Supporting Information

Access to Poly-β-Peptides with Functionalized Side Chains and End Groups via Controlled Ring-Opening Polymerization of β-Lactams

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Part One

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Experimental Section

General Considerations. All chemicals were purchased from Aldrich (Milwaukee, WI), Acros Organics or TCI America, and used as received, unless stated otherwise. β-Lactams 1 – 3,\(^1\) co-initiator I\(_6\),\(^2\) and \(^{13}\)C labeled chlorosulfonyl isocyanate (CSI)\(^3\) were prepared according to literature procedures. β-Lactam 2 with a \(^{13}\)C labeled carbonyl group was synthesized in the same way as the non-labeled analog, except that \(^{13}\)C labeled CSI was used. \(^1\)H and \(^{13}\)C NMR spectra were recorded on Bruker AC-300 spectrometers at 300 and 75 MHz, respectively. Monomer conversion was estimated by gas chromatography (GC) on a Shimadzu GC-17A instrument equipped with a RTX-5 column using triphenylmethane as the internal standard. The number-average molecular weight (\(M_n\)), weight-average molecular weight (\(M_w\)) and polydispersity (\(M_w/M_n\)) were obtained using a gel permeation chromatography (GPC) instrument equipped with a Shimadzu LC-10AD liquid chromatography (HPLC) pump and a Wyatt Technology miniDAWN multi-angle light scattering (MALS) detector (690 nm, 30 mW) in series with a Wyatt Technology Optilab-rEX refractive index detector (690 nm). GPC with organic solvents was performed using two Viscotek columns (ViscoGEL GMH\(_{10R}\)-H, particle size 5 \(\mu m\)) or two Waters columns (Styragel HR4E, particle size 5 \(\mu m\)) with THF as mobile phase at a flow rate of 1.0 mL/min at 40\(^\circ\)C. Aqueous GPC was performed using two Waters columns (Ultrasoundgel 250, pore size 25 nm) with 0.1 % (v/v) trifluoroacetic acid (TFA) in Millipore water as mobile phase at a flow rate of 0.8 mL/min at 40\(^\circ\)C. The refractive index increment (dn/dc) of the polymers was measured in appropriate solvents at 30\(^\circ\)C by using a Wyatt Technology Optilab-rEX refractive index detector set at 690 nm. The data were processed using ASTRA 5.3.2.15 software (Wyatt Technology). Matrix-assisted laser desorption/ionization - time of flight (MALDI-TOF) mass-spectrometry was performed on a Bruker Reflex II instrument using α-
cyano-4-hydroxycinnamic acid as the matrix. A polymer solution of 1-10 mg/mL was spotted on top of a dried layer of the matrix and allowed to dry at room temperature before analysis.

(±)-trans-3-Phthalimidylmethyl-4-methyl azetidin-2-one (6). To a 1 L round-bottom flask was added 21 g (0.16 mol, 1 eq.) crotyl bromide, 44 g (0.24 mol, 1.5 eq.) potassium phthalimide and 500 mL DMF. The reaction mixture was stirred at 60°C overnight. The reaction mixture was allowed to cool and then poured into 2000 mL ice and water with vigorous stirring until the ice melted. The resulting white precipitate was isolated by filtration and dissolved in CH₂Cl₂. The solution was dried over MgSO₄, and the solvent was evaporated to give the crude product, 1-phthalimidyl-2-butene (29.5 g, 94%), which was carried on without purification. In a 100 mL round-bottom flask was placed 1-phthalimidyl-2-butene (17 g, 0.085 mol, 1 eq.). This material was dissolved in 30 mL CHCl₃, and the flask was cooled to 0°C. CSI (2.9 mL, 0.033 mL, 1 eq.) was slowly added to the flask. The reaction mixture was stirred under N₂ and heated to 60°C for 5 days. Then the reaction mixture was poured into a suspension of Na₂SO₃ (40 g) and Na₂HPO₄ (40 g) in water (700 mL) for hydrolysis. The pH was maintained between 5 and 7 by using 2 N NaOH, and the reaction mixture was stirred at room temperature for 2 days. The layers were separated, and the aqueous phase was extracted with CH₂Cl₂. The combined organic phases were dried over MgSO₄. After the drying agent was filtered off and the solvent was removed, the crude product was recrystallized from CH₂Cl₂ and hexane to afford 7.6 g of 4 as white solid (38%): mp = 165-166°C, ¹H NMR (CDCl₃): δ 1.32 (d, 3 H, J = 6.0 Hz, Me), 3.16 (t, 1 H, J = 6.9 Hz, CHMe), 3.79-3.83 (m, 1 H, CH(CH₂Phth)), 4.00 (dd, 1 H, J = 14, 9.6 Hz, CH₂), 4.00 (dd, 1 H, J = 14, 5.7 Hz, CH₂), 5.87 (br s, 1H, NH), 7.74 – 7.77 (m, 2 H, Ph), 7.87 – 7.90 (m, 2 H, Ph). ¹³C NMR (CDCl₃): δ 20.75, 36.62, 50.46, 57.12, 123.69, 132.11, 134.37, 167.07, 168.23. MS-ESI: m/z = Calc.: 267.1[M+Na]+ Obs.: 267.2 [M+Na]+.
(±)-trans-3-tert-Butyloxycarbonylaminomethyl-4-methyl azetidin-2-one (4). To a 50 mL round-bottom flask was added 6 (2.44 g, 10 mmol, 1 eq.) and methanol (20 mL). Anhydrous hydrazine (0.96 mL, 30 mmol, 3 eq.) was then added, and the mixture was stirred under N₂ at room temperature overnight. The resulting precipitate was removed by filtration and washed with copious methanol. The solvent and excess hydrazine were removed from the filtrate by rotary evaporation. The residue was transferred to a 250 mL round-bottom flask, to which was added di-tert-butyl dicarbonate (Boc₂O, 8.7g, 40 mmol, 4 eq.), triethylamine (5.5 mL, 40 mmol, 4 eq.) and 100 mL methanol. The reaction mixture was refluxed for 1 hour. After filtration the solvent was then removed by rotary evaporation. The residue was extracted with ethyl acetate, and the organic solution washed with 1 N HCl, 1 N NaOH and brine before being dried over MgSO₄. The solvent was removed to afford the crude product, which was then purified by SiO₂ column chromatography using ethyl acetate as eluent. β-Lactam 4 was obtained as white solid (0.97 g, 43%): mp = 100–102 °C. ¹H NMR (CDCl₃): δ 1.37 (d, 3 H, J = 6.0 Hz, Me), 1.45 (s, 9 H, 'Bu), 2.90 (tdd, 1 H, J = 6.0, 2.1, 0.9 Hz, CHMe), 3.50 (m, 2 H, CH₂), 3.65 (qd, 1 H, J = 6.0, 2.1 Hz, CH(CH₂NHBoc)), 4.90 (br s, 1H, NHboc), 5.87 (br s, 1H, lactam NH). ¹³C NMR (CDCl₃): δ 20.54, 28.55, 38.46, 48.84, 58.57, 79.89, 164.71, 168.99. MS-ESI: m/z = Calc.: 237.1[M+Na]⁺; Obs.: 267.1 [M+Na]⁺. FTIR(ATR): 1522, 1680, 1733, 3243, 3378 cm⁻¹.

