indole	CH_2Ph	DMSO-d_6	8.15	—	2.34	1.99	4.06	3.12	2.98	3.65	3.12[b] 3.01[b]	0.0	4.8	4.8
12a	Indole	CH_2Ph	$CDCl_3$	5.79	—	2.73	2.33	4.09	3.36	2.70	3.67	3.36[b] 3.21[b]	0.0	3.4	10.3
12b	Indole	CH_2Ph	DMSO-d_6	8.09	—	2.68	2.43	3.87	3.00	2.81	3.50	3.21[b] 3.12[b]	2.6	4.3	6.7
12b	Indole	CH_2Ph	$CDCl_3$	5.79	—	2.89	2.62	3.58	3.42	2.70	3.74	3.52[b] 3.09[b]	c	3.1	c
13a	Ph	CH_2CO_2Et	$CDCl_3$	5.87	—	3.04	2.69	4.23	3.37	2.74	3.74	3.12[b] 3.00[b]	0.0	3.6	10.5
13b	Ph	CH_2CO_2Et	$CDCl_3$	5.86	—	3.28	3.00	4.14	3.52	2.74	3.79	3.18[b] 2.97[b]	c	3.2	c
14a	Indole	CH_2CO_2Et	DMSO-d_6	8.16	—	2.75	2.47	4.16	3.22	3.06	3.61	2.97[b] 2.61[b]	0.0	5.3	4.5
14a	Indole	CH_2CO_2Et	$CDCl_3$	5.91	—	3.17	3.11	4.31	3.54	2.92	3.71	3.03[b]	0.0	3.6	10.7
14b	Indole	CH_2CO_2Et	DMSO-d_6	8.7	—	3.06	2.76	4.16	3.18	2.93	3.51	3.06[b] 2.81[b]	c	5.3	7.4
14b	Indole	CH_2CO_2Et	$CDCl_3$	5.93	—	3.29	3.04	4.24	3.69	2.93	3.80	3.04[b]	1.0	3.4	c
15a	Ph	CH_3	DMSO-d_6	8.21	—	2.77	2.01	4.25	3.07	2.94	3.62	1.03	0.0	4.2	5.4
15b	Ph	CH_3	DMSO-d_6	8.11	—	2.68	2.54	4.25	3.01	2.85	3.56	1.30	1.2	4.6	5.7
16a	Indole	CH_3	DMSO-d_6	8.08	—	2.69	2.07	4.18	3.20	3.11	3.61	1.04	0.0	4.6	5.5
16a	Indole	CH_3	$CDCl_3$	5.91	—	2.95	2.53	4.26	3.50	2.91	3.71	1.49	0.0	3.7	10.3
16b	Indole	CH_3	DMSO-d_6	8.02	—	2.60		4.18	3.13	3.02	3.52	1.29	1.9	5.0	5.8
16b	Indole	CH_3	$CDCl_3$	5.91	—	3.12	2.69	4.15	3.58	2.92	3.79	1.52	c	3.3	c

[a] From the spectra of the diastereoisomeric mixtures. [b] 3-CH_2 protons. [c] They can not be exactly measured.

Upfield shifts, specially marked in DMSO, were also observed when the proton resonances of the 3-methyl group of compounds **15a** and **16a** were compared with those of the corresponding minor diastereoisomers **15b** and **16b** (Table 3). Therefore, the major isomers **15a** and **16a** were assigned as 3*S* and compounds **15b** and **16b** as 3*R*. In the case of the 3-ethoxycarbonylmethyl substituted analogues **13ab** and **14ab**, the proton resonances of the 3-CH_2 group could not be exactly determined from their ^{1}H-NMR spectra. For this reason stereochemical assignment of these compounds was made by correlation between their ^{1}H-NMR spectra and those of the corresponding 3-methyl analogues **15ab** and **16ab**.[21]

A shielding effect was also observed for the H-6 proton in the 6-aralkyl-3-benzyl-3-carboxylate substituted derivatives **11b** and **12b** when compared to the same proton in the diastereoisomers **11a** and **12a**, respectively (Table 3). This effect indicates that compounds **11b** and **12b** exist preferentially in the conformations containing the 6-H proton and the 3-benzyl group in *cis* disposition and, therefore, the 3*R*,6*S* configuration was assigned. However, in this case, the shielding effect is higher in $CDCl_3$ than in DMSO ($\Delta\delta_{CDCl_3}$ ~0.5 ppm, $\Delta\delta_{DMSO}$ ~0.2 ppm). This fact seems to indicate that the contribution of a folded conformation of the 3-benzyl group in compounds **11ab** and **12ab** is more important in $CDCl_3$ than in DMSO, while the 6-aralkyl moiety preferentially adopts this type of conformation in DMSO.

