Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 3411–3420

TETRAHEDRON: *ASYMMETRY*

A new stereoselective synthesis of sterically constrained uncommon α,α′-dialkylated α-amino acids. Part 2 †

Gianni Porzi and Sergio Sandri *

Dipartimento di Chimica 'G. Ciamician', Via Selmi 2, Università degli Studi di Bologna, Bologna, Italy

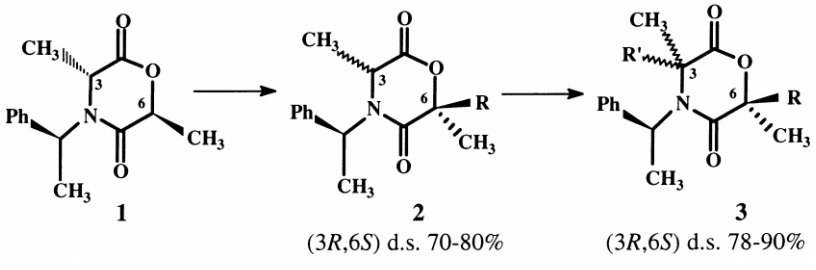
Received 24 July 1998; accepted 7 September 1998

Abstract

The alkylation of the diastereomeric mixture of the chiral morpholinone derivatives **5** and **6** occurs with good yield and a prevalence of the *cis* isomer. Cleavage of the alkylated intermediates **7b**,**c** yields enantiomerically pure sterically constrained uncommon α,α′-dialkylated α-amino acids. The absolute configuration of the new stereocentres has been assigned on the basis of the ^{1}H NMR spectra and NOE measurements. A model to explain the observed diastereoselection is proposed. © 1998 Elsevier Science Ltd. All rights reserved.

1. Introduction

In a previous paper[1] we described a new enantioselective approach to the synthesis of uncommon α,α′-dialkylated α-amino acids, which have recently received considerable attention through the stereoselective alkylation of (3*R*,6*S*)-4-*N*[(*S*)-1-phenethyl]-3,6-dimethyl-1,4-morpholin-2,5-dione **1** reported in Scheme 1.



Scheme 1.

* Corresponding author. E-mail: porzi@ciam.unibo.it

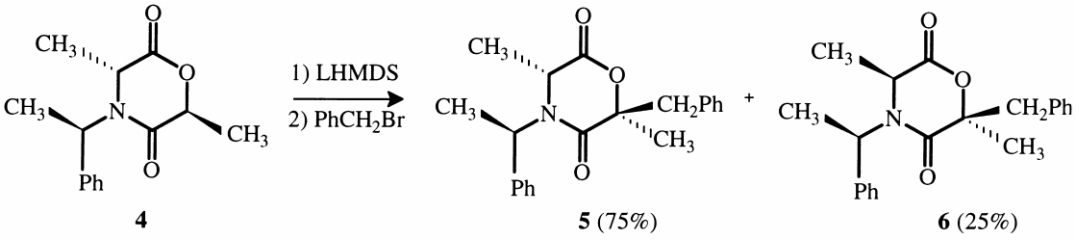
† Ref. 1 is considered to be Part 1.

0957-4166/98/$ - see front matter
PII: S0957-4166(98)00360-7

Therefore, as a continuation of our studies, we have directed our attention to investigating the influence of the chiral auxiliary configuration (the phenethyl group) on the stereochemical outcome of this reaction.

2. Results and discussion

To this end, the alkylation was also performed on the morpholinone derivative **4** in which the (N-4)-phenethyl group possesses the *R* instead of the *S* configuration. By comparing the stereochemical results reported in Scheme 2 to those previously found for the alkylation of diastereomer **1**[1] and summarized in Scheme 1, it is evident that the change in the auxiliary configuration does not produce any effect on the diastereomeric ratio of the reaction products: in fact, the alkylation at the C-6 occurs with the same diastereoselectivity (1,4-*trans* induction with respect to the (C-3)–CH_3).

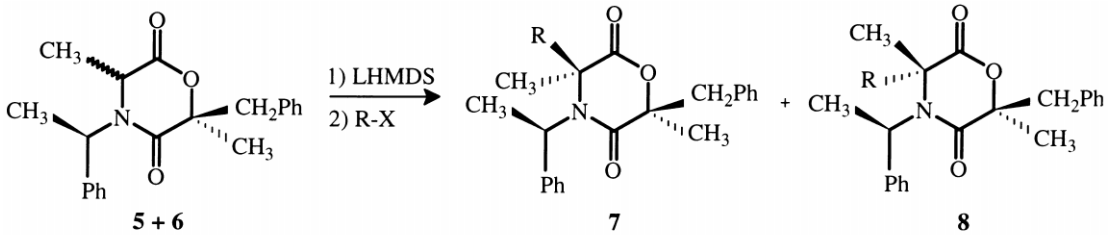


Scheme 2.

