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Synthesis of Diacetylene-Containing Peptide Building Blocks and Amphiphiles, Their Self-Assembly and Topochemical Polymerization in Organic Solvents

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Abstract: A series of functional iodoacetylenes was prepared and converted into the corresponding diacetylene-substituted amino acids and peptides via Pd/Cu-promoted sp–sp carbon cross-coupling reactions. The unsymmetrically substituted diacetylenes can be incorporated into oligopeptides without a change in the oligopeptide strand's directionality. Thus, a series of oligopeptide-based, amphiphilic diacetylene model compounds was synthesized, and their self-organization as well as their UV-induced topochemical polymerizability was investigated in comparison to related polymer-substituted macromonomers. Solution-phase IR spectroscopy, gelation experiments, and UV spectroscopy helped to confirm that a minimum of five N-H···O=C hydrogen-bonding sites was required in order to obtain reliable aggregation into stable β-sheet-type secondary structures in organic solvents. Furthermore, the non-equidistant spacing of these hydrogen-bonding sites was proven to invariably lead to β-sheets with a parallel β-strand orientation, and the characteristic IR-spectroscopic signatures of the latter in organic solution was identified. Scanning force micrographs of the organogels revealed that compounds with six hydrogen-bonding sites gave rise to high aspect ratio nanoscopic fibrils with helical superstructures but, in contrast to the related macromonomers, did not lead to uniform supramolecular polymers. The UV-induced topochemical polymerization within the β-sheet aggregates was successful, proving parallel β-strand orientation and highlighting the effect of the number and pattern of N-H···O=C hydrogen-bonding sites as well as the hydrophobic residue in the molecular structure on the formation of higher structures and reactivity.

Keywords: acetylenes · oligopeptides · organogels · self-assembly · supramolecular chemistry

Introduction

Typical examples of biopolymers exhibit hierarchical structure formation;[1] they have a well-defined molecular structure (primary structure), fold segment-wise into distinct conformations (secondary structure), arrange the folded segments into specific topologies (tertiary structure), and then spontaneously self-assemble into the final material (quaternary structure). Combining this kind of higher-order structure formation with properties only observed in synthetic polymers, such as the optoelectronic activity of π-conjugated polymers, might lead to interesting materials for applications at the interface of microelectronics and the life sciences. Significant advances in this field have been achieved in recent years on the basis of concerted efforts in synthetic organic, supramolecular, as well as preparative polymer chemistry.[2–4] Hierarchically structured, dynamically folded polymers have, for example, been prepared by extending the foldamer approach[5,6] toward high molecular weight materials[7–9] including helical poly(acetylene)s as a prominent class of folded, fully π-conjugated polymers.[10–16]

We recently described a complementary strategy to obtain well-defined, hierarchically structured π-conjugated polymers that was based on the self-assembly and topochemical polymerization of the diacetylene macromonomers **1** (see below).[17–20] Related attempts to extend the scope of the UV-induced topochemical diacetylene polymerization from single crystals[21,22] or crystalline mono- and multilayers[23–27] toward less geometrically constrained systems such as vesicles and other types of colloidal structures[28–33] or fibrillar aggregates in organogels[34–40] have been spurred by the prospect of potential applications, for example, in biosensing.

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Thus, a variety of diacetylene-containing lipid amphiphiles with chiral polar head groups, such as phosphatidyl cholines,[41–44] aldonamides,[45,46] amino acids,[47,48] and oligopeptides[49] was found to furnish one-dimensional supramolecular aggregates with helical superstructures that could be covalently cross-linked by UV irradiation. While, in all of these examples, hydrogen bonding between the head groups plays an important role to translate the molecular chirality into a helical superstructure, the phase segregation and crystallization of the long-chain hydrophobic tails (or spacers) was the decisive factor for the formation of supramolecular aggregates. Furthermore, the diacetylene moieties were always incorporated into these hydrophobic segments so that the packing of the latter controlled the topochemical polymerization. Hence, the observed helical structures are to be regarded as micellar or vesicular structures and typically exhibited a mixture of superstructures and a distribution of diameters from dozens of nanometers to, in some cases, several micrometers. Consequently, the topochemical diacetylene polymerization inside these aggregates may serve as a convenient way of covalent capture but it does not lead to well-defined polymers with a uniform tertiary or quaternary structure.

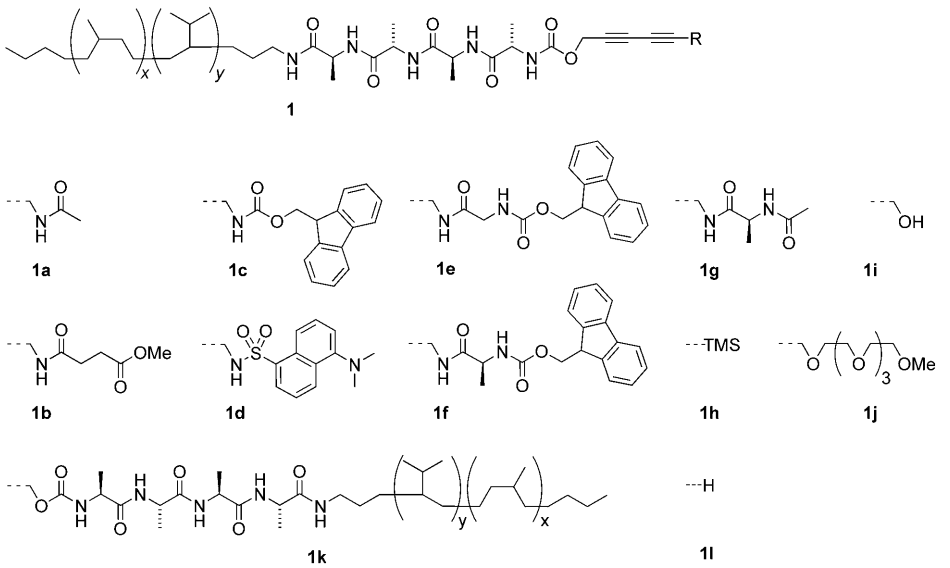


Figure 1. Diacetylene macromonomers with (5+x) N–H···O=C hydrogen-bonding sites (x = 0, 1, 2, 5) used as precursors for the preparation of π-conjugated polymers with a well-defined, multiple-helical quaternary structure.[17–20]

In marked contrast to the above examples, macromonomers **1** (Figure 1) comprised hydrogenated poly(isoprene) as a non-crystallizable hydrophobic segment, and the diacetylene functions were incorporated directly into the hydrogen-bonding array.[17–20] As a consequence of the chosen molecular architecture, the self-assembly was driven exclusively by β-sheet formation in organic solution. Thus, the molecules self-organized into distinct, uniform helical superstructures constituted from a defined, finite number of stacked β-sheet tapes, presumably controlled by the number and pattern of the molecules' N–H···O=C hydrogen-bonding sites.[17–20,50] These aggregates may, hence, be regarded as hierarchically structured supramolecular polymers rather than micellar or vesicular structures. As the packing of the oligopeptide β-strands inside the constituting β-sheet tapes controlled the arrangement of the diacetylene moieties, their topochemical polymerization proceeded under complete preservation of the previously assembled superstructures and, consequently, furnished oligopeptide-functionalized poly(diacetylene)s with defined multiple-helical quaternary structures. The obtained polymers also exhibited a rich dynamic folding behavior in solution which was associated with their solvatochromic transitions.[19,20]

In the present paper, we report on the synthesis of a series of functionalized iodopropargylamine derivatives and their conversion into a variety of peptide-substituted diacetylenes which may be used as building blocks in oligopeptide synthesis. Starting from these building blocks, we synthesized the diacetylene-containing oligopeptide amphiphiles **2a–e** (Figure 2) as a set of simplified, low molecular weight model compounds. These were designed to test some of the molecular parameters controlling the self-assembly of the macromonomers **1**. The results from IR spectroscopy, scanning force microscopy (SFM), gelation experiments, UV, and CD spectroscopy proved that compounds with a minimum of five N–H···O=C hydrogen-bonding sites reliably gave rise to β-sheet aggregates with a parallel β-strand orientation which, in contrast to macromonomers **1**, led to the formation of organogels that could then be polymerized. In conclusion, the molecular design of the model compounds **2** helped to elucidate the detailed role of the N–H···O=C hydrogen-bonding sites and the hydrophobic polymer segments in order to achieve well-defined, self-assembled superstructures from **1**. This understanding is essential for the preparation of tailored supramolecular scaffolds and will hopefully serve as a guideline for the preparation of hierarchically structured synthetic materials in the future.

Results and Discussion

Preparation of synthetic building blocks: In order to synthesize the desired diacetylene-containing peptide building blocks via an sp–sp carbon cross-coupling analogous to Sonogashira–Hagihara reaction conditions,[51–54] a series of iodoacetylene derivatives was required, in particular, iodopropargyl amine derivatives. As various attempts to prepare

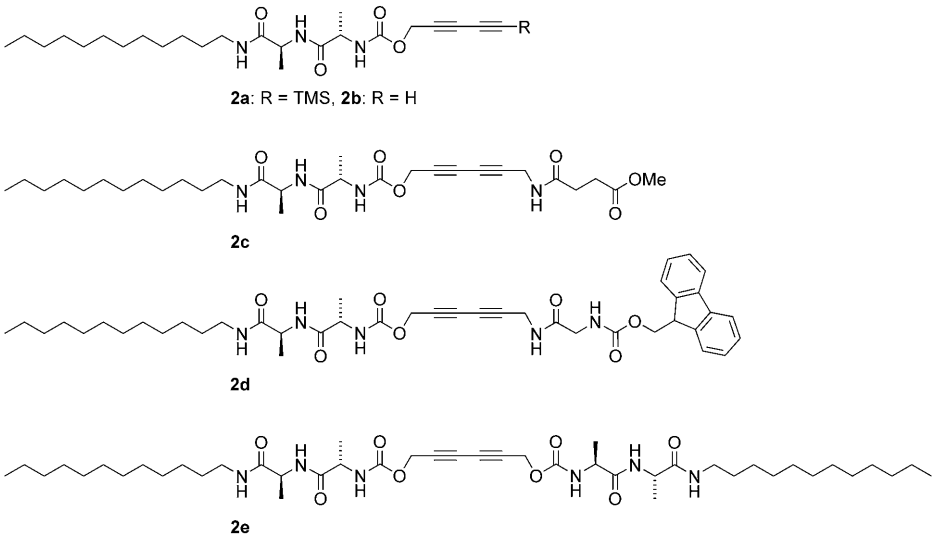


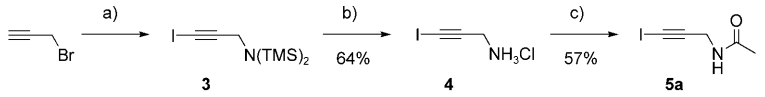
Figure 2. Diacetylene-containing oligopeptide amphiphiles as model monomers with (3+x) N–H···O=C hydrogen-bonding sites (x = 0–3) investigated for their self-assembly and topochemical polymerizability.

these compounds via direct iodination of propargyl amine had failed in our hands, we resorted to preparing 3-iodopropargyl amine hydrochloride **4** from commercially available propargyl bromide in a simple one-pot procedure which was an adaptation of a previously published procedure for the synthesis of other propargyl and allyl compounds carrying silylated amine functionalities (Scheme 1).[55] Thus, propargyl bromide was added to a solution of two equivalents of lithium hexamethyldisilazane (LHMDS) in diethyl ether at −78 °C. The reaction was allowed to reach room temperature in order to be complete, before iodine was added, again, at −78 °C. An aqueous workup and a subsequent removal of the excess hexamethyldisilazane (HMDS) by distillation afforded the crude silylated iodopropargylamine **3** which was directly subjected to alcoholysis in a freshly prepared mixture of anhydrous HCl in $MeOH/CH_2Cl_2$. The corresponding acetamide **5a** was then straightforwardly prepared by acetylation of **4** (Scheme 1).

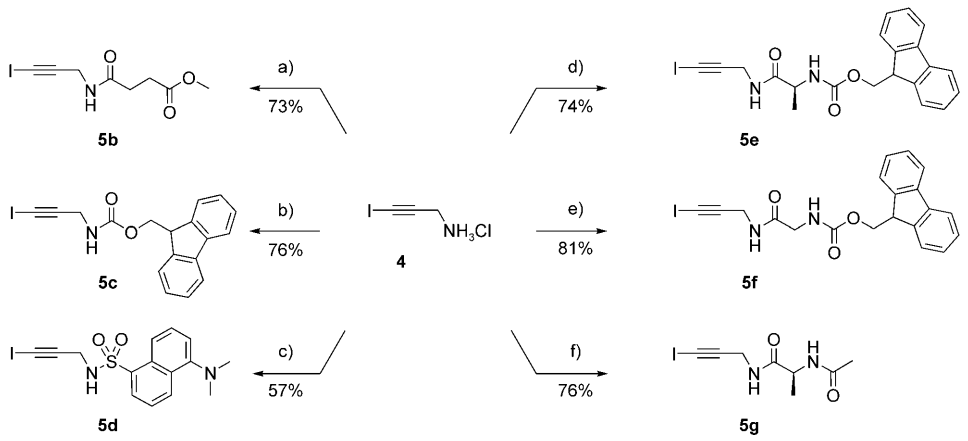
By analogy, iodopropargyl amide **5b**, carbamate **5c**, sulfonamide **5d**, as well as the L-alanyl and glycyl peptides **5e–g** were obtained from **4** by appropriate acylation or peptide coupling reactions (Scheme 2).

Additionally, 1-iodo-2-trimethylsilylacetylene **5h**, iodopropargyl alcohol **5i**, as well as the analogous oligo(ethylene oxide) derivative **5j** were straightforwardly prepared from the corresponding terminal acetylenes via (modified) literature procedures (Scheme 3).[56]

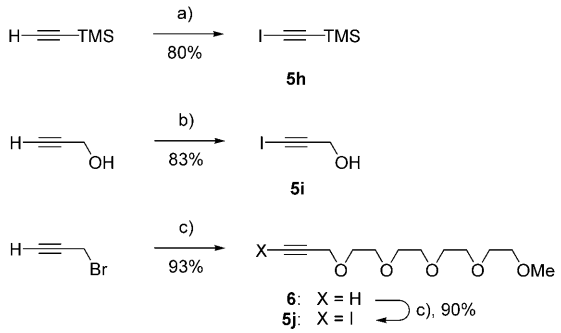
With the functional iodoacetylenes **5a–j** in hands, the corresponding diacetylene-containing amino acids **8a–j** were synthesized via a Pd-catalyzed sp–sp carbon cross-coupling utilizing conditions analogous to the Sonogashira–Hagihara[51] coupling (Scheme 4), starting from the *N*-propargyloxycarbonyl-L-alanine *tert*-butyl ester (**7**) which had been synthesized in analogy to a published procedure for propargyloxycarbonyl-protected amino acids.[57] Among various different reaction conditions and catalyst systems investigated, the coupling reaction in tetrahydrofuran (THF) using [$PdCl_2(PPh_3)_2$] as the catalyst, CuI as the cocatalyst, and diisopropylamine (DIPA) as the base delivered the most satisfactory results for almost all iodoacetylene derivatives. Thus, the desired unsymmetrically substituted diacetylenes were obtained in isolated yields of 50–70%. Typically, only minor amounts of the symmetric diacetylenes resulting from either the homocoupling of **7** (≈10%) or the self-coupling of the



Scheme 1. Synthesis of iodopropargylamine derivatives: a) 2 equiv HMDS, 2 equiv BuLi; then I_2, Et_2O, −78 °C to RT; b) HCl in $MeOH/CH_2Cl_2$; c) Ac_2O, TEA, CH_2Cl_2.



Scheme 2. Derivatization of iodopropargylamine **4**: a) Methyl succinyl chloride, CH_2Cl_2, DIEA, 0 °C; b) Fmoc-Cl, CH_2Cl_2, DIEA, 0 °C; c) dansyl chloride, CH_2Cl_2, DIEA, 0 °C; d) Fmoc-L-Ala-OH, PyBOP, CH_2Cl_2/DMF, DIEA, 0 °C; e) Fmoc-Gly-OH, PyBOP, CH_2Cl_2/DMF, DIEA, 0 °C; f) Ac-L-Ala-OH, PyBOP, CH_2Cl_2/DMF, DIEA, 0 °C.

