DOI: 10.1002/ejoc.201402787

Turning Around the L-Phe-D-Oxd Moiety for a Versatile Low-Molecular-Weight Gelator

Lorenzo Milli,[a] Nicola Castellucci,[a] and Claudia Tomasini*[a]

Dedicated to C.I.N.M.P.I.S. on the occasion of its 20th anniversary

Keywords: Peptidomimetics / Peptides / Gels / Hydrophobic effect / Solvent effects

We have prepared a small library of 13 peptidomimetics containing the L-Phe-D-Oxd unit (or the isosteric L-Phe-D-pGlu unit), which is a privileged scaffold for the preparation of supramolecular materials. These compounds were prepared in solution in excellent yields and tested as organogelators and/or hydrogelators at 10 mM concentration with a plethora of solvents and solvent mixtures. Two molecules were very efficient gelators: one is a organogelator and the other is a hydrogelator. As these compounds have quite different skeletons, a rationale to explain the different behaviour of these molecules as gelators takes into consideration their hydrophobicity, expressed as log *P*. Finally, Fmoc-L-Phe-D-pGlu-OH (**6b**) efficiently gelated phosphate-buffered saline (PBS 1X) at 1.5 % w/w concentration and is an excellent candidate for the preparation of novel materials for applications in, for example, drug release, biological assays, and tissue engineering.

Introduction

Gels are solid-like materials composed mainly of liquids that maintain distinct three-dimensional structures as a result of assembled molecular networks capable of capturing large numbers of liquid molecules.

Gels may be divided into two families: chemical gels, in which the gelator is a polymer (e.g., silica gel),[1] or physical gels, which are formed when the gelator is a small molecule (low-molecular-weight gelator, LMWG)[2] held together by non-covalent interactions such as hydrogen bonds and hydrophobic, aromatic π–π stacking and electrostatic interactions. The transition of the soluble form to the gel state (sol/gel transition) is much simpler in the case of physical gels as it does not involve the formation of any new covalent bonds. Moreover, non-covalent interactions can be disrupted by external stimuli and so the formation of physical hydrogels is a topic of great interest because these materials may find applications in the field of bionanotechnology.[3]

There are a large number of LMWGs.[4] A typical gelator molecule must be partly soluble and partly insoluble in the solvent, it must have the potential to form weak intermolecular interactions and, finally, the non-covalent interactions should be directional, leading to the assembly of anisotropic nanoscale fibres.[5]

Over the years, a large number of building blocks have been identified as LMWGs, but their rational design and the prediction of their behaviour is still a challenge.[6]

We have recently described the preparation of several compounds containing the L-Phe-D-Oxd moiety (Phe = phenylalanine; Oxd = 4-carboxy-5-methyloxazolidin-2-one) that exhibit smart properties in the solid state[7] as they tend to form infinite β-sheet layers. Derivatives of the L-Phe-D-Oxd moiety may behave as fibre-like materials,[8] interact with lipid membranes,[9] form supramolecular helices[10] or be excellent organo- and hydrogelators,[11] also in the presence of metal ions.[12] For this reason we envisaged the L-Phe-D-Oxd moiety as a "privileged scaffold" for the formation of supramolecular materials.[13]

In the continued search for new compounds that are able to gelate solvents, in this work we wished to analyse and compare the effect of substituent modification of the L-Phe-D-Oxd core and its replacement by the isosteric L-Phe-pGlu core (pGlu = pyroglutamic acid) and for this purpose we prepared a small library of 13 compounds.

In particular, we were interested in the preparation of hydrogelators able to form reversible gels containing phosphate-buffered saline (PBS), which is a buffer solution commonly used in biological research. In biomedicine, there is significant interest in exploiting self-assembly to construct mimics of the extracellular matrix (ECM) for cell culture applications.[14]

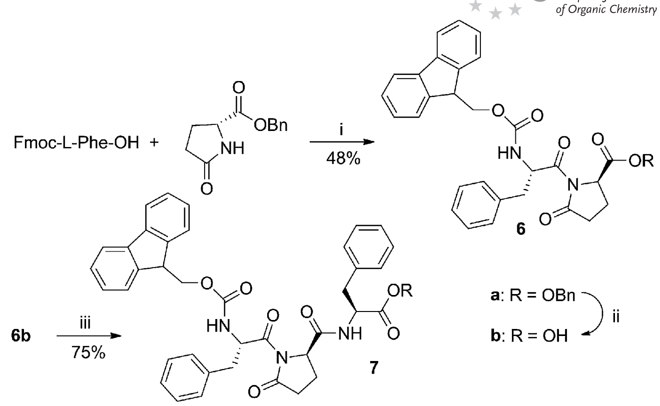
[a] Dipartimento di Chimica "G. Ciamician", Università di Bologna,
Via Selmi, 2, 40126 Bologna, Italy
E-mail: claudia.tomasini@unibo.it
www.unibo.it/faculty/claudia.tomasini
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201402787.

Results and Discussion

Synthesis

Compounds **1a**–**5a** were selected randomly, introducing the most common protecting groups, azelaic acid (a long-chain dicarboxylic acid that may form bolaamphiphile gelators[15]) and an additional L-Phe moiety. They were prepared by standard coupling reactions and all contain a benzyl ester as aromatic rings generally favour gelation.[16] Four additional candidates were prepared by hydrogenolysis of **1a**–**3a** and **5a**; **4a** could not be transformed into the corresponding acid without also removing the benzoxycarbonyl group. The synthetic details are presented in Scheme 1.

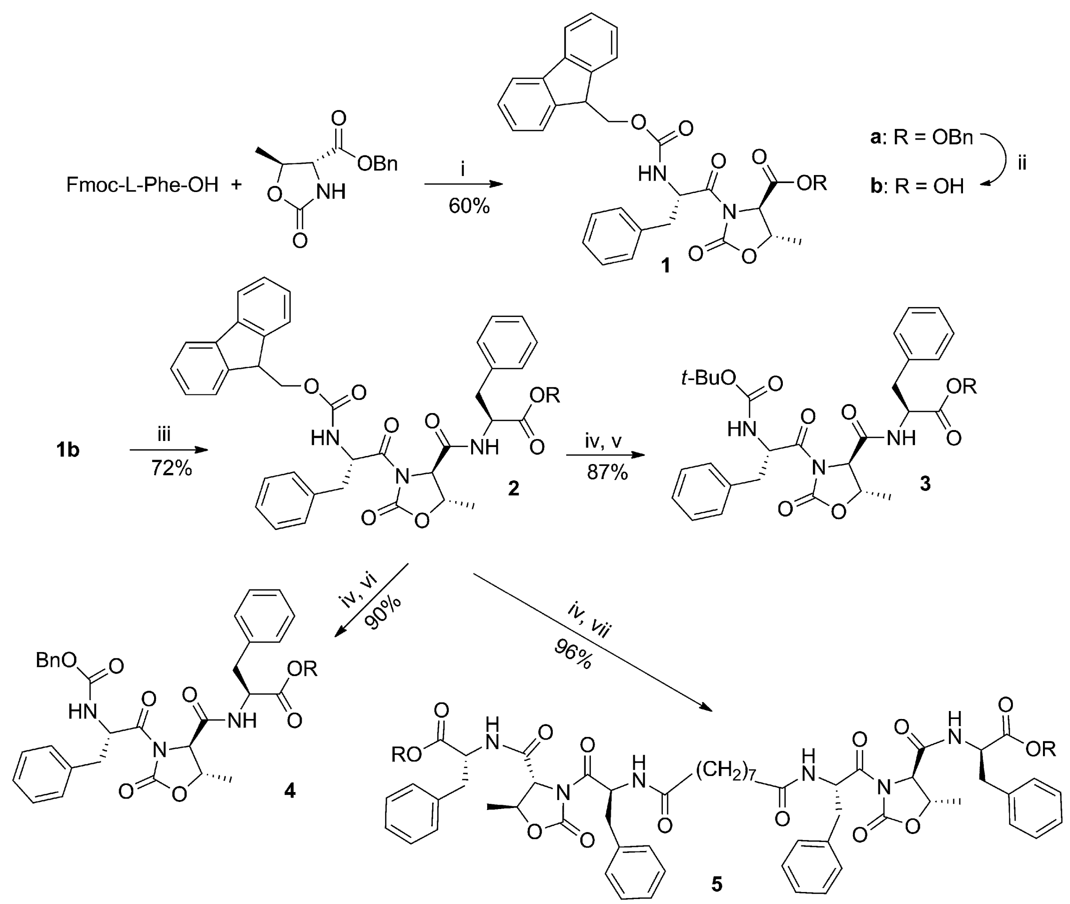
To further extend our library to possible efficient gelators, the Oxd moiety was replaced by the pyroglutamic moiety (pGlu). This choice of replacement was made due to the similar conformational behaviour of the two groups.[17] The synthesis of the esters **6a** and **7a** and the corresponding acids **6a** and **7b** is described in Scheme 2.



