Solid-Phase Synthesis of Oligourea Peptidomimetics

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A procedure for the solid-phase synthesis of oligourea peptidomimetics starting from Boc-protected monomers is described. The compounds are prepared on Tentagel® resin and can be obtained selectively either as the C-terminal free acids with UV irradiation when a photocleavable linker is used or as C-terminal hydantoins with 10% TEA/MeOH and a catalytic amount of KCN.

Introduction

In recent years, an increasing amount of attention has been focused on the application of the urea moiety as a replacement for the amide bond in peptidomimetics (Figure 1).[1−4] The resulting *oligourea peptidomimetics* offer several advantages in comparison with natural peptides regarding prospective therapeutic applications. As in other types of peptidomimetics, replacing the amide bond leads to a decrease in degradation by proteolytic enzymes in the gastrointestinal tract, which opens perspectives for the oral delivery of these compounds.

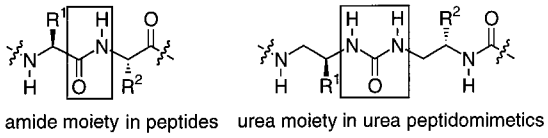

Figure 1. The backbone of oligourea peptidomimetics compared with the peptide backbone

The backbone in each repeating unit of oligourea peptidomimetics is generally extended by one carbon atom in comparison with the natural amino acid (Figure 1). This is done for reasons of synthetic accessability and product stability. In addition, the extra carbon atom may also increase the lipophilicity and flexibility of the compounds which makes it easier to pass barriers like the cell wall and the blood−brain barrier. The hydrogen-bond-forming capacity of the urea unit[5] on the other hand might help in rendering the urea compounds more water soluble than the natural peptide. Moreover, an appropriately placed hydrogen-bonding unit may cause additional affinity in interaction with a receptor.

The only examples of solid-phase synthesis of oligourea peptidomimetics in the literature have been described by the groups of Burgess and Schultz.[1][2] Burgess et al. were the first to describe a solid-phase synthesis of oligourea peptidomimetics, employing phthalimide-protected isocyanates as monomers.[1] The phthalimido group, since it has to be removed under relatively harsh conditions (60% $N_2H_4 \cdot H_2O$ in DMF), is generally considered a less suitable α-amino protective group.

Schultz et al. have developed an elegant procedure in which azido 4-nitrophenyl carbamate monomers are used for the solid-phase synthesis of oligoureas.[2] In their procedure the final product is cleaved off as a urea instead of the *C*-terminal carboxylic acid or amide.

We set out to develop a procedure for the synthesis of oligourea peptidomimetics using more usual protective groups, instead of the phthalimido and azido groups (vide supra), which could be easily implemented on commercial peptide or robot synthesizers. Moreover, we were interested in the preparation of the *C*-terminal free acids, since a carboxyl terminus is often essential for the biological activity of peptides and peptidomimetics.[6]

In this paper we describe a procedure for the solid-phase synthesis of oligourea peptidomimetics on Tentagel without and with a photocleavable linker starting from Boc-protected monomers. These monomers were prepared as Boc-protected activated 4-nitrophenyl carbamate derivatives, which were converted in situ into the isocyanates in the coupling step.[2][4] In a versatile method, the immobilized oligourea peptidomimetic was converted into either a linear urea with a *C*-terminal free acid or a hydantoin by tuning of the cleavage conditions.[7]

Results and Discussion

Preparation of the Monomers

The monomers required for the solid-phase synthesis of oligourea peptidomimetics could be prepared in a straightforward manner analogous to the preparation of monomers required for the synthesis of oligo ureapeptoids[4] (Scheme 1). First, the Boc-protected amino acid **1** was converted into the C-terminal amide **2**.[8] The amide was then converted into the corresponding nitrile **3**[9] followed by its reduction to amine **4** . The benzylic side-chain protecting groups remained intact under the applied conditions. Crude amine **4** was converted directly into active carbamate **5** with

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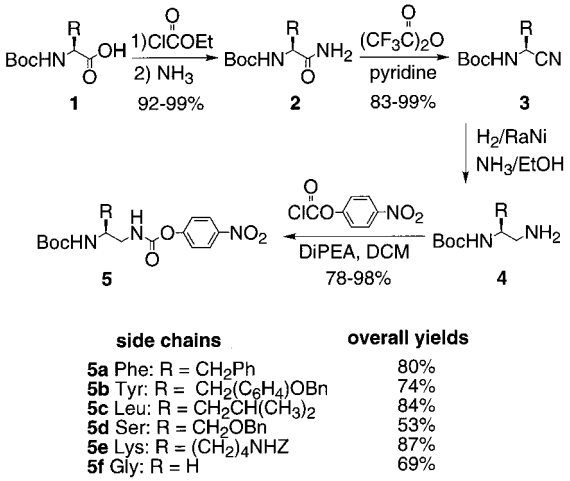
4-nitrophenyl chloroformate using diisopropylethylamine (DiPEA) as a base. The 4-nitrophenyl carbamates often crystallized from the reaction mixtures and could simply be isolated by filtration. All reactions proceeded in high yields and the end products were stable white to yellowish-white solids.



side chains	overall yields
5a Phe: R = CH_2Ph	80%
5b Tyr: R = $CH_2(C_6H_4)OBn$	74%
5c Leu: R = $CH_2CH(CH_3)_2$	84%
5d Ser: R = CH_2OBn	53%
5e Lys: R = $(CH_2)_4NHZ$	87%
5f Gly: R = H	69%

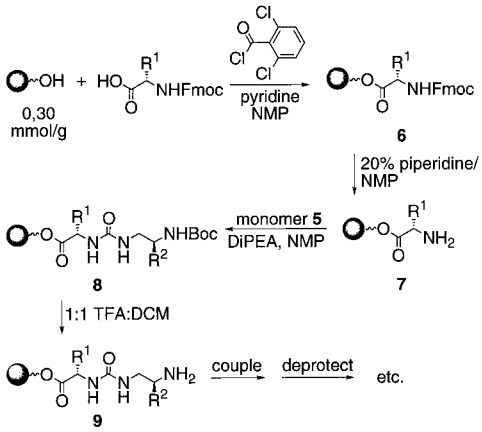
Scheme 1. Synthesis of monomers **5** required for the preparation of oligourea peptidomimetics

The only activated monomer which was prepared via a slightly different route was glycine derivative **5f**. The corresponding amine **4f** was prepared directly by mono-Boc-protection of ethylenediamine.

Solid-Phase Synthesis of the Oligomers

The original approach for the solid-phase synthesis of the urea oligomers involved the use of Tentagel® S−OH, without any additional linkers (Scheme 2). Since we were interested in the synthesis of urea compounds which still contained a free carboxyl terminus, first an Fmoc-protected amino acid was esterified to Tentagel® S−OH according to Sieber,[10] to give resin **6**. The Fmoc group was removed,[11] and the liberated amino functionality of resin-bound amino acid **7** was treated with a solution of three equivalents of a monomer **5** and 3.5 equivalents of DiPEA in NMP.[12] Coupling was complete in three hours, as was verified by the Kaiser test.[13] After removal of the Boc group in immobilized urea **8** followed by neutralization, resin-bound amine **9** was ready for the next coupling cycle.

Using the procedure described above, in principle any desired urea oligomer can be assembled on the resin. Here, the urea derivative of Leu enkephaline (YGGFL) was used as a model compound. A series of resin-bound YGGFL-derived urea oligomers (dimer **10**, trimer **11**, tetramer **12** and pentamer **13**) were prepared by subsequent coupling of leucine, activated phenylalanine monomer **5a**, activated glycine monomer **5f** (twice) and activated tyrosine monomer **5b** to Tentagel S−OH (Figure 2).



Scheme 2. Outline of the solid-phase synthesis of oligourea peptidomimetics

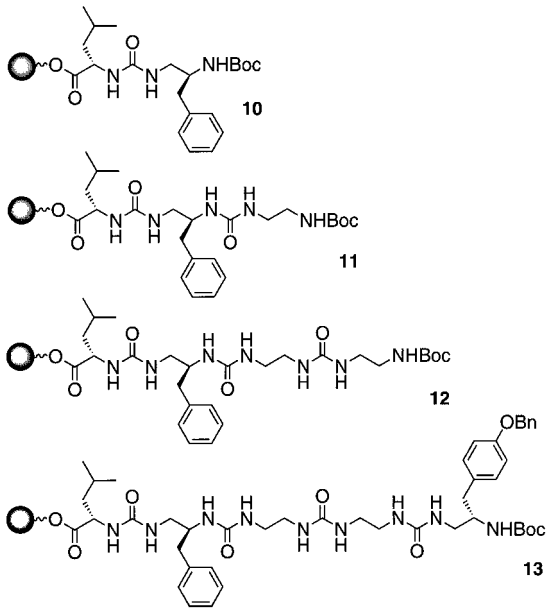
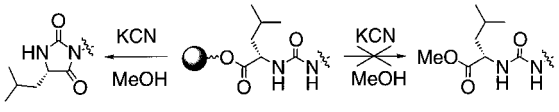


Figure 2. Structure of the resin-bound YGGFL-derived oligourea peptidomimetics

Cleavage from the Resin

At first, cleavage of the oligourea peptidomimetics from the Tentagel resin seemed to be a rather straightforward reaction. It was expected that transesterification in basic methanol would give the desired methyl esters of the urea compounds in high yields. However, NMR analysis showed the absence of a methyl signal, indicating that instead of the linear methyl esters, hydantoins were formed exclusively.[14] This was confirmed by mass spectrometry. Apparently, instead of just attacking the ester carbonyl, the base also abstracted a proton from the urea N−H, ultimately leading to the five-membered hydantoin ring structure (Scheme 3).



