Stereocontrolled Synthesis of Unnatural Tetrapeptides Containing L-Valine Units

Part 3[1])

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The stereoselective synthesis of the new nonproteinogenic branched tetrapeptides **9a**–**9d** and **15a**,**b**, containing two L-valine units and unnatural α-amino acids, was accomplished starting from the chiral synthon **1a**, a monolactim ether easily obtained from L-valine.

Introduction. – The present communication is a continuation of our studies directed at the stereoselective synthesis of pseudopeptides with the objective that the unnatural peptides, as some natural ones, could exhibit biological activity with the advantage of proteolytic stability. The presence of α-alkyl α-amino acids may influence the conformation of these unnatural peptides altering their properties [3]. Thus, we have focused our attention towards new peptidomimetic structures containing nonproteinogenic α-alkylated α-amino acids (modified proline or aspartic acid) and L-valine units [4]. This communication is connected with previous articles which addressed the stereocontrolled synthesis of unnatural tetrapeptides, C-terminal at both ends of the chain, containing L-valine units [1][2]. Here, we report a versatile and simple approach to the stereoselective synthesis of branched unnatural tetrapeptides containing two L-valine units, one 2-methyl-D-aspartic acid and one other α-amino acid. The latter α-amino acid was either (2*R*)-2,4-diaminobutanoic acid (in **9a**), its (2*R*)-2-methyl (*i.e.*, D-isovaline; in **9b**), or its (2*S*)-2-methyl derivative (*i.e.*, L-isovaline; in **15a**), or D-ornithine (in **9c**), its 2-methyl (in **9d**), or the corresponding 2-methyl-L derivative (in **15b**).

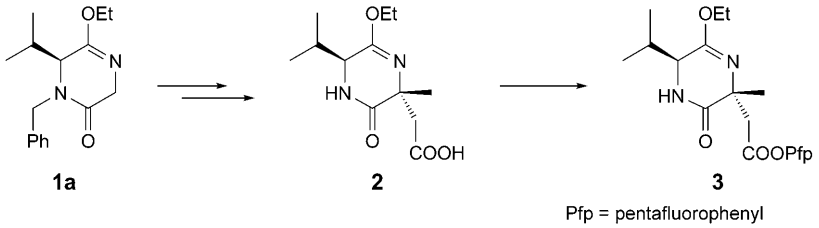
The synthetic strategy adopted in the stereocontrolled synthesis of the title pseudotetrapeptides is based on the experience already acquired in previous approaches [1][2][4] making use of the chiral monolactim ether **1a**, easily obtained from L-valine [5]. *Schöllkopf*'s strategy, aimed to the asymmetric synthesis of nonproteinogenic dipeptides, was based on the use of the bis-lactim ether which is subsequently converted to the corresponding monolactim derivative [6].

Result and Discussion. – The stereoselective synthesis of unnatural tetrapeptides **8a**–**8d** and **14a**,**b** was performed making use of the chiral synthons **2** or **3**, **4a**–**4d** and

[1]) For Part 1 and 2, see [1][2].

10a,**b** (synthesized as reported in [4c] and [2], resp.), starting from the chiral monolactim ether **1a** (*Schemes 1–3*).

Scheme 1

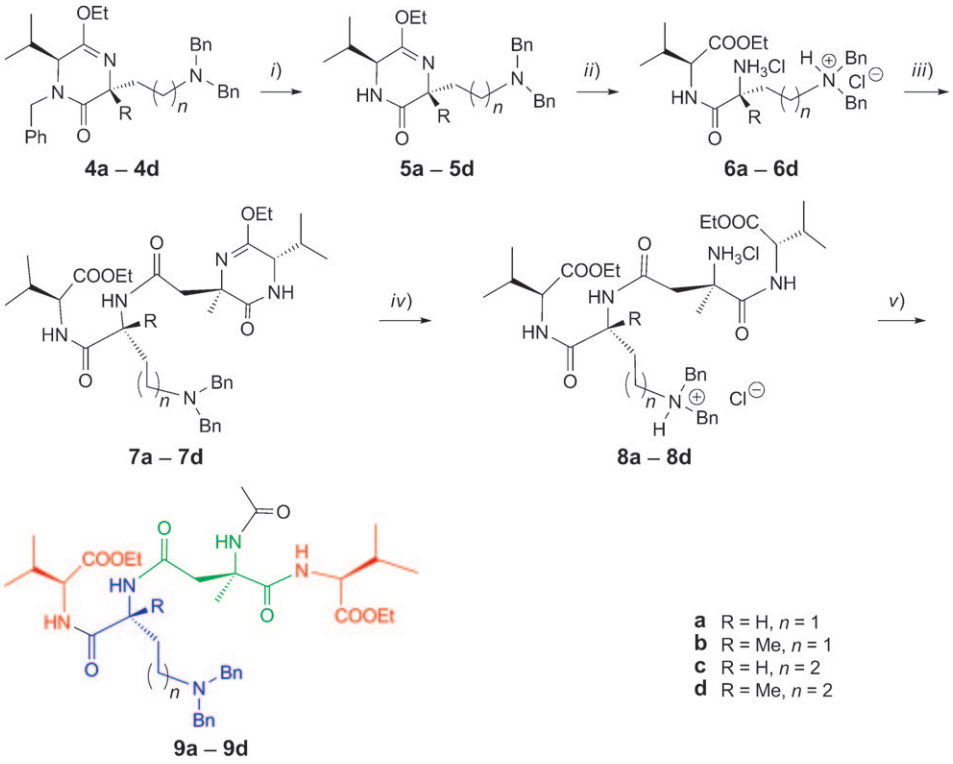


The intermediates **5a**–**5d** were obtained in very good yields by hydrogenolysis under *Birch* conditions [4f] of the 3-(aminoalkyl)-substituted 5-ethoxy-3,6-dihydro-6-isopropylpyrazin-2(1*H*)-ones **4a**–**4d**. The subsequent acidic hydrolysis under mild conditions gave the salts **6a**–**6d**, which can act as a nucleophile through the newly formed α-amino group (*Scheme 2*). These intermediates were then treated with electrophile **3**, synthesized starting from the chiral synthon **1a**, as already reported [4c] (*Scheme 1*). The coupling reaction between **6a**,**c** and the activated ester **3** to give **7a**,**c** occurred in good yields. Conversely, the substrates **6b**,**d** did not react with **3** even by refluxing in THF. The products **7b**,**d** were obtained in satisfactory yields by carrying out the coupling reaction with acid **2** in the presence of the activating reagent 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride [4b] (DMTMM) (*Scheme 2*). The different reactivity of the substrates **6a**,**c** and **6b**,**d** is most likely due to the greater steric hindrance of the latter substrate caused by the presence of a Me group at the C(α) with respect to the NH_2 group. The acidic hydrolysis of **7a**–**7d** under mild conditions gave the pseudotetrapeptides **8a**–**8d** which were converted into the corresponding acetyl derivatives **9a**–**9d** containing two L-valine units (red), 2-methyl-D-aspartic acid (green), and either D-ornithine or its 2-methyl derivative and (2*R*)-2,4-diaminobutanoic acid or its (2*R*)-2-methyl derivative (*i.e.*, D-isovaline; blue; *Scheme 2*).