Differences in the ^{13}C-NMR spectra of diastereoisomeric 3,6-disubstituted diketopiperidines **11ab-16ab** were also found (Table 4). Thus, major isomers **11a-16a**, with a *cis* disposition between the 3- and 6-alkyl substituents, show upfield shieldings for C-4, C-6, C-7 and CH_2-3 carbons when compared to the corresponding diastereoisomers **11b-16b**. A downfield shift of about 1 ppm for the C-5 ketone carbon in compounds **11a-16a** is also observed.

Table 4.—Significant ^{13}C-NMR chemical shifts of compounds **11-16** ($CDCl_3$, 75 MHz)[a]

Compd.	C-2	C-3	C-4	C-5	C-6	C-7	3-CH_2[b]
11a	170.34	54.85	42.80	203.25	61.39	38.36	38.93
11b	171.00	54.77	43.57	202.06	62.49	39.30	39.74
12a	170.36	54.98	42.72	203.74	60.01	28.60	39.05
12b	171.20	54.91	43.60	202.65	61.19	29.42	39.84
14a	170.49	52.01	43.02	203.21	60.27	28.97	37.67
14b	170.42	51.57	43.98	201.52	61.86	29.15	37.82
15a	171.24	49.96	46.04	203.26	61.79	38.36	20.41
15b	171.24	49.71	46.28	202.43	62.83	39.31	20.65
16a	171.31	50.10	45.88	203.79	60.48	28.67	20.49
16b	171.31	49.79	46.27	202.90	61.55	29.43	20.65

[a] Compound **13ab** decomposed in the time needed for registered the ^{13}C spectrum.
[b] CH_3 for compounds **15** and **16**.

Finally, as with the 3-carboxylates **4ab** and the 3-benzyl-3-carboxylate derivatives **11ab** and **12ab**, the configurational assignment at C-3 of the diastereomeric cyclic ketomethylene dipeptides **20a** and **20b** was made on the basis of the chemical shift differences in H-3 and H-6 protons between both diastereoisomers. This criterion allowed us to establish a 3*R* configuration for **20a** and a 3S configuration for **20b**.

In conclusion, 2,5-diketopiperidines derived from amino acids [*cycle*[Xaaψ($COCH_2$)Yaa]] are accessible compounds from the corresponding 3-carboxylic acid substituted analogues. These analogues are easily synthesized, in one pot reaction, by catalytic hydrogenation and subsequent lactamization of conveniently substituted 4-ketodiesters, prepared from Z-protected amino acid halomethyl ketones and dimethyl malonate. *Cycle*[Xaaψ($COCH_2$)Yaa] derivatives (Xaa=aromatic amino acid) seem to adopt a preferred conformation in DMSO solution in which the aralkyl side chain of Xaa folds over the 2,5-diketopiperidine ring. This conformational preference can be used to determine the absolute configuration at the new chiral centre.

EXPERIMENTAL

^{1}H-NMR spectra were recorded with a Varian EM-390 or a Varian XL-300 spectrometers operating at 90 or 300 MHz, respectively, using Me_4Si as internal standard. ^{13}C-NMR spectra were recorded with a XL-300 (75 MHz). Mass spectra were recorded with a Vacuum Generators VG 12-250 instrument. Elemental analysis were obtained on a CHN-O-RAPID instrument.

