Electronic Supplementary Material (ESI) for Polymer Chemistry

Supplementary Information

Lysine-Based Dendronized Polymers with Preferred Chirality

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Contents

Nomenclature: *S* and *R* represent the absolute configurations of the chiral centers from the lysine units in the order from the core to the periphery.

Experimental Section

Materials. Compound **1** was purchased from GL Biochem Ltd. Compounds ***SS*-2a**, ***SS*-2b** and ***SS*-3a** were synthesized according to previous report.[1] Azobis (isobutyronitrile) (AIBN) was recrystallized twice from methanol. Triethyl amine (TEA) and diisopropylethyl amine (DiPEA) were dried over NaOH pallets. Tetrahydrofuran (THF) was heated at reflux over lithium aluminum hydride. Dichloromethane (DCM) was dried over CaH_2. Methacryloyl chloride (MAC) was freshly distilled before use. Other reagents and solvents were purchased and used as received unless otherwise stated. All reactions were run under a nitrogen atmosphere. Macherey-Nagel precoated TLC plates (silica gel 60 G/UV254, 0.25 mm) were used for thin-layer chromatography (TLC) analysis. Silica gel 60 M (Macherey-Nagel, 0.04-0.063 mm, 200-300 mesh) was used as the stationary phase for column chromatography.

Instrumentation and Measurements. *^{1}H NMR spectra* were recorded on a Bruker AV 500 (^{1}H: 500 MHz) spectrometer in $CDCl_3$, DMSO-[d_6], D_2O and methanol-[d_4] solutions at room temperature. *High resolution MALDI-TOF-MS analyses* were performed on IonSpec Ultra instruments. *Gel Permeation Chromatography (GPC) measurements* were carried out on a Waters GPC e2695 instrument with 3 column set (Styragel HR3 + HR4 + HR5) equipped with refractive index detector (Waters 2414), and DMF (containing 1 g·L^{-1} LiBr) as eluent at 45 °C. The calibration was performed with poly(methyl methacrylate) standards in the range of M_p = 2580 to 981000 (Polymer Standards Service-USA Inc). *Circular dichroism measurements* were performed on a JASCO J-815 spectropolarimeter with a thermo-controlled 1-mm quartz cell (10 accumulations, continues scanning mode, scanning speed 100 nm·min^{-1}, data pitch: 0.5 nm, response: 1 sec, band width: 2.0 nm). Dynamic light scattering (DLS) measurements were performed on the DynaPro Nanostar instrument (Wyatt Technology Corporation, He-Ne laser, λ_0 = 658 nm).

General Procedure for Boc Deprotection (A). 25% of HCl (10.00 mmol) was added into a solution of Boc-protected lysine compound (1.00 mmol) in THF (25 mL) at 0 ^{o}C, and

then the mixture was stirred at room temperature overnight. Evaporation of all solvents under vacuum afforded the corresponding ammonium salt.

General Procedure for Amide Coupling (B). (*R*) or (*S*)-Boc-Lys(Boc)-ONp (**1**) (4.40 mmol) in DMF (30 mL) was added dropwise into a solution of lysinol ammonium (1.00 mmol) and DiPEA (10.00 mmol) in H_2O (10 mL) and DMF (10 mL) at 0 ^oC. The mixture was kept at that temperature for 2 h, and then allowed to react overnight at room temperature. Evaporation of the solvents under vacuum at room temperature gave a residue. It was dissolved with DCM, and washed successively with $NaHCO_3$ and brine. All aqueous phases were extracted with DCM three times. The combined organic phases were dried over $MgSO_4$. Purification with column chromatography afforded the product as white solid.

General Procedure for Macromonomer Synthesis (C). MAC (2.00 mmol) in THF (10 mL) was dropped into a solution of the dendron alcohol (1.00 mmol), triethyl amine (10.00 mmol), and 4-dimethylaminopyridine (0.10 g) in dry THF (25 mL) at 0 ^oC. The mixture was stirred for 2 h at that temperature, followed by overnight at room temperature. Evaporation of the solvents under vacuum at room temperature gave a residue, which was dissolved with DCM. It was washed successively with saturated $NaHCO_3$ and brine. All aqueous phases were extracted with DCM three times, and the combined organic phases were dried over $MgSO_4$. After filtration, the solvent was evaporated under vacuum at room temperature. Purification with column chromatography afforded the white solid, which was stored at fridge before use.

General Procedure for Radical Polymerization (D). A solution of macromonomer **MG3** (0.40 g) and AIBN (0.5 wt% based on the macromonomer) in DMF (0.2 mL) inside a Schlenk tube was degassed by several freeze-pump-thaw cycles, and then kept at 80 ^oC with stirring for a predetermined time. The polymerization was stopped by cooling, and the polymer was dissolved in DCM and purified by column chromatography (silica gel, DCM eluent), which afforded **PG3** as a white foam.

(*S*)-2,6-bis(((*S*)-1,5-bisaminopentylcarbonyl)amino)hexyl alcohol × 4HCl (***SS*-3b**). According to the general procedure A from ***SS*-3a** (1.00 g, 1.27 mmol) and 25% HCl (1.85 g, 12.70 mmol), compound ***SS*-3b** was yielded as a white foam (0.68 g, 100%). ^{1}H NMR (D_2O): δ = 1.24-1.60 (m, 10H, CH_2), 1.61-1.73 (m, 4H, CH_2), 1.81-1.94 (m, 4H, CH_2), 2.91-3.01 (m, 4H, CH_2), 3.13-3.27 (m, 2H, CH_2), 3.43-3.51 (m, 1H, CH_2), 3.55-3.63 (m, 1H, CH_2), 3.83-3.99 (m, 3H, CH). HR-MS: *m/z*: calcd. for $C_{18}H_{40}N_6O_3Na$ $[M+Na]^+$ 411.3060; found 411.5056.

(*S*)-2,6-bis(((*S*)-1,5-bis(((*S*)-1,5-bis(*tert*-butoxycarbonylamino)pentylcarbonyl)amino)pentylcarbonyl)amino)hexyl alcohol (***SSS*-4**). The title compound was synthesized according to the general procedure B from ***SS*-3b** (0.60 g, 1.12 mmol), DiPEA (1.45 g, 11.20 mmol) and (*S*)- Boc-Lys(Boc)-ONp (2.30 g, 4.93 mmol) in a mixed solvent of DMF (30 mL) and H_2O (10 mL). Purification by column chromatography with ethyl acetate, and then ethyl acetate/MeOH (100/6, v/v) afforded ***SSS*-4** as a white foam (1.34 g, 70%). ^{1}H NMR ($CDCl_3$): δ = 1.10-1.56 (m, 102H, CH_2+CH_3), 1.56-1.80 (m, 12H, CH_2), 2.90-3.72 (m, 17H, CH_2+OH), 3.79-3.97 (m, 1H, CH), 4.21-4.48 (m, 6H, CH), 4.75-4.91 (br, 2H, NH), 5.06-5.30 (br, 2H, NH), 5.54-6.00 (br, 4H, NH), 6.99-7.21 (br, 2H, NH), 7.40-7.89 (br, 4H, NH). HR-MS: *m/z*: calcd. for $C_{82}H_{152}N_{14}O_{23}Na$ $[M+Na]^+$ 1724.1052; found 1723.9626.

(*S*)-2,6-bis(((*S*)-1,5-bis(((*S*)-1,5-bis(*tert*-butoxycarbonylamino)pentylcarbonyl)amino)pentylcarbonyl)amino)hexyl Methacrylate (***SSS*-MG3**). The title compound was synthesized according to the general procedure C from ***SSS*-4** (1.00 g, 0.59 mmol), TEA (0.60 g, 5.90 mmol), DMAP (0.10 g), and MAC (0.12 g, 1.18 mmol). Purification by column chromatography with DCM/MeOH (20/1, v/v) afforded ***SSS*-MG3** as a white foam (0.94 g, 90%), which was stored in the fridge before use. ^{1}H NMR ($CDCl_3$): δ = 1.02-1.54 (m, 102H, CH_2+CH_3), 1.54-1.82 (m, 12H, CH_2), 1.90 (s, 3H, CH_3), 2.80-3.17 (m, 12H, CH_2), 3.28-3.59 (m, 2H, CH_2), 3.94-4.55 (m, 9H, CH+CH_2), 4.72-4.92 (br, 2H, NH), 5.15-5.35 (br, 2H, NH), 5.54 (s, 1H, CH_2), 5.57-6.06 (br, 4H, NH), 6.08 (s, 1H, CH_2), 6.74-7.22 (br, 2H, NH), 7.35-8.00 (br, 4H, NH). HR-MS: *m/z*: calcd. for $C_{86}H_{156}N_{14}O_{24}Na$ $[M+Na]^+$ 1792.1315;

found 1792.1635.

