Tetrahedron 65 (2009) 9165–9179

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Straightforward, racemization-free synthesis of peptides with fairly to very bulky di- and trisubstituted glycines

Filipa C.S.C. Pinto, Sílvia M.M.A. Pereira-Lima, Hernâni L.S. Maia *

Centro de Química, University of Minho, Gualtar, P-4710-057 Braga, Portugal

ARTICLE INFO

Article history:
Received 30 July 2009
Received in revised form 2 September 2009
Accepted 7 September 2009
Available online 12 September 2009

Keywords:
α,α-Dialkylglycines
N,α,α-Trialkylglycines
Peptide synthesis
Ugi–Passerini reaction

ABSTRACT

Several fully protected tri- and pentapeptides containing a central symmetrical α,α-dialkyl glycine residue, with the alkyl group varying from methyl or ethyl to benzyl, were synthesized in good yields by a strategy based on the Ugi–Passerini reaction. Each Ugi–Passerini adduct was selectively cleaved and the product submitted to an assisted *N*,*N*′-dicyclohehylcarbodiimide coupling to an amino acid or dipeptide ester, respectively. Tripeptides as the above but containing a 4-methoxybenzyl group at the nitrogen atom of the central residue were also synthesized in fair to good yields by *N*-[(1*H*-benzotriazol-1-yl)-(dimethylamino)methylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide assisted couplings. The results reported here show that our strategy is appropriate for routine synthesis of peptides incorporating these moieties.

1. Introduction

During the last decades several authors have been concerned with the investigation of the conformation preferences imparted to peptides by inclusion of one or more residues of α,α-dialkyl glycines in the peptide chain.[1] Such preferences are governed by steric crowding and/or hindrance to rotation usually associated to α,α-dialkyl glycines, thus leading to conformational rigidity. Since rigidity increases potency and selectivity of bioactive peptides, improving their bioavailability and enhancing resistance to peptidases,[2] synthetic modifications of natural peptides and peptidomimetics needed for biological or medical applications may require generating or imposing restrictions to backbone flexibility.[3,4] Consequently, design of conformational constrained peptides is one of the approaches for development of bioactive species with high activity and selectivity toward a specific receptor.[5,6] Therefore, the above amino acids are good candidates for incorporation into the peptide chain of peptidomimetics for biological and eventual pharmacological use. In fact, with the purpose to develop antagonists able to prevent or retard recognition by enzymes, various important applications of the above compounds have been devised in connection with the modification of natural peptides or in molecules mimicking them, usually when restriction of backbone flexibility is required.[5] In addition, special conformational features imparted to the peptide backbone by these amino acid residues[6–9] may be used to modulate activity and selectivity. This can be best achieved by previous parametrization of these amino acids[10] followed by molecular dynamics simulations of the bioactive peptides[11] as modified at strategic positions by one or more of these amino acid units. After the most promising peptide sequences have been predicted, it is necessary to synthesize the required compounds. Usually, this has to start with the synthesis of the modified glycines, as with the exception of dimethyl and diethyl glycine these amino acids are not commercially available. Unfortunately, the same structural features that make these compounds interesting for the purposes described above always make their incorporation into peptides become problematic, mainly when the amino acid side chains are larger than methyl. In fact, steric crowding and conformational restriction not only make the synthetic reactions very slow, but also they tend to modify their course and lead to undesired products, which hinder purification and lower yields considerably. These difficulties are usually met already at the preliminary stages related to the synthesis of the amino acids. In our early work[12] with this class of compounds we found that the Ugi–Passerini reaction[13] is most appropriate to synthesize symmetric α,α-dialkyl glycines, since it is not affected and may even be assisted by the presence of bulky substituents within the reagent molecules; lately we have used this reaction to make various of these compounds and their simple derivatives.[14] The interest these amino acids have raised in late years led to the recent development of a few other interesting and sometimes ingenious approaches for preparation of either symmetric[15–17] or asymmetric

---

* Corresponding author. Tel.: +351 967 096 958; fax: +351 253 617 959.
E-mail address: h.maia@netcabo.pt (H.L.S. Maia).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.09.022

compounds.[18,19] Obtaining the amino acids required for incorporation into a peptide is not sufficient to reach our goal, as again steric crowding makes their insertion into a peptide chain even more problematic than the amino acid synthesis; in fact, conventional methods of peptide synthesis become unpractical as reflected by the low yields observed in the rare cases where a product is obtained.[20] On the contrary, the Ugi–Passerini reaction would seem appropriate to synthesize also peptides if one had not to cope with the two difficulties it brings about, viz. (i) the unavoidable racemization of the amino acid residue that follows the newly synthesized amino acid unit and (ii) a usually unwanted alkyl group bounded to the nitrogen atom of the dialkylated center. The former difficulty results from the increased acidity imparted to the α-carbon atom of the isonitrile component of the reaction when chiral isonitriles would be required to generate a chiral amino acid residue at the C-terminus of the dialkyl/trialkyl glycine within the peptide chain. This difficulty could be circumvented by the use of 'convertible isonitriles', which have been developed just in connection with the Ugi–Passerini reaction.[22] Such isonitriles generate a labile amide that could then be cleaved to yield a peptide acid suitable for coupling to the next amino acid within the sequence, or even to a peptide. However, when investigating the lability to acid of the amide bond that follows the disubstituted amino acid residue in *N*-acyl-*N*-methyl-α,α-dimetyl glycine amides, we have observed[15] that several 'ordinary isonitriles' were equally suitable to allow the required amide cleavage.[23] Moreover, we have shown that cyclohexyl isonitrile is most appropriate because it is commercially available, inexpensive, stable on standing and easy to manipulate. With respect to the unwanted *N*-alkyl group at the disubstituted amino we have assumed that if 4-methoxybenzylamine were used as the amine component in the Ugi–Passerini reaction the 4-methoxybenzyl group (Pmb) remaining attached the final adduct would be cleavable with acid as demonstrated by Sheppard and his colleagues[24] in the case of amide bond protection during solid phase peptide synthesis. Our experimental results showed that this cleavage occurs easily, although requiring more forcing conditions than those needed for breaking the amide bond. This was a fortunate outcome because full selectivity of cleavage can thus be accomplished, if required, to keep the *N*-alkyl group until the end of the syntheses.[25] Prior to engage in routine peptide synthesis under this approach we have investigated the effect of increasing bulk of the α,α-dialkyl glycine side chains on these cleavages to find out that bulkier chains tend to decrease the rate of both cleavages but without affecting selectivity or the yields considerably.[26–28] We have also tested the alternative use of various *para*-substituted benzylamines and anilines of different polarities in comparison with the unsubstituted compounds. The results obtained showed that, with exception of the 4-methoxybenzylamine derivatives, in none of the Ugi–Passerini adducts can the *N*-alkyl group be cleaved even when submitted to treatment with boiling trifluoracetic acid (TFA) for long periods; in addition, they showed that the amide cleavage becomes slower in the case of the less electron-releasing substituents and also in that of the corresponding anilines.[29] This may be particularly useful if one wants to incorporate *N*,α,α-trialkyl glycine residues into peptide chains. In fact, *N*-alkylamino acid residues are useful to replace proline with advantage in peptidomimetics. Like proline they are helix-breaking amino acids as do not allow hydrogen bonding at the amino acid nitrogen atom, but differently from proline they allow some flexibility of the neighboring peptide chain varying with the size and structure of the neighboring substituents. Now, we report the synthesis of various peptides, including tri and pentapeptides having a central residue of one α,α-dialkyl glycine and the results obtained thereof, which allowed to confirm the strategy based on the Ugi–Passerini reaction we have previously proposed[15] for routine peptide synthesis with α,α-dialkyl and *N*, α,α-trialkyl glycines.

2. Results and discussion

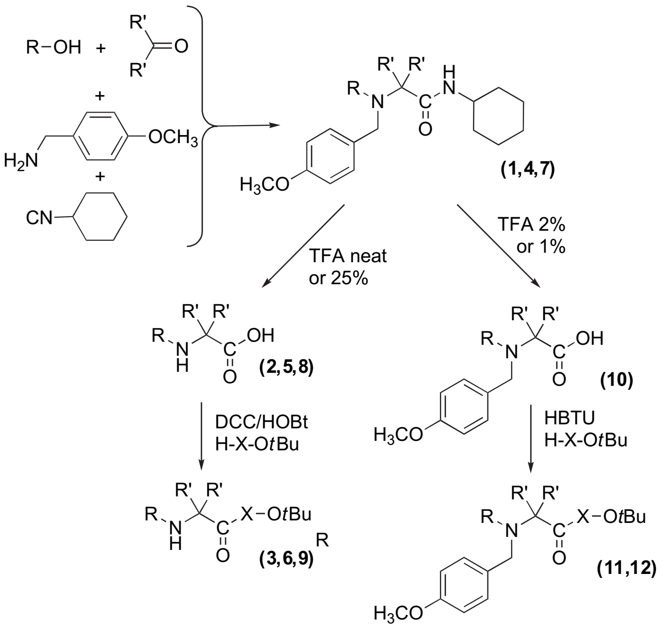
At this stage we were able to make *N*-acyl-amino and peptide acids with an α,α-dialkyl or an *N*,α,α-trialkyl glycine residue at the C-terminus. The aim of this investigation was to find out the feasibility and conditions for their coupling to amino acid and peptide esters and how far one could reach with regard to increasing crowding of the final products. For this purpose we have envisaged four sets of compounds of growing difficulty, each one comprehending two, five or six derivatives of different α,α-dialkyl glycines (Scheme 1) with bulkiness varying from α,α-dimethyl (or α,α-diethyl) to α,α-dibenzyl glycine.

2.1. Synthesis of dipeptides

The first of these sets (compounds **1**–**3**) offered the possibility to develop the best and, thus, set standard conditions for coupling various *N*-acetyl-α,α-trialkyl glycines ($CH_3CO–NR'CR_2CO_2H$) with the *tert*-butyl (*t*Bu) ester of the simplest amino acid, glycine. All these *N*-acetyl derivatives but compounds **1a** and **2a** had been previously described,[27] and **2** were prepared by full acidolysis of the corresponding Ugi–Passerini products **1** by boiling for 15 min with neat TFA. The earlier work with α,α-dialkyl glycines showed that attempts to activate their *N*-acyl derivatives for coupling tend to yield oxazolones (2,3,5,5-tetraalkyl-4,5-dihydrooxazol-5-ones),[13,20,21] which can then be used as active moieties in coupling reactions with some advantage over the classical methods of synthesis (Scheme 2-A). More recently it has been shown[23] that the C-terminal amide bond cleavage of *N*-acyl-*N*,α,α-trimethyl glycine amides proceeds via an oxazolonium-type intermediate (Scheme 2-B), which we have been able to confirm and extend to various *N*,α,α-trialkyl glycine derivatives.[25] Having found that this oxazolonium intermediate can be captured by simple nucleophiles,[30] we have tried to carry out one-pot syntheses by using them as coupling reagents without prior isolation of the cleavage products, but found an imidazolone (1,2,4,4-tetralkyl-4,5-dihydroimidazol-5-one) derivative as the major coupling product (Scheme 2-C).[31] This resulted from attack at the position 2 instead of position 5 of the oxazolonium ring followed by rearrangement. Reasoning that, since the attack at the unwanted position would be favored by the positive charge at the nitrogen atom, attempts were made to obtain better results by neutralizing the oxazolonium salt to the corresponding oxazolone with triethylamine. Nevertheless, imidazolone was still obtained in an appreciable amount, thus suggesting that the amino acid side chains also contribute to the attack at position 2. Better results were achieved when the compounds obtained by acid cleavage of the Ugi–Passerini adducts (**2**) were coupled to H-Gly-O*t*Bu via oxazolone, formed by the action of *N*,*N*′-dicyclohexylcarbodiimide (DCC), under refluxed in acetonitrile for 1–3 days (Table 1). Under these conditions compound **2a** did not behave satisfactorily; however, the results improved when it was submitted to standard 1-hydroxy-1,2,3-benzotriazole (HOBt) assisted carbodiimide couplings.[32]

2.2. Synthesis of tripeptides with a central dialkyl glycine residue

The next step was to repeat the above syntheses, but using *N*-benzyloxycarbonyl-L-phenylalanine ($PhCH_2OCO$-L-Phe-OH or Z-L-Phe-OH) as the acid component in the Ugi–Passerini reactions and thus generate a second set of compounds (**4**). The reactions proceeded smoothly and in good yields, although with a clear tendency to decrease as the bulkiness of the newly formed amino acid residue increased, as shown in Table 2. In order to preserve the integrity of the N-protecting group, the acidolysis of these compounds had to be performed with 25% TFA in dichloromethane instead of neat acid, which required refluxing for 25–60 min. Coupling of the



1a,2a,3a: R = Ac, R_2' = $(CH_2)_5$, X = Gly
1b,2b,3b: R = Ac, R' = Et, X = Gly
1c,1c,3c: R = Ac, R' = Pr, X = Gly
1d,2d,3d: R = Ac, R' = *i*Bu, X = Gly
1e,2e,3e: R = Ac, R' = Bn, X = Gly

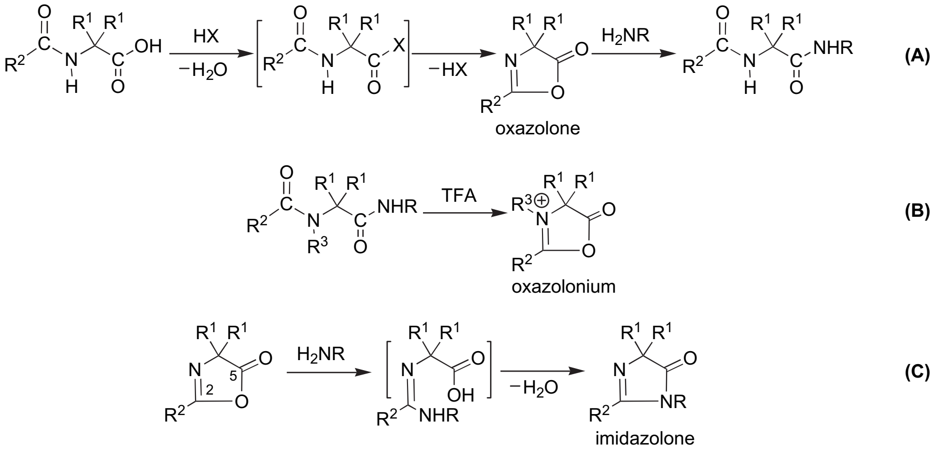
4a,5a,6a: R = Z-L-Phe, R_2' = $(CH_2)_5$, X = Gly
4b,5b,6b: R = Z-L-Phe, R' = Me, X = Gly
4c,5c,6c: R = Z-L-Phe, R' = Et, X = Gly
4d,5d,6d: R = Z-L-Phe, R' = Pr, X = Gly
4e,5e,6e: R = Z-L-Phe, R' = *i*Bu, X = Gly
4f,5f,6f: R = Z-L-Phe, R' = Bn, X = Gly

7a,8a,9a: R = Z-L-Phe-Gly, R' = Et, X = L-Phe-Gly
7b,8b,9b: R = Z-L-Phe-Gly, R' = Bn, X = L-Phe-Gly

10a,11a: R = Z-L-Phe, R_2' = $(CH_2)_5$, X = L-Phe
10b,11b: R = Z-L-Phe, R' = Me, X = L-Phe
10c,11c: R = Z-L-Phe, R' = Et, X = L-Phe
10d,11d: R = Z-L-Phe, R' = Pr, X = L-Phe
10e,11e: R = Z-L-Phe, R' = *i*Bu, X = L-Phe
10f,11f: R = Z-L-Phe, R' = Bn, X = L-Phe

12: R = Z-L-Phe, R' = Me, X = Gly

Scheme 1.



Scheme 2.

Table 1
Synthesis of dipeptides [Ac-N(Pmb)CR$_2$CO-NHC$_6$H$_{11}$ (**1**)→Ac-NHCR$_2$CO$_2$H (**2**)→Ac-NHCR$_2$CO-Gly-O*t*Bu (**3**)]

R	Ugi–Passerini reaction			Acidolysis			Coupling			Final peptide	Overall yield (%)
		Mp (°C)	Yield (%)		Mp (°C)	Yield (%)		Mp (°C)	Yield (%)		
–(CH$_2$)$_5$–	**1a**	155.2–156.0	90.2	**2a**	201.0–202.4	70.5	**3a**	139.5–140.2	55.1	Ac-Ac6c-Gly-O*t*Bu	35
Et	**1b**	113–115[a]	85.7[a]	**2b**	209–211[a]	93.6	**3b**	144–145	53.7	Ac-Deg-Gly-O*t*Bu	43
Pr	**1c**	128–130[a]	91.7[a]	**2c**	196–197[a]	98.1	**3c**	120–121	53.8	Ac-Dpg-Gly-O*t*Bu	48
*i*Bu	**1d**	90–92[a]	84.8[a]	**2d**	216–218[a]	79.8	**3d**	141–143	42.7	Ac-Dibg-Gly-O*t*Bu	29
Bn	**1e**	193–194[a]	72.9[a]	**2e**	233–235[a]	89.1	**3e**	202–204	43.1	Ac-Dbng-Gly-O*t*Bu	28

[a] These results have been previously reported.[27] The meaning of the abbreviations may be clarified by Scheme 1.

Table 2
Synthesis of tripeptides [Z-L-Phe-N(Pmb)CR_2CO-NHC_6H_{11} (**4**)→Z-L-Phe-$NHCR_2CO_2H$ (**5**)→Z-L-Phe-$NHCR_2CO$-Gly-O*t*Bu (**6**)]

R	Ugi–Passerini reaction			Acidolysis			Coupling			Final peptide	Overall yield (%)
		Mp (°C)	Yield (%)		Mp (°C)	Yield (%)		Mp (°C)	Yield (%)		
–$(CH_2)_5$–	**4a**	68.2–69.9	91.4	**5a**	188.0–189.2	82.0	**6a**	181.4–182.8	91.9	Z-L-Phe-Ac6c-Gly-O*t*Bu	68.9
Me	**4b**	126.2–127.0	97.6	**5b**	185.9–186.9	61.4	**6b**	156.6–157.9	88.8	Z-L-Phe-Aib-Gly-O*t*Bu	53.2
Et	**4c**	67.0–69.0	87.6	**5c**	177.4–178.6	84.4	**6c**	150.5–152.0	80.8	Z-L-Phe-Deg-Gly-O*t*Bu	59.7
Pr	**4d**	65.0–67.0	82.2	**5d**	156.3–157.4	85.4	**6d**	134.5–135.8	79.0	Z-L-Phe-Dpg-Gly-O*t*Bu	55.5
*i*Bu	**4e**	72.0–74.0	70.1	**5e**	170.2–171.6	83.5	**6e**	116.5–118.0	67.4	Z-L-Phe-Dibg-Gly-O*t*Bu	39.5
Bn	**4f**	114.3–115.3	60.5	**5f**	178.3–179.5	66.8	**6f**	166.0–167.8	53.8	Z-L-Phe-Dbng-Gly-O*t*Bu	21.7

dipeptide acid **5d** with glycine *tert*-butyl ester by the oxazolone method described above yielded the expected tripeptide **6d** and the corresponding imidazolone (**13**) in almost equal amounts (39.9% and 37.1%, respectively). The yield in tripeptide was much improved by a DCC/HOBt coupling (79.0%), which was then extended to the other compounds of this set. Nevertheless, in all cases traces of an impurity could still be observed by thin-layer chromatography (TLC) on the reaction mixture, which were assigned to imidazolone. A steady decrease of the overall yields with increasing bulkiness of the synthesized tripeptides could also be observed; this is most visible in the case of the compounds **6e** and **6f**, which exhibit branching at the β-position of their side chains.

2.3. Synthesis of pentapeptides with a central dialkyl glycine residue

Two pentapeptides having α,α-diethyl glycine (**9a**) and α,α-dibenzyl glycine (**9b**) at their central position and twice the sequence L-Phe-Gly protected as above were synthesized (Table 3). Straightforward Ugi–Passerini reactions with Z-L-Phe-Gly-OH as the acid component yielded 90.2% and 16.1% of the required tripeptides derivatives **7a** and **7b**, respectively. In face of the low yield obtained in the latter case, the reaction was repeated after previous preparation of the Schiff's base from the amine and the ketone components, which afforded an appreciably improved yield of 53.7%. Acidolysis of **7a** could be performed with 25% TFA as above, affording **8a** in good yield, but in the case of **7b** much starting material remained unreacted. By refluxing for one hour in 50% TFA all starting material was consumed and the yield was improved; however, TLC showed formation of secondary products to which competitive cleavage of the N-protecting group would have contributed.

The coupling of tripeptide acids **8a** and **8b** with H-L-Phe-Gly-O*t*Bu was performed by the DCC/HOBt method to yield 74.2% of the diethyl pentapeptide **9a**, but only 25.7% of its dibenzyl analog **9b** when the corresponding imidazolone was the main product (42.6%). This coupling was also attempted using *N*-[(1*H*-benzotriazol-1-yl)-(dimethylamino)methylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide (HBTU)[33] as the coupling reagent, but unfortunately no improvement could be achieved.