The diastereomer **6** was presumably produced owing to the isomerization of the stereocentre C-3 of the prevalent *cis* isomer **5**, as previously[1] observed for the alkylation of **1**.

Thus, the alkylation appears prevalently stereocontrolled by the configuration of the C-3 stereocentre, probably because the chiral auxiliary is remote enough from the C-6 centre to induce appreciable control during the nucleophilic attack of the enolate ion on the alkylating reagent.

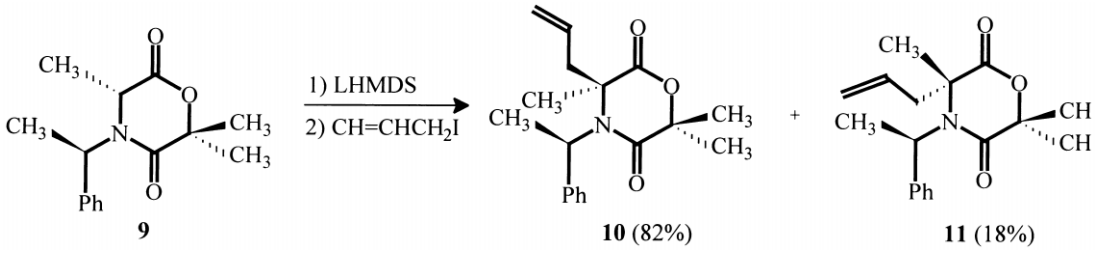
This result prompted us to also investigate the influence of the (*R*)-phenethyl group on the alkylation of the diastereomeric mixture **5**+**6** (Scheme 3) in order to compare the stereochemical results with those previously registered for the analogous diastereomeric mixture **2**.[1]



a) R-X : CH_3CH_2I	83%	17%
b) R-X : $PhCH_2Br$	78%	22%
c) R-X : $CH{=}CHCH_2I$	75%	25%
d) RX : $PhCH{=}CHCH_2Br$	73%	27%

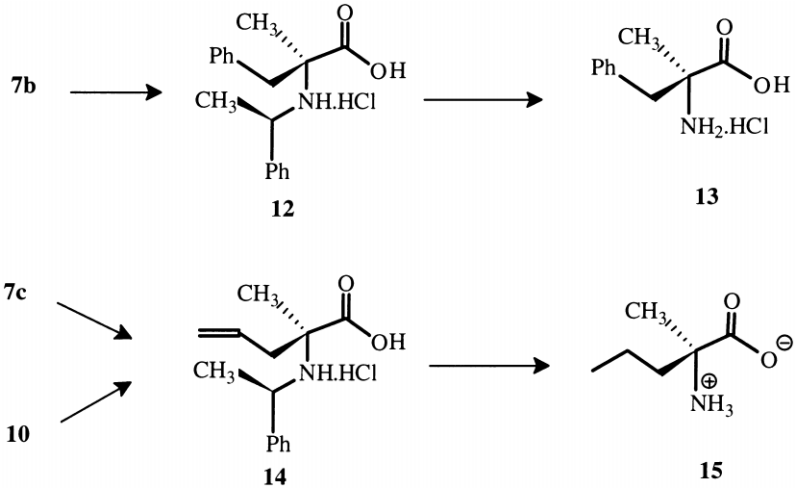
Scheme 3.

The data reported in Scheme 3 show that in this case the *cis* isomer predominates, in contrast to the previous[1] observation for the alkylation of the diastereomeric mixture **2**. A *cis*-induction by the (C-6)–CH_2Ph group is hardly conceivable, so we carried out the alkylation of compound **9**, lacking the C-6 stereocentre, in order to clarify the influence of the chiral auxiliary configuration on the alkylation at C-3 (Scheme 4). The substrate **9** was obtained by alkylating **4** with methyl iodide.



Scheme 4.

The C-3 stereocentre of the prevalent diastereomer **10** possesses the same configuration as **7c** (see Scheme 5) but the opposite to that of the more abundant isomer obtained by the alkylation of diastereomeric mixture **2**[1] (Scheme 1). The absolute configurations of the new stereocentres have been determined by ^{1}H NMR data (see later the stereochemical assignments) using the approach previously employed for similar molecules.[1,3]



Scheme 5.

However, in a model study, the compounds **7b**,**c** and **10** were converted into the corresponding α,α′-dialkyl α-amino acids following the same procedure already described[1] (Scheme 5). The specific rotation values, according to those reported in the literature, validated the approach used to assign the absolute configuration of the stereocentre C-3 through the ^{1}H NMR data.