Scheme 2. Reagents and conditions: (i) HBTU (1.1 equiv.), DBU (2.5 equiv.), dry acetonitrile, room temp., 50 min; (ii) H_2, Pd/C (10% w/w), MeOH, room temp., 4 h; (iii) HCl·H_2N-L-Phe-OBn (1.0 equiv.), HBTU (1.1 equiv.), Et_3N (3.0 equiv.), dry acetonitrile, room temp., 50 min.

Gelation Studies

The propensity of compounds **1a**–**7a** to form organogels was investigated in a variety of organic solvents and solvent



Scheme 1. Reagents and conditions: (i) HBTU (1.1 equiv.), Et_3N (2.0 equiv.), dry acetonitrile, room temp., 50 min; (ii) H_2, Pd/C (10% w/w), MeOH, room temp., 4 h; (iii) HCl·H_2N-L-Phe-OBn (1.0 equiv.), HBTU (1.1 equiv.), Et_3N (3.0 equiv.), dry acetonitrile, room temp., 50 min; (iv) piperidine (20% v/v) in DCM, room temp., 30 min; (v) Boc_2O (1.0 equiv.), 1 M NaOH (1.1 equiv.), *t*BuOH, room temp., 16 h; (vi) CbzCl (1.1 equiv.), 3 M NaOH (1.1 equiv.), acetone, 0 °C, 3 h; (vii) azelaic acid (0.5 equiv.), HBTU (1.1 equiv.), Et_3N (2.0 equiv.), dry acetonitrile, room temp., 50 min.

Table 1. Gelation properties of compounds **1a**–**7a** in selected solvents at 10 mM concentration.[a]

Solvent	1a	2a	3a (T_{gel} [°C])	4a	5a (T_{gel} [°C])	6a	7a
EtOAc/cHex (1:1)	S	S	S	P	P	S	P
EtOAc/DCM (1:1)	S	S	S	S	P	S	P
EtOAc	S	S	S	P	P	S	P
DCM	S	S	S	S	P	S	S
MeCN	S	P	S	S	G (82)[b]	S	P
DCM/EtOH (1:1)	S	S	S	S	P	S	P
Toluene	S	S	G (50)[c]	P	P	S	S
Toluene/DCM (1:1)	S	S	S	P	P	S	P
Toluene/EtOH (1:1)	S	S	S	P	P	S	P
TFE (500 µL)	S	S	S	P	P	S	P
MTBE	P	S	G (56)[b]	P	P	S	P
EtOH	P	S	G (40)[c]	P	P	P	P
$CHCl_3$	S	S	S	S	PG	S	S

[a] The gel melting points (T_{gel}) are reported in parentheses. G = gel; PG = partial gel; S = solution; P = precipitate. [b] Solvent evaporation. [c] Thermoreversible gel.

mixtures. The general method adopted to form gels was to place one compound in a small test tube (8 mm in diameter) and to dissolve it in a suitable solvent. Sonication (15 min, 305 W) was used to speed up dissolution by breaking up intermolecular interactions and then the tubes were left to stand overnight. The most common diagnostic test of gelation is tube inversion.[18] In this test, a sample tube containing a mixture of the compound and solvent was inverted to ascertain if the sample would flow under its own weight. A gel was taken to have formed if the sample had a yield stress that prevented it from flowing down the tube, whereas a sol was taken to be a sample that flowed down the tube. When a partial gel is formed, the compound sticks to the bottom of the test tube, but a little solvent (<20%) flows down. The results of the gelation tests of compounds **1a**–**7a** are reported in Table 1 together with the gel melting points (T_{gel}).

The best outcomes were obtained with compounds **3a** and **5a**, which do not contain an aromatic protecting group at the nitrogen atom. In particular, **5a** formed a strong gel with acetonitrile that is so stable that it reached the solvent boiling point (82 °C) without melting. Compound **3a** formed stable thermoreversible gels in toluene and ethanol, whereas the gel formed with methyl *tert*-butyl ether (MTBE) reached the solvent boiling point (56 °C) without melting (Figure 1 and the Supporting Information).

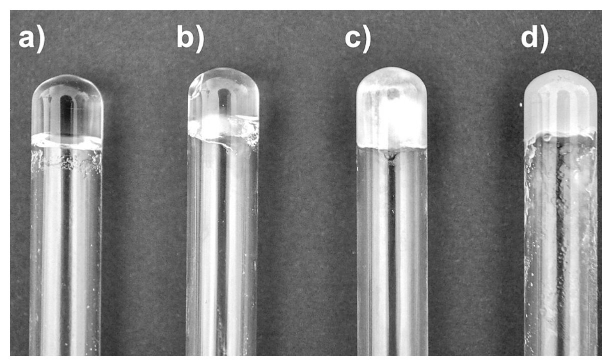


Figure 1. Photographs of organogels reported in Table 1: a) **3a** in toluene; b) **3a** in MTBE; c) **3a** in EtOH; d) **5a** in CH_3CN. All the organogels were obtained after sonication (15 min, 305 W) and then were left to stand overnight.

Then compounds **1b**–**7b** were tested as hydrogelators of ethanol, methanol, water and some mixtures of these solvents at 10 mM concentration. The results are shown in Table 2 together with the gel melting points (T_{gel}).

Table 2. Gelation properties of compounds **1b**–**7b** in selected solvents at 10 mM concentration.[a]

Solvent	1b	2b	3b	5b (T_{gel} [°C])	6b (T_{gel} [°C])	7b
EtOH	PG	S	S	PG	P	P
H_2O/EtOH (3:7)	S	S	S	G (79)[b]	S	P
H_2O/EtOH (1:1)	S	S	S	PG	PG	P
H_2O/EtOH (7:3)	P	PG	S	PG	G (58)[c]	P
H_2O/EtOH (9:1)	P	P	S	P	G (66)[d]	P
MeOH	P	P	S	PG	PG	P
H_2O/MeOH (3:7)	P	PG	S	PG	PG	P
H_2O/MeOH (1:1)	S	PG	S	PG	G (60)[c]	P
H_2O/MeOH (7:3)	PG	P	S	P	G (76)[c]	P
H_2O/MeOH (9:1)	P	P	S	P	G (82)[d]	P
H_2O	P	P	P	P	P	P

[a] The gel melting points (T_{gel}) are reported in parentheses. G = gel; PG = partial gel; S = solution; P = precipitate. [b] Solvent evaporation. [c] Thermoreversible gel. [d] Non-thermoreversible gel.

