Versatile Approach for the Synthesis of Sequence-Defined Monodisperse 18- and 20-mer Oligoacrylates

Supplementary material

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SUPPORTING INFORMATION

Versatile Approach for the Synthesis of Sequence-Defined Monodisperse 18- and 20-mer Oligoacrylates

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1. Materials

The monomers *n*-butyl acrylate (*n*BA, Acros, +99%), 2-ethylhexyl acrylate (EHA, Acros, +99%), methyl acrylate (MA, Acros, 99%) and ethyl acrylate (EA, Acros, 99,5%) were deinhibited over a column of activated basic alumina prior to use. 2,2'-azobis(2-methylpropionitrile) (AIBN, Sigma-Aldrich, 98%) was recrystallized twice from ethanol prior to use. 2-cyano-2-propyl ethyl trithiocarbonate (CPE-TTC), see synthetic procedure in section 3. Hexylamine (Acros, 99%) was used as received. All solvents and chemicals used are obtained from commercial sources (Acros and Sigma-Aldrich) and used without further purification.

2. Characterization

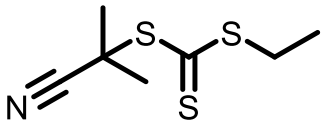
NMR spectra were recorded in deuterated chloroform with a Varian Inova 300 spectrometer at 300 MHz for ^{1}H NMR and at 75 MHz for ^{13}C NMR using a Varian probe (5 mm-4-nucleus AutoSWPFG) and a pulse delay of 12 s. NMR spectra were analyzed in MestReNova software.

ESI-MS was performed using an LTQ orbitrap velos pro mass spectrometer (ThermoFisher Scientific) equipped with an atmospheric pressure ionization source operating in the nebulizer assisted electro spray mode. The instrument was calibrated in the m/z range 220-2000 using a standard solution containing caffeine, MRFA and Ultramark 1621. A constant spray voltage of 5 kV was used and nitrogen at a dimensionless sheath gas flow-rate of 7 was applied. Capillary temperature was set to 275°C. A mixture of THF and methanol (THF:MeOH = 3:2), all HPLC grade, were used as solvent. Spectra were analyzed in Thermo Xcalibur Qual Browser software.

Purification of oligomer mixtures was performed via **flash column chromatography** performed on a Büchi sepacore system equipped with GRACE Resolve normal phase silica cartridges (40 gram). Flash column chromatography was discussed in more detail in section 6.

3. Synthesis Procedures

3.1 Synthesis of CPE-TTC RAFT agent



Ethanethiol (4.71 g, 75.99 mmol) was added over 10 min to a stirred suspension of sodium hydride (60 wt % in oil, 3.15 g, 78.7 mmol) in diethyl ether (150 mL) while the reaction was cooled in an ice-bath. The gray sodium hydride was converted to a thick white slurry of sodium thiododecylate. Carbon disulfide (6.0 g, 78.9 mmol) was added. The resulting thick yellow precipitate was isolated by filtration to give sodium dodecyl trithiocarbonate in quantitative yield.

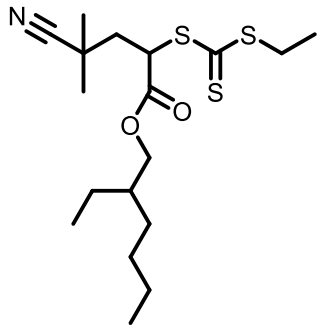
Iodine (6.3 g, 0.025 mol) was added portionwise to a suspension of sodium dodecyl trithiocarbonate (14.6 g, 0.049 mol) in diethyl ether (100 mL). The resultant mixture was then stirred at room temperature for 1 h when the white sodium iodide which settled was removed by filtration. The yellow-brown filtrate was washed with aqueous sodium thiosulfate, to remove excess iodine, and water, dried over sodium sulfate and evaporated to leave a residue of bis(ethylsulfanylthiocarbonyl) disulfide.

A solution of AIBN (4.93 g, 0.03 mol) and bis(ethylsulfanylthiocarbonyl)disulfide (5.5 g, 0.020 mol) in ethyl acetate (100 mL) was heated at 70 °C overnight. After evaporation of the volatiles, the crude mixture was purified by silica column chromatography with petroleum ether:ethyl acetate (49:1) as eluent to obtain CPE-TTC as orange liquid (7.2 g, 88% yield).^{1}H NMR ($CDCl_3$, ppm): 1.35 (t, 3H, CH3CH2); 1.28 (s, 6H, (CH3)2CCN); 3.33 (q, 2H, CH3CH2S). ^{13}C NMR ($CDCl_3$, ppm): 218.2, 121.0, 43.0, 31.9, 27.7, 13.4. ESI-MS: $[227.994]^{Na+}$

3.2 General synthesis procedure for RAFT polymerizations

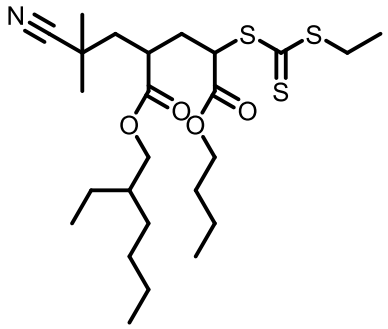
In a typical procedure the acrylate monomer, 1,1'-azobis(isobutyronitrile) (AIBN), 2-cyano-2-propyl ethyl trithiocarbonate (CPE-TTC) and butyl acetate as a reaction solvent were added into a glass vial together with a magnetic stirring bar. The glass vial was sealed by a rubber septa. The solution was degassed for 15 min by N_2 purging, and subsequently inserted into the glovebox with inert atmosphere. The reaction mixture was heated in a copper heat block and quenched by cooling in liquid nitrogen. After evaporation of the volatiles (monomer and solvent) the reaction mixture was analyzed by ESI-MS to observe oligomer distribution and endgroups before purification with flash column chromatography. Isolated oligomers were analyzed by ESI-MS. ESI-MS spectra are included and discussed in section 4.

3.2.1 Synthesis of α-[EHA]$_1$-ω macroRAFT agent (1)



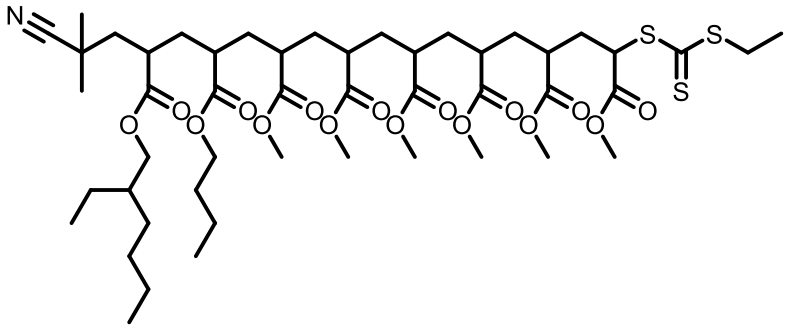
Synthesis of macroRAFT is performed according to general procedure discussed above. 13.17 mmol (2.24 g, 1 equiv.) of the monomer EHA, 0.61 mmol (0.1 g, 0.05 equiv.) of AIBN, 12.17 mmol (2.5 g, 1 equiv.) of CPE-TTC RAFT agent and 2.5 mL of butyl acetate were added into a glass vial. The mixture was reacted at 100 °C for 30 min. ESI-MS: $[412.140]^{Na+}$.

