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Enantioselective Synthesis of (*R*)-and (*S*)-α-Aminoacids using (6*S*)- and (6*R*)-6-Methyl-morpholine-2,5-dione Derivatives

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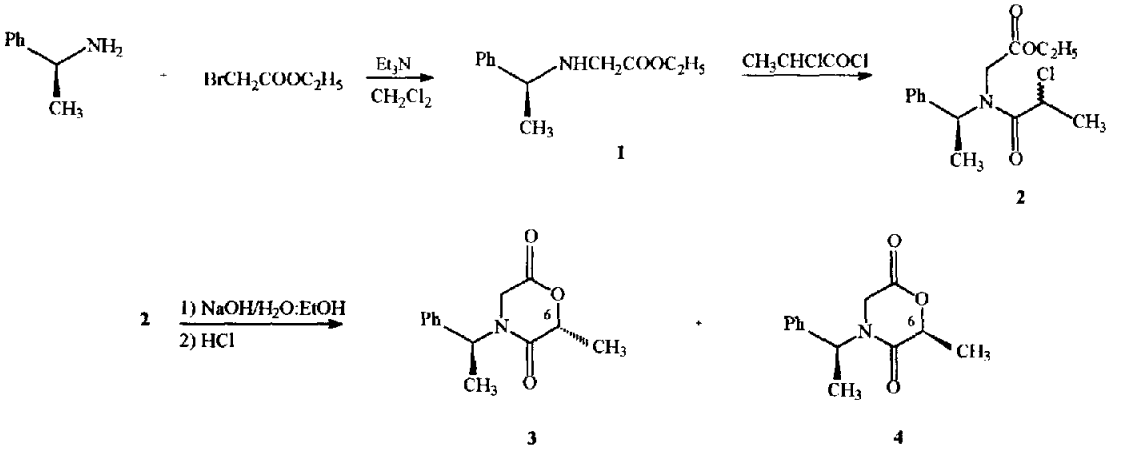
Abstract : The alkylation of both **3** and **4** gives exclusively the *trans* derivatives **5** and **6**, respectively, with >98% diastereoselectivity. Cleavage of the morpholine-2,5-dione ring of **5** and **6** leads to enantiomerically pure (*S*)- and (*R*)-α-aminoacids, respectively. The configurations of stereogenic centers introduced on **3**, **4**, **5** and **6** have been assigned on the basis of the ^{1}H-NMR data, conformational analysis and nOe measurements.

The use of chiral glycine anion equivalents for the synthesis of α-aminoacids, as optically active starting materials for various applications, has recently received considerable attention[1]. In fact, the stereoselective alkylation of 1,3-imidazolidin-4-ones, described by Seebach[2], and 5-phenyl or 5,6-diphenyl-oxazinones reported by Dellaria[3], Baldwin[4] and Williams[5], has proved useful for the synthesis of α-aminoacids. As part of a program aimed at the enantioselective synthesis of α-aminoacids, we have previously reported an approach involving the alkylation[6-8] and recently the aldol condensation[9] of the versatile synthons (3*S*)- and (3*R*)-1,4-N,N-((*S*)-1-phenethyl)-3-methyl-piperazine-2,5-dione. In a continuation of our studies, we have directed our interest to investigating the stereochemical behaviour of new chiral substrates, such as (6*R*)-**3** and (6*S*)-4-N-((*S*)-1-phenethyl)-6-methyl-1,4-morpholine-2,5-dione **4** (synthesized as reported in Scheme 1), in the alkylation reaction.



Scheme 1.

Chloropropionamide **2** was obtained in good yield (as a diastereomeric mixture) from the Schotten-Baumann reaction of chloropropionyl chloride with intermediate **1**. Subsequent treatment of **2** with NaOH in 50% water/ethanol, followed by 1N HCl, gave a mixture of the diastereoisomers **3** and **4** which were easily separated by silica gel chromatography.

The absolute configuration of stereogenic center C-6 of **3** and **4** was determined on the basis of the ^{1}H-NMR data, nOe experiments and our experiences with the piperazine-2,5-dione derivatives[6-9] previously studied.

