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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

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ABSTRACT

Different α-hydrazinoesters with high optical purity have been obtained in large scale via an S_N2 protocol. A coupling reaction with a natural amino acid 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.

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 activity[3] 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-hydrazino acids[4] 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.

More recent works have shown that mixed oligomers alternating a natural amino acid and an amino acid analogous 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 an 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 was investigated in order to assess the impact of the chirality on the conformation.

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,

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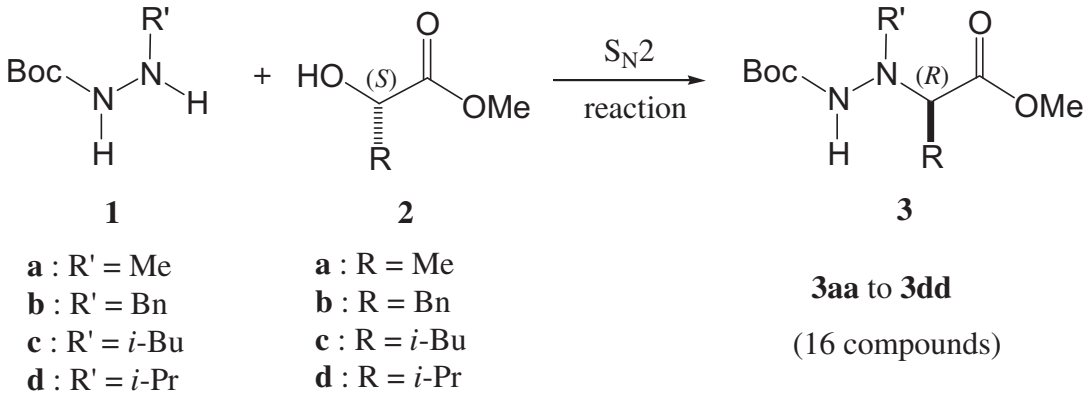
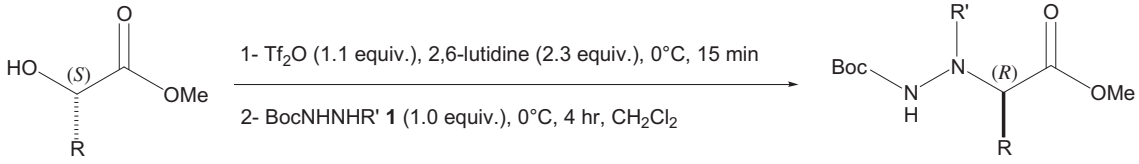


Scheme 1. Synthesis of α-hydrazinoesters **3**.

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



2 (1 equiv.) **3**

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

[a] Yields calculated after purification by flash chromatography.
[b] Yields determined by ^{1}H NMR after purification by flash chromatography.
[c] No reaction after 3 days.

indicate that the S$_N$2 reaction also gives good yields (58–87%) when R is Me, Bn, and *i*-Bu groups. α-Hydrazinoesters **3aa**–**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**–**3bd** (R=*i*-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.

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 [α/α-N^{α}-hydrazino]mer series (Scheme 2).

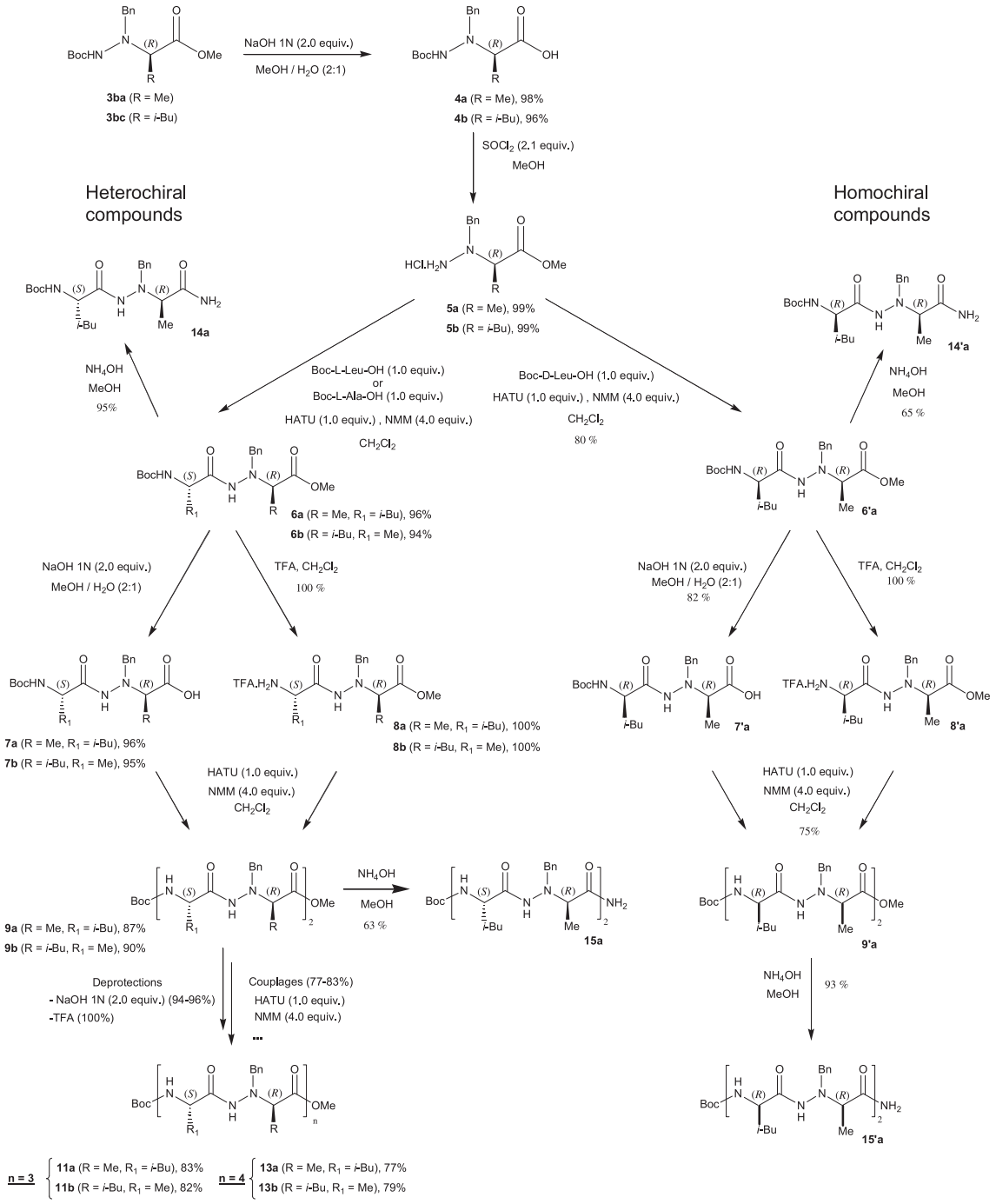
Heterochiral compounds **6a**,**b**, **9a**,**b**, **11a**,**b**, and **13a-b** were obtained in very good yields ranging from 77 to 96% by an iterative sequence of deprotection and coupling reactions as described in Scheme 2. The saponification of the ester group of **3ba** and **3bc** led to corresponding free C-terminal compounds **4a** and **4b**, respectively. The use of thionyl chloride in methanol[8] 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 ^{13}C 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, δ=171.8 ppm and δ=172.1 ppm for **9a** and **9′a**, respectively. This result confirms the absence of epimerization (ee>95%) during the coupling reaction and during the formation of corresponding α-hydrazinoesters **3aa**.

