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Oligomerization of *N*-aminodipeptides: to the synthesis of heterogeneous backbone with 1:1 α:α-*N*-amino aminoacid residue patterns

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ABSTRACT

A large number of *N*-aminodipeptides compounds have been obtained via a Mitsunobu protocol performed in solution or by solid-phase synthesis. The oligomerization of some of them has been studied in solution or on solid support leading to the formation of 1:1[α:α-*N*-amino]mers.

1. Introduction

Specific folding of protein backbones creates specific side-chain arrangements that lead to complex molecular activities. The relationship between function and conformation has inspired many chemists to create new oligomers, which provide a new basis for creating useful molecules.[1] In this spirit, it has been shown that many classes of oligomers of pseudopeptides as aliphatic β-, γ- or δ-peptides can fold in solution and belongs to the so-called foldamers family.[2] More recently, it was shown that heterogeneous backbones with a 1:1 alternation of α- and β-aminoacid residues can also adopt helical conformation.[3] Some years ago Marraud et al.[4] demonstrated that *N*-aminodipeptides, where the amidic proton is replaced by an amino group, can present a folding conformation in the solid state by the formation of an intramolecular hydrogen bond. More interestingly, they demonstrated that NH_2 protons were not involved in the folding. A few years ago, we developed an easy and convenient method to synthesize bis-nitrogen containing analogues such as α-hydrazinoacid and *N*-aminodipeptide derivatives.[5] They could be easily obtained via an original protocol involving a Mitsunobu reaction. All these results let us to think that the synthesis of heterogeneous oligomers alternating α- and α-*N*-amino aminoacids could be of interest. In this paper, we wish to demonstrate that the method described before for the synthesis of *N*-aminodipeptides can be extended to form a large number of compounds with different types of protecting groups. Moreover, we will also compare methods of oligomerization of *N*-aminodipeptides in solution and on solid phase.

2. Results and discussion

N-Aminodipeptides **3** are obtained via a Mitsunobu protocol, which involved α-hydroxyesters **2** and an *N*-aminophthalimide derivatives **1** as acidic partners (Scheme 1).[5a] The success of this reaction has been attributed to the structure of the acidic partner bearing a phthalimide moiety, which first confers electron withdrawing properties able to enhance the acidity of the NH proton and second because of its small steric hindrance. First, we will demonstrate that conditions of reaction performed in solution can be extended to the synthesis of a large number of dipeptides.

The Mitsunobu reaction leads in solution to the formation of compounds **3**, the results are gathered in Table 1. Whatever be the protecting groups present on the acidic partners or on the alcohol, compounds **3** are obtained with very good yields. So, this protocol allowed the preparation of *N*-aminodipeptides bearing different

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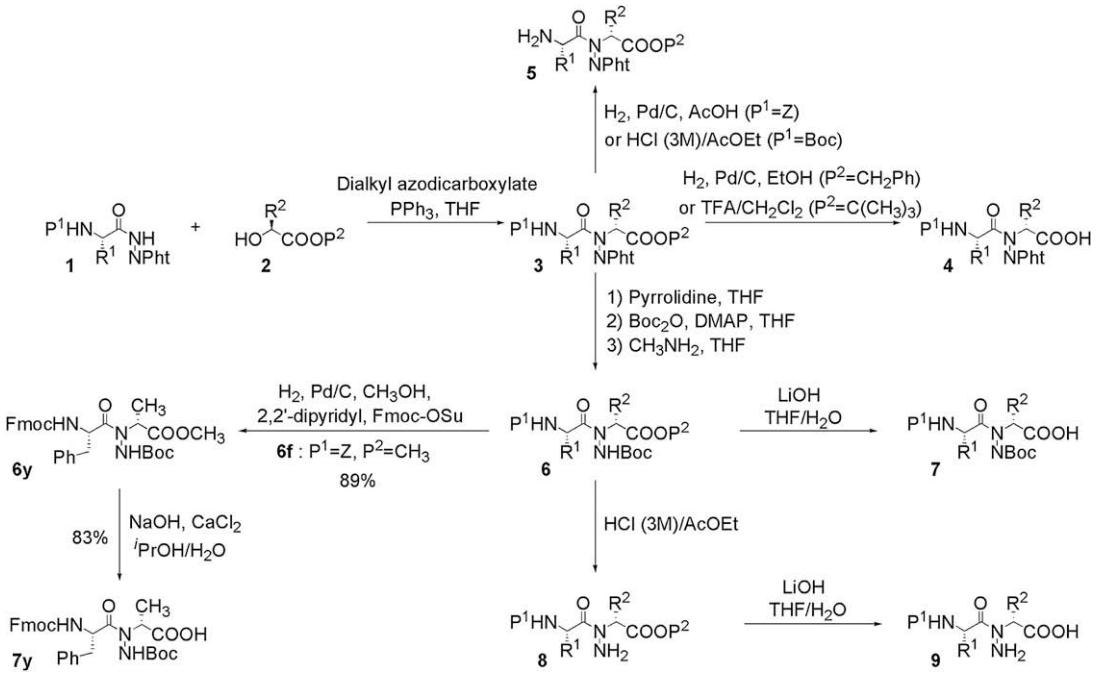


Scheme 1. Synthesis of *N*-aminodipeptides from α-Z or α-Boc-*N*-protected aminohydrazides **1** and α-hydroxyesters **2**. Pht=phthaloyl group.

protecting groups onto the C-terminal, the N-terminal or the lateral amino group.

As a result, *N*-aminodipeptides **3** can be obtained starting from α-hydroxymethyl, ethyl, *tert*-butyl or benzyl esters as alcohol partners **2**. This protocol is also compatible with a Z or a Boc protection of the N-terminal position and a phthalimide group on the lateral amino group. Moreover, the formation of **3k** and **3r** with good yields indicated that the steric hindrance due to the presence of aminoacid side chain did not affect drastically the yield of the reaction. More interestingly, compounds **3p** and **3q** issued from the reaction of an alcohol bearing a ramified lateral chain with an acidic partner can still be obtained with acceptable yield. X-ray data have been

Table 1
Synthesis in solution and on solid support of protected *N*-aminodipeptides

R^1	R^2	P^1	P^2	**3** (%)[a]	**4** (%)	**5** (%)[b]	**6** (%)[e]	**7** (%)[c]	**8** (%)[c]	**9** (%)[d]
CH_3	CH_3	Z	CH_3	**3a** (85)	—	—	**6a** (87)	**7a** (98)	**8a** (86)	—
			Wang	—	**4a** (37)[f]	—	—	—	—	—
CH_3	(L,D) CH_3	Z	CH_3	**3b** (87)	—	—	**6b** (68)	—	—	—
CH_3	CH_3	Z	CH_2CH_3	**3c** (85)	—	—	**6c** (73)	—	—	—
CH_3	CH_3	Z	$C(CH_3)_3$	**3d** (75)	—	—	**6d** (87)	—	—	—
CH_3	H	Z	CH_3	**3e** (77)	—	—	**6e** (86)	**7e** (99)	**8e** (72)	—
			Wang	—	**4e** (38)[f]	—	—	—	—	—
CH_2Ph	CH_3	Z	CH_3	**3f** (100)	—	—	**6f** (95)	—	**8f** (70)	**9f** (85)
CH_2Ph	CH_3	Z	$C(CH_3)_3$	**3g** (70)	**4g** (100)[b]	**5g** (57)	—	—	—	—
			Wang	—	**4g** (55)[f]	—	—	—	—	—
CH_2Ph	H	Boc	CH_3	**3h** (97)	—	—	—	—	—	—
CH_2Ph	CH_3	Boc	CH_3	**3i** (98)	—	—	**6i** (93)	**7i** (75)	—	—
CH_2Ph	CH_3	Boc	CH_2Ph	**3j** (79)	**4j** (100)[b]	**5j** (100)	—	—	—	—
$CH_2CH(CH_3)_2$	H	Boc	CH_3	**3k** (91)	—	—	—	—	—	—
$CH_2CH(CH_3)_2$	H	Boc	CH_2Ph	**3l** (92)	**4l** (87)[b]	—	—	—	—	—
$CH(CH_3)_2$	CH_3	Boc	CH_3	**3m** (47)	—	—	—	—	—	—
H	H	Z	CH_3	**3n** (90)	—	—	—	—	—	—
			Wang	—	**4n** (49)[f]	—	—	—	—	—
H	CH_3	Z	CH_3	**3o** (84)	—	—	—	—	—	—
			Wang	—	**4o** (47)[f]	—	—	—	—	—
H	$CH(CH_3)_2$	Z	CH_2Ph	**3p** (79)	—	—	—	—	—	—
CH_3	$CH(CH_3)_2$	Z	CH_2Ph	**3q** (77)	—	—	—	—	—	—
$CH(CH_3)_2$	H	Z	CH_3	**3r** (79)	—	—	—	—	—	—
$CH_2CH(CH_3)_2$	H	Z	Wang	—	**4s** (39)[f]	—	—	—	—	—
CH_2Ph	H	Z	Wang	—	**4t** (48)[f]	—	—	—	—	—
$CH_2CH(CH_3)_2$	CH_3	Z	Wang	—	**4u** (44)[f]	—	—	—	—	—
CH_2Ph	$CH(CH_3)_2$	Z	Wang	—	**4w** (21)[f]	—	—	—	—	—
CH_3	$CH(CH_3)_2$	Z	Wang	—	**4x** (21)[f]	—	—	—	—	—

[a] Yields calculated from **1**.
[b] Yields calculated from **3**.
[c] Yields calculated from **6**.
[d] Yields calculated from **8**.
[e] Yields calculated from **3**.
[f] Yields calculated from the substitution level of the resin (1.2 mmol/g of hydroxy groups).

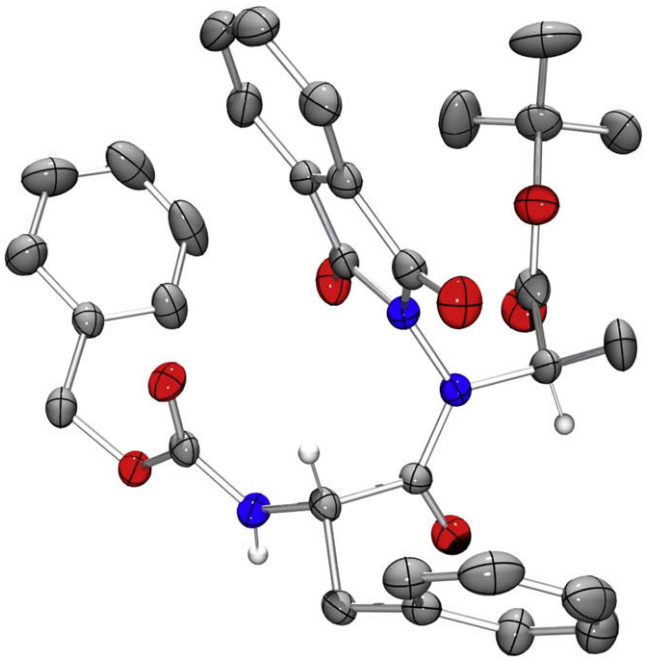


Figure 1. Ortep drawing of **3g**.

collected for *N*-aminodipeptide **3g**.[6] This crystal structure showed that phthalimide moiety is located in a perpendicular plane relative to the peptide backbone (Fig. 1), which contributes to decreased steric hindrance. In order to be more efficient and to avoid the purification steps during the synthesis, we found conditions, which allow the synthesis of these pseudodipeptides on solid support.

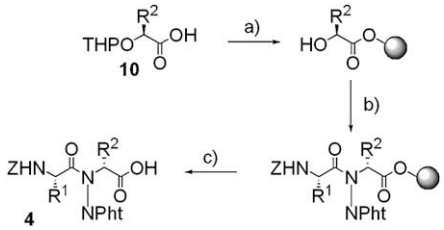
The best way consisted in anchoring the alcohol partners of the Mitsunobu reaction on the resin (Scheme 2). So, the protected α-hydroxyacids **10** were linked to a Wang resin via their carboxylic group.[5e] The use of PTSA allowed the removal of the THP protection and then to recover the supported alcohol, which can react via the Mitsunobu protocol with the free acidic partners **1** P^1=Z. This protocol has been successfully used for different values of R^1 and R^2 corresponding to different aminoacid side chains. The results are gathered in Table 1. So, starting from a Wang resin we were able to release the *N*-aminodipetides **4** P^1=Z by using classical protocol (TFA in CH_2Cl_2). The overall yields in **4** P^1=Z (calculated from the substitution level of the solid support) varied from 21 to 55% depending on the nature of the lateral chain. These results corresponding to an average yield for each step (varying from 67 to 86%) show that the Mitsunobu reaction is not affected by the steric hindrance generated by the presence of the solid support. Furthermore and as expected, whatever be the method of synthesis used (solution or solid phase), we checked that this Mitsunobu reaction occurred with a total inversion of configuration of the carbon bearing the hydroxyl group.[5a,f]

This stereospecificity enabled the formation of a series of (L,D)-diastereoisomers **3** or **4** in high optical purity starting from the corresponding supported (*S*)-α-hydroxyacids and (*S*)-aminoacid phthaloyl hydrazide derivatives.[5a] The optical purity of the formed compounds was checked by ^{1}H NMR (diastereoisomeric excess >95% for **3a**).[5a,e]

As it is shown in Scheme 1, new protecting groups also can be introduced after the Mitsunobu reaction. First of all, we develop a very elegant three-step one-pot protocol allowing the transformation of the phthalimide group present on the lateral primary amino group into a mono-*tert*-butyloxycarbonyl group leading to the formation of compound **6**.[5b] The first interest of this transprotection is to introduce a Boc protection, which is among the most used protecting groups and plays a critical role in aminoacids and peptides chemistry since it is compatible with solid-phase synthesis[7–9] and easily removed. Moreover, starting from compounds **6** we were able to obtain with good yields the corresponding free *N*-aminodipeptides **8** by using classical acidic conditions HCl (3 M)/EtOAc. At this stage, it is interesting to note that, if the presence of the phthaloyl group was essential for the success of the Mitsunobu reaction by contributing to increase the acidity of the sole proton and concomitantly to reduce steric hindrance, unfortunately, as other authors reported,[10] we were confronted to the difficulty to find general and mild conditions to remove the phthaloyl group. On the other hand, we showed that conversion of the Z protection of the N-terminal of **6f** into an Fmoc group can be done easily by using a one-pot hydrogenolysis performed in the presence of Fmoc-OSu and led to the formation of **6y** in good yield.

With the idea in mind to undergo oligomerization of *N*-aminodipeptides, we demonstrated that deprotected N- or C-terminal *N*-aminodipeptides can be easily obtained. The choice of orthogonal protections for the different functions of the molecule allowed us to find selective conditions of deprotection. So, the deprotection conditions we used depend on the nature of the protecting groups that have to be removed but also of the nature of the other protecting groups present on the molecule. As a result, hydrogenolysis conditions have been applied to remove the benzyl ester of *N*-aminodipeptides **3** bearing a Boc protection on the N-terminal and a phthalimide group on the lateral amino group. On the other hand, acidic conditions can be used to remove the *tert*-butyl ester of compound **3g** bearing a Z protecting group on the N-terminal chain and a phthalimide on the lateral amino group. These conditions allowed the formation of the corresponding compound **4g**. Finally, when a Boc is present on the molecule (compounds **6**) or when the lateral amino group is free (compounds **8**), LiOH in a mixture of THF and water or NaOH with $CaCl_2$ salt in a mixture of isopropanol and water is used in order to remove the methyl ester and to lead to the corresponding carboxylic acids **7** and **9**. It is interesting to notice that the use of NaOH with $CaCl_2$ salt[11] allowed the removal of ester group of compound **6y** without affecting the Fmoc protection. One advantage of the use of solid-phase synthesis of *N*-aminodipeptides is to obtain directly free C-terminal compounds **4** after release of the resin by TFA. Free N-terminal aminodipeptides **5** can be obtained by hydrogenolysis (P^1=Z) or HCl (3 M) in EtOAc (P^1=Boc). When P^2=CH_2Ph, the latter conditions lead to the formation of a stable chlorhydrate salt. On the contrary, the use of TFA leads to the formation of *N*-aminodiketopiperazine **11** (Fig. 2) due to the cyclization of the instable corresponding trifluoroacetate salt.

The oligomerization of *N*-aminodipeptides was performed in solution (Scheme 3) and on solid support (Scheme 4).



Scheme 2. (a) (1) Wang resin, DIC, DMAP cat., THF; (2) PTSA, CH_2Cl_2/MeOH (97/3); (b) **1**, DIAD, PPh_3, THF; (c) TFA/CH_2Cl_2 (1/1).