β-Lactams 5 and 7 were prepared via analogous procedures starting from 1-chloro-3-methyl-2-butene; in these cases the CSI coupling reactions were carried out in CH₂Cl₂ at room temperature for 2 days.

(±)-3-tert-Butyloxycarbonylaminomethyl-4,4-dimethyl azetidin-2-one (5) was obtained as a white solid (yield 60%): mp = 112 – 114 °C. ¹H NMR (CDCl₃): δ 1.38 (s, 3 H, Me), 1.44 (s, 3 H, Me), 1.46 (s, 9H, 'Bu), 2.98 (t, 1 H, J = 7.8 Hz, CH(CH₂NHBoc)), 3.29 (m, 1 H, CH₂), 3.63 (m, 1
1H, CH₂), 4.97 (br s, 1H, NHBOc), 5.92 (br s, 1H, lactam NH). ¹³C NMR (CDCl₃): δ 22.92, 28.49, 28.68, 37.20, 54.83, 58.34, 79.61, 155.89, 169.32. MS-ESI/EMM: m/z = Calc.: 251.1 [M+Na]^+ Obs.: 251.1 [M+Na]^+. FTIR(ATE): 1688 cm⁻¹, 1716 cm⁻¹, 1744 cm⁻¹, 3194 cm⁻¹, 3280 cm⁻¹.

(±)-3-Phthalimidymethyl-4,4-dimethyl azetidin-2-one (7) was obtained as white solid (overall yield 82%): mp = 157–159 °C. ¹H NMR (CDCl₃): δ 1.45 (s, 3 H, Me), 1.47 (s, 3 H, Me), 3.42 (td, 1 H, J = 8.0, 0.9 Hz, CH(CH₂Phth)), 3.93 (dd, 1 H, J = 14.1, 8.1 Hz, CH₂), 4.07 (dd, 1 H, J = 14.1, 8.1 Hz, CH₂), 5.97 (br s, 1H, NH), 7.71 – 7.74 (m, 2 H, Ph), 7.85 – 7.88 (m, 2 H, Ph). ¹³C NMR (CDCl₃): δ 14.31, 21.15, 23.38, 25.58, 34.31, 55.18, 56.66, 60.48, 123.52, 132.11, 134.17, 167.47, 168.06. MS-ESI: m/z = Calc.: 259.2 [M+H]^+ Obs.: 259.3 [M+H]^+. FTIR(ATE): 1715, 1741, 3200 cm⁻¹.

1-Benzoyl-4-phenyl azetidin-2-one (II). In a 1 L round-bottom flask were combined DL-3-amino-3-phenyl propionic acid (1.156 g, 0.007 mol), 2-chloro-1-methyl pyridinium iodide (1.74 g, 0.0077 mol, 1.1 eq.), triethylamine (2.15 mL, 0.0154 mol, 2.2 eq.) and anhydrous acetonitrile (700 mL). The reaction mixture was stirred under nitrogen and heated to reflux overnight. The solvent was removed by rotary evaporation, and the residue was purified by SiO₂ column chromatography with 1:1 hexane: ethyl acetate to yield the intermediate compound 4-phenyl-2-azetidinone, 0.808 g (40%). This material was carried on without purification. In a 25 mL round-bottom flask were combined 4-phenyl-2-azetidinone (0.250 g, 1.70 mmol, 1 eq.), triethylamine (1.02 mL, 7.30 mmol, 4.3 eq.), dry CH₂Cl₂ (10 mL) and N,N’-dimethylamino pyridine (0.021 g, 0.17 mmol, 0.1 eq.). The reaction mixture was cooled to 0 °C, and benzoyl chloride (0.21 mL, 1.80 mmol, 1.1 eq.) was added. The reaction mixture was warmed to room temperature and stirred for 1 hour. The reaction was quenched with saturated NH₄Cl (30 mL) and diluted with
CH₂Cl₂ (150 mL). The reaction mixture was then washed with a saturated aqueous solution of NaHCO₃ followed by brine. The organic portion was dried over MgSO₄, and after filtration the solvent was removed by rotary evaporation. The crude product was purified by SiO₂ column chromatography eluting with 1:1 hexanes: ethyl acetate to give the product as a white solid (0.320 g, 75%): mp = 152-153°C. ¹H NMR (CDCl₃): δ 3.09 (dd, 1 H, J = 16.5, 3.9 Hz, C₆H₅cisH₆transCHPh), 3.53 (dd, 1 H, J = 16.5, 3.9 Hz, C₆H₅cisH₆transCHPh), 5.29 (dd, 1 H, J = 6.9, 3.9 Hz, C₆H₅cisH₆transC₆H₅), 7.26 – 7.98 (m, 10 H, Ph). MS-ESI: m/z = Calc.: 525.2 [2 M + Na]⁺ Obs.: 525.2 [2 M + Na]⁺.