To synthesize the tetrapseudopeptides **14a**,**b** (*Scheme 3*), which differ from **8b**,**d** in the configuration of 2-methylornithine unit, we employed the masked dipeptides **10a**,**b**, which were easily obtained starting from the chiral synthon **1a** [2]. After debenzylation of **10a**,**b**, performed under *Birch* conditions, the intermediates **11a**,**b** were recovered and subsequently hydrolyzed under mild acidic conditions. The amino derivatives **12a**,**b** obtained were treated with acid **2** in the presence of DMTMM [4b] to yield **13a**,**b**, which, following the same reaction sequence as described in *Scheme 2*, furnished *via* the **14a**,**b** tetrapseudopeptides **15a**,**b** as the acetyl derivatives in overall satisfactory yields (*Scheme 3*).

The authors are grateful to Prof. *Sergio Sandri* for helpful advice and discussions and to the University of Bologna for financial support ('Ricerca Fondamentale Orientata').

Scheme 2



i) Li/NH_3, −78°, dry THF/^{t}BuOH 9:1. *ii*) 0.5N HCl in EtOH, r.t. *iii*) **6a**,**c** was treated with **3** in CH_2Cl_2/Et_3N, while **6b**,**d** was treated with **2** in THF/Et_3N in the presence of DMTMM [4b]. *iv*) 0.5N HCl in EtOH, r.t. *v*) AcCl in CH_2Cl_2/Et_3N.

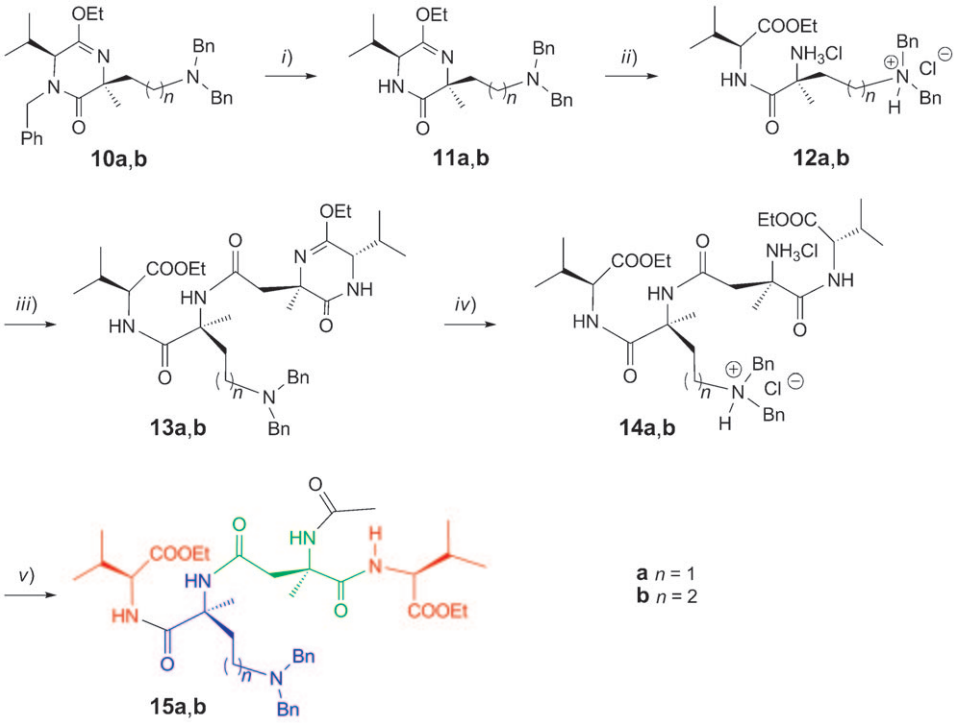
Experimental Part

General. Dry THF was distilled from sodium benzophenone ketyl (=sodium diphenylketyl). Column chromatography (CC): silica gel *60* (SiO_2; 230–400 mesh); eluent hexane/AcOEt. Optical rotation: *Perkin-Elmer-343* polarimeter; at 25°. ^{1}H- and ^{13}C-NMR Spectra: *Gemini* spectrometer, at 300 and 75 MHz, resp.; $CDCl_3$ as solvent, unless otherwise stated; δ in ppm rel. to $CDCl_3$, J in Hz.

The synthesis and spectroscopic data of compounds **2** and **3** are reported in [4c] and the data of compounds **4a**–**4d** and **10a**,**b** in [2].

*(3*R*,6*S*)-3-[2-(Dibenzylamino)ethyl]-5-ethoxy-3,6-dihydro-6-isopropylpyrazin-2(1*H*)-one* (**5a**). Intermediate **4a** (5 g, 10 mmol) in dry THF/^{t}BuOH 9:1 (40 ml), was added to a soln. of Li (0.07 g, 10 mmol) in liq. NH_3 (*ca.* 60 ml), cooled at *ca.* −78°, and stirred under Ar. After 5 min, the reaction was quenched with NH_4Cl (1 g) and the cooling bath removed allowing the complete evaporation of NH_3. After addition of H_2O, the product was extracted with AcOEt, and the org. soln. concentrated, and the residue subjected to CC: **5a** (85% after CC). Oil. $[\alpha]_D^{25} = +62.9$ ($c = 1.1$, $CHCl_3$). ^{1}H-NMR: 0.86 (*d*, $J = 7$, 3 H); 0.98 (*d*, $J = 7$, 3 H); 1.15 (*t*, $J = 7.2$, 3 H); 1.88–1.98 (*m*, 1 H); 2.06–2.4 (*m*, 2 H); 2.64 (*t*, $J = 7$, 2 H); 3.59 (*q*, *AB*, $J = 13.6$, 4 H); 3.7–3.9 (*m*, 3 H); 4.0–4.14 (*m*, 1 H); 5.95–6.1 (br. *s*, 1 H); 7.2–7.4 (*m*, 10 arom. H). ^{13}C-NMR: 14.0; 16.2; 18.1; 30.9; 32.1; 49.2; 55.3; 58.1; 58.2; 60.8; 126.4; 127.8; 128.7; 139.8; 158.2; 172.8. Anal. calc. for $C_{25}H_{33}N_3O_2$ (407.26): C 73.68, H 8.16, N 10.31; found: C 73.92, H 8.18, N 10.28.

Scheme 3



i) Li/NH_3, −78°, dry THF/^{t}BuOH 9 : 1. *ii*) 0.5N HCl in EtOH, r.t. *iii*) **2** in the presence of DMTMM [4b] in THF/Et_3N. *iv*) 0.5N HCl in EtOH, r.t. *v*) AcCl in CH_2Cl_2/Et_3N.

*(3*R,6S*)-3-[2-(Dibenzylamino)ethyl]-5-ethoxy-3,6-dihydro-6-isopropyl-3-methylpyrazin-2(1*H*)-one* (**5b**). As described for **5a**, from **4b**: **5b** (88% after CC). Oil. $[\alpha]_D^{25} = +14.3$ ($c = 1.4$, $CHCl_3$). ^{1}H-NMR: 0.83 (*d*, *J* = 7, 3 H); 0.96 (*d*, *J* = 7, 3 H); 1.15 (*t*, *J* = 7, 3 H); 1.41 (*s*, 3 H); 1.77–1.87 (*m*, 1 H); 2.05–2.42 (*m*, 4 H); 3.62 (*s*, 4 H); 3.7–4.02 (*m*, 3 H); 5.72–5.78 (br. *s*, 1 H); 7.2–7.4 (*m*, 10 arom. H). ^{13}C-NMR: 13.9; 16.1; 18.2; 28.8; 30.9; 38.3; 48.6; 58.0; 58.2; 58.7; 60.6; 126.4; 127.8; 128.6; 139.6; 156.1; 174.3. Anal. calc. for $C_{26}H_{35}N_3O_2$ (421.58): C 74.07, H 8.37, N 9.97; found: C 74.34, H 8.39, N 9.95.

