Solid-Phase Synthesis of Oligourea Peptidomimetics Employing the Fmoc Protection Strategy

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A solid-phase−Fmoc-based−synthesis strategy is described for oligourea peptidomimetics as well as a convenient general synthesis approach for the preparation of the required building blocks **5a**−**j** and **5k**. These are suitable for use in peptide or robot synthesizers, which is illustrated by the synthesis of oligourea peptidomimetics of part of Leu-enkephalin (**10**) and a neurotensin derivative (**17**).

Introduction

Oligopeptidomimetics are interesting not only as "foldamers" [1] capable of folding into defined three-dimensional structures similar to those of natural peptides,[2] but also in view of noteworthy as well as promising biological properties. Recent examples illustrate and underline this perspective. Degrado et al. have published the de novo design of antibacterial β-peptides.[3] Wender and Rothbard and their co-workers have shown that peptoid peptidomimetics can serve as molecular transporters by enabling or enhancing the cellular uptake of agents.[4] A third example is targeting RNA using oligourea peptidomimetics.[5]

In the last years, we have spent considerable effort on developing convenient and reliable syntheses for oligopeptidomimetics. This has resulted in the solid-phase syntheses of peptoids using Fmoc-protected *N*-substituted glycines[6] and, more recently, in a practical solid-phase synthesis of oligopeptidosulfonamide foldamers using *N*-Fmoc-protected β-aminoethanesulfonyl chlorides.[7] In addition, we have been interested for quite some time in developing a synthesis strategy for oligourea peptidomimetics. As is the case with the synthesis of other oligopeptidomimetics, the synthesis of the required building blocks is just as important as the construction of the oligomeric structure. Burgess et al.[8] were the first to describe a solid-phase synthesis of oligourea peptidomimetics, employing phthalimido-protected isocyanates as monomers. Subsequently, Schultz and co-workers developed an elegant procedure using azido 4-nitrophenyl carbamate monomers.[9] Recently, we developed a procedure for the solid-phase synthesis of oligoureas featuring Boc-protected monomers.[10] Boc-protected monomers were also used for solution synthesis of oligoureas.[11]

However, none of the procedures mentioned above are completely compatible with the solid-phase synthesis of peptides using Fmoc-protected amino acids, which is more often becoming the standard. Certainly, the Fmoc protection strategy is very attractive, since Fmoc groups can be removed using mildly basic conditions and their cleavage monitored by UV.[12,13] The latter is very important for establishing the progress of a solid-phase synthesis. Moreover, when using the Fmoc protection strategy, acid-labile groups can be used for protection of the side chains. As a consequence, final deprotection and cleavage from the resin can be carried out under less vigorous conditions than is the case using, e.g., the Boc protection strategy.

Therefore, we describe in this paper a convenient general method for the synthesis of Fmoc-protected urea monomers, including examples having functional side chains, as well as their incorporation into oligourea peptidomimetics. Use of the Fmoc group also makes these monomers fully compatible with usage of standard Fmoc-protected amino acids or other Fmoc-protected building blocks.[7,14] Thus, urea−peptide hybrids can be synthesized, but "mixed" peptidomimetics are accessible as well.

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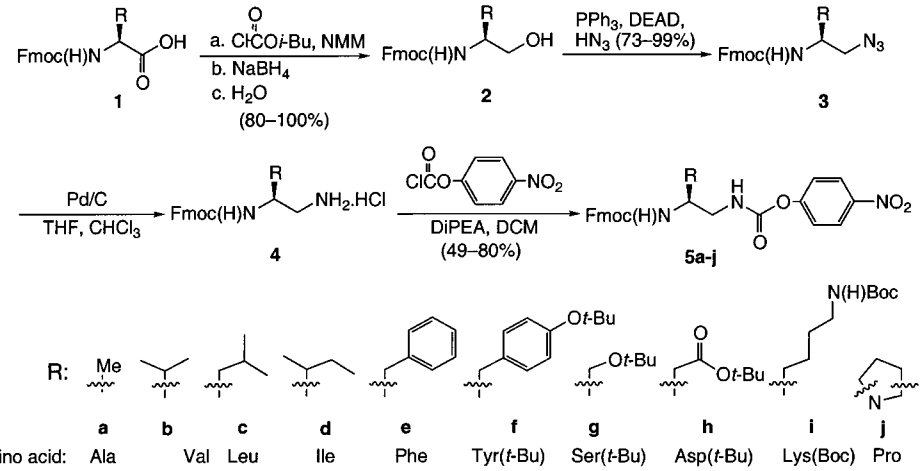
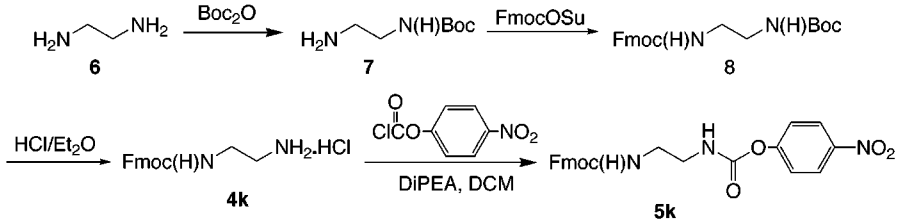
Scheme 1. Synthesis of Fmoc-Protected Urea Monomers 5a−j



Scheme 2. Synthesis of Fmoc-Protected Glycine Urea Monomer 5k



A further advantage of this strategy is the ability to use these monomers on (commercial) automated (peptide) synthesizers. Monitoring of the progress and validation of the solid-phase synthesis is demonstrated by the solid-phase synthesis of oligourea peptidomimetics of part of Leu-enkephalin and a neurotensin derivative.

Results and Discussion

Preparation of Monomers. The required Fmoc-protected monomers for the solid-phase synthesis of oligourea peptidomimetics could be prepared in a relatively straightforward manner (Scheme 1). First, an Fmoc-protected amino acid (**1**) was converted into the corresponding alcohol **2** according to Martinez et al.[15] This alcohol was then transformed into the corresponding azide **3** by a Mitsunobu reaction with hydrogen azide, followed by reduction of the azide to amine **4** in the presence of Pd on carbon. This amine was converted in situ into its HCl salt by addition of chloroform to prevent autocleavage of the Fmoc group. Initially, the crude HCl salt **4** was directly converted to carbamate **5** with 4-nitrophenyl chloroformate using DiPEA as a base. Later on, it became clear that HCl salt **4** was sufficiently stable for isolation by precipitation prior to the preparation of carbamate **5**. The Mitsunobu reaction step gave appreciable variations in the yields, probably because of difficulties in purifying the product. All reactions proceeded in satisfactory to good yields, and the end products **5a−j** were stable white to yellow-white solids.

Glycine derivative **5k** (Scheme 2) was prepared via a slightly different route. First, amine **7** was prepared by mono-Boc protection of ethylenediamine (**6**), according to an earlier developed procedure.[16] Subsequently, amine **7** was Fmoc-protected with Fmoc-OSu, after which the Boc group in bisprotected amine **8** was removed with HCl/ether. Finally, amine **4k** was converted to carbamate **5k** by reaction with 4-nitrophenyl carbamate, as was described above.

Automated Solid-Phase Synthesis of Urea Oligomers. Oligourea peptidomimetic **10** of the tetrapeptide sequence Gly-Gly-Phe-Leu **9** (part of the endorphin Leu-enkephalin) was chosen as a model compound to determine the appropriate procedures for automated synthesis of oligourea peptidomimetics (Figure 1).

The synthesis was carried out on a commercial automatic peptide synthesizer, and the urea oligomer was prepared on Argogel Rink-N(H)-Fmoc ("Argogel S-Ram") resin (0.33 mmol/g, 0.73 g, 0.25 mmol) using the protocol of the synthesizer for a 0.25 mmol scale. The general procedure for the solid-phase synthesis of oligoureas using Fmoc-protected monomers is depicted in Scheme 3. Prior to coupling of the first monomer, the Fmoc group in resin **11** was removed with piperidine to afford **12**.

In earlier investigations on the solid-phase synthesis of oligoureas using Boc-protected monomers,[10] it was found that treatment of a resin-bound amine with 3 equiv of a 4-nitrophenyl carbamate monomer and 3.5 equiv of DiPEA for 3 h resulted in quantitative formation of the desired urea compound. However, it was decided to follow the standard synthesizer protocols as closely as possible: in each *coupling* step, the resin-bound amine (i.e., **12** or **14**) was treated with a solution of 4 equiv (1 mmol) of urea monomer **5** and 8 equiv of DiPEA (2 mmol) in NMP for 90 min (45 min when normal Fmoc-amino acids are used). This corresponded to the number of equivalents of an Fmoc-amino acid and DiPEA used in auto-

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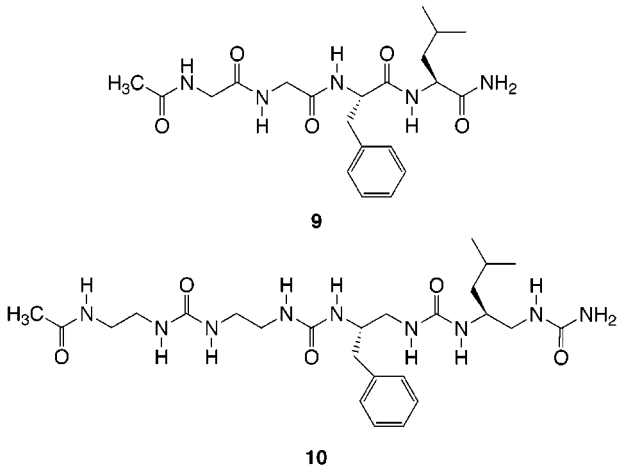


Figure 1. Structure of peptide Ac-Gly-Gly-Phe-Leu-NH_2 (**9**) and the corresponding oligourea mimic Ac-Gly^u-Gly^u-Phe^u-Leu^u-NH_2 (**10**).

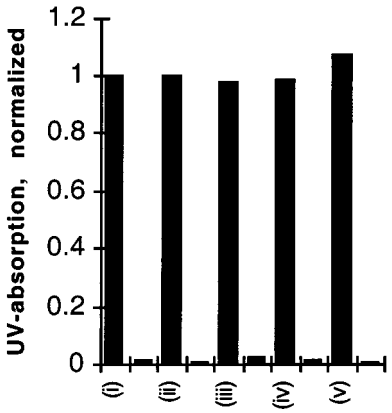


Figure 2. UV monitoring profile of the synthesis of resin-bound urea tetramer **15**. (i) Fmoc cleavage of resin **11** to yield **12**; (ii) Fmoc cleavage after coupling of Fmoc-Leu^u-pNP (**5c**); (iii) Fmoc cleavage after coupling of Fmoc-Phe^u-pNP (**5e**); (iv) Fmoc cleavage after coupling of Fmoc-Gly^u-pNP (**5k**); (v) Fmoc cleavage after coupling of Fmoc-Gly^u-pNP (**5k**).

mated solid-phase peptide synthesis. After each coupling step, the remaining free amino groups were acetylated (*capping*) with a solution of Ac_2O, HOBt, and DiPEA in NMP followed by removal of the Fmoc group using piperidine (*deprotection*). The coupling efficiencies were monitored by measuring the UV absorption of the dibenzofulvene−piperidine adduct, which has an absorption maximum at 301 nm. As is evident from the monitoring profile (Figure 2), the synthesis of the urea oligomer proceeded smoothly.