cis-9-(4-tert-Butylbenzoyl)-9-aza-bicyclo[6.2.0]decan-10-one (12). To a solution of 2 (1.0 g, 6.5 mmol, 1 eq.), triethylamine (2.9 ml, 21 mmol, 3.2 eq.) and N,N'-dimethylamino pyridine (0.080 g, 0.65 mmol, 0.1 eq.) in 30 ml of CH₂Cl₂, 4-tert-butylbenzoyl chloride (2.4 ml, 13 mmol, 2 eq.) was added dropwise at 0 °C. The reaction mixture was allowed to warm gradually to room temperature and stirred overnight. The reaction mixture was quenched with saturated aqueous NaHCO₃. The organic layer was washed twice with water, and then the organic layer was dried over MgSO₄, and after filtration the solvent was removed by rotary evaporation. The residue was purified by SiO₂ column chromatography using ethyl acetate as eluent followed by recrystallization from hexane to give the product as a white crystalline solid (1.07g, 53%): mp = 112-114°C. ¹H NMR (CDCl₃): δ 1.19 (s, 9 H, 'Bu), 1.28-2.22 (m, 14H, -CH(CH₂)₆CH=O), 3.16 (dd, 1 H, J = 12.0, 8.1 Hz, NHCH(CH₂)₆CH=O), 4.26 (dd, 1 H, J = 12.0, 8.7 Hz, NHCH(CH₂)₆CH=O), 7.48 (d, 2 H, J = 9.0 Hz, Ph), 7.78 (d, 2 H, J = 9.0 Hz, Ph). MS-ESI: m/z = Calc.: 336.2 [M+Na]⁺ Obs: 336.2 [M+Na]⁺.

Polymerization. All polymerizations were carried out in a nitrogen-purged dry box at room temperature unless otherwise noted. In a typical polymerization, the β-lactam monomer was
weighed and placed in a reaction vial with a magnetic stirring bar. Then the appropriate amounts of co-initiator and anhydrous THF were added to achieve the desired monomer to co-initiator ratio ([M]₀/[I]₀) and monomer concentration. The mixture was allowed to stir until all solid material was dissolved. The polymerization was started by addition of a LiN(SiMe₃)₂ solution in THF. The polymerization was stopped by adding a small amount of methanol. The resultant polymer was precipitated by pouring the reaction solution into pentane. The precipitate was collected by filtration or centrifugation. The precipitate was then re-dissolved in CHCl₃ and re-precipitated by pouring this solution into pentane. The resulting polymer was dried under vacuum to constant weight.

Block-copolymerization was performed according to the above procedures; the monomer for the second block was added to the reaction vial after the first polymerization was finished.

**Synthesis of poly-2b with ^13^C(=O) labeled imide group.** Initial polymerization was carried out according to the protocol described above using 0.153 g (1.0 mmol) of 2, 0.042 g (0.25 mmol) of LiN(SiMe₃)₂ and 20 µL (0.1 mmol) of 13. After one hour 0.013 g (0.085 mmol) of ^13^C(=O) labeled 2 was added, and the reaction mixture was stirred at ambient temperature for 5 h. Poly-2b was isolated as described above.

**Deprotection of Boc-protected amino-containing polymers.** The deprotection reactions were accomplished in either neat trifluoroacetic acid (TFA) or 5 M hydrochloride acid (HCl) in 1,4-dioxane, with essentially quantitative conversion to give the deprotected polymers as TFA salts or HCl salts, respectively. In a typical reaction, 100 mg of Boc-protected amino-containing polymer was dissolved in 2 mL of TFA (usually in 1-5 min), and the reaction solution was allowed to stand at room temperature for 2 hr. The reaction mixture was then poured into cold diethyl ether to induce precipitation of the TFA salt of the free amino-containing polymer as a white solid.
Chart S1. Examples of β-lactams that lead to polymers insoluble in organic solvents.

Table S1. GPC characterization and yields of poly-2b and poly-5 under different [M]₀/[I]₀. a

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a Conditions: [M]₀ = 0.1 M, 13 as co-initiator, 2.0 eq. LiN(SiMe3)2 (relative to 13) as base, THF as solvent, 25°C. b Monomer conversion measured by GC. c Isolated yield. d Determined by GPC-MALS. dn/dc25 in THF.
(mL/g): poly-2, 0.138; poly-5, 0.074; "Estimated by RI signal using PMMA as standard. "DP: degree of polymerization.

Figure S1. $M_n$ versus $[M]_0/[I]_0$ for polymerization of 5. Conditions: see Table S1.

**Polymer characterizations**
Poly-2a: 94% isolated yield. $^1$H NMR (CDCl$_3$/CD$_3$OD/CD$_3$COOD 20:3:15): $\delta$ 1.33, 1.52 (br s, 122 H, -CH(CH$_2$)$_6$CH-), 2.48, 2.67, 3.01 (br s, 10 H, -CH(CH$_2$)$_6$CH-), 3.17, 3.39, 3.79, 4.03, 4.27 (br s, 12 H, -CH(CH$_2$)$_6$CH-, -CH$_2$CH(Ph)-), 5.35 (br s, 2 H, -CH$_2$CH(Ph)-), 6.98-7.68 (br m, 13 H, J = 9.3 Hz, PhC(=O)-, -CH$_2$CH(Ph)-, CHCl$_3$). $M_n = 1,900$ g/mol, polydispersity index (PDI) = 1.22 (GPC); $M_n = 1,870$ g/mol, polydispersity index (PDI) = 1.08 (MALDI-TOF).
Poly-2b: 98% isolated yield. $^1$H NMR (CDCl$_3$/CD$_3$OD/CD$_3$COOD 20:3:15): δ 0.97, 1.21, 1.40 (br s, 87 H, -CH(CH$_2$)$_6$CH-, tBu-end group), 2.35, 2.52 (br s, 7 H, -CH(CH$_2$)$_6$CH-), 3.90, 4.15 (br s, 7 H, -CH(CH$_2$)$_6$CH-), 7.06 (d, 2 H, J = 7.4 Hz, C$_6$H$_4$), 7.35, 7.56 (d, 2 H, J = 7.4 Hz, C$_6$H$_4$). $M_n$ = 1,350 g/mol, polydispersity index (PDI) = 1.22 (GPC); $M_n$ = 1,210 g/mol, polydispersity index (PDI) = 1.05 (MALDI-TOF).

