Novel Approaches Towards Sequence-Defined Macromolecules using Isocyanide-Based Multicomponent Reactions

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"We absolutely must leave room for doubt or there is no progress and there is no learning. There is no learning without having to pose a question. And a question requires doubt."
Richard P. Feynman

Die vorliegende Arbeit wurde von Juni 2013 bis Juni 2016 unter Anleitung von Prof. Dr. Michael A. R. Meier am Institut für Organische Chemie (IOC) des Karlsruher Instituts für Technologie (KIT) angefertigt.

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Abstract

The synthesis of sequence-defined macromolecules is inspired by highly-defined biomacromolecules like DNA and peptides. The high degree of definition allows complex processes like DNA replication or enzyme-catalyzed reactions to proceed, which explains the fascination behind sequence-defined macromolecules. However, the synthesis of defined structures was restricted to control over polymer architectures and molecular weights for a long time. The synthesis of defined monomer sequences, in contrast, was limited to chemical DNA- and peptide synthesis. In this thesis, the investigation of three novel approaches towards the synthesis of sequence-defined macromolecules are described. Therefore, isocyanide-based multicomponent reactions were employed due to their versatility. Furthermore, they provide the possibility to simply introduce tailored side chains to the sequence-defined materials. First, a protecting group-free approach was investigated, making use of the Passerini and the Ugi reaction. Hereby, sequence-defined tetramers and pentamers were synthesized in good overall yields and high purity. Interestingly, each P-3CR allowed the introduction of a tailored side chain, whereas the U-4CR allows the introduction of two tailored side chains per monomer unit. Moreover, the synthesis protocol was transferred to a polymeric support, benefitting from an easier purification of the products by simple precipitation. Secondly, a benzylester-protected isocyanide monomer was prepared and employed in the synthesis of a sequence-defined decamer by the iteration of the Passerini reaction and a subsequent deprotection step. Here, the yield of each step was above 90 % and a quantity of more than two grams of the decamer was obtained. Additionally, in each Passerini reaction, a tailored side chain was incorporated. The introduction of a double bond in the tenth repeating unit, enabled the sequence-defined decamer to be dimerized by a self-metathesis reaction, resulting in a sequence-defined icosamer with 20 tailored side chains. Finally, a convergent synthesis approach towards sequence-defined macromolecules was investigated by combination of multicomponent reactions and thiolactone chemistry. Therefore, a set of sequence-defined trimers with a terminal double bond and a thiolactone-moiety were prepared and subsequently ring-opened by aminolysis. Thereby, a thiol-functionality is liberated, which was reacted in the same pot with an isocyanide-containing acrylate in a Thia-Michael addition. In this way tetrameric

isocyanide building blocks with terminal double bonds were obtained. The isocyanide building block was subsequently coupled to a carboxylic acid trimer in a Passerini reaction resulting in a sequence-defined octamer. Attractively, the sequence-defined octamer bears a terminal double bond, which can subsequently be functionalized in a Thiol-Ene addition. The use of 3-mercaptopropionic acid as thiol-compound, allows the subsequent coupling with another isocyanide building block in a Passerini reaction and thus, the iteration of the cycle and the synthesis of larger macromolecules. All in all, different approaches towards sequence-defined macromolecules by the use of isocyanide-based multicomponent reactions were investigated and macromolecules of up to 20 monomer units were synthesized. Moreover, all obtained products were thoroughly characterized by NMR, GPC, mass spectrometry and infrared spectroscopy.

Zusammenfassung

Die Synthese sequenzdefinierter Makromoleküle ist von hochdefinierten, in der Natur vorkommenden Polymeren wie DNA oder Peptide inspiriert. Die perfekt definierte Primärstruktur dieser Makromoleküle erlaubt hochkomplexe und raffinierte Prozesse wie die Replikation von DNA oder enzymkatalysierte Reaktionen, was die Faszination für sequenzdefinierte synthetische Polymere hervorruft. Jedoch beschränkte sich die Synthese von definierten Polymeren lange Zeit darauf, Polymerarchitekturen gezielt aufzubauen und dabei das Molekulargewicht der Polymere genau einzustellen. Die Synthese definierter Monomerabfolgen in Makromolekülen hingegen, war lange Zeit auf die chemische Synthese von Biopolymeren wie DNA und Peptide beschränkt. In der vorliegenden Arbeit wurden drei unterschiedliche Ansätze zur Synthese sequenzdefinierter, synthetischer Makromoleküle untersucht und dabei zwei unterschiedliche, isocyanid-basierte Multikomponentenreaktionen verwendet. Multikomponentenreaktionen bieten vielerlei Vorteile: sie profitieren von der Vielseitigkeit der einsetzbaren Reaktanden, sie können im Gramm-Maßstab durchgeführt werden und sie erlauben zusätzlich das Einführen von maßgeschneiderten Seitenkennten in jeder Monomereinheit. Zuerst wurde ein Ansatz untersucht, der die Synthese von Makromolekülen mit definierter Sequenz in Abwesenheit von Schutzgruppen ermöglicht. Mithilfe der Passerini-Reaktion wurde ein sequenzdefiniertes Tetramer hergestellt und das Syntheseprotokoll wurde darüber hinaus an einem löslichen polymeren Träger untersucht. Durch die Polymer-gestützte Synthese konnte die Aufarbeitung der Produkte stark vereinfacht werden und es konnte ein Pentamer-Block synthetisiert werden. Unter Verwendung der Ugi-Reaktion wurden ein sequenzdefiniertes Tetramer und ein Pentamer synthetisiert. Die Ugi-Reaktion erlaubt hierbei das Einführen von zwei unterschiedlichen Seitenketten pro Monomereinheit in einer einzigen Multikomponentenreaktion. Außerdem wurde ein Monomer mit Isocyanid- und Benzylester-Funktionalität hergestellt und durch die abwechselnde Durchführung einer Passerini-Reaktion und einer Entschützungsreaktion ein sequenzdefiniertes Decamer mit zehn unterschiedlichen Seitenketten synthetisiert. Die Ausbeute betrug hierbei in jedem Schritt über 90 % und es wurden über zwei Gramm des sequenzdefinierten Decamers erhalten. Die Einführung einer olefinischen Doppelbindung in der Seitenkette

der zehnten Wiederholeinheit ermöglichte die anschließende Dimerisierung durch eine Selbstmetathese-Reaktion. Hierbei wurde ein sequenzdefiniertes Icosamer mit 20 maßgeschneiderten Seitenketten erhalten. Schließlich wurde die konvergente Synthese von sequenzdefinierten Makromolekülen unter Verwendung von Thiolactonen in Kombination mit Multikomponentenreaktionen untersucht. Hierfür wurde eine Reihe an sequenzdefinierten Trimeren mit einer terminalen Doppelbindung und einem Thiolacton synthetisiert. Durch Ring-Öffnung des Thiolactons wurde ein Thiol frei gesetzt, welches anschließend mit einem Isocyanid-funktionalisierten Acrylat in einer Thia-Michael Addition umgesetzt wurde. Die so erhaltenen Isocyanid-Tetramere können anschließend für den konvergenten Aufbau von Makromolekülen verwendet werden. Die Reaktion eines Carbonsäure-Trimers mit einem Isocyanid-Tetramer sowie einer Aldehyd-Komponente ergab ein sequenzdefiniertes Octamer mit terminaler Doppelbindung. Die terminale Doppelbindung erlaubt die Funktionalisierung mit, z.B. 3-Mercaptopropionsäure und dadurch die Wiederholung der Schritte und schließlich die Synthese größerer Makromoleküle. Zusammenfassend wurden unterschiedliche Ansätze zum Aufbau sequenzdefinierter Makromoleküle untersucht und Makromoleküle mit bis zu einer Kettenlänge von 20 synthetisiert. Darüber hinaus wurden alle erhaltenen Produkte sorgfältig mittels NMR, GPC, Massenspektrometrie und Infrarotspektroskopie charakterisiert.

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1 Introduction

Nature plays a role model in the field of sequence control, since it developed complex biosynthetic procedures in its evolutionary process that allow the synthesis of perfectly defined macromolecules.[1] Processes like the amplification of genetic material by the polymerase chain reaction display fascinatingly the high sophistication of the biological machinery. Moreover, the formation of three-dimensional structures, such as the DNA double helix by Watson-Crick base-pairing or the precise conformation of enzymes enabling the catalytic reaction of specific substrates, emphasize the importance of sequence definition in biopolymers.[2-3] A major breakthrough in the chemical synthesis of sequence-defined macromolecules was the development of the solid phase peptide synthesis in 1963.[4] The importance of the invention of the solid phase peptide synthesis was emphasized by the Nobel Prize, awarded in 1984.[4-5] On the other hand, sequence control in synthetic polymer chemistry was an unsolved problem for a long time, and sequence-control was even named the "holy grail" of polymer science.[6] Although synthetic polymer chemists developed powerful methods for the synthesis of defined macromolecular architectures along with the precise synthesis of polymers with narrow molecular weight distributions, especially by using controlled radical polymerization techniques, the synthesis of defined sequences remained an unsolved problem.[7-11] However, a large variety of novel approaches were developed in order to narrow the gap between the biosynthesis and the chemical synthesis of sequence-defined polymers.[12] One impressive synthetic example, resembling natural processes, is the enzyme-free translation of DNA into non-natural polymers, developed by Liu and coworkers in 2013.[13] Moreover, numerous other interesting approaches, which are for instance based on templates, step-growth and chain growth reactions are described.[12, 14-16] Recently, ever more research groups turn their attention to the synthesis of sequence-controlled and sequence-defined polymers. This is certainly correlated with the numerous envisioned applications for these novel materials. Sequence-defined polymers can be used to fine-tune material properties and to design smart materials.[17-18] Moreover, the design of highly sophisticated catalysts or even artificial enzymes seems possible. Alternatively, the use as molecular bar codes for product identification is discussed due to worldwide increased product piracy.[19] Interestingly, the application

in the field of data storage is most frequently discussed because the storage density could be drastically increased if information could be stored on a molecular level.[20] Furthermore, the chemical diversity allows the use of numerous different monomers, resulting in immense storage capacity.[19] However, only efficient read-out techniques allow the storage of data on molecules, and to date mostly tandem MS/MS techniques are employed therefore, which is nowadays only feasible for experts.[21] Another important issue when discussing applications of materials is scalability. Many approaches towards sequence-defined polymers lack the possibility of large scale synthesis of the materials, which is without a doubt necessary for certain applications. Therefore, efficient approaches allowing the synthesis of sequence-defined macromolecules on a larger scale and in high purity are of great importance. In this thesis, novel approaches towards sequence-defined macromolecules by the use of isocyanide-based multicomponent reactions are investigated. Multicomponent reactions have the inherent advantage of simple reaction protocols, high yields and high atom economy.[22] Moreover, a large chemical diversity can simply be reached by the variance of the employed components.[23-24] The reactions are scalable and most of the employed components are commercially available.[22] Owing to the simple reaction protocol, the scalability, the high yields and the easily obtainable structural diversity, multicomponent reactions are highly attractive for the efficient synthesis of sequence-defined macromolecules.

2 Theoretical Background and State of the Art

2.1 Multicomponent Reactions

Multicomponent reactions (MCRs) are reactions where three or more components react in one-pot to form complex products, into which most atoms of the reactants are incorporated.[25-26] Some of the key features of MCRs are the high atom-efficiency, the formation of many covalent bonds in one reaction and the convergent character of the reactions.[26] Due to the use of readily available starting materials, simple procedures, environmentally friendly components, high atom economy and high yields, MCRs can be regarded as "ideal reactions" in the concept of Wender *et al.*[27] The convergent character should however be considered as one of the main advantages of MCRs, because the synthesis of complex architectures in one-pot is rendered possible without time consuming purification steps of intermediates. Additionally, multicomponent reactions are used in combinatorial chemistry, because of the easy synthesis of substance libraries by simple variation of the different components in the MCR.[25] In general, MCRs can be differentiated depending on their basic reaction mechanism (Figure 1).[25]

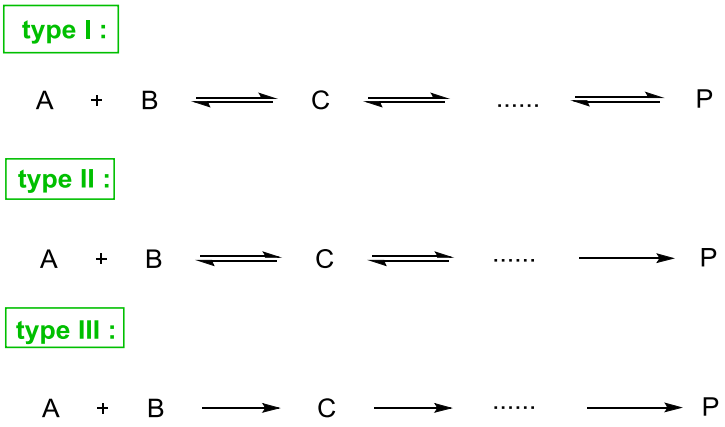


Figure 1: The three basic types of MCRs: type I describes reactions in which all steps are reversible, type II describes reactions with an irreversible last step and type III describes reactions in which each step is irreversible.[25]

In type I MCRs, all reactions steps are reversible leading to low yields, depending on the individual equilibrium constants. Type II MCRs have an irreversible last step, which is favorable in terms of the obtainable yields, since the overall equilibrium is shifted

towards product formation. The ideal case are type III MCRs, in which each individual step is irreversible. However, type III reactions are very rare in preparative chemistry, but some biochemical reactions in nature can be grouped into this category.[25] It has to be noted that this classification is not strict and that the transitions between the different types are fluent.

The Strecker three-component reaction (S-3CR), discovered in 1850, is said to be the first known multicomponent reaction and is an example for type I MCRs.[25, 28] In the S-3CR, an aldehyde is reacted with hydrogen cyanide and ammonia to form *α*-aminonitriles, which can subsequently be hydrolyzed in acidic media to obtain racemic mixtures of the corresponding amino acids (Figure 2).[28] Nowadays, also many asymmetric and asymmetric catalytic variants of the S-3CR are reported enabling the synthesis of enantiopure amino acids.[29-30] In 1882, Hantzsch reported on a four-component reaction (H-4CR) between two equivalents of a *β*-ketoester, ammonia and an aldehyde to obtain dihydropyrimidines, which can be converted to the corresponding pyridines by oxidation (Figure 2).[31] The discovery of this simple, one-step dihydropyrimidine synthesis route enabled the development of Nifedipin, a commercially available drug, which is employed in the treatment of angina and cardiovascular deceases.[25] In 1890, another historically important MCR, the Hantzsch pyrrole synthesis (H-3CR), was reported.[32] Therein, a *β*-ketoester reacts with ammonia and *α*-haloketones to the corresponding pyrrole-derivative (Figure 2).[32] Interestingly, pyrrole-derivatives show advantageous physiological and biological properties, such as antimalarial activity.[33-34] In 1891, Biginelli reported on the synthesis of 3,4-dihydro-2(H)-pyrimidinone-compounds, which are the aza-analogues of Hanztsch's dihydropyridines.[35] In the Biginelli reaction (B-3CR), an aldehyde component is condensed with urea and the formed imine reacts subsequently with a *β*-ketoester. After intramolecular condensation with the second urea-amine function, the dihydropyrimidinones are obtained (Figure 2).[35] The products of Biginelli reactions are pharmacologically interesting, for instance as calcium channel blockers or as antitumor-agents.[36-37] Another historically important MCR is the Mannich three-component reaction (M-3CR) of formaldehyde, amines and an oxo-component (aldehydes or ketones) (Figure 2).[38]

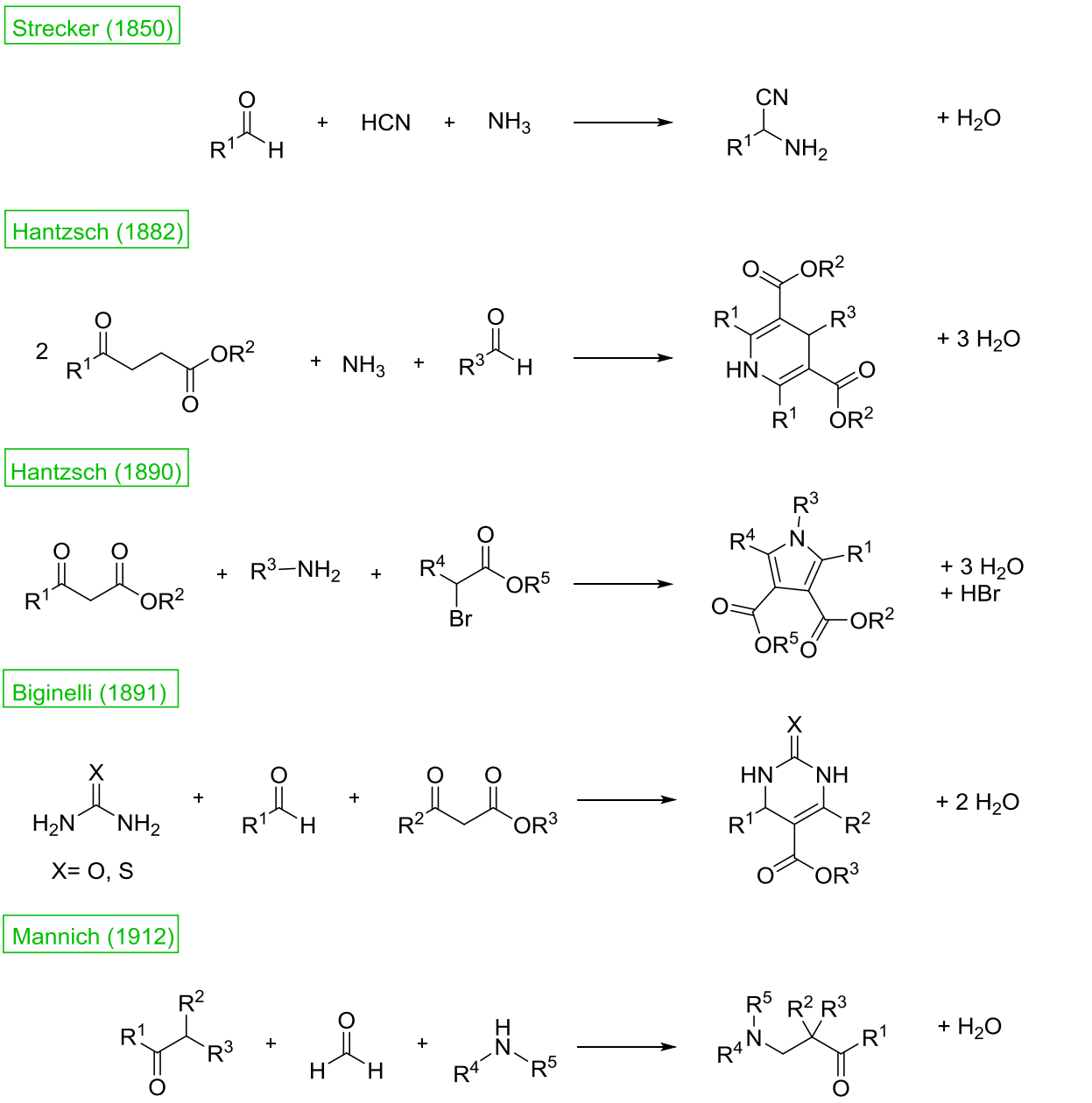


Figure 2: Some historically important MCRs in chronologic order. [25, 28, 31-32, 35, 38]

Here, formaldehyde and the amine are condensed to the corresponding iminium-ion, which is subsequently attacked by the oxo-component (enol) and the *β*-aminocarbonyl is formed.[38] In general, the Mannich reaction can be considered as an aminoalkylation of ketones or aldehydes and is often used in alkaloid syntheses, for instance for the synthesis of tropinone.[39]

In 1952, Kabachnik[1] and Fields reported independently on a novel multicomponent reaction of aldehydes or ketones, amines and dialkylphosphates.[40] The Kabachnik-Fields reaction is also based on the formation of the imine, which then reacts with alkylphosphates to form aminophosphonates (Figure 3).[40]

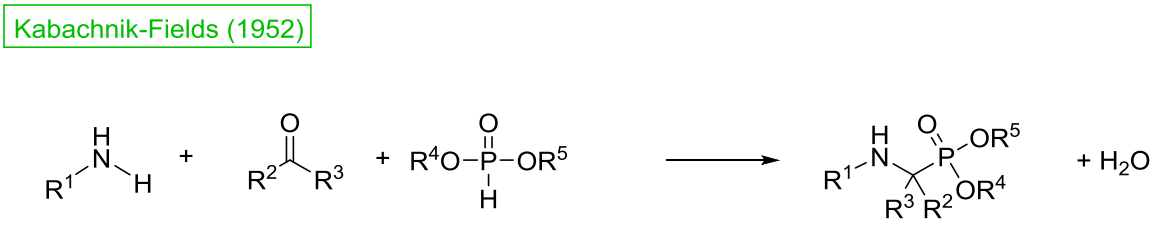


Figure 3: The Kabachnik-Fields reaction of amines, aldehydes or ketones and dialkylphosphates yielding aminophosphonates.[40]

The so far discussed MCRs are non-isocyanide-based MCRs, however, there are two more important subclasses of MCRs: metal-catalyzed MCRs and the isocyanide-based MCRs (IMCRs).[41] Before discussing in detail the IMCRs in the following chapter, some metal-catalyzed MCRs are introduced.

In synthetic organic chemistry, the Pauson-Khand reaction is a valuable tool to synthesize substituted cyclopentenones, which are useful precursors in the synthesis of prostaglandins.[42-43] The Pauson-Khand reaction is a [2+2+1]-cycloaddition of an alkyne with an alkene and carbon monoxide, which is catalyzed by transition metal complexes, mostly dicobalt octacarbonyl.[44] Back in 1977, the transition metal complex was required in stoichiometric amounts. However, the high synthetic potential of the reaction motivated many groups to develop catalytic variants.[42] Nowadays, there are many catalytic as well as enantioselective variants reported.[42, 45] The works of Reppe and Roelen describe the hydrocarboxylation of alkynes and the hydroformylation of alkenes, respectively. Both of them are nowadays industrially important processes.[46-47] A more modern metal catalyzed MCR is the three-component reaction between alkynes, amines and aldehydes (A^3-coupling) to synthesize propargyl amines.[41, 48-49] The three-component reaction was reported by Li *et al.* in 2004 and is catalyzed by copper, iridium or gold-complexes. Recently, also the use of rhodium was investigated.[48-49] The Cu(I)-

[1] The publication of Kabachnik is written in Cyrillic, therefore no citation can be given. Since the reaction is named after both authors, Kabachnik is mentioned here as well.

catalyzed three-component reaction between nucleophiles, alkynes and sulfonyl azides (CuMCR) to yield amidines was reported in 2005 by Chang *et al*.[41, 50] Another five-component reaction was lately reported by Orru *et al.* describing the synthesis of pyrido-pyrimidones, which are biologically and pharmacologically interesting compounds.[51] These recent examples show that the field of MCRs, though its history started already in 1850, is a developing and modern research area and that the potential of MCRs is still not fully exploited.

2.1.1 Isocyanide-based Multicomponent Reactions

The class of isocyanide-based MCRs is a very important subclass in the field of multicomponent reactions, due to the interesting reactivity of isocyanides. The intrinsic reactivity of isocyanides, their synthesis and properties will be discussed in the next chapter, before the Passerini three-component reaction (P-3CR) and the Ugi four-component reaction (U-4CR), which are the most popular examples, will be introduced.

2.1.1.1 Isocyanides (Isonitriles)

Isocyanides, also named isonitriles, are characterized by the reactivity of the formally divalent carbon atom. Besides isocyanides, only carbon monoxide and carbenes exhibit stable divalent carbon atoms.[25] Figure 4 shows two resonance structures of isocyanides, explaining their extraordinary reactivity. Beside the carbene-like reactivity, the negatively charged carbon in the zwitterionic resonance structure is able to react as nucleophile and upon the nucleophilic attack, it becomes an electrophile, enabling a nucleophilic attack at the same carbon atom. This process is referred to as *α*-addition.

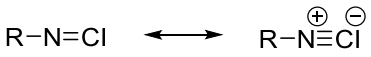


Figure 4: The two resonance structures of isocyanides, including the carbene- and the zwitterionic-structure.

The chemistry of isocyanides is further based on the *α*-acidity and the easy formation of radicals.[25] The *α*-acidity can be explained by the positively charged nitrogen atom in the zwitterionic resonance structure and it can be increased by electron withdrawing substituents in *α*-position.[25] Due to this remarkable reactivity, isocyanides are valuable

reagents in heterocycle synthesis, for instance the synthesis of oxazoles or imidazoles.[52-54] Furthermore, isocyanides are applied in steroid-synthesis, such as the one of Progesterone.[55] Additionally, isocyanides can be polymerized easily by initiation with Brønstedt or Lewis acids, or by decomposition of metallo-isocyanide-complexes.[56-57] Isocyanides are very stable in basic media, but tend to hydrolyze in acidic media. Moreover, volatile isocyanides have an unpleasant odor, which is decreasing with increasing molecular weight.[25, 58]

Naturally occurring isocyanides are grouped into terrestrial isocyanides, which are amino acid-derived and the larger group of marine isocyanides, which are terpene-based.[59-60] Many of the isolated natural isocyanides show antibiotic and/or fungicidal effects.[60]

In 1859, Lieke accidentally synthesized allyl isocyanide for the first time by reacting allyl iodide with silver cyanide.[58] Lieke intended to synthesize allyl cyanide, however, in 1868 Gautier proved that the isocyanide was synthesized.[61] Hydrolysis of the product resulted in the corresponding formamide; in the case of a nitrile, the corresponding carboxylic acid would have been obtained.[61] In 1867, Hofmann discovered the formation of isocyanides by reacting primary amines in the presence of chloroform and potassium hydroxide.[62-63] Almost 100 years later, Ugi reported on a novel isocyanide synthesis by dehydration of *N*-formamides using phosgene in the presence of bases, which is since then the method of choice in isocyanide-synthesis.[64] This novel synthesis method for isocyanides contributed strongly to the fast development in the field of IMCRs. Though phosgene is still used as dehydration agent in industrial procedures for economic reasons, it is replaced in synthetic laboratories by other reagents, such as triphosgene, diphosgene and phosphorous (V) oxychloride, due to the high toxicity of phosgene.[65-67] Lately, Dömling *et al.* discovered the Leuckart-Wallach reaction as valuable tool for the synthesis of *N*-formamides, starting from oxo-components, and thus, the amount of chemically accessible isocyanides is further enlarged.[68] Figure 5 shows the isocyanide synthesis approaches proposed by Lieke, Hofmann, Ugi and Dömling.

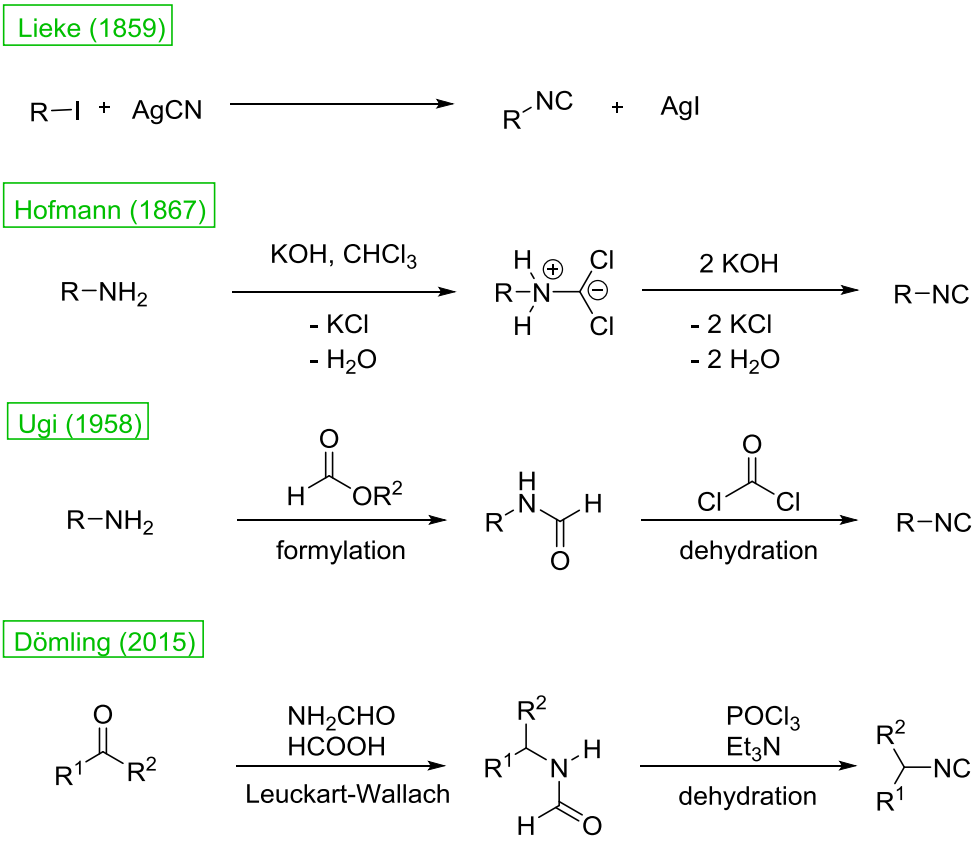


Figure 5: The isocyanide syntheses of Lieke, Hofmann, Ugi and Dömling. The synthesis route proposed by Ugi via N-formamides is nowadays the method of choice.[58, 62, 64, 68]

In order to avoid the unpleasant odor of isocyanides, Dömling *et al.* recently introduced a method for the *in-situ* synthesis of isocyanides from *N*-formamides using triphosgene as *in-situ*-dehydrating agent and applied the method for various IMCRs.[69]

2.1.1.2 The Passerini Three-Component Reaction (P-3CR)

The Passerini three-component reaction (P-3CR), reported in 1921, is the first known IMCR and describes the reaction of oxo-components (aldehydes or ketones) with isocyanides and carboxylic acids to yield *α*-acyloxy carboxamides (Figure 6).[70] The P-3CR is usually conducted at room temperature in aprotic solvents, like dichloromethane (DCM) and in high concentrations of the reactants.[71]

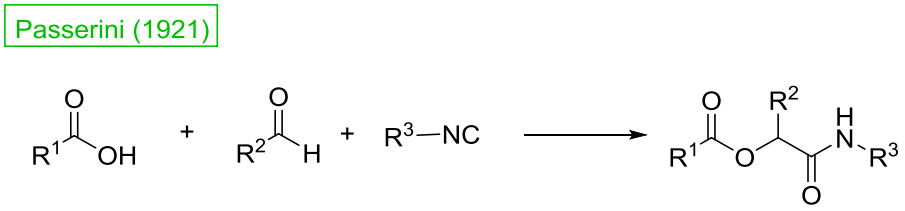


Figure 6: The Passerini three-component reaction of a carboxylic acid, an oxo-component (here an aldehyde) and an isocyanide yielding α-acyloxy carboxamides.[70]

Although the reaction is known since almost 100 years, the mechanism is still not fully understood. One plausible mechanism of the P-3CR is shown in Figure 7.

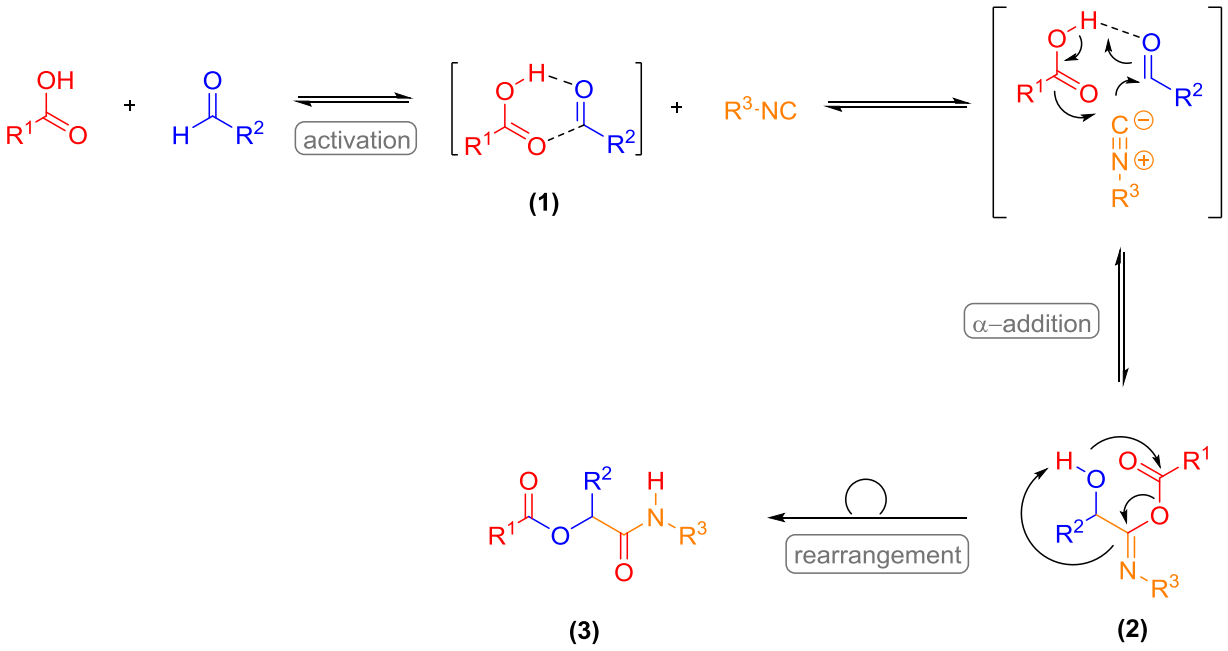


*Figure 7: Mechanism of the P-3CR: activation of the oxo-component by hydrogen-bonding (**1**), α-addition of the isocyanide yielding intermediate (**2**), which subsequently rearranges to the α-acyloxy carboxamide (**3**).*[72-73]

First, the oxo-component is activated for the *α*-addition of the isocyanide by hydrogen bonding with the carboxylic acid. In the *α*-addition of the isocyanide, the carbon atom of the isocyanide adds as a nucleophile to the activated aldehyde component, while the carboxylic acids adds to the same, now electrophilic, carbon atom. Intermediate (**2**), being the aza-analogue of an anhydride, undergoes an intramolecular transacylation and the product of the Passerini reaction (**3**) is obtained. Since the rearrangement is an ultimate, irreversible step, the P-3CR can be classified as type II MCR (compare Figure 1). This mechanism is commonly accepted and was confirmed by kinetic investigations

of Baker and Ugi in 1959 and 1961, respectively.[72, 74] As already mentioned, the mechanism of the P-3CR is still in doubt. In 1965, Eholzer *et al.* proposed another mechanism, where the isocyanide is protonated by the carboxylic acid in a first step.[75] This mechanism was postulated due to their observation that the P-3CR is accelerated under mineral acid catalysis.[75] This observation is in agreement with a recent publication of Pirrung *et al.* reporting on accelerated Passerini reactions in water,[76] but is not conform with the observation of Ugi that the reaction is accelerated in unpolar, aprotic solvents.[77] In 2011, another mechanism was postulated which is based on quantum mechanical calculations in the gas phase.[78] In this postulated mechanism, the P-3CR is rather a four-component reaction involving two carboxylic acid molecules. However, the additional carboxylic acid molecule acts as a catalyst, so the P-3CR can be described as organo-catalyzed three-component reaction. Figure 8 shows the proposed mechanism of Maeda *et al.* involving a second carboxylic acid molecule. In the presented mechanism, the activation steps and the *α*-addition are as postulated previously, but the rearrangement is postulated to be acid catalyzed due to a significantly lower energy for the transition state (TS) involving another carboxylic acid molecule (**4**). The resulting cyclic intermediate undergoes subsequently a carboxylic acid catalyzed rearrangement *via* another four-component TS (**5**), to yield the product of the P-3CR (**3**).[78] Later on, DFT calculations confirmed the carboxylic acid catalyzed mechanism, which was postulated by Meada *et al*.[79]

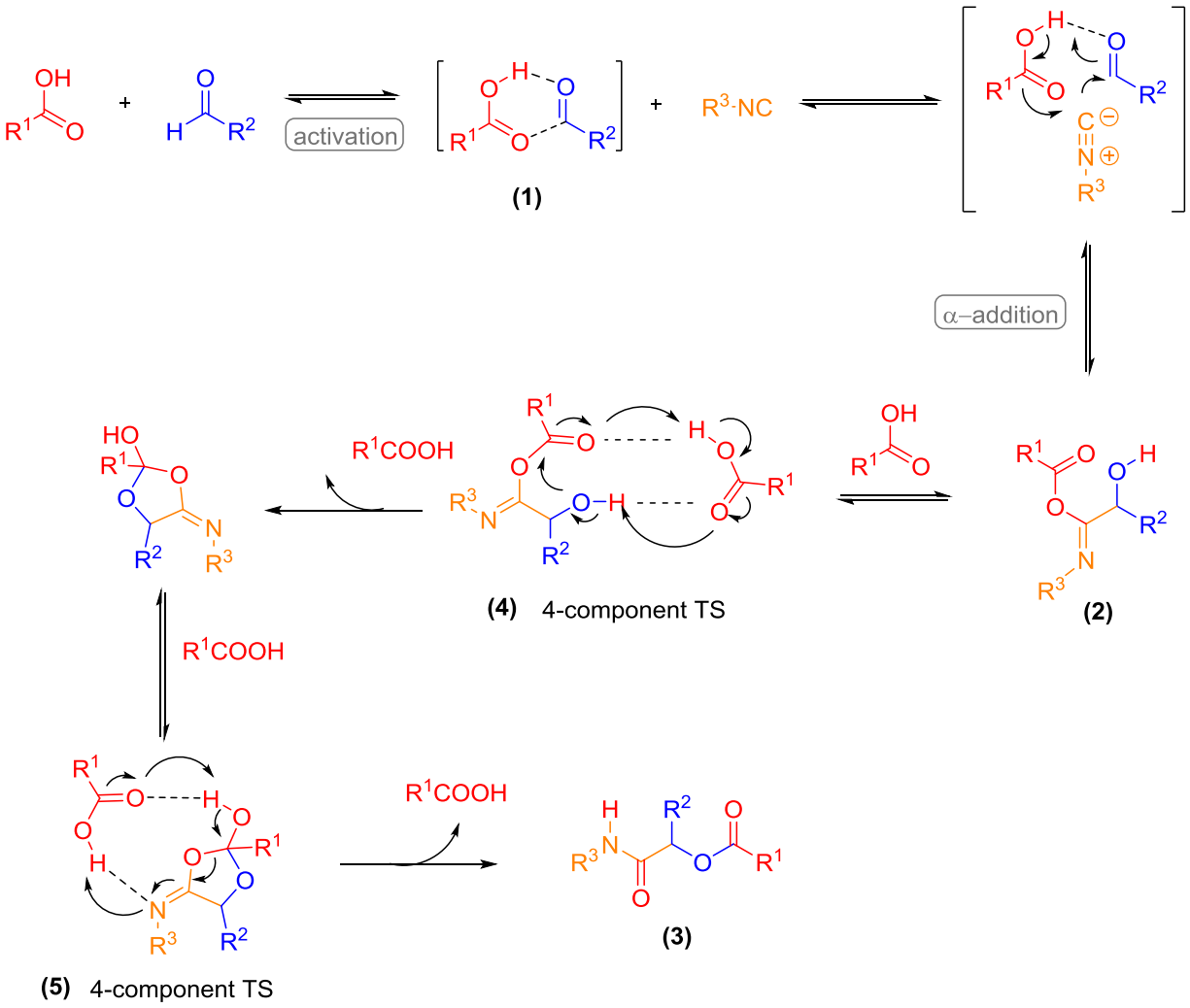


Figure 8: Proposed mechanism for the P-3CR involving two molecules of the carboxylic acid. This mechanism was postulated based on quantum mechanical calculations in the gas phase.[78]

Though the mechanism of the P-3CR is still in doubt, there is no doubt about the potential of the P-3CR in preparative chemistry. The P-3CR allows, for instance, the synthesis of pharmacologically interesting depsipeptides and is often applied in medicinal chemistry for the development of pharmaceuticals.[26, 80] Additionally, many variants of the P-3CR were reported, including the use of hydrazoic acid leading to substituted tetrazoles or the use of electron-poor phenols in Passerini-Smiles couplings yielding *α*-hydroxyamides.[25, 81] Furthermore, the P-3CR was employed in the synthesis of butenolides. Therefore, the P-3CR was followed by a subsequent Wittig-type reaction.[82] Another very interesting variation is the use of alcohols and their *in-situ* oxidation to aldehydes using 2-iodoxybenzoic acid (IBX) as oxidizing agent.[83] The use

of alcohols in the P-3CR is an interesting alternative in case of limited commercial availability or difficult synthesis and isolation of the required aldehydes. Furthermore, it addresses the problem of the limited shelf-life of aldehydes, which is no issue with the corresponding alcohols. A drawback is the use of IBX in a twofold excess, reducing the atom economy of the P-3CR drastically. Furthermore, IBX needs to be synthesized from 2-iodobenzoic acid and has itself a limited shelf-life.

In the P-3CR, a new stereocenter is formed, which cannot be influenced in conventional P-3CRs; thus, the products are obtained as racemic or diastereomeric mixtures. The stereoselctivity in the P-3CR can be influenced by the use of chiral isocyanides,[84] chiral carboxylic acids,[85] chiral aldehydes[86] or by the use of chiral additives (*e.g.* titanium isopropoxide and TADDOL).[87] These approaches towards stereocontrolled Passerini reactions are summarized in Figure 9. Another approach uses a chiral Lewis acid as additive, namely a tridentate *bis*-(oxazolinyl)pyridine (pybox)-Cu(II) complex, achieving high yields and impressive *ee* values of up to 98 %.[88]

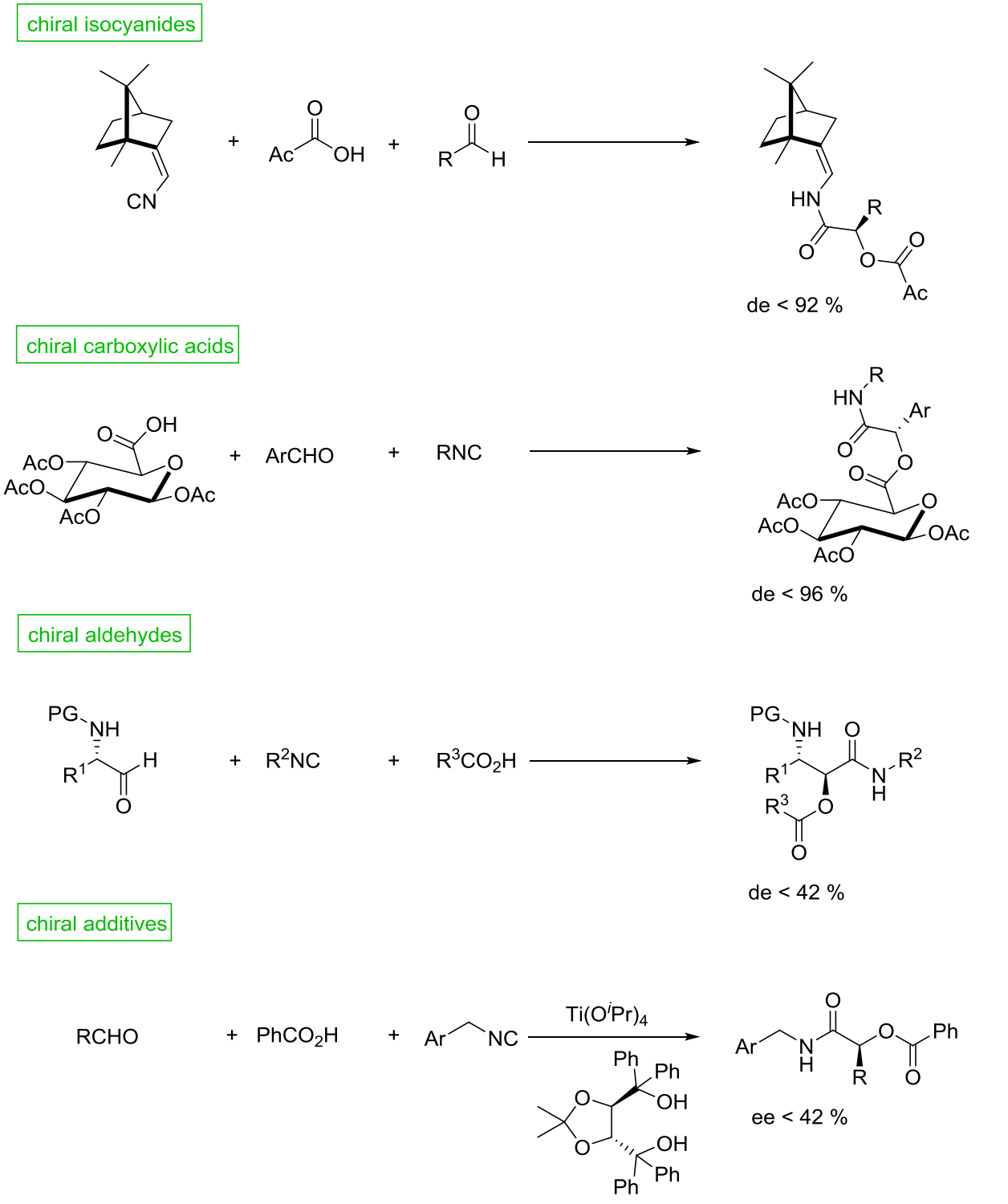


Figure 9: Some examples for stereoselective P-3CRs controlled by the isocyanide, the carboxylic acid, chiral aldehydes or chiral additives.[84-87]

2.1.1.3 The Ugi Four-Component Reaction (U-4CR)

The Ugi four-component reaction (U-4CR) was discovered by Ivar Ugi in 1959 and uses, in comparison to the P-3CR, as additional fourth component an amine.[89-90] The reaction of a carboxylic acid with an oxo-component (aldehydes or ketones), an isocyanide and an amine yields *α*-aminoacylamides, while water is released (Figure 10). Due to the use of an amine as fourth component, the number of accessible products is drastically increased and therefore, the U-4CR is an even more interesting reaction for combinatorial chemistry, compared to the P-3CR. Due to the formation of two amide bonds during the U-4CR, the products are characterized by a higher chemical stability, compared to the products of the P-3CR, which are sensitive to hydrolysis due to the ester bond.

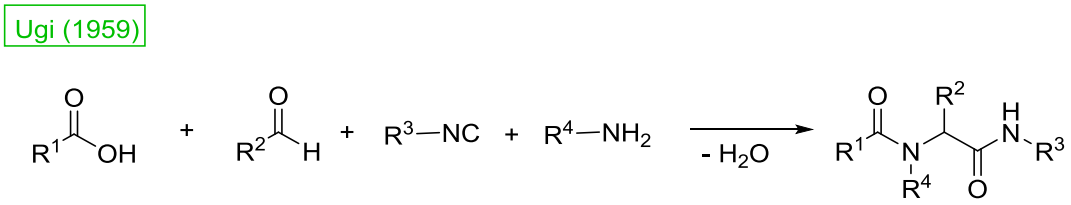


Figure 10: The Ugi four-component reaction of a carboxylic acid with an aldehyde, an isocyanide and an amine yielding α-aminoacylamides.[89-90]

In the U-4CR, the amine and the aldehyde component are usually precondensed to the corresponding imine, and subsequently the carboxylic acid and the isocyanide are added.[91] The preformation of the imine usually has positive effects on the obtainable yields.[25] The reactions are conducted at high concentrations (0.5 - 2.0 molar) in order to obtain high yields and the commonly used solvent is methanol (compare Chapter 4.1.2).[25, 91] However, also the use of other alcohols like ethanol and trifluoroethanol or polar aprotic solvents like dimethyl formamide (DMF), tetrahydrofuran (THF) or dichloromethane (DCM) were investigated.[25, 91] The use of methanol as protic, polar solvent and the acceleration of the reaction by Lewis acids led to the assumption of an ionic mechanism. The commonly accepted mechanism of the U-4CR starts with the imine-condensation of the oxo-component and the amine (Figure 11). The imine is subsequently protonated by the carboxylic acid to increase the electrophilicity and to facilitate the *α*-addition of the isocyanide. Other ways of imine-activation include the use

of Lewis acids, such as $TiCl_4$ or BF_3*OEt_2.[25] The resulting aza-analogue of an anhydride, the imidate, is then rearranged in an irreversible Mumm rearrangement to form the Ugi-product. The Mumm rearrangement describes the rearrangement of hydroxylimines to amides and is known since 1910.[92] Due to the irreversibility of the Mumm rearrangement, the U-4CR can be classified as type II-MCR (compare Figure 1).

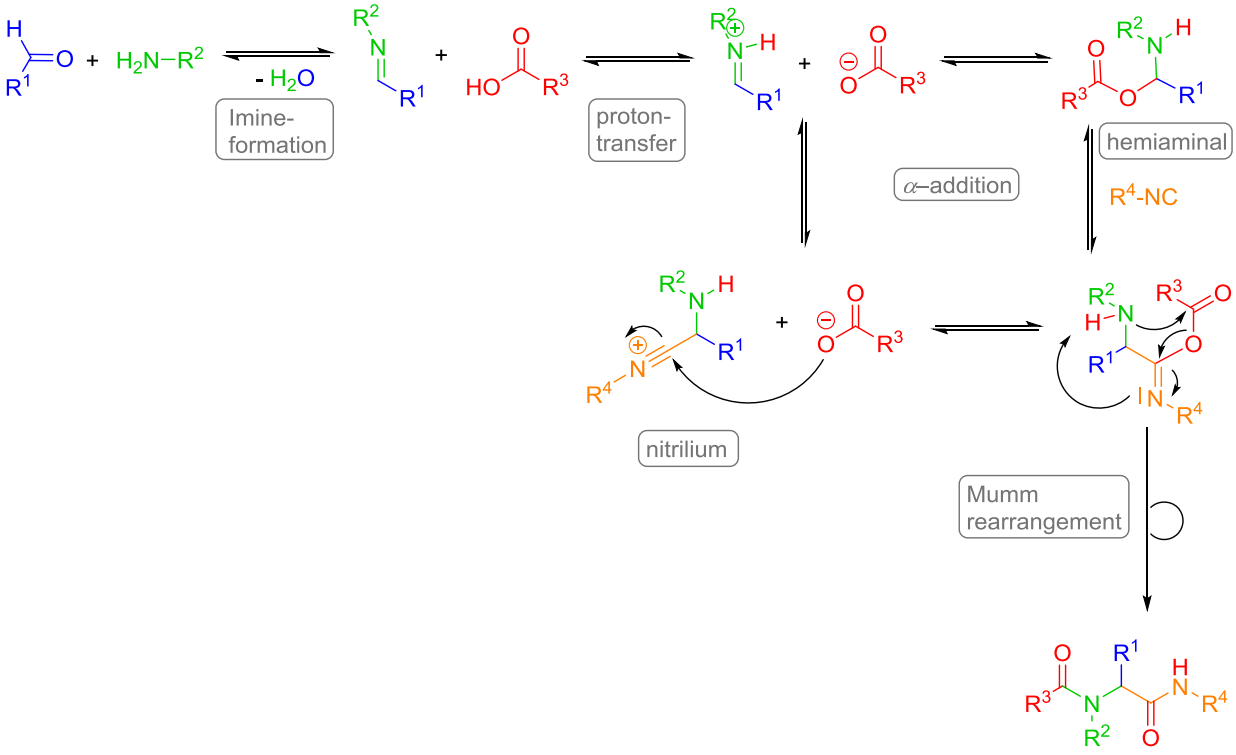


Figure 11: The commonly accepted mechanism of the U-4CR; the formed imine is protonated, the α-addition takes place via the hemiaminal or the nitrilium intermediate, followed by the irreversible Mumm rearrangement.[25, 84, 93]

The *α*-addition can have two possible pathways: On the one hand, the carboxylic acid reacts with the protonated imine to the hemiaminal, followed by the isocyanide-insertion and, on the other hand, the protonated imine reacts with the isocyanide to the nitrilium, followed by the addition of the carboxylic acid (Figure 11). In 2012, Fleurat-Lessard *et al.* studied both pathways for the formation of the imidate, based on DFT calculations.[94] It was revealed that the imine is protonated in protic solvents like methanol but the mechanism was found to be non-ionic in aprotic solvents like toluene.[94] The Mumm rearrangement was also part of the calculations, revealing that in toluene, another carboxylic acid molecule might catalyze the rearrangement, confirming the calculations

of Maeda *et al.* for the P-3CR.[78, 94] Though, if the reaction is conducted in methanol, methanol catalyzes the Mumm rearrangement. Furthermore, the Mumm rearrangement and the imidate-formation were determined as highly exothermic reaction steps and thus they display the driving-force of the reaction. Therefore, it is suggested that the formation of the imidate is no longer considered as equilibrium reaction.[94] Additionally, the hemiaminal pathway was only found using toluene as solvent. These calculations were further confirmed by *in-situ* ESI-MS(/MS) investigations of Ugi reactions in methanol.[95-96]

Interestingly, the mechanism was partially confirmed experimentally by Faggi *et al.* who were able to isolate the imidate-intermediate.[97] These mechanistic studies are in very good agreement with experimental observations: the reaction is conducted at room temperature, which is thermodynamically favorable due to the highly exothermic steps. Besides, methanol is confirmed as the solvent of choice, which can be explained by the fact that methanol is able to catalyze the Mumm rearrangement.[91, 94]

In the U-4CR, the carboxylic acid component can be substituted by plenty of other components, for instance the use of hydrazoic acid in combination with isocyanides, oxo-components and amines leads to the formation of 1,5-substituted tetrazoles.[93] Besides, cyanates, thiocyanates, water, or hydrogensulfide are valuable substitutes for carboxylic acids in the U-4CR leading to a variety of scaffolds.[90, 98] As amine-component, primary and secondary amines, hydrazine-derivatives as well as hydroxylamines can be used.[90] By the use of methanol and CO_2 instead of the carboxylic acid, carbamates can be synthesized in impressive yields of up to 97 %. The first report on this Ugi five-component reaction (U-5CR) was published in 1961 by Ugi *et al.*[99] This concept was later on extended to other alcohols, though the yields were only moderate.[100] Additionally, carbon disulfide and carbonyl sulfide (COS) were investigated in the U-5CR, leading to *α*-aminothioamides and carbamate-thioamides, respectively.[100] Another interesting variant of the U-4CR is the so called Ugi-Smiles reaction, employing electron deficient phenols as carboxylic acid substitutes.[101] The Ugi-Smiles reaction is conducted in methanol at elevated temperatures (40 - 60 ° C) and the use of *o*-nitrophenols results in highest yields.[101] Furthermore, the last step of the reaction consists of a Smiles-rearrangement instead of a Mumm-rearrangement. The

Smiles rearrangement was discovered in 1931 as rearrangement of hydroxy sulphones to the corresponding sulphinic acids.[102] Later on, the Smiles variant of the U-4CR was also investigated using quinoline and pyridine derivatives.[103] The U-5CR and the Ugi-Smiles reaction are shown in Figure 12.

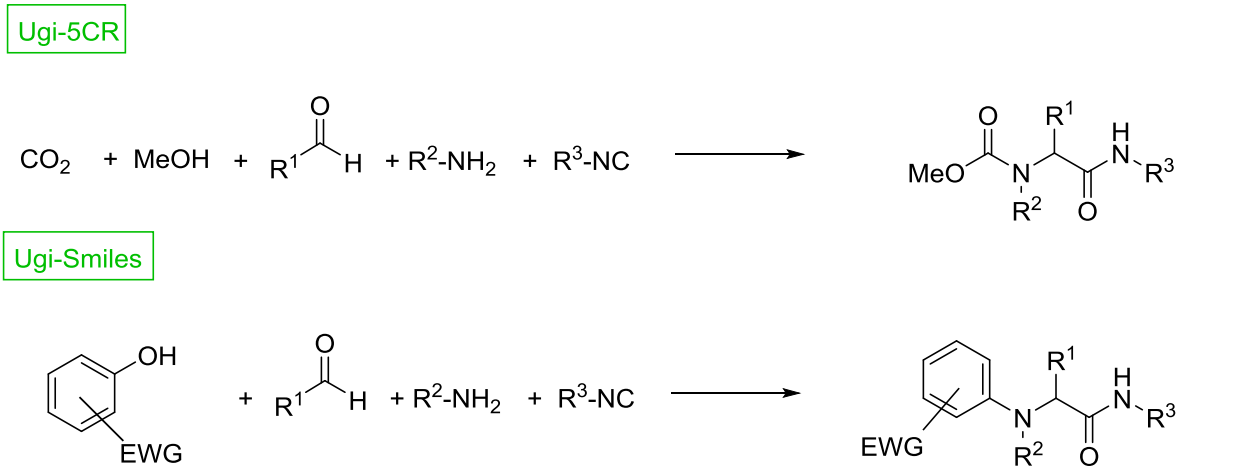


Figure 12: The Ugi-5CR using methanol and carbon dioxide as carboxylic acid surrogates and the Ugi-Smiles reaction using electron deficient phenols as substitute for the carboxylic acid.[99, 101]

The control over the stereochemistry in U-4CRs is more difficult to achieve than in the P-3CR and thus still displays a difficult challenge. For instance, if chiral isocyanides are employed, good stereocontrol can be achieved in the P-3CR, whereas there is no stereocontrol in the U-4CR.[84] Ugi and co-workers found out that the stereochemistry is controlled, unlike in the P-3CR, during the addition of the carboxylate to the iminium ion.[84] Therefore mainly the amine component is responsible for stereochemical induction in the U-4CR. In 1975, Urban and Ugi reported on the synthesis of peptide fragments in a stereochemically controlled way. Here, the control over the stereoselctivity was achieved by the use of optically active ferrocenylalkyl amines as chiral auxiliaries.[104] A downside of this approach was the lack of reisolation procedures for the chiral auxiliary, since they were destroyed during their cleavage. Later on, an improved method was reported allowing the reisolation of the chiral auxiliary by a mild hydrolysis procedure, thereby enabling high yields of the desired peptide fragments.[105] Furthermore, the use of a chiral galactopyranosyl amine as chiral auxiliary was investigated, indicating good control over the stereochemistry of the reaction yielding

high diastereomeric excesses.[106] Interestingly, the chiral auxiliary can be cleaved by hydrolysis after the Ugi reaction, thereby the (R)-*α*-amino acids can be obtained in high purity. Furthermore, the previously cleaved chiral auxiliary can be reisolated in high yields.[106] The same group also reported on a stereoselective Ugi reaction on a solid support, allowing the reisolation of the chiral auxiliary as well.[107] Additionally, many other chiral glycosylamines have been reported for stereoselctive U-4CRs.[26] Due to the induction of stereochemistry during the reaction of the iminium ion with the carboxylic acid, the use of chiral isocyanides, carboxylic acids or oxo-components does not have a significant effect on the stereochemical course of the U-4CR.[26, 84]

2.1.2 Multicomponent Reactions in Polymer Chemistry

In this section, some selected examples of MCRs in polymer chemistry will be introduced with a major focus on the P-3CR and the U-4CR, since they were investigated by several groups in great detail.

The use of multicomponent reactions was limited to the field of organic, medicinal and combinatorial chemistry for a long time. However, the synthetic advantages of MCRs, such as the easy synthesis protocol, the high atom economy, the high chemical diversity and the use of commercially available starting materials also caused growing interest amongst polymer chemists. Furthermore, the increasing demand on smart materials with special material properties made MCRs interesting candidates for polymer science, due to the easy tuning of material properties by the use of different components in the MCR. However, the chosen reaction has to be highly efficient, since side reactions would lead to low molecular weights or unequal structures in the resulting polymers. The simplest and most obvious way of transferring an organic reaction into polymer chemistry is the synthesis of monomers, with polymerizable end groups by the respective reaction and the subsequent polymerization of the obtained monomers. Alternatively, the reactions can be used as polymerization methods themselves and a third way would be the use of the MCR as post-polymerization modification method.

In 2010, Gianneschi, Yang and co-workers reported on the synthesis of monomers *via* the P-3CR for the first time. They used a convertible isocyanide in the P-3CR, allowing the cleavage of the convertible group and thereby the synthesis of *α*-hydroxy carboxylic

acid-monomers, which were subsequently incorporated into poly(*α*-hydroxy acid)-copolymers.[108] Meier *et al.* reported on the synthesis of monomers for acyclic diene metathesis polymerization (ADMET) *via* the P-3CR and the U-4CR and their subsequent polymerizations obtaining polyesters with amide side chains (P-3CR) and polyamides with amide side chains (U-4CR), respectively (Figure 13a) and b)).[109-110] The monomers derived from the U-4CR were additionally co-polymerized with butanedithiol in a Thiol-Ene addition polymerization (Figure 13c)).[110]

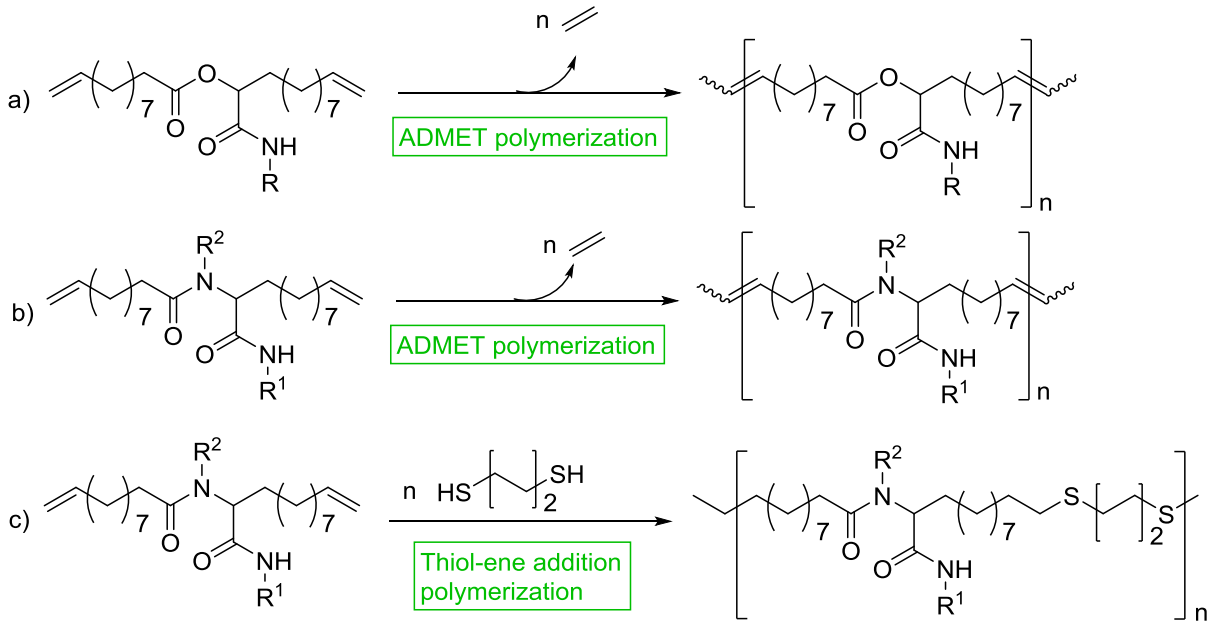


Figure 13: a): Synthesis of an ADMET-monomer via the P-3CR and the subsequent polymerization, obtaining polyesters with amide side chains. b): Synthesis of an ADMET-monomer via the U-4CR and the subsequent polymerization to obtain polyamides with amide side-chains. c): Thiol-Ene addition polymerization of an Ugi-derived monomer using butanedithiol as co-monomer.[109-110]

Furthermore, diverse asymmetric *α*-*ω*-dienes have been prepared by the P-3CR and polymerized in ADMET polymerizations achieving excellent head-to-tail selectivity.[111-112] Likewise, several acrylate and acrylamide monomers were prepared *via* the P-3CR and the U-4CR using acrylic acid in combination with various aldehydes, isocyanides and amines (only in the U-4CR).[113-114] The acrylate monomers were polymerized in a free radical polymerization and the obtained polymers showed interesting material properties, such as tunable glass transition temperatures T_g and thermoresponsive behavior (upper critical solution temperature, UCST).[113] Moreover, the acrylamide polymers showed

potential biocompatibility.[114] Additionally, Wright *et al.* synthesized substituted norbornenes *via* the U-4CR and polymerized them subsequently in a ring opening metathesis polymerization (ROMP).[115] Shen *et al.* synthesized monomers *via* the Biginelli three-component reaction and polymerized the resulting acrylates subsequently in a free radical polymerization obtaining polymers with dihydropyrimidinone-side chains.[116] Interestingly, the Hantzsch reaction was combined with reversible addition fragmentation chain transfer polymerization (RAFT) in a one-pot manner, synthesizing polymers with the pharmaceutically interesting 1,4-(poly)-dihidropyridine structural motif.[117] Here, the Hanztsch reaction and the RAFT-polymerization proceeded simultaneously in the same reaction vessel.[117] Besides the monomer-approaches, a more elegant way to introduce MCRs into polymer science is their use as polymerization method, which was achieved for instance for the P-3CR and the U-4CR.[109, 118] By the use of bifunctional monomers, polyaddition took place in case of the P-3CR and polycondensation in case of the U-4CR.[109, 118] It has to be noted that in the Ugi-polycondensation, polyamides are synthesized under very mild conditions at room temperature, which is in sharp contrast with the usually harsh conditions in polyamide synthesis.[119-120] The Passerini polyaddition was first described in 2011 using dicarboxylic acids and bifunctional aldehydes in combination with monofunctional isocyanides yielding poly(esters) with amide side-chains (Figure 14a)).[109] The same procedure has been reported for the synthesis of poly(ester-amides) using a dicarboxylic acid and a bifunctional isocyanide in combination with a monofunctional aldehyde component.[121] Moreover, the synthesis of poly(amides) with ester side-chains was achieved by the P-3CR using a dialdehyde and a diisocyanide in combination with monofunctional carboxylic acids.[122] Another strategy for the Passerini addition polymerization includes the use of a bifunctional AB-monomer. Therefore, a monomer, equipped with a carboxylic acid and an aldehyde function, was prepared *via* Thiol-Ene addition of 10-undecenal and 3-mercaptopropionic acid.[123] Subsequent polymerization was performed and different isocyanides were used in order to investigate the influence of the side chains. The use of the AB-type monomer makes the reaction a two component-three center reaction.[123-124] The synthesis of polymers *via* the P-3CR with sequence-ordered side chains was also reported.[125] Li *et al.* synthesized sequence-defined macromonomers and polymerized them subsequently in a Passerini

polyaddition polymerization.[125] Thereby, the sequence of monomer units in the macromonomer induced the monomer sequence in the resulting polymer.[125] Recently, the synthesis of star-shaped block copolymers with tailored side chains and adjustable block lengths *via* the P-3CR was described.[126] The U-4CR was also employed as polymerization method. By the use of two bifunctional components and two monofunctional components, polycondensations can be achieved (Figure 14b)).[118] Hereby, the choice of the solvent-mixture is crucial. While conventional U-4CRs are mostly conducted in methanol, most polymers are insoluble therein. Therefore, other solvents or solvent-mixtures had to be tested. It was revealed that a mixtures of tetrahydrofuran (THF) and methanol are suitable for the U-4CR polycondensation. Remarkably, all six different combinations of AA- and BB-type monomers in combination with monofunctional components were successfully polymerized.[118] Moreover, the direct polymerization of levulinic acid as AB-monomer in an Ugi polycondensation was described very recently.[127]

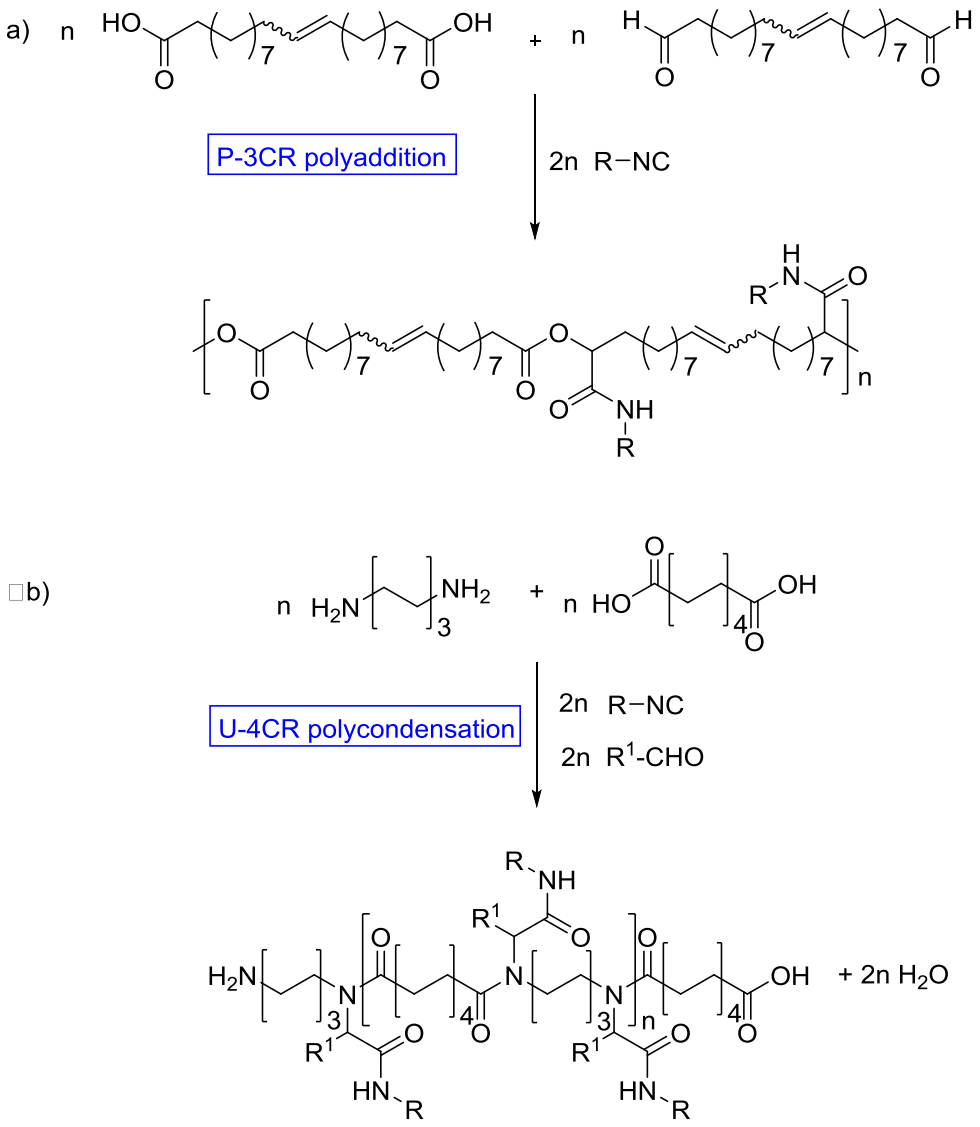


Figure 14: a) The P-3CR polyaddition polymerization using bifunctional acid- and aldehyde components in combination with monofunctional isocyanides. b) The U-4CR polycondensation using bifunctional amine and carboxylic acid in combination with monofunctional isocyanides and aldehydes.[109, 118]

Also, the U-5CR was used as polymerization method using diamines and diisocyanides in combination with isobutyraldehyde, methanol and CO_2.[128] Interestingly, the U-5C-polymerization allows the mild and isocyanate-free synthesis of polyurethanes and the products can subsequently be transformed to poly(hydantoins) by cyclization of the obtained polymer backbone.[128-129]

Also non-isocyanide-based MCR were used as polymerization methods. For instance, the Biginelli reaction enabled the synthesis of polymers containing the pharmaceutically

interesting dihydropyrimidinone structural motif.[130-131] Remarkably, even two MCR were conducted in one-pot to form structurally diverse polymers.[117] Here, the Hantzsch and the Biginelli reaction were conducted as competitive reactions, which was easily achievable due to the use of *β*-ketoesters and aldehydes in both types of reactions.[117] Another example for non-isocyanide-based MCR polymerizations is the copper catalyzed polymerization of diynes, sulfonylazides and diamines, yielding poly(*N*-sulfonylamidines).[132]

The third way of transferring organic reactions into the field of polymer chemistry is their use in post-polymerization modifications. Therefore, functional polymers need to be synthesized, which can subsequently be reacted in a MCR. For instance, Theato *et al.* synthesized poly(4-vinylbenzaldehyde) by free radical polymerization. The aromatic aldehyde groups, present in the monomer units, were then reacted in a Kabachnik-Fields reaction using various amines and phosphites and thus leading to *α*-amino phosphonate side chains.[133] The CuMCR of alkynes, amines and sufonyl azides, the Biginelli reaction as well as the P-3CR have also been used for post-polymerization modifications.[134-136]

2.2 Sequence-Control in Polymer Chemistry

The control over monomer sequences is up to now an unachieved goal in synthetic polymer chemistry. However, the synthesis of highly defined macromolecules could allow the precise tuning of material properties, the development of highly active and tailored catalyst systems or, on the very long term, complex processes like self-replication.[137] In this aspect, nature is a master in the synthesis of perfectly-defined primary structures. Peptides and proteins, as well as DNA are examples of macromolecules with a high degree of precision.[1] Due to the very well defined primary structure in peptides, certain secondary and tertiary structures can be formed and complex processes, like enzyme catalyzed reactions, are rendered possible. The prerequisite for enzyme catalyzed reactions and the "key-and-lock-principle" is an exactly defined monomer sequence, allowing the perfect match of substrate and enzyme.[3] In general, synthetic approaches yielding sequence-controlled macromolecules can be grouped into two categories: the chemical synthesis of bio-macromolecules and the synthesis of sequence-controlled synthetic polymers.[1] Before discussing some important syntheses of biopolymers, important terms in the field of sequence-controlled polymers are introduced. Afterwards some synthetic approaches towards sequence-controlled macromolecules are described, which include the use of solid supports, (DNA-) templates, and molecular machines.

2.2.1 Definitions

In 2013, Lutz, Ouchi and Sawamoto defined sequence-controlled polymers in a review as follows:[15]

"Sequence-controlled polymers are macromolecules in which monomer units of different chemical nature are arranged in an ordered fashion."

This definition implies that the term *sequence-controlled polymers* is an umbrella term for polymers of any level of control over the monomer sequence, including block copolymers, gradient copolymers but also highly defined polymers, such as

polypeptides. Therefore, some more strict definitions are necessary to distinguish between different levels of sequence-controlled polymers (Figure 15).[137-138]

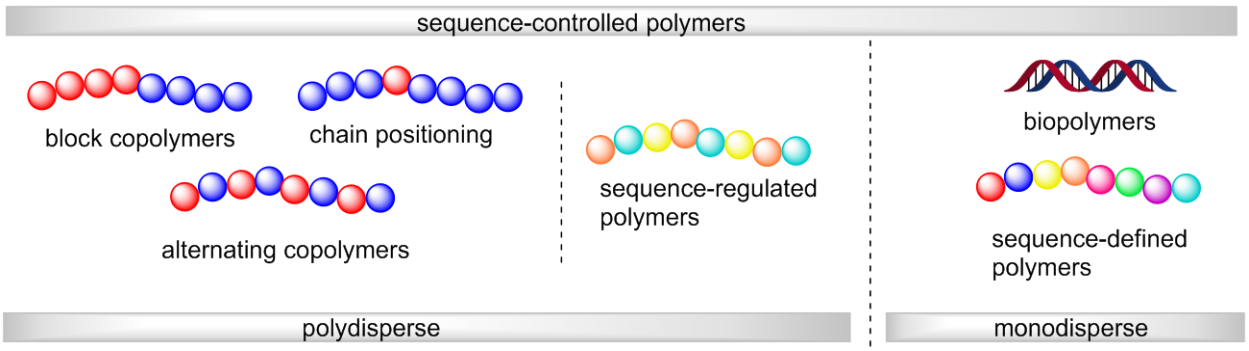


Figure 15: Classification and examples of different types of sequence-controlled polymers.[137-138]

According to Lutz, *sequence-controlled polymers* can be differentiated into polydisperse and monodisperse polymers (Figure 15).[137-138] Polydisperse, sequence-controlled polymers include for instance, alternating copolymers, periodic copolymers and chain positioned polymers (ideally one different co-monomer unit in a homopolymer chain). *Sequence-defined polymers* are monodisperse macromolecules with a perfectly defined primary structure.[137] Other commonly used terms are *sequence-ordered* and *sequence-regulated polymer*. The latter is frequently used for polydisperse polymers having a certain sequence of monomer units.[121] *Sequence-ordered* and *sequence-defined polymers* both describe polymers of defined length and monomer sequence.[137]

However, the terminology in the field of sequence controlled polymers is not yet clearly defined and to date there is no general consensus about the nomenclature.[139-140] In this work, sequence-defined, monodisperse macromolecules are investigated.

2.2.2 Synthesis of Biopolymers

In this section, the chemical synthesis of naturally occurring biopolymers with defined primary structures, namely polypeptides, oligonucleotides and oligopeptoids, are described. The chemical synthesis of polypeptides had its breakthrough with Merrifields invention of the solid-phase peptide synthesis (SPPS).[4] This method allowed the rather simple synthesis of oligomeric peptides and later on, the automation of the whole

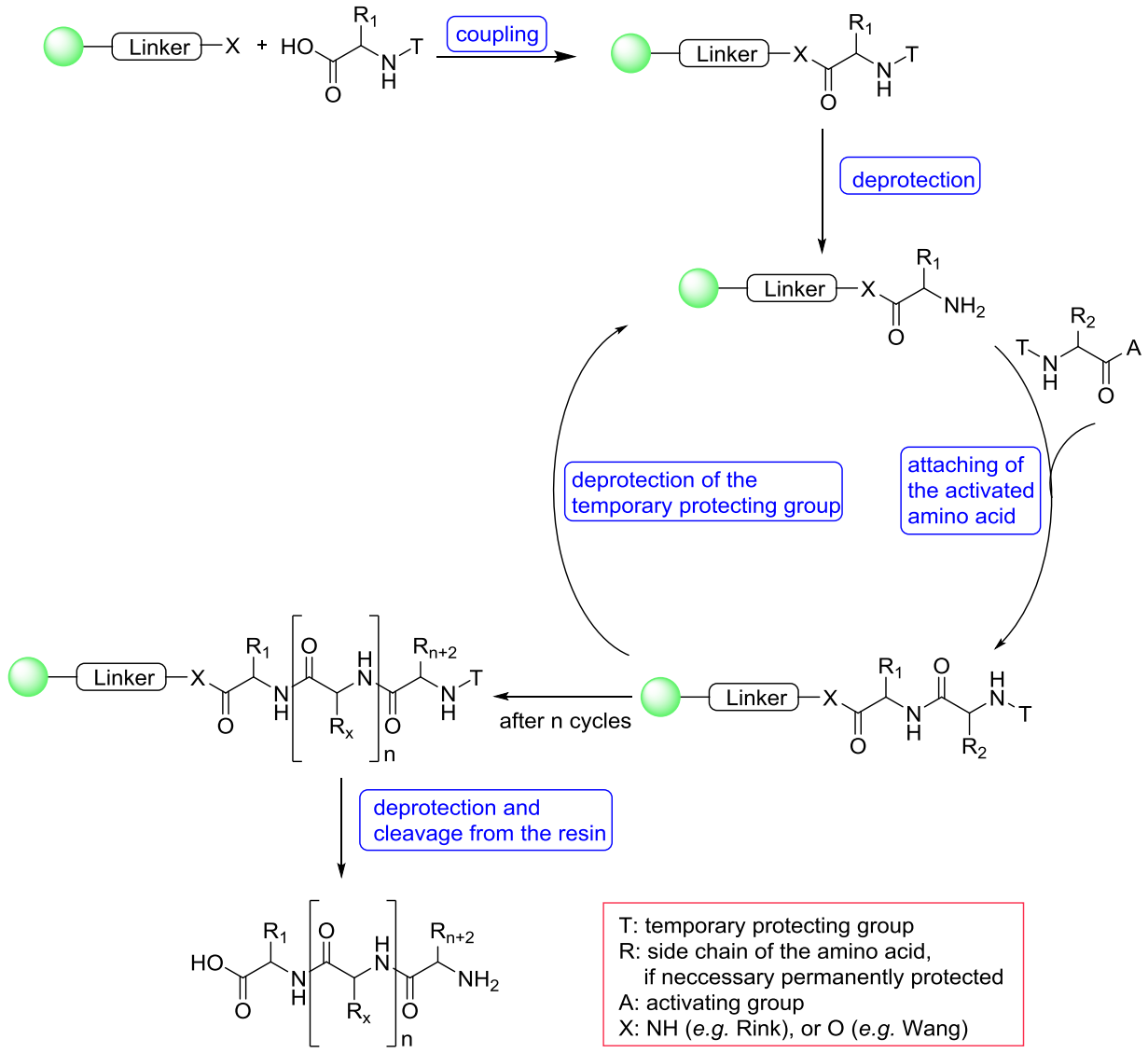
process. The same strategy was applied for the oligonucleotide synthesis, allowing simple and fast synthesis of oligopeptides and oligonucleotides in an automated fashion. However, in principle, the concept of SPPS is applicable to any bifunctional monomer, which can selectively be protected on one reactive side.[5] Taking into account the importance of the development of highly efficient synthesis methods for biopolymers, some aspects on the chemical synthesis and the properties of peptides, peptoids and oligonucleotides will be introduced and discussed in this chapter.[141]

2.2.2.1 Polypeptide Synthesis

As already mentioned, Merrifield did pioneering work with the development of the solid-phase peptide synthesis, and was therefore awarded the Nobel Prize in 1984.[4-5] The synthesis of peptides on a solid support bears eminent advantages: The products can be collected by simple filtration and the reagents can be used in high excess in order to ensure complete conversion.[5] Afterwards, the excess components can be removed by simple filtration and subsequent washing cycles.[5] Due to the simple workup procedure, losses during isolation and purification of intermediates are reduced to a minimum.[5] The solid-phase concept is, as already mentioned, not limited to peptide synthesis, but also depsipeptides, oligoamides, oligonucleotides and oligosaccharides were synthesized on a solid support already in the 1970s.[142-145] Some more recent examples include, for instance, the synthesis of peptide nucleic acids (PNA) and polypeptoids. [146-147]

For the coupling of two amino acids, the amino acids need to be equipped with orthogonal protecting groups to avoid unwanted reactions of the carboxylic acids with amines, leading to product mixtures. Therefore, one amino acid needs to be protected at the amine group and the other at the carboxylic acid function to ensure the exclusive formation of one product (temporary protecting groups).[141] Moreover, the side chains of the amino acids need to be protected, if functional groups are present, to avoid side reactions (permanent protecting groups).[141] The synthesis of polypeptides includes therefore a thoroughly planned and orthogonal protecting group strategy. A general overview of the SPPS is shown in Scheme 1. Synthetic peptide synthesis follows the

C → *N*-strategy, meaning that the *C*-terminus of the first amino acid is bound to the linker at the solid support (See Scheme 1).[141, 148]



Scheme 1: Schematic picture of the solid phase peptide synthesis.[73, 148]

The linker is bound to the resin by an ester or amide bond, depending on the type of resin (alcohol: *e.g.* Wang-resin or amine: *e.g.* Rink-resin, Figure 16).[149-150]

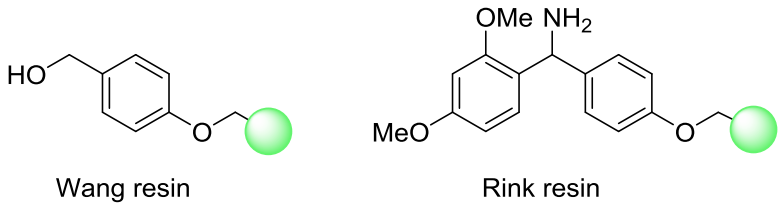


Figure 16: The Wang- and the Rink-resin, which are frequently applied as solid supports in SPPS.[149-150]

The resin itself mostly consists of a highly crosslinked co-polymer of styrene and 1,4-divinyl benzene and is swelling in organic solvents to solvate the growing peptide well and to make it freely accessible for the diffusing reagents.[4, 141] Alternatively, polyacrylamide resins were reported for the use in SPPS.[151] Once the first amino acid is attached to the linker and the resin, the SPPS-cycle starts with the deprotection of the temporary protecting group at the *N*-terminus (Scheme 1). The free amine-group is then reacted with an activated and *N*-protected amino acid in a second step. The carboxy function of the amino acid needs to be activated in order to avoid the acid-base reaction of the basic amine and the acidic carboxylic acid and to allow mild reaction conditions.[5] This activation can, for instance, be achieved by the synthesis of (mixed) anhydrides, acyl azides, *N,N*-dicyclohexylcarbodiimide (DCC) or the use of phosphonium- or uronium-based activating agents, such as PyBOP (benzotriazol-1-yl-oxytripyrrolidino phosphonium hexafluorophosphate) and HBTU (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (Figure 17).[5, 141, 152-156]

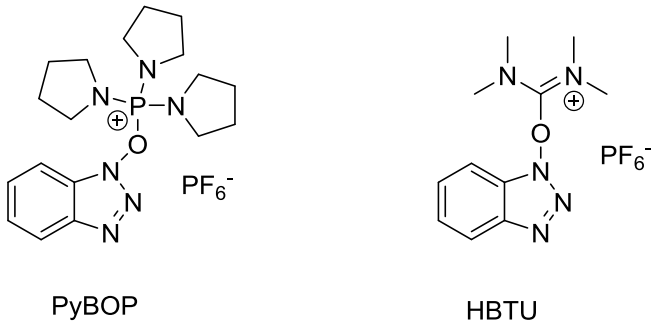


Figure 17: Two examples for phosphonium and uronium-based activation agents: PyBOP and HBTU.[155-156]

The activation is formally the generation of an active ester, enhancing the reaction rate of the peptide-bond formation by increasing the electrophilicity of the carboxy group and

installing very good leaving groups.[141] After successful coupling of the amino acids, the temporary protecting group of the *N*-terminus is cleaved and another activated amino acid can be attached (see circle in Scheme 1). Once the desired peptide sequence is synthesized, the temporary and the permanent protecting groups are removed and the peptide is cleaved from the solid support.[148] As already mentioned, SPPS requires an orthogonal protecting group strategy. The temporary *N*-terminus protecting group of choice is nowadays commonly the base labile 9-fluorenyl-methoxy carbonyl (Fmoc) protecting group (Figure 18).[148, 157]

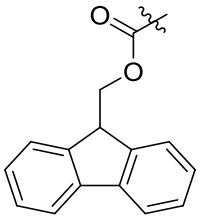


Figure 18: The base labile 9-fluorenyl-methoxy carbonyl (Fmoc) protecting group.[157]

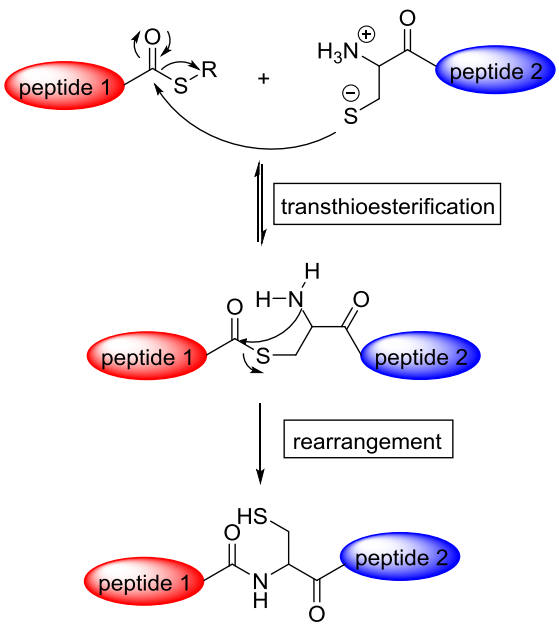
Due to the use of a base-labile group for the temporary protecting groups, the permanent protecting groups and the linker should be acid-labile to ensure orthogonal deprotection and to avoid side reactions, like the cleavage from the resin or reactions of the side chain functionalities of the amino acids.[148]

Another breakthrough in peptide chemistry was the automation of the whole process. In 1965, Merrifield reported on the first peptide synthesizer, which was able to perform all the necessary operations in the stepwise synthesis of polypeptides on a solid support.[158-159] The automated synthesis protocol was then used in the synthesis of the oligomeric peptides bradykinin (nonamer), angiotensin (octamer) and oxytocin (nonamer).[160-162]

The key requirements for the SPPS are rapid reactions along with high yields and the absence of side reactions. This is necessary in order to prevent the accumulation of by-products since the separation of byproducts after cleavage from the solid support is challenging.[5, 141] Due to incomplete conversion in each synthesis-cycle, the formation of mismatched sequences is unavoidable.[141] However, it should be limited to a minimum

extend, which can be visualized by a simple calculation: If the yield of each cycle was 99 %, the overall yield after 10 and 100 cycles reached 90 % and 37 %, respectively.[141]

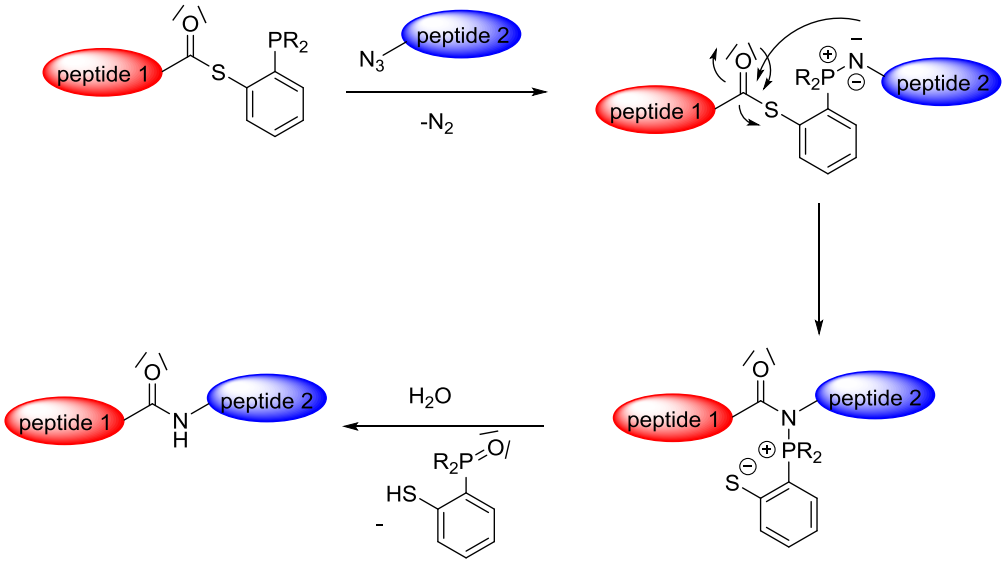
For the synthesis of proteins and enzymes, amino acid sequences of at least 125 amino acids are required.[163] However, by means of classical peptide synthesis strategies this is a very challenging task taking into account the poor solubility of protected peptide intermediates in solution phase synthesis and the accumulation of side products due to incomplete conversion in SPPS.[163] SPPS allows the routine synthesis of peptide chains of 60 to 80 amino acids, therefore a major milestone was the development of chemical ligation methods.[164-166] Chemical ligation describes the covalent linkage of two unprotected peptide fragments making use of a chemoselective reaction, in order to provide the products in high yields and purity.[163, 165] In the native chemical ligation, a reversible transthioesterification is followed by an irreversible amide formation (Scheme 2).[166-167] Thereby, a "native" polypeptide with a cysteine residue at the position of the ligation can be obtained.[163] Scheme 2 shows the basic principle of native chemical ligation: the nucleophilic attack of the thiol at the carbonyl group of the thioester forms the transthioesterification product reversibly, which then rapidly rearranges irreversibly *via* a five-membered ring to the desired ligation product.[166-167]



Scheme 2: The principle of native chemical ligation: A thioester-peptide fragment is coupled to another unprotected peptide fragment with a terminal cysteine by a reversible transthioesterification and subsequent irreversible rearrangement to yield the targeted peptide.[166]

Hereby, the reversible addition of the thiol to the thioester fragment is crucial, because the subsequent intramolecular rearrangement exclusively takes place when the thiol is located next to the *N*-terminal cysteine moiety.[163] Therefore, only the desired amide bond between the two fragments can be formed even in the presence of other internal cysteine moieties in either peptide fragment.[163] Interestingly, the ligation is performed in water as solvent in the absence of protecting groups.[168] However, the synthesis of peptides and proteins *via* native chemical ligation is technically limited to proteins containing cysteine residues within the sequence.[168] However, this can be overcome by simple insertion of an additional cysteine and it was shown for some cases that there is no effect on the folding of the peptide or its biological activity.[169] Moreover, cysteine-like auxiliaries have been used during the native chemical ligation and were cleaved afterwards.[170-171] Alternatively, the Staudinger-ligation can be employed, having the advantage that the method is not restricted to certain amino acids in the peptide sequence.[172] The Staudinger ligation is based on the Staudinger reaction of alkyl azides with phosphines, leading to amines after aqueous workup.[173] Bertozzi *et al.* and Raines *et al.* developed the Staudinger-ligation system for cell surface modifications and

peptide couplings, respectively in 2000.[172, 174] Scheme 3 shows the principle of the so called traceless Staudinger-ligation introduced by Raines *et al.*[174]



Scheme 3: Proposed mechanism of the traceless Staudinger-ligation as amino-acid sequence-independent ligation method for protein synthesis.[174]

The term traceless was coined due to the cleavage of the phosphine oxide after the ligation reaction and the exclusive formation of a new peptide bond.[174] The major advantage of the traceless Staudinger-ligation compared to the native chemical ligation is the independency of cysteine residues in the protein sequence.

All in all, more than 300 biologically active proteins of 20 protein families were synthesized by chemical ligation methods and it was shown that the synthetic polypeptides fold spontaneously *in vitro*, forming protein molecules of defined tertiary structures.[168] The development of the ligation methods enabled, for instance, the synthesis of tethered dimers of the HIV-1 protease (~ 22 kDa) and the chemical synthesis of a polymer-modified analogue of erythropoietin (~ 50 kDa), a glycoprotein mimetic.[175-176] The latter was synthesized by subsequent chemical ligations obtaining the polypeptide with 166 amino acids.[176]

Although the development of ligation chemistry displays a major breakthrough in the chemical protein synthesis, SPPS still plays a very important role in the field since the peptide fragments, required for ligation, are mostly synthesized using SPPS.[163]

2.2.2.2 Oligopeptoids

Oligopeptoids, oligomers of *N*-substituted glycines, differ from oligopeptides by the position of the side chain: peptides are C_α-substituted, whereas peptoids are *N*-substituted (Figure 19).[177]

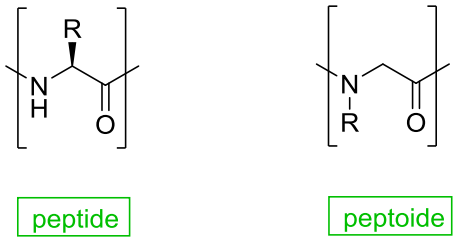
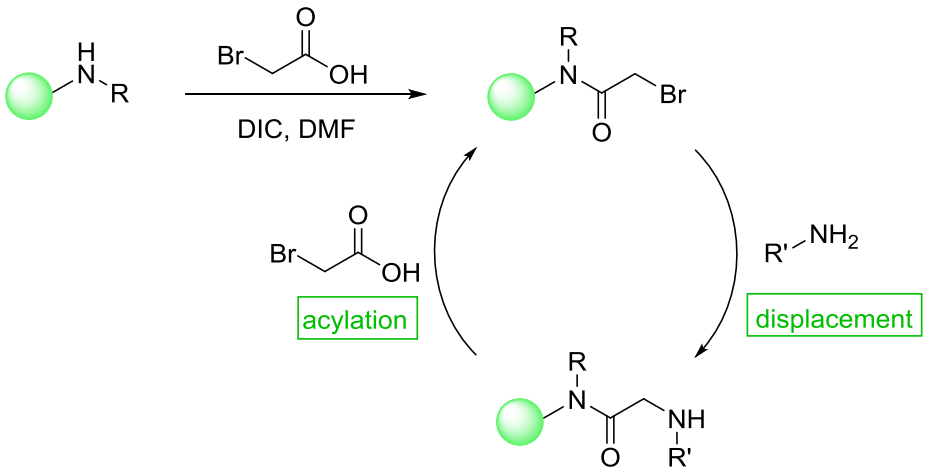


Figure 19: General structures of peptides (oligo-amino acids) and peptoids (oligo-N-substituted glycines).[177]

In contrast to peptides, peptoids are achiral leading to easier synthesis of peptoids avoiding epimerization issues.[178] Furthermore, the *N*-substitution prevents the formation of hydrogen bonds, resulting in conformationally unstable structures. However, it was shown that the formation of secondary structures can be influenced significantly by the choice of the side chains.[178-180] Another difference to peptides is the comparably higher proteolytic stability arising from the non-natural backbone as well as the higher solubility in organic solvents.[181] However, some peptoids show high biological activity, which makes peptoids interesting candidates for the pharmaceutical industry as peptide-mimics.[177]

Peptoids can be synthesized, analogous to peptides, by coupling of Fmoc-protected *N*-substituted glycine monomers on a solid support.[177] But due to the slower couplings of secondary amines, the method of choice is the submonomer approach developed by Zuckermann in 1992.[147] Here, the synthesis of different monomers is not necessary and commercially available reagents can be employed in the synthesis of peptoids.[147] Furthermore, the submonomer approach avoids the use of backbone-protecting groups.[147] In the submonomer approach, the glycine monomer-units are formed by the reaction of two so called submonomers, an amine and a haloacetic acid. Therefore, a resin-bound secondary amine reacts with a haloacetic acid upon activation with diisopropylcarbodiimide (DIC) (acylation). The activated haloacetic acid is a much more

reactive compound than the amino acid analogue due to the electron withdrawing effect of the halide.[182] Therefore, and because of the use of commercially available primary amines, the submonomer approach is superior to the coupling of *N*-glycines.[182] In the following nucleophilic displacement, an amine substitutes the halide and the *N*-glycine monomer unit is formed (Scheme 4).[147]



Scheme 4: Synthesis of polypeptoids with the submonomer strategy: the amine is acylated using for instance bromoacetic acid upon DIC activation. By addition of an amine component in excess, the displacement reaction takes place and the N-glycine monomer unit is formed.[147]

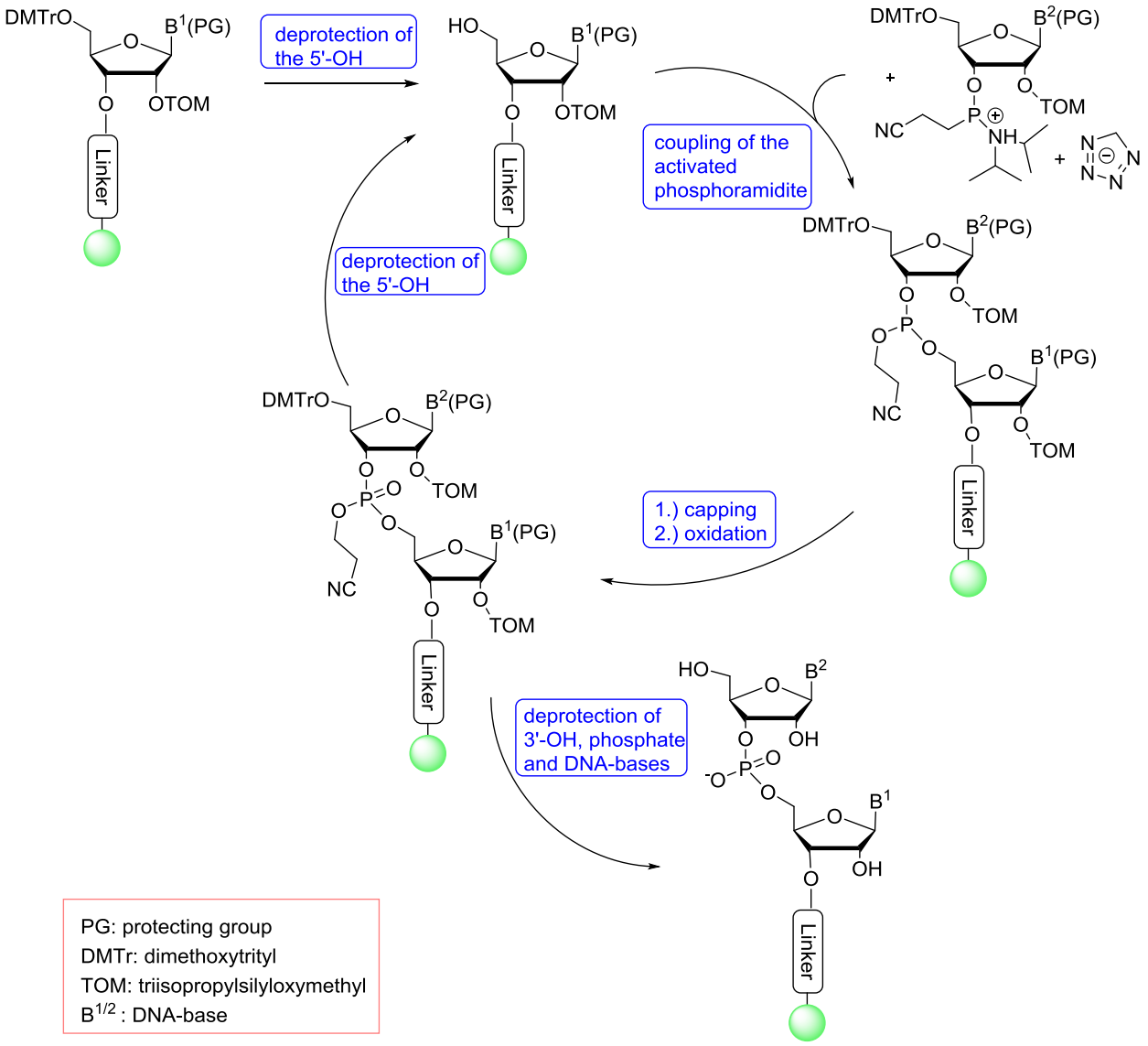
The submonomer-synthesis of polypeptoids on a solid support can be performed automatically making use of commercially available peptide synthesizers.[147, 182] This strategy allows the routine synthesis of polypeptoids of up to 50 *N*-glycine monomer units.[183-185] The rather simple synthesis of sequence-defined oligopeptoides led to the investigation of sequence-property relationships and the investigation of the influence of the side chains on the secondary structure in polypeptoids.[179-180] It was shown that oligopeptoids with *α*-chiral side chains fold in solution to helices and a threaded loop structure was formed by peptoid-nonamers *via* intramolecular hydrogen bonding.[186-188] Thereby, the formation of helices is mostly caused by bulky, *α*-chiral side chains, such as *N*-(S)-(1-phenylethyl)-glycine.[180] The analysis of the crystal structure of a pentamer of *N*-(1-cyclohexylethyl)glycine revealed that one turn in the helical structure contained three *N*-glycine units and that the amide bonds are all *cis*-configured.[189] However, solution NMR measurements indicated conformational heterogeneity, which was reduced by introduction of electron withdrawing, positively charged substituents (e.g.

pyridinium) or the introduction of very sterically demanding side chains, such as naphthyl groups.[190-192] Also, the formation of *β*-sheets was achieved by the mixing of two oppositely charged peptoid 36-mers of a certain sequence in solution.[193] Thereby, self-assembly of the polypeptoids to well-defined two-dimensional nanosheets was achieved.[193] Moreover, the synthesis of a biomimetic diblock co-polypeptoid, which self-assembles to homochiral superhelices, was reported in 2010.[194] Here, the self-assembly is evoked by the interplay of hydrophobic and electrostatic forces within the amphiphilic and partially charged diblock co-polypeptoid of a defined sequence. Therefore, *N*-(2-carboxyethyl)glycine and *N*-(2-phenylethyl)glycine were used as monomers, allowing the formation of homochiral superhelices in aqueous solution. However, the origin of the homochirality in the diblock system is not entirely clear.[181, 194] All in all, polypeptoids display an interesting group of peptidomimetics and a very interesting class of non-natural sequence-defined macromolecules. Particularly interesting in the field of sequence control are the already well investigated sequence-property relationships.

2.2.2.3 Oligonucleotide Synthesis

The chemical synthesis of oligonucleotides is conducted, like the peptide synthesis, mostly on a solid support. The first report on the solid phase synthesis of oligonucleotides was published by Letsinger and Mahadevan in 1965.[144] Since then, the oligonucleotide synthesis was improved and finally the phosphoramidite chemistry was developed.[195] In this section, the nowadays applied synthesis protocol and the commonly used protecting groups will be briefly introduced, as it displays one aspect of current research on sequence-controlled polymers.[196-198]

Scheme 5 shows the general principle of the solid phase oligonucleotide synthesis employing the phosphoramidite strategy.[73, 144, 199-200]



Scheme 5: General methodology of the chemical oligonucleotide synthesis applying the phosphoramidite-strategy.[73, 144, 199-200]

In contrast to biological systems, synthetic chemistry synthesizes oligonucleotides from the 3' to the 5' position.[200] For this purpose, a highly orthogonal protecting group strategy is required. The chemical oligonucleotide synthesis starts with the deprotection of the 5' position of a solid-phase-bound nucleoside (Scheme 5). The solid phase, unlike in SPPS, commonly consists of controlled pore glass (CPG) due to its non-swelling properties.[201] The swelling of polystyrene-resins leads to inhibited diffusion of reagents and solvents through the matrix and thus to reduced coupling efficiencies.[201] The deprotected primary OH-group is then reacted with an excess of tetrazole-activated

phosphoramidite yielding a phosphite triester.[200] Similar to SPPS, the reagents are used in large excess in order to force the reaction to completion.[202] However, it is not always possible to fully convert the 5' OH group; thus, a capping step is necessary after the coupling step. Hereby, the remaining primary OH groups are acylated using acetic anhydride and 4-dimethylaminopyridine (DMAP) in order to facilitate the isolation of the desired product, once the desired sequence is synthesized.[200] The capping step is followed by an oxidation of the rather unstable phosphite triester to the corresponding phosphotriester using iodine as mild oxidation agent and 2,6-lutidine as base.[199] Subsequently, the deprotection, coupling, capping and oxidation steps can be repeated until the desired sequence is obtained.[200] Once the desired primary structure is synthesized, all permanent protecting groups are removed and the oligonucleotide is cleaved from the solid support.[200] As already mentioned, the solid-phase oligonucleotide synthesis requires a highly orthogonal protecting group strategy for the different OH-groups, the exocyclic amine groups of the DNA bases, for the phosphite triester and for the cleavage from the solid support.[201] The most common protecting groups, applied in the phosphoramidite-oligonucleotide synthesis, are shown in Figure 20. Guanine, adenine and cytosine are typically protected with a base labile benzoyl protecting group, whereas uracil and thymine do not need a protecting group due to the lack of an exocyclic amine function.[200] The 5' OH group is usually protected using the acid-labile dimethoxytrityl group due to the excellent regioselectivity to the primary OH group and the facile acidic cleavage, which can be followed by photometry due to the formation of the orange triphenyl cation.[200] The 2' OH group is only present in RNA, where it is commonly protected using the fluorine-labile triisopropyl silyloxymethyl (TOM) protecting group.[202] The development of the TOM protecting group enabled the synthesis of RNA under similar reaction conditions like in DNA syntheses.[202-203] The *β*-cyanoethyl group acts as base-labile protecting group for the phoshotriester, whereas the diisopropylamino group acts as leaving group during the coupling step.[201, 204-206]

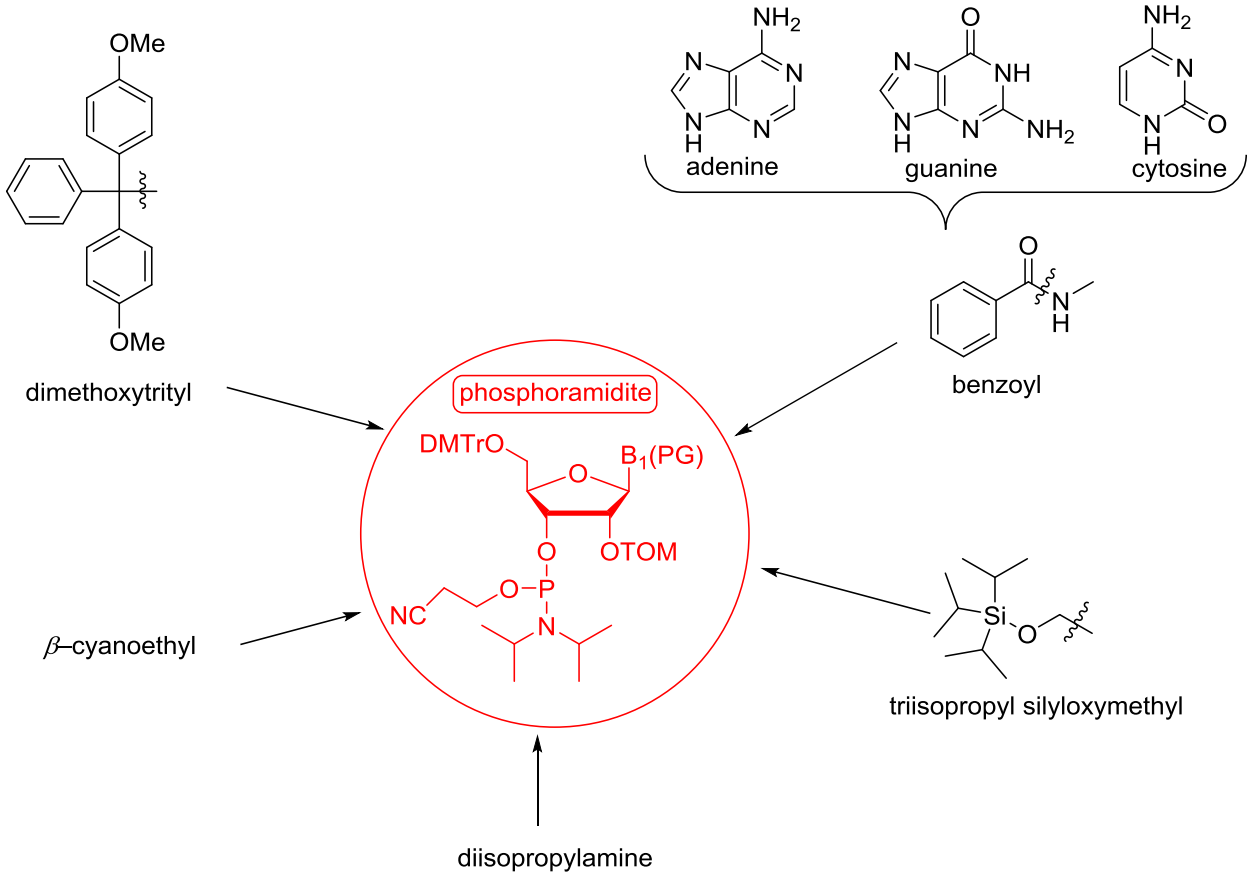


Figure 20: The commonly used protecting groups for the solid phase oligonucleotide synthesis via the phosphoramidite approach.[73, 200, 202, 207]

The chemical oligonucleotide synthesis is nowadays a fully automated procedure: The desired sequence can automatically be synthesized by a computer-controlled device.[208-210] The first report on an automated DNA synthesis was already reported in 1985;[208] since then, for instance, the synthesis of 98-mers and even 120-mers have been described.[211-212]

2.2.3 Synthesis of Sequence-Controlled Polymers *via* Chain-Growth Polymerizations

In chain-growth polymerizations, the propagating chain ends are highly reactive species, such as radicals or ions. Therefore, the obtained comonomer sequences are in many cases randomly distributed. Though, in radical polymerizations there are certain selected

monomer pairs, which can be polymerized in conventional radical polymerization obtaining alternating sequences. In these specific examples, the cross reactivity of the monomers is remarkably higher than the homo-propagation reactivity due to donor/acceptor properties of the monomers.[213] However, this outstanding reactivity is only shown by a few monomer pairs such as maleic anhydride and styrene, maleimide and styrene or maleimide and limonene.[214-218] Remarkably, the high cross reactivity of maleic anhydride was already reported in 1945.[214] The development of controlled radical polymerization methods, such as atom transfer radical polymerization (ATRP), nitroxide mediated polymerization (NMP) and reversible addition fragmentation transfer polymerization (RAFT), allowed the precise synthesis of macromolecular architectures along with the synthesis of polymers with narrow molecular weight distributions.[7-8, 10-11] These highly controlled processes allow the synthesis of more precisely controlled polymers. In 2000, Russel *et al*. synthesized a copolymer of maleic anhydride and styrene *via* NMP.[219] Hereby, a 1:9 mixture of the comonomers maleic anhydride and styrene were copolymerized and a diblockcopolymer with a narrow dispersity ($Đ_M$ = 1.19) was obtained in a one-pot procedure.[219] The first block consisted of an alternating maleic anhydride-styrene block, whereas the second block was a homo-styrene block, which was formed after the complete consumption of maleic anhydride.[219] Kamigaito and coworkers reported on the synthesis of copolymers of limonene and maleimides by RAFT polymerization.[218] Hereby, a 1:2 limonene/maleimide incorporation was observed independently of the comonomer feed-ratio, which was explained by the steric demand of the limonene-monomer.[218, 220] The copolymerizations incorporating maleimides have in common that (functional) substituents can easily be introduced to the final polymers owing to the *N*-substitution of the maleimides.[221] One basic idea towards sequence control makes use of living-radical copolymerizations of acceptor-donor comonomer pairs. The concept takes advantage of the fact that in "living" polymerizations the chain propagation starts at the same time and that the chains grow almost simultaneously.[222] In combination with the high cross propagation reactivity of the comonomer pairs it is possible to introduce statistically, for instance, one maleimide monomer in a polystyrene chain by adding one equivalent (relative to the initiator) of the maleimide monomer.[222] Furthermore, it was shown that the maleimide could be positioned within the growing chain by introduction of the

maleimide monomer at different styrene conversions.[221] By the introduction of different maleimides (one equivalent each) at different styrene conversions, it is possible to decorate the polystyrene chains with different maleimides sequentially (Figure 21). [223-224]

However, owing to the statistical nature of a radical polymerization process, chain to chain deviations as well as over and under functionalization of single polymer chains cannot be avoided and the obtained products display chain length deviations. In order to reduce these undesired effects to a minimum, the approach was further improved by the addition of the maleimide monomer at a high conversion of styrene, leading to a narrow distribution of the maleimide monomer within the polymer chain (Figure 21).[225] This can be explained statistically: the higher the donor/acceptor monomer ratio, the broader the sequence distribution. Thus, the addition of the acceptor monomer at high conversions of the donor monomer leads to a more precise incorporation of the acceptor monomer (Figure 21).

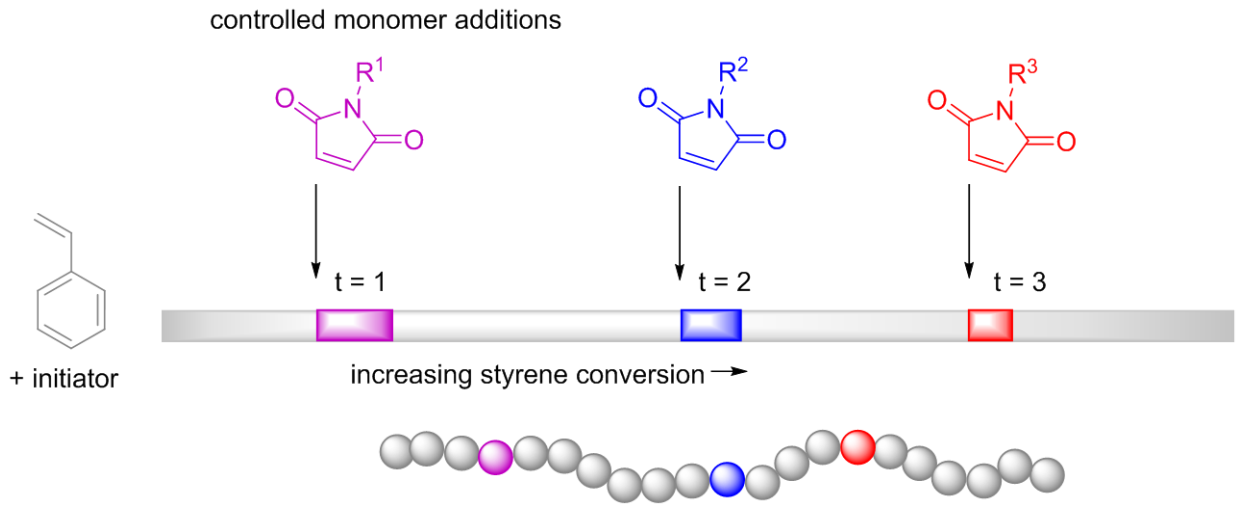


Figure 21: The concept of Lutz et al. using controlled polymerization methods for the copolymerization of styrene and different maleimides. At certain times of the polymerization process, one equivalent of the maleimide is added and incorporated rapidly, enabling a positioning of the maleimide in certain polymer regions.[223] The positioning gets more precise with an increased conversion of styrene due to a more favorable styrene/maleimide ratio.[225-226]

These findings were investigated in detail by addition of the maleimide monomer at different styrene conversions.[225] Although the positioning of the maleimides along the polystyrene chain is achieved in more narrow regions of the polymer, still over and under

functionalized polymer chains are obtained.[226] Moreover, the same concept was investigated in NMP copolymerizations of styrene or styrene derivatives and maleimides synthesizing, for instance, polyelectrolytes or water soluble polymers.[227-231]

In 2016, Kamigaito and coworkers reported on the synthesis of side chain and main chain regulated polymers by combining two approaches for sequence-regulation.[232] First, sequenced macromonomers were synthesized by atom transfer radical addition, also referred to as the Kharasch reaction, using acrylate and styrene monomers.[233-235] The carbon chlorine bond was then displaced by phtalimide in a nucleophilic substitution reaction, followed by a retro Diels-Alder reaction to obtain sequenced-maleimide monomers. These sequence-regulated maleimide monomers were then copolymerized with styrene or limonene to yield a 1:1 or 2:1 alternating copolymer, respectively.[232] In that way, the main chain sequence could be regulated by the choice of monomers, whereas the side chain regulation was accomplished by the monomer-design. This approach elegantly combines two different approaches and accomplishes thereby a higher degree of control, namely control over side- and main chain sequences.

Another different approach towards sequence-controlled polymers includes the control over tacticity. The Ziegler-Natta polymerization of propylene allows, for instance, the syndiospecific incorporation of monomer units, which can be influenced by the employed catalyst system.[236-237] The control over monomer sequences and the introduction of different and tailored side chains can hardly be achieved with this approach. However, Thomas and co-workers introduced an elegant approach for the synthesis of alternating copolyesters by ring-opening polymerization (ROP) of enantiopure, but different *β*-lactones.[238] Yttrium-*bis*phenolate complexes allowed the syndiospecific incorporation of monomer units, depending on their configuration, resulting in alternating copolyesters.[238]

Perrier *et al.* synthesized a icosablock copolymer, applying the RAFT technique, in a one-pot procedure.[239] Therefore, each monomer was polymerized until the conversion exceeded 99 %, before the next monomer was added. By the successive polymerization of different monomers, the icosablock copolymer was obtained in a one-pot fashion without the workup of intermediates.[239] This method provided sequence-controlled

multiblock copolymers, but the polymerization time for each individual block was 24 hours in order to ensure complete consumption of the employed monomer.[239] By changing the solvent from dioxane to dioxane / water (1:4) the reaction times could be reduced drastically and the individual blocks were synthesized within two hours.[240] Comparably, Haddleton and coworkers synthesized multiblock copolymers *via* photo-mediated copolymerization of different acrylates and obtained undecablock copolymers of narrow dispersity ($Đ_M$ < 1.2).[241]

Another polymerization technique with chain-growth characteristics investigated in the context of sequence-controlled polymers is the ring opening metathesis polymerization (ROMP).[242-245] ROMP is a controlled polymerization method providing polymers with narrow molecular weight distributions and is extensively studied for applications in material science.[246-247] The synthesis of sequence-controlled polymers by the use of ROMP was investigated by different groups, indicating the versatility of ROMP.[242-245] In 2012, Hillmyer and co-workers reported on the synthesis of sequence-regulated polyalkenes by regioselective ROMP of multiply substituted cyclooctenes.[242] Taking advantage of the already known head-to-tail- and *E*-selectivity in ROMP of 3-substituted cyclooctenes, this new approach allows the synthesis of sequence regulated polymers resembling the substitution pattern of the cyclooctene monomers (Figure 22).[248]

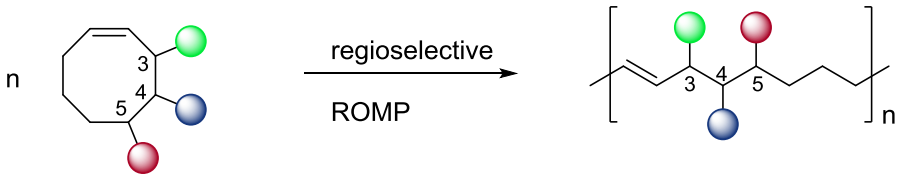


Figure 22: Synthesis of sequence-regulated polyalkenes by regioselective ROMP of multiply substituted cyclooctenes.[242]

Hereby, the substituent at 3-position is mandatory, whereas the positions of other substituents are variable. Though the monomer sequence of the resulting polymers can be controlled applying this approach, the products show dispersity and the monomer synthesis is demanding.

