

Synthesis of (S)- and (R)-5-oxo-piperazine-2-carboxylic acid and its application to peptidomimetics.

Journal:	<i>The Journal of Organic Chemistry</i>
Manuscript ID:	jo-2009-01389q.R1
Manuscript Type:	Note
Date Submitted by the Author:	31-Jul-2009
Complete List of Authors:	Guitot, Karine; Università degli Studi dell'Insubria, Dipartimento di Scienze Chimiche e Ambientali Carboni, Stefano; Università degli Studi dell'Insubria, Dipartimento di Scienze Chimiche e Ambientali Reiser, Oliver; University of Regensburg, Organic Chemistry Piarulli, Umberto; Università degli Studi dell'Insubria, Dipartimento di Scienze Chimiche e Ambientali



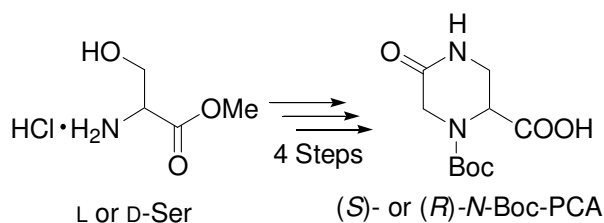
Synthesis of (*S*)- and (*R*)-5-oxo-piperazine-2-carboxylic acid and its application to peptidomimetics.

Karine Guitot,^{†,‡} Stefano Carboni,[†] Oliver Reiser^{*,‡} and Umberto Piarulli^{*,†}

Dipartimento di Scienze Chimiche e Ambientali, Università degli Studi dell'Insubria, Via Valleggio, 11, 22100 Como, Italy and Institut für Organische Chemie, Universität Regensburg, Universitätstrasse, 31, 93053 Regensburg, Germany.

umberto.piarulli@uninsubria.it
oliver.reiser@chemie.uni-regensburg.de

RECEIVED DATE (will be automatically inserted after manuscript is accepted).



A straightforward synthesis of (*S*)- and (*R*)-*N*-Boc-5-oxo-piperazine-2-carboxylic acid, is reported starting from L- or D-serine and ethyl glyoxylate. Those were evaluated as constituents in two tetrapeptides by studying their secondary structure by ¹H-NMR spectroscopy. In the case of Boc-Val-(*S*)-PCA-Gly-Leu-OMe, two readily interconverting conformations (in a 40:60 % ratio) were observed, differing for the *cis-trans* isomerization of the tertiary amide bond, while, Boc-Val-(*R*)-PCA-Gly-Leu-OMe, displayed an equilibrium between a γ -turn and a type II β -turn conformation.

The design and synthesis of conformationally restricted amino acids has been the focus of extensive research, because these compounds mimic or induce specific secondary structural features of peptides and proteins.¹ Since the discovery of the crucial role of proline in protein structures, cyclic α -amino acids containing a heterocyclic ring have attracted considerable attention both from synthetic and medicinal chemists.² In particular several six-membered ring heterocyclic amino acids have been synthesized, comprising derivatives of pipercolic,³ piperazine-2-carboxylic,⁴ 1,4-thiazine-3-carboxylic,⁵ 1,3-thiazine-4-carboxylic⁶ and morpholine-3-carboxylic acid.⁷ 5-Oxo-piperazine-2-carboxylic acid (PCA, Figure 1), on the other hand, has received much less attention, and only few reports deal with its synthesis, structural and biological properties.⁸

In the frame of our studies directed towards the synthesis of peptidomimetics with well defined conformational properties,⁹

we became interested in the synthesis of 5-oxo-piperazine-2-carboxylic acid (PCA), and its introduction into peptide sequences as an inducer of secondary structures.

Herein we report a practical synthesis of (*S*)- and (*R*)-*N*-Boc-5-oxo-piperazine-2-carboxylic acid **1** (Figure 1), its introduction into peptides by a solution-phase peptide-synthesis strategy, and a conformational analysis of two tetrapeptide mimics incorporating a PCA residue.