The best gelators were **5b**, which efficiently gelates only the 3:7 H_2O/EtOH mixture, and **6b**, which is more versatile (Figure 2a–c and the Supporting Information), as it forms thermoreversible gels with a wide variety of ethanol/water and methanol/water mixtures.

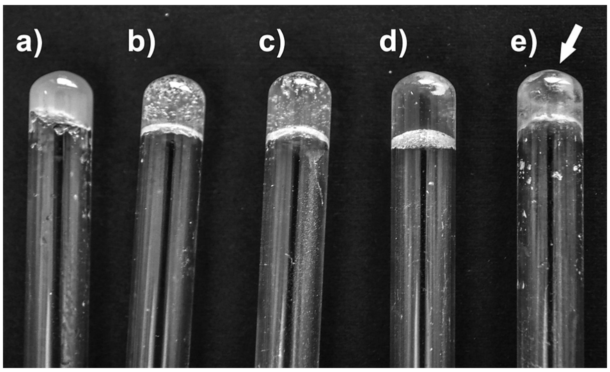


Figure 2. Photographs of selected hydrogels reported in Table 2 and Table 3: a) **5b** in H_2O/EtOH (3:7); b) **6b** in H_2O/EtOH (7:3); c) **6b** in H_2O/EtOH (9:1); d) **6b** (1.5% w/w) in PBS 1X; e) **6b** (1.5% w/w) in PBS 1X after melting and cooling (the arrow indicates the dropped ball trapped in the gel). The hydrogels were obtained after sonication (15 min, 305 W) and then left to stand overnight.

We also investigated whether **6b** can gelate phosphate-buffered saline (PBS), which is a water-based buffer solution commonly used in biological research that contains sodium hydrogen phosphate, sodium chloride, potassium chloride and potassium dihydrogen phosphate. The osmolarity and ion concentrations of the solutions match those of the human body (isotonic). The results for the gelation of PBS (1X) in the presence of various concentrations of **6b** are shown in Table 3.

Table 3. Gelation properties of various concentrations of **6b** in PBS (1X).

Conc. [mM]	Conc. [% w/w]	Outcome	T_{gel} [°C]
10	0.5	Gel	25
20	1.0	Gel	25
30	1.5	Gel	58[a]
40	2.0	Gel	100[b]

[a] Thermoreversible gel. [b] Solvent evaporation.

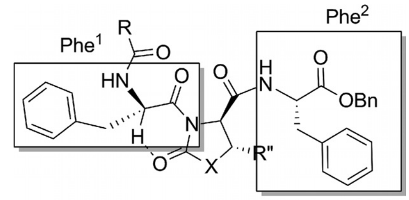
A gel was formed at all the concentrations studied, with a strong and thermoreversible gel being formed at 30 mM concentration (1.5% w/w; Figure 2d,e and the Supporting Information). This interesting result indicates that **6b** is an excellent candidate for the preparation of novel materials that may be used for drug release, biological assays and tissue engineering.[19]

Studies on the Relationship between Molecular Structure and Gelation Behaviour

The results shown in Tables 1–3 suggest that the correlation between gelation behaviour and molecular structure is not straightforward. Although both bolaamphiphilic **5a** and **5b** gelate selected solvents, as we could foresee from our previous results,[12,13] the best hydrogelator, Fmoc-L-Phe-D-pGlu-OH (**6b**), is totally different from the best organogelator, Boc-L-Phe-D-Oxd-L-Phe-OBn (**3a**).

To rationalize the gelation behaviour of **1a**–**7a**, we studied their conformational preferences by comparing their IR and ^{1}H NMR spectra. Selected signals are reported in Table 4.

Table 4. Selected ^{1}H NMR and IR data for compounds **1a**–**7a**. The ^{1}H NMR spectra were recorded as 3 mM solutions in $CDCl_3$ and the IR spectra as 3 mM solutions in dichloromethane.



X = O, CH_2
R = Fmoc, Boc, Cbz, azelaic acid
R' = CH_3, H

	^{1}H NMR [ppm]				IR [cm^{-1}] NH stretching band	
	CHα-Phe^1	NH-Phe^1	CHα-Phe^2	NH-Phe^2		
1a	5.90	5.41	–	–	3428	–
2a	5.65	5.41	4.76	7.20	3419	3351 (weak)
3a	5.59	5.04	4.75	7.14	3432	3350 (weak)
4a	5.70	5.28	4.77	7.22	3427	3351 (weak)
5a	5.66	5.97	4.72	7.65	3435 (weak)	3325
6a	5.88	5.47	–	–	3429	–
7a	5.78	5.45	4.77	6.69	3421	–

The results shown in Table 4 did not lead to a deeper understanding of the correlation between the molecular structures and gelation propensities of compounds **1a**–**7a**. The very deshielded ^{1}H NMR signal of CHα-Phe^1 indicates that in all the compounds a C–H···O=C hydrogen bond is formed with the endocyclic C=O.[20]

Moreover, **5a** contains an N–H···O=C hydrogen bond, as suggested by the strong stretching band at 3325 cm^{-1} and the very deshielded signal of NH–Phe^2 at δ = 7.65 ppm. In contrast, the spectra of **3a** do not suggest the formation of a stable N–H···O=C hydrogen bond owing to the weak 3350 cm^{-1} stretching band and the poorly deshielded signal of NH–Phe^2 at δ = 7.14 ppm. The spectra of all the other compounds show similar signals. ROESY experiments performed on these compounds (see the Supporting Information) did not reveal any interesting cross peaks. Analysis of the IR and ^{1}H NMR spectra of acids **1b**–**7b** also did not furnish any useful information.

As the analysis of the preferential conformations of the gelators provided no help in the rationalization of these outcomes, the hydrophobicity of the molecules was considered, expressed as log *P* (octanol/water partition coefficient), which is calculated as the sum of fragment-based contributions and correction factors. This method is very robust and can be applied to practically all organic and most organometallic molecules. The results are presented in Table 5 for compounds **1**–**7**.

Table 5. Estimated hydrophobicity of compounds **1**–**7**.

	log *P*[a]	Compound	log *P*[a]
1a	7.756	**1b**	4.089
2a	8.503	**2b**	4.986
3a	6.489	**3b**	2.822
4a	6.899	–	–
5a	8.535	**5b**	1.372
6a	7.406	**6b**	3.738
7a	8.265	**7b**	4.636

[a] Hydrophobicities calculated by using an online prediction program.[21]

Of the compounds **1a**–**7a**, **3a** has the smallest value, and thus it is the least hydrophobic compound. Hydrophobicity is a measure of a compound's solubility in organic solvents and a low value favours gel formation as the kinetics of assembly are known to have an effect on the properties of the gels prepared with LMWG.[22] The mechanism through which LMWGs operates depends on a hierarchical self-assembly process that occurs by the following sequence of steps: 1) multiple non-covalent interactions between molecular-scale building blocks allow them to self-assemble into supramolecular polymers referred to as fibrils, 2) the fibrils often then assemble into nanoscale bundles, referred to as fibres and 3) the fibres tangle and interact with one another to form a self-supporting, sample-spanning "solid-like" network, which underpins the macroscopic gel.[23] Gels formed from **3a** are obtained after self-assembly into fibrils, which are clearly visible by SEM analysis of the xerogels (see the Supporting Information).

The log *P* value of **6b** is between 3 and 4, which indicates a moderate hydrophobicity, as at the low end ($\log P < 2.6$) syneresis occurs.[24] Thus, both for organogels and hydrogels, an intermediate value of log *P* (about 6.5 for organogels and 3.5 for hydrogels) is a good starting point for the design of new LMWG.