*(3*R,6S*)-3-[3-(Dibenzylamino)propyl]-5-ethoxy-3,6-dihydro-6-isopropylpyrazin-2(1*H*)-one* (**5c**). As described for **5a**, from **4c**: **5c** (83% after CC). Oil. $[\alpha]_D^{25} = +47.1$ ($c = 1.0$, $CHCl_3$). ^{1}H-NMR: 0.86 (*d*, *J* = 7, 3 H); 0.98 (*d*, *J* = 7, 3 H); 1.27 (*t*, *J* = 7.2, 3 H); 1.5–2.0 (*m*, 4 H); 2.1–2.3 (*m*, 1 H); 2.46 (*t*, *J* = 7, 2 H); 3.57 (*s*, 4 H); 3.8–3.84 (*m*, 1 H); 4.0–4.2 (*m*, 3 H); 5.98–6.14 (br. *s*, 1 H); 7.2–7.44 (*m*, 10 arom. H). ^{13}C-NMR: 14.0; 16.1; 18.0; 22.1; 31.5; 32.0; 52.9; 57.0; 58.0; 58.1; 60.9; 126.4; 127.9; 128.6; 139.7; 158.3; 172.6. Anal. calc. for $C_{26}H_{35}N_3O_2$ (421.58): C 74.07, H 8.37, N 9.97; found: C 73.84, H 8.35, N 10.01.

*(3*R,6S*)-3-[3-Dibenzylamino)propyl]-5-ethoxy-3,6-dihydro-6-isopropyl-3-methylpyrazin-2(1*H*)-one* (**5d**). As described for **5a**, from **4d**: **5d** (85%). Oil. $[\alpha]_D$: product not sufficiently pure. ^{1}H-NMR: 0.86 (*d*, *J* = 7, 3 H); 0.99 (*d*, *J* = 7, 3 H); 1.2–1.36 (*m*, 3 H); 1.41 (*s*, 3 H); 1.30–1.45 (*m*, 2 H); 1.48–1.6 (*m*, 1 H); 1.88–2.0 (*m*, 1 H); 2.2–2.3 (*m*, 1 H); 2.41 (*t*, *J* = 6.9, 2 H); 3.55 (*q*, *AB*, *J* = 14.8, 4 H); 3.76–3.88 (*m*, 1 H); 4.05–4.15 (*m*, 2 H); 5.64–5.8 (br. *s*, 1 H); 7.15–7.45 (*m*, 10 arom. H). ^{13}C-NMR: 14.1; 16.0; 18.2; 21.8; 28.7; 30.9; 39.5; 53.3; 58.0; 58.2; 59.8; 60.7; 126.5; 127.9; 128.6; 139.7; 156.1; 174.6.

N-*[(2*R*)-2-Amino-4-(dibenzylamino)]-1-oxobutyl]-*L*-valine Ethyl Ester Hydrochloride (1:2)* (**6a**). To a soln. of **5a** (4.07 g, 10 mmol) in EtOH (60 ml) was added 0.5M HCl (20 ml), and the mixture was

stirred at r.t. for *ca.* 12 h. The acidic soln. was concentrated, and the crude product stirred with a 10% aq. K_2CO_3 soln. The product was extracted with AcOEt, the org. soln. washed with H_2O, and the org. solvent evaporated: **6a** (90%). Wax. $[\alpha]_D^{25} = -31.4$ ($c = 1.5$, MeOH). ^{1}H-NMR (CD_3OD): 0.87 (*d*, *J* = 6.9, 3 H); 0.93 (*d*, *J* = 6.9, 3 H); 1.31 (*t*, *J* = 7.2, 3 H); 2.0–2.2 (*m*, 1 H); 2.4–2.6 (*m*, 2 H); 3.20–3.44 (*m*, 2 H); 4.1–4.3 (*m*, 4 H); 4.4–4.6 (br. *s*, 4 H); 4.95 (*s*, 4 H); 7.45–7.75 (*m*, 10 arom. H). ^{13}C-NMR (CD_3OD): 14.8; 19.2; 19.8; 27.5; 31.7; 52.3; 58.7; 59.8; 59.9; 62.6; 130.6; 131.3; 132.8; 169.3; 172.6. Anal. calc. for $C_{25}H_{37}Cl_2N_3O_3$ (498.49): C 60.24, H 7.48, N 8.43; found: C 59.89, H 7.07, N 8.71.

*4-(Dibenzylamino)-*D*-isovalyl-*L*-valine Ethyl Ester Hydrochloride (1:2)* (**6b**). As described for **6a**, from **5b**: **6b** (89% after CC). Wax. $[\alpha]_D^{25} = -21.6$ ($c = 0.2$, MeOH). ^{1}H-NMR (CD_3OD): 0.90 (*d*, *J* = 7, 3 H); 0.92 (*d*, *J* = 7, 3 H); 1.28 (*t*, *J* = 7, 3 H); 1.7 (*s*, 3 H); 2.0–2.2 (*m*, 1 H); 2.6–2.8 (*m*, 2 H); 3.0–3.4 (*m*, 2 H); 4.1–4.3 (*m*, 3 H); 4.3–4.6 (*m*, 4 H); 7.4–7.66 (*m*, 10 arom. H). ^{13}C-NMR: 14.8; 19.8; 20.1; 22.8; 31.3; 32.4; 58.8; 60.4; 61.0; 62.6; 130.6; 130.8; 131.6; 132.9; 171.3; 172.7. Anal. calc. for $C_{26}H_{39}Cl_2N_3O_3$ (512.51): C 60.93, H 7.67, N 8.2; found: C 61.03, H 7.69, N 8.18.

N^5,N^5*-Dibenzyl-*D*-ornithyl-*L*-valine Ethyl Ester Hydrochloride (1:2)* (**6c**). As described for **6a**, from **5c**: **6c** (86% after CC). Wax oil. $[\alpha]_D^{25} = -22.9$ ($c = 1.0$, MeOH). ^{1}H-NMR (CD_3OD): 1.0 (*d*, *J* = 6.9, 3 H); 1.01 (*d*, *J* = 6.9, 3 H); 1.32 (*t*, *J* = 7, 3 H); 1.8–2.1 (*m*, 5 H); 2.14–2.26 (*m*, 1 H); 3.1–3.2 (*m*, 2 H); 4.04–4.16 (*m*, 1 H); 4.2–4.3 (*q*, *J* = 7, 2 H); 4.3–4.48 (*m*, 4 H); 7.4–7.65 (*m*, 10 arom. H). ^{13}C-NMR (CD_3OD): 14.8; 19.0; 19.9; 21.0; 30.2; 31.8; 52.9; 54.0; 58.3; 59.7; 59.8; 62.5; 130.5; 130.8; 131.3; 132.7; 170.4; 172.8. Anal. calc. for $C_{26}H_{39}Cl_2N_3O_3$ (512.51): C 60.93, H 7.67, N 8.2; found: C 60.81, H 7.7, N 8.16.

N^5,N^5*-Dibenzyl-2-methyl-*D*-ornithyl-*L*-valine Ethyl Ester Hydrochloride (1:2)* (**6d**). As described for **6a**, from **5d**: **6d** (88% after CC). Wax. $[\alpha]_D^{25} = -19.1$ ($c = 1.2$, $CHCl_3$). ^{1}H-NMR (CD_3OD): 0.99 (*d*, *J* = 7, 6 H); 1.3 (*t*, *J* = 6.9, 3 H); 1.67 (*s*, 3 H); 1.8–2.0 (*m*, 3 H); 2.0–2.3 (*m*, 2 H); 3.14 (*t*, *J* = 7.2, 2 H); 4.12–4.3 (*m*, 3 H); 4.44 (*s*, 4 H); 7.45–7.65 (*m*, 10 arom. H). ^{13}C-NMR (CD_3OD): 14.8; 19.7; 19.9; 22.8; 31.3; 35.1; 52.9; 58.6; 60.8; 61.5; 62.5; 130.7; 130.8; 131.5; 132.8; 172.4; 172.9. Anal. calc. for $C_{27}H_{41}Cl_2N_3O_3$ (526.54): C 61.59, H 7.85, N 7.98; found: C 61.38, H 7.87, N 7.97.