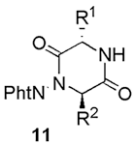
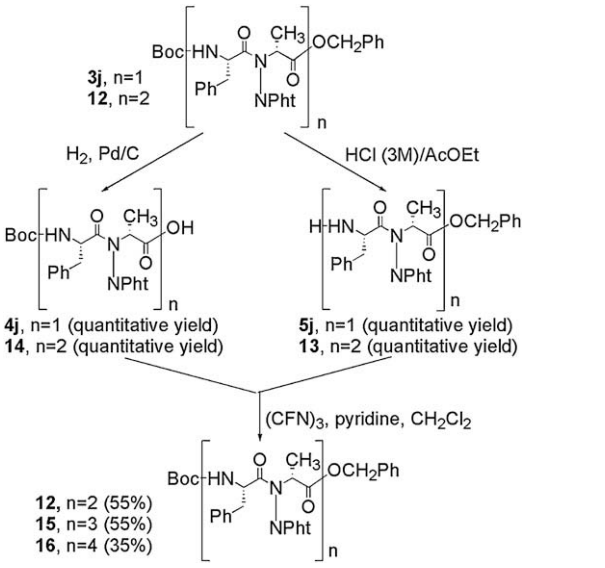


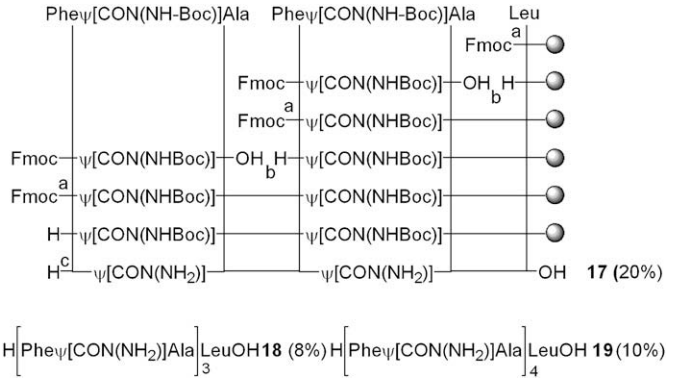
Figure 2. *N*-Aminodiketopiperazine **11**.



Scheme 3.

Oligomers were synthesized in solution using a convergent Boc strategy. Different standard peptides coupling methods have been tested in solution in order to find the best conditions, which allowed the coupling reaction between **4** P^1=Boc and **5** P^2=CH_2Ph in the series (R^1=CH_2Ph and R^2=CH_3).

Surprisingly, coupling reactions were not easy to perform. Whatever be the conditions used like HOBt, DCC or HOBt, DIC in THF or CH_2Cl_2, the reaction led to the formation of diketopiperazine **11** as major product. The best results were obtained when using the acid fluoride method, which led to the formation of the tetramer **12** with a yield of 55%. In order to avoid the formation of diketopiperazine, we decided to synthesize the hexamer **15** by condensing the free N-terminal tetramer **13** on the free C-terminal dimer **4j**, hexamer is obtained in 55% yield. Finally, the corresponding octamer **16** is the result of the coupling reaction between the free N-terminal tetramer **13** on the free C-terminal tetramer **14**. Concerning the solid-phase synthesis, we used an Fmoc/Boc strategy on a Wang resin. As described above (Scheme 1), it was possible to undergo the saponification of the ester of compound **6y** without deprotection of the Fmoc group. This behaviour allowed the formation of **7y** that can be involved in an oligomerization process (Scheme 4). In order to be able to count the number of units fixed on the resin, we decided to perform the reaction on an Fmoc-Leu-Wang resin, the presence of the leucine served as a standard in NMR. Oligomers were obtained by an iterative sequence consisting in using TBTU/HOBt as coupling reagent and piperidine in DMF for



Scheme 4. Reagents: (a) piperidine/DMF; (b) TBTU, HOBt, DIEA/DMF; (c) TFA.

the deprotection of the Fmoc group. The release from the resin by the action of TFA led to the formation of pentamer **17**, heptamer **18** and nonamer **19** possessing a free lateral amine, respectively, with the overall yield of 20%, 8% and 10%. The conformational analysis of these oligomers is under active investigation in order to determine their ability to fold in solution.

3. Experimental section

3.1. General

Tetrahydrofuran was dried by distillation over sodium benzophenone ketyl. Unless otherwise stated, reagents were purchased from chemical companies and used without prior purification. Reactions were monitored by thin-layer chromatography (TLC) using aluminium-baked 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). Reagent grade solvents were used as-received. Diisopropyl azodicarboxylate (DIAD), *N*,*N*′-diisopropylcarbodiimide (DIC) and *N*,*N*′-dicyclohexylcarbodiimide (DCC) were purchased from Aldrich. 9-Fluorenylmethyl succinimidyl carbonate (Fmoc-OSu), 1-hydroxybenzotriazole (HOBt), *O*-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) and diisopropylethylamine (DIEA) were purchased from Senn Chemicals or Novabiochem. Aminohydrazides **1** were obtained from phthalic anhydride and hydrazine derivatives.[12] Diethyl azodicarboxylate (DEAD) and di-*tert*-butyl azodicarboxylate (DBAD) were purchased from Alfa Aesar. Solid-phase *N*-aminodipeptides' **4** syntheses were performed on a Heidolph SYNTHESIS 1 apparatus. They were purified by reverse-phase HPLC using a preparative HPLC system (Waters Corp., Milford, MA, USA) on a Waters DELTA PAK column (15 mm, 300 Å, 7.8×300 mm). *N*-Aminodipeptides were eluted with a linear gradient of solution A (water containing 0.1% of TFA) and solution B (20% of water in CH_3CN with 0.1% of TFA) from 95 to 0% of solution A over 25 min at a flow rate of 2 mL/min with UV detection at 254 nm. Solid-phase oligomer syntheses were performed on a multichannel peptide synthesizer PSP 4000[13] according to a classical Fmoc/^{t}Bu methodology. They were purified by reverse-phase HPLC on an Interchim column (250×21,2 mm). Oligomers were eluted with a linear gradient of solution A (water containing 0.1% of TFA) and solution B (20% of water in acetonitrile with 0.1% of TFA) from 100 to 0% of solution A over 35 min at a flow rate of 15 mL/min with UV detection at 254 nm. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 spectrometer. Multiplicities are reported as follow: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad, arom=aromatic. The observation of two sets of resonances for some groups in ^{1}H and ^{13}C NMR spectra suggested that 1:1[α/α-*N*-amino]mers were present as two isomers. We and others have observed this phenomenon before in the preparation of hydrazide derivatives[12] or amide containing compounds.[14] IR spectra were recorded on a Bruker Tensor 27. Melting points were obtained on a 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.

3.2. Typical experimental procedure for the preparation of 3

Under nitrogen atmosphere and to a stirred solution of aminohydrazide **1** (3 mmol), PPh_3 (4.5 mmol) and α-hydroxyester **2**

(4.5 mmol) in anhydrous THF (50 mL), dialkyl azodicarboxylate (4.5 mmol) was added portionwise at 0–5 °C. The resulting solution was stirred at room temperature until completion (monitored by TLC) and concentrated in vacuo. The residue was purified by column chromatography using a mixture of EtOAc/petroleum ether as eluent for column chromatography.

3.2.1. Z-Alaψ[CON(NPht)]Ala-OMe ***3a***

Dialkyl azodicarboxylate: DBAD; eluent for column chromatography: EtOAc/petroleum ether (15/85 then 40/60); yield 85%, white solid, mp=109 °C; IR (KBr) ν_{max}/cm^{-1} 3271 (NH), 1797, 1747, 1693, 1674 (C=O); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.95–7.80 (m, 4H, Hpht), 7.37–7.32 (m, 5H, *H* arom), 5.40 (d, 1H, *J*=8.5 Hz, N*H*), 5.15–5.11 (m, 1H, C*H*CH_3), 5.01–4.88 (m, 2H, COOCH_2Ph), 4.41–4.29 (m, 1H, C*H*CH_3), 3.76 (s, 3H, OCH_3), 1.35 (d, 3H, *J*=8.3 Hz, CHCH_3), 1.28 (d, 3H, *J*=8.5 Hz, CHCH_3); ^{13}C NMR ($CDCl_3$) δ (ppm) 174.5 (*C*ON(NPht)), 170.9 (*C*OOMe), 165.8, 163.1 (*C*=O Pht), 155.6 (NHCOOCH_2Ph), 136.9 (Ar*C*), 136.0, 135.5 (Pht *C*H), 129.8 (Pht*C*), 129.2, 128.7 (Ar*C*H), 125.3, 124.8 (Pht *C*H), 67.9, 67.5 (COOCH_2Ph), 56.1, 55.4 (*C*HCH_3), 53.6, 53.3 (OCH_3), 48.3, 47.8 (*C*HCH_3), 20.0, 19.7 (CH*C*H_3), 14.5, 14.3 (CH*C*H_3); HRMS (ESI) calculated for $C_{23}H_{23}N_3NaO_7$ $[M+Na]^+$ *m*/*z* 476.1428, found 476.1374.

3.2.2. Z-Alaψ[CON(NPht)](L,D)Ala-OMe ***3b***

Dialkyl azodicarboxylate: DBAD; eluent for column chromatography: EtOAc/petroleum ether (15/85 then 40/60); yield 87%, white solid, mp=109 °C; IR (KBr) ν_{max}/cm^{-1} 3271 (NH), 1797, 1747, 1693, 1674 (C=O); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.93–7.80 (m, 4H, Hpht), 7.36–7.26 (m, 5H, *H* arom), 5.49 (d, 0.5H, *J*=8.0 Hz, N*H*), 5.38 (d, 0.5H, *J*=8.0 Hz, N*H*), 5.27–4.94 (m, 3H, COOCH_2Ph and C*H*CH_3), 4.39 (qd, 1H, *J*=7.3, 6.8 Hz, C*H*CH_3), 3.83, 3.81 (2s, 0.6H, OCH_3), 3.77, 3.75 (2s, 2.4H, OCH_3), 1.52–1.25 (m, 6H, 2CHCH_3); ^{13}C NMR ($CDCl_3$) δ (ppm) 174.5 (*C*ON(NPht)), 170.9 (*C*OOMe), 165.8, 163.1 (*C*=O Pht), 155.6 (NHCOOCH_2Ph), 136.9 (Ar*C*), 136.0, 135.5 (Pht*C*H), 129.8 (Pht*C*), 129.2, 128.7 (Ar*C*H), 125.3, 124.8 (Pht*C*H), 67.9, 67.5 (COOCH_2Ph), 56.1, 55.4 (*C*HCH_3), 53.6, 53.3 (OCH_3), 48.3, 47.8 (*C*HCH_3), 20.0, 19.7 (CH*C*H_3), 14.5, 14.3 (CH*C*H_3); HRMS (ESI) calculated for $C_{23}H_{23}N_3NaO_7$ $[M+Na]^+$ *m*/*z* 476.1428, found 476.1401.

3.2.3. Z-Alaψ[CON(NPht)]Ala-OEt ***3c***

Dialkyl azodicarboxylate: DBAD; eluent for column chromatography: EtOAc/petroleum ether (15/85 then 30/70); yield 85%, white solid, mp=158 °C; IR (KBr) ν_{max}/cm^{-1} 3284 (NH), 1796, 1746, 1674 (C=O); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.87–7.75 (m, 4H, Hpht), 7.30–7.18 (m, 5H, *H* arom), 5.35 (d, 1H, *J*=8.0 Hz, NH), 5.20–5.05 (m, 1H, C*H*CH_3), 5.05–4.88 (m, 2H, COOCH_2Ph), 4.32 (qd, 1H, *J*=7.3, 6.8 Hz, C*H*CH_3), 4.16–4.09 (m, 2H, OC$H_2$$CH_3$), 1.62–1.13 (m, 9H, OCH$_2$C*H*$_3$ and 2CHCH_3); ^{13}C NMR ($CDCl_3$) δ (ppm) 174.1 (*C*ON(NPht)), 170.2 (*C*OOEt), 165.9, 165.0 (*C*=O Pht), 155.8 (NHCOOCH_2Ph), 136.9 (Ar*C*), 135.9, 135.8, 135.5, 134.7 (Pht*C*H), 130.1, 129.9 (Pht*C*), 129.1, 128.9, 128.7, 128.6 (Ar*C*H), 125.1, 125.0, 124.8, 124.6 (Pht*C*H), 67.9, 67.5 (COOCH_2Ph), 62.9, 62.4 (OC$H_2$$CH_3$), 57.5, 56.7 (*C*H$CH_3$), 47.6 (*C*H$CH_3$), 19.7, 19.4 (CH*C*$H_3$), 15.3 (OCH$_2$C*H*$_3$), 15.0, 14.6 (CH*C*$H_3$); HRMS (ESI) calculated for $C_{24}H_{25}N_3NaO_7$ $[M+Na]^+$ *m*/*z* 490.1585, found 490.1557.

3.2.4. Z-Alaψ[CON(NPht)]Ala-O^{t}Bu ***3d***

Dialkyl azodicarboxylate: DBAD; eluent for column chromatography: EtOAc/petroleum ether (15/85 then 40/60); yield 75%, white solid, mp=150 °C; IR (KBr) ν_{max}/cm^{-1} 3281 (NH), 1795, 1751, 1695, 1675 (C=O); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.95–7.78 (m, 4H, Hpht), 7.73–7.28 (m, 5H, *H* arom), 5.73 (d, 0.2H, *J*=8.0 Hz, NH), 5.50 (d, 0.8H, *J*=8.0 Hz, NH), 5.15–4.92 (m, 3H, COOCH_2Ph and C*H*CH_3), 4.60 (qd, 0.2H, *J*=7.3, 6.8 Hz, C*H*CH_3), 4.38 (qd, 0.8H, *J*=7.3, 6.8 Hz, C*H*CH_3), 1.52–1.37 (m, 15H, OC(CH_3)$_3$ and 2CHCH_3); ^{13}C NMR ($CDCl_3$) δ (ppm) 174.4 (*C*ON(NPht)), 169.3 (*C*OO^{t}Bu), 165.7, 165.3 (*C*=O Pht), 155.8 (NHCOOCH_2Ph), 136.9 (Ar*C*), 135.9, 135.4 (Pht*C*H), 130.7, 129.8 (Pht*C*), 129.1, 128.6 (Ar*C*H), 125.2, 124.8 (Pht*C*H), 82.7 (OC(CH$_3$)$_3$), 67.5 (COOCH_2Ph), 58.0, 57.2 (C*H*CH_3), 48.3, 47.8 (*C*HCH_3), 28.5, 28.4 (OC(*C*H$_3$)$_3$), 20.7, 20.1 (CH*C*H_3), 14.3 (CH*C*H_3); HRMS (ESI) calculated for $C_{26}H_{29}N_3NaO_7$ $[M+Na]^+$ *m*/*z* 518.1898, found 518.1875.

3.2.5. Z-Alaψ[CON(NPht)]Gly-OMe ***3e***

Dialkyl azodicarboxylate: DBAD; eluent for column chromatography: EtOAc/petroleum ether (15/85 then 40/60); yield 77%, oil; IR (KBr) ν_{max}/cm^{-1} 3281 (NH), 1795, 1751, 1695, 1675 (C=O); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.93–7.62 (m, 4H, Hpht), 7.37–7.17 (m, 5H, *H* arom), 5.83–5.71 (m, 1H, NH), 5.24–5.10 (m, 3H, COOCH_2Ph and C*H*CH_3), 3.81 (d, 2H, *J*=14.4 Hz, CH_2COOMe), 3.72 (s, 1H, OCH_3), 3.69 (s, 2H, OCH_3), 1.42 (d, 1H, *J*=6.7 Hz, CHCH_3), 1.31 (d, 2H, *J*=6.7 Hz, CHCH_3); ^{13}C NMR ($CDCl_3$) δ (ppm) 170.4 (*C*ON(NPht)), 169.7 (*C*OOMe), 165.3, 164.6 (*C*=O Pht), 156.3 (NHCOOCH_2Ph), 136.6, 135.9 (Pht*C*H), 135.3 (Ar*C*), 129.5, 129.4, 128.5 (Ar*C*H), 124.9, 124.6 (Pht*C*H), 67.4 (COOCH_2Ph), 56.5, 55.1 (*C*HCH_3), 53.5, 53.1 (OCH_3), 43.1, 42.7 (*C*H$_2$COOMe), 14.6, 14.3 (CH*C*H_3); HRMS (ESI) calculated for $C_{22}H_{21}N_3NaO_7$ $[M+Na]^+$ *m*/*z* 462.1272, found 462.1246.