Compounds **5a** and **5b** are bolaamphiphilic pseudo-peptides and have extreme values of log *P* as **5a** is very hydrophobic whereas **5b** is very hydrophilic. They are both able to form gels only in selected conditions, which suggests that for this family of molecules the self-aggregation process proceeds in a different way that is not fully described by log *P* values.

Conclusions

We have reported the preparation of a small library of 13 peptidomimetics containing the L-Phe-D-Oxd or L-Phe-D-pGlu moieties. All the compounds were tested as organo- or hydrogelators at 10 mM concentration with a plethora of solvents and solvent mixtures. Two molecules were found to be very efficient gelators, namely Boc-L-Phe-D-Oxd-L-Phe-OBn (**3a**) and Fmoc-L-Phe-D-pGlu-OH (**6b**). This latter compound also efficiently gelates phosphate-buffered saline (PBS 1X) at 1.5% (w/w) concentration and is an excellent candidate for the preparation of novel materials for drug release, biological assays and tissue engineering.

A rationale to explain the gelation behaviour of these molecules takes into consideration their hydrophobicity, expressed as log *P* (octanol/water partition coefficient), which is calculated as the sum of fragment-based contributions and correction factors. Compound **3a** has the smallest log *P* value among compounds **1a**–**7a**, which indicates lower solubility in organic solvents. Moreover, **6b** has an intermediate log *P* value (3.738), which indicates moderate hydrophobicity. For both organo- and hydrogels, an intermediate value of log *P* (about 6.5 for organogels and 3.5 for hydrogels) is a good starting point for the design of new LMWGs.

Experimental Section

Synthesis: The melting points of the compounds were determined in open capillaries. High quality IR spectra (64 scans) were obtained at 2 cm^{-1} resolution by using a 1 mm NaCl solution cell and a Nicolet 210 FTIR spectrometer. All spectra were recorded in 3 mM solutions in dry CH_2Cl_2 or in Nujol at 297 K. All compounds were dried in vacuo and samples were prepared under nitrogen. NMR spectra were recorded with a Varian Inova 400 spectrometer at 400 MHz (^1H NMR) and 100 MHz (^{13}C NMR). The measurements were carried out in CD_3OD, $CDCl_3$ or [D_6]DMSO. The proton signals were assigned by gCOSY spectra. Chemical shifts are reported in δ relative to the solvent peak.

Fmoc-L-Phe-D-Oxd-OBn (1a): D-Oxd-OBn (1 mmol, 0.24 g) in dry acetonitrile (5 mL) followed by a solution of triethylamine (2.2 mmol, 0.30 mL) were added to a stirred solution of Fmoc-L-Phe-OH (1 mmol, 0.39 g) and HBTU (1.1 mmol, 0.42 g) in dry acetonitrile (10 mL) under an inert atmosphere at room temperature. The solution was then stirred for 50 min under the inert atmosphere and then acetonitrile was removed under reduced pressure and replaced by ethyl acetate. The mixture was washed with brine, 1 N aqueous HCl (3× 30 mL) and 5% aqueous $NaHCO_3$ (1× 30 mL), dried with sodium sulfate and concentrated in vacuo. The product was obtained pure after silica gel chromatography (cyclohexane/ethyl acetate, 9:1→7:3, as eluent) in 60% yield (0.6 mmol, 0.36 g), m.p. 153–156 °C. $[\alpha]_D^{20}$ = 25.1 (c = 0.26, CH_2Cl_2). IR (CH_2Cl_2, 3 mM): $\tilde{\nu}$ = 3428, 1752, 1727, 1701, 1605 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.42 (d, J = 6.4 Hz, 3 H, Me-Oxd), 3.00 (dd, J = 8.0, 12.4 Hz, 1 H, CHβ-Phe), 3.16 (dd, J = 4.0, 12.4 Hz, 1 H, CHβ-Phe), 4.06–4.44 (m, 4 H, O-C*H*-C*H*$_2$-fluorene + CHN-Oxd), 4.52 (dq, J = 4.8, 6.4 Hz, CHO-Oxd), 5.16 (s, 2 H, OCH_2Ph), 5.42 (d, J = 8.4 Hz, 1 H, NH), 5.87 (dt, J = 6.0, 8.4 Hz, 1 H, CHα-Phe), 7.11–7.80 (m, 18 H, 2 Phe, fluorene) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1, 29.7, 38.9, 47.1, 54.2, 61.8, 67.0, 68.1, 73.6, 119.9, 125.1, 127.0, 127.2, 127.6, 128.5, 128.9, 129.5, 134.5, 135.4, 141.2, 143.8, 151.1, 155.2, 167.3, 172.1 ppm. $C_{36}H_{32}N_2O_7$ (604.66): calcd. C 71.51, H 5.33, N 4.63; found C 71.48, H 5.37, N 4.60.

Fmoc-L-Phe-D-Oxd-OH (1b): Compound **1a** (0.36 g, 0.6 mmol) was dissolved in MeOH (30 mL) under nitrogen and C/Pd (35 mg, 10% w/w) was added also under nitrogen. A vacuum was created inside the flask by using the vacuum line. The flask was then filled with hydrogen using a balloon (1 atm). The solution was stirred for 4 h under a hydrogen atmosphere. The product was obtained pure as an oil in 98% yield (0.59 mmol, 0.30 g) after filtration through filter paper and concentration in vacuo, m.p. 221–223 °C. $[\alpha]_D^{20}$ = 31.6 (c = 0.1, DMF). IR (Nujol): $\tilde{\nu}$ = 3322, 1783, 1719, 1690, 1559 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ = 1.45 (d, J = 6.4 Hz, 3 H, Me-Oxd), 2.80 (dd, J = 9.6, 14.0 Hz, 1 H, CHβ-Phe), 3.17 (dd, J = 4.0, 14.0 Hz, 1 H, CHβ-Phe), 4.01–4.30 (m, 3 H, O-CH-CH_2-fluorene, O-CH-CH_2-fluorene), 4.38–4.45 (m, 1 H, CHN-Oxd), 4.68 (dq, J = 6.0, 6.4 Hz, CHO-Oxd), 5.71–5.80 (m, 1 H, CHα-Phe), 7.05–7.85 (m, 13 H, Phe, fluorene) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.8, 22.7, 37.8, 54.7, 62.1, 66.6, 74.7, 119.4, 124.8, 126.7, 127.2, 127.9, 128.7, 129.1, 136.8, 141.0, 143.7, 170.3, 172.3 ppm. $C_{29}H_{26}N_2O_7$ (514.53): calcd. C 67.70, H 5.09, N 5.44; found C 67.73, H 5.10, N 5.47.

