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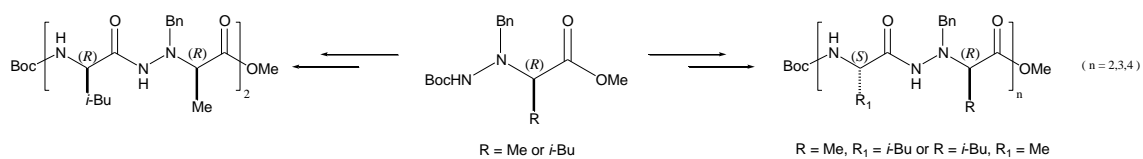
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An expedient and short synthesis of chiral α -hydrazinoesters: Synthesis and conformational analysis of 1:1 [α/α - N^α -hydrazino]mers

Ralph-Olivier Moussodia, Samir Acherar, Andrea Bordessa, Régis Vanderesse and Brigitte Jamart-Grégoire*

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Graphical Abstract



An expedient and short synthesis of chiral α -hydrazinoesters: Synthesis and conformational analysis of 1:1 [α/α - N^α -hydrazino] mers

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Abstract – Different α -hydrazinoesters with high optical purity have been obtained in large scale via a S_N2 protocol. A coupling reaction with a natural aminoacid leads to the corresponding dimers which have been oligomerized in order to obtain the 1:1 [α/α - N^α -hydrazino]mer series.. Conformational studies show that these mixed oligomers are self-organized in solution via a succession of γ -turn and hydrazinoturn whatever the absolute configuration of the chiral carbons.

Keywords: Pseudopeptide; α -Hydrazinoester; Hydrazinopeptide; 1:1 [α/α - N^α -hydrazino]mers; S_N2 ; hydrazinoturn

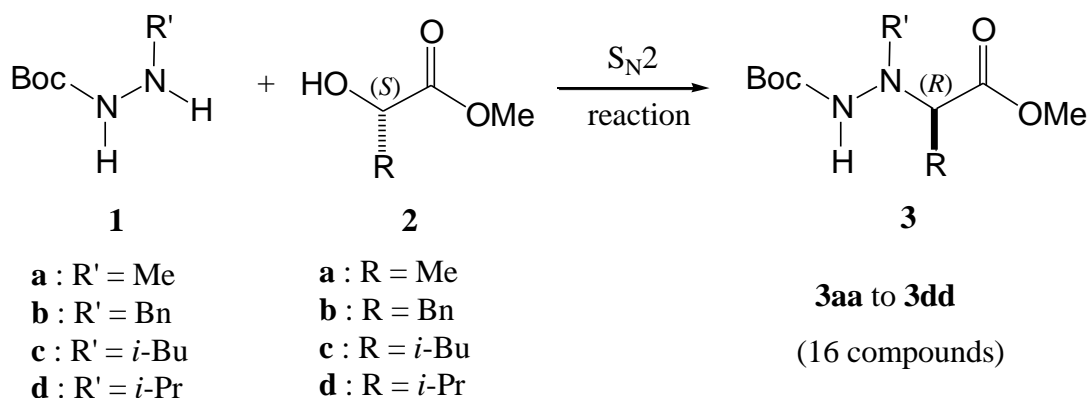
1. Introduction

For several years now, important efforts have been devoted to improve the pharmacological properties of natural peptides by a structure modification of the peptide bond CONH group.¹ Among the numerous possibilities, the replacement of one (or more) peptidic bond(s) by one (or more) hydrazidic bond(s) leads to hydrazinopeptides.² Hydrazinopeptides represent a valuable class of mimetic replacements for the natural peptides backbone often leading to analogous of bioactive peptides which preserve biological activity³ and enhanced proteolytic stability.⁴ Furthermore, this additional backbone nitrogen might behave as a hydrogen bond acceptor able to stabilize secondary structure in oligomers.^{4,5} In 2003, Lelais and Seebach succeeded in building oligomers of optically pure α -hydrazinoacids⁴ units. Unfortunately, due to poor resonance dispersion and fast exchange between the NH signals, the NMR structural analyses performed on these kinds of oligomers didn't yield definitive conclusion on the conformation. However, X-Ray diffraction of the starting α -hydrazinoacid (compound **4a**) showed that the N^α -atom adopts a pyramidal conformation with an (*S*)-configuration and participates in the stabilization of a hydrazinoturn.

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More recent works have shown that mixed oligomers alternating a natural amino acid and an amino acid analogs were also able to fold in solution leading to the formation of a new kind of foldamers.⁶ In this paper, we describe the synthesis and the conformational analysis of two series of 1:1 [α/α - N^α -hydrazino]mers alternating natural α -amino acid units and α -hydrazino acid ones.

In our preliminary work,⁷ we demonstrated that bis-nitrogen containing amino acid analogs such as N^α -Me, N^β -Boc-protected α -hydrazinoesters derivatives **3a** could be easily synthesized in large scale with high optical purity via a S_N2 reaction between *tert*-butyl 2-methylhydrazinecarboxylate **1a** and the triflate derivative of (*S*)- α -hydroxyesters **2** (Scheme 1). In this paper, we decided to extend this protocol in order to obtain new α -hydrazinoesters **3** bearing an alkyl or a benzyl group (Bn, *i*-Bu and *i*-Pr) on the N^α atom, and to study the impact of their presence on the yield of the S_N2 reaction (Scheme 1). In a second part, we will describe the oligomerization of these new building blocks leading to a series of 1:1 [α/α - N^α -hydrazino]mers. The conformational analysis of homo (*R,R*) and hetero (*S,R*) series were investigated in order to assess the impact of the chirality on the conformation.



Scheme 1. Synthesis of α -hydrazinoesters derivatives **3**.

2. Results and Discussion

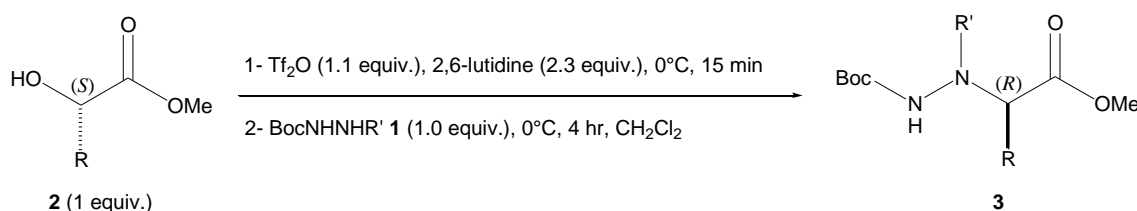
2.1. Synthesis of α -hydrazinoesters **3** and 1:1 [α/α - N^α -hydrazino]mers

α -hydrazinoesters **3** were prepared by using the same protocol as described in a previous work.⁷ The results summarized in Table 1, indicate that the S_N2 reaction also gives good yields (58-87%) when R corresponds to Me, Bn and *i*-Bu groups. α -

hydrazinoesters **3aa** to **3dc** can be obtained on a multigram scale in only one reaction. Conversely, we showed that this reaction was very sensitive to the steric hindrance of **2**. As a result, compounds **3ad** to **3bd** ($R = i\text{-Pr}$) were obtained with very poor yields and no reaction occurs between **1d** and **2d**. As a consequence, compounds **3ad** and **3bd** cannot be isolated in a pure form but are mixed with **2d** even after purification by flash chromatography.

On the contrary the comparison of the yields obtained for the synthesis of compounds **3aa** to **3da**, **3bb** to **3db** and **3ac** to **3dc** shows that the steric hindrance of R' has little influence on the yield of the reaction.

Table 1. Synthesis of α -hydrazinoesters **3** performed on a 30 mmol scale.



3	1 (R')	2 (R)	Yield (%)	$[\alpha]_{\text{D}}^{25}$ ($c=1$, MeOH)	3	1 (R')	2 (R)	Yield (%)	$[\alpha]_{\text{D}}^{25}$ ($c=1$, MeOH)
3aa	1a (Me)	2a (Me)	87 ⁽ⁱ⁾	-9.1	3ac	1a (Me)	2c (<i>i</i> -Bu)	80 ⁽ⁱ⁾	-20.2
3ba	1b (Bn)	2a (Me)	83 ⁽ⁱ⁾	-9.2	3bc	1b (Bn)	2c (<i>i</i> -Bu)	78 ⁽ⁱ⁾	-29.0
3ca	1c (<i>i</i> -Bu)	2a (Me)	80 ⁽ⁱ⁾	-20.9	3cc	1c (<i>i</i> -Bu)	2c (<i>i</i> -Bu)	62 ⁽ⁱ⁾	-19.7
3da	1d (<i>i</i> -Pr)	2a (Me)	62 ⁽ⁱ⁾	-28.2	3dc	1d (<i>i</i> -Pr)	2c (<i>i</i> -Bu)	58 ⁽ⁱ⁾	-21.7
3ab	1a (Me)	2b (Bn)	84 ⁽ⁱ⁾	-37.0	3ad	1a (Me)	2d (<i>i</i> -Pr)	15 ⁽ⁱⁱ⁾	-
3bb	1b (Bn)	2b (Bn)	82 ⁽ⁱ⁾	-5.2	3bd	1b (Bn)	2d (<i>i</i> -Pr)	10 ⁽ⁱⁱ⁾	-
3cb	1c (<i>i</i> -Bu)	2b (Bn)	78 ⁽ⁱ⁾	-25.6	3cd	1c (<i>i</i> -Bu)	2d (<i>i</i> -Pr)	22 ⁽ⁱ⁾	-0.6
3db	1d (<i>i</i> -Pr)	2b (Bn)	60 ⁽ⁱ⁾	-40.9	3dd	1d (<i>i</i> -Pr)	2d (<i>i</i> -Pr)	0 ⁽ⁱⁱⁱ⁾	-

(i): Yields calculated after purification by flash chromatography, (ii): Yields determined by ^1H NMR integration relative peaks after purification by flash chromatography, (iii): No reaction after 3 days.

Compounds **3ba** and **3bc** were then involved in an oligomerization process in order to obtain the hetero (S,R) and homo (R,R) 1:1 [$\alpha/\alpha\text{-}N^\alpha$ -hydrazino]mer series (Scheme 2).

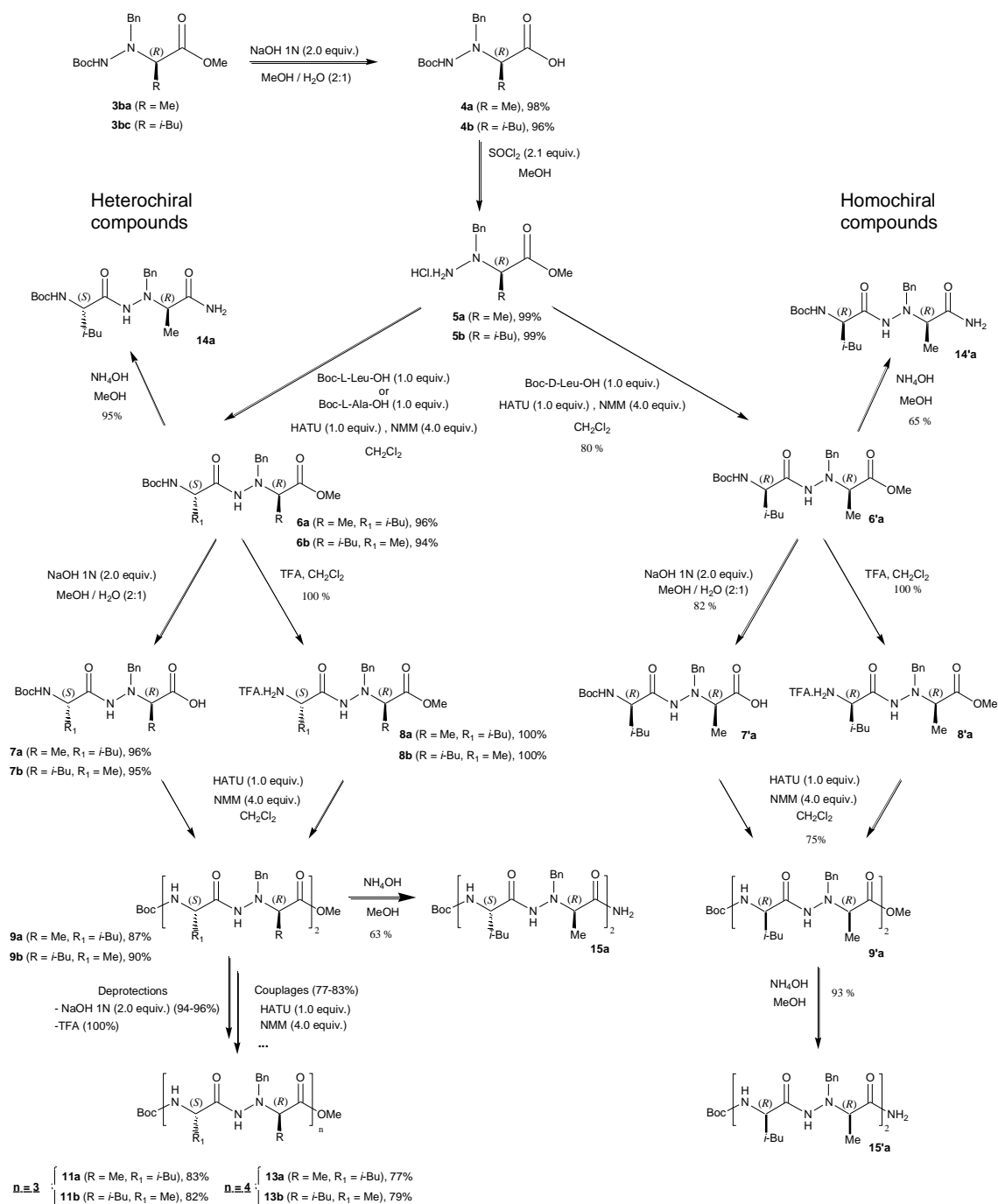
Heterochiral compounds **6a-b**, **9a-b**, **11a-b** and **13a-b** were obtained in very good yields ranging from 77 to 96% by an iterative sequence of deprotection and coupling reactions as described in Scheme 2. The saponification of the ester group of **3ba** and

3bc led to corresponding free C-terminal compounds **4a** and **4b** respectively. The use of thionyl chloride in methanol⁸ led simultaneously to the deprotection of hydrazine group and to the esterification of carboxylic to give compounds **5a** and **5b** in quantitative yields directly.