N-*{(2*R*)-4-(Dibenzylamino)-2-{[2-[(2*R*,5*S*)-6-ethoxy-2,3,4,5-tetrahydro-2-methyl-5-isopropyl-3-oxopyrazin-2-yl]acetyl}amino}-1-oxobutyl}-*L*-valine Ethyl Ester* (**7a**). The activated ester **3** (1.81 g, 4.3 mmol) was added to a soln. of **6a** (2.15 g, 4.3 mmol) and Et_3N (1.8 ml, 13 mmol) in dry CH_2Cl_2 (30 ml) under Ar, and the mixture was stirred at r.t. for 24 h. The org. phase was rapidly washed with 0.1M HCl, then with H_2O, and dried ($CaCl_2$). After evaporation the residue was purified by CC: **7a** (85%). Oil. $[\alpha]_D^{25} = +20.0$ ($c = 0.2$, $CHCl_3$). ^{1}H-NMR: 0.8–1.0 (*m*, 12 H); 1.2–1.4 (*m*, 6 H); 1.42 (*s*, 3 H); 1.88–2.18 (*m*, 2 H); 2.18–2.38 (*m*, 1 H); 2.45 (*d*, *J* = 15, 1 H); 2,5–2.7 (*m*, 3 H); 2.86 (*d*, *J* = 15, 1 H); 3.5–3.7 (br. *s*, 4 H); 4.0–4.3 (*m*, 5 H); 4.32–4.4 (*dd*, *J* = 5.7, 8.1, 1 H); 4.4–4.58 (*m*, 1 H); 5.71 (br. *s*, 1 H); 6.77 (*d*, *J* = 8.7, 1 H); 7.2 (*d*, *J* = 8.1, 1 H); 7.24–7.42 (*m*, 10 arom. H). ^{13}C-NMR: 14.0; 16.2; 17.9; 18.1; 18.9; 28.6; 30.5; 30.7; 47.3; 50.3; 52.5; 57.3; 7.8; 58.4; 58.7; 61.3; 61.5; 127.0; 128.2; 129.0; 138.6; 157.6; 171.0; 171.8; 172.6. Anal. calc. for $C_{37}H_{53}N_5O_6$ (663.85): C 66.94, H 8.05, N 10.55; found: C 67.05, H 8.03, N 10.52.

*4-(Dibenzylamino)-*N*-{2-[(2*R*,5*S*)-6-ethoxy-2,3,4,5-tetrahydro-2-methyl-5-isopropyl-3-oxopyrazin-2-yl]acetyl}-*D*-isovalyl-*L*-valine Ethyl Ester* (**7b**). The intermediate **6b** (1.02 g, 2 mmol) was added to a soln. of **2** (0.51 g, 2 mmol) dissolved in dry THF (15 ml) and Et_3N (0.55 ml, 4 mmol). After 10 min, DMTMM [4b] (0.56 g, 2.4 mmol) was added, and the mixture was stirred at r.t. for 12 h. The mixture was concentrated, and the residue dissolved with AcOEt. The org. soln. was washed with 1M NaOH and then with 1M HCl and concentrated. The residue was purified by CC: **7b** (*ca.* 70%). Oil. $[\alpha]_D^{25} = +33.4$ ($c = 2.5$, $CHCl_3$). ^{1}H-NMR: 0.84–0.94 (*m*, 9 H); 0.99 (*d*, *J* = 7, 3 H); 1.23 (*t*, *J* = 7, 3 H); 1.26 (*t*, *J* = 7, 3 H); 1.40 (*s*, 3 H); 1.43 (*s*, 3 H); 1.9–2.3 (*m*, 4 H); 2.39 (*d*, *J* = 15, 1 H); 2.6–2.78 (*m*, 2 H); 2.95 (*d*, *J* = 15, 1 H); 3.58 (*q*, *AB*, *J* = 13.2, 4 H); 3.98–4.28 (*m*, 5 H); 4.38 (*dd*, *J* = 5.4, 8.4, 1 H); 5.99 (br. *s*, 1 H); 7.18–7.4 (*m*, 10 arom. H, 1 CONH); 8.19 (br. *s*, 1 H). ^{13}C-NMR: 13.8; 13.9; 16.1; 17.8; 18.2; 18.7; 22.7; 28.7; 30.4; 30.7; 33.9; 47.7; 49.7; 57.4; 57.9; 58.2; 58.4; 60.6; 60.7; 61.1; 126.9; 128.1; 129.0; 138.2; 157.2; 170.1; 171.6; 173.4; 173.7. Anal. calc. for $C_{38}H_{55}N_5O_6$ (677.87): C 67.33, H 8.18, N 10.33; found: C 67.24, H 8.2, N 10.35.

N^2-*{2-[(2*R*,5*S*)-6-Ethoxy-2,3,4,5-tetrahydro-2-methyl-5-isopropyl-3-oxopyrazin-2-yl]acetyl}*-N^5,N^5-*dibenzyl-*D*-ornithyl-*L*-valine Ethyl Ester* (**7c**). As described for **7a**, from **6c**: pure **7c** (80% after CC). Oil. $[\alpha]_D^{25} = +13.8$ ($c = 1.0$, $CHCl_3$). ^{1}H-NMR: 0.8–1.16 (*m*, 12 H); 1.18–1.38 (*m*, 6 H); 1.4–2.0 (*m*, 4 H); 1.46 (*s*, 3 H); 2.03–2.25 (*m*, 2 H); 2.38–2.48 (*m*, 2 H); 2.74 (*q*, *AB*, *J* = 15, 2 H); 3.57 (*s*, 4 H); 3.96–4.30 (*m*, 5 H); 4.30–4.50 (*m*, 2 H); 5.97 (br. *s*, 1 H); 6.56 (*d*, *J* = 8.4, 1 H); 6.91 (*d*, *J* = 7.8, 1 H); 7.2–7.5 (*m*, 10

arom. H). ^{13}C-NMR: 14.0; 14.1; 16.3; 17.7; 18.3; 18.9; 23.2; 27.9; 30.2; 30.9; 31.0; 47.0; 52.7; 52.9; 57.0; 58.1; 58.4; 58.6; 61.0; 61.6; 126.7; 128.1; 128.6; 139.5; 157.5; 170.1; 171.6; 173.2. Anal. calc. for $C_{38}H_{55}N_5O_6$ (677.87): C 67.33, H 8.18, N 10.33; found: C 67.45, H 8.21, N 10.3.