Fmoc-L-Phe-D-Oxd-L-Phe-OBn (2a): A mixture of HCl·H_2N-L-Phe-OBn (1 mmol, 0.29 g) and triethylamine (3.1 equiv., 0.43 mL) in dry acetonitrile (5 mL) was added to a stirred solution of Fmoc-L-Phe-D-Oxd-OH (**1b**; 1 mmol, 0.52 g) and HBTU (1.1 mmol, 0.42 g) in dry acetonitrile (10 mL) under an inert atmosphere at room temperature. The solution was stirred for 40 min under an inert atmosphere, and then acetonitrile was removed under reduced pressure and replaced by ethyl acetate. The mixture was washed with brine, 1 N aqueous HCl (3× 30 mL) and 5% aqueous $NaHCO_3$ (1× 30 mL), dried with sodium sulfate and concentrated in vacuo. The product was obtained pure after silica gel chromatography (dichloromethane/ethyl acetate, 99:1→97:3, as eluent) in 72% yield (0.72 mmol, 0.48 g), m.p. 150 °C. $[\alpha]_D^{20}$ = 24.8 (c = 0.1, CH_2Cl_2). IR (CH_2Cl_2, 3 mM): $\tilde{\nu}$ = 3419, 3350, 1792, 1788, 1704, 1683 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29 (d, J = 6.4 Hz, 3 H, Me-Oxd), 2.93–3.24 (m, 4 H, 2 CH_2β-Phe), 4.07–4.37 (m, 4 H, O-CH-CH_2-fluorene, O-CH-CH_2-fluorene, CHN-Oxd), 4.53 (dq, J = 5.2, 6.4 Hz, CHO-Oxd), 4.75 (q, J = 6.0 Hz, CHα-Phe), 5.03 (AB, J = 10.8 Hz, 2 H, OCH_2Ph), 5.36 (br. s, 1 H, NH), 5.65 (br. s, 1 H, CHα-Phe), 6.92–7.82 (m, 24 H, 3 Phe, fluorene, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.8, 29.7, 37.3, 46.9, 54.0, 54.4, 62.6, 67.1, 67.4, 74.9, 120.0, 125.0, 127.1, 127.4, 127.7, 128.3, 128.4, 128.5, 128.8, 129.2, 129.4, 135.0, 135.2, 141.2, 143.4, 151.5, 166.8, 170.1, 172.6 ppm. $C_{45}H_{41}N_3O_8$ (751.83): calcd. C 71.89, H 5.50, N 5.59; found C 71.93, H 5.53, N 5.55.

Fmoc-L-Phe-D-Oxd-L-Phe-OH (2b): For the synthetic procedure from **2a**, see the preparation of **1b** given above, yield 99%, m.p. = 155 °C. $[\alpha]_D^{20}$ = 41.5 (c = 0.1 in MeOH). IR (Nujol): $\tilde{\nu}$ = 3351, 1776, 1727, 1691, 1663, 1529 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD): δ = 1.25 (d, J = 6.8 Hz, 3 H, Me-Oxd), 2.79 (dd, J = 10.0, 13.6 Hz, 1 H, CHβ-Phe), 2.89 (dd, J = 9.6, 13.6 Hz, 1 H, CHβ-Phe), 3.04–3.30 (m, 2 H, CH_2β-Phe), 3.80–4.38 (m, 5 H, O-CH-CH_2-fluorene, O-CH-CH_2-fluorene, CHN-Oxd, CHO-Oxd), 4.51–4.61 (m, 1 H, CHα-Phe), 5.68–5.76 (m, 1 H, CHα-Phe), 7.09–7.80 (m, 18 H, 2 Phe, fluorene) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 19.4, 37.1, 37.3, 37.7, 53.8, 54.7, 61.3, 62.5, 66.6, 71.1, 74.9, 76.9, 119.4, 124.8, 124.9, 126.7, 127.3, 128.0, 128.9, 129.2, 136.7, 137.1, 141.0, 143.7, 152.3, 156.6, 168.4, 172.2, 173.0 ppm. $C_{38}H_{34}N_3O_8$ (660.70): calcd. C 69.08, H 5.19, N 6.36; found C 69.06, H 5.21, N 6.38.

Boc-L-Phe-D-Oxd-L-Phe-OBn (3a): Fmoc-L-Phe-D-Oxd-L-Phe-OBn (**2a**; 0.5 mmol, 0.38 g) was added to a solution of piperidine (4 mmol, 0.4 mL) in dichloromethane (2 mL) and the mixture was stirred for 30 min at room temperature then concentrated in vacuo. The product was dissolved in *tert*-butanol (3 mL) and then Boc_2O (0.6 mmol, 0.13 g) and 1 M NaOH (0.6 mmol, 0.6 mL) were added at 0 °C and the mixture stirred for 16 h at 0 °C. Then ethyl acetate (30 mL) was added to the mixture, which was washed with brine, 1 N aqueous HCl (3× 30 mL) and 5% aqueous $NaHCO_3$ (1× 30 mL), dried with sodium sulfate and concentrated in vacuo. The product was obtained pure after silica gel chromatography (dichloromethane→dichloromethane/ethyl acetate, 95:5, as eluent) in 87% yield (0.44 mmol, 0.27 g), m.p. 196–198 °C. $[\alpha]_D^{20}$ = 31.1 (c = 0.1, CH_2Cl_2). IR (CH_2Cl_2, 3 mM): $\tilde{\nu}$ = 3432, 3350, 1788, 1740, 1700, 1684 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (d, J = 6.4 Hz, 3 H, Me-Oxd), 1.33 (s, 9 H, O-tBu), 2.80–2.92 (m, 1 H, CHβ-Phe), 3.01–3.21 (m, 3 H, CHβ-Phe, CH_2β-Phe), 4.21 (br. s, 1 H, CHN-Oxd), 4.53 (dq, J = 5.2, 6.4 Hz, CHO-Oxd), 4.75 (q, J = 6.8 Hz, CHα-Phe), 4.98–5.17 (m, 3 H, NH, OCH_2Ph), 5.59 (br. s, 1 H, CHα-Phe), 6.94–7.44 (m, 16 H, 3 Phe, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.7, 28.2, 37.3, 54.1, 62.6, 67.2, 74.7, 80.5, 127.2, 128.5, 128.7, 129.2, 129.4, 135.2, 135.5, 136.0, 151.5, 166.9, 170.5, 172.8 ppm. $C_{35}H_{39}N_3O_8$ (629.71): calcd. C 66.76, H 6.24, N 6.67; found C 66.80, H 6.28, N 6.71.

Boc-L-Phe-D-Oxd-L-Phe-OH (3b): For the synthetic procedure from **3a**, see the preparation of **1b** given above, yield 98%, m.p. = 227–230 °C. $[\alpha]_D^{20}$ = 21.9 (c = 1.0, MeOH). IR (Nujol): $\tilde{\nu}$ = 3322, 1779, 1717, 1693, 1653 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD): δ = 1.02–1.26 (m, 12 H, Me-Oxd, tBu), 2.46–2.67 (m, 1 H, CHβ-Phe), 2.69–2.83 (m, 1 H, CHβ-Phe), 2.83–2.97 (m, 1 H, CHβ-Phe), 3.04–3.20 (m, 1 H, CHβ-Phe), 3.69–4.78 (m, 1 H, CHN-Oxd), 4.08–4.18 (m, 1 H, CHO-Oxd), 4.45–4.61 (m, 1 H, CHα-Phe), 5.45–5.56 (m, 1 H, CHα-Phe), 6.98–7.18 (m, 10 H, 2 Phe) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 19.4, 26.8, 27.2, 37.3, 38.1, 54.1, 62.4, 74.8, 79.1, 126.4, 127.9, 128.0, 129.0, 129.2, 136.6, 137.1, 152.3, 156.0, 168.5, 172.4 ppm. $C_{28}H_{33}N_3O_8$ (539.58): calcd. C 62.33, H 6.16, N 7.79; found C 62.37, H 6.13, N 7.82.