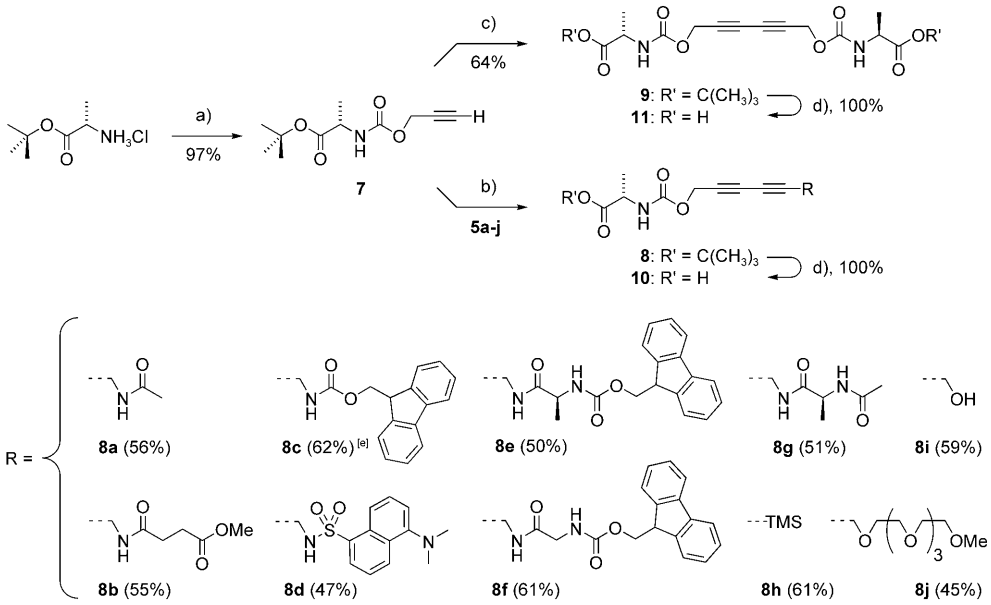


Scheme 3. Preparation of other iodoacetylene building blocks: a) *n*BuLi, THF, −78 to 0 °C; then I_2, −78 °C to RT, 16 h; b) 4 equiv KOH, I_2, MeOH, RT, 16 h; c) tetra(ethylene glycol) monomethyl ether, NaH, THF, 0 °C, 16 h; then 4 equiv KOH, I_2, MeOH, RT, 16 h.

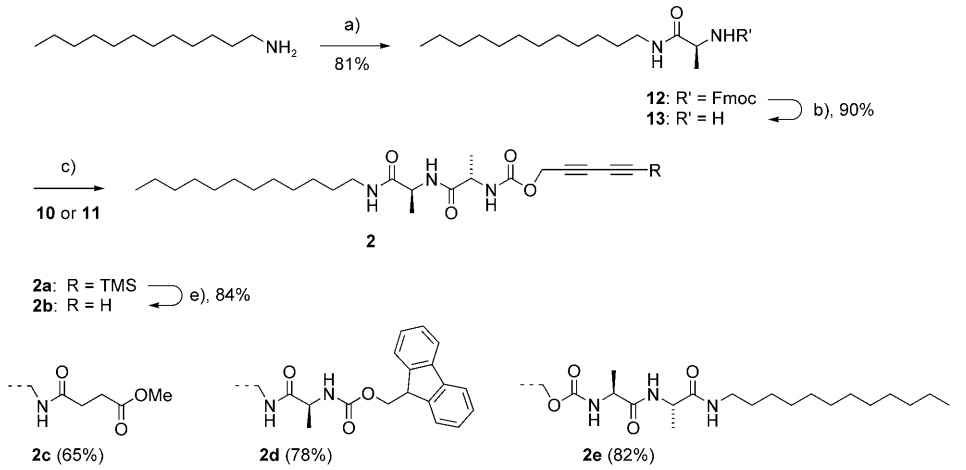
respective iodoacetylene **8** (≈10–25%, depending on the excess of **8**) were observed. A notable exception turned out to be the Fmoc-substituted derivative **8c**, which was obtained as an inseparable ternary mixture of the three coupling products that could only be purified after the following step. Furthermore, iodopropargylamine hydrochloride **4** failed to deliver any isolable product at all, making its derivatization prior to the acetylene heterocoupling reactions inevitable.

In addition to the thus obtained unsymmetrically substituted diacetylene amino acid derivatives, the symmetric bis-(L-alanyl)-substituted diacetylene **9** was prepared by an acetylene homocoupling reaction under Hay[58] conditions (Scheme 4). The *tert*-butyl esters **8a–j** and **9** were finally converted into the free carboxylic acids **10a–j** and **11**, respectively, by treatment with trifluoroacetic acid (TFA) in CH_2Cl_2. After removal of the solvent and TFA in high vacuum, the free acids were typically obtained in quantitative yields and used in subsequent peptide coupling reactions without further purification. It is worth noting that, in particular, the Fmoc-protected, unsymmetrically substituted diacetylenes **10c**, **10e**, and **10f** are useful peptide building blocks that can be incorporated into oligopeptides without a change in the strand directionality and may, for instance, be applied as non-natural amino acids in solid-phase peptide synthesis.

Design and synthesis of diacetylene model monomers: All of the free carboxylic acid building blocks **10a–j** were utilized in the synthesis of macromonomers **1** by coupling them to prefabricated oligopeptide–polymer conjugates such as hPI-NH-Ala_3-H (hPI = hydrogenated poly(isoprene) with an average degree of polymerization P_n = 10–12) analogous to previously published procedures.[17–20] Additionally, a subset of these building blocks was also used to prepare a series of simple diacetylene monomers as low molecular weight, monodisperse model compounds for the macromonomers. For this purpose, the hydrophobic polymer segments used in **1** were substituted with simple dodecyl residues. The model compounds were to comprise the same end groups and also retain a comparable hydrophilic–hydrophobic balance, so that the amino acid sequence was appropriately shortened. Hence, the model compounds **2** utilized L-alanyl-L-alanine self-assembling segments, resulting in a total of (3+*x*) N–H···O=C hydrogen-bonding sites (*x* = 0–3). Starting from the appropriate diacetylene-containing peptides **10** or **11**, the diacetylene monomers **2a** and **2c–e** were obtained by simple PyBOP-promoted peptide-coupling reactions and conveniently purified by precipitation into water (Scheme 5). The terminal diacetylene **2b** was then obtained via desilylation of **2a**. While the removal of the TMS group with tetrabutylammonium fluoride (TBAF) in $CHCl_3$/THF



Scheme 4. Synthesis of diacetylene-containing amino acid building blocks: a) Propargyl chloroformate, TEA, CH_2Cl_2, 0 °C; b) **5a–j**, [$PdCl_2(PPh_3)_2$] (2 mol%), CuI (10 mol%), DIPA, THF, 0 °C; c) TMEDA, CuCl, air, acetone; d) TFA, CH_2Cl_2, 3–16 h; e) isolated yield of **10c** over two steps.



Scheme 5. Synthesis of diacetylene model monomers. a) Fmoc-L-Ala-OH, PyBOP, DIEA, CH_2Cl_2/DMF, RT; b) piperidine, $CHCl_3$, RT; c) PyBOP, DIEA, CH_2Cl_2/DMF, RT; d) $AgNO_3$, EtOH/MeOH/H_2O; then KI.

or K_2CO_3 in CH_2Cl_2/MeOH had failed in our hands because of an epimerization of the peptides, **2b** was cleanly obtained in 91% yield following a mild deprotection protocol using $AgNO_3$/KI in a MeOH/EtOH/H_2O mixture as the solvent.[59,60]

Gelation in organic solvents: The diacetylene model monomers **2** were investigated concerning their ability to self-assemble into nanostructures in organic solution that would allow for a topochemical polymerization in analogy to their more complex macromolecular siblings **1**. We, therefore, attempted to dissolve the model compounds in various solvents such as CH_2Cl_2, $CHCl_3$, THF and cyclohexane, typically at a concentration of 1 gL^{-1}. Compound **2a** formed clear solutions in all of these solvents and did not cause gelation or undergo polymerization upon UV irradiation (see below). Thus, more than 45 gL^{-1} could be dissolved in CH_2Cl_2, $CHCl_3$ and THF without any visible gel formation. Likewise, **2b** showed no tendency toward gel formation in any solvent, although its overall solubility was lower, and it was virtually insoluble in cyclohexane. Upon heating these solutions, their color typically turned to orange-brown, probably due to random cross-linking of the diacetylene functions. In the solid state, the compound was found to be unstable toward degradation, changing its color to brown within a few days even when stored in the dark.

By contrast, compounds **2c–e** showed trends in their solubility and gelation properties which qualitatively scaled with their number of hydrogen-bonding sites (Figure 3). Thus, **2c** was found to form a mechanically weak gel in CH_2Cl_2 at a concentration of 1 gL^{-1} at room temperature but gave rise to solutions in $CHCl_3$ as well as THF. Compound **2d** formed weak gels in CH_2Cl_2 and $CHCl_3$ under the same conditions which were stable up to about 35 °C, but it remained soluble in THF. Finally, **2e** was an efficient organogelator and formed stable gels in CH_2Cl_2, $CHCl_3$ and even in THF at concentrations as low as 0.5 gL^{-1}. These gels were stable up to the solvents' boiling points, attaining only a slight red hue indicative of a heat-induced polymerization. For all model monomers, the UV irradiation of solutions did not lead to a color change, but the organogels immediately turned violet to dark purple, clearly indicating poly(diacetylene) formation (see below). The gel formed from **2e** in THF appeared to be the most reactive as it already turned dark purple when stored at room temperature in the dark. It is very important to acknowledge that these observed gelation properties are distinctly different from the behavior of the macromonomers **1** and more in line with the properties of typical diacetylene-containing amphiphiles.[34–49] Despite their significantly larger number of N–H···O=C hydrogen bonds and resulting tendency to aggregate at even micromolar concentrations, the macromonomers **1** had not shown any tendency to form macroscopic gels in organic solvents at all even at high concentrations, presumably due to the presence of more soluble[61] and uniform supramolecular polymers without branching points with extreme persistence lengths, and, accordingly, little tendency to form entanglement networks.

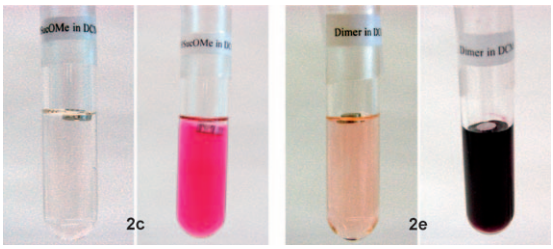


Figure 3. Representative pictures of the mechanically stable gels formed from **2c** and **2e** before and after UV irradiation.

IR Spectroscopy in organic solvents: Macromonomers **1** had been found to give rise to IR spectra with different characteristic signatures depending on the number and pattern of N–H···O=C hydrogen-bonding sites in the molecules, which we had tentatively attributed to parallel versus antiparallel β-sheet formation.[17–20] It should be noted, however, that problems in the detailed interpretation of the IR spectra arose from the conflicting, contradictory, and often arbitrary assignments of IR bands to certain secondary structures in the literature,[62] from the presence of non-peptidic (carbamate, amide) hydrogen-bonding sites in the macromonomers, and from the use of an organic solvent instead of water. IR spectra of the drastically simplified diacetylene

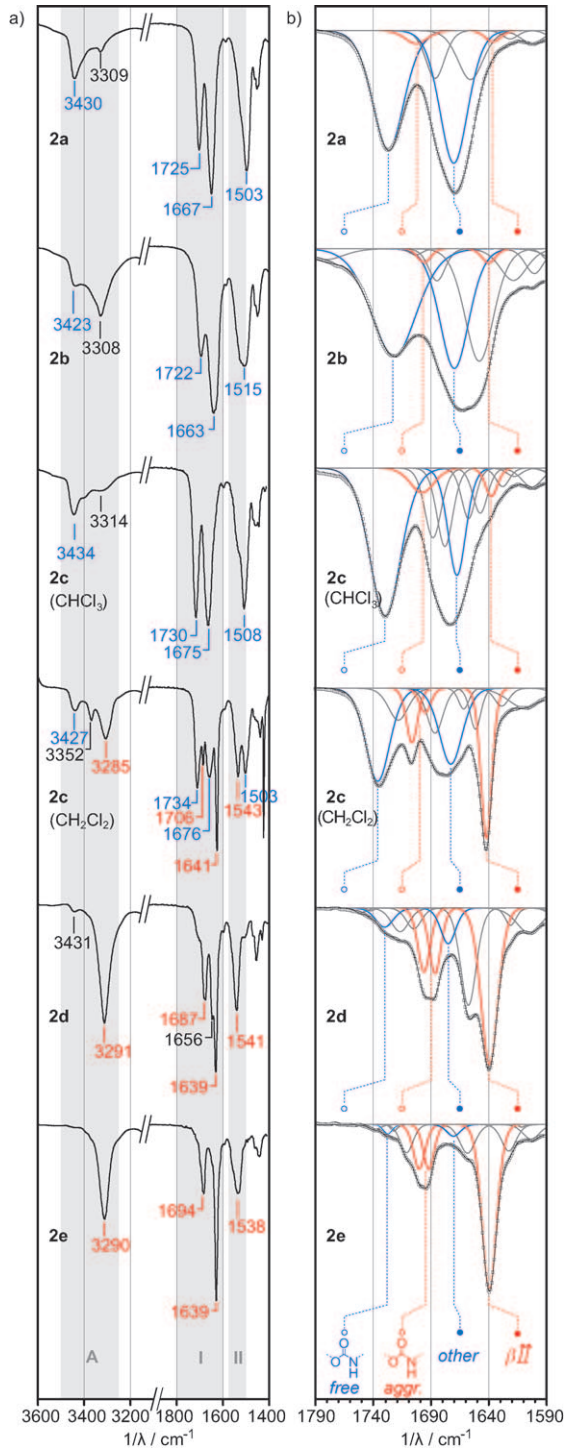


Figure 4. a) IR spectra and b) the corresponding peak deconvolution in the amide I region proved that **2a–c** gave no indication of aggregation in chloroform solutions (indicative peaks marked in blue). By contrast, the weak gel obtained from **2c** in CH_2Cl_2 as well as the gels from **2d** and **2e** in chloroform exhibited IR spectra consistent with an aggregation into parallel β-sheets (indicative peaks marked in red). The degree of order increased with the number of N–H···O=C hydrogen-bonding sites in the molecules.

model monomers **2a–e** (Figure 4a) ought to help clarify the remaining issues and also establish a set of guidelines for the use of N–H···O=C hydrogen-bonding sites in order to achieve specific types of aggregation in organic solvents.

Thus, all model compounds which remained soluble and did not form gels gave rise to non-aggregated secondary structures in organic solvents. For example, the IR spectra of the TMS-functionalized derivative **2a**, which comprised (3+0) N–H···O=C hydrogen-bonding sites and was well-soluble in $CHCl_3$, revealed an amide A absorption at 3430 cm^{-1}, that is, far above the value of 3300 cm^{-1} that would be expected for N–H bonds in an aggregated state. Only the small IR band observed at 3309 cm^{-1} may be regarded as indicative of a low degree of β-sheet formation. In the amide I region, first of all, a broad peak at 1725 cm^{-1} was observed that can be assigned to the carbamate function in a non-hydrogen-bonded state.[63] The observed broad and featureless amide I absorption with a maximum at 1667 cm^{-1} implied that the molecules gave rise to a mixture of non-aggregated secondary structures, such as random coil and "turn-like" structures.[61] Likewise, the amide II region contained one broad and featureless band with a maximum at 1503 cm^{-1}, corroborating this interpretation. Derivative **2b**, featuring the same number and pattern of hydrogen-bonding sites, showed a strikingly similar IR signature. The main amide A absorption was observed at 3308 cm^{-1} accompanied by a smaller band at 3423 cm^{-1}, showing that β-sheet formation was still not predominant but might be slightly more favorable as compared to **2a**, probably because of the reduced steric hindrance of the H-terminated versus the TMS-protected diacetylene. The IR absorptions in the amide I and II regions at 1722, 1663 (broad), and 1515 cm^{-1} proved that the situation was essentially the same as in **2a**, that is, the carbamate was not hydrogen-bonded, and the molecule attained random coil or "turn-like" conformations.

