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Synthesis of (3*R*,6*R*)- and (3*S*,6*S*)-3,6-dialkylpiperazin-2,5-dione derivatives as useful intermediates to both (*R*) and (*S*) α-aminoacids

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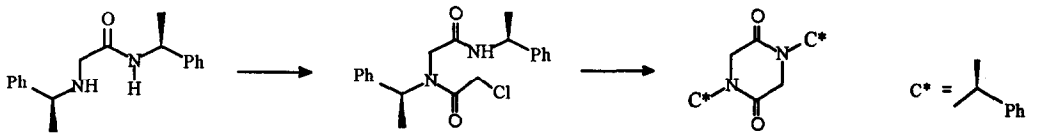
Abstract : The alkylation of **2** leads to a diastereomeric mixture where **4** is generally present in greater amounts than **3**. The successive alkylation of **4** affords exclusively the *cis* derivative **7**, while a *cis/trans* mixture is obtained from isomer **3**. In alkaline solution, the *trans* isomer **6** suffers a total conversion into a 1:1 mixture of the *cis* isomers **5** and **7** easily separated by silica gel chromatography. The configurations of the introduced stereogenic centers at C-3 and C-6 have been assigned on the basis of ^{1}H-NMR spectroscopic data. Cleavage of heterocyclic ring of **5** and **7** leads to the corresponding (*R*)- and (*S*)-α-aminoacids respectively. Therefore, the substrate **2** appears a very useful chiral template to synthetize enantiomerically pure α-amino acids.

In previous papers [1,2] we have described the observed cis 1,4-induction in the alkylation of (3*S*)- and (3*R*)-1,4-*N*,*N*-((*S*)-1-phenethyl)-3-methyl-piperazine-2,5-diones which appear versatile and useful synthons in the enantioselective synthesis of optically active α-amino acids. In a continuation of our studies on the reactivity of these derivatives, containing the chiral moiety (*S*)-1-phenethylamine, we wish to report here an extension and an improvement of the enantioselective synthesis of α-amino acids via the cyclic intermediate **2**. The procedure we followed consists in a double alkylation of **2** and allows to obtain optically pure α-amino acids avoiding the tedious separation of the desired α-amino ester from the alanine ester, separation instead required in the previous synthetic method [2].

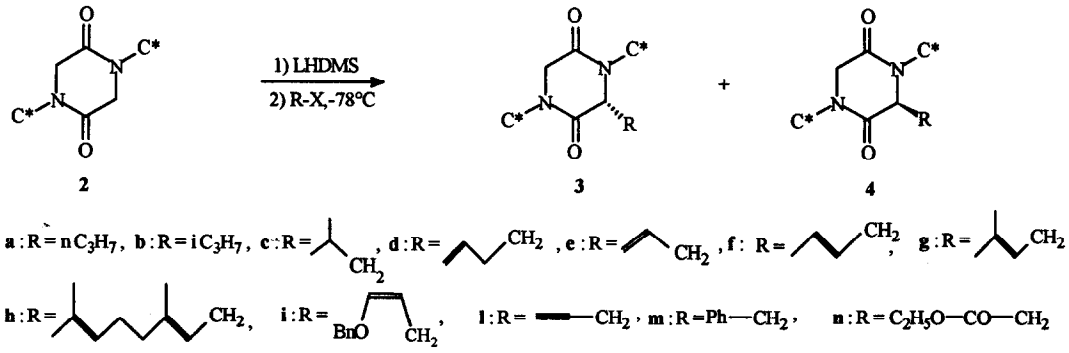
The compoud **1** is obtained in 90% yield from the Schotten-Baumann reaction of chloroacetyl chloride with (4*S*)-*N*-[(*S*)-1-phenethyl]-4-phenyl-3-azapentanamide obtained as previously described[1]. The treatment of **1** with n-BuLi in THF at 0°C gives the 1,4-substituted piperazine-2,5-dione **2** (Scheme 1), which is obtained pure in 80% yield after crystallization from ether or ethyl acetate.



1 **2**

Scheme 1

Metallation of **2**, performed in THF at 0°C with LHMDS, followed by alkylation with alkyl halide at -78°C (Scheme 2) affords a diastereomeric mixture (**3** + **4**) where the (3*S*)-**4** isomer generally predominates (Table 1). The same reaction, carried out on both (3*R*)-**3** (a,e,g,h,m) and (3*S*)-**4** (a,e,g,h,m), occurs in good yield (Scheme 3), but the stereochemical outcome is different (see Table 2). In fact, in agreement with the previous results [1,2], the alkylation of (3*S*)-**4** (a,e,g,h,m) brings to a total *cis* 1,4-induction and always affords the *cis*-isomer (3*S*,6*S*)-**7** independently on the steric hindrance of both C-3 substituents and alkylating reagents.



Scheme 2

Table 1. Diastereoselective alkylation of **2** and selected chemical shifts (δ) for **3** and **4**

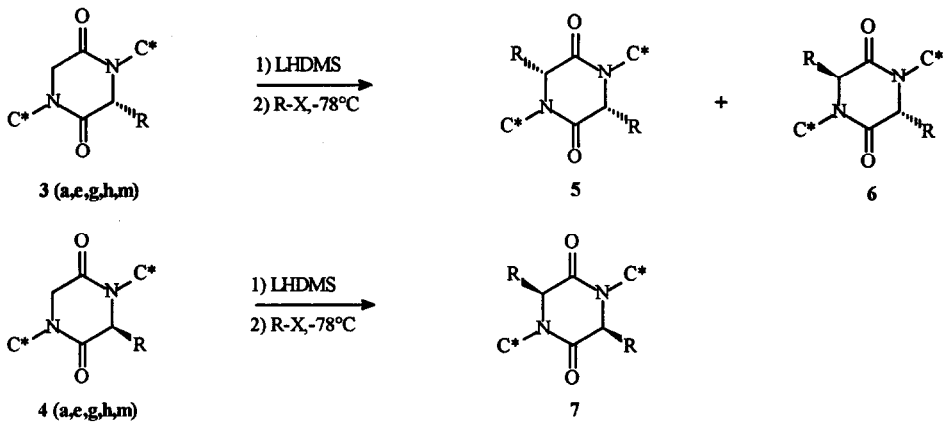
R of R-X	% yield (3+4)	ratio[a] (4:3)	isomer (3*R*)-**3** 3-CH_2	isomer (3*R*)-**3** 3-H	isomer (3*S*)-**4** 3-CH_2	isomer (3*S*)-**4** 3-H
a)	92	60:40	1.0	3.94	1.45	3.75
b)	90	60:40	1.35	3.91	2.2	3.6
c)	95	75:25	0.35 ; 1.20	3.89	1.78	3.76
d)	90	70:30	0.95	3.96	1.90	3.9
e)	95	55:45	1.66 ; 1.89	4.05	2.60 ; 2.70	3.8
f)	95	55:45	1.56 ; 1.95	4.04	2.60	3.78
g)	92	65:35	1.58 ; 2.05	4.05	2.40 ; 2.75	3.8
h)	90	72:25	1.85 ; 2.06	4.06	2.52 ; 2.76	3.81
i)	90	70:30	1.70 ; 1.85	4.02	2.55 ; 2.75	3.78
l)	90	90:10	1.60 ; 2.46	4.09	2.75 ; 2.90	3.76
m)	96	75:25	2.00 ; 2.66	4.31	3.15 ; 3.33	4.1
n)	92	75:25	2.10 ; 2.45	4.36	2.76 ; 3.04	3.92

a) calculated by ^{1}H-NMR

On the other hand, when the isomer (3*R*)-**3** (a,e,g,h,m) is submitted to the same reaction, a mixture of **5** and **6** is recovered, the *cis*:*trans* ratio being strongly dependent on the structure of the alkylating reagent (Table 2).

A totally different stereochemical outcome was instead observed for the propargyl derivatives **3l** and **4l** which give the *trans* isomer **6l** in obout 95% yield.