2.4. Synthesis of tripeptides with a central *N*-(4-methoxybenzyl)-dialkyl glycine residue

Having in mind to attempt the never performed synthesis of peptides from peptide acids containing an *N*,α,α-trialkylglycine residue at their C-terminus other than the least sterically crowded in the series, the trimethyl compound (MeAib), the dipeptide amides **4a**–**4f** were submitted to partial acidolysis with 2% TFA in acetonitrile at room temperature until no modification of the reaction mixture could be detected by TLC (2–5 days). In all cases some starting material remained unreacted; however, with compound **4d**, in addition to the required product **10d**, some of the undesired fully cleaved product **5d** was also obtained and compound **4e** only yielded the fully cleaved compound **5e**. This discouraging result could be overcome by repeating both reactions with 1% instead of 2% TFA in acetonitrile for one week, also at room temperature, to produce the desired compounds **10d** and **10e** in better yields (Table 4). A yield of 48.6% was obtained in the coupling of dipeptide **10b** with glycine *tert*-butyl ester by the DCC/HOBt method, but this method failed with the remaining compounds **10**. In our experience this results from increased hindrance of the coupling reaction caused by the increased bulkiness of the amino

Table 3
Synthesis of pentapeptides [Z-L-Phe-Gly-N(Pmb)CR_2CO-NHC_6H_{11} (**7**)→Z-L-Phe-Gly-$NHCR_2CO_2H$ (**8**)→Z-L-Phe-Gly-$NHCR_2CO$-L-Phe-Gly-O*t*Bu (**9**)]

R	Ugi–Passerini reaction			Acidolysis			Coupling			Final peptide	Overall yield (%)
		Mp (°C)	Yield (%)		Mp (°C)	Yield (%)		Mp (°C)	Yield (%)		
Et	**7a**	117.8–118.8	90.2	**8a**	123.6–124.8	83.8	**9a**	119.9–121.3	74.2	Z-L-Phe-Gly-Deg-L-Phe-Gly-O*t*Bu	57.2
Bn	**7b**	210.0–211.9	53.7	**8b**	129.9–131.0	50.0	**9b**	137.2–139.0	25.7	Z-L-Phe-Gly-Dbng-L-Phe-Gly-O*t*Bu	6.9

Table 4
Synthesis of fully crowded tripeptides [Z-L-Phe-N(Pmb)CR_2CO-NHC_6H_{11} (**4**)→Z-L-Phe-N(Pmb)CR_2CO_2H (**10**)→Z-L-Phe-N(Pmb)CR_2CO-X-O*t*Bu (**11**, **12**)]

R	Acidolysis			Coupling			Final peptide	Overall[a] yield (%)
		Mp (°C)	Yield (%)		Mp (°C)	Yield (%)		
–$(CH_2)_5$–	**10a**	159.9–161.8	85.8	**11a′**	125.3–126.6	34.1	Z-L-Phe-(Pmb)Ac6c-L-Phe-O*t*Bu	39.8
				11a″	—	16.7		
Me	**10b**	194.6–196.0	85.8	**12**	131.3–133.0	48.6	Z-L-Phe-(Pmb)Aib-Gly-O*t*Bu	40.6
				11b	65.9–67.0	92.7	Z-L-Phe-(Pmb)Aib-L-Phe-O*t*Bu	77.4
Et	**10c**	191.0–192.8	84.9	**11c**	100.8–102.0	94.8 w	Z-L-Phe-(Pmb)Deg-L-Phe-O*t*Bu	70.5
Pr	**10d**	178.1–180.0	75.4	**11d**	130.9–131.9	92.9	Z-L-Phe-(Pmb)Dpg-L-Phe-O*t*Bu	57.6
*i*Bu	**10e**	181.0–182.4	70.6	**11e**	139.9–141.7	70.7	Z-L-Phe-(Pmb)Dibg-L-Phe-O*t*Bu	35.0
Bn	**10f**	114.3–115.3	68.9	**11f′**	129.5–131.0	38.6	Z-L-Phe-(Pmb)Dbng-L-Phe-O*t*Bu	22.6
				11f″	109.4–111.1	15.6		

[a] From the acid used in the corresponding Ugi–Passerini reactions.

acid side chains when they are larger than methyl and suggested that this method was not sufficiently powerful for our purpose. Thus, it was decided to try acyl fluoride couplings, but attempts to convert dipeptides **10b** and **10c** into the corresponding fluorides with cyanuryl fluoride[34] failed, the starting material being fully recovered. Similar result was obtained in attempts with different reaction temperatures and concentrations of the fluorinating agent.[35,36] The required couplings could finally be achieved in acceptable yields with the aid of (HBTU) in acetonitrile at room temperature, which is generally recognized as a powerful coupling method in peptide chemistry. Once more a visible dependence of the overall yields on the bulkiness of the amino acid side chains was observed. The room temperature proton nuclear magnetic resonance spectrometry (^{1}H NMR) spectra of compounds **11c**, **11d** and **11e**, but not those of compounds **11b** and **12**, showed doubling of some of the spectral lines, which was no more observed at 70 °C. This behavior was expected, as it is typical of fully substituted amides[37] and is related to a slow *cis–trans* interconversion within the amide bond preceding the *N*,α,α-trialkyl glycine residue. The different behavior of compounds **11b** and **12**, shows that two methyl groups at the α-carbon atom of the disubstituted glycine residue do not impart sufficient bulkiness to slow down the *cis–trans* interconversion enough for this effect to be observed at room temperature. In the synthesis of compounds **11a** and **11f** two major products were isolated from the reaction mixture (**11a**′, **11a**″, **11f**′ and **11f**″). After purification, the room temperature ^{1}H NMR spectra of the two products of each synthesis were both consistent with the structure of the required compound, differing slightly only in the shape of the signal of one of the CH_2 groups and the frequencies found for the NH signals. However, no doubling of spectral lines was observed in either case, which was most unexpected as at least the molecule of compound **11f**, with its two benzyl groups at α-carbon atom, was the most crowded in this series. The results of the elemental analysis of **11f**′ and **11f**″ were in both cases consistent with the values calculated for the required product **11f**, but their melting points differed slightly. The same was observed with the analytical results for compound **11a**′ and **11a**″; however, in this case the minor product did not crystallize properly and a sharp melting point could not be obtained. Suspecting that the molecules of these compounds were so crowded that *cis–trans* interconversion of the corresponding conformers were sufficiently slow to allow their isolation, the following test was performed. Products **11a**′ and **11a**″ were heated for 1 h at 120 °C in a dimethyl sulfoxide (DMSO) solution as prepared for NMR spectroscopy. After cooling to room temperature, the two products showed identical ^{1}H NMR spectra, each spectrum being the sum of the spectrum obtained for one of the products with that obtained for the other before heating. With products **11f**′ and **11f**″ in an experiment run under identical conditions only a slight modification was observed after cooling; nevertheless, a full result as above could be achieved but only when the samples were submitted to heating for 6 h at 150 °C. These results allowed concluding that *cis–trans* interconversion of these two compounds at room temperature is so slow that it leads to isolation of their two conformers, each isolated conformer requiring heating at a fairly high temperature for an appreciably long period to be converted into a mixture of both conformers. This conclusion was further supported by electrospray ionization high resolution (ESI-HR) mass spectrometry as both products isolated for **11a** and **11f** had the same $[M+Na]^+$ value.

3. Conclusions

The results presented above show that our strategy based on the Ugi–Passerini reaction followed by full or partial acidolysis of the products and coupling of these with an amino acid or dipeptide ester seems to be suitable for routine peptide synthesis with α,α-dialkyl and even *N*,α,α-trialkyl glycines. The use of a residue of L-phenylalanine preceding and, chiefly, of another following the crowded center of the molecule served to show that this strategy solves the problem concerning racemization associated with amino acid (or peptide) isonitriles otherwise required for the Ugi–Passerini reactions. As depicted above, in all sets of compounds explored in this work a decrease of the overall yield of the syntheses was observed as the size and degree of branching of the dialkyl glycine residue increased. However, the differences in the yields obtained in the synthesis of the diethyl glycine (Deg) derivatives **4c** and **5c** (Table 2) as compared to those registered for their analogs **7a** and **8a** (Table 3) are meaningless with regard to the size of peptide chain. However, a small drop in the yields was observed when going from the tri- to the pentapeptide syntheses corresponding to the much bulkier dibenzyl derivatives (Dbng) (**4f** and **5f** as compared to **7f** and **8f**). This shows that the yields are not much affected by the length of the peptide chain at the N-terminus of the α,α-dialkyl glycine residue even in the extreme case of Dbng. With regard to the C-terminus, although the yield obtained for the synthesis of compound **6a** (Table 2) is slightly higher than that reported for the case of the corresponding pentapeptide **9c** (Table 3), in our experience this difference is not related to the length of the chain at the C-terminus of the α,α-dialkyl glycine residue but to the bulkiness of the amino acid that is bonded to it (glycine in the former case against the much bulkier phenylalanine in the latter). This sensitivity of coupling yields to the bulkiness within the added moiety at the vicinity of the bond that is going to be formed at the C-terminus of the α,α-dialkyl glycine residue is much amplified when the bulkiness of the dialkyl glycine increases. This is clearly shown with the meaningful drop in yield from 53.8% to 25.7% in the case of the corresponding Dbng analogs **6f** and **9b**. Consequently, as the size of the peptide chain increased from three to five amino acid residues the fall in the overall yields seem to be more related to the molecular bulkiness in the vicinity of the reaction centers than to the length of the peptide chains involved. Thus, we believe that a further increase of the length of the peptide chain to more than five units may not bring about any appreciable fall of the final yields. Tripeptide **11f** is unique in the fact that its short linear chain contains as much as six benzyl rings; the so slow *cis–trans* interconversion of its conformers shows how crowded its molecules are and, in some way, also shows how far our strategy may be used to synthesize this difficult class of compounds. In the cases when it was necessary to preserve the *N*-(4-methoxybenzyl) group, acidolysis of the product of the Ugi–Passerini reaction required setting the best experimental conditions for selective cleavage. The same applied to the acidolyses of *N*-benzyloxycarbonyl protected amino acids or peptides in order to preserve the integrity of the protecting group when boiling with TFA. Despite the sensitivity of this group to acid, this did not prevent attaining our aim and suggests that our synthetic approach would be not only of potential use but possibly more satisfactory in connection with the so widely explored fluorenyl-9-methoxycarbonyl (Fmoc) protecting strategy. Although two of the compounds synthesized were so sterically crowded that their *cis* and *trans* rotamers could be separated at and above room temperature, the fair yields we obtained in the syntheses are somehow a measure of the efficiency of this method.

4. Experimental

4.1. General

Except for dibenzyl ketone, all ketones were freshly distilled. Methanol, acetonitrile, and triethylamine were dried by standard procedures. All other solvents and reagents were used as obtained from commercial sources. TLC analyses were carried out on 0.25 mm thick precoated silica plates (Merck Fertigplatten

Kieselgel 60F$_{254}$) and spots were visualized under ultraviolet (UV) light or by exposure to vaporized iodine. Preparative layer chromatography was carried out on Merck Kieselgel 60 (230–400 mesh). All melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 25 °C in ca. 5% solution on a Varian Unity Plus-300 spectrometer. In some cases, measurements at 70 °C were also performed. All shifts are given in δ ppm using δ$_H$ Me$_4$Si=0, *J*-values are given in Hz, and assignments were made by comparison of chemical shifts, peak multiplicity and *J*-values. ^{13}C NMR spectra were recorded with the same instrument at 75.4 MHz and using the solvent peak as internal reference; assignments were carried out using DEPT 135, HMBC and HMQC techniques. Elemental analyses were performed on a Leco CHNS 932 instrument. Optical rotations were obtained on an Optical Activity Automatic Polarimeter type AA-1000. ESI mass spectra were recorded on a Bruker FTMS APEXIII spectrometer.

4.2. Synthesis of Ugi–Passerini products 1a, 4a–4f, 7a and 7b

All reactions were carried out under previously described conditions[15,27] and, if not otherwise stated, three weeks were allowed for completion.

*4.2.1. 1-[N-Acetyl-N-(4-methoxybenzyl)amino]-cyclohexylcarboxyl-(N′-cyclohexyl)-amide (**1a**).* The reaction was carried out on a 0.01-M scale with acetic acid as the acid component and required 3 days. The crude product purified by column chromatography and then recrystallized from ethyl acetate to yield **1a** (3.48 g, 90.2%) as a white solid, mp 155.2–156.0 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.08–1.45 (6H, m, CC$_6$H$_{10}$+NHC$_6$H$_{11}$), 1.48–1.78 (10H, m, CC$_6$H$_{10}$+NHC$_6$H$_{11}$), 1.82–1.98 (2H, m, NHC$_6$H$_{11}$), 2.11 (3H, s, CH$_3$CO), 2.41 (2H, br d, *J*=10.5 Hz, CC$_6$H$_{10}$), 3.67–3.80 (1H, m, NHC$_6$H$_{11}$-*H1*), 3.80 (3H, s, OCH$_3$), 4.59 (2H, s, NCH$_2$), 6.25 (1H, d, *J*=5.4 Hz, CONH), 6.89 (2H, d, *J*=8.7 Hz, NCH$_2$Ph-*H3,5*), 7.24 (2H, d, *J*=8.7 Hz, NCH$_2$Ph-*H2,6*); ^{13}C NMR (75 MHz, CDCl$_3$): δ 22.85 (CC$_6$H$_{10}$-*C3,5*), 24.08 (CH$_3$CO), 24.65 (NHC$_6$H$_{11}$-*C3,5*), 25.29, 25.54 (CC$_6$H$_{10}$-*C4*+NHC$_6$H$_{11}$-*C4*), 32.79, 32.96 (CC$_6$H$_{10}$-*C2,6*+NHC$_6$H$_{11}$-*C2,6*), 47.97 (NCH$_2$Ph), 48.05 (NHC$_6$H$_{11}$-*C1*), 55.17 (OCH$_3$), 65.91 (C$^\alpha$), 114.09 (NCH$_2$Ph-*C3,5*), 127.09 (NCH$_2$Ph-*C2,6*), 130.52 (NCH$_2$Ph-*C1*), 158.58 (NCH$_2$Ph-*C4*), 172.28 (CONH), 172.85 (CH$_3$CO). Anal. Calcd for C$_{23}$H$_{34}$N$_2$O$_3$: C, 71.47; H, 8.87; N, 7.25. Found: C, 71.23; H, 8.67; N, 7.21.

*4.2.2. 1-[N-(N′-Benzyloxycarbonyl-L-phenylalanyl)-N-(4-methoxybenzyl)-amino]-cyclohexylcarboxyl-(N″-cyclohexyl)-amide (**4a**).* The reaction was carried out on a 0.01-M scale with *N*-benzyloxycarbonyl-L-phenylalanine as the acid component and required 28 days. The crude product was purified by column chromatography, yielding the pure compound **4a** (5.72 g, 97.6%) as a white solid, mp 68.2–69.9 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.01–1.25 (4H, m, NHC$_6$H$_{11}$+CC$_6$H$_{10}$), 1.26–1.73 (12H, m, NHC$_6$H$_{11}$+CC$_6$H$_{10}$), 1.76–1.95 (2H, m, NHC$_6$H$_{11}$), 2.04–2.08 (1H, m, CC$_6$H$_{10}$), 2.58 (1H, br d, *J*=12.9 Hz, CC$_6$H$_{10}$), 2.92 (2H, ddd, *J*=6.9, 13.5, 47.6 Hz, CHCH$_2$Ph), 3.71–3.80 (1H, m, NHC$_6$H$_{11}$-*H1*), 3.80 (3H, s, OCH$_3$), 4.44 (2H, q, *J*=18.3 Hz, NCH$_2$), 4.71 (1H, q, *J*=7.5 Hz, CHCH$_2$Ph), 5.06 (2H, s, CH$_2$OCO), 5.43 (1H, d, *J*=8.7 Hz, OCONH), 5.91 (1H, d, *J*=8.1 Hz, CONH), 6.84 (2H, d, *J*=8.7 Hz, NCH$_2$Ph-*H3,5*), 7.04 (2H, br t, *J*=3.3 Hz, CHCH$_2$Ph-*2,6*), 7.13 (2H, d, *J*=8.4 Hz, NCH$_2$Ph-*H2,6*), 7.23–7.34 (8H, m, CHCH$_2$Ph-*H3,4,5*+OCOCH$_2$Ph); ^{13}C NMR (75 MHz, CDCl$_3$): δ 22.67, 22.85 (CC$_6$H$_{10}$-*C3,5*), 24.74 (NHC$_6$H$_{11}$-*C3,5*), 25.29, 25.60 (CC$_6$H$_{10}$-*C4*+NHC$_6$H$_{11}$-*C4*), 32.31, 33.21 (CC$_6$H$_{10}$-*C2,6*), 32.83, 32.91 (NHC$_6$H$_{11}$-*C2,6*), 39.69 (CHCH$_2$Ph), 46.62 (NCH$_2$Ph), 48.03 (NHC$_6$H$_{11}$-*C1*), 53.97 (CHCH$_2$Ph), 55.26 (OCH$_3$), 66.55 (C$^\alpha$), 66.76 (OCOCH$_2$), 114.31 (NCH$_2$Ph-*C3,5*), 126.92 (CHCH$_2$Ph-*C4*), 127.30 (NCH$_2$Ph-*C2,6*), 128.83 (OCOCH$_2$Ph-*C2,6*), 128.06 (OCOCH$_2$Ph-*C4*), 128.43, 128.46 (CHCH$_2$Ph-*C3,5*+OCOCH$_2$Ph-*C3,5*), 129.48 (CHCH$_2$Ph-*C2,6*), 130.31 (NCH$_2$Ph-*C1*), 136.08, 136.18 (OCOCH$_2$Ph-*C1*+CHCH$_2$Ph-*C1*), 155.54 (OCONH), 158.81 (NCH$_2$Ph-*C4*), 171.89 (CONH), 173.48 (CON). Anal. Calcd for C$_{38}$H$_{47}$N$_3$O$_5$: C, 72.93; H, 7.57; N, 6.71. Found: C, 72.50; H, 7.30; N, 6.69.

*4.2.3. N-Benzyloxycarbonyl-L-phenylalanyl-N′-(4-methoxybenzyl)-α,α-dimethylglycine cyclohexylamide (**4b**).* The reaction was carried out on a 0.02-M scale with *N*-benzyloxycarbonyl-L-phenylalanine as the acid component. The crude product purified by column chromatography and then recrystallized from ethyl acetate to yield **4b** (11.4 g, 97.6%) as a white crystals, mp 126.2–127.0 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.02–1.24 (3H, m, C$_6$H$_{11}$), 1.30–1.48 (2H, m, C$_6$H$_{11}$), 1.35 (3H, s, 2×CH$_3$), 1.56–1.74 (3H, m, C$_6$H$_{11}$), 1.87–2.02 (2H, m, C$_6$H$_{11}$), 2.89 (2H, ddd, *J*=6.3, 13.7, 43.8 Hz, CHCH$_2$Ph), 3.69–3.77 (1H, m, C$_6$H$_{11}$-*H1*), 3.80 (3H, s, OCH$_3$), 4.39 (1H, d, *J*=18.0 Hz, NCH$_2$), 4.60 (1H, d, *J*=18.0 Hz, NCH$_2$), 4.64–4.69 (1H, m, CHCH$_2$Ph), 5.05 (2H, d, *J*=3.3 Hz, CH$_2$OCO), 5.34 (1H, d, *J*=7.8 Hz, OCONH), 5.58 (1H, d, *J*=8.1 Hz, CONH), 6.88 (2H, d, *J*=8.7 Hz, NCH$_2$Ph-*H3,5*), 6.98 (2H, br s, CHCH$_2$Ph-*H2,6*), 7.21–7.36 (10H, m, CHCH$_2$Ph-*H3,4,5*+OCOCH$_2$Ph+NCH$_2$Ph-*H2,6*); ^{13}C NMR (75 MHz, CDCl$_3$): δ 23.98 (CCH$_3$), 24.50 (CCH$_3$), 24.84 (C$_6$H$_{11}$-*C3,5*), 25.57 (C$_6$H$_{11}$-*C4*), 32.87 (C$_6$H$_{11}$-*C2,6*), 39.22 (CHCH$_2$Ph), 46.63 (NCH$_2$Ph), 48.28 (C$_6$H$_{11}$-*C1*), 53.44 (CHCH$_2$Ph), 55.26 (OCH$_3$), 63.01 (C$^\alpha$), 66.75 (OCOCH$_2$Ph), 114.31 (NCH$_2$Ph-*C3,5*), 126.86 (CHCH$_2$Ph-*C4*), 127.32 (NCH$_2$Ph-*C2,6*), 127.80 (OCOCH$_2$Ph-*C2,6*), 128.03 (OCOCH$_2$Ph-*C4,*), 128.40, 128.44 (OCOCH$_2$Ph-*C3,5*+CHCH$_2$Ph-*C3,5*), 129.37 (CHCH$_2$Ph-*C2,6*), 130.29 (NCH$_2$Ph-*C1*), 136.07, 136.17 (OCOCH$_2$Ph-*C1*+CHCH$_2$Ph-*C1*), 155.74 (OCONH), 158.84 (NCH$_2$Ph-*C4*), 172.82 (CON), 173.43 (CONH). Anal. Calcd for C$_{35}$H$_{43}$N$_3$O$_5$: C, 71.77; H, 7.40; N, 7.17. Found: C, 71.70; H, 7.43; N, 7.13.

*4.2.4. N-Benzyloxycarbonyl-L-phenylalanyl-N′-(4-methoxybenzyl)-α,α-diethylglycine cyclohexylamide (**4c**).* The reaction was carried out on a 0.02-M scale with *N*-benzyloxycarbonyl-L-phenylalanine as the acid component. The crude product was purified by column chromatography, yielding **4c** (10.8 g, 87.6%) as a white solid, mp 67–69 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.80 (6H, dt, *J*=7.2, 10.8 Hz, CH$_3$), 1.08–2.28 (14H, m, 2×CH$_2$+C$_6$H$_{11}$), 2.65–2.87 (2H, m, CHCH$_2$Ph), 3.72–3.86 (1H, m, C$_6$H$_{11}$-*H1*), 3.81 (3H, s, OCH$_3$), 4.51 (1H, d, *J*=17.0 Hz, NCH$_2$), 4.56–4.66 (1H, m, CHCH$_2$Ph), 4.83 (1H, d, *J*=17.0 Hz, NCH$_2$), 5.00 (2H, q, *J*=8.7 Hz, CH$_2$OCO), 5.26 (1H, d, *J*=9.5 Hz, OCONH), 5.52 (1H, d, *J*=8.1 Hz, CONH), 6.75 (2H, br s, CHCH$_2$Ph-*H2,6*), 6.93 (2H, d, *J*=8.4 Hz, NCH$_2$Ph-*H3,5*), 7.13–7.38 (8H, m, CHCH$_2$Ph-*H3,4,5*+OCOCH$_2$Ph), 7.61 (2H, d, *J*=8.1 Hz, NCH$_2$Ph-*H2,6*); ^{13}C NMR (75 MHz, CDCl$_3$): δ 7.94 (CH$_3$CH$_2$), 8.43 (CH$_3$CH$_2$), 23.17 (CCH$_2$), 24.27 (CCH$_2$), 24.83 (C$_6$H$_{11}$-*C3,5*), 25.57 (C$_6$H$_{11}$-*C4*), 32.94 (C$_6$H$_{11}$-*C2,6*), 38.83 (CHCH$_2$Ph), 47.79 (NCH$_2$Ph), 48.27 (C$_6$H$_{11}$-*C1*), 53.58 (CHCH$_2$Ph), 55.24 (OCH$_3$), 66.56 (OCOCH$_2$Ph), 68.90 (C$^\alpha$), 114.33 (NCH$_2$Ph-*C3,5*), 126.53 (CHCH$_2$Ph-*C4*), 127.52 (NCH$_2$Ph-*C2,6*), 127.69 (OCOCH$_2$Ph-*C2,6*), 127.90 (OCOCH$_2$Ph-*C4,*), 128.28, 128.32 (OCOCH$_2$Ph-*C3,5*+CHCH$_2$Ph-*C3,5*), 129.15 (CHCH$_2$Ph-*C2,6*), 131.41 (NCH$_2$Ph-*C1*), 136.24, 136.50 (OCOCH$_2$Ph-*C1*+CHCH$_2$Ph-*C1*), 155.72 (OCONH), 158.80 (NCH$_2$Ph-*C4*), 172.19 (CON), 173.41 (CONH). Anal. Calcd for C$_{37}$H$_{49}$N$_3$O$_5$: C, 72.17; H, 8.02; N, 6.82. Found: C, 72.02; H, 7.89; N, 6.82.