A preliminary investigation carried out by molecular mechanics calculations[10] on the model compound 6-methyl-1,4-morpholine-2,5-dione, depicted in Figure 1, showed that the preferred geometry of the heterocyclic ring is a quasiboat (or sofa') conformation with the atoms O-1, C-2, N-4, C-5 coplanar, while C-3 and C-6 are about 35° and 15° out of the plane respectively (i.e. the boat is deeper on the C-3 than on the C-6 side). Moreover the substituents at C-3 can lie in an axial or equatorial position, while both the substituents at C-6 are in a pseudoequatorial arrangement (Figure 1).

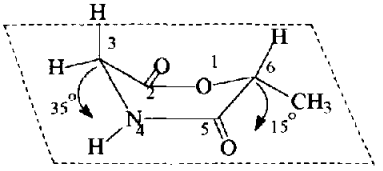


Figure 1. Calculated geometry of (6R)-methyl-morpholine-2,5-dione.

The conformational analysis of the diastereomers **3** and **4**, accomplished by flipping the heterocyclic ring and through a full rotation around the C*-(N-4) bond, suggested that the phenethyl side chain can exist in two low energy conformers, with the benzylic hydrogen syn or antiperiplanar to the adjacent carbonyl (the former being more stable than the latter) analogously to what had been previously observed for piperazine-2,5-dione derivatives[6]. However it is only the conformer with the benzylic hydrogen synperiplanar (even if it is scarcely present) which can anisotropically affect the chemical shift of the C-6 protons, as conveniently described by Newman projections reported in Fig.2.

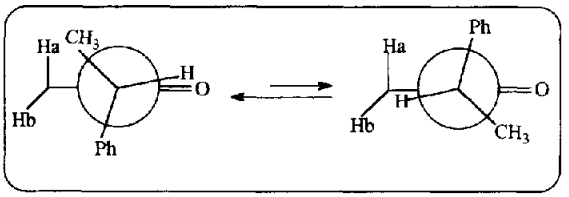
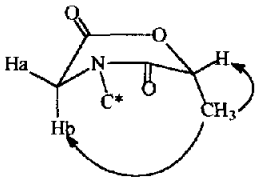


Figure 2. Newman projections along the C*-(N-4) bond.

Thus, it is possible to distinguish the protons at C-3 owing to the different shielding induced by the phenyl ring of

the adjacent chiral moiety. Indeed, the ^{1}H-NMR spectra both of **3** and **4** showed two doublets for the C-3 protons, one of which (H_b) lies at higher (3.65 ppm) and the other one (H_a) at lower (3.95 ppm) field. Therefore the assignment of the signals to H_a and H_b allowed the absolute configuration of the C-6 center of isomers **3** and **4** to be assigned by the nOe experiments. In fact, by irradiating the (C-6)-CH_3 a 2 % and a 2.5 % nOe were registered on H_b of **3** and on H_a of **4** respectively (Figure 3).



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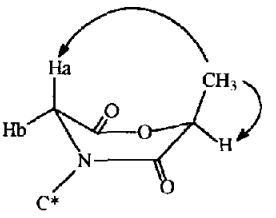

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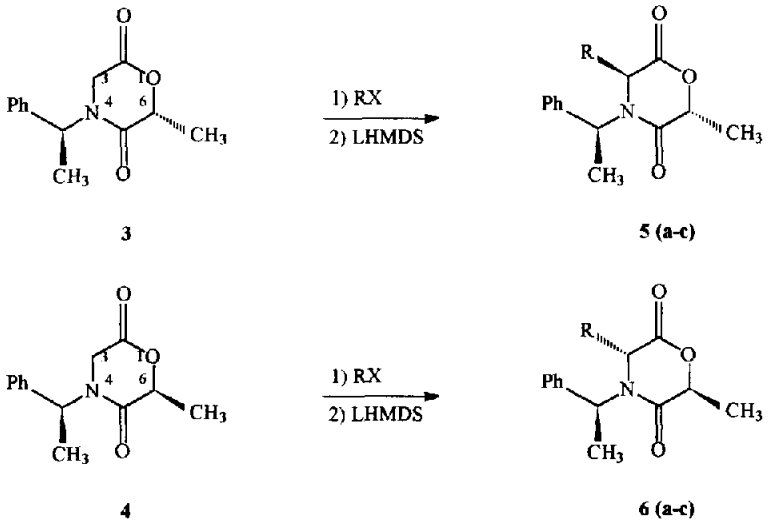
Figure 3. nOes registered on **3** and **4** [C* = (1S)-phenethyl group].