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 and Ehrlich's reagent. Compounds **1**, **2**, **3a**, **4ab** and **9** were prepared as described. [11-13]

Alkylation of compounds 1 and 2 with benzyl bromide, ethyl bromoacetate and methyl iodide

A stirred solution of the 4-ketodiesters **1** or **2** (3 mmol) and freshly prepared soldium methoxide (3.3 mmol) in dimethoxyethane (20 mL) was treated with the corresponding alkyl halide (9 mmol). Stirring was continued overnight at room temperature, the solvent was evaporated, the residue was extracted with EtOAc and washed with water. The organic extract was dried (Na_2SO_4) and evaporated to leave a residue which was purified as specified in each case.

Methyl 2-benzyl-5(S)-benzyloxycarbonylamino-2-methoxycarbonyl-6-phenyl-4-oxohexanoate (5)

Chromatographed on a silica gel column using EtOAc-hexane (1:4). 85% yield: syrup. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 7.3-6.8 (m, 10H, C_6H_5 and Z C_6H_5), 5.02 (d, 1H, 5-

NH), 5.0 (s, 2H, Z CH_2), 4.5 (m, 1H, 5-H), 3.6 (s, 6H, CO_2CH_3), 3.3 (m, 2H, 2-CH_2), 2.9 (m, 4H, 3-H and 6-H). Anal. Calcd. for $C_{30}H_{31}NO_7$: C 69.62, H 6.04, N 2.71. Found: C 69.71, H 5.95, N 2.56.

Methyl 2-benzyl-5(S)-benzyloxycarbonylamino-6-(indole-3-yl)-2-methoxycarbonyl-4-oxohexanoate (6)

This compound was purified on a silica gel column using EtOAc-hexane (1:3). 82 % yield: syrup. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 10.87 (s, 1H, NH^i), 7.88 (d, 1H, 5-NH, J=8.1), 7.53-6.87 (m, 10H, indole and Z C_6H_5), 5.04 (d, 1H, Z CH_2, J=12.9), 4.98 (d, 1H, 5-NH), 4.31 (m, 1H, 5-H), 3,61 (s, 6H, CO_2CH_3), 3.22 (s, 2H, 2-CH_2), 3.10 (m, 2H, 3-H and 6-H), 2.,98 (d, 1H, 3'-H, J=19.2), 2.89 (dd, 1H, 6'-H, J=14.7 and 9.3). Anal. Calcd. for $C_{32}H_{32}N_2O_7$: C 69.05, H 5.79, N 5.03. Found: C 68.89, H 5.77, N 5.22.

Ethyl 6(S)-benzyloxycarbonylamino-3,3-dimethoxycarbonyl-7-phenyl-5-oxoheptanoate (7)

This compound was purified on a silica gel column using EtOAc-hexane (1:3). 82% yield: syrup. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 7.3-7.0 (m, 10H, C_6H_5 and Z C_6H_5), 5.2 (d, 1H, 6-NH), 5.0 (s, 2H, Z CH_2), 4.5 (m, 1H, 6-H), 4.0 (q, 2H, OCH_2CH_3), 3.6 (s, 6H, CO_2CH_3), 3.3 (s, 2H, 2-H), 3.0 (m, 4H, 4-H and 7-H), 1.1 (t, 3H, OCH_2CH_3). Anal. Calcd. for $C_{27}H_{31}NO_9$: C 63.15, H 6.08, N 2.73. Found: C 63.08, H 6.27, N 2.81.

Ethyl 6(S)-benzyloxycarbonylamino-3,3-dimethoxycarbonyl-7-(indole-3-yl)-5-oxoheptanoate (8)

Purified on a silica gel column using EtOAc-hexane (1:3). 89% yield: foam. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 8.2 (s, 1H, NH^i), 7.6-6.9 (m, 10H, indole and Z C_6H_5), 5.4 (d, 1H, 6-NH), 5.0 (s, 2H, Z CH_2), 4.6 (m, 1H, 6-H), 4.0 (q, 2H, OCH_2CH_3), 3.6 (s, 6H, CO_2CH_3), 3.3 (s, 2H, 2-H), 3.1 (m, 2H, 7-H), 3.0 (s, 2H, 4-H), 1.2 (t, 3H, OCH_2CH_3). Anal. Calcd. for $C_{29}H_{32}N_2O_9$: C 63.04, H 5.84, N 5.07. Found: C 62.97, H 5.77, N 4.84.