It is very interesting to point out that the *trans* isomer (3*R*,6*S*)-**6** (a,e,g,h,m) can be isomerized in alkaline solution (LiOH in 3:1 water:ethanol, 2 hrs at reflux) to a 1:1 mixture of the *cis* isomers (3*R*,6*R*)-**5** and (3*S*,6*S*)-**7** which are easily separated by silica gel chromatography. The observed *trans-cis* isomerization confirms the previous assertions about the greater stability of *cis* isomers with respect to the *trans* ones[1,2].



Scheme 3

Table 2. Diastereoselective alkylation of **3** (a,e,g,h,m) and **4** (a,e,g,h,m).

	3a	**4a**	**3e**	**4e**	**3g**	**4g**	**3h**	**4h**	**3m**	**4m**
% yield (7)		90		96		94		92		95
% yield (5+6)	90		95		90		92		96	
ratio [a] (6:5)	1.25		3.0		1.0		1.0		0.1	

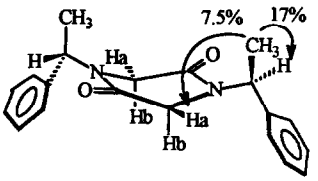
a) calculated by ^{1}H-NMR

The absolute configuration of the introduced stereogenic center C-3 of both **3** and **4** has been determined on the basis of ^{1}H-NMR data using the approach previously employed for similar molecules [1,2]. In fact the ^{1}H-NMR spectra can be explained on the basis of the phenyl shielding suffered by the substituents at C-3 and C-6 which preferentially lie in an axial position rather than in equatorial one [1]. These shieldings exclusively take place in the conformers where the benzylic hydrogens lie syn-periplanar with respect to the carbonyl group, the heterocyclic ring being in the preferred boat conformation [1,2]. Such a conformation is further confirmed by the ^{1}H-NMR spectrum of **2** : in fact the signals for (C-3)-H_a and (C-6)-H_a overlap (3.85 ppm) as do the signals for (C-3)-H_b and (C-6)-H_b (3.5 ppm), indicating their magnetic equivalence. It is worth pointing out the signals overlaping of the methyls (1.55 ppm), as those of the benzylic protons (5.95 ppm). In addition, upon irradiation of the methyl, a 7.5% nOe has been observed only for H_a (Figure 1).

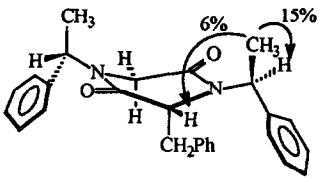
From the ^{1}H-NMR data reported on Table 1, one can deduce that the (C-3)-H is more shielded in **4** than in **3**, while the α-protons to C-3 suffer a greater phenyl shielding in **3** than in **4**. Therefore, the observed chemical shifts trend is consistent with the (*S*) configuration in the isomer **4** and the (*R*) one in **3**.

Moreover, nOe experiments performed on both **3m** and **4m** confirm the absolute configuration of C-3 : in fact, on the **3m** isomer a 6% nOe is observed between the CH_3 and the (C-3)-H, while on the **4m** isomer a 9% and a 6% nOes are registered on the (C-3)-CH_2 and the (C-3)-H respectively (Figure 1). It is interesting to point out

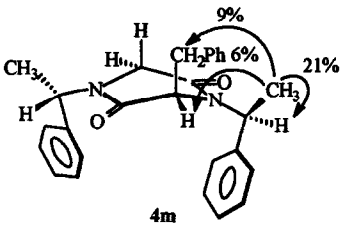
the unusually high field resonance observed for the axially arranged (C-6)-H both on **3m** (2.05 ppm) and **4m** (2.15 ppm) instead of 3.9-4.0 and 3.3-3.45 ppm respectively registered for others (3*S*)- and (3*R*)-monoalkylderivatives (see experimental part). As in analogous cases [3,4], a similar upfield shift can be ascribed to the (C-3)-benzyl group which preferentially adopts the "aryl inside" conformation causing the high shielding of the axial (C-6)-H. This is confirmed by a full conformational analysis [5] that allows the identification of energetic minima from whose geometry results that the (C-3)-benzyl group adopts the conformation with the phenyl internal to the heterocyclic ring.



2



3m



4m

Figure 1. nOe observed on **2**, **3m** and **4m**

Table 3. Selected chemical shifts (δ) for (3*R*,6*R*)-**5**, (3*R*,6*S*)-**6** and (3*S*,6*S*)-**7**

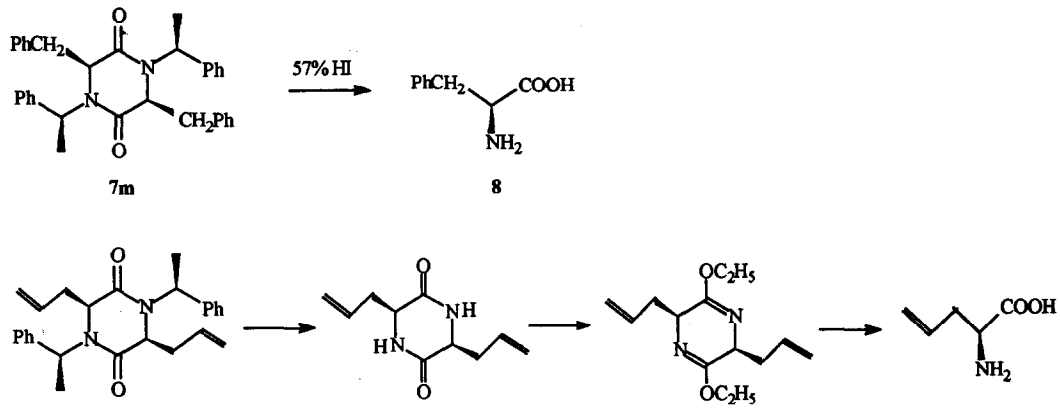
R	isomer **7**		isomer **5**		isomer **6**			
	3-CH_2 6-CH_2	3-H 6-H	3-CH_2 6-CH_2	3-H 6-H	3-CH_2	3-H	6-CH_2	6-H
a)	1.55	3.63	0.85	3.86	1.40	4.30	1.62	3.74
e)	2.65	3.75	1.74 2.15	4.0	2.25	4.32	2.55	3.75
g)	2.60	3.70	1.85 2.20	3.96	2.09 2.31	4.30	2.70	3.80
h)	2.64	3.7	2.0	3.96	2.10 2.35	4.32	2.70	3.81
m)	2.70 2.9	4.0	2.30 2.42	4.24	2.60 2.95	4.02	3.0	3.65

Accordingly, the absolute configuration of the stereogenic centre C-6 of **5**, **6** and **7** has been assigned on the basis of the phenyl shielding exerted on C-6 substituents. From the chemical shifts reported in the Table 3, it results that both the (C-3)-H and (C-6)-H are magnetically equivalent (the signals being overlapped) and the protons resonate at higher field in **7** with respect to **5**. In addition, also the α-protons to both C-3 and C-6 are magnetically equivalent and suffer a greater phenyl shielding in **5** than in **7**. Taking what above mentioned into consideration, it is possible to infer that both **5** and **7** are symmetrical molecules: therefore they are *cis* isomers and we can assign the absolute configuration (3*S*,6*S*) to **7** and (3*R*,6*R*) to **5**. In contrast, to the isomer **6**, which shows different signals for substituents to both C-3 and C-6, the *trans* (3*R*,6*S*) configuration is consequently attributed.

In a model study, we have converted both **7e** and **7m** to the corresponding α-amino acids (see Scheme 4) to confirm the absolute configuration of introduced stereogenic centers and to prove the synthetic usefulness of

these intermediates. Debenzylation and heterocyclic ring cleavage of saturated 7m, carried out conveniently in one step with refluxing 57% HI, leads to the pure (*S*)-phenylalanine 8.

Owing to the presence of a double bond, the intermediate 7e was instead submitted to a Birch reaction (Li/NH_3) followed by the treatment with Et_3OBF_4[2]. After hydrolysis of bis-lactim **10**, the pure (*S*)-α-allylglycine **11** was isolated. Submitting both the intermediates **5e** and **5m** to the same reaction sequence, we obtained the (*R*)-allylglycine and (*R*)-phenylalanine, respectively.



7m **8**

7e **9** **10** **11**

Scheme 4

In conclusion, the above reported results confirm the previously reported data [2] and permit confirmation that the *cis* 1,4-induction observed in (3*S*)-derivatives shows a general trend.

