SUPPORTING INFORMATION

Controlled Ring-Opening Polymerization of Macrocyclic Monomers Based on Ring-Opening/Ring-Closing Cascade Reaction

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Experimental

1. Materials

3,5-dimethylphenol, concentrated hydrochloric acid (wt 37%), sodium nitrate (NaNO₃), methyl 3-methyl-2-butenoate, methanesulfonic acid (MSA), Sodium borohydride (NaBH₄), lithium borohydride (LiBH₄), tert-butyldimethylsilyl chloride (TBSCI), triethylamine (TEA), di-tert-butyl decarbonate (Boc₂O), 6-amino-1-hexanol, succinic anhydride, 1,3-propanediol, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC·HCl), 4-dimethylaminopyridine (DMAP), bis(trichloromethyl) carbonate, pyridine, Amberlyst 15, Celite 545RV, Pyridinium dichromate (PDC), pentafluorophenol, trifluoroacetic acid (TFA), p-toluenesulfonyl chloride (TsCl), hexaethylene glycol, 1,1',4,7,7'-pentamethyldiethylenetriamine (PMDETA), sodium azide (NaN₃), triphenylphosphine (PPh₃), 4-pentyn-1-ol, 4-nitrophenyl chloroformate, 6-aminocaproic acid, 1,4-butanediol, glutaric anhydride, 2,2-dimethyl-4-oxo-3,8,11,14-tetraoxa-5-azahexadecan-16-oic acid, 1-hydroxybenzotriazole, (HOBt), N,N-diisopropylethylamine (DIPEA), L-valine methyl ester hydrochloride, L-alanine methyl ester hydrochloride, glycine methyl ester hydrochloride, 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), acetic acid, sodium hydroxide (NaOH), lithium hydroxide (LiOH), copper(I) bromide (CuBr), sodium bicarbonate (NaHCO₃), magnesium sulfate (MgSO₄), PEG₄₅OH (M₉ = 2000) methanol (MA), diethyl ether (Et₂O), dichloromethane (DCM), tetrahydrofuran (THF), ethyl acetate (EA), petroleum ether (PE), and dimethylformamide (DMF) were purchased as reagent grade from Alfa Aesar, Aldrich, Acros, J&K Chemical, or Beijing Chemical Reagent Co. and used as received unless otherwise noted.

2. Characterization
High resolution mass spectra (HRMS) were recorded on a Bruker 9.4T Solarix FT-ICR-MS (Bruker, Germany).

$^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker Avance 400, Avance III 500WB and NEO 700 spectrometer at room temperature.

Matrix-Assisted Laser Desorption/Ionization Time of Flight (MALDI-TOF) mass spectra were recorded on an Autoflex III MALDI-TOF mass spectrometer equipped with a 355 nm YAG laser. It was operated at an accelerating potential of 20 kV in linear modes. The MALDI mass spectra represent averages over 256 consecutive laser shots (3 Hz repetition rate). Polymer was dissolved in THF with a concentration of 5 g/L. α-Cyano-4-hydroxycinnamic acid (CCA; 23 g/L in THF) was used as the matrix and NaCl (saturated in THF) was used as the cation source. The sample was prepared by mixing 10 μL of the polymer solution with 10 μL of the matrix solution and 2 μL of the NaCl or trifluoroacetate solution. A 1 μL portion of the final solution was deposited onto the sample target and allowed to dry in air at 25°C. Internal standards (peptides or porphyrine derivatives) were used to calibrate the mass scale using the two-point calibration software 3.07.1 from Autoflex III systems.

Gel permeation chromatography (GPC) in DMF was conducted on a system comprised of a Waters 515 HPLC pump, and a Waters 2414 RI detector equipped with two Agilent mixed columns (one PLgel MIXED-C and one PLgel MIXED-D). DMF with 0.01 M LiBr was used as the eluent at a flow rate of 1.0 mL/min. Polystyrene standards were used for the calibration.