Comparable to the copolymerization of maleimides and styrenes, O'Reilly *et al.* investigated the ROMP copolymerization of *exo*- and *endo*-norbornenes.[243] It is well

known that *exo*-norbornenes polymerize with considerably higher reaction rates compared to *endo*-norbornenes due to steric interactions between the growing chain and the incoming monomer units in *endo*-norbornene-polymerizations.[249-250] By addition of small amounts (*e.g.* one equivalent in respect to the catalyst) of an *exo*-norbornene to an *endo*-norbornene homopolymerization, the *exo*-norbornene is quickly incorporated due to its higher reactivity. Therefore, statistically one *exo*-monomer is incorporated in each growing chain if one equivalent (in respect to the catalyst) of the *exo*-norbornene is added owing to the fast addition of the more reactive *exo*-monomer.[243] It was shown that four different *exo*-norbornenes can be incorporated into the polynorbornene. An advantage in this kinetically driven concept is the synthesis of a homogeneous backbone along with variable side chains. Nevertheless, this approach allows no absolute control over the primary structure of the obtained polymer and enantiomerically pure monomers are needed.

Hawker *et al.* synthesized a polyester-based macrocycle containing an eneyne-trigger, which facilitates the ROMP of unstrained macrocycles.[244, 251] Hereby, the high reactivity of alkynes towards metathesis catalysts is utilized to conduct the ring-opening of unstrained macrocycles. The macrocycles consisted of glycolate, lactate, phenyl acetate and *β*-alanine monomer units, forming an ester backbone, which could be degraded after ROMP.[244] Very similarly, Meyer and coworkers prepared sequence-regulated polymers *via* entropy-driven ROMP of unstrained oligoester-macrocycles.[245] Hereby, they synthesized a *α*-*ω*-diolefin containing a symmetric sequence of three different esters. The diolefin underwent ring closing metathesis (RCM) under dilute conditions and was subsequently polymerized in a entropy-driven ROMP at high concentration. [252-255] Thereby, sequence-regulated polymers with molecular weights of up to 60 kDa were obtained.[245]

Very recently, Harrisson *et al*. investigated "the limits of precision monomer placement in chain growth polymerizations" in a statistical manner.[256] By the use of Poisson and the related beta distributions, the monomer locations in sequence-controlled copolymers were calculated and the degree of control was quantified by means of yield and standard deviation values. Hereby, high yields along with low standard deviations indicate a high level of control.[256] In this statistical approach, the degree of control of anionic

polymerizations and reversible deactivation radical polymerizations (RDRP), or "living" radical polymerizations could clearly be differentiated. The results indicate that RDRP processes are hardly suitable for precision positioning of single monomer units along a polymer chain, because the uncertainty of the monomer position grows in proportion to the square root of the length of the polymer chain.[256] The authors investigated several examples of chain-growth and ionic polymerizations and illustrated the results with some examples.[224-225, 243, 257] For instance, if monomer pairs of unequal reactivities, such as styrene (S) and maleic anhydride (M), are copolymerized with the target to obtain a $S_{10}M_1S_{10}$ triblock copolymer, only 12.5 % of the polymer chains incorporate M at the eleventh position.[256] However, it is stated that the control over relative positions within polymer chains is achievable and that the degree of control can be increased with an increasing block length. Furthermore, the synthesis of multiblock copolymers with the goal that almost every chain contains each block is easily achievable using RDRP techniques as long as the individual blocks have a sufficient chain length.[241, 256] These results confirm that the statistical nature of chain growth processes lead to chain to chain deviations and that absolute control over monomer sequences can hardly be achieved by RDRP processes.

2.2.4 Synthesis of Sequence-Controlled Polymers *via* Step-Growth Polymerizations

Step-growth polymerizations are polymerizations, in which di- or multifunctional monomers form dimers, the dimers react with each other to form tetramers and eventually polymers are formed at high conversions. Classical polycondensations like polyester and polyamide syntheses are mostly condensation reactions of diesters with diols and diacids or diesters and diamines, respectively.[258-259] On the other hand, some more recent polymerization methods, such as acyclic diene metathesis polymerizations (ADMET), can be categorized as polycondensations. [260-261] Wagener and coworkers succeeded in the synthesis of the first ADMET-derived polymer in 1991.[260] Almost two decades later, the same group reported on the synthesis of sequence-controlled polymers *via* ADMET polymerizations, which they called "precision polyethylene" at that

time. Hereby, different ADMET monomers containing branching groups were synthesized, subsequently polymerized and hydrogenated in order to study the crystallization behavior depending on the introduced side chains (Figure 23).[262] Hereby, the side-chain substitution in the monomer dictates the sequence of the obtained polymers.

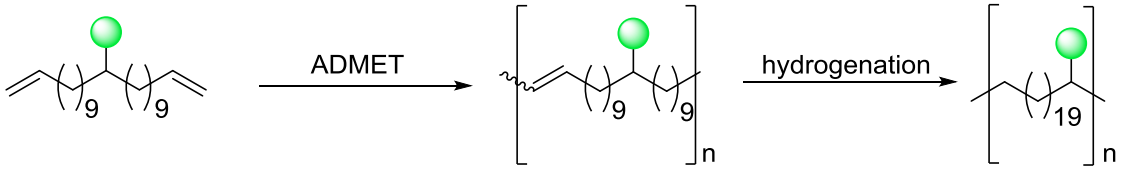


Figure 23: Synthesis of precision polyethylene via ADMET polymerization of substituted dienes and subsequent hydrogenation.[262]

In 2010, Kamigaito *et al.* synthesized sequence-regulated vinyl copolymers by a metal catalyzed step-growth radical polymerization and obtained *ABC*- or *ABCC*-sequences, depending on the employed monomer.[263] The monomer and polymer synthesis obtaining *ABC*-sequence-regulated polymers is shown in Figure 24.

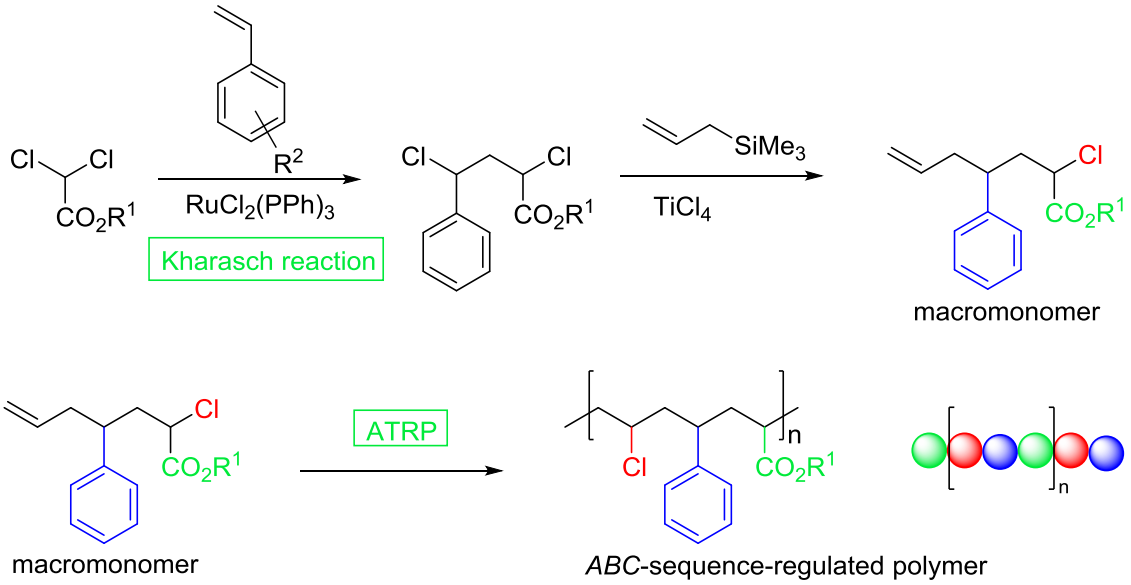


Figure 24: Synthesis of an ABC-monomer by the Kharasch reaction and subsequent ATRA step-growth polymerization of the obtained macromonomer.[263]

The *ABC* and *ABCC* comonomers were prepared by the atom transfer radical addition (ATRA), also known as Kharasch reaction.[233-235] The resulting monomers contained an unconjugated double bond and a C-Cl bond, allowing subsequent atom transfer radical

addition step-growth. Hereby, the C-Cl bond is activated by metal catalysts, enabling the radical addition to unconjugated double bonds. A very similar approach was followed by Li and coworkers synthesizing sequence-regulated methyl methacrylate-styrene copolymers and acrylonitrile-styrene copolymers.[264]

2.2.5 Synthesis of Monodisperse Macromolecules

This section provides an overview of selected examples for the synthesis of monodisperse, though not sequence-defined polymers. Hereby, all chains have the same length, but consist of one and the same monomer unit along the polymer chain.

Conjugated polymers, such as poly(*p*-phenylenevinylene)s, are valuable candidates for applications in photovoltaics, organic light-emitting displays or in field-effect transistors.[265-267] In order to investigate structure-property relationships more easily, monodisperse conjugated oligomers are of great importance.[268] The synthesis of monodisperse *p*-phenylenevinylene oligomers can be accomplished, for instance, by the use of an acetal protected phosphonate containing a stilbene core, which is oligomerized stepwise by the iteration of Horner-Wadsworth Emmons (HWE) reactions and subsequent deprotection.[268] But also the synthesis of monodisperse *p*-phenylenevinylene oligomers by protecting group free approaches were described.[269-270] Moreover, monodisperse, *π*-conjugated *cis*- and *trans*- oligo-eneynes can be synthesized *via* consecutive Sonogashira couplings.[271]

On the other hand, also the solution phase synthesis of monodisperse oligoesters was described.[272] This synthesis approach relies on the use of two orthogonally protected monomers, which were synthesized by the ring-opening of *ε*-caprolactone and subsequent orthogonal protection reactions of the carboxylic acid and the hydroxy function.[272] These two monomers are then orthogonally deprotected and reacted upon DCC activation to yield in turn, a orthogonally protected dimer. The dimer is then divided in two parts, orthogonally deprotected and coupled to yield the tetramer. The repetition of these steps allowed the synthesis of a monodisperse 64-mer (Figure 25).

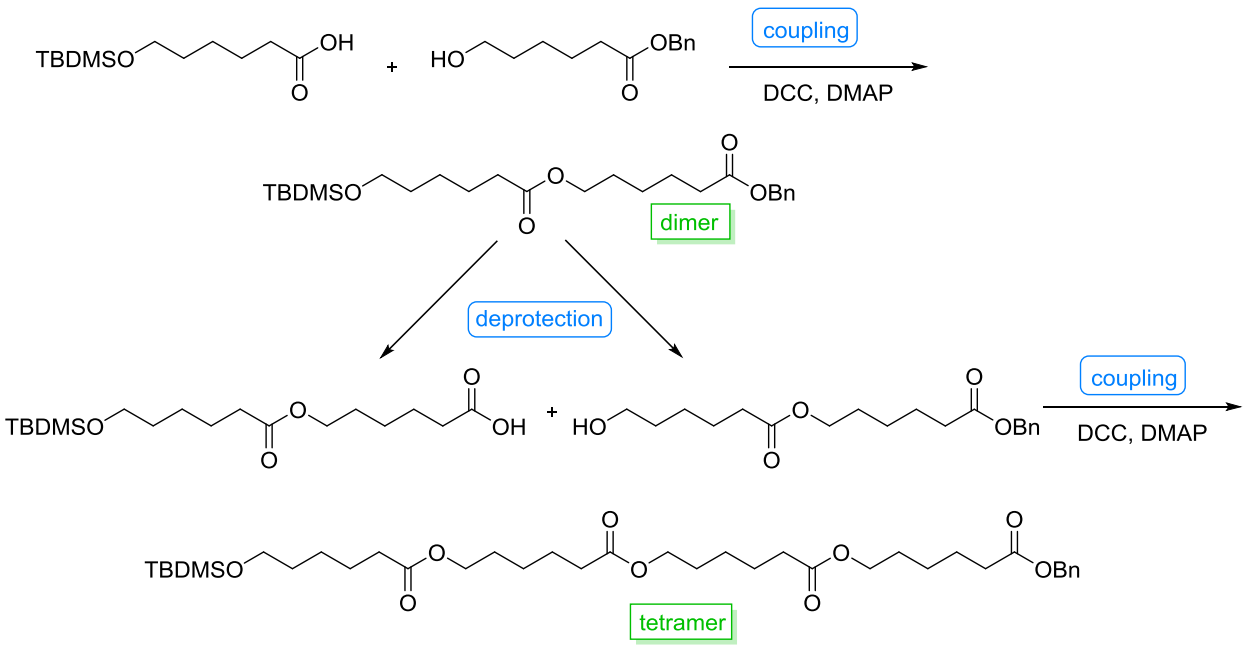


Figure 25: Exponential growth strategy towards monodisperse oligo-ε-caprolactones making use of orthogonal protecting groups.[73, 272]

The exponential growth allowed the synthesis of a monodisperse oligo-ε-caprolactone with a molecular weight of 7522 Da. However, the purity of the 64-mer reached only around 94 % and the efficiency of the couplings decreased with an increasing chain length.[272] Attractively, the physical properties of the monodisperse oligomers were compared with the properties of a commercially available, polydisperse sample revealing, for instance, differences in crystal sizes.[272] The same synthesis strategy was followed for the synthesis of oligo-(*L*)-lactides.[273] On the other hand, monodisperse oligomers were prepared on a polymeric support in a protecting-group free synthesis approach.[274] Therefore, Lutz and coworkers made use of two orthogonal reactions, namely the copper catalyzed 1,3-dipolar cycloaddition of azides and alkynes (CuAAC) and the amidification of carboxylic acids with primary amines.[274] Owing to the orthogonal reactions, which were applied iteratively, the synthesis of monodisperse trimers succeeds without the use of protecting groups and, attractively, the employed polymeric support could be cleaved afterwards.[274]

2.2.6 Synthesis of Sequence-Defined Macromolecules

2.2.6.1 Single-Unit Monomer Insertions (SUMI)

The basic idea of single-unit monomer insertions (SUMIs) is to reduce the reactivity in conventional RDRP processes drastically in order to enable the addition of a single monomer unit or to adjust the ratio of growing chains and monomers in a way that the addition of one single monomer unit is statistically possible.[275-278]

The first report on SUMIs for the synthesis of sequence-defined macromolecules was published in 2011 by Huang and coworkers.[275] Therefore, the low reactivity of allyl alcohol in ATRA reactions was used to introduce a single allyl alcohol unit to the chain end of the polymeric support. Though, the SUMI of allyl alcohol into ATRP-derived polymers was already described earlier in the context of polymer end group modifications.[279-280] In order to synthesize sequence-defined oligomers, the SUMI of allyl alcohol was followed by an Anelli oxidation using 2,2,6,6-(tetramethylpiperidin-1-yl)oxyl (TEMPO) and sodium hypochlorite as well as potassium bromide as secondary oxidants.[281] After oxidation of the alcohol to the corresponding carboxylic acid, the latter was esterified using isopropyl alcohol in combination with 1-ethyl-3-(3-dimethyl aminopropyl) carbodiimide (EDC) and DMAP. The esterification activated the chain end for another ATRA and therefore, the insertion of another monomer unit is enabled. However, around 20 % of the growing chains loose the bromine functionality during the ATRA reactions and therefore, only two successive ATRA reactions were completed successfully. Due to the use of a polymeric support, the loss of reactive endgroups resulted in hardly separable product mixtures, which were in the end purified by high-performance liquid chromatography (HPLC).[275]

Comparable to ATRA reactions as endgroup modification method for ATRP-derived polymers, SUMIs were investigated to modify the endgroups of RAFT polymers with maleimide groups, taking advantage of the unlikely homopolymerization of maleimide and maleic anhydride monomers.[282-285] Besides, also two sequential SUMIs were performed in a RAFT process. By the use of an electron poor monomer as first unit (*e.g.* vinyl phthalimide), followed by the addition of an electron rich and less activated

monomer (*e.g.* vinyl acetate), a dimer was synthesized.[286] In 2012, Tsanaktsidis *et al*. investigated different RAFT reagents for SUMIs of styrene and *N*-isopropylacrylamide and described the synthesis of dimers.[278] The concept of SUMIs in RAFT processes was further investigated by Junkers and coworkers, succeeding in the synthesis of a sequence-defined tetramer.[276] Here, the RAFT reagent, a radical initiator and ten equivalents of the first acrylate monomer are reacted in short reaction times and the product mixture (monomer, dimer and trimer) was purified by preparative recycling size-exclusion chromatography (SEC). In the preparative recycling SEC, the samples are continuously recycled and reinjected to the SEC system until the products are well separated.[276] The SUMI and recycling SEC were subsequently performed three more times using different acrylate monomers to finally obtain a sequence-defined tetramer. However, the coupling efficiencies decreased drastically with increasing chain length (from 55 % to 4 %) and the difficulty of the automated separation increased. Thus, larger numbers of SEC-cycles were necessary to fully separate the products. Moreover, large quantities of undesired sequences are produced and the overall yields of the desired products are very low (< 1 %). In 2015, the same group introduced a SUMI protocol making use of photo induced controlled radical additions.[277, 287] Photo reactions allow polymerizations at room temperature, thus minimizing side reactions, such as backbiting. Moreover, the photo-SUMI approach avoids the loss of Br-endgroups, which displayed a considerable problem in the ATRA approach of Huang *et al*.[275] Therefore, the photo induced controlled radical polymerization seemed to be an appropriate candidate for the synthesis of sequence-defined oligomers *via* SUMIs.[277] The photo-SUMI approach was then applied in the synthesis of a library of sequence-defined oligomers, which were synthesized by the use of different commercially available acrylate monomers. The products of each SUMI reaction were also purified by preparative recycling SEC. But also in the photo-SUMI approach the overall yields of the obtained tetramers and pentamers were very low (< 1 %), which is apparently due to the fast insertion of additional monomer units. However, also the oligomers that inserted for instance two monomer units of the respective acrylate were isolated and display sequence-defined oligomers, which might be useful.[277] Regarding yields, achievable chain lengths and workup procedures, the RAFT and the photo-SUMI processes are

comparable. Nevertheless, the mild reaction conditions for photo-SUMI approach reduce the thermally activated side reactions to a minimum.[277]

2.2.6.2 Template-Mediated Polymerizations

In the biosynthesis of DNA, the template mechanism plays an important role, arranging activated monomer units in the correct order to enable the biosynthesis of defined DNA sequences.[1] In biological systems, biocatalysts advance along the template strands affording the recognition of each monomer unit. In synthetic polymer chemistry, template systems mostly rely on DNA-templates, forcing the monomer units into a certain order and thus allowing the synthesis of targeted sequences.[288-290] On the other hand, there are also a few reports on non-DNA templated systems.[13, 291-293]

The basic idea of DNA-templated synthesis (DTS) is to bring reactive chain ends in near proximity by the hybridization of complementary DNA strands, thus allowing reactions to proceed even in very low concentrations (Figure 26).[294-295] Hereby, the reaction partners are bound to complementary DNA strands and upon hybridization of the DNA strands, the reaction is facilitated due to their near proximity, inducing a high local concentration of the reaction partners.

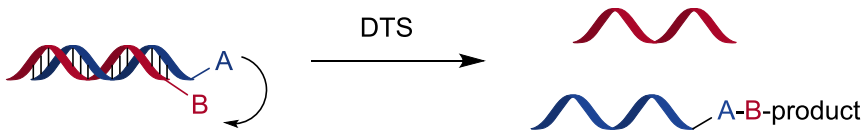


Figure 26: The DTS principle allows the reaction of A and B, due to their close proximity, which is evoked by the DNA-template.[73, 295]

The DTS principle is widely applied in organic synthesis. Pioneering work was done by Naylor and Gilham, who investigated oligonucleotide couplings in aqueous solution and Orgel *et al.*, who coupled peptide nucleic acids (PNA) on DNA-templates.[296-297] Lynn *et al.* reported on reductive aminations between modified DNA oligomers, whereas Liu and coworkers described the synthesis of structurally diverse products, making for instance use of Wittig reactions, reductive aminations, Heck-couplings and the Huisgen cycloaddition.[294, 298-299] In 2003, Liu and coworkers synthesized a sequence-defined PNA 20-mer by five successive reductive aminations of PNA tetramers.[288] Remarkably,

the use of mismatched codons at different positions along the sequence was investigated, resulting in truncated products and the obtained chain length depended on the position of the mismatched codon.[288] This concept was followed up and the group succeeded in the synthesis of a sequence-defined 60-mer by the consecutive coupling of twelve PNA building blocks.[300] Another interesting reversible coupling approach of oligonucleotides was reported by Saito and coworkers. The sequence-defined oligonucleotides were coupled by [2+2] cycloadditions of 3' pyrimidine and 5' vinyl deoxyuridine, forming cyclobutane linkages.[301-302] Moreover, the use of Wittig reactions for oligonucleotide couplings was investigated, applying a strand displacement system.[289, 303] The advantage of this system is the creation of the same reaction conditions for each coupling reaction, independent of the chain length of the growing chain. Therefore, the template is removed after the reaction by a "remover" DNA strand, which is added in excess in order to introduce another functional aptamer, which is able to react with the growing chain. With this strategy, the synthesis of tetramers and decamers was reported.[289, 303] The field of DNA-templated synthesis of sequence-defined macromolecules includes some more approaches, which were recently reviewed by Ten Brummelhuis.[14]

Another system allows the non-enzymatic translation of DNA-templates into sequence-defined synthetic macromolecules, which do not resemble nucleic acids.[13, 304] In this system, a synthetic polymer building block is bound reversibly to a PNA adapter, which can be recognized by the DNA template.[13] The recognition of the PNA adapters by the template allows the reaction of the reversibly bound polymer building blocks and thus the synthesis of sequence-defined macromolecules. By cleavage of the PNA adapter-molecules, the sequence-defined macromolecule can be released.[13] With this system, the synthesis of polymers of 26 kDa, containing 90 *β*-amino acid side chains by 16 consecutive coupling steps, was described.[13] Moreover, sequence-defined *α*-peptides and monodisperse polyethylene glycol were synthesized using this approach.[13]

Beyond that, some templated systems are reported, where the template does not rely on DNA. However, these non-DNA templated approaches are rare and do not always lead to sequence-defined macromolecules, but allow the synthesis of sequence-regulated structures.[293] Sawamoto *et al*. described the synthesis of a template *via* living cationic

polymerization by single monomer unit additions, which allows the recognition of specific monomers on the one hand, and their living radical polymerization on the other hand.[291-292, 305] The templates contain, for instance, amine groups as recognition site, allowing the preferred insertion of methacrylic acid over methyl acrylate in a living radical copolymerization of the two monomers.[291, 305] In another study, a crown ether moiety was introduced to the template, favoring the incorporation of sodium methacrylate over a monomer containing a cationic tertiary amine due to ionic interactions between the monomer units and the template.[292]

Although the template-based approaches are very elegant, they have the inherent disadvantage of small scale reactions (pmol to nmol scale for DNA-templated reactions and mmol scale for non-DNA templated reactions).[289, 292, 295] Moreover, most of the approaches are structurally restricted to DNA-like molecules.

2.2.6.3 Molecular Machines

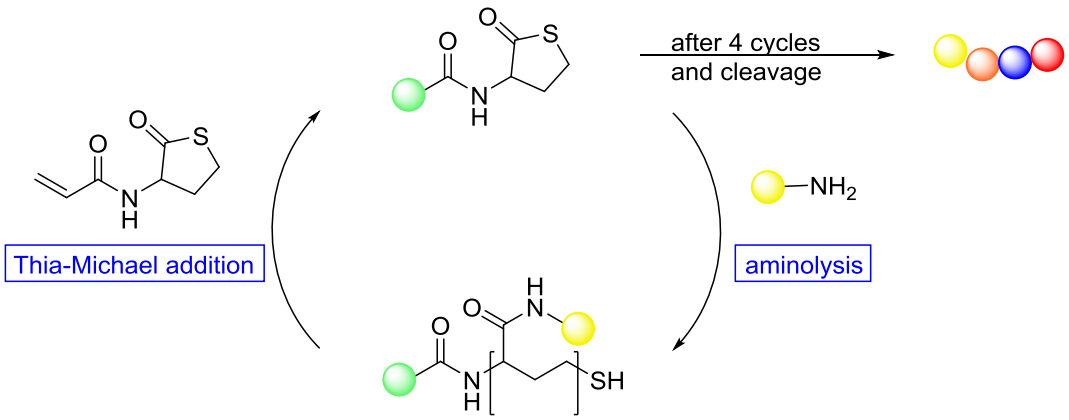
Leigh and coworkers reported on the synthesis of sequence-defined peptides using a rotaxane-based molecular machine.[306-307] Therefore, the desired amino acid sequence strand was synthesized and a macrocycle was designed, which is able to move along the strand, and to pick up the programmed amino acids by successive native chemical ligations. Once the final amino acid is removed from the strand, the macrocycle is cleaved from the synthesized peptide tetramer. Though this approach is highly elegant, the synthesis of the strand with the preprogrammed amino acid sequence displays a sequence-defined macromolecule itself, which needs to be synthesized in multiple steps. Furthermore, the products are obtained in milligram scale (2 mg) and the overall yields, considering every step, are very low (< 1 %).[306]

2.2.6.4 Solid Supported Synthesis

The synthesis of sequence-defined macromolecules on an insoluble resin is inspired by the polypeptide synthesis and takes advantage of simple product isolation by filtration.

[4-5] However, the obtained sequences are mostly separated by preparative HPLC in order to remove truncated and inaccurate sequences, which are formed in case of incomplete conversions or side reactions. Moreover, the solid phase synthesis only allows the synthesis of sequence-defined macromolecules on relatively small scale, which limits the applicability of the final products. However, the simplicity of the workup procedures and the possibility of automated processes make the synthesis on a solid support attractive in the field of sequence control.

An interesting approach, which enables the introduction of tailored side groups to the final sequence-defined macromolecules, was reported by Du Prez *et al.* in 2013.[308] Here, a resin bound thiolactone is ring opened by an aminolysis reaction and the intermediately obtained thiol is reacted with a thiolactone-acrylamide building block in a Thia-Michael addition. Hereby, a thiolactone functionality is introduced, which can be reacted in another iterative cycle of aminolysis and Thia-Michael addition (Scheme 6). By the use of different primary amines, tailored side chains can be introduced to the sequence-defined macromolecules. The use of the orthogonal aminolysis and the acrylate addition is beneficial, as it allows the synthesis of sequence-defined oligomers in absence of protecting groups.



Scheme 6: Synthesis of sequence-defined oligomers on a solid support: The aminolysis of the thiolactone and the subsequent Thia-Michael addition are conducted iteratively, thereby, desired side chains can be introduced by the choice of the amine component. Upon reaching the desired sequence, the oligomer can be cleaved from the resin.[308]

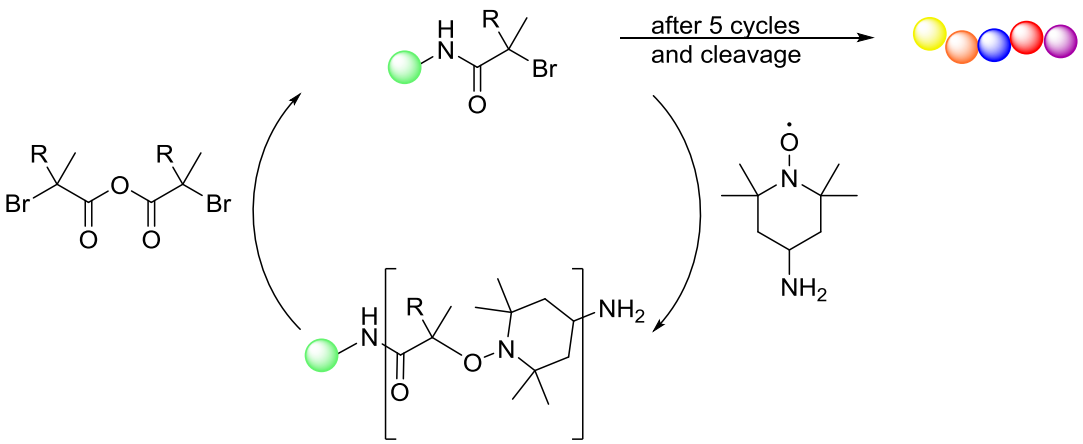
The reactions were carried out using 200 mg of the 2-chlorotrityl chloride resin, indicating small scale reactions. However, there is no information on the isolated yields of the sequence-defined tetramer.

On the other hand, Lutz and coworkers synthesized "molecularly encoded" oligomers by iterative amidifications and 1,3-dipolar cycloadditions on a Wang resin.[274, 309] For this purpose, 4-pentynoic acid and 2-methyl-4-pentynoic acid were defined as "0" and "1" bits, allowing the synthesis of different sequence-defined oligomers, which are in principle readable *via* MS/MS techniques and thus molecularly encoded.[19, 309] The applied strategy is an "AB + CD" strategy meaning that two different *bis*functional monomers are reacted iteratively applying orthogonal reactions and thereby avoiding the use of protecting groups. Here, the AB-monomer is, for instance, 4-pentynoic acid, bearing an acid and an alkyne functionality, whereas the CD-monomer is equipped with an azide and an amine functionality. Using this approach, sequence-defined trimers were obtained, but there is no report on the obtained yields. The obtained sequences were later on analyzed by tandem MS/MS techniques in order to read out the synthesized sequences.[310]

Inspired by the synthesis of biological polymers, Sleiman, Serpell and coworkers synthesized sequence-defined macromolecules appended to DNA using the chemical oligonucleotide synthesis (compare chapter 2.2.2.3).[195-196] First, the DNA sequence was synthesized in a conventional DNA synthesizer and subsequently, two different, non-natural phosphoramidite monomers were added iteratively in order to synthesize the sequence-defined macromolecules appended to DNA. The monomers were hydrophobic (hexaethylene-phosphoramidite) and hydrophilic (hexaethylene glycol-phosphoramidite) and the self-assembly behavior of the obtained materials was investigated. In this study, sequence-defined dodecamers were synthesized. Due to indifferent yields of the coupling steps (compared to commonly used phosphoramidites in oligonucleotide syntheses) it was discussed that also longer sequences of up to 100 monomer units should be obtainable using this approach.[196] Later on, the same group investigated the influence of the sequence-defined oligomers appended to DNA on the formation of three-dimensional self-assemblies.[311] This idea was taken up by Lutz *et al.* who synthesized non-natural polyphosphates on an insoluble polystyrene support.[197] Taking

advantage of the already very well optimized synthesis procedures for oligonucleotides, a sequence-defined 24-mer was isolated in an overall yield of 87 % (no information on the reaction scale).[197] By the use of different phosphoramidite monomers it was possible to introduce alkyne functions, allowing the post-polymerization modification *via* CuAAC. Lutz and coworkers aimed for the synthesis of encoded sequences and defined two different monomers as "0" and "1" bits, targeting the application of sequence-defined macromolecules in the field of data storage. The proposed read-out strategies include tandem mass spectrometry,[312] nuclear magnetic resonance spectroscopy (NMR) as well as depolymerization methods and are discussed in detail in a recent minireview.[21] In this study, the solid-phase synthesis was conducted manually,[197] contrary a sequence-defined non-natural polyphosphate with a degree of polymerization (DP) above 100 was synthesized making use of a conventional DNA synthesizer.[313] Here, the synthesis protocol established by Beaucage and Carothers (Scheme 5) was applied, but non-natural phosphoramidites served as monomers.[195, 201] By the use of two different phosphoramidite-monomers (defined as "0" and "1" bits), sequence-defined polyphosphates of different chain lengths (DPs of 16, 24, 56, 104) and different sequences were synthesized and analyzed by mass spectrometry and HPLC.[313]

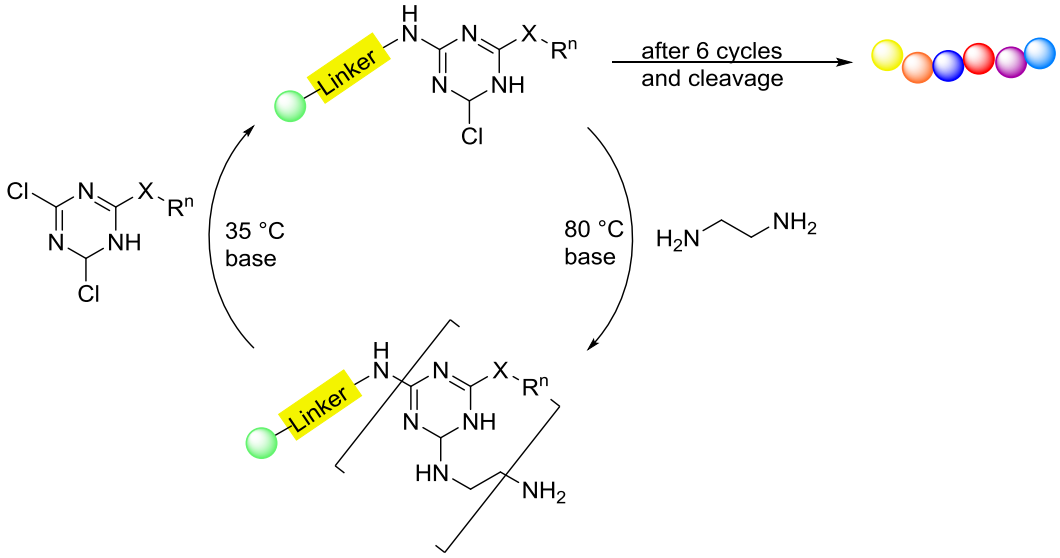
Another approach includes the synthesis of oligo(alkoxyamine amide)s *via* an "AB + CD" iterative approach, with an AB-monomer that contains an amine and a nitroxide functionality and a CD-monomer that contains an anhydride and an alkyl bromide functionality.[314] The iterative reaction of an amine with an anhydride and a nitroxide with an alkyl bromide allows the synthesis of sequence-defined and thermally degradable macromolecules (Scheme 7).



Scheme 7: Synthesis of sequence-defined oligo(alkoxyamine amide)s by iterative reactions of primary amines with symmetric anhydrides and alkylbromides with nitroxides.[314]

It was shown that the sequence-defined oligomers are thermally degradable, due to the thermally labile alkoxyamine bond. The thermal degradation of the sequence-defined macromolecules allowed the MS-analysis of the obtained fragments and thus, the decoding of the synthesized sequences.[314] In order to avoid the formation of many different products upon thermolysis of the sequence-defined materials, TEMPO was added in large excess as a spin trap, resulting in the formation of easily analyzable fragments.[314] The overall yields in this approach reached 24 % for the synthesis of a sequence-defined tetramer on a cleavable soluble polymer support; but there is no report on the obtained overall yields for the solid phase synthesis. The obtained sequence-defined and encoded oligomers were subsequently investigated in detail using MS/MS techniques in the positive and negative mode in order to study the fragmentation behavior.[312, 315] The fragmentation behavior in the positive and negative mode were found to follow the same pathways: The labile C-ON bonds dissociate and the thereof obtained fragments allow sequencing of the oligomers.[312, 315] Moreover, the same group reported on the synthesis of sequence-defined oligomers by a convergent approach.[316] Here, dyad-monomers were synthesized, subsequently coupled on a solid support and a 10-mer was obtained in an overall yield of 31 % (no information on the reaction scale). However, due to side reactions and incomplete conversions, the obtained products were not monodisperse and the authors suggest capping steps (comparable to the oligonucleotide synthesis) and HPLC purification in order to obtain oligomers of high purity, which would in turn decrease the final yields drastically.

Very recently, a novel synthesis approach towards sequence-defined macromolecules was reported, allowing the introduction of tailored side chains along with specific non-covalent backbone interactions.[317] This approach makes use of the nucleophilic substitution of cyanuric chlorides in such a way, that each reaction deactivates the cyanuric chloride compound, making elevated temperatures necessary for further reaction steps (Scheme 8).



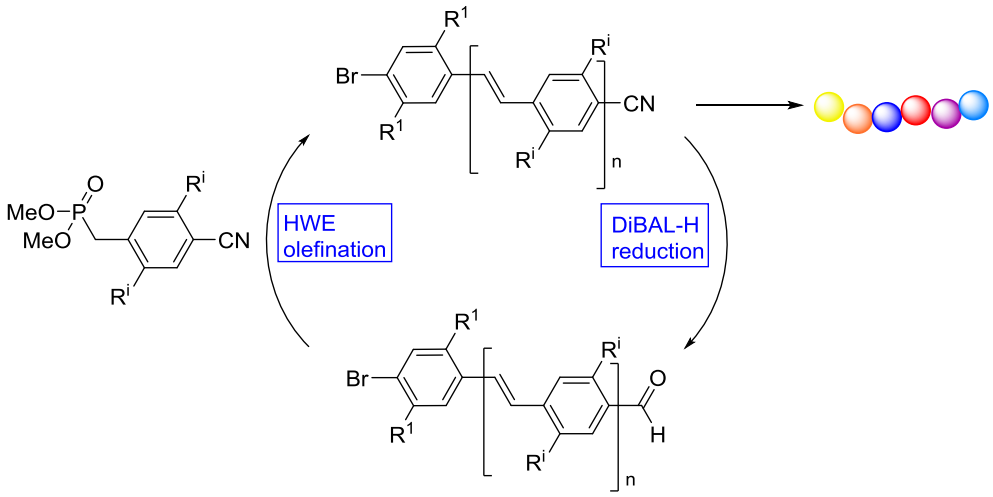
Scheme 8: Synthesis of triazine-based sequence-defined macromolecules making use of nucleophilic substitutions of cyanuric chloride. Upon reaction, the cyanuric chloride is deactivated allowing further reactions only at elevated temperatures.[317]

In order to synthesize diversely substituted, monodisperse and sequence-defined macromolecules, different mono-substituted cyanuric chloride submonomers were synthesized and incorporated. Owing to the deactivation of the cyanuric chloride submonomer upon reaction, this approach does not require protecting groups for the synthesis of the sequence-defined materials. Moreover, molecular dynamics simulations show backbone interactions, such as hydrogen bonding and *π*-*π*-interactions, which might be interesting in terms of intermolecular self-assembly and the formation of three-dimensional structures.[317] The synthesis of sequence-defined hexamers was reported and the overall yields were relatively high (between 43 and 75 %). However, due to the solid phase synthesis, the products were only obtained in milligram scale (~ 50 mg).[317]

2.2.6.5 Solution-Phase Synthesis

Solution-phase approaches include the synthesis of sequence-defined macromolecules on a soluble polymer support as well as conventional oligomer synthesis in solution. Solution-phase syntheses take advantage of easily scalable reactions, straightforward analysis methods for the obtained products and simple reaction protocols. However, the workup is often demanding and time consuming.

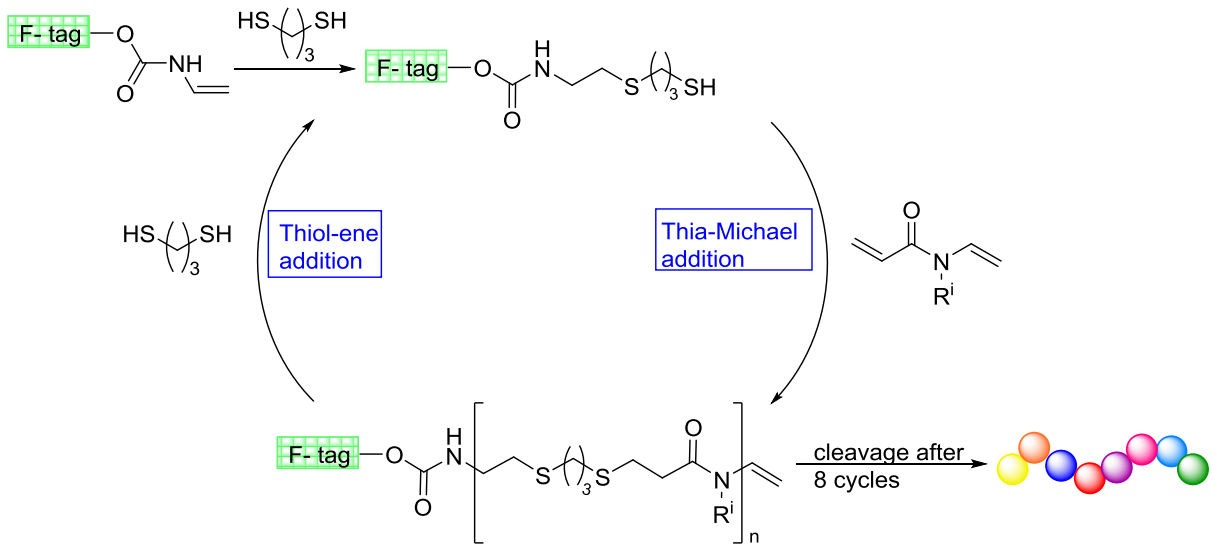
Meyer and coworkers synthesized sequence-defined oligo(*p*-phenylene-vinylene)s (OPVs) in solution and varied the sequence of electron-poor (non-substituted *p*-phenylene-vinylene) and electron rich (dialkoxy-substituted *p*-phenylene-vinylene) monomers in order to investigate sequence-property realtionships.[318] The aim was to find optimal optical, energetic and charge-transfer properties for π-conjugated polymers, which are promising candidates for organic photovoltaics.[319-320] Moreover, OPVs are well known for the substituent-dependent optoelectronic properties.[321] The synthesis strategy of the sequence-defined OPVs includes *E*-selective Horner-Wadsworth-Emmons (HWE) olefinations followed by the reduction of cyanides to the corresponding aldehydes using diisobutylaluminium hydride (DIBAL-H), allowing another cycle of HWE reactions and subsequent reductions. The synthesis strategy towards sequence-defined OPVs is shown in Scheme 9.



Scheme 9: Synthesis of sequence-defined OPVs by iterative cyanide reductions using DIBAL-H and HWE olefinations.[318]

The HWE reaction using cyanide monomers and the subsequent reduction is favorable in terms of *E*/*Z*-selectivity compared to the previously reported acetal-deprotection strategy, which was applied in the synthesis of monodisperse macromolecules.[268, 318] The synthesized hexamers were obtained in overall yields between 21 and 49 % and the reactions were conducted in milligram scales, yielding between 65 and 150 mg of the products. Though, it has to be noted that the tetramers were synthesized on gram scales and the yields for each step decreased with an increasing chain length due to solubility issues.[318]

Another interesting solution phase-approach towards sequence-defined macromolecules was introduced by Alabi and Porel, who employed fluorous tags as soluble supports, taking advantage of the simple isolation of the sequence-defined materials.[322-323] In this approach, Thiol-Ene additions and Thia-Michael reactions are conducted iteratively, allowing the protecting-group-free synthesis of sequence-defined oligomers with tailored side-chains, which can be introduced by the use of different *N*-substituted acrylamide monomers in each cycle (Scheme 10).

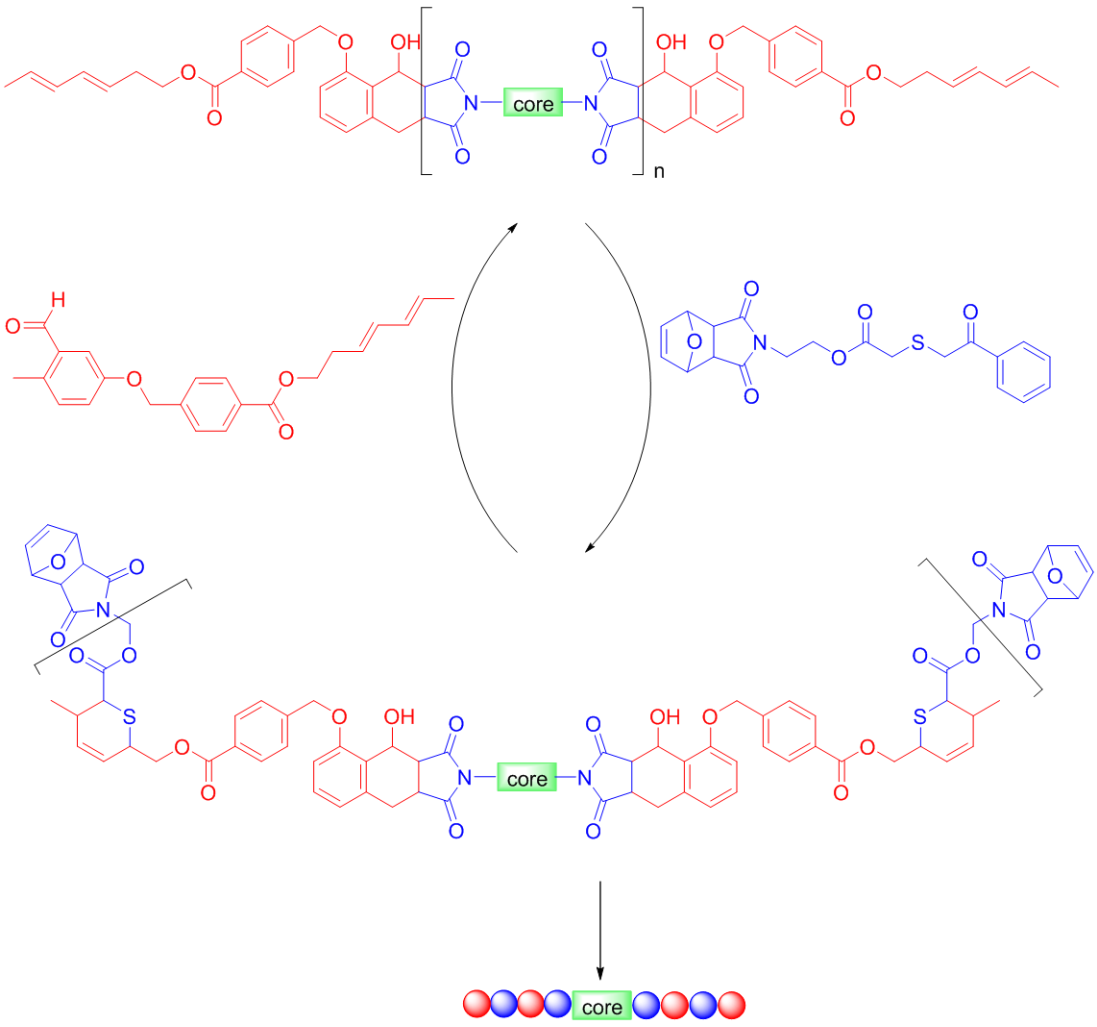


Scheme 10: Synthesis of sequence-defined macromolecules by the iterative application of Thia-Michael additions and Thiol-Ene additions on a soluble and cleavable fluorous tag-support, which allows the simple purification of the desired products.[322]

Applying this approach, sequence-defined octamers were obtained and characterized by NMR and mass spectrometry. Furthermore, the sequence was proven by tandem MS/MS spectrometry. The yield of a sequence-defined pentamer was 68 % after cleavage of the fluorous tag, but there is no information about the reaction scales. Moreover, the synthesis of sequence-defined macrocycles on a fluorous support, using the same strategy, was recently reported.[324] Hereby, the cleavage from the fluorous support goes hand in hand with a acetal deprotection of a side chain, allowing the formation of the macrocycle by oxime formation. Interestingly, the macrocycles bear biologically active side chains, permitting the investigation how the side-chain and main chain sequence as well as the size of the macrocycles influence the antibacterial activity.[324]

A photochemical pathway towards sequence-defined macromolecules was investigated by Barner-Kowollik *et al*. in 2015 (Scheme 11).[325] Photochemical reactions take advantage of temporal- and spatial control. Moreover the reactions can be conducted at room temperature, enable high yields and equimolar amounts of the reactants, which altogether make photochemical approaches interesting candidates for the synthesis of sequence-defined materials.[326-327] In the presented approach, a symmetric core unit, equipped with two maleimide functions, served as starting substrate for the synthesis of

a symmetric, sequence-defined decamer (Scheme 11).[325] Upon photochemical activation of the phenacylsulfide (blue monomer in Scheme 11), a dienophile is formed, which is able to react with the sorbyl-ester derivative. The obtained protected maleimide is deprotected by the thermally activated retro-Diels-Alder reaction enabling the Diels-Alder reaction (DAR) with an activated photoenol-monomer (red monomer in Scheme 11).



Scheme 11: Photchemical synthesis of sequence-defined macromolecules via two different photoreactions. The reaction of the photoenol with the maleimide takes place after the thermally activated retro-Diels-Alder-deprotection of the furan-protected maleimide and photochemical activation of the photoenol. The phenacyl sulfide reacts subsequently with the sorbyl moiety upon photochemical activation.[325]

The photoenol-monomer contains the sorbyl-group, allowing the iteration of the reaction steps and thus the synthesis of sequence-defined macromolecules. The reactions (starting from the trimer) were conducted in a 150 mg scale and the overall yield (seven reaction steps) of the sequence-defined decamer reached 1.2 %.

Beyond that, the convergent synthesis of oligo(triazole amide)s on a soluble and on a cleavable polystyrene support, by iterative amidifications of carboxylic acids with amines and copper catalyzed azide-alkyne 1,3-dipolar cycloadditions, was reported.[328] The same approach was described for the solid phase and the polymer-supported synthesis of sequence-defined macromolecules adding the sub-monomers in a stepwise manner.[274] The convergent approach allowed the synthesis of sequence-defined octamers by subsequent reactions of dyads or tetrads but there is no information on reaction scales and obtained yields.

In 2015, Johnson and coworkers developed an interesting and scalable approach for the synthesis of sequence-defined macromolecules by the iterative exponential growth (IEG) strategy (compare Figure 25).[329-330] IEG approaches usually take advantage of orthogonal deprotection reactions, allowing the coupling of *α*-*ω*-end functionalized molecules, thereby doubling the molecular weight of the obtained products.[331-332] This novel approach describes the semi-automated coupling of ester monomers.[329] Therefore, an appropriate monomer was synthesized, bearing an alkyl bromide, which can be substituted with sodium azide and a triisopropylsilyl (TIPS) protected alkyne, which can be orthogonally deprotected using a fluorine reagent, such as tetrabutylammonium fluoride (TBAF). The flow-IEG system allows the separation of the monomer in two parts, the orthogonal deprotection, an in-line purification of the deprotected monomers as well as their subsequent coupling by CuAAC (Figure 27). The coupled product was collected, purified by column chromatography and subjected to another flow-IEG cycle. Using this approach, 600 mg of a monodisperse octamer were prepared in an overall yield of 58 %. However, the increasing chain length of the monodisperse oligomers resulted in solubility issues due to crystallization. Therefore, the use of a second, ethylene-glycol-based comonomer allowed the synthesis of sequence-defined hexadecamer. The use of the ethylene-glycol monomer solved the solubility problem but worse yields were reported, without mentioning exact values. The lowering

of the isolated yields was explained by side reactions (Glaser-coupling of the alkyne-monomer), incomplete conversions and increased partitioning of the oligomers into the water phase during the in-line purification owing to the increased water solubility introduced by the ethylene glycol monomer.

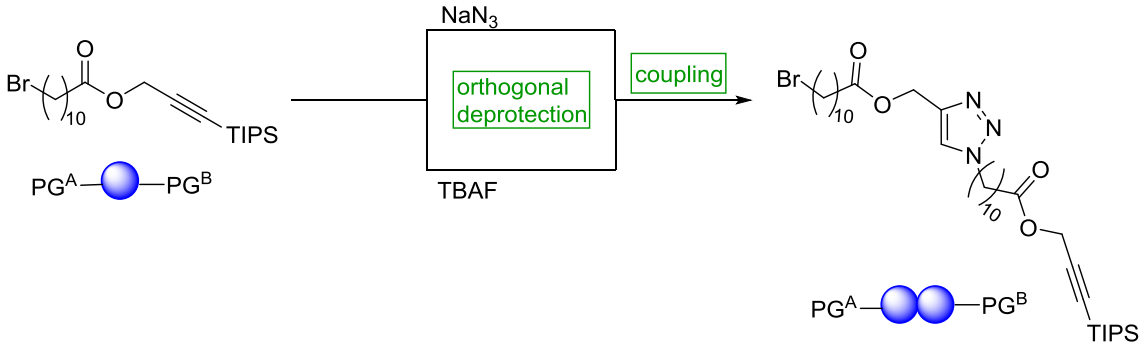


Figure 27: Flow-IEG strategy allowing the orthogonal deprotection, the in-line purification and the coupling in a continous flow system. (PG = protecting group, TBAF = tetrabutylammonium fluoride, TIPS = triisoproplsilyl)[329]

However, the semi-automated flow-IEG approach is promising in terms of scaling up, enabling the synthesis of sequence-defined macromolecules on a larger scale and to allow the investigation of structure-property-relationships of the sequence-defined products. The same group developed a modified approach, offering the possibility to control chain lengths, sequence and stereoconfiguration of the obtained macromolecules.[330] Therefore, the previously reported approach was slightly altered.[330] Here, chiral *tert*-butyl dimethylsilyl (TBS) protected epoxy-alkynes were regioselectively ring-opened by an azide anion, affording the azide group along with a secondary hydroxyl functional group. The secondary hydroxy group can be esterified in order to introduce the desired side-chain, whereas the azide can be used for the chain elongation by addition of a deprotected alkyne-monomer. The control over the stereoconfiguration is accomplished by the use of enantiopure epoxide-monomers, which can be synthesized from epichlorohydrine and propargyl alcohol, whereas the sequence can be controlled by the side chain modification of the secondary hydroxy function. In the presented approach, benzyl and acetyl groups were introduced and an alternating 16-mer was synthesized in an overall yield of 26 %. Moreover, a monodisperse, syndiotactic 32-mer was synthesized in 16 steps in an overall yield of 16 %. The authors discuss their approach in the context of large scale synthesis and indeed, the dimer synthesis was conducted in six gram scale, however, the 16-mers and

32-mer were synthesized in 600 mg and 140 mg scale, respectively. Although the scales of the reactions for larger oligomers were not really high, the strategy is auspicious, allowing the control over multiple parameters.

Very recently, Sawamoto et al. described the design of a sophisticated system, making use of repetitive and iterative radical intramolecular cyclizations.[333] The employed system carries two types of reversibly cleavable bonds: a *N*-hydroxysuccinimidyl ester (NHS), which can be cleaved upon reaction with a primary amine and a *ortho*-pyridyl disulfide (Py-SS), which can be cleaved in the presence of an excess of alkyl thiols. The regeneration of the NHS is accomplished by the esterification with acid halides, whereas the disulfide can be regenerated by the reaction with activated disulfides. Upon the reversible ring-opening of the employed system, the intramolecular radical monoaddition of an acrylate-monomer is enabled and the macromolecule is elongated by the subsequent ring-closing of the system. This cycle was successfully conducted at both cleavable sites of the cyclic system and the synthesis of a sequence-defined trimer in an overall yield of 74 % (~ 60 mg scale) was reported.[333]

3 Aims

The aim of this work was to investigate and develop novel approaches for the synthesis of sequence-defined macromolecules based on efficient IMCRs in solution. Therefore, the preliminary results, obtained during the diploma thesis studies, served as starting point.[73] The stepwise synthesis of sequence-defined macromolecules in solution has certain requirements, which need to be fulfilled by the developed approaches. In fact, the reactions have to reach full conversion to enable high yields, ideally in absence of side reactions. Moreover, the product isolation must be straightforward and the products need to be isolated in high purity. Finally, the synthesis of considerable amounts of the sequence-defined materials is an important goal in order to provide enough material to establish sequence-property-relationships in the future and to aim for certain applications, for instance as active ingredients in pharmaeuticals. For the synthesis of sequence-defined macromolecules using isocyanide-based multicomponent reactions, three different approaches were developed and two different IMCRs were investigated. First, a protecting-group-free approach was explored, which is based on orthogonal reaction conditions for the IMCR and the subsequent Thiol-Ene addition. Hereby, the P-3CR as well as the U-4CR were investigated and different sequence-defined macromolecules were synthesized in high overall yields and purities in multigram scale. Remarkably, the U-4CR allowed "dual side chain control" because two different and selectable side chains could be introduced in one MCR-step. Secondly, a mono-protected AB-monomer, suitable for the P-3CR and the U-4CR, was designed and synthesized in order to improve the reaction conditions and to avoid side-reactions. The monomer-approach revealed that the workup of the sequence-defined materials could be simplified and thus the synthesis of longer sequences was enabled. Moreover, the approach served as synthesis protocol for sequence-defined materials on a multigram scale. Finally, a convergent synthesis approach was investigated, combining thiolactone chemistry and multicomponent reactions. The synthesis of a small library of oligomeric building blocks was accomplished and their subsequent coupling by a multicomponent reaction was investigated.

4 Results and Discussion

4.1 Synthesis of Sequence-Defined Macromolecules by Protecting-Group-free Approaches

In this section, the synthesis of sequence-defined oligomers by protecting group-free approaches is discussed. The avoidance of protecting groups can be achieved by the iterative application of orthogonal reactions. Comparable to the submonomer approach developed by Zuckermann *et al.* (see introduction chapter 2.2.2.2) two different, orthogonal reactions are performed iteratively.[147] The approaches described herein for the U-4CR and the P-3CR make use of an aldehyde component bearing a terminal double bond. This terminal double bond can subsequently be functionalized in an efficient Thiol-Ene addition using, for instance, 3-mercaptopropionic acid. This end-group modification enables another MCR and by stepwise iterative reactions, sequence-defined oligomers of high purity can be synthesized. The following sections describe the synthesis procedures in detail and discuss the analytic results of the sequence-defined products.

4.1.1 Synthesis of Sequence-Defined Macromolecules by the Passerini-Thiol-Ene Approach

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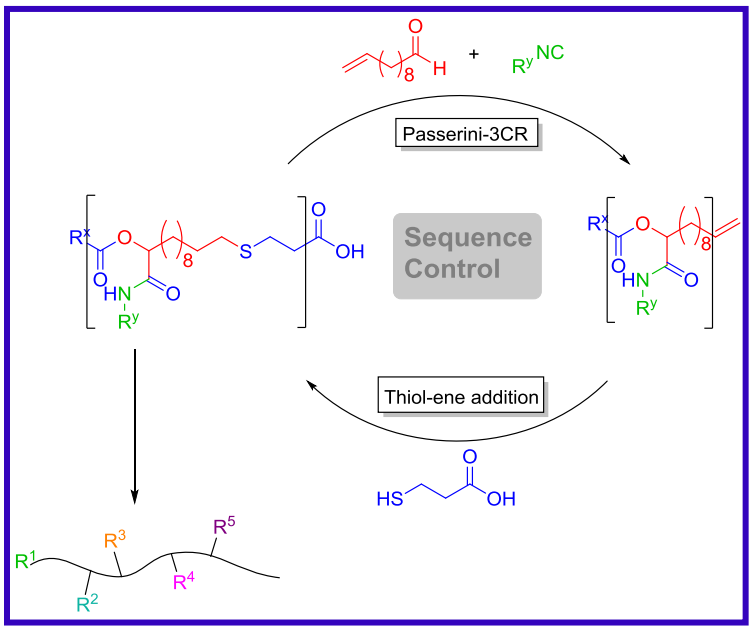
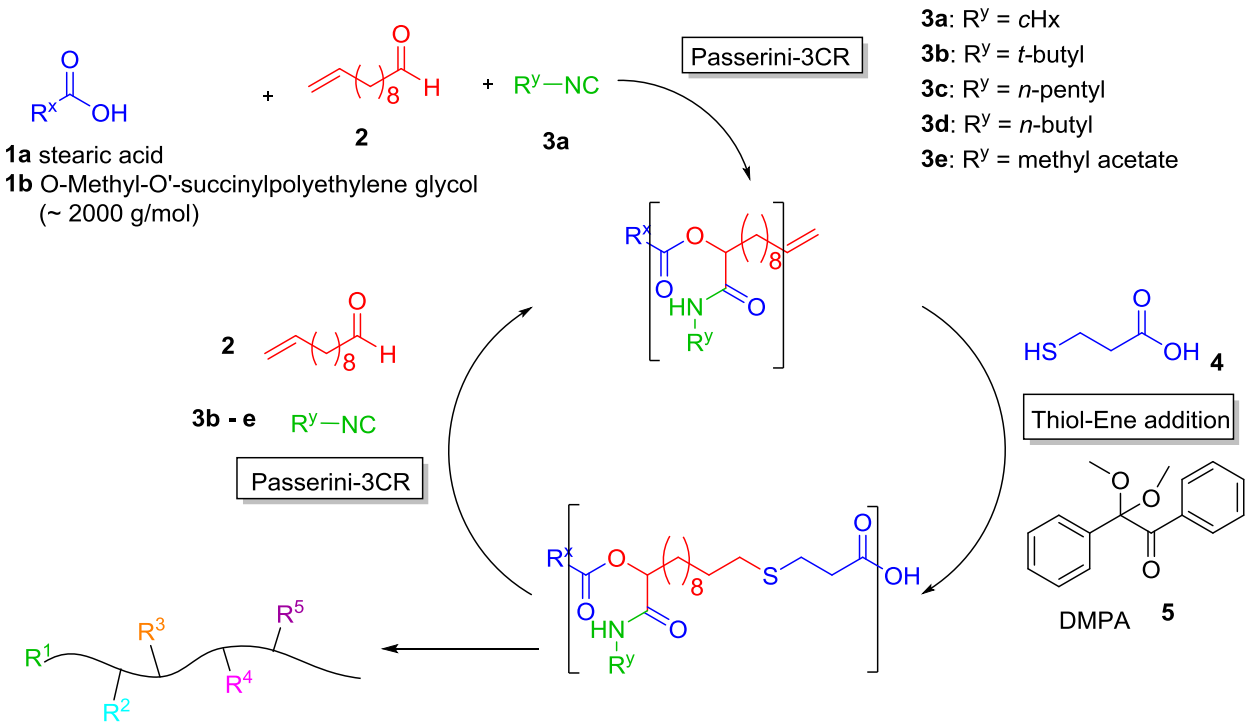


Abstract:

A new strategy to achieve sequence control in polymer chemistry based on the iterative application of the versatile Passerini three-component reaction (P-3CR) in combination with efficient Thiol-Ene addition reactions is described within this chapter. First, stearic acid was used as a starting substrate to build up a sequence-defined pentamer with a molecular weight of 2022.13 gmol^{-1}. Using an acid-functionalized PEG allowed for an easier isolation of the sequence-defined macromolecules by simple precipitation and led to a sequence-defined pentamer in a block-copolymer architecture. Importantly, this novel strategy completely avoids protecting group chemistry. By following this strategy, a different side chain can be introduced in each MCR step to the polymer/oligomer backbone in a straightforward fashion and at a defined position within the macromolecule.

Within this chapter, the synthesis of a sequence-defined pentamer as well as the synthesis of a block-copolymer bearing a sequence-defined pentamer block is described. In order to achieve sequence control, orthogonal reactions were applied iteratively to synthesize the sequence-defined macromolecules in a stepwise manner without the utilization of protecting groups. In this aspect, the versatile P-3CR and the efficient Thiol-Ene addition reaction proved to be a powerful combination. Applying this approach, the introduction of different side chains to each monomer unit was achieved by simply employing different isocyanides in each step of the P-3CR (Scheme 12). By the use of 10-undecenal **2** in the P-3CR a terminal double bond is introduced, enabling a subsequent Thiol-Ene addition with 3-mercaptopropionic acid **4** and thus another cycle of a P-3CR and a Thiol-Ene addition is possible for further chain elongation.



*Scheme 12: Synthesis of a sequence defined pentamer (starting from **1a**) or a sequence-defined block-copolymer (starting from **1b**) by iterative application of the P-3CR and the Thiol-Ene addition reaction.*

Compared to other sequential approaches (i.e. polypeptide synthesis), this strategy has several advantages. The use of coupling or activating reagents is avoided and protecting groups are not necessary for the backbone synthesis. Furthermore, there is no need of using different monomers to achieve sequence-control and to introduce different and

tailored side chains to the polymer chains. These facts make this approach versatile (easy choice of side groups), scalable, as well as more efficient and sustainable since less waste is produced.

First, the P-3CR of stearic acid **1a** with **2** and **3a** was investigated and optimized. Therefore, THF and dichloromethane (DCM) were used as solvents and different concentrations of the reactants were investigated (Table 1). The reactants **1**, **2** and **3a** were used in a 1:1:1 ratio and the reactions were followed by GC to determine the conversion of **2**.

*Table 1: Comparison of THF and DCM as solvents in the Passerini-3CR (at room temperature) of **1a** with **2** and **3a** (1.0 eq. of **1a**, **2** and **3a**, respectively).*

entry	concentration [a]	conversion (THF) /% [b]	conversion (DCM) /%[b]
1	0.18 M	3.40	70.6
2	0.25 M	4.40	80.1
3	0.35 M	15.0	86.9
4	0.59 M	37.7	91.8
5	1.19 M	66.6	95.9

[a] concentration of **1a** in mmol/ mL solvent. [b] conversion of **2** was determined by GC after 5 hours reaction time, using 10 mol% tetradecane as internal standard.

The results revealed that high concentrations of the reactants resulted in higher conversions within shorter reaction times and higher yields and that the reaction proceeds faster in DCM. However, when using an equimolar ratio of the reactants **1**, **2** and **3a**, traces of **1a** were observed in the obtained product after recrystallization, indicating incomplete conversion. Therefore, in order to ensure full conversion of the carboxyl groups, **2** and **3a** were used in a 1.5-fold excess. Full conversion of the carboxyl groups is essential in order to facilitate the workup procedures after each P-3CR and to maximize the resulting yields. After this short optimization, the conditions for the Thiol-Ene addition reaction were examined, revealing that highest yields can be obtained by using a five-fold excess of the thiol **4**, 5.0 mol% 2,2-dimethoxy-2-phenylacetophenone (DMPA) **5** as initiator and irradiation with UV-light for two hours. The optimization of the reaction conditions as well as the synthesis of a sequence-defined tetramer were part of a diploma thesis.[73] However, these basic insights were of great importance for the whole research project and therefore they were also discussed in this part.

These optimized procedures were used in the further synthesis steps of a sequence-defined pentamer on a larger scale (5.1 g of the pentamer **14**) and also in the synthesis of a block-copolymer having a sequence-defined pentamer-block **23**. Using the previously optimized reaction conditions, the sequence-defined pentamer **14** (Figure 28) with a molecular weight of 2022.13 g/mol was prepared in nine reaction steps in an overall yield of 22 %.

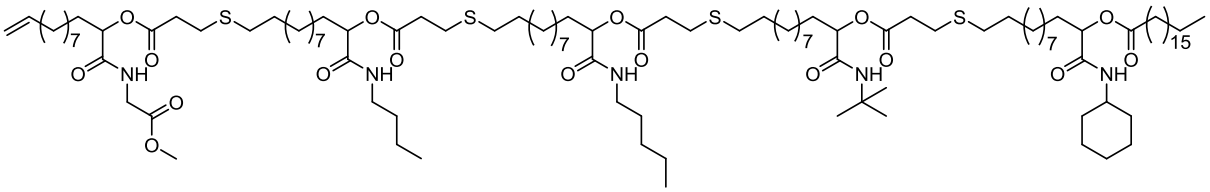


*Figure 28: Structure of the obtained sequence-defined pentamer **14** having five different side chains attached.*

The results obtained after each synthesis step of the sequence-defined pentamer **14** are summarized in *Table 2*. The reaction times for the P-3CR were between 15 and 48 hours, and for the Thiol-Ene addition between two and six hours. The isolated yields are high and the analytically found masses are in very good agreement with the calculated values.

*Table 2: Summary of the results obtained after each synthetic step in the synthesis of the sequence-defined tetramer **14**.*

reaction (product)	reaction time /hours	yield /%[a/b]	exact mass calculated	mass found
1st P-3CR (**6**)	24	96[a]	562.5	562.5
1st Thiol-Ene addition (**7**)	2	95[a]	668.5	668.5
2nd P-3CR (**8**)	14	97[b]	919.8	919.6
2nd Thiol-Ene addition (**9**)	2	84[a]	1025.8	1025.7
3rd P-3CR (**10**)	30	64[b]	1290.0	1290.8
3rd Thiol-Ene addition (**11**)	3	98[a]	1396.0	1396.5
4th P-3CR (**12**)	18	81[b]	1648.2	1648.6
4th Thiol-Ene addition (**13**)	6	85[a]	1755.2	1755.4
5th P-3CR (**14**)	48	68	2020.4	2020.8

[a] after recrystallization; [b] after column chromatography

The NMR-data of the obtained products show the success of each experimental step by the appearance of characteristic signals and appropriate integrals for the introduced amide protons after the P-3CR and the absence of double bond signals after the Thiol-Ene addition reaction (Figure 29), respectively. Figure 29 shows the obtained ^{1}H NMRs for the products of the first Passerini reaction (Figure 29, top) and the first Thiol-Ene addition (Figure 29, bottom) as an example.

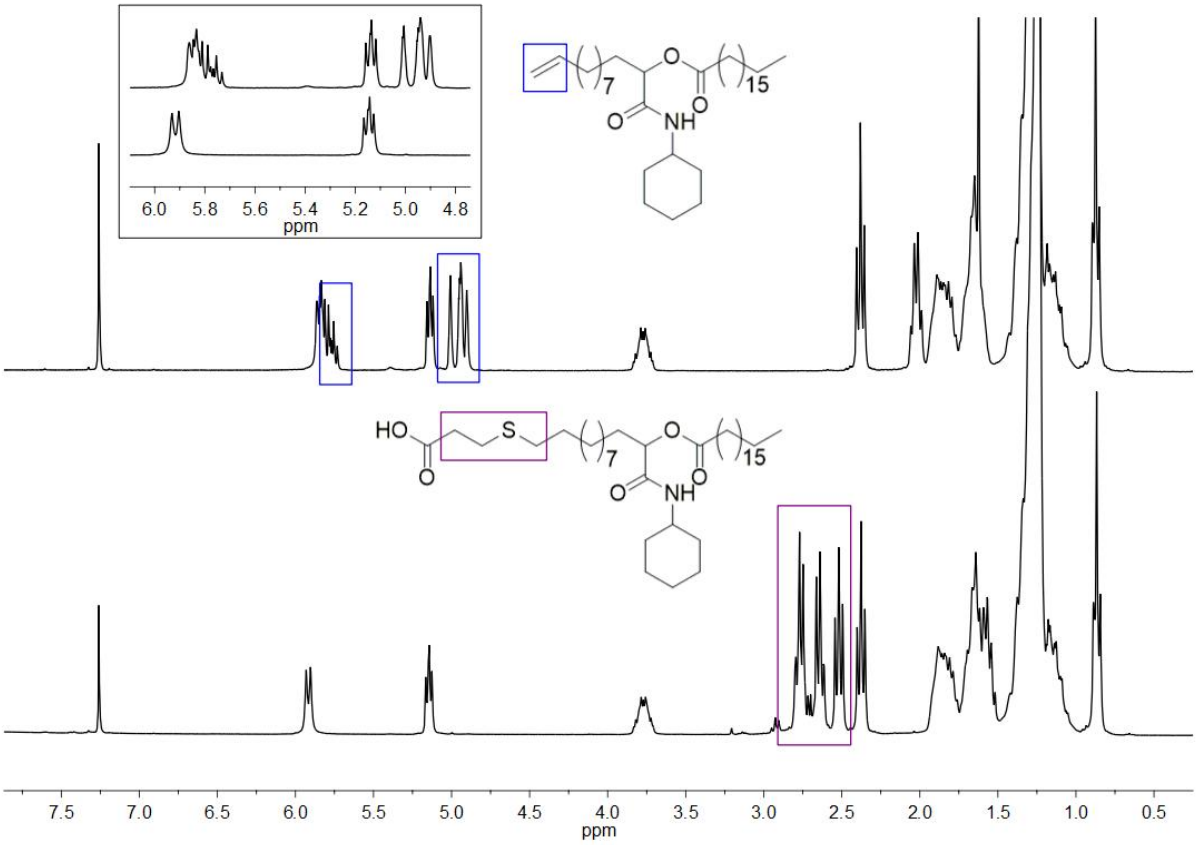


*Figure 29: Comparison of the NMR spectra obtained for the product of the first P-3CR (**6**) (top) and the product of the first Thiol-Ene addition (**7**) (bottom). The disappearance of the signals of the double bond (zoom-box and blue boxes) and the appearance of the thioether signals (purple box) can clearly be seen.*

Gel Permeation Chromatography (GPC) analysis (Figure 30) of the obtained products further demonstrates the successful formation of the desired products and verifies the high purity of the products by the shifting towards higher molecular weights (lower retention times) after each step and the absence of low molecular weight by-products.

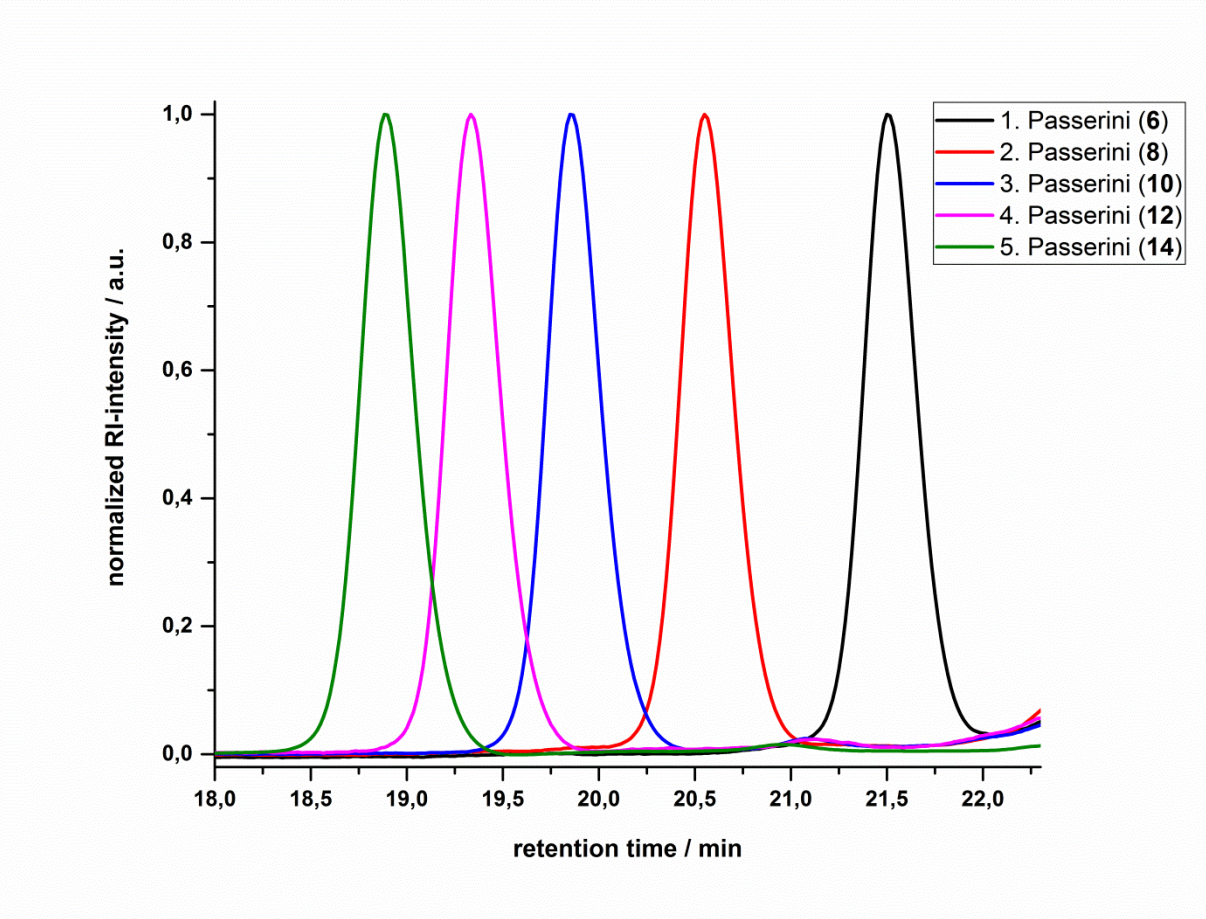


Figure 30: GPC traces of the obtained products after each P-3CR. To make it well arranged, the GPC traces for the products of the Thiol-Ene additions were left out.

The successful synthesis of **14** in an overall yield of 22 % (nine steps) revealed valuable details about the used synthesis procedures and also on the behavior and stability of the oligomers. In order to improve the yields and to significantly simplify the work-up, the initial acid substrate was substituted by an end-group functionalized polymer. Thus, as also reported earlier,[336] the use of an acid functionalized polymer significantly facilitates the purification of the sequence-defined products by straightforward precipitation and also speeds up the overall synthesis procedure. Therefore, a PEG-acid was synthesized from a commercially available PEG-monomethyl ether (M_n ~2000 gmol^{-1}). Starting from the PEG-acid **1b**, the sequence-defined pentamer block was synthesized according to the aforementioned procedure. As anticipated, complicated purification steps were not required in this case: the products were isolated by simple precipitation in ice-cold diethyl ether and filtration. For the block-copolymer synthesis, the GPC results (Figure

31) also revealed a shift of the complete molecular weight distribution (MWD) towards higher molecular weights, which is in agreement with the successful formation of the desired sequence-defined products. In all GPC traces a small shoulder is observed, which was already present in the initially used PEG and probably arises from *bis*-OH functional PEG chains. Additional GPC/ESI-MS measurements confirm the success of each reaction step (see Experimental Section, Chapter 6.3.1).

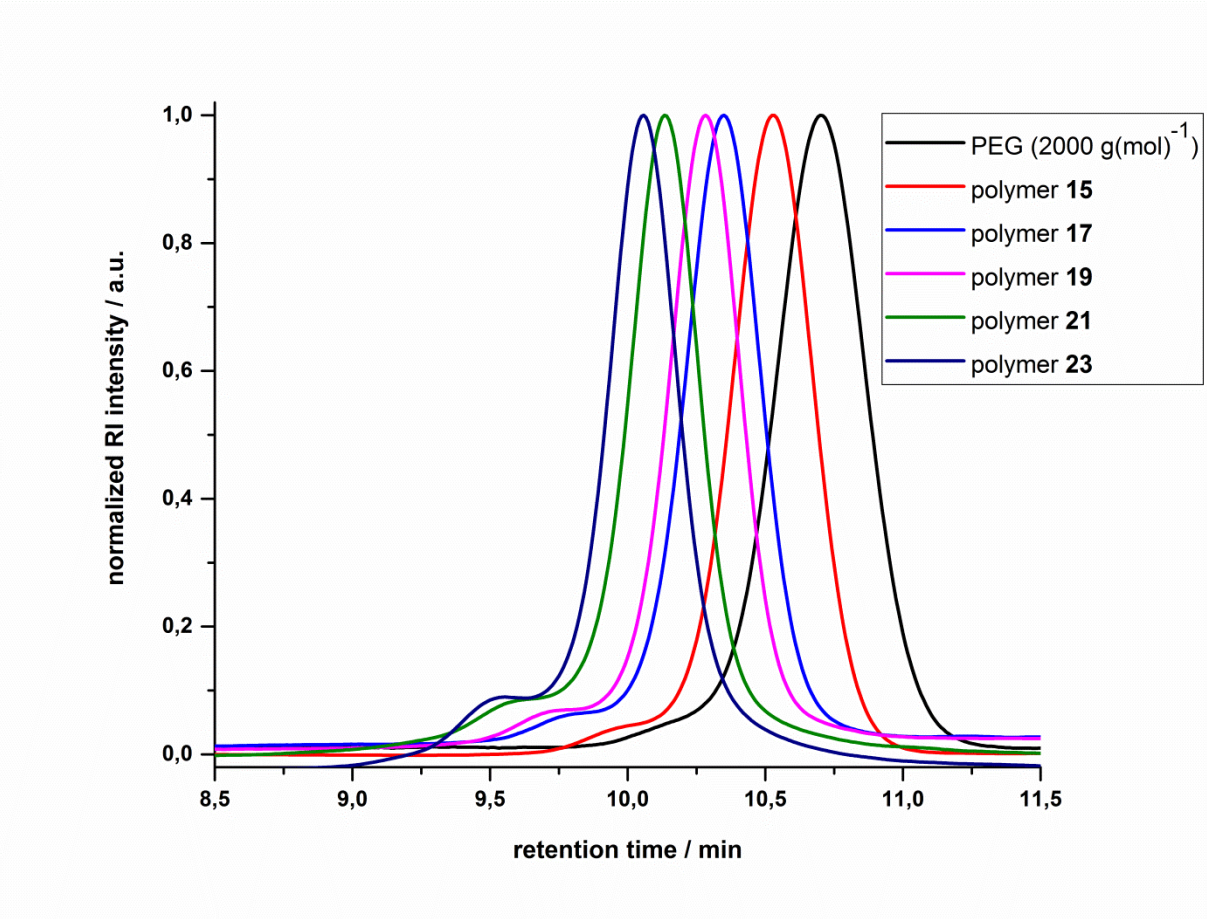


Figure 31: GPC traces obtained from the block-copolymer synthesis for the products of the Passerini reactions. To make it well-arranged, the GPC traces of the products of the Thiol-Ene additions were left out. The whole distribution shifts towards lower retention times (higher molecular weights), indicating successful reactions and complete conversions.

Figure 32 illustrates the mass spectra of **15** and **17** obtained after the first and the second P-3CR, respectively. It is obvious that all polymer chains are functionalized, which is apparent due to the shift of the whole MWD by 357.3 Da (119.1 *m/z*), which exactly corresponds to the mass of 3-mercaptopropionic acid **4**, 10-undecenal **2** and *tert*-butyl isocyanide **3b**.

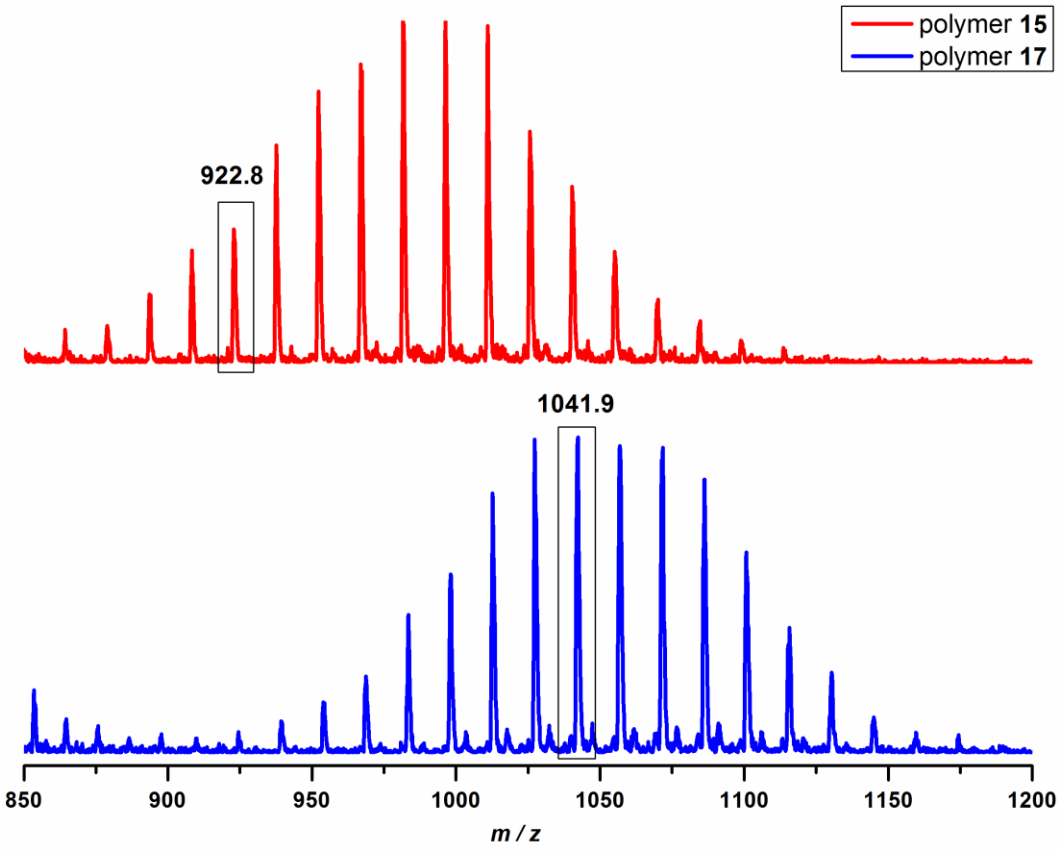


*Figure 32 ESI-MS spectra of **15** (product of the first P-3CR) and **17** (product of the second P-3CR), showing a shift of the MWD towards higher molecular weights. The peaks shown in the spectra correspond to chains carrying three sodium ions and the selected peaks correspond to polymer chains having 51 PEG monomer units. The peak shifts by 119.1 m/z (357.3 Da), which is exactly the sum of the masses of 3-mercaptopropionic acid **4**, 10-undecenal **2** and tert-butyl isocyanide **3b**.*

Furthermore, the introduction of the desired functional groups can be followed by ^{1}H NMR spectroscopy (Figure 33). The presence or absence of the terminal double bond and the presence of amide signals also verify full conversion of the starting material to the desired products in each reaction step. Figure 33 shows exemplary the ^{1}H NMR spectra obtained after the first P-3CR (Figure 33, top) and the first Thiol-Ene addition (Figure 33, bottom). The presence or absence of the signals for the terminal double bond is clearly observed (Figure 33, zoom and blue boxes).

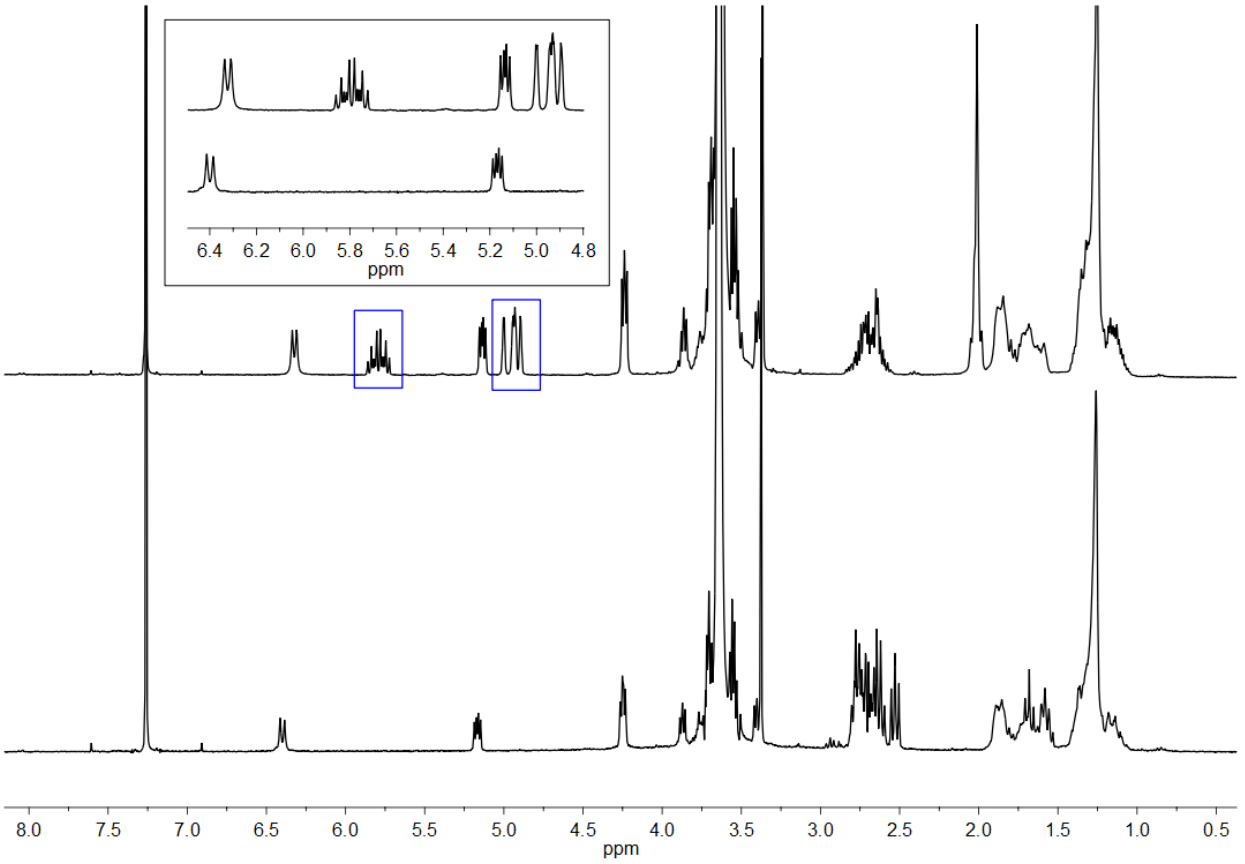


*Figure 33: NMR spectra obtained for polymer **15** (first P-3CR, top) and polymer **16** (first Thiol-Ene addition, bottom). The disappearance of the double bond signals (blue boxes) after the Thiol-Ene addition reaction can be followed (zoom-box).*

Moreover, the integration of the ^{1}H NMR signals of the modified polymer end-groups are in good agreement with those of the desired products and confirm the success of the synthetic steps.

Table 3 summarizes the results obtained from Gel Permeation Chromatography (M_n, M_w, M_p and Đ) and Differential Scanning Calorimetry (DSC, T_m) for each polymer after precipitation in ice cold diethyl ether.

Table 3: Summary of the results obtained in the synthesis of a block-copolymer containing a sequence-defined pentamer-block.

reaction (product)	M_n / g mol^{-1} [a]	M_w / g mol^{-1} [a]	M_p / g mol^{-1} [c]	Đ [a]	T_m / °C	yield / % [b]
PEG	2705	2859	2990	1.06	53.1	-
PEG-COOH (**1b**)	2871	3001	3118	1.05	52.1	89
1st Passerini (**15**)	3338	3473	3757	1.04	48.9	96
1st Thiol-Ene (**16**)	3429	3512	3719	1.02	47.4	88
2nd Passerini (**17**)	4317	4515	4657	1.05	47.0	89
2nd Thiol-Ene (**18**)	4313	4525	4426	1.05	45.9	92
3rd Passerini (**19**)	5016	5290	5000	1.05	46.0	92
3rd Thiol-Ene (**20**)	4915	5178	5051	1.05	45.4	89
4th Passerini (**21**)	5971	6342	5999	1.06	45.8	81
4th Thiol-Ene (**22**)	6064	6403	6121	1.06	45.1	87
5th Passerini (**23**)	6597	7028	6570	1.07	45.0	85

[a] values determined by GPC (calibrated on narrow linear PMMA standards). [b] yield after precipitation in ice cold diethyl ether (0°C) and filtration. [c] values calculated from the calibration curve.

Compared to the oligomer synthesis, the synthesis of the block-copolymer revealed to be much easier regarding the time saving purification procedure by precipitation. Moreover, higher yields can be obtained in the synthesis of **23** having a sequence-defined pentamer structural motif. An overall yield of 34 % of **23** was obtained after nine reaction steps.

All in all, the synthesis of the sequence-defined block utilizing the PEG-acid is more efficient with regard to ease of purification and reaction efficiency, but also the overall preparation procedure is significantly accelerated.

In conclusion, a novel synthesis approach towards sequence-defined maromolecules was successfully applied to synthesize pentamer **14** as well as block-copolymer **23** containing a sequence-defined block of five units and bearing five different side chains. The products were obtained in high yields and purity. Thereby, the iterative utilization of the P-3CR and the Thiol-Ene addition reaction proved to be a powerful combination in the preparation of the sequence-defined materials and enabled an easy and versatile introduction of different side chains. Moreover, the use of a PEG-acid allowed for a straightforward isolation of the sequence defined products by precipitation. It should be

emphasized that this novel synthesis protocol does not require any protecting groups or activating reagents, which is feasible due to the orthogonal reactions. Above all, there is no need for complex monomer synthesis, since the used compounds for each step are commercially available.

4.1.2 Synthesis of Sequence-Defined Macromolecules by the Ugi-Thiol-Ene Approach

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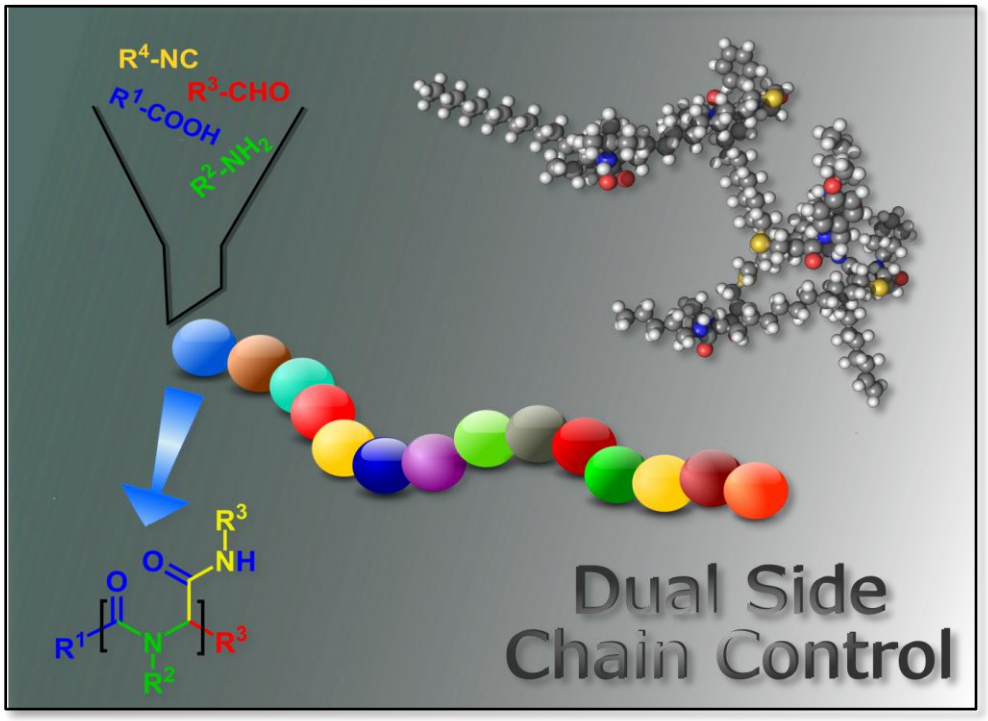
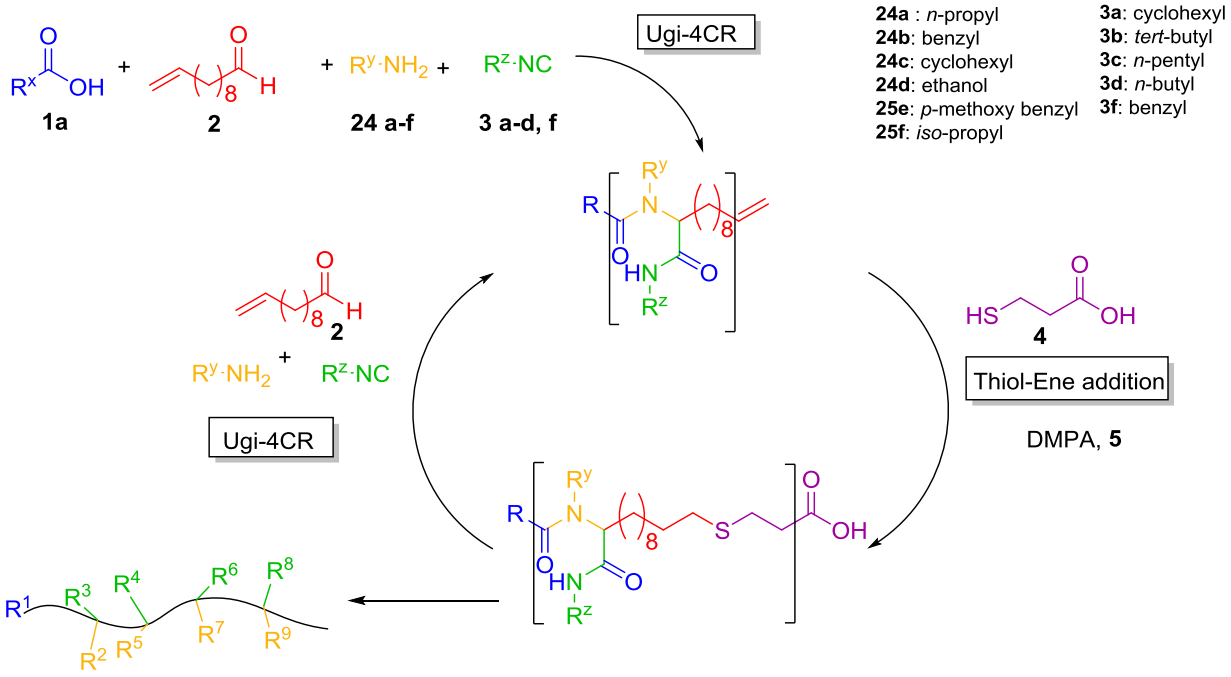


Abstract:

The synthesis of sequence-defined oligomers by the iterative application of the modular Ugi four-component reaction (U-4CR) and the efficient Thiol-Ene addition reaction is described within this chapter. By varying the amine component in the U-4CR, a sequence-defined and monodisperse tetramer (M= 1861.5 g mol^{-1}) was obtained. More interestingly, if both the amine and the isocyanide components were varied simultaneously in the U-4CR, a double sequence-controlled, monodisperse pentamer (M= 2411.8 g mol^{-1}) bearing ten different and selectable side chains was obtained. All oligomers were thoroughly characterized by NMR and IR spectroscopy, mass spectrometry and GPC.

Compared to the P-3CR, the U-4CR offers the possibility to introduce two different side chains in one single reaction step within the same synthetic strategy. The carboxylic acid functionality and the double bond of the aldehyde component were utilized for chain elongations, comparable to the previously discussed P-3CR approach (Chapter 4.1.1).[334] However, in the U-4CR, an amine is used as an additional component. Thus, the isocyanide and the amine can be used to introduce two tailored side chains to the sequence-defined polymers in one single reaction step. Moreover, the resulting oligomers offer a comparably higher chemical stability due to formed amide backbone. Therefore, the iterative use of the U-4CR and the Thiol-Ene addition reaction is a valuable combination of reactions to prepare sequence-defined oligomers with great structural diversity (Scheme 13). Conceptually, this is the first synthesis approach that introduces two defined side groups to the growing macromolecular chain in one reaction step, thus offering a significant advance in the design of sequence-defined polymers.



Scheme 13: Synthesis strategy towards dual side chain controlled, sequence-defined oligomers through the iterative application of the Ugi four-component and the Thiol-Ene addition reaction.

To synthesize the sequence-defined oligomers, stearic acid **1a** was used as starting substrate and 10-undecenal **2** as the aldehyde component, allowing for a subsequent Thiol-Ene addition reaction of 3-mercaptopropionic acid **4**, which enables another

U-4CR and completes one sequence of the oligomer-synthesis (Scheme 13). In each U-4CR, the amine and the isocyanide-component can be varied to obtain macromolecules with tailored side chains. An optimization of the reaction conditions in the U-4CR revealed that the use of 10-undecenal **2**, propyl amine **24a** and *tert*-butyl isocyanide **3b** in a 1.7-fold excess relative to stearic acid **1a** leads to isolated yields of the product **25** of up to 91 % (Table 4, entry 3). In this optimization study, the reactions of **1a**, **2**, **3b** and **24a** were conducted at room temperature in a 1.0-molar concentration of **1a** in methanol (Figure 34).

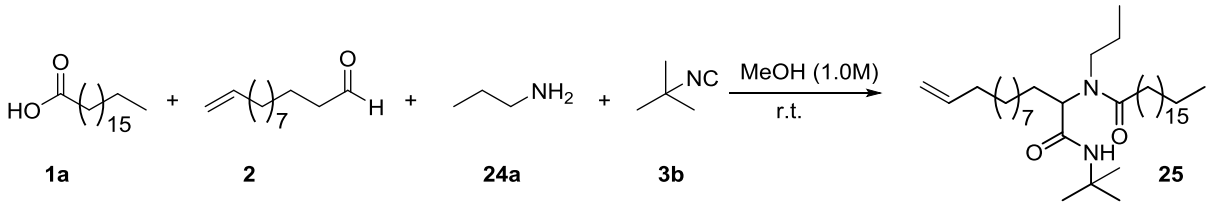


*Figure 34: First U-4CR of stearic acid **1a**, 10-undecenal **2**, propyl amine **24a** and tert-butyl isocyanide **3b**, yielding product **25**.*

Here, the conversion could not be determined from the reaction mixtures due to the rapid formation of the imine (condensation of the aldehyde and the amine) and its invisibility in GC or GC-MS measurements. Also in ^{1}H NMR measurements, no distinctive, non overlapping signal for the imine could be found. Therefore, the reactions with different ratios of reactants were performed and after workup by column chromatography the yields were determined (Table 4).

*Table 4: Comparison of the yields obtained in the first U-4CR using stearic acid **1a**, 10-undecenal **2**, tert-butyl isocyanide **3b** and propyl amine **24a** in different ratios.*

entry	ratio **1a** : **2** : **3b** : **24a**	yield [%][a]
1	1.0 : 1.0: 1.0: 1.0	53
2	1.0 : 1.1 : 1.1 : 1.1	56
3	1.0 : 1.7 : 1.7 : 1.7	91
4	1.0 : 2.0 : 2.0 : 2.0	51

[a] yield after isolation of product **25** by column chromatography.

According to this optimization study, the U-4CR was conducted using a 1.7-fold excess of the aldehyde, the isocyanide and the amine component. Since high concentrations of

the reactants are favorable, all U-4CR reactions were performed in a minimum amount of methanol (1.0 molar solution with respect to the acid component).[71, 91] The obtained products of the Ugi reactions were purified by column chromatography in order to ensure the complete removal of the excess components and to provide the products in high purity. The subsequent Thiol-Ene addition reaction was conducted at room temperature under UV irradiation, using 5.0 equivalents of mercaptopropionic acid **4** and 5.0 mol% DMPA **5** as UV-initiator. The products of the Thiol-Ene addition reactions were, unlike the products of the P-3CR and Thiol-Ene addition approach (Chapter 4.1.1), purified by vacuum distillation of the excess of 3-mercaptopropionic acid **4** and simple washing with water. The workup could be simplified in this case due to the higher stability of the amide-backbone, which is formed in the U-4CR compared to the ester-backbone, which is formed in the P-3CR (see Figure 35). Interestingly, the distillation of the excess amount of 3-mercaptopropionic acid **4** allowed the recycling of the thiol and its reuse in subsequent Thiol-Ene addition reactions.

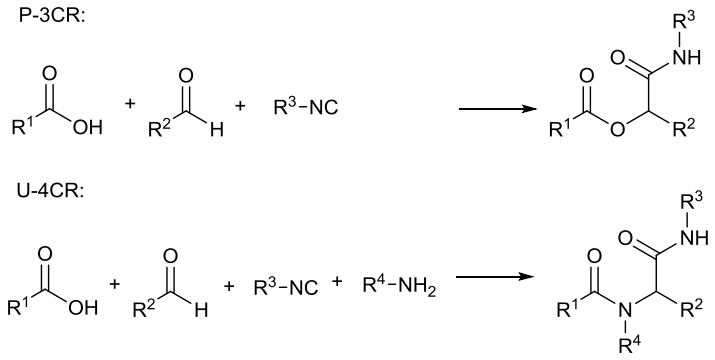


Figure 35: Comparison of the P-3CR and the U-4CR: The iterative sequence of the P-3CR and the Thiol-Ene addition provides a poly(ester)-backbone (top), whereas the iterative sequence of the U-4CR and the Thiol-Ene addition provides the more stable poly(amide)-backbone (bottom).

In this first synthesis of sequence-defined macromolecules through the U-4CR, the amine component (**24a-d**) was varied while using *tert*-butyl isocyanide **3b** in each U-4CR, yielding tetramer **31** (Figure 36, top) in an overall yield of 15 % (seven steps).

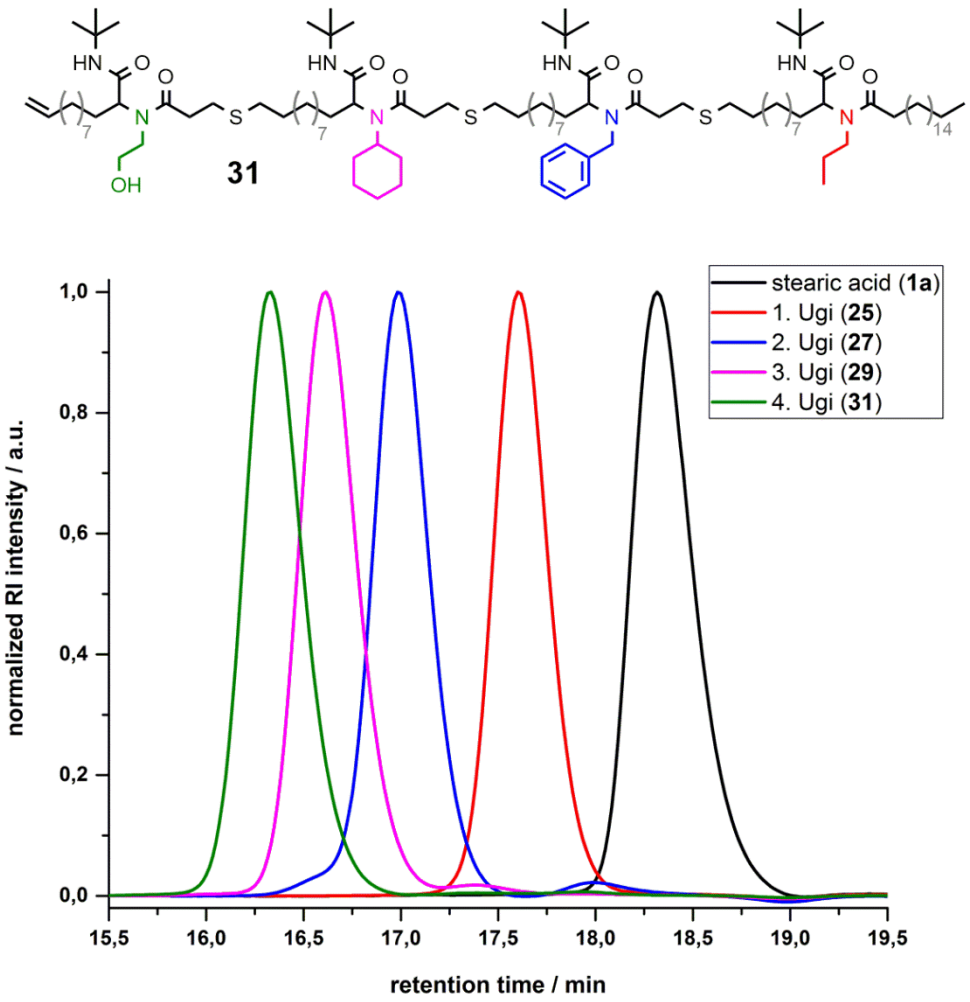


*Figure 36: Structure of the synthesized tetramer **31** (top) with four different side chains and the obtained GPC traces after each Ugi four-component reaction (bottom). To make it well arranged, the GPC traces obtained for the products of the Thiol-Ene additions were left out.*

The obtained GPC traces clearly show the success of each synthetic step by the shifting towards higher molecular weights (lower retention times). Additionally, the GPC traces prove the high purity of the synthesized sequence-defined macromolecules. Table 5 gives an overview of the obtained results in each U-4CR in the synthesis of tetramer **31**. The reaction times for the U-4CR were between 24 and 48 hours, whereas the Thiol-Ene additions were performed in reaction times between one and two hours. The results obtained from mass spectrometry are in very good agreement with the calculated values.

*Table 5: Summary of the results obtained after each U-4CR and each Thiol-Ene addition in the synthesis of the sequence-defined tetramer **31**.*

reaction (product)	reaction time /hours	yield /%[a/b]	exact mass calculated	mass found
1st U-4CR (**25**)	24	91[a]	577.6	577.6
1st Thiol-Ene addition (**26**)	2	91[b]	683.6	683.6
2nd U-4CR (**27**)	24	76[a]	1022.9	1022.9
2nd Thiol-Ene addition (**28**)	1	81[b]	1129.9	1129.4
3rd U-4CR (**29**)	48	81[a]	1461.2	1460.9
3rd Thiol-Ene addition (**30**)	2	75[b]	1567.2	1567.3
4th U-4CR (**31**)	48	48[a]	1862.5	1861.9

[a] after column chromatography; [b] after distillation of the excess of **4** and washing with water

In the fourth U-4CR, ethanolamine **24d** was used as amine component, introducing a functional group to the backbone, which can be used, for instance, as initiator for ring-opening polymerizations. However, the relatively low yield (48 %) of this U-4CR indicates that protecting groups could be advantageous for the introduction of primary alcohols. The overall yield in the synthesis of tetramer **31** was 15 % and a sequence-defined macromolecule with a molecular weight of 1861.5 g mol^{-1} was obtained in seven reaction steps.

The synthesis of tetramer **31** confirmed that the U-4CR is a valuable tool to prepare sequence-defined and structurally diverse oligomers. To further benefit from the versatility of the U-4CR, the monodisperse pentamer **40** was synthesized by variation of both the amine and the isocyanide component in each U-4CR (Figure 37, top) using the previously optimized reaction conditions. In this way, two different side chains were introduced at each monomer unit in one single step leading to dual side chain control. By combination of *tert*-butyl isocyanide **3b** and propylamine **24a**, cyclohexyl isocyanide **3a** and benzylamine **24b**, *n*-butyl isocyanide **3d** and *p*-methoxy benzylamine **24e**, *n*-pentyl isocyanide **3c** and *iso*-propyl amine **24f**, benzyl isocyanide **3f** and cyclohexyl amine **24c**, ten different side chains were sequentially introduced in five subsequent Ugi reactions.

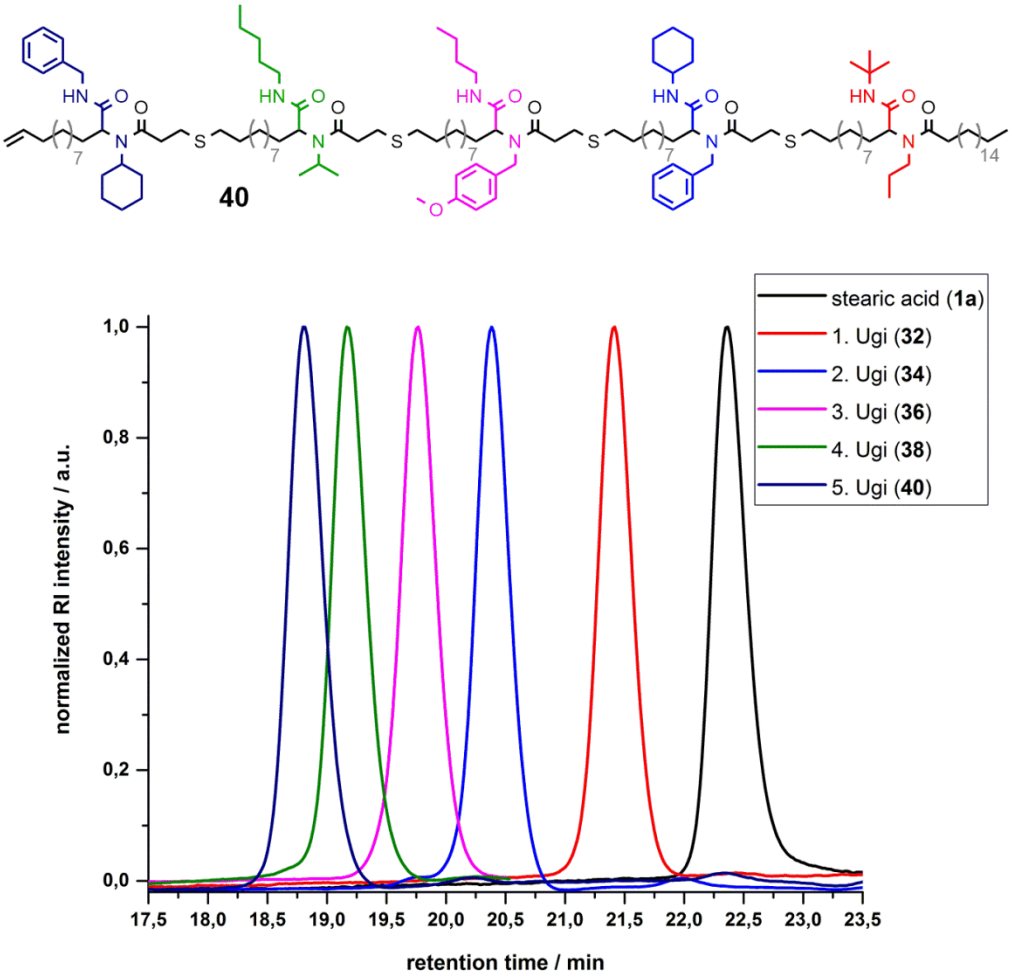


*Figure 37: Structure of the obtained pentamer **40** (top). In each U-4CR, two different side chains were introduced, yielding a sequence-defined pentamer with ten different and selectable side chains. GPC traces obtained in the synthesis of the sequence-defined pentamer **40** after each U-4CR (bottom). To make it well arranged, the GPC traces obtained after the Thiol-Ene additions were left out.*

Table 6 provides an overview of the yields and reaction times for each U-4CR and Thiol-Ene addition in the synthesis of pentamer **40**. Furthermore, the results of the mass analyses are shown. The overall yield of the pentamer-synthesis was 15 % (nine steps) and a highly defined, monodisperse macromolecule with ten different side chains and a molecular weight of 2411.8 g mol^{-1} was obtained.

*Table 6: Summary of the results obtained after each U-4CR and each Thiol-Ene addition in the synthesis of the sequence-defined pentamer **40**.*

reaction (product)	reaction time /hours	yield /%[a/b]	exact mass calculated	mass found
1st U-4CR (**32**)	24	91[a]	577.6	577.6
1st Thiol-Ene addition (**33**)	1	99[b]	683.6	683.6
2nd U-4CR (**34**)	48	53[a]	1049.9	1049.7
2nd Thiol-Ene addition (**35**)	3	92[b]	1155.9	1155.6
3rd U-4CR (**36**)	40	80[a]	1526.2	1526.3
3rd Thiol-Ene addition (**37**)	3	99[b]	1632.2	1632.1
4th U-4CR (**38**)	48	77[a]	1937.5	1937.7
4th Thiol-Ene addition (**39**)	4	99[b]	2043.5	2043.1
5th U-4CR (**40**)	24	56[a]	2409.8	2410.1

[a] after column chromatography; [b] after distillation of the excess of **4** and washing with water

The success of the reactions in the synthesis of tetramer **31** and pentamer **40** can be followed by ^{1}H NMR analysis (see Figure 38); Characteristic signals for the amide protons and the olefin protons appeared after each U-4CR, whereas the olefin protons were absent after the Thiol-Ene addition reactions. Figure 38 shows the comparison of the ^{1}H NMR spectra obtained after the first U-4CR **32** (Figure 38, top) and the first Thiol-Ene addition reaction **33** (Figure 38, bottom). The disappearance of the double bond signals (5.8 and 5.0 ppm) after the Thiol-Ene addition can be clearly seen (Figure 38). Furthermore, the signals for the newly formed thioether group (between 2.9 and 2.4 ppm) can be observed. The ^{1}H NMR of product **33** still shows traces of the photoinitiator DMPA **5**, which cannot be removed by the chosen workup procedure. However, it does not interfere with the subsequent U-4CR, so it was removed by column chromatography after the following U-4CR.

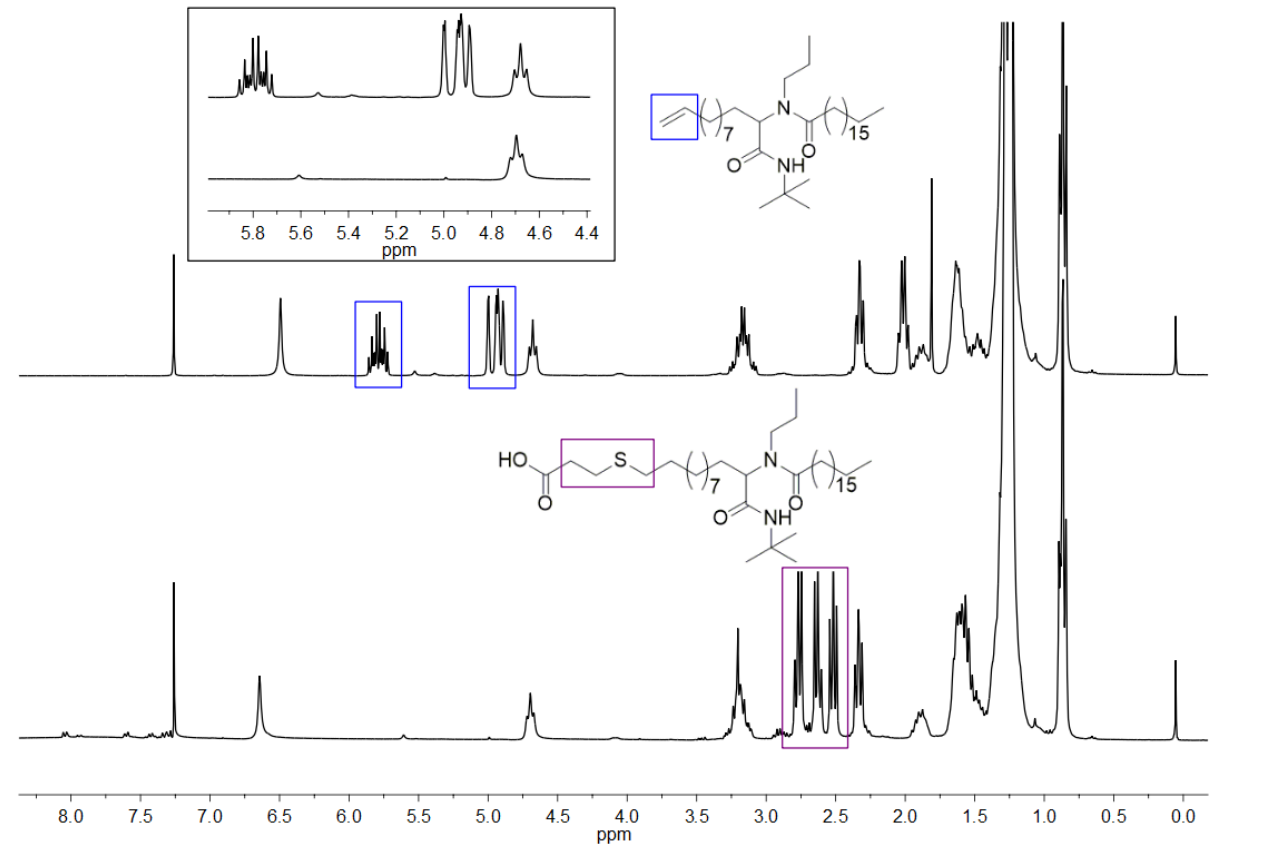


*Figure 38: Comparison of the NMR spectra obtained for the product of the first U-4CR (**32**) (top) and the product of the first Thiol-Ene addition (**33**) (bottom). The disappearance of the signals of the double bond (zoom-box and blue boxes) and the appearance of the thioether signals (purple box) can clearly be seen*

Furthermore, the high purity of the sequence-defined oligomers is confirmed by GPC and their structure by mass spectrometry (see Table 5 and Table 6 and Experimental Section Chapter 6.3.2).

In conclusion, it was shown that the Ugi four-component reaction is a valuable tool for the synthesis of sequence-defined macromolecules. By iteration of the modular U-4CR and the efficient Thiol-Ene addition reaction it is possible to tailor the side chains of the synthesized macromolecule by either varying one or two components in each U-4CR. The presented approach is highly orthogonal, thus no protecting groups or activating agents are needed. Beside mass and GPC analysis, the success of each reaction step is evidenced by proton and carbon NMR analysis. The overall yields over seven or nine steps are around 15 %, which might be improved in the future by, for instance, transferring the procedure to solid-phase synthesis. Most interestingly, the use of the U-

4CR proved to be a powerful tool in the field of sequence control, offering the unique possibility to introduce two tailored side chains to the macromolecule in a single reaction step while maintaining a stable amide backbone.

4.2 Synthesis of Sequence-Defined Macromolecules Using the Monomer-Approach

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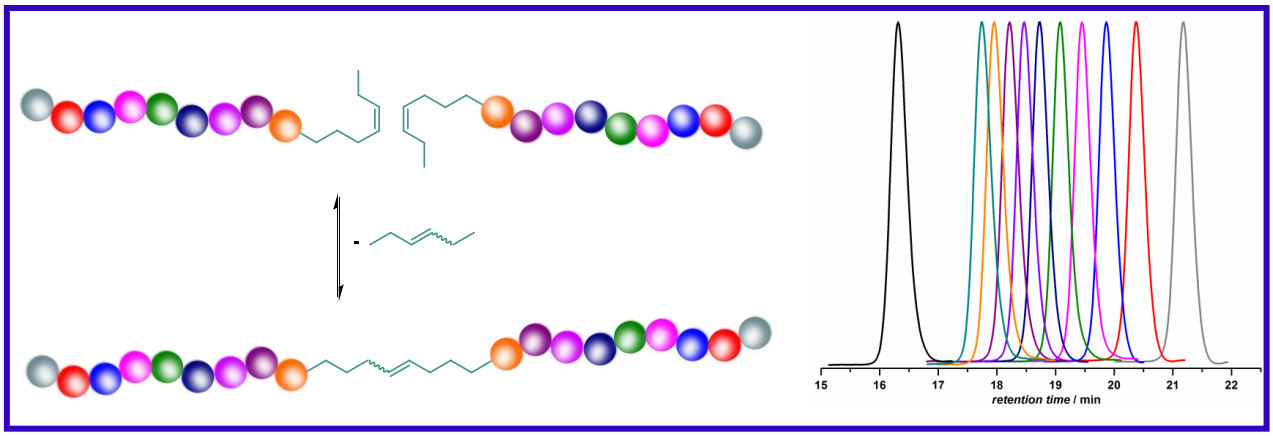
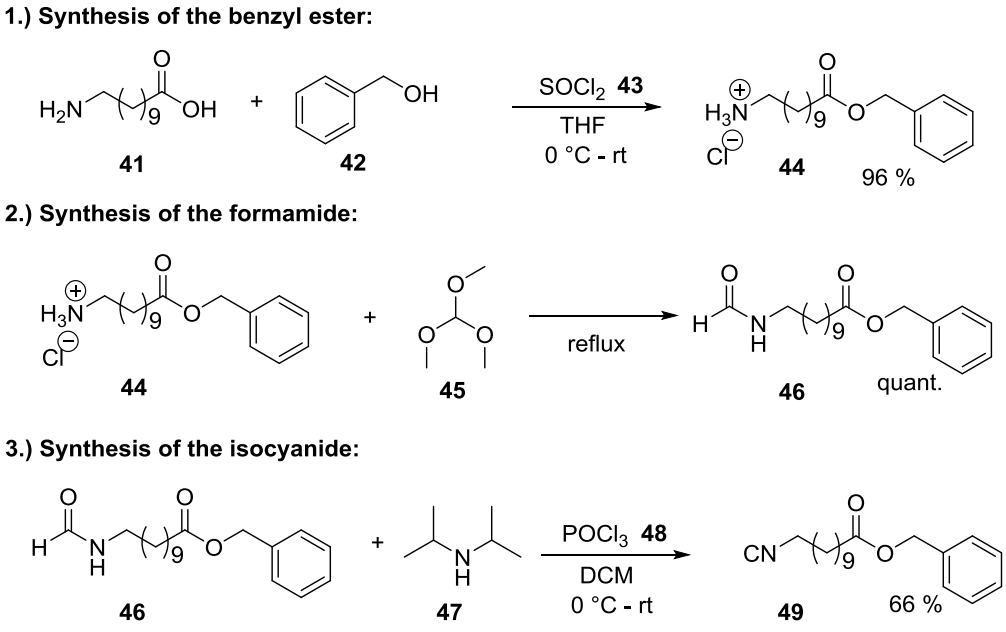


Abstract:

The efficient synthesis as well as the characterization of a sequence-defined decamer and its straightforward dimerization by self-metathesis is described. For this purpose, a monoprotected AB-monomer was designed and successfully applied for the synthesis of a decamer bearing ten different and selectable side chains by using an alternating protocol of the Passerini three-component reaction (P-3CR) and subsequent deprotection. The highly efficient procedure provided excellent yields and allows for multigram scale synthesis of such perfectly defined macromolecules. By the introduction of an olefin at the end of the synthesis, a self-metathesis reaction of the decamer resulted in a sequence-defined 20-mer with a molecular weight of 7046.40 g mol^{-1}. The obtained oligomers were carefully characterized by NMR and IR spectroscopy, GPC and GPC coupled to ESI-MS, as well as by mass spectrometry (FAB and orbitrap ESI-MS).

