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Stereoselective Reductive Amination of β-Keto Esters Derived from Dipeptides. Stereochemical and Mechanistic Studies on the Formation of 5-Carboxymethyl-2-Oxopiperazine Derivatives

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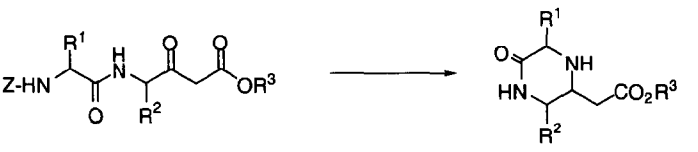
Abstract. The stereoselective generation of 3,5-disubstituted and 3,5,6-trisubstituted 2-oxopiperazine derivatives can be accomplished by intramolecular reductive amination of β-keto esters derived from Z-Xaa-Gly-OH and Z-Xaa-Yaa-OH dipeptides, respectively. Differences in the stereoselectivity between the use of $NaBH_3CN$ and hydrogen as reducing agents are due to the reduction of different intermediates, as deduced from experiments of isotopic labelling with deuterium.

Keywords: Peptide mimetics, piperazinones, β-keto esters

The growing use of small organic molecules as non-peptide scaffolds in the search for peptidomimetics has created a demand for new methodology for the synthesis of these molecules.[1-3] Ideally, approaches for making conformationally constrained scaffolds should overcome two important challenges: the appendage of amino acid side chains onto the heterocycle and the stereocontrolled generation of the new chiral centers.[4] Among the variety of lactams which have been used successfully as scaffolds,[5-8] chiral piperidones, pyrrolidinones and piperazinones have emerged as preferred structures for the development of low molecular receptor ligands.[8] Moreover, these templates and structurally related bicyclic analogues have been shown to be effective structural tools for probing the active conformation of bioactive peptides and enzyme inhibitors.[9,10]

Our current interest in templates onto which pharmacologically relevant groups can be appended, led us to describe the preparation of 3,5- and 3,6-disubstituted 2-oxopiperazines from cyanomethyleneamino and methyleneamino pseudopeptides, respectively.[11] Due to the known possibility of obtaining high receptor binding affinity with three conveniently oriented binding groups,[12] we have now focused our attention on the 2-oxopiperazine derivatives **1** able to carry three amino acid side chains. In this sense, β-keto esters derived from dipeptides were envisaged as appropriate precursors to the corresponding 3,5,6-trisubstituted derivatives. Thus, the keto ester moiety could serve the dual purpose of allowing intramolecular cyclization, via reductive amination, and providing the Asp side chain at C-5 position of the heterocyclic ring. In addition to that, the versatility of the carboxylate group could supply opportunities for diversification.



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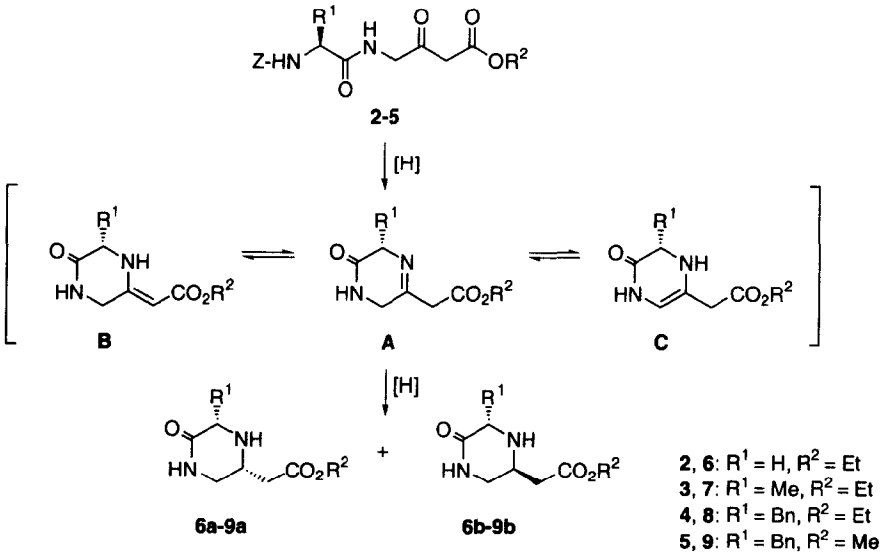
To explore the suitability of the proposed synthetic route, we first investigated the synthesis of 3,5-disubstituted piperazines (**1**, R^2 = H), derived from Z-Xaa-Gly-OH. The stereochemical control found by application of two different reducing agents will be discussed and an explanation will be given in terms of reaction mechanism. The preparation of a 3,5,6-trisubstituted piperazine (**1**, $R^2 \neq$ H) was also undertaken.