3. Synthesis of macrocyclic monomers M1-M4

3.1 Synthesis of trimethyl lock spacer F
Scheme S1. Synthesis of trimethyl lock spacer F.

3,5-dimethyl-2-nitrophenol: To a stirred solution of 3,5-dimethylphenol (40 g, 327.9 mmol) in diethyl ether and water (640 mL, v/v = 1/1), concentrated hydrochloric acid (40 mL) and NaNO₃ (27.87 g, 327.9 mmol) were slowly added. After stirring the mixed solution to show dark red color, the diethyl ether phase was collected and the water phase was extracted by ethyl acetate (3 × 150 mL). The combined organic phase was dried over anhydrous MgSO₄ and concentrated. The resultant crude product was purified by a silica column with PE as the eluent to afford the 3,5-dimethyl-2-nitrophenol (23.0 g, 42%): ¹H NMR (400 MHz, DMSO-d₆), δ ppm: 10.62(s, 1H), 6.69(s, 1H), 6.62(s, 1H), 2.23(s, 3H), 2.16(s, 3H). ¹³C NMR (101 MHz, DMSO-d₆), δ (ppm): 149.48, 141.68, 139.09, 130.52, 121.98, 115.49, 21.31, 17.06. HRMS (ESI): m/z calculated for C₈H₉NO₃ [M - H⁺] 166.0582, found 166.0510.

Compound C: 3,5-Dimethyl-2-nitrophenol (23 g, 137.7 mmol) was dissolved in methanesulfonic acid (100 mL) at 70 °C, to which methyl 3-methyl-2-butenoate (15.7g, 137.7 mmol) was added. After performing the reaction for 6 h, ethyl acetate (300 mL) was added and the mixture was washed by water (3 × 150 mL) and saturated NaHCO₃ aqueous solution (150 mL). The organic phase was dried over anhydrous MgSO₄ and concentrated. The crude product was purified by a silica column with PE/EA (v/v = 50/1) to afford compound C (20.5 g, 60%). Recrystallized from a mixture of DCM and PE, pure compound 1a was obtained as white solid.
$^1$H NMR spectrum (400 MHz, DMSO-d$_6$), δ ppm: 7.06 (s, 1H), 2.85 (s, 2H), 2.51 (s, 3H), 2.21 (s, 3H), 1.39 (s, 6H). $^1$H NMR spectrum (400 MHz, CDCl$_3$), δ ppm: 6.83 (s, 1H), 2.65 (s, 2H), 2.50 (s, 3H), 2.27 (s, 3H), 1.47 (s, 6H). $^{13}$C NMR (101 MHz, DMSO-d$_6$), δ (ppm): 166.34, 142.45, 139.41, 139.03, 130.07, 129.59, 128.58, 44.04, 35.69, 27.27, 22.97, 16.22. HRMS (ESI): m/z calculated for C$_{13}$H$_{15}$NNaO$_4$ [M + Na$^+$] 272.0893, found 272.0893.

**Compound 1a:** To a stirred solution of 1a (10 g, 40 mmol) in THF (160 mL), NaBH$_4$ (4.10 g, 108.4 mmol) was added slowly. After stirring for 12 h at 70 °C, saturated ammonium chloride aqueous solution was added slowly to quench the reaction under ice bath. After tuning pH of the mixture to 3 by adding HCl aqueous solution (1 M), the mixture was extracted by EA (2 × 100 mL). The combined organic phase was dried over anhydrous MgSO$_4$ and concentrated. The resultant crude product was purified by a silica column with PE/EA (v/v = 5/1) as the eluent to afford compound 1b (9.28 g, 92.4%). $^1$H NMR (400 MHz, DMSO-d$_6$), δ ppm: 7.36 (s, 1H), 6.70 (d, 1H), 5.28 (m, 1H), 2.44 (s, 3H), 2.11 (s, 3H), 1.89-1.74 (m, 2H), 1.42 (s, 3H), 1.37 (s, 3H). $^{13}$C NMR (101 MHz, DMSO-d$_6$), δ (ppm): 144.77, 140.51, 139.59, 128.69, 127.29, 125.89, 92.67, 46.73, 33.53, 29.31, 28.91, 22.81, 16.11. HRMS (ESI): m/z calculated for C$_{13}$H$_{17}$NNaO$_4$ [M + Na$^+$] 273.0977, found 274.1050.