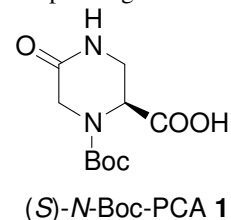
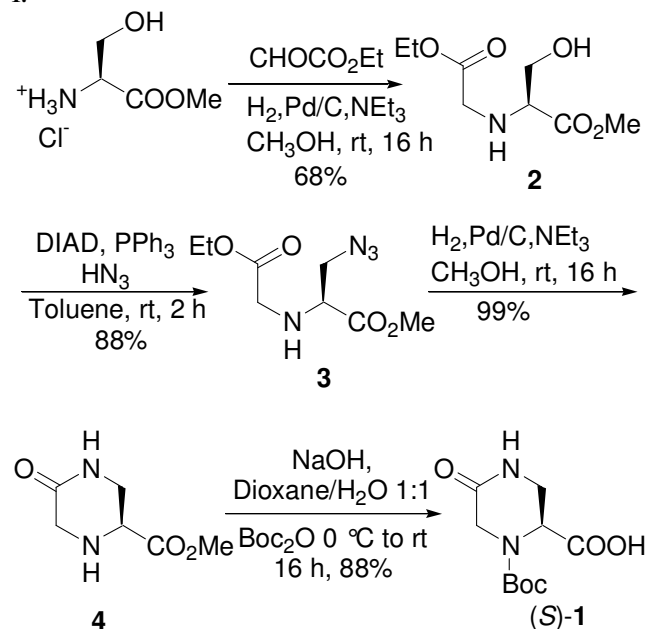


Figure 1. (*S*)-*N*-Boc-5-oxo-piperazine-2-carboxylic acid **1**.

Our synthetic approach (Scheme 1) started from L-serine methyl ester hydrochloride which was *N*-alkylated using ethyl glyoxylate in the presence of Pd/C and under an atmosphere of H₂. Following a procedure that has been reported for the synthesis of 2,3-diamino propionic acid starting from serine derivatives,¹⁰ the resulting alcohol **2** was transformed into the azide **3** by a Mitsunobu reaction using a solution of hydrazoic acid in toluene. Other methodologies involving the activation of the hydroxyl group of serine were hampered by a concurrent elimination reaction leading to the corresponding dehydroalanine derivative as the major reaction product.

Scheme 1. Synthesis of (*S*)-*N*-Boc-5-oxo-piperazine-2-carboxylic acid **1**.



Catalytic hydrogenation of **3** with Pd/C caused reduction of the azide to the primary amine with concurrent cyclization to methyl 5-oxo-piperazine-2-carboxylate **4** in quantitative yield. Finally, a one pot hydrolysis of the methyl ester and *N*-Boc protection afforded *N*-Boc-5-oxo-piperazine-2-carboxylic acid **1** in pure form. The synthesis of (*R*)-**1** was analogously

achieved starting from D-serine. The protection of the amino group of methyl (*S*)-5-oxo-piperazinone-2-carboxylate **4** was then realized using FmocCl in a biphasic aqueous NaHCO₃ dioxane medium in good yield. (*S*)-*N*-Fmoc-5-oxo-piperazine-2-carboxylic acid methyl ester **5** could be crystallized from a mixture of methanol and diethylether to allow an X-ray structure analysis: the piperazinone ring adopts a half-chair conformation with the methoxycarbonyl group in a pseudo-axial and the *N*-protecting group in an equatorial orientation. This arrangement, which has been reported for pipercolic acid containing peptides,¹¹ was found also in solution as judged by the coupling constants for the protons on C2/C3 being smaller than 5 Hz (typically 4.4 Hz). The amide group displays a planar geometry as expected with the N-H bond bisecting the angle of the vicinal CH₂ group.

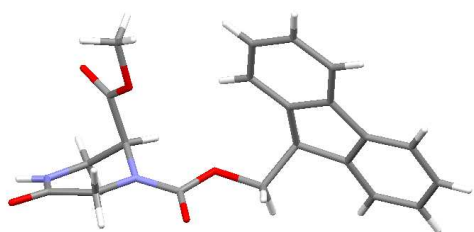


Figure 2. X-ray structure of methyl (*S*)-*N*-Fmoc-5-oxo-piperazine-2-carboxylate **5**.