By contrast, those model compounds which formed stable organogels showed a completely different behavior. Thus, the symmetric model compound **2e** as the other extreme, featuring (3+3) hydrogen-bonding sites and forming the most stable organogels in $CHCl_3$, showed a single, sharp amide A band at 3290 cm^{-1}, consistent with predominantly aggregated N–H bonds in a β-sheet arrangement and matching exactly the values observed in the cases of the corresponding macromonomers **1**. The amide I region of **2e** was dominated by a band at 1639 cm^{-1}. The position of this main amide I band was curiously shifted away from the typical values of 1625–1630 cm^{-1} reported for antiparallel β-sheet-type secondary structures from related oligopeptides and their polymer conjugates in solution,[63–68] and it did not match the value of 1626 cm^{-1} calculated for a single antiparallel poly(alanine) β-sheet,[69] either. However, it was very close to the value of 1637 cm^{-1} calculated for the hypothetical infinite, single, parallel poly(alanine) β-sheet,[69,70] as well as the experimental value of 1642 cm^{-1} observed in a tripeptide that formed parallel β-sheet structures in the crystalline state.[71] Likewise, the amide II region revealed a single peak at 1538 cm^{-1} which also closely matched the calculated value for a single parallel β-sheet[69,70] and was distinctly different from typical examples of antiparallel β-sheets.[63–68]

Finally, the absorption of the carbamate function was observed at 1694 cm^{-1}, which was clearly indicative of a carbamate in a hydrogen-bonded state.[63] Hence, the band observed at around 1690 cm^{-1} does not necessarily originate from the presence of antiparallel β-sheet structures in this particular case and is, hence, not contradictory to the above interpretation. This interpretation is, moreover, supported by the fact that **2e** should be expected to aggregate into parallel β-sheets due to its symmetry, if the molecules are aligned in-register and the maximum number of N–H···O=C hydrogen bonds is to be achieved.

The remaining model compounds **2c** and **2d** exhibited a behavior between the above extremes, according to the respective number of (3+1) or (3+2) hydrogen-bonding sites. Thus, the IR spectra of **2c** in $CHCl_3$ solution showed amide A absorptions at 3434 and 3314 cm^{-1} and two broad bands at 1730 and 1675 cm^{-1} which can be assigned to the $\nu_{C=O}$ vibrations of, on one hand, the ester and the free carbamate as well as, on the other hand, the amide and peptide $\nu_{C=O}$ vibrations, proving that the molecules were i) not aggregated and ii) the peptide mainly attained a "turn-like" conformation, just like **2a** and **2b**. However, the IR signature of **2c** changed drastically when the weak gel obtained in CH_2Cl_2 was investigated. The amide A region was now dominated by an absorption located at 3285 cm^{-1}, well in line with an aggregation into β-sheet structures. The additional, smaller bands at 3352 and 3427 cm^{-1} indicated that a certain fraction of molecules remained non-aggregated and the degree of order was still not very high. This interpretation was confirmed by the main amide I absorption located at 1641 cm^{-1} accompanied with a smaller one at 1676 cm^{-1}. The ester and the carbamate groups were now separated into two bands at 1734 and 1706 cm^{-1}, respectively, the latter being indicative of a carbamate in a hydrogen-bonded state. Finally, the amide II region revealed two peaks at 1543 and 1503 cm^{-1}, the former exactly matching the value calculated for a single, parallel β-sheet[69,70] and the latter proving the coexistence of molecules with a different secondary structure. In conclusion, the amide A, carbamate, amide I, and amide II absorptions together converged into a consistent picture. Apparently, model compound **2c** with its (3+1) hydrogen-bonding sites was just on the border of being able to aggregate, as it predominantly remained disordered in $CHCl_3$ as the more polar solvent[72] but formed the desired parallel β-sheet-type aggregates in CH_2Cl_2 to a certain extent. Finally, the IR spectrum of the gel (in $CHCl_3$) of **2d** with its (3+2) N–H···O=C hydrogen bonds, exhibited a ν_{N-H} vibration at 3291 cm^{-1} with only a minor shoulder at 3431 cm^{-1}. The amide I region was dominated by a band at 1639 cm^{-1}, the carbamate band was observed at 1687 cm^{-1}, and the single amide II absorption band was located at 1541 cm^{-1}, all consistent with the presence of highly ordered parallel β-sheet aggregates, as in the case of **2e**.

It is worth mentioning that the observed band structure in the IR spectra, in particular in the case of **2d** and **2e**, was considerably more clear and better interpretable than in related literature examples.[64–66,73,74] This allowed for a straightforward deconvolution of the IR absorptions in the region between 1580 and 1780 cm^{-1} with a limited number of peaks at almost constant positions and reasonable peak widths (Figure 4b). Consistent with the global analysis of the spectra discussed above, the IR spectra of chloroform solutions of **2a–c** were dominated by a peak at around 1670 cm^{-1}, and the predominant peak in the case of gels of **2c–e** was located at around 1640 cm^{-1}. Interestingly, the normalized areas of these two peaks showed a systematic dependence on the number of hydrogen-bonding sites.[75] Accordingly, a plot of the area fraction of the peak at around 1640 cm^{-1} (Figure 5), which may be taken as a coarse estimate for the degree of parallel β-sheet formation, exhibited a strong increase between four and five hydrogen-bonding sites and then appeared to level off, reaching a value of approximately 94% in the case of **2e**.[76]

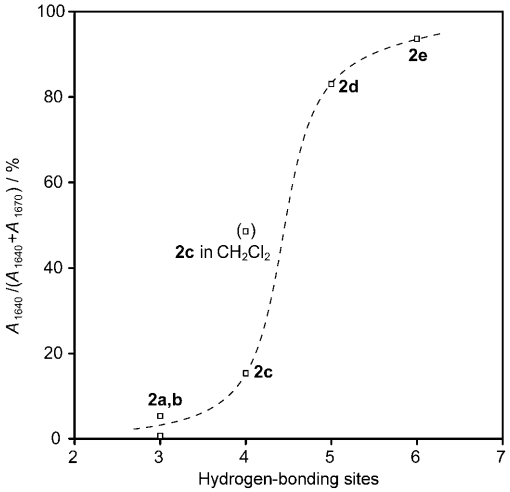


Figure 5. Area fractions of the peaks at 1640 and 1670 cm^{-1} as a coarse estimate for the degree of β-sheet formation (in solutions or gels in chloroform) systematically increased with the number of hydrogen-bonding sites, reaching a value of 94% in the case of **2e** (line serves as guides to the eye).

In summary, IR spectroscopy indicated that, in apolar organic solvents, a minimum number of (3+1) N–H···O=C hydrogen bonds is the lower limit for the formation of β-sheet aggregates. However, even minor changes of the solvent polarity are enough to change the nature of the secondary structures, and stable β-sheet aggregates are only obtained for (3+2) or (3+3) N–H···O=C hydrogen bonds. These findings are in line with related investigations concerning oligopeptide–PEG conjugates in the solid state.[63,77] They are also in good agreement with our own previous investigations on macromonomers **1** where derivatives such as **1h–j** were found to aggregate into relatively flexible fibrillar features (via antiparallel β-sheet formation); only macromonomers with (5+1) or more hydrogen-bonding sites gave rise to many micrometers long, uniform, well-defined helical ribbons or fibrils. Furthermore, the exclusive observation of parallel β-sheet secondary structures in the model com-

pounds **2c**–**e** goes to prove that, in apolar organic solvents and in the absence of competitive hydrogen-bonding partners, the non-equidistant placement of hydrogen-bonding sites in a molecule, that is, a default configuration for the maximization of hydrogen-bonding interactions upon parallel aggregation, constitutes a sufficient driving force to control parallel versus antiparallel orientation and even overcompensates other factors favoring the latter.

SFM Imaging of organogel samples: SFM investigations of solutions or gels of the model compounds confirmed the results of the IR measurements and helped to establish a link between the molecular structure and the macroscopic gelation behavior. In the case of **2c**, samples spin-coated from CH_2Cl_2 gave rise to aggregates the majority of which had a thin, flat tape-like appearance and a length of up to 100 nm (Figure 6a). As these aggregates exhibited a preferred orientation parallel to the HOPG lattice axes, it could not even be excluded that they had only been formed upon the evaporation of the solvent during sample preparation. Somewhat larger aggregates with a length of up to about 200 nm and an apparently smaller tendency to align on the HOPG substrate predominated in SFM images of samples from **2d** (Figure 6b). Finally, the symmetric compound **2e** was the only derivative that gave rise to better-defined, many micrometers long fibrillar features with helical superstructures (Figure 6c) reminiscent of those formed by the macromonomers **1** to a certain degree. In marked contrast to the latter, however, these one-dimensional aggregates were not uniform species but exhibited a distribution of diameters and a variety of helical superstructures. Thus, several distinctly different types of aggregates with heights on the order of 5–11 nm, apparent widths of 16–34 nm, and helix pitches of 25–64 nm were observed. However, all different types of fibrils had a right-handed helical superstructure in common. This seems to be a remarkable detail because the fibrils obtained from macromonomers **1a** and **1b** with the same total number of hydrogen-bonding sites were, to the best of our knowledge, the first example of β-sheet aggregates with a right-handed helical superstructure[17–20] whereas, with one notable, recently reported exception,[78] all literature examples of fibrils from synthetic oligopeptides or amyloid proteins give rise to left-handed helical superstructures,[50] presumably due to their preferred molecular conformations.[79]

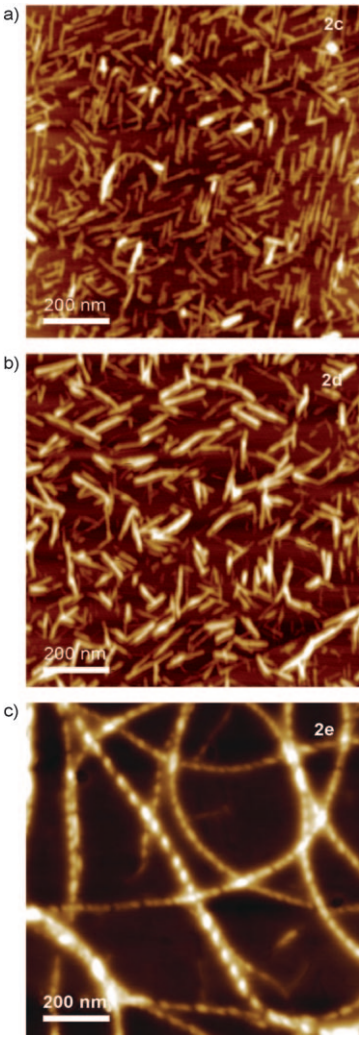


Figure 6. SFM images of samples of **2c**–**e** spin-coated onto a monolayer of octadecylamine on HOPG; only in the case of **2e** with its (3+3) hydrogen-bonding sites, high aspect ratio fibrillar aggregates with helical superstructures were observed.

Combined with the observed gelation properties, these results serve to elucidate the role of hydrogen bonding as well as the difference between using flexible, amorphous, polydisperse polymer segments in macromonomers **1** as opposed to simple alkyl tails in the model compounds **2**. In agreement with both the IR spectra discussed above and our findings concerning the self-assembly of macromonomers **1**, it appears that four or five N−H···O=C hydrogen-bonding sites are sufficient for unspecific aggregation. However, a total of six hydrogen-bonding sites, that is, (3+3) for the model compounds **2** or (5+1) for the macromonomers **1**, are an indispensable prerequisite for obtaining high aspect ratio, one-dimensional aggregates in organic solvents.

Contrary to Boden's findings concerning the hierarchical self-organization of (more elaborately designed) oligopeptides into distinct levels of β-sheet superstructures,[67,68,79] the inherent helicity of the aggregates from the very short and simple oligopeptide derivatives **2** alone does not appear to be able to prevent the formation of a variety of superstructures as well as defect structures via β-sheet stacking, β-sheet edge-interactions, and imperfections in the hydrogen-bonding network. For this reason, the utilization of the flexible and polydisperse, non-crystallizable polymer segments in the macromonomers **1** is a decisive element in the molecular design, as well, as opposed to the solubilizing but also crystallizable dodecyl residues in the model monomers. The attached polymer segments, presumably, guide the system into the formation of better soluble and uniform superstructures from a finite number of stacked β-sheets, resulting in the formation of well-defined supramolecular polymers with an extraordinary persistence length, without branching points,

and, as a consequence, without any tendency to form organogels.

Topochemical polymerization in the organogels: In order to investigate the UV-induced topochemical polymerization of the model compounds in organic solvents and organogels, thoroughly degassed CH_2Cl_2 or $CHCl_3$ solutions of **2a–e** at a typical concentration of 0.5–1 $g\,L^{-1}$ were homogenized in an ultrasonic bath, heated and transferred immediately into quartz cuvettes under nitrogen. Upon cooling, the solutions of **2c–e** formed organogels inside the cuvettes. The samples were then subjected to UV irradiation for 2 h, using a 250 W Ga-doped Hg lamp equipped with a black bandpass filter. Whereas none of the solutions were polymerizable, all organogel samples underwent topochemical diacetylene polymerization, which helped to independently corroborate the presence of parallel β-sheet structures, as inferred from the IR spectroscopic signature.

Thus, solutions of the TMS-protected diacetylene **2a** did not show any significant change in the UV/Vis spectra upon UV irradiation, and solutions of the terminal diacetylene **2b** only developed a broad, featureless absorption below 500 nm indicative of a random cross-linking process.[75] Likewise, $CHCl_3$ solutions of **2c** were not polymerizable, either. By contrast, organogels formed from **2c** in CH_2Cl_2 exhibited the typical absorption spectra known from poly(diacetylene)s upon UV irradiation (Figure 7b). The global absorption maximum was located at 573 nm with the first vibronic progression observed at 528 nm, resembling the spectra of the poly(diacetylene) obtained from the corresponding macromonomer **1b**.[17–20] As expected from the higher degree of order according to the IR spectra, organogels obtained from **2d** turned purple more quickly. However, the polymerization also resulted in the relatively rapid disruption of the gel under precipitation of purple polymer that could not be redissolved (Figure 7a). Supposedly, the overall hydrophobic/hydrophilic ratio may be inappropriate in **2d**, highlighting the role of the attached alkyl residues as solubilizing groups. Finally, UV/Vis spectra of the organogels from **2e** after UV irradiation exhibited the characteristic UV absorption bands for poly(diacetylene)s (Figure 7c), and the molar extinction coefficient of the obtained polydiacetylene) **P2e** of around $\varepsilon = 8 \times 10^6\ cm^2\,mol^{-1}$ was on the order of other (pure) poly(diacetylene)s reported in the literature,[80] suggesting that the achieved conversions were high in this case. The shape of the spectra was reminiscent of that of the macromonomers and, at the same time, proved the presence of different types of spectroscopic aggregates in the gels from **P2e**. Thus, the global maximum at $\lambda_{max} = 534$ nm corresponded exactly to the value observed for poly(diacetylene)s prepared from macromonomers **1b**, **1f**, and **1g**, and the shoulder at 495 nm could straightforwardly be assigned as a vibronic side band. The maxima at 588 and 571 nm, however, appeared to belong to a different spectroscopic species. Interestingly, the spectrum of the $CHCl_3$ gel exhibited essentially the same peaks but the higher wavelength absorptions were much less pronounced and the vibronic fine structure

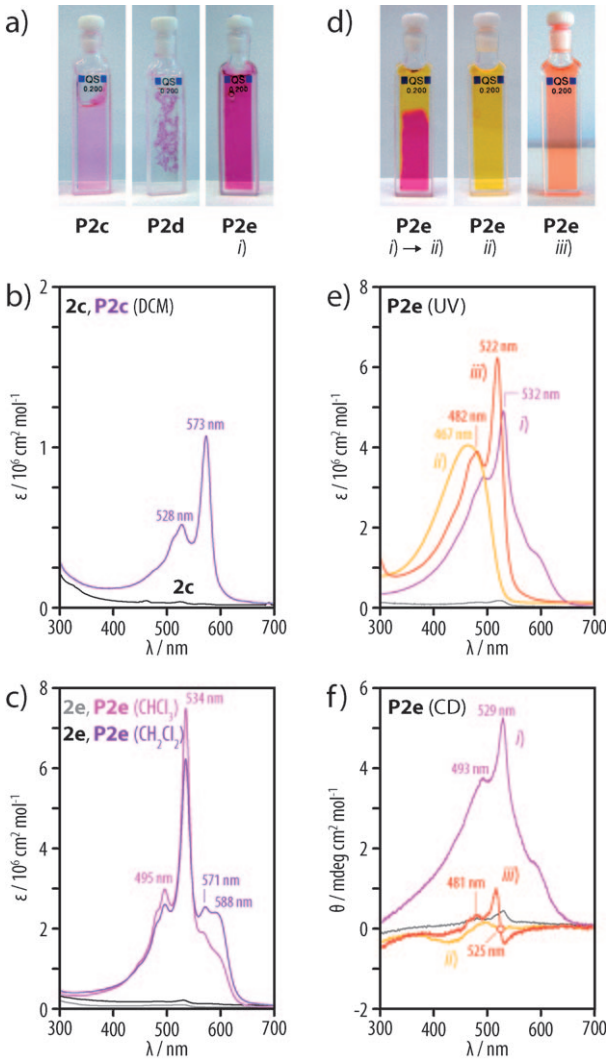


Figure 7. a) Organogels of **2c–e** in $CHCl_3$ or CH_2Cl_2 turned red or purple upon UV irradiation; in the case of **2d**, the polymerized material precipitated; b),c) UV spectra of the organogels of **2c** and **2e** after 2 h of UV irradiation proved the formation of poly(diacetylene)s; however, high conversions were only achieved in the case of **2e**. d)–f) Color changes, UV, and CD spectra of **P2e** upon the addition of TFA; the purple gel i) of **P2e** formed a yellow solution, ii) upon the addition of TFA, accompanied with a hypsochromic shift in the UV/Vis spectrum; subsequent addition of TEA yielded a red solution, iii) from which the polymer slowly precipitated.

better developed, suggesting a more uniform and less aggregated distribution of superstructures in $CHCl_3$ as the better solvent. The gels remained stable throughout the polymerization, and no precipitation of polymer occurred, probably because of both the more appropriate hydrophobic–hydrophilic balance and the presence of the very long entwined fibrils which may not have enough mobility to aggregate into larger bundles during polymerization.

