Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 15 (2004) 1085–1093

Enantioselective synthesis of pseudotripeptides incorporating a γ-methylene derivative of 2,6-diaminopimelic acid: Part 6 ☆

Daniele Balducci, Gianni Porzi* and Sergio Sandri*

Dipartimento di Chimica 'G.Ciamician', Università di Bologna, Via Selmi 2, 40126 Bologna, Italy

Received 22 December 2003; revised 5 February 2004; accepted 11 February 2004

Abstract—An efficient enantioselective synthesis of pseudotripeptides **5**, **8a**–**d** and **13a** and **b** incorporating a 2,6-diamino-4-methylene-1,7-heptandioic acid residue, has been accomplished starting from the glycine derived chiral synthon **1** (from L-valine). The absolute configuration of the new stereocentres was assigned on the basis of ^{1}H NMR spectra. The geometry of derivative **4** was deduced on the basis of ^{1}H NMR parameters (δ_{NH} value, temperature coefficient, δ_{NH} change upon addition of DMSO or CD_3OD, NOE studies) and IR spectra.

1. Introduction

Our interest in the mimetics of 2,6-diamino-1,7-heptandioic acid (2,6-DAP)[1–5] is due to the fact that they can function as inhibitors in the biosynthesis of L-lysine (DAP/lysine pathway) and also have potential biological activity both as antibacterial[6] and herbicide agents.[7] Recently, we reported an efficient enantioselective synthesis of both the enantiomers of the 2,6-diamino-4-methylene-1,7-heptanedioic acid[5] since Jean-Marc Girodeau et al.[8] found that this γ-methylene derivative of 2,6-DAP is an inhibitor of bacterial growth (*Escherichia coli*). We also accomplished the synthesis both enantiomerically pure forms of new structural analogues of 2,6-diamino-4-methylene-1,7-heptanedioic acid starting from a chiral dichetopiperazine derivative[5] and of uncommon tripeptides, structural variants of 2,6-DAP, by using the chiral synthon **1**, a mono-lactim ether, easily synthesized from L-valine.[9,10]

2. Synthesis and stereochemical assignments

Herein we followed the strategy previously employed for obtaining analogous derivatives of 2,6-DAP. Deprotonation of synthon **1** with LHMDS followed by alkylation with 0.5 equiv of 2-iodomethyl-3-iodopropene (obtained from 2-chloromethyl-3-chloropropene and NaI) afforded isomer **2** in good yield and with a high diastereoselectivity (de ⩾94%). The diastereomer (3′*R*,6′*S*,3″*R*,6″*S*)-**2** originated from a practically total double 1,4-*trans* induction with respect to the isopropyl group (Scheme 1) with the (3′*S*,6′*S*,3″*R*,6″*S*)-diastereomer being recovered in a very small amount (2–3%). However, the two diastereomers were easily separable by silica gel chromatography and their stereochemistry established on the basis of the ^{1}H NMR spectra, as already observed for a similar substrate.[9] In fact, intermediate **2** exhibited half the number of proton signals, indicating the magnetic equivalence of symmetrical protons and the existence of a C_2 axis of symmetry. For example, the signals for both *iso*-propyl groups (at 0.94 and 1.05 ppm) overlap as do the signals for the benzylic protons (at 3.93 and 5.50 ppm), the (C-6′)-H and (C-6″)-H (at 3.68 ppm), the (C-3′)-H and (C-3″)-H (at 4.3 ppm) and the methyl protons of ethoxy group (at 1.22 ppm).

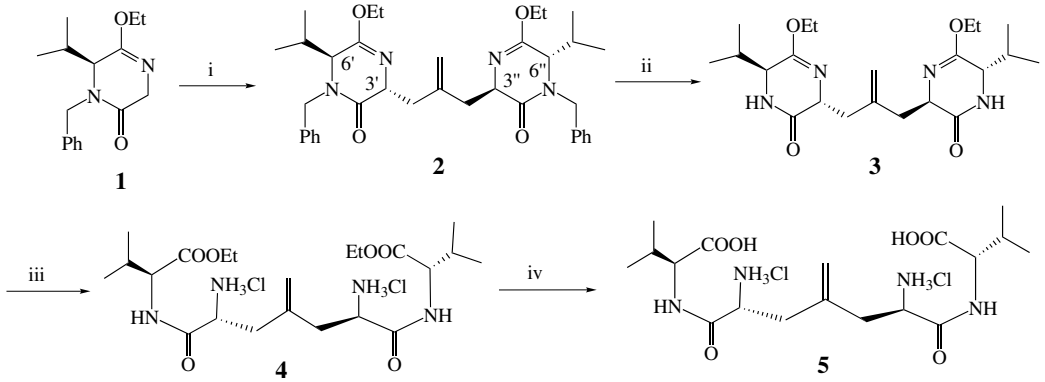
From the intermediate **2**, submitted to a Birch reaction to remove the benzyl groups, the aminoester **4** was obtained, as a hydrochloride, after acid hydrolysis of **3** under mild conditions. Through a further acid hydrolysis, the intermediate **4** was converted into **5**, a 'non-classical tripeptide' C-terminal at both ends of the chain, which can be considered as a 2,6-DAP derivative.

Intermediate **2**, after alkylation with various electrophiles, gave **6** in good to very good chemical yields with practically total regio- and diastereoselectivity (>98%) (Scheme 2). The total 1,4-*trans*-stereoselection, induced by the isopropyl group, was demonstrated by comparing

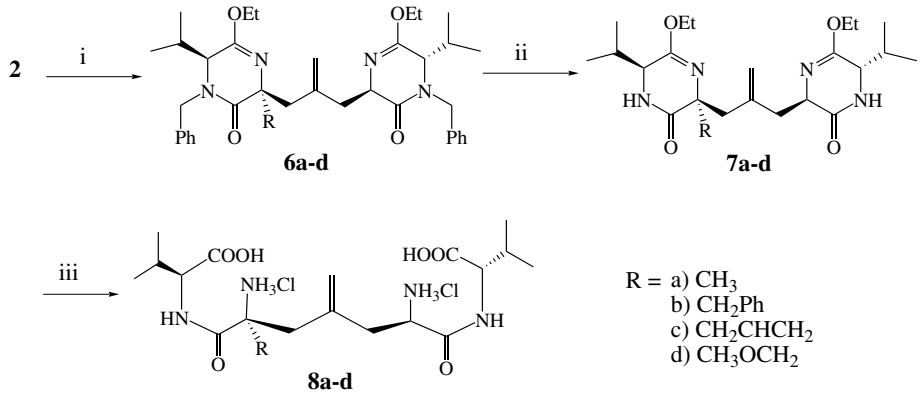
☆ Refs. 1–5 are considered to be Parts 1–5, respectively.

* Corresponding authors. E-mail: gianni.porzi@unibo.it

0957-4166/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2004.02.005



Scheme 1. Reagents and conditions: (i) 1 M LHMDS/THF, $(ICH_2)_2C{=}CH_2$; (ii) Li/NH_3; (iii) 0.5 M HCl at rt; (iv) 1 M HCl at 60 °C.



Scheme 2. Reagents and conditions: (i) LHMDS/THF, R–X; (ii) Li/NH_3; (iii) 1 M HCl at 60 °C.

the ^{1}H NMR spectra of **6a** and **6b**, on the basis of the upfield shift induced on the H-6′ by the phenyl shielding of the benzyl group introduced on C-3′. In fact, as already observed in analogous substrates,[9,10] the phenyl ring preferentially adopted the 'aryl inside' arrangement causing significant shielding on the *cis*-substituent at C-6′. The shielding of 0.53 ppm registered on **6b** with respect to **6a** provided clear evidence of the *cis*-relationship between (C-3′)-CH_2Ph and (C-6′)-H. Consequently, the absolute configuration of C-3′ followed on from the note (*S*)-configuration at the C-6′ stereocentre.

The intermediates **6**, submitted to debenzylation, afforded **7**, in good chemical yields, and, after acid hydrolysis the amino acids **8**, were easily obtained as hydrochlorides (Scheme 2).

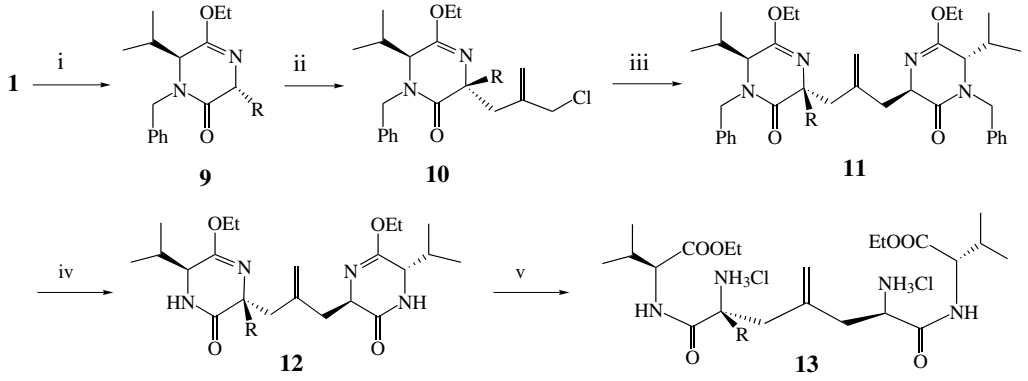
Diastereomeric derivatives with opposite configurations at the stereocentre C-3′, in comparison to the compounds described above, were obtained by using the following alternative strategy. The protocol consisted of an alkylation of the chiral synthon **1** to obtain **9**, followed by a second alkylation with 2-chloromethyl-3-chloropropene to furnish **10**.