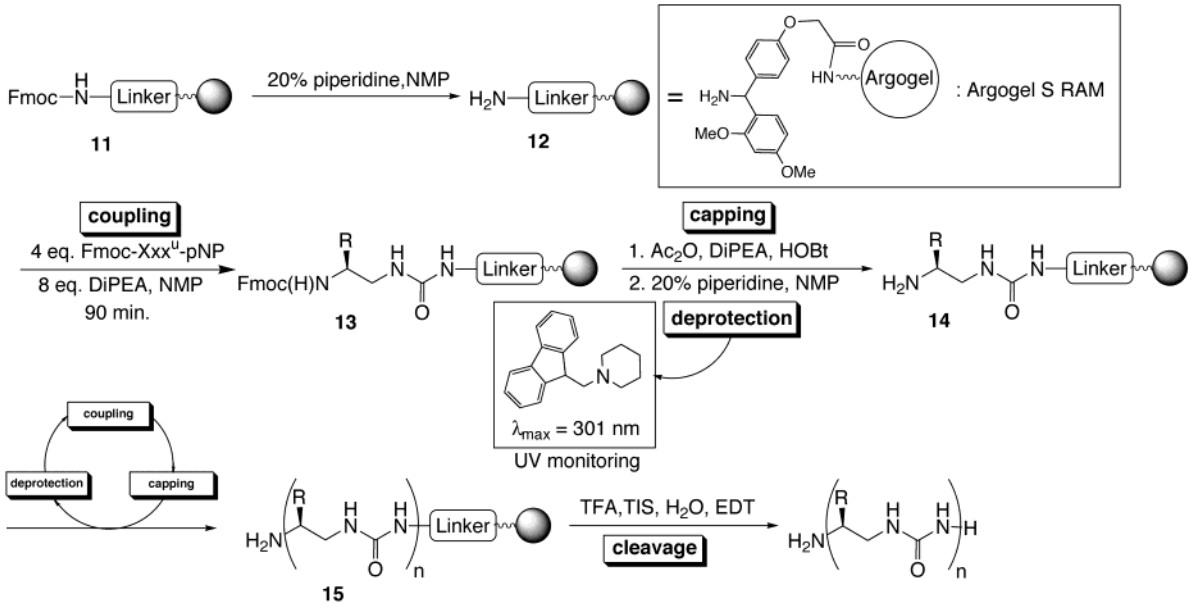
After coupling of the last monomer and removal of the Fmoc protecting group to give resin-bound urea oligomer **15** ($n = 4$ Scheme 3), the amino terminus was acetylated, after which the compound was cleaved from the resin by treatment with TFA/TIS/H_2O/EDT (92.5/2.5/2.5/2.5) for 3 h. After precipitation from 1/1 MTBE/hexanes, oligourea mimic **10** was obtained in 53% yield and in high purity.

Having established the procedure for the solid-phase synthesis of oligourea peptidomimetics, we chose as a second example a more difficult sequence for transformation into the corresponding urea peptidomimetic, viz., preparation of the urea oligopeptidomimetic of a neurotensin derivative 8−13 (**16**).

The tridecapeptide neurotensin (NT) displays a variety of biological effects, the most important of which are located in the central nervous system (CNS). NT plays important roles in thermoregulation, as a modulator of dopamine neurotransmission, and in the perception of pain.[17] The highly conserved 8−13 region (i.e., H-Arg-Arg-Pro-Tyr-Ile-Leu-OH, **16**, Figure 3) shows potency similar to or greater than that of NT itself in a variety of in vitro binding and functional assays.[17,18]

Because replacement of arginine with lysine in NT 8−13 does not result in a substantial loss in biological activity, we aimed for the preparation of an oligourea derivative, viz., **17**, in which the arginines of **16** are replaced by lysine urea residues.[19] Furthermore, it was decided to prepare an oligomer in which the leucine-13 residue is not replaced by a urea monomer, since it has been shown that a free carboxyl terminus is essential for the biological activity.

Scheme 3. General Procedure for the Solid-Phase Synthesis of Oligourea Peptidomimetics



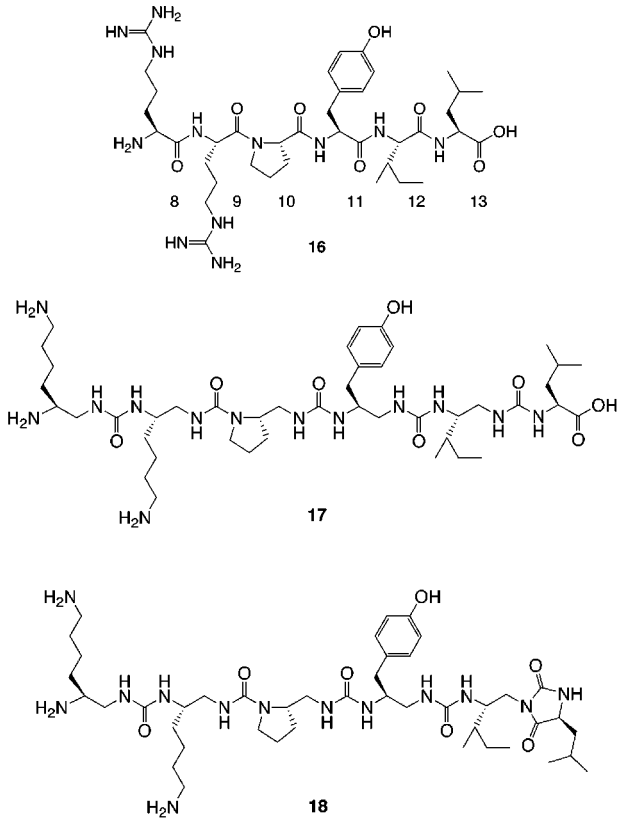


Figure 3. Structure of neurotensin 8−13 (**16**) and the corresponding urea peptidomimetics **17** and **18**.

The synthesis of **17** was carried out on Argogel Wang-OH, which after cleavage with TFA will result in the formation of a carboxyl group. Prior to the automated synthesis, the leucine residue was esterified to the hydroxyl group of the resin using the procedure of Sieber.[20] After completion of the synthesis according to Scheme 3 and cleavage from the resin, a byproduct was formed: an acid-catalyzed cyclization reaction resulted in formation of the corresponding hydantoin **18** (Figure 3). The estimated ratio of linear and cyclic product was 2/1 (according to the HPLC peak areas). The formation of hydantoins had been observed earlier as a *base*-catalyzed reaction in the synthesis of oligourea peptidomimetics using Boc-protected monomers.[10] However, in contrast to the procedure using Boc-protected monomers where the hydantoins were the only products, here the hydantoin is a byproduct which can in principle be separated from the linear compound with preparative HPLC.

This procedure was also excellently suitable for the preparation of urea peptidomimetic−peptide hybrids as was applied to a positional urea scan of **16**.[21]

Conclusions

A procedure for the synthesis of oligourea peptidomimetics using Fmoc-protected monomers has been developed. The monomers are conveniently accessible starting from Fmoc-protected amino acids and are prepared and can be stored as the stable, solid 4-nitrophenyl carbamate derivatives.

The preparation of oligoureas using Fmoc-protected monomers has the advantage that the oligomers can be prepared on resins with acid-labile linkers such as the Rink and Wang linkers which are standard in (automated) solid-phase peptide synthesis. Moreover, when Fmoc-protected monomers are used, the efficiency of the coupling reactions can be monitored by measuring the UV absorption of the dibenzofulvene−piperidine adduct which is formed after cleavage of the Fmoc group. Finally and most importantly, a procedure employing Fmoc-protected monomers enables the preparation of urea peptidomimetics on automated peptide synthesizers without any major adjustments in the synthesis protocols, since the Fmoc protecting group is the standard in automated peptide synthesis today. Thus, libraries of all-urea peptidomimetics, peptide−urea peptidomimetic hybrids and of mixed peptidomimetics are easily accessible, thereby greatly enhancing the potential of these compounds for combinatorial chemistry purposes.

Experimental Section

General Procedures. Unless stated otherwise, the chemicals were obtained from commercial sources and used without further purification. Argogel S-RAM and Argogel Wang-OH were purchased from Argonaut (Muttenz, Switzerland). All protected amino acids were purchased from Advanced Chemtech (Machelen, Belgium). THF, NMP, and DCM were purchased from Biosolve (Valkenswaard, The Netherlands). THF was distilled immediately from $LiAlH_4$ prior to use. 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 spectra were obtained at 300.1 and 75.5 MHz for ^{1}H and ^{13}C, respectively. ^{1}H NMR: $CDCl_3$ as solvent, TMS as internal standard; [D_6]DMSO as solvent, δ_H = 2.50. ^{13}C NMR: $CDCl_3$ as solvent, δ_X = 77.0; [D_6]DMSO as solvent, δ_X = 39.5. FAB MS was performed on a four-sector spectrometer. Analytical HPLC was performed using an automated HPLC instrument 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 was performed using an automated HPLC instrument equipped with a 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}.

Fmoc-Protected Amino Alcohols 2. General Procedure. Fmoc-protected amino alcohols **2** were prepared according to Martinez et al.[15] A solution of Fmoc-protected amino acid **1** (25 mmol) in DME (50 mL) was cooled to −15 °C (ice/salt bath) under a nitrogen atmosphere. NMM (25 mmol, 2.78 mL, 1 equiv) and ICF (25 mmol, 3.40 mL, 1 equiv) were added successively in a dropwise manner. After 1 h, the reaction mixture was filtered. The filtrate was cooled to −15 °C (ice/salt bath), and a solution of $NaBH_4$ (37.5 mmol, 1.42 g, 1.5 equiv) in H_2O (12.5 mL) was added in one portion, followed by H_2O (625 mL). After precipitation of the product, the suspension was filtered. The residue was washed with H_2O and hexanes, and dried in a vacuum desiccator to give alcohol **2** as a white solid.

Fmoc-Protected Alanine Alcohol 2a (R = CH_3). Yield: 7.45 g (25.0 mmol, 100%) of white solid. Mp: 120 °C. R_f (5%

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MeOH/DCM): 0.43. $[\alpha]_D^{24} = -0.58$ ($c = 1.02$, $CHCl_3$). ^1H NMR ($CDCl_3$): $\delta = 1.16$ (d, $J = 6.2$ Hz, 3 H, CH_3), 2.46 (br s, 1 H, OH), 3.57 (br m, 2 H, CH_2OH), 3.81 (m, 1 H, C*H*NH), 4.20 (t, $J = 5.9$ Hz, 1 H, Fmoc CH), 4.41 (d, $J = 5.9$ Hz, 2 H, Fmoc CH_2), 5.03 (d, $J = 7.7$ Hz, 1 H, NH), 7.25−7.42 (m, 4 H, Fmoc Ar CH), 7.58 (d, 2 H, Fmoc Ar CH), 7.76 (d, 2 H, Fmoc Ar CH). ^{13}C NMR ($CDCl_3$): $\delta = 17.2$ (CH_3), 47.2 (Fmoc CH), 48.9 (CHNH), 66.6 (CH_2OH, Fmoc CH_2), 119.9, 124.9, 127.0, 127.6 (Fmoc Ar CH), 141.3, 143.8 (Fmoc Ar quat C), 156.5 [C(O)]. Anal. Calcd for $C_{18}H_{19}NO_3$ (297.35): C, 72.71; H, 6.44; N, 4.71. Found: C, 72.59; H, 6.48; N, 4.65. ES MS: $m/z = 320.1$ $[M + Na]^+$.

