Supporting Information

Synthesis and Functionalization of Thiol-reactive Biodegradable Polymers

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Experimental Section

Materials and Methods. *L*-Lactide was purchased from Aldrich and purified by either by recrystallisation from dry dichloromethane or by drying over 4 Å molecular sieves in dichloromethane solution before sublimation. Dichloromethane was dried over CaH_2, distilled and degassed before polymerizations or was used after distillation over P_2O_5 (J. T. Baker) prior to functionalizations. Compound **1** was prepared according to literature procedure.[i] All other reagents were obtained from Aldrich and used without further purification. Monomer **3** was dried over activated 4 Å molecular sieves in dry THF, filtered and dried *in vacuo*. The solvents were purchased from Merck or Aldrich. Polymerizations and monomer drying were performed under moisture and oxygen free conditions in either a nitrogen filled glove box or by standard Schlenk techniques. The size-exclusion chromatography (SEC) measurements of the homopolymers were carried out with a Polymer Laboratories Midas autosampler and LC1120 HPLC pump equipped with a guard column (Polymer

Laboratories PLGel 5 μM,50×7.5 mm), two mixed D columns (Polymer Laboratories PLGel 5 μM, 300 × 7.5 mm) and a Polymer Laboratories ERC-7515A differential refractive index (DRI) detector. The mobile phase was chloroform/triethyl amine (95/5) eluent at a flow rate of 1.0 $mL.min^{-1}$ and samples were calibrated against linear poly(styrene) standards (540 to 2.9×10^4 $g.mol^{-1}$) using Cirrus v3.0; elution time was standardized against that of toluene. The second SEC was used for the analysis of copolymers and functionalized polymers and is a TD-SEC with a Agilent 1200 model pump, four Waters Styragel columns (guard, HR 5E, HR 4, HR 3, and HR 2), and a Viscotek TDA 302 triple detector (RI, dual laser light scattering (LS) and a differential pressure viscometer), was conducted to measure the absolute molecular weights in THF with a flow rate of 0.5 mL/min at 35 ºC. All three detectors were calibrated with a PS standard having narrow molecular weight distribution (M_n = 115 000 g/mol, M_w/M_n = 1.02) provided by Viscotek. Data analyses were performed with Omni-Sec version 4.5 software from Viscotek. ^{1}H NMR spectra was recorded on a Bruker DPX 300 MHz, DPX 400 MHz or Varian 400 MHz spectrometer at 293 K. Mass spectra were acquired by MALDI-ToF (matrix-assisted laser desorption and ionization time-of-flight) mass spectrometry using a Bruker Daltonics Ultraflex II MALDI-ToF mass spectrometer, equipped with a nitrogen laser delivering 2 ns laser pulses at 337 nm with positive ion ToF detection performed using an accelerating voltage of 25 kV. The samples were measured in reflectron ion mode and calibrated by comparison to 2×10^3 and 5×10^3 g mol^{-1} poly(ethylene glycol) standards. Elemental analysis of the maleimide functional carbonate monomer was done on a FlashEA^R 1112 Series Elemental Analyzer (CHNS Separation Column, PTFE; 2 m; 6 x 5 mm) Thermogravimetric analysis (TGA) was performed on a TA Instruments at a heating rate of 10 ° C/min under a nitrogen atmosphere.