Scheme 3. Cleavage of oligourea peptidomimetics with TEA/KCN/MeOH; formation of the methyl ester versus formation of the hydantoin

Using the described conditions, resin-bound oligourea peptidomimetics **10**−**13** were cleaved off as the corresponding hydantoins **14**−**17** (Figure 3). Thus, serendipitously, a mild procedure for the formation of hydantoins was found, which was used to our advantage for the preparation of libraries of substituted hydantoins.[7]

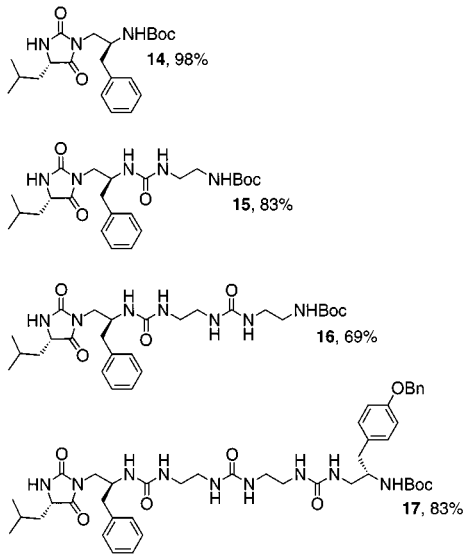
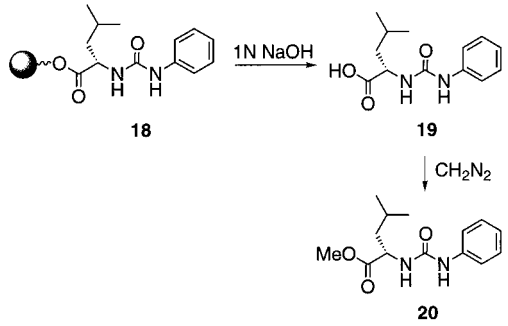


Figure 3. Structure and yields of the hydantoin products

In order to enable synthesis of the linear compounds, the conditions for cleavage from the resin had to be adjusted. For cleavage of the linear oligourea peptidomimetics the use of OH^- as a nucleophile was attempted. Once the carboxylate is formed by attack of OH^- on the ester carbonyl, it will no longer be susceptible to cyclization to the hydantoin. Cleavage of the model compound **18** with 1 N NaOH indeed resulted in predominant formation of the urea **19** (Scheme 4). This was confirmed by successful esterification of the carboxylic acid with diazomethane to the ester **20**.



Scheme 4. Cleavage of compound **18** as the linear free acid with NaOH and subsequent methylation of **19**

Encouraged by this result, we proceeded with the cleavage of the somewhat larger urea dimer **10** from the resin under the same conditions. In this case, the linear product was strongly contaminated with the corresponding hydantoin in an almost 1:1 ratio. Cleavage of the trimer **11** resulted in formation of even larger amounts of the hydantoin. It seemed that more of the hydantoin was formed as the chain length of the urea compound increased.

It was decided to change the alkali metal counterion, which should give rise to a more "naked" and therefore more nucleophilic OH^- ion in aqueous solution. This should result in a fast attack on the ester carbonyl and therefore result in a favourable shift of the product ratio towards formation of the linear urea. Once the urea carboxylate is formed, it should no longer be susceptible to formation of the hydantoin ring.

Aliquots of resin loaded with urea dimer **10** were treated with 1 N solutions of OH^- with different counterions. As shown in Table 1, no clear trend in the yields of free acid was observed in going from Li^+ to Cs^+. However, the use of LiOH, KOH or CsOH did lead to increasing formation of the desired acid. Even better results were obtained using tetramethylammonium and tetrabutylammonium hydroxide, which gave almost exclusive formation of the linear product in the case of dimer **10**.

Table 1. Ratio of carboxylic acid versus hydantoin by treatment of **10** with MOH

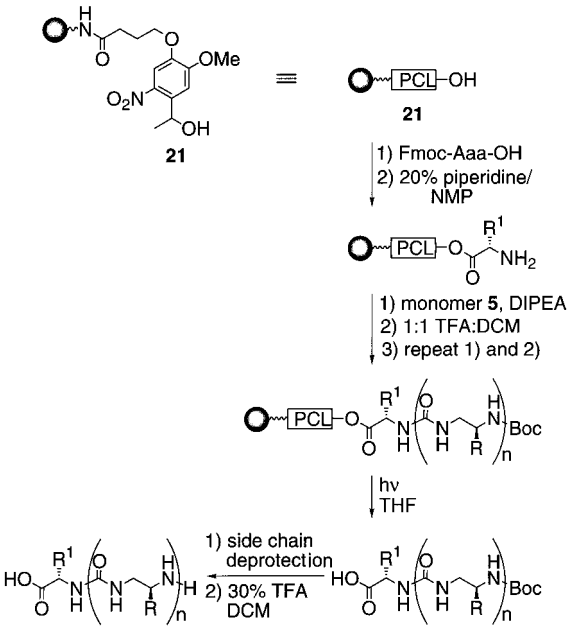
Alkali metal counterion M	Ratio acid/hydantion Acid	Hydantoin
Li^+	80	20
Na^+	55	45
K^+	80	20
Cs^+	75	25
Me_4N^+	95	5
Bu_4N^+	>98	<2

Unfortunately, treatment of resin loaded with the urea derivatives of the YGGFL C-terminal tri-, tetra- and pentapeptide **11**, **12**, and **13** with tetramethylammonium hydroxide again resulted in at least partial formation of the corresponding hydantoins. Change in reaction conditions did not lead to significant improvement. Finally, the use of methylamine as an alternative base also was not succesful.

Photocleavable Linker

The results described above show that a linker apparently has to be incorporated between the resin and the desired oligourea peptidomimetic, which allows liberation of the linear product under very mild conditions. It was clear that cleavage from the resin-bound linker should take place under neutral conditions, as basic reaction conditions resulted in, at least partial, formation of the cyclic products (vide supra), and formation of hydantoins under acidic ester hydrolysis conditions was reported by the group of Hobbs DeWitt in 1993.[15] Moreover, an acid-labile linker cannot be employed in a solid-phase strategy using the Boc group.[16] Therefore, a photocleavable linker was used (e.g. as in **21**, Scheme 5)[17][18] for the preparation of the resin-bound ureas employing the coupling procedures which were described above (Scheme 5).

After completion of the synthesis, irradiation at 366 nm of an aliquot of photolinker resin loaded with dimer **22** showed that cleavage was complete after 24 hours. Removal

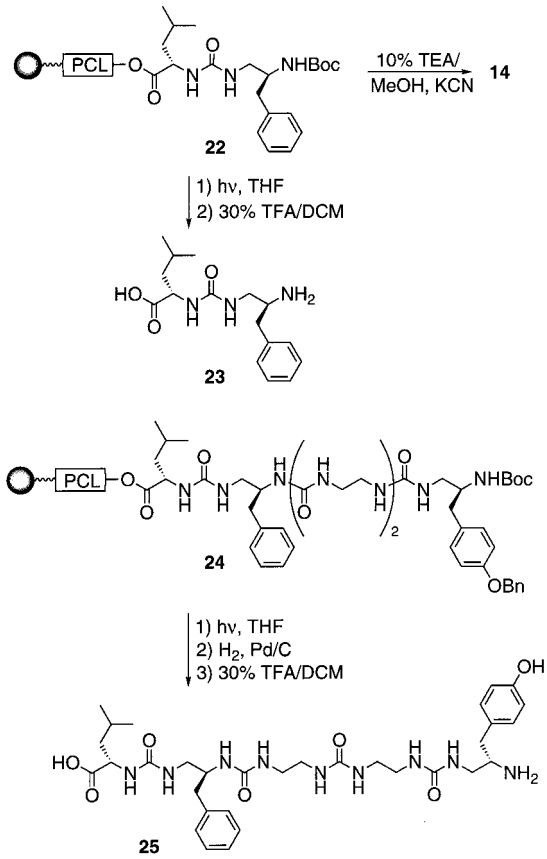


Scheme 5. Synthesis of linear oligourea peptidomimetics using photocleavable linker **21**; general procedure

of the Boc group gave unprotected linear urea **23** in 80% yield after purification (Scheme 6).

After succesful preparation of the linear dimer, we proceeded with the cleavage of resin-bound pentamer **24**. After photolytic cleavage, deprotection and purification, pure product **25** was obtained in 40% yield (Scheme 6).

As expected, cleavage of the urea dimer from photolinker resin **22** under basic conditions resulted in the formation of the corresponding hydantoin **14** (Scheme 6).



Scheme 6. Synthesis of linear oligourea peptidomimetics **23** and **25**

Conclusions

We have developed a procedure for the solid-phase synthesis of oligourea peptidomimetics as the *C*-terminal free acids starting from Boc-protected monomers. The monomers are prepared and stored as the stable, crystalline Boc-protected activated *p*-nitrophenyl carbamate derivatives, which are converted in situ into the isocyanates in the coupling step. The use of standard protective group chemistry has the advantage that the urea monomers can be incorporated simply into peptides or peptidomimetics, even using automated procedures, with minimum adjustment of the protocols and reagents needed for the coupling and deprotection.