When 1 equivalent of alkylating reagent has been added to the lithium enolate of the pure isomer (6R)-**3**, cooled to -78°C, the *trans* products **5(a-c)** were obtained in good yields. Thus, the electrophile adds trans to the methyl group at C-6 with very high 1,4-asymmetric induction, since the diastereomeric excess (determined by ^{1}H-NMR) is greater than 98%. Analogously, when the isomer (6S)-**4** has been submitted to the same rections exclusively the product of *trans* substitution **6** was observed (Scheme 2).



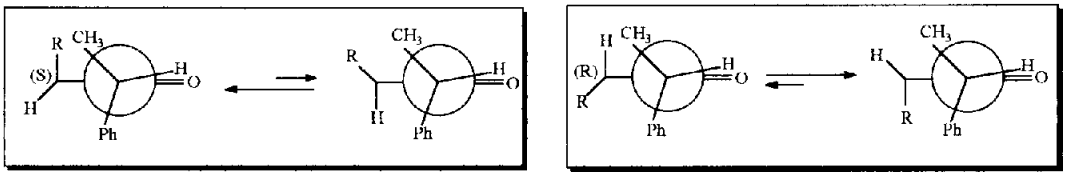
3 **5 (a-c)**

4 **6 (a-c)**

Scheme 2. Diastereoselective alkylation of **3** and **4** [R = (a) CH_3; (b) n-C_3H_7; (c) $PhCH_2$]

The absolute configuration of the introduced stereogenic center C-3 of **5** and **6** has been determined on the basis of the ^{1}H-NMR data, using the approach above employed for the compounds **3** and **4**, and confirmed by nOe experiments.

Molecular mechanics calculations[10] performed on **5a** and **6a** showed that the (C-3)-CH_3 preferentially lies in the axial position (according to what was previously reported for the piperazine-2,5-dione derivatives) and the C-3 is 26° out of the plane (less than observed in **3** and **4**). Besides, both for **5a** and **6a** the antiperiplanar conformation substantially appeared as populated as the synperiplanar one, in any case this conformer being the only one to explain the remarkable differences in chemical shifts registered for the substituents at C-3 (Figure 4). In fact, as can be seen from Figure 4, only the proton attached to the C-3 with (*S*) configuration is significantly shielded, resonating this way at a lower chemical shift than one at a (*R*) centre. The opposite is true for the CH_2 protons bonded to a (3*R*) centre that resonate upfield from their corresponding (3*S*) isomer.



(3*S*)-**5** (3*R*)-**6**

Figure 4. Newman projections along the C*-(N-4) bond of synperiplanar conformers of **5** and **6**, obtained by flipping the heterocyclic ring.

Table 1. Diastereoselective alkylation of **3** and **4** and selected chemical shift (δ) for **5** and **6**.

alkylating reagent		% yield		isomer (3*S*)-**5**		isomer (3*R*)-**6**	
R	X	**5**	**6**	3-CH_2	3-H	3-CH_2	3-H
a	J	90	90	1.57(*)	3.95	0.85(*)	4.18
b	J	70	60	1.75 - 2.0	3.78	0.73 ; 1.43	4.00
c	Br	85	85	3.16 ; 3.25	4.16	2.28 ; 2.58	4.40

(*) chemical shift of the CH_3 doublet.

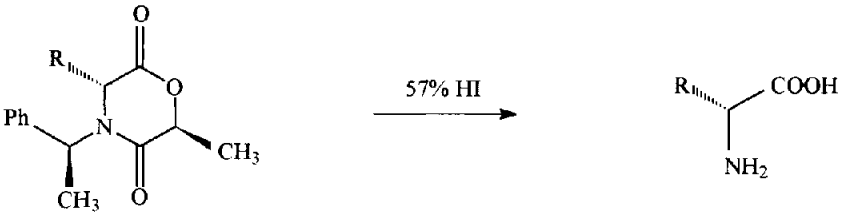
Therefore we have assigned the absolute configuration of stereogenic centre C-3 of **5** and **6** by means of a comparative analysis of the (C-3)-H and the (C-3)-CH_2 chemical shifts listed in Table 1 that reflect the shieldings pointed out by the Newman projections of Figure 4. In fact, the (C-3)-CH_2 are in all cases more shielded in the (3*R*)-**6** isomers than in the (3*S*)-**5** ones; in contrast, the (C-3)-H absorbs at higher field in (3*S*)-**5** than in (3*R*)-**6**. Thus the

^{1}H-NMR data agree with the results of the conformational analysis and confirm the geometries obtained by molecular mechanic calculations.