Synthesis of Furan-Protected Maleimide-Containing Carbonate Monomer (3). A few beads of Dowex 50W-X2 acidic resin were added to a MeOH solution (25 mL) of **1** (1.7 g, 4.5 mmol). The resulting mixture was stirred at 40 ºC until complete consumption of **1** was observed by TLC. The resin was filtered off and washed with MeOH before the filtrate was purified by precipitation into cold CH_2Cl_2 and concentrated in *vacuo* to give a white solid **2** (1.50 g, 99% yield). ^1H NMR ($CDCl_3$, δ, ppm) 6.49 (s, 2H, C*H*=C*H*), 5.24 (s, 2H, C*H* bridgehead protons), 4.59 (t, 2H, *J* = 5.8 Hz, OCH_2), 3.86 (dd, 2H, *J* = 11.2, 6.4 Hz, OCH_2), 3.74 (dd, 2H, *J* = 11.2, 5.6 Hz, OCH_2), 3.59 (t, 2H, *J*= 6.6 Hz, NCH_2), 3.11 (t, 2H, *J*= 6.2 Hz, OH), 2.84 (s, 2H, C*H*-C*H* bridgehead protons), 1.97-1.91 (m, 2H, $NCH_2CH_2CH_2O$), 1.09 (s, 3H, C(CH_3)). ^{13}C NMR ($CDCl_3$, δ, ppm) = 176.5, 175.6, 136.4, 80.9, 67.7, 60.9, 49.6, 47.4, 35.2, 26.4, 17.2. Anal. Calcd. [$C_{19}H_{25}N_1O_7$]: C, 56.63; H, 6.24; N, 4.13. Found: C, 56.94; H, 6.27; N, 4.32. Compound **2** (1.50 g, 4.4 mmol) was then added to a solution of pyridine (2.08 mL, 25.8 mmol) in dry CH_2Cl_2 (60 mL). To this solution, bis(trichloromethyl)carbonate (0.63 g, 2.14 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise at -78 ºC. The resulting mixture was left to stir for 2 hours at room temperature. The organic phase was extracted with saturated NH_4Cl (1 x 100 mL), 1 M HCl (3 x 30 mL) and saturated $NaHCO_3$ (1 x 100 mL) before the combined organic layers were dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The residue was purified via recrystallization from diethyl ether to give 1.35 g of the carbonate monomer **3** as a white solid (84% yield). ^1H NMR ($CDCl_3$, δ, ppm) 6.50 (s, 2H, C*H* = C*H*), 5.25 (s, 2H, C*H* bridgehead protons), 4.73 (d, 2H, *J* = 10.7 Hz, CH_2 ester protons), 4.20 (d, 2H, *J* = 10.7 Hz, CH_2 ester protons), 4.10 (t, 2H, J = 6.1 Hz, OCH_2), 3.57 (t, 2H, *J* = 6.6 Hz, NCH_2), 2.84 (s, 2H, bridge protons), 1.99 – 1.92 (m, 2H, $NCH_2CH_2CH_2O$), 1.37 (s, 3H, CCH_3). ^{13}C NMR ($CDCl_3$, d, ppm) 175.2, 169.8, 146.6, 135.6, 80.1, 72.1, 61.5, 46.6, 39.1, 34.1, 25.5, 16.8. Anal. Calcd. [$C_{17}H_{19}NO_8$]: C, 55.89; H, 5.24; N, 3.83. Found: C, 55.45; H, 5.24; N, 3.84.

Synthesis of Unprotected Maleimide-Containing Carbonate Monomer (4). Furan-protected maleimide-containing carbonate monomer **3** (100.0 mg, 0.34 mmol) was dissolved in toluene (50 mL) heated at 110 °C for 24 h under nitrogen. Toluene was evaporated under reduced pressure to give a white solid residue that was purified using column chromatography using SiO_2 as a stationary bed and EtOAc/hexanes to give a the carbonate monomer white solid **4** as a white solid. A quantitative conversion of the oxabicyclic moiety to the maleimide functional group was shown by ^{1}H NMR analysis. ^{1}H NMR (CDCl$_3$, δ, ppm) 6.70 (s, 2H, C*H*=C*H*), 4.72 (d, 2H, *J* = 12.0 Hz, CH$_2$ ester protons), 4.20 (d, 2H, *J* = 12.0 Hz, C*H*$_2$ ester protons), 4.12 (t, 2H, *J* = 6.0 Hz, OC*H*$_2$), 3.61 (t, 2H, *J*= 8.0 Hz, NC*H*$_2$), 2.00-1.94 (m, 2H, NCH$_2$C*H*$_2$CH$_2$O), 1.36 (s, 3H, C(C*H*$_3$)). ^{13}C NMR (CDCl$_3$, δ, ppm) 170.9, 170.5, 147.4, 134.2, 72.9, 62.7, 40.2, 34.1, 27.3, 17.6. Anal. Calcd. [$C_{13}H_{15}NO_7$]: C, 51.37; H, 5.22; N, 4.61; O, 38.80. Found: C, 51.67; H, 5.61; N, 4.24; O, 38.46.

