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A Combined Photochemical and Multi-Component Reaction Approach to Precision Oligomers

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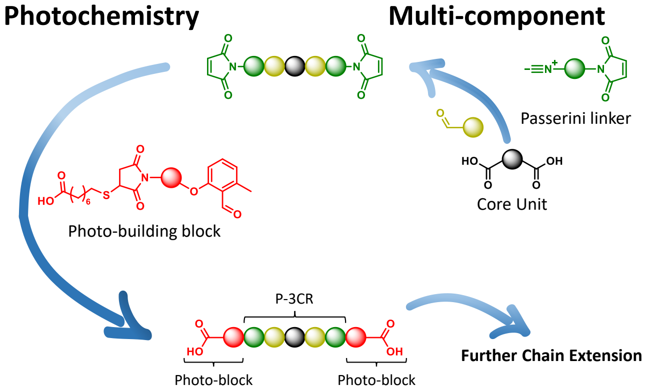
Abstract: We introduce an avenue for the convergent synthesis of linear monodisperse sequence-defined oligomers via a unique approach, combining the Passerini three-component reaction (P-3CR) and a Diels-Alder reaction based on photo-caged dienes. Based on a Passerini linker unit carrying an isocyano group for chain extension via P-3CR and a maleimide moiety for photo-enol conjugation enabling a modular approach for chain extension. Monodisperse oligomers are accessible in a stepwise fashion by switching between both reaction types. Employing sebacic acid as a core unit allows for the synthesis of a library of symmetric sequence-defined oligomers. Consisting of alternating P-3CR and photo-blocks with molecular weights up to 3532.16 g mol^{-1}, the oligomers demonstrate the successful switching from P-3CR to photo-enol conjugation. In depth characterization is carried out including SEC, high resolution mass spectrometry (ESI-MS) and NMR, evidencing the monodisperse nature of the precision oligomers.

Naturally occurring key macromolecules, such as DNA or proteins, feature absolute sequence-definition in their structure, which is necessary to execute complex biological functions (i.e. information storage or enzymatic activity) that are vital to life. Inspired by nature's precision, the generation of perfectly monodisperse sequence-defined oligomers and polymers containing chemical information by coding monomer units into a predefined order via a simple process, is – for example – envisaged for data storage materials, molecular bar coding, biological applications in synthetic enzyme design or precision network synthesis.[1] Therefore, viable synthetic concepts featuring simple, scalable and orthogonal strategies for the accurate placement of functional groups – for instance through monomer units – at predetermined positions in synthetic macromolecules are important tools.[2] Historically, the field of sequence-defined macromolecules emerged with the pioneering work of Merrifield in the year 1963[3] for which a Nobel prize was awarded in 1984.[4] The concept was later extended for the synthesis of precise natural and non-natural peptides,[5] glycopeptides,[6] oligonucleotides,[7] peptoids[8] and conjugated oligomers.[9] In addition, dendrimers[10] and exponential growth strategies[11] significantly enriched the field. Many research groups introduced different strategies to produce coded sequence-defined oligomers including single unit monomer insertions (SUMIs) based on radical processes,[1d, 12] liquid phase reactions in bulk or flow systems[11a, 13] as well as approaches using solid templates,[2c, 14] mainly resting on modular insertion of building blocks or iterative addition of single monomer units, summarized in recent reviews.[1j, 1k] Modular chain growth employing larger sequence-defined building blocks instead of single monomers for coupling contributes to the overall reaction efficiency by an accelerated increase of the molecular weight for each synthetic step. Therefore, modular synthetic concepts significantly contributed towards a high level of control over sequence-defined macromolecular formation processes.[2a] Herein, we extend the synthetic toolbox for preparing monodisperse multifunctional sequence-defined macromolecules (i.e. unique according to IUPAC recommendations)[15] by an approach combining highly efficient methods in an orthogonal fashion, i.e. the Passerini three component reaction (P-3CR) and a photochemical reaction relying on a benzaldehyde species (photo-caged dienes termed photo-enols) as well as maleimides (**Scheme 1**).[1f, 2a] Our synthetic strategy is based on P-3CRs and photo-enols leading to macromolecules consisting of alternating Passerini and photo-blocks, possibly leading to applications ranging from bio-conjugation, photoresists, network formation for NMR orientation media or information storage.[1h, 16]



Scheme 1. Consecutive chain extension starting from a symmetric core unit employing a multi-component reaction and photochemistry.

