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# Stereoselective synthesis of uncommon $\alpha,\alpha'$ -dialkyl- $\alpha$ -aminoacids. Part 1

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## Abstract

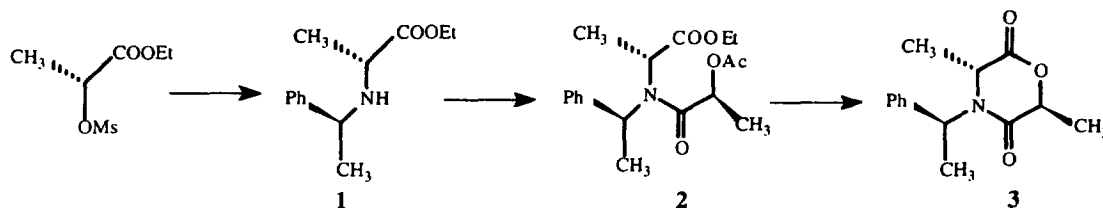
The alkylation of the diastereomeric mixture of chiral morpholinone derivatives **4** and **5** occurs with good yield and *trans* induction. Cleavage of the alkylated products **6a,b,c,e** gives enantiomerically pure uncommon (and sterically constrained)  $\alpha,\alpha'$ -dialkyl- $\alpha$ -aminoacids. The absolute configuration of the new stereocentres of **4**, **5**, **6** and **7** has been assigned on the basis of the  $^1\text{H-NMR}$  spectra and NOE measurements. © 1998 Elsevier Science Ltd. All rights reserved.

## 1. Introduction

In recent years, optically active non-proteinogenic and rigidified  $\alpha$ -amino acids have gained relevance because of their potential biological activity.<sup>1</sup> In fact, several molecules with therapeutic effects contain unnatural amino acids which can also act as enzyme inhibitors. For instance,  $\alpha,\alpha'$ -dialkyl- $\alpha$ -aminoacids are able to influence remarkably the peptides into which they can be incorporated by reducing the conformational freedom.

In a previous paper<sup>2</sup> we reported a new approach to the enantioselective synthesis of uncommon  $\alpha$ -amino acids through the stereoselective alkylation of (6*S*)- and (6*R*)-6-methyl-morpholine-2,5-dione derivatives. Therefore, as a continuation of our studies, we have directed our interest to investigating the mono and dialkylation of the chiral synthon (3*R*,6*S*)-4-*N*-((*S*)-1-phenethyl)-3,6-dimethyl-1,4-morpholin-2,5-dione **3**, our aim being the accomplishment of a new strategy to the stereoselective synthesis of uncommon  $\alpha,\alpha'$ -dialkyl- $\alpha$ -aminoacids. The starting synthon **3** we used was synthesized in satisfactory yield as previously reported<sup>2</sup> or starting from methansulfonate of (*S*)-ethyl lactate and (2*S*)-2-acethoxypropanoylchloride (Scheme 1).

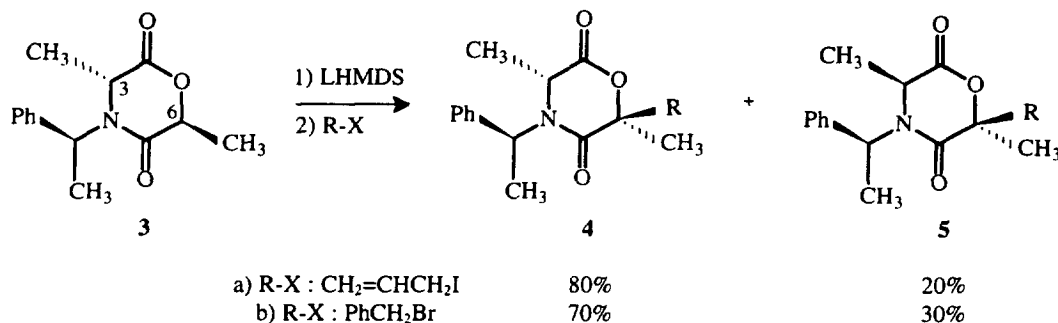
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Scheme 1.

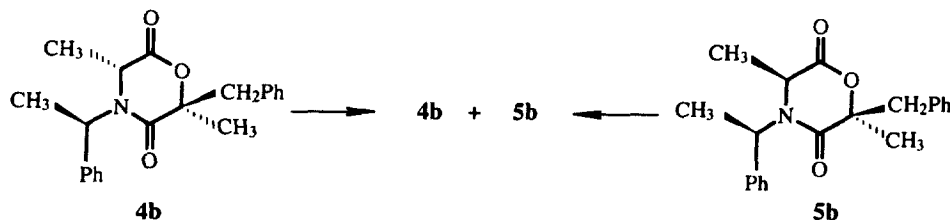
## 2. Results and discussion

The alkylation of **3** with both allyl iodide and benzyl bromide occurs in very good chemical yield exclusively at C-6 and with total *trans* stereoselection, the new stereocentre C-6 having the *S* configuration. In fact, the diastereomer **5**, isolated in only 20–30% yield, was produced owing to the isomerization of the stereocentre C-3 of the prevalent *cis* isomer **4** (see Scheme 2). A very good alkylation of **3** (yield >95%) was achieved by using 1.6 equivalents of LHMDS, 1 equivalent of alkylating agent and performing the reaction at  $-78^{\circ}\text{C}$  for 6 hours. Employing one equivalent of LHMDS the reaction occurred in lower yield (about 60%). The alkylation of the chiral synthon **3** at C-6 was probed with NOE measurements on the reaction products. In fact, by irradiating both the  $\text{CH}_3$  and the hydrogen of the chiral auxiliary, NOEs were exclusively registered on the (C-3)–H and the (C-3)– $\text{CH}_3$  both at **4** and at **5**.



Scheme 2.

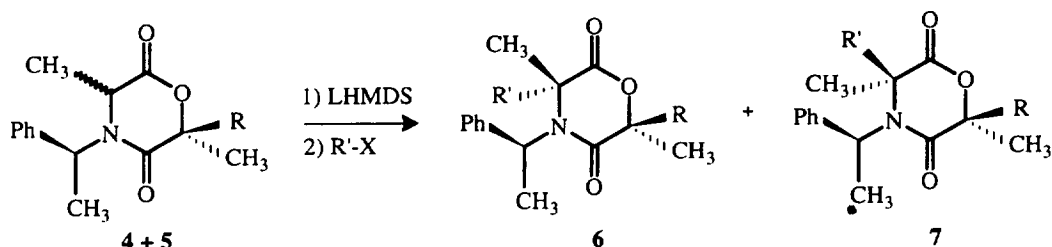
The absolute configurations of stereocentres C-3 and C-6 in **4** and **5** were assigned by  $^1\text{H}$ -NMR data (see the following stereochemical assignments): however, we confirmed that **4** and **5** are diastereomers with opposite configuration to the C-3, because, after metallation followed by water addition, both **4b** and **5b** gave a mixture of **4b** and **5b** (see Scheme 3).



Scheme 3.

The second alkylation, performed at  $-40^{\circ}\text{C}$  directly on the diastereomeric mixture (**4+5**) (Scheme 4), occurs with a good chemical yield (>90%) and diastereoselectivity, as it appears in the data collected in Table 1. It is interesting to emphasize that by using the same alkylating reagent (entry c and e, Table 1) for

either of the alkylation processes it is possible to do both steps in one-pot, i.e. avoiding the purification of the monoalkylated diastereomers.