3. Comments

The experimental data reported in Scheme 3 allowed us to deduce that the stereochemical outcome of the second alkylation, i.e. at C-3, is largely stereocontrolled by the configuration of the vicinal chiral auxiliary at N-4 and the C-6 stereocentre does not considerably influence the diastereoselectivity (see Scheme 4). Thus, it is possible to prepare uncommon α-amino acids α,α′-dialkylated with *R* or *S* configuration by using the chiral auxiliary of the *S* or *R* configuration, respectively.

The observed diastereoselection, i.e. the large proportion of the diastereomer with the 3*S* configuration (**7** or **10**), could be explained by considering the differences in the steric hindrance of the lithium enolate diastereotopic faces (induced by the chiral auxiliary) during the attack of electrophile R–X. For instance, in the *anti*-periplanar conformation of the lithium enolate of **9**, the phenyl ring gives rise to steric

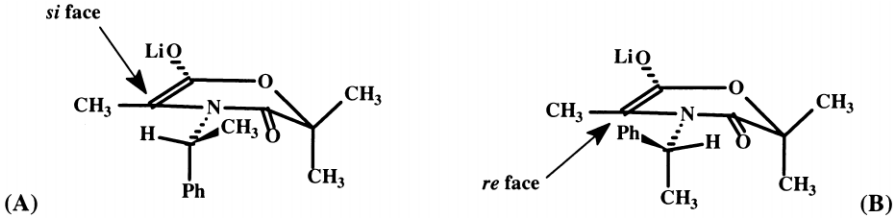


Fig. 1. Model proposed for the lithium enolate of **9**.

hindrance on the *re* face when the chiral auxiliary is in the *R* configuration, thereby the electrophilic attack on the *si* face appears preferred (see model **A** in Fig. 1), as results in Schemes 3 and 4. Conversely, in the *syn*-periplanar conformation, the phenyl ring causes steric hindrance on the *si* face favouring the electrophilic attack on the *re* face (see model **B** in Fig. 1). Following the same reasoning, the opposite diastereoselection can be explained when the chiral auxiliary possesses the *S* configuration. In fact, as reported in a previous paper[1] and summarized in Scheme 1, the alkylations of the synthon **1** prevalently gave the 3*R* diastereomer.

In order to substantiate the above proposed model, semiempirical quantomechanical calculations[2] were performed on the lithium enolate of **9** and the results obtained were indeed consistent with the model hypothesized in Fig. 1. In the preferred geometry of the enolate, the atoms O-1, C-2, C-3, and N-4 are practically coplanar while C-5 and C-6 are about 20° and 26° out of the plane, respectively. It is interesting to note that the molecular modelling studies give a geometry similar to that obtained by Davies et al.[4] for a morpholinone enolate. A complete conformational analysis, accomplished by full rotation around the (N-4)–(C-1′) bond, showed that the (*R*)-phenethyl side chain can exist in two low energy geometries with the benzylic hydrogen quasi *anti*- or *syn*-periplanar (enolates **A** and **B** in Fig. 1, respectively) with respect to the adjacent carbonyl group, the former being 1.5 kcal/mol more stable than the latter. As already observed for similar tetrasubstituted morpholindiones,[1] NOE experiments and energy optimization performed, for instance, on the 6-allyl-3-benzyl-3,6-dimethyl-4-*N*-[(*R*)-phenethyl]-1,4-morpholin-2,5-dione by the semiempirical quantomechanical AM1 method are consistent with a preferred *anti*-periplanar conformation.

In the more populated conformer **A** of the enolate, the dihedral angle H–(C-1′)–(N-4)–(C-5) is 160°, while in the conformer **B** it is −14°. Thus, we can assert that the model proposed to explain the observed diastereoselectivity is in good agreement with the results of the conformational analysis in spite of the moderate difference in energy between the two more stable conformers.

In conclusion, in this report we have shown that the C-3 stereocentre completely controls the C-6 alkylation and subsequently is partially epimerized itself. In contrast, the C-6 stereocentre has no affect on the stereocontrol of the alkylation at C-3. While the (*N*-4)-phenethyl group influences the adjacent C-3 stereocentre, it has no effect on C-6.

4. Stereochemical assignments

The introduction of the $PhCH_2$ group at the C-6 position in the derivatives **5** and **6** was shown through NOE measurements. By irradiating the proton of the *N*-phenethyl group in both the diastereomers, a significant NOE was registered on (C-3)–H (Fig. 2), but not on (C-6)–CH_3 nor on CH_2Ph. However, we confirmed that the two reaction products are diastereomers with opposite configurations of the C-3, because both **5** and **6**, after metallation followed by water addition, give a mixture of **5** and **6**.[1]

The absolute configuration of the diastereomers **5** and **6** was established on the basis of ^1H NMR data