Various conditions (EDC, HOBT, HATU, HBTU...) were used in order to perform the coupling reaction between **5a** and Boc-L-Leu-OH and between **5b** and Boc-L-Ala-OH. The best results were obtained when using HATU and NMM which generate dimers **6a** and **6b** with excellent yields. The same protocol was also used for the synthesis of tetramers **9a-b**, hexamers **11a-b** and octamers **13a-b**.

When applied to **5a** and Boc-D-Leu-OH, these conditions led to the corresponding homochiral compounds **6'a** and **9'a**. Compounds **6a**, **9a**, **6'a** and **9'a** can easily be transformed into corresponding C-terminal amide compounds **14a**, **15a**, **14'a**, **15'a** which will be used for the conformational analysis.

It is interesting to notice that both ¹³C NMR spectra of **9a** and **9'a** present a unique set of signals. Moreover, the signals of the hydrazidic carbonyl groups were assigned at different chemical shifts, $\delta = 171.8$ ppm and $\delta = 172.1$ ppm for **9a** and **9'a**, respectively. This result confirms the absence of epimerisation (ee > 95%) during the coupling reaction and during the formation of corresponding α -hydazinoesters **3aa**.



Scheme 2. Synthesis of hetero (*S,R*) and homo (*R,R*) 1:1 [α - N^α -hydrazino]mers.

IR and NMR experiments were carried out in order to determine the ability of these oligomers to fold in solution. Then we compared the conformation of homo (*R,R*) and hetero (*S,R*) dimers **14a** and **14'a** and of tetramers **15a** and **15'a**.

2.2. Conformational analysis of homo and hetero oligomer series

2.2.1. Conformational analysis of homo and hetero dimers **14a** and **14'a**

Le Grel et al.⁹ demonstrated that chemical shifts difference $\Delta\delta$, calculated from the ¹H NMR signals of the two C-terminal amidic protons, can give information on the structuration of aza- β^3 and amidoxy derivatives (Figure 1).^{9,10} We decided to use this parameter to obtain information on the conformation of **14a** and **14'a**.

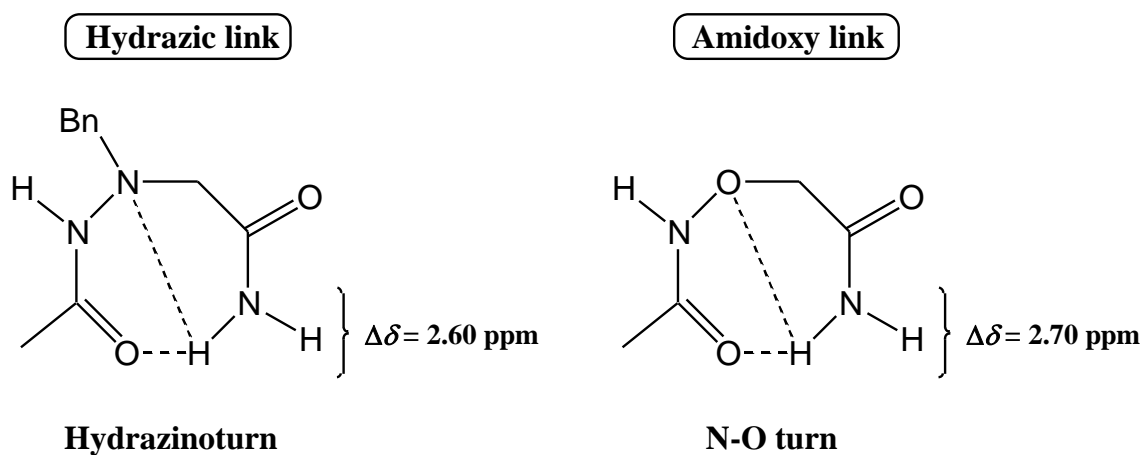


Figure 1. Comparison of $\Delta\delta$ values between hydrazidic and amidoxy links by ¹H NMR (300 MHz, CDCl₃/10 mM).

First of all, the ¹H-NMR signals of dimers **14a** and **14'a** were fully assigned using a combination of 2D-COSY and 2D-NOESY experiments (see Figures S1-S4 in Supporting Information).

- The signals of the two amidic NH protons respectively at $\delta = 7.98$ ppm and $\delta = 5.24$ ppm allowed us to calculate a $\Delta\delta = 2.74$ ppm for hetero dimer **14a**.
- Similarly, we assigned the two amidic NH protons of homo dimer **14'a**, at $\delta = 7.99$ ppm and $\delta = 5.40$ ppm respectively which accounts for a $\Delta\delta = 2.59$ ppm. These values were in the same order as those obtained by P. Le Grel in the aza- β^3 series which is known to fold via an eight-membered H-bonded ring (hydrazinoturn).

To confirm this result, we decided to study the effect of varying ratios of solvent in the mixture of CDCl₃ and DMSO-*d*₆ on the chemical shift of the NH protons of compounds **14a** and **14'a** (Figure 2a). Solvents with hydrogen bond acceptor atoms, such as DMSO-*d*₆, are able to form intermolecular H-bonds producing a downfield displacement for free acidic protons which is less significant when protons are involved in an intramolecular H-bond.

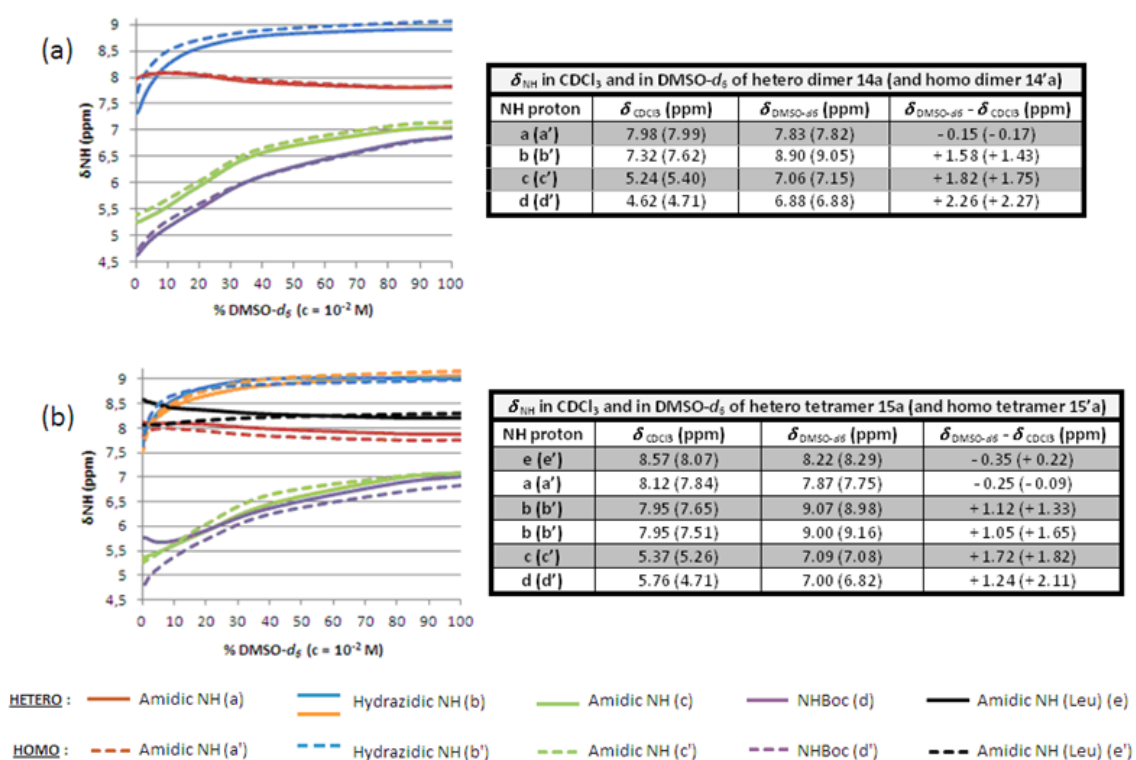


Figure 2. Effects of varying ratios of solvent in the mixture of CDCl₃ and DMSO-*d*₆ on the chemical shift of the NH protons of a) hetero dimer **14a** and (homo dimer **14'a**) and of b) hetero tetramer **15a** (and homo tetramer **15'a**) in ¹H NMR (300 MHz, 10 mM).

- We observed that the chemical shift of both NHc and NHd (amidic and NHBoc) of hetero dimer **14a** shifted downfield when the volume of DMSO-*d*₆ increased ($\delta_{\text{DMSO-}d_6} - \delta_{\text{CDCl}_3} = +1.82$ ppm and $+2.26$ ppm respectively) confirming that the NH protons were not involved in an intramolecular H-bond (free) (Figure 2a).
- A downfield shift was also observed for NHb. However, the difference between $\delta_{\text{DMSO-}d_6}$ and δ_{CDCl_3} was lower ($\delta_{\text{DMSO-}d_6} - \delta_{\text{CDCl}_3} = +1.58$ ppm) and suggested

that the hydrazidic proton was free or was involved in a weak intramolecular H-bond. If we take into account the results obtained by Le Grel and al. for the β^3 -oligomers (Figure 3), this weak H-bond may well be the result of the presence of a γ -turn.^{5b,11}

- Finally, and more interestingly, a very low variation of the chemical shift was observed for the NH_a amidic proton when switching from CDCl₃ to DMSO-*d*₆ ($\delta_{\text{DMSO-}d_6} - \delta_{\text{CDCl}_3} = - 0.15$ ppm) confirming the presence of a strong H-bond. This result is in agreement with the proposed hydrazinoturn structuration (bifurcated H-bond, Figure 3).

It is important to note that same results were obtained for both hetero and homo dimers **14a** and **14'a**. This showed that the structuration was not dependent on the chirality of the α -carbon and that both series fold via a succession of seven- (γ -turns) and eight-membered H-bonded rings (hydrazinoturns).

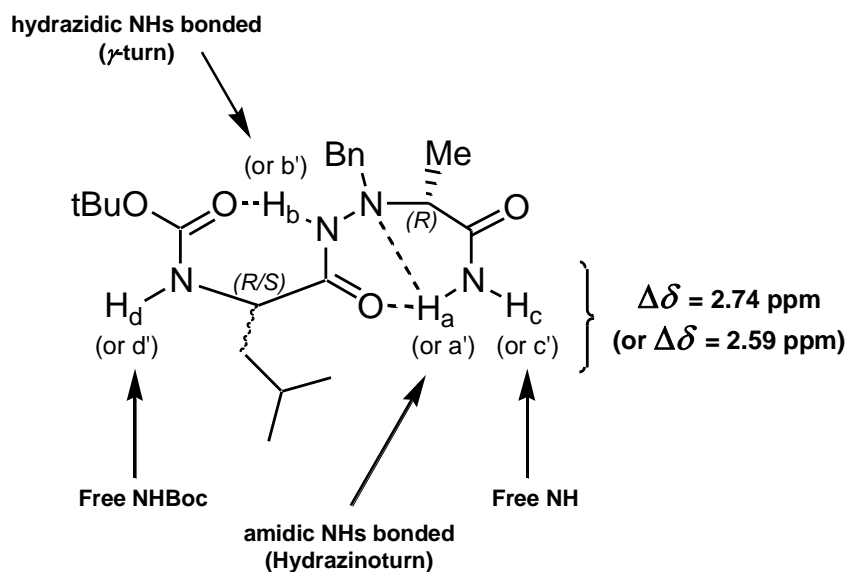


Figure 3. Postulated structuration of **14a** (and **14'a**) in CDCl₃ solution.

2.2.2. Conformational analysis of homo and hetero tetramers **15a** and **15'a**

¹H-NMR signals of tetramers **15a** and **15'a** were fully assigned using a combination of 2D-COSY and 2D-ROESY experiments (see Figures S5-S8 in Supporting

Information). As observed in the dimer series, the variation of the chemical shift of all NH protons (Figure 2b) was quite similar for homo tetramer **15'a** and hetero tetramer **15a** which suggested an identical self-structuration for both series.

- The chemical shifts of the two amidic NH protons of hetero tetramer **15a**, were respectively at $\delta = 8.12$ ppm and $\delta = 5.37$ ppm, given a $\Delta\delta = 2.75$ ppm).
- Similarly, a $\Delta\delta = 2.58$ ppm was calculated for the homo tetramer **15'a** ($\delta = 7.84$ ppm and $\delta = 5.26$ ppm for the two amidic NH protons)
- The chemical shifts of amidic protons NH**a** and NH**e** of tetramers **15a** and **15'a** were very poorly affected by the addition of DMSO- d_6 ($\delta_{\text{DMSO-}d_6} - \delta_{\text{CDCl}_3} = - 0.25$ ppm for NH**a** and $\delta_{\text{DMSO-}d_6} - \delta_{\text{CDCl}_3} = - 0.35$ ppm for NH**e**) (see Figure 2b) which confirmed the presence of a hydrazinoturn.
- In contrast, the evolution of the chemical shifts of hydrazidic protons NH**b** of tetramers **15a** and **15'a** was similar to that of hydrazidic proton NH**b** in dimers **14a** and **14'a** confirming their involvement in a weak intramolecular H-bond (γ -turns). Finally, as observed in the dimer, NH**c** and NH**d** (amidic and NHBoc protons) are free and shifted downfield when the volume of DMSO- d_6 increases ($\delta_{\text{DMSO-}d_6} - \delta_{\text{CDCl}_3} = + 1.72$ ppm and $+1.24$ ppm respectively).