Scheme 4.

The *trans*-3,6-dimethyl derivative **6** was obtained in large proportion with respect to the *cis* isomer **7** in all cases investigated regardless of the alkylating reagent used. The data collected in Table 1 show that the reaction occurs with good *trans* induction with respect to (C-6)–R, i.e. the bulkier substituent at C-6. Thus, the prevalent *trans* stereocontrol observed could be ascribed mainly to the configuration of the C-6 stereocentre that causes a different steric hindrance between the diastereotopic faces of the enolate ion of **4** or **5**. In fact, better diastereoselection is achieved when both the alkylating reagent and the alkyl substituent at C-6 are rather sterically hindered. Nevertheless, further studies are in progress in order to investigate the influence of the chiral auxiliary (phenethyl group) on the stereochemical outcome of this alkylation.

Finally, in a model study, the intermediates **6a**, **6b** and **6e** were converted into the corresponding  $\alpha,\alpha'$ -dialkyl- $\alpha$ -aminoacids whose specific rotation values are reported in the literature (Scheme 5). Thus, the correct absolute configuration assigned to the stereocentre C-3 through the  $^1\text{H-NMR}$  data was also confirmed.

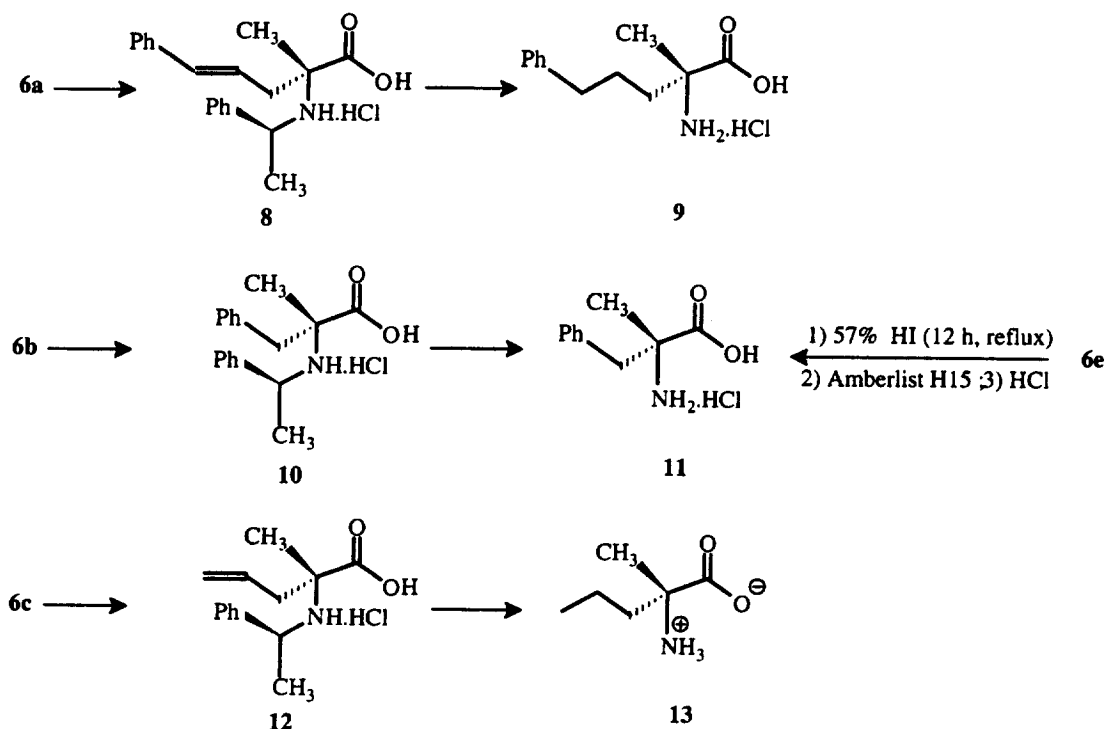
Starting from derivative **6c** the unnatural  $\alpha$ -aminoacid **13**, that to our knowledge is not reported in the literature, was obtained. The one step conversion of **6e** into the (2*R*)-2-benzylalanine hydrochloride **11** refluxing with 57% HI, as previously described for similar compounds,<sup>2</sup> occurred in a low yield (~30%).

In conclusion, the stereocontrolled double alkylation of the chiral synthon **3**, described in this report, gives access to a variety of enantiomerically pure unusual  $\alpha,\alpha'$ -dialkyl- $\alpha$ -aminoacids (sterically constrained) which are an interesting class of products that can exhibit important and diverse biological functions.

Table 1  
Diastereoselectivity on the alkylation of (4+5) mixture

Entry		(C-6)-R	(C-3)-R'	Yield <sup>(a)</sup>	
				<b>6</b>	<b>7</b>
1	a	CH <sub>2</sub> =CH-CH <sub>2</sub>	PhCH=CH-CH <sub>2</sub>	86	14
2	b	CH <sub>2</sub> =CH-CH <sub>2</sub>	Ph-CH <sub>2</sub>	86	14
3	c	CH <sub>2</sub> =CH-CH <sub>2</sub>	CH <sub>2</sub> =CH-CH <sub>2</sub>	83	17
4	d	CH <sub>2</sub> =CH-CH <sub>2</sub>	CH <sub>3</sub> -CH <sub>2</sub>	82	18
5	e	Ph-CH <sub>2</sub>	Ph-CH <sub>2</sub>	90	10
6	f	Ph-CH <sub>2</sub>	PhCH=CH-CH <sub>2</sub>	87	13
7	g	Ph-CH <sub>2</sub>	CH <sub>2</sub> =CH-CH <sub>2</sub>	85	15
8	h	Ph-CH <sub>2</sub>	CH <sub>3</sub> -CH <sub>2</sub>	78	22

(a) The reported yields were calculated by  $^1\text{H-NMR}$ .



Scheme 5.

### 3. Stereochemical assignments

The configuration of the stereocentres in the derivatives **4** and **5** was deduced on the basis of NOE experiments and  $^1\text{H}$ -NMR spectra using the approach previously employed for similar molecules.<sup>2,3</sup> In previous papers we showed that: (a) the favoured geometry of the morpholindione derivative **3** is a quasiboat (or sofa) conformation in which the (C-3)–CH<sub>3</sub> preferentially lies in the pseudo-axial arrangement;<sup>2</sup> (b) the configuration of C-3 can be easily assigned by means of the different shielding induced by the phenyl ring of the adjacent chiral auxiliary.<sup>3,4</sup> Thus, on the basis of the registered chemical shifts, we could assign the *R* and the *S* configuration to the C-3 stereocentre of **4** and **5**, respectively. In fact, in **4a** the (C-3)–CH<sub>3</sub> doublet lies at higher field (0.95 ppm) than in **5a** (1.65 ppm), whereas the (C-3)–H resonates at a lower field (4.25 ppm) in the former than in the latter isomer (3.87 ppm). Besides, the significant NOE observed between the methyls bonded at C-3 and C-6 stereocentres allowed us to assign the 6*S* configuration to **4a** (Fig. 1). By irradiating the CH<sub>3</sub> of the chiral auxiliary in **4b** the NOE was exclusively registered on (C-3)–H, while in **5b** a largely prevalent NOE was observed on (C-3)–CH<sub>3</sub>. Thus, we assigned the 3*R* configuration to **4b** and the 3*S* one to **5b**. In addition, the significant NOE registered between the (C-3)–CH<sub>3</sub> and (C-6)–CH<sub>3</sub> (in analogy to **4a**) allowed us to ascribe the 6*S* configuration to **4b**. The *S* configuration of the C-6 centre was confirmed by the greater shielding observed for both (C-3)–H (3.57 ppm) and (C-3)–CH<sub>3</sub> (0.41 ppm) in **5b** in comparison to **4b** (3.79 and 0.87 ppm, respectively). In fact, the high field resonance of the (C-3)–CH<sub>3</sub> doublet observed in **5b** is diagnostic for a *cis* diaxial relationship between the methyl and the (C-6)–CH<sub>2</sub>Ph which can actually adopt the 'aryl inside' arrangement<sup>3</sup> (Fig. 1).

