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# β-Lactam Derivatives as Enzyme Inhibitors: Peptidic Derivatives of (*RS*)-2-Oxo-4-phenylazetidine-1-alkanoic Acids

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**Summary.** 4-Phenylazetidine-2-one was transformed into 4-phenylazetidine-1-alkanoic acids, which were reacted in the presence of diphenylphosphoroazidate with amino acid esters and dipeptide esters yielding β-lactam peptides with different spacers between the lactam ring and the peptide moiety. All structures were established by elementary analyses, HPLC, optical rotation, and spectroscopic data and all new compounds were tested as inhibitors of *PPE* using standard procedures. Four compounds exhibited a weak activity compared with the standard inhibitor trifluoroacetyl-L-val-L-tyr-L-val.

**Keywords.** β-Lactam peptides; Elastase inhibitors; β-Lactam 1-alkanoic acids.

## Introduction

Elastase is a human serine protease from which at least two forms are known. The human pancreatic elastase (HPE, EC 3.4.21.36) produced in the pancreas is liberated into the intestine, whereas the human neutrophil or leukocyte elastase (HNE, HLE, EC 3.4.21.37) produced in the medulla ossium and stored in the granula of polymorphous leucocytes plays an important role in the metabolism of human peptides as fibrin, hemoglobin, albumins, caseins, and elastin [1]. Elastin is responsible for the elasticity of the lung tissue, and excessive activity of elastase might cause a number of diseases like ARDS [2], cystic fibrosis [3], arthritis [4], and emphysema [5]. A number of natural inhibitors of elastase is known, some inhibitors are (or were) used in the therapy of emphysema, and great effort was done to find effective and orally applicable compounds, but until today the great success was not reported [6]. The active center of elastase seems to be similar to the active center of transpeptidases. Therefore, experiments are reported to use β-lactam structures as elastase inhibitors, and indeed, some of these experiments were successful [7]. We have reported about the synthesis of elastase inhibitors based on the saccharin nucleus [8], and the β-lactam structure [9]. In continuation of these results we report here about the synthesis and properties of peptidic derivatives of (*RS*)-2-oxo-4-phenylazetidine-1-alkanoic acids. These compounds we hoped should be able to attack the active center of the enzyme by the β-lactam moiety, whereas the peptidic side chain should be able to improve the selectivity. We selected as building blocks for the side chain the amino acids L-alanine, L-phenylalanine, L-valine, and L-leucine, as these amino acids could fit into the pockets around the active center of elastase. Furthermore, we introduced spacers between the β-lactam ring and the peptidic side chain.

## Results and Discussion

As the β-lactam moiety we used 4-phenylazetidin-2-one (**1**) prepared according to literature [10]. The

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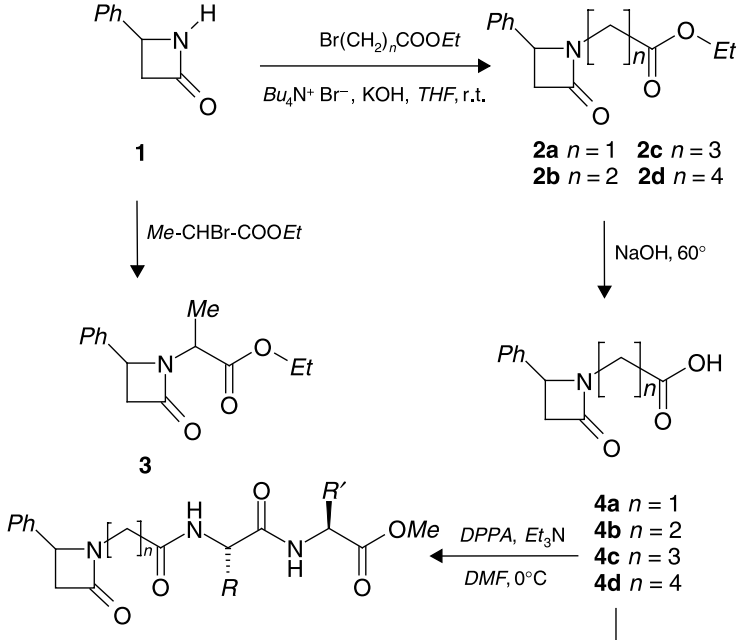
alkylation with $\omega$-bromoalkanoic esters was successful when we used the solid–liquid-phase transfer method with $Bu_4NBr$ and KOH in *THF* [11]. We obtained the $\beta$-lactam-*N*-alkanoyl esters **2a**–**2d** after purification by CC as colorless liquids with yields of 20–70% [12]. Compound **3** was isolated from the reaction between **1** and ethyl 2-bromopropionate.

The hydrolysis of the ester groups using enzymatic methods [13] was not successful, but by hydrolysis with NaOH in $H_2O$ at maximum 60°C we obtained the $\beta$-lactam-*N*-alkanoic acids **4a**–**4d** as colorless viscous liquids with yields up to 87%.

Esters and acids were characterized mainly by their spectroscopic data. The IR spectra showed intensive carbonyl bands. These were found in the spectra of the acetates **2a** and **3** around 1770 $cm^{-1}$, whereas in the spectra of the other esters and of all acids these bands were registered around 1730 $cm^{-1}$. All $^1H$ NMR (200 MHz) spectra were characterized by an AMX system of the $\beta$-lactam protons at *ca.* 2.8–2.9




**5a** $n = 1$, $R = R' = CHMe_2$
**5b** $n = 1$, $R = CHMe_2$, $R' = CH_2CHMe_2$
**5c** $n = 1$, $R = R' = Bn$
**5d** $n = 1$, $R = Bn$, $R' = CHMe_2$
**5e** $n = 1$, $R = Bn$, $R' = CH_2CHMe_2$
**5f** $n = 1$, $R = Me$, $R' = CHMe_2$
**5g** $n = 1$, $R = CHMe_2$, $R' = Bn$
**5h** $n = 2$, $R = CHMe_2$, $R' = CH_2CHMe_2$
**5i** $n = 2$, $R = R' = Bn$
**5j** $n = 2$, $R = Bn$, $R' = CHMe_2$
**5k** $n = 2$, $R = Bn$, $R' = CH_2CHMe_2$
**5l** $n = 3$, $R = Me$, $R' = CHMe_2$
**5m** $n = 3$, $R = R' = CHMe_2$
**5n** $n = 3$, $R = CHMe_2$, $R' = CH_2CHMe_2$
**5o** $n = 3$, $R = Bn$, $R' = CH_2CHMe_2$
**5p** $n = 3$, $R = Bn$, $R' = CHMe_2$
**5q** $n = 3$, $R = CHMe_2$, $R' = Bn$
**5r** $n = 3$, $R = R' = Bn$
**5s** $n = 4$, $R = CHMe_2$, $R' = CH_2CHMe_2$
**5t** $n = 4$, $R = Bn$, $R' = CHMe_2$
**5u** $n = 4$, $R = CHMe_2$, $R' = Bn$
**5v** $n = 4$, $R = R' = Bn$

**6a** $n = 1$, $R = CHMe_2$, $R' = Me$
**6b** $n = 2$, $R = Me$, $R' = Bn$
**6c** $n = 3$, $R = CHMe_2$, $R' = Me$
**6d** $n = 4$, $R = CHMe_2$, $R' = Me$
**6e** $n = 4$, $R = (CH_2)_2CO_2Bn$, $R' = Bn$
**6f** $n = 4$, $R = Me$, $R' = Bn$

**Scheme 1**

and 3.3–3.5 (3-H), and 4.6–4.9 ppm (4-H) and coupling constants of 2.1–2.4, 5.0–5.3, and 14.6–15.9 Hz establishing the intact β-lactam ring.

The salts of amino acid esters and of dipeptide esters were synthesized using standard procedures described in Ref. [14]. The reactions of these building blocks with the acids **4a**–**4d** were performed under an $N_2$ atmosphere in dry *DMF* with diphenylphosphoroazidate (*DPPA*) and $Et_3N$ at 0°C. The compounds were purified by CC (*AcOEt*), and all compounds were isolated as viscous liquids. We obtained by this way the amino acid ester derivatives **6a**–**6f** and the dipeptide derivatives **5a**–**5v**.

As expected, the HPLC analyses (RP-18 column) of **6a**–**6f** showed for these compounds two peaks with a ratio of 1:1 (or 3:2) indicating that these compounds were isolated as mixtures of diastereoisomers. This was established by the $^1$H NMR spectra (see Experimental). Furthermore, the structures were in agreement with the IR data showing the NH-bands around 3300 $cm^{-1}$ and 3 carbonyl bands, *ca.* 1730–1750 (β-lactam CO), 1650–1670 (ester CO), and 1540 $cm^{-1}$ (amide CO). Similar results were obtained from analyzing **5a**–**5v**. In some cases, the separation of the signals of the diastereoisomers in the HPLC spectra was possible only when we used a chiral column with chiral adsorbent. All dipeptide derivatives were formed as 1:1 mixtures of diastereoisomers, which were not separated.

Testing the biological activity of these compounds was done as described earlier [9]. Compounds **5g**, **5i**, **5l**, and **6a** showed a weak activity against *PPE* compared to that of the standard inhibitor trifluoroacetyl-L-val-L-tyr-L-val.

## Experimental

*General*: Mp: PHMX 80/2778 (Küstner, Dresden) apparatus. IR Spectra: Perkin-Elmer FTIR 1600; in KBr or as film ($cm^{-1}$), if not noted otherwise. NMR Spectra: Bruker DPX 200 (200 MHz), ARX 300 (300 MHz) for $^1$H; δ (ppm) rel. to *TMS* as internal standard, *J* in Hz; $^1$H-values from DPX 200 spectra in $CDCl_3$, if not noted otherwise. Mass Spectra: Intectra AMD 402/3. Optical rotation: Polatronic D. Elementary analyses: Perkin-Elmer Analyzer 2400 CHN, Pharmazeutisches Institut der Universität Greifswald. All compounds gave satisfactory elemental analyses or were proven by high resolution MS. Column chromatography (CC) with Silica Gel 60 Merck Nr. 7734 or 9385. HPLC with LaChrom apparatus series 7000 Merck Hitachi, LiChrospher 250-4, RP-18, 5 μm, and LiChroCART 250-4, (*S*,*S*)-Whelk-O1, 5 μm. *PPE* (Porcine pancreatic elastase, ≈200 U/mg) was purchased from Serva, Suc-$(Ala)_3$-pNA from Fluka. *THF* was stored with $CaCl_2$, refluxed with Na and benzophenone, and distilled prior to use. Other solvents were dried/purified according to literature procedures. *(RS)-4-Phenylazetidin-2-one* (**1**) see Ref. [10].