Poly-3: 98% isolated yield. $^1$H NMR (CDCl$_3$/CD$_3$OD/CD$_3$COOD 20:3:15): δ 1.06, 1.11 (br s, 133 H, -CH$_3$, tBu-end group), 2.33, 2.50 (br s, 7 H, -CH$_2$-), 3.82, 4.06 (br s, 7 H, -CH$_2$-), 7.06 (d, 2 H, J = 9.0 Hz, C$_6$H$_4$), 7.38, 7.64 (d, 2 H, J = 9.0 Hz, C$_6$H$_4$). $M_n$ = 1,870 g/mol, polydispersity index (PDI) = 1.10 (GPC); $M_n$ = 1,840 g/mol, polydispersity index (PDI) = 1.12 (MALDI-TOF).

Poly-4: 98% isolated yield. $^1$H NMR (CDCl$_3$/CD$_3$OD/CD$_3$COOD 20:3:15): δ 0.95, 1.09, 1.18 (br s, 86 H, -CH$_3$, tBu-end group, tBu-BOC), 2.39, 2.88, 3.21, 4.02 (br s, 25 H, -CH$_2$NHBOC, -CH(NH)CH(Me)-), 7.21, 7.57 (d, 2 H, J = 8.4 Hz, C$_6$H$_4$). $M_n$ = 1,700 g/mol, polydispersity index (PDI) = 1.16 (GPC).

Poly-5: 98% isolated yield. $^1$H NMR (CDCl$_3$/CD$_3$OD/CD$_3$COOD 20:3:15): δ 1.02, 1.11 (br s, 105 H, -CH$_3$, tBu-end group, tBu-BOC), 3.16 (br s, 21 H, -CH$_2$NHBOC, -CH(NH)CH(Me)-), 7.13, 7.46 (d, 2 H, J = 6.0 Hz, C$_6$H$_4$). $M_n$ = 1,820 g/mol, polydispersity index (PDI) = 1.11 (GPC).

Poly-2c: $p$-ClCH$_2$C$_6$H$_4$C(=O)Cl was used as a co-initiator, 93% isolated yield. $^1$H NMR (CDCl$_3$/CD$_3$OD/CD$_3$COOD 20:3:15): δ 1.59, 1.75 (br s, 120 H, -CH(CH$_2$)$_6$CH-), 2.74, 2.89 (br s, 8 H, -CH(CH$_2$)$_6$CH-), 3.93, 4.06, 4.26, 4.52 (br s, 8 H, -CH(CH$_2$)$_6$CH-), 4.65 (s, 2 H, ClCH$_2$), 7.20 (d, 2 H, J = 8.4 Hz, C$_6$H$_4$), 7.46, 7.79, 8.01 (d, 2 H, J = 8.4 Hz, C$_6$H$_4$). Anal. Calcd for C$_7$_H$_{124}$ClN$_7$O$_8$ (n = 7): Cl, 2.86. Found: Cl, 3.10. $M_n$ = 1,310 g/mol, polydispersity index (PDI) = 1.07 (GPC); $M_n$ = 1,480 g/mol, polydispersity index (PDI) = 1.04 (MALDI-TOF).

Poly-2d: $p$-Me$_2$NC$_6$H$_4$C(=O)Cl was used as a co-initiator, 95% isolated yield. $^1$H NMR (CDCl$_3$/CD$_3$OD/CD$_3$COOD 20:3:15): δ 1.32, 1.45 (br s, 147 H, -CH(CH$_2$)$_6$CH-), 2.47, 2.63, 2.96
(br s, 10 H, \(-CH(CH_2)_6CH\)-), 3.74, 4.0, 4.21 (br s, 13 H, \(-CH(CH_2)_6CH\)-), 2.76 (s, 6 H, Me_2N), 6.43 (d, 2 H, J = 9.3 Hz, C_6H_4), 7.41, 7.64 (d, 2 H, J = 9.3 Hz, C_6H_4). M_n = 1,480 g/mol, polydispersity index (PDI) = 1.22 (GPC); M_n = 1,420 g/mol, polydispersity index (PDI) = 1.08 (MALDI-TOF).

Poly-2e: \(p-N_3C_6H_4C(=O)Cl\) was used as a co-initiator, 93% isolated yield. ^1H NMR (CDCl_3/CD_3OD/CD_3COOD 20:3:15): δ 1.58, 1.76 (br s, 132 H, \(-CH(CH_2)_6CH\)-), 2.73, 2.90 (br s, 13 H, \(-CH(CH_2)_6CH\)-), 4.28, 4.52 (br s, 13 H, \(-CH(CH_2)_6CH\)-), 7.06 (d, 2 H, J = 9.0 Hz, C_6H_4), 7.82, 8.05 (d, 2 H, J = 9.0 Hz, C_6H_4). M_n = 1,390 g/mol, polydispersity index (PDI) = 1.10 (GPC); M_n = 1,240 g/mol, polydispersity index (PDI) = 1.07 (MALDI-TOF).

Poly-2f: \([p-ClC(=O)C_6H_4N]=_2\) was used as a co-initiator, 97% isolated yield. ^1H NMR (CDCl_3/CD_3OD/CD_3COOD 20:3:15): δ 1.30, 1.37 (br s, 142 H, \(-CH(CH_2)_6CH\)-), 2.20, 2.45, 2.63 (br s, 10 H, \(-CH(CH_2)_6CH\)-), 3.63, 3.75, 4.14, 3.4.25, 4.01 (br s, 12 H, \(-CH(CH_2)_6CH\)-), 7.70 (br s, 6 H, C_6H_4), 7.91 (br s, 2 H, C_6H_4). UV λ_{max} (CHCl_3) nm (log ε): 456 (0.06), 331 (3.76), 245 (0.82). M_n = 1,800 g/mol, polydispersity index (PDI) = 1.08 (GPC); M_n = 1,920 g/mol, polydispersity index (PDI) = 1.11 (MALDI-TOF).