N^2-*{2-[(2*R,5S*)-6-Ethoxy-2,3,4,5-tetrahydro-2-methyl-5-isopropyl-3-oxopyrazin-2-yl]acetyl}*-N^5,N^5-*dibenzyl-2-methyl*-D-*ornithyl*-L-*valine Ethyl Ester* (**7d**). As described for **7b**, from **6d**: **7d** (65% after CC). $[\alpha]_D$: product not sufficiently pure. ^{1}H-NMR: 0.8–1.0 (*m*, 12 H); 1.2–1.3 (*m*, 6 H); 1.47 (*s*, 3 H); 1.53 (*s*, 3 H); 1.6–1.8 (*m*, 3 H); 2.1–2.38 (*m*, 3 H); 2.42 (*t*, *J* = 6.6, 2 H); 2.54 (*d*, *J* = 14.4, 1 H); 2.97 (*d*, *J* = 14.4, 1 H); 3.57 (*s*, 4 H); 4.0–4.3 (*m*, 5 H); 4.49 (*dd*, *J* = 5.5, 8.1, 1 H); 5.75 (br. *s*, 1 H); 6.8 (*s*, 1 H); 6.85 (*d*, *J* = 8.4, 1 H); 7.2–7.4 (*m*, 10 arom. H). ^{13}C-NMR: 14.0; 14.1; 16.2; 17.7; 18.3; 18.9; 21.6; 23.1; 28.4; 30.8; 31.0; 35.3; 48.1; 53.1; 57.4; 58.0; 58.6; 58.7; 60.4; 61.0; 61.4; 126.7; 128.0; 128.7; 139.4; 157.3; 169.8; 171.8; 173.4; 173.8.

N-*{(1*R*)-3-(Dibenzylamino)-1-{{[(1*S*)-1-(ethoxycarbonyl)-2-methylpropyl]amino}carbonyl}propyl}-2-methyl*-D-*asparaginyl*-L-*valine Ethyl Ester Hydrochloride (1:2)* (**8a**). As described for **6a**, by submitting **7a** to acid hydrolysis: **8a** (70% after CC). Wax. $[\alpha]_D^{25} = -18$ (*c* = 0.3, MeOH). ^{1}H-NMR (CD_3OD): 0.9–1.14 (*m*, 12 H); 1.3 (*t*, *J* = 7, 6 H); 1.68 (*s*, 3 H); 2.02–2.42 (*m*, 4 H); 3.03 (*d*, *J* = 16.5, 1 H); 3.25 (*d*, *J* = 16.5, 1 H); 3.3–3.4 (*m*, 2 H); 4.1–4.36 (*m*, 6 H); 4.4–4.6 (*m*, 5 H); 7.5–7.7 (*m*, 10 arom. H). ^{13}C-NMR (CD_3OD): 14.9; 19.1; 19.4; 19.9; 20.0; 22.8; 28.0; 31.6; 32.0; 39.3; 41.4; 51.8; 52.9; 58.9; 59.7; 60.5; 62.5; 62.6; 130.8; 131.0; 131.5; 132.7; 171.4; 172.3; 172.8; 172.9; 173.0. Anal. calc. for $C_{37}H_{57}Cl_2N_5O_7$ (754.78): C 58.88, H 7.61, N 9.28; found: C 58.78, H 7.62, N 9.25.

N-*[(1*S*)-1-(Ethoxycarbonyl)-2-methylpropyl]-2-methyl*-D-*α-asparaginyl-4-(dibenzylamino)*-D-*isovalyl*-L-*valine Ethyl Ester Hydrochloride (1:2)* (**8b**). As described for **6a**, by submitting **7b** to acid hydrolysis: **8b** (65% after CC). Wax. $[\alpha]_D$: product not sufficiently pure. ^{1}H-NMR (CD_3OD): 0.9–1.1 (*m*, 12 H); 1.2–1.4 (*m*, 9 H); 1.73 (*s*, 3 H); 2.1–2.34 (*m*, 3 H); 2.75–2.85 (*m*, 1 H); 3.03 (*q*, *AB*, *J* = 16.2, 2 H); 3.3–3.4 (*m*, 2 H); 4.15–4.35 (*m*, 10 H); 7.4–7.7 (*m*, 10 arom. H). ^{13}C-NMR (CD_3OD): 14.8; 14.9; 19.1; 19.6; 19.8; 20.1; 22.5; 24.0; 31.6; 32.0; 32.8; 41.9; 58.3; 58.9; 59.5; 59.9; 60.8; 60.9; 62.6; 130.7; 130.8; 131.5; 132.6; 171.1; 172.3; 172.8; 1750; 176.2.

N-*[(1*S*)-1-(Ethoxycarbonyl)-2-methylpropyl]-2-methyl*-D-*α-asparaginyl*-N^5,N^5-*dibenzyl*-D-*ornithyl*-L-*valine Ethyl Ester Hydrochloride (1:2)* (**8c**). As described for **6a**, by submitting **7c** to acid hydrolysis: **8c** (70% after CC). Wax. $[\alpha]_D$: product not sufficiently pure. ^{1}H-NMR (CD_3OD): 0.9–1.1 (*m*, 12 H); 1.1–1.4 (*m*, 6 H); 1.69 (*s*, 3 H); 1.7–1.9 (*m*, 2 H); 1.9–2.1 (*m*, 2 H); 2.1–2.3 (*m*, 2 H); 3.03 (*d*, *J* = 17.1, 1 H); 3.1–3.24 (*m*, 2 H); 3.34 (*d*, *J* = 17.1, 1 H); 4.1–4.28 (*m*, 4 H); 4.29 (*d*, *J* = 6.6, 1 H); 4.30 (*d*, *J* = 6.6, 1 H); 4.38–4.58 (*m*, 5 H); 7.45–7.65 (*m*, 10 arom. H). ^{13}C-NMR (CD_3OD): 14.9; 19.1; 19.5; 19.9; 20.2; 21.6; 23.0; 30.6; 31.5; 31.9; 41.2; 53.4; 54.3; 58.4; 59.6; 59.7; 60.4; 60.5; 62.4; 130.7; 130.9; 131.4; 132.7; 171.3; 172.3; 172.9; 173.2; 173.8.

N-*[(1*S*)-1-(Ethoxycarbonyl)-2-methylpropyl]-2-methyl*-D-*α-asparaginyl*-N^5,N^5-*dibenzyl-2-methyl*-D-*ornithyl*-L-*valine Ethyl Ester Hydrochloride (1:2)* (**8d**). As described for **6a**, by submitting **7d** to acid hydrolysis: **8d** (66% after CC). Wax. $[\alpha]_D^{25} = -9.7$ (*c* = 0.7, MeOH). ^{1}H-NMR (CD_3OD): 0.9–1.1 (*m*, 12 H); 1.27 (*t*, *J* = 7.4, 3 H); 1.28 (*t*, *J* = 7.4, 3 H); 1.5 (*s*, 3 H); 1.69 (*s*, 3 H); 1.8–2.0 (*m*, 4 H); 2.1–2.3 (*m*, 2 H); 2.9–3.2 (*m*, 4 H); 4.1–4.3 (*m*, 6 H); 4.40 (*s*, 4 H); 7.4–7.6 (*m*, 10 arom. H). ^{13}C-NMR (CD_3OD): 14.8; 14.9; 19.6; 20.0; 22.9; 23.1; 31.5; 31.7; 35.9; 41.6; 53.5; 58.3; 58.5; 59.8; 60.1; 60.2; 60.6; 61.3; 62.5; 130.7; 131.0; 131.4; 132.7; 171.2; 172.3; 172.9; 173.8; 175.6. Anal. calc. for $C_{39}H_{61}Cl_2N_5O_7$ (782.84): C 59.84, H 7.85, N 8.95; found: C 60.04, H 7.87, N 8.92.

