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ORIGINAL ARTICLE

(*S*)-α-methyl,α-amino acids: a new stereocontrolled synthesis

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Abstract A new and convenient stereocontrolled synthesis of the optically pure (*S*)-α-methyl,α-amino acids **6**(**a**–**d**) that exploits the chiral synthon 1,4-*N*,*N*-[(*S*)-1-phenylethyl]-piperazine-2,5-dione (**1**) is described. The (*S*)-1-phenylethyl group, bonded to each of the *N*-atoms of the 2,5-diketopiperazine, acts as a chiral inductor in the first alkylation, while the steric hindrance appears to be the determining factor of stereocontrol in third and forth alkylation.

Keywords Diketopiperazine derivatives · α-Methyl-α-amino acids · Asymmetric synthesis

Introduction

The stereocontrolled synthesis of optically active unnatural α,α-dialkyl-α-amino acids containing quaternary stereocenter, represents a very interesting goal for synthetic chemistry (Williams 1989). The interest toward the α,α-disubstituted α-amino acids, especially α-methyl,α-amino acids, is due to their metabolic stability and rigidity that may reduce the conformational freedom of peptides incorporating such amino acids and then alter their biological properties (Wirth 1997; Gibson et al. 1999). Moreover, several molecules with therapeutic effects containing unnatural α-amino acids are known: α-methyl, α-amino acids are present in natural antibiotics (Yano et al. 1997; Becker et al. 1997) and α-alkylated,α-amino acids are useful in studies of enzyme mechanisms (Walsh et al. 1980). Furthermore, these compounds can also be used as chiral building blocks in organic synthesis.

Various asymmetric synthetic approaches to this class of non-proteinogenic α-amino acids have been developed, as reported in very useful reviews by Cativiela and Diaz-De-Villegas (1998), Xu et al. (2005), Vogt and Brase (2007), and recently in a paper of Davies et al. (2007). However, to the best of our knowledge, a general and efficient synthesis of enantiomerically pure α-methyl,α-amino acids with potential macro scale applicability has not been reported so far. Thus, we have developed a versatile and economical stereocontrolled synthesis which is an extension of our original strategy accomplished for the stereoselective approach to natural and unnatural α-amino acids. In fact, the procedure here reported is based on our experience acquired in many years making use of the chiral 2,5-diketopiperazine derivative **1** (Piccinelli et al. 2003; Ferioli et al. 2002; Paradisi et al. 2000a, b, 2002; Porzi and Sandri 1994; Orena et al. 1992, 1993) and represents an improvement of the synthetic methodology previously employed by us (Carloni et al. 1998; Porzi and Sandri 1998) which involves the use of an optically active morpholinone derivative as chiral synthon. This procedure provides a more convenient synthetic route as two equivalents of α-methyl-α-amino acids are produced from one equivalent of the corresponding synthon with a remarkable improvement of atom-economy. The advantage of our new method is the stereocontrolled alkylation of the

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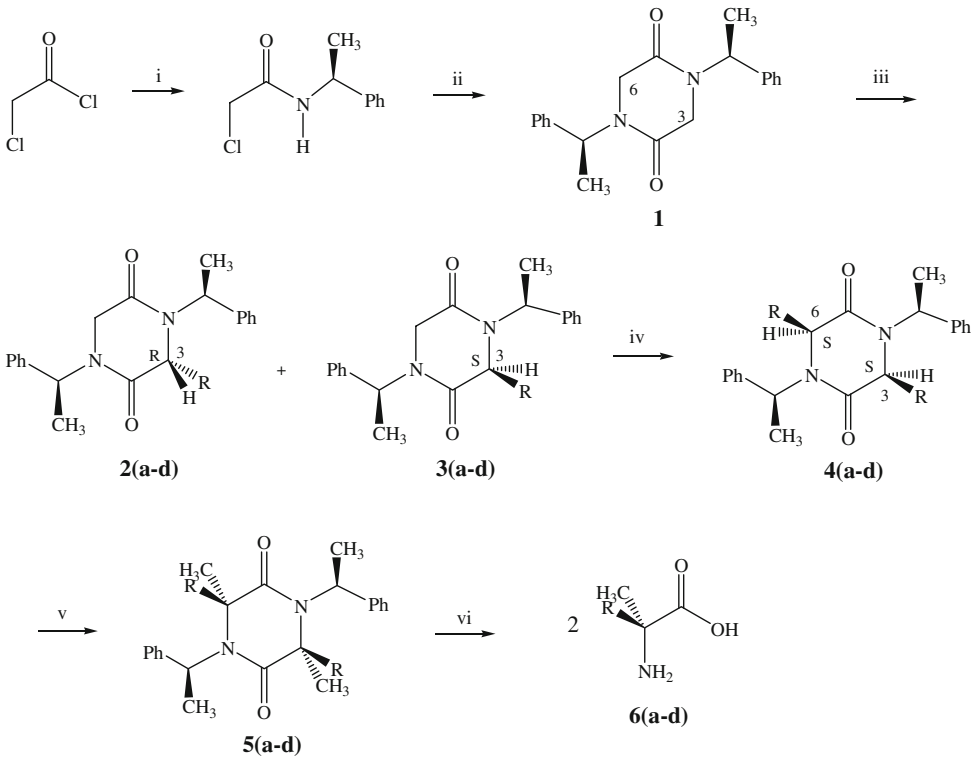