(*S*)-2,6-bis(((*S*)-1,5-bis(((*R*)-1,5-bis(*tert*-butoxycarbonylamino)pentylcarbonyl)amino)pentylcarbonyl)amino)hexyl alcohol (***SSR*-4**). The title compound was synthesized according to the general procedure B from ***SS*-3b** (0.60 g, 1.12 mmol), DiPEA (1.45 g, 11.20 mmol) and (*R*)-Boc-Lys(Boc)-ONp (2.30 g, 4.93 mmol) in a mixed solvent of DMF (30 mL) and H_2O (10 mL). Purification by column chromatography with ethyl acetate, and then ethyl acetate/MeOH (100/6, v/v) afforded ***SSR*-4** as a white foam (1.34 g, 70%). ^{1}H NMR ($CDCl_3$): δ = 0.92-1.57 (m, 102H, CH_2+CH_3), 1.57-1.92 (m, 12H, CH_2), 2.97-3.23 (m, 12H, CH_2), 3.23-3.73 (m, 5H, CH_2+OH), 3.76-3.96 (m, 1H, CH), 3.96-4.25 (m, 4H, CH), 4.25-4.56 (m, 2H, CH), 4.65-5.20 (br, 4H, NH), 5.52-6.04 (br, 4H, NH), 6.77-7.22 (br, 4H, NH), 7.42-7.71 (br, 2H, NH).

(*S*)-2,6-bis(((*S*)-1,5-bis(((*R*)-1,5-bis(*tert*-butoxycarbonylamino)pentylcarbonyl)amino)pentylcarbonyl)amino)hexyl Methacrylate (***SSR*-MG3**). The title compound was synthesized according to the general procedure C from ***SSR*-4** (1.20 g, 0.71 mmol), TEA (0.72 g, 7.10 mmol), DMAP (0.10 g), and MAC (0.15 g, 1.42 mmol). Purification by column chromatography with DCM/MeOH (20/1, v/v) afforded ***SSR*-MG3** as a white foam (1.13 g, 90%), which was stored in the fridge before use. ^{1}H NMR ($CDCl_3$): δ = 1.00-1.57 (m, 102H, CH_2+CH_3), 1.57-1.86 (m, 12H, CH_2), 1.93 (s, 3H, CH_3), 2.79-3.48 (m, 14H, CH_2), 3.79-4.54 (m, 9H, CH+CH_2), 4.68-5.15 (br, 4H, NH), 5.40-5.91 (m, 5H, NH+CH_2), 6.12 (s, 1H, CH_2), 6.70-7.22 (br, 4H, NH), 7.34-7.81 (br, 2H, NH). MS: *m/z*: calcd. for $C_{86}H_{156}N_{14}O_{24}Na$ $[M+Na]^+$ 1792.13; found 1793.51.

(*R*)-2,6-bis(*tert*-butoxycarbonylamino)hexyl alcohol (***R*-2a**). $NaBH_4$ (0.49 g, 12.83 mmol) and LiCl (0.82 g, 19.25 mmol) was added into a stirred solution of ***R*-1** (2.00 g, 4.28 mmol) in dry THF (80 mL) at -10 ^{o}C. The mixture was stirred for 2 h at -10 ^{o}C, followed by overnight at room temperature. The reaction was terminated with addition of excess H_2O. Evaporation of the solvents under vacuum at room temperature gave a residue, which was dissolved with DCM. It was washed successively with saturated

$NaHCO_3$ and brine. After the combined organic phase had been dried over $MgSO_4$, purification by column chromatography with hexane/ethyl acetate (2/1, v/v) afforded ***R*-2a** as a colorless oil (1.35 g, 95%). ^{1}H NMR ($CDCl_3$): δ = 1.27-1.52 (m, 23H, CH_2+CH_3), 1.52-1.64 (m, 1H, CH_2), 2.97-3.25 (m, 2H, CH_2), 3.45-3.70 (m, 3H, CH+CH_2), 4.49-4.70 (br, 1H, NH), 4.73-4.89 (br, 1H, NH).

(*R*)-2,6-bis-aminohexyl alcohol × 2HCl (***R*-2b**). According to the general procedure A from ***R*-2a** (1.00 g, 3.01 mmol) and 25% HCl (4.39 g, 30.10 mmol), compound ***R*-2b** was yielded as a white foam (0.62 g, 100%). ^{1}H NMR (D_2O): δ = 1.43-1.53 (m, 2H, CH_2), 1.61-1.77 (m, 4H, CH_2), 2.96-3.05 (m, 2H, CH_2), 3.30-3.40 (m, 1H, CH), 3.59-3.68 (m, 1H, CH_2), 3.79-3.87 (m, 1H, CH_2).

(*R*)-2,6-bis(((*S*)-1,5-bis(*tert*-butoxycarbonylamino) pentylcarbonyl)amino)hexyl alcohol (***RS*-3a**). The title compound was synthesized according to the general procedure B from ***R*-2b** (0.50 g, 2.44 mmol), DiPEA (1.58 g, 12.20 mmol) and (*S*)-Boc-Lys(Boc)-ONp (2.51 g, 5.37 mmol) in a mixed solvent of DMF (30 mL) and H_2O (10 mL). Purification by column chromatography with ethyl acetate afforded ***RS*-3a** as a white foam (1.69 g, 88%). ^{1}H NMR ($CDCl_3$): δ = 1.08-1.55 (m, 50H, CH_2+CH_3), 1.56-1.69 (m, 2H, CH_2), 1.69-1.85 (m, 2H, CH_2), 2.97-3.17 (m, 5H, CH_2), 3.35 (br, 1H, OH), 3.47-3.67 (m, 3H, CH_2), 3.74-3.94 (m, 1H, CH), 3.93-4.15 (m, 2H, CH), 4.71-4.98 (br, 2H, NH), 5.35-5.71 (br, 2H, NH), 6.66-7.02 (br, 2H, NH).

(*R*)-2,6-bis(((*S*)-1,5-bisaminopentylcarbonyl)amino)hexyl alcohol × 4HCl (***RS*-3b**). According to the general procedure A from ***RS*-3a** (1.00 g, 1.27 mmol) and 25% HCl (1.85 g, 12.70 mmol), compound ***RS*-3b** was yielded as a white foam (0.68 g, 100%). ^{1}H NMR (D_2O): δ = 1.22-1.63 (m, 10H, CH_2), 1.63-1.77 (m, 4H, CH_2), 1.81-1.97 (m, 4H, CH_2), 2.93-3.04 (m, 4H, CH_2), 3.15-3.27 (m, 2H, CH_2), 3.47-3.55 (m, 1H, CH_2), 3.59-3.68 (m, 1H, CH_2), 3.84-4.00 (m, 3H, CH).

(*R*)-2,6-bis(((*S*)-1,5-bis(((*S*)-1,5-bis(*tert*-butoxycarbonylamino)pentylcarbonyl)amino

)pentylcarbonyl)amino)hexyl alcohol (***RSS*-4**). The title compound was synthesized according to the general procedure B from ***RS*-3b** (0.60 g, 1.12 mmol), DiPEA (1.45 g, 11.20 mmol) and (*S*)- Boc-Lys(Boc)-ONp (2.09 g, 4.48 mmol) in a mixed solvent of DMF (30 mL) and H_2O (10 mL). Purification by column chromatography with ethyl acetate, and then ethyl acetate/MeOH (100/6, v/v) afforded ***RSS*-4** as a white solid (1.34 g, 70%). ^{1}H NMR ($CDCl_3$): δ = 0.95-2.05 (m, 114H, CH_2+CH_3), 2.88-3.23 (m, 12H, CH_2), 3.24-3.70 (m, 5H, CH_2+OH), 3.74-3.94 (m, 1H, CH), 4.03-4.54 (m, 6H, CH), 4.68-4.94 (br, 2H, NH), 4.94-5.18 (br, 2H, NH), 5.50-6.05 (br, 4H, NH), 6.85-7.24 (br, 4H, NH), 7.36-7.75 (br, 2H, NH).