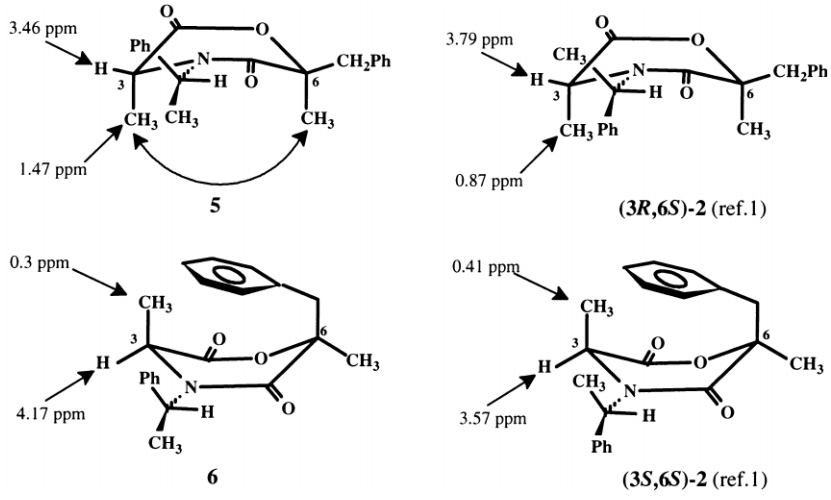


Fig. 2.

using the approach often employed by us[1,3,5] for similar molecules. The isomer **5** showed a significant NOE between (C-3)–CH_3 and (C-6)–CH_3, as previously shown also in (3*R*,6*S*)-**2**,[1] which is indicative of a *cis*-diaxial arrangement. Thus, the C-3 configuration could be easily assigned by comparing the chemical shifts of either the (C-3)–CH_3 and (C-3)–H of **5** with those of the corresponding isomer (3*R*,6*S*)-**2**. To this end, it is necessary to take into consideration: (a) the opposite configuration of the chiral auxiliary phenethyl in **5** and in **2**; (b) that the preferred geometry of the morpholindione derivatives is a quasiboat (or sofa) conformation in which the (C-3)–CH_3 preferentially lies in the pseudo-axial position and the proton in the pseudo-equatorial position.[3] As previously demonstrated,[5] the shielding effects can only take place in the rotamer in which the phenethyl hydrogen lies *syn* periplanar to the carbonyl group. Therefore, the shielding of (C-3)–H and the deshielding of (C-3)–CH_3 registered in **5**, with respect to (3*R*,6*S*)-**2**, are a result of the different shielding effects induced by the chiral phenethyl group which possesses the *R* configuration in **5**, but the *S* configuration in **2** (see Fig. 2). These findings and the NOE between the (C-3)–CH_3 and the (C-6)–CH_3, reasonably allowed us to assign the 3*R* configuration to the diastereomer **5**. The 3*S* configuration of **6** was assigned owing to the strong upfield shift suffered by the (C-3)–CH_3 which can be exclusively induced by the shielding of –CH_2Ph in the *cis*-diaxial relationship, analogous to that already observed for (3*S*,6*S*)-**2** (Fig. 2). In addition, because a substituent in the pseudo-equatorial position can be exclusively shielded by the phenethyl moiety in the *S* configuration, the chemical shift difference of the (C-3)–H between **6** and (3*S*,6*S*)-**2** can be ascribed to the opposite configuration of the auxiliary in the two isomers (see Fig. 2). Thus, we were able to infer that in the isomers **5** and **6**, diastereomers at C-3 as mentioned above, the C-6 stereocentre possesses the *S* configuration also on the basis of the NOE between the methyls at C-3 and C-6 registered only on the isomer **5**.

Having established the C-6 configuration of **5** and **6**, the stereochemistry of C-3 in the diastereomers **7** and **8** was ascertained on the basis of the shielding effects induced by the phenyl ring of (C-6)–CH_2Ph, according to that previously observed in similar substrates.[1] In fact, in the isomers **8**, the singlet of (C-3)–CH_3 (0.76, 0.82 and 0.88 ppm in **8a**, **8c** and **8d**, respectively) is shifted upfield with respect to distereomers **7** (1.56, 1.55 and 1.58 ppm in **7a**, **7c** and **7d**, respectively) which is representative of a *cis*-diaxial relationship between the methyl at C-3 and the (C-6)–CH_2Ph (Fig. 3). Thus, we were able to assign the 3*S* configuration to the isomers **7** and the 3*R* configuration to the isomers **8**. The 3*R* configuration of **8b** was established considering that the (C-3)–CH_3 and (C-6)–CH_3 suffer the same

