Sequence-Defined Polymers Hot Paper
International Edition: DOI: 10.1002/anie.201509398
German Edition: DOI: 10.1002/ange.201509398

A Scalable and High-Yield Strategy for the Synthesis of Sequence-Defined Macromolecules

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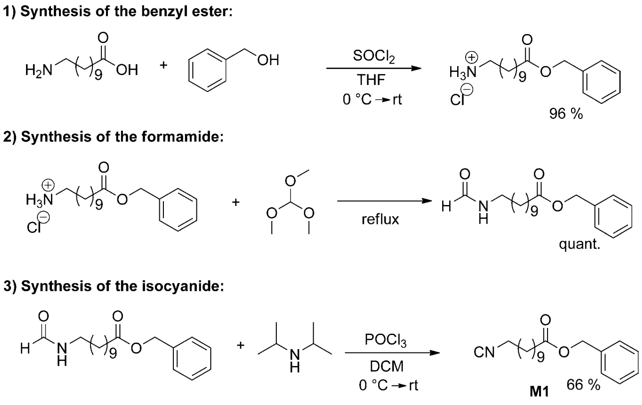
Abstract: *The efficient synthesis of a sequence-defined decamer, its characterization, and its straightforward dimerization through self-metathesis are described. For this purpose, a monoprotected AB monomer was designed and used to synthesize a decamer bearing ten different and selectable side chains by iterative Passerini three-component reaction (P-3CR) and subsequent deprotection. The highly efficient procedure provided excellent yields and allows for the multi-gram-scale synthesis of such perfectly defined macromolecules. An olefin was introduced at the end of the synthesis, allowing the self-metathesis reaction of the resulting decamer to provide 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, and mass spectrometry (FAB and orbitrap ESI-MS).*

In recent years, the potential of sequence-controlled and sequence-defined polymers has attracted researchers all over the world. Hence, tremendous progress has been made in the synthesis of sequence-controlled polymers, which in turn led to the possibility of tuning material properties and three-dimensional structures depending on the monomer sequence.[1] Furthermore, possible applications of sequence-defined polymers as catalysts and data storage materials are envisioned.[2] In general, the synthetic approaches can be divided into three subgroups, which are based on chain-growth, templated, and stepwise reactions.[2a,3] The chain-growth methods rely on controlled (living) polymerizations, synthesizing sequence-controlled polymers. These approaches take advantage of simple one-pot reactions; however, the statistical nature of these processes leads to polymers of different chain lengths and to a distribution of the placed functional groups.[4] For the synthesis of sequence-defined polymers, templated systems and iterative reactions have to be considered. Although templated systems and the use of molecular machines are highly sophisticated and elegant, the products are only obtained on a milligram scale, which limits the applicability of the obtained products.[3a,5] Also stepwise approaches are mostly conducted on a (soluble) solid support, which simplifies and accelerates the synthesis and workup procedures but limits the reaction scale.[6] On the other hand, some solution-phase approaches exist that theoretically allow scalable reactions.[7] Here, high yields in each reaction step are crucial in the synthesis of longer sequences. Therefore, scalable synthesis protocols that allow for high overall yields are required in order to bring sequence-defined macromolecules into application, for instance as artificial enzymes, catalysts, and active ingredients for pharmaceutical applications. However, some of the envisioned applications of sequence-defined materials, for instance in the field of data storage, do not necessarily need larger scales.[8]

In order to achieve high yields and scalability with one strategy, an appropriate monomer was synthesized and subsequently used for the synthesis of sequence-defined oligomers through iterative Passerini three-component reaction (P-3CR) and deprotection. Thus, a monomer having both an isocyanide and a benzyl ester protected carboxylic acid function was prepared, which is similar to the monomer employed for the synthesis of dendrimers using the Ugi four-component reaction (Ugi-4CR).[9] This combination of functional groups seemed to be the most convenient from our point of view 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 1. The overall yield over three steps was 63 % and the reaction was performed on a 15-gram scale. This synthesis protocol can be adapted to other amino acid derivatives, allowing a variety of structural backbones along with selectable side chains.



Scheme 1. Three-step synthesis of the monoprotected AB-type monomer **M1**, having both a benzyl ester and an isocyanide functionality.