RESULTS AND DISCUSSION

According to the method reported for the preparation of β-keto esters derived from amino acids,[13] starting compounds **2-5** were synthesized by reaction of the corresponding dipeptide with carbonyldiimidazole followed by the treatment of the generated imidazolide with monoethyl or monomethyl malonate magnesium salt. The desired 3,5-disubstituted piperazines **6-9** were formed in high yield when the corresponding β-ketoesters **2-5** were hydrogenated at 45°C and 45 psi of pressure, using Pd-C as catalyst (Scheme 1, Table 1). Using this procedure, the removal of the Z protecting group and the reductive amination take place in a one-pot reaction. Although in slightly lower yield (Table 1), the piperazine ring is also formed in two steps involving removal of Z group, by catalytic hydrogenation, and reduction of the resulting intermediate(s) with $NaBH_3CN$ in the presence of $ZnCl_2$.

The absolute configuration at C-5 was assigned by means of NOE experiments. Thus, isomers with *R* configuration at this position showed a weak (2-3%), but significant, NOE between H-3 and H-5 , indicating that these hydrogens are located on the same side of the heterocyclic ring. Similarly, the observed NOE (3-4%) between H-5 and 3-CH_3 or 3-CH_2 in the 5*S* diastereoisomers revealed a *cis*-relationship between these groups.



Scheme 1

Concerning the stereochemical course of the reaction, it can be noted that diastereoisomers with *R* configuration at C-5 were always obtained as major products. This result can be rationalized by reduction of any of the reaction intermediates (**A**, **B** or **C**) by attack on the less hindered side of the molecule and,

therefore, on the opposite side to the R^1 substituent. Accordingly, better stereoselectivities were found for the Phe derivatives **8** and **9** (Table 1, entries 5 to 7), for which R^1 is a benzyl group, than for the Ala analogue **7** (R^1 = Me, entries 3 and 4). Although the conjugated enamine **B** was the only intermediate that can be isolated and characterized, the participation of imine **A** and enamine **C** in the reductive amination process could not be ruled out. In fact, reduction with $NaBH_3CN/ZnCl_2$ led to higher diastereoisomeric excesses than catalytic hydrogenation (Table 1), indicating that the reduction proceeds either through different intermediates in the two methods or that the extent of reduction of each intermediate is different in both reactions.

Table 1.– 3,5–Disubstituted-2-oxopiperazines from β-Ketoesters Derived from Z-Xaa-Gly-OH Dipeptides

Entry	Starting Compd.	R^1	R^2	Method[a]	Solvent	Final Compd.	Yield (%)	**a/b** ratio
1	**2**	H	Et	A	EtOH	**6**	96	–
2	**2**	H	Et	B	EtOH	**6**	20[b]	–
3	**3**	Me	Et	A	EtOH	**7ab**	89	1.7:1
4	**3**	Me	Et	B	EtOH	**7ab**	80	3.9:1
5	**4**	Bn	Et	A	EtOH	**8ab**	91	3.2:1
6	**4**	Bn	Et	B	EtOH	**8ab**	77	5.3:1
7	**5**	Bn	Me	A	MeOH	**9ab**	97	3.5:1
8	**5**	Bn	Me	A	MeOD	**9ab**	90	3.5:1
9	**5**	Bn	Me	B	MeOD	**9ab**	75	5.6:1
10	**5**	Bn	Me	B[c]	MeOH	**9ab**	64	5.7:1

[a] Method A: H_2/Pd-C, 45 psi, 45°C, 48-72 h; Method B: a)H_2/Pd-C, 15 psi, 25°C, 2 h; b) $NaBH_3CN/ZnCl_2$, 25°C, 3 h. [b] This low yield is due to the difficulties found for the extraction of compound **6** from H_2O. [c] Reaction with $NaBD_3CN$