3.2.2 Synthesis of α-[EHA]$_1$-[nBA]$_1$-ω macroRAFT agent (2)



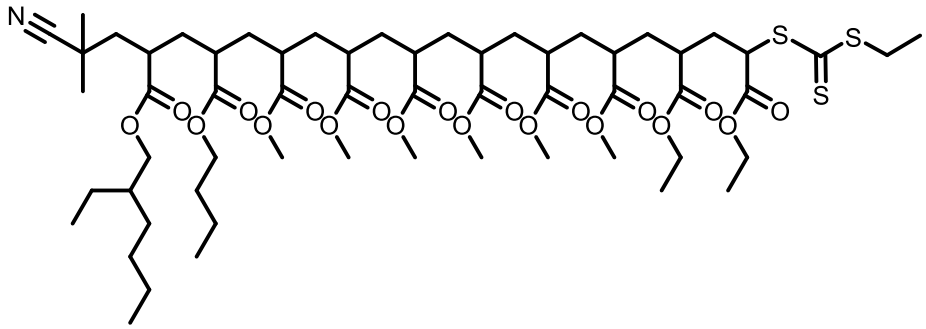
Synthesis of macroRAFT is performed according to general procedure discussed above. 2.35 mmol (0.3 g, 1 equiv.) of the monomer nBA, 0.12 mmol (0.02 g, 0.05 equiv.) of AIBN, 2.35 mmol (0.92 g, 1 equiv.) of macroRAFT agent 1 and 1 mL of butyl acetate were added into a glass vial. The mixture was reacted at 100 °C for 30 min. ESI-MS: $[540.223]^{Na+}$.

3.2.3 Synthesis of α-[EHA]$_1$-[nBA]$_1$-[MA]$_6$-ω macroRAFT agent (3)



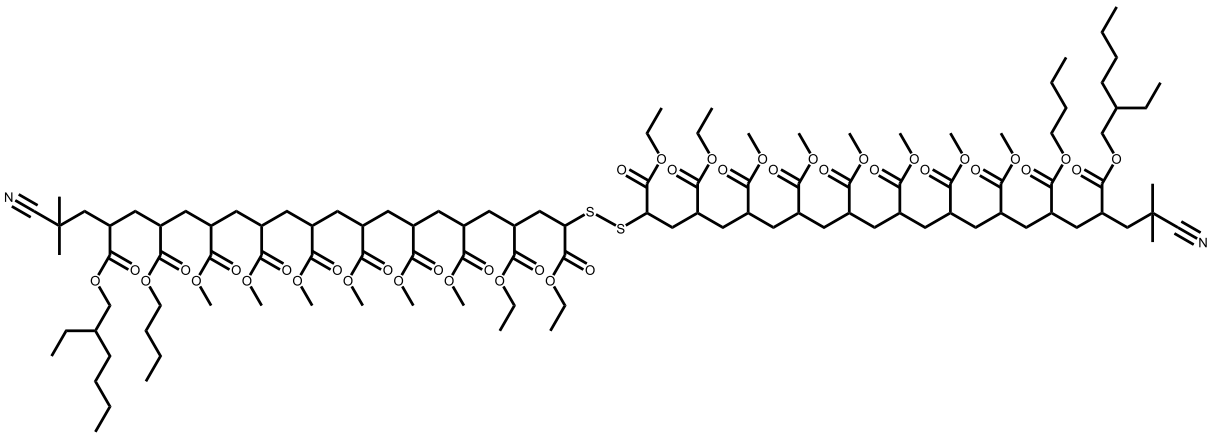
Synthesis of macroRAFT is performed according to general procedure discussed above. 3 mmol (0.26 g, 3 equiv.) of the monomer nBA, 0.05 mmol (0.082 g, 0.05 equiv.) of AIBN, 1 mmol (0.52 g, 1 equiv.) of macroRAFT agent 2 and 0.5 mL of butyl acetate were added into a glass vial. The mixture was reacted at 100 °C for 30 min. ESI-MS: $[1056.446]^{Na+}$.

3.2.4 Synthesis of α-[EHA]$_1$-[nBA]$_1$-[MA]$_6$-[EA]$_2$-ω macroRAFT agent (4)



Synthesis of macroRAFT is performed according to general procedure discussed above. 0.1 mmol (0.010 g, 2 equiv.) of the monomer EA, 0.002 mmol (0.5 mg, 0.05 equiv.) of AIBN, 0.05 mmol (0.053 g, 1 equiv.) of macroRAFT agent 3 and 0.25 mL of butyl acetate were added into a glass vial. The mixture was reacted at 85 °C for 2.5 h. ESI-MS: $[1256.551]^{Na+}$.

3.2.5 Synthesis of α-[EHA]$_1$-[nBA]$_1$-[MA]$_6$-[EA]$_2$-S-S-[EA]$_2$-[MA]$_6$-[nBA]$_1$-[EHA]$_2$-α 20-mer (5)



MacroRAFT 4 (5 mg, 1 equiv.) and hexylamine (15 µL, 5 equiv.) were dissolved in 0.2 mL $CHCl_3$ as reaction solvent. The reaction was performed under ambient atmosphere at room temperature and stirred for 48 h. The 20-mer oligoacrylate was isolated by silica column chromatography and analyzed by ESI-MS: $[2280.141]^{Na+}$.

3.2.6 Synthesis of α-$[EHA]_1$-$[nBA]_1$-$[MA]_6$-$[EA]_1$-S-S-$[EA]_1$-$[MA]_6$-$[nBA]_1$-$[EHA]_1$-α 18-mer (6)

Synthesis of the 18-mer oligoacrylate is identical to the synthesis of the 20-mer oligoacrylate 5. Starting macroRAFT agent is α-$[EHA]_1$-$[nBA]_1$-$[MA]_6$-$[EA]_1$-ω (8 mg). ESI-MS: $[2080.030]^{Na+}$.

4. ESI-MS analysis

α-[EHA]$_{0-2}$-ω macroRAFT agent

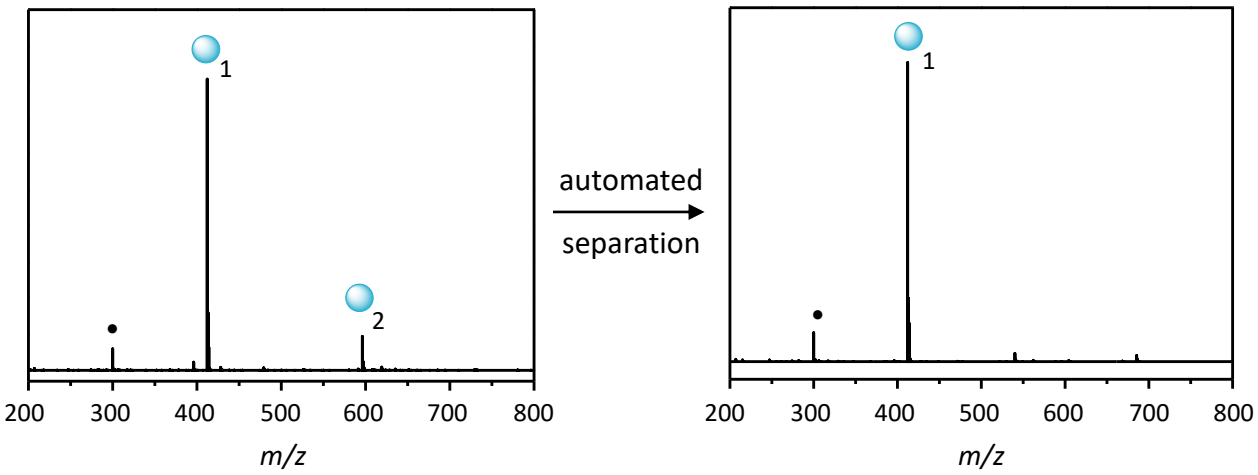


Figure S4.1. Electrospray ionization mass spectrometry (ESI-MS) analysis after chain extension with a single unit monomer insertion (SUMI) of 2-ethylhexyl acrylate (EHA) into the RAFT agent 2-cyano-2-propyl ethyl trithiocarbonate (CPE-TTC). SUMI reaction was performed at 100 °C for 30 minutes. Left) ESI-MS of the crude oligomer mixture with 1 and 2 insertions of EHA into CPE-TTC. Right) ESI-MS after automated separation via flash column chromatography with the targeted isolated single unit insertion product α-[EHA]$_1$-ω macroRAFT agent (1.9 g, 58% isolated yield). The small $[300{,}016]^{Na+}$ peak can be assigned to hydrolysis of the 2-ethylhexyl acrylate single unit insertion which is generated in situ in the ESI-MS nozzle.