The intermediate **10** was then reacted with the Li-enolate of **1** to give **11**, which is an epimer of **6** at the C-3′ stereocentre (Scheme 3). The alkylation occurred with a practically total regio- and diastereoselectivity (>98%) giving **11** in very good chemical yield, as previously observed for a similar substrate.[10] From **11**, submitted to a Birch reaction to remove the benzyl groups, **12** was obtained and after acid hydrolysis under mild conditions, aminoester **13** was recovered as the hydrochloride.

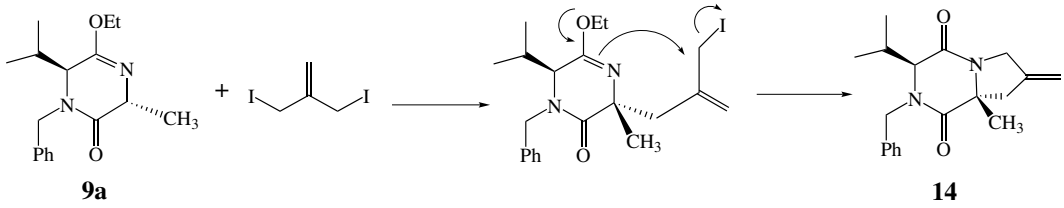
In this strategy, 2-chloromethyl-3-chloropropene was employed because by using 2-iodomethyl-3-iodopropene, compound **14** could be obtained owing to the intramolecular nucleophilic attack of the iminic nitrogen on the iodoallyl group of the dialkylated intermediate, which is not isolable as it quickly converts into the bicyclic derivative (Scheme 4).

3. ^{1}H NMR and IR studies

First of all, it is noteworthy that the ^{1}H NMR of the 'nonclassical tripeptide' **4** is consistent with a symmetrical structure having a C_2 axis. In fact, the signals for both the *iso*-propyl groups overlap, as do the signals for the methylene, methine and amide hydrogens, indicating their magnetic equivalence (see Experimental). The chemical shift of the magnetically equivalent amide protons did not display concentration dependence, suggesting that this pseudotripeptide did not exist in an aggregate form, at least not in the concentration range



Scheme 3. Reagents and conditions: (i) LHMDS/THF, R–X; (ii) LHMDS/THF, $(ClCH_2)_2C{=}CH_2$; (iii) Li-enolate of **1**/THF; (iv) Li/NH_3; (v) 0.5 M HCl at rt.



Scheme 4.

examined. The amide protons, which absorbed at 8.24 ppm ($J = 9.6$ Hz) in 1.5 mM $CDCl_3$, suffered a downfield shift to 9.2 ppm in DMSO. Upon addition of 8% DMSO (a competitive solvent in the hydrogen bond formation) to a solution of **4** in $CDCl_3$ a downfield shift of δ_{NH} of about 0.5 ppm was registered (Fig. 1). On addition of DMSO, the allylic proton at 2.83 ppm remained unchanged while that at 3.88 ppm underwent, step by step, an upfield shift reaching 3.0 ppm upon addition of about 10% DMSO (plot not reported). On adding 10% of CD_3OD to a solution of **4** in $CDCl_3$, the NH doublet at 8.24 ppm shifted to 8.78 ppm, after which, owing to proton–deuterium exchange, the signal slowly decreased in intensity until it disappeared after about 30 min.

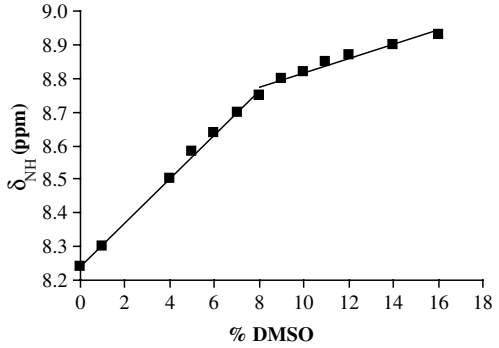


Figure 1. Dependence of δ_{NH} amide protons on addition of DMSO to a solution of **4** in $CDCl_3$.

The downfield shift of δ_{NH} induced by CD_3OD or DMSO was coherent with the presence of a hydrogen bonded structure in $CDCl_3$, which is disrupted by the competitive solvent.[11] Such an organized molecular aggregation, presumably induced by two intramolecular hydrogen bonds, was strengthened by the upfield shift registered for the allylic protons on addition of DMSO. The relatively slow H/D exchange rate of the amide protons was probably due to the formation of a stronger hydrogen bond between the amide protons of **4** and methanol.[11]

Furthermore, from the linear dependence of δ_{NH} amide protons on temperature, run on a 1.5 mM $CDCl_3$ solution (plot not reported), a low value for the temperature coefficient for the amide protons, $\Delta\delta_{NH}/\Delta T = 0.4$ ppb/°C, was found.

These findings (i.e., high δ_{NH} value, no concentration dependence of δ_{NH}, low temperature coefficient and $\Delta\delta_{NH} \cong 0.5$ ppm upon addition of a competitive solvent) suggested the existence of a weak intramolecular hydrogen bond between the –NH and C=O, giving rise to a 10-membered ring (i.e., a 'nonclassical peptide' mimetic β-turn structure), which was broken when a competitive solvent (such as DMSO or CD_3OD) reached about 8–10% of concentration.[12]

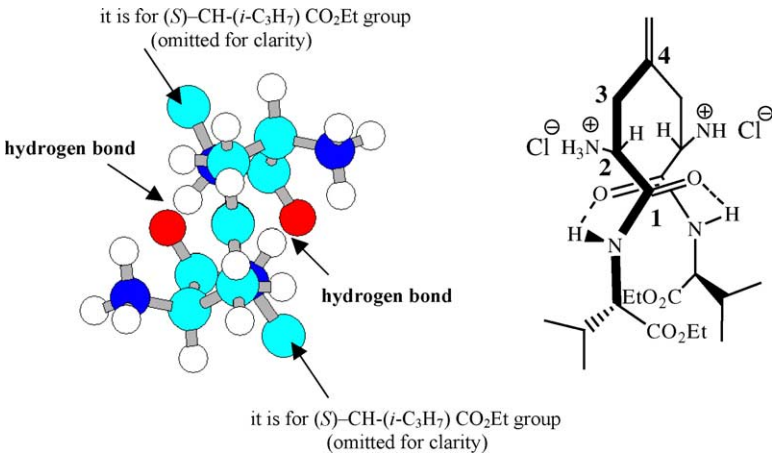


Figure 2. Geometry assumed for **4** on the basis of the spectroscopic data described in Section 3.

Further support for the presence of an intramolecular hydrogen bond came from IR spectra in $CHCl_3$. In fact, both in 20 and in 2 mM solutions in $CHCl_3$ a broad band in the region of 3160–3320 cm^{-1} ascribable to the stretching of $–NH_3^+$ and to the amide (–NH) hydrogen bonded is displayed. Additionally, the absence of a narrow adsorption at about 3420 cm^{-1}, typical of free –NH stretching, is indicative of the nonexistence of free –NH.[11]

Thus, we believe that compound **4** most probably exists in a very compact conformation with two intramolecular hydrogen bonds between the amide NH's and the carbonyl groups producing a bicyclic 10-membered structure. Figure 2 shows such a molecular structure, which can be assumed as an inverse β-turn. Nevertheless, the conformation drawn in Figure 2 is also supported by NOE experiments. By irradiating the –NH a prevalent NOE was registered on (C-2)-H while a minor NOE was registered on the proton at C-3. The irradiation of –NH gave a good NOE on the isopropyl group, but not on the –COOEt. The NOE was also observed on both the (C-2)-H and –NH by irradiating a proton bonded at C-3. Conversely, irradiation of the other proton at C-3 registered only a NOE on the methylene protons.

4. Conclusion

A simple stereoselective approach to 'nonclassical tripeptides' C-terminal at both ends of the chain, containing the 2,6-diaminoipimelic acid (2,6-DAP) framework, was accomplished starting from L-valine. The synthesis occurred in good chemical yields with high stereocontrol.