In order to clarify which intermediate(s) is(are) involved in each reducing method, the formation of compounds **9** was performed in MeOD following methods A and B (Table 1, entries 8 and 9).[14] First of all, intermediate **B** was generated by hydrogenolysis of the Z group under mild conditions (MeOD, 15 psi, r.t., 2 h). Then, this intermediate was stirred in MeOD at room temperature for 24 h, to facilitate the maximum incorporation of deuterium into the molecule (measured by the decrease in the corresponding signal in the ^1H NMR spectrum). The low incorporation of this isotope at C-6 and the high isotopic labelling at the 5-CH (Figure 1), indicated that, under these conditions, imine **A** and enamine **B** are predominant in the equilibrium. According to this, the isotopic labelling at the 6-position of compound **9a** and **9b**, obtained by method B ($NaBH_3CN$, r.t., 3 h), is almost insignificant. In this experiment, the predominant reduction of imine **A** was deduced from the almost complete deuteration of the 5-CH_2 group, and afterwards confirmed by a similar reaction using $NaBD_3CN$ (Table 1, entry 10), in which compounds **9a** and **9b** showed the labelling exclusively at C-5 (Figure 1). When the hydrogenation reaction (45 psi, 45°C, 48 h) was applied to deuterated enamine **B**, the compounds **9a** and **9b** obtained showed a high incorporation of deuterium at both C-6 and 5-CH_2 positions. This result indicates that, as expected, the **B** ⇌ **A** ⇌ **C** equilibrium is favoured by the higher temperature and prolonged reaction time used in method A. However, the fact that the isotopic labelling at the 5-CH_2 group was lower for compounds **9** coming from the hydrogenation reaction (method A) than for those

obtained from method B, could only be explained if an approximately 20% of enamine intermediate **B** is reduced in the hydrogenation. As the incorporation of deuterium at the 5-CH_2 position in **9a** and **9b** was the same, it seems that, within the experimental error, reduction of enamine **B** by method A is not a selective process. On the other hand, the different isotopic labelling at C-6 position in compounds **9a** and **9b**, obtained from method A, could indicate that hydrogenation of enamine **C** preferentially takes place by the lower face of the molecule. From the above results, the partial hydrogenation of enamines **B** and **C** could account for the lower diastereoselectivity found in method A when compared to the reduction with $NaBH_3CN$, for which we have demonstrated that the reductive amination exclusively take place through the imine intermediate **A**. Under the $NaBH_3CN/ZnCl_2$ reduction conditions, a "chelation mechanism", involving the formation of a six-membered cyclic complex through interactions between the $ZnCl_2$ catalyst and the carbonyl oxygen of the ester and the imine nitrogen, could contribute to the stabilization of imine **A**.

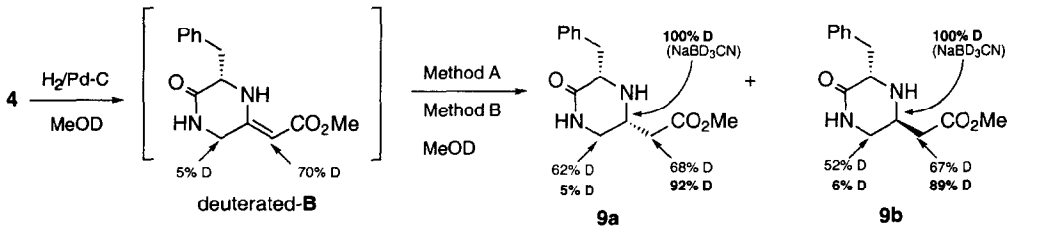
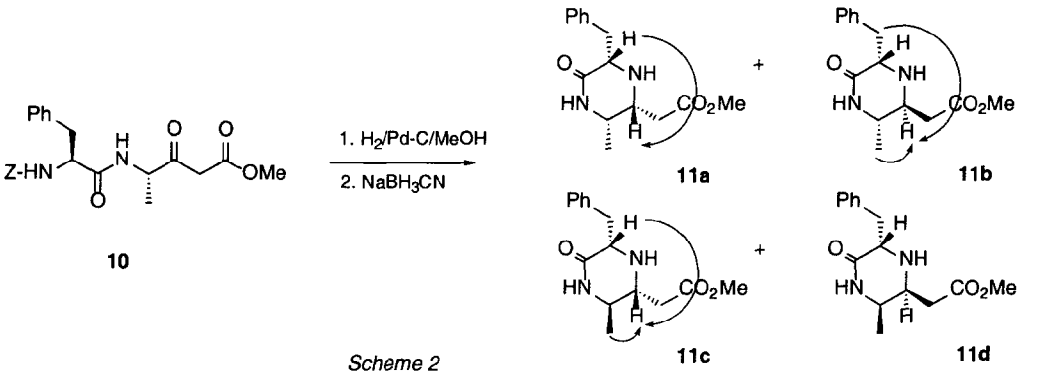


Figure 1.– Percentages of incorporation of deuterium (method B in bold)