α-[EHA]$_1$-[nBA]$_{0-3}$-ω macroRAFT agent

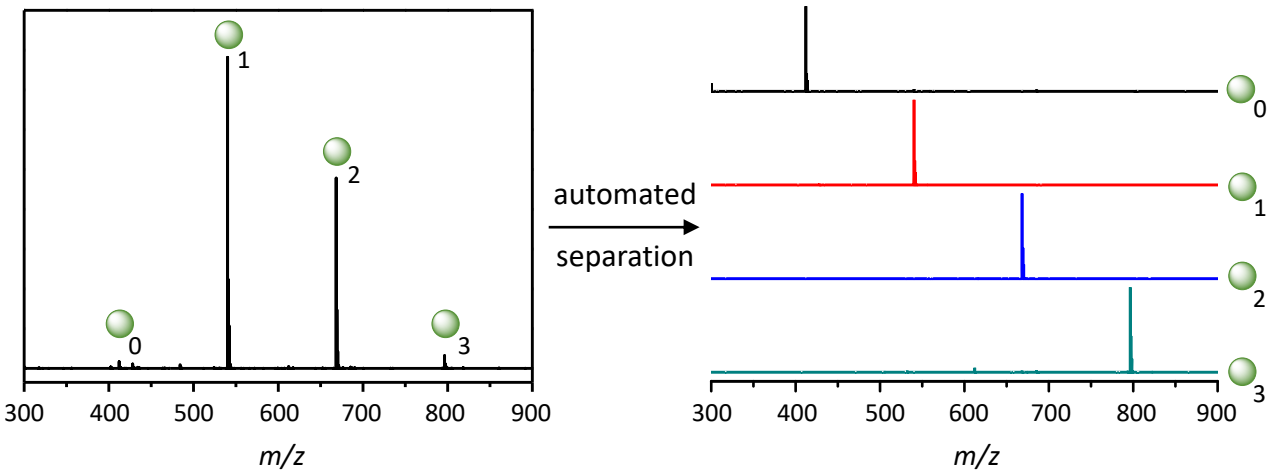


Figure S4.2. Electrospray ionization mass spectrometry (ESI-MS) analysis after chain extension with a single unit monomer insertion (SUMI) of *n*-butyl acrylate (*n*BA) into the macroRAFT agent α-[EHA]$_1$-[*n*BA]$_{0-3}$-ω. SUMI reaction was performed at 100 °C for 30 minutes. Left) ESI-MS of the crude oligomer mixture with 0, 1, 2 and 3 insertions of *n*BA into α-[EHA]$_1$-ω. Right) ESI-MS after automated separation via flash column chromatography with the targeted isolated single unit monomer insertion (SUMI) product α-[EHA]$_1$-[*n*BA]$_1$-ω macroRAFT agent (540 mg, 45% isolated yield). Starting material (α-[EHA]$_1$-ω) and higher insertions (2 and 3 *n*BA insertions) were also isolated and purified in this step but not utilized further in this manuscript.

α-[EHA]$_1$-[nBA]$_1$-[MA]$_{0\text{-}8}$-ω macroRAFT agent

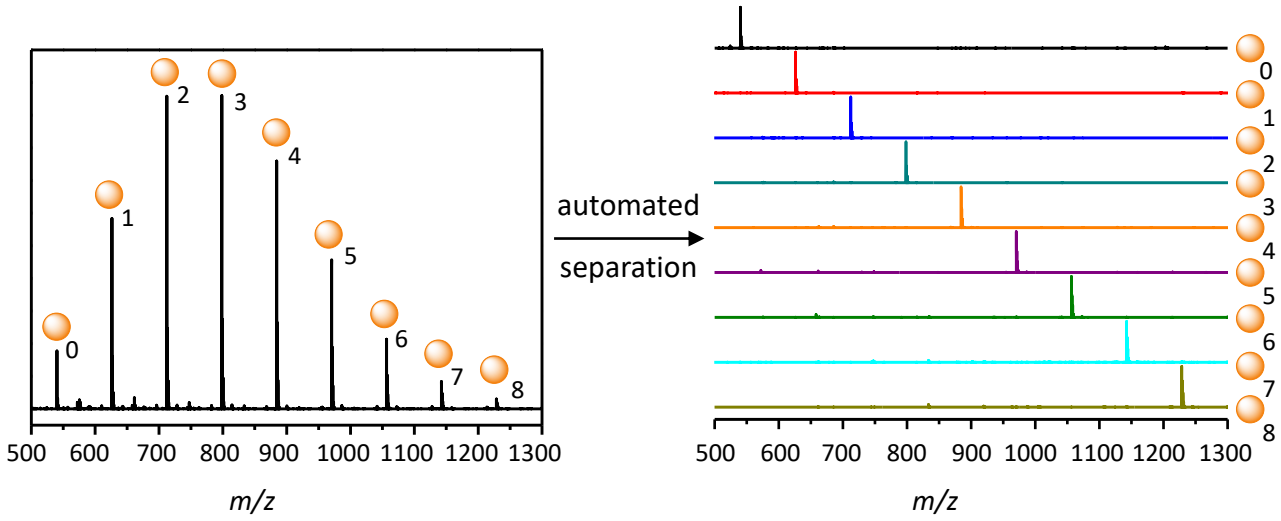


Figure S4.3. Electrospray ionization mass spectrometry (ESI-MS) analysis after chain extension of α-[EHA]$_1$-[*n*BA]$_1$-ω macroRAFT agent with methyl acrylate (MA) into the macroRAFT agent α-[EHA]$_1$-[*n*BA]$_1$-[MA]$_{0\text{-}8}$-ω. Reaction was performed at 100 °C for 30 minutes. Left) ESI-MS of the crude oligomer mixture with 0, 1, 2, 3, 4, 5, 6, 7 and 8 insertions of MA into α-[EHA]$_1$-[nBA]$_1$-ω macroRAFT agent. Right) ESI-MS after automated separation via flash column chromatography with the targeted isolated oligomer insertion product α-[EHA]$_1$-[*n*BA]$_1$-[MA]$_6$-ω macroRAFT agent (53 mg, 5% isolated yield). Starting material and higher insertions were also isolated and purified in this step but not utilized further in this manuscript. Yields of the isolated oligomers are mentioned in the main text.