In order to combine high yields and scalability in one strategy, another strategy to prepare sequence-defined oligomers using the P-3CR including the use of protecting groups, was investigated. Therefore, an appropriate monomer was synthesized and subsequently used for the synthesis of sequence-defined oligomers in an iterative protocol of a Passerini reaction and subsequent deprotection. Thus, a monomer having both an isocyanide and a benzyl ester protected carboxylic acid function was prepared, similarly as for the synthesis of dendrimers prepared by the U-4CR.[340] This combination of functional groups seemed to be the most convenient one, due to the limited stability and difficult synthesis of aldehydes on the one hand and the lack of protecting groups for isocyanides on the other hand. Moreover, the efficient, simple and orthogonal deprotection of benzyl esters is highly valuable for this strategy. An overview of the reaction conditions for the monomer synthesis is shown in Scheme 14. The overall yield over three steps was 63 % and the reaction was performed on a 15 gram scale.



*Scheme 14: Three-step synthesis of the monoprotected AB-type monomer **49**, having both a benzyl ester and an isocyanide functionality.*

Attractively, this synthesis protocol is adaptable to other amino acid derivatives, allowing structural backbone variety along with selectable side chains. Following this synthesis approach, three other monomers, starting from *β*-alanine, 6-aminohexanoic acid and 4-(aminomethyl)benzoic acid were synthesized, but not yet applied for the synthesis of

sequence-defined macromolecules (Figure 39). The use monomer **49c** allows the introduction of rigid monomer units, whereas the density of side chains in the sequence-defined macromolecules can be tailored by the choice of monomer **49a**, monomer **49b** or monomer **49**.

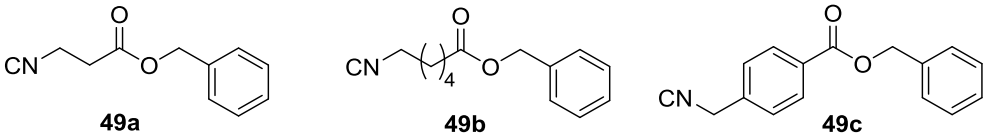
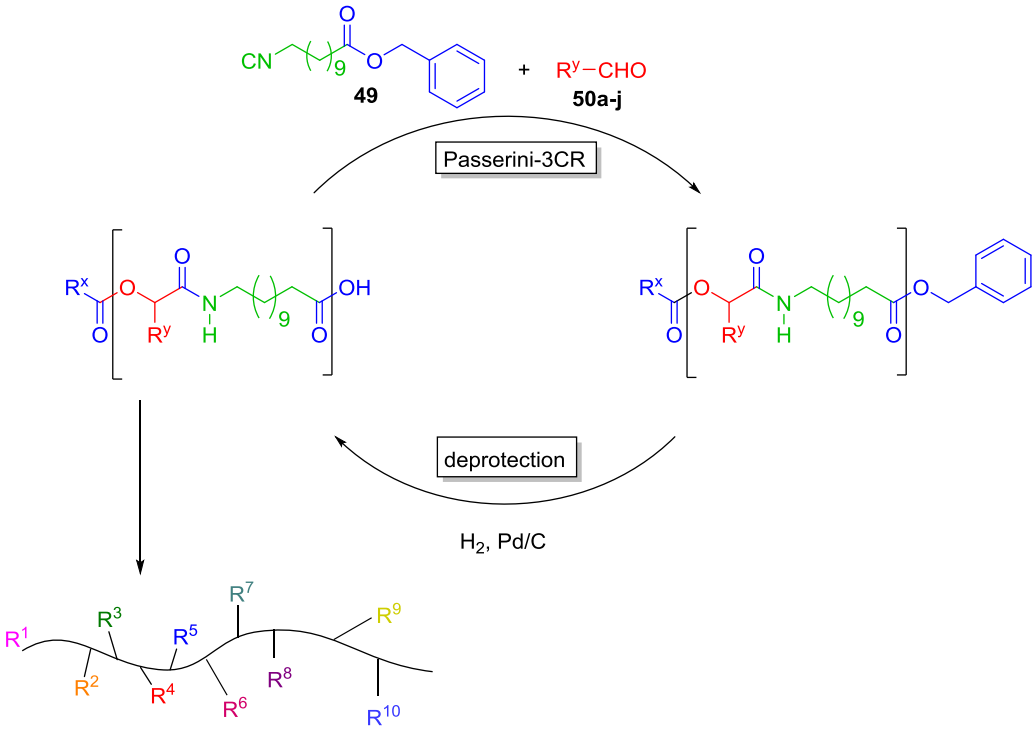


Figure 39: Three other isocyanide-monomers, which have been synthesized, but not yet applied in the synthesis of sequence-defined macromolcules. ***49a*** *was synthesized in three steps starting from ß-alanine,* ***49b*** *was synthesized in three steps starting from 6-aminohexanoic acid and* ***49c*** *was synthesized in four steps starting from 4-(aminomethyl)benzoic acid.*

Subsequently, monomer **49** was applied in the efficient iterative sequence of a P-3CR and subsequent deprotection of the benzyl ester yielding the sequence-defined decamer **69** with ten different side chains (Scheme 15).



Scheme 15: Synthesis strategy towards sequence-defined macromolecules using the monoprotected AB-monomer ***49****.*

In detail, the isocyanide functionality of monomer **49** was reacted in a P-3CR with, *e.g.*, stearic acid **1a** as starting substrate and an aldehyde component **50a-j**. The thus obtained product of the P-3CR bears a benzylester moiety, which can be used for another P-3CR after hydrogenolysis by heterogeneous Pd/C catalyst and hydrogen gas, followed by a simple workup by filtration.

Remarkably, the workup by column chromatography after the P-3CR step turned out to be simpler with increasing chain lengths: the excess of the low molecular weight reactants (monomer **49** and the aldehyde **50a-j**) were recovered using apolar eluents and subsequently, polar eluents allowed the simple collection of the sequence-defined oligomers. By the use of different aldehydes **50a-j** for the P-3CR, ten different side chains were introduced to the sequence-defined decamer, including aliphatic, aromatic and olefinic moieties (Figure 40, top).

It has to be noted that, if olefins are introduced to the oligomer, the deprotection step also leads to a reduction of the double bonds. Thus, olefins have to be introduced either at the end of the sequence, or the double bonds must be protected or further functionalized prior to the hydrogenolysis of the benzyl ester.

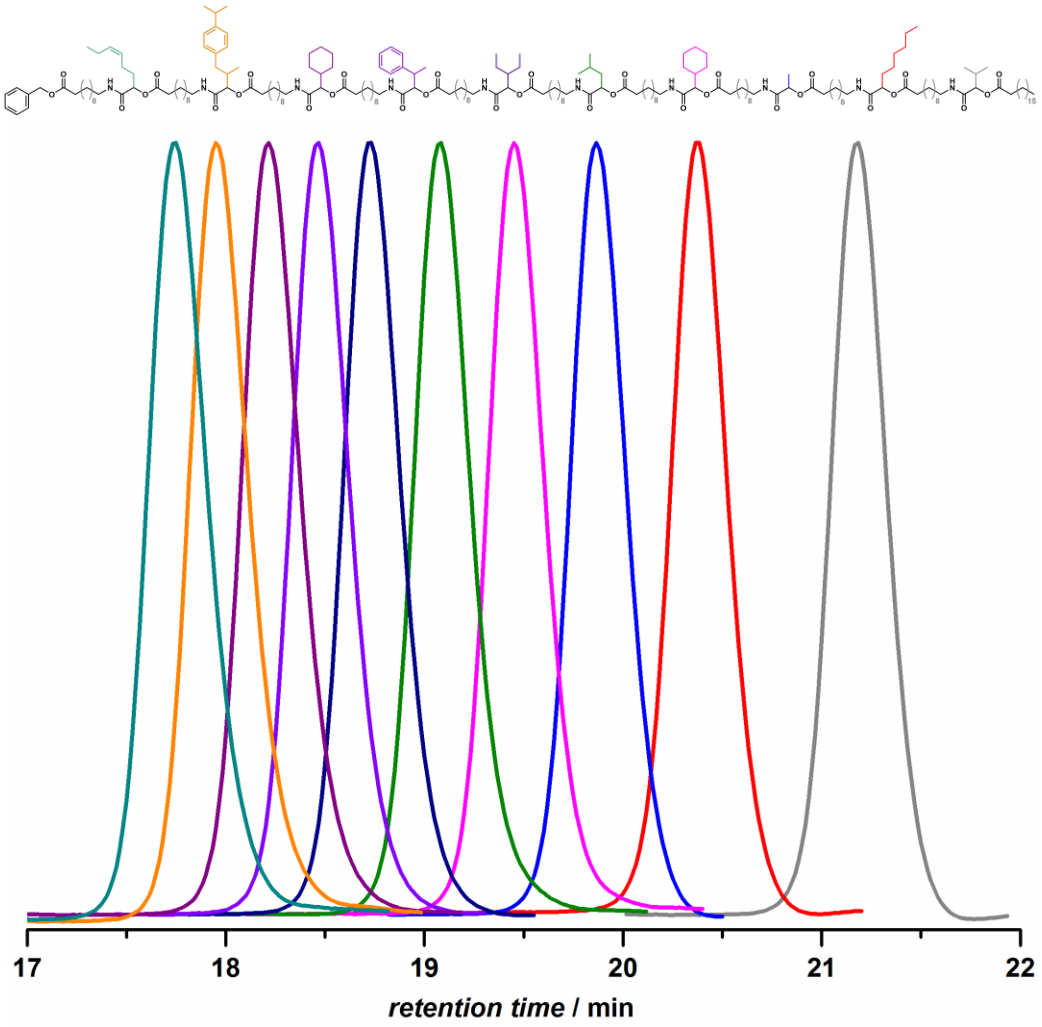


*Figure 40 Top: Structure of the sequence-defined decamer **69** with ten side chains, including aliphatic, aromatic, and olefinic side chains. Bottom: GPC traces of the obtained products after each P-3CR; To make it well arranged, the GPC traces obtained for the products of the deprotections were left out.*

The overall yields in the synthesis of the sequence-defined macromolecules were very high. Especially compared to the previously described procedure (Chapter 4.1.1), the yields increased considerably and the workup was simplified (see Table 7, entries 1 - 5).[334] In addition, only one single monoprotected building block was required, the reactions could be conducted on a multigram scale and activating agents were not necessary, making this synthesis protocol advantageous compared to other stepwise procedures, such as the well-established polypeptide synthesis.

Table 7: Comparison of the yields of the Passerini/Thiol-Ene approach (Chapter 4.1.1)[334] with the monomer approach (this Chapter).

sequence [a]	Passerini/Thiol-Ene	Passerini/deprotection
1st	92 %	97 %
2nd	81 %	96 %
3rd	63 %	88 %
4th	69 %	90 %
5th	68 %	91 %
6th		92 %
7th		91 %
8th		92 %
9th		89 %
10th		95 %
overall yield	22 % (for 5-mer)	44 % (for 10-mer)

[a] sequence includes the Passerini reaction as well as the Thiol-Ene addition or the deprotection.

The sequence-defined decamer **69** (Figure 40, top) was obtained in 19 reaction steps in an excellent overall yield of 44 % and very high purity. It has to be highlighted that the reactions were carried out on multigram scale. Hence, 2.4 grams of the sequence-defined decamer **69** were obtained, allowing for the synthesis of defined macromolecules for certain applications and the establishment of structure-property relationships in the future. Table 8 summarizes the reaction times, yields and the results of the mass analysis for each step in the synthesis of decamer **69**. The high purity of the obtained products was evidenced by GPC (Figure 40, bottom) and ^{1}H NMR, and the macromolecules were further characterized by GPC-ESI-MS and mass spectrometry (Experimental Section, Chapter 6.3.3).

*Table 8: Summary of the results obtained in each synthetic step in the synthesis of the sequence-defined decamer **69**.*

reaction (product)	reaction time /hours	yield /%	calculated mass [a/b/c]	found mass [a/b/c]
1st P-3CR (**51**)	24	97	658.5405[a]	658.5407[a]
1st deprotection (**52**)	15	> 99	568.4936[a]	568.4937[a]
2nd P-3CR (**53**)	24	96	983.8022[a]	983.8021[a]
2nd deprotection (**54**)	15	> 99	893.7552[a]	893.7551[a]
3rd P-3CR (**55**)	24	93	1260.9676[b]	1260.9667[b]
3rd deprotection (**56**)	15	95	1170,9206[b]	1170.9196[b]
4th P-3CR (**57**)	30	93	1584.2136[b]	1584.2126[b]
4th deprotection (**58**)	15	97	1494.1667[b]	1494.1658[b]
5th P-3CR (**59**)	24	92	1881.4440[b]	1881.4518[b]
5th deprotection (**60**)	15	99	1791.3971[b]	1791.4048[b]
6th P-3CR (**61**)	42	93	2192.6901[b]	2192.6970[b]
6th deprotection (**62**)	15	99	2102.6431[b]	2102.6492[b]
7th P-3CR (**63**)	38	93	2537.9205[b]	2537.9294[b]
7th deprotection (**64**)	15	98	2447.8735[b]	2447.8809[b]
8th P-3CR (**65**)	40	94	2859.1509[b]	2859.1558[b]
8th deprotection (**66**)	15	98	2771.1196[b]	2771.1306[b]
9th P-3CR (**67**)	20	95	3262.4595[b]	3262.4719[b]
9th deprotection (**68**)	15	94	3172.4125[b]	3172.4177[b]
10th P-3CR (**69**)	48	95	1804.3474[c]	1804.3574[c]

[a] $[M+H]^+$ determined by HRMS-FAB ; [b] $[M+Na]^+$ determined by orbtitrap ESI-MS;
[c] $[M+2Na]^+$ determined by orbitrap ESI-MS

Figure 41 shows the obtained ESI-MS spectrum of the sequence-defined decamer **69**; the doubly (1805.36 *m/z*) and triply (1211.23 *m/z*) charged sodium cations are clearly observed.

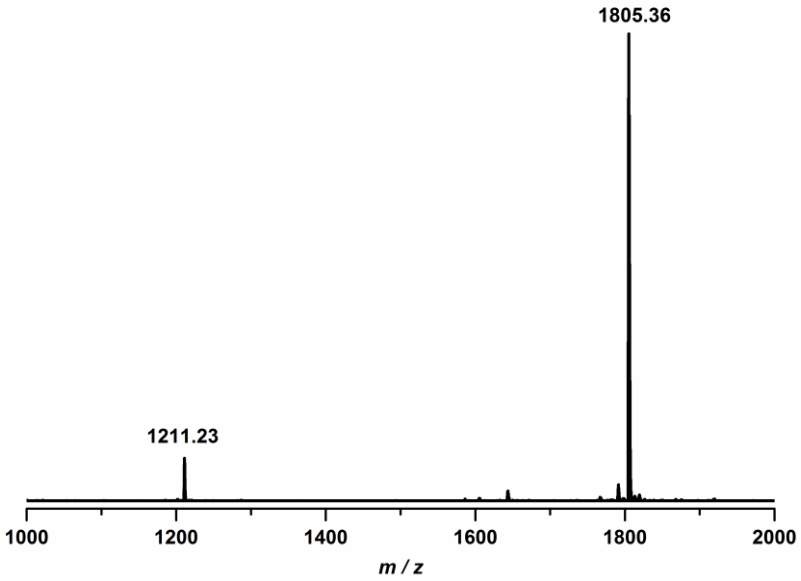


*Figure 41: ESI mass spectrum of the sequence-defined decamer **69**. The assigned masses correspond to the doubly (1805.36 m/z) and the triply (1211.23 m/z) charged sodium cations.*

Moreover, the isotope pattern was compared with the calculated one, showing excellent agreement and confirming the chemical structure of the sequence-defined decamer **69** (Figure 42).

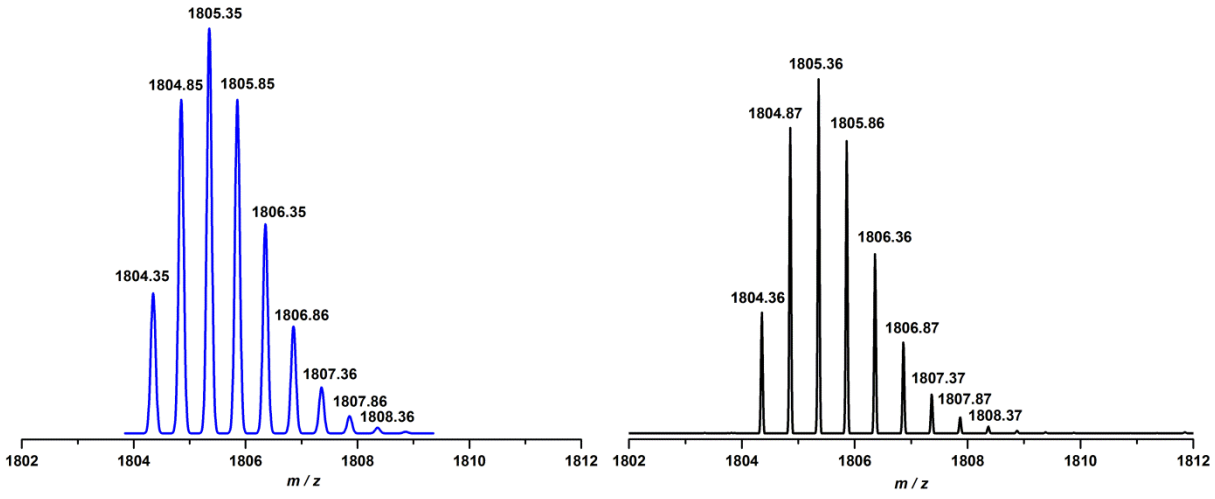


*Figure 42: Comparison of the calculated (left, blue) and the measured (right, black) isotope pattern of the sequence-defined decamer **69**. The very good agreement verifies the chemical structure of the sequence-defined decamer **69**.*

Monomer **49** was also investigated for the synthesis of sequence-defined macromolecules using the Ugi four-component reaction. However, the use of methanol as solvent in combination with an amine as reactant in the U-4CR led to partial transesterification of the benzyl ester with methanol and thus to an undesired side reaction. This side reaction leads to product mixtures, as well as decreased yields and purities of the obtained products. In order to avoid complicated purification steps, the use of a monomer bearing a methyl-ester protecting group should be investigated for the application in the U-4CR. The use of the base-labile methyl-ester protecting group is possible in the synthesis of sequence-defined macromolecules using the U-4CR, in contrast to using the P-3CR, due to the higher chemical stability of the formed poly(amide)-backbone and the absence of additional ester groups in the products.

In order to highlight the versatility of the monomer approach using the P-3CR, a *cis*-double bond was introduced to the side chain of the tenth repeating unit allowing further modifications. Thus, a self-metathesis reaction of the sequence-defined decamer **69** was successfully conducted (see Figure 43, left) using the Hoveyda-Grubbs second generation catalyst in combination with *p*-benzoquinone in order to prevent possible isomerization reactions.[261, 341] Thereby, a sequence-defined 20-mer was synthesized in a yield of 48 %, resulting in an overall yield of 21 % over 20 reaction steps. The GPC trace of the 20-mer **70** shows a clear shift in retention time compared to the decamer **69** due to the significant increase in molecular weight (Figure 43, right). Additionally, the GPC-trace evidences the high purity of the obtained product **70**.

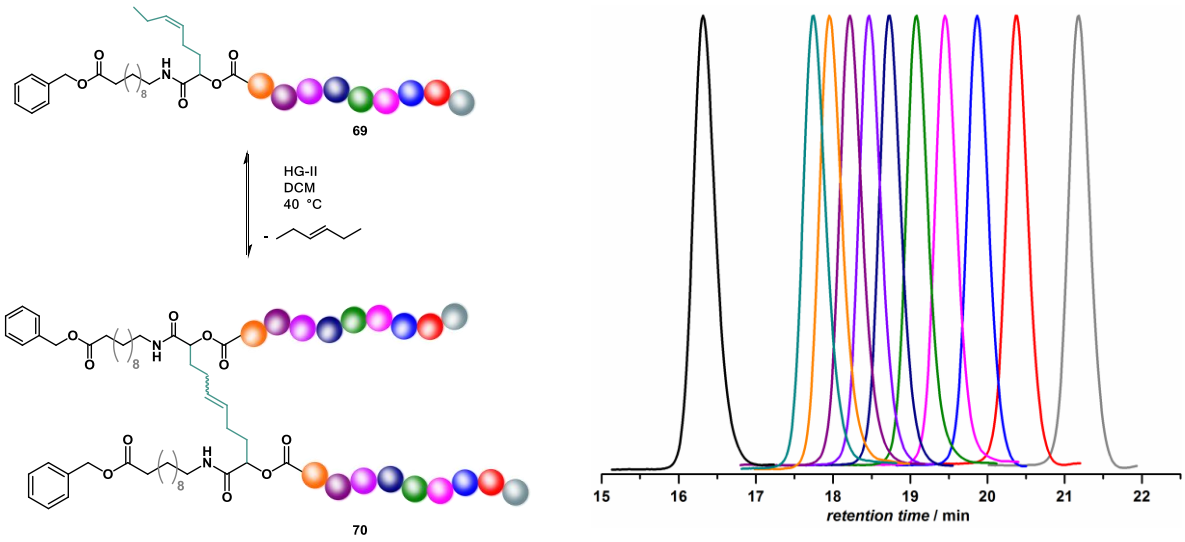


*Figure 43: Left: Reaction scheme of the self-metathesis reaction of the sequence-defined decamer **69** yielding the sequence-defined 20-mer **70**. Right : GPC traces of the obtained products, indicating the clear shift of the 20-mer **70** compared to the decamer **69** due to the almost doubling of the molecular weight.*

In order to characterize the sequence-defined 20-mer **70** in more detail, a coupled GPC-ESI-MS measurement was conducted. The GPC graph, as well as the ESI-MS spectrum at a retention time of 13.56 minutes are displayed in Figure 44.

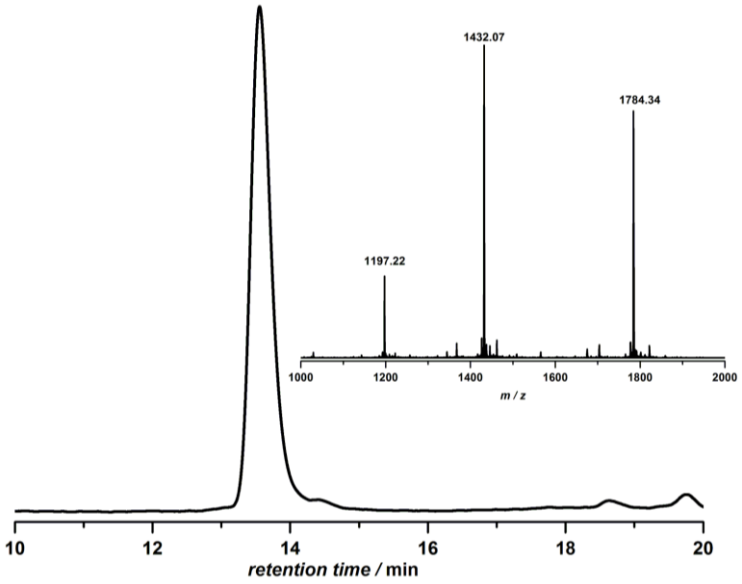


*Figure 44: GPC trace of the sequence-defined 20-mer **70** and the corresponding ESI mass spectrum at a retention time of 13.56 minutes. The fourfold (1784.34 m/z), fivefold (1432.07 m/z) and six-fold (1197.22 m/z) charged sodium ions are clearly observed.*

The ESI-MS spectrum clearly shows the fourfold (1784.34 *m/z*), fivefold (1432.07 *m/z*) and six-fold (1197.22 *m/z*) charged sodium cations of the sequence-defined 20-mer **70**.

Additionally, the isotope pattern of the spectrum was analyzed and shows very good agreement with the calculated one, thereby verifying the chemical structure of the sequence-defined 20-mer (Figure 45).

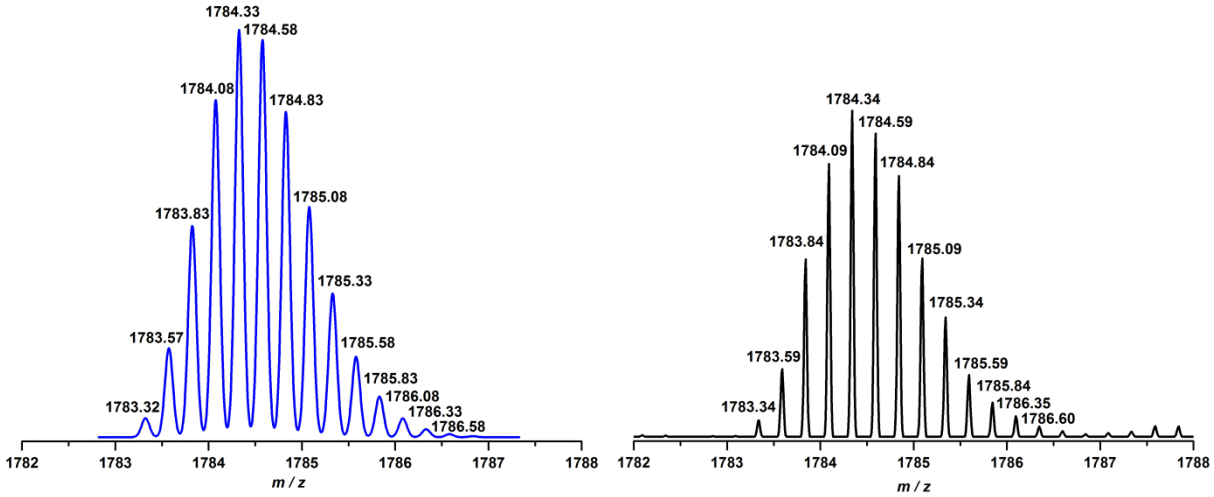


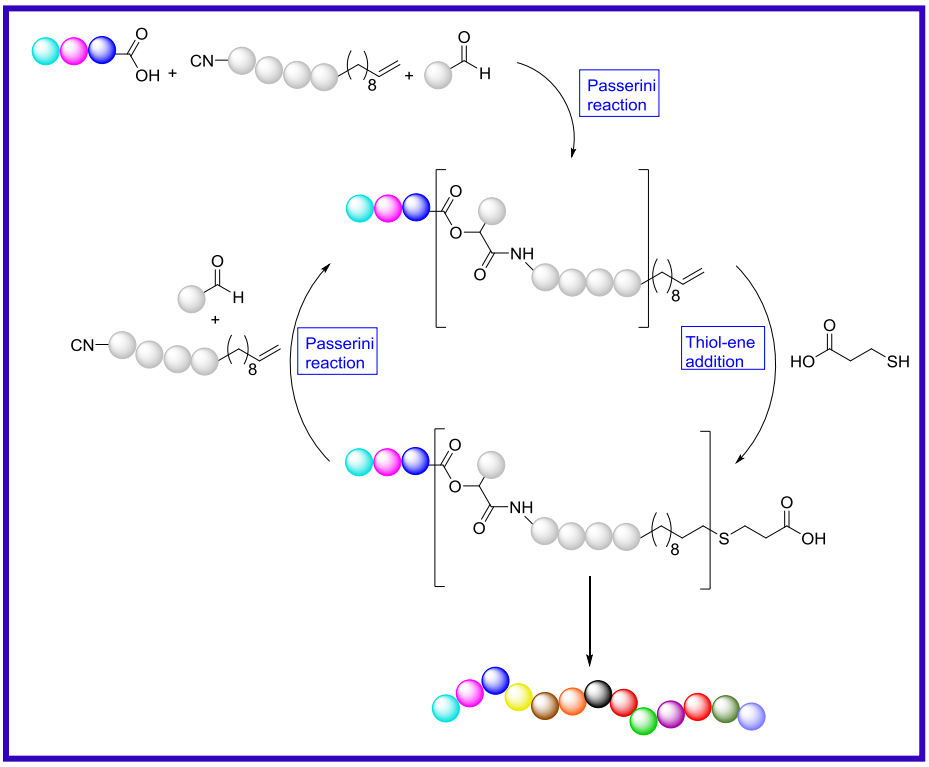
*Figure 45: Analysis of the isotope pattern of the sequence-defined 20-mer **70**. The left, blue graph shows the calculated isotope pattern and the figure on the right (black) shows the measured isotope pattern. The calculated and the measured isotope patterns are in very good agreement, verifying the chemical structure of the obtained sequence-defined 20-mer **70**.*

In conclusion, an easy, scalable and high-yield strategy towards sequence-defined macromolecules was developed and successfully applied in the synthesis of a sequence-defined decamer with a molecular weight of 3565.28 g mol^{-1}. It must be emphasized that the workup procedures could be simplified compared to the previous approaches: the products of the deprotection reactions were isolated by simple filtration. The purification by column chromatography after the P-3CR allowed the collection of the excess components by the use of apolar eluents and the subsequent simple collection of the product by the use of polar eluents. Remarkably, a quantity of more than two grams was synthesized applying this strategy. Furthermore, functional side chains, such as unsaturated ones, were introduced, which allow further modifications. Here, the self-metathesis reaction of the sequence-defined decamer led to a sequence-defined 20-mer

with a molecular weight of 7046.40 g mol^{-1}. In addition, the high purity of the products was confirmed by in-depth analysis including NMR, GPC, GPC-ESI-MS and ESI orbitrap mass spectrometry.

4.3 Convergent Synthesis of Sequence-Defined Macromolecules

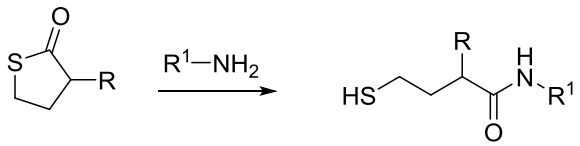
Parts of this project were performed at the University of Ghent in the working group of F. E. Du Prez.



Abstract:

The convergent synthesis of sequence-defined macromolecules is described within this chapter. Therefore, two efficient approaches towards sequence-control were combined in order to achieve convergent couplings of sequence-defined oligomeric building blocks. First, a start-sequence was synthesized by the monomer approach (Chapter 4.2),[338-339] yielding a sequence-defined trimer with carboxylic acid end group. Then, a library of sequence-defined α-ω-functionalized tetramers with isocyanide and alkene end groups were synthesized, making use of thiolactone chemistry.[308] Finally, the sequence-defined building blocks were coupled by a P-3CR. Thus oligomers bearing a terminal double bond were obtained. Interestingly, the alkene moiety of the obtained coupled product can be reacted in a subsequent Thiol-Ene addition, allowing the iteration of the synthetic cycle, which makes the synthesis of larger oligomers (DP > 20) feasible.

Convergent synthesis approaches were developed in order to reduce the number of consecutive steps in multistep synthesis and thus to improve the overall yields.[342-343] Convergent synthesis approaches are very often used in peptide chemistry for the synthesis of longer polypeptide or protein sequences by the native chemical ligation of two or more smaller fragments (compare chapter 2.2.2.1).[168] Moreover, dendrimers can be synthesized in a convergent manner, meaning that the dendrons are synthesized separately and subsequently coupled to the core. On the other hand, dendrimer synthesis in a divergent manner means that the core is the starting material and branching points are introduced in each step.[344-345] For instance, the convergent and divergent synthesis of dendrimers *via* IMCRs, are described.[340, 346-347] For the synthesis of sequence-defined macromolecules, up to now, convergent approaches are barely used. However, the synthesis of monodisperse macromolecules is well explored and convergent approaches for the synthesis of sequence-defined macromolecules are recently more and more investigated.[272, 316, 330] In this study, a convergent synthesis approach towards sequence-defined macromolecules was investigated by combination of thiolactone chemistry and multicomponent reactions. Thiolactones are valuable precursors for thiols, since ring-opening can be conducted by nucleophiles, such as amines, releasing a thiol functional group, which is able to undergo subsequent reactions (Scheme 16).[348] This reaction was first described in 1958 and was applied as thiolation reaction for proteins.[348]

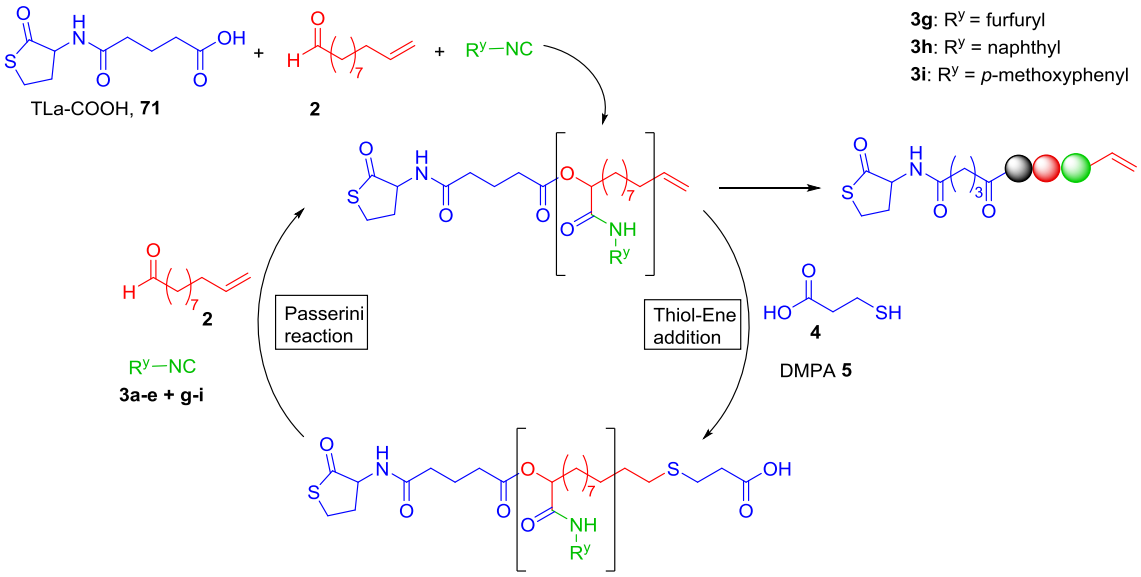


Scheme 16: Aminolysis of a thiolactone by primary amines, releasing a thiol-group, which is able to undergo subsequent reactions.[348]

Around 50 years later, thiolactones were shown to be valuable thiol-precursors for the synthesis of polymers.[349] For example, the direct polymerization of thiolactones bearing double bonds was shown. Hereby, the thiolactone was ring-opened by primary amines enabling the subsequent Thiol-Ene polymerization in the same pot under UV irradiation along with the introduction of side chains by the primary amine.[350-351] Besides, as

discussed in chapter 2.2.6.4 and shown in Scheme 6, thiolactones were employed in the synthesis of sequence-defined macromolecules on a solid support.[308]

In the herein described approach, thiolactones are used to protect the thiol-function and to be subsequently released by aminolysis, allowing the Thia-Michael addition with an isocyanide-containing acrylate. In this way, *α*-*ω*-functionalized sequence-defined building blocks can be obtained and employed for the convergent synthesis of larger structures. The synthesis strategy towards sequence-defined thiolactone-functionalized oligomeric building blocks is shown in Scheme 17. The utilization of the thiolactone-carboxylic acid **71** (TLa-COOH) in presence of 10-undecenal **2** and an isocyanide component, allows the formation of a Passerini-product containing the thiolactone moiety as well as a terminal double bond. Moreover, a tailored side chain can be introduced by the isocyanide component. The terminal double bond is subsequently functionalized with 3-mercaptopropionic acid **4**, allowing adjacent iterative cycles of P-3CR and Thiol-Ene addition reactions (Scheme 17).



*Scheme 17: Synthesis of sequence-defined building blocks by the P-3CR using thiolactone-carboxylic acid **71** (TLa-COOH) as starting material. By the use of 10-undecenal **2** as aldehyde component a terminal double bond is installed, which can be reacted in a subsequent Thiol-Ene addition with mercaptopropionic acid **4**. The introduction of the carboxylic acid functionality allows the repetition of the cycle and the elongation of the macromolecular chain.*

Hereby, the previously optimized reaction conditions (Chapter 4.1.1) were adapted: the first P-3CR using the thiolactone carboxylic acid **71** was conducted in a 4: 1 mixture of

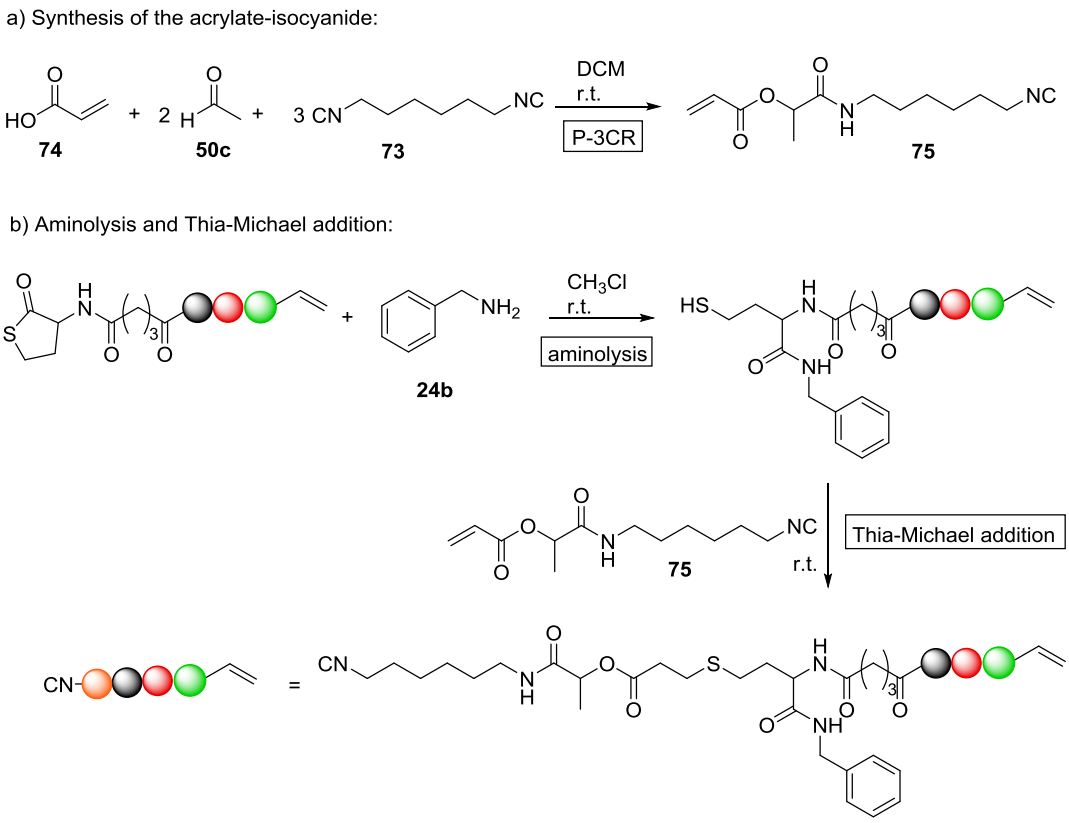
THF and water due to the insolubility of **71** in DCM and in THF. Moreover, for the Thiol-Ene addition reactions only 1.2 equivalents of 3-mercaptopropionic acid were used and the subsequent P-3CR was carried out without the purification of the intermediately obtained carboxylic acid. Owing to the small excess of the thiol, the amount of DMPA **5** needed to be adjusted carefully, due to an observed side reaction, which was independent of the reaction time and of the amount of solvent. It was observed that the side reaction can be suppressed by lower radical concentrations. Therefore, the Thiol-Ene additions were conducted using 1.7 mol% DMPA **5** for the first and 2.6 mol% of DMPA **5** for the second Thiol-Ene addition, respectively. In the second Thiol-Ene addition, larger amounts of DMPA **5** were required to obtain full conversion of the double bond. Since the residual 3-mercaptopropionic acid **4** undergoes the P-3CR with 10-undecenal **2** and the isocyanide, a larger excess of the isocyanide and 10-undecenal **2** was used (1.8 equivalents) in the subsequent P-3CR. The formed side product (P-3CR of **4**, **2** and the isocyanide) was easily separated during workup by column chromatography. This simplified procedure resulted in larger overall yields for the obtained trimers: Without purification of the product of the Thiol-Ene addition, the trimers were obtained in an average overall yield of 64 %, whereas the trimer **10** (chapter 4.1.1) was obtained in an overall yield of 48 %. The structures of the obtained sequence-defined macromolecules are shown in Figure 47, but it has to be noted that the chemical structures of the products after ring-opening of the thiolactone and the Thia-Michael addition are depicted there. Table 9 gives an overview of the reaction times, the obtained yields and the mass analysis results in the synthesis of the four different sequence-defined trimers. The yields are good to excellent in each step and the masses, obtained by ESI-MS measurements, are in very good agreement with the calculated values.

*Table 9: Overview of the reaction times, obtained yields and mass analysis for the synthesis of the four different sequence-defined trimers **78**, **81**, **86** and **87** with a thiolactone-moiety at the α-terminus and a double bond at the ω-terminus.*

reaction (product)	reaction time /hours	yield /%[a/b/c]	exact mass calculated[e]	mass found[e]
Building block 1				
1st P-3CR (**76**)	24	93[c]	505.2707	505.2698
2nd P-3CR (**77**)	28	88[a,b]	876.5201	876.5211
3rd P-3CR (**78**)	30	82[a,b]	1259.7695	1259.7716
Building Block 2				
1st P-3CR (**79**)	48	90[c]	531.2863	531.2861
2nd P-3CR (**80**)	48	86[a,b]	888.5201	888.5209
3rd P-3CR (**81**)	26	84[a,b]	1295.7331	1295.7340
Building Block 3				
1st P-3CR (**82**)	24	95[b]	505.2707	505.2700
2nd P-3CR (**83**)	24	85[a,b]	878.4630	878.4630
3rd P-3CR (**86**)	24	79[a,b]	1259.6603	1259.6605
Building Block 4				
1st P-3CR (**82**)	24	95[b]	505.2707	505.2700
2nd P-3CR (**83**)	24	85[a,b]	878.4630	878.4630
3rd P-3CR (**87**)	30	68[a,b,d]	1305.6811	1305.6818

[a] yield for two steps (Thiol-Ene addition and P-3CR) [b] after column chromatography; [c] after recrystallization [d] only 1.35 eq. of isocyanide added [e] $[M+Na]^+$

With four different sequence-defined trimers in hand, the thiolactone was ring-openend by benzylamine **24b** and the obtained thiol was reacted with an acrylate isocyanide *in situ* (Scheme 18 b). By the ring-opening of the thiolactone, the amine component allows the introduction of another tailored side chain and thus a tetramer is obtained after the aminolysis and the subsequent Thia-Michael addition. The required acrylate-isocyanide **75** was prepared by a simple P-3CR of acrylic acid **74**, acetaldehyde **50c** and an excess of diisocyanohexane **73** in a one-pot procedure. Alternative approaches (esterification, formamide synthesis and dehydration) starting from ethanolamine failed (Scheme 18 a). The synthesis of the acrylate-isocyanide **75** further proves the versatility and the modular nature of multicomponent reactions.



*Scheme 18: a) Synthesis of the acrylate-isocyanide **75** via the Passerini reaction of acrylic acid **74**, acetaldehyde **50c** and 1,6-diisocyanohexane **73**. b) Aminolysis of the sequence-defined thiolactone building blocks using benzylamine **24b** and the subsequent Thia-Michael addition of the isocyanide-acrylate **75**, yielding sequence-defined tetrameric α-ω-functionalized isocyanide building blocks.*

For the synthesis of the acrylate-isocyanide **75**, 1,6-diisocyanohexane **73** was used in threefold excess in respect to acrylic acid **74** in order to favor the monoaddition over the double addition. Attractively, the excess of the diisocyanide **73** could be recovered and reused, while the product **75** was isolated by column chromatography in a yield of 77 %. By the use of a larger excess of the diisocyanide **73**, even higher yields of the acrylate-isocyanide **75** might be obtained due to the more effective suppression of the double addition. The procedure for the aminolysis of the thiolactone is, as already mentioned, a two-step one-pot procedure, due to an observed side reaction of the amine and the acrylate-isocyanide. It was observed that the addition of the amine to the acrylate-isocyanide **75** proceeds faster than the nucleophilic ring-opening of the thiolactone, which might occur due to the inherent structure of the Passerini-derived acrylate **75**. Therefore, the amine was added to the thiolactone, allowing the ring-opening to proceed and after five to eight hours reaction time at room temperature (r.t.), the acrylate-

isocyanide **75** was added to enable the Thia-Michael addition. However, this two-step, one-pot procedure displays a compromise between high conversion of the thiolactone into the corresponding thiol and a minimum level of the undesired disulfide-formation. Therefore, the tetrameric isocyanide building blocks were obtained in yields between 69 % and 50 %, due to the aforementioned reasons. The structures of the four tetrameric isocyanide building blocks **88**, **89**, **90** and **91** are shown in Figure 47. Tetramer **90** contains a furan side-chain allowing orthogonal modifications *via* Diels-Alder reactions. The furfurylisocyanide **3g** is not commercially available and was therefore synthesized in a two-step procedure starting from the commercially available furfurylamine **84** (Figure 46).

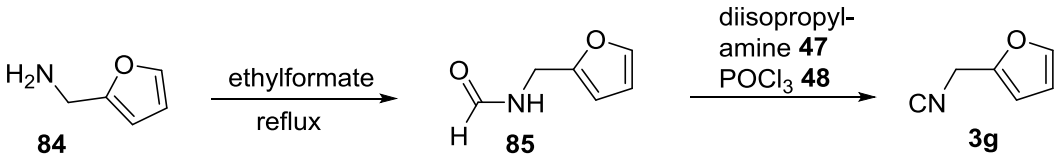


*Figure 46: Two-step synthesis of furfurylisocyanide **3g** starting from the commercially available furfurylamine **84**.*

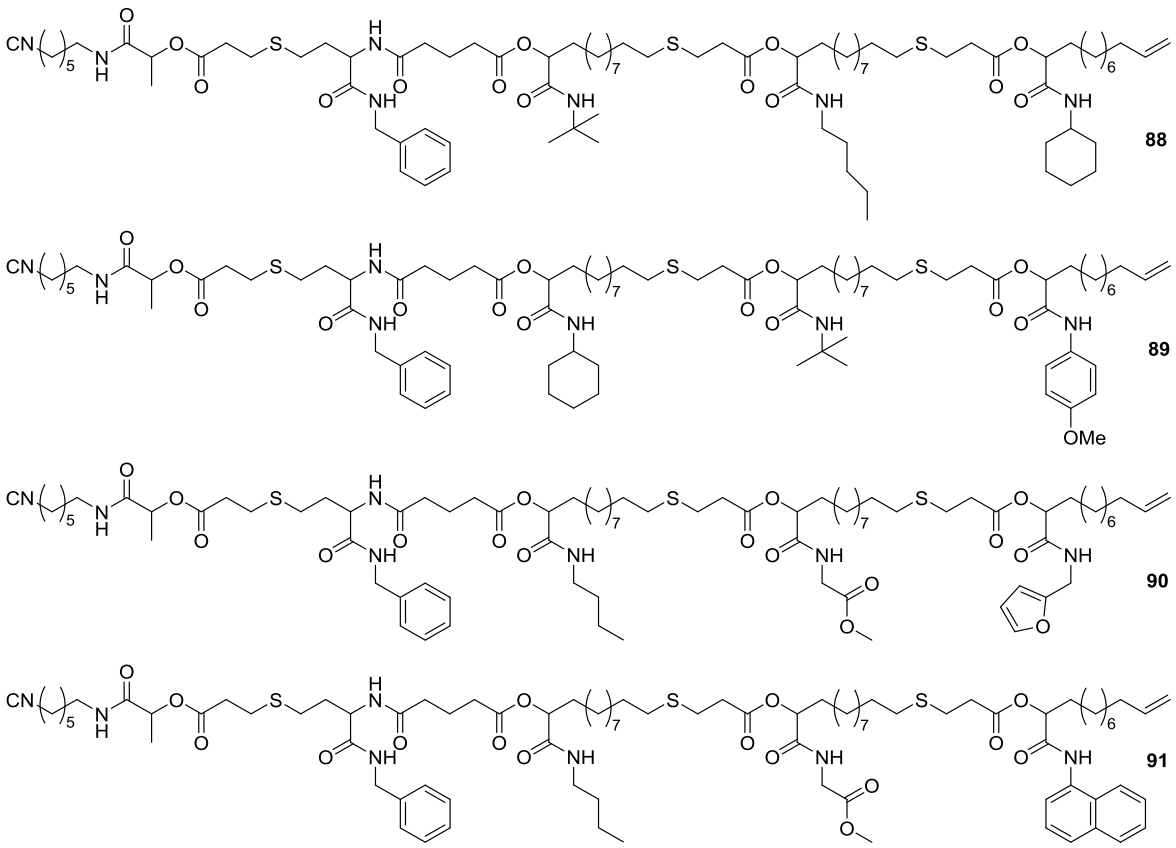


Figure 47: Library of sequence-defined isocyanide building blocks, which can be used in the convergent synthesis of larger sequence-defined macromolecules.

The four different isocyanide building blocks were obtained in high purities, which was confirmed by GPC measurements of the products of each P-3CR as well as the product of the aminolysis and the subsequent Thia-Michael addition (Figure 48 and Figure 50). However, small traces of the formed disulfide in the final isocyanide building blocks cannot be avoided in some cases. Moreover, the existence of the desired products was evidenced by mass spectrometry and the analysis of the obtained isotope patterns (Figure 49 and Figure 50). Figure 48 shows the GPC chromatograms obtained after each P-3CR and after the aminolysis in the synthesis of the sequence-defined tetramer **88**, verifying the high purity of the obtained products.

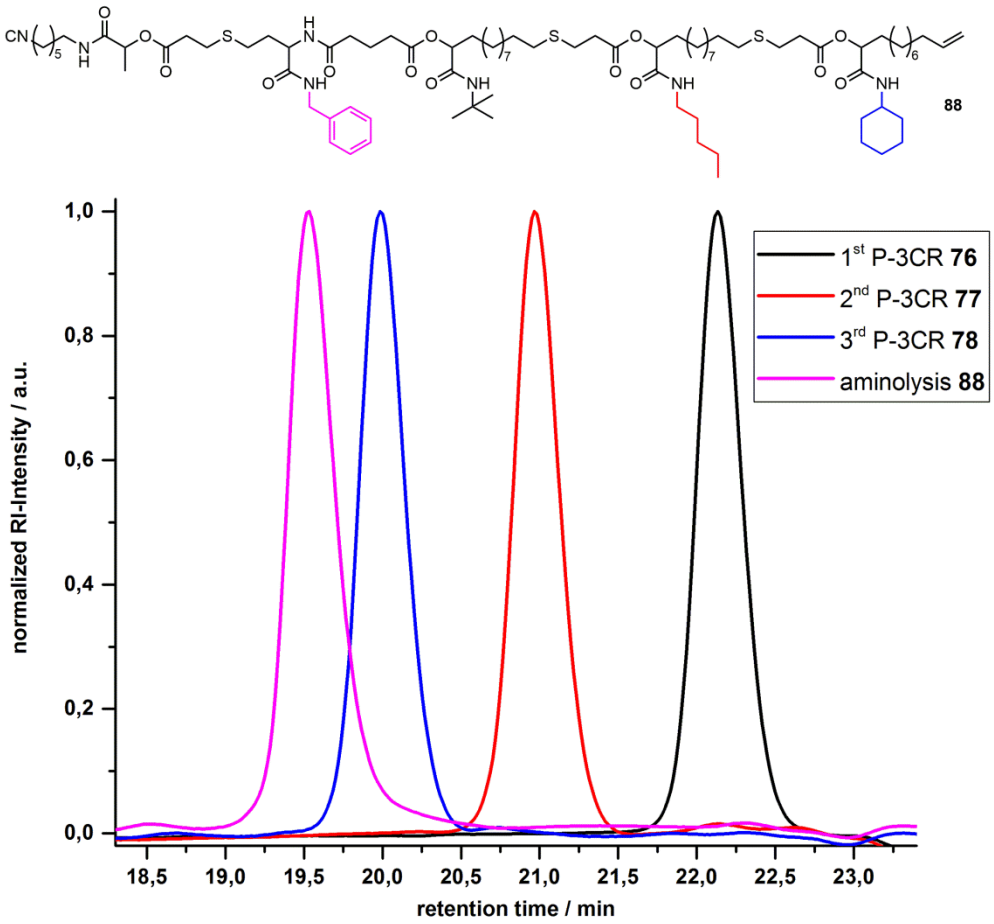


*Figure 48: Top: Structure of the first isocyanide building block **88**. Bottom: GPC traces of the products of the Passerini reactions and the aminolysis in the synthesis of the isocyanide building block **88**.*

Figure 49 shows the obtained mass spectrum for tetramer **88** along with the measured (black) and the calculated (blue) isotope pattern. The molecular ion is clearly observed and the measured isotope pattern is in very good agreement with the calculated one, proving the structure of the isocyanide building block **88**.

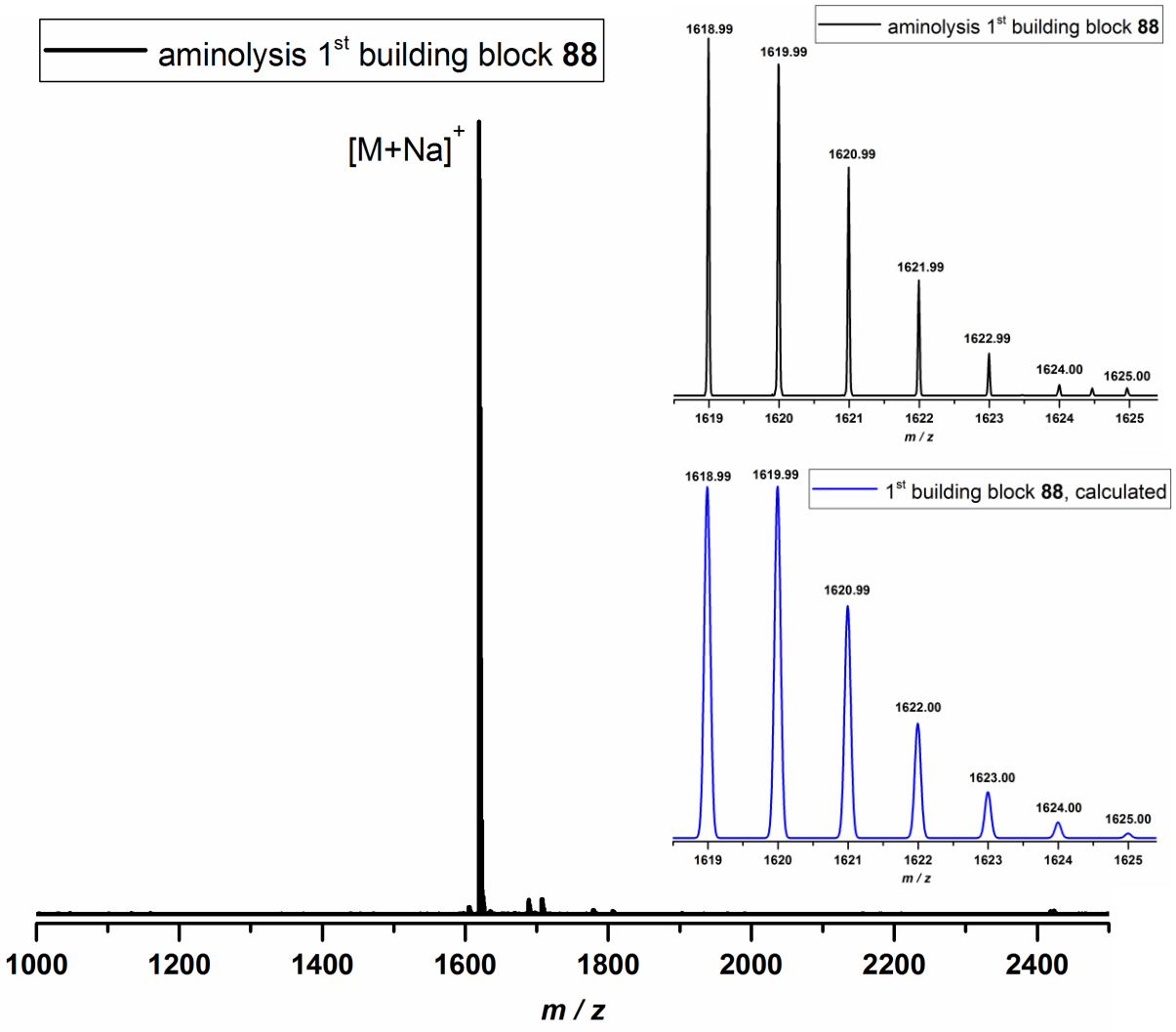


*Figure 49: ESI-MS spectrum of the sequence-defined tetramer **88**, where the molecular ion ([M+Na]$^+$ calculated: 1618.99 m/z, found: 1618.99 m/z) is clearly observed. Moreover the isotope pattern is shown (black), which is in very good agreement with the calculated one (blue) and thus confirming the structure of tetramer **88**.*

Figure 50 shows the obtained GPC traces, mass spectra and isotope patterns for the remaining three sequence-defined isocyanide-tetramers **89**, **90** and **91**. The GPC traces confirm the high purity of the products and the mass spectra as well as the isotope patterns prove the structures of the targeted tetramers.

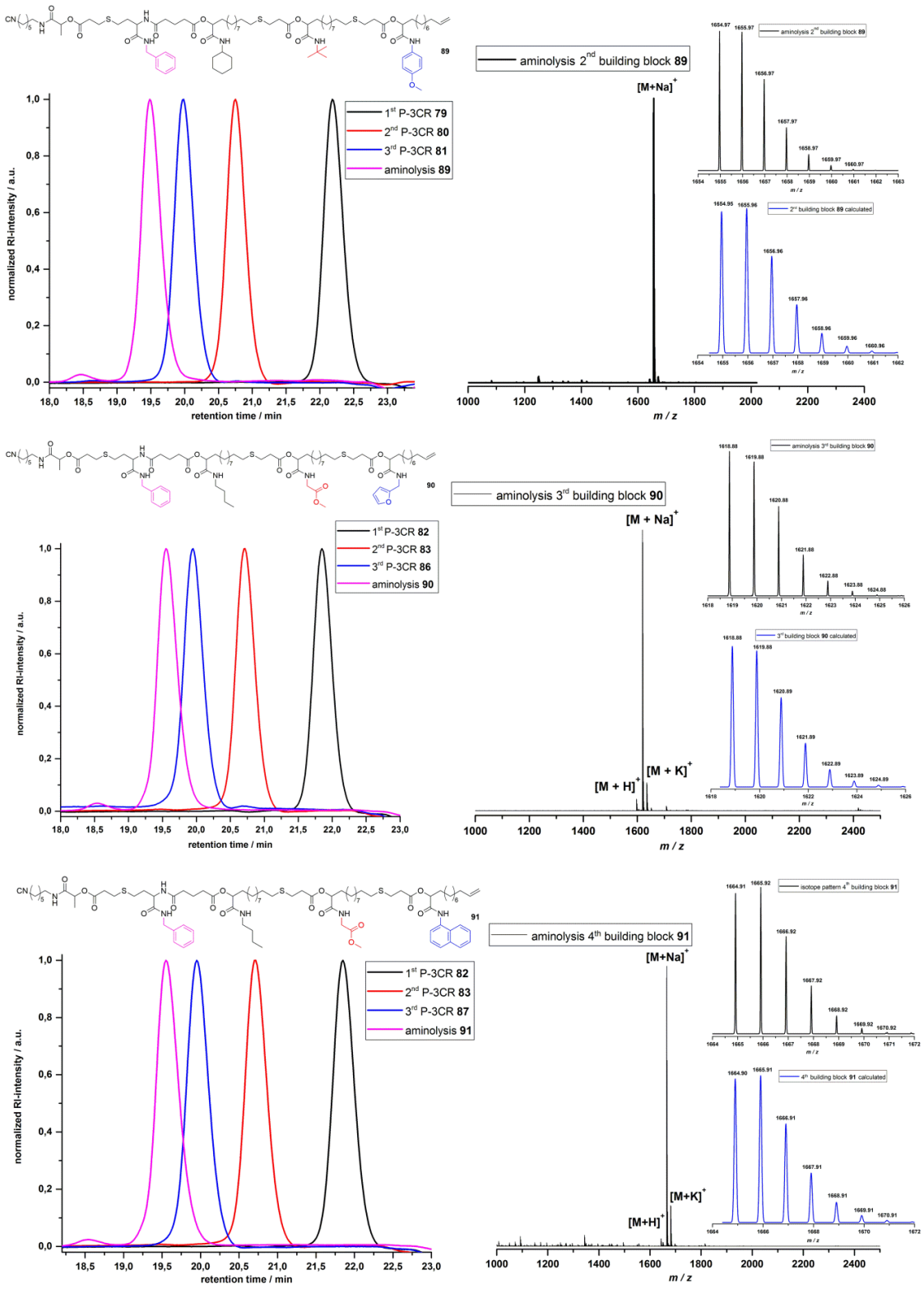


*Figure 50: GPC traces, mass spectra and isotope patterns (black: measured, blue: calculated) of the isocyanide building blocks **89** (top, $[M+Na]^+$ calculated:1654.95 m/z, found: 1654.97 m/z), **90** (middle, $[M+Na]^+$ calculated:1618.88 m/z, found: 1618.88 m/z) and **91** (bottom, $[M+Na]^+$ calculated:1664.90 m/z, found: 1664.91 m/z).*

Moreover, the successful end group transformation can be followed by ^{1}H NMR (Figure 51): The signals of the thiolactone disappear (purple boxes in Figure 51), whereas signals for the formed benzyl amide appear after aminolysis and the Thia-Michael addition (red and blue boxes in Figure 51).

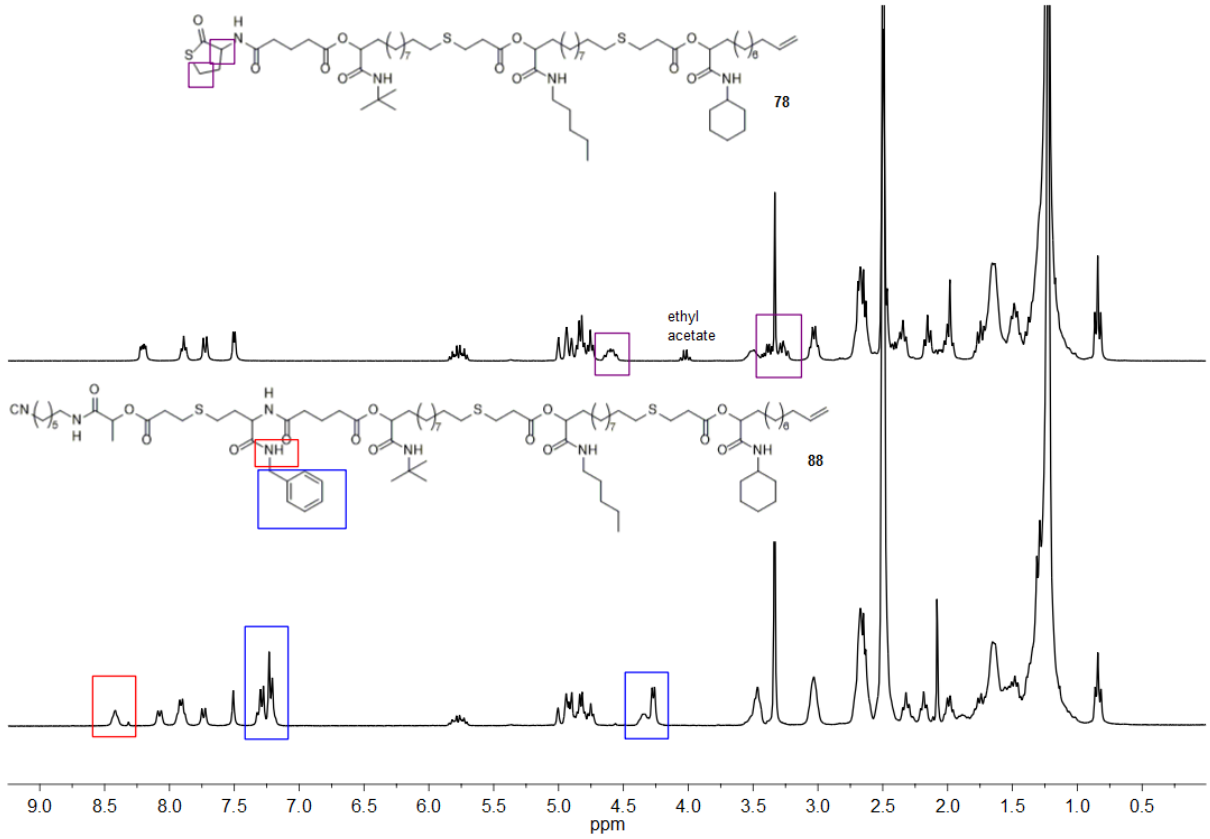


*Figure 51: NMR spectra obtained for the product of the third P-3CR **78** (top) and for the product of the aminolysis and Thiol-Michael addition **88** (bottom). It is obvious that the signals for the thiolactone disappear (purple boxes) and that signals for the newly formed benzyl amide appear (red and blue boxes).*

Moreover, infrared (IR) spectra show a characteristic band around 2150 cm^{-1}, if aliphatic isocyanides are present. Therefore, the IR spectra of the diisocyanide **73**, of the acrylate-isocyanide **75** and the product of the aminolysis **88** were compared (Figure 52). In each spectrum, a signal at 2146.88 cm^{-1} is observed, further confirming the introduction of the isocyanide end group.

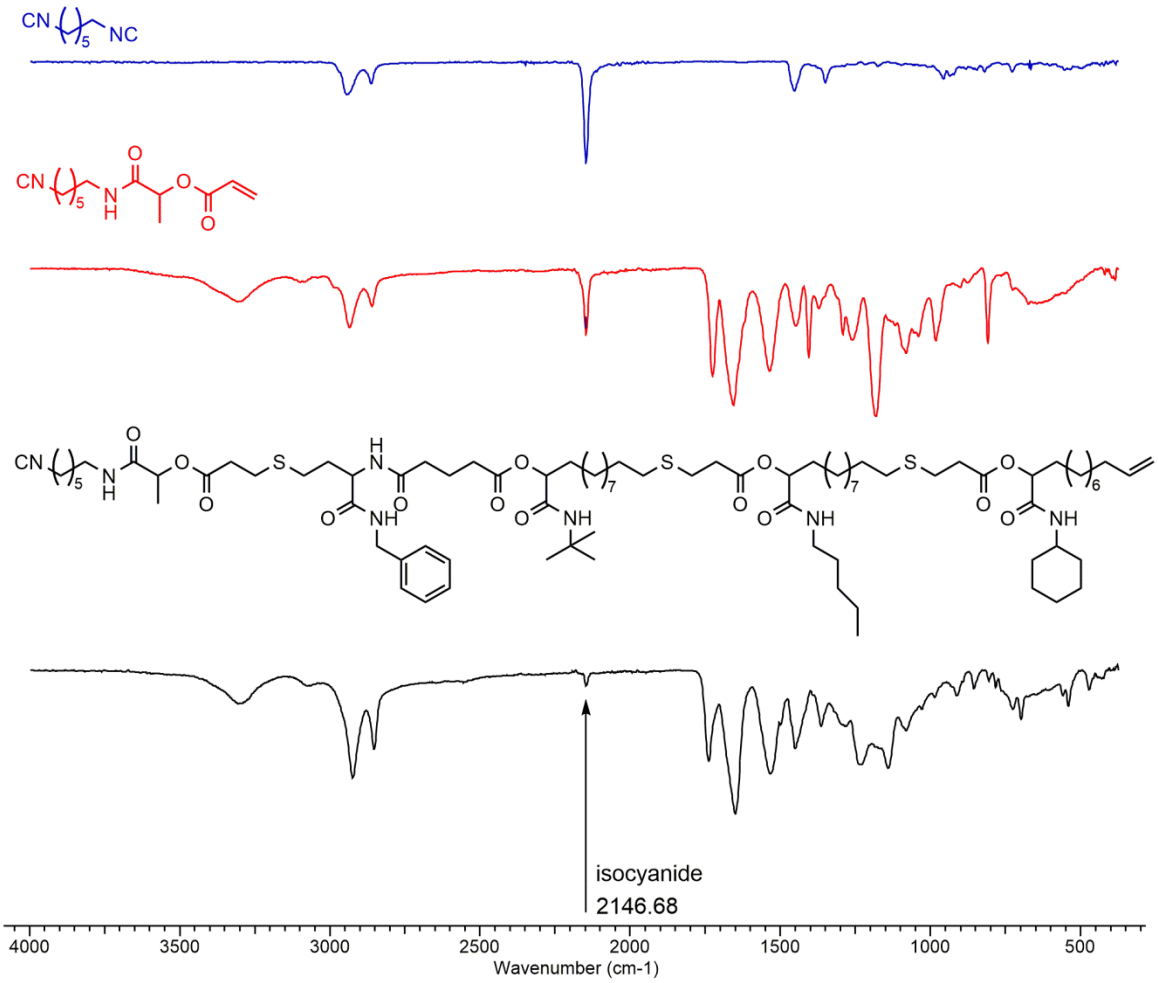


*Figure 52: Infrared spectra and structures of the synthesized isocyanides: The diisocyanide **73** (blue curve), the isocyanide acrylate **75** (red curve) as well as the isocyanide building block **88** (black curve) show a signal at 2146.88 cm^{-1}, indicating the presence of the aliphatic isocyanide.*

Having four different sequence-defined isocyanide building blocks in hand, a sequence-defined trimer with a carboxylic acid end group was synthesized as start-sequence. Therefore, the monomer approach, which was introduced in chapter 4.2, was employed for the synthesis of a sequence-defined trimer with a carboxylic acid end group in an overall yield of 70 % (six steps). Figure 53 shows the GPC chromatograms obtained after the first (**92**) and second P-3CR (**93**) as well as the structure and the GPC chromatogram of the deprotected trimer **95**. The GPC chromatogram evidences the high purity of the intermediate products **92** and **93** and the deprotected trimer **95**.

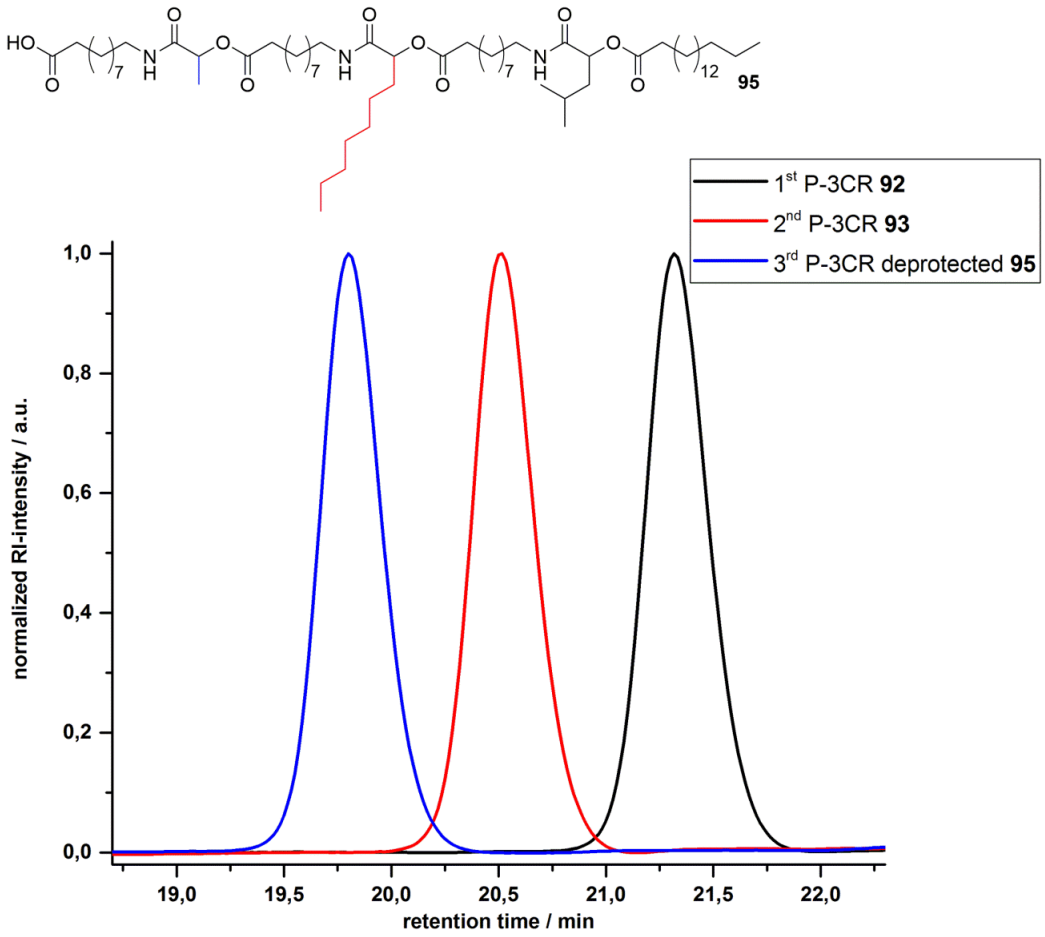


*Figure 53: Top: Structure of the sequence-defined trimer **95**. Bottom: GPC traces of the products obtained after the first and second P-3CR (**92**, black curve and **93**, red curve) and after the deprotection of the product of the third P-3CR (**95**, blue curve).*

Moreover, the structure was proven by ^{1}H NMR measurements (see Experimental Section Chapter 6.3.4), mass spectrometry and the obtained isotope pattern (Figure 54). In the mass spectrum (Figure 54), the molecular ion is clearly observed and the measured isotope pattern (black) agrees very well with the calculated one (blue).

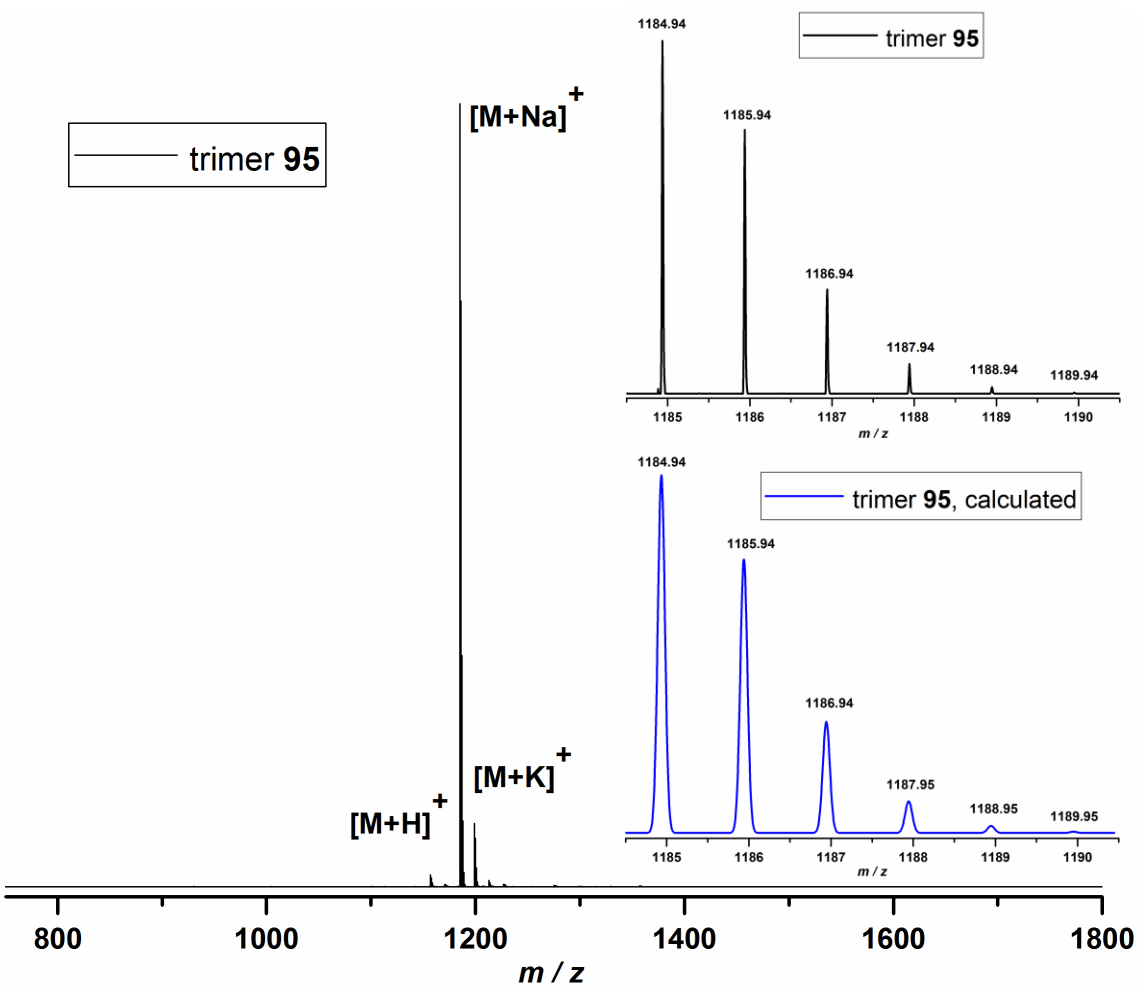
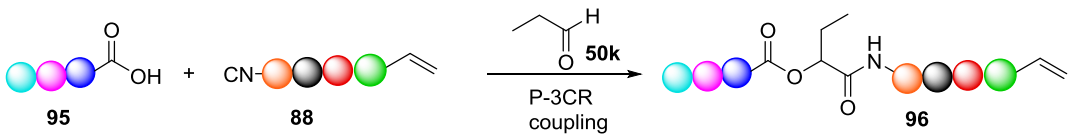


*Figure 54: Mass spectrum of the obtained trimer **95**, clearly showing the hydrogen, sodium and potassium adducts as well as the corresponding isotope pattern (black curve), which is in very good agreement with the calculated one (blue curve). $[M+Na]^+$ calculated: 1184.94 Da, found: 1184.94 Da.*

Having the start-sequence (trimer **95**), as well as the isocyanide building blocks (tetramers **88**, **89**, **90** and **91**) prepared, the convergent synthesis of larger structures was investigated. Therefore, 1.00 equivalent of the starting trimer **95** was reacted with 1.05 equivalents of the first isocyanide building block **88** and 10.0 equivalents of propionaldehyde **50k** in a P-3CR (Scheme 19).



*Scheme 19: The Passerini three-component coupling of the trimer carboxylic acid **95** and the isocyanide building block **88** yielding the sequence-defined octamer **96**.*

For this purpose, the trimer **95** serves as carboxylic acid component and the tetramer **88** as isocyanide component while another tailored side chain is introduced by the aldehyde component **50k**. The sequence-defined octamer **96** was obtained as product of the Passerini reaction after column chromatography in a yield of 80 %. The structure of the sequence-defined octamer **96** is shown in Figure 55.

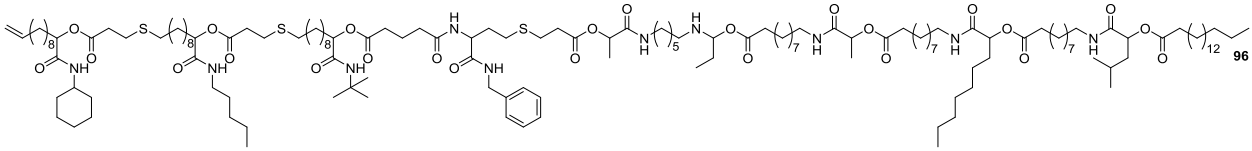


*Figure 55: Structure of the sequence-defined octamer **96**.*

Figure 56 shows the GPC traces of the two oligomeric building blocks **95** and **88** as well as the GPC trace of the sequence-defined octamer **96**. The GPC trace of **96** proves the high purity of the product and due to the large increase in molecular weight, the GPC trace of the octamer **96** is shifted considerably towards shorter retention times.

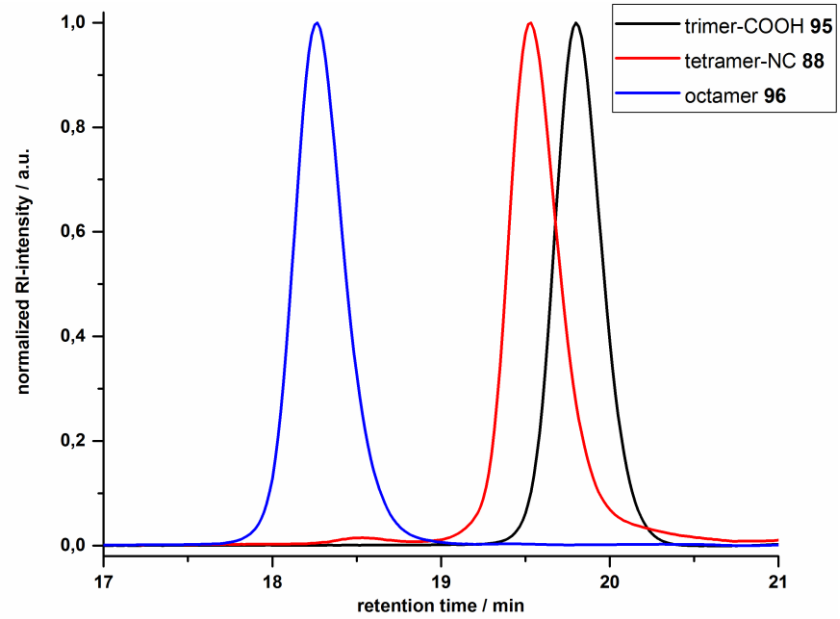


*Figure 56: GPC traces of the carboxylic acid trimer **95** (black curve) , the isocyanide tetramer **88** (red curve) and the sequence-defined octamer **96** (blue curve).*

Additionally the structure was verified by NMR measurements (Experimental Section, Chapter 6.3.4), mass spectrometry and the analysis of the isotope pattern (Figure 57). The single and the doubly charged sodium cations are clearly observed and the isotope pattern (black) is in very good agreement with the calculated one (blue). Due to the congruency of the isotope patterns, the chemical formula of the sequence-defined octamer **96** is evidenced.

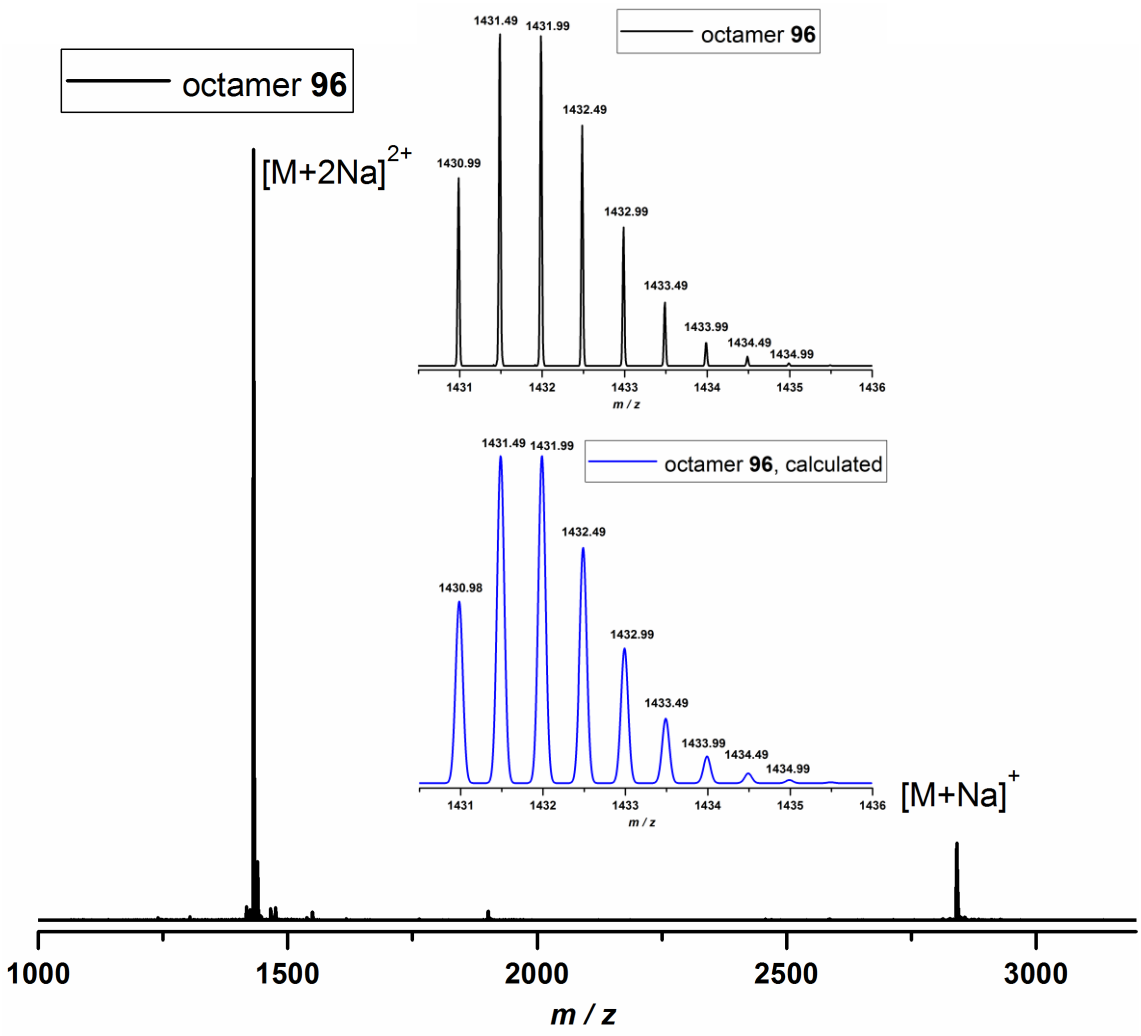
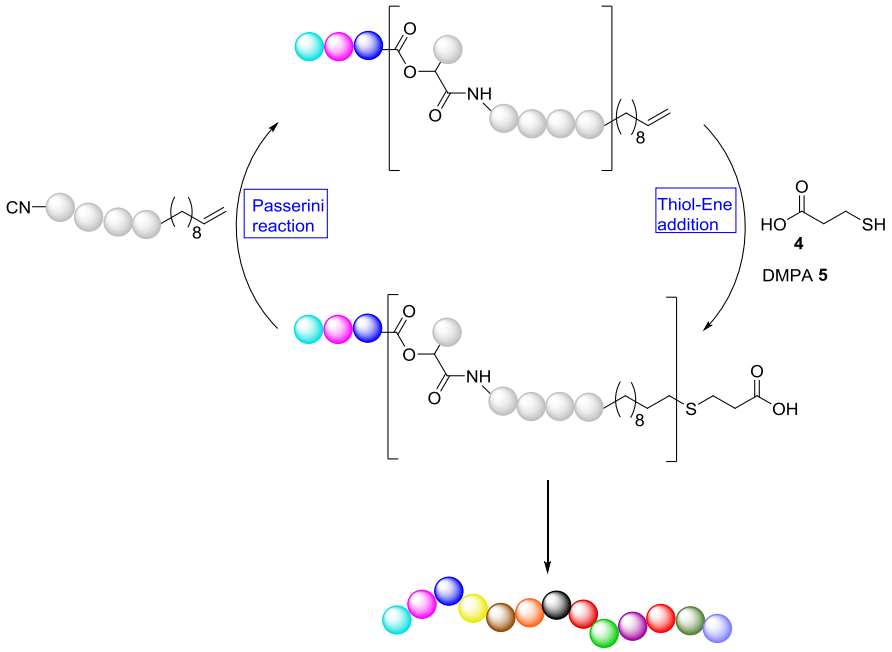


*Figure 57: Mass spectra obtained for octamer **96**. The single ($[M+Na]^+$ calculated: 2839.98 Da, found: 2839.99 Da) and doubly charged sodium cations ($[M+2Na]^+$ calculated: 1431.49 Da, found: 1431.49) are clearly observed. Moreover, the isotope pattern for the doubly charged sodium cation (black) is in very good agreement with the calculated one (blue).*

Since the obtained product **96** bears a terminal double bond, the iteration of the cycle is possible. Comparable to the approach of chapter 4.1.1, the double bond can be functionalized in a Thiol-Ene addition using 3-mercaptopropionic acid **4** and catalytic amounts of DMPA **5**. In turn, the introduction of the carboxylic end group allows another P-3CR. Along with the use of another isocyanide building block, the convergent synthesis of macromolecules with a higher DP can be accomplished (Scheme 20).



Scheme 20: Convergent synthesis of larger sequence-defined macromolecules. The iteration of the Thiol-Ene addition and the P-3CR using different isocyanide building blocks allows the convergent synthesis of sequence-defined macromolecules.

First preliminary results show that the iteration of the cycle is possible, however, further optimization is necessary in order to force the Thiol-Ene addition to completion. Therefore, a larger excess of the thiol can be used since the product of the Thiol-Ene addition **97** can be precipitated in hexane/ethyl acetate mixtures, in order to remove the excess of the thiol. Also, the P-3CR with the isocyanide building block **89** was tested, indicating the successful formation of the sequence-defined 13-mer **98** (Figure 58) by a shift of the GPC trace towards shorter retention times.

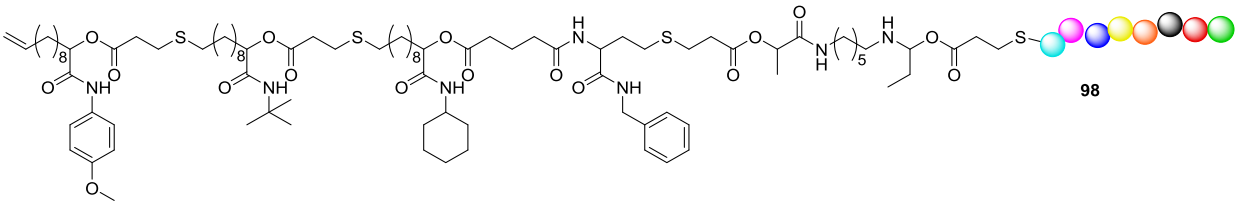


*Figure 58: Structure of the sequence-defined 13-mer **98**. The structure of the synthesized octamer **96** (Figure 55) is shown schematically. Each sphere displays one repeating unit containing a tailored side chain.*

In conclusion, it was shown that by combination of thiolactone chemistry with multicomponent reactions, the convergent synthesis of sequence-defined macromolecules is possible. First, sequence-defined building blocks, with a thiolactone end group were prepared, allowing the introduction of an isocyanide functionality by aminolysis and the adjacent Thia-Michael addition. Moreover, it was shown that the coupling of a sequence-defined carboxylic acid containing trimer with an isocyanide building block can be successfully conducted and that the product can be obtained in high yield and purity. In that way, a sequence-defined octamer with a molecular weight of 2818.18 g mol^{-1} and eight different side chains was prepared. Additionally, the iteration of the Thiol-Ene addition and the coupling of oligomers *via* the P-3CR was tested, indicating the successful formation of larger sequence-defined oligomers. All in all, the combination of thiolactone chemistry and MCRs demonstrates a promising synthesis concept. Due to the versatility of the two approaches, the introduction of many different and tailored side chains can be achieved and oligomers of higher DPs are obtainable.

5 Conclusion and Outlook

In summary, it was shown that the P-3CR and the U-4CR are highly valuable reactions for the synthesis of sequence-defined macromolecules, also in larger scale. The inherent versatility and straightforwardness of the described approaches is built into the nature of multi-component reactions, which seem to be the natural choice for this task. The scalability is furthermore an important factor in order to bring sequence-defined materials into application. Moreover, IMCRs were shown to be very versatile, allowing the introduction of various tailored and functional side chains. Furthermore, the products can be obtained in high purity and high yields, which is especially important in the synthesis of larger oligomers. Within this thesis, the P-3CR and the U-4CR were investigated in a protecting group-free approach by the iteration with a Thiol-Ene addition reaction (Chapter 4.1.1 and Chapter 4.1.2). Hereby, tetramers and pentamers were synthesized and different side chains were introduced. Interestingly, the use of the U-4CR allows the introduction of two tailored side chains per monomer unit. Moreover, the iterative application of the P-3CR and the Thiol-Ene addition was investigated on a soluble polymeric support, benefitting from easier and time-saving purification by precipitation. The use of a monomer containing a benzylester-protected acid functionality as well as an isocyanide group allowed additionally the synthesis of a sequence-defined decamer with ten different (functional) side chains (Chapter 4.2). It has to be emphasized that each step of the decamer synthesis enabled isolated yields above 90 % and thus a quantity of more than two grams of the sequence-defined decamer was obtained. Due to the introduction of a double bond in the tenth side chain of the decamer, the subsequent self-metathesis resulted in a symmetric icosamer with a perfectly-defined monomer sequence along with 20 tailored side chains. Finally, a convergent synthesis approach, combining thiolactone chemistry and the P-3CR was investigated (Chapter 4.3). Therefore, a library of tetrameric isocyanide building blocks was synthesized, making use of a thiolactone carboxylic acid as starting compound. Moreover, a trimer with a carboxylic acid end group was synthesized by the monomer approach. The carboxylic acid trimer and an isocyanide building block were subsequently reacted with an aldehyde in a P-3CR and a sequence-defined octamer was thus obtained. Interestingly, the sequence-defined octamer bears a terminal double

bond, which enables a Thiol-Ene addition and thus subsequent couplings with (other) isocyanide building blocks (compare Chapter 4.1.1). Besides, one of the isocyanide building blocks bears a furan-moiety, serving for post-polymerization modifications. All in all, three different approaches and two different MCRs were investigated within this thesis. Hereby, sequence-defined macromolecules of up to a DP of 20 were successfully synthesized and fully characterized. These results clearly show the potential of MCRs in the synthesis of sequence-defined macromolecules.

In the future, the research on new monomers for sequence-control *via* MCRs should be deepened in order to reach control over multiple parameters at the same time. By the use of monomers of different chain lengths, the density of functional groups, the density of the side chains and the backbone structure could be fine-tuned. Accompanied with the introduction of tailored side chains, the full control over the synthesized macromolecules could be accomplished. Moreover, the use of chiral amino acid-based monomers allows the introduction of chirality, which might evoke interesting material properties. The use of rigid (*e.g.* aromatic) monomers allows the fine-tuning of the material properties. Besides, a monomer with another protecting group (*e.g.* methyl ester) should be investigated for its use in Ugi reactions due to the observed side reaction with the benzylester-protected monomer. Additionally, the examination of side-chain property relationships will be interesting. For instance, the introduction of bulky side chains might allow the formation of helical structures. Another very interesting future topic is the investigation of sequence-property relationships, which might reveal valuable guidelines for the synthesis of sequence-defined macromolecules for certain applications, such as enzyme-mimics. The introduction of catalytically active side-chains along with the study of the three-dimensional structures of the highly-defined materials might be important steps towards the synthesis of artificial enzymes.

6 Experimental Section

6.1 Materials:

The following chemicals were used as received: 10-undecenal **2** (>90 %, Sigma-Aldrich), 3-mercaptopropionic acid **4** (99 %, Sigma-Aldrich), cyclohexyl isocyanide **3a** (98 %, Sigma-Aldrich), *tert*-butyl isocyanide **3b** (98 %, Sigma-Aldrich), stearic acid **1a** (95 %, Sigma-Aldrich), 2,2 dimethoxy-2-phenylacetophenone **5** (DMPA, 99 %, Sigma-Aldrich), 1-pentyl isocyanide **3c** (97 %, Sigma-Aldrich), *n*-butyl isocyanide **3d** (98 %, Acros Organics), methyl isocyanoacetate **3e** (>97 %, Sigma-Aldrich), benzyl isocyanide **3f** (98 %, Sigma-Aldrich), propylamine **24a** (>99 %, Sigma-Aldrich), benzylamine **24b** (>99.5 %, Sigma-Aldrich), cyclohexylamine **24c** (99 %, Sigma-Aldrich), ethanolamine **24d** (>98 %, Sigma-Aldrich), 4-methoxybenzylamine **24e** (98 %, Sigma-Aldrich), isopropylamine **24f** (>98.5 %, Sigma-Aldrich), 11-aminoundecanoic acid **41** (97 %, Sigma-Aldrich), benzyl alcohol **42** (99 %, Sigma-Aldrich), thionyl chloride **43** (99 %, Sigma-Aldrich), trimethyl orthoformate **45** (99 %, Sigma-Aldrich), diisopropylamine **47** (>99.5 %, Sigma-Aldrich), phosphorous (V) oxychloride **48** (99 %, Sigma-Aldrich), isobutyraldehyde **50a** (98 %, Sigma-Aldrich), heptaldehyde **50b** (95 %, Sigma-Aldrich), acetaldehyde **50c** (99 %, Sigma-Aldrich), cyclohexanecarboxaldehyde **50d** (97 %, Sigma-Aldrich), isovaleraldehyde **50e** (95 %, Sigma-Aldrich), 2-ethylbutyraldehyde **50f** (90 %, Sigma-Aldrich), 2-phenylpropionaldehyde **50g** (98 %, Sigma-Aldrich), 3-cyclohexene-1-carboxaldehyde **50h** (97 %, Sigma-Aldrich), 2-methyl-3-(*p*-isopropylphenyl)propionaldehyde **50i** (>95 %, Sigma-Aldrich), *cis*-4-hepten-1-al **50j** (>98 %, Sigma-Aldrich), propionaldehyde **50 k** (>97 %, Sigma-Aldrich), *ß*-alanine (99 %, Sigma-Aldrich), 6-aminohexanoic acid (>98.5 %, Sigma-Aldrich), 4-(aminomethyl)benzoic acid (97 %, Sigma-Aldrich), palladium on activated charcoal (10 % palladium basis, Sigma-Aldrich), hydrogen (99,999 %, Air Liquide), *p*-benzoquinone (>98 %, Sigma-Aldrich), Hoveyda-Grubbs 2nd generation catalyst (97 %, Sigma-Aldrich), thiolactone-COOH **71** was synthesized by Dr. Pieter Espeel (Ghent University) according to a previously reported procedure,[308] hexamethylenediamine **72** (98 %, Sigma-Aldrich), 1,6-diisocyanohexane **73** was synthesized according to a literature-procedure,[118] acrylic acid **74** (99 %, Sigma-Aldrich; acrylic acid was distilled

before use), butyl formate (97 %, Sigma-Aldrich), 2-naphthyl isocyanide **3h** (95 %, Sigma-Aldrich), furfurylamine **84** (>99 %, Sigma-Aldrich), ethyl formate (97 %, Sigma-Aldrich), 4-methoxyphenyl isocyanide **3i** (97 %, Sigma-Aldrich), silica gel 60 (0.040 - 0.063 mm, Sigma-Aldrich), TLC silica gel F_{254} (Sigma-Aldrich), cerium(IV)-sulfate (99 %, Sigma-Aldrich), phosphomolybdic acid hydrate (99 %, Sigma-Aldrich), chloroform-d (99.8 atom-% D, Euriso-Top), sodium hydrogencarbonate (>95 %, Sigma-Aldrich), sodium sulfate (>99 %, anhydrous, Sigma-Aldrich), pyridine (99.5 %, Acros Organics), poly(ethylene glycol) methyl ether (average M_n ~ 2000 Da, Sigma-Aldrich), succinic anhydride (>99 % Sigma-Aldrich), methanol-d_4 (99,8 atom-% D, Euriso-Top), DMSO-d_6 (99,8 atom-% D, Euriso-Top), sodium carbonate (98 %, Sigma-Aldrich). All solvents were used without further purification, unless otherwise noted.

6.2 Instrumentation

NMR spectra were recorded on a Bruker AVANCE DPX spectrometer operating at 300 MHz for ^{1}H- and at 75 MHz for ^{13}C- NMR measurements. $CDCl_3$, CD_3OD and DMSO-D_6 were used as solvents and the resonance signals at 7.26 ppm and 2.50 ppm (^{1}H) and 77.16 ppm and 39.52 ppm (^{13}C) served as reference for the chemical shift *δ*.

Polymers **13**-**21** were characterized on a **GPC** System LC-20A (Shimadzu) equipped with a SIL-20A autosampler, RID-10A refractive index detector in THF (flow rate 1 mL/min) at 50 ° C, The analysis was performed on the following column system: main-column PSS SDV analytical (5 µm, 300 mm × 8.0 mm, 10000 Å) with a PSS SDV analytical precolumn (5 µm, 50 mm × 8.0 mm). For the calibration narrow linear poly(methyl methacrylate) standards (Polymer Standards Service PPS, Germany) ranging from 1100 to 981000 Da were used.

Oligomers (**6**-**12** and **23**-**29)** were characterized on a Varian 390-LC **gel permeation chromatography** (**GPC**) system equipped with a LC-290 pump (Varian), refractive index detector (24 ° C), PL AS RT GPC-autosampler (Polymer laboratories) and a Varian Pro Star column oven Model 510, operating at 40 ° C. For separation two PLgel 5 µm Mixed-D columns and a guard column were used. Detection was done by a refractive index detector operating in THF (flow rate 1 mL min^{-1}). For calibration linear poly(methylmethacrylate) standards (Agilent) ranging from 875 to 1 677 000 Da were used.

Oligomers (**30-38, 49-67, 70, 76-83, 86-98**) were characterized on a Varian 390-LC **gel permeation chromatography (GPC)** system equipped with a LC-290 pump (Varian), refractive index detector (24 ° C), PL AS RT GPC-autosampler (Polymer laboratories) and a Varian Pro Star column oven Model 510, operating at 40 ° C. For separation two SDV 5 µm linear S columns (8 x 300 mm) and a guard column (8 x 50 mm) were used. Detection was done by a refractive index detector operating in THF (flow rate 1.0 mL min^{-1}). For calibration linear poly(methylmethacrylate) standards (Agilent) ranging from 875 to 1 677 000 Da were used.

Thermal properties of the prepared substances were studied *via* differential scanning calorimetry (DSC) with a Mettler Toledo DSC star^{e} system operating under nitrogen atmosphere using about 5 mg of the respective sample for the analysis. Method: heating from 25 to 200 ° C with a heating rate of 20 K/minute, then cooling from 200 to – 75 ° C with a cooling rate of 20 K/minute, the second scan starts at -75 ° C and heats up until 200 ° C with a heating rate of 10 K/minute. Melting points were determined as peak temperature of the second heating scan.

Infrared spectra (IR) were recorded on a Bruker Alpha-p instrument in a frequency range from 3998 to 374 cm^{-1} applying KBr and ATR technology.

Fast atom bombardment (FAB) mass spectra were recorded on a *Finnigan* MAT 95 instrument. The protonated molecule ion is expressed by the term: $[(M+H)]^{+}$.

GPC/ESI-MS spectra for oligomers **6**-**12** and polymers **13**-**21** were recorded on a LXQ mass spectrometer (Thermo Fisher Scientific, San Jose, CA) equipped with an atmospheric pressure ionization source operating in the nebulizer-assisted electrospray mode. The instrument was calibrated in the m/z range 195 - 1822 using a standard containing caffeine, Met-Arg-Phe-Ala acetate (MRFA), and a mixture of fluorinated phosphazenes (Ultramark 1621) (all from Aldrich). A constant spray voltage of 4.5 kV, a dimensionless sweep gas flow rate of 2, and a dimensionless heat gas flow rate of 12 were applied. The capillary voltage, the tube lens offset voltage, and the capillary temperature was set to 60 V, 110 V, and 275 ° C, respectively. The LXQ was coupled to a Series 1200 HPLC-system (Agilent, Santa Clara, CA) consisting of a solvent degasser (G1322A), a binary pump (G1312A), and a high-performance autosampler (G1367B), followed by a thermostated column compartment (G1316A). Separation was performed on two mixed bed size exclusion chromatography columns (Polymer Laboratories, Mesopore 2504.6 mm, particle diameter 3 µm) with precolumn (Mesopore 50-4.6 mm) operating at 30 ° C. THF at a flow rate of 0.30 mL min^{-1} was used as eluent. The mass spectrometer was coupled to the column in parallel to an RI-detector (G1362A with SS420x A/D) in a set-up described previously, 0.27 mL min^{-1} of the eluent was directed through the RI detector, and 30 µL min^{-1} was infused into the electrospray source after post column addition of a 100 µM solution of sodium iodide in methanol at 20 µL min^{-1}

by a micro flow HPLC syringe pump (Teledyne ISCO, Model 100DM). 20 µL of a polymer solution with a concentration of ~3 mg mL^{-1} was injected onto the HPLC system.

GPC-ESI-MS spectra for oligomers **69**, **70**, **76-38**, and **86**-**98** were recorded on a Q Exactive (Orbitrap) mass spectrometer (Thermo Fisher Scientific, San Jose, CA, USA) equipped with an HESI II probe. The instrument was calibrated in the *m/z* range 74–1822 using premixed calibration solutions (Thermo Scientific). A constant spray voltage of 4.6 kV, a dimensionless heath gas of 8, and a dimensionless auxiliary gas flow rate of 2 were applied. The capillary temperature and the S-lens RF level were set to 320 ° C and 62.0, respectively. The Q Exactive was coupled to a UltiMate 3000 UHPLC System (Dionex, Sunnyvale, CA, USA) consisting of a pump (LPG 3400SD), autosampler (WPS 3000TSL), and a thermostated column department (TCC 3000SD). Separation was performed on two mixed bed size exclusion chromatography columns (Polymer Laboratories, Mesopore 250 × 4.6 mm, particle diameter 3 µm) with precolumn (Mesopore 50 × 4.6 mm) operating at 30 ° C. THF at a flow rate of 0.30 $mL \cdot min^{-1}$ was used as eluent. The mass spectrometer was coupled to the column in parallel to a RI-detector (RefractoMax520, ERC, Japan). 0.27 $mL \cdot min^{-1}$ of the eluent were directed through the RI-detector and 30 $\mu L \cdot min^{-1}$ infused into the electrospray source after postcolumn addition of a 100 µM solution of sodium iodide in methanol at 20 $\mu L \cdot min^{-1}$ by a micro-flow HPLC syringe pump (Teledyne ISCO, Model 100DM). A 20 µL aliquot of a polymer solution with a concentration of 2 $mg \cdot mL^{-1}$ was injected onto the HPLC system.

Orbitrap Electrospray-Ionization Mass Spectrometry (ESI-MS): mass spectra for oligomers **49** - **67** and **70** were recorded on a Q Excative (Orbitrap) mass spectrometer (Thermo Fisher Scientific, San Jose, CA, USA) equipped with an atmospheric pressure ionization source operating in the nebulizer assisted electrospray mode. The instrument was calibrated in the m/z-range 150-2000 using a standard containing caffeine, Met-Arg-Phe-Ala acetate (MRFA) and a mixture of fluorinated phosphazenes (Ultramark 1621) (all from Aldrich). A constant spray voltage of 3.5 kV and a dimensionless sheath gas of

6 and a sweep gas flow rate of 2 were applied. The capillary voltage and the S-lens RF level were set to 68.0 V and 320 ° C, respectively.

***UV-Lamps*:** Thiol-Ene additions were conducted using two handheld UV-lamps from Vetter Laborgeräte (Wiesloch) UVKL4U operating at 365 nm or 254 nm (4 W) or two handheld UV-lamps from Vilber, VL-6.LC operating at 365 nm or 254 nm (6 W).

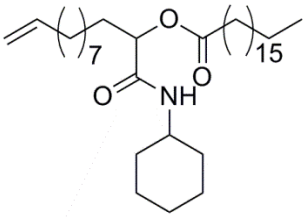
All **thin layer chromatography** experiments were performed on silica gel coated aluminum foil (silica gel 60 F_{254}, Aldrich). Compounds were visualized by staining with Seebach-solution (mixture of phosphomolybdic acid hydrate, cerium(IV)-sulfate, sulfuric acid and water).

6.3 Experimental Procedures

6.3.1 Experimental Procedures Chapter 4.1.1

Synthesis of the sequence-defined tetramer:

1st Passerini-3CR:



6

5.09 g of stearic acid **1a** (17.91 mmol, 1.00 eq.) were dissolved in 18 mL (1.00 M) dichloromethane. 4.48 g of 10-undecenal **2** (26.59 mmol, 1.48 eq.) and 2.79 g of cyclohexyl isocyanide **3a** (26.57 mmol, 1.43 eq.) were added to this solution and stirred at room temperature for 24 hours. The solvent was evaporated under reduced pressure and the crude product was purified by recrystallization from hexane/ethyl acetate (10:1). Due to the excess of the isocyanide **3a** and 10-undecenal **2** the recrystallization process was repeated twice. The desired product **6** was isolated as a white solid in a yield of 96 % (9.54 g).

^{1}H NMR: ($CDCl_3$, 300 MHz) δ /ppm: 5.94 – 5.69 (m, 2H, NH, CH, ^{2,7}), 5.13 (dd, J = 6.7, 5.1 Hz, 1H, CH, ^{6}), 4.94 (ddd, J = 14.2, 12.1, 1.2 Hz, 2H, $CH_{2,}$ ^{1}), 3.84 – 3.68 (m, 1H, CH, ^{8}), 2.37 (t, J = 7.4 Hz, 2H, $CH_{2,}$ ^{10}), 2.01 (q, J = 7.0 Hz, 2H, $CH_{2,}$ ^{3}), 1.95 – 1.52 (m, 10H, 5 $CH_{2,}$ ^{9}), 1.38 – 1.17 (m, 44H, 22 $CH_{2,}$ ^{4,5}), 0.86 (t, J = 6.6 Hz, 3H, $CH_{3,}$ ^{11}).

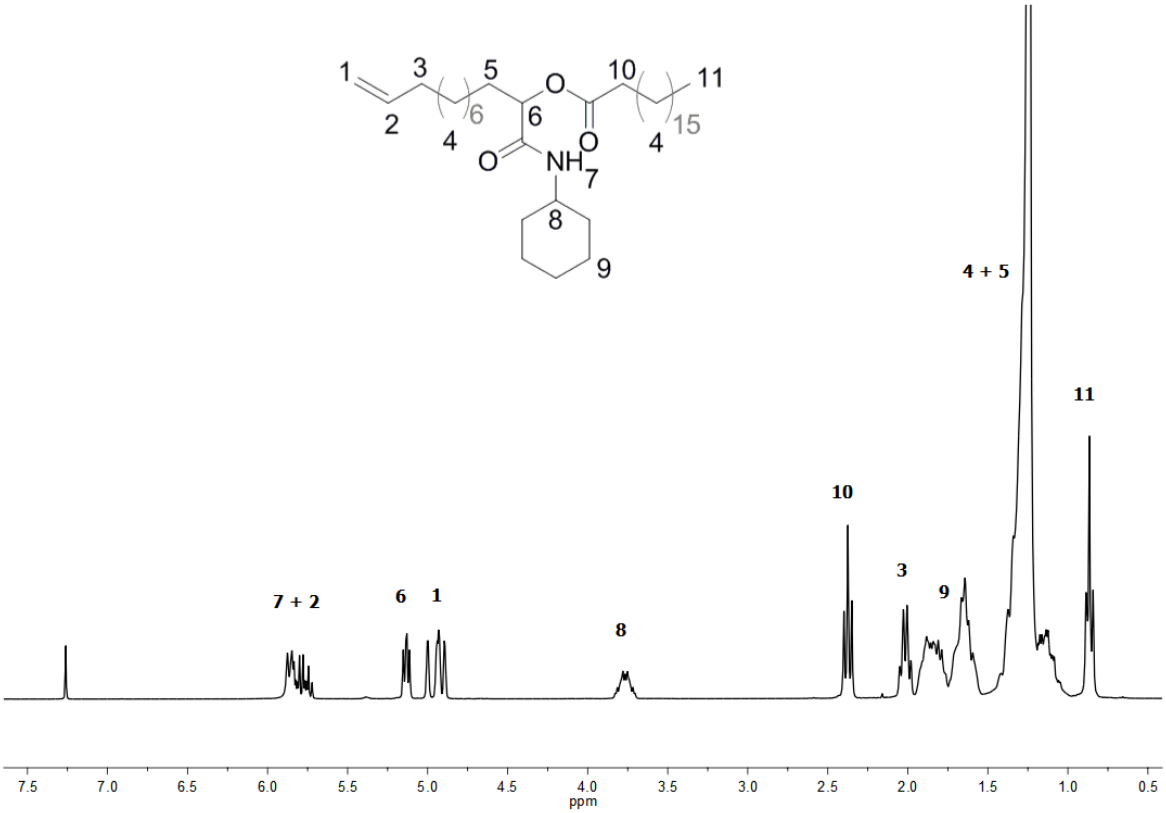
^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 172.6, 169.1, 139.3, 114.3, 74.0, 47.9, 34.5, 33.9, 33.2, 32.0, 29.8, 29.7, 29.6, 29.5, 29.4, 29.4, 29.3, 29.2, 29.0, 25.6, 25.2, 24.9, 22.8, 14.2.

HRMS-FAB of $[C_{36}H_{68}NO_3]^+$: calculated: 562.5199, found: 562.5198.

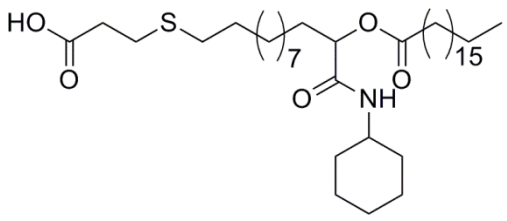
IR (ATR platinum diamond): ν [cm^{-1}] = 3288.9, 3086.5, 2916.6, 2849.2, 1744.4, 1655.7, 1555.6, 1466.2, 1447.4, 1378.4, 1312.0, 1272.2, 1251.3, 1233.9, 1213.3, 1191.9, 1162.4, 1107.0, 1074.0, 991.2, 911.9, 762.1, 720.3, 683.5, 493.3, 429.5.

SEC/ESI-MS: $[C_{36}H_{67}NO_3Na]^+$: calculated: 584.5, found: 584.7.

Melting point: 70.7 ° C.



1st Thiol-Ene addition:



7

17.79 g of 3-mercaptopropionic acid **4** (167.6 mmol, 10.0 eq.) were added to 9.41 g of substance **6** (16.74 mmol, 1.00 eq.). Subsequently, 0.22 g of 2,2 dimethoxy-2-phenyl acetophenone **5** (DMPA) (0.85 mmol, 5.1 mol%) were added and the mixture was stirred

under UV-irradiation (360 nm) at room temperature for two hours. Full conversion of the double bond was confirmed by ^{1}H NMR. The excess of 3-mercaptopropionic acid **4** was removed under reduced pressure, whereby 13.5 g (84 % of the excess) were recycled. The crude product was purified by recrystallization from hexane/ethyl acetate (4:1). The desired product **7** was isolated as a white solid in a yield of 95 % (10.67 g).

^{1}H NMR: (300 MHz, $CDCl_3$) δ /ppm: 5.91 (d, J = 8.3 Hz, 1H, NH, ^{9}), 5.15 (dd, J = 6.8, 5.0 Hz, 1H, CH, ^{8}), 3.78 (td, J = 14.4, 7.1 Hz, 1H, CH, ^{10}), 2.78 (t, J = 7.4 Hz, 2H, $CH_{2,}$ ^{3}), 2.64 (t, J = 7.1 Hz, 2H, $CH_{2,}$ ^{2}), 2.52 (t, J = 7.4 Hz, 2H, $CH_{2,}$ ^{4}), 2.38 (t, J = 7.4 Hz, 2H, $CH_{2,}$ ^{12}), 1.96 – 1.49 (m, 12H, 6 $CH_{2,}$ $^{11, 5}$), 1.39 – 1.10 (m, 46H, 23 $CH_{2,}$ ^{6,7}), 0.87 (t, J = 6.6 Hz, 3H, $CH_{3,}$ ^{13}).

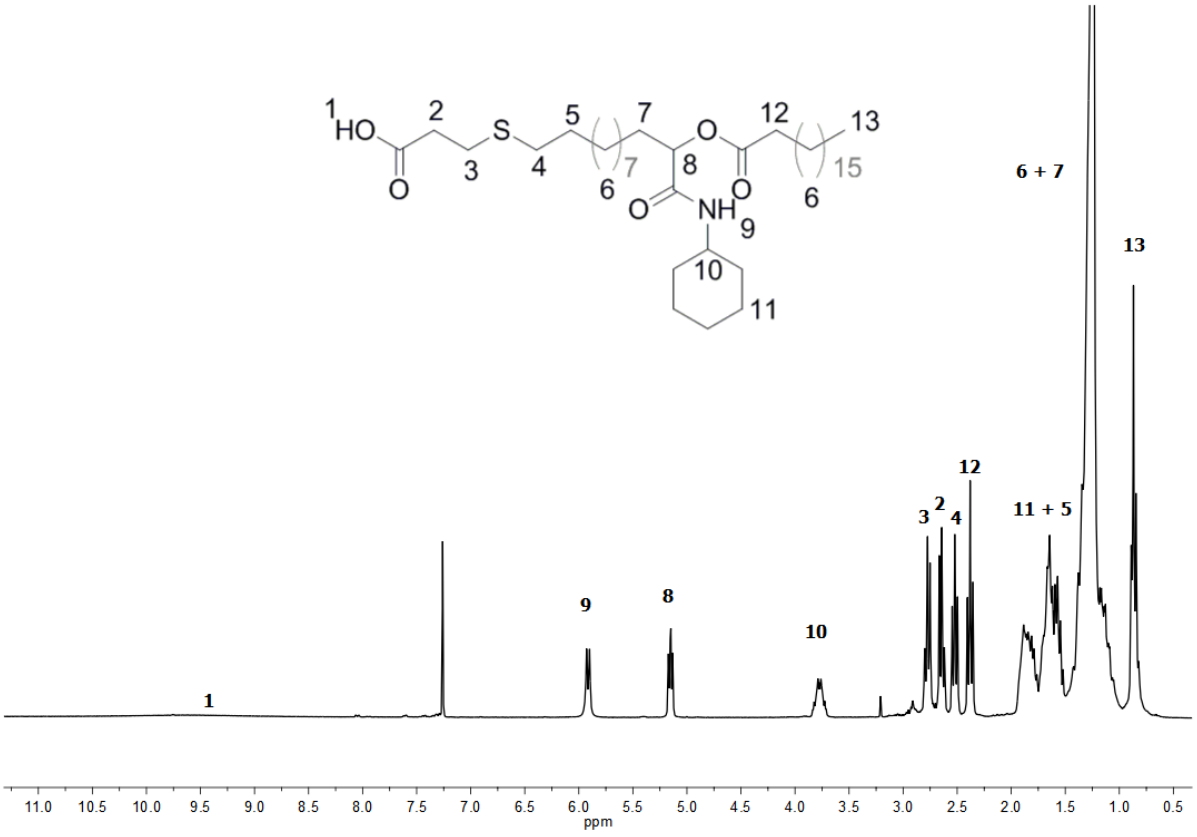
^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 176.3, 172.6, 169.5, 74.0, 48.1, 34.8, 34.5, 33.1, 33.0, 32.3, 32.1, 32.0, 29.8, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 29.2, 28.8, 26.9, 25.6, 25.2, 24.8, 22.8, 14.2.

HRMS-FAB of $[C_{39}H_{74}NO_5S]^+$: calculated: 668.5288, found: 668.5286.

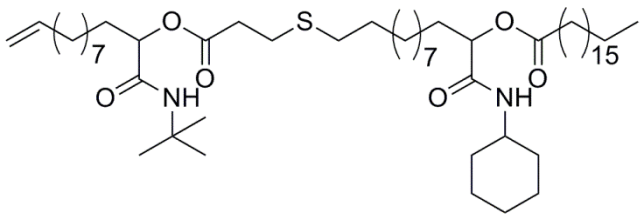
IR (ATR platinum diamond): ν [cm^{-1}] = 3289.7, 2916.5, 2848.9, 1741.8, 1700.1, 1654.8, 1555.6, 1465.9, 1421.1, 1378.2, 1332.1, 1235.0, 1213.7, 1193.3, 1162.7, 1108.1, 1072.7, 934.4, 892.0, 813.1, 720.5, 657.3, 490.0, 432.2.