Cbz-L-Phe-D-Oxd-L-Phe-OBn (4a): Fmoc-L-Phe-D-Oxd-L-Phe-OBn (**2a**; 0.5 mmol, 0.38 g) was added to a solution of piperidine (4 mmol, 0.4 mL) in dichloromethane (2 mL) and the mixture was stirred for 30 min at room temperature and then concentrated in vacuo. The product was dissolved in acetone (5 mL) and 1 M NaOH (0.6 mmol, 0.6 mL), and then CbzCl (0.6 mmol, 0.10 g) in acetone (2 mL) was added dropwise at 0 °C and the mixture stirred for 3 h at 0 °C. Then acetone was removed in vacuo and ethyl acetate (30 mL) was added to the mixture, which was washed with brine, 1 N aqueous HCl (3× 30 mL) and 5% aqueous $NaHCO_3$ (1× 30 mL), dried with sodium sulfate and concentrated in vacuo. The product was obtained pure after silica gel chromatography (dichloromethane→dichloromethane/ethyl acetate, 95:5, as eluent) in 90% yield (0.45 mmol, 0.30 g), m.p. 197–199 °C. $[\alpha]_D^{20}$ = 20.6 (c = 0.2, CH_2Cl_2). IR (CH_2Cl_2, 3 mM): $\tilde{\nu}$ = 3427, 3351, 1789, 1704, 1605 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29 (d, J = 6.4 Hz, 3 H, Me-Oxd), 2.90 (dd, J = 8.8, 13.6 Hz, 1 H, CHβ-Phe), 3.02 (dd, J = 7.2, 13.6 Hz, 1 H, CHβ-Phe), 3.11–3.20 (m, 2 H, CH_2β-Phe), 4.27 (br. s, 1 H, CHN-Oxd), 4.54 (dq, J = 5.6, 6.4 Hz, 1 H, CHO-Oxd), 4.77 (dt, J = 6.0, 8.0 Hz, 1 H, CHα-Phe), 4.83–5.14 (m, 4 H, 2 OCH_2Ph), 5.70 (m, 1 H, CHα-Phe), 6.96–7.38 (m, 21 H, 4 Phe, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 37.3, 37.8, 53.3, 54.3, 62.5, 67.3, 74.9, 127.0, 127.4, 128.0, 128.1, 128.3, 128.5, 128.6, 128.8, 129.2, 129.4, 135.3, 135.6, 151.5, 156.2, 166.9, 170.2, 170.6, 170.7, 172.8 ppm. $C_{38}H_{37}N_3O_8$ (663.73): calcd. C 68.77, H 5.62, N 6.33; found C 68.74, H 5.66, N 6.38.

CH_2-[(CH_2)$_3$-CO-L-Phe-D-Oxd-L-Phe-OBn]$_2$ (5a): Fmoc-L-Phe-D-Oxd-L-Phe-OBn (**2a**; 0.5 mmol, 0.38 g) was added to a solution of piperidine (4 mmol, 0.4 mL) in dichloromethane (2 mL) and the mixture was stirred for 30 min at room temperature and then concentrated in vacuo. The residue was dissolved in dry acetonitrile (5 mL) and added to a stirred solution of azelaic acid (0.25 mmol, 50 mg) and HBTU (0.55 mmol, 0.21 g) in dry acetonitrile (10 mL) at room temperature under an inert atmosphere, followed by a solution of triethylamine (2.0 mmol, 0.28 mL). The final solution was stirred for 40 min under an inert atmosphere and then acetonitrile was removed under reduced pressure and replaced by ethyl acetate. The mixture was washed with brine, 1 N aqueous HCl (3× 30 mL) and 5% aqueous $NaHCO_3$ (1× 30 mL), dried with sodium sulfate and concentrated in vacuo. The product was sonicated in diethyl ether (3× 10 mL) for 10 min each and then filtered and dried in vacuo. It was obtained pure in 96% yield (0.26 mmol, 0.61 g), m.p. 227–229 °C. $[\alpha]_D^{20}$ = 49.9 (*c* = 0.4, CH_2Cl_2). IR (CH_2Cl_2, 3 mM): $\tilde{\nu}$ = 3435, 3325, 1787, 1743, 1716, 1677, 1660 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01–1.09 (m, 6 H, 3 CH_2 azelaic acid), 1.27 (d, *J* = 6.4 Hz, 6 H, 2 Me-Oxd), 1.33–1.43 (m, 4 H, 2 CH_2 azelaic acid), 1.92–2.02 (m, 4 H, 2 CH_2 azelaic acid), 2.89 (dd, *J* = 9.2, 13.2 Hz, 2 H, 2 CHβ-Phe), 3.07 (dd, *J* = 8.0, 13.2 Hz, 2 H, 2 CHβ-Phe), 3.11–3.21 (m, 4 H, 2 CH_2β-Phe), 4.30 (d, *J* = 5.2 Hz, 2 H, 2 CHN-Oxd), 4.50 (dq, *J* = 5.2, 6.4 Hz, 2 H, 2 CHO-Oxd), 4.72 (dt, *J* = 6.4, 7.6 Hz, 2 H, 2 CHα-Phe), 5.03 (AB, *J* = 12.4 Hz, 4 H, 2 OCH_2Ph), 5.62–5.70 (m, 2 H, 2 CHα-Phe), 5.97 (d, *J* = 4.4 Hz, 2 H, 2 NH), 7.04–7.34 (m, 30 H, 6 Phe), 7.65 (d, *J* = 7.6 Hz, 2 H, 2 NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 24.5, 28.6, 29.6, 35.3, 36.4, 36.9, 53.4, 54.2, 59.8, 62.3, 66.9, 75.1, 126.7, 127.4, 128.1, 128.3, 128.4, 128.8, 129.1, 135.2, 136.6, 151.6, 167.3, 170.7, 172.5, 173.8 ppm. $C_{69}H_{74}N_6O_{14}$ (1211.38): calcd. C 68.41, H 6.16, N 6.94; found C 68.38, H 6.14, N 6.97.

CH_2-[(CH_2)$_3$-CO-L-Phe-D-Oxd-L-Phe-OH]$_2$ (5b): For the synthetic procedure from **5a**, see the preparation of **1b** given above, yield 97%, m.p. 233 °C. $[\alpha]_D^{20}$ = 49.9 (*c* = 0.4, CH_2Cl_2). IR (Nujol): $\tilde{\nu}$ = 3292, 1784, 1718, 1654, 1603, 1545 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]-DMSO): δ = 0.86–1.08 (m, 6 H, 3 CH_2 azelaic acid), 1.14–1.43 (m, 10 H, 2 Me-Oxd, 2 CH_2 azelaic acid), 1.87–2.02 (m, 4 H, 2 CH_2 azelaic acid), 2.56–2.71 (m, 2 H, 2 CHβ-Phe), 2.71–2.89 (m, 2 H, 2 CHβ-Phe), 2.89–3.12 (m, 4 H, 2 CH_2β-Phe), 3.88 (d, *J* = 4.4 Hz, 2 H, 2 CHN-Oxd), 4.26–4.33 (m, 2 H, 2 CHα-Phe), 4.51 (dq, *J* = 4.4, 5.6 Hz, 2 H, 2 CHO-Oxd), 5.65–5.75 (m, 2 H, 2 CHα-Phe), 7.09–7.25 (m, 20 H, 4 Phe), 8.00 (br. s, 2 H, 2 NH), 8.13 (d, *J* = 7.6 Hz, 2 H, 2 NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 21.2, 21.3, 25.5, 28.7, 35.5, 37.8, 52.8, 53.8, 55.3, 60.2, 62.3, 74.8, 75.1, 77.2, 126.7, 126.8, 128.5, 128.6, 129.6, 137.8, 138.2, 152.6, 158.2, 170.1, 172.3, 172.5, 172.7, 173.7 ppm. $C_{55}H_{62}N_6O_{14}$ (1031.13): calcd. C 64.07, H 6.06, N 8.15; found C 64.12, H 6.10, N 8.18.