α-[EHA]$_1$-[nBA]$_1$-[MA]$_6$-[EA]$_{0\text{-}3}$-ω macroRAFT agent

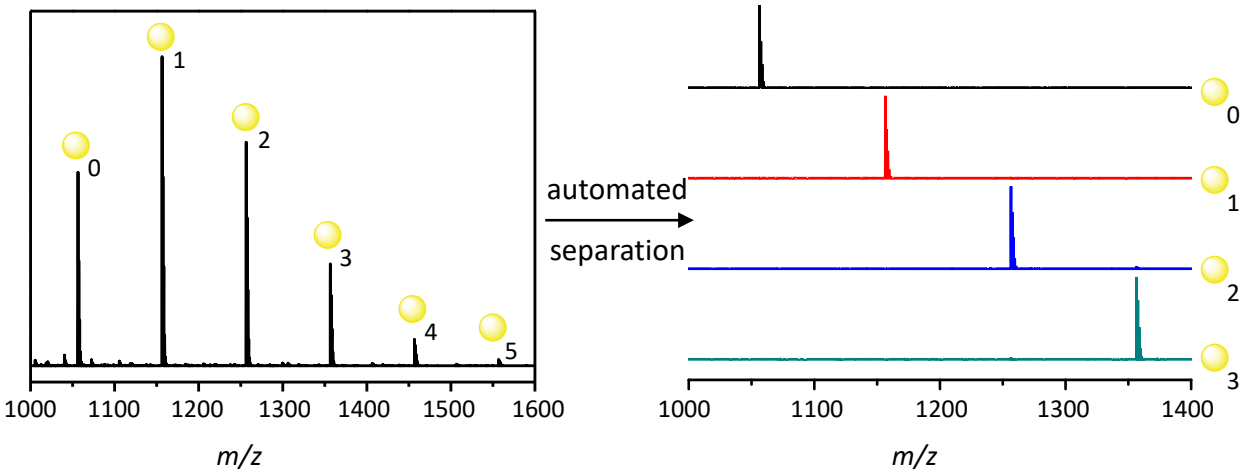


Figure S4.4. Electrospray ionization mass spectrometry (ESI-MS) analysis after chain extension of α-[EHA]$_1$-[*n*BA]$_1$-[MA]$_6$-ω macroRAFT agent with ethyl acrylate (EA) into the macroRAFT agent α-[EHA]$_1$-[*n*BA]$_1$-[MA]$_6$-[EA]$_{0\text{-}3}$-ω. Reaction was performed at 85 °C for 2.5 hours. Left) ESI-MS of the crude oligomer mixture with 0, 1, 2, 3, 4 and 5 insertions of EA into α-[EHA]$_1$-[*n*BA]$_1$-[MA]$_6$-ω macroRAFT agent. Right) ESI-MS after automated separation via flash column chromatography with the targeted isolated oligomer insertion products α-[EHA]$_1$-[*n*BA]$_1$-[MA]$_6$-[EA]$_1$-ω (8 mg, 14% isolated yield) and α-[EHA]$_1$-[*n*BA]$_1$-[MA]$_6$-[EA]$_2$-ω (7 mg, 11% isolated yield) macroRAFT agent. Starting material and higher insertions were also isolated and purified in this step but not utilized further in this manuscript. Yields of the isolated oligomers are mentioned in the main text.

α-[EHA]$_1$-[nBA]$_1$-[MA]$_6$-[EA]$_1$-S-S-[EA]$_1$-[MA]$_6$-[nBA]$_1$-[EHA]$_1$-α 18-mer

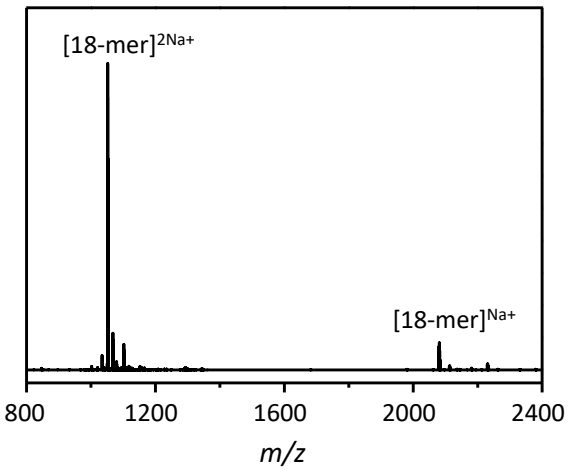


Figure S4.5. Electrospray ionization mass spectrometry (ESI-MS) analysis after 18-mer (α-[EHA]$_1$-[*n*BA]$_1$-[MA]$_6$-[EA]$_1$-S-S-[EA]$_1$-[MA]$_6$-[*n*BA]$_1$-[EHA]$_1$-α) synthesis. ESI-MS of the purified monodisperse 18-mer after aminolysis and in situ oxidation of the trithiocarbonate RAFT endgroups of the 9-mer α-[EHA]$_1$-[*n*BA]$_1$-[MA]$_6$-[EA]$_1$-ω for the formation of a disulfide bridge linker. The small signals other than the 18-mer observed in the pure ESI-MS spectrum are assigned to a single –and double sodium charged 19-mer (< 10%) due to coupling of a 9- and 10-mer trace left from the starting material.

α-[EHA]$_1$-[nBA]$_1$-[MA]$_6$-[EA]$_2$-S-S-[EA]$_2$-[MA]$_6$-[nBA]$_1$-[EHA]$_1$-α 20-mer

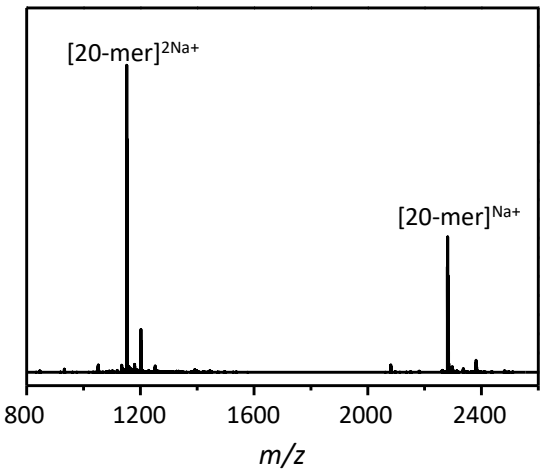


Figure S4.6. Electrospray ionization mass spectrometry (ESI-MS) analysis after 20-mer (α-[EHA]$_1$-[*n*BA]$_1$-[MA]$_6$-[EA]$_2$-S-S-[EA]$_2$-[MA]$_6$-[*n*BA]$_1$-[EHA]$_1$-α) synthesis. ESI-MS of the purified monodisperse 20-mer after aminolysis and in situ oxidation of the trithiocarbonate RAFT endgroups of the 10-mer α-[EHA]$_1$-[*n*BA]$_1$-[MA]$_6$-[EA]$_2$-ω for the formation of a disulfide bridge linker. The small signals other than the 20-mer observed in the pure ESI-MS spectrum are assigned to a single –and double sodium charged 21-mer (< 10%) due to coupling of a 10- and 11-mer trace left from the starting material.

5. NMR analysis

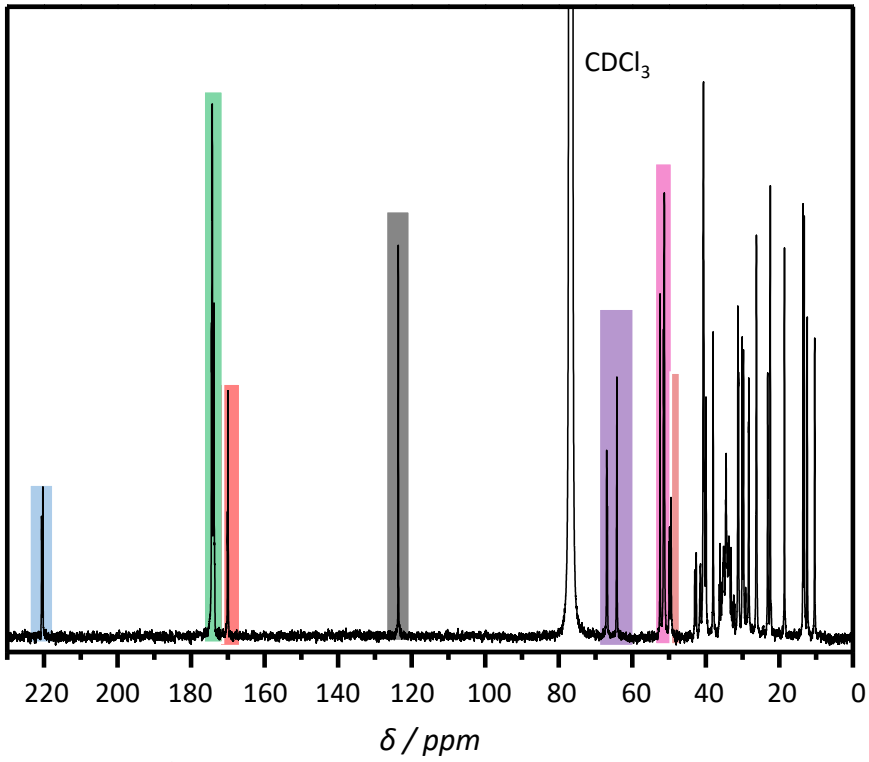


Figure S5.1. ^{13}CNMR spectrum of the macroRAFT agent.