N^2-*Acetyl*-N-*[(1*R*)-3-(dibenzylamino)-1-{{[(1*S*)-1-(ethoxycarbonyl)-2-methylpropyl]amino}carbonyl}propyl]-2-methyl*-D-*asparaginyl*-L-*valine Ethyl Ester* (**9a**). Et_3N (0.3 ml, 2 mmol) was added to **8a** (1.5 g, 2 mmol) in CH_2Cl_2 (10 ml) and the soln. cooled to $-10°$. AcCl (0.15 ml, 2.1 mmol) was then added, and after 10–15 min, the cooling bath was removed. The mixture was stirred for 2–3 h (TLC monitoring) and then the org. solvent evaporated. The residue was dissolved in AcOEt, the org. soln. washed with 2N HCl, dried (Na_2SO_4), and concentrated, and the residue purified by CC: **9a** (90%). Oil. $[\alpha]_D$: product not sufficiently pure. ^{1}H-NMR: 0.9–1.0 (*m*, 12 H); 1.2–1.4 (*m*, 6 H); 1.67 (*s*, 3 H); 2.0–2.4 (*m*, 7 H); 2.6 (*d*, *J* = 14.2, 1 H); 2.93 (*d*, *J* = 14.2, 1 H); 3.0–3.18 (*m*, 2 H); 3.90–4.30 (*m*, 8 H); 4.3–4.46 (*m*, 2 H); 4.6–4.8 (*m*, 1 H); 7.3–7.7 (*m*, 10 arom. H, 1 CONH); 7.85 (br. *s*, 2 H); 8.15 (*d*, *J* = 8.0, 1 H). ^{13}C-NMR: 14.1; 17.6; 18.0; 18.1; 23.5; 24.0; 27.6; 29.6; 30.7; 30.9; 42.4; 50.3; 51.5; 57.2; 57.7; 59.5; 61.0; 61.2; 129.0; 130.6; 170.8; 171.4; 171.5; 171.6; 172.0; 173.7.

N^2-*Acetyl*-N-*[(1*S*)-1-(ethoxycarbonyl)-2-methylpropyl]-2-methyl*-D-*α-asparaginyl-4-(dibenzylamino)*-D-*isovalyl*-L-*valine Ethyl Ester* (**9b**). As described for **9a**, from **8b**: **9b** (85% after CC). Oil. $[\alpha]_D$: product not sufficiently pure. ^{1}H-NMR: 0.85–1.1 (*m*, 12 H); 1.23 (*t*, *J* = 7, 3 H); 125 (*t*, *J* = 7, 3 H); 1.39 (*s*, 3 H); 1.63 (*s*, 3 H); 2.01 (*s*, 3 H); 2.12–2.22 (*m*, 2 H); 2.38–2.5 (*m*, 3 H); 2.79 (*d*, *J* = 14.1, 1 H); 2.98–3.1 (*m*, 2 H); 3.95–4.23 (*m*, 8 H); 4.26–4.36 (*m*, 1 H); 4.36–4.41 (*m*, 1 H); 7.3–7.6 (*m*, 10 arom. H); 7.53 (*d*, *J* = 8.4, 1 H); 7.85 (br. *s*, 1 H); 7.99 (*d*, *J* = 8.1, 1 H); 8.16 (br. *s*, 1 H). ^{13}C-NMR: 14.0; 14.1; 17.8; 17.9; 18.9; 20.9; 23.3; 23.5; 23.8; 30.7; 30.8; 31.7; 42.9; 48.8; 56.9; 57.5; 57.8; 59.1; 59.7; 61.0; 128.8; 130.4; 171.1; 171.2; 171.8; 171.9; 173.6.

N^2-*Acetyl*-N-*[(1*S*)-1-(ethoxycarbonyl)-2-methylpropyl]-2-methyl*-D-*α-asparaginyl*-N^5,N^5-*dibenzyl*-D-*ornithyl*-L-*valine Ethyl Ester* (**9c**). As described for **9a**, from **8c**: **9c** (88% after CC). Oil. $[\alpha]_D^{25} = +33$ ($c = 1.9$, $CHCl_3$). ^{1}H-NMR: 0.9–1.0 (*m*, 12 H); 1.2–1.4 (*m*, 6 H); 1.5–1.7 (*m*, 3 H); 1.66 (*s*, 3 H); 1.9–2.0 (*m*, 1 H); 2.04 (*s*, 3 H); 2.18–2.28 (*m*, 2 H); 2.4–2.6 (*m*, 2 H); 2.62 (*d*, *J* = 13.8, 1 H); 3.02 (*d*, *J* = 13.8, 1 H); 3.5–3.7 (*m*, 4 H); 4.1–4.3 (*m*, 4 H); 4.3–4.4 (*m*, 1 H); 4.45 (*dd*, *J* = 4.8, 8.7, 1 H); 4.51 (*dd*, *J* = 4.8, 8.7, 1 H); 6.57 (*d*, *J* = 8.7, 1 H); 6.70 (*d*, *J* = 7.5, 1 H); 7.2–7.4 (*m*, 10 arom. H); 7.48 (*s*, 1 H); 8.37 (*d*, *J* = 8.1, 1 H). ^{13}C-NMR: 14.0; 17.4; 17.6; 18.8; 18.9; 22.9; 23.9; 29.2; 30.8; 30.9; 42.0; 52.6; 53.0; 57.0; 57.5; 58.1; 59.0; 60.9; 61.0; 126.7; 128.0; 128.6; 139.4; 170.9; 171.2; 171.5; 171.6; 173.6. Anal. calc. for $C_{40}H_{59}N_5O_8$ (737.93): C 65.11, H 8.06, N 9.49; found: C 64.98, H 8.04, N 9.52.

N^2-*Acetyl*-N-*[(1*S*)-1-(ethoxycarbonyl)-2-methylpropyl]-2-methyl*-D-*α-asparaginyl*-N^5,N^5-*dibenzyl-2-methyl*-D-*ornithyl*-L-*valine Ethyl Ester* (**9d**). As described for **9a**, from **8d**: pure **9d** (87% after CC). Oil. $[\alpha]_D^{25} = +27$ ($c = 0.7$, $CHCl_3$). ^{1}H-NMR: 0.9–1.0 (*m*, 12 H); 1.2–1.38 (*m*, 6 H); 1.48 (*s*, 3 H); 1.48–2.0 (*m*, 4 H); 1.69 (*s*, 3 H); 2.03 (*s*, 3 H); 2.1–2.3 (*m*, 2 H); 2.42 (*d*, *J* = 13.8, 1 H); 2.43–2.57 (*m*, 2 H); 2.94 (*d*, *J* = 13.8, 1 H); 3.57 (*s*, 4 H); 4.0–4.3 (*m*, 4 H); 4.38 (*dd*, *J* = 5.2, 8, 1 H); 4.52 (*dd*, *J* = 5, 8.4, 1 H); 6.73 (*d*, *J* = 8.4, 1 H); 6.83 (br. *s*, 1 H); 7.2–7.5 (*m*, 10 arom. H); 7.56 (*s*, 1 H); 8.24 (*d*, *J* = 8, 1 H). ^{13}C-NMR: 14.0; 17.7; 18.9; 19.0; 21.0; 22.8; 23.7; 24.0; 30.7; 31.1; 34.5; 43.4; 52.9; 57.1; 57.9; 58.0; 59.2; 60.3; 60.9; 61.0; 126.9; 128.1; 128.9; 138.7; 170.5; 171.1; 171.7; 171.9; 173.4; 173.7. Anal. calc. for $C_{41}H_{61}N_5O_8$ (751.95): C 65.49, H 8.18, N 9.31; found: C 65.75, H 8.15, N 9.33.