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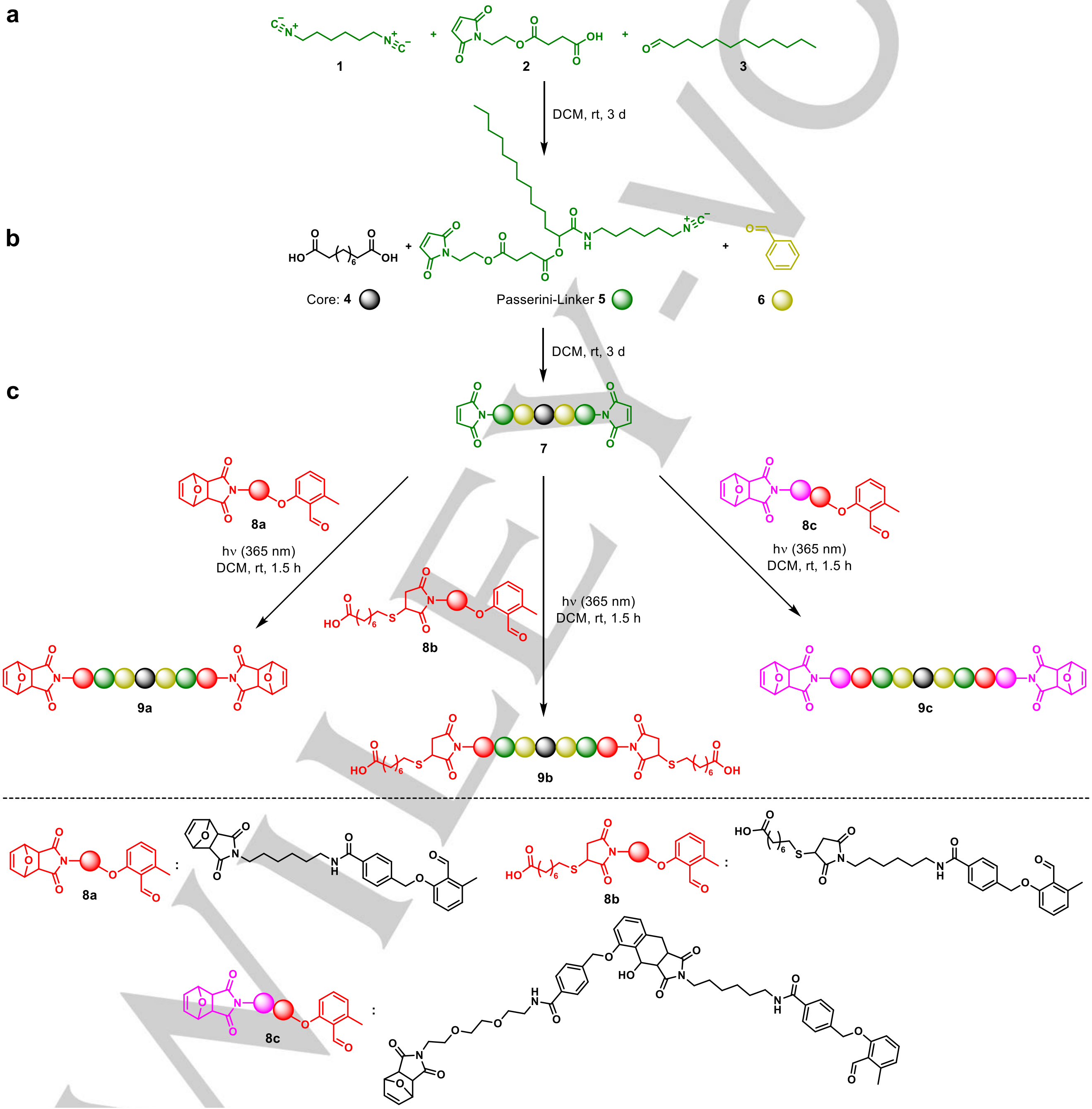
Our here explored synthesis of sequence-defined macromolecules is based on convergent chain extension starting from a symmetric core unit via multi-component reactions followed by a photochemically induced Diels–Alder (DA) reaction, in which each building block carries functional groups allowing the respective attachment of Passerini linkers and photo-caged dienes. Initially, in order to grow oligomers in as few chain extension steps as possible, a Passerini linker unit **5** (**Scheme 2a**) was synthesized exhibiting an isocyano functionality, allowing for further chain extensions via P-3CRs. **5** also bears a maleimide moiety required for photochemically induced DA reactions. The targeted Passerini linker was obtained from diisocyanohexane **1**, a maleimide equipped with a carboxylic acid group **2** and lauric aldehyde **3** in one step by a P-3CR as shown in **Scheme 2a**. As Passerini reactions show higher reaction rates and yields in aprotic, non-polar solvents, all P-3CRs were conducted in DCM. For the linker formation, DMSO was added to increase the solubility of the maleimide **2**. In order to prevent the reaction of both isocyano functionalities, a fourfold excess of the diisocyanohexane **1** was employed. Due to extended reaction