Scheme 1 *i* $Na_2CO_3 \cdot 10H_2O$, in water/acetone (Orena et al. 1992), *ii* NaOH, in CH_3CN (Cho et al. 2004), *iii* Metallation of **1** with 1 M LHMDS in dry THF, then R-X, *iv* Metallation of **3** with 1 M LHMDS in dry THF, then R-X; *v* Metallation of **4** with 1 M LHMDS in dry THF, then CH_3I, *vi* Refluxing in 57% HI, then treatment with Dowex 50 WX 8 ion-exchange resin. R = (a) CH_3–CH_2, (b) CH_3–CH_2–CH_2, (c) CH_3–$(CH_2)_2$–CH_2, (d) Ph–CH_2

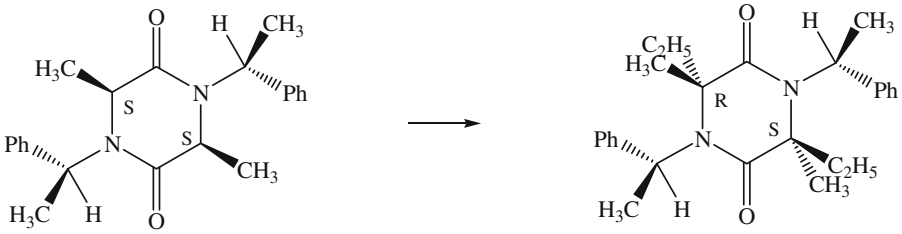
intermediate **3** which occurs with practically total diastereoselectivity furnishing only the *cis* derivative (3*S*,6*S*)-**4**, as we have already observed in analogous cases (Piccinelli et al. 2003; Ferioli et al. 2002; Paradisi et al. 2000a, b, 2002; Porzi and Sandri 1994; Orena et al. 1992, 1993). Besides, by a simple one pot procedure the intermediate **5** is converted to the title products in high yield (Scheme 1).

Results and discussion

The versatile chiral synthon 1,4-*N*,*N*-[(*S*)-phenethyl]-piperazine-2,5-dione (**1**) previously employed by us (Piccinelli et al. 2003; Ferioli et al. 2002; Paradisi et al. 2000a, b, 2002; Porzi and Sandri 1994; Orena et al. 1992, 1993), was easily obtained in good yield by a modified procedure (Porzi and Sandri 1994; Orena et al. 1992). In fact, the chloroacetamide of (*S*)-phenylethylamine, obtained from chloroacetyl chloride and (*S*)-phenyl ethylamine, was coupled in one pot in an alkaline medium furnishing **1** (Scheme 1) in good yield (Cho et al. 2004). In the first alkylation reaction the diastereomer (3*S*)-**3** was obtained in 20–50% d.e. because of the presence of the chiral inductor group (*S*)-1-phenylethyl bonded to each *N*-atom of the 2,5-diketopiperazine. The second alkylation gave the dialkyl derivative (3*S*,6*S*)-**4** with a total 1,4-*cis* induction, the d.e. determined by ^{1}H NMR being greater than 98%, as we have already observed for similar substrates (Piccinelli et al. 2003; Ferioli et al. 2002; Paradisi et al. 2000a, b, 2002; Porzi and Sandri 1994; Orena et al. 1992, 1993). Along with the intermediate **4**, also the corresponding trialkylderivative is recovered in about 20% of the overall yield of the reaction except when R = CH_2Ph.

The 3,6-dialkyl derivative **4** was then alkylated twice in a one pot procedure with CH_3I obtaining the tetraalkylated 2,5-diketopiperazine (3*S*,6*S*)-**5** (Scheme 1). The stereochemistry of compounds **5** was confirmed by X-ray crystallography where possible. Otherwise, determination of the stereochemistry was achieved by analysis of the NMR spectra, in which half of the expected signals were present in relation to the number of protons and carbon atoms in the compound. This is evidently due to the magnetic equivalence of protons and carbon atoms (Orena et al. 1992, 1993; Porzi and Sandri 1994), that is a C2 symmetry axis, which is not present in the *trans* derivatives (see as example compounds **5a** and **8**). In this step, the steric interaction appears to be the determining factor of the stereochemical control because the alkylation occurs with a practically total stereoselectivity because the second alkyl group, presently CH_3, is introduced at C-3 in *trans* configuration with respect to the bulkier group at C-6 position. Thus, the stereochemical outcome of the third and fourth alkylation is most likely controlled by the relative bulkiness of the R group with respect to CH_3. Consequently, it can be asserted that the first alkyl group introduced must be bulkier than the second one in order to obtain both centres

Scheme 2 Dimethyl-**7** and tetraalkyl-**8**-intermediates



7 **8**

in the *S*-configuration. As a matter of fact, when R = CH_3, the alkylation of **7** with C_2H_5I gave only the undesired tetralkyl derivative (3*S*,6*R*)-**8** as confirmed from the NMR spectra of the product (Scheme 2). The stereochemistry of compound **8** has been determinate by X-ray (Fig. 5). Debenzylation to remove the chiral inductor and hydrolytic cleavage of heterocyclic ring were simply carried out in one step by refluxing in 57% HI, according to the procedure described already (Orena et al. 1992). After adsorption on an ion-exchange resin in acid form (Dowex 50WX 8, 20–50 mesh), the pure α-methyl,α-amino acids **6** were recovered by eluting with 5 M NH_4OH. The conversion of the intermediates **5** to the (*S*)-α-substituted alanine derivatives **6** was monitored by TLC and ^{1}H NMR showing that the debenzylation reaction occurs before the heterocyclic ring opening.