SEC/ESI-MS: $[C_{39}H_{73}NO_5SNa]^+$: calculated: 690.5, found: 690.7.

Melting point: 71.0 ° C.



2nd Passerini-3CR:



8

To 10.58 g of substance **7** (15.84 mmol, 1.00 eq.), 4.01 g of 10-undecenal **2** (23.80 mmol, 1.50 eq.) and 15.0 mL (1.06 M) dichloromethane were added and stirred for ten minutes at room temperature. Subsequently, 1.82 g of *tert*-butyl isocyanide **3b** (21.88 mmol, 1.38 eq.) were added and the reaction mixture was stirred at room temperature overnight. The reaction progress was followed by GPC-analysis. After complete consumption of substance **7**, the solvent was evaporated under reduced pressure and the crude reaction mixture was purified by column chromatography (hexane/ethyl acetate 9:1 → 4:1). The silica gel used for column chromatography was

pretreated with triethylamine (3 vol%). The desired product **8** was obtained as viscous oil in a yield of 97 % (14.18 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 6.08 (s, 1H, NH, ^{7}), 5.93 – 5.71 (m, 2H, NH, CH, $^{2, 11}$), 5.22 – 4.86 (m, 4H, 2 CH, $CH_{2,}$ $^{1, 6}$), 3.86 – 3.67 (m, 1H, CH, ^{12}), 2.97 – 2.64 (m, 4H, 2 $CH_{2,}$ $^{8, 9}$), 2.59 – 2.49 (t, J = 7,4 Hz, 2H, CH_2, ^{10}), 2.38 (t, J = 7.4 Hz, 2H, CH_2, ^{14}), 2.11 – 1.01 (m, 73H, 32 CH_2, 3 CH_3, $^{3, 4, 5, 13}$), 0.88 (t, J = 6.6 Hz, 3H, CH_3, ^{15}).

^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 172.5, 170.8, 169.1, 169.0, 139.2, 114.3, 74.8, 77.0, 51.5, 47.9, 35.0, 34.5, 33.9, 33.2, 33.1, 32.3, 32.0, 31.9, 29.8, 29.8, 29.7, 29.7, 29.6, 29.5, 29.4, 29.3, 29.3, 29.2, 29.0, 28.9, 27.2, 25.6, 25.2, 24.8, 22.8, 14.2.

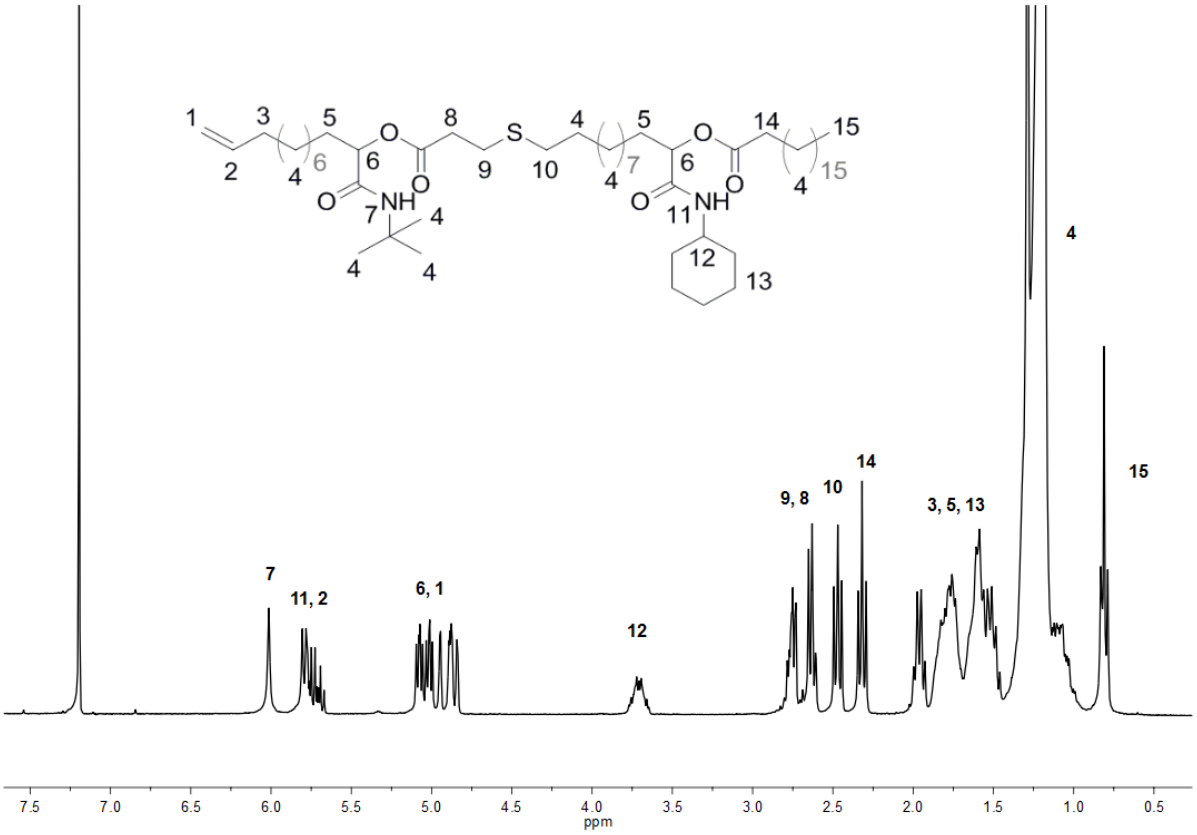
FAB of $[C_{55}H_{103}N_2O_6S]^+$: calculated: 919.8, found 919.6.

IR (KBr): ν [cm^{-1}] = 3293.0, 3083.5, 2921.0, 2851.9, 1743.1, 1659.0, 1555.4, 1466.3, 1364.5, 1214.9, 1166.5, 1103.7, 909.2, 721.6.

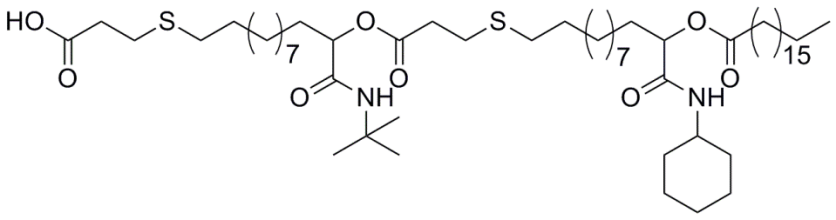
SEC/ESI-MS: $[C_{55}H_{103}N_2O_6SNa]^+$: calculated: 941.7, found: 941.8.

***R*$_f$:** (hexane/ethyl acetate 3:1) = 0.47.

Melting point: 50.1 ° C.



2nd Thiol-Ene addition:



9

To 14.03 g of substance **8** (15.25 mmol, 1.00 eq.), 8.09 g 3-mercaptopropionic acid **4** (76.23 mmol, 5.00 eq.) were added and stirred at room temperature. Subsequently, 0.19 g of 2,2-dimethoxy-2-phenylacetophenone (DMPA) **5** (0.72 mmol, 4.70 mol%) were added and the reaction mixture was stirred at room temperature under UV-irradiation (360 nm) for two hours. Full conversion of the double bond was confirmed by ^{1}H NMR. After removing the excess of 3-mercaptopropionic acid **4** (5.01 g, 77 % of the excess were recycled) under reduced pressure, the crude reaction mixture was recrystallized from hexane/ethyl acetate 3:1 to obtain **9** as a white solid in a yield of 84 % (13.15 g).

^{1}H NMR: (300 MHz, $CDCl_3$) δ /ppm: 6.14 (s, 1H, NH, ^{8}), 5.91 (d, J = 8.3 Hz, 1H, NH, ^{10}), 5.13 (ddd, J = 15.9, 6.9, 4.9 Hz, 2H, 2 CH, ^{7}), 3.85 – 3.69 (m, 1H, CH, ^{11}), 2.85 – 2.60 (m, 8H, 4 $CH_{2,}$ ^{2}), 2.53 (t, J = 7.3 Hz, 4H, 2 $CH_{2,}$ ^{3}), 2.38 (t, J = 7.4 Hz, 2H, $CH_{2,}$ ^{13}), 1.97 – 1.47 (m, 16H, 8 $CH_{2,}$ ^{12,4}), 1.30 (m, 69H, 3 CH_3, 30 $CH_{2,}$ ^{5}), 0.87 (t, J = 6.6 Hz, 3H, $CH_{3,}$ ^{14}).

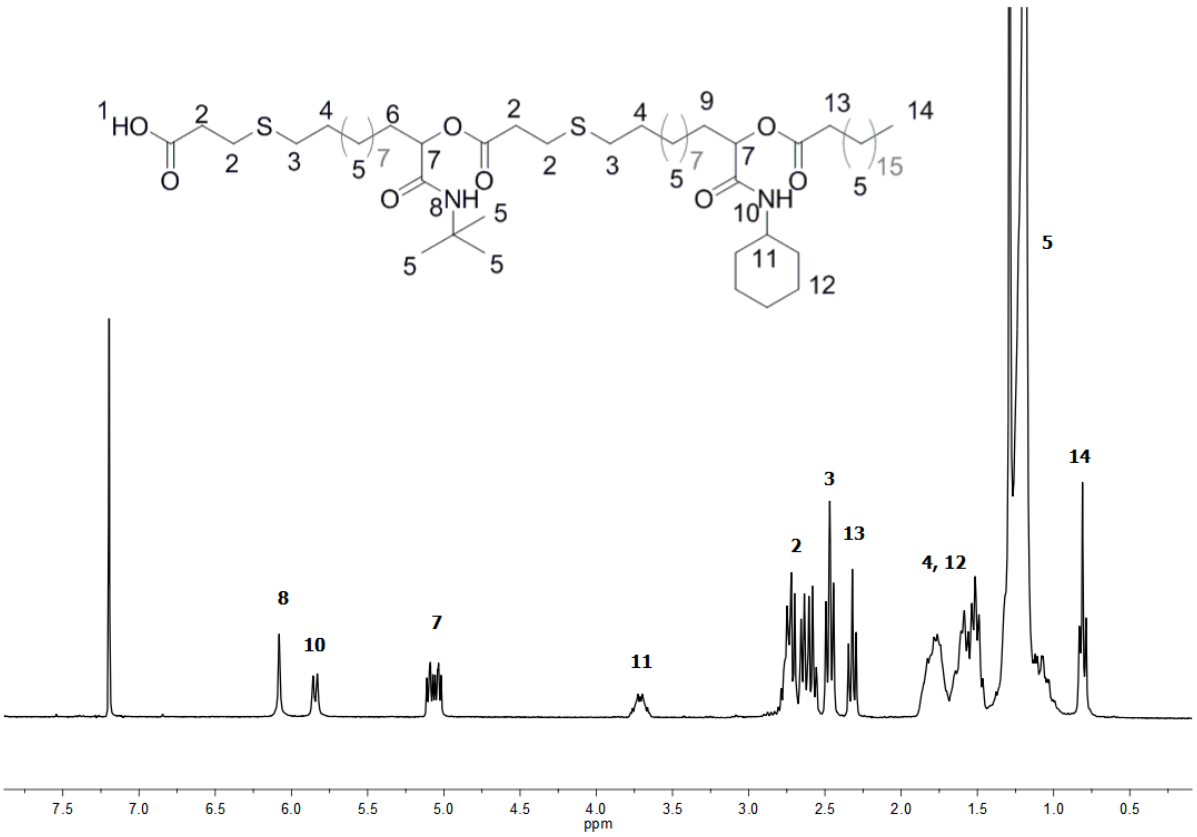
^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 175.8, 172.6, 170.8, 169.3, 74.8, 74.0, 51.6, 48.0, 34.9, 34.8, 34.5, 33.1, 33.1, 32.3, 32.2, 32.0, 32.0, 31.9, 29.8, 29.8, 29.7, 29.7, 29.6, 29.6, 29.5, 29.5, 29.4, 29.3, 29.7, 29.1, 29.0, 28.8, 28.8, 27.2, 26.9, 25.6, 25.2, 24.8, 22.8, 14.2.

FAB of $[C_{58}H_{109}N_2O_8S_2]^+$ calculated: 1025.8, found: 1025.7.

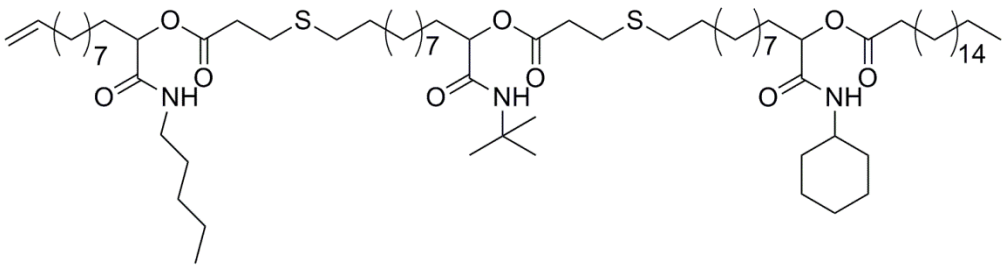
IR: (ATR platinum diamond) ν [cm^{-1}] = 3293.4, 2919.1, 2850.2, 1735.8, 1658.1, 1640.9, 1547.9, 1465.5, 1364.5, 1280.9, 1189.7, 1143.7, 1107.0, 1074.1, 930.8, 806.5, 721.6, 615.0, 433.5, 401.6.

SEC/ESI-MS: $[C_{58}H_{108}N_2O_8S_2Na]^+$: calculated: 1047.7, found:1047.8.

Melting point: 54.3 ° C.



3rd Passerini-3CR:



10

13.04 g of substance **9** (12.71 mmol, 1.00 eq.) were diluted in 13 mL DCM (0.98 M), subsequently, 3.21 g of 10-undecenal **2** (19.05 mmol, 1.50 eq.) and 1.89 g of 1-pentyl isocyanide **3c** (19.42 mmol, 1.53 eq.) were added and the reaction mixture was stirred at room temperature for 15 hours. The solvent was removed under reduced pressure and the crude reaction mixture purified by column chromatography (hexane/ethyl acetate 9:1 → 2:1). The silica gel used in the column chromatography was pretreated with

triethylamine (3 vol%). The product **10** was obtained as viscous oil in a yield of 64 % (10.54 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 6.55 (t, J = 5.5 Hz, 1H, NH, ^{5}), 6.10 (s, 1H, NH, ^{9}), 5.92 – 5.69 (m, 2H, NH, CH, ^{10,2}), 5.24 – 4.86 (m, 5H, 3 CH, CH_2, ^{4,1}), 3.85 – 3.66 (m, 1H, CH, ^{11}), 3.32 – 3.13 (m, 2H, CH_2, ^{6}), 2.89 – 2.61 (m, 8H, 4 CH_2, ^{7}), 2.53 (td, J = 7.4, 4.0 Hz, 4H, 2 CH_2, ^{8}), 2.37 (t, J = 7.4 Hz, 2H, CH_2, ^{12}), 1.95 – 0.99 (m, 107H, 3 CH_3, 49 CH_2, ^{3}), 0.92 – 0.82 (m, 6H, 2 CH_3, ^{13}).

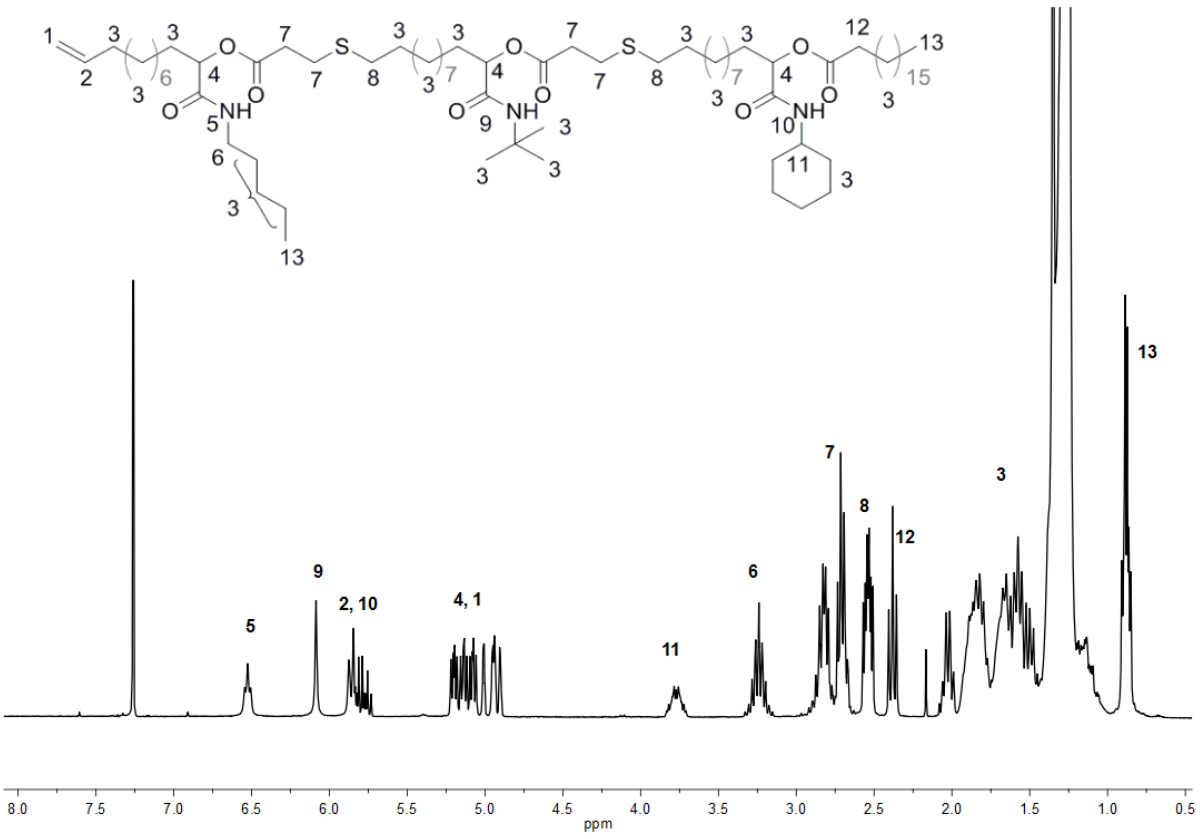
^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 172.6, 170.7, 169.8, 169.1, 139.3, 114.3, 74.8, 74.7, 74.0, 51.5, 47.9, 39.4, 35.0, 34.8, 34.5, 33.9, 33.2, 33.1, 32.4, 32.3, 32.1, 32.0, 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.3, 29.2, 29.0, 28.9, 27.4, 27.3, 25.6, 25.2, 25.0, 24.9, 22.8, 22.5, 14.2, 14.1.

FAB of $[C_{75}H_{140}N_3O_9S_2]$: calculated: 1290.0, found: 1290.8.

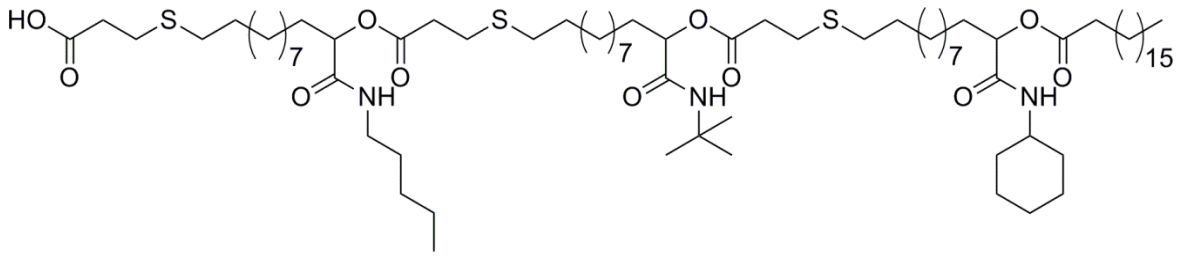
IR (KBr): ν [cm^{-1}] = 3304.9, 3078.0, 2925.3, 2854.2, 1743.7, 1659.6, 1455.3, 1365.1, 1237.3, 1166.3, 909.4, 722.4.

SEC/ESI-MS: $[C_{75}H_{139}N_3O_9S_2Na]^+$: calculated: 1313.0, found: 1313.1.

R_f (hexane/ethyl acetate 2:1) = 0.45.



3rd Thiol-Ene addition:



11

10.26 g of substance **10** (7.94 mmol, 1.00 eq.) were stirred together with 4.27 g of 3-mercaptopropionic acid **4** (39.82 mmol, 5.02 eq.) and 0.10 g of DMPA **5** (0.41 mmol, 5.1 mol%) under UV-irradiation (360 nm) at room temperature overnight. Subsequently, the excess of **4** was removed under reduced pressure and the crude product was recrystallized from hexane/ethyl acetate 2.5:1. The product **11** was obtained as white solid in a yield of 98 % (10.87 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 6.59 (t, J = 5.7 Hz, 1H, NH, ^{6}), 6.13 (s, 1H, NH, ^{8}), 5.89 (d, J = 8.3 Hz, 1H, NH, ^{9}), 5.30 – 4.96 (m, 3H, 3 CH, ^{5}), 3.86 – 3.67 (m, 1H, CH, ^{10}), 3.36 – 3.12 (m, 2H, CH_2, ^{7}), 2.97 – 2.45 (m, 12H, 6 CH_2, ^{2}), 2.38 (t, J = 7.4 Hz, 2H, CH_2, ^{11}), 2.00 – 1.03 (m, 109H, 50 CH_2, 3 CH_3, ^{4}), 0.94 – 0.83 (m, 6H, 2 CH_3, ^{12}).

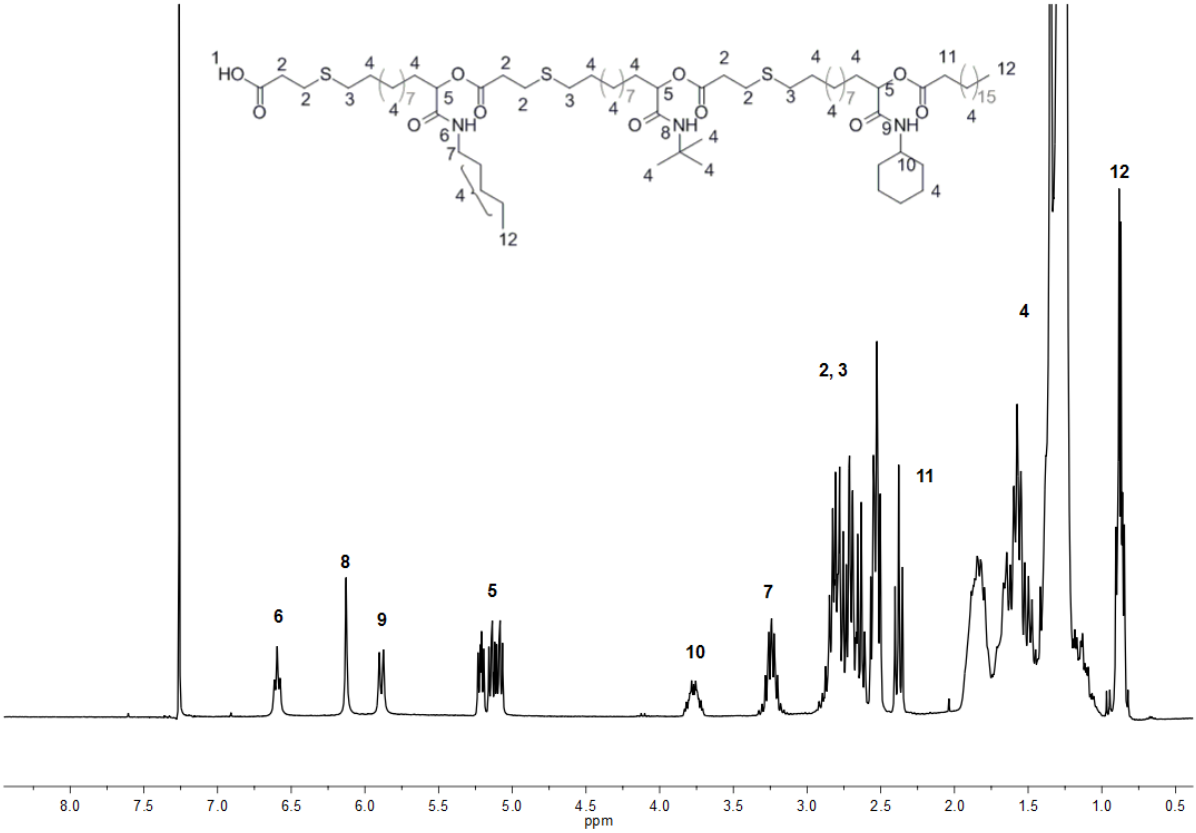
^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 176.2, 172.6, 170.8, 170.1, 169.3, 77.6, 77.2, 76.7, 74.6, 51.6, 48.0, 39.5, 33.1, 32.3, 32.2, 32.0, 29.8, 29.6, 29.5, 29.4, 29.3, 29.3, 29.1, 29.0, 28.8, 26.8, 25.2, 24.8, 22.8, 22.4, 14.3, 14.1.

FAB of $[C_{78}H_{146}N_3O_{11}S_3]^+$: calculated: 1396.0, found: 1396.5.

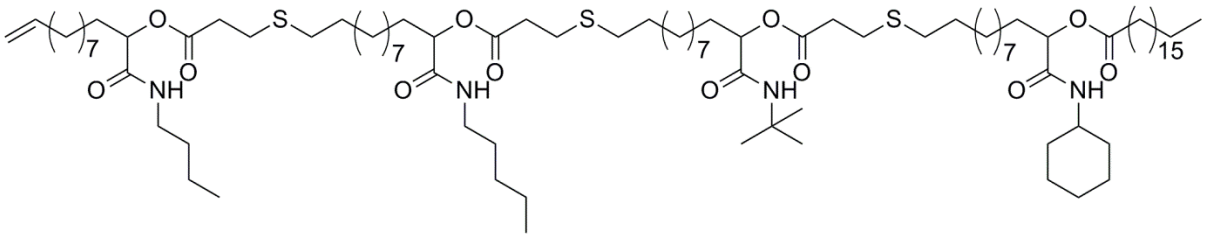
IR (ATR platinum diamond): ν [cm^{-1}] = 3286.5, 2919.6, 2850.6, 1738.1, 1697.1, 1648.1, 1537.8, 1465.7, 1398.3, 1364.8, 1207.3, 1138.0, 1068.4, 934.7, 813.2, 721.4, 470.4.

SEC/ESI-MS: $[C_{78}H_{145}N_3O_{11}S_3Na]^+$: calculated: 1419.0, found: 1419.2.

Melting point: 58.6 ° C.



4th Passerini-3CR:



12

10.36 g of substance **11** (7.42 mmol, 1.00 eq.), 2.42 g of 10-undecenal **2** (14.38 mmol, 1.94 eq.) and 1.30 g of *n*-butyl isocyanide **3d** (15.59 mmol, 2.10 eq.) were diluted in 10 mL (0.74 M) DCM and stirred at room temperature for 18 hours. Subsequently, the solvent was removed under reduced pressure and the crude product was purified by column chromatography (hexane/ethyl acetate 9:1 → 2:1). The silica gel used in the column chromatography was pretreated with triethylamine (3 vol%). The product **12** was obtained as highly viscous oil in a yield of 81 % (9.91 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 6.64 – 6.44 (m, 2H, 2 NH, [1]), 6.10 (s, 1H, NH, [2]), 5.93 – 5.69 (m, 2H, CH, NH, [3, 4]), 5.26 – 4.84 (m, 6H, 4 CH, CH_2, [5, 6]), 3.87 – 3.66 (m, 1H, CH, [7]), 3.37 – 3.13 (m, 4H, 2 CH_2, [8]), 2.98 – 2.63 (m, 12H, 6 CH_2, [9]), 2.53 (td, J = 7.4, 4.0 Hz, 6H, 3 CH_2, [10]), 2.38 (t, J = 7.4 Hz, 2H, CH_2, [11]), 2.10 – 1.01 (m, 129H, 3 CH_3, 60 CH_2, [12]), 0.98 – 0.79 (m, 9H, 3 CH_3, [13]).

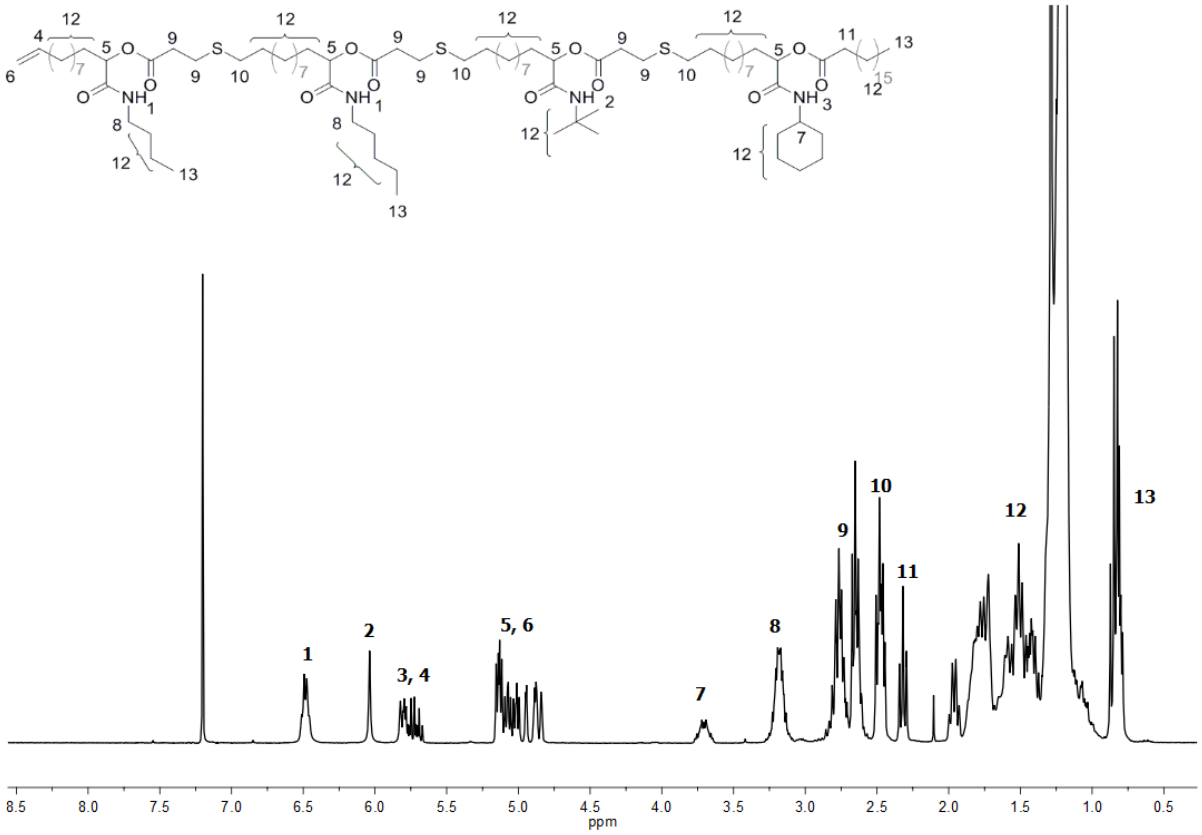
^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 172.6, 170.8, 169.8, 169.8, 169.1, 169.0, 139.3, 114.3, 74.8, 74.6, 74.6, 74.0, 51.5, 39.4, 39.1, 35.0, 34.8, 34.5, 33.9, 33.1, 32.3, 32.2, 32.1, 32.0, 31.7, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.2, 29.0, 28.9, 27.4, 27.2, 25.6, 25.2, 25.0, 24.9, 22.8, 22.5, 20.2, 14.3, 14.1, 13.9.

FAB of $[C_{94}H_{175}N_4O_{12}S_3]^+$: calculated: 1648.2, found: 1648.6.

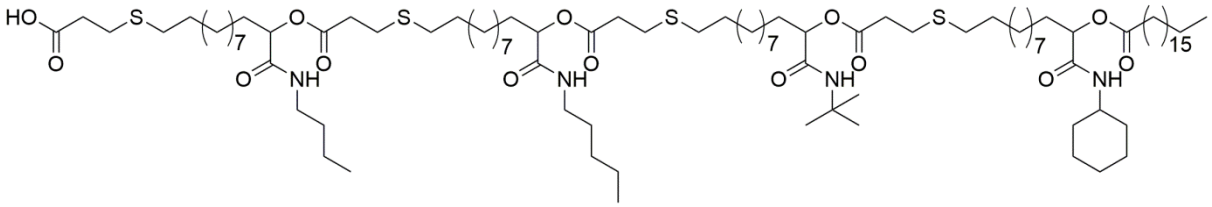
IR (ATR platinum diamond): ν [cm^{-1}] = 3304.9, 2921.1, 2851.3, 1740.1, 1654.5, 1530.2, 1453.3, 1362.8, 1226.8, 1144.9, 907.9, 720.3.

SEC/ESI-MS: $[C_{94}H_{174}N_4O_{12}S_3Na]^+$: calculated: 1670.2, found: 1670.2.

R_f: (hexane/ethyl acetate 2:1) = 0.43.



4th Thiol-Ene addition:



13

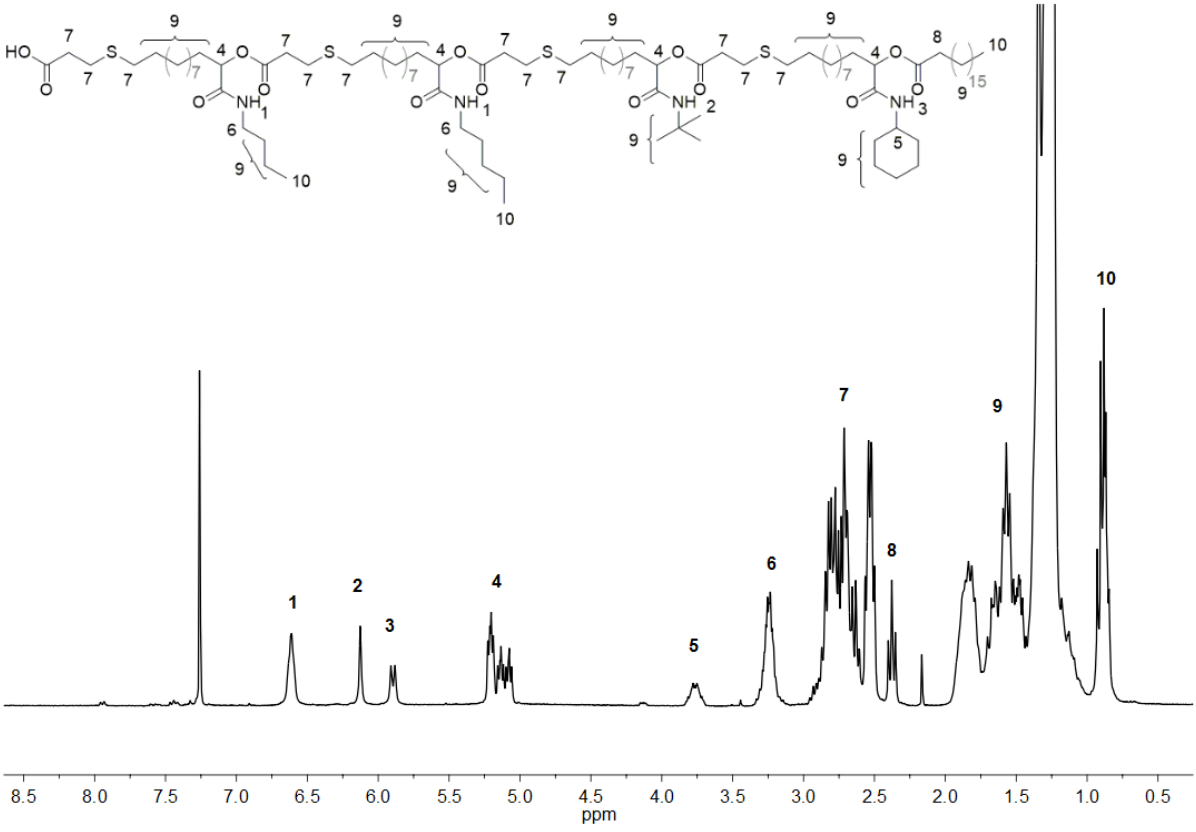
7.43 g of substance **12** (4.51 mmol, 1.00 eq.) were stirred together with 2.42 g of 3-mercaptopropionic acid **4** (22.80 mmol, 5.06 eq.) and 61.3 mg of DMPA **5** (0.24 mmol, 5.3 mol%) were added. The mixture was stirred under UV-irradiation (360 nm) at room temperature overnight. Subsequently, the excess of **4** was removed under reduced pressure and the crude product was recrystallized from hexane/ethyl acetate 2:1. The product **13** was obtained as white solid in a yield of 85 % (6.76 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 6.65 (m, 2H, 2 NH, [1]), 6.14 (s, 1H, NH, [2]), 5.93 (d, J = 8.3 Hz, 1H, NH, [3]), 5.28 – 4.93 (m, 4H, 4 CH, [4]), 3.85 – 3.60 (m, 1H, CH, [5]), 3.35 – 3.06 (m, 4H, 2 CH_2, [6]), 2.95 – 2.42 (m, 24H, 12 CH_2, [7]), 2.34 (t, J = 7.4 Hz, 2H, CH_2, [8]), 1.95 – 0.96 (m, 133H, 3 CH_3, 62 CH_2, [9]), 0.93 – 0.74 (m, 9H, 3 CH_3, [10]).

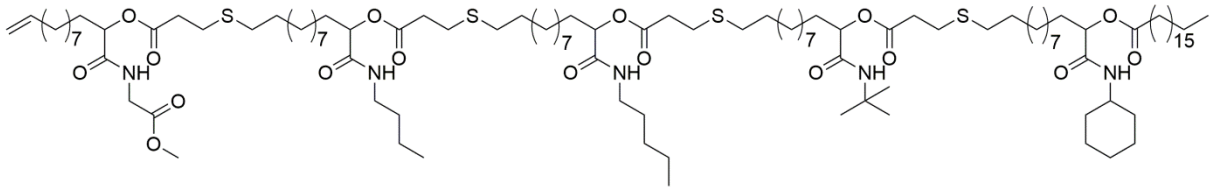
^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 175.2, 172.5, 170.7, 170.0, 169.9, 169.2, 169.2, 74.6, 74.4, 73.8, 51.5, 47.9, 39.3, 39.0, 34.8, 34.7, 34.6, 34.3, 33.0, 32.9, 32.2, 32.1, 32.0, 31.9, 31.9, 31.8, 31.5, 29.7, 29.7, 29.6, 29.5, 29.4, 29.3, 29.3, 29.2, 29.2, 29.1, 29.1, 29.0, 28.9, 28.8, 28.7, 27.3, 27.1, 26.8, 25.5, 25.0, 24.9, 24.8, 24.7, 22.7, 22.3, 20.0, 14.2, 14.0, 13.8.

FAB of $[C_{97}H_{181}N_4O_{14}S_4]^+$: calculated: 1755.2, found: 1755.4.

IR (ATR platinum diamond): ν [cm^{-1}] = 3289.1, 2920.0, 2850.2, 1738.3, 1654.4, 1538.6, 1465.4, 1363.0, 1223.5, 1137.8, 1067.9, 720.2.



5th Passerini-3CR:



14

6.50 g of substance **13** (3.70 mmol, 1.00 eq.), 1.05 g of 10-undecenal **2** (6.22 mmol, 1.68 eq.) and 0.56 g of methyl isocyanoacetate **3e** (5.63 mmol, 1.52 eq.) were diluted in 5 mL (0.74 M) DCM and stirred at room temperature for 18 hours. Subsequently, the solvent was removed under reduced pressure and the crude product was purified by column chromatography (hexane/ethyl acetate 6:1 → 1:1). The silica gel used in the column chromatography was pretreated with triethylamine (3 vol%). The product **14** was obtained as highly viscous oil in a yield of 68 % (5.09 g).

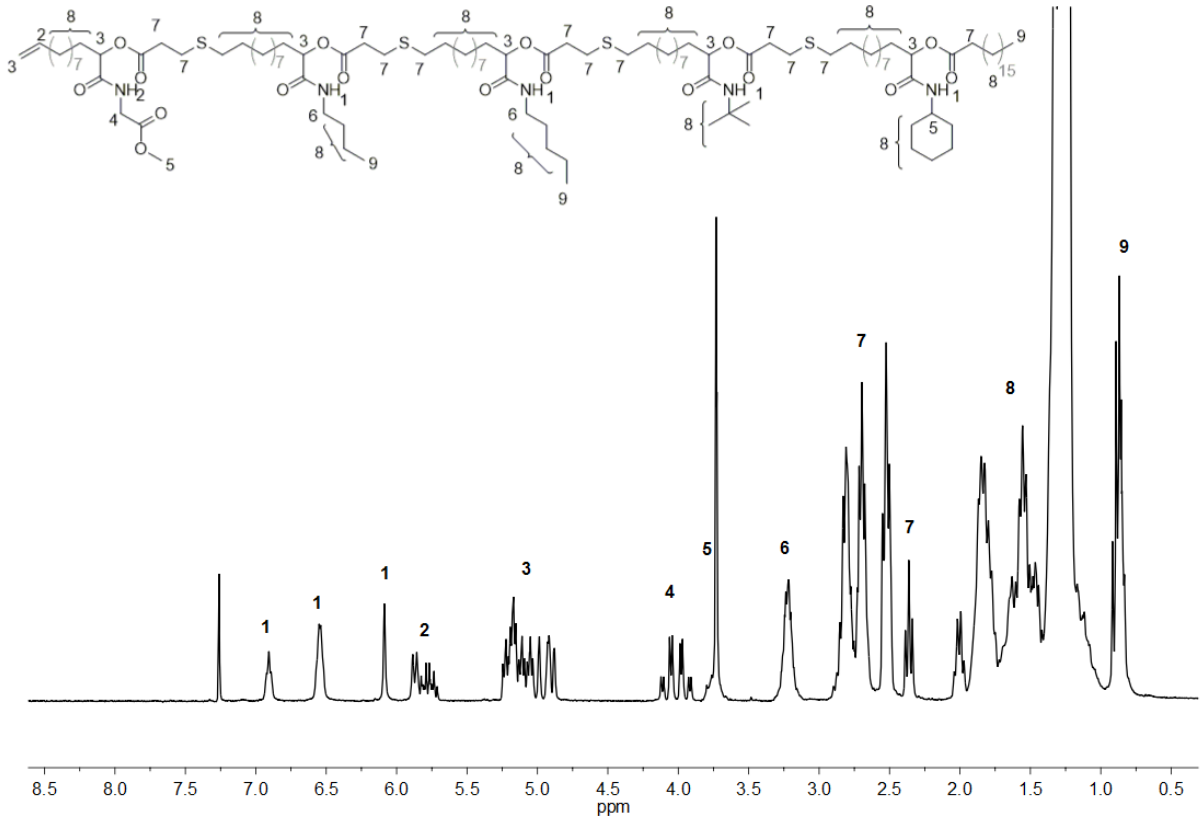
^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 6.91 (s, 1H, NH, [1]), 6.54 (m, 2H, 2 NH, [1]), 6.08 (s, 1H, NH, [1]), 5.94 – 5.67 (m, 2H, NH, CH, [2]), 5.27 – 4.84 (m, 7H, CH_2, 5 CH, [3]), 4.01 (qd, J = 18.2, 5.4 Hz, 2H, CH_2, [4]), 3.75 (m, 4H, CH_3, CH, [5]), 3.33 – 3.10 (m, 4H, 2 CH_2, [6]), 2.94 – 2.28 (m, 26H, 13 CH_2, [7]), 2.06 – 0.97 (m, 147H, 3 CH_3, 69 CH_2, [8]), 0.95 – 0.74 (m, 9H, 3 CH_3, [9]).

^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 172.5, 170.8, 170.7, 170.3, 170.0, 169.8, 169.7, 169.1, 169.0, 139.3, 114.2, 74.8, 74.6, 74.5, 74.3, 74.0, 73.9, 51.5, 48.1, 47.7, 40.1, 39.3; 39.0, 34.9, 34.7, 34.5, 33.9, 33.1, 32.3, 32.2, 31.9, 31.9, 31.6, 29.8, 29.7, 29.6, 29.5, 29.3, 29.2, 29.1, 29.0, 29.0, 28.9, 28.8, 28.7, 28.6, 27.3, 27.2, 25.1, 25.0, 24.8, 24.8, 14.1, 14.0, 13.9.

FAB of $[C_{112}H_{205}N_5O_{17}S_4]^+$: calculated: 2020.4, found: 2020.8.

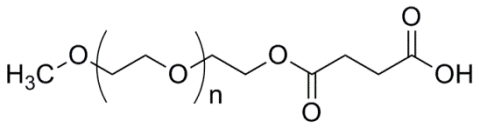
IR (ATR platinum diamond): ν [cm^{-1}] = 3296.8, 2921.1, 2851.2, 1740.4, 1655.6, 1530.3, 1454.3, 1363.5, 1141.4, 908.8, 720.5.

R_f: (hexane/ethyl acetate 1:1) = 0.50.



Synthesis of the sequence-defined block-copolymer **23**:

Synthesis of *O*-Methyl-*O'*-succinylpolyethylene glycol **1b**



1b

5.18 g of dry polyethylene glycol (M_n ~ 2000 g/mol) (2.59 mmol, 1.00 eq.) were dissolved in 25 mL dry dichloromethane. Polyethylene glycol was dried by co-evaporation with toluene, dichloromethane was dried over CaH_2. Subsequently, 0.78 g succinic anhydride (7.76 mmol, 3.0 eq.) and 650 µL (0.64 g, 8.13 mmol, 3.1 eq.) dry pyridine were added and the mixture was refluxed at 55 ° C for 48 hours. Subsequently, the solvent was evaporated under reduced pressure and the residue was dissolved in aqueous sodium hydrogencarbonate solution (10 wt%). The solution was filtered, cooled to 0 ° C, acidified with hydrochloric acid and extracted with dichloromethane (3 x 25 mL).

The combined organic layers were washed with water (3 x 25 mL) dried over sodium sulfate and filtered. The crude product was precipitated in cold (0 ° C) diethyl ether to yield the desired product **1b** as a white solid in a yield of 89 % (4.83 g).

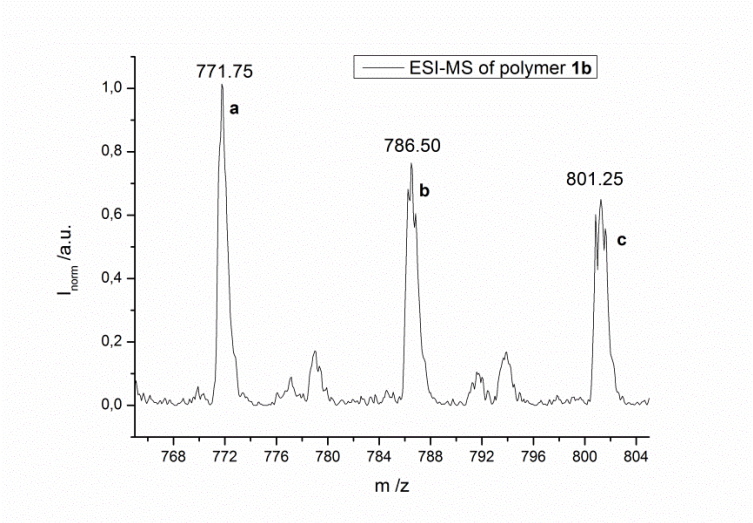
^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 4.25 (dd, J = 5.4, 3.8 Hz, 2H, OCH_2, ^{3}), 3.90 – 3.84 (m, 1H, CH_2, $^{4'}$), 3.66 (s, 180H, OCH_2, ^{2}), 3.43 – 3.34 (m, 4H, CH_3, CH_2, $^{1, 4''}$), 2.70 – 2.56 (m, 4H, $OCCH_2$, ^{5}).

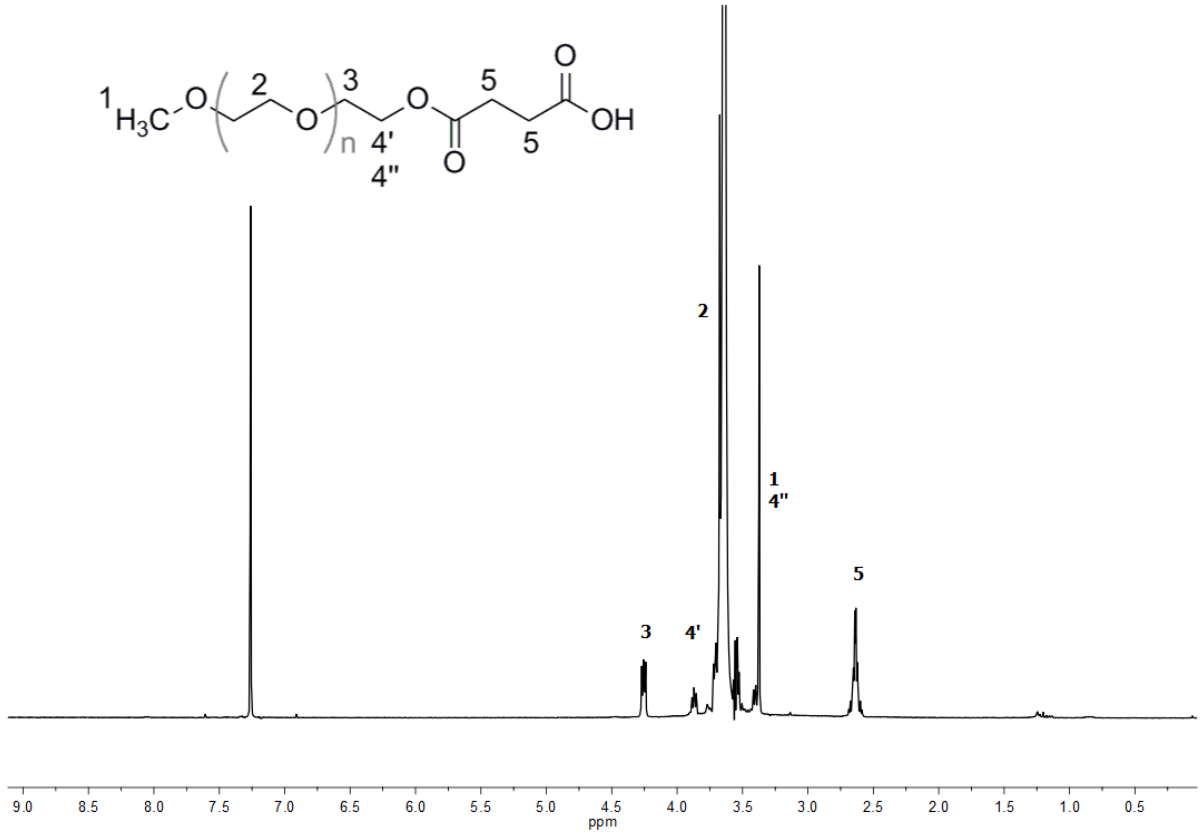
Melting point: 52.1 ° C.

IR (ATR platinum diamond): ν [cm^{-1}] = 2881.8, 2739.1, 1967.5, 1734.1, 1465.6, 1358.9, 1339.1, 1278.5, 1238.9, 1146.0, 1102.2, 1058.9, 945.5, 840.9, 528.1, 508.4.

SEC/ESI-MS:

m/z exp.	ion assignment	formula	m/z theo	Δ m/z
771.75	**a** (n = 47) + 3 Na^+	$[C_{101}H_{200}O_{52}Na_3]^{3+}$	771.67	0.08
786.50	**b** (n = 48) + 3 Na^+	$[C_{103}H_{204}O_{53}Na_3]^{3+}$	786.35	0.15
801.25	**c** (n = 49) + 3 Na^+	$[C_{105}H_{208}O_{54}Na_3]^{3+}$	801.04	0.21

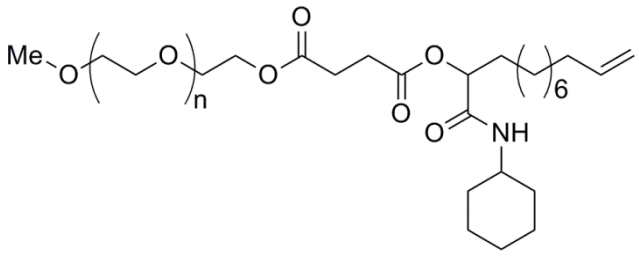




General procedure of Passerini-3CRs:

The carboxylic acid (1.00 eq.), 10-undecenal **2** (1.80 eq.) and dichloromethane (0.50 M in respect of the carboxylic acid compound) were stirred at room temperature for ten minutes. Subsequently, the isocyanide **3a-e** (1.80 eq.) was added and the reaction mixture was stirred at room temperature for 12 hours. The crude reaction mixture was purified by precipitation into ice cold diethyl ether, filtered and dried to afford the solid product.

1st Passerini-3CR of **1b** with cyclohexyl isocyanide **3a** and 10-undecenal **2** yielding polymer **15**:



15

Polymer **15**: white crystalline solid (1.94 g, 96 %).

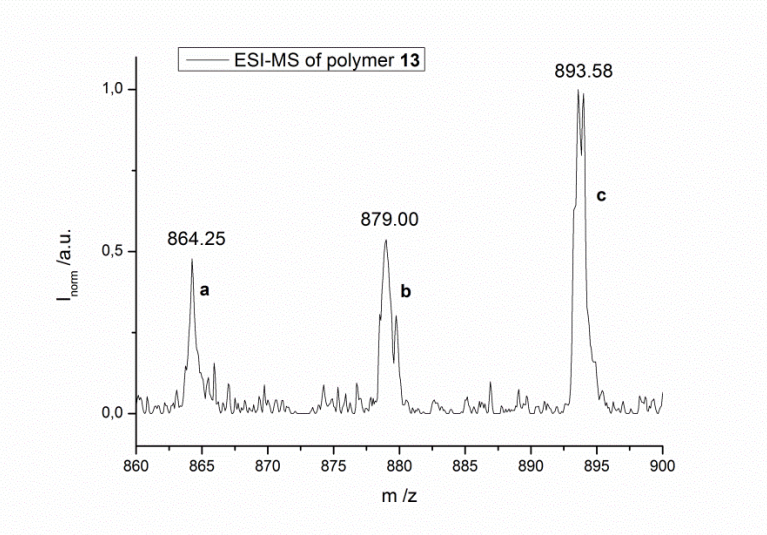
^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 6.33 (d, J = 8.4 Hz, 1H, NH, ^{7}), 5.90 – 5.69 (m, 1H, CH, ^{10}), 5.14 (dd, J = 7.4, 4.3 Hz, 1H, CH, ^{6}), 5.03 – 4.87 (m, 2H, CH_2, ^{11}), 4.28 – 4.20 (m, 2H, CH_2, ^{3}), 3.93 – 3.82 (m, 1H, CH_2, $^{4'}$), 3.63 (s, 185 H, OCH_2, $^{2, 8}$), 3.44 – 3.34 (m, 4H, CH_3, CH_2, $^{1, 4''}$), 2.88 – 2.52 (m, 4H, 2 CH_2, ^{5}), 2.36 – 0.98 (m, 26 H, 13 CH_2, ^{9}).

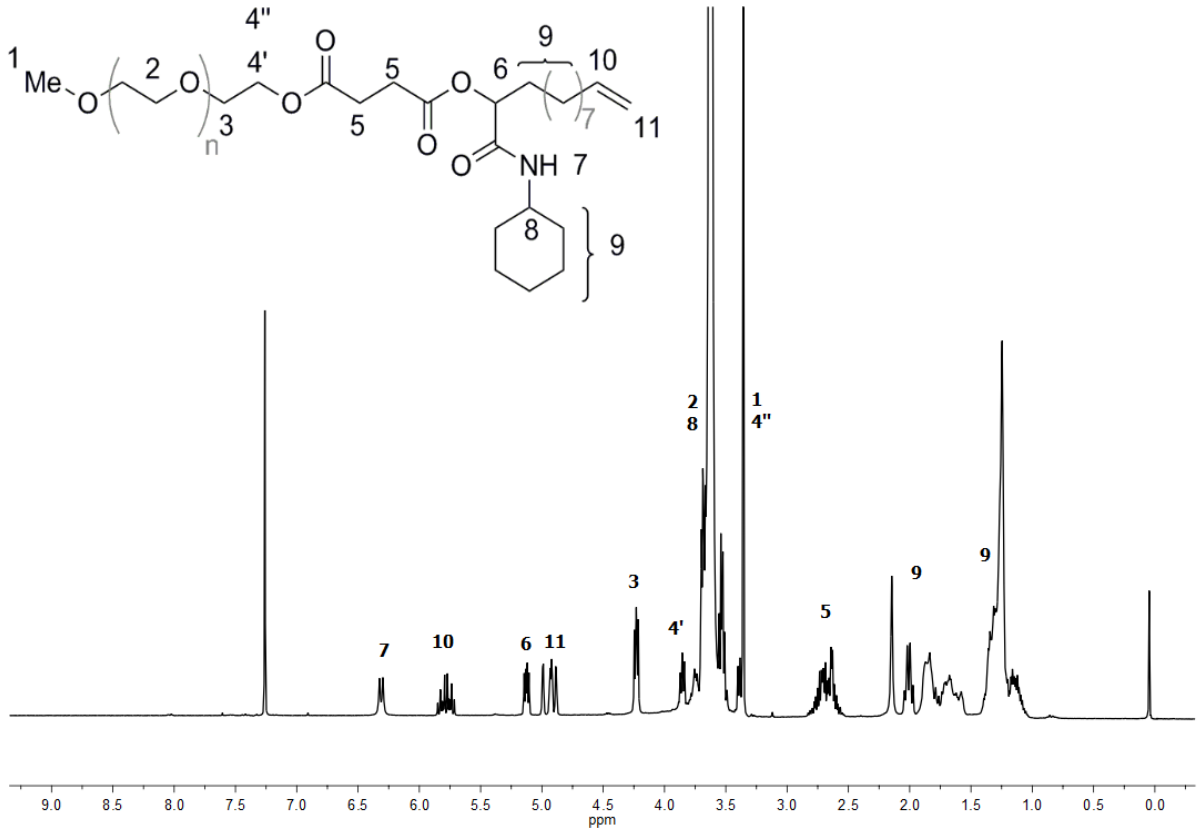
Melting point = 48.9 ° C.

IR (ATR platinum diamond) ν [cm^{-1}] = 2882.1, 1736.4, 1655.9, 1535.3, 1465.6, 1358.9, 1340.1, 1278.7, 1239.6, 1146.0, 1101.3, 1059.2, 946.4, 841.1, 528.3, 509.0.

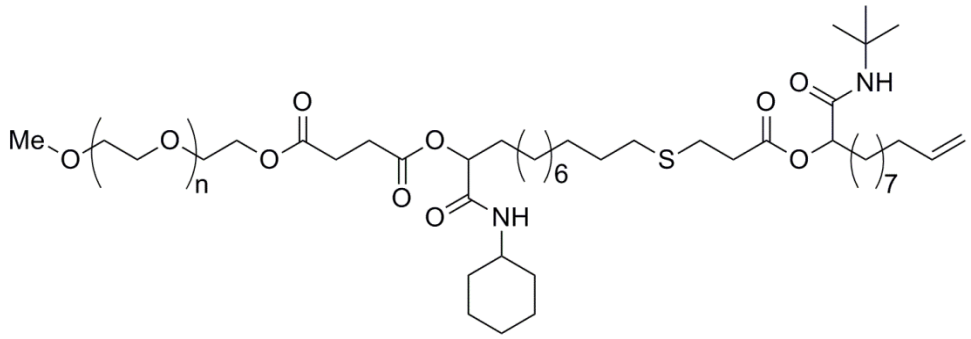
SEC /ESI-MS:

m/z exp.	ion assignment	formula	m/z theo	Δ m/z
864.25	**a** (n = 47) + 3 Na^+	$[C_{119}H_{231}O_{53}NNa_3]^{3+}$	864.08	0.17
879.00	**b** (n = 48) + 3 Na^+	$[C_{121}H_{235}O_{54}NNa_3]^{3+}$	878.77	0.23
893.58	**c** (n = 49) + 3 Na^+	$[C_{123}H_{239}O_{55}NNa_3]^{3+}$	893.45	0.13


ESI-MS of polymer 13
893.58
879.00
864.25
a
b
c
I_{norm} /a.u.
m /z


Me
n
NH
ppm

2nd Passerini-3CR of **16** with 10-undecenal **2** and *t*-butyl isocyanide **3b** yielding polymer **17**:



17

Polymer **17**: white solid, (1.31 g, 89 %).

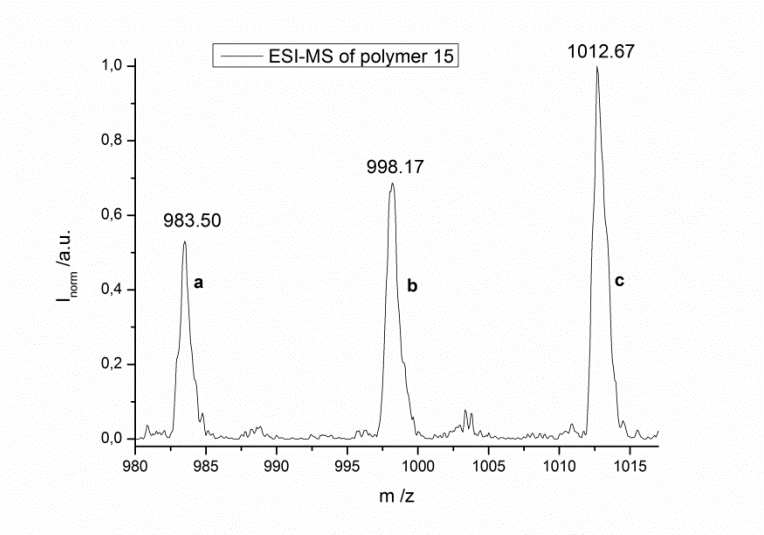
^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 6.34 (d, J = 8.3 Hz, 1H, NH, ^{7}), 6.08 (s, 1H, NH, ^{10}), 5.88 – 5.71 (m, 1H, CH, ^{11}), 5.19 – 4.87 (m, 4H, CH_2, 2 CH, $^{6, 12}$), 4.30 – 4.19 (m, 2H, CH_2, ^{3}), 3.86 (m, 1H, CH_2, $^{4'}$), 3.64 (m, 190 H, OCH_2, CH, $^{2, 8}$), 3.43 – 3.34 (m, 4H, CH_3, CH_2, $^{1,4''}$), 2.93 - 2.45 (m, 10 H, 5 CH_2, ^{5}), 1.80 (m, 53H, 22 CH_2, 3 CH_3, ^{9}).

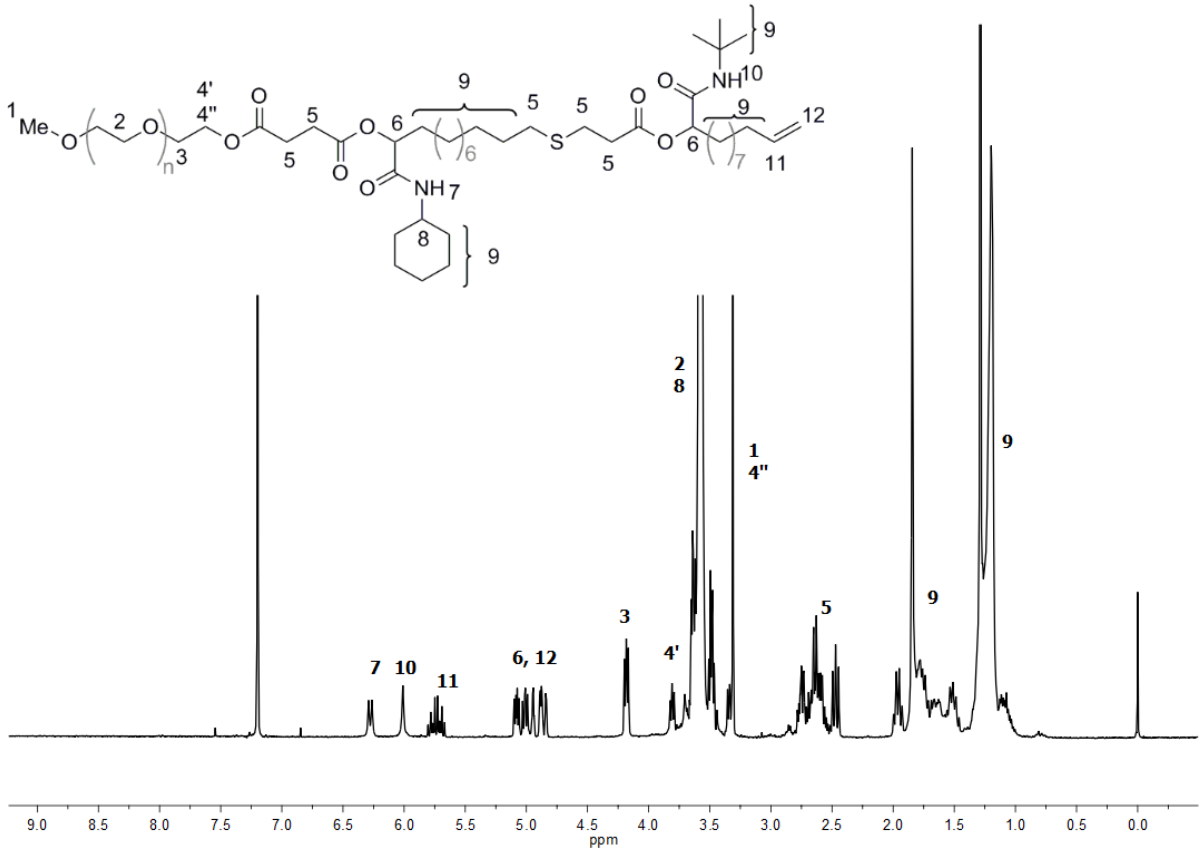
Melting point: 47.0 ° C.

IR (ATR platinum diamond) ν [cm^{-1}] = 2882.5, 2739.8, 1736.5, 1664.1, 1528.9, 1465.5, 1359.0, 1340.3, 1278.7, 1239.5, 1145.8, 1103.2, 1059.5, 957.0, 841.2, 527.9, 508.8, 420.1.

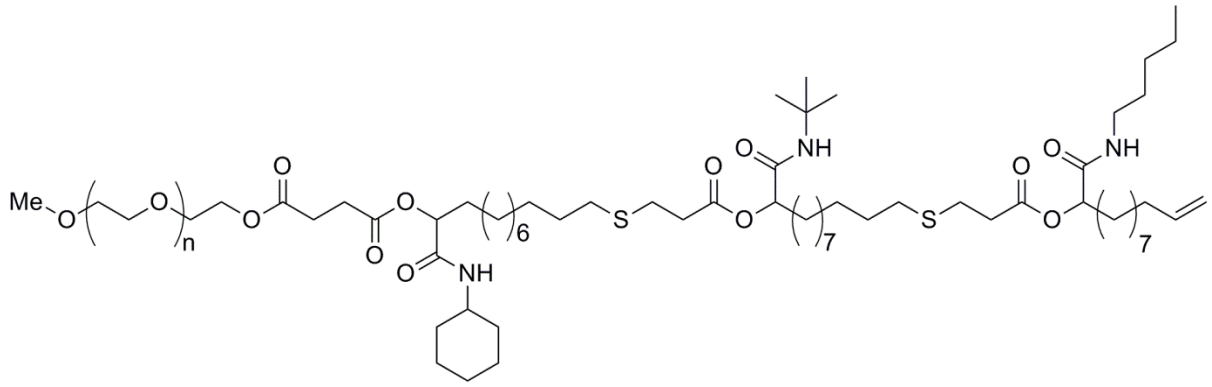
SEC /ESI-MS:

m/z exp.	ion assignment	formula	m/z theo	Δ m/z
983.50	**a** (n = 47) + 3 Na^+	$[C_{138}H_{265}O_{56}N_2SNa_3]^{3+}$	983.17	0.33
998.17	**b** (n = 48) + 3 Na^+	$[C_{140}H_{269}O_{57}N_2SNa_3]^{3+}$	997.85	0.32
1012.67	**c** (n = 49) + 3 Na^+	$[C_{142}H_{273}O_{58}N_2SNa_3]^{3+}$	1012.53	0.14


ESI-MS of polymer 15
1012.67
998.17
983.50
a
b
c
I_{norm} /a.u.
m /z


Me
NH
ppm

3rd Passerini-3CR of polymer **18** with 10-undecenal **2** and 1-pentyl isocyanide **3c** yielding polymer **19**:



19

Polymer **19**: white solid, (0.82 g, 92 %).

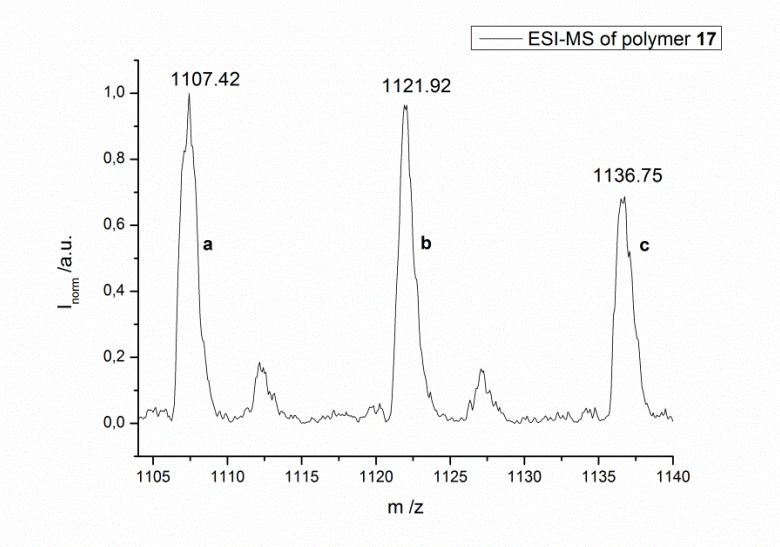
^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 6.52 – 6.39 (m, 1H, NH, [11]), 6.26 (d, J = 16.7 Hz, 1H, NH, [7]), 5.99 (s, 1H, NH, [10]), 5.82 – 5.65 (m, 1H, CH, [13]), 5.19 – 4.80 (m, 5H, CH_2, 3 CH, [6, 14]), 4.23 – 4.13 (m, 2H, CH_2, [3]), 3.82 (dd, J = 9.4, 4.9 Hz, 1H, CH_2, [4']), 3.58 (s, 192 H, OCH_2, CH, [2, 8]), 3.38 – 3.28 (m, 4H, CH_3, CH_2, [1, 4'']), 3.26 – 3.09 (m, 2H, CH_2, [12]), 2.94 – 2.40 (m, 16H, 8 CH_2, [5]), 2.12 – 0.60 (m, 80H, 4 CH_3, 34 CH_2, [9]).

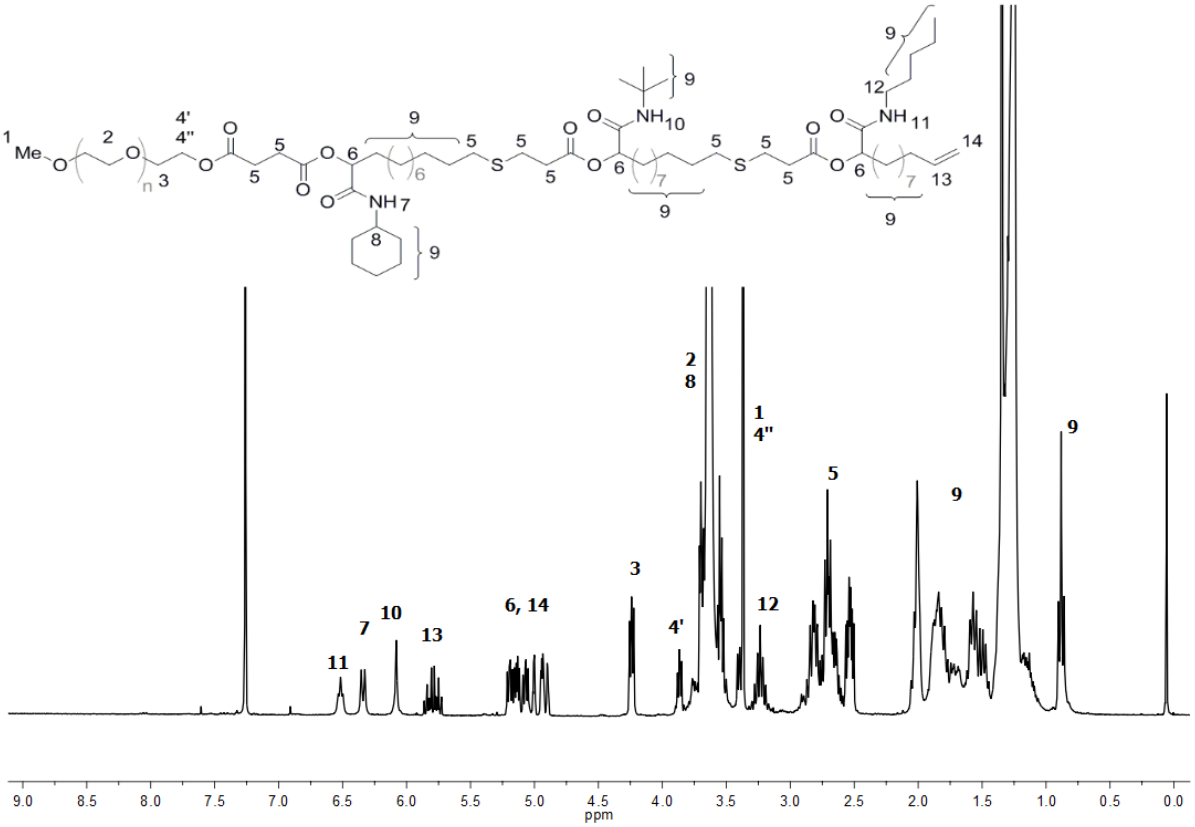
Melting point: 46.0 ° C.

IR (ATR platinum diamond) ν [cm^{-1}] = 3304.3, 2884.1, 1737.7, 1660.1, 1534.2, 1465.5, 1359.1, 1340.8, 1278.9, 1239.7, 1145.9, 1103.3, 1059.7, 958.7, 841.4, 722.0, 528.5.

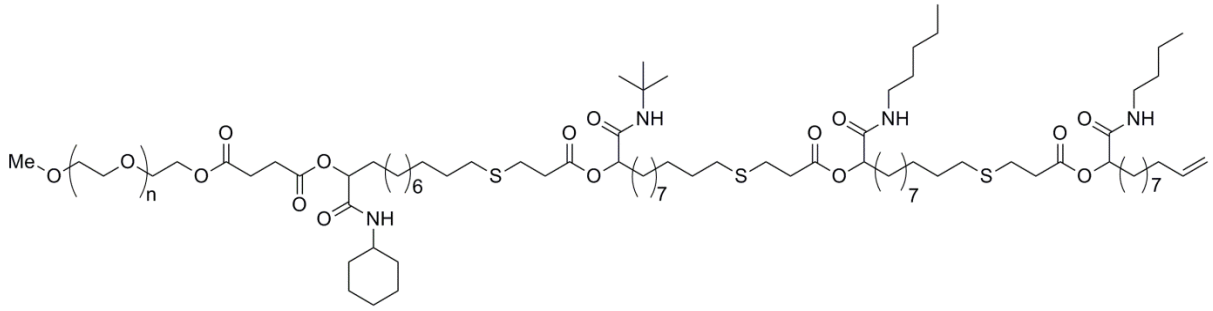
SEC /ESI-MS:

m/z exp.	ion assignment	formula	m/z theo	Δ m/z
1107.42	**a** (n = 47) + 3 Na^+	$[C_{158}H_{303}O_{59}N_3S_2Na_3]^{3+}$	1106.92	0.50
1121.92	**b** (n = 48) + 3 Na^+	$[C_{160}H_{307}O_{60}N_3S_2Na_3]^{3+}$	1121.60	0.32
1136.75	**c** (n = 49) + 3 Na^+	$[C_{162}H_{311}O_{61}N_3S_2Na_3]^{3+}$	1136.28	0.47


ESI-MS of polymer 17
1107.42
1121.92
1136.75
a
b
c
I_{norm} /a.u.
m /z


ppm

4th Passerini-3CR of polymer **21** with 10-undecenal **2** and *n*-butyl isocyanide **3d** yielding polymer **23**:



23

Polymer **23**: sticky, brown solid, (0.32 g, 80.5 %).

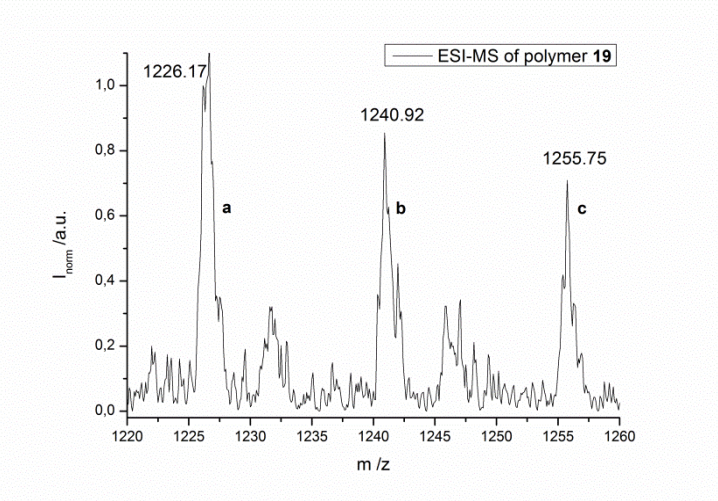
^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 6.53 (d, J = 4.5 Hz, 2H, 2 NH, [11]), 6.36 (d, J = 8.3 Hz, 1H, NH, [7]), 6.10 (s, 1H, NH, [10]), 5.89 – 5.69 (m, 1H, CH, [14]), 5.25 – 4.88 (m, 6H, 4 CH, CH_2, [6, 15]), 4.27 – 4.21 (m, 2H, CH_2, [3]), 3.87 (dd, J = 9.4, 4.9 Hz, 1H, CH_2, [4']), 3.64 (s, 189 H, OCH_2, CH, [2, 8]), 3.44 – 3.35 (m, 4H, CH_3, CH_2, [1, 4'']), 3.32 – 3.15 (m, 4H, 2 CH_2, [12]), 3.00 – 2.46 (m, 22H, 11 CH_2, [5]), 2.11 – 0.72 (m, 105H, 5 CH_3, 45 CH_2, [9]).

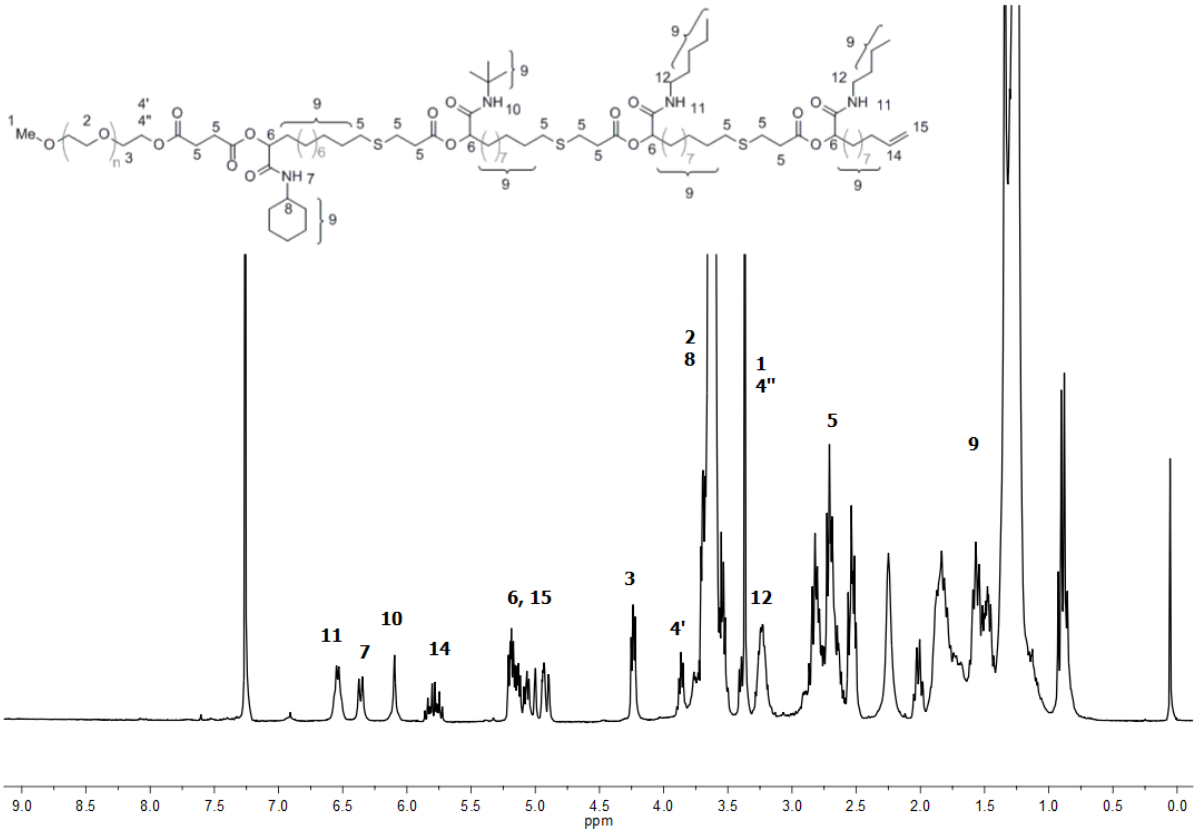
Melting point: 45.8 ° C.

IR (ATR platinum diamond) ν [cm^{-1}] = 3307.0, 2923.0, 2885.1, 2856.2, 1738.1, 1657.8, 1535.1, 1465.2, 1359.1, 1341.1, 1279.0, 1239.6, 1145.9, 1105.1, 1060.0, 958.8, 841.5, 722.0, 528.1.

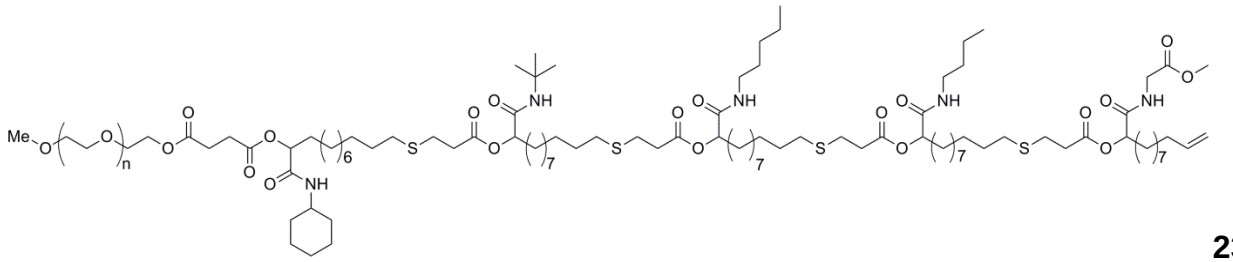
SEC /ESI-MS:

m/z exp.	ion assignment	formula	m/z theo	Δ m/z
1226.17	**a** (n = 47) + 3 Na^+	$[C_{177}H_{337}O_{62}N_4S_3Na_3]^{3+}$	1225.99	0.18
1240.92	**b** (n = 48) + 3 Na^+	$[C_{179}H_{341}O_{63}N_4S_3Na_3]^{3+}$	1240.67	0.25
1255.75	**c** (n = 49) + 3 Na^+	$[C_{181}H_{345}O_{64}N_4S_3Na_3]^{3+}$	1255.35	0.40


ESI-MS of polymer 19
1226.17
1240.92
1255.75
a
b
c
I norm /a.u.
m /z


2
8
1
4"
5
9
11
7
10
14
6, 15
3
4'
12
ppm

5th Passerini-3CR of polymer **22** with 10-undecenal **4** and methyl isocyanoacetate **3e**, yielding polymer **23**:



23

Polymer **23**: brown solid (0.10 g, 85 %).

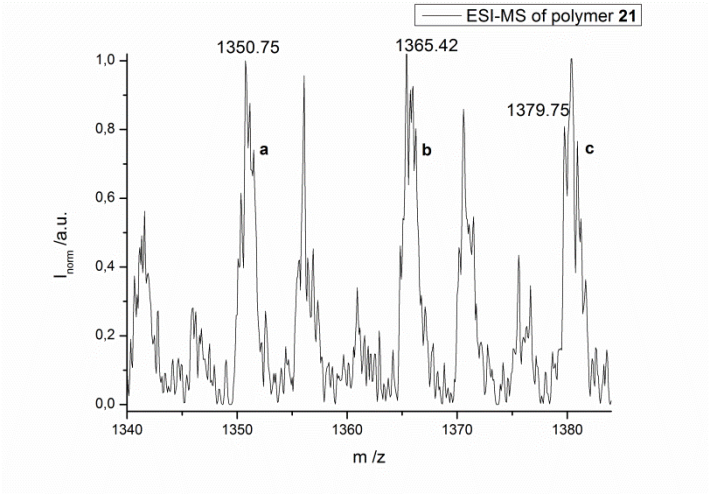
^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 6.83 (t, *J* = 9.1 Hz, 1H, NH, [13]), 6.49 (d, *J* = 4.5 Hz, 2H, 2 NH [11]), 6.29 (d, *J* = 8.2 Hz, 1H, NH, [7]), 6.02 (s, 1H, NH, [10]), 5.83 – 5.65 (m, 1H, CH, [14]), 5.23 – 4.81 (m, 7H, 5 CH, CH_2, [6, 15]), 4.21 – 4.15 (m, 2H, CH_2, [3]), 4.10 – 3.85 (m, 2H, NCH_2, [16]), 3.81 (dd, *J* = 9.4, 4.9 Hz, 1H, CH_2, [4']), 3.58 (s, 210 H, OCH_2, CH, OCH_3, [2, 8, 17]), 3.37 – 3.29 (m, 4H, CH_3, CH_2, [1, 4'']), 3.24 – 3.12 (m, 4H, 2 CH_2, [12]), 2.94 – 2.40 (m, 28 H, 14 CH_2, [5]), 2.29 – 0.64 (m, 121 H, 5 CH_3, 53 CH_2, [9]).

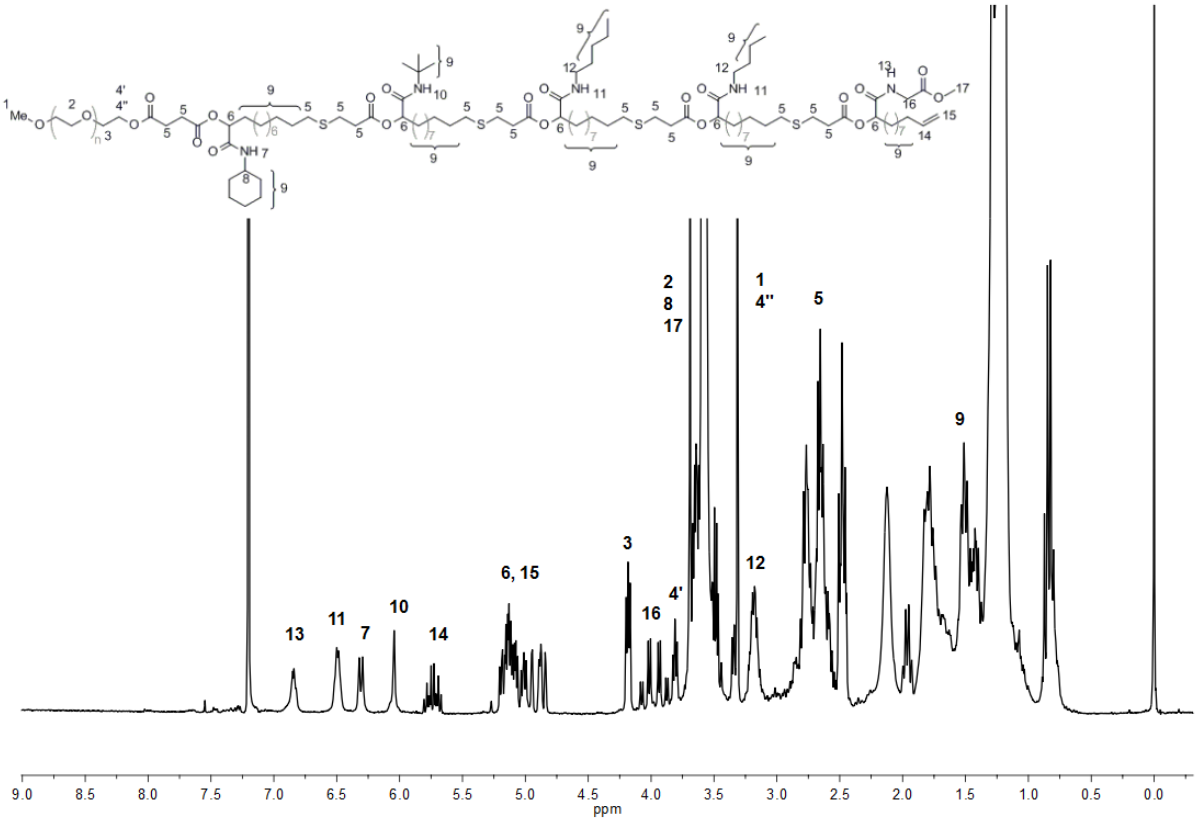
Melting Point: 45.0 ° C.

IR (ATR platinum diamond) ν [cm^{-1}] = 3304.9, 2887.1, 2855.8, 1737.9, 1664.2, 1535.3, 1465.0, 1359.2, 1341.2, 1279.0, 1239.7, 1145.5, 1105.8, 1060.1, 959.8, 841.6, 721.5, 528.3.

SEC /ESI-MS:

m/z exp.	ion assignment	formula	m/z theo	Δ m/z
1350.75	**a** (n = 47) + 3 Na^+	$[C_{195}H_{368}O_{67}N_5S_4Na_3]^{3+}$	1350.39	0.36
1365.42	**b** (n = 48) + 3 Na^+	$[C_{197}H_{372}O_{68}N_5S_4Na_3]^{3+}$	1365.01	0.41
1379.75	**c** (n = 49) + 3 Na^+	$[C_{199}H_{376}O_{69}N_5S_4Na_3]^{3+}$	1379.75	0.00



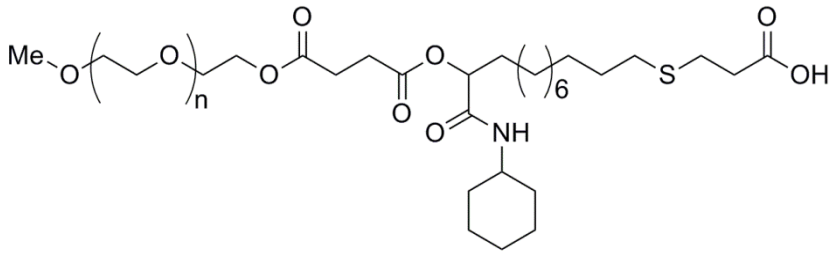


General procedure of the Thiol-Ene addition reaction:

To the product of the Passerini-3CR (1.00 eq.) 3-mercaptopropionic acid **4** (5.00 eq.), THF (0.40 M) and 2,2-dimethoxyphenylacetophenone **5** (DMPA, 5.0 mol%) were added and the mixture was stirred under UV-irradiation (360 nm) at room temperature for four

hours. The crude reaction mixture was precipitated into ice cold diethyl ether and filtered to afford the solid product.

1st Thiol-Ene addition of polymer **15** with 3-mercaptopropionic acid **4** and catalytic amounts of DMPA **5** yielding polymer **16**:



16

Polymer **16**: white solid (0.59 g, 88 %).

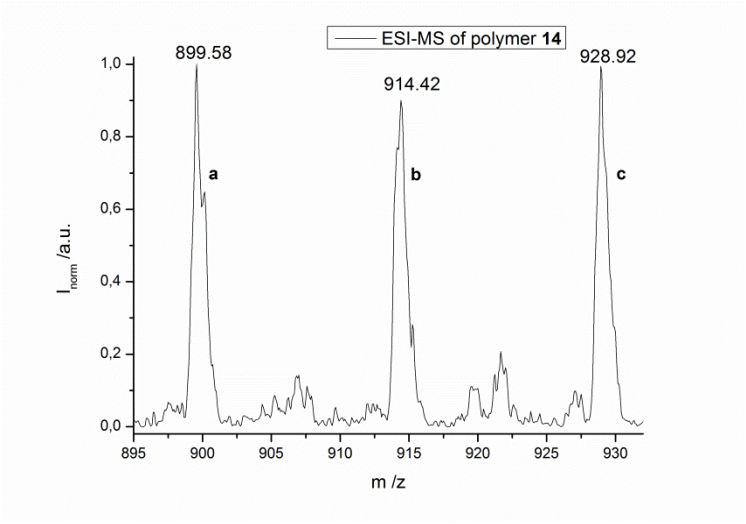
^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 6.34 (d, J = 8.2 Hz, 1H, NH, [7]), 5.11 (dd, J = 7.5, 4.2 Hz, 1H, CH, [6]), 4.10 - 4.23 (m, 2H, CH_2, [3]), 3.84 – 3.78 (dd, J = 9.4, 4.9 Hz, 1H, CH_2, [4']), 3.58 (s, 184H, OCH_2, CH, [2, 8]), 3.37 – 3.29 (m, 4H, CH_3, CH_2, [1, 4"]), 2.77 – 2.40 (m, 10H, 5 CH_2, [5]), 1.95 – 0.88 (m, 28H, 14 CH_2, [9]).

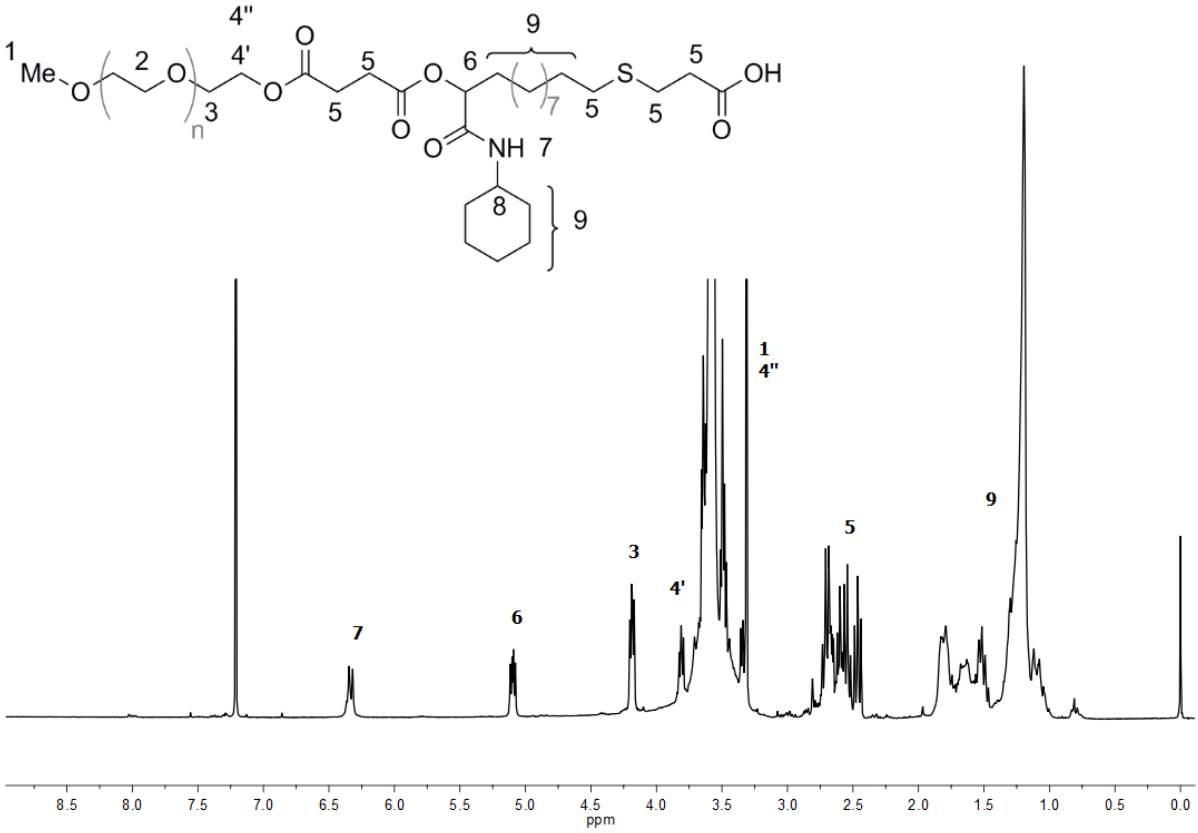
Melting point: 47.4 ° C.

IR (ATR platinum diamond) ν [cm^{-1}] = 2882.9, 1734.7, 1654.4, 1540.3, 1465.5, 1358.9, 1339.9, 1278.7, 1239.4, 1145.9, 1103.0, 1059.3, 946.3, 841.1, 528.1, 508.6.

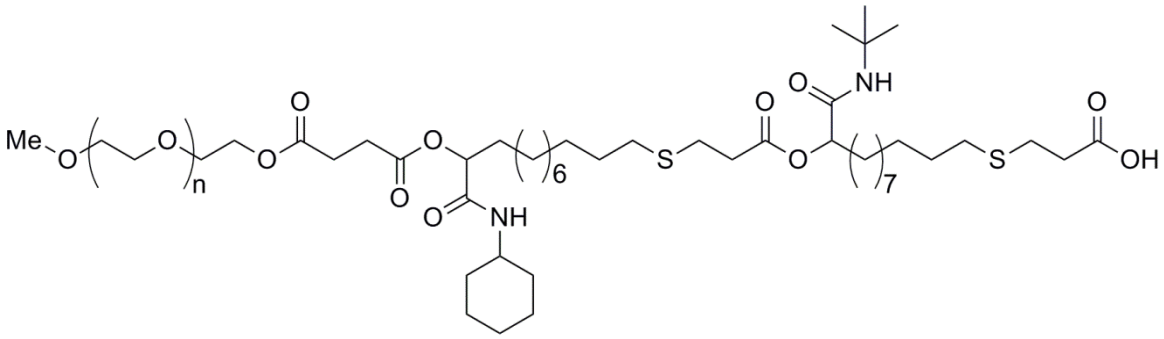
SEC /ESI-MS:

m/z exp.	ion assignment	formula	m/z theo	Δ m/z
899.58	**a** (n = 47) + 3 Na^+	$[C_{122}H_{237}O_{55}NSNa_3]^{3+}$	899.42	0.16
914.42	**b** (n = 48) + 3 Na^+	$[C_{124}H_{241}O_{56}NSNa_3]^{3+}$	914.10	0.32
928.92	**c** (n = 49) + 3 Na^+	$[C_{126}H_{245}O_{57}NSNa_3]^{3+}$	928.79	0.13


ESI-MS of polymer 14
899.58
914.42
928.92
a
b
c
1,0
0,8
0,6
0,4
0,2
0,0
I norm /a.u.
895
900
905
910
915
920
925
930
m /z


Me
n
NH
OH
1
4"
7
6
3
4'
5
9
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

2nd Thiol-Ene addition of polymer **17** with 3-mercaptopropionic acid **4** and catalytic amounts of DMPA **5** yielding polymer **18**:



18

Polymer **18**: white solid (0.93 g, 92 %).

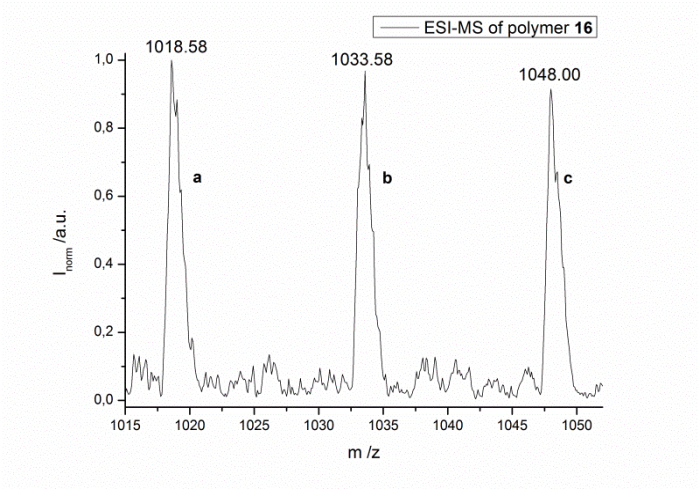
^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 6.40 (d, J = 8.3 Hz, 1H, NH, ^{7}), 6.12 (s, 1H, NH, ^{10}), 5.04-5.19 (m, 2H, 2 CH, ^{6}), 4.27 – 4.20 (m, 2H, CH_2, ^{3}), 3.86 (dd, J = 9.4, 4.9 Hz, 1H, CH_2, $^{4'}$), 3.63 (s, 198H, OCH_2, CH, $^{2, 8}$), 3.43 – 3.32 (m, 4H, CH_3, CH_2, $^{1, 4''}$), 2.88 – 2.43 (m, 16H, 8 CH_2, ^{5}), 2.02 – 0.94 (m, 55H, 3 CH_3, 23 CH_2, ^{9}).

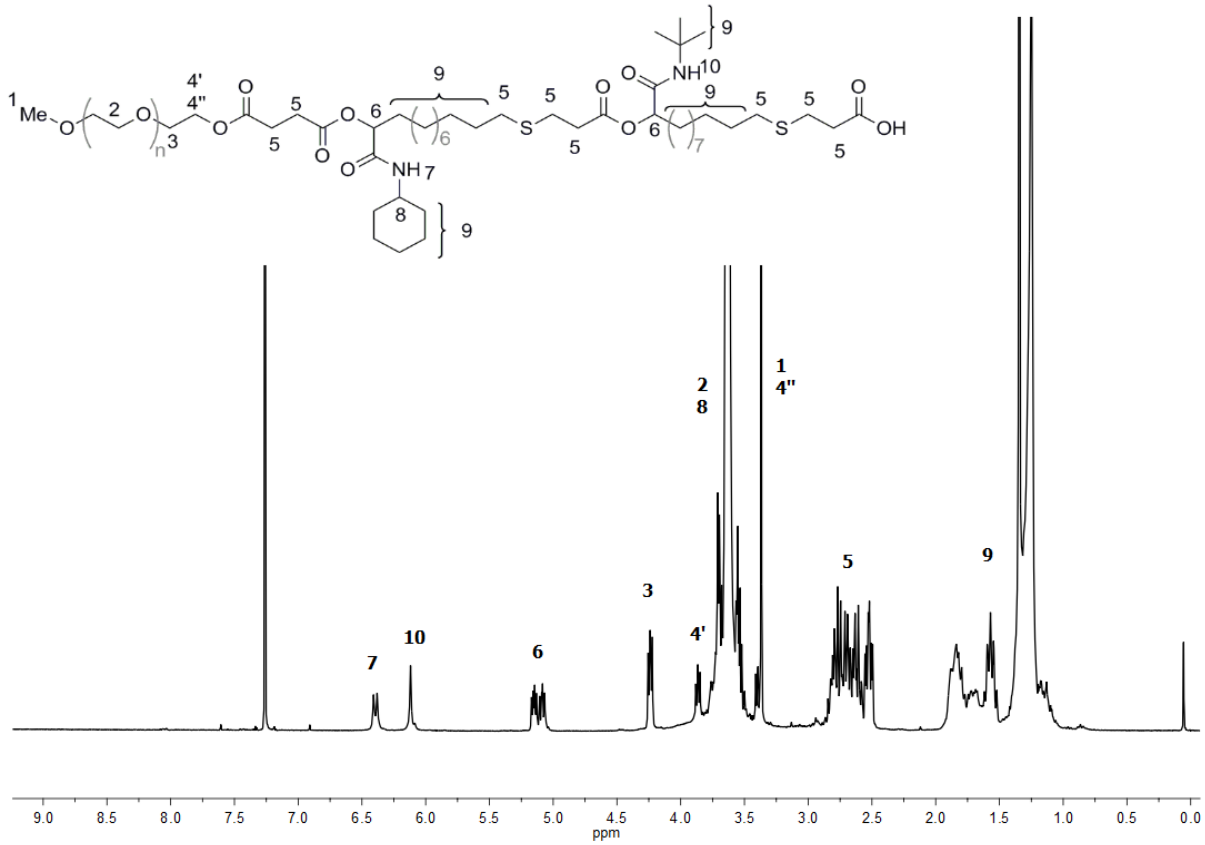
Melting Point: 45.9 ° C.

IR (ATR platinum diamond) ν [cm^{-1}] = 2883.4, 1735.7, 1657.9, 1533.7, 1465.5, 1359.1, 1340.7, 1278.8, 1239.7, 1145.9, 1102.4, 1059.5, 958.7, 841.2, 528.5.

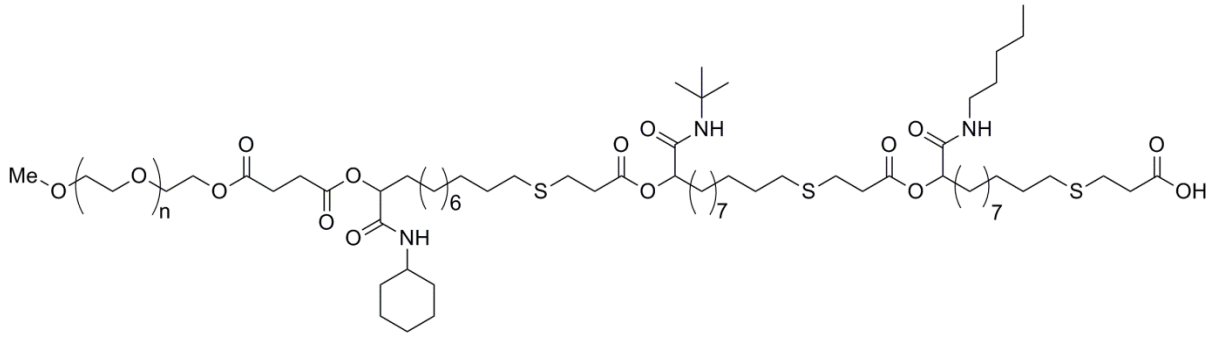
SEC /ESI-MS:

m/z exp.	ion assignment	formula	m/z theo	Δ m/z
1018.58	**a** (n = 47) + 3 Na^+	$[C_{141}H_{271}O_{58}N_2S_2Na_3]^{3+}$	1018.50	0.08
1033.58	**b** (n = 48) + 3 Na^+	$[C_{143}H_{275}O_{59}N_2S_2Na_3]^{3+}$	1033.18	0.40
1048.00	**c** (n = 49) + 3 Na^+	$[C_{145}H_{279}O_{60}N_2S_2Na_3]^{3+}$	1047.86	0.14


ESI-MS of polymer 16
1018.58
1033.58
1048.00
a
b
c
I_{norm} /a.u.
m /z


Me
OH
NH
ppm

3rd Thiol-Ene addition of polymer **19** with 3-mercaptopropionic acid **4** and catalytic amounts of DMPA **5**, yielding polymer **20**:



20

Polymer **20**: brown, sticky solid (0.65 g, 89 %).

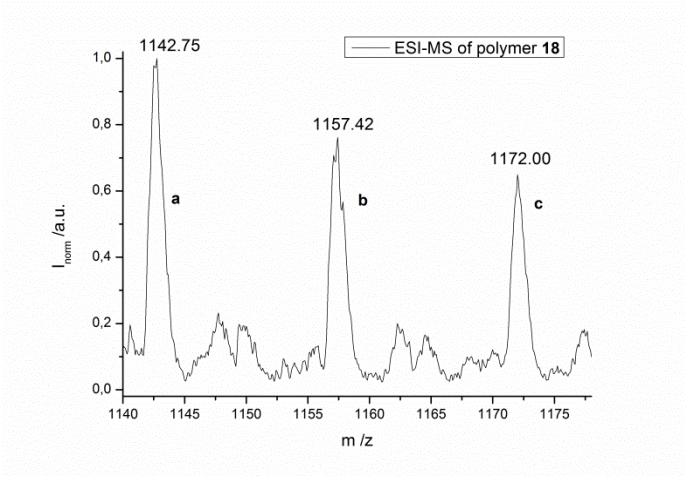
^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 6.58 (t, J = 5.6 Hz, 1H, NH, [11]), 6.37 (d, J = 8.2 Hz, 1H, NH, [7]), 6.12 (s, 1H, NH, [10]), 5.25 – 5.01 (m, 3H, 3 CH, [6]), 4.28 – 4.20 (m, 2H, CH_2, [3]), 3.86 (dd, J = 9.4, 4.9 Hz, 1H, CH_2, [4']), 3.63 (s, 197H, OCH_2, CH, [2, 8]), 3.43 – 3.34 (m, 4H, CH_3, CH_2, [1, 4'']), 3.34 – 3.13 (m, 2H, CH_2, [12]), 2.95 – 2.44 (m, 22H, 11 CH_2, [5]), 1.99 – 0.60 (m, 82H, 4 CH_3, 35 CH_2, [9]).

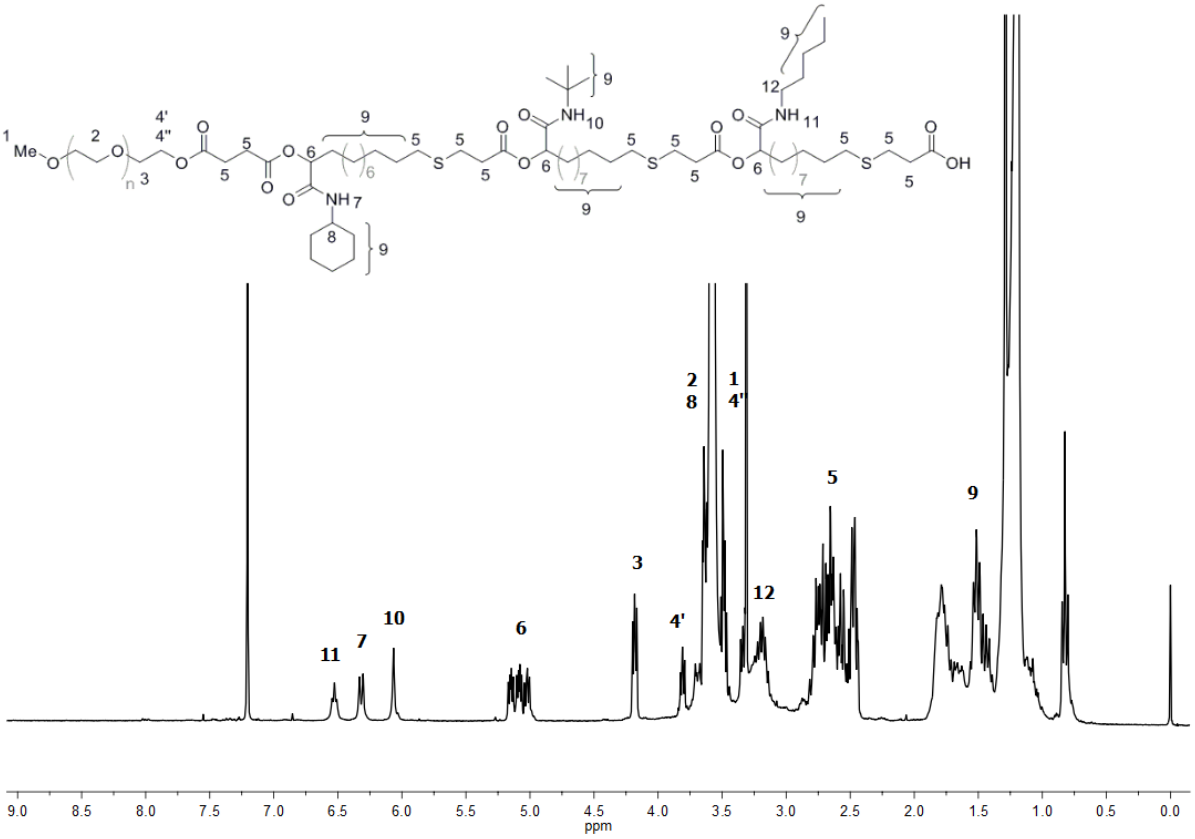
Melting point: 45.4 ° C.

IR (ATR platinum diamond) ν [cm^{-1}] = 2884.9, 1736.2, 1661.7, 1535.2, 1465.2, 1359.1, 1340.6, 1278.9, 1239.5, 1145.7, 1104.7, 1059.9, 957.5, 841.4, 528.3.

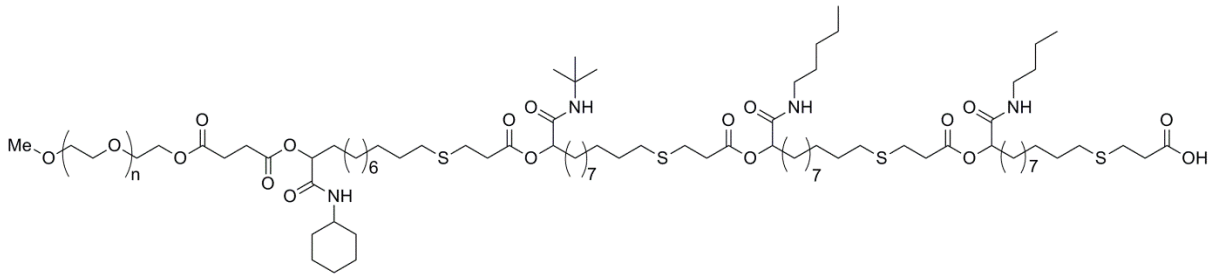
SEC /ESI-MS:

m/z exp.	ion assignment	formula	m/z theo	Δ m/z
1142.75	**a** (n = 47) + 3 Na^+	$[C_{161}H_{309}O_{61}N_3S_3Na_3]^{3+}$	1142.25	0.50
1157.42	**b** (n = 48) + 3 Na^+	$[C_{163}H_{313}O_{62}N_3S_3Na_3]^{3+}$	1156.93	0.49
1172.00	**c** (n = 49) + 3 Na^+	$[C_{165}H_{317}O_{63}N_3S_3Na_3]^{3+}$	1171.61	0.39


ESI-MS of polymer 18
1142.75
1157.42
1172.00
a
b
c
I_{norm} /a.u.
m /z


Me
OH
NH
ppm

4th Thiol-Ene addition of polymer **21** with 3-mercaptopropionic acid **4** and catalytic amounts of DMPA **5** yielding polymer **22**:



22

Polymer **22**: yellowish solid (0.14 g, 87 %).

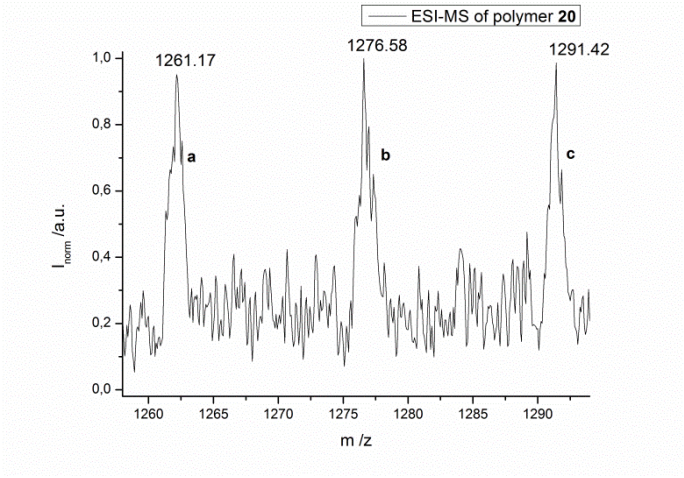
^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 6.60 (d, J = 2.3 Hz, 2H, 2 NH, [11]), 6.38 (d, J = 8.3 Hz, 1H, NH, [7]), 6.12 (s, 1H, NH, [10]), 5.27 – 5.00 (m, 4H, 4 CH, [6]), 4.29 – 4.19 (m, 2H, CH_2, [3]), 3.86 (dd, J = 9.4, 4.9 Hz, 1H, CH_2, [4']), 3.63 (s, 201H, OCH_2, CH, [2, 8]), 3.43 – 3.34 (m, 4H, CH_3, CH, [1, 4'']), 3.32 – 3.13 (m, 4H, 2 CH_2, [12]), 2.91 – 2.45 (m, 28H, 14 CH_2, [5]), 2.00 – 0.69 (m, 107H, 5 CH_3, 46 CH_2, [9]).

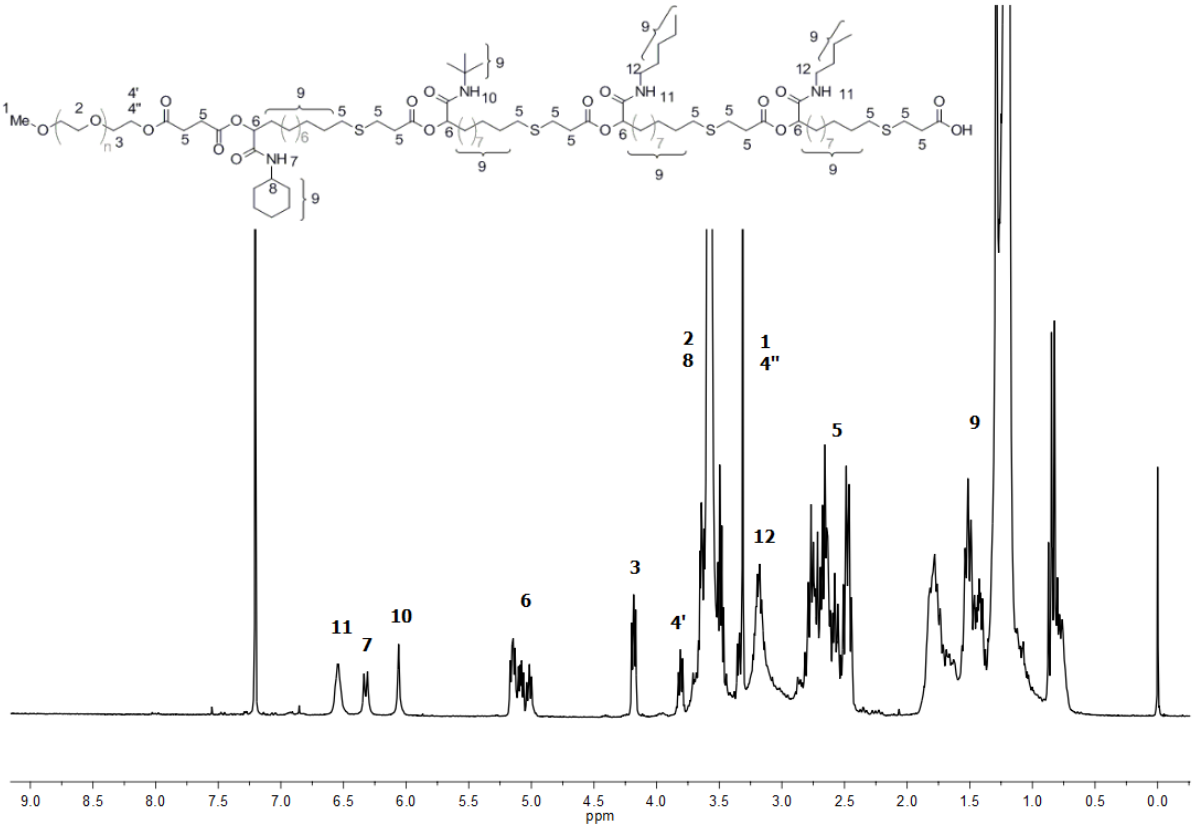
Melting point: 45.1 ° C.

IR (ATR platinum diamond) ν [cm^{-1}] = 3307.7, 2922.7, 2885.6, 2855.8, 1736.7, 1658.8, 1535.4, 1465.1, 1359.1, 1341.2, 1279.0, 1239.7, 1145.4, 1105.5, 1060.1, 959.5, 841.5, 721.8, 527.5.

SEC /ESI-MS:

m/z exp.	ion assignment	formula	m/z theo	Δ m/z
1261.17	**a** (n = 47) + 3 Na^+	$[C_{180}H_{343}O_{64}N_4S_4Na_3]^{3+}$	1261.33	0.16
1276.58	**b** (n = 48) + 3 Na^+	$[C_{182}H_{347}O_{65}N_4S_4Na_3]^{3+}$	1276.01	0.57
1291.42	**c** (n = 49) + 3 Na^+	$[C_{184}H_{351}O_{66}N_4S_4Na_3]^{3+}$	1290.69	0.73

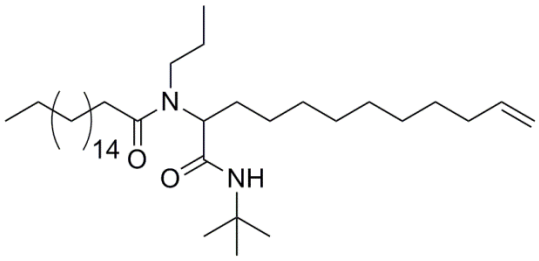

ESI-MS of polymer 20
1261.17
1276.58
1291.42
a
b
c
I_{norm} /a.u.
m /z


ppm

6.3.2 Experimental Procedures Chapter 4.1.2

Variation of the amine component:

1st Ugi reaction:



25

1.34 g 10-Undecenal **2** (7.98 mmol, 1.70 eq.) were stirred for 15 minutes with 0.47 g propylamine **24a** (7.88 mmol, 1.70 eq.) at room temperature. Subsequently, 1.30 g stearic acid **1a** (4.59 mmol, 1.00 eq.), 0.70 g *t*-butyl isocyanide **3b** (8.43 mmol, 1.80 eq.) and 5.25 mL (0.87 M) methanol were added and stirred for 24 hours at room temperature. The reaction was followed *via* GPC and after completion of the reaction, the solvent was removed under reduced pressure and the product was purified by column chromatography (hexane/ethyl acetate 30:1 → 12:1). Product **25** was obtained as a colorless liquid in a yield of 91 % (2.42 g).