To evaluate the enantiomeric purity of these derivatives, (*S*)-**1** and (*R*)-**1** were then coupled to (*R*)-1-phenylethylamine.⁷⁻¹² The coupling was achieved in good yield using EDC (*N*-ethyl,*N*'-[3'-(dimethylamino)propyl] carbodiimide) / HOBT (1-hydroxybenzotriazole) / *i*Pr₂NEt, however, the optical purity of the resulting *N*-Boc amides could not be established neither by HPLC nor by NMR, the latter being complicated by doubling of the signals due to rotamers caused by the *N*-Boc group. Removal of the Boc protecting group revealed a single set of NMR signals, whereas HPLC analysis of the single amides and of the 1:1 mixture showed that in both (*S*)-**1** and (*R*)-**1** cases the amides were obtained with a d.e. greater than 95%.

The ability of both (*S*)- and (*R*)-PCA to act as proline mimics in inducing turn structures when inserted into peptide sequences, was then studied. Two tetrapeptide sequences: Boc-Val-(*S*)-PCA-Gly-Leu-OMe **6** and Boc-Val-(*R*)-PCA-Gly-Leu-OMe, **7** were prepared by solution phase peptide synthesis (Boc strategy) using HATU (*O*-(7-azobenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate) to couple Boc-PCA to the Gly-Leu-OMe dipeptide and Boc-Val to the PCA moiety. Similar sequences containing L- or D-proline,¹³ and other proline mimics among which (*S*)- (*R*)-pipercolic acid¹¹ have been studied and their preferred conformations in solutions were determined by ¹H-NMR. In the latter case both thermodynamic and kinetic aspects of the *cis-trans* isomerization about pipercolic peptide bonds have been studied.

A conformational study of **6** and **7** was performed in CDCl₃ solution by ¹H-NMR. In the case of Boc-Val-(*S*)-PCA-Gly-Leu-OMe **6**, the ¹H-NMR spectrum (5 mM) showed two sets

of signals in a 1.7 : 1 ratio, which were attributed to the *trans* and *cis* tertiary amide isomers, respectively (37 % of the *cis*-conformer). It has been reported that the presence of a pipercolic acid residue leads to a significant increase in population of the *cis* conformer (35-50%),¹¹ whereas the *cis* amide-content in tetrapeptides containing L-proline appears to be definitely lower (up to 21% if an aromatic amino acid, Phe or Tyr, is preceding proline in the sequence).¹⁴ Analogously, the introduction of a morpholine-3-carboxylic acid (Mor) in the tetrapeptide sequence Ac-Val-(*S*)-Mor-Gly-Leu-OMe resulted in a 2:3 mixture of *cis* and *trans* rotamers (40 % of the *cis*-conformer) at the Val-Mor amide bond.^{7b} NOESY experiments conducted at 298 K revealed the presence of intense exchange cross peaks (EXSY) between the *cis* and *trans* PCA containing peptides, which hampered the correct attribution of the signals to the *cis* and *trans* conformers. This is indicative of a rather low barrier to isomerization, as can also be inferred from the coalescence of several backbone (and amide) signals, which is observed by heating the sample to 313 K. The presence of pipercolic acid ring is reported to increase the kinetics of *cis-trans* isomerization with respect to proline, but with PCA an even faster isomerization is observed. When a NOESY experiment was conducted at 273 K the exchange peaks were far less intense and contacts for the two conformers could be assigned. The *trans* conformer did not show the presence of relevant cross-peaks indicative of a well organized structure. This fact, together with the relatively low chemical shift value of the NH signals ($\delta \leq 7.0$ ppm) and their high temperature coefficients (see the Supporting Information for the ¹H-NMR spectra and the determination of the $\Delta\delta/\Delta T$ values), is indicative of a random coil structure. In the case of the *cis*-conformer (Figure 3), the Gly-NH appears at a remarkably deshielded chemical shift value ($\delta = 8.27$ ppm) and with a temperature coefficient indicative of an equilibrium between an intramolecularly bonded and a non-bonded status. The NOESY experiments showed a rather strong contact between Val H- α and H-2 of the PCA moiety, indicating both the *cis*-conformation of the amide bond and the presence of a β -turn structure stabilized by a 10-membered cyclic hydrogen bond.