The presence of free and bonded NH protons in dimer and tetramers were also confirmed by IR analysis (see Figures S9-S12 in Supporting Information)

All these results are in agreement with a structuration of 1:1 [α/α - N^α -hydrazino]mer series via a succession of γ -turns and hydrazinoturns. Moreover, the self-structuration does not seem to be affected by the nature of the absolute configuration of the α -carbon (Figure 4).

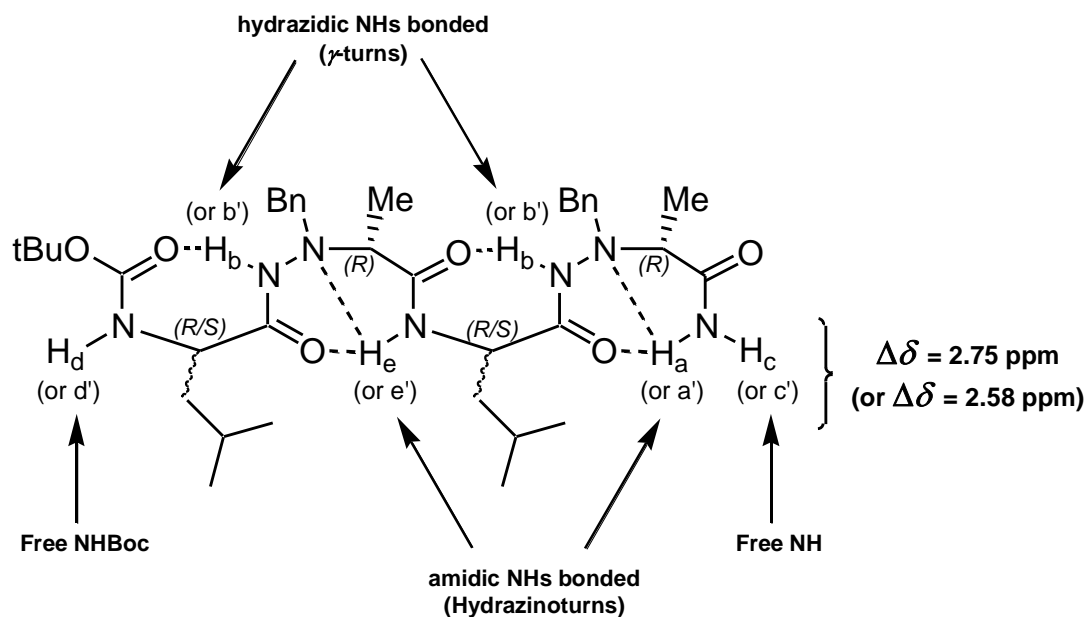


Figure 4. Postulated structuration of **15a** (and **15'a**) in CDCl_3 solution.

3. Conclusion

Various α -hydrazinoesters **3aa** to **3dc** building blocks can be obtained with high optical purity using a general protocol. Starting from **3ba** and **3bc**, we were able to obtain the synthesis of two 1:1 [α/α - N^α -hydrazino]mer series. Conformational studies by ^1H NMR show that 1:1 [α/α - N^α -hydrazino] mers are self-organized in solution via a succession of γ -turn and hydrazinoturn whatever the absolute configuration of the chiral carbons.

4. Experimental

4.1. General

Unless otherwise stated, all chemicals were purchased as the highest purity commercially available and were used without further purification. Reactions were monitored by thin-layer chromatography (TLC) using aluminium-backed silica gel plates (Macherey–Nagel ALUGRAM[®] SIL G/UV254). TLC spots were viewed under ultraviolet light and by heating the plate after treatment with a staining solution of phosphomolybdic acid. Product purifications were performed using Geduran 60 H Silica Gel (63–200 mesh). Dichloromethane was distilled from phosphorous pentoxide

under argon atmosphere and others reagent grade solvents were used as received. ^1H and ^{13}C NMR spectra were recorded on a Bruker Advance 300 spectrometer. Multiplicities are reported as follow: s = singlet, d = doublet, q = quartet, sept = septuplet, m = multiplet, br = broad, Ar. = aromatic and coupling constants (J) are given in Hertz (Hz). IR spectra were recorded on a Bruker Tensor 27. Melting points (mp) were recorded on a Kofler hot-stage apparatus and were uncorrected. Electron spray ionization mass spectra (ESI-MS) were recorded on a Bruker MicroTof-Q HR spectrometer in the “Service commun de Spectrométrie de Masse”, Faculté des Sciences et Techniques, Vandoeuvre-lès-Nancy, France. Optical rotations were determined on an Anton Paar MCP 300 polarimeter in 5 cm cells. Tert-butyl hydrazinecarboxylate derivatives **1a-d** and (*S*)- α -hydroxyesters **2a-d** were prepared according to ref [12] and [13] respectively.

4.2. Representative procedure for the preparation of α -hydrazinoesters **3**

A solution of (*S*)- α -hydroxyester **2** (1.0 equiv., 30 mmol) and 2,6-lutidine (2.3 equiv., 69 mmol) in CH_2Cl_2 (40 mL) at 0°C , under an atmosphere of nitrogen, was treated with triflic anhydride (1.1 equiv., 33 mmol). After 15 min, a solution of BocNHNHR' **1** (1.0 equiv., 30 mmol) in CH_2Cl_2 (30 mL) was added dropwise for 30 min and the mixture was stirred for 4-6 h at 0°C until completion (monitored by TLC). After evaporation of the solvent, Et_2O (50 mL) was added and 2,6-lutidinium triflate was precipitated by storing the reaction mixture overnight in the refrigerator. The 2,6-lutidinium triflate was filtered and the filtrate was diluted in Et_2O (100 mL) and washed with water (20 mL), dried over MgSO_4 , filtered, and evaporated *in vacuo*. The resulting crude material was purified and characterized as reported below.

4.2.1. (R)-(-)- N^α -methyl- N^β -Boc-(D)-hydrazinoalanine methyl ester or Boc- α -h(Me)D-Ala-OMe, **3aa.** Purified by flash chromatography (Petroleum ether/AcOEt = 50:50), Yield: 87%, yellow oil, $[\alpha]_{\text{D}}^{25} = -9.1$ ($c=1.00$, MeOH); IR (ATR) $\nu_{\text{max}}/\text{cm}^{-1}$: 3362, 3005, 2982, 2955, 2890, 2843, 2799, 1746, 1728, 1689, 1658, 1641, 1630, 1564, 1553, 1513, 1483, 1462, 1450, 1414, 1393, 1368, 1242, 1210, 1163, 1130, 1111; ^1H NMR (300 MHz, CDCl_3) δ 1.37 (d, 3H, $J = 7.2$ Hz, βCH_3 Ala), 1.45 (s, 9H, Boc), 2.67 (s, 3H, N^α -Me), 3.57-3.64 (q, 1H, $J = 7.2$ Hz, αCH Ala), 3.72 (s, 3H, O- CH_3) 6.52 (br s,

1H, NH); ¹³C NMR (75 MHz, CDCl₃) δ 16.6 (βCH₃ Ala), 28.8 (3 CH₃, Boc), 44.0 (*N*^α-Me), 52.0 (O-CH₃), 63.1 (αCH Ala), 80.2 (C, Boc), 155.9 (C=O, Boc), 174.6 (C=O, ester); HRMS (ESI) calculated for C₁₀H₂₀N₂O₄ [M+Na]⁺ *m/z* 255.1321, found 255.1315.

4.2.2. (R)-(-)-*N*^α-benzyl-*N*^β-Boc-(D)-hydrazinoalanine methyl ester or Boc-*α*-h(Bn)D-Ala-OMe, 3ba. Purified by flash chromatography (Petroleum ether/AcOEt = 80:20), Yield: 83%, yellow oil, [α]_D²⁵ = -9.2 (*c*=1.00, MeOH); IR (ATR) *v*_{max}/cm⁻¹: 3370, 3091, 3064, 3032, 2984, 2955, 2907, 2846, 1737, 1728, 1709, 1659, 1641, 1630, 1564, 1494, 1486, 1462, 1456, 1435, 1424, 1393, 1367, 1237, 1213, 1159; ¹H NMR (300 MHz, CDCl₃) δ 1.28 (s, 9H, Boc), 1.31 (d, 3H, *J* = 7.2 Hz, βCH₃ Ala), 3.56 (q, 1H, *J* = 7.2 Hz, αCH Ala), 3.66 (s, 3H, O-CH₃) 3.82-4.01 (m, 2H, CH₂, *N*^α-Bn), 6.48 (br s, 1H, NH), 7.13-7.36 (m, 5H, Ar.); ¹³C NMR (75 MHz, CDCl₃) δ 16.9 (βCH₃ Ala), 28.9 (3 CH₃, Boc), 52.2 (O-CH₃), 60.8 (αCH Ala), 61.3 (CH₂, *N*^α-Bn), 80.3 (C, Boc), 128.1 (CH, Ar.), 128.9 (2 CH, Ar.), 130.0 (2 CH, Ar.), 137.6 (C, Ar.), 156.1 (C=O, Boc), 175.2 (C=O, ester); HRMS (ESI) calculated for C₁₆H₂₄N₂O₄ [M+Na]⁺ *m/z* 331.1634, found 331.1628.

4.2.3. (R)-(-)-*N*^α-isobutyl-*N*^β-Boc-(D)-hydrazinoalanine methyl ester or Boc-*α*-h(*i*-Bu)D-Ala-OMe, 3ca. Purified by flash chromatography (Petroleum ether/AcOEt = 70:30), Yield: 80%, yellow oil, [α]_D²⁵ = -20.9 (*c*=1.00, MeOH); IR (ATR) *v*_{max}/cm⁻¹: 3362, 2982, 2857, 2908, 2873, 2843, 1740, 1734, 1710, 1690, 1678, 1659, 1562, 1510, 1483, 1469, 1462, 1452, 1412, 1389, 1380, 1368, 1238, 1200, 1160, 1124; ¹H NMR (300 MHz, CDCl₃) δ 0.9 (d, 3H, *J* = 6.5 Hz, CH₃, *N*^α-*i*Bu), 0.97 (d, 3H, *J* = 6.5 Hz, CH₃, *N*^α-*i*Bu), 1.37 (d, 3H, *J* = 7.2 Hz, βCH₃ Ala), 1.44 (s, 9H, Boc), 1.62-1.81 (m, 1H, CH, *N*^α-*i*Bu), 2.20-2.45 (m, 1H, CH₂, *N*^α-*i*Bu), 2.55-2.77 (m, 1H, CH₂, *N*^α-*i*Bu), 3.48-3.65 (m, 1H, αCH Ala), 3.71 (s, 3H, O-CH₃), 6.33 (br s, 1H, NH); ¹³C NMR (75 MHz, CDCl₃) δ 16.7 (βCH₃ Ala), 21.7 (2 CH₃, *N*^α-*i*Bu), 27.2 (CH, *N*^α-*i*Bu), 28.9 (3 CH₃, Boc), 52.0 (O-CH₃), 63.4 (αCH Ala); 65.3 (CH₂, *N*^α-*i*Bu), 80.0 (C, Boc), 156.3 (C=O, Boc), 175.2 (C=O, ester); HRMS (ESI) calculated for C₁₃H₂₆N₂O₄ [M+Na]⁺ *m/z* 297.1791, found 297.1785.

4.2.4. (R)-(-)-*N*^α-isopropyl-*N*^β-Boc-(D)-hydrazinolalanine methyl ester or Boc- α -h(*i*-Pr)D-Ala-OMe, 3da. Purified by flash chromatography (Petroleum ether/AcOEt = 70:30), Yield: 62%, yellow oil, $[\alpha]_{\text{D}}^{25} = -28.2$ ($c=1.00$, MeOH); IR (ATR) $\nu_{\text{max}}/\text{cm}^{-1}$: 3371, 2982, 2944, 2908, 2881, 2843, 1745, 1728, 1711, 1692, 1683, 1498, 1490, 1486, 1471, 1460, 1452, 1391, 1383, 1366, 1332, 1275, 1246, 1198, 1161, 1128; ¹H NMR (300 MHz, CDCl₃) δ 1.08 (d, 6H, $J = 6.2$ Hz, CH₃, *N*^α-*i*Pr), 1.37 (d, 3H, $J = 7.1$ Hz, β CH₃ Ala), 1.44 (s, 9H, Boc), 3.03 (sept, 1H, $J = 6.2$ Hz, CH, *N*^α-*i*Pr), 3.70 (s, 3H, O-CH₃), 3.82 (q, 1H, $J = 7.1$ Hz, α CH Ala), 6.47 (br s, 1H, NH); ¹³C NMR (75 MHz, CDCl₃) δ 17.1 (β CH₃ Ala), 20.9 (CH₃, *N*^α-*i*Pr), 21.1 (CH₃, *N*^α-*i*Pr), 28.9 (3 CH₃, Boc), 52.1 (O-CH₃), 56.0 (CH, *N*^α-*i*Pr), 58.7 (α CH Ala), 79.9 (C, Boc), 157.0 (C=O, Boc), 175.9 (C=O, ester); HRMS (ESI) calculated for C₁₂H₂₄N₂O₄ [M+Na]⁺ m/z 283.1634, found 283.1628.

