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TETRAHEDRON: *ASYMMETRY*

A new stereoselective approach to β-hydroxy-α-aminoacids and dipeptides

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Abstract

The chiral synthons **1**, **2** and **1′** were submitted to aldol condensation to achieve both β-hydroxy-α-aminoacids and dipeptides. The configuration of the new stereogenic centers was assigned on the basis of ^{1}H NMR spectroscopic data. © 1999 Elsevier Science Ltd. All rights reserved.

1. Introduction

In a continuation of our studies directed to the stereoselective synthesis of common and uncommon α-aminoacids[1] and dipeptides,[2] we focused our attention on the synthesis of enantiomerically pure β-hydroxy-α-aminoacids and dipeptides. Previously, we have described the diastereoselective aldol condensation of piperazine-2,5-dione derivatives[3] as a possible approach to natural and unnatural β-hydroxy-α-aminoacids. Now, we wish to report the results of the aldol condensation of the chiral synthons (6*R*,1′*S*)-5-ethoxy-6-methyl- **1** and (6*R*,1′*S*)-5-ethoxy-6-benzyl-1-(1′-phenethyl)-3,6-dihydro-1*H*-pyrazine-2-one **2** in order to investigate an alternative diastereoselective synthesis of both β-hydroxy-α-aminoacids and dipeptides (see Scheme 1).

2. Results and discussion

The synthons **1** (obtained in high diastereomeric excesses as previously described[2]) and **2** (synthesized starting from **10**,[1] as summarized in Scheme 2) were converted into the corresponding lithium enolates and reacted with acetaldehyde and benzaldehyde (Scheme 1). The aldol condensations were complete in a few minutes with a total conversion of the lactims and the stereochemical results are collected in Table 1.

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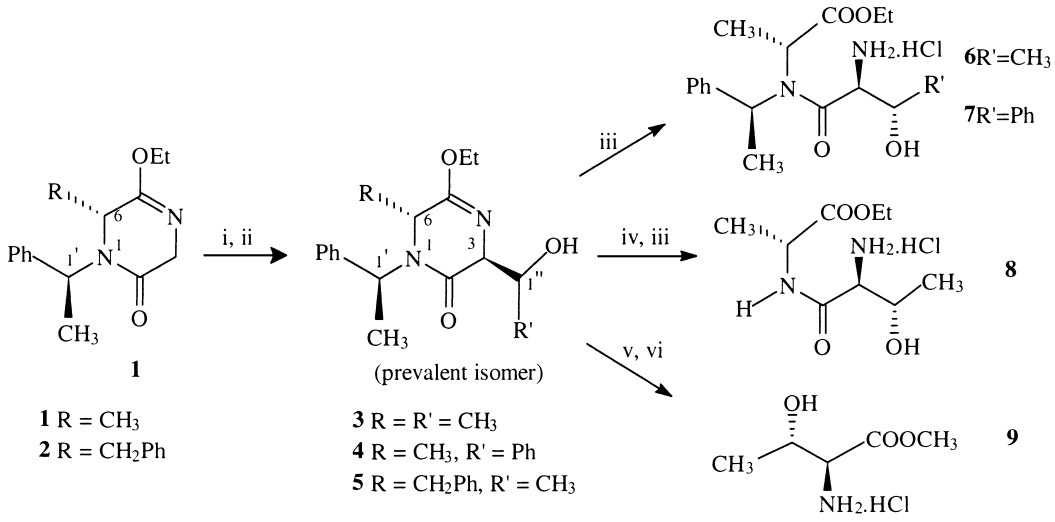
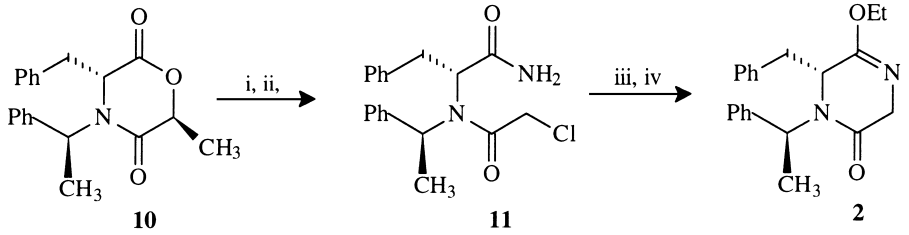


Scheme 1. (i) LHMDS (1.3 equiv.) 1 h at −50°C in dry THF; (ii) R′CHO (2 equiv.) at −78°C for 15 min; (iii) 0.5N HCl 2 h at 0°C; (iv) Li/NH_3 at −60°C; (v) 5N HCl at reflux for 12 h; (vi) $CH_3OH/SOCl_2$



Scheme 2. (i) 5 M NH_3 in *i*-PrOH at rt; (ii) $ClCH_2COCl/Et_3N$ in CH_2Cl_2 at 0°C; (iii) 5 M NH_3 in EtOH at rt; (iv) Et_3OBF_4 in CH_2Cl_2

Table 1
Aldol condensation of **1**, **2** and **1′** with acetaldehyde and benzaldehyde

Entry	C-1'	R	R'		(3*S*,1''*S*) **a**	(3*S*,1''*R*) **b**	(3*R*,1''*R*) **c**	(3*R*,1''*S*) **d**	***trans/cis* ratio**	***anti/syn* selectivity**
1	S	CH_3	CH_3	**3**	45 %	25 %	30 %		70 : 30	75 : 25
2	S	CH_3	Ph	**4**	38 %	27 %	25 %	10 %	65 : 35	63 : 37
3	S	$PhCH_2$	CH_3	**5**	60 %	20 %	20 %		80 . 20	80 : 20
4	R	CH_3	CH_3	**3'**	23 %	45 %	32 %		68 : 32	55 : 45

Comparing the entries 1 and 3 in Table 1, it appears that a bulkier substituent at C-6 induces both greater *trans* induction and greater *anti* facial selectivity. This prompted us to also investigate the influence of the chiral inductor configuration on the diastereoselectivity. Thus, we submitted the lactim **1′** to a reaction in which the C-1′ of the phenethyl group possesses the *R*- instead of the *S*-configuration (entry 4). This substrate showed the same *trans:cis* ratio and a significant decrease in the *anti:syn* ratio (compare entries 1 and 4). However, it is interesting to note that the facial selectivity was inverted: in fact, with **1′** the prevalent diastereomer was **3′**-(3*S*,1′′*R*) while with the lactim **1** it was **3**-(3*S*,1′′*S*). Thus, it is clear that the change in the inductor configuration produces an inversion of the facial diastereoselection, while the steric bulkiness of the substituent at C-6 causes an increase in the *trans* induction on C-3.