However the *trans* relationship on **5** and **6** were supported by the nOe measurements; indeed in all the substrates examined significative nOes have been exclusively observed between the (C-6)-H and the (C-3)-CH_2 protons.

The assigned absolute configuration of centre C-3 was unequivocally confirmed by converting **6(a,c)** into the corresponding α-aminoacids **7(a,c)** (Scheme 3). Debenzylation and heterocyclic ring cleavage was carried out conveniently in one step with refluxing 57% HI and the α-aminoacids were recovered pure after adsorption on Amberlyst H-15 ion exchange resin and successive elution with 5M NH_4OH.

The specific rotation values of **7(a,c)**, corresponding to those of the α-aminoacids in *R* configuration, are a further confirmation of the usefulness and reliability of the approach used to assign the absolute configuration of **5** and **6**.



6 (a,c) **7 (a,c)**

Scheme 3.

In conclusion, the reported strategy provides a new, versatile and efficient approach to the asymmetric synthesis of α-aminoacids with very high stereoselectivity, starting from easily accessible chiral synthons as **3** and **4**. Both chiral substrates **3** and **4**, employed in this strategy, giving exclusively *trans* alkylation, show a stereochemical outcome opposite to that previously observed on the piperazine-2,5-dione derivatives[6-9].

To explain the different outcome between morpholin-2,5-dione and piperazin-2,5-dione derivatives, it is reasonable to assume that the chiral moiety in the enolate species (derived from **3** and **4**) does not exert an appreciable influence on the stereochemical control of the alkylation reaction. In fact, the observed total *trans* induction could mainly be ascribed to the different steric hindrance, induced by the (C-6)-CH_3, between the diastereotopic faces of the heterocyclic ring. Such a stereocontrolled induction could be analogous to the diastereofacial selectivity observed by Schollkopf[11] on the alkylation of bis-lactim ether derivatives. Indeed, from semiempirical calculations[12], performed on the lithium enolate of **3** and **4** (whose heterocyclic ring results substantially planar), the syn and the antiperiplanar conformers appear equally populated, the differences in energy being less than 0.3 Kcal/mol.

Because the methodology described herein appears quite interesting for the preparation of a wide variety of α-aminoacids with desired stereochemistry (starting from substrate **3** or **4**), further investigations are in progress in order to use this protocol for the synthesis of uncommon α-aminoacids.

EXPERIMENTAL

^{1}H-NMR spectra were recorded at 300 Mhz using $CDCl_3$ as solvent. Optical rotation values were recorded on a Perkin Elmer 541 polarimeter at 25°C. All reactions involving organometallic reagents were carried out under an argon atmosphere in dry THF, distilled from sodium benzophenone ketyl. Chromatographic separation was performed with silica gel 60 (230-400 mesh). Melting points were determined in open capillaries and are uncorrected.

(4S)-N-((S)-1-Phenethyl)-4-phenyl-3-aza-ethylpentanoate 1. To a solution of 32.2 ml of (S)-1-phenethylamine (250 mmol) and 41.5 ml of triethylamine (300 mmol) in 150 ml of dichloromethane stirred at 0°C, were slowly dropped 39.8 ml (250 mmol) of ethylbromoacetate in 20 ml of CH_2Cl_2. The cooling bath was then removed allowing the reaction to warm up to room temperature and the mixture was stirred for an additional 24 h at r.t. After addition of 2M HCl (25 ml) the reaction product was extracted with dichloromethane. The organic extract was dried, evaporated in vacuo and the residue was then submitted to silica gel chromatographic separation eluting with hexane/ethyl acetate. The product was isolated pure, as an oil, in 90% yield; ^{1}H-NMR δ 1.25 (t,3H,J=7.2Hz), 1.4 (d,3H, J=7.1Hz), 1.9 (bs,1H), 3.25 (d,1H, J=18Hz), 3.3 (d,1H,J=18Hz), 3.8 (q,1H,J=7.1Hz), 4.15 (q,2H,J=7.2 Hz), 7.3 (m,5ArH); ^{13}C-NMR δ 14.1, 24.1, 48.7, 57.7, 60.6, 126.7, 127.1, 128.4, 144.4, 172.4; $[\alpha]_D$=-64.4 (c=2.27, $CHCl_3$). Anal. Calcd for $C_{12}H_{17}NO_2$: C,69.54; H,8.27. Found C,69.4; H,8.3.