4.2.5. (R)-(-)-*N*^α-methyl-*N*^β-Boc-(D)-hydrazinophenylalanine methyl ester or Boc- α -h(Me)D-Phe-OMe, 3ab. Purified by flash chromatography (Petroleum ether/AcOEt = 70:30), Yield: 84%, yellow oil, $[\alpha]_{\text{D}}^{25} = -37.0$ ($c=1.00$, MeOH); IR (ATR) $\nu_{\text{max}}/\text{cm}^{-1}$: 3357, 3089, 3064, 3028, 3006, 2982, 2957, 2939, 2893, 1737, 1727, 1710, 1659, 1642, 1630, 1603, 1583, 1498, 1482, 1456, 1446, 1415, 1393, 1367, 1241, 1211, 1165; ¹H NMR (300 MHz, CDCl₃) δ 1.47 (s, 9H, Boc), 2.64 (s, 3H, *N*^α-Me), 2.96 (dd, 1H, $J = 13.6$ Hz and 8.3 Hz, β CH Phe), 3.14 (dd, 1H, $J = 13.6$ Hz and 6.5 Hz β CH Phe), 3.59 (s, 3H, O-CH₃), 3.67 (dd, 1H, $J = 8.3$ Hz and 6.5 Hz, α CH Phe), 6.55 (br s, 1H, NH), 7.1-7.35 (m, 5H, Ar.); ¹³C NMR (75 MHz, CDCl₃) δ 29.0 (3 CH₃, Boc), 37.3 (β CH₂ Phe); 45.0 (*N*^α-Me), 52.0 (O-CH₃), 70.1 (α CH Phe), 80.6 (C, Boc), 127.2 (CH, Ar.), 129.0 (2 CH, Ar.), 129.8 (2 CH, Ar.), 138.2 (C, Ar.); 156.1 (C=O, Boc), 173.9 (C=O, ester); HRMS (ESI) calculated for C₁₆H₂₄N₂O₄ [M+Na]⁺ m/z 331.1634, found 331.1628.

4.2.6. (R)-(-)-*N*^α-benzyl-*N*^β-Boc-(D)-hydrazinophenylalanine methyl ester or Boc- α -h(Bn)D-Phe-OMe, 3bb. Purified by flash chromatography (Petroleum ether/AcOEt = 80:20), Yield: 82%, yellow oil, $[\alpha]_{\text{D}}^{25} = -5.2$ ($c=1.00$, MeOH); IR (ATR) $\nu_{\text{max}}/\text{cm}^{-1}$: 3362, 3091, 3065, 3031, 2980, 2958, 2907, 2842, 1741, 1726, 1707, 1661, 1626, 1605, 1587, 1496, 1482, 1454, 1389, 1367, 1241, 1217, 1157; ¹H NMR

(300 MHz, CDCl₃) δ 1.36 (s, 9H, Boc), 2.93-3.05 (dd, 1H, J = 13.9 Hz and 6.8 Hz, β CH₂ Phe), 3.07-3.17 (dd, 1H, J = 13.9 Hz and 7.6 Hz, β CH₂ Phe), 3.64 (s, 3H, O-CH₃) 3.62-3.83 (m, 1H, α CH Phe), 3.86-4.03 (m, 2H, CH₂, N^α -Bn), 6.60 (br s, 1H, NH), 7.20-7.36 (m, 10H, Ar.); ¹³C NMR (75 MHz, CDCl₃) δ 29.0 (3 CH₃, Boc), 37.1 (β CH₂ Phe), 52.1 (O-CH₃), 61.0 (CH₂, N^α -Bn), 67.3 (α CH Phe), 80.5 (C, Boc), 127.1 (CH, Ar.), 128.0 (CH, Ar.), 128.1 (CH, Ar.), 128.2 (CH, Ar.), 128.8 (CH, Ar.), 129.3 (CH, Ar.), 129.4 (CH, Ar.), 129.5 (CH, Ar.), 129.9 (CH, Ar.), 130.1 (CH, Ar.), 137.2 (C, Ar.), 138.5 (C, Ar.), 155.8 (C=O, Boc), 174.0 (C=O, ester); HRMS (ESI) calculated for C₂₂H₂₈N₂O₄ [M+Na]⁺ m/z 407.1947, found 407.1941.

4.2.7. (R)-(-)- N^α -isobutyl- N^β -Boc-(D)-hydrazinophenylalanine methyl ester or Boc- α -h(*i*-Bu)D-Phe-OMe, 3cb. Purified by flash chromatography (Petroleum ether/AcOEt = 80:20), Yield: 78%, yellow oil, $[\alpha]_D^{25}$ = - 25.6 (c =1.00, MeOH); IR (ATR) $\nu_{\max}/\text{cm}^{-1}$: 3362, 3064, 3030, 3006, 2980, 2955, 2909, 2870, 2844, 1743, 1728, 1705, 1678, 1658, 1498, 1484, 1470, 1456, 1440, 1391, 1383, 1367, 1237, 1201, 1167; ¹H NMR (300 MHz, CDCl₃) δ 0.84 (d, 3H, J = 6.6 Hz, CH₃, N^α -*i*Bu), 0.96 (d, 3H, J = 6.6 Hz, CH₃, N^α -*i*Bu), 1.44 (s, 9H, Boc), 1.62-1.80 (m, 1H, CH, N^α -*i*Bu), 2.29-2.42 (m, 1H, CH₂, N^α -*i*Bu), 2.53-2.64 (m, 1H, CH₂, N^α -*i*Bu), 2.90-3.02 (m, 1H, β CH₂ Phe), 3.07-3.19 (m, 1H, β CH₂ Phe), 3.61 (s, 3H, O-CH₃), 3.65-3.81 (m, 1H, α CH Phe), 6.42 (br s, 1H, NH), 7.15-7.32 (m, 5H, Ar.); ¹³C NMR (75 MHz, CDCl₃) δ 21.2 (2 CH₃, N^α -*i*Bu), 27.1 (CH, N^α -*i*Bu), 29.2 (3 CH₃, Boc), 37.1 (β CH₂ Phe), 52.3 (O-CH₃), 66.3 (CH₂, N^α -*i*Bu), 70.2 (α CH Phe), 80.2 (C, Boc), 127.7 (CH, Ar.), 128.8 (2 CH, Ar.), 130.4 (2 CH, Ar.), 138.7 (C, Ar.), 155.6 (C=O, Boc), 174.0 (C=O, ester); HRMS (ESI) calculated for C₁₉H₃₀N₂O₄ [M+Na]⁺ m/z 373.2104, found 373.2098.

4.2.8. (R)-(-)- N^α -isopropyl- N^β -Boc-(D)-hydrazinophenylalanine methyl ester or Boc- α -h(*i*-Pr)D-Phe-OMe, 3db. Purified by flash chromatography (Petroleum ether/AcOEt = 80:20), Yield: 60%, yellow oil, $[\alpha]_D^{25}$ = - 40.9 (c =1.00, MeOH); IR (ATR) $\nu_{\max}/\text{cm}^{-1}$: 3366, 3089, 3064, 3030, 2980, 2955, 2937, 1743, 1728, 1710, 1680, 1644, 1603, 1496, 1486, 1453, 1393, 1385, 1369, 1274, 1243, 1201, 1163; ¹H NMR (300 MHz, CDCl₃) δ 1.05-1.09 (m, 6H, CH₃, N^α -*i*Pr), 1.47 (s, 9H, Boc), 2.90-3.01 (m, 2H, β CH₂ Phe), 3.08-3.20 (m, 1H, CH, N^α -*i*Pr), 3.54 (s, 3H, O-CH₃), 3.75-3.86 (m, 1H,

α CH Phe), 6.62 (br s, 1H, NH), 7.13-7.36 (m, 5H, Ar.); ^{13}C NMR (75 MHz, CDCl_3) δ 21.1 (2 CH_3 , N^α -*i*Pr), 28.6 (3 CH_3 , Boc), 38.0 (βCH_2 Phe), 52.3 (O- CH_3), 56.7 (CH, N^α -*i*Pr), 66.2 (αCH Phe), 80.1 (C, Boc), 127.2 (CH, Ar.), 129.0 (2 CH, Ar.), 130.0 (2 CH, Ar.), 138.4 (C, Ar.); 156.8 (C=O, Boc), 175.0 (C=O, ester); HRMS (ESI) calculated for $\text{C}_{18}\text{H}_{28}\text{N}_2\text{O}_4$ $[\text{M}+\text{Na}]^+$ m/z 359.1947, found 359.1941.

4.2.9. (R)-(-)- N^α -methyl- N^β -Boc-(D)-hydrazinoleucine methyl ester or Boc- α -h(Me)D-Leu-OMe, 3ac. Purified by flash chromatography (Petroleum ether/AcOEt = 85:15), Yield: 80%, yellow oil, $[\alpha]_{\text{D}}^{25} = -20.2$ ($c=1.00$, MeOH); IR (ATR) $\nu_{\text{max}}/\text{cm}^{-1}$: 3368, 2979, 2956, 2937, 2907, 2871, 2843, 2803, 1744, 1728, 1710, 1690, 1677, 1659, 1641, 1564, 1513, 1483, 1467, 1453, 1444, 1413, 1390, 1367, 1261, 1235, 1200, 1160, 1125; ^1H NMR (300 MHz, CDCl_3) δ 0.91 (d, 6H, $J = 6.6$ Hz, δCH_3 Leu), 1.45 (s, 9H, Boc), 1.36-1.53 (m, 1H, βCH_2 Leu), 1.59-1.73 (m, 1H, βCH_2 Leu), 1.85-1.99 (m, 1H, γCH Leu), 2.63 (s, 3H, N^α -Me), 3.45 (dd, 1H, $J = 9.0$ Hz and 6.0 Hz, αCH Leu), 3.72 (s, 3H, O- CH_3) 6.53 (br s, 1H, NH); ^{13}C NMR (75 MHz, CDCl_3) δ 22.5 (γCH Leu), 23.6 (δCH_3 Leu), 25.0 (δCH_3 Leu), 29.0 (3 CH_3 , Boc), 39.9 (βCH_2 Leu), 44.7 (N^α -Me), 52.0 (O- CH_3), 66.2 (αCH Leu), 80.3 (C, Boc), 156.4 (C=O, Boc), 175.1 (C=O, ester); HRMS (ESI) calculated for $\text{C}_{13}\text{H}_{26}\text{N}_2\text{O}_4$ $[\text{M}+\text{Na}]^+$ m/z 297.179, found 297.177.

4.2.10. (R)-(-)- N^α -benzyl- N^β -Boc-(D)-hydrazinoleucine methyl ester or Boc- α -h(Bn)D-Leu-OMe, 3bc. Purified by flash chromatography (Petroleum ether/AcOEt = 70:30), Yield: 78%, yellow oil, $[\alpha]_{\text{D}}^{25} = -29.0$ ($c=1.00$, MeOH); ^1H NMR (300 MHz, CDCl_3) δ 0.72-0.74 (m, 3H, δCH_3 Leu), 0.86-0.90 (m, 3H, δCH_3 Leu), 1.38 (s, 9H, Boc), 1.49-1.82 (m, 2H, βCH_2 Leu), 2.04-2.13 (m, 1H, γCH Leu), 3.44-3.48 (m, 1H, αCH Leu), 3.73 (s, 3H, O- CH_3), 3.88-4.05 (m, 2H, CH_2 , N^α -Bn), 6.74 (br s, 1H, NH), 7.23-7.40 (m, 5H, Ar.); ^{13}C NMR (75 MHz, CDCl_3) δ 22.7 (γCH Leu), 24.2 (δCH_3 Leu), 24.8 (δCH_3 Leu), 28.8 (3 CH_3 , Boc), 39.8 (βCH_2 Leu), 52.0 (O- CH_3), 61.8 (CH_2 , N^α -Bn), 62.8 (αCH Leu), 80.1 (C, Boc), 128.1 (CH, Ar.), 128.8 (2 CH, Ar.), 130.1 (2 CH, Ar.), 137.6 (C, Ar.), 155.1 (C=O, Boc), 175.3 (C=O, ester). The physical data (NMR and $[\alpha]_{\text{D}}^{25}$) are in agreement with the values reported in the reference [4]. Measured : $[\alpha]_{\text{D}}^{25} = -24.6$ ($c=0.99$, CHCl_3), Literature : $[\alpha]_{\text{D}}^{25} = +25.4$ ($c=0.99$, CHCl_3 , (*S*)-isomer).

4.2.11. (R)-(-)-*N*^α-isobutyl-*N*^β-Boc-(D)-hydrazinoleucine methyl ester or Boc- α -h(*i*-Bu)D-Leu-OMe, 3cc. Purified by flash chromatography (Petroleum ether/AcOEt = 90:10), Yield: 62%, yellow oil, $[\alpha]_D^{25} = -19.7$ ($c=1.00$, MeOH); IR (ATR) $\nu_{\max}/\text{cm}^{-1}$: 3368, 2959, 2935, 2907, 2872, 2852, 1745, 1729, 1711, 1678, 1658, 1642, 1564, 1512, 1494, 1483, 1470, 1451, 1440, 1396, 1366, 1273, 1241, 1195, 1174, 1158, 1130; ¹H NMR (300 MHz, CDCl₃) δ 0.83-1.05 (m, 12H, , 4 CH₃, *N*^α-*i*Bu and δ CH₃ Leu), 1.44 (s, 9H, Boc), 1.68-1.82 (m, 3H, β CH₂ Leu and CH, *N*^α-*i*Bu), 2.05-2.17 (m, 1H, γ CH Leu), 2.20-2.37 (m, 1H, CH₂, *N*^α-*i*Bu), 2.64-2.72 (m, 1H, CH₂, *N*^α-*i*Bu), 3.35-3.55 (m, 1H, α CH Leu), 3.70 (s, 3H, O-CH₃), 6.43 (br s, 1H, NH); ¹³C NMR (75 MHz, CDCl₃) δ 20.8 (2 CH₃, *N*^α-*i*Bu), 23.2 (γ CH Leu), 25.2 (2 δ CH₃ Leu), 27.1 (CH, *N*^α-*i*Bu), 28.5 (3 CH₃, Boc), 39.9 (β CH₂ Leu), 51.8 (O-CH₃); 66.2 (α CH Leu), 68.0 (CH₂, *N*^α-*i*Bu), 80.5 (C, Boc), 155.8 (C=O, Boc), 175.2 (C=O, ester); HRMS (ESI) calculated for C₁₆H₃₂N₂O₄ [M+Na]⁺ m/z 339.2260, found 339.2254.