General synthesis of furan-protected maleimide-functional homopolymers. Monomer **3** (50 mg, 0.14 mmol), benzyl alcohol (0.71 μL, 6.8 x 10^{-3} mmol) and 1,8-diazabicycloundec-7-ene (1.93 μL, 1.37 x 10^{-3} mmol) were placed in a vial under nitrogen atmosphere in a glove box. Dry CDCl$_3$ (1 mL) was added to the reaction mixture and left to stir for 4 hours at room temperature. The resulting polymer was purified by precipitation from 1:3 methanol:diethyl ether. The polymer was dried for 24 h in a vacuum oven at room temperature. ($[M]_0/[I]_0$ = 20, monomer conversion = 50%, $M_{n,theo}$ = 3.8 kg/mol, $M_{n,NMR}$ = 2.6 kg/mol, $M_{n,SEC}$ = 2.8 kg/mol, M_w/M_n = 1.07) ^{1}H NMR (CDCl$_3$, δ, ppm) 7.35 – 7.30 (m, 5H, aromatic C*H* = C*H*), 6.47 (s, 12H, C*H* = C*H*), 5.23 (s, 12H, C*H* bridgehead protons), 5.12 (s, 2H, benzylic protons) 4.32 (s, 24H, C*H*$_2$ ester protons), 4.04 (t, 12H, *J* = 5.0 Hz, OC*H*$_2$), 3.55 (t, 12H, J = 6.6 Hz, NC*H*$_2$), 3.07 (s, 1H, O*H*), 2.82 (s, 12H, bridge protons), 1.93 – 1.86 (m, 12H, NCH$_2$C*H*$_2$CH$_2$O), 1.22 (s, 18H, CC*H*$_3$).

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General procedure for deprotection of homopolymers by retro Diels-Alder reaction. Polymer P**4** was heated to 100 ºC in a vacuum oven for 24 hours. ^{1}H NMR analysis proves that oxabicyclic moiety conversion to the maleimide functional group has been achieved. ($M_{n,SEC}$ = 2.7 kg/mol, M_w/M_n = 1.11) ^{1}H NMR (CDCl$_3$, δ, ppm) 7.34 – 7.31 (m, 5H, aromatic C*H* = C*H*), 6.69 (s, 12H, C*H* = C*H*), 5.12 (s, 2H, benzylic protons) 4.30 (s, 24H, C*H*$_2$ ester protons), 4.06 (t, 12H, *J* = 6.1 Hz, OC*H*$_2$), 3.58 (t, 12H, J = 7.3 Hz, NC*H*$_2$), 2.82 (s, 1H, O*H*), 1.94 (m, 12H, NCH$_2$C*H*$_2$CH$_2$O), 1.23 (s, 18H, CC*H*$_3$).

General synthesis of furan-protected maleimide-containing PLLA copolymers. Monomer **3** (0.5 g, 1.37 mmol), benzyl alcohol (7.09 μL, 6.85 x 10^{-2} mmol), L-lactide (0.79 g, 5.47 mmol) and 1,8-diazabicycloundec-7-ene (DBU) (3.95 μL, 2.74 x 10^{-2} mmol) were placed in a vial under nitrogen atmosphere in a glove box. Dry $CDCl_3$ (9 mL) was added to the reaction mixture and left to stir for 24 h at room temperature. The resulting polymer was purified by precipitation from 1:1 methanol:diethyl ether mixture. The polymer was dried for 24 h in a vacuum oven at room temperature. ($[M]_0/[I]_0 = 100$, conversion = 85%, $M_{\mathrm{n,theo}} = 16.1$ kg/mol, $M_{\mathrm{n,NMR}} = 13.7$ kg/mol, $M_{\mathrm{n,SEC}} = 17.1$ kg/mol, $M_{\mathrm{w}}/M_{\mathrm{n}} = 1.16$) ^{1}H NMR ($CDCl_3$, δ, ppm) 7.35 – 7.31 (m, 5H, aromatic C*H* = C*H*), 6.48 (s, 12H, C*H* = C*H*), 5.28 (s, 12H, C*H* bridgehead protons), 5.14 (q, 158H, C*H* protons of lactide) 4.30 (d, *J* = 5.7 Hz, 24H, $\mathrm{C}H_2$ ester protons), 4.04 (t, 12H, *J* = 5.0 Hz, $\mathrm{OC}H_2$), 3.54 (t, 12H, *J* = 6.5 Hz, $\mathrm{NC}H_2$), 2.83 (s, 12H, bridge protons), 1.93 – 1.86 (m, 12H, $\mathrm{NCH_2C}H_2\mathrm{CH_2O}$), 1.56 (d, *J* = 6.4 Hz, 474H, $\mathrm{C}H_3$ protons of lactide), 1.23 (s, 18H, $\mathrm{CC}H_3$).