The stereochemistry at C-3 of the diastereomers **6** and **7** was ascertained by NOE experiments, the C-6 configuration being established, or through the shielding effects induced by the phenyl ring of the

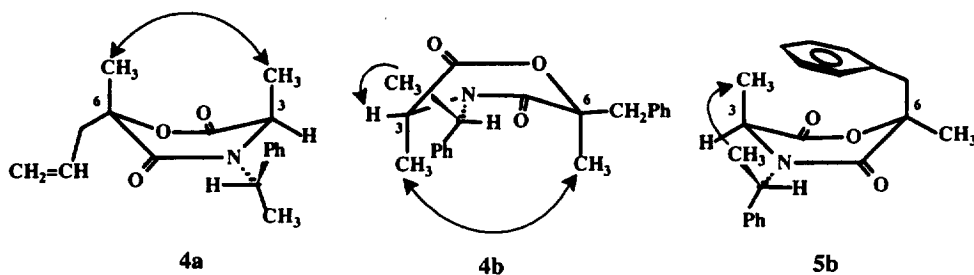


Fig. 1. NOE registered on **4a**, **4b**, **5b** (curved arrows) and phenyl shielding of (C-3)–CH<sub>3</sub> observed on **5b**

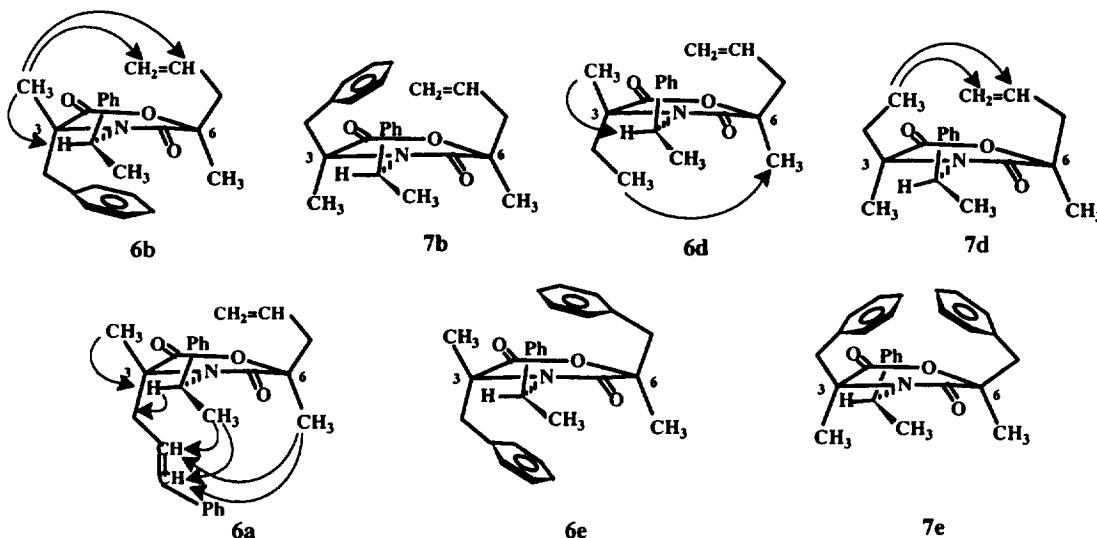


Fig. 2. Representative NOEs (curved arrows) and shielding effects

Ph–CH<sub>2</sub> substituent. For instance, the representative NOE registered between the (C-6)–CH<sub>3</sub> and the methyl group of (C-3)–C<sub>2</sub>H<sub>5</sub> allowed us to assign the *3R* configuration to **6d**. Analogously, it was possible to confirm the *3S* configuration of **7d** owing to the NOE observed on the (C-6)–CH<sub>2</sub>–CH=CH<sub>2</sub> vinylic protons, by irradiating the CH<sub>3</sub> of (C-3)–C<sub>2</sub>H<sub>5</sub>. Besides, the *3R* configuration of **6a** was inferred through the NOEs registered on the vinylic protons of cinnamyl substituent by irradiating the (C-6)–CH<sub>3</sub> (see Fig. 2).

It is interesting to point out that a conformational analysis performed by semiempirical quantummechanical calculations<sup>5</sup> on tetra-substituted morpholindione **6b** showed that: (a) the morpholine ring becomes quasi planar (O-1, C-2, C-3, N-4, and C-5 being practically coplanar, while C-6 is ~23° out of the plane); (b) the benzylic hydrogen of the (*S*)-phenethyl group is preferentially arranged in the antiperiplanar conformation with respect to the adjacent carbonyl (this conformer being 2.3 kcal/mol more stable than the synperiplanar one), as evidenced by the NOE measurements. In fact, by irradiating the (C-3)–CH<sub>3</sub> of **6b** a NOE was observed on the benzylic proton of the chiral auxiliary, but not on the CH<sub>3</sub> (see Fig. 2). In addition, the irradiation of the CH<sub>3</sub> of (*S*)-phenethyl group in **6a** gave NOEs on the vinylic protons of the cinnamyl substituent, but not on the (C-3)–CH<sub>3</sub> (see Fig. 2).

In the compounds having the Ph–CH<sub>2</sub> as a substituent, the configuration at C-3 was assigned on the basis of the shielding effect<sup>3</sup> suffered by the group that lies in front of the Ph–CH<sub>2</sub> and exerted by the phenyl ring. For instance, the (C-6)–CH<sub>3</sub> resonates at a higher field on **6b** (0.86 ppm) than in **7b** (1.54 ppm) and conversely the vinylic protons at C-6 absorb at lower field (5.1 and 5.6 ppm) on the former

diastereomer than in the latter one (4.95 and 5.35 ppm). Therefore, these findings, confirmed by the NOEs registered on the vinylic protons of (C-6)–CH<sub>2</sub>–CH=CH<sub>2</sub> by irradiating the (C-3)–CH<sub>3</sub> (as shown in Fig. 2), indicated that the (C-3)–CH<sub>2</sub>–Ph lies *trans* to (C-6)–CH<sub>3</sub> in **7b** and *cis* in **6b**.

The 3*R* configuration of **6e** was established considering that the (C-3)–CH<sub>3</sub> and (C-6)–CH<sub>3</sub> substantially show the same chemical shift (1.0 and 1.06 ppm), i.e. both methyls are shielded in the same manner. On the other hand, in **7e** these methyls resonate at different fields (1.6 and 1.8 ppm) and, furthermore, are strongly deshielded with respect to **6e**. These findings suggested a *trans* relationship between the (C-3)–CH<sub>3</sub> and (C-6)–CH<sub>3</sub> in **6e**, both methyls being equally shielded by the phenyl ring of both PhCH<sub>2</sub> groups bonded at C-3 and C-6 (see Fig. 2). Thus, it allowed us to assign the 3*S* configuration to the diastereomer **7e**.