*4.2.5. N-Benzyloxycarbonyl-L-phenylalanyl-N′-(4-methoxybenzyl)-α,α-dipropylglycine cyclohexylamide (**4d**).* The reaction was carried out on a 0.02-M scale with *N*-benzyloxycarbonyl-L-phenylalanine as the acid component. The crude product purified by column chromatography, yielding **4d** (10.6 g, 82.2%) as a white solid, mp 65–67 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.88 (6H, dt, *J*=7.2, 18.6 Hz, CH$_3$), 1.02–2.18 (18H, m, 4×CH$_2$+C$_6$H$_{11}$), 2.62–2.85 (2H, m, CHCH$_2$Ph), 3.71–3.87 (1H, m, C$_6$H$_{11}$-*H1*), 3.81 (3H, s, OCH$_3$), 4.46 (1H, d, *J*=18.3 Hz, NCH$_2$), 4.59 (1H, q, *J*=5.7 Hz, CHCH$_2$Ph), 4.76 (1H, d, *J*=18.0 Hz, NCH$_2$), 4.99 (2H, q, *J*=11.7 Hz, CH$_2$OCO), 5.26 (1H, d, *J*=8.1 Hz, OCONH), 5.53 (1H, d, *J*=7.8 Hz, CONH), 6.75 (2H, br s, CHCH$_2$Ph-*H2,6*), 6.93 (2H, d, *J*=8.7 Hz, NCH$_2$Ph-*H3,5*), 7.13–7.39 (8H, m, CHCH$_2$Ph-*H3,4,5*+OCOCH$_2$*Ph*), 7.59 (2H, d, *J*=8.7 Hz, NCH$_2$Ph-*H2,6*); ^{13}C NMR (75 MHz, CDCl$_3$): δ 14.47 (*C*H$_3$CH$_2$), 14.57 (*C*H$_3$CH$_2$), 17.00 (CH$_3$*C*H$_2$), 17.29 (CH$_3$*C*H$_2$), 24.88 (C$_6$H$_{11}$-*C3,5*), 25.60 (C$_6$H$_{11}$-*C4*), 32.98 (C$_6$H$_{11}$-*C2,6*), 33.72 (C*C*H$_2$), 34.58 (C*C*H$_2$), 38.88 (CH*C*H$_2$Ph), 47.68 (N*C*H$_2$Ph), 48.30 (C$_6$H$_{11}$-*C1*), 53.64 (*C*HCH$_2$Ph), 55.26 (O*C*H$_3$), 66.56 (OCO*C*H$_2$Ph), 68.24 (C^{α}), 114.35 (NCH$_2$Ph-*C3,5*), 126.55 (CHCH$_2$Ph-*C4*), 127.58 (NCH$_2$Ph-*C2,6*), 127.71 (OCOCH$_2$Ph-*C2,6*), 127.92 (OCOCH$_2$Ph-*C4,*), 128.24, 128.35 (OCOCH$_2$Ph-*C3,5*+CHCH$_2$Ph-*C3,5*), 129.15 (CHCH$_2$Ph-*C2,6*), 131.47 (NCH$_2$Ph-*C1*), 136.26, 136.54 (OCOCH$_2$Ph-*C1*+CHCH$_2$Ph-*C1*), 155.69 (O*C*ONH), 158.81 (NCH$_2$Ph-*C4*), 172.37 (*C*ON), 173.36 (*C*ONH). Anal. Calcd for C$_{39}$H$_{51}$N$_3$O$_5$: C, 72.98; H, 8.01; N, 6.55. Found: C, 72.79; H, 7.98; N, 6.51.

*4.2.6. N-Benzyloxycarbonyl-L-phenylalanyl-N′-(4-methoxybenzyl)-α,α-diisobutylglycine cyclohexylamide (**4e**).* The reaction was carried out on a 0.02-M scale with *N*-benzyloxycarbonyl-L-phenylalanine as the acid component. The crude product was purified by column chromatography, yielding **4e** (9.4 g, 70.1%) as a white solid, mp 72–74 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.85 (3H, d, *J*=6.3 Hz, C*H*$_3$), 0.89 (3H, d, *J*=6.3 Hz, C*H*$_3$), 0.95 (6H, d, *J*=6.6 Hz, C*H*$_3$), 1.08–2.00 (14H, m, 2×C*H*$_2$+C$_6$*H*$_{11}$), 2.00–2.12 (1H, m, C*H*), 2.32–2.41 (1H, m, C*H*), 2.53–2.78 (2H, m, CHC*H*$_2$Ph), 3.73–3.85 (1H, m, C$_6$H$_{11}$-*H1*), 3.82 (3H, s, OC*H*$_3$), 4.58–4.70 (2H, m, NC*H*$_2$+ C*H*CH$_2$Ph), 4.88–5.04 (3H, m, NC*H*$_2$+C*H*$_2$OCO), 5.22 (1H, d, *J*=10.2 Hz, OCON*H*), 5.56 (1H, d, *J*=8.8 Hz, CON*H*), 6.61–6.70 (2H, m, CHCH$_2$Ph-*H2,6*), 6.98 (2H, d, *J*=8.4 Hz, NCH$_2$Ph-*H3,5*), 7.08–7.38 (8H, m, CHCH$_2$Ph-*H3,4,5*+OCOCH$_2$*Ph*), 7.76 (2H, d, *J*=8.9 Hz, NCH$_2$Ph-*H2,6*); ^{13}C NMR (75 MHz, CDCl$_3$): δ 23.45 (*C*H$_3$CH), 23.74 (*C*H$_3$CH), 24.38 (*C*H$_3$CH), 23.68 (*C*H$_3$CH), 24.88 (C$_6$H$_{11}$-*C3,5*), 25.32 (CH$_3$*C*H), 25.61 (C$_6$H$_{11}$-*C4*), 25.65 (CH$_3$*C*H), 32.94 (C$_6$H$_{11}$-*C2,6*), 38.49 (CH*C*H$_2$Ph), 39.31 (C*C*H$_2$), 41.93 (C*C*H$_2$), 47.65 (N*C*H$_2$Ph), 48.51 (C$_6$H$_{11}$-*C1*), 53.32 (*C*HCH$_2$Ph), 55.27 (O*C*H$_3$), 66.52 (OCO*C*H$_2$Ph), 68.01 (C^{α}), 114.37 (NCH$_2$Ph-*C3,5*), 126.33 (CHCH$_2$Ph-*C4*), 127.61 (NCH$_2$Ph-*C2,6*), 127.84 (OCOCH$_2$Ph-*C2,6*+OCOCH$_2$Ph-*C4,*), 128.05, 128.32 (OCOCH$_2$Ph-*C3,5*+CHCH$_2$Ph-*C3,5*), 129.19 (CHCH$_2$Ph-*C2,6*), 131.77 (NCH$_2$Ph-*C1*), 136.24, 136.63 (OCOCH$_2$Ph-*C1*+CHCH$_2$Ph-*C1*), 155.80 (O*C*ONH), 158.84 (NCH$_2$Ph-*C4*), 172.42 (*C*ON), 173.81 (*C*ONH). Anal. Calcd for C$_{41}$H$_{55}$N$_3$O$_5$: C, 73.51; H, 8.28; N, 6.27. Found: C, 73.80; H, 8.10; N, 6.30.

*4.2.7. N-Benzyloxycarbonyl-L-phenylalanyl-N′-(4-methoxybenzyl)-α,α-dibenzylglycine cyclohexylamide (**4f**).* The reaction was carried out on a 0.01-M scale with *N*-benzyloxycarbonyl-L-phenylalanine as the acid component. The crude product purified by column chromatography and then recrystallized from diethyl ether/petroleum ether (40–60 °C) to yield **4f** (4.46 g, 60.5%) as a white crystals, mp 114.3–115.3 °C. ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ 0.78–1.25 (6H, m, C$_6$*H*$_{11}$), 1.45–1.68 (3H, m, C$_6$*H*$_{11}$), 1.77 (1H, br d, *J*=10.8 Hz, C$_6$*H*$_{11}$), 2.65 (2H, dt, *J*=12.7, 28.8 Hz, CHC*H*$_2$Ph), 2.78 (1H, d, *J*=12.0 Hz CC*H*$_2$Ph), 2.94 (1H, d, *J*=12.6 Hz, CC*H*$_2$Ph), 3.09 (1H, d, *J*=12.3 Hz, CC*H*$_2$Ph), 3.32–3.41 (1H, m, C$_6$H$_{11}$-*H1*), 3.46 (1H, br d, *J*=18.6 Hz, NC*H*$_2$), 3.56 (1H, d, *J*=12.9 Hz, CC*H*$_2$Ph), 3.74 (3H, s, OC*H*$_3$), 4.22 (1H, td, *J*=2.7, 9.6 Hz, C*H*CH$_2$Ph), 4.34 (1H, d, *J*=19.8 Hz, NC*H*$_2$), 5.01 (2H, s, C*H*$_2$OCO), 6.48 (1H, d, *J*=7.8 Hz, CCON*H*), 6.66 (2H, br d, *J*=6.0 Hz, CHCH$_2$Ph-*H2,6*), 6.93 (2H, d, *J*=8.7 Hz, NCH$_2$Ph-*H3,5*), 7.04–7.10 (3H, m, CHCH$_2$Ph-*H3,4,5*), 7.18–7.34 (15H, m, 2×CCH$_2$*Ph*+OCOCH$_2$*Ph*), 7.66 (2H, d, *J*=8.4 Hz, NCH$_2$Ph-*H2,6*), 7.96 (1H, d, *J*=9.0 Hz, OCON*H*); ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ 24.90, 25.07 (C$_6$H$_{11}$-*C3,5*), 25.33 (C$_6$H$_{11}$-*C4*), 31.16, 32.19 (C$_6$H$_{11}$-*C2,6*), 34.71 (C*C*H$_2$Ph), 37.39 (CH*C*H$_2$Ph), 37.66 (C*C*H$_2$Ph), 46.75 (N*C*H$_2$Ph), 48.15 (C$_6$H$_{11}$-*C1*), 53.71 (*C*HCH$_2$Ph), 55.18 (O*C*H$_3$), 65.13 (OCO*C*H$_2$), 68.95 (C^{α}), 113.97 (NCH$_2$Ph-*C3,5*), 126.12 (CHCH$_2$Ph-*C4*), 126.69 (2×CCH$_2$Ph-*C4*), 127.10 (OCOCH$_2$Ph-*C2,6*), 127.40 (NCH$_2$Ph-*C2,6*), 127.64 (OCOCH$_2$Ph-*C4,*), 127.84, 127.92 (CHCH$_2$Ph-*C3,5*+OCOCH$_2$Ph-*C3,5*), 128.34 (2×CCH$_2$Ph-*C3,5*), 129.03 (CHCH$_2$Ph-*C2,6*), 130.81, 130.99 (2×CCH$_2$Ph-*C2,6*), 132.23 (NCH$_2$Ph-*C1*), 135.35, 136.01 (2×CCH$_2$Ph-*C1*), 137.25 (OCOCH$_2$Ph-*C1*), 137.89 (CHCH$_2$Ph-*C1*), 155.81 (O*C*ONH), 158.27 (NCH$_2$Ph-*C4*), 170.23 (C*C*ONH), 173.92 (*C*ON). Anal. Calcd for C$_{47}$H$_{51}$N$_3$O$_5$: C, 76.50; H, 6.97; N, 5.69. Found: C, 76.65; H, 6.68; N, 5.56.

*4.2.8. N-Benzyloxycarbonyl-L-phenylalanylglycyl-N′-(4-methoxybenzyl)-α,α-diethylglycine cyclohexylamide (**7a**).* The reaction was carried out on a 0.02-M scale with *N*-benzyloxycarbonyl-L-phenylalanylglycine as the acid component. The product was purified by column chromatography (dichloromethane, dichloromethane/methanol 100:1, 50:1) and recrystallized from ethyl acetate/*n*-hexane to yield **7a** (3.02 g, 90.2%), as a white solid, mp 117.8–118.8 °C, ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ 0.72 (6H, t, *J*=7.2 Hz, 2×CH$_2$C*H*$_3$), 1.00–1.34 (5H, m, C$_6$*H*$_{11}$), 1.48–1.78 (7H, m, C$_6$*H*$_{11}$+CC*H*$_2$), 1.98–2.16 (2H, m, CC*H*$_2$), 2.68 (1H, dd, *J*=11.4, 13.5 Hz, CHC*H*$_2$Ph), 3.01 (1H, dd, *J*=3.3, 13.8 Hz, CHC*H*$_2$Ph), 3.48–3.66 (1H, m, C$_6$H$_{11}$-*H1*), 3.74 (3H, s, OC*H*$_3$), 3.78–3.98 (2H, m, NHC*H*$_2$), 4.22–4.35 (1H, m, C*H*CH$_2$Ph), 4.60 (2H, s, NC*H*$_2$), 4.90 (2H, d, *J*=1.5 Hz, C*H*$_2$OCO), 6.54 (1H, d, *J*=7.8 Hz, CON*H*), 6.92 (2H, d, *J*=8.7 Hz, NCH$_2$Ph-*H3,5*), 7.12–7.36 (10H, m, CHCH$_2$*Ph*+OCOCH$_2$*Ph*), 7.51 (1H, d, *J*=9.0 Hz, OCON*H*), 7.65 (2H, d, *J*=8.4 Hz, NCH$_2$Ph-*H2,6*), 8.06 (1H, t, *J*=4.8 Hz, N*H*CH$_2$); ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ 8.09 (2×CH$_2$*C*H$_3$), 23.34 (2×C*C*H$_2$), 24.84 (C$_6$H$_{11}$-*C3,5*), 25.27 (C$_6$H$_{11}$-*C4*), 32.28 (C$_6$H$_{11}$-*C2,6*), 37.42 (CH*C*H$_2$Ph), 41.75 (NH*C*H$_2$), 46.46 (N*C*H$_2$Ph), 48.00 (C$_6$H$_{11}$-*C1*), 55.02 (O*C*H$_3$), 56.06 (*C*HCH$_2$Ph), 65.15 (OCO*C*H$_2$), 68.57 (C^{α}), 113.89 (NCH$_2$Ph-*C3,5*), 126.17 (CHCH$_2$Ph-*C4*), 127.31, 127.36 (OCOCH$_2$Ph-*C2,6*+NCH$_2$Ph-*C2,6*), 127.60 (OCOCH$_2$Ph-*C4*), 128.00, 128.26 (CHCH$_2$Ph-*C3,5*+OCOCH$_2$Ph-*C3,5*), 129.16 (CHCH$_2$Ph-*C2,6*), 131.61 (NCH$_2$Ph-*C1*), 136.98 (OCOCH$_2$Ph-*C1*), 138.22 (CHCH$_2$Ph-*C1*), 155.78 (O*C*ONH), 158.08 (NCH$_2$Ph-*C4*), 168.72 (*C*ON), 171.52, 171.58 (*C*ONH+*C*ONHCH$_2$). Anal. Calcd for C$_{39}$H$_{50}$N$_4$O$_6$: C, 69.83; H, 7.51; N, 8.35. Found: C, 69.64; H, 7.44; N, 8.42.

*4.2.9. N-Benzyloxycarbonyl-L-phenylalanylglycyl-N′-(4-methoxybenzyl)-α,α-dibenzylglycine cyclohexylamide (**7b**).* The reaction was carried out on a 0.02-M scale with *N*-benzyloxycarbonyl-L-phenylalanylglycine as the acid component. The product was purified by column chromatography using the following eluents: dichloromethane/hexane 2:1, dichloromethane, dichloromethane/methanol 200:1 and 100:1. The product obtained is recrystallized from ethyl acetate/petroleum ether (40–60 °C) to yield **7b** (4.27 g, 53.7%), as a white solid, mp 210.0–211.9 °C, ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.76–0.98 (2H, m, C$_6$*H*$_{11}$), 0.99–1.44 (4H, m, C$_6$*H*$_{11}$), 1.58–1.76 (3H, m, C$_6$*H*$_{11}$), 1.88–1.99 (1H, m, C$_6$*H*$_{11}$), 2.99 (2H, d, *J*=12.3 Hz, CC*H*$_2$Ph), 3.05–3.18 (2H, m, CHC*H*$_2$Ph), 3.37 (2H, d, *J*=11.7 Hz, CC*H*$_2$Ph), 3.44–3.62 (1H, m, C$_6$H$_{11}$-*H1*), 3.59 (2H, s, NC*H*$_2$), 3.78 (3H, s, OC*H*$_3$), 3.86–4.03 (2H, m, NHC*H*$_2$), 4.52 (1H, br q, *J*=6.9 Hz, C*H*CH$_2$Ph), 5.01–5.15 (3H, m, CON*H*+C*H*$_2$OCO), 5.34 (1H, d, *J*=7.8 Hz, OCON*H*), 6.79 (1H, br t, *J*=5.4 Hz, N*H*CH$_2$), 6.88 (2H, d, *J*=9.0 Hz, NCH$_2$Ph-*H3,5*), 7.18 (2H, br d, *J*=6.6 Hz, CHCH$_2$Ph-*H2,6*), 7.20–7.43 (18H, m, CHCH$_2$Ph-*H3,4,5*+2×CCH$_2$*Ph*+OCOCH$_2$*Ph*), 7.53 (2H, d, *J*=8.4 Hz, NCH$_2$Ph-*H2,6*); ^{13}C NMR (75 MHz, CDCl$_3$): δ 24.81, 24.90 (C$_6$H$_{11}$-*C3,5*), 25.49 (C$_6$H$_{11}$-*C4*), 32.55, 33.90 (C$_6$H$_{11}$-*C2,6*), 35.84 (2×C*C*H$_2$Ph), 38.80 (CH*C*H$_2$Ph), 42.42 (NH*C*H$_2$), 46.59 (N*C*H$_2$Ph), 48.30 (C$_6$H$_{11}$-*C1*), 55.19 (O*C*H$_3$), 55.96 (*C*HCH$_2$Ph), 66.90 (OCO*C*H$_2$), 69.68 (C^{α}), 114.25 (NCH$_2$Ph-*C3,5*), 126.84 (NCH$_2$Ph-*C2,6*), 126.95 (CHCH$_2$Ph-*C4*), 127.31 (2×CCH$_2$Ph-*C4*), 127.94 (OCOCH$_2$Ph-*C2,6*), 128.05 (OCOCH$_2$Ph-*C4*), 128.45, 128.51, 128.57 (CHCH$_2$Ph-*C3,5*+2×CCH$_2$Ph-*C3,5*+OCOCH$_2$Ph-*C3,5*), 129.25 (CHCH$_2$Ph-*C2,6*), 129.60 (NCH$_2$Ph-*C1*), 130.75 (2×CCH$_2$Ph-*C2,6*), 135.07 (2×CCH$_2$Ph-*C1*), 136.18 (OCOCH$_2$Ph-*C1*), 136.26 (CHCH$_2$Ph-*C1*), 155.69 (O*C*ONH), 158.64 (NCH$_2$Ph-*C4*), 169.41 (*C*ON), 170.51 (*C*ONH+*C*ONHCH$_2$).

Anal. Calcd for $C_{49}H_{54}N_4O_6$: C, 74.03, H, 6.85; N, 7.05. Found: C, 73.58; H, 6.84; N, 7.20.

4.3. Synthesis of *N*-acetylamino acids 2a–2e

All reactions were carried out by full acidolysis of compounds **1a**–**1e** under conditions previously described.[27]

*4.3.1. 1-(N-Acetylamino)-cyclohexylcarboxylic acid (**2a**).* The reaction was carried out using 1.0 g of compound **1a**. The product was purified by recrystallization from ethyl acetate/hexane to yield **2a** (340 mg, 70.5%), as a white crystals, mp 201.0–202.4 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.15–1.27 (1H, m, CC_6H_{10}), 1.37–1.53 (5H, m, CC_6H_{10}), 1.61 (2H, td, J=4.7, 10.5 Hz, CC_6H_{10}), 1.83 (3H, s, CH_3CO), 1.90 (2H, br d, J=13.2 Hz, CC_6H_{10}), 7.78 (1H, *s*, CON*H*), 11.99 (1H, br s, O*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.08 (CC_6H_{10}-*C3,5*), 22.64 (CH_3CO), 25.03 (CC_6H_{10}-*C4*), 31.78 (CC_6H_{10}-*C2,6*), 57.63 (C^{α}), 169.05 (CH_3CO), 175.72 (*C*OOH). Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.60; H, 8.04; N, 7.76.

*4.3.2. N-Acetyl-α,α-diethylglycine (**2b**).* The reaction was carried out on a 0.01-M scale, yielding **2b** (1.62 g, 93.6%) as a white solid, mp 209–211 °C (lit.[15] 209–211 °C).

*4.3.3. N-Acetyl-α,α-dipropylglycine (**2c**).* The reaction was carried out on a 0.005-M scale, yielding **2c** (1.02 g, 98.1%) as a white solid, mp 196–197 °C (lit.[15] 196–197 °C).

*4.3.4. N-Acetyl-α,α-diisobutylglycine (**2d**).* The reaction was carried out on a 0.01-M scale, yielding **2d** (1.83 g, 79.8%) as a white solid, mp 216–218 °C (lit.[15] 216–218 °C).

*4.3.5. N-Acetyl-α,α-dibenzylglycine (**2e**).* The reaction was carried out on a 0.02-M scale, yielding **2e** (5.30 g, 89.1%) as a white solid, mp 233–235 °C (lit.[15] 233–235 °C).

4.4. Synthesis of dipeptide acids 5a–5f and tripeptide acids 8a and 8b

The Ugi–Passerini products (1.0 g) were dissolved in 20 mL of 25% TFA in dichloromethane and refluxed for 25–60 min. The solvent was evaporated under reduced pressure at 30 °C and 2 M aqueous NaOH was added until pH=3. The mixture was stirred overnight and then extracted into ethyl acetate (3×30 mL). The combined organic layers were washed with water (2×40 mL), dried over anhydrous $MgSO_4$ and filtrated. The filtrate was concentrated under reduced pressure and the residue thus obtained purified by column chromatography and/or recrystallization.

*4.4.1. 1-(N-Benzyloxycarbonyl-L-phenylalanylamino)-cyclohexylcarboxylic acid (**5a**).* The reaction was carried out with 0.75 g of **4a** and the product purified by column chromatography (dichloromethane/methanol, 50:1) and recrystallized from ethyl acetate/hexane to yield **5a** (557 mg, 82.0%), as a white solid, mp 188.0–189.2 °C, $[\alpha]_D$ −11.6 (*c* 1, ethanol). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.17–1.68 (8H, m, CC_6H_{10}), 1.97 (2H, br t, J=11.7 Hz CC_6H_{10}), 2.71 (1H, dd, J=11.0, 13.7 Hz, $CHCH_2Ph$), 2.96 (1H, dd, J=4.1, 14.1 Hz, $CHCH_2Ph$), 4.32–4.42 (1H, m, $CHCH_2Ph$), 4.92 (2H, s, CH_2OCO), 7.17–7.32 (10H, m, $CHCH_2Ph$+$OCOCH_2Ph$), 7.40 (1H, d, J=9.0 Hz, OCON*H*), 7.91 (1H, s, CON*H*), 12.14 (1H, br s, O*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.98, 21.03 (CC_6H_{10}-*C3,5*), 24.98 (CC_6H_{10}-*C4*), 31.51, 31.76 (CC_6H_{10}-*C2,6*), 37.70 ($CHCH_2Ph$), 55.76 ($CHCH_2Ph$), 57.82 (C^{α}), 65.10 (CH_2OCO), 126.19 ($CHCH_2Ph$-*C4*), 127.37 ($OCOCH_2Ph$-*C2,6*), 127.65 ($OCOCH_2Ph$-*C4*), 127.98, 128.26 ($CHCH_2Ph$-*C3,5*+$OCOCH_2Ph$-*C3,5*), 129.27 ($CHCH_2Ph$-*C2,6*), 137.02 ($OCOCH_2Ph$-*C1*), 138.13 ($CHCH_2Ph$-*C1*), 155.75 (*O*CONH), 171.13 (*C*ONH), 175.49 (*C*OOH). Anal. Calcd for $C_{24}H_{28}N_2O_5$: C, 67.91; H, 6.65; N, 6.60. Found: C, 67.59; H, 6.75; N, 6.14.