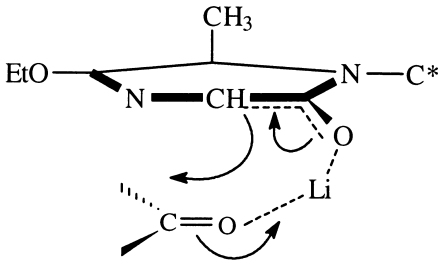


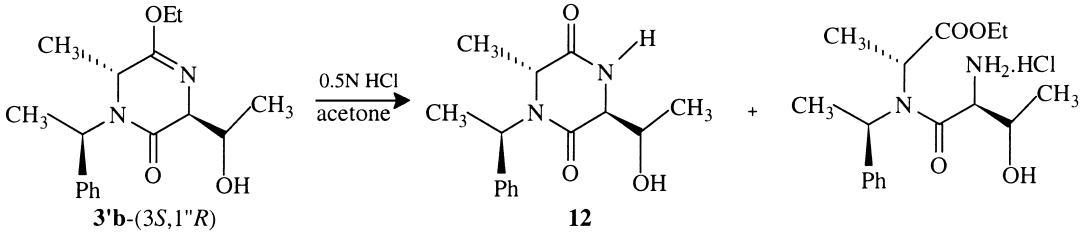
Figure 1. C* represents the chiral inductor

This is a process that involves a prevalent 1,4-*trans* induction by the stereocenter C-6 and occurs with a relative topicity *lk* in the addition of the two trigonal faces of enolate and aldehyde.

These preliminary experiments, which have, to date, shown only fairly good diastereoselectivity (entry 3), might open an interesting route to the synthesis of β-hydroxy-α-aminoacids and dipeptides. Thus, in order to improve the diastereoselection, further investigations are in progress.

In order to find a reasonable explanation for the observed stereochemical results, a complete conformational analysis[4] was performed for the lithium enolates of both **1** and **1′**. In the lowest energy conformations the atoms N-1, C-2, C-3, N-4 and C-5 are substantially coplanar, while C-6 is about 20° out of the plane. Furthermore, as already observed for similar compounds,[5] the benzylic hydrogen of the chiral inductor phenethyl preferentially lies *syn*-periplanar with respect to C-2. An important feature is that, in the geometries corresponding to the energetic minima, the –O–Li bond, which is placed about 25° out of the plane (N1, C-2, C-3), lies *trans* with respect to the (C-6)-CH_3 group. In fact, such a conformation is 0.9 kcal/mol and 0.65 kcal/mol more stable than the *cis* conformation for the lithium enolates of **1** and **1′**, respectively. These findings lead us to believe that the selection between the two faces of the enolate double bond is governed by the ground state conformation of the lithium enolate (Fig. 1) and the transition state is then reagent-like. This explanation agrees well with the observed prevalent *trans* induction described by us independently of the chiral inductor configuration (see entries 1 and 4 in Table 1).

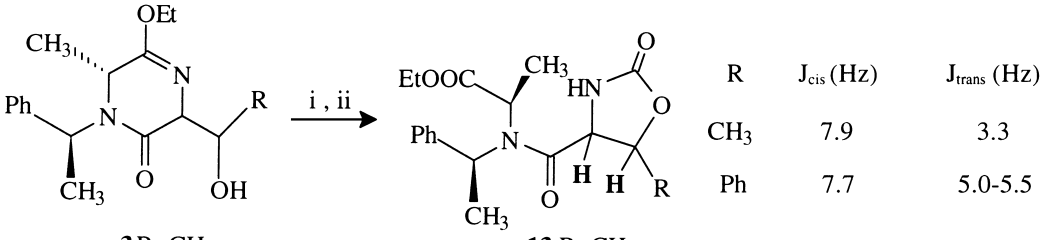
The configuration of the new stereocenters C-3 and C-1′′ introduced on **3**, **4** and **5** was assigned on the basis of ^{1}H NMR spectroscopic data using the approaches previously employed for similar compounds.[1–3] The *cis/trans* relationship of **3** and **4** derivatives was established on the basis of NOE registered on (C-3)-H by irradiating the (C-6)-CH_3. However, when the doublet of (C-6)-CH_3 could not be selectively irradiated, as for example in the condensation product **3′b**-(3*S*,1′′*R*), the configuration of the C-1′′ stereocenter was established on the piperazine-2,5-dione derivative **12** obtained as a minor product (20–30%) by acid hydrolysis of **3′b** (Scheme 3).



Scheme 3.

As previously done for similar compounds,[2,3] the *cis/trans* relationship for **5** was established on the basis of the shielding effect induced by the phenyl ring of the (C-6)-CH_2Ph (axially arranged) on the substituent at C-3.

The configuration of the stereocenter C-1′′ was assigned by the analysis of the coupling constants between the hydrogens of the cyclic derivatives **13** and **14**, obtained from **3** and **4**, respectively (Scheme 4). In fact, the *anti* and the *syn* diastereomers of **3** and **4** can be converted into the cyclic *cis* and *trans* 2-oxazolidones **13** and **14**, respectively. Thus, consistent with literature reports,[6] we assigned a *cis* H_a–H_b relationship (corresponding to an *anti* configuration of **3** or **4**) to the isomer with the greater $J_{a,b}$ (7.7 or 7.9 Hz) and a *trans* H_a–H_b relationship (corresponding to a *syn* configuration of **3** or **4**) to the isomer with the lower $J_{a,b}$ (3.3 or 5–5.5 Hz) (see Scheme 4).