#### 4. Experimental

General information: <sup>1</sup>H- and <sup>13</sup>C-NMR were recorded on a Gemini spectrometer at 300 MHz using CDCl<sub>3</sub> as solvent, unless otherwise stated, and the chemical shifts are reported in ppm relative to the solvent. Optical rotation values were measured on a Perkin–Elmer 343 polarimeter. Chromatographic separations were performed with silica gel 60 (230–400 mesh). Dry THF was distilled from benzophenone ketyl.

##### 4.1. (2*R*,4*S*)-3-Aza-2-methyl-4-phenyl-ethylpentanoate **1**

(2*S*)-Ethyl lactate (9.3 g, 47.4 mmol), triethylamine (7 ml, 50 mmol) and (*S*)-1-phenethylamine (6.45 ml, 50 mmol) dissolved in benzene (60 ml) and DMF (30 ml) were stirred at 80°C. After 24 h the reaction was cooled at r.t. then water was added and the solution extracted with ethyl acetate. The organic layer was extracted with diluted HCl, then the aqueous solution was made alkaline with NaOH and extracted with ethyl acetate. After removal of the organic solvent the residue was purified by silica gel chromatography eluting with hexane/ethyl acetate and the pure product was isolated in 90% yield. The NMR data and the [α]<sub>D</sub><sup>25</sup> value are identical to those previously reported.<sup>4</sup>

##### 4.2. (2*R*,3*S*,4*S*)-3-Aza-3-acetoxypropanoyl-2-methyl-4-phenyl-ethylpentanoate **2**

(2*S*)-2-Acetoxy-propanoylchloride (6.7 ml, 53.7 mmol) was dropped into a solution of **1** (11.9 g, 52.7 mmol) and triethylamine (8.75 ml, 58 mmol) and stirred at 0°C. After 1 h, the reaction was slowly warmed to r.t. and dilute HCl and CH<sub>2</sub>Cl<sub>2</sub> were added. The organic extract was dried, evaporated in vacuo and the residue was purified by silica gel chromatography eluting with hexane/ethyl acetate. The pure product was isolated in 85% yield. <sup>1</sup>H-NMR δ 0.97 (d, 2H, J=6.9 Hz), 1.21 (t, 3H, J=7 Hz), 1.53 (d, 1H, J=6.8 Hz), 1.67 (d, 1H, J=6 Hz), 2.13 (s, 3H), 3.43 (q, 1H, J=6.9 Hz), 4.1 (m, 2H), 5.21 (q, 1H, 6.8 Hz), 5.54 (q, 1H, J=6.8 Hz), 7.38 (m, 5ArH); <sup>13</sup>C-NMR δ 14.0, 14.7, 16.7, 18.8, 20.7, 52.8, 54.5, 60.1, 67.0, 127.9, 128.2, 128.6, 138.1, 169.0, 170.8, 171.2. Anal. calcd for C<sub>18</sub>H<sub>25</sub>NO<sub>5</sub>: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.7; H, 7.49; N, 4.2.

##### 4.3. (3*R*,6*S*,1'*S*)-3,6-Dimethyl-4-*N*-(1'-phenethyl)-1,4-morpholin-2,5-dione **3**

2 N NaOH (60 ml) was added to the intermediate **2** (6.7 g, 20 mmol) dissolved in ethanol (60 ml) and the reaction mixture was stirred at r.t. After about 3 h the reaction mixture was concentrated in vacuo,

acidified with 2 N HCl then extracted with ethyl acetate. The organic layer was dried and evaporated in vacuo. The pure product was isolated in 80% yield after purification by silica gel chromatography eluting with hexane/ethyl acetate. The NMR data and the  $[\alpha]_D^{25}$  value are identical to those previously reported.<sup>2</sup>

#### 4.4. Alkylation of 3: general procedure

A quantity (8 ml) of LHMDs (1 M solution in THF) was dropped into a stirred solution of **3** (1.24 g, 5 mmol) in dry THF (50 ml) and cooled at  $-78^\circ\text{C}$  under an inert atmosphere. After 1 h, 5 mmol of the appropriate alkyl halide was added and the reaction mixture was stirred for 6 h. The reaction mixture, was slowly warmed to r.t., and was quenched with water and extracted with ethyl acetate. The organic layer was dried, evaporated under reduced pressure and the diastereomers were separated by silica gel chromatography (hexane/ethyl acetate as eluant) and recovered as oil.

#### 4.5. (3R,6S,1'S)-6-Allyl-3,6-dimethyl-4-N-(1'-phenethyl)-1,4-morpholin-2,5-dione **4a**

<sup>1</sup>H-NMR  $\delta$  0.95 (d, 3H,  $J=7.1$  Hz), 1.6 (d, 3H,  $J=7.1$  Hz), 1.65 (s, 3H), 2.5 (dd, 1H,  $J=7.4$ , 13.9 Hz), 2.9 (dd, 1H,  $J=6.9$ , 13.9 Hz), 4.25 (q, 1H,  $J=7.1$  Hz), 5.17 (m, 2H), 5.7 (m, 1H), 5.80 (q, 1H,  $J=7.1$  Hz), 7.36 (m, 5ArH); <sup>13</sup>C-NMR  $\delta$  16.4, 21.2, 26.2, 44.4, 51.8, 52.1, 84.4, 120.7, 127.7, 128.2, 128.7, 131, 139.6, 167.1, 168.0. Anal. calcd for C<sub>17</sub>H<sub>21</sub>NO<sub>3</sub>: C, 71.06; H, 7.37; N, 4.87. Found: C, 71.26; H, 7.4; N, 4.85.

#### 4.6. (3S,6S,1'S)-6-Allyl-3,6-dimethyl-4-N-(1'-phenethyl)-1,4-morpholin-2,5-dione **5a**

<sup>1</sup>H-NMR  $\delta$  1.52 (d, 3H,  $J=7.2$  Hz), 1.65 (d, 3H,  $J=7.2$  Hz), 1.67 (s, 3H), 2.58 (dd, 1H,  $J=7.5$ , 13.8 Hz), 2.75 (dd, 1H,  $J=7.2$ , 13.8 Hz), 3.87 (q, 1H,  $J=7.2$  Hz), 5.2 (m, 2H), 5.7 (q, 1H,  $J=7.2$  Hz), 5.8 (m, 1H), 7.37 (m, 5ArH); <sup>13</sup>C-NMR  $\delta$  17.5, 22, 25.6, 44.5, 51.6, 53.2, 83.9, 120.8, 120.1, 128, 130.4, 137.5, 167, 167.7.