The addition of minuscule amounts of a hydrogen-bond-breaking cosolvent, such as trifluoroacetic acid (TFA), to the polymerized purple gel of **P2e** (about 7 μL of TFA for 0.7 mL of the gel) led to its slow dissolution, a color change to yellow, and a drastic hypsochromic shift in the UV/Vis

spectrum (Figure 7d and e). The subsequent addition of triethylamine (TEA, about 14 μL) induced another color change to red. In comparison to the original polymerized gel, this newly formed red species exhibited an absorption maximum slightly shifted to shorter wavelengths (λ_{max} = 522 nm) with an even higher extinction coefficient and a well-resolved vibronic fine structure. No gelation occurred in the red state and, moreover, precipitation of the polymer was observed over time.[75] Although the UV spectra of the purple, yellow, and red species resembled those of the poly(diacetylene)s **P1** (upon TFA addition) to a certain degree, the observed processes were fundamentally different in nature and, in the present case, more in line with previously reported examples of poly(diacetylene) solvatochromism.[39,81–85] **P1** had been observed to undergo two distinct, consecutive solvatochromic transitions with the red form as a defined intermediate, and the presence of three different, well-defined states had further been confirmed by CD spectroscopy. Accordingly, the CD-spectroscopic behavior of **P2e** (Figure 7f) was found to be different from **P1**. The original red-purple organogels exhibited a strong but difficult to reproduce CD signal which, in marked contrast to **P1**, did not have a clean signature with zero-crossings from bisignate Cotton effects and, hence, probably rather resulted from circular intensity dichroic scattering (c.i.d.s.)[86] like many other examples of poly(diacetylene) CD spectra.[87] The CD signal almost completely disappeared upon TFA addition but, in contrast to the reversible red-yellow transition in the case of **P1**, was not recovered upon neutralization with TEA. Only a weak CD signal was observed which, like the red form of **P1**, exhibited a negative bisignate Cotton effect at the position of the highest wavelength UV absorption. All these results served to confirm the assumption that only the poly(diacetylene)s **P1** were present in the form of defined aggregation states (single tapes, dimeric ribbons, tetrameric fibrils) which were able to reversibly unfold and refold. By contrast, the poly(diacetylene) **P2e**, due to its simpler molecular architecture, gave rise to a variety of poorly defined superstructures, as had been observed in the SFM images of samples before UV irradiation, as well.

Conclusions

In summary, we prepared a number of functionalized iodopropargyl derivatives and applied them in the synthesis of a series of diacetylene-containing peptides via Pd-catalyzed sp–sp cross-coupling reactions. These diacetylene–peptide conjugates may be useful building blocks for the preparation of non-natural oligopeptides. Thus, the diacetylene amphiphiles **2** were synthesized which served as low molecular weight model compounds for the previously reported, self-assembling diacetylene macromonomers **1**. The model compounds were found to reliably self-assemble into β-sheet secondary structures in apolar organic solvents if a minimum number of five N–H···O=C hydrogen bonds was present in the molecule, and six such hydrogen bonds were required for the formation of high aspect ratio nanoscopic fibrils, according to SFM imaging. The exclusive formation of parallel β-sheet structures was observed, indicating that the non-equidistant placement of the N–H···O=C hydrogen-bonding sites in such molecules is a useful parameter to control the intermolecular orientation in detail. In marked contrast to the macromonomers **1**, the diacetylenes **2** were found to be efficient organogelators, and gel formation was, in this case, a prerequisite for their polymerization upon UV irradiation. The origin of the macroscopic gelation in the case of **2e** on the nanoscopic length scale was found to be the presence of entwined, entangled, and branched nanoscopic fibrils with a distribution of diameters on the order of a few nanometers and a variety of helical superstructures. Apparently, the more elaborate molecular design of the macromonomers **1**, including a flexible, non-crystallizable, polydisperse hydrophobic polymer segment, was required for the formation of well-defined supramolecular polymers from a defined, finite number of laminated β-sheet tapes which, despite the smaller number of hydrogen bonds and the higher propensity toward aggregation, showed no tendency toward gelation. In conclusion, the work presented here extends the knowledge about the requirements for an appropriate molecular design in order to achieve well-defined, oligopeptide-based nanostructures via supramolecular self-assembly. This improved understanding will hopefully establish a set of guidelines for the detailed control of the self-organization of oligopeptide-based materials, which may then be utilized as a universal supramolecular scaffold to control the placement of reactive molecules and moieties other than diacetylenes and, thus, provide a pathway toward hierarchically structured carbon-rich or organic optoelectronic materials.

Experimental Section

Instrumentation: NMR spectroscopy was carried out on a Bruker Avance 300 spectrometer operating at a frequency of 300.23 MHz for ^{1}H and 75.49 MHz for ^{13}C nuclei. The UV/Vis spectra were recorded on a Perkin–Elmer UV-20 spectrometer with a scan speed of 480 nm per minute using 1 cm quartz cuvettes from Hellma. High resolution mass spectra were recorded on IonSpec ULTIMA FTMS: 6211 HiRes-MALDI and 494 HiRes-ESI-MS machines, respectively. Elemental analyses were carried out as service measurements at the Laboratory of Organic Chemistry at the Department of Chemistry and Applied Biosciences at ETH Zurich using a LECO CHN/900 instrument. Solution phase IR spectra were recorded on a "Spectrum One" IR spectrometer from Perkin–Elmer using a solution phase cuvette with KBr windows and a light path of 0.5 mm. TLC Analyses were performed on TLC plates from Macherey–Nagel (Alugramm Sil G/UV_{254}). UV-light (254 nm) or standard coloring reagents were used for detection. Column chromatography was conducted on Geduran Silica gel Si 60 from Merck (40–60 μm). UV polymerizations were performed using a 250 W Ga-doped low pressure Hg lamp from UV Light Technology, Birmingham, UK, using a "black bandpass filter" with a transparency window from 315 to 405 nm.

SFM Imaging: Samples were analyzed in tapping mode using a Nanoscope IIIa instrument operating at room temperature in air. Microfabricated silicon nanoprobes with a resonating frequency of 300 kHz on average were used. Scan rates between 0.5 and 2 Hz were applied and the image size was 512×512 pixels. Samples were prepared by spin-coating

(3800 rpm) a solution of octadecylamine in chloroform (0.1 mg mL^{-1}) onto freshly cleaved HOPG. Dilute solutions of the macromolecules were ultrasonicated for 30 min and left standing for 16 h, and then spin-coated onto the amphiphile monolayer on HOPG.

General synthetic procedures: Unless otherwise noted, all reactions were carried out in dried Schlenk glassware in an inert N_2 atmosphere. Solvents were purchased as reagent grade and distilled prior to use. Ether, toluene and THF were dried over sodium/benzophenone, CH_2Cl_2 over CaH_2, and acetone was dried using P_2O_5. The solvents were freshly distilled and stored over molecular sieves prior to use. *N*-Fmoc-L-alanine, L-alanine *tert*-butyl ester hydrochloride, *N*-acetyl-L-alanine, propargyl amine, propargyl bromide, propargyl alcohol, TMS-acetylene, and all peptide coupling promoters were commercially obtained and used without further purification.

General procedure for Sonogashira couplings (GP A): *N*-Propargyloxycarbonyl-L-alanine *tert*-butyl ester **7** (1 equiv), the iodoacetylene compound (1.2 equiv) and diisopropylamine (4 equiv) were dissolved in dry THF. The solution was degassed in three freeze-pump-thaw cycles. After covering the flask with aluminum foil and cooling to 0 °C, $[PdCl_2(PPh_3)_2]$ (2.0 mol %) and CuI (10 mol %) were added. The solution was stirred for 2 to 12 h, followed by the removal of the solvent. The crude product was taken up in CH_2Cl_2 followed by an aqueous workup, unless otherwise noted. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The purification was carried out by column chromatography (silica gel) to separate the desired product from homo- and self-coupling side products.

General procedure for the cleavage of *tert*-butyl esters (GP B): The *tert*-butyl ester derivatives **9** and **10** were dissolved in dry CH_2Cl_2. Then, a large excess ($\geq$13 equiv) of trifluoroacetic acid (TFA) was added, and the solution was stirred for 3 to 16 h. The reaction was monitored by TLC. After completion of the reaction, the solvents were removed in vacuo. The crude product was typically used in the next step without further purification.

General procedure for PyBOP-promoted peptide couplings (GP C): The carboxylic acid component was dissolved in a mixture of dry CH_2Cl_2 and dry DMF. The amine component (1 equiv) was added, as well as diisopropylethylamine (DIEA; 4 equiv). The resulting solution was cooled to 0 °C, and (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP; 1.05 equiv) was added in one portion. The cooling bath was removed, and the reaction mixture was stirred at room temperature for 3 to 16 h. The solvents were removed and the crude product was purified by column chromatography, unless otherwise noted.

***N*-(5-Trimethylsilylpenta-2,4-diynyl-1-oxycarbonyl)-L-alanyl-L-alanine dodecylamide (2a)**: Following GP C, **13** (148 mg, 0.58 mmol) and **10h** (150 mg, 0.56 mmol) were dissolved in a mixture of dry CH_2Cl_2 (30 mL) and dry DMF (5 mL). DIEA (0.30 g, 2.32 mmol) and PyBOP (1.06 g, 2.04 mmol) were added, and the solution was stirred at room temperature overnight. The solvents were removed in vacuo. The crude product was dissolved in a 1:1 mixture of THF (5 mL) and MeOH (5 mL), and purified by precipitation in water (120 mL). The precipitate was filtered off and dried in HV to yield a slightly brown solid (240 mg, 84 %). R_f = 0.6 (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.19 (s, 9H, $Si(CH_3)_3$), 0.88 (t, J = 6.6 Hz, 3H, $(CH_2)_{11}CH_3$), 1.25 (br s, 18H, $(CH_2)_9CH_3$), 1.38 (d, J = 6.9 Hz, 6H, 2 $CHCH_3$), 1.50 (m, 2H, CH_2-$(CH_2)_9CH_3$), 3.24 (m, 2H, $NHCH_2(CH_2)_{10}CH_3$), 4.26 (m, 1H, $CHCH_3$), 4.44 (m, 1H, $CHCH_3$), 4.74 (s, 2H, $NHCO_2CH_2$), 5.55 (d, J = 7.5 Hz, 1H, NH), 6.27 (m, 1H, NH), 6.78 ppm (d, J = 7.2 Hz, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = −0.5 ($Si(CH_3)_3$), 14.1 ($(CH_2)_{11}CH_3$), 18.6, 19.0 (2 $CHCH_3$), 22.7, 26.9, 29.3, 29.3, 29.4, 29.6, 29.6, 31.9 (10 CH_2), 39.7 ($NHCH_2(CH_2)_{10}CH_3$), 49.0, 50.8 (2 $CHCH_3$), 53.1 ($NHCO_2CH_2$), 71.4, 71.7, 86.9, 88.2 (diacetylene *C*), 155.0 (carbamate *C*=O), 171.8 (amide *C*=O), 172.0 ppm (amide *C*=O); elemental analysis calcd (%) for $C_{27}H_{47}N_3O_4Si$: C 64.12, H 9.37, N 8.31; found: C 64.16, H 9.22, N 8.59; HRMS (MALDI): m/z: calcd for $C_{27}H_{47}N_3O_4SiNa$: 528.3234; found: 528.3228 $[M+Na]^+$.

***N*-(Penta-2,4-diynyl-1-oxycarbonyl)-L-alanyl-L-alanine dodecylamide (2b)**: The TMS-protected derivative **2a** (0.10 g, 0.22 mmol) was dissolved in a mixture of MeOH (10 mL), EtOH (20 mL), and H_2O (2 mL). $AgNO_3$ (44 mg, 0.26 mmol) was added, and the reaction was monitored by TLC. After 90 min, all starting material (R_f = 0.6, CH_2Cl_2/MeOH 10:1) was transformed into the silver acetylide (R_f = 0, CH_2Cl_2/MeOH 10:1), and KI (50 mg, 0.30 mmol) was added to the solution. The reaction mixture was stirred overnight, and a fine yellow precipitate of AgI formed. The solvents were removed in vacuo, the crude product was taken up in chloroform, and the AgI was filtered off. The residue was dried and purified by column chromatography (silica gel, $CHCl_3$/MeOH 24:1) to yield the title compound as a slightly yellow, light-sensitive solid (77 mg, 91 %). R_f = 0.6 (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 0.91 (t, J = 6.9 Hz, 3H, $(CH_2)_{11}CH_3$),), 1.2–1.6 (m, 26H, $(CH_2)_{10}CH_3$, 2 $CHCH_3$), 2.20 (s, 1H, C≡C*H*), 3.26 (m, 2H, $NHCH_2(CH_2)_{10}CH_3$), 4.26 (m, 1H, $CHCH_3$), 4.45 (m, 1H, $CHCH_3$), 4.77 (s, 2H, $NHCO_2CH_2$), 5.50 (br s, 1H, NH), 6.17 (br s, 1H, NH), 6.68 ppm (br s, 1H, NH); HRMS (MALDI): m/z: calcd for $C_{24}H_{39}N_3O_4Na$: 456.2838; found: 456.2833 $[M+Na]^+$.

***N*-{6-[*N*′-(4-Methoxysuccinyl)amido]hexa-2,4-diynyl-1-oxycarbonyl}-L-alanyl-L-alanine dodecylamide (2c)**: Following GP C, **13** (228 mg, 0.88 mmol) and **10b** (297 mg, 0.88 mmol) were dissolved in a mixture of dry CH_2Cl_2 (30 mL) and dry DMF (5 mL). DIEA (0.46 g, 3.56 mmol) and PyBOP (502 mg, 0.96 mmol) were added, and the solution was stirred at room temperature overnight. The solvents were removed in vacuo. The crude product was dissolved in a 1:1 mixture of THF (10 mL) and MeOH (10 mL), and purified by precipitation in water (120 mL). The precipitate was filtered off and dried in HV to yield the title compound as a slightly brownish solid (0.36 g, 65 %). R_f = 0.3 (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 0.86 (t, J = 6.9 Hz, 3H, $(CH_2)_{11}CH_3$), 1.1–1.5 (m, 26H, $(CH_2)_{10}CH_3$, 2 $CHCH_3$), 2.39 (t, J = 6.4 Hz, 2H, $NHCOCH_2$), 2.52 (t, J = 6.4 Hz, 2H, CH_2CO_2Me), 3.03 (m, 2H, $NHCH_2(CH_2)_{10}CH_3$), 4.00 (d, J = 5.1 Hz, 2H, C≡CCH_2NH), 4.05 (m, 1H, $CHCH_3$), 4.21 (m, 1H, $CHCH_3$), 4.74 (s, 2H, $NHCO_2CH_2$), 7.61 (d, J = 7.2 Hz, 1H, NH), 7.74 (m, 1H, NH), 7.93 (d, J = 7.8 Hz, 1H, NH), 8.43 ppm (t, J = 5.4 Hz, 1H, NH); HRMS (MALDI): m/z: calcd for $C_{30}H_{48}N_4O_7Na$: 577.3595; found: 577.3588 $[M+Na]^+$.