R	J_{cis} (Hz)	J_{trans} (Hz)
CH_3	7.9	3.3
Ph	7.7	5.0-5.5

3 R=CH_3
4 R = Ph

13 R=CH_3
14 R=Ph

Scheme 4. (i) 0.5N HCl in acetone; (ii) $COCl_2$/Et_3N in CH_2Cl_2 at −10°C, then chromatographic separation

In a model study, as summarized in Scheme 1, the cyclic intermediate (3*S*,1′′*S*)-**3** was converted into the corresponding dipeptides **6** and **8** and into the hydrochloride of (2*S*,3*S*)-threonine methyl ester **9**. Analogously, the intermediate (3*S*,1′′*S*)-**4** was converted into the dipeptide **7**. The concordance of the specific rotation value ($[\alpha]_D$=8.5 (*c* 1, H_2O)) of the L-*allo*-threonine, obtained from the hydrolysis of **9**, with that reported in the literature,[7] validates the approach used to assign the absolute configuration of the C-3 and C-1′′ stereocenters through the ^{1}H NMR data.

3. Experimental

3.1. General information

^{1}H NMR spectra were recorded at 300 MHz using $CDCl_3$ as solvent, unless otherwise stated. Optical rotation values were recorded on a Perkin–Elmer 343 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 separations were performed with silica gel 60 (230–400 mesh).

3.2. (6R,1′S)-*1* and (6R,1′R)-5-Ethoxy-6-methyl-1-(1′-phenethyl)-3,6-dihydro-1H-pyrazine-2-one *1′*

The products were synthesized following the procedure described in the literature.[2]

3.3. (6R,1′S)-6-Benzyl-5-ethoxy-1-(1′-phenethyl)-3,6-dihydro-1H-pyrazine-2-one *2*

The morpholin-2,5-dione derivative **10** (6.2 g, 20 mmol) (obtained as described in the literature[1]) was dissolved in 100 mL of isopropanol saturated with NH_3 at 0°C. The reaction flask was stoppered and kept at rt for 24 h. The volatiles were evaporated in vacuo, to the residue was added water and the mixture

was extracted with ethyl acetate. After complete evaporation of the organic solvent the crude reaction product was dissolved in CH_2Cl_2 and $N(C_2H_5)_3$ (3.5 mL) was added. Chloroacetylchloride (2 mL, 25 mmol) was added dropwise to the solution stirred at 0°C, and after 1 h the organic solution was washed with dilute HCl, dried and then evaporated in vacuo. The intermediate **11** was isolated pure in 80% yield after chromatographic separation eluting with hexane/ethyl acetate. ^{1}H NMR: δ 1.67 (d, 3H, J=6.8 Hz), 3.0 (dd, 1H, J=6.6, 14 Hz), 3.39 (dd, 1H, J=8.8, 14 Hz), 3.81 (m, 1H), 4.23 (s, 2H), 5.17 (q, 1H, J=6.8 Hz), 5.47 (b s, 1H), 6.64 (d, 2H, J=6.1 Hz), 7.2 (m, 10ArH); ^{13}C NMR: δ 17.4, 36.2, 42.4, 57.2, 62.6, 126.5, 127.4, 128.1, 128.5, 128.7, 128.8, 129.1, 129.5, 137.0, 137.7, 167.8, 173.5.

The intermediate **11** (3.45 g, 10 mmol) was dissolved in ethanol saturated with NH_3 (about 7 M solution) at 0°C. The reaction flask was stoppered and kept at rt for 24 h. After evaporation of NH_3, the intermediate (6*R*,1′*S*)-6-benzyl-1-(1′-phenethyl)-piperazine-2,5-dione was recovered pure as a solid in 85% yield. ^{1}H NMR: δ 1.62 (d, 3H, J=7.2 Hz), 2.05 (dd, 1H, J=5.9, 13.8 Hz), 2.43 (d, 1H, J=17 Hz), 2.69 (dd, 1H, J=3.7, 13.8 Hz), 3.42 (dd, 1H, J=4.3, 17 Hz), 4.24 (dd, 1H, J=3.7, 5.9 Hz), 5.98 (q, 1H, J=7.2 Hz), 6.85–7.7 (m, 10ArH); ^{13}C NMR: δ 16.6, 38.1, 44.7, 52.3, 58.0, 127.5, 128.4, 128.7, 129.0, 130.0, 134.8, 139.1, 164.9, 169.2.

The piperazine-2,5-dione derivative intermediate (7.7 g, 25 mmol) was treated with Et_3OBF_4 (7.6 g, 40 mmol) dissolved in dry CH_2Cl_2 following the procedure described in the literature.[2] After chromatographic elution with hexane/ethyl acetate, the lactim **2** was recovered in 80% yield. ^{1}H NMR: δ 1.17 (t, 3H, J=7.1 Hz), 1.60 (d, 3H, J=7.1 Hz), 2.1 (dd, 1H, J=6.6, 13.5 Hz), 2.37 (dd, 1H, J=3.8, 13.5 Hz), 2.90 (dd, 1H, J=1.2, 19.8 Hz), 3.83 (d, 1H, J=19.8 Hz), 4.0 (m, 2H), 4.18 (m, 1H), 6.01 (q, 1H, J=7.1 Hz), 7.1–7.6 (m, 10ArH); ^{13}C NMR: δ 14.0, 16.4, 37.9, 50.7, 51.6, 54.8, 61.5, 127.0, 128.1, 128.3, 128.5, 128.7, 129.5, 135.1, 139.6, 161.7, 168.3.

*3.4. Condensation of **1**, **2** or **1′** with aldehydes: general procedure*

To 10 mmol of the lactim **1** (or **2** or **1′**) dissolved in dry THF cooled to −50°C under an inert atmosphere, 10 mL of LHMDS (1 M solution in THF) were slowly added. After 1 h the reaction bath was cooled to −78°C and 20 mmol of aldehyde were added. After a few minutes the reaction, followed by TLC, was practically complete. Then the reaction was quenched with phosphate buffer (pH=7) and extracted with ethyl acetate. The organic solution was evaporated in vacuo and the residue was submitted to chromatographic separation by eluting with hexane/ethyl acetate.