#### 4.7. (3R,6S,1'S)-6-Benzyl-3,6-dimethyl-4-N-(1'-phenethyl)-1,4-morpholin-2,5-dione **4b**

<sup>1</sup>H-NMR  $\delta$  0.87 (d, 3H,  $J=7.1$  Hz), 1.14 (d, 3H,  $J=7.2$  Hz), 1.8 (s, 3H), 3.03 (d, 1H,  $J=13.4$  Hz), 3.45 (d, 1H,  $J=13.4$  Hz), 3.79 (q, 1H,  $J=7.1$  Hz), 5.68 (q, 1H,  $J=7.2$  Hz), 7.28 (m, 10ArH); <sup>13</sup>C-NMR  $\delta$  15.3, 21.2, 26.4, 46.2, 51.0, 51.3, 85.1, 127.0, 127.2, 127.7, 128.0, 128.4, 130.7, 134.5, 139.5, 166.5, 167.0. Anal. calcd for C<sub>21</sub>H<sub>23</sub>NO<sub>3</sub>: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.9; H, 6.9; N, 4.14.

#### 4.8. (3S,6S,1'S)-6-Benzyl-3,6-dimethyl-4-N-(1'-phenethyl)-1,4-morpholin-2,5-dione **5b**

<sup>1</sup>H-NMR  $\delta$  0.41 (d, 3H,  $J=7.2$  Hz), 1.53 (d, 3H,  $J=7.2$  Hz), 1.8 (s, 3H), 2.97 (d, 1H,  $J=13.5$  Hz), 3.45 (d, 1H,  $J=13.5$  Hz), 3.57 (q, 1H,  $J=7.2$  Hz), 5.61 (q, 1H,  $J=7.2$  Hz), 7.2 (m, 10ArH); <sup>13</sup>C-NMR  $\delta$  17.1, 20.2, 28.0, 46.1, 51.7, 53.4, 85.4, 127.0, 127.5, 127.8, 128.1, 128.5, 128.7, 130.9, 134.6, 136.9, 166.2, 167.2.

#### 4.9. Alkylation of diastereomeric mixture 4+5: general procedure

The diastereomeric mixture of **4** and **5** (2 mmol) in dry THF (20 ml) was metallated with 2 ml of LHMDs (1 M solution in THF) at  $-40^{\circ}\text{C}$ , then submitted to alkylation with the appropriate halide (3 mmol). The reaction mixture was slowly warmed to  $0^{\circ}\text{C}$ , then quenched with water and extracted with ethyl acetate. After removal of the organic solvent, from the crude reaction product the diastereomers were separated by silica gel chromatography using hexane/ethyl acetate as eluant. All the products are oil-like

##### 4.10. (3R,6S,1'S)-6-Allyl-3,6-dimethyl-4-N-(1'-phenethyl)-3-[(E)-3-phenyl-2-propenyl]-1,4-morpholin-2,5-dione **6a**

Cinnamyl bromide was used as the alkylating reagent. The reaction occurred in 4 h and the pure product was isolated in 81% yield.  $^1\text{H-NMR}$   $\delta$  1.41 (s, 3H), 1.70 (s, 3H), 1.95 (d, 3H,  $J=7$  Hz), 2.34 (dd, 1H,  $J=6.6, 13.9$  Hz), 2.68 (dd, 1H,  $J=7.3, 13.9$  Hz), 2.87 (m, 2H), 4.52 (q, 1H,  $J=7.0$  Hz), 5.02 (m, 2H), 5.50 (m, 1H), 6.09 (m, 1H), 6.51 (d, 1H,  $J=15.9$  Hz), 7.27 (m, 10ArH);  $^{13}\text{C-NMR}$   $\delta$  19.5, 26.9, 27.0, 43.0, 45.1, 55.3, 66.9, 83.4, 121.3, 121.7, 126.1, 126.9, 127.0, 127.9, 128.5, 130.5, 136.0, 136.1, 140.9, 166.6, 168.6.  $[\alpha]_{\text{D}}=-46.0$  ( $c=0.2$ ,  $\text{CHCl}_3$ ). Anal. Calcd for  $\text{C}_{26}\text{H}_{29}\text{NO}_3$ : C, 77.39; H, 7.24; N, 3.47. Found: C, 77.19; H, 7.27; N, 3.46.

##### 4.11. (3S,6S,1'S)-6-Allyl-3,6-dimethyl-4-N-(1'-phenethyl)-3-[(E)-3-phenyl-2-propenyl]-1,4-morpholin-2,5-dione **7a**

The pure product was isolated in 13% yield.  $^1\text{H-NMR}$   $\delta$  1.63 (s, 3H), 1.85 (s, 3H), 1.92 (d, 3H,  $J=7$  Hz), 2.39 (dd, 1H,  $J=6.6, 13.9$  Hz), 2.83 (m, 3H), 4.57 (q, 1H,  $J=7$  Hz), 4.72 (m, 1H), 5.02 (m, 1H), 5.5 (m, 1H), 5.68 (m, 1H), 6.05 (d, 1H,  $J=15.1$  Hz), 7.25 (m, 10ArH);  $^{13}\text{C-NMR}$   $\delta$  21.4, 26.5, 27.4, 42.2, 43.9, 57.1, 67.0, 83.4, 120.1, 122.5, 126.2, 127.2, 127.5, 127.8, 128.2, 128.3, 131.0, 135.2, 136.5, 141.3, 167.3, 169.0.  $[\alpha]_{\text{D}}=165.8$  ( $c=0.5$ ,  $\text{CHCl}_3$ ).

##### 4.12. (3R,6S,1'S)-6-Allyl-3-benzyl-3,6-dimethyl-4-N-(1'-phenethyl)-1,4-morpholin-2,5-dione **6b**

Benzyl bromide was used as the alkylating reagent. The reaction occurred over 5 h and the pure product was isolated in 81% yield.  $^1\text{H-NMR}$   $\delta$  0.86 (s, 3H), 1.69 (s, 3H), 2.05 (d, 3H,  $J=7$ ), 2.32 (dd, 1H,  $J=7.3, 13.8$  Hz), 2.7 (dd, 1H,  $J=7.2, 13.8$  Hz), 3.28 ( $q_{\text{AB}}$ , 2H,  $J=14.3$  Hz), 4.68 (q, 1H,  $J=7$  Hz), 5.12 (m, 2H), 5.6 (m, 1H), 7.25–7.5 (m, 10 ArH);  $^{13}\text{C-NMR}$   $\delta$  22.2, 25.8, 28.0, 45.4, 56.7, 68.1, 83.5, 121.3, 127.0, 127.1, 127.8, 128.2, 128.7, 130.5, 130.7, 134.3, 142.2, 167.4, 168.5.  $[\alpha]_{\text{D}}=3.9$  ( $c=1.0$ ,  $\text{CHCl}_3$ ). Anal. calcd for  $\text{C}_{24}\text{H}_{27}\text{NO}_3$ : C, 76.36; H, 7.21; N, 3.71. Found: C, 76.16; H, 7.2; N, 3.7.

##### 4.13. (3S,6S,1'S)-6-Allyl-3-benzyl-3,6-dimethyl-4-N-(1'-phenethyl)-1,4-morpholin-2,5-dione **7b**

The product was isolated in 13% yield.  $^1\text{H-NMR}$   $\delta$  1.54 (s, 3H), 1.93 (s, 3H), 1.94 (d, 3H,  $J=7$  Hz), 2.18 (m, 2H), 3.3 ( $q_{\text{AB}}$ , 2H,  $J=14.4$  Hz), 4.7 (q, 1H,  $J=7$  Hz), 4.95 (m, 2H), 5.35 (m, 1H), 6.7 (m, 2H), 7.25 (m, 8ArH);  $^{13}\text{C-NMR}$   $\delta$  21.0, 26.6, 27.3, 43.7, 45.0, 57.1, 67.6, 83.1, 119.8, 127.2, 128.1, 128.4, 130.6, 130.9, 134.2, 141.1, 167.4, 168.5.