Cleavage of the linear oligomers from the resin took a considerable amount of effort. Instead of the linear compounds the thermodynamically more stable cyclic hydantoins were formed with great ease under the basic cleavage conditions. A versatile solution to this problem was found by preparing the oligomers on a resin containing a photocleavable linker. Cleavage could thus take place under neutral conditions, resulting in formation of the linear free acids. Finally, it has to be noted that under the appropriate conditions, oligourea peptidomimetics can be cleaved from photolinker resin as the corresponding hydantoins. We have thus developed a procedure which allows for the selective cleavage of oligourea peptidomimetics from the resin as either the linear free acids or the corresponding hydantoins, as desired.

Experimental Section

General Remarks: Unless stated otherwise, chemicals were obtained from commercial sources and used without further purification. Tentagel S−OH was purchased from Rapp Polymere, Tübingen, Germany. Hydroxyethyl Photolinker Novasyn® TG resin **21** was purchased from NovaBiochem, Laüfelfingen, Switzerland. All protected amino acids were purchased from Advanced Chemtech (Belgium). THF, NMP and DCM were purchased from Biosolve, the Netherlands. THF was distilled immediately prior to use from $LiAlH_4$. NMP and DCM were stored on molecular sieves (4 Å). Hexanes had a boiling range of 60−80°C. DiPEA and TEA were distilled from ninhydrin and KOH. Pyridine was distilled from KOH. Column chromatography was perfomed on Merck Kieselgel 60 (40−63 μm). − NMR: Varian G-300 (300.1 and 75.5 MHz, for ^1H and ^{13}C, respectively). For ^1H NMR, $CDCl_3$ as solvent, TMS as internal standard; [D_6]DMSO as solvent, δ_H = 2.50. For ^{13}C NMR, $CDCl_3$ δ_C = 77.0; [D_6]DMSO δ_C = 39.5 . − FAB MS: JEOL MS SX/SX 102A four-sector spectrometer coupled with a HP-9000 data system. − Analytical HPLC: Gilson automated HPLC with Unipoint software, equipped with an analytical reversed-phase column (Alltech Adsorbosphere C8, 5 μm, 250 × 4.6 mm) and a UV detector operating at 220 nm. Elution was effected using an appropriate gradient from 0.1% TFA in water to

0.085% TFA in acetonitrile/water (95:5, v/v), at a flow rate of 1 mL min^{-1}. – Preparative HPLC: Gilson automated HPLC with Unipoint software, equipped with an preparative reversed-phase column (Alltech Adsorbosphere C8, 10 µm, 250 × 22 mm) and a UV detector operating at 220 nm. Elution was effected using an appropriate gradient from 0.1% TFA in water to 0.085% TFA in acetonitrile/water (95:5, v/v), at a flow rate of 11.5 mL min^{-1}. – UV lamp:Vilber Lourmat TFP-35L UV table. – IR: Bio-RAD FTS-25. – Polarimeter: Jasco P-1010.

Amino Acid Amides 2. – General Procedure: A solution of Boc-protected amino acid **1** (10.0 mmol) and TEA (1.55 mL, 11.0 mmol) in THF (6 mL) was cooled to −15°C (ice/salt bath) under a nitrogen atmosphere. A solution of ethyl chloroformate (1.05 mL, 11.0 mmol) in THF (10 mL) was added dropwise. After stirring for 25 min at −15°C, a 25% solution of NH_3 in water (3.75 mL) was added in one portion and stirring was continued for 3 h at 0−5°C. The volatiles were evaporated in vacuo and the pH was adjusted to 2−3 with 1 N $KHSO_4$. The aqueous layer was extracted with EtOAc (2 ×) and the combined organic layers were washed with 1 N $NaHCO_3$ (3 ×), water (1 ×) and brine, and dried (Na_2SO_4). The solvent was removed in vacuo to give the Boc-protected amino acid amide.

Phenylalanine Amide 2a: Yield 2.52 g (9.5 mmol, 95%) white solid; m.p. 144−145°C. – R_f (EtOAc): 0.66. – $[\alpha]_D^{24}$ = + 1.26 (*c* = 1.02, dioxane). – ^{1}H NMR ($CDCl_3$): δ = 1.40 [s, 9 H, C(CH_3)$_3$], 3.06 (d, *J* = 4.1 Hz, 2 H, CH_2C$_6$H$_5$), 4.39 (m, 1 H, C*H*NH), 5.14 (d, *J* = 8.1 Hz, 1 H, NH), 5.68 and 5.96 (s, br., 2 H, NH_2), 7.22−7.33 (m, 5 H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 28.2 [C(*C*H$_3$)$_3$], 38.5 (*C*H$_2$C$_6$H$_5$), 55.5 (CHNH), 80.2 [*C*(CH$_3$)$_3$], 126.9, 128.6, 129.3, 136.7, 157.9 (*C*$_6$H$_5$), 155.4 [*C*(O)OC(CH$_3$)$_3$], 173.9 [*C*(O)NH_2]. – FAB MS: *m/z* = 265.2 [M + H]$^+$.

Tyrosine Amide 2b: Yield 3.65 g (9.9 mmol, 99%) white solid; m.p.171−172°C. – R_f (EtOAc): 0.68. – $[\alpha]_D^{24}$ = + 4.59 (*c* = 0.76, dioxane). – ^{1}H NMR ($CDCl_3$): δ = 1.41 [s, 9 H, C(CH_3)$_3$], 3.00 (d, *J* = 5.9 Hz, 2 H, CH_2Ar), 4.32 (m, 1 H, C*H*NH), 5.03 (s, 2 H, benzyl CH_2), 5.08 (s, br., 1 H, NH), 5.60 and 5.88 (s, br., 2 H, NH_2), 6.91 (d, *J* = 8.4 Hz, 2 H, CH$_2$C$_6$*H*$_4$O), 7.14 (d, *J* = 8.1 Hz, 2 H, CH$_2$C$_6$*H*$_4$O), 7.26−7.48 (m, 9 H, OCH$_2$C$_6$*H*$_5$). – ^{13}C NMR ($CDCl_3$): δ = 28.3 [C(*C*H$_3$)$_3$], 37.6 (CH*C*H$_2$C$_6$H$_4$O), 55.7 (CHNH), 70.1 (O*C*H$_2$C$_6$H$_5$), 80.3 [*C*(CH$_3$)$_3$], 115.2, 127.4, 128.0, 128.6, 128.9, 129.3, 130.4, 137.0 (CH$_2$*C*$_6$H$_4$O, OCH$_2$*C*$_6$H$_5$), 155.4 [*C*(O)OC(CH$_3$)$_3$], 174.0 [*C*(O)NH_2]. – FAB MS: *m/z* = 371.2 [M + H]$^+$.

Leucine Amide 2c: Yield 2.23 g (9.7 mmol, 97%) white solid; m.p. 137−138°C. – R_f (EtOAc): 0.64. – $[\alpha]_D^{24}$ = − 32.7 (*c* = 1.01, dioxane). – ^{1}H NMR ($CDCl_3$): δ = 0.93 [m, 6 H, CH(CH_3)$_2$], 1.43 [s, 9 H, C(CH_3)$_3$], 1.43−1.80 [m, 3 H, C*H*(CH$_3$)$_2$ + CH_2CH(CH$_3$)$_2$], 4.16 (m, 1 H, C*H*NH), 5.03 (d, br., 1 H, CHN*H*), 5.83 and 6.37 (s, br., 2 H, NH_2). – ^{13}C NMR ($CDCl_3$): δ = 21.9 [*C*H(CH$_3$)$_2$], 22.9 [1 × CH(CH_3)$_2$], 24.7 [1 × CH(CH_3)$_2$], 28.3 [C(*C*H$_3$)$_3$], 41.3 [*C*H$_2$CH(CH$_3$)$_2$], 52.6 (CHNH), 80.0 [*C*(CH$_3$)$_3$], 155.8 [*C*(O)OC(CH$_3$)$_3$], 175.6 [*C*(O)NH_2]. – FAB MS: *m/z* = 231.2 [M + H]$^+$.

Serine Amide 2d: Yield 2.91 g (9.9 mmol, 99%) white solid; m.p. 96−97°C. – R_f (EtOAc): 0.63. – $[\alpha]_D^{24}$ = + 29.4 (*c* = 1.01, dioxane). – ^{1}H NMR ($CDCl_3$): δ = 1.44 [s, 9 H, C(CH_3)$_3$], 3.56−3.89 (m, br., 2 H, CHCH_2O), 4.31 (m, 1 H, C*H*NH), 4.54 (dd, 2 H, CH_2C$_6$H$_5$), 5.46 (d, *J* = 7.4 Hz, 1 H, NH), 6.16 and 6.52 (s, br., 2 H, NH_2), 7.27−7.37 (m, 5 H, CH$_2$C$_6$*H*$_5$). – ^{13}C NMR ($CDCl_3$): δ = 28.2 [C(*C*H$_3$)$_3$], 53.6 (CHNH), 69.8 (CH*C*H$_2$), 73.4 (*C*H$_2$C$_6$H$_5$), 80.3 [*C*(CH$_3$)$_3$], 127.8, 128.0, 128.5, 137.4 (CH$_2$*C*$_6$H$_5$), 155.5 [*C*(O)OC(CH$_3$)$_3$], 172.3 [*C*(O)NH_2]. – FAB MS: *m/z* = 295.1 [M + H]$^+$.