Poly-2g: \([CH_2=C(Me)C(=O)-]_2O\) was used as a co-initiator, 95% isolated yield. ^1H NMR (CDCl_3/CD_3OD 1:1): δ 1.37, 1.52, 1.72 (br s, 126 H, \(-CH(CH_2)_6CH\)-, CH_2=C(Me)-), 2.29, 2.53, 2.72 (br s, 11 H, \(-CH(CH_2)_6CH\)-), 3.06, 3.24, 3.41 (br s, 11 H, \(-CH(CH_2)_6CH\)-), 5.13, 5.48, 5.64 (s, 2 H, CH_2=C(Me)-). M_n = 1,080 g/mol, polydispersity index (PDI) = 1.05 (GPC); M_n = 1,020 g/mol, polydispersity index (PDI) = 1.04 (MALDI-TOF).

**Synthesis of poly-2h and poly-2i.**

**General procedure.**

To a solution of a 0.153 g (1.0 mmol) of \(2\) in ca. 3 ml of THF 0.019 g (0.10 mmol), (4-chloromethyl)benzoyl chloride was added. In a separate vial 0.042 g (0.25 mmol) of LiN(SiMe_3)_2 was dissolved in 1 ml of THF, and this solution was added to the stirred solution of monomer and co-initiator. The reaction mixture was stirred for 1 h, whereupon the 0.12 mmol of the appropriate lithium salt nucleophile (see below) was added in ca. 4 ml of N,N-dimethylacetamide (DMAc), and the reaction mixture was stirred for 5 h at ambient temperature.
The mixture was filtered through Celite, and all the volatiles were removed in vacuo. The residue was re-dissolved in 3 ml of AcOH and precipitated with 15 ml of an acetone/H₂O (1:1) mixture. The resulting precipitate was dried under high vacuum at ambient temperature to yield the corresponding polymer.

Poly-2h: Lithium (3,5-dimethoxy)benzoate was generated from 0.022 g (0.12 mmol) of (3,5-dimethoxy)benzoic acid and 0.020 g (0.12 mmol) of LiN(SiMe₃)₂; 94% isolated yield. ¹H NMR (CDCl₃/CD₃OD/CD₃COOD 20:3:15): δ 1.28, 1.43 (br s, 253 H, -CH(CH₂)₆CH-), 3.55 (s, 6 H, (MeO)₂C₆H₃), 4.0, 4.23 (br s, 19 H, -CH(CH₂)₆CH-), 5.12 (s, 2 H, C₆H₄CH₂O), 6.41 (s, 1 H, (MeO)₂C₆H₃), 6.92 (s, 2 H, (MeO)₂C₆H₃), 7.22 (d, 2 H, J = 7.2 Hz, C₆H₄CH₂), 7.53 (d, 2 H, J = 7.2 Hz, C₆H₄CH₂). Mn = 2,140 g/mol, polydispersity index (PDI) = 1.13 (GPC); Mₙ = 1,820 g/mol, polydispersity index (PDI) = 1.09 (MALDI-TOF).

Poly-2i: Lithium (4-imidazolo-1-yl)phenolate was generated from 0.019 g (0.12 mmol) of (4-imidazolo-1-yl)phenol and 0.020 g (0.12 mmol) of LiN(SiMe₃)₂; 87% isolated yield. ¹H NMR (CDCl₃/CD₃OD/CD₃COOD 20:3:15): δ 1.49, 1.64 (br s, 179 H, -CH(CH₂)₆CH-), 4.17, 4.42 (br s, 16 H, -CH(CH₂)₆CH-), 5.13 (s, 2 H, OCH₂), 7.08 (d, 2 H, J = 8.8 Hz, -C₆H₄O-), 7.50-7.92 (m, 10 H, -C₆H₄O-, CH₂C₆H₄, -NCH=CHN=CH-, CHCl₃), 8.98 (s, 1 H, -NCH=CHN=CH-). Mn = 1,940 g/mol, polydispersity index (PDI) = 1.07 (GPC); Mₙ = 1,310 g/mol, polydispersity index (PDI) = 1.04 (MALDI-TOF).

Synthesis of polymer poly-2j.

To a solution of a 0.153 g (1.0 mmol) of 2 in ca. 3 ml of THF 0.019 g (0.1 mmol) (4-chloromethyl)benzoyl chloride was added. In a separate vial 0.042 g (0.25 mmol) of LiN(SiMe₃)₂ was dissolved in 1 ml of THF, and the solution was added to the stirred solution of monomer and co-initiator. The reaction mixture was stirred for 1 h, whereupon all the volatiles were removed in vacuo. The solid was dissolved in 1 ml of DMSO-d₆ and irradiated in a microwave reactor (CEM Discover) at 150 °C for 30 minutes in a sealed tube. The completeness of conversion was confirmed by ¹H NMR spectroscopy. Subsequently, the product was precipitated from the DMSO solution by addition of 15 ml of Et₂O; the precipitate was collected after centrifugation. The precipitate was dried under vacuum, re-dissolved in 3 ml of AcOH and
precipitated by addition of 15 ml of acetone/H₂O (1:1) mixture. The resulting polymer precipitate was dried under high vacuum at ambient temperature to yield 0.178 g (97%) of poly-2j.

¹H NMR (DMSO-d₆): δ 1.41 (br s, 117 H, -CH(CH₂)₆CH-), 2.19, 2.60 (br s, 14 H, -CH(CH₂)₆CH-, DMSO-d₆), 3.96, 4.19 (br s, 14 H, -CH(CH₂)₆CH-, DMSO-d₆), 6.86-8.16 (m, 11 H, NH), 7.82 (d, 4 H, J = 6.0 Hz, C₆H₄), 9.96 (s, 1 H, C(=O)H). Mₙ = 1,380 g/mol, polydispersity index (PDI) = 1.07 (GPC); Mₙ = 1,340 g/mol, polydispersity index (PDI) = 1.04 (MALDI-TOF).