3.2.6. Z-Pheψ[CON(NPht)]Ala-OMe ***3f***

Dialkyl azodicarboxylate: DEAD; eluent for column chromatography: EtOAc/petroleum ether (20/80); yield 100%, oil; IR (ATR) ν_{max}/cm^{-1} 3320 (NH), 1733, 1701, 1681 (C=O); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.86–7.75 (m, 4H, Hpht), 7.31–7.08 (m, 10H, *H* arom), 5.55 (d, 0.35H, *J*=9.4 Hz, NH), 5.42 (d, 0.65H, *J*=9.4 Hz, NH), 5.41–4.62 (m, 4H, COOCH_2Ph, C*H*CH$_2$Ph and C*H*CH_3), 4.12 (s, 1H, OCH_3), 4.10 (s, 2H, OCH_3), 3.41–2.83 (m, 2H, CHCH_2Ph), 1.49 (d, 1H, *J*=9.3 Hz, CHCH_3), 1.42 (d, 2H, *J*=9.3 Hz, CHCH_3); ^{13}C NMR ($CDCl_3$) δ (ppm) 172.7 (*C*ON(NPht)), 170.5, 170.4 (*C*OOMe), 166.0, 164.9 (*C*=O Pht), 156.4, 155.9 (NHCOOCH_2Ph), 136.8, 136.4 (Ar*C*), 135.8, 135.6, 135.4 (Pht*C*H), 130.6, 130.2, 130.0, 129.9, 128.9, 128.7, 128.5, 128.3, 127.5, 127.3 (Ar*C*H), 124.8, 124.6 (Pht*C*H), 67.7, 67.3 (COOCH_2Ph), 57.3, 56.1 (*C*HCH$_2$Ph), 53.4, 53.1 (*C*HCH_3), 52.6 (OCH_3), 38.7 (CHCH_2Ph), 15.0, 14.9, 14.8 (CH*C*H_3); HRMS (ESI) calculated for $C_{29}H_{27}N_3NaO_7$ $[M+Na]^+$ *m*/*z* 552.1741, found 552.1758.

3.2.7. Z-Pheψ[CON(NPht)]Ala-O^{t}Bu ***3g***

Dialkyl azodicarboxylate: DEAD; eluent for column chromatography: EtOAc/petroleum ether (20/80); yield 71%, white solid, mp<50 °C; IR (KBr) ν_{max}/cm^{-1} 3295 (NH), 1798, 1753, 1679 (C=O); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.95–7.80 (m, 4H, Hpht), 7.31–7.09 (m, 10H, *H* arom), 5.24–4.80 (m, 5H, COOCH_2Ph, C*H*CH_3, C*H*CH$_2$Ph and N*H*), 3.13–2.82 (m, 2H, CHCH_2Ph), 1.50–1.44 (m, 12H, CHCH_3 and NHCOOC(CH_3)$_3$); ^{13}C NMR ($CDCl_3$) δ (ppm) 172.6 (*C*ON(NPht)), 170.5 (*C*OO^{t}Bu), 166.1, 165.1, 165.0 (*C*=O Pht), 156.0 (NHCOOCH_2Ph), 137.0, 136.5, 136.2 (Ar*C*), 135.8, 135.6, 135.4, 134.7, 134.6, 135.4 (Pht*C*H), 130.4, 130.1, 129.9, 128.7, 128.6, 128.4, 127.6, 127.4 (Ar*C*H), 124.9, 124.7 (Pht*C*H), 82.7 (COOC(CH$_3$)$_3$), 67.6 (NHCOOCH_2Ph), 58.7 (*C*HCH_3), 58.1, 52.6 (*C*HCH$_2$Ph), 38.9 (CHCH_2Ph), 28.5 (COOC(*C*H$_3$)$_3$), 14.8 (CH*C*H_3); HRMS (ESI) calculated for $C_{32}H_{33}N_3NaO_7$ $[M+Na]^+$ *m*/*z* 594.2211, found 594.2195.

3.2.8. Boc-Pheψ[CON(NPht)]Gly-OMe ***3h***

Dialkyl azodicarboxylate: DBAD; eluent for column chromatography: EtOAc/petroleum ether (30/70); yield 97%, oil; IR (ATR) ν_{max}/cm^{-1} 3341 (NH), 1798, 1741, 1698 (C=O); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.85–7.80 (m, 4H, Hpht), 7.24–7.05 (m, 5H, *H* arom), 5.05 (d, 0.25H, *J*=9.5 Hz, NH), 4.88 (d, 0.75H, *J*=9.5 Hz, NH), 4.62–4.57 (m, 2H, C*H*CH$_2$Ph and CH_2COOMe), 4.19 (d, 1H, *J*=16.9 Hz, CH_2COOMe), 3.67 (s, 0.75H, OCH_3), 3.63 (s, 2.25H, OCH_3), 3.10–2.73 (m, 2H, CHCH_2Ph), 1.35 (s, 2.25H, NHCOOC(CH_3)$_3$), 1.06 (s, 6.75H,

NHCOOC(CH_3)$_3$); ^{13}C NMR ($CDCl_3$) δ (ppm) 173.4, 171.1 (*C*ON(NPht)), 168.1 (*C*OOMe), 164.9, 164.5 (*C*=O Pht), 155.2 (NHCOO^{t}Bu), 136.7 (Ar*C*), 135.6, 135.5, 135.2 (Pht*C*H), 130.2 (Ar*C*), 129.3, 129.2, 128.9, 127.7, 127.6, 127.2 (Ar*C*H), 125.0, 124.8, 124.7, 124.6 (Pht*C*H), 80.4 (NHCOO*C*(CH_3)$_3$), 53.3, 53.0 (O*C*H_3), 51.6 (*C*HCH$_2$Ph), 49.9 (*C*H$_2$COOMe), 39.8, 38.9 (CH*C*H$_2$Ph), 28.9, 28.7 (NHCOOC(CH_3)$_3$); HRMS (ESI) calculated for $C_{25}H_{27}N_3NaO_7$ [M+Na]$^+$ *m*/*z* 504.1741, found 504.1739.

3.2.9. Boc-Pheψ[CON(NPht)]Ala-OMe **3i**

Dialkyl azodicarboxylate: DBAD; eluent for column chromatography: EtOAc/petroleum ether (25/75); yield 98%, oil; IR (ATR) ν_{max}/cm^{-1} 3351 (NH), 1799, 1744, 1693 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.93–7.79 (m, 4H, Hpht), 7.29–7.14 (m, 5H, *H* arom), 5.49–5.11 (m, 1H, C*H*CH$_3$), 5.00 (d, 0.3H, *J*=7.8 Hz, NH), 4.89 (d, 0.7H, *J*=7.8 Hz, NH), 4.86–4.72 (m, 1H, C*H*CH$_2$Ph), 3.79 (s, 0.9H, OCH_3), 3.75 (s, 2.1H, OCH_3), 3.21–2.81 (m, 2H, CHCH_2Ph), 1.49–1.22 (m, 12H, NHCOOC(CH_3)$_3$ and CHCH_3); ^{13}C NMR ($CDCl_3$) δ (ppm) 172.9 (*C*ON(NPht)), 170.8, 170.4 (*C*OOMe), 166.1, 165.1 (*C*=O Pht), 155.8, 155.2 (NHCOO^{t}Bu), 136.9 (Ar*C*), 135.6, 135.5 (Pht*C*H), 130.7 (Ar*C*), 130.3 (Ar*C*H), 130.2 (Ar*C*), 130.1, 129.1, 128.9, 127.5, 127.3 (Ar*C*H), 125.0, 124.9, 124.8 (Pht*C*H), 81.1, 80.4 (NHCOO*C*(CH_3)$_3$), 57.2, 56.0 (*C*HCH$_3$), 53.4, 53.2 (*C*HCH$_2$Ph), 52.1 (O*C*H_3), 39.1, 38.9 (CH*C*H$_2$Ph), 28.9, 28.7 (NHCOOC(*C*H_3)$_3$), 14.9 (CH*C*H$_3$); HRMS (ESI) calculated for $C_{26}H_{29}N_3NaO_7$ [M+Na]$^+$ *m*/*z* 518.1898, found 518.1883.

3.2.10. Boc-Pheψ[CON(NPht)]Ala-OCH$_2$Ph **3j**

Dialkyl azodicarboxylate: DEAD; eluent for column chromatography: EtOAc/petroleum ether (20/80); yield 80%, gum; IR (KBr) ν_{max}/cm^{-1} 3430 (NH), 1799, 1750, 1702 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.98–7.62 (m, 4H, Hpht), 7.30–6.90 (m, 10H, *H* arom), 5.40 (q, 0.3H, *J*=6.9 Hz, C*H*CH$_3$), 5.12–5.00 (m, 3H, OCH_2Ph, C*H*CH$_2$Ph and C*H*CH$_3$), 4.85 (d, 0.3H, *J*=9.4 Hz, N*H*), 4.76 (d, 0.7H, *J*=9.8 Hz, N*H*), 4.53 (q, 0.7H, *J*=5.9 Hz, C*H*CH$_2$Ph), 3.06–2.77 (m, 2H, CHCH_2Ph), 1.26–1.03 (m, 12H, NHCOOC(CH_3)$_3$ and CHCH_3); ^{13}C NMR ($CDCl_3$) δ (ppm) 172.7 (*C*ON(NPht)), 170.0 (*C*OOCH$_2$Ph), 166.0, 164.8 (*C*=O Pht), 155.0 (NHCOO^{t}Bu), 136.9 (Ar*C*), 136.1, 135.3 (Pht*C*H), 130.2, 129.8, 129.7, 129.5, 129.0, 128.7, 127.0 (Ar*C*H), 124.8, 124.6, 124.5 (Pht*C*H), 80.0 (NHCOO*C*(CH_3)$_3$), 68.6, 67.8 (O*C*H$_2$Ph), 57.0, 56.0 (*C*HCH$_3$), 51.8 (*C*HCH$_2$Ph), 38.8, 38.2 (CH*C*H$_2$Ph), 28.5 (NHCOOC(*C*H_3)$_3$), 14.6, 14.4 (CH*C*H$_3$); HRMS (ESI) calculated for $C_{32}H_{33}N_3NaO_7$ [M+Na]$^+$ *m*/*z* 594.2211, found 594.2219.

3.2.11. Boc-Leuψ[CON(NPht)]Gly-OMe **3k**

Dialkyl azodicarboxylate: DIAD; eluent for column chromatography: EtOAc/petroleum ether (30/70); yield 91%, oil; IR (ATR) ν_{max}/cm^{-1} 3251 (NH), 1802, 1742, 1695 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.98–7.85 (m, 4H, Hpht), 5.08 (d, 0.25H, *J*=9.9 Hz, NH), 4.92 (d, 0.75H, *J*=9.9 Hz, NH), 4.73 (d, 1H, *J*=17.0 Hz, CH_2COOMe), 4.60–4.47 (m, 1H, C*H*CH$_2$CH(CH$_3$)$_2$), 4.40 (d, 1H, *J*=17.0 Hz, CH_2COOMe), 3.74 (s, 0.75H, OCH_3), 3.67 (s, 2.25H, OCH_3), 1.64–1.23 (m, 12H, NHCOOC(CH_3)$_3$, and CHCH_2C*H*(CH$_3$)$_2$), 1.02–0.95 (m, 6H, CHCH$_2$CH(CH_3)$_2$); ^{13}C NMR ($CDCl_3$) δ (ppm) 174.6 (*C*ON(NPht)), 168.2 (*C*OOMe), 164.9, 164.5 (*C*=O Pht), 155.4 (NH*C*OO^{t}Bu), 135.5, 135.3 (Pht*C*H), 130.4 (Ar*C*), 124.8, 124.6 (Pht*C*H), 80.3 (NHCOO*C*(CH_3)$_3$), 53.3 (O*C*H_3), 49.6 (*C*H$_2$COOMe), 48.7 (*C*HCH$_2$CH(CH$_3$)$_2$), 42.6 (CH*C*H$_2$CH(CH$_3$)$_2$), 28.9, 28.8 (NHCOOC(*C*H_3)$_3$), 25.2, 25.0 (CHCH$_2$*C*H(CH$_3$)$_2$), 23.8, 23.6, 22.7, 22.4 (CHCH$_2$CH(*C*H_3)$_2$); HRMS (ESI) calculated for $C_{22}H_{29}N_3NaO_7$ [M+Na]$^+$ *m*/*z* 470.1898, found 470.1850.

3.2.12. Boc-Leuψ[CON(NPht)]Gly-OCH$_2$Ph **3l**

Dialkyl azodicarboxylate: DIAD; eluent for column chromatography: EtOAc/petroleum ether (30/70); yield 92%, oil; IR (ATR) ν_{max}/cm^{-1} 3370 (NH), 1798, 1741, 1618 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.92–7.77 (m, 4H, Hpht), 7.37–7.27 (m, 5H, *H* arom), 5.13 (s, 2H, COOCH_2Ph), 4.94 (d, 1H, *J*=9.8 Hz, NH), 4.74 (d, 1H, *J*=17.0 Hz, CH_2COOCH$_2$Ph), 4.44–4.32 (m, 1H, C*H*CH$_2$CH(CH$_3$)$_2$), 4.24 (d, 1H, *J*=17.0 Hz, CH_2COOCH$_2$Ph), 1.61–1.52 (m, 2H, CHCH_2CH(CH$_3$)$_2$), 1.44–1.31 (m, 10H, NHCOOC(CH_3)$_3$ and CHCH$_2$C*H*(CH$_3$)$_2$), 0.85 (d, 3H, *J*=5.8 Hz, CHCH$_2$CH(CH_3)$_2$), 0.73 (d, 3H, *J*=5.8 Hz, CHCH$_2$CH(CH_3)$_2$); ^{13}C NMR ($CDCl_3$) δ (ppm) 174.5 (*C*ON(NPht)), 167.5 (*C*OOCH$_2$Ph), 164.8, 164.5 (*C*=O Pht), 155.4 (NHCOO^{t}Bu), 135.6 (Ar*C*), 135.4, 135.3 (Pht*C*H), 130.3 (Ar*C*), 129.3, 129.2, 129.1, 129.0, 128.9 (Ar*C*H), 124.7, 124.6, 124.5 (Pht*C*H), 80.2 (NHCOO*C*(CH_3)$_3$), 67.8 (COO*C*H$_2$Ph), 49.9 (*C*H$_2$COOCH$_2$Ph), 48.6 (*C*HCH$_2$CH(CH$_3$)$_2$), 42.5 (CHCH$_2$CH(CH$_3$)$_2$), 28.7 (NHCOOC(*C*H_3)$_3$), 24.9 (CHCH$_2$*C*H(CH$_3$)$_2$), 23.6, 22.4 (CHCH$_2$CH(*C*H_3)$_2$); HRMS (ESI) calculated for $C_{28}H_{33}N_3NaO_7$ [M+Na]$^+$ *m*/*z* 546.2367, found 546.2345.

3.2.13. Boc-Leuψ[CON(NPht)]Ala-OMe **3m**

Dialkyl azodicarboxylate: DBAD; eluent for column chromatography: EtOAc/petroleum ether (15/85); yield 47%, oil; IR (ATR) ν_{max}/cm^{-1} 3359 (NH), 1754, 1691 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.92–7.77 (m, 4H, Hpht), 5.50–4.94 (m, 2H, N*H* and C*H*CH$_3$), 4.7 (dd, 0.3H, *J*=9.9, 9.3 Hz, C*H*CH(CH$_3$)$_2$), 3.93 (dd, 0.7H, *J*=9.9, 9.3 Hz, C*H*CH(CH$_3$)$_2$), 3.79 (s, 0.9H, OCH_3), 3.73 (s, 2.1H, OCH_3), 2.01–1.99 (m, 1H, CHC*H*(CH$_3$)$_2$), 1.46–1.38 (m, 12H, NHCOOC(CH_3)$_3$ and CHCH_3), 0.87–0.81 (m, 6H, C*H*CH(CH_3)$_2$); ^{13}C NMR ($CDCl_3$) δ (ppm) 173.5 (*C*ON(NPht)) 171.2, 170.7 (*C*OOMe), 165.9, 164.7 (*C*=O Pht), 156.4, 155.8 (NHCOO^{t}Bu), 135.7, 135.5, 135.3, 135.2 (Ar*C*H), 130.7, 130.5, 129.9 (Ar*C*), 125.0, 124.9, 124.6, 124.4 (Pht*C*H), 80.9, 80.3 (NHCOO*C*(CH_3)$_3$), 60.9, 57.2 (*C*HCH(CH$_3$)$_2$), 56.2, 55.9 (*C*HCH$_3$), 53.0 (O*C*H_3), 31.5, 31.2 (CHCH(CH$_3$)$_2$), 28.7, 28.6 (NHCOOC(*C*H_3)$_3$), 20.0, 18.0 (CHCH(*C*H_3)$_2$), 15.2, 14.9 (CH*C*H$_3$); HRMS (ESI) calculated for $C_{22}H_{29}N_3NaO_7$ [M+Na]$^+$ *m*/*z* 470.1898, found 470.1887.