**Compound 1b:** Compound 1b (9.28 g, 37 mmol) was dissolved in THF (140 mL), then LiBH$_4$ (2.04 g, 92.5 mmol) was added slowly to the solution. After stirring for 12 h at 70 °C, saturated ammonium chloride solution was added slowly to quench the reaction under ice bath. After tuning pH of the mixture to 3 by adding HCl aqueous solution (1 M), the mixture was extracted by EA (2 × 100 mL). The combined organic layers were dried over anhydrous MgSO$_4$ and concentrated. The resultant crude product was purified by a silica column with PE/EA (v/v = 3/1) as the eluent to afford compound 1c (7.50 g, 80%). $^1$H NMR (400 MHz, DMSO-d$_6$), δ ppm: 6.67 (s, 1H), 3.25 (t,
2H), 2.45(s, 3H), 2.14(s, 3H), 2.06-1.99(m, 2H), 1.48(s, 6H). $^{13}$C NMR (101 MHz, DMSO-d$_6$), δ (ppm): 148.81, 142.66, 140.96, 135.26, 127.75, 127.62, 59.16, 45.17, 40.43, 32.02, 25.60, 17.39. HRMS (ESI): m/z calculated for C$_{13}$H$_{18}$NO$_4$ [M - H$^+$] 252.1241, found 252.1241.

 **Compound F:** Compound 1c (7.5 g, 29.6 mmol) was dissolved in DCM (60 mL) containing TEA (2.48 g, 44.4 mmol). Tert-butyldimethylsilyl chloride (4.88 g, 32.6 mmol) was added and the reaction was performed at room temperature for 2 h. After concentrating the reaction mixture, the crude product was purified by a silica column with PE/EtO (v/v = 10/1) as the eluent to afford compound 1d (10.54 g, 97%). $^1$H NMR (400 MHz, DMSO-d$_6$), δ ppm: 9.57(s, 1H), 6.67(s, 1H), 3.44(t, 2H), 2.46(s, 3H), 2.15(s, 3H), 2.09(t, 2H), 1.49(s, 6H), 0.80(s, 9H), -0.07(s, 6H). $^{13}$C NMR (101 MHz, DMSO-d$_6$), δ (ppm): 148.91, 142.37, 140.99, 134.90, 127.83, 127.82, 61.65, 45.10, 40.57, 31.94, 31.94, 26.24, 25.63, 18.27, 17.54, -4.97. HRMS (ESI): m/z calculated for C$_{19}$H$_{32}$NO$_4$Si [M - H$^+$] 366.2106, found 366.2106.

 **3.2 Synthesis of M1**
Scheme S2. Synthesis of M1.

Compound 2a: Di-tert-butyl decarbonate (9.94 g, 45.6 mmol) were added to a stirred solution of 6-amino-1-hexanol (4.45 g, 38 mmol) in DCM (190 mL) at 0 °C. After performing the reaction at room temperature for overnight, the reaction solution was washed by citric acid aqueous solution (10%) (1 × 150 mL), saturated NaHCO₃ aqueous solution (1 × 150 mL), and brine (1 × 150 mL). The organic phase was dried over anhydrous MgSO₄ and concentrated to produce the product 2a (8.16 g, 99%). ¹H NMR (400 MHz, DMSO-d₆), δ (ppm): 6.75 (t, 1H), 4.32(t, 1H), 3.37(td, 2H),
2.89(dd, 2H), 1.41-1.19(m, 17H). $^{13}$C NMR (101 MHz, DMSO-d$_6$), δ (ppm): 156.05, 77.72, 61.13, 32.97, 30.01, 28.73, 26.66, 25.68. HRMS: (ESI) m/z calculated for C$_{11}$H$_{23}$NNaO$_3$ [M + Na$^+$] 240.1570, found 240.1571.

**Compound 2b:** Compound 2a (7.94 g, 36.6 mmol) and succinic anhydride (5.49 g, 54.9 mmol) were dissolved in DCM (70 mL), to which DMAP (893 mg, 7.32 mmol) was added. The reaction mixture was performed at room temperature for overnight and concentrated. The crude product was purified by a silica column with DCM/MA (v/v = 20/1) as the eluent to afford compound 1d (11.47 g, 98.9%). $^1$H NMR (400 MHz, DMSO-d$_6$), δ (ppm): 12.18 (s, 1H), 6.75(s, 1H), 3.99(t, 2H), 2.89(dd, 2H), 2.50-2.44(m, 4H), 1.55-1.50(m, 2H), 1.37-1.50(m, 15H). $^{13}$C NMR (101 MHz, DMSO-d$_6$), δ (ppm): 172.33, 156.04, 77.73, 64.45, 64.41, 61.08, 32.86, 29.80, 29.15, 28.72, 28.63, 28.54, 26.35, 25.70, 25.61, 25.50. HRMS (ESI): m/z calculated for C$_{21}$H$_{39}$NNaO$_7$ [M + Na$^+$] 440.2619, found 440.2618.