(*R*)-2,6-bis(((*S*)-1,5-bis(((*S*)-1,5-bis(*tert*-butoxycarbonylamino)pentylcarbonyl)amino)pentylcarbonyl)amino)hexyl methacrylate (***RSS*-MG3**). The title compound was synthesized according to general procedure C from ***RSS*-4** (1.10 g, 0.65 mmol), TEA (0.66 g, 6.49 mmol), DMAP (0.10 g), and MAC (0.13 g, 1.30 mmol). Purification by column chromatography with DCM/MeOH (20/1, v/v) afforded ***RSS*-MG3** as a white solid (1.03 g, 90%), which was stored in the fridge before use. ^{1}H NMR ($CDCl_3$): δ = 1.14-1.58 (m, 102H, CH_2+CH_3), 1.58-1.81 (m, 12H, CH_2), 1.92 (s, 3H, CH_3), 2.92-3.20 (m, 12H, CH_2), 3.22-3.50 (m, 2H, CH_2), 3.91-4.41 (m, 9H, CH+CH_2), 4.64-5.16 (br, 4H, NH), 5.50-5.59 (s, 1H, CH_2), 5.59-5.98 (br, 4H, NH), 6.09 (s, 1H, CH_2), 6.87-7.24 (br, partly overlapped with solvent signal, NH). MS: *m/z*: calcd. for $C_{86}H_{156}N_{14}O_{24}Na$ $[M+Na]^+$ 1792.13; found 1792.52.

Poly((*S*)-2,6-bis(((*S*)-1,5-bis(((*S*)-1,5-bis(*tert*-butoxycarbonylamino)pentylcarbonyl)a mino)pentylcarbonyl)amino)hexyl methacrylate) (**SSS-PG3**). The title compound was synthesized according to the general procedure D from ***SSS*-MG3** (0.40 g), AIBN (2.00 mg), DMF (0.2 mL) (8 h at 80 ^{o}C). Purification by column chromatography (silica gel, DCM eluent), which afforded ***SSS*-PG3** as a white foam (0.20 g, 50%). ^{1}H NMR (d_6-DMSO, 80 ^{o}C): δ = 1.27-1.38 (m, CH_2+CH_3), 1.61-1.66 (m, CH_2), 2.91-2.93 (m, CH_2), 3.91 (br, CH+CH_2), 4.27 (br, CH+CH_2), 6.16 (br, NH), 6.38-6.48 (br, NH), 7.39-7.48 (br, NH).

Poly((*S*)-2,6-bis(((*S*)-1,5-bis(((*R*)-1,5-bis(*tert*-butoxycarbonylamino)pentylcarbonyl)amino)pentylcarbonyl)amino)hexyl methacrylate) (***SSR*-PG3**). The title compound was synthesized according to the general procedure D from ***SSR*-MG3** (0.40 g), AIBN (2.00 mg), DMF (0.2 mL) (12 h at 80 ^{o}C). Purification by column chromatography (silica gel, DCM eluent), which afforded ***SSR*-PG3** as a white foam (0.20 g, 50%). ^{1}H NMR (d_6-DMSO, 80 ^{o}C): δ = 1.27-1.30 (m, CH_2+CH_3), 1.64 (m, CH_2), 2.93 (m, CH_2), 3.94 (br, CH+CH_2), 4.23 (br, CH+CH_2), 6.09-6.22 (br, NH), 6.40-6.43 (br, NH), 7.27-7.76 (br, NH).

Poly((*R*)-2,6-bis(((*S*)-1,5-bis(((*S*)-1,5-bis(*tert*-butoxycarbonylamino)pentylcarbonyl)amino)pentylcarbonyl)amino)hexyl Methacrylate) (***RSS*-PG3**). The title compound was synthesized according to the general procedure D from ***RSS*-MG3** (0.30 g), AIBN (1.50 mg), DMF (0.2 mL) (9 h at 80 ^{o}C). Purification by column chromatography (silica gel, DCM eluent), which afforded ***RSS*-PG3** as a white foam (0.16 g, 53%). ^{1}H NMR (d_6-DMSO, 80 ^{o}C): δ = 1.27-1.38 (m, CH_2+CH_3), 1.59-1.63 (m, CH_2), 2.92 (m, CH_2), 3.90 (br, CH+CH_2), 4.27-4.32 (br, CH+CH_2), 6.15 (br, NH), 6.48-6.56 (br, NH), 7.39-7.51 (br, NH).

Reference

S1 A. Zhang, *Macromol. Rapid Commun.*, 2008, **29**, 839.

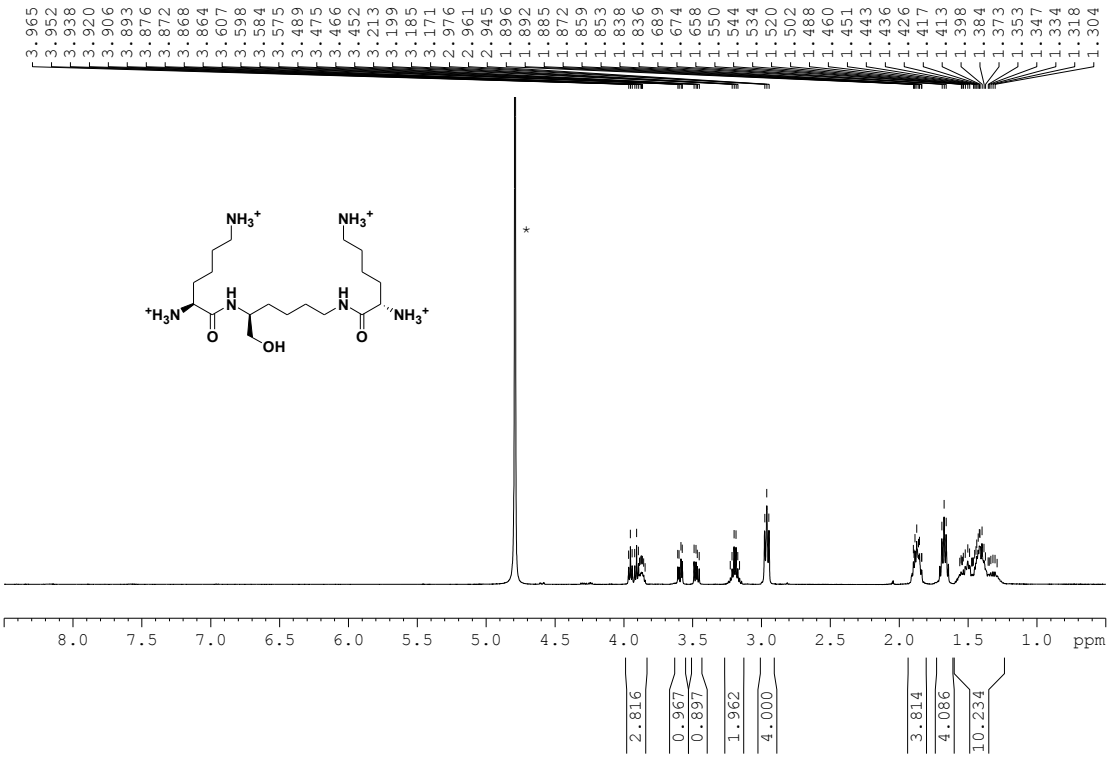

Figure S1. ^{1}H NMR spectrum of compound ***SS*-3b** in D_2O.

