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Sequence-Defined Dithiocarbamate Oligomers *via* a Scalable, Support-free, Iterative Strategy

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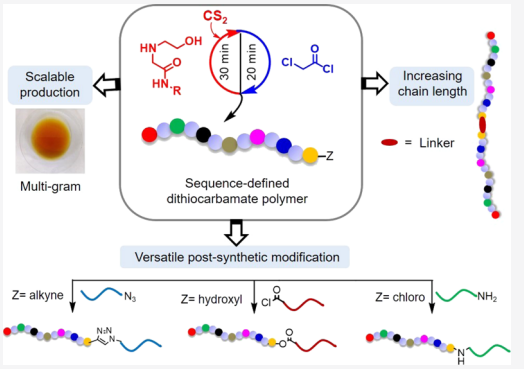
ABSTRACT: Precise control over the monomeric sequence on natural sequence-defined polymers (SDPs) leads to their structural diversity and functions. However, absolute control over the monomeric sequence on a synthetic polymer remains a challenging process. Herein, we describe a support-free, protection−deprotection-free, cost-effective, and fast iterative strategy for multigram production of a new class of SDP with a unique functional group, dithiocarbamate, a potential group for material and biomedical applications. The strategy is based on a unique monomer, named as amine-hydroxyl monomer, and a three-component reaction between the monomer, CS_2, and terminal chloro group of the growing chain. The fast strategy allows us to synthesize a 5-mer sequence-defined oligomer in 6 h. For a proof of concept, a range of aliphatic and aromatic groups have been incorporated at different sequences in the sequence-defined oligomer. This SDP platform has further been advanced by two ways: (i) multiple approaches for postsynthetic modification of SDP and (ii) increasing the chain length in a single step.



INTRODUCTION

Natural sequence-defined polymers (SDPs) including nucleic acids and proteins are crucial for a living system because of their structural and functional diversity. The monomeric sequence is the key parameter that tunes their structure and properties, which eventually leads to their unique functions. However, precise control over the monomeric sequence on nonnatural synthetic polymer backbones is challenging. A nonnatural SDP possesses a wider scope of unlimited functional groups at the side chain and backbone, leading to extensive structural diversity and tunable properties. In the last few decades, chemists have made great efforts for developing nonnatural SDPs.[1−8] An iterative strategy is an efficient strategy to precisely control monomer sequences. Solid-supported iterative synthesis[9−13] is the pioneer and efficient strategy to build SDPs for its ease of purification and automation. However, kinetics of the solid-supported coupling reaction is limited for poor diffusion into a solid support. Soluble-supported strategies have been developed to overcome this *via* solution-phase homogenous kinetics.[14−19] Another notable strategy is the support-free strategy[20−26] which has added advantages including fast solution-phase kinetics and avoiding attaching and removal steps of the polymer from the support. However, precise control over the monomeric sequence *via* a support-free iterative process is difficult. Hence, a limited number of support-free iterative strategies have been developed so far. Motivated by the promises of synthetic SDPs and the pressing need for developing an efficient strategy for synthesizing the same, we report here a highly efficient, support-free, and iterative strategy to yield multigram scale of a new class of monodispersed SDPs. The unique feature of this class of SDP is that its backbone harbors an important functional group—dithiocarbamate (DTC)—which is reported as an excellent candidate for both material (*e.g.,* heavy metal sensors[27] and vulcanizing accelerators in rubber industries[28]) and biomedical applications (*e.g.,* anti-leishmanial,[29] antiacute myelogenous leukaemia,[30] antitrypanosomatids,[31] and anticancer agents[32]). To our knowledge, this is the first report on a DTC-based SDP. Our strategy possesses multiple advantages including (i) a support-free and protection−deprotection-free synthesis with readily available starting materials under mild reaction conditions; (ii) yielding multigram-scale product; and (iii) modular postsynthetic modification of the SDP *via* versatile paths. The strategy is based on (a) the design and synthesis of a unique monomer and strategic incorporation of commercially available comonomer and (b) two key reactions yielding fast quantitative conversion. Employing this strategy, more than 5 g of a 5-mer was synthesized in 6 h, indicating the high-scalability, fast, and efficient production of sequence-defined DTC oligomers (SD-

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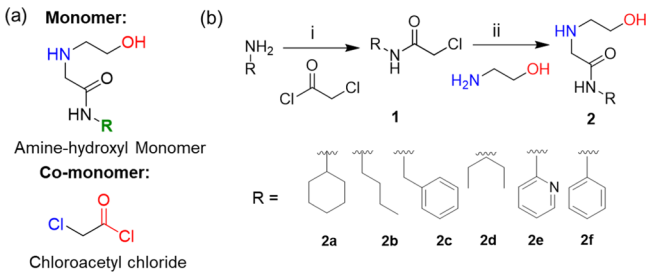
DTCO). This methodology can be considered eco-friendly because no hazardous waste is liberated except HCl gas which can be neutralized by sodium bicarbonate base. A wide range of functional groups has been incorporated in the SD-DTCO through the custom synthesis of a monomer.

RESULTS AND DISCUSSION

Design and Synthesis of a Unique Monomer. In the present study, an effort was made to synthesize SD-DTCO *via* strategic design of a unique bifunctional monomer, named as amine-hydroxyl monomer (Scheme 1a). This monomer framework consists of two reactive groups: a secondary amine (blue) and a hydroxyl group (red) to provide reactive sites for two key reactions. Chloroacetyl chloride was selected as a comonomer to couple two amine-hydroxyl monomers together to build the SD-DTCO (Scheme 1a). The amino group of the monomer was utilized to generate in-situ active thiol by the addition of CS_2 and this active thiol was reacted with the alkyl-chloro group of the comonomer to yield a DTC.