**4.14. (3R,6S,1'S)-3,6-Diallyl-3,6-dimethyl-4-N-(1'-phenethyl)-1,4-morpholin-2,5-dione 6c**

Allyl iodide was used as the alkylating reagent. The reaction occurred over 4 h and the pure product was isolated in 79% yield.  $^1\text{H-NMR}$   $\delta$  1.63 (s, 3H), 1.72 (s, 3H), 1.95 (d, 3H,  $J=7$  Hz), 2.41 (dd, 1H,  $J=7.5, 13.8$  Hz), 2.75 (dd, 1H,  $J=7.2, 13.8$  Hz), 2.78 (m, 2H), 4.52 (q, 1H,  $J=7$  Hz), 5.1 (m, 2H), 5.3 (m, 2H), 5.6 (m, 1H), 5.8 (m, 1H), 7.35 (m, 5ArH);  $^{13}\text{C-NMR}$   $\delta$  18.5, 25.6, 26.2, 42.9, 44.4, 54.2, 66.0, 82.5, 116.6, 120.2, 125.9, 126.3, 127.3, 130.6, 131.3, 141.1, 165.8, 167.8.  $[\alpha]_{\text{D}}=-52.0$  ( $c=1.4$ ,  $\text{CHCl}_3$ ). Anal. calcd for  $\text{C}_{20}\text{H}_{25}\text{NO}_3$ : C, 73.37; H, 7.7; N, 4.28. Found: C, 73.29; H, 7.68; N, 4.3.

**4.15. (3S,6S,1'S)-3,6-Diallyl-3,6-dimethyl-4-N-(1'-phenethyl)-1,4-morpholin-2,5-dione 7c**

The product was isolated in 16% yield.  $^1\text{H-NMR}$   $\delta$  1.62 (s, 3H), 1.8 (s, 3H), 1.91 (d, 3H,  $J=6.8$  Hz), 2.51 (dd, 1H,  $J=7.1, 14.6$  Hz), 2.73 (m, 2H), 2.87 (dd, 1H,  $J=7.4, 14.6$  Hz), 4.54 (q, 1H,  $J=6.8$  Hz), 4.94 (m, 2H), 5.18 (m, 2H), 5.42 (m, 1H), 5.76 (m, 1H), 7.35 (m, 5ArH);  $^{13}\text{C-NMR}$   $\delta$  20.9, 26.5, 27.2, 43.3, 44.1, 56.7, 66.8, 83.5, 120.5, 120.8, 127.1, 127.7, 128.1, 131.3, 140.6, 167.1, 168.0.

**4.16. (3R,6S,1'S)-6-Allyl-3-ethyl-3,6-dimethyl-4-N-(1'-phenethyl)-1,4-morpholin-2,5-dione 6d**

Ethyl iodide was used as the alkylating reagent. The reaction occurred over 8 h and the pure product was isolated in 74% yield.  $^1\text{H-NMR}$   $\delta$  1.02 (t, 3H,  $J=7.2$  Hz), 1.62 (s, 3H), 1.75 (s, 3H), 1.87 (d, 3H,  $J=7$  Hz), 2.03 (m, 2H), 2.47 (dd, 1H,  $J=7.5, 13.7$  Hz), 2.69 (dd, 1H,  $J=7.2, 13.7$  Hz), 4.45 (q, 1H,  $J=7$  Hz), 5.05 (m, 2H), 5.50 (m, 1H), 7.32 (m, 5ArH);  $^{13}\text{C-NMR}$   $\delta$  9.1, 20.8, 26.4, 27.1, 32.2, 43.7, 56.3, 66.9, 82.9, 120.2, 126.9, 127.4, 127.6, 127.9, 131.0, 141.2, 167.3, 169.3.  $[\alpha]_{\text{D}}=-48.7$  ( $c=1.2$ ,  $\text{CHCl}_3$ ). Anal. calcd for  $\text{C}_{19}\text{H}_{25}\text{NO}_3$ : C, 72.35; H, 7.99; N, 4.44. Found: C, 72.64; H, 7.97; N, 4.43.

**4.17. (3S,6S,1'S)-6-Allyl-3-ethyl-3,6-dimethyl-4-N-(1'-phenethyl)-1,4-morpholin-2,5-dione 7d**

The product was isolated in 16% yield.  $^1\text{H-NMR}$   $\delta$  0.63 (t, 3H,  $J=7.3$  Hz), 1.63 (s, 3H), 1.77 (s, 3H), 1.87 (d, 3H,  $J=7$  Hz), 1.83–2.15 (m, 2H), 2.49 (dd, 1H,  $J=7.3, 14$  Hz), 2.89 (dd, 1H,  $J=7.1, 13.8$  Hz), 4.43 (q, 1H,  $J=7$  Hz), 5.2 (m, 2H), 5.75 (m, 1H), 7.35 (m, 5ArH);  $^{13}\text{C-NMR}$   $\delta$  9.2, 18.7, 26.8, 27.1, 32.8, 45.3, 54.8, 66.7, 83.1, 121.2, 126.7, 127.0, 127.7, 130.4, 140.7, 166.6, 168.9.

**4.18. (3R,6S,1'S)-3,6-Dibenzyl-3,6-dimethyl-4-N-(1'-phenethyl)-1,4-morpholin-2,5-dione 6e**

Benzyl bromide was used as the alkylating reagent. The reaction occurred over 5 h and the pure product was obtained in 85% yield.  $^1\text{H-NMR}$   $\delta$  1.0 (s, 3H), 1.06 (s, 3H), 1.93 (d, 3H,  $J=7$  Hz), 2.85 (d, 1H,  $J=13.7$  Hz), 3.2 ( $q_{\text{AB}}$ , 2H,  $J=14.3$  Hz), 3.25 (d, 1H,  $J=13.7$  Hz), 4.49 (q, 1H,  $J=7$  Hz), 7.24 (m, 15ArH);  $^{13}\text{C-NMR}$   $\delta$  21.7, 26.8, 27.1, 45.1, 46.5, 56.4, 67.9, 84.2, 126.8, 126.9, 127.6, 127.7, 127.9, 128.1, 128.4, 130.3, 131.0, 134.3, 134.4, 141.4, 166.5, 168.1.  $[\alpha]_{\text{D}}=-50.2$  ( $c=1.1$ ,  $\text{CHCl}_3$ ). Anal. calcd for  $\text{C}_{28}\text{H}_{29}\text{NO}_3$ : C, 78.66; H, 6.84; N, 3.28. Found: C, 78.45; H, 6.87; N, 3.27.