*Synthesis of **2a**–**2d** and **3**. General Procedure*

Compound **1** (1.61 g, 11 mmol), 10 mmol ω-bromoalkanoic ester, and 0.36 g $Bu_4NBr$ were dissolved in 50 $cm^3$ *THF*, 0.67 g pulv. KOH (11 mmol) was added, and the mixture was stirred for 6–12 h. Then, the mixture was filtrated, concentrated *in vacuo*, and the residue was crystallized or purified by CC.

*Ethyl (RS)-2-(2-oxo-4-phenylazetidin-1-yl)acetate* (**2a**, $C_{13}H_{15}NO_3$)

From ethyl bromoacetate (1.67 g, 10 mmol), CC (*AcOEt*). Yield 1.65 g (71%); colorless liquid; $R_f = 0.57$; IR: $\bar{\nu} =$ 3030, 2983 (CH), 1769 (CO) $cm^{-1}$; $^1$H NMR: $\delta = 1.71$ (t, $J = 7.15$ Hz, *Me*), 2.82 (dd, $J_{AX} = 2.4$ Hz, $J_{AM} = 14.8$ Hz, 3-H), 3.31 (d, $J = 17.8$ Hz, 1H, $CH_2$), 3.40 (dd, $J_{MX} = 5.2$ Hz, $J_{AM} = 14.8$ Hz, 3′-H), 4.16 (m, $CH_2$), 4.35 (d, $J = 17.8$ Hz, 1H, $CH_2$), 4.78 (dd, $J_{AX} = 2.4$ Hz, $J_{MX} = 5.2$ Hz, 4-H), 7.26 (m, 5 *ar* H) ppm.

*Ethyl (RS)-3-(2-oxo-4-phenylazetidin-1-yl)propionate* (**2b**, $C_{14}H_{17}NO_3$)

From ethyl 3-bromopropionate (1.81 g, 11 mmol), at 0°C, 1–2 h, CC (Cyclohexane/*AcOEt* 1/1). Yield 1.75 g (71%); colorless liquid; $R_f = 0.55$; IR: $\bar{\nu} = 3031$ (CH), 2981, 2930 (CH), 1731 (CO) $cm^{-1}$; $^1$H NMR: $\delta = 1.24$ (t, $J = 7.2$ Hz, *Me*), 2.48 (dt, $J = 6.8$ Hz, $J = 14.0$ Hz, $CH_2$), 2.76 (dd, $J_{AX} = 2.2$ Hz, $J_{AM} = 14.6$ Hz, 3-H), 3.17 (dt, $J = 6.8$ Hz, $J = 14.0$ Hz, 1H, $CH_2$), 3.32 (dd, $J_{MX} = 5.2$ Hz, $J_{AM} = 14.6$ Hz, 3′-H), 3.63 (dt, $J = 6.8$ Hz, $J = 14.0$ Hz, 1H, $CH_2$), 4.01 (m, $CH_2$), 4.60 (dd, $J_{AX} = 2.3$ Hz, $J_{MX} = 5.2$ Hz, 4-H), 7.34 (m, 10 *ar* H) ppm.

*Ethyl (RS)-4-(2-oxo-4-phenylazetidin-1-yl)butyrate* (**2c**, $C_{15}H_{19}NO_3$)

From ethyl 4-bromobutyrate (1.95 g, 10 mmol), CC (Cyclohexane/*AcOEt* 1/1). Yield 0.55 g (21%); colorless liquid; $R_f = 0.4$; IR: $\bar{\nu} = 2956$ (CH), 1731 (CO) $cm^{-1}$; $^1$H NMR: $\delta = 1.23$ (t, $J = 7.2$ Hz, *Me*), 1.79 (m, $CH_2$), 2.3 (m, $CH_2$), 2.81 (dd, $J_{AX} = 2.1$ Hz, $J_{AM} = 14.6$ Hz, 3-H), 2.89 (dt, $J = 6.5$, 14.6 Hz, 1H, $CH_2$), 3.36 (dd, $J_{MX} = 5.0$ Hz, $J_{AM} = 14.6$ Hz, 3′-H), 4.09 (q, $J = 7.2$ Hz, $CH_2$), 4.65 (dd, $J_{AX} = 2.1$ Hz, $J_{MX} = 5.0$ Hz, 4-H), 7.31 (m, 5 *ar* H) ppm.

*Ethyl (RS)-5-(2-oxo-4-phenylazetidin-1-yl)valerianate* (**2d**, $C_{16}H_{21}NO_3$)

From ethyl 5-bromovalerianate (2.05 g, 10 mmol), CC (Cyclohexane/*AcOEt* 1/1). Yield 1.45 g (51%); colorless liquid; $R_f =$ 0.4; IR: $\bar{\nu} = 3030$, 2951 (CH), 1734 (CO), 1397, 701 $cm^{-1}$; $^1$H NMR: $\delta = 1.25$ (t, $J = 7.1$ Hz, *Me*), 1.57 (m, $2CH_2$), 2.27 (m, $CH_2$), 2.77 (dd, $J_{AX} = 1.7$ Hz, $J_{AM} = 14.6$ Hz, 3-H), 2.85 (m, 1H, $CH_2$), 3.34 (dd, $J_{MX} = 5.1$ Hz, $J_{AM} = 14.75$ Hz, 3′-H), 3.43 (m, 1H, $CH_2$), 4.08 (q, $J = 7.1$ Hz, $CH_2$), 4.55 (dd, $J_{AX} = 2.24$ Hz, $J_{MX} = 5.1$ Hz, 4-H), 7.34 (m, 5 *ar* H) ppm.

*Ethyl (RS)-2-methyl-2-(2-oxo-4-phenylazetidin-1-yl)acetate* (**3**, $C_{14}H_{17}NO_3$)
From ethyl 2-bromopropionate (1.81 g, 11 mmol), CC (*Ac*O*Et*). Yield 0.91 g (33%); colorless liquid; $R_f = 0.75$; IR: $\bar{\nu} = 3031$, 2984 (CH), 1767 (CO) $cm^{-1}$; $^1H$ NMR: $\delta = 1.25$ (t, $J = 7.0$ Hz, *Me*), 1.48 (d, $J = 7.4$ Hz, *Me*), 2.82 (dd, $J_{AX} = 2.5$ Hz, $J_{AM} = 14.8$ Hz, 3-H), 3.40 (dd, $J_{MX} = 5.3$ Hz, $J_{AM} = 14.8$ Hz, 3′-H), 4.01 (q, $J = 7.4$ Hz, CH), 4.67 (dd, $J_{AX} = 2.5$ Hz, $J_{MX} = 5.3$ Hz, 4-H), 7.31 (m, 5 *ar* H) ppm.

*Synthesis of **4a–4d**. General Procedure*
Ester **2** (8.6 mmol) and 20 $cm^3$ 1 *N* NaOH were warmed to 60°C for 20 min. The mixture was cooled to room temperature, twice extracted with 50 $cm^3$ *Ac*O*Et*, the aqueous layer was acidified with dil. HCl to $pH \sim 2$, and extracted with $3 \times 50$ $cm^3$ *Ac*O*Et*. The combined extracts were dried ($Na_2SO_4$), and the solvent was removed *in vacuo*.

*(RS)-2-(2-oxo-4-phenylazetidin-1-yl)acetic acid* (**4a**, $C_{11}H_{11}NO_3$)
From **2a**. Yield 1.5 g (87%); colorless liquid; IR: $\bar{\nu} = 3432$ (OH), 2988 (CH), 1735 (CO), 758, 700 $cm^{-1}$; $^1H$ NMR: $\delta = 2.9$ (dd, $J_{AX} = 2.2$ Hz, $J_{AM} = 14.95$ Hz, 3-H), 3.45 (d, $J = 18.2$ Hz, 1H, $CH_2$), 3.49 (dd, $J_{MX} = 5.1$ Hz, $J_{AM} = 14.95$ Hz, 3′-H), 4.38 (d, $J = 18.2$ Hz, 1H, $CH_2$), 4.89 (dd, $J_{AX} = 2.3$ Hz, $J_{MX} = 5.1$ Hz, 4-H), 7.36 (m, 5 *ar* H), 8.41 (s, br, COOH) ppm.

*(RS)-3-(2-oxo-4-phenylazetidin-1-yl)propionic acid* (**4b**, $C_{12}H_{13}NO_3$)
From **2b**. Yield 0.6 g (62%); colorless liquid; IR: $\bar{\nu} = 3484$ (OH), 3031, 2981 (CH), 1731 (CO) 701 $cm^{-1}$; $^1H$ NMR: $\delta = 2.52$ (dt, $J = 6.7$ Hz, $J = 16.8$ Hz, $CH_2$), 2.80 (dd, $J_{AX} = 2.2$ Hz, $J_{AM} = 14.75$ Hz, 3-H), 3.16 (dt, $J = 6.8$, 14.15 Hz, 1H, $CH_2$), 3.36 (dd, $J_{MX} = 5.1$ Hz, $J_{AM} = 14.75$ Hz, 3′-H), 3.64 (dt, $J = 6.6$, 14.5 Hz, 1H, $CH_2$), 4.61 (dd, $J_{AX} = 2.3$ Hz, $J_{MX} = 5.1$ Hz, 4-H), 7.31 (m, 5 *ar* H), 10.31 (s, br, COOH) ppm.