3.2.14. Z-Glyψ[CON(NPht)]Gly-OMe **3n**

Dialkyl azodicarboxylate: DBAD; yield 90%, white solid, mp=128 °C; IR (KBr) ν_{max}/cm^{-1} 3364 (NH), 1793, 1760, 1736, 1718, 1697 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.01–7.82 (m, 4H, Hpht), 7.42–7.21 (m, 5H, *H* arom), 5.63–5.52 (m, 1H, N*H*), 5.09 (s, 2H, COOCH_2Ph), 4.55 (s, 2H, CH_2COOCH$_3$), 4.01 (d, 2H, *J*=4.4 Hz, NHCH_2CO), 3.75 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$) δ (ppm) 170.3 (*C*ONNPht), 167.8 (*C*OOCH$_3$), 164.3 (*C*=O Pht), 156.3 (NHCOOCH$_2$Ph), 136.6 (Ar*C*), 135.8 (Pht*C*H), 129.7 (Ar*C*), 128.8, 128.5 (Ar*C*H), 124.9 (Pht*C*H), 67.4 (NHCOOCH$_2$Ph), 52.9 (COOCH$_3$), 49.1 (*C*H$_2$COOCH$_3$), 42.4 (NH*C*H$_2$CO).

3.2.15. Z-Glyψ[CON(NPht)]Ala-OMe **3o**

Dialkyl azodicarboxylate: DBAD; yield 84%, white solid, mp=55 °C; IR (KBr) ν_{max}/cm^{-1} 3408 (NH), 1797, 1746, 1736, 1710 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.93–7.62 (m, 4H, Hpht), 7.37–7.17 (m, 5H, *H* arom), 5.83–5.71 (m, 1H, N*H*), 5.24–5.10 (m, 3H, C*H*CH$_3$ and COOCH_2Ph), 3.81 (d, 2H, *J*=4.4 Hz, NHCH_2CO), 3.72 (s, 0.45H, OCH_3), 3.69 (s, 2.55H, OCH_3), 1.42 (d, 0.45H, *J*=6.7 Hz, CHCH_3), 1.31 (d, 2.55H, *J*=6.7 Hz, CHCH_3); ^{13}C NMR ($CDCl_3$) δ (ppm) 170.4 (*C*ONNPht), 169.7 (*C*OOCH$_3$), 165.3, 165.6 (*C*=O Pht), 156.3 (NHCOOCH$_2$Ph), 136.6 (Ar*C*), 135.9, 135.3 (Pht*C*H), 129.5 (Ar*C*), 129.4, 128.5 (Ar*C*H), 124.9, 124.6 (Pht*C*H), 67.4 (NHCOOCH$_2$Ph), 56.5, 55.1 (*C*HCH$_3$), 53.5, 53.1 (COOCH$_3$), 43.1, 42.7 (NHCH$_2$CO), 14.6, 14.3 (CH*C*H$_3$).

3.2.16. Z-Glyψ[CON(NPht)]Val-OCH$_2$Ph **3p**

Dialkyl azodicarboxylate: DBAD; yield 79%, white solid; IR (KBr) ν_{max}/cm^{-1} 3291 (NH), 1794, 1733, 1678 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.01–7.65 (m, 4H, Hpht), 7.45–7.22 (m, 10H, *H* arom), 5.64 (d, 1H, *J*=4.6 Hz, N*H*), 5.23–5.01 (m, 4H, NHCH_2CO and NHCOOCH_2Ph), 4.42–4.38 (m, 1H, *C*HCH(CH$_3$)$_2$), 3.92 (dq, 2H, *J*=17.5, 4.6 Hz, NHCH$_2$CO), 2.23–2.05 (m, 1H, CHC*H*(CH$_3$)$_2$), 1.43 (d, 0.5H, *J*=6.5 Hz, CHCH(CH_3)$_2$), 1.22 (d, 2.5H, *J*=6.5 Hz, CHCH(CH_3)$_2$),

0.94 (d, 0.5H, J=6.6 Hz, CHCH(CH_3)$_2$), 0.86 (d, 2.5H, J=6.5 Hz, CHCH(CH_3)$_2$); ^{13}C NMR ($CDCl_3$) δ (ppm) 170.3 (*C*ONNPht), 168.8 (*C*OOCH$_2$Ph), 165.5, 165.3 (*C*=O Pht), 156.3 (NH*C*OOCH$_2$Ph), 136.6 (Ar*C*), 135.8, 135.7 (Pht*C*H), 129.7 (Ar*C*), 129.2, 128.9, 12.8, 128.5 (Ar*C*H), 124.9, 124.7 (Pht*C*H), 67.9, 67.8, 67.4 (NHCOO*C*H$_2$Ph and COO*C*H$_2$Ph), 42.8 (NH*C*H$_2$CO) 64.9 (*C*HCH(CH_3)$_2$), 29.8 (CH*C*H(CH_3)$_2$), 19.7, 19.3 (CHCH(*C*H$_3$)$_2$).

3.2.17. Z-Alaψ[CON(NPht)]Val-OCH$_2$Ph ***3q***

Dialkyl azodicarboxylate: DBAD; yield 77%, white solid, mp=163 °C; IR (KBr) ν_{max}/cm^{-1} 3299 (NH), 1798, 1752,1672 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.01–7.70 (m, 4H, Hpht), 7.51–7.12 (m, 10H, *H* arom), 5.62–5.51 (m, 1H, N*H*), 5.33–4.91 (m, 5H, *CH*CH$_3$, NHCOOC*H*$_2$Ph and COOC*H*$_2$Ph), 4.53–4.31 (m, 1H, *CH*CH(CH_3)$_2$), 2.30–2.13 (m, 1H, CHC*H*(CH_3)$_2$), 1.51 (d, 0.6H, J=6.8 Hz, CHC*H*$_3$), 1.35 (d, 2.4H, J=6.8 Hz, CHC*H*$_3$), 1.29 (d, 0.6H, J=6.5 Hz, CHCH(C*H*$_3$)$_2$), 1.20 (d, 2.4H, J=6.5 Hz, CHCH(C*H*$_3$)$_2$), 0.96 (d, 0.6H, J=6.7 Hz, CHCH(C*H*$_3$)$_2$), 0.85 (d, 2.4H, J=6.7 Hz, CHCH(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$) δ (ppm) 175.0 (*C*ONNPht), 169.2 (*C*OOCH$_2$Ph), 166.0, 165.5 (*C*=O Pht), 155.5 (NH*C*OOCH$_2$Ph), 136.6 (Ar*C*), 135.9 (Pht*C*H), 135.6, 129.7 (Ar*C*), 129.6, 129.5, 129.2, 128.9, 128.8, 128.5 (Ar*C*H), 124.9, 124.7 (Pht*C*H), 68.7, 67.9, 67.4, 67.2 (NHCOO*C*H$_2$Ph and COO*C*H$_2$Ph), 60.3, 57.6 (*C*H(CH_3)$_2$ and *C*HCH(CH_3)$_2$), 25.2, 24.9, 23.3, 23.1, 22.6, 22.4 (CH(*C*H$_3$)$_2$, CH*C*H$_3$ and *C*HCH(CH_3)$_2$).

3.2.18. Z-Valψ[CON(NPht)]Gly-OMe ***3r***

Dialkyl azodicarboxylate: DBAD; yield 79%, white solid, mp=135 °C; IR (KBr) ν_{max}/cm^{-1} 3290 (NH), 1796, 1743, 1699 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.02–7.63 (m, 4H, Hpht), 7.41–7.22 (m, 5H, *H* arom), 5.54 (d, 0.25H, J=9.9 Hz, N*H*), 5.39 (d, 0.75H, J=9.9 Hz, N*H*), 5.26–4.91 (m, 2H, NHCOOC*H*$_2$Ph), 4.85 (d, 0.25H, J=17.0 Hz, NHCOOC*H*$_2$Ph), 4.72 (d, 0.75H, J=17.0 Hz, C*H*$_2$COOCH$_3$), 4.63 (dd, 0.25H, J=9.9, 7.7 Hz, C*H*CH(CH_3)$_2$), 4.51 (d, 0.25H, J=17.0 Hz, C*H*$_2$COOCH$_3$), 4.21 (dd, 0.75H, J=9.9, 7.7 Hz, C*H*CH(CH_3)$_2$), 4.13 (d, 0.75H, J=17.0 Hz, C*H*$_2$COOCH$_3$), 3.77 (s, 0.75H, COOC*H*$_3$), 3.71 (s, 2.25H, COOC*H*$_3$), 2.25–2.00 (m, 1H, CHC*H*(CH_3)$_2$), 1.09 (d, 0.75H, J=6.7 Hz, CHCH(C*H*$_3$)$_2$), 0.99 (d, 0.75H, J=6.7 Hz, CHCH(C*H*$_3$)$_2$), 0.93 (d, 2.25H, J=6.7 Hz, CHCH(C*H*$_3$)$_2$), 0.87 (d, 2.25H, J=6.5 Hz, CHCH(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$) δ (ppm) 173.7, 171.1 (*C*ONNPht), 167.8, 165.1 (*C*OOCH$_3$), 165.5, 164.6 (*C*=O Pht), 156.7, 156.4 (NHCOOCH$_2$Ph), 136.7 (Ar*C*), 135.5, 135.4 (Pht*C*H), 129.9, 129.0 (Ar*C*), 128.8, 128.7, 128.4, 128.3 (Ar*C*H), 124.7, 124.5 (Pht*C*H), 67.6, 67.4 (NHCOO*C*H$_2$Ph), 56.4, 55.9 (*C*HCH(CH_3)$_2$), 53.1, 52.8 (COO*C*H$_3$), 49.7 (*C*H$_2$COOCH$_3$), 31.2 (CH*C*H(CH_3)$_2$), 19.8, 19.7, 17.7, 17.6 (CH(*C*H$_3$)$_2$).

3.3. Typical experimental procedure for the preparation of 4 (P^2=OCH$_2$Ph) and 14 in solution

To a stirred solution of **3** (0.9 mmol) in ethanol (20 mL), a catalytic amount of 10% Pd/C was added. The resulting mixture was flushed with H_2 and vigorously stirred until completion (monitored by TLC). The reaction mixture was filtered on Celite and evaporated to dryness. The product was used without further purification.

3.3.1. Boc-Pheψ[CON(NPht)]Ala-OH ***4j***

Yield 100%, white solid, mp=95 °C; IR (KBr) ν_{max}/cm^{-1} 3340 (NH and COOH), 1798, 1745 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.8 (br s, 1H, COO*H*), 8.00–7.82 (m, 4H, Hpht), 7.26–7.11 (m, 5H, *H* arom), 5.10 (d, 1H, J=9.9 Hz, N*H*), 4.90 (q, 1H, J=7.1 Hz, *CH*CH$_3$), 4.54–4.52 (dd, 1H, J=8.9, 6.1 Hz, *CH*CH$_2$Ph), 3.17–3.11 (dd, 1H, J=8.5, 5.6 Hz, CHC*H*$_2$Ph), 2.91–2.83 (dd, 1H, J=8.3, 5.6 Hz, CHC*H*$_2$Ph), 1.50–1.18 (m, 12H, NHCOOC(C*H*$_3$)$_3$ and CHC*H*$_3$); ^{13}C NMR ($CDCl_3$) δ ppm 173.7 (*C*OOH), 172.2 (*C*ON(NPht)), 166.0, 165.9 (*C*=O Pht), 155.5 (NHCOO^{t}Bu), 136.7 (Ar*C*), 135.9, 135.6 (Pht*C*H), 130.3, 130.2 (Ar*C*H), 129.8 (Ar*C*), 129.0, 127.5, 127.3 (Ar*C*H), 125.3, 125.2, 124.9 (Pht*C*H), 80.7 (NHCOO*C*(CH$_3$)$_3$), 58.0 (*C*HCH$_3$), 52.2 (*C*HCH$_2$Ph), 38.7 (CH*C*H$_2$Ph), 28.8 (NHCOOC(*C*H$_3$)$_3$), 15.0, 14.2 (CH*C*H$_3$).

3.3.2. Boc-Leuψ[CON(NPht)]Gly-OH ***4l***

Yield 87%, gum; IR (ATR) ν_{max}/cm^{-1} 2968 (NH), 1798, 1741, 1692 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 9.87 (s, 1H, COO*H*), 7.98–7.85 (m, 4H, Hpht), 5.08 (d, 0.25H, J=9.9 Hz, N*H*COOC(CH$_3$)$_3$), 4.92 (d, 0.75H, J=9.9 Hz, N*H*COOC(CH$_3$)$_3$), 4.73 (d, 1H, J=17.0 Hz, C*H*$_2$COOH), 4.60–4.47 (m, 1H, C*H*CH$_2$CH(CH$_3$)$_2$), 4.40 (d, 1H, J=17.0 Hz, C*H*$_2$COOH), 1.64–1.23 (m, 12H, NHCOOC(C*H*$_3$)$_3$ and CHC*H*$_2$C*H*(CH$_3$)$_2$), 1.02–0.95 (m, 6H, CHCH$_2$CH(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$) δ (ppm) 174.6 (*C*OOH), 168.2 (*C*ON(NPht)), 164.9, 164.5 (*C*=O Pht), 155.4 (NHCOO^{t}Bu), 135.5, 135.3 (Pht*C*H), 130.4 (Ar*C*), 124.8, 124.6 (Pht*C*H), 80.3 (NHCOO*C*(CH$_3$)$_3$), 49.6 (*C*H$_2$COOH), 48.7 (*C*HCH$_2$CH(CH$_3$)$_2$), 42.6 (CH*C*H$_2$CH(CH$_3$)$_2$), 28.9, 28.8 (NHCOOC(*C*H$_3$)$_3$), 25.2, 25.0 (CHCH$_2$CH(*C*H$_3$)$_2$), 23.8, 23.6, 22.7, 22.4 (CHCH$_2$CH(*C*H$_3$)$_2$); HRMS (ESI) calculated for $C_{22}H_{33}N_3NaO_7$ [M+Na]$^+$ m/z 456.1741, found 456.1723.

3.3.3. Boc-[Pheψ[CON(NPht)]Ala]$_2$-OH ***14***

Yield 100%, white solid, mp=130 °C; IR (KBr) ν_{max}/cm^{-1} 3325 (NH and COOH), 1799, 1741, 1695 (CO); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.35 (d, 0.7H, J=8.1 Hz, N*H*CH(CH$_3$)), 8.25 (d, 0.3H, J=8.0 Hz, N*H*CH(CH$_3$)), 8.10–7.80 (m, 8H, Hpht), 7.33–7.00 (m, 10H, *H* arom), 5.00–4.26 (m, 5H, *CH*CH$_3$, *CH*CH$_2$Ph and N*H*COOC(CH$_3$)$_3$), 3.40–2.50 (m, 4H, CHC*H*$_2$Ph), 1.40–1.09 (m, 15H, COOC(*CH*$_3$)$_3$ and CHC*H*$_3$).

3.4. Experimental procedure for the preparation of 4g in solution

To a stirred solution of **3g** (0.51 g, 0.9 mmol) in anhydrous CH_2Cl_2 (12 mL), trifluoroacetic acid (3 mL, 40 mmol) was added with stirring. The resulting solution was stirred at room temperature until completion (monitored by TLC) and concentrated in vacuo. The residue was used directly in oligomerization.

3.4.1. Z-Pheψ[CON(NPht)]Ala-OH ***4g***

Yield 100%, white solid, mp=80 °C; IR (KBr) ν_{max}/cm^{-1} 3356 (NH, COOH), 1798, 1745, 1692 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.95–7.80 (m, 4H, Hpht), 7.31–7.06 (m, 5H, *H* arom), 5.60 (d, 1H, J=9.3 Hz, N*H*), 5.40 (q, 0.1H, J=8.8 Hz, *CH*CH$_3$), 5.10–5.00 (m, 1.1H, COOC*H*$_2$Ph and *CH*CH$_2$Ph), 5.00–4.80 (m, 1.9H, COOC*H*$_2$Ph and *CH*CH$_3$), 4.65 (dd, 0.9H, J=5.8, 8.5 Hz, *CH*CH$_2$Ph), 3.20–2.82 (m, 2H, CHC*H*$_2$Ph), 1.49–1.43 (d, 3H, J=7.9 Hz, CHC*H*$_3$); ^{13}C NMR ($CDCl_3$) δ (ppm) 173.5 (*C*OOH), 172.6 (*C*ON(NPht)), 165.9 (*C*=O Pht), 156.4 (NHCOOCH$_2$Ph), 136.6, 136.3 (Ar*C*), 136.2, 136.0, 135.7 (Pht*C*H), 130.3, 130.0 (Ar*C*H), 129.7 (Ar*C*), 129.0, 128.7, 128.6, 128.4, 127.5 (Ar*C*H), 125.2, 125.0 (Pht*C*H), 67.8 (NHCOO*C*H$_2$Ph), 58.0 (*C*HCH$_3$), 52.8 (*C*HCH$_2$Ph), 38.6 (CH*C*H$_2$Ph), 14.3 (CH*C*H$_3$); HRMS (ESI) calculated for $C_{28}H_{25}N_3NaO_7$ [M+Na]$^+$ m/z 538.1585, found 538.1572.