**4.19. (3S,6S,1'S)-3,6-Dibenzyl-3,6-dimethyl-4-N-(1'-phenethyl)-1,4-morpholin-2,5-dione 7e**

The pure product was isolated in 9% yield.  $^1\text{H-NMR}$   $\delta$  1.60 (s, 3H), 1.80 (s, 3H), 1.90 (d, 3H,  $J=7$  Hz), 2.59 (d, 1H,  $J=14.2$  Hz), 2.59 (d, 1H,  $J=14.1$  Hz), 2.85 ( $q_{\text{AB}}$ , 2H,  $J=13.8$  Hz), 3.18 (d, 1H,  $J=14.1$  Hz), 4.63 (q, 1H,  $J=7$  Hz), 6.72 (m, 2H), 7.17 (m, 13ArH);  $^{13}\text{C-NMR}$   $\delta$  19.8, 26.0, 27.5, 45.0, 45.2, 56.2,

66.6, 83.7, 126.9, 127.1, 127.9, 128.1, 130.4, 131.0, 134.4, 134.6, 140.3, 167.0, 168.2.  $[\alpha]_D=2.9$  ( $c=0.8$ ,  $\text{CHCl}_3$ ).

**4.20. (3R,6S,1'S)-6-Benzyl-3,6-dimethyl-4-N-(1'-phenethyl)-3-[(E)-3-phenyl-2-propenyl]-1,4-morpholin-2,5-dione 6f**

Cinnamyl bromide was used as the alkylating reagent. The reaction occurred over 5 h and the pure product was isolated in 83% yield.  $^1\text{H-NMR}$   $\delta$  1.0 (s, 3H), 1.6 (s, 3H), 1.93 (d, 3H,  $J=6.9$  Hz), 2.77 (m, 2H), 2.9 (d, 1H,  $J=13.6$  Hz), 3.26 (d, 1H,  $J=13.6$  Hz), 4.38 (q, 1H,  $J=6.9$  Hz), 6.12 (m, 1H), 6.55 (d, 1H,  $J=15$  Hz), 7.15 (m, 15ArH);  $^{13}\text{C-NMR}$   $\delta$  19.1, 26.0, 27.8, 42.8, 46.5, 55.5, 66.7, 84.0, 121.7, 126.0, 126.8, 126.9, 127.7, 127.8, 128.1, 128.3, 128.5, 130.9, 134.0, 135.9, 136.0, 139.9, 165.9, 168.1.  $[\alpha]_D=-63.7$  ( $c=1.0$ ,  $\text{CHCl}_3$ ). Anal. calcd for  $\text{C}_{30}\text{H}_{31}\text{NO}_3$ : C, 79.44; H, 6.89; N, 3.09. Found: C, 79.65; H, 6.85; N, 3.1.

**4.21. (3S,6S,1'S)-6-Benzyl-3,6-dimethyl-4-N-(1'-phenethyl)-3-[(E)-3-phenyl-2-propenyl]-1,4-morpholin-2,5-dione 7f**

The pure product was isolated in 12% yield.  $^1\text{H-NMR}$   $\delta$  1.71 (s, 3H), 1.73 (s, 3H), 1.88 (d, 3H,  $J=6.9$  Hz), 2.38 (dd, 1H,  $J=6.3$ , 14.9 Hz), 2.74 (dd, 1H,  $J=8.2$ , 14.9 Hz), 2.98 (d, 1H,  $J=13.8$  Hz), 3.37 (d, 1H,  $J=13.8$  Hz), 4.5 (q, 1H,  $J=6.9$  Hz), 5.35 (m, 1H), 6.0 (d, 1H,  $J=15.6$  Hz), 6.9–7.45 (m, 15ArH);  $^{13}\text{C-NMR}$   $\delta$  20.7, 26.4, 28.0, 42.7, 45.1, 56.0, 66.2, 84.1, 122.4, 126.6, 126.7, 127.1, 127.2, 127.4, 127.9, 128.0, 128.2, 131.0, 134.5, 134.9, 136.6, 140.5, 166.9, 169.0.  $[\alpha]_D=77.5$  ( $c=0.6$ ,  $\text{CHCl}_3$ ).

**4.22. (3R,6S,1'S)-6-Benzyl-3-allyl-3,6-dimethyl-4-N-(1'-phenethyl)-1,4-morpholin-2,5-dione 6g**

Allyl iodide was used as the alkylating reagent. The reaction occurred over 4 h and the pure product was isolated in 81% yield.  $^1\text{H-NMR}$   $\delta$  0.9 (s, 3H), 1.75 (s, 3H), 1.87 (d, 3H,  $J=7$  Hz), 2.62 (m, 2H), 2.9 (d, 1H,  $J=13.6$  Hz), 3.28 (d, 1H,  $J=13.6$  Hz), 4.29 (q, 1H,  $J=7$  Hz), 5.25 (m, 2H), 5.76 (m, 1H), 7.15 (m, 10ArH);  $^{13}\text{C-NMR}$   $\delta$  18.8, 26.0, 28.1, 43.5, 46.5, 55.4, 66.4, 83.8, 121.3, 126.8, 126.9, 127.6, 128.1, 128.3, 130.8, 130.9, 133.9, 139.8, 165.7, 168.0.  $[\alpha]_D=-88.7$  ( $c=1.2$ ,  $\text{CHCl}_3$ ). Anal. calcd for  $\text{C}_{24}\text{H}_{27}\text{NO}_3$ : C, 76.36; H, 7.21; N, 3.71. Found: C, 76.65; H, 7.19; N, 3.7.

**4.23. (3S,6S,1'S)-6-Benzyl-3-allyl-3,6-dimethyl-4-N-(1'-phenethyl)-1,4-morpholin-2,5-dione 7g**

The product was isolated in 14% yield.  $^1\text{H-NMR}$   $\delta$  1.7 (s, 3H), 1.72 (s, 3H), 1.84 (d, 3H,  $J=6.9$  Hz), 2.25–2.55 (m, 2H), 2.9 (d, 1H,  $J=13.5$  Hz), 3.48 (d, 1H,  $J=13.5$  Hz), 4.4 (q, 1H,  $J=6.9$  Hz), 4.5–4.75 (m, 3H), 7.2 (m, 10ArH).

**4.24. (3R,6S,1'S)-6-Benzyl-3-ethyl-3,6-dimethyl-4-N-(1'-phenethyl)-1,4-morpholin-2,5-dione 6h**

Ethyl iodide was used as the alkylating reagent. The reaction occurred over 8 h and the pure product was isolated in 70% yield.  $^1\text{H-NMR}$   $\delta$  0.9 (s, 3H), 0.95 (t, 3H,  $J=7$  Hz), 1.76 (s, 3H), 1.81 (d, 3H,  $J=7$  Hz), 1.9 (m, 2H), 2.9 (d, 1H,  $J=13.6$  Hz), 3.26 (d, 1H,  $J=13.6$  Hz), 4.21 (q, 1H,  $J=7$  Hz), 6.85 (m, 2H), 7.2 (m, 8ArH);  $^{13}\text{C-NMR}$   $\delta$  9.3, 18.3, 26.3, 28.0, 32.6, 46.7, 55.2, 66.7, 83.8, 126.9, 127.0, 127.6, 128.2, 128.7, 131.0, 134.0, 139.8, 166.0, 168.6.  $[\alpha]_D=-100.7$  ( $c=1.0$ ,  $\text{CHCl}_3$ ). Anal. calcd for  $\text{C}_{23}\text{H}_{27}\text{NO}_3$ : C, 75.59; H, 7.45; N, 3.83. Found: C, 75.75; H, 7.44; N, 3.82.