**Compound 2c:** To a stirred solution of compound 2b (11.47 g, 36.2 mmol) in THF (180 mL), 1,3-propanediol (13.76 g, 181 mmol), EDC·HCl (13.83 g, 72.4 mmol) and DMAP (0.88 g, 7.24 mmol) were added and the reaction was performed at room temperature for overnight. The reaction mixture was concentrated and then purified by a silica column with DCM/MA (v/v = 20/1) as the eluent to afford compound 2c (9.5 g, 70%). $^1$H NMR (400 MHz, DMSO-d$_6$), δ ppm: 6.74(t, 1H), 4.49(s, 1H), 4.07(t, 2H), 3.99(t, 2H), 3.44(t, 2H), 2.90(q, 2H), 2.54(s, 4H), 1.70(m, 2H), 1.54(m, 2H), 1.39-1.19(m, 15H). $^{13}$C NMR (101 MHz, DMSO-d$_6$), δ (ppm): 172.41, 156.04, 77.76, 64.44, 61.92, 57.68, 31.99, 29.82, 29.12, 28.73, 28.54, 26.36, 25.51. HRMS (ESI): m/z calculated for C$_{18}$H$_{33}$NNaO$_7$ [M + Na$^+$] 398.2149, found 398.2149.

**Compound 2d:** A solution of bis(trichloromethyl) carbonate (3.76 g, 12.7 mmol) in THF (42 mL) was cooled to 0 °C, to which pyridine (2.8 g, 35.5 mmol) was added slowly. Then compound
**2c** (9.5 g, 25.3 mmol) dissolved in THF (63 mL) was dropwise added and the reaction was stirred for 1 h at 0°C. The reaction system was filtered and concentrated to afford a reactive intermediate, which was used directly in the next reaction step. Next, compound **F** (10.2 g, 27.83 mmol) and TEA (3.8 g, 37.95 mmol) were dissolved in DCM (125 mL), to which the resultant reactive intermediate was added. After stirring at room temperature for 0.5 h, the reaction solution was concentrated and then purified by a silica column with PE/EA (v/v = 5/1) as the eluent to afford the product **2d** (15.5 g, 80%). $^1$H NMR spectrum (400 MHz, DMSO-d$_6$), δ ppm: 7.23(s, 1H), 6.75(s, 1H), 4.28(t, 2H), 4.08(t, 2H), 3.99(t, 2H), 3.46(t, 2H), 2.89(q, 2H), 2.57(s, 3H), 2.55(s, 4H), 2.21(s, 3H), 2.01-1.94(m, 4H), 1.55-1.50(m, 2H), 1.43(s, 6H), 1.36(s, 9H), 1.31-1.15(m, 6H), 0.79(s, 9H), -0.07(s, 6H). $^{13}$C NMR (101 MHz, DMSO-d$_6$), δ (ppm): 172.33, 172.24, 156.04, 152.73, 144.07, 142.45, 141.02, 137.94, 134.22, 128.88, 77.72, 66.71, 64.45, 60.76, 60.34, 60.21, 45.28, 39.96, HRMS (ESI): m/z calculated for C$_{38}$H$_{64}$N$_2$NaO$_{12}$Si [M + Na$^+$] 791.4121, found 791.4121.