Scheme 2. Sequential and modular strategies for the synthesis of sequence-defined oligomers alternatingly consisting of Passerini and photo-blocks. Synthesis of the α-ω-functionalized Passerini linker **5** in a P-3CR allowing growth of the symmetrical tetramer **7** from sebacic acid **4** as core unit. The tetramer **7** is subsequently extended with the photo-monomer **8a**, a modified photo-monomer **8b** and a photo-dimer **7c** to afford the functional oligomers equipped with furan capped maleimides **9a** and **9c** or a terminal carboxylic acid group at both chain ends **9b**.

periods of several days required for the Passerini reaction under the present conditions, all operations were conducted under nitrogen atmosphere to prevent the isocyano groups from degradation. The reaction mixture was stirred for two days at ambient temperature, resulting in the target compound **5**. Chromatographic purification allowed separation of the target compound **5** (57 % yield) and partial recovery of the exceeding precursor **1** (up to 65 %). Introduction of further functional groups to the Passerini linker is conceivable. However, carboxylic acids, aldehydes, ketones, amines and isocyanides can be challenging, as they may compete in a P-3CR or Ugi reaction. The obtained linker **5** features three anchor points for consecutive oligomerizations. First, the isocyano group enables chain extension via P-3CR. Second, the introduced maleimide moiety – able to undergo [4+2] DA cycloaddition with *ortho*-quinodimethanes – allows chain extension with photo-blocks and third, a variable alkylic or aromatic side-group can be introduced to the linker.

In a subsequent P-3CR, the linker **5** was added to a symmetrical core unit, i.e. sebacic acid **4**, introducing two side-chain substituents into the growing oligomer on each side in a single step yielding in the symmetric tetrafunctional macromolecule **7** as depicted in **Scheme 2b**. Employing the bifunctional sebacic acid **4** for the synthesis of linear oligomers enables bidirectional growth and, thus, the formation of symmetric macromolecules resulting in a significant increase in molecular weight per chain extension step. For the formation of the tetra-substituted macromolecule **7**, similar reaction conditions were applied according to the synthesis of the Passerini linker **5** using benzaldehyde **6** for the introduction of a side-chain substituent. Benzaldehyde **6** was employed in a threefold excess, the linker **5** in a 3.6-fold excess for driving the reaction towards higher yields. The mixture was stirred in DCM (0.5 M relative to sebacic acid **4**) for three days at ambient temperature to afford the symmetric tetra-substituted macromolecule **7**. Flash chromatography employing a gradient of cyclohexane/ethyl acetate yielded 67 % of the desired symmetric sequence-defined oligomer **7** and the excess of the linker **5** could be recovered (up to 45 %).