*(3*S*,6*S*)-3-[2-(Dibenzylamino)ethyl]-5-ethoxy-3,6-dihydro-6-isopropyl-3-methylpyrazin-2(1*H*)-one* (**11a**). As described for **5a**, from **10a**: pure **11a** (85% after CC). Oil. $[\alpha]_D^{25} = -16.9$ ($c = 1.3$, $CHCl_3$). ^{1}H-NMR: 0.72 (*d*, *J* = 7, 3 H); 0.96 (*d*, *J* = 7, 3 H); 1.15 (*t*, *J* = 7.2, 3 H); 1.36 (*s*, 3 H); 1.9–2.0 (*m*, 1 H); 2.2–2.6 (*m*, 4 H); 3.48 (*d*, *J* = 15, 2 H); 3.7 (*d*, *J* = 15, 2 H); 3.8–4.0 (*m*, 3 H); 5.93 (br. *s*, 1 H); 7.2–7.4 (*m*, 10 arom. H). ^{13}C-NMR: 14.0; 16.1; 18.3; 26.8; 28.6; 30.5; 37.8; 48.9; 57.9; 58.1; 59.0; 60.8; 126.5; 127.9; 128.6; 139.8; 155.8; 174.6. Anal. calc. for $C_{26}H_{35}N_3O_2$ (421.58): C 74.07, H 8.37, N 9.97; found: C 74.25, H 8.38, N 9.95.

*(3*S*,6*S*)-3-[3-(Dibenzylamino)propyl]-5-ethoxy-3,6-dihydro-6-isopropyl-3-methylpyrazin-2(1*H*)-one* (**11b**). As described for **5a**, from **10b**: **11b** (85% after CC). Oil. $[\alpha]_D$: product not sufficiently pure. ^{1}H-NMR: 0.89 (*d*, *J* = 7, 3 H); 1.02 (*d*, *J* = 7, 3 H); 1.28 (*t*, *J* = 7, 3 H); 1.37 (*s*, 3 H); 1.4–1.7 (*m*, 3 H); 1.9–2.0 (*m*, 1 H); 2.3–2.5 (*m*, 1 H); 2.43 (*t*, *J* = 7, 2 H); 3.55 (*q*, *AB*, *J* = 15.3, 4 H); 3.99–4.03 (*m*, 1 H); 4.06–4.18 (*m*, 2 H); 5.8 (br. *s*, 1 H); 7.2–7.4 (*m*, 10 arom. H). ^{13}C-NMR: 14.1; 16.2; 18.3; 22.2; 28.7; 30.5; 38.3; 53.4; 57.9; 59.9; 60.8; 126.5; 127.9; 128.6; 139.7; 156.0; 175.0.

4-(Dibenzylamino)-L-*isovalyl*-L-*valine Ethyl Ester Hydrochloride (1:2)* (**12a**). As described for **6a**, from **11a**: **12a** (80% after CC). Wax. $[\alpha]_D$: product not sufficiently pure. ^{1}H-NMR (CD_3OD): 1.0–1.1 (*m*, 6 H); 1.33 (*t*, *J* = 7, 3 H); 1.77 (*s*, 3 H); 2.2–2.4 (*m*, 1 H); 2.54–2.7 (*m*, 1 H); 2.8–3.0 (*m*, 1 H); 3.2–3.5 (*m*, 3 H); 4.2–4.34 (*m*, 2 H); 4.34–4.6 (*m*, 5 H); 7.45–7.65 (*m*, 10 arom. H). ^{13}C-NMR (CD_3OD): 15.0; 19.8; 19.9; 23.4; 31.2; 32.2; 49.9; 58.1; 58.5; 60.6; 60.7; 62.6; 130.6; 131.2; 132.7; 171.4; 173.2.

N^5,N^5-*Dibenzyl-2-methyl*-L-*ornithyl*-L-*valine Ethyl Ester Hydrochloride (1:2)* (**12b**). As described for **6a**, from **11b**: pure **12b** (87% after CC). Wax. $[\alpha]_D^{25} = -8.9$ ($c = 0.9$, MeOH). ^{1}H-NMR (CD_3OD): 1.0–1.1 (*m*, 6 H); 1.2–1.4 (*m*, 3 H); 1.70 (*s*, 3 H); 1.84–2.24 (*m*, 4 H); 2.24–2.40 (*m*, 1 H); 3.14 (*t*, *J* = 7.8, 2 H); 4.10–4.27 (*m*, 2 H); 4.3–4.5 (*m*, 5 H); 7.5–7.6 (*m*, 10 arom. H). ^{13}C-NMR (CD_3OD): 14.9; 19.1; 19.5; 19.9; 23.3; 31.4; 35.4; 58.8; 59.3; 60.5; 61.6; 62.7; 130.8; 130.9; 131.5; 132.8; 172.5; 173.7. Anal. calc. for $C_{27}H_{41}Cl_2N_3O_3$ (526.54): C 61.59, H 7.85, N 7.98; found: C 61.51, H 7.81, N 7.95.

4-(Dibenzylamino)-N-*{2-[(2*R*,5*S*)-6-ethoxy-2,3,4,5-tetrahydro-2-methyl-5-isopropyl-3-oxopyrazin-2-yl]acetyl}*-L-*isovalyl*-L-*valine Ethyl Ester* (**13a**). As described for **7b**, from **12a**: pure **13a** (90% after CC). Oil. $[\alpha]_D^{25} = -73.8$ ($c = 1.2$, $CHCl_3$). ^{1}H-NMR: 0.8–1.0 (*m*, 9 H); 1.0 (*d*, *J* = 7, 3 H); 1.26 (*t*, 6 H);

1.45 (*s*, 3 H); 1.50 (*s*, 3 H); 1.80–2.34 (*m*, 4 H); 2.35 (*d*, *J* = 14, 1 H); 2.44–2.80 (*m*, 2 H); 2.88 (*d*, *J* = 14, 1 H); 3.54 (*q*, *AB*, *J* = 13.2, 4 H); 4.0–4.3 (*m*, 6 H); 6.10 (br. *s*, 1 H); 7.2–7.4 (*m*, 10 arom. H); 7.60 (*d*, *J* = 8.2, 1 H); 8.51 (br. *s*, 1 H). ^{13}C-NMR: 14.0; 14.1; 15.9; 18.2; 19.1; 23.3; 29.2; 30.3; 30.6; 34.3; 48.5; 50.2; 57.9; 58.4; 58.5; 59.0; 60.8; 61.2; 61.6; 127.3; 128.4; 129.4; 138.0; 157.2; 170.8; 172.0; 173.7; 174.2. Anal. calc. for $C_{38}H_{55}N_5O_6$ (677.87): C 67.33, H 8.18, N 10.33; found: C 67.55, H 8.15, N 10.32.

N^2-*{2-[(2*R*,5*S*)-6-Ethoxy-2,3,4,5-tetrahydro-2-methyl-5-isopropyl-3-oxopyrazin-2-yl]acetyl}*-N^5,N^5-*dibenzyl-2-methyl*-L-*ornithyl*-L-*valine Ethyl Ester* (**13b**). As described for **7b**, from **12b**: **13b** (85% after CC). Oil. $[\alpha]_D^{25} = -11.5$ (*c* = 1.0, MeOH). ^{1}H-NMR: 0.8–1.0 (*m*, 12 H); 1.1–1.4 (*m*, 6 H); 1.45 (*s*, 3 H); 1.48 (*s*, 3 H); 1.5–2.1 (*m*, 4 H); 2.1–2.4 (*m*, 2 H); 2.4–2.6 (*m*, 2 H); 2.52 (*d*, *J* = 14.7, 1 H); 3.02 (*d*, *J* = 14.7, 1 H); 3.60 (br. *s*, 4 H); 3.9–4.0 (*m*, 1 H); 4.0–4.1 (*m*, 1 H); 4.1–4.26 (*m*, 3 H); 4.42 (*dd*, *J* = 5.1, 8.4, 1 H); 6.06 (br. *s*, 1 H); 6.75 (*s*, 1 H); 6.94 (*d*, *J* = 8.4, 1 H); 7.25–7.45 (*m*, 10 arom. H). ^{13}C-NMR: 14.0; 14.1; 16.6; 17.9; 18.2; 19.1; 19.7; 21.2; 21.8; 22.6; 27.0; 28.9; 30.4; 31.9; 38.5; 48.0; 52.9; 57.8; 58.7; 59.1; 60.2; 61.4; 127.0; 128.2; 129.9; 138.8; 157.7; 171.5; 173.1; 174.0; 174.5. Anal. calc. for $C_{39}H_{57}N_5O_6$ (691.90): C 67.7, H 8.3, N 10.12; found: C 67.87, H 8.32, N 10.08.