(4S)-N-((S)-1-Phenethyl)-4-phenyl-3-((2S,R)-2-chlropropionyl)-3-aza-ethylpentanoate 2. To 9.6 g of **1** (46.4 mmol) in water-acetone (1:1, 100 ml) at O°C was added $Na_2CO_3.10H_2O$ (13.5 g). Then 5 ml of (R,S)-2-chloropropionyl chloride (50 mmol) in 5 ml of acetone were added dropwise. After 3 h, the solvent was removed under reduced pressure and the residue was acidified with 6M HCl. After extraction with ethyl acetate and removal of the solvent, the mixture of diastereomers was obtained as an oil in 90% yield. The pure diastereomers can be separated by silica gel chromatography eluting with hexane/ethyl acetate.

(4S,2S)-2 (mixture of conformers) : ^{1}H-NMR δ 1.23 (t,3H,J=7.2Hz), 1.29 (t,3H,J=7.2Hz), 1.4 (d,3H, J=7.1Hz), 1.7 (d,3H,J=7.1Hz), 1.73, (d,3H,J=6.4Hz), 1.75 (d,3H,J=6.4Hz), 3.6 (d,1H,J=18Hz), 3.61 (d,1H,J=17Hz), 4.05 (d,1H,J=17Hz), 4.12 (m,2H), 4.16 (d,1H,J=18Hz), 4.2 (m,2H), 4.4 (q,1H,J=6.4Hz), 4.74 (q,1H,J=6.4Hz), 5.38 (q,1H,J=7.1Hz), 6.08 (q,1H,J=7.1Hz), 7.3 (m,5ArH);^{13}C-NMR δ 13.8, 15.4, 17.6, 20.4, 20.8, 44.4, 44.5, 49.1, 49.9, 51, 55, 60.7, 61.6, 126.1, 126.8, 127.3, 127.6, 128.4, 128.6, 139.8, 168.3, 168.9, 169.6, 169.9; $[\alpha]_D$=-105.7 (c=2.06, $CHCl_3$). Anal. Calcd for $C_{15}H_{20}ClNO_3$: C,60.5; H,6.72. Found C,60.1; H,6.5.

(4S,2R)-2 (mixture of conformers) : ^{1}H-NMR δ 1.02 (t,3H,J=7.2Hz), 1.22 (t,3H,J=7.2Hz), 1.5 (d,3H, J=7.1Hz), 1.66 (d,3H,J=7.1Hz), 1.75 (d,3H,J=6.4Hz), 1.78 (d,3H,J=6.4Hz), 3.32 (d,1H,J=17Hz), 3.7 (d,1H,J=17Hz), 3.8 (m,2H), 4 (d,1H,J=17Hz), 4.1 (m,2H), 4.18 (d,1H,J=17Hz), 4.45 (q,1H,J=6.4Hz), 4.78 (q,1H,J=6.4Hz), 5.45 (q,1H,J=7.1Hz), 6.03 (q,1H,J=7.1Hz), 7.35 (m,5ArH);^{13}C-NMR δ 13.7, 13.8, 15.3, 17.9, 20.6, 21, 44.4, 48.9, 49.1, 50.3, 51.8, 54.8, 60.8, 61.2, 127.2, 127.7, 127.9, 128.1, 128.3, 128.5, 138.2, 138.6, 168.6, 168.9, 169.1, 169.4; mp 54-5°C; $[\alpha]_D$=-74.6 (c=2.13, $CHCl_3$). Anal. Calcd for $C_{15}H_{20}ClNO_3$: C,60.5; H,6.72. Found C,60.8; H,6.7.

(6R)- and (6S)-4-N-((S)-1-Phenethyl)-6-methyl-1,4-morpholin-2,5-dione 3 and 4. To 10.7 g of **2** (46 mmol) was added 3.7 g of NaOH (92 mmol) disolved in 60 ml of 50% water:ethanol. After about 1h, the reaction mixture was evaporated in vacuo to dryness and the residue was dissolved in water. The diastereomeric mixture of **3** and **4**

was precipitated by adding 2MHCl (30 ml) to the aqueous solution. The crude white solid (9.6g, 90% yield) was filtered off and submitted to chromatographic separation eluting with hexane/ethyl acetate.