Lysine Amide 2e: Yield 3.49 g (9.2 mmol, 92%) white solid; m.p.137−138°C. – R_f (EtOAc): 0.49. – $[\alpha]_D^{24}$ = − 6.99 (*c* = 0.99, dioxane). – ^{1}H NMR ($CDCl_3$): δ = 1.43 [s, 9 H, C(CH_3)$_3$], 1.50−1.84 [m, br., 6 H, CHCH$_2$(CH_2)$_3$], 3.19 (m, br., 2 H, CHCH_2), 4.11 (m, 1 H, C*H*NH), 5.01 [s, 1 H, C$_6$H$_5$CH$_2$O-C(O)N*H*], 5.09 (s, 2 H, CH_2C$_6$H$_5$), 5.30 (s, br., 1 H, CHN*H*), 5.75 and 6.29 (s, br., 2 H, NH_2), 7.27−7.36 (m, 5 H, C$_6$*H*$_5$). – ^{13}C NMR ($CDCl_3$): δ = 22.4 (CH_2), 28.3 [C(*C*H$_3$)$_3$], 29.4 (CH_2), 31.8 (CH_2), 40.3 (CH_2), 53.8 (CHNH), 66.6 (*C*H$_2$C$_6$H$_5$), 80.0 [*C*(CH$_3$)$_3$], 128.1, 128.5, 136.6 (*C*$_6$H$_5$), 155.8 [*C*(O)OC(CH$_3$)$_3$], 156.6 [*C*(O)-OCH$_2$C$_6$H$_5$], 174.8 [*C*(O)−NH_2]. – FAB MS: *m/z* = 380.2 [M + H]$^+$.

Amino Acid Nitriles 3. – General Procedure: Under a nitrogen atmosphere, a solution of amino acid amide **2** (5.0 mmol) in pyridine (6 mL) was cooled to 0°C (ice bath) and trifluoroacetic anhydride (1.5 mL, 7.3 mmol) was added dropwise. After stirring for 2.5 h, the solvent was removed in vacuo. The residue was dissolved in EtOAc and the organic layer was washed with 1 N $KHSO_4$, water and brine, and dried (Na_2SO_4). After evaporation of the solvent, the crude product was purified by column chromatography.

Phenylalanine Nitrile 3a: 1.14 g (4.6 mmol, 93%) white solid was obtained from **2a** (1.32 g, 5.0 mmol) after column chromatography (silica, 1.5% MeOH/DCM); m.p. 114−115°C. – R_f (hexanes/EtOAc, 4:1): 0.42. – $[\alpha]_D^{25}$ = − 16.4 (*c* = 0.98, dioxane). – ^{1}H NMR ($CDCl_3$): δ = 1.44 [s, 9 H, C(CH_3)$_3$], 3.08 (m, 2 H, CH_2Ph), 4.84 (m, 1 H, C*H*NH), 4.94 (d, *J* = 8.7 Hz, 1 H, NH), 7.27−7.40 (m, 5 H, C$_6$*H*$_5$). – ^{13}C NMR ($CDCl_3$): δ = 28.1 [C(*C*H$_3$)$_3$], 39.1 (*C*H$_2$C$_6$H$_5$), 43.4 (CHNH), 81.2 [*C*(CH$_3$)$_3$], 118.3 (CN), 127.7, 128.9, 129.3, 134.0 (*C*$_6$H$_5$), 154.0 [*C*(O)OC(CH$_3$)$_3$]. – IR: $\tilde{\nu}$ = 2249 cm^{-1} (CN). – FAB MS: *m/z* = 247.1 [M + H]$^+$.

Tyrosine Nitrile 3b: 3.35 g (9.9 mmol, 99%) white solid was obtained from **2b** (3.55 g, 10.0 mmol) after column chromatography (silica, 1% MeOH/DCM); m.p. 126−127°C. – R_f (hexanes/EtOAc, 4:1): 0.33. – $[\alpha]_D^{25}$ = − 4.62 (*c* = 1.03, dioxane). – ^{1}H NMR ($CDCl_3$): δ = 1.45 [s, 9 H, C(CH_3)$_3$], 3.03 (m, 2 H, CHCH_2Ph), 4.79 (m, 1 H, C*H*NH), 5.07 (s, 2 H, OCH_2C$_6$H$_5$), 6.98 (d, *J* = 8.8 Hz, 2 H, CH$_2$C$_6$*H*$_4$O), 7.21 (d, *J* = 8.8 Hz, 2 H, CH$_2$C$_6$*H*$_4$O), 7.34−7.46 (m, 5 H, OCH$_2$C$_6$*H*$_5$). – ^{13}C NMR ($CDCl_3$): δ = 28.2 [C(*C*H$_3$)$_3$], 38.4 (CH*C*H$_2$Ph), 43.7 (CHNH), 70.1 (O*C*H$_2$Ph), 81.3 [*C*(CH$_3$)$_3$], 118.4 (CN), 115.4, 126.2, 127.4, 128.0, 128.6, 130.6, 136.9 (CH$_2$*C*$_6$H$_4$O, OCH$_2$*C*$_6$H$_5$), 158.6 [*C*(O)OC(CH$_3$)$_3$]. – IR: $\tilde{\nu}$ = 2250 cm^{-1} (CN). – FAB MS: *m/z* = 353.2 [M + H]$^+$.

Leucine Nitrile 3c: 2.23 g (8.9 mmol, 89%) white solid was obtained from **2c** (2.31 g, 10.0 mmol) after column chromatography (silica, 1% MeOH/DCM); m.p. 46−47°C. – R_f (hexanes/EtOAc, 4:1): 0.53. – $[\alpha]_D^{25}$ = − 58.9 (*c* = 0.98, dioxane). – ^{1}H NMR ($CDCl_3$): δ = 0.98 [d, 6 H, CH(CH_3)$_2$], 1.47 [s, 9 H, C(CH_3)$_3$], 1.58−1.89 [m, br., 3 H, C*H*(CH$_3$)$_2$ + CH_2CH(CH$_3$)$_2$], 4.60 (m, 1 H, C*H*NH), 4.74 (d, *J* = 8.1 Hz, 1 H, CHN*H*). – ^{13}C NMR ($CDCl_3$): δ = 21.8 [*C*H(CH$_3$)$_2$], 22.1 [1 × CH(CH_3)$_2$], 24.7 [1 × CH(CH_3)$_2$], 28.2 [C(*C*H$_3$)$_3$], 40.9 [*C*H$_2$CH(CH$_3$)$_2$], 42.0 (CHNH), 81.0 [*C*(CH$_3$)$_3$], 119.1 (CN), 154.2 [*C*(O)OC(CH$_3$)$_3$]. – IR: $\tilde{\nu}$ = 2243 cm^{-1} (CN). – FAB MS: *m/z* = 213.2 [M + H]$^+$.

Serine Nitrile 3d: 2.20 g (8.0 mmol, 83%) white solid was obtained from **2d** (2.82 g, 9.6 mmol) after column chromatography (silica, 0.25% MeOH/DCM); m.p. 62−63°C. – R_f (hexanes/EtOAc, 4:1): 0.60. – $[\alpha]_D^{25}$ = − 9.28 (*c* = 1.03, dioxane). – ^{1}H NMR ($CDCl_3$): δ = 1.47 [s, 9 H, C(CH_3)$_3$], 3.62−3.74 (m, br., 2 H, CHCH_2O), 4.62 (s, 2 H, CH_2C$_6$H$_5$), 4.73 (m, 1 H, C*H*NH), 5.36 (d, br., 1 H, NH), 7.27−7.37 (m, 5 H, C$_6$*H*$_5$). – ^{13}C NMR ($CDCl_3$): δ = 28.1 [C(*C*H$_3$)$_3$], 42.5 (CHNH), 68.9 (CH*C*H$_2$) 73.5 (*C*H$_2$C$_6$H$_5$), 81.1 [*C*(CH$_3$)$_3$], 117.5 (CN), 127.8, 128.1, 128.5, 136.7 (*C*$_6$H$_5$), 154.2

[*C*(O)OC(CH$_3$)$_3$]. – IR: $\tilde{\nu}$ = 2247 cm^{-1} (CN). – FAB MS: *m/z* = 277.1 [M + H]$^+$.

Lysine Nitrile 3e: 0.87 g (2.4 mmol, 96%) white solid was obtained from **2e** (0.95 g, 2.5 mmol) after column chromatography (silica, 0.5% MeOH/DCM); m.p. 108–110°C. – R_f (hexanes/EtOAc, 2:1): 0.43. ^{1}H. – $[\alpha]_D^{25}$ = – 25.0 (*c* = 0.99, dioxane). – NMR (CDCl$_3$): δ = 1.45 [s,9 H, C(C*H*$_3$)$_3$], 1.45–1.81 [m, br., 6 H, CHCH$_2$(C*H*$_2$)$_3$], 3.20 (m, br., 2 H, CHC*H*$_2$), 4.49 (m, 1 H, C*H*NH), 5.03 [s, 1 H, C$_6$H$_5$CH$_2$OC(O)N*H*], 5.09 (s, 2 H, C*H*$_2$C$_6$H$_5$), 5.28 (d, br., 1 H, CHN*H*), 7.27–7.35 (m, 5 H, C$_6$*H*$_5$). – ^{13}C NMR (CDCl$_3$): δ = 22.1 (CH$_2$), 28.0 [C(*C*H$_3$)$_3$], 28.9 (CH$_2$), 32.2 (CH$_2$), 40.0 (CH$_2$), 42.0 (CHNH), 66.4 (*C*H$_2$C$_6$H$_5$), 80.7 [*C*(CH$_3$)$_3$], 118.8 (CN), 127.8, 127.8, 128.3, 136.4 (*C*$_6$H$_5$), 154.4 [*C*(O)OC(CH$_3$)$_3$], 156.5 [*C*(O)OCH$_2$C$_6$H$_5$]. – IR: $\tilde{\nu}$ = 2244 cm^{-1} (CN). – FAB MS: *m/z* = 362.2 [M + H]$^+$.