*3.4.1. (3*S,6R,*1′*S,*1″*S*)-5-Ethoxy-3-(1″-hydroxyethyl)-6-methyl-1-(1′-phenethyl)-3,6-dihydro-1*H-*pyrazine-2-one **3a***

This was obtained starting from **1** and acetaldehyde. ^{1}H NMR: δ 0.70 (d, 3H, J=6.9 Hz), 1.27 (t, 3H, J=7.1 Hz), 1.31 (d, 3H, J=6.2 Hz), 1.54 (d, 3H, J=7.1 Hz), 3.65 (dd, 1H, J=1.2, 7.9 Hz), 3.92 (dq, 1H, J=1.2, 6.9 Hz), 4.12 (q, 2H, J=7.1 Hz), 4.19 (m, 1H), 4.76 (d, 1H, J=3 Hz), 5.91 (q, 1H, J=7.1 Hz), 7.35 (m, 5ArH); ^{13}C NMR: δ 14.0, 15.9, 17.2, 19.2, 49.7, 50.8, 61.7, 62.1, 69.2, 127.9, 128.0, 128.6, 139.5, 164.1, 170.6. $[\alpha]_D$ −214.2 (*c* 1.2, CCl_4).

*3.4.2. (3*S,6R,*1′*S,*1″*R*)-5-Ethoxy-3-(1″-hydroxyethyl)-6-methyl-1-(1′-phenethyl)-3,6-dihydro-1*H-*pyrazine-2-one **3b***

This was obtained starting from **1** and acetaldehyde. ^{1}H NMR: δ 0.72 (d, 3H, J=6.9 Hz), 1.28 (t, 3H, J=7.1 Hz), 1.30 (d, 3H, J=6.4 Hz), 1.55 (d, 3H, J=7.1 Hz), 3.88 (m, 2H), 3.94 (dq, 1H, J=1.2, 6.9 Hz),

4.14 (m, 2H), 4.32 (m, 1H), 5.93 (q, 1H, J=7.1 Hz), 7.35 (m, 5ArH); ^{13}C NMR: δ 14.0, 16.1, 17.9, 18.7, 49.6, 50.8, 60.8, 62.1, 68.9, 127.9, 128.0, 128.6, 139.7, 164.0, 169.5. $[\alpha]_D$ −192.2 (*c* 0.5, CCl_4).

*3.4.3. (3*R,*6*R,*1′*S,*1′′*R*)-5-Ethoxy-3-(1′′-hydroxyethyl)-6-methyl-1-(1′-phenethyl)-3,6-dihydro-1*H-*pyrazine-2-one* ***3c***

This was obtained starting from **1** and acetaldehyde. ^{1}H NMR: δ 0.96 (d, 3H, J=6.8 Hz), 1.28 (t, 3H, J=7.1 Hz), 1.33 (d, 3H, J=6.1 Hz), 1.67 (d, 3H, J=7.2 Hz), 3.74 (d, 1H, 2.2 Hz), 3.9 (m, 1H), 4.1 (m, 4H), 5.74 (q, 1H, J=7.2 Hz), 7.35 (m, 5ArH); ^{13}C NMR: δ 14.0, 15.9, 20.3, 21.7, 50.3, 51.8, 61.6, 65.0, 70.2, 127.3, 127.6, 128.5, 140.6, 161.5, 168.9. $[\alpha]_D$ −152.4 (*c* 2.7, CCl_4).

*3.4.4. (3*S,*6*R,*1′*R,*1′′*S*)-5-Ethoxy-3-(1′′-hydroxyethyl)-6-methyl-1-(1′-phenethyl)-3,6-dihydro-1*H-*pyrazine-2-one* ***3′a***

This was obtained starting from **1′** and acetaldehyde. ^{1}H NMR: δ 1.18 (t, 3H, J=7.2 Hz), 1.31 (d, 3H, J=6.3 Hz), 1.38 (d, 3H, J=7 Hz), 1.64 (d, 3H, J=7.2 Hz), 3.62 (dq, 1H, J=1.2, 7 Hz), 3.83 (m, 1H), 3.96 (dd, 1H, J=1.2, 4.3 Hz), 4.08 (q, 2H, J=7.2 Hz), 4.31 (m, 1H), 5.85 (q, 1H, J=7.2 Hz), 7.25 (m, 5ArH); ^{13}C NMR: δ 13.9, 17.7, 18.7, 19.3, 49.5, 51.4, 60.8, 61.7, 68.9, 126.9, 127.5, 128.6, 139.0, 163.5, 169.7.

*3.4.5. (3*S,*6*R,*1′*R,*1′′*R*)-5-Ethoxy-3-(1′′-hydroxyethyl)-6-methyl-1-(1′-phenethyl)-3,6-dihydro-1*H-*pyrazine-2-one* ***3′b***

This was obtained starting from **1′** and acetaldehyde. ^{1}H NMR: δ 1.18 (t, 3H, J=7.2 Hz), 1.32 (d, 3H, J=6.2 Hz), 1.39 (d, 3H, J=7 Hz), 1.63 (d, 3H, J=7.2 Hz), 3.65 (dq, 1H, J=1.2, 7 Hz), 3.75 (dd, 1H, J=1.2, 7.6 Hz), 4.01 (q, 2H, J=7.2 Hz), 4.2 (m, 1H), 4.6 (b s, 1H), 5.87 (q, 1H, J=7.3 Hz), 7.15–7.4 (m, 5ArH); ^{13}C NMR: δ 13.6, 17.4, 18.5, 19.0, 49.6, 51.1, 61.5, 61.6, 69.0, 126.6, 127.4, 128.4, 139.0, 163.7, 175.0.