Scheme 1. (a) Structure of the Amine-Hydroxyl Monomer and the Comonomer and (b) Synthesis of the Amine-Hydroxyl Monomer[a]

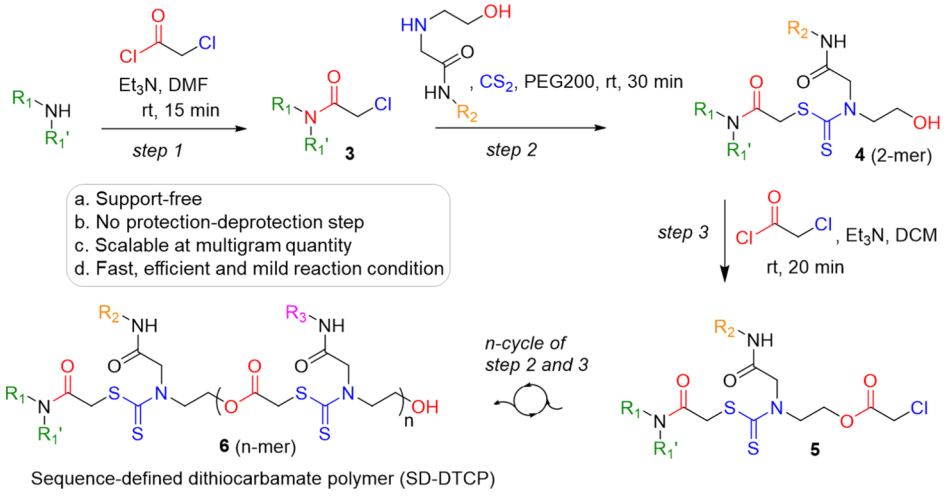


[a]Reaction conditions: i = DMF, rt, 15 min; ii = ACN, 85 °C, 30 min.

At room temperature, this three-component reaction was selective towards the amine group of the monomer, keeping the hydroxyl group inert. The hydroxyl group was reacted with the acyl-chloro group of the comonomer to assemble the SD-DTCO. A primary amine with the desired functional group was reacted with chloroacetyl chloride to form a chloro-terminal amide (**1**, Scheme 1b), which was further reacted with ethanolamine to yield the amine-hydroxyl monomer (**2**, Scheme 1b). The reaction mixture was extracted with 1:1 ethyl acetate/water, and >95% pure product was isolated from the ethyl acetate layer. The monomers were directly used for polymerization reaction without further purification. The monomers were characterized by ^{1}H NMR and liquid chromatography−mass spectrometry (LC−MS) (Figures S2−S7). Monomers with six different functional groups (Scheme 1b, **2a−f**) were synthesized for the proof of concept of incorporation of different groups in SD-DTCO.

Synthesis of SD-DTCO *via* a Three-Component Reaction Strategy. SD-DTCO synthesis starts with a secondary amine reacting with chloroacetyl chloride (comonomer) to yield chloroacetyl amide with the desired functional group (**3**, Scheme 2). The next monomer was reacted with **3** in the presence of CS_2 to yield a 2-mer with two (or three when $R_1 \neq R_1'$) different functional groups (**4**, Scheme 2). Thereafter, the hydroxyl functionality of **4** was reacted with chloroacetyl chloride to yield **5** (Scheme 2). Subsequently, repetition of steps 2 and 3 will produce a desired n-mer of SD-DTCO (**6**, Scheme 2). For a proof of concept, *N*,*N*-diphenyl amine was reacted with chloroacetyl chloride in dimethylformamide (DMF) at room temperature to form **7** (Figure 1). The quantitative conversion occurred in 20 min. The reaction mixture was washed with water, and the pure product was extracted in ethylacetate. This compound was utilized for the next step without any further purification. The next reaction between **7** and the cyclohexyl amine-hydroxyl monomer (**2a**, Scheme 1) in the presence of CS_2 yielded the 2-mer (**8**, Figure 1). According to the three-component reaction strategy, the first reaction generates active thiol by the reaction of secondary amine of **2a** and CS_2 (Figure 1). The second reaction involves nucleophilic substitution of the terminal chloride of **7** by the active thiol generated in the first reaction to yield the 2-mer (**8**, Figure 1) at quantitative conversion in 30 min with >95% purity without silica gel column chromatography purification.

Scheme 2. Synthetic Strategy for Sequence-Defined DTC Polymers; Inset: Merits of the Strategy[a]



[a]Purification procedure: for step 1 and step 2, the reaction mixture was extracted in 1:1 ethyl acetate/water and the product was obtained in the ethyl acetate layer. For step 3, the reaction mixture was extracted in 1:1 dichloromethane/water and the product was obtained in the dichloromethane layer.