From the analysis of both ^1H NMR and IR data, it is reasonable to deduce that compound **4** is aggregated through the formation of two intramolecular hydrogen bonds between the carbonyl oxygens and the amide protons to form an inverse β-turn, that is the 'U structure' schematized in Figure 2. Such a compact symmetrical conformation (having a C_2 axis) is strengthened by the NMR spectra where half signals were registered.

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. Chemical shifts are reported in ppm relative to $CDCl_3$. The coupling constants (J) are in Hz. IR spectra were recorded on a Nicolet 210 spectrometer. Optical rotation values were measured at 25 °C on a Perkin–Elmer 343 polarimeter. Dry THF was distilled from sodium benzophenone ketyl. Chromatographic separations were performed by using silica gel 60 (230–400 mesh).

5.2. 1-[(3′*R*,6′*S*)-1′-Benzyl-3′,6′-dihydro-5′-hetoxy-6′-isopropyl-pirazin-3′-yl-2′-one]-3-[(3″*R*,6″*S*)-1″-benzyl-3″,6″-dihydro-5″-hetoxy-6″-isopropyl-pirazin-3″-yl-2″-one]-2-methylenepropane, 2

To a stirred solution of **1** (5.48 g, 20 mmol) in dry THF (50 mL) and cooled at −78 °C, a solution of LHMDS in THF (1 M, 21 mL) was dropped under an inert atmosphere. After about 1 h, 10 mmol of 2-iodomethyl-3-iodopropene (obtained from 11 mmol of 2-chloromethyl-3-chloropropene and 20 mmol of NaI in acetone, overnight at rt) was added and the reaction monitored by TLC. When the reaction went to completion, the mixture was allowed to warm up to room temperature while stirring. Water and ethyl acetate were added and after separation, the organic solvent was completely removed in vacuo. The residue was submitted to silica gel chromatography eluting with hexane/ethyl acetate and the pure product obtained as an oil in 80% yield and a de ⩾94%. ^1H NMR δ 0.94 (d, 6H, $J = 7$); 1.05 (d, 6H, $J = 7$); 1.22 (t, 6H, $J = 7$); 2.13–2.32 (m, 2H); 2.57 (dd, 2H, $J = 8.6, 14.2$); 3.10 (dd, 2H, $J = 4, 14.2$); 3.68 (dd, 2H, $J = 1.8, 4$); 3.93 (d, 2H, $J = 15$); 4.15 (m, 4H); 4.30 (ddd, 4H, $J = 1.4, 4, 8.6$); 5 (s, 2H); 5.5 (d, 2H, $J = 15$); 7.16–7.39 (m, 10ArH). ^{13}C NMR δ 13.7, 17.0, 19.5, 30.9, 39.9, 46.8, 57.3, 60.5, 61.3, 113.8, 126.9, 127.3, 127.4, 128.0, 128.1, 135.8, 144.0, 157.9, 169.6. $[\alpha]_D = +41.6$ (c 1, $CHCl_3$). IR (neat) $\nu_{cm^{-1}}$: 1694 (C═N), 1642 (C═O).

Anal. Calcd for $C_{36}H_{48}N_4O_4$: C, 71.97; H, 8.05; N, 9.33. Found: C, 72.15; H, 8.03; N, 9.35.

5.3. 1-[(3′*R*,6′*S*)-3′,6′-Dihydro-5′-hetoxy-6′-isopropyl-pirazin-3′-yl-2′-one]-3-[(3″*R*,6″*S*)-3″,6″-dihydro-5″-hetoxy-6″-isopropyl-pirazin-3″-yl-2″-one]-2-methylenepropane, 3

To a stirred solution of Li (0.35 g, 50 mmol) dissolved in liquid ammonia (ca. 50 mL), cooled at about −50 °C and stirred under an inert atmosphere, was added a solution of intermediate **2** (4.2 g, 7 mmol) in dry THF/*tert*-butanol 9:1 (10 mL). After 5 min, the reaction was quenched with 1 g of NH_4Cl and the cooling bath removed allowing complete removal of NH_3. After the addition of water, the aqueous solution was extracted with ethyl acetate and the organic solution evaporated to dryness under vacuum. The product was recovered as a wax in a practically quantitative yield. ^{1}H NMR δ 0.88 (d, 6H, $J = 7$); 0.99 (d, 6H, $J = 7$); 1.28 (t, 6H, $J = 7$); 2.13–2.28 (m, 2H); 2.51 (dd, 2H, $J = 7.8$, 14); 2.85 (dd, 2H, $J = 4.4$, 14); 3.9 (m, 2H); 4.16 (q, 4H, $J = 7$); 4.23 (m, 2H); 4.96 (s, 2H); 5.83 (br s, 2H). ^{13}C NMR δ 14.1, 16.1, 18.1, 31.8, 40.4, 57.5, 58.0, 60.8, 114.8, 143.2, 157.8, 172.1. $[\alpha]_D = +58.7$ (*c* 1.1, $CHCl_3$). IR ($CHCl_3$) $\nu_{cm^{-1}}$: 1672 (br, C=N and C=O). Anal. Calcd for $C_{22}H_{36}N_4O_4$: C, 62.83; H, 8.63; N, 13.32. Found: C, 63.02; H, 8.65; N, 13.28.

5.4. Tripeptide [(L)-Val ethylester-4-methylene-(2*R*,6*R*)-DAP-(L)-Val ethylester]·2HCl, 4

To a solution of **3** (2.1 g, 5 mmol) in ethanol (50 mL) was added 2.5 M HCl (5 mL) and the reaction mixture, monitored by TLC and/or ^{1}H NMR, stirred at room temperature for about 12 h. The acid solution was evaporated in vacuo and the pure product isolated as a solid (mp 73–75 °C) in a practically quantitative yield. ^{1}H NMR (CD_3OD) δ 1.02 (d, 6H, $J = 7.2$); 1.06 (d, 6H, $J = 7$); 1.31 (t, 6H, $J = 7$); 2.18–2.38 (m, 2H); 2.54 (dd, 2H, $J = 10.8$, 14.4); 2.96 (dd, 2H, $J = 4.8$, 14.4); 4.22 (q, 4H, $J = 7$); 4.32 (d, 2H, $J = 6.2$); 4.54 (dd, 2H, $J = 4.8$, 10.8); 5.33 (br s, 2H). ^{13}C NMR (CD_3OD) δ 14.6, 19.0, 19.7, 31.5, 38.3, 51.9, 59.8, 62.3, 123.9, 137.3, 170.3, 172.5. $[\alpha]_D = -23.5$ (*c* 0.8, 1 M HCl). IR ($CHCl_3$) $\nu_{cm^{-1}}$: 1548 (N–C=O), 1689 (N–C=O), 1732 (ester), 3160–3320 (NH and NH_3^+). Anal. Calcd for $C_{22}H_{42}Cl_2N_4O_6$: C, 49.9; H, 8.0; Cl, 13.39; N, 10.58. Found: C, 49.8; H, 8.01; Cl, 13.42; N,10.55.

5.5. Tripeptide [(OH)-(L)-Val-4-methylene-(2*R*,6*R*)-DAP-(L)-Val(OH)]·2HCl, 5

A solution of **4** (0.53 g, 1 mmol) in 1 M HCl (10 mL) was stirred for about 48 h at 60 °C and the reaction monitored by TLC and/or ^{1}H NMR. The acid solution was evaporated in vacuo and the product, in a semisolid state, isolated in a practically quantitative yield. ^{1}H NMR (D_2O) δ 1.15 (m, 12H); 2.2–2.5 (m, 2H); 2.85–3.0 (m, 4H); 4.4–4.7 (m, 5H); 5.53 (s, 2H). ^{13}C NMR (D_2O) δ 18.0, 19.7, 30.7, 38.3, 52.8, 61.8, 121.5, 136.9, 171.3, 178.7, $[\alpha]_D = -47.2$ (*c* 1.1, 1 M HCl). IR ($CHCl_3$) $\nu_{cm^{-1}}$: 1545 (N–C=O), 1685 (N–C=O), 1760 (COOH), 3100–3350 (OH and NH_3^+). Anal. Calcd for $C_{18}H_{34}Cl_2N_4O_6$: C, 45.67; H, 7.24; Cl, 14.98; N, 11.84. Found: C,45.75; H, 7.26; Cl, 15.03 N, 11.8.

5.6. Alkylation of 2

To a solution of **2** (0.6 g, 1 mmol), in dry THF (30 mL) and cooled at −78 °C, 1 M LHMDS in THF (1.1 mL) was added under stirring. After about 1 h, the appropriate alkylating reagent (1 mmol) was added and the reaction monitored by TLC. When the reaction went to completion, the mixture was allowed to warm up to room temperature, after which water and ethyl acetate were added. After separation, the organic solution was dried and evaporated in vacuo. The residue was submitted to silica gel chromatography eluting with hexane/ethyl acetate and the products, isolated as viscous oils, obtained with a diastereoselectivity higher than 98%.