*3.4.6. (3*R,*6*R,*1′*R,*1′′*R*)-5-Ethoxy-3-(1′′-hydroxyethyl)-6-methyl-1-(1′-phenethyl)-3,6-dihydro-1*H-*pyrazine-2-one* ***3′c***

This was obtained starting from **1′** and acetaldehyde. ^{1}H NMR: δ 1.20 (t, 3H, J=7.2 Hz), 1.31 (d, 3H, J=6.3 Hz), 1.38 (d, 3H, J=6.9 Hz), 1.67 (d, 3H, J=7.2 Hz), 3.58 (dq, 1H, J=1.8, 6.9 Hz), 3.71 (m, 1H), 3.89 (m, 1H), 4.1 (m, 3H), 5.7 (q, 1H, J=7.2 Hz), 7.3 (m, 5ArH); ^{13}C NMR: δ 13.9, 17.9, 20.1, 22.3, 49.8, 52.8, 61.4, 64.7, 70.1, 127.7, 127.8, 128.7, 138.0, 161.4, 168.6.

*3.4.7. (3*S,*6*R,*1′*S,*1′′*S*)-5-Ethoxy-3-(1′′-hydroxybenzyl)-6-methyl-1-(1′-phenethyl)-3,6-dihydro-1*H-*pyrazine-2-one* ***4a***

This was obtained starting from **1** and benzaldehyde. ^{1}H NMR: δ 0.66 (d, 3H, J=7 Hz), 1.19 (t, 3H, J=7.1 Hz), 1.50 (d, 3H, J=7.1 Hz), 3.86 (dq, 1H, J=1.2, 7 Hz), 4.0 (m, 3H), 5.08 (dd, 1H, J=3.5, 8.9 Hz), 5.55 (d, 1H, J=3.5 Hz), 5.9 (q, 1H, J=7.1 Hz), 7.35 (m, 10ArH); ^{13}C NMR: δ 13.8, 15.8, 17.4, 49.6, 51.0, 61.6, 62.1, 75.2, 127.1, 127.3, 127.7, 127.8, 128.0, 128.5, 139.4, 141.3, 163.6, 170.4. $[\alpha]_D$ −102.9 (*c* 2.05, CCl_4).

*3.4.8. (3*S,*6*R,*1′*S,*1′′*R*)-5-Ethoxy-3-(1′′-hydroxybenzyl)-6-methyl-1-(1′-phenethyl)-3,6-dihydro-1*H-*pyrazine-2-one* ***4b***

This was obtained starting from **1** and benzaldehyde. ^{1}H NMR: δ 0.71 (d, 3H, J=6.9 Hz), 1.26 (t, 3H, J=7.1 Hz), 1.43 (d, 3H, J=7.1 Hz), 3.81 (dq, 1H, J=1.3, 6.9 Hz), 4.13 (m, 2H), 4.26 (dd, 1H, J=1.3, 3.9 Hz), 4.52 (d, 1H, J=8.7 Hz), 5.39 (dd, 1H, J=3.9, 8.7 Hz), 5.82 (q, 1H, J=7.1 Hz), 7.35 (m, 10ArH); ^{13}C

NMR: δ 14.0, 15.9, 18.4, 49.6, 51.1, 61.7, 61.9, 73.9, 127.0, 127.3, 127.5, 127.6, 127.9, 128.2, 139.7, 141.6, 163.4, 169.0. $[\alpha]_D$ −105.6 (*c* 2.3, CCl_4).

*3.4.9. (3*R,*6*R,*1′*S,*1″*R*)-5-Ethoxy-3-(1″-hydroxybenzyl)-6-methyl-1-(1′-phenethyl)-3,6-dihydro-1*H-*pyrazine-2-one* ***4c***

This was obtained starting from **1** and benzaldehyde. ^{1}H NMR: δ 0.27 (d, 3H, J=6.9 Hz), 1.25 (t, 3H, J=7.1 Hz), 1.62 (d, 3H, J=7.2 Hz), 3.91 (m, 2H), 4.15 (q, 2H, J=7.1 Hz), 4.55 (dd, 1H, J=1.8, 6 Hz), 5.24 (t, 1H, J=6 Hz), 5.40 (q, 1H, J=7.2 Hz), 7.35 (m, 10ArH); ^{13}C NMR: δ 14.1, 16.1, 20.1, 51.0, 52.8, 61.7, 65.2, 75.0, 127.1, 127.3, 127.5, 127.8, 128.2, 140.2, 140.6, 161.6, 166.9.

*3.4.10. (3*R,*6*R,*1′*S,*1″*S*)-5-Ethoxy-3-(1″-hydroxybenzyl)-6-methyl-1-(1′-phenethyl)-3,6-dihydro-1*H-*pyrazine-2-one* ***4d***

This was obtained starting from **1** and benzaldehyde. ^{1}H NMR: δ 0.22 (d, 3H, J=6.9 Hz), 1.29 (t, 3H, J=7 Hz), 1.65 (d, 3H, J=7.2 Hz), 3.89 (dq, 1H, J=2, 6.9 Hz), 4.15 (m, 2H), 4.55 (dd, 1H, J=2, 3.6 Hz), 5.11 (m, 2H), 5.20 (q, 1H, J=7.2 Hz), 7.3 (m, 10ArH); ^{13}C NMR: δ 14.3, 16.2, 19.3, 51.4, 53.5, 61.5, 63.7, 75.2, 127.0, 127.1, 127.4, 127.7, 127.8, 128.2, 140.5, 140.8, 160.8, 168.3. $[\alpha]_D$ −55.8 (*c* 0.6, CCl_4).