The photo-monomer **8a** – exhibiting a benzaldehyde moiety that undergoes photo-enolization upon irradiation as well as a maleimide for DA-trapping – employed for the current work and the sequence-defined polymerization has been reported previously by our team.[2a] In the current study, three different types of α,ω-functionalized photo-building blocks are employed for the chain extension after P-3CR: (*i*) a non-modified monomer **8a** exhibiting a photo-caged diene on the one hand side and a furan caged maleimide on the other; (*ii*) a modified monomer **8b** equipped with an α-methyl benzaldehyde moiety and a carboxylic acid in order to conduct chain extension via P-3CR in further steps; (*iii*) a photo-dimer **8c** functionalized with an α-methyl benzaldehyde group and a furan protected maleimide. The maleimide group of monomer **8a** offered a facile attachment point

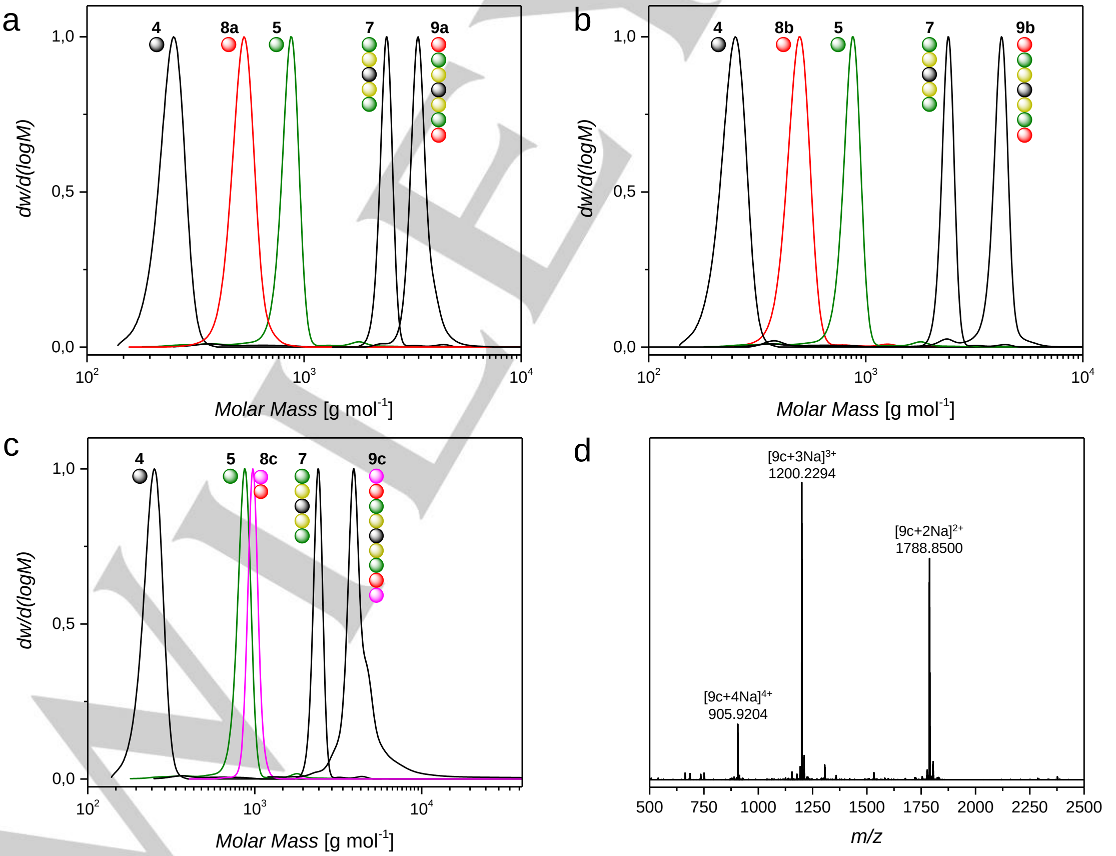


Figure 1. SEC traces (a-c) of the successively synthesized sequence-defined oligomers alternatingly consisting of Passerini and photo-blocks **9a-c** illustrating their successful formation. The core unit sebacic acid **4**, the building blocks **5** and **8a-c** as well as the tetramer **7** are presented. All SEC traces were recorded in THF. Full MS spectrum of **9c** in the mass range of *m/z* 500 to 2500 (d) recorded in positive ion mode.