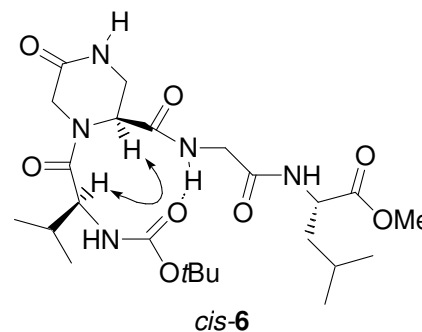


Figure 3. Hypothesized conformation of tetrapeptide Boc-Val-(*S*)-PCA-Gly-Leu-OMe **6**: the arrow indicates the NOE contact between Val H- α and H-2 of the PCA moiety.

The ¹H-NMR spectrum of the heterochiral Boc-Val-(*R*)-PCA-Gly-Leu-OMe (**7**) showed a single set of signals indicating the existence of a single rotamer in solution, which,

owing to a strong NOE contact between the Val H- α and the H-6 protons of the PCA residue, was assigned to the *trans* isomer. A study of the chemical shift of the amide protons and their temperature coefficients determination (Table 1) indicated for Gly-NH an equilibrium between hydrogen-bonded and nonhydrogen-bonded states; a similar behavior could be assumed for Leu-NH, although with a distinctively lower chemical shift.

Table 1. $^1\text{H-NMR}$ chemical shifts at rt and temperature coefficients for tetrapeptide **7**.

NH	δ (ppm)	$\Delta\delta/\Delta T$ (ppb/K)
Val-NH	5.13	-1.82
PCA-NH	6.38	-10.25
Gly-NH	7.79	-4.59
Leu-NH	6.53	-2.78

The NOESY experiments showed strong contacts of Gly NH with H-2 and on H-6 of the PCA moiety as well as with Leu-NH. These findings are consistent with an equilibrium between a γ -turn and a type II β -turn conformations (Figure 4).

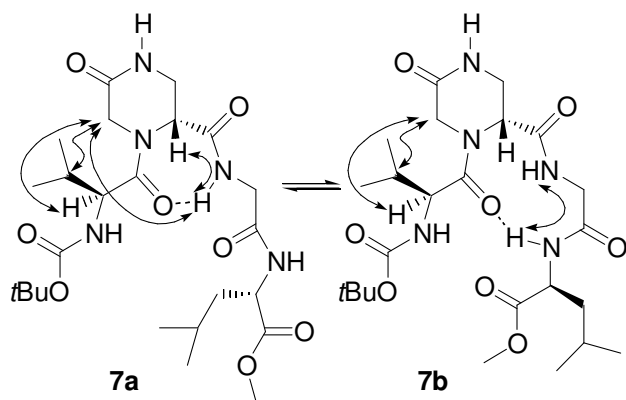


Figure 4. Hydrogen-bonded structures for tetrapeptide Boc-Val(*R*)-PCA-Gly-Leu-OMe **7**: the arrows indicate significant NOE contacts.

A $^1\text{H-NMR}$ study in $\text{DMSO-}d_6$ revealed, two sets of signals in a 1.7 : 1 ratio, which were attributed to the *trans* and *cis* tertiary amide isomers, respectively. The NOESY experiment showed intense exchange peaks and the absence of significant long range interactions. This behavior is in agreement with other similar cases.^{13,15}

Conformational preferences of compounds **6** and **7** were investigated by Monte Carlo simulations without imposing any constraint, using Spartan 06 version 1.03. The lowest energy conformations calculated substantially reflect the experimentally observed structures (see the Supporting Information for a more detailed description of these results).

In conclusion we have reported a straightforward synthesis of both (*S*)- and (*R*)-*N*-Boc-5-oxo-piperazine-2-carboxylic acid **1**, starting from serine and ethyl glyoxylate. The incorporation of both enantiomeric tertiary amino acids into a model tetrapeptide was obtained by solution phase peptide synthesis and their turn inducing abilities studied by $^1\text{H-NMR}$ spectroscopy. Interestingly Boc-Val(*S*)-PCA-Gly-Leu-OMe **6**, showed two readily interconverting conformations (in a 40:60 % ratio), differing in the *cis* and *trans* configuration of the

tertiary amide bond. The barrier to isomerization of the tertiary amide is unusually low with a coalescence temperature of 313 K. On the other hand, Boc-Val(*R*)-PCA-Gly-Leu-OMe **7**, which contains the *R*-PCA enantiomer showed a more defined turn conformation.