*4.4.2. N-Benzyloxycarbonyl-L-phenylalanyl-α,α-dimethylglycine (**5b**).* The reaction was carried out with 2.0 g of **4b** and the product purified by column chromatography (dichloromethane/methanol, 25:1) and recrystallized from ethyl acetate to yield **5b** (804 mg, 61.4%), as a white solid, mp 186.9–188.0 °C, $[\alpha]_D$ −3.48 (*c* 1, ethanol). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.34 (6H, d, J=9.6 Hz, 2×CH_3), 2.71 (1H, dd, J=10.7, 13.6 Hz, $CHCH_2Ph$), 2.96 (1H, dd, J=3.9, 13.8 Hz, $CHCH_2Ph$), 4.27 (1H, td, J=3.7, 10.2 Hz, $CHCH_2Ph$), 4.93 (2H, d, J=2.7 Hz, CH_2OCO), 7.15–7.36 (10H, m, $CHCH_2Ph$+$OCOCH_2Ph$), 7.40 (1H, d, J=9.0 Hz, OCON*H*), 8.17 (1H, s, CON*H*), 12.27 (1H, br s, O*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ 24.84 (2×CCH_3), 37.72 ($CHCH_2Ph$), 54.93 (C^{α}), 55.79 ($CHCH_2Ph$), 65.12 ($OCOCH_2$), 126.22 ($CHCH_2Ph$-*C4*), 127.35 ($OCOCH_2Ph$-*C2,6*), 127.65 ($OCOCH_2Ph$-*C4*), 128.00 ($CHCH_2Ph$-*C3,5*), 128.28 ($OCOCH_2Ph$-*C3,5*), 129.30 ($CHCH_2Ph$-*C2,6*), 137.09 ($OCOCH_2Ph$-*C1*), 138.08 ($CHCH_2Ph$-*C1*), 155.73 (*O*CONH), 170.78 (*C*ONH), 175.45 (*C*OOH). Anal. Calcd for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N, 7.29. Found: C, 65.70; H, 6.18; N, 7.42.

*4.4.3. N-Benzyloxycarbonyl-L-phenylalanyl-α,α-diethylglycine (**5c**).* The reaction was carried out with 1.0 g of **4c** and the product purified by column chromatography (dichloromethane/methanol, 25:1) and recrystallized from ethyl acetate to yield **5c** (557 mg, 84.4%), as a white crystals, mp 177.5–178.6 °C, $[\alpha]_D$ −0.8 (*c* 1, ethanol). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.65 (6H, dt, J=7.5, 18.3 Hz, 2×CH_2CH_3), 1.71 (2H, sept, J=7.2 Hz, CH_2CH_3), 2.12 (2H, sept, J=6.6 Hz, CH_2CH_3), 2.74 (1H, dd, J=2.7, 10.8 Hz, $CHCH_2Ph$), 3.03 (1H, dd, J=4.2, 9.6 Hz, $CHCH_2Ph$), 4.18–4.26 (1H, m, $CHCH_2Ph$), 4.95 (2H, q, J=12.9 Hz, CH_2OCO), 7.15–7.33 (10H, m, $CHCH_2Ph$+$OCOCH_2Ph$), 7.59 (1H, s, CON*H*), 7.73 (1H, d, J=8.7 Hz, OCON*H*), 12.96 (1H, br s, O*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ 8.03 (2×CH_2CH_3), 26.53 (CCH_2CH_3), 26.69 (CCH_2CH_3), 37.05 ($CHCH_2Ph$), 56.82 ($CHCH_2Ph$), 63.81 (C^{α}), 65.17 ($OCOCH_2$), 126.25 ($CHCH_2Ph$-*C4*), 127.25 ($OCOCH_2Ph$-*C2,6*), 127.61 ($OCOCH_2Ph$-*C4*), 128.09 ($CHCH_2Ph$-*C3,5*), 128.27 ($OCOCH_2Ph$-*C3,5*), 129.16 ($CHCH_2Ph$-*C2,6*), 137.05 ($OCOCH_2Ph$-*C1*), 138.23 ($CHCH_2Ph$-*C1*), 155.89 (*O*CONH), 170.30 (*C*ONH), 174.62 (*C*OOH). Anal. Calcd for $C_{23}H_{28}N_2O_5$: C, 66.97; H, 6.84; N, 6.79. Found: C, 66.86; H, 6.75; N, 6.84.

*4.4.4. N-Benzyloxycarbonyl-L-phenylalanyl-α,α-dipropylglycine (**5d**).* The reaction was carried out with 2.0 g of **4d** and the product purified by column chromatography (dichloromethane/methanol, 25:1) and recrystallized from diethyl ether to yield **5d** (1.17 g, 85.4%), as a white solid, mp 156.3–157.6 °C, $[\alpha]_D$ −1.6 (*c* 1, ethanol). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.78 (6H, q, J=7.2 Hz, 2×CH_2CH_3), 0.89–1.24 (4H, m, 2×CH_2CH_3), 1.56–1.70 (2H, m, CCH_2), 2.02–2.16 (2H, m, CCH_2), 2.72 (1H, dd, J=10.5, 13.5 Hz, $CHCH_2Ph$), 3.01 (1H, dd, J=4.2, 9.6 Hz, $CHCH_2Ph$), 4.16–4.24 (1H, m, $CHCH_2Ph$), 4.95 (2H, q, J=12.6 Hz, CH_2OCO), 7.16–7.32 (10H, m, $CHCH_2Ph$+$OCOCH_2Ph$), 7.56 (1H, s, CON*H*), 7.72 (1H, d, J=8.4 Hz, OCON*H*), 12.97 (1H, br s, O*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.10 (2×CH_2CH_3), 16.62 (CH_2CH_3), 16.77 (CH_2CH_3), 36.42 (CCH_2), 36.49 (CCH_2), 37.01 ($CHCH_2Ph$), 56.86 ($CHCH_2Ph$), 62.81 (C^{α}), 65.20 ($OCOCH_2$), 126.24 ($CHCH_2Ph$-*C4*), 127.28 ($OCOCH_2Ph$-*C2,6*), 127.65 ($OCOCH_2Ph$-*C4*), 128.10 ($CHCH_2Ph$-*C3,5*), 128.30 ($OCOCH_2Ph$-*C3,5*), 129.19 ($CHCH_2Ph$-*C2,6*), 137.09 ($OCOCH_2Ph$-*C1*), 138.21 ($CHCH_2Ph$-*C1*), 155.91 (*O*CONH), 170.17 (*C*ONH), 174.93 (*C*OOH). Anal. Calcd for $C_{25}H_{32}N_2O_5$: C, 68.16; H, 7.32; N, 6.36. Found: C, 68.33; H, 7.21; N, 6.50.

*4.4.5. N-Benzyloxycarbonyl-L-phenylalanyl-α,α-diisobutylglycine (**5e**).* The reaction was carried out with 1.0 g of **4e** and the product purified by column chromatography (dichloromethane/methanol, 25:1) and recrystallized from ethyl acetate to yield **5e** (587 mg, 83.5%), as a white crystals, mp 170.2–171.6 °C, $[\alpha]_D$ −1.6 (*c* 1, ethanol). ^{1}H NMR

(300 MHz, DMSO-d_6): δ 0.70–0.81 (12H, m, 2×CH(CH$_3$)$_2$), 1.38 (2H, sept, J=6.5 Hz, 2×CH(CH$_3$)$_2$), 1.44–1.56 (2H, m, CCH$_2$), 2.23–2.34 (2H, m, CCH$_2$), 2.72 (1H, dd, J=11.1, 13,5 Hz, CHCH$_2$Ph), 3.05 (1H, dd, J=4.1, 13.8 Hz, CHCH$_2$Ph), 4.14–4.22 (1H, m, CHCH$_2$Ph), 4.95 (2H, dd, J=12.6, 32.7 Hz, CH$_2$OCO), 7.16–7.32 (10H, m, CHCH$_2$Ph+OCOCH$_2$Ph), 7.60 (1H, s, CONH), 7.91 (1H, d, J=8.4 Hz, OCONH), 13.41 (1H, br s, OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 22.62 (CH(CH$_3$)$_2$), 22.89 (CH(CH$_3$)$_2$), 23.83 (CHCH$_3$), 23.89 (CHCH$_3$), 23.92 (CHCH$_3$), 23.97 (CHCH$_3$), 36.62 (CHCH$_2$Ph), 43.77 (CCH$_2$), 43.90 (CCH$_2$), 57.34 (CHCH$_2$Ph), 62.22 (C^{α}), 65.26 (OCOCH$_2$), 126.26 (CHCH$_2$Ph-*C4*), 127.28 (OCOCH$_2$Ph-*C2,6*), 127.66 (OCOCH$_2$Ph-*C4*), 128.13 (CHCH$_2$Ph-*C3,5*), 128.29 (OCOCH$_2$Ph-*C3,5*), 129.14 (CHCH$_2$Ph-*C2,6*), 137.00 (OCOCH$_2$Ph-*C1*), 138.33 (CHCH$_2$Ph-*C1*), 155.94 (OCONH), 170.08 (CONH), 176.19 (COOH). Anal. Calcd for $C_{27}H_{36}N_2O_5$: C, 69.21; H, 7.74; N, 5.98. Found: C, 69.52; H, 7.64; N, 6.17.

*4.4.6. N-Benzyloxycarbonyl-L-phenylalanyl-α,α-dibenzylglycine (**5f**).* The reaction was carried out with 1.0 g of **4f** and the product purified by column chromatography (dichloromethane/methanol, 25:1) and recrystallized from diethyl ether/petroleum ether (40–60 °C) to yield **5f** (488 mg, 66.8%), as a white solid, mp 178.3–179.5 °C, $[\alpha]_D$ −10 (*c* 1, ethanol). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.63 (1H, br t, J=12.6 Hz, CHCH$_2$Ph), 2.90 (1H, br d, J=12.6 Hz, CHCH$_2$Ph), 3.14 (2H, d, J=12.6 Hz, CCH$_2$Ph), 3.69 (2H, br t, J=14.6 Hz, CCH$_2$Ph), 4.08–4.22 (1H, m, CHCH$_2$Ph), 4.88 (2H, d, J=5.7 Hz, CH$_2$OCO), 7.02–7.32 (21H, m, 2×CCH$_2$Ph+CHCH$_2$Ph+OCOCH$_2$Ph+CONH), 7.72 (1H, d, J=8.7 Hz, OCONH), 13.75 (1H, br s, OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 36.95 (CHCH$_2$Ph), 39.83, 39.95 (2×CCH$_2$Ph), 57.24 (CHCH$_2$Ph), 65.16 (OCOCH$_2$), 66.00 (C^{α}), 126.24 (CHCH$_2$Ph-*C4*), 126.47 (2×CCH$_2$Ph-*C4*), 127.26 (OCOCH$_2$Ph-*C2,6*), 127.60 (OCOCH$_2$Ph-*C4*), 127.90 (CCH$_2$Ph-*C3,5*), 127.95 (CCH$_2$Ph-*C3,5*), 128.08 (CHCH$_2$Ph-*C3,5*), 128.26 (OCOCH$_2$Ph-*C3,5*), 129.23 (CHCH$_2$Ph-*C2,6*), 129.84 (CCH$_2$Ph-*C2,6*), 129.90 (CCH$_2$Ph-*C2,6*), 136.54 (2×CCH$_2$Ph-*C1*), 136.96 (OCOCH$_2$Ph-*C1*), 138.38 (CHCH$_2$Ph-*C1*), 155.87 (OCONH), 171.40 (CONH), 172.85 (COOH). Anal. Calcd for $C_{33}H_{32}N_2O_5$: C, 73.86; H, 6.01; N, 5.22. Found: C, 73.69; H, 6.02; N, 5.38.

*4.4.7. N-Benzyloxycarbonyl-L-phenylalanylglycyl-α,α-diethylglycine (**8a**).* The reaction was carried out with 1.0 g of **7a** and the product purified by column chromatography (dichloromethane/methanol, 9:1) and recrystallized from ethyl acetate/hexane to yield **8a** (590 mg, 83.8%), as a white solid, mp 123.6–124.8 °C, $[\alpha]_D$ −15.2 (*c* 1, ethanol). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.68 (6H, q, J=7.2 Hz, 2×CH$_2$CH$_3$), 1.72 (2H, q, J=7.0 Hz, CCH$_2$), 1.95–2.14 (2H, m, CCH$_2$), 2.75 (1H, dd, J=11.4, 13.8 Hz, CHCH$_2$Ph), 3.06 (1H, dd, J=3.3, 13.8 Hz, CHCH$_2$Ph), 3.72 (2H, qd, J=5.8, 16.8 Hz, NHCH$_2$), 4.18–4.35 (1H, m, CHCH$_2$Ph), 4.92 (2H, s, CH$_2$OCO), 7.10–7.38 (10H, m, CHCH$_2$Ph+OCOCH$_2$Ph), 7.42 (1H, s, CONH), 7.58 (1H, d, J=8.4 Hz, OCONH), 8.50 (1H, t, J=5.7 Hz, NHCH$_2$); ^{13}C NMR (75 MHz, DMSO-d_6): δ 8.06 (CH$_2$CH$_3$), 8.17 (CH$_2$CH$_3$), 26.54 (CCH$_2$), 26.67 (CCH$_2$), 37.43 (CHCH$_2$Ph), 42.52 (NHCH$_2$), 56.34 (CHCH$_2$Ph), 63.62 (C^{α}), 65.24 (OCOCH$_2$), 126.30 (CHCH$_2$Ph-*C4*), 127.46 (OCOCH$_2$Ph-*C2,6*), 127.72 (OCOCH$_2$Ph-*C4*), 128.10, 128.32 (CHCH$_2$Ph-*C3,5*+OCOCH$_2$Ph-*C3,5*), 129.21 (CHCH$_2$Ph-*C2,6*), 137.01 (OCOCH$_2$Ph-*C1*), 138.26 (CHCH$_2$Ph-*C1*), 155.98 (OCONH), 167.53 (CON), 172.22 (CONHCH$_2$), 174.59 (COOH). Anal. Calcd for $C_{25}H_{31}N_3O_6$.1/3H$_2$O: C, 63.14, H, 6.71; N, 8.84. Found: C, 63.28; H, 6.88; N, 8.36.

*4.4.8. N-Benzyloxycarbonyl-L-phenylalanylglycyl-α,α-dibenzylglycine (**8b**).* For this compound 50% of TFA in dichloromethane was used. The reaction was carried out with 0.25 g of **7b** and the product purified by column chromatography (dichloromethane/methanol, 50:1) and recrystallized from ethyl acetate/petroleum ether (40–60 °C) to yield **8b** (92 mg, 50.0%), as a white solid, mp 129.9–131.0 °C, $[\alpha]_D$ −16.0 (*c* 1, ethanol). ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.83–3.10 (2H, m, CHCH$_2$Ph), 3.31 (2H, dd, J=6.3, 13.2 Hz, CCH$_2$Ph), 3.52 (2H, ddd, J=4.2, 17.0, 50.0 Hz, NHCH$_2$), 3.69–3.85 (2H, m, CCH$_2$Ph), 4.37 (1H, br q, J=6.6 Hz, CHCH$_2$Ph), 4.93 (2H, q, J=12.0 Hz, CH$_2$OCO), 5.54 (1H, d, J=6.9 Hz, OCONH), 6.56 (1H, s, CONH), 6.96–7.42 (21H, *m*, NHCH$_2$+CHCH$_2$Ph+2×C$^{\alpha}$CH$_2$Ph+OCOCH$_2$Ph); ^{13}C NMR (75 MHz, CDCl$_3$): δ 38.20 (CHCH$_2$Ph), 40.59 (2×CCH$_2$Ph), 43.35 (NHCH$_2$), 55.98 (CHCH$_2$Ph), 67.04 (C^{α}), 67.13 (OCOCH$_2$), 126.78 (CHCH$_2$Ph-*C4*), 127.09 (2×CCH$_2$Ph-*C4*), 127.90 (OCOCH$_2$Ph-*C2,6*), 128.17 (CHCH$_2$Ph-*C3,5*), 128.24 (OCOCH$_2$Ph-*C4*), 128.53, 128.67 (2×CCH$_2$Ph-*C3,5*+OCOCH$_2$Ph-*C3,5*), 129.12 (CHCH$_2$Ph-*C2,6*), 129.94 (2×CCH$_2$Ph-*C2,6*), 135.82 (OCOCH$_2$Ph-*C1*), 136.00 (CHCH$_2$Ph-*C1*), 136.44 (CCH$_2$Ph-*C1*), 136.52 (CCH$_2$Ph-*C1*), 156.11 (OCONH), 168.29 (CONH), 171.67 (CONHCH$_2$), 175.45 (COOH). Anal. Calcd for $C_{35}H_{35}N_3O_6$: C, 70.81; H, 5.94; N, 7.08. Found: C, 70.40; H, 6.20; N, 6.89.

4.5. Oxazolone synthesis of *N*-acetyl dipeptides 3b–3e

The amino acids **2b–2e** (1.3 mmol) were dissolved in dry diethyl ether (10 mL) and 1.0 equiv DCC (0.27 g) was added. The mixture was stirred overnight at room temperature and, after removing the urea by filtration, the solvent was evaporated and the residue taken up in 10 mL dry acetonitrile. Glycine *tert*-butyl ester hydrochloride (1 equiv) was suspended in dry acetonitrile (10 mL) and neutralized with 1.0 equiv triethylamine. After stirring at room temperature for 1 h, the salts were filtrated off and the filtrate added to the above reaction mixture, which was refluxed until the reagents had been consumed (1–3 days), while being monitored by TLC (chloroform/methanol, 9:1). Then, the solvent was evaporated and the residue taken into ethyl acetate and washed with 1 M aqueous HCl and with 10% aqueous solution of Na$_2$CO$_3$. The organic layer was dried over anhydrous MgSO$_4$ and after concentration the residue purified by column chromatography and/or recrystalization.

*4.5.1. N-Acetyl-α,α-diethylglycylglycine tert-butyl ester (**3b**).* Differently from the general procedure described above, the residue obtained by concentration of the reaction mixture was purified directly by column chromatography (dichloromethane/methanol 18:1) without previous washings and recrystallized from ethyl ether/petroleum ether (40–60 °C) to yield **3b** (0.20 g, 53.7%), as a white solid, mp 144–145 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.80 (6H, t, J=7.2 Hz, CH$_3$), 1.49 (9H, s, C(CH$_3$)$_3$), 1.55 (2H, sex, J=7.2 Hz, CCH$_2$), 2.03 (3H, s, CH$_3$CO), 2.64 (2H, sex, J=7.2 Hz, CCH$_2$), 3.97 (2H, d, J=4.8 Hz, NHCH$_2$), 6.23 (1H, br t, J=5.8 Hz, NHCH$_2$), 6.70 (1H, s, CONH); ^{13}C NMR (75 MHz, CDCl$_3$): δ 8.19 (CH$_3$), 24.16 (CH$_3$CO), 28.00 (C(CH$_3$)$_3$), 28.75 (CCH$_2$), 42.23 (NHCH$_2$), 65.25 (C^{α}), 82.51 (C(CH$_3$)$_3$), 168.63 (COOC(CH$_3$)$_3$), 169.09 (CH$_3$CO), 173.29 (CONHCH$_2$). Anal. Calcd for $C_{14}H_{26}N_2O_4$: C, 58.72; H 9.15; N, 9.78. Found: C, 58.52; H, 8.94; N, 9.76.

*4.5.2. N-Acetyl-α,α-dipropylglycylglycine tert-butyl ester (**3c**).* The crude product was recrystallized from ethyl acetate/petroleum ether (40–60 °C) yielding **3c** (0.22 g, 53.8%), as a white solid, mp 120–121 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.88 (6H, t, J=6.9 Hz, CH$_3$), 0.99–1.18 (2H, m, CH$_3$CH$_2$), 1.20–1.36 (2H, m, CH$_3$CH$_2$), 1.45 (2H, ddd, J=4.5, 12.5, 14.0 Hz, CCH$_2$), 1.49 (9H, s, C(CH$_3$)$_3$), 2.01 (3H, s, CH$_3$CO), 2.59 (2H, ddd, J=4.5, 12.5, 14.0 Hz, CCH$_2$), 3.95 (2H, d, J=4.8 Hz, NHCH$_2$), 6.28 (1H, br t, J=5.8 Hz, NHCH$_2$), 6.73 (1H, s, CONH); ^{13}C NMR (75 MHz, CDCl$_3$): δ 13.97 (CH$_3$), 17.08 (CH$_3$CH$_2$), 24.20 (CH$_3$CO), 28.00 (C(CH$_3$)$_3$), 38.26 (CCH$_2$), 42.31 (NHCH$_2$), 64.22 (C^{α}), 82.50 (C(CH$_3$)$_3$), 168.60 (COOC(CH$_3$)$_3$), 169.05 (CH$_3$CO), 173.61 (CONHCH$_2$). Anal. Calcd for $C_{16}H_{30}N_2O_4$: C, 61.12; H 9.62; N, 8.91. Found: C, 61.23; H, 9.45; N, 9.07.

*4.5.3. N-Acetyl-α,α-diisobutylglycylglycine tert-butyl ester (**3d**).* The crude product was recrystallized from ethyl acetate/petroleum ether (40–60 °C) yielding **3d** (0.19 g, 42.7%), as a white solid, mp 141–143 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.83 (12H, dd, J=6.3, 30.3 Hz, CH_3), 1.34 (2H, dd, *J*=6.6, 14.4 Hz, CCH_2), 1.49 (9H, s, $C(CH_3)_3$), 1.50–1.60 (2H, m, CH_3CH), 2.00 (3H, s, CH_3CO), 2.69 (2H, dd, *J*=6.0, 14.7 Hz, CCH_2), 3.95 (2H, d, *J*=4.8 Hz, $NHCH_2$), 6.22 (1H, br t, *J*=5.0 Hz, $NHCH_2$), 7.04 (1H, s, CON*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.17 (CH_3), 23.61 (CH_3), 24.38 (CH_3CH), 24.51 (CH_3CO), 28.00 ($C(CH_3)_3$), 42.24 ($NHCH_2$), 45.41 (CCH_2), 63.17 (C^{α}), 82.82 ($C(CH_3)_3$), 168.54 ($COOC(CH_3)_3$), 168.91 (CH_3CO), 174.26 ($CONHCH_2$). Anal. Calcd for $C_{18}H_{34}N_2O_4$: C, 63.13; H 10.01; N, 8.18. Found: C, 63.37; H, 10.05; N, 8.42.

*4.5.4. N-Acetyl-α,α-dibenzylglycylglycine tert-butyl ester (**3e**).* The crude product was recrystallized from ethyl acetate/petroleum ether (40–60 °C) yielding **3e** (0.23 g, 43.1%), as a white solid, mp 202–204 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.53 (9H, s, $C(CH_3)_3$), 1.94 (3H, s, CH_3CO), 3.21 (2H, d, *J*=13.8 Hz, CH_2Ph), 3.88 (2H, d, *J*=13.8 Hz, CH_2Ph), 3.94 (2H, d, *J*=4.5 Hz, $NHCH_2$), 6.32 (1H, s, CON*H*), 6.55 (1H, br t, *J*=5.4 Hz, $NHCH_2$), 7.08–7.15 (4H, m, Ph-*H2,6*), 7.20–7.30 (6H, m, Ph-*H3,4,5*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.49 (CH_3CO), 28.02 ($C(CH_3)_3$), 41.26 (CH_2Ph), 42.25 ($NHCH_2$), 65.75 (C^{α}), 82.87 ($C(CH_3)_3$), 126.97 (Ph-*C4*), 128.23 (Ph-*C3,5*), 129.87 (Ph-*C2,6*), 135.81 (Ph-*C1*), 168.67 ($COOC(CH_3)_3$), 170.18 (CH_3CO), 171.31 ($CONHCH_2$). Anal. Calcd for $C_{24}H_{30}N_2O_4$: C, 70.22; H 7.37; N, 6.82. Found: C, 70.41; H, 7.20; N, 6.89.

4.6. DCC/HOBt-assisted synthesis of peptides 3a, 6a–6f, 9a and 9b

To a 0.1-M solution of **2a**, **5a**–**5f**, **8a** and **8b** in dry acetonitrile 1.0 equiv of HOBt was added and the mixture stirred for 1 h; then, 1.0 equiv of DCC was added and the new mixture stirred for 2 h at room temperature. Glycine *tert*-butyl ester hydrochloride or L-phenylalanylglycine *tert*-butyl ester hydrochloride (1.5 equiv) was suspended in an amount of dry acetonitrile equal to the above and neutralized with 2.0 equiv triethylamine. After stirring at room temperature for 1 h, the salts were filtered off and the filtrate added to the previous reaction mixture; this was refluxed until no starting material could be detected (1–3 days) as monitored by TLC (chloroform/methanol, 100:1). Then, the solvent was evaporate and the residue taken up in ethyl acetate (25 mL per mmol of starting material). The solution thus obtained was washed with 1 M aqueous HCl and with a 10% aqueous solution of Na_2CO_3. The organic layer was dried over anhydrous $MgSO_4$ and after concentration the residue purified by column chromatography and/or recrystalization.