4.2.12. (R)-(-)-*N*^α-isopropyl-*N*^β-Boc-(D)-hydrazinoleucine methyl ester or Boc- α -h(*i*-Pr)D-Leu-OMe, 3dc. Purified by flash chromatography (Petroleum ether/AcOEt = 90:10), Yield: 58%, yellow oil, $[\alpha]_D^{25} = -21.7$ ($c=1.00$, MeOH); IR (ATR) $\nu_{\max}/\text{cm}^{-1}$: 3374, 2978, 2961, 2937, 2911, 2872, 1745, 1728, 1705, 1689, 1484, 1472, 1456, 1438, 1391, 1366, 1268, 1252, 1233, 1195, 1163, 1130; ¹H NMR (300 MHz, CDCl₃) δ 0.89 (d, 6H, $J = 6.5$ Hz, δ CH₃ Leu), 1.05-1.09 (m, 6H, CH₃, *N*^α-*i*Pr), 1.44 (s, 9H, Boc), 1.63-1.77 (m, 2H, β CH₂ Leu) 1.91-2.03 (m, 1H, γ CH Leu), 2.98 (sept, 1H, $J = 6.2$ Hz, CH, *N*^α-*i*Pr), 3.69 (s, 3H, O-CH₃), 3.72-3.82 (m, 1H, α CH Leu), 6.61 (br s, 1H, NH); ¹³C NMR (75 MHz, CDCl₃) δ 20.5 (CH₃, *N*^α-*i*Pr), 21.1 (CH₃, *N*^α-*i*Pr), 22.2 (γ CH Leu), 23.3 (δ CH₃ Leu), 24.6 (δ CH₃ Leu), 28.7 (3 CH₃, Boc), 40.1 (β CH₂ Leu), 51.7 (O-CH₃), 56.1 (CH, *N*^α-*i*Pr), 61.3 (α CH Leu), 79.4 (C, Boc), 156.4 (C=O, Boc), 175.9 (C=O, ester); HRMS (ESI) calculated for C₁₅H₃₀N₂O₄ [M+H]⁺ m/z 303.2284, found 303.2278.

4.2.13. (R)-(-)-*N*^α-methyl-*N*^β-Boc-(D)-hydrazinovaline methyl ester or Boc- α -h(Me)D-Val-OMe, 3ad. Purified by flash chromatography (Petroleum ether/AcOEt = 85:15), Yield: 15% determined by ¹H NMR integration relative peaks (inseparable mixture of **2d** and **3ad**), For **3ad**: Yellow oil; ¹H NMR (300 MHz, CDCl₃) δ (d, 3H, $J =$

6.7 Hz, γCH_3 Val), 1.10 (d, 3H, $J = 6.7$ Hz, γCH_3 Val) 1.45 (s, 9H, Boc), 1.98-2.13 (m, 1H, βCH Val), 2.57 (s, 3H, N^α -Me), 3.02 (d, 1H, $J = 9.5$ Hz, αCH Val), 3.73 (s, 3H, O-CH₃) 6.53 (br s, 1H, NH).

4.2.14. (R)-(-)- N^α -benzyl- N^β -Boc-(D)-hydrazinovaline methyl ester or Boc- α -h(Bn)D-Val-OMe, 3bd. Purified by flash chromatography (Petroleum ether/AcOEt = 80:20), Yield: 10% determined by ¹H NMR integration relative peaks (inseparable mixture of **2d** and **3bd**), For **3bd**: Yellow oil; ¹H NMR (300 MHz, CDCl₃) δ 0.87 (d, 3H, $J = 6.9$ Hz, γCH_3 Val), 1.02 (d, 3H, $J = 6.9$ Hz, γCH_3 Val), 1.36 (s, 9H, Boc), 2.03-2.15 (m, 1H, βCH Val), 3.79 (s, 3H, O-CH₃), 3.70-3.83 (m, 1H, αCH Val), 3.97-4.07 (m, 2H, CH₂, N^α -Bn), 6.03 (br s, 1H, NH), 7.20-7.42 (m, 5H, Ar.).

4.2.15. (R)-(-)- N^α -isobutyl- N^β -Boc-(D)-hydrazinovaline methyl ester or Boc- α -h(*i*-Bu)D-Val-OMe, 3cd. Purified by flash chromatography (Petroleum ether/AcOEt = 85:15), Yield: 22%, yellow oil, $[\alpha]_{\text{D}}^{25} = -0.6$ ($c=1.00$, MeOH); IR (ATR) $\nu_{\text{max}}/\text{cm}^{-1}$: 3351, 2980, 2963, 2937, 2915, 2874, 1740, 1724, 1711, 1694, 1680, 1482, 1470, 1454, 1446, 1389, 1371, 1284, 1252, 1171, 1146; ¹H NMR (300 MHz, CDCl₃) δ 0.87 (d, 3H, $J = 6.9$ Hz, γCH_3 Val), 0.92 (d, 6H, $J = 6.7$ Hz, CH₃, N^α -*i*Bu), 1.02 (d, 3H, $J = 6.9$ Hz, γCH_3 Val), 1.46 (s, 9H, Boc), 1.65-1.80 (m, 1H, CH, N^α -*i*Bu), 2.01-2.13 (m, 1H, βCH Val), 2.65 (d, 2H, $J = 6.8$ Hz, CH₂, N^α -*i*Bu), 3.79 (s, 3H, O-CH₃), 4.05 (d, 1H, $J = 3.6$ Hz, αCH Val), 6.04 (br s, 1H, NH); ¹³C NMR (75 MHz, CDCl₃) δ 16.7 (2 γCH_3 Val), 19.4 (βCH Val), 21.1 (2 CH₃, N^α -*i*Bu), 27.5 (CH, N^α -*i*Bu), 29.0 (3 CH₃, Boc), 52.9 (O-CH₃), 60.6 (CH₂, N^α -*i*Bu), 75.8 (αCH Val), 81.0 (C, Boc), 157.4 (C=O, Boc), 176.0 (C=O, ester); HRMS (ESI) calculated for C₁₅H₃₀N₂O₄ [M+Na]⁺ m/z 325.2104, found 325.2101.

4.3. Representative procedure for the C-terminal deprotection with NaOH 1N

To a solution of ester (1.0 equiv., 22 mmol) in MeOH (80 mL) was added at 0°C a solution of NaOH 1N (2.0 equiv., 44 mmol) and the mixture was vigorously stirred for 3-6 h at room temperature until completion (monitored by TLC). After evaporation of MeOH, the aqueous layer was washed with cyclohexane (2 x 10 mL). The aqueous phase was cooled to 0°C and acidified with HCl 1N until pH=1 and extracted with

EtOAc (3 x 20 mL). The residue was dried over MgSO₄, filtered and evaporated *in vacuo* to give the corresponding carboxylic acid.

4.3.1. (R)-(-)-N^α-benzyl-N^β-Boc-(D)-hydrazinoalanine acid or Boc- α -h(Bn)D-Ala-OH, 4a. Yield: 98%, yellow oil, $[\alpha]_D^{25} = -14.9$ ($c=1.00$, MeOH); ¹H NMR (300 MHz, CDCl₃) δ 1.34 (s, 9H, Boc), 1.39 (d, 3H, $J = 7.2$ Hz, β CH₃ Ala), 3.66 (q, 1H, $J = 7.2$ Hz, α CH Ala), 3.97 (s, 2H, CH₂, N^α-Bn), 5.82 (br s, 1H, NH), 7.27-7.42 (m, 5H, Ar.), 9.65 (br s, 1H, OH). The physical data (NMR and $[\alpha]_D^{25}$) are in agreement with the values reported in the reference [14]. Measured : $[\alpha]_D^{25} = -21.7$ ($c=1.14$, MeOH), Literature : $[\alpha]_D^{25} = +22.8$ ($c=1.14$, MeOH, (S)-isomer).

4.3.2. (R)-(-)-N^α-benzyl-N^β-Boc-(D)-hydrazinoleucine acid or Boc- α -h(Bn)D-Leu-OH, 4b. Yield: 96%, yellow oil, $[\alpha]_D^{25} = -16.9$ ($c=1.00$, MeOH); IR (ATR) $\nu_{\max}/\text{cm}^{-1}$: 3358, 3089, 3066, 3032, 2959, 2936, 2902, 2872, 1767, 1750, 1740, 1723, 1711, 1681, 1496, 1483, 1471, 1452, 1441, 1410, 1395, 1368, 1273, 1252, 1162; ¹H NMR (300 MHz, CDCl₃) δ 0.78 (br s, 3H, δ CH₃ Leu), 0.92 (d, 3H, $J = 6.0$ Hz, δ CH₃ Leu), 1.36 (s, 9H, Boc), 1.36-1.52 (m, 1H, β CH₂ Leu), 1.68-1.77 (m, 1H, β CH₂ Leu), 2.08 (br s, 1H, γ CH Leu), 3.45-3.55 (m, 1H, α CH Leu), 3.95-4.16 (m, 2H, CH₂, N^α-Bn), 6.54 (br s, 1H, NH), 7.26-7.41 (m, 5H, Ar.), 9.62 (br s, 1H, OH); ¹³C NMR (75 MHz, CDCl₃) δ 22.1 (γ CH Leu), 24.1 (δ CH₃ Leu), 25.0 (δ CH₃ Leu), 28.8 (3 CH₃, Boc), 39.5 (β CH₂ Leu), 61.8 (CH₂, N^α-Bn), 63.4 (α CH Leu), 81.0 (C, Boc), 128.2 (CH, Ar.), 128.9 (2 CH, Ar.), 130.1 (CH, Ar.), 130.4 (CH, Ar.), 137.9 (C, Ar.), 156.3 (C=O, Boc), 178.2 (C=O, acid); HRMS (ESI) calculated for C₁₈H₂₈N₂O₄ [M+H]⁺ m/z 337.2127, found 337.2122. ¹H-NMR spectral data were in agreement with those reported in the reference [4].

4.3.3. Boc-L-Leu- α -h(Bn)D-Ala-OH, 7a. Yield: 96%, white amorphous solid; ¹H NMR (300 MHz, CDCl₃) δ 0.83 (d, 6H, $J = 6.0$ Hz, 2 δ CH₃ Leu), 1.38-1.44 (m, 6H, β CH₃ Ala, β CH₂ Leu, γ CH Leu), 1.42 (s, 9H, Boc), 3.71-3.80 (q, 1H, $J = 7.2$ Hz, α CH Ala), 4.01-4.17 (m, 2H, CH₂, N^α-Bn), 4.19-4.30 (m, 1H, α CH Leu), 5.07 (br d, 1H, $J = 8.2$ Hz, NHBoc), 7.25-7.43 (m, 5H, Ar.), 8.37 (br s, 1H, NH hydrazidic). The crude product was used in a next step without further purification.

4.3.4. Boc-L-Ala- α -h(Bn)D-Leu-OH, 7b. Yield: 95%, white amorphous solid; ^1H NMR (300 MHz, CDCl_3) δ 0.73 (d, 3H, $J = 6.0$ Hz, δCH_3 Leu), 0.85 (d, 3H, $J = 6.0$ Hz, δCH_3 Leu), 1.25 (d, 3H, $J = 7.2$ Hz, βCH_3 Ala), 1.40 (s, 9H, Boc), 1.40-1.52 (m, 1H, βCH_2 Leu), 1.60-1.71 (m, 1H, βCH_2 Leu), 1.96-2.06 (m, 1H, γCH Leu), 3.48-3.57 (m, 1H, αCH Leu), 3.97-4.16 (m, 2H, CH_2 , N^α -Bn), 4.31-4.47 (m, 1H, αCH Ala), 5.69 (d, 1H, $J = 7.2$ Hz, NHBoc), 7.22-7.43 (m, 5H, Ar.), 8.39 (br s, 1H, NH hydrazidic), 8.62 (s, 1H, OH). The crude product was used in a next step without further purification.

4.3.5. Boc-(L-Leu- α -h(Bn)D-Ala) $_2$ -OH, 10a. Yield: 94%, white amorphous solid; ^1H NMR (300 MHz, CDCl_3) δ 0.79 (d, 3H, $J = 6.3$ Hz, δCH_3 Leu), 0.83 (d, 6H, $J = 6.3$ Hz, 2 δCH_3 Leu), 0.87 (d, 3H, $J = 6.3$ Hz, δCH_3 Leu), 1.27 (d, 3H, $J = 6.9$ Hz, βCH_3 Ala), 1.37 (d, 3H, $J = 6.9$ Hz, βCH_3 Ala), 1.45 (s, 9H, Boc), 1.49-1.68 (m, 6H, 2 βCH_2 Leu, 2 γCH Leu), 3.47 (q, 1H, $J = 6.9$ Hz, αCH Ala), 3.62-3.72 (m, 1H, αCH Ala), 3.82-4.06 (m, 5H, 2 CH_2 , N^α -Bn, αCH Leu), 4.08-4.21 (m, 1H, αCH Leu), 5.31 (br s, 1H, NHBoc), 7.22-7.42 (m, 10H, Ar.), 7.82 (s, 1H, NH), 8.23 (s, 1H, NH), 8.52 (br s, 1H, NH). The crude product was used in a next step without further purification.

4.3.6. Boc-(L-Ala- α -h(Bn)D-Leu) $_2$ -OH, 10b. Yield: 96%, white amorphous solid; ^1H NMR of the major form (300 MHz, CDCl_3) δ 0.72-1.15 (m, 18H, 4 δCH_3 Leu, 2 δCH_3 Leu), 1.24-1.99 (m, 6H, 2 βCH_2 Leu, 2 γCH Leu), 1.39 (s, 9H, Boc), 3.42-3.63 (m, 2H, 2 αCH Leu), 3.67-3.81 (m, 4H, 2 CH_2 , N^α -Bn), 3.88-4.23 (m, 2H, 2 αCH Ala), 4.94 (br s, $J = 5.7$ Hz, NHBoc), 7.15-7.51 (m, 10H, Ar.), 8.02 (br s, 1H, NH), 8.12 (s, 1H, NH), 8.56 (s, 1H, NH), 9.17 (br s, 1H, OH). The crude product was used in a next step without further purification.