Fmoc-Protected Valine Alcohol 2b [R = CH(CH$_3$)$_2$]. Yield: 7.15 g (22.0 mmol, 88%) of white solid. Mp: 107−108 °C. R_f (5% MeOH/DCM): 0.44. $[\alpha]_D^{24} = -18.4$ ($c = 1.02$, $CHCl_3$). ^1H NMR ($CDCl_3$): $\delta = 0.93$ [t, 6 H, $(CH_3)_2$], 1.84 [m, 1 H, C*H*$(CH_3)_2$], 2.37 (br s, 1 H, OH), 3.55 (br m, 2 H, CH_2-OH), 3.81 (m, 1 H, C*H*NH), 4.21 (t, $J = 6.6$ Hz, 1 H, Fmoc CH), 4.43 (m, 2 H, Fmoc CH_2), 5.03 (d, $J = 8.0$ Hz, 1 H, NH), 7.26−7.42 (m, 4 H, Fmoc Ar CH), 7.58 (d, 2 H, Fmoc Ar CH), 7.76 (d, 2 H, Fmoc Ar CH). ^{13}C NMR ($CDCl_3$): $\delta = 18.6$ (CH_3), 19.5 (CH_3), 29.1 [*C*H$(CH_3)_2$], 47.3 (Fmoc CH), 58.5 (CHNH), 63.6 (CH_2OH), 66.5 (Fmoc CH_2), 119.9, 124.9, 127.0, 127.6 (Fmoc Ar CH), 141.3, 143.8 (Fmoc Ar quat C), 157.0 [C(O)]. Anal. Calcd for $C_{20}H_{23}NO_3$ (325.41): C, 74.31; H, 7.12; N, 4.30. Found: C, 73.74; H, 7.18; N, 4.20. ES MS: $m/z = 348.2$ $[M + Na]^+$.

Fmoc-Protected Leucine Alcohol 2c [R = CH$_2$CH-(CH$_3$)$_2$]. Yield: 7.99 g (23.7 mmol, 95%) of white solid. Mp: 112−113 °C. R_f (5% MeOH/DCM): 0.45. $[\alpha]_D^{24} = -20.8$ ($c = 1.01$, $CHCl_3$). ^1H NMR ($CDCl_3$): $\delta = 0.93$ [d, $J = 5.2$ Hz, 6 H, $(CH_3)_2$], 1.33 [m, 2 H, CH_2CH$(CH_3)_2$], 1.63 [m, 1 H, C*H*$(CH_3)_2$], 2.80 (br s, 1 H, OH), 3.55 (br m, 2 H, CH_2OH), 3.77 (m, 1 H, C*H*NH), 4.19 (t, $J = 6.6$ Hz, 1 H, Fmoc CH), 4.41 (m, 2 H, Fmoc CH_2), 5.07 (d, $J = 8.8$ Hz, 1 H, NH), 7.27−7.41 (m, 4 H, Fmoc Ar CH), 7.58 (d, 2 H, Fmoc Ar CH), 7.75 (d, 2 H, Fmoc Ar CH). ^{13}C NMR ($CDCl_3$): $\delta = 22.0$ (CH_3), 23.0 (CH_3), 24.6 [*C*H$(CH_3)_2$], 40.3 [*C*H$_2$CH$(CH_3)_2$], 47.2 (Fmoc CH), 51.2 (CHNH), 65.5 (CH_2OH), 66.4 (Fmoc CH_2), 119.8, 124.9, 126.9, 127.6 (Fmoc Ar CH), 141.2, 143.8 (Fmoc Ar quat C), 156.7 [C(O)]. Anal. Calcd for $C_{21}H_{25}NO_3$ (339.43): C, 74.31; H, 7.42; N, 4.13. Found: C, 74.21; H, 7.54; N, 4.04. ES MS: $m/z = 362.2$ $[M + Na]^+$.

Fmoc-Protected Isoleucine Alcohol 2d [R = CH-(CH$_2$CH$_3$)(CH$_3$)]. Yield: 8.23 g (24.3 mmol, 95%) of white solid. Mp: 114−115 °C. R_f (5% MeOH/DCM): 0.45. $[\alpha]_D^{24} = -20.0$ ($c = 1.02$, $CHCl_3$). ^1H NMR ($CDCl_3$): $\delta = 0.91$ (m, 6 H, 2 × CH_3), 1.13 [m, 1 H, C*H*$(CH_2CH_3)(CH_3)$], 1.53 [m, 2 H, CH-(CH_2CH$_3$)(CH$_3$)], 2.11 (t, $J = 5.5$ Hz, 1 H, OH), 3.64 (br m, 3 H, CH_2OH + C*H*NH), 4.21 (t, $J = 6.6$ Hz, 1 H, Fmoc CH), 4.44 (m, 2 H, Fmoc CH_2), 4.91 (d, $J = 8.8$ Hz, 1 H, NH), 7.25−7.42 (m, 4 H, Fmoc Ar CH), 7.59 (d, 2 H, Fmoc Ar CH), 7.76 (d, 2 H, Fmoc Ar CH). ^{13}C NMR ($CDCl_3$): $\delta = 11.3$ (CH_3), 15.5 (CH_3), 25.4 [CH(*C*H$_2$CH$_3$)(CH$_3$)], 35.8 [*C*H$(CH_2CH_3)(CH_3)$], 47.3 (Fmoc CH), 57.3 (CHNH), 63.3 (CH_2OH), 66.5 (Fmoc CH_2), 119.9, 125.0, 127.0, 127.6 (Fmoc Ar CH), 141.3, 143.8 (Fmoc Ar quat C), 157.0 [C(O)]. Anal. Calcd for $C_{21}H_{25}NO_3$ (339.43): C, 74.31; H, 7.42; N, 4.13. Found: C, 74.22; H, 7.52; N, 4.08. ES MS: $m/z = 362.2$ $[M + Na]^+$.

Fmoc-Protected Phenylalanine Alcohol 2e (R = CH$_2$C$_6$-H$_5$). Yield: 8.70 g (23.3 mmol, 95%) of white solid. Mp: 129−130 °C. R_f (5% MeOH/DCM): 0.44. $[\alpha]_D^{24} = -23.2$ ($c = 1.02$, $CHCl_3$). ^1H NMR ($CDCl_3$): $\delta = 2.07$ (s, 1 H, OH), 2.87 (d, $J = 6.2$ Hz, 2 H, C$H_2C_6H_5$), 3.64 (m, 2 H, CH_2OH), 3.96 (m, 1 H, C*H*NH), 4.18 (t, $J = 6.6$ Hz, 1 H, Fmoc CH), 4.40 (m, 2 H, Fmoc CH_2), 5.96 (br s, 1 H, NH), 7.10−7.42 (m, 9 H, C_6H_5 + 4 × Fmoc Ar CH), 7.55 (m, 2 H, Fmoc Ar CH), 7.76 (d, 2 H, $J = 7.3$ Hz, Fmoc Ar CH). ^{13}C NMR ($CDCl_3$): $\delta = 37.3$ (*C*H$_2C_6H_5$), 47.2 (Fmoc CH), 54.1 (CHNH), 64.0 (CH_2OH), 66.6 (Fmoc *C*H$_2$), 120.0, 125.0 (Fmoc Ar CH), 126.7 ($CH_2C_6H_5$), 127.0, 127.7 (Fmoc Ar CH), 128.6, 129.2 (C_6H_5), 137.5 (C_6H_5 quat C), 141.3, 143.9 (Fmoc Ar quat C), 156.4 [C(O)]. Anal. Calcd for $C_{24}H_{23}$-NO_3 (373.45): C, 77.19; H, 6.21; N, 3.75. Found: C, 76.89; H, 6.32; N, 3.68. ES MS: $m/z = 396.2$ $[M + Na]^+$.

Fmoc-Protected Tyrosine Alcohol 2f (R = CH$_2$C$_6$H$_4$-OtBu). Yield: 10.7 g (23.9 mmol, 95%) of white solid. Mp: 114−115 °C. R_f (5% MeOH/DCM): 0.43. $[\alpha]_D^{24} = -18.5$ ($c = 1.02$, $CHCl_3$). ^1H NMR ($CDCl_3$): $\delta = 1.22$ [s, 9 H, $(CH_3)_3$], 2.22 (d, $J = 6.9$ Hz, 1 H, OH), 2.87 (d, $J = 6.2$ Hz, 2H, C$H_2C_6H_5$), 3.57 (m, 2 H, CH_2OH), 3.89 (m, 1 H, C*H*NH), 4.18 (t, $J = 6.6$ Hz, 1 H, Fmoc CH), 4.40 (m, 2 H, Fmoc CH_2), 5.96 (br s, 1 H, NH), 6.89−7.08 (m, 4 H, C_6H_4), 7.25−7.42 (m, 4 H, 4 · Fmoc Ar CH), 7.55 (m, 2 H, Fmoc Ar CH), 7.75 (d, 2 H, $J = 7.3$ Hz, Fmoc Ar CH). ^{13}C NMR ($CDCl_3$): $\delta = 28.7$ [$(CH_3)_3$], 36.5 (*C*H$_2C_6H_5$), 47.2 (Fmoc CH), 54.1 (CHNH), 63.8 (CH_2OH), 66.6 (Fmoc CH_2), 78.3 [*C*$(CH_3)_3$], 120.0 (Fmoc Ar CH), 124.3 ($CH_2C_6H_4$), 125.0, 127.1, 127.8 (Fmoc Ar CH), 129.7 (C_6H_4), 132.4 (C_6H_4 quat C), 141.4, 144.0 (Fmoc Ar quat C), 154.2 (C_6H_4 quat C), 156.4 [C(O)]. Anal. Calcd for $C_{28}H_{31}NO_3$ (445.56): C, 75.48; H, 7.01; N, 3.14. Found: C, 75.36; H, 7.05; N, 3.06. ES MS: $m/z = 468.2$ $[M + Na]^+$.

Fmoc-Protected Serine Alcohol 2g (R = CH$_2$OtBu). Yield: 8.3 g (22.4 mmol, 90%) of white solid. Mp: 97−98 °C. R_f (5% MeOH/DCM): 0.46. $[\alpha]_D^{24} = +12.3$ ($c = 1.02$, $CHCl_3$). ^1H NMR ($CDCl_3$): $\delta = 1.19$ [s, 9 H, $(CH_3)_3$], 3.30−3.85 (m, 4 H, OH, CH_2OH, C*H*NH), 4.22 (t, $J = 6.4$ Hz, 1 H, Fmoc CH), 4.41 (m, 2 H, Fmoc CH_2), 5.75 (d, $J = 7.7$ Hz, 1 H, NH), 7.28−7.45 (m, 4 H, Fmoc Ar CH), 7.58 (d, 2 H, Fmoc Ar CH), 7.76 (d, 2 H, Fmoc Ar CH). ^{13}C NMR ($CDCl_3$): $\delta = 27.0$ [$(CH_3)_3$], 46.7 (Fmoc CH), 51.8 (CHNH), 62.1 (*C*H$_2$OtBu), 63.1 (CH_2OH), 66.5 (Fmoc CH_2), 73.3 [*C*$(CH_3)_3$], 119.7, 124.8, 126.7, 127.3 (Fmoc Ar CH), 140.9, 143.6 (Fmoc Ar quat C), 156.2 [C(O)]. Anal. Calcd for $C_{22}H_{27}NO_4$ (369.46): C, 71.52; H, 7.37; N, 3.79. Found: C, 71.36; H, 7.30; N, 3.78. ES MS: $m/z = 392.2$ $[M + Na]^+$.