IR and NMR experiments were carried out in order to determine the ability of these oligomers to fold in solution. Then



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

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 Δδ, calculated from the ^{1}H NMR signals of the two C-terminal amidic protons, can give information on the structuration of aza-β^3 and amidoxy derivatives (Fig. 1).[9,10] We decided to use this parameter to obtain information on the conformation of **14a** and **14′a.**

First of all, the ^{1}H NMR signals of dimers **14a** and **14′a** were fully assigned using a combination of 2D-COSY and 2D-NOESY experiments (see Figs. S1–S4 in Supplementary data).

- The signals of the two amidic NH protons, respectively, at δ=7.98 ppm and δ=5.24 ppm allowed us to calculate a Δδ=2.74 ppm for hetero dimer **14a.**
- Similarly, we assigned the two amidic NH protons of homo dimer **14′a**, at δ=7.99 ppm and δ=5.40 ppm, respectively, which accounts for a Δδ=2.59 ppm. Theses values were in the

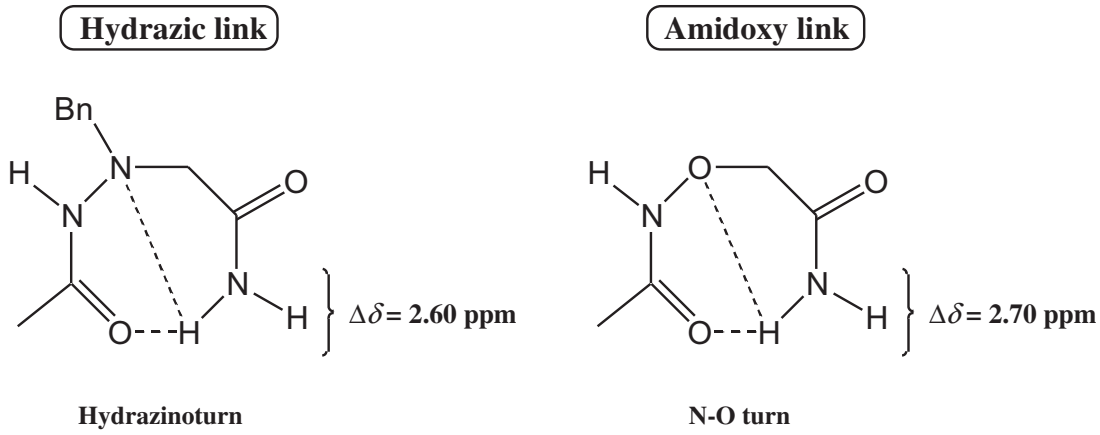
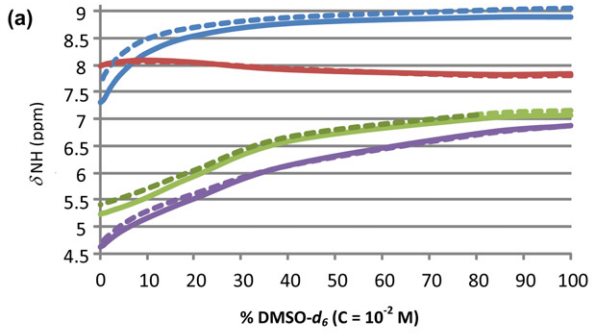


Fig. 1. Comparison of $\Delta\delta$ values between hydrazidic and amidoxy links by ^{1}H NMR (300 MHz, $CDCl_3$/10 mM).

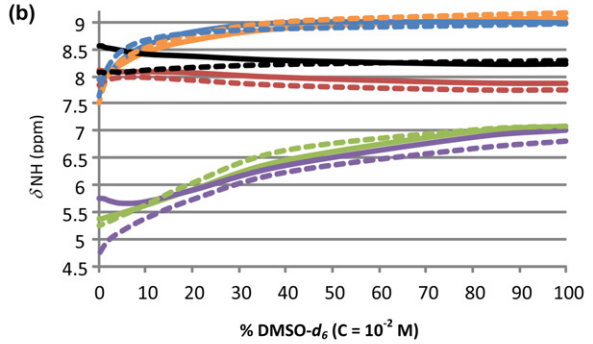
same order as those obtained by P. Le Grel in the aza-β^3 series, which is known to fold via an eight-membered H-bonded ring (hydrazinoturn).

To confirm this result, we decided to study the effect of varying ratios of solvent in the mixture of $CDCl_3$ and DMSO-d_6 on the chemical shifts of the NH protons of compounds **14a** and **14′a** (Fig. 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.

- We observed that the chemical shifts of both NH*c* and NH*d* (amidic and NHBoc) of hetero dimer **14a** shifted downfield when the volume of DMSO-d_6 increased ($\delta_{DMSO-d_6} - \delta_{CDCl_3} = +1.82$ ppm and $+2.26$ ppm, respectively) confirming that the NH protons were not involved in an intramolecular H-bond (free) (Fig. 2a).
- A downfield shift was also observed for NH*b*. However, the difference between δ_{DMSO-d_6} and δ_{CDCl_3} was lower $\delta_{DMSO-d_6} - \delta_{CDCl_3} = +1.58$ 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 et al. for the aza-β^3-oligomers (Fig. 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 $CDCl_3$ to DMSO-d_6 ($\delta_{DMSO-d_6} - \delta_{CDCl_3} =$



Hetero dimer 14a (and Homo dimer 14′a) with C-terminal amide			
NH proton	δ_{CDCl3} (ppm)	$\delta_{DMSO-d6}$ (ppm)	$\delta_{DMSO-d6} - \delta_{CDCl3}$ (ppm)
a (a′)	7.98 (7.99)	7.83 (7.82)	-0.15 (-0.17)
b (b′)	7.32 (7.62)	8.90 (9.05)	+1.58 (+1.43)
c (c′)	5.24 (5.40)	7.06 (7.15)	+1.82 (+1.75)
d (d′)	4.62 (4.71)	6.88 (6.88)	+2.26 (+2.27)



Hetero tetramer 15a (and Homo tetramer 15′a) with C-terminal amide			
NH proton	δ_{CDCl3} (ppm)	$\delta_{DMSO-d6}$ (ppm)	$\delta_{DMSO-d6} - \delta_{CDCl3}$ (ppm)
e (e′)	8.57 (8.07)	8.22 (8.29)	-0.35 (+0.22)
a (a′)	8.12 (7.84)	7.87 (7.75)	-0.25 (-0.09)
b (b′)	7.95 (7.65)	9.07 (8.98)	+1.12 (+1.33)
b (b′)	7.95 (7.51)	9.00 (9.16)	+1.05 (+1.65)
c (c′)	5.37 (5.26)	7.09 (7.08)	+1.72 (+1.82)
d (d′)	5.76 (4.71)	7.00 (6.82)	+1.24 (+2.11)

Fig. 2. Effects of varying ratios of solvent in the mixture of $CDCl_3$ and DMSO-d_6 on the chemical shifts 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 ^{1}H NMR (300 MHz, 10 mM).