*(RS)-4-(2-oxo-4-phenylazetidin-1-yl)butyric acid* (**4c**, $C_{13}H_{15}NO_3$)
From **2c**. Yield 0.95 g (53%); colorless liquid; $^1H$ NMR: $\delta = 1.72$–1.93 (m, $CH_2$), 2.33–2.40 (m, $CH_2$), 2.81(dd, $J_{AX} = 2.2$ Hz, $J_{AM} = 14.8$ Hz, 3-H), 2.92 (dt, $J = 7.5$ Hz, 14.5 Hz, 1H, $CH_2$), 3.33 (dd, $J_{MX} = 5.1$ Hz, $J_{AM} = 14.8$ Hz, 3′-H), 3.43 (dt, $J = 7.5$, 14.5 Hz, 1H, $CH_2$), 4.58 (dd, $J_{AX} = 2.2$ Hz, $J_{MX} = 5.1$ Hz, 4-H), 7.30–7.45 (m, 5 *ar* H), 10.55 (s, br, COOH) ppm.

*(RS)-5-(2-oxo-4-phenylazetidin-1-yl)valerianic acid* (**4d**, $C_{14}H_{17}NO_3$) [12]
From **2d**. Yield 1.37 g (76%); colorless liquid; IR: $\bar{\nu} = 3434$ (OH), 2951 (CH), 1732 (CO), 759, 701 $cm^{-1}$; $^1H$ NMR: $\delta = 1.58$ (m, $2CH_2$), 2.3 (m, $CH_2$), 2.83 (dd, $J_{AX} = 2.8$ Hz, $J_{AM} = 14.7$ Hz, 3-H), 2.87 (m, 1H, $CH_2$), 3.36 (dd, $J_{MX} = 4.95$ Hz, $J_{AM} = 14.7$ Hz, 3′-H), 3.47 (m, 1H, $CH_2$), 4.57 (dd, $J_{AX} = 2.8$ Hz, $J_{MX} = 5.8$ Hz, 4-H), 7.24 (m, 5 *ar* H), 10.86 (s, br, COOH) ppm.

*Synthesis of Dipeptide Ester Salts*
The following dipeptide ester salts were prepared in analogy to the method reported in Ref. [9], *Venz C.*: L-*Ala*-L-*Val*-O*Me*-HCl, yield 0.29 g (84%), $C_9H_{19}N_2O_3Cl$; L-*Phe*-L-*Leu*-O*Me*-HCl, yield 0.81 g (98%), $C_{16}H_{24}N_2O_3Cl$; L-*Phe*-L-*Phe*-O*Me*-HCl, yield 0.6 g (100%), $C_{19}H_{23}N_2O_3Cl$; L-*Phe*-L-*Val*-O*Me*-HCl, yield 1.57 g (95%), $C_{15}H_{23}N_2O_3Cl$; L-*Val*-L-*Leu*-O*Me*-HCl, yield 2.12 g (87%), $C_{12}H_{25}N_2O_3Cl$; L-*Val*-L-*Phe*-O*Me-HCl*, yield 1.57 g (95%), $C_{15}H_{23}N_2O_3Cl$; L-*Val*-L-*Val-OMe-HCl*, yield 1.44 g (90%), $C_{11}H_{23}N_2O_3Cl$.

*Synthesis of the β-Lactam Peptides **5** and **6**. General Procedure*
Under $N_2$, the β-lactam alkanoic acid and the amino acid ester salt or the dipeptide ester salt were dissolved in 20 $cm^3$ *DMF*, and 1.1 eq. of diphenylphosphoroazidate, and 2.1 eq. of $Et_3N$ were added. The mixture was stirred for 10 h at 0°C. Then, 100 $cm^3$ *Ac*O*Et* were added, and the mixture was washed with $3 \times 50$ $cm^3$ $H_2O$, once with a satd. solution of $NaHCO_3$, and twice with a satd. solution of NaCl. The organic layer was separated, dried ($Na_2SO_4$), and the solvent was evaporated *in vacuo*. The residue was purified by CC with *Ac*O*Et*. All products were obtained as colorless viscous liquids, if not otherwise noted.

*N-{-2-[(RS)-2-oxo-4-phenylazetidin-1-yl]acetyl}-L-valyl-L-valine methyl ester* (**5a**, $C_{22}H_{31}N_3O_5$)
From **4a** (0.3 g, 1.53 mmol) and L-*Val*-L-*Val*-O*Me*-HCl (0.43 g, 1.61 mmol). Yield 0.31 g (49%); $R_f = 0.60$; $[\alpha]_D^{20} = -43.00°$ $cm^2$ $g^{-1}$ ($c = 2$, *Me*OH); IR: $\bar{\nu} = 3380$, 3317 (NH), 2977 (CH), 1731, 1702, 1651, 1543 (CO) $cm^{-1}$; $^1H$ NMR: $\delta = 0.88$, 0.91 (2d, $J = 7.1$ Hz, $Me_{Val}$), 0.94, 0.97 (2d, $J = 6.9$ Hz, $Me_{Val}$), 1.28 (m, β-$H_{Val}$), 2.11 (m, β-$H_{Val}$), 2.92 (dd, $J_{AM} = 2.4$ Hz, $J_{AX} = 14.9$ Hz, H-3), 3.47 (dd, $J_{MX} = 5.2$ Hz, $J_{AM} = 14.9$ Hz, 3′-H), 3.52 (d, $J = 14.1$ Hz, 1H, $CH_2$), 3.74 (s, O*Me*), 4.22 (d, $J = 14.0$ Hz, 1H, $CH_2$), 4.28 (m, α-$H_{Val}$), 4.50 (m, α-$H_{Val}$), 4.79 (dd, $J_{AX} = 2.4$ Hz, $J_{MX} = 5.2$ Hz, 4-H), 6.28 (m, N–$H_{Val}$), 6.87 (d, $J = 8.4$ Hz, N–$H_{Val}$), 7.24 (m, 5 *ar* H) ppm; HPLC: $k'_1 = 1.57$, $k'_2 = 2.26$, $t_0 = 2.13$ (RP-18, *Me*CN/$H_2O$ 1/1), ratio of diastereoisomers 49:51.

*N-{-2-[(RS)-2-oxo-4-phenylazetidin-1-yl]acetyl}-L-valyl-L-leucine methyl ester* (**5b**, $C_{23}H_{33}N_3O_5$)
From **4a** (0.2 g, 0.99 mmol) and L-*Val*-L-*Leu*-O*Me*-HCl (0.3 g, 1.02 mmol). Yield 0.22 g (51%); $R_f = 0.77$; $[\alpha]_D^{20} = -46.25°$ $cm^2$ $g^{-1}$ ($c = 2$, *Me*OH); IR: $\bar{\nu} = 3265$ (NH), 3068, 2959 (CH), 1762, 1650, 1548 (CO) $cm^{-1}$; $^1H$ NMR: $\delta = 0.89$, 0.91 (2d, $J = 7.0$ Hz, $Me_{Val}$), 0.93, 0.94 (2d, $J = 6.4$ Hz, $Me_{Leu}$), 1.48–1.62 (m, 2 β-H, γ-$H_{Leu}$), 2.08–2.14 (m, β-$H_{Val}$), 2.96 (dd, $J_{AX} = 2.5$ Hz, $J_{AM} = 14.9$ Hz, 3-H), 3.41 (d, $J = 16.9$ Hz, 1H, $CH_2$), 3.51 (dd, $J_{MX} = 5.4$ Hz, $J_{AM} = 14.9$ Hz, 3′-H), 3.72 (s, O*Me*), 4.27 (d, $J = 16.9$ Hz, 1H, $CH_2$), 4.29 (m, α-$H_{Val}$), 4.56 (m, α-$H_{Leu}$), 4.82 (dd, $J_{AX} = 2.5$ Hz, $J_{MX} = 5.4$ Hz, 4-H), 6.53, 6.65 (d, $J = 7.9$ Hz, N–$H_{Val}$), 6.88, 6.92 (d, $J = 8.5$ Hz, N–$H_{Leu}$), 7.35 (m, 5 *ar* H) ppm; HPLC: $k' = 2.60$, $t_0 = 1.89$ (RP-18, *Me*CN/$H_2O$ 1/1), $k'_1 = 11.79$, $k'_2 = 12.09$, $t_0 = 2.23$ (RP-18, *Me*CN/$H_2O$ 3/7), ratio of diastereoisomers 46:54.

*N-{-2-[(RS)-2-oxo-4-phenylazetidin-1-yl]acetyl}-L-phenylalanyl-L-phenylalanine methyl ester* (**5c**, $C_{30}H_{31}N_3O_5$)
From **4a** (0.21 g, 1.04 mmol) and L-*Phe*-L-*Phe*-O*Me*-HCl (0.35 g, 1.08 mmol). Yield 0.1 g (19%); $R_f = 0.40$; IR: $\bar{\nu} =$ 3286 (NH), 3060, 2926 (CH), 1774, 1753, 1731, 1692, 1655, 1546 (CO) $cm^{-1}$; $^1H$ NMR: $\delta = 2.84–2.94$ (dd, $J_{AX} = 2.3$ Hz, $J_{AM} = 14.8$ Hz, 3-H), 2.98–3.14 (m, 2 $\beta$-$H_{Phe}$), 3.23–3.45 (dd, $J_{MX} = 5.2$ Hz, $J_{AM} = 14.8$ Hz, 3′-H; 2d, $J =$ 16.8 Hz, 1H, $CH_2$), 3.70 (s, O*Me*), 3.98–4.13 (2d, $J = 16.8$ Hz, Hz, 1H, $CH_2$), 4.37–4.41 (dd, $J_{AX} = 2.3$ Hz, $J_{MX} = 5.2$ Hz, 4-H), 4.52–4.66 (m, $\alpha$-$H_{Phe}$), 4.70–4.79 (m, $\alpha$-$H_{Phe}$), 6.20, 6.27 (2d, $J = 7.0$ Hz, N–H), 6.57, 6.74 (2d, $J = 7.3$ Hz, N–H), 6.95–7.38 (m, 15 *ar* H) ppm; HPLC: $k' = 1.36$, $t_0 = 2.13$ (RP-18, *Me*CN/$H_2O$ 4/6).