**Compound 2e:** Compound **2d** (15 g, 19.5 mmol) was dissolved in methanol (200 mL) and Amberlyst 15 (12.59 g, 68.25 mmol) was added. The reaction was performed at room temperature for 1 h. The reaction mixture was filtered and concentrated. The crude product was dissolved in DMF (150 mL), to which then Celite 545RV (51.2 g) and pyridinium dichromate (51.2 g, 136.5 mmol) were added. After reacting overnight at room temperature, 150 mL diethyl ether was added to the system. After filtering the mixture by diatomite, pH of the filtrate was tuned to 3 by adding 1M HCl aqueous solution. After washed by water twice, the filtrate was concentrated and purified by a silica column with PE/EA (v/v = 2/3) as the eluent to afford the product **2e** (7.56 g, 58%). $^1$H NMR (400 MHz, DMSO-d$_6$), δ ppm: 11.97(s, 1H), 7.22(s, 1H), 6.76(s, 1H), 4.29(t, 2H), 4.09(t, 2H), 3.99(t, 2H), 2.89(q, 2H), 2.76(s, 2H), 2.58(s, 3H), 2.56(s, 4H), 2.22(s, 3H), 1.96(m, 2H), 1.55-
1.49(m, 8H), 1.37-1.31(m, 15H). $^{13}$C NMR (101 MHz, DMSO-$d_6$), $\delta$ (ppm): 172.41, 166.37, 156.06, 142.44, 139.42, 139.02, 130.07, 129.58, 128.58, 124.69, 77.76, 64.44, 61.92, 57.68, 44.01, 40.01, 35.69, 32.00, 29.82, 29.13, 28.73, 28.54, 27.27, 26.36, 25.51, 22.99, 16.23. HRMS (ESI): m/z calculated for C$_{32}$H$_{48}$N$_2$NaO$_{13}$ [M + Na$^+$] 691.3049, found 691.3049.

**Compound 2f:** To a stirred solution of compound 2e (7.5 g, 11.2 mmol) in THF (56 mL), pentafluorophenol (3.1 g, 16.8 mmol), EDC·HCl (4.31 g, 22.5 mmol) and DMAP (0.27 g, 2.25 mmol) were added. After performing the reaction at room temperature for overnight, the reaction mixture was concentrated and then purified by a silica column with PE/EA (v/v = 3/1) as the eluent to afford compound 2f (6.54 g, 70%). $^1$H NMR (400 MHz, DMSO-$d_6$), $\delta$ ppm: 7.26(s, 1H), 6.74(s, 1H), 4.31(t, 2H), 4.09(t, 2H), 3.98(t, 2H), 3.36(s, 2H), 2.88(q, 2H), 2.61(s, 3H), 2.54(s, 4H), 2.22(s, 3H), 1.96(m, 2H), 1.58-1.51 (m, 8H), 1.36-1.22(m, 15H). $^{13}$C NMR (101 MHz, DMSO-$d_6$), $\delta$ (ppm): 172.37, 172.28, 167.61, 156.05, 152.62, 143.85, 142.09, 140.98, 136.54, 134.43, 129.40, 77.74, 66.91, 64.45, 60.71, 60.22, 55.37, 46.53, 39.51, 30.14, 29.81, 28.53, 27.84, 26.35, 25.49, 24.91, 21.21, 16.90, 14.54. HRMS (ESI): m/z calculated for C$_{38}$H$_{47}$F$_3$N$_2$NaO$_{13}$ [M + Na$^+$] 857.2891, found 857.2891.

**M1:** compound 2f (6.54 g, 7.84 mmol) were dissolved in a mixed solution of DCM (40 mL) and TFA (40 mL). The reaction was performed at room temperature for 30 minutes and then concentrated. The residue was dissolved in DCM (150 mL), which was then dropwise added to a large amount of DCM (1 L) containing TEA (9.5 g, 94.08 mmol) at room temperature in 3 h by a syringe pump. After that, the solvent was removed and the residue was purified by a silica column with DCM/acetone (v/v = 8/1) as the eluent to afford the M1 (3.88 g, 90%). $^1$H NMR (400 MHz, DMSO-$d_6$) (Figure S1A), $\delta$ (ppm): 7.68(t, 1H), 7.21(s, 1H), 4.27(t, 2H), 4.09(t, 2H), 4.01(t, 2H), 2.98 (q, 2H), 2.58(s, 3H), 2.58-2.56(m, 4H), 2.52(s, 2H), 2.21 (s, 3H), 1.96(m, 2H), 1.52-1.47(m,
8H), 1.34-1.23(m, 6H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) (Figure S1B), δ (ppm): 172.23, 172.08, 169.90, 152.81, 143.87, 142.45, 140.71, 138.65, 134.04, 128.59, 66.52, 64.25, 60.82, 48.10, 38.41, 30.42, 29.66, 29.51, 29.26, 28.45, 27.88, 26.21, 25.38, 25.12, 16.90. HRMS (ESI): m/z calculated for C$_{27}$H$_{38}$N$_2$NaO$_{10}$ [M + Na$^+$] 573.2419, found 573.2419.