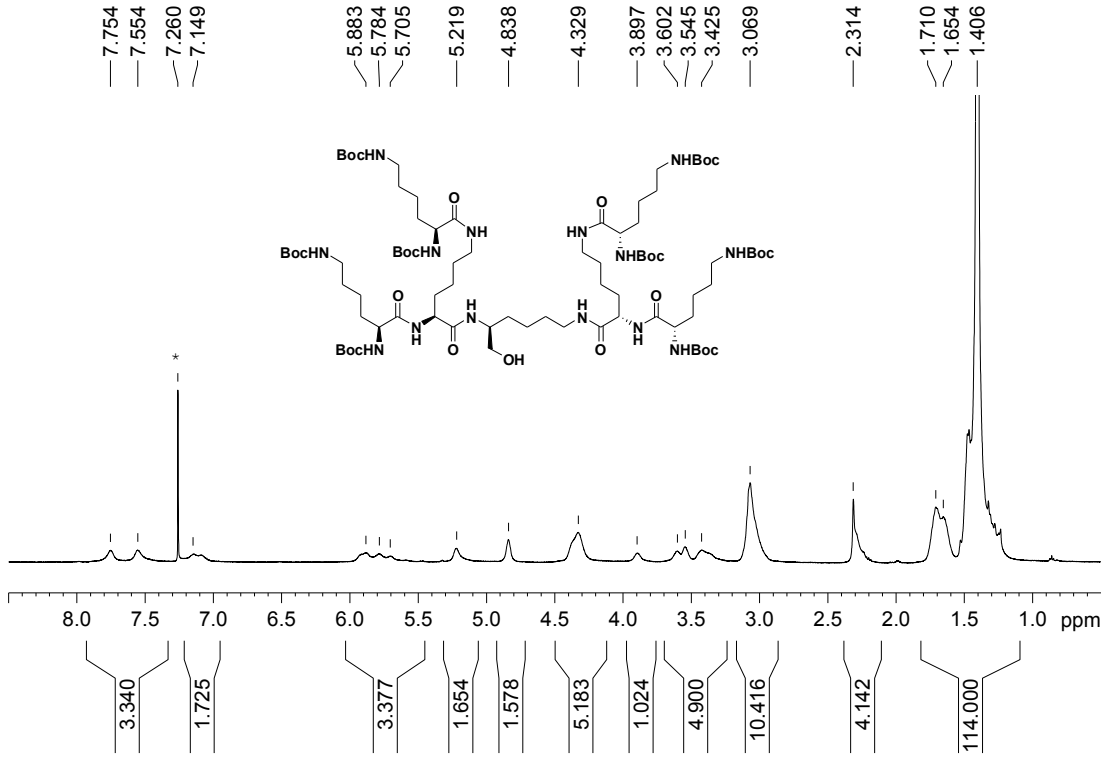

Figure S2. ^{1}H NMR spectrum of compound ***SSS*-4** in $CDCl_3$.

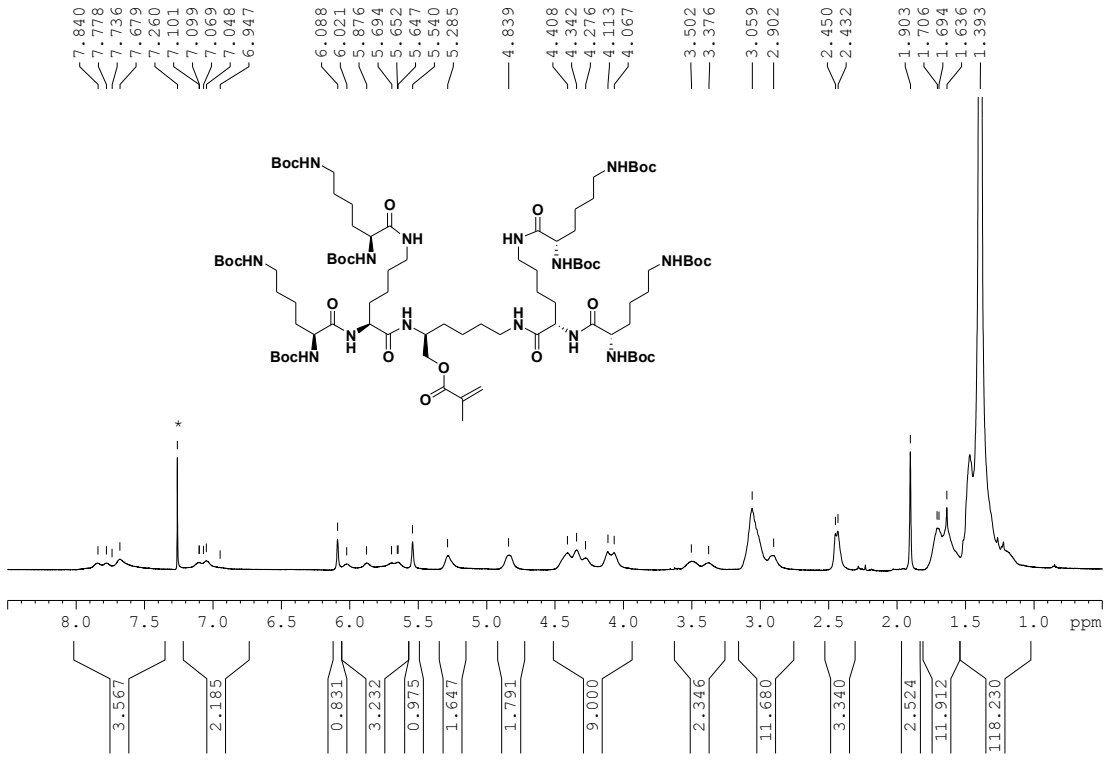

Figure S3. ^{1}H NMR spectrum of compound ***SSS*-MG3** in $CDCl_3$.

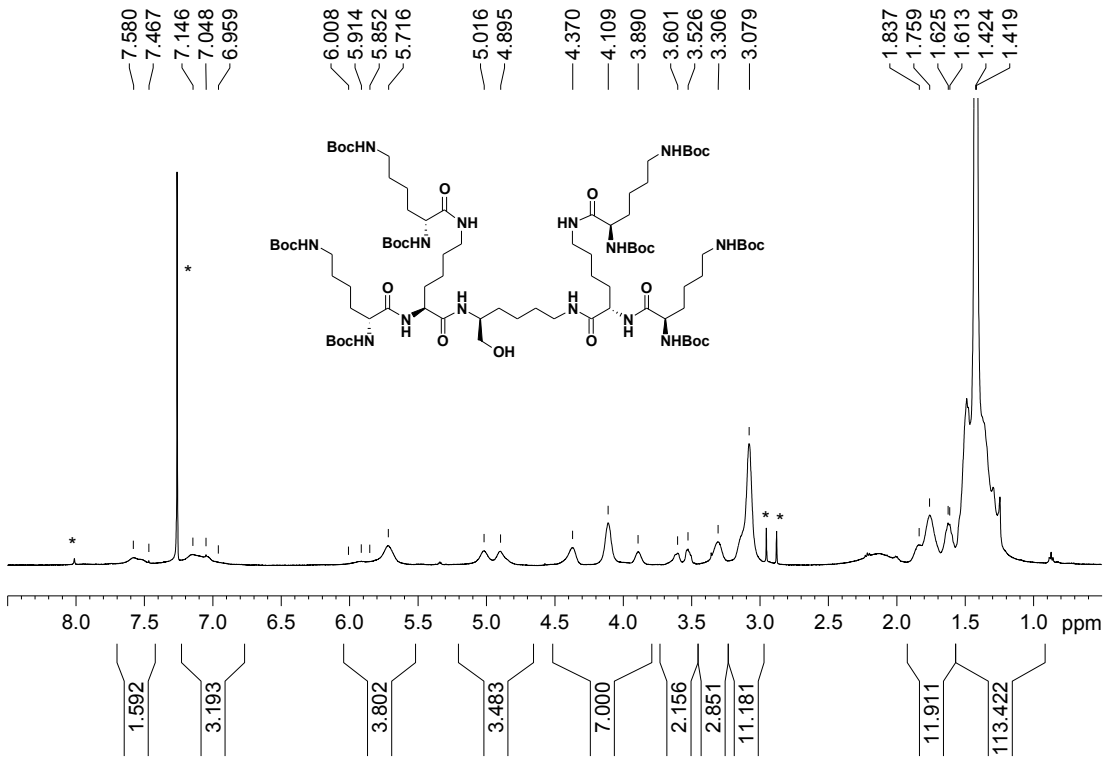

Figure S4. ^{1}H NMR spectrum of compound ***SSR*-4** in $CDCl_3$.