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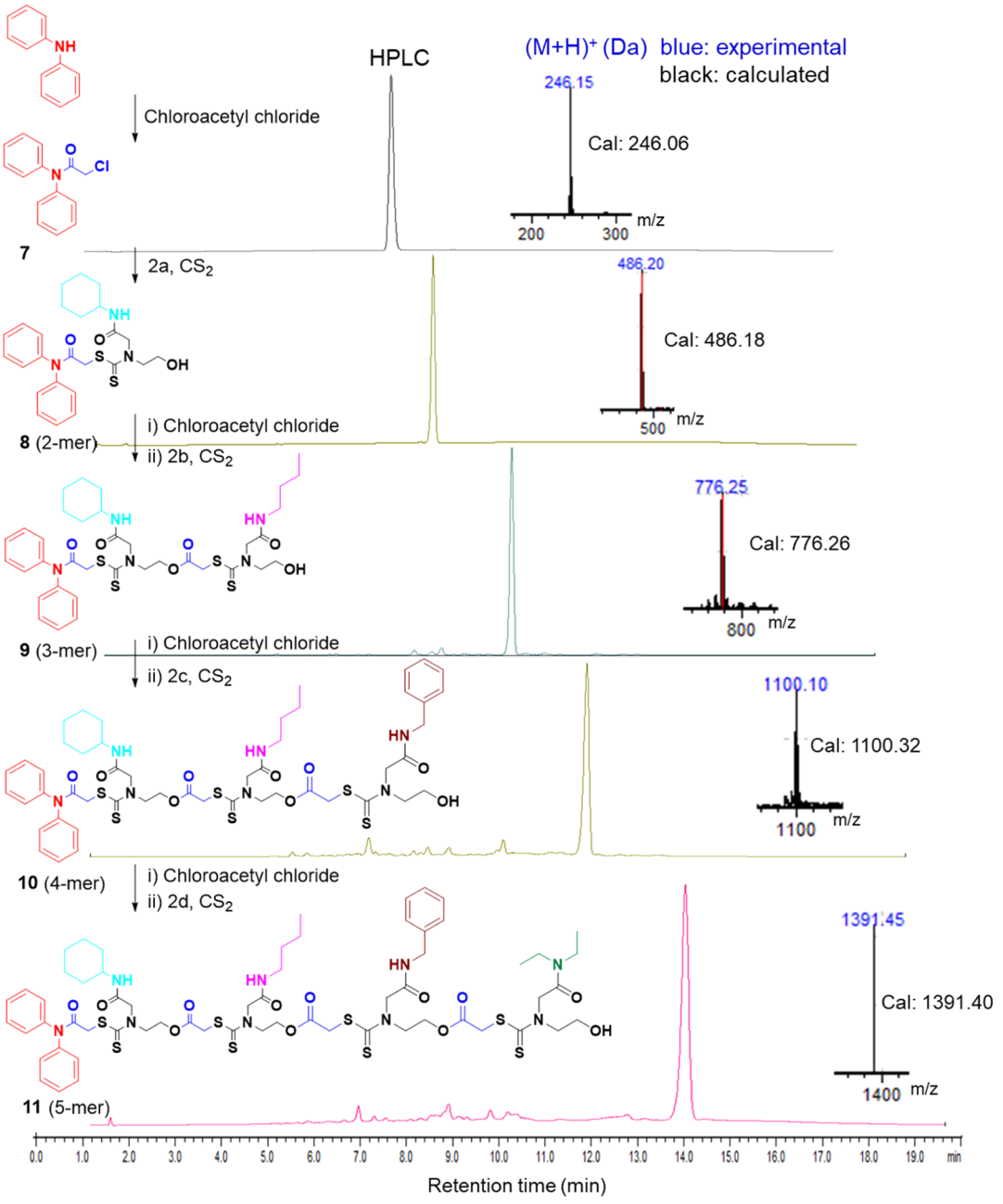

Figure 1. Assembly of a 5-mer; left-structure, middle—HPLC, and right—$(M + H)^+$ in LC−MS.

Kinetic study has been performed for the two above-mentioned key reactions to establish the time required for the quantitative conversion of each reaction (Figures S8 and S9).

High-performance liquid chromatography (HPLC) trace of the corresponding **7** and **8** (Figure 1) shows high purity without silica gel column chromatography purification. **7** and **8** showed the expected $(M + H)^+$ peaks at 246.15 and 486.20 Da, respectively, in the LC−MS spectrum (Figure 1). Both the cyclohexyl (δ = 1−1.8 ppm) and aromatic (δ = 7.3−7.6 ppm) protons in the ^{1}H NMR spectrum of **8** (Figure S10) confirmed the presence of these groups in the 2-mer. Thereafter, the 2-mer was reacted with chloroacetyl chloride to make a chloro derivative of the 2-mer which was further reacted with butyl amine-hydroxyl monomer (**2b**, Scheme 1) and CS_2 *via* the above-mentioned three-component reaction strategy to yield a 3-mer (**9**, Figure 1). The 3-mer showed the expected $(M + H)^+$ at 776.25 Da in LC−MS (Figure 1) and the proton signal corresponding to butyl group in the ^{1}H NMR spectrum (Figure S10). Similarly, the reaction strategy was continued until 5-mer (**11**, Figure 1) with the benzyl and diethyl monomers respectively (**2c** and **2d**, Scheme 1) under identical conditions. 4-mer and 5-mer SD-DTCOs were characterized by their $(M + H)^+$ at 1100.10 and 1391.45 Da, respectively, in LC−MS spectra (Figure 1). Retention time of the HPLC traces of **7**-**11** (Figure 1-middle) indicates that the hydrophobicity of SD-DTCOs increases with the increase in chain length as retention time is proportional to hydrophobicity.

The sequence was validated *via* a tandem-MS (MS/MS) experiment on $(M + H)^+$ ion of the 5-mer (Figure 2). From the fragmentation analysis, it was identified that cleavage occurs between β-carbon of DTC nitrogen and oxygen of ester,