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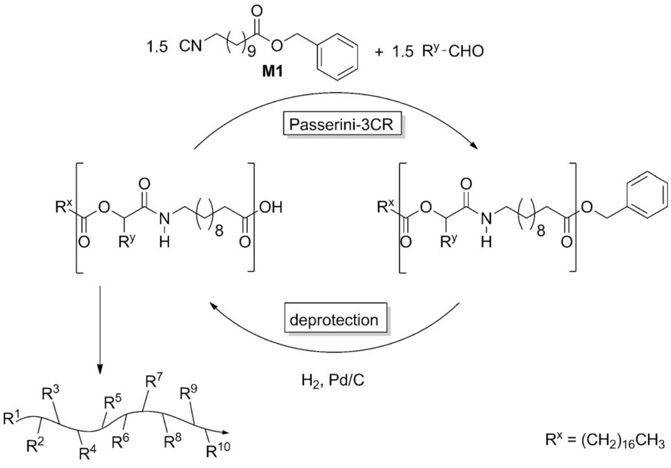
Supporting information for this article (including experimental details and in-depth characterization of the products) is available on the WWW under http://dx.doi.org/10.1002/anie.201509398.

Subsequently, monomer **M1** was applied in the efficient iterative sequence consisting of a P-3CR and subsequent deprotection of the benzyl ester to yield a sequence-defined decamer with ten different side chains (Scheme 2). In detail, the isocyanide functionality of monomer **M1** was reacted in a P-3CR with, for example, stearic acid as the starting substrate and an aldehyde component.

The thus obtained product of the P-3CR bears a benzyl ester moiety, which can be used for another P-3CR after hydrogenolysis with a heterogeneous Pd/C catalyst and 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 low-molecular-weight reactants (monomer **M1** and the aldehyde) were recovered by elution with apolar solvents and subsequently, polar eluents allowed the simple collection of the sequence-defined oligomers. By the use of different aldehydes for the P-3CR, we were able to introduce ten different side chains to the sequence-defined oligomer, including aliphatic, aromatic, and olefinic moieties (Figure 1, 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 must be introduced either at the end of the sequence, or the double bond must be protected or further functionalized prior to the hydrogenolysis of the benzyl ester.



Scheme 2. Synthesis strategy towards sequence-defined macromolecules using the monoprotected AB monomer **M1**.

The overall yields in the synthesis of the sequence-defined oligomers were very high. The yields were considerably higher and the workup was simplified compared to that in a previously reported procedure (see Table 1, entries 1–5).[7b] 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 over other stepwise procedures, such as the well-established polypeptide synthesis.

The sequence-defined decamer (Figure 1, top) was obtained in 19 reaction steps in an excellent overall yield of 44%. It has to be highlighted that the reactions were carried out on multigram scale; hence 2.4 g of the sequence-defined decamer was obtained (see Figure S4). This implies