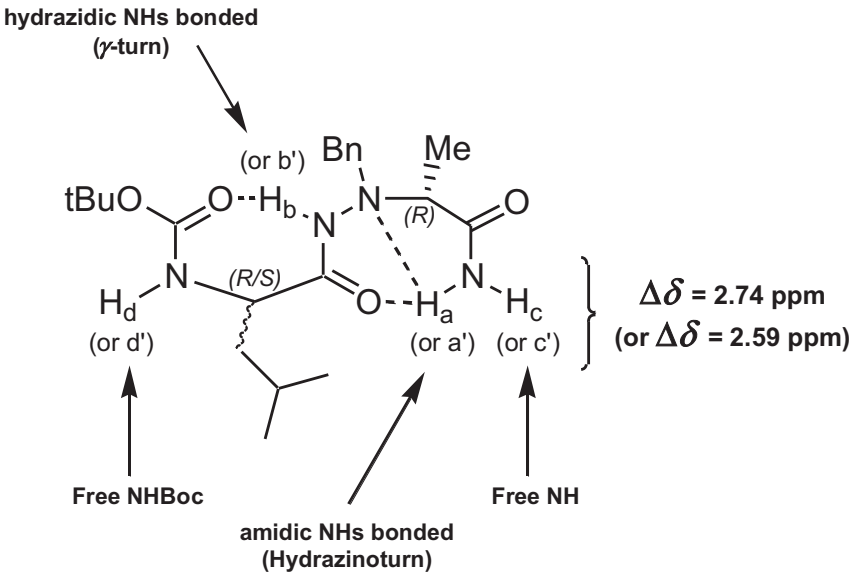


Fig. 3. Postulated structuration of **14a** (and **14′a**) in $CDCl_3$ solution.

+0.15 ppm) confirming the presence of a strong H-bond. This result is in agreement with the proposed hydrazinoturn structuration (bifurcated H-bond, Fig. 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).

*2.2.2. Conformational analysis of homo and hetero tetramers **15a** and **15′a**.* ^{1}H NMR signals of tetramers **15a** and **15′a** were fully assigned using a combination of 2D-COSY and 2D-ROESY experiments (see Figs. S5–S8 in Supplementary data). As observed in the dimer series, the variation of the chemical shifts of all NH protons (Fig. 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 δ=8.12 ppm and δ=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** (δ=7.84 ppm and δ=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 (see Fig. 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 those of hydrazidic protons NH*b* and 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*,NH*d* and NH′*c*,NH′*d* (amidic and NHBoc protons) are free and shifted downfield when the volume of DMSO-d_6 increases ($\delta_{DMSO-d_6} - \delta_{CDCl_3}$ = +1.72 ppm and + 1.24 ppm, respectively).

The presence of free and bonded NH protons in dimer and tetramers was also confirmed by IR analysis (see Figs. S9–S12 in Supplementary data).

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 (Fig. 4).

3. Conclusion

Various α-hydrazinoesters **3aa**–**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 ^{1}H 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 aluminum-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. ^{1}H 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 Brucker 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 Brucker 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

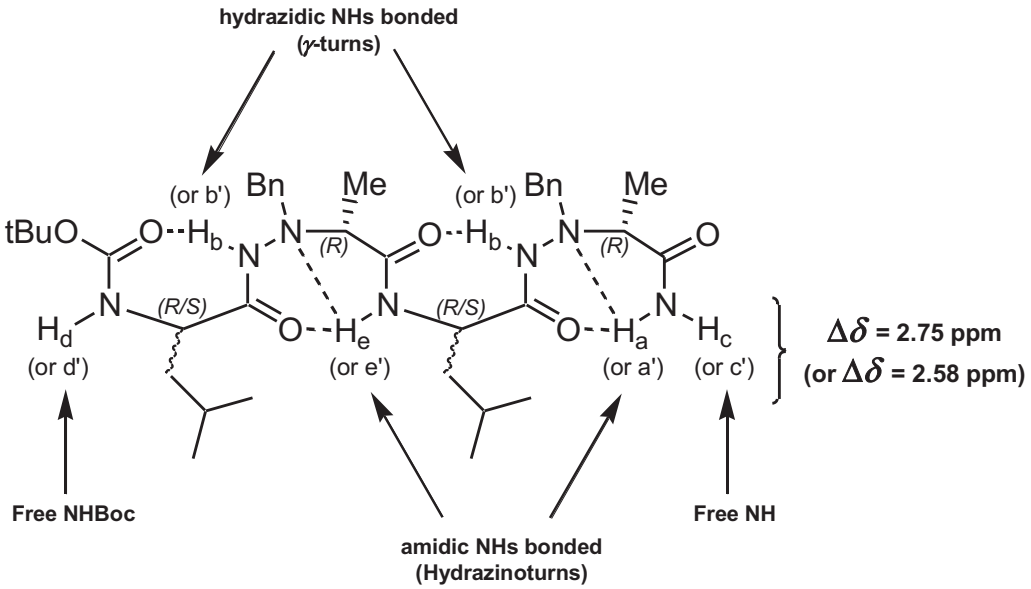


Fig. 4. Postulated structuration of **15a** (and **15′a**) in $CDCl_3$ solution.

derivatives **1a**–**d** and (*S*)-α-hydroxyesters **2a**–**d** were prepared according to Refs. 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$^{\alpha}$-Methyl-N$^{\beta}$-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, $[\alpha]_D^{25}$ −9.1 (*c* 1.00, MeOH); IR (ATR) ν_{max}/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; ^{1}H 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$^{\alpha}$-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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.6 (βCH$_3$ Ala), 28.8 (3CH$_3$, Boc), 44.0 (N$^{\alpha}$-Me), 52.0 (O–CH$_3$), 63.1 (αCH Ala), 80.2 (C, Boc), 155.9 (C=O, Boc), 174.6 (C=O, ester); HRMS (ESI) calculated for $C_{10}H_{20}N_2O_4$ $[M+Na]^+$ *m*/*z* 255.1321, found 255.1315.

4.2.2. (R)-(−)-N$^{\alpha}$-Benzyl-N$^{\beta}$-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, $[\alpha]_D^{25}$ −9.2 (*c* 1.00, MeOH); IR (ATR) ν_{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; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (s, 9H, Boc), 1.31 (d, 3H, *J*=7.2 Hz, βCH$_3$ Ala), 3.56 (q, 1H, *J*=7.2 Hz, αCH Ala), 3.66 (s, 3H, O–CH$_3$), 3.82–4.01 (m, 2H, CH$_2$, N$^{\alpha}$-Bn), 6.48 (br s, 1H, NH), 7.13–7.36 (m, 5H, Ar.); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.9 (βCH$_3$ Ala), 28.9 (3CH$_3$, Boc), 52.2 (O–CH$_3$), 60.8 (αCH Ala), 61.3 (CH$_2$, N$^{\alpha}$-Bn), 80.3 (C, Boc), 128.1 (CH, Ar.), 128.9 (2CH, Ar.), 130.0 (2CH, Ar.), 137.6 (C, Ar.), 156.1 (C=O, Boc), 175.2 (C=O, ester); HRMS (ESI) calculated for $C_{16}H_{24}N_2O_4$ $[M+Na]^+$ *m*/*z* 331.1634, found 331.1628.