Therefore the total *cis* alkylation induced by the (3*S*)-4 isomer in connection to the observed *trans-cis* isomerization of **6** make the substrate **2** a very useful chiral block to the enantiomerically pure synthesis of α-amino acids.

EXPERIMENTAL

Magnetic resonance spectra were recorded at 300 MHz with $CDCl_3$ as a solvent, unless otherwise stated. Optical rotation values were recorded on a Perkin Elmer 541 polarimeter. All reactions involving organometallic reagents were carried out under an argon atmosphere in dry solvents. As alkylating reagents were used alkyl bromides, unless otherwise stated.

(4*S*)-*N*-((*S*)-1-Phenethyl)-4-phenyl-3-chloroacetyl-3-azapentanamide (1). To a solution of (4*S*)-*N*-((*S*)-1-Phenethyl)-4-phenyl-3-azapentanamide (36.66 g, 0.13 mol) in water-acetone (1:1, 280 ml) at 0°C was added $Na_2CO_3.10H_2O$ (20 g). Then chloroacetyl chloride (10.6 ml, 0.13 mol) in acetone (50 ml) at 0°C was added dropwise. After 2 h, the solvent was removed under reduced pressure and the residue was acidified with 6 M HCl. After extraction with ethyl acetate and removal of the solvent, the reaction product was purified by crystallization from ethyl acetate (42 g, 90% yield); mp 96-7°C; ^{1}H-NMR (as a mixture of conformers) δ 1.32 (d,3H,J=7.1Hz), 1.43 (d,3H,J=7.1Hz), 1.55 (d,3H,J=7.1Hz), 1.72 (d,3H,J=7.1Hz), 3.5 (d,1H,J=15.2Hz), 3.70

(d,1H, J=18Hz), 3.85 (d,1H,J=18Hz), 4.05 (d,1H,J=15.2Hz), 4.08 (d,1H,J=15.2Hz), 4.1 (d,1H,J=15.2Hz), 4.20 (d,1H,J=12Hz), 4.30 (d,1H,J=12Hz), 4.8-5.0 (m,2H), 5.22 (q,1H,J=7.1Hz), 5.52 (m,1H), 6.02 (q,1H,J=7.1Hz), 6.58 (m,1H), 7.3 (m,10ArH); ^{13}C-NMR δ 15.4, 17.8, 21.4, 21.8, 40.8, 41.9, 45.7, 46.3, 48.5, 48.8, 51.6, 56.0, 125.4, 125.6, 126.3, 126.7, 127.0, 127.2, 127.8, 127.9, 128.1, 128.4, 128.5, 138.4, 139.1, 142.7, 142.8, 166.9, 167.3, 167.7; $[\alpha]_D$=-120.4 (c 2.2, $CHCl_3$).

1,4-*N,N*-((*S*)-1-Phenethyl)-piperazine-2,5-dione (2). To a solution of **1** (35.8 g, 0.1 mol) in dry THF (300 ml) at 0°C, under an inert atmosphere, was added n-BuLi (40 ml of 2.5M solution in hexane, 0.1 mol). After 2h, the cooling bath was removed, 2M HCl was added, and the mixture was extracted with ethyl acetate. After the extract was dried and the solvent was removed, the crude product was purified by crystallization from ethyl acetate (30 g, 93% yield); mp 109-110°C; ^{1}H-NMR δ 1.55 (d,6H,J=7.2Hz), 3.48 (d,2H,J=16.4Hz), 3.8 (d,2H,J=16.4Hz), 5.9 (q,2H,J=7.2Hz), 7.23 (m,10ArH); ^{13}C-NMR δ 15.1, 44.7, 50.1, 127.4, 128.1, 128.8, 138.2, 163.8; $[\alpha]_D$= -323.2 (c 2.1, $CHCl_3$).

General procedure for the alkylation of 2 and 3 or 4. To 20 mmol of **2** (or 3 or **4**) dissolved in dry THF (70 ml) at -10°C, 20 ml (1M solution in THF) of LHMDS (20 mmol) was slowly added. After 2h, the reaction mixture was cooled to -78°C and the alkyl halide (20 mmol) in dry THF (10 ml) was dropped. After 3h, the cooling bath was removed allowing the reaction mixture to warm up to room temperature. 2M HCl (10 ml) was then added and the mixture extracted with ethyl acetate. The organic extract was dried, evaporated in vacuo and the residue was then submitted to silica gel chromatographic separation eluting with hexane/ethyl acetate.

(3*R*)-1,4-*N,N*-((*S*)-1-Phenethyl)-3-propylpiperazine-2,5-dione (3a). The pure product is obtained in 95% yield, by catalitic hydrogenation of **3e** with Pd/C in ethanol at room temperature, because the chromatographic separation from **4a** is very difficult. The product is obtained pure after crystallization from ether (mp 134°C) ^{1}H-NMR δ 0.55 (t,3H,J=7.2Hz), 1.0 (m,4H), 1.55 (d,3H, J=7.1Hz), 1.6 (d,3H,J=7.1Hz), 3.38 (d,1H,J=17.3 Hz), 3.67 (d,1H,J=17.3Hz), 3.94 (dd,1H,J=4.3, 8.7Hz), 5.9 (m,2H), 7.3 (m,10ArH); ^{13}C-NMR δ 13.2, 14.9, 15.9, 17.8, 34.2, 44.9, 50.0, 51.0, 56.9, 127.0, 127.8, 127.9, 128.4, 128.5, 138.4, 139.2, 164.7, 166.6; $[\alpha]_D$=-314.4 (c=1.65, $CHCl_3$).

(3*S*)-1,4-*N,N*-((*S*)-1-Phenethyl)-3-propylpiperazine-2,5-dione (4a). Using n-iodopropane as alkylating agent, the product was obtained pure after chromatographic separation (mp 81°C). ^{1}H-NMR δ 1.0 (t,3H,J=7.2Hz), 1.45 (m,2H), 1.55 (d,3H, J=7.1Hz), 1.68 (d,3H, J=7.1Hz), 1.85 (m.2H), 3.65 (d,1H,J=17Hz), 3.75 (dd,1H,J=4.3, 8.7Hz), 4.0 (d,1H, J=17Hz), 5.85 (q,1H, J=7.1Hz), 5.95 (q,1H,J=7.1Hz), 7.2-7.5 (m,10ArH); ^{13}C-NMR δ 13.7, 15.2, 17.1, 18.2, 36.1, 44.3, 49.5, 51.7, 57.0, 126.8, 126.9, 127.7, 127.8, 128.5, 128.6, 138.6, 138.8, 165.0, 165.5; $[\alpha]_D$=-207 (c=2.3, $CHCl_3$).

(3*R*)-1,4-*N,N*-((*S*)-1-Phenethyl)-3-(1-methylethyl)piperazine-2,5-dione (3b). It was prepared using 2-iodopropane as alkylating agent; mp.126°C (from hexane); ^{1}H-NMR δ 0.6 (d,3H,J=7Hz), 0.8 (d,3H,J=6.5Hz), 1.35 (m,1H), 1.5 (d,3H,J=7.2Hz), 1.65 (d,3H,J=7.2Hz), 3.44 (d,1H,J=17.6Hz), 3.65 (d,1H, J=17.6Hz), 3.91 (d,1H,J=4.7Hz), 5.6 (q,1H,J=7.2Hz), 5.95 (q,1H,J=7.2Hz), 7.3(m,10ArH); ^{13}C-NMR δ 14.9, 16.7, 16.8, 32.9, 45.6, 50.5, 53.7, 63.8, 127.5, 127.6, 127.9, 128.0, 128.5, 128.7, 138.4, 139.9, 164.8, 165.2.