3.5. Typical experimental procedure for the preparation of 4 on solid support

Step a: to a suspension of 0.30 g of Wang PS resin (cross-linked with 1% DVB, 200–400 mesh, 1.2 mequiv/g) in THF (1 mL/100 mg of resin) were added DIC (3 equiv), a catalytic amount of DMAP and THPO-hydroxy acid **10** (3 equiv). The resulting mixture was stirred for 2 h and then filtered and washed with CH_2Cl_2 (3×1 min), MeOH (3×1 min) and then THF (3×1 min).

Step b: 10 mL of a solution of PTSA (5 mg/mL) in CH_2Cl_2/MeOH (97/3) was added to the resin and the resulting mixture was stirred for 1 h. The reaction was performed two times and

the resin was then filtered and washed with CH_2Cl_2 (3×1 min), MeOH (3×1 min) and then with THF (3×1 min).

Step c: PPh_3 (3 equiv) and α-Z-*N*-protected aminohydrazide **1** (3 equiv) in 5 mL of anhydrous THF were added to the resin. DIAD (3 equiv) was added dropwise to the reaction and the resulting mixture was stirred for 4 h. The reaction was performed two times and the resin was filtered and washed.

Cleavage: 10 mL of a mixture of CH_2Cl_2/TFA (1/1) was added to the resin. After 30 min, the polymer was removed by filtration and the filtrate concentrated under vacuum.

3.5.1. Z-Alaψ[CON(NPht)]Ala-OH ***4a***

Yield 37%, gum; IR (ATR) ν_{max}/cm^{-1} 3293 (NH), 1794, 1745, 1676 (C=O); ^1H NMR (DMSO-d_6, 300 MHz) δ (ppm) 12.60 (s, 1H, COO*H*), 7.98–7.91 (m, 4H, Hpht), 7.71 (d, 1H, *J*=8.9 Hz, N*H*COOCH$_2$Ph), 7.36–7.26 (m, 5H, *H* arom), 4.80–4.62 (m, 3H, C*H*CH$_3$ and NHCOOC*H*$_2$Ph), 4.25–4.23 (m, 1H, C*H*CH$_3$), 1.34 (d, 3H, *J*=10.0 Hz, CHC*H*$_3$), 1.12 (d, 3H, *J*=10.0 Hz, CHC*H*$_3$); ^{13}C NMR (DMSO-d_6) δ (ppm) 172.4 (*C*OOH), 170.5 (*C*ON(NPht)), 164.9, 164.5 (*C*=O Pht), 155.2 (NHCOOCH$_2$Ph), 136.6 (Ar*C*), 135.5, 135.1 (Pht*C*H), 129.5, 129.3 (Ar*C*), 129.4, 129.2, 128.3, 127.7 (Ar*C*H), 123.8, 123.5 (Pht*C*H), 65.5 (NHCOOCH$_2$Ph), 57.6 (*C*HCH$_3$), 46.3 (*C*HCH$_3$), 17.5 (CH*C*H$_3$), 14.7 (CH*C*H$_3$); HRMS (ESI) calculated for $C_{22}H_{21}N_3NaO_7$ $[M+Na]^+$ *m*/*z* 462.1271, found 462.1261.

3.5.2. Z-Glyψ[CON(NPht)]Ala-OH ***4e***

Yield 38%, gum; IR (ATR) ν_{max}/cm^{-1} 3316 (NH), 1798, 1741, 1693 (C=O); ^1H NMR (DMSO-d_6, 300 MHz) δ (ppm) 7.97–7.86 (m, 4H, Hpht), 7.66–7.56 (m, 1H, N*H*COOCH$_2$Ph), 7.41–7.33 (m, 5H, *H* arom), 5.04–4.72 (m, 3H, C*H*CH$_3$ and NHCOOC*H*$_2$Ph), 4.35–3.92 (m, 2H, NHC*H*$_2$CO), 1.39 (d, 1H, *J*=6.7 Hz, CHC*H*$_3$), 1.31 (d, 2H, *J*=6.7 Hz, CHC*H*$_3$); ^{13}C NMR (DMSO-d_6) δ (ppm) 170.4 (*C*OOH), 169.7, 168.8 (*C*ON(NPht)), 164.7 (*C*=O Pht), 156.4, 156.3 (NHCOOCH$_2$Ph), 137.1, 136.9 (Ar*C*), 135.5, 135.3 (Pht*C*H), 130.1 (Ar*C*), 129.4, 129.2, 128.2, 127.7, 127.6 (Ar*C*H), 123.9, 123.7 (Pht*C*H), 65.4, 65.2 (NHCOOC*H*$_2$Ph), 56.7, 55.7 (*C*HCH$_3$), 41.7 (NHCH$_2$CO), 14.6, 14.2 (CH*C*H$_3$); HRMS (ESI) calculated for $C_{21}H_{19}N_3NaO_7$ $[M+Na]^+$ *m*/*z* 448.1115, found 448.1114.

3.5.3. Z-Glyψ[CON(NPht)]Gly-OH ***4n***

Yield 49%, white solid, mp=107 °C; IR (ATR) ν_{max}/cm^{-1} 3355 (NH), 1798, 1732, 1698 (C=O); ^1H NMR (DMSO-d_6, 300 MHz) δ (ppm) 7.98–7.87 (m, 4H, Hpht), 7.63–7.54 (m, 1H, N*H*COOCH$_2$Ph), 7.50–7.33 (m, 5H, *H* arom), 5.04–4.95 (m, 2H, NHCOOC*H*$_2$Ph), 4.32–3.79 (m, 4H, NHC*H*$_2$CO and C*H*$_2$COOH); ^{13}C NMR (DMSO-d_6) δ (ppm) 170.8, 170.5(*C*OOH), 168.1 (*C*ON(NPht)), 164.2, 164.1 (*C*=O Pht), 156.4, 156.3 (NH*C*OOCH$_2$Ph), 136.9 (Ar*C*), 135.1, 135.0 (Pht*C*H), 129.7, 129.3 (Ar*C*), 128.2, 128.0, 127.7, 127.6 (Ar*C*H), 123.7 (Pht*C*H), 65.4 (NHCOOCH$_2$Ph), 49.5 (*C*H$_2$COOH), 41.5 (NH*C*H$_2$CO); HRMS (ESI) calculated for $C_{20}H_{17}N_3NaO_7$ $[M+Na]^+$ *m*/*z* 434.09587, found 434.0958.

3.5.4. Z-Alaψ[CON(NPht)]Gly-OH ***4o***

Yield 47%, gum; IR (ATR) ν_{max}/cm^{-1} 3339 (NH), 1798, 1693 (C=O); ^1H NMR (DMSO-d_6, 300 MHz) δ (ppm) 7.97–7.90 (m, 4H, Hpht), 7.72 (d, 1H, *J*=8.9 Hz, N*H*COOCH$_2$Ph), 7.36–7.24 (m, 5H, *H* arom), 4.76–4.72 (m, 2H, NHCOOC*H*$_2$Ph), 4.41 (d, 1H, *J*=17.0 Hz, C*H*$_2$COOH), 4.35 (m, 1H, C*H*CH$_3$), 4.21 (d, 1H, *J*=17.0 Hz, C*H*$_2$COOH), 1.24, 1.15 (2d, 3H, *J*=6.9 Hz, CHC*H*$_3$); ^{13}C NMR (DMSO-d_6) δ (ppm) 173.4 (*C*OOH), 168.1 (*C*ON(NPht)), 164.4, 164.0 (*C*=O Pht), 155.2 (NH*C*OOCH$_2$Ph), 136.0, 135.5 (Ar*C*), 134.9 (Pht*C*H), 129.7 (Ar*C*), 128.2, 127.6 (Ar*C*H), 123.6, 123.5 (Pht*C*H), 65.5 (NHCOOCH$_2$Ph), 49.9 (*C*H$_2$COOH), 46.1 (*C*HCH$_3$), 17.5 (CH*C*H$_3$); HRMS (ESI) calculated for $C_{21}H_{19}N_3NaO_7$ $[M+Na]^+$ *m*/*z* 448.1115, found 448.1113.

3.5.5. Z-Leuψ[CON(NPht)]Gly-OH ***4s***

Yield 39%, white solid, mp=69 °C; IR (ATR) ν_{max}/cm^{-1} 3335 (NH), 1799, 1741, 1698 (C=O); ^1H NMR (DMSO-d_6, 300 MHz) δ (ppm) 7.99–7.91 (m, 4H, Hpht), 7.65 (d, 1H, *J*=9.2 Hz, N*H*COOCH$_2$Ph), 7.38–7.26 (m, 5H, *H* arom), 5.08–5.01 (m, 2H, NHCOOC*H*$_2$Ph), 4.40 (d, 1H, *J*=17.0 Hz, NC*H*$_2$COOH), 4.31–4.18 (m, 3H, NC*H*$_2$COOH and C*H*CH$_2$CH(CH$_3$)$_2$), 1.88–1.44 (m, 3H, CHC*H*$_2$C*H*(CH$_3$)$_2$), 0.80 (d, 3H, *J*=5.3 Hz, CHCH$_2$CH(C*H*$_3$)$_2$), 0.61 (d, 3H, *J*=5.3 Hz, CHCH$_2$CH(C*H*$_3$)$_2$); ^{13}C NMR (DMSO-d_6) δ (ppm) 173.1 (*C*OOH), 168.1 (*C*ON(NPht)), 164.3, 164.1 (*C*=O Pht), 155.6 (NHCOOCH$_2$Ph), 136.7 (Ar*C*), 135.0 (Pht*C*H), 129.8, 129.6 (Ar*C*), 128.2, 127.7, 127.6 (Ar*C*H), 123.5, 123.5 (Pht*C*H), 65.6, 65.4 (NHCOOC*H*$_2$Ph), 49.7 (*C*H$_2$COOH), 48.6 (*C*HCH$_2$CH(CH$_3$)$_2$), 40.2 (CHC*H*$_2$CH(CH$_3$)$_2$), 23.8 (CHCH$_2$*C*H(CH$_3$)$_2$), 22.8, 21.1 (CHCH$_2$CH(*C*H$_3$)$_2$); HRMS (ESI) calculated for $C_{23}H_{25}N_3NaO_7$ $[M+Na]^+$ *m*/*z* 490.1584, found 490.1584.

3.5.6. Z-Pheψ[CON(NPht)]Gly-OH ***4t***

Yield 48%, gum; IR (ATR) ν_{max}/cm^{-1} 3363 (NH), 1798, 1739, 1693 (C=O); ^1H NMR (DMSO-d_6, 300 MHz) δ (ppm) 7.97–7.86 (m, 5H, Hpht and N*H*COOCH$_2$Ph), 7.30–7.06 (m, 10H, *H* arom), 4.64–4.60 (m, 2H, NHCOOC*H*$_2$Ph), 4.48 (d, 1H, *J*=17.1 Hz, C*H*$_2$COOH), 4.43–4.35 (m, 1H, C*H*CH$_2$Ph), 4.27 (d, 1H, *J*=17.1 Hz, C*H*$_2$COOH), 3.02–2.78 (m, 2H, CHC*H*$_2$Ph); ^{13}C NMR (DMSO-d_6) δ (ppm) 172.9 (*C*OOH), 168.1 (*C*ON(NPht)), 164.4, 163.9 (*C*=O Pht), 155.4 (NHCOOCH$_2$Ph), 137.8, 136.7 (Ar*C*), 135.2, 134.9 (Pht*C*H), 129.8, 129.6 (Ar*C*), 129.2, 128.9, 128.1, 128.0, 127.5, 127.2, 127.1, 126.2 (Ar*C*H), 123.6, 123.4 (Pht*C*H), 65.4, 65.1 (NHCOOC*H*$_2$Ph), 51.8 (*C*HCH$_2$Ph), 49.9 (*C*H$_2$COOH), 36.6 (CHC*H*$_2$Ph); HRMS (ESI) calculated for $C_{27}H_{23}N_3NaO_7$ $[M+Na]^+$ *m*/*z* 524.1428, found 524.1427.

3.5.7. Z-Leuψ[CON(NPht)]Ala-OH ***4u***

Yield 44%, gum; IR (ATR) ν_{max}/cm^{-1} 3376 (NH), 1798, 1742, 1688 (C=O); ^1H NMR (DMSO-d_6, 300 MHz) δ (ppm) 7.95–7.89 (m, 4H, Hpht), 7.58 (d, 1H, *J*=9.2 Hz, N*H*COOCH$_2$Ph), 7.32–7.06 (m, 5H, *H* arom), 4.82–4.73 (m, 2H, NHCOOC*H*$_2$Ph), 4.61–4.56 (m, 1H, C*H*CH$_3$), 4.18–4.14 (m, 1H, C*H*CH$_2$CH(CH$_3$)$_2$), 1.56–1.19 (m, 6H, CHC*H*$_3$ and CHC*H*$_2$C*H*(CH$_3$)$_2$), 0.74–0.36 (m, 6H, CHCH$_2$CH(C*H*$_3$)$_2$); ^{13}C NMR (DMSO-d_6) δ (ppm) 172.3 (*C*OOH), 169.9 (*C*ON(NPht)), 165.0, 164.5 (*C*=O Pht), 155.6 (NHCOOCH$_2$Ph), 136.7 (Ar*C*), 135.4, 135.1 (Pht*C*H), 129.5, 129.4 (Ar*C*), 128.2, 127.7, 127.6 (Ar*C*H), 123.6 (Pht*C*H), 65.4 (NHCOOC*H*$_2$Ph), 57.5 (*C*HCH$_3$), 48.9 (*C*HCH$_2$CH(CH$_3$)$_2$), 40.2 (CHC*H*$_2$CH(CH$_3$)$_2$), 24.0, 23.8 (CHCH$_2$*C*H(CH$_3$)$_2$), 22.7, 21.1 (CHCH$_2$CH(*C*H$_3$)$_2$), 15.0 (CH*C*H$_3$); HRMS (ESI) calculated for $C_{25}H_{27}N_3NaO_7$ $[M+Na]^+$ *m*/*z* 504.1741, found 504.1740.

3.5.8. Z-Pheψ[CON(NPht)]Val-OH ***4w***

Yield 21%, gum; IR (ATR) ν_{max}/cm^{-1} 3451 (NH), 1798, 1742, 1693 (C=O); ^1H NMR (DMSO-d_6, 300 MHz) δ (ppm) 13.0 (s, 1H, COO*H*), 8.03–7.84 (m, 5H, Hpht and N*H*COOCH$_2$Ph), 7.38–7.04 (m, 10H, *H* arom), 4.97–4.67 (m, 3H, NHCOOC*H*$_2$Ph and C*H*CH$_2$CH(CH$_3$)$_2$), 4.41–4.38 (C*H*CH$_2$Ph), 2.98–2.76 (m, 2H, CHC*H*$_2$Ph), 1.91–1.89 (m, 1H, CHC*H*(CH$_3$)$_2$), 0.92 (d, 3H, *J*=3.4 Hz, CHCH(C*H*$_3$)$_2$), 0.81 (d, 3H, *J*=3.4 Hz, CHCH(C*H*$_3$)$_2$); ^{13}C NMR (DMSO-d_6) δ (ppm) 172.5 (*C*OOH), 169.6 (*C*ON(NPht)), 165.8, 164.5 (*C*=O Pht), 155.3 (NH*C*OOCH$_2$Ph), 137.0, 136.7 (Ar*C*), 135.5, 135.3 (Pht*C*H), 129.2 (Ar*C*), 129.1, 128.9, 128.2, 128.0, 127.6, 127.4, 127.2, 126.5, 126.3 (Ar*C*H), 123.9, 123.6 (Pht*C*H), 65.4, 65.2 (NHCOOC*H*$_2$Ph), 64.3 (*C*HCH(CH$_3$)$_2$), 52.4 (*C*HCH$_2$Ph), 37.6 (CHCH$_2$Ph), 29.4 (CHCH(CH$_3$)$_2$), 19.1, 18.9, 18.8 (CHCH(CH$_3$)$_2$); HRMS (ESI) calculated for $C_{30}H_{29}N_3NaO_7$ $[M+Na]^+$ *m*/*z* 566.1897, found 566.1895.