Fmoc-L-Phe-D-pGlu-OBn (6a): D-pGlu-OBn (1 mmol,0.22 g) in dry acetonitrile (5 mL) was added to a stirred solution of Fmoc-L-Phe-OH (1 mmol, 0.39 g) and HBTU (1.1 mmol, 0.42 g) in dry acetonitrile (10 mL) under an inert atmosphere at room temperature, followed by a solution of DBU (2.5 mmol, 0.37 mL). The solution was stirred for 50 min under an inert atmosphere and then acetonitrile was removed under reduced pressure and replaced by ethyl acetate. The mixture was washed with brine, 1 N aqueous HCl (3× 30 mL) and 5% aqueous $NaHCO_3$ (1× 30 mL), dried with sodium sulfate and concentrated in vacuo. The product was obtained pure after silica gel chromatography (cyclohexane/ethyl acetate, 8:2→7:3, as eluent) in 48% yield (0.48 mmol, 0.28 g), m.p. 83–84 °C. $[\alpha]_D^{20}$ = 63.9 (*c* = 0.18, $CHCl_3$). IR (CH_2Cl_2, 3 mM): $\tilde{\nu}$ = 3429, 1794, 1755, 1711, 1605 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.00–2.11 (m, 1 H, CHβ-pGlu), 2.16–2.31 (m, 1 H, CHβ-pGlu), 2.43–2.56 (m, 1 H, CHγ-pGlu), 2.63–2.80 (m, 1 H, CHγ-pGlu), 2.94 (dd, *J* = 7.6, 13.6 Hz, 1 H, CHβ-Phe), 3.16 (dd, *J* = 7.6, 13.6 Hz, 1 H, CHβ-Phe), 4.12–4.27 (m, 2 H, O-CH-CH_2-fluorene), 4.34–4.41 (m, 1 H, O-C*H*-CH_2-fluorene), 4.64 (m, 1 H, CHα-pGlu), 5.14 (s, 2 H, OCH_2Ph), 5.47 (d, *J* = 8.4 Hz, 1 H, NH), 5.85 (dt, *J* = 6.4, 8.4 Hz, 1 H, CHα-Phe), 7.11–7.76 (m, 18 H, Phe, fluorene) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 29.7, 31.6, 39.0, 47.1, 53.4, 55.3, 58.2, 66.9, 67.5, 119.9, 125.2, 127.0, 127.6, 128.2, 128.4, 128.5, 128.6, 129.5, 135.0, 135.8, 141.2, 143.9, 155.1, 170.2, 172.6, 173.8 ppm. $C_{36}H_{32}N_2O_6$ (588.66): calcd. C 73.45, H 5.48, N 4.76; found C 73.48, H 5.51, N 4.73.

Fmoc-L-Phe-D-pGlu-OH (6b): For the synthetic procedure from **6a**, see the preparation of **1b** given above, yield 99%, m.p. 197–200 °C. $[\alpha]_D^{20}$ = 34.7 (*c* = 0.15, $CHCl_3$). IR (Nujol): $\tilde{\nu}$ = 1735, 1714, 1695, 1538 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.96 (dd, *J* = 9.2, 10.4 Hz, 1 H, CHβ-pGlu), 2.26–2.40 (m, 1 H, CHβ-pGlu), 2.49–2.72 (m, 3 H, CH_2γ-pGlu, CHβ-Phe), 3.02 (dd, *J* = 1.1, 13.2 Hz, 1 H, CHβ-Phe), 4.01–4.15 (m, 3 H, O-C*H*-CH_2-fluorene), 4.52 (dd, *J* = 1.8, 9.6 Hz, 1 H, CHα-pGlu), 5.40 (dd, *J* = 9.6, 10.8 Hz, 1 H, CHα-Phe), 7.12–7.87 (m, 13 H, Phe, fluorene) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 21.7, 32.1, 37.2, 46.9, 56.7, 58.6, 66.1, 120.5, 125.7, 126.8, 127.5, 128.0, 128.5, 128.6, 129.6, 138.3, 141.0, 144.1, 144.2, 156.1, 172.7, 173.5, 175.6 ppm. $C_{29}H_{26}N_2O_6$ (498.53): calcd. C 69.87, H 5.26, N 5.62; found C 69.90, H 5.30, N 5.59.

Fmoc-L-Phe-D-pGlu-L-Phe-OBn (7a): For the synthetic procedure from **6b**, see the preparation of **2a** given above, but with dichloromethane/ethyl acetate, 98:2→90:10, as eluent, yield 75%, m.p. = 210–213 °C. $[\alpha]_D^{20}$ = 39.6 (*c* = 0.2, CH_2Cl_2). IR (CH_2Cl_2, 3 mM): $\tilde{\nu}$ = 3421, 1749, 1695, 1605 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.94–2.13 (m, 2 H, CH_2β-pGlu), 2.25–2.40 (m, 1 H, CHα-pGlu), 2.55–2.73 (m, 1 H, CHα-pGlu), 2.91 (dd, *J* = 8.0, 13.6 Hz, 1 H, CHβ-Phe), 3.00 (dd, *J* = 6.4, 13.6 Hz, 1 H, CHβ-Phe), 3.08–3.18 (m, 2 H, CH_2β-Phe), 4.06–4.25 (m, 2 H, O-CH-CH_2-fluorene), 4.29–4.37 (m, 1 H, O-C*H*-CH_2-fluorene), 4.52–4.56 (m, 1 H, pGlu), 4.77 (dq, *J* = 6.4, 6.4 Hz, 1 H, CHα-Phe), 5.05 (AB, *J* = 12.0 Hz, 2 H, OCH_2Ph), 5.42 (d, *J* = 6.4 Hz, 1 H, NH), 5.78 (dt, *J* = 6.0, 6.4 Hz, 1 H, CHα-Phe), 6.67 (d, *J* = 7.6 Hz, 1 H, NH), 6.94–7.75 (m, 23 H, 3 Phe, fluorene) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.7, 29.7, 37.4, 38.2, 47.0, 53.4, 55.2, 59.1, 67.1, 67.3, 77.1, 119.9, 125.1, 127.0, 127.1, 127.6, 128.5, 129.2, 129.4, 134.9, 135.6, 135.9, 141.2, 143.7, 155.7, 169.3, 170.9, 173.0, 174.5 ppm. $C_{45}H_{41}N_3O_7$ (735.83): calcd. C 73.45, H 5.62, N 5.71; found C 73.49, H 5.68, N 5.73.

Fmoc-L-Phe-D-pGlu-L-Phe-OH (7b): For the synthetic procedure from **7a**, see the preparation of **1b** given above, yield 98%, m.p. = 199–201 °C. $[\alpha]_D^{20}$ = 45 (*c* = 0.2, CH_2Cl_2). IR (Nujol): $\tilde{\nu}$ = 3326, 1733, 1694, 1650, 1548 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.54–1.64 (m, 1 H, CHβ-pGlu), 2.06–2.19 (m, 1 H, CHβ-pGlu), 2.30–2.43 (m, 1 H, CHα-pGlu), 2.43–2.57 (m, 1 H, CHα-pGlu), 2.73 (dd, *J* = 8.8, 13.6 Hz, 1 H, CHβ-Phe), 2.92 (dd, *J* = 10.0, 14.0 Hz, 1 H, CHβ-Phe), 3.12 (dd, *J* = 3.6, 13.6 Hz, 1 H, CHβ-Phe), 3.22 (dd, *J* = 4.8, 14.0 Hz, 1 H, CHβ-Phe), 4.03–4.12 (m, 2 H, O-CH-CH_2-fluorene), 4.18–4.27 (m, 1 H, O-C*H*-CH_2-fluorene), 4.54–4.60 (m, 1 H, pGlu), 4.65–4.72 (m, 1 H, CHα-Phe), 5.66–5.74 (m, 1 H, CHα-Phe), 7.06–7.77 (m, 20 H, 2 Phe, fluorene, 2 NH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 19.0, 23.0, 32.7, 37.5, 37.9, 46.9, 53.3, 56.4, 56.5, 59.0, 66.0, 120.4, 125.7, 126.8, 127.5, 128.0, 128.5, 129.6, 129.7, 137.8, 138.3, 140.1, 141.1, 144.1, 155.9, 170.3, 173.0, 173.2, 175.9 ppm. $C_{38}H_{35}N_3O_7$ (645.71): calcd. C 70.68, H 5.46, N 6.51; found C 70.65, H 5.48, N 6.54.