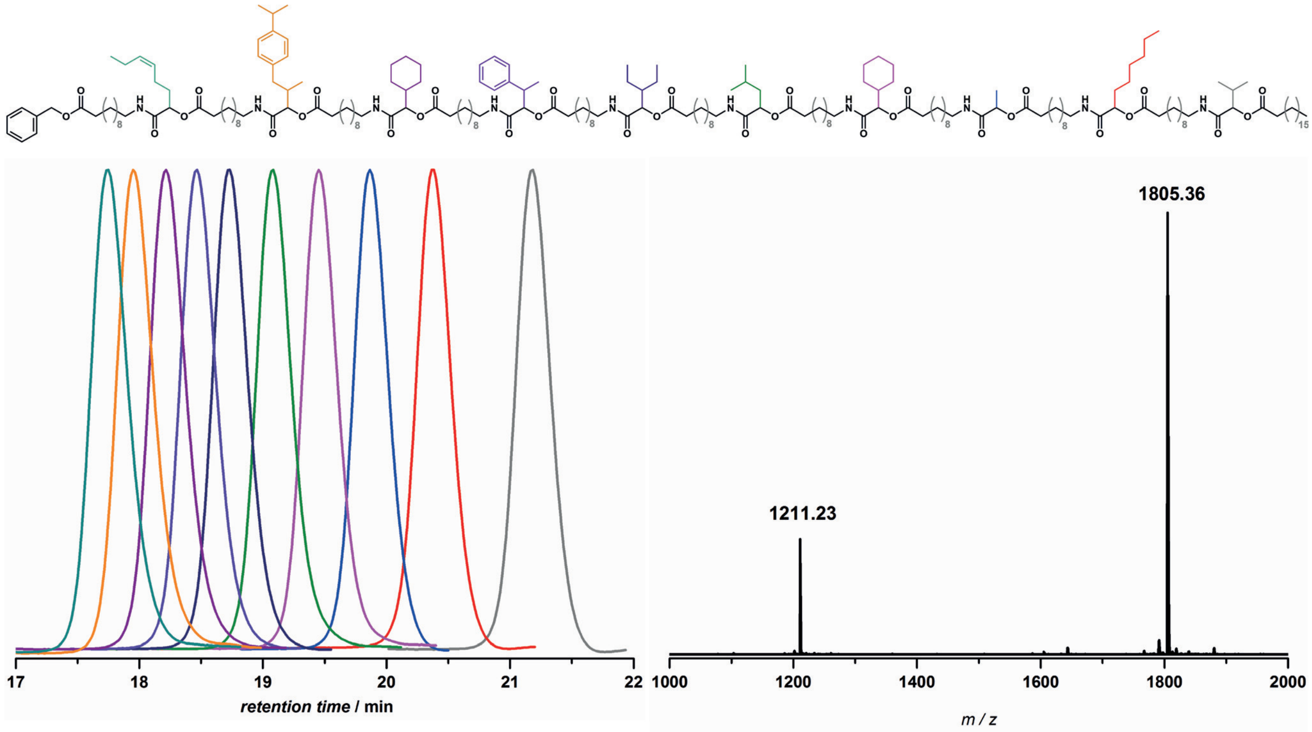


Figure 1. Top: Structure of the sequence-defined decamer with ten side chains, including aliphatic, aromatic, and olefinic side chains. Bottom left: GPC traces of the obtained products after each P-3CR. Bottom right: ESI mass spectrum of the sequence-defined decamer. The assigned masses correspond to the doubly (*m*/*z* 1805.36) and the triply (*m*/*z* 1211.23) charged sodium ions ($[M+z\,Na]^{z+}$).

Table 1: Comparison of the yields of the previously published Passerini/thiol–ene[7b] approach with the monomer approach reported here.

Sequence[a]	Passerini/thiol–ene	Passerini/deprotection
1st	71 %	97 %
2nd	73 %	96 %
3rd	65 %	88 %
4th	65 %	90 %
5th	68 %	91 %
6th		92 %
7th		91 %
8th		92 %
9th		89 %
10th		95 %
overall yield	**15 % (for 5-mer)**	**44 % (for 10-mer)**

[a] Sequence includes the Passerini reaction as well as the thiol–ene addition or the deprotection.

that the synthesis of defined macromolecules for certain applications and the establishment of structure–property relationships will be possible in the future. The high purity of the obtained products was evidenced by GPC (Figure 1, bottom left) and NMR spectroscopy, and the macromolecules were further characterized by GPC-ESI-MS and mass spectrometry (see the Supporting Information). Figure 1 (bottom, right) shows the obtained ESI mass spectrum of the sequence-defined decamer. The doubly (m/z 1805.36) and triply (m/z 1211.23) charged sodium cations ($[M+z\mathrm{Na}]^{z+}$) are clearly observed. Moreover, the isotope pattern was compared with the calculated one, confirming the chemical structure of the sequence-defined decamer (Figure S2). Beyond that, MS/MS techniques were recently reported in order to obtain a post-synthetic proof of the synthesized sequences.[10]

In order to highlight the versatility of our approach, we introduced a *cis* double bond to the side chain of the tenth repeating unit allowing further modifications. Thus, we successfully conducted the self-metathesis of the sequence-defined decamer (see Figure 2, left) using the Hoveyda–Grubbs second-generation catalyst in combination with p-benzoquinone in order to prevent possible isomerization reactions.[11] In this way, a sequence-defined 20-mer was synthesized in 48 % yield, resulting in an overall yield of 21 % over 20 reaction steps. The GPC trace of the 20-mer shows a clear shift in retention time compared to the decamer due to the significant increase in molecular weight (Figure 2, right). In addition, the high purity of the 20-mer is evidenced. In order to characterize the sequence-defined 20-mer in more detail, we further conducted a coupled GPC-ESI-MS measurement. The GPC trace and the ESI mass spectrum recorded at a retention time of 13.56 min are displayed in Figure 3. The ESI mass spectrum clearly shows the fourfold (m/z 1784.34), fivefold (m/z 1432.07), and sixfold (m/z 1197.22) charged sodium ions ($[M+z\mathrm{Na}]^{z+}$) of the sequence-defined 20-mer. Additionally, we analyzed the isotope pattern of the spectrum, which is in very good agreement with the calculated one and verifies the chemical structure of the product (Figure S3).

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 $\mathrm{g\,mol^{-1}}$. Remarkably, a quantity of more than two grams could be synthesized applying this strategy. Furthermore, functional side chains, such as double bonds, were introduced, which allow for 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 $\mathrm{g\,mol^{-1}}$. In addition, the high purity of the products was evidenced by in-depth analysis including NMR spectroscopy, GPC, and GPC-ESI-MS and ESI orbitrap mass spectrometry.