(3*S*)-1,4-*N,N*-((*S*)-1-Phenethyl)-3-(1-methylethyl)piperazine-2,5-dione (4b). It was obtained as an oil using 2-iodopropane as alkylating reagent; ^{1}H-NMR δ 1.05 (d,3H,J=7Hz), 1.1 (d,3H,J=6.5Hz), 1.47 (d,3H,J=7.2Hz), 1.65 (d,3H,J=7.2Hz), 2.2 (m,1H), 3.54 (d,1H,J=17.4Hz), 3.6 (d,1H,J=4.4Hz), 3.96 (d,1H, J=17.4Hz), 5.7 (q1H,J=7.2Hz), 5.95 (q,1H,J=7.2Hz), 7.15-7.4 (m,10ArH); ^{13}C-NMR δ 15.4, 16.9, 17.9, 20.5, 34.3, 44.9, 49.5, 53.4, 62.7, 127.0, 127.2, 127.8, 128.0, 128.2, 128.7, 128.8, 138.7, 138.9, 164.7, 165.3.

(3*R*)-1,4-*N*,*N*-((*S*)-1-Phenethyl)-3-(2-methylpropyl)piperazine-2,5-dione (3c). It was isolated as an oil; ^{1}H-NMR δ 0.35 (m,1H), 0.59 (d,3H,J=6.4Hz), 0.61 (d,3H,J=6.4Hz), 1.2 (m,1H), 1.45 (m,1H), 1.55 (d,3H, J=7.2Hz), 1.6 (d,3H,J=7.2Hz), 3.37 (d,1H,J=17Hz), 3.65 (d,1H,J=17Hz), 3.89 (dd,1H, J=3.6, 12Hz), 5.85 (m,2H), 7.27 (m,10ArH); ^{13}C-NMR δ 15.4, 16.1, 20.7, 23.2, 24.2, 40.3, 45.1, 49.5, 51.0, 55.3, 126.7, 126.9, 127.1, 127.6, 127.8, 128.1, 128.5, 128.6, 138.6, 138.7, 163.7, 165.0.

(3*S*)-1,4-*N*,*N*-((*S*)-1-Phenethyl)-3-(2-methylpropyl)piperazine-2,5-dione (4c). It was obtained as an oil; ^{1}H-NMR δ 0.94 (d,3H,J=6.4Hz), 0.99 (d,3H,J=6.4Hz), 1.49 (d,3H,J=7.2Hz), 1.56 (m,1H), 1.61 (d,3H,J=7.2Hz), 1.78 (m,2H), 3.61 (d,1H,J=17Hz), 3.76 (dd,1H,J=3.8, 11.3Hz), 3.93 (d,1H,J=17Hz), 5.8 (q,1H,J=7.2Hz), 5.85 (q,1H,J=7.2Hz), 7.27 (m,10ArH); ^{13}C-NMR δ 15.0, 17.1, 21.4, 23.7, 24.9, 42.5, 44.5, 49.9, 51.5, 55.5, 126.7, 126.8, 127.2, 127.7, 127.8, 128.2, 128.6, 128.7, 138.9, 139.3, 165.4, 166.6.

(3*R*)-1,4-*N*,*N*-((*S*)-1-Phenethyl)-3-(3-butenyl)piperazine-2,5-dione (3d). It was obtained as an oil; ^{1}H-NMR δ 0.95 (m,2H), 1.15 (m,2H), 1.55 (d,3H,J=7.2Hz), 1.6 (d,3H,J=7.2Hz), 3.4 (d,1H,J=17Hz), 3.7 (d,1H,J=17 Hz), 3.96 (dd,1H,J=4.3, 9Hz), 4.8 (m,2H), 5.3 (m,1H), 5.85 (q,2H,J=7.2Hz), 7.27 (m,10 ArH); ^{13}C-NMR δ 14.9, 15.9, 28.8, 31.6, 44.9, 50.1, 51.0, 56.5, 115.5, 126.8, 126.9, 127.0, 127.8, 127.9, 128.0, 128.4, 128.5, 138.4, 138.9, 164.7, 166.2.

(3*S*)-1,4-*N*,*N*-((*S*)-1-Phenethyl)-3-(3-butenyl)piperazine-2,5-dione (4d). It was obtained as an oil; ^{1}H-NMR δ 1.51 (d,3H,J=7.2Hz), 1.61 (d,3H,J=7.2Hz), 1.85 (s,3H), 1.9 (m,2H), 2.15 (m,2H), 2.55 (m,2H), 3.6 (d,1H,J=17Hz), 3.9 (dd,1H,J=4.3, 9Hz), 4.0 (d,1H,J=17Hz), 4.9 (m,2H), 5.8 (m,1H), 5.85 (q,1H, J=7.2Hz), 5.95 (q,1H,J=7.2Hz), 7.27 (m,10ArH); ^{13}C-NMR δ 15.3, 17.2, 29.0, 33.2, 44.4, 49.7, 51.9, 56.6, 116.1, 126.8, 126.9, 127.0, 127.1, 127.8, 128.5, 128.6, 128.7, 138.6, 139.1, 165.0, 166.3.

(3*R*)-1,4-*N*,*N*-((*S*)-1-Phenethyl)-3-(2-propenyl)piperazine-2,5-dione (3e). It was isolated pure after crystallization from hexane (mp 128°C); ^{1}H-NMR δ 1.55 (d,3H,J=7.2Hz), 1.6 (d,3H,J=7.2Hz), 1.66 (m,1H), 1.89 (m,1H), 3.43 (d,1H,J=17.4 Hz), 3.65 (d,1H,J=17.4Hz), 4.05 (dd,1H,J=3.8, 8Hz), 4.7 (m,1H), 4.83 (m,1H), 5.36 (m,1H), 5.9 (m,2h), 7.3 (m,10ArH); ^{13}C-NMR δ 14.9, 15.8, 37.0, 44.8, 50.1, 51.1, 56.9, 119.3, 127.2, 127.8, 128.0, 128.38, 128.4, 131.0, 138.1, 139.2, 164.7, 165.9; $[\alpha]_D$=-344.8 (c= 2.2, $CHCl_3$).

(3*S*)-1,4-*N*,*N*-((*S*)-1-Phenethyl)-3-(2-propenyl)piperazine-2,5-dione (4e). It was obtained as an oil; ^{1}H-NMR δ 1.5 (d,3H,J=7.2Hz), 1.65 (d,3H,J=7.2Hz), 2.6 (m,1H), 2.7 (m,1H), 3.51 (d,1H,J=17.1Hz), 3.8 (dd,1H,J=3.8, 7Hz); 3.96 (d,1H,J=17.1Hz), 5.2 (m,2H), 5.8 (m,1H), 5.82 (q,1H,J=7.2Hz); 5.9 (q,1H,J=7.2 Hz), 7.3 (m,10ArH); ^{13}C-NMR δ 15.1, 17.3, 38.6, 44.3, 49.7, 52.0, 56.9, 120.0, 126.8, 126.9, 127.7, 127.8, 128.5, 128.6, 131.2, 138.3, 138.5, 165.0, 166.0; $[\alpha]_D$=-161 (c=1.1, $CHCl_3$).

(3*R*)-1,4-*N*,*N*-((*S*)-1-Phenethyl)-3-((2E)-butenyl)piperazine-2,5-dione (3f). It was isolated as an oil; ^{1}H-NMR δ 1.3 (d,3H,J=6.2Hz), 1.53 (d,3H,J=7.2Hz), 1.56 (m,1H), 1.59 (d,3H,J=7.2Hz), 1.95 (m,1H), 3.38 (d,1H,J=17Hz), 3.65 (d,1H,J=17Hz), 4.04 (dd,1H,J=3.5, 6.8Hz), 4.9 (m,1H), 5.09 (m,1H), 5.85 (q,1H, J=7.2Hz), 5.95 (q,1H,J=7.2Hz), 7.32 (m,10ArH); ^{13}C-NMR δ 15.1, 16.0, 17.7, 36.0, 44.9, 60.2, 51.3, 57.4, 123.5, 127.5, 127.8, 127.9, 128.0, 128.1, 128.6, 130.4, 138.3, 139.4, 164.9, 166.4.