***N*-{6-[*N*′-(9-Fluorenylmethyloxycarbonyl-L-alanyl)amido]hexa-2,4-diynyl-1-oxycarbonyl}-L-alanyl-L-alanine dodecylamide (2d)**: Following GP C, **13** (186 mg, 0.73 mmol) and **10f** (370 mg, 0.72 mmol) were dissolved in a mixture of dry CH_2Cl_2 (30 mL) and dry DMF (5 mL). DIEA (0.37 g, 2.86 mmol) and PyBOP (394 mg, 0.76 mmol) were added, and the solution was stirred at room temperature overnight. The solvents were removed in vacuo. The crude product was dissolved in a 1:1 mixture of THF (10 mL) and MeOH (10 mL), and purified by precipitation in water (120 mL). The precipitate was filtered off and dried in HV to yield the title compound as a slightly brown solid (0.43 g, 78 %). R_f = 0.4 (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 0.82 (t, J = 6.9 Hz, 3H, $(CH_2)_{11}CH_3$), 1.1–1.5 (m, 29H, $(CH_2)_{10}CH_3$, 3 $CHCH_3$), 3.15 (m, 2H, $NHCH_2(CH_2)_{10}CH_3$), 4.03 (s, 2H, C≡CCH_2NH), 4.1–4.2 (m, 3H, 2 $CHCH_3$, fluorenyl C*H*), 4.2–4.4 (m, 3H, $CHCH_3$, Fmoc-CO_2CH_2), 4.65 (s, 2H, $NHCO_2CH_2$), 7.26 (t, J = 7.2 Hz, 2H, aromatic *H*), 7.35 (t, J = 7.2 Hz, 2H, aromatic *H*), 7.5–7.8 (m, 3H, NH), 7.74 (m, 2H, aromatic *H*), 7.85–7.95 (m, 3H, 2 aromatic *H*, NH), 8.42 ppm (m, 1H, NH); HRMS (MALDI): m/z: calcd for $C_{43}H_{57}N_5O_7Na$: 778.4156; found: 778.4150 $[M+Na]^+$.

Hexa-2,4-diynylene-1,6-bis(oxycarbonyl-L-alanyl-L-alanine dodecylamide) (2e): Following GP C, **13** (513 mg, 2 mmol) and **11** (340 mg, 1 mmol) were dissolved in a mixture of dry CH_2Cl_2 (50 mL) and dry DMF (5 mL). DIEA (0.65 g, 5 mmol) and PyBOP (1.06 g, 2.04 mmol) were added, and the solution was stirred at room temperature overnight. The solvents were removed in vacuo. The crude product was dissolved in a 1:1 mixture of THF (10 mL) and MeOH (10 mL), and purified by precipitation in water (200 mL). The precipitate was filtered off and dried in HV to yield the title compound as a colorless solid (0.67 g, 82 %). R_f = 0.4 (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 0.83 (t, J = 6.9 Hz, 6H, $(CH_2)_{11}CH_3$), 1.1–1.5 (m, 52H, 2 $(CH_2)_{10}CH_3$, 4 $CHCH_3$), 2.9–3.1 (m, 4H, 2 $NHCH_2(CH_2)_{10}CH_3$), 4.0–4.1 (m, 2H, 2 $CHCH_3$), 4.15–4.3 (m, 2H, 2 $CHCH_3$), 4.74 (s, 4H, 2 $NHCO_2CH_2$), 7.60 (d, J = 7.5 Hz, 2H, NH), 7.7–7.8 (m, 2H, NH), 7.90 ppm (d, J = 7.5 Hz, 2H, NH); HRMS (MALDI): m/z: calcd for $C_{44}H_{76}N_6O_8Na$: 839.5617; found: 839.5618 $[M+Na]^+$.

3-Iodo-*N*,*N*-bis(trimethylsilyl)propargylamine (3) and 3-iodopropargylamine hydrochloride (4): Hexamethyldisilazane (HMDS, 9.68 g, 60 mmol) was dissolved in ether (30 mL) at 0 °C, and *n*-butyl lithium (60 mmol, 1.6 M solution in hexanes) was added slowly. The mixture was allowed to reach room temperature and stirred for another 30 min. The flask was covered with aluminum foil, the solution was cooled to −78 °C, and propargyl bromide (3.57 g, 30 mmol) in dry ether (20 mL) was added dropwise. The reaction mixture was allowed to reach room temperature again and stirred for 2 h. Then, I_2 (7.61 g, 30 mmol) was added at −78 °C, and the reaction mixture was stirred at room temperature overnight. The reaction was quenched by washing with saturated $Na_2S_2O_3$ solution. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo at room temperature. Residual HMDS was distilled off the crude mixture at 0 °C (4×10^{-2} mbar). The remaining crude 3-iodo-*N*,*N*-bis(trimethylsilyl)propargylamine (**3**; 9.17 g, 80 %), a slightly orange oil, was deprotected without further purification. For this purpose, acetyl chloride (7.85 g, 100 mmol) was dissolved in dry MeOH (25 mL) at 0 °C in order to generate anhydrous HCl in MeOH. The solution was stirred for 30 min at room temperature and diluted with CH_2Cl_2 (25 mL). The protected amine derivative **3** (6.0 g, 18.4 mmol) was added at 0 °C, and a fine brown precipitate formed instantaneously. The precipitate was filtered off and dried in vacuo. **4** (3.21 g, 80 %) was obtained as a slightly brown powder. M.p. 168–169 °C (decomposition); ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 3.79 (s, 2H, CH_2), 8.46 ppm (s, 3H, NH_3Cl); ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 20.2 (C≡*C*I), 30.3 (*C*H$_2$), 84.9 ppm (*C*≡CI); HRMS (EI): *m*/*z*: calcd for C_3H_4IN: 180.9384; found 180.9383 [*M*−HCl]$^+$.

***N*-(3-Iodoprop-2-ynyl)acetamide (5a)**: Compound **4** (3.0 g, 13.8 mmol) was dissolved in a mixture of dry CH_2Cl_2 (70 mL) and DIEA (8.91 g, 68.9 mmol). The reaction mixture was cooled to 0 °C, and acetic anhydride (14.1 g, 138 mmol) was added via a syringe. The flask was covered with aluminum foil, and the reaction mixture was stirred at room temperature overnight. The solution was diluted with CH_2Cl_2, and the organic phase was washed twice with saturated $NaHCO_3$ solution and once with saturated NaCl solution. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo at room temperature in the dark. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 100:1) to yield the title compound as a slightly yellow crystalline solid (1.76 g, 57 %). R_f = 0.35 (CH_2Cl_2/MeOH 10:1); m.p. 104–106 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.99 (s, 3H, CH_3), 4.16 (d, *J* = 5.1 Hz, 2H, CH_2), 6.29 ppm (br s, 1H, N*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ = −0.1 (C≡*C*I), 22.9 (*C*H$_3$), 31.1 (*C*H$_2$), 89.7 (*C*≡CI), 170.0 ppm (amide *C*=O); elemental analysis calcd (%) for C_5H_6INO: C 26.93, H 2.71, N 6.28, I 56.90; found: C 26.76, H 2.62, N 6.12, I 56.99; HRMS (EI): *m*/*z*: calcd for C_5H_6INO: 222.9489; found 222.9488 [*M*]$^+$.

***N*-(4-Methoxysuccinyl) 3-iodopropargylamide (5b)**: Compound **4** (3.04 g, 14 mmol) was dissolved in a mixture of dry CH_2Cl_2 (60 mL) and DIEA (9.0 g, 70 mmol). The solution was cooled to 0 °C. Succinic acid monomethyl ester chloride (2.10 g, 14 mmol) was added dropwise, and the solution was stirred overnight. After an acidic aqueous work-up, the organic solution was concentrated in vacuo. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 50:1) to yield the title compound as a colorless solid (2.96 g, 73 %). R_f = 0.5 (CH_2Cl_2/MeOH 10:1); m.p. 104–105 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 2.37 (t, *J* = 6.3 Hz, 2H, CH_2), 2.52 (t, *J* = 6.3 Hz, 2H, CH_2), 3.58 (s, 3H, CH_3), 3.97 (d, *J* = 5.4 Hz, 2H, CH_2N), 8.32 ppm (s, 1H, N*H*); ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 8.1 (C≡*C*I), 29.0, 30.0, 30.2 (*C*H$_2$NH, *C*H$_2$CO$_2$Me, NHCO*C*H$_2$), 51.8 (*C*H$_3$), 90.5 (*C*≡CI), 170.9, 173.2 ppm (2*C*=O); elemental analysis calcd (%) for $C_8H_{10}INO_3$: C 32.56, H 3.42, N 4.75, I 43.01; found: C 32.77, H 3.40, N 4.62, I 42.84; HMRS (EI): *m*/*z*: calcd for $C_8H_{10}NO_3I$: 294.9700; found: 294.9700 [*M*]$^+$.

***N*-(9-Fluorenylmethyloxycarbonyl) 3-iodopropargylamine (5c)**: Compound **4** (2.90 g, 13.3 mmol) was dissolved in a mixture of dry CH_2Cl_2 (60 mL) and DIEA (9.10 g, 70.4 mmol). Fmoc-Cl (3.45 g, 13.3 mmol) was added at 0 °C, and the solution was stirred at room temperature overnight. The solvents were removed in vacuo, and the crude product was recrystallized from CH_2Cl_2 to yield the title compound as a colorless solid (4.10 g, 76 %). R_f = 0.7 (CH_2Cl_2/MeOH 10:1); m.p. 159–160 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 3.93 (d, *J* = 5.4 Hz, 2H, NHCH_2), 4.24 (m, 1H, fluorenyl-C*H*), 4.33 (d, *J* = 6.9 Hz, 2H, Fmoc-CO$_2$CH_2), 7.34 (t, *J* = 7.2 Hz, 2H, aromatic *H*), 7.43 (t, *J* = 7.5 Hz, 2H, aromatic *H*), 7.70 (d, *J* = 7.2 Hz, 2H, aromatic *H*), 7.80 (t, *J* = 5.4 Hz, 1H, N*H*), 7.90 ppm (d, *J* = 7.5 Hz, 2H, aromatic *H*); ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 8.4 (C≡*C*I), 32.2 (NH*C*H$_2$), 47.1 (fluorenyl-*C*H), 66.2 (Fmoc-CO$_2$*C*H$_2$), 90.8 (*C*≡CI), 120.6, 125.6, 127.6, 128.1, 141.2, 144.3 (aromatic *C*), 156.4 ppm (carbamate *C*=O); elemental analysis calcd (%) for $C_{18}H_{14}NO_2I$: C 53.62, H 3.50, N 3.47, I 31.47; found: C 53.78, H 3.60, N 3.47, I 31.47; HRMS (EI): *m*/*z*: calcd for $C_{18}H_{14}NO_2I$: 403.0064; found: 403.0067 [*M*]$^+$.

***N*-(5-Dimethylamino-1-naphthalenesulfonyl) 3-iodopropargylamide (5d)**: Compound **4** (0.50 g, 2.3 mmol) was dissolved in a mixture of dry CH_2Cl_2 (20 mL) and DIEA (0.74 g, 5.8 mmol). The solution was cooled to 0 °C and 5-dimethylamino-1-naphthalenesulfonyl chloride (0.68 g, 2.5 mmol) was added. The mixture was stirred for 20 min at 0 °C. The reaction was quenched by the addition of MeOH (10 mL). The resulting solution was washed twice with water. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) to yield the title compound as a slightly brown powder (0.63 g, 57 %). R_f = 0.7 (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 2.85 (s, 6H, N-(CH_3)$_2$), 3.86 (d, *J* = 6 Hz, 2H, NHCH_2), 7.27 (d, *J* = 7.2 Hz, 1H, aromatic *H*), 7.62 (m, 2H, aromatic *H*), 8.15 (dd, *J* = 7.2 Hz, 1.2 Hz, 1H, aromatic *H*), 8.26 (d, *J* = 8.7 Hz, 1H, aromatic *H*), 8.36 (t, *J* = 6 Hz, 1H, amide N*H*), 8.5 ppm (d, *J* = 8.7 Hz, 1H, aromatic *H*); ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 10.0 (C≡*C*I), 34.0 (NH*C*H$_2$), 45.7 (N(*C*H$_3$)$_2$), 88.4 (*C*≡CI), 115.5, 119.7, 124.0, 128.3, 129.2, 129.6, 129.7, 130.2, 136.4, 151.8 ppm (aromatic *C*); elemental analysis calcd (%) for $C_{15}H_{15}IN_2O_2S$: C 43.49, H 3.65, N 6.76, O 7.72, S 7.74, I 30.63; found: C 43.66, H 3.52, N 6.70, O 7.76, S 7.56, I 30.80; HRMS (EI): *m*(*z*: calcd for $C_{15}H_{14}IN_2O_2S$: 412.9816; found: 412.9816 [*M*+H]$^+$.

***N*-[*N*′-(9-Fluorenylmethyloxycarbonyl)-L-alanyl] 3-iodopropargylamide (5e)**: DIEA (9.69 g, 75 mmol) was dissolved in a mixture of dry CH_2Cl_2 (60 mL) and dry DMF (20 mL). Compound **4** (3.26 g, 15 mmol) and *N*-Fmoc-L-alanine (4.67 g, 15 mmol) were added. At 0 °C, PyBOP (8.32 g, 16 mmol) was added, and the solution was stirred overnight. After removal of the solvent, the crystalline product was washed with CH_2Cl_2 to yield the title compound as colorless crystalline product (5.24 g, 74 %). R_f = 0.8 (CH_2Cl_2/MeOH 10:1); m.p. 189–190 °C (decomposition); ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.21 (d, *J* = 7.2 Hz, 3H, CHCH_3), 4.0–4.1 (m, 3H, CH_2NH, fluorenyl C*H*), 4.2–4.4 (m, 3H, C*H*CH$_3$, CO$_2$CH_2), 7.34 (t, *J* = 7.2 Hz, 2H, aromatic *H*), 7.43 (t, *J* = 7.2 Hz, 2H, aromatic *H*), 7.55 (d, *J* = 7.8 Hz, 1H, carbamate N*H*), 7.74 (t, *J* = 6.0 Hz, 2H, aromatic *H*), 7.90 (d, *J* = 7.5 Hz, 2H, aromatic *H*), 8.31 ppm (t, *J* = 5.3 Hz, 1H, amide N*H*); ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 8.4 (C≡*C*I), 18.6 (CH*C*H$_3$), 30.5 (*C*H$_2$N), 47.2 (fluorenyl *C*H), 50.4 (CHCH$_3$), 66.1 (CO$_2$*C*H$_2$), 90.4 (*C*≡CI), 120.6, 125.8, 127.6, 128.1, 141.2, 144.3 (aromatic *C*), 156.2 (carbamate *C*=O), 172.8 ppm (amide *C*=O); elemental analysis calcd (%) for $C_{21}H_{19}IN_2O_3$: C 53.89, H 4.04, I 26.76, N 5.91; found: C 52.89, H 4.34, I 26.57, N 5.77; HRMS (EI): *m*/*z*: calcd for $C_{21}H_{19}IN_2O_3$: 474.0435; found: 474.0432 [*M*]$^+$.

***N*-[*N*′-(9-Fluorenylmethyloxycarbonyl)glycyl] 3-iodopropargylamide (5f)**: DIEA (6.65 g, 45.0 mmol) was dissolved in a mixture of dry CH_2Cl_2 (30 mL) and dry DMF (10 mL). Compound **4** (1.96 g, 9.0 mmol) and Fmoc-Gly-OH (2.68 g, 9.0 mmol) were added. At 0 °C, PyBOP (4.92 g, 9.45 mmol) was added, and the solution was stirred overnight. After removal of the solvent, the crystalline product was washed with CH_2Cl_2 to yield the title compound as a colorless solid (3.35 g, 81 %). R_f = 0.8 (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 3.62 (d, *J* = 6.3 Hz, 2H, Gly-CH_2), 4.01 (d, *J* = 5.4 Hz, 2H, C≡CCH_2NH), 4.2–4.4 (m, 3H, fluorenyl-C*H*, Fmoc-CO$_2$CH_2), 7.34 (t, *J* = 7.2 Hz, 2H, aromatic *H*), 7.43 (t, *J* = 7.2 Hz, 2H, aromatic *H*), 7.57 (t, *J* = 6.0 Hz, 1H, N*H*), 7.73 (d, *J* = 7.2 Hz, 2H, aromatic *H*), 7.90 (d, *J* = 7.2 Hz, 2H, aromatic *H*), 8.32 ppm (t, *J* = 5.4 Hz, 1H, N*H*); ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 8.4 (C≡*C*I), 30.3 (NH*C*H$_2$), 43.8 (Gly-*C*H$_2$), 47.1 (fluorenyl *C*H), 66.2 (Fmoc-CO$_2$*C*H$_2$), 90.4 (*C*≡CI), 120.6, 125.7, 127.6, 128.1, 141.2, 144.3 (aromatic *C*), 157.0 (carbamate *C*=O), 169.4 ppm (amide *C*=O); elemental analysis calcd (%) for $C_{20}H_{17}N_2O_3I$: C 52.19, H 3.72, N 6.09, O, 10.43, I

27.57; found: C 52.20, H 3.78, N 6.00; HRMS (ESI): *m/z*: calcd for $C_{20}H_{17}N_2O_3I$: 460.0279; found: 460.0281 $[M]^+$.