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General procedure for deprotection of copolymers by retro Diels-Alder reaction. Polymer **6** was heated to 100 ºC for 24 hours under high vacuum. ^{1}H NMR analysis proved that quantitative deprotection of the maleimide group was achieved. ($M_{\mathrm{n,SEC}} = 17.0$ kg/mol, $M_{\mathrm{w}}/M_{\mathrm{n}} = 1.18$) ^{1}H NMR ($CDCl_3$,δ, ppm) 7.34 – 7.30 (m, 5H, aromatic C*H* = C*H*), 6.69 (s, 12H, C*H* = C*H*), 5.16 (q, 158H, C*H* protons of lactide) 4.29 (d, *J* = 5.7 Hz, 24H, $\mathrm{C}H_2$ ester protons), 4.07 (t, 12H, *J* = 5.0 Hz, $\mathrm{OC}H_2$), 3.56 (t, 12H, *J* = 6.5 Hz, $\mathrm{NC}H_2$), 3.09 (1.96 – 1.89 (m, 12H, $\mathrm{NCH_2C}H_2\mathrm{CH_2O}$), 1.55 (d, *J* = 6.7 Hz, 474H, $\mathrm{C}H_3$ protons of lactide), 1.26 (s, 18H, $\mathrm{CC}H_3$).

Functionalization of copolymer P14-Retro with 6-(ferrocenyl)hexanethiol. Copolymer **P14-Retro** (20 mg, 1.2 x 10^{-3} mmol), 6-(ferrocenyl)hexanethiol (7.26 mg, 2.4 x 10^{-3} mmol) and NEt_3 (3.4 μL, 2.4 x 10^{-3} mmol) were dissolved in 1 mL dry CH_2Cl_2 and left to stir at room temperature under nitrogen atmosphere for 24 hours. The resultant polymer was purified by precipitation from 1:1 methanol:diethyl ether mixture. ($M_{\mathrm{n,SEC}} = 18.4$ kg/mol, $M_{\mathrm{w}}/M_{\mathrm{n}} = 1.20$) ^{1}H NMR ($CDCl_3$,δ, ppm) 7.33 – 7.31 (m, 5H, aromatic C*H* = C*H*), 5.14 (q, 158H, C*H* protons of lactide), 4.29 (d, *J* = 5.7 Hz, 24H, CH_2 ester protons), 4.08 (s, 30H, C*H* protons of ferrocene), 4.07 (t, 12H, *J* = 5.0 Hz, OCH_2), 4.01 (s, 24H, C*H* protons of ferrocene), 3.58 (t, 12H, *J* = 6.5 Hz, NCH_2), 3.09 (br, 6H, CH_2-CH-S), 2.84 (br, 6H, C*H*-S-CH_2), 2.72 (br, 12H, CH_2-S), 2.50 (br, 6H, CH_2-CH-S), 2.28 (t, 12H, Fer-CH_2), 1.93 – 1.80 (m, 12H, $NCH_2CH_2CH_2O$), 1.55 (d, *J* = 6.7 Hz, 474H, CH_3 protons of lactide), 1.26 (s, 18H, CCH_3).

Functionalization of copolymer P14-Retro with 1-hexanethiol. Funtionalization was carried out as for the above procedure using 1-hexanethiol in preference to 6-(ferrocenyl)hexane thiol. ($M_{n,SEC}$ = 17.8 kg/mol, M_w/M_n = 1.19) ^{1}H NMR ($CDCl_3$,δ, ppm) 7.34 – 7.30 (m, 5H, aromatic C*H* = C*H*), 5.16 (q, 158H, C*H* protons of lactide) 4.29 (d, *J* = 5.7 Hz, 24H, CH_2 ester protons), 4.07 (t, 12H, *J* = 5.0 Hz, OCH_2), 3.58 (t, 12H, *J* = 6.5 Hz, NCH_2), 3.06 (br, 6H, CH_2-CH-S), 2.85 (br, 6H, C*H*-S-CH_2), 2.74 (br, 12H, CH_2-S), 2.47 (br, 6H, CH_2-CH-S), 1.96 – 1.89 (m, 12H, $NCH_2CH_2CH_2O$), 1.55 (d, *J* = 6.7 Hz, 474H, CH_3 protons of lactide), 1.26 (s, 18H, CCH_3), 0.87 (t, 18H, *J* = 6.4 Hz, CH_3 protons of hexanethiol).