5.7. 1-[(3′*S*,6′*S*)-1′-Benzyl-3′-methyl-6′-hydro-5′-hetoxy-6′-isopropyl-pirazin-3′-yl-2′-one]-3-[(3″*R*,6″*S*)-1″-benzyl-3″,6″-dihydro-5″-hetoxy-6″-isopropyl-pirazin-3″-yl-2″-one]-2-methylenepropane, 6a

Iodomethane was used as the alkylating reagent and the pure product obtained in 90% yield. ^{1}H NMR δ 0.93 (d, 3H, $J = 7.2$); 0.95 (d, 3H, $J = 7.2$); 1.06 (d, 3H, $J = 7$); 1.10 (d, 3H, $J = 7$); 1.24 (t, 3H, $J = 7$); 1.26 (t, 3H, $J = 7$); 1.45 (s, 3H); 2.22 (m, 2H); 2.59 (dd, 2H, $J = 9.3$, 14.1); 2.69 (d, 1H, $J = 13.2$); 2.80 (d, 1H, $J = 13.2$); 3.18 (dd, 1H, $J = 4.8$, 14.1); 3.68 (dd, 1H, $J = 1.5$, 4); 3.76 (d, 1H, $J = 2.7$); 3.92 (d, 1H, $J = 15$); 3.95 (d, 1H, $J = 15$); 4.15 (m, 5H); 5.08 (s, 2H); 5.50 (d, 1H, $J = 15$); 5.53 (d, 1H, $J = 15$); 7.20–7.42 (m, 10ArH). ^{13}C NMR δ 14.2, 14.3, 17.4, 17.6, 20.0, 20.6, 29.4, 30.1, 31.5, 41.0, 46.8, 46.9, 47.3, 57.6, 60.7, 61.1, 61.3, 61.8, 116.9, 127.4, 127.8, 127.9, 128.6, 136.3, 136.4, 143.3, 154.7, 158.4, 170.3, 173. $[\alpha]_D = +29.4$ (*c* 1.6, $CHCl_3$). IR (neat) $\nu_{cm^{-1}}$: 1640 (C=O), 1699 (C=N). Anal. Calcd for $C_{37}H_{50}N_4O_4$: C, 72.28; H, 8.2; N, 9.11. Found: C, 72.46; H, 8.22; N, 9.07.

5.8. 1-[(3′*R*,6′*S*)-1′,3′-Dibenzyl-6′-hydro-5′-hetoxy-6′-isopropyl-pirazin-3′-yl-2′-one]-3-[(3″*R*,6″*S*)-1″-benzyl-3″,6″-dihydro-5″-hetoxy-6″-isopropyl-pirazin-3″-yl-2″-one]-2-methylenepropane, 6b

Benzylbromide was used as an alkylating reagent and the product obtained in 88% yield. ^{1}H NMR 0.84 (d, 3H, $J = 7$); 0.90 (d, 3H, $J = 7$); 0.94 (d, 3H, $J = 7$); 1.07 (d, 3H, $J = 7$); 1.27 (m, 6H); 2.02 (m, 1H); 2.25 (m, 1H); 2.65 (dd, 1H, $J = 9$, 14.1); 2.84 (d, 1H, $J = 13.2$); 2.99 (d, 1H, $J = 13.2$); 3.05 (d, 1H, $J = 12.6$); 3.17 (d, 1H, $J = 2.4$); 3.26 (dd, 1H, $J = 3.9$, 14.1); 3.3 (d, 1H, $J = 12.6$); 3.71 (dd, 1H, $J = 1.8$, 3.9); 3.92 (d, 1H, $J = 15.3$); 3.95 (d, 1H, $J = 15.3$); 4.11 (m, 5H); 5.14 (m, 2H); 5.18 (d, 1H, $J = 15.3$); 5.50 (d, 1H, $J = 15.3$); 6.60 (m, 2ArH); 7.13–7.38 (m, 13ArH). ^{13}C NMR δ 14.0, 14.3, 16.5, 17.4, 19.8, 20.2, 28.9, 31.3, 40.9, 46.3, 46.4, 47.2, 47.5, 57.3, 60.0,

60.4, 60.9, 61.7, 65.6, 117.0, 125.8, 126.7, 127.2, 127.4, 127.6, 127.7, 128.0, 128.3, 130.5, 135.0, 136.1, 137.5, 143.0, 155.7, 158.3, 170.0, 170.3. $[\alpha]_D = -10.5$ (*c* 1.6, $CHCl_3$). IR (neat) $\nu_{cm^{-1}}$: 1645 (C=O), 1700 (C=N). Anal. Calcd for $C_{43}H_{54}N_4O_4$: C, 74.75; H, 7.88; N, 8.11. Found: C, 74.95; H, 7.91; N, 8.05.

5.9. 1-[(3′*S*,6′*S*)-1′-Benzyl-3′-allyl-6′-hydro-5′-hetoxy-6′-isopropyl-pirazin-3′-yl-2′-one]-3-[(3″*R*,6″*S*)-1″-benzyl-3″,6″-dihydro-5″-hetoxy-6″-isopropyl-pirazin-3″-yl-2″-one]-2-methylenepropane, 6c

Allylbromide was used as an alkylating reagent and the product obtained in 92% yield. ^{1}H NMR δ 0.91 (d, 6H, $J = 7$); 1.04 (d, 3H, $J = 7$); 1.06 (d, 3H, $J = 7$); 1.23 (t, 3H, $J = 7$); 1.26 (t, 3H, $J = 7$); 2.2 (m, 2H); 2.42–2.7 (m, 3H); 2.73 (d, 1H, $J = 13.2$); 2.85 (d, 1H, $J = 13.2$); 3.17 (dd, 1H, $J = 4$, 14); 3.67 (dd, 1H, $J = 1.4$, 4); 3.71 (d, 1H, $J = 2.6$); 3.96 (d, 1H, $J = 15$); 4.04–4.23 (m, 5H); 5–5.17 (m, 4H); 5.47 (d, 1H, $J = 15$); 5.49 (d, 1H, $J = 15$); 5.44–5.62 (m, 1H); 7.17–7.4 (m, 10ArH). ^{13}C NMR δ 14.0, 14.2, 16.7, 17.3, 19.8, 20.4, 26.7, 29.3, 31.3, 40.8, 45.2, 46.5, 46.7, 47.1, 57.4, 60.6, 60.9 61.6, 64.3, 116.9, 117.9, 127.2, 127.5, 128.2, 128.3, 128.4, 133.8, 135.7, 136.1, 143.0, 155.4, 158.2, 170.0, 170.8. $[\alpha]_D = +6.7$ (*c* 1, $CHCl_3$). IR (neat) $\nu_{cm^{-1}}$: 1640 (C=O), 1698 (C=N). Anal. Calcd for $C_{39}H_{52}N_4O_4$: C, 73.09; H, 8.18; N, 8.74. Found: C, 73.01; H, 8.16; N, 8.75.

5.10. 1-[(3′*R*,6′*S*)-1′-Benzyl-3′-methoxymethyl-6′-hydro-5′-hetoxy-6′-isopropyl-pirazin-3′-yl-2′-one]-3-[(3″*R*,6″*S*)-1″-benzyl-3″,6″-dihydro-5″-hetoxy-6″-isopropyl-pirazin-3″-yl-2″-one]-2-methylenepropane, 6d

Methoxymethylbromide was used as an alkylating reagent and the product obtained in 85% yield. ^{1}H NMR δ 0.93 (d, 6H, $J = 6.9$); 1.06 (d, 3H, $J = 6.8$); 1.08 (d, 3H, $J = 6.8$); 1.23 (t, 3H, $J = 7.5$); 1.28 (t, 3H, $J = 7.5$); 2.22 (m, 2H); 2.59 (dd, 1H, $J = 9.0$, 14.4); 2.66 (d, 1H, $J = 13.5$); 2.67 (d, 1H, $J = 13.5$); 3.22 (dd, 1H, $J = 4.2$, 14.4); 3.34 (s, 3H); 3.47 (d, 1H, $J = 8.1$); 3.68 (m, 1H); 3.79 (d, 1H, $J = 2.1$); 3.89 (d, 1H, $J = 8.1$); 3.94 (d, 1H, $J = 15.3$); 3.97 (d, 1H, $J = 15.3$); 4.00–4.28 (m, 5H); 5.04 (m, 2H); 5.49 (d, 1H, $J = 15.3$); 5.67 (d, 1H, $J = 15.3$); 7.17–7.41 (m, 10ArH). ^{13}C NMR δ 14.0, 14.1, 17.0, 17.5, 19.9, 20.4, 29.5, 31.4, 40.7, 43.7, 46.5, 47.3, 57.5, 59.1, 60.4, 60.7, 61.0, 61.8, 64.9, 80.1, 116.6, 127.1, 127.4, 127.8, 128.0, 128.4, 128.6, 135.9, 136.3, 142.8, 156.7, 158.5, 170.3, 170.5. $[\alpha]_D = +38$ (*c* 0.6, $CHCl_3$). IR (neat) $\nu_{cm^{-1}}$: 1646 (C=O), 1700 (C=N). Anal. Calcd for $C_{38}H_{52}N_4O_5$: C, 70.78; H, 8.13; N, 8.69. Found: C, 70.98; H, 8.15; N, 8.66.