Fmoc-Protected Aspartic Alcohol 2h (R = CH$_2$C(O)-OtBu). Yield: 9.25 g (23.3 mmol, 93%) of white solid. Mp: 89−90 °C. R_f (5% MeOH/DCM): 0.47. $[\alpha]_D^{24} = +1.89$ ($c = 1.03$, $CHCl_3$). ^1H NMR ($CDCl_3$): $\delta = 1.44$ [s, 9 H, $(CH_3)_3$], 2.55 (br d, 2 H, CH_2C(O)OtBu), 2.90 (br s, 1 H, OH), 3.67 (d, $J = 4.4$ Hz, 2 H, CH_2OH), 4.04 (br s, 1 H, C*H*NH), 4.20 (t, $J = 6.6$ Hz, 1 H, Fmoc CH), 4.38 (d, $J = 6.5$ Hz, 2 H, Fmoc CH_2), 5.67 (d, $J = 8.4$ Hz, 1 H, NH), 7.27−7.41 (m, 4 H, Fmoc Ar CH), 7.58 (d, 2 H, Fmoc Ar CH), 7.75 (d, 2 H, Fmoc Ar CH). ^{13}C NMR ($CDCl_3$): $\delta = 27.9$ [$(CH_3)_3$], 37.2 [*C*H$_2$C(O)OtBu], 47.0 (Fmoc CH), 49.9 (CHNH), 64.1 (CH_2OH), 66.7 (Fmoc CH_2), 81.3 [*C*$(CH_3)_3$], 119.9, 124.9, 126.9, 127.6 (Fmoc Ar CH), 141.1, 143.7 (Fmoc Ar quat C), 156.2 [C(O)NH], 170.9 [C(O)OtBu]. Anal. Calcd for $C_{23}H_{27}NO_5$ (397.47): C, 69.50; H, 6.85; N, 3.52. Found: C, 69.63; H, 6.84; N, 3.44. ES MS: $m/z = 420.2$ $[M + Na]^+$.

Fmoc-Protected Lysine Alcohol 2i [R = (CH$_2$)$_4$N(H)-Boc]. Yield: 10.9 g (24.0 mmol, 96%) of white solid. Mp: 130−131 °C. R_f (5% MeOH/DCM): 0.33. $[\alpha]_D^{24} = -8.05$ ($c = 1.02$, $CHCl_3$). ^1H NMR ($CDCl_3$): $\delta = 1.43$ [m, 15 H, $(CH_3)_3$ + CH_2-(CH_2)$_3$NHBoc], 2.50 (br s, 1 H, OH), 3.07 [m, 2 H, CH_2(CH$_2$)$_3$-NHBoc], 3.62 (br m, 2 H, CH_2OH + C*H*NH), 4.19 (t, $J = 6.9$ Hz, 1 H, Fmoc CH), 4.39 (d, $J = 6.9$ Hz, 2 H, Fmoc CH_2), 4.66 (br m, 1 H, NHBoc), 5.22 (d, $J = 7.0$ Hz, 1 H, NHFmoc), 7.26−7.41 (m, 4 H, Fmoc Ar CH), 7.58 (d, 2 H, Fmoc Ar CH), 7.75 (d, 2 H, Fmoc Ar CH). ^{13}C NMR ($CDCl_3$): $\delta = 22.5$, 29.9, 30.4 [CH_2(*C*H$_2$)$_3$NHBoc], 28.3 [$(CH_3)_3$], 39.6 [*C*H$_2$(CH$_2$)$_3$], 47.2 (Fmoc CH), 52.9 (CHNH), 64.5 (CH_2OH), 66.5 (Fmoc CH_2), 79.2 [*C*$(CH_3)_3$], 119.9, 125.0, 127.0, 127.6 (Fmoc Ar CH), 141.2, 143.9 (Fmoc Ar quat C), 156.4 [C(O)], 156.7 [C(O)]. Anal. Calcd for $C_{26}H_{34}N_2O_5$ (454.57): C, 68.70; H, 7.54; N, 6.16. Found: C, 68.59; H, 7.44; N, 6.08. ES MS: $m/z = 477.2$ $[M + Na]^+$.

Fmoc-Protected Proline Alcohol 2j. Proline alcohol **2j** did not precipitate from the reaction mixture as a solid after the addition of water, but as an oil. Therefore, the DME was removed in vacuo, whereupon the residual water phase was extracted with DCM (2×). The DCM layers were combined and washed with water (3×) and brine. The organic phase was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was crystallized from EtOAc/hexanes. Yield: 2.58 g (8.0 mmol, 80%) of white crystals starting from 10 mmol of Fmoc-Pro-OH. Mp: 89−90 °C. R_f (5% MeOH/DCM): 0.46. $[\alpha]_D^{24} = -30.3$ ($c = 1.02$, $CHCl_3$). ^1H NMR ($CDCl_3$): $\delta = 1.21$−2.07 (m, 4 H, CHCH_2CH_2CH$_2$), 3.20−3.67 (m, 4 H, CHCH$_2$-

$CH_2CH_2N + CH_2OH$), 4.00 (m, 1 H, CHN), 4.19 (m, 2 H, Fmoc CH + OH), 4.41 (m, 2 H, Fmoc CH_2), 7.26−7.43 (m, 4 H, Fmoc Ar CH), 7.60 (d, 2 H, Fmoc Ar CH), 7.77 (d, 2 H, Fmoc Ar CH). ^{13}C NMR ($CDCl_3$): δ = 24.1 (CH_2), 28.6 (CH_2), 47.3 (Fmoc CH), 47.3 (CH_2N), 60.8 (CHN), 67.0 (CH_2OH), 67.5 (Fmoc CH_2), 120.0, 125.0, 127.0, 127.7 (Fmoc Ar CH), 141.3, 143.9 (Fmoc Ar quat C), 157.1 [C(O)]. Anal. Calcd for $C_{20}H_{21}NO_3$ (323.39): C, 74.28; H, 6.54; N, 4.33. Found: C, 74.17; H, 6.55; N, 4.26. ES MS: m/z = 346.2 $[M + Na]^+$.

Fmoc-Protected Azides 3. General Procedure. Under a nitrogen atmosphere, DEAD (10 mmol, 1.55 mL, 1 equiv) was added dropwise to a cooled (0 °C) solution of PPh_3 (10 mmol, 2.63 g) in THF (30 mL). Subsequently, a 1.5 M solution of HN_3 in benzene[22] (10 mmol, 6.62 mL, 1 equiv) was added dropwise, whereupon Fmoc-protected amino alcohol **13** (10 mmol, 1 equiv) was added in one portion. The reaction mixture was stirred overnight at room temperature, and was concentrated in vacuo. After column chromatography, azide **7** was obtained as a white solid.

Fmoc-Protected Alanine Azide 3a. Yield: 2.98 g (9.8 mmol, 98%) of white solid obtained from **2a** after column chromatography (EtOAc/hexanes, 1/5). Mp: 109−110 °C. R_f (EtOAc/hexanes, 1/5): 0.27. $[\alpha]_D^{24} = -10.3$ (c = 0.96, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.16 (d, J = 6.6 Hz, 3 H, CH_3), 3.39 (br m, 2 H, CH_2N_3), 3.93 (m, 1 H, C*H*NH), 4.22 (t, J = 6.6 Hz, 1 H, Fmoc CH), 4.41 (m, 2 H, Fmoc CH_2), 4.84 (d, J = 8.1 Hz, 1 H, NH), 7.25−7.42 (m, 4 H, Fmoc Ar CH), 7.58 (d, 2 H, Fmoc Ar CH), 7.76 (d, 2 H, Fmoc Ar CH). ^{13}C NMR ($CDCl_3$): δ = 18.2 (CH_3), 46.6 (CHNH), 47.2 (Fmoc Ar CH), 55.8 (CH_2N_3), 66.6 (Fmoc CH_2), 119.9, 124.9, 127.0, 127.7 (Fmoc Ar CH), 141.3, 143.8 (Fmoc Ar quat C), 155.5 [C(O)]. Anal. Calcd for $C_{18}H_{18}N_4O_2$ (422.47): C, 67.07; H, 5.63; N, 17.38. Found: C, 67.19; H, 5.70; N, 17.33. ES MS: m/z = 345.1 $[M + Na]^+$.

Fmoc-Protected Valine Azide 3b. Yield: 2.80 g (8.0 mmol, 80%) of white solid obtained from **2b** after column chromatography (EtOAc/hexanes, 1/6). Mp: 109 °C. R_f (EtOAc/hexanes, 1/5): 0.34. $[\alpha]_D^{24} = -26.4$ (c = 1.03, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 0.95 [t, 6 H, $(CH_3)_2$], 1.82 [m, 1 H, C*H*$(CH_3)_2$], 3.55 (d, J = 4.8 Hz, 2 H, CH_2N_3), 3.60 (m, 1 H, C*H*NH), 4.24 (t, J = 7.0 Hz, 1 H, Fmoc CH), 4.46 (d, J = 7.0 Hz, 2 H, Fmoc CH_2), 4.92 (d, J = 9.2 Hz, 1 H, NH), 7.30−7.44 (m, 4 H, Fmoc Ar CH), 7.61 (d, 2 H, Fmoc Ar CH), 7.77 (d, 2 H, Fmoc Ar CH). ^{13}C NMR ($CDCl_3$): δ = 18.4 (CH_3), 19.3 (CH_3), 29.6 [*C*H-$(CH_3)_2$], 47.2 (Fmoc CH), 52.9 (CH_2N_3), 56.1 (CHNH), 66.5 (Fmoc CH_2), 119.9, 124.9, 126.9, 127.6 (Fmoc Ar CH), 141.2, 143.7 (Fmoc Ar quat C), 156.0 [C(O)]. Anal. Calcd for $C_{20}H_{22}N_4O_2$ (350.42): C, 68.55; H, 6.33; N, 15.99. Found: C, 68.63; H, 6.39; N, 16.08. ES MS: m/z = 373.1 $[M + Na]^+$.

Fmoc-Protected Leucine Azide 3c. Yield: 3.17 g (8.8 mmol, 88%) of white solid obtained from **2c** after column chromatography (EtOAc/hexanes, 1/9). Mp: 85 °C. R_f (EtOAc/hexanes, 1/5): 0.51. $[\alpha]_D^{24} = -26.4$ (c = 1.03, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 0.91 [d, J = 6.2 Hz, 6 H, $(CH_3)_2$], 1.35 [m, 2 H, C*H*$_2$CH$(CH_3)_2$], 1.60 [m, 1 H, C*H*$(CH_3)_2$], 3.55 (br m, 2 H, CH_2N_3), 3.86 (m, 1 H, C*H*NH), 4.21 (t, J = 6.6 Hz, 1 H, Fmoc CH), 4.43 (d, J = 6.6 Hz, 2 H, Fmoc CH_2), 4.72 (d, J = 8.8 Hz, 1 H, NH), 7.24−7.42 (m, 4 H, Fmoc Ar CH), 7.58 (d, 2 H, Fmoc Ar CH), 7.75 (d, 2 H, Fmoc Ar CH). ^{13}C NMR ($CDCl_3$): δ = 21.9 (CH_3), 22.8 (CH_3), 24.6 [*C*H$(CH_3)_2$], 41.2 [*C*H$_2$CH$(CH_3)_2$], 47.2 (Fmoc CH), 49.0 (CHNH), 55.1 (CH_2N_3), 66.5 (Fmoc CH_2), 120.0, 125.1, 127.1, 127.7 (Fmoc Ar CH), 141.4, 143.9 (Fmoc Ar quat C), 155.9 [C(O)]. Anal. Calcd for $C_{21}H_{24}N_4O_2$ (364.45): C, 69.21; H, 6.64; N, 15.37. Found: C, 69.29; H, 6.66; N, 15.33. ES MS: m/z = 387.2 $[M + Na]^+$.