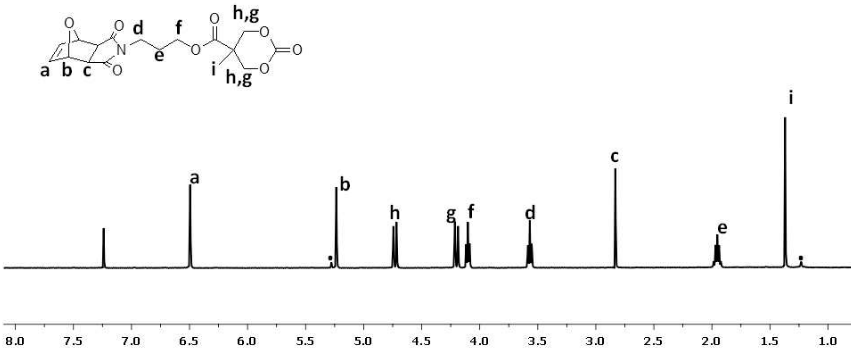

Figure S1. ^{1}H NMR of furan-protected maleimide-containing carbonate monomer **3** ($CDCl_3$, 400 MHz). Resonances indicated with dots at δ = 5.27 and 1.20 ppm denote trace residual solvent impurities.

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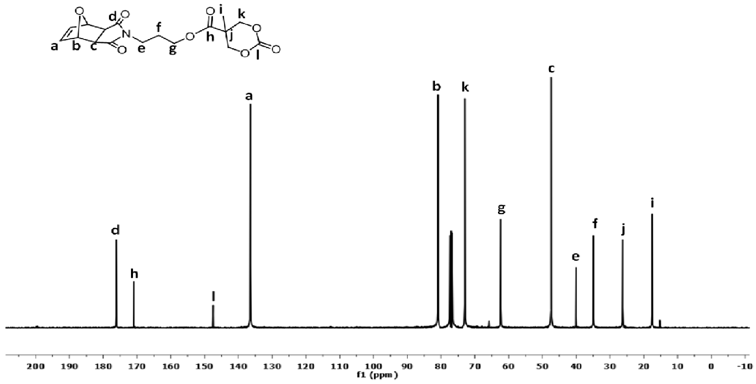

Figure S2. ^{13}C-NMR in CDCl$_3$ of maleimide functional carbonate monomer **3** (CDCl$_3$, 400 MHz).

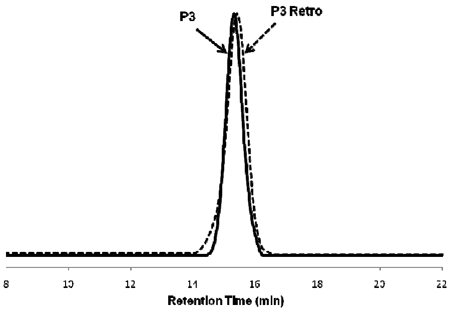

Figure S3. GPC traces of the homopolymer **P3** ($M_{n,GPC}$ = 2,800 g.mol^{-1}, M_w/M_n = 1.10) and homopolymer after the rDA reaction, **P3 Retro**, ($M_{n,GPC}$ = 2,700 g.mol^{-1}, M_w/M_n = 1.10).

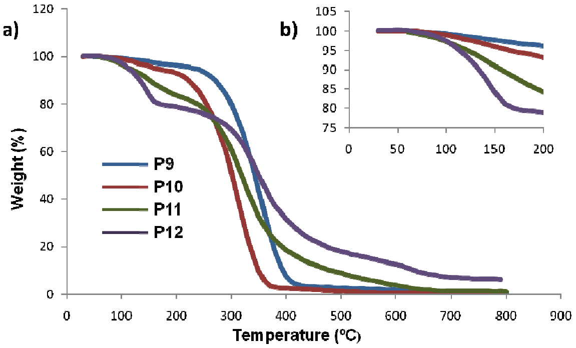

Figure S4. TGA thermograms of different copolymers containing different maleimide percentages between (a) 0ºC–600ºC (b) 0ºC–200ºC. (Observed weight loss P9: 2.9%, P10: 4.3%; P11: 13.4%, P12: 17.8%; Expected weight loss P9: 2.8%, P10: 4.34%; P11: 14.7%, P12: 24.4%).