Conditions for Gel Formation: Compounds **1a**–**f** or **2a**–**f** (5 µmol) and the solvent reported in Table 1 and Table 2 (0.5 mL) were placed in a glass test tube (diameter: 8 mm). The mixture was sonicated for 20 min (15 min, 305 W) until the solid had totally dissolved and then left to stand for 16 h for the gel formation to occur.

Conditions for the Determination of T_{gel}: The gel/sol transition temperatures (T_{gel}) were determined by heating test tubes (diameter: 8 mm) containing the gel with a glass ball (diameter: 5 mm; weight: 165 mg) on top of it. When the gel formed, the ball floated on it. The T_{gel} is the temperature at which the gel becomes a sol; at this temperature the ball drops.

Supporting Information (see footnote on the first page of this article): ROESY spectra of compounds **3a** and **5a**, photographs of the organogels reported in Table 1–3.

Acknowledgments

Financial support by the Italian Ministero dell'Università e della Ricerca (MIUR) (program PRIN, grant number 2010NRREPL_009), the Consorzio Spinner Regione Emilia Romagna and by the Consorzio CINMPIS is acknowledged.

[1] S. Van Vlierberghe, P. Dubruel, E. Schacht, *Biomacromolecules* **2011**, *12*, 1387–1408.
[2] a) C. Tomasini, N. Castellucci, *Chem. Soc. Rev.* **2013**, *42*, 156–172; b) N. M. Sangeetha, U. Maitra, *Chem. Soc. Rev.* **2005**, *34*, 821–836; c) D. J. Adams, P. D. Topham, *Soft Matter* **2010**, *6*, 3707–3721; d) D. M. Ryan, B. L. Nilsson, *Polym. Chem.* **2012**, *3*, 18–33; e) E. K. Johnson, D. J. Adams, P. J. Cameron, *J. Mater. Chem.* **2011**, *21*, 2024–2027; f) J. W. Steed, *Chem. Commun.* **2011**, *47*, 1379–1383.
[3] a) N. A. Peppas, J. Z. Hilt, A. Khademhosseini, R. Larger, *Adv. Mater.* **2006**, *18*, 1345–1360; b) J. L. Drury, D. J. Mooney, *Biomaterials* **2003**, *24*, 4337–4351; c) S. Van Vlierberghe, P. Dubruel, E. Schacht, *Biomacromolecules* **2011**, *12*, 1387–1408; d) M. W. Tibbitt, K. S. Anseth, *Biotechnol. Bioeng.* **2009**, *103*, 655–663.
[4] D. K. Smith, *Chem. Soc. Rev.* **2009**, *38*, 684–694.
[5] A. Aggeli, I. A. Nyrkova, M. Bell, R. Harding, L. Carrick, T. C. B. McLeish, A. N. Semenov, N. Boden, *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 11857–11862.
[6] G. Fichman, E. Gazit, *Acta Biomater.* **2014**, *10*, 1671–1682.
[7] C. Tomasini, G. Angelici, N. Castellucci, *Eur. J. Org. Chem.* **2011**, 3648–3669.
[8] a) C. Tomasini, G. Angelici, N. Castellucci, *Eur. J. Org. Chem.* **2011**, 3648–3669; b) G. Angelici, G. Falini, H.-J. Hofmann, D. Huster, M. Monari, C. Tomasini, *Chem. Eur. J.* **2009**, *15*, 8037–8048.
[9] H. A. Scheidt, A. Sickert, T. Meier, N. Castellucci, C. Tomasini, D. Huster, *Org. Biomol. Chem.* **2011**, *9*, 6998–7006.
[10] G. Angelici, N. Castellucci, G. Falini, D. Huster, M. Monari, C. Tomasini, *Cryst. Growth Des.* **2010**, *10*, 923–929.
[11] N. Castellucci, G. Sartor, N. Calonghi, C. Parolin, G. Falini, C. Tomasini, *Beilstein J. Org. Chem.* **2013**, *9*, 417–424.
[12] N. Castellucci, G. Falini, G. Angelici, C. Tomasini, *Amino Acids* **2011**, *41*, 609–620.
[13] N. Castellucci, G. Angelici, G. Falini, M. Monari, C. Tomasini, *Eur. J. Org. Chem.* **2011**, 3082–3088.
[14] V. Jayawarna, M. Ali, T. A. Jowitt, A. F. Miller, A. Saiani, J. E. Gough, R. V. Ulijin, *Adv. Mater.* **2006**, *18*, 611–614.
[15] a) M. Suzuki, T. Abe, K. Hanabusa, *J. Colloid Interface Sci.* **2010**, *341*, 69–74; b) T. Shimizu, *Macromol. Rapid Commun.* **2002**, *23*, 311–331; c) J.-H. Fuhrhop, T. Wang, *Chem. Rev.* **2004**, *104*, 2901–2937.
[16] a) S. S. Babu, V. K. Praveen, A. Ajayaghosh, *Chem. Rev.* **2014**, *114*, 1973–2139; b) Y. Zhang, Z. Yang, F. Yuan, H. Gu, P. Gao, B. Xu, *J. Am. Chem. Soc.* **2004**, *126*, 15028–15029; c) Y. Zhang, H. Gu, Z. Yang, B. Xu, *J. Am. Chem. Soc.* **2003**, *125*, 13680–13681.
[17] a) S. Lucarini, C. Tomasini, *J. Org. Chem.* **2001**, *66*, 727–732; b) F. Bernardi, M. Garavelli, M. Scatizzi, C. Tomasini, V. Trigari, M. Crisma, F. Formaggio, C. Peggion, C. Toniolo, *Chem. Eur. J.* **2002**, *8*, 2516–2525; c) C. Tomasini, V. Trigari, S. Lucarini, F. Bernardi, M. Garavelli, C. Peggion, F. Formaggio, C. Toniolo, *Eur. J. Org. Chem.* **2003**, 259–267.
[18] a) K. Takahashi, M. Sakai, T. Kato, *Polym. J.* **1980**, *12*, 335–341; b) M. Yamanaka, H. Fujii, *J. Org. Chem.* **2009**, *74*, 5390–5394.
[19] a) N. M. Sangeetha, U. Maitra, *Chem. Soc. Rev.* **2005**, *34*, 821–836; b) L. A. Estroff, A. D. Hamilton, *Chem. Rev.* **2004**, *104*, 1201–1217.
[20] C. Tomasini, M. Villa, *Tetrahedron Lett.* **2001**, *42*, 5211–5214.
[21] http://www.molinspiration.com.
[22] Z. Yang, G. Liang, M. Ma, Y. Gao, B. Xu, *Small* **2007**, *3*, 558–562.
[23] C. Tang, A. M. Smith, R. F. Collins, R. V. Ulijn, A. Saiani, *Langmuir* **2009**, *25*, 9447–9453.
[24] D. J. Adams, L. M. Mullen, M. Berta, L. Chen, W. J. Frith, *Soft Matter* **2010**, *6*, 1971–1980.

Received: June 20, 2014
Published Online: August 20, 2014