The absolute configuration of **2** and **3** was assigned by means of ^{1}H-NMR spectroscopy on the basis of the observed shielding effect (Porzi and Sandri 1994; Orena et al. 1992) exerted by the phenyl ring on the (C-3)-H in **3** with respect to **2**. Analogously, the stereochemistry of **4** and **5** was deduced taking into account such a shielding effect suffered by (C-3)-H and (C-6)-H in **4** and by (C-3)-CH_3 and (C-6)-CH_3 in **5**. For instance, the (C-3)-H in **2d** and **3d** resonates as dd at 4.3 ppm and at 4.1 ppm, respectively, and the signals of (C-3)-H and (C-6)-H in **4d** are overlapped resonating at 4.0 ppm according to that previously observed (Paradisi et al. 2002). In addition, as already registered for analogous substrates (Porzi and Sandri 1994; Orena et al. 1992), the ^{1}H- and ^{13}C NMR spectra of the intermediates **4** and **5** show half signals indicating the presence of a C_2 symmetry axis, typical of the *cis* derivative, which causes the overlapping of the magnetically equivalent nucleus. Furthermore, the configuration of the new C-3 and C-6 stereocenters was confirmed both by single crystal X-ray determination (see later) performed on **5**(**a**, **d**) and the *cis*-3,6-dibenzyl-3-methyl derivative **9** precursor of **5d** (Fig. 1) and by the coincidence of the specific rotation values of the title α-methyl-α-amino acids **6**(**a–d**) with those reported in literature (see "Experimental").

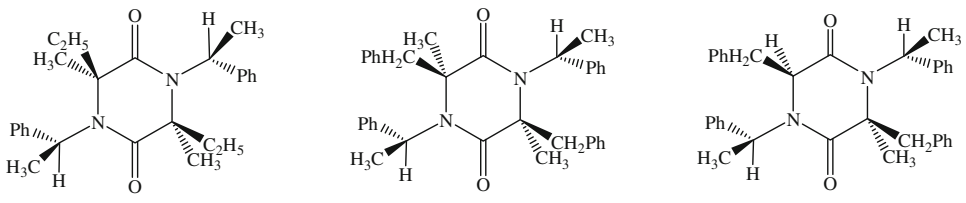
We believe that the strategy described above is interesting as the (3*R*)-diastereomer **2** can also be utilized. In fact, as we have already observed (Ferioli et al. 2002; Paradisi et al. 2002) alkylation of the isomer **2** gave a mixture of *cis* and *trans* isomers and the latter one can be isomerized in an alkaline solution to a 50% mixture of the *cis* isomers (3*R*,6*R*) and (3*S*,6*S*). Both the *cis* isomers, separable by silica gel chromatography, can be employed to obtain the α,α′-disubstituted α-amino acids in enantiomeric pure form.

X-ray diffraction studies

The X-ray crystal structures of **5**(**a**, **d**) and **9** are shown in Fig. 2 and the ORTEP drawing of **5**(**a**, **d**), **8** and **9** are reported in Fig. 3. The absolute configuration of C(2) and C(4) stereogenic carbons in **5**(**a**, **d**), **8** and **9** was determined from the X-ray data with the help of known configuration at C(5) and C(13) stereocenters fixed by the synthetic route.

It is worth mentioning that the C(2) and C(4) carbon stereocentres have the same (*S*) configuration in all molecules. The diketopiperazine ring conformations, in the three solid state structures, are different (see Fig. 4): in **5a**, the heterocyclic ring slightly deviates from planarity, **5d** has a boat conformation and **9** has five almost coplanar atoms of the ring [C(1), C(2), C(3), N(1) and N(2)] and

Fig. 1 Tetraalkyl-**5**(**a**, **d**) and trialkyl-**9** intermediates



5a **5d** **9**

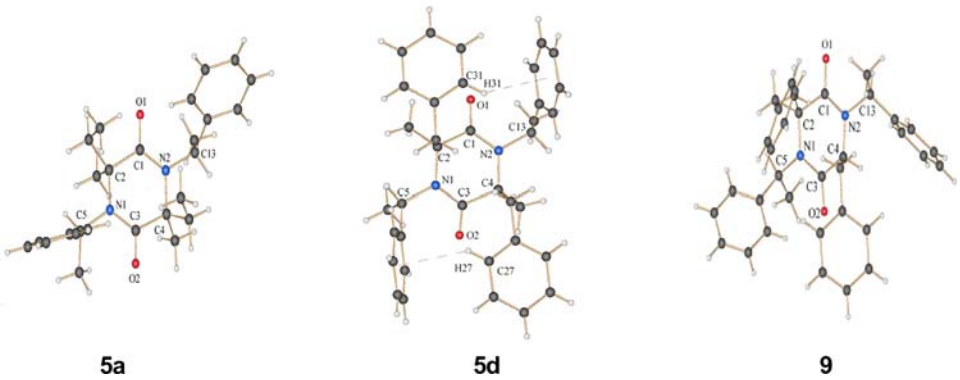


Fig. 2 X-ray crystal structures of **5**(**a**, **d**) and **9**. Configurations of the stereogenic carbons (in the three structures): C(2) (S); C(4) (S); C(5) (S); C(13) (S). C(2) and C(4) atoms correspond to C(3) and C(6) atoms in Scheme 1