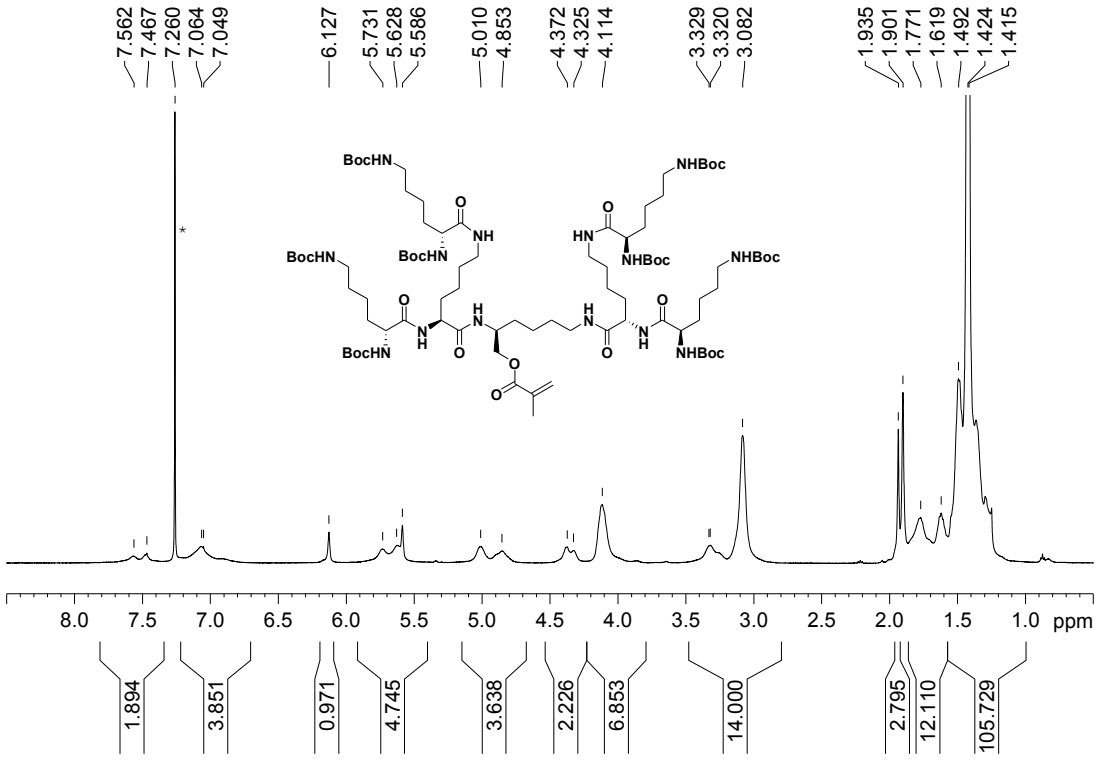

Figure S5. ^{1}H NMR spectrum of compound ***SSR*-MG3** in $CDCl_3$.

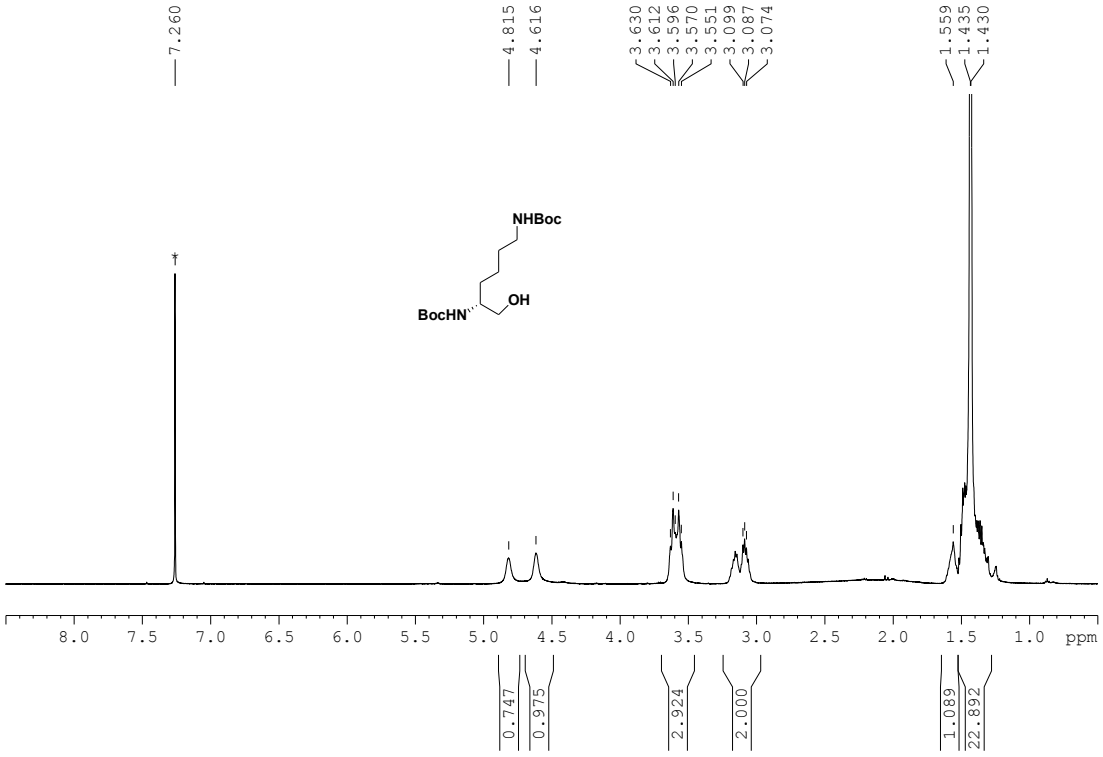

Figure S6. ^{1}H NMR spectrum of compound ***R*-2a** in $CDCl_3$.

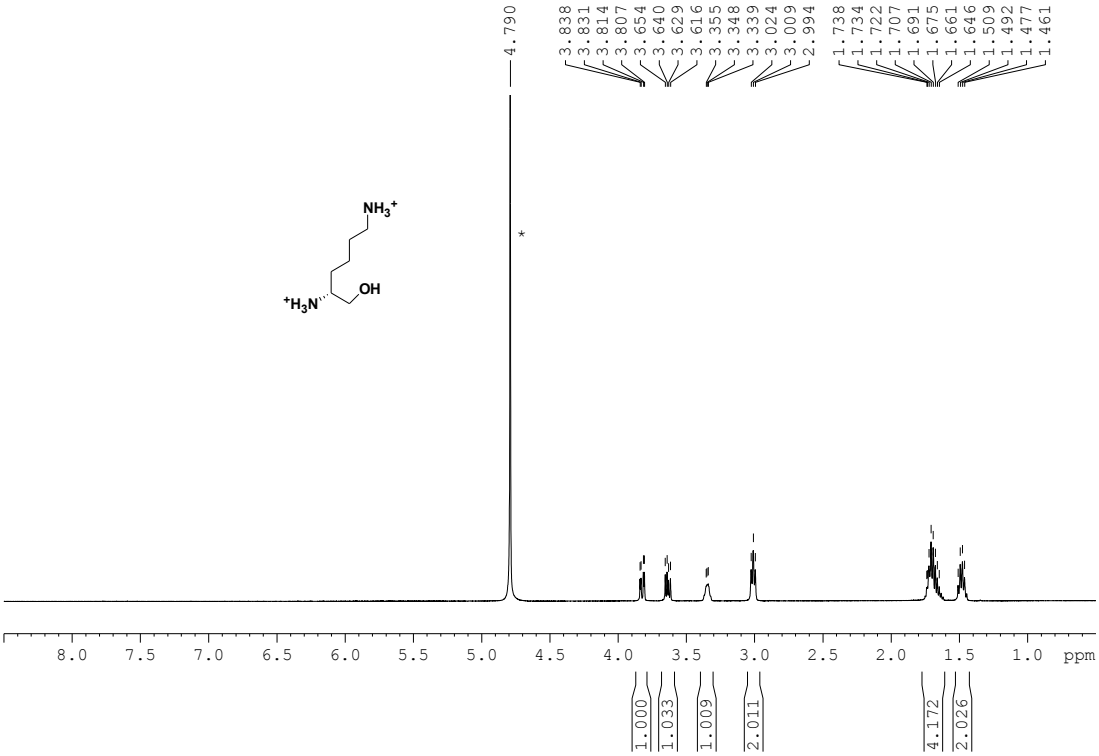

Figure S7. ^{1}H NMR spectrum of compound ***R*-2b** in D_2O.