(3*S*)-1,4-*N*,*N*-((*S*)-1-Phenethyl)-3-((2E)-butenyl)piperazine-2,5-dione (4f). It was obtained as an oil; ^{1}H-NMR δ 1.49 (d,3H,J=7.2Hz), 1.65 (d,3H,J=7.2Hz), 1.7 (d,3H,J=6.2Hz), 2.6 (m,2H), 3.49 (d,1H, J=17.1Hz), 3.78 (dd,1H,J=3.7, 6.3Hz), 3.89 (d,1H,J=17.1Hz), 5.42 (m,1H), 5.62 (m,1H), 5.8 (q,1H, J=7.2Hz), 5.9 (q,1H,J=7.2Hz), 7.3 (m,10ArH); ^{13}C-NMR δ 15.0, 17.4, 18.0, 37.6, 44.3, 49.7, 52.1, 57.3, 123.7, 126.8, 126.9, 127.0, 127.1, 127.7, 127.9, 128.4, 128.6, 128.7, 130.8, 138.4, 138.6, 165.1, 166.4.

(3*R*)-1,4-*N*,*N*-((*S*)-1-Phenethyl)-3-(3-methyl-2-butenyl)piperazine-2,5-dione (3g). It was obtained pure after crystallization from ether (mp 147°C); ^{1}H-NMR δ 1.25 (s,3H), 1.41 (s,3H), 1.53 (d,3H,J=7.1Hz), 1.58 (m,1H), 1.6 (d,3H, J=7.1Hz), 2.05 (m,1H), 3.45 (d,1H,J=17.1Hz), 3.67 (d,1H,J=17.1Hz), 4.05 (dd,1H,J=3.9, 7.1Hz), 4.75 (m,1H), 5.82 (q,1H,J=7.1Hz), 5.92 (q,1H,J=7.1Hz), 7.32 (m,10ArH); ^{13}C-NMR δ 15.4, 16.4, 17.8, 25.7, 31.5, 45.2, 50.4, 51.8, 57.6, 116.9, 127.5, 127.9, 128.0, 128.2, 128.6, 135.8, 138.4, 139.3, 165.2, 166.6; $[\alpha]_D$=-351 (c= 2.0, $CHCl_3$).

(3*S*)-1,4-*N*,*N*-((*S*)-1-Phenethyl)-3-(3-methyl-2-butenyl)piperazine-2,5-dione (4g). It was recovered as an oil; ^{1}H-NMR δ 1.45 (d,3H,J=7.1Hz), 1.65 (s,3H), 1.68 (d,3H,J=7.1Hz), 1.75 (s,3H), 2.48 (m,1H), 2.75 (m,1H), 3.5 (d,1H,J=17.1Hz), 3.8 (dd,1H,J=3.7, 6.4Hz), 3.9 (d,1H,J=17.1Hz), 5.2 (m,1H), 5.8 (q,1H,J= 7.1Hz), 5.88 (q,1H,J=7.1Hz), 7.3 (m,10ArH); ^{13}C-NMR δ 14.9, 17.3, 18.0, 25.9, 33.0, 44.5, 49.6, 52.1, 57.3, 117.2, 126.9, 127.0, 127.7, 127.8, 127.9, 128.4, 128.6, 128.7, 136.5, 138.6, 138.9, 165.3, 166.7; $[\alpha]_D$= -166.4 (c= 2.7, $CHCl_3$).

(3*R*)-1,4-*N*,*N*-((*S*)-1-Phenethyl)-3-(3,7-dimethyl-(2E,6E)-octadienyl)piperazine-2,5-dione (3h). It was obtained as a solid after chromatographic separation (mp 114°C); ^{1}H-NMR δ 1.22 (s,3H), 1.52 (d,3H, J=7Hz),1.53 (s,3H), 1.59 (d,3H, J=7Hz), 1.65 (s,3H), 1.7 (m,4H), 1.85 (m,1H), 2.06 (m,1H), 3.46 (d,1H, J=17Hz), 3.66 (d,1H,J=17Hz), 4.06 (dd,1H,J=3.8, 7.2Hz), 4.75 (m,1H), 4.9 (m,1H), 5.82 (q,1H,J=7Hz), 5.91 (q,1H,J=7Hz), 7.33 (m,10ArH); ^{13}C-NMR δ 15.3, 16.2, 16.3, 17.6, 25.6, 26.0, 31.4, 39.5, 45.1, 50.3, 51.8, 57.5, 116.6, 123.8, 127.4, 127.9, 128.0, 128.1, 128.6, 131.4, 138.4, 139.2, 139.4, 165.1, 166.6; $[\alpha]_D$= -302.6 (c= 2.12, $CHCl_3$).

(3*S*)-1,4-*N*,*N*-((*S*)-1-Phenethyl)-3-(3,7-dimethyl-(2E,6E)-octadienyl)piperazine-2,5-dione (4h). It was obtained as an oil; ^{1}H-NMR δ 1.45 (d,3H,J=7.2Hz), 1.61 (s,3H), 1.65 (s,3H), 1.67 (d,3H, J=7.2Hz), 1.7 (s, 3H), 2.05 (m,4H), 2.52 (m,1H); 2.76 (m,1H), 3.5 (d,1H,J=17Hz), 3.81 (dd,1H,J=3.6, 6.4Hz), 3.95 (d,1H, J=17Hz), 5.07 (m,1H), 5.2 (m,1H), 5.81 (q,1H,J=7.2Hz), 5.87 (q,1H,J=7.2Hz), 7.27 (m,10ArH); ^{13}C-NMR δ 15.0, 16.4, 17.4, 17.7, 25.6, 26.2, 33.0, 40.0, 44.5, 50.0, 52.1, 57.3, 116.8, 123.6, 127.0, 127.1, 127.8, 128.0, 128.7, 128.8, 131.9, 138.6, 138.9, 140.1, 165.3, 166.8; $[\alpha]_D$= -101.8 (c= 2.0, $CHCl_3$).

(3*R*)-1,4-*N*,*N*-((*S*)-1-Phenethyl)-3-(4-benzyloxy-2(Z)-butenyl)piperazine-2,5-dione (3i). It was prepared using the methanesufonate as alkylating agent and it was obtained as an oil; ^{1}H-NMR δ 1.5 (d,3H, J=7.2Hz), 1.56 (d,3H,J=7.2Hz), 1.7 (m,1H), 1.85 (m,1H),3.4 (d,1H,J=17Hz), 3.58 (m,2H), 4.02 (dd,1H,J=4, 7Hz), 4.34 (m,2H), 5.25 (m,1H), 5.49 (m,1H), 5.95 (q,2H,J=7.2Hz), 7.1-7.4 (m,15 ArH); ^{13}C-NMR δ 14.9, 15.9, 28.8, 31.6, 44.9, 50.1, 51.0, 56.5, 115.5, 126.8, 126.9, 127.0, 127.8, 127.9, 128.0, 128.4, 128.5, 136.7, 138.4, 138.9, 164.7, 166.2.

(3*S*)-1,4-*N*,*N*-((*S*)-1-Phenethyl)-3-(4-benzyloxy-2(Z)-butenyl)piperazine-2,5-dione (4i). It was prepared using the methanesulfonate as alkylating agent and it was recovered as an oil; ^{1}H-NMR δ 1.4 (d,3H, J=7.2Hz), 1.55 (d,3H,J=7.2Hz), 2.55 (m,1H), 2.75 (m,1H), 3.5 (d,1H,J=17Hz), 3.78 (dd,1H,J=4, 7Hz), 3.92 (d,1H,J=17Hz), 4.04 (d,2H,J=7Hz), 4.5 (s,2H), 5.65 (m,1H), 5.7 (m,1H), 5.85 (q,2H,J=7.2Hz), 7.1-7.4 (m, 15ArH); ^{13}C-NMR δ 15.3, 17.2, 29.0, 33.2, 44.4, 49.7, 51.9, 56.7, 116.1, 126.8, 126.9, 127.0, 127.1, 127.8, 128.5, 128.6, 128.7, 136.3, 138.6, 139.1, 165.0, 166.3.

(3*R*)-1,4-*N*,*N*-((*S*)-1-Phenethyl)-3-(2-propynyl)piperazine-2,5-dione (3l). It was isolated as a solid after chromatographic separation (mp 175°C); ^{1}H-NMR δ 1.55 (d,3H,J=7.1Hz), 1.6 (ddd,1H,J=2.8, 5.4, 17.3Hz), 1.62 (d,3H,J=7.1Hz), 1.65 (t,1H, J=2.8Hz), 2.46 (ddd,1H,J=2.8, 2.8, 17.3Hz), 3.62 (d,1H,J=17.4Hz), 3.83 (d,1H,J=17.4Hz), 4.09 (dd,1H,J=2.8, 5.4Hz), 5.95 (q,1H,J=7.1Hz), 6.0 (q,1H,J=7.1Hz), 7.33 (m,10ArH);

^{13}C-NMR δ 14.8, 15.8, 23.8, 45.3, 50.5, 51.3, 55.6, 72.2, 78.3, 127.7, 127.9, 128.2, 128.4, 128.6, 137.8, 139.1, 165.1, 165.4.