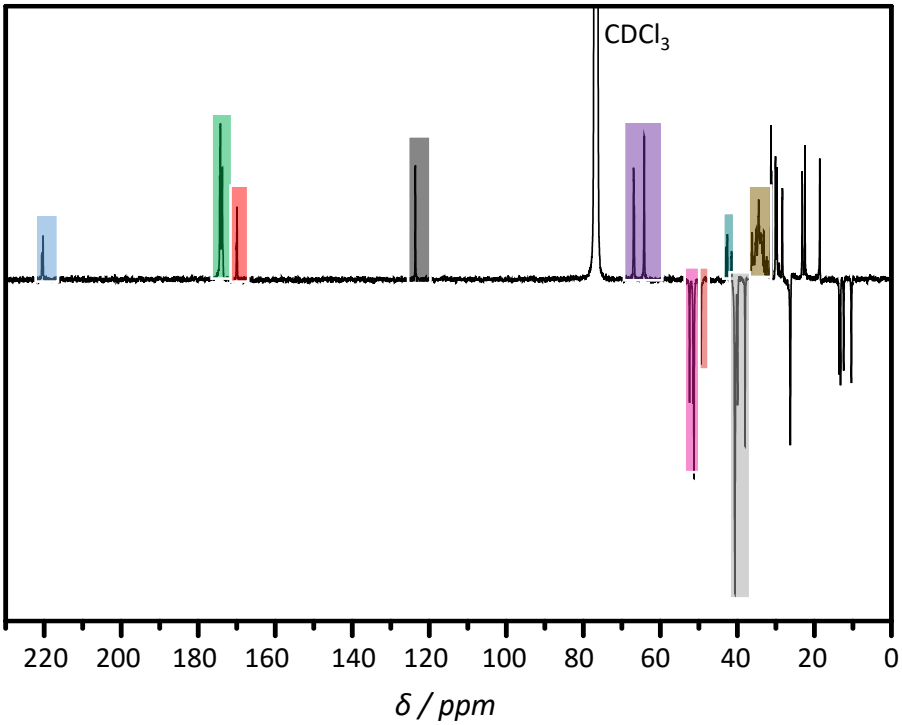


Figure S5.2. APT^{13}CNMR spectrum of the macroRAFT agent.

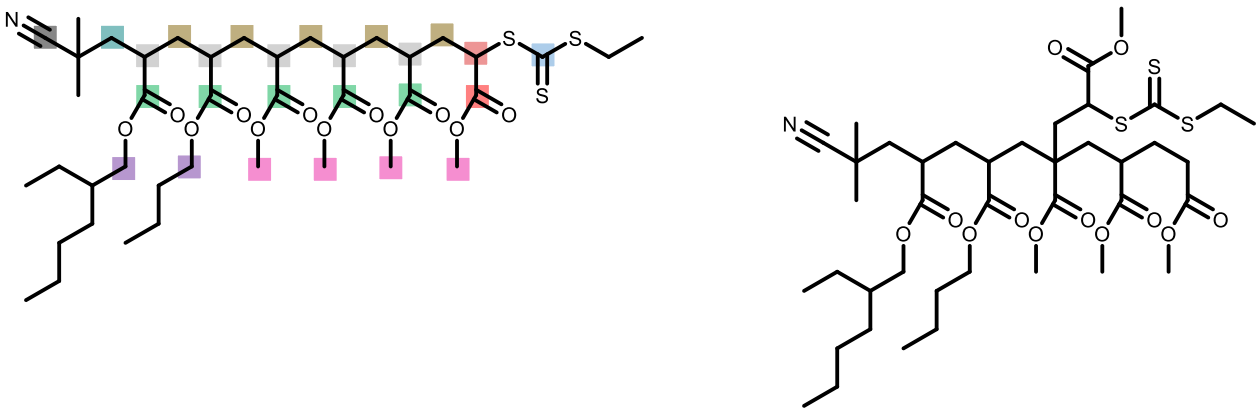


Figure S5.3. Left) Linear backbone of the α-[EHA]$_1$-[*n*BA]$_1$-[MA]$_4$-ω macroRAFT agent and Right) branched backbone due to presence of mid chain radical caused by backbiting.

The isolated oligomer α-[EHA]$_1$-[*n*BA]$_1$-[MA]$_4$-ω was utilized to investigate the effects of mid-chain radical formation and chain branching, this process is likely to happen after 3 consecutive monomer insertions and hence might influence the product from the 4th insertion on. To exclude branching – which would lead to defects in the encoded information of the oligomer structure – and to proof a linear growth of the oligomers without defects in the structure, carbon (^{13}C) nuclear magnetic resonance (NMR) and APT ^{13}CNMR were studied to determine the chemical structure of the α-[EHA]$_1$-[*n*BA]$_1$-[MA]$_4$-ω macroRAFT agent. All peaks can be neatly assigned to the linear structure of the macroRAFT agent. It can thus safely be assumed that backbiting did not occur during the RAFT insertion reactions revealing no branching and thus a linear growth of the oligomer chains. Typical resonances for branched structures are not present:

- No resonances typical for quaternary carbons in the polymer backbone are present. Typically APT CNMR would show a positive resonance peak around 49 ppm.[1]
- If a branched structure was formed, then the CH_2 carbon next to the resulting methacrylate-like quaternary substituted carbon would give rise to a positive resonance around 52-54 ppm.[2]
- In case of branching, three carbonyl resonance peaks are expected around 170 ppm. Only two are observed for which indicates a linear macroRAFT structure.

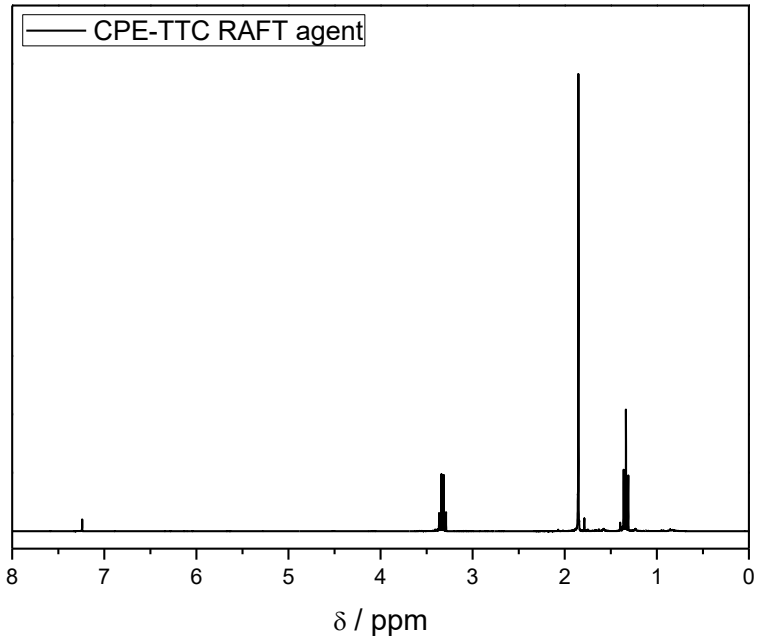


Figure S5.4. ^{1}HNMR spectrum of the initial CPE-TTC RAFT agent.