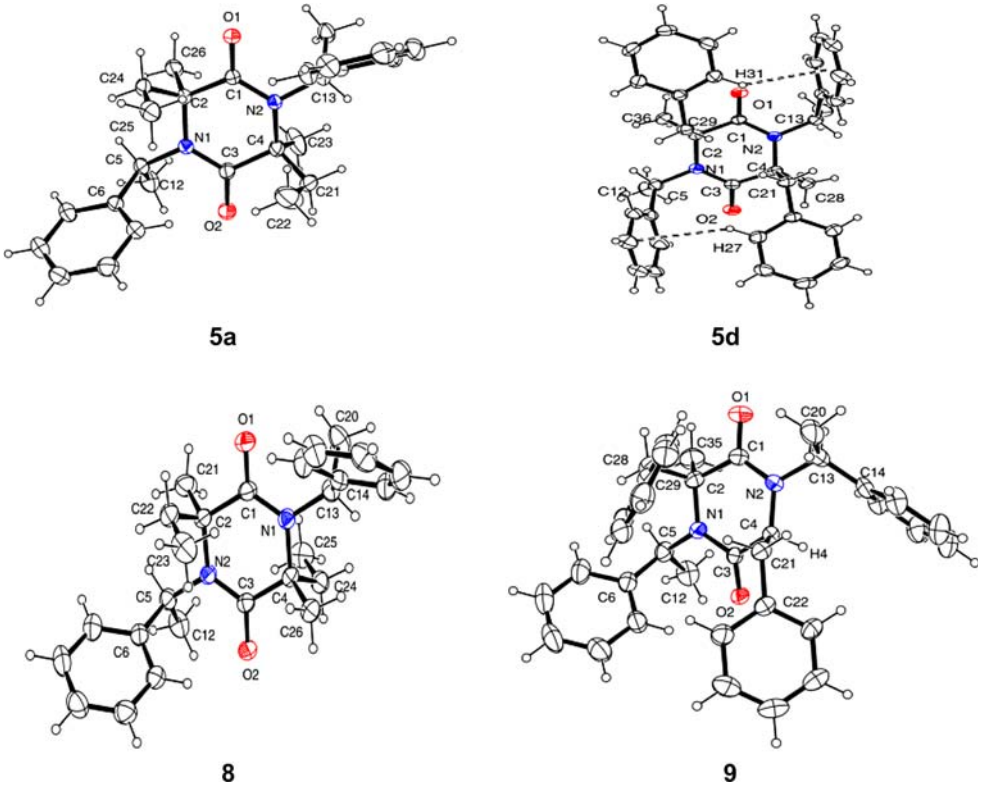


Fig. 3 ORTEP drawing of **5**(**a**, **d**), **8** and **9.** Thermal ellipsoids are at 30% probability level

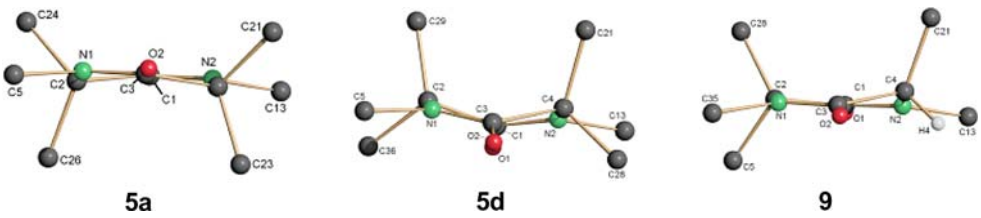


Fig. 4 Conformations of diketopiperazine rings in **5**(**a**, **d**) and **9**

C(4) is out of the plane of 0.317(2) Å. The three molecules differ also for the orientation of both alkyl groups and of the (*S*)-phenylethyl chiral fragment. In this context, the conformation of **5d** is influenced by two weak intramolecular C--H $\cdots$ πPh hydrogen bonds [H(31)—π 2.75(3) Å, C(31)—π 3.52(4) Å and C(31)-H(31)—π 141.3(5)° and H(27)—π 2.83(2) Å, C(31)—π 3.59(3) Å and C(31)-H(31)—π 140.2(4)°] (Fig. 2). These values are in agreement with the ones reported in literature for X–H—π interaction (Najera et al. 2000). A close inspection of the crystal packings reveals the absence of significant intermolecular contacts except for an hydrogen bond interaction between an amidic oxygen and a proton of a molecule of methanol that crystallized in **5a** [O(methanol)-H1 1.03(4) Å,

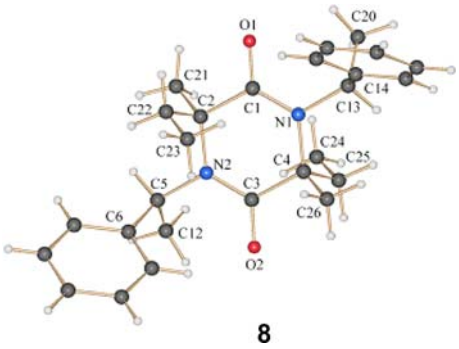


Fig. 5 Molecular structure of **8.** Configurations of the stereogenic carbons are: C(2) (*S*), C(4) (*R*), C(5) (*S*), C(13) (*S*)

O(methanol)-H1 ··· O(1) 167(4)°, O(methanol) ··· O(1) 2.765(3) Å].

The stereochemistry of **8** (Fig. 5) shows that the molecule differs from **5a** for the configuration of the stereogenic carbon C(4) which is *R* instead of *S*.