*3.4.11. (3*S,*6*R,*1′*S,*1″*S*)-6-Benzyl-5-ethoxy-3-(1″-hydroxyethyl)-1-(1′-phenethyl)-3,6-dihydro-1*H-*pyrazine-2-one* ***5a***

This was obtained starting from **2** and acetaldehyde. ^{1}H NMR: δ 1.09 (t, 3H, J=7 Hz), 1.17 (d, 3H, J=6.2 Hz), 1.57 (d, 3H, J=7 Hz), 2.23 (m, 2H), 2.88 (d, 1H, J=7.8 Hz), 3.9–4.15 (m, 4H), 5.94 (q, 1H, J=7 Hz), 6.73 (m, 2ArH), 7.1–7.6 (m, 8ArH); ^{13}C NMR: δ 13.8, 16.4, 19.1, 37.5, 51.7, 55.5, 61.5, 61.7, 69.0, 127.0, 128.1, 128.4, 128.5, 128.8, 129.3, 135.2, 139.2, 161.9, 171.1.

*3.4.12. (3*S,*6*R,*1′*S,*1″*R*)-6-Benzyl-5-ethoxy-3-(1″-hydroxyethyl)-1-(1′-phenethyl)-3,6-dihydro-1*H-*pyrazine-2-one* ***5b***

This was obtained starting from **2** and acetaldehyde. ^{1}H NMR: δ 1.14 (t, 3H, J=7.1 Hz), 1.16 (d, 3H, J=6.4 Hz), 1.59 (d, 3H, J=7.1 Hz), 2.14 (dd, 1H, J=6.2, 13.8 Hz), 2.32 (dd, 1H, J=4.2, 13.8 Hz), 2.91 (dd, 1H, J=1.1, 4.3 Hz), 3.9–4.2 (m, 4H), 5.98 (q, 1H, J=7.1 Hz), 6.75 (m, 2ArH), 7.1–7.6 (m, 8ArH); ^{13}C NMR: δ 13.9, 16.7, 18.6, 37.8, 51.8, 55.3, 60.6, 61.7, 68.8, 127.1, 128.2, 128.4, 128.5, 128.8, 129.5, 135.2, 139.3, 161.7, 170.3.

*3.4.13. (3*R,*6*R,*1′*S,*1″*R*)-6-Benzyl-5-ethoxy-3-(1″-hydroxyethyl)-1-(1′-phenethyl)-3,6-dihydro-1*H-*pyrazine-2-one* ***5c***

This was obtained starting from **2** and acetaldehyde. ^{1}H NMR: δ 1.05 (d, 3H, J=6.1 Hz), 1.18 (t, 3H, J=7.1 Hz), 1.76 (d, 3H, J=7.2 Hz), 2.34 (m, 1H), 2.45 (dd, 1H, J=6, 13.8 Hz), 2.73 (dd, 1H, J=4.3, 13.8 Hz), 3.72 (dd, 1H, J=1.5, 8.7 Hz), 4.02 (m, 3H), 4.33 (m, 1H), 5.7 (q, 1H, J=7.2 Hz), 6.7 (m, 2ArH), 7.15–7.6 (m, 8ArH); ^{13}C NMR: δ 14.0, 17.1, 20.2, 39.4, 53.6, 55.9, 61.4, 64.9, 69.9, 127.2, 128.3, 128.5, 128.8, 129.6, 135.3, 140.1, 158.7, 170.6.

3.5. Hydrolysis of intermediate lactim ***3****,* ***3′*** *and* ***4*** *to the corresponding dipeptide hydrochloride: general procedure*

To a solution of lactim **3**, **3′** or **4** (5 mmol) in acetone (50 mL), stirred at 0°C, 13 mL of 0.5N HCl were added. After 2 h the acetone was evaporated in vacuo and the aqueous layer extracted with ethyl acetate.

The aqueous solution was then evaporated in vacuo to dryness and the reaction product was obtained as a solid in 70–80% yield. As reported in Scheme 3, the corresponding piperazine-2,5-dione can be recovered from the organic solution (see later).

*3.5.1. (2*R,*5*S,*6*S,*1′*S*)-5-Amino-3-aza-6-hydroxy-2-methyl-4-oxo-3-(1′-phenethyl)-ethylheptanoate hydrochloride* ***6a***

This was obtained starting from the lactim **3a**. ^{1}H NMR: δ 0.88 (d, 3H, J=6.8 Hz), 1.25 (t, 3H, J=7.2 Hz), 1.26 (d, 3H, J=6.6 Hz), 1.75 (d, 3H, J=6.8 Hz), 3.88 (q, 1H, J=6.8 Hz), 4–4.25 (m, 2H), 4.46 (m, 1H), 4.91 (d, 1H, J=4.1 Hz), 5.45 (q, 1H, J=6.8 Hz), 7.45 (m, 5ArH); ^{13}C NMR (D_2O, dioxane as internal standard): δ 13.3, 13.7, 15.8, 16.3, 52.8, 55.5, 56.4, 62.5, 63.9, 127.9, 128.7, 128.9, 137.6, 165.3, 173.0. $[\alpha]_D$ −14.5 (*c* 1.6, CH_3OH).

*3.5.2. (2*R,*5*S,*6*R,*1′*S*)-5-Amino-3-aza-6-hydroxy-2-methyl-4-oxo-3-(1′-phenethyl)-ethylheptanoate hydrochloride* ***6b***

This was obtained starting from the lactim **3b**. ^{1}H NMR (CD_3OD): δ 0.91 (d, 3H, J=6.8 Hz), 1.24 (t, 3H, J=7.1 Hz), 1.43 (d, 3H, J=6.5 Hz), 1.76 (d, 3H, J=6.8 Hz), 3.96 (q, 1H, J=6.8 Hz), 4.13 (m, 3H), 4.69 (d, 1H, J=5.8 Hz), 5.50 (q, 1H, J=6.8 Hz), 7.3–7.55 (m, 5ArH); ^{13}C NMR (CD_3OD): δ 14.4, 15.1, 17.0, 20.2, 53.9, 56.8, 57.0, 62.3, 68.0, 129.0, 129.4, 129.6, 129.7, 129.8, 140.2, 167.4, 172.8. $[\alpha]_D$ −12.0 (*c* 2.3, CH_3OH).