(6R)-3 : ^{1}H-NMR δ 1.55 (d,3H,J=7.1Hz), 1.65 (d,3H,J=6.9Hz), 3.65 (d,1H,J=17.8Hz), 3.95 (d,1H,J=17.8 Hz), 4.92 (q,1H,J=6.9Hz), 5.96 (q,1H,J=7.1Hz), 7.3 (m,5ArH);^{13}C-NMR δ 15.2, 17.1, 42.7, 50.4, 74.9, 127.1, 128.3, 129, 137.8, 165.6, 165.9; mp 98-9°C; $[\alpha]_D$=-106.8 (c=2.25, $CHCl_3$). Anal. Calcd for $C_{13}H_{15}NO_3$: C,66.94; H,6.48. Found C,67.15; H,6.45.

(6S)-4 : ^{1}H-NMR δ 1.55 (d,3H,J=7.1Hz), 1.65 (d,3H,J=6.9Hz), 3.64 (d,1H,J=17.8Hz), 3.9 (d,1H,J=17.8), 4.9 (q,1H, J=6.9), 5.95 (q,1H,J=7.1Hz), 7.3 (m,5ArH); ^{13}C-NMR δ 15.2, 17.1, 42.8, 50.5, 74.9, 127.2, 128.3, 128.9, 137.8, 165.9, 166; mp 118-9°C; $[\alpha]_D$=-199.4 (c=2.05, $CHCl_3$). Anal. Calcd for $C_{13}H_{15}NO_3$: C,66.94; H,6.48. Found C,66.7; H,6.5.

Alkylation of 3 and 4 : general procedure. 10 ml of LHMDS (1M solution in THF) (10 mmol) were slowly dropped to a solution of 2.3 g (10 mmol) of **3** (or **4**) in dry THF (100 ml), cooled at -40°C under an inert atmosphere. After 1 h, the bath was cooled at -78°C and the alkylating reagent (10 mmol) was added. After about 5 h, the cooling bath was removed allowing the reaction mixture to warm up to r.t., then 1M HCl (about 10 ml) was added and the mixture extracted with ethyl acetate. The organic extract was dried, evaporated in vacuo and the residue was submitted to silica gel chromatographic separation eluting with hexane/ethyl acetate.

(3S,6R)-4-N-((S)-1-Phenethyl)-3,6-dimethyl-1,4-morpholin-2,5-dione 5a. The pure product was isolated as an oil; ^{1}H-NMR δ 1.57 (d,3H,J=7.4Hz), 1.63 (d,3H,J=7.2Hz), 1.68 (d,3H,J=6.8Hz), 3.95 (q,1H,J=7.4 Hz), 4.99 (q,1H,J=6.8Hz), 5.88 (q,1H,J=7.2Hz), 7.3 (m,5ArH); ^{13}C-NMR δ 16.2, 17.3, 18.6, 51.3, 51.7, 73.5, 126.8, 128.1, 128.9, 138.3, 166.1, 168.3; $[\alpha]_D$=42.2 (c=0.64, $CHCl_3$). Anal. Calcd for $C_{14}H_{17}NO_3$: C,68.; H,6.93. Found C,68.2; H,6.92.

(3S,6R)-4-N-((S)-1-Phenethyl)-3-n-propyl-6-methyl-1,4-morpholin-2,5-dione 5b. The product was obtained as an oil; ^{1}H-NMR δ 0.94 (t,3H,J=7.1Hz), 1.35-1.5 (m,2H), 1.59 (d,3H,J=7), 1.65 (d,3H,J=6.7Hz), 1.75-2 (m, 2H), 3.78 (dd,1H,J=4.7, 10.4Hz), 5.01 (q,1H,J=6.7Hz), 5.85 (q,1H,J=7Hz), 7.3 (m,5ArH); ^{13}C-NMR δ 13.4, 16.3, 17.3, 18.9, 34.7, 52, 55.8, 73.4, 126.8, 128.1, 128.9, 138.4, 166.4, 166.9; $[\alpha]_D$=49.4 (c=0.84, $CHCl_3$). Anal. Calcd for $C_{16}H_{21}NO_3$: C,69.79; H,7.69. Found C,69.92; H,7.68.