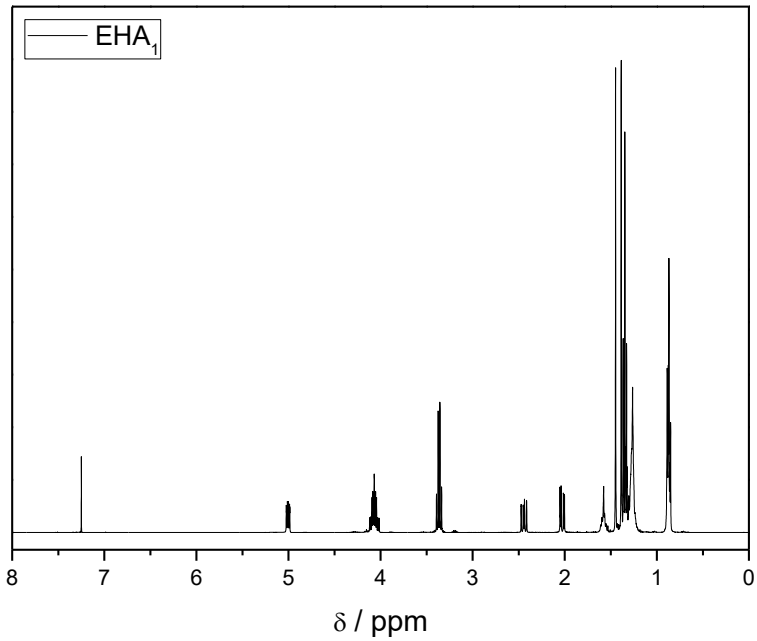


Figure S5.5. ^{1}HNMR spectrum of the 1-mer (EHA_1).

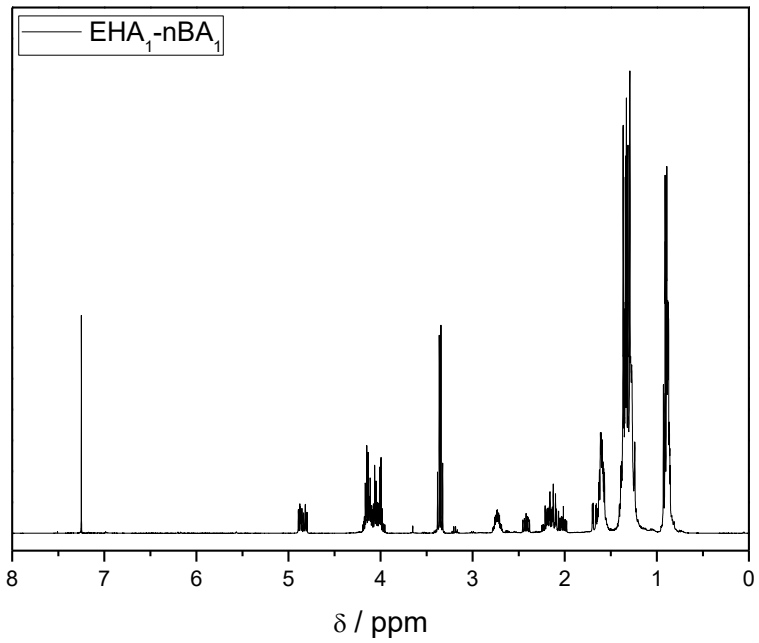


Figure S5.6. ^{1}HNMR spectrum of the 2-mer (EHA_1-nBA_1).

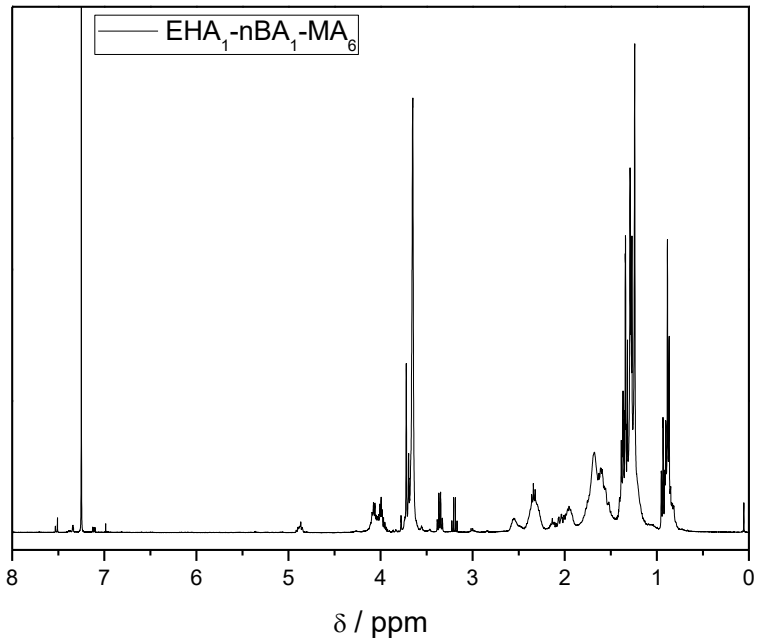


Figure S5.7. ^{1}HNMR spectrum of the 8-mer (EHA_1-nBA_1-MA_6).

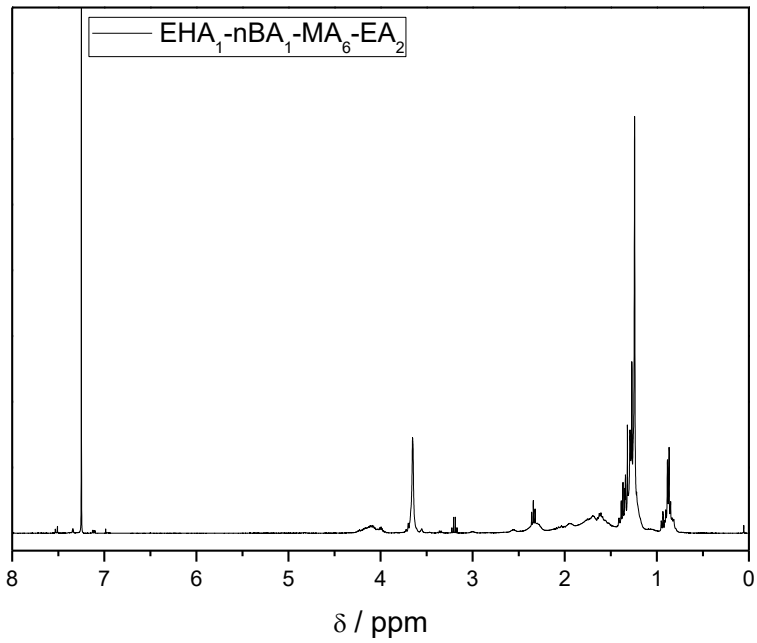


Figure S5.8. ^{1}HNMR spectrum of the 10-mer (EHA_1-nBA_1-MA_6-EA_2).