To explore the preparation of 3,5,6-trisubstituted 2-oxopiperazines, β-ketoester **10** was prepared from Z-Phe-Ala-OH. This keto ester was obtained as an inseparable 10:1 mixture of L-L and L-D diastereoisomers due to the partial epimerization of the *C*-terminal residue during activation of the dipeptide with carbonyldiimidazole.[15] When this mixture was allowed to react under the conditions used in Method B, 2-oxopiperazines **11a**, (35%), **11b** (2%) and **11c** (7%) were isolated. Traces of (3*S*,5*S*,6*R*) diastereoisomer **11d** (= 1%) were also detected in the ^1H NMR spectrum of the crude reaction products. During the reductive amination of the β-keto ester **10** of L-L configuration the hydrogen preferentially enters on the opposite side to the R^1 and R^2 substituents, giving **11a** as major compound. As expected, the **11a/11b** ratio (18:1, R^2 = Me) is higher than that obtained for compounds **8** (**a/b**, 5.3:1, R^2 = H).



Scheme 2

The absolute configurations at C-5 and C-6 in **11a**, **11b** and **11c** were assigned by means of the coupling constants values and NOE experiments. Thus, The $J_{5,6}$ value of 4 Hz for **11a** indicated a *cis*-relationship between H-5 and H-6, while $J_{5,6}$ values of 7 and 9.5 Hz for **11b** and **11c**, respectively, agreed with a *trans* disposition of these hydrogens. Concerning NOE experiments, isomers **11a** and **11c** show a weak NOE between H-3 and H-5 indicating that these atoms are located in the same face of the heterocyclic ring. Moreover, in the case of isomer **11c** the weak NOE between H-5 and the 6-CH_3 group allowed us to propose an (3*S*,5*R*,6*R*) configuration for this isomer. On the other hand, irradiation of H-5 of compound **11b** produces an enhancement in the signals due to the 3-CH_2 and 6-CH_3 groups, in agreement with a (3*S*,5*S*,6*S*) configuration.

Considering that the reductive amination of both L-L and L-D diastereoisomers of **10** proceeds to the same extent, the relative percentage of **11c**, when compared to that obtained for **11a** + **11b**, is higher than that expected for the existence of 9% of L-D **10**. Therefore, it seems that in the case of the 6-substituted piperazines, a certain amount of epimerization at C-6 occurred, probably due to the fact that the imine **A**-enamine **C** equilibrium is favoured by the presence of a substituent in position α to the imine carbon.

In summary, we have demonstrated that the reductive amination of β-keto esters derived from dipeptides is a flexible method for the preparation of 2-oxopiperazines bearing amino acid side chains at C-3, C-5 and C-6 positions. The stereochemical course of this reaction was found to be dependent on the starting dipeptide derivative and on the reducing agent. As deduced from experiments of isotopic labelling with deuterium, the exclusive reduction of imine intermediates could account for the higher selectivities found for the reactions carried out with $NaBH_3CN$. According to the synthetic approach described in this paper, variable amino acid side chains could be incorporated on the heterocyclic template in different spatial dispositions by starting from different dipeptide derivatives.

EXPERIMENTAL SECTION

^1H NMR spectra were recorded with a Varian Unity 300 or a Varian Unity 500 spectrometers operating at 300 and 500 MHz, respectively, using TMS as internal standard. ^{13}C NMR spectra were recorded on the same instruments (75 MHz and 125 MHz); ^{13}C NMR assignments were made by means of heteronuclear H-C correlations (HMQC, HMBC). Elemental analyses 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 F254 (Merck). Silica gel 60 (230-400 mesh, Merck) was used for column chromatography. Analytical HPLC was performed on a Waters Nova-pak C_{18} (3.9 x 150 mm, 4 μm) column, with a flow rate of 1 mL/min, using a tuneable UV detector set at 214 nm. Mixtures of MeCN (solvent A) and 0.05% TFA in H_2O (solvent B) were used as mobile phase. Dipeptide derivatives were purchased from Bachem. Monoethyl and momomethyl malonate magnesium salts were prepared as described.[16]

Synthesis of β-keto esters derived from dipeptides

General procedure.– A solution of the corresponding Z-dipeptide (5.4 mmol) in dry THF (15 mL) was treated with carbonyldiimidazole (0.96 g, 5.9 mmol) and stirred at r.t. for 1 h. Then, the corresponding monoalkyl malonate magnesium salt (5.9 mmol) was added. After stirring for 18 h at r.t., the solvent was

evaporated and the resulting residue was treated with 1N HCl (5 mL) and extracted twice with EtOAc (25 mL). The organic layer was washed with 10% $NaHCO_3$ and brine, dried over Na_2SO_4 and evaporated, leaving a residue which was purified on a silica gel column as specified in each case.