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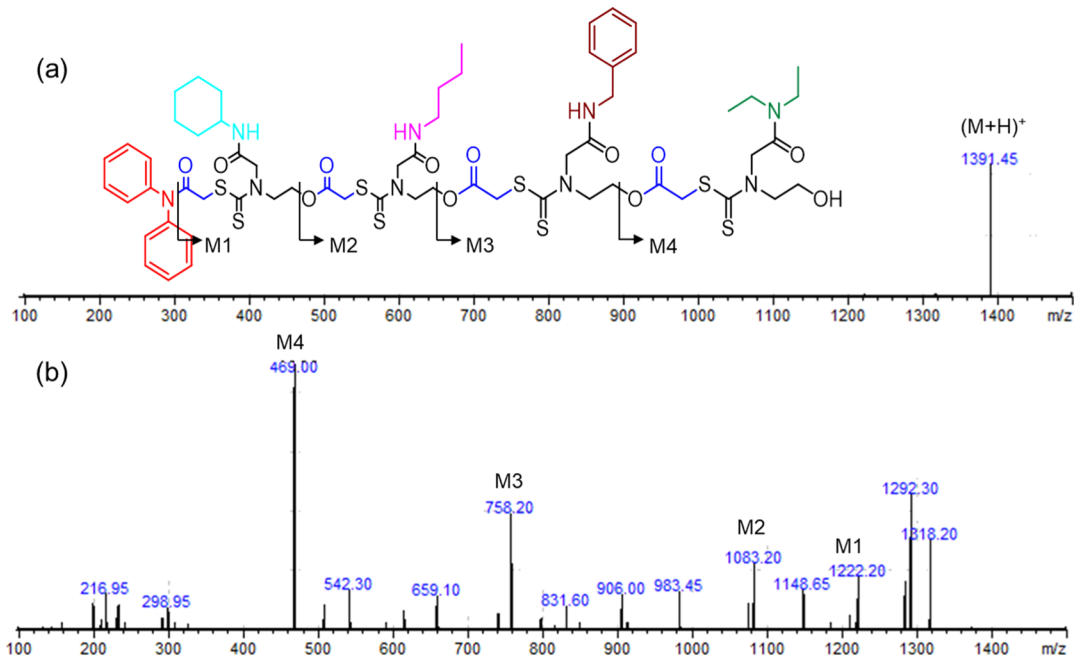

Figure 2. (a) LC−MS (inset: structure) and (b) tandem-MS spectrum of a 5-mer.

and this pattern was consistent for all SD-DTCOs. The expected mass of all the sequence-specific fragmentation ions of 5-mer was identified in the MS/MS spectrum, confirming the precisely arranged sequence of diphenyl−cyclohexyl−butyl−benzyl−diethyl groups on the 5-mer (Figure 2).

Four more 5-mer SD-DTCOs were synthesized by changing the functional groups and their sequence to prove that the strategy is robust and consistent. The sequence of all the synthesized SD-DTCO, their characterization (MS, MS/MS and ^{1}H NMR), and yield are shown in Figures 3a and S21−S29. The overall yield of the synthesis of the 5-mer is 60−75%. The product conversion at each reaction is quantitative. However, the loss at each step occurred because of the extraction process. The retention time of different 5-mer SD-DTCOs in HPLC spectra (Figure 3b) suggests that by changing the functional groups and their sequence, the hydrophobic property of SD-DTCOs was modulated. Thermal stability of the SD-DTCO was tested by thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) experiments. The results indicate that the SD-DTCO is stable up to 180 °C (Figures S30 and S31). It was also observed that SD-DTCO is stable under a free-radical atmosphere (Figure S32) and under acidic and basic pH conditions (at least in the range of pH 4−9, Figure S33).

(a)

No	Sequence					(M+H)+ (Da)		Yield (%)
	R_1	R_2	R_3	R_4	R_5	Calculated	Observed	
11	Phenyl	2a	2b	2c	2d	1391.39	1391.45	72
11a	Ethyl	2b	2a	2c	2e	1315.36	1315.30	68
11b	Phenyl	2b	2d	2e	Naphthalene	1348.32	1348.30	63
11c	Ethyl	2c	2f	2e	2b	1309.71	1310.20	62
11d	Phenyl	2a	2b	2b	2b	1356.41	1356.35	65

(b)

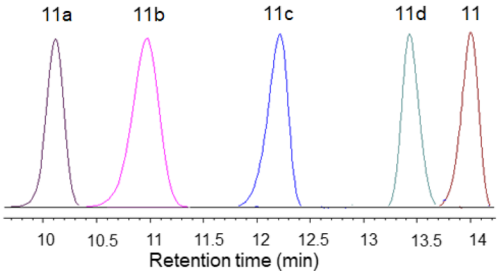

Figure 3. (a) Sequence and mass of the synthesized 5-mer SD-DTCOs and (b) their HPLC traces.

Postsynthetic Modifications. Postsynthetic modification is an important strategy for many applications in biomedical and material sciences.[33,34] Keeping this in mind, we made our synthetic strategy versatile for postsynthetic modification of SD-DTCO *via* three different paths (Figure 4). Multiple paths for postsynthetic modification are important when availability of the functional group of the secondary system is limited. In path 1, an alkyne-terminal 3-mer and an azide terminal molecule were synthesized (Figures 4a left, S34 and S35). Reaction between them *via* Cu(I)-catalyzed azide−alkyne click reaction yielded the expected product **12** (Figure 4a), which was characterized by its $(M + H)^+$ peak in the LC−MS spectrum (Figures 4a-right and S36). In path 2, a naphthalene moiety was attached with a 3-mer SD-DTCO *via* reaction of the chloro-terminal 3-mer SD-DTCO and *N*-methyl-1-naphthylmethylamine (Figure 4b). The product **13** was characterized by its $(M + H)^+$ peak in the LC−MS spectrum (Figures 4b-right and S37). The fluorophore (naphthalene)-conjugated SD-DTCO can be a potential candidate for photophysical studies. In path 3, a 4-mer hydroxy terminal SD-DTCO was reacted with adipoyl chloride to demonstrate that postsynthetic modification is possible *via* any functional group that can react with the hydroxy group (Figure 4c). The product was confirmed by LC−MS (Figures 4c-right and S38). As the reaction mixture was worked up in aqueous solution, the second acyl-chloride (after postsynthetic modification) was transformed into an acid group. The versatile postsynthetic modification paths will make SD-DTCO potential for various applications.

Strategy for Increasing the Chain Length of SDOs. Furthermore, we developed a strategy to increase the chain length of the SD-DTCO by twofold in a single step *via* a linker.