(3*S*)-1,4-*N,N*-((*S*)-1-Phenethyl)-3-(2-propynyl)piperazine-2,5-dione (4l). It was obtained as a white solid after chromatographic separation (mp 103°C); ^{1}H-NMR δ 1.55 (d,3H,J=7.1Hz), 1.7 (d,3H,J=7.1Hz), 2.1 (t,1H,J=2.7Hz), 2.75 (ddd,1H,J=2.7, 5.5, 17.5), 2.9 (ddd,1H,J=2.7, 2.7, 17.5Hz), 3.53 (d,1H,J=17Hz), 3.76 (dd,1H,J=2.7, 5.5Hz), 4.4 (d,1H,J=17Hz), 5.81 (q,1H,J=7.1Hz), 5.95 (q,1H,J=7.1Hz), 7.3 (m,10ArH); ^{13}C-NMR δ 14.9, 17.1, 25.2, 44.7, 50.3, 52.4, 55.5, 72.7, 78.4, 127.2, 127.4, 127.6, 128.0, 128.3, 128.7, 129.0, 137.8, 138.3, 165.2, 165.5.

(3*R*)-1,4-*N,N*-((*S*)-1-Phenethyl)-3-benzylpiperazine-2,5-dione (3m). It was obtained pure after crystallization from ethyl acetate (mp 173°C); ^{1}H-NMR δ 1.4 (d,3H,J=7.1Hz), 1.6 (d,3H,J=7.1Hz), 2.0 (dd,1H,J=6, 18.3Hz), 2.05 (d,1H,J=17Hz), 2.66 (dd,1H,J=3.5, 18.3Hz), 3.35 (d,1H,J=17Hz), 4.31 (dd,1H, J=3.5, 6Hz), 5.8 (q,1H,J=7.1Hz), 5.95 (q,1H, J=7.1Hz), 6.7-7.6 (m,15ArH); ^{13}C-NMR δ 15.9, 16.7, 37.9, 44.6, 50.7, 52.2, 58.2, 126.9, 127.9, 128.1, 128.2, 128.4, 128.5, 128.6, 128.9, 129.6, 134.6, 137.8, 138.9, 165.5, 166.2; $[\alpha]_D$=-202.1 (c= 2.0, $CHCl_3$).

(3*S*)-1,4-*N,N*-((*S*)-1-Phenethyl)-3-benzylpiperazine-2,5-dione (4m). It was obtained pure after crystallization from ethyl acetate (mp 114°C);^{1}H-NMR δ 1.22 (d,3H,J=7.1Hz), 1.83 (d,3H,J=7.1Hz), 2.15 (d,1H,J=17.2Hz), 3.03 (d,1H,J=17.2Hz), 3.14 (dd,1H,J=4.8, 13.9Hz), 3.33 (dd,1H,J=3.6, 13.9Hz), 4.1 (dd, 1H, J=3.6, 4.8Hz), 5.8 (q,1H,J=7.1Hz), 5.95 (q,1H,J=7.1Hz), 7.1-7.4 (m,15ArH); ^{13}C-NMR δ 14.4, 17.9, 40.1, 43.7, 49.6, 52.2, 58.2, 126.7, 127.0, 127.7, 127.8, 128.1, 128.5, 128.7, 128.8, 130.3, 135.0, 138.8, 139.2, 166.0, 166.1; $[\alpha]_D$=-144.0 (c= 2.1, $CHCl_3$).

(3*R*)-1,4-*N,N*-((*S*)-1-Phenethyl)-3-(ethoxycarbonylmethyl)piperazine-2,5-dione (3n). It was recovered as an oil; ^{1}H-NMR δ 1.1 (m,3H), 1.55 (d,3H,J=7.2Hz), 1.65 (d,3H,J=7.2Hz), 2.1 (dd,1H,J=5.9, 17Hz), 2.45 (dd,1H,J=3, 17Hz), 3.65 (d,1H,J=16.9Hz), 3.75 (d,1H,J=16.9Hz), 3.85 (m,2H), 4.36 (dd,1H,J=3, 5.9Hz), 5.9 (m,2H), 7.3 (m,10ArH); ^{13}C-NMR δ 13.8, 15.0, 15.4, 36.4, 45.0, 50.2, 50.5, 53.9, 60.6, 127.2, 127.3, 127.7, 128.4, 137.9, 139.8, 164.9, 165.3, 168.9.

(3*S*)-1,4-*N,N*-((*S*)-1-Phenethyl)-3-(ethoxycarbonylmethyl)piperazine-2,5-dione (4n). It was obtained as an oil; ^{1}H-NMR δ 1.25 (m,3H), 1.55 (d,3H,J=7.2Hz), 1.62 (d,3H,J=7.2Hz), 2.76 (dd,1H,J=5.9, 17Hz), 3.04 (dd,1H,J=3, 17Hz), 3.55 (d,1H,J=16.9Hz), 3.92 (dd,1H,J=3, 5.9Hz), 4.15 (m,2H), 4.16 (d,1H, J=16.9Hz), 5.7 (q,1H,J=7.2Hz), 5.95 (q,1H,J=7.2Hz), 7.33 (m,10ArH); ^{13}C-NMR δ 13.9, 14.0, 17.0, 37.5, 44.3, 50.2, 52.6, 54.2, 60.8, 127.0, 127.3, 127.7, 128.0, 128.5, 128.7, 137.6, 138.3, 164.8, 165.6, 169.6.

(3*R*,6*R*)-1,4-*N,N*-((*S*)-1-Phenethyl)-3,6-(dipropyl)piperazine-2,5-dione (5a). It was obtained as an oil; ^{1}H-NMR δ 0.6 (t,6H, J=7.2Hz), 0.85 (m,2H), 1.1 (m,2H), 1.45 (m,4H), 1.57 (d,6H,J=7.1Hz), 3.86 (dd,2H,J=3.6, 9.6Hz), 5.7 (q,2H,J=7.1Hz), 7.3 (m,10ArH); ^{13}C-NMR δ 13.4, 15.9, 19.9, 37.2, 51.9, 57.8, 127.8, 128.4, 139.4, 166.9; $[\alpha]_D$=-220.9 (c= 2.08, $CHCl_3$).

(3*R*,6*S*)-1,4-*N,N*-((*S*)-1-Phenethyl)-3,6-(dipropyl)piperazine-2,5-dione (6a). It was isolated as a solid after chromatographic separation (mp 125°C); ^{1}H-NMR δ 0.5 (t,3H, J=7.2Hz), 0.75 (t,3H,J=7.2Hz), 1.0 (m,4H), 1.4 (m,1H), 1.62 (m,1H), 1.67 (d,3H,J=7.1Hz), 1.7 (d,3H, J=7.1Hz), 1.85 (m,2H), 3.74 (dd,1H,J=3.1, 4.2Hz), 4.3 (dd,1H,J= 3.8, 3.8Hz), 5.45 (q,1H,J=7.1Hz), 5.55 (q,1H,J=7.1Hz), 7.2-7.5 (m,10ArH); ^{13}C-NMR δ 13.3, 13.5, 15.7, 16.0, 17.5, 34.6, 35.8, 52.9, 54.6, 57.7, 58.2, 127.5, 127.9, 128.0, 128.2, 128.7, 138.1, 140.7, 166.6, 167.0; $[\alpha]_D$=-145.0 (c= 2.23, $CHCl_3$).