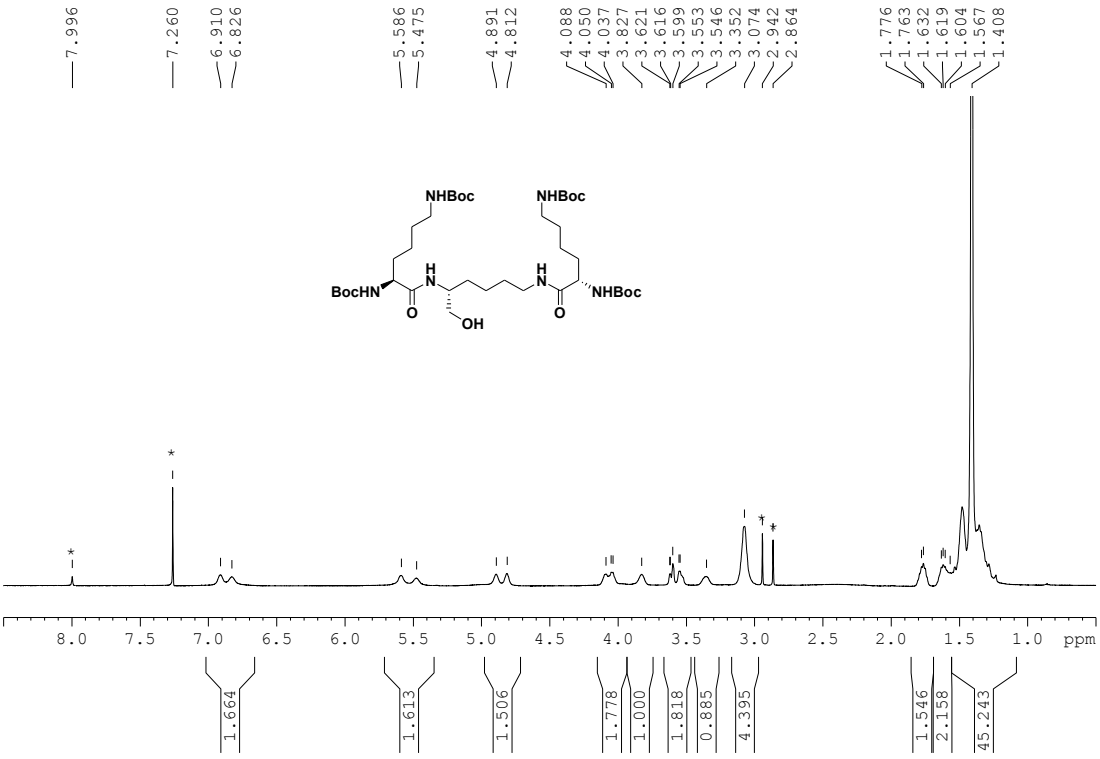

Figure S8. ^{1}H NMR spectrum of compound ***RS*-3a** in $CDCl_3$.

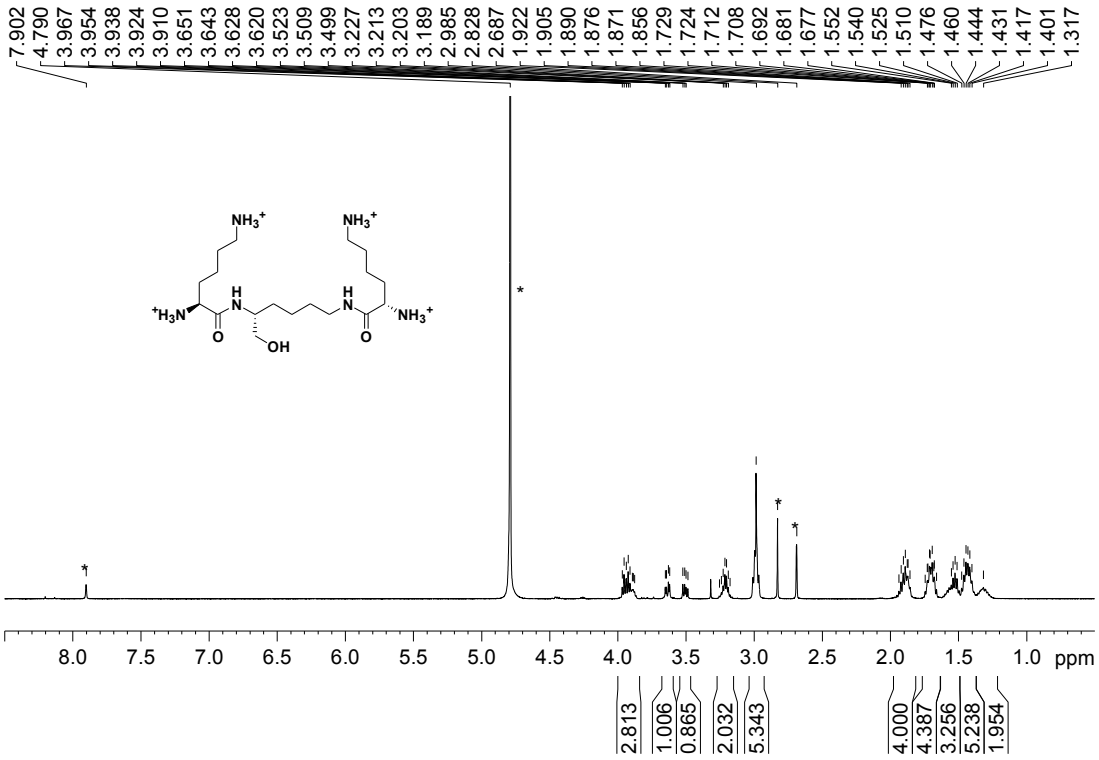

Figure S9. ^{1}H NMR spectrum of compound ***RS*-3b** in D_2O.