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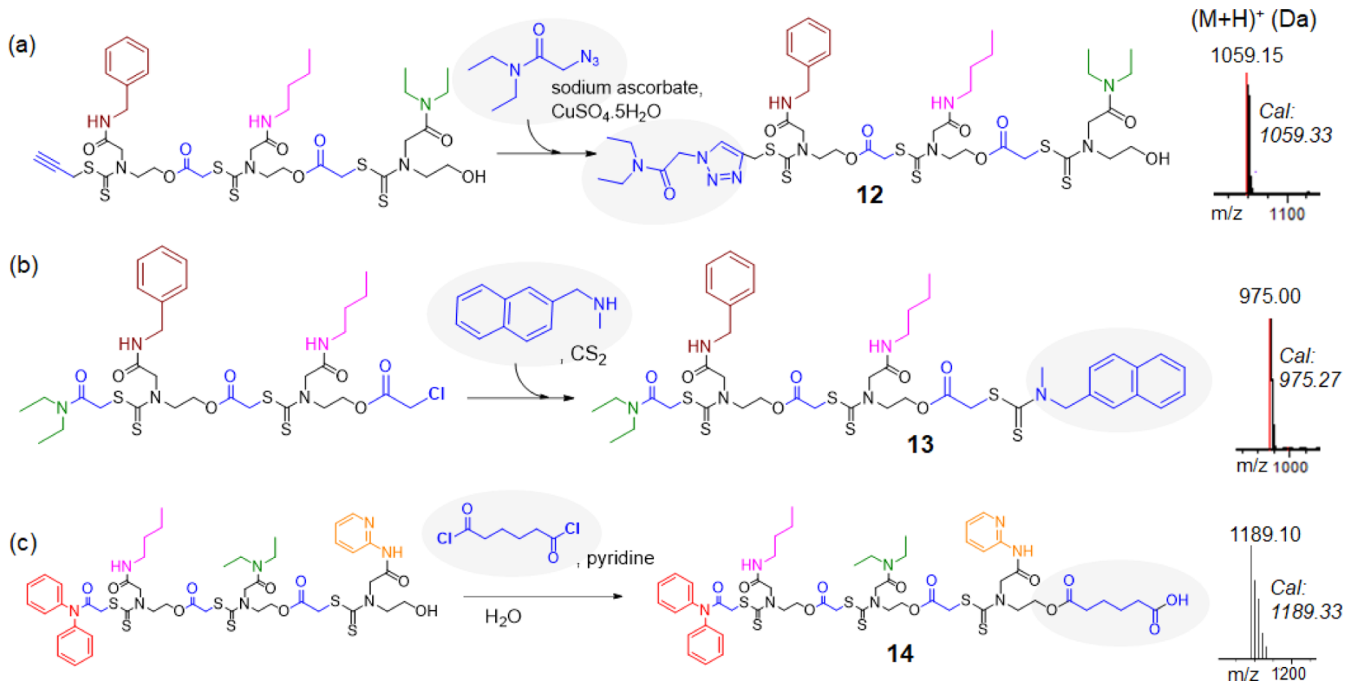

Figure 4. Postsynthetic modifications of the SD-DTCO *via* three approaches: (a) Cu(I)-catalyzed azide−alkyne click reaction between alkyne of the SD-DTCO and azide of the secondary system, (b) chloro−amine reaction between chloro of the SD-DTCO and amine of the secondary system, and (c) hydroxyl−acylchloride reaction between hydroxyl of the SD-DTCO and acyl chloro of the secondary system.

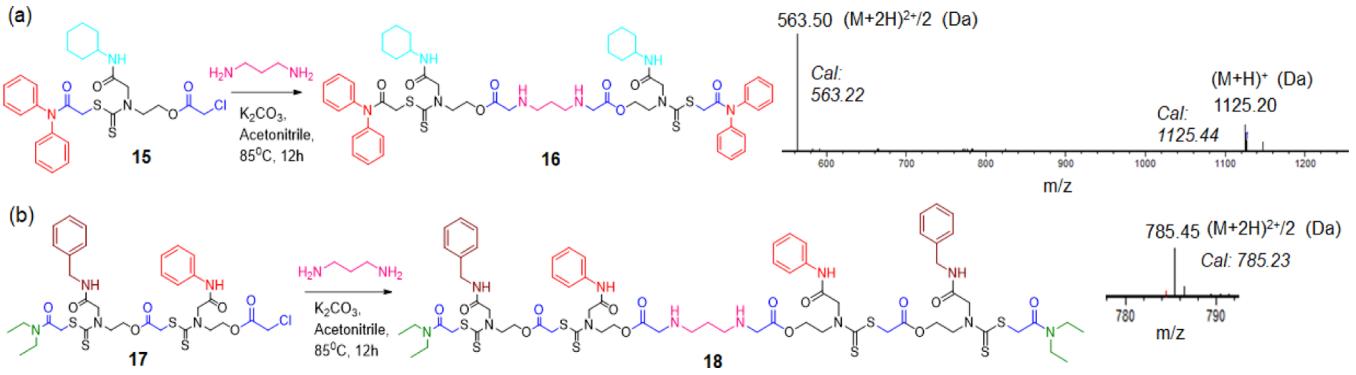

Figure 5. Synthesis of (a) 4-mer from a 2-mer (left) and its MS spectrum (right) and (b) 6-mer from a 3-mer (left) and its MS spectrum (right) *via* a 1,3-propane-diamine linker.

One equivalent of 1,3-propane di-amine (linker) was reacted with two equivalents of a chloro-terminal 2-mer and 3-mer to generate a 4-mer and 6-mer, respectively (Figure 5). The products were confirmed by the $(M + H)^+$ and $(M+2H)^{2+}/2$ peaks of the 4-mer (Figures 5a right, S39) and $(M + H)^{2+}/2$ peak of the 6-mer (Figures 5b right and S40) in the respective LC−MS spectrum. The 2-mer and 3-mer were selected to prove this strategy because the masses of the 4-mer and 6-mer fall in the detection range (50−2000 Da) of the LC−MS instrument used in this study.