*N-{-2-[(RS)-2-oxo-4-phenylazetidin-1-yl]acetyl}-L-phenylalanyl-L-valine methyl ester* (**5d**, $C_{26}H_{31}N_3O_5$)
From **4a** (0.41 g, 1.98 mmol) and L-*Phe*-L-*Val*-O*Me*-HCl (0.57 g, 2.06 mmol). Yield 0.11 g (12%); $R_f = 0.70$; $[\alpha]_D^{20} = -28.00°\ cm^2\ g^{-1}$ ($c = 2$, *Me*OH); IR: $\bar{\nu} = 3287$ (NH), 3064, 2964 (CH), 1734, 1660, 1643, 1536 (CO) $cm^{-1}$; $^1H$ NMR: $\delta = 0.83$ (d, $J = 6.8$ Hz, $Me_{Val}$), 0.88 (d, $J = 6.95$ Hz, $Me_{Val}$), 2.03–2.13 (m, $\beta$-$H_{Val}$), 2.83–2.92 (dd, $J_{AX} = 2.3$ Hz, $J_{AM} =$ 14.8 Hz, 3-H), 2.95–3.09 (m, $CH_{2Phe}$), 3.26–3.49 (m, 1H, $CH_2$; dd, $J_{MX} = 5.2$ Hz, $J_{AM} = 14.8$ Hz, 3′-H), 3.68 (s, O*Me*), 4.05–4.26 (m, 1H, $CH_2$), 4.38–4.51 (m, $\alpha$-$H_{Val}$; dd, $J_{AX} =$ 2.3 Hz, $J_{MX} = 5.2$ Hz, 4-H), 4.72–4.79 (m, $\alpha$-$H_{Phe}$), 6.93 (d, $J = 8.2$ Hz, N–$H_{Val}$), 6.97 (d, $J = 6.8$ Hz, N–$H_{Phe}$), 7.16–7.42 (m, 15 *ar* H) ppm; HPLC: $k' = 15.78$, $t_0 = 2.23$ (RP-18, *Me*CN/$H_2O$ 3/7).

*N-{-2-[(RS)-2-oxo-4-phenylazetidin-1-yl]acetyl}-L-phenylalanyl-L-leucine methyl ester* (**5e**, $C_{27}H_{33}N_3O_5$)
From **4a** (0.25 g, 1.2 mmol) and L-*Phe*-L-*Leu*-O*Me-TFA* (0.5 g, 1.26 mmol). Yield 0.24 g (42%); colorless solid; $R_f = 0.4$; IR: $\bar{\nu} = 3290$ (NH), 3064, 2955 (CH), 1746, 1651, 1543 (CO) $cm^{-1}$; $^1H$ NMR: $\delta = 0.9$ (d, 2 $Me_{Leu}$), 1.45–1.58 (m, 2 $\beta$-H, $\gamma$-$H_{Leu}$), 2.85–2.94 (dd, $J_{AX} = 2.4$ Hz, $J_{AM} = 14.9$ Hz, 3-H), 3.0–3.12 (m, $CH_{2Phe}$), 3.32–3.40 (2d, $J = 16.8$ Hz, 1H, $CH_2$), 3.43 (dd, $J_{BX} = 5.0$ Hz, $J_{AM} = 14.9$ Hz, 3′-H), 3.71 (s, O*Me*), 4.08 (2d, $J = 16.9$ Hz, 1H, $CH_2$), 4.45 (m, $\alpha$-$H_{Leu}$), 4.60 (dd, $J_{AX} = 2.5$ Hz, $J_{MX} = 5.0$ Hz, 4-H), 4.7 (m, $\alpha$-$H_{Phe}$), 6.09 (2d, $J = 7.8$ Hz, N–$H_{Leu}$), 6.54, 6.69 (2d, $J = 7.4$ Hz, N–$H_{Phe}$), 7.23 (m, 10 *ar* H) ppm; HPLC: $k' = 4.39$, $t_0 =$ 2.20 (RP-18, *Me*CN/$H_2O$ 1/1), $k'_1 = 1.08$, $k'_2 = 1.22$, $t_0 =$ 2.41 ((S,S)-Whelk 01, *n*-hexane/2-propanol 1/1); ratio of diastereoisomers 46:54.

*N-{-2-[(RS)-2-oxo-4-phenylazetidin-1-yl]acetyl}-L-alanyl-L-valine methyl ester* (**5f**, $C_{20}H_{27}N_3O_5$)
From **4a** (0.3 g, 1.46 mmol) and L-*Ala*-L-*Val*-O*Me*-HCl (0.48 g, 1.51 mmol). Yield 0.26 g (46%); $R_f = 0.53$; IR: $\bar{\nu} = 3307$ (NH), 3065, 2965 (CH), 1746, 1653, 1540 (CO) $cm^{-1}$; $^1H$ NMR: $\delta = 0.87$ (d, $J = 6.8$ Hz, $Me_{Val}$), 0.90 (d, $J = 6.7$ Hz, $Me_{Val}$), 1.31–1.35 (d, $J = 7.0$ Hz, $Me_{Ala}$), 2.06–2.22 (m, $\beta$-$H_{Val}$), 2.86–2.95 (dd, $J_{AX} = 2.0$ Hz, $J_{AM} = 14.8$ Hz, 3-H), 3.38–3.46 (d, $J = 16.7$ Hz, 1H, $CH_2$), 3.42–3.52 (dd, $J_{MX} =$ 5.2 Hz, $J_{AM} = 14.8$ Hz, 3′-H), 3.72 (s, O*Me*), 4.18–4.26 (d, $J = 16.8$ Hz, 1H, $CH_2$), 4.41–4.57 (m, $\alpha$-$H_{Ala}$, $\alpha$-$H_{Val}$), 4.82–4.84 (dd, $J_{AX} = 2.0$ Hz, $J_{MX} = 5.2$ Hz, 4-H), 6.90 (d, $J = 8.7$ Hz, N–$H_{Val}$), 7.16 (d, $J = 7.3$ Hz, N–$H_{Ala}$), 7.29–7.34 (m, 5 *ar* H) ppm; HPLC: $k' = 4.74$, $t_0 = 2.39$ (RP-18, *Me*CN/$H_2O$ 3/7).

*N-{-2-[(RS)-2-oxo-4-phenylazetidin-1-yl]acetyl}-L-valyl-L-*phenylalanine methyl ester (**5g**, $C_{26}H_{31}N_3O_5$)
From **4a** (0.3 g, 1.46 mmol) and L-*Val*-L-*Phe*-O*Me*-HCl (0.59 g, 1.51 mmol). Yield 212 mg (31%); $R_f = 0.70$; $[\alpha]_D^{20} = -31.75°\ cm^2\ g^{-1}$ ($c = 2$, *Me*OH); IR: $\bar{\nu} = 3290$ (NH), 2965 (CH), 1731, 1681, 1537 (CO) $cm^{-1}$; $^1H$ NMR: $\delta = 0.79$ (d, $J = 6.8$ Hz, $Me_{Val}$), 0.85 (d, $J = 6.7$ Hz, $Me_{Val}$), 1.98–2.20 (m, $\beta$-$H_{Val}$), 2.89–2.97 (d, $J_{AM} = 14.6$ Hz, 3-H), 3.01–3.19 (m, 2 $\beta$-$H_{Phe}$), 3.37–3.52 (dd, $J_{MX} = 5.2$ Hz, $J_{AM} = 13.8$ Hz, 3′-H), 3.46 (d, $J = 16.5$ Hz, 1H, $CH_2$), 3.70, 3.71 (2s, O*Me*), 4.15 (d, $J = 16.5$ Hz, 1H, $CH_2$), 4.25 (m, $\alpha$-$H_{Val}$), 4.76–4.79 (dd, $J_{AX} = 2.5$ Hz, $J_{MX} = 5.2$ Hz, 4-H), 4.83 (m, $\alpha$-$H_{Phe}$), 6.40, 6.54 (2d, $J = 7.8$ Hz, N–$H_{Val}$), 6.74, 6.79 (2d, $J = 8.6$ Hz, N-$H_{Phe}$), 7.06–7.39 (m, 10 *ar* H) ppm; HPLC: $k'_1 = 2.89$, $k'_2 = 3.22$, $t_0 = 2.01$ (RP-18, *Me*CN/$H_2O$ 4/6); ratio of diastereoisomers 45:55.

*N-{-4-[(RS)-2-oxo-4-phenylazetidin-1-yl]propionyl}-L-valyl-L-Leucine methyl ester* (**5h**, $C_{24}H_{35}N_3O_5$)
From **4b** (0.14 g, 657 $\mu$mol) and L-*Val*-L-*Leu*-O*Me*-HCl (200 mg, 686 $\mu$mol). Yield 89 mg (30%); $R_f = 0.57$; $[\alpha]_D^{20} = -47.2°\ cm^2\ g^{-1}$ ($c = 0.65$, *Me*OH); IR: $\bar{\nu} = 3473$ (NH), 2993 (CH), 1757, 1643, 1540 (CO) $cm^{-1}$; $^1H$ NMR: $\delta = 0.93$ (d, $J = 6.6$ Hz, 2 $Me_{Leu}$), 0.95 (d, $J = 6.7$ Hz, 2 $Me_{Val}$), 1.60 (m, 2 $\beta$-$H_{Leu}$, $\gamma$-$H_{Leu}$), 2.0–2.11 (m, $\beta$-$H_{Val}$), 2.48–2.59 (m, $CH_2$), 2.75–2.82 (d, $J_{AM} = 14.6$ Hz, 3-H), 3.21–3.33 (m, 1H, $CH_2$, 3′-H), 3.36 (m, 1H, $CH_2$), 3.70, 3.71 (2s, O*Me*), 4.36 (m, $\alpha$-$H_{Leu}$), 4.56–4.59 (m, $\alpha$-$H_{Val}$, 4-H), 6.84 (d, $J = 8.8$ Hz, N–$H_{Leu}$), 6.96 (d, $J = 7.8$ Hz, N–$H_{Val}$), 7.31–7.34 (m, 5 *ar* H) ppm; HPLC: $k'_1 = 6.97$, $k'_2 = 7.33$, $t_0 = 2.01$ (RP-18, *Me*CN/$H_2O$ 4/6); ratio of diastereoisomers 49:51.