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for a carboxylic acid via base-catalyzed Thia-Michael addition using mercaptooctanoic acid (refer to the Supporting Information section 3.2.9, Figure S8 and S9). Prior to the Thia-Michael addition, deprotection of the furan trapped maleimide was carried out at 115 °C in vacuum for 24 hours in order to initiate the retro DA reaction. High vacuum was employed to remove the released furan from the crude reaction mixture and shift the DA equilibrium towards cycloreversion. Thia-Michael addition was performed with triethylamine as a base and mercaptooctanoic acid to afford **8b** quantitatively. An efficient way for increasing the molecular weight of the oligomer is a modular strategy, in which the symmetric linear molecule is ligated with a previously synthesized dimer. Therefore, the unmodified photo-dimer **8c** was synthesized exploiting selected transformation of monomer end-groups via subsequent photo-induced DA together with the monomer unit **8a** bearing a caged maleimide group. In the first instance, the photo-monomer unit **8a** was thermally furan-deprotected on the maleimide side and the photo-reactive aldehyde functionality was locked as a dimethyl acetal in order to prevent non-controlled photo-polymerization of the monomer. The complementary reactive groups – i.e. the photo-enol moiety of a PEG derived monomer and the bare thermally deprotected maleimide of **8a** – were allowed to react under irradiation of UV-light at 365 nm resulting in dimer **8c**, which carries a furan-protected maleimide and a benzaldehyde group itself after converting the labile dimethyl acetal by acidic hydrolysis to an aldehyde functionality.

Modular strategies can be employed in order to design complex sequence-defined macromolecules utilizing building blocks with different functional groups and thus variation of the oligomer backbone can be achieved. Here, three photo-building blocks – i.e. a photo-monomer **8a**, a modified photo-monomer **8b** and a photo-dimer **8c** – are employed for chain extension, varying in their chemical structure and therefore diversifying the composition of the symmetrical sequence-defined oligomers. Consequently, the photoreaction between the symmetric Passerini tetramer **7** and the photo-building blocks **8a**, **8b** and **8c** employing a PL-L lamp (λ_{max} = 365 nm) as irradiation source leads to the symmetric hexamers **9a** (2571.13 g mol^{-1}) and **9b** (2851.52 g mol^{-1}) as well as to the symmetric octamer **9c** with a molecular weight of 3532.16 g mol^{-1} after only two chain extension reactions, alternatingly consisting of P-3CR and photo-blocks (**Scheme 2c**). An isolated overall yield of 55 % from the building blocks to the final octamer was achieved. The low yield results from the necessary purification of the intermediates via flash chromatography since the Passerini chain extension requires reactants in excess and the photoreaction demands equimolar stoichiometry. In addition, the sequence-defined oligomers require quantitative conversion of the chain ends due to their bidirectional growth, leading to a certain loss in overall efficiency. However, in contrast to the report by Zydziak *et al.*, an intermolecular maleimide-maleimide coupling side reaction under UV irradiation has not been observed for the preparation of the herein described building blocks and oligomers.[2a]

The successful formation of the corresponding building blocks and intermediates was verified by SEC, high resolution Orbitrap ESI-MS and NMR. All SEC traces of the core unit **4**, Passerini linker **5**, tetramer **7**, photo-building blocks **8a-c** and the final sequence-defined oligomers **9a-c** that are depicted in **Figure 1a-c** have been measured using THF as eluent. An increase in molecular weight (corresponding to a decrease in retention volume) from the core unit sebacic acid **4** and the respective building blocks **5** and **8a-c** to the consecutive symmetrical sequence-defined oligomers **9a-c** can be observed by inspecting the SEC traces at each synthetic step of the sequence-defined macromolecules. The increase in molecular weight and the traces resulting from the sequential approach confirm the purity and the success of the successive multi-component reaction and photochemical synthetic strategy. The molecular weights have been obtained relative to a polystyrene calibration and the chromatographically determined dispersities of *Đ* = 1.01 for the macromolecules **9a** and **9b** as well as *Đ* = 1.03 for **9c** are verifying the monodisperse nature of the synthesized sequence-defined oligomers **9a-c**. It is interesting to note that the SEC trace of **9c** shows a shoulder towards higher molecular weight, leading to a slight increase of the dispersity going from tetramer to the octamer (**Figure 1c**). Further, the trace of **9c** appears to be broadened compared to the traces of **9a** and **9b**, which may be associated with the higher interaction of the – in contrast to the Passerini blocks – more polar photo-monomers incorporated into the oligomer resulting in an adsorption driven column interaction leading to signal broadening. However, inspection of the high resolution ESI-MS spectrum depicted in **Figure 1d**, only reveals mass signals associated with macromolecule **9c** at m/z = 1788.8500 ([**9c**+2Na]$^{2+}$, $m/z_{calc.}$ = 1788.8516, $\Delta m/z$ = 0.0016), m/z = 1200.2294 ([**9c**+3Na]$^{3+}$, $m/z_{calc.}$ = 1200.2308, $\Delta m/z$ = 0.0014) and m/z = 905.9188