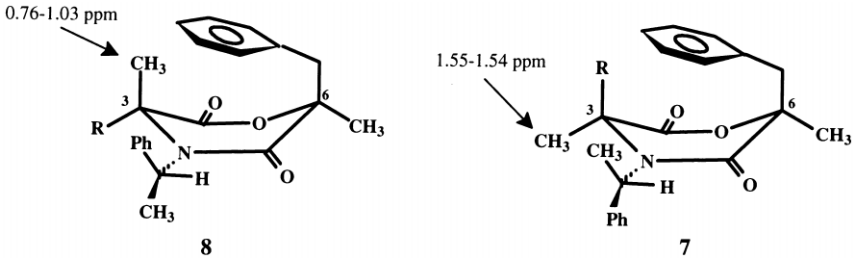


Fig. 3.

shielding effect (1.03 and 1.07 ppm). On the contrary, in **7b**, these methyl groups resonate at different fields (1.54 and 1.67 ppm) and furthermore, are deshielded with respect to **8b**. These findings suggested a *trans* relationship between the (C-3)–CH_3 and (C-6)–CH_3 in **8b** (both methyl groups being equally shielded by the phenyl ring of both $PhCH_2$ groups) and allowed us to assign the 3*S* configuration to the diastereomer **7b**.

5. Experimental

5.1. General information

^1H and ^{13}C NMR spectra were recorded on a Gemini spectrometer at 300 MHz using $CDCl_3$ 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. Dry THF was distilled from benzophenone ketyl. Chromatographic separations were performed with silica gel 60 (230–400 mesh). Some products, after chromatographic separation were not isolated pure enough to measure the optical rotation.

5.2. (3R,6S,1′R)-3,6-Dimethyl-4-N-(1′-phenethyl)-1,4-morpholin-2,5-dione **4**

The title compound was synthesized by following the procedure already reported for **1**[1] starting from the methanesulfonate of (*S*)-ethyl lactate, (2*S*)-2-acetoxy-propanoylchloride and (*R*)-phenethyl amine. ^1H NMR δ 1.57 (d, 3H, *J*=7.3 Hz), 1.63 (d, 3H, *J*=7.3 Hz), 1.68 (d, 3H, *J*=6.7 Hz), 3.95 (q, 1H, *J*=7.3 Hz), 5.0 (q, 1H, *J*=6.7 Hz), 5.88 (q, 1H, *J*=7.3 Hz), 7.32 (m, 5ArH); ^{13}C NMR δ 16.0, 17.2, 18.4, 51.3, 51.7, 73.4, 126.7, 128.0, 128.8, 138.4, 166.0, 168.2. Anal. calcd for $C_{14}H_{17}NO_3$: C, 68; H, 6.93; N, 5.66. Found: C, 68.2; H, 6.95; N, 5.65.

5.3. (3R,6S,1′R)-**5** and (3S,6S,1′R)-**6** 6-Benzyl-3,6-dimethyl-4-N-(1′-phenethyl)-1,4-morpholin-2,5-diones

LHMDS (8 ml, 1M solution in THF) was added dropwise to a stirred solution of **4** (1.24 g, 5 mmol) in dry THF (50 ml) cooled at −78°C under an inert atmosphere. After 1 h, benzyl bromide (0.85 g, 5 mmol) was added and the reaction mixture was stirred for 6 h. The reaction, slowly warmed to rt, was quenched with water and extracted with ethyl acetate. The organic layer was dried, evaporated under reduced presssure and the residue containing the diastereomeric mixture (90% yield) was separated by silica gel chromatography (hexane:ethyl acetate as eluent).

(3*R*,6*S*,1′*R*)-**5**. ^{1}H NMR δ 1.47 (d, 3H, *J*=7.2 Hz), 1.58 (d, 3H, *J*=7.2 Hz), 1.82 (s, 3H), 3.07 (d, 1H, *J*=13.5 Hz), 3.46 (q, 1H, *J*=7.2 Hz), 3.50 (d, 1H, *J*=13.5 Hz), 5.51 (q, 1H, *J*=7.2 Hz), 6.55 (m, 2H), 7.25 (m, 8ArH); ^{13}C NMR δ 17.4, 22.2, 26.8, 45.8, 50.8, 52.4, 85.3, 126.8, 127.0, 128.1, 128.3, 128.4, 130.9, 134.8, 137.1, 166.3, 167.0. Anal. calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.9; H, 6.9; N, 4.14.

(3*S*,6*S*,1′*R*)-**6**. ^{1}H NMR δ 0.30 (d, 3H, *J*=7.1 Hz), 1.65 (d, 3H, *J*=6.6 Hz), 1.69 (s, 3H), 3.01 (d, 1H, *J*=13.8 Hz), 3.45 (d, 1H, *J*=13.8 Hz), 4.17 (q, 3H, *J*=7.1 Hz), 5.3 (q, 3H, *J*=6.6 Hz), 7.25 (m, 10ArH); ^{13}C NMR δ 16.2, 19.9, 27.8, 45.9, 53.3, 53.8, 85.8, 127.1, 127.6, 127.9, 128.4, 128.6, 131.1, 134.9, 140.2, 166.6, 167.2.