4.2.3. (R)-(−)-N$^{\alpha}$-iso-Butyl-N$^{\beta}$-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, $[\alpha]_D^{25}$ −20.9 (*c* 1.00, MeOH); IR (ATR) ν_{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; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.9 (d, 3H, *J*=6.5 Hz, CH$_3$, N$^{\alpha}$-*i*-Bu), 0.97 (d, 3H, *J*=6.5 Hz, CH$_3$, N$^{\alpha}$-*i*-Bu), 1.37 (d, 3H, *J*=7.2 Hz, βCH$_3$ Ala), 1.44 (s, 9H, Boc), 1.62–1.81 (m, 1H, CH, N$^{\alpha}$-*i*-Bu), 2.20–2.45 (m, 1H, CH$_2$, N$^{\alpha}$-*i*-Bu), 2.55–2.77 (m, 1H, CH$_2$, N$^{\alpha}$-*i*-Bu), 3.48–3.65 (m, 1H, αCH Ala), 3.71 (s, 3H, O–CH$_3$), 6.33 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.7 (βCH$_3$ Ala), 21.7 (2CH$_3$, N$^{\alpha}$-*i*-Bu), 27.2 (CH, N$^{\alpha}$-*i*-Bu), 28.9 (3CH$_3$, Boc), 52.0 (O–CH$_3$), 63.4 (αCH Ala); 65.3 (CH$_2$, N$^{\alpha}$-*i*-Bu), 80.0 (C, Boc), 156.3 (C=O, Boc), 175.2 (C=O, ester); HRMS (ESI) calculated for $C_{13}H_{26}N_2O_4$ $[M+Na]^+$ *m*/*z* 297.1791, found 297.1785.

4.2.4. (R)-(−)-N$^{\alpha}$-iso-Propyl-N$^{\beta}$-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, $[\alpha]_D^{25}$ −28.2 (*c* 1.00, MeOH); IR (ATR) ν_{max}/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; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (d, 6H, *J*=6.2 Hz, CH$_3$, N$^{\alpha}$-*i*-Pr), 1.37 (d, 3H, *J*=7.1 Hz, βCH$_3$ Ala), 1.44 (s, 9H, Boc), 3.03 (sept., 1H, *J*=6.2 Hz, CH, N$^{\alpha}$-*i*-Pr), 3.70 (s, 3H, O–CH$_3$), 3.82 (q, 1H, *J*=7.1 Hz, αCH Ala), 6.47 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.1 (βCH$_3$ Ala), 20.9 (CH$_3$, N$^{\alpha}$-*i*-Pr), 21.1 (CH$_3$, N$^{\alpha}$-*i*-Pr), 28.9 (3CH$_3$, Boc), 52.1 (O–CH$_3$), 56.0 (CH, N$^{\alpha}$-*i*-Pr), 58.7 (αCH Ala), 79.9 (C, Boc), 157.0 (C=O, Boc), 175.9 (C=O, ester); HRMS (ESI) calculated for $C_{12}H_{24}N_2O_4$ $[M+Na]^+$ *m*/*z* 283.1634, found 283.1628.

4.2.5. (R)-(−)-N$^{\alpha}$-Methyl-N$^{\beta}$-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, $[\alpha]_D^{25}$ −37.0 (*c* 1.00, MeOH); IR (ATR) ν_{max}/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; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (s, 9H, Boc), 2.64 (s, 3H, N^{α}-Me), 2.96 (dd, 1H, J=13.6 and 8.3 Hz, βCH Phe), 3.14 (dd, 1H, J=13.6 and 6.5 Hz, βCH Phe), 3.59 (s, 3H, O–CH_3), 3.67 (dd, 1H, J=8.3 and 6.5 Hz, αCH Phe), 6.55 (br s, 1H, NH), 7.1–7.35 (m, 5H, Ar.); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.0 ($3CH_3$, Boc), 37.3 (βCH_2 Phe); 45.0 (N^{α}-Me), 52.0 (O–CH_3), 70.1 (αCH Phe), 80.6 (C, Boc), 127.2 (CH, Ar.), 129.0 (2CH, Ar.), 129.8 (2CH, Ar.), 138.2 (C, Ar.); 156.1 (C=O, Boc), 173.9 (C=O, ester); HRMS (ESI) calculated for $C_{16}H_{24}N_2O_4$ $[M+Na]^+$ 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, $[\alpha]_D^{25}$ −5.2 (*c* 1.00, MeOH); IR (ATR) ν_{max}/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; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 9H, Boc), 2.93–3.05 (dd, 1H, J=13.9 and 6.8 Hz, βCH_2 Phe), 3.07–3.17 (dd, 1H, J=13.9 and 7.6 Hz, βCH_2 Phe), 3.64 (s, 3H, O–CH_3), 3.62–3.83 (m, 1H, αCH Phe), 3.86–4.03 (m, 2H, CH_2, N^{α}-Bn), 6.60 (br s, 1H, NH), 7.20–7.36 (m, 10H, Ar.); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.0 ($3CH_3$, Boc), 37.1 (βCH_2 Phe), 52.1 (O–CH_3), 61.0 (CH_2, N^{α}-Bn), 67.3 (αCH 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 $C_{22}H_{28}N_2O_4$ $[M+Na]^+$ m/z 407.1947, found 407.1941.

4.2.7. (R)-(−)-N^{α}-iso-Butyl-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) ν_{max}/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; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (d, 3H, J=6.6 Hz, CH_3, N^{α}-*i*-Bu), 0.96 (d, 3H, J=6.6 Hz, CH_3, 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, CH_2, N^{α}-*i*-Bu), 2.53–2.64 (m, 1H, CH_2, N^{α}-*i*-Bu), 2.90–3.02 (m, 1H, βCH_2 Phe), 3.07–3.19 (m, 1H, βCH_2 Phe), 3.61 (s, 3H, O–CH_3), 3.65–3.81 (m, 1H, αCH Phe), 6.42 (br s, 1H, NH), 7.15–7.32 (m, 5H, Ar.); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2 ($2CH_3$, N^{α}-*i*-Bu), 27.1 (CH, N^{α}-*i*-Bu), 29.2 ($3CH_3$, Boc), 37.1 (βCH_2 Phe), 52.3 (O–CH_3), 66.3 (CH_2, N^{α}-*i*-Bu), 70.2 (αCH Phe), 80.2 (C, Boc), 127.7 (CH, Ar.), 128.8 (2CH, Ar.), 130.4 (2CH, Ar.), 138.7 (C, Ar.), 155.6 (C=O, Boc), 174.0 (C=O, ester); HRMS (ESI) calculated for $C_{19}H_{30}N_2O_4$ $[M+Na]^+$ m/z 373.2104, found 373.2098.