3.5.9. Z-Alaψ[CON(NPht)]Val-OH ***4x***

Yield 21%, white solid, mp=81 °C; IR (ATR) ν_{max}/cm^{-1} 3451 (NH), 1798, 1737, 1693 (C=O); ^1H NMR (DMSO-d_6, 300 MHz) δ (ppm) 7.97 (m, 4H, Hpht), 7.75–7.67 (m, 1H, N*H*COOCH$_2$Ph), 7.34–7.27 (m, 5H, *H*

arom), 5.05–4.80 (m, 3H, NHCOOCH_2Ph and CHCH$(CH_3)_2$), 4.35–4.29 (m, 1H, CHCH$_3$), 2.05–1.90 (m, 1H, CHC$H$$(CH_3)_2$), 1.49–0.81 (m, 9H, CHC$H_3$ and CHCH$(CH_3)_2$); ^{13}C NMR (DMSO-d_6) δ (ppm) 173.9 (*C*OOH), 169.6 (*C*ON(NPht)), 165.7, 164.6 (*C*=O Pht), 155.1 (NH*C*OOCH$_2$Ph), 136.5 (Ar*C*), 135.4 (Pht*C*H), 129.1, 128.2, 127.2 (Ar*C*H), 123.6 (Pht*C*H), 65.4 (NHCOOCH_2Ph), 64.3 (*C*HCH$(CH_3)_2$), 47.3, 46.8 (*C*HCH$_3$), 29.5, 28.4 (CH*C*H$(CH_3)_2$), 18.9, 18.2 (CHCH$(CH_3)_2$), 17.1 (CHCH$_3$); HRMS (ESI) calculated for $C_{23}H_{25}N_3NaO_7$ $[M+Na]^+$ *m*/*z* 490.1584, found 490.1584.

3.6. Experimental procedure for the preparation of 5g (P^1=Z)

To a stirred solution of **3g** (0.91 g, 1.6 mmol) in glacial acetic acid (50 mL), 10% Pd/C (0.09 g) was added. The resulting mixture was flushed with H_2 and vigorously stirred until completion (monitored by TLC). The reaction mixture was filtered on Celite and evaporated to dryness. The residue was dissolved in EtOAc, washed with sodium bicarbonate solution (4%) and dried over $MgSO_4$. After evaporation of EtOAc, the product was purified by column chromatography.

3.6.1. H-Pheψ[CON(NPht)]Ala-O^{t}Bu **5g**

Eluent for column chromatography: EtOAc/petroleum ether (20/80); yield 55%, white solid, mp=55 °C; IR (2 mM in CH_2Cl_2) ν_{max}/cm^{-1} 3360 (NH_2), 1777, 1717, 1673 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.76–7.73 (m, 4H, Hpht), 7.28–7.14 (m, 5H, *H* arom), 5.92 (dd, 1H, *J*=5.6, 5.2 Hz, C*H*CH$_2$Ph), 5.20 (q, 1H, *J*=7.3 Hz, C*H*CH$_3$), 3.78–3.70 (s, 2H, NH_2), 3.61–3.55 (dd, 2H, *J*=8.7, 5.2 Hz, CHCH_2Ph), 1.45–1.43 (m, 12H, NHCOOC(CH_3)$_3$ and CHCH_3); ^{13}C NMR ($CDCl_3$) δ (ppm) 172.2 (*C*ON(NPht)), 171.4 (*C*OO^{t}Bu), 168.7 (*C*=O Pht), 138.4 (Ar*C*), 134.4 (Pht*C*H), 132.5 (Ar*C*), 129.6, 129.0, 127.2 (Ar*C*H), 123.8 (Pht*C*H), 82.9 (NHCOOC(*C*H$_3$)$_3$), 54.4 (*C*HCH$_2$Ph), 54.3 (*C*HCH$_3$), 34.9 (CHCH$_2$Ph), 28.6 (COOC(*C*H$_3$)$_3$), 14.5 (CHCH$_3$); HRMS (ESI) calculated for $C_{24}H_{27}N_3NaO_5$ [M+Na$^+$] *m*/*z* 460.1843, found 460.1812.

3.7. Typical experimental procedure for the preparation of 5j and 13

A solution of 3 M dry hydrogen chloride in EtOAc (10 mL) was added to the carbamate **3j** or **12** (1 mmol). The resulting solution was stirred 1 h and co-evaporated several times with CH_2Cl_2 until dryness without residual HCl.

3.7.1. HCl, H-Pheψ[CON(NPht)]Ala-OCH$_2$Ph **5j**

Yield 55%, white solid, mp=62 °C; IR (KBR) ν_{max}/cm^{-1} 2928 (NH), 1798, 1738, 1694 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.60 (s, 1.5H, NH_3^+), 8.38 (s, 1.5H, NH_3^+), 7.80–7.60 (m, 4H, Hpht), 7.25–7.10 (m, 5H, *H* arom), 5.23–4.90 (m, 4H, C*H*CH$_3$, C*H*CH$_2$Ph and OCH_2Ph), 4.12–3.14 (m, 2H, CHCH_2Ph), 1.53–1.43 (m, 3H, CHCH$_3$); ^{13}C NMR ($CDCl_3$) δ (ppm) 170.4, 169.5, 169.1, 167.9 (*C*=O), 165.8, 165.6, 165.4 (*C*=O Pht), 136.1, 135.4 (Pht*C*H), 133.4, 133.0 (Ar*C*), 131.3, 130.7, 130.3 (Ar*C*H), 129.9, 129.4, 129.3 (Ar*C*), 129.2, 128.8, 128.1, 128.0 (Ar*C*H), 126.0, 124.8, 124.5 (Pht*C*H), 68.1, 67.7 (OCH$_2$Ph), 58.6, 57.9 (*C*HCH$_2$Ph), 52.6, 52.3 (*C*HCH$_3$), 36.0 (CHCH$_2$Ph), 16.2, 15.4 (CHCH$_3$); HRMS (ESI) calculated for $C_{27}H_{26}N_3O_5$ $[M+H]^+$ *m*/*z* 472.1867, found 472.1847.

3.7.2. H-[Pheψ[CON(NPht)]Ala]$_2$-OCH$_2$Ph **13**

Yield 100%, white solid, mp=94 °C; IR (1 mM in CH_2Cl_2) ν_{max}/cm^{-1} 3429, 3400, 3353(NH) 1798, 1745, 1708, 1677(C=O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.00–7.50 (m, 8H, Hpht), 7.30–7.10 (m, 15H, *H* arom), 6.80 (d, 0.7H, *J*=9.8 Hz, N*H*CH(CH$_3$)), 6.65 (d, 0.3H, *J*=9.8 Hz, N*H*CH(CH$_3$)), 5.60–4.60 (6H, C*H*CH$_3$, C*H*CH$_2$Ph and COOCH_2Ph), 3.65–3.05 (m, 6H, CHCH_2Ph and NH_2), 1.34–1.05 (m, 6H, 2CHCH_3); HRMS (ESI) calculated for $C_{47}H_{42}N_6NaO_9$ $[M+Na]^+$ *m*/*z* 857.3430, found 857.2918.

3.8. Typical experimental procedure for the preparation of 6a–6i

To a stirred solution of **3** (3 mmol) in anhydrous THF was added pyrrolidine (9 mmol) in one portion. The resulting solution was stirred at room temperature until completion (monitored by TLC). Solvent and excess of pyrrolidine were evaporated under vacuum. The residue thus obtained was dissolved in anhydrous THF (20 mL). Boc_2O (4.5 mmol) and a catalytic amount of DMAP were added in one portion and the resulting solution was stirred at room temperature until completion (monitored by TLC). Solvent was evaporated under vacuum and the mixture obtained was dissolved in anhydrous THF (20 mL). A solution of 2 M methylamine in methanol (4.5 mmol) was then added and the resulting solution was stirred at room temperature until completion (monitored by TLC) and evaporated under vacuum. A yellowish oil was obtained and purified by column chromatography using a mixture EtOAc/petroleum ether as eluent.

3.8.1. Z-Alaψ[CON(NHBoc)]Ala-OMe **6a**

Eluent for column chromatography: EtOAc/petroleum ether (15/85 then 40/60); yield 87%, oil; IR (NaCl) ν_{max}/cm^{-1} 3324 (NH), 1731, 1681 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.34–7.27 (m, 5H, *H* arom), 7.19 (s, 1H, NN*H*COOC(CH$_3$)$_3$), 5.43 (s, 1H, N*H*COOCH$_2$Ph), 5.23 (d, 1H, *J*=6.0 Hz, C*H*CH$_3$), 5.14–5.05 (m, 2H, NHCOOCH_2Ph), 4.92–4.70 (m, 1H, C*H*CH$_3$), 3.70 (s, 3H, OCH_3), 1.49–1.42 (m, 12H, CHCH_3 and NNHCOOC(CH_3)$_3$), 1.36 (d, 3H, *J*=6.0 Hz, CHCH_3); ^{13}C NMR ($CDCl_3$) δ (ppm) 172.9 (*C*ON(NHBoc)), 165.7 (*C*OOMe), 156.0 (NH*C*OOCH$_2$Ph), 137.0 (Ar*C*), 129.2, 128.8, 128.6 (Ar*C*H), 82.8 (NNHCOO*C*(CH$_3$)$_3$), 67.5 (NHCOOCH_2Ph), 55.2 (*C*HCH$_3$), 53.2 (OCH$_3$), 47.4 (*C*HCH$_3$), 28.7 (NNHCOOC(CH_3)$_3$), 19.2 (CH*C*H$_3$), 14.5 (CH*C*H$_3$); HRMS (ESI) calculated for $C_{20}H_{29}N_3NaO_7$ $[M+Na]^+$ *m*/*z* 446.1898, found 446.1885.

3.8.2. Z-Alaψ[CON(NHBoc)](L,D)Ala-OMe **6b**

Eluent for column chromatography: EtOAc/petroleum ether (15/85 then 40/60); yield 68%, oil; IR (NaCl) ν_{max}/cm^{-1} 3313 (NH), 1742, 1678 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.33–7.27 (m, 5H, *H* arom), 7.04 (s, 0.5H, NN*H*COOC(CH$_3$)$_3$), 6.94 (s, 0.5H, NN*H*COOC(CH$_3$)$_3$), 5.49 (s, 0.5H, N*H*COOCH$_2$Ph), 5.38 (s, 0.5H, N*H*COOCH$_2$Ph), 5.34–5.03 (m, 3H, NHCOOCH_2Ph and C*H*CH$_3$), 4.39 (qd, 1H, *J*=7.3, 6.8 Hz, C*H*CH$_3$), 3.71 (s, 1.5H, OCH_3), 3.69 (s, 1.5H, OCH_3), 1.47–1.30 (m, 15H, 2CHCH_3 and NHCOOC(CH_3)$_3$); ^{13}C NMR ($CDCl_3$) δ (ppm) 177.3, 176.1 (*C*ON(NHBoc)), 173.4, 172.6 (*C*OOMe), 156.2 (NNHCOO^{t}Bu), 155.7, 155.1 (NH*C*OOCH$_2$Ph), 137.1, 136.9 (Ar*C*), 129.0, 128.6 (Ar*C*H), 83.8, 82.9, 82.6 (NNHCOO*C*(CH$_3$)$_3$), 67.5 (NHCOOCH_2Ph), 55.2, 54.3 (*C*HCH$_3$), 53.2, 53.0 (OCH$_3$), 48.0, 47.3 (*C*HCH$_3$), 28.6, 28.4 (NNHCOOC(CH_3)$_3$), 19.4, 19.0 (CH*C*H$_3$), 14.4, 14.2 (CH*C*H$_3$); HRMS (ESI) calculated for $C_{20}H_{29}N_3NaO_7$ $[M+Na]^+$ *m*/*z* 446.1898, found 446.1885.

3.8.3. Z-Alaψ[CON(NHBoc)]Ala-OEt **6c**

Eluent for column chromatography: EtOAc/petroleum ether (15/85 then 30/70); yield 73%, oil; IR (NaCl) ν_{max}/cm^{-1} 3313 (NH), 1742, 1678 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.33–7.20 (m, 6H, *H* arom and NN*H*COOC(CH$_3$)$_3$), 5.48–5.31 (m, 1H, C*H*CH$_3$), 5.20 (d, 1H, *J*=6.4 Hz, N*H*COOCH$_2$Ph), 5.14 (d, 1H, *J*=12.2 Hz, NHCOOCH_2Ph), 5.03 (d, 1H, *J*=12.2 Hz, NHCOOCH_2Ph), 4.90–4.68 (m, 1H, C*H*CH$_3$), 4.16 (q, 2H, *J*=7.1 Hz, OCH_2CH$_3$), 1.49 (s, 9H, NNHCOOC(CH_3)$_3$), 1.36 (d, 3H, *J*=6.8 Hz, CHCH_3), 1.32–1.29 (m, 3H, CHCH_3), 1.25 (t, 3H, *J*=7.1 Hz, OCH$_2$CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm) 177.4 (*C*ON(NHBoc)), 172.6 (*C*OOEt), 156.2 (NNHCOO^{t}Bu), 155.6 (NH*C*OOCH$_2$Ph), 137.0 (Ar*C*), 129.1, 128.6 (Ar*C*H), 82.6 (NHCOO*C*(CH$_3$)$_3$), 67.4 (NHCOOCH$_2$Ph), 66.2 (OCH$_2$CH$_3$), 55.3 (*C*HCH$_3$), 47.4 (*C*HCH$_3$), 28.7 (NNHCOOC(CH_3)$_3$), 19.2 (CH*C*H$_3$), 14.7 (OCH$_2$CH_3), 14.5 (CH*C*H$_3$);

HRMS (ESI) calculated for $C_{21}H_{31}N_3NaO_7$ $[M+Na]^+$ m/z 460.2054, found 460.2042.

3.8.4. Z-Alaψ[CON(NHBoc)]Ala-O^{t}Bu ***6d***

Eluent for column chromatography: EtOAc/petroleum ether (15/85 then 30/70); yield 87%, white solid, mp=146 °C; IR (KBr) ν_{max}/cm^{-1} 3282 (NH), 1795, 1751, 1695, 1677 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.34 (s, 5H, *H* arom), 6.90 (s, 0.5H, NN*H*COOC$(CH_3)_3$), 6.55 (s, 0.5H, NN*H*COOC$(CH_3)_3$), 5.71 (d, 0.5H, *J*=6.0 Hz, N*H*COOCH$_2$Ph), 5.56 (d, 0.5H, *J*=6.0 Hz, N*H*COOCH$_2$Ph), 5.29–5.03 (m, 3H, NHCOOC*H*$_2$Ph and C*H*CH$_3$), 4.74–4.64 (m, 1H, C*H*CH$_3$), 1.66–1.37 (m, 24H, NNHCOOC(C*H*$_3$)$_3$, COOC(C*H*$_3$)$_3$, and 2CHC*H*$_3$); ^{13}C NMR ($CDCl_3$) δ (ppm) 176.1 (*C*ON(NHBoc)), 172.3 (*C*OO^{t}Bu), 155.8 (NNH*C*OO^{t}Bu), 155.2 (NH*C*OOCH$_2$Ph), 137.2 (Ar*C*), 129.1, 128.6 (Ar*C*H), 83.8, 83.0 (NNHCOO*C*$(CH_3)_3$ and COO*C*$(CH_3)_3$), 67.2 (NHCOO*C*H$_2$Ph), 55.0 (*C*HCH$_3$), 48.1 (*C*HCH$_3$), 28.7, 28.6 (NNHCOOC(*C*H$_3$)$_3$ and COOC(*C*H$_3$)$_3$), 19.7 (CH*C*H$_3$), 14.4 (CH*C*H$_3$); HRMS (ESI) calculated for $C_{23}H_{35}N_3NaO_7$ $[M+Na]^+$ m/z 488.2373, found 488.2337.