5.11. 1-[(3′*S*,6′*S*)-3′-Methyl-6′-hydro-5′-hetoxy-6′-isopropyl-pirazin-3′-yl-2′-one]-2-[(3″*R*,6″*S*)-3″,6″-dihydro-5″-hetoxy-6″-isopropyl-pirazin-3″-yl-2″-one]-3-methylenepropane, 7a

Intermediate **6a** was submitted to a Birch reaction following the procedure employed for preparing **3**. The product was obtained as a wax in a practically quantitative yield. ^{1}H NMR δ 0.83 (d, 3H, $J = 7$); 0.84 (d, 3H, $J = 6.6$); 0.98 (d, 6H, $J = 7.2$); 1.25 (t, 3H, $J = 7.4$); 1.26 (t, 3H, $J = 7.2$); 1.35 (s, 3H); 2.24 (m, 2H); 2.44 (dd, 1H, $J = 8$, 14); 2.49 (d, 1H, $J = 13.2$); 2.76 (d, 1H, $J = 13.2$); 2.83 (dd, 1H, $J = 4.4$, 14); 3.85 (m, 1H); 3.93 (dd, 1H, $J = 1.4$, 2.8); 4.05–4.23 (m, 5H); 4.94 (m, 2H); 6.37 (br s, 1H); 6.61 (br s, 1H). ^{13}C NMR δ 14.3, 16.1, 16.3, 18.2, 18.4, 28.7, 29.6, 30.6, 31.8, 41.5, 46.3, 57.8, 58.0, 58.2, 61.0, 61.1, 116.8, 142.7, 155.3, 157.8, 172.0, 174.3. $[\alpha]_D = +56$ (*c* 1.7, $CHCl_3$). IR ($CHCl_3$) $\nu_{cm^{-1}}$: 1670 (br, C=N and C=O). Anal. Calcd for $C_{23}H_{38}N_4O_4$: C, 63.57; H, 8.81; N, 12.89. Found: C, 63.62; H, 8.84; N, 12.92.

5.12. 1-[(3′*R*,6′*S*)-3′-Benzyl-6′-hydro-5′-hetoxy-6′-isopropyl-pirazin-3′-yl-2′-one]-3-[(3″*R*,6″*S*)-3″,6″-dihydro-5″-hetoxy-6″-isopropyl-pirazin-3″-yl-2″-one]-2-methylenepropane, 7b

Compound **7b** was obtained as a wax in a practically quantitative yield starting from **6b** following the same procedure used for **6a**. ^{1}H NMR δ 0.70 (d, 3H, $J = 6.8$); 0.77 (d, 3H, $J = 7.2$); 0.87 (d, 3H, $J = 6.8$); 1.0 (d, 3H, $J = 7$); 1.29 (t, 3H, $J = 7.2$); 1.30 (t, 3H, $J = 7.2$); 2.04 (m, 1H); 2.23 (m, 1H); 2.51 (dd, 1H, $J = 8.4$, 14); 2.61 (d, 1H, $J = 13.2$); 2.74 (dd, 1H, $J = 1.2$, 2.6); 2.79 (d, 1H, $J = 12.4$); 2.82 (dd, 1H, $J = 4.4$, 14); 3.03 (d, 1H, $J = 13.2$ Hz); 3.23 (d, 1H, $J = 12.4$); 3.88 (m, 1H); 4.09–4.33 (m, 5H); 5.0 (m, 2H); 5.51 (br s, 1H); 6.05 (br s, 1H); 7.03–7.38 (m, 5ArH). ^{13}C NMR 14.2, 14.4, 15.7, 16.0, 18.0, 18.2, 29.7, 31.7, 41.6. 46.1, 47.2, 57.3, 58.0, 58.5, 61.1, 61.3, 117.2, 126.4, 127.7, 130.5, 136.7, 142.6, 156.8, 157.8, 171.8, 172.1. $[\alpha]_D = +10.2$ (*c* 1, $CHCl_3$). IR ($CHCl_3$) $\nu_{cm^{-1}}$: 1673 (br, C=N and C=O). Anal. Calcd for $C_{29}H_{42}N_4O_4$: C, 68.21; H, 8.29; N, 10.97. Found: C, 68.38; H, 8.31; N, 10.99.

5.13. 1-[(3′*S*,6′*S*)-3′-Allyl-6′-hydro-5′-hetoxy-6′-isopropyl-pirazin-3′-yl-2′-one]-3-[(3″*R*,6″*S*)-3″,6″-dihydro-5″-hetoxy-6″-isopropyl-pirazin-3″-yl-2″-one]-2-methylenepropane, 7c

Compound **7c** was obtained as a wax in a practically quantitative yield starting from **6c** following the same procedure used for **6a**. ^{1}H NMR δ 0.82 (d, 3H, $J = 7$); 0.84 (d, 3H, $J = 6.6$); 0.96 (d, 3H, $J = 7.4$); 0.98 (d, 3H, $J = 7$); 1.26 (t, 3H, $J = 7$); 1.27 (t, 3H, $J = 7$); 2.10–2.85 (m, 6H); 2.47 (d, 1H, $J = 13$); 2.81 (d, 1H, $J = 13$); 3.85 (m, 2H); 4.10–4.26 (m, 5H); 4.9–5.1 (m, 4H); 5.5–5.77 (m, 1H); 6.33 (br s, 1H); 6.63 (br s, 1H). ^{13}C NMR δ 14.0, 14.2, 16.1, 16.2, 18.0, 18.2, 30.5, 31.8, 41.3, 45.5, 45.6, 57.7, 57.9, 58.0, 60.8, 64.4, 116.8, 118.2, 133.0, 142.4, 156.3, 157.8, 172.2, 172.8. $[\alpha]_D = +42.6$ (*c* 0.8, $CHCl_3$). IR ($CHCl_3$) $\nu_{cm^{-1}}$: 1675 (br, C=N and C=O). Anal. Calcd for $C_{25}H_{40}N_4O_4$: C, 65.19; H, 8.75; N, 12.16. Found: C, 65.25; H, 8.77; N, 12.2.

5.14. 1-[(3′*R*,6′*S*)-3′-Methoxymethyl-6′-hydro-5′-hetoxy-6′-isopropyl-pirazin-3′-yl-2′-one]-3-[(3″*R*,6″*S*)-3″,6″-dihydro-5″-hetoxy-6″-isopropyl-pirazin-3″-yl-2″-one]-2-methylenepropane, 7d

Compound **7d** was obtained as a wax in a practically quantitative yield starting from **6d** following the same

procedure used for **6a** ^{1}H NMR δ 0.81 (d, 3H, $J = 7$); 0.84 (d, 3H, $J = 7$); 0.96 (d, 3H, $J = 7$); 0.97 (d, 3H, $J = 7.2$); 1.25 (t, 3H, $J = 7$); 1.26 (t, 3H, $J = 7.3$); 2.17–2.32 (m, 2H); 2.41 (d, 1H, $J = 13.2$); 2.44 (dd, 1H, $J = 4.8$, 14); 2.69 (d, 1H, $J = 13.2$); 2.82 (dd, 1H, $J = 4.4$, 14); 3.26 (d, 1H, $J = 8.4$); 3.27 (s, 3H); 3.72 (d, 1H, $J = 8.4$); 3.83 (m, 1H); 3.98 (dd, 1H, $J = 1$, 2.6); 4.05–4.25 (m, 5H); 4.93 (m, 2H); 6.31 (br s, 1H); 6.77 (br s, 1H). ^{13}C NMR δ 14.1, 16.0, 16.1, 18.1, 18.2, 30.1, 31.8, 41.4, 41.9, 57.6, 57.8, 58.2, 59.3, 61.0, 65.3, 79.8, 116.7, 141.8, 157.5, 157.8, 172.0, 172.1. $[\alpha]_D = +17.9$ (c 2.5, $CHCl_3$). IR ($CHCl_3$) $\nu_{cm^{-1}}$: 1672 (br, C=N and C=O). Anal. Calcd for $C_{24}H_{40}N_4O_5$: C, 62.04; H, 8.68; N, 12.06. Found: C, 61.81; H, 8.66; N, 12.1.