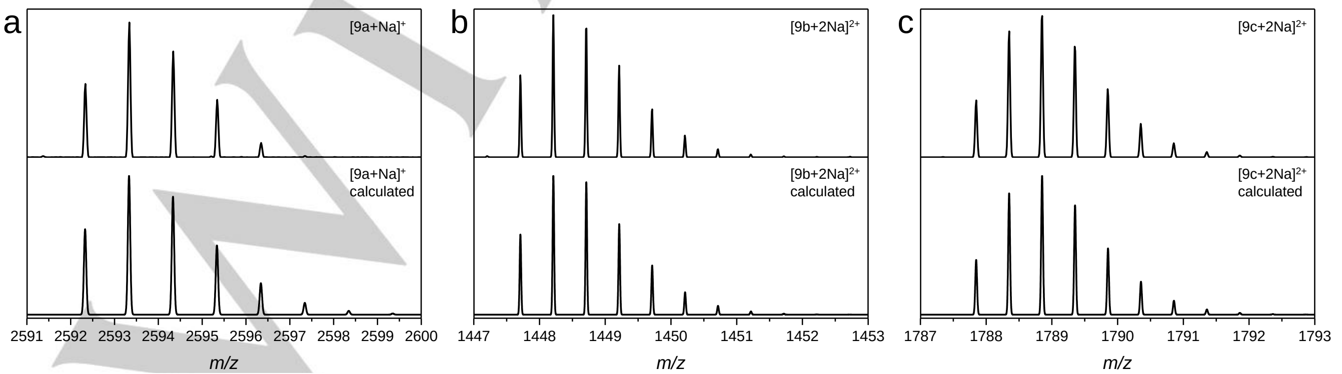

Figure 2. ESI-MS spectra of the oligomers isotopic pattern **9a** (a), **9b** (b) and **9c** (c). The recorded mass spectra shown on top are in excellent agreement with the calculated isotope pattern of the oligomers (bottom).

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([**9c**+4Na]$^{4+}$, $m/z_{\text{calc.}} = 905.9204$, $\Delta m/z = 0.0016$) for the respective charged sodium adducts, in excellent agreement with the resolution limits of the employed mass analyzer. The mass spectrum of **9c** clearly indicates monodispersity for the same compound, as well as the characterization via SEC evidences the monodisperse character of the synthesized sequence-defined oligomers **9a-c**. In addition, SEC analysis confirms the successful modular chain extension with an increase of molecular weight with the addition of each the respective building blocks, which is a total molecular weight of 1500 g mol^{-1} for the tetramer **7** and an increase in molecular weight of 1000 g mol^{-1} for **8a**, 1200 g mol^{-1} for **8b** and 2000 g mol^{-1} for **8c**. Recorded as well as predicted spectra of **9a-c** are depicted in **Figure 2**. It is interesting to note that the symmetric hexamer **9b** is oxidized during ESI-MS analysis. A single charged signal was detected at $m/z = 2593.3369$ in the ESI-MS spectrum and was assigned to a sodium adduct of the sequence-defined macromolecule **9a** ($m/z_{\text{calc.}} = 2593.3317$, $\Delta m/z = 0.0052$), a double charged signal recorded at $m/z = 1448.2110$ was assigned to the adduct of **9b** as sulfone containing two sodium ($m/z_{\text{calc.}} = 1448.2111$, $\Delta m/z = 0.0001$) and further a double charged species was detected at $m/z = 1788.8500$ ($m/z_{\text{calc.}} = 1788.8516$, $\Delta m/z = 0.0016$) associated with **9c** containing two sodium counter ions. The recorded mass spectra of the sequence-defined oligomers **9a-c** shown are in excellent agreement with the calculated isotopic pattern evidencing the monodisperse character and the successful synthesis of the multifunctional sequence-defined macromolecules (full MS spectra of **9a** and **9b** can be found in the Supporting Information).