***N*-Boc-Ethylenediamine 4f:** A solution of di-*tert*-butyl dicarbonate (21.8 g, 100 mmol) in dioxane (330 mL) was added dropwise to a solution of ethylenediamine (46.7 mL, 700 mmol) in dioxane (330 mL) over a period of 5 h. After evaporation of the solvent, water (450 mL) was added to the residue, and the insoluble *bis*-substituted product was removed by filtration. The aqueous layer was extracted with DCM (3 × 200 mL), and the combined organic layers were washed with brine and dried (Na$_2$SO$_4$). After evaporation of the solvent, the product was obtained as a slightly yellow oil (14.2 g, 89 mmol, 89% based on di-*tert*-butyl dicarbonate). – ^{1}H NMR (CDCl$_3$): δ = 1.33 [s,9 H, C(C*H*$_3$)$_3$], 1.44 (s, 2 H, NH$_2$), 2.67 (t, *J* = 5.9 Hz, 2 H, C*H*$_2$NH), 3.07 (q, *J* = 5.9 Hz, 2 H, NH$_2$C*H*$_2$), 5.23 (s, br., 1 H, CH$_2$N*H*). – ^{13}C NMR (CDCl$_3$): δ = 28.2 [C(*C*H$_3$)$_3$], 41.6 (CH$_2$NH$_2$), 66.8 (CH$_2$NHBoc), 79.0 [*C*(CH$_3$)$_3$], 156.1 [C(O)OC(CH$_3$)$_3$].

Activated Monomers 5. – General Procedure: Raney nickel (50% slurry in water, 3 g) was washed with absolute ethanol (3 ×), and nitrile **3** (5.0 mmol) and a saturated solution of NH$_3$ in ethanol (50 mL) was added. After hydrogenation in a Parr apparatus under 3 bar pressure for 4 h, the reaction mixture was filtered over Celite and the volatiles were removed in vacuo. Subsequently, crude amine **4** (5.0 mmol) was dissolved in DCM (15 mL) and DiPEA (0.87 mL, 5.0 mmol) was added. Under a nitrogen atmosphere, the resulting solution was added slowly to a cooled (0°C; ice bath) solution of *p*-nitrophenylchloroformate (1.1 g, 5.5 mmol) in DCM (10 mL) and stirring was continued for 1 h. The solvent was evaporated in vacuo and the residue was redissolved in EtOAc. The organic layer was washed with 1 N KHSO$_4$ (2 ×) and dried (Na$_2$SO$_4$). After the solvent was removed in vacuo, the product was crystallized from EtOAc/hexanes. If the reaction product crystallized from the reaction mixture, the mixture was filtered before work up. The residue was washed with hexanes to give a first crop of product. The filtrate was subjected to work up as described above.

Activated Phenylalanine Monomer 5a: The product precipitated during the synthesis. 3.1 g (5.8 mmol, 90% over two steps) white solid was obtained from **3a** (1.60 g, 6.5 mmol); m.p. > 128°C (decomp.). – R_f (hexanes/EtOAc, 2:1): 0.38. – $[\alpha]_D^{23}$ = – 11.1 (*c* = 0.48, dioxane). – ^{1}H NMR (CDCl$_3$): δ = 1.42 [s, 9 H, C(C*H*$_3$)$_3$], 2.80–2.87 (m, 2 H, C*H*$_2$C$_6$H$_5$), 3.26–3.46 (m, 2 H, CH$_2$NH), 4.04 (m, 1 H, C*H*NH), 4.66 (s, br., 1 H, BocNH), 5.76 [s, br. 1 H, N*H*C(O)O*p*–C$_6$H$_4$NO$_2$], 7.20–7.35 (m, 7 H, C$_6$*H*$_5$ + 2 × *p*-C$_6$*H*$_4$NO$_2$), 8.21–8.25 (m, 2 H, 2 × *p*-C$_6$*H*$_4$NO$_2$) – ^{13}C NMR (CDCl$_3$): δ = 28.3 [C(*C*H$_3$)$_3$], 38.9 (*C*H$_2$C$_6$H$_5$), 45.6 (*C*H$_2$NH), 51.9 (*C*HNH), 80.1 [*C*(CH$_3$)$_3$], 121.9, 125.1, 126.9, 128.7, 129.1, 136.9, 144.8, 155.9 (*C*$_6$H$_5$ + *p*-*C*$_6$H$_4$NO$_2$), 155.9 [*C*(O)OC(CH$_3$)$_3$], 156.2 [*C*(O)], 156.3 [*C*(O)]. – FAB MS: *m/z* = 416.2 [M + H]$^+$. – C$_{21}$H$_{25}$N$_3$O$_6$ (415.45) calcd. C 60.71, H 6.07, N 10.11; found C 60.11, H 6.05, N 9.98.

Activated Tyrosine Monomer 5b: The product precipitated during the synthesis. 2.7 g (5.2 mmol, 81% over two steps) white solid was obtained from **3b** (2.27 g, 6.4 mmol); m.p. > 136°C (decomp.). – R_f (hexanes/EtOAc, 2:1): 0.36. – $[\alpha]_D^{23}$ = – 5.2 (*c* = 0.53, dioxane). – ^{1}H NMR (CDCl$_3$): δ = 1.43 [s, 9 H, C(C*H*$_3$)$_3$], 2.71–2.86 (m, 2 H, C*H*$_2$C$_6$H$_4$O), 3.21–3.50 (m, 2 H, C*H*$_2$NH), 3.99 (s, br., 1 H, C*H*NH), 4.66 (s, br., 1 H, BocNH), 5.05 (s, 2 H, C*H*$_2$C$_6$H$_5$), 5.81 [s, br., 1 H, N*H*C(O)O*p*-C$_6$H$_4$NO$_2$], 6.94 (d, *J* = 8.8 Hz, 2 H, CH$_2$C$_6$*H*$_4$O), 7.13 (d, *J* = 8.8 Hz, 2 H, CH$_2$C$_6$*H*$_4$O) 7.27–7.45 (m, 7 H, OCH$_2$C$_6$*H*$_5$ + 2 × *p*-C$_6$*H*$_4$NO$_2$), 8.21–8.26 (m, 2 H, 2 × *p*-C$_6$*H*$_4$NO$_2$). – ^{13}C NMR (CDCl$_3$): δ = 28.3 [C(*C*H$_3$)$_3$], 38.2 (CH$_2$C$_6$H$_4$O), 45.6 (*C*H$_2$NH), 52.0 (*C*HNH), 70.1 (O*C*H$_2$C$_6$H$_5$), 80.1 [*C*(CH$_3$)$_3$], 115.2, 121.9, 125.0, 127.4, 128.0, 128.6, 129.1, 130.2, 137.0, 144.8, 153.6, 157.9 (CH$_2$*C*$_6$H$_4$O, OCH$_2$*C*$_6$H$_5$, *p*-*C*$_6$H$_4$NO$_2$), 156.0 [*C*(O)]. – FAB MS: *m/z* = 522.2 [M + H]$^+$. – C$_{28}$H$_{31}$N$_3$O$_6$ (521.57) calcd. C 64.48, H 5.99, N 8.06; found C 64.53, H 5.97, N 8.05.

Activated Leucine Monomer 5c: 1.9 g (4.9 mmol, 89%) white solid was obtained from **3c** (1.3 g, 6.12 mmol); m.p. > 110°C (decomp.). – R_f (hexanes/EtOAc, 2:1): 0.47. – $[\alpha]_D^{23}$ = – 34.0 (*c* = 0.51, dioxane). – ^{1}H NMR (CDCl$_3$): δ = 0.94 [m, 6 H, CH(C*H*$_3$)$_2$], 1.25–1.80 [m, br., 3 H, C*H*(CH$_3$)$_2$ + C*H*$_2$CH(CH$_3$)$_2$], 1.44 [s, 9 H, C(C*H*$_3$)$_3$], 3.16–3.40 (m, 2 H, C*H*$_2$NH), 3.84 (s, br., 1 H, C*H*NH), 4.52 (d, *J* = 7.7 Hz, 1 H, CHN*H*), 5.96 [s, br., 1 H, N*H*C(O)O*p*-C$_6$H$_4$NO$_2$], 7.27–7.33 (m, 2 H, 2 × *p*-C$_6$*H*$_4$NO$_2$), 8.20–8.25 (m, 2 H, 2 × *p*-C$_6$*H*$_4$NO$_2$). – ^{13}C NMR (CDCl$_3$): δ = 22.0 [*C*H(CH$_3$)$_2$], 23.0 [1 × CH(*C*H$_3$)$_2$], 24.8 [1 × CH(*C*H$_3$)$_2$], 28.4 [C(*C*H$_3$)$_3$], 41.9 [*C*H$_2$CH(CH$_3$)$_2$], 47.2 (CH$_2$NH), 49.0 (CHNH), 79.9 [*C*(CH$_3$)$_3$], 121.9, 125.1, 144.7, 153.6 (*p*-*C*$_6$H$_4$NO$_2$), 156.1 [*C*(O)], 156.6 [*C*(O)]. – FAB MS: *m/z* = 382.2 [M + H]$^+$. – C$_{18}$H$_{27}$N$_3$O$_6$ (381.43) calcd. C 56.68, H 7.13, N 11.02; found C 56.25, H 7.01, N 10.89.