Methyl 5(S)-benzyloxycarbonylamino-6-(indole-3-yl)-2-methoxycarbonyl-2-methyl-4-oxohexanoate (10)

This compound was purified on a silica gel column using EtOAc-hexane (1:2). 88% yield: foam. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 10.86 (s, 1H, NH^i), 7.80 (d, 1H, 5-NH, J=7.8) 7.56-6.96 (m, 10H, indole and Z C_6H_5), 5.03 (d, 1H, Z CH_2, J=12.7), 4.96 (d, 1H, Z CH_2), 4.30 (m, 1H, 5-H), 3,60 (s, 6H, CO_2CH_3), 3.23 (d, 1H, 3-H, J=18.4), 3.10 (dd, 1H, H-6, J=14.3 and 5.7), 3.08 (d, 1H, 3'-H), 2.89 (dd, 1H, 6'-H, J=14.3 and 9.3), 1.31 (s, 3H, CH_3). Anal. Calcd. for $C_{26}H_{28}N_2O_7$: C 64.99, H 5.87, N 5.83. Found: C 64.87, H 5.91, N 5.55.

Synthesis of methyl 3-substituted-6-aralkyl-2,5-diketopiperidine-3-carboxylates 11ab-16ab

Method A: Alkylation of methyl 6-aralkyl-2,5-diketopiperidine-3-carboxylates 3a and 4ab using sodium methoxide as base

To a solution of the 2,5-diketopiperidine derivatives **3a** or **4ab** (1.5 mmol) and sodium methoxide (1.6 mmol) in dimethoxyethane (10 mL), the corresponding alkyl halide (4.5 mmol) was added. After 6-7 h of stirring at room temperature, the solvent was evaporated, the residue extracted with EtOAc and washed with H_2O. The organic layer was dried over Na_2SO_4, evaporated to dryness and the products purified as specified in each case (Table 1).

Method B: Alkylation of 3a and 4ab with methyl iodide in phase-transfer conditions

To a solution of compound **3a** or **4ab** (1 mmol) and methyliodide (8 mmol) in CH_2Cl_2 (1 mL), 2N NaOH (2 mmol) and tetrabutyl hydrogen sulfate (1 mmol) were added. After stirring at room temperature for 6 days, H_2O (5 mL) and CH_2Cl_2 (50 mL) were added. The separated organic layer was dried over Na_2SO_4 and evaporated to give **15ab** or **16ab** which were purified as indicated in Table 1.

Method C: Cyclization of the 4-ketodiesters 5-10

A solution of the corresponding 4-ketodiester (2 mmol) in MeOH (200 mL) was hydrogenated at 30 psi and room temperature, in the presence of 10% Pd/C for 7 days. The catalyst was removed by filtration, and the filtrate was evaporated to dryness to leave a residue which was purified on a silica gel column using the solvent systems specified in each case (Table 1).

Characterization data of all products obtained by these methods are recorded in Tables 1, 3 and 4.

6(S)-(Indole-3-yl)methyl-2,5-diketopiperidine-3(ξ)-carboxylate (17ab)

A solution of compound **4ab** (0.6 g, 2 mmol) in MeOH (40 mL) was treated with 2N NaOH (1 mL, 2 mmol) and the mixture was stirred at room temperature for 3 h. After evaporation of the MeOH the remaining aqueous mixture was diluted with H_2O (20 mL), acidified with 1N HCl to pH 3, and extracted with EtOAc (150 mL). The extract was dried (Na_2SO_4) and evaporated. The residue was purified on a silica gel column using CH_2Cl_2-MeOH (8:1) containing 0.1% AcOH, to give **17ab** as a solid (0.24 g, 42%). ^{1}H-NMR (300 MHz, DMSO-d_6): (3S,6S) isomer: δ 10.93 (s, 1H, NH^i), 7.50-6.88 (m, 5H, indole), 4.07 (m, 1H, 6-H), 3.20 (dd, 1H, 6-CH_2, J-14.6 and 5.0), 3.02 (m, 2H, 3-H and 6-CH_2), 2.61 (dd, 1H, 4-H, J=16.4 and 7.0), 2.21 (dd, 1H, 4'-H, J=16.4 and 5.5). (3*R*,6*S*) isomer: δ 10.75 (s, 1H, NH^i), 7.50-6.88 (m, 5H, indole), 4.15 (m, 1H, 6-H),