N-*[(1*S*)-1-(Ethoxycarbonyl)-2-methylpropyl]-2-methyl*-D-*α-asparaginyl-4-(dibenzylamino)*-L-*valine Ethyl Ester Hydrochloride (1:2)* (**14a**). As described for **8b**, from **13a**: pure **14a** (80% after CC). Wax. $[\alpha]_D^{25} = +13.3$ (*c* = 1.1, MeOH). ^{1}H-NMR (CD_3OD): 0.9–1.1 (*m*, 12 H); 1.2–1.4 (*m*, 9 H); 1.69 (*s*, 3 H); 2.1–2.3 (*m*, 3 H); 2.78–2.9 (*m*, 1 H); 3.06 (*d*, *J* = 16.8, 1 H); 3.21 (*d*, *J* = 16.8, 1 H); 3.3–3.4 (*m*, 2 H); 4.1–4.42 (*m*, 9 H); 4.64 (*d*, *J* = 13.5, 1 H); 7.4–7.7 (*m*, 10 arom. H). ^{13}C-NMR (CD_3OD): 14.8; 14.9; 19.6; 19.9; 20.0; 20.1; 22.8; 23.9; 31.6; 33.0; 39.5; 41.5; 50.7; 58.4; 58.8; 59.7; 60.7; 60.9; 62.6; 130.7; 130.8; 131.2; 131.4; 132.4; 132.5 171.4; 172.3; 172.9; 173.0; 176.5. Anal. calc. for $C_{38}H_{59}Cl_2N_5O_7$ (768.81): C 59.37, H 7.74, N 9.11; found: C 59.57, H 7.77, N 9.08.

N-*[(1*S*)-1-(Ethoxycarbonyl)-2-methylpropyl]-2-methyl*-D-*α-asparaginyl*-N^5,N^5-*dibenzyl-2-methyl*-L-*ornithyl*-L-*valine Ethyl Ester Hydrochloride (1:2)* (**14b**). As described for **8d**, from **13b**: pure **14b** (75% after CC). Wax. $[\alpha]_D^{25} = -6.4$ (*c* = 0.7, MeOH). ^{1}H-NMR (CD_3OD): 0.9–1.1 (*m*, 12 H); 1.2–1.4 (*m*, 6 H); 1.59 (*s*, 3 H); 1.66 (*s*, 3 H); 1.8–2.0 (*m*, 4 H); 2.1–2.3 (*m*, 2 H); 3.04 (*q*, *AB*, *J* = 18.4, 2 H); 3.0–3.1 (*m*, 2 H); 4.1–4.3 (*m*, 6 H); 4.4 (br. *s*, 4 H); 7.44–7.6 (*m*, 10 arom. H). ^{13}C-NMR (CD_3OD): 14.9; 19.5; 19.6; 20.0; 22.9; 23.5; 34.6; 41.6; 53.7; 58.4; 59.8; 60.2 60.5; 61.4; 62.5; 130.6; 131.0; 131.3; 132.7; 170.8; 172.3; 172.8; 173.6; 175.9. Anal. calc. for $C_{39}H_{61}Cl_2N_5O_7$ (782.84): C 59.84, H 7.85, N 8.95; found: C 59.94, H 7.88, N 8.98.

N^2-*Acetyl*-N-*[(1*S*)-1-(ethoxycarbonyl)-2-methylpropyl]-2-methyl*-D-*α-asparaginyl-4-(dibenzylamino)*-L-*isovalyl*-L-*valine Ethyl Ester* (**15a**). As described for **9b**, from **14a**: **15a** (78% after CC). Oil. $[\alpha]_D$: product not sufficiently pure. ^{1}H-NMR: 0.8–1.0 (*m*, 12 H); 1.1–1.5 (*m*, 6 H); 1.3 (*s*, 3 H); 1.7 (*s*, 3 H); 2.0–2.1 (*m*, 3 H); 2.1–2.3 (*m*, 2 H); 2.4–2.7 (*m*, 3 H); 2.78 (*d*, *J* = 14.4, 1 H); 2.85–3.1 (*m*, 2 H); 3.8–4.3 (*m*, 8 H); 4.3–4.5 (*m*, 2 H); 7.2–7.6 (*m*, 10 arom. H); 7.6 (*d*, *J* = 8.1, 1 H); 7.8 (*s*, 1 H); 7.9 (*d*, *J* = 8.4, 1 H); 8.17 (br. *s*, 1 H). ^{13}C-NMR: 14.0; 14.1; 17.7; 18.4; 19.0; 19.1; 23.9; 29.6; 30.5; 31.0; 43.2; 49.4; 56.7; 57.6; 58.1; 59.6; 59.9; 60.9; 129.1; 130.5; 171.5; 171.6; 171.7; 173.7; 173.8.

N^2-*Acetyl*-N-*[(1*S*)-1-(ethoxycarbonyl)-2-methylpropyl]-2-methyl*-D-*α-asparaginyl*-N^5,N^5-*dibenzyl-2-methyl*-L-*ornithyl*-L-*valine Ethyl Ester* (**15b**). As described for **9d**, from **14b**: pure **15b** (80% after CC). $[\alpha]_D^{25} = +73$ (*c* = 0.7, $CHCl_3$). ^{1}H-NMR: 0.9–1.0 (*m*, 12 H); 1.25 (*t*, *J* = 7, 3 H); 1.27 (*t*, *J* = 7, 3 H); 1.46–2.0 (*m*, 4 H); 1.5 (*s*, 3 H); 1.69 (*s*, 3 H); 2.02 (*s*, 3 H); 2.1–2.26 (*m*, 2 H); 2.34–2.5 (*m*, 3 H); 2.90 (*d*, *J* = 13.6, 1 H); 3.58 (*s*, 4 H); 4.05–4.25 (*m*, 4 H); 4.39 (*dd*, *J* = 5, 8, 1 H); 4.52 (*dd*, *J* = 5.6, 8.0, 1 H); 6.74 (*s*, 1 H); 6.93 (*d*, *J* = 8, 1 H); 7.2–7.4 (*m*, 10 arom. H); 7.63 (*s*, 1 H); 8.18 (*d*, *J* = 8, 1 H). ^{13}C-NMR: 14.0; 17.8; 18.9; 20.9; 21.7; 23.9; 30.7; 31.0; 35.9; 43.5; 52.9; 57.1; 57.8; 59.1; 60.4; 60.8; 126.7; 128.0; 128.6; 139.1; 170.3; 171.1; 171.9; 173.3; 173.6. Anal. calc. for $C_{41}H_{61}N_5O_8$ (751.95): C 65.49, H 8.18, N 9.31; found: C 65.52, H 8.22, N 9.29.

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