Experimental Section

(S)-2-(Ethoxycarbonylmethyl-amino)-3-hydroxypropionic acid methyl ester (2). L-serine methyl ester hydrochloride (1.0 g, 6.45 mmol) was dissolved in methanol, then triethylamine (902 μL , 6.48 mmol), a 50% solution of ethyl glyoxalate in toluene, and 10% Pd/C (90 mg), were successively added, and the resulting mixture was stirred overnight under a hydrogen atmosphere. The suspension was filtered over a pad of Celite, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 98:2) to afford the desired product as a colorless oil (902 mg, 68%). [α]_D²⁰ -27.8 (*c* 1.0, CHCl_3); $^1\text{H NMR}$ (CDCl_3) δ 4.21-4.15 (q, 2H, $J = 8.7$ Hz), 3.79 (dd, 1H, $J_1 = 11.1$ Hz, $J_2 = 4.5$ Hz), 3.75 (s, 3H), 3.69 (dd, 1H, $J_1 = 5.8$ Hz, $J_2 = 11.1$ Hz), 3.52 (d, 1H, $J = 17.4$ Hz), 3.40 (d, 1H, $J = 17.5$ Hz), 2.76 (br, 1H), 1.26 (t, 3H, $J = 7.1$ Hz). $^{13}\text{C NMR}$ δ 172.5, 172.0, 62.4, 62.3, 61.1, 52.3, 48.9, 14.1. IR (nujol) ν_{max} 3329, 3184, 1723, 1377, 1201, 1068; Anal calcd for $\text{C}_8\text{H}_{15}\text{NO}_5$: C 46.82%, H 7.37%, N 6.83%. Found: C 46.74%, H 7.32%, N 6.46%.

(S)-3-Azido-2-(ethoxycarbonylmethyl-amino)-propionic acid methyl ester (3). Triphenylphosphine (1.44 g, 5.50 mmol) was added to a solution of **2** (807 mg, 3.93 mmol) in dry toluene 30.0 mL under nitrogen at room temperature. After complete dissolution of the phosphine, HN_3 (0.5 M in toluene) (15.70 mL, 7.86 mmol) was added, followed by diisopropylazodicarboxylate (DIAD, 1.10 mL, 5.50 mmol). After 2 hours the mixture was directly purified by flash chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 99:1) to give the desired product as a colorless oil (796 mg, 88%). [α]_D²⁰ -37.6 (*c* 0.5, CHCl_3); $^1\text{H NMR}$ (CDCl_3) δ 4.19 (q, 2H, $J = 7.1$ Hz), 3.77 (s, 3H), 3.58-3.56 (m, 2H), 3.52-3.46 (m, 3H), 2.33 (br, 1H), 1.25 (t, 3H, $J = 7.1$ Hz); $^{13}\text{C NMR}$ (CDCl_3) δ 171.9, 171.5, 60.9, 60.2, 53.0, 52.3, 49.0, 14.1; IR (CH_2Cl_2) ν_{max} 3352, 3063, 2108, 1744, 1445; HRMS (ESI+) m/z calcd for $[\text{C}_8\text{H}_{14}\text{N}_4\text{NaO}_4]^+$ 253.09073 [$\text{M}+\text{Na}$]⁺ found 253.09097

(S)-5-Oxo-piperazine-2-carboxylic acid methyl ester (4). Pd/C (0.112 mmol 0.1 eq) was added to a solution of **3** (260 mg, 1.12 mmol) in MeOH (5 mL). The reaction was stirred overnight at rt under 1.0 atm of H_2 . The solution medium was then filtrated through a pad of celite and the solvent was evaporated under reduced pressure. The crude was purified by flash chromatography (DCM/MeOH , 92:8) to obtain the desired product as a white paste (176 mg, 99%). [α]_D²⁰ -46.3 (*c* 1.0, CHCl_3); $^1\text{H NMR}$ (CDCl_3) δ 6.87 (br, 1H), 3.77 (s, 3H), 3.75 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 4.4$ Hz), 3.66 (d, 1H, $J = 17.1$ Hz), 3.61 (ddd, 1H, $J_1 = 11.8$ Hz, $J_2 = 4.4$ Hz, $J_3 = 3.1$ Hz), 3.53 (d, 1H, $J = 17.4$ Hz), 3.52 (ddd, 1H, $J_1 = 11.8$ Hz, $J_2 = 8.0$ Hz, $J_3 = 1.8$ Hz), 2.15 (br, 1H); $^{13}\text{C NMR}$ (CDCl_3) δ 171.3, 169.8, 54.3, 53.0, 48.3, 44.2; IR (CH_2Cl_2) ν_{max} 3406, 3354, 3211, 1744, 1678; HRMS (EI) m/z calcd for $[\text{C}_6\text{H}_{10}\text{N}_2\text{O}_3]^+$ 158.06910 [M]⁺ found 158.06920