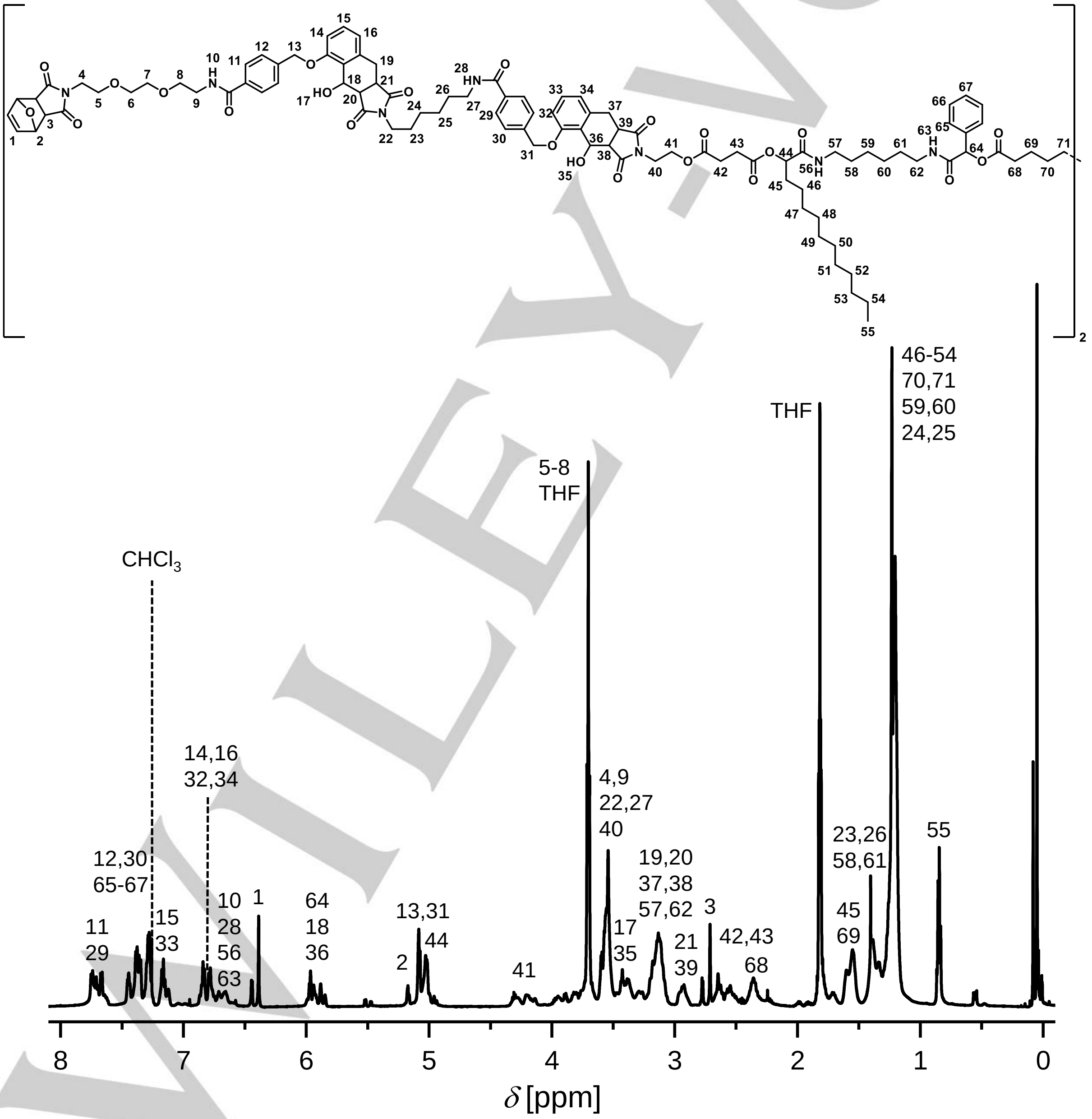

Figure 3. ^{1}H-NMR spectrum of the obtained octamer **9c** recorded in CDCl$_3$ at 400 MHz. For the signal assignments refer to the depicted structure.

Additional characterization was carried out via NMR spectroscopy, with the spectrum of the octamer **9c** depicted in **Figure 3** (refer to the Supporting Information Figure S15 and S17 for **9a** and **9b**). A proton resonance between 6.00-5.84 (64) and 5.04-5.00 ppm (44) was assigned to the chiral methine group adjacent to the phenyl ring introduced upon formation of the tetra-substituted oligomer **7** via P-3CR as well as to the methine group introduced during the Passerini linker **5** formation, as was already observed for the tetramer **7** (refer to the Supporting Information for comparison). Successful formation of the isoindole structure formed upon irradiation of photo-enol in presence of maleimides evidencing the synthesis of the octamer was confirmed by resonances detected at 6.00-5.84 (18/36), 3.20-3.06 (19/20/37/38) as well as 2.96-2.88 ppm (21/39) (refer to the NMR of the photo-dimer **8c** in Supporting Information). In addition, the furan caged maleimide functionality at the chain-ends was verified by proton resonances at 6.39 (1), 5.17 (2) and 2.77 ppm (3).

For the first time, a combination of multi-component reactions and photo-conjugation methods was applied for the synthesis of precision alternating oligomers consisting of P-3CR and photo-blocks with molecular weights up to 3532.16 g mol^{-1}. Symmetric sequence-defined oligomers have been prepared from sebacic acid extended via P-3CR with a Passerini linker at both chain ends leading to a tetra-substituted macromolecule. Upon irradiation, consecutive chain extensions with a set of photo-building blocks led to the desired