Model compound S1. To a solution of 1.0 g (5.3 mmol) of (4-chloromethyl)benzoyl chloride in 100 ml of CH₂Cl₂, 1.21 ml (10.6 mmol) of cyclohexylamine was added dropwise at 0 °C. The reaction mixture was allowed to warm up to ambient temperature and stirred overnight, whereupon it was poured into 200 ml of cold water. Organic layer was separated, dried over anhydrous MgSO₄, and after filtration all the volatiles were removed in vacuo. The residue was crystallized from 10 ml of EtOH to yield 0.99 g (74%) compound S1 as white powder: mp = 183.5-184.5°C. ¹H NMR (CDCl₃): δ 1.14 – 2.01 (m, 10 H, Cy), 3.94 (m, 1 H, Cy), 4.55 (s, 2 H, ClCH₂), 5.98 (d, 1 H, J = 6.3 Hz, NH), 7.41 (d, 2 H, J = 7.8 Hz, p-C₆H₅), 7.32 (t, 2 H, J = 2.7 Hz, m-C₆H₅), 7.47, 7.62, 7.84 (d, 2 H, o-C₆H₅, CH₂C₆H₄). HRMS: m/z (ESI) calc. [M+Na]⁺ 252.12, found [M+Na]⁺ 252.12.

Model compound S2. To a solution of 0.154 g (0.60 mmol) of S1 in 10 ml of THF, 0.60 mmol of the (4-imidazolo-1-yl)phenolate, generated from 0.097 g (0.60 mmol) of (4-imidazolo-1-yl)phenol and 0.102 g (0.60 mmol) of LiN(SiMe₃)₂, was added in c.a. 4 ml of DMAc, and the reaction mixture was stirred for 5 h at ambient temperature. Then the mixture was poured into 20 ml of cold water. Organic layer was separated, dried over anhydrous MgSO₄ and all the volatiles
were removed in vacuo. The residue was crystallized from 5 ml of EtOH to yield 0.205 g (91%) compound S2 as a white powder: \(^1\)H NMR (CDCl\(_3\)/CD\(_3\)OD/CD\(_3\)COOD 20:3:15): \(\delta\) 1.034 – 1.88 (m, 10 H, Cy), 3.77 (m, 1 H, Cy), 4.55 (s, 2 H, ClCH\(_2\)), 5.07 (s, 2 H, OCH\(_2\)), 7.01, 7.69 (d, 2 H, J = 9.0 Hz, OCH\(_2\)C\(_6\)H\(_4\)), 7.40 (m, 6 H, -C\(_6\)H\(_4\)O-, NCH=CHN=CH-), 8.73 (s, 1 H, -NCH=CHN=CH-). \(^{13}\)C NMR (CDCl\(_3\)): \(\delta\) 24.7, 25.4, 33.1, 48.6 (Cy), 69.7 (OCH\(_2\)C\(_6\)H\(_4\)), 115.9, 123.2, 127.2, 127.3, 134.7, 139.7, 157.8, 168.7 (OCH\(_2\)C\(_6\)H\(_4\), -C\(_6\)H\(_4\)O-, NCH=CHN=CH-), 166.0 (NHC=O). HRMS: m/z (ESI) calc. \([M+Na]^+\) 376.20, found \([M+Na]^+\) 376.20.

In a test reaction, compound S1 was found to be unreactive when combined with β-lactamate anion derived from 2 in THF under conditions identical to those for the polymerization. This result suggests that the benzylic chloride at the N-terminus of poly-2c is intact during the polymerization because of the similar reactivity of the benzylic chloride in S1 to that in poly-2c.

In a test reaction, compound S1, lithium (4-imidazolo-1-yl)phenolate and the β-lactamate anion derived from 2 were combined in a 1:1:1 ratio. This reaction produced poly-(cyclooctyl-β-lactam) with broad polydispersity (PDI = 2.4, as estimated by MALDI-TOF MS) and compound S2 in ~100% yield (estimated by 1H NMR). This result supports our conclusion that the benzylic chloride functional group, as found in S1 and poly-2c, does not undergo reaction with β-lactamate anions; however, this benzylic chloride does react with other nucleophiles, such as the phenolate used in this experiment.

Supporting Information

Part Two

NMR, MALDI-TOF, UV and GPC characterization data
Poly-2a

$M_n$ (NMR) $\approx 1170$

$^1$H NMR spectrum for poly-2a;
300 MHz, CDCl$_3$/CD$_3$OD/CD$_3$CO$_2$D 20:3:15
MALDI TOF spectrum for poly-2a (Mₙ = 1870, PDI = 1.08)
Isotope pattern of the 1023.3 Da oligomer ([M+Li]+) of poly-2a (n = 4)
M_n (observed) 1,900 g/mol
M_n (calcd) 1,785 g/mol
polydispersity index (PDI) = 1.22

GPC chromatograph for poly-2a in THF
RI detection, ViscoGEL GMH_MR-H columns, 1.0 mL/min, PMMA standard
1H NMR spectrum for poly-2b;
300 MHz, CDCl$_3$/CD$_3$OD/CD$_3$CO$_2$D 20:3:15

Poly-2b
$M_n$ (NMR) ≈ 930

$\text{tBuCHMeCOOH}$

-S$_3$H$_4$, CHCl$_3$
MALDI TOF spectrum for poly-2b (M_n = 1210, PDI = 1.05)

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</table>
Isotope pattern of the 1085.3 Da oligomer ([M+Li]+) of poly-2b (n = 5)
$M_n$ (observed) 1,350 g/mol
$M_n$ (calcd) 1,650 g/mol
polydispersity index (PDI) = 1.22

GPC chromatograph for poly-2b in THF
RI detection, ViscoGEL GMH$_{HR}$-H columns, 1.0 mL/min, PMMA standard
$\text{-C}_6\text{H}_4^-, \text{CHCl}_3$