*N-{-3-(RS)-2-oxo-4-phenylazetidin-1-yl]propionyl}-L-phenylalanyl-L-phenylalanine methyl ester* (**5i**, $C_{31}H_{33}N_3O_5$)
From **4b** (0.34 g, 1.53 mmol) and L-*Phe*-L-*Phe*-O*Me*-HCl (0.7 g, 1.58 mmol). Yield 0.35 g (43%); $R_f = 0.64$ (*Ac*O*Et*/cyclohexane 1/1); $[\alpha]_D^{20} = -17.0°\ cm^2\ g^{-1}$ ($c = 1.0$, *Me*OH); IR: $\bar{\nu} = 3289$ (NH), 3061, 2950 (CH), 1745, 1645, 1543 (CO) $cm^{-1}$; $^1H$ NMR (300 MHz): $\delta = 2.37–2.44$ (m, $CH_2$), 2.77 (dd, $J_{AX} = 2.3$ Hz, $J_{AM} = 14.7$ Hz, 3-H), 2.97–3.07 (m, 4 $\beta$-$H_{Phe}$), 3.09–3.16 (m, 1H, $CH_2$), 3.21–3.3 (dd, $J_{MX} = 5.25$ Hz, $J_{AM} = 14.7$ Hz, 3′-H), 3.50 (m, 1H, $CH_2$), 3.67, 3.68 (2s, O*Me*), 4.39–4.52 (dd, $J_{AX} = 2.3$ Hz, $J_{MX} = 5.2$ Hz, 4-H), 4.56–4.64 (m, $\alpha$-$H_{Phe}$), 4.70–4.79 (m, $\alpha$-$H_{Phe}$), 6.00, 6.19 (2d, $J = 7.6$ Hz, N–$H_{Phe}$), 6.27, 6.35 (2d, $J = 7.7$ Hz, N–$H_{Phe}$), 7.00–7.36 (m, 15 *ar* H) ppm; HPLC: $k' = 3.36$, $t_0 = 1.89$ (RP-18, *Me*CN/$H_2O$ 1/1), $k' = 7.80$, $t_0 = 1.89$ (Chiralcel OJ-R, *Me*CN/$H_2O$ 3/7).

*N-{-3-[(RS)-2-oxo-4-phenylazetidin-1-yl]propionyl}-L-phenylalanyl-L-valine methyl ester* (**5j**, $C_{27}H_{33}N_3O_5$)
From **4b** (0.15 g, 700 $\mu$mol) and L-*Phe*-L-*Val*-O*Me*-HCl (0.2 g, 500 $\mu$mol). Yield 0.11 g (33%); $R_f = 0.72$; $[\alpha]_D^{20} =$

$-10.0°\ cm^2\ g^{-1}$ ($c = 1.1$, *Ac*O*Et*); IR: $\bar{\nu} = 3284$ (NH), 3064, 2967(CH), 1741, 1645, 1548 (CO) $cm^{-1}$; $^1H$ NMR: $\delta =$ 0.81–0.84 (d, $J = 7.0$ Hz, $Me_{Val}$), 0.84–0.88 (d, $J = 7.2$ Hz, $Me_{Val}$), 2.05 (m, $\beta$-$H_{Val}$), 2.42 (m, $CH_2$), 2.73–2.81 (d, 3-H), 3.05–3.08 (m, $CH_{2Phe}$), 3.19–3.39 (m, 1H, $CH_2$, 3′-H), 3.49 (m, 1H, $CH_2$), 3.69 (s, O*Me*), 4.39–4.45 (m, $\alpha$-$H_{Phe}$), 4.47–4.54 (m, 4-H), 4.65–4.72 (m, $\alpha$-$H_{Val}$), 6.25, 6.39 (2d, $J = 8.0$ Hz, N–$H_{Phe}$), 6.60 (d, N–$H_{Val}$), 7.23–7.38 (m, 10 *ar* H) ppm; HPLC: $k' = 0.69$, $t_0 = 1.89$ (RP-18, *Me*CN/$H_2O$ 7/3).

*N-{-3-[(RS)-2-oxo-4-phenylazetidin-1-yl]propionyl}-L-phenylalanyl-L-leucine methyl ester* (**5k**, $C_{28}H_{35}N_3O_5$)
From **4b** (0.15 g, 700 $\mu$mol) and L-*Phe*-L-*Leu*-O*Me*-HCl (0.31 g, 730 $\mu$mol). Yield 0.22 g (63%); $R_f = 0.93$; $[\alpha]_D^{20} = -19.0°\ cm^2\ g^{-1}$ ($c = 2$, *Me*OH); IR: $\bar{\nu} = 3284$ (NH), 3064, 2956 (CH), 1747, 1645, 1550 (CO) $cm^{-1}$; $^1H$ NMR: $\delta = 0.87$ (d, $J = 5.4$ Hz, 2 $Me_{Leu}$), 1.42–1.55 (m, $\gamma$-H, 2 $\beta$-$H_{Leu}$), 2.34–2.58 (m, $CH_2$), 2.73–2.79 (dd, $J_{AX} = 2.4$ Hz, $J_{AM} = 14.6$ Hz, 3-H), 3.04–3.09 (m, $CH_{2Phe}$), 3.31 (m, 1H, $CH_2$), 3.38 (dd, $J_{MX} = 5.1$ Hz, $J_{MB} = 14.6$ Hz, 3′-H), 3.5 (m, 1H, $CH_2$), 3.69, 3.70 (2s, O*Me*), 4.38–4.42 (dd, $J_{AX} = 2.4$ Hz, $J_{MX} = 5.2$ Hz, 4-H), 4.52–4.55 (m, $\alpha$-$H_{Leu}$), 4.66–4.77 (m, $\alpha$-$H_{Phe}$), 6.32–6.43 (2d, $J = 8.0$, 8.0 Hz, N–$H_{Leu}$), 6.45–6.52 (2d, $J = 6.0$, 8.0 Hz, N–$H_{Phe}$), 7.23–7.38 (m, 10 *ar* H) ppm; HPLC: $k' = 3.51$, $t_0 = 2.01$ (RP-18, *Me*CN/$H_2O$ 4/6).

*N-{-4-[(RS)-2-oxo-4-phenylazetidin-1-yl]butyryl}-L-alanyl-L-valine methyl ester* (**5l**, $C_{22}H_{31}N_3O_5$)
From **4c** (0.33 g, 1.6 mmol) and L-*Ala*-L-*Val*-O*Me*-HCl (0.3 g, 1.74 mmol). Yield 0.1 g (15%); $R_f = 0.66$; IR: $\bar{\nu} = 3302$ (NH), 3067, 2964, 2934 (CH), 1744, 1649, 1545 (CO) $cm^{-1}$; $^1H$ NMR: $\delta = 0.88$ (d, $J = 6.9$ Hz, $Me_{Val}$), 0.89 (d, $J = 6.6$ Hz, $Me_{Val}$), 0.92 (d, $J = 6.0$ Hz, $Me_{Ala}$), 1.22–1.32 (m, $CH_2$), 2.03 (m, $CH_2$), 2.13 (m, $\beta$-$H_{Val}$), 2.95 (dd, $J_{AX} = 2.2$ Hz, $J_{AM} = 14.9$ Hz, 3-H), 3.43 (m, 1H, $CH_2$), 3.55 (dd, $J_{MX} = 5.3$ Hz, $J_{AM} = 14.9$ Hz, 3′-H), 3.73, 3.74 (2s, O*Me*), 4.00–4.35 (2m, 1H, $CH_2$, $\alpha$-$H_{Ala}$), 4.47–4.55 (m, $\alpha$-$H_{Val}$), 4.79–4.83 (dd, $J_{AX} = 2.3$ Hz, $J_{MX} = 5.1$ Hz, 4-H), 6.44–6.55 (m, N–H), 6.86 (d, $J = 7.8$ Hz, N–H), 7.34 (m, 5 *ar* H) ppm.

*N-{-4-[(RS)-2-oxo-4-phenylazetidin-1-yl]butyryl}-L-valyl-L-valine methyl ester* (**5m**, $C_{24}H_{35}N_3O_5$)
From **4c** (0.4 g, 1.71 mmol) and L-*Val*-L-*Val*-O*Me*-HCl (0.41 g, 1.78 mmol). Yield 0.1 g (12%); $R_f = 0.59$; $[\alpha]_D^{20} = -35.25°\ cm^2\ g^{-1}$ ($c = 2$, *Me*OH); IR: $\bar{\nu} = 3300$ (NH), 3067, 2964, 2934 (CH), 1732, 1644, 1548 (CO) $cm^{-1}$; $^1H$ NMR: $\delta = 0.90$, 0.92 (d, $J = 6.9$ Hz, $Me_{Val}$), 0.95, 0.98 (d, $J =$ 7.0 Hz, $Me_{Val}$), 1.67–1.86 (m, $CH_2$), 2.07–2.22 (m, 2 $\beta$-$H_{Val}$), 2.29–2.42 (m, $CH_2$), 2.81–2.91 (dd, $J_{AX} = 2.15$ Hz, $J_{AM} = 14.8$ Hz, 3-H), 3.00–3.13 (m, 1H, $CH_2$), 3.33–3.41 (dd, $J_{MX} = 5.2$ Hz, $J_{AM} = 14.8$ Hz, 3′-H), 3.44–3.62 (m, 1H, $CH_2$), 3.70 (s, O*Me*), 4.36–4.47 (m, $\alpha$-$H_{Val}$), 4.50–4.57 (m, $\alpha$-$H_{Val}$), 4.60–4.64 (dd, $J_{AX} = 2.15$ Hz, $J_{MX} = 5.2$ Hz, 4-H), 7.03–7.19 (m, 2 N–H), 7.31–7.44 (m, 5 *ar* H) ppm; HPLC: $k' = 1.67$, $t_0 = 2.13$ (RP-18, *Me*CN/$H_2O$ 1/1), $k'_1 = 8.40$, $k'_2 = 8.72$, $t_0 = 2.23$ (RP-18, *Me*CN/$H_2O$ 3/7); ratio of diastereoisomers 42:58.