***N*-(*N'*-Acetyl-L-alanyl) 3-iodopropargylamide (5g)**: Compound **4** (1.66 g, 7.63 mmol) was dissolved in dry CH_2Cl_2 (20 mL) and dry DMF (10 mL). *N*-Acetyl-L-alanine (1.02 g, 7.63 mmol) and DIEA (4.92 g, 38.2 mmol) were added. At 0 °C, PyBOP (3.98 g, 7.63 mmol) was added, and the solution was stirred overnight. The solvents were removed in vacuo, and the purification was carried out by column chromatography (silica gel, CH_2Cl_2/MeOH 24:1) to yield the title compound as a colorless crystalline solid (1.80 g, 76%). R_f = 0.4 (CH_2Cl_2/MeOH 10:1); m.p. 173–174 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.15 (d, J = 6.9 Hz, 3H, CHCH_3), 1.82 (s, 3H, C(O)CH_3), 3.96 (m, 2H, CH_2NH), 4.22 (m, 1H, CHCH$_3$), 8.03 (d, J = 7.5 Hz, 1H, NH), 8.29 ppm (t, J = 5.1 Hz, 1H, NH); ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 8.2 (C≡*C*I), 18.6 (CH*C*H$_3$), 23.0 (C(O)*C*H$_3$), 30.3 (*C*H$_2$NH), 48.4 (*C*HCH$_3$), 90.4 (*C*≡CI), 169.4, 172.6 ppm (amide *C*=O); elemental analysis calcd (%) for $C_8H_{11}IN_2O_2$: C 32.67, H 3.77, I 43.15, N 9.53; found: C 32.86, H 3.83, I 43.01, N 9.50; HRMS (EI): *m/z*: calcd for $C_8H_{11}IN_2O_2$: 293.9860; found: 293.9861 $[M]^+$.

1-Iodo-2-trimethylsilylacetylene (5h): Trimethylsilylacetylene (1.96 g, 20.0 mmol) was dissolved in dry THF (25 mL). The solution was cooled to −78 °C, and *n*-butyl lithium (1.6 M in hexanes, 20.0 mmol) was added. The reaction mixture was stirred for 10 min, allowed to warm up to 0 °C, and stirred for another 10 min. Then, the temperature was, again, adjusted to −78 °C, and I_2 (5.08 g, 20.0 mmol) was added in one portion. The flask was covered with aluminum foil, and the reaction mixture was stirred at room temperature overnight. The solution was diluted with CH_2Cl_2 and washed with saturated $Na_2S_2O_3$ solution as well as water. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the crude product was carried out by distillation (20 mbar, 70 °C), and **5h** (3.60 g, 80%) was obtained as a colorless liquid. R_f = 0.8 (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.18 ppm (s, 9H, Si(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = −0.1 (Si(*C*H$_3$)$_3$), 20.6 (C≡*C*I), 104.2 ppm (*C*≡CI).

3-Iodoprop-2-yn-1-ol (5i): Propargyl alcohol (16.0 g, 285.3 mmol) was dissolved in MeOH (400 mL). A solution of KOH (56.0 g, 1.0 mol) in H_2O (100 mL) was prepared, cooled to 0 °C, and added to the reaction mixture. I_2 (63.5 g, 250 mmol) was added in one portion, and the solution was stirred at room temperature overnight. The reaction mixture was neutralized with 1 M HCl and extracted with diethyl ether. The organic phase was washed with saturated $Na_2S_2O_3$ solution, dried over Na_2SO_4, filtered, and concentrated in vacuo to yield the title compound as a colorless solid (43.3 g, 83%). R_f = 0.7 (CH_2Cl_2/MeOH 10:1); m.p. 42–43 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.04 (t, J = 5.4 Hz, 1H, OH), 4.41 ppm (d, J = 5.4 Hz, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 2.8 (C≡*C*I), 52.6 (*C*H$_2$), 92.5 ppm (*C*≡CI); elemental analysis calcd (%) for C_3H_3IO: C 19.80, H 1.66, I 69.74; found: C 19.85, H 1.64, I 69.77; HRMS (EI): *m/z*: calcd for C_3H_3IO: 181.9233; found: 181.9236 $[M]^+$.

1-{2‴-[2″-(2′-(2-Methoxyethoxy)ethoxy]ethoxy}ethoxy}-3-iodoprop-2-yne (5j) and 1-{2‴-{2″-[2′-(2-methoxyethoxy)ethoxy]ethoxy}ethoxy}prop-2-yne (6): In a thoroughly dried Schlenk flask, NaH (60% dispersion in mineral oil, 0.40 g, 10.0 mmol) was mixed with THF (100 mL), and the mixture was degassed in two freeze-pump-thaw cycles. Tetra(ethylene glycol) monomethyl ether (2.08 g, 10.0 mmol) was added at 0 °C, forming a suspension. The mixture was stirred for 30 min before propargyl bromide (80% in toluene, 2.23 g, 15 mmol) was added. Stirring was continued overnight. The reaction mixture was concentrated in vacuo and taken up in diethyl ether. The organic phase was washed with water, dried over $MgSO_4$ and concentrated. Thus, **6** (2.29 g, 93%) was obtained as a yellow liquid, which was directly used in the following step without further purification. For the iodination reaction, **6** (2.12 g, 8.61 mmol) was dissolved in MeOH (50 mL). A solution of KOH (1.45 g, 25.84 mmol) in H_2O (3 mL) was prepared, cooled to 0 °C, and added to the reaction mixture. After 10 min, I_2 (2.35 g, 9.25 mmol) was added in one portion, and the solution was stirred at room temperature overnight. The solvent was removed in vacuo, and the residue was taken up in 1 M HCl. The aqueous phase was extracted with $CHCl_3$. The organic phase was washed with saturated $Na_2S_2O_3$ solution, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 24:1). Compound **5j** (2.25 g, 70%) was obtained as a yellowish oil. R_f = 0.5 (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.28 (s, 3H, CH_3), 3.42–3.46 (m, 2H, CH_2), 3.51–3.60 (m, 14H, CH_2), 4.24 ppm (s, 2H, CH_2-C≡C); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 3.6 (C≡*C*I), 59.0, 60.0, 69.2, 70.3, 70.4, 70.5, 70.5, 70.5, 71.9 (O-*C*H$_2$, O-*C*H$_3$), 90.4 ppm (*C*≡CI); elemental analysis calcd (%) for $C_{12}H_{21}IO_5$: C 38.72, H 5.69, I 34.10; found: C 38.82, H 5.47, I 34.20.

***N*-Propargyloxycarbonyl-L-alanine *tert*-butyl ester (7)**: L-Alanine *tert*-butyl ester hydrochloride (3.30 g, 18.15 mmol) was dissolved in dry CH_2Cl_2 (50 mL). TEA (3.86 g, 38.12 mmol) was added, which led to the precipitation of its hydrochloride. The mixture was cooled to −78 °C, and propargyl chloroformate (2.15 g, 18.15 mmol) was added dropwise. The solution was stirred for 1 h at −78 °C and for 2 h at 0 °C before it was allowed to warm up to room temperature. The organic phase was washed with water and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. **7** (3.87 g, 93%) was obtained as a colorless oil, and no further purification was necessary. R_f = 0.7 (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (d, J = 7.2 Hz, 3H, CHCH_3), 1.41 (s, 9H, C(CH_3)$_3$), 2.44 (t, J = 2.5 Hz, 1H, C≡CH), 4.18 (m, 1H, CHCH$_3$), 4.63 (m, 2H, NHCO$_2$CH_2), 5.6 ppm (d, J = 6.6 Hz, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.6 (CH*C*H$_3$), 27.9 (C(*C*H$_3$)$_3$), 50.2 (*C*HCH$_3$), 52.4 (NHCO$_2$*C*H$_2$), 74.7 (C≡*C*H), 78.2 (*C*≡CH), 81.8 (*C*(CH$_3$)$_3$), 154.6 (carbamate *C*=O), 171.9 ppm (ester *C*=O); elemental analysis calcd (%) for $C_{11}H_{17}NO_4$: C 58.14, H 7.54, N 6.16; found: C 57.85, H 7.50, N 6.14; HRMS (EI): *m/z*: calcd for $C_7H_9NO_3$: 154.0499; found: 154.0501 $[M-C_4H_9O]^+$.

***N*-[6-(*N'*-Acetamido)hexa-2,4-diynyl-1-oxycarbonyl]-L-alanine *tert*-butyl ester (8a)**: Following GP A, **7** (0.65 g, 2.86 mmol), **5a** (0.8 g, 3.59 mmol), and the catalysts were dissolved in dry THF (30 mL). The solution was stirred overnight, and the solvents were removed in vacuo. After purification by column chromatography (silica gel, CH_2Cl_2/MeOH 50:1 to 20:1), **8a** (0.52 g, 56%) was obtained as a brownish solid. R_f = 0.5 (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (d, J = 7.2 Hz, 3H, CHCH_3), 1.41 (s, 9H, C(CH_3)$_3$), 1.96 (s, 3H, C(O)CH_3), 4.05 (d, J = 5.4 Hz, 2H, CH_2NHAc), 4.15 (m, 1H, CHCH$_3$), 4.67 (m, 2H, NHCO$_2$CH_2), 5.63 (d, J = 7.5 Hz, 1H, NH), 6.76 ppm (m, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.4 (CH*C*H$_3$), 22.7 (C(O)*C*H$_3$), 27.8 (C-(*C*H$_3$)$_3$), 29.5 (*C*H$_2$NHAc), 50.2 (*C*HCH$_3$), 52.8 (NHCO$_2$*C*H$_2$), 66.8, 70.4, 72.3, 76.0 (diacetylene *C*), 82.0 (*C*(CH$_3$)$_3$), 154.6 (carbamate *C*=O), 170.2 (amide *C*=O), 171.9 ppm (ester *C*=O); HRMS (EI): *m/z*: calcd for $C_{16}H_{22}N_2O_5$: 322.1524; found: 322.1523 $[M]^+$.

***N*-{6-[*N'*-(4-Methoxysuccinyl)amido]hexa-2,4-diynyl-1-oxycarbonyl}-L-alanine *tert*-butyl ester (8b)**: Following GP A, **7** (0.58 g, 2.55 mmol), **5b** (0.92 g, 3.12 mmol) and the catalysts were dissolved in dry THF (30 mL). The solution was stirred for 4 h, and the solvents were removed in vacuo. After purification by column chromatography (silica gel, CH_2Cl_2/MeOH 20:1), **6f** (0.55 g, 55%) was obtained as a brownish solid. R_f = 0.4 (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (d, J = 7.2 Hz, 3H, CHCH_3), 1.41 (s, 9H, C(CH_3)$_3$), 2.48 (t, J = 6.7 Hz, 2H, NHCOCH_2), 2.62 (t, J = 6.7 Hz, 2H, CH_2CO$_2$Me), 3.63 (s, 3H, OCH_3), 4.07 (d, J = 5.4 Hz, 2H, CH_2NH), 4.16 (m, 1H, CHCH$_3$), 4.67 (s, 2H, CO$_2$CH_2C≡C), 5.61 (d, J = 7.5 Hz, 2H, NH), 6.71 ppm (t, J = 5.1 Hz, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.4 (CH*C*H$_3$), 27.8 (C(*C*H$_3$)$_3$), 29.1, 29.6, 30.4 (*C*H$_2$NH, *C*H$_2$CO$_2$Me, NHCO*C*H$_2$), 50.3 (*C*HCH$_3$), 51.8 (O*C*H$_3$), 52.8 (CO$_2$*C*H$_2$C≡C), 66.7, 70.5, 72.4, 76.3 (diacetylene *C*), 81.9 (*C*(CH$_3$)$_3$), 154.7 (carbamate *C*=O), 171.4, 171.9, 173.3 ppm (2 ester *C*=O, amide *C*=O); HRMS (EI): *m/z*: calcd for $C_{19}H_{26}N_2O_7$: 394.1735; found: 394.1733 $[M]^+$.

***N*-{6-[*N'*-(9-Fluorenylmethyloxycarbonyl)amino]hexa-2,4-diynyl-1-oxycarbonyl}-L-alanine *tert*-butyl ester (8c)**: Following GP A, **7** (1.0 g, 4.4 mmol), **5c** (2.1 g, 5.3 mmol) and the catalysts were dissolved in dry THF (50 mL). The solution was stirred for 3 h, and the solvents were removed in vacuo. The crude product was purified by repeated column chromatography (silica gel, $CHCl_3$/toluene 10:1) and preparative GPC ($CHCl_3$). However, only mixtures of **8c** and the homo- as well as hetero-coupling side products were obtained, which were used in the next step

without further purification. $R_f = 0.75$ (CH_2Cl_2/MeOH 10:1); HRMS (EI): m/z: calcd for $C_{29}H_{30}N_2O_6$: 502.2098; found 502.2085 $[M]^+$.

***N*-{6-[*N'*-(5-Dimethylamino-1-naphthalenesulfonyl)amido]hexa-2,4-diynyl-1-oxycarbonyl}-L-alanine *tert*-butyl ester (8d)**: Following GP A, **7** (0.18 g, 0.81 mol), **5d** (0.46 g, 0.97 mmol) and the catalysts were dissolved in THF (30 mL). The solution was stirred overnight, diluted with $CHCl_3$ (40 mL) and washed twice with saturated $NaHCO_3$ solution. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, ethyl acetate/hexane 1:3) to yield the title compound as a yellow powder (0.20 g, 47%). $R_f = 0.5$ (EtOAc/Hex 1:1); ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 1.39$ (d, $J = 7.2$ Hz, 3H, CHCH_3), 1.48 (s, 9H, C(CH_3)$_3$), 2.90 (s, 6H, N(CH_3)$_2$), 3.87 (d, $J = 6.3$ Hz, 2H, NHCH_2), 4.24 (m, 1H, CHCH$_3$), 4.62 (m, 2H, NHCO$_2$CH_2), 5.27 (br s, 1H, NH), 5.46 (m, 1H, NH), 7.21 (d, $J = 7.5$ Hz, 1H, aromatic H), 7.56 (m, 2H, aromatic H), 8.26 (m, 2H, aromatic H), 8.57 ppm (d, $J = 8.4$ Hz, 1H, aromatic H); ^{13}C NMR (75 MHz, [D$_6$]DMSO): $\delta = 18.8$ (CHCH$_3$), 27.9 (C(CH_3)$_3$), 33.6 (NHCH$_2$), 45.4 (N(CH_3)$_2$), 50.3 (CHCH$_3$), 52.7 (NHCO$_2$$CH_2$), 68.2, 69.9, 72.9, 73.7 (diacetylene C), 82.2 (C(CH$_3$)$_3$), 115.2, 118.5, 123.2, 128.6, 129.7, 129.9, 129.9, 131.0, 134.1, 151.4 (aromatic C), 154.4 (carbamate C=O), 171.9 ppm (ester C=O); elemental analysis calcd (%) for $C_{26}H_{31}N_3O_6S$: C 60.80, H 6.08, N 8.18; found: C 59.69, H 5.90, N 7.97.