5.15. Tripeptide [(OH)-(L)-Val-2-methyl-4-methylene-(2*S*,6*R*)-DAP-(L)-Val(OH)]·2HCl, 8a

The product, isolated in a semisolid state, was obtained in a practically quantitative yield by submitting **7a** to acid hydrolysis as described for **5**. ^{1}H NMR (D_2O) δ 0.84–0.90 (m, 12H); 1.64 (s, 3H); 2.02–2.33 (m, 2H); 2.44–2.60 (m, 2H); 2.67 (q_{AB}, 2H, $J = 15$); 4.1–4.3 (m, 3H); 5.24 (m, 2H). ^{13}C NMR (D_2O) δ 18.1, 18.6, 19.2, 23.2, 30.3, 30.4, 38.6, 42.3, 52.3, 59.4, 59.9, 60.7, 124.0, 135.1, 169.7, 172.0, 175.0, 175.2. $[\alpha]_D = -25.5$ (c 0.6, 1 M HCl). IR ($CHCl_3$) $\nu_{cm^{-1}}$: 1545 (N–C=O), 1685 (N–C=O), 1750 (COOH), 3150–3350 (OH and NH_3^+). Anal. Calcd for $C_{19}H_{36}Cl_2N_4O_6$: C, 46.82; H, 7.44; Cl, 14.55; N, 11.49. Found: C, 46.73; H, 7.42; Cl, 14.6; N, 11.51.

5.16. Tripeptide [(OH)-(L)-Val-2-benzyl-4-methylene-(2*R*,6*R*)-DAP-(L)-Val(OH)]·2HCl, 8b

The product, isolated in a semisolid state, was obtained in a practically quantitative yield by submitting **7b** to acid hydrolysis as described for **5**. ^{1}H NMR (D_2O) δ 0.53 (d, 3H, $J = 6.6$); 0.66 (d, 3H, $J = 7$); 0.86 (d, 3H, $J = 6.8$); 0.87 (d, 3H, $J = 6.8$); 1.85–2 (m, 1H); 2.1–2.25 (m, 1H); 2.39 (d, 1H, $J = 14.2$); 2.46–2.51 (m, 2H); 2.88 (q_{AB}, 2H, $J = 14.6$); 3.16 (d, 1H, $J = 14.2$); 4.13–4.27 (m, 3H); 5.16 (m, 2H); 7–7.2 (m, 5ArH). ^{13}C NMR (D_2O) δ 16.0, 18.0, 18.3, 19.3, 30.6, 31.1, 39.9, 42.1, 48.0, 52.2, 59.0, 59.3, 65.1, 123.8, 128.4, 129.2, 131.2, 134.5, 136.5, 170.1, 170.7, 171.0, 175.2. $[\alpha]_D = +11.5$ (c 2.4, 1 M HCl). IR ($CHCl_3$) $\nu_{cm^{-1}}$: 1548 (N–C=O), 1687 (N–C=O), 1765 (COOH), 3120–3330 (OH and NH_3^+). Anal. Calcd for $C_{25}H_{40}Cl_2N_4O_6$: C, 53.28; H, 7.15; Cl, 12.58; N, 9.94. Found: C, 53.37; H, 7.18; Cl, 12.62; N, 9.96.

5.17. Tripeptide [(OH)-(L)-Val-2-allyl-4-methylene-(2*S*,6*R*)-DAP-(L)-Val(OH)]·2HCl, 8c

The product, isolated in a semisolid state, was obtained in a practically quantitative yield by submitting **7c** to acid hydrolysis as described for **5**. ^{1}H NMR (CD_3OD) δ 0.9–1.07 (m, 12H); 2.08–2.29 (m, 5H); 2.41 (dd, 1H, $J = 4.4$, 13.6); 2.62 (dd, 1H, $J = 4.4$, 13.6); 2.82 (d, 1H, $J = 13.6$); 3.6 (dd, 1H, $J = 4.8$, 9.2); 4.22 (d, 1H, $J = 5.6$); 4.36 (d, 1H, $J = 6$); 5–5.21 (m, 4H); 5.7–5.93 (m, 1H). ^{13}C NMR (D_2O) δ 18.1, 18.8, 19.1, 30.3, 30.4, 38.6, 41.3, 52.3, 59.4, 60.3, 63.5, 124.0, 124.1, 128.8, 134.9, 169.7, 170.9, 175.0, 175.3. $[\alpha]_D = -17.4$ (c 1.1, 1 M HCl). IR ($CHCl_3$) $\nu_{cm^{-1}}$: 1550 (N–C=O), 1690 (N–C=O), 1770 (COOH), 3100–3300 (OH and NH_3^+). Anal. Calcd for $C_{21}H_{38}Cl_2N_4O_6$: C, 49.12; H, 7.46; Cl, 13.81; N, 10.91. Found: C, 48.98; H, 7.42; Cl, 13.85; N, 10.93.

5.18. Tripeptide [(OH)-(L)-Val-2-metoxymethyl-4-methylene-(2*R*,6*R*)-DAP-(L)-Val(OH)]·2HCl, 8d

The product, isolated in a semisolid state, was obtained in a practically quantitative yield by submitting **7d** to acid hydrolysis as described for **5**. ^{1}H NMR (D_2O) δ 0.75–0.93 (m, 12H); 1,97–2.2 (m, 2H); 2.44 (m, 2H); 2.65 (q_{AB}, 2H, $J = 15$); 3.29 (s, 3H); 3.61 (d, 1H, $J = 10.6$); 3.82 (d, 1H, $J = 10.6$); 4.09 (m, 1H); 4.11 (d, 1H, $J = 5.8$); 4.2 (d, 1H, $J = 6.2$); 5.21 (m, 2H). ^{13}C NMR (D_2O) δ 18.1, 18.3, 19.1, 19.2, 30.3, 30.6, 38.0, 38.4, 52.2, 59.4, 59.7, 59.9, 63.9, 73.7, 124.2, 134.3, 169.8, 175.0, 175.3. $[\alpha]_D = -32.9$ (c 0.55, 1 M HCl). IR ($CHCl_3$) $\nu_{cm^{-1}}$: 1548 (N–C=O), 1687 (N–C=O), 1765 (COOH), 3100–3300 (OH and NH_3^+). Anal. Calcd for $C_{20}H_{38}Cl_2N_4O_7$: C, 46.42; H, 7.4; Cl, 13.7; N, 10.83. Found: C, 46.52; H, 7.41; Cl, 13.72; N, 10.81.

5.19. (3*R*,6*S*)-1-Benzyl-5-hetoxy-6-isopropyl-3-methyl-6-dihydropirazin-2-one, 9a

The pure product was obtained as an oil in 80% yield by alkylating **1** with iodomethane and following the procedure as described for **2**. ^{1}H NMR δ 0.95 (d, 3H, $J = 7$); 1.06 (d, 3H, $J = 7$); 1.26 (t, 3H, $J = 7.2$); 1.57 (d, 3H, $J = 7$); 2.22 (m, 1H); 3.7 (dd, 1H, $J = 1.4$, 4); 3.95 (d, 1H, $J = 15$); 4.02–4.2 (m, 3H); 5.47 (d, 1H, $J = 15$); 7.15–7.2 (m, 5ArH). ^{13}C NMR δ 14.2, 17.7, 20.1, 20.7, 31.6, 47.5, 53.9, 61.1, 62.4, 127.4, 127.7, 128.6, 136.3, 159.2, 171.3. $[\alpha]_D = +24.2$ (c 1.7, $CHCl_3$). IR (neat) $\nu_{cm^{-1}}$: 1690 (N–C=O), 1640 (C=O). Anal. Calcd for $C_{17}H_{24}N_2O_2$: C, 70.8; H, 8.39; N, 9.71. Found: C, 70.92; H, 8.38; N, 9.69.

5.20. (3*R*,6*S*)-3-Allyl-1-benzyl-5-hetoxy-6-isopropyl-6-dihydropirazin-2-one, 9b

The pure product was obtained as an oil in 85% yield by alkylating **1** with allylbromide and following the procedure as described for **2**. ^{1}H NMR δ 0.92 (d, 3H, $J = 6.6$); 1.04 (d, 3H, $J = 7$); 1.24 (t, 3H, $J = 7$); 2.22 (m, 1H); 2.75 (m, 2H); 3.66 (m, 1H); 3.87 (d, 1H, $J = 15$); 4.13 (m, 3H); 5.11 (m, 2H); 5.5 (d, 1H, $J = 15$); 5.87 (m, 1H); 7.35 (m, 5ArH). ^{13}C NMR δ 14.1, 17.4, 19.9, 31.5, 38.1, 47.1, 58.0, 61.0, 61.7, 117.1, 127.4, 127.7, 128.5, 134.9, 136.0, 158.8, 169.7. $[\alpha]_D = +44.8$ (c 2.1, $CHCl_3$). IR (neat) $\nu_{cm^{-1}}$: 1692 (N–C=O), 1645 (C=O). Anal. Calcd for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.33; N, 8.91. Found: C, 72.49; H, 8.31; N, 8.94.