**Poly-2c**

$M_n (\text{NMR}) \approx 1070$

$^1\text{H} \text{ NMR spectrum for poly-2c; 300 MHz, CDCl}_3/\text{CD}_3\text{OD}/\text{CD}_3\text{CO}_2\text{D 20:3:15}$
**Poly-2c**

MALDI TOF spectrum for poly-2c ($M_n = 1480$, PDI = 1.04)

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<td>1689</td>
</tr>
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<td>10</td>
<td>1842</td>
</tr>
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</table>
Mₙ (observed) 1,310 g/mol
Mₙ (calcd) 1,233 g/mol
polydispersity index (PDI) = 1.07

GPC chromatograph for poly-2c in THF
RI detection, ViscoGEL GMH₉₅-H columns, 1.0 mL/min, PMMA standard
\[ \text{CD3COOH} \cdot \text{-C6H4-}, \text{CHCl3} \]

\[
\begin{align*}
\text{Me}_2\text{N-} & \quad \text{CH}_3 \quad \text{COOH} \\
\text{Me}_2\text{C=O} & \\
\text{pentane} & \quad \text{-CH(\text{CH}_2)_6\text{CH-}} \\
\end{align*}
\]

\[ \text{Poly-2d} \]

\[ M_n (\text{NMR}) \approx 1220 \]

\[ ^1\text{H NMR spectrum for poly-2d; 300 MHz, CDCl}_3/\text{CD}_3\text{OD/CD}_3\text{CO}_2\text{D 20:3:15} \]
MALDI TOF spectrum for poly-2d (Mₙ = 1420, PDI = 1.08)

<table>
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Isotope pattern of the 1255.5 Da oligomer ([M+Li]\(^+\)) of poly-2d (n = 6)
$\text{M}_n$ (observed) 1,480 g/mol
$\text{M}_n$ (calcd) 1,647 g/mol
polydispersity index (PDI) = 1.22

GPC chromatograph for poly-2d in THF
RI detection, ViscoGEL GMH$_{HR}$-H columns, 1.0 mL/min, PMMA standard
$\text{-C}_6\text{H}_4^-, \text{CHCl}_3$

Poly-2e

$M_n \text{ (NMR)} \approx 1220$

$\text{CH}_3\text{COOH}$

$\text{Me}_2\text{C}=O$

$\text{CD}_3\text{COOH}$

$\text{Mn (NMR)} = 1220$

$\text{CH}_3\text{COOH}$

$\text{Me}_2\text{C}=O$

$\text{CD}_3\text{COOH}$

$\text{Mn (NMR)} = 1220$

$\text{CH}_3\text{COOH}$

$\text{Me}_2\text{C}=O$

$\text{CD}_3\text{COOH}$

$\text{Mn (NMR)} = 1220$

$\text{CH}_3\text{COOH}$

$\text{Me}_2\text{C}=O$

$\text{CD}_3\text{COOH}$

$\text{Mn (NMR)} = 1220$

$\text{CH}_3\text{COOH}$

$\text{Me}_2\text{C}=O$

$\text{CD}_3\text{COOH}$

$\text{Mn (NMR)} = 1220$

$\text{CH}_3\text{COOH}$

$\text{Me}_2\text{C}=O$

$\text{CD}_3\text{COOH}$

$\text{Mn (NMR)} = 1220$

$\text{CH}_3\text{COOH}$

$\text{Me}_2\text{C}=O$

$\text{CD}_3\text{COOH}$

$\text{Mn (NMR)} = 1220$

$\text{CH}_3\text{COOH}$

$\text{Me}_2\text{C}=O$

$\text{CD}_3\text{COOH}$

$\text{Mn (NMR)} = 1220$

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$\text{Me}_2\text{C}=O$

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$\text{Mn (NMR)} = 1220$

$\text{CH}_3\text{COOH}$

$\text{Me}_2\text{C}=O$

$\text{CD}_3\text{COOH}$

$\text{Mn (NMR)} = 1220$
MALDI TOF spectrum for poly-2e ($M_n = 1240$, PDI = 1.07)
Isotope pattern of the 1351.7 Da oligomer ([M+2H+Li-N₂]⁺) of poly-2e (n = 7)
$M_n$ (observed) 1,390 g/mol
$M_n$ (calcd) 1,691 g/mol
polydispersity index (PDI) = 1.10

GPC chromatograph for poly-2e in THF
RI detection, ViscoGEL GMH$_{HR}$-H columns, 1.0 mL/min, PMMA standard
$\text{CD}_3\text{COOH}$

$\text{-C}_6\text{H}_4\text{-CHCl}_3$

$\text{CH}_3\text{COOH}$

$\text{Me}_2\text{C}=\text{O}$

$\text{-CH(CH}_2\text{)}_6\text{CH-}$

$\text{Poly-2f}$

$M_n (\text{NMR}) \approx 1160$

$\text{1H NMR spectrum for poly-2f; 300 MHz, CDCl}_3/\text{CD}_3\text{OD/CD}_3\text{CO}_2\text{D 20:3:15}$
MALDI TOF spectrum for poly-2f ($M_n = 1920$, PDI = 1.11)
Isotope pattern of the 1926.2 Da oligomer ([M+Li]⁺) of poly-2f (n = 9)
UV spectrum for poly-2f; CHCl₃
Poly-2f

$M_n$ (observed) 1,800 g/mol
$M_n$ (calcd) 1,764 g/mol
polydispersity index (PDI) = 1.08

GPC chromatograph for poly-2f in THF
RI detection, ViscoGEL GMHHR-H columns, 0.8 mL/min, PMMA standard
Poly-2g

$M_n (NMR) \approx 1050$

$^1H$ NMR spectrum for polymer poly-2g;
300 MHz, CDCl$_3$/CD$_3$OD/CD$_3$CO$_2$D 20:3:15
MALDI TOF spectrum for poly-2g ($M_n = 1020, \text{PDI} = 1.04$)
Isotope pattern of the 993.3 Da oligomer ([M+Li]+) of poly-2g (n = 5)
Poly-2g

$M_n$ (observed) 1,080 g/mol
$M_n$ (calcd) 1,593 g/mol
polydispersity index (PDI) = 1.05