*N-{-4-[(RS)-2-oxo-4-phenylazetidin-1-yl]butyryl}-L-valyl-L-leucine methyl ester* (**5n**, $C_{25}H_{37}N_3O_5$)
From **4c** (0.4 g, 1.71 mmol) and L-*Val*-L-*Leu*-O*Me*-HCl (0.44 g, 1.78 mmol). Yield 0.26 g (33%); $R_f = 0.55$ (*Ac*O*Et*/cyclohexane 1/1); $[\alpha]_D^{20} = -52.00°\ cm^2\ g^{-1}$ ($c = 2$, *Me*OH); IR: $\bar{\nu} = 3294$ (NH), 3060 (CH), 2959, 2872 (CH), 1750, 1642, 1543 (CO) $cm^{-1}$; $^1H$ NMR: $\delta = 0.93$ (d, $J = 6.9$ Hz, 2 $Me_{Val}$), 0.96 (d, $J = 6.4$ Hz, 2 $Me_{Leu}$), 1.69 (m, $\gamma$-$H_{Leu}$), 1.73 (m, $\beta$-$H_{Leu}$), 176 (m, $CH_2$), 2.13 (m, $\beta$-$H_{Val}$), 2.16 (m, $CH_2$), 2.88 (dd, $J_{AX} = 2.2$ Hz, $J_{AM} = 14.6$ Hz, 3-H), 3.05 (d, 1H, $CH_2$), 3.31 (dd, $J_{MX} = 5.1$ Hz, $J_{AM} = 14.6$ Hz, 3′-H), 3.52–3.59 (m, 1H, $CH_2$), 3.70 (s, O*Me*), 4.34 (m, $\alpha$-$H_{Val}$), 4.44 (m, $\alpha$-$H_{Leu}$), 4.60 (dd, $J_{AX} = 2.2$ Hz, $J_{MX} = 5.1$ Hz, 4-H), 7.11 (d, $J = 8.8$ Hz, N–H), 7.18 (d, $J = 8.9$ Hz, N–H), 7.34 (m, 5 *ar* H) ppm; HPLC: $k'_1 = 14.15$, $k'_2 = 14.99$, $t_0 = 2.23$ (RP-18, *Me*CN/$H_2O$ 3/7); ratio of diastereoisomers 57:43.

*N-{-4-[(RS)-2-oxo-4-phenylazetidin-1-yl]butyryl}-L-phenylalanyl-L-leucine methyl ester* (**5o**, $C_{29}H_{37}N_3O_5$)
From **4c** (0.41 g, 1.73 mmol) and L-*Phe*-L-*Leu*-O*Me*-HCl (0.53 g, 1.80 mmol). Yield 0.24 g (27%); $R_f = 0.67$; $[\alpha]_D^{20} = -27.00°\ cm^2\ g^{-1}$ ($c = 2$, *Me*OH); IR: $\bar{\nu} =$ 3287 (NH), 3063, 2955, 2869 (CH), 1751, 1643, 1547 (CO) $cm^{-1}$; $^1H$ NMR: $\delta = 0.89$ (d, 2 *Me*), 1.56 (m, $\gamma$-H, 2 $\beta$-$H_{Leu}$), 1.71 (m, $CH_2$), 2.18–2.21 (m, $CH_2$), 2.77–2.87 [(m, 1H, $CH_2$), (dd, $J_{AX} =$ 2.9 Hz, $J_{AM} = 14.6$ Hz, 3-H), 3.04–3.22 (m, 2 $\beta$-$H_{Phe}$), 3.30–3.40 (m, 1H, $CH_2$; dd, $J_{MX} = 5.0$ Hz, $J_{AM} = 14.6$ Hz, 3′-H), 3.69 (s, O*Me*), 4.53–4.55 {(m, 4-H, $\alpha$-$H_{Leu}$), 4.71–4.78 (m, $\alpha$-$H_{Phe}$), 6.43 (2d, N-$H_{Leu}$), 6.81–6.99 (m, N–$H_{Phe}$), 7.35 (m, 10 *ar* H) ppm; HPLC: $k'_1 = 10.39$, $k'_2 = 10.69$, $t_0 = 1.83$ (RP-18, *Me*CN/$H_2O$ 4/6); ratio of diastereoisomers 48:52.

*N-{-4-[(RS)-2-oxo-4-phenylazetidin-1-yl]butyryl}-L-phenylalanyl-L-valine methyl ester* (**5p**, $C_{28}H_{35}N_3O_5$)
From **4c** (0.3 g, 1.28 mmol) and L-*Phe*-L-*Val*-O*Me*-HCl (0.52 g, 1.33 mmol). Yield 0.38 g (60%); $R_f = 0.58$; $[\alpha]_D^{20} = -11.00°\ cm^2\ g^{-1}$ ($c = 2$, *Me*OH); IR: $\bar{\nu} = 3290$ (NH), 3064, 2962 (CH), 1749, 1645,1541 (CO) $cm^{-1}$; $^1H$ NMR: $\delta = 0.81$–0.89 (d, $J = 7.0$ Hz, 2 $Me_{Val}$), 1.56–173 (m, $CH_2$), 2.04–2.26 (m, $\beta$-$H_{Val}$, $CH_2$), 2.70–2.91 (dd, $J_{AX} = 2.2$ Hz, $J_{AM} = 14.6$ Hz, 3-H, m, 1H, $CH_2$), 2.97–3.22 (m, 2 $\beta$-$H_{Phe}$), 3.31–3.45 (dd, $J_{MX} = 5.0$ Hz, $J_{AM} = 14.8$ Hz, 3′-H, m, 1H, $CH_2$), 3.69 (s, O*Me*), 4.38–4.47 (m, $\alpha$-$H_{Val}$), 4.50–4.55 (dd, $J_{AX} = 2.1$ Hz, $J_{MX} = 4.95$ Hz, 4-H), 4.66–4.80 (m, $\alpha$-$H_{Phe}$), 6.36, 6.50 (2d, $J = 7.2$ Hz, N–$H_{Val}$), 6.75, 6.81 (2d, $J = 8.6$ Hz, N–$H_{Phe}$), 7.11–7.40 (m, 10 *ar* H) ppm; HPLC: $k' = 5.51$, $t_0 = 1.89$ (RP-18, *Me*CN/$H_2O$ 1/1).

*N-{-4-[(RS)-2-oxo-4-phenylazetidin-1-yl]butyryl}-L-valyl-L-phenylalanine methyl ester* (**5q**, $C_{28}H_{35}N_3O_5$)
From **4c** (0.3 g, 1.28 mmol) and L-*Val*-L-*Phe*-O*Me*-HCl (0.52 g, 1.33 mmol). Yield 169 mg (27%); $R_f = 0.41$; $[\alpha]_D^{20} = -31.25°\ cm^2\ g^{-1}$ ($c = 2$, *Me*OH); IR: $\bar{\nu} = 3291$ (NH), 3063, 2960 (CH), 1748, 1641, 1540 (CO) $cm^{-1}$; $^1H$ NMR: $\delta = 0.84$ (d, $J = 7.1$ Hz, $Me_{Val}$), 0.92 (d, $J = 8.0$ Hz, $Me_{Val}$), 1.57–1.87 (m, $CH_2$), 2.00–2.22 (m, $\beta$-$H_{Val}$), 2.22–2.37 (m, $CH_2$), 2.76–2.90 (dd, $J_{AX} = 2.1$ Hz, $J_{AM} = 14.6$ Hz, 3-H), 3.00–3.26 (m, 1H, $CH_2$, $CH_{2Phe}$), 3.32–3.57 (m, 1H, $CH_2$), 3.34–3.44 (dd,

$J_{MX}$ = 5.1 Hz, $J_{AM}$ = 14.6 Hz, 3′-H), 3.69 (s, O*Me*), 4.25–4.32 (m, α-$H_{Val}$), 4.55–4.60 (dd, $J_{AX}$ = 2.1 Hz, $J_{MX}$ = 5.1 Hz, 4-H), 4.82–4.94 (m, α-$H_{Phe}$), 6.71–6.78 (2d, $J$ = 8.2, 7.3 Hz, N–$H_{Val}$), 6.91–6.94 (2d, $J$ = 8.8, 8.0 Hz, N–$H_{Phe}$), 7.13–7.37 (m, 10 *ar* H) ppm; HPLC: $k'_1$ = 5.76, $k'_2$ = 6.01, $t_0$ = 1.89 (RP-18, *Me*CN/$H_2O$ 1/1), $k'_1$ = 8.18, $k'_2$ = 8.65, $t_0$ = 2.01 (RP-18, *Me*CN/$H_2O$ 4/6); ratio of diastereoisomers 54:46.