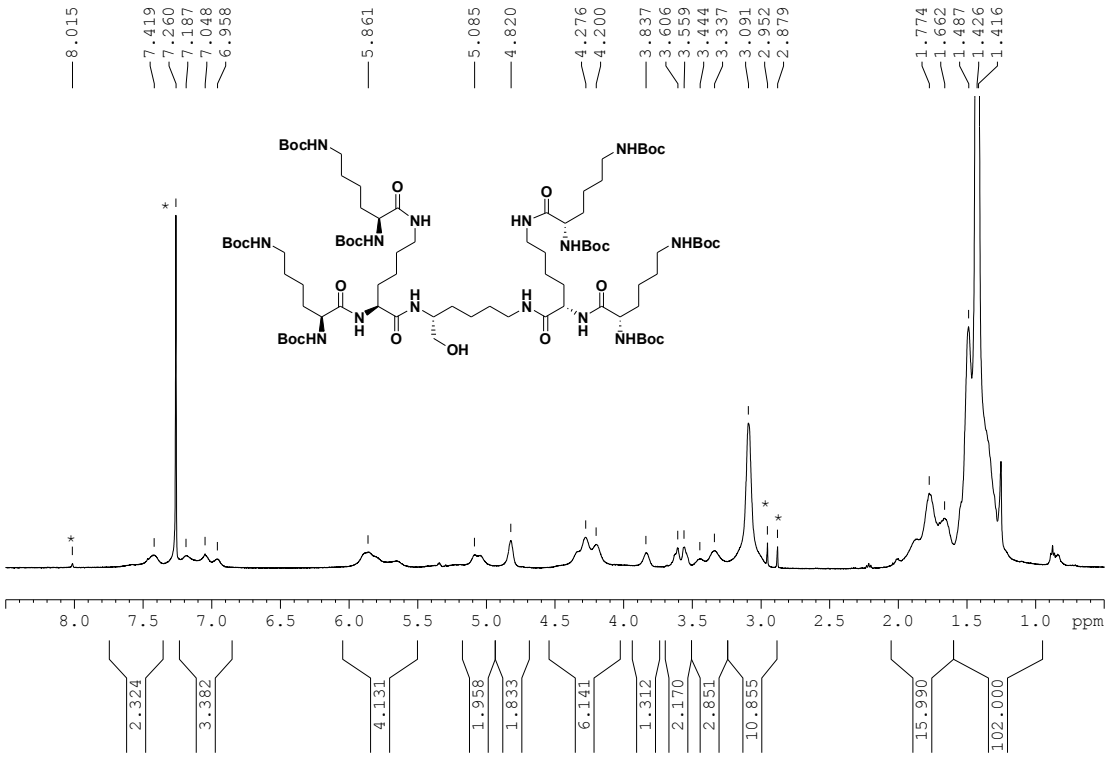

Figure S10. ^{1}H NMR spectrum of compound ***RSS*-4** in $CDCl_3$.

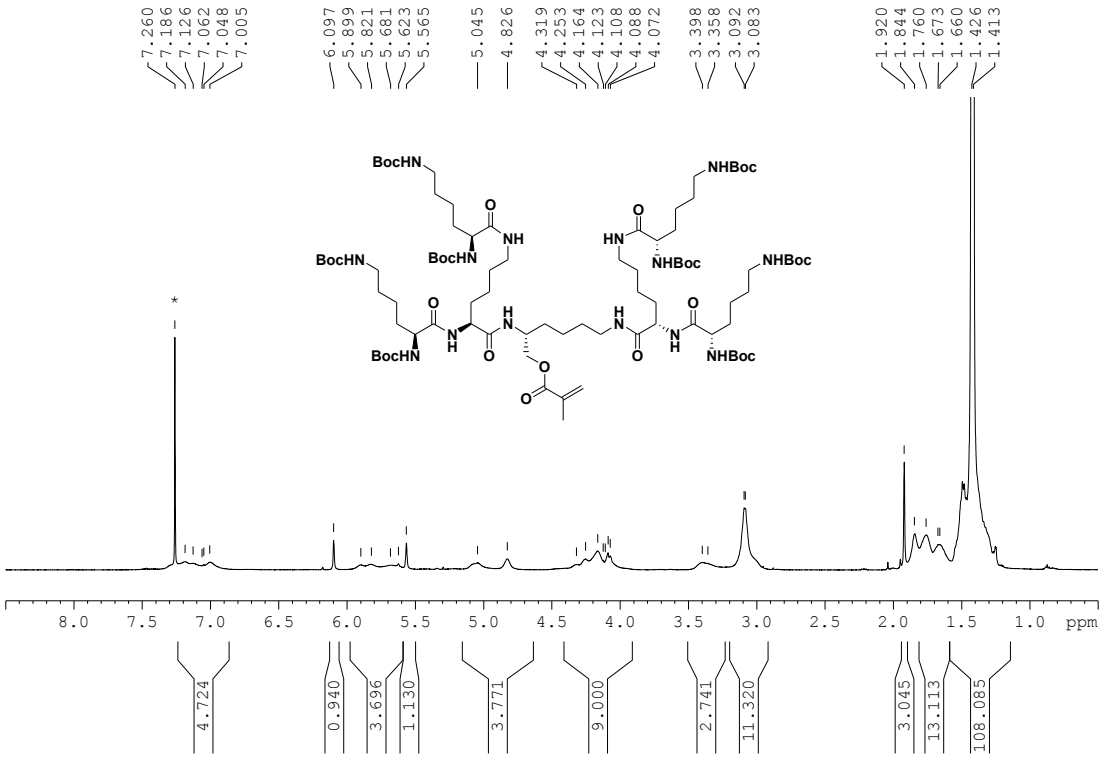

Figure S11. ^{1}H NMR spectrum of compound ***RSS*-MG3** in $CDCl_3$.

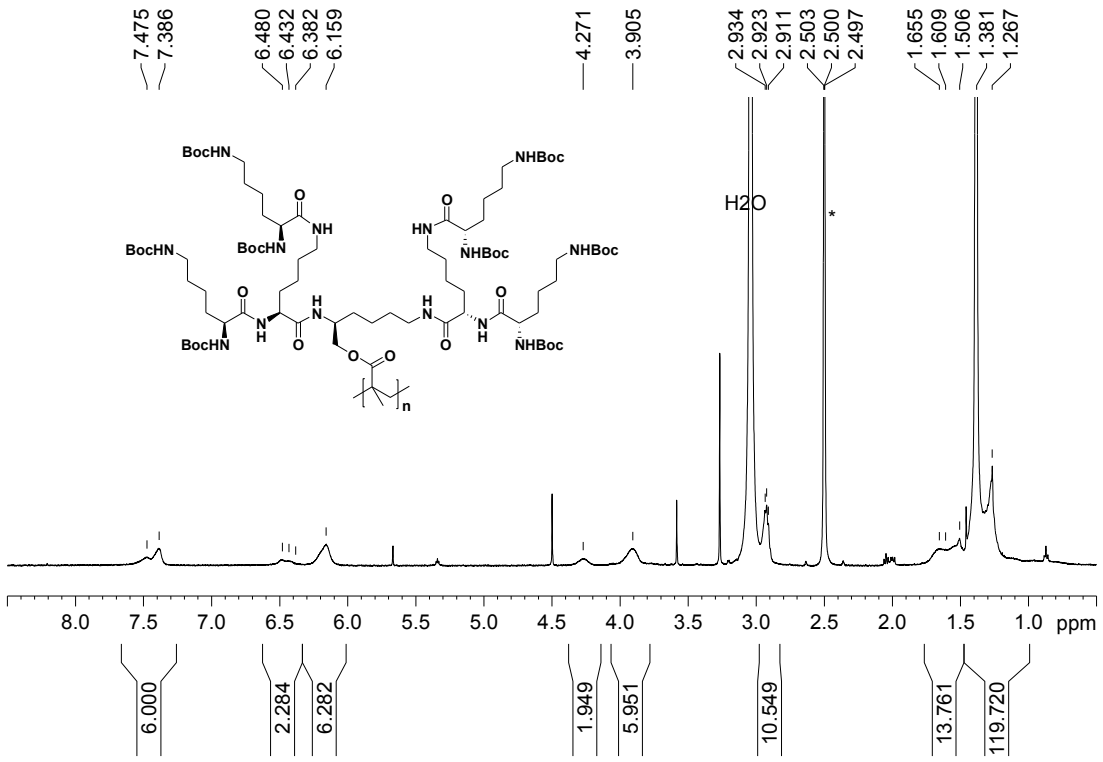

Figure S12. ^{1}H NMR spectrum of compound ***SSS*-PG3** in DMSO-[d_6] at 80 ^{o}C.