(S)-5-Oxopiperazine-1,2-dicarboxylic acid 1-tert-butyl ester (1). Compound **4** (120 mg, 0.76 mmol) was dissolved in a 1:1 dioxane/NaOH (1.0 M) solution (2.0 mL) at rt. The mixture was cooled to 0°C and Boc₂O (331 mg, 1.52 mmol) was added. After 15 minutes the ice bath was removed and the reaction was stirred for 10 h at rt. The reaction was quenched by addition of water 5.0 mL, and the aqueous phase was washed with EtOAc (2 x 3.0 mL). The aqueous solution was acidified until pH = 3 mediating addition of a 1.0 M solution of KHSO₄. The acid phase was extracted with EtOAc (5 x 5.0 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure and after purification by flash chromatography (CH₂Cl₂/MeOH, 97:3) the product (**S**)-**1** was collected as a white powder (163 mg, 88%). Mp 103-104 °C; $[\alpha]_D^{20}$ -33.8 (*c* 0.5, CH₃OH); Two sets of signals were observed in the ¹H and ¹³C NMR spectrum due to the presence of two rotational isomers A:B (2:1 ratio) ¹H NMR (CDCl₃) δ 8.35 (d, 1H_B, *J* = 3.2 Hz), 8.20 (d, 1H_A, *J* = 4.0 Hz), 4.99 (d, 1H_A, *J* = 4.0 Hz), 4.79 (d, 1H_B, *J* = 4.0 Hz), 4.23 (d, 1H_A and 1H_B, *J* = 18.8 Hz), 4.07 (d, 1H_A and 1H_B, *J* = 18.8 Hz), 3.88 (dd, 1H_A, *J*₁ = 12.6 Hz, *J*₂ = 3.9 Hz), 3.84 (dd, 1H_B, *J*₁ = 17.3 Hz, *J*₂ = 4.1 Hz), 3.65 (dd, 1H_A and 1H_B, *J*₁ = 17.3 Hz, *J*₂ = 4.9 Hz), 1.50 (s, 9H_A), 1.48 (s, 9H_B); ¹³C NMR (CDCl₃) δ 174.3 (A), 174.0 (B), 170.7 (A), 170.1 (B), 154.4 (A), 153.6 (B), 81.9 (A), 81.8 (B), 52.6 (A), 51.1 (B), 45.9 (A), 45.3 (B), 42.4 (A), 40.7 (B), 28.3 (A), 28.2 (B); IR (CH₂Cl₂) ν_{\max} 3408, 3230, 1707, 1647; HRMS (ESI+) *m/z* calcd for [C₁₀H₁₆N₂O₅]⁺ 244.1059 [M+H]⁺ found 244.1060