4.2.8. (R)-(−)-N^{α}-iso-Propyl-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) ν_{max}/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; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05–1.09 (m, 6H, CH_3, N^{α}-*i*-Pr), 1.47 (s, 9H, Boc), 2.90–3.01 (m, 2H, βCH_2 Phe), 3.08–3.20 (m, 1H, CH, N^{α}-*i*-Pr), 3.54 (s, 3H, O–CH_3), 3.75–3.86 (m, 1H, αCH Phe), 6.62 (br s, 1H, NH), 7.13–7.36 (m, 5H, Ar.); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1 ($2CH_3$, N^{α}-*i*-Pr), 28.6 ($3CH_3$, 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 (2CH, Ar.), 130.0 (2CH, Ar.), 138.4 (C, Ar.), 156.8 (C=O, Boc), 175.0 (C=O, ester); HRMS (ESI) calculated for $C_{18}H_{28}N_2O_4$ $[M+Na]^+$ 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, $[\alpha]_D^{25}$ −20.2 (*c* 1.00, MeOH); IR (ATR) ν_{max}/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; ^{1}H 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 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 ($3CH_3$, 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 $C_{13}H_{26}N_2O_4$ $[M+Na]^+$ 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, $[\alpha]_D^{25}$ −29.0 (*c* 1.00, MeOH); ^{1}H 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 ($3CH_3$, 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 (2CH, Ar.), 130.1 (2CH, Ar.), 137.6 (C, Ar.), 155.1 (C=O, Boc), 175.3 (C=O, ester). The physical data (NMR and $[\alpha]_D^{25}$) are in agreement with the values reported in Ref. 4. *Measured*: $[\alpha]_D^{25}$ −24.6 (*c* 0.99, $CHCl_3$), *literature*: $[\alpha]_D^{25}$ +25.4 (*c* 0.99, $CHCl_3$) (*S*)-isomer.

4.2.11. (R)-(−)-N^{α}-iso-Butyl-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) ν_{max}/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; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83–1.05 (m, 12H, $4CH_3$, N^{α}-*i*-Bu and δCH_3 Leu), 1.44 (s, 9H, Boc), 1.68–1.82 (m, 3H, βCH_2 Leu and CH, N^{α}-*i*-Bu), 2.05–2.17 (m, 1H, γCH Leu), 2.20–2.37 (m, 1H, CH_2, N^{α}-*i*-Bu), 2.64–2.72 (m, 1H, CH_2, N^{α}-*i*-Bu), 3.35–3.55 (m, 1H, αCH Leu), 3.70 (s, 3H, O–CH_3), 6.43 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8 ($2CH_3$, N^{α}-*i*-Bu), 23.2 (γCH Leu), 25.2 ($2\delta CH_3$ Leu), 27.1 (CH, N^{α}-*i*-Bu), 28.5 ($3CH_3$, Boc), 39.9 (βCH_2 Leu), 51.8 (O–CH_3), 66.2 (αCH Leu), 68.0 (CH_2, N^{α}-*i*-Bu), 80.5 (C, Boc), 155.8 (C=O, Boc), 175.2 (C=O, ester); HRMS (ESI) calculated for $C_{16}H_{32}N_2O_4$ $[M+Na]^+$ m/z 339.2260, found 339.2254.

4.2.12. (R)-(−)-N^{α}-iso-Propyl-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) ν_{max}/cm^{-1}: 3374, 2978, 2961, 2937, 2911, 2872, 1745, 1728, 1705, 1689, 1484, 1472, 1456, 1438, 1391, 1366, 1268, 1252, 1233, 1195, 1163, 1130; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, 6H, J=6.5 Hz, δCH_3 Leu), 1.05–1.09 (m, 6H, CH_3, N^{α}-*i*-Pr), 1.44 (s, 9H, Boc), 1.63–1.77 (m, 2H, βCH_2 Leu), 1.91–2.03 (m, 1H, γCH Leu), 2.98 (sept, 1H, J=6.2 Hz, CH, N^{α}-*i*-Pr), 3.69 (s, 3H, O–CH_3), 3.72–3.82 (m, 1H, αCH Leu), 6.61 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5 (CH_3, N^{α}-*i*-Pr), 21.1 (CH_3, N^{α}-*i*-Pr), 22.2 (γCH Leu), 23.3 (δCH_3 Leu), 24.6 (δCH_3 Leu), 28.7 ($3CH_3$, Boc), 40.1 (βCH_2 Leu), 51.7 (O–CH_3), 56.1 (CH, N^{α}-*i*-Pr), 61.3 (αCH Leu), 79.4 (C, Boc), 156.4 (C=O, Boc), 175.9 (C=O, ester); HRMS (ESI) calculated for $C_{15}H_{30}N_2O_4$ $[M+H]^+$ 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 ^{1}H NMR integration relative peaks (inseparable mixture of **2d** and **3ad**). For

3ad: yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) 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–CH_3), 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 ^{1}H NMR integration relative peaks (inseparable mixture of **2d** and **3bd**). For **3bd**: yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) 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–CH_3), 3.70–3.83 (m, 1H, αCH Val), 3.97–4.07 (m, 2H, CH_2, N^{α}-Bn), 6.03 (br s, 1H, NH), 7.20–7.42 (m, 5H, Ar.).

4.2.15. (R)-(−)-N^{α}-iso-Butyl-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, $[\alpha]_D^{25}$ −0.6 (*c* 1.00, MeOH); IR (ATR) ν_{max}/cm^{-1}: 3351, 2980, 2963, 2937, 2915, 2874, 1740, 1724, 1711, 1694, 1680, 1482, 1470, 1454, 1446, 1389, 1371, 1284, 1252, 1171, 1146; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, 3H, J=6.9 Hz, γCH_3 Val), 0.92 (d, 6H, J=6.7 Hz, CH_3, 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, CH_2, N^{α}-*i*-Bu), 3.79 (s, 3H, O–CH_3), 4.05 (d, 1H, J=3.6 Hz, αCH Val), 6.04 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.7 (2γCH_3 Val), 19.4 (βCH Val), 21.1 (2CH_3, N^{α}-*i*-Bu), 27.5 (CH, N^{α}-*i*-Bu), 29.0 (3CH_3, Boc), 52.9 (O–CH_3), 60.6 (CH_2, 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 $C_{15}H_{30}N_2O_4$ $[M+Na]^+$ *m*/*z* 325.2104, found 325.2101.

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

To a solution of ester (1.0 equiv, 22 mmol) in MeOH (80 mL) was added at 0 °C a solution of NaOH 1 N (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 (2×10 mL). The aqueous phase was cooled to 0 °C and acidified with HCl 1 N until pH=1 and extracted with EtOAc (3×20 mL). The residue was dried over $MgSO_4$, 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); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 9H, Boc), 1.39 (d, 3H, J=7.2 Hz, βCH_3 Ala), 3.66 (q, 1H, J=7.2 Hz, αCH Ala), 3.97 (s, 2H, CH_2, 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 Ref. 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) ν_{max}/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; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78 (br s, 3H, δCH_3 Leu), 0.92 (d, 3H, J=6.0 Hz, δCH_3 Leu), 1.36 (s, 9H, Boc), 1.36–1.52 (m, 1H, βCH_2 Leu), 1.68–1.77 (m, 1H, βCH_2 Leu), 2.08 (br s, 1H, γCH Leu), 3.45–3.55 (m, 1H, αCH Leu), 3.95–4.16 (m, 2H, CH_2, N^{α}-Bn), 6.54 (br s, 1H, NH), 7.26–7.41 (m, 5H, Ar.), 9.62 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1 (γCH Leu), 24.1 (δCH_3 Leu), 25.0 (δCH_3 Leu), 28.8 (3CH_3, Boc), 39.5 (βCH_2 Leu), 61.8 (CH_2, N^{α}-Bn), 63.4 (αCH Leu), 81.0 (C, Boc), 128.2 (CH, Ar.), 128.9 (2CH, 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 $C_{18}H_{28}N_2O_4$ $[M+H]^+$ *m*/*z* 337.2127, found 337.2122. ^{1}H NMR spectral data were in agreement with those reported in Ref. 4.