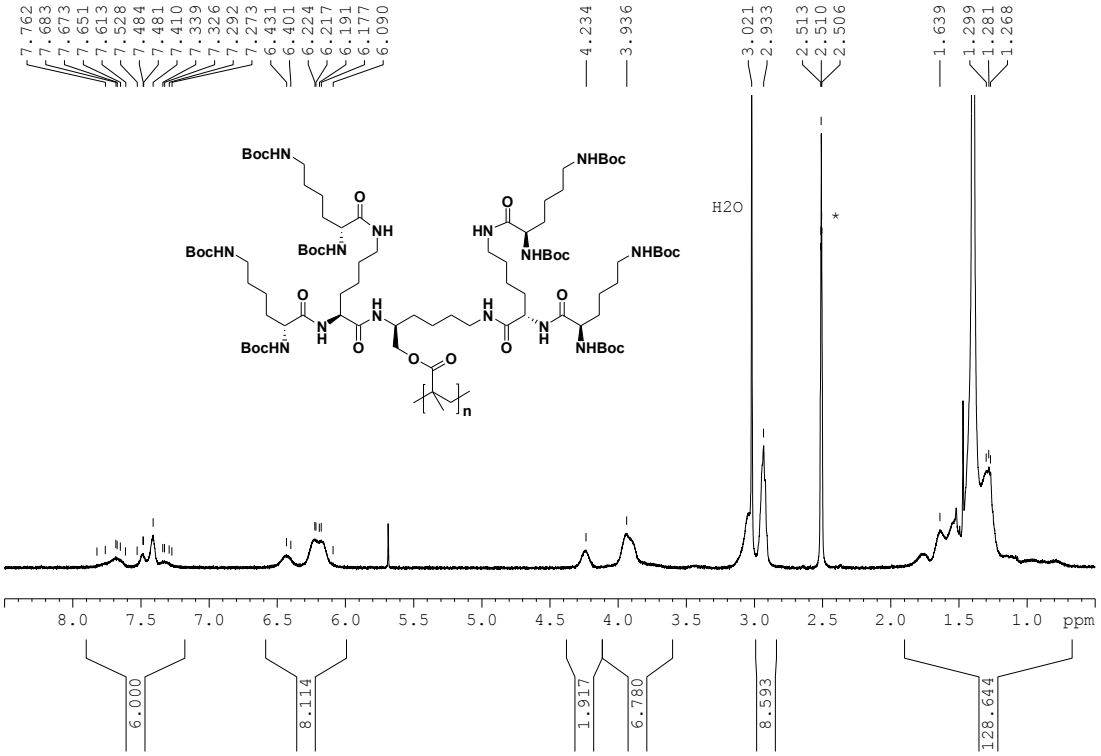

Figure S13. ^{1}H NMR spectrum of compound ***SSR*-PG3** in DMSO-[d_6] at 80 ^{o}C.

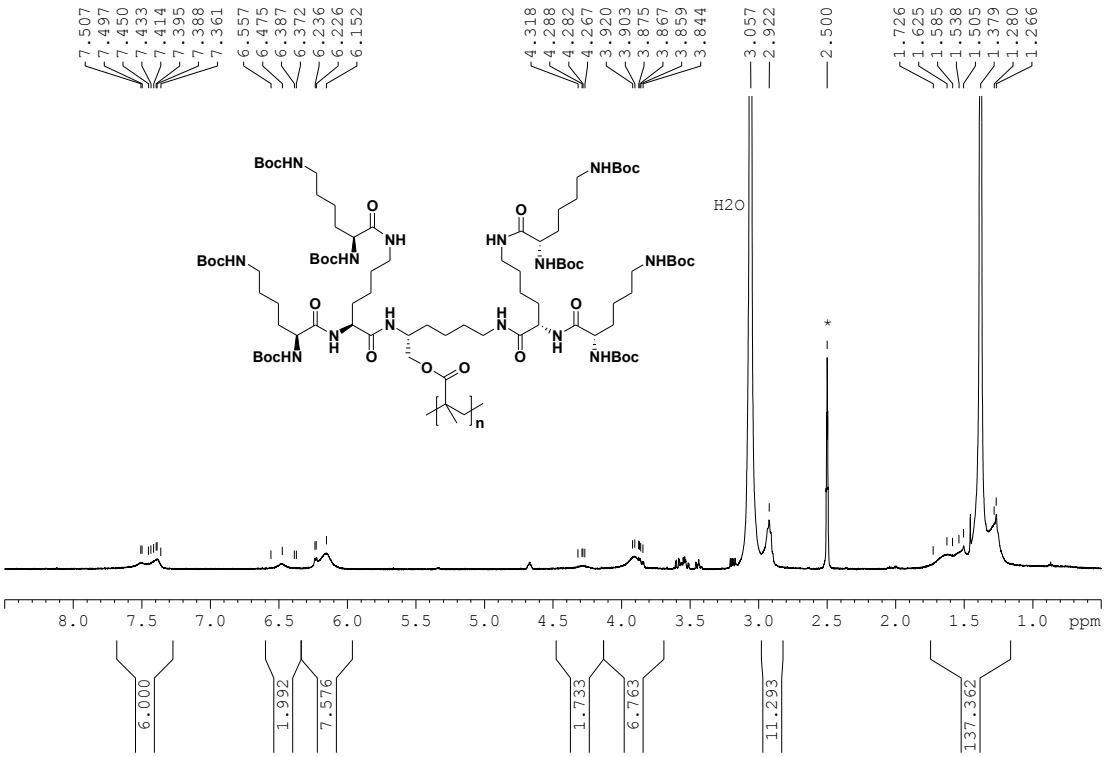

Figure S14. ^{1}H NMR spectrum of compound ***RSS*-PG3** in DMSO-[d_6] at 80 ^{o}C.

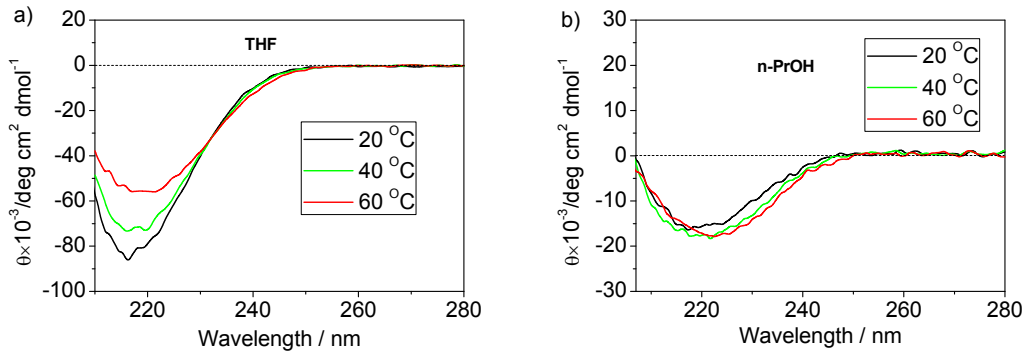

Figure S15. CD spectra of ***SSS*-PG3** at different temperatures in THF (a) and n-PrOH (b).

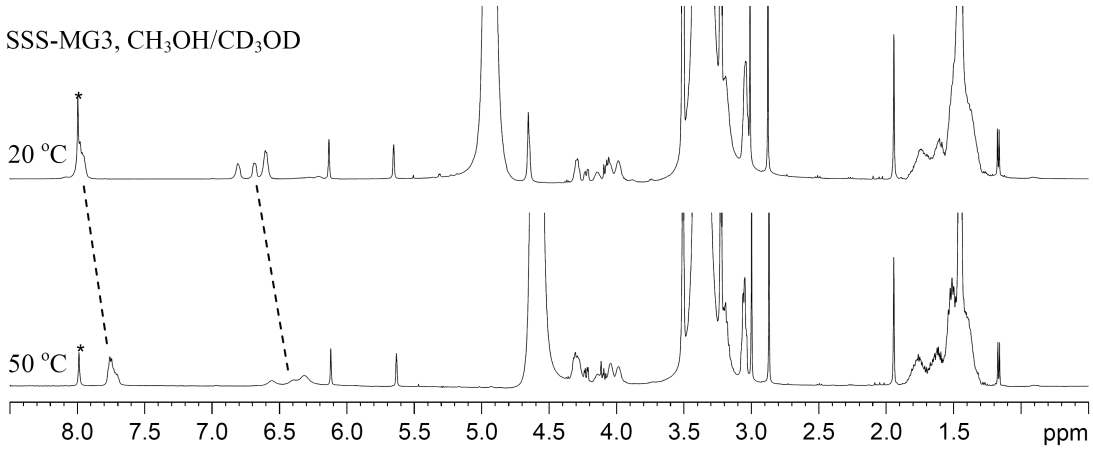

Figure S16. ^{1}H NMR spectra of ***SSS*-MG3** in CD_3OD/CH_3OH (v/v = 1/3) at different temperatures. The dot lines are guide for eye.