4.3.7. Boc-D-Leu- α -h(Bn)D-Ala-OH, 7'a. Yield: 82%, white amorphous solid; ^1H NMR (300 MHz, CDCl_3) δ 0.84 (d, 3H, $J = 6.0$ Hz, δCH_3 Leu), 0.86 (d, 3H, $J = 6.0$ Hz, δCH_3 Leu), 1.20-1.50 (m, 6H, βCH_3 Ala, βCH_2 Leu, γCH Leu), 1.43 (s, 9H, Boc), 3.65-3.80 (m, 1H, αCH Ala), 4.06 (s, 2H, CH_2 , N^α -Bn), 4.10-4.25 (m, 1H, αCH Leu), 4.93 (m, 1H, NHBoc), 7.20-7.50 (m, 5H, Ar.), 8.14 (br s, 1H, NH hydrazidic). The crude product was used in a next step without further purification.

4.4. Representative procedure for the preparation of compounds **5a** and **5b**

To a solution of Boc-acid **4a** or **4b** (1.0 equiv., 22 mmol) in MeOH (50 mL) was added SOCl₂ (2.1 equiv., 46.2 mmol) dropwise at 0°C and the mixture was stirred for 48 h at room temperature until completion (monitored by TLC). Evaporation of MeOH *in vacuo* gives the corresponding chlorhydrate ester **5a** or **5b** as a white amorphous solid in 99% yield. Compounds **5a** and **5b** were engaged immediately in the next step.

4.5. Representative procedure for the N-terminal deprotection with TFA

Boc-ester compound (1.0 equiv., 9 mmol) was treated with a mixture of CH₂Cl₂ / TFA (9 mL / 6 mL) and stirred for 3 h at room temperature. Excess of TFA was co-evaporated with MeOH and Et₂O until to obtain the corresponding trifluoroacetate salt compound as a white amorphous solid in quantitative yield. Compounds **8a**, **8b**, **12a**, **12b** and **8'a** were engaged immediately in the next step.

4.6. Representative procedure for the coupling reaction with HATU/NMM

The appropriate trifluoroacetate or hydrochloride salt (1.0 equiv., 9 mmol) was dissolved in CH₂Cl₂ (10 mL) and cooled to 0°C. This solution was treated successively with NMM (4.0 equiv., 36 mmol), a solution of the Boc-protected fragment (1.0 equiv., 9 mmol) in CH₂Cl₂ (5 mL), and a solution of HATU (1.0 equiv., 9 mmol) in a minimum amount of DMF. The mixture was allowed to warm to room temperature and then stirred until TLC indicated complete reaction. Subsequent addition of CH₂Cl₂ was followed by washing with HCl 1N (1 x 25 mL), saturated aqueous NaHCO₃ solution (1 x 25 mL), and saturated aqueous NaCl solution (2 x 25 mL). The organic layer was dried over MgSO₄ and concentrated under reduced pressure. The resulting crude material was purified and characterized as reported below.

4.6.1. Boc-L-Leu- α -h(Bn)D-Ala-OMe dimer, **6a.** Purified by flash chromatography (Petroleum ether/AcOEt = 70:30), Yield: 96%, white powder: mp = 112 °C; IR (ATR) $\nu_{\max}/\text{cm}^{-1}$: 3322, 3217, 3072, 3037, 2983, 2958, 2938, 2873, 2853, 1754, 1738, 1707, 1681, 1671, 1612, 1558, 1523, 1501, 1457, 1439, 1392, 1368, 1319, 1297, 1271, 1247, 1198, 1172, 1125; ¹H NMR (300 MHz, CDCl₃) δ 0.86 (d, 6H, *J* = 6.6 Hz, 2 δ CH₃ Leu),

1.38 (d, 3H, $J = 7.2$ Hz, βCH_3 Ala), 1.43 (s, 9H, Boc), 1.46-1.79 (m, 3H, βCH_2 Leu, γCH Leu), 3.63-3.78 (m, 1H, αCH Ala), 3.73 (s, 3H, OCH_3), 3.88-4.09 (m, 3H, CH_2 , $N^\alpha\text{-Bn}$, αCH Leu), 4.77 (br d, $J = 6.0$ Hz, NHBoc), 7.23-7.43 (m, 5H, Ar.), 7.98 (s, 1H, NH hydrazidic); ^{13}C NMR (75 MHz, CDCl_3) δ 17.0 (βCH_3 Ala), 22.3 (γCH Leu), 23.4 (δCH_3 Leu), 25.4 (δCH_3 Leu), 29.0 (3 CH_3 , Boc), 41.9 (βCH_2 Leu), 48.2 (αCH Ala), 52.3 (O-CH_3), 60.7 (αCH Leu), 60.8 (CH_2 , $N^\alpha\text{-Bn}$), 80.6 (C, Boc), 128.3 (CH, Ar.), 129.0 (2 CH, Ar.), 130.0 (2 CH, Ar.), 137.0 (C, Ar.), 156.0 (C=O, Boc), 171.8 (C=O, hydrazid), 175.3 (C=O, ester); HRMS (ESI) calculated for $\text{C}_{22}\text{H}_{35}\text{N}_3\text{O}_5$ $[\text{M}+\text{H}]^+$ m/z 422.2655, found 422.2649.

4.6.2. Boc-L-Ala- α -h(Bn)D-Leu-OMe dimer, 6b. Purified by flash chromatography (Petroleum ether/AcOEt = 80:20), Yield: 94%, white powder: mp = 68 °C; IR (ATR) $\nu_{\text{max}}/\text{cm}^{-1}$: 3338, 3280, 3068, 3031, 2977, 2963, 2939, 2909, 2869, 1704, 1688, 1509, 1500, 1456, 1394, 1371, 1289, 1249, 1205, 1165; ^1H NMR (300 MHz, CDCl_3) δ 0.72 (d, 3H, $J = 6.0$ Hz, δCH_3 Leu), 0.86 (d, 3H, $J = 6.0$ Hz, δCH_3 Leu), 1.24 (d, 3H, $J = 7.2$ Hz, βCH_3 Ala), 1.44 (s, 9H, Boc), 1.60-1.73 (m, 2H, βCH_2 Leu), 1.88-2.03 (m, 1H, γCH Leu), 3.45-3.54 (m, 1H, αCH Leu), 3.72 (s, 3H, OCH_3), 3.85-4.12 (m, 3H, CH_2 , $N^\alpha\text{-Bn}$, αCH Ala), 4.98 (br s, NHBoc), 7.23-7.45 (m, 5H, Ar.), 8.08 (br s, 1H, NH hydrazidic); ^{13}C NMR (75 MHz, CDCl_3) δ 19.5 (βCH_3 Ala), 21.9 (γCH Leu), 23.7 (δCH_3 Leu), 24.7 (δCH_3 Leu), 29.0 (3 CH_3 , Boc), 39.9 (βCH_2 Leu), 49.9 (αCH Ala), 52.2 (O-CH_3), 61.2 (CH_2 , $N^\alpha\text{-Bn}$), 62.5 (αCH Leu), 80.4 (C, Boc), 128.3 (CH, Ar.), 128.9 (2 CH, Ar.), 130.0 (2 CH, Ar.), 137.0 (C, Ar.), 155.8 (C=O, Boc), 171.5 (C=O, hydrazid), 175.5 (C=O, ester); HRMS (ESI) calculated for $\text{C}_{22}\text{H}_{35}\text{N}_3\text{O}_5$ $[\text{M}+\text{Na}]^+$ m/z 444.2475, found 444.2469.

4.6.3. Boc-(L-Leu- α -h(Bn)D-Ala) $_2$ -OMe tetramer, 9a. Purified by flash chromatography (Petroleum ether/AcOEt = 20:80), Yield: 87%, white powder: mp = 125 °C; IR (ATR) $\nu_{\text{max}}/\text{cm}^{-1}$: 3352, 3247, 3066, 3033, 2958, 2940, 2871, 1740, 1729, 1723, 1711, 1691, 1680, 1674, 1657, 1561, 1513, 1499, 1467, 1457, 1388, 1368, 1321, 1293, 1253, 1214, 1168, 1125; ^1H NMR of the major form (300 MHz, CDCl_3) δ 0.81 (d, 3H, $J = 6.6$ Hz, δCH_3 Leu), 0.83 (d, 3H, $J = 6.6$ Hz, δCH_3 Leu), 0.85 (d, 3H, $J = 6.6$ Hz, δCH_3 Leu), 0.90 (d, 3H, $J = 6.6$ Hz, δCH_3 Leu), 1.29 (d, 3H, $J = 7.2$ Hz, βCH_3 Ala),

1.34 (d, 3H, $J = 7.2$ Hz, βCH_3 Ala), 1.41 (s, 9H, Boc), 1.50-1.73 (m, 6H, 2 βCH_2 Leu, 2 γCH Leu), 3.51 (q, 1H, $J = 7.2$ Hz, αCH Ala), 3.68 (q, 1H, $J = 7.2$ Hz, αCH Ala), 3.71 (s, 3H, OCH_3), 3.69-3.88 (m, 1H, αCH Leu), 3.91-4.28 (m, 5H, 2 CH_2 , $N^\alpha\text{-Bn}$, αCH Leu), 5.54 (br d, 1H, $J = 7.5$ Hz, NHBoc), 7.22-7.48 (m, 10H Ar.), 7.83 (s, 1H, NH), 7.91 (br s, 1H, NH), 8.34 (br d, 1H, $J = 7.5$ Hz, NH); ^{13}C NMR (75 MHz, CDCl_3) δ 17.0 (2 βCH_3 Ala), 22.2 (γCH Leu), 23.0 (γCH Leu), 23.3 (δCH_3 Leu), 23.6 (δCH_3 Leu), 25.1 (δCH_3 Leu), 25.6 (δCH_3 Leu), 29.0 (3 CH_3 , Boc), 40.6 (βCH_2 Leu), 41.2 (βCH_2 Leu), 52.3 (αCH Ala), 52.5 (αCH Ala), 52.9 (O-CH_3), 60.7 (αCH Leu), 60.8 (CH_2 , $N^\alpha\text{-Bn}$), 62.3 (CH_2 , $N^\alpha\text{-Bn}$), 62.9 (αCH Leu), 80.9 (C, Boc), 128.3 (CH, Ar.), 128.5 (CH, Ar.), 128.9 (2 CH, Ar.), 129.1 (2 CH, Ar.), 129.8 (2 CH, Ar.), 130.1 (2 CH, Ar.), 136.2 (C, Ar.), 137.2 (C, Ar.), 156.9 (C=O, Boc), 172.6 (C(NH)=O), 172.7 (C(NH)=O), 172.9 (C(NH)=O), 176.0 (C=O, ester); HRMS (ESI) calculated for $\text{C}_{38}\text{H}_{58}\text{N}_6\text{O}_7$ $[\text{M}+\text{H}]^+$ m/z 711.4445, found 711.4440.

4.6.4. Boc-(L-Ala- α -h(Bn)D-Leu)₂-OMe tetramer, 9b. Purified by flash chromatography (Petroleum ether/AcOEt = 50:50), Yield: 90%, white powder: mp = 88 °C; IR (ATR) $\nu_{\text{max}}/\text{cm}^{-1}$: 3354, 3265, 3061, 3033, 2960, 2932, 2869, 2850, 1732, 1726, 1717, 1696, 1685, 1671, 1655, 1554, 1537, 1519, 1507, 1498, 1470, 1458, 1382, 1369, 1324, 1270, 1249, 1205, 1167, 1118; ^1H NMR of the major form (300 MHz, CDCl_3) δ 0.73 (d, 3H, $J = 6.6$ Hz, δCH_3 Leu), 0.84 (d, 3H, $J = 6.6$ Hz, δCH_3 Leu), 0.88 (d, 3H, $J = 6.6$ Hz, δCH_3 Leu), 0.92 (d, 3H, $J = 6.6$ Hz, δCH_3 Leu), 1.14 (d, 3H, $J = 7.2$ Hz, βCH_3 Ala), 1.34 (d, 3H, $J = 7.2$ Hz, βCH_3 Ala), 1.42 (s, 9H, Boc), 1.51-2.03 (m, 6H, 2 βCH_2 Leu, 2 γCH Leu), 3.35-3.64 (m, 2H, 2 αCH Leu), 3.64-4.06 (m, 4H, 2 CH_2 , $N^\alpha\text{-Bn}$), 3.71 (s, 3H, OCH_3), 4.09 (q, 1H, $J = 7.2$ Hz, αCH Ala), 4.32 (q, 1H, $J = 7.2$ Hz, αCH Ala), 5.09 (br d, 1H, $J = 6.6$ Hz, NHBoc), 7.15-7.48 (m, 10H, Ar.), 7.68 (br s, 1H, NH), 8.01 (s, 1H, NH), 8.49 (br s (1H, NH); ^{13}C NMR of the major form (75 MHz, CDCl_3) δ 19.0 (βCH_3 Ala), 19.5 (βCH_3 Ala), 22.1 (γCH Leu), 22.9 (γCH Leu), 23.4 (δCH_3 Leu), 23.6 (δCH_3 Leu), 24.8 (δCH_3 Leu), 25.7 (δCH_3 Leu), 28.9 (3 CH_3 , Boc), 38.0 (βCH_2 Leu), 40.0 (βCH_2 Leu), 48.9 (αCH Ala), 50.1 (αCH Ala), 52.3 (O-CH_3), 61.1 (CH_2 , $N^\alpha\text{-Bn}$), 61.4 (CH_2 , $N^\alpha\text{-Bn}$), 62.5 (αCH Leu), 65.4 (αCH Leu), 80.7 (C, Boc), 127.8 (CH, Ar.), 128.4 (CH, Ar.), 128.8 (2 CH, Ar.), 129.0 (2 CH, Ar.), 129.3 (2 CH, Ar.), 130.1 (2 CH, Ar.), 136.8 (C, Ar.), 137.9 (C, Ar.), 156.6 (C=O, Boc), 171.8 (C(NH)=O), 172.2

(C(NH)=O), 172.8 (C(NH)=O), 176.0 (C=O, ester); HRMS (ESI) calculated for $C_{38}H_{58}N_6O_7$ $[M+H]^+$ m/z 711.4445, found 711.4140.