6. Flash column chromatography

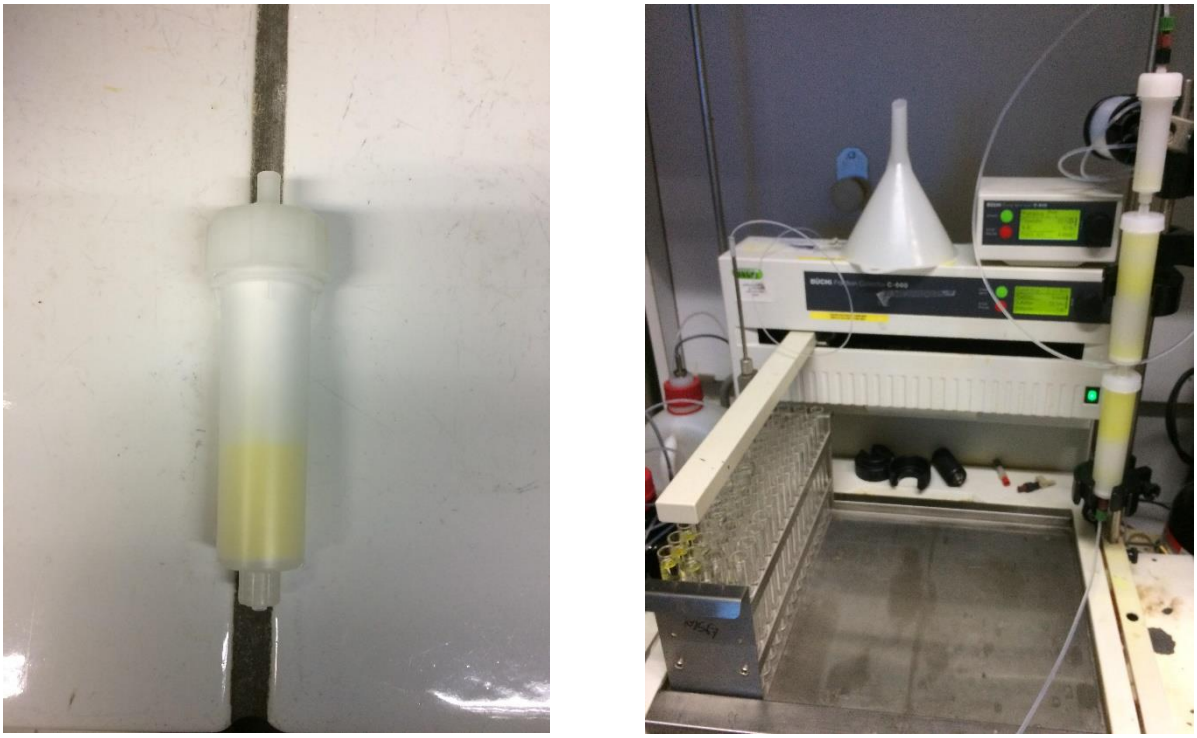


Figure S6.1. Pictures of the Büchi sepacore system equipped with GRACE Resolve normal phase silica cartridges (40 gram). Left) Crude oligomer mixtures were embedded on silica and loaded into a pre-column cartridge and placed on top of the GRACE resolve normal phase silica cartridges. Right) Picture of the Büchi sepacore setup during oligomer separation.

α-[EHA]$_{0\text{-}2}$-ω macroRAFT agent

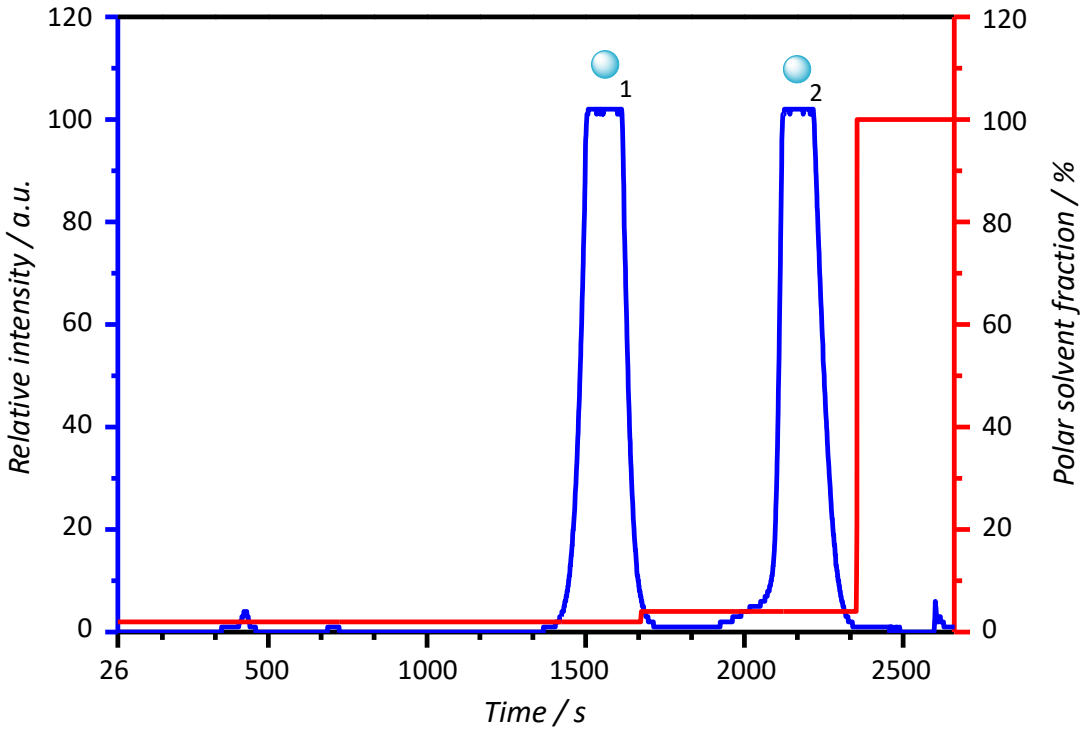


Figure S6.2. UV detector trace (λ = 305 nm, blue trace) during oligomer purification of α-[EHA]$_{0\text{-}2}$-ω macroRAFT agent. The flash column system could be easily operated under UV detection due to the high absorption of the trithiocarbonate RAFT living chain end at λ = 305 nm. Solvent mixture was petroleum ether : ethyl acetate, the red trace indicates the percentage of ethyl acetate polar solvent fraction utilized in time. Both the 1st and 2nd insertion of EHA is baseline separated. Via this approach almost no product losses are encountered during purification.

α-[EHA]$_1$-[nBA]$_{0-3}$-ω macroRAFT agent

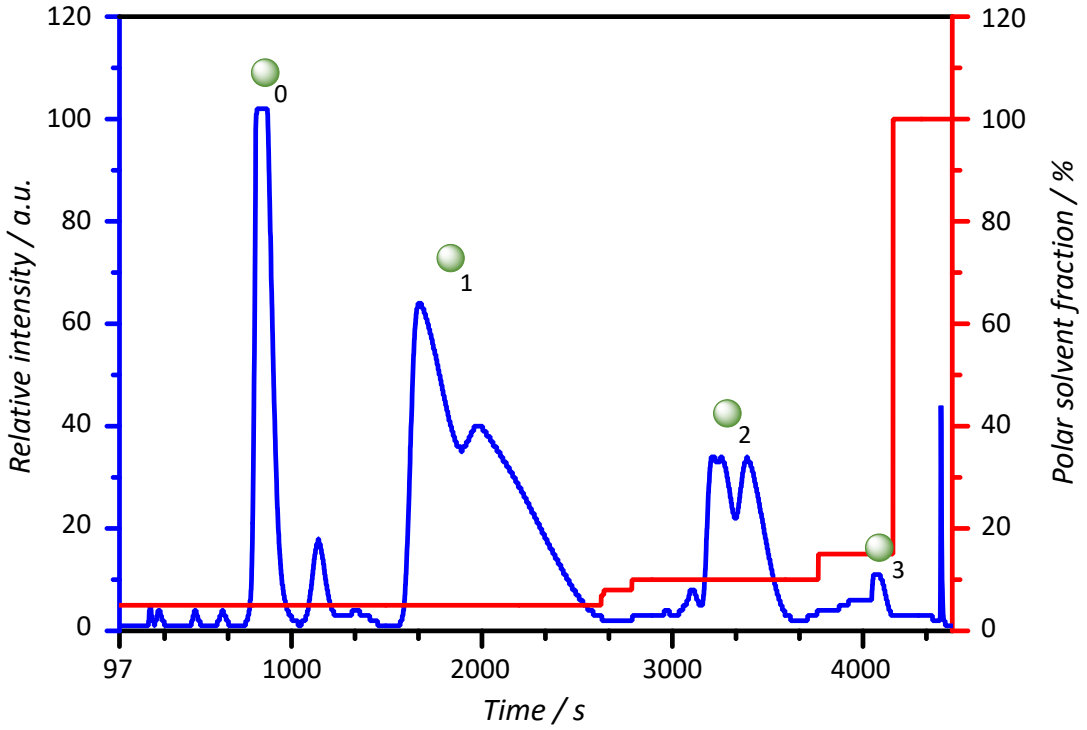


Figure S6.3. UV detector trace (λ = 305 nm, blue trace) during oligomer purification of α-[EHA]$_1$-[*n*BA]$_{0-3}$-ω macroRAFT agent. The flash column system could be easily operated under UV detection due to the high absorption of the trithiocarbonate RAFT living chain end at λ = 305 nm. Solvent mixture was petroleum ether : ethyl acetate, the red trace indicates the percentage of ethyl acetate polar solvent fraction utilized in time. Both the starting material, 1st, 2nd and 3th insertion of *n*BA are baseline separated. Via this approach almost no product losses are encountered during purification. From the 2nd insertion on UV traces show bimodal peaks, this is due to the chiral separation of diastereoisomer mixtures of a monodisperse oligomer chain length.