4.3.3. Boc–L-Leu-α-h(Bn)D-Ala–OH, ***7a****.* Yield: 96%, white amorphous solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (d, 6H, J=6.0 Hz, 2δCH_3 Leu), 1.38–1.44 (m, 6H, βCH_3 Ala, ββCH_2 Leu, γCH Leu), 1.42 (s, 9H, Boc), 3.71–3.80 (q, 1H, J=7.2 Hz, αCH Ala), 4.01–4.17 (m, 2H, CH_2, N^{α}-Bn), 4.19–4.30 (m, 1H, αCH 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; ^{1}H 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; ^{1}H 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, 2δCH_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, 2βCH_2 Leu, 2γCH 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, 2CH_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; ^{1}H NMR of the major form (300 MHz, $CDCl_3$) δ 0.72–1.15 (m, 18H, 4δCH_3 Leu, 2δCH_3 Leu,), 1.24–1.99 (m, 6H, 2βCH_2 Leu, 2γCH Leu), 1.39 (s, 9H, Boc), 3.42–3.63 (m, 2H, 2αCH Leu), 3.67–3.81 (m, 4H, 2CH_2, N^{α}-Bn), 3.88–4.23 (m, 2H, 2αCH 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; ^{1}H 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 $SOCl_2$ (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 CH_2Cl_2/TFA (9 mL/6 mL) and stirred for 3 h at room