(S)-5-Oxopiperazine-1,2-dicarboxylic acid 1-(fluoren-9-yl) ester 2-methyl ester (5). **4** (128 mg, 0.81 mmol) was dissolved in a 2:1 water:dioxane (3.0 mL) solution and NaHCO₃ (136 mg, 1.61 mmol) was added. The mixture was cooled to 0°C and a solution of Fmoc-Cl (209 mg, 0.81 mmol) in dioxane (1.5 mL) was added dropwise over 15 min. The ice bath was removed and the reaction mixture was left stirring for 2.5 h at rt. Successively, the mixture was partitioned between EtOAc 14.0 mL and water 7.0 mL, and the organic phase was washed with 1.0 M HCl and brine and dried over Na₂SO₄. The organic solvent was removed and the crude product was purified by flash chromatography (DCM/MeOH, 95:5) to afford desired compound **5** (258 mg, 87%). Mp 143-144 °C; $[\alpha]_D^{20}$ -11.9 (*c* 1.0, CHCl₃); two sets of signals were observed in the ¹H and ¹³C NMR spectrum due to the presence of two rotational isomers A:B (3:1 ratio) ¹H NMR (CDCl₃) δ 6.57 (bs, 1H_B), 6.54 (bs, 1H_A), 5.04 (t, 1H_A, *J* = 2.0 Hz), 4.61 (bs, 1H_B), 4.60-4.49 (m, H_A and H_B), 4.44 (dd, 1H_A, *J*₁ = 7.2 Hz, *J*₂ = 3.6 Hz), 4.28-4.15 (m, 2H_A and 1H_B), 4.12 (d, 1H_A, *J* = 18.0 Hz), 4.03 (d, 1H_B, *J* = 18.4 Hz) 3.84 (dd, 1H_B, *J*₁ = 5.2 Hz, *J*₂ = 1.6 Hz), 3.81 (dd, 1H_B, *J*₁ = 3.6 Hz, *J*₂ = 1.6 Hz), 3.78 (s, 3H_A), 3.71 (s, 3H_B), 3.68 (dd, 1H_A, *J*₁ = 13.2 Hz, *J*₂ = 4.8 Hz), 3.57 (dd, 1H_A, *J*₁ = 12.8 Hz, *J*₂ = 4.4 Hz); ¹³C NMR (CDCl₃) δ 169.7(A), 169.6(B), 167.4(B), 166.9(A), 155.2(A), 154.3(B), 143.6 (A and B), 143.5(B), 143.4(A), 141.4(A and B), 141.3(A and B), 127.92(A), 127.88(B), 127.82(B), 127.22(A), 127.20(A), 127.15(B), 127.1(B), 124.9(A), 124.7(B), 124.6(B), 120.1(A), 120.0(B), 68.4(A), 67.8(B), 53.1(A and B), 52.5(B), 52.0(A), 47.2(B), 47.1(A), 46.0(A and B), 42.3(A and B); IR (nujol) ν_{\max} 3195, 1745, 1694, 1410, 1315, 1232, 1099; Anal calcd for C₂₁H₂₀N₂O₅: C

66.29%, H 5.30%, N 7.37%. Found C 66,20%, H 5,35%, N 7,28%.

X-Ray crystallographic data of 5: C₂₁H₂₀N₂O₅; MW = 380.39 g.mol⁻¹; T = 123 K; λ (Mo Kα) = 1.54184 Å; Orthorhombic, space group P 21 21 21, a = 6.5176(2) Å, b = 11.6690(5) Å, c = 23.9190(9) Å, α = 90°, β = 90°, γ = 90°, V = 1819.13(12) Å³, ρ_{calc} = 1.389 mg.m⁻³, Z = 4; μ(Mo, Kα) = 0.828 mm⁻¹, R₁ 0.0283, wR₂ 0.0713, for 2679 unique data collected in the 3.70-66.5° θ range.

ACKNOWLEDGMENT We thank the European Commission (contract MEST-CT-2004-515968, "Foldamers") for financial support and for PhD Fellowships (to K. G.). Financial support from the Deutsche Forschungsgemeinschaft (Graduiertenkolleg Medizinische Chemie 760) is also gratefully acknowledged We like to thank Dr D. Potenza (University of Milano) and Prof. Dr C. Cabrele (Bochum University) for helpful discussions.

Supporting Information Available: Synthetic schemes, experimental procedures and characterization of compounds **6-7**. ¹H and ¹³C NMR of all reported compounds, conformational studies of compounds **6-7**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

¹ (a) Kaul, R.; Balam, P. *Bioorg. Med. Chem.* **1999**, *7*, 105-117; (b) Venkatraman, J.; Shankaramma, S. C.; Balam, P. *Chem. Rev.* **2001**, *101*, 3131-3152.

² Park, K.-H.; Kurth, M. J. *Tetrahedron* **2002**, *58*, 8629-8659.

³ (a) Kadouri-Puchot, C.; Comesse S. *Amino Acids* **2005**, *29*, 101-130 and references therein; (b) Watanabe, L. A.; Haranaka, S.; Jose, B.; Yoshida, M.; Kato, T.; Moriguchi, M.; Soda, K.; Nishino N. *Tetrahedron: Asymmetry* **2005**, *16*, 903-908; (c) Kumar, P.; Bodas M. S. *J. Org. Chem.* **2005**, *70*, 360-363; (d) Liang, N.; Datta A. *J. Org. Chem.* **2005**, *70*, 10182-10185; (e) Le Corre, L.; Dhiman H. *Tetrahedron Lett.* **2005**, *46*, 7495-7497; (f) Alegret, C.; Santacana, F.; Riera A. *J. Org. Chem.* **2007**, *72*, 7688-7692; Pham, V.-T.; Joo, J.-E.; Tian, Y.-S.; Chung, Y.S.; Lee, K.-Y.; Oh, C.-Y.; Ham W.-H. *Tetrahedron: Asymmetry* **2008**, *19*, 318-321.