Activated Serine Monomer 5d: 0.65 g (1.60 mmol, 64%) white solid was obtained from **3d** (0.69 g, 2.5 mmol); m.p. > 120°C (decomp.). – R_f (hexanes/EtOAc, 2:1): 0.48. – $[\alpha]_D^{23}$ = + 2.1 (*c* = 0.53, dioxane). – ^{1}H NMR (CDCl$_3$): δ = 1.45 [s, H, C(C*H*$_3$)$_3$], 3.44–3.61 (m, 4 H, CHC*H*$_2$O + C*H*$_2$NH), 3.97 (m, 1 H, C*H*NH), 4.54 (d, *J* = 1.8 Hz, 2 H, C*H*$_2$C$_6$H$_5$), 5.11 (d, *J* = 8.0 Hz, 1 H, CHN*H*), 5.88 (s, 1 H, CH$_2$N*H*), 7.26–7.39 (m, 7 H, C$_6$*H*$_5$ + 2 × *p*-C$_6$*H*$_4$NO$_2$), 8.20–8.25 (m, 2 H, 2 × *p*-C$_6$*H*$_4$NO$_2$). – ^{13}C NMR (CDCl$_3$): δ = 28.2 [C(*C*H$_3$)$_3$], 44.1 (CH*C*H$_2$O), 50.0 (CHNH), 70.3 (O*C*H$_2$C$_6$H$_5$), 73.5 (CH$_2$NH), 80.0 [*C*(CH$_3$)$_3$], 121.9, 125.1, 127.8, 128.0, 128.6, 137.5, 144.8, 153.7 (*C*$_6$H$_5$, *p*-*C*$_6$H$_4$NO$_2$), 156.1 [*C*(O)]. – FAB MS: *m/z* = 446.2 [M + H]$^+$. – C$_{22}$H$_{27}$N$_3$O$_7$ (445.47) calcd. C 59.32, H 6.11, N 9.43; found C 59.17, H 6.23, N 9.09.

Activated Lysine Monomer 5e: 1.1 g (2.0 mmol, 98% over two steps) white solid was obtained from **2e** (0.75 g, 2.1 mmol); m.p. > 103°C (decomp.). – (hexanes/EtOAc, 1:1): 0.46. – $[\alpha]_D^{23}$ = – 17.6 (*c* = 0.52, dioxane). – ^{1}H NMR (CDCl$_3$): δ = 1.44 [s, H, C(C*H*$_3$)$_3$], 3.18–3.40 [m, 4 H, CHC*H*$_2$(CH$_2$)$_3$ + C*H*$_2$NH], 3.74 (m, 1 H, C*H*NH), 4.74 (d, 1 H, *J* = 8.0 Hz, NH), 4.86 (s, 1 H, NH), 5.10 (s, 1 H, C*H*$_2$C$_6$H$_5$), 5.95 (s, 1 H, CH$_2$N*H*), 7.26–7.36 (m, 7 H, C$_6$*H*$_5$ + 2 × *p*-C$_6$*H*$_4$NO$_2$), 8.20–8.24 (m, 2 H, 2 × *p*-C$_6$*H*$_4$NO$_2$). – ^{13}C NMR (CDCl$_3$): δ = 28.3 [C(*C*H$_3$)$_3$], 44.2 (CH*C*H$_2$O), 50.1 (CHNH), 70.3 (O*C*H$_2$C$_6$H$_5$), 73.6 (CH$_2$NH), 80.2 [*C*(CH$_3$)$_3$], 115.6, 121.9, 125.1, 127.7, 128.6, 137.4, 144.8 (*C*$_6$H$_5$, *p*-*C*$_6$H$_4$NO$_2$), 153.6 [*C*(O)], 155.6 [*C*(O)]. – FAB MS: *m/z* = 531.2 [M + H]$^+$. – C$_{26}$H$_{34}$N$_4$O$_8$ (530.58) calcd. C 58.86, H 6.46, N 10.56; found C 58.17, H 6.45, N 10.28.

Activated Glycine Monomer 5f: The product precipitated during the synthesis. 1.3 g (4.0 mmol, 78%) white solid was obtained from **4f**

(0.81 g, 5.1 mmol); m.p. > 133°C (decomp.) − (hexanes/EtOAc, 1:1): 0.48. − ^{1}H NMR ([D$_6$]DMSO): δ = 1.38 [s, H, C(CH$_3$)$_3$], 3.00−3.20 [m, 4 H, C*H*$_2$NHC(O)O*p*-C$_6$H$_4$NO$_2$ + BocNHC*H*$_2$], 6.87 (m, 1 H, N*H*Boc) 7.37−7.41 (m, 2 H, 2 × *p*-C$_6$*H*$_4$NO$_2$), 8.00 (m, 1 H, N*H*C(O)O*p*-C$_6$H$_4$NO$_2$], 8.23−8.27 (2 × *p*-C$_6$*H*$_4$NO$_2$). − ^{13}C NMR ([D$_6$]DMSO): δ = 28.2 [C(*C*H$_3$)$_3$], 77.7 [*C*(CH$_3$)$_3$], 122.3, 125.1, 144.8, 153.1 (*p*-*C*$_6$H$_4$NO$_2$), 155.6 [*C*(O)], 156.3 [*C*(O)]. − FAB MS: *m/z* = 326.1 [M + H]$^+$. − C$_{14}$H$_{19}$N$_3$O$_6$ (325.13) calcd. C 51.69, H 5.89, N 12.92; found C 51.25, H 5.76, N 12.62.

Coupling of Resin with Fmoc-Leu-OH. − General Procedure: Tentagel S−OH (0.36 mmol/g) or photolinker resin **21** (0.23 mmol/g) were coupled with Fmoc-Leu-OH using the procedure of Sieber.[10] The loading was determined by Fmoc cleavage from a resin sample, and was generally 0.28 mmol/g for Tentagel S−OH and 0.20 mmol/g for photolinker resin **21**. The resin was treated for 15 min with 5 mL of a capping solution (a solution of acetic anhydride (0.5 M), DiPEA (0.125 M), HOBt (0.015 M) and a catalytic amount of DMAP in NMP) per g resin to acetylate the remaining hydroxyl functions. Agitation was effected by nitrogen bubbling. The resin was filtered, washed with NMP (3 ×) and DCM (3 ×), and dried.

Preparation of Resin-Bound Urea Derivatives Of YGGFL 10−13. − General Procedure: Tentagel S−OH esterified with Fmoc-Leu-OH (1 g, 0.28 mmol/g), or photolinker resin **21** esterified with Fmoc-Leu-OH (1 g, 0.20 mmol/g), was washed with NMP (3 ×) and treated with a solution of 20% piperidine in NMP (5 mL). After 20 min the solvent was removed by filtration and the resin was washed with NMP (5 ×). Subsequently, a solution of activated phenylalanine monomer **5a** (3 equiv.) and DiPEA (3.5 equiv.) in NMP (5 mL) was added. After 3 h, the solution was drained and the resin was washed with NMP (3 ×) and DCM (3 ×). Synthesis of resin-bound dimer **10** was now complete. For synthesis of trimer **11**, the Boc-groups were removed by treatment with a 1:1 TFA:DCM mixture (10 mL) for 30 min. The resin was washed with DCM (3 ×), 10% TEA/DCM (3 ×), DCM (3 ×) and NMP (3 ×), and subjected to a coupling cycle with activated glycine monomer **5f**. Resin-bound tetramer **12** and pentamer **13** were prepared by similar deprotection and coupling cycles with subsequently activated glycine monomer **5f** and tyrosine monomer **5b**.

Hydantoins 14−17: Oligourea peptidomimetics **10−13** were cleaved from Tentagel S−OH as the corresponding hydantoins by shaking of the resin (250 mg, 0.28 mmol/g) with 10% TEA/MeOH (2 mL) and a catalytic amount of KCN for 16 h. The solution was removed by filtration and the resin was washed with MeOH (3 ×). The filtrate was evaporated and each product was purified by column chromatography.

Dimer Hydantoin 14: Yield 26.7 mg (0.069 mmol, 98%) white solid after column chromatography (silica, EtOAc/hexanes, 2:3). R_f (10% MeOH/DCM): 0.68. − ^{1}H NMR ([D$_6$]DMSO): δ = 0.84 [m, 6 H, CH(C*H*$_3$)$_2$], 1.25 [s, 9 H, C(C*H*$_3$)$_3$], 1.20−1.45 [m, 2 H, C*H*$_2$CH(CH$_3$)$_2$], 1.71−1.77 [m, 1 H, C*H*(CH$_3$)$_2$], 2.64−2.70 (m, 2 H, C*H*$_2$C$_6$H$_5$), 3.30−3.38 (m, 2 H, NC*H*$_2$CH), 3.88−3.94 (m, 2 H, ring C*H* + NCH$_2$C*H*), 6.63−6.68 (m, 1 H, N*H*), 6.18 (s, br., 1 H, ring N*H*), 7.12−7.26 (m, 5 H, C$_6$*H*$_5$), 8.22 (d, *J* = 3.3 Hz, 1 H, N*H*). − ^{13}C NMR ([D$_6$]DMSO): δ = 21.2 [*C*H(CH$_3$)$_2$, 2×, diast.], 23.0 [1 × CH(C*H*$_3$)$_2$], 24.0 [1 × CH(C*H*$_3$)$_2$], 28.1 [C(*C*H$_3$)$_3$], 37.5, 37.6 (*C*H$_2$, 2×, diast.) 40.6 (*C*H$_2$), 42.1, 42.4 (*C*H$_2$, 2×, diast.), 49.6, 49.9 (NCH$_2$*C*H, 2×, diast.), 54.6, 54.7 (ring *C*H, 2×, diast.), 77.4 [*C*(CH$_3$)$_3$], 126.1, 128.2, 129.1, 138.7 (*C*$_6$H$_5$), 155.4 [*C*(O)-OC(CH$_3$)$_3$, 2×, diast.], 156.9, 157.0 [ring *C*(O), 2×, diast.], 174.9 [ring *C*(O), 2×, diast.]. − FAB MS: *m/z* = 390.2 [M + H]$^+$. − HPLC: >99% pure.