temperature. Excess of TFA was co-evaporated with MeOH and Et_2O 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 CH_2Cl_2 (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 CH_2Cl_2 (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 CH_2Cl_2 was followed by washing with HCl 1 N (1×25 mL), saturated aqueous $NaHCO_3$ solution (1×25 mL), and saturated aqueous NaCl solution (2×25 mL). The organic layer was dried over $MgSO_4$ 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) ν_{max}/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, $CDCl_3$) δ 0.86 (d, 6H, J=6.6 Hz, 2δCH_3 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^{α}-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 ($3CH_3$, Boc), 41.9 (βCH_2 Leu), 48.2 (αCH Ala), 52.3 (O–CH_3), 60.7 (αCH Leu), 60.8 (CH_2, N^{α}-Bn), 80.6 (C, Boc), 128.3 (CH, Ar.), 129.0 (2CH, Ar.), 130.0 (2CH, Ar.), 137.0 (C, Ar.), 156.0 (C=O, Boc), 171.8 (C=O,), 175.3 (C=O, ester); HRMS (ESI) calculated for $C_{22}H_{35}N_3O_5$ $[M+H]^+$ 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) ν_{max}/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^{α}-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 ($3CH_3$, Boc), 39.9 (βCH_2 Leu), 49.9 (αCH Ala), 52.2 (O–CH_3), 61.2 (CH_2, N^{α}-Bn), 62.5 (αCH Leu), 80.4 (C, Boc), 128.3 (CH, Ar.), 128.9 (2CH, Ar.), 130.0 (2CH, Ar.), 137.0 (C, Ar.), 155.8 (C=O, Boc), 171.5 (C=O, hydrazidic), 175.5 (C=O, ester); HRMS (ESI) calculated for $C_{22}H_{35}N_3O_5$ $[M+Na]^+$ 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) ν_{max}/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, 2βCH_2 Leu, 2γCH 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, $2CH_2$, N^{α}-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 (2βCH_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 ($3CH_3$, 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^{α}-Bn), 62.3 (CH_2, N^{α}-Bn), 62.9 (αCH Leu), 80.9 (C, Boc), 128.3 (CH, Ar.), 128.5 (CH, Ar.), 128.9 (2CH, Ar.), 129.1 (2CH, Ar.), 129.8 (2CH, Ar.), 130.1 (2CH, 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 $C_{38}H_{58}N_6O_7$ $[M+H]^+$ 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) ν_{max}/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, 2βCH_2 Leu, 2γCH Leu), 3.35–3.64 (m, 2H, 2αCH Leu), 3.64–4.06 (m, 4H, $2CH_2$, N^{α}-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 ($3CH_3$, 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^{α}-Bn), 61.4 (CH_2, N^{α}-Bn), 62.5 (αCH Leu), 65.4 (αCH Leu), 80.7 (C, Boc), 127.8 (CH, Ar.), 128.4 (CH, Ar.), 128.8 (2CH, Ar.), 129.0 (2CH, Ar.), 129.3 (2CH, Ar.), 130.1 (2CH, 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, 6δCH_3 Leu), 1.25–1.38 (3, 9H, 3βCH_3 Ala), 1.40 (s, 9H, Boc), 1.37–1.74 (m, 9H, 3βCH_2 Leu, 3γCH Leu), 3.45–3.79 (m, 3H, 3αCH Leu), 3.71 (s, 3H, OCH_3), 3.82–4.47 (m, 9H, $3CH_2$, N^{α}-Bn, 3αCH Ala), 5.27 (br d, 1H, J=6.3 Hz, NHBoc), 7.18–7.48 (m, 15H, Ar.), 7.72–8.39 (m, 4H, 4NH), 8.75 (br s, 1H, NH); ^{13}C NMR of the major form (75 MHz, $CDCl_3$) δ 17.0 (3βCH_3 Ala), 23.1 (3γCH Leu), 23.4 (δCH_3 Leu), 23.7 (δCH_3 Leu), 24.9 (2δCH_3 Leu), 25.5 (δCH_3 Leu), 25.6 (δCH_3 Leu), 29.0 ($3CH_3$, 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 (2αCH 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 (2CH, Ar.), 129.0 (3CH, Ar.), 129.6 (6CH, Ar.), 129.8 (2CH, 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; ^{1}H NMR of the major form (300 MHz, $CDCl_3$) δ 0.70–1.48 (m, 27H, 6δCH_3 Leu, 3βCH_3 Ala), 1.39 (s, 9H, Boc), 1.51–2.08 (m, 9H, 3βCH_2 Leu, 3γCH Leu), 3.23–3.61 (m, 3H, 3αCH Leu), 3.62–4.42 (m, 9H, 3CH_2, N^{α}-Bn, 3αCH 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); ^{13}C NMR of the major form (75 MHz, $CDCl_3$) δ 17.1 (βCH_3 Ala), 17.8 (βCH_3 Ala), 18.0 (βCH_3 Ala), 22.1 (γCH Leu), 23.1 (γCH Leu), 23.4 (γCH Leu), 23.7 (2δCH_3 Leu), 24.9 (2δCH_3 Leu), 26.0 (δCH_3 Leu), 26.2 (δCH_3 Leu), 29.0 (3CH_3, Boc), 37.7 (βCH_2 Leu), 39.5 (βCH_2 Leu), 40.1 (βCH_2 Leu), 50.5 (αCH Ala), 50.6 (αCH Ala), 51.1 (αCH Ala), 52.4 (O–CH_3), 60.8 (CH_2, N^{α}-Bn), 61.5 (2CH_2, 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 (4CH, Ar.), 129.1 (4CH, Ar.), 129.3 (2CH, Ar.), 130.0 (CH, Ar.), 130.2 (2CH, 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 $C_{54}H_{81}N_9O_9$ $[M+Na]^+$ 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) ν_{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; ^{1}H NMR of the major form (300 MHz, $CDCl_3$) δ 0.66–1.01 (m, 24H, 8δCH_3 Leu), 1.18–1.38 (m, 12H, 4βCH_3 Ala), 1.40 (s, 9H, Boc), 1.45–1.82 (m, 12H, 4βCH_2 Leu, 4γCH Leu), 3.42–3.79 (m, 4H, 4αCH Leu), 3.71 (s, 3H, OCH_3), 3.81–4.35 (m, 12H, 4CH_2, N^{α}-Bn, 4αCH Ala), 5.29 (m, 1H, NHBoc), 7.08–7.49 (m, 20H, Ar.), 7.50–9.27 (m, 7H, 7NH); ^{13}C NMR of the major form (75 MHz, $CDCl_3$) δ 17.1 (4βCH_3 Ala), 23.1 (2γCH Leu), 23.2 (2γCH Leu), 23.7 (δCH_3 Leu), 24.9 (3δCH_3 Leu), 25.5 (2δCH_3 Leu), 29.0 (3CH_3, Boc), 40.2 (βCH_2 Leu), 40.4 (βCH_2 Leu), 41.0 (βCH_2 Leu), 41.7 (βCH_2 Leu), 51.7 (O–CH_3), 52.5 (αCH Ala), 52.8 (αCH Ala), 53.3 (αCH Ala), 53.5 (αCH Ala), 59.8 (αCH Leu), 60.6 (CH_2, N^{α}-Bn), 60.8 (CH_2, N^{α}-Bn), 61.0 (αCH Leu), 62.3 (CH_2, N^{α}-Bn), 62.4 (CH_2, 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 (3CH, Ar.), 128.9 (4CH, Ar.), 129.4 (3CH, Ar.), 129.6 (3CH, Ar.), 130.0 (2CH, Ar.), 130.1 (2CH, Ar.), 136.3 (C, Ar.), 137.3 (C, Ar.), 138.1 (C, Ar.), 138.7 (C, Ar.), 157.1 (C=O, Boc), 172.1 (4C(NH)=O), 172.5 (3C(NH)=O), 175.3 (C=O, ester); HRMS (ESI) calculated for $C_{70}H_{104}N_{12}O_{11}$ $[M+Na]^+$ 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) ν_{max}/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; ^{1}H NMR of the major form (300 MHz, $CDCl_3$) δ 0.71–1.48 (m, 36H, 8δCH_3 Leu, 4βCH_3 Ala), 1.39 (s, 9H, Boc), 1.52–2.02 (m, 12H, 4βCH_2 Leu, 4γCH Leu), 3.41–3.62 (m, 4H, 4αCH Leu), 3.66–4.44 (m, 12H, 4CH_2, N^{α}-Bn, 4αCH Ala), 3.72 (s, 3H, OCH_3), 4.81 (br d, 1H, J=6.0 Hz, NHBoc), 7.12–7.51 (m, 20H, Ar.), 8.10 (br s, 2H, 2NH), 8.42 (br s, 2H, 2NH), 8.68 (br s, 1H, NH), 8.82 (s, 1H, NH), 9.23 (s, 1H, NH); ^{13}C NMR of the major form (75 MHz, $CDCl_3$) δ 16.8 (βCH_3 Ala), 17.2 (βCH_3 Ala), 17.7 (βCH_3 Ala), 17.8 (βCH_3 Ala), 22.2 (γCH Leu), 23.2 (γCH Leu), 23.4 (2γCH Leu), 23.6 (3δCH_3 Leu), 23.7 (δCH_3 Leu), 24.9 (δCH_3 Leu), 26.0 (δCH_3 Leu), 26.3 (δCH_3 Leu), 26.5 (δCH_3 Leu), 28.9 (3CH_3, Boc), 37.6 (3βCH_2 Leu), 40.2 (βCH_2 Leu), 50.6 (2αCH Ala), 51.4 (αCH Ala), 51.6 (αCH Ala), 52.4 (O–CH_3), 54.0 (CH_2, N^{α}-Bn), 54.2 (CH_2, N^{α}-Bn), 61.2 (CH_2, N^{α}-Bn), 61.5 (CH_2, N^{α}-Bn), 62.2 (αCH Leu), 66.3 (αCH Leu), 66.6 (3αCH Leu), 81.0 (C, Boc), 127.3 (CH, Ar.), 127.5 (2CH, Ar.), 128.6 (9CH,Ar.), 129.0 (2CH, Ar.), 129.1 (2CH, Ar.), 129.4 (2CH, Ar.), 130.2 (2CH, Ar.), 136.8 (C, Ar.), 138.5 (2C, Ar.), 138.9 (C, Ar.), 156.8 (C=O, Boc), 171.4 (C(NH)=O), 171.8 (2C(NH)=O), 171.9 (2C(NH)=O), 173.6 (C(NH)=O), 173.9 (C(NH)=O), 175.9 (C=O, ester); HRMS (ESI) calculated for $C_{70}H_{104}N_{12}O_{11}$ $[M+Na]^+$ 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) ν_{max}/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; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78 (d, 3H, J=6.0 Hz, δCH_3 Leu), 0.79 (d, 3H, J=6.0 Hz, δCH_3 Leu), 1.16–1.50 (m, 5H, βCH_3 Ala, βCH_2 Leu), 1.40 (s, 9H, Boc), 1.54–1.63 (m, 1H, γCH Leu), 3.64–3.80 (m, 1H, αCH Ala), 3.74 (s, 3H, OCH_3), 3.81–3.92 (m, 1H, αCH Leu), 3.93–4.07 (m, 2H, CH_2, 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.8 (βCH_3 Ala), 22.9 (γCH Leu), 23.3 (δCH_3 Leu), 25.1 (δCH_3 Leu), 28.9 (3CH_3, Boc), 41.8 (βCH_2 Leu), 48.3 (αCH Ala), 52.3 (O–CH_3), 61.0 (CH_2, N^{α}-Bn), 61.3 (αCH Leu), 80.4 (C, Boc), 128.3 (CH, Ar.), 128.9 (2CH, Ar.), 129.9 (2CH, Ar.), 137.1 (C, Ar.), 156.2 (C=O, Boc), 172 (C=O, hydrazidic), 175.1 (C=O, ester); HRMS (ESI) calculated for $C_{22}H_{35}N_3O_5$ $[M+H]^+$ 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) ν_{max}/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; ^{1}H NMR of the major form (300 MHz, $CDCl_3$) δ 0.67–0.91 (m, 12H, 4δCH_3 Leu), 1.13–1.49 (m, 12H, 2βCH_3 Ala, 2βCH_2 Leu, 2γCH Leu), 1.40 (s, 9H, Boc), 3.43–3.62 (m, 1H, αCH Ala), 3.65–3.90 (m, 3H, αCH Ala, CH_2, N^{α}-Bn), 3.74 (s, 3H, OCH_3), 3.90–4.11 (m, 3H, CH_2, N^{α}-Bn, αCH Leu), 4.12–4.27 (m, 1H, αCH 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.2 (βCH_3 Ala), 17.6 (βCH_3 Ala), 22.4 (γCH Leu), 23.0 (γCH Leu), 23.3 (δCH_3 Leu), 23.4 (δCH_3 Leu), 24.8 (δCH_3 Leu), 25.4 (δCH_3 Leu), 29.0 (3CH_3, Boc), 40.6 (βCH_2 Leu), 40.7 (βCH_2 Leu), 52.3 (αCH Ala), 52.4 (αCH Ala), 52.8 (O–CH_3), 60.9 (CH_2, N^{α}-Bn), 61.1 (αCH Leu), 61.1 (CH_2, N^{α}-Bn), 64.7 (αCH Leu), 80.6 (C, Boc), 128.2 (CH, Ar.), 128.3 (CH, Ar.), 128.8 (2CH, Ar.), 128.9 (2CH, Ar.), 129.8 (2CH, Ar.), 130.1 (2CH, Ar.), 137.1 (C, Ar.), 137.3 (C, Ar.), 156.6 (C=O, Boc), 172.4 (3C(NH)=O), 175.4 (C=O, ester); HRMS (ESI) calculated for $C_{38}H_{58}N_6O_7$ $[M+H]^+$ m/z 711.4445, found 711.4440.