α-[EHA]$_1$-[nBA]$_1$-[MA]$_{0-8}$-ω macroRAFT agent

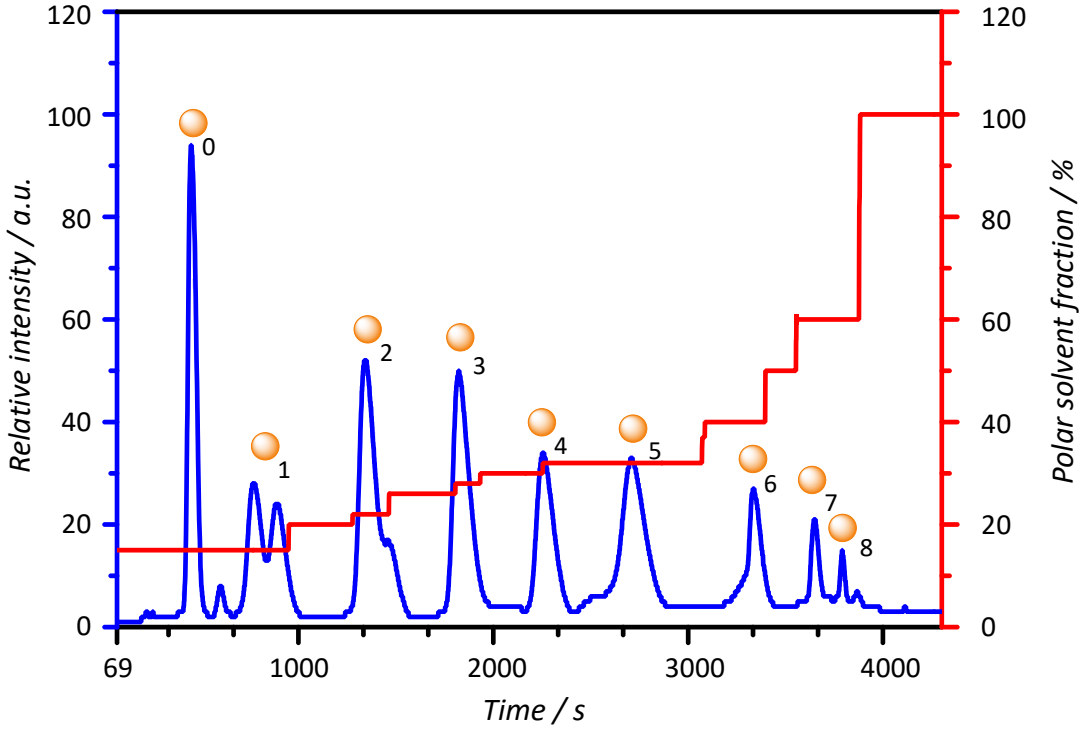


Figure S6.4. UV detector trace (λ = 305 nm, blue trace) during oligomer purification of α-[EHA]$_1$-[*n*BA]$_1$-[MA]$_{0-8}$-ω macroRAFT agent. The flash column system could be easily operated under UV detection due to the high absorption of the trithiocarbonate RAFT living chain end at λ = 305 nm. Solvent mixture was petroleum ether : ethyl acetate, the red trace indicates the percentage of ethyl acetate polar solvent fraction utilized in time. Via this approach almost no product losses are encountered during purification. Some UV traces show bimodal peaks, this is due to the chiral separation of diastereoisomer mixtures of a monodisperse oligomer chain length.

α-[EHA]$_1$-[nBA]$_1$-[MA]$_6$-[EA]$_{0-3}$-ω macroRAFT agent

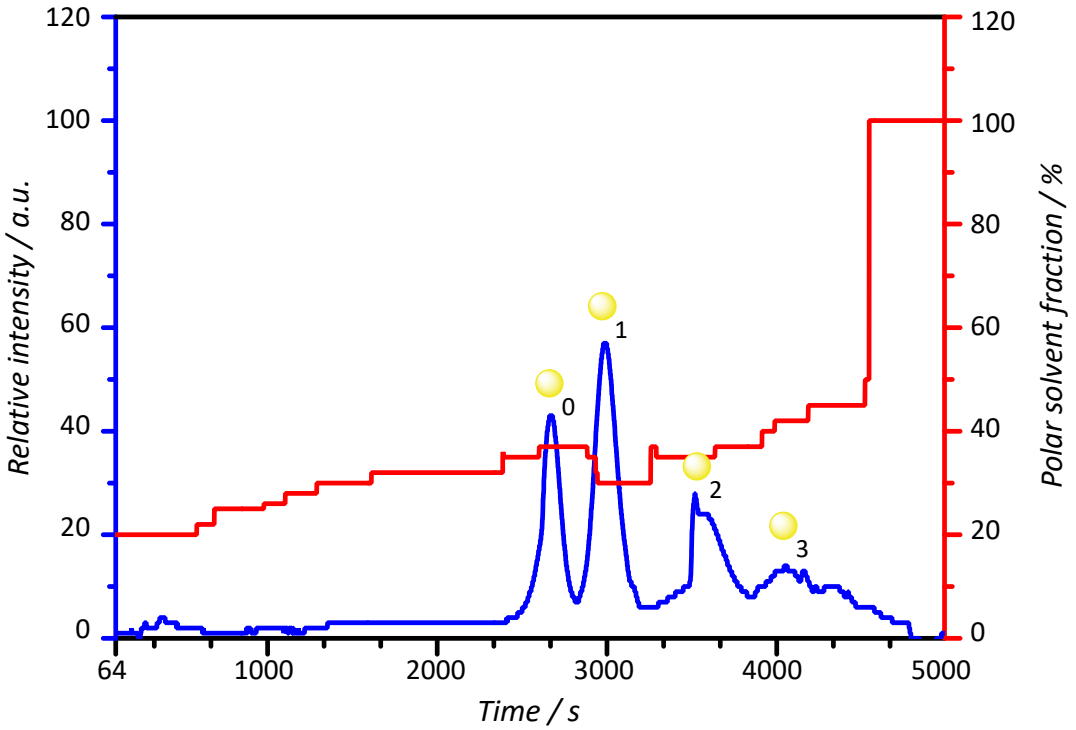


Figure S6.5. UV detector trace (λ = 305 nm, blue trace) during oligomer purification of α-[EHA]$_1$-[nBA]$_1$-[MA]$_6$-[EA]$_{0-3}$-ω macroRAFT agent. The flash column system could be easily operated under UV detection due to the high absorption of the trithiocarbonate RAFT living chain end at λ = 305 nm. Solvent mixture was petroleum ether : ethyl acetate, the red trace indicates the percentage of ethyl acetate polar solvent fraction utilized in time. It can be observed that more losses are encountered which can be explained by mixed insertions fractions collected after column chromatography as seen in the UV detection trace.

(1) (a) Wenn, B.; Junker, T.; *Macromol. Rapid Commun*. **2016**, *37*, 781-787. (b) Wenn, B.; Reekmans, G.; Adriaensens, P.; Junkers, T.; *Macromol. Rapid Commun*. **2015**, *36*, 1479-1485.
(2) Vandenbergh, J.; Reekmans, G.; Adriaensens, P.; Junkers, T.; *Chem. Commun*. **2013**, *49*, 10358-10360.