CONCLUSIONS

In conclusion, an efficient strategy has been developed for the synthesis of a new class of SD-oligomers incorporating DTC in the backbone *via* strategic design of a unique bifunctional monomer. This strategy is support-free, protection−deprotection-free, scalable at a multigram level, and consistent for fast production of SD-oligomers from readily available inexpensive starting materials under mild reaction conditions. For example, a 5-mer was synthesized at >5 g in about 6 h. Five SD-DTCOs were synthesized by changing functional groups and their sequence and were characterized by LC−MS and MS/MS study. The ease of monomer preparation along with the efficient strategy facilitates the incorporation of a wide range of functional groups into the SD-DTCO structure, which will lead us for developing novel materials in the future. Additionally, the strategy leads us to generate terminal hydroxyl/chloro/alkyne reactive groups which can be utilized for postsynthetic modifications by a secondary system to extend its potential for various applications. Furthermore, a strategy was developed to double the chain length of the SD-DTCO *via* connecting the SD-DTCO at two terminals of a linker in a single step. Postsynthetic modifications will enable the SD-DTCO platform to engineer structural diversity, tunable properties, and applications in material and biomedical sciences. We are currently working on developing different architectures of SD-DTCOs and exploration of their potential applications.

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EXPERIMETAL SECTION

Synthesis of Amine-Hydroxyl Monomers. Chloro-terminal amide (**1**, Scheme 1) was synthesized *via* the reaction of a primary amine with the desired functional group (1 mmol) and chloroacetyl chloride (2 mmol) in DMF (5 mL). The reaction was completed in 20 min at room temperature. After completion of the reaction, the excess chloroacetyl chloride was quenched by the addition of sodium bicarbonate solution. Thereafter, 1:1 water: ethyl acetate was added in the reaction mixture and the product (chloro-terminal amide) was extracted in the ethyl acetate layer with >95% purity. The chloro-terminal amides (**1**, Scheme 1) were directly used for the next reaction without column chromatography purification. Next, in a solution of chloro-terminal amides (1 mmol) in acetonitrile (5 mL), ethanolamine (5 mmol) and potassium carbonate (10 mmol) were added and the reaction mixture was refluxed at 85 °C for 30 min. Thereafter, the reaction mixture was cooled at room temperature and 1:1 water: ethyl acetate was added in the reaction mixture. The product (**2**, Scheme 1, amine-hydroxyl monomer) was extracted in the ethyl acetate layer. The solvent was removed under reduced pressure, and the amine-hydroxyl monomer (**2**, Scheme 1) was obtained at 90−95% yield with >95% purity. All the monomers were characterized by ^{1}H NMR and LC−MS. Monomers (**2**, Scheme 1) were directly used for polymerization reaction without further purification.

Synthesis of SD-DTCOs. A secondary amine (1 mmol) with the desired functional group and chloroacetyl chloride (2 mmol) were stirred in DMF (5 mL) at room temperature to yield **3** (Scheme 2). The reaction was completed in 20 min. After completion of the reaction, excess chloroacetyl chloride was quenched by the addition of sodium bicarbonate solution. Thereafter, 1:1 water: ethyl acetate was added in the reaction mixture and the product was extracted in the ethyl acetate layer with >95% purity. Thereafter, the respective monomer (**2a**−**2f**, Scheme 1, 2 mmol) and CS_2 (4 mmol) were added in a chloro derivative of 1-mer (**3**, Scheme 2, 1 mmol) solution in polyethylene glycol (PEG)-200 (1 mL). The reaction mixture was stirred at room temperature for 30 min. 1:1 water: ethyl acetate was added in the reaction mixture, and the 2-mer (**4**, Scheme 2, 3-mer) was extracted in the ethyl acetate layer and was employed for the next step without column chromatography purification. Next, the chloro derivative of the 2-mer (**5**, Scheme 2) was prepared *via* the reaction of the 2-mer (1 mmol) and chloroacetyl chloride (2 mmol) in the presence of triethylamine (2 mmol) in dichloromethane (5 mL) at room temperature. The reaction was completed in 20 min, and thereafter, the excess chloroacetyl chloride was quenched with sodium bicarbonate solution. The dichloromethane was removed under reduced pressure. This product (**5**, Scheme 2) was used directly for the next reaction without further purification. The same cycle of reactions was repeated for the synthesis of different SD-DTCOs (**6**, Scheme 2). SD-DTCOs were characterized by LC−MS and MS/MS study.

Postsynthetic Modifications. Postsynthetic modification of SD-DTCOs was performed in three different approaches according to the following procedures.

Cu(I)-Catalyzed Azide−Alkyne Click Reaction. Alkyne-substituted SD-DTCO (0.5 mmol) and azide terminal diethyl amide (0.5 mmol) (see section 8 under the Supporting Information for synthetic procedure for both the starting materials) were suspended in a 1:1 mixture of water and tetrahydrofuran (6 mL). Sodium ascorbate (0.3 mmol) was added, followed by the addition of $CuSO_4{\cdot}5H_2O$ (0.03 mmol). The heterogeneous mixture was stirred vigorously for 1h at room temperature. 1:1 ethyl acetate: water was added in the reaction mixture and the product was extracted in the ethyl acetate layer. Then, the solvent was removed under vacuum to afford 84% of the product (**12**, Figure 4a). The post synthetically modified product was further purified using silica gel column chromatography and characterized by LC−MS analysis.

Chloro-Amine Reaction. To a solution of a chloro derivative of the 3-mer (0.5 mmol) in PEG-200 (1 mL), *N*-methyl-1-naphthylmethylamine (0.5 mmol) was added and stirred for 10 min at room temperature. Then, CS_2 (2 mmol) was added and stirred at room temperature for 1 h. 1:1 ethyl acetate: water was added in the reaction mixture and the product (**13**, Figure 4b) was extracted in the ethyl acetate layer. Removal of solvent under reduced pressure yielded an oily naphthalene-attached product which was further confirmed by LC−MS analysis.