4.6.5. Boc-(L-Leu- α -h(Bn)D-Ala)₃-OMe hexamer, 11a. Purified by flash chromatography (Petroleum ether/AcOEt = 30:70), Yield: 83%, white powder: mp = 184 °C; IR (ATR) ν_{max}/cm^{-1} : 3332, 3286, 3065, 3033, 2958, 2936, 2876, 2853, 1740, 1722, 1704, 1684, 1665, 1534, 1513, 1495, 1470, 1459, 1382, 1370, 1299, 1275, 1254, 1236, 1216, 1170, 1129; 1H NMR of the major form (300 MHz, $CDCl_3$) δ 0.61-0.99 (m, 18H, 6 δCH_3 Leu), 1.25-1.38 (3, 9H, 3 βCH_3 Ala), 1.40 (s, 9H, Boc), 1.37- 1.74 (m, 9H, 3 βCH_2 Leu, 3 γCH Leu), 3.45-3.79 (m, 3H, 3 αCH Leu), 3.71 (s, 3H, OCH_3), 3.82-4.47 (m, 9H, 3 CH_2 , N^α -Bn, 3 αCH Ala), 5.27 (br d, 1H, J = 6.3 Hz, NHBoc), 7.18-7.48 (m, 15H, Ar.), 7.72-8.39 (m, 4H, 4 NH), 8.75 (br s, 1H, NH); ^{13}C NMR of the major form (75 MHz, $CDCl_3$) δ 17.0 (3 βCH_3 Ala), 23.1 (3 γCH Leu), 23.4 (δCH_3 Leu), 23.7 (δCH_3 Leu), 24.9 (2 δCH_3 Leu), 25.5 (δCH_3 Leu), 25.6 (δCH_3 Leu), 29.0 (3 CH_3 , Boc), 40.3 (βCH_2 Leu), 40.4 (βCH_2 Leu), 41.2 (βCH_2 Leu), 52.4 ($O-CH_3$), 52.6 (αCH Ala), 52.8 (αCH Ala), 53.3 (αCH Ala), 60.0 (CH_2 , N^α -Bn), 60.7 (2 αCH Leu), 62.3 (αCH Leu), 62.5 (CH_2 , N^α -Bn), 63.5 (CH_2 , N^α -Bn), 80.7 (C, Boc), 127.8 (CH, Ar.), 128.1 (CH, Ar.), 128.8 (2 CH, Ar.), 129.0 (3 CH, Ar.), 129.6 (6 CH, Ar.), 129.8 (2 CH, Ar.), 136.3 (C, Ar.), 137.4 (C, Ar.), 138.1 (C, Ar.), 157.1 (C=O, Boc), 172.0 (C(NH)=O), 172.1 (C(NH)=O), 172.4 (C(NH)=O), 172.5 (C(NH)=O), 172.8 (C(NH)=O), 175.5 (C=O, ester); HRMS (ESI) calculated for $C_{54}H_{81}N_9O_9$ $[M+H]^+$ m/z 1000.6235, found 1000.6230.

4.6.6. Boc-(L-Ala- α -h(Bn)D-Leu)₃-OMe hexamer, 11b. Purified by flash chromatography (Petroleum ether/AcOEt = 30:70), Yield: 82%, white powder: mp = 102 °C; IR (ATR) ν_{max}/cm^{-1} : 3333, 3244, 3061, 3031, 2953, 2930, 2920, 2869, 2848, 1734, 1717, 1697, 1685, 1671, 1655, 1554, 1528, 1495, 1465, 1456, 1385, 1364, 1320, 1268, 1247, 1209, 1167; 1H NMR of the major form (300 MHz, $CDCl_3$) δ 0.70-1.48 (m, 27H, 6 δCH_3 Leu, 3 βCH_3 Ala), 1.39 (s, 9H, Boc), 1.51- 2.08 (m, 9H, 3 βCH_2 Leu, 3 γCH Leu), 3.23-3.61 (m, 3H, 3 αCH Leu), 3.62-4.42 (m, 9H, 3 CH_2 , N^α -Bn, 3 αCH Ala), 3.72 (s, 3H, OCH_3), 4.84 (br d, 1H, J = 5.7 Hz, NHBoc), 7.11-7.41 (m, 15H, Ar.), 8.02 (br s, 1H, NH), 8.09 (br s, 1H, NH), 8.14 (s, 1H, NH), 8.45 (s, 1H, NH), 9.10 (br s,

¹H, NH); ¹³C NMR of the major form (75 MHz, CDCl₃) δ 17.1 (βCH₃ Ala), 17.8 (βCH₃ Ala), 18.0 (βCH₃ Ala), 22.1 (γCH Leu), 23.1 (γCH Leu), 23.4 (γCH Leu), 23.7 (2 δCH₃ Leu), 24.9 (2 δCH₃ Leu), 26.0 (δCH₃ Leu), 26.2 (δCH₃ Leu), 29.0 (3 CH₃, Boc), 37.7 (βCH₂ Leu), 39.5 (βCH₂ Leu), 40.1 (βCH₂ Leu), 50.5 (αCH Ala), 50.6 (αCH Ala), 51.1 (αCH Ala), 52.4 (O-CH₃), 60.8 (CH₂, N^α-Bn), 61.5 (2 CH₂, N^α-Bn), 62.2 (αCH Leu), 66.2 (αCH Leu), 66.6 (αCH Leu), 80.9 (C, Boc), 127.4 (CH, Ar.), 127.5 (CH, Ar.), 128.8 (4 CH, Ar.), 129.1 (4 CH, Ar.), 129.3 (2 CH, Ar.), 130.0 (CH, Ar.), 130.2 (2 CH, Ar.), 136.8 (C, Ar.), 138.4 (C, Ar.), 138.7 (C, Ar.), 156.8 (C=O, Boc), 171.9 (C(NH)=O), 172.0 (C(NH)=O), 172.8 (C(NH)=O), 173.4 (C(NH)=O), 174.4 (C(NH)=O), 175.9 (C=O, ester); HRMS (ESI) calculated for C₅₄H₈₁N₉O₉ [M+Na]⁺ *m/z* 1022.6055, found 1022.6049.

4.6.7. Boc-(L-Leu-α-h(Bn)D-Ala)₄-OMe octamer, 13a. Purified by flash chromatography (Petroleum ether/AcOEt = 50:50), Yield: 77%, white powder: mp = 190 °C; IR (ATR) *v*_{max}/cm⁻¹: 3334, 3278, 3233, 3088, 3068, 3031, 2958, 2940, 2871, 1735, 1722, 1702, 1683, 1665, 1651, 1534, 1515, 1495, 1457, 1384, 1366, 1297, 1279, 1255, 1243, 1216, 1170, 1125; ¹H NMR of the major form (300 MHz, CDCl₃) δ 0.66-1.01 (m, 24H, 8 δCH₃ Leu), 1.18-1.38 (m, 12H, 4 βCH₃ Ala), 1.40 (s, 9H, Boc), 1.45-1.82 (m, 12H, 4 βCH₂ Leu, 4 γCH Leu), 3.42-3.79 (m, 4H, 4 αCH Leu), 3.71 (s, 3H, OCH₃), 3.81-4.35 (m, 12H, 4 CH₂, N^α-Bn, 4 αCH Ala), 5.29 (m, 1H, NHBoc), 7.08-7.49 (m, 20H, Ar.), 7.50-9.27 (m, 7H, 7 NH); ¹³C NMR of the major form (75 MHz, CDCl₃) δ 17.1 (4 βCH₃ Ala), 23.1 (2 γCH Leu), 23.2 (2 γCH Leu), 23.7 (δCH₃ Leu), 24.9 (3 δCH₃ Leu), 25.5 (2 δCH₃ Leu), 29.0 (3 CH₃, Boc), 40.2 (βCH₂ Leu), 40.4 (βCH₂ Leu), 41.0 (βCH₂ Leu), 41.7 (βCH₂ Leu), 51.7 (O-CH₃), 52.5 (αCH Ala), 52.8 (αCH Ala), 53.3 (αCH Ala), 53.5 (αCH Ala), 59.8 (αCH Leu), 60.6 (CH₂, N^α-Bn), 60.8 (CH₂, N^α-Bn), 61.0 (αCH Leu), 62.3 (CH₂, N^α-Bn), 62.4 (CH₂, N^α-Bn), 62.6 (αCH Leu), 63.5 (αCH Leu), 80.7 (C, Boc), 128.3 (CH, Ar.), 128.5 (CH, Ar.), 128.6 (CH, Ar.), 128.8 (3 CH, Ar.), 128.9 (4 CH, Ar.), 129.4 (3 CH, Ar.), 129.6 (3 CH, Ar.), 130.0 (2 CH, Ar.), 130.1 (2 CH, Ar.), 136.3 (C, Ar.), 137.3 (C, Ar.), 138.1 (C, Ar.), 138.7 (C, Ar.), 157.1 (C=O, Boc), 172.1 (4 C(NH)=O), 172.5 (3 C(NH)=O), 175.3 (C=O, ester); HRMS (ESI) calculated for C₇₀H₁₀₄N₁₂O₁₁ [M+Na]⁺ *m/z* 1311.7846, found 1311.7840.

4.6.8. Boc-(L-Ala- α -h(Bn)D-Leu)₄-OMe octamer, 13b. Purified by flash chromatography (Petroleum ether/AcOEt = 50:50), Yield: 79%, white powder: mp = 116 °C; IR (ATR) $\nu_{\max}/\text{cm}^{-1}$: 3346, 3264, 3064, 3035, 2957, 2932, 2873, 1736, 1729, 1717, 1696, 1686, 1649, 1557, 1528, 1504, 1496, 1456, 1387, 1370, 1322, 1271, 1250, 1219, 1164, 1107; ¹H NMR of the major form (300 MHz, CDCl₃) δ 0.71-1.48 (m, 36H, 8 δ CH₃ Leu, 4 β CH₃ Ala), 1.39 (s, 9H, Boc), 1.52- 2.02 (m, 12H, 4 β CH₂ Leu, 4 γ CH Leu), 3.41-3.62 (m, 4H, 4 α CH Leu), 3.66-4.44 (m, 12H, 4 CH₂, *N* ^{α} -Bn, 4 α CH Ala), 3.72 (s, 3H, OCH₃), 4.81 (br d, 1H, *J* = 6.0 Hz, NHBoc), 7.12-7.51 (m, 20H, Ar.), 8.10 (br s, 2H, 2 NH), 8.42 (br s, 2H, 2 NH), 8.68 (br s, 1H, NH), 8.82 (s, 1H, NH), 9.23 (s, 1H, NH); ¹³C NMR of the major form (75 MHz, CDCl₃) δ 16.8 (β CH₃ Ala), 17.2 (β CH₃ Ala), 17.7 (β CH₃ Ala), 17.8 (β CH₃ Ala), 22.2 (γ CH Leu), 23.2 (γ CH Leu), 23.4 (2 γ CH Leu), 23.6 (3 δ CH₃ Leu), 23.7 (δ CH₃ Leu), 24.9 (δ CH₃ Leu), 26.0 (δ CH₃ Leu), 26.3 (δ CH₃ Leu), 26.5 (δ CH₃ Leu), 28.9 (3 CH₃, Boc), 37.6 (3 β CH₂ Leu), 40.2 (β CH₂ Leu), 50.6 (2 α CH Ala), 51.4 (α CH Ala), 51.6 (α CH Ala), 52.4 (O-CH₃), 54.0 (CH₂, *N* ^{α} -Bn), 54.2 (CH₂, *N* ^{α} -Bn), 61.2 (CH₂, *N* ^{α} -Bn), 61.5 (CH₂, *N* ^{α} -Bn), 62.2 (α CH Leu), 66.3 (α CH Leu), 66.6 (3 α CH Leu), 81.0 (C, Boc), 127.3 (CH, Ar.), 127.5 (2 CH, Ar.), 128.6 (9 CH, Ar.), 129.0 (2 CH, Ar.), 129.1 (2 CH, Ar.), 129.4 (2 CH, Ar.), 130.2 (2 CH, Ar.), 136.8 (C, Ar.), 138.5 (2 C, Ar.), 138.9 (C, Ar.), 156.8 (C=O, Boc), 171.4 (C(NH)=O), 171.8 (2 C(NH)=O), 171.9 (2 C(NH)=O), 173.6 (C(NH)=O), 173.9 (C(NH)=O), 175.9 (C=O, ester); HRMS (ESI) calculated for C₇₀H₁₀₄N₁₂O₁₁ [M+Na]⁺ *m/z* 1311.7846, found 1311.7840.

4.6.9. Boc-D-Leu- α -h(Bn)D-Ala-OMe dimer, 6'a. Purified by flash chromatography (Petroleum ether/AcOEt = 70:30), Yield: 80%, white powder: mp = 83 °C; IR (ATR) $\nu_{\max}/\text{cm}^{-1}$: 3438, 3348, 3312, 3089, 3065, 2983, 2958, 2938, 2873, 2853, 1732, 1702, 1657, 1507, 1497, 1457, 1439, 1392, 1369, 1318, 1291, 1261, 1251, 1165; ¹H NMR (300 MHz, CDCl₃) δ 0.78 (d, 3H, *J* = 6.0 Hz, δ CH₃ Leu), 0.79 (d, 3H, *J* = 6.0 Hz, δ CH₃ Leu), 1.16-1.50 (m, 5H, β CH₃ Ala, β CH₂ Leu), 1.40 (s, 9H, Boc), 1.54-1.63 (m, 1H, γ CH Leu), 3.64-3.80 (m, 1H, α CH Ala), 3.74 (s, 3H, OCH₃), 3.81-3.92 (m, 1H, α CH Leu), 3.93-4.07 (m, 2H, CH₂, *N* ^{α} -Bn), 4.82 (br d, *J* = 7.2 Hz, NHBoc), 7.19-7.43 (m, 5H, Ar.), 7.77 (br s, 1H, NH hydrazidic); ¹³C NMR (75 MHz, CDCl₃) δ 16.8 (β CH₃ Ala), 22.9 (γ CH Leu), 23.3 (δ CH₃ Leu), 25.1 (δ CH₃ Leu), 28.9 (3 CH₃, Boc), 41.8

(β CH₂ Leu), 48.3 (α CH Ala), 52.3 (O-CH₃), 61.0 (CH₂, *N* ^{α} -Bn), 61.3 (α CH Leu), 80.4 (C, Boc), 128.3 (CH, Ar.), 128.9 (2 CH, Ar.), 129.9 (2 CH, Ar.), 137.1 (C, Ar.), 156.2 (C=O, Boc), 172. (C=O, hydrazid), 175.1 (C=O, ester); HRMS (ESI) calculated for C₂₂H₃₅N₃O₅ [M+H]⁺ *m/z* 422.2655, found 422.2649.