(3S,6R)-4-N-((S)-1-Phenethyl)-3-benzyl-6-methyl-1,4-morpholin-2,5-dione 5c. The product was recovered as an oil; ^{1}H-NMR δ 1.42 (d,3H,J=7.1Hz), 1.75 (d,3H,J=6.8Hz), 3.16 (dd,1H,J=6, 14Hz), 3.25 (dd,1H,J=4.2, 14 Hz), 3.6 (q,1H,J=6.8Hz), 4.16 (dd,1H,J=4.2, 6Hz), 5.9 (q,1H,J=7.1Hz), 7.3 (m,10ArH); ^{13}C-NMR δ 16.9, 18, 39.6, 52.9, 58, 73.4, 127.2, 128, 128.4, 128.5, 128.8, 129.1, 129.2, 129.6, 134.6, 138.3, 167.1, 167.5; $[\alpha]_D$=54.1 (c=2.27, $CHCl_3$). Anal. Calcd for $C_{20}H_{21}NO_3$: C,74.28; H,6.55. Found C,74.05; H,6.57.

(3R,6S)-4-N-((S)-1-Phenethyl)-3,6-dimethyl-1,4-morpholin-2,5-dione 6a. The product was isolated pure as an oil; ^{1}H-NMR δ 0.85 (d,3H,J=7.1Hz), 1.56 (d,3H,J=7.1Hz), 1.66 (d,3H,J=6.7Hz), 4.18 (q,1H,J=7.1Hz), 4.92 (q,1H,J=6.7Hz), 5.97 (q,1H,J=7.1Hz), 7.4 (m,5ArH); ^{13}C-NMR δ 15.7, 16.1, 17, 50.9, 51.1, 73.6, 127.8, 128.3, 128.7, 138.6, 165.7, 168.6; $[\alpha]_D$=-290.7 (c=1.08, $CHCl_3$)

(3R,6S)-4-N-((S)-1-Phenethyl)-3-n-propyl-6-methyl-1,4-morpholin-2,5-dione 6b. The product was obtained as an oil; ^{1}H-NMR δ 0.6 (t,3H,J=7.2Hz), 0.73 (m,1H), 1.03 (m,1H), 1.2 (m,1H), 1.43 (m,1H), 1.56 (d,3H, J=7.1 Hz), 1.63 (d,3H,J=6.7Hz), 4 (dd,1H,J=4, 11Hz), 4.96 (q,1H,J=6.7Hz), 5.94 (q,1H,J=7.1Hz), 7.4 (m,5ArH); ^{13}C-

NMR δ 13, 15.9, 16.2, 18.7, 33.1, 51.3, 55.4, 73.5, 127.9, 128.3, 128.6, 138.5, 165.9, 167.3; $[\alpha]_D$=-254.7 (c=0.55, $CHCl_3$)

(3R,6S)-4-N-((S)-1-Phenethyl)-3-benzyl-6-methyl-1,4-morpholin-2,5-dione 6c. The pure product is an oil, ^{1}H-NMR δ 1.42 (d,3H,J=7.1Hz), 1.6 (d,3H,J=6.4Hz), 2.28 (dd,1H,J=7.4, 14Hz), 2.58 (dd,1H,J=3.9, 14Hz), 3.7 (q,1H,J=6.4Hz), 4.4 (dd,1H,J=3.9, 7.4Hz), 6 (q,1H,J=7.1Hz), 6.8-7.6 (m,10ArH); ^{13}C-NMR δ 16.3, 16.7, 37.9, 52.1, 57.6, 73.4, 127.8, 128.5, 128.9, 129.1, 129.4, 134.5, 138.4, 166.5, 167.4; $[\alpha]_D$=-19.6 (c=2.13, $CHCl_3$).

Procedure to obtain 7(a,c). 5 mmol of **6a** or **6c** were added to 10 ml of 57%HI and the mixture was refluxed for about 1h. Then the resulting solution was extracted with ethyl acetate, and the aqueous extract was evaporated under reduced pressure. The residue was dissolved in 10 ml of water and adsorbed on ion exchange resin amberlist H-15. The resin, washed with distilled water, was then eluted with 5MNH_4OH to recover the α-aminoacids **7a** and **7c**, in practically quantitative yield, after evaporation to dryness.

(R)-Alanine 7a; $[\alpha]_D$=-2.6 (c=6, H_2O)[13].

(R)-Phenylalanine 7c; $[\alpha]_D$=34.8 (c=2, H_2O)[13].

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