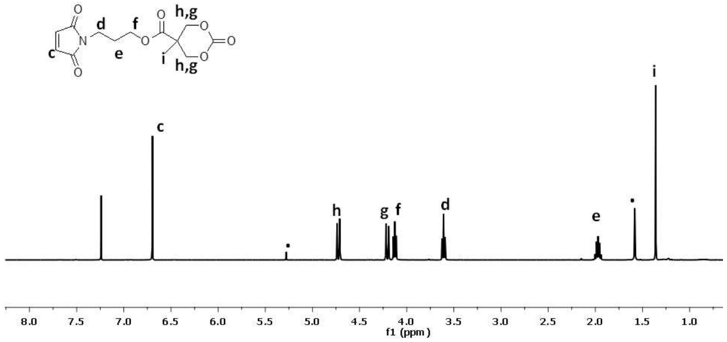

Figure S5. ^{1}H NMR of maleimide-containing carbonate monomer **4** ($CDCl_3$, 400 MHz) Resonances indicated with dots at $\delta = 5.27$ and 1.50 ppm denote trace residual solvent impurities.

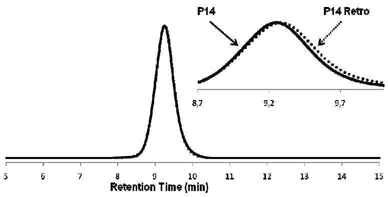

Figure S6. GPC traces of copolymer **P14** ($M_{n,GPC}$ = 17 000 g.mol^{-1}, M_w/M_n = 1.20) and copolymer after the rDA reaction, **P14 Retro**, ($M_{n,GPC}$ = 17 000 g.mol^{-1}, M_w/M_n = 1.18).

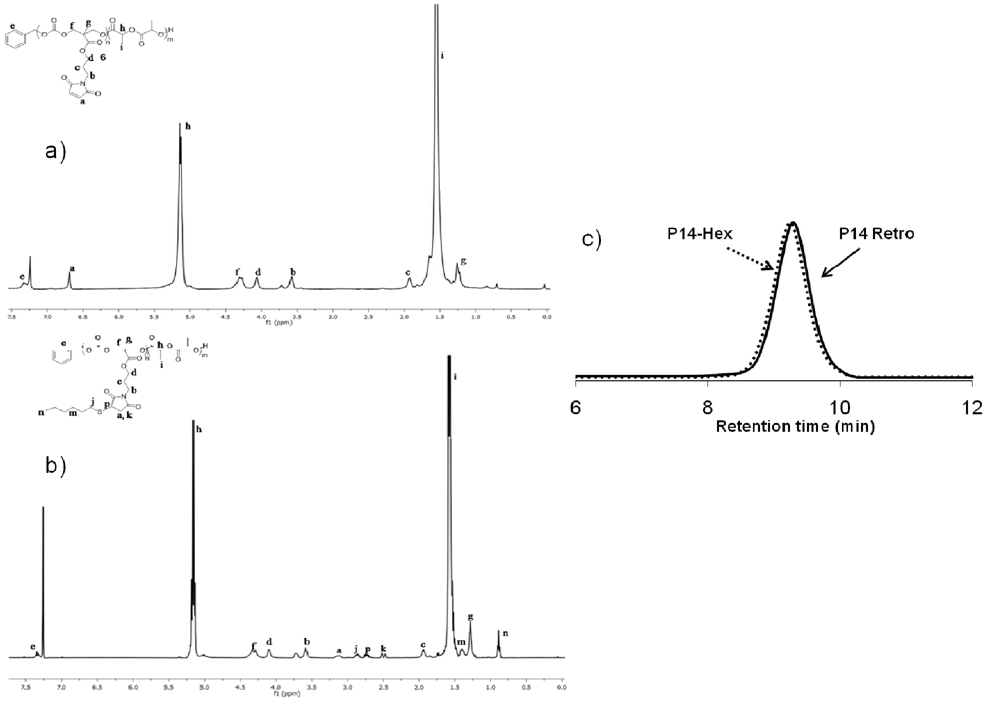

Figure S7. ^{1}H-NMR spectra (CDCl$_3$, 400 MHz) of (a) **P14** Retro, (b) 1-hexanethiol functionalized polymer (**P14**-Hex) and (c) GPC traces **P14**Retro ($M_{n,GPC}$ = 17,000 g.mol^{-1}, M_w/M_n = 1.18) & **P14**-Hex ($M_{n,GPC}$ = 17,800 g.mol^{-1}, M_w/M_n = 1.19).

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[i] Tonga, M.; Cengiz, N.; Kose, M. M.; Dede, T.; Sanyal, A. *J. Polym. Sci., Part A: Polym. Chem.* **2010**, *48*, 410–416.