symmetric sequence-defined oligomers in a modular approach. Synthesis of symmetric macromolecules in a modular approach enables a higher increase in molecular weight and higher overall yields per chain extension step. Due to the monodisperse character, the macromolecules feature absolute chain-end fidelity and side chain positioning. Successful formation of the sequence-defined oligomers **9a-c** was confirmed by in depth characterization including SEC, ESI-MS and NMR. Thus, the evolution of retention time and the monodisperse nature of the molecular weight distributions of the different synthetic steps obtained evidence the successful ligation, confirming the versatility of P-3CRs and photoreactions as well as switching from Passerini-blocks to photo-enol ligation. The current convergent approach combining P-3CRs and photo-conjugation using photo-enols demonstrates its efficiency for the synthesis of sequence-defined polymers, extending the toolbox for mimicking complex features of naturally occurring macromolecules.

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Conflict of Interest: The authors declare no conflict of interest.

Keywords: sequence-defined macromolecules • sequence control • photochemistry • multi-component reactions • convergent

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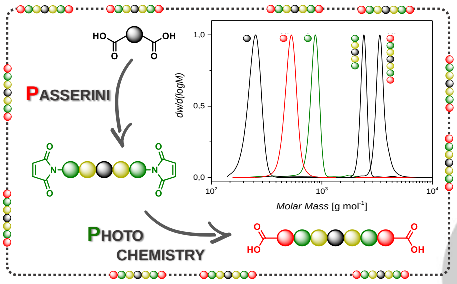
COMMUNICATION

The synthesis of multi-functional precision sequence-defined linear macromolecules becomes possible by fusing a highly efficient photochemical and multi-component reaction approach entailing alternating Passerini and photo-blocks. The growth of the oligomers is based on a convergent chain extension concept of sebacic acid with building blocks on demand in an orthogonal fashion.



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