5.4. *Alkylation of diastereomeric mixture **5**+**6**: general procedure*

The diastereomeric mixture of **5** and **6** (0.67 g, 2 mmol) in dry THF (20 ml) was treated with LHMDS (2 ml, 1M solution in THF) then submitted to the alkylation with the appropriate halide (3 mmol). The reaction was performed by following the same procedure employed for the alkylation of **4**. From the crude reaction product the diastereomers were separated by silica gel chromatography (hexane:ethyl acetate as eluent).

5.5. *(3*S*,6*S*,1′*R*)-6-Benzyl-3-ethyl-3,6-dimethyl-4-*N*-(1′-phenethyl)-1,4-morpholin-2,5-dione **7a***

Ethyl iodide was used as the alkylating reagent. The reaction was completed in 8 h and the pure product was isolated in 75% yield. ^{1}H NMR δ 0.17 (t, 3H, *J*=7.4 Hz), 1.45 (m, 1H), 1.56 (s, 3H), 1.69 (s, 3H), 1.76 (d, 3H, *J*=6.9 Hz), 1.80 (m, 1H), 2.86 (d, 1H, *J*=13.5 Hz), 3.50 (d, 1H, *J*=13.5 Hz), 4.31 (q, 1H, *J*=6.9 Hz), 7.27 (m, 10ArH); ^{13}C NMR δ 7.6, 19.4, 26.8, 28.6, 32.3, 44.8, 54.5, 66.5, 84.1, 126.1, 126.7, 127.1, 128.1, 128.2, 131.3, 135, 141.4, 166.1, 168.9. $[\alpha]_D$ −81.2 (*c* 0.9, $CHCl_3$). Anal. calcd for $C_{23}H_{27}NO_3$: C, 75.59; H, 7.45; N, 3.83. Found: C, 75.75; H, 7.44; N, 3.82.

5.6. *(3*R*,6*S*,1′*R*)-6-Benzyl-3-ethyl-3,6-dimethyl-4-*N*-(1′-phenethyl)-1,4-morpholin-2,5-dione **8a***

The pure product was isolated in 15% yield. ^{1}H NMR δ 0.67 (t, 3H, *J*=7.2 Hz), 0.76 (s, 3H), 1.72 (d, 3H, *J*=7 Hz), 1.73 (s, 3H), 1.79 (m, 2H), 2.92 (d, 1H, *J*=13.5 Hz), 3.44 (d, 1H, *J*=13.5 Hz), 4.14 (q, 1H, *J*=7 Hz), 7.34 (m, 10ArH); ^{13}C NMR δ 9.1, 20.1, 25.1, 28.2, 32.7, 46.7, 56.1, 66.9, 84.3, 127.1, 127.5, 127.9, 128.1, 128.5, 131.5, 134.5, 140.9, 166.6, 168.9.

5.7. *(3*S*,6*S*,1′*R*)-3,6-Dibenzyl-3,6-dimethyl-4-*N*-(1′-phenethyl)-1,4-morpholin-2,5-dione **7b***

Benzyl bromide was used as the alkylating reagent. The reaction was completed in 5 h and the pure product was isolated in 70% yield. ^{1}H NMR δ 1.54 (s, 3H), 1.67 (s, 3H), 1.90 (d, 3H, *J*=6.9 Hz), 2.33 (d, 1H, *J*=14.3 Hz), 2.97 (d, 1H, *J*=13.5 Hz), 3.0 (q_{AB}, 2H, *J*=13.6 Hz), 4.54 (q, 1H, *J*=6.9 Hz), 7.2 (m, 15ArH); ^{13}C NMR δ 21.2, 26.9, 27.5, 44.8, 44.9, 55.8, 66.4, 83.8, 125.9, 126.5, 127.0, 128.0, 128.1, 130.0, 130.8, 134.5, 134.7, 141.8, 167.1, 167.5. $[\alpha]_D$ −30 (*c* 2.1, $CHCl_3$). Anal. calcd for $C_{28}H_{29}NO_3$: C, 78.66; H, 6.84; N, 3.28. Found: C, 78.45; H, 6.87; N, 3.27.