*3.5.3. (2*R,*5*R,*6*R,*1′*R*)-5-Amino-3-aza-6-hydroxy-2-methyl-4-oxo-3-(1′-phenethyl)-ethylheptanoate hydrochloride* ***6′c***

This was obtained starting from the lactim **3′c**. ^{1}H NMR (D_2O): δ 0.97 (t, 3H, J=7.2 Hz), 1.23 (d, 3H, J=6.5 Hz), 1.44 (d, 3H, J=6.8 Hz), 1.71 (d, 3H, J=7 Hz), 3.85 (m, 3H), 4.43 (m, 1H), 4.99 (d, 1H, J=4.8 Hz), 5.39 (q, 1H, J=7 Hz), 7.45 (m, 5ArH); ^{13}C NMR (D_2O, dioxane as internal standard): δ 13.1, 14.7, 16.1, 17.0, 52.2, 55.9, 62.0, 64.2, 128.1, 128.3, 128.4, 128.7, 137.3, 165.4, 172.4.

*3.5.4. (2*R,*5*S,*6*S,*1′*S*)-5-Amino-3-aza-6-hydroxy-2-methyl-4-oxo-6-phenyl-3-(1′-phenethyl)-ethylhexanoate hydrochloride* ***7a***

This was obtained starting from the lactim **4a**. ^{1}H NMR (D_2O): δ 0.84 (d, 3H, J=6.6 Hz), 1.28 (t, 3H, J=7 Hz), 1.64 (d, 3H, J=6.6 Hz), 3.97 (q, 1H, J=6.6 Hz), 4.2 (m, 2H), 5.14 (d, 1H, J=5.3 Hz), 5.23 (d, 1H, J=5.3 Hz), 5.45 (q, 1H, J=6.6 Hz), 7.5 (m, 10ArH); ^{13}C NMR (CD_3OD): δ 14.5, 15.0, 17.4, 54.0, 57.0, 57.7, 62.4, 73.5, 128.6, 129.0, 129.4, 129.8, 130.0, 138.8, 140.1, 166.7, 172.7. $[\alpha]_D$ −31 (*c* 0.9, CH_3OH).

*3.5.5. (2*R,*5*S,*6*R,*1′*S*)-5-Amino-3-aza-6-hydroxy-2-methyl-4-oxo-6-phenyl-3-(1′-phenethyl)-ethylhexanoate hydrochloride* ***7b***

This was obtained starting from the lactim **4b**. ^{1}H NMR (D_2O): δ 0.81 (d, 3H, J=6.7 Hz), 0.86 (d, 3H, J=6.6 Hz), 1.27 (t, 3H, J=7 Hz), 3.77 (q, 1H, J=6.7 Hz), 4–4.3 (m, 2H), 5.09 (m, 3H), 7.3–7.6 (m, 10ArH).

*3.6. (2*R,*5*S,*6*S*)-5-Amino-3-aza-6-hydroxy-2-methyl-4-oxo-ethylheptanoate hydrochloride* ***8***

To a stirred solution of Li (0.64 g, 28 mmol) in liquid NH_3 (100 mL) at −60°C, **3a** (1.04 g, 4 mmol) in dry THF (25 mL) and ethanol (2.5 mL) was added under an inert atmosphere. After 5 min the reaction was quenched with NH_4Cl (1.48 g, 28 mmol) and the cooling bath was removed to completely eliminate NH_3. Water was added to the residue and the solution was extracted with ethyl acetate. Then the

organic solvent was removed in vacuo and the residue was purified by silica gel chromatography eluting with hexane/ethyl acetate. The intermediate (3*S*,6*R*,1′′*S*)-5-ethoxy-3-(1′′-hydroxyethyl)-6-methyl-3,6-dihydro-1*H*-pyrazine-2-one was submitted to acid hydrolysis following the procedure reported to obtain **6** and **7**. The reaction product **8** was not isolated pure enough to measure the optical rotation. ^{1}H NMR: δ 1.21 (d, 3H, J=6.4 Hz), 1.28 (t, 3H, J=6.7 Hz), 1.43 (d, 3H, J=7.2 Hz), 3.94 (d, 1H, J=4.5 Hz), 4.2 (m, 3H), 4.44 (q, 1H, J=7.2 Hz); ^{13}C NMR: δ 14.4, 17.5, 17.8, 59.3, 62.6, 66.5, 167.6, 173.9.

*3.7. Conversion of the lactim **3(a–c)** into the threonine methyl ester **9**: general procedure*

The intermediate lactims **3**(**a**–**c**) (1.3 g, 5 mmol) were refluxed for 12 h in 50 mL of 5N HCl. Then the solution was evaporated in vacuo to dryness and the residue was submitted to esterification by the usual procedure[8] ($SOCl_2$ and CH_3OH). The crude reaction product was concentrated under vacuum then dissolved in water. The aqueous layer was neutralized by adding 1N NaOH, extracted with CH_2Cl_2 and the organic solution was dried. The organic solvent and the (*R*)-alanine methyl ester were removed under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate).

(2*S*,3*S*)-Threonine methyl ester **9a**. ^{1}H NMR: δ 1.10 (d, 3H, J=6.9 Hz), 2.1 (b s, 3H), 3.55 (b s, 1H), 3.74 (s, 3H), 4.12 (m, 1H).

(2*S*,3*R*)-Threonine methyl ester **9b**. ^{1}H NMR: δ 1.23 (d, 3H, J=6.3 Hz), 2.1 (m, 3H), 3.28 (d, 1H, J=4.8 Hz), 3.73 (s, 3H), 3.88 (m, 1H).

*3.8. Conversion of lactim **3′** into the piperazine-2,5-dione derivative **12***

The lactims **3′**(**a**,**b**) were hydrolyzed following the procedure previously described to obtain the corresponding dipeptide hydrochloride **6** and **7**. The piperazine-2,5-dione derivative was extracted with ethyl acetate.