Trimer Hydantoin 15: Yield 27.7 mg (0.058 mmol, 83%) white solid after column chromatography (silica, EtOAc). R_f (10% MeOH/DCM): 0.45. − ^{1}H NMR ([D$_6$]DMSO): δ = 0.85 [m, 6 H, CH(C*H*$_3$)$_2$], 1.28−1.46 [m, 11 H, C(C*H*$_3$)$_3$ + C*H*$_2$CH(CH$_3$)$_2$], 1.72−1.78 [m, 1 H, C*H*(CH$_3$)$_2$], 2.63−2.70 (m, 2 H, C*H*$_2$C$_6$H$_5$), 2.86−2.96 (m, 4 H, C*H*$_2$C*H*$_2$), 3.28−3.38 (m, 2 H, NC*H*$_2$CH), 3.83−3.95 (m, 1 H, NCH$_2$C*H*), 4.05−4.17 (m, 1 H, ring C*H*), 5.68−5.82 (m, 3 H, NH), 6.60−6.64 (m, 1 H, N*H*), 7.16−7.25 (m, 5 H, C$_6$*H*$_5$), 8.18−8.22 (m, 1 H, NH). − ^{13}C NMR ([D$_6$]DMSO): δ = 21.3 [*C*H(CH$_3$)$_2$, 2×, diast.], 23.1 [1 × CH(C*H*$_3$)$_2$], 24.0 [1 × CH(C*H*$_3$)$_2$], 28.5 [C(*C*H$_3$)$_3$], 38.5 (*C*H$_2$), 40.4 (*C*H$_2$), 40.6 (*C*H$_2$), 42.2 (*C*H$_2$), 48.6 (NCH$_2$*C*H), 54.6, 54.7 (ring *C*H, 2×, diast.), 77.6 [*C*(CH$_3$)$_3$], 126.2, 128.2, 129.2, 138.5 (*C*$_6$H$_5$), 155.4 [*C*(O)-OC(CH$_3$)$_3$, 2×, diast.], 157.0, 157.1 [ring *C*(O), 2×, diast.], 157.7, 157.8 [urea *C*(O), 2×, diast.], 174.9, 175.0 [ring *C*(O), 2×, diast.]. − FAB MS: *m/z* = 476.2 [M + H]$^+$. − HPLC: >99% pure.

Tetramer Hydantoin 16: Yield 24.0 mg (0.043 mmol, 69%) white solid after column chromatography (silica, 8% MeOH/DCM). R_f (10% MeOH/DCM): 0.35. − ^{1}H NMR ([D$_6$]DMSO): δ = 0.84 [m, 6 H, CH(C*H*$_3$)$_2$], 1.20−1.50 [m, 11 H, C(C*H*$_3$)$_3$ + C*H*$_2$CH(CH$_3$)$_2$], 1.65−1.78 [m, 1 H, C*H*(CH$_3$)$_2$], 2.60−2.75 (m, 2 H, C*H*$_2$C$_6$H$_5$), 2.83−3.05 (m, 8 H, 2 × C*H*$_2$C*H*$_2$), 3.25−3.38 (m, 2 H, NC*H*$_2$CH), 3.84−3.98 (m, 1 H, NCH$_2$C*H*), 4.05−4.18 (m, 1 H, ring C*H*), 5.62−5.97 (m, 4 H, urea NH), 6.70−6.80 (m, 1 H, NH), 7.13−7.27 (m, 5 H, C$_6$*H*$_5$), 8.20 (br. s, 1 H, N*H*). − ^{13}C NMR ([D$_6$]DMSO): δ = 21.3 [*C*H(CH$_3$)$_2$, 2×, diast.], 23.0 [1 × CH(C*H*$_3$)$_2$], 24.0 [1 × CH(C*H*$_3$)$_2$], 28.1 [C(*C*H$_3$)$_3$], 28.5 (*C*H$_2$), 38.4 (*C*H$_2$), 40.5 (*C*H$_2$), 40.7 (*C*H$_2$), 42.1 (*C*H$_2$), 48.6 (NCH$_2$*C*H), 54.6, 54.7 (ring *C*H, 2×, diast.), 77.5 [*C*(CH$_3$)$_3$], 126.1, 128.2, 129.2, 138.5 (*C*$_6$H$_5$), 155.8 [urea *C*(O)], 156.9, 157.0 [*C*(O)OC(CH$_3$)$_3$, 2×, diast.], 157.8 [urea *C*(O)], 158.3 [urea *C*(O)], 174.9, 175.0 [ring *C*(O), 2×, diast.]. − FAB MS: *m/z* = 562.2 [M + H]$^+$. − HPLC: >99% pure.

Pentamer Hydantoin 17: Yield 17.6 mg (0.021 mmol, 83%) white solid after column chromatography (silica, 8% MeOH/DCM) starting from 90 mg resin. − R_f (10% MeOH/DCM): 0.36. − ^{1}H NMR ([D$_6$]DMSO): δ = 0.85 [m, 6 H, CH(C*H*$_3$)$_2$], 1.20−1.50 [m, 11 H, C(C*H*$_3$)$_3$ + C*H*$_2$CH(CH$_3$)$_2$], 1.65−1.78 [m, 1 H, C*H*(CH$_3$)$_2$], 2.45−2.75 (m, 2 H, CHC*H*$_2$C$_6$H$_5$ + C*H*$_2$C$_6$H$_4$O), 2.83−3.05 (m, 10 H, 2 × C*H*$_2$C*H*$_2$ + C*H*$_2$CHNHBoc), 3.25−3.38 (m, 2 H, NC*H*$_2$CHCH$_2$C$_6$H$_5$), 3.42−3.58 (m, 1 H, C*H*CH$_2$C$_6$H$_4$O), 3.84−3.98 (m, 1 H, NCH$_2$C*H*CH$_2$C$_6$H$_5$), 4.03−4.18 (m, 1 H, ring C*H*), 4.51 (s, 1 H, NH), 5.03 (s, 2 H, benzyl C*H*$_2$), 5.65−6.10 (m, 5 H, urea NH), 6.60−6.70 (m, 1 H, NH), 6.88 (d, *J* = 8.4 Hz, 2 H, C$_6$*H*$_4$O), 7.07 (d, *J* = 8.4 Hz, 2 H, C$_6$*H*$_4$O), 7.13−7.42 (m, 5 H, CHCH$_2$C$_6$*H*$_5$ + C$_6$*H*$_4$O), 8.22 (d, *J* = 4.3 Hz, 1 H, N*H*). − ^{13}C NMR ([D$_6$]DMSO): δ = 21.3 [*C*H(CH$_3$)$_2$], 23.1 [1 × CH(C*H*$_3$)$_2$], 24.0 [1 × CH(C*H*$_3$)$_2$], 28.2 [C(*C*H$_3$)$_3$], 28.5 (*C*H$_2$), 37.0 (*C*H$_2$), 38.5 (*C*H$_2$), 40.6 (*C*H$_2$), 42.2 (*C*H$_2$), 42.6 (*C*H$_2$), 48.7 (NCH$_2$*C*HCH$_2$C$_6$H$_5$), 52.7 (CHCH$_2$NHBoc), 54.6, 54.7 (ring *C*H, 2×, diast.), 69.2 (benzyl *C*H$_2$), 77.5 [*C*(CH$_3$)$_3$], 114.5, 126.1, 127.7, 127.8, 128.2, 128.5, 129.2, 130.2 (Ar *C*H), 131.1, 137.4, 138.6, 155.4 (quat. *C* Ar), 156.9 [*C*(O)], 157.0, 157.1 [*C*(O) 2×, diast.], 157.8, 157.9 [*C*(O) 2×, diast.], 158.4 [*C*(O)], 158.6 [*C*(O)], 174.9, 175.0 [ring *C*(O), 2×, diast.]. − FAB MS: *m/z* = 844.5 [M + H]$^+$. − HPLC: >99% pure.

Model Compound 18: Tentagel S−OH esterified with Fmoc-Leu-OH (1 g, 0.22 mmol/g) was washed with NMP (3 ×) and treated with a solution of 20% piperidine in NMP (5 mL). After 20 min the solvent was removed by filtration and the resin was washed with NMP (5 ×). Subsequently, the resin was treated with a solution of phenylisocyanate (170 μL, 1.32 mmol) and DiPEA (47 μL, 0.22 mmol) in NMP (5 mL) for 3 h. Finally, the solution was

drained and the resin was washed with NMP (3 ×) and DCM (3 ×) to give resin-bound urea **18**.

Cleavage of Linear Urea 19 from the Resin with Sodium Hydroxide: Resin **18** (1 g) was shaken with 1 N NaOH (20 mL) for 3 h. The resin was filtered and washed with water (3 ×). The filtrate was acidified to pH = 2−3 with 1 N HCl and extracted with EtOAc (3 ×). The combined organic layers were washed with brine, dried (Na_2SO_4) and the solvent was removed in vacuo to give the product as a white solid (54 mg, 0.22 mmol, 99% calculated as the free acid). − 1H NMR (CD_3CN): δ = 1.00 [t, *J* = 6.0 Hz, 6 H, $CH(CH_3)_2$], 1.62−1.84 [m, 3 H, $CH(CH_3)_2$ + $CH_2CH(CH_3)_2$], 4.35 [m, 1 H, C(O)CHNH], 5.64 (d, *J* = 6.9 Hz, 1 H, NH), 7.04 (m, 1 H, NH), 7.29−7.46 (m, 5 H, C_6H_5). − FAB MS: *m/z* = 251.1 $[M + H]^+$. − For characterization the product was converted into the methyl ester using diazomethane (see below).