3.8.5. Z-Alaψ[CON(NHBoc)]Gly-OMe ***6e***

Eluent for column chromatography: EtOAc/petroleum ether (15/85 then 40/60); yield 86%, oil; IR (NaCl) ν_{max}/cm^{-1} 3324 (NH), 1731, 1681 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.35–6.80 (m, 6H, *H* arom and NN*H*COOC$(CH_3)_3$), 5.55 (d, 1H, *J*=7.1 Hz, N*H*COOCH$_2$Ph), 5.14 (d, 1H, *J*=12.0 Hz, NHCOOC*H*$_2$Ph), 5.05 (d, 1H, *J*=12.0 Hz, NHCOOC*H*$_2$Ph), 5.00–4.50 (m, 1H, C*H*CH$_3$), 4.91–4.51 (m, 2H, C*H*$_2$COOMe), 3.75 (s, 3H, OC*H*$_3$), 1.48 (s, 9H, NNHCOOC(C*H*$_3$)$_3$), 1.33 (d, 3H, *J*=6.8 Hz, CHC*H*$_3$); ^{13}C NMR ($CDCl_3$) δ (ppm) 176.2 (*C*ON(NHBoc)), 170.1 (*C*OOMe), 156.1 (NNH*C*OO^{t}Bu), 154.4 (NH*C*OOCH$_2$Ph), 137.1 (Ar*C*), 129.2, 128.7 (Ar*C*H), 83.5 (NNHCOO*C*$(CH_3)_3$), 67.5 (NHCOO*C*H$_2$Ph), 53.1 (O*C*H$_3$), 48.9 (*C*H$_2$COOMe), 47.3 (*C*HCH$_3$), 28.7 (NNHCOOC(*C*H$_3$)$_3$), 19.4 (CH*C*H$_3$); HRMS (ESI) calculated for $C_{19}H_{27}N_3NaO_7$ $[M+Na]^+$ m/z 432.1741, found 432.1724.

3.8.6. Z-Pheψ[CON(NHBoc)]Ala-OMe ***6f***

Eluent for column chromatography: EtOAc/petroleum ether (20/80); yield 95%, oil; IR (ATR) ν_{max}/cm^{-1} 3331, 3251 (NH), 1720, 1702, 1681 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.32–7.19 (m, 11H, *H* arom and NN*H*COOC$(CH_3)_3$), 5.70 (d, 1H, *J*=6.9 Hz, N*H*COOCH$_2$Ph), 5.21–4.94 (m, 4H, NHCOOC*H*$_2$Ph, C*H*CH$_2$Ph and C*H*CH$_3$), 3.66 (s, 3H, OC*H*$_3$), 3.19–3.12 (m, 1H, CHC*H*$_2$Ph), 2.86–2.77 (m, 1H, CHC*H*$_2$Ph), 1.55–1.40 (m, 12H, NNHCOOC(C*H*$_3$)$_3$ and CHC*H*$_3$); ^{13}C NMR ($CDCl_3$) δ (ppm) 176.1 (*C*ON(NHBoc)), 172.7 (*C*OOMe), 157.9 (NNH*C*OO^{t}Bu), 156.4 (NH*C*OOCH$_2$Ph), 137.0, 136.8 (Ar*C*), 130.2, 129.9, 128.8, 128.2, 127.2, 126.6 (Ar*C*H), 82.4 (NNHCOO*C*$(CH_3)_3$), 67.1 (NHCOOCH$_2$Ph), 55.3 (*C*HCH$_2$Ph), 52.8 (O*C*H$_3$), 52.5 (*C*HCH$_3$), 28.5 (NNHCOOC(*C*H$_3$)$_3$), 14.3 (CH*C*H$_3$); HRMS (ESI) calculated for $C_{26}H_{33}N_3NaO_7$ $[M+Na]^+$ m/z 522.2211, found 522.2185.

3.8.7. Boc-Pheψ[CON(NHBoc)]Ala-OMe ***6i***

Eluent for column chromatography: EtOAc/petroleum ether (30/70); yield 93%, oil; IR (ATR) ν_{max}/cm^{-1} 3320 (NH) 1733, 1720, 1681 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.39–7.18 (m, 6H, *H* arom and NN*H*COOC$(CH_3)_3$), 5.29–4.90 (m, 3H, N*H*COOCH$_2$Ph, C*H*CH$_2$Ph and C*H*CH$_3$), 3.71 (s, 3H, OC*H*$_3$), 3.18–3.15 (m, 1H, CHC*H*$_2$Ph), 2.83–2.72 (m, 1H, CHC*H*$_2$Ph), 1.56–1.21 (m, 21H, NHCOOC(C*H*$_3$)$_3$, NNHCOOC(C*H*$_3$)$_3$ and CHC*H*$_3$); ^{13}C NMR ($CDCl_3$) δ (ppm) 176.5 (*C*ON(NHBoc)), 171.8 (*C*OOMe), 171.7 (*C*ON(NH*C*OO^{t}Bu)), 155.8 (NH*C*OO^{t}Bu), 137.3 (Ar*C*), 130.2, 128.9, 127.3 (Ar*C*H), 82.7 (NNHCOO*C*$(CH_3)_3$), 80.3 (NHCOO*C*$(CH_3)_3$), 55.4 (*C*HCH$_2$Ph), 54.1 (CHCH$_2$Ph), 53.1 (O*C*H$_3$), 52.0 (*C*HCH$_3$), 29.0, 28.9, 28.7 (NNHCOOC(*C*H$_3$)$_3$ and NHCOOC(*C*H$_3$)$_3$), 14.6 (CH*C*H$_3$); HRMS (ESI) calculated for $C_{23}H_{35}N_3NaO_7$ $[M+Na]^+$ m/z 488.2367, found 488.2337.

3.9. Preparation of 6y

To a stirred solution of 2,2′-dipyridyl (0.5 mmol) in methanol (12 mL) were added successively a catalytic amount of 10% Pd/C, a solution of *Z*-Pheψ[CON(NHBoc)]Ala-OMe **6f** (0.50 g, 1 mmol) in methanol (12 mL) and Fmoc-OSu (1 mmol). The resulting mixture was flushed with H_2 and vigorously stirred until completion (monitored by TLC). The reaction mixture was filtered on Celite and evaporated to dryness. The resulting oily solid was dissolved in EtOAc (125 mL) and washed with 10% aqueous HCl (3×125 mL), water (3×125 mL) and dried over $MgSO_4$. Solvent was evaporated under vacuum and the crude product was purified by column chromatography.

3.9.1. Fmoc-Pheψ[CON(NHBoc)]Ala-OMe ***6y***

Eluent for column chromatography: EtOAc/petroleum ether (15/85); yield 89%, oil; IR (ATR) ν_{max}/cm^{-1} 3310 (NH), 1736, 1676 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.82–7.70 (m, 2H, *H* arom), 7.44–7.24 (m, 12H, *H* arom and NHBoc), 5.86–5.59 (m, 1H, N*H*Fmoc), 5.28–5.02 (m, 3H, C*H*$_{Fmoc}$ and C*H*$_{2Fmoc}$), 4.37–4.35 (m, 1H C*H*CH$_3$), 4.19–4.11 (m, 1H, C*H*CH$_2$Ph), 3.66 (s, 3H, OC*H*$_3$), 3.28–3.24 (m, 1H, CHC*H*$_2$Ph), 2.99–2.95 (m, 1H, CHC*H*$_2$Ph), 1.55–1.50 (m, 12H, NNHCOOC(C*H*$_3$)$_3$ and CHC*H*$_3$); ^{13}C NMR ($CDCl_3$) δ (ppm) 176.1 (*C*ON(NHBoc)), 172.7 (*C*OOMe), 156.3 (NNH*C*OO^{t}Bu), 155.8 (*C*O$_{Fmoc}$), 144.7, 144.3, 137.1, 136.9 (Ar*C*), 130.3, 128.8, 128.4, 128.1, 127.5, 127.3, 125.7, 125.6, 120.3 (Ar*C*H), 82.5 (NNHCOO*C*$(CH_3)_3$), 67.5, 67.1 (FmocCH$_2$), 55.3 (FmocCH), 52.9 (*C*HCH$_2$Ph), 52.5 (O*C*H$_3$), 47.5 (*C*HCH$_3$), 38.2 (CHCH$_2$Ph), 28.6 (NNHCOOC(*C*H$_3$)$_3$), 14.7, 14.4 (CH*C*H$_3$); HRMS (ESI) calculated for $C_{33}H_{37}N_3NaO_7$ $[M+Na]^+$ m/z 610.2524, found 610.2518.

3.10. Typical experimental procedure for the preparation of 7

Compound **6** (1 mmol) was dissolved in THF (10 mL). A solution of 2.5 M LiOH (10 mL, 25 mmol) was added in one portion and the resulting solution was stirred for 1 h. The reaction was quenched by addition of ice and extracted with chloroform (3×20 mL). The aqueous layer was acidified until pH=2 by 1 M HCl and extracted with EtOAc (8×20 mL). The organic layers were combined, dried over $MgSO_4$ and evaporated to dryness to give the pure product.

3.10.1. Z-Alaψ[CON(NHBoc)]Ala-OH ***7a***

Yield 98%, gum; IR (NaCl) ν_{max}/cm^{-1} 3291 (OH), 1727, 1684 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 10.00 (s, 1H, COO*H*), 7.83 (s, 1H, NN*H*COO^{t}Bu), 7.32–7.27 (m, 5H, *H* arom), 5.9 (d, 1H, *J*=6.0 Hz, N*H*COOCH$_2$Ph), 5.2–4.7 (m, 4H, COOC*H*$_2$Ph and 2C*H*CH$_3$), 1.48 (s, 9H, NNHCOOC(C*H*$_3$)$_3$), 1.41 (d, 3H, *J*=6.8 Hz, CHC*H*$_3$), 1.33 (d, 3H, *J*=6.8 Hz, CHC*H*$_3$); ^{13}C NMR ($CDCl_3$) δ (ppm) 177.5 (*C*OOH), 176.5 (*C*ON(NHBoc)), 156.8 (NH*C*OOCH$_2$Ph), 156.1 (NNH*C*OO^{t}Bu), 136.6 (Ar*C*), 129.1, 128.6, 128.6 (Ar*C*H), 82.7 (NNHCOO*C*$(CH_3)_3$), 67.6 (NHCOOCH$_2$Ph), 56.4, 47.5 (*C*HCH$_3$), 28.6 (NNHCOOC(*C*H$_3$)$_3$), 18.6, 14.1 (CH*C*H$_3$); HRMS (ESI) calculated for $C_{19}H_{27}N_3NaO_7$ $[M+Na]^+$ m/z 432.1741, found 432.1760.

3.10.2. Z-Alaψ[CON(NHBoc)]Gly-OH ***7e***

Yield 99%, gum; IR (KBr) ν_{max}/cm^{-1} 3304 (OH), 1730, 1680 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.86 (s, 1H, COO*H*), 7.35–7.20 (m, 5H, *H* arom), 7.03 (s, 1H, NN*H*COO^{t}Bu), 5.55 (s, 1H, N*H*COOCH$_2$Ph), 5.13–4.90 (m, 4H, COOC*H*$_2$Ph, C*H*CH$_3$ and C*H*$_2$COOH), 3.80 (s, 1H, C*H*$_2$COOH), 1.48 (s, 9H, NNHCOOC(C*H*$_3$)$_3$), 1.32 (d, 3H, *J*=5.8 Hz, CHC*H*$_3$); ^{13}C NMR ($CDCl_3$) δ (ppm) 176.4 (*C*OOH), 172.3 (*C*ON(NHBoc)), 156.8 (NH*C*OOCH$_2$Ph), 155.1 (NNH*C*OO^{t}Bu), 136.7 (Ar*C*), 129.1, 128.8, 128.7 (Ar*C*H), 83.7 (NNHCOO*C*$(CH_3)_3$), 67.8 (NHCOOCH$_2$Ph), 49.8 (*C*H$_2$COOH), 47.4 (*C*HCH$_3$), 28.7 (NNHCOOC(*C*H$_3$)$_3$), 18.8 (CH*C*H$_3$); HRMS (ESI) calculated for $C_{18}H_{25}N_3NaO_7$ $[M+Na]^+$ m/z 418.1585, found 418.1567.

3.10.3. Boc-Pheψ[CON(NHBoc)]Ala-OH ***7i***

Yield 75%, white solid, mp=172 °C; IR (ATR) ν_{max}/cm^{-1} 3343, 3238 (NH), 1748, 1733 (C=O); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.39–7.18 (m, 6H, *H* arom and NN*H*COOC(CH_3)$_3$), 5.29–4.90 (m, 3H, N*H*COOC(CH_3)$_3$, C*H*CH$_3$ and C*H*CH$_2$Ph), 3.18–3.15 (m, 1H, CHC*H*$_2$Ph), 2.83–2.72 (m, 1H, CHC*H*$_2$Ph), 1.56–1.21 (m, 21H, NHCOOC(C*H*$_3$)$_3$, NNHCOOC(C*H*$_3$)$_3$ and CHC*H*$_3$); ^{13}C NMR ($CDCl_3$) δ (ppm) 176.5 (*C*OOH), 171.8 (*C*ON(NHBoc)), 155.8 (NH*C*OO^{t}Bu and NNH*C*OO^{t}Bu), 137.3 (Ar*C*), 130.2, 128.9, 127.3 (Ar*C*H), 82.7 (NNHCOO*C*(CH$_3$)$_3$), 80.3 (NHCOO*C*(CH$_3$)$_3$), 55.4 (*C*HCH$_2$Ph), 54.1 (*C*HCH$_3$), 52.0 (CH*C*H$_2$Ph), 29.0, 28.9 (NHCOOC(*C*H$_3$)$_3$ and NNHCOOC(*C*H$_3$)$_3$), 14.6 (CH*C*H$_3$); HRMS (ESI) calculated for $C_{22}H_{33}N_3NaO_7$ $[M+Na]^+$ *m/z* 474.2211, found 474.2214.

3.10.4. Fmoc-Pheψ[CON(NHBoc)]Ala-OH ***7y***

Yield 83%, white solid, mp=65 °C; IR (ATR) ν_{max}/cm^{-1} 3310 (NH), 1736, 1676 (C=O); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.44–7.24 (m, 14H, *H* arom and NHBoc), 5.61–5.59 (m, 1H, N*H*COOFm), 5.27–4.80 (m, 3H, C*H*$_{Fmoc}$ and C*H*$_{2Fmoc}$), 4.27–4.08 (m, 2H, C*H*CH$_2$Ph and C*H*CH$_3$), 3.22–3.18 (m, 1H, CHC*H*$_2$Ph), 2.89–2.86 (m, 1H, CHC*H*$_2$Ph), 1.49–1.44 (m, 12H, NNHCOOC(C*H*$_3$)$_3$ and CHC*H*$_3$); ^{13}C NMR ($CDCl_3$) δ (ppm) 175.7 (*C*OOH), 174.3 (*C*ON(NHBoc)), 157.0 (NNH*C*OO^{t}Bu), 156.3 (*C*O$_{Fmoc}$), 144.4, 141.9, 136.8 (Ar*C*), 130.3, 129.2, 128.3, 127.7, 125.7, 120.6 (Ar*C*H), 83.3 (NNHCOO*C*(CH$_3$)$_3$), 68.0 (Fmoc*C*H$_2$), 57.1 (Fmoc*C*H), 52.6 (*C*HCH$_2$Ph), 47.6 (*C*HCH$_3$), 38.3 (CH*C*H$_2$Ph), 28.2 (NNHCOOC(*C*H$_3$)$_3$), 14.8, 14.4 (CH*C*H$_3$); HRMS (ESI) calculated for $C_{32}H_{35}N_3NaO_7$ $[M+Na]^+$ *m/z* 596.2367, found 596.2359.

3.11. Typical experimental procedure for the preparation of 8

Compound **6** (1 mmol) was dissolved in a solution of HCl (3 M) in EtOAc (10 mL). The resulting solution was stirred until completion (monitored by TLC), cooled with an ice-water bath, adjusted to pH=7 by addition of $NaHCO_3$ (saturated solution) and extracted with EtOAc (3×10 mL). The organic extracts were combined, washed with a saturated solution of NaCl (3×10 mL) and dried over $MgSO_4$. Solvent was evaporated under vacuum to give the crude product. Purification by column chromatography was performed using EtOAc/petroleum ether as eluent if necessary.

3.11.1. Z-Alaψ[CON(NH$_2$)]Ala-OMe ***8a***

Eluent for column chromatography: EtOAc/petroleum ether (60/40); yield 86%, oil; IR (KBr) ν_{max}/cm^{-1} 3342, 3246 (NH), 1654 (C=O); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.34–7.27 (m, 5H, *H* arom), 5.73 (d, 1H, *J*=7.4 Hz, N*H*COOCH$_2$Ph), 5.33–5.24 (m, 1H, C*H*CH$_3$), 5.19–5.09 (m, 3H, NHCOOC*H*$_2$Ph and C*H*CH$_3$), 4.08 (s, 2H, NN*H*$_2$), 3.72 (s, 3H, OC*H*$_3$), 1.44 (d, 3H, *J*=7.4 Hz, CHC*H*$_3$), 1.35 (d, 3H, *J*=6.8 Hz, CHC*H*$_3$); ^{13}C NMR ($CDCl_3$) δ (ppm) 176.3 (*C*ON(NH$_2$)), 172.5 (*C*OOCH$_3$), 156.1 (NH*C*OOCH$_2$Ph), 137.2 (Ar*C*), 129.1, 128.8, 128.6 (Ar*C*H), 67.5, 67.2 (NHCOO*C*H$_2$Ph), 53.3 (*C*HCH$_3$), 53.9 (OCH$_3$), 48.1 (*C*HCH$_3$), 19.9 (CH*C*H$_3$), 14.4 (CH*C*H$_3$); HRMS (ESI) calculated for $C_{15}H_{21}N_3NaO_5$ $[M+Na]^+$ *m/z* 346.1373, found 346.1367.