*5.8. (3*R*,6*S*,1′*R*)-3,6-Dibenzyl-3,6-dimethyl-4-*N*-(1′-phenethyl)-1,4-morpholin-2,5-dione* ***8b***

The pure product was isolated in 20% yield. ^{1}H NMR δ 1.03 (s, 3H), 1.07 (s, 3H), 1.70 (d, 3H, *J*=7.1 Hz), 2.82 (d, 1H, *J*=13.5 Hz), 3.03 (q_{AB}, 2H, *J*=14 Hz), 3.34 (d, 1H, *J*=13.5 Hz), 4.36 (q, 1H, *J*=7.1 Hz), 6.52 (m, 2H), 7.31 (m, 13ArH); ^{13}C NMR δ 21.1, 25.7, 26.8, 44.9, 46.9, 57.9, 67.8, 84.2, 127.2, 127.4, 127.5, 128.0, 128.3, 129.3, 130.5, 131.5, 134.2, 134.6, 141.4, 166.7, 168.1. $[\alpha]_D$ −102.5 (*c* 0.9, $CHCl_3$).

*5.9. (3*S*,6*S*,1′*R*)-3-Allyl-6-benzyl-3,6-dimethyl-4-*N*-(1′-phenethyl)-1,4-morpholin-2,5-dione* ***7c***

Allyl iodide was used as the alkylating reagent. The reaction was completed in 4 h and the pure product was isolated in 67% yield. ^{1}H NMR δ 1.55 (s, 3H), 1.72 (s, 3H), 1.77 (d, 3H, *J*=6.9 Hz), 2.15 (m, 1H), 2.45 (m, 1H), 2.91 (d, 1H, *J*=13.6 Hz), 3.52 (d, 1H, *J*=13.6 Hz), 4.35 (q, 1H, *J*=6.9 Hz), 4.79 (m, 2H), 4.92 (m, 1H), 7.27 (m, 10ArH); ^{13}C NMR δ 20.0, 26.3, 28.4, 43.3, 45.2, 55.1, 65.7, 84.2, 119.6, 126.1, 126.7, 127.0, 128.2, 131.3, 134.9, 141.5, 166.2, 168.4. $[\alpha]_D$ −57.9 (*c* 0.6, $CHCl_3$). Anal. calcd for $C_{24}H_{27}NO_3$: C, 76.36; H, 7.21; N, 3.71. Found: C, 76.65; H, 7.19; N, 3.7.

*5.10. (3*R*,6*S*,1′*R*)-3-Allyl-6-benzyl-3,6-dimethyl-4-*N*-(1′-phenethyl)-1,4-morpholin-2,5-dione* ***8c***

The pure product was isolated in 22% yield. ^{1}H NMR δ 0.82 (s, 3H), 1.70 (d, 3H, *J*=7 Hz), 1.72 (s, 3H), 2.47 (m, 2H), 2.95 (d, 1H, *J*=13.6 Hz), 3.43 (d, 1H, *J*=13.6 Hz), 4.22 (q, 1H, *J*=7 Hz), 4.9 (m, 2H), 5.31 (m, 1H), 7.3 (m, 10ArH); ^{13}C NMR δ 20.5, 25.0, 28.3, 43.4, 46.6, 56.6, 66.7, 84.4, 121.2, 127.2, 127.4, 127.9, 128.1, 128.4, 130.9, 131.5, 134.6, 141.0, 166.5, 168.2. $[\alpha]_D$ −56 (*c* 0.3, $CHCl_3$).

*5.11. (3*S*,6*S*,1′*R*)-6-Benzyl-3,6-dimethyl-4-*N*-(1′-phenethyl)-3-[(*E*)-3-phenyl-2-propenyl]-1,4-morpholin-2,5-dione* ***7d***

Cinnamyl bromide was used as the alkylating reagent. The reaction was completed in 4 h and the product was isolated in 65% yield. ^{1}H NMR δ 1.58 (s, 3H), 1.71 (s, 3H), 1.83 (d, 3H, *J*=6.9 Hz), 1.95 (m, 1H), 2.45 (m, 1H), 2.98 (d, 1H, *J*=13.7 Hz), 3.43 (d, 1H, *J*=13.7 Hz), 4.46 (q, 1H, *J*=6.9 Hz), 5.75 (m, 1H), 6.33 (d, 1H, *J*=15.7 Hz), 7.03–7.52 (m, 15ArH); ^{13}C NMR δ 20.4, 25.8, 27.8, 42.8, 45.5, 55.2, 65.8, 84.0, 122.8, 126.1, 126.4, 126.7, 127.6, 128.1, 128.3, 131.1, 134.5, 134.9, 136.6, 141.4, 166.8, 168.2. Anal. calcd for $C_{30}H_{31}NO_3$: C, 79.44; H, 6.89; N, 3.09. Found: C, 79.65; H, 6.85; N, 3.1.