*4.6.1. 1-(N-Acetylamino)-cyclohexylcarbonylglycine tert-butyl ester (**3a**).* The reaction was carried out on a 0.55-mM scale and the product obtained purified by column chromatography (dichloromethane/methanol 50:1) and recrystallized from ethyl acetate/hexane to yield **3a** (90.4 mg, 55.1%), as a white solid, mp 139.5–140.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20–1.50 (2H, m, CC_6H_{10}), 1.44 (9H, s, $C(CH_3)_3$), 1.52–1.70 (4H, m, CC_6H_{10}), 1.78–1.92 (2H, m, CC_6H_{10}), 2.04 (3H, s, CH_3CO), 2.13 (2H, br d, *J*=13.8 Hz, CC_6H_{10}), 3.88 (2H, d, *J*=5.1 Hz, $NHCH_2$), 5.85 (1H, s, CON*H*), 7.31 (1H, br t, *J*=6.3 Hz, $NHCH_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.41 (CC_6H_{10}-*C3,5*), 23.84 (CH_3CO), 25.11 (CC_6H_{10}-*C4*), 27.99 ($C(CH_3)_3$), 32.06 (CC_6H_{10}-*C2,6*), 42.18 ($NHCH_2$), 60.13 (C^{α}), 81.93 ($C(CH_3)_3$), 169.06 ($COOC(CH_3)_3$), 170.83 (CH_3CO), 174.34 ($CONHCH_2$). Anal. Calcd for $C_{15}H_{26}N_2O_4$: C, 60.38; H 8.78; N, 9.39. Found: C, 60.05; H, 8.44; N, 9.26.

*4.6.2. 1-(N-Benzyloxycarbonyl-L-phenylalanylamino)-cyclohexylcarbonylglycine tert-butyl ester (**6a**).* The reaction was carried out on a 0.55-mM scale and the product obtained purified by column chromatography (dichloromethane/methanol, 50:1) and recrystallized from diethyl ether/petroleum ether (40–60 °C) to yield **6a** (272 mg, 91.9%), as a white crystals, mp 181.4–182.8 °C, $[\alpha]_D$ +0.13 (*c* 1, ethanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95–1.38 (4H, m, CC_6H_{10}), 1.45 (9H, s, $C(CH_3)_3$), 1.46–1.62 (2H, m, CC_6H_{10}), 1.79 (2H, td, *J*=3.3, 13.1 Hz, CC_6H_{10}), 2.02 (2H, br dd, *J*=13.8, 35.1 Hz, CC_6H_{10}), 3.09 (2H, dd, *J*=3.9, 7.2 Hz, $CHCH_2Ph$), 3.83 (2H, t, *J*=5.3 Hz, $NHCH_2$), 4.40 (1H, q, *J*=7.2 Hz, $CHCH_2Ph$), 5.08 (2H, d, *J*=2.4 Hz, CH_2OCO), 5.51 (1H, d, *J*=6.9 Hz, OCON*H*), 6.08 (1H, s, CON*H*), 7.09 (1H, br t, *J*=5.1 Hz, $NHCH_2$), 7.20–7.40 (10H, m, $CHCH_2Ph$+$OCOCH_2Ph$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.97, 21.08 (CC_6H_{10}-*C3,5*), 24.91 (CC_6H_{10}-*C4*), 28.00 ($C(CH_3)_3$), 31.36, 32.34 (CC_6H_{10}-*C2,6*), 37.64 ($CHCH_2Ph$), 42.06 ($NHCH_2$), 56.93 ($CHCH_2Ph$), 60.41 (C^{α}), 67.18 ($OCOCH_2$), 81.78 ($C(CH_3)_3$), 127.13 ($CHCH_2Ph$-*C4*), 127.99 ($OCOCH_2Ph$-*C2,6*), 128.25 ($OCOCH_2Ph$-*C4*), 128.51, 128.80 ($CHCH_2Ph$-*C3,5*+$OCOCH_2Ph$-*C3,5*), 129.20 ($CHCH_2Ph$-*C2,6*), 135.91 ($OCOCH_2Ph$-*C1*), 136.31 ($CHCH_2Ph$-*C1*), 156.38 (OCONH), 169.00 ($COOC(CH_3)_3$), 170.92 (CONHC), 173.90 ($CONHCH_2$). Anal. Calcd for $C_{30}H_{39}N_3O_6$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.27; H, 7.30; N, 7.85.

*4.6.3. N-Benzyloxycarbonyl-L-phenylalanyl-α,α-dimethylglycylglycine tert-butyl ester (**6b**).* The reaction was carried out on a 0.5-mM scale and the product obtained purified by column chromatography (chloroform/methanol, 100:1) and recrystallized from ethyl acetate/hexane to yield **6b** (221 mg, 88.8%), as a white crystals, mp 156.6–157.9 °C, $[\alpha]_D$ −0.92 (*c* 1, ethanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.42 (6H, d, *J*=15.6 Hz, 2×CCH_3), 1.45 (9H, s, $C(CH_3)_3$), 2.90–3.15 (2H, m, $CHCH_2Ph$), 3.84 (2H, t, *J*=4.5 Hz, $NHCH_2$), 4.33 (1H, q, *J*=7.2 Hz, $CHCH_2Ph$), 5.07 (2H, s, CH_2OCO), 5.58 (1H, d, *J*=6.9 Hz, OCON*H*), 6.36 (1H, s, CON*H*), 6.83 (1H, br t, *J*=6.6 Hz, $NHCH_2$), 7.18–7.40 (10H, m, $CHCH_2Ph$+$OCOCH_2Ph$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.54 (CCH_3), 25.38 (CCH_3), 27.97 ($C(CH_3)_3$), 38.21 ($CHCH_2Ph$), 42.13 ($NHCH_2$), 56.81 ($CHCH_2Ph$), 57.19 (C^{α}), 67.03 ($OCOCH_2$), 81.94 ($C(CH_3)_3$), 127.07 ($CHCH_2Ph$-*C4*), 127.93 ($OCOCH_2Ph$-*C2,6*), 128.16 ($OCOCH_2Ph$-*C4*), 128.48, 128.66 ($OCOCH_2Ph$-*C3,5*+$CHCH_2Ph$-*C3,5*), 129.29 ($CHCH_2Ph$-*C2,6*), 136.01 ($OCOCH_2Ph$-*C1*), 136.25 ($CHCH_2Ph$-*C1*), 156.14 (OCONH), 168.83 ($COOC(CH_3)_3$), 170.45 (CONHC), 173.87 ($CONHCH_2$). Anal. Calcd for $C_{27}H_{35}N_3O_6$: C, 65.17; H, 7.09; N, 8.44. Found: C, 65.05; H, 6.95; N, 8.47.

*4.6.4. N-Benzyloxycarbonyl-L-phenylalanyl-α,α-diethylglycylglycine tert-butyl ester (**6c**).* The reaction was carried out on a 1-mM scale and the product obtained purified by recrystalization from diethyl ether/petroleum ether (40–60 °C) to yield **6c** (425 mg, 80.8%), as a white solid, mp 150.5–152.0 °C, $[\alpha]_D$ +0.13 (*c* 1, ethanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.60–0.73 (6H, m, 2×CH_2CH_3), 1.47 (9H, s, $C(CH_3)_3$), 1.62 (2H, sext, *J*=7.1 Hz, CH_2CH_3), 2.45 (2H, sext, *J*=6.5 Hz, CH_2CH_3), 2.98–3.18 (2H, m, $CHCH_2Ph$), 3.92 (2H, d, *J*=5.4 Hz, CH_2NH), 4.45 (1H, br q, *J*=7.2 Hz, $CHCH_2Ph$), 5.07 (2H, s, CH_2OCO), 5.38 (1H, d, *J*=7.8 Hz, OCON*H*), 6.39 (1H, br t, *J*=4.2 Hz, $NHCH_2$), 7.06 (1H, s, CON*H*), 7.17–7.38 (10H, m, $CHCH_2Ph$+$OCOCH_2Ph$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 7.88 (CH_2CH_3), 7.98 (CH_2CH_3), 27.96 ($C(CH_3)_3$), 28.39 (2×CH_2CH_3), 38.10 ($CHCH_2Ph$), 42.13 ($NHCH_2$), 56.74 ($CHCH_2Ph$), 65.11 (C^{α}), 66.92 ($OCOCH_2$), 82.38 ($C(CH_3)_3$), 126.93 ($CHCH_2Ph$-*C4*), 127.92 ($OCOCH_2Ph$-*C2,6*), 128.02 ($OCOCH_2Ph$-*C4*), 128.40, 128.65 ($OCOCH_2Ph$-*C3,5*+$CHCH_2Ph$-*C3,5*), 129.22 ($CHCH_2Ph$-*C2,6*), 136.13 ($OCOCH_2Ph$-*C1*), 136.31 ($CHCH_2Ph$-*C1*), 155.92 (OCONH), 168.69 ($COOC(CH_3)_3$), 169.66 (CONHC), 172.69 ($CONHCH_2$). Anal. Calcd for $C_{29}H_{39}N_3O_6$: C, 66.26; H, 7.48; N, 7.99. Found: C, 66.15; H, 7.37; N, 8.33.

*4.6.5. N-Benzyloxycarbonyl-L-phenylalanyl-α,α-dipropylglycylglycine tert-butyl ester (**6d**).* The reaction was carried out on a 0.8-mM scale and the product obtained purified by recrystalization from diethyl ether/petroleum ether (40–60 °C) to yield **6d** (350 mg, 79.0%), as a white solid, mp 134.5–135.8 °C, $[\alpha]_D$ +0.52 (*c* 1, ethanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.77–0.86 (6H, m, 2×CH_2CH_3), 0.90–1.14 (4H, m, 2×CH_2CH_3), 1.47 (9H, s, $C(CH_3)_3$), 1.47–1.66 (2H, m, CCH_2), 2.28–2.48 (2H, m, CCH_2), 3.08 (2H, d, *J*=6.6 Hz, $CHCH_2Ph$), 3.90 (2H, d, *J*=5.1 Hz, $NHCH_2$), 4.45 (1H, br q, *J*=6.9 Hz, $CHCH_2Ph$), 5.09 (2H, s, CH_2OCO), 5.34 (1H, d, *J*=7.5 Hz, OCON*H*), 6.36 (1H, br t, *J*=6.9 Hz, $NHCH_2$), 7.07

(1H, s, CON*H*), 7.14–7.40 (10H, m, CHCH$_2$*Ph*+OCOCH$_2$*Ph*); ^{13}C NMR (75 MHz, CDCl$_3$): δ 14.00 (2×CH$_2$*C*H$_3$), 16.70, 16.81 (2×*C*H$_2$CH$_3$), 27.97 (C(*C*H$_3$)$_3$), 37.96, 38.00 (CH*C*H$_2$Ph+2×C*C*H$_2$), 42.20 (NH*C*H$_2$), 56.67 (*C*HCH$_2$Ph), 64.12 (*C*$^{\alpha}$), 66.94 (OCO*C*H$_2$), 82.42 (*C*(CH$_3$)$_3$), 126.92 (CHCH$_2$Ph-*C4*), 127.94 (OCOCH$_2$Ph-*C2,6*), 128.05 (OCOCH$_2$Ph-*C4*), 128.44, 128.61 (OCOCH$_2$Ph-*C3,5*+CHCH$_2$Ph-*C3,5*), 129.26 (CHCH$_2$Ph-*C2,6*), 136.16 (OCOCH$_2$Ph-*C1*), 136.28 (CHCH$_2$Ph-*C1*), 155.89 (O*C*ONH), 168.63 (*C*OOC(CH$_3$)$_3$), 169.43 (*C*ONHC), 172.94 (*C*ONHCH$_2$). Anal. Calcd for $C_{31}H_{43}N_3O_6$: C, 67.25; H, 7.83; N, 7.59. Found: C, 67.32; H, 7.74; N, 7.67.

*4.6.6. N-Benzyloxycarbonyl-L-phenylalanyl-α,α-diisobutylglycylglycine tert-butyl ester (**6e**).* The reaction was carried out on a 1-mM scale and the product obtained purified by column chromatography (chloroform) and recrystallized from diethyl ether/petroleum ether (40–60 °C) to yield **6e** (392 mg, 67.4%), as a white solid, mp 116.5–118.0 °C, [α]$_D$ +0.40 (*c* 1, ethanol). ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.72 (6H, dd, *J*=6.0, 37.8 Hz, 2×CHC*H*$_3$), 0.78 (6H, dd, *J*=6.5, 24.9 Hz, CHC*H*$_3$), 1.20–1.48 (4H, m, 2×C*H*(CH$_3$)$_2$+CC*H*$_2$), 1.49 (9H, s, C(C*H*$_3$)$_3$), 2.50–2.64 (2H, m, CC*H*$_2$), 3.07 (2H, ddd, *J*=7.1, 13.8, 36.8 Hz, CHC*H*$_2$Ph), 3.92 (2H, d, *J*=4.8 Hz, NHC*H*$_2$), 4.50 (1H, br q, *J*=7.2 Hz, C*H*CH$_2$Ph), 5.07 (2H, s, C*H*$_2$OCO), 5.30 (1H, d, *J*=8.1 Hz, OCON*H*), 6.23 (1H, br t, *J*=4.5 Hz, N*H*CH$_2$), 7.16–7.39 (10H, m, CHCH$_2$*Ph*+OCOCH$_2$*Ph*), 7.52 (1H, s, CON*H*); ^{13}C NMR (75 MHz, CDCl$_3$): δ 22.44 (CH*C*H$_3$), 23.05 (CH*C*H$_3$), 23.81 (CH*C*H$_3$), 24.05 (CH*C*H$_3$), 24.07 (*C*H(CH$_3$)$_2$), 24.23 (*C*H(CH$_3$)$_2$), 27.98 (C(*C*H$_3$)$_3$), 38.04 (CH*C*H$_2$Ph), 42.17 (NH*C*H$_2$), 45.44 (C*C*H$_2$), 45.51 (C*C*H$_2$), 56.67 (*C*HCH$_2$Ph), 63.05 (*C*$^{\alpha}$), 66.89 (OCO*C*H$_2$), 82.78 (*C*(CH$_3$)$_3$), 126.82 (CHCH$_2$Ph-*C4*), 127.88 (OCOCH$_2$Ph-*C2,6*), 128.00 (OCOCH$_2$Ph-*C4*), 128.43, 128.56 (CHCH$_2$Ph-*C3,5*+OCOCH$_2$Ph-*C3,5*), 129.28 (CHCH$_2$Ph-*C2,6*), 136.25 (OCOCH$_2$Ph-*C1*), 136.48 (CHCH$_2$Ph-*C1*), 155.83 (O*C*ONH), 168.57 (*C*OOC(CH$_3$)$_3$), 169.27 (*C*ONHC), 173.67 (*C*ONHCH$_2$). Anal. Calcd for $C_{33}H_{47}N_3O_6$: C, 68.13; H, 8.14; N, 7.22. Found: C, 68.02; H, 8.03; N, 7.23.

*4.6.7. N-Benzyloxycarbonyl-L-phenylalanyl-α,α-dibenzylglycylglycine tert-butyl ester (**6f**).* The reaction was carried out on a 0.5-mM scale and the product obtained purified by column chromatography (chloroform) and recrystallized from ethyl acetate/hexane to yield **6f** (175 mg, 53.8%), as a white solid, mp 166.2–167.8 °C, [α]$_D$ −12.4 (*c* 1, ethanol). ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.51 (9H, s, C(C*H*$_3$)$_3$), 2.95 (2H, ddd, *J*=7.1, 14.1, 82.0 Hz, CHC*H*$_2$Ph), 3.32–3.64 (4H, m, 2×CC*H*$_2$Ph), 3.87 (2H, d, *J*=4.8 Hz, NHC*H*$_2$), 4.28 (1H, br q, *J*=6.9 Hz, C*H*CH$_2$Ph), 4.96 (2H, dd, *J*=12.1, 21.6 Hz, C*H*$_2$OCO), 5.17 (1H, d, *J*=6.9 Hz, OCON*H*), 6.57 (1H, br t, *J*=5.4 Hz, N*H*CH$_2$), 6.63 (1H, s, CON*H*), 6.98–7.14 (6H, m, 2×CCH$_2$Ph-*H2,6*+CHCH$_2$Ph-*H2,6*), 7.15–7.38 (14H, m, CHCH$_2$Ph-*H3,4,5*+OCOCH$_2$*Ph*+2×CCH$_2$Ph-*H3,4,5*); ^{13}C NMR (75 MHz, CDCl$_3$): δ 27.99 (C(*C*H$_3$)$_3$), 37.80 (CH*C*H$_2$Ph), 41.17 (2×C*C*H$_2$Ph), 42.28 (NH*C*H$_2$), 56.91 (*C*HCH$_2$Ph), 65.15 (*C*$^{\alpha}$), 66.98 (OCO*C*H$_2$), 82.37 (*C*(CH$_3$)$_3$), 126.95 (CHCH$_2$Ph-*C4*), 127.05 (2×CCH$_2$Ph-*C4*), 127.89 (OCOCH$_2$Ph-*C2,6*), 128.09 (OCOCH$_2$Ph-*C4*), 128.25 (CCH$_2$Ph-*C3,5*), 128.29 (CCH$_2$Ph-*C3,5*), 128.45, 128.66 (CHCH$_2$Ph-*C3,5*+OCOCH$_2$Ph-*C3,5*), 129.25 (CHCH$_2$Ph-*C2,6*), 130.17 (2×CCH$_2$Ph-*C2,6*), 135.46 (2×CCH$_2$Ph-*C1*), 136.02 (OCOCH$_2$Ph-*C1*), 136.46 (CHCH$_2$Ph-*C1*), 155.89 (O*C*ONH), 168.45 (*C*OOC(CH$_3$)$_3$), 170.50 (*C*ONHC), 171.24 (*C*ONHCH$_2$). Anal. Calcd for $C_{39}H_{43}N_3O_6$: C, 72.09; H, 6.67; N, 6.47. Found: C, 71.92; H, 6.69; N, 6.45.

*4.6.8. N-Benzyloxycarbonyl-L-phenylalanylglycyl-α,α-diethylglycyl-L-phenylalanylglycine tert-butyl ester (**9a**).* The reaction was carried out with 0.5 mmol of compound **8a** and the product obtained purified by column chromatography (dichloromethane/methanol, 25:1) and recrystallized from ethyl acetate/petroleum ether (40–60 °C) to yield **9a** (271 mg, 74.2%), as a white solid, mp 119.9–121.3 °C, [α]$_D$ −18.0 (*c* 1, ethanol). ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ 0.18 (3H, t, *J*=7.2 Hz, CH$_2$C*H*$_3$), 0.44 (3H, t, *J*=7.2 Hz, CH$_2$C*H*$_3$), 1.37 (9H, s, C(C*H*$_3$)$_3$), 1.54–1.81 (2H, m, CC*H*$_2$), 1.95 (2H, sept, *J*=7.2 Hz, CC*H*$_2$), 2.71 (1H, dd, *J*=11.4, 12.6 Hz, CHC*H*$_2$Ph), 2.84 (1H, t, *J*=12.9 Hz, CHC*H*$_2$Ph), 3.08 (2H, ddd, *J*=3.3, 13.9, 23.6 Hz, CHC*H*$_2$Ph), 3.58–3.83 (4H, m, NHC*H*$_2$), 4.19–4.31 (1H, m, C*H*CH$_2$Ph), 4.54–4.67 (1H, m, C*H*CH$_2$Ph), 4.91 (2H, d, *J*=3.6 Hz, C*H*$_2$OCO), 7.05–7.35 (15H, m, 2×CHCH$_2$*Ph*+OCOCH$_2$*Ph*), 7.54 (1H, s, CON*H*C), 7.55 (1H, d, *J*=8.1 Hz, OCON*H*), 7.94 (1H, d, *J*=9.0 Hz, CCON*H*), 8.25 (1H, t, *J*=5.7 Hz, N*H*CH$_2$), 8.49 (1H, t, *J*=5.7 Hz, N*H*CH$_2$); ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ 7.21 (CCH$_2$*C*H$_3$), 7.64 (CCH$_2$*C*H$_3$), 26.17 (C*C*H$_2$), 27.02 (C*C*H$_2$), 27.69 (C(*C*H$_3$)$_3$), 36.85 (CH*C*H$_2$Ph), 37.33 (CH*C*H$_2$Ph), 41.53 (NH*C*H$_2$), 42.91 (NH*C*H$_2$), 54.10 (*C*HCH$_2$Ph), 56.24 (*C*HCH$_2$Ph), 63.71 (*C*$^{\alpha}$), 65.23 (OCO*C*H$_2$), 80.59 (*C*(CH$_3$)$_3$), 126.14 (CHCH$_2$Ph-*C4*), 126.26 (CHCH$_2$Ph-*C4*), 127.44 (OCOCH$_2$Ph-*C2,6*), 127.69 (OCOCH$_2$Ph-*C4*), 128.02 (CHCH$_2$Ph-*C3*,5), 128.07 (CHCH$_2$Ph-*C3*,5), 128.29 (OCOCH$_2$-Ph-*C3,5*), 129.05 (CHCH$_2$Ph-*C2,6*), 129.22 (CHCH$_2$Ph-*C2,6*), 136.98 (OCOCH$_2$Ph-*C1*), 138.33 (2×CHCH$_2$Ph-*C1*), 155.92 (O*C*ONH), 167.94 (*C*ONHC), 168.77 (*C*OOC(CH$_3$)$_3$), 171.81 (*C*ONHCH$_2$), 172.13 (C*C*ONH), 172.36 (*C*ONHCH$_2$). Anal. Calcd for $C_{40}H_{51}N_5O_8$: C, 65.82; H, 7.04; N, 9.60. Found: C, 65.82; H, 7.00; N, 9.56.