Ethyl 4-[N-(benzyloxycarbonyl)glycyl]amino-3-oxobutanoate (2).– Yield: 80%. Eluent: EtOAc/hexane (2:1). White solid: mp 200-201°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, 3H, CH_3 OEt, J = 7.1), 3.46 (s, 2H, H-2), 3.89 (m, 2H, α-Gly), 4.17 (m, 4H, H-4 and CH_2 OEt), 5.09 (CH_2 Z), 5.82 (brs, 1H, α-NH Gly), 7.03 (brs, 1H, 4-NH), 7.25 (m, 5H, C_6H_5 Z). ^{13}C NMR (75 MHz, $CDCl_3$): 13.94 (CH_3 Et), 44.17 (C-2), 46.48 (α-Gly), 49.14 (C-4), 61.67 (CH_2 OEt), 67.08 (CH_2 Z), 127.97, 128.14 and 128.45 (CH Ar), 136.01 (C Ar), 156.62, 166.57 and 169.54 (CO), 198.21 (C-3). Anal. Calcd for $C_{16}H_{20}N_2O_6$: C 57.14, H 5.99, N 8.33. Found: C 57.02, H 6.11, N 8.17.

Ethyl 4-[N-(benzyloxycarbonyl)-L-alanyl]amino-3-oxobutanoate (3).– Yield: 65%. Eluent: EtOAc/hexane (1:1). White solid: mp 87-89°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (t, 3H, CH_3 OEt, J = 7.1), 1.37 (d, 3H, α-CH_3 Ala, J = 7.1), 3.47 (s, 2H, H-2), 4.17 (m, 4H, H-4 and CH_2 OEt), 4.32 (m, 1H, α-Ala), 5.08 (m, 2H, CH_2 Z), 5.63 (d, 1H, α-NH Ala, J = 7.4), 7.01 (brs, 1H, 4-NH), 7.29 (m, 5H, C_6H_5 Z). ^{13}C NMR (75 MHz, $CDCl_3$): 13.98 (CH_3 Et), 18.50 (α-CH_3 Ala), 46.55 (C-2), 49.24 (C-4), 50.39 (α-Ala), 61.69 (CH_2 OEt), 66.98 (CH_2 Z), 127.99, 128.14 and 128.48 (CH Ar), 136.05 (C Ar), 155.95, 166.57 and 172.37 (CO), 198.13 (C-3). Anal. Calcd for $C_{17}H_{22}N_2O_6$: C 58.28, H 6.33, N 8.00. Found: C 57.98, H 6.01, N 7.85.

Ethyl 4-[N-(benzyloxycarbonyl)-L-phenylalanyl]amino-3-oxobutanoate (4).– Yield: 76%. Eluent: EtOAc/hexane (1:2). White solid: mp 102-104°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (t, 3H, CH_3 OEt, J = 7.2), 3.09 (m, 2H, β-CH_2 Phe), 3.41 (s, 2H, H-2), 4.17 (m, 4H, H-4 and CH_2 OEt), 4.24 (m, 1H, α-Phe), 5.05 (m, 2H, CH_2 Z), 5.51 (d, 1H, α-NH Phe, J = 8.0), 6.77 (brs, 1H, 4-NH), 7.16-7.36 (m, 10H, C_6H_5 Phe and Z). ^{13}C NMR (75 MHz, $CDCl_3$): 14.01 (CH_3 Et), 38.35 (β-CH_2 Phe), 46.53 (C-2), 49.24 (C-4), 56.01 (α-CH Phe), 61.71 (CH_2 OEt), 67.03 (CH_2 Z), 127.02, 127.95, 128.14, 128.48, 128.64 and 129.19 (CH Ar), 136.01 and 136.19 (C Ar), 155.97, 166.49 and 171.27 (CO), 197.77 (C-3). Anal. Calcd for $C_{23}H_{26}N_2O_6$: C 64.78, H 6.14, N 6.57. Found: C 64.55, H 6.20, N 6.39.