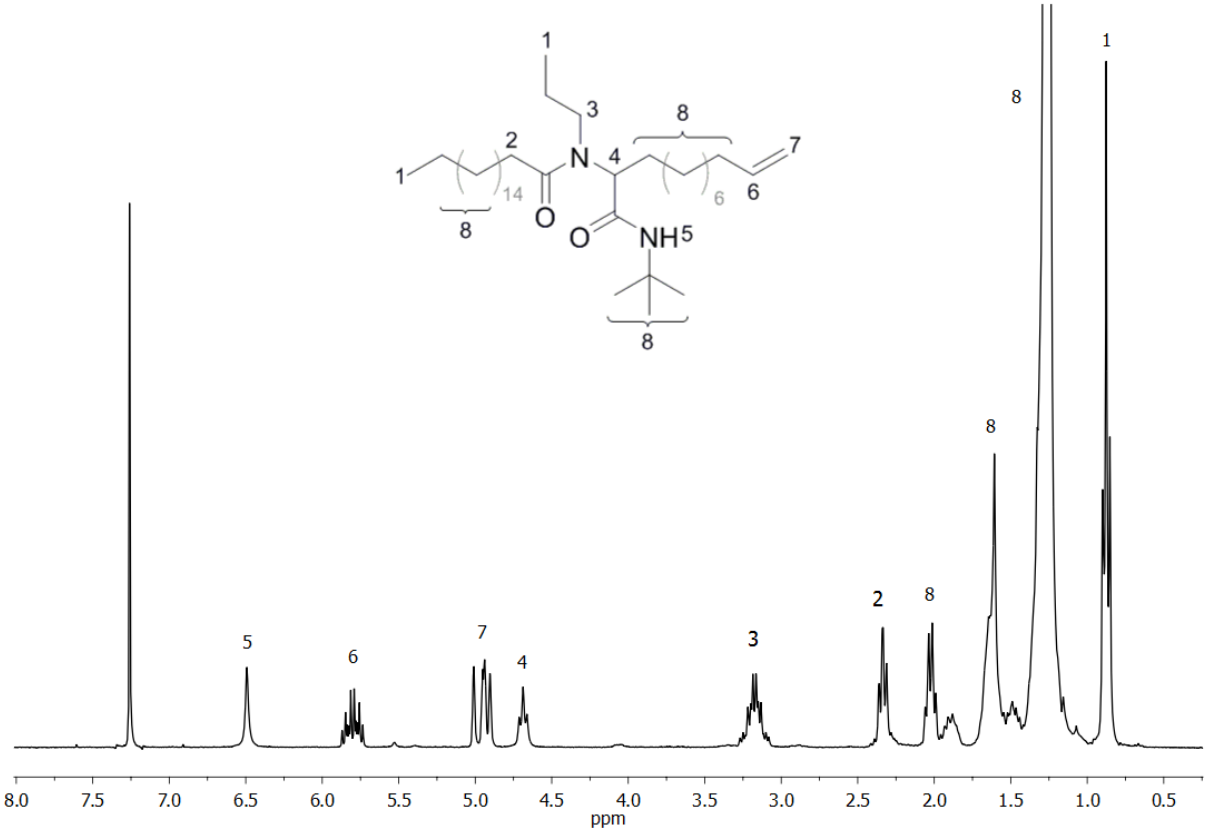
^{1}H NMR: (300 MHz, $CDCl_3$) δ /ppm: 6.49 (s, 1H, NH, ^{5}), 5.80 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H, CH, ^{6}), 4.95 (dd, J = 17.3, 13.8 Hz, 2H, CH_2, ^{7}), 4.69 (t, J = 7.6 Hz, 1H, CH, ^{4}), 3.30 – 3.06 (m, 2H, CH_2, ^{3}), 2.34 (dd, J = 8.1, 6.3 Hz, 2H, CH_2, ^{2}), 2.08 – 1.00 (m, 57H, 24 CH_2, 3 CH_3, ^{8}), 0.88 (t, J = 7.1 Hz, 6H, CH_3, ^{1}).

^{13}C NMR: (75 MHz, $CDCl_3$) δ /ppm: 175.0, 171.0, 139.3, 114.2, 58.2, 50.9, 50,0, 33.9, 33.7, 32.1, 29.8, 29.8, 29.7, 29.6, 29.6, 29.6, 29.5, 29.5, 29.5, 29.2, 29.0, 28.8, 28.0, 26.3, 25.9, 23.5, 22.8, 14.2, 11.6.

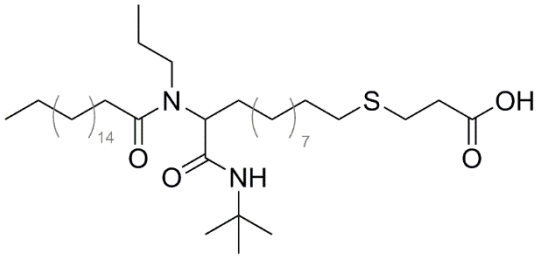
FAB-MS: $[C_{37}H_{73}O_2N_2]^+$ calculated: 577.5669, found: 577.5667.

IR: (ATR): ν [cm^{-1}] = 3312.0, 2920.7, 2851.4, 1682.5, 1625.3, 1534.7, 1454.0, 1362.3, 1225.0, 1112.5, 991.3, 907.1, 720.5, 470.5.

***R*f:** (hexane/ethyl acetate (9:1)) = 0.44.



1st Thiol-Ene addition:



26

2.38 g of substance **25** (4.12 mmol, 1.00 eq.) were diluted with 2.20 g 3-mercaptopropionic acid **4** (20.7 mmol, 5.00 eq.) and 32 mg 2,2-dimethoxy-2-phenylacetophenone (DMPA) **5** (0.12 mmol, 3.00 mol%) were added. The reaction mixture was stirred under UV irradiation at room temperature for one hour. Full conversion of the double bonds was detected *via* ^{1}H NMR. The excess of 3-

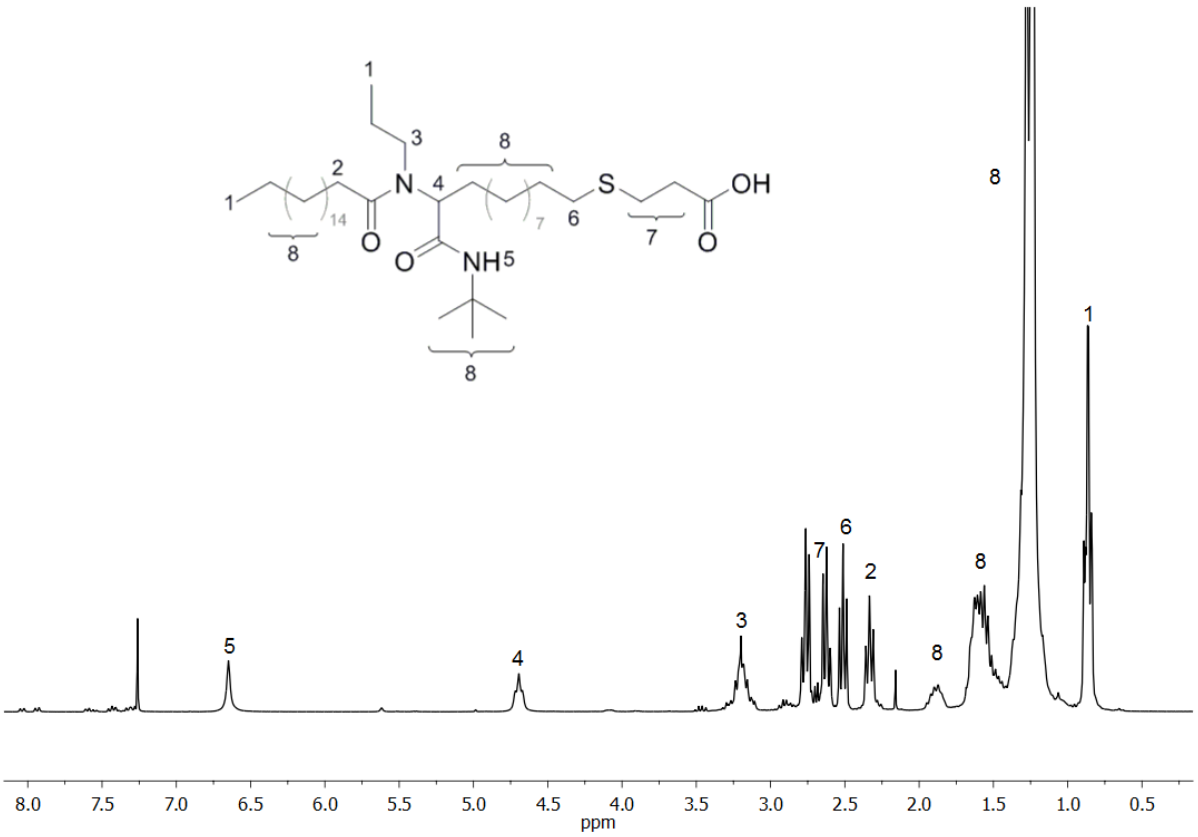
mercaptopropionic acid was removed by vacuum distillation and the residue was dissolved in diethyl ether. The organic layer was washed with water (3 x 100 mL) and brine (1 x 100 mL) and dried over sodium sulfate. After removing the solvent under reduced pressure, the desired product **26** was obtained as yellowish oil in a yield of 91 % (2.56 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 6.65 (s, 1H, NH, ^{5}), 4.69 (t, J = 7.1 Hz, 1H, CH, ^{4}), 3.34 – 3.07 (m, 2H, CH_2, ^{3}), 2.81 – 2.57 (m, 4H, 2 CH_2, ^{7}), 2.51 (t, J = 7.3 Hz, 2H, CH_2, ^{6}), 2.33 (t, J = 7.5 Hz, 2H, CH_2, ^{2}), 2.00 – 0.74 (m, 67H, 26 CH_2, 5 CH_3, ^{8,1}).

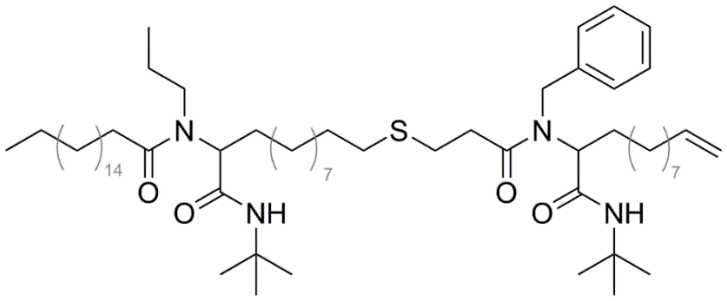
^{13}C NMR (75 MHz, $CDCl_3$) δ / ppm: 175.9, 175.2, 170.9, 58.3, 51.0, 47.0, 34.7, 33.5, 32.1, 31.9, 29.7, 29.6, 29.5, 29.4, 29.4, 29.3, 29.0, 28.7, 28.5, 28.1, 26.7, 26.1, 25.7, 23.4, 23.4, 22.7, 14.1, 11.4.

FAB-MS: $[C_{40}H_{79}O_2N_4S]^+$ calculated: 683.6, found: 683.6.

IR: (ATR): ν [cm^{-1}] = 2920.3, 2850.8, 1717.2, 1681.4, 1621.5, 1535.9, 1454.5, 1363.8, 1223.8, 8993.3, 720.4, 634.4.



2nd Ugi reaction:



27

4.92 g of substance **26** (7.20 mmol, 1.00 eq.) were stirred with 2.07 g 10-undecenal **2** (12.27 mmol, 1.70 eq.), and 1.34 g benzylamine **24b** (12.5 mmol, 1.70 eq.) in 7.2 mL methanol (1.00 M) at room temperature. Subsequently, 1.08 g *tert*-butyl isocyanide **3b** (13.0 mmol, 1.80 eq.) were added and the mixture was stirred at room temperature for 24 hours. After completion of the reaction, the solvent was removed under reduced

pressure and the crude product was purified by column chromatography. (hexane/ethyl acetate 12:1 → 3:1). Product **27** was obtained as yellowish oil in a yield of 76 % (5.62 g).

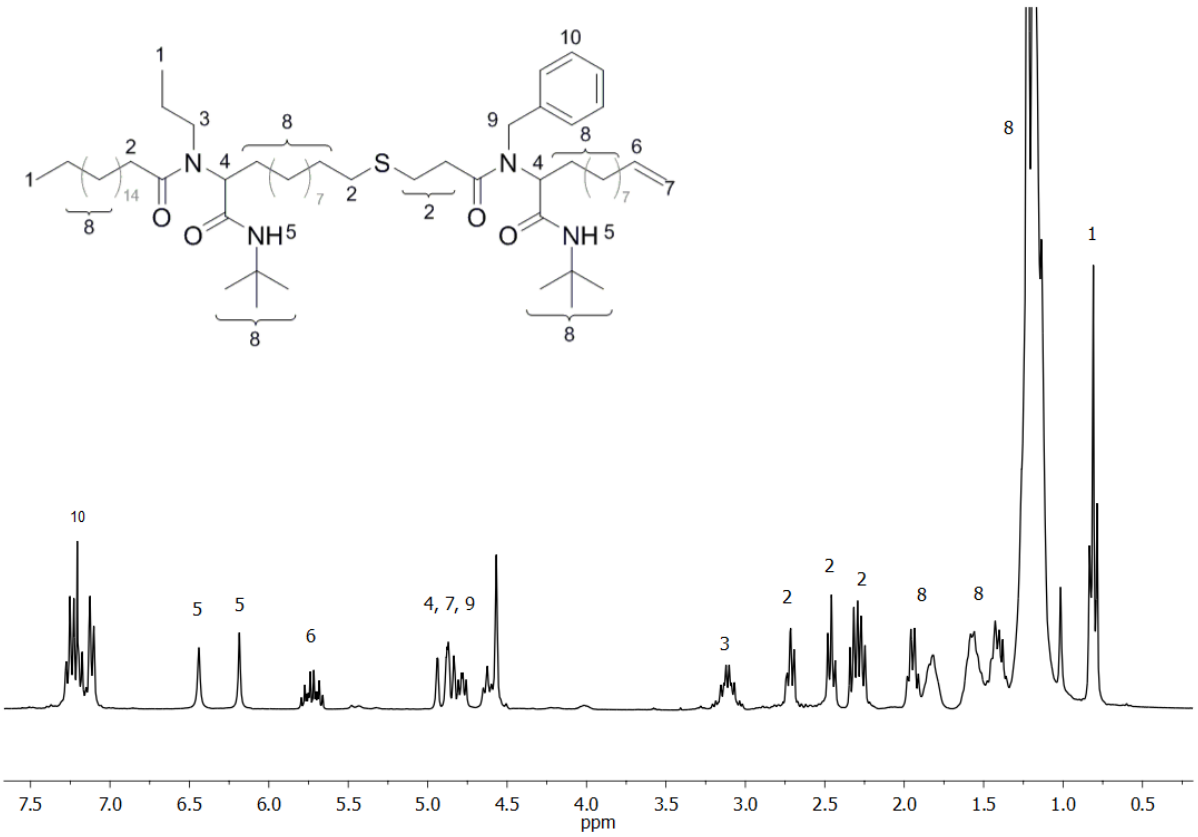
^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 7.25 (ddd, J = 22.1, 14.5, 7.1 Hz, 5H, 5 CH aromatic, ^{10}), 6.50 (s, 1H, NH, ^{5}), 6.23 (s, 1H, NH, ^{5}), 5.89 – 5.68 (m, 1H, CH, ^{6}), 5.04 – 4.55 (m, 6H, 2 CH, 2 CH_2, ^{4,7,9}), 3.29 – 3.06 (m, 2H, CH_2, ^{3}), 2.85 – 2.69 (m, 2H, CH_2, ^{2}), 2.60 – 2.45 (m, 2H, CH_2, ^{2}), 2.42 – 2.27 (m, 4H, 2 CH_2, ^{2}), 2.08 – 0.99 (m, 84H, 33 CH_2, 6 CH_3, ^{8}), 0.87 (t, J = 7.1 Hz, 6H, 2 CH_3, ^{1}).

^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 175.0, 173.9, 171.0, 169.9, 139.3, 137.8, 128.8, 127.4, 126.1, 114.22, 58.7, 51.3, 50.9, 48.2, 47.0, 34.4, 33.9, 33.7, 32.6, 32.0, 29.8, 29.8, 29.7, 29.7, 29.6, 29.6, 29.5, 29.5, 29.4, 29.3, 29.2, 29.0, 29.0, 28.8, 28.7, 28.5, 28.0, 28.0, 26.5, 26.3, 25.9, 23.5, 22.8, 14.2, 11.6.

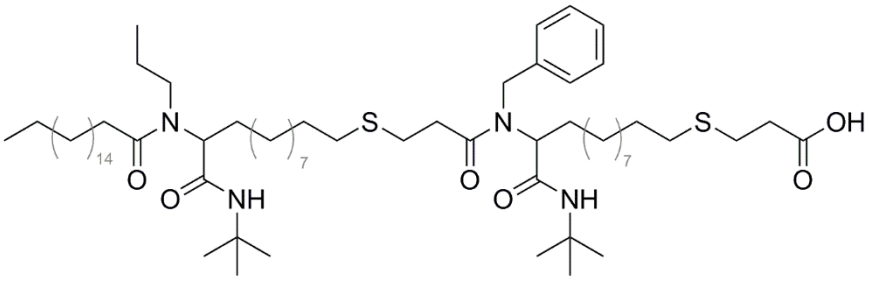
FAB-MS: $[C_{63}H_{115}O_4N_4S]^+$ calculated: 1023.8632, found: 1023.8634.

IR: (ATR): ν [cm^{-1}] = 3322.0, 2920.9, 2851.2, 1680.2, 1625.9, 1536.9, 1452.3, 1419.2, 1390.2, 1361.7, 1224.6, 991.3, 907.5, 723.1, 695.7.

***R*$_f$:** (hexane/ethyl acetate (3:1)) = 0.48.



2nd Thiol-Ene addition:



28

5.57 g of substance **27** (5.44 mmol, 1.00 eq.) were diluted with 2.89 g 3-mercaptopropionic acid **4** (27.3 mmol, 5.00 eq.) and 65 mg DMPA **5** (0.25 mmol, 5.00 mol%) were added. The reaction mixture was stirred under UV-irradiation at room temperature for one hour. Complete conversion of the double bonds was confirmed by proton NMR. Subsequently, the excess of 3-mertcaptopropionic acid **4** was removed applying vacuum distillation; the residue was diluted with diethyl ether (50 mL) and

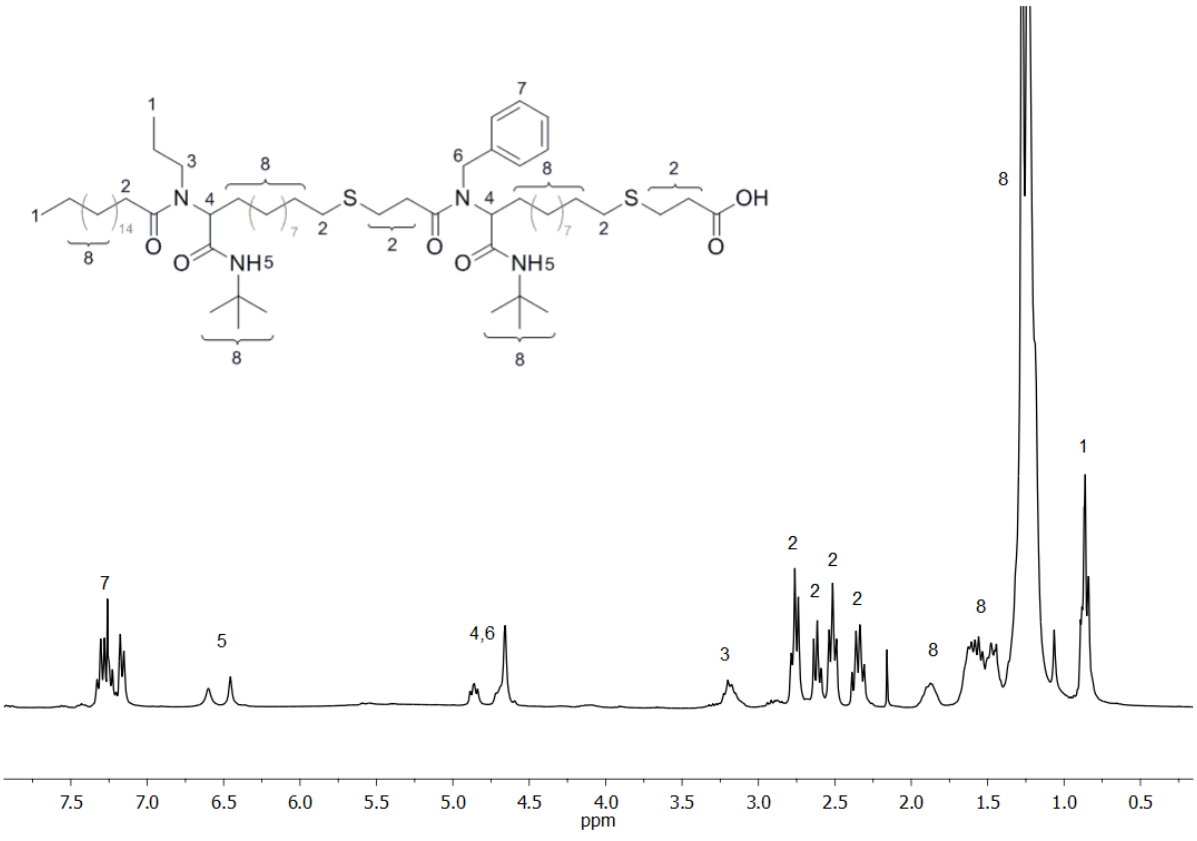
washed with water (3 x 50 mL). The organic layer was dried over sodium sulfate and concentrated in vacuo. The product **28** was obtained as yellowish oil in a yield of 81 % (4.98 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ / ppm: 7.37 – 7.12 (m, 5H, 5 CH aromatic, ^{7}), 6.60 (s, 1H, NH, ^{5}), 6.46 (s, 1H, NH, ^{5}), 4.97 – 4.53 (m, 4H, 2 CH, 2 CH_2, ^{4,6}), 3.30 – 3.06 (m, 2H, CH_2, ^{3}), 2.82 – 2.26 (m, 14H, 7 CH_2, ^{2}), 1.99 – 0.74 (m, 92H, 34 CH_2, 8 CH_3, ^{8,1}).

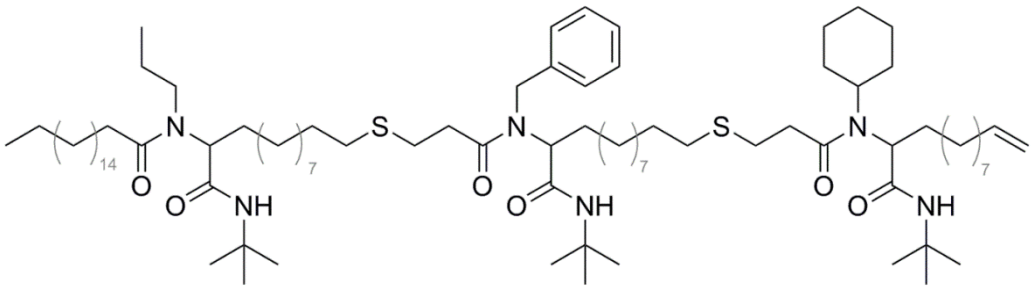
^{13}C NMR (75 MHz, $CDCl_3$) *δ* / ppm: 175.3, 175.2, 174.1, 171.4, 171.0, 170.0, 164.3, 137.7, 132.3, 131.7, 128.8, 127.4, 126.1, 95.1, 51.4, 51.0, 48.3, 34.8, 34.4, 33.7, 32.6, 32.2, 32.0, 29.8, 29.8, 29.7, 29.6, 29.6, 29.5, 29.3, 29.3, 29.0, 28.7, 28.2, 28.0, 26.9, 26.4, 26.3, 25.9, 24.9, 23.5, 22.8, 22.6, 21.3, 14.6, 14.2, 11.53.

FAB-MS: $[C_{66}H_{122}O_4N_6S_2]^+$ calculated: 1129.9, found: 1129.4.

IR: (KBr): ν [cm^{-1}] = 3332.0, 2924.8, 2853.7, 1729.1, 1681.6, 1631.7, 1538.1, 1454.5, 1364.4, 1226.3, 725.6.



3rd Ugi reaction:



29

4.94 g of subtance **28** (4.37 mmol, 1.00 eq.), 1.26 g 10-undecenal **2** (7.46 mmol, 1.70 eq.) and 0.74 g cyclohexyl amine **24c** (7.44 mmol, 1.70 eq.) were dissolved in 4.4 mL methanol (1.00 M). Subsequently, 0.62 g *tert*-butyl isocyanide **3b** (7.45 mmol, 1.70 eq.) were added and the mixture was stirred at room temperature for 48 hours. After completion of the reaction, the solvent was removed under reduced pressure and the crude product was purified by column chromatography (hexane/ethyl acetate 10:1 → 3:1). Product **29** was obtained as yellowish oil in a yield of 81 % (5.17 g).

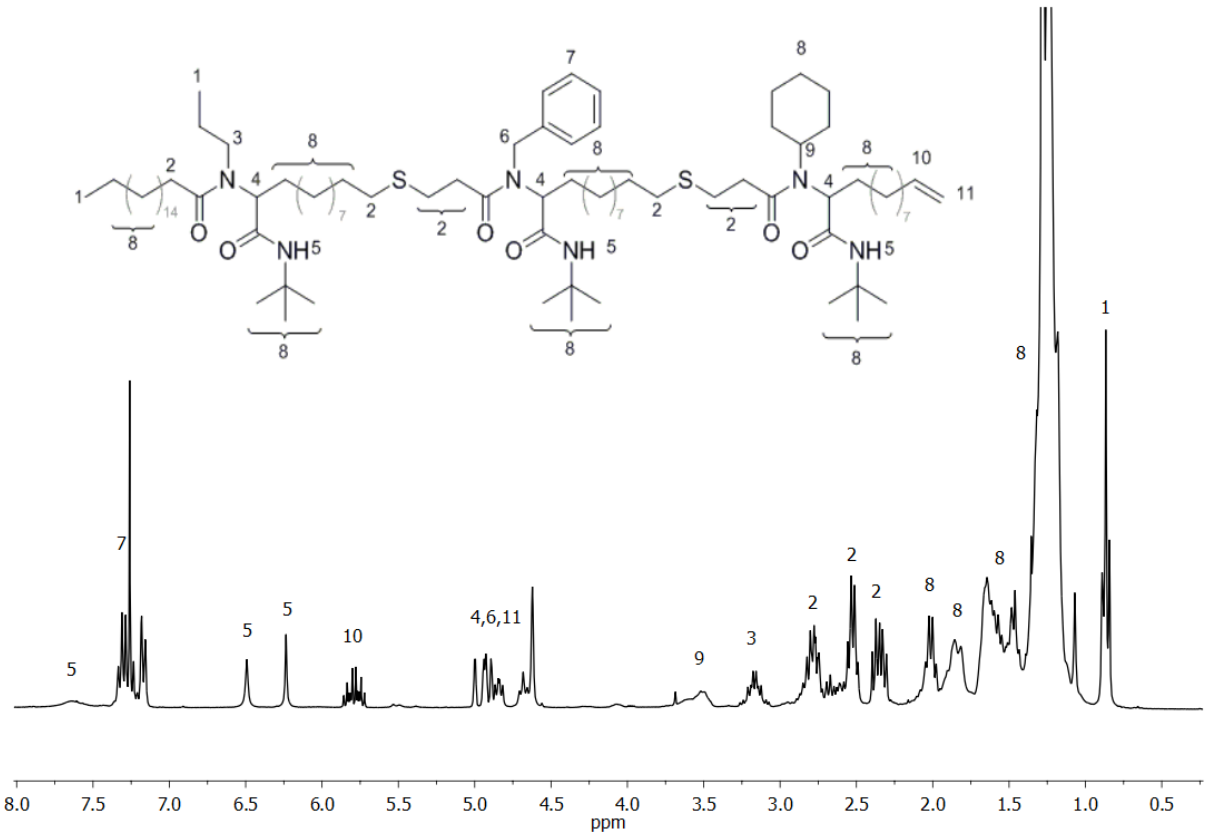
^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 7.62 (s, J = 7.5 Hz, 1H, NH, ^{5}), 7.38 – 7.08 (m, 5H, 5 CH aromatic, ^{7}), 6.49 (s, 1H, NH, ^{5}), 6.23 (s, 1H, NH, ^{5}), 5.87 – 5.69 (m, 1H, CH, ^{10}), 5.04 – 4.49 (m, 7H, 3 CH, 2 CH_2, ^{4,6,11}), 3.53 (dd, J = 42.7, 35.2 Hz, 1H, CH, ^{9}), 3.29 – 3.01 (m, 2H, CH_2, ^{3}), 2.94 – 2.20 (m, 14H, 7 CH_2, ^{2}), 2.17 – 0.71 (m, 127H, 47 CH_2, 11 CH_3, ^{1,8}).

^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 175.0, 173.9, 171.0, 169.9, 169.0, 168.6, 163.1, 157.0, 139.3, 128.9, 126.2, 126.1, 114.2, 99.7, 62.6, 58.7, 51.3, 50.9, 45.9, 33.9, 33.7, 32.9, 32.6, 32.0, 29.9, 29.8, 29.8, 29.8, 29.6, 29.6, 29.5, 29.5, 29.4, 29.2, 29.1, 29.0, 28.8, 28.8, 28.7, 28.5, 28.0, 27.3, 26.2, 25.9, 23.5, 23.5, 23.5, 22.8, 19.3, 14.3, 11.6.

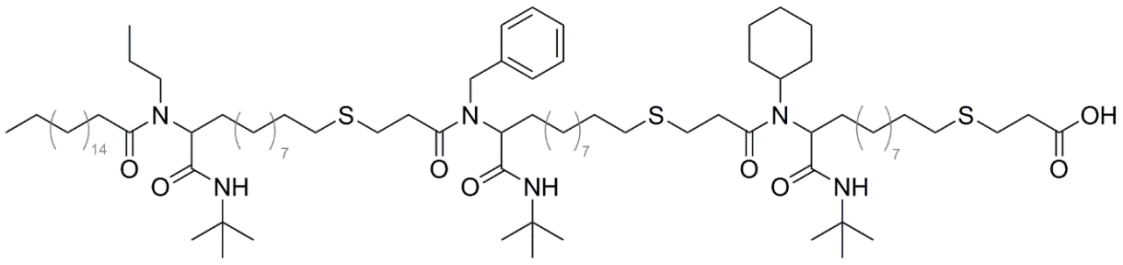
FAB-MS: $[C_{88}H_{160}O_6N_6S_2]^+$ calculated: 1461.2, found: 1460.9.

IR: (ATR): ν [cm^{-1}] = 3317.6, 2921.0, 2851.2, 1673.2, 1625.5, 1540.8, 1452.1, 1389.7, 1361.5, 1224.8, 1121.3, 992.9, 907.1, 722.5, 695.3.

***R*$_f$:** (hexane/ethyl acetate (5:2)) = 0.48.



3rd Thiol-Ene addition:



30

1.85 g 3-mercaptopropionic acid **4** (17.4 mmol, 5.00 eq.) were added to 5.06 g of substance **29** (3.46 mmol, 1.00 eq.) and 53.0 mg DMPA **5** (0.21 mmol, 6.00 mol%) and the mixture was stirred under UV-irradiation at room temperature for two hours. Complete consumption of the double bonds was confirmed by a NMR measurement. The excess of 3-mercaptopropionic acid **4** was removed by vacuum distillation and the residue was dissolved in diethyl ether (50 mL) and washed with water (3 x 50 mL). The

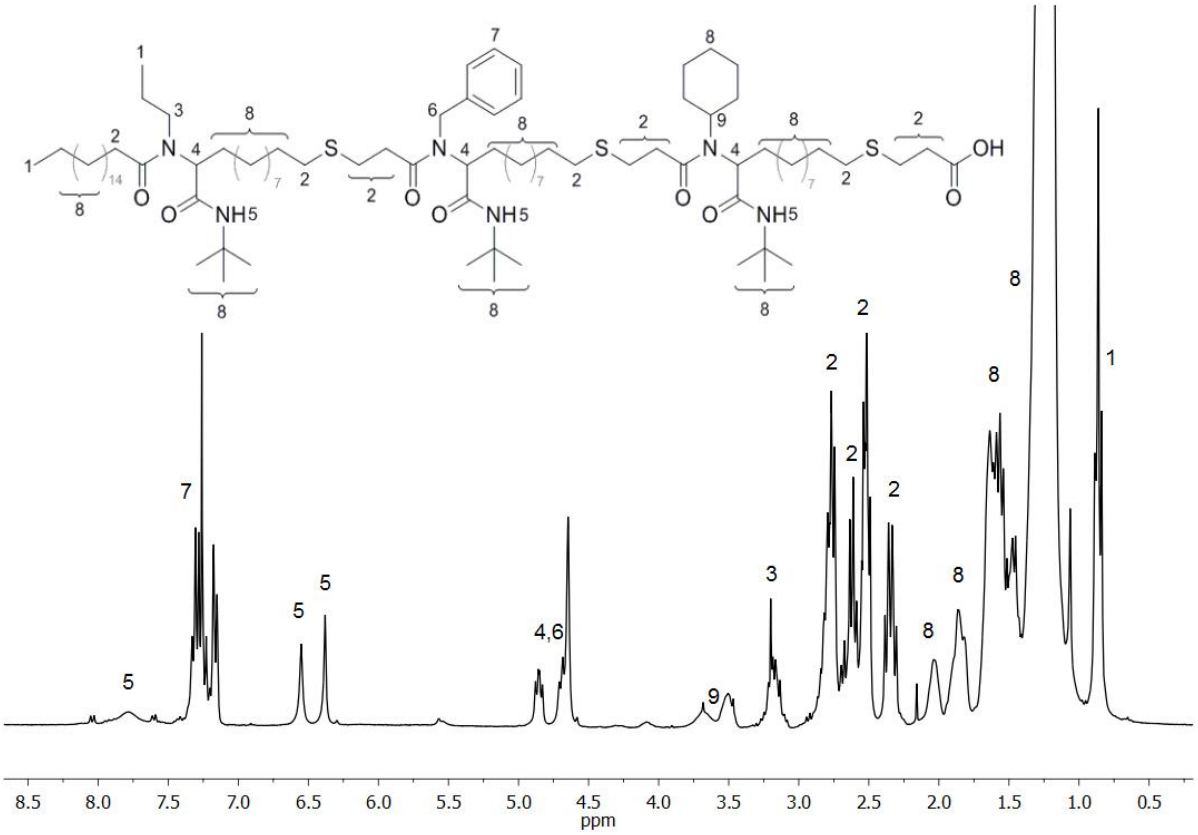
organic layer was dried over sodium sulfate, filtered and the solvent was removed under reduced pressure to obtain product **30** as highly viscous oil in a yield of 75 % (4.08 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 7.78 (s, 1H, NH, ^{5}), 7.24 (m, 5H, 5 CH aromatic, ^{7}), 6.55 (s, 1H, NH, ^{5}), 6.38 (s, 1H, NH, ^{5}), 4.92 – 4.55 (m, 5H, 3 CH, CH_2, ^{4,6}), 3.83 – 3.04 (m, 3H, CH, CH_2, ^{3,9}), 2.99 – 2.18 (m, 20H, 10 CH_2, ^{2}), 2.16 – 0.48 (m, 129H, 48 CH_2, 11 CH_3, ^{1,8}).

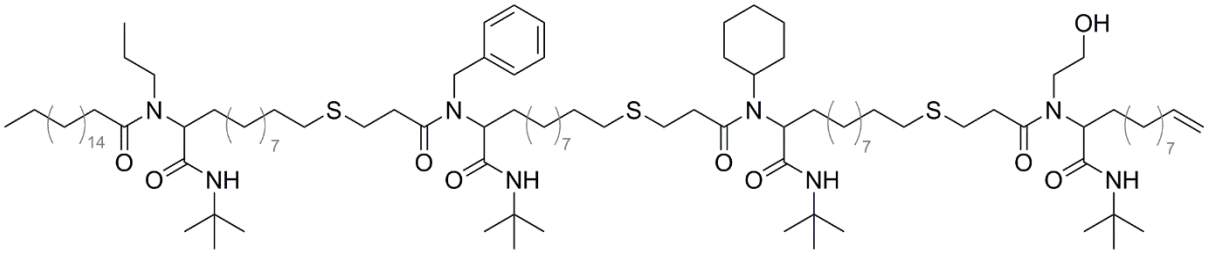
^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm:175.1, 174.7, 172.8, 171.0, 169.9, 163.1, 137.8, 128.8, 127.4, 126.1, 58.7, 51.4, 51.0, 50.8, 48.3, 47.0, 47.0, 35.4, 34.8, 34.4, 33.7, 32.9, 32.6, 32.1, 32.0, 29.8, 29.7, 29.7, 29.6, 29.5, 29.5, 29.4, 29.3, 29.1, 29.0, 29.0, 28.7, 28.7, 28.6, 28.2, 28.1, 28.0, 27.1, 27.0, 26.5, 26.3, 26.2, 26.0, 25.9, 25.1, 23.5, 22.8, 14.3, 11.6.

FAB-MS: $[C_{91}H_{167}O_6N_8S_3]^+$ calculated: 1567.2, found:1567.3.

IR: (ATR): ν [cm^{-1}] = 3306.9, 2921.2, 2851.0, 1720.6, 1675.4, 1626.7, 1541.0, 1452.4, 1390.5, 1362.3, 1223.8, 894.8, 723.9, 695.8.



4th Ugi reaction:



31

4.01 g of substance **30** (2.55 mmol, 1.00 eq.), 0.73 g of 10-undecenal **2** (4.35 mmol, 1.70 eq.) and 0.27 g ethanolamine **24d** (4.50 mmol, 1.70 eq.) were stirred with 2.5 mL methanol (1.00 M). Subsequently, 0.37 g *tert*-butyl isocyanide **3b** (4.43 mmol, 1.70 eq.) were added and the reaction mixture was stirred at room temperature for 48 hours. Afterwards, the solvent was evaporated under reduced pressure and the crude reaction mixture was purified by column chromatography (hexane/ethyl acetate 9:1 → 1:2). The desired product **31** was obtained as highly viscous oil in a yield of 48 % (2.30 g).

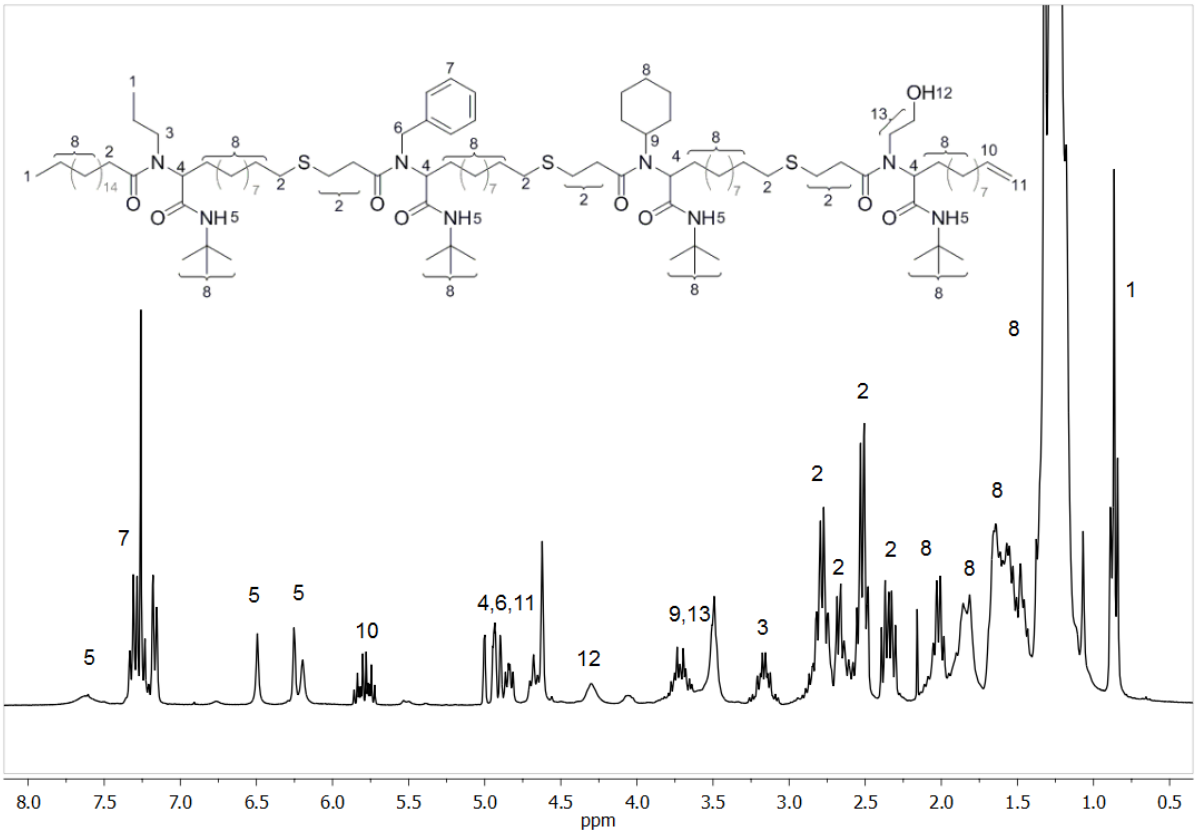
^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 7.61 (bs, 1H, NH, ^{5}), 7.40 – 7.09 (m, 5H, 5 CH aromatic, ^{7}), 6.49 (s, 1H, NH, ^{5}), 6.22 (m, 2H, 2 NH, ^{5}), 5.79 (m, 1H, CH, ^{10}), 5.07 – 4.45 (m, 8H, 4 CH, 2 CH_2, ^{4,6,11}), 4.30 (bs, 1H, OH, ^{12}), 3.91 – 3.31 (m, 5H, 1 CH, 2 CH_2, ^{9,13}), 3.17 (m, 2H, CH_2, ^{3}), 3.00 – 2.21 (m, 20H, 10 CH_2, ^{2}), 2.18 – 0.76 (m, 154H, 56 CH_2, 14 CH_3, ^{1,8}).

^{13}C NMR (75 MHz, $CDCl_3$) δ / ppm: 175.0, 173.9, 173.0, 172.5, 171.0, 169.9, 162.9, 139.3, 128.8, 127.4, 126.2, 126.1, 114.3, 101.3, 61.8, 58.7, 51.7, 51.3, 50.9, 50.7, 34.5, 34.4, 33.9, 33.7, 32.9, 32.7, 32.6, 32.0, 29.8, 29.8, 29.8, 29.6, 29.5, 29.5, 29.4, 29.2, 29.1, 29.0, 29.0, 28.8, 28.7, 28.7, 28.6, 28.0, 26.6, 26.4, 25.9, 25.1, 23.5, 22.8, 14.2, 11.6.

FAB-MS: $[C_{109}H_{201}O_8N_9S_3]^+$ calculated: 1861.5, found: 1861.1.

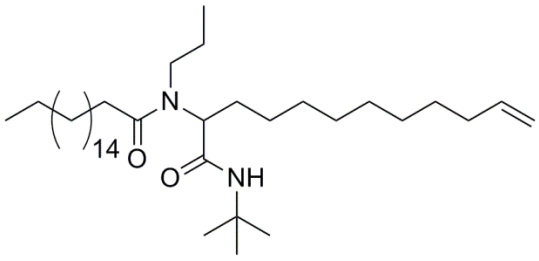
IR: (ATR): ν [cm^{-1}] = 3306.1, 2921.3, 2851.4, 2625.5, 1541.5, 1452.5, 1390.5, 1361.9, 1224.7, 1077.1, 994.4, 907.4, 723.3, 696.0, 503.3.

***R*$_f$:** (hexane/ethyl acetate (3:2)) = 0.5.



Variation of the amine and the isocyanide component:

1st Ugi reaction:



32

1.34 g 10-undecenal **2** (7.98 mmol, 1.70 eq.) and 0.47 g propylamine **24a** (7.88 mmol, 1.70 eq.) were stirred for 15 minutes at room temperature. Subsequently, 1.30 g stearic acid **1a** (4.59 mmol, 1.00 eq.), 0.70 g *tert*-butyl isocyanide **3b** (8.43 mmol, 1.80 eq.) and 5.25 mL (0.87 M) methanol were added and stirred for 24 hours at room temperature. The reaction was followed *via* GPC and after completion of the reaction, the solvent was

removed under reduced pressure and the product was purified by column chromatography (hexane/ethyl acetate 30:1 → 12:1). Product **32** was obtained as a colorless liquid in a yield of 91 % (2.42 g).

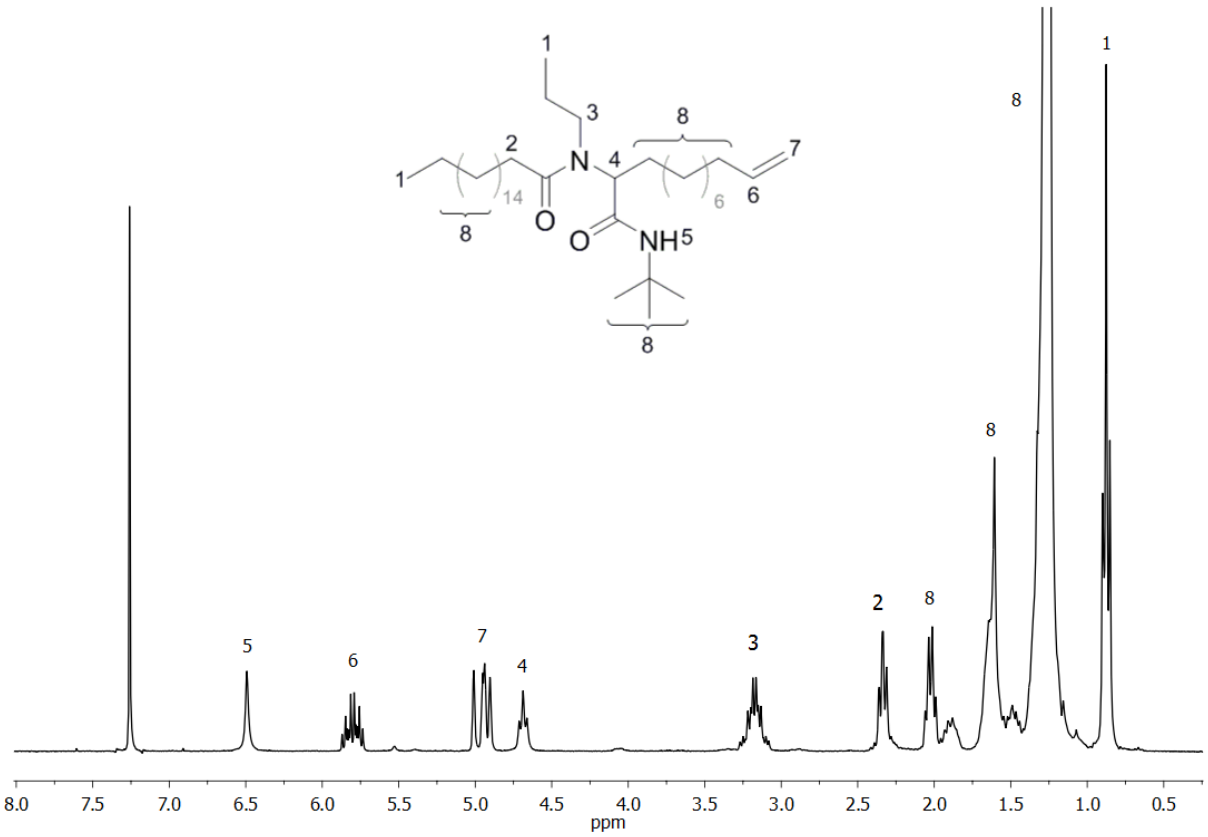
^{1}H NMR: (300 MHz, $CDCl_3$) δ /ppm: 6.49 (s, 1H, NH, ^{5}), 5.80 (m, 1H, CH, ^{6}), 4.95 (dd, J = 17.3, 13.8 Hz, 2H, CH_2, ^{7}), 4.69 (t, J = 7.6 Hz, 1H, CH, ^{4}), 3.30 – 3.06 (m, 2H, CH_2, ^{3}), 2.34 (dd, J = 8.1, 6.3 Hz, 2H, CH_2, ^{2}), 2.08 – 1.00 (m, 57H, 24 CH_2,3 CH_3, ^{8}), 0.88 (t, J = 7.1 Hz, 6H, 2 CH_3, ^{1}).

^{13}C NMR: (75 MHz, $CDCl_3$) δ /ppm: 175.0, 171.0, 139.3, 114.2, 58.2, 50.9, 50,0, 33.9, 33.7, 32.1, 29.8, 29.8, 29.7, 29.6, 29.6, 29.6, 29.5, 29.5, 29.5, 29.2, 29.0, 28.8, 28.0, 26.3, 25.9, 23.5, 22.8, 14.2, 11.6.

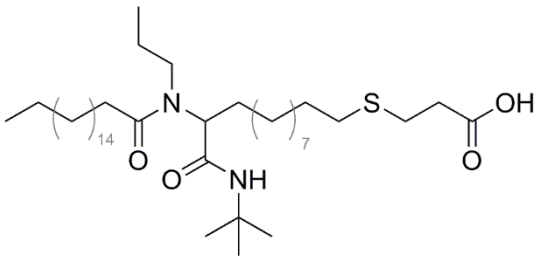
FAB-MS: $[C_{37}H_{73}O_2N_2]^+$ calculated: 577.5669, found: 577.5667.

IR: (ATR): ν [cm^{-1}] = 3312.0, 2920.7, 2851.4, 1682.5, 1625.3, 1534.7, 1454.0, 1362.3, 1225.0, 1112.5, 991.3, 907.1, 720.5, 470.5.

***R*$_f$:** (hexane/ethyl acetate (9:1)) = 0.44.



1st Thiol-Ene addition:



33

3.02 g of substance **32** (5.23 mmol, 1.00 eq.) were diluted with 2.82 g 3-mercaptopropionic acid **4** (27.0 mmol, 5.20 eq.) and 72.3 mg DMPA **5** (0.28 mmol, 5.40 mol%) were added. The reaction mixture was stirred under UV irradiation at room temperature for one hour. Full conversion of the double bonds was detected *via* ^{1}H NMR. The excess of 3-mercaptopropionic acid was removed by vacuum distillation and the residue was dissolved in diethyl ether. The organic layer was washed with water (3 x 100 mL) and brine (100 mL) and dried over sodium sulfate. After removing the

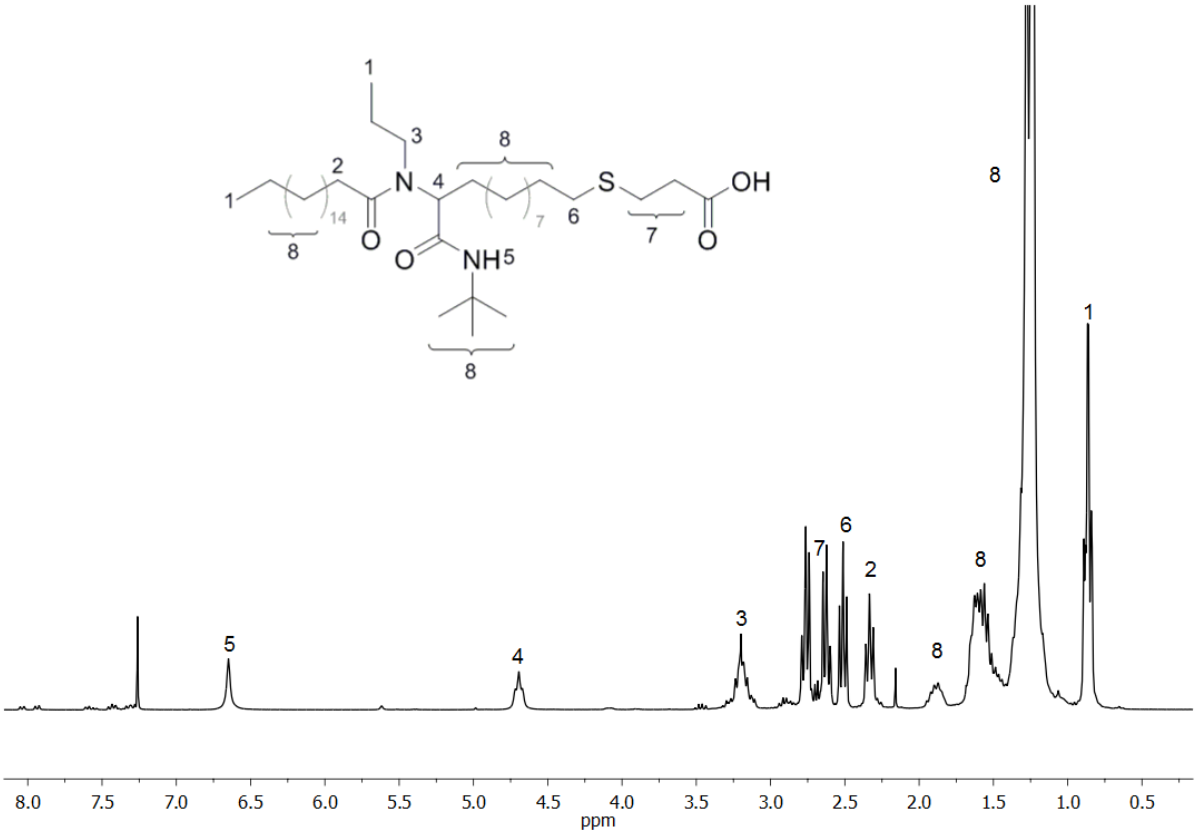
solvent under reduced pressure, the desired product **33** was obtained as yellowish oil in a yield of 99 % (3.54 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 6.65 (s, 1H, NH, ^{5}), 4.69 (t, J = 7.1 Hz, 1H, CH, ^{4}), 3.34 – 3.07 (m, 2H, CH_2, ^{3}), 2.81 – 2.57 (m, 4H, 2 CH_2, ^{7}), 2.51 (t, J = 7.3 Hz, 2H, CH_2, ^{6}), 2.33 (t, J = 7.5 Hz, 2H, CH_2, ^{2}), 2.00 – 0.74 (m, 67H, 26 CH_2, 5 CH_3, ^{8,1}).

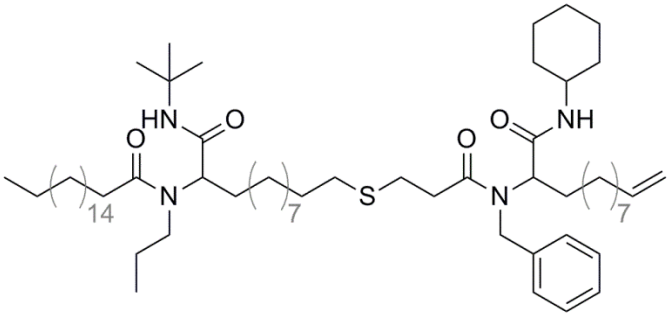
^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 175.9, 175.2, 170.9, 58.3, 51.0, 47.0, 34.7, 33.5, 32.1, 31.9, 29.7, 29.6, 29.5, 29.4, 29.4, 29.3, 29.0, 28.7, 28.5, 28.1, 26.7, 26.1, 25.7, 23.4, 23.4, 22.7, 14.1, 11.4.

FAB-MS: $[C_{40}H_{79}O_2N_4S]^+$ calculated: 683.6, found: 683.6.

IR: (ATR): ν [cm^{-1}] = 2920.3, 2850.8, 1717.2, 1681.4, 1621.5, 1535.9, 1454.5, 1363.8, 1223.8, 8993.3, 720.4, 634.4.



2nd Ugi reaction:



34

1.44 g of 10-undecenal **2** (8.56 mmol, 1.70 eq.) were mixed with 0.93 g benzylamine **24b** (8.69 mmol, 1.70 eq.) and 5.0 mL (1.00 M relative to the acid) methanol and stirred for 30 minutes. Subsequently, 3.43 g of substance **33** (5.02 mmol, 1.00 eq.) and 0.86 g of cyclohexyl isocyanide **3a** (7.92 mmol, 1.60 eq.) were added and the reaction mixture was stirred at room temperature for 48 hours. The solvent was removed under reduced pressure and the product was separated by column chromatography (hexane/ethyl acetate 10:1 → 3:1) to afford 53 % of substance **34** (2.79 g).

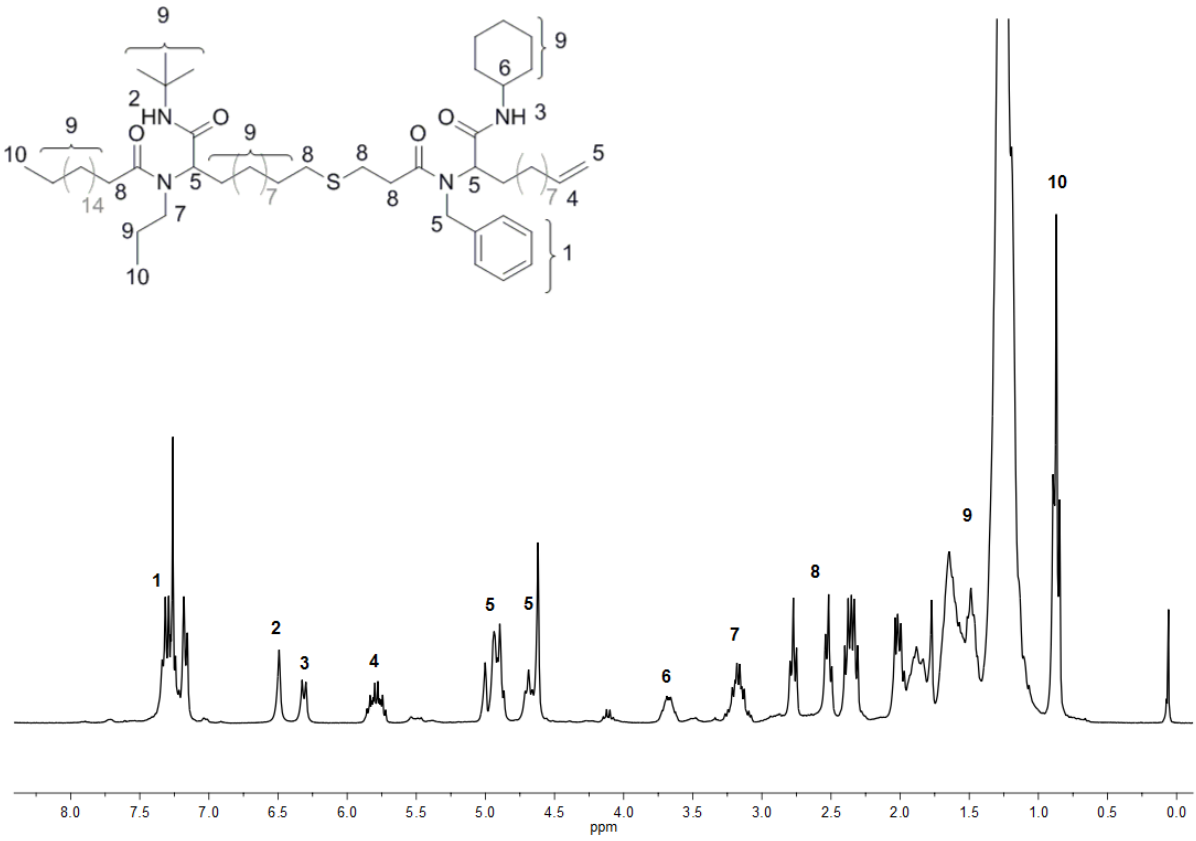
^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 7.44 – 7.08 (m, 5H, 5 CH aromatic, [1]), 6.49 (s, 1H, NH, [2]), 6.31 (d, J = 8.1 Hz, 1H, NH, [3]), 5.92- 5.69 (m, 1H, CH, [4]), 5.06 – 4.81 (m, 3H, CH_2, CH, [5]), 4.75 – 4.52 (m, 3H, CH_2, CH, [5]), 3.80 – 3.55 (m, 1H, CH, [6]), 3.30-3,04 (m, 2H, CH_2, [7]), 2.86 – 2.21 (m, 8 H, 4 CH_2, [8]), 2.14 – 0.97 (m, 85 H, 38 CH_2, 3 CH_3, [9]), 0.90 - 0.78 (m, 6H, 2 CH_3, [10]).

^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm 175.0, 173.9, 171.0, 169.7, 139.3; 137.7, 128.9, 127.4, 126.0, 114.2, 58.3, 50.9, 48.5, 48.2, 34.4, 33.9, 33.7, 33.1, 32.9, 32.6, 32.0, 29.8, 29.8, 29.7, 29.6, 29.4, 29.3, 29.1, 29.0, 28.9, 28.7, 28.5, 28.0, 26.5, 26.3, 25.8, 25.6, 24.8, 23.5, 22.8, 14.2, 11.6.

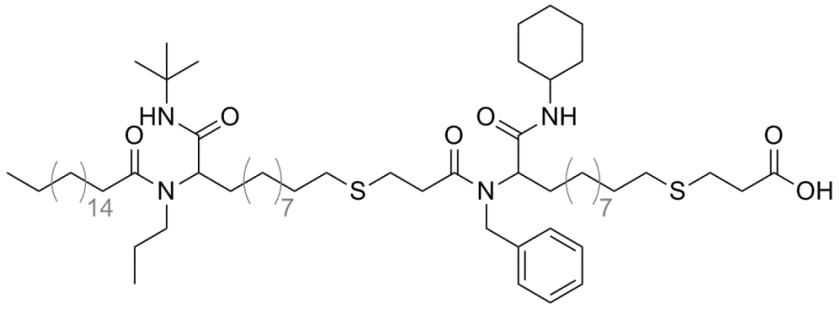
FAB-MS of $[C_{65}H_{117}O_4N_4S]^+$: calculated: 1049.9, found: 1049.7.

IR (KBr): ν [cm^{-1}] = 3320.0, 2925.0, 2853.7, 1680.6, 1631.3, 1537.8, 1453.5, 1363.4, 1227.4, 992.6, 908.7, 725.4, 696.9.

***R*$_f$:** (hexane/ethyl acetate (4:1)) = 0.36.



2nd Thiol-Ene addition:



35

2.36 g of substance **34** (2.25 mmol, 1.00 eq.) were diluted with 1.21 g 3-mercaptopropionic acid **4** (11.4 mmol, 5.10 eq.) and 29.3 mg DMPA **5** (0.12 mmol, 5.10 mol%) were added. The mixture was stirred under UV-irradiation at room temperature for three hours and the full conversion of the double bond was confirmed by NMR. Subsequently, the excess of 3-mercaptopropionic acid was removed *via* vacuum distillation. The residue was diluted with diethyl ether (25 mL) and washed with water (3

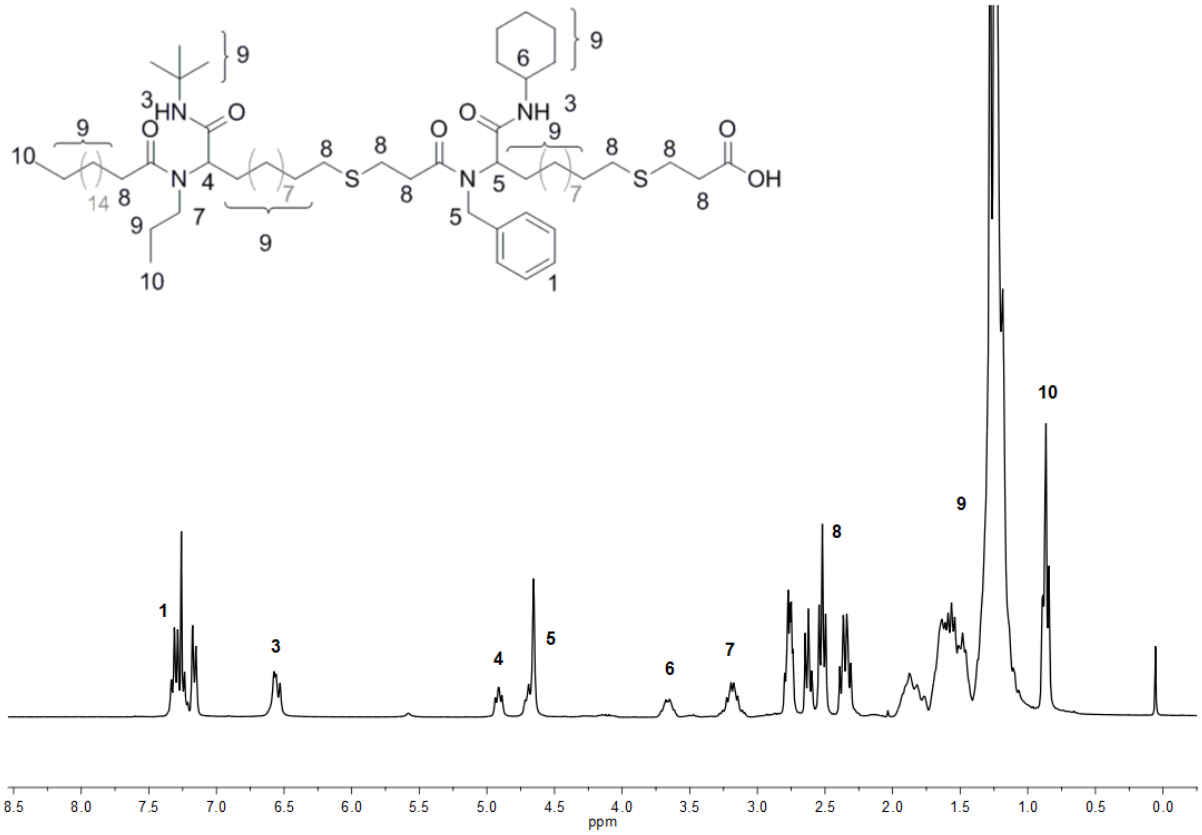
x 50 mL) and brine (50 mL). The organic layer was dried over sodium sulfate and the solvent was removed under reduced pressure to afford the desired product **35** as slightly yellow oil in a yield of 92 % (2.38 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 7.38 – 7.12 (m, 5H, 5 CH aromatic, [1]), 6.66 – 6.47 (m, 2H, 2 NH, [2]), 4.99 – 4.83 (m, 1H, CH, [3]), 4.77 – 4.55 (m, 3H, CH_2, CH, [3]), 3.77 – 3.57 (m, 1H, CH, [4]), 3.31 – 3.05 (m, 2H, CH_2, [5]), 2.90 – 2,21 (m, 14H, 7 CH_2, [6]), 2.01 – 1.00 (m, 87H, 3 CH_3, 39 CH_2, [7]), 0.94 – 0.77 (m, 6H, 2 CH_3, [8]).

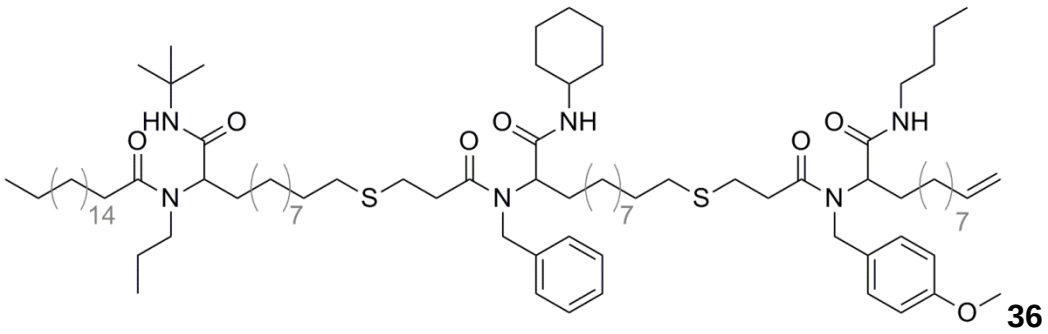
^{13}C NMR (75 MHz, CDCl3) δ /ppm 175.2, 174.1, 171.0, 171.0, 169.8, 137.6, 128.9, 127.4, 126.0, 114.0, 51.0, 48.5, 48.3, 34.8, 33.7, 33.0, 32.8, 32.6, 32.2, 32.0, 29.8, 29.8, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 29.0, 28.7, 28.1, 28.0, 26.9, 26.4, 26.3, 25.9, 25.6, 25.6, 24.8, 23.5, 22.8, 14.2, 11.5.

FAB-MS of $[C_{68}H_{123}O_6N_4S_2]^+$: calculated: 1155.9, found: 1155.6.

IR (KBr): ν [cm^{-1}] = 3317.5, 2920.7, 2850.8, 1723.9, 1677.4, 1623.7, 1534.7, 1451.2, 1418.8, 1362.9, 1224.4, 891.2, 724.0, 695.8, 458.5.



3rd Ugi reaction:



36

0.05 g of 10-undecenal **2** (0.30 mmol, 1.70 eq.) were mixed with 0.05 g 4-methoxy benzylamine **24e** (0.34 mmol, 1.90 eq.) and 0.25 mL (0.72 M relative to the acid) methanol and stirred for 30 minutes. Subsequently, 0.21 g of substance **33** (0.18 mmol, 1.00 eq.) and 0.03 g of *n*-butyl isocyanide **3d** (0.30 mmol, 1.70 eq.) were added and the reaction mixture was stirred at room temperature for 40 hours. The solvent was removed

under reduced pressure and the product was separated by column chromatography (hexane/ethyl acetate 6:1 → 1:1) to afford 80 % of substance **36** (0.23 g).

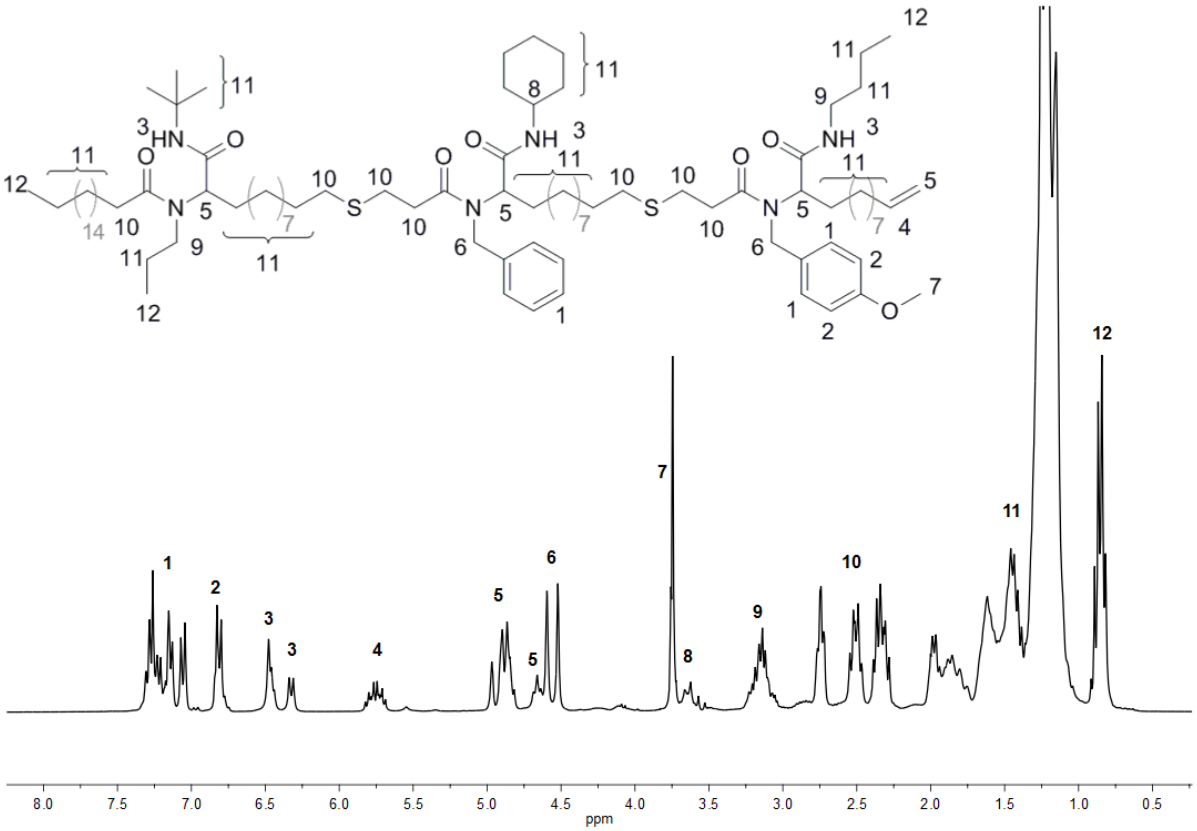
^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 7.39 – 7.00 (m, 7H, 7 CH aromatic, [1]), 6.88 – 6.73 (m, 2H, 2 CH aromatic, [2]), 6.53 – 6.40 (m, 2H, 2 NH, [3]), 6.32 (d, J = 8.1 Hz, 1H, NH, [3]), 5.86 – 5.64 (m, 1H, CH, [4]), 5.02 – 4.78 (m, 4H, 2 CH, CH_2, [5]), 4.74 – 4.45 (m, 5H, CH, 2 CH_2, [5,6]), 3.84 – 3.55 (m, 4H, CH, OCH_3, [7,8]), 3.28 – 3.01 (m, 4H, 2 CH_2, [9]), 2.92 – 2.21 (m, 14 H, 7 CH_2, [10]), 2.18 – 0.95 (m, 107 H, 3 CH_3, 49 CH_2, [11]), 0.97 – 0.72 (m, 9H, 3 CH_3, [12]).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ ppm: 174.9, 173.8, 173.8, 170.9, 170.6, 169.6, 158.9, 139.2, 137.7, 129.4, 129.3, 128.8, 127.3, 127.2, 126.0, 114.2, 58.3, 58.2, 55.3, 52.4, 50.8, 48.4, 48.1, 48.0, 46.9, 39.1, 38.6, 34.3, 33.8, 33.6, 33.0, 32.8, 32.6, 32.5, 32.0, 31.9, 31.6, 29.7, 29.7, 29.7, 29.6, 29.5, 29.5, 29.4, 29.3, 29.2, 29.1, 28.9, 28.7, 28.4, 28.4, 27.9, 27.9, 26.5, 26.3, 25.8, 25.6, 24.8, 23.4, 22.7, 20.1, 14.2, 13.8, 11.5.

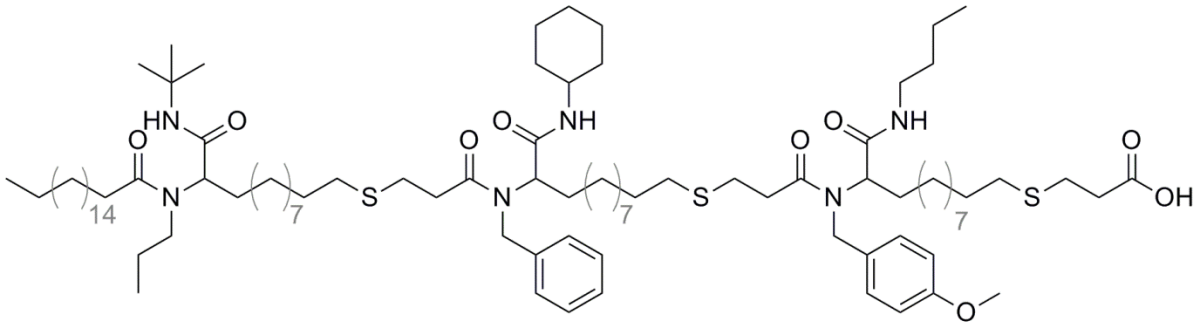
FAB-MS of $[C_{92}H_{161}O_7N_6S_2]^+$: calculated: 1526.2, found: 1526.3.

IR (film KBr): ν [cm^{-1}] = 3321.4, 2925.3, 2853.7, 1631.3, 1513.7, 1454.5, 1363.1, 1247.9, 1037.9, 909.0, 820.0, 725.3.

***R*$_f$:** (hexane/ethyl acetate (3:2)) = 0.47.



3rd Thiol-Ene addition:



37

1.57 g of substance **36** (1.03 mmol, 1.00 eq.) were diluted with 0.58 g 3-mercaptopropionic acid **4** (5.50 mmol, 5.50 eq.) and 13.5 mg DMPA **5** (0.05 mmol, 5.10 mol%) were added. The mixture was stirred under UV-irradiation at room temperature for three hours and the full conversion of the double bond was confirmed by NMR. Subsequently, the excess of 3-mercaptopropionic acid was removed by vacuum distillation. The residue was diluted with diethyl ether (25 mL) and washed with water (3

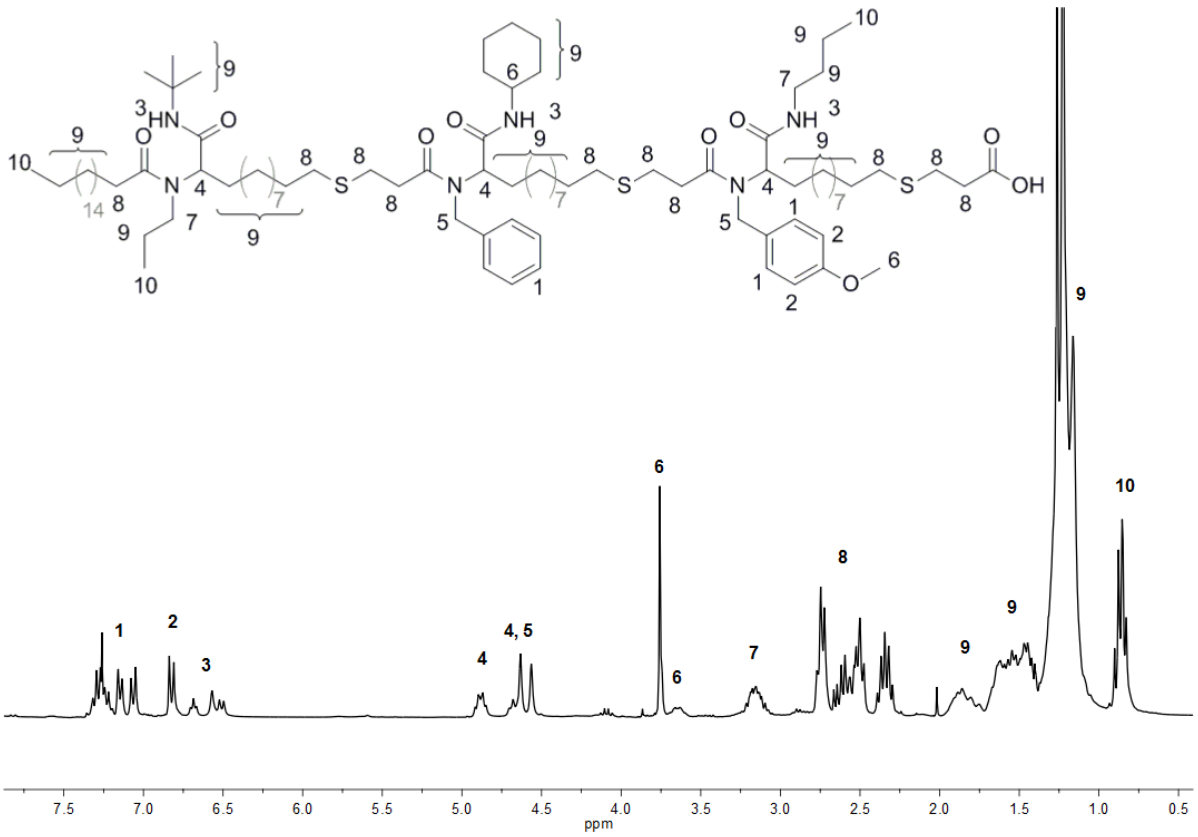
x 50 mL) and brine (50 mL). The organic layer was dried over sodium sulfate and the solvent was removed under reduced pressure to afford the desired product **37** as slightly yellow oil in a yield of 99 % (1.66 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 7.39 – 7.00 (m, 7H, 7 CH aromatic, [1]), 6.82 (d, J = 8.6 Hz, 2H, 2 CH aromatic, [2]), 6.69 (t, J = 5.6 Hz, 1H, NH, [3]), 6.61 – 6.43 (m, 2H, 2 NH, [3]), 4.97 – 4.76 (m, 2H, 2 CH, [4]), 4.73 – 4.37 (m, 5H, 2 CH_2, 1 CH, [4,5]), 3.80 – 3.56 (m, 4H, CH_3, CH, [6]), 3.31 – 3.00 (m, 4H, 2 CH_2, [7]), 2.80 – 2.24 (m, 20H, 10 CH_2, [8]), 1.98 – 0.95 (m, 109 H, 3 CH_3, 50 CH_2, [9]), 0.94 – 0.72 (m, 9H, 3 CH_3, [10]).

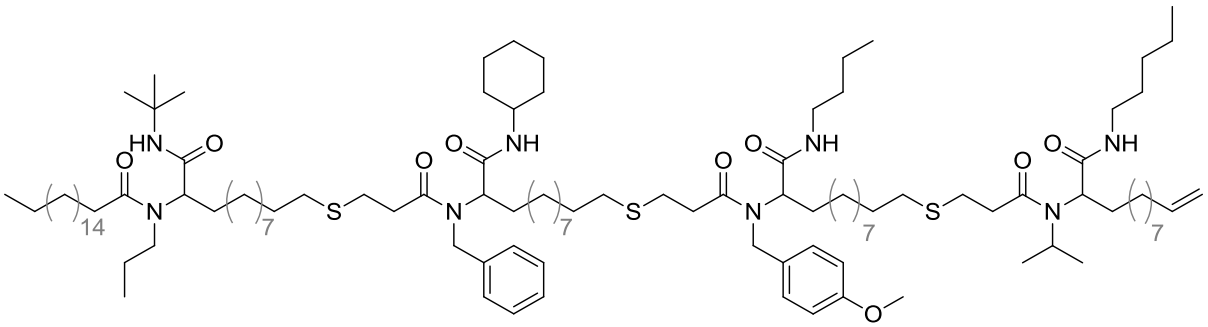
^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 175.2, 175.1, 174.9, 174.0, 171.0, 170.8, 169.7, 158.9, 137.6, 129.3, 128.8, 127.4, 127.3, 126.0, 114.2, 58.3, 55.3, 50.9, 48.4, 48.2, 48.1, 47.0, 39.2, 38.4, 34.8, 34.4, 33.6, 32.9, 32.8, 32.6, 32.5, 32.1, 32.0, 31.5, 29.8, 29.7, 29.7, 29.6, 29.5, 29.4, 29.4, 29.3, 29.1, 29.0, 28.7, 28.6, 28.5, 28.1, 27.9, 26.9, 26.5, 26.4, 26.3, 25.8, 25.6, 24.8, 23.5, 22.8, 20.1, 19.8, 14.2, 13.8, 11.5.

FAB-MS of $[C_{95}H_{167}O_9N_6S_3]^+$: calculated: 1632.2, found: 1632.1.

IR (ATR): ν [cm^{-1}] = 3322.6, 2920.8, 2850.8, 1726.4, 1624.7, 1535.3, 1512.4, 1452.1, 1362.2, 1245.5, 1175.4, 1033.5, 890.9, 805.0, 722.7, 696.0, 460.1.



4th Ugi reaction:



38

0.05 g of 10-undecenal **2** (0.32 mmol, 2.50 eq.) were mixed with 0.02 g *iso*-propylamine **24f** (0.34 mmol, 1.90 eq.) and 0.20 mL (0.65 M relative to the acid) methanol and stirred for 30 minutes. Subsequently, 0.21 g of substance **37** (0.13 mmol, 1.00 eq.) and 0.03 g of *n*-pentyl isocyanide **3c** (0.28 mmol, 2.20 eq.) were added and the reaction mixture was stirred at room temperature for 48 hours. The solvent was removed under reduced

pressure and the product was separated by column chromatography (hexane/ethyl acetate 5:1 → 1:3) to afford 77 % of substance **38** (0.19 g).

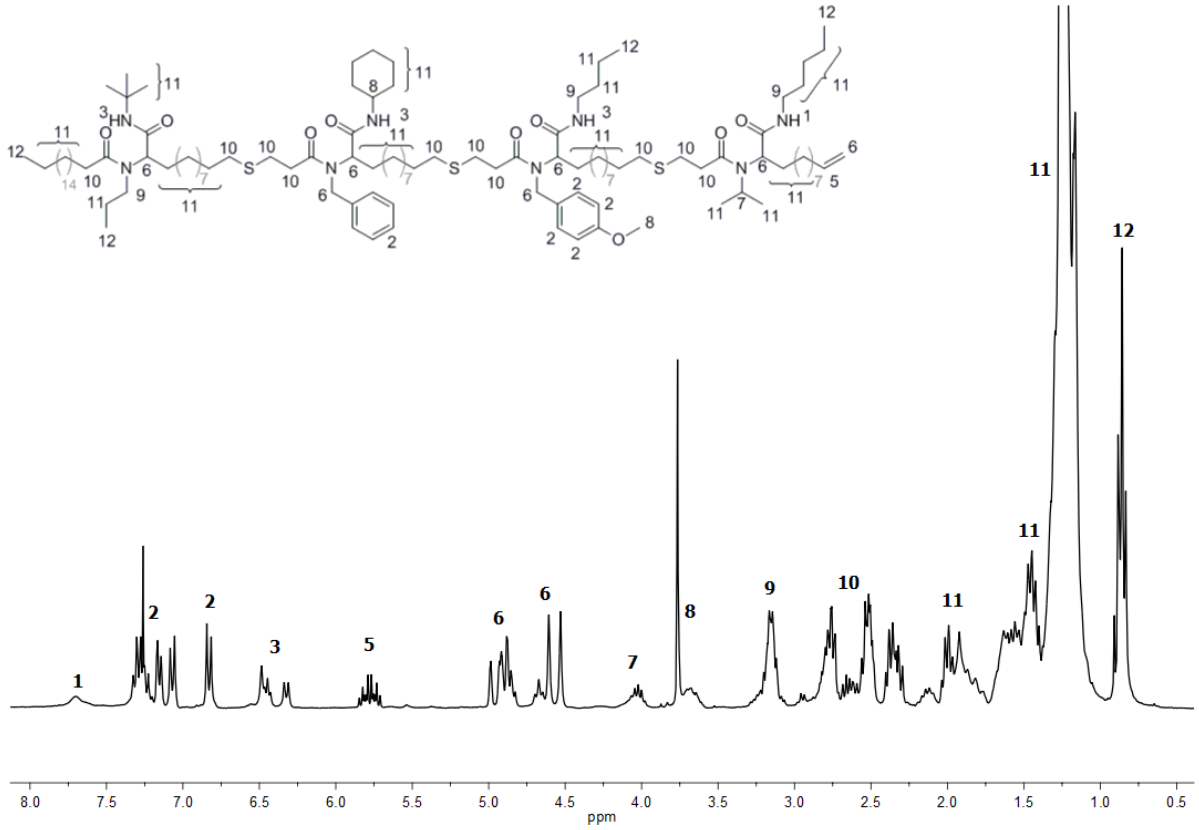
^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 7.66 (s, 1H, NH [1]), 7.36 – 6.95 (m, 7H, 7 CH aromatic, [2]), 6.78 (d, J = 8.6 Hz, 2H, 2 CH aromatic, [2]), 6.58 – 6.34 (m, 2H, 2 NH, [3]), 6.28 (d, *J* = 8.1 Hz, 1H, NH, [3]), 5.73 (m, 1H, CH, [5]), 4.99 – 4.72 (m, 5H, CH_2, 3 CH, [6]), 4.69 – 4.37 (m, 5H, 2 CH_2, CH, [6]), 3.97 (m, 1H, CH, [7]), 3.79 – 3.50 (m, 4H, CH_3, CH, [8]), 3.31 – 2.96 (m, 6H, 3 CH_2 [9]), 2.95 – 2.17 (m, 20H, 10 CH_2, [10]), 2.17 – 0.91 (m, 137H, 5 CH_3, 61 CH_2, [11]), 0.91 – 0.57 (m, 12H, 4 CH_3 [12]).

^{13}C NMR (75 MHz, $CDCl_3$) *δ* /ppm: 175.0, 173.9, 173.9, 173.2, 172.6, 171.0, 170.7, 169.6, 158.9, 139.3, 137.7, 129.4, 128.8, 127.4, 127.3, 126.0, 114.2, 58.3, 58.3, 55.4, 50.9, 49.8, 48.2, 39.3, 39.1, 35.4, 34.4, 33.9, 33.6, 33.0, 32.9, 32.8, 32.6, 32.6, 32.0, 31.6, 30.2, 29.8, 29.7, 29.7, 29.6, 29.6, 29.5, 29.5, 29.3, 29.2, 29.0, 28.7, 28.5, 28.4, 28.0, 27.2, 26.6, 26.6, 26.3, 25.8, 25.6, 24.8, 23.5, 22.8, 22.4, 21.2, 21.0, 20.1, 14.2, 14.1, 13.9, 11.5.

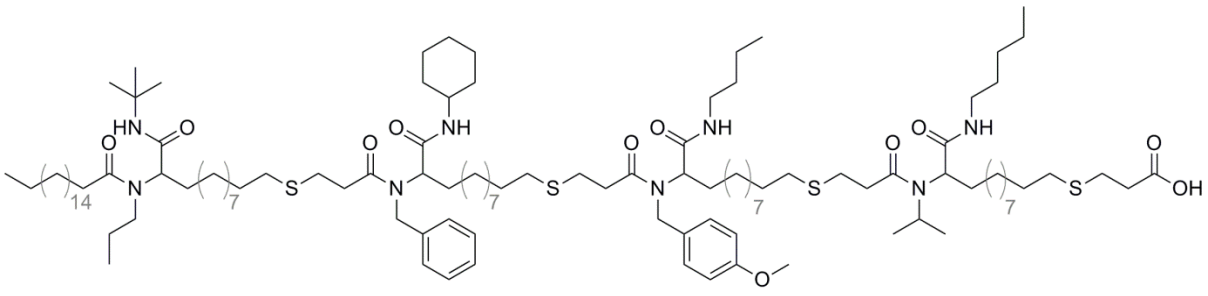
FAB-MS of $[C_{115}H_{204}N_8O_9S_3]^+$: calculated: 1937.5, found: 1937.9

IR (ATR platinum diamond): ν [cm^{-1}] = 3306.6, 2921.3, 2851.3, 1626.4, 1536.5, 1512.8, 1451.2, 1362.1, 1293.0, 1246.4, 1036.4, 907.9, 819.2, 723.6, 696.1.

***R*$_f$:** (hexane/ethyl acetate (3:2)) = 0.48.



4th Thiol-Ene addition:



39

0.57 g of substance **38** (0.29 mmol, 1.00 eq.) were diluted with 0.18 g 3-mercaptopropionic acid **4** (1.65 mmol, 5.60 eq.) and 4.1 mg DMPA **5** (0.02 mmol, 5.50 mol%) were added. The mixture was stirred under UV-irradiation at room temperature for four hours and the full conversion of the double bond was confirmed by NMR. Subsequently, the excess of 3-mercaptopropionic acid was removed by vacuum distillation. The residue was diluted with diethyl ether (25 mL) and washed with water (3

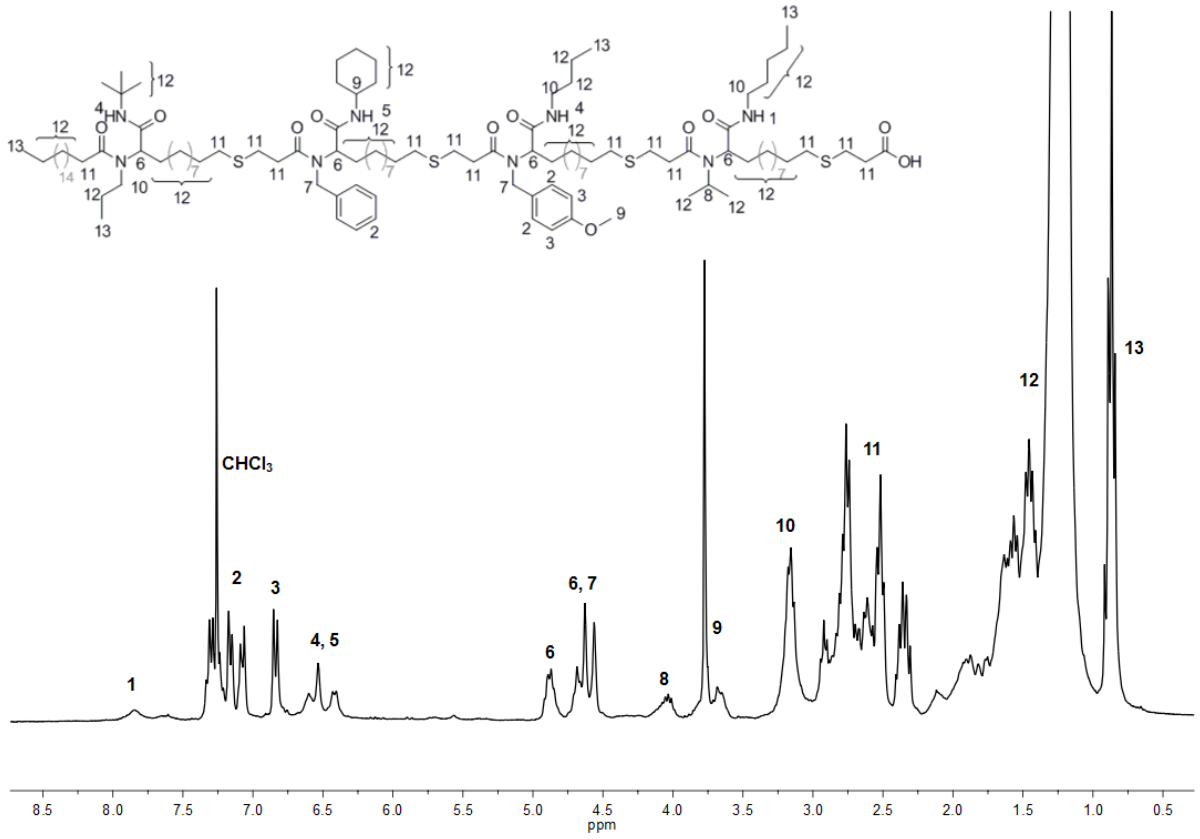
x 50 mL) and brine (50 mL). The organic layer was dried over sodium sulfate and the solvent was removed under reduced pressure to afford the desired product **39** as slightly yellow oil in a yield of 99 % (0.60 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 7.84 (s, 1H, NH, [1]), 7.41 – 6.98 (m, 7H, 7 CH aromatic, [2]), 6.84 (d, J = 8.6 Hz, 2H, 2 CH aromatic, [3]), 6.68 – 6.28 (m, 3H, 3 NH, [4, 5]), 4.78 - 4.88 (m, 3H, 3 CH, [6]), 4.59 - 4.62 (m, 5H, 2 CH_2, 1CH, [6, 7]), 4.00 - 4.05 (m, 1H, CH, [8]), 3.89 – 3.58 (m, 4H, CH_3, CH, [9]), 3.40 – 3.00 (m, 6H, 3 CH_2, [10]), 3.00 – 2.22 (m, 26H, 13 CH_2, [11]), 2.00 – 0.98 (m, 139H, 5 CH_3, 62 CH_2, [12]), 0.98 – 0.60 (m, 12H, 4 CH_3, [13]).

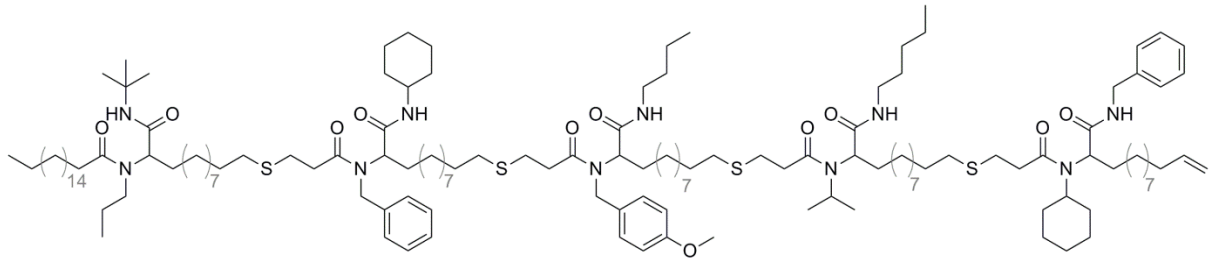
^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 175.1, 174.6, 174.0, 173.0, 172.8, 171.0, 169.7, 159.0, 139.2, 137.7, 129.4, 128.9, 127.4, 127.3, 126.0, 114.3, 58.4, 58.2, 55.4, 51.0, 48.3, 47.0, 39.5, 39.2, 35.4, 34.4, 33.7, 33.0, 32.9, 32.6, 32.0, 31.6, 29.8, 29.8, 29.7, 29.6, 29.5, 29.4, 29.2, 29.0, 28.7, 28.6, 28.1, 28.0, 27.3, 27.2, 27.0, 26.6, 26.3, 25.9, 25.6, 24.9, 23.5, 22.8, 22.4, 20.2, 14.3, 14.2, 13.9, 11.6.

FAB-MS of $[C_{118}H_{210}O_{11}N_8S_4]^+$: calculated: 2043.5, found: 2044.1.

IR (ATR): ν [cm^{-1}] = 3315.6, 2920.9, 2850.8, 1725.7, 1625.5, 1535.3, 1512.4, 1451.1, 1361.7, 1245.2, 1033.7, 891.2, 816.5, 722.8, 695.7, 616.9.



5th Ugi reaction:



40

0.04 g of 10-undecenal **2** (0.22 mmol, 3.20 eq.) were mixed with 0.02 g cyclohexylamine **24c** (0.19 mmol, 2.80 eq.) and 0.30 mL (0.23 M relative to the acid) methanol and stirred for 30 minutes. Subsequently, 0.14 g of substance **39** (0.07 mmol, 1.00 eq.) and 0.02 g of benzyl isocyanide **3f** (0.21 mmol, 3.00 eq.) were added and the reaction mixture was stirred at room temperature for 24 hours. The solvent was removed under reduced pressure and the product was separated by column chromatography (hexane/ethyl acetate 7:1 → 1:1) to afford 56 % of substance **40** (0.09 g).

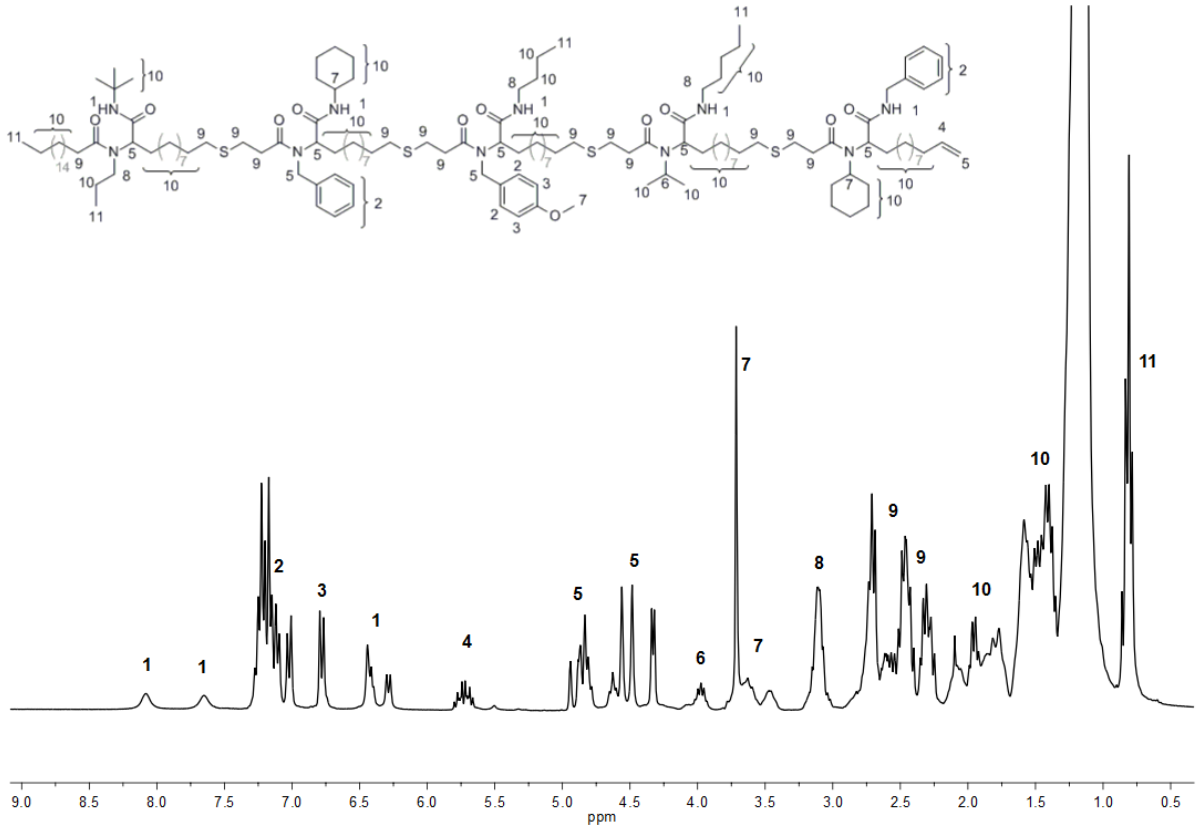
^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 8.14 (bs, 1H, NH, [1]), 7.71 (bs, 1H, NH, [1]), 7.40 – 7.00 (m, 12H, 12 CH aromatic, [2]), 6.84 (d, J = 8.5 Hz, 2H, 2 CH aromatic, [3]), 6.60 – 6.23 (m, 3H, 3 NH, [1]), 5.89 - 5.78 (m, 1H, CH, [4]), 5.07 – 4.19 (m, 13H, 5 CH, 4 CH_2, [5]), 4.17 – 3.93 (m, 1H, CH, [6]), 3.87 – 3.42 (m, 5H, CH_3, 2 CH, [7]), 3.29 – 3.01 (m, 6H, 3 CH_2, [8]), 2.98 – 2.26 (m, 26H, 13 CH_2, [9]), 2.23 – 0.95 (m, 165H, 5 CH_3, 75 CH_2, [10]), 0.88 (m, 12H, 4 CH_3, [11]).

^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 174.9, 173.8, 173.8, 173.2, 173.1, 172.7, 172.5, 170.9, 170.6, 169.6, 158.8, 139.2, 138.7, 137.6, 129.4, 128.8, 128.5, 127.4, 127.2, 127.1, 125.9, 114.2, 58.8, 58.2, 55.3, 50.8, 48.4, 48.1, 48.0, 43.2, 39.3, 39.1, 35.3, 35.2, 34.3, 33.8, 33.6, 33.0, 32.8, 32.8, 32.6, 32.5, 32.0, 31.6, 31.5, 31.3, 30.3, 30.2, 29.7, 29.7, 29.7, 29.6, 29.5, 29.5, 29.4, 29.4, 29.3, 29.1, 28.9, 28.9, 28.7, 28.4, 27.9, 27.3, 27.2, 26.5, 26.5, 26.3, 26.0, 25.8, 25.8, 25.6, 25.0, 24.8, 23.4, 22.7, 22.4, 21.2, 21.0, 20.1, 14.2, 14.1, 13.8, 11.5.

FAB-MS of $[C_{143}H_{248}N_{10}O_{11}S_4]^+$: calculated: 2409.8, found: 2410.3.

IR (KBr): ν [cm^{-1}] = 3314.8, 2923.0, 2851.6, 1629.6, 1536.3, 1513.1, 1452.6, 1361.8, 1245.8, 1030.7, 906.7, 817.4, 723.1, 697.2.

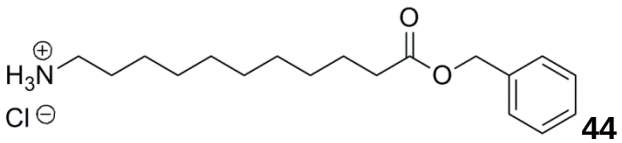
***R*$_f$:** (hexane/ethyl acetate (3:2)) = 0.33.



6.3.3 Experimental Procedures Chapter 4.2

Monomer synthesis:

11-(Benzyloxy)-11-oxoundecan-1-aminium chloride 44:



44

15.0 g 11-aminoundecanoic acid **41** (74.5 mmol, 1.00 eq.) were suspended in 75 mL THF and 96.7 g benzyl alcohol **42** (0.89 mol, 12.00 eq.) were added. The suspension was cooled in an ice bath and subsequently 16.5 mL thionyl chloride **43** (27.1 g, 0.23 mol, 3.10 eq.) were added dropwise at 0 ° C. After addition of the thionyl chloride, the solution was warmed to room temperature and stirred overnight. The yellow solution was then poured into 500 mL diethylether and stored in the freezer for one hour. The

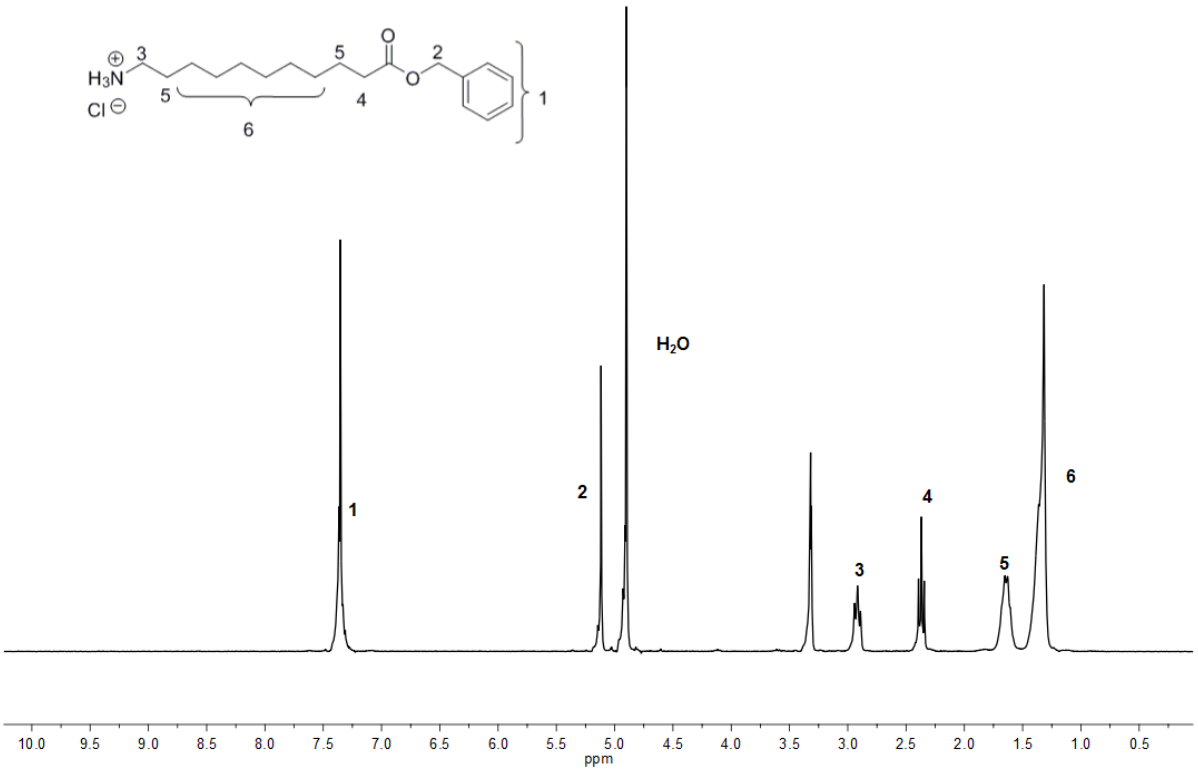
product was the filtered off and dried under high vacuum. 11-(Benzyloxy)-11-oxoundecan-1-aminium chloride **44** was obtained as a white solid in a yield of 96 % (23.5 g).

^{1}H-NMR: (300 MHz, CD_3OD) δ /ppm: 7,43 - 7,26 (m, 5H, 5 CH aromatic, ^{1}); 5,11 (s, 2H, CH_2, ^{2}); 2,96 - 2,86 (m, 2H, CH_2, ^{3}); 2,36 (t, J = 7,3 Hz, 2H, CH_2, ^{4}); 1,72 - 1,55 (m, 4H, 2 CH_2, ^{5}); 1,46 - 1,26 (m, 12H, 6 CH_2, ^{6}).

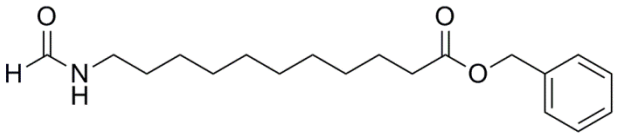
^{13}C NMR (75 MHz, CD_3OD) δ /ppm: 175.2, 137.7, 129.5, 129.5, 129.2, 129.2, 67.1, 40.8, 35.0, 30.4, 30.3, 30.2, 30.1, 28.5, 27.4, 26.0.

HRMS-FAB-MS of $[C_{18}H_{30}NO_2]^+$: calculated: 292.2271, found: 292.2272.

IR (ATR platinum diamond): ν [cm^{-1}] = 2915.7, 2847.3, 1740.3, 1601.3, 1527.6, 1495.9, 1462.9, 1385.2, 1347.4, 1332.3, 1307.8, 1279.1, 1246.1, 1206.2, 1158.7, 1042.4, 992.2, 960.0, 827.3, 743.2, 722.3, 695.5, 580.8, 508.4, 474.3, 416.6.



Benzyl 11-formamidoundecanoate 46:



46

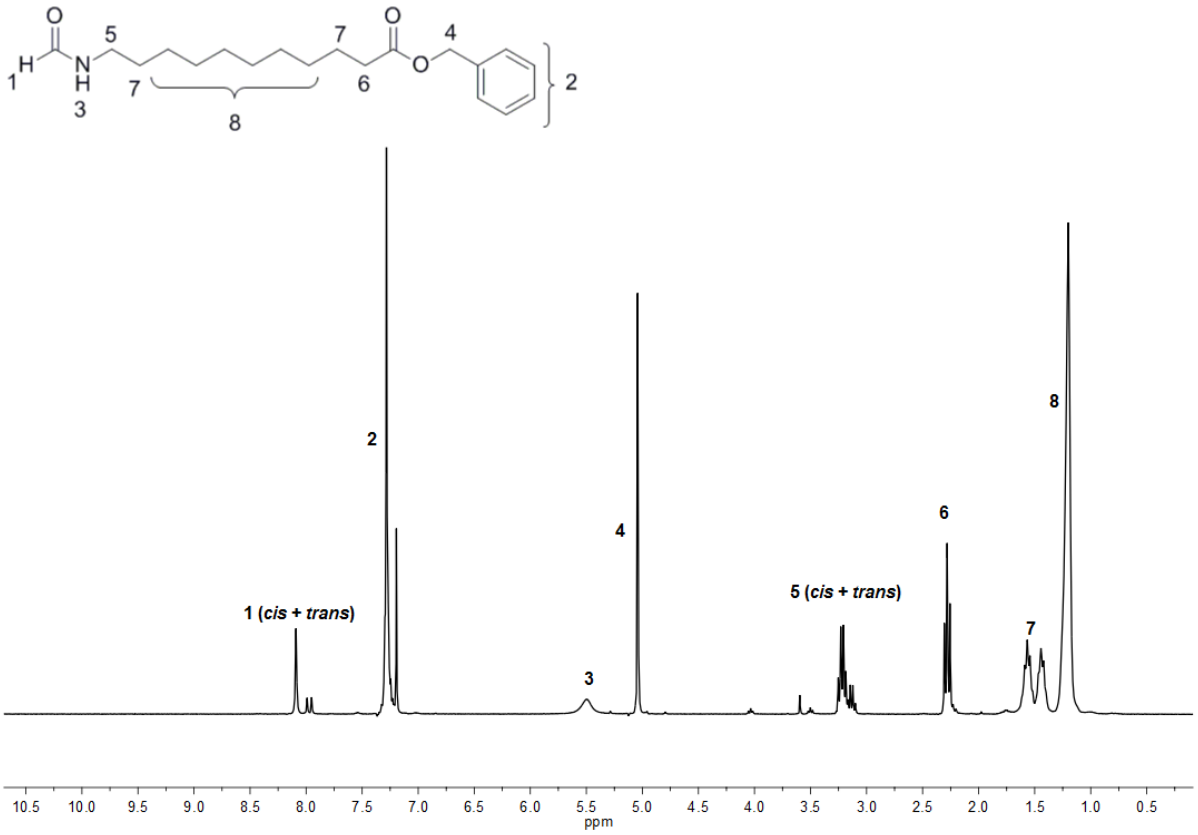
23.4 g 11-(Benzyloxy)-11-oxoundecan-1-aminium chloride **44** (71.3 mmol, 1.00 eq.), were dissolved in 75.7 g trimethyl orthoformate **45** (0.71 mol, 10.00 eq.) and heated to 100 ° C for 12 hours. Trimethyl orthoformate was removed under reduced pressure and the product was used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 8.21 – 7.96 (m, 1H, CH, [1]), 7.43 – 7.28 (m, 5H, aromatic, [2]), 5.56 (s, 1H, NH, [3]), 5.11 (s, 2H, CH_2, [4]), 3.24-3.14 (m, 2H, CH_2, [5]), 2.35 (t, *J* = 7.5 Hz, 2H, CH_2, [6]), 1.76 – 1.41 (m, 4H, 2 CH_2, [7]), 1.27 (s, 12H, 6 CH_2, [8]).

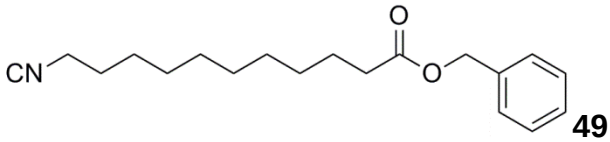
^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 173.8, 164.7, 161.3, 136.2, 128.6, 128.2, 66.1, 41.8, 38.2, 34.4, 31.3, 29.5, 29.4, 29.3, 29.2, 29.1, 26.9, 26.4, 25.0.

HRMS-FAB-MS of $[C_{19}H_{30}NO_3]^+$: calculated: 320.2220, found: 320.2222.

IR (ATR platinum diamond): ν [cm^{-1}] = 3265.8, 3068.1, 2913.4, 2847.8, 1732.4, 1651.5, 1555.5, 1496.4, 1470.6, 1449.4, 1417.1, 1379.4, 1329.7, 1299.4, 12674, 1233.7, 1212.7, 1199.7, 1159.5, 1054.9, 1028.8, 996.9, 938.7, 923.2, 903.5, 866.4, 825.3, 806.1, 752.8, 718.2, 695.4, 609.0, 519.7, 487.3, 451.4.



Benzyl 11-isocyanoundecanoate 49:



49

21.0 g of Benzyl 11-formamidoundecanoate **46** (65.8 mmol, 1.00 eq.) were dissolved in 200 mL dichloromethane (0.33 M), 29.0 mL diisopropylamine **47** (20.9 g, 207 mmol, 3.10 eq.) were added and the reaction mixture was cooled to 0 ° C. Subsequently, 7.8 mL phosphorous oxy chloride **48** (12.8 g, 83.7 mmol, 1.31 eq.) were added dropwise and the reaction mixture was then stirred at room temperature for two hours. The reaction was quenched by addition of sodium carbonate solution (20 %, 75 mL) at 0 ° C. After stirring this mixture for 30 minutes, 50 mL water and 50 mL dichloromethane were added. The aqueous phase was separated and the organic layer was washed with water (3 x 80 mL) and brine (80 mL). The combined organic layers were dried over sodium sulfate and the solvent was evaporated under reduced pressure. The crude product was

then purified by column chromatography (hexane/ethyl acetate 19:1 → 8:1). The product **49** was obtained as slightly yellow oil in a yield of 66 % (14.4 g).

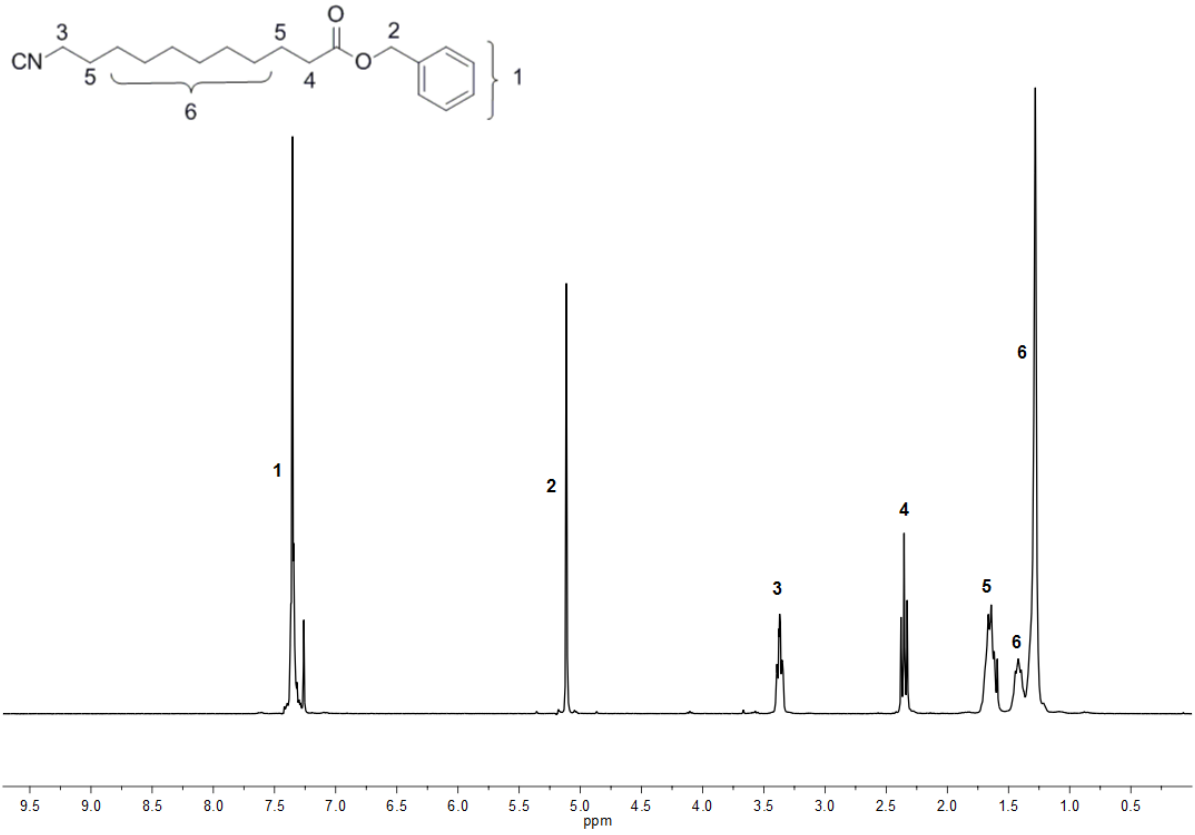
^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 7.44 – 7.28 (m, 5H, aromatic, ^{1}), 5.11 (s, 2H, CH_2, ^{2}), 3.44 – 3.31 (m, 2H, CH_2, ^{3}), 2.35 (t, J = 7.5 Hz, 2H, CH_2, ^{4}), 1.63-1.58 (m, 4H, 2 CH_2, ^{5}), 1.50 – 1.15 (m, 12H, 6 CH_2, ^{6}).

^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 173.8, 155.8, 155.7, 155.6, 136.2, 128.6, 128.3, 66.2, 41.7, 41.6, 41.6, 34.4, 29.4, 29.3, 29.2, 29.2, 28.8, 26.4, 25.0.

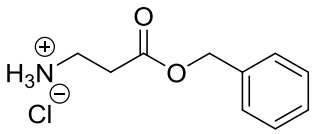
HRMS-FAB-MS of $[C_{19}H_{28}NO_2]^+$: calculated: 302.2115, found: 302.2113.

IR (ATR platinum diamond): ν [cm^{-1}] = 3031.9, 2924.4, 2853.2, 2145.6 (isocyanide), 1732.6, 1497.1, 1454.4, 1380.2, 1350.2, 1212.1, 1161.2, 1101.1, 1001.1, 736.4, 697.1, 579.3, 500.5.

***R*$_f$:** (hexane/ethyl acetate (5:1)) = 0.45.



3-(Benzyloxy)-3-oxopropane-1-ammoniumchloride:



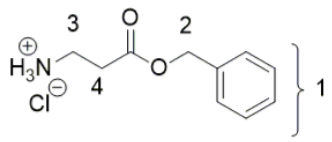
2.06 g of *ß*-alanine (23.1 mmol, 1.00 eq.) were suspended in 25 mL THF and 27.8 mL of benzyl alcohol **42** (28.9 g, 0.27 mol, 11.50 eq.) were added. The suspension was cooled in an ice bath and subsequently 5.0 mL thionyl chloride **43** (8.16 g, 68.6 mmol, 2.96 eq.) were added dropwise at 0 ° C. After addition of the thionyl chloride, the solution was warmed to room temperature and stirred overnight. The yellow solution was then poured into 230 mL diethylether and stored in the freezer for one hour. The product was the filtered off and dried under high vacuum. 3-(Benzyloxy)-3-oxopropane-1-ammoniumchloride was obtained as a white solid in a yield of 81 % (4.05 g).