Methyl Ester 20: A 0.1 M solution of diazomethane in diethyl ether was added dropwise to a solution of crude product **19** (26 mg, 0.10 mmol) in THF (10 mL) until the solution remained slightly yellow. Excess of diazomethane was allowed to evaporate in the fume hood and the solvent was removed in vacuo. The residue was purified by column chromatography (silica, eluent hexanes/EtOAc, 3:1). This yielded 20.6 mg (0.078 mmol, 78%) of the purified product as a white solid. NMR analysis clearly showed the presence of a methyl signal. − R_f (EtOAc/hexanes, 1:2): 0.47. − ^{1}H NMR ($CDCl_3$): δ = 0.93 [t, *J* = 6.0 Hz, 6 H, $CH(CH_3)_2$], 1.47−1.73 [m, 3 H, $CH(CH_3)_2$] + $CH_2CH(CH_3)_2$], 3.72 (s, 1 H, OMe), 4.57 [m, 1 H, C(O)CHNH], 5.63 (d, *J* = 6.9 Hz, 1 H, NH), 7.06 (m, 1 H, NH), 7.23−7.32 (m, 5 H, C_6H_5) − ^{13}C NMR ($CDCl_3$): δ = 21.8 [$CH(CH_3)_2$], 22.7 [1 × $CH(CH_3)_2$], 24.8 [1 × $CH(CH_3)_2$], 41.7 (CH_2), 51.5 (CH), 52.3 (OMe), 120.8, 123.8, 129.3, 138.6 (C_6H_5), 155.7 [C(O)], 175.2 ester C(O)]. − FAB MS: *m/z* = 265.2 $[M + H]^+$.

Cleavage of Urea Dimer 10 from Tentagel S−OH with Hydroxide Anion and Different Counterions. − HPLC Experiments: Six 100 mg aliquots of resin **10** (0.22 mmol/g) were shaken with one of six 1 N aqueous solutions of the following bases: LiOH, NaOH, KOH, CsOH, Me_4NOH and Bu_4NOH (2 mL) for 3 h. Each aliquot was filtered and washed with water (3 ×). The filtrates were acidified to pH = 2−3 with 1 N HCl and extracted with EtOAc (3 ×). The organic layers were washed with brine and the solvent was removed in vacuo. The residues were redissolved in THF (10 mL) and these solutions were analyzed by HPLC (Table 1). Tetramethyl- and tetrabutylammonium hydroxide gave the best results: 95% and >98% of the linear free acid, respectively.

Cleavage of Oligourea Peptidomimetics 11−13 from Tentagel S−OH with Tetramethylammonium Hydroxide: Oligourea peptidomimetics were cleaved from Tentagel S−OH (250 mg) by treatment with 1 N Me_4NOH (5 mL). After 3 h the solution was removed by filtration and the resin was washed with water (3 ×). The filtrate was acidified to pH = 2−3 with 1 N HCl and extracted with EtOAc (3 ×). The combined organic layers were washed with brine, and dried (Na_2SO_4) and the solvent was removed in vacuo. TLC analysis showed that the hydantoin products had formed in each case, although apparently in different amounts.

Cleavage of Oligourea Peptidomimetics 10−13 from Tentagel S−OH with Methylamine: Oligourea peptidomimetics **10−13** were cleaved from Tentagel S−OH (250 mg) by treatment with 2 M $MeNH_2$ in THF (2 mL) at 0°C. TLC analysis showed the hydantoin products had formed in each case, although in different amounts: for the dimer, the linear product was formed almost exclusively, whereas the pentamer had been cleaved off as the hydantoin.

Linear Urea Dimer 23: To resin **22** (250 mg, 0.19 mmol/g), THF (10 mL) was added. The reaction vessel was evacuated and filled with Argon (3 ×), and suspended above the UV lamp in a shaking device. The set up was covered with aluminium foil and irradiated for 24 h, under continuous shaking. Samples were taken after 10 min, 1, 2, 3, 4, 5, 6, 7, 8, 22, 23 and 24 h, and analyzed by HPLC. Cleavage was complete after 24 h. The resin was filtered and washed with THF (3 ×). The filtrate was evaporated. This yielded 21.1 mg (>100%) of the crude product. The Boc group in 11 mg of the crude product was removed directly with 30% TFA/DCM at 0°C, and the product was purified by preparative HPLC. The pure product **23** was obtained after lyophilisation as a white solid (6.1 mg, 0.0199 mmol, 80%). − ^{1}H NMR ([D_6]DMSO): δ = 0.84 [m, 6 H, $CH(CH_3)_2$], 1.15−1.50 [m, 2 H, $CH_2CH(CH_3)_2$], 1.58−1.74 [m, 1 H, $CH(CH_3)_2$], 2.45−2.49 (m, 2 H, $CH_2C_6H_5$), 2.75−2.85 (m, 2 H, NCH_2CH), 3.17 (m, 1 H, $CHCH_2C_6H_5$), 4.10 (m, 1 H, CHCOOH), 6.32 (m, 2 H, NH), 6.43(d, *J* = 8.4 Hz, 1 H, NH), 7.24−7.36 (m, 5 H, C_6H_5). − ^{13}C NMR ([D_6]DMSO): δ = 21.6 [$CH(CH_3)_2$, 2×, diast.], 22.7 [1 × $CH(CH_3)_2$], 24.2 [1 × $CH(CH_3)_2$], 37.5, 37.6 (CH_2, 2×, diast.) 40.6 (CH_2), 42.1, 42.4 (CH_2, 2×, diast.), 49.6, 49.9 (NCH_2CH, 2×, diast.), 54.6, 54.7 (ring CH, 2×, diast.), 77.4 [$C(CH_3)_3$], 126.1, 128.2, 129.1, 138.7 (C_6H_5), 155.4 [C(O)$OC(CH_3)_3$, 2×, diast.], 156.9, 157.0 [ring C(O), 2×, diast.], 174.9 [ring C(O), 2×, diast.]. − FAB MS: *m/z* = 308.2 $[M+H]^+$. − HPLC: >99% pure.

Linear Urea Pentamer 25: To resin **24** (500 mg, 0.20 mmol/g), THF (10 mL) was added. The reaction vessel was evacuated and filled with Argon (3 ×), and suspended above the UV lamp in a shaking device. The set up was covered with aluminium foil and irradiated for 24 h, under continuous shaking. After 24 h, the resin was filtered and washed with THF (3 ×), and the filtrate was evaporated. The benzyl group in the tyrosine side chain of the crude product was removed by catalytic hydrogenation with 5% Pd/C. Preparative HPLC and subsequential lyophilisation gave the pure product **25** as a white solid (27 mg, 0.040 mmol, 40%). − ^{1}H NMR ([D_6]DMSO): δ = 0.85 [m, 6 H, $CH(CH_3)_2$], 1.20−1.50 [m, 2 H, $CH_2CH(CH_3)_2$], 1.65−1.78 [m, 1 H, $CH(CH_3)_2$], 2.45−2.75 (m, 2 H, $CHCH_2C_6H_5$ + $CH_2C_6H_4O$), 2.83−3.05 (m, 10 H, 2 × CH_2CH_2 + $CH_2CHNHBoc$), 3.25−3.38 (m, 2 H, $NCH_2CHCH_2C_6H_5$), 3.42−3.58 (m, 1 H, $CHCH_2C_6H_4O$), 3.84−3.98 (m, 1 H, $NCH_2CHCH_2C_6H_5$), 4.03−4.18 (m, 1 H, ring CH), 4.51 (s, 1 H, NH), 5.03 (s, 2 H, benzyl CH_2), 5.65−6.10 (m, 5 H, urea NH), 6.60−6.70 (m, 1 H, NH), 6.88 (d, *J* = 8.4 Hz, 2 H, C_6H_4O), 7.07 (d, *J* = 8.4 Hz, 2 H, C_6H_4O), 7.13−7.42 (m, 5 H, $CHCH_2C_6H_5$ + C_6H_4O), 8.22 (d, *J* = 4.3 Hz, 1 H, NH). − ^{13}C NMR ([D_6]DMSO): δ = 21.5 [$CH(CH_3)_2$], 22.8 [1 × $CH(CH_3)_2$], 24.2 [1 × $CH(CH_3)_2$], 35.2 (CH_2), 38.4 (CH_2), 38.7 (CH_2), 40.6 (CH_2), 41.1 (CH_2), 42.8 (CH_2), 50.9 (CH), 51.6 (CH), 53.4 (CH), 115.5, 126.1, 128.2, 129.3, 130.3 (Ar CH), 126.3, 139.0, 156.5 (quat. C Ar), 156.9 158.2, 158.7, 159.1, 175.5 [C(O)]. − FAB MS: *m/z* = 672.4 $[M + H]^+$. − HPLC: >90% pure.

Cleavage of Hydantoin 14 from Resin 22: Resin **22** (250 mg, 0.20 mmol/g) was treated with 10% TEA/MeOH and a catalytic amount of KCN for 3 h. The resin was filtered and washed with MeOH (3 ×). The filtrate was evaporated to give the hydantoin (**14**) as a white solid (16.2 mg, 0.045 mmol, 90%).

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