The C_1 molecular symmetry of **8**, derived from the rationalization of the ^{1}H and ^{13}C-NMR spectra in solution, is in agreement with the observed molecular structure.

Crystallographic in CIF format for **5a** (CCDC 715767), **5d** (CCDC 715768), **8** (CCDC 715769) and **9** (CCDC 715770) are available free of charge via the internet at http://pubs.acs.org.

Conclusions

We have demonstrated that the readily available chiral diketopiperazine **1** is a very useful synthon for the stereocontrolled synthesis of α-substituted alanine derivatives. Thus, we believe that it would be interesting to undertake further work to optimize and extend the methodology to other unnatural α-amino acids present in biologically active compounds. Our synthetic route is suitable for macro scale applicability. In fact, simply and well-understood reactions are employed and all the reaction intermediates are obtained in good yield. The procedure here described was patented (deposition number RM2008A000118).

Experimental

General

Melting points are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on a Gemini spectrometer at 300 MHz using $CDCl_3$ as the solvent, unless otherwise stated. Chemical shifts are reported in ppm using the residual solvent signal as reference and the coupling constants (*J*) are in Hz. Optical rotation values were measured at 25°C on a Perkin-Elmer 343 polarimeter. Dry THF was distilled from sodium benzophenone ketyl. Chromatographic separations were performed with silica gel 60 (230–400 mesh).

For the spectroscopic data of compounds **2**(**b**, **d**), **3**(**b**, **d**) and **4**(**b**, **d**) see Porzi and Sandri (1994), while the data of compound **7** were described by Orena et al. (1992).

The diffraction experiments for the **5**(**a**, **d**), **8** and **9** were carried out at room temperature on a Bruker APEX II CCD-based diffractometer using graphite monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å). Intensity data were measured over full diffraction spheres using 0.3° wide ω scans, crystal-to-detector distance 5.0 cm. The software SMART was used for collecting frames of data, indexing reflections and determination of lattice parameters. The collected frames were then processed for integration by software SAINT and an empirical absorption correction was applied with SADABS. The structures were solved by direct methods (SIR 97) and subsequent Fourier syntheses, and refined by full-matrix least-squares calculations on F^2 (SHELXTL) attributing anisotropic thermal parameters to the non-hydrogen atoms.

General procedure for the conversion of 1–2 and 3

To a stirred solution of **1** (4.67 g, 14.5 mmol) in dry THF (70 mL), cooled at −78°C, 14.5 mL (1 M solution in THF) of LHMDS was added. After 1 h the alkyl halide (14.5 mmol) was added dropwise to the reaction mixture and stirred for about 1 h at −78°C. Subsequently, the cooling bath was removed and after about 2 h the reaction was quenched by the addition of water (70 mL) and extracted with ethyl acetate. The organic solution was dried and the solvent evaporated under reduced pressure. The residue was submitted to silica gel chromatography eluting with hexane/ethyl acetate to separate the diastereomers **2** and **3**.

(3R)-1,4-N,N-[(S)-phenylethyl]-3-ethylpiperazine-2,5-dione 2a

After chromatography (EtAc-Hex: 25/75) the product was obtained as a white solid in 35% yield by alkylating **1** with iodoethane. ^{1}H NMR δ: 0.61 (t,3H,J = 7.5); 1.09 (m,2H), 1.56 (d,3H,J = 7.2); 1.60 (d,3H,J = 7.2), 3.54 (q_{AB},2H, J = 17.4), 3.92 (dd, 1H,J = 4.8, 8.1), 5.85 (q,1H,J = 7.2), 5.94 (q,1H,J = 7.2), 7.31 (m,10ArH). ^{13}C NMR δ: 9.2, 15.1, 16.1, 25.8, 45.0, 50.2, 51.4, 58.5, 127.2, 127.8, 128.0, 128.1, 128.5, 128.7, 138.5, 139.4, 164.9, 166.5. $[\alpha]_D$ −324.3 (c 1.0, $CHCl_3$). M.p. 156–157°C. Anal. Calcd. for $C_{22}H_{26}N_2O_2$: C,75.4; H,7.48; N,7.99. Found: C,75.65; H,7.50; N,7.95 ($R_f = 0.60$, EtAc/Hex: 35/65).

(3R)-1,4-N,N-[(S)-phenylethyl]-3-butylpiperazine-2,5-dione 2c

After chromatography (EtAc-Hex: 25/75 the product was obtained as white solid in 25% yield by alkylating **1** with iodobutane. ^{1}H NMR δ: 0.66 (m,3H), 0.8–1.17 (m,6H), 1.58 (d,3H,J = 7.2), 1.62 (d,3H,J = 7.2), 3.57 (q_{AB},2H,J = 17.4), 3.97 (m,1H), 5.91 (q,1H,J = 7.2); 5.96 (q,1H,J = 7.2), 7.38 (m,10ArH). ^{13}C NMR δ: 13.6, 15.0, 16.0, 22.0, 26.7, 32.2, 45.0, 50.2, 51.2, 57.3, 127.2, 127.9, 128.0, 128.1, 128.6, 128.7, 138.6, 139.4, 164.9, 166.8. $[\alpha]_D$ −350.1 (c 0.4, $CHCl_3$). M.p. 135–136°C. Anal. Calcd. for $C_{24}H_{30}N_2O_2$: C,76.16; H,7.99; N,7.40. Found: C,75.98; H,7.96; N,7.42 (R_f = 0.52, EtAc/Hex: 35/65).