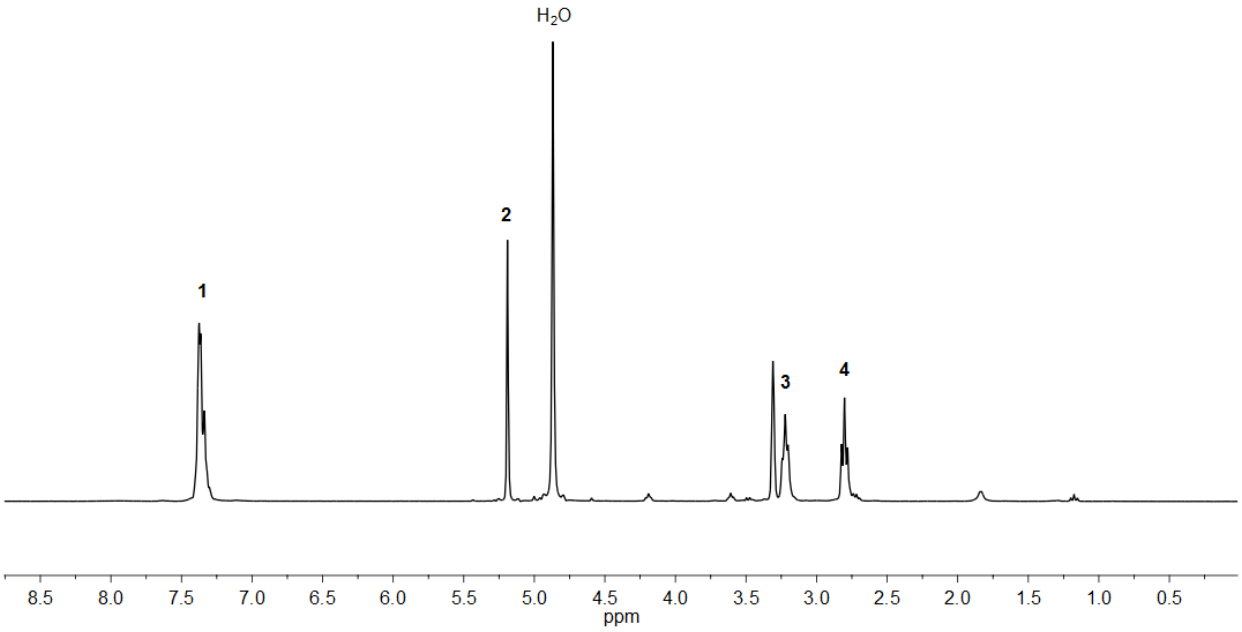
^{1}H-NMR: (300 MHz, CD_3OD) *δ* /ppm: 7.55 - 7.14 (m, 5H, 5 CH aromatic, ^{1}), 5.19 (s, 2H, CH_2, ^{2}), 3.22 (t, *J* = 5.9 Hz, 2H, CH_2, ^{3}), 2.76 (dt, *J* = 25.4, 6.3 Hz, 2H, CH_2, ^{4}).

^{13}C NMR (75 MHz, CD_3OD) δ /ppm: 171.9, 137.1, 129.6, 129.4, 67.9, 36.4, 32.3.

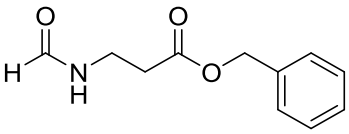
FAB-MS of $[C_{10}H_{14}NO_2]^+$: calculated: 180.1, found: 180.1.

IR (ATR platinum diamond): ν [cm^{-1}] = 3243.9, 2795.8, 2038.6, 1709.8, 1597.0, 1494.9, 1452.4, 1404.8, 1362.8, 1324.6, 1222.6, 1135.4, 1103.6, 1056.5, 981.9, 857.8, 801.7, 748.1, 698.8, 585.4, 569.0, 458.1, 409.1.





Benzyl 3-formamidopropanoate:



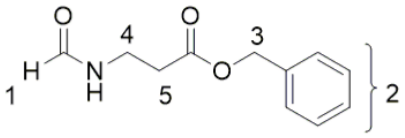
4.05 g of benzyl 3-formamidopropanoate (18.7 mmol, 1.00 eq.), were dissolved in 20.4 mL trimethyl orthoformate **45** (19.8 g, 1.87 mol, 10.00 eq.) and heated to 100 ° C for 12 hours. Trimethyl orthoformate was removed under reduced pressure and the product was purified by column chromatography (hexane/ethyl acetate 2:1 → ethyl acetate), and a yellowish liquid was obtained in a yield of 52 % (2.00 g).

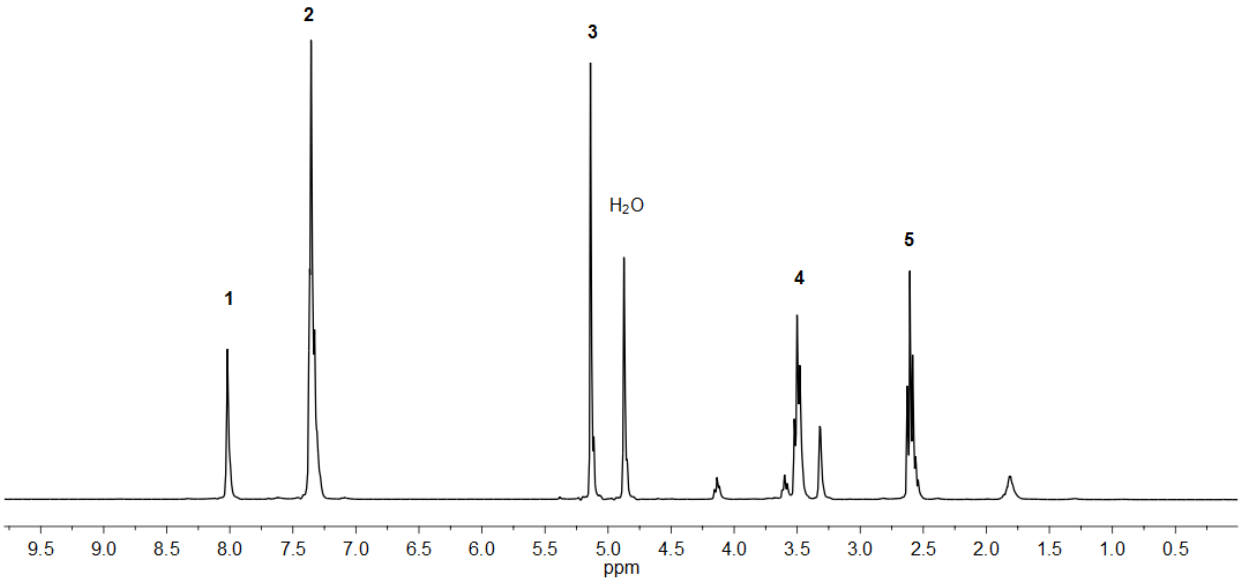
^{1}H NMR (300 MHz, $CDCl_3$) *δ* /ppm: 8.01 (s, 1H, COH, ^{1}), 7.46 – 7.16 (m, 5H, 5 CH aromatic, ^{2}), 5.12 (s, 2H, CH_2, ^{3}), 3.55 - 3.38 (m, 2H, CH_2, ^{4}), 2.69 - 2.46 (m, 2H, CH_2, ^{5}).

^{13}C NMR (75 MHz, $CDCl_3$) *δ* /ppm: 173.0, 163.8, 137.5, 129.5, 129.2, 67.4, 34.8.

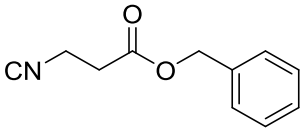
HRMS-FAB-MS of $[C_{11}H_{14}NO_3]^+$: calculated: 208.0968, found: 208.0967.

IR (ATR platinum diamond): ν [cm^{-1}] = 3291.1, 3033.7, 2947.3, 2869.9, 1729.1, 1658.6, 1521.0, 1454.2, 1383.4, 1315.1, 1213.8, 1166.6, 1066.5, 1002.3, 821.1, 738.0, 696.8, 467.5.





Benzyl 3-isocyanopropanoate 49a:

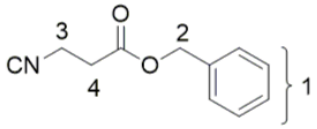


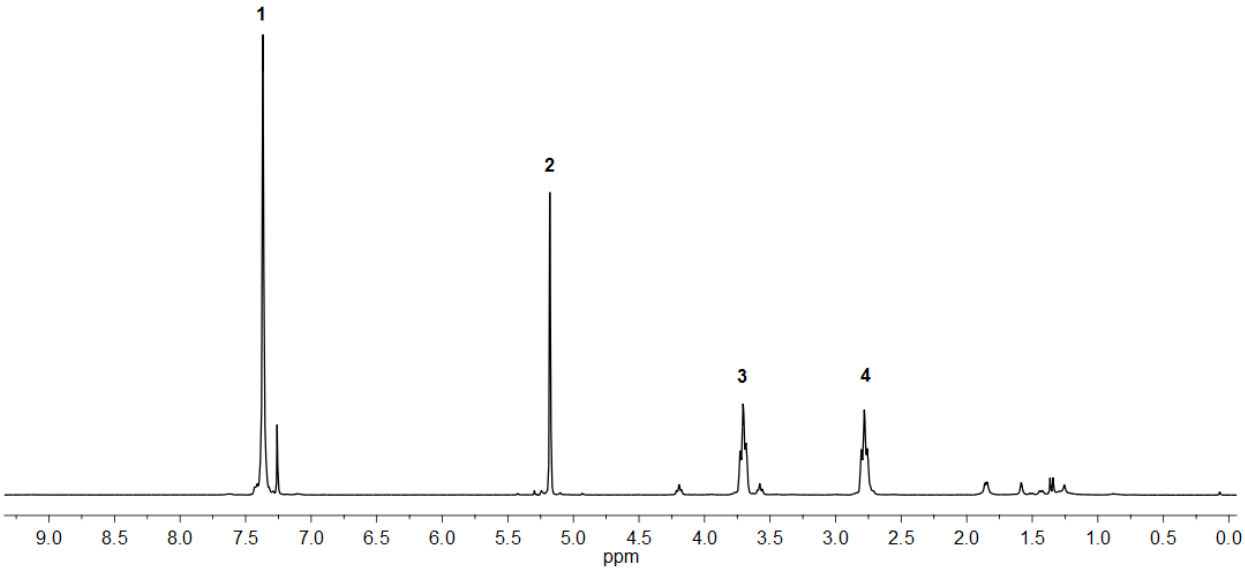
49a

1.06 g of benzyl 3-formamidopropanoate (5.12 mmol, 1.00 eq.) were dissolved in 25 mL dichloromethane (0.20 M), 2.33 mL diisopropylamine **47** (1.68 g, 16.6 mmol, 3.24 eq.) were added and the reaction mixture was cooled to 0 °C. Subsequently, 0.60 mL phosphorous oxy chloride **48** (0.98 g, 6.39 mmol, 1.25 eq.) were added dropwise and the reaction mixture was then stirred at room temperature for two hours. The reaction

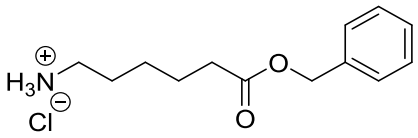
was quenched by addition of sodium carbonate solution (20 %, 9.0 mL) at 0 ° C. After stirring this mixture for 30 minutes, 20 mL water and 20 mL dichloromethane were added. The aqueous phase was separated and the organic layer was washed with water (3 x 20 mL) and brine (20 mL). The combined organic layers were dried over sodium sulfate and the solvent was evaporated under reduced pressure. The crude product was then purified by column chromatography (hexane/ethyl acetate 5:1 → 2:1). The product was obtained as brown oil in a yield of 74 % (0.72 g).

^{1}H NMR (300 MHz, $CDCl_3$) *δ* /ppm: 7.39 (s, 5H, 5 CH aromatic, ^{1}), 5.18 (s, 2H, CH_2, ^{2}), 3.71 (t, *J* = 6.8 Hz, 2H, CH_2, ^{3}), 2.78 (t, *J* = 6.8 Hz, 2H, CH_2, ^{4}).





6-(Benzyloxy)-6-oxohexane-1-ammoniumchloride:



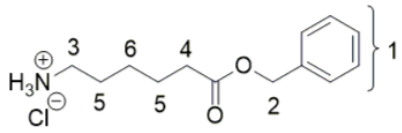
1.98 g of 6-aminohexanoic acid (15.0 mmol, 1.00 eq.) were suspended in 10 mL THF and 20.3 mL of benzyl alcohol **42** (20.9 g, 0.19 mol, 12.9 eq.) were added. The suspension was cooled in an ice bath and subsequently 3.4 mL thionyl chloride **43** (5.53 g, 46.5 mmol, 3.10 eq.) were added dropwise at 0 ° C. After addition of the thionyl chloride, the solution was warmed to room temperature and stirred overnight. The yellow solution was then poured into 200 mL diethylether and stored in the freezer for one hour. The product was the filtered off and dried under high vacuum. 6-(benzyloxy)-6-oxohexane-1-ammoniumchloride was obtained as a white solid in a yield of 96 % (3.71 g).

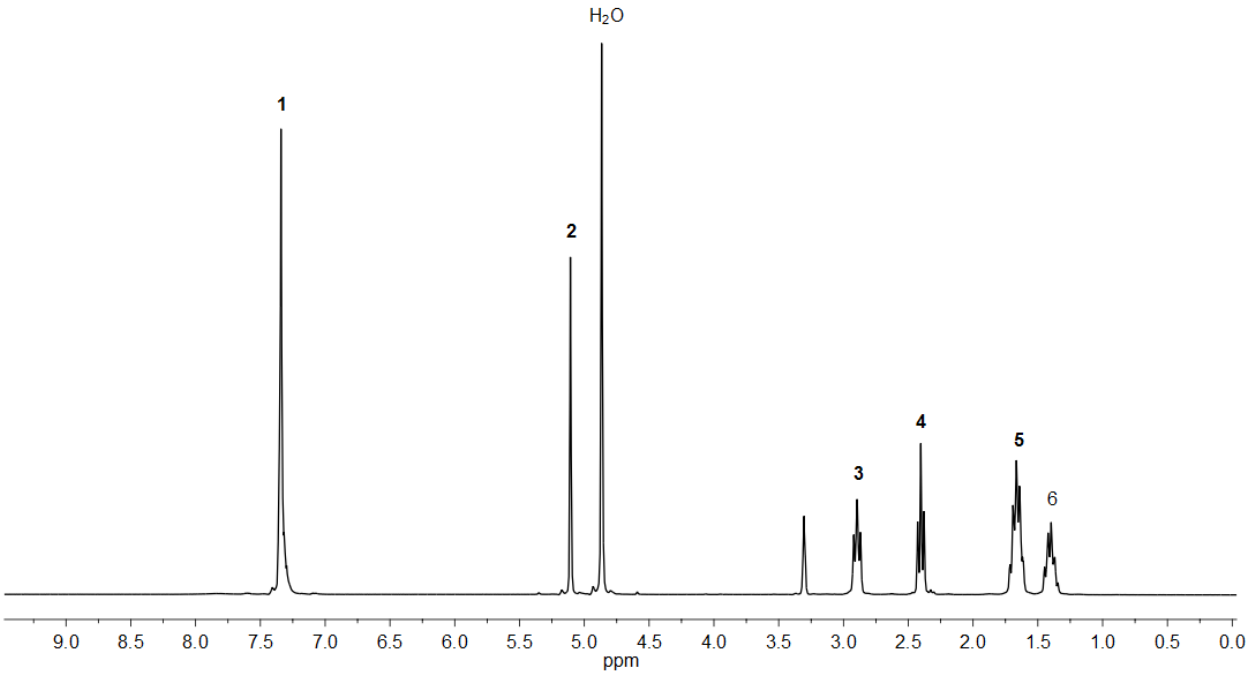
^{1}H-NMR: (300 MHz, CD_3OD) δ /ppm: 7.51 – 7.13 (m, 5H, 5 CH aromatic, ^{1}), 5.11 (s, 2H, CH_2, ^{2}), 2.90 (t, J = 7.6 Hz, 2H, CH_2, ^{3}), 2.41 (t, J = 7.3 Hz, 2H, CH_2, ^{4}), 1.84 – 1.54 (m, 4H, 2 CH_2, ^{5}), 1.54 – 1.25 (m, 2H, CH_2, ^{6}).

^{13}C NMR (75 MHz, CD_3OD) δ /ppm: 174.8, 137.7, 129.5, 129.2, 67.2, 40.5, 34.6, 28.2, 26.8, 25.4.

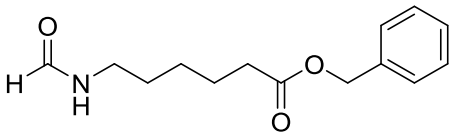
HRMS FAB-MS of $[C_{13}H_{20}NO_2]^+$: calculated: 222.1489, found: 222.1489.

IR (ATR platinum diamond): ν [cm^{-1}] = 3383.3, 3031.0, 2940.1, 1731.7, 1605.1, 1497.1, 1467.6, 1454.4, 1387.4, 1356.4, 1311.1, 1248.2, 1214.9, 1166.3, 1143.5, 1045.2, 1013.3, 964.0, 937.9, 827.1, 748.1, 695.7, 578.8, 520.4, 474.2.





Benzyl-6-formamidohexanoate:



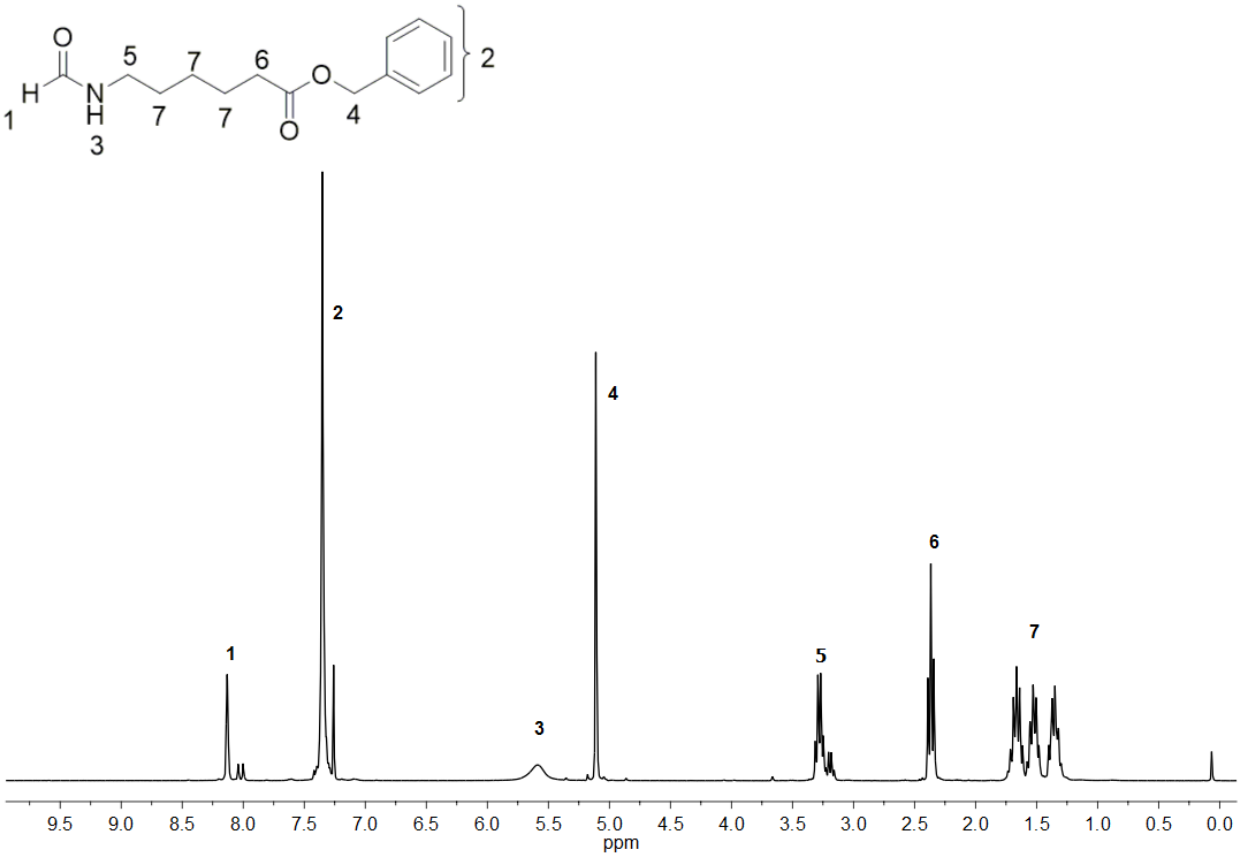
3.29 g 6-(benzyloxy)-6-oxohexane-1-ammoniumchloride (12.7 mmol, 1.00 eq.), were dissolved in 14.1 mL trimethyl orthoformate **45** (13.6 g, 0.13 mol, 10.1 eq.) and heated to 100 ° C for 12 hours. Trimethyl orthoformate was removed under reduced pressure and the product was purified by column chromatography (hexane/ethyl acetate 3:1 → ethyl acetate), and a yellowish liquid was obtained in a yield of 73 % (2.31 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 8.13 (s, 1H, CHO, ^{1}), 7.45 – 7.27 (m, 5H, 5 CH aromatic, ^{2}), 5.59 (bs, 1H, NH, ^{3}), 5.11 (s, 2H, CH_2, ^{4}), 3.41 – 3.06 (m, 2H, CH_2, ^{5}), 2.37 (t, J = 7.3 Hz, 2H, CH_2, ^{6}), 1.78 – 1.59 (m, 2H, CH_2, ^{7}), 1.59 – 1.44 (m, 2H, CH_2, ^{7}), 1.42 – 1.24 (m, 2H, CH_2, ^{7}).

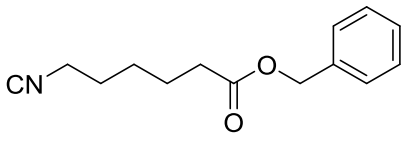
^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 173.4, 164.7, 161.3, 136.1, 128.6, 128.3, 66.2, 41.5, 37.9, 34.1, 30.9, 29.1, 26.3, 25.9, 24.4, 24.4.

HRMS-FAB-MS of $[C_{14}H_{20}NO_3]^+$: calculated: 250.1438, found: 250.1437.

IR (ATR platinum diamond): ν [cm^{-1}] = 3291.8, 3032.8, 2934.5, 2859.8, 1730.0, 1658.2, 1528.3, 1454.5, 1382.6, 1213.2, 1154.0, 1100.2, 1000.9, 736.8, 697.2, 497.6.



Benzyl 3-isocyanohexanoate 49b:



49b

1.70 g of benzyl-6-formamidohexanoate (6.84 mmol, 1.00 eq.) were dissolved in 20 mL dichloromethane (0.34 M), 2.98 mL diisopropylamine **47** (2.15 g, 21.2 mmol, 3.10 eq.) were added and the reaction mixture was cooled to 0 °C. Subsequently, 0.83 mL

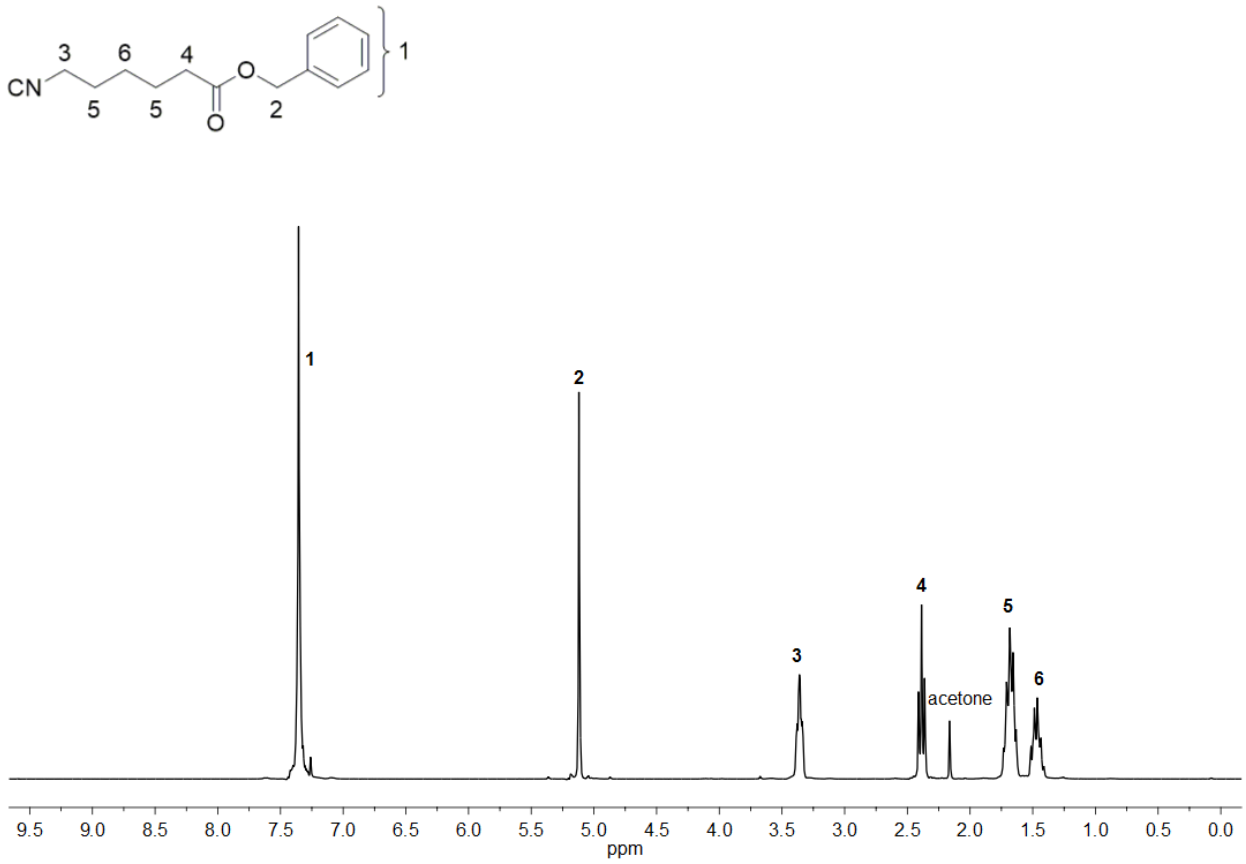
phosphorous oxy chloride **48** (1.36 g, 8.89 mmol, 1.30 eq.) were added dropwise and the reaction mixture was then stirred at room temperature for two hours. The reaction was quenched by addition of sodium carbonate solution (20 %, 9.0 mL) at 0 ° C. After stirring this mixture for 30 minutes, 20 mL water and 20 mL dichloromethane were added. The aqueous phase was separated and the organic layer was washed with water (3 x 20 mL) and brine (20 mL). The combined organic layers were dried over sodium sulfate and the solvent was evaporated under reduced pressure. The crude product was then purified by column chromatography (hexane/ethyl acetate 9:1 → 3:1). The product was obtained as brown oil in a yield of 74 % (1.17 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 7.50 – 7.29 (m, 5H, 5 CH aromatic, ^{1}), 5.12 (s, 2H, CH_2, ^{2}), 3.47 - 3.27 (m, 2H, CH_2, ^{3}), 2.39 (t, J = 7.4 Hz, 2H, CH_2, ^{4}), 1.80 – 1.58 (m, 4H, 2 CH_2, ^{5}), 1.55 - 1.36 (m, 2H, CH_2, ^{6}).

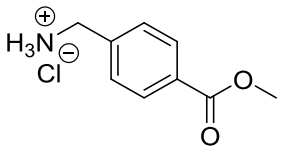
^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 173.1, 156.1, 136.0, 128.6, 128.3, 66.3, 41.4, 34.0, 28.8, 25.9, 24.1.

HRMS-FAB-MS of $[C_{14}H_{18}NO_2]^+$: calculated: 232.1332, found: 232.1331.

IR (ATR platinum diamond): ν [cm^{-1}] = 3023.3, 2943.9, 2863.6, 2146.5 (isocyanide), 1730.2, 1496.6, 1454.1, 1382.3, 1351.9, 1257.5, 1152.2, 1093.8, 1001.3, 737.4, 697.6, 578.7, 504.9, 454.9.



4-Methoxycarbonylphenylmethane ammoniumchloride:



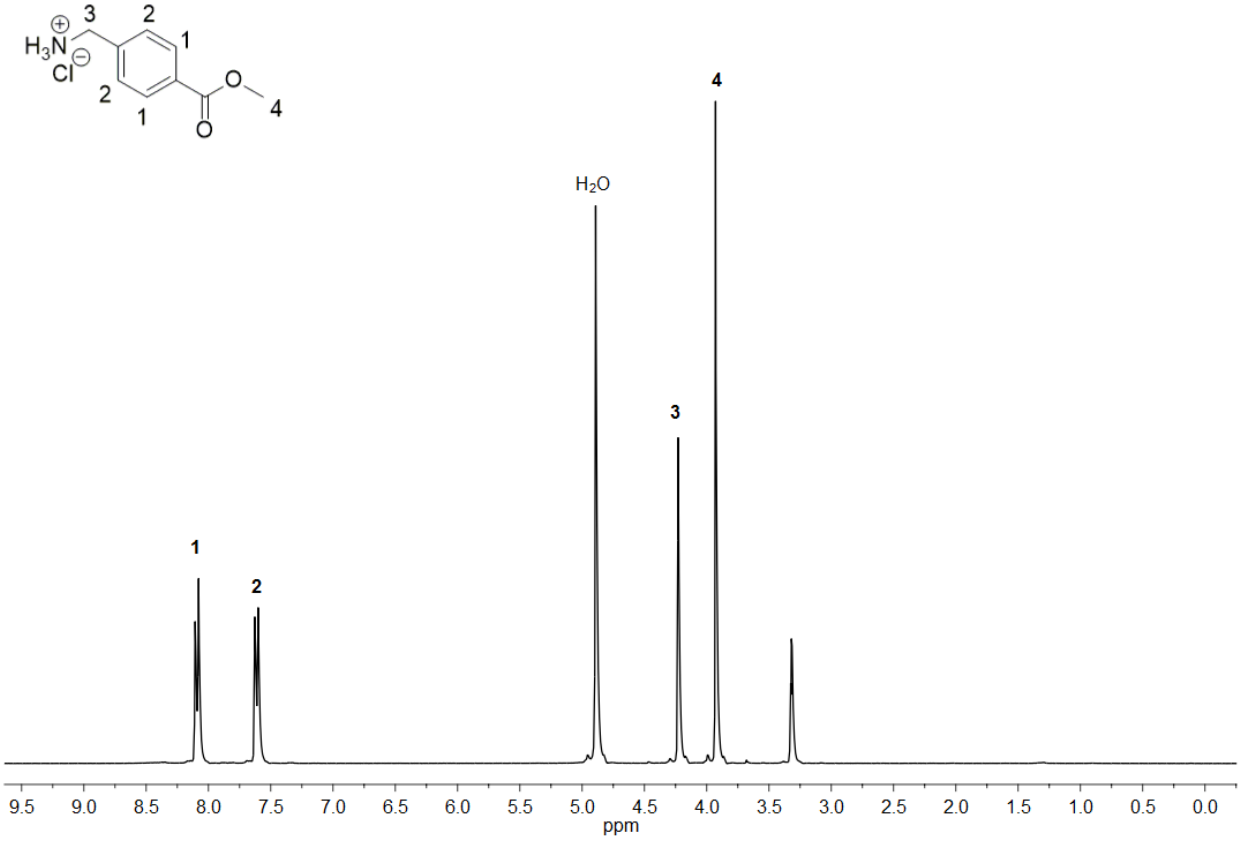
0.99 g of 4-methylaminobenzoic acid (6.55 mmol, 1.00 eq.) were suspended in 9.5 mL methanol. The suspension was cooled in an ice bath and subsequently 5.0 mL thionyl chloride **43** (8.16 g, 68.6 mmol, 2.96 eq.) were added dropwise at 0 ° C. After addition of the thionyl chloride, the solution was warmed to room temperature and stirred for 43 hours. The suspension was poured into 200 mL diethylether and stored in the freezer for one hour. The product was the filtered off, washed with 50 mL of diethyl ether and dried under high vacuum. 4-Methoxycarbonylphenylmethane ammoniumchloride was obtained as a white solid in a yield of 79 % (0.94 g).

^{1}H-NMR: (300 MHz, CD_3OD) δ /ppm: 8.15 – 7.99 (m, 2H, 2 CH aromatic, [1]), 7.60 (d, J = 8.2 Hz, 2H, 2 CH aromatic, [2]), 4.19 (d, J = 17.3 Hz, 2H, CH_2, [3]), 3.92 (s, 3H, OCH_3, [4]).

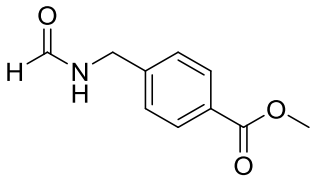
^{13}C NMR (75 MHz, CD_3OD) δ /ppm: 167.8, 139.5, 132.0, 131.2, 130.3, 52.8, 43.9.

FAB-MS of $[C_9H_{12}NO_2]^+$: calculated: 166.1, found: 166.1.

IR (ATR platinum diamond): ν [cm^{-1}] = 3291.8, 3032.8, 2934.5, 2859.8, 1730.0, 1658.2, 1528.3, 1454.5, 1382.6, 1213.2, 1154.0, 1100.2, 1000.9, 736.8, 697.2, 497.6.



Methyl-4-formamidomethylbenzoate:



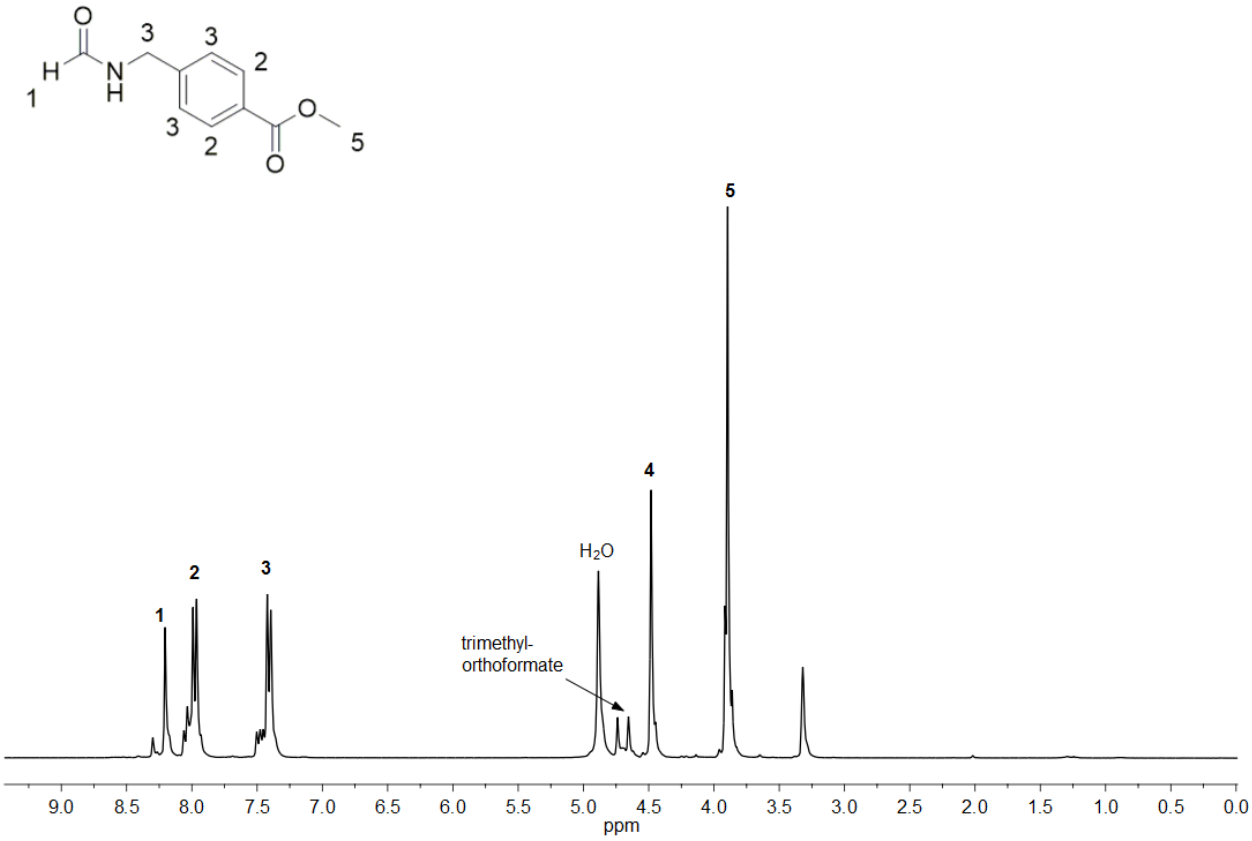
0.90 g 4-methoxycarbonylphenylmethane ammoniumchloride (4.98 mmol, 1.00 eq.), were dissolved in 5.4 mL trimethyl orthoformate **45** (5.28 g, 49.8 mmol, 10.0 eq.) and heated to 100 ° C for 23 hours. Trimethyl orthoformate was removed under reduced pressure and the product was obtained as white solid in a yield of 90 % (0.86 g) and was used without further purification.

^{1}H NMR (300 MHz, CD_3OD) δ /ppm: 8.36 – 8.11 (m, 1H, CHO, [1]), 8.11 – 7.84 (m, 2H, 2 CH aromatic, [2]), 7.57 – 7.25 (m, 2H, 2 CH aromatic, [3]), 4.58 – 4.36 (m, 2H, CH_2, [4]), 4.00 – 3.72 (m, 3H, OCH_3, [5]).

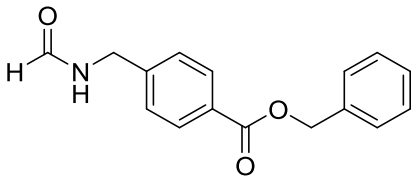
^{13}C NMR (75 MHz, CD_3OD) δ /ppm: 168.3, 163.8, 145.1, 130.8, 130.3, 128.8, 128.5, 52.6, 42.3.

HRMS-FAB-MS of $[C_{10}H_{12}NO_3]^+$: calculated: 194.0812, found: 194.0812.

IR (ATR platinum diamond): ν [cm^{-1}] = 3267.8, 2957.3, 1719.7, 1691.9, 1654.0, 1630.3, 1538.6, 1430.5, 1412.8, 1393.3, 1275.1, 1235.5, 1217.3, 1174.1, 1100.0, 1017.2, 952.0, 842.5, 764.7, 751.1, 723.6, 702.3, 625.9, 513.7, 488.9, 391.7.



Benzyl-4-formamidomethylbenzoate:



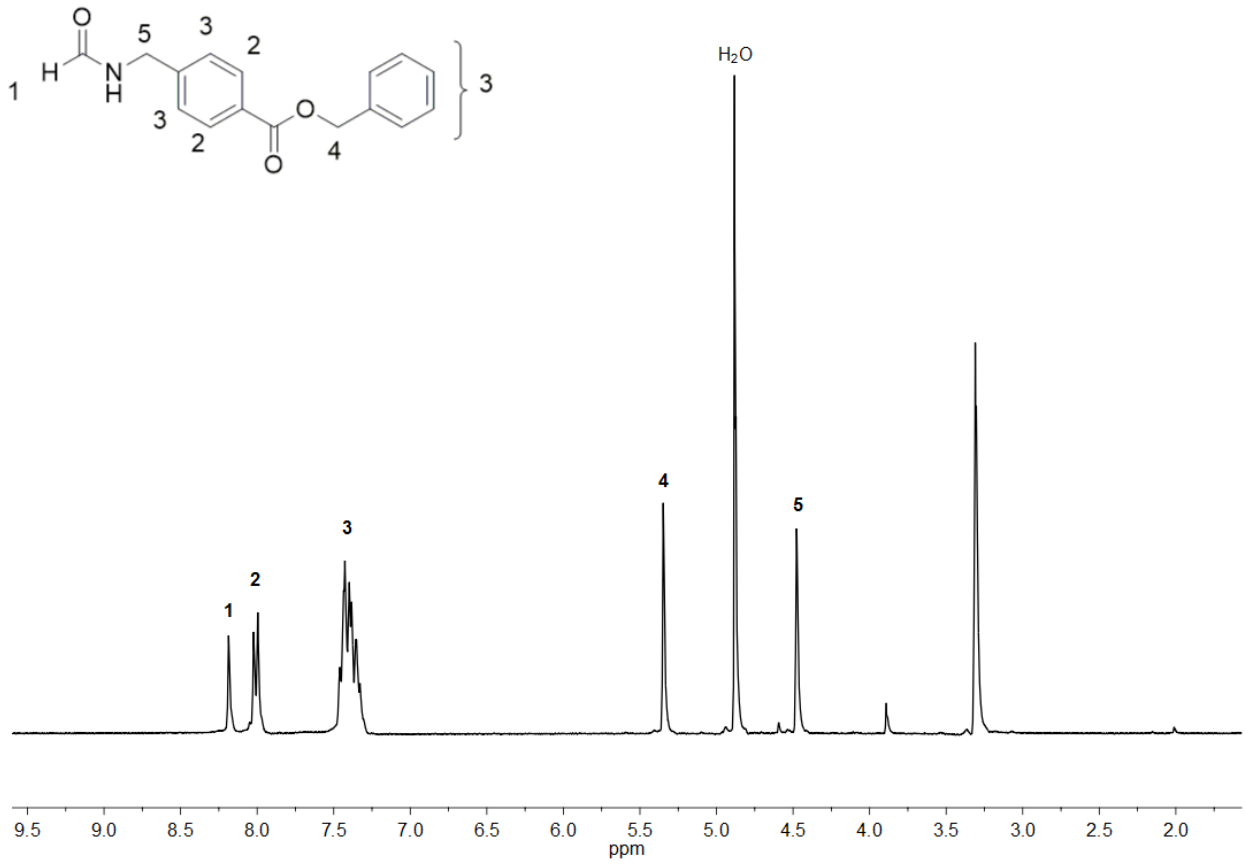
0.86 g methyl-4-formamidomethylbenzoate (4.45 mmol, 1.00 eq.), 2.41 g benzyl alcohol **42** (22.3 mmol, 5.00 eq.) and 37.0 mg 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD, 0.22 mmol, 5.0 mol%) were heated to 80 ° C overnight in an open vessel to ensure the release of methanol. The crude product was purified by column chromatography (hexane/ethyl acetate 5:1 → 2:1) and the product was obtained in a yield of 61 % (0.73 g).

^{1}H NMR (300 MHz, CD_3OD) δ /ppm: 8.19 (s, 1H, CHO, ^{1}), 8.01 (d, J = 8.3 Hz, 2H, 2 CH aromatic, ^{2}), 7.54 - 7.22 (m, 7H, 7 CH aromatic, ^{2}), 5.35 (s, 2H, CH_2, ^{3}), 4.48 (s, 2H, CH_2, ^{4}).

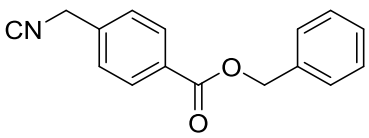
^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 166.2, 164.8, 161.3, 143.1, 136.0, 130.3, 130.2, 129.4, 128.7, 128.4, 128.2, 127.6, 126.9, 66.9, 66.8, 41.7.

HRMS-FAB-MS of $[C_{16}H_{16}NO_3]^+$: calculated: 270.1125, found: 270.1126.

IR (ATR platinum diamond): ν [cm^{-1}] = 3263.9, 2953.8, 1714.5, 1648.6, 1627.2, 1529.3, 1447.4, 1415.6, 1364.3, 1266.7, 1175.2, 1091.3, 1017.7, 940.7, 915.6, 850.1, 822.4, 754.4m 693.5, 624.6, 596.7, 511.2, 386.7.



Benzyl-4-isocyanomethylbenzoate 49c:



49c

0.66 g of benzyl-4-formamidomethylbenzoate (2.46 mmol, 1.00 eq.) were dissolved in 7.5 mL dichloromethane (0.30 M), 1.06 mL diisopropylamine **47** (2.15 g, 7.63 mmol,

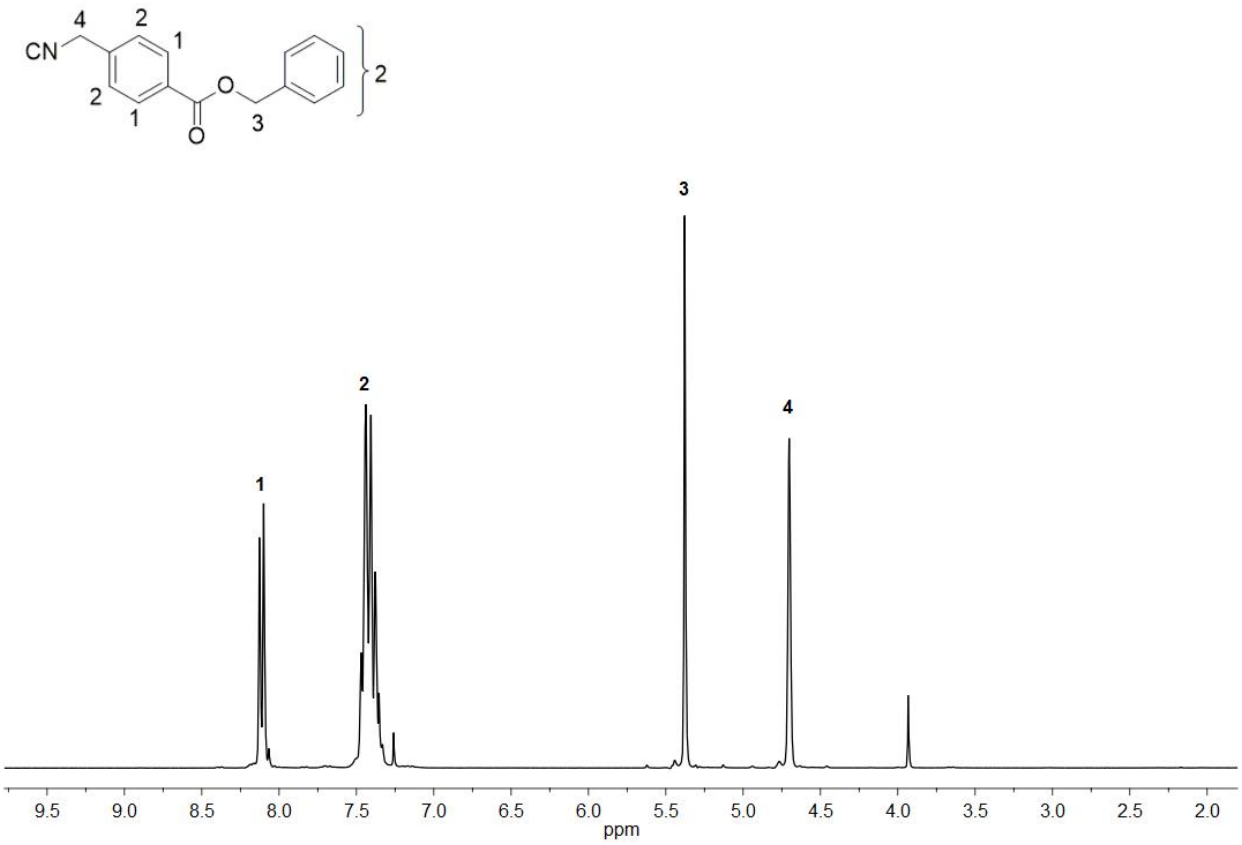
3.10 eq.) were added and the reaction mixture was cooled to 0 ° C. Subsequently, 0.29 mL phosphorous oxy chloride **48** (0.48 g, 3.19 mmol, 1.30 eq.) were added dropwise and the reaction mixture was then stirred at room temperature for two hours. The reaction was quenched by addition of sodium carbonate solution (20 %, 4.0 mL) at 0 ° C. After stirring this mixture for 30 minutes, 10 mL water and 10 mL dichloromethane were added. The aqueous phase was separated and the organic layer was washed with water (3 x 10 mL) and brine (10 mL). The combined organic layers were dried over sodium sulfate and the solvent was evaporated under reduced pressure. The crude product was then purified by column chromatography (hexane/ethyl acetate 5:1 → 3:1). The product was obtained as brown oil in a yield of 18 % (0.10 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 8.10 (s, 2H, 2 CH aromatic, ^{1}), 7.56 – 7.29 (m, 7H, 7 CH aromatic, ^{2}), 5.38 (s, 2H, CH_2, ^{3}), 4.70 (s, 2H, CH_2, ^{4}).

^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 165.8, 158.9, 137.2, 135.9, 130.5, 128.7, 128.4, 128.3, 126.6, 67.0, 45.3.

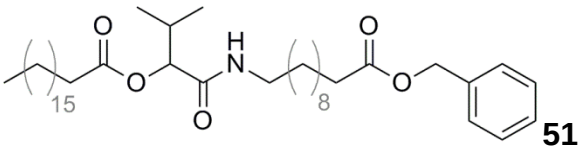
FAB-MS of $[C_{16}H_{14}NO_2]^+$: calculated: 252.1, found: 252.1.

IR (ATR platinum diamond): ν [cm^{-1}] = 3033.1, 2950.5, 2148.5 (isocyanide), 1713.7, 1613.3, 1580.4, 1496.8, 1454.3, 1436.1, 1416.1, 1376.2, 1311.9, 1267.5, 1178.6, 1100.0, 1018.7, 952.5, 913.1, 842.2, 786.8, 749.0, 695.7, 585.4, 526.7, 454.3.



Synthesis of oligomers using monomer **49** in the Passerini reaction:

1st Passerini reaction:



51

2.01 g stearic acid **1a** (7.03 mmol, 1.00 eq.) were dissolved in 7 mL dichloromethane (DCM) (1.01 M) and 0.76 g isobutyraldehyde **50a** (10.6 mmol, 1.52 eq.) and 3.16 g of monomer **49** (10.4 mmol, 1.51 eq.) were added. The mixture was stirred at room temperature for 24 hours and subsequently the solvent was removed under reduced pressure. The crude product was purified by column chromatography (hexane/ethyl acetate 10:1 → 5:1) to afford product **51** as a white solid in a yield of 97 % (4.51 g).

Furthermore, the excess of the monomer **49** was partially recovered (0.58 g, 0.32 eq.) and can be reused.

^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 7.41 – 7.28 (m, 5H, aromatic, [1]), 5.93 (s, 1H, NH, [2]), 5.11 (s, 2H, CH_2, [3]), 5.06 (d, J = 4.4 Hz, 1H, CH, [4]), 3.37 – 3.13 (m, 2H, CH_2, [5]), 2.48 – 2.21 (m, 5H, CH, 2 CH_2, [6]), 1.77 – 1.10 (m, 46H, 23 CH_2, [7]), 0.99 – 0.81 (m, 9H, 3 CH_3, [8]).

^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 173.7, 172.6, 169.4, 136.3, 128.6, 128.2, 78.0, 66.1, 39.2, 34.4, 32.0, 30.6, 29.8, 29.8, 29.7, 29.6, 29.5, 29.5, 29.4, 29.4, 29.3, 29.3, 29.2, 26.9, 25.1, 25.0, 22.8, 18.9, 17.0, 14.2.

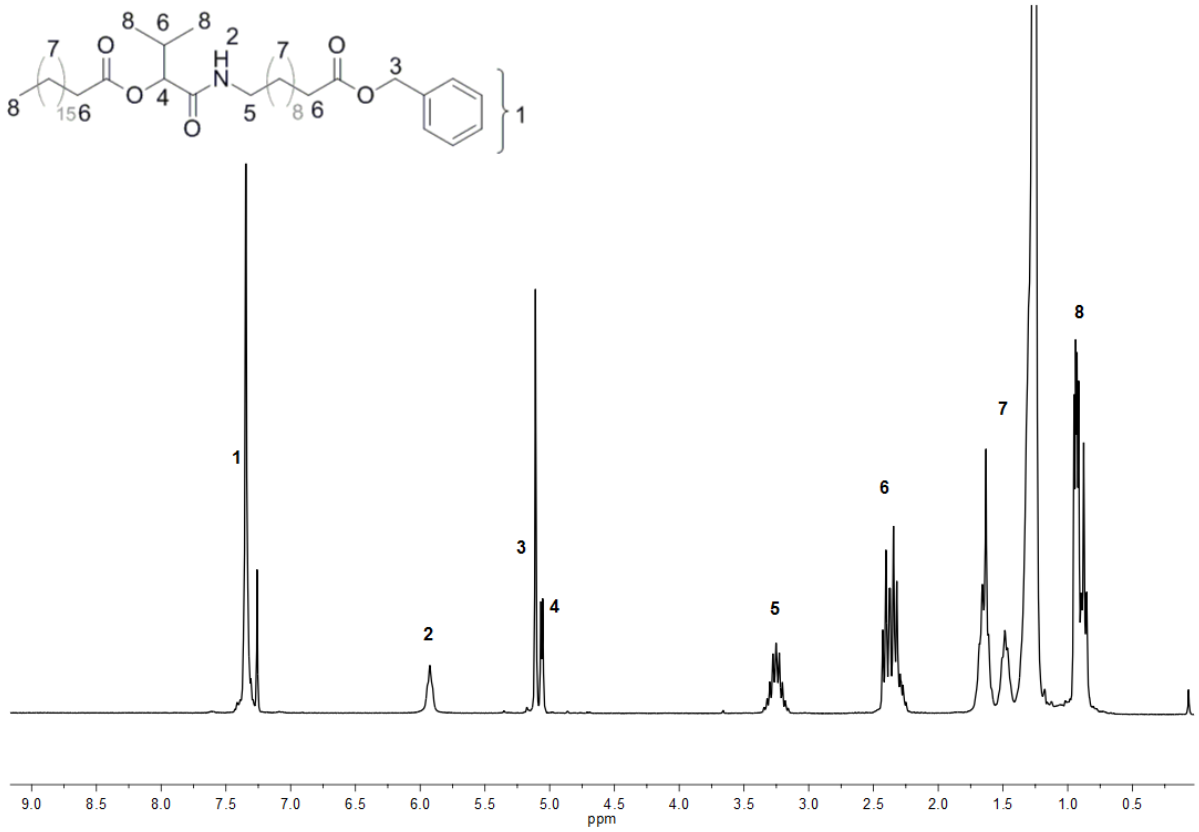
HRMS-FAB-MS of $[C_{41}H_{72}NO_5]^+$: calculated: 658.5405, found: 658.5407.

ESI-MS of $[C_{41}H_{71}NO_5Na]^+$: calculated: 680.5224, found: 680.5209.

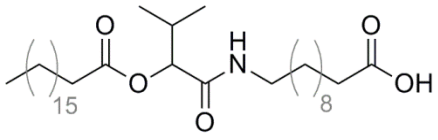
IR (ATR platinum diamond): ν [cm^{-1}] = 3283.7, 2915.4, 2848.0, 1737.1, 1648.7, 1571.4, 1467.4, 1380.3, 1254.0, 1212.3, 1157.0, 1012.5, 927.0, 720.8, 693.8, 578.4, 473.3.

***R*$_f$:** (hexane/ethyl acetate (5:1)) = 0.32.

T_m (DSC): 49.4 ° C



1st Deprotection:



52

4.38 g **51** (6.65 mmol, 1.00 eq.) were dissolved in a 2:1 mixture of ethyl acetate and methanol (0.50 M) and 0.44 g (10 wt%) palladium on activated charcoal were added. Subsequently, the mixture was purged with hydrogen (balloon) and stirred under hydrogen atmosphere overnight. The heterogeneous catalyst was filtered off and the solvent was evaporated under reduced pressure. The product **52** was obtained as a white solid in quantitative yield (3.79 g) and was used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 6.01 (t, J = 5.4 Hz, 1H, NH, ^{1}), 5.05 (d, J = 4.4 Hz, 1H, CH, ^{2}), 3.40 – 3.06 (m, 2H, CH_2, ^{3}), 2.51 – 2.16 (m, 5H, 2 CH_2, CH, ^{4}), 1.76 – 1.06 (m, 46H, 23 CH_2, ^{5}), 0.99 – 0.72 (m, 9H, 3 CH_3, ^{6}).

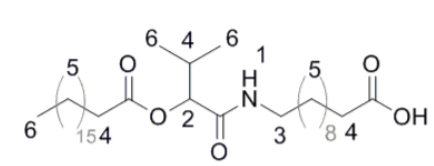
^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 179.3, 172.7, 169.6, 78.00, 39.3, 34.4, 34.2, 32.0, 30.6, 29.8, 29.8, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 29.1, 26.9, 25.1, 24.8, 22.8, 18.9, 17.0, 14.2.

HRMS-FAB-MS of $[C_{34}H_{65}NO_5]^+$: calculated: 568.4936, found: 568.4937.

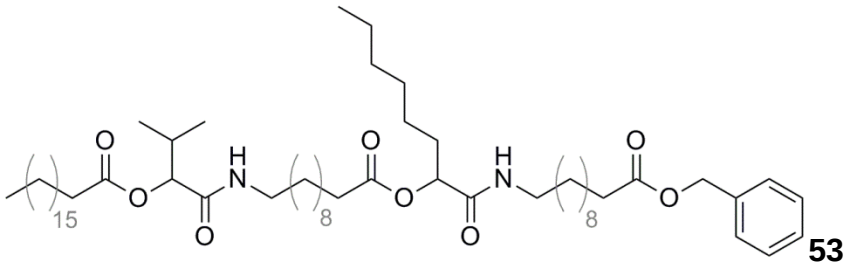
ESI-MS of $[C_{34}H_{65}NO_5Na]^+$: calculated: 590.4755, found: 590.4741.

IR (ATR platinum diamond): ν [cm^{-1}] = 3286.6, 2915.1, 2848.0, 1742.2, 1699.9, 1652.0, 1542.7, 1466.8, 1433.8, 1370.6, 1294.2, 1271.9, 1253.1, 1233.4, 1213.9, 1190.8, 1159.5, 1013.2, 951.3, 721.4, 678.8.

T_m (DSC): 63.8 ° C



2nd Passerini reaction:



3.38 g **52** (5.94 mmol, 1.00 eq.) were dissolved in 6.0 mL DCM (1.02 M), 1.10 g heptaldehyde **50b** (9.66 mmol, 1.50 eq.) and 2.70 g of monomer **49** (8.97 mmol, 1.53 eq.) were added. The mixture was stirred at room temperature for 24 hours and subsequently the solvent was removed under reduced pressure. The crude product was purified by column chromatography (hexane/ethyl acetate 8:1 → 2:1) to afford product **53** as a white solid in a yield of 96 % (5.62 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 7.42 – 7.27 (m, 5H, aromatic, ^{1}), 6.03 (dt, J = 11.8, 5.6 Hz, 2H, 2 NH, ^{2}), 5.20 – 4.97 (m, 4H, CH_2, 2 CH, ^{3}), 3.36 – 3.09 (m, 4H, 2 CH_2, ^{4}), 2.49 – 2.18 (m, 7H, 3 CH_2, CH, ^{5}), 1.99 – 1.03 (m, 72H, 36 CH_2, ^{6}), 1.03 – 0.67 (m, 12H, 4 CH_3, ^{7}).

^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 173.7, 172.6, 172.5, 169.9, 169.3, 136.2, 128.6, 128.2, 78.0, 74.0, 66.1, 39.2, 39.2, 34.4, 32.0, 31.7, 30.6, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.3, 29.2, 29.0, 26.9, 25.1, 25.0, 24.8, 22.7, 22.6, 18.8, 17.0, 14.2, 14.1.

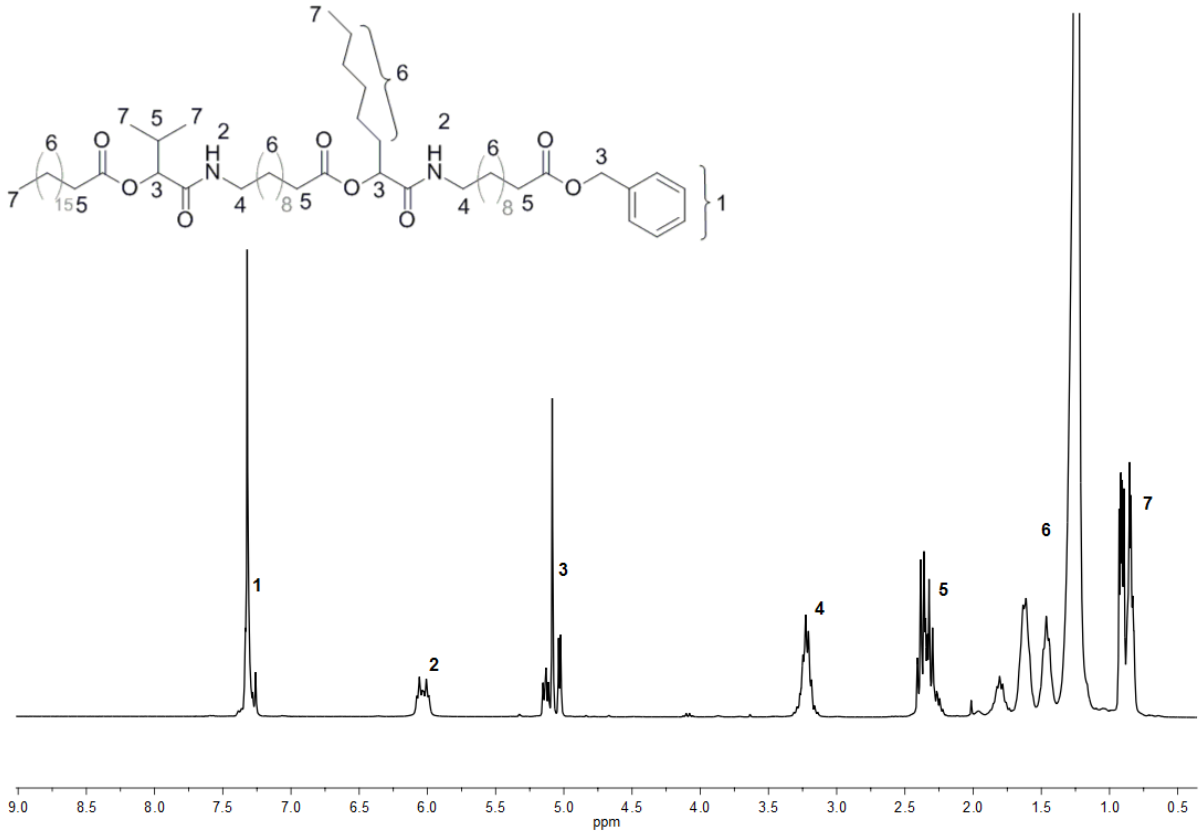
HRMS-FAB-MS of $[C_{60}H_{107}N_2O_8]^+$: calculated: 983.8022, found: 983.8021.

ESI-MS of $[C_{60}H_{106}N_2O_8Na]^+$: calculated: 1005.7841, found: 1005.7829.

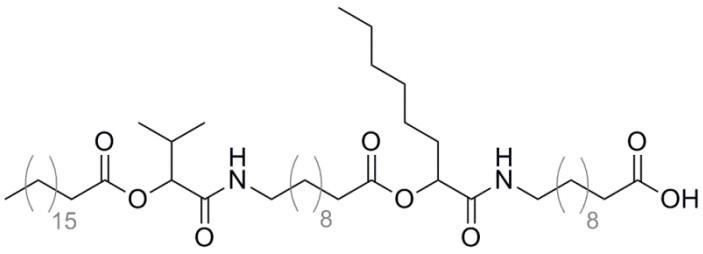
IR (ATR platinum diamond): ν [cm^{-1}] = 3276.0, 3090.6, 2916.1, 2848.9, 1739.6, 1650.0, 1546.0, 1465.8, 1378.1, 1233.0, 1213.4, 1158.2, 1103.1, 1076.8, 1012.5, 928.8, 860.0, 721.5, 696.6, 577.8, 499.0, 426.2.

R_f: (hexane/ethyl acetate (5:2)) = 0.42.

T_m (DSC): 38.8 ° C



2nd Deprotection:



54

5.29 g **53** (5.38 mmol, 1.00 eq.) were dissolved in a 2:1 mixture of ethyl acetate and methanol (0.52 M) and 0.40 g (7.6 wt%) palladium on activated charcoal were added. Subsequently, the mixture was purged with hydrogen (balloon) and stirred under hydrogen atmosphere overnight. The heterogeneous catalyst was filtered off and the solvent was evaporated under reduced pressure. The product **54** was obtained as a white solid in quantitative yield (4.85 g) and was used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 7.58 (bs, 1H, COOH, [1]), 6.18 – 6.00 (m, 2H, 2 NH, [2]), 5.13 (t, J = 5.9 Hz, 1H, CH, [3]), 5.02 (d, J = 4.5 Hz, 1H, CH, [4]), 3.33 – 3.11 (m, 4H, 2 CH_2, [5]), 2.47 – 2.18 (m, 7H, 3 CH_2, CH, [6]), 1.90 – 1.06 (m, 72H, 36 CH_2, [7]), 0.96 – 0.72 (m, 12H, 4 CH_3, [8]).

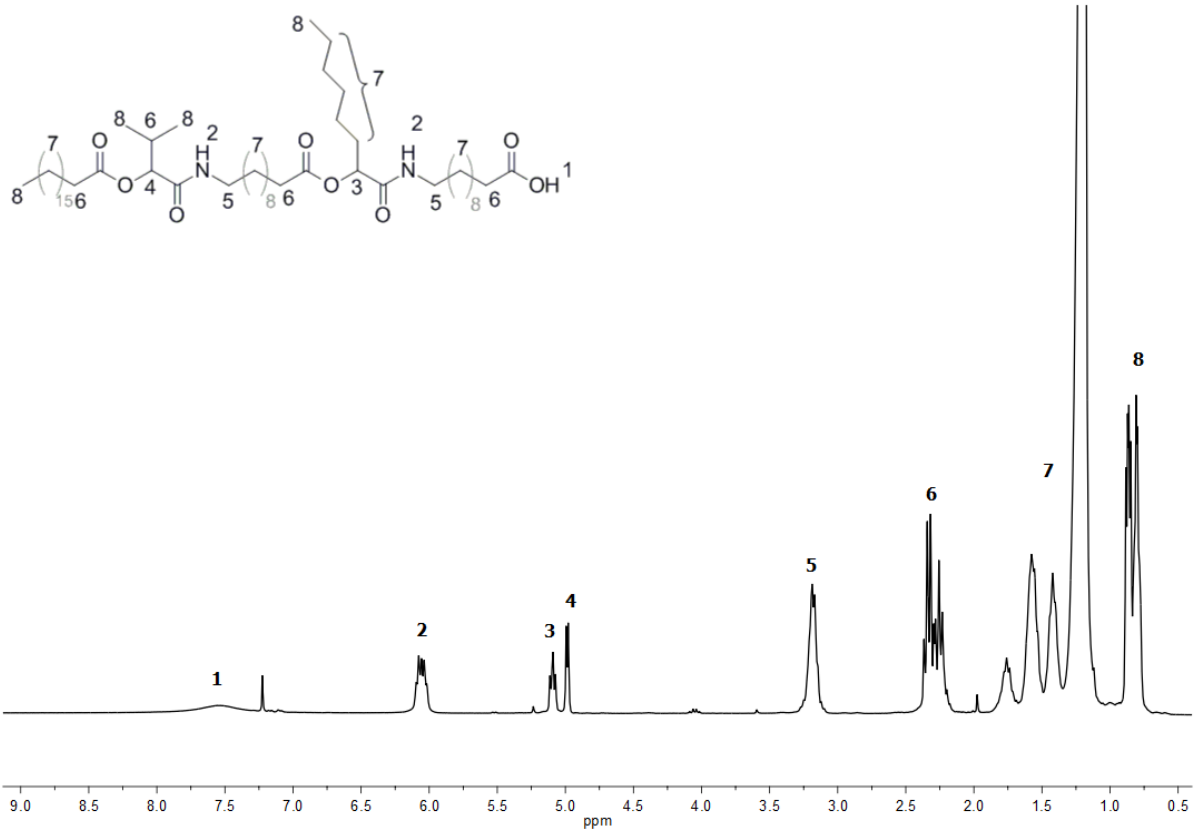
^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 178.4, 172.7, 172.6, 170.1, 169.6, 78.0, 74.0, 39.3, 34.4, 34.2, 32.0, 31.9, 31.7, 30.6, 29.8, 29.7, 29.7, 29.6, 29.5, 29.5, 29.4, 29.4, 29.3, 29.3, 29.2, 29.2, 29.1, 29.0, 26.9, 26.9, 25.1, 25.0, 24.8, 24.8, 22.8, 22.6, 18.8, 17.0, 14.2, 14.1.

HRMS-FAB-MS of $[C_{53}H_{101}N_2O_8]^+$: calculated: 893.7552, found: 893.7551.

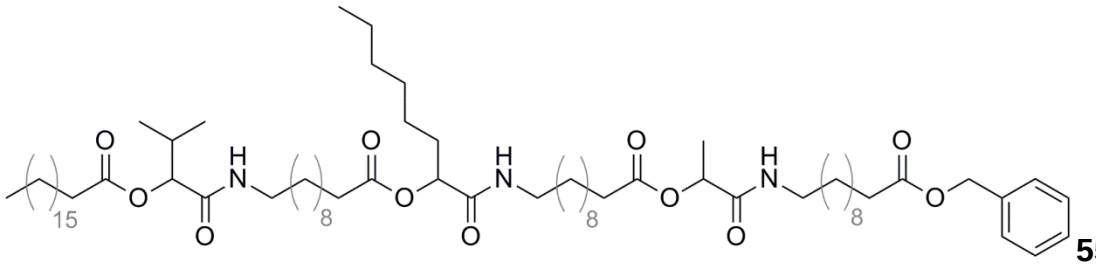
ESI-MS of $[C_{53}H_{100}N_2O_8Na]^+$: calculated: 915.7372, found: 915,7430.

IR (ATR platinum diamond): ν [cm^{-1}] = 3281.2, 3088.7, 2915.6, 2848.6, 1741.7, 1650.0, 1545.9, 1466.2, 1370.3, 1272.0, 1233.4, 1212.8, 1191.0, 1163.5, 1099.8, 927.1, 721.3.

T_m (DSC): 36.1 ° C



3rd Passerini reaction:



55

4.00 g **54** (4.47 mmol, 1.09 eq.) were dissolved in 5.0 mL DCM (0.94 M) and 0.38 g acetaldehyde **50c** (8.55 mmol, 1.93 eq.) and 2.21 g of monomer **49** (7.32 mmol, 1.58 eq.) were added. The mixture was stirred at room temperature for 24 hours and subsequently the solvent was removed under reduced pressure. The crude product was purified by column chromatography (hexane/ethyl acetate 7:1 → 1.5:1) to afford product **55** as a white solid in a yield of 93 % (5.15 g). Furthermore, the excess of the monomer **49** was partially recovered (0.73 g, 0.54 eq.) and can be reused.

^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 7.32 (s, 5H, aromatic, [1]), 6.22 – 5.93 (m, 3H, 3 NH, [2]), 5.23 – 4.98 (m, 5H, 3 CH, CH_2, [3]), 3.36 – 3.09 (m, 6H, 3 CH_2, [4]), 2.50 – 2.18 (m, 9H, 4 CH_2, CH, [5]), 2.04 – 1.10 (m, 91H, CH_3, 44 CH_2, [6]), 0.97 – 0.77 (m, 12H, 4 CH_3, [7]).

^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 173.7, 172.6, 172.5, 172.3, 170.4, 169.9, 169.4, 136.2, 128.6, 128.2, 77.9, 74.0, 70.5, 66.1, 39.3, 39.2, 39.2, 34.4, 32.0, 31.7, 31.0, 30.6, 29.7, 29.7, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 29.3, 29.2, 29.2, 29.1, 29.0, 26.9, 25.1, 25.0, 25.0, 24.9, 24.8, 22.7, 22.6, 18.8, 18.0, 17.0, 14.2, 14.1.

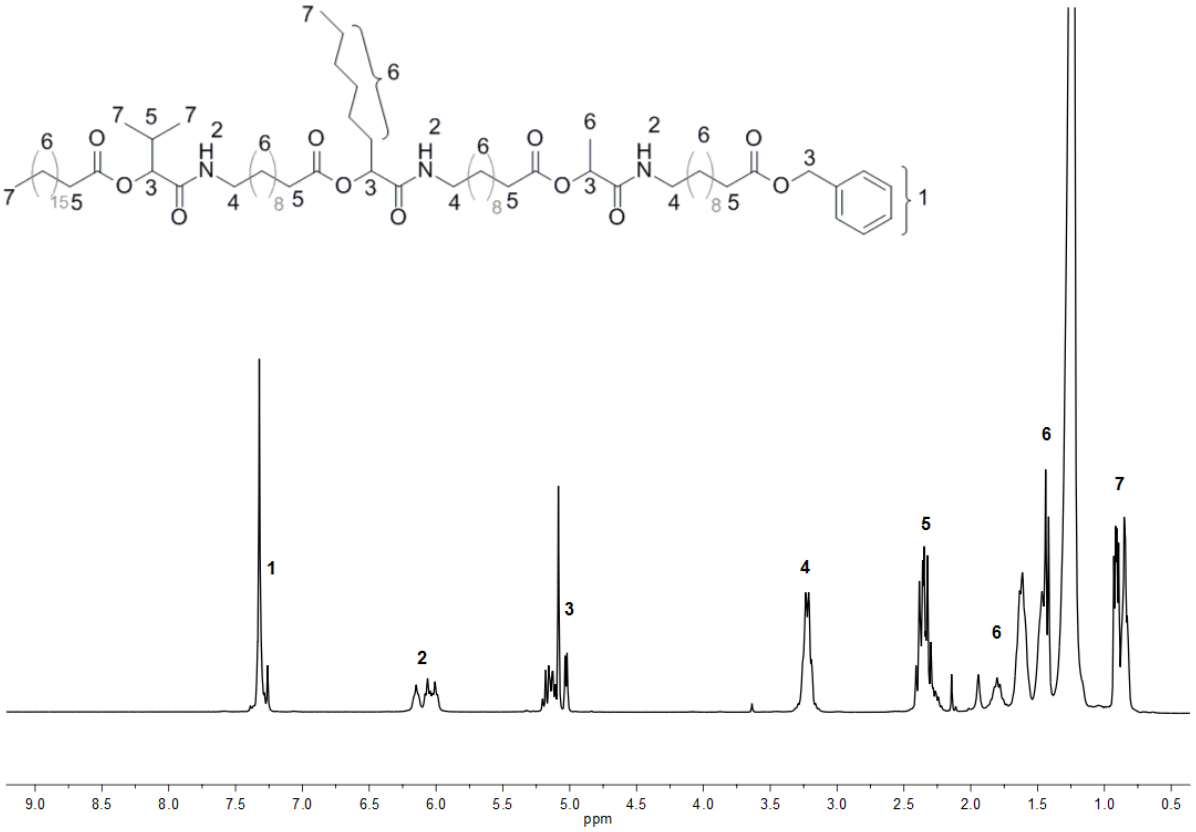
FAB-MS of $[C_{74}H_{132}N_3O_{11}]^+$: calculated: 1238.9, found: 1238.8.

ESI-MS of $[C_{74}H_{131}N_3O_{11}Na]^+$: calculated: 1260.9676, found: 1260.9667.

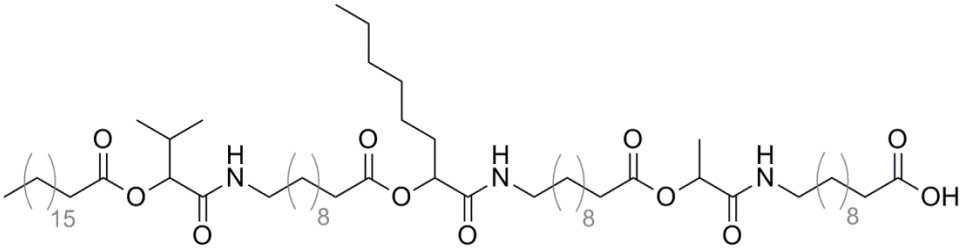
IR (ATR platinum diamond): ν [cm^{-1}] = 3269.3, 3088.7, 2916.3, 2849.3, 1739.4, 1649.8, 1540.6, 1465.6, 1371.4, 1233.0, 1213.0, 1162.3, 1101.2, 927.3, 720.7, 696.7, 427.1.

R_f: (hexane/ethyl acetate (3:2)) = 0.50.

T_m (DSC): 36.4 ° C



3rd Deprotection:



56

4.91 g **55** (3.96 mmol, 1.00 eq.) were dissolved in a 2:1 mixture of ethyl acetate and methanol (0.52 M) and 0.26 g (5.4 wt%) palladium on activated charcoal were added. Subsequently, the mixture was purged with hydrogen (balloon) and stirred under hydrogen atmosphere overnight. The heterogeneous catalyst was filtered off and the solvent was evaporated under reduced pressure. The product **56** was obtained as a white solid in a yield of 95 % (4.32 g) and was used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 7.61 (bs, 1H, COOH, [1]), 6.33 – 5.94 (m, 3H, 3 NH, [2]), 5.10 (m, 3H, 3 CH, [3]), 3.39 – 3.02 (m, 6H, 3 CH_2, [4]), 2.49 – 2.12 (m, 9H, 4 CH_2, CH, [5]), 1.91 – 1.01 (m, 91H, CH_3, 44 CH_2, [6]), 0.95 – 0.70 (m, 12H, 4 CH_3, [7]).

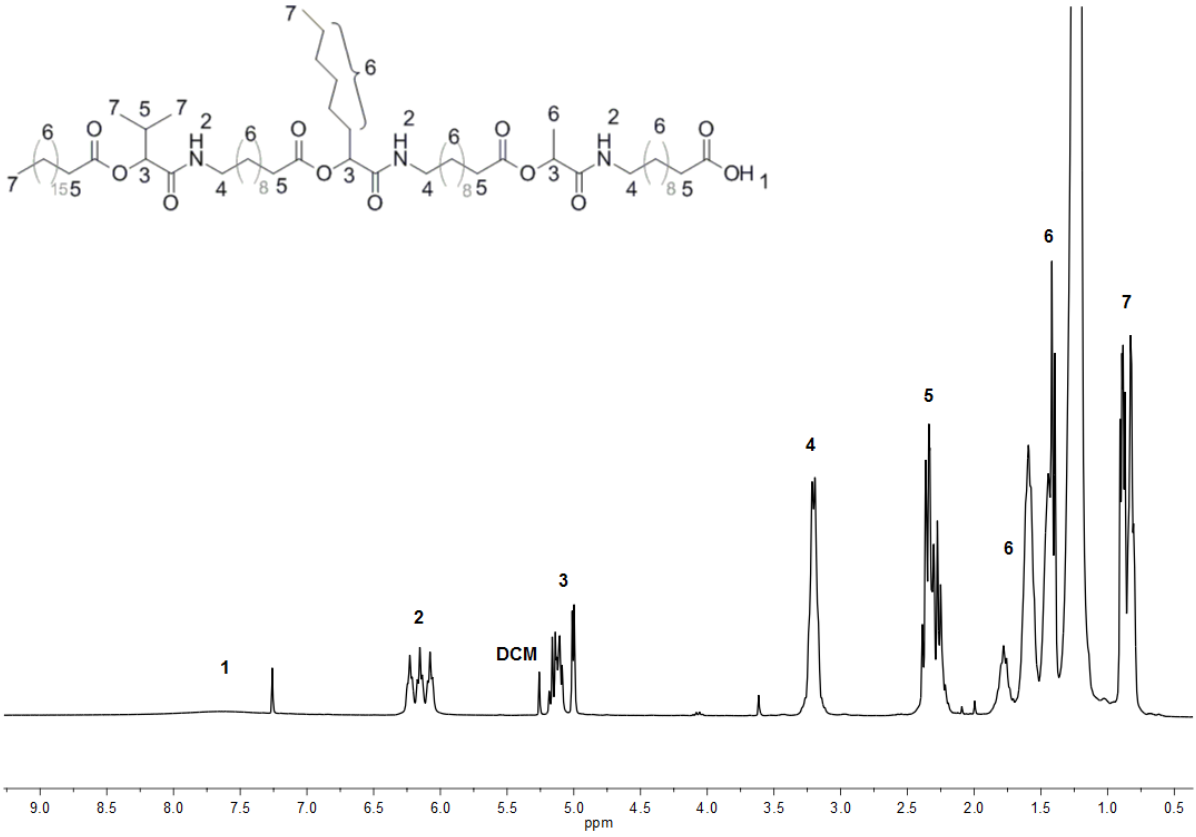
^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 177.7, 172.7, 172.6, 172.3, 170.6, 170.1, 169.5, 77.9, 73.9, 70.4, 39.3, 39.3, 39.2, 34.3, 34.1, 31.9, 31.6, 30.5, 29.7, 29.7, 29.6, 29.6, 29.5, 29.5, 29.4, 29.4, 29.3, 29.4, 29.2, 29.2, 29.1, 29.1, 29.1, 28.9, 26.9, 26.8, 26.8, 25.0, 25.0, 24.9, 24.8, 24.7, 22.7, 22.5, 18.8, 18.0, 17.0, 14.1, 14.1.

FAB-MS of $[C_{67}H_{126}N_3O_{11}]^+$: calculated: 1148.9, found: 1148.4.

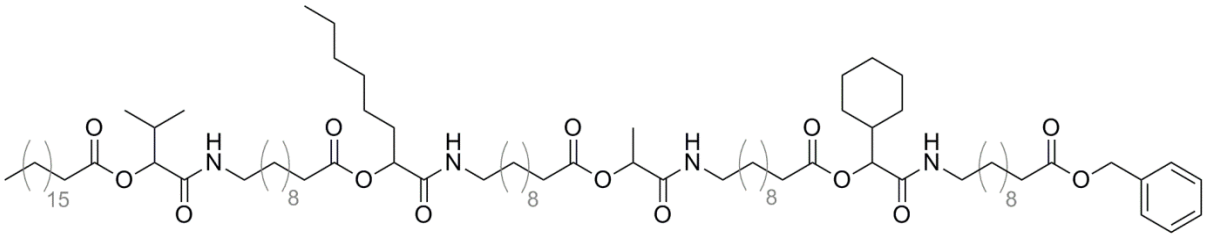
ESI-MS of $[C_{67}H_{125}N_3O_{11}]^+$: calculated: 1170.9206, found: 1170.9196.

IR (ATR platinum diamond): ν [cm^{-1}] = 3268.7, .3089.7, 2916.5, 2849.3, 1740.5, 1649.7, 1542.5, 1465.8, 1371.8, 1233.7, 1213.1, 1162.4, 1101.3, 1011.8, 926.5, 720.8, 426.9.

T_m (DSC): 45.4 ° C



4th Passerini reaction:



57

3.85 g **56** (3.35 mmol, 1.00 eq.) were dissolved in 3.5 mL DCM (1.04 M) and 0.63 g cyclohexanecarboxaldehyde **50d** (5.61 mmol, 1.69 eq.) and 1.51 g of monomer **49** (5.02 mmol, 1.48 eq.) were added. The mixture was stirred at room temperature for 30 hours and subsequently the solvent was removed under reduced pressure. The crude product was purified by column chromatography (hexane/ethyl acetate 6:1 → 1:1) to afford product **57** as a white solid in a yield of 93 % (4.90 g). Furthermore, the excess of the monomer was partially recovered (0.41 g, 0.40 eq.) and can be reused.

^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 7.35 (s, 5H, aromatic, [1]), 6.19 – 5.88 (m, 4H, 4 CH, [2]), 5.26 – 4.99 (m, 6H, 4 CH, CH_2, [3]), 3.25 (m, 8H, 4 CH_2, [4]), 2.50 – 2.22 (m, 11H, 5 CH_2, CH, [5]), 2.03 – 1.01 (m, 118H, CH_3, CH, 57 CH_2, [6]), 0.97 – 0.77 (m, 12H, 4 CH_3, [7]).

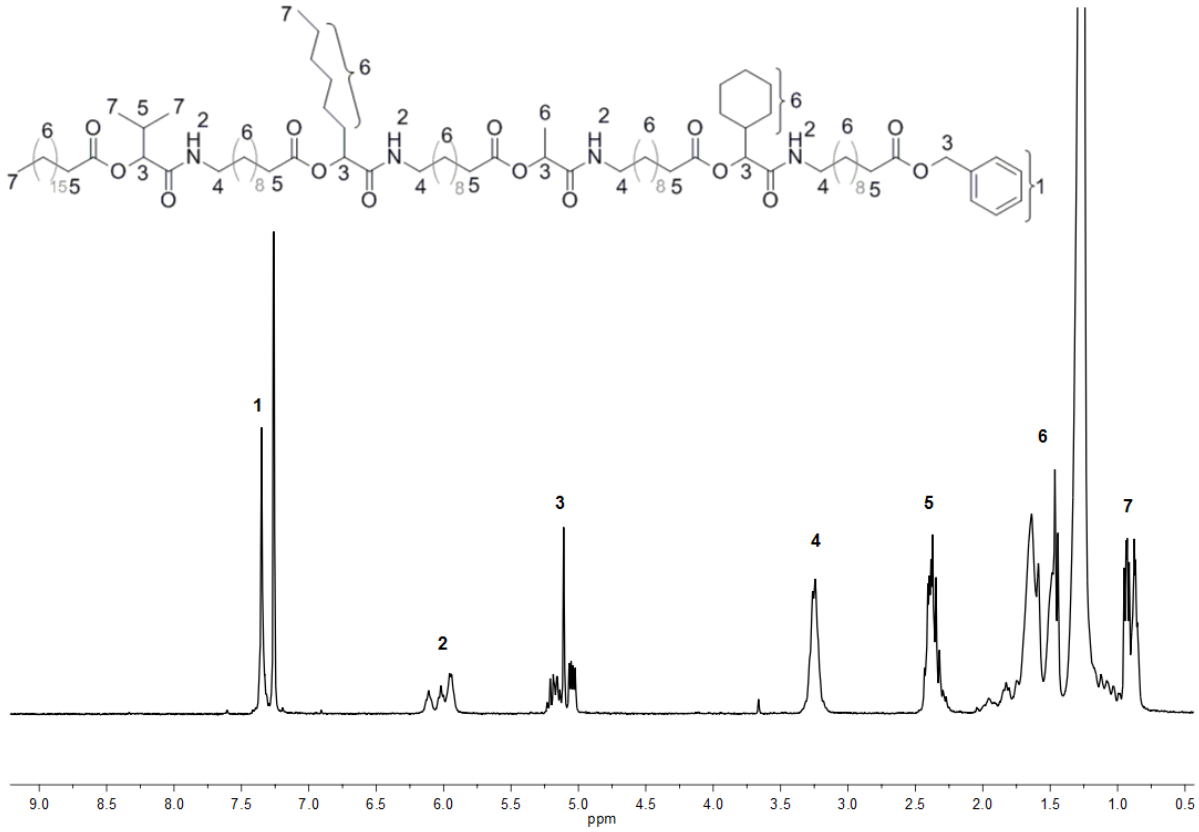
^{13}C NMR (75 MHz, $CDCl_3$) δ/ ppm: 173.7, 172.6, 172.6, 172.5, 172.3, 170.4, 169.91, 169.3, 169.2, 136.1, 128.6, 1282, 77.9, 73.9, 70.4, 66.1, 40.0, 39.2, 39.2, 34.3, 31.9, 31.7, 30.5, 29.7, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 29.2, 29.2, 29.1, 29.1, 28.9, 27.3, 26.9, 26.1, 26.0, 25.9, 25.1, 25.0, 24.9, 24.8, 22.7, 22.6, 18.8, 18.0, 17.0, 14.2, 14.1.

FAB-MS of $[C_{93}H_{164}N_4O_{14}]^+$: calculated: 1562.2, found: 1562.5.

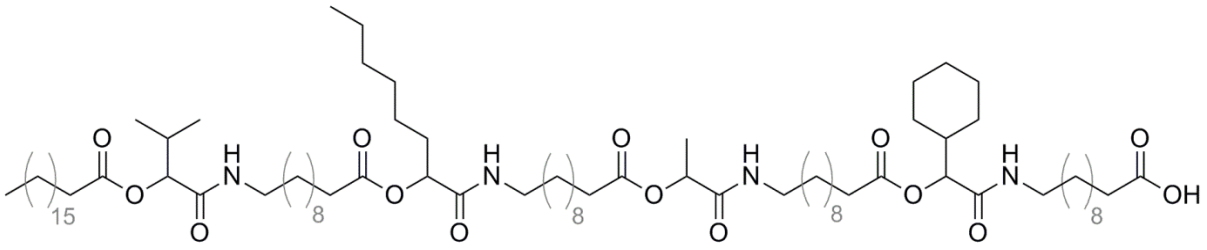
ESI-MS of $[C_{93}H_{164}N_4O_{14}]^+$: calculated: 1584.2136, found: 1584.2126

IR (ATR platinum diamond): ν [cm^{-1}] = 3304.9, 2921.1, 2851.2, 1738.8, 1652.4, 1535.1, 1454.9, 1369.9, 1233.2, 1161.0, 1101.2, 721.3, 696.3.

***R*$_f$:** (hexane/ethyl acetate (1:1)) = 0.62.



4th Deprotection:



58

4.61 g **57** (2.95 mmol, 1.00 eq.) were dissolved in a 2:1 mixture of ethyl acetate and methanol (0.32 M) and 0.33 g (7.3 wt%) palladium on activated charcoal were added. Subsequently, the mixture was purged with hydrogen (balloon) and stirred under hydrogen atmosphere overnight. The heterogeneous catalyst was filtered off and the solvent was evaporated under reduced pressure. The product **58** was obtained as a white solid in a yield of 97 % (4.19 g) and was used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 6.13 (m, 4H, 4 NH, ^{1}), 5.25 – 4.90 (m, 4H, 4 CH, ^{2}), 3.38 – 3.07 (m, 8H, 4 CH_2, ^{3}), 2.59 – 2.12 (m, 11H, 1 CH, 5 CH_2, ^{4}), 2.05 – 0.95 (m, 118H, CH_3, CH, 57 CH_2, ^{5}), 0.95 – 0.62 (m, 12H, 4 CH_3, ^{6}).

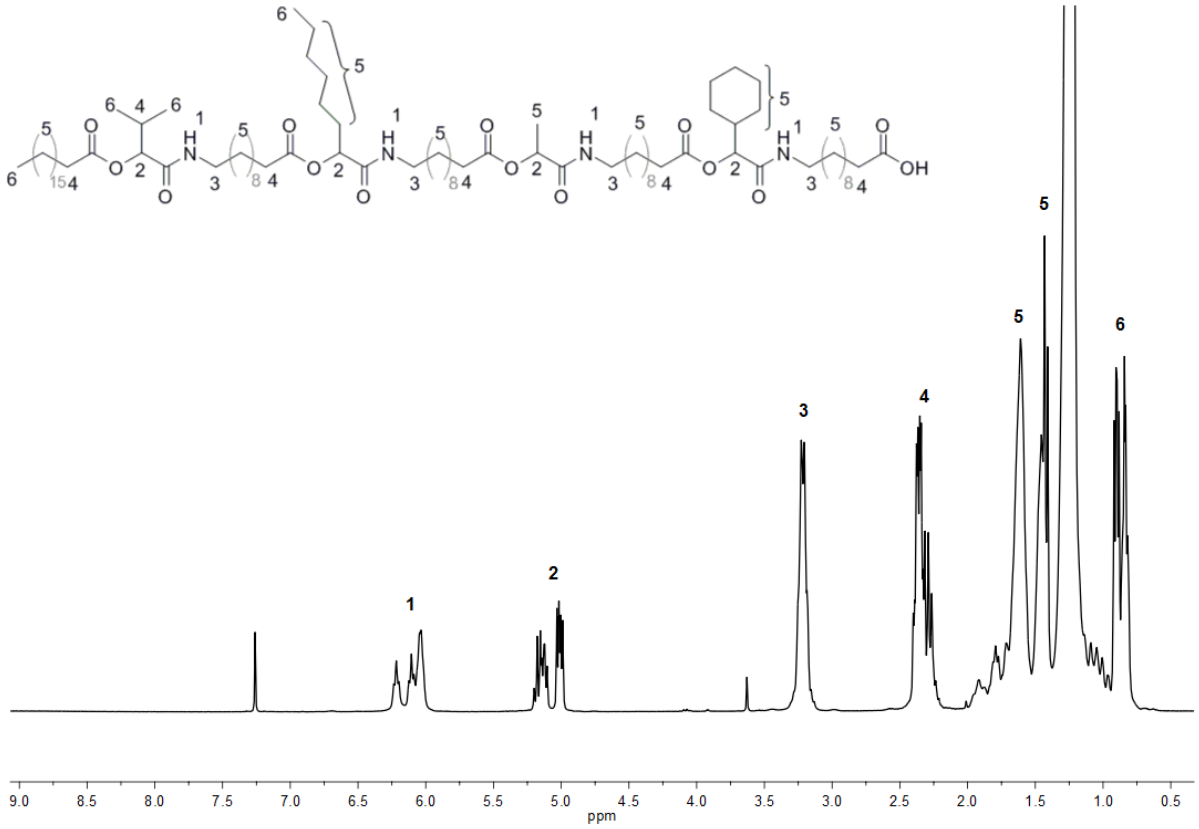
13C NMR (75 MHz, CDCl3) δ /ppm: 177.6, 172.7, 172.7, 172.6, 172.4, 170.6, 170.1, 169.5, 169.4, 77.9, 77.7, 74.0, 70.5, 40.0, 39.3, 39.3, 39.2, 34.4, 34.1, 32.0, 31.7, 30.6, 29.8, 29.7, 29.7, 29.6, 29.6, 29.6, 29.5, 29.4, 29.3, 29.3, 29.2, 29.2, 29.2, 29.1, 29.1, 29.0, 27.4, 26.9, 26.1, 26.1, 25.9, 25.1, 25.1, 25.0, 24.9, 24.9, 24.8, 22.8, 22.6, 18.8, 18.0, 17.0, 14.2, 14.1.

FAB-MS of $[C_{86}H_{159}N_4O_{14}]^+$: calculated: 1472.2, found: 1472.6.

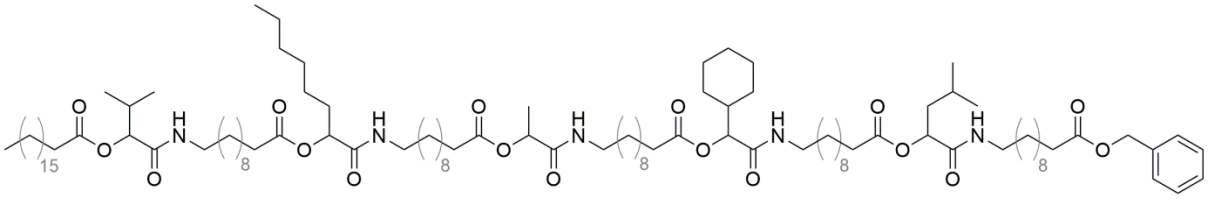
ESI-MS of $[C_{86}H_{158}N_4O_{14}Na]^+$: calculated: 1494.1667, found: 1494.1658.

IR (ATR platinum diamond): ν [cm^{-1}] = 3289.6, 2919.8, 2850.5, 1740.1, 1650.0, 1537.0, 1464.2, 1370.0, 1233.1, 1163.2, 1100.4, 720.7.

T_m (DSC): 48.7 ° C



5th Passerini reaction:



59

4.00 g **58** (2.72 mmol, 1.00 eq.) were dissolved in 3.00 mL DCM (0.91 M) and 0.36 g isovaleraldehyde **50e** (4.13 mmol, 1.50 eq.) and 1.23 g of monomer **49** (4.08 mmol, 1.50 eq.) were added. The mixture was stirred at room temperature for 24 hours and subsequently the solvent was removed under reduced pressure. The crude product was purified by column chromatography (hexane/ethyl acetate 4:1 → 1:1) to afford product **59** as viscous oil in a yield of 92 % (4.64 g). Furthermore, the excess of the monomer was partially recovered (0.29 g, 0.35 eq.) and can be reused.

^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 7.30 (m, 5H, 5 CH aromatic, [1]), 6.24 – 5.89 (m, 5H, 5 NH, [2]), 5.25 – 4.92 (m, 7H, 5 CH, CH_2, [3]), 3.23 (m, 10H, 5 CH_2, [4]), 2.48 – 2.16 (m, 13H, 6 CH_2, CH. [5]), 2.04 – 0.98 (m, 137H, 66 CH_2, CH_3, 2 CH, [6]), 0.88 (m, 18H, 6 CH_3 [7]).

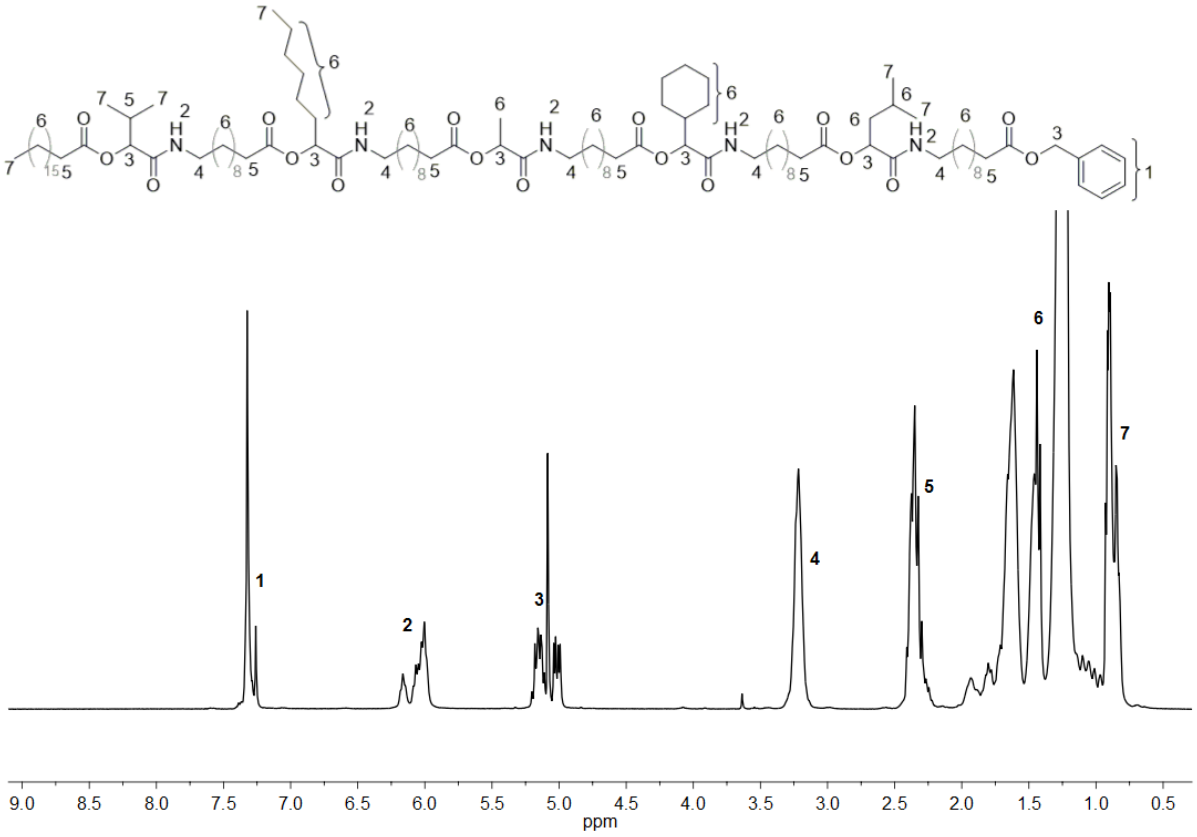
^{13}C NMR (75 MHz, $CDCl_3$) δ/ ppm: 173.8, 172.7, 172.7, 172.6, 172.6, 172.4, 170.4, 170.3, 167.0, 169.4, 169.3, 136.2, 128.6, 128.2, 77.9, 74.0, 72.7, 70.5, 66.1, 40.9, 40.0, 39.3, 39.2, 39.2, 34.4, 34.4, 32.0, 31.7, 30.6, 29.8, 29.7, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 29.3, 29.2, 29.1, 29.0, 27.4, 26.9, 26.9, 26.1, 26.1, 26.0, 25.1, 25.1, 25.0, 25.0, 24.9, 24.8, 24.6, 23.2, 22.8, 22.6, 21.9, 18.9, 18.1, 17.0, 14.2, 14.1.

FAB-MS of $[C_{110}H_{195}N_5O_{17}]^+$: calculated: 1859.5, found: 1859.4.

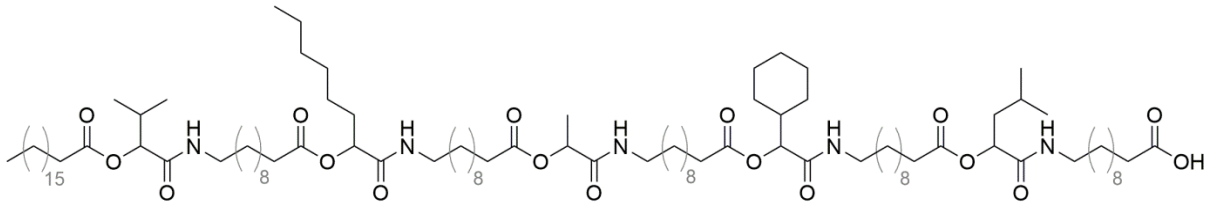
ESI-MS of $[C_{110}H_{195}N_5O_{17}]^+$: calculated: 1881.4440, found: 1881.4518.

IR (ATR platinum diamond): ν [cm^{-1}] =3304.7, 2921.6, 2851.4, 1738.8, 1652.8, 1534.3, 1455.5, 1368.7, 1231.8, 1158.7, 1100.8, 721.3, 696.5.

***R*$_f$:** (hexane/ethyl acetate (1:1)) = 0.53.



5th Deprotection:



60

4.38 g **59** (2.35 mmol, 1.00 eq.) were dissolved in a 2:1 mixture of ethyl acetate and methanol (0.33 M) and 0.24 g (5.6 wt%) palladium on activated charcoal were added. Subsequently, the mixture was purged with hydrogen (balloon) and stirred under hydrogen atmosphere overnight. The heterogeneous catalyst was filtered off and the solvent was evaporated under reduced pressure. The product **60** was obtained as viscous oil in a yield of 99 % (4.12 g) and was used without further purification.

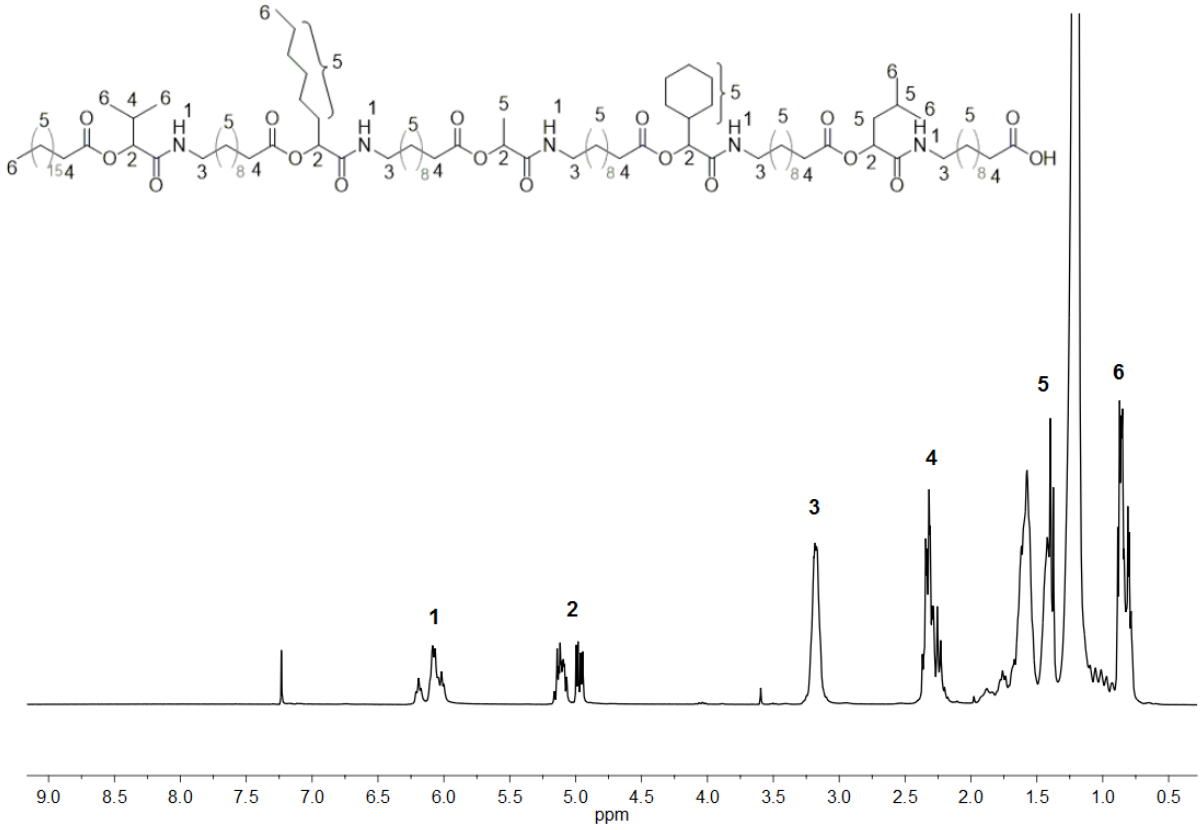
^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 6.30 – 5.91 (m, 5H, 5 NH, ^{1}), 5.22 – 4.91 (m, 5H, 5 CH, ^{2}), 3.35 – 3.05 (m, 10H, 5 CH_2, ^{3}), 2.48 – 2.15 (m, 13H, 6 CH_2, CH, ^{4}), 2.00 – 0.97 (m, 137H, CH_3, 66 CH_2, 2 CH, ^{5}), 0.93 – 0.71 (m, 18H, 6 CH_3, ^{6}).

^{13}C NMR (75 MHz, CDCl3) δ/ ppm: 177.3, 172.7, 172.7, 172.7, 172.6, 172.4, 170.5, 170.4, 170.0, 169.5, 169.2, 77.9, 73.9, 72.6, 70.4, 40.9, 40.0, 39.3, 39.2, 34.3, 34.1, 32.0, 31.7, 30.5, 29.7, 29.7, 29.6, 29.6, 29.6, 29.5, 29.4, 29.3, 29.3, 29.2, 29.2, 29.1, 29.1, 28.9, 27.4, 26.9, 26.9, 26.8, 26.1, 26.0, 25.9, 25.1, 25.0, 25.0, 24.9, 24.9, 24.8, 24.6, 23.2, 22.7, 22.6, 21.8, 18.8, 18.0, 17.0, 14.2, 14.1.

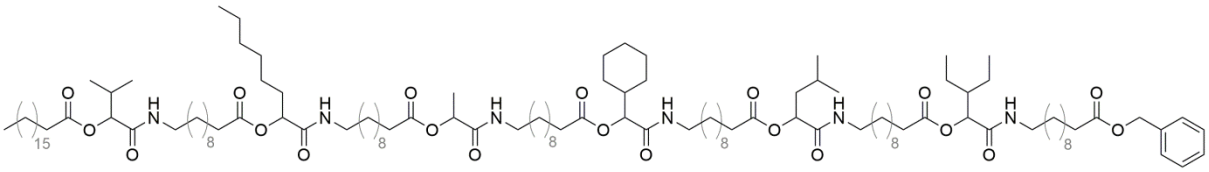
FAB-MS of $[C_{103}H_{190}N_5O_{17}]^+$: calculated: 1770.4, found: 1770.1.

ESI-MS of $[C_{103}H_{189}N_5O_{17}Na]^+$: calculated: 1791.3971, found: 1791.4048.

IR (ATR platinum diamond): ν [cm^{-1}] =.3305.0, 2921.6, 2851.5, 1739.7, 1651.8, 1536.2, 1462.7, 1368.9, 1231.5, 1159.1, 1100.7, 720.4, 651.6, 397.0.



6th Passerini reaction:


61

3.39 g **60** (1.92 mmol, 1.00 eq.) were dissolved in 3.00 mL DCM (0.64 M) and 0.32 g 2-ethylbutyraldehyde **50f** (3.20 mmol, 1.67 eq.) and 0.87 g of monomer **49** (2.89 mmol, 1.50 eq.) were added. The mixture was stirred at room temperature for 42 hours and subsequently the solvent was removed under reduced pressure. The crude product was purified by column chromatography (hexane/ethyl acetate 4:1 → 1:1) to afford product **61** as viscous oil in a yield of 93 % (3.86 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 7.39 – 7.27 (m, 5H, 5 CH aromatic, [1]), 6.11 (m, 6H, 6 NH, [2]), 5.29 – 4.87 (m, 8H, 1 CH_2, 6 CH, [3]), 3.25 (m, 12H, 6 CH_2, [4]), 2.55 – 2.11 (m, 15H, 7 CH_2, CH, [5]), 2.05 – 0.99 (m, 158H, CH_3, 76 CH_2, 3 CH, [6]), 0.95 – 0.66 (m, 24 H, 8 CH_3, [7]).

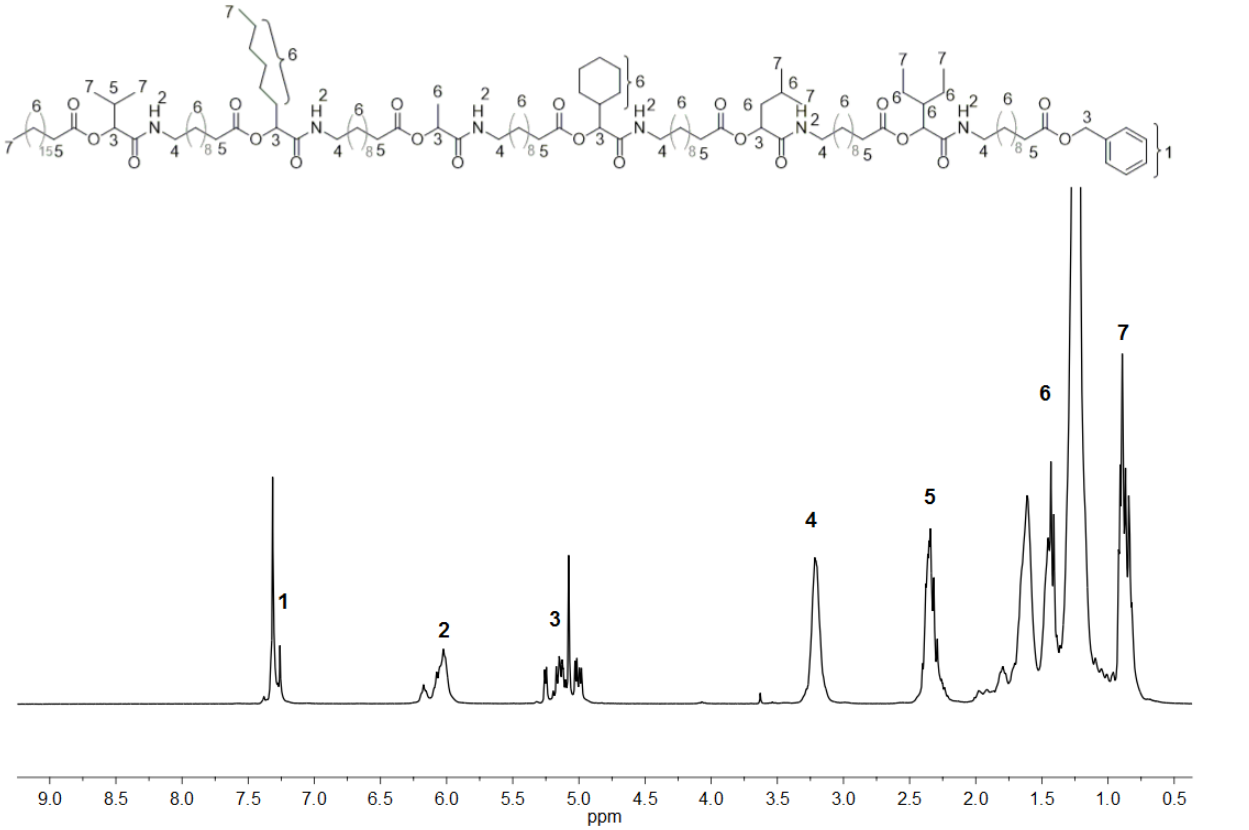
^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 173.7, 172.7, 172.6, 172.5, 172.4, 170.4, 170.3, 169.9, 169.8, 169.4, 169.3, 136.2, 128.6, 128.2, 77.9, 75.0, 74.0, 72.7, 70.5, 66.1, 43.5, 40.9, 40.0, 39.3, 39.2, 34.3, 32.0, 31.7, 30.6, 29.7, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.0, 27.4, 26.9, 26.9, 26.1, 26.0, 25.9, 25.1, 25.0, 24.9, 24.8, 24.6, 23.2, 22.7, 22.6, 22.23, 21.9, 21.8, 18.9, 18.0, 17.0, 14.2, 14.1, 11.7, 11.6.

FAB-MS of $[C_{128}H_{228}N_6O_{20}]^+$: calculated: 2170.7, found: 2170.8.

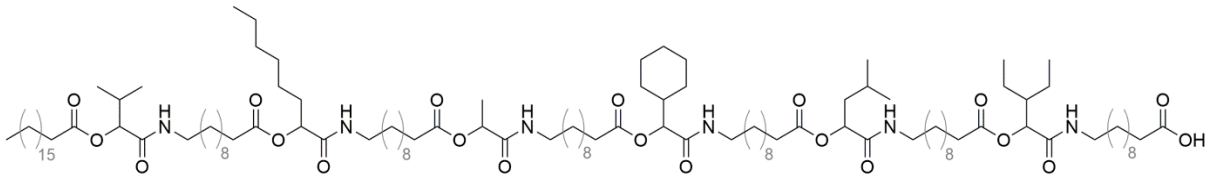
ESI-MS of $[C_{128}H_{228}N_6O_{20}Na]^+$: calculated: 2192.6901, found: 2192.6970.

IR (ATR platinum diamond): ν [cm^{-1}] = 3294.2, 2921.8, 2851.7, 1739.1, 1651.8, 1534.1, 1457.3, 1369.1, 1232.9, 1158.4, 1104.5, 721.1, 696.6, 653.4, 390.6.

***R*$_f$:** (hexane/ethyl acetate (1:1)) = 0.45.



6th Deprotection:



62

3.64 g **61** (1.68 mmol, 1.00 eq.) were dissolved in a 2:1 mixture of ethyl acetate and methanol (0.33 M) and 0.30 g (8.20 wt%) palladium on activated charcoal were added. Subsequently, the mixture was purged with hydrogen (balloon) and stirred under hydrogen atmosphere overnight. The heterogeneous catalyst was filtered off and the solvent was evaporated under reduced pressure. The product **62** was obtained as viscous oil in a yield of 99 % (3.46 g) and was used without further purification.

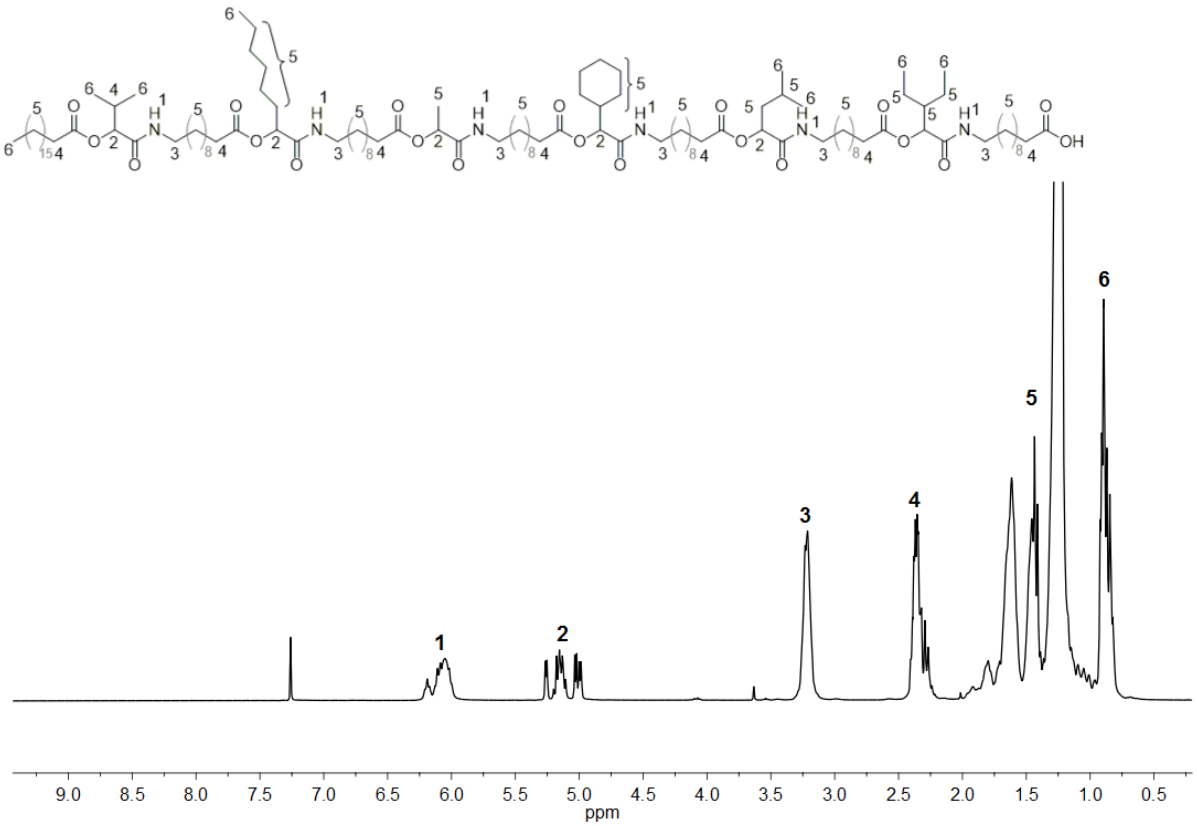
^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 6.26 – 5.86 (m, 6H, 6 NH, ^{1}), 5.35 – 4.89 (m, 6H, 6 CH, ^{2}), 3.22 (m, 12H, 6 CH_2, ^{3}), 2.48 – 2.19 (m, 15H, 7 CH_2, CH, ^{4}), 1.98 – 1.00 (m, 158 H, CH_3, 76 CH_2, 3 CH, ^{5}), 0.96 – 0.72 (m, 24H, 8 CH_3, ^{6}).

^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 177.0, 172.8, 172.7, 172.6, 172.4, 170.5, 170.5, 170.0, 169.9, 169.4, 169.4, 78.0, 75.1, 74.0, 72.7, 70.5, 43.5, 40.9, 40.0, 39.3, 39.3, 39.2, 34.4, 34.3, 34.0, 32.0, 31.7, 30.6, 29.8, 29.7, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 29.3, 29.3, 29.2, 29.1, 29.0, 27.4, 26.9, 26.1, 26.1, 26.0, 25.1, 25.1, 25.0, 24.9, 24.9, 24.8, 24.6, 23.2, 22.8, 22.6, 22.3, 22.0, 21.9, 18.9, 18.0, 17.0, 14.2, 14.1, 11.7, 11.6.

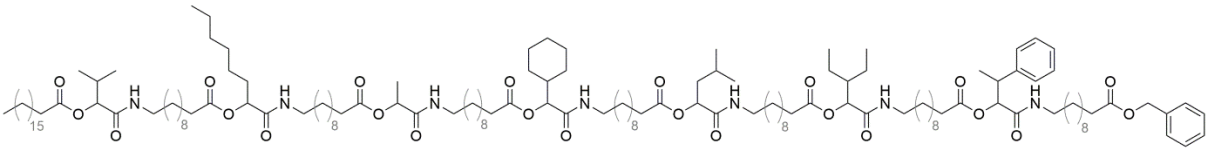
FAB-MS of $[C_{121}H_{222}N_6O_{20}]^+$: calculated: 2079.7, found: 2079.9.

ESI-MS of $[C_{121}H_{222}N_6O_{20}Na]^+$: calculated: 2102.6431, found: 2102.6492.

IR (ATR platinum diamond): ν [cm^{-1}] = 3304.2, 2921.9, 2851.8, 1740.2, 1651.7, 1535.8, 1462.6, 1369.4, 1231.2, 1159.4, 1108.8, 720.9, 398.8.



7th Passerini reaction:


63

3.29 g **62** (1.58 mmol, 1.00 eq.) were dissolved in 2.50 mL DCM (0.63 M) and 0.34 g 2-phenylpropionaldehyde **50g** (2.55 mmol, 1.62 eq.) and 0.74 g of monomer **49** (2.44 mmol, 1.55 eq.) were added. The mixture was stirred at room temperature for 38 hours and subsequently the solvent was removed under reduced pressure. The crude product was purified by column chromatography (hexane/ethyl acetate 4:1 → 1:1) to afford product **63** as viscous oil in a yield of 93 % (3.70 g).