Fmoc-Protected Isoleucine Azide 3d. Yield: 2.80 g (8.0 mmol, 80%) of white solid obtained from **2d** after column chromatography (EtOAc/hexanes, 1/8). Mp: 111 °C. R_f (EtOAc/hexanes, 1/5): 0.50. $[\alpha]_D^{24} = -24.6$ (c = 0.99, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 0.92 (m, 6 H, 2 × CH_3), 1.13 [m, 1 H, C*H*$(CH_2$-$CH_3)(CH_3)$], 1.52 [m, 2 H, CH$(CH_2CH_3)(CH_3)$], 3.54 (br m, 2 H, CH_2N_3), 3.62 (m, 1 H, C*H*NH), 4.23 (t, J = 6.9 Hz, 1 H, Fmoc CH), 4.45 (d, J = 6.9 Hz, 2 H, Fmoc CH_2), 4.77 (d, J = 9.2 Hz, 1 H, NH), 7.24−7.43 (m, 4 H, Fmoc Ar CH), 7.59 (d, 2 H, Fmoc Ar CH), 7.76 (d, 2 H, Fmoc Ar CH). ^{13}C NMR ($CDCl_3$): δ = 11.2 (CH_3), 15.5 (CH_3), 25.2 [CH(*C*H$_2$CH$_3$)(CH_3)], 36.2 [*C*H$(CH_2CH_3)(CH_3)$], 47.3 (Fmoc CH), 52.9 (CH_2N_3), 54.9 (CHNH), 66.6 (Fmoc CH_2), 120.0, 125.0, 127.0, 127.6 (Fmoc Ar CH), 141.3, 143.8 (Fmoc Ar quat C), 156.0 [C(O)]. Anal. Calcd for $C_{21}H_{24}N_4O_2$ (364.44): C, 69.21; H, 6.64; N, 15.37. Found: C, 69.30; H, 6.72; N, 15.24. ES MS: m/z = 387.2 $[M + Na]^+$.

Fmoc-Protected Phenylalanine Azide 3e. Yield: 2.80 g (8.0 mmol, 80%) of white solid obtained from **2e** after column chromatography (EtOAc/hexanes, 1/8). Mp: 81−82 °C. R_f (EtOAc/hexanes, 1/4.5): 0.31. $[\alpha]_D^{24} = -14.5$ (c = 1.01, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 2.87 (m, 2 H, C*H*$_2C_6H_5$), 3.39 (m, 2 H, CH_2N_3), 4.02 (m, 1 H, C*H*NH), 4.19 (t, J = 6.6 Hz, 1 H, Fmoc CH), 4.39 (m, 2 H, Fmoc CH_2), 4.87 (br d, J = 8.1 Hz, 1 H, NH), 7.20−7.43 (m, 9 H, C_6H_5 + 4 × Fmoc Ar CH), 7.55 (m, 2 H, Fmoc Ar CH), 7.76 (d, 2 H, J = 7.3 Hz, Fmoc Ar CH). ^{13}C NMR ($CDCl_3$): δ = 37.9 (*C*H$_2C_6H_5$), 47.2 (Fmoc CH), 51.9 (CHNH), 53.0 (CH_2N_3), 66.7 (Fmoc CH_2), 120.1, 125.1 (Fmoc Ar CH), 127.0 (C_6H_5), 127.1, 127.8 (Fmoc Ar CH), 128.8, 129.3 (C_6H_5), 136.9 (C_6H_5 quat C), 141.4, 143.9 (Fmoc Ar quat C), 156.4 [C(O)]. Anal. Calcd for $C_{24}H_{22}N_4O_2$ (398.46): C, 72.34; H, 5.56; N, 14.06. Found: C, 72.31; H, 5.68; N, 14.07. ES MS: m/z = 421.2 $[M + Na]^+$.

Fmoc-Protected Tyrosine Azide 3f. Yield: 8.21 g (17.4 mmol, 87%) of white solid obtained from 20 mmol of **2f** after column chromatography (EtOAc/hexanes, 1/6). Mp: 84−85 °C. R_f (EtOAc/hexanes, 1/5): 0.27. $[\alpha]_D^{24} = -6.1$ (c = 1.01, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.33 [s, 9 H, $(CH_3)_3$], 2.80 (m, 2 H, C*H*$_2C_6H_5$), 3.40 (m, 2 H, CH_2N_3), 4.00 (m, 1 H, C*H*NH), 4.20 (t, J = 7.0 Hz, 1 H, Fmoc CH), 4.40 (d, J = 7.0 Hz, 2 H, Fmoc CH_2), 4.92 (d, J = 8.1 Hz, 1 H, NH), 6.91−7.08 (m, 4 H, C_6H_4), 7.26−7.43 (m, 4 H, 4 × Fmoc Ar CH), 7.57 (m, 2 H, Fmoc Ar CH), 7.76 (d, 2 H, J = 7.3 Hz, Fmoc Ar CH). ^{13}C NMR ($CDCl_3$): δ = 28.8 [$(CH_3)_3$], 37.3 (*C*H$_2C_6H_5$), 47.2 (Fmoc CH), 51.9 (CHNH), 53.0 (CH_2N_3), 66.7 (Fmoc CH_2), 78.4 [*C*$(CH_3)_3$], 120.0 (Fmoc Ar CH), 124.3 (C_6H_4), 125.0, 127.0, 127.7 (Fmoc Ar CH), 129.6 (C_6H_4), 131.5 (C_6H_4 quat C), 141.3, 143.8 (Fmoc Ar quat C), 154.2 (C_6H_4 quat C), 155.6 [C(O)]. Anal. Calcd for $C_{28}H_{30}N_4O_3$ (470.57): C, 71.47; H, 6.43; N, 11.91. Found: C, 71.33; H, 6.48; N, 11.69. ES MS: m/z = 493.2 $[M + Na]^+$.

Fmoc-Protected Serine Azide 3g. Yield: 2.86 g (7.3 mmol, 73%) of colorless oil, which solidified upon standing, obtained from **2g** after column chromatography (EtOAc/hexanes, 1/6). Mp: 83 °C. R_f (EtOAc/hexanes, 1/4): 0.36. $[\alpha]_D^{24}$ = +1.32 (c = 1.02, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.19 [s, 9 H, $(CH_3)_3$], 3.36−3.52 (m, 4 H, CH_2N_3 + CH_2O), 3.90 (br s, 1 H, C*H*NH), 4.22 (t, J = 6.6 Hz, 1 H, Fmoc CH), 4.42 (m, 2 H, Fmoc CH_2), 5.13 (d, J = 8.8 Hz, 1 H, NH), 7.26−7.43 (m, 4 H, Fmoc Ar CH), 7.59 (d, 2 H, Fmoc Ar CH), 7.77 (d, 2 H, Fmoc Ar CH). ^{13}C NMR ($CDCl_3$): δ = 27.4 [$(CH_3)_3$], 47.2 (Fmoc CH), 50.6 (CHNH), 51.4 (CH_2N_3), 60.4 (*C*H$_2$OtBu), 66.8 (Fmoc CH_2), 73.4 [*C*$(CH_3)_3$], 119.7, 124.8, 126.7, 127.3 (Fmoc Ar CH), 140.9, 143.6 (Fmoc Ar quat C), 156.2 [C(O)NH]. Anal. Calcd for $C_{22}H_{26}N_4O_3$ (394.47): C, 66.99; H, 6.64; N, 14.20. Found: C, 67.16; H, 6.63; N, 14.22. ES MS: m/z = 417.2 $[M + Na]^+$.

Fmoc-Protected Aspartic Azide 3h. Yield: 4.20 g (10.0 mmol, 100%) of white solid obtained from **2h** after column chromatography (EtOAc/hexanes, 1/6). Mp: 88−89 °C. R_f (EtOAc/hexanes, 1/4): 0.34. $[\alpha]_D^{24} = -1.68$ (c = 1.01, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.46 [s, 9 H, $(CH_3)_3$], 2.54 (d, J = 5.8 Hz, 2 H, C*H*$_2$C(O)OtBu), 3.51 (m, 2 H, CH_2N_3), 4.16 (br s, 1 H, C*H*NH), 4.22 (m, 1 H, Fmoc CH), 4.40 (m, 2 H, Fmoc CH_2), 5.42 (d, J = 8.8 Hz, 1 H, NH), 7.26−7.43 (m, 4 H, Fmoc Ar CH), 7.59 (m, 2 H, Fmoc Ar CH), 7.77 (d, 2 H, Fmoc Ar CH). ^{13}C NMR ($CDCl_3$): δ = 28.0 [$(CH_3)_3$], 37.3 [*C*H$_2$C(O)OtBu], 47.2 (Fmoc CH), 47.9 (CHNH), 53.7 (CH_2N_3), 66.9 (Fmoc CH_2), 81.7 [*C*$(CH_3)_3$], 120.0, 125.0 127.0, 127.7 (Fmoc Ar CH), 141.3, 143.8 (Fmoc Ar quat C), 155.6 [C(O)NH], 170.2 [*C*(O)OtBu]. Anal. Calcd for $C_{23}H_{26}N_4O_4$ (422.40): C, 65.39; H, 6.20; N, 13.26. Found: C, 65.47: H, 6.31; N, 13.29. ES MS: m/z = 445.2 $[M + Na]^+$.

(22) Wolff, H. In *Organic Reactions*; Adams, R., Bachmann, W. E., Fieser, L. F., Johnson, J. R., Snyder, H. R., Eds.; John Wiley & Sons: New York, 1947; Vol. 3, p 327.

Fmoc-Protected Lysine Azide 3i. Yield: 4.17 g (8.7 mmol, 87%) of white solid obtained from **2i** after column chromatography (EtOAc/hexanes, 1/3). Mp: 97−98 °C. R_f (EtOAc/hexanes, 1/3): 0.33. $[\alpha]_D^{24} = -16.4$ ($c = 0.99$, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.43 [m, 15 H, $(CH_3)_3 + CH_2(CH_2)_3$-NHBoc], 3.10 [m, 2 H, $CH_2(CH_2)_3NHBoc$], 3.39 (br m, 2 H, CH_2N_3), 3.75 (br m, 1 H, CHNH), 4.20 (t, J = 6.9 Hz, 1 H, Fmoc CH), 4.39 (m, 2 H, Fmoc CH_2), 4.59 (br m, 1 H, NHBoc), 5.00 (d, J = 8.1 Hz, 1 H, NHFmoc), 7.25−7.41 (m, 4 H, Fmoc Ar CH), 7.59 (d, 2 H, Fmoc Ar CH), 7.75 (d, 2 H, Fmoc Ar CH). ^{13}C NMR ($CDCl_3$): δ = 22.8, 29.7, 31.6 ($CH_2(CH_2)_3$-NHBoc), 28.4 [$(CH_3)_3$], 40.0 [$CH_2(CH_2)_3$], 47.2 (Fmoc CH), 50.7 (CHNH), 54.7 (CH_2N_3), 66.6 (Fmoc CH_2), 79.1 [$C(CH_3)_3$], 119.9, 125.0, 127.0, 127.6 (Fmoc Ar CH), 141.2, 143.8 (Fmoc Ar quat C), 155.9 [C(O)], 156.0 [C(O)]. ES MS: m/z = 502.3 $[M + Na]^+$.