(3S)-1,4-N,N-[(S)-phenylethyl]-3-ethylpiperazine-2,5-dione 3a

After chromatography (EtAc-Hex: 25/75) the product was obtained as a wax in 55% yield by alkylating **1** with iodoethane. ^{1}H NMR δ**:** 1.03 (t,3H,J = 7.4), 1.54 (d,3H,J = 7.2), 1.65 (d,3H,J = 7.2), 1.78–2.07 (m,2H), 3.71 (dd,1H,J = 4.0, 8.4), 3.78 (q_{AB},2H,J = 17.4), 5.82 (q,1H,J = 7.2), 5.93 (q,1H,J = 7.2), 7.29 (m,10ArH). ^{13}C NMR δ: 9.4, 15.4, 17.3, 27.5, 44.5, 49.8, 52.0, 58.4, 127.0, 127.1, 127.9, 128.0, 128.7, 128.8, 138.7, 139.0, 165.2, 166.5. $[\alpha]_D$ −263.5 (c 0.3, $CHCl_3$). Anal. Calcd. for $C_{22}H_{26}N_2O_2$: C,75.40; H,7.48; N,7.99. Found: C,75.55; H,7.45; N,8.02 (R_f = 0.50, EtAc/Hex: 35/65).

(3S)-1,4-N,N-[(S)-phenylethyl]-3-butylpiperazine-2,5-dione 3c

After chromatography (EtAc-Hex: 25/75 the product was obtained as a wax in 65% yield by alkylating **1** with iodobutane. ^{1}H NMR δ: 0.94 (m,3H), 1.39(m,4H), 1.53 (d,3H,J = 7.4), 1.64(d,3H,J = 7.4), 1.84 (m,2H), 3.74 (dd, 1H,J = 4.4, 8.4), 3.78 (q_{AB},2H,J = 17), 5.80 (q,1H,J = 7.4), 5.90 (q,1H,J = 7.4), 7.30 (m,10ArH). ^{13}C NMR δ: 13.8, 15.4, 17.3, 22.5, 27.1, 34.0, 44.6, 49.8, 52.0, 57.4, 127.0, 127.1, 127.9, 128.1, 128.8, 128.9, 138.8, 139.1, 165.3, 166.8. $[\alpha]_D$ −127.9 (c 0.7, $CHCl_3$). Anal. Calcd. for $C_{24}H_{30}N_2O_2$: C,76.16; H,7.99; N,7.40. Found: C,76.26; H,7.98; N,7.44 (R_f = 0.62, EtAc/Hex: 35/65).

General procedure to (3*S*,6*S*)-dialkyl derivatives 4

To a stirred solution of **3** (12.5 mmol) in dry THF (60 mL), cooled at −78°C, 12.5 mL (1 M solution in THF) of LHMDS was added and after 1 h the alkyl halide (12.55 mmol) was added dropwise to the reaction mixture. The reaction was stirred for about 1 h at −78°C and then the cooling bath removed. The reaction, followed by TLC, was quenched after 5–6 h by adding water (60 mL). The reaction product was extracted with ethyl acetate, the organic solution dried and the solvent evaporated under reduced pressure. The residue was purified by silica gel chromatography eluting with hexane/ethyl acetate.

(3S,6S)-1,4-N,N-[(S)-phenylethyl]-3,6-diethylpiperazine-2,5-dione 4a

After chromatography (EtAc-Hex: 25/75) the product was obtained as a wax in 85% yield by alkylating **3a** with iodoethane**.** ^{1}H NMR δ: 1.11 (t,6H,J = 7.4), 1.63 (d,6H,J = 7.2); 1.95 (m,4H), 3.58 (dd,2H,J = 5.8, 8.4), 5.84 (q,2H,J = 7.2), 7.28 (m,10ArH). ^{13}C NMR δ: 11.2, 17.2, 29.6, 51.4, 58.6, 126.8, 127.3, 127.9, 128.5, 139.2, 166.7. $[\alpha]_D$ −136 (c 0.2, $CHCl_3$). Anal. Calcd. for $C_{24}H_{30}N_2O_2$: C,76.16; H,7.99; N,7.4. Found: C,76.76; H,8.01; N,7.38 (R_f = 0.60, EtAc/Hex: 35/65).

(3S,6S)-1,4-N,N-[(S)-phenylethyl]-3,6-dibutylpiperazine-2,5-dione 4c

After chromatography (EtAc-Hex: 25/75) the product was obtained as a wax in 90% yield by alkylating **3c** with iodobutane. The reaction was quenched after 7–8 h ^{1}H NMR δ: 0.94 (t,6H,J = 7), 1.24–2.61 (m,8H), 1.63 (d,6H,J = 7.2), 1.89 (m,4H), 3.65 (dd,2H,J = 5.4, 8.6), 5.84 (q,2H,J = 7.2), 7.32 (m,10ArH). ^{13}C NMR δ: 13.8, 17.5, 22.5, 29.1, 36.5, 51.6, 57.5, 127.0, 127.9, 128.7, 139.5, 167.4. $[\alpha]_D$ −103.2 (c 1.3, $CHCl_3$). Anal. Calcd. for $C_{28}H_{38}N_2O_2$: C,77.38; H,8.81; N,6.45. Found: C,77.52; H,8.82; N,6.43 (R_f = 0.60, EtAc/Hex: 35/65).