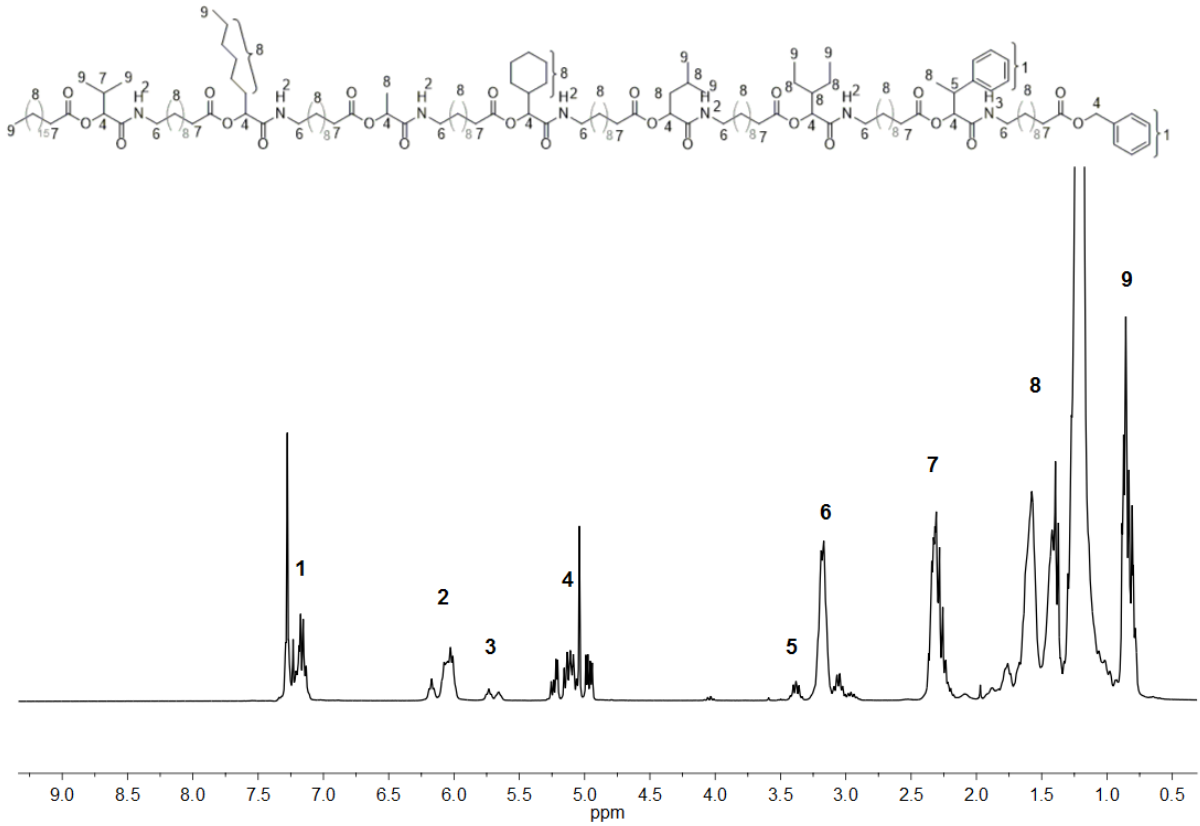
^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 7.38 – 7.10 (m, 10H, 10 CH aromatic, [1]), 6.30 – 5.92 (m, 6H, 6 NH, [2]), 5.74 (m, 1H, NH, [3]), 5.34 – 4.92 (m, 9H, CH_2, 7 CH, [4]), 3.49 – 2.89 (m, 15H, 7 CH_2, CH, [5]), 2.48 – 2.17 (m, 17H, 8 CH_2, CH, [6]), 1.96 – 0.97 (m, 177H, 2 CH_3, 84 CH_2, 3 CH, [8]), 0.96 – 0.68 (m, 24H, 8 CH_3, [9]).

^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 173.7, 172.7, 172.6, 172.5, 172.5, 172.3, 170.4, 170.3, 169.9, 169.8, 169.3, 169.2, 168.8, 168.5, 157.0, 141.7, 141.1, 136.2, 128.5, 128.4, 128.2, 128.2, 127.9, 127.0, 126.9, 77.9, 75.0, 73.9, 72.6, 70.4, 66.1, 43.5, 41.5, 41.2, 40.9, 40.0, 39.2, 39.2, 39.2, 34.3, 34.3, 34.2, 31.9, 31.6, 30.5, 29.7, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 29.1, 29.0, 28.9, 27.4, 26.9, 26.8, 26.8, 26.7, 26.1, 26.0, 25.9, 25.1, 25.0, 25.0, 24.9, 24.8, 24.8, 24.6, 23.2, 22.7, 22.5, 22.3, 21.9, 21.8, 18.8, 18.0, 17.6, 17.0, 15.2, 14.1, 14.1, 11.6, 11.6.

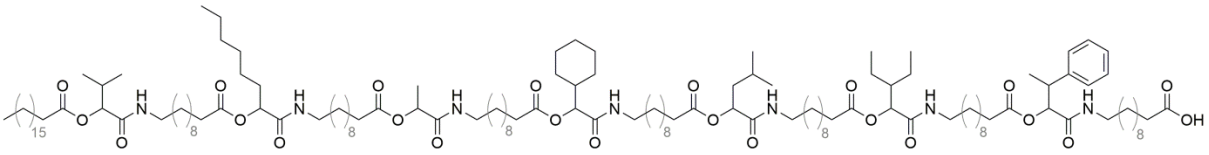
ESI-MS of $[C_{149}H_{259}N_7O_{23}Na]^+$: calculated: 2537.9205, found: 2537.9294.

IR (ATR platinum diamond): ν [cm^{-1}] = 3305.0, 2922.1, 2851.8, 1739.0, 1652.0, 1534.8, 1455.1, 1369.9, 1232.2, 1158.1, 1104.5, 721.4, 698.1.

***R*$_f$:** (hexane/ethyl acetate (1:1)) = 0.42.



7th Deprotection:



64

3.41 g **63** (1.35 mmol, 1.00 eq.) were dissolved in a 2:1 mixture of ethyl acetate and methanol (0.33 M) and 0.24 g (7.02 wt%) palladium on activated charcoal were added. Subsequently, the mixture was purged with hydrogen (balloon) and stirred under hydrogen atmosphere overnight. The heterogeneous catalyst was filtered off and the solvent was evaporated under reduced pressure. The product **64** was obtained as a viscous oil in a yield of 98 % (3.22 g) and was used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 7.33 – 7.13 (m, 5H, 5 H aromatic, ^{1}), 6.29 – 5.90 (m, 6H, 6 NH, ^{2}), 5.71 (m, 1H, NH, ^{3}), 5.38 – 4.93 (m, 7H, 7 CH, ^{4}), 3.45 (m, 1H, CH, ^{5}), 3.37

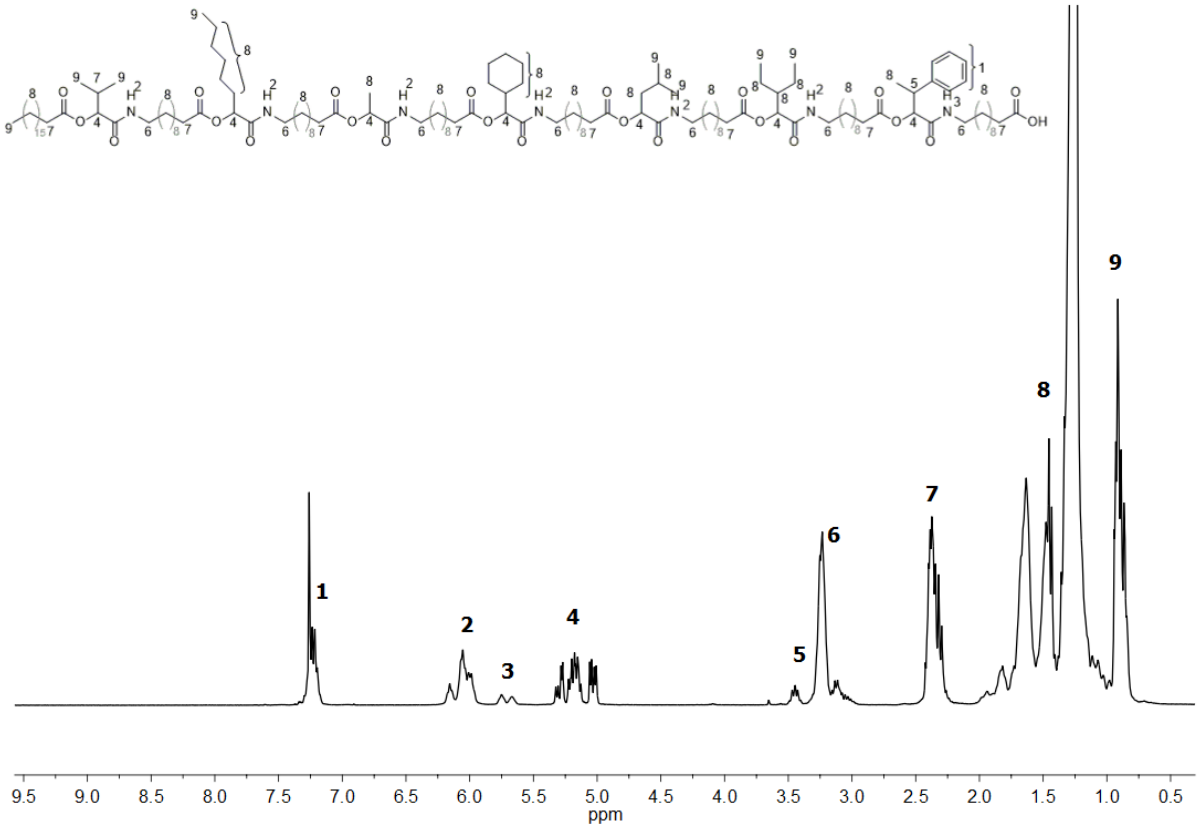
– 2.93 (m, 14H, 7 CH_2, ^{6}), 2.63 – 2.13 (m, 17H, 8 CH_2, CH, ^{7}), 2.04 – 1.00 (m, 177H, 2 CH_3, 84 CH_2, 3 CH, ^{8}), 0.98 – 0.63 (m, 24H, 8 CH_3, ^{9}).

^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 172.8, 172.7, 172.6, 172.5, 172.4, 170.5, 170.4, 170.0, 170.0, 169.5, 169.4, 168.9, 168.7, 128.5, 128.3, 128.0, 127.1, 127.0, 78.0, 75.2, 74.1, 72.8, 70.6, 43.6, 41.6, 41.3, 41.0, 40.1, 39.4, 39.3, 39.3, 34.4, 34.4, 34.3, 34.3, 34.0, 32.0, 31.7, 30.6, 29.8, 29.8, 29.7, 29.7, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.2, 29.2, 29.1, 29.0, 27.4, 27.0, 27.0, 26.2, 26.1, 26.0, 25.2, 25.1, 25.0, 25.0, 24.9, 24.8, 24.7, 23.3, 22.8, 22.7, 22.3, 22.0, 21.9, 18.9, 18.1, 17.1, 14.2, 14.2, 11.7, 11.7.

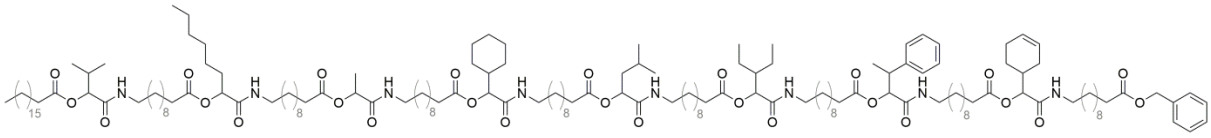
FAB-MS of $[C_{142}H_{253}N_7O_{23}]^+$: calculated: 2425.9, found: 2525.7.

ESI-MS of $[C_{142}H_{253}N_7O_{23}Na]^+$: calculated: 2447.8735, found: 2447.8809.

IR (ATR platinum diamond): ν [cm^{-1}] = 3304.4, 2922.0, 2851.7, 1740.0, 1651.6, 1536.1, 1462.4, 1370.0, 1232.3, 1160.1, 1106.9, 721.0, 699.6.



8th Passerini reaction:



65

3.12 g **64** (1.29 mmol, 1.00 eq.) were dissolved in 2.50 mL DCM (0.63 M) and 0.23 g 3-cyclohexene-1-carboxaldehyde **50h** (2.11 mmol, 1.64 eq.) and 0.58 g of monomer **49** (1.94 mmol, 1.50 eq.) were added. The mixture was stirred at room temperature for 40 hours and subsequently the solvent was removed under reduced pressure. The crude product was purified by column chromatography (hexane/ethyl acetate 4:1 → 1:2) to afford product **65** as viscous oil in a yield of 94 % (3.46 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 7.39 – 7.09 (m, 10H, 10 H aromatic, [1]), 6.10 (m, 7H, 7 NH, [2]), 5.81 – 5.48 (m, 3H, 1 NH, 2 CH, [3]), 5.35 – 4.88 (m, 10H, CH_2, 8 CH, [4]), 3.49 – 3.35 (m, 1H, CH, [5]), 3.34 – 2.90 (m, 16H, 8 CH_2, [6]), 2.49 – 2.12 (m, 19H, 9 CH_2, CH, [7]), 2.11 – 0.96 (m, 200H, 2 CH_3, 95 CH_2, 4 CH, [8]), 0.94 – 0.63 (m, 24H, 8 CH_3, [9]).

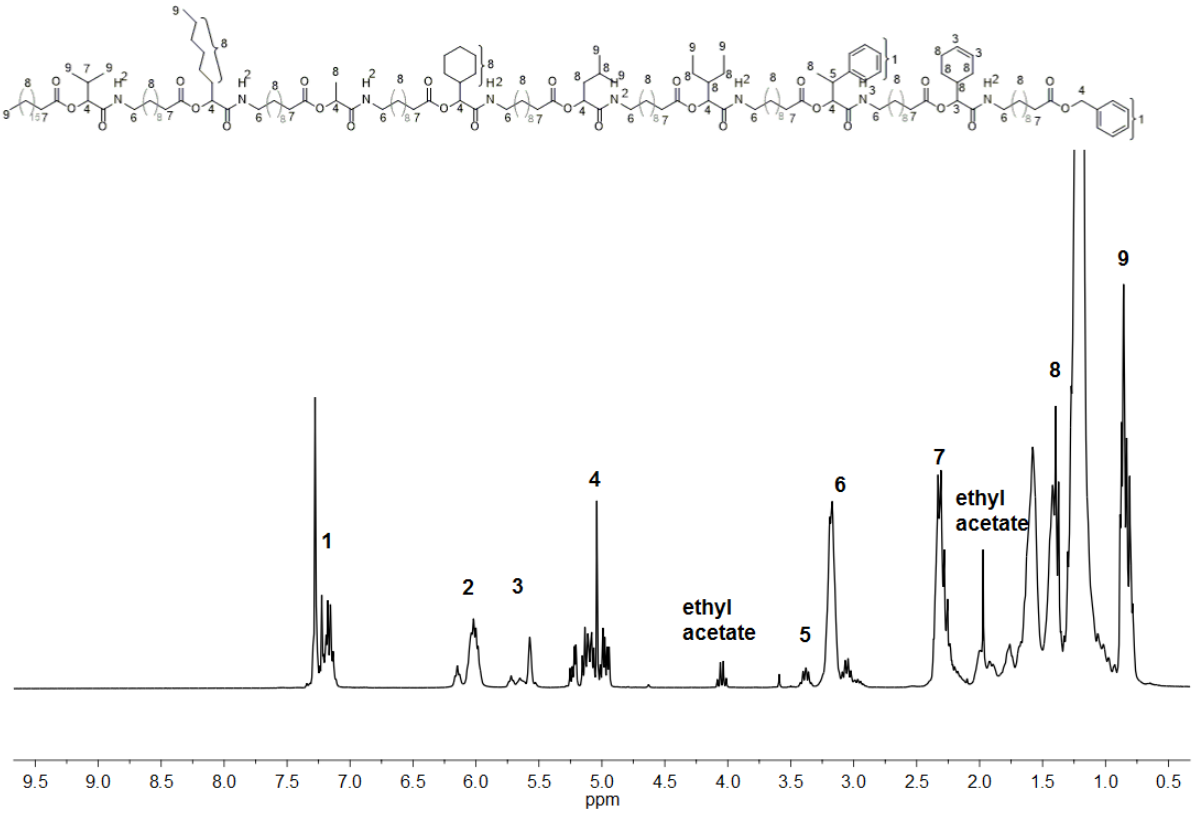
^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 173.7, 172.8, 172.7, 172.6, 172.6, 172.5, 172.4, 172.3, 170.4, 170.3, 169.9, 169.8, 169.3, 169.3, 169.1, 169.0, 168.8, 168.6, 141.7, 141.2, 136.2, 128.6, 128.4, 128.2, 128.2, 127.9, 127.0, 127.0, 126.8, 125.6, 77.9, 75.0, 74.0, 72.7, 70.5, 66.1, 60.4, 43.5, 41.5, 41.2, 40.9, 40.0, 39.3, 39.2, 36.2, 36.0, 34.4, 34.3, 34.2, 32.0, 31.7, 30.6, 29.7, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 29.2, 29.2, 29.1, 29.1, 29.1, 29.0, 27.7, 27.4, 26.9, 26.9, 26.1, 26.0, 26.0, 25.2, 25.1, 25.0, 25.0, 24.9, 24.8, 24.6, 23.6, 23.2, 22.7, 22.6, 22.3, 22.0, 21.8, 18.8, 18.0, 17.6, 17.0, 15.2, 14.3, 14.2, 14.1, 11.7, 11.6.

FAB-MS of $[C_{168}H_{290}N_8O_{26}]^+$: calculated: 2837.2, found: 2837.4.

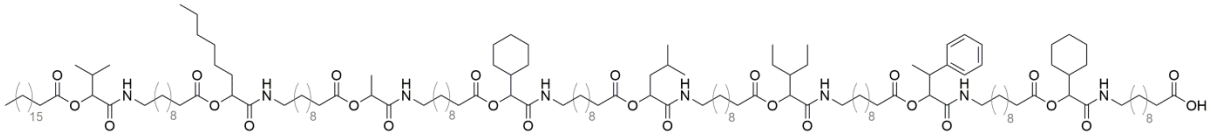
ESI-MS of $[C_{168}H_{290}N_8O_{26}Na]^+$: calculated: 2859.1509, found: 2859.1558.

IR (ATR platinum diamond): ν [cm^{-1}] =3305.2, 2922.3, 2851.8, 1739.1, 1652.0, 1534.4, 1455.8, 1370.1, 1233.8, 1158.1, 1106.2, 721.5, 698.3.

***R*$_f$:** (hexane/ethyl acetate (1:1.5)) = 0.64.



8th Deprotection:



66

3.27 g **65** (1.15 mmol, 1.00 eq.) were dissolved in a 2:1 mixture of ethyl acetate and methanol (0.32 M) and 0.28 g (8.51 wt%) palladium on activated charcoal were added. Subsequently, the mixture was purged with hydrogen (balloon) and stirred under hydrogen atmosphere overnight. The heterogeneous catalyst was filtered off and the solvent was evaporated under reduced pressure. The product **66** was obtained as a viscous oil in a yield of 98 % (3.08 g) and was used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 7.31 – 7.08 (m, 5H, 5 H aromatic, ^{1}), 6.29 – 5.92 (m, 7H, 7 NH, ^{2}), 5.79 (m, 1H, NH, ^{3}), 5.34 – 4.92 (m, 8H, 8 CH, ^{4}), 3.48 – 3.36 (m, 1H, CH,

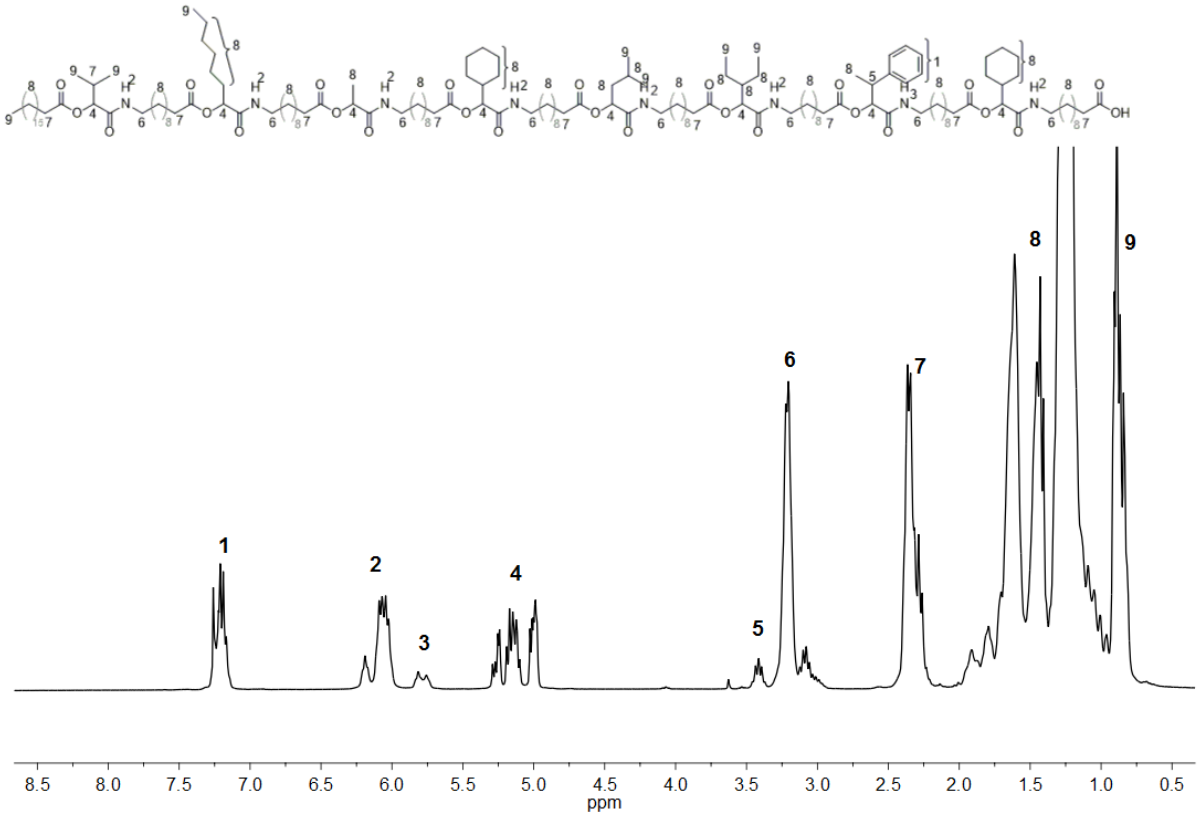
[5]), 3.34 – 2.89 (m, 16H, 8 CH_2, [6]), 2.29 (m, 19H, 9 CH_2, CH, [7]), 2.04 – 0.94 (m, 204H, 2 CH_3, 97 CH_2, 4 CH, [8]), 0.86 (m, 24H, 8 CH_3, [9]).

^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 176.7, 172.7, 172.7, 172.6, 172.6, 172.5, 172.4, 170.5, 170.4, 170.0, 169.9, 169.4, 169.4, 168.9, 168.7, 141.6, 141.2, 128.4, 128.2, 127.9, 127.0, 127.0, 78.0, 77.7, 75.1, 74.0, 72.7, 70.5, 43.5, 41.5, 41.2, 40.9, 40.0, 39.3, 39.2, 34.4, 34.3, 34.0, 32.0, 31.7, 30.6, 29.7, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 29.3, 29.2, 29.1, 29.0, 27.4, 26.9, 26.9, 26.8, 26.7, 26.1, 26.1, 25.9, 25.1, 25.1, 25.0, 25.0, 24.9, 24.8, 24.8, 24.6, 23.2, 22.7, 22.6, 22.3, 22.0, 21.9, 18.8, 18.0, 17.6, 17.0, 15.3, 14.2, 14.1, 11.7, 11.6.

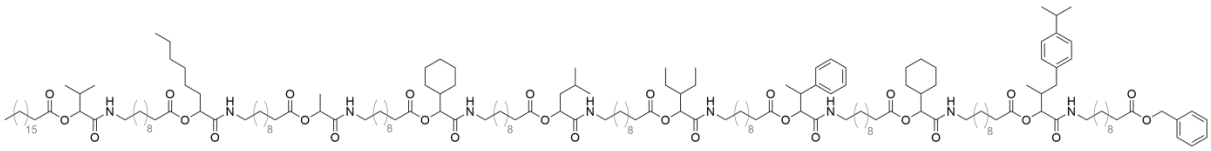
FAB-MS of $[C_{161}H_{286}N_8O_{26}]^+$: calculated: 2748.1, found: 2748.2.

ESI-MS of $[C_{161}H_{286}N_8O_{26}Na]^+$: calculated: 2771.1196, found: 2771.1306.

IR (ATR platinum diamond): ν [cm^{-1}] = 3305.7, 2921.8, 2851.7, 1740.2, 1651.5, 1536.0, 1462.6, 1369.9, 1230.7, 1160.0, 1103.4, 720.9, 699.6, 430.5, 398.5.



9th Passerini reaction:



67

2.63 g **66** (0.96 mmol, 1.00 eq.) were dissolved in 1.50 mL DCM (0.64 M) and 0.28 g 2-methyl-3-(p-isopropylphenylpropionaldehyde **50i** (1.48 mmol, 1.54 eq.) and 0.44 g of monomer **49** (1.46 mmol, 1.52 eq.) were added. The mixture was stirred at room temperature for 20 hours and subsequently the solvent was removed under reduced pressure. The crude product was purified by column chromatography (hexane/ethyl acetate 4:1 → 1:2) to afford product **67** as viscous oil in a yield of 95 % (2.97 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 7.34 – 6.87 (m, 14H, 14 H aromatic, [1]), 6.04 - 6.24 (m, 8H, 8 NH, [2]), 5.66 - 5.72 (m, 1H, NH, [3]), 5.29 – 4.84 (m, 11H, CH_2, 9 CH [4]), 3.43 – 3.29 (m, 1H, CH, [5]), 3.27 – 2.87 (m, 18H, CH_2, [6]), 2.85 – 2.55 (m, 2H, 2 CH, [7]), 2.46 – 2.11 (m, 23H, 11 CH_2, CH, [8]), 2.03 – 0.90 (m, 226H, 4 CH_3, 105 CH_2, 4 CH, [9]), 0.90 – 0.50 (m, 27H, 9 CH_3, [10]).

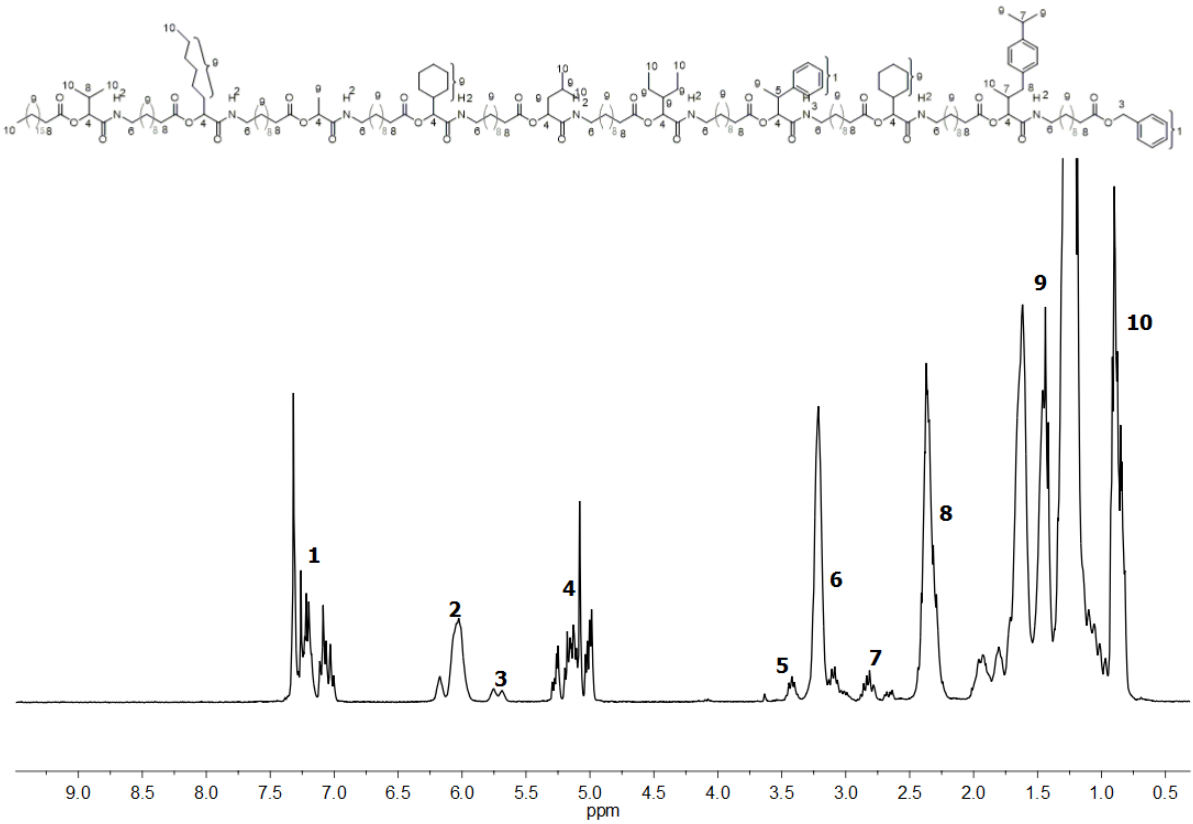
^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 173.7, 172.7, 172.6, 172.6, 172.6, 172.4, 172.4, 170.4, 170.3, 169.9, 169.8, 169.4, 169.3, 169.0, 168.8, 168.6, 146.7, 146.6, 141.6, 137.1, 137.0, 136.2, 129.2, 129.1, 128.7, 128.4, 128.4, 128.1, 77.8, 75.0, 74.0, 72.6, 71.0, 70.6, 66.1, 43.5, 40.0, 39.3, 39.2, 34.5, 34.4, 34.2, 32.0, 29.7, 29.6, 29.6, 29.4, 29.3, 29.2, 27.4, 26.9, 26.1, 26.0, 25.0, 24.5, 22.7, 22.6, 22.6, 18.8, 18.0, 15.3, 14.2, 14.1, 11.7, 11.6.

FAB-MS of $[C_{193}H_{332}N_9O_{29}]^+$: calculated: 3242.5, found: 3242.6.

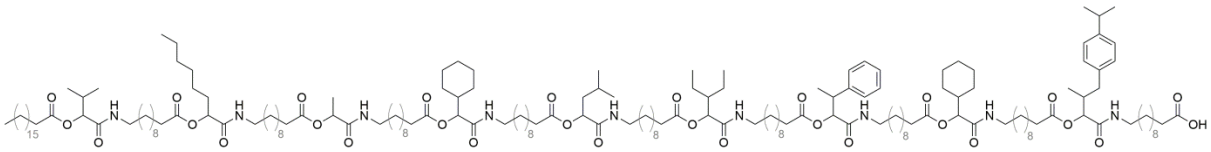
ESI-MS of $[C_{193}H_{331}N_9O_{29}Na]^+$: calculated: 3262.4595, found: 3262.4719.

IR (ATR platinum diamond): ν [cm^{-1}] = 3305.4, 2922.3, 2851.8, 1739.1, 1651.7, 1534.7, 1455.3, 1370.7, 1236.1, 1159.1, 1102.7, 721.5, 698.5.

***R*$_f$:** (hexane/ethyl acetate (1:1.5)) = 0.68.



9th Deprotection:



68

2.76 g **67** (0.85 mmol, 1.00 eq.) were dissolved in a 2:1 mixture of ethyl acetate and methanol (0.28 M) and 0.20 g (7.88 %w) palladium on activated charcoal were added. Subsequently, the mixture was purged with hydrogen (balloon) and stirred under hydrogen atmosphere overnight. The heterogeneous catalyst was filtered off and the solvent was evaporated under reduced pressure. The product **68** was obtained as viscous oil in a yield of 94 % (2.52 g) and was used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 7.36 – 6.92 (m, 9H, 9H aromatic, ^{1}), 6.34 – 5.93 (m, 8H, 8 NH, ^{2}), 5.77 - 5.68 (m, 1H, NH, ^{3}), 5.13 - 5.02 (m, 9H, 9 CH, ^{4}), 3.42 - 3.45 (m, 1H,

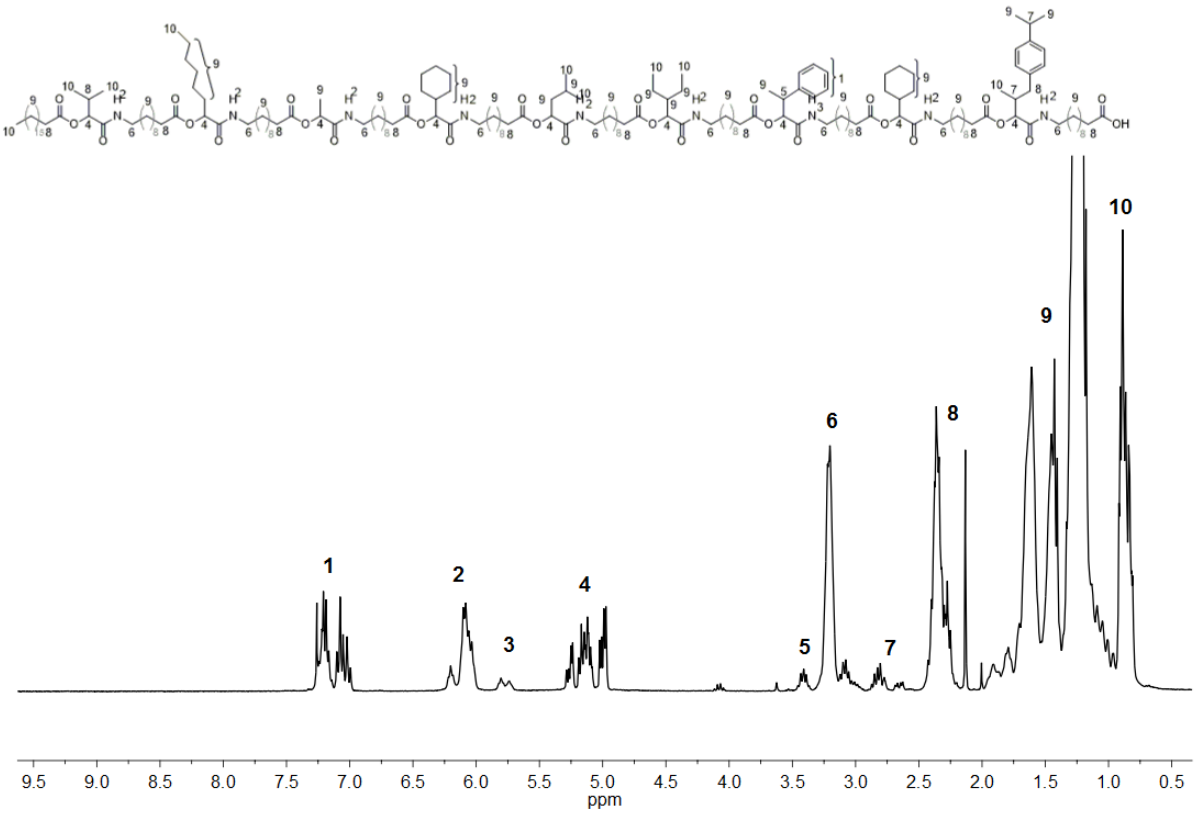
CH, [5]), 3.32 – 2.93 (m, 18H, 9 CH_2, [6]), 2.91 – 2.55 (m, 2H, 2 CH, [7]), 2.50 – 2.17 (m, 21H, 10 CH_2, CH, [8]), 1.98 – 0.97 (m, 228H, 4 CH_3, 106 CH_2, 4 CH, [9]), 0.86 - 0.75 (m, 27H, 9 CH_3, [10]).

^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 176.6, 172.7, 172.6, 172.6, 172.5, 172.5, 172.4, 172.3, 170.4, 170.3, 169.9, 169.8, 169.4, 169.3, 169.3, 169.1, 168.8, 168.6, 146.6, 146.5, 141.5, 141.1, 137.0, 136.9, 129.0, 128.9, 128.5, 128.3, 128.2, 126.4, 126.3, 77.7, 75.0, 74.9, 72.5, 70.4, 70.3, 43.4, 40.8, 40.8, 39.9, 39.4, 39.2, 39.2, 39.1, 38.9, 34.4, 34.3, 34.2, 34.2, 34.0, 33.6, 31.9, 30.5, 30.4, 29.6, 29.6, 29.5, 29.4, 29.3, 29.2, 28.9, 27.4, 27.3, 27.3, 26.8, 26.1, 26.0, 26.0, 25.8, 25.8, 25.0, 24.9, 24.8, 24.8, 24.7, 24.5, 24.1, 24.0, 22.7, 22.5, 18.0, 17.8, 16.9, 13.9, 11.5, 11.2.

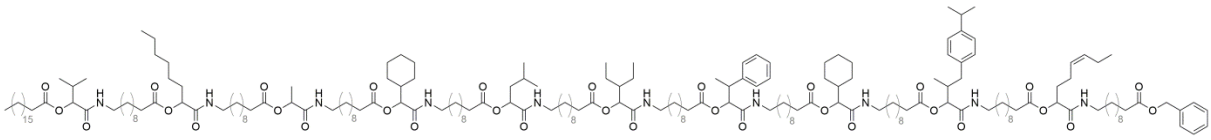
FAB-MS of $[C_{186}H_{325}N_9O_{29}]^+$: calculated: 3152.4, found: 3152.5.

ESI-MS of $[C_{186}H_{325}N_9O_{29}Na]^+$: calculated: 3172.4125, found: 3172.4177.

IR (ATR platinum diamond): ν [cm^{-1}] = 3303.0, 2922.2, 2851.8, 1739.8, 1651.1, 1535.5, 1461.2, 1370.3, 1231.3, 1159.5, 1103.1, 1018.3, 720.9, 699.7.



10th Passerini reaction:



69

2.25 g **68** (0.71 mmol, 1.00 eq.) were dissolved in 1.20 mL DCM (0.59 M) and 0.13 g *cis*-4-heptenal **50j** (1.15 mmol, 1.61 eq.) and 0.35 g of monomer **49** (1.15 mmol, 1.61 eq.) were added. The mixture was stirred at room temperature for 48 hours and subsequently the solvent was removed under reduced pressure. The crude product was purified by column chromatography (hexane/ethyl acetate 4:1 → 1:1.5) to afford product **69** as viscous oil in a yield of 95 % (2.40 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 7.36 – 6.87 (m, 14H, 14 H aromatic, [1]), 6.31 – 5.90 (m, 9H, 9 NH, [2]), 5.85 – 5.66 (m, 1H, NH, [3]), 5.44 – 4.86 (m, 14H, CH_2, 12 CH, [4]), 3.48 – 3.34 (m, 1H, CH, [5]), 3.33 – 2.90 (m, 20H, 10 CH_2, [6]), 2.90 – 2.59 (m, 2H, 2 CH, [7]), 2.49 – 2.17 (m, 23H, 11 CH_2, CH, [8]), 2.14 – 0.95 (m, 250H, 4 CH_3, 117 CH_2, 4 CH, [9]), 0.95 – 0.59 (m, 30H, 10 CH_3, [10]).

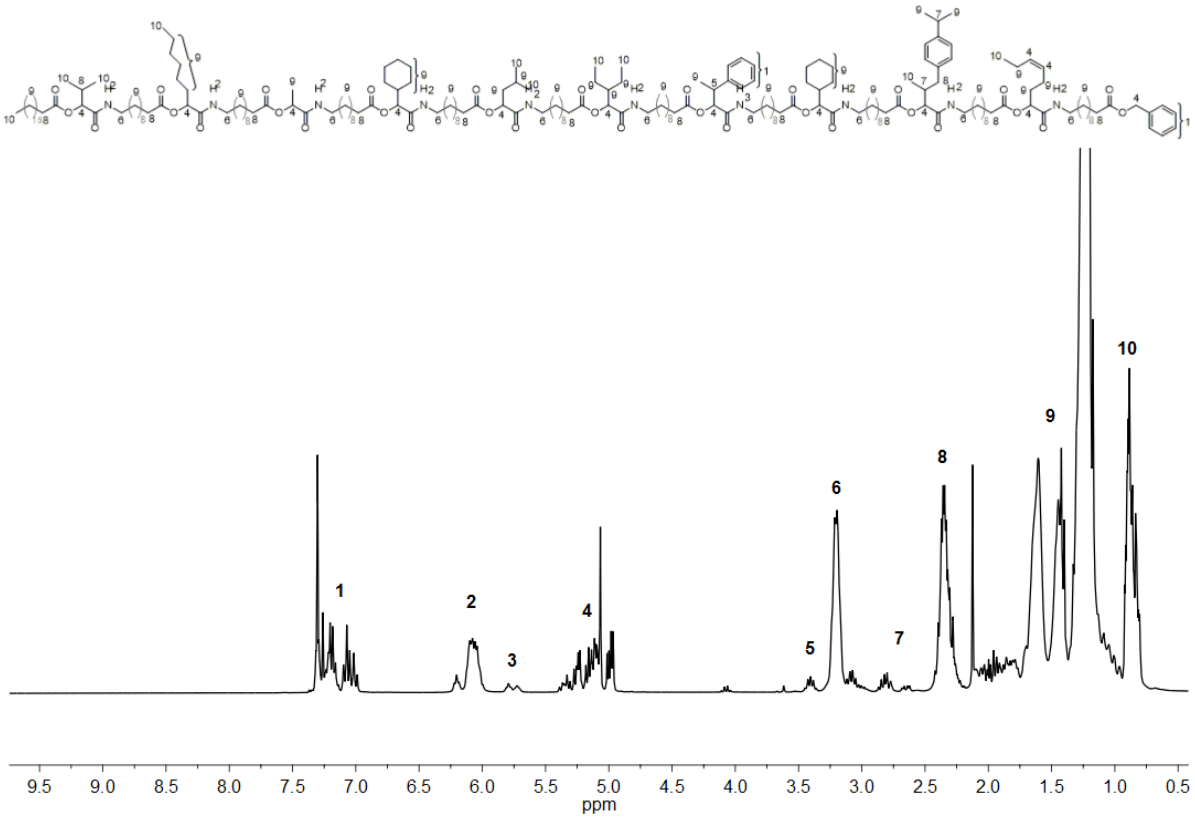
^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 173.7, 172.7, 172.6, 172.5, 172.5, 172.4, 172.3, 170.4, 170.3, 169.9, 169.8, 169.7, 169.4, 169.3, 169.3, 169.0, 168.8, 168.6, 146.7, 146.6, 141.7, 141.2, 137.1, 136.9, 136.2, 132.9, 129.1, 129.0, 128.5, 128.4, 128.2, 128.2, 128.1, 127.9, 127.2, 127.0, 126.9, 126.4, 126.3, 77.9, 76.3, 75.0, 73.9, 73.5, 72.7, 70.4, 66.1, 43.5, 41.5, 41.2, 40.9, 40.0, 39.2, 39.2, 37.6, 37.5, 37.3, 34.3, 34.3, 34.2, 33.7, 31.9, 31.6, 30.9, 30.5, 29.7, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 29.1, 28.9, 27.4, 26.9, 26.8, 26.8, 26.7, 26.1, 26.0, 25.9, 25.1, 25.0, 25.0, 24.9, 24.8, 24.8, 24.6, 24.1, 23.1, 22.7, 22.6, 22.5, 22.3, 21.9, 21.8, 20.5, 18.8, 18.0, 17.6, 17.0, 15.5, 15.2, 14.3, 14.1, 14.1, 11.6, 11.6.

FAB-MS of $[C_{212}H_{364}N_{10}O_{32}]^{+}$: calculated: 3564.7, found: 3564.7.

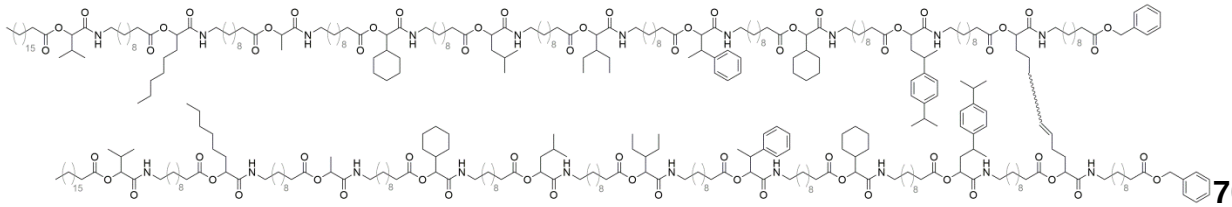
ESI-MS of $[C_{212}H_{364}N_{10}O_{32}Na_2]^{2+}$: calculated: 1804.3474, found: 1804.3574.

IR (ATR platinum diamond): ν [cm^{-1}] = 3292.6, 2922.5, 2851.8, 1739.4, 1651.8, 1534.8, 1455.2, 1370.4, 1231.7, 1158.9, 1102.7, 698.3.

***R*f:** (hexane/ethyl acetate (1:1.2)) = 0.64.



Self-metathesis of the decamer:



70

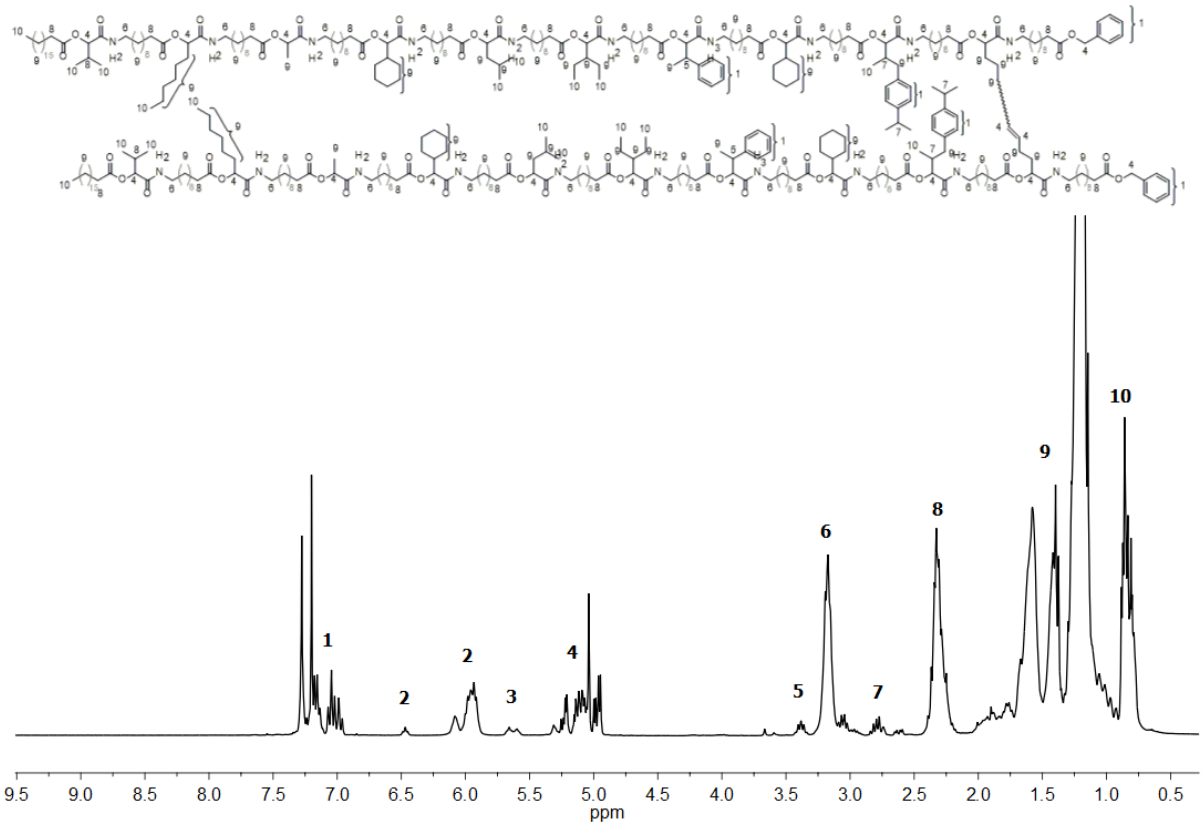
0.41 g **69** (0.11 mmol, 1.00 eq.) were dissolved in 2.0 mL DCM (0.06 M), and subsequently, 14.2 mg *p*-benzoquinone (0.13 mmol, 1.19 eq.) and 14.1 mg Hoveyda-Grubbs 2nd generation catalyst (0.02 mmol, 19.7 mol%) were added and the reaction mixture was refluxed at 40 ° C for 5 hours under an argon atmosphere. This mixture was filtered over silica, redissolved in 2.0 mL DMC (0.06 M), and again, 16.3 mg benzoquinone (0.15 mmol, 1.36 eq.) and 12.8 mg Hoveyda-Grubbs 2nd generation

catalyst (0.02 mmol, 18.2 mol%) were added and the reaction mixture was refluxed for another 5 hours. The product was then isolated by column chromatography (hexane/ethyl acetate 4:1 → 1:3) to afford the sequence-defined 20-mer **70** as a viscous oil in a yield of 48 % (0.18 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 7.41 – 6.98 (m, 28H, 28 H aromatic, [1]), 6.53 (t, J = 5.6 Hz, 1H, NH, [2]), 6.25 – 5.86 (m, 19H, 19 NH, [2]), 5.78 - 5.60 (m, 2H, 2 CH, [3]), 5.42 – 4.93 (m, 26H, 2 CH_2, 22 CH, [4]), 3.52 - 3.38 (m, 2H, 2 CH, [5]), 3.36 – 2.95 (m, 40H, 20 CH_2, [6]), 2.94 – 2.63 (m, 4H, 4 CH [7]), 2.52 – 2.19 (m, 46H, 22 CH_2, 2 CH), 2.14 – 0.99 (m, 494H, 8 CH_3, 231 CH_2, 8 CH, [9]), 0.95 – 0.57 (m, 54H, 27 CH_3, [10]).

ESI-MS of $[C_{418}H_{716}N_{20}O_{64}Na_2]^{2+}$: calculated: 3543.6586, found: 3543.6765.

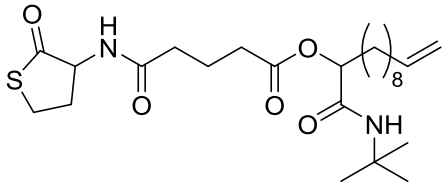
***R*$_f$:** (hexane / ethyl acetate (1:1.2)) =0.24.



6.3.4 Experimental Procedures Chapter 4.3

Synthesis of the Isocyanide Building Blocks

1st P-3CR of the 1st building block:



76

0.51 g of thiolactone carboxylic acid **71** (2.20 mmol, 1.00 eq.) were dissolved in 3.3 mL of a 4:1 mixture of THF and water (0.67 M). Subsequently, 0.56 g of 10-undecenal **2** (3.30 mmol, 1.50 eq.) and 0.26 g of *tert*-butyl isocyanide **3b** (3.13 mmol, 1.42 eq.) were added and the reaction mixture was stirred for 24 hours at room temperature. Then, 80 mL of ethyl acetate and 50 mL of water were added and the mixture was extracted. The organic layer was separated, washed with brine (50 mL) and dried over sodium sulfate. The solvent was evaporated and the residue was recrystallized from hexane/ethyl acetate 7:1. The product **76** was obtained as white solid in a yield of 93 % (0.99 g).

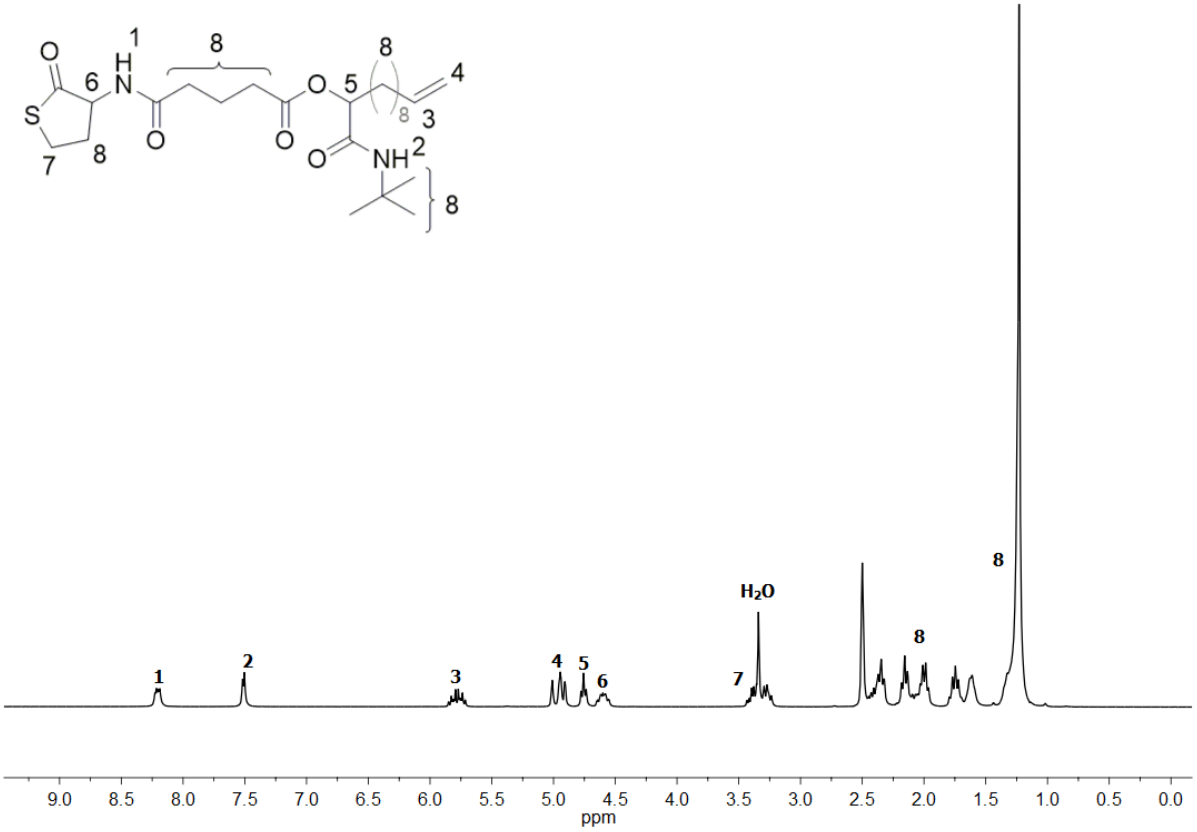
^{1}H NMR (300 MHz, DMSO-D_6) δ /ppm: 8.21 (dd, J = 8.1, 3.8 Hz, 1H, NH, [1]), 7.51 (d, J = 4.4 Hz, 1H, NH, [2]), 5.90 - 5.65 (m, 1H, CH, [3]), 5.07 – 4.84 (m, 2H, CH_2, [4]), 4.76 (t, J = 6.3 Hz, 1H, CH, [5]), 4.67 – 4.48 (m, 1H, CH, [6]), 3.49 – 3.16 (m, 2H, CH_2, [7]), 2.44 – 0.98 (m, 33H, 3 CH_3, 12 CH_2, [8]).

^{13}C NMR (75 MHz, DMSO-D_6) δ /ppm: 205.4, 172.1, 171.7, 168.7, 138.8, 114.6, 73.4, 58.1, 50.2, 34.1, 33.2, 32.6, 31.5, 30.1, 28.8, 28.7, 28.6, 28.5, 28.4, 28.3, 26.7, 24.5, 20.7.

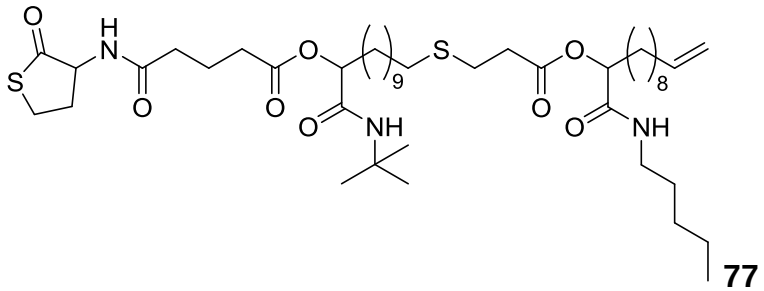
FAB-MS of $[C_{25}H_{43}N_2O_5S]^+$: calculated:483.2887, found: 483.2889.

ESI-MS of $[C_{25}H_{43}N_2O_5SNa]^+$: calculated: 505.2707, found: 505.2698.

IR (ATR platinum diamond): ν [cm^{-1}] = 3269.2, 3078.7, 2925.9, 2855.3, 1742.4, 1702.9, 1646.2, 1559.7, 1532.4, 1448.9, 1360.8, 1339.0, 1274.0, 1214.0, 1190.1, 1155.7, 1055.6, 1020.8, 915.1, 855.8, 679.9, 618.4, 537.0, 482.1, 432.2.



2nd P-3CR of the 1st building block:



77

2.01 g of **76** (4.16 mmol, 1.00 eq.) were dissolved in 8.0 mL stabilized THF (0.52 M). Subsequently, 0.53 g of 3-mercaptopropionic acid **4** (5.02 mmol, 1.21 eq.) and 18.4 mg of DMPA **5** (0.07 mmol, 1.72 mol%) were added and the reaction mixture was irradiated

with UV light at room temperature for one hour. The solvent was removed under reduced pressure and the residue was redissolved in 4.3 mL DCM (0.99 M). Subsequently, 1.27 g of 10-undecenal **2** (7.56 mmol, 1.82 eq.) and 0.74 g 1-pentyl isocyanide **3c** (7.60 mmol, 1.83 eq.) were added and the reaction mixture was stirred at room temperature for 28 hours. The solvent was evaporated and the crude product was purified by column chromatography (hexane/ethyl acetate 3:1→1:4). Product **77** was obtained as slightly yellow oil in a yield of 88 % (3.10 g).

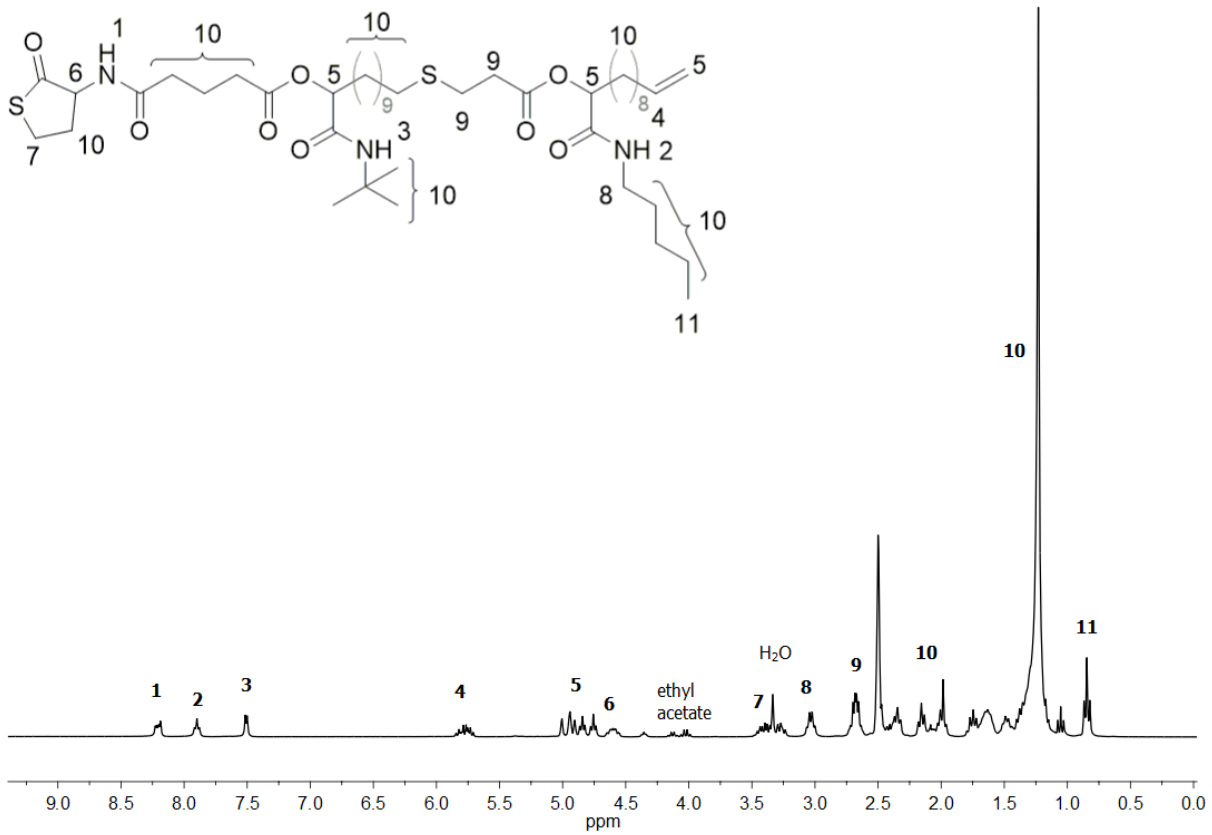
^{1}H NMR (300 MHz, DMSO-D_6) δ /ppm: 8.21 (dd, J = 8.3, 4.0 Hz, 1H, NH, ^{1}), 7.90 (t, J = 5.6 Hz, 1H, NH, ^{2}), 7.51 (d, J = 4.5 Hz, 1H, NH, ^{3}), 5.89 – 5.65 (m, 1H, CH, ^{4}), 5.07 – 4.70 (m, 4H, CH_2, 2 CH, ^{5}), 4.69 – 4.50 (m, 1H, CH, ^{6}), 3.50 – 3.15 (m, 2H, CH_2, ^{7}), 3.14 - 2.92 (m, 2H, CH_2, ^{8}), 2.80 – 2.60 (m, 4H, 2 CH_2, ^{9}), 2.43 – 1.08 (m, 59H, 3 CH_3, 25 CH_2, ^{10}), 0.85 (t, J = 6.8 Hz, 3H, CH_3, ^{11}).

^{13}C NMR (75 MHz, DMSO-D_6) δ /ppm: 205.4, 172.0, 171.7, 171.0, 168.9, 168.7, 138.8, 114.6, 73.4, 58.1, 50.2, 38.2, 34.4, 34.1, 33.2, 32.6, 31.6, 31.4, 31.0, 30.1, 29.1, 29.0, 28.9, 28.9, 28.7, 28.7, 28.6, 28.5, 28.4, 28.3, 28.2, 26.7, 26.3, 26.1, 24.5, 24.4, 21.8, 20.7, 13.9.

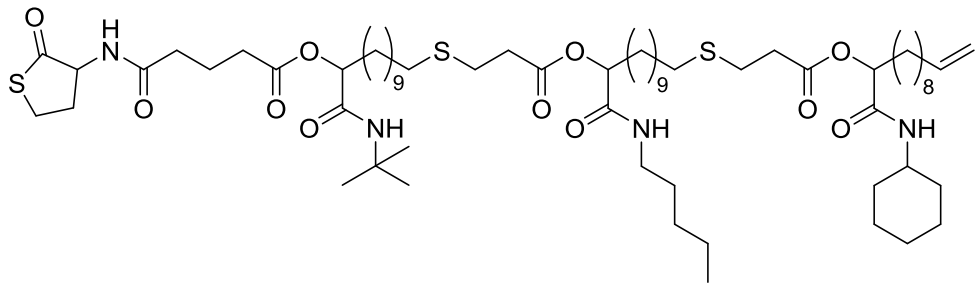
ESI-MS of $[C_{45}H_{79}N_3O_8S_2Na]^+$: calculated: 876.5201, found: 876.5211.

IR (ATR platinum diamond): ν [cm^{-1}] = 3291.8, 2923.2, 2852.6, 1737.3, 1711.0, 1651.8, 1534.8, 1453.4, 1363.2, 1223.0, 1149.0, 1052.9, 910.1, 847.2, 615.0, 533.6, 432.7.

***R_f*:** (hexane/ethyl acetate (1:1)) = 0.21.



3rd P-3CR of the 1st building block:



78

1.51 g of **77** (1.77 mmol, 1.00 eq.) were dissolved in 3.5 mL stabilized THF (0.51 M). Subsequently, 0.23 g of 3-mercaptopropionic acid **4** (2.18 mmol, 1.23 eq.) and 13.1 mg of DMPA **5** (0.05 mmol, 2.88 mol%) were added and the reaction mixture was irradiated with UV light at room temperature for one hour. The solvent was removed under reduced pressure and the residue was redissolved in 1.8 mL DCM (0.96 M). Subsequently, 0.55 g of 10-undecenal **2** (3.29 mmol, 1.91 eq.) and 0.34 g cyclohexyl

isocyanide **3a** (3.15 mmol, 1.83 eq.) were added and the reaction mixture was stirred at room temperature for 24 hours. The solvent was evaporated and the crude product was purified by column chromatography (hexane/ethyl acetate 3:1→ ethyl acetate). Product **77** was obtained as slightly yellow oil in a yield of 82 % (1.73 g).

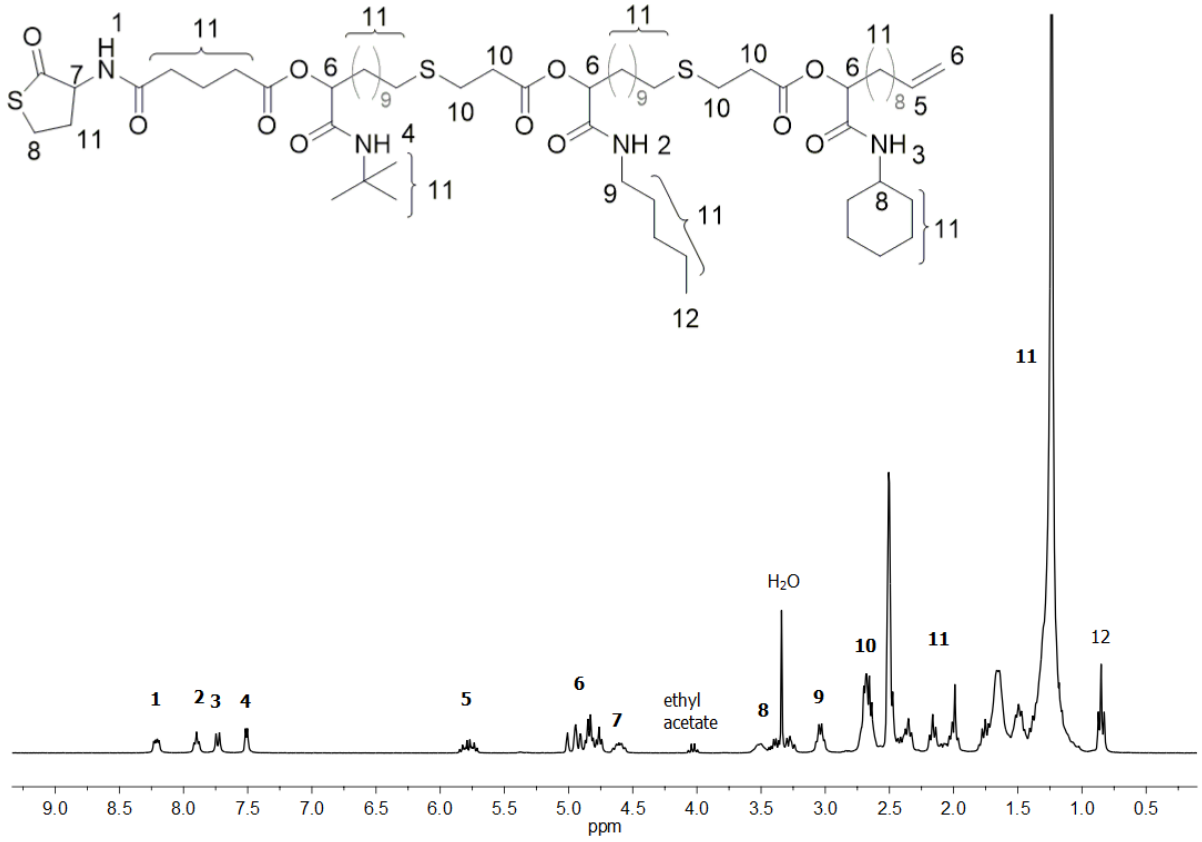
^{1}H NMR (300 MHz, DMSO-D_6) δ /ppm: 8.21 (dd, J = 8.2, 4.1 Hz, 1H, NH, ^{1}), 7.89 (t, J = 5.6 Hz, 1H, NH, ^{2}), 7.73 (d, J = 7.9 Hz, 1H, NH, ^{3}), 7.50 (d, J = 4.5 Hz, 1H, NH, ^{4}), 5.88 - 5.67 (m, 1H, CH, ^{5}), 5.05 – 4.69 (m, 5H, CH_2, 3 CH, ^{6}), 4.67 – 4.49 (m, 1H, CH, ^{7}), 3.62 – 3.19 (m, 3H, CH_2, CH, ^{8}), 3.16 - 2.90 (m, 2H, CH_2, ^{9}), 2.79 - 2.56 (m, 8H, 4 CH_2, ^{10}), 2.44 – 0.94 (m, 89H, 3 CH_3, 40 CH_2, ^{11}), 0.84 (t, J = 6.8 Hz, 3H, CH_3, ^{12}).

^{13}C NMR (75 MHz, DMSO-D_6) δ /ppm: 205.3, 172.0, 171.7, 170.9, 168.9, 168.8, 168.1, 138.8, 114.6, 73.4, 50.2, 38.2, 34.4, 34.1, 33.2, 32.6, 32.3, 31.6, 31.5, 31.0, 30.1, 29.1, 29.0, 28.9, 28.7, 28.5, 28.4, 28.3, 28.3, 26.9, 26.7, 26.3, 26.3, 26.1, 25.7, 25.2, 24.6, 24.4, 21.8, 20.6, 13.9.

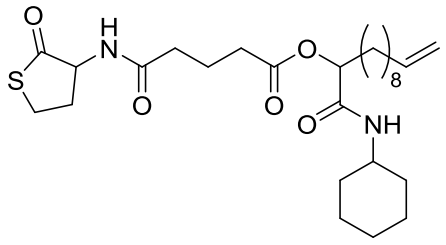
ESI-MS of $[C_{66}H_{116}N_4O_{11}S_3Na]^+$: calculated: 1259.7695, found: 1259.7716.

IR (ATR platinum diamond): ν [cm^{-1}] = 3292.3, 2922.8, 2852.1, 1737.8, 1651.2, 1533.7, 1451.5, 1363.3, 1225.5, 1148.4, 1053.5, 910.7, 846.6, 721.4, 534.2, 433.3.

***R_f*:** (ethyl acetate) = 0.58.



1st P-3CR of the 2nd building block:



79

1.01 g of thiolactone carboxylic acid **71** (4.36 mmol, 1.00 eq.) were dissolved in 6.6 mL of a 4:1 mixture of THF and water (0.66 M). Subsequently, 1.02 g of 10-undecenal **2** (6.03 mmol, 1.38 eq.) and 0.73 g of cyclohexyl isocyanide **3a** (6.71 mmol, 1.53 eq.) were added and the reaction mixture was stirred for 48 hours at room temperature. Then, 100 mL of ethyl acetate and 50 mL of water were added and the mixture was extracted. The organic layer was separated, washed with brine (80 mL) and dried over sodium sulfate. The solvent was evaporated and the residue was recrystallized from

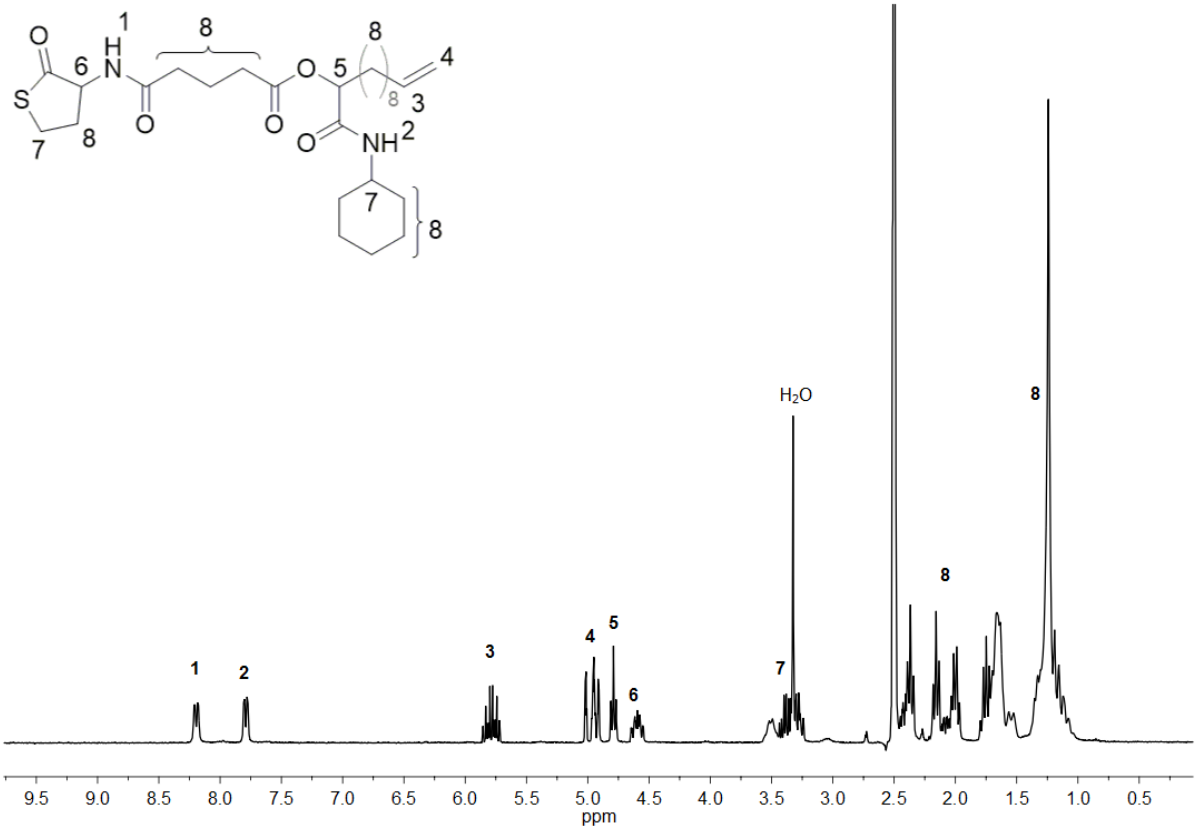
hexane/ethyl acetate 3:1. The product **79** was obtained as white solid in a yield of 90 % (2.01 g).

^{1}H NMR (300 MHz, DMSO-D_6) δ /ppm: 8.19 (dd, J = 8.3, 2.4 Hz, 1H, NH, ^{1}), 7.79 (d, J = 6.2 Hz, 1H, NH, ^{2}), 5.90 - 5-68 (m, 1H, CH, ^{3}), 5.06 – 4.87 (m, 2H, CH_2, ^{4}), 4.79 (t, J = 6.3 Hz, 1H, CH, ^{5}), 4.68 – 4.50 (m, 1H, CH, ^{6}), 3.61 – 3.17 (m, 3H, CH_2, CH, ^{7}), 2.46 – 0.95 (m, 34H, 17 CH_2, ^{8}).

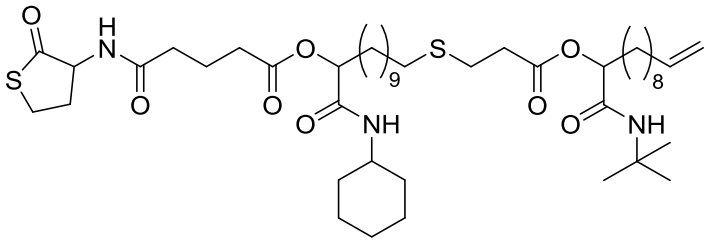
^{13}C NMR (101 MHz, DMSO-D_6) δ /ppm: 205.4, 172.1, 171.8, 168.4, 138.8, 114.6, 73.2, 58.1, 47.5, 34.1, 33.2, 32.6, 32.3, 32.2, 31.5, 30.1, 28.8, 28.7, 28.6, 28.5, 28.3, 26.7, 25.2, 24.6, 24.4, 20.6.

ESI-MS of $[C_{27}H_{44}N_2O_5SNa]^+$: calculated: 531.2863, found: 531.2861.

IR (ATR platinum diamond): ν [cm^{-1}] = 3283.1, 3076.4, 2923.3, 2851.4, 1730.1, 1701.3, 1646.1, 1544.9, 1447.5, 1368.9, 1301.7, 1249.0, 1217.0, 1186.0, 1149.5, 1090.9, 1053.6, 1021.5, 977.0, 909.2, 846.0, 676.4, 621.2, 590.1, 551.0, 484.3, 427.5, 405.7.



2nd P-3CR of the 2nd building block:



80

1.59 g of **79** (4.16 mmol, 1.00 eq.) were dissolved in 6.0 mL stabilized THF (0.52 M). Subsequently, 0.41 g of 3-mercaptopropionic acid **4** (3.90 mmol, 1.25 eq.) and 12.1 mg of DMPA **5** (0.05 mmol, 1.52 mol%) were added and the reaction mixture was irradiated with UV light at room temperature for one hour. The solvent was removed under reduced pressure and the residue was redissolved in 3.2 mL DCM (0.93 M). Subsequently, 0.96 g of 10-undecenal **2** (5.69 mmol, 1.90 eq.) and 0.43 g *tert*-butyl isocyanide **3b** (5.02 mmol, 1.74 eq.) were added and the reaction mixture was stirred at room temperature for 48 hours. The solvent was evaporated and the crude product was purified by column chromatography (hexane/ethyl acetate 4:1→1:3). Product **80** was obtained as slightly yellow oil in a yield of 86 % (2.24 g).

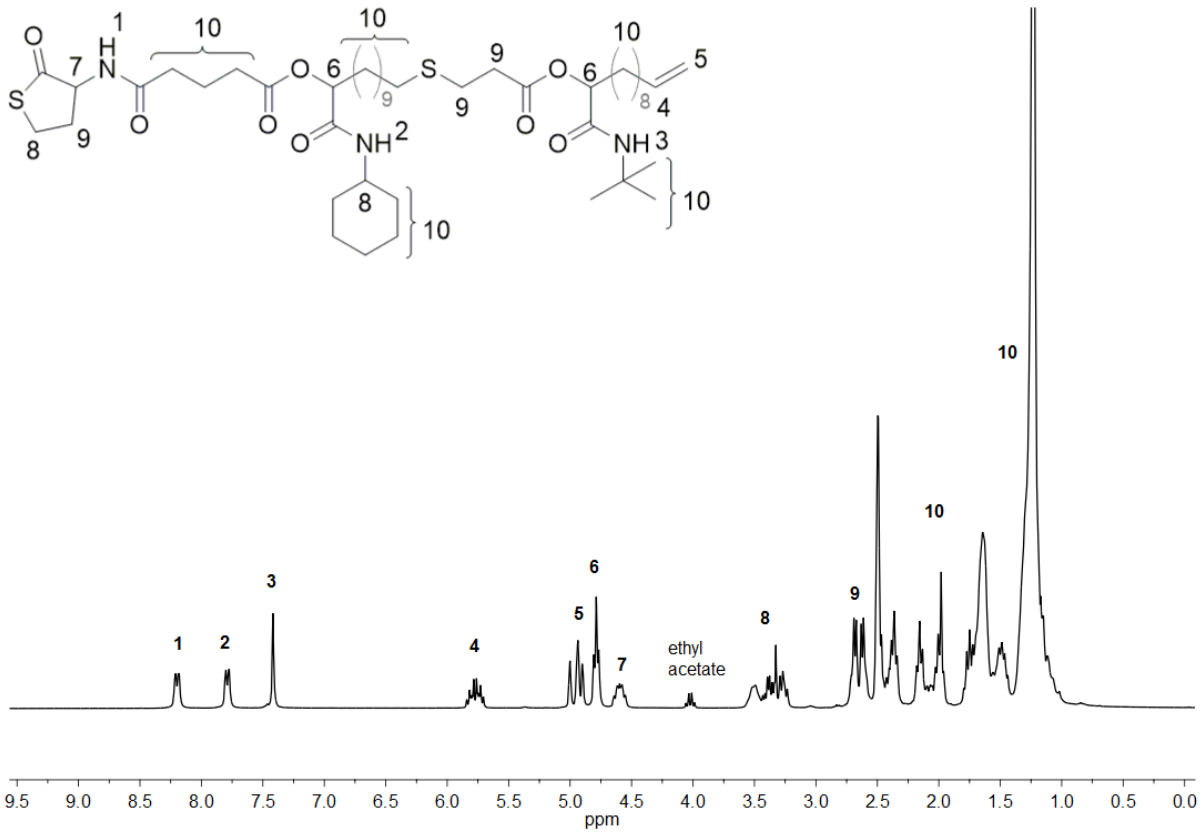
^{1}H NMR (300 MHz, DMSO-D_6) δ /ppm: 8.28 – 8.10 (m, 1H, NH, [1]), 7.79 (d, J = 7.6 Hz, 1H, NH, [2]), 7.44 (d, J = 13.7 Hz, 1H, NH, [3]), 5.90 - 5.64 (m, 1H, CH, [4]), 5.07 – 4.87 (m, 2H, CH_2, [5]), 4.79 (t, J = 6.1 Hz, 2H, 2 CH, [6]), 4.69 – 4.49 (m, 1H, CH, [7]), 3.64 – 3.16 (m, 3H, CH_2, CH, [8]), 2.79 – 2.55 (m, 4H, 2 CH_2, [9]), 2.43 – 0.76 (m, 67H, 3 CH_3, 29 CH_2, [10]).

^{13}C NMR (75 MHz, DMSO-D_6) δ /ppm: 205.3, 172.1, 171.7, 170.9, 168.5, 168.3, 138.8, 114.6, 73.6, 73.2, 58.1, 50.2, 47.4, 34.4, 34.1, 33.2, 32.5, 32.3, 31.5, 31.0, 30.1, 29.1, 29.0, 28.9, 28.7, 28.7, 28.6, 28.5, 28.4, 28.3, 28.2, 26.7, 26.3, 25.2, 24.6, 24.5, 20.6.

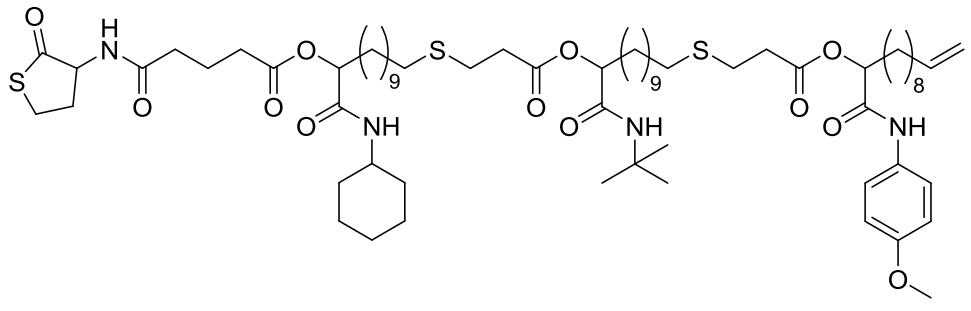
ESI-MS of $[C_{46}H_{79}N_3O_8S_2Na]^+$: calculated: 888.5201, found: 888.5209.

IR (ATR platinum diamond): ν [cm^{-1}] = 3281.4, 3078.2, 2921.8, 2851.4, 1733.2, 1701.9, 1646.8, 1544.0, 1450.8, 1363.7, 1215.9, 1175.9, 1054.6, 1021.1, 910.5, 845.8, 721.4, 678.1, 620.7, 549.6, 482.7, 433.9.

***R*$_f$:** (hexane/ethyl acetate (1:3)) = 0.53.



3rd P-3CR of the 2nd building block:



81

1.78 g of **80** (2.06 mmol, 1.00 eq.) were dissolved in 4.0 mL stabilized THF (0.52 M). Subsequently, 0.27 g of 3-mercaptopropionic acid **4** (2.54 mmol, 1.23 eq.) and 14.4 mg of DMPA **5** (0.06 mmol, 2.73 mol%) were added and the reaction mixture was irradiated with UV light at room temperature for one hour. The solvent was removed under reduced pressure and the residue was redissolved in 2.4 mL DCM (0.84 M). Subsequently, 0.63 g of 10-undecenal **2** (3.73 mmol, 1.85 eq.) and 0.48 g *p*-

methoxyphenyl isocyanide **3i** (3.61 mmol, 1.79 eq.) were added and the reaction mixture was stirred at room temperature for 26 hours. The solvent was evaporated and the crude product was purified by column chromatography (hexane/ethyl acetate 2:1→ 1:2). Product **81** was obtained as slightly yellow oil in a yield of 84 % (1.98 g).

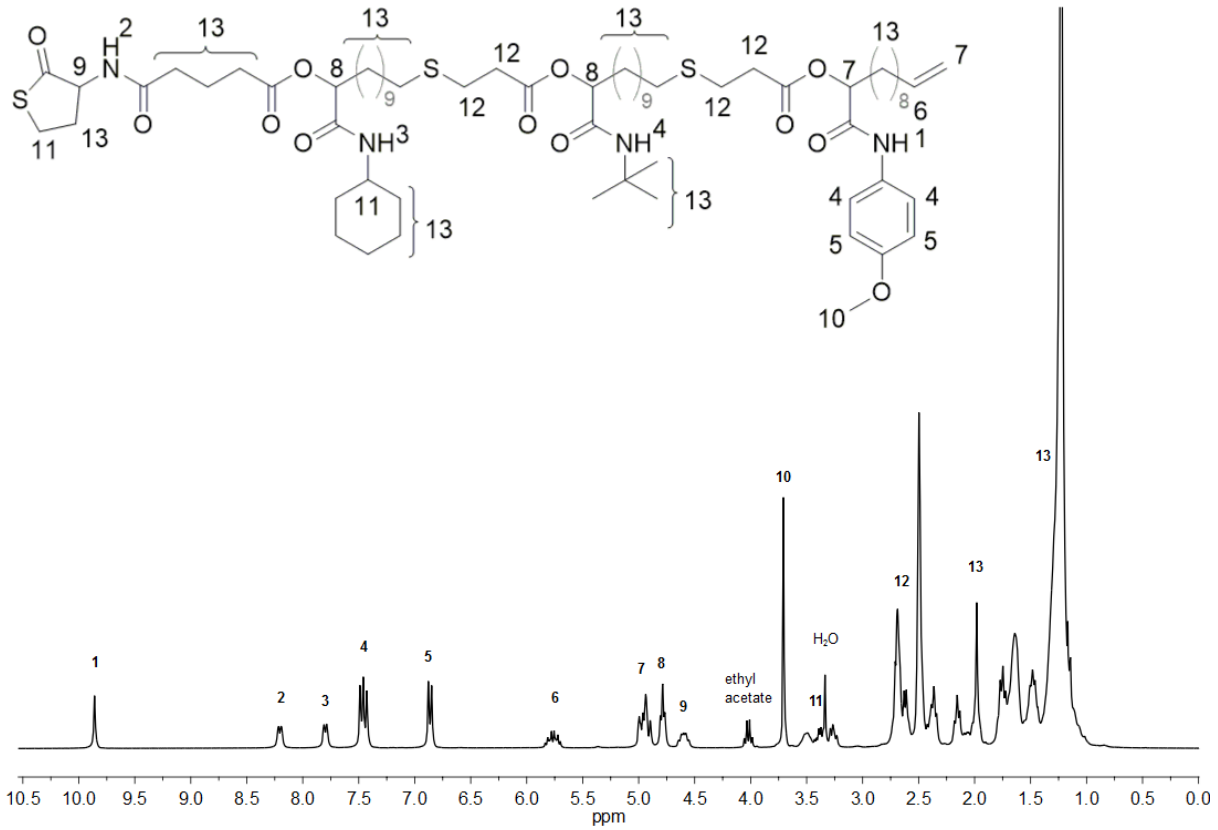
^{1}H NMR (300 MHz, DMSO-D_6) δ /ppm: 9.86 (s, 1H, NH, ^{1}), 8.27 – 8.14 (m, 1H, NH, ^{2}), 7.80 (d, J = 7.2 Hz, 1H, NH, ^{3}), 7.56 – 7.36 (m, 3H, NH, 2 CH aromatic, ^{4}), 6.87 (d, J = 8.9 Hz, 2H, 2 CH aromatic, ^{5}), 5.88 - 5.66 (m, 1H, CH, ^{6}), 5.09 - 4.86 (m, 3H, CH_2, CH, ^{7}), 4.79 (t, J = 6.0 Hz, 2H, 2 CH, ^{8}), 4.69 – 4.49 (m, 1H, CH, ^{9}), 3.71 (s, 3H, OCH_3, ^{10}), 3.58 – 3.18 (m, 3H, CH_2, CH, ^{11}), 2.85 – 2.57 (m, 8H, 4 CH_2, ^{12}), 2.42 – 0.71 (m, 83H, 3 CH_3, 37 CH_2, ^{13}).

^{13}C NMR (75 MHz, DMSO-D_6) δ /ppm: 205.3, 172.1, 171.7, 171.1, 170.9, 168.5, 168.3, 167.6, 155.5, 138.8, 131.5, 121.1, 114.6, 113.8, 73.7, 73.6, 73.2, 59.7, 58.1, 55.1, 50.2, 47.4, 34.4, 34.1, 33.2, 32.5, 32.3, 31.5, 31.4, 31.0, 30.1, 29.1, 29.0, 28.9, 28.8, 28.7, 28.5, 28.4, 28.3, 28.2, 26.7, 26.3, 25.2, 24.6, 24.5, 20.8, 20.6, 14.1.

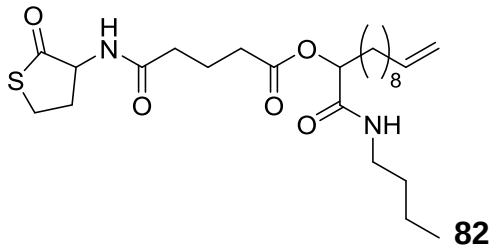
ESI-MS of $[C_{68}H_{112}N_4O_{12}S_3Na]^+$: calculated: 1295.7331, found: 1295.7340.

IR (ATR platinum diamond): ν [cm^{-1}] = 3303.7, 3076.1, 2922.9, 2851.8, 1737.9, 1653.1, 1530.3, 1510.3, 1452.5, 1414.3, 1363.5, 1298.3, 1233.7, 1148.0, 1034.7, 912.1, 829.5, 721.7, 684.6, 524.5, 431.8.

***R_f*:** (hexane/ethyl acetate (1:3)) = 0.57.



1st P-3CR of the 3rd and 4th building block:



82

2.00 g of thiolactone carboxylic acid **71** (8.67 mmol, 1.00 eq.) were dissolved in 17.5 mL of a 4:1 mixture of THF and water (0.50 M). Subsequently, 2.18 g of 10-undecenal **2** (12.98 mmol, 1.50 eq.) and 1.03 g of *n*-butyl isocyanide **3d** (12.45 mmol, 1.44 eq.) were added and the reaction mixture was stirred for 24 hours at room temperature. Then, 200 mL of ethyl acetate and 100 mL of water were added and the mixture was extracted. The organic layer was separated, washed with brine (160 mL) and dried over sodium sulfate. The solvent was evaporated and the residue was purified by column

chromatography (hexane/ethyl acetate 3:1 → ethyl acetate). The product **82** was obtained as white solid in a yield of 95 % (3.97 g).

^{1}H NMR (300 MHz, DMSO-D_6) δ /ppm: 8.21 (d, J = 8.0 Hz, 1H, NH, ^{1}), 7.94 (t, J = 5.5 Hz, 1H, NH, ^{2}), 5.90 - 5.66 (m, 1H, CH, ^{3}), 5.08 – 4.87 (m, 2H, CH_2, ^{4}), 4.81 (t, J = 6.1 Hz, 1H, CH, ^{5}), 4.68 - 4.48 (m, 1H, CH, ^{6}), 3.50 – 3.17 (m, 2H, CH_2, ^{7}), 3.14 – 2.91 (m, 2H, CH_2, ^{8}), 2.46 – 1.00 (m, 28H, 14 CH_2, ^{9}), 0.85 (t, J = 7.2 Hz, 3H, CH_3, ^{10}).

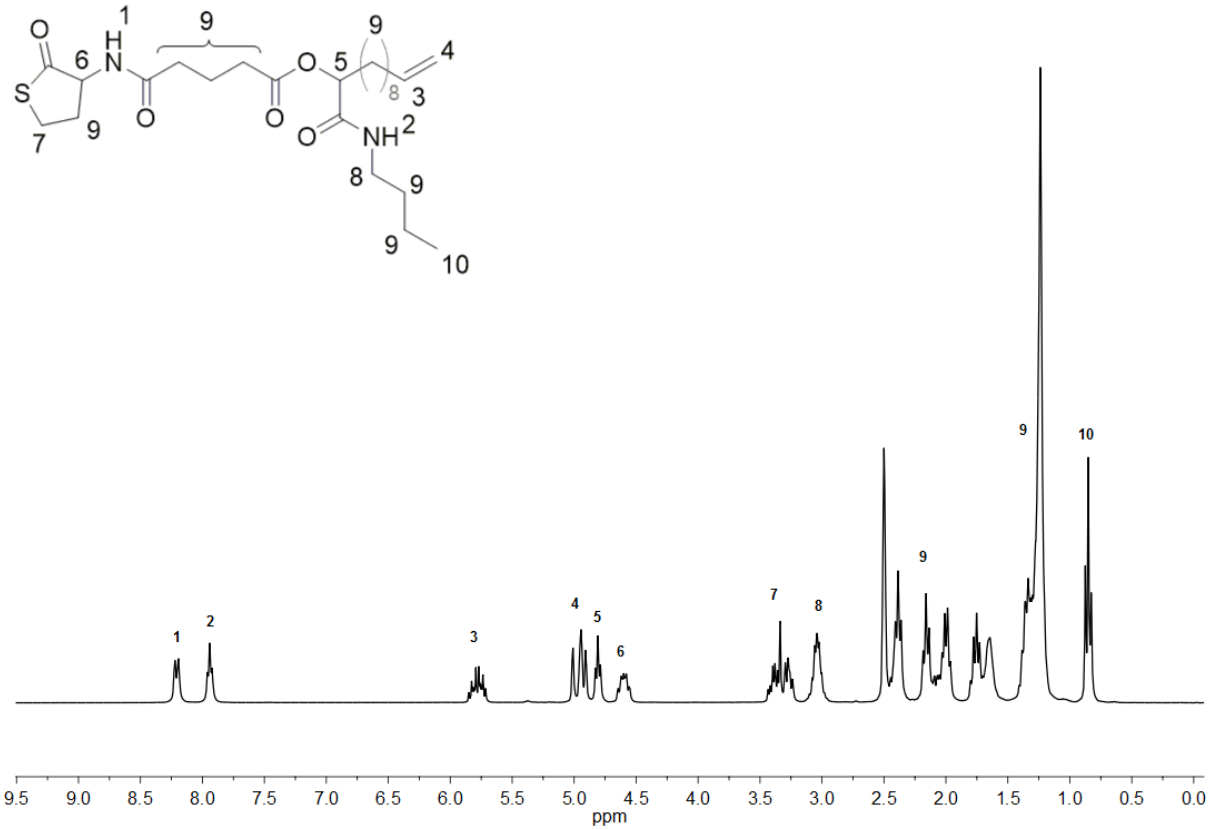
^{13}C NMR (101 MHz, DMSO-D_6) δ /ppm: 205.4, 172.1, 171.7, 169.1, 138.8, 114.6, 73.2, 58.1, 38.0, 34.1, 33.2, 32.6, 31.5, 31.1, 30.1, 28.8, 28.7, 28.6, 28.5, 28.3, 26.7, 24.5, 20.5, 19.4, 13.6.

FAB-MS of $[C_{25}H_{43}N_2O_5S]^+$: calculated: 483.2887, found: 483.2887.

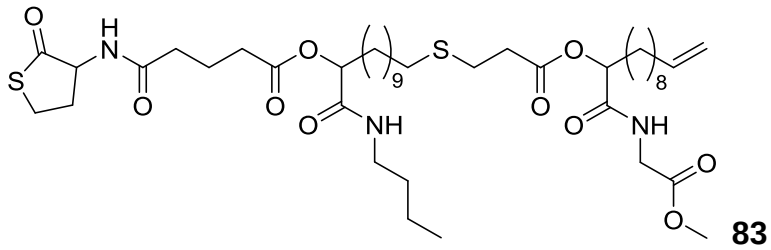
ESI-MS of $[C_{25}H_{42}N_2O_5SNa]^+$: calculated: 505.2707, found: 505.2700.

IR (ATR platinum diamond): ν [cm^{-1}] = 3281.7, 2922.3, 2851.9, 1715.5, 1699.1, 1650.9, 1544.1, 1364.2, 1307.9, 1218.2, 1185.7, 1056.8, 1022.3, 909.0, 846.7, 680.7, 550.8, 403.2.

***R_f*:** (ethyl acetate) = 0.55.



2nd P-3CR of the 3rd and 4th building block:



83

3.54 g of **82** (7.33 mmol, 1.00 eq.) were dissolved in 14.0 mL stabilized THF (0.52 M). Subsequently, 1.00 g of 3-mercaptopropionic acid **4** (9.47 mmol, 1.29 eq.) and 42.0 mg of DMPA **5** (0.16 mmol, 2.32 mol%) were added and the reaction mixture was irradiated with UV light at room temperature for one hour. The solvent was removed under reduced pressure and the residue was redissolved in 7.5 mL DCM (0.96 M). Subsequently, 2.19 g of 10-undecenal **2** (13.00 mmol, 1.80 eq.) and 1.34 g methyl isocyanoacetate **3e** (14.67 mmol, 2.03 eq.) were added and the reaction mixture was

stirred for 24 hours at room temperature. The solvent was evaporated and the crude product was purified by column chromatography (hexane/ethyl acetate 5:1→ ethyl acetate). Product **83** was obtained as slightly yellow oil in a yield of 85 % (5.27 g).

^{1}H NMR (300 MHz, DMSO-D_6) δ /ppm: 8.40 (s, 1H, NH, [1]), 8.21 (d, J = 6.4 Hz, 1H NH, [2]), 7.94 (s, 1H, NH, [3]), 5.90 - 5.66 (m, 1H, CH, [4]), 5.08 – 4.87 (m, 3H, CH_2, CH, [5]), 4.81 (t, J = 5.9 Hz, 1H, CH, [6]), 4.70 - 4.47 (m, 1H, CH, [7]), 3.84 (d, J = 5.6 Hz, 2H, CH_2, [8]), 3.62 (s, 3H, OCH_3, [9]), 3.47 – 3.18 (m, 2H, CH_2, [10]), 3.16 – 2.89 (m, 2H, CH_2, [11]), 2.80 – 2.59 (m, 4H, 2 CH_2, [12]), 2.44 – 0.97 (m, 48H, 24 CH_2, [13]), 0.85 (t, J = 7.1 Hz, 3H, CH_3, [14]).

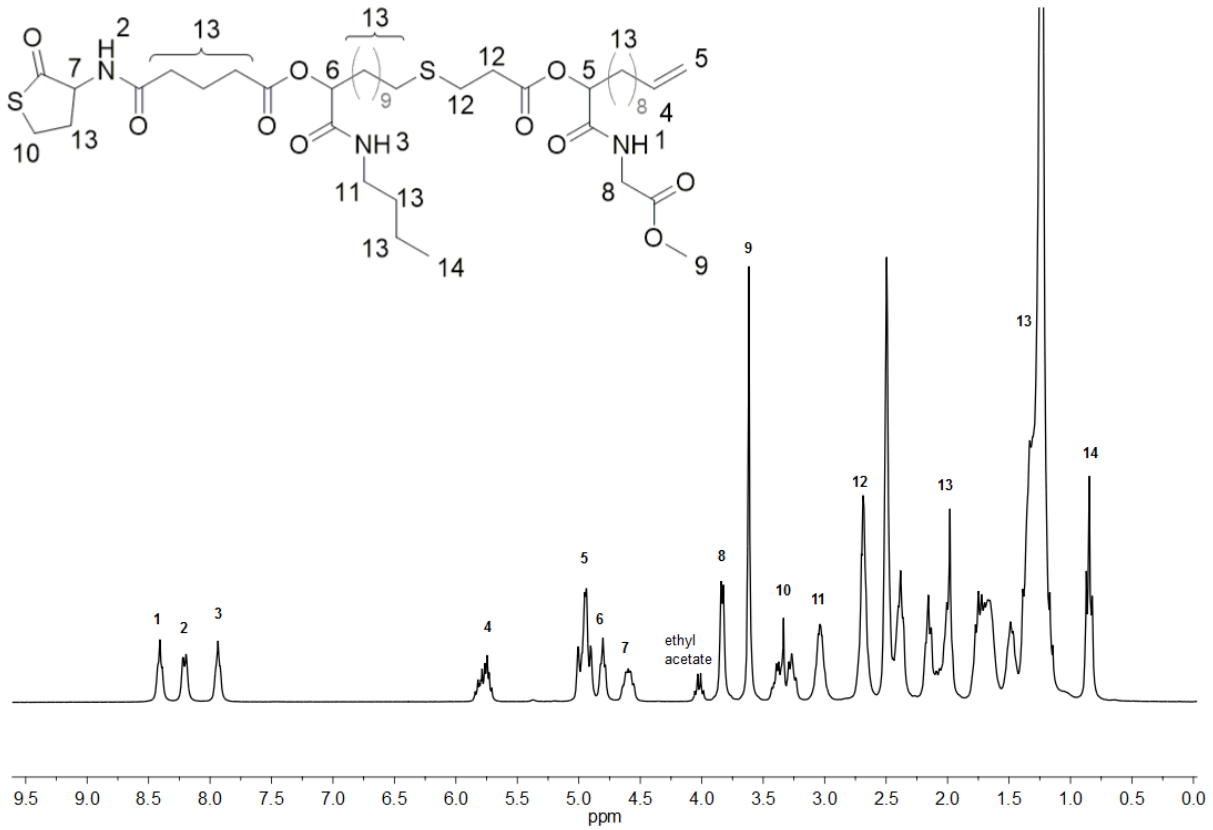
^{13}C NMR (75 MHz, DMSO-D_6) δ /ppm: 205.4, 172.1, 171.7, 170.9, 167.0, 169.9, 169.1, 138.8, 114.6, 73.2, 73.0, 58.1, 51.7, 38.0, 34.4, 34.1, 33.2, 32.6, 31.4, 31.1, 31.0, 30.1, 29.1, 29.0, 28.9, 28.9, 28.8, 28.7, 28.6, 28.5, 28.3, 28.2, 26.7, 26.2, 24.5, 24.2, 20.5, 19.5, 13.6.

FAB-MS of $[C_{43}H_{74}N_3O_{10}S_2]^+$: calculated: 856.4810, found: 856.4811.

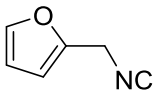
ESI-MS of $[C_{43}H_{73}N_3O_{10}S_2Na]^+$: calculated: 878.4630, found: 878.4630.

IR (ATR platinum diamond): ν [cm^{-1}] = 3284.6, 2921.9, 2851.5, 1736.2, 1716.1, 1651.1, 1540.8, 1436.2, 1365.8, 1215.8, 1185.0, 1056.7, 1022.2, 910.8, 847.5, 682.4, 550.0.

***R*$_f$:** (ethyl acetate) = 0.49.



Synthesis of furfurylisocyanide 3g:



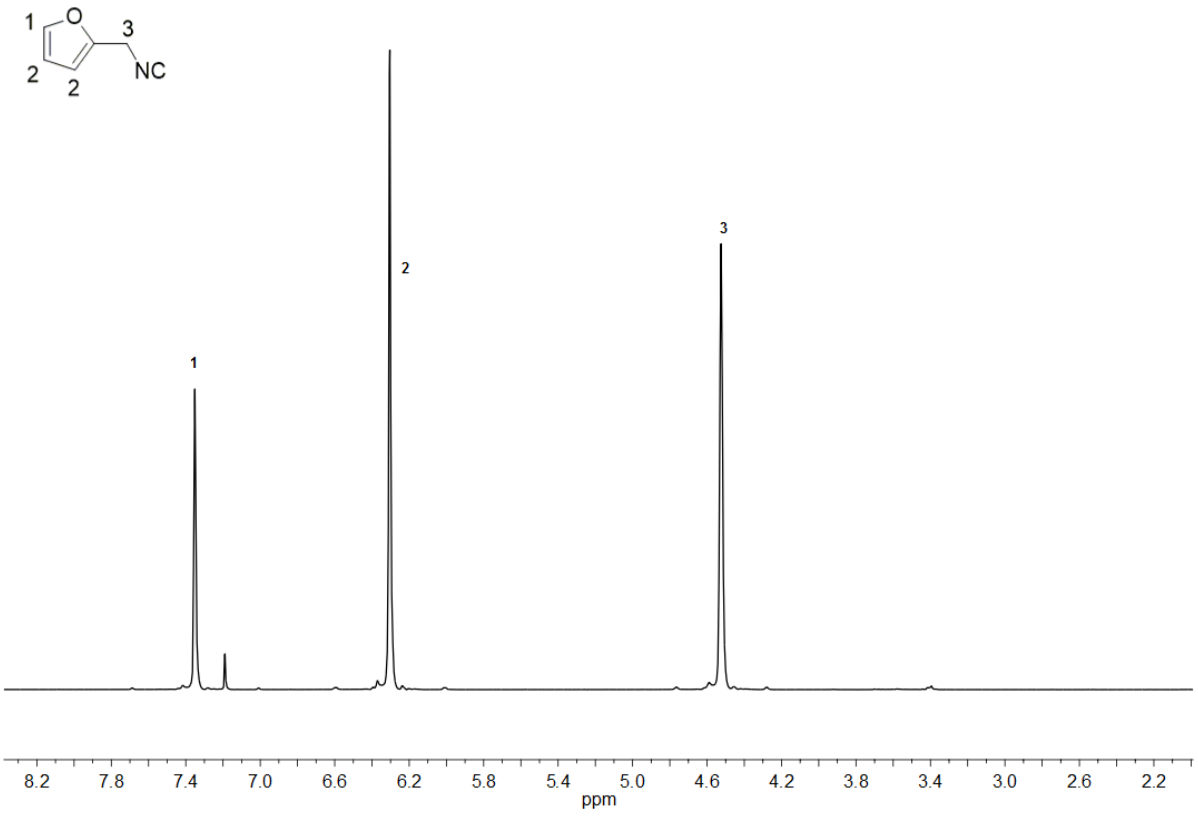
3g

5.08 g furfurylamine **84** (52.32 mmol, 1.00 eq.) were dissolved in 38.14 g ethyl formate (51.40 mmol, 9.84 eq.) and refluxed for eight hours. Subsequently, the excess of ethyl formate was evaporated under reduced pressure. The residue was redissolved in 100 mL DCM (0.52 M) and 22 mL diisopropylamine **47** (30.47 g, 156.7 mmol, 3.00 eq.) were added and the mixture was cooled to 0 ° C. Then, 7 mL phosphorous oxychloride **48** (4.26 g, 73.25 mmol, 1.40 eq.) were added dropwise. The mixture was allowed to warm to room temperature and was subsequently stirred for two hours. Then it was again cooled to 0 ° C and the reaction was quenched by addition of 250 mL water containing 60 g of potassium carbonate. The mixture was stirred for another 30 minutes at room temperature and then the organic layer was separated. The aqueous phase was

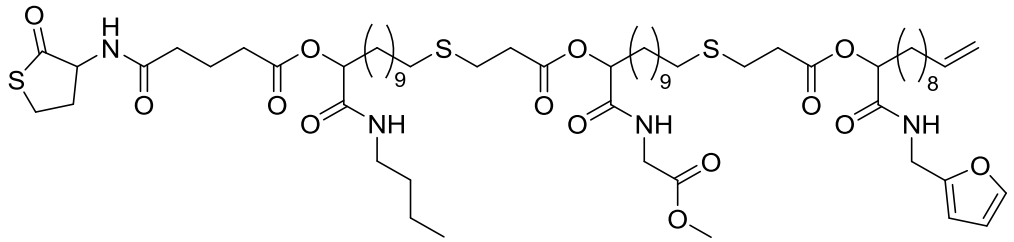
extracted twice with 100 mL of DCM. The combined organic layers were washed with water (2 x 100 mL) and with brine (100 mL) and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the product was purified by column chromatography (hexane/ethyl acetate (10:1 → 8:1)) to afford the product **3g** as a brown liquid in a yield of 67 % (3.74 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 7.42 (s, 1H, CH aromatic, ^{1}), 6.37 (s, 2H, 2 CH aromatic, ^{2}), 4.59 (s, 2H, CH2, ^{3}).

^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 158.0, 145.6, 143.4, 110.8, 109.1, 38.9.



3rd P-3CR of the 3rd building block:



86

2.01 g of **83** (2.35 mmol, 1.00 eq.) were dissolved in 5.0 mL stabilized THF (0.47 M). Subsequently, 0.30 g of 3-mercaptopropionic acid **4** (2.78 mmol, 1.18 eq.) and 20.4 mg of DMPA **5** (0.08 mmol, 3.38 mol%) were added and the reaction mixture was irradiated with UV light at room temperature for two hours. The solvent was removed under reduced pressure and the residue was redissolved in 2.5 mL DCM (0.94 M). Subsequently, 0.72 g of 10-undecenal **2** (4.27 mmol, 1.82 eq.) and 0.45 g furfuryl isocyanide **3g** (4.21 mmol, 1.79 eq.) were added and the reaction mixture was stirred for 24 hours at room temperature. The solvent was evaporated and the crude product was purified by column chromatography (hexane/ethyl acetate 3:1→ ethyl acetate). Product **86** was obtained as slightly yellow liquid in a yield of 79 % (2.31 g).

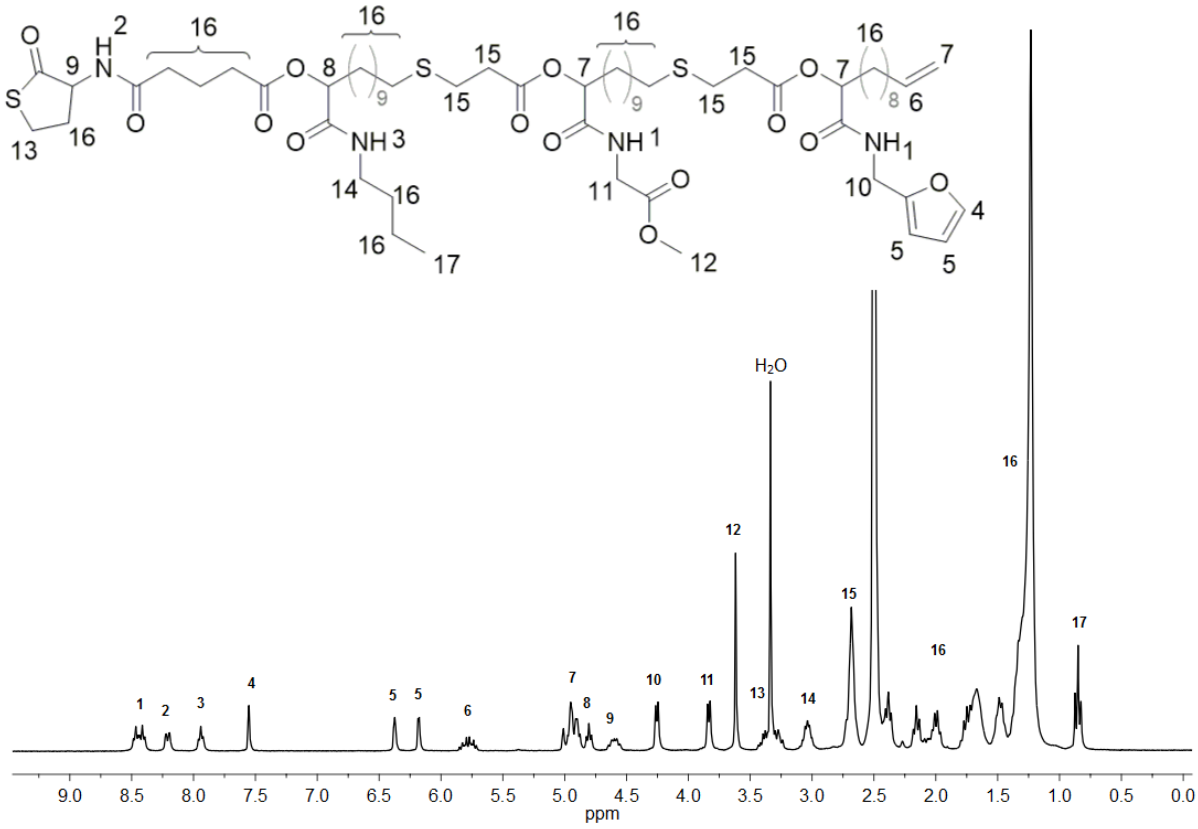
^{1}H NMR (300 MHz, DMSO-D_6) *δ* /ppm: 8.43 (s, 2H, 2 NH, [1]), 8.21 (d, *J* = 7.4 Hz, 1H, NH, [2]), 7.93 (t, *J* = 5.5 Hz, 1H, NH, [3]), 7.55 (s, 1H, CH aromatic, [4]), 6.37 (d, *J* = 1.4 Hz, 1H, CH aromatic, [5]), 6.18 (d, *J* = 3.0 Hz, 1H, CH aromatic, [5]), 5.87 – 5.67 (m, 1H, CH, [6]), 5.06 - 4.86 (m, 4H, CH_2, 2 CH, [7]), 4.81 (t, *J* = 6.2 Hz, 1H, CH, [8]), 4.68 - 4.52 (m, 1H, CH, [9]), 4.26 (d, *J* = 5.6 Hz, 2H, CH_2, [10]), 3.84 (d, *J* = 5.9 Hz, 2H, CH_2, [11]), 3.62 (s, 3H, OCH_3, [12]), 3.46 – 3.20 (m, 2H, CH_2, [13]), 3.05 (d, J = 5.3 Hz, 2H, CH_2, [14]), 2.69 (s, 8H, 4 CH_2, [15]), 2.43 – 1.00 (m, 68H, 34 CH_2, [16]), 0.85 (t, *J* = 7.1 Hz, 3H, CH_3, [17]).

^{13}C NMR (75 MHz, DMSO-D_6) δ /ppm: 205.4, 172.2, 171.8, 171.0, 170.9, 170.0, 169.9, 169.2, 152.1, 143.1, 138.8, 110.5, 106.6, 73.9, 72.5, 54.9, 52.7, 50.8, 38.0, 35.4, 34.9, 34.4, 34.1, 33.2, 32.6, 31.4, 31.2, 31.0, 30.1, 29.3, 29.1, 29.0, 28.9, 28.8, 28.7, 28.6, 28.4, 28.3, 28.2, 28.0, 27.8, 27.3, 26.8, 26.5, 26.3, 25.8, 24.5, 24.5, 24.3, 20.5, 19.5, 14.3.

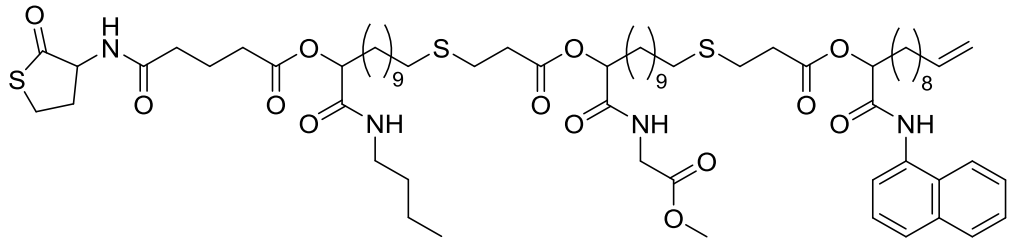
ESI-MS of $[C_{63}H_{104}N_4O_{14}S_3Na]^+$: calculated: 1259.6603, found: 1259.6605.

IR (ATR platinum diamond): ν [cm^{-1}] = 3285.6, 2919.6, 2849.7, 1735.6, 1654.3, 1540.3, 1436.5, 1364.7, 1213.0, 1142.2, 1054.9, 1016.9, 911.5, 848.0, 721.8, 599.1, 430.7.

***R*$_f$:** (ethyl acetate) = 0.50.



3rd P-3CR of the 4th building block:



87

2.03 g of **83** (2.37 mmol, 1.00 eq.) were dissolved in 5.0 mL stabilized THF (0.47 M). Subsequently, 0.31 g of 3-mercaptopropionic acid **4** (2.89 mmol, 1.22 eq.) and 20.4 mg of DMPA **5** (0.08 mmol, 3.46 mol%) were added and the reaction mixture was irradiated

with UV light at room temperature for two hours. The solvent was removed under reduced pressure and the residue was redissolved in 2.5 mL DCM (0.86 M). Subsequently, 0.68 g of 10-undecenal **2** (4.04 mmol, 1.87 eq.) and 0.45 g naphthyl isocyanide **3h** (2.91 mmol, 1.35 eq.) were added and the reaction mixture was stirred for 30 hours at room temperature. The solvent was evaporated and the crude product was purified by column chromatography (hexane/ethyl acetate 3:1→ ethyl acetate). Product **87** was obtained as slightly yellow oil in a yield of 68 % (1.83 g).

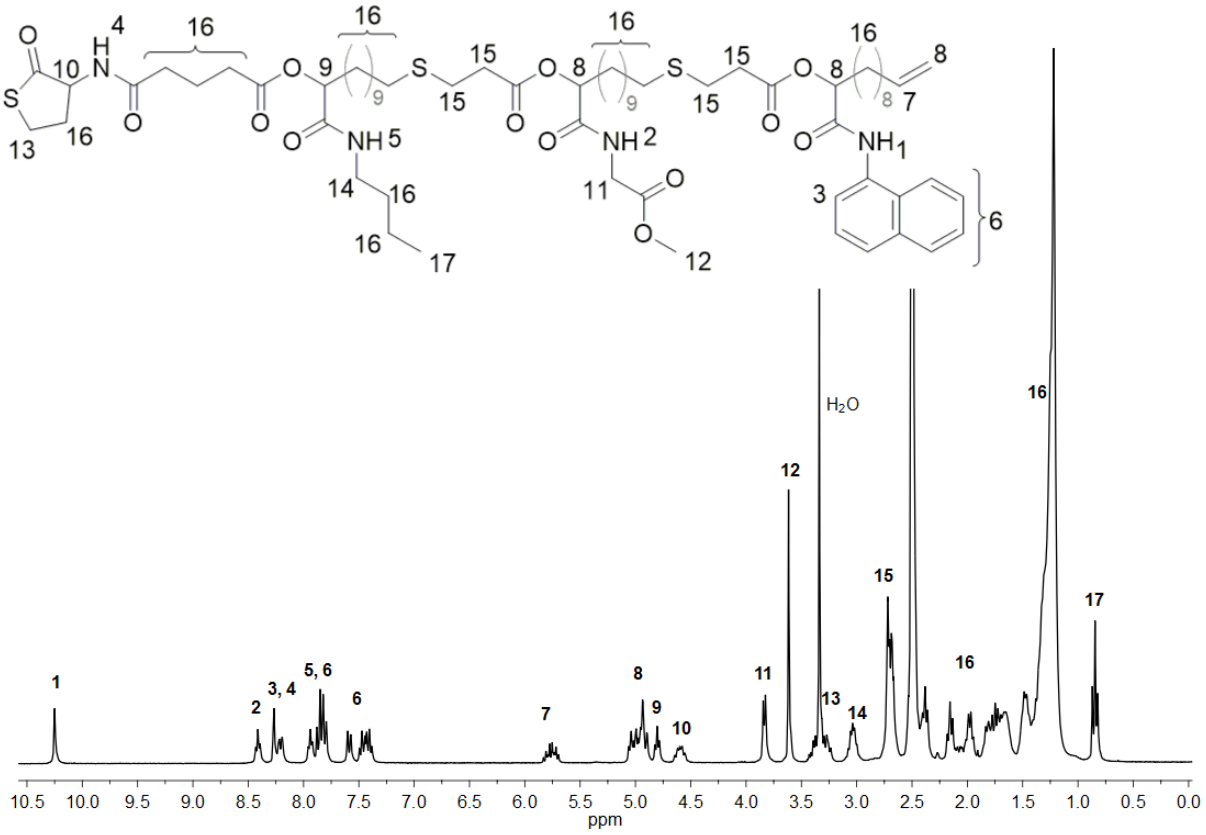
^{1}H NMR (300 MHz, DMSO-D_6) δ /ppm: 10.25 (s, 1H, NH, [1]), 8.41 (t, *J* = 5.8 Hz, 1H, NH, [2]), 8.32 – 8.11 (m, 2H, CH aromatic, NH, [3, 4]), 7.94 (t, *J* = 5.6 Hz, 1H, NH, [5]), 7.90 - 7.69 (m, 3H, 3 CH aromatic, [6]), 7.66 – 7.53 (m, 1H, CH aromatic, [6]), 7.44 (dt, *J* = 18.4, 6.8 Hz, 2H, 2 H aromatic, [6]), 5.87 - 5.63 (m, 1H, CH, [7]), 5.12 - 4.85 (m, 4H, CH_2, 2 CH, [8]), 4.80 (t, *J* = 6.2 Hz, 1H, CH, [9]), 4.68 – 4.48 (m, 1H, CH, [10]), 3.84 (d, *J* = 6.0 Hz, 2H, CH_2, [11]), 3.62 (s, 3H, OCH_3, [12]), 3.46 – 3.18 (m, 2H, CH_2, [13]), 3.05 (dd, *J* = 11.1, 5.8 Hz, 2H, CH_2, [14]), 2.80 - 2.60 (m, 8H, 4 CH_2, [15]), 2.43 – 0.95 (m, 68H, 34 CH_2, [16]), 0.85 (t, *J* = 7.2 Hz, 3H, CH_3, [17]).

^{13}C NMR (75 MHz, DMSO-D_6) δ /ppm: 205.4, 172.1, 171.7, 171.2, 170.9, 167.0, 169.9, 169.2, 168.4, 138.7, 136.0, 133.3, 129.9, 128.3, 127.4, 127.3, 126.4, 124.7, 120.1, 115.8, 114.6, 73.8, 73.2, 73.0, 58.1, 51.7, 38.0, 34.4, 34.1, 33.2, 32.6, 31.5, 31.4, 31.3, 31.1, 31.0, 30.1, 29.1, 29.1, 29.0, 28.9, 28.9, 28.8, 28.7, 28.6, 28.5, 28.3, 28.3, 26.7, 26.3, 26.2, 24.7, 24.5, 24.3, 20.5, 19.4, 13.6.

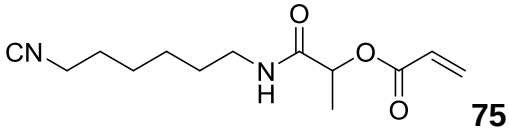
ESI-MS of $[C_{68}H_{106}N_4O_{13}S_3Na]^+$: calculated: 1305.6811, found: 1305.6818.

IR (ATR platinum diamond): ν [cm^{-1}] = 3290.9, 2923.0, 2851.8, 1738.4, 1654.6, 1586.1, 1535.0, 1434.4, 1364.5, 1205.5, 1142.9, 1052.7, 911.7, 853.8, 815.1, 746.0, 720.5, 474.2.