3.11.2. Z-Alaψ[CON(NH$_2$)]Gly-OMe ***8e***

Eluent for column chromatography: EtOAc/petroleum ether (60/40); yield 72%, oil; IR (ATR) ν_{max}/cm^{-1} 3339 (NH), 1721, 1659 (C=O); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.34–7.26 (m, 5H, *H* arom), 5.70 (d, 1H, *J*=7.6 Hz, N*H*COOCH$_2$Ph), 5.29–5.24 (m, 1H, C*H*CH$_3$), 5.11 (d, 2H, *J*=10.1 Hz, NHCOOC*H*$_2$Ph), 5.09 (d, 1H, *J*=12.8 Hz, C*H*$_2$COOMe), 4.60 (d, 1H, *J*=12.8 Hz, C*H*$_2$COOMe), 3.76 (s, 3H, OC*H*$_3$), 2.07 (s, 2H, NN*H*$_2$), 1.38 (d, 3H, *J*=6.8 Hz, CHC*H*$_3$); ^{13}C NMR ($CDCl_3$) δ (ppm) 176.7 (*C*ON(NH$_2$)), 170.0 (*C*OOMe), 156.4 (NH*C*OOCH$_2$Ph), 137.2 (Ar*C*), 129.1, 128.7 (Ar*C*H), 67.3 (NHCOO*C*H$_2$Ph), 53.1 (*C*HCH$_3$), 51.6 (*C*H$_2$COOMe), 47.7 (OCH$_3$), 19.4 (CH*C*H$_3$); HRMS (ESI) calculated for $C_{14}H_{19}N_3NaO_5$ $[M+Na]^+$ *m/z* 332.1217, found 332.1182.

3.11.3. Z-Pheψ[CON(NH$_2$)]Ala-OMe ***8f***

Eluent for column chromatography: EtOAc/petroleum ether (30/70 then 50/50); yield 70%, oil; IR (ATR) ν_{max}/cm^{-1} 3356, 3256 (NH), 1718, 1658 (C=O); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.38–7.19 (m, 10H, *H* arom), 5.96–5.55 (m, 2H, N*H*COOCH$_2$Ph and C*H*CH$_2$Ph), 5.25 (q, 1H, *J*=6.6 Hz, C*H*CH$_3$), 5.10 (d, 1H, *J*=12.4 Hz, NHCOOC*H*$_2$Ph), 5.04 (d, 1H, *J*=12.4 Hz, NHCOOC*H*$_2$Ph), 3.66 (s, 3H, OC*H*$_3$), 3.55 (s, 2H, NN*H*$_2$), 3.08 (dd, 1H, *J*=5.7, 7.6 Hz, CHC*H*$_2$Ph), 2.95 (dd, 1H, *J*=5.7, 7.6 Hz, CHC*H*$_2$Ph), 1.23 (d, 3H, *J*=6.6 Hz, CHC*H*$_3$); ^{13}C NMR ($CDCl_3$) δ (ppm) 174.5 (*C*ON(NH$_2$)), 172.4 (*C*OOMe), 156.1 (NH*C*OOCH$_2$Ph), 137.2, 137.1 (Ar*C*), 130.1, 129.3, 128.9, 128.7, 128.5, 128.4, 127.3 (Ar*C*H), 67.1 (NHCOO*C*H$_2$Ph), 53.2 (*C*HCH$_3$), 52.9 (OCH$_3$), 52.2 (*C*HCH$_2$Ph), 40.6 (CH*C*H$_2$Ph), 14.1 (CH*C*H$_3$); HRMS (ESI) calculated for $C_{21}H_{25}N_3NaO_5$ $[M+Na]^+$ *m/z* 422.1686, found 422.1683.

3.12. Preparation of 9f

Compound **8f** (0.40 g, 1 mmol) was dissolved in THF (10 mL). A solution of 2.5 M LiOH (10 mL, 25 mmol) was added in one portion and the resulting solution was stirred for 1 h. The reaction was quenched by addition of ice and extracted with chloroform (3×20 mL). The aqueous layer was acidified until pH=2 by 1 M HCl and extracted with EtOAc (8×20 mL). The organic layers were combined, dried over $MgSO_4$ and evaporated to dryness to give the pure product.

3.12.1. Z-Pheψ[CON(NH$_2$)]Ala-OH ***9f***

Yield 85%, oil; IR (ATR) ν_{max}/cm^{-1} 3650 (OH), 3425 (NH), 1721, 1661, 1606 (C=O); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.32–7.21 (m, 10H, *H* arom), 6.03 (d, 1H, *J*=8.7 Hz, N*H*COOCH$_2$Ph), 5.69–5.66 (m, 1H, C*H*CH$_3$), 5.28–5.24 (m, 1H, C*H*CH$_2$Ph), 5.09 (d, 1H, *J*=12.5 Hz, NHCOOC*H*$_2$Ph), 5.01 (d, 1H, *J*=12.5 Hz, NHCOOC*H*$_2$Ph), 3.05–2.97 (m, 2H, CHC*H*$_2$Ph), 2.07 (s, 2H, NN*H*$_2$), 1.24 (d, 3H, *J*=9.0 Hz, CHC*H*$_3$); ^{13}C NMR ($CDCl_3$) δ (ppm) 177.1 (*C*OOH), 175.2 (*C*ON(NH$_2$)), 156.6 (NH*C*OOCH$_2$Ph), 137.0, 136.9 (Ar*C*), 130.1, 129.9, 129.0, 128.9, 128.6, 128.4, 127.4 (Ar*C*H), 67.4 (NHCOO*C*H$_2$Ph), 53.5 (*C*HCH$_3$), 52.3 (*C*HCH$_2$Ph), 40.2 (CH*C*H$_2$Ph), 13.9 (CH*C*H$_3$); HRMS (ESI) calculated for $C_{20}H_{23}N_3NaO_7$ $[M+Na]^+$ *m/z* 408.1530, found 408.1554.

3.13. Typical experimental procedure for the oligomerization reaction in solution

To a stirred solution of the 1:1[α:α-*N*-amino]mer acid form **4j** or **14** (2 mmol) and pyridine (2 mmol) in dry CH_2Cl_2 (10 mL) kept under nitrogen atmosphere was added cyanuric fluoride (0.4 mL, 5 mmol) at −20 °C. After stirring at room temperature for 3 h, crushed ice and 10 mL of CH_2Cl_2 were added. The organic layer was separated and the aqueous layer extracted once with 5 mL of CH_2Cl_2. The combined organic layers were extracted with 10 mL of ice-cold water and dried ($MgSO_4$) and then the solvent was removed under vacuum at room temperature to give the pure acid fluoride. A solution of acid fluoride in 2.5 mL of CH_2Cl_2 was added dropwise to a cold stirred solution (−10 °C) of amine **13** (1.77 mmol) and $NaHCO_3$ (3.76 mmol) in 6.3 mL of dry CH_2Cl_2. The mixture was allowed to warm to room temperature and stirred for 10 h. NaF salt was filtered and the solvent was evaporated. The residue was chromatographied on silica gel.

To obtain oligomer **12**, amine **5j** was added to a mixture of acid fluoride of **4j** and $NaHCO_3$ in CH_2Cl_2 in order to minimize the formation of diketopiperazine **11**.

3.13.1. Boc-[Pheψ[CON(NPht)]Ala]$_2$OCH$_2$Ph ***12***

Eluent for column chromatography: EtOAc/petroleum ether (20/80 then 30/70); Yield 55%, white solid, mp=95 °C; IR (1 mM in CH_2Cl_2) ν_{max}/cm^{-1} 3430, 3396, 3310 (NH), 1790, 1745, 1701, 1682 (C=O); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.15 (d, 0.3H, *J*=8.8 Hz,

NHCH(CH_3)), 8.10 (d, 0.7H, J=8.6 Hz, NHCH(CH_3)), 7.95–7.60 (m, 8H, Hpht), 7.50–6.90 (m, 15H, *H* arom), 5.85 (q, 0.3H, J=6.8 Hz, CHCH$_3$), 5.40–4.90 (m, 4H, CHCH$_3$, CHCH$_2$Ph and COOCH_2Ph), 4.65 (q, 0.7H, J=7.3 Hz, CHCH$_3$), 4.50 (q, 0.3H, J=7.3 Hz, CHCH$_3$), 4.30–4.20 (m, 1.7H, NHCO^{t}Bu and CHCH$_2$Ph), 4.00 (d, 3H, J=10.6 Hz, NH), 3.30–2.50 (m, 4H, CHCH_2Ph), 1.54 (d, 2H, J=6.9 Hz, CHCH_3), 1.45 (d, 1H, J=6.8 Hz, CHCH_3), 1.26–1.08 (m, 12H, CHCH_3 and COOC(CH_3)$_3$); HRMS (ESI) calculated for $C_{52}H_{50}N_6NaO_{11}$ $[M+Na]^+$ m/z 957.3430, found 957.3422.

3.13.2. Boc-[Pheψ[CON(NPht)]Ala]$_3$OCH$_2$Ph ***15***

Eluent for column chromatography: EtOAc/petroleum ether (40/60 then 50/50); yield 55%, white solid, mp=116 °C; IR (0.7 mM in CH_2Cl_2) ν_{max}/cm^{-1} 3396, 3313 (NH), 1797, 1743, 1702, 1677 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.40–8.20 (m, 2H, 2NHCH(CH_3)), 8.00–7.70 (m, 12H, Hpht), 7.50–6.90 (m, 20H, *H* arom), 5.50–4.00 (m, 9H, COOCH_2Ph, 3CHCH$_3$, 3CHCH$_2$Ph and NH), 3.30–2.50 (m, 6H, 3CHCH_2Ph), 1.40–1.00 (m, 18H, COOC(CH_3)$_3$ and 3CHCH_3); HRMS (ESI) calculated for $C_{72}H_{67}N_9Na_2O_{15}$ $[M+2Na]^{2+}$ m/z 671.7271, found 671.7258.

3.13.3. Boc-[Pheψ[CON(NPht)]Ala]$_4$OCH$_2$Ph ***16***

Eluent for column chromatography: EtOAc/petroleum ether (50/50 then 70/30); yield 35%, white solid, mp=118 °C; IR (0.5 mM in CH_2Cl_2) ν_{max}/cm^{-1} 3396, 3313 (NH), 1795, 1741, 1704, 1677 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.30–8.00 (m, 3H, 3NHCH(CH_3)), 7.90–7.50 (m, 16H, Hpht), 7.40–6.70 (m, 25H, *H* arom), 5.40–4.20 (m, 10H, COOCH_2Ph, 4CHCH$_3$ and 4CHCH$_2$Ph), 3.90 (m, 1H, NHCOOC(CH_3)$_3$), 3.20–2.30 (m, 8H, 4CHCH_2Ph), 1.40–0.90 (m, 21H, COOC(CH_3)$_3$ and 4CHCH_3); HRMS (ESI) calculated for $C_{92}H_{84}N_{12}Na_2O_{19}$ $[M+2Na]^{2+}$ m/z 853.2880, found 852.2853.

3.14. Typical experimental procedure for the oligomerization reaction on solid phase

Step 1: Fmoc-Leu-WANG (cross linked with 1% DVB, 200–400 mesh, 0.85 mequiv/g) was placed in a dry flask and sufficient DMF was added to cover the resin, which was allowed to swell at room temperature for 30 min and filtered.

Step 2: Fmoc group was removed by three treatments with a solution of piperidine (25% in DMF) for 2, 5 and 8 min. The resin was filtered and washed successively with CH_2Cl_2 (3×1 min), MeOH (3×1 min) and then with DMF (3×1 min).

Step 3: a solution of dipeptide **7y**, TBTU and HOBt (3 equiv relative to the resin loading) was added to the resin. DIEA (9 equiv) was added and the resulting mixture was stirred for 2 h. The reaction was performed a second time for 4 h. The resin was then filtered and washed with CH_2Cl_2 (3×1 min), MeOH (3×1 min) and DMF (3×1 min).

Steps 2 and 3 were repeated until the desired number of dipeptides had been attached.

Step 4: the dried peptide–resin was placed in a round-bottom flask that contained a magnetic stir bar and cooled in an ice-water bath. The cleavage mixture was cooled (0.5 mL H_2O/9.5 mL TFA) and added to the cooled peptide–resin. After all the cleavage mixture had been added, the flask was removed from the ice bath and allowed to warm to room temperature. The reaction mixture was stirred at room temperature for 1.5 h. Cold Et_2O (50 mL or more) was added into the flask after the reaction time had elapsed to precipitate the peptide. If the peptide did not precipitate, the resin was washed several times with TFA and the solution obtained was concentrated under vacuum and lyophylised.

3.14.1. H-[Pheψ[CON(NH$_2$)]Ala]$_2$Leu-OH ***17***

Yield 20%, gum; ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm) 8.34–8.30 (m, 2H, 2NH), 8.30 (s, 2H, NNH_2), 7.34–7.19 (m, 10H, *H* arom), 5.61–5.58 (m, 1H, CHCH$_2$Ph), 5.06–5.00 (m, 2H, 2CHCH$_3$), 4.20–4.16 (m, 1H, CHCH$_2$CH(CH_3)$_2$), 4.47 (s, 5H, CHCH$_2$Ph and NNH_2), 3.33–3.09 (m, 4H, 2CHCH_2Ph), 1.70–1.45 (m, 3H, CHC$H_2$$CH$($CH_3$)$_2$), 1.33 (d, 3H, J=7.2 Hz, CHCH_3), 1.08 (d, 3H, J=7.2 Hz, CHCH_3), 0.89 (d, 3H, J=6.2 Hz, CHCH$_2$CH(CH_3)$_2$), 0.83 (d, 3H, J=6.2 Hz, CHCH$_2$CH(CH_3)$_2$); HRMS (ESI) calculated for $C_{30}H_{43}N_7NaO_6$ $[M+Na]^+$ m/z 620.3169, found 620.3169.

3.14.2. H-[Pheψ[CON(NH$_2$)]Ala]$_3$Leu-OH ***18***

Yield 8%, gum; ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm) 8.25–7.98 (m, 5H, 5NH), 7.32–7.18 (m, 15H, *H* arom), 5.70–5.58 (m, 2H, 2CHCH$_2$Ph), 5.02–4.99 (m, 3H, 3CHCH$_3$), 4.74–4.64 (s, 7H, CHCH$_2$Ph and 3NNH_2), 4.30–4.05 (m, 1H, CHCH$_2$CH(CH_3)$_2$), 3.31–2.66 (m, 6H, 3CHCH_2Ph), 1.70–1.45 (m, 3H, CHC$H_2$$CH$($CH_3$)$_2$), 1.29–1.06 (m, 9H, 3CHCH_3), 0.89 (d, 3H, J=6.2 Hz, CHCH$_2$CH(CH_3)$_2$), 0.83 (d, 3H, J=6.2 Hz, CHCH$_2$CH(CH_3)$_2$); HRMS (ESI) calculated for $C_{42}H_{58}N_{10}NaO_8$ $[M+Na]^+$ m/z 853.4336, found 853.4337.

3.14.3. H-[Pheψ[CON(NH$_2$)]Ala]$_4$Leu-OH ***19***

Yield 10%, gum; NMR ^{1}H (DMSO-d_6, 300 MHz) δ (ppm) 8.26–7.98 (m, 6H, 6NH), 7.32–7.18 (m, 20H, *H* arom), 5.69–5.29 (m, 2H, 2CHCH$_2$Ph), 5.02–4.99 (m, 4H, 4CHCH$_3$), 4.74–4.64 (s, 10H, 2CHCH$_2$Ph and 4NNH_2), 4.36–4.04 (m, 1H, CHCH$_2$CH(CH_3)$_2$), 3.30–2.61 (m, 8H, 4CHCH_2Ph), 1.70–1.40 (m, 3H, CHC$H_2$$CH$($CH_3$)$_2$), 1.28–1.06 (m, 12H, 4CHCH_3), 0.89 (d, 3H, J=6.2 Hz, CHCH$_2$CH(CH_3)$_2$), 0.84 (d, 3H, J=6.2 Hz, CHCH$_2$CH(CH_3)$_2$); HRMS (ESI) calculated for $C_{54}H_{73}N_{13}NaO_{10}$ $[M+Na]^+$ m/z 1086.5495, found 1086.5487.

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