**4.25. (3S,6S,1'S)-6-Benzyl-3-ethyl-3,6-dimethyl-4-N-(1'-phenethyl)-1,4-morpholin-2,5-dione 7h**

The product was isolated in 20% yield.  $^1\text{H-NMR}$   $\delta$  -0.1 (t, 3H,  $J=7$  Hz), 1.67 (s, 3H), 1.75 (s, 3H), 1.8 (m, 2H), 1.86 (d, 3H,  $J=7$  Hz), 2.9 (d, 1H,  $J=13.6$  Hz), 3.5 (d, 1H,  $J=13.6$  Hz), 4.3 (q, 1H,  $J=7$  Hz), 7.2 (m, 10ArH).

**4.26. (2R,4S)-3-Aza-2-[(E)-3'-phenyl-2'-propenyl]-2-methyl-4-phenyl-pentanoic acid hydrochloride 8**

1 M LiOH (20 ml) was added to **6a** (0.8 g, 2 mmol) dissolved in ethanol (20 ml) and the solution was refluxed for 40 h. After complete evaporation of ethanol in vacuo, the residue was acidified with 10% HCl and evaporated to dryness under reduced pressure. The residue was dissolved in water and the solution was adsorbed on an ion exchange resin Amberlist H-15. The resin was washed with distilled water then eluted with 5 M  $\text{NH}_4\text{OH}$ . After evaporation to dryness of the eluted solution, the aminoacid was recovered in practically quantitative yield and converted into the hydrochloride by refluxing for 1 h in 2 N HCl.  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  1.62 (s, 3H), 1.74 (d, 3H,  $J=6.6$  Hz), 2.85 (m, 2H), 3.3 (m, 1H), 4.64 (q, 1H,  $J=6.6$  Hz), 6 (m, 1H), 6.5 (d, 1H,  $J=15.9$  Hz), 7.35 (m, 10ArH);  $^{13}\text{C-NMR}$  ( $\text{CD}_3\text{OD}$ ) 19.8, 22.0, 41.3, 58.2, 67.2, 121.5, 127.5, 129.0, 129.6, 130.2, 130.8, 137.3, 137.9, 171.7.  $[\alpha]_{\text{D}}=-52.2$  ( $c=0.42$ ,  $\text{CH}_3\text{OH}$ ). Anal. calcd for  $\text{C}_{20}\text{H}_{23}\text{NO}_2$ : C, 77.64; H, 7.49; N, 4.53. Found: C, 77.95; H, 7.47; N, 4.52.

**4.27. (2R)-2-(3'-Phenylpropyl)alanine hydrochloride 9**

The sodium salt of **8** (0.66 g, 2 mmol), dissolved in ethanol (20 ml), was hydrogenated at 50 psi for 12 h in the presence of  $\text{Pd}(\text{OH})_2$  (0.04 g, 0.3 mmol). The catalyst was removed by filtration through Celite, the ethanol was evaporated in vacuo and the residue dissolved in 2 N HCl. The product, isolated in 85% yield after treatment with the ion exchange resin Amberlist H-15, was converted into the hydrochloride. After evaporation to dryness the residue was triturated with diethyl ether.  $[\alpha]_{\text{D}}=-8$  ( $c=0.2$ ,  $\text{H}_2\text{O}$ ), [lit.<sup>6</sup> 8.1 ( $c=0.2$ ,  $\text{H}_2\text{O}$ )].

**4.28. (2R,4S)-3-Aza-2-benzyl-2-methyl-4-phenyl-pentanoic acid hydrochloride 10**

The product was recovered in practically quantitative yield starting from **6b** and following the same procedure used to obtain **8**.  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  1.52 (s, 3H), 1.76 (d, 3H,  $J=6.9$  Hz), 3.15 (d, 1H,  $J=13.2$  Hz), 3.35 (d, 1H,  $J=13.2$  Hz), 4.55 (q, 1H,  $J=6.9$  Hz), 7.2 (m, 10ArH);  $^{13}\text{C-NMR}$  ( $\text{D}_2\text{O}$ )  $\delta$  16.4, 20.4, 43.7, 56.8, 66.3, 128.1, 128.7, 128.9, 129, 130, 130.4, 132.6, 134.7, 171.  $[\alpha]_{\text{D}}=-79.9$  ( $c=0.9$ , 1 N HCl). Anal. calcd for  $\text{C}_{18}\text{H}_{21}\text{NO}_2$ : C, 76.3; H, 7.47; N, 4.94. Found: C, 76.6; H, 7.5; N, 4.92.

**4.29. (2R)-2-Benzylalanine hydrochloride 11**

The product, obtained in 90% yield by hydrogenation of the sodium salt of **10**, in the same conditions employed for **8**, was then converted into the hydrochloride. After evaporation to dryness the residue was triturated with diethyl ether.  $[\alpha]_{\text{D}}=9.5$  ( $c=0.2$ ,  $\text{H}_2\text{O}$ ), [lit.<sup>6</sup> 9.6 ( $c=0.2$ ,  $\text{H}_2\text{O}$ )].

**4.30. (2R,4S)-3-Aza-2-allyl-2-methyl-4-phenyl-pentanoic acid hydrochloride 12**

The product was obtained in practically quantitative yield by refluxing **6c** for 60 h with LiOH and following the same procedure used to prepare **8**. <sup>1</sup>H-NMR (D<sub>2</sub>O) δ 1.52 (s, 3H), 1.70 (d, 3H, J=6.9 Hz), 2.4 (m, 2H), 4.42 (q, 1H, J=6.9 Hz), 5 (m, 2H), 5.35 (m, 1H), 7.25 (m, 5ArH). [α]<sub>D</sub>=−19.5 (c=0.7, 1 N HCl). Anal. calcd for C<sub>14</sub>H<sub>19</sub>NO<sub>2</sub>: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.3; H, 8.2; N, 6.02.

**4.31. (2R)-2-Propylalanine 13**

The product was obtained by hydrogenation of the sodium salt of **12**, as reported for **9**, and it was recovered pure in 90% yield after treatment with the ion exchange resin Amberlist H-15. <sup>1</sup>H-NMR (D<sub>2</sub>O) δ 0.88 (t, 3H, J=7.2 Hz), 1.22 (m, 2H), 1.41 (s, 3H), 1.9 (m, 2H); <sup>13</sup>C-NMR (D<sub>2</sub>O) δ 13.8, 17.2, 24.3, 41.3, 60.2, 181.0. [α]<sub>D</sub>=−1.4 (c=0.86, 1 N HCl). Anal. calcd for C<sub>6</sub>H<sub>13</sub>NO<sub>2</sub>: C, 54.94; H, 9.99; N, 10.68. Found: C, 55.14; H, 10.02; N, 10.65.

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**References**

1. (a) Wirth, T. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 225; (b) Trost, B. M.; Ariza, X. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2635; (c) Hanessian, S.; McNaughton-Smith, G.; Lombart, H. G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789.
2. Porzi, G.; Sandri, S. *Tetrahedron: Asymmetry* **1996**, *7*, 189 and references therein.
3. Porzi, G.; Sandri, S.; Verrocchio, P. *Tetrahedron: Asymmetry* **1998**, *9*, 119 and references therein.
4. Favero, V.; Porzi, G.; Sandri, S. *Tetrahedron: Asymmetry* **1997**, *8*, 599 and references therein.
5. Energy calculations have been performed by the AM1 method (HyperChem programme, 1994) by using the 'Polak-Ribiere algorithm (conjugate gradient)' with a RMS gradient 0.01 kcal.
6. Williams, R.; Im, M.-N. *J. Am. Chem. Soc.* **1991**, *113*, 9276.