*N-{-4-[(RS)-2-oxo-4-phenylazetidin-1-yl]butyryl}-L-phenylalanyl-L-phenylalanine methyl ester* (**5r**, $C_{32}H_{35}N_3O_5$)
From **4c** (0.3 g, 1.28 mmol) and L-*Phe*-L-*Phe*-O*Me*-HCl (0.58 g, 1.61 mmol). Yield 0.28 g (41%); $R_f$ = 0.61; $[\alpha]_D^{20}$ = −13.75° cm$^2$ g$^{-1}$ (*c* = 2, *Me*OH); IR: $\bar{\nu}$ = 3278 (NH), 3061, 2949 (CH), 1732, 1651, 1538 (CO) cm$^{-1}$; $^1$H NMR: δ = 1.57–1.78 (m, $CH_2$), 2.04–2.20 (m, $CH_2$), 2.66–3.14 (dd, $J_{AX}$ = 2.2 Hz, $J_{AM}$ = 14.6 Hz, 3-H), 2.66–2.76 (m, 1H, $CH_2$), 2.89–3.14 (m, 4 β-$H_{Phe}$), 3.25–3.40 (m, 1H, $CH_2$), 3.30–3.40 (dd, $J_{MX}$ = 5.0 Hz, $J_{AM}$ = 14.6 Hz, 3′-H), 3.67 (s, O*Me*), 4.50–4.54 (dd, $J_{AX}$ = 2.2 Hz, $J_{MX}$ = 5.0 Hz, 4-H), 4.59–4.70 (m, α-$H_{Phe}$), 4.78 (m, α-$H_{Phe}$), 6.70 (d, $J$ = 7.8 Hz, N–$H_{Phe}$), 6.79 (d, $J$ = 7.4 Hz, N–$H_{Phe}$), 7.06–7.39 (m, 15 *ar* H) ppm; HPLC: $k'$ = 11.12, $t_0$ = 2.12 (RP-18, *Me*CN/$H_2O$ 3/7), $k'_1$ = 7.30, $k'_2$ = 7.97, $t_0$ = 2.73 ((S,S)-Whelk 01, *n*-hexane/2-propanol 1/1); ratio of diastereoisomers 54:46.

*N-{-5-[(RS)-2-oxo-4-phenylazetidin-1-yl]valerianyl}-L-valyl-L-leucine methyl ester* (**5s**, $C_{26}H_{39}N_3O_5$)
From **4d** (0.32 g, 1.21 mmol) and L-*Val*-L-*Leu*-O*Me*-HCl (0.45 g, 1.26 mmol). Yield 0.39 g (67%); $R_f$ = 0.54; IR: $\bar{\nu}$ = 3290 (NH), 3066, 2958 (CH), 1750, 1645,1540 (CO) cm$^{-1}$; $^1$H NMR: δ = 0.92 (d, $J$ = 6.0 Hz, 2 $Me_{Leu}$), 0.95 (d, $J$ = 7.0 Hz, 2 $Me_{Val}$), 1.49–1.62 (m, 2$CH_2$, 2 β-H, γ-$H_{Leu}$), 2.02–2.20 (m, $CH_2$, β-$H_{Val}$), 2.72–2.86 (m, 3-H, 1H, $CH_2$), 3.31–3.43 (m, 3′-H, 1H, $CH_2$), 3.72 (s, O*Me*), 4.25–4.33 (m, α-$H_{Val}$), 4.55–4.58 (m, α-$H_{Leu}$, 4-H), 6.31 (d, $J$ = 8.6 Hz, N-$H_{Leu}$), 6.51 (d, $J$ = 7.8 Hz, N–$H_{Val}$), 7.33 (m, *ar* H) ppm; HPLC: $k'$ = 2.46, $t_0$ = 2.13 (RP-18, *Me*CN/$H_2O$ 1/1).

*N-{-5-[(RS)-2-oxo-4-phenylazetidin-1-yl]valerianyl}-L-phenylalanyl-L-valine methyl ester* (**5t**, $C_{29}H_{37}N_3O_5$)
From **4d** (0.3 g, 1.21 mmol) and L-*Phe*-L-*Val*-O*Me*-HCl 493 mg (1.26 mmol). Yield 0.2 g (32%); $R_f$ = 0.54; $[\alpha]_D^{20}$ = −10.80° cm$^2$ g$^{-1}$ (*c* = 2, *Me*OH); IR: $\bar{\nu}$ = 3287 (NH), 3064, 2962 (CH), 1748, 1640, 1542 (CO) cm$^{-1}$; $^1$H NMR: δ = 0.81 (d, $J$ = 7.1 Hz, $Me_{Val}$), 0.84 (d, $J$ = 6.9 Hz, $Me_{Val}$), 1.41–1.59 (m, 2$CH_2$), 2.04–2.15 (m, β-$H_{Val}$, $CH_2$), 2.79–2.85 (m, 3-H, 1H, $CH_2$), 3.04 (d, $J$ = 7.1 Hz, 2 β-$H_{Phe}$), 3.28–3.41 (dd, $J_{MX}$ = 5.1 Hz, $J_{AM}$ = 14.5 Hz, 3′-H, m, 1H, $CH_2$), 3.69 (s, O*Me*), 4.39–4.46 (dd, $J$ = 5.0, 8.4 Hz, α-$H_{Val}$), 4.53 (dd, $J_{AX}$ = 2.4 Hz, $J_{MX}$ = 5.0 Hz, 4-H), 4.62–4.73 (dd, $J$ = 7.4, 14.7 Hz, α-$H_{Phe}$), 6.29 (d, $J$ = 4.2 Hz, N–$H_{Val}$), 6.38 (d, $J$ = 6.8 Hz, N–$H_{Phe}$), 7.23–7.39 (m, 10 *ar* H) ppm; HPLC: $k'$ = 5.10, $t_0$ = 1.89 (RP-18, *Me*CN/$H_2O$ 1/1).

*N-{-5-[(RS)-2-oxo-4-phenylazetidin-1-yl]valerianyl}-L-valyl-L-phenylalanine methyl ester* (**5u**, $C_{29}H_{37}N_3O_5$)
From **4d** (0.3 g, 1.21 mmol) and L-*Val*-L-*Phe*-O*Me*-HCl (0.5 g, 1.25 mmol). Yield 0.14 g (23%); $R_f$ = 0.39; $[\alpha]_D^{20}$ = −24.00° cm$^2$ g$^{-1}$ (*c* = 2, *Me*OH); IR: $\bar{\nu}$ = 3292 (NH), 3063, 2956 (CH), 1746, 1643, 1540 (CO) cm$^{-1}$; $^1$H NMR: δ = 0.84 (d, $J$ = 6.15 Hz, $Me_{Val}$), 0.92 (d, $J$ = 6.6 Hz, $Me_{Val}$),1.48–1.78 (m, 2$CH_2$), 2.04–2.11 (m, β-$H_{Val}$), 2.16–2.33 (m, $CH_2$), 2.77–2.91 (dd, $J_{AX}$ = 2.7 Hz, $J_{AM}$ = 14.3 Hz, 3-H, m, 1H, $CH_2$), 3.08 (dd, $J$ = 6.2, 14.5 Hz, 2 β-$H_{Phe}$), 3.29–3.48 (dd, $J_{MX}$ = 5.4 Hz, $J_{AM}$ = 14.9 Hz, 3′-H, m, 1H, $CH_2$), 3.69, 3.71 (2s, O*Me*), 4.20–4.34 (m, α-$H_{Val}$), 4.53–4.60 (dd, $J_{AX}$ = 2.6 Hz, $J_{MX}$ = 5.2 Hz, 4-H), 4.81–4.94 (dd, $J$ = 6.1, 7.8 Hz, α-$H_{Phe}$), 6.19 (d, $J$ = 8.3 Hz, N–$H_{Val}$), 6.39 (d, $J$ = 7.9 Hz, N–$H_{Phe}$), 7.08–7.36 (m, 10 *ar* H) ppm; HPLC: $k'$ = 5.61, $t_0$ = 1.89 (RP-18, *Me*CN/$H_2O$ 1/1), $k'_1$ = 32.99, $k'_2$ = 35.57, $t_0$ = 2.39 (RP-18, *Me*CN/$H_2O$ 3/7); ratio of diastereoisomers 21:79.

*N-{-5-[(RS)-2-oxo-4-phenylazetidin-1-yl]valerianyl}-L-phenylalanyl-L-phenylalanine methyl ester* (**5v**, $C_{33}H_{37}N_3O_5$)
From **4d** (0.3 g, 1.21 mmol) and L-*Phe*-L-*Phe*-O*Me*-HCl (0.55 g, 1.25 mmol). Yield 0.14 g (10%); $R_f$ = 0.55; IR: $\bar{\nu}$ = 3281 (NH), 3061, 2949 (CH), 1747, 1642, 1543 (CO) cm$^{-1}$; $^1$H NMR: δ = 1.39–1.66 (m, 2 $CH_2$), 2.04–2.12 (m, $CH_2$), 2.76–2.83 (dd, $J_{AX}$ = 2.2 Hz, $J_{AM}$ = 14.4 Hz, 3-H), 2.92–3.15 (m, 1H, $CH_2$, 4 β-$H_{Phe}$), 3.27–3.37 (dd, $J_{MX}$ = 5.2 Hz, $J_{AM}$ = 14.4 Hz, 3′-H), 3.33–3.43 (m, 1H, $CH_2$), 3.67, 3.68 (2s, O*Me*), 4.51–4.55 (dd, $J_{AX}$ = 2.2 Hz, $J_{MX}$ = 5.2 Hz, 4-H), 4.55–4.66 (dd, $J$ = 7.2, 7.4 Hz, α-$H_{Phe}$), 4.7–4.8 (dd, $J$ = 6.2, 7.2 Hz, α-$H_{Phe}$), 6.12 (d, $J$ = 7.4 Hz, N–$H_{Phe}$), 6.24 (d, $J$ = 7.5 Hz, N–$H_{Phe}$), 6.98–7.39 (m, 15 *ar* H) ppm; HPLC: $k'$ = 5.85, $t_0$ = 1.89 (RP-18, *Me*CN/$H_2O$ 1/1), $k'$ = 9.65, $t_0$ = 1.89 (Chiralcel OJ-R, *Me*CN/$H_2O$ 3/7).