⁴ (a) Eichorn, E.; Roduit, J.-P.; Shaw, N.; Heinzmann, K.; Kiener A. *Tetrahedron: Asymmetry* **1997**, *8*, 2533-2536; (b) Letavic, M. A.; Barberia, J. T.; Carty, T. J.; Hardinik, J. R.; Liras, J.; Lopresti-Morrow, L. L.; Mitchell, P. G.; Noe, M. C.; Reeves, L. M.; Snow, S. L.; Stam, E. J.; Sweeney, F. J.; Vaughn, M. L.; Yu C. H. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3243-3246; (c) Palucki, B. L.; Park, M. K.; Nargund, R. P.; Tang, R.; MacNeil, T.; Weinberg, D. H.; Vongs, A.; Rosenblum, C. I.; Doss, G. A. Miller, R. R.; Stearns, R. A.; Peng, Q.; Tamvakopoulos, C.; Van der Ploeg, L. H. T.; Partchett A. A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1993-1996; (d) Morley, R. M.; Tse, H.-W.; Feng, B.; Miller, J. C.; Monaghan, D. T.; Jane D. E. *J. Med. Chem.* **2005**, *48*, 2627-2637; (e) Olsen, C. A.; Christensen, C.; Nielsen, B.; Clausen, R. C.; Kristensen, J. L.; Franzyk, H. H.; Jaroszewski J. W. *Org. Lett.* **2005**, *8*, 3371-3374.

⁵ Shiraiwa, T.; Tadokoro, K.; Tanaka, H.; Namba, K.; Yokono, N.; Shibazaki, K.; Kubo, M.; Kurokawa H. *Biosci. Biotechnol. Biochem.* **1998**, *62*, 2382-2387.

⁶ Zabriskie, T. M.; Liang X. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 457-462.

⁷ (a) Sladojevich, F.; Trabocchi, A.; Guarna A. *J. Org. Chem.* **2007**, *72*, 4254-4257; (b) Trabocchi, A.; Sladojevich, F.; Guarna A. *Chirality* **2009**, *21*, 584-594.

⁸ (a) Koegel, R. J.; Birnbaum, S. M.; Baker, C. G.; Sober, H. A.; Greenstein J. P. *J. Biol. Chem.* **1953**, *201*, 547-551; (b) Hardegger, E.; Liechti, P.; Jackman, L. M.; Boller, A. Plattner P. A. *Helv. Chim. Acta* **1963**, *46*, 60-74; (c) Bogdanovaky, D.; Barbier M. *Bull. Soc. Chim. Fr.* **1965**, 832-834.

⁹ Ressurreicao, A. S. M.; Bordessa, A.; Civera, M.; Belvisi, L.; Gennari, C. Piarulli, U. *J. Org. Chem.* **2008**, *73*, 652-660.

¹⁰ (a) Boger, D. L.; Lee, J. K. *J. Org. Chem.* **2000**, *65*, 5996-6000. (b) Pickersgill, I. F.; Rapoport H. *J. Org. Chem.* **2000**, *65*, 4048-4057.

¹¹ Wu, W.-J.; Raleigh, D. P. *J. Org. Chem.* **1998**, *63*, 6689-6698.

¹² Souers, J. A.; Ellman, J. A. *J. Org. Chem.* **2000**, *65*, 1222-1224.

¹³ Haque, T. S.; Little, J. C.; Gellman, S. H. *J. Am. Chem. Soc.*, **1996**, *118*, 6975-6985.

¹⁴ Wu, W.-J.; Raleigh, D. P. *Biopolymers* **1998**, *45*, 381-394.

¹⁵ D'Elia, V.; Zwicknagl, H.; Reiser, O. *J. Org. Chem.* **2008**, *73*, 3262-3265.