*4.6.9. N-Benzyloxycarbonyl-L-phenylalanylglycyl-α,α-dibenzylglycyl-L-phenylalanylglycine tert-butyl ester (**9b**).* The reaction was carried out with 0.25 mmol of compound **8b** and the product obtained purified by column chromatography (dichloromethane/methanol, 100:1) and recrystallized from ethyl acetate/petroleum ether (40–60 °C) to yield **9b** (55 mg, 25.7%), as a white solid, mp 137.2–139.0 °C, [α]$_D$ +16.4 (*c* 1, ethanol). ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ 1.39 (9H, s, C(C*H*$_3$)$_3$), 2.57 (1H, dd, *J*=11.4, 13.8 Hz, CHC*H*$_2$Ph), 2.85 (1H, dd, *J*=3.0, 13.8 Hz, CHC*H*$_2$Ph), 2.92–3.12 (3H, m, CHC*H*$_2$Ph+CC*H*$_2$Ph), 3.27–3.84 (7H, m, CC*H*$_2$Ph+2×NHC*H*$_2$), 4.17–4.29 (1H, m, C*H*CH$_2$Ph), 4.47–4.58 (1H, m, C*H*CH$_2$Ph), 4.89 (2H, *s*, C*H*$_2$OCO), 6.48 (2H, d, *J*=7.5 Hz, CCH$_2$Ph-*H2,6*), 6.92 (2H, t, *J*=7.5 Hz, CCH$_2$Ph-*H3,5*), 7.00 (2H, d, *J*=7.5 Hz, 2×CCH$_2$Ph-*H4*), 7.05–7.34 (18H, m, CCH$_2$Ph-*H2,3,5,6*+CHCH$_2$Ph-*H3,4,5*+CHCH$_2$*Ph*+OCOCH$_2$*Ph*+CON*H*C), 7.41 (2H, d, *J*=7.2 Hz, CHCH$_2$Ph-*H2,6*), 7.46 (1H, d, *J*=8.7 Hz, OCON*H*), 8.38 (2H, dt, *J*=6.0, 12.0 Hz, 2×N*H*CH$_2$), 8.61 (1H, d, *J*=7.2 Hz, CCON*H*); ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ 27.72 (C(*C*H$_3$)$_3$), 37.38 (2×CH*C*H$_2$Ph), 39.78 (2×C*C*H$_2$Ph), 41.34 (NH*C*H$_2$), 43.05 (NH*C*H$_2$), 55.27 (*C*HCH$_2$Ph), 56.03 (*C*HCH$_2$Ph), 65.05 (*C*$^{\alpha}$), 65.17 (OCO*C*H$_2$), 80.66 (*C*(CH$_3$)$_3$), 125.94, 126.19, 126.23 (2×CCH$_2$Ph-*C4*), 126.65, 126.73 (2×CHCH$_2$Ph-*C4*), 127.44 (OCOCH$_2$Ph-*C2,6*), 127.66 (OCOCH$_2$Ph-*C4*), 127.78, 128.02, 128.27, 128.34 (CCH$_2$Ph-*C3,5*+CCH$_2$Ph-*C3,5*+2×CHCH$_2$Ph-*C3*,5+OCOCH$_2$Ph-*C3,5*), 129.21 (CHCH$_2$Ph-*C2,6*), 129.38 (CHCH$_2$Ph-*C2,6*), 129.72 (CCH$_2$Ph-*C2,6*), 130.18 (CCH$_2$Ph-*C2,6*), 136.09 (CCH$_2$Ph-*C1*), 136.22 (CCH$_2$Ph-*C1*), 136.99 (OCOCH$_2$Ph-*C1*), 138.13 (CHCH$_2$Ph-*C1*), 138.32 (CHCH$_2$Ph-*C1*), 155.85 (O*C*ONH), 168.68 (*C*OOC(CH$_3$)$_3$), 168.76 (*C*ONHC), 170.73 (C*C*ONH), 171.59 (*C*ONHCH$_2$), 172.07 (*C*ONHCH$_2$). Anal. Calcd for $C_{50}H_{55}N_5O_8$: C, 70.32; H, 6.49; N, 8.20. Found: C, 69.76; H, 6.69; N, 7.94.

4.7. Synthesis of *N*-(4-methoxybenzyl) dipeptide acids 10a–10f

The reactions were carried out by selective acidolysis of compounds **4a**–**4f** under conditions previously described,[15] using 1% or 2% TFA in dry acetonitrile.

4.7.1. 1-[N-(N′-Benzyloxycarbonyl-L-phenylalanyl)-N-(4-methoxybenzyl)-amino]-cyclohexylcarboxylic acid (10a). Compound **4a** (0.5 g) was treated with 2% TFA and the product purified by recrystalization from ethyl acetate/hexane to yield **10a** (369 mg, 85.8%), as a white solid, mp 159.9–161.8 °C, [α]$_D$ −2.68 (*c* 1, ethanol). ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ 1.07 (1H, br q, *J*=11.4 Hz, CC$_6$*H*$_{10}$), 1.29 (1H, td, *J*=3.6, 12.9 Hz, CC$_6$*H*$_{10}$), 1.35–1.65 (5H, m, CC$_6$*H*$_{10}$), 1.80 (1H, br q, *J*=12.0 Hz, CC_6H_{10}), 1.99 (1H, d, *J*=11.4 Hz, CC_6H_{10}), 2.20 (1H, d, *J*=12.3 Hz, CC_6H_{10}), 2.62–2.85 (2H, m, $CHCH_2Ph$), 3.73 (3H, s, OCH_3), 4.20–4.35 (1H, m, $CHCH_2Ph$), 4.60 (1H, d, *J*=18.9 Hz, NCH_2), 4.81–5.00 (3H, m, NCH_2+CH_2OCO), 6.82–6.94 (4H, m, NCH_2Ph-*H3,5*+$CHCH_2Ph$-*H2,6*), 7.04–7.36 (10H, m, $CHCH_2Ph$-*H3,4,5*+$OCOCH_2Ph$+NCH_2Ph-*H2,6*), 7.80 (1H, d, *J*=8.7 Hz, OCON*H*), 12.07 (1H, br s, O*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ 22.07, 22.16 (CC_6H_{10}-*C3,5*), 24.70 (CC_6H_{10}-*C4*), 30.69, 31.64 (CC_6H_{11}-*C2,6*), 37.58 ($CHCH_2Ph$), 45.51 (NCH_2Ph), 54.02 ($CHCH_2Ph$), 55.11 (OCH_3), 64.11 (C^α), 65.31 ($OCOCH_2$), 113.87 (NCH_2Ph-*C3,5*), 126.35 ($CHCH_2Ph$-*C4*), 127.25, 127.34 (NCH_2Ph-*C2,6*+$OCOCH_2Ph$-*C2,6*), 127.68 ($OCOCH_2Ph$-*C4,*), 128.03 ($CHCH_2Ph$-*C3,5*), 128.28 ($OCOCH_2Ph$-*C3,5*), 129.17 ($CHCH_2Ph$-*C2,6*), 131.19 (NCH_2Ph-*C1*), 136.98 ($OCOCH_2Ph$-*C1*), 137.65 ($CHCH_2Ph$-*C1*), 155.90 (OCONH), 158.20 (NCH_2Ph-*C4*), 172.82 (CON), 173.78 (COOH). Anal. Calcd for $C_{32}H_{36}N_2O_6$: C, 70.57; H, 6.66; N, 5.14. Found: C, 70.49; H, 6.65; N, 5.15.

*4.7.2. N-Benzyloxycarbonyl-L-phenylalanyl-N′-(4-methoxybenzyl)-α,α-dimethylglycine (**10b**).* Compound **4b** (1.0 g) was treated with 2% TFA and the product purified by column chromatography (dichloromethane/methanol, 25:1) and recrystallized from ethyl acetate to yield **10b** (739 mg, 85.8%), as a white crystals, mp 194.6–196.0 °C, $[\alpha]_D$ +36.8 (*c* 1, ethanol). ^1H NMR (300 MHz, DMSO-d_6): δ 1.28 (6H, d, *J*=6.3 Hz, 2×CH_3), 2.60–2.82 (2H, m, $CHCH_2Ph$), 3.74 (3H, s, OCH_3), 4.22–4.37 (1H, m, $CHCH_2Ph$), 4.59 (1H, d, *J*=18.3 Hz, NCH_2), 4.87 (1H, d, *J*=18.6 Hz, NCH_2), 4.93 (2H, d, *J*=1.5 Hz, CH_2OCO), 6.78–6.94 (4H, m, $CHCH_2Ph$-*H2,6*+NCH_2Ph-*H3,5*), 7.06–7.35 (10H, m, $CHCH_2Ph$-*H3,4,5*+$OCOCH_2Ph$+NCH_2Ph-*H2,6*), 7.80 (1H, d, *J*=8.4 Hz, OCON*H*), 12.10 (1H, br s, O*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ 22.57 (CCH_3), 23.84 (CCH_3), 37.37 ($CHCH_2Ph$), 45.63 (NCH_2Ph), 53.65 ($CHCH_2Ph$), 55.13 (OCH_3), 60.93 (C^α), 65.29 ($OCOCH_2$), 113.97 (NCH_2Ph-*C3,5*), 126.32 ($CHCH_2Ph$-*C4*), 127.25, 127.32 (NCH_2Ph-*C2,6*+$OCOCH_2Ph$-*C2,6*), 128.67 ($OCOCH_2Ph$-*C4,*), 128.00 ($CHCH_2Ph$-*C3,5*), 128.27 ($OCOCH_2Ph$-*C3,5*), 129.14 ($CHCH_2Ph$-*C2,6*), 131.17 (NCH_2Ph-*C1*), 136.97 ($OCOCH_2Ph$-*C1*), 137.65 ($CHCH_2Ph$-*C1*), 155.94 (OCONH), 158.27 (NCH_2Ph-*C4*), 172.47 (CON), 175.06 (COOH). Anal. Calcd for $C_{29}H_{32}N_2O_6$: C, 69.03; H, 6.39; N, 5.55. Found: C, 68.95; H, 6.41; N, 5.55.

*4.7.3. N-Benzyloxycarbonyl-L-phenylalanyl-N′-(4-methoxybenzyl)-α,α-diethylglycine (**10c**).* Compound **4c** (0.5 g) was treated with 2% TFA and the product purified by column chromatography (dichloromethane/methanol, 25:1) and recrystallized from ethyl acetate to yield **10c** (366 mg, 84.9%), as a white solid, mp 191.0–192.8 °C, $[\alpha]_D$ +0.68 (*c* 1, ethanol). ^1H NMR (300 MHz, DMSO-d_6): δ 0.73 (6H, dt, *J*=7.8, 10.2 Hz 2×CH_2CH_3), 1.48–1.70 (2H, m, CCH_2), 2.04 (1H, sext, *J*=7.0 Hz, CCH_2), 2.19 (1H, sext, *J*=7.3 Hz, CCH_2), 2.50–2.72 (2H, m, $CHCH_2Ph$), 3.75 (3H, s, OCH_3), 4.23 (1H, td, *J*=3.1, 9.2 Hz, $CHCH_2Ph$), 4.60 (1H, d, *J*=18.5 Hz, NCH_2), 4.94 (2H, q, *J*=12.9 Hz, CH_2OCO), 5.06 (1H, d, *J*=18.9 Hz, NCH_2), 6.66 (2H, br d, *J*=5.7 Hz, $CHCH_2Ph$-*H2,6*), 6.94 (2H, d, *J*=8.7 Hz, NCH_2Ph-*H3,5*), 7.00–7.39 (8H, m, $CHCH_2Ph$-*H3,4,5*+$OCOCH_2Ph$), 7.47 (2H, d, *J*=8.4 Hz, NCH_2Ph-*H2,6*), 7.81 (1H, d, *J*=8.7 Hz, OCON*H*), 12.16 (1H, br s, O*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ 7.52 (CH_2CH_3), 8.57 (CH_2CH_3), 22.78 (CCH_2CH_3), 24.29 (CCH_2CH_3), 37.01 ($CHCH_2Ph$), 47.10 (NCH_2Ph), 53.65 ($CHCH_2Ph$), 55.20 (OCH_3), 65.21 ($OCOCH_2$), 67.27 (C^α), 114.01 (NCH_2Ph-*C3,5*), 126.22 ($CHCH_2Ph$-*C4*), 127.17 (NCH_2Ph-*C2,6*), 127.28 ($OCOCH_2Ph$-*C2,6*), 127.67 ($OCOCH_2Ph$-*C4*), 127.88 ($CHCH_2Ph$-*C3,5*), 128.27 ($OCOCH_2Ph$-*C3,5*), 129.04 ($CHCH_2Ph$-*C2,6*), 132.23 (NCH_2Ph-*C1*), 137.08 ($OCOCH_2Ph$-*C1*), 137.71 ($CHCH_2Ph$-*C1*), 156.01 (OCONH), 158.28 (NCH_2Ph-*C4*), 173.09 (CON), 173.70 (COOH). Anal. Calcd for $C_{31}H_{36}N_2O_6$: C, 69.90; H, 6.81; N, 5.26. Found: C, 69.80; H, 6.79; N, 5.27.

*4.7.4. N-Benzyloxycarbonyl-L-phenylalanyl-N′-(4-methoxybenzyl)-α,α-dipropylglycine (**10d**).* Compound **4d** (1.0 g) was treated with 1% TFA and the product purified by column chromatography (dichloromethane/methanol, 25:1) and recrystallized from ethyl acetate to yield **10d** (659 mg, 75.4%), as a white solid, mp 178.1–180.0 °C, $[\alpha]_D$ −0.92 (*c* 1, ethanol). ^1H NMR (300 MHz, DMSO-d_6): δ 0.72–0.89 (6H, m, 2×CH_2CH_3), 0.95–1.36 (4H, m, 2×CH_2CH_3), 1.53 (2H, qd, *J*=3.9, 12.6 Hz, CCH_2), 2.05 (2H, dtd, *J*=3.9, 12.9, 52.8 Hz, CCH_2), 2.44–2.52 (1H, m, $CHCH_2Ph$), 2.62 (1H, dd, *J*=10.1, 13.8 Hz, $CHCH_2Ph$), 3.75 (3H, s, OCH_3), 4.15–4.25 (1H, m, $CHCH_2Ph$), 4.59 (1H, d, *J*=18.6 Hz, NCH_2), 4.93 (2H, dd, *J*=12.6, 42.3 Hz, CH_2OCO), 5.02 (1H, d, *J*=19.2 Hz, NCH_2), 6.62 (2H, br d, *J*=6.0 Hz, $CHCH_2Ph$-*H2,6*), 6.95 (2H, d, *J*=8.7 Hz, NCH_2Ph-*H3,5*), 7.00–7.14 (2H, m, $CHCH_2Ph$-*H3,4,5*), 7.15–7.36 (5H, m, $OCOCH_2Ph$), 7.47 (2H, d, *J*=8.7 Hz, NCH_2Ph-*H2,6*), 7.78 (1H, d, *J*=8.7 Hz, OCON*H*), 12.17 (1H, br s, O*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.42 (CH_2CH_3), 14.53 (CH_2CH_3), 16.09 (CH_2CH_3), 17.25 (CH_2CH_3), 33.41 (CCH_2), 34.45 (CCH_2), 36.95 ($CHCH_2Ph$), 47.00 (NCH_2Ph), 53.63 ($CHCH_2Ph$), 55.20 (OCH_3), 65.17 ($OCOCH_2$), 66.50 (C^α), 114.04 (NCH_2Ph-*C3,5*), 126.21 ($CHCH_2Ph$-*C4*), 127.19 (NCH_2Ph-*C2,6*), 127.29 ($OCOCH_2Ph$-*C2,6*), 127.70 ($OCOCH_2Ph$-*C4,*), 127.86 ($CHCH_2Ph$-*C3,5*), 128.30 ($OCOCH_2Ph$-*C3,5*), 129.02 ($CHCH_2Ph$-*C2,6*), 132.28 (NCH_2Ph-*C1*), 137.06 ($OCOCH_2Ph$-*C1*), 137.68 ($CHCH_2Ph$-*C1*), 155.99 (OCONH), 158.29 (NCH_2Ph-*C4*), 173.06 (CON), 173.88 (COOH). Anal. Calcd for $C_{33}H_{40}N_2O_6$: C, 70.69; H, 7.19; N, 5.00. Found: C, 70.46; H, 7.19; N, 5.07.

*4.7.5. N-Benzyloxycarbonyl-L-phenylalanyl-N′-(4-methoxybenzyl)-α,α-diisobutylglycine (**10e**).* Compound **4e** (0.5 g) was treated with 1% TFA and the product purified by column chromatography (dichloromethane/methanol, 25:1) and recrystallized from diethyl ether/petroleum ether (40–60 °C) to yield **10e** (312 mg, 70.6%), as a white crystals, mp 181.0–182.4 °C, $[\alpha]_D$ +0.52 (*c* 1, ethanol). ^1H NMR (300 MHz, DMSO-d_6): δ 0.76 (6H, dd, *J*=6.6, 16.5 Hz, $CH(CH_3)_2$), 0.88 (6H, d, *J*=6.6 Hz, $CH(CH_3)_2$), 1.51 (1H, dd, *J*=4.8, 12.9 Hz, CCH_2), 1.58–1.74 (3H, m, 2×$CH(CH_3)_2$+CCH_2), 1.98 (1H, dd, *J*=4.5, 13.2 Hz, CCH_2), 2.24 (1H, dd, *J*=6.0, 14.7 Hz, CCH_2), 2.41–2.49 (1H, m, $CHCH_2Ph$), 2.64 (1H, dd, *J*=10.7, 13.7 Hz, $CHCH_2Ph$), 3.76 (3H, s, OCH_3), 4.18–4.30 (1H, m, $CHCH_2Ph$), 4.67 (1H, d, *J*=18.9 Hz, NCH_2), 4.88 (2H, dd, *J*=12.8, 27.0 Hz, CH_2OCO), 5.10 (1H, d, *J*=18.3 Hz, NCH_2), 6.58 (2H, br d, *J*=6.0 Hz, $CHCH_2Ph$-*H2,6*), 6.97 (2H, d, *J*=8.7 Hz, NCH_2Ph-*H3,5*), 7.01–7.12 (2H, m, $CHCH_2Ph$-*H3,4,5*), 7.12–7.35 (5H, m, $OCOCH_2Ph$), 7.54 (2H, d, *J*=8.7 Hz, NCH_2Ph-*H2,6*), 7.83 (1H, d, *J*=8.7 Hz, OCON*H*), 12.23 (1H, br s, O*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ 22.24 ($CH(CH_3)_2$), 23.22 ($CH(CH_3)_2$), 24.29 ($CHCH_3$), 24.52 ($CHCH_3$), 25.00 ($CHCH_3$), 25.70 ($CHCH_3$), 37.13 ($CHCH_2Ph$), 39.50 (CCH_2), 41.19 (CCH_2), 46.92 (NCH_2Ph), 53.46 ($CHCH_2Ph$), 55.22 (OCH_3), 65.14 ($OCOCH_2$), 66.30 (C^α), 114.03 (NCH_2Ph-*C3,5*), 126.15 ($CHCH_2Ph$-*C4*), 127.26 (NCH_2Ph-*C2,6* +$OCOCH_2Ph$-*C2,6*), 127.65 ($OCOCH_2Ph$-*C4,*), 127.82 ($CHCH_2Ph$-*C3,5*), 128.26 ($OCOCH_2Ph$-*C3,5*), 129.04 ($CHCH_2Ph$-*C2,6*), 132.47 (NCH_2Ph-*C1*), 137.03 ($OCOCH_2Ph$-*C1*), 137.75 ($CHCH_2Ph$-*C1*), 155.89 (OCONH), 158.30 (NCH_2Ph-*C4*), 173.19 (CON), 174.18 (COOH). Anal.Calcd for $C_{35}H_{44}N_2O_6$: C, 71.40; H, 7.53; N, 4.76. Found: C, 71.03; H, 7.53; N, 5.85.

*4.7.6. N-Benzyloxycarbonyl-L-phenylalanyl-N′-(4-methoxybenzyl)-α,α-dibenzylglycine (**10f**).* Compound **4f** (0.5 g) was treated with 1% TFA and the product purified by column chromatography (dichloromethane/methanol, 25:1) and recrystallized from diethyl ether/petroleum ether (40–60 °C) to yield **10f** (308 mg, 68.9%), as a white solid, mp 181.9–183.8 °C, $[\alpha]_D$ +26.0 (*c* 1, ethanol). ^1H NMR (300 MHz, DMSO-d_6): δ 2.61–2.78 (3H, m, $CHCH_2Ph$+ CCH_2Ph), 2.90 (1H, d, *J*=13.8 Hz, CCH_2Ph), 3.17 (1H, d, *J*=12.6 Hz, CCH_2Ph), 3.46–3.60 (2H, m, CCH_2Ph+NCH_2), 3.72 (3H, s, OCH_3), 4.18–4.29 (1H, m, $CHCH_2Ph$), 4.42 (1H, d, *J*=19.2 Hz, NCH_2), 5.01 (2H, s, CH_2OCO), 6.69–6.78 (2H, m, $CHCH_2Ph$-*H2,6*), 6.89 (2H, d, *J*=8.7 Hz, NCH_2Ph-*H3,5*), 7.04–7.40 (20H, m, $CHCH_2Ph$-*H3,4,5*+2×CCH_2Ph+$OCOCH_2Ph$+NCH_2Ph-*H2,6*), 8.03

(1H, d, *J*=9.3 Hz, OCON*H*), 12.45 (1H, br s, O*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ 34.84 ($\mathrm{CCH_2Ph}$), 37.50 ($\mathrm{CCH_2Ph}$), 37.69 ($\mathrm{CHCH_2Ph}$), 46.80 ($\mathrm{NCH_2Ph}$), 53.41 ($\mathrm{CHCH_2Ph}$), 55.15 ($\mathrm{OCH_3}$), 65.29 ($\mathrm{OCOCH_2}$), 68.24 (C^{α}), 114.04 ($\mathrm{NCH_2Ph}$-*C3,5*), 126.23 ($\mathrm{CHCH_2Ph}$-*C4*), 126.70 ($\mathrm{CCH_2Ph}$-*C4*), 126.86 ($\mathrm{NCH_2Ph}$-*C2,6*), 126.95 ($\mathrm{CCH_2Ph}$-*C4*), 127.25 ($\mathrm{OCOCH_2Ph}$-*C2,6*), 127.70 ($\mathrm{OCOCH_2Ph}$-*C4*), 127.94 ($\mathrm{CHCH_2Ph}$-*C3,5*), 128.15 ($\mathrm{CCH_2Ph}$-*C3,5*), 128.25 ($\mathrm{CCH_2Ph}$-*C3,5*), 128.35 ($\mathrm{OCOCH_2Ph}$-*C3,5*), 129.15 ($\mathrm{CHCH_2Ph}$-*C2,6*), 130.84 (2×$\mathrm{CCH_2Ph}$-*C2,6*), 131.55 ($\mathrm{NCH_2Ph}$-*C1*), 134.98 ($\mathrm{CCH_2Ph}$-*C1*), 136.16 ($\mathrm{CCH_2Ph}$-*C1*), 137.14 ($\mathrm{OCOCH_2Ph}$-*C1*), 137.55 ($\mathrm{CHCH_2Ph}$-*C1*), 155.70 (OCONH), 158.21 ($\mathrm{NCH_2Ph}$-*C4*), 173.58 (COOH), 173.58 (CON). Anal. Calcd for $C_{41}H_{40}N_2O_6$: C, 74.98; H, 6.14; N, 4.27. Found: C, 74.54; H, 5.91; N, 4.24.

4.8. HBTU-assisted synthesis of *N*-(4-methoxybenzyl) tripeptides 11a–11f

To a 0.1-M solution of peptides **10a**–**10f** in acetonitrile L-phenylalanine *tert*-butyl ester hydrochloride (1.04 equiv) and triethylamine (2 equiv) were added, followed by HBTU[33] (1.04 equiv), and the mixture stirred at room temperature for 24 h. Then, to the reaction mixture a saturated sodium chloride solution was added (28 mL per mmol of starting material), the peptide was extracted into ethyl acetate (3×10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed under reduced pressure to yield a crude product ready for purification.

*4.8.1. 1-[N-(Benzyloxycarbonyl-L-phenylalanyl)-N-(4-methoxybenzyl)-amino]-cyclohexylcarbonyl-L-phenylalanine tert-butyl ester (**11a**).* The reaction was carried out with 0.218 g (0.4 mmol) of compound **10a** and the product purified by column chromatography (dichloromethane/methanol 100:1) followed by preparative layer chromatography (dichloromethane/methanol, 50:1): the two major fractions obtained were **11a**′ (102 mg, 34.1%) and **11a**″ (50.0 mg, 16.7%).