Methyl 4-[N-(benzyloxycarbonyl)-L-phenylalanyl]amino-3-oxobutanoate (5).– Yield: 63%. Eluent: EtOAc/hexane (1:2). White solid: mp 101-103°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.09 (m, 2H, β-CH_2 Phe), 3.44 (s, 2H, H-2), 3.73 (s, 3H, OMe), 4.17 (m, 4H, H-4), 4.49 (m, 1H, α-Phe), 5.06 (m, 2H, CH_2 Z), 5.37 (d, 1H, α-NH Phe, J = 7.2), 6.62 (brs, 1H, 4-NH), 7.16-7.37 (m, 10H, C_6H_5 Phe and Z). ^{13}C NMR (75 MHz, $CDCl_3$): 38.32 (β-CH_2 Phe), 46.21 (C-2), 49.26 (C-4), 52.54 (OMe), 55.98 (α-CH Phe), 67.02 (CH_2 Z), 127.00, 127.92, 128.13, 128.46, 128.62 and 129.17 (CH Ar), 135.99 and 136.19 (C Ar), 155.96, 166.90 and 171.32 (CO), 197.68 (C-3). Anal. Calcd for $C_{22}H_{24}N_2O_6$: C 64.07, H 5.86, N 6.79. Found: C 64.23, H 6.07, N 6.52.

Ethyl 4(*R,S*)-[N-(benzyloxycarbonyl)-L-phenylalanyl]amino-3-oxopentanoate (10).– Yield: 64% (mixture of 4*S* and 4*R* diastereoisomersin 10:1 ratio). Eluent: EtOAc/hexane (1:2). **4*S* isomer**: White solid: mp 129-131°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (t, 3H, CH_3 OEt, J = 7.2), 1.28 (d, 3H, 5-H, J= 7.1), 3.08 (m, 2H, β-CH_2 Phe), 3.41 (s, 2H, H-2), 4.17 (q, 2H, CH_2 Et, J = 7.2), 4. 45 (m 1H, H-4), 4.58 (m, 1H, α-Phe), 5.07 (s, 2H, CH_2 Z), 5.34 (d, 1H, α-NH Phe, J = 7.6), 6.65 (d, 1H, 4-NH, J = 7.5), 7.16-7.38 (m, 10H, C_6H_5 Phe and Z). ^{13}C NMR (75 MHz, $CDCl_3$): 14.06 (CH_3 Et), 16.67 (C-5), 38.34 (β-CH_2 Phe), 45.71 (C-2), 54.25 (C-4), 56.12 (α-CH Phe), 61.62 (CH_2 OEt), 67.15 (CH_2 Z), 127.19, 128.06, 128.25, 128.54, 128.76 and 129.26 (CH Ar), 135.99 (C Ar), 155.83, 166.67 and 170.56 (CO), 201.15 (C-3). Anal. Calcd for

$C_{24}H_{28}N_2O_6$: C 65.44, H 6.41, N 6.36. Found: C 64.30, H 6.27, N 6.05. **4*R* isomer**: White foam. ^1H NMR (300 MHz, $CDCl_3$): δ 1.17 (d, 3H, 5-H, J = 7.1), 1.25 (t, 3H, CH_3 OEt, J = 7.1), 3.06 (m, 2H, β-CH_2 Phe), 3.47 (m, 2H, H-2), 4.16 (q, 2H, CH_2 Et, J = 7.1), 4. 43 (m 1H, H-4), 4.58 (m, 1H, α-Phe), 5.08 (s, 2H, CH_2 Z), 5.42 (d, 1H, α-NH Phe, J = 7.3), 6.44 (d, 1H, 4-NH, J = 7.1), 7.16-7.35 (m, 10H, C_6H_5 Phe and Z).

General procedures for the synthesis of 2-oxopiperazine derivatives

Method A.– A solution of the corresponding β-ketoester (2 mmol) in MeOH or MeOD (50 mL) was hydrogenated at 45°C and 45 psi of pressure for 2-3 days, using 10% Pd-C as catalyst. After filtration of the catalyst, the solvent was evaporated and the resulting residue was purified on a silica gel column, as specified.

Method B.– A solution of the corresponding β-ketoester (2 mmol) in MeOH or MeOD (50 mL) was hydrogenated at r.t. and 15 psi of pressure for 2 h, using 10% Pd-C as catalyst. The catalyst was filtered and $ZnCl_2$ (0.14 g, 1 mmol) and $NaBH_3CN$ or $NaBD_3CN$ (0.38 g, 6 mmol) were added to the filtrate. After stirring for 3 h at r.t., the solvent was evaporated to dryness. The residue was extracted with EtOAc (50 mL) and washed with H_2O. The organic layer was dried over Na_2SO_4 and, after evaporation, the residue was purified on a silica gel column as specified in each case.

5(*R*,*S*)-(Ethoxycarbonyl)methyl-2-oxopiperazine (6).– Yield: 96% (from **2**, method A) and 20% (from **2**, method B). Eluent: CH_2Cl_2/MeOH (30:1). Syrup. Anal. Calcd for $C_8H_{14}N_2O_3$: C 51.60 H 7.58, N 15.04. Found: C 51.58, H 7.69, N 14.82.