General procedure to (3*S*,6*S*)-3,6-dimethyl-3,6-dialkylderivatives 5

To a stirred solution of **4** (11.26 mmol) in dry THF (60 mL), cooled at −78°C, 11.3 mL (1 M solution in THF) of LHMDS was added and after 1 h iodomethane (0.71 mL, 11.26 mmol) was added dropwise to the reaction mixture. The reaction was stirred for about 1 h at −78°C and then the cooling bath removed. After 2 h the reaction was cooled at −78°C and 1.5 equivalents of 1 M LHMDS (17 mL) was added. After 1 h iodomethane (0.71 mL, 11.3 mmol) was added, then the cooling bath was removed and the reaction mixture was stirred overnight. The reaction was quenched by adding water (60 mL) and the title product was extracted with ethyl acetate. The organic solution was dried and the solvent evaporated under reduced pressure. The residue was purified by silica gel chromatography eluting with hexane/ethyl acetate.

3S,6S)-1,4-N,N-[(S)-phenylethyl]-3,6-diethyl-3,6-dimethylpiperazine-2,5-dione 5a

After chromatography (EtAc-Hex: 25/75) the product was obtained as a white solid in 85% yield. ^{1}H NMR δ: 0.52 (t,6H,J = 7); 1.68 (s,6H), 1.78 (m,2H), 1.89 (d,6H,J = 7), 2.19 (m,2H), 4.47 (q,2H,J = 7), 7.21–7.59 (m,10ArH). ^{13}C NMR δ: 9.2, 20.6, 27.1, 31.2, 56.8, 66.5, 126.8, 127.8, 128.0, 141.7, 168.2. $[\alpha]_D$ +44.9 (c 0.6, $CHCl_3$). Anal. Calcd. for $C_{26}H_{34}N_2O_2$: C,76.81; H,8.43; N,6.89. Found: C,76.87; H,8.41; N,6.86. M.p. = 134–135°C (R_f = 0.65, EtAc/Hex: 35/65).

(3S,6S)-1,4-N,N-[(S)-phenylethyl]-3,6-dipropyl-3,6-dimethylpiperazine-2,5-dione 5b

After chromatography (EtAc-Hex: 25/75) the product was obtained as white solid in 90% yield. ^{1}H NMR δ: 0.52 (t,6H,J = 7), 0.63–1.11 (m,4H), 1.67 (s,6H), 1.68 (m,2H), 1.88 (d,6H,J = 7), 2.13 (m,2H), 4.47 (q,2H,J = 7), 7.27 (m,6ArH), 7.56 (m,4ArH). ^{13}C NMR δ: 13.3, 17.6, 21.1, 27.4, 40.5, 57.3, 66.1, 126.9, 128, 142.3, 168.4. $[\alpha]_D$ +67.1 (c 1.0, $CHCl_3$). M.p. 169°C (dec). Anal. Calcd. for $C_{28}H_{38}N_2O_2$: C,77.38; H,8.81; N,6.45. Found: C,77.67; H,8.85; N,6.46 (R_f = 0.62, EtAc/Hex: 35/65).

(3S,6S)-1,4-N,N-[(S)-phenylethyl]-3,6-dibutyl-3,6-dimethylpiperazine-2,5-dione 5c

After chromatography (EtAc-Hex: 25/75) the product was obtained as a wax in 80% yield. ^{1}H NMR δ: 0.55 (m,6H), 0.65–1.18 (m,8H), 1.67 (s,6H), 1.87 (m,2H), 1.89 (d,6H,J = 7), 2.09 (m,2H), 4.47 (q,2H,J = 7), 7.19–7.61 (m,10ArH). ^{13}C NMR δ: 13.7, 21.1, 22.2, 27.0, 27.4, 38.5, 57.3, 66.2, 127.0, 127.9, 128.1, 142.2, 168.4. $[\alpha]_D$ +29.3 (c 0.3, $CHCl_3$). Anal. Calcd. for $C_{30}H_{42}N_2O_2$: C,77.88; H,9.15; N,6.05. Found: C,77.99; H,9.19; N,6.06 (R_f = 058, EtAc/Hex: 35/65).

(3S,6S)-1,4-N,N-[(S)-phenylethyl]-3,6-dibenzyl-3,6-dimethylpiperazine-2,5-dione 5d

After chromatography (EtAc-Hex: 25/75) the product was obtained as a white solid in 90% yield. ^{1}H NMR δ: 1.73 (s,6H), 1.89 (d,6H,J = 7), 3.0 (q_{AB},4H,J = 14.2), 4.66 (q,2H,J = 7), 6.60 (m,4ArH), 6.96 (m,4ArH), 7.12 (m,2ArH), 7.30 (m,10ArH). ^{13}C NMR δ: 16.6, 26.8, 44.7, 56.8, 66.0, 126.5, 126.9, 127.7, 127.9, 128.8, 130.7, 135.8, 140.8, 167.0. $[\alpha]_D$ +86.2 (c 0.5, $CHCl_3$). Anal. Calcd. for $C_{36}H_{38}N_2O_2$: C,81.47; H,7.22; N,5.28. Found: C,81.60; H,7.19; N,5.27. M.p. 134.5–135.5°C (R_f = 0.65, EtAc/Hex: 35/65).