5.21. (3*R*,6*S*)-1-Benzyl-5-hetoxy-6-isopropyl-3-methyl-3-(2-chloromethyl-2-propenyl)-6-hydro pirazin-2-one, 10a

The pure product was obtained as an oil in 88% yield by alkylating **9a** with 2-chloromethyl-3-chloropropene and

following the procedure as described for **2**. ^{1}H NMR δ 0.89 (d, 3H, $J = 7$); 1.05 (d, 3H, $J = 7$); 1.26 (t, 3H, $J = 7$); 1.49 (s, 3H); 2.2 (m, 1H); 2.53 (d, 1H, $J = 13.2$); 2.72 (d, 1H, $J = 13.2$); 3.72 (m, 1H); 3.91 (d, 1H, $J = 15.3$); 4.02 (q_{AB}, 2H, $J = 11.7$) 4–4.25 (m, 2H) 5.03 (s, 1H); 5.11 (s, 1H); 5.42 (d, 1H, $J = 15.3$) 7.17–7.4 (m, 5ArH). ^{13}C NMR δ 14.3, 17.4, 20.6, 29.1, 29.8, 45.5, 46.7, 49.7, 60.8, 61.2, 61.7, 118.4, 127.5, 128.3, 128.6, 135.7, 141.7, 156.1, 171.3. $[\alpha]_D = -51.5$ (c 1, $CHCl_3$). Anal. Calcd for $C_{21}H_{29}ClN_2O_2$: C,66.92; H, 7.76; Cl, 9.41; N, 7.43. IR (neat) $\nu_{cm^{-1}}$: 1690 (N–C=O), 1642 (C=O). Found: C, 66.74; H, 7.72; Cl, 9.44; N, 7.42.

5.22. (3*R*,6*S*)-3-Allyl-1-benzyl-5-hetoxy-6-isopropyl-3-(2-chloromethyl-2-propenyl)-6-hydro pirazin-2-one, 10b

The pure product was obtained as an oil in 90% yield by alkylating **9b** with 2-chloromethyl-3-chloropropene and following the procedure as described for **2**. ^{1}H NMR δ 0.93 (d, 3H, $J = 7$); 1.06 (d, 3H, $J = 7$); 1.28 (t, 3H, $J = 7$); 2.09–2.24 (m, 1H); 2.05 (d, 1H, $J = 13.2$); 2.55–2.65 (m, 2H); 2.85 (d, 1H, $J = 13.2$); 3.73 (d, 1H, $J = 2.6$); 3.94–4.38 (m, 4H); 4.04 (d, 1H, $J = 15$); 5–5.23 (m, 4H); 5.33 (d, 1H, $J = 15$); 5.85–6.07 (m, 1H); 7.17–7.4 (m, 5ArH). ^{13}C NMR δ 14.0, 16.9, 20.5, 29.3, 42.7, 46.1, 46.7, 48.7, 60.5, 61.0, 64.0, 117.8, 118.0, 127.2, 127.9, 128.2, 133.2, 135.4, 141.2, 156.2, 169.9. $[\alpha]_D = -36$ (c 1.7, $CHCl_3$). IR (neat) $\nu_{cm^{-1}}$: 1692 (N–C=O), 1642 (C=O). Anal. Calcd for $C_{23}H_{31}ClN_2O_2$: C, 68.55; H, 7.75; Cl, 8.8; N, 6.95. Found: C, 68.72; H, 7.77; Cl, 8.78; N, 6.93.

5.23. 1-[(3′*R*,6′*S*)-1′-Benzyl-3′-methyl-6′-hydro-5′-hetoxy-6′-isopropyl-pirazin-3′-yl-2-one]-3-[(3″*R*,6″*S*)-1″-benzyl-3″,6″-dihydro-5″-hetoxy-6″-isopropyl-pirazin-3″-yl-2″-one]-2-methylenepropane, 11a

The pure product was obtained as a viscous oil in 85% yield by alkylating the Li-enolate of **1** with **10a**. ^{1}H NMR δ 0.88 (d, 3H, $J = 7$); 0.94 (d, 3H, $J = 7$); 1.02 (d, 3H, 7); 1.05 (d, 3H, $J = 7$); 1.19 (t, 3H, $J = 7.2$); 1.24 (t, 3H, $J = 7.2$); 1.56 (s, 3H); 2.2 (m, 2H); 2.47 (m, 1H); 2.49 (d, 1H, $J = 13.2$); 2.98 (m, 1H); 3 (d, 1H, $J = 13.2$); 3.66 (dd, 1H, $J = 1.5, 4$); 3.7 (d, 1H, $J = 2.4$); 3.94 (d, 1H, $J = 15$); 3.97 (d, 1H, $J = 15$); 4.07 (m, 3H); 4.23 (m, 2H); 4.92 (s, 2H); 5.48 (d, 1H, $J = 15$); 5.49 (d, 1H, $J = 15$); 7.2 (m, 10ArH). ^{13}C NMR δ 13.8, 13.9, 16.7, 17.2, 19.7, 20.1, 28.9, 29.2, 31.1, 40.9, 46.2, 47.0, 48.3, 57.3, 60.2, 60.5, 60.6, 61.5, 62.0, 115.5, 127.2, 127.5, 127.9, 128.2, 128.3, 135.5, 136.1, 143.4, 155.1,158.2, 170.0, 171.4. $[\alpha]_D = -26.6$ (c 1, $CHCl_3$). IR (neat) $\nu_{cm^{-1}}$: 1695 (C=N), 1640 (C=O). Anal. Calcd for $C_{37}H_{50}N_4O_4$: C, 72.28; H, 8.2; N, 9.11. Found: C, 72.47; H, 8.21; N, 9.1.

5.24. 1-[(3′*R*,6′*S*)-3′-Allyl-1′-benzyl-6′-hydro-5′-hetoxy-6′-isopropyl-pirazin-3′-yl-2-one]-3-[(3″*R*,6″*S*)-1″-benzyl-3″,6″-dihydro-5″-hetoxy-6″-isopropyl-pirazin-3″-yl-2″-one]-2-methylenepropane, 11b

The pure product was obtained as a viscous oil in 87% yield by alkylating the Li-enolate of **1** with **10b**. ^{1}H NMR δ 0.84 (d, 3H, $J = 6.6$); 0.92 (d, 3H, $J = 7$); 1.01 (d, 3H, $J = 7$); 1.04 (d, 3H, $J = 7$); 1.2 (t, 3H, $J = 7$); 1.26 (t, 3H, $J = 7$); 2.04–2.32 (m, 2H); 2.38–2.97 (m, 4H); 2.54 (d, 1H, $J = 13.2$); 2.87 (d, 1H, $J = 13.2$); 3.64 (dd, 1H, $J = 1.8, 3.6$); 3.73 (d, 1H, $J = 2.6$); 3.90 (d, 1H, $J = 15$); 3.99–4.37 (m, 6H); 4.9 (br s, 2H); 5.05–5.2 (m, 2H); 5.25 (d, 1H, $J = 15$); 5.47 (d, 1H, $J = 15$), 5.83–6.11 (m, 1H); 7.13–7.43 (m, 10ArH). ^{13}C NMR δ 14.0, 14.1, 16.6, 17.4. 19.8, 20.6, 29.0, 31.3, 40.8, 46.1, 46.3, 47.1, 57.1, 60.4, 60.9, 61.5, 64.9, 115.9, 117.4 127.1 127.6, 128.2, 128.4, 134.1, 135.7, 136.0, 143.3, 155.6, 158.2, 170.0, 170.6. $[\alpha]_D = -31$ (c 0.5, $CHCl_3$). IR (neat) $\nu_{cm^{-1}}$: 1695 (C=N), 1640 (C=O). Anal. Calcd for $C_{39}H_{52}N_4O_4$: C, 73.09; H, 8.18; N, 8.74. Found: C, 72.82; H, 8.13; N, 8.76.

5.25. 1-[(3′*R*,6′*S*)-3′-Methyl-6′-hydro-5′-hetoxy-6′-isopropyl-pirazin-3′-yl-2-one]-3-[(3″*R*,6″*S*)-6″-dihydro-5″-hetoxy-6″-isopropyl-pirazin-3″-yl-2″-one]-2-methylene-propane, 12a

Compound **12a** was obtained as a wax in 95% yield by submitting **11a** to a Birch reaction as described for **3**. The product was not obtained in a sufficiently pure form to measure the specific rotation. ^{1}H NMR δ 0.85 (d, 3H, $J = 7$); 0.86 (d, 3H, $J = 7$); 0.98 (d, 3H, $J = 7$); 0.99 (d, 3H, $J = 7$); 1.27 (t, 6H, $J = 7$); 1.42 (s, 3H); 2.22 (m, 2H); 2.35 (d, 1H, $J = 13.2$); 2.37 (dd, 1H, $J = 8, 14.4$); 2.72 (dd, 1H, $J = 4.4, 14.4$); 2.82 (d, 1H, $J = 13.2$); 3.85 (m, 1H); 3.9 (dd, 1H, $J = 1.7, 2.6$); 4.05–4.3 (m, 5H); 4.88 (m, 2H); 6.51 (br s, 1H); 6.7 (br s, 1H). ^{13}C NMR δ 14.3, 16, 16.1, 18.3, 29, 30.9, 31.8, 41.1, 47.9, 58.2, 58.3, 60.9, 61.1, 61.3, 116.1, 142.8, 155.9, 157.8, 171.9, 174. IR ($CHCl_3$) $\nu_{cm^{-1}}$: 1670 (br, C=N and C=O).