***N*-{6-{*N'*-[*N''*-(9-Fluorenylmethyloxycarbonyl)-L-alanyl]amido}hexa-2,4-diynyl-1-oxycarbonyl}-L-alanine *tert*-butyl ester (8e)**: Following GP A, **7** (1.53 g, 6.73 mmol), **5e** (3.80 g, 8.01 mmol), and the catalysts were dissolved in THF (80 mL). The solution was stirred for 3 h, diluted with CH_2Cl_2, and subjected to an acidic aqueous workup. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 50:1) to yield the title compound as slightly brown crystals (1.94 g, 50%). $R_f = 0.4$ (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 1.36$ (d, $J = 6.9$ Hz, 6H, 2CHCH_3), 1.46 (s, 9H, C(CH_3)$_3$), 4.11 (m, 2H, CH_2NH), 4.2–4.3 (m, 3H, Fmoc CO$_2$CH_2, fluorenyl CH), 4.4–4.5 (m, 2H, 2 CHCH$_3$), 4.69 (m, 2H, OCH_2C≡C), 5.44 (d, $J = 6.6$ Hz, 2H, NH), 6.62 (s, 1H, NH), 7.29 (dt, $J = 1.2$ Hz, 7.5 Hz, 2H, aromatic H), 7.39 (t, $J = 7.5$ Hz, 2H, aromatic H), 7.57 (d, $J = 7.5$ Hz, 2H, aromatic H), 7.75 ppm (d, $J = 7.5$ Hz, 2H, aromatic H); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 18.5$, 18.8 (2 CHCH$_3$), 28.0 (C(CH_3)$_3$), 29.8 (CH_2NH), 47.2 (fluorenyl CH), 50.3 (2 CHCH$_3$), 52.9 (CO$_2$CH_2C≡C), 67.1, 67.4, 70.5, 72.7, 75.6 (diacetylene C, CO$_2$CH_2), 82.1 (C(CH$_3$)$_3$), 120.0, 125.0, 127.1, 127.8, 141.3, 143.7 (aromatic C), 154.5, 156.1 (2 carbamate C=O), 172.0, 172.1 ppm (amide and ester C=O); elemental analysis calcd (%) for $C_{32}H_{35}N_3O_7$: C 67.00, H 6.15, N 7.33; found: C 66.72, H 6.19, N 7.08; HRMS (MALDI): m/z: calcd for $C_{32}H_{35}N_3O_7Na$: 596.2367; found: 596.2367 $[M+Na]^+$.

***N*-{6-{*N'*-[*N''*-(9-Fluorenylmethyloxycarbonyl)glycyl]amido}hexa-2,4-diynyl-1-oxycarbonyl}-L-alanine *tert*-butyl ester (8f)**: Following GP A, **7** (0.45 g, 2.0 mmol), **5f** (1.10 g, 2.4 mmol) and the catalysts were dissolved in dry THF (30 mL). The solution was stirred for 3 h, diluted with CH_2Cl_2, and subjected to an acidic aqueous workup. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 20:1) to yield the title compound as a slightly brown solid (0.68 g, 61%). $R_f = 0.4$ (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (300 MHz, CDCl$_3$): $\delta =$ 1.39 (d, $J = 7.2$ Hz, 3H, CHCH_3), 1.49 (s, 9H, C(CH_3)$_3$), 3.90 (s, 2H, Gly-CH_2), 4.14 (m, 2H, C≡CCH_2NH), 4.2–4.3 (m, 2H, CHCH$_3$, fluorenyl-CH), 4.48 (d, $J = 6.9$ Hz, 2H, Fmoc-CO$_2$CH_2), 4.73 (s, 2H, NHCO$_2$CH_2C≡C), 5.65 (s, 1H, NH), 6.59 (s, 1H, NH), 7.33 (t, $J =$ 7.2 Hz, 2H, aromatic H), 7.42 (t, $J = 7.2$ Hz, 2H, aromatic H), 7.61 (d, $J =$ 7.2 Hz, 2H, aromatic H), 7.78 ppm (d, $J = 7.2$ Hz, 2H, aromatic H); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 18.5$ (CHCH$_3$), 27.9 (C(CH_3)$_3$), 29.6 (NHCH$_2$C≡C), 47.1 (fluorenyl-CH), 50.4 (Gly-CH$_2$), 52.9 (CHCH$_3$), 53.6 (NHCO$_2$$CH_2$), 67.0 (Fmoc-CO$_2$$CH_2$), 67.1, 70.6, 72.8, 76.1 (diacetylene C), 82.0 (C(CH$_3$)$_3$), 120.0, 125.1, 127.1, 127.7, 141.3, 143.8 (aromatic C), 154.8 (carbamate C=O), 156.9 (carbamate C=O), 169.6 (amide C=O), 172.2 ppm (ester C=O); HRMS (ESI): m/z: calcd for $C_{31}H_{33}N_3O_7Na$: 582.2211; found: 582.2210 $[M+Na]^+$.

***N*-{6-[*N'*-(*N''*-Acetyl-L-alanyl)amido]hexa-2,4-diynyl-1-oxycarbonyl}-L-alanine *tert*-butyl ester (8g)**: Following GP A, **7** (0.90 g, 3.96 mmol), **5g** (1.4 g, 4.76 mmol), and the catalysts were dissolved in dry THF (30 mL). The solution was stirred for 3 h, diluted with CH_2Cl_2, and subjected to an acidic aqueous workup. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 50:1 to 20:1) to yield the title compound as colorless solid (0.80 g, 51%). $R_f = 0.5$ (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 1.32$ (d, $J = 7.2$ Hz, 3H, CHCH_3), 1.33 (d, $J = 7.5$ Hz, 3H, CHCH_3), 1.43 (s, 9H, C(CH_3)$_3$), 1.99 (s, 3H, C(O)CH_3), 4.07 (d, $J = 5.1$ Hz, 2H, CH_2NH), 4.18 (m, 1H, CHCH$_3$), 4.58 (m, 1H, CHCH$_3$), 4.68 (m, 2H, NHCO$_2$CH_2), 5.77 (d, $J = 7.8$ Hz, 1H, NH), 7.03 (d, $J = 7.8$ Hz, 1H, NH), 7.68 ppm (m, 1H, NH); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 18.2$, 18.3 (2 CHCH$_3$), 23.0 (C(O)CH_3), 27.9 (C-(CH_3)$_3$), 29.7 (CH_2NH), 48.7, 50.3 (2 CHCH$_3$), 52.9 (NHCO$_2$CH_2), 67.1, 70.6, 72.6, 75.7 (diacetylene C), 82.1 (C(CH$_3$)$_3$), 154.7 (carbamate C=O), 170.6, 172.1, 172.6 ppm (2 amide C=O, ester C=O); HRMS (EI): m/z: calcd for $C_{19}H_{27}N_3O_6$: 393.1895; found: 393.1896 $[M]^+$.

***N*-(5-Trimethylsilylpenta-2,4-diynyl-1-oxycarbonyl)-L-alanine *tert*-butyl ester (8h)**: Following GP A, **7** (0.98 g, 4.41 mmol), **5h** (1.22 g, 5.35 mmol), and the catalysts were dissolved in dry THF (50 mL). The solution was stirred overnight, diluted with CH_2Cl_2, and subjected to an acidic aqueous workup. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, CH_2Cl_2). **8h** (0.85 g, 61%) was obtained as an orange oil. $R_f = 0.3$ (CH_2Cl_2); ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 0.16$ (s, 9H, Si(CH_3)$_3$), 1.34 (d, $J = 7.2$ Hz, 3H, CHCH_3), 1.44 (s, 9H, C(CH_3)$_3$), 4.20 (m, 1H, CHCH$_3$), 4.70 (m, 2H, NHCO$_2$CH_2), 5.45 ppm (d, $J =$ 7.2 Hz, 1H, NH); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = -0.6$ (Si(CH_3)$_3$), 18.8 (CHCH$_3$), 27.9 (C(CH_3)$_3$), 50.3 (CHCH$_3$), 52.8 (NHCO$_2$CH_2), 71.2, 72.0, 87.1, 87.9 (diacetylene C), 82.1 (C(CH$_3$)$_3$), 154.5 (carbamate C=O), 171.9 ppm (ester C=O); elemental analysis calcd (%) for $C_{16}H_{25}N_2O_4Si$: C 59.41, H 7.79, N 4.33; found: C 59.40, H 8.04, N 4.31; HRMS (EI): m/z: calcd for $C_{16}H_{25}NO_4Si$: 323.1547; found: 323.1546 $[M]^+$.

***N*-(6-Hydroxyhexa-2,4-diynyl-1-oxycarbonyl)-L-alanine *tert*-butyl ester (8i)**: Following GP A, **7** (1.02 g, 4.49 mmol), **5i** (0.98 g, 5.39 mmol), and the catalysts were dissolved in dry THF (30 mL). The solution was stirred for 4 h, diluted with CH_2Cl_2, and subjected to an acidic aqueous workup. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 24:1) to yield the title compound as a yellowish oil (0.74 g, 59%). $R_f = 0.4$ (CH_2Cl_2/MeOH 24:1); ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 1.32$ (d, $J = 7.2$ Hz, 3H, CHCH_3), 1.41 (s, 9H, C(CH_3)$_3$), 3.34 (s, 1H, OH), 4.16 (m, 1H, CHCH$_3$), 4.26 (s, 2H, CH_2OH), 4.71 (m, 2H, NHCO$_2$CH_2), 5.64 ppm (d, $J = 7.5$ Hz, 1H, NH); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 18.6$ (CHCH$_3$), 27.9 (C(CH_3)$_3$), 50.3 (CHCH$_3$), 51.0 (CH_2OH), 53.0 (NHCO$_2$CH_2), 69.1, 70.5, 73.4, 78.3 (diacetylene C), 82.2 (C(CH$_3$)$_3$), 154.8 (carbamate C=O), 172.1 ppm (ester C=O); elemental analysis calcd (%) for $C_{14}H_{19}NO_5$: C 59.78, H 6.81, N 4.98; found: C 59.98, H 6.89, N 5.12; HRMS (EI): m/z: calcd for $C_{14}H_{19}NO_5$: 281.1258; found: 281.1258 $[M]^+$.

***N*-{6-{2'''-{2''-[2'-(2-Methoxyethoxy)ethoxy]ethoxy}ethoxy}hexa-2,4-diynyl-1-oxycarbonyl}-L-alanine *tert*-butyl ester (8j)**: Following GP A, **7** (0.31 g, 1.32 mmol), **5j** (0.60 g, 1.61 mmol), and the catalysts were dissolved in dry THF (25 mL). The solution was stirred overnight, and the solvents were removed in vacuo. The purification was carried out by column chromatography (silica gel, CH_2Cl_2/MeOH 24:1) to yield the title compound as a yellowish oil (0.29 g, 45%). $R_f = 0.5$ (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 1.30$ (d, $J = 7.2$ Hz, 3H, CHCH_3), 1.39 (s, 9H, C(CH_3)$_3$), 3.30 (s, 3H, OCH_3), 3.47 (m, 2H, CH_2O), 3.55–3.65 (m, 14H, CH_2O), 4.14 (m, 1H, CHCH$_3$), 4.19 (s, 2H, C$_4$CH_2O), 4.66 (m, 2H, NHCO$_2$CH_2), 5.50 ppm (d, $J = 7.5$ Hz, 1H, NH); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 18.7$ (CHCH$_3$), 27.9 (C(CH_3)$_3$), 50.3 (CHCH$_3$), 52.8 (NHCO$_2$CH_2), 58.8 (OCH_3), 58.9 (CH_2O), 69.3, 70.2–70.5, 73.4, 76.0 (6 CH_2O, diacetylene C), 82.0 (C(CH$_3$)$_3$), 154.5 (carbamate C=O), 171.9 ppm (ester C=O); HRMS (EI): m/z: calcd for $C_{16}H_{28}NO_7$: 370.1861; found: 370.1861 $[M-C_5H_9O_2]^+$.

Hexa-2,4-diynylene-1,6-bis(oxycarbonyl-L-alanine *tert*-butyl ester) (9): A solution of CuCl (0.96 g, 9.7 mmol) and TMEDA (1.2 g, 10 mmol) in acetone (20 mL) was added to a solution of **7** (2 g, 8.8 mmol) in acetone

(60 mL), and the resulting green mixture was stirred for 5 h at room temperature with dry air bubbling through the reaction mixture. The solution was diluted with acetone and filtered through a pad of silica gel. After evaporation of the solvent, the residue was taken up in CH_2Cl_2 and washed twice with water. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography afforded **9** (1.28 g, 64%) as a yellow oil which slowly crystallized. R_f=0.7 (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.31 (d, J=7.2 Hz, 6H, 2 CHCH_3), 1.40 (s, 18H, 2 C(CH_3)$_3$), 4.16 (m, 2H, 2 CHCH$_3$), 4.67 (m, 4H, 2 NHCO$_2$CH_2), 5.59 ppm (d, J=7.5 Hz, 2H, 2 NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=18.6 (2 CHCH$_3$), 27.9 (2 C(CH_3)$_3$), 50.3 (2 CHCH$_3$), 52.7 (2 NHCO$_2$CH_2), 70.2, 74.0 (diacetylene C), 81.9 (2 C(CH$_3$)$_3$), 154.5 (2 carbamate C=O), 171.9 ppm (2 ester C=O); elemental analysis calcd (%) for $C_{22}H_{32}N_2O_8$: C 58.40, H 7.13, N 6.19; found: C 58.42, H 7.2, N 6.13; HRMS (EI): m/z: calcd for $C_{22}H_{32}N_2O_8$: 452.2153; found: 452.2195 $[M]^+$.

***N*-[6-(*N'*-Acetamido)hexa-2,4-diynyl-1-oxycarbonyl]-L-alanine (10a)**: Following GP B, **8a** (0.86 g, 2.67 mmol) was dissolved in dry CH_2Cl_2 (10 mL), a large excess of TFA was added and the solution was stirred overnight. **10a** (0.71 g, 100%) was obtained as a brown amorphous product, and no further purification was carried out before the next step. R_f= 0.1 (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.40 (d, J= 7.2 Hz, 3H, CHCH_3), 2.00 (s, 3H, C(O)CH_3), 4.06 (d, J=5.1 Hz, 2H, CH_2NHAc), 4.26 (m, 1H, CHCH$_3$), 4.68 (s, 2H, NHCO$_2$CH_2), 5.77 (d, J=7.5 Hz, 1H, NH), 7.00 (m, 1H, NH), 8.82 ppm (brs, 1H, COOH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=18.4 (CHCH$_3$), 22.6 (C(O)CH$_3$), 29.7 (CH$_2$NHAc), 49.7 (CHCH$_3$), 52.9 (NHCO$_2$$CH_2$), 67.0, 70.5, 72.6, 76.0 (diacetylene C), 154.8 (carbamate C=O), 170.9 (amide C=O), 174.9 ppm (acid C=O).

***N*-{6-[*N'*-(4-Methoxysuccinyl)amido]hexa-2,4-diynyl-1-oxycarbonyl}-L-alanine (10b)**: Following GP B, **8b** (0.32 g, 0.8 mmol) was dissolved in dry CH_2Cl_2 (10 mL), a large excess of TFA was added and the solution was stirred overnight. **10b** (0.34 g, 100%) was obtained as a brown amorphous product. A further purification was not necessary before the next step. R_f=0.1 (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=1.26 (d, J=7.2 Hz, 3H, CHCH_3), 2.39 (t, J=6.6 Hz, 2H, NHCOCH_2), 2.52 (t, J=6.6 Hz, 2H, CH_2CO$_2$Me), 3.58 (s, 3H, OCH_3), 3.9–4.0 (m, 3H, C≡CCH_2NH, CHCH$_3$), 4.75 (s, 2H, C≡CCH_2O), 7.57 (d, J=7.5 Hz, 1H, NH), 8.43 ppm (t, J=5.4 Hz, 1H, NH); ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ=17.5 (CHCH$_3$), 29.0, 30.0 (CH$_2$NH, CH$_2$CO$_2$Me, NHCOCH$_2$), 49.8 (CHCH$_3$), 51.7 (OCH$_3$), 52.4 (CO$_2$$CH_2$C≡C), 65.7, 70.0, 74.2, 78.7 (diacetylene C), 155.3 (carbamate C=O), 171.2, 173.2, 174.6 ppm (ester C=O, amide C=O, acid C=O).

***N*-{6-[*N'*-(9-Fluorenylmethyloxycarbonyl)amino]hexa-2,4-diynyl-1-oxycarbonyl}-L-alanine (10c)**: Following GP B, **8c** (1.8 g, impure) was dissolved in dry CH_2Cl_2 (20 mL), a large excess of TFA was added, and the solution was stirred overnight. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 10:1) to yield the title compound as a nearly colorless solid (1.0 g, 62%). R_f=0.1 (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=1.28 (d, J=7.5 Hz, 3H, CHCH_3), 3.95 (d, J=5.7 Hz, 2H, NHCH_2), 4.02 (m, 1H, CHCH$_3$), 4.24 (t, J= 6.3 Hz, 1H, fluorenyl CH), 4.36 (d, J=6.9 Hz, 2H, Fmoc-CO$_2$CH_2), 4.77 (m, 2H, NHCO$_2$CH_2), 7.34 (t, J=7.2 Hz, 2H, aromatic H), 7.43 (t, J= 7.5 Hz, 2H, aromatic H), 7.70 (d, J=7.5 Hz, 2H, aromatic H), 7.76 (d, J=7.5 Hz, 1H, NH), 7.8–8.0 ppm (m, 3H, 2 aromatic H, NH).