Fraction **11a**′ was recrystallized from ethyl acetate/hexane to yield a white solid, mp 125.3–126.6 °C, $[\alpha]_D$ +16.9 (*c* 1, ethanol). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.82–0.98 (1H, m, $C^{\alpha}C_6H_{10}$), 1.23–1.72 (7H, m, $C^{\alpha}C_6H_{10}$), 1.27 (9H, s, $\mathrm{C(CH_3)_3}$), 2.19 (2H, br dd, *J*=12.0, 25.5 Hz, $C^{\alpha}C_6H_{10}$), 2.73 (1H, dd, *J*=10.5, 14.1 Hz, $\mathrm{CHCH_2Ph}$), 2.84–3.20 (3H, m, $\mathrm{CHCH_2Ph}$), 3.73 (3H, s, $\mathrm{OCH_3}$), 4.45 (2H, quint, *J*=7.2 Hz, 2×$\mathrm{CHCH_2Ph}$), 4.68 (1H, d, *J*=18.0 Hz, $\mathrm{NCH_2}$), 4.84 (1H, d, *J*=18.0 Hz, $\mathrm{NCH_2}$), 4.90 (2H, d, *J*=7.2 Hz, $\mathrm{CH_2OCO}$), 6.86 (2H, d, *J*=8.7 Hz, $\mathrm{NCH_2Ph}$-*H3,5*), 7.01 (1H, d, *J*=7.5 Hz, CON*H*), 7.06–7.12 (2H, m, $\mathrm{CHCH_2Ph}$-*H2,6*), 7.13–7.32 (15H, m, $\mathrm{CHCH_2Ph}$-*H3,4,5*+$\mathrm{CHCH_2Ph}$+$\mathrm{OCOCH_2Ph}$+$\mathrm{NCH_2Ph}$-*H2,6*), 7.74 (1H, d, *J*=8.7 Hz, OCON*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ 22.09 ($C^{\alpha}C_6H_{10}$-*C3,5*), 24.89 ($C^{\alpha}C_6H_{10}$-*C4*), 27.51 ($\mathrm{C(CH_3)_3}$), 31.67, 32.28 ($C^{\alpha}C_6H_{10}$-*C2,6*), 37.34 ($\mathrm{CHCH_2Ph}$), 37.80 ($\mathrm{CHCH_2Ph}$), 46.41 ($\mathrm{NCH_2Ph}$), 53.56 ($\mathrm{CHCH_2Ph}$), 54.52 ($\mathrm{CHCH_2Ph}$), 55.07 ($\mathrm{OCH_3}$), 65.19 (C^{α}), 65.31 ($\mathrm{OCOCH_2}$), 80.81 ($\mathrm{C(CH_3)_3}$), 113.97 ($\mathrm{NCH_2Ph}$-*C3,5*), 126.35 ($\mathrm{CHCH_2Ph}$-*C4*), 126.44 ($\mathrm{CHCH_2Ph}$-*C4*), 127.31 ($\mathrm{OCOCH_2Ph}$-*C2,6*), 127.65 ($\mathrm{OCOCH_2Ph}$-*C4*), 127.83, 128.13 ($\mathrm{NCH_2Ph}$-*C2,6*+2×$\mathrm{CHCH_2Ph}$-*C3,5*), 128.24 ($\mathrm{OCOCH_2Ph}$-*C3,5*), 129.15 ($\mathrm{CHCH_2Ph}$-*C2,6*), 129.27 ($\mathrm{CHCH_2Ph}$-*C2,6*), 130.69 ($\mathrm{NCH_2Ph}$-*C1*), 136.87 ($\mathrm{OCOCH_2Ph}$-*C1*), 137.09 ($\mathrm{CHCH_2Ph}$-*C1*), 137.93 ($\mathrm{CHCH_2Ph}$-*C1*), 156.04 (OCONH), 158.31 ($\mathrm{NCH_2Ph}$-*C4*), 170.55 ($\mathrm{COOC(CH_3)_3}$), 172.15 (CONH), 172.76 (CON). Anal. Calcd for $C_{45}H_{53}N_3O_7$: C, 72.26; H, 7.14; N, 5.62. Found: C, 71.88; H, 6.95; N, 5.70. ESI MS Calcd for $[M+Na]^+$ 770.38. Found: 770.38.

Fraction **11a**″ was isolated as white foam, $[\alpha]_D$ +14.9 °C (*c* 1, ethanol). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.80–0.85 (1H, m, $C^{\alpha}C_6H_{10}$), 1.21–1.48 (7H, m, $C^{\alpha}C_6H_{10}$), 1.27 (9H, s, $\mathrm{C(CH_3)_3}$), 2.22 (2H, d, *J*=9.9 Hz, $C^{\alpha}C_6H_{10}$), 2.66 (1H, dd, *J*=9.6, 13.5 Hz, $\mathrm{CHCH_2Ph}$), 2.86–2.95 (2H, m, $\mathrm{CHCH_2Ph}$), 3.01–3.07 (1H, m, $\mathrm{CHCH_2Ph}$), 3.72 (3H, s, $\mathrm{OCH_3}$), 4.38–4.46 (2H, m, 2×$\mathrm{CHCH_2Ph}$), 4.70 (2H, q, *J*=18.9 Hz, $\mathrm{NCH_2}$), 4.94 (2H, q, *J*=12.3 Hz, $\mathrm{CH_2OCO}$), 6.82 (2H, d, *J*=8.7 Hz, $\mathrm{NCH_2Ph}$-*H3,5*), 7.11–7.34 (17H, m, 2×$\mathrm{CHCH_2Ph}$+$\mathrm{OCOCH_2Ph}$+$\mathrm{NCH_2Ph}$-*H2,6*), 7.37 (1H, d, *J*=7.5 Hz, CON*H*), 7.54 (1H, d, *J*=8.4 Hz, OCON*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ 22.13 ($C^{\alpha}C_6H_{10}$-*C3,5*), 25.01 ($C^{\alpha}C_6H_{10}$-*C4*), 27.57 ($\mathrm{C(CH_3)_3}$), 32.05, 32.42 ($C^{\alpha}C_6H_{10}$-*C2,6*), 37.42 (2×$\mathrm{CHCH_2Ph}$), 46.72 ($\mathrm{NCH_2Ph}$), 53.86 ($\mathrm{CHCH_2Ph}$), 54.82 ($\mathrm{CHCH_2Ph}$), 55.13 ($\mathrm{OCH_3}$), 65.12 (C^{α}), 65.45 ($\mathrm{OCOCH_2}$), 80.74 ($\mathrm{C(CH_3)_3}$), 113.96 ($\mathrm{NCH_2Ph}$-*C3,5*), 126.51 (2×$\mathrm{CHCH_2Ph}$-*C4*), 127.40 ($\mathrm{OCOCH_2Ph}$-*C2,6*), 127.78 ($\mathrm{OCOCH_2Ph}$-*C4*), 128.09, 128.26 ($\mathrm{NCH_2Ph}$-*C2,6*+2×$\mathrm{CHCH_2Ph}$-*C3,5*), 128.36 ($\mathrm{OCOCH_2Ph}$-*C3,5*), 129.18 ($\mathrm{CHCH_2Ph}$-*C2,6*), 129.30 ($\mathrm{CHCH_2Ph}$-*C2,6*), 130.28 ($\mathrm{NCH_2Ph}$-*C1*), 136.98 ($\mathrm{OCOCH_2Ph}$-*C1*), 137.35 ($\mathrm{CHCH_2Ph}$-*C1*), 137.98 ($\mathrm{CHCH_2Ph}$-*C1*), 156.04 (OCONH), 158.39 ($\mathrm{NCH_2Ph}$-*C4*), 171.20 ($\mathrm{COOC(CH_3)_3}$), 172.17 (CON), 172.51 (CONH). Anal. Calcd for $C_{45}H_{53}N_3O_7$: C, 72.26; H, 7.14; N, 5.62. Found: C, 72.09, H, 7.03, N, 5.72. ESI MS Calcd for $[M+Na]^+$ 770.38. Found: 770.38.

*4.8.2. N-Benzyloxycarbonyl-L-phenylalanyl-N′-(4-methoxybenzyl)-α,α-dimethylglycyl-L-phenylalanine tert-butyl ester (**11b**).* The reaction was carried out with 0.252 g of compound **10b** and the product purified by column chromatography (chloroform) followed by preparative layer chromatography (chloroform/methanol 100:1) to yield **11b** (328 mg, 92.7%), as a white solid, mp 65.9–67.0 °C, $[\alpha]_D$ +18.5 (*c* 1, ethanol). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.26 (6H, d, *J*=21.3 Hz, 2×$\mathrm{CCH_3}$), 1.28 (9H, *s*, $\mathrm{C(CH_3)_3}$), 2.71 (2H, dd, *J*=10.5, 13.8 Hz, $\mathrm{CHCH_2Ph}$), 2.85–3.05 (2H, m, $\mathrm{CHCH_2Ph}$), 3.73 (3H, s, $\mathrm{OCH_3}$), 4.37 (1H, q, *J*=6.9 Hz, $\mathrm{CHCH_2Ph}$), 4.40–4.51 (1H, m, $\mathrm{CHCH_2Ph}$), 4.66 (1H, d, *J*=18.3 Hz, $\mathrm{NCH_2}$), 4.82 (1H, d, *J*=18.6 Hz, $\mathrm{NCH_2}$), 4.91 (2H, d, *J*=6.0 Hz, $\mathrm{CH_2OCO}$), 6.88 (2H, d, *J*=8.4 Hz, $\mathrm{NCH_2Ph}$-*H3,5*), 6.99–7.95 (3H, m, $\mathrm{CHCH_2Ph}$-*H2,6*+CON*H*), 7.11–7.31 (13H, m, $\mathrm{CHCH_2Ph}$+$\mathrm{CHCH_2Ph}$-*H3,4,5*+$\mathrm{OCOCH_2Ph}$), 7.34 (2H, d, *J*=8.4 Hz, $\mathrm{NCH_2Ph}$-*H2,6*), 7.75 (1H, d, *J*=8.1 Hz, OCON*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ 23.18 ($\mathrm{CCH_3}$), 24.10 ($\mathrm{CCH_3}$), 27.54 ($\mathrm{C(CH_3)_3}$), 37.20 ($\mathrm{CHCH_2Ph}$), 37.38 ($\mathrm{CHCH_2Ph}$), 46.51 ($\mathrm{NCH_2Ph}$), 54.06 ($\mathrm{CHCH_2Ph}$), 54.10 ($\mathrm{CHCH_2Ph}$), 55.11 ($\mathrm{OCH_3}$), 62.25 (C^{α}), 65.31 ($\mathrm{OCOCH_2}$), 80.74 ($\mathrm{C(CH_3)_3}$), 113.96 ($\mathrm{NCH_2Ph}$-*C3,5*), 126.34 ($\mathrm{CHCH_2Ph}$-*C4*), 126.42 ($\mathrm{CHCH_2Ph}$-*C4*), 127.33 ($\mathrm{OCOCH_2Ph}$-*C2,6*), 127.67 ($\mathrm{OCOCH_2Ph}$-*C4*), 127.78 ($\mathrm{NCH_2Ph}$-*C2,6*), 128.10 (2×$\mathrm{CHCH_2Ph}$-*C3*,5), 128.26 ($\mathrm{OCOCH_2Ph}$-*C3,5*), 129.15 ($\mathrm{CHCH_2Ph}$-*C2,6*), 129.33 ($\mathrm{CHCH_2Ph}$-*C2,6*), 130.90 ($\mathrm{NCH_2Ph}$-*C1*), 136.89 ($\mathrm{OCOCH_2Ph}$-*C1*), 137.28 ($\mathrm{CHCH_2Ph}$-*C1*), 137.92 ($\mathrm{CHCH_2Ph}$-*C1*), 156.08 (OCONH), 158.35 ($\mathrm{NCH_2Ph}$-*C4*), 170.49 ($\mathrm{COOC(CH_3)_3}$), 172.34 (CON), 173.29 (CONH). Anal. Calcd for $C_{42}H_{49}N_3O_7$: C, 71.26; H, 6.98; N, 5.94. Found: C, 70.88; H, 7.19; N, 5.65. ESI MS Calcd for $[M+Na]^+$ 730.35. Found: 730.35.

*4.8.3. N-Benzyloxycarbonyl-L-phenylalanyl-N′-(4-methoxybenzyl)-α,α-diethylglycyl-L-phenylalanine tert-butyl ester (**11c**).* The reaction was carried out with 0.266 g of compound **10c** and the product purified by column chromatography (chloroform and chloroform/methanol, 100:1) to yield **11c** (349 mg, 94.8%), as a pale yellow solid, mp 100.8–102.0 °C, $[\alpha]_D$ +30.0 (*c* 1, ethanol). ^{1}H NMR (300 MHz, DMSO-d_6, 70 °C): δ 0.56–0.76 (6H, m, 2×$\mathrm{CH_2CH_3}$), 1.30 (9H, d, *J*=9.0 Hz, $\mathrm{C(CH_3)_3}$), 1.47–1.70 (2H, m, $\mathrm{CCH_2}$), 1.93–2.09 (1H, m, $\mathrm{CCH_2}$), 2.10–2.31 (1H, m, $\mathrm{CCH_2}$), 2.66–2.80 (2H, m, $\mathrm{CHCH_2Ph}$), 2.87–3.10 (2H, m, $\mathrm{CHCH_2Ph}$), 3.76 (3H, d, *J*=2.7 Hz, $\mathrm{OCH_3}$), 4.40–4.64 (3H, m, 2×$\mathrm{CHCH_2Ph}$+$\mathrm{NCH_2}$), 4.78–5.08 (3H, m, $\mathrm{NCH_2}$+$\mathrm{CH_2OCO}$), 6.58 (1H, dd, *J*=7.5, 13.5 Hz, CON*H*), 6.80–6.97 (4H, m, $\mathrm{NCH_2Ph}$-*H3,5*+$\mathrm{CHCH_2Ph}$-*H2,6*), 7.06–7.36 (13H, m, $\mathrm{CHCH_2Ph}$-*H3,4,5*+$\mathrm{CHCH_2Ph}$+$\mathrm{OCOCH_2Ph}$), 7.41 (2H, d, *J*=8.4 Hz, $\mathrm{NCH_2Ph}$-*H2,6*), 7.51 (1H, br d, *J*=6.3 Hz, OCON*H*); ^{13}C NMR (75 MHz, DMSO-d_6, 70 °C): δ 7.24, 7.27 ($\mathrm{CCH_2CH_3}$), 7.67, 7.80 ($\mathrm{CCH_2CH_3}$), 22.51, 22.90 ($\mathrm{CCH_2}$), 24.15, 24.37 ($\mathrm{CCH_2}$), 27.21, 27.23 ($\mathrm{C(CH_3)_3}$), 37.35 ($\mathrm{CHCH_2Ph}$), 37.52 ($\mathrm{CHCH_2Ph}$), 46.82, 46.90 ($\mathrm{NCH_2Ph}$), 53.40, 53.60, 53.74 (2×$\mathrm{CHCH_2Ph}$), 54.89 ($\mathrm{OCH_3}$), 65.05 ($\mathrm{OCOCH_2}$), 68.47, 68.50 (C^{α}), 80.56, 80.66 ($\mathrm{C(CH_3)_3}$), 113.87, 113.94 ($\mathrm{NCH_2Ph}$-*C3,5*), 125.81, 125.84 ($\mathrm{CHCH_2Ph}$-*C4*), 126.02, 126.06 ($\mathrm{CHCH_2Ph}$-*C4*), 126.85, 126.89 ($\mathrm{OCOCH_2Ph}$-*C2,6*+$\mathrm{OCOCH_2Ph}$-*C4*), 127.20, 127.23 ($\mathrm{NCH_2Ph}$-*C2,6*), 127.54, 127.57, 127.72, 127.83 ($\mathrm{CHCH_2Ph}$-*C3*,5+$\mathrm{OCOCH_2Ph}$-*C3,5*+$\mathrm{CHCH_2Ph}$-*C3*,5), 128.66, 128.78, 228.80, 128.88 (2×$\mathrm{CHCH_2Ph}$-

C2,6), 131.42, 131.63 (NCH$_2$Ph-*C1*), 136.72 (OCOCH$_2$Ph-*C1*), 136.94, 137.26, 137.43 (2×CHCH$_2$Ph-*C1*), 155.52 (OCONH), 158.16, 158.20 (NCH$_2$Ph-*C4*), 170.07, 170.16 (*C*OOC(CH$_3$)$_3$), 171.61, 171.68 (*C*ONH), 172.32, 172.75 (*C*ON). Anal. Calcd for $C_{44}H_{53}N_3O_7$: C, 71.81; H, 7.26; N, 5.71. Found: C, 71.43; H, 7.14; N, 5.85. ESI MS Calcd for $[M+Na]^+$ 758.38. Found: 758.37.

*4.8.4. N-Benzyloxycarbonyl-L-phenylalanyl-N′-(4-methoxybenzyl)-α,α-dipropylglycyl-L-phenylalanine tert-butyl ester (**11d**).* The reaction was carried out with 0.280 g of compound **10d** and the product purified by column chromatography (chloroform/hexane 2:1) followed by recrystallized from diethyl ether/petroleum ether (40–60 °C) to yield **11d** (355 mg, 92.9%), as a white solid, mp 130.9–131.9 °C, $[\alpha]_D$ +27.7 (*c* 1, ethanol). ^{1}H NMR (300 MHz, DMSO-d_6, 70 oC): δ 0.66–0.85 (6H, m, 2×CH$_2$CH$_2$C*H*$_3$), 0.98 (2H, sext, *J*=7.7 Hz, C*H*$_2$CH$_3$), 1.03–1.20 (2H, m, C*H*$_2$CH$_3$), 1.31 (9H, d, *J*=10.5 Hz, C(C*H*$_3$)$_3$), 1.43–1.63 (2H, m, CC*H*$_2$), 1.83–2.25 (2H, m, CC*H*$_2$), 2.71 (2H, br d, *J*=3.6 Hz,CHC*H*$_2$Ph), 2.86–3.04 (2H, m, CHC*H*$_2$Ph), 3.75 (3H, d, *J*=3.3 Hz, OC*H*$_3$), 4.38–4.63 (3H, m, 2×C*H*CH$_2$Ph+NC*H*$_2$), 4.74–5.05 (3H, m, NC*H*$_2$+C*H*$_2$OCO), 6.58 (1H, dd, *J*=7.7, 16.1 Hz, CON*H*), 6.80–6.95 (4H, m, NCH$_2$Ph-*H3,5*+CHCH$_2$Ph-*H2,6*), 7.04–7.35 (13H, m, CHCH$_2$Ph-*H3,4,5*+CHCH$_2$*Ph*+OCOCH$_2$*Ph*), 7.39 (2H, d, *J*=8.1 Hz, NCH$_2$Ph-*H2,6*), 7.49 (1H, br d, *J*=6.6 Hz, OCON*H*); ^{13}C NMR (75 MHz, DMSO-d_6, 70 oC): δ 14.05 (2×CH$_2$CH$_2$CH$_3$), 15.99, 16.06 (*C*H$_2$CH$_3$), 16.29, 16.45 (*C*H$_2$CH$_3$), 27.25, 27.28 (C(*C*H$_3$)$_3$), 33.11, 33.45 (C*C*H$_2$), 34.58, 34.81 (C*C*H$_2$), 37.36 (CH*C*H$_2$Ph), 37.54 (CH*C*H$_2$Ph), 46.80, 46.88 (N*C*H$_2$Ph), 53.45, 53.66, 53.75 (2×*C*HCH$_2$Ph), 54.95 (O*C*H$_3$), 65.11 (OCO*C*H$_2$), 67.88, 67.92 (C^α), 80.66, 80.74 (*C*(CH$_3$)$_3$), 113.92, 113.99 (NCH$_2$Ph-*C3,5*), 125.89 (CHCH$_2$Ph-*C4*), 126.09, 126.14 (CHCH$_2$Ph-*C4*), 126.91, 126.95 (OCOCH$_2$Ph-*C2,6*), 127.24, 127.29, 127.32 (NCH$_2$Ph-*C2,6*+OCOCH$_2$Ph-*C4*), 127.61, 127.76, 127.92 (CHCH$_2$Ph-*C3*,5+OCOCH$_2$Ph-*C3,5*+CHCH$_2$Ph-*C3*,5), 128.71, 128.82, 128.83, 128.93 (2×CHCH$_2$Ph-*C2,6*), 131.48, 131.65 (NCH$_2$Ph-*C1*), 136.74 (OCOCH$_2$Ph-*C1*), 136.96, 137.28, 137.45 (2×CHCH$_2$Ph-*C1*), 155.60 (O*C*ONH), 158.21, 158.25 (NCH$_2$Ph-*C4*), 170.15, 170.29 (*C*OOC(CH$_3$)$_3$), 171.86, 171.96 (*C*ONH), 172.32, 172.79 (*C*ON). Anal. Calcd for $C_{46}H_{57}N_3O_7$: C, 72.32; H, 7.52; N, 5.50. Found: C, 72.12; H, 7.54; N, 5.56. ESI MS Calcd for $[M+Na]^+$ 786.41. Found: 786.41.

*4.8.5. N-Benzyloxycarbonyl-L-phenylalanyl-N′-(4-methoxybenzyl)-α,α-diisobutylglycyl-L-phenylalanine tert-butyl ester (**11e**).* The reaction was carried out with 0.294 g of compound **10e** and the product purified first by column chromatography (chloroform) followed by preparative layer chromatography (PLC) (chloroform/methanol, 100:1) and recrystallized from diethyl ether/petroleum ether (40–60 °C) to yield **11e** (280 mg, 70.7%), as a white solid, mp 139.9–141.7 °C, $[\alpha]_D$ +29.2 (*c* 1, ethanol). ^{1}H NMR (300 MHz, DMSO-d_6, 70 °C): δ 0.63 (3H, dd, *J*=6.3, 27.0 Hz, CHC*H*$_3$), 0.81 (3H, d, *J*=6.6 Hz, CHC*H*$_3$), 0.88 (6H, t, *J*=6.6 Hz, CH(C*H*$_3$)$_2$), 1.29 (9H, d, *J*=12.3 Hz, C(C*H*$_3$)$_3$), 1.40–1.78 (4H, m, 2×CC*H*$_2$), 1.98 (1H, td, *J*=5.0, 13.2 Hz, C*H*(CH$_3$)$_2$), 2.32 (1H, td, *J*=6.0, 14.8 Hz, C*H*(CH$_3$)$_2$), 2.56–2.79 (2H, m, CHC*H*$_2$Ph), 2.86–3.07 (2H, m, CHC*H*$_2$Ph), 3.77 (3H, d, *J*=4.2 Hz, OC*H*$_3$), 4.37–4.72 (3H, m, 2×C*H*CH$_2$Ph+NC*H*$_2$), 4.89 (2H, br s, C*H*$_2$OCO), 5.03 (1H, br d, *J*=17.7 Hz, NC*H*$_2$), 6.68 (1H, dd, *J*=7.8, 18.0 Hz, CON*H*), 6.79 (2H, br d, *J*=3.3 Hz, CHCH$_2$Ph-*H2,6*), 6.94 (2H, br t, *J*=7.5 Hz, NCH$_2$Ph-*H3,5*), 7.04–7.34 (13H, m, CHCH$_2$Ph-*H3,4,5*+CHCH$_2$*Ph*+OCOCH$_2$*Ph*), 7.54 (2H, br d, *J*=7.5 Hz, NCH$_2$Ph-*H2,6*), 7.66 (1H, br d, *J*=5.4 Hz, OCON*H*); ^{13}C NMR (75 MHz, DMSO-d_6, 70 °C): δ 22.40, 22.43 (CH(*C*H$_3$)$_2$), 22.59, 22.70 (CH(*C*H$_3$)$_2$), 23.91, 24.34, 24.37, 24.37, 24.47, 25.02 (2×*C*H(CH$_3$)$_2$), 27.16, 27.22 (C(*C*H$_3$)$_3$), 36.92, 37.21 (CH*C*H$_2$Ph), 37.56, 37.76 (CH*C*H$_2$Ph), 38.94 (C*C*H$_2$), 41.56, 41.76 (C*C*H$_2$), 46.64, 46.70 (N*C*H$_2$Ph), 53.44 (*C*HCH$_2$Ph), 54.15 (*C*HCH$_2$Ph), 54.92, 54.94 (O*C*H$_3$), 64.99 (OCO*C*H$_2$), 67.72 (C^α), 80.59, 80.72 (*C*(CH$_3$)$_3$), 113.88, 113.93 (NCH$_2$Ph-*C3,5*), 125.72 (CHCH$_2$Ph-*C4*), 126.06, 126.10 (CHCH$_2$Ph-*C4*), 126.88, 126.90 (OCOCH$_2$Ph-*C2,6*), 127.20 (NCH$_2$Ph-*C2,6*), 127.45 (OCOCH$_2$Ph-*C4*+CHCH$_2$Ph-*C3*,5), 127.74, 127.82 (OCOCH$_2$Ph-*C3,5*+CHCH$_2$Ph-*C3*,5), 128.66, 128.72, 128.82, 128.94 (2×CHCH$_2$Ph-*C2,6*), 131.89 (NCH$_2$Ph-*C1*), 136.74 (OCOCH$_2$Ph-*C1*), 136.99 (CHCH$_2$Ph-*C1*), 137.38, 137.51 (CHCH$_2$Ph-*C1*), 155.56 (O*C*ONH), 158.14, 158.21 (NCH$_2$Ph-*C4*), 169.99, 170.10 (*C*OOC(CH$_3$)$_3$), 171.95, 172.27 (*C*ONH), 172.54, 172.84 (*C*ON). Anal. Calcd for $C_{48}H_{61}N_3O_7$: C, 72.79; H, 7.76; N, 5.31. Found: C, 72.43; H, 7.76; N, 5.29. ESI MS Calcd for $[M+Na]^+$ 814.44. Found: 814.44.

*4.8.6. N-benzyloxycarbonyl-L-phenylalanyl-N′-(4-methoxybenzyl)-α,α-dibenzylglycyl-L-phenylalanine tert-butyl ester (**11f**).* The reaction was carried out with 0.328 g of compound **11f** and the product obtained purified by column chromatography (chloroform/hexane 1:1), followed by preparative layer chromatography (chloroform/methanol, 200:1); the two major fractions obtained were recrystallized from diethyl ether/petroleum ether (40–60 °C) to yield **11f′** (166 mg, 38.6%) and **11f″** (67 mg, 15.6%) as a white solids.

Fraction **11f′**: mp 129.5–131.0 °C, $[\alpha]_D$ +140.4 (*c* 1, ethanol).^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.18 (9H, s, C(C*H*$_3$)$_3$), 2.64–2.80 (3H, m, CHC*H*$_2$Ph+CC*H*$_2$Ph), 2.86–3.02 (3H, m, CHC*H*$_2$Ph+CC*H*$_2$Ph), 3.20 (2H, d, *J*=12.6 Hz, CC*H*$_2$Ph), 3.66 (1H, d, *J*=12.0 Hz, NC*H*$_2$), 3.74 (3H, s, OC*H*$_3$), 4.22–4.35 (2H, m, 2×C*H*CH$_2$Ph), 4.45 (1H, d, *J*=18.6 Hz, NC*H*$_2$), 5.02 (2H, s, C*H*$_2$OCO), 6.22 (1H, br s, CON*H*), 6.78 (2H, br s, CHCH$_2$Ph-*H2,6*), 6.94 (2H, d, *J*=8.7 Hz, NCH$_2$Ph-*H3,5*), 7.04–7.42 (25H, m, 2×CHCH$_2$*Ph*+2×CCH$_2$*Ph*+OCOCH$_2$*Ph*), 7.55 (2H, d, *J*=8.4 Hz, NCH$_2$Ph-*H2,6*), 8.09 (1H, d, *J*=9.0 Hz, OCON*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ 27.45 (C(*C*H$_3$)$_3$), 37.37, 37.83 (2×CH*C*H$_2$Ph +2×C*C*H$_2$Ph), 46.82 (N*C*H$_2$Ph), 53.57 (*C*HCH$_2$Ph), 53.82 (*C*HCH$_2$Ph), 55.19 (O*C*H$_3$), 65.31 (OCO*C*H$_2$), 69.08 (C^α), 81.40 (*C*(CH$_3$)$_3$), 114.17 (NCH$_2$Ph-*C3,5*), 126.23 (CHCH$_2$Ph-*C4*), 126.60 (CHCH$_2$Ph-*C4*), 127.01 (2×CCH$_2$Ph-*C4*), 127.23 (NCH$_2$Ph-*C2,6*+OCOCH$_2$Ph-*C2,6*), 127.70 (OCOCH$_2$Ph-*C4*), 127.95, 128.05 (OCOCH$_2$Ph-*C3,5*+2×CHCH$_2$Ph-*C3*,5), 128.35 (2×CCH$_2$Ph-*C3,5*), 129.08, 129.62 (CHCH$_2$Ph-*C2,6*+CCH$_2$Ph-*C2,6*), 130.64, 130.86 (CHCH$_2$Ph-*C2,6*+CCH$_2$Ph-*C2,6*), 131.78 (NCH$_2$Ph-*C1*), 134.76, 135.24 (2×CCH$_2$Ph-*C1*), 136.68 (CHCH$_2$Ph-*C1*), 137.10 (OCOCH$_2$Ph-*C1*), 137.74 (CHCH$_2$Ph-*C1*), 155.87 (O*C*ONH), 158.33 (NCH$_2$Ph-*C4*), 169.30 (*C*OOC(CH$_3$)$_3$), 170.50 (*C*ONH), 174.10 (*C*ON). Anal. Calcd for $C_{54}H_{57}N_3O_7$: C, 75.41; H, 6.68; N, 4.89. Found: C, 74.88; H, 6.60; N, 4.96. ESI MS Calcd for $[M+Na]^+$ 882.41. Found: 882.41.

Fraction **11f″**: mp 109.4–111.1 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.21 (9H, s, C(C*H*$_3$)$_3$), 2.53–2.78 (4H, m, 2×CHC*H*$_2$Ph), 3.08 (2H, d, *J*=11.4 Hz, CC*H*$_2$Ph), 3.19 (2H, d, *J*=12.0 Hz, CC*H*$_2$Ph), 3.60 (1H, d, *J*=12.0 Hz, NC*H*$_2$), 3.73 (3H, s, OC*H*$_3$), 4.14 (1H, br q, *J*=4.6 Hz, C*H*CH$_2$Ph), 4.23 (1H, br q, *J*=5.1 Hz, C*H*CH$_2$Ph), 4.37 (1H, d, *J*=18.9 Hz, NC*H*$_2$), 5.01 (2H, s, C*H*$_2$OCO), 6.72 (2H, br s, CHCH$_2$Ph-*H2,6*), 6.83 (1H, br s, CON*H*), 6.90 (2H, d, *J*=8.4 Hz, NCH$_2$Ph-*H3,5*), 6.99 (2H, br d, *J*=5.7 Hz, CHCH$_2$Ph-*H2,6*), 7.04–7.35 (21H, m, 2×CHCH$_2$Ph-*H3,4,5*+2×CCH$_2$*Ph*+OCOCH$_2$*Ph*), 7.50 (2H, d, *J*=7.8 Hz, NCH$_2$Ph-*H2,6*), 8.06 (1H, d, *J*=8.7 Hz, OCON*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ 27.43 (C(*C*H$_3$)$_3$), 37.37, 37.53 (2×CH*C*H$_2$Ph +2×C*C*H$_2$Ph), 46.71 (N*C*H$_2$Ph), 53.62 (*C*HCH$_2$Ph), 54.32 (*C*HCH$_2$Ph), 55.11 (O*C*H$_3$), 65.24 (OCO*C*H$_2$), 69.00 (C^α), 80.40 (*C*(CH$_3$)$_3$), 113.99 (NCH$_2$Ph-*C3,5*), 126.15 (CHCH$_2$Ph-*C4*), 126.50 (CHCH$_2$Ph-*C4*), 126.81 (NCH$_2$Ph-*C2,6*), 126.92 (2×CCH$_2$Ph-*C4*), 127.21 (OCOCH$_2$Ph-*C2,3,5,6*), 127.66, 127.90 (OCOCH$_2$Ph-*C4*+2×CHCH$_2$Ph-*C3*,5), 128.12 (CCH$_2$Ph-*C3,5*), 128.32 (CCH$_2$Ph-*C3,5*), 129.11, 129.18 (CHCH$_2$Ph-*C2,6*+CCH$_2$Ph-*C2,6*), 130.83, 130.91 (CHCH$_2$Ph-*C2,6*+CCH$_2$Ph-*C2,6*), 131.88 (NCH$_2$Ph-*C1*), 135.25 (CHCH$_2$Ph-*C1*), 135.64 (CCH$_2$Ph-*C1*), 136.83 (OCOCH$_2$Ph-*C1*), 137.13 (CCH$_2$Ph-*C1*), 137.71 (CHCH$_2$Ph-*C1*), 155.79 (O*C*ONH), 158.19 (NCH$_2$Ph-*C4*), 170.18 (*C*OOC(CH$_3$)$_3$), 170.72 (*C*ONH), 173.63 (*C*ON). Anal. Calcd for $C_{54}H_{57}N_3O_7$: C, 75.41; H, 6.68; N, 4.89. Found: C, 74.95; H, 6.55; N, 4.88. ESI MS Calcd for $[M+Na]^+$ 882.41. Found: 882.41.

4.9. DCC/HOBt-assisted synthesis of tripeptide 12

This synthesis was performed under the same experimental conditions reported in section 4.6 above.

*4.9.1. N-Benzyloxycarbonyl-L-phenylalanyl-N-(4-methoxybenzyl)-α,α-dimethylglycyl-glycine tert-butyl ester (**12**).* The reaction was carried out with 0.4 mmol of compound **10b** and the product obtained purified by column chromatography (chloroform) and preparative layer chromatography (hexane/ethyl acetate, 3:2) to yield **12** (120 mg, 48.6%) and recrystallized from diethyl ether/petroleum ether (40–60 °C), as a white solid, mp 131.3–133.0 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.40 (6H, d, J=15.0 Hz, 2×CC*H*$_3$), 1.46 (9H, s, C(C*H*$_3$)$_3$), 2.96 (2H, ddd, J=7.1, 13.4, 61.4 Hz, CHC*H*$_2$Ph), 3.79 (3H, s, OC*H*$_3$), 3.93 (2H, qd, J=4.8, 18.5 Hz, NHC*H*$_2$), 4.39 (1H, d, J=18.0 Hz, NC*H*$_2$), 4.63 (1H, d, J=18.3 Hz, NC*H*$_2$), 4.71 (1H, q, J=7.8 Hz, C*H*CH$_2$Ph), 5.05 (2H, d, J=4.8 Hz, C*H*$_2$OCO), 5.61 (1H, d, J=8.1 Hz, OCON*H*), 6.17 (1H, br t, J=3.9 Hz, N*H*CH$_2$), 6.83 (2H, d, J=8.4 Hz, NCH$_2$Ph-*H3,5*), 7.02–7.08 (2H, m, CHCH$_2$Ph-*H2,6*), 7.11 (2H, d, J=8.1 Hz, NCH$_2$Ph-*H2,6*), 7.16–7.40 (8H, m, CHCH$_2$Ph-*H3,4,5*+OCOCH$_2$*Ph*); ^{13}C NMR (75 MHz, CDCl$_3$): δ 23.86 (C*C*H$_3$), 24.16 (C*C*H$_3$), 27.99 (C(*C*H$_3$)$_3$), 39.23 (CH*C*H$_2$Ph), 42.18 (NH*C*H$_2$), 46.72 (N*C*H$_2$Ph), 53.69 (*C*HCH$_2$Ph), 55.25 (O*C*H$_3$), 62.90 (C^{α}), 66.76 (OCO*C*H$_2$), 82.20 (*C*(CH$_3$)$_3$), 114.32 (NCH$_2$Ph-*C3,5*), 126.82 (CHCH$_2$Ph-*C4*), 127.33 (NCH$_2$Ph-*C2,6*), 127.80 (OCOCH$_2$Ph-*C2,6*), 128.00 (OCOCH$_2$Ph-*C4*), 128.41 (CHCH$_2$Ph-*C3,5*+OCOCH$_2$Ph-*C3,5*), 129.59 (CHCH$_2$Ph-*C2,6*), 129.77 (NCH$_2$Ph-*C1*), 136.24 (OCOCH$_2$Ph-*C1*), 136.44 (CHCH$_2$Ph-*C1*), 155.78 (*C*ONH), 158.87 (NCH$_2$Ph-*C4*), 169.50 (*C*OOC(CH$_3$)$_3$), 172.55 (*C*ON), 174.31 (*C*ONHCH$_2$). Anal. Calcd for $C_{35}H_{43}N_3O_7$: C, 68.05; H, 7.02; N, 6.80. Found: C, 67.69; H, 7.02; N, 6.69.

4.10. Synthesis and characterization of imidazolone 13

Compound **5d** was treated according to the general method described in Section 4.4 above for the synthesis of compounds **3b**–**3e**.

*4.10.1. 2-(1-Benzyloxycarbonylamino-2-phenylethyl)-4,4-dipropyl-1-tert-butyloxycarbonylmetyl-4,5-dihydroimidazol-5-one (**13**).* The products obtained by reaction of **5d** (0.441 g) were purified by column chromatography (chloroform and chloroform/methanol 200:1) to yield **6d** (221 mg, 39.9%) and **13** (199 mg, 37.1%) as a white solid, mp 131.2–132.7 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.85 (6H, dt, J=7.2, 11.1 Hz, 2×CH$_2$C*H*$_3$), 0.99–1.20 (4H, m, 2×C*H*$_2$CH$_3$), 1.47 (9H, s, C(C*H*$_3$)$_3$), 1.66–1.76 (2H, m, 2×CC*H*$_2$), 3.21 (2H, ddd, J=6.9, 14.1, 55.6 Hz, CHC*H*$_2$Ph), 4.09 (2H, dd, J=18.2, 60.5 Hz, NC*H*$_2$), 4.67 (1H, q, J=7.5 Hz, C*H*CH$_2$Ph), 5.04 (2H, d, J=2.4 Hz, C*H*$_2$OCO), 5.45 (1H, d, J=8.1 Hz, OCON*H*), 7.19–7.38 (10H, m, CHCH$_2$*Ph*+OCOCH$_2$*Ph*); ^{13}C NMR (75 MHz, CDCl$_3$): δ 14.07 (CH$_2$*C*H$_3$), 14.52 (CH$_2$*C*H$_3$), 16.60 (*C*H$_2$CH$_3$), 16.77 (*C*H$_2$CH$_3$), 27.94 (C(*C*H$_3$)$_3$), 39.18, 39.28, 39.36 (CH*C*H$_2$Ph+2×C*C*H$_2$), 41.78 (N*C*H$_2$), 50.01 (*C*HCH$_2$Ph), 67.01 (OCO*C*H$_2$), 74.23 (Imidazol-*C4*), 83.04 (*C*(CH$_3$)$_3$), 127.09 (CHCH$_2$Ph-*C4*), 127.90 (OCOCH$_2$Ph-*C2,6*), 128.19 (OCOCH$_2$Ph-*C4*), 128.51, 128.58 (OCOCH$_2$Ph-*C3,5*+CHCH$_2$Ph-*C3,5*), 129.33 (CHCH$_2$Ph-*C2,6*), 136.02 (OCOCH$_2$Ph-*C1*), 136.13 (CHCH$_2$Ph-*C1*), 155.71 (*C*ONH), 162.52 (Imidazol-*C2*), 169.95 (*C*OOC(CH$_3$)$_3$), 184.65 (Imidazol-*C5*). Anal. Calcd for $C_{31}H_{41}N_3O_5$: C, 69.51; H, 7.71; N, 7.84. Found: C, 69.15; H, 7.41; N, 7.78.

Acknowledgements

We wish to acknowledge Miss Elisa Pinto for running the NMR spectra and for the elemental analyses and also the Fundação para a Ciência e Tecnologia (Portugal) for financial support to the Centro de Química (University of Minho) and for a scholarship to one of us (F.C.S.C.P.).

References and notes

1. Toniolo, C. *Janssen Chim. Acta* **1993**, *11*, 10–16 (review article); Mazeleyrat, J.-P.; Wright, K.; Wakselman, M.; Fromaggio, F.; Crisma, M.; Toniolo, C. *Eur. J. Org. Chem.* **2001**, 1821–1829; Toniolo, C.; Crisma, M.; Formaggio, F.; Peggion, C. *Biopolymers* **2001**, *60*, 396–419.
2. Lombardi, A.; De Simone, G.; Galdiero, S.; Nastri, F.; Di Costanzo, L.; Makihira, K.; Yamada, T.; Pavone, V. *Biopolymers* **2000**, *53*, 150–160.
3. De Filippis, V.; De Antoni, F.; Frigo, M.; Laureto, P.; Fontana, A. *Biochemistry* **1998**, *37*, 1686–1696.
4. Medzihradszky-Schweiger, H.; Medzihradszky, K.; Nádasi, H.; Suli-Vargha, H. In *Peptides 1998*; Bajusz, S., Hudecz, F., Eds.; Akadémiai Kiadó: Budapest, 1999; pp 606–607.
5. Peggion, C.; Crisma, M.; Formaggio, F.; Toniolo, C.; Wright, K.; Wakselman, M.; Mazaleyrat, J.-P. *Biopolymers* **2002**, *63*, 314–324.
6. Rodrigues, L. M.; Fonseca, J. I.; Maia, H. L. S. *Tetrahedron* **2004**, *60*, 8929–8936.
7. Pratt, D. A.; DiLabio, G. A.; Mulder, P.; Ingold, K. U. *Acc. Chem. Res.* **2004**, *37*, 334–340.
8. Mazaleyrat, J.-P.; Wright, K.; Gaucher, A.; Toulemonde, N.; Wakselman, M.; Oancea, S.; Peggion, C.; Formaggio, F.; Setnicka, V.; Keiderling, T. A.; Toniolo, C. *J. Am. Chem. Soc.* **2004**, *126*, 12874–12879.
9. Ramesh, K.; Balaram, P. *Bioorg. Med. Chem.* **1999**, *7*, 105–117.
10. Preto, M. A. C.; Melo, A.; Costa, S. P. G.; Maia, H. L. S.; Ramos, M. J. *J. Phys. Chem. B* **2003**, *107*, 14556–14562.
11. Preto, M. A. C.; Melo, A.; Maia, H. L. S.; Mavromoustakos, T.; Ramos, M. J. *J. Phys. Chem. B* **2005**, *109*, 17743–17751.
12. Maia, H. L.; Ridge, B.; Rydon, H. N. *J. Chem. Soc., Perkin Trans. 1* **1973**, 98–105.
13. Gokel, G.; Lüdke, G.; Ugi, I. In *Isonitrile Chemistry*; Ugi, I., Ed.; Academic: New York, NY, 1971; pp 145–199.
14. Costa, S. P. G.; Maia, H. L. S.; Pereira-Lima, S. M. M. A. *Org. Biomol. Chem.* **2003**, *1*, 1475–1479.
15. Tantry, S. J.; Rao, R. V. R.; Babu, V. V. S. *ARKIVOC* **2006**, *i*, 21–30.
16. Ellis, T. K.; Martin, C. H.; Ueki, H.; Soloshonok, V. A. *Tetrahedron Lett.* **2003**, *44*, 1063–1066.
17. Ellis, T. K.; Martin, C. H.; Tsai, G. M.; Ueki, H.; Soloshonok, V. A. *J. Org. Chem.* **2003**, *68*, 6208–6214.
18. Belokon, Y. N.; Bhave, D.; D'Addario, D.; Groaz, E.; North, M.; Tagliazucca, V. *Tetrahedron* **2004**, *60*, 1849–1861.
19. Harding, C. I.; Dixon, D. J.; Ley, S. V. *Tetrahedron* **2004**, *60*, 7679–7692.
20. Jones, D. S.; Kenner, G. W.; Preston, J.; Sheppard, R. C. *J. Chem. Soc.* **1965**, 6227–6239.
21. Freitas, A. M.; Maia, H. L. S. In *Peptides 1988*; Jung, G., Bayer, E., Eds.; Walter de Gruyter: Berlin, 1989; pp 13–15.
22. Linderman, R. J.; Binet, S.; Petrich, S. R. *J. Org. Chem.* **1999**, *64*, 336–337.
23. Creighton, C. J.; Romoff, T. T.; Bu, J. H.; Goodman, M. *J. Am. Chem. Soc.* **1999**, *121*, 6786–6791.
24. Johnson, T.; Quibell, M.; Owen, D.; Sheppard, R. C. *J. Chem. Soc., Chem. Commun.* **1992**, 1573.
25. Jiang, W.-Q.; Costa, S. P. G.; Maia, H. L. S. *Org. Biomol. Chem.* **2003**, *1*, 3804–3810.
26. Jiang, W.-Q.; Ventura, C.; Costa, S. P. G.; Albuquerque, L.; Gonçalves-Maia, R.; Maia, H. L. S. *J. Peptide Sci.* **2005**, *11*, 472–480.
27. Jiang, W.-Q.; Pereira-Lima, S. M. M. A.; Ventura, C.; Costa, S. P. G.; Albuquerque, L.; Gonçalves-Maia, R.; Maia, H. L. S. *J. Peptide Sci.* **2005**, *11*, 627–632.
28. Ventura, C.; Jiang, W.-Q.; Albuquerque, L.; Gonçalves-Maia, R.; Maia, H. L. S. *J. Peptide Sci.* **2006**, *12*, 239–242.
29. Pinto, F. C. S. C.; Pereira-Lima, S. M. M. A.; Ventura, C.; Albuquerque, L.; Gonçalves-Maia, R.; Maia, H. L. S. *Tetrahedron* **2006**, *62*, 8184–8198.
30. Costa, S. P. G.; Maia, H. L. S.; Pereira-Lima, S. M. M. A. In *Peptides 2002*; Benedetti, E., Pedone, C., Eds.; Edizioni Ziino: Napoli, 2002; pp 250–251.
31. Costa, S. P. G.; Maia, H. L. S.; Pereira-Lima, S. M. M. A. In *Peptide Revolution: Genomics, Proteomics & Therapeutics*; Chorev, M., Sawyer, T., Eds.; American Peptide Society/Kluwer: Norwel, 2004; pp 85–86.
32. Benoiton, N. L. *Chemistry of Peptide Synthesis*; CRC, Taylor & Francis Group: Boca Raton, FL, 2006.
33. Carpino, L. A.; Imazumi, I.; El-Faham, A.; Ferrer, F. J.; Zhang, C.; Lee, Y.; Foxman, B. M.; Henklein, P.; Hanay, C.; Mügge, C.; Wenschuh, H.; Klose, J.; Beyermann, M.; Bienert, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 441–445.
34. Savrda, J.; Chertanova, L.; Wakselman, M. *Tetrahedron* **1994**, *50*, 5309–5322.
35. Carpino, L. A.; Mansour, E.-S. M. E.; Sadat-Aalaee, D. *J. Org. Chem.* **1991**, *56*, 2611–2614.
36. Carpino, L. A.; Mansour, E.-S. M. E.; El-Faham, A. *J. Org. Chem.* **1993**, *58*, 4162–4164.
37. Maia, H. L. S.; Orrell, K. G.; Ridge, B. L.; Rydon, H. N. *J. Chem. Soc., Perkin Trans. 2* **1976**, 761–763.