*3.8.1. (3*S,*6*R,*1′*R,*1′′*S*)-3-(1′′-Hydroxyethyl)-6-methyl-1*-N-*(1′-phenethyl)-piperazine-2,5-dione **12a***

This was obtained starting from **3′a**. ^{1}H NMR: δ 1.34 (d, 3H, J=6.6 Hz), 1.5 (d, 3H, J=7 Hz), 1.65 (d, 3H, J=7.2 Hz), 3.67 (q, 1H, J=7 Hz), 4.02 (d, 1H, J=3.7 Hz), 4.28 (m, 1H), 5.84 (q, 1H, J=7.2 Hz), 6.8 (b s, 1H), 7.3 (m, 5ArH).

*3.8.2. (3*S,*6*R,*1′*R,*1′′*R*)-3-(1′′-Hydroxyethyl)-6-methyl-1*-N-*(1′-phenethyl)-piperazine-2,5-dione **12b***

This was obtained starting from **3′b**. ^{1}H NMR: δ 1.26 (d, 3H, J=6.3 Hz), 1.5 (d, 3H, J=7.2 Hz), 1.64 (d, 3H, J=7.2 Hz), 3.69 (q, 1H, J=7.2 Hz), 4.09 (d, 1H, J=5.1 Hz), 4.46 (m, 1H), 5.82 (q, 1H, J=7.2 Hz), 6.5 (b s, 1H), 7.3 (m, 5ArH).

*3.9. Conversion of lactims **3** and **4** into the corresponding 2-oxazolidones **13** and **14***

The lactim **3** (or **4**) was converted into the corresponding dipeptide hydrochloride **6** (or **7**) as previously reported. To 2 mmol of **6** (or **7**), dissolved in CH_2Cl_2 at −10°C, 3 mL (6 mmol) of phosgene (20% in toluene), then pyridine (0.44 mL, 6.6 mmol) were added. After stirring for about 2 h the reaction mixture was acidified with dilute HCl and extracted with CH_2Cl_2. The organic layer was dried, evaporated to dryness and the residue purified by silica gel chromatography (hexane/ethyl acetate).

*3.9.1. (4*S,*5*S,*1′*R,*1′′*S*)-4-[*N*-*(1′-Ethoxycarbonylethyl)*-N-*(1′′-phenethyl)-carboxamido]-5-methyl-2-oxazolidone* ***13a***

This was obtained starting from **3a**. ^{1}H NMR: δ 1.10 (d, 3H, J=6.8 Hz), 1.25 (t, 3H, J=7.1 Hz), 1.5 (d, 3H, J=6.3 Hz), 1.74 (d, 3H, 6.9 Hz), 3.67 (q, 1H, J=6.8 Hz), 4.2 (m, 2H), 4.98 (m, 2H), 5.11 (d, 1H, J=7.9 Hz), 5.45 (b s, 1H), 7.2–7.45 (m, 5ArH); ^{13}C NMR: δ 13.9, 14.6, 16.4, 17.1, 52.7, 54.6, 56.9, 61.1, 74.3, 127.1, 127.7, 127.8, 128.4, 128.5, 128.6, 128.8, 138.2, 158.5, 166.3, 170.7.

*3.9.2. (4*S,*5*R,*1′*R,*1′′*S*)-4-[*N*-*(1′-Ethoxycarbonylethyl)*-N-*(1′′-phenethyl)-carboxamido]-5-methyl-2-oxazolidone* ***13b***

This was obtained starting from **3b**. ^{1}H NMR: δ 1.09 (d, 3H, J=6.9 Hz), 1.25 (t, 3H, J=7.2 Hz), 1.53 (d, 3H, J=6.4 Hz), 1.72 (d, 3H, J=7 Hz), 3.59 (q, 1H, J=6.9 Hz), 4.15 (m, 2H), 4.59 (dq, 1H, J=3.3, 6.4 Hz), 4.98 (d, 1H, J=3.3 Hz), 5.23 (q, 1H, J=7 Hz), 7.45 (m, 5ArH).

*3.9.3. (4*S,*5*S,*1′*R,*1′′*S*)-4-[*N*-*(1′-Ethoxycarbonylethyl)*-N-*(1′′-phenethyl)-carboxamido]-5-methyl-2-oxazolidone* ***14a***

This was obtained starting from **4a**. ^{1}H NMR: δ 1.0 (d, 3H, J=7.5 Hz), 1.3 (m, 6H), 3.64 (q, 1H, J=7.5 Hz), 4.2 (m, 2H), 4.4 (d, 1H, J=7.7 Hz), 5.3 (b s, 1H), 5.58 (q, 1H, 6.8 Hz), 5.75 (d, 1H, J=7.7 Hz), 6.4 (m, 2ArH), 7.3 (m, 8ArH).

*3.9.4. (4*S,*5*R,*1′*R,*1′′*S*)-4-[*N*-*(1′-Ethoxycarbonylethyl)*-N-*(1′′-phenethyl)-carboxamido]-5-methyl-2-oxazolidone* ***14b***

This was obtained starting from **4b**. ^{1}H NMR: δ 1.09 (d, 3H, J=6.9 Hz), 1.25 (t, 3H, J=7 Hz), 1.53 (d, 3H, J=6.7 Hz), 3.6 (q, 1H, J=6.9 Hz), 4.14 (q, 2H, J=7 Hz), 4.82 (q, 1H, J=6.7 Hz), 4.9 (d, 1H, J=5 Hz), 5.64 (d, 1H, J=5 Hz), 7.25 (m, 10ArH).

*3.9.5. (4*R,*5*S,*1′*R,*1′′*S*)-4-[*N*-*(1′-Ethoxycarbonylethyl)*-N-*(1′′-phenethyl)-carboxamido]-5-methyl-2-oxazolidone* ***14d***

This was obtained starting from **4d**. ^{1}H NMR: δ 1.15 (d, 3H, J=6.8 Hz), 1.26 (t, 3H, J=7 Hz), 1.62 (d, 3H, J=7 Hz), 3.61 (q, 1H, J=6.8 Hz), 4.12 (q, 2H, J=7 Hz), 4.71 (d, 1H, J=5.5 Hz), 4.9 (q, 1H, J=7 Hz), 5.88 (d, 1H, J=5.5 Hz), 7.25 (m, 10ArH).

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