(3*R*,6*R*)-1,4-*N*,*N*-((*S*)-1-Phenethyl)-3,6-bis-(2-propenyl)piperazine-2,5-dione (5e). It was obtained as a solid after chromatographic separation (mp 89°C); ^{1}H-NMR δ 1.6 (d,6H,J=7.1Hz), 1.74 (ddd,2H,J=4.7, 7.2, 13.5Hz), 2.15 (ddd,2H,J=4.7, 9.6, 13.5Hz), 4.0 (dd,2H,J=4.7, 9.6Hz), 4.73 (m,2H), 4.97 (m,2H), 5.6 (m,2H), 5.72 (q,2H,J=7.1Hz), 7.3 (m,10ArH); ^{13}C-NMR δ 15.9, 39.5, 52.0, 58.0, 117.7, 127.8, 128.0, 128.6, 133.0, 139.6, 166.0; $[\alpha]_D$=-235.9 (c= 1.74, $CHCl_3$).

(3*R*,6*S*)-1,4-*N*,*N*-((*S*)-1-Phenethyl)-3,6-bis-(2-propenyl)piperazine-2,5-dione (6e). It was obtained as an oil; ^{1}H-NMR δ 1.6 (d,3H,J=7.1Hz), 1.65 (d,3H,J=7.1Hz), 2.25 (m,1H), 2.55 (m,3H), 3.75 (m,1H), 4.32 (m,1H), 5.0 (m,4H), 5.4 (m,2H), 5.5 (q,1H,J=7.1Hz), 5.6 (q,1H,J=7.1Hz), 7.2-7.5 (m,10ArH); ^{13}C-NMR δ 16.2, 17.6, 36.8, 37.6, 53.2, 54.4, 57.2, 58.2, 119.8, 120.2, 127.6, 127.7, 127.8, 128.0, 128.1, 128.6, 130.4, 130.9, 137.6, 140.3, 165.7, 166.2; $[\alpha]_D$=-122.2 (c= 2.25, $CHCl_3$).

(3*R*,6*R*)-1,4-*N*,*N*-((*S*)-1-Phenethyl)-3,6-bis-(3-methyl-2-butenyl)piperazine-2,5-dione (5g). It was obtained as a solid after chromatographic separation (mp 59°C); ^{1}H-NMR δ 1.35 (s,6H), 1.6 (d,6H,J=7.1Hz), 1.7 (s,6H), 1.85 (m,2H), 2.2 (m,2H), 3.96 (dd, 2H,J=4.9, 9Hz), 4.98 (dd,2H,J=7, 7.5Hz), 5.67 (q,2H, J=7.1Hz), 7.33 (m,10ArH); ^{13}C-NMR δ 16.1, 17.8, 25.7, 33.7, 52.5, 58.6, 118.9, 127.7, 127.8, 128.5, 128.6, 134.2, 139.9, 166.5; $[\alpha]_D$=-291.2 (c= 1.2, $CHCl_3$).

(3*R*,6*S*)-1,4-*N*,*N*-((*S*)-1-Phenethyl)-3,6-bis-(3-methyl-2-butenyl)piperazine-2,5-dione (6g). It was obtained as a solid after chromatographic separation (mp 129°C); ^{1}H-NMR δ 1.46 (d,3H,J=7.1Hz), 1.62 (s,3H), 1.67 (s,3H), 1.68 (d,3H,J=7.1Hz), 2.09 (m,1H), 2.31 (m,1H), 2.7 (m,2H), 3.8 (m,1H), 4.3 (m,1H), 4.8 (m,1H), 4.86 (m,1H), 5.38 (q,1H,J=7.1Hz), 5.55 (q,1H,J=7.1Hz), 7.33 (m,10ArH); ^{13}C-NMR δ 16.5, 17.3, 18.2, 26.0, 26.1, 31.6, 32.1, 53.8, 54.0, 57.2, 58.4, 116.4, 116.8, 127.55, 127.7, 127.8, 128.0, 128.2, 128.7, 136.3, 140.4, 166.7, 167.0; $[\alpha]_D$=-170.9 (c= 2.0, $CHCl_3$).

(3*R*,6*R*)-1,4-*N*,*N*-((*S*)-1-Phenethyl)-3,6-bis-(3,7-dimethyl-(2E,6E)-octadienyl)piperazine-2,5-dione (5h). It was obtained as an oil; ^{1}H-NMR δ 1.34 (s,6H), 1.58 (s,6H), 1.59 (d,6H,J=7.1Hz), 1.67 (s,6H), 2.0 (m,8H), 2.2 (m,4H), 3.96 (dd,2H,J=5, 9Hz), 4.98 (m,2H), 5.06 (m,2H), 5.62 (q,2H,J=7.1Hz), 7.3 (m,10ArH); ^{13}C-NMR δ 16.1, 17.6, 25.6, 26.4, 33.8, 39.6, 52.7, 58.8, 118.7, 124.0, 127.7, 127.8, 128.5, 131.3, 137.7, 140.0, 166.5; $[\alpha]_D$=-232.4 (c= 2.35, $CHCl_3$).

(3*R*,6*S*)-1,4-*N*,*N*-((*S*)-1-Phenethyl)-3,6-bis-(3,7-dimethyl-(2E,6E)-octadienyl)piperazine-2,5-dione (6h). It was obtained as an oil; ^{1}H-NMR δ 1.44 (s,3H), 1.47 (s,3H), 1.59 (s,3H), 1.6 (s,3H), 1.66 (d,3H,J=7.1Hz), 1.67 (d,3H, J=7.1Hz), 1.68 (s,3H), 1.69 (s,3H), 1.9 (m,8H), 2.1 (m,1H), 2.35 (m,1H), 2.7 (m,2H), 3.81 (dd,1H,J=2.8, 4.4Hz), 4.32 (dd,1H,J=2.8, 4.4Hz), 4.79 (m,1H), 4.88 (m,1H), 5.05 (m,2H), 5.45 (q,1H,J=7.1Hz), 5.53 (q,1H, J=7.1Hz), 7.2-7.5 (m,10ArH); ^{13}C-NMR δ 16.3, 16.5, 17.2, 17.6, 25.6, 26.2, 26.3, 29.5, 31.3, 31.9, 39.7, 39.8, 53.3, 54.0, 57.2, 58.1, 116.1, 116.2, 123.8, 123.84, 127.3, 127.5, 127.6, 127.8, 128.1, 128.5, 131.4, 138.1, 139.2, 139.6, 140.4, 166.5, 166.9; $[\alpha]_D$= -119.5 (c= 1.7, $CHCl_3$).

(3*R*,6*R*)-1,4-*N*,*N*-((*S*)-1-Phenethyl)-3,6-(dibenzyl)piperazine-2,5-dione (5m). After chromatographic elution with hexane ehtyl acetate, the product was obtained pure as a solid (mp 102°C); ^{1}H-NMR δ 1.6 (d,6H, J=7.1Hz), 2.3 (dd,2H,J=5.2, 14Hz), 2.42 (dd,2H,J=7.2, 14Hz), 4.24 (dd,2HJ=5.2, 7.2Hz), 5.37 (q,2H, J=7.1Hz), 6.9-7.4 (m,20ArH); ^{13}C-NMR δ 16.6, 40.0, 54.1, 60.8, 126.9, 128.0, 128.1, 128.3, 128.6, 129.4, 136.7, 139.8, 166.0; $[\alpha]_D$=-155.2 (c= 1.3, $CHCl_3$).

(3*R*,6*S*)-1,4-*N*,*N*-((*S*)-1-Phenethyl)-3,6-(dibenzyl)piperazine-2,5-dione (6m). It was obtained as a solid after chromatographic separation (mp 145°C); ^{1}H-NMR δ 1.3 (d,3H, J=7.1Hz), 1.85 (d,3H,J=7.1Hz), 2.6 (dd,1H,J=4.4, 14.4Hz), 2.95 (dd,1H,J=4.1, 14.4Hz), 3.0 (m,2H), 3.65 (dd,1H,J=4.1, 4.1Hz), 4.02 (dd,1H,

J=4.1, 4.4Hz), 5.35 (q,1H,J=7.1Hz), 5.55 (q,1H,J=7.1Hz), 6.7-7.5 (m,20ArH); ^{13}C-NMR δ 15.6, 17.7, 37.5, 38.5, 52.6, 54.3, 57.7, 126.6, 126.9, 127.8, 127.9, 128.1, 128.2, 128.3, 128.4, 128.5, 128.7, 129.7, 129.9, 135.7, 137.9, 140.4, 166.1, 166.6; $[\alpha]_D$=-202.1 (c= 2.04, $CHCl_3$).