3.72 (dd, 1H, 3-H, J=10.4 and 5.6), 3.13 (m, 1H, 6-CH_2), 3.02 (m, 1H, 6-CH_2), 2.65 (dd, 1H, 4-H, J=16.6 and 5.6), 2.41 (dd, 1H, 4'-H, J=16.6 and 10.4). Anal. Calcd. for $C_{15}H_{14}N_2O_4.H_2O$: C 59.21, H 5.30, N 9.20. Found: C 58.95, H 5.51, N 9.07.

Cycle[L-Trpψ(COCH$_2$)Gly] (19)

Compound **17ab** (0.2 g, 0.7 mmol) was refluxed in dioxane (20 mL) for 2.5 h. After evaporation to dryness the residue was purified on a silica gel column using $CHCl_3$-MeOH (10:1) to give the product (0.07 g, 41%) as a foam. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 10.92 (s, 1H, NH^1), 7.73 (d, 1H, 1-H, J=2.1), 7.48-6.93 (m, 5H, indole), 4.07 (m, 1H, 6-H), 3.19 (dd, 1H, 6-CH_2, J-15.9 and 5.3), 3.02 (dd, 1H, 6-CH_2, J=15.9 and 5.1), 2.51 (m, 1H, 3-H),2.25 (m, 1H, 4-H), 2.11 (m, 1H, 4'-H), 1.78 (m, 1H, 3'-H). MS: 242 (M^+, 3.5), 130 (C_9H_8N, 100). Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C 69.41, H 5.82, N 11.56. Found: C 69.35, H 5.99, N 11.50.

Cycle[L-Pheψ(COCH$_2$)-ξ-Phe] (20ab)

A solution of compound **11ab** (0.35 g, 1 mmol) in MeOH (20 mL) was treated with 6N NaOH (0.16 mL, 1 mmol) and stirred under argon atmosphere for 3 h. After evaporation of the solvents, H_2O (30 mL) was added, the aqueous solution was acidified with 1N HCl to pH 3 and extracted with EtOAc (100 mL). The organic layer was dried (Na_2SO_4) and evaporated to give crude **18ab**, which was refluxed in dioxane (25 mL) for 5 h. The residue, obtained after evaporation of the solvent, was purified on a silica gel column using EtOAc-hexane (1:2) to provide **20ab** as a solid (0.18 g, 63% from **9ab**). ^{1}H-NMR (300 MHz, DMSO-d_6): (3*R*,6*S*) isomer **20a**: δ 7.87 (s, 1H, 1-H), 7.25-6.96 (m, 10H, C_6H_5), 4.26 (m, 1H, 6-H), 2.96-2.80 (m, 4H, 3-H, 6-CH_2 and 3-CH_2), 2.28 (dd, 1H, 4-H, J=16.6 and 5.4), 2.10 (m, 1H, 3-CH_2), 1.85 (m, 1H, 4'-H. (3S,6S) Isomer **20b**: δ 7.92 (d, 1H, 1-H, J=2.0), 7.25-6.96 (m, 10H, C_6H_5), 4.04 (m, 1H, 6-H), 308 (dd, 1H, 6-CH_2, J=13.4 and 4.9), 2.96-2.80 (m, 2H, 3-CH_2 and 6-CH_2), 2.49 (m, 1H, 3-H), 2.41 (dd, 1H, 3-CH_2, J=14.2 and 5.0), 2.32 (m, 1H, 4-H), 1.94 (dd, 1H, 4'-H, J=16.3 and 4.2). MS: 293 (M^+, 45), 202 (M^+, 91, 5.4), 91 (Bn, 100). Anal. Calcd. for $C_{19}H_{19}NO_2$: C 77.79, H 6.53, N 4.77. Found: C 77.60, H 6.70, N 4.53.

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21 Taking into account that the ethoxycarbonylmethyl group has preference over the $COCH_2$ branch of the ring, the main diastereoisomers **13a** and **14a** have 3*R* configuration.