Hydroxy-Acyl Chloro Reaction. Pyridine (0.6 mmol) was added to a solution of a 4-mer SD-DTCO (0.3 mmol) in dichloromethane (10 mL) and stirred for 10 min at room temperature. Then, adipoyl chloride (0.4 mmol in 5 mL DCM) was added slowly. The reaction mixture was stirred for 2h at room temperature. After completion of the reaction, the reaction mixture was neutralized with aqueous $NaHCO_3$ solution. Thereafter, the reaction mixture was washed with water and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the product (**14**, Figure 4c) was characterized by LC−MS analysis.

Increasing the Chain Length of SD-DTCO by Twofold *via* a Single Step. To a chloro derivative of a 2-mer SD-DTCO (**15**, Figure 5a, 0.106 mmol) dissolved in acetonitrile (10 mL), potassium carbonate (0.424 mmol) and 1,3 propane diamine (0.048 mmol) were added. The reaction mixture was refluxed at 85 °C for 12 h. Thereafter, the reaction mixture was cooled and filtered to remove potassium carbonate, and the filtrate was extracted with ethyl acetate, washed with water, and dried over anhydrous Na_2SO_4. After the removal of the solvent, the product (**16**, Figure 5a, 4-mer) was obtained and confirmed by LC−MS analysis. The same procedure was followed to synthesize a 6-mer from a 3-mer (**18**, Figure 5b)

HPLC Analysis. The purity of all the synthesized compounds was analyzed by HPLC analysis, as shown in Figure 1. A binary solvent system (water with 0.1% formic acid and acetonitrile with 0.1% formic acid) was used for the HPLC experiment, and the gradient is detailed in the Supporting Information. The flow rate of the HPLC experiment was maintained at 1 mL/min, and the spectrum was monitored at 210 and 254 nm wavelength. Being a reverse-phase chromatographic separation, increasing the retention time of the HPLC spectrum indicates the increase in hydrophobicity of the compound. The relative hydrophobicity of all synthesized SD-DTCOs was analyzed by HPLC experiment (Figure 3b).

LC−MS Analysis. The product of each reaction was characterized by its mass/charge (m/z) analysis using an LC−MS instrument monitoring at 210 and 254 nm with a positive mode for mass detection. The sequence of the synthesized SD-DTCOs was identified by LC−MS/MS fragmentation. A binary solvent system (water with 0.1% formic acid and acetonitrile with 0.1% formic acid) was used for the LC−MS experiment, and the gradient is detailed in the Supporting

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Information. The flow rate of the LC−MS/MS experiment was maintained at 0.7 mL/min, and the spectrum was monitored at 210 nm and 254 nm wavelength.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.macromol.0c00412.

Synthesis and characterizations of different oligomers including NMR, HPLC−MS, MS/MS, TGA, and DSC (PDF)

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

SDP sequence-defined polymers
DTC dithiocarbamate
PEG polyethylene glycol
THF tetrahydrofuran

■ REFERENCES

(1) Lutz, J.-F.; Ouchi, M.; Liu, D. R.; Sawamoto, M. Sequence-controlled polymers. *Science* **2013**, *341*, 1238149.

(2) Meier, M. A. R.; Barner-Kowollik, C. A new class of materials: Sequence-defined macromolecules and their emerging applications. *Adv. Mater.* **2019**, *31*, 1806027.

(3) Badi, N.; Lutz, J.-F. Sequence control in polymer synthesis. *Chem. Soc. Rev.* **2009**, *38*, 3383−3390.

(4) Lutz, J.-F. Sequence-controlled polymerizations: the next Holy Grail in polymer science? *Polym. Chem.* **2010**, *1*, 55−62.

(5) Solleder, S. C.; Schneider, R. V.; Wetzel, K. S.; Boukis, A. C.; Meier, M. A. R. Recent progress in the design of monodisperse, sequence-defined macromolecules. *Macromol. Rapid Commun.* **2017**, *38*, 1600711.

(6) Lutz, J. F. Defining the field of sequence-controlled polymers. *Macromol. Rapid Commun.* **2017**, *38*, 1700582.

(7) Szymanski, J. K.; Abul-Haija, Y. M.; Cronin, L. Exploring strategies to bias sequence in natural and synthetic oligomers and polymers. *Acc. Chem. Res.* **2018**, *51*, 649−658.

(8) Pandurangan, N.; Porel, M. Sequence-defined non-natural polymers: synthesis and applications. *Polym. Chem.* **2019**, *10*, 5406−5424.

(9) Espeel, P.; Carrette, K.-F.; Bury, K.; Capenberghs, S.; Martins, J. C.; Du-prez, F. E.; Madder, A. Multifunctionalized sequence-defined oligomers from a single building block. *Angew. Chem., Int. Ed.* **2013**, *52*, 13261−13264.

(10) Davidson, E. C.; Rosales, A. M.; Patterson, A. L.; Russ, B.; Yu, B.; Zuckermann, R. N.; Segalman, R. A. Impact of helical chain shape in sequence-defined polymers on polypeptoid block copolymer self-assembly. *Macromolecules* **2018**, *51*, 2089−2098.

(11) Kos, P.; Lächelt, U.; He, D.; Nie, Y.; Gu, Z.; Wagner, E. Dual-targeted polyplexes based on sequence-defined peptide-PEG-oligoamino amides. *J. Pharm. Sci.* **2015**, *104*, 464−475.

(12) Trinh, T. T.; Laure, C.; Lutz, J.-F. Synthesis of monodisperse sequence-defined polymers using protecting-group-free iterative strategies. *Macromol. Chem. Phys.* **2015**, *216*, 1498−1506.

(13) Grate, J. W.; Mo, K. F.; Daily, M. D. Triazine-based sequence-defined polymers with side-chain diversity and backbone-backbone interaction motifs. *Angew. Chem., Int. Ed.* **2016**, *55*, 3925−3930.