(3*S*,6*S*)-1,4-*N*,*N*-((*S*)-1-Phenethyl)-3,6-(dipropyl)piperazine-2,5-dione (7a). It was obtained as an oil; ^{1}H-NMR δ 0.95 (t,6H, J=7.2Hz), 1.55 (m,4H), 1.65 (d,6H,J=7.1Hz), 11.85 (m,4H,), 3.63 (dd,2H,J=4.6, 9.5Hz), 5.8 (q,2H, J=7.1Hz), 7.1-7.4 (m,10ArH); ^{13}C-NMR δ 13.9, 17.3, 20.2, 38.7, 51.5, 57.1, 126.9, 127.8, 128.6, 139.4, 167.2; $[\alpha]_D$=-151 (c= 1.86, $CHCl_3$).

(3*S*,6*S*)-1,4-*N*,*N*-((*S*)-1-Phenethyl)-3,6-bis-(2-propenyl)piperazine-2,5-dione (7e). It was obtained as an oil; ^{1}H-NMR δ 1.6 (d,6H,J=7.1Hz), 2.65 (m,4H), 3.75 (dd,2H,J=3.6, 7.5Hz), 5.1 (m,2H), 5.15 (m,2H), 5.75 (q,2H,J=7.1Hz), 5.85 (m,2H), 7.27 (m,10ArH); ^{13}C-NMR δ 17.3, 40.4, 51.8, 57.0, 117.5, 126.8, 127.6, 128.4, 132.9, 138.5, 166.1; $[\alpha]_D$=-77.9 (c= 3.06, $CHCl_3$).

(3*S*,6*S*)-1,4-*N*,*N*-((*S*)-1-Phenethyl)-3,6-bis-(3-methyl-2-butenyl)piperazine-2,5-dione (7g). It was obtained as an oil; ^{1}H-NMR δ 1.6 (d,6H,J=7.1Hz), 1.63 (s,6H), 1.73 (s,6H), 2.6 (ddd,4H,J=6.7, 6.7, 6.7Hz), 3.7 (dd,2H,J=6.7Hz), 5.2 (dd,2H,J=6.7Hz), 5.75 (q,2H,J=7.1Hz), 7.27 (m,10ArH); ^{13}C-NMR δ 17.4, 18.1, 25.7, 34.9, 52.2, 58.0, 119.3, 126.8, 127.2, 127.8, 127.9, 128.2, 1128.6, 128.9, 134.4, 139.1, 167.0; $[\alpha]_D$= -29.9 (c= 1.79, $CHCl_3$).

(3*S*,6*S*)-1,4-*N*,*N*-((*S*)-1-Phenethyl)-3,6-bis-(3,7-dimethyl-(2E,6E)-octadienyl)piperazine-2,5-dione (7h). It was obtained as an oil; ^{1}H-NMR δ 1.6 (s,6H), 1.61 (d,6H,J=7.1Hz), 1.62 (s,6H), 11.68 (s,6H), 2.1 (m,8H), 2.64 (m,4H), 3.7 (dd,2H,J=5.6, 7.5Hz), 5.1 (m,2H), 5.23 (m,2H), 5.74 (q,2H,J=7.1Hz), 7.27 (m,10ArH); ^{13}C-NMR δ 16.5, 17.4, 17.7, 25.7, 26.55, 35.1, 39.7, 52.3, 58.1, 119.2, 124.0, 127.2, 127.8, 131.5, 1138.0, 139.3, 167.1; $[\alpha]_D$= 4.9 (c= 2.7, $CHCl_3$)

(3*S*,6*S*)-1,4-*N*,*N*-((*S*)-1-Phenethyl)-3,6-(dibenzyl)piperazine-2,5-dione (7m). It was obtained as a solid after chromatographic separation (mp 99°C); ^{1}H-NMR δ 1.6 (d,6H, J=7.1Hz), 2.7 (dd,2H,J=6.9, 14.6Hz), 2.9 (dd,2H,J=4.3, 14.6Hz), 4.0 (dd,2H,J=4.3, 6.9Hz), 5.75 (q,2H, J=7.1Hz), 7-7.74 (m,20ArH); ^{13}C-NMR δ 17.9, 40.9, 53.1, 59.0, 127.0, 127.5, 128.0, 128.5, 128.7, 129.5, 136.9, 138.7, 166.7; $[\alpha]_D$=-31.2 (c= 2.4, $CHCl_3$)

(*S*)-Phenylalanine (8). To 10 ml of 57% hydriodic acid was added **7m** (2.5 g, 5 mmol), and the mixture was refluxed for 1 hr. Then the resulting solution was extracted with ethyl acetate, and the aqueous solution was evaporated under reduced pressure. The residue was dissolved in water (10 ml) and adsorbed on ion-exchange resin Amberlyst H-15. The resin was washed with distilled water and then eluted with 5 M NH_4OH to give (*S*)-phenylalanine (0.7 g, 85% yield); $[\alpha]_D$=-34.5 (c=2.0, H_2O) [lit.[6] $[\alpha]_D$=-35.1 (c= 1.94, H_2O)].

(3*S*,6*S*)-Bis-(2-propenyl)piperazine-2,5-dione (9). Li wire (0.42 g, 60 mmol) in 250 ml of liquid ammonia, cooled at -70°C, was stirred until the metal was completely dissolved. A solution of **7e** (4 g, 10 mmol) in dry THF (50 ml) and t-butanol (5 ml) was then added dropwise. After 5 minutes the reaction was quenched with NH_4Cl (6.36 g, 120 mmol) and the cooling bath was removed allowing the complete removal of ammonia. To the residue was added water (10 ml) and the product was isolated as a white solid (2.2 g, 88% yield) (mp 227°C);. ^{1}H-NMR (DMSO) δ 1.6 (m,4H), 3.08 (m,2H), 4.25 (m,4H), 4.85 (m,2H), 7.2 (bs,2H); ^{13}C-NMR (DMSO) δ 37.2, 53.7, 118.6, 133.4, 166.8; $[\alpha]_D$=-107.9 (c=1.0, CH_3OH).

(2*S*,5*S*)-Bis-(2-propenyl)-3,6-(diethoxy)-2,5-dihydropyrazine (10). The intermediate **9** (2.5 g, 10 mmol) was dissolved in dry CH_2Cl_2 (30 ml) and added to triethyl-oxonium tetrafluoroborate prepared from BF_3.etherate (8 ml) and epichlorohydrin (4 ml)[7]. The reaction mixture was stirred at r.t. under argon atmosphere and after 24 hr 80 ml of a phosphate buffer solution (pH=7) were added. The organic layer was separated and the

aqueous solution extracted with dichloromethane. The combined extracts were evaporated under vacuum and submitted to chromatographic separation by silica gel eluting with hexane/ethyl acetate 90:10. The bis-lactim **10** was recovered as an oil (1 g, 70 % yield); ^{1}H-NMR δ 1.25 (m,6H), 2.4 (m,2H), 2.55 (m,2H), 4.05 (m,2H), 4.1 (m,4H), 5.05 (m,2H), 5.1 (m,2H), 5.8 (m,2H); ^{13}C-NMR δ 14.3, 39.6, 55.9, 60.6, 117.2, 134.8, 162.8; $[\alpha]_D$= 59.2 (c=1.9, $CHCl_3$)

(*S*)-Allylglycine (11). To bis-lactim **10** (1.43 g, 10 mmol) in acetone (20 ml) was added 0.25 M HCl (10 ml) and the solution was stirred at room temperature for one day. The acetone was then evaporated and the residue was submitted to the alkaline hydrolysis (2M NaOH, 5 ml) in 50% water-ethanol (20 ml) at room temperature. Pure (*S*)-allylglycine was then recovered after adsorption on Amberlyst H-15 ion exchange resin and elution with 5M NH_4OH (1 g, 90% yield); $[\alpha]_D$=-6.2 (c= 2.0, 6M HCl) [lit.[8] $[\alpha]_D$=-6.4 (c= 2.1, 6M HCl)].

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