General procedure to α-methyl-α-amino acids 6

The intermediate **5** (1 mmol) was refluxed in 57% HI (10 mL) for 8–9 h. The reaction solution was then evaporated under vacuum and the residue dissolved in water (10 mL) and extracted with ethyl acetate. The aqueous solution was eluted more than once on a column filled with the acid ion-exchange resin Dowex 50 WX 8 (20–50 mesh) carefully washed with distilled water. The resin was again washed with distilled water until neutral pH of eluent and then the title product was recovered eluting with 5 M NH_4OH. The aqueous solution was evaporated under vacuum until dryness and the pure α-methyl,α-aminoacid was obtained in practically quantitative yield.

(S)-2-ethylalanine 6a

^{1}H NMR (CD_3OD) δ: 0.99 (t,3H,J = 7.4), 1.45 (s,3H), 1.73 (m,1H), 1.93 (m,1H). ^{13}C NMR δ: 8.7, 23.5, 32.0, 63.0, 176.8. $[\alpha]_D$ +10.2 (c 1, H_2O) [(Najera et al. 2000) $[\alpha]_D$ +10.1 (c 1, H_2O)].

(S)-2-propylalanine 6b

^{1}H NMR (D_2O) δ: 0.85 (t,3H,J = 7), 1.2 (m,2H), 1.38 (s,3H), 1.7 (m,2H). ^{13}C NMR (D_2O) δ: 14.0, 17.5, 23.2, 40.1, 62.3, 177.7. The title compound was converted into the hydrochloride salt: $[\alpha]_D$ +6.3 (c 1.0, H_2O) [(Moretto et al. 2000) $[\alpha]_D$ +6.5 (c 1, H_2O)].

(S)-2-butylalanine 6c

^{1}H NMR (CD_3OD) δ: 0.94 (m,3H), 1.36 (m,4H), 1.44 (s,3H), 1.58–1.97 (m,2H). ^{13}C NMR δ: 14.3, 24.0, 27.2, 39.0, 62.6, 176.8. The title compound was converted into the hydrochloride salt: $[\alpha]_D$ +10.1 (c 1, H_2O) [(Davis et al. 2000) $[\alpha]_D$ +10.5 (c 1, H_2O)].

(S)-2-benzylalanine 6d

^{1}H NMR (CD_3OD) δ: 1.52 (s,3H), 3.11 (q_{AB},2H,J = 14.2), 7.31 (m,5ArH). ^{13}C NMR δ: 23.7, 44.5, 63.0, 128.6, 129.9, 131.5, 136.3, 176.3. $[\alpha]_D$ −21.7 (c 0.3, H_2O) [(Kruizinga et al.1988) $[\alpha]_D$−22.0 (c 1.0, H_2O)]. The title compound was converted into the hydrochloride salt: $[\alpha]_D$ −5.8 (c 1, H_2O) [(Kolb and Barth 1980) $[\alpha]_D$−5.6 (c 1, H_2O)].

(3*S*,6*R*)-1,4-*N*,*N*-[(*S*)-phenylethyl]-3,6-diethyl-3,6-dimethylpiperazine-2,5-dione 8

It was obtained starting from **7** and following the procedure described for **5**. The title product was isolated as a white

solid (M.p. 170.2–171.6°C) in about 80% yield after crystallization from methanol. ^{1}H NMR δ: 0.4 (t,3H,J = 7.2), 1.02 (t,3H,J = 7.2), 1.71 (s,3H), 1.78 (s,3H), 1.92 (d,6H, J = 7), 1.8 (m,3H), 2.2 (m,1H), 4.49 (m,2H), 7.2–7.6 (m,10ArH). ^{13}C NMR δ: 8.5, 9.3, 17.6, 20.1, 27.2, 28.6, 32.2, 32.5, 55.0, 56.3, 66.1, 66.2, 126.8, 127.7, 127.8, 127.9, 128.2, 141.2, 141.4, 167.7, 168.0. $[\alpha]_D$ −80.9 (c 0.7, $CHCl_3$). Anal. Calcd. for $C_{26}H_{34}N_2O_2$: C,76.81; H,8.43; N,6.89. Found: C,76.97; H,8.40; N,6.88.

(3*S*,6*S*)-1,4-*N*,*N*-[(*S*)-phenylethyl]-3,6-dibenzyl-3-methylpiperazine-2,5-dione 9

The product was obtained as a white solid in 70% yield by the monoalkylation of **4d** with CH_3I and following the general procedure employed to synthesize **4**. ^{1}H NMR δ**:** 1.51 (dd,1H,J = 9.2, 14.6), 1.61 (d,3H,J = 7), 1.88 (d,3H,J = 7), 1.92 (s,3H), 2.27 (dd,1H,J = 4, 14.6); 3.14 (q_{AB},2H,J = 13.6), 3.68 (dd,1H,J = 4, 9.2), 4.71 (q,1H,J = 7), 5.58 (q,1HJ = 7), 6.68 (m,4ArH), 7.07–7.38 (m,14ArH), 7.62 (m,2ArH). ^{13}C NMR δ **:** 17.7, 21.4, 27.9, 41.3, 44.1, 55.0, 57.7, 59.0, 68.7, 126.3, 127.0, 127.1, 127.5, 128.0, 128.1, 128.2, 128.3, 128.6, 128.7, 128.8, 128.9, 129.4, 131.3, 135.8, 137.3, 138.3, 142.4, 165.8, 167.6. $[\alpha]_D$ +224.4 (c 0.5, $CHCl_3$). Anal. Calcd. for $C_{35}H_{36}N_2O_2$: C,81.36; H,7.02; N,5.42. Found: C,81.56; H,6.99; N,5.40. M.p. 204–205°C.

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