*N-{2-[(RS)-2-oxo-4-phenylazetidin-1-yl]acetyl}-L-valine methyl ester* (**6a**, $C_{17}H_{22}N_2O_4$)
From **4a** (0.3 g, 1.46 mmol) and L-*Val*-O*Me*-HCl (0.26 g, 1.52 mmol). Yield 0.46 g (99%); $R_f$ = 0.66; $[\alpha]_D^{20}$ = −18.00° cm$^2$ g$^{-1}$ (*c* = 2, *Me*OH); IR: $\bar{\nu}$ = 3291 (NH), 3061, 2959 (CH), 1754, 1649, 1540 (CO) cm$^{-1}$; $^1$H NMR: δ = 0.92, 0.93 (2d, each $J$ = 6.8 Hz, 2 $Me_{Val}$), 2.15 (m, β-$H_{Val}$), 2.91–2.98 (dd, $J_{AX}$ = 2.4 Hz, $J_{AM}$ = 14.9 Hz, 3-H), 3.41–3.56 (m, 1H, $CH_2$), 3.47 (dd, $J_{MX}$ = 5.2 Hz, $J_{AM}$ = 14.9 Hz, 3′-H), 3.74 (s, O*Me*), 4.14 (m, 1H, $CH_2$), 4.47 (dd, $J$ = 4.9, 8.5 Hz, α-$H_{Val}$), 4.82 (dd, $J_{AX}$ = 2.4 Hz, $J_{MX}$ = 5.2 Hz, 4-H), 6.74 (d, $J$ = 8.2 Hz, N–$H_{Val}$), 7.26 (m, 5 *ar* H) ppm; HPLC: $k'_1$ = 6.74, $k'_2$ = 7.27, $t_0$ = 1.81 (RP-18, *Me*CN/$H_2O$ 4/6), ratio of diastereoisomers 54:46.

*N-{-3-[(RS)-2-oxo-4-phenylazetidin-1-yl]propionyl}-L-alanine benzyl ester* (**6b**, $C_{22}H_{24}N_2O_4$)
From **4b** (0.5 g, 2.28 mmol) and L-*Ala*-O*Bn*-tosylate (0.83 g, 2.37 mmol). Yield 0.43 g (50%); $R_f$ = 0.45; $[\alpha]_D^{20}$ = −29.0° cm$^2$ g$^{-1}$ (*c* = 1.0, *Me*OH); IR: $\bar{\nu}$ = 3323 (NH), 3065, 2924 (CH), 1733, 1669, 1540 (CO) cm$^{-1}$; $^1$H NMR: δ = 1.37, 1.42 (2d, each $J$ = 7.2 Hz, $Me_{Ala}$), 2.44–2.57 (m, $CH_2$), 2.77 (dd, $J_{AX}$ = 3.6 Hz, $J_{AM}$ = 14.7 Hz, 3-H), 3.20 (m, 1H, $CH_2$), 3.28 (dd, $J_{MX}$ = 4.2 Hz, $J_{AM}$ = 14.7 Hz, 3′-H), 3.54 (m, 1H, $CH_2$), 4.52 (m, α-$H_{Ala}$), 4.57 (dd, $J_{AX}$ = 3.6 Hz, $J_{MX}$ = 4.2 Hz, 4-H), 5.17 (d, $J$ = 2.2 Hz, $CH_{2benzyl}$), 6.40 (s, br, N–H), 7.30–7.35 (m, 10 *ar* H) ppm; HPLC: $k'$ = 0.74, $t_0$ = 1.78 (RP-18, *Me*CN/$H_2O$ 3/7), $k'_1$ = 1.13, $k'_2$ = 2.02,

$t_0 = 1.80$ (Chiralcel OJ-R, *Me*CN/$H_2O$ 4/6); ratio of diastereoisomers 52:48.

*N-{-4-[(RS)-2-oxo-4-phenylazetidin-1-yl]butyryl}-L-valine methyl ester* (**6c**, $C_{19}H_{26}N_2O_4$)
From **4c** (0.3 g, 1.28 mmol) and L-*Val*-O*Me*-HCl (0.22 g, 1.34 mmol). Yield 0.25 g (57%); $R_f = 0.69$; $[\alpha]_D^{20} = -15.25^\circ\,cm^2\,g^{-1}$ ($c = 2$, *Me*OH); IR: $\bar{\nu} = 3299$ (NH), 3033, 2963 (CH), 1740, 1654, 1540 (CO) $cm^{-1}$; $^1H$ NMR: $\delta = 0.95$, 0.97 (2d, each $J = 6.8$ Hz, 2 $Me_{Val}$), 1.76 (m, $CH_2$), 2.19 (m, $\beta$-$H_{Val}$), 2.33 (m, $CH_2$), 2.85 (dd, $J_{AX} = 2.0$ Hz, $J_{AM} = 14.7$ Hz, 3-H), 3.31 (dt, $J = 8.5$, 14.5 Hz, 1H, $CH_2$), 3.35 (dd, $J_{MX} = 5.2$ Hz, $J_{AM} = 14.7$ Hz, 3′-H), 3.62 (dt, $J = 8.3$, 14.5 Hz, 1H, $CH_2$), 3.72 (s, O*Me*), 4.48 (dd, $J = 4.5$, 8.7 Hz, $\alpha$-$H_{Val}$), 4.59 (dd, $J_{AX} = 2.2$ Hz, $J_{MX} = 5.2$ Hz, 4-H), 7.06 (d, $J = 8.25$ Hz, N–$H_{Val}$), 7.31 (m, 5 *ar* H) ppm; HPLC: $k' = 9.27$, $t_0 = 2.12$ (RP-18, *Me*CN/$H_2O$ 3/7).

*N-{-5-[(RS)-2-oxo-4-phenylazetidin-1-yl]valerianyl}-L-valine methyl ester* (**6d**, $C_{20}H_{28}N_2O_4$)
From **4d** (0.3 g, 1.21 mmol) and L-*Val*-O*Me*-HCl (0.21 g, 1.26 mmol). Yield 0.26 g (57%); $R_f = 0.52$; $[\alpha]_D^{20} = -18.50^\circ\,cm^2\,g^{-1}$ ($c = 2$, *Me*OH); IR: $\bar{\nu} = 3330$ (NH), 2963 (CH), 1742, 1650, 1537 (CO) $cm^{-1}$; $^1H$ NMR: $\delta = 0.91$, 0.93 (2d, each $J = 6.7$ Hz, 2 $Me_{Val}$), 1.51 (m, $CH_2$), 1,67 (m, $CH_2$), 2.07 (m, $\beta$-$H_{Val}$), 2.26 (m, $CH_2$), 2.82 (dd, $J_{AX} = 2.0$ Hz, $J_{AM} = 14.4$ Hz, 3-H), 2.86 (m, 1H, $CH_2$), 3.35 (dd, $J_{MX} = 4.6$ Hz, $J_{AM} = 14.5$ Hz, 3′-H), 3.43 (m, 1H, $CH_2$), 3.73 (s, O*Me*), 4.50 (dd, $J = 5.1$, 8.8 Hz, $\alpha$-$H_{Val}$), 4.57 (dd, $J_{AX} = 2.8$ Hz, $J_{MX} = 4.6$ Hz, 4-H), 6.21 (d, $J = 5.6$, N–$H_{Val}$), 7.42 (m, 5 *ar* H) ppm; HPLC: $k' = 2.82$, $t_0 = 1.89$ (RP-18, *Me*CN/$H_2O$ 1/1).

*N-{-5-[(RS)-2-oxo-4-phenylazetidin-1-yl]valerianyl}-L-aspartic acid dibenzyl ester* (**6e**, $C_{32}H_{34}N_2O_6$)
From **4d** (0.5 g, 1.02 mmol) and L-*Asp*(O*Bn*)$_2$-HCl (1.0 g, 2.1 mmol). Yield 0.31 g (55%); $R_f = 0.64$; $[\alpha]_D^{20} = -11.9^\circ\,cm^2\,g^{-1}$ ($c = 2$, *Me*OH); IR: $\bar{\nu} = 3305$ (NH), 3062, 2949 (CH), 1737, 1672, 1537 (CO) $cm^{-1}$; $^1H$ NMR: $\delta = 1.44$ (m, $2CH_2$), 2.15 (m, $CH_2$), 2.79 (m, $CH_{2Asp}$), 3.02 (dd, $J = 2.9$, 14.4 Hz, 3-H), 3.29 (dd, $J = 5.2$, 14.4 Hz, 3′-H), 3.37 (m, 1H, $CH_2$), 3.84 (m, 1H, $CH_2$), 4.53 (dd, $J = 2.9$, 5.2 Hz, 4-H), 4.87 (m, $\alpha$-$H_{Asp}$), 5.05, 5.13 (2d, $2CH_{2benzyl}$), 6.48 (d, $J = 7.8$, N–H), 7.33 (m, 15 *ar* H) ppm; HPLC: $k' = 9.81$, $t_0 = 1.89$ (RP-18, *Me*CN/$H_2O$ 1/1), $k'_1 = 21.68$, $k'_2 = 22.94$, $t_0 = 1.89$ (Chiralcel OJ-R, *Me*CN/$H_2O$ 3/7), ratio of diastereoisomers 60:40.

*N-{-5-[(RS)-2-oxo-4-phenylazetidin-1-yl]valerianyl}-L-alanine benzyl ester* (**6f**, $C_{24}H_{28}N_2O_4$)
From **4d** (0.5 g, 2.02 mmol) and L-*Ala*-O*Bn*-tosylate (0.74 g, 2.10 mmol). Yield 0.2 g (24%); $R_f = 0.50$; $[\alpha]_D^{20} = -31.83^\circ\,cm^2\,g^{-1}$ ($c = 1.0$, *Me*OH); IR: $\bar{\nu} = 3452$ (NH), 2929 (CH), 1735, 1652, 1540 (CO) $cm^{-1}$; $^1H$ NMR: $\delta = 1.35$ (d, $J = 7.1$ Hz, $Me_{Ala}$), 1.59 (m, $2CH_2$), 2.20 (m, $CH_2$), 2.71–2.78 (m, 3-H, 1H, $CH_2$), 3.26–3.42 (m, 3′-H, 1H, $CH_2$), 4.54–4.61 (m, 4-H, $\alpha$-$H_{Ala}$), 5.12 (dd, $CH_{2benzyl}$), 7.01 (d, $J = 7.3$ Hz, N–H), 7.30 (m, 10 *ar* H) ppm; HPLC: $k' = 0.86$, $t_0 = 1.78$ (RP-18, *Me*CN/$H_2O$ 7/3), $k'_1 = 1.28$, $k'_2 = 1.46$, $t_0 = 1.89$ (Chiralcel OJ-R, *Me*CN/$H_2O$ 4/6), ratio of diastereoisomers 52:48.

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