### 3.3 Synthesis of M2

![Scheme S3. Synthesis of M2.](image-url)
**Compound 3a:** p-Toluenesulfonyl chloride (16.93 g, 88.65 mmol) was added to a solution of hexaethylene glycol (25 g, 88.65 mmol) and TEA (17.9 g, 177.3 mmol) in DCM (150 mL) at 0 °C. The reaction was performed at room temperature for overnight and concentrated. The crude product was purified by a silica column with DCM/MA (v/v = 30/1) as the eluent to afford the compound 3a (17.5 g, 45%). $^1$H NMR (400 MHz, DMSO-d$_6$), δ (ppm): 7.79 (d, 2H), 7.49 (d, 2H), 4.52 (t, 1H), 4.12 (t, 2H), 3.59-3.40 (m, 22H), 2.43 (s, 3H). $^{13}$C NMR (101 MHz, DMSO-d$_6$), δ (ppm): 145.34, 132.93, 130.59, 128.08, 72.82, 70.44, 70.25, 70.18, 70.12, 68.36, 60.69, 21.54. HRMS (ESI): m/z calculated for C$_{19}$H$_{32}$NaO$_9$S [M + Na$^+$] 459.1659, found 459.1641.

**Compound 3b:** Compound 3a (16.5 g, 37.8 mmol) and NaN$_3$ (3.69 g, 56.77 mmol) were dissolved in 75 mL DMF. The reaction was performed at 50 °C for 2 h. After concentrating the reaction solution, the residue was purified by a silica column with DCM/MA (v/v = 30/1) as the eluent to afford the product 3b (11.6 g, 100%). $^1$H NMR (400 MHz, DMSO-d$_6$), δ (ppm): 4.57 (t, 1H), 3.61-3.46 (m, 20H), 3.40 (m, 4H). $^{13}$C NMR (101 MHz, DMSO-d$_6$), δ (ppm): 72.82, 70.27, 70.17, 69.72, 60.69, 50.48. HRMS (ESI): m/z calculated for C$_{12}$H$_{25}$N$_3$NaO$_6$ [M + Na$^+$] 330.1636, found 330.1636.

**Compound 3c:** Compound 3b (11.6 g, 37.8 mmol) and PPh$_3$ (11.9 g, 45.36 mmol) were dissolved in a mixed solvent of THF (120 ml) and H$_2$O (6 mL). The reaction was performed at room temperature for overnight and concentrated. The residue was dissolved in DCM (120 mL) containing TEA (5.73 g, 56.7 mmol), to which di-tert-butyl decarbonate (12.36 g, 56.7 mmol) was added at 0°C. After stirring at room temperature for 2 h, the reaction mixture was concentrated and the residue was purified by a silica column with DCM/MA (v/v = 30/1) as the eluent to afford the product 3c (11.76 g, 82%). $^1$H NMR (400 MHz, DMSO-d$_6$), δ (ppm): 6.73 (t, 1H), 4.55(t, 1H), 3.49-3.35 (m, 22H), 3.07 (q, 2H), 1.37(s, 9H). $^{13}$C NMR (101 MHz, DMSO-d$_6$), δ (ppm): 156.04,
Compound 3d: A solution of bis(trichloromethyl) carbonate (4.52 g, 15.2 mmol) in THF (50 mL) was cooled to 0°C, to which pyridine (2.4 g, 30.4 mmol) was added slowly. Then compound 3c (11.7 g, 30.4 mmol) dissolved in THF (50 mL) was dropwise added and the reaction was stirred for 1 h at 0°C. The reaction system was filtered and concentrated to afford a reactive intermediate, which was used directly in the next reaction step. Next, compound F (12.27 g, 42.56 mmol) and TEA (3.38g, 42.56 mmol) were dissolved in DCM (150 mL), to which the resultant reactive intermediate was added. After stirring at room temperature for 0.5 h, the reaction solution was concentrated and