Microwave-Assisted Synthesis of 2,5-Piperazinediones under Solvent-Free Conditions

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This paper is dedicated to Professor Steven V. Ley on the occasion of his 60th birthday.

Abstract: A general, efficient and environmentally friendly procedure for the synthesis of 2,5-piperazinediones is described, involving the microwave irradiation of *N*-Boc dipeptide esters.

Key words: microwave irradiation, diketopiperazines, dipeptides, cyclizations, heterocycles

Peptides are increasingly important in drug design, although a number of problems, especially poor bioavailability and stability, prevent their direct therapeutic use. This has led to the concept of peptidomimetics, which can be defined as non-peptidic compounds that behave as ligands of peptide receptors. In this context, 2,5-piperazinediones (2,5-diketopiperazines, DKPs) have often been used to circumvent the limitations of peptides. Their structure contains two hydrogen bond accepting centers and two hydrogen donating sites, which are often necessary for potential interactions between the lead compound and its target. On the other hand, they are conformationally restrained by the presence of a six-membered ring with side chains that are orientated in a spatially defined manner, allowing one to make easy and accurate conformational predictions. In contrast to classical linear peptides, DKPs are very stable to hydrolysis, a very important feature when designing potential lead structures.

Natural products with the 2,5-piperazinedione skeleton are quite common, and they have shown a wide variety of biological activities.[1] Unnatural DKPs have also been employed often in medicinal chemistry and show a broad spectrum of interesting pharmacological properties.[2] Supramolecular chemistry is another field of where DKPs have proved useful, and thus a class of artificial receptors consisting of a rigid diketopiperazine backbone and peptidic side chains has been developed that interact with peptidic substrates with high specificity.[3] Finally, 2,5-piperazinediones have proven to be very useful synthetic intermediates. Besides their well-known role as chiral auxiliaries in the preparation of unnatural aminoacids using Schöllkopf-related chemistry,[4] and Diels–Alder reactions,[5] they are useful starting materials for the synthesis of many natural products containing nitrogen heterocyclic moieties.[6] Due to their importance, the development of improved, environmentally benign routes to DKPs is of great interest.

A variety of methods are available for the preparation of DKPs.[7] However, because they can be considered as 'head to tail' cyclic dipeptides, the simplest methods are those that take advantage of the chirality and commercial availability of amino acids, and normally involve the preparation of a suitable linear dipeptide followed by N-deprotection and cyclization. The cyclization step is normally carried out under basic[8] or acidic[9] conditions, and epimerization is the most common undesired reaction. Cyclization of dipeptide esters can also be carried out under thermal conditions, normally by refluxing in high-boiling solvents such as toluene or xylene for 24 hours,[10] or, when starting from the formate salt of the dipeptide, in toluene–*sec*-BuOH.[11] In unfavorable cases, cyclization sometimes requires hydrolysis of the ester group and amide bond formation using peptide coupling methods. Ideally, the choice of N-protecting group and cyclization method should be such that deprotection takes place under the same conditions as cyclization, leading to a one-step preparation of the target DKP.

Since *N*-Boc groups can be deprotected under thermal conditions and heating can also lead to cyclization of dipeptides to DKPs, pyrolysis of *N*-Boc dipeptides can provide a solvent-free synthesis of our target compounds. One drawback of this approach is the potential for stereocenter epimerization in sensitive cases due to the harsh reaction conditions required. In this context, we reasoned that, because *N*-Boc deprotection has been described under microwave conditions, albeit not from dipeptides,[12] perhaps Boc-protected dipeptides could be cyclized to DKPs by microwave irradiation in one step under environmentally benign conditions, provided that the intramolecular amidation step can also be achieved under the same conditions. We report here in full[13] our results on this subject, prompted by several synthetic projects involving the construction of antitumour alkaloids from DKPs. Microwave irradiation[14] is considered as a green technology because it normally allows solvent-free reactions and its level of energy consumption is low compared with more traditional methods.[15] Although not related to our work, two recent reports have been published where preparation of 2,5-piperazinediones was assisted by microwave irradiation, namely an HBTU-induced dimeriza-

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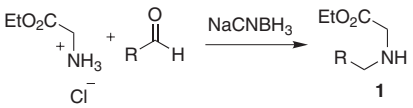
tion of a biologically active peptide to a DKP[16] and the microwave-assisted synthesis of DKP derivatives using the Ugi four-center, three-component reaction.[17]

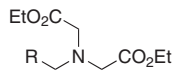
The *N*-Boc protected dipeptide esters **3** required as starting materials were prepared, normally as mixtures of rotamers, from the corresponding *N*-Boc protected amino acids and amino acid ester hydrochlorides with prior liberation of the free bases, in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC). With the exception of sarcosine, the N-substituted glycine derivatives employed in these reactions (compounds **1**) were not commercially available, and were prepared by reductive amination of the suitable aldehydes with glycine ethyl ester hydrochloride in the presence of sodium cyanoborohydride[18] or, alternatively, by alkylation of the suitable arylalkylamines with ethyl bromoacetate,[19] although in the latter case dialkylation products **2** could not be avoided (Scheme 1). Compound **1d**, also prepared by reductive amination or by alkylation of ethyl glycinate with gramine, had been previously described by us.[20]



1

Comp.	R	Yield, %
1a	C_6H_5	53
1b	4-$MeOC_6H_4$	53
1c	3,4-$(MeO)_2C_6H_3$	37
1d[a]	3-indolyl	57
1e	$PhCH_2$	49
1f	2-naphthyl	93

[a] Reference 20



2

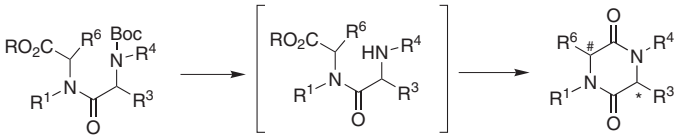
Scheme 1 Preparation of some N-substituted glycine esters as starting materials.

We show in Table 1 the comparison between the results obtained in the preparation of variously substituted DKPs from the corresponding *N*-Boc dipeptide esters **3** using conventional and microwave heating, without isolation of the intermediate N-deprotected derivatives **4**. Regarding simple derivatives substituted at the C-3 and/or N-1 positions (compounds **5a**–**n**), the reactions were carried out in two to eight minutes under microwave irradiation compared to 2–4.5 hours at 200 °C for the conventional heating reactions, and yields were also normally higher for the microwave-assisted reactions. We employed a domestic microwave oven with the power set at 600 W, employing an alumina heat sink.[21] In our initial experiments we irradiated the reactions in one-minute pulses to prevent excessive heating (e.g., entry 1, where six pulses were required). Subsequent experimentation proved that the precaution of irradiating in short pulses was unnecessary, since irradiations of up to five consecutive minutes at 600 W were tolerated without decomposition (e.g. entry 3). Although the typical reaction scale for the results shown in Table 1 was about 200–500 mg of starting material, microwave reactions were scaled-up with only slight yield loss. For instance, the preparation of compound **5a** in entry 2 could be performed in 91% yield starting from 1 g of dipeptide and in 83% yield from 6 g of dipeptide. Similarly, compound **5g** was isolated in 97% yield from 1 g of dipeptide and in 88% yield from 3 g of dipeptide.[22] Because DKP ring formation is strongly sequence-dependent, being particularly favored for Gly or Pro residues acting as nucleophiles, but more difficult when hindered amino acids like Val, Leu, Ile, Phe, Trp, Tyr, etc. are involved,[23] we also studied some of these cases, finding yields only slightly lower than the one achieved with the alanine derivative under similar conditions (entries 3–7). Compound **5c** (entry 4) has been recently isolated from marine bacteria associated with the sponge *Ircinia variabilis*.[24] Regarding the N-substituted dipeptides, they reacted more slowly (e.g. R^1 = Me, which required 8 min irradiation, entry 8) or not at all (e.g. R^1 = $ArCH_2$ or $ArCH_2CH_2$, entries 9 and 15) under our initial conditions involving one-minute pulses. In these cases, we found that addition of 10% silica gel to the reaction mixture accelerated the reactions, and allowed to carry out the desired transformations in five pulses (5 min total time), normally with improved yields with regard to the thermal reaction (entries 10, 13 and 17), although these reactions were not completely solvent-free because of the need of extracting the products from the silica gel. Under modified conditions involving irradiation for up to three consecutive minutes, addition of silica gel was unnecessary and the DKPs were obtained in improved yields in all cases (entries 11, 12, 14, 16, 18 and 19). Long pulses were advisable in the more difficult cases; for instance, during the preparation of compound **5g** a 66% yield was obtained after 6 pulses of two minutes, with intermediate two-minute pauses, while three pulses of three–two–two minutes with similar pauses led to a 98% yield.

Besides yield and experimental convenience, stereochemical integrity is also a very important aspect of the preparation of DKPs. In this regard, compound **5a** (obtained under thermal conditions) has been previously shown to be enantiomerically pure by ^{1}H NMR in the presence of $Eu(hfc)_3$.[25] As far as compounds bearing a single stereocenter on the DKP framework are concerned, we have found that samples of the valine derivative **5k** prepared according to three different procedures, namely thermal and microwave cyclization of a *N*-Boc dipeptide ester and hydrogenolysis of a *N*-Cbz dipeptide ester followed by cyclization, which is known to be safe from a stereochemical point of view,[10] were identical in all respects, including optical rotation. Furthermore, none of these samples showed splitting of any ^{1}H NMR signal upon addition of $Eu(hfc)_3$, under conditions previously established on a reference racemic sample of **5k** prepared from (±)-Val.

However, the reaction in entry 5, involving (*S*,*S*)-Ile, which is known to epimerize very easily,[26] led to a 1:1 mixture of diastereomers under thermal conditions. In this case, the microwave conditions afforded a 9:1 mixture of diastereomers, showing an advantage in terms of stereochemical integrity, besides the improved yield and shorter reaction time.