(14) Brown, J. S.; Acevedo, Y. M.; He, G. D.; Freed, J. H.; Clancy, P.; Alabi, C. A. Synthesis and solution-phase characterization of sulfonated oligothioetheramides. *Macromolecules* **2017**, *50*, 8731−8738.

(15) Chan-Seng, D.; Lutz, J.-F. Primary structure control of oligomers based on natural and synthetic building blocks. *ACS Macro Lett.* **2014**, *3*, 291−294.

(16) Porel, M.; Alabi, C. A. Sequence-defined polymers via orthogonal allyl acrylamide building blocks. *J. Am. Chem. Soc.* **2014**, *136*, 13162−13165.

(17) Porel, M.; Thornlow, D. N.; Phan, N. N.; Alabi, C. A. Sequence-defined bioactive macrocycles via an acid-catalysed cascade reaction. *Nat. Chem.* **2016**, *8*, 590−596.

(18) Kanasty, R. L.; Vegas, A. J.; Ceo, L. M.; Maier, M.; Charisse, K.; Nair, J. K.; Langer, R.; Anderson, D. G. Sequence-defined oligomers from hydroxyproline building blocks for parallel synthesis applications. *Angew. Chem., Int. Ed.* **2016**, *55*, 9529−9533.

(19) Dong, R.; Liu, R.; Gaffney, P. R. J.; Schaepertoens, M.; Marchetti, P.; Williams, C. M.; Chen, R.; Livingston, A. G. Sequence-defined multifunctional polyethers via liquid-phase synthesis with molecular sieving. *Nat. Chem.* **2019**, *11*, 136−145.

(20) Wang, S.; Tao, Y.; Wang, J.; Tao, Y.; Wang, X. A versatile strategy for the synthesis of sequence-defined peptoids with side-chain and backbone diversity via amino acid building blocks. *Chem. Sci.* **2019**, *10*, 1531−1538.

(21) Solleder, J.-F.; Meier, M. A. R. Sequence control in polymer chemistry through the Passerini three-component reaction. *Angew. Chem., Int. Ed.* **2014**, *53*, 711−714.

(22) Leibfarth, F. A.; Johnson, J. A.; Jamison, T. F. Scalable synthesis of sequence-defined, unimolecular macromolecules by Flow-IEG. *Proc. Natl. Acad. Sci. U.S.A.* **2015**, *112*, 10617−10622.

(23) Barnes, J. C.; Ehrlich, D. J. C.; Gao, A. X.; Leibfarth, F. A.; Jiang, Y.; Zhou, E.; Jamison, T. F.; Johnson, J. A. Iterative exponential growth of stereo- and sequence-controlled polymers. *Nat. Chem.* **2015**, *7*, 810−815.

(24) Zhao, B.; Gao, Z.; Zheng, Y.; Gao, C. Scalable synthesis of positively charged sequence-defined functional polymers. *J. Am. Chem. Soc.* **2019**, *141*, 4541−4546.

(25) Lutz, J.-F. Coding Macromolecules: Inputting Information in Polymers Using Monomer-Based Alphabets. *Macromolecules* **2015**, *48*, 4759−4767.

(26) Solleder, S. C.; Wetzel, K. S.; Meier, M. A. R. Dual side chain control in the synthesis of novel sequence-defined oligomers through the Ugi four-component reaction. *Polym. Chem.* **2015**, *6*, 3201−3204.

(27) Pal, S.; Hatai, J.; Samanta, M.; Shaurya, A.; Bandyopadhyay, S. A highly selective chemodosimeter for fast detection and intracellular imaging of Hg^{2+} ions based on a dithiocarbamate−isothiocyanate conversion in aqueous ethanol. *Org. Biomol. Chem.* **2014**, *12*, 1072−1078.
(28) Hans-Wilhelm, E.; Herrmann-Josef, W.; Manfred, P.; Werner, H.; Karl-Hans, M.; Thomas, M.; Ralf, S.; Stefan, U. Rubber, 9. Chemicals and Additives. *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH, 2011, ISBN 978-3527306732.
(29) Pal, D. S.; Mondal, D. K.; Datta, R. Identification of metal dithiocarbamates as a novel class of antileishmanial agents. *Antimicrob. Agents Chemother.* **2015**, *59*, 2144−2152.
(30) Ding, Y.; Yang, Z.; Ge, W.; Kuang, B.; Xu, J.; Yang, J.; Chen, Y.; Zhang, Q. Synthesis and biological evaluation of dithiocarbamate esters of parthenolide as potential anti-acute myelogenous leukaemia agents. *J. Enzyme Inhib. Med. Chem.* **2018**, *33*, 1376−1391.
(31) Oliveira, J. W. D. F.; Rocha, H. A. O.; Medeiros, W. M. T. Q. D.; Silva, M. S. Application of dithiocarbamates as potential new antitrypanosomatids-drugs: approach chemistry, functional and biological. *Molecules* **2019**, *24*, 2806.
(32) Gaspari, P.; Banerjee, T.; Malachowski, W. P.; Muller, A. J.; Prendergast, G. C.; DuHadaway, J.; Bennett, S.; Donovan, A. M. Structure-activity study of Brassinin derivatives as indoleamine 2,3-dioxygenase inhibitors. *J. Med. Chem.* **2006**, *49*, 684−692.
(33) Edwardson, T. G. W.; Carneiro, K. M. M.; Serpell, C. J.; Sleiman, H. F. An efficient and modular route to sequence-defined polymers appended to DNA. *Angew. Chem., Int. Ed.* **2014**, *53*, 4567−4571.
(34) Kanasty, R.; Dorkin, J. R.; Vegas, A.; Anderson, D. Delivery materials for siRNA therapeutics. *Nat. Mater.* **2013**, *12*, 967−977.

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