***R*$_f$:** (ethyl acetate) = 0.61.



Synthesis of acrylate-isocyanide 75:



75

8.70 g of 1,6-diisocyanohexane **73** (63.90 mmol, 3.09 eq.) were dissolved in 106 mL DCM (0.20 M) and subsequently, 1.49 g freshly distilled acrylic acid **74** (20.68 mmol, 1.00 eq.) as well as 1.87 g acetaldehyde **50c** (42.45 mmol, 2.05 eq.) were added. The mixture was stirred at room temperature for 30 hours and the solvent was evaporated under reduced pressure thereafter. The crude product was purified by column chromatography (hexane/ethyl acetate 3:1 → 1:3) to afford product **75** as a yellow oil in a yield of 77 % (4.01 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 6.53 – 6.38 (m, 1H, 0.5 CH_2, ^{1}), 6.29 . 6.03 (m, 2H, CH, NH, ^{2}), 5.98 – 5.85 (m, 1H, 0.5 CH_2, ^{3}), 5.24 (q, J = 6.8 Hz, 1H, CH, ^{4}), 3.45 – 3.30

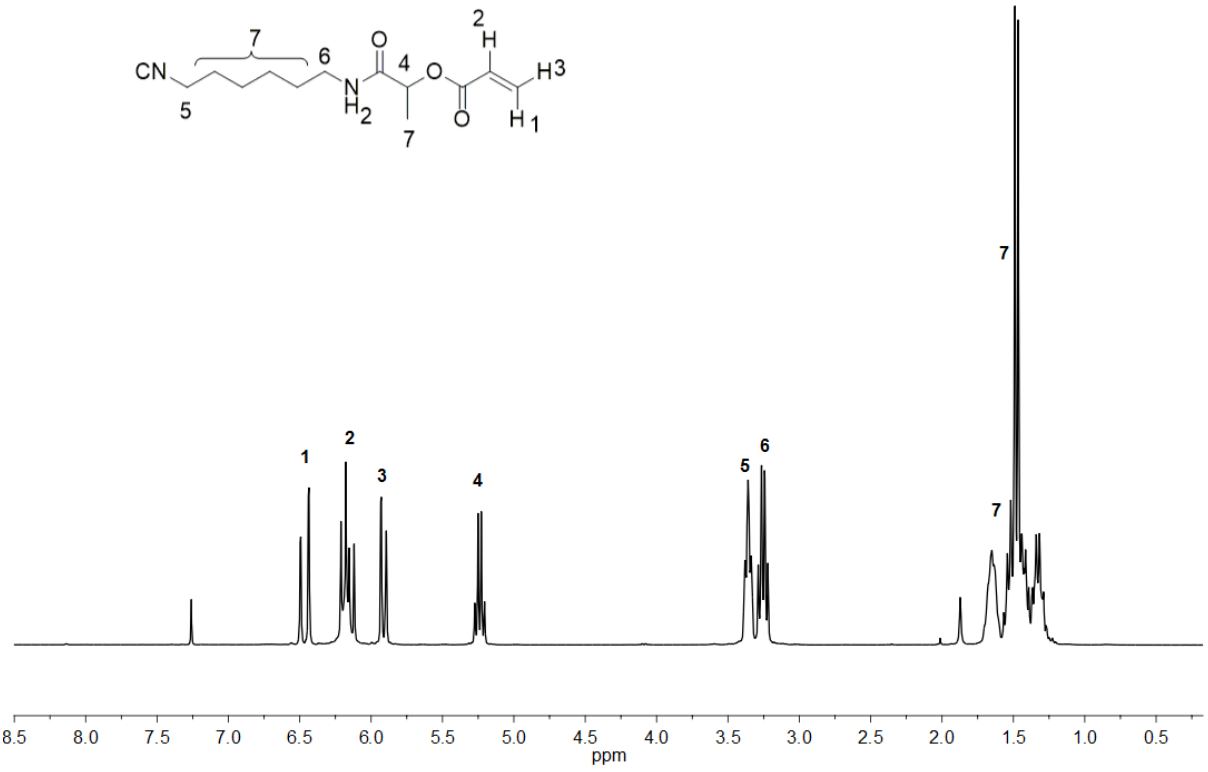
(m, 2H, CH_2, [5]), 3.25 (dd, J = 13.3, 6.9 Hz, 2H, CH_2, [6]), 1.77 – 1.15 (m, 11H, CH_3, 4 CH_2, [7]).

^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 170.3, 164.8, 155.9, 132.3, 127.8, 70.8, 41.5, 39.1, 29.4, 29.0, 26.0, 25.9, 17.9.

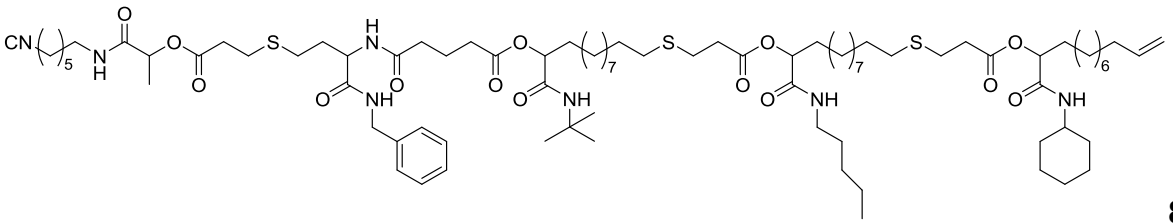
ESI-MS of $[C_{13}H_{21}N_2O_7]^+$: calculated: 253.1547, found: 253.1546.

IR (ATR platinum diamond): ν [cm^{-1}] = 3306.5, 2934.9, 2859.7, 2146.7 (isocyanide), 1725.6, 1655.4, 1535.4, 1448.3, 1405.0, 1371.3, 1291.8, 1260.5, 1182.5, 1081.0, 982.4, 808.8, 673.1, 385.5.

R_f: (ethyl acetate) = 0.55.



Aminolysis and Thiol-Michael addition of the 1st building block:



88

0.51 g of **78** (0.42 mmol, 1.00 eq.) were dissolved in 1.0 mL chloroform (0.42 M) and subsequently, 65.0 mg of benzylamine **24b** (0.61 mmol, 1.55 eq.) were added and the mixture was stirred at room temperature for seven hours. Then, 0.16 g of the acrylate-isocyanide **75** (0.63 mmol, 1.49 eq.), dissolved in 0.1 mL chloroform, were added and the mixture was stirred over night at room temperature. The product **88** was isolated by column chromatography (DCM/acetone 4:1 → 2:1) as a slightly yellow oil in a yield of 69 % (0.43 g).

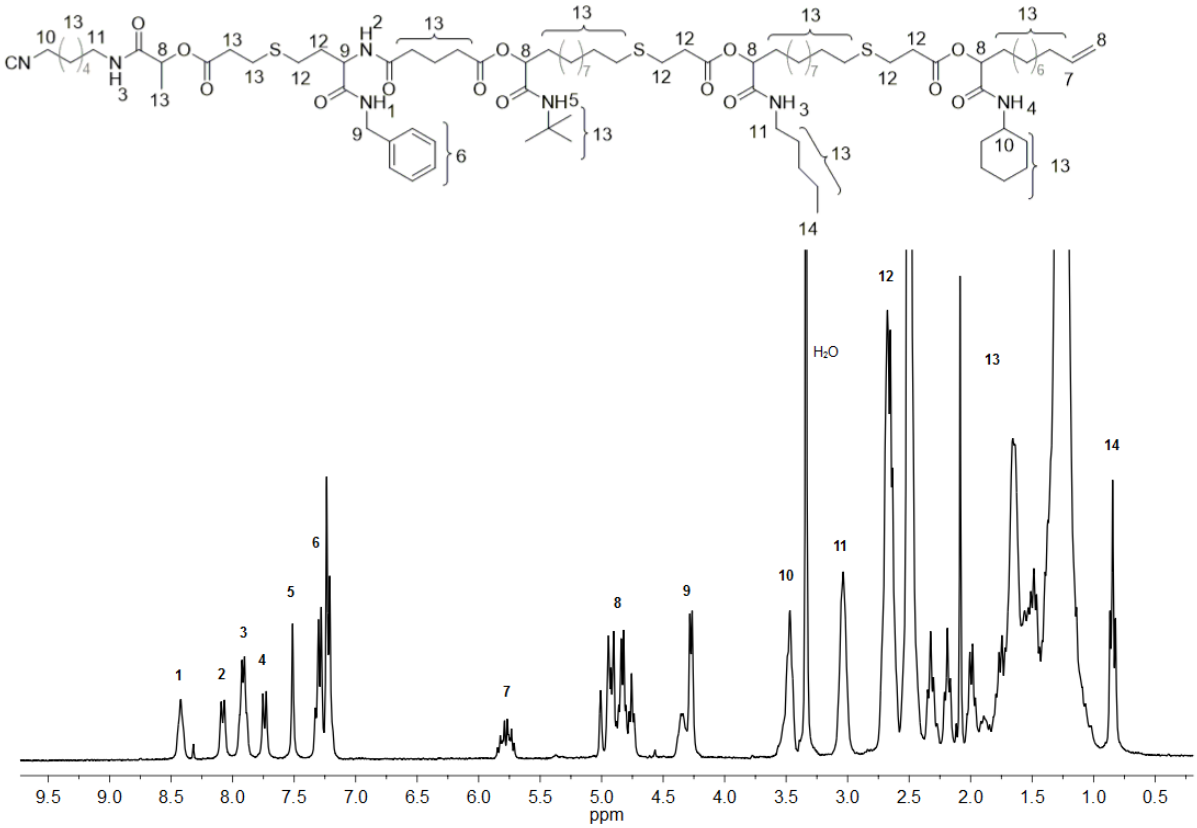
^{1}H NMR (300 MHz, DMSO-D_6) δ /ppm: 8.42 (s, 1H, NH, [1]), 8.08 (d, J = 7.6 Hz, 1H, NH, [2]), 7.91 (m, 2H, 2 NH, [3]), 7.74 (d, J = 8.0 Hz, 1H, NH, [4]), 7.51 (s, 1H, NH, [5]), 7.37 – 7.10 (m, 5H, 5 CH aromatic, [6]), 5.87 – 5.67 (m, 1H, CH, [7]), 5.07 - 4.68 (m, 6H, CH_2, 4 CH, [8]), 4.43 - 4-17 (m, 3H, CH_2, CH, [9]), 3.47 (s, 3H, CH_2, CH, [10]), 3.15 - 2.92 (m, 4H, 2 CH_2, [11]), 2.83 – 2.58 (m, 12H, 6 CH_2, [12]), 2.39 – 0.94 (m, 102H, 4 CH_3, 45 CH_2, [13]), 0.84 (t, J = 6.7 Hz, 3H, CH_3, [14]).

^{13}C NMR (75 MHz, DMSO-D_6) δ /ppm: 172.1, 171.8, 171.3, 171.0, 170.8, 169.6, 169.0, 168.7, 168.1, 139.4, 138.8, 128.2, 127.0, 114.6, 73.4, 69.9, 52.0, 50.2, 47.5, 42.0, 38.2, 34.4, 34.2, 33.2, 32.3, 31.6, 31.5, 31.0, 29.1, 29.0, 28.9, 28.9, 28.8, 28.7, 28.7, 28.6, 28.6, 28.5, 28.4, 28.3, 28.2, 27.5, 26.5, 26.4, 26.3, 25.9, 25.5, 25.4, 24.6, 24.5, 21.8, 17.7, 13.9.

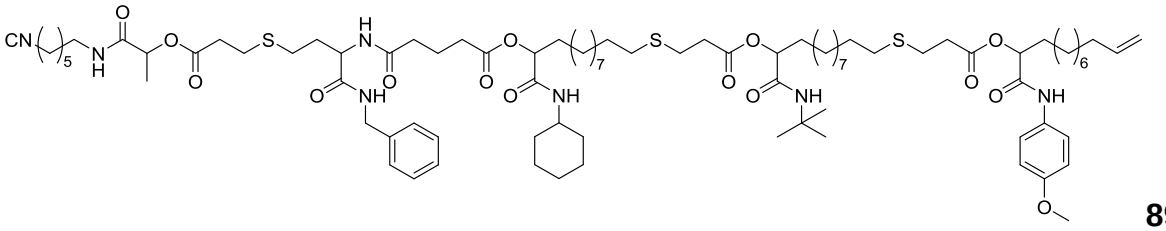
ESI-MS of $[C_{86}H_{145}N_7O_{14}S_3Na]^+$: calculated: 1618.9904, found: 1618.9924.

IR (ATR platinum diamond): ν [cm^{-1}] = 3305.0, 2923.6, 2852.7, 2146.4 (isocyanide), 1738.1, 1649.6, 1533.1, 1450.6, 1364.0, 1230.9, 1141.0, 1080.8, 913.3, 855.3, 725.5, 698.1, 541.0, 472.0.

***R*f:** (DCM/acetone (2:1)) = 0.78.



Aminolysis and Thiol-Michael addition of the 2nd building block:



89

1.59 g of product **81** (1.37 mmol, 1.00 eq.) were dissolved in 3.0 mL chloroform (0.46 M) and subsequently, 0.25 g of benzylamine **24b** (2.37 mmol, 1.73 eq.) were added and the mixture was stirred at room temperature for nine hours. Then, 0.81 g of the acrylate-isocyanide **75** (3.22 mmol, 2.35 eq.), dissolved in 0.4 mL chloroform, were added and the mixture was stirred over night at room temperature. The product **89** was isolated by

column chromatography (DCM/acetone 12:1 → 4:1) as a slightly yellow oil in a yield of 55 % (1.16 g).

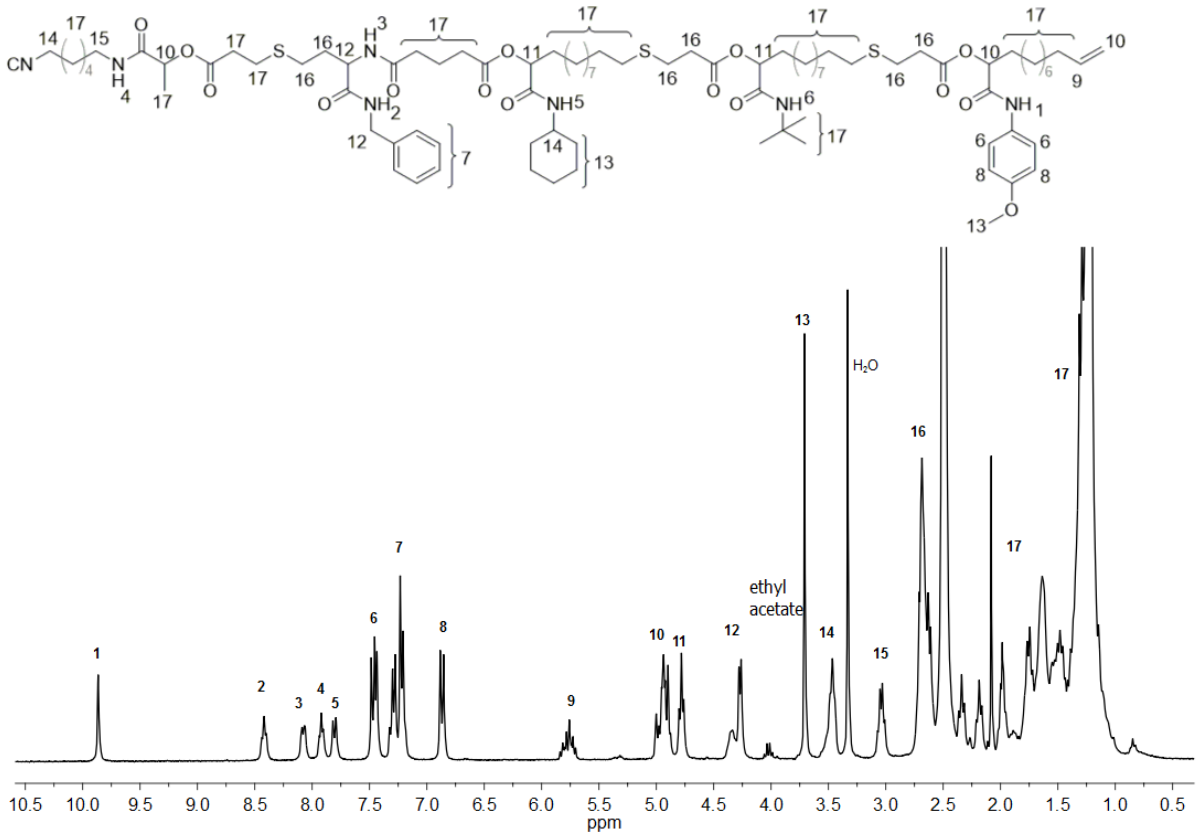
^{1}H NMR (300 MHz, DMSO-D_6) δ /ppm: 9.87 (s, 1H, NH, [1]), 8.52 - 8.32 (m, 1H, NH, [2]), 8.08 (d, *J* = 6.7 Hz, 1H, NH, [3]), 7.91 (d, *J* = 5.2 Hz, 1H, NH, [4]), 7.81 (d, *J* = 7.7 Hz, 1H, NH, [5]), 7.56 – 7.39 (m, 3H, 2 CH aromatic, NH, [6]), 7.36 – 7.13 (m, 5H, 5 CH aromatic, [7]), 6.87 (d, *J* = 8.9 Hz, 2H, 2 CH aromatic, [8]), 5.88 – 5.66 (m, 1H, CH, [9]), 5.06 – 4.85 (m, 4H, CH_2, 2 CH, [10]), 4.78 (t, *J* = 6.1 Hz, 2H, 2 CH, [11]), 4.43 – 4.17 (m, 3H, CH_2, CH, [12]), 3.71 (s, 3H, OCH_3, [13]), 3.59 - 3.40 (m, 3H, CH_2, CH, [14]), 3.16 – 2.93 (m, 2H, CH_2, [15]), 2.66 (dd, *J* = 23.0, 6.5 Hz, 12H, 6 CH_2, [16]), 2.40 – 0.89 (m, 94H, 4 CH_3, 41 CH_2, [17]).

^{13}C NMR (75 MHz, DMSO-D_6) δ /ppm: 172.2, 171.8, 171.3, 171.1, 170.8, 170.7, 169.6, 168.5, 168.3, 167.6, 155.5, 139.4, 138.8, 131.5, 128.2, 127.0, 126.7, 121.1, 114.6, 113.8, 73.6, 73.2, 69.9, 55.1, 50.2, 47.5, 42.0, 41.0, 38.2, 34.4, 34.2, 34.0, 33.2, 32.7, 32.2, 31.5, 31.4, 31.0, 29.1, 29.0, 28.9, 28.8, 28.7, 28.6, 28.6, 28.5, 28.4, 28.3, 28.2, 27.5, 26.3, 25.9, 25.4, 25.3, 25.2, 24.6, 24.5, 20.7, 17.7.

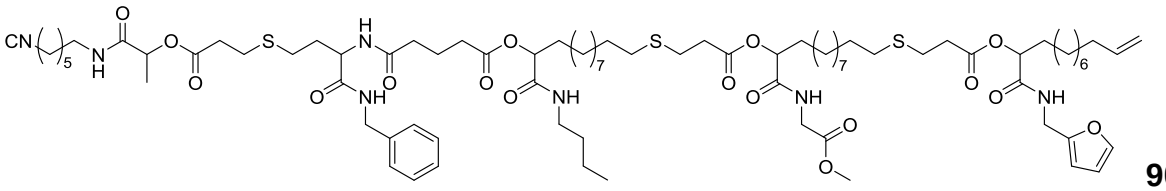
ESI-MS of $[C_{88}H_{141}N_7O_{15}S_3Na]^+$: calculated: 1654.9540, found: 1654.9634.

IR (ATR platinum diamond): ν [cm^{-1}] = 3304.1, 2923.2, 2852.3, 2145.6 (isocyanide), 1738.0, 1650.6, 1510.8, 1452.3, 1363.6, 1233.8, 1143.7, 1032.5, 830.1, 698.4, 429.2.

***R_f*:** (ethyl acetate) = 0.62.



Aminolysis and Thiol-Michael addition of the 3rd building block:



90

1.95 g of product **86** (1.57 mmol, 1.00 eq.) were dissolved in 4.0 mL chloroform (0.44 M) and subsequently, 0.36 g of benzylamine **24b** (3.33 mmol, 1.89 eq.) were added and the mixture was stirred at room temperature for nine hours. Then, 1.13 g of the acrylate-isocyanide **75** (4.46 mmol, 2.54 eq.), dissolved in 1.0 mL chloroform, were added and the mixture was stirred over night at room temperature. The product **90** was isolated by column chromatography (DCM/acetone 12:1 → 3:1) as a slightly yellow oil in a yield of 50 % (1.25 g).

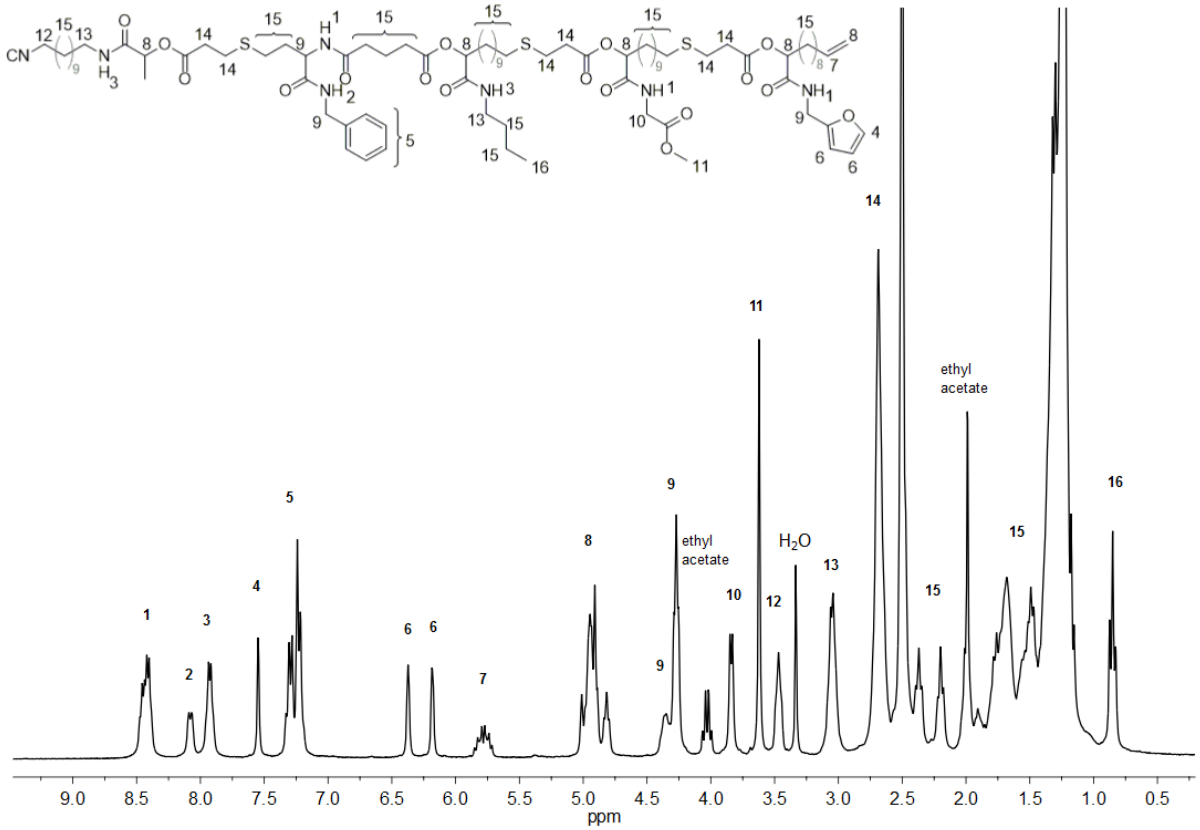
^{1}H NMR (300 MHz, DMSO-D_6) δ /ppm: 8.43 (dd, J = 10.7, 5.5 Hz, 3H, 3 NH, [1]), 8.08 (d, J = 6.5 Hz, 1H, NH, [2]), 7.93 (d, J = 5.3 Hz, 2H, 2 NH, [3]), 7.55 (s, 1H, CH aromatic, [4]), 7.39 – 7.11 (m, 5H, 5 CH aromatic, [5]), 6.37 (s, 1H, CH aromatic, [6]), 6.19 (s, 1H, CH aromatic, [6]), 5.89 - 5.67 (m, 1H, CH, [7]), 5.10 - 4.74 (m, 6H, CH_2, 4 CH, [8]), 4.47 - 4.13 (m, 5H, 2 CH_2, CH, [9]), 3.84 (d, J = 5.5 Hz, 2H, CH_2, [10]), 3.66 (s, 3H, OCH_3, [11]), 3.47 (s, 2H, CH_2, [12]), 3.19 - 2.91 (m, 4H, 2 CH_2, [13]), 2.69 (s, 12H, 4 CH_3, [14]), 2.42 – 0.97 (m, 81H, CH_3, 39 CH_2, [16]), 0.85 (t, J = 7.0 Hz, 3H, CH_3, [16]).

^{13}C NMR (75 MHz, DMSO-D_6) δ /ppm: 172.2, 171.8, 171.3, 171.3, 171.0, 170.9, 170.8, 170.3, 170.0, 169.9, 169.6, 169.2, 169.1, 152.1, 142.0, 139.4, 138.8, 128.2, 127.0, 126.7, 114.6, 110.4, 106.6, 73.2, 73.0, 69.9, 59.8, 52.0, 51.7, 42.0, 41.1, 38.2, 38.0, 35.4, 34.4, 34.2, 34.1, 33.2, 32.8, 32.1, 31.5, 31.4, 31.1, 31.0, 29.1, 29.0, 28.9, 28.8, 28.8, 28.7, 28.7, 28.5, 28.4, 28.3, 28.2, 27.5, 26.3, 26.2, 25.9, 25.4, 25.3, 24.5, 24.4, 24.2, 20.8, 20.6, 19.4, 17.7, 14.1, 13.6.

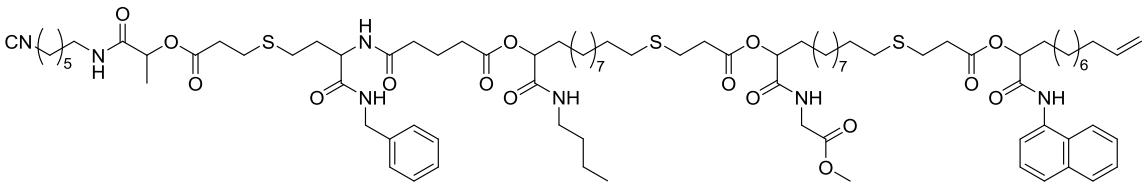
ESI-MS of $[C_{83}H_{133}N_7O_{17}S_3Na]^+$: calculated: 1618.8812, found: 1618.8799.

IR (ATR platinum diamond): ν [cm^{-1}] = 3285.7, 2921.3, 2851.0, 2147.1 (isocyanide), 1736.1, 1655.3, 1535.8, 1436.8, 1364.9, 1174.2, 1142.5, 912.3, 722.6, 698.5, 446.2.

***R_f*:** (ethyl acetate) = 0.48.



Aminolysis and Thiol-Michael addition of the 4th building block:



91

1.32 g of product **87** (1.06 mmol, 1.00 eq.) were dissolved in 2.3 mL chloroform (0.46 M) and subsequently, 0.21 g of benzylamine **24b** (1.97 mmol, 1.86 eq.) were added and the mixture was stirred at room temperature for nine hours. Then, 0.69 g of the acrylate-isocyanide **75** (2.72 mmol, 2.57 eq.), dissolved in 1.0 mL chloroform, were added and the mixture was stirred over night at room temperature. The product **91** was isolated by column chromatography (DCM/acetone 12:1 → 3:1) as a slightly yellow oil in a yield of 51 % (0.88 g).

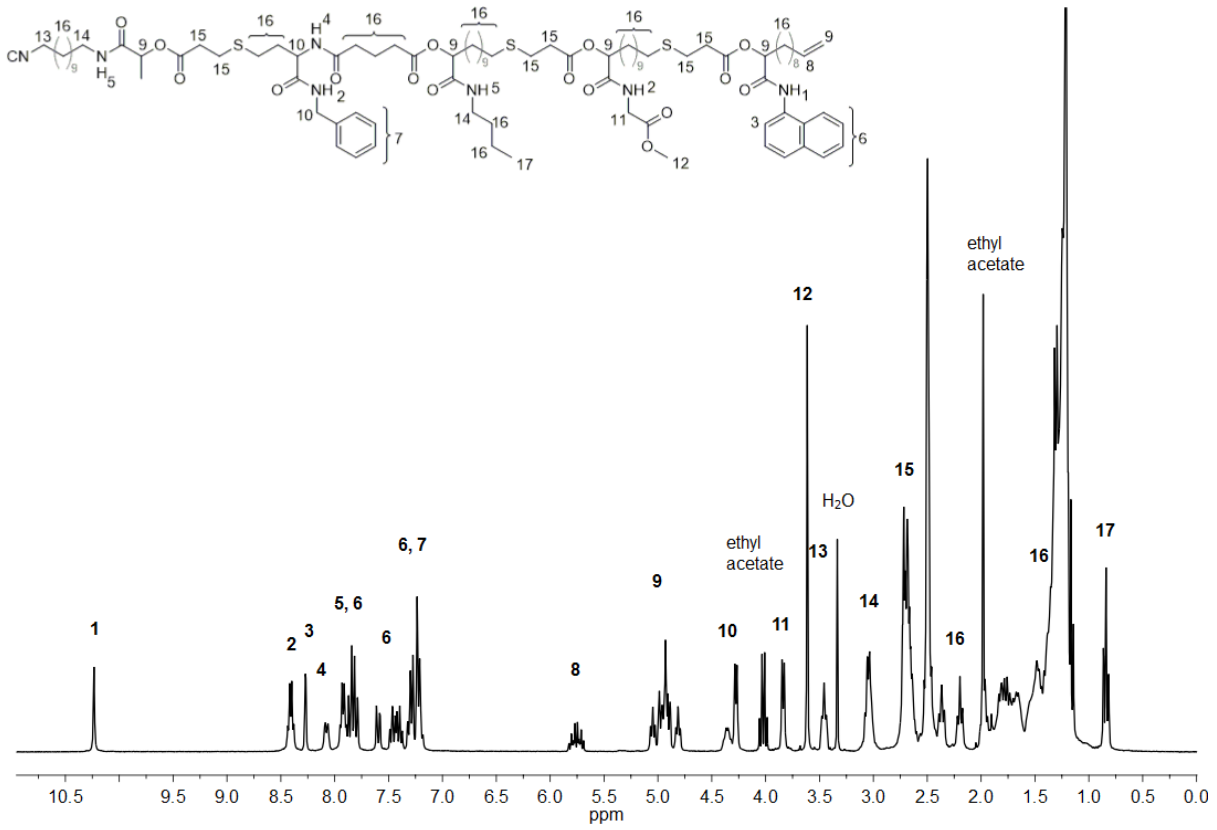
^{1}H NMR (300 MHz, DMSO-D_6) δ /ppm: 10.24 (s, 1H, NH, [1]), 8.49 - 8.33 (m, 2H, 2 NH, [2]), 8.28 (s, 1H, CH aromatic, [3]), 8.08 (d, J = 7.4 Hz, 1H, NH, [4]), 7.98 - 7.75 (m, 5H, 2 NH, 3 CH aromatic, [5, 6]), 7.60 (dd, J = 8.9, 1.7 Hz, 1H, CH aromatic, [6]), 7.52 - 7.35 (m, 2H, 2CH aromatic, [6]), 7.35 – 7.15 (m, 5H, 5 CH aromatic, [7]), 5.89 - 5.62 (m, 1H, CH, [8]), 5.13 – 4.73 (m, 6H, CH_2, 4 CH, [9]), 4.48 - 4.18 (m, 3H, CH_2, CH, [10]), 3.93 – 3.74 (m, 2H, CH_2, [11]), 3.62 (s, 3H, OCH_3 [12]), 3.52 – 3.39 (m, 2H, CH_2, [13]), 3.19 – 2.88 (m, 4H, 2 CH_2, [14]), 2.85 – 2.59 (m, 12H, 6 CH_2, [15]), 2.41 – 0.96 (m, 81H, CH_3, 39 CH_2, [16]), 0.84 (t, J = 7.2 Hz, 3H, CH_3, [17]).

^{13}C NMR (75 MHz, DMSO-D_6) δ /ppm: 172.2, 171.8, 171.3, 171.3, 171.2, 170.9, 170.8, 170.3, 170.0, 169.9, 169.6, 169.2, 168.4, 155.5, 155.4, 139.4, 138.7, 136.0, 133.3, 129.9, 128.4, 128.2, 127.4, 127.3, 127.0, 126.7, 126.4, 124.7, 120.1, 115.8, 114.6, 73.8, 73.2, 73.0, 69.9, 59.8, 52.0, 51.7, 42.0, 38.2, 38.0, 34.4, 34.2, 34.1, 33.2, 32.8, 32.7, 32.2, 31.5, 31.4, 31.3, 31.1, 31.0, 29.1, 29.1, 29.0, 28.9, 28.9, 28.8, 28.8, 28.7, 28.6, 28.5, 28.4, 28.3, 28.3, 27.5, 26.3, 26.2, 25.9, 25.4, 25.3, 24.7, 24.5, 24.2, 20.8, 20.6, 19.4, 17.7, 14.1, 13.6.

ESI-MS of $[C_{88}H_{135}N_7O_{16}S_3Na]^+$: calculated: 1664.9020, found: 1664.9134.

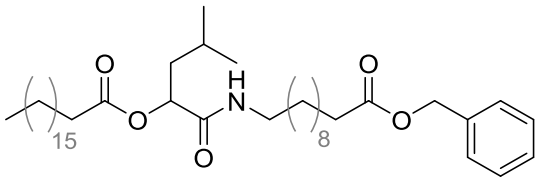
IR (ATR platinum diamond): ν [cm^{-1}] = 3286.0, 2922.5, 2851.9, 2147.2 (isocyanide), 1736.4, 1655.3, 1632.9, 1537.2, 1434.8, 1362.9, 1173.1, 1141.8, 910.6, 855.9, 815.1, 699.1, 474.1.

***R_f*:** (ethyl acetate) = 0.55.



Synthesis of the Carboxylic Acid Trimer by the Monomer Approach

1st P-3CR:



92

2.07 g stearic acid **1a** (7.28 mmol, 1.00 eq.) were dissolved in 8.0 mL DCM (0.91 M) and 1.02 g isovaleraldehyde **50e** (11.90 mmol, 1.63 eq.) as well as 3.31 g of monomer **49** (11.0 mmol, 1.51 eq.) were added. The mixture was stirred at room temperature for 24 hours and subsequently the solvent was removed under reduced pressure. The crude product was purified by column chromatography (hexane/ethyl acetate 10:1 → 5:1) to afford product **92** as a white solid in a yield of 85 % (4.01 g). Furthermore, the excess of the monomer **49** was partially recovered (0.53 g, 0.15 eq.) and can be reused.

^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 7.37 – 7.28 (m, 5H, 5 CH aromatic, ^{1}), 5.99 (t, J = 5.3 Hz, 1H, NH, ^{2}), 5.24 – 5.13 (m, 1H, CH, ^{3}), 5.10 (s, 2H, CH_2, ^{4}), 3.23 (dd, J = 13.4, 6.7 Hz, 2H, CH_2, ^{5}), 2.44 – 2.23 (m, 4H, 2 CH_2, ^{6}), 1.78 – 1.04 (m, 49 H, 24 CH_2, CH, ^{7}), 1.00 – 0.71 (m, 9H, 3 CH_3, ^{8}).

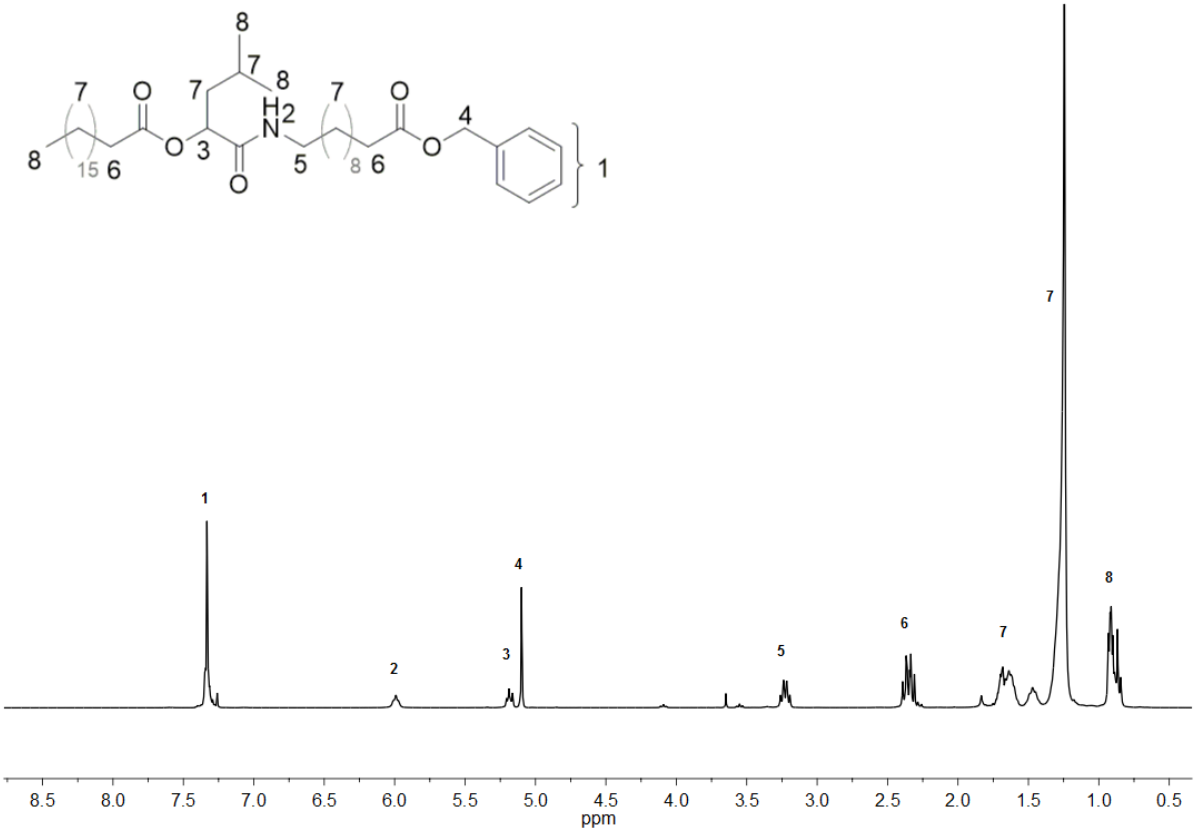
^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 173.7, 172.7, 170.3, 136.3, 128.6, 128.2, 72.7, 66.1, 41.0, 39.3, 34.4, 32.0, 29.8, 29.7, 29.7, 29.6, 29.6, 29.5, 29.4, 29.4, 29.4, 29.3, 29.2, 29.2, 26.9, 25.0, 24.7, 23.2, 22.8, 21.9, 14.2.

HRMS-FAB-MS of $[C_{42}H_{74}NO_5]^+$: calculated: 672.5562, found: 672.5563.

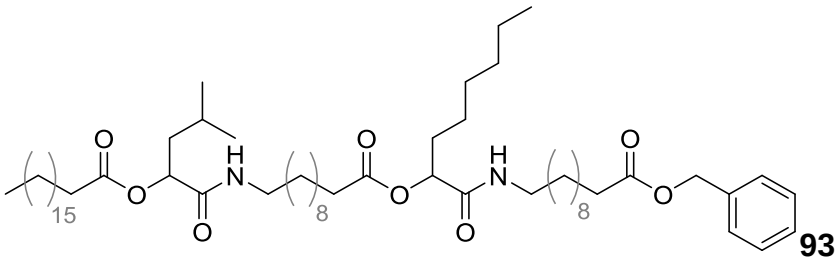
ESI-MS of $[C_{42}H_{74}NO_5Na]^+$: calculated: 694.5381, found: 694.5385

IR (ATR platinum diamond): ν [cm^{-1}] = 3262.7, 2916.4, 2849.6, 1736.9, 1654.9, 1560.6, 1466.1, 1371.9, 1272.5, 1253.1, 1233.1, 1212.8, 1165.7, 1110.8, 722.7, 694.5.

R_f: (hexane/ethyl acetate (5:1)) = 0.37.



2nd P-3CR:



93

3.12 g of **92** (4.64 mmol, 1.00 eq.) were dissolved in 18.0 mL of a 2:1-mixture of ethyl acetate and methanol (0.32 M) and 0.29 g (9.29 %w) palladium on activated charcoal were added. Subsequently, the mixture was purged with hydrogen (balloon) and stirred under hydrogen atmosphere overnight. The heterogeneous catalyst was filtered off and the solvent was evaporated under reduced pressure. The residue was redissolved in 5.0 mL DCM (0.93 M) and 0.79 g heptaldehyde **50b** (6.94 mmol, 1.50 eq.) as well as 2.11 g of monomer **49** (7.00 mmol, 1.51 eq.) were added. The mixture was stirred at room temperature for 24 hours and subsequently the solvent was removed under reduced pressure. The crude product was purified by column chromatography (hexane/ethyl acetate 8:1 → 5:2) to afford product **93** as a white solid in a yield of 87 % (3.96 g).

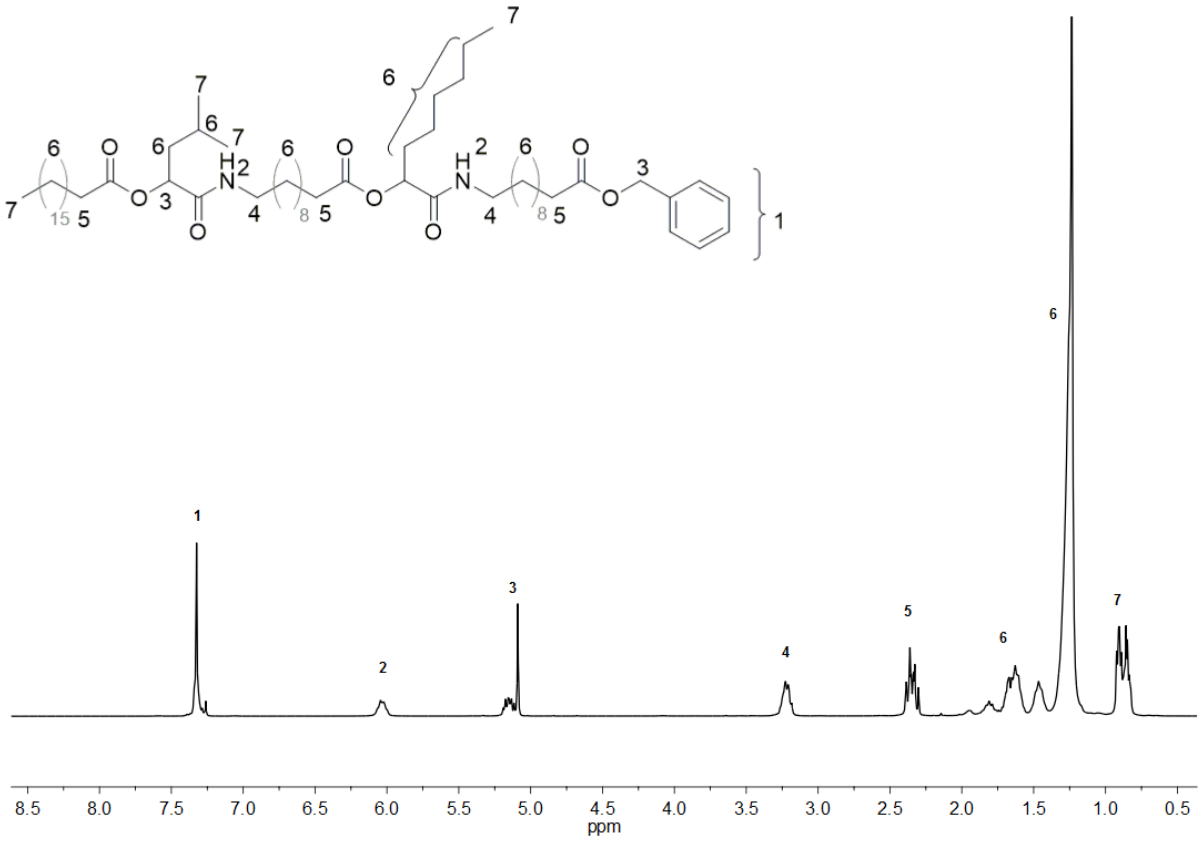
^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 7.38 – 7.27 (m, 5H, 5 CH aromatic, [1]), 6.13 – 5.94 (m, 2H, 2 NH, [2]), 5.21 – 5.04 (m, 4H, CH_2, 2 CH, [3]), 3.32 – 3.12 (m, 4H, 2 CH_2, [4]), 2.46 - 2.24 (m, 6H, 3 CH_2, [5]), 2.03 – 1.09 (m, 75H, 37 CH_2, CH, [6]), 0.97 – 0.76 (m, 12H, 4 CH_3, [7]).

^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 173.7, 172.7, 172.5, 170.3, 169.9, 136.2, 128.6, 128.2, 74.0, 72.7, 66.1, 40.9, 39.3, 34.4, 32.0, 31.7, 29.8, 29.7, 29.7, 29.6, 29.6, 29.5, 29.5, 29.4, 29.3, 29.3, 29.2, 29.1, 29.0, 26.9, 25.0, 24.7, 24.6, 23.2, 22.8, 22.6, 21.9, 14.2, 14.1.

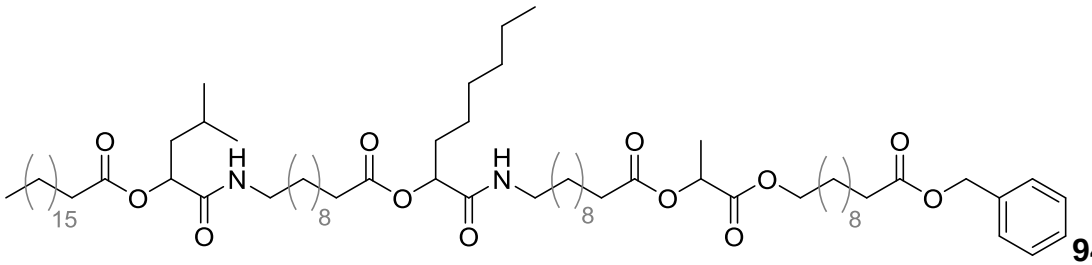
ESI-MS of $[C_{61}H_{108}N_2O_8Na]^+$: calculated: 1019.7998, found: 1019.7997

IR (ATR platinum diamond): ν [cm^{-1}] = 3268.5, 3089.6, 2917.0, 2850.1, 1738.3, 1658.7, 1548.9, 1465.6, 1374.5, 1310.7, 1272.7, 1253.0, 1233.1, 1213.2, 1190.8, 1165.2, 1112.1, 721.6, 696.3, 480.6.

***R*$_f$:** (hexane/ethyl acetate (5:2)) = 0.51.



3rd P-3CR:



94

3.66 g of **93** (3.72 mmol, 1.00 eq.) were dissolved in 11.2 mL of a 2:1-mixture of ethyl acetate and methanol (0.33 M) and 0.25 g (6.96 %w) palladium on activated charcoal were added. Subsequently, the mixture was purged with hydrogen (balloon) and stirred under hydrogen atmosphere overnight. The heterogeneous catalyst was filtered off and the solvent was evaporated under reduced pressure. The residue (3.04 g, 3.34 mmol, 1.00 eq.) was redissolved in 3.5 mL DCM (0.95 M) and 0.32 g acetaldehyde **50c** (7.27 mmol, 2.18 eq.) as well as 1.56 g of monomer **49** (5.17 mmol, 1.55 eq.) were added. The mixture was stirred at room temperature for 24 hours and subsequently the solvent was removed under reduced pressure. The crude product was purified by column chromatography (hexane/ethyl acetate 7:1 → 3:2) to afford product **94** as a white solid in a yield of 99 % (4.08 g).

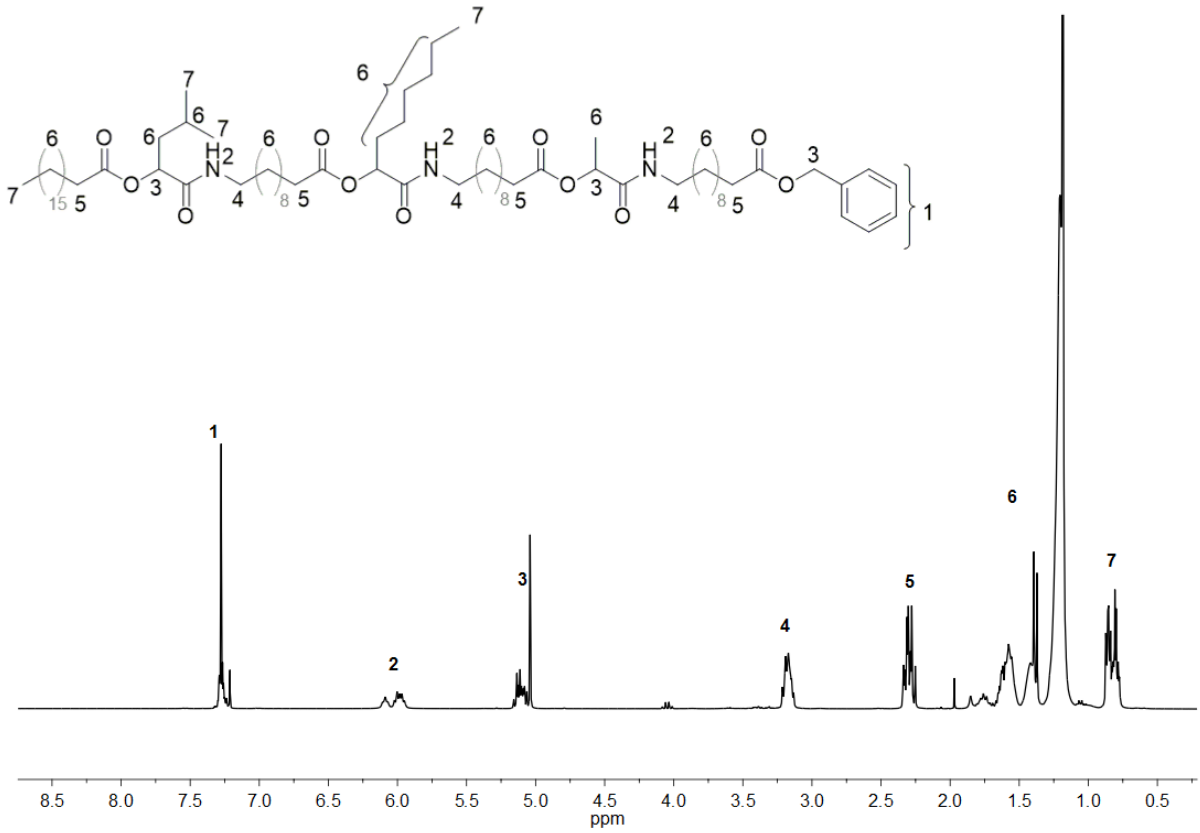
^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 7.38 – 7.28 (m, 5H, 5 CH aromatic, [1]), 6.26 - 5.89 (m, 3H, 3 NH, [2]), 5.27 – 4.97 (m, 5H, CH_2, 3 CH, [3]), 3.31 – 3.11 (m, 6H, 3 CH_2, [4]), 2.45 – 2.22 (m, 8H, 4 CH_2, [5]), 1.96 – 1.00 (m, 94H, CH_3, 45 CH_2, CH, [6]), 0.97 – 0.73 (m, 12H, 4 CH_3, [7]).

^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 173.7, 172.7, 172.5, 172.3, 170.4, 170.3, 169.9, 143.3, 136.2, 128.6, 128.2, 74.0, 72.7, 70.5, 66.1, 40.9, 39.3, 39.3, 39.2, 34.4, 32.0, 31.7, 29.8, 29.7, 29.7, 29.6, 29.6, 29.5, 29.5, 29.3, 29.3, 29.2, 29.0, 26.9, 25.0, 25.9, 24.9, 24.8, 24.6, 23.2, 22.7, 22.6, 21.8, 18.0, 14.2, 14.1.

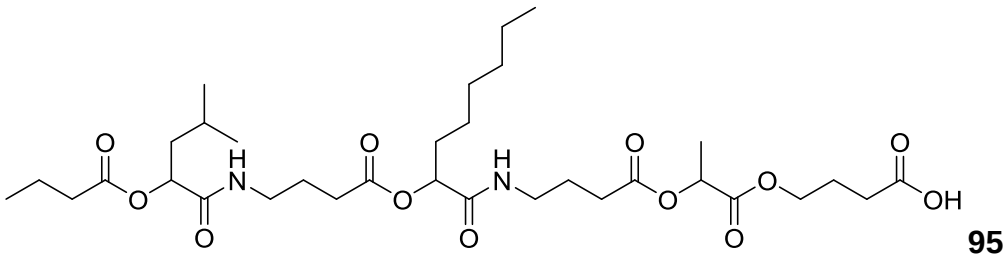
ESI-MS of $[C_{74}H_{133}N_3O_{11}Na]^+$: calculated: 1274.9832, found: 1274.9844.

IR (ATR platinum diamond): ν [cm^{-1}] = 3270.2, 3089.6, 2917.3, 2850.2, 1738.5, 1658.2, 1543.5, 1465.3, 1371.6, 1272.6, 1252.8, 1233.1, 1213.2, 1165.2, 1111.7, 721.4, 696.3, 380.4.

***R*$_f$:** (hexane/ethyl acetate (2:1)) = 0.38.



Deprotection of 94:



95

3.87 g **94** (3.13 mmol, 1.00 eq.) were dissolved in 10.0 mL of a 2:1 mixture of ethyl acetate and methanol (0.31 M) and 0.38 g (9.80 wt%) palladium on activated charcoal

were added. Subsequently, the mixture was purged with hydrogen (balloon) and stirred under hydrogen atmosphere overnight. The heterogeneous catalyst was filtered off and the solvent was evaporated under reduced pressure. The product **95** was obtained as a white solid in a yield of 98 % (3.53 g).

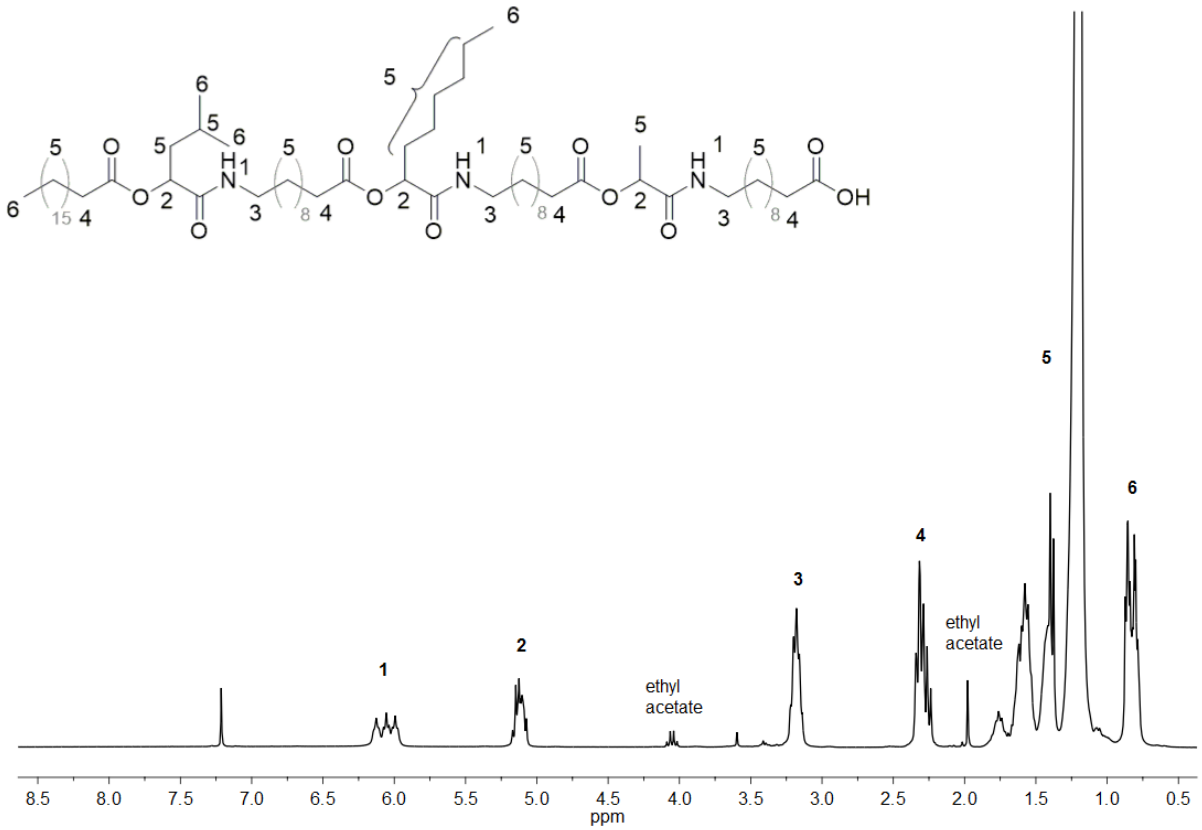
^{1}H NMR (300 MHz, $CDCl_3$) δ /ppm: 6.26 - 5.84 (m, 3H, 3 NH, ^{1}), 5.28 – 5.04 (m, 3H, 3 CH, ^{2}), 3.33 – 3.11 (m, 6H, 3 CH_2, ^{3}), 2.49 – 2.23 (m, 8H, 4 CH_2, ^{4}), 1.90 – 1.02 (m, 94H, CH_3, 45 CH_2, CH, ^{5}), 0.99 - 0.58 (m, 12H, 4 CH_3, ^{5}).

^{13}C NMR (75 MHz, $CDCl_3$) δ /ppm: 177.8, 172.8, 172.6, 172.4, 170.6, 170.5, 170.2, 74.0, 72.7, 70.5, 40.9, 39.3, 34.4, 34.0, 32.0, 31.7, 29.8, 29.8, 29.7, 29.6, 29.5, 29.5, 29.4, 29.3, 29.3, 29.2, 29.2, 29.1, 29.0, 26.9, 25.1, 25.0, 24.9, 24.8, 24.6, 23.2, 22.8, 22.6, 21.9, 18.0, 14.2, 14.1.

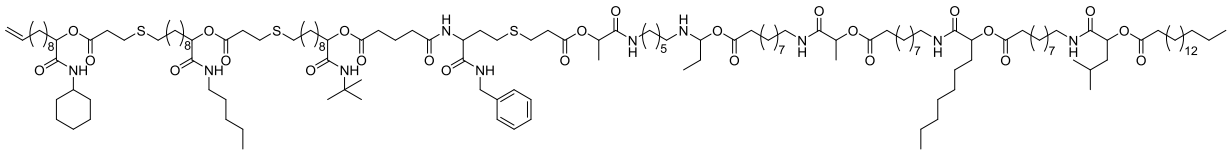
FAB-MS of $[C_{68}H_{128}N_3O_{11}]^+$: calculated: 1162.9, found: 1162.1.

ESI-MS of $[C_{142}H_{253}N_7O_{23}Na]^+$: calculated: 1184.9363, found:1184.9381.

IR (ATR platinum diamond): ν [cm^{-1}] = 3280.4, 3084.4, 2915.7, 2848.1, 1743.2, 1653.2, 1544.1, 1464.6, 1369.5, 1254.0, 1233.3, 1213.1, 1159.4, 1102.1, 720.0, 488.1, 397.5.



Coupling of the Carboxylic Acid Trimer 95 and the Isocyanide Building Block 88:



96

0.33 g of carboxylic acid trimer **95** (0.28 mmol, 1.00 eq.) were dissolved in 1.0 mL DCM (0.28 M). Subsequently, 0.47 g of the isocyanide-tetramer **88** (0.30 mmol, 1.05 eq.), as well as 0.17 g of propionaldehyde **50k** (2.98 mmol, 10.60 eq.) were added and the reaction mixture was stirred for 48 hours at room temperature. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (hexane/ethyl acetate 6:1 → 1:2). The product **96** was obtained as viscous oil in a yield of 80 % (0.63 g).

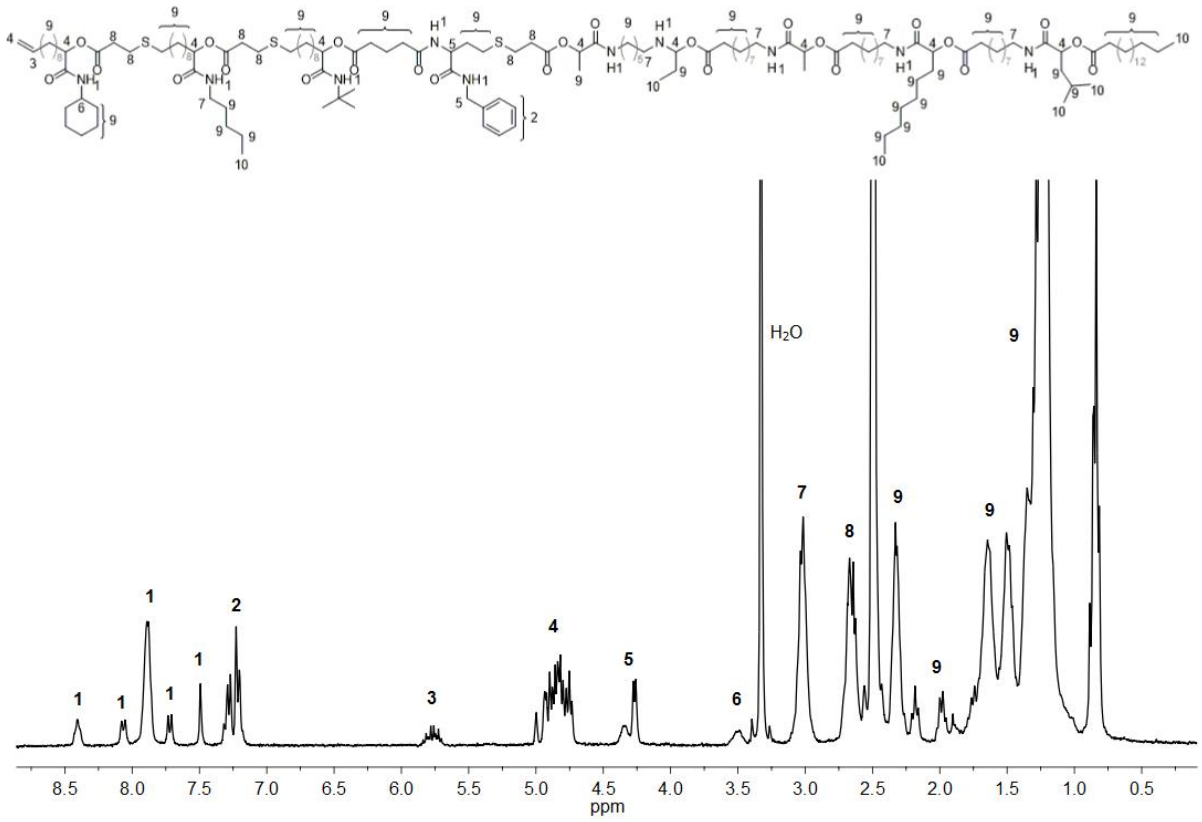
^{1}H NMR (300 MHz, DMSO-D_6) δ /ppm: 8.41 (s, 1H, NH, [1]), 8.07 (d, J = 8.1 Hz, 1H, NH, [1]), 7.99 - 7.80 (m, 6H, 6 NH, [1]), 7.72 (d, J = 7.9 Hz, 1H, NH, [1]), 7.50 (s, 1H, NH, [1]), 7.35 – 7.12 (m, 5H, 5 CH aromatic, [2]), 5.89 – 5.67 (m, 1H, CH, [3]), 5.01 - 4.63 (m, 10H, CH_2, 8 CH, [4]), 4.44 – 4.18 (m, 3H, CH_2, CH, [5]), 3.49 (s, 1H, CH, [6]), 3.17 - 2.87 (m, 12H, 6 CH_2, [7]), 2.80 – 2.59 (m, 12H, 6 CH_2, [8]), 2.41 – 0.95 (m, 206H, 5 CH_3, 95 CH_2, CH, [9]), 0.85 (m, 18H, 6 CH_3, [10]).

^{13}C NMR (101 MHz, DMSO-D_6) δ /ppm: 172.4, 172.2, 172.1, 171.8, 171.3, 170.9, 170.7, 169.8, 169.6, 169.5, 169.1, 169.0, 168.7, 168.1, 139.4, 138.8, 128.2, 127.0, 114.6, 73.4, 50.3, 38.2, 38.2, 34.4, 34.3, 33.4, 33.2, 32.3, 32.1, 31.5, 31.3, 31.2, 31.1, 29.1, 29.0, 28.9, 28.8, 28.7, 28.6, 28.6, 28.5, 28.5, 28.4, 28.3, 28.3, 28.2, 28.2, 26.4, 26.3, 26.2, 26.1, 26.0, 25.9, 25.2, 24.6, 24.5, 24.4, 24.3, 24.1, 22.9, 22.1, 22.0, 21.8, 21.6, 21.5, 20.7, 17.7, 17.6, 13.9, 13.8.

ESI-MS of $[C_{157}H_{278}N_{10}O_{26}S_3\ Na]^+$: calculated: 2839.9827, found: 2839.9897.

IR (ATR platinum diamond): ν [cm^{-1}] = 3303.8, 2922.3, 2852.0, 1739.5, 1650.7, 1534.9, 1435.9, 1365.7, 1231.5, 1148.1, 909.0, 722.0, 698.1, 397.3.

R_f: (ethyl acetate) = 0.62.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4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

7 Abbreviations

3-CR	three-component reaction
4-CR	four-component reaction
5-CR	five-component reaction
ADMET	acyclic diene metathesis polymerization
ATRA	Kharash reaction, atom transfer radical addition
ATRP	atom transfer radical polymerization
B-3CR	Biginelli three-component reaction
Bn	benzyl
CPG	controlled pore glass
CuAAC	Cu(I)-catalyzed azide-alkyne cycloaddition
CuMCR	copper catalyzed multicomponent reaction
DAR	Diels-Alder reaction
DCC	*N*-*N*'-dicyclohexylcarbodiimide
DCM	dichloromethane
de	diastereomeric excess
DFT	density functional theory
DIBAL-H	diisobutylaluminium hydride
DIC	diisopropylcarbodiimide
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMPA	2,2-dimethoxyphenyl-2-acetophenone
DMTr	dimethoxytrityl
DNA	desoxyribo nucleic acid
DP	degree of polymerization

DTS	DNA-templated synthesis
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
ESI-MS	electrospray ionisation mass spectrometry
FAB	fast atom bombardement
Fmoc	9-fluorenylmethyloxycarbonyl
GC	gas chromatography
GPC	gel permeation chromatography
H-3CR	Hanztsch three-component reaction
H-4CR	Hantzsch four-component reaction
HBTU	*N*-[(1H-benzotriazol-1-yl) (dimethylamino)methylene]-*N*-methylmethan-aminium hexafluorophosphate
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectrometry
HWE	Horner-Wadsworth-Emmons
IBX	2-iodoxybenzoic acid
IEG	iterative exonential growth
IMCR(s)	isocyanide-based multicomponent reaction(s)
IR	infrared
kDA	kilo Dalton
M-3CR	Mannich three-component reaction
MCR(s)	multicomponent reaction(s)
MS	mass spectrometry
MWD	molecular weight distribution
NHS	*N*-hydroxysuccinimidyl ester
NMP	nitroxide mediated polymerization

NMR	nuclear magnetic resonance
OPV	oligo(phenylene-vinylene)
P-3CR	Passerini three-component reaction
PDI	polydispersity index
PEG	poly(ethylene glycol)
PG	protecting group
PNA	peptide nucleic acid
PSS	*ortho*-pyridyl-disulfide
PyBOP	benzotriazol-1-yl-oxytripyrrolidino phosphonium hexafluorophosphate
pybox	*bis*-(oxazolinyl)pyridine
RAFT	reversible addition fragmentation chain transfer polymerization
RCM	ring closing metathesis
RDRP	reversible deactivation radical polymerization
RNA	ribonucleic acid
ROMP	ring opening metathesis polymerization
ROP	ring opening polymerization
S-3CR	Strecker three-component reaction
SEC	size exclusion chromatography
SM	self metathesis
SPPS	solid phase peptide synthesis
SUMI(s)	single unit monomer insertion(s)
TADDOL	*α*,*α*,*α*',*α*'-tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol
TBAF	*tetra*-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl

THF	tetrahydrofuran
TIPS	triisopropylsilyl
TOM	triisopropylsilyl oxy methyl
TS	transition state
U-4CR	Ugi four-component reaction
U-5CR	Ugi five-component reaction
UCST	upper critical solution temperature
UV	ultra violet

8 Bibliography

[1] N. Badi, J.-F. Lutz, *Chem. Soc. Rev.* **2009**, *38*, 3383-3390.

[2] J. D. Watson, F. H. C. Crick, *Nature* **1953**, *171*, 737-738.

[3] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 3479-3483.

[4] R. B. Merrifield, *J. Am. Chem. Soc.* **1963**, *85*, 2149-2154.

[5] R. B. Merrifield, *Angew. Chem. Int. Ed.* **1985**, *24*, 799-810.

[6] J.-F. Lutz, *Polym. Chem.* **2010**, *1*, 55-62.

[7] G. Moad, E. Rizzardo, *Macromolecules* **1995**, *28*, 8722-8728.

[8] J. Chiefari, Y. K. Chong, F. Ercole, J. Krstina, J. Jeffery, T. P. T. Le, R. T. A. Mayadunne, G. F. Meijs, C. L. Moad, G. Moad, E. Rizzardo, S. H. Thang, *Macromolecules* **1998**, *31*, 5559-5562.

[9] M. Szwarc, *Nature* **1956**, *178*, 1168-1169.

[10] M. Kato, M. Kamigaito, M. Sawamoto, T. Higashimura, *Macromolecules* **1995**, *28*, 1721-1723.

[11] J.-S. Wang, K. Matyjaszewski, *J. Am. Chem. Soc.* **1995**, *117*, 5614-5615.

[12] J.-F. Lutz, J.-M. Lehn, E. W. Meijer, K. Matyjaszewski, *Nat. Rev Mater.* **2016**, *1*, 16024.

[13] J. Niu, R. Hili, D. R. Liu, *Nat. Chem.* **2013**, *5*, 282-292.

[14] N. ten Brummelhuis, *Polym. Chem.* **2015**, *6*, 654-667.

[15] J.-F. Lutz, M. Ouchi, D. R. Liu, M. Sawamoto, *Science* **2013**, *341*.

[16] T. T. Trinh, C. Laure, J.-F. Lutz, *Macromol. Chem. Phys.* **2015**, *216*, 1498-1506.

[17] C. M. Thomas, J.-F. Lutz, *Angew. Chem. Int. Ed.* **2011**, *50*, 9244-9246.

[18] W. van Zoelen, R. N. Zuckermann, R. A. Segalman, *Macromolecules* **2012**, *45*, 7072-7082.

[19] J.-F. Lutz, *Macromolecules* **2015**, *48*, 4759-4767.

[20] H. Colquhoun, J.-F. Lutz, *Nat. Chem.* **2014**, *6*, 455-456.

[21] H. Mutlu, J.-F. Lutz, *Angew. Chem. Int. Ed.* **2014**, *53*, 13010-13019.

[22] A. Dömling, *Curr. Opin. Chem. Biol.* **2002**, *6*, 306-313.

[23] J. G. Rudick, *J. Polym. Sci., Part A: Polym. Chem.* **2013**, *51*, 3985-3991.

[24] I. Ugi, A. Dömling, W. Hörl, *Endeavour* **1994**, *18*, 115-122.

[25] A. Dömling, I. Ugi, *Angew. Chem. Int. Ed.* **2000**, *39*, 3168-3210.

[26] A. Dömling, *Chem. Rev.* **2006**, *106*, 17-89.

[27] P. A. Wender, S. T. Handy, D. L. Wright, *Chem. Ind.* **1997**, 765.

[28] A. Strecker, *Justus Liebigs Ann. Chem.* **1850**, *75*, 27-45.

[29] J. Wang, X. Liu, X. Feng, *Chem. Rev.* **2011**, *111*, 6947-6983.

[30] S. J. Zuend, M. P. Coughlin, M. P. Lalonde, E. N. Jacobsen, *Nature* **2009**, *461*, 968-970.

[31] A. Hantzsch, *Justus Liebigs Ann. Chem.* **1882**, *215*, 1-82.

[32] A. Hantzsch, *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 1474-1476.

[33] A. Fürstner, *Angew. Chem. Int. Ed.* **2003**, *42*, 3582-3603.

[34] A. J. Castro, *Nature* **1967**, *213*, 903-904.

[35] P. Biginelli, *Ber. Dtsch. Chem. Ges.* **1891**, *24*, 1317-1319.

[36] G. C. Rovnyak, K. S. Atwal, A. Hedberg, S. D. Kimball, S. Moreland, J. Z. Gougoutas, B. C. O'Reilly, J. Schwartz, M. F. Malley, *J. Med. Chem.* **1992**, *35*, 3254-3263.

[37] S. Sandhu, J. S. Sandhu, *Arkivoc* **2012**, *1*, 66-133.

[38] C. Mannich, W. Krösche, *Arch. Pharm.* **1912**, *250*, 647-667.

[39] R. Robinson, *J. Chem. Soc., Trans.* **1917**, *111*, 762-768.

[40] E. K. Fields, *J. Am. Chem. Soc.* **1952**, *74*, 1528-1531.

[41] R. Kakuchi, in *Multi-Component and Sequential Reactions in Polymer Synthesis* (Ed.: P. Theato), Springer International Publishing, Cham, **2015**, 1-15.

[42] O. Geis, H.-G. Schmalz, *Angew. Chem. Int. Ed.* **1998**, *37*, 911-914.

[43] A. Vázquez-Romero, L. Cárdenas, E. Blasi, X. Verdaguer, A. Riera, *Org. Lett.* **2009**, *11*, 3104-3107.

[44] P. L. Pauson, I. U. Khand, *Ann. N.Y. Acad. Sci.* **1977**, *295*, 2-14.

[45] P. L. Pauson, *Tetrahedron* **1985**, *41*, 5855-5860.

[46] W. Reppe, in *Neue Entwicklungen auf dem Gebiete der Chemie des Acetylens und Kohlenoxyds*, Springer Berlin Heidelberg, Berlin, Heidelberg, **1949**, 94-165.

[47] B. Cornils, W. A. Herrmann, M. Rasch, *Angew. Chem. Int. Ed.* **1994**, *33*, 2144-2163.

[48] C. Wei, Z. Li, C.-J. Li, *Synlett* **2004**, *2004*, 1472-1483.

[49] L. Rubio-Pérez, M. Iglesias, J. Munárriz, V. Polo, J. J. Pérez-Torrente, L. A. Oro, *Chem. - Eur. J.* **2015**, *21*, 17701-17707.

[50] I. Bae, H. Han, S. Chang, *J. Am. Chem. Soc.* **2005**, *127*, 2038-2039.

[51] M. Heravi, M. Daraie, *Molecules* **2016**, *21*, 441-453.

[52] S. Marcaccini, T. Torroba, *Org. Prep. Proced. Int.* **1993**, *25*, 141-208.

[53] R. Schröder, U. Schöllkopf, E. Blume, I. Hoppe, *Justus Liebigs Ann. Chem.* **1975**, *1975*, 533-546.

[54] A. M. Van Leusen, J. Wildeman, O. H. Oldenziel, *J. Org. Chem.* **1977**, *42*, 1153-1159.

[55] D. van Leusen, A. M. van Leusen, *Synthesis* **1991**, *1991*, 531-532.

[56] T. J. Deming, B. M. Novak, *J. Am. Chem. Soc.* **1992**, *114*, 7926-7927.

[57] F. Millich, *Chem. Rev.* **1972**, *72*, 101-113.

[58] W. Lieke, *Justus Liebigs Ann. Chem.* **1859**, *112*, 316-321.

[59] M. S. Edenborough, R. B. Herbert, *Nat. Prod.* **1988**, *5*, 229-245.

[60] P. J. Scheuer, *Acc. Chem. Res.* **1992**, *25*, 433-439.

[61] A. Gautier, *Justus Liebigs Ann. Chem.* **1868**, *146*, 119-124.

[62] A. W. Hofmann, *Justus Liebigs Ann. Chem.* **1867**, *144*, 114-120.

[63] A. W. Hofmann, *Ber. Dtsch. Chem. Ges.* **1870**, *3*, 826-827.

[64] I. Ugi, R. Meyr, *Angew. Chem.* **1958**, *70*, 702-703.

[65] I. Ugi, U. Fetzer, U. Eholzer, H. Knupfer, K. Offermann, *Angew. Chem.* **1965**, *77*, 492-504.

[66] H. Eckert, B. Forster, *Angew. Chem.* **1987**, *99*, 922-923.

[67] G. Skorna, I. Ugi, *Angew. Chem. Int. Ed.* **1977**, *16*, 259-260.

[68] C. G. Neochoritis, T. Zarganes-Tzitzikas, S. Stotani, A. Dömling, E. Herdtweck, K. Khoury, A. Dömling, *ACS Comb. Sci.* **2015**, *17*, 493-499.

[69] C. G. Neochoritis, S. Stotani, B. Mishra, A. Dömling, *Org. Lett.* **2015**, *17*, 2002-2005.

[70] M. Passerini, *Gazz. Chim. Ital.* **1921**, *51*, 126-129.

[71] J. W. McFarland, *J. Org. Chem.* **1963**, *28*, 2179-2181.

[72] I. Ugi, R. Meyr, *Chem. Ber.* **1961**, *94*, 2229-2233.

[73] S. C. Solleder, Diploma Thesis KIT, Karlsruhe, *Sequence-Control in Polymer Chemistry via Multicomponent Reactions* **2013**.

[74] R. H. Baker, D. Stanonis, *J. Am. Chem. Soc.* **1951**, *73*, 699-702.

[75] I. Hagedorn, U. Eholzer, *Chem. Ber.* **1965**, *98*, 936-940.

[76] M. C. Pirrung, K. D. Sarma, *J. Am. Chem. Soc.* **2004**, *126*, 444-445.

[77] I. Ugi, *Angew. Chem.* **1962**, *74*, 9-22.

[78] S. Maeda, S. Komagawa, M. Uchiyama, K. Morokuma, *Angew. Chem. Int. Ed.* **2011**, *50*, 644-649.

[79] R. Ramozzi, K. Morokuma, *J. Org. Chem.* **2015**, *80*, 5652-5657.

[80] U. Fetzer, I. Ugi, *Justus Liebigs Ann. Chem.* **1962**, *659*, 184-189.

[81] L. El Kaïm, L. Grimaud, *Eur. J. Org. Chem.* **2014**, *2014*, 7749-7762.

[82] B. Beck, M. Magnin-Lachaux, E. Herdtweck, A. Dömling, *Org. Lett.* **2001**, *3*, 2875-2878.

[83] T. Ngouansavanh, J. Zhu, *Angew. Chem. Int. Ed.* **2006**, *45*, 3495-3497.

[84] H. Bock, I. Ugi, *J. Prakt. Chem.* **1997**, *339*, 385-389.

[85] R. Frey, S. G. Galbraith, S. Guelfi, C. Lamberth, M. Zeller, *Synlett* **2003**, *2003*, 1536-1538.

[86] L. Banfi, G. Guanti, R. Riva, *Chem. Commun.* **2000**, 985-986.

[87] U. Kusebauch, B. Beck, K. Messer, E. Herdtweck, A. Dömling, *Org. Lett.* **2003**, *5*, 4021-4024.

[88] P. R. Andreana, C. C. Liu, S. L. Schreiber, *Org. Lett.* **2004**, *6*, 4231-4233.

[89] R. M. I. Ugi, U. Fetzer, C. Steinbrückner, *Angew. Chem.* **1959**, *71*, 373-388.

[90] I. Ugi, C. Steinbrückner, *Angew. Chem.* **1960**, *72*, 267-268.

[91] S. Marcaccini, T. Torroba, *Nat. Protocols* **2007**, *2*, 632-639.

[92] O. Mumm, *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 886-893.

[93] I. Ugi, C. Steinbrückner, *Chem. Ber.* **1961**, *94*, 734-742.

[94] N. Chéron, R. Ramozzi, L. E. Kaïm, L. Grimaud, P. Fleurat-Lessard, *J. Org. Chem.* **2012**, *77*, 1361-1366.

[95] G. A. Medeiros, W. A. da Silva, G. A. Bataglion, D. A. C. Ferreira, H. C. B. de Oliveira, M. N. Eberlin, B. A. D. Neto, *Chem. Commun.* **2014**, *50*, 338-340.

[96] C. Iacobucci, S. Reale, J.-F. Gal, F. De Angelis, *Eur. J. Org. Chem.* **2014**, *2014*, 7087-7090.

[97] C. Faggi, M. García-Valverde, S. Marcaccini, G. Menchi, *Org. Lett.* **2010**, *12*, 788-791.

[98] I. Ugi, F. K. Rosendahl, F. Bodesheim, *Justus Liebigs Ann. Chem.* **1963**, *666*, 54-61.

[99] I. Ugi, C. Steinbrückner, *Chem. Ber.* **1961**, *94*, 2802-2814.

[100] T. A. Keating, R. W. Armstrong, *J. Org. Chem.* **1998**, *63*, 867-871.

[101] L. El Kaïm, L. Grimaud, J. Oble, *Angew. Chem. Int. Ed.* **2005**, *44*, 7961-7964.

[102] A. A. Levy, H. C. Rains, S. Smiles, *J. Chem. Soc* **1931**, 3264-3269.

[103] L. El Kaïm, M. Gizolme, L. Grimaud, J. Oble, *J. Org. Chem.* **2007**, *72*, 4169-4180.

[104] R. Urban, I. Ugi, *Angew. Chem. Int. Ed.* **1975**, *14*, 61-62.

[105] G. Eberle, I. Ugi, *Angew. Chem.* **1976**, *88*, 509-510.

[106] H. Kunz, W. Pfrengle, *J. Am. Chem. Soc.* **1988**, *110*, 651-652.

[107] K. Oertel, G. Zech, H. Kunz, *Angew. Chem. Int. Ed.* **2000**, *39*, 1431-1433.

[108] M. Rubinshtein, C. R. James, J. L. Young, Y. J. Ma, Y. Kobayashi, N. C. Gianneschi, J. Yang, *Org. Lett.* **2010**, *12*, 3560-3563.

[109] O. Kreye, T. Tóth, M. A. R. Meier, *J. Am. Chem. Soc.* **2011**, *133*, 1790-1792.

[110] O. Kreye, O. Türünç, A. Sehlinger, J. Rackwitz, M. A. R. Meier, *Chem. - Eur. J.* **2012**, *18*, 5767-5776.

[111] A. Sehlinger, L. M. de Espinosa, M. A. R. Meier, *Macromol. Chem. Phys.* **2013**, *214*, 2821-2828.

[112] L. Montero de Espinosa, M. A. R. Meier, *Chem. Commun.* **2011**, *47*, 1908-1910.

[113] A. Sehlinger, O. Kreye, M. A. R. Meier, *Macromolecules* **2013**, *46*, 6031-6037.

[114] A. Sehlinger, K. Ochsenreither, N. Bartnick, M. A. R. Meier, *Eur. Polym. J.* **2015**, *65*, 313-324.

[115] C. V. Robotham, C. Baker, B. Cuevas, K. Abboud, D. L. Wright, *Mol. Divers.* **2003**, *6*, 237-244.

[116] G.-M. Wu, W.-l. Sun, Z.-Q. Shen, *Chin. J. Polym. Sci.* **2009**, *27*, 293-296.

[117] H. Wu, C. Fu, Y. Zhao, B. Yang, Y. Wei, Z. Wang, L. Tao, *ACS Macro Lett.* **2015**, *4*, 1189-1193.

[118] A. Sehlinger, P.-K. Dannecker, O. Kreye, M. A. R. Meier, *Macromolecules* **2014**, *47*, 2774-2783.

[119] M. Winkler, M. A. R. Meier, *Green Chem.* **2014**, *16*, 3335-3340.

[120] M. Winkler, M. A. R. Meier, *Green Chem.* **2014**, *16*, 1784-1788.

[121] X.-X. Deng, L. Li, Z.-L. Li, A. Lv, F.-S. Du, Z.-C. Li, *ACS Macro Lett.* **2012**, *1*, 1300-1303.

[122] Y.-Z. Wang, X.-X. Deng, L. Li, Z.-L. Li, F.-S. Du, Z.-C. Li, *Polym. Chem.* **2013**, *4*, 444-448.

[123] A. Sehlinger, R. Schneider, M. A. R. Meier, *Eur. Polym. J.* **2014**, *50*, 150-157.

[124] A. Sehlinger, M. A. R. Meier, in *Multi-Component and Sequential Reactions in Polymer Synthesis* (Ed.: P. Theato), Springer International Publishing, Cham, **2015**, 61-86.

[125] A. Lv, X.-X. Deng, L. Li, Z.-L. Li, Y.-Z. Wang, F.-S. Du, Z.-C. Li, *Polym. Chem.* **2013**, *4*, 3659-3662.

[126] S. Oelmann, S. C. Solleder, M. A. R. Meier, *Polym. Chem.* **2016**, *7*, 1857-1860.

[127] M. Hartweg, C. R. Becer, *Green Chem.* **2016**, *18*, 3272-3277.

[128] A. Sehlinger, R. Schneider, M. A. R. Meier, *Macromol. Rapid Commun.* **2014**, *35*, 1866-1871.

[129] C. Hulme, L. Ma, J. J. Romano, G. Morton, S.-Y. Tang, M.-P. Cherrier, S. Choi, J. Salvino, R. Labaudiniere, *Tetrahedron Lett.* **2000**, *41*, 1889-1893.

[130] Y. Zhao, Y. Yu, Y. Zhang, X. Wang, B. Yang, Y. Zhang, Q. Zhang, C. Fu, Y. Wei, L. Tao, *Polym. Chem.* **2015**, *6*, 4940-4945.

[131] A. C. Boukis, A. Llevot, M. A. R. Meier, *Macromol. Rapid Commun.* **2016**, *37*, 643-649.

[132] I.-H. Lee, H. Kim, T.-L. Choi, *J. Am. Chem. Soc.* **2013**, *135*, 3760-3763.

[133] R. Kakuchi, P. Theato, *ACS Macro Lett.* **2014**, *3*, 329-332.

[134] R. Kakuchi, P. Theato, *ACS Macro Lett.* **2013**, *2*, 419-422.

[135] N. Kolb, M. A. R. Meier, *Eur. Polym. J.* **2013**, *49*, 843-852.

[136] C. Zhu, B. Yang, Y. Zhao, C. Fu, L. Tao, Y. Wei, *Polym. Chem.* **2013**, *4*, 5395-5400.

[137] J.-F. Lutz, in *Sequence-Controlled Polymers: Synthesis, Self-Assembly, and Properties, Vol. 1170*, American Chemical Society, Washington DC, **2014**, 1-11.

[138] J.-F. Lutz, *ACS Macro Lett.* **2014**, *3*, 1020-1023.

[139] S. J. Rowan, C. Barner-Kowollik, B. Klumperman, P. Gaspard, R. B. Grubbs, M. A. Hillmyer, L. R. Hutchings, M. K. Mahanthappa, D. Moatsou, R. K. O'Reilly, M. Ouchi, M. Sawamoto, T. P. Lodge, *ACS Macro Lett.* **2016**, *5*, 1-3.

[140] T. Lodge, S. Rowan, *ACS Macro Lett.* **2014**, *3*, 1036-1036.

[141] N. Sewald, H.-D. Jakubke, in *Peptides: Chemistry and Biology*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, **2003**, 135-267.

[142] B. F. Gisin, R. B. Merrifield, D. C. Tosteson, *J. Am. Chem. Soc.* **1969**, *91*, 2691-2695.

[143] P. Kusch, *Angew. Chem.* **1966**, *78*, 611-611.

[144] R. L. Letsinger, V. Mahadevan, *J. Am. Chem. Soc.* **1965**, *87*, 3526-3527.

[145] C. Schuerch, J. M. Frechet, *J. Am. Chem. Soc.* **1971**, *93*, 492-496.

[146] L. Christensen, R. Fitzpatrick, B. Gildea, K. H. Petersen, H. F. Hansen, T. Koch, M. Egholm, O. Buchardt, P. E. Nielsen, J. Coull, R. H. Berg, *J. Pept. Sci.* **1995**, *1*, 175-183.

[147] R. N. Zuckermann, J. M. Kerr, S. B. H. Kent, W. H. Moos, *J. Am. Chem. Soc.* **1992**, *114*, 10646-10647.

[148] M. Amblard, J.-A. Fehrentz, J. Martinez, G. Subra, *Mol. Biotechnol.*, *33*, 239-254.

[149] S.-S. Wang, *J. Am. Chem. Soc.* **1973**, *95*, 1328-1333.

[150] H. Rink, *Tetrahedron Lett.* **1987**, *28*, 3787-3790.

[151] E. Atherton, D. L. J. Clive, R. C. Sheppard, *J. Am. Chem. Soc.* **1975**, *97*, 6584-6585.

[152] T. Shioiri, K. Ninomiya, S. Yamada, *J. Am. Chem. Soc.* **1972**, *94*, 6203-6205.

[153] T. Wieland, C. Birr, F. Flor, *Angew. Chem.* **1971**, *83*, 333-334.

[154] J. C. Sheehan, G. P. Hess, *J. Am. Chem. Soc.* **1955**, *77*, 1067-1068.

[155] J. Coste, D. Le-Nguyen, B. Castro, *Tetrahedron Lett.* **1990**, *31*, 205-208.

[156] V. Dourtoglou, J.-C. Ziegler, B. Gross, *Tetrahedron Lett.* **1978**, *19*, 1269-1272.

[157] L. A. Carpino, G. Y. Han, *J. Org. Chem.* **1972**, *37*, 3404-3409.

[158] R. B. Merrifield, J. M. Stewart, N. Jernberg, *Anal. Chem.* **1966**, *38*, 1905-1914.

[159] R. B. Merrifield, J. M. Stewart, *Nature* **1965**, *207*, 522-523.

[160] R. B. Merrifield, *Science* **1965**, *150*, 178-185.

[161] G. R. Marshall, R. B. Merrifield, *Biochemistry* **1965**, *4*, 2394-2401.

[162] M. Manning, *J. Am. Chem. Soc.* **1968**, *90*, 1348-1349.

[163] S. Kent, *J. Pept. Sci.* **2003**, *9*, 574-593.

[164] M. Schnölzer, P. Alewood, A. Jones, D. Alewood, S. B. H. Kent, *Int. J. Pept. Protein Res.* **1992**, *40*, 180-193.

[165] M. Schnolzer, S. Kent, *Science* **1992**, *256*, 221-225.

[166] P. Dawson, T. Muir, I. Clark-Lewis, S. Kent, *Science* **1994**, *266*, 776-779.

[167] T. Wieland, E. Bokelmann, L. Bauer, H. U. Lang, H. Lau, *Justus Liebigs Ann. Chem.* **1953**, *583*, 129-149.

[168] P. E. Dawson, S. B. H. Kent, *Annu. Rev. Biochem* **2000**, *69*, 923-960.

[169] W. Lu, M. Randal, A. Kossiakoff, S. B. H. Kent, *Chem. Biol.* **1999**, *6*, 419-427.

[170] L. E. Canne, S. J. Bark, S. B. H. Kent, *J. Am. Chem. Soc.* **1996**, *118*, 5891-5896.

[171] D. W. Low, M. G. Hill, M. R. Carrasco, S. B. H. Kent, P. Botti, *Proc. Natl. Acad. Sci.* **2001**, *98*, 6554-6559.

[172] E. Saxon, C. R. Bertozzi, *Science* **2000**, *287*, 2007-2010.

[173] H. Staudinger, J. Meyer, *Helv. Chim. Acta* **1919**, *2*, 635-646.

[174] B. L. Nilsson, L. L. Kiessling, R. T. Raines, *Org. Lett.* **2000**, *2*, 1939-1941.

[175] M. Baca, T. W. Muir, M. Schnoelzer, S. B. H. Kent, *J. Am. Chem. Soc.* **1995**, *117*, 1881-1887.

[176] G. G. Kochendoerfer, S.-Y. Chen, F. Mao, S. Cressman, S. Traviglia, H. Shao, C. L. Hunter, D. W. Low, E. N. Cagle, M. Carnevali, V. Gueriguian, P. J. Keogh, H. Porter, S. M. Stratton, M. C. Wiedeke, J. Wilken, J. Tang, J. J. Levy, L. P. Miranda, M. M. Crnogorac, S. Kalbag, P. Botti, J. Schindler-Horvat, L. Savatski, J. W. Adamson, A. Kung, S. B. H. Kent, J. A. Bradburne, *Science* **2003**, *299*, 884-887.

[177] R. J. Simon, R. S. Kania, R. N. Zuckermann, V. D. Huebner, D. A. Jewell, S. Banville, S. Ng, L. Wang, S. Rosenberg, C. K. Marlowe, *Proc. Natl. Acad. Sci.* **1992**, *89*, 9367-9371.

[178] C. W. Wu, T. J. Sanborn, K. Huang, R. N. Zuckermann, A. E. Barron, *J. Am. Chem. Soc.* **2001**, *123*, 6778-6784.

[179] J. Seo, A. E. Barron, R. N. Zuckermann, *Org. Lett.* **2010**, *12*, 492-495.

[180] A. M. Rosales, R. A. Segalman, R. N. Zuckermann, *Soft Matter* **2013**, *9*, 8400-8414.

[181] D. Zhang, S. H. Lahasky, L. Guo, C.-U. Lee, M. Lavan, *Macromolecules* **2012**, *45*, 5833-5841.

[182] R. N. Zuckermann, *Peptide Science* **2011**, *96*, 545-555.

[183] J. E. Murphy, T. Uno, J. D. Hamer, F. E. Cohen, V. Dwarki, R. N. Zuckermann, *Proc. Natl. Acad. Sci.* **1998**, *95*, 1517-1522.

[184] A. S. Culf, R. J. Ouellette, *Molecules* **2010**, *15*, 5282-5335.

[185] T. Uno, E. Beausoleil, R. A. Goldsmith, B. H. Levine, R. N. Zuckermann, *Tetrahedron Lett.* **1999**, *40*, 1475-1478.

[186] P. Armand, K. Kirshenbaum, R. A. Goldsmith, S. Farr-Jones, A. E. Barron, K. T. V. Truong, K. A. Dill, D. F. Mierke, F. E. Cohen, R. N. Zuckermann, E. K. Bradley, *Proc. Natl. Acad. Sci.* **1998**, *95*, 4309-4314.

[187] K. Kirshenbaum, A. E. Barron, R. A. Goldsmith, P. Armand, E. K. Bradley, K. T. V. Truong, K. A. Dill, F. E. Cohen, R. N. Zuckermann, *Proc. Natl. Acad. Sci.* **1998**, *95*, 4303-4308.

[188] K. Huang, C. W. Wu, T. J. Sanborn, J. A. Patch, K. Kirshenbaum, R. N. Zuckermann, A. E. Barron, I. Radhakrishnan, *J. Am. Chem. Soc.* **2006**, *128*, 1733-1738.

[189] C. W. Wu, K. Kirshenbaum, T. J. Sanborn, J. A. Patch, K. Huang, K. A. Dill, R. N. Zuckermann, A. E. Barron, *J. Am. Chem. Soc.* **2003**, *125*, 13525-13530.

[190] B. C. Gorske, B. L. Bastian, G. D. Geske, H. E. Blackwell, *J. Am. Chem. Soc.* **2007**, *129*, 8928-8929.

[191] B. C. Gorske, J. R. Stringer, B. L. Bastian, S. A. Fowler, H. E. Blackwell, *J. Am. Chem. Soc.* **2009**, *131*, 16555-16567.

[192] J. R. Stringer, J. A. Crapster, I. A. Guzei, H. E. Blackwell, *J. Am. Chem. Soc.* **2011**, *133*, 15559-15567.

[193] K. T. Nam, S. A. Shelby, P. H. Choi, A. B. Marciel, R. Chen, L. Tan, T. K. Chu, R. A. Mesch, B.-C. Lee, M. D. Connolly, C. Kisielowski, R. N. Zuckermann, *Nat. Mater.* **2010**, *9*, 454-460.

[194] H. K. Murnen, A. M. Rosales, J. N. Jaworski, R. A. Segalman, R. N. Zuckermann, *J. Am. Chem. Soc.* **2010**, *132*, 16112-16119.

[195] S. L. Beaucage, M. H. Caruthers, *Tetrahedron Lett.* **1981**, *22*, 1859-1862.

[196] T. G. W. Edwardson, K. M. M. Carneiro, C. J. Serpell, H. F. Sleiman, *Angew. Chem. Int. Ed.* **2014**, *53*, 4567-4571.

[197] A. Al Ouahabi, L. Charles, J.-F. Lutz, *J. Am. Chem. Soc.* **2015**, *137*, 5629-5635.

[198] A. A. Ouahabi, M. Kotera, L. Charles, J.-F. Lutz, *ACS Macro Lett.* **2015**, *4*, 1077-1080.

[199] J.-H. Fuhrhop, G. Penzlin, *Organic synthesis : concepts, methods, starting materials*, 2., rev. and enlarged ed., VCH, Weinheim, **1994**.

[200] W. S. Marshall, R. J. Kaiser, *Curr. Opin. Chem. Biol.* **2004**, *8*, 222-229.

[201] S. L. Beaucage, R. P. Iyer, *Tetrahedron* **1992**, *48*, 2223-2311.

[202] S. Pitsch, P. A. Weiss, L. Jenny, A. Stutz, X. Wu, *Helv. Chim. Acta* **2001**, *84*, 3773-3795.

[203] H. Cramer, R. Rhea, J. Okicki, K. Yirava, R. Silverman, *Nucleosides, Nucleotides and Nucleic Acids* **2003**, *22*, 1733-1736.

[204] L. J. McBride, M. H. Caruthers, *Tetrahedron Lett.* **1983**, *24*, 245-248.

[205] N. D. Sinha, J. Biernat, J. McManus, H. Köster, *Nucleic Acids Res.* **1984**, *12*, 4539-4557.

[206] S. P. Adams, K. S. Kavka, E. J. Wykes, S. B. Holder, G. R. Galluppi, *J. Am. Chem. Soc.* **1983**, *105*, 661-663.

[207] C. B. Reese, *Org. Biomol. Chem.* **2005**, *3*, 3851-3868.

[208] M. Caruthers, *Science* **1985**, *230*, 281-285.

[209] N. Usman, R. T. Pon, K. K. Ogilvie, *Tetrahedron Lett.* **1985**, *26*, 4567-4570.

[210] N. Usman, K. K. Ogilvie, M. Y. Jiang, R. J. Cedergren, *J. Am. Chem. Soc.* **1987**, *109*, 7845-7854.

[211] C. McCollum, A. Andrus, *Tetrahedron Lett.* **1991**, *32*, 4069-4072.

[212] J. Katzhendler, S. Cohen, E. Rahamim, M. Weisz, I. Ringel, J. Deutsch, *Tetrahedron* **1989**, *45*, 2777-2792.

[213] Z. M. O. Rzaev, *Prog. Polym. Sci.* **2000**, *25*, 163-217.

[214] T. Alfrey, E. Lavin, *J. Am. Chem. Soc.* **1945**, *67*, 2044-2045.

[215] E. Tsuchida, T. Tomono, *Makromol. Chem.* **1971**, *141*, 265-298.

[216] G.-Q. Chen, Z.-Q. Wu, J.-R. Wu, Z.-C. Li, F.-M. Li, *Macromolecules* **2000**, *33*, 232-234.

[217] A. Matsumoto, T. Kubota, T. Otsu, *Macromolecules* **1990**, *23*, 4508-4513.

[218] K. Satoh, M. Matsuda, K. Nagai, M. Kamigaito, *J. Am. Chem. Soc.* **2010**, *132*, 10003-10005.

[219] D. Benoit, C. J. Hawker, E. E. Huang, Z. Lin, T. P. Russell, *Macromolecules* **2000**, *33*, 1505-1507.

[220] M. Matsuda, K. Satoh, M. Kamigaito, *Macromolecules* **2013**, *46*, 5473-5482.

[221] S. Pfeifer, J.-F. Lutz, *Chem. - Eur. J.* **2008**, *14*, 10949-10957.

[222] S. Pfeifer, J.-F. Lutz, *J. Am. Chem. Soc.* **2007**, *129*, 9542-9543.

[223] J.-F. Lutz, B. V. K. J. Schmidt, S. Pfeifer, *Macromol. Rapid Commun.* **2011**, *32*, 127-135.

[224] D. Chan-Seng, M. Zamfir, J.-F. Lutz, *Angew. Chem.* **2012**, *124*, 12420-12423.

[225] M. Zamfir, J.-F. Lutz, *Nat. Commun.* **2012**, 1138.

[226] J.-F. Lutz, *Acc. Chem. Res.* **2013**, *46*, 2696-2705.

[227] S. Srichan, D. Chan-Seng, J.-F. Lutz, *ACS Macro Lett.* **2012**, *1*, 589-592.

[228] S. Srichan, L. Oswald, M. Zamfir, J.-F. Lutz, *Chem. Commun.* **2012**, *48*, 1517-1519.

[229] S. Srichan, H. Mutlu, N. Badi, J.-F. Lutz, *Angew. Chem. Int. Ed.* **2014**, *53*, 9231-9235.

[230] S. Srichan, H. Mutlu, J.-F. Lutz, *Eur. Polym. J.* **2015**, *62*, 338-346.

[231] D. Chan-Seng, M. Zamfir, J.-F. Lutz, in *Functional Polymers by Post-Polymerization Modification*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim **2012**, 173-192.

[232] T. Soejima, K. Satoh, M. Kamigaito, *J. Am. Chem. Soc.* **2016**, *138*, 944-954.

[233] M. S. Kharasch, E. V. Jensen, W. H. Urry, *Science* **1945**, *102*, 128-128.

[234] M. S. Kharasch, E. V. Jensen, W. H. Urry, *J. Am. Chem. Soc.* **1947**, *69*, 1100-1105.

[235] M. S. Kharasch, B. M. Kuderna, W. Urry, *J. Org. Chem.* **1948**, *13*, 895-902.

[236] H. H. Brintzinger, D. Fischer, R. Mülhaupt, B. Rieger, R. M. Waymouth, *Angew. Chem. Int. Ed.* **1995**, *34*, 1143-1170.

[237] E. P. Bierwagen, J. E. Bercaw, W. A. Goddard, *J. Am. Chem. Soc.* **1994**, *116*, 1481-1489.

[238] J. W. Kramer, D. S. Treitler, E. W. Dunn, P. M. Castro, T. Roisnel, C. M. Thomas, G. W. Coates, *J. Am. Chem. Soc.* **2009**, *131*, 16042-16044.

[239] G. Gody, T. Maschmeyer, P. B. Zetterlund, S. Perrier, *Nat. Commun.* **2013**, *4,* 2505.

[240] G. Gody, T. Maschmeyer, P. B. Zetterlund, S. Perrier, *Macromolecules* **2014**, *47*, 3451-3460.

[241] A. Anastasaki, V. Nikolaou, G. S. Pappas, Q. Zhang, C. Wan, P. Wilson, T. P. Davis, M. R. Whittaker, D. M. Haddleton, *Chem. Sci.* **2014**, *5*, 3536-3542.

[242] J. Zhang, M. E. Matta, M. A. Hillmyer, *ACS Macro Lett.* **2012**, *1*, 1383-1387.

[243] D. Moatsou, C. F. Hansell, R. K. O'Reilly, *Chem. Sci.* **2014**, *5*, 2246-2250.

[244] W. R. Gutekunst, C. J. Hawker, *J. Am. Chem. Soc.* **2015**, *137*, 8038-8041.

[245] R. M. Weiss, A. L. Short, T. Y. Meyer, *ACS Macro Lett.* **2015**, *4*, 1039-1043.

[246] C. Slugovc, *Macromol. Rapid Commun.* **2004**, *25*, 1283-1297.

[247] A. Leitgeb, J. Wappel, C. Slugovc, *Polymer* **2010**, *51*, 2927-2946.

[248] S. Kobayashi, L. M. Pitet, M. A. Hillmyer, *J. Am. Chem. Soc.* **2011**, *133*, 5794-5797.

[249] V. Lapinte, J.-C. Brosse, L. Fontaine, *Macromol. Chem. Phys.* **2004**, *205*, 824-833.

[250] J. D. Rule, J. S. Moore, *Macromolecules* **2002**, *35*, 7878-7882.

[251] T. R. Hoye, C. S. Jeffrey, M. A. Tennakoon, J. Wang, H. Zhao, *J. Am. Chem. Soc.* **2004**, *126*, 10210-10211.

[252] P. Hodge, H. M. Colquhoun, *Polym. Adv. Technol.* **2005**, *16*, 84-94.

[253] A. Ben-Haida, L. Conzatti, P. Hodge, B. Manzini, P. Stagnaro, *Macromol. Symp.* **2010**, *297*, 6-17.

[254] Z. Xue, M. F. Mayer, *Soft Matter* **2009**, *5*, 4600-4611.

[255] S. Strandman, J. E. Gautrot, X. X. Zhu, *Polym. Chem.* **2011**, *2*, 791-799.

[256] G. Gody, P. B. Zetterlund, S. Perrier, S. Harrisson, *Nat. Commun.* **2016**, *7*, 10514.

[257] W. Lee, H. Lee, J. Cha, T. Chang, K. J. Hanley, T. P. Lodge, *Macromolecules* **2000**, *33*, 5111-5115.

[258] M. Winkler, T. M. Lacerda, F. Mack, M. A. R. Meier, *Macromolecules* **2015**, *48*, 1398-1403.

[259] N. Kolb, M. Winkler, C. Syldatk, M. A. R. Meier, *Eur. Polym. J.* **2014**, *51*, 159-166.

[260] K. B. Wagener, J. M. Boncella, J. G. Nel, *Macromolecules* **1991**, *24*, 2649-2657.

[261] H. Mutlu, L. M. de Espinosa, M. A. R. Meier, *Chem. Soc. Rev.* **2011**, *40*, 1404-1445.

[262] G. Rojas, B. Inci, Y. Wei, K. B. Wagener, *J. Am. Chem. Soc.* **2009**, *131*, 17376-17386.

[263] K. Satoh, S. Ozawa, M. Mizutani, K. Nagai, M. Kamigaito, *Nat. Commun.* **2010**, *1*, 6.

[264] C.-H. Wang, Z.-Y. Song, X.-X. Deng, L.-J. Zhang, F.-S. Du, Z.-C. Li, *Macromol. Rapid Commun.* **2014**, *35*, 474-478.

[265] J. H. Burroughes, D. D. C. Bradley, A. R. Brown, R. N. Marks, K. Mackay, R. H. Friend, P. L. Burns, A. B. Holmes, *Nature* **1990**, *347*, 539-541.

[266] M. Granstrom, K. Petritsch, A. C. Arias, A. Lux, M. R. Andersson, R. H. Friend, *Nature* **1998**, *395*, 257-260.

[267] R. H. Friend, R. W. Gymer, A. B. Holmes, J. H. Burroughes, R. N. Marks, C. Taliani, D. D. C. Bradley, D. A. D. Santos, J. L. Bredas, M. Logdlund, W. R. Salaneck, *Nature* **1999**, *397*, 121-128.

[268] M. Jørgensen, F. C. Krebs, *J. Org. Chem.* **2004**, *69*, 6688-6696.

[269] W. Li, H. Wang, L. Yu, T. L. Morkved, H. M. Jaeger, *Macromolecules* **1999**, *32*, 3034-3044.

[270] T. Maddux, W. Li, L. Yu, *J. Am. Chem. Soc.* **1997**, *119*, 844-845.

[271] Y. Takayama, C. Delas, K. Muraoka, M. Uemura, F. Sato, *J. Am. Chem. Soc.* **2003**, *125*, 14163-14167.

[272] K. Takizawa, C. Tang, C. J. Hawker, *J. Am. Chem. Soc.* **2008**, *130*, 1718-1726.

[273] K. Takizawa, H. Nulwala, J. Hu, K. Yoshinaga, C. J. Hawker, *J. Polym. Sci., Part A: Polym. Chem.* **2008**, *46*, 5977-5990.

[274] S. Pfeifer, Z. Zarafshani, N. Badi, J.-F. Lutz, *J. Am. Chem. Soc.* **2009**, *131*, 9195-9197.

[275] X. Tong, B.-h. Guo, Y. Huang, *Chem. Commun.* **2011**, *47*, 1455-1457.

[276] J. Vandenbergh, G. Reekmans, P. Adriaensens, T. Junkers, *Chem. Commun.* **2013**, *49*, 10358-10360.

[277] J. Vandenbergh, G. Reekmans, P. Adriaensens, T. Junkers, *Chem. Sci.* **2015**, *6*, 5753-5761.

[278] S. Houshyar, D. J. Keddie, G. Moad, R. J. Mulder, S. Saubern, J. Tsanaktsidis, *Polym. Chem.* **2012**, *3*, 1879-1889.

[279] V. Coessens, K. Matyjaszewski, *Macromol. Rapid Commun.* **1999**, *20*, 127-134.

[280] V. Coessens, J. Pyun, P. J. Miller, S. G. Gaynor, K. Matyjaszewski, *Macromol. Rapid Commun.* **2000**, *21*, 103-109.

[281] P. Lucio Anelli, C. Biffi, F. Montanari, S. Quici, *J. Org. Chem.* **1987**, *52*, 2559-2562.

[282] X.-S. Feng, C.-Y. Pan, *Macromolecules* **2002**, *35*, 4888-4893.

[283] G.-Y. Shi, X.-Z. Tang, C.-Y. Pan, *J. Polym. Sci., Part A: Polym. Chem.* **2008**, *46*, 2390-2401.

[284] B. Sasso, M. Dobinson, P. Hodge, T. Wear, *Macromolecules* **2010**, *43*, 7453-7464.

[285] S. M. Henry, A. J. Convertine, D. S. W. Benoit, A. S. Hoffman, P. S. Stayton, *Bioconjugate Chem.* **2009**, *20*, 1122-1128.

[286] B. Quiclet-Sire, G. Revol, S. Z. Zard, *Tetrahedron* **2010**, *66*, 6656-6666.

[287] A. Anastasaki, V. Nikolaou, Q. Zhang, J. Burns, S. R. Samanta, C. Waldron, A. J. Haddleton, R. McHale, D. Fox, V. Percec, P. Wilson, D. M. Haddleton, *J. Am. Chem. Soc.* **2014**, *136*, 1141-1149.

[288] D. M. Rosenbaum, D. R. Liu, *J. Am. Chem. Soc.* **2003**, *125*, 13924-13925.

[289] M. L. McKee, P. J. Milnes, J. Bath, E. Stulz, A. J. Turberfield, R. K. O'Reilly, *Angew. Chem. Int. Ed.* **2010**, *49*, 7948-7951.

[290] R. E. Kleiner, Y. Brudno, M. E. Birnbaum, D. R. Liu, *J. Am. Chem. Soc.* **2008**, *130*, 4646-4659.

[291] S. Ida, T. Terashima, M. Ouchi, M. Sawamoto, *J. Am. Chem. Soc.* **2009**, *131*, 10808-10809.

[292] S. Ida, M. Ouchi, M. Sawamoto, *J. Am. Chem. Soc.* **2010**, *132*, 14748-14750.

[293] Y. Hibi, M. Ouchi, M. Sawamoto, *Angew. Chem. Int. Ed.* **2011**, *50*, 7434-7437.

[294] Z. J. Gartner, D. R. Liu, *J. Am. Chem. Soc.* **2001**, *123*, 6961-6963.

[295] X. Li, D. R. Liu, *Angew. Chem. Int. Ed.* **2004**, *43*, 4848-4870.

[296] R. Naylor, P. T. Gilham, *Biochemistry* **1966**, *5*, 2722-2728.

[297] C. Bohler, P. E. Nielsen, L. E. Orgel, *Nature* **1995**, *376*, 578-581.

[298] J. C. Leitzel, D. G. Lynn, *Chem. Rec.* **2001**, *1*, 53-62.

[299] C. T. Calderone, J. W. Puckett, Z. J. Gartner, D. R. Liu, *Angew. Chem. Int. Ed.* **2002**, *41*, 4104-4108.

[300] Y. Brudno, M. E. Birnbaum, R. E. Kleiner, D. R. Liu, *Nat. Chem. Biol.* **2010**, *6*, 148-155.

[301] K. Fujimoto, S. Matsuda, N. Takahashi, I. Saito, *J. Am. Chem. Soc.* **2000**, *122*, 5646-5647.

[302] S. T. Kim, A. Sancar, C. Essenmacher, G. T. Babcock, *J. Am. Chem. Soc.* **1992**, *114*, 4442-4443.

[303] P. J. Milnes, M. L. McKee, J. Bath, L. Song, E. Stulz, A. J. Turberfield, R. K. O'Reilly, *Chem. Commun.* **2012**, *48*, 5614-5616.

[304] R. K. O'Reilly, *Nat. Chem.* **2013**, *5*, 252-253.

[305] S. Ida, M. Ouchi, M. Sawamoto, *Macromol. Rapid Commun.* **2011**, *32*, 209-214.

[306] B. Lewandowski, G. De Bo, J. W. Ward, M. Papmeyer, S. Kuschel, M. J. Aldegunde, P. M. E. Gramlich, D. Heckmann, S. M. Goldup, D. M. D'Souza, A. E. Fernandes, D. A. Leigh, *Science* **2013**, *339*, 189-193.

[307] G. De Bo, S. Kuschel, D. A. Leigh, B. Lewandowski, M. Papmeyer, J. W. Ward, *J. Am. Chem. Soc.* **2014**, *136*, 5811-5814.

[308] P. Espeel, L. L. G. Carrette, K. Bury, S. Capenberghs, J. C. Martins, F. E. Du Prez, A. Madder, *Angew. Chem. Int. Ed.* **2013**, *52*, 13261-13264.

[309] T. T. Trinh, L. Oswald, D. Chan-Seng, J.-F. Lutz, *Macromol. Rapid Commun.* **2014**, *35*, 141-145.

[310] J.-A. Amalian, T. T. Trinh, J.-F. Lutz, L. Charles, *Anal. Chem.* **2016**, *88*, 3715-3722.

[311] C. J. Serpell, T. G. W. Edwardson, P. Chidchob, K. M. M. Carneiro, H. F. Sleiman, *J. Am. Chem. Soc.* **2014**, *136*, 15767-15774.

[312] L. Charles, C. Laure, J.-F. Lutz, R. K. Roy, *Rapid Commun. Mass Spectrom.* **2016**, *30*, 22-28.

[313] A. A. Ouahabi, M. Kotera, L. Charles, J.-F. Lutz, *ACS Macro Lett.* **2015**, 1077-1080.

[314] R. K. Roy, A. Meszynska, C. Laure, L. Charles, C. Verchin, J.-F. Lutz, *Nat. Commun.* **2015**, *6*, 7237.

[315] L. Charles, C. Laure, J.-F. Lutz, R. K. Roy, *Macromolecules* **2015**, *48*, 4319-4328.

[316] R. K. Roy, C. Laure, D. Fischer-Krauser, L. Charles, J.-F. Lutz, *Chem. Commun.* **2015**, *51*, 15677-15680.

[317] J. W. Grate, K.-F. Mo, M. D. Daily, *Angew. Chem. Int. Ed.* **2016**, *55*, 3925-3930.

[318] B. N. Norris, S. Zhang, C. M. Campbell, J. T. Auletta, P. Calvo-Marzal, G. R. Hutchison, T. Y. Meyer, *Macromolecules* **2013**, *46*, 1384-1392.

[319] J. J. M. Halls, R. H. Friend, *Synth. Met.* **1997**, *85*, 1307-1308.

[320] J. J. M. Halls, K. Pichler, R. H. Friend, S. C. Moratti, A. B. Holmes, *Appl. Phys. Lett.* **1996**, *68*, 3120-3122.

[321] A. C. Grimsdale, K. Leok Chan, R. E. Martin, P. G. Jokisz, A. B. Holmes, *Chem. Rev.* **2009**, *109*, 897-1091.

[322] M. Porel, C. A. Alabi, *J. Am. Chem. Soc.* **2014**, *136*, 13162-13165.

[323] W. Zhang, D. P. Curran, *Tetrahedron* **2006**, *62*, 11837-11865.

[324] M. Porel, D. N. Thornlow, N. N. Phan, C. A. Alabi, *Nat. Chem.* **2016**, *8*, 590-596.

[325] N. Zydziak, F. Feist, B. Huber, J. O. Mueller, C. Barner-Kowollik, *Chem. Commun.* **2015**, *51*, 1799-1802.

[326] C. Barner-Kowollik, F. E. Du Prez, P. Espeel, C. J. Hawker, T. Junkers, H. Schlaad, W. Van Camp, *Angew. Chem. Int. Ed.* **2011**, *50*, 60-62.

[327] R. Göstl, S. Hecht, *Angew. Chem. Int. Ed.* **2014**, *53*, 8784-8787.

[328] T. T. Trinh, L. Oswald, D. Chan-Seng, L. Charles, J.-F. Lutz, *Chem. - Eur. J.* **2015**, *21*, 11961-11965.

[329] F. A. Leibfarth, J. A. Johnson, T. F. Jamison, *Proc. Natl. Acad. Sci.* **2015**, *112*, 10617-10622.

[330] J. C. Barnes, D. J. C. Ehrlich, A. X. Gao, F. A. Leibfarth, Y. Jiang, E. Zhou, T. F. Jamison, J. A. Johnson, *Nat. Chem.* **2015**, *7*, 810-815.

[331] S. Binauld, D. Damiron, L. A. Connal, C. J. Hawker, E. Drockenmuller, *Macromol. Rapid Commun.* **2011**, *32*, 147-168.

[332] O. I. Paynter, D. J. Simmonds, M. C. Whiting, *J. Chem. Soc., Chem. Commun.* **1982**, 1165-1166.

[333] Y. Hibi, M. Ouchi, M. Sawamoto, *Nat. Commun.* **2016**, *7*, 11064.

[334] S. C. Solleder, M. A. R. Meier, *Angew. Chem. Int. Ed.* **2014**, *53*, 711-714.

[335] S. C. Solleder, M. A. R. Meier, *Angew. Chem.* **2014**, *126*, 729-732.

[336] E. Bayer, M. Mutter, *Nature* **1972**, *237*, 512-513.

[337] S. C. Solleder, K. S. Wetzel, M. A. R. Meier, *Polym. Chem.* **2015**, *6*, 3201-3204.

[338] S. C. Solleder, D. Zengel, K. S. Wetzel, M. A. R. Meier, *Angew. Chem. Int. Ed.* **2016**, *55*, 1204-1207.

[339] S. C. Solleder, D. Zengel, K. S. Wetzel, M. A. R. Meier, *Angew. Chem.* **2016**, *128*, 1222-1225.

[340] L. A. H. Wessjohann, Michael; Kreye, Oliver; Rivera, Daniel Garcia, WO2011/134607A1, **2011**.

[341] S. H. Hong, D. P. Sanders, C. W. Lee, R. H. Grubbs, *J. Am. Chem. Soc.* **2005**, *127*, 17160-17161.

[342] J. B. Hendrickson, *J. Am. Chem. Soc.* **1977**, *99*, 5439-5450.

[343] L. Velluz, J. Valls, J. Mathieu, *Angew. Chem. Int. Ed.* **1967**, *6*, 778-789.

[344] C. J. Hawker, J. M. J. Frechet, *J. Am. Chem. Soc.* **1990**, *112*, 7638-7647.

[345] D. A. Tomalia, H. Baker, J. Dewald, M. Hall, G. Kallos, S. Martin, J. Roeck, J. Ryder, P. Smith, *Polym. J.* **1985**, *17*, 117-132.

[346] O. Kreye, D. Kugele, L. Faust, M. A. R. Meier, *Macromol. Rapid Commun.* **2014**, *35*, 317-322.

[347] J.-A. Jee, L. A. Spagnuolo, J. G. Rudick, *Org. Lett.* **2012**, *14*, 3292-3295.

[348] R. Benesch, R. E. Benesch, *Proc. Natl. Acad. Sci.* **1958**, *44*, 848-853.

[349] C. E. Hoyle, A. B. Lowe, C. N. Bowman, *Chem. Soc. Rev.* **2010**, *39*, 1355-1387.

[350] P. Espeel, F. Goethals, F. E. Du Prez, *J. Am. Chem. Soc.* **2011**, *133*, 1678-1681.

[351] P. Espeel, F. Goethals, M. M. Stamenovic, L. Petton, F. E. Du Prez, *Polym. Chem.* **2012**, *3*, 1007-1015.

9 Publications

(5) S. Oelmann, S. C. Solleder, M. A. R. Meier, *Polym. Chem* **2016**, *7*, 1857-1860.

(4) S. C. Solleder, D. Zengel, K. S. Wetzel, M. A. R. Meier, *Angew. Chem. Int. Ed.,* **2016**, *55,* 1204-1207; *Angew. Chem.* **2016**, *128,* 1222-1225.

(3) S. C. Solleder, K. S. Wetzel, M. A. R. Meier, *Polym. Chem.* **2015**, *6*, 3201-3204.

(2) S. C. Solleder, M. A. R. Meier, *Angew. Chem. Int. Ed.* **2014**, *53*, 711-714; *Angew. Chem.* **2014**, 126, 729-732.

(1) H. Mutlu, J. Ruiz, S. C. Solleder, M. A. R. Meier, *Green Chem.* **2012**, 14, 1728-1735.