***N*-{6-[*N'*-(5-Dimethylamino-1-naphthalenesulfonyl)amido]hexa-2,4-diynyl-1-oxycarbonyl}-L-alanine (10d)**: Following GP B, **8d** (0.14 g, 0.27 mmol) was dissolved in CH_2Cl_2 (10 mL), a large excess of TFA was added, and the solution was stirred overnight. **10d** (0.11 g, 90%) was obtained as a dark amorphous substance. A further purification was not necessary before the next step. R_f=0.3 (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=1.27 (d, J=7.5 Hz, 3H, CHCH_3), 2.90 (s, 6H, N(CH_3)$_2$), 3.90 (d, J=5.7 Hz, 2H, NHCH_2), 3.99 (m, 1H, CHCH$_3$), 4.66 (m, 2H, NHCO$_2$CH_2), 7.35 (d, J=7.5 Hz, 1H, aromatic H), 7.65 (m, 2H, aromatic H, NH), 7.74 (d, J=7.5 Hz, 1H, aromatic H), 8.17 (d, J= 6.9 Hz, 1H, aromatic H), 8.31 (d, J=8.7 Hz, 1H, aromatic H), 8.5–8.6 ppm (m, 2H, aromatic H, NH); ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ= 17.5 (CHCH$_3$), 32.7 (NHCH$_2$), 46.0 (N(CH$_3$)$_2$), 49.7 (CHCH$_3$), 52.3 (NHCO$_2$$CH_2$), 66.9, 69.5, 74.6, 76.7 (diacetylene C), 116.0, 120.2, 124.3, 128.4, 129.2, 129.3, 129.5, 130.0, 136.1, 150.7 (aromatic C), 155.2 (carbamate C=O), 174.6 ppm (acid C=O).

***N*-{6-{*N'*-[*N''*-(9-Fluorenylmethyloxycarbonyl)-L-alanyl]amido}hexa-2,4-diynyl-1-oxycarbonyl}-L-alanine (10e)**: Following GP B, **8e** (0.52 g, 0.9 mmol) was dissolved in dry CH_2Cl_2 (20 mL), a large excess of TFA was added, and the solution was stirred overnight. **10e** (0.59 g, 100%) was obtained as a brownish, crystalline product. A further purification was not necessary before the next step. R_f=0.1 (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=1.1–1.4 (m, 6H, 2 CHCH_3), 3.9–4.1 (m, 4H, 2CHCH$_3$, CH_2NH), 4.2–4.4 (m, 3H, Fmoc-CO$_2$CH$_2$, fluorenyl CH), 4.76 (s, 2H, CO$_2$CH_2C≡C), 7.32 (t, J=7.2 Hz, 2H, aromatic H), 7.43 (t, J=7.2 Hz, 2H, aromatic H), 7.57 (d, J=7.5 Hz, 1H, NH), 7.7–7.8 (m, 3H, aromatic H, NH), 7.89 (d, J=7.5 Hz, 2H, aromatic H), 8.43 ppm (m, 1H, NH); ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ=17.5, 18.5 (2 CCH$_3$), 29.2 (CH_2NH), 47.1 (fluorenyl CH), 49.8, 50.4 (2 CHCH$_3$), 52.4 (CO$_2$CH$_2$C≡C), 65.77, 66.12, 70.08, 74.31, 78.64 (diacetylene C, Fmoc-CO$_2$$CH_2$), 120.6, 125.8, 127.5, 128.1, 141.2, 144.4 (aromatic C), 155.3, 156.2 (2 carbamate C=O), 172.9 (amide C=O), 174.6 ppm (acid C=O); HRMS (MALDI): m/z: calcd for $C_{28}H_{27}N_3O_7$: 518.1922; found: 518.1922 $[M]^+$.

***N*-{6-{*N'*-[*N''*-(9-Fluorenylmethyloxycarbonyl)glycyl]amido}hexa-2,4-diynyl-1-oxycarbonyl}-L-alanine (10f)**: Following GP B, **8f** (0.4 g, 0.71 mmol) was dissolved in dry CH_2Cl_2 (20 mL), a large excess of TFA was added, and the solution was stirred overnight. The crude product was dried in HV and purified by column chromatography (silica gel, CH_2Cl_2/MeOH/TFA 199:10:1). **10f** (0.33 g, 92%) was obtained as a brown solid. R_f=0.1 (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=1.25 (d, J=7.2 Hz, 3H, CHCH_3), 3.64 (s, 2H, Gly-CH_2), 4.03 (d, J=5.1 Hz, 2H, NHCH_2C≡C), 4.11 (m, 1H, CHCH$_3$), 4.2–4.3 (m, 3H, fluorenyl-CH, Fmoc-CO$_2$CH_2), 4.76 (s, 2H, NHCO$_2$CH_2), 7.34 (t, J= 7.5 Hz, 2H, aromatic H), 7.43 (t, J=7.5 Hz, 2H, aromatic H), 7.59 (t, J= 6.0 Hz, 1H, NH), 7.73 (d, J=7.5 Hz, 2H, aromatic H), 7.90 (d, J=7.5 Hz, 2H, aromatic H), 8.42 ppm (t, J=5.4 Hz, 1H, NH); ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ=17.5 (CHCH$_3$), 29.0 (NHCH$_2$C≡C), 47.1 (fluorenyl-CH), 49.8 (CHCH$_3$), 52.4 (CO$_2$CH$_2$C≡C), 55.3 (Gly-CH$_2$), 66.2 (Fmoc-CO$_2$$CH_2$), 65.7, 70.0, 74.3, 78.7 (diacetylene C), 120.6, 125.7, 127.5, 128.1, 141.2, 144.3 (aromatic C), 155.3, 157.0 (2carbamate C=O), 169.7 (amide C=O), 174.6 ppm (acid C=O); HRMS (MALDI): m/z: calcd for $C_{27}H_{25}N_3O_7Na$: 526.1585; found: 526.1588 $[M+Na]^+$.

***N*-{6-[*N'*-(*N''*-Acetyl-L-alanyl)amido]hexa-2,4-diynyl-1-oxycarbonyl}-L-alanine (10g)**: Following GP B, **8g** (0.16 g, 0.40 mmol) was dissolved in dry CH_2Cl_2 (20 mL), a large excess of TFA was added, and the solution was stirred for 5 h. **10g** (0.13 g, 100%) was obtained as a brownish solid. A further purification was not necessary before the next step. R_f=0.1 (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=1.18 (d, J= 7.2 Hz, 3H, CHCH_3), 1.27 (d, J=7.2 Hz, 3H, CHCH_3), 1.84 (s, 3H, C(O)CH_3), 3.9–4.1 (m, 3H, CH_2NH, CHCH$_3$), 4.23 (m, 1H, CHCH$_3$), 4.75 (s, 2H, NHCO$_2$CH_2), 7.76 (d, J=7.5 Hz, 1H, NH), 8.08 (d, J= 7.2 Hz, 1H, NH), 8.40 ppm (m, 1H, NH); ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ=17.5, 18.5 (2 CHCH$_3$), 23.0 (C(O)CH$_3$), 29.1 (CH_2NH), 48.4, 49.7 (2 CHCH$_3$), 52.4 (NHCO$_2$$CH_2$), 65.7, 70.1, 74.3, 78.7 (diacetylene C), 155.3 (carbamate C=O), 169.5, 172.8 (2 amide C=O), 174.6 ppm (acid C=O).

***N*-(5-Trimethylsilylpenta-2,4-diynyl-1-oxycarbonyl)-L-alanine (10h)**: Following GP B, **8h** (0.85 g, 2.6 mmol) was dissolved in dry CH_2Cl_2 (20 mL), a large excess of TFA was added, and the solution was stirred overnight. **10h** (0.70 g, 100%) was obtained as a brown amorphous product, and no further purification was carried out before the next step. R_f=0.15 (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=0.19 (s, 9H, Si(CH_3)$_3$), 1.27 (d, J=7.2 Hz, 3H, CHCH_3), 4.01 (m, 1H, CHCH$_3$), 4.76 (s, 2H, NHCO$_2$CH_2), 7.74 (d, J=7.5 Hz, 1H, NH) 9.3 ppm (brs, 1H, COOH); ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ=−0.3 (Si(CH$_3$)$_3$), 17.5 (CHCH$_3$), 49.7 (CHCH$_3$), 52.3 (NHCO$_2$$CH_2$), 70.3, 74.8, 87.6, 88.3 (diacetylene C), 155.3 (carbamate C=O), 174.6 ppm (acid C=O); HRMS (EI): m/z: calcd for $C_{12}H_{17}NO_4Si$: 267.0921; found: 267.0923 $[M]^+$.

***N*-(6-Hydroxyhexa-2,4-diynyl-1-oxycarbonyl)-L-alanine (10i)**: Following GP B, **8i** (1.20 g, 4.27 mmol) was dissolved in dry CH_2Cl_2 (20 mL), a large excess of TFA was added, and the solution was stirred for 4 h. **10i**

(0.90 g, 92%) was obtained as a brownish amorphous product, and no further purification was carried out before the next step. $R_f = 0.1$ (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 1.27$ (d, $J = 7.2$ Hz, 3H, CHCH_3), 3.18 (s, 1H, OH), 4.00 (m, 1H, CHCH$_3$), 4.18 (s, 2H, CH_2OH), 4.75 (s, 2H, NHCO$_2$CH_2), 7.72 ppm (d, $J = 7.5$ Hz, 1H, NH); ^{13}C NMR (75 MHz, [D$_6$]DMSO): $\delta = 17.4$ (CHCH$_3$), 49.0 (CHCH$_3$), 49.8 (CH$_2$OH), 52.4 (NHCO$_2C$H$_2$), 67.9, 70.0, 75.1, 81.1 (diacetylene C), 155.3 (carbamate C=O), 174.6 ppm (acid C=O).

***N*-{6-{2‴-{2″-[2′-(2-Methoxyethoxy)ethoxy]ethoxy}ethoxy}hexa-2,4-diynyl-1-oxycarbonyl}-L-alanine (10j)**: Following GP B, **8j** (0.22 g, 0.47 mmol) was dissolved in dry CH_2Cl_2 (20 mL), a large excess of TFA was added, and the solution was stirred for 5 h. **10j** (0.19 g, 99%) was obtained as a brownish oil, and no further purification was carried out before the next step. $R_f = 0.2$ (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.38$ (d, $J = 6.9$ Hz, 3H, CHCH_3), 3.33 (s, 3H, OCH_3), 3.52 (m, 2H, CH_2O), 3.6–3.7 (m, 14H, CH_2O), 4.22 (s, 2H, C$_4$CH_2O), 4.25 (m, 1H, CHCH$_3$), 4.75 (m, 2H, NHCO$_2$CH_2), 5.81 (d, $J = 4.2$ Hz, 1H, NH), 8.4 ppm (s, 1H, COOH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.5$ (CHCH$_3$), 50.0 (CHCH$_3$), 52.9 (NHCO$_2C$H$_2$), 58.8, 58.9 (CH$_2$O), 69–71 (6 CH$_2$O, 2 diacetylene C), 73.5, 76.0 (diacetylene C), 154.8 (carbamate C=O), 176.5 ppm (acid C=O).

Hexa-2,4-diynylene-1,6-bis(oxycarbonyl-L-alanine) (11): Following GP B, **9** (0.45 g, 1.0 mmol) was dissolved in dry CH_2Cl_2 (20 mL), a large excess of TFA was added, and the solution was stirred for 5 h. **11** (0.34 g, 99%) was obtained as a brown solid. A further purification was not necessary before the next step. $R_f = 0.05$ (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 1.27$ (d, $J = 7.2$ Hz, 3H, CHCH_3), 4.00 (m, 1H, CHCH$_3$), 4.77 (s, 2H, CO$_2$CH_2), 7.76 ppm (d, $J = 7.8$ Hz, 1H, NH); ^{13}C NMR (75 MHz, [D$_6$]DMSO): $\delta = 17.5$ (CHCH$_3$), 49.8 (CHCH$_3$), 52.4 (CO$_2C$H$_2$), 69.4, 76.3 (diacetylene C), 155.3 (carbamate C=O), 174.6 ppm (acid C=O).

***N*-(9-Fluorenylmethyloxycarbonyl)-L-alanine dodecylamide (12)**: Following GP A, dodecylamine (3.22 g, 17.37 mmol) and *N*-(9-fluorenylmethyloxycarbonyl)-L-alanine (5.52 g, 17.73 mmol) were dissolved in a mixture of dry CH_2Cl_2 (90 mL) and dry DMF (30 mL). DIEA (6.7 g, 52.60 mmol) and PyBOP (9.4 g, 18.07 mmol) were added, and the reaction mixture was stirred overnight. The organic phase was washed with saturated $NaHCO_3$ solution, 1M HCl and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, gradient from CH_2Cl_2/MeOH 24:1 to 10:1) to yield the title compound as a colorless solid (5.83 g, 81%). $R_f = 0.75$ (CH_2Cl_2/MeOH 10:1); m.p. 136–137°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.89$ (t, $J = 6.9$ Hz, 3H, (CH$_2$)$_{11}$CH_3), 1.2–1.35 (m, 18H, (CH_2)$_9$CH$_3$), 1.38 (d, $J = 6.9$ Hz, 3H, CHCH_3), 1.44 (t, $J = 6.6$ Hz, 2H, CH_2(CH$_2$)$_9$CH$_3$), 3.22 (m, 2H, NHCH_2(CH$_2$)$_{10}$CH$_3$), 4.15–4.3 (m, 2H, CHCH$_3$, fluorenyl CH), 4.37 (d, $J = 6.9$ Hz, 2H, CO$_2$CH_2), 5.63 (d, $J = 7.2$ Hz, 1H, NH), 6.30 (brs, 1H, NH), 7.29 (t, $J = 7.5$ Hz, 2H, aromatic H), 7.39 (t, $J = 7.5$ Hz, 2H, aromatic H), 7.57 (d, $J = 7.2$ Hz, 2H, aromatic H), 7.75 ppm (d, $J = 7.5$ Hz, 2H, aromatic H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.1$ ((CH$_2$)$_{11}$CH$_3$), 18.9 (CHCH$_3$), 22.7, 26.9, 29.3, 29.4, 29.5, 29.6, 29.7, 31.9 (10 CH$_2$), 39.6 (NHCH$_2$(CH$_2$)$_{10}$CH$_3$), 47.1 (fluorenyl CH), 50.6 (CHCH$_3$), 67.1 (CO$_2C$H$_2$), 120.0, 125.0, 127.1, 127.8, 141.3, 143.8 (aromatic C), 156.1 (carbamate C=O), 172.2 ppm (amide C=O); elemental analysis calcd (%) for $C_{30}H_{42}N_2O_3$: C 75.28, H 8.84, N 5.85; found: C 75.15, H 8.84, N 5.93; HRMS (EI): m/z: calcd for $C_{30}H_{42}N_2O_3$: 478.3190; found: 478.3200 $[M]^+$.

L-Alanine dodecylamide (13): The Fmoc-protected derivative **12** (5.63 g, 12.17 mmol) was dissolved in chloroform (40 mL), and piperidine (8 mL, 81 mmol) was added. The reaction mixture was stirred overnight, and the solvents were removed in vacuo. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 24:1) to yield the title compound as a colorless solid (2.82 g, 90%). $R_f = 0.2$ (CH_2Cl_2/MeOH 10:1); m.p. 54–55°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.85$ (t, $J = 6.9$ Hz, 3H, (CH$_2$)$_{11}$CH_3), 1.15–1.35 (m, 18H, (CH_2)$_9$CH$_3$), 1.30 (d, $J = 6.9$ Hz, 3H, CHCH_3), 1.48 (t, $J = 6.6$ Hz, 2H, CH_2(CH$_2$)$_9$CH$_3$), 1.95 (brs, 2H, NH_2), 3.20 (q, $J = 6.6$ Hz, 2H, NHCH_2(CH$_2$)$_{10}$CH$_3$), 3.44 (m, 1H, CHCH$_3$), 7.29 ppm (brs, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.1$ ((CH$_2$)$_{11}$CH$_3$), 21.7 (CHCH$_3$), 22.6, 26.9, 29.3, 29.5, 29.5, 29.6, 31.9 (10 CH$_2$), 39.1 (NHCH$_2$(CH$_2$)$_{10}$CH$_3$), 50.7 (CHCH$_3$), 175.7 ppm (amide C=O); HRMS (EI): calcd for $C_{15}H_{32}N_2O$: 256.2509; found: 256.2507 $[M]^+$.

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