Fmoc-Protected Proline Azide 3j. Yield: 3.20 g (9.2 mmol, 92%) of colorless oil, which solidified upon standing, obtained from **2j** after column chromatography (EtOAc/hexanes, 1/6). Mp: 64−65 °C. R_f (EtOAc/hexanes, 1/5): 0.26. $[\alpha]_D^{24} = -32.8$ ($c = 1.09$, $CHCl_3$). The NMR spectrum indicates the presence of two conformers. ^{1}H NMR ($CDCl_3$): δ = 1.68−2.03 (m, 4 H, $CHCH_2CH_2CH_2N$), 2.71−2.89 (m, 1 H, CH_2N), 3.34−3.63 (m, 3.5 H, $CH_2N_3 + 1 \times CH_2$ N + 0.5 × CHN), 4.03 (m, 0.5 H, CHN), 4.25 (t, 1 H, Fmoc CH), 4.32−4.49 (m, 1 H, Fmoc CH_2), 4.59−4.71 (m, 1 H, Fmoc CH_2), 7.30−7.44 (m, 4 H, Fmoc Ar CH), 7.56−7.62 (m, 2 H, Fmoc Ar CH), 7.78 (d, 2 H, Fmoc Ar CH). ^{13}C NMR ($CDCl_3$): δ = 22.8, 23.9 ($CHCH_2CH_2CH_2 \rightarrow$ N), 28.4, 29.1 ($CHCH_2CH_2CH_2N$), 46.9, 46.9 (CH_2N), 47.3 (Fmoc CH), 52.6 (CH_2N_3), 56.0, 57.0 (CHN), 66.3, 67.1 (Fmoc CH_2), 119.9, 119.9, 124.4, 124.5, 127.0, 127.0 127.6 (Fmoc Ar CH), 141.3, 141.3, 143.9, 144.0 (Fmoc Ar quat C), 154.9, 155.0 [C(O)]. Anal. Calcd for $C_{20}H_{20}N_4O_2$ (348.40): C, 68.95; H, 5.79; N, 16.08. Found: C, 69.07; H, 5.88; N, 15.97. ES MS: m/z = 371.2 $[M + Na]^+$.

Fmoc-Protected Activated Monomers 5. General Procedure. Azide **3** (5.0 mmol) was dissolved in THF (50 mL), and $CHCl_3$ (1.0 mL) was added. To this solution, a catalytic amount of 10% palladium on carbon (100 mg) was added. The resulting mixture was stirred overnight at room temperature under a hydrogen atmosphere. Then, water (4.0 mL) was added to redissolve precipitated material. Subsequently, the reaction mixture was filtered over Celite, and the solvents were evaporated. The resulting HCl salt **4** was dried in vacuo over P_2O_5. Then, DCM (40 mL) and 4-nitrophenyl chloroformate (5.5 mmol, 1.11 g, 1.1 equiv) were added. The resulting suspension was cooled to 0 °C with an ice bath, and a solution of DiPEA (10 mmol, 1.74 mL, 2 equiv) in DCM (10 mL) was added dropwise. After being stirred for 30 min, the reaction mixture was allowed to warm to room temperature, and stirring was continued for another 2 h. The reaction mixture was then washed with 1 N $KHSO_4$ (3×), water, and brine. The organic fraction was dried on Na_2SO_4, and the solvents were removed in vacuo. Subsequent precipitation from DCM/hexanes gave monomer **5** as a white to yellow-white solid.

Fmoc-Protected Activated Alanine Monomer 5a. Yield: 1.67 g (3.7 mmol, 75%) of white solid obtained after trituration with 2-propanol and Et_2O. Mp: >161−163 °C dec. R_f (EtOAc/hexanes, 1/1): 0.35. $[\alpha]_D^{24} = +7.64$ ($c = 0.25$, dioxane). ^{1}H NMR ([D$_8$]THF): δ = 1.15 (d, J = 6.6 Hz, 3 H, CH_3), 3.23 (br m, 2 H, CH_2NH), 3.84 (m, 1 H, CHNH), 4.19 (t, J = 6.6 Hz, 1 H, Fmoc CH), 4.35 (m, 2 H, Fmoc CH_2), 6.51 (d, J = 8.4 Hz, 1 H, NH), 7.21−7.37 (m, 7 H, 4 × Fmoc Ar CH + 2 · $C_6H_4NO_2$ + NH), 7.62 (d, 2 H, Fmoc Ar CH), 7.77 (d, 2 H, Fmoc Ar CH), 8.16 (d, 2 H, $C_6H_4NO_2$). ^{13}C NMR ([D$_8$]THF]): δ = 18.4 (CH_3), 47.3 (CH_2NH), 48.0 (Fmoc CH), 48.4 (CHNH), 66.8 (Fmoc CH_2), 120.6 (Fmoc Ar CH), 122.6, 125.5 ($C_6H_4NO_2$), 125.9, 127.7, 128.3 (Fmoc Ar CH), 142.3 (Fmoc Ar quat C), 145.3, 154.4 ($C_6H_4NO_2$ quat C), 156.9 [Fmoc C(O)], 157.7 [C(O)-$OC_6H_4NO_2$]. Anal. Calcd for $C_{25}H_{23}N_3O_6$ (461.47): C, 65.07; H, 5.02; N, 9.11. Found: C, 65.15; H, 5.04; N, 8.98. ES MS: m/z = 484.2 $[M + Na]^+$.

Fmoc-Protected Activated Valine Monomer 5b. Yield: 1.49 g (3.1 mmol, 64%) of white solid. Mp: >144−145 °C dec. R_f (EtOAc/hexanes, 1/1): 0.56. $[\alpha]_D^{24} = -36.3$ ($c = 0.25$, dioxane). ^{1}H NMR ([D$_8$]THF): δ = 0.95 [m, 7 H, $(CH_3)_2$ + $CH(CH_3)_2$], 3.37 (m, 2 H, CH_2NH), 4.20 (t, J = 6.6 Hz, 1 H, Fmoc CH), 4.40 (m, 2 H, Fmoc CH_2), 6.42 (d, J = 9.5 Hz, 1 H, NH), 7.19−7.36 (m, 7 H, 4 × Fmoc Ar CH + 2 × $C_6H_4NO_2$ + NH), 7.63 (m, 2 H, Fmoc Ar CH), 7.77 (d, 2 H, Fmoc Ar CH), 8.14 (d, 2 H, $C_6H_4NO_2$). ^{13}C NMR ($CDCl_3$): δ = 18.1 (CH_3), 19.3 (CH_3), 30.5 [$CH(CH_3)_2$], 44.3 (CH_2NH), 47.3 (Fmoc CH), 56.8 (CHNH), 66.8 (Fmoc CH_2), 120.0 (Fmoc Ar CH), 121.8, 124.9 ($C_6H_4NO_2$), 125.0, 127.1, 127.8 (Fmoc Ar CH), 141.3, 143.7 (Fmoc Ar quat C), 144.7, 153.7 (quat $C_6H_4NO_2$), 155.8 [Fmoc C(O)], 157.2 [C(O)$OC_6H_4NO_2$]. Anal. Calcd for $C_{27}H_{27}N_3O_6$ (489.53): C, 66.25; H, 5.56; N, 8.58. Found: C, 66.03; H, 5.62; N, 8.40. ES MS: m/z = 512.2 $[M + Na]^+$.

Fmoc-Protected Activated Leucine Monomer 5c. Yield: 2.10 g (4.2 mmol, 83%) of white solid. Mp: >144−146 °C dec. R_f (EtOAc/hexanes, 1/1): 0.67. $[\alpha]_D^{24} = -18.7$ ($c = 0.48$, dioxane). ^{1}H NMR ([D$_8$]THF): δ = 0.93 [m, 6 H, $(CH_3)_2$], 1.27−1.40 [m, 3 H, $CH_2CH(CH_3)_2$], 3.20 (br m, 2 H, CH_2NH), 3.84 (m, 1 H, CHNH), 4.19 (t, J = 7.0 Hz, 1 H, Fmoc CH), 4.34 (m, 2 H, Fmoc CH_2), 6.44 (d, J = 9.1 Hz, 1 H, CHNH), 7.20−7.36 (m, 5 H, 2 × $C_6H_4NO_2$ + 2 × Fmoc Ar CH + CH_2NH), 7.63 (m, 2 H, Fmoc Ar CH), 7.77 (d, 2 H, Fmoc Ar CH), 8.13 (d, 2 H, Fmoc Ar CH), 8.13 (d, 2 H, $C_6H_4NO_2$). ^{13}C NMR ($CDCl_3$): δ 22.0 (CH_3), 23.0 (CH_3), 24.8 [$CH(CH_3)_2$], 41.7 [$CH_2CH(CH_3)_2$], 46.8 (CH_2NH), 47.3 (Fmoc CH), 49.8 (CHNH), 66.7 (Fmoc CH_2), 120.0 (Fmoc Ar CH), 121.8, 124.9 ($C_6H_4NO_2$), 125.0, 127.1, 127.8 (Fmoc Ar CH), 141.3, 143.7 (Fmoc Ar quat C), 144.7, 153.6 (quat $C_6H_4NO_2$), 155.8 [Fmoc C(O)], 156.9 [C(O)OC_6H_4-NO_2]. Anal. Calcd for $C_{28}H_{29}N_3O_6$ (503.55): C, 66.79; H, 5.80; N, 8.34. Found: C, 66.62; H, 6.01; N, 8.30. ES MS: m/z = 526.2 $[M + Na]^+$.

Fmoc-Protected Activated Isoleucine Monomer 5d. Yield: 2.00 g (4.0 mmol, 80%). Mp: >138−140 °C dec. R_f (EtOAc/hexanes, 1/1): 0.63. $[\alpha]_D^{24} = -18.3$ ($c = 0.55$, dioxane). ^{1}H NMR ([D$_8$]THF): δ = 0.94 (m, 6 H, 2 × CH_3), 1.18 [m, 1 H, $CH(CH_2CH_3)(CH_3)$], 1.55 [m, 2 H, $CH(CH_2CH_3)(CH_3)$], 3.30 (br m, 2 H, CH_2NH), 3.68 (m, 1 H, CHNH), 4.20 (t, J = 6.6 Hz, 1 H, Fmoc CH), 4.28−4.45 (m, 2 H, Fmoc CH_2), 6.46 (d, J = 9.1 Hz, 1 H, CHNH), 7.20−7.36 (m, 7 H, 4 × Fmoc Ar CH + C_6H_4-NO_2 + CH_2NH), 7.64 (m, 2 H, Fmoc Ar CH), 7.78 (d, 2 H, Fmoc Ar CH), 8.13 (d, 2 H, $C_6H_4NO_2$). ^{13}C NMR ([D$_8$]THF): δ = 11.5 (CH_3), 15.7 (CH_3), 26.0 [$CH(CH_2CH_3)(CH_3)$], 37.8 [$CH(CH_2$-$CH_3)(CH_3)$], 43.7 (CH_2NH), 48.3 (Fmoc CH), 56.3 (CHNH), 120.5 (Fmoc Ar CH), 122.5, 125.4 ($C_6H_4NO_2$), 125.8, 127.6, 128.1 (Fmoc Ar CH), 142.2, 144.3 (Fmoc Ar quat C), 144.7, 153.6 (quat $C_6H_4NO_2$), 156.3 [Fmoc C(O)], 157.3 [C(O)OC_6H_4-NO_2]. Anal. Calcd for $C_{28}H_{29}N_3O_6$ (503.55): C, 66.79; H, 5.80; N, 8.34. Found: C, 66.87; H, 5.73; N, 8.26. ES MS: m/z = 526.3 $[M + Na]^+$.