4.6.10. Boc-(D-Leu- α -h(Bn)D-Ala)₂-OMe tetramer, 9'a. Purified by flash chromatography (Petroleum ether/AcOEt = 20:80), Yield: 75%, white powder: mp = 143 °C; IR (ATR) $\nu_{\max}/\text{cm}^{-1}$: 3440, 3348, 3311, 3234, 3089, 3065, 2961, 2937, 2872, 2855, 1740, 1728, 1697, 1660, 1655, 1548, 1551, 1520, 1498, 1470, 1457, 1438, 1391, 1369, 1318, 1293, 1259, 1162; ¹H NMR of the major form (300 MHz, CDCl₃) δ 0.67-0.91 (m, 12H, 4 δ CH₃ Leu), 1.13-1.49 (m, 12H, 2 β CH₃ Ala, 2 β CH₂ Leu, 2 γ CH Leu), 1.40 (s, 9H, Boc), 3.43-3.62 (m, 1H, α CH Ala), 3.65-3.90 (m, 3H, α CH Ala, CH₂, *N* ^{α} -Bn), 3.74 (s, 3H, OCH₃), 3.90-4.11 (m, 3H, CH₂, *N* ^{α} -Bn, α CH Leu), 4.12-4.27 (m, 1H, α CH Leu), 4.82 (m, 1H, NHBoc), 7.08-7.47 (m, 10H Ar.), 7.57 (br s, 1H, NH), 7.75 (br s, 1H, NH), 8.30 (br s, 1H, NH); ¹³C NMR (75 MHz, CDCl₃) δ 17.2 (β CH₃ Ala), 17.6 (β CH₃ Ala), 22.4 (γ CH Leu), 23.0 (γ CH Leu), 23.3 (δ CH₃ Leu), 23.4 (δ CH₃ Leu), 24.8 (δ CH₃ Leu), 25.4 (δ CH₃ Leu), 29.0 (3 CH₃, Boc), 40.6 (β CH₂ Leu), 40.7 (β CH₂ Leu), 52.3 (α CH Ala), 52.4 (α CH Ala), 52.8 (O-CH₃), 60.9 (CH₂, *N* ^{α} -Bn), 61.1 (α CH Leu), 61.1 (CH₂, *N* ^{α} -Bn), 64.7 (α CH Leu), 80.6 (C, Boc), 128.2 (CH, Ar.), 128.3 (CH, Ar.), 128.8 (2 CH, Ar.), 128.9 (2 CH, Ar.), 129.8 (2 CH, Ar.), 130.1 (2 CH, Ar.), 137.1 (C, Ar.), 137.3 (C, Ar.), 156.6 (C=O, Boc), 172.4 (3 C(NH)=O), 175.4 (C=O, ester); HRMS (ESI) calculated for C₃₈H₅₈N₆O₇ [M+H]⁺ *m/z* 711.4445, found 711.4440.

4.7. Representative procedure for the amidation reaction with NH₄OH/MeOH

Ammonium hydroxide (10 mL, 25% aq.) was added to a stirred solution of the appropriate oligomer ester (0.6 mmol) in MeOH (10 mL). The reaction flask was sealed with a rubber septum and stirred vigorously at room temperature for 2 days. The reaction mixture was then concentrated, neutralized with HCl 1N until pH=7, extracted with AcOEt (3 x 20 mL) and evaporated *in vacuo*. The resulting crude material was purified and characterized as reported below.

4.7.1. Boc-L-Leu- α -h(Bn)D-Ala-NH₂, 14a

The residue was purified by flash chromatography (Petroleum ether/AcOEt = 30:70) to afford **14a** (0.23 g, 95%) as a white powder: mp = 150 °C; IR (ATR) $\nu_{\text{max}}/\text{cm}^{-1}$: 3481, 3438, 3346, 3312, 3034, 3009, 2960, 2932, 2902, 2871, 2841, 1730, 1725, 1704, 1687, 1662, 1656, 1602, 1505, 1498, 1457, 1436, 1391, 1370, 1291, 1262, 1166, 1123; ^1H NMR (300 MHz, $\text{CDCl}_3/10$ mM) δ 0.77 (d, 3H, $J = 6.5$ Hz, δCH_3 Leu), 0.80 (d, 3H, $J = 6.5$ Hz, δCH_3 Leu), 1.35 (d, 3H, $J = 7.1$ Hz, βCH_3 Ala), 1.45 (s, 9H, Boc), 1.40-1.62 (m, 3H, βCH_2 Leu, γCH Leu), 3.51 (q, 1H, $J = 7.1$ Hz, αCH Ala), 3.79-4.03 (m, 3H, CH_2 , N^α -Bn, αCH Leu), 4.69 (br d, 1H, $J = 7.5$ Hz, NHBoc), 5.32 (s, 1H, NH_2), 7.26-7.38 (m, 6H, Ar., NH hydrazidic), 8.06 (br s, 1H, NH_2); ^{13}C NMR (75 MHz, CDCl_3) δ 22.9 (γCH Leu), 23.2 (βCH_3 Ala), 25.1 (2 δCH_3 Leu), 29.0 (3 CH_3 , Boc), 40.5 (βCH_2 Leu), 52.2 (αCH Ala), 61.7 (CH_2 , N^α -Bn), 62.9 (αCH Leu), 81.3 (C, Boc), 128.7 (CH, Ar.), 129.9 (2 CH, Ar.), 130.8 (2 CH, Ar.), 136.4 (C, Ar.), 156.5 (C=O, Boc), 172.6 (C=O, hydrazid), 176.2 (C=O, amide); HRMS (ESI) calculated for $\text{C}_{21}\text{H}_{34}\text{N}_4\text{O}_4$ $[\text{M}+\text{Na}]^+$ m/z 429.2478, found 429.2472.

4.7.2. Boc-(L-Leu- α -h(Bn)D-Ala)₂-NH₂, **15a**.

The residue was purified by flash chromatography (AcOEt /MeOH = 95:5) to afford **15a** (0.26 g, 63%) as a white powder: mp = 162 °C; IR (ATR) $\nu_{\text{max}}/\text{cm}^{-1}$: 3482, 3446, 3435, 3400, 3350, 3339, 3308, 3290, 3090, 3064, 2965, 2939, 2871, 2851, 1734, 1717, 1697, 1685, 1672, 1655, 1607, 1540, 1496, 1470, 1455, 1391, 1321, 1292, 1260, 1166, 1107; ^1H NMR (300 MHz, $\text{CDCl}_3/10$ mM) δ 0.69-0.91 (m, 12H, 4 δCH_3 Leu), 1.29-1.80 (m, 12H, 2 βCH_3 Ala, 2 βCH_2 Leu, 2 γCH Leu), 1.44 (s, 9H, Boc), 3.40-3.60 (m, 2H, 2 αCH Ala), 3.80-4.05 (m, 5H, 2 CH_2 , N^α -Bn, αCH Leu), 4.06-4.20 (m, 1H, αCH Leu), 5.39 (br s, 1H, NH_2), 5.78 (br d, 1H, $J = 7.2$ Hz, NHBoc), 7.20-7.47 (m, 10H, Ar.), 7.95 (br s, 2H, 2 NH hydrazidic), 8.12 (br s, 1H, NH_2), 8.57 (br d, 1H, $J = 5.1$ Hz, 1H, NH amidic); ^{13}C NMR (75 MHz, CDCl_3) δ 22.4 (γCH Leu), 22.7 (γCH Leu), 23.4 (βCH_3 Ala), 23.6 (βCH_3 Ala), 25.0 (2 δCH_3 Leu), 25.3 (2 δCH_3 Leu), 29.0 (3 CH_3 , Boc), 39.8 (2 βCH_2 Leu), 51.5 (αCH Ala), 51.8 (αCH Ala), 61.3 (2 CH_2 , N^α -Bn), 62.3 (2 αCH Leu), 80.9 (C, Boc), 128.5 (CH, Ar.), 128.6 (CH, Ar.), 129.1 (2 CH, Ar.), 129.2 (2 CH, Ar.), 129.7 (2 CH, Ar.), 130.0 (2 CH, Ar.), 136.8 (2 C, Ar.), 157.4 (C=O, Boc), 172.8 (C(NH)=O), 173.0 (C(NH)=O), 174.0 (C(NH)=O), 176.6 (C=O, amide); HRMS (ESI) calculated for $\text{C}_{37}\text{H}_{57}\text{N}_7\text{O}_6$ $[\text{M}+\text{Na}]^+$ m/z 718.4268, found 718.4263.

4.7.3. Boc-D-Leu- α -h(Bn)D-Ala-NH₂, 14'a

The residue was purified by trituration in Et₂O to afford **14'a** (0.16 g, 65%) as a white powder: mp = 177 °C; IR (ATR) $\nu_{\max}/\text{cm}^{-1}$: 3484, 3439, 3340, 3305, 3151, 3020, 2985, 2963, 2939, 2872, 2852, 1734, 1717, 1696, 1685, 1639, 1603, 1575, 1558, 1496, 1472, 1456, 1392, 1369, 1340, 1321, 1291, 1261, 1243, 1165; ¹H NMR (300 MHz, CDCl₃/10 mM) δ 0.85 (d, 6H, *J* = 6.0 Hz, 2 δ CH₃ Leu), 1.37 (d, 3H, *J* = 6.9 Hz, β CH₃ Ala), 1.44 (s, 9H, Boc), 1.39-1.54 (m, 3H, β CH₂ Leu, γ CH Leu), 3.53-3.69 (m, 1H, α CH Ala), 3.79-4.15 (m, 3H, CH₂, *N* ^{α} -Bn, α CH Leu), 4.70 (br d, 1H, *J* = 5.8 Hz, NHBoc), 5.39 (s, 1H, NH₂), 7.22-7.44 (m, 5H, Ar.), 7.62 (br s, 1H, NH hydrazidic), 7.99 (br s, 1H, NH₂); ¹³C NMR (75 MHz, CDCl₃) δ 22.9 (γ CH Leu), 23.2 (β CH₃ Ala), 25.1 (2 δ CH₃ Leu), 29.0 (3 CH₃, Boc), 40.7 (β CH₂ Leu), 52.4 (α CH Ala), 61.0 (CH₂, *N* ^{α} -Bn), 62.2 (α CH Leu), 81.2 (C, Boc), 128.7 (CH, Ar.), 129.2 (2 CH, Ar.), 129.9 (2 CH, Ar.), 136.3 (C, Ar.), 156.5 (C=O, Boc), 172.7 (C=O, hydrazid), 176.0 (C=O, amide); HRMS (ESI) calculated for C₂₁H₃₄N₄O₄ [M+Na]⁺ *m/z* 429.2478, found 429.2472.

4.7.4. Boc-(D-Leu- α -h(Bn)D-Ala)₂-NH₂, 15'a.

The residue was purified by trituration in Et₂O to afford **15'a** (0.39 g, 93%) as a white powder: mp = 185 °C; IR (ATR) $\nu_{\max}/\text{cm}^{-1}$: 3483, 3446, 3438, 3400, 3351, 3338, 3308, 3260, 3067, 3029, 3006, 2965, 2939, 2877, 2854, 1733, 1718, 1698, 1685, 1672, 1653, 1607, 1564, 1508, 1499, 1470, 1455, 1394, 1371, 1318, 1289, 1263, 1164; ¹H NMR (300 MHz, CDCl₃/10 mM) δ 0.68-0.95 (m, 12H, 4 δ CH₃ Leu), 1.19-1.90 (m, 12H, 2 β CH₃ Ala, 2 β CH₂ Leu, 2 γ CH Leu), 1.42 (s, 9H, Boc), 3.34-3.58 (m, 2H, 2 α CH Ala), 3.69-4.08 (m, 5H, 2 CH₂, *N* ^{α} -Bn, α CH Leu), 4.08-4.23 (m, 1H, α CH Leu), 4.79 (br d, 1H, *J* = 7.5 Hz, NHBoc), 5.33 (s, 1H, NH₂), 7.14-7.45 (m, 10H, Ar.), 7.58 (br s, 1H, NH hydrazidic), 7.73 (br s, 1H, NH hydrazidic), 7.91 (br s, 1H, NH₂), 8.14 (br s, 1H, NH amidic); ¹³C NMR (75 MHz, CDCl₃) δ 22.9 (γ CH Leu), 23.0 (γ CH Leu), 23.1 (2 β CH₃ Ala), 25.0 (2 δ CH₃ Leu), 25.4 (2 δ CH₃ Leu), 29.0 (3 CH₃, Boc), 39.8 (β CH₂ Leu), 40.6 (β CH₂ Leu), 51.8 (α CH Ala), 52.5 (α CH Ala), 60.9 (CH₂, *N* ^{α} -Bn), 61.0 (CH₂, *N* ^{α} -Bn), 62.1 (α CH Leu), 63.4 (α CH Leu), 81.1 (C, Boc), 128.5 (2 CH, Ar.), 129.1 (4 CH, Ar.), 129.8 (2 CH, Ar.), 129.9 (2 CH, Ar.), 136.5 (C, Ar.), 136.6 (C, Ar.),

156.6 (C=O, Boc), 172.7 (2 C(NH)=O), 173.3 (C(NH)=O), 176.2 (C=O, amide); HRMS (ESI) calculated for C₃₇H₅₇N₇O₆ [M+Na]⁺ *m/z* 718.4268, found 718.4263.

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