GPC chromatograph for poly-2g in THF
RI detection, ViscoGEL GMH$_{HR}$-H columns, 0.8 mL/min, PMMA standard
$M_n$ (NMR) $\approx 1720$

$^{1}$H NMR spectrum for poly-2h; 300 MHz, CDCl$_3$/CD$_3$OD/CD$_3$CO$_2$D 20:3:15
MALDI TOF spectrum for poly-2a ($M_n = 1820$, PDI = 1.09).
Isotope pattern of the 1376.8 Da oligomer ([M+Li]^+) of poly-2h (n = 6)
Poly-2h

$M_n$ (observed) 2,140 g/mol
$M_n$ (calcd) 1,799 g/mol
polydispersity index (PDI) = 1.13

GPC chromatograph for poly-2h in THF
RI detection, ViscoGEL GMH$_{HR}$-H columns, 1.0 mL/min, PMMA standard
Poly-2i

$M_n \ (\text{NMR}) \approx 1610 \ \text{CH}_3\text{COOH}$

$\text{Me}_2\text{C}=\text{O}$

$1^H \text{NMR spectrum for poly-2i}; \ 300 \text{ MHz}, \ \text{CDCl}_3/\text{CD}_3\text{OD/CD}_3\text{CO}_2\text{D} \ 20:3:15$
MALDI TOF spectrum for poly-2i ($M_n = 1310$, PDI = 1.04)
Isotope pattern of the 1201.6 Da oligomer ([M+Li]+) of poly-2i (n = 5)
Poly-$2i$

$M_n$ (observed) 1,940 g/mol
$M_n$ (calcd) 1,806 g/mol
polydispersity index (PDI) = 1.07

GPC chromatograph for poly-$2i$ in THF
RI detection, ViscoGEL GMH$_{HR}$-H columns, 1.0 mL/min, PMMA standard
Poly-2j

$M_n$ (NMR) $\approx 1100$

$^1H$ NMR spectrum for poly-2j; 300 MHz, DMSO-d$_6$
MALDI TOF spectrum for poly-2j (Mₙ = 1340, PDI = 1.04)
Isotope pattern of the 1210.9 Da oligomer ([M+Li]+) of poly-2j (n = 6)
$M_n$ (observed) 1,380 g/mol
$M_n$ (calcd) 1,630 g/mol
polydispersity index (PDI) = 1.07

GPC chromatograph for poly-2j in THF
RI detection, ViscoGEL GMH$_{HR}$-H columns, 1.0 mL/min, PMMA standard
Polymer poly-3

$M_n (\text{NMR}) \approx 1100$

$^1H$ NMR spectrum for polymer poly-3;
300 MHz, CDCl$_3$/CD$_3$OD/CD$_3$CO$_2$D 20:3:15
MALDI TOF spectrum for poly-3 (Mn = 1840, PDI = 1.12)
Isotope pattern of the 1631.4 Da oligomer ([M+Li]^+) of poly-3 (n = 6)
$M_n$ (observed) 1,970 g/mol
$M_n$ (calcd) 2,175 g/mol
polydispersity index (PDI) = 1.10

GPC chromatograph for poly-3 in THF
RI detection, ViscoGEL GMH$_{HR}$-H columns, 1.0 mL/min, PMMA standard
Poly-4 doesn’t produce a MALDI TOF mass-spectrum.

$\text{Poly-4} \quad M_n (\text{NMR}) \approx 1510$

$^1\text{H NMR spectrum for polymer poly-4; 300 MHz, CDCl}_3$

Poly-4 doesn’t produce a MALDI TOF mass-spectrum.
$M_n$ (observed) 1,700 g/mol
$M_n$ (calcd) 2,1250 g/mol
polydispersity index (PDI) = 1.16

GPC chromatograph for poly-4 in THF
RI detection, ViscoGEL GMH$_{HR}$-H columns, 1.0 mL/min, PMMA standard
Poly-5 doesn’t produce a MALDI TOF mass-spectrum.

$M_n \text{ (NMR)} \approx 1780$
Poly-5

$M_n$ (observed) 1,820 g/mol
$M_n$ (calcd) 2,265 g/mol
polydispersity index (PDI) = 1.11

GPC chromatograph for poly-5 in THF
RI detection, ViscoGEL GMH$_{HR}$-H columns, 1.0 mL/min, PMMA standard
Poly-9

$M_n$ (NMR) ≈ 3070

$^{1}H$ NMR spectrum for poly-9 from deprotection of poly-5; 300 MHz, D$_2$O
**Poly-7**

\[ \text{CD}_3\text{COOH} \]

\[ \text{tBu}, \text{Me} \]

\[ \text{Phth}, \text{-C}_6\text{H}_4-, \text{CHCl}_3 \]

\[ \text{CH}_3\text{COOD} \]

\[ -\text{CH}_2\text{CH}-, \text{CD}_2\text{HOD} \]

**1H NMR spectrum for poly-7; 300 MHz, CDCl\textsubscript{3}/CD\textsubscript{3}OD/CD\textsubscript{3}CO\textsubscript{2}D 20:3:15**

Poly-7 doesn't produce a MALDI TOF mass-spectrum.
Mn (observed) 6,804 g/mol
Mn (calcd) 5,327 g/mol
polydispersity index (PDI) = 1.01

GPC chromatograph for poly-7 in THF
RI detection, Styragel HR4E columns, 1.0 mL/min, dn/dc = 0.133
Poly-9

$M_n$ (NMR) $\approx 2470$

$^{1}H$ NMR spectrum for poly-9 from deprotection of poly-7; 300 MHz, $D_2O$
Poly(2) (black):
Mₙ (observed) 3,330 g/mol
Mₙ (calcd) 3,225 g/mol
PDI = 1.07

Poly(2)-b-poly(3) (red):
Mₙ (observed) 10,110 g/mol
Mₙ (calcd) 9,609 g/mol
PDI = 1.05

GPC chromatographs for poly(2) (black) and block copolymer poly(2)-b-poly(3) (red) in THF
RI detection, Styrage HR4E columns, 1.0 mL/min, dn/dc = 0.138