5.26. 1-[(3′*R*,6′*S*)-3′-Allyl-6′-hydro-5′-hetoxy-6′-isopropyl-pirazin-3′-yl-2-one]-3-[(3″*R*,6″*S*)-3″,6″-dihydro-5″-hetoxy-6″-isopropyl-pirazin-3″-yl-2″-one]-2-methylenepropane, 12b

Compound **12b** was obtained as a wax in 95% yield by submitting **11b** to a Birch reaction as described for **3**. The product was not obtained in a sufficiently pure form to measure the specific rotation. ^{1}H NMR δ 0.83 (d, 3H, $J = 7$); 0.87 (d, 3H, $J = 7$); 0.98 (d, 3H, $J = 7$); 1.11 (d, 3H, $J = 7$); 1.29 (t, 3H, $J = 7$); 1.31 (t, 3H, $J = 7$); 2.17–2.45 (m, 3H); 2.36 (d, 1H, $J = 12.9$); 2.67 (m, 1H); 2.78 (d, 1H, $J = 12.9$); 3.87 (m, 1H); 3.91 (m, 1H); 4.1–4.35 (m, 5H); 4.89 (s, 1H); 4.93 (s, 1H); 5.06 (m, 2H); 5.7 (m, 1H); 6.77 (br s, 1H); 7.12 (br s, 1H). ^{13}C NMR δ 14.2, 16.1, 16.3, 18.2, 18.3, 30.3, 31.8, 40.9, 45.4, 47, 57.9, 58.2, 58.6, 61, 61.1, 64.2, 116.7, 117.8, 134.2, 142.6, 156.8, 158, 172, 172.9. IR ($CHCl_3$) $\nu_{cm^{-1}}$: 1670 (br, C=N and C=O).

5.27. Tripeptide [(L)-Val ethylester-2-methyl-4-methylene-(2*R*,6*R*)-DAP-(L)-Val ethyl ester]·2HCl, 13a

The product, isolated in a semisolid state, was obtained in 95% yield by submitting **12a** to acid hydrolysis as

described for **4**. The product was not obtained in a sufficiently pure form to measure the specific rotation. ^{1}H NMR (CD_3OD) δ 0.97–1.1 (m, 12H), 1.28 (t, 3H, $J = 7$); 1.29 (t, 3H, $J = 7$); 1.76 (s, 3H), 2.18–2.3 (m, 2H); 2.51 (dd, 1H, $J = 9.8, 14.2$); 2.79 (dd, 1H, $J = 4.4, 14.2$); 2.93 (q_{AB}, 2H, $J = 14.8$); 4.13–4.3 (m, 5H); 4.34 (d, 1H, $J = 6.8$); 4.4 (dd, 1H, $J = 4.4, 7$); 5.28 (s, 1H); 5.35 (s, 1H). ^{13}C NMR (CD_3OD) δ 14.5, 18.8, 19.7, 20.0, 22.8, 30.9, 31.6, 40.8, 42.0, 52.4, 59.8, 61.1, 61.7, 62,2, 62.4, 123.7, 137.2, 142.2, 170.3, 172.7, 172.8. IR ($CHCl_3$) $\nu_{cm^{-1}}$: 1545 (N–C=O), 1690 (N–C=O), 1730 (ester), 3150–3300 (NH and NH_3^+).

5.28. Tripeptide [(L)-Val ethylester-2-allyl-4-methylene-(2*R*,6*R*)-DAP-(L)-Val ethyl ester]·2HCl, 13b

Compound **13b** was obtained in 95% yield by submitting **12b** to acid hydrolysis as described for **4**. The product, isolated in semisolid state, was not recovered in a sufficiently pure form to measure the specific rotation. ^{1}H NMR (CD_3OD) δ 0.92–1.18 (m, 12H); 1.31 (t, 6H, $J = 7.2$); 2.23–2.57 (m, 3H); 2.44 (d, 1H, $J = 13.6$); 2.72 (m, 1H); 2.7 (d, 1H, $J = 13.6$); 3.82 (d, 1H, $J = 3$); 4.15–4.4 (m, 6H); 5.2 (m, 4H); 5.8 (m, 1H). ^{13}C NMR (CD_3OD) δ 14.5, 17.4, 18.7, 19, 19.6, 31.7, 32.9, 40.8, 45.4, 52.8, 59.7, 61.2, 62.4, 64.5, 120.7, 122.6, 133.2, 139, 169.7, 170.1, 171.2, 172.8. IR ($CHCl_3$) $\nu_{cm^{-1}}$: 1550 (N–C=O), 1685 (N–C=O), 1735 (ester), 3150–3300 (NH and NH_3^+).

5.29. (3*S*,6*R*)-4-Benzyl-6-methyl-8-methylene-2,5-diketo-3-isopropyl-1,4-diazabicyclo[4,3,0] nonane, 14

Compound **14** was obtained as an oil by following the procedure used for preparing **2**. ^{1}H NMR δ 1.07 (d, 3H, $J = 6.9$); 1.18 (d, 3H, $J = 6.9$); 1.58 (s, 3H); 2.25 (m, 1H); 2.75 (br s, 2H); 3.72 (d, 1H, $J = 6.2$); 3.92 (m, 1H); 3.94 (d, 1H, $J = 14.8$); 4.61 (m, 1H); 5.18 (m, 2H); 5.48 (d, 1H, $J = 14.8$); 7.17–7.43 (m, 5ArH). ^{13}C NMR δ 18.6, 20, 24.5, 31.5, 45.6, 47.9, 48.4, 63.8, 65.6, 109.2, 127.3, 128.4, 135.5, 140.1, 163.1, 169.3. IR (neat) $\nu_{cm^{-1}}$: 1675 (N–C=O).

Acknowledgements

Thanks are due to the MIUR (COFIN 2002) and to the University of Bologna ('Ricerca fondamentale orientata') for financial supports.

References and notes

1. Paradisi, F.; Porzi, G.; Rinaldi, S.; Sandri, S. *Tetrahedron: Asymmetry* **2000**, *11*, 1259–1262.
2. Paradisi, F.; Porzi, G.; Rinaldi, S.; Sandri, S. *Tetrahedron: Asymmetry* **2000**, *11*, 4617–4622.
3. Paradisi, F.; Piccinelli, F.; Porzi, G.; Sandri, S. *Tetrahedron: Asymmetry* **2002**, *13*, 497–502.
4. Ferioli, F.; Piccinelli, F.; Porzi, G.; Sandri, S. *Tetrahedron: Asymmetry* **2002**, *13*, 1181–1187.
5. Piccinelli, F.; Porzi, G.; Sandri, M.; Sandri, S. *Tetrahedron: Asymmetry* **2003**, *14*, 393–398.
6. Williams, R. M.; Yuan, C. *J. Org. Chem.* **1992**, *57*, 6519.
7. Dereppe, C.; Bold, G.; Ghisalba, O.; Erbert, E.; Schar, H. P. *Plant Physiol.* **1992**, *98*, 813.
8. Girodeau, J. M.; Agouridas, C.; Masson, M.; Pineaau, R.; Le Goffic, F. *J. Med. Chem.* **1986**, *29*, 1023.
9. Paradisi, F.; Porzi, G.; Sandri, S. *Tetrahedron: Asymmetry* **2001**, *12*, 3319–3324.
10. Galeazzi, R.; Garavelli, M.; Grandi, A.; Monari, M.; Porzi, G.; Sandri S. *Tetrahedron: Asymmetry*, **2003**, *14*, 2639–2649.
11. Fernandez, M. M.; Diez, A.; Rubiralta, M.; Montenegro, E.; Casamitjana, N. *J. Org. Chem.* **2002**, *67*, 7587; Trabocchi, A.; Occhiato, E. G.; Potenza, D.; Guarna, A. *J. Org. Chem.* **2002**, *67*, 7483; Belvisi, L.; Bernardi, A.; Manzoni, L.; Potenza, D.; Scolastico, C. *Eur. J. Org. Chem.* **2000**, 2563, and references cited therein.
12. Estiarte, M. A.; Rubiralta, M.; Diez, A. *J. Org. Chem.* **2000**, *65*, 6992–6999.