Fmoc-Protected Activated Phenylalanine Monomer 5e. Yield: 2.69 g (3.5 mmol, 69%) of white solid. Mp: >166−168 °C dec. R_f (EtOAc/hexanes, 1/1): 0.53. $[\alpha]_D^{24} = -10.1$ (c = 0.50, dioxane). ^{1}H NMR ([D$_8$]THF): δ = 2.84 (d, J = 7.0 Hz, 2 H, $CH_2C_6H_5$), 3.30 (m, 2 H, CH_2NH), 4.01 (m, 1 H, CHNH), 4.16 (t, J = 7.0 Hz, 1 H, Fmoc CH), 4.31 (m, 2 H, Fmoc CH_2), 6.57 (d, J = 8.5 Hz, 1 H, CHNH), 7.05−7.36 (m, 12 H, 4 × Fmoc Ar CH + 2 × $C_6H_4NO_2$ + C_6H_5 + CH_2NH), 7.57 (m, 2 H, Fmoc Ar CH), 7.77 (d, 2 H, Fmoc Ar CH), 8.16 (d, 2 H, C_6H_4-NO_2). ^{13}C NMR ($CDCl_3$): δ = 38.9 ($CH_2C_6H_5$), 45.3 (CH_2NH), 47.2 (Fmoc CH), 52.7 (CHNH), 66.7 (Fmoc CH_2), 120.0 (Fmoc Ar CH), 121.9, 125.1 ($C_6H_4NO_2$) 125.1 (Fmoc Ar CH), 127.0 ($CH_2C_6H_5$), 127.1, 127.8 (Fmoc Ar CH), 128.8, 129.1 ($CH_2C_6H_5$), 136.9 (C_6H_5 quat C), 141.3, 143.7 (Fmoc Ar quat C), 144.4, 153.7 (quat $C_6H_4NO_2$), 155.7 [Fmoc C(O)], 156.3 [C(O)OC_6H_4-NO_2]. Anal. Calcd for $C_{31}H_{27}N_3O_6$ (537.57): C, 69.26; H, 5.06; N, 7.82. Found: C, 69.20; H, 5.12; N, 7.76. ES MS: m/z = 560.2 $[M + Na]^+$.

Fmoc-Protected Activated Tyrosine Monomer 5f. Yield: 3.38 g (5.5 mmol, 60%) of white solid obtained from 9.2 mmol of **7g**. Mp: >142−143 °C dec. R_f (EtOAc/hexanes, 1/1): 0.54. $[\alpha]_D^{24} = -6.2$ ($c = 0.49$, dioxane). ^{1}H NMR ([D$_8$]THF): δ = 1.27 [s, 9 H, $(CH_3)_3$], 2.79 (d, J = 7.0 Hz, 2 H, $CH_2C_6H_4$), 3.35 (m, 2 H, CH_2NH), 3.96 (m, 1 H, CHNH), 4.16 (t, J = 6.6 Hz, 1 H, Fmoc CH), 4.32 (m, 2 H, Fmoc CH_2), 6.58 (d, J = 8.4 Hz, 1 H, CHNH), 6.86 (d, 2 H, 2 × $CH_2C_6H_4$), 7.12 (d, 2 H, 2 × $CH_2C_6H_4$), 7.20−7.36 (m, 7 H, 4 × Fmoc Ar CH + 2 × C_6H_4-

NO_2 + CH_2NH), 7.59 (m, 2 H, 2 × Fmoc Ar CH), 7.77 (d, 2 H, Fmoc Ar CH), 8.16 (d, 2 H, $C_6H_4NO_2$). ^{13}C NMR ($CDCl_3$): δ = 28.8 [$(CH_3)_3$], 38.1 ($CH_2C_6H_4$), 47.2 (Fmoc CH), 52.7 (CHNH), 66.7 (Fmoc CH_2), 67.1 (CH_2NH), 78.4 [$C(CH_3)_3$], 120.0 (Fmoc Ar CH), 121.9 ($C_6H_4NO_2$), 124.3 ($CH_2C_6H_4$), 124.9 ($C_6H_4NO_2$), 125.0, 127.0, 127.7 (Fmoc Ar CH), 129.5 ($CH_2C_6H_4$), 131.3 ($CH_2C_6H_4$ quat C), 141.3, 143.7 (Fmoc Ar quat C), 144.7, 153.7 ($C_6H_4NO_2$ quat C), 154.3 ($CH_2C_6H_4$ quat C), 155.7 [Fmoc C(O)], 156.6 [$C(O)OC_6H_4NO_2$]. Anal. Calcd for $C_{35}H_{35}N_3O_7$ (609.67): C, 68.95; H, 5.79; N, 6.89. Found: C, 68.42; H, 5.58; N, 6.45. ES MS: m/z = 610.3 $[M + H]^+$.

Fmoc-Protected Activated Serine Monomer 5g. Yield: 2.19 g (3.6 mmol, 73%) of white solid. Mp: >140−142 °C dec. R_f (EtOAc/hexanes, 1/1): 0.57. $[\alpha]_D^{24}$ = +4.35 (c = 0.49, dioxane). ^1H NMR ([D$_8$]THF): δ = 1.19 [s, 9 H, $(CH_3)_3$], 3.30−3.50 (m, 4 H, $CH_2C_6H_4$ + CH_2NH), 3.87 (m, 1 H, $CHNH$), 4.20 (t, J = 6.6 Hz, 1 H, Fmoc CH), 4.32 (m, 2 H, Fmoc CH_2), 6.47 (d, J = 8.8 Hz, 1 H, $CHNH$), 7.21−7.40 (m, 7 H, 4 • Fmoc Ar CH + 2 × $C_6H_4NO_2$ + CH_2NH), 7.63 (d, 2 H, 2 × Fmoc Ar CH), 7.77 (d, 2 H, 2 • Fmoc Ar CH), 8.16 (d, 2 H, 2 × $C_6H_4NO_2$). ^{13}C NMR ($CDCl_3$): δ = 27.4 [$(CH_3)_3$], 44.4 (CH_2NH), 47.2 (Fmoc CH), 50.6 (CHNH), 62.4 (CH_2OtBu), 66.9 (Fmoc CH_2), 73.6 [$C(CH_3)_3$], 120.0 (Fmoc Ar CH), 121.9, 124.9 ($C_6H_4NO_2$), 125.0, 127.0, 127.7 (Fmoc Ar CH), 141.3, 143.7 (Fmoc Ar quat C), 144.6, 153.5 (quat $C_6H_4NO_2$), 155.9 [Fmoc C(O)], 156.7 [$C(O)OC_6H_4NO_2$]. Anal. Calcd for $C_{29}H_{31}N_3O_7$ (533.58): C, 65.28; H, 5.86; N, 7.88. Found: C, 65.20; H, 5.85; N, 7.93. ES MS: m/z = 556.2 $[M + Na]^+$.

Fmoc-Protected Activated Aspartic Acid Monomer 5h. Yield: 1.30 g (2.5 mmol, 49%) of white solid. Mp: >146−148 °C dec. R_f (EtOAc/hexanes, 1/1): 0.64. $[\alpha]_D^{24}$ = −19.4 (c = 0.53, dioxane). ^1H NMR ([D$_8$]THF): δ = 1.42 [s, 9 H, $(CH_3)_3$], 2.45 [m, 2 H, $CH_2C(O)OtBu$], 3.31 (m, 2 H, CH_2NH), 4.23 (m, 4 H, Fmoc CH + Fmoc CH_2 + $CHNH$), 6.61 (m, 1 H, NH), 7.21−7.36 (m, 7 H, 4 × Fmoc Ar CH + 2 × $C_6H_4NO_2$ + CH_2NH), 7.65 (m, 2 H, 2 × Fmoc Ar CH), 8.09 (d, 2 H, 2 × Fmoc Ar CH), 8.16 (d, 2 H, $C_6H_4NO_2$). ^{13}C NMR ($CDCl_3$): δ = 28.0 [$(CH_3)_3$], 37.8 ($CH_2C(O)OtBu$), 45.0 (CH_2NH), 47.2 (Fmoc CH), 48.5 (CHNH), 67.0 (Fmoc CH_2), 81.9 [$C(CH_3)_3$], 120.0 (Fmoc Ar CH), 121.9, 125.1 ($C_6H_4NO_2$), 125.1, 127.0, 127.8 (Fmoc Ar CH), 141.3, 143.6 (Fmoc Ar quat C), 144.7, 153.6 ($C_6H_4NO_2$ quat C), 155.7 [C(O)], 156.5 [C(O)], 170.2 [C(O)OtBu]. ES MS: m/z = 584.3 $[M + Na]^+$.

Fmoc-Protected Activated Lysine Monomer 5i. Yield: 2.19 g (3.6 mmol, 73%) of white solid. Mp: >148−150 °C dec. R_f (EtOAc/hexanes, 1/1): 0.25. $[\alpha]_D^{24}$ = −10.9 (c = 0.51, dioxane). ^1H NMR ([D$_8$]THF): δ = 1.40 [m, 15 H, $(CH_3)_3$ + $CH_2(CH_2)_3NHBoc$], 3.03 [m, 2 H, $CH_2(CH_2)_3NHBoc$], 3.24 (br m, 2H, CH_2NH), 3.74 (br m, 1 H, $CHNH$), 4.19 (t, J = 6.9 Hz, 1 H, Fmoc CH), 4.34 (m, 2 H, Fmoc CH_2), 6.01 (br m, 1 H, NHBoc), 6.46 (d, J = 8.8 Hz, 1 H, NHFmoc), 7.21−7.37 (m, 7 H, 4 × Fmoc Ar CH + 2 × $C_6H_4NO_2$ + NH), 7.64 (m, 2 H, Fmoc Ar CH), 7.77 (d, 2 H, Fmoc Ar CH), 8.15 (d, 2 H, $C_6H_4NO_2$). ^{13}C NMR ($CDCl_3$): δ = 22.5, 29.9, 31.6 ($CH_2(CH_2)_3NHBoc$), 28.4 [$(CH_3)_3$], 39.6 [$CH_2(CH_2)_3$], 45.8 (CH_2NH), 47.2 (Fmoc CH), 51.6 (CHNH), 66.7 (Fmoc CH_2), 79.3 [$C(CH_3)_3$], 120.0 (Fmoc Ar CH), 121.8, 125.0 ($C_6H_4NO_2$), 125.0, 127.0, 127.7 (Fmoc Ar CH), 141.3, 143.8 (Fmoc Ar quat C), 144.6, 153.8 ($C_6H_4NO_2$ quat C), 155.8 [C(O)], 156.3 [C(O)], 156.9 [C(O)]. Anal. Calcd for $C_{33}H_{38}N_4O_8$ (618.67): C, 64.07; H, 6.19; N, 9.06. Found: C, 64.15; H, 6.11; N, 8.88. ES MS: m/z = 619.3 $[M + H]^+$

Fmoc-Protected Activated Proline Monomer 5j. Yield: 2.08 g (4.3 mmol, 86%) of white solid. Mp: >134−136 °C dec. R_f (EtOAc/hexanes, 1/1): 0.40. $[\alpha]_D^{24}$ = −44.0 (c = 0.55, dioxane). ^1H NMR ($CDCl_3$): δ = 1.58−2.10 (m, 4 H, $CHCH_2CH_2CH_2$ + $CHCH_2CH_2CH_2$), 3.22−3.51 (m, 4 H, $CHCH_2CH_2CH_2$ + CH_2NH), 4.10 (m, 1 H, CHN), 4.24 (t, J = 7.0 Hz, 1 H, Fmoc CH), 4.45 (d, J = 7.3 Hz, 2 H, Fmoc CH_2), 6.79 (s, 1 H, CH_2NH), 7.25−7.44 (m, 6 H, 4 × Fmoc Ar CH + 2 × $C_6H_4NO_2$), 7.60 (d, 2 H, Fmoc Ar CH), 7.77 (d, 2 H, Fmoc Ar CH), 8.19 (d, 2 H, $C_6H_4NO_2$). ^{13}C NMR ($CDCl_3$): δ = 24.0 (CH_2), 29.5 (CH_2), 46.9 (CH_2NH), 47.0 (CH_2N), 47.3 (Fmoc CH), 60.8 (CHN), 67.6 (Fmoc CH_2), 120.0 (Fmoc Ar CH), 121.9, 125.0 ($C_6H_4NO_2$), 125.0, 127.0, 127.8 (Fmoc Ar CH), 141.3, 143.8 (Fmoc Ar quat C), 144.6, 153.4 (quat $C_6H_4NO_2$), 156.1 [Fmoc C(O)], 156.9 [$C(O)OC_6H_4NO_2$]. Anal. Calcd for $C_{27}H_{25}N_3O_6$ (487.51): C, 66.52; H, 5.17; N, 8.62. Found: C, 66.40; H, 5.16; N, 8.55. ES MS: m/z = 488.2 $[M + H]^+$.