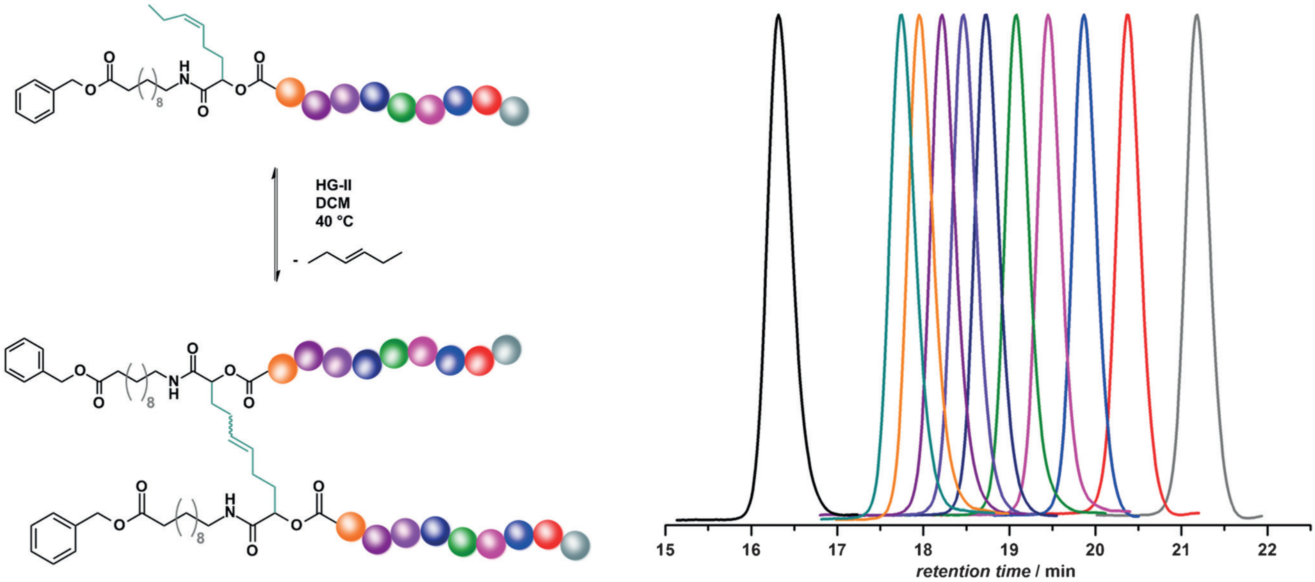


Figure 2. Left: Reaction scheme of the self-metathesis reaction of the sequence-defined decamer. Right: GPC traces of the obtained products, indicating the clear shift of the 20-mer compared to the decamer due to the almost doubling of the molecular weight.

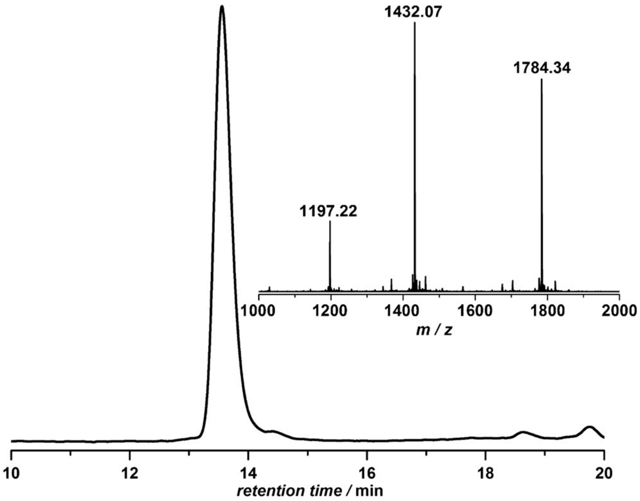


Figure 3. GPC-ESI-MS analysis of the sequence-defined 20-mer showing the GPC chromatogram and the ESI mass spectrum at a retention time of 13.56 min. The assigned peaks correspond to the fourfold (*m*/*z* 1784.34), fivefold (*m*/*z* 1432.07), and sixfold (*m*/*z* 1197.22) charged sodium ions ($[M+z\,\mathrm{Na}]^{z+}$).

Acknowledgements

We thank Prof. Barner-Kowollik and his group for access to the GPC-ESI-MS equipment. We are grateful to the Deutsche Forschungsgemeinschaft (German Research Council, DFG) in the context of §91b application under the auspices of Prof. C. Barner-Kowollik for funding the orbitrap mass spectrometer. S.C.S. is grateful for a PhD scholarship from the Verband der Chemischen Industrie (VCI). We kindly thank the DFG for funding this project in the framework of the collaborative research center 1176 (SFB 1176, project A3).

Keywords: metathesis · multicomponent reactions · Passerini reaction · polymers · sequence control

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 1204–1207
Angew. Chem. **2016**, *128*, 1222–1225

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Received: October 8, 2015