*5.12. (3*R*,6*S*,1′*R*)-6-Benzyl-3,6-dimethyl-4-*N*-(1′-phenethyl)-3-[(*E*)-3-phenyl-2-propenyl]-1,4-morpholin-2,5-dione* ***8d***

The pure product was isolated in 24% yield. ^{1}H NMR δ 0.88 (s, 3H), 1.59 (s, 3H), 1.76 (d, 3H, *J*=6.8 Hz), 2.62 (m, 2H), 2.90 (d, 1H, *J*=13.4 Hz), 3.42 (d, 1H, *J*=13.4 Hz), 4.30 (q, 1H, *J*=6.8 Hz), 5.70 (m, 1H), 5.97 (d, 1H, *J*=15.5 Hz), 7.25 (m, 15ArH); ^{13}C NMR δ 20.9, 25.0, 27.9, 42.4, 46.5, 56.9, 66.9, 84.4, 121.9, 126.0, 127.2, 127.4, 127.5, 127.9, 128.2, 128.4, 131.4, 134.8, 135.5, 136.3, 141.4, 166.6, 168.4.

*5.13. (3*R*,1′*R*)-3,6,6-Trimethyl-4-*N*-(1′-phenethyl)-1,4-morpholin-2,5-dione* ***9***

A solution of **4** (0.5 g, 2 mmol) in dry THF (20 ml) was treated with LHMDS (2 ml, 1M solution in THF) then alkylated with methyl iodide (0.42 g, 3 mmol). The reaction was performed by following the same procedure employed to obtain the products **5** and **6** and the reaction product (90% yield) was

purified by silica gel chromatography (hexane:ethyl acetate as eluent). ^{1}H NMR δ 1.6 (d, 3H, *J*=7 Hz), 1.65 (d, 3H, *J*=7.1 Hz), 1.7 (s, 3H), 1.72 (s, 3H), 3.90 (q, 1H, *J*=7 Hz), 5.75 (q, 1H, *J*=7.1 Hz), 7.37 (m, 5ArH). Anal. calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.7; H, 7.35; N, 5.37.

*5.14. (3S,1′R)-**10** and (3R,1′R)-**11** 3-Allyl-3,6,6-trimethyl-4-N-(1′-phenethyl)-1,4-morpholin-2,5-dione*

The allylation of **9** was performed with allyl iodide by following the same procedure described for the alkylation of the mixture **5**+**6**. The diastereomers, obtained in about 90% yield, were separated by silica gel chromatography (hexane:ethyl acetate as eluent).

(3*S*,1′*R*)-**10**. ^{1}H NMR δ 1.6 (s, 3H), 1.65 (s, 3H), 1.70 (s, 3H), 1.95 (d, 3H, *J*=7 Hz), 2.8 (m, 2H), 4.55 (q, 1H, *J*=7 Hz), 5.30 (m, 2H), 5.80 (m, 1H), 7.3 (m, 5ArH). Anal. calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.85; H, 7.67; N, 4.66.

(3*R*,1′*R*)-**11**. ^{1}H NMR δ 1.65 (s, 6H), 1.8 (s, 3H), 1.9 (d, 3H, *J*=7 Hz), 2.7 (m, 2H), 4.55 (q, 1H, *J*=7 Hz), 4.98 (m, 2H), 5.4 (m, 1H), 7.37 (m, 5ArH).

*5.15. (2S,4R)-3-Aza-2-benzyl-2-methyl-4-phenyl-pentanoic acid hydrochloride **12***

The product was recovered in practically quantitative yield by hydrolysis of **7b** with LiOH for 40 h at reflux and following the same procedure previously described.[1] The NMR data are consistent with those reported.[1] $[\alpha]_D$ 80 (*c* 1, 1N HCl). Anal. calcd for $C_{18}H_{21}NO_2$: C, 76.3; H, 7.47; N, 4.94. Found: C, 76.6; H, 7.5; N, 4.92.

*5.16. (2S)-2-Benzylalanine hydrochloride **13***

The product, obtained in about 90% yield by hydrogenolysis of **12** using the same conditions previously employed,[1] was then converted into the hydrochloride. $[\alpha]_D$ −9.4 (*c* 0.2, H_2O) [lit.[6] −9.6 (*c* 0.2, H_2O)].

*5.17. (2S,4R)-3-Aza-2-allyl-2-methyl-4-phenyl-pentanoic acid hydrochloride **14***

The product was obtained in practically quantitative yield by refluxing **7c** or **10** for 60 h with LiOH and following the same procedure previously used.[1] The NMR data are consistent with those reported[1] $[\alpha]_D$ 19 (*c* 1, 1N HCl). Anal. calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6. Found: C, 72.3; H, 8.2; N, 6.02.

*5.18. (2S)-2-Propylalanine **15***

The product was obtained by hydrogenolysis of **14**, as previously reported[1] and it was recovered pure in about 90% yield after treatment with the ion exchange resin Amberlist H-15. $[\alpha]_D$ 1.5 (*c* 1, 1N HCl).

Acknowledgements

Investigation supported by the University of Bologna (Funds for selected research topics and Fondi Ricerca Istituzionale, ex quota 60%).

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