(3*S*,5*R*) 5-(Ethoxycarbonyl)methyl-3-methyl-2-oxopiperazine (7a).– Yield: 56% (from **3**, method A) and 64% (from **3**, method B). Eluent: CH_2Cl_2/MeOH (30:1). Syrup. Anal. Calcd for $C_9H_{16}N_2O_3$: C 53.99 H 8.05, N 13.99. Found: C 54.13, H 7.85, N 14.06.

(3*S*,5*S*) 5-(Ethoxycarbonyl)methyl-3-methyl-2-oxopiperazine (7b).– Yield: 33% (from **3**, method A) and 16% (from **3**, method B). Eluent: CH_2Cl_2/MeOH (30:1). Syrup. Anal. Calcd for $C_9H_{16}N_2O_3$: C 53.99 H 8.05, N 13.99. Found: C 53.77, H 7.91, N 13.64.

(3*S*,5*R*) 3-Benzyl-5-(ethoxycarbonyl)methyl-2-oxopiperazine (8a).– Yield: 69% (from **4**, method A) and 65% (from **4**, method B). Eluent: acetone/hexane (2:1). Syrup. HPLC: t_R 10.24 min (mobile phase A/B 10:90). Anal. Calcd for $C_{15}H_{20}N_2O_3$: C 65.20 H 7.29, N 10.14. Found: C 65.08, H 6.95, N 10.00.

(3*S*,5*S*) 3-Benzyl-5-(ethoxycarbonyl)methyl-2-oxopiperazine (8b).– Yield: 22% (from **4**, method A) and 12% (from **4**, method B). Eluent: acetone/hexane (2:1). Syrup. HPLC: t_R 14.50 min (mobile phase A/B 10:90). Anal. Calcd for $C_{15}H_{20}N_2O_3$: C 65.20 H 7.29, N 10.14. Found: C 65.11, H 7.25, N 10.03.

(3*S*,5*R*) 3-Benzyl-5-(methoxycarbonyl)methyl-2-oxopiperazine (9a).– Yield: 76% (from **5**, method A) and 54% (from **5**, method B). Eluent: CH_2Cl_2/MeOH (30:1). Syrup. HPLC: t_R 6.94 min (mobile phase A/B 8:92). Anal. Calcd for $C_{14}H_{18}N_2O_3$: C 64.11, H 6.92, N 10.68 Found: C 64.22, H 6.59, N 10.38.

(3*S*,5*S*) 3-Benzyl-5-(methoxycarbonyl)methyl-2-oxopiperazine (9b).– Yield: 21% (from **5**, method A) and 11% (from **5**, method B). Eluent: CH_2Cl_2/MeOH (30:1). Syrup. HPLC: t_R 9.87 min (mobile phase A/B 8:92). Anal. Calcd for $C_{14}H_{18}N_2O_3$: C 64.11, H 6.92, N 10.68 Found: C 63.94, H 7.15, N 10.55.

(1*S*,3*S*,5*R*) 3-Benzyl-5-(ethoxycarbonyl)methyl-1-methyl-2-oxopiperazine (11a).– Yield: 35% (from **10**, method B). Eluent: CH_2Cl_2/MeOH (30:1). Syrup. HPLC: t_R 6.26 min (mobile phase A/B 15:85). Anal. Calcd for $C_{16}H_{22}N_2O_3$: C 66.19, H 7.64, N 9.65 Found: C 66.06, H 7.71, N 9.28.

(1*S*,3*S*,5*S*) 3-Benzyl-5-(ethoxycarbonyl)methyl-1-methyl-2-oxopiperazine (11b).– Yield: 2% (from **10**, method B). Eluent: CH_2Cl_2/MeOH (30:1). Syrup. HPLC: t_R 9.83 min (mobile phase A/B 15:85). Anal. Calcd for $C_{16}H_{22}N_2O_3$: C 66.19, H 7.64, N 9.65 Found: C 65.96, H 7.44, N 9.37.

(1*R*,3*S*,5*R*) 3-Benzyl-5-(ethoxycarbonyl)methyl-1-methyl-2-oxopiperazine (11c).–Yield: 7% (from **10**, method B). Eluent: CH_2Cl_2/MeOH (30:1). Syrup. HPLC: t_R 4.93 min (mobile phase A/B 15:85). Anal. Calcd for $C_{16}H_{22}N_2O_3$: C 66.19, H 7.64, N 9.65 Found: C 66.13, H 7.59, N 9.55.