4.7. Representative procedure for the amidation reaction with NH_4OH/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 capped with a rubber septum and stirred vigorously at room temperature for 2 days. The reaction mixture was then concentrated, neutralized with HCl 1 N until pH=7, extracted with AcOEt (3×20 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–NH_2, ***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) ν_{max}/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; ^{1}H NMR (300 MHz, $CDCl_3$/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 (2δCH$_3$ Leu), 29.0 (3CH$_3$, 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 (2CH, Ar.), 130.8 (2CH, Ar.), 136.4 (C, Ar.), 156.5 (C=O, Boc), 172.6 (C=O, hydrazidic), 176.2 (C=O, amide); HRMS (ESI) calculated for $C_{21}H_{34}N_4O_4$ [M+Na]$^+$ *m*/*z* 429.2478, found 429.2472.

4.7.2. Boc–(L-Leu-α-h(Bn)D-Ala)$_2$–NH$_2$, ***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) ν_{max}/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; ^{1}H NMR (300 MHz, CDCl$_3$/10 mM) δ 0.69–0.91 (m, 12H, 4δCH$_3$ Leu), 1.29–1.80 (m, 12H, 2βCH$_3$ Ala, 2βCH$_2$ Leu, 2γCH Leu), 1.44 (s, 9H, Boc), 3.40–3.60 (m, 2H, 2αCH Ala), 3.80–4.05 (m, 5H, 2CH$_2$, 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 (2δCH$_3$ Leu), 25.3 (2δCH$_3$ Leu), 29.0 (3CH$_3$, Boc), 39.8 (2βCH$_2$ Leu), 51.5 (αCH Ala), 51.8 (αCH Ala), 61.3 (2CH$_2$, N^{α}-Bn), 62.3 (2αCH Leu), 80.9 (C, Boc), 128.5 (CH, Ar.), 128.6 (CH, Ar.), 129.1 (2CH, Ar.), 129.2 (2CH, Ar.), 129.7 (2CH, Ar.), 130.0 (2CH, Ar.), 136.8 (2C, 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 $C_{37}H_{57}N_7O_6$ [M+Na]$^+$ *m*/*z* 718.4268, found 718.4263.

4.7.3. Boc–D-Leu-α-h(Bn)D-Ala–NH$_2$, ***14′a****.* The residue was purified by trituration in Et$_2$O to afford **14′a** (0.16 g, 65%) as a white powder: mp=177 °C; IR (ATR) ν_{max}/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; ^{1}H NMR (300 MHz, CDCl$_3$/10 mM) δ 0.85 (d, 6H, *J*=6.0 Hz, 2δCH$_3$ Leu), 1.37 (d, 3H, *J*=6.9 Hz, βCH$_3$ Ala), 1.44 (s, 9H, Boc), 1.39–1.54 (m, 3H, βCH$_2$ Leu, γCH Leu), 3.53–3.69 (m, 1H, αCH Ala), 3.79–4.15 (m, 3H, CH$_2$, N^{α}-Bn, αCH Leu), 4.70 (br d, 1H, *J*=5.8 Hz, NHBoc), 5.39 (s, 1H, NH$_2$), 7.22–7.44 (m, 5H, Ar.), 7.62 (br s, 1H, NH hydrazidic), 7.99 (br s, 1H, NH$_2$); ^{13}C NMR (75 MHz, CDCl$_3$) δ 22.9 (γCH Leu), 23.2 (βCH$_3$ Ala), 25.1 (2δCH$_3$ Leu), 29.0 (3CH$_3$, Boc), 40.7 (βCH$_2$ Leu), 52.4 (αCH Ala), 61.0 (CH$_2$, N^{α}-Bn), 62.2 (αCH Leu), 81.2 (C, Boc), 128.7 (CH, Ar.), 129.2 (2CH, Ar.), 129.9 (2CH, Ar.), 136.3 (C, Ar.), 156.5 (C=O, Boc), 172.7 (C=O, hydrazidic), 176.0 (C=O, amide); HRMS (ESI) calculated for $C_{21}H_{34}N_4O_4$ [M+Na]$^+$ *m*/*z* 429.2478, found 429.2472.

4.7.4. Boc–(D-Leu-α-h(Bn)D-Ala)$_2$–NH$_2$, ***15′a****.* The residue was purified by trituration in Et$_2$O to afford **15′a** (0.39 g, 93%) as a white powder: mp=185 °C; IR (ATR) ν_{max}/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; ^{1}H NMR (300 MHz, CDCl$_3$/10 mM) δ 0.68–0.95 (m, 12H, 4δCH$_3$ Leu), 1.19–1.90 (m, 12H, 2βCH$_3$ Ala, 2βCH$_2$ Leu, 2γCH Leu), 1.42 (s, 9H, Boc), 3.34–3.58 (m, 2H, 2αCH Ala), 3.69–4.08 (m, 5H, 2CH$_2$, N^{α}-Bn, αCH Leu), 4.08–4.23 (m, 1H, αCH Leu), 4.79 (br d, 1H, *J*=7.5 Hz, NHBoc), 5.33 (s, 1H, NH$_2$), 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, NH$_2$), 8.14 (br s, 1H, NH amidic); ^{13}C NMR (75 MHz, CDCl$_3$) δ 22.9 (γCH Leu), 23.0 (γCH Leu), 23.1 (2βCH$_3$ Ala), 25.0 (2δCH$_3$ Leu), 25.4 (2δCH$_3$ Leu), 29.0 (3CH$_3$, Boc), 39.8 (βCH$_2$ Leu), 40.6 (βCH$_2$ Leu), 51.8 (αCH Ala), 52.5 (αCH Ala), 60.9 (CH$_2$, N^{α}-Bn), 61.0 (CH$_2$, N^{α}-Bn), 62.1 (αCH Leu), 63.4 (αCH Leu), 81.1 (C, Boc), 128.5 (2CH, Ar.), 129.1 (4CH, Ar.), 129.8 (2CH, Ar.), 129.9 (2CH, Ar.), 136.5 (C, Ar.), 136.6 (C, Ar.), 156.6 (C=O, Boc), 172.7 (2C(NH)=O), 173.3 (C(NH)=O), 176.2 (C=O, amide); HRMS (ESI) calculated for $C_{37}H_{57}N_7O_6$ [M+Na]$^+$ *m*/*z* 718.4268, found 718.4263.

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Supplementary data

Supplementary data related to this article can be found in the online version, at doi:10.1016/j.tet.2012.04.018.

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