Bisprotected Amine 8. Mono-Boc-protected ethylenediamine (**7**)[16] (7.70 g, 50 mmol) was dissolved in water (50 mL). The pH was adjusted to 9−9.5 using 1 N NaOH. Subsequently, a solution of Fmoc-OSu (16.9 g, 50 mmol) in acetonitrile (100 mL) was added in one portion. The product, which precipitated from the reaction mixture, was collected by filtration. The residue was washed with water and acetonitrile, redissolved in $CHCl_3$ and MeOH, and coevaporated with toluene. The residue was dried in a vacuum desiccator over P_2O_5 to give the product (16.2 g, 42 mmol, 84%) as a white solid. Mp: 155−156 °C. R_f (5% MeOH/DCM): 0.66. ^1H NMR ($CDCl_3$): δ = 1.43 [s, 9 H, $C(CH_3)_3$], 3.27 (br s, 4 H, 2 × CH_2NH), 4.19 (t, 1 H, Fmoc CH), 4.39 (d, 2 H, Fmoc CH_2), 4.85 (br s, 1 H, NH), 5.26 (br s, 1 H, NH), 7.25−7.41 (m, 4 H, Fmoc Ar CH), 7.58 (d, 2 H, Fmoc Ar CH), 7.75 (d, 2 H, Fmoc Ar CH). ^{13}C NMR ($CDCl_3$): δ = 28.3 [$(CH_3)_3$], 40.6 (CH_2NH), 41.6 (CH_2NH), 47.2 (Fmoc CH), 66.7 (Fmoc CH_2), 79.6 [$C(CH_3)_3$], 120.0, 125.0, 127.0, 127.7 (Fmoc Ar CH), 141.3, 143.9 (Fmoc Ar quat C), 156.6 [C(O)], 156.8 [C(O)]. Anal. Calcd for $C_{22}H_{26}N_2O_4$ (382.46): C, 69.09; H, 6.85; N, 7.32. Found: C, 68.93; H, 6.76; N, 7.26. ES MS: m/z = 383.2 $[M + H]^+$.

Fmoc-Protected Ethylenediamine Hydrochloride Salt (4k). A solution of bisprotected amine **8** (15.2 g, 40 mmol) in $CHCl_3$ (200 mL) was cooled to 0 °C. A saturated solution of HCl in ether (50 mL) was added dropwise, and the solution was allowed to warm to room temperature. A white precipitate was formed, which was collected by filtration. The residue was recrystallized from MeOH/ether/hexanes and dried in a vacuum desiccator over P_2O_5 to give product **4k** as a white solid (10.5 g, 33 mmol, 82%). ^1H NMR (D$_6$[DMSO]): δ = 2.80 (t, 2 H, CH_2NH_3), 3.22 (q, 2 H, CH_2NHFmoc), 4.22 (t, J = 5.9 Hz, 1 H, Fmoc CH), 4.31 (d, J = 5.9 Hz, 2 H, Fmoc CH_2), 7.29−7.48 (m, 5 H, 4 × Fmoc Ar CH + NHFmoc), 7.67 (d, 2 H, Fmoc Ar CH), 7.87 (d, 2 H, Fmoc Ar CH), 7.97 (br s, 3 H, NH_3). ^{13}C NMR ([D$_6$]DMSO): δ = 38.3 (CH_2), 38.8 (CH_2), 46.9 (Fmoc CH), 65.9 (Fmoc CH_2), 120.4, 125.5, 127.3, 127.9 (Fmoc Ar CH), 141.0, 144.1 (Fmoc Ar quat C), 156.5 [C(O)]. ES MS: m/z = 283.2 $[M + H]^+$.

Fmoc-Protected Activated Glycine Monomer 5k. A suspension of Fmoc-protected ethylenediamine hydrochloride (**4k**) (3.18 g, 10 mmol) and 4-nitrophenyl chloroformate (2.22 g, 11 mmol) in $CHCl_3$ (75 mL) was cooled to 0 °C. A solution of DiPEA (2.48 mL, 20 mmol) in $CHCl_3$ (25 mL) was added dropwise. The reactants slowly dissolved. When the product started to precipitate, the reaction mixture was allowed to warm to room temperature. After 2 h, the product was collected by filtration, washed with $CHCl_3$ and ether, and dried in a vacuum desiccator over P_2O_5 to give product **5k** as a white solid (4.2 g, 9.5 mmol, 95%). Mp: >174−175 °C dec. R_f (EtOAc/hexanes, 1/1): 0.20. ^1H NMR ([D$_8$]THF): δ = 3.27 (br s, 4 H, 2 × CH_2NH), 4.19 (t, 1 H, Fmoc CH), 4.38 (m, 2 H, Fmoc CH_2), 6.73 (br s, 1 H, NH), 7.24−7.35 (m, 7 H, 4 × Fmoc Ar CH + 2 × $C_6H_4NO_2$ + NH), 7.63 (d, 2 H, Fmoc Ar CH), 7.78 (d, 2 H, Fmoc Ar CH), 8.20 (d, 2 H, $C_6H_4NO_2$). ^{13}C NMR ([D$_8$]THF): δ = 41.3 (CH_2NH), 42.2 (CH_2NH), 48.4 (Fmoc CH), 120.6 (Fmoc Ar CH), 122.7, 125.6 ($C_6H_4NO_2$), 125.9, 127.7, 128.3 (Fmoc Ar CH), 142.3, 145.4 (Fmoc Ar quat C), 145.4, 154.2 ($C_6H_4NO_2$ quat C), 157.5 [C(O)], 157.6 [C(O)]. ES MS: m/z = 448.2 $[M + H]^+$.

Automated Preparation of Resin-Bound Urea Tetramer 10. Resin-bound tetraurea peptidomimetic **10** was prepared using an automated ABI 433A peptide synthesizer using slightly altered ABI Fastmoc 0.25 mmol protocols. Although the deprotection, washing, and acetylation modules were left unchanged, a few modifications were introduced into the coupling module. The coupling time was 90 min instead of 20 min, and since no coupling reagent was required for the couplings of the urea monomers, the coupling reagent flask was filled with NMP instead of a solution of HBTU and HOBt in NMP.

The apparatus was mounted with a reaction vessel filled with Argogel Rink-NH-Fmoc resin (0.74 g, 0.34 mmol/g, 0.25 mmol), and with four cartridges loaded with 1 mmol of leucine urea monomer **5c**, phenylalanine urea monomer **5e**, glycine urea monomer **5k**, and glycine urea monomer **5k**, respectively. The resin was preswelled with DCM (6×) and NMP (5×) and treated twice with 20% piperidine in NMP (3.6 and 7 min) to effect cleavage of the Fmoc group. After removal of the piperidine, the resin was washed with NMP (5×). Subsequently, the activated leucine urea monomer **5c** (1.0 mmol, 4 equiv) in the cartridge was dissolved in NMP (4 mL). To this solution was added 1 mL of 2 M DiPEA in NMP (2.0 mmol, 8 equiv), whereupon the resulting mixture was transferred into the reaction vessel, where an additional amount of NMP (approximately 5 mL) was added. After the resulting mixture was vortexed for 90 min, the reaction vessel was drained, and the resin was washed with NMP (4×). The resin was then treated for 10 min with 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) to acetylate any unreacted amino groups.

To complete the synthesis of immobilized tetramer **10**, the resin was subjected to similar deprotection, coupling, and capping cycles with the remaining three urea monomers (**5e**, **5k** (twice), respectively). The deprotection and coupling cycles were followed by monitoring the absorption of the dibenzofulvene−piperidine adduct at 301 nm (Figure 2). The loading was determined by Fmoc cleavage from a resin sample, and was 0.282 mmol/g, corresponding to an overall yield of 83% over eight steps. Finally, the Fmoc group was removed with piperidine to obtain resin-bound oligourea peptidomimetic **15**.

Cleavage of Urea Tetramer 10 from the Resin. Resin-bound urea tetramer **15** (0.355 g, 0.282 mmol/g, 0.10 mmol) was washed with NMP (5×). The amino terminus was acetylated by treatment with 5 mL of capping solution (vide supra). After 15 min, the solution was drained, and the resin was washed with NMP (6×) and DCM (5×) and dried in vacuo over P_2O_5. Tetramer **10** was then cleaved from the solid support by shaking of the resin (0.355 g, 0.288 mmol/g, 0.10 mmol) with 5 mL of TFA/H_2O/TIS/EDT (92.5/2.5/2.5/2.5) for 3 h. Subsequently, the resin was filtered and washed with 2 mL of TFA. The filtrate was concentrated in vacuo to a volume of approximately 1 mL and extruded into 40 mL of cold MTBE/hexanes (1/1). A white fluffy precipitate was formed, which was collected by centrifugation (3500 rpm, 5 min). The supernatant was decanted, after which the residue was resuspended in 40 mL of MTBE/hexanes (1/1) and centrifuged again. This was repeated twice. Finally, the residue was purified by preparative HPLC to give 29 mg (0.053 mmol, 53%) of tetramer **10** after lyophilization. Exact mass: 550.349 [M + H]$^+$ (calcd 550.347). HPLC: >99% pure. ^{1}H NMR ([D_6]-DMSO): δ = 0.83 [m, 6H, (CH_3)$_2$], 1.14 [t, 2H, CH_2CH(CH_3)$_2$], 1.58 [m, 1H, CH(CH_3)$_2$], 1.78 (s, 3H, C(O)CH_3), 2.64 (m, 4H, ArCH_2 + CH_2NAc), 2.8−3.2 (m, 10H, 5 × CH_2NHC(O)NH), 3.4−4.0 (m, 8H, 2 × CHNH + NHC(O)NH_2 + H_2O), 5.7−6.1 (m, 6H, 3 × NHC(O)NH), 7.21 (m, 5H, ArH), 7.89 (br s, NHAc).

Preparation of Resin-Bound Neurotensin Derivative 17. Resin-bound neurotensin derivative **17** was prepared analogously to **10**. First, Argogel S-OH (0.38 mmol/g) was coupled with Fmoc-Leu-OH using the procedure of Sieber.[20] The loading was determined by Fmoc cleavage from a resin sample, and was 0.33 mmol/g. Next, isoleucine monomer **5d**, tyrosine monomer **5f**, proline monomer **5j**, and lysine monomer **5i** (twice) were coupled, respectively. After removal of the Fmoc group, cleavage from the resin was carried out as was described above for urea tetramer **10** to yield a mixture of the desired oligourea peptidomimetic **17** along with hydantoin **18** in a 2/1 ratio (according to HPLC). Total yield: 105 mg (0.116 mmol, 46%). Exact mass: 906.625 [M + H]$^+$ (calcd 906.625 for the linear oligomer **17**) and 888.614 [M + H]$^+$ (calcd 888.615 for the hydantoin **18**).

^{1}H NMR (D_2O) (**17**): δ = 0.86 (m, 13H), 1.07 (m, 1H), 1.3−1.9 (m, 20H), 2.42 (m, 1H), 2.7−3.0 (m, 3H), 3.0−3.4 (m, 10H), 3.4−4.0 (m, 9H), 4.05 (m, 1H), 5.4 (s, 3H), 6.77 (d, J = 8.2 Hz, 2H), 7.09 (m, 2H).

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Supporting Information Available: ^{1}H NMR spectra of compounds **10** and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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