Table 2.– Significant ^{1}H-NMR Chemical Shifts (δ, ppm) and Coupling Constants (Hz) of Piperazine Derivatives (300 MHz, $CDCl_3$)

Compd.	1–H	3–H	5-H	6-H	5-CH_2	R^1	R^2	R^3
6	7.28 (br s)	3.58 (s)	3.36 (m)	3.36 (m) 3.18 (m)	2.50 (m)	–	–	4.19 (q) 1.30 (t) (J = 7.1)
7a	7.44 (br s)	3.39 (m)	3.22 (m)	3.11 (m) 2.96 (m)	2.92 (m)	1.17 (d) (5.8)	–	3.98 (q) 1.09 (t) (J = 7.2)
7b	7.26 (br s)	3.59 (m)	3.51 (m)	3.36 (m) 3.09 (m)	2.46 (m)	1.38 (d) (6.7)	–	4.12 (q) 1.23 (t) (J = 7.1)
8a	7.48 (br s)	3.68 (dd) (9.7, 3.1)	3.24 (m)	3.24 (m) 3.03 (m)	2.35 (m)	3.43 (dd) (13.6, 3.1) 2.79 (dd) (13.6, 9.7)	–	4.01 (q) 1.10 (t) (J = 7.1)
8b	7.01 (br s)	3.72 (dd) (10.6, 3.2)	3.55 (m)	3.27 (m) 3.12 (m)	2.41 (m)	3.24 (dd) (13.5, 3.2) 2.95 (dd) (13.5, 10.6)	–	4.08 (q) 1.19 (t) (J = 7.1)
9a	7.19 (br s)	3.66 (dd) (9.8, 3.3)	3.25 (m)	3.25 (m) 3.03 (m)	2.36 (m)	3.42 (dd) (13.8, 3.3) 2.80 (dd) (13.8, 9.8)	–	3.55 (s)
9b	6.85 (br s)	3.72 (dd) (10.6, 3.1)	3.57 (m)	3.37 (m) 3.12 (m)	2.42(m)	3.263 (dd) (13.8, 3.1) 2.97 (dd) (13.8, 10.6)	–	3.63 (s)
11a[a]	6.70 (br s)	3.70 (dd) (8.4, 3.3)	3.43 (m)	3.43 (m) ($J_{5,6}$=4.0)	2.28 (m)	3.30 (dd) (13.7, 3.3) 2.94 (dd) (13.7, 8.4)	0.95 (d) (5.7)	4.04 (q) 1.13 (t) (J = 7.2)
11b[a]	5.93 (br s)	3.71 (dd) (9.9, 3.3)	3.14 (m)	3.32 (m) ($J_{5,6}$ 7.0)	2.55 (dd) (15.4, 4.1) 2.28 (dd) (15.4, 8.8)	3.22 (dd) (13.7, 3.3) 2.99 (dd) (13.7, 9.9)	1.14 (d) (6.4)	4.08 (q) 1.19 (t) (J = 7.2)
11c[a]	5.91 (br s)	3.67 (dd) (9.5, 3.3)	2.83 (m)	3.46 (m) ($J_{5,6}$ 9.5)	2.53 (dd) (15.7, 2.2) 2.28 (dd) (15.7, 9.9)	3.46 (dd) (13.8, 3.3) 2.83 (m)	1.12 (d) (5.2)	4.01 (q) 1.09 (t) (J = 7.1)

[a] Registered at 500 MHz.

Table 3.– Significant ^{13}C-NMR Chemical Shifts of Piperazine Derivatives (75 MHz, $CDCl_3$)

Compd.	C-2	C-3	C-5	C-6	5-CH_2	R^{1a}	R^2	R
6	171.08	48.91	48.70	46.85	37.38	–	–	14.05 60.83
7a	172.74	54.05	48.88	47.00	37.36	17.63	–	13.80 60.54
7b	173.46	51.80	44.36	47.06	37.12	18.78	–	14.06 60.71
8a	171.34	59.88	49.32	47.39	37.89	37.94	–	13.97 60.78
8b	171.95	58.07	44.37	47.10	37.40	37.88	–	14.07 60.80
9a	171.44	59.66	49.13	48.18	37.52	37.73	–	51.71
9b	171.88	58.13	44.37	47.15	37.24	37.86	–	51.84
11a[b]	171.24	59.97	50.46	52.09	37.84	36.98	16.36	14.02 60.75
11b[b]	171.49	57.76	52.87	51.23	36.97	37.94	20.34	14.21 60.84
11c[b]	170.97	59.87	53.35	56.42	37.72	36.83	19.33	13.99 60.85

[a] CH_3 and CH_2 groups in Ala and Phe derivatives, respectively. [b] Registered at 125 MHz.

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