Table 1 Comparison of the Results Obtained in the Synthesis of 2,5-Piperazinediones Substituted at N-1, C-3, N-4 and C-6 from *N*-Boc Dipeptide Esters under Conventional Thermal and Microwave-Assisted Conditions



3 **4** **5**

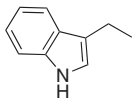
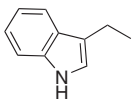
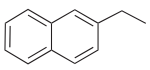
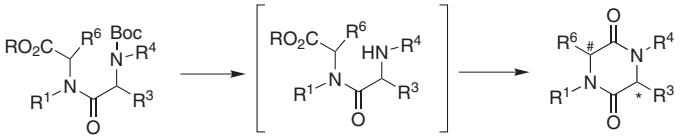
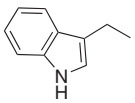
Entry	Comp.	R	R^1	R^6	R^3	R^4	Conf. at *	Conf. at #	Heating (200 °C)		Microwave (600 W)	
									Time (h)	Yield (%) (dr)	Time (min)	Yield (%) (dr)
1	**5a**	Et	H	H	Me	H	*S*	–	2	98	5[a]	65
2	**5a**	Et	H	H	Me	H	*S*	–			6[b]	98
3	**5b**	Et	H	H	*i*-Pr	H	*S*	–	3.5	56	5[b]	87
4	**5c**	Et	H	H	*i*-Bu	H	*S*	–	3	81	2[b]	89
5	**5d**	Et	H	H		H	*S*	–	4.5	81 (1:1)	5[b]	91 (9:1)
6	**5e**	Et	H	H	Bn	H	*S*	–	4.5	72	2[b]	82
7	**5f**	Et	H	H		H	*S*	–	3	69	2[b]	92
8	**5g**	Me	Me	H	H	H	–	–	3 (220 °C)	84	8[c]	98
9	**5h**	Et	Bn	H	Me	H	*S*	–	2	81	5[a]	0
10	**5h**	Et	Bn	H	Me	H	*S*	–			5[d]	64
11	**5h**	Et	Bn	H	Me	H	*S*	–			3[b]	84
12	**5i**	Et	4-MeOBn	H	H	H	–	–	–	–	3[b]	72
13	**5j**	Et	3,4-$(MeO)_2$Bn	H	Me	H	*S*	–	2	79	5[d]	99
14	**5k**	Et		H	*i*-Pr	H	*S*	–	2	90	3[b]	90
15	**5l**	Et	$Ph(CH_2)_2$	H	H	H	–	–	2	80	5[a]	0
16	**5l**	Et	$Ph(CH_2)_2$	H	H	H	–	–			3[b]	99
17	**5m**	Et	$Ph(CH_2)_2$	H	*i*-Pr	H	*S*	–	2	81	5[d]	65
18	**5m**	Et	$Ph(CH_2)_2$	H	*i*-Pr	H	*S*	–	–	–	3[b]	90
19	**5n**	Et		H	Me	H	*S*	–	2	79	5[b]	81
20	**5o**	Et	H	*i*-Pr	Bn	H	*S*	*S*	2	92 (1:1)	8[a]	98
21	**5p**	Me	H	*i*-Pr	Bn	H	*S*	*R*	2	92 (2.6:1)	8[a]	98

Table 1 Comparison of the Results Obtained in the Synthesis of 2,5-Piperazinediones Substituted at N-1, C-3, N-4 and C-6 from *N*-Boc Dipeptide Esters under Conventional Thermal and Microwave-Assisted Conditions (continued)



3 **4** **5**

Entry	Comp.	R	R^1	R^6	R^3	R^4	Conf. at *	Conf. at #	Heating (200 °C)		Microwave (600 W)	
									Time (h)	Yield (%) (dr)	Time (min)	Yield (%) (dr)
22	**5q**	Et	H	*i*-Pr	4-MeOBn	H	*S*	*S*	2	95 (3:1)	8[a]	98
23	**5r**	Me	H	*i*-Pr	4-MeOBn	H	*S*	*R*	2	95 (3:1)	8[a]	98
24	**5s**	Me	H		$(CH_2)_3$		*S*	*R*	2	82 (2:1)	2[b]	95 (2:1)
25	**5t**	Et	H	*i*-Pr	$(CH_2)_3$		*R*	*S*	2	0	5[b,e]	76 (3:1)
26	**5t**	Et	H	*i*-Pr	$(CH_2)_3$		*R*	*S*			5[b,e]	99 (1:1)

[a] In cycles of 1-min irradiation followed by 1-min cooling.
[b] Irradiation without intermediate cooling,
[c] Three irradiations (3 + 3 + 2 min), with 2-min intermediate cooling periods.
[d] The starting dipeptide was mixed with 10% silica gel prior to irradiation using conditions a.
[e] The difference between entries 25 and 26 lies in the longer time of alumina preheating in the second case (12 min vs 8 min).

In order to extend the scope of our microwave-enhanced method, we next examined the preparation of 3,6-disubstituted DKPs (compounds **5o–t**), as shown in entries 20–26 of Table 1. Again, improved yields and shortened reaction times were observed in all cases. An advantage of these compounds is that, because they bear two stereocenters and therefore epimerization of one of them would lead to a pair of diastereomers, they provide a simple way to assess the course of the reactions in terms of stereochemical integrity. As shown in entries 20–23, both the *S*,*S* and *S*,*R* isomers of cyclo-(Phe-Val) and *cyclo*-(*O*-MeTyr-Val) (compounds **5o–r**) could be prepared in pure form using the microwave-assisted conditions, while the thermal reaction led to mixtures of diastereomers in all cases. On the other hand, *cyclo*-(D-Trp-L-Pro), a natural product isolated from strains of *Aspergillus ustus*,[27] was obtained as a 2:1 diastereomer mixture in both types of conditions, although microwave irradiation led to an improved yield (entry 24). Finally, because several cyclo-(Pro-Val) diastereomers are natural products,[28] some of them with antibacterial activity,[28b] we studied the preparation of compound **5t**. As shown in entry 25, this compound was obtained in 76% yield and as a 3:1 diastereomer mixture under microwave irradiation, while the thermal conditions failed to give any cyclization product. An attempt to increase the yield by preheating the alumina for 12 minutes prior to introduction of the reaction mixture was successful (99% yield), but a 1:1 diastereomeric mixture was isolated in this case (entry 26).

In conclusion, microwave irradiation of *N*-Boc dipeptide esters provides fast and efficient access to polysubstituted 2,5-piperazinedione derivatives, normally in optically pure form.

All reagents (Aldrich, Fluka, SDS, Probus) and solvents (SDS) were of commercial quality and were used as received. Some of the *N*-Boc-protected amino acids were not commercially available, and were prepared from the corresponding amino acids and *tert*-butyl pyrocarbonate, under standard conditions.[29] Microwave-enhanced reactions were carried out on a Moulinex domestic microwave oven operating at 600 W, employing as reaction vessels glass vials or round-bottom flasks submerged into an alumina bath. Reactions were monitored by TLC, on aluminium plates coated with silica gel with fluorescent indicator (SDS CCM221254). Separations by flash chromatography were performed on silica gel (SDS 60 ACC 40–63 μm). Melting points were measured on a Reichert 723 hot stage microscope, and are uncorrected. IR spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrophotometer, with solid compounds compressed into KBr pellets and liquid compounds examined as films on NaCl disks. NMR spectra were obtained on a Bruker Avance 250 spectrometer operating at 250 MHz for ^{1}H and 63 MHz for ^{13}C (CAI de Resonancia Magnética Nuclear, Universidad Complutense). Polarimetric measurements were carried out on a Perkin Elmer 240 polarimeter operating at the emission wavelength of a sodium lamp; concentrations for these measurements are given in g/100 mL. Elemental analyses were determined by the CAI de Microanálisis Elemental, Universidad Complutense, using a Leco 932 CHNS combustion microanalyzer.

Preparation of Compounds 1 by Reductive Amination (Method A); General Procedure

A solution of the suitable aldehyde, aminoester hydrochloride and $NaCNBH_3$ in EtOH was stirred at r.t. for 24 h. The solvent was

evaporated under reduced pressure, the residue was dissolved in 2 M HCl (10 mL) and this solution was extracted with Et_2O (2 × 10 mL). The aqueous phase was neutralized with sat. aq K_2CO_3 and it was then extracted with $CHCl_3$ (3 × 25 mL). The combined extracts were dried over anhyd Na_2SO_4, filtered, evaporated under reduced pressure and purified by flash column chromatography, eluting with EtOAc).

Preparation of Compounds 1 by Alkylation (Method B); General Procedure

To a solution of the suitable arylalkylamine in EtOH was dropwise added ethyl bromoacetate. The mixture was stirred until the precipitation of solid amine hydrobromide was complete and was then filtered. The filtrate was evaporated under reduced pressure and purified by flash column chromatography, eluting with EtOAc, affording, by order of elution, the di- and monoalkylated derivatives of the starting amine.

Ethyl *N*-Benzylglycinate (1a)

Method A: Starting from benzaldehyde (4.281 g, 40 mmol), ethyl glycinate hydrochloride (16.701 g, 120 mmol) and $NaCNBH_3$ (2.559 g, 40 mmol) in EtOH (100 mL), compound **1a** (4.002 g, 53%) was obtained as a colorless oil.

Method B: Starting from benzylamine (10.701 g, 100 mmol) and ethyl bromoacetate (5.801 g, 35 mmol) in EtOH (250 mL), after stirring for 48 h, the following products were obtained, by order of elution: diethyl benzyliminodiacetate (**2a**; 2.441 g, 25%) and ethyl *N*-benzylglycinate (**1a**; 2.631 g, 39%), both as colorless oils.

IR (NaCl): 3341, 3062, 2981, 2932, 1735, 1603, 1405 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 7.22–7.31 (m, 5 H, ArH), 4.17 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 3.78 (s, 2 H, $PhCH_2N$), 3.38 (s, 2 H, $COCH_2N$), 1.89 (br s, 1 H, NH), 1.25 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 172.37 (CO_2Et), 139.46 (C-1′), 128.39, 128.21, 127.09 (C-2′, C-3′, C-4′, C-5′, C-6′), 60.89 (OCH_2CH_3), 53.57 (NCH_2CO), 50.18 ($ArCH_2N$), 14.34 (OCH_2CH_3).

Anal. Calcd for $C_{11}H_{15}NO_2$ (193): C, 68.37; H, 7.82; N, 7.25. Found: C, 68.18; H, 7.99; N, 7.10.

Diethyl Benzyliminodiacetate (2a)

IR (NaCl): 3062, 2983, 2935, 1737, 1604, 1405 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 7.31–7.22 (m, 5 H, Ph), 4.13 (q, *J* = 7.1 Hz, 4 H, OCH_2CH_3), 3.89 (s, 2 H, $PhCH_2N$), 3.52 (s, 4 H, $COCH_2N$), 1.24 (t, *J* = 7.1 Hz, 6 H, OCH_2CH_3).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 171.14 (CO_2Et), 138.07 (C-1′), 128.97, 128.27, 127.26 (C-2′, C-3′, C-4′, C-5′, C-6′), 60.35 (OCH_2CH_3), 57.72 (NCH_2CO), 54.11 ($ArCH_2N$), 14.19 (OCH_2CH_3).

Anal. Calcd for $C_{15}H_{21}NO_4$ (279): C, 64.51; H, 7.52; N, 5.01. Found: C, 64.78; H, 7.32; N, 5.25.

Ethyl *N*-(4-Methoxybenzyl)glycinate (1b)

Method A: Starting from anisaldehyde (5.441 g, 40 mmol), ethyl glycinate hydrochloride (16.701 g, 120 mmol) and $NaCNBH_3$ (2.559 g, 40 mmol) in EtOH (100 mL) compound **1b** (4.721 g, 53%) was obtained as a colorless oil.

Method B: Starting from 4-methoxybenzylamine (5.50 g, 50 mmol) and ethyl bromoacetate (3.321 g, 20 mmol) in EtOH (250 mL), after stirring for 24 h, the following products were obtained, by order of elution: diethyl (4-methoxybenzyl)iminodiacetate (**2b**; 1.851 g, 30%) and **1b** (1.670 g, 37%), both as colorless oils.

IR (NaCl): 3341, 2981, 2835, 1733, 1611, 1585 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 6.4 Hz, 2 H, H-2′, H-6′), 6.80 (d, *J* = 6.4 Hz, 2 H, H-3′, H-5′), 4.11 (q, *J* = 6.9 Hz, 2 H, OCH_2CH_3), 3.72 (s, 3 H, OCH_3), 3.68 (s, 2 H, $ArCH_2N$), 3.32 (s, 2 H, $COCH_2N$), 1.85 (br s, 1 H, NH), 1.21 (t, *J* = 6.9 Hz, 3 H, OCH_2CH_3).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 172.39 (CO_2Et), 158.70 (C-4), 131.13 (C-1′), 129.43 (C-2′, C-6′), 113.73 (C-3′, C-5′), 60.64 (OCH_2CH_3), 55.16 (OCH_3), 52.60 (NCH_2CO), 49.91 ($ArCH_2N$), 14.18 (OCH_2CH_3).

Anal. Calcd for $C_{12}H_{17}NO_3$ (223): C, 64.55; H, 7.67; N, 6.27. Found: C, 64.38; H, 7.79; N, 6.21.

Diethyl (4-Methoxybenzyl)iminodiacetate (2b)

IR (NaCl): 3084, 2981, 1740, 1603, 1496, 1453, 1370 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 7.31–7.12 (m, 5 H, Ph), 4.14 (q, *J* = 7.2 Hz, 4 H, OCH_2CH_3), 3.56 (s, 4 H, $COCH_2N$), 2.90–2.80 (m, 4 H, $ArCH_2CH_2N$), 1.21 (t, *J* = 7.2 Hz, 6 H, OCH_2CH_3).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 172.75 (CO_2Et), 139.44 (C-1′), 128.60, 128.26, 125.99 (C-2′, C-3′, C-4′, C-5′, C-6′), 60.42 (OCH_2CH_3), 56.17 ($ArCH_2CH_2N$), 55.09 (NCH_2CO), 50.70 (NCH_2CO), 34.68 ($ArCH_2CH_2N$), 14.17 (OCH_2CH_3).

Anal. Calcd for $C_{16}H_{23}NO_4$ (293): C, 65.52; H, 7.90; N, 4.77. Found: C, 65.30; H, 7.89; N, 4.94.

Ethyl *N*-(3,4-Dimethoxybenzyl)glycinate (1c)

Starting from veratraldehyde (3.332 g, 20 mmol), ethyl glycinate hydrochloride (8.350 g, 60 mmol) and $NaCNBH_3$ (1.279 g, 20 mmol) in EtOH (50 mL), using Method A, compound **1c** (1.851 g, 37%) was obtained as a colorless oil.

IR (NaCl): 3342, 2936, 2834, 1737, 1591, 1514, 1464 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 6.72–6.98 (m, 3 H, ArH), 4.11 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 3.82 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 3.67 (s, 2 H, $ArCH_2N$), 3.33 (s, 2 H, $COCH_2N$), 1.98 (br s, 1 H, NH), 1.20 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 172.28 (CO_2Et), 148.75, 147.92 (C-3′, C-4′), 131.84 (C-1′), 120.24 (C-6′), 111.13, 110.68 (C-2′, C-5′), 60.57 (OCH_2CH_3), 55.68, 55.61 (2 × OCH_3), 52.87 ($ArCH_2N$), 49.75 (NCH_2CO), 14.05 (OCH_2CH_3).

Anal. Calcd for $C_{13}H_{19}NO_4$ (253): C, 61.64; H, 7.56; N, 5.53. Found: C, 61.59; H, 7.38; N, 5.67.

Ethyl *N*-(3-Indolylmethyl)glycinate (1d)

This compound was prepared according to ref. 20.

Ethyl *N*-(2-Phenylethyl)glycinate (1e)

Method A: Starting from 2-phenylacetaldehyde (2.401 g, 20 mmol), ethyl glycinate hydrochloride (8.370 g, 60 mmol) and $NaCNBH_3$ (1.28 g, 20 mmol) in EtOH (100 mL) compound **1e** (2.042 g, 49%) was obtained as a colorless oil.

Method B: Starting from 2-phenylethylamine (6.051 g, 50 mmol) and ethyl bromoacetate (3.322 g, 20 mmol) in EtOH (50 mL), stirring for 24 h, the following products were obtained, by order of elution: diethyl 2-phenylethyliminodiacetate (**2e**; 0.882 g, 15%) and ethyl *N*-(2-phenylethyl)glycinate (**1e**; 1.861 g, 45%), both as colorless oils.

IR (NaCl): 3335, 3025, 2950, 2935, 1733, 1603 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 7.15–7.35 (m, 5 H, ArH), 4.12 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 3.36 (s, 2 H, $COCH_2N$), 2.70–2.94 (m, 4 H, $ArCH_2CH_2N$), 1.80 (br s, 1 H, NH), 1.21 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 171.13 (CO_2Et), 139.44 (C-1′), 128.62, 128.48 (C-2′, C-3′, C-4′, C-5′, C-6′), 60.52 (OCH_2CH_3),

50.70 (N*C*H$_2$CO), 50.53 (ArCH$_2$*C*H$_2$N), 36.24 (Ar*C*H$_2$CH$_2$N), 14.03 (OCH$_2$*C*H$_3$).

Anal. Calcd for $C_{12}H_{17}NO_2$ (207): C, 69.54; H, 8.27; N, 6.76. Found: C, 69.18; H, 8.02; N, 7.09.

Diethyl (2-Phenylethyl)iminodiacetate (2e)

IR (NaCl): 3084, 2981, 1740, 1603, 1496, 1453, 1370 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.31–7.12 (m, 5 H, Ph), 4.14 (q, *J* = 7.2 Hz, 4 H, OC*H*$_2$CH$_3$), 3.56 (s, 4 H, COCH$_2$N), 2.90–2.80 (m, 4 H, ArCH$_2$CH$_2$N), 1.21 (t, *J* = 7.2 Hz, 6 H, OCH$_2$C*H*$_3$).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 172.75 (CO_2Et), 139.44 (C-1′), 128.60, 128.26, 125.99 (C-2′, C-3′, C-4′, C-5′, C-6′), 60.42 (O*C*H$_2$CH$_3$), 56.17 (ArCH$_2$*C*H$_2$N), 55.09 (N*C*H$_2$CO), 50.70 (N*C*H$_2$CO), 34.68 (Ar*C*H$_2$CH$_2$N), 14.17 (OCH$_2$*C*H$_3$).

Anal. Calcd for $C_{16}H_{23}NO_4$ (293): C, 65.52; H, 7.90; N, 4.77. Found: C, 65.30; H, 7.89; N, 4.94.

Ethyl *N*-(2-Naphthylmethyl)glycinate (1f)

Starting from naphthalene-2-carbaldehyde (6.241 g, 40 mmol), ethyl glycinate hydrochloride (16.702 g, 120 mmol) and $NaCNBH_3$ (2.559 g, 40 mmol) in EtOH (250 mL), using Method A, compound **1f** (9.031 g, 93%) was obtained as a white solid.

IR (KBr): 3334, 3052, 1736, 1631, 1600 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.74–7.81 (m, 4 H, ArH), 7.42–7.45 (m, 3 H, ArH), 4.16 (q, *J* = 7.2 Hz, 2 H, OC*H*$_2$CH$_3$), 3.95 (s, 2 H, CH$_2$Ar), 3.42 (s, 2 H, NCH$_2$CO), 1.82 (br s, 1 H, NH), 1.25 (t, *J* = 7.2 Hz, 3 H, OCH$_2$C*H*$_3$).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 172.35 (CO_2Et), 136.84, 133.26, 132.61, 128.06, 127.60, 127.53, 126.59, 126.48, 125.92, 125.54 (Ar), 60.67 (O*C*H$_2$CH$_3$), 53.25 (N*C*H$_2$CO), 49.94 (ArCH$_2$N), 14.12 (OCH$_2$*C*H$_3$).

Anal. Calcd for $C_{15}H_{17}NO_2$ (243): C, 74.05; H, 7.04; N, 5.76. Found: C, 73.86; H, 7.15; N, 5.85.

Preparation of Dipeptides (3); General Procedure

Compounds **3a**,[25] **3b**,[25] **3f**,[33] and **3k**[20] were prepared using literature conditions. Other dipeptides were prepared as follows: A solution of the suitable commercially available amino ester hydrochloride (30 mmol) in 20% aq K_2CO_3 (45 mL) was extracted with Et_2O or EtOAc (5 × 50 mL). The combined organic phases were dried (Na_2SO_4) and evaporated (in the reactions starting from compounds **1a**–**f**, this step was unnecessary, since they were obtained as free bases). To the residue was added a solution of the suitable *N*-Boc protected amino acid (1 equiv) and EDC hydrochloride (1 equiv) in anhyd CH_2Cl_2 (60 mL), and the solution was stirred at r.t. for 24 h under an Ar atmosphere. The solution was washed with 1 M aq HCl (20 mL) and 1 M aq $NaHCO_3$ (20 mL). Both aqueous layers were extracted with CH_2Cl_2 (2 × 30 mL), and the combined organic extracts were dried (Na_2SO_4) and evaporated, to give the desired dipeptides as thick colorless syrups that slowly solidified upon standing at r.t. Conditions for the preparation of compounds **3h**–**n** and **3t** were slightly different, and are specified below.

Ethyl *N*′-(*tert*-Butoxycarbonyl)-L-leucylglycinate (3c)

Starting from ethyl glycinate (1.278 g, 12.4 mmol), compound **3c** (4.060 g, 100%) was obtained; $[\alpha]_D^{26}$ –24.19 (*c* = 1.68, CH_2Cl_2).

IR (NaCl): 3305, 1747, 1698, 1660, 1169 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.64 (t, *J* = 5.5 Hz, 1 H, NH_{Gly}), 4.88 (d, *J* = 6.9 Hz, 1 H, NH_{Leu}), 4.21 (q, *J* = 7.1 Hz, 2 H, OC*H*$_2$CH$_3$), 4.11–4.25 (m, 1 H, CH*i*-Bu), 4.03 (d, *J* = 5.3 Hz, 2 H, NCH$_2$CO), 1.64–1.76 [m, 2 H, C*H*$_2$CH(CH$_3$)$_2$], 1.48–1.56 [m, 1 H, CH$_2$C*H*(CH$_3$)$_2$], 1.44 [s, 9 H, C(C*H*$_3$)$_3$], 1.28 (t, *J* = 7.1 Hz, 3 H, OCH$_2$C*H*$_3$), 0.92–1.00 [m, 6 H, CH$_2$CH(C*H*$_3$)$_2$].

^{13}C NMR (63 MHz, $CDCl_3$): δ = 173.28 (*C*O$_2$CH$_2$CH$_3$), 170.12 (CO amide), 156.11 (CO carbamate), 80.44 [*C*(CH$_3$)$_3$], 61.83 (CO$_2$*C*H$_2$CH$_3$), 56.34 (CH*i*-Bu), 41.58 (N*C*H$_2$CO), 31.31 [*C*H$_2$CH(CH$_3$)$_2$], 28.67 [C(*C*H$_3$)$_3$], 25.02 [CH$_2$*C*H(CH$_3$)$_2$], 23.32, 22.11 [CH$_2$CH(*C*H$_3$)$_2$], 14.48 (OCH$_2$*C*H$_3$).

Anal. Calcd for $C_{15}H_{28}N_2O_5$ (316): C, 56.94; H, 8.92; N, 8.85. Found: C, 57.10; H, 8.94; N, 8.99.

Ethyl *N*′-(*tert*-Butoxycarbonyl)-L-isoleucylglycinate (3d)

Starting from ethyl glycinate (3.276 g, 31.8 mmol), compound **3d** (10.293 g, 100%) was obtained, as a rotamer mixture; $[\alpha]_D^{26}$ –4.15 (*c* = 1.06, CH_2Cl_2).

IR (NaCl): 3313, 1745, 1702, 1664, 1171 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.71 (br s, 1 H, NH_{Gly}), 5.10–5.30 (m, 1 H, NH_{Leu}), 4.22 (q, *J* = 6.9 Hz, 2 H, OC*H*$_2$CH$_3$), 4.40–4.55, 3.20–3.75 (2 × m, 1 H, CH*s*-Bu), 4.02–4.07 (m, 2 H, NCH$_2$CO), 1.82–1.96 [m, 1 H, C*H*(CH$_3$)CH$_2$CH$_3$], 1.44 [s, 9 H, C(CH$_3$)$_3$], 1.26 (t, *J* = 7.1 Hz, 3 H, OCH$_2$C*H*$_3$), 1.13–1.20 [m, 2 H, CH(CH$_3$)C*H*$_2$CH$_3$], 0.95–1.10 [m, 6 H, CH(C*H*$_3$)CH$_2$C*H*$_3$].

^{13}C NMR (63 MHz, $CDCl_3$): δ = 172.4 (*C*O$_2$CH$_2$CH$_3$), 170.11 (CO amide), 156.23 (CO carbamate), 80.32 [*C*(CH$_3$)$_3$], 61.89 (CO$_2$*C*H$_2$CH$_3$), 59.45 (CH*s*-Bu), 41.71 (N*C*H$_2$CO), 37.74 [*C*H(CH$_3$)CH$_2$CH$_3$], 28.78 [C(*C*H$_3$)$_3$], 25.32, 25.04 [CH(CH$_3$)*C*H$_2$CH$_3$], 15.89, 14.51, 12.32, 11.93 [CH(*C*H$_3$)CH$_2$*C*H$_3$].

Anal. Calcd for $C_{15}H_{28}N_2O_5$ (316): C, 56.94; H, 8.92; N, 8.85. Found: C, 56.60; H, 8.82; N, 9.11.

Ethyl *N*′-(*tert*-Butoxycarbonyl)-L-phenylalanylglycinate (3e)

Starting from ethyl glycinate (3.441 g, 33.4 mmol), compound **3e** (11.910 g, 100%) was obtained; $[\alpha]_D^{26}$ +2.72 (*c* = 1.08, CH_2Cl_2).

IR (NaCl): 3314, 1748, 1702, 1666, 1170 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.22–7.29 (m, 5 H, ArH), 6.45 (br s, 1 H, NH_{Gly}), 5.04 (br s, 1 H, NH_{Phe}), 4.37–4.52 (m, 1 H, CHBn), 4.22 (q, *J* = 7.1 Hz, 2 H, OC*H*$_2$CH$_3$), 4.06 (dd, *J* = 18.5, 5.4 Hz, 1 H, CH$_2$Ph), 3.94 (dd, *J* = 18.5, 5.4 Hz, 1 H, CH$_2$Ph), 3.00–3.20 (m, 2 H, NCH$_2$CO), 1.42 [s, 9 H, C(CH$_3$)$_3$], 1.30 (t, *J* = 7.1 Hz, 3 H, OCH$_2$C*H*$_3$).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 171.86 (*C*O$_2$CH$_2$CH$_3$), 169.88 (CO amide), 155.13 (CO carbamate), 136.95 (C-1′), 129.71, 129.09 (C-2′, C-3′, C-5′, C-6′), 127.39 (C-4′), 80.06 [*C*(CH$_3$)$_3$], 61.95 (O*C*H$_2$CH$_3$), 55.85 (*C*HCH$_2$Ph), 41.75 (N*C*H$_2$CO), 38.79 (*C*H$_2$Ph), 28.65 [C(*C*H$_3$)$_3$], 14.55 (OCH$_2$*C*H$_3$).

Anal. Calcd for $C_{18}H_{26}N_2O_5$ (350): C, 61.70; H, 7.48; N, 7.99. Found: C, 61.65; H, 7.44; N, 8.25.

Methyl *N*′-(*tert*-Butoxycarbonyl)glycylsarcosinate (3g)

Starting from methyl sarcosinate (3.322 g, 28.4 mmol), a yield of 8.094 g (93%) of compound **3g** was obtained as a rotamer mixture.

IR (NaCl): 3350, 1747, 1714, 1661, 1168 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.46 (br s, 1 H, NH), 4.15 (s, 2 H, C*H*$_2$NCH$_3$), 4.00–4.05, 3.85–3.89 (2 × m, 2 H, NCH$_2$CO), 3.78, 3.74 (2 × s, 3 H, CO_2CH_3), 3.04, 3.01 (2 × s, 3 H, NCH_3), 1.45 [s, 9 H, C(CH$_3$)$_3$].

^{13}C NMR (63 MHz, $CDCl_3$): δ = 169.91 (CO_2CH_3), 169.75 (CO amide), 155.33 (CO carbamate), 80.24 [*C*(CH$_3$)$_3$], 52.70 (CO$_2$*C*H$_3$), 49.90 (N*C*H$_2$CO$_2$CH$_3$), 42.64 (*C*H$_2$NBoc), 35.70 (NCH_3), 28.71, 28.22 [C(C*H*$_3$)$_3$].

Anal. Calcd for $C_{11}H_{20}N_2O_5$ (260): C, 50.76; H, 7.74; N, 10.76. Found: C, 50.87; H, 7.61; N, 10.43.

Ethyl *N*′-(*tert*-Butoxycarbonyl)-l-alanyl-*N*-benzylglycinate (3h)
Starting from ethyl *N*-benzylglycinate (**1a**; 0.41 g, 2.15 mmol), *N*-Boc-L-alanine (0.44 g, 2.36 mmol) and EDC (0.62 g, 3.22 mmol), compound **3i** (0.54 g, 69%) was obtained as a colorless syrup (60:40 rotamer mixture); $[\alpha]_D^{25}$ –2.2 (*c* = 0.18, CH_2Cl_2).

IR (NaCl): 3333, 1747, 1709, 1654, 1497, 1452, 1027 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 7.12–7.35 (m, 5 H, ArH), 5.47, 5.40 (2 × d, *J* = 8.1 Hz, 1 H, NH), 3.62–5.30 (m, 7 H, OCH_2CH_3, NCH_2CO, $CHCH_3$, $ArCH_2N$), 1.38 [s, 9 H, $C(CH_3)_3$], 1.29–1.35 (m, 3 H, $CHCH_3$), 1.05 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 174.04, 173.91 ($CO_2CH_2CH_3$), 169.11, 168.94 (CO amide), 155.30, 115.06 (CO carbamate), 136.22, 135.41 (C-1′), 129.15, 129.08, 128.76, 128.45, 128.23, 127.70, 127.36 (C-2′, C-3′, C-4′, C-5′, C-6′), 79.78, 79.66 [$C(CH_3)_3$], 61.78, 61.32 ($CO_2CH_2CH_3$), 54.30, 53.56 (NCH_2CO), 51.89 ($ArCH_2N$), 46.43, 46.26 ($CHCH_3$), 28.42, 28.37 [$C(CH_3)_3$], 19.45, 19.03 ($CHCH_3$), 14.19, 14.13 (OCH_2CH_3).

Anal. Calcd for $C_{19}H_{28}N_2O_5$ (364): C, 62.62: H, 7.74; N, 7.69. Found: C. 62.51; H, 7.47: N, 7.33.

Ethyl *N*′-(*tert*-Butoxycarbonyl)glycyl-*N*-(4-methoxybenzyl)glycinate (3i)
Starting from ethyl *N*-(4-methoxybenzyl)glycinate (**1b**; 3.192 g, 14.3 mmol), *N*-Boc-glycine (2.751 g, 15.7 mmol) and EDC (2.926 g, 15.3 mmol), compound **3i** (4.56 g, 84%) was obtained as a colorless syrup (65:35 rotamer mixture).

^1H NMR (250 MHz, $CDCl_3$): δ = 7.10–7.20 (m, 2 H, ArH), 6.80–6.90 (m, 2 H, ArH), 5.52 (br s, 1 H, NH), 3.85–4.59 (m, 8 H, 4 × CH_2), 3.80, 3.79 (2 × s, 3 H, OCH_3), 1.44 [s, 9 H, $C(CH_3)_3$], 1.20–1.30 (m, 3 H, OCH_2CH_3).

Ethyl *N*′-(*tert*-Butoxycarbonyl)-l-alanyl-*N*-(3,4-dimethoxybenzyl)glycinate (3j)
Starting from ethyl *N*-(3,4-dimethoxy)benzylglycinate (**1c**; 2.65 g, 10 mmol), *N*-Boc-L-alanine (1.89 g, 10 mmol) and EDC (1.91 g, 10 mmol), compound **3j** (3.68 g, 87%) was obtained as a colorless syrup (60:40 rotamer mixture); $[\alpha]_D^{25}$ –8.3 (*c* = 2.56, $CHCl_3$).

IR (NaCl): 3334, 2979, 2935, 1746, 1707, 1654 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 6.72–6.83 (m, 3 H, ArH), 5.41, 5.38 (2 × d, *J* = 7.9 Hz, 1 H, NH), 3.60–4.84 (m, 13 H, OCH_2CH_3, NCH_2CO, $CHCH_3$, 2 × OCH_3, $ArCH_2N$), 1.19–1.55 [m, 15 H, $C(CH_3)_3$, $CHCH_3$, OCH_2CH_3].

^{13}C NMR (63 MHz, $CDCl_3$): δ = 173.70 ($CO_2CH_2CH_3$), 168.83 (CO amide), 155.04 (CO carbamate), 149.41 (C-4′), 148.74 (C-3′), 128.42, 127.48 (C-1′), 119.74, 110.88, 110.75 (C-2′, C-5′, C-6′), 79.52 [$C(CH_3)_3$], 61.57, 61.10 (OCH_2CH_3), 55.84, 55.80 (2 × OCH_3), 51.47 ($CHCH_3$), 49.59 (NCH_2CO_2Et), 46.35, 46.22 ($ArCH_2N$), 28.20 [$C(CH_3)_3$], 18.99 ($CHCH_3$), 14.00 (OCH_2CH_3).

Anal. Calcd for $C_{21}H_{32}N_2O_7$ (424): C, 59.42; H, 7.60; N, 6.60. Found: C, 59.21; H, 7.91; N, 6.34.

Ethyl *N*′-(*tert*-Butoxycarbonyl)glycyl-*N*-(2-phenylethyl)glycinate (3l)
Starting from ethyl *N*-(2-phenylethyl)glycinate (**1e**; 0.440 g, 2.150 mmol), *N*-Boc-glycine (0.411 g, 2.361 mmol) and EDC (0.442 g, 2.361 mmol), compound **3l** (0.702 g, 90%) was obtained as a colorless syrup (55:45 rotamer mixture).

IR (NaCl): 3329, 2978, 1750, 1710, 1654, 1497, 1454, 1367 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 7.13–7.33 (m, 5 H, ArH), 5.35–5.45 (2 × br s, 1 H, NH), 4.17 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 3.50–4.00 (m, 6 H, NCH_2CO, NCH_2CO_2Et, $PhCH_2CH_2N$), 2.94–2.84 (m, 2 H, $PhCH_2CH_2N$), 1.40 [s, 9 H, $C(CH_3)_3$], 1.24 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 169.18 (CO_2Et), 168.71 (CO amide), 155.78 (CO carbamate), 138.43, 137.30 (C-1′), 128.80, 128.67, 128.48, 128.35, 127.90, 126.34 (C-2′, C-3′, C-4′, C-5′, C-6′), 79.73 [$C(CH_3)_3$], 62.03, 61.48 (OCH_2CH_3), 50.83, 49.95 (NCH_2CO_2Et), 49.46, 48.13 ($ArCH_2CH_2N$), 41.98 (NCH_2CO), 35.25, 33.93 ($ArCH_2CH_2N$), 28.43 [$C(CH_3)_3$], 14.23 (OCH_2CH_3).

Anal. Calcd for $C_{19}H_{28}N_2O_5$ (364): C, 62.62; H, 7.74; N, 7.69. Found: C, 62.48; H, 7.80; N, 7.97.

Ethyl *N*′-(*tert*-Butoxycarbonyl)-L-valyl-*N*-(2-phenylethyl)glycinate (3m)
Starting from ethyl *N*-(2-phenylethyl)glycinate (**1e**; 0.45g, 2.15 mmol), *N*-Boc-L-valine (0.51 g, 2.36 mmol) and EDC (0.44 g, 2.36 mmol) compound **3m** (0.74 g, 85%) was obtained as a colorless oil (80:20 rotamer mixture); $[\alpha]_D^{25}$ –6.3 (*c* = 1.3, CH_2Cl_2).

IR (NaCl): 3313, 3062, 1749, 1710, 1651, 1604 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 7.13–7.30 (m, 5 H, Ph), 5.19, 5.15 (2 × br s, 1 H, NHCO), 3.30–4.49 [m, 7 H, OCH_2CH_3, NCH_2CO, $CHCH(CH_3)_2$, $ArCH_2CH_2N$], 2.81–2.89 (m, 2 H, $ArCH_2CH_2N$), 1.88–1.99 [m, 1 H, $CHCH(CH_3)_2$], 1.40 [s, 9 H, $C(CH_3)_3$], 1.20–1.30 (m, 3 H, OCH_2CH_3), 0.83–0.95 [m, 6 H, $CHCH(CH_3)_2$].

^{13}C NMR (63 MHz, $CDCl_3$): δ = 168.12 ($CO_2CH_2CH_3$), 168.62 (CO amide), 151.08 (CO carbamate), 138.00 (C-1′), 128.92, 128.66, 126.91 (C-2′, C-3′, C-4′, C-5′, C-6′), 79.00 [$C(CH_3)_3$], 61.35 ($CO_2CH_2CH_3$), 55.04 [$CHCH(CH_3)_2$], 48.37 ($ArCH_2CH_2N$), 42.30, 42.10 (NCH_2CO), 35.00 ($ArCH_2CH_2N$), 32.11 [$CHCH(CH_3)_2$], 28.44 [$C(CH_3)_3$], 19.02, 17.98 [$CH(CH_3)_2$], 14.20 ($CO_2CH_2CH_3$).

Anal. Calcd for $C_{22}H_{34}N_2O_5$ (406): C, 65.00; H, 8.43; N, 6.89. Found: C, 64.85; H, 8.52; N, 7.12.

Ethyl *N*′-(*tert*-Butoxycarbonyl)-L-alanyl-*N*-(2-naphthylmethyl)glycinate (3n)
Starting from ethyl *N*-(2-naphthylmethyl)glycinate (**1f**; 0.52 g, 2.15 mmol), *N*-Boc-L-alanine (0.441 g, 2.36 mmol) and EDC (0.440 g, 2.36 mmol), compound **3n** (0.802 g, 90%) was obtained as a colorless syrup (60:40 rotamer mixture); $[\alpha]_D^{25}$ +9.4 (*c* = 2.9, $CHCl_3$).

IR (NaCl): 3328, 3054, 2978, 2934, 1746, 1709, 1657, 1602 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 7.29–7.87 (m, 7 H, ArH), 5.47, 5.39 (2 × d, *J* = 8.0 Hz, 1 H, NH), 3.80–4.98 (m, 7 H, OCH_2CH_3, NCH_2CO, $CHCH_3$, $ArCH_2N$), 1.20–1.42 [s, 12 H, $C(CH_3)_3$, OCH_2CH_3], 1.10–1.20 (m, *J* = 7.1 Hz, 3 H, $CHCH_3$).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 174.07 (CO_2Et), 168.99 (CO amide), 155.14 (CO carbamate), 133.70, 133.38, 133.31, 132.97, 132.83, 129.10, 128.67, 127.87, 127.23, 126.67, 126.39, 126.15, 125.06 (Ar), 79.85, 79.74 [$C(CH_3)_3$], 61.80, 61.35 (OCH_2CH_3), 52.11 ($CHCH_3$), 48.35 (NCH_2CO_2Et), 46.36, 46.12 ($ArCH_2N$), 28.44, 28.36 [$C(CH_3)_3$], 19.25, 19.07 [$CH(CH_3)$], 14.20, 14.12 (OCH_2CH_3).

Anal. Calcd for $C_{23}H_{30}N_2O_5$ (414): C, 66.65; H, 7.30; N, 6.76. Found: C, 66.57; H, 7.04; N. 6.44.

Ethyl *N*′-(*tert*-Butoxycarbonyl)-L-phenylalanyl-L-valinate (3o)
Starting from ethyl L-valinate (1.550 g, 10.7 mmol) compound **3o** (3.813, 91%) was obtained; $[\alpha]_D^{25}$ –61.8 (*c* = 0.165, $CHCl_3$).

IR (KBr): 3300, 3122, 1742, 1683, 1652, 1174 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 7.08–7.27 (m, 5 H, ArH), 6.61 (d, *J* = 8.4 Hz, 1 H, NH), 5.19 (br s, 1 H, NH), 4.39–4.47 (m, 2 H, $CHCH_2Ar$, C*i*-Pr), 4.13 (q, 2 H, OCH_2CH_3), 2.99–3.07 (m, 2 H, CH_2Ar), 2.06–2.13 [m, 1 H, $CH(CH_3)_2$], 1.38 [s, 9 H, $C(CH_3)_3$], 1.23 (t, 3 H, OCH_2CH_3), 0.81–0.88 [m, 6 H, $CH(CH_3)_2$].

^{13}C NMR (63 MHz, $CDCl_3$): δ = 171.73, 171.53 ($CO_2CH_2CH_3$, CO amide), 155.82 (CO carbamate), 137.04 (C-1′), 129.74, 129.05 (C-2′, C-6′, C-3′, C-5′), 127.32 (C-4′), 80.37 [$C(CH_3)_3$], 61.62

($CO_2CH_2CH_3$), 57.62 (*C*H*i*-Pr), 56.28 (*C*HCH$_2$Ar), 31.74 (CH*C*H$_2$Ar), 31.75 [*C*H(CH$_3$)$_2$], 28.67 [C(*C*H$_3$)$_3$], 19.22, 18.15 [CH(*C*H$_3$)$_2$], 14.63 ($CO_2CH_2CH_3$).

Anal. Calcd for $C_{21}H_{32}N_2O_5$ (392): C, 64.26; H, 8.22; N, 7.14. Found: C, 64.58; H, 7.98; N, 7.39.

Methyl *N*′-(*tert*-Butoxycarbonyl)-L-phenylalanyl-D-valinate (3p)

Starting from methyl D-valinate (1.218 g, 9.3 mmol), compound **3p** (3.212, 89%) was obtained; $[\alpha]_D^{25}$ –37.8 (*c* = 0.405, $CHCl_3$).

IR (KBr): 3337, 3028, 1739, 1685, 1666, 1169 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.10–7.27 (m, 5 H, ArH), 6.64 (d, *J* = 7.8 Hz, 1 H, NH), 5.22 (d, *J* = 7.6 Hz, 1 H, NH), 4.30–4.49 (m, 2 H, C*H*CH$_2$Ar, CH*i*-Pr), 3.66 (s, 3 H, OCH$_3$), 2.95–3.10 (m, 2 H, CH$_2$Ar), 1.90–2.08 [m, 1 H, C*H*(CH$_3$)$_2$], 1.37 [s, 9 H, C(CH$_3$)$_3$], 0.71–0.76 [m, 6 H, CH(C*H*$_3$)$_2$].

^{13}C NMR (63 MHz, $CDCl_3$): δ = 172.45, 171.61 (*C*O$_2$CH$_3$, CO amide), 156.25 (CO carbamate), 136.99 (C-1′), 129.66, 129.16 (C-2′, C-3′, C-5′, C-6′), 127.40 (C-4′), 80.70 [*C*(CH$_3$)$_3$], 57.52 (*C*H*i*-Pr), 56.50 (*C*HCH$_2$Ar), 52.57 (CH$_3$O), 38.70 (CH*C*H$_2$Ar), 31.49 [*C*H(CH$_3$)$_2$], 28.65 [C(*C*H$_3$)$_3$], 19.19, 18.01 [CH(*C*H$_3$)$_2$].

Anal. Calcd for $C_{20}H_{30}N_2O_5$ (378): C, 63.47; H, 7.99; N, 7.40. Found: C, 63.82; H, 7.71; N, 7.78.

Ethyl *N*′-(*tert*-Butoxycarbonyl)-L-(*O*-methyltyrosyl)-L-valinate (3q)

Starting from ethyl L-valinate (1.324 g, 9.1 mmol), compound **3q** (3.468 g, 90%) was obtained; $[\alpha]_D^{25}$ –59.0 (*c* = 0.29, $CHCl_3$).

IR (KBr): 3331, 3134, 1739, 1654, 1513, 1399, 1249, 1178 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.03–7.14 (m, 2 H, ArH), 6.78–6.84 (m, 2 H, ArH), 6.42 (d, *J* = 8.6 Hz, 1 H, NH), 5.03 (br s, 1 H, NH), 4.43 (dd, *J* =8 .6, 5.0 Hz, 1 H, C*H*CH$_2$Ar), 4.21–4.38 (m, 1 H, CH*i*-Pr), 4.15 (q, *J* = 6.8 Hz, 2 H, OC*H*$_2$CH$_3$), 3.78 (s, 3 H, OCH$_3$), 3.00 (d, *J* = 6.8 Hz, 2 H, CH$_2$Ar), 2.00–2.20 [m, 1 H, C*H*(CH$_3$)$_2$], 1.41 [s, 9 H, C(CH$_3$)$_3$], 1.25 (t, *J* = 7.13 Hz, 3 H, OCH$_2$C*H*$_3$), 0.81–0.91 [m, 6 H, CH(C*H*$_3$)$_2$].

^{13}C NMR (63 MHz, $CDCl_3$): δ = 171.73, 171.63 (*C*O$_2$CH$_2$CH$_3$, CO amide), 158.95 (*C*$_4$′OCH$_3$), 155.84 (CO carbamate), 130.75 (C-2′, C-6′), 128.95 (C-1′), 114.44 (C-3′, C-5′), 80.50 [*C*(CH$_3$)$_3$], 61.60 (CO$_2$*C*H$_2$CH$_3$), 57.62 (*C*H*i*-Pr), 56.38 (OCH$_3$), 55.63 (*C*HCH$_2$Ar), 37.63 (CH*C*H$_2$Ar), 31.75 [*C*H(CH$_3$)$_2$], 28.67 [C(*C*H$_3$)$_3$], 19.22, 18.17 [CH(*C*H$_3$)$_2$], 14.61 ($CO_2CH_2CH_3$).

Anal. Calcd for $C_{22}H_{34}N_2O_6$ (422): C, 62.54; H, 8.11; N, 6.63. Found: C, 62.86; H, 7.91; N, 6.96.

Methyl *N*′-(*tert*-Butoxycarbonyl)-L-(*O*-methyltyrosyl)-D-valinate (3r)

Starting from methyl D-valinate (1.136 g, 8.67 mmol), compound **3r** (3.183 g, 87%) was obtained as a rotamer mixture; $[\alpha]_D^{25}$ = –54.1 (*c* = 0.365, $CHCl_3$).

IR (KBr): 3325, 3127, 1737, 1688, 1650, 1399, 1250, 1179 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.04–7.13 (m, 2 H, ArH), 6.78–6.83 (m, 2 H, ArH), 6.50 (br s, 1 H, NH), 5.05 (br s, 1 H, NH), 4.46 (dd, *J* = 8.7, 4.9 Hz, 1 H, C*H*CH$_2$Ar), 4.22–4.39 (m, 1 H, CH*i*-Pr), 3.77 (s, 3 H, OCH$_3$), 3.69 (s, 3 H, CO$_2$CH$_3$), 2.90–3.00 (m, 2 H, CH$_2$Ar), 1.95–2.10 [m, 1 H, C*H*(CH$_3$)$_2$], 1.39 [s, 9 H, C(CH$_3$)$_3$], 0.76–0.81 [m, 6 H, CH(C*H*$_3$)$_2$].

^{13}C NMR (63 MHz, $CDCl_3$): δ = 172.48, 171.80 (*C*O$_2$CH$_3$, CO amide), 158.96 (C$_4$′O*C*H$_3$), 155.50 (CO carbamate), 130.68 (C-2′, C-6′), 128.92 (C-1′), 114.48 (C-3′, C-5′), 80.50 [*C*(CH$_3$)$_3$], 57.52 [*C*H*i*-Pr], 55.64 (CO$_2$*C*H$_3$), 52.52 (*C*HCH$_2$Ar), 37.85 (CH*C*H$_2$Ar), 31.47 [*C*H(CH$_3$)$_2$], 28.65 [C(*C*H$_3$)$_3$], 19.19, 18.16 [CH(*C*H$_3$)$_2$].

Anal. Calcd for $C_{21}H_{32}N_2O_6$ (408): C, 61.75; H, 7.90; N, 6.86. Found: C, 62.07; H, 7.90; N, 6.99.

Methyl *N*′-(*tert*-Butoxycarbonyl)-L-prolyl-D-tryptophanate (3s)

Starting from methyl D-tryptophanate (4.443 g, 20.360 mmol), compound **3s** (8.375 g, 99%) was obtained; $[\alpha]_D^{26}$ –40.6 (*c* = 1.15, CH_2Cl_2).

IR (KBr): 3276, 1750, 1672, 1163 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.16 (br s, 1 H, N$_{indole}$-H), 7.54 (d, *J* = 7.5 Hz, 1 H, H-4′), 7.34 (d, *J* = 7.5 Hz, 1 H, H-7′), 7.04–7.21 (m, 3 H, H-2′, H-5′, H-6′), 6.55 (br s, 1 H, NH), 4.90 (br d, *J* = 6.1 Hz, 1 H, C*H*CH$_2$indole), 4.08–4.38 (m, 1 H, NCHCO), 3.71 (s, 3 H, CO$_2$CH$_3$), 3.12–3.51 (m, 4 H, CH$_2$indole, NC*H*$_2$CH$_2$CH$_2$), 1.79–1.96 (m, 2 H, NCH$_2$CH$_2$C*H*$_2$), 1.21–1.65 [m, 11 H, NCH$_2$C*H*$_2$CH$_2$, C(CH$_3$)$_3$].

^{13}C NMR (63 MHz, $CDCl_3$): δ = 172.40 (*C*O$_2$CH$_3$, CO amide), 160.13 (CO carbamate), 136.56 (C-7′a), 127.80 (C-3′a), 122.51 (C-2′, C-6′), 120.21 (C-5′), 118.79 (C-4′), 111.74 (C-7′), 110.12 (C-3′), 80.88 [*C*(CH$_3$)$_3$], 61.64 (N*C*HCO), 53.23 (*C*HCH$_2$indole), 52.72 (CO$_2$*C*H$_3$), 47.50 (N*C*H$_2$CH$_2$CH$_2$), 28.71 [*C*(CH$_3$)$_3$], 28.19 (NCH$_2$CH$_2$*C*H$_2$), 25.86 (*C*H$_2$indole), 24.78 (NCH$_2$CH$_2$*C*H$_2$).

Anal. Calcd for $C_{22}H_{29}N_3O_5$ (415): C, 63.60; H, 7.04; N, 10.11. Found: C, 63.34; H, 7.07; N, 10.38.

Ethyl *N*′-(*tert*-Butoxycarbonyl)-D-prolyl-L-valinate (3t)

Starting from ethyl l-valinate (1.136 g, 7.83 mmol), *N*-Boc-D-proline (1.050 g, 4.878 mmol) and EDC (0.950 mg, 4.955 mmol), compound **3t** (1.538 g, 92%) of was obtained as a rotamer mixture; $[\alpha]_D^{25}$ –2.0 (*c* = 0.54, $CHCl_3$).

IR (KBr): 3287, 1736, 1699, 1661, 1395, 1162 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.21, 6.56 (2 × br s, 1 H, NH), 4.46–4.67, 4.24–4.45 (2 × m, 2 H, C*H*i-Pr, NCHCO), 4.12–4.25 (m, 2 H, CO$_2$C*H*$_2$CH$_3$), 2.21–2.67 (m, 2 H, NC*H*$_2$CH$_2$CH$_2$), 2.11–2.43 [m, 3 H, NCH$_2$CH$_2$C*H*$_2$, C*H*(CH$_3$)$_2$], 1.79–2.09 (m, 2 H, NCH$_2$C*H*$_2$CH$_2$), 1.48 [s, 9 H, C(CH$_3$)$_3$], 1.28 (t, *J* = 7.1 Hz, 3 H, CO$_2$CH$_2$C*H*$_3$), 0.97 [d, *J* = 6.9 Hz, 3 H, CH(C*H*$_3$)$_2$], 0.90 [d, *J* = 6.9 Hz, 3 H, CH(C*H*$_3$)$_2$].

^{13}C NMR (63 MHz, $CDCl_3$): δ = 172.87 (*C*O$_2$CH$_2$CH$_3$), 171.90 (CO amide), 154.72 (CO carbamate), 82.45 [*C*(CH$_3$)$_3$], 61.36 (CO$_2$*C*H$_2$CH$_3$), 60.48 (N*C*HCO), 57.11 (*C*H*i*-Pr), 47.37 (N*C*H$_2$CH$_2$CH$_2$), 28.59 [C(*C*H$_3$)$_3$], 24.65 (NCH$_2$CH$_2$*C*H$_2$), 23.98 (NCH$_2$*C*H$_2$CH$_2$), 19.33 [CH(*C*H$_3$)$_2$], 17.75 [CH(*C*H$_3$)$_2$], 14.46 ($CO_2CH_2CH_3$).

Anal. Calcd for $C_{17}H_{30}N_2O_5$ (342): C, 59.63; H, 8.83; N, 8,18. Found: C, 59.35; H, 8.57; N, 8.32.

Preparation of Diketopiperazines (5) by Pyrolysis of Dipeptides (3) under Thermal Conditions; General Procedure

The suitable dipeptide, neat and preferably as a syrup rather than in crystalline form, was distributed as thinly as possible on the walls of a round-bottom flask and then heated for 2 h in a poly(ethylene glycol) bath at 200 °C (220 °C in the case of **3g**), under an Ar atmosphere, yielding the desired diketopiperazine.

Preparation of Diketopiperazines (5) by Pyrolysis of Dipeptides (3) under Microwave Irradiation; General Procedure

Methods A, B and C: The suitable dipeptide **3**, neat and preferably as a syrup rather than in crystalline form, was introduced in a glass vial or distributed as thinly as possible on the walls of a round-bottom flask, depending on the reaction scale. The vial or flask was covered with an inverted glass funnel, in order to prevent projections, and submerged in a beaker containing alumina. The reaction mixture was irradiated in a microwave oven at 600 W in 1-min pulses, with 1-min cooling periods (Method A), in 3- or 4-min pulses,

with a 2-min cooling period (Method B), or for the times indicated in Table 1, without intermediate cooling (Method C). The crude reaction products were washed with EtOH, or recrystallized from acetone or EtOH.

Method D: The suitable dipeptide **3** was thoroughly mixed with silica gel (10% in weight) and irradiated as in Method A. The crude reaction products were extracted with refluxing EtOH.

Data for compounds **5a**,[25] **5b**,[10,25] **5f**,[30] **5s**,[30] and **5t**[31] were identical to those found in the literature. Data for other compounds are given below.

(3*S*)-3-Isobutyl-2,5-piperazinedione (5c)
Mp 246–248 °C (EtOH) (lit.[32] 243–245 °C); $[\alpha]_D^{25}$ –2.2 (*c* = 1.0, DMSO) {lit.[32] $[\alpha]_D^{20}$ = +31.7 (*c* = 1.82, H_2O}.

IR (KBr): 3434, 3196, 1679 cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 8.26 (br s, 1 H, H-1), 7.99 (br s, 1 H, H-4), 4.10–4.15 (m, 1 H, H-3), 3.82 (d, *J* = 17.4 Hz, 1 H, H-6), 3.59 (d, *J* = 17.3 Hz, 1 H, H-6), 1.69–2.07 (m, 1 H, H-2′), 1.45–1.50 (m, 2 H, H-1′), 0.87 (d, *J* = 6.7 Hz, 3 H, CH_3), 0.85 (d, *J* = 6.7 Hz, 3 H, CH_3).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 169.03 (C-2), 166.32 (C-5), 53.24 (C-3), 44.45 (C-6), 42.37 (C-1′), 23.91, 23.22 (2 × CH_3), 22.13 (C-2′).

(3*S*,1′*S*)-3-*sec*-Butyl-2,5-piperazinedione (5d)
IR (KBr): 3191, 3052, 1668, 1463, 1343 cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 8.17 (br s, 1 H, H-1), 8.01 (br s, 1 H, H-4), 4.09–4.14 (m, 1 H, H-3), 3.80 (d, *J* = 17.8 Hz, 1 H, H-6), 3.60 (dd, *J* = 17.7, 3.1 Hz, 1 H, H-6), 1.77–2.08 (m, 1 H, H-1′), 1.36–1.42 (m, 1 H, H-2′), 1.13–1.20 (m, 1 H, H-2′), 0.74–0.93 (m, 6 H, 2 × CH_3).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 167.51 (C-2), 166.32 (C-5), 59.34 (C-3), 44.48 (C-6), 31.03 (C-1′), 24.51 (C-2′), 15.33, 11.89 (2 × CH_3).

Anal. Calcd for $C_8H_{14}N_2O_2$ (170): C, 56.45; H, 8.29; N, 16.46. Found: C, 56.33; H, 8.08; 16.22.

(3*S*)-3-Benzyl-2,5-piperazinedione (5e)
Mp 271–273 °C (EtOH) (lit.[33] 265.5 °C); $[\alpha]_D^{26}$ +7.3 (*c* = 0.95, DMSO).

IR (KBr): 3446, 3185, 1678 cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 8.16 (br s, 1 H, H-1), 7.90 (br s, 1 H, H-4), 7.24–7.31 (m, 3 H, H-3′, H-4′, H-5′), 7.13–7.21 (m, 2 H, H-2′, H-6′), 4.00–4.09 (m, 1 H, H-3), 3.34 (dd, *J* = 17.4, 2.8 Hz, 1 H, CH_2Ar), 3.08 (dd, *J* = 13.5, 4.4 Hz, 1 H, H-6), 2.86 (dd, *J* = 13.5, 4.9 Hz, 1 H, H-6), 2.73 (d, *J* = 17.4 Hz, 1 H, CH_2Ar).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 167.51 (C-2), 166.02 (C-5), 136.34 (C-1′), 130.41 (C-3′, C-5′), 128.52 (C-2′, C-6′), 127.13 (C-4′), 55.78 (C-3), 44.01 (C-6), 31.02 (*C*H_2Ar).

1-Methyl-2,5-piperazinedione (5g)
Mp 138–140 °C (EtOH) [lit.[34] 140–143 °C (EtOH–H_2O)].

IR (KBr): 3392, 3192, 1672, 1659 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 6.76 (br s, 1 H, NH), 4.03, 3.99 (2 × s, 4 H, H-3, H-6), 3.00 (s, 3 H, NCH_3).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 165.32, 164.33 (C-2, C-5), 51.41 (C-6), 44.62 (C-3), 33.12 (NMe).

(3*S*)-1-Benzyl-3-methyl-2,5-piperazinedione (5h)
Mp 110 °C; $[\alpha]_D^{25}$ –38.1 (*c* = 0.31, CH_2Cl_2).

IR (KBr): 3274, 2979, 2935, 1694, 1662, 1495 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 7.21–7.36 (m, 5 H, ArH), 6.66 (s, 1 H, H-4), 4.57 (s, 2 H, ArCH_2N), 4.10 (q, *J* = 7.0 Hz, 1 H, H-3), 3.82 (s, 2 H, H-6), 1.48 (d, *J* = 7.0 Hz, 3 H, CH_3).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 165.98, 165.93 (C-2, C-5), 135.27 (C-1′), 129.08, 128.45, 128.28 (C-2′, C-3′, C-4′, C-5′, C-6′), 51.19 (C-3), 49.80, 49.14 (C-6, N*C*H_2Ph), 20.30 (C*C*H_3).

Anal. Calcd for $C_{12}H_{14}N_2O_2$ (218): C, 66.04; H, 6.47; N, 12.84. Found: C, 65.82; H, 6.43; N, 12.65.

1-(4-Methoxybenzyl)-2,5-piperazinedione (5i)
^1H NMR (250 MHz, $CDCl_3$): δ = 7.20–7.32 (m, 2 H, ArH), 6.85–6.95 (m, 2 H, ArH), 6.07 (br s, 1 H, NH), 4.54 (s, 2 H, ArCH_2), 4.08 (s, 2 H, H-3), 3.85 (s, 2 H, H-6), 3.81 (s, 3 H, OCH_3).

(3*S*)-1-(3,4-Dimethoxybenzyl)-3-methyl-2,5-piperazinedione (5j)
IR (KBr): 3273, 2927, 1684, 1659, 1590 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 7.06 (s, 1 H, H-4), 6.62–6.75 (m, 3 H, ArH), 4.50 (s, 2 H, ArCH_2), 4.12 (q, *J* = 7.0 Hz, 1 H, H-3), 3.84 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 3.81 (s, 2 H, H-6), 1.49 (d, *J* = 7.0 Hz, 3 H, CCH_3).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 166.73 (C-2), 166.19 (C-5), 149.45 (C-4′), 149.05 (C-3′), 127.10 (C-1′), 121.13, 111.47, 111.17 (C-3′, C-5′, C-6′), 56.01 (2 × OCH_3), 51.19 (C-3), 49.63, 48.93 (Ar*C*H_2N, C-6), 20.31 (C*C*H_3).

Anal. Calcd for $C_{14}H_{18}N_2O_4$ (278): C. 60.42; H, 6.52; N, 10.07. Found: C, 60.25; H, 6.34; N, 10.29.

(3*S*)-1-(3-Indolylmethyl)-3-isopropyl-2,5-piperazinedione (5k)
Mp 228–229 °C; $[\alpha]_D^{23}$ +6.0 (*c* = 0.40, MeOH).

IR (KBr): 3403, 3559, 1682, 1647, 742 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 8.23 (br s, 1 H, NH_{indole}), 7.71 (d, *J* = 7.5 Hz, 1 H, H-4′), 7.37 (d, *J* = 8.0 Hz, 1 H, H-7′), 7.09–7.20 (m, 3 H, H-2′, H-5′, H-6′), 6.15 (br s, 1 H, H-4), 4.90 (d, *J* = 14.5 Hz, 1 H, ArCH_2), 4.71 (d, *J* = 14.5 Hz, 1 H, ArCH_2), 3.89–3.92 (m, 1 H, H-3), 3.85 (s, 2 H, H-6), 2.51–2.41 [m, 1 H, C*H*$(CH_3)_2$], 1.00 [d, *J* = 7.0 Hz, 3 H, CH(C*H*$_3)_2$], 0.82 (d, *J* = 7.0 Hz, 3 H, CH(C*H*$_3)_2$].

^{13}C NMR (63 MHz, $CDCl_3$): δ = 166.3, 165.2 (2 × CO), 136.2 (C-7a′), 127.7 (C-3a′), 124.7 (C-2′), 122.8 (C-5′), 120.3 (C-4′), 119.2 (C-6′), 111.4 (C-3′), 110.1 (C-7′), 61.0 (C-3), 48.3 (C-6), 40.8 (Ar*C*H_2), 33.0 [*C*H$(CH_3)_2$], 19.0 [CH(*C*$H_3)_2$], 16.1 [CH(*C*$H_3)_2$].

Anal. Calcd for $C_{16}H_{19}N_3O_2$ (285): C, 67.36; H, 6.66; N, 14.73. Found: C, 66.92; H, 6.33; N, 14.53.

1-(2-Phenylethyl)-2,5-piperazinedione (5l)
Mp 225–227 °C.

IR (KBr): 3228, 2929, 1678, 1646, 1491 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 7.20–7.32 (m, 5 H, ArH), 6.13 (br s, 1 H, H-4), 3.97 (s, 2 H, H-3), 3.77 (s, 2 H, H-6), 3.61 (t, *J* = 7.1 Hz, 2 H, ArCH_2C*H*$_2$N), 2.88 (t, *J* = 7.6 Hz, 2 H, ArC*H*$_2$$CH_2$N).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 167.00 (C-2), 165.00 (C-5), 138.05 (C-1′), 128.90, 128.79, 126.97 (C-2′, C-3′, C-4′, C-5′, C-6′), 50.43 (C-3), 48.51, 45.28 (ArCH_2*C*H_2N, C-6), 36.27 (Ar*C*$H_2$$CH_2$N).

Anal. Calcd for $C_{12}H_{14}N_2O_2$ (218): C, 66.04; H, 6.42; N, 12.84. Found: C, 65.84; H, 6.31; N, 12.71.

(3*S*)-3-Isopropyl-1-(2-Phenylethyl)-2,5-piperazinadione (5m)
Mp 165–166 °C; $[\alpha]_D^{25}$ +38.6 (*c* = 0.22, CH_2Cl_2).

IR (KBr): 3235, 3086, 2969, 1679, 1651, 1496 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 7.18–7.31 (m, 5 H, ArH), 6.68 (br s, 1 H, H-4), 3.65–3.91 (m, 4 H, H-6, ArCH_2C*H*$_2$N, H-3), 3.42 (m, 1 H, ArCH_2C*H*$_2$N), 2.87 (t, *J* = 7.3 Hz, 2 H, ArC*H*$_2$$CH_2$N), 2.29–

2.41 [m, 1 H, C*H*(CH_3)$_2$], 0.95 [d, *J* = 7.1 Hz, 3 H, CH(C*H*$_3$)$_2$], 0.80 [d, *J* = 6.8 Hz, 3 H, CH(C*H*$_3$)$_2$].

^{13}C NMR (63 MHz, $CDCl_3$): δ = 165.82 (C-2), 165.26 (C-5), 137.81 (C-1′), 128.36, 128.59, 126.71 (C-2′, C-3′, C-4′, C-5′, C-6′), 60.76 (C-3), 49.98 (C-6), 48.18 (ArCH$_2$*C*H$_2$N), 33.08, 32.77 [Ar*C*H$_2$CH$_2$N, *C*H(CH_3)$_2$], 18.77 [CH(*C*H$_3$)$_2$], 16.08 [CH(C*H*$_3$)$_2$].

Anal. Calcd for $C_{15}H_{20}N_2O_2$ (260): C, 69.20; H, 7.74; N, 10.76. Found: C, 68.90; H, 7.70; N, 10.70.

(3*S*)-1-(2-Naphthylmethyl)-3-methyl-2,5-piperazinedione (5n)
Mp 132–134 °C; $[\alpha]_D^{25}$ –33.3 (*c* = 0.15, CH_2Cl_2).

IR (KBr): 3239, 2931, 1688, 1658, 1508 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.78–7.74 (m, 3 H, ArH), 7.65 (s, 1 H, H-1′), 7.48–7.23 (m, 3 H, ArH), 7.21 (br s, 1 H, H-4), 4.75 (d, *J* = 15.3 Hz, 1 H, ArCH_2N), 4.69 (d, *J* = 15.3 Hz, 1 H, ArCH_2N), 4.12 (q, *J* = 7.0 Hz, 1 H, H-3), 3.84 (s, 2 H, H-6), 1.48 (d, *J* = 7.0 Hz, 3 H, CH_3).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 166.81 (C-2), 165.99 (C-5), 133.09, 132.51, 132.80, 129.15, 127.84, 127.71, 126.70, 126.64, 126.44, 125.99 (Ar), 51.17 (C-3), 49.70, 48.90 (C-6, N*C*H$_2$Ar), 19.95 (C*C*H$_3$).

Anal. Calcd for $C_{16}H_{16}N_2O_2$ (268): C, 71.62; H, 6.01; N, 10.42. Found: C, 71.52; H, 6.13; N, 10.31.

(3*S*,6*S*)-3-Benzyl-6-isopropyl-2,5-piperazinedione (5o)
Mp 176–178 °C; $[\alpha]_D^{25}$ –43.30 (*c* = 0.27, DMSO).

IR (KBr): 1663, 1452 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 8.14 (br s, 1 H, NH), 7.93 (br s, 1 H, NH), 7.15–7.30 (m, 5 H, ArH), 4.19 (m, 1 H, H-3), 3.38 (m, 1 H, H-6, overlapped with the H_2O resonance), 3.13 (dd, *J* = 13.4, 4.2 Hz, 1 H, CH_2Ar), 2.84 (dd, *J* = 13.4, 4.2 Hz, 1 H, CH_2Ar), 1.50–1.75 [m, 1 H, C*H*(CH_3)$_2$], 0.61 [d, *J* = 7.0 Hz, 3 H, CH(C*H*$_3$)$_2$], 0.21 (d, *J* = 7.0 Hz, 3 H, CH(C*H*$_3$)$_2$].

^{13}C NMR (63 MHz, DMSO-d_6): δ = 164.89, 164.78 (2 × CO), 134.66 (C-1′), 128.69 (C-3′, C-5′), 126.30 (C-2′, C-6′), 124.86 (C-4′), 57.50 (C-6), 53.37 (C-3), 36.10 (*C*H$_2$Ar), 29.34 [*C*H(CH_3)$_2$], 16.59, 14.45 [CH(*C*H$_3$)$_2$].

Anal. Calcd for $C_{14}H_{18}N_2O_2$ (246): C, 68.27; H, 7.37; N, 11.37. Found: C, 68.02; H, 7.23; N, 11.12.

(3*S*,6*R*)-3-Benzyl-6-isopropyl-2,5-piperazinedione (5p)
Mp 269–271 °C; $[\alpha]_D^{25}$ –70.98 (*c* = 0.355, DMSO).

IR (KBr): 1674, 1453 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 8.14 (br s, 1 H, NH), 7.93 (br s, 1 H, NH), 7.05–7.30 (m, 5 H, ArH), 4.16 (m, 1 H, H-3), 3.14 (dd, *J* = 13.6, 3.7 Hz, 1 H, CH_2Ar), 2.92 (m, 1 H, H-6), 2.86 (dd, *J* = 13.6, 3.7 Hz, 1 H, CH_2Ar), 1.90–2.10 [m, 1 H, C*H*(CH_3)$_2$], 0.79 [d, *J* = 7.0 Hz, 3 H, CH(C*H*$_3$)$_2$], 0.72 (d, *J* = 7.0 Hz, 3 H, CH(C*H*$_3$)$_2$].

^{13}C NMR (63 MHz, DMSO-d_6): δ = 167.11, 166.81 (2 × CO), 135.79 (C-1′), 129.92 (C-3′, C-5′), 125.95 (C-2′, C-6′), 126.33 (C-4′), 58.63 (C-6), 54.45 (C-3), 37.63 (*C*H$_2$Ar), 31.24 [*C*H(CH_3)$_2$], 17.89, 16.28 [CH(*C*H$_3$)$_2$].

Anal. Calcd for $C_{14}H_{18}N_2O_2$ (246): C, 68.27; H, 7.37; N, 11.37. Found: C, 67.98; H, 7.63; N, 11.01.

(3*S*,6*S*)-6-Isopropyl-3-(4-methoxybenzyl)-2,5-piperazinedione (5q)
Mp 182–184 °C; $[\alpha]_D^{25}$ –37.9 (*c* = 0.14, DMSO).[35]

IR (KBr): 1668, 1514 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 8.13 (br s, 1 H, NH), 7.96 (br s, 1 H, NH), 7.05 (d, *J* = 8.5 Hz, 2 H, H-2′, H-6′), 6.78 (d, *J* = 8.5 Hz, 2 H, H-3′, H-5′), 4.07 (m, 1 H, H-3), 3.65 (s, 3 H, OCH_3), 3.48 (m, 1 H, H-6), 3.03 (dd, *J* = 13.4, 5.1 Hz, 1 H, CH_2Ar), 2.77 (dd, *J* = 13.4, 5.1 Hz, 1 H, CH_2Ar), 1.60 [m, 1 H, C*H*(CH_3)$_2$], 0.61 [d, *J* = 7.0 Hz, 3 H, CH(C*H*$_3$)$_2$], 0.23 (d, *J* = 7.0 Hz, 3 H, CH(C*H*$_3$)$_2$].

^{13}C NMR (63 MHz, DMSO-d_6): δ = 166.92, 166.73 (2 × CO), 158.52 (C-4′), 131.71 (C-2′, C-6′), 128.48 (C-1′), 113.97 (C-3′, C-5′), 59.47 (C-6), 55.48, 55.36 (OCH_3, C-3), 37.25 (*C*H$_2$Ar), 31.34 [*C*H(CH_3)$_2$], 18.58, 16.48 [CH(*C*H$_3$)$_2$].

Anal. Calcd for $C_{15}H_{20}N_2O_3$ (276): C, 65.20; H, 7.30; N, 10.14. Found: C, 65.48; H, 7.65; N, 9.93.

(3*S*,6*R*)-6-Isopropyl-3-(4-methoxybenzyl)-2,5-piperazinedione (5r)[35]
Mp 230–232 °C; $[\alpha]_D^{25}$ –48.6 (*c* = 0.51, DMSO).

IR (KBr): 1662, 1514 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 8.13 (br s, 1 H, NH), 7.96 (br s, 1 H, NH), 7.15 (d, *J* = 8.5 Hz, 2 H, H-2′, H-6′), 6.8 (d, *J* = 8.5 Hz, 2 H, H-3′, H-5′), 4.10 (m, 1 H, H-3), 3.69 (s, 3 H, OCH_3), 3.07 (dd, *J* = 13.8, 4.3 Hz, 1 H, CH_2Ar), 2.97 (m, 1 H, H-6), 2.77 (dd, *J* = 13.6, 4.5 Hz, 1 H, CH_2Ar), 2.02 [m, 1 H, C*H*(CH_3)$_2$], 0.81 [d, *J* = 7.0 Hz, 3 H, CH(C*H*$_3$)$_2$], 0.74 [d, *J* = 7.0 Hz, 3 H, CH(C*H*$_3$)$_2$].

^{13}C NMR (63 MHz, DMSO-d_6): δ = 167.62, 167.41 (2 × CO), 158.36 (C-4′), 131.53 (C-2′, C-6′), 128.11 (C-1′), 113.97 (C-3′, C-5′), 59.28 (C-6), 55.30, 55.26 (OCH_3, C-3), 37.30 (*C*H$_2$Ar), 31.96 [*C*H(CH_3)$_2$], 18.50, 16.90 [CH(*C*H$_3$)$_2$].

Anal. Calcd for $C_{15}H_{20}N_2O_3$ (276): C, 65.20; H, 7.30; N, 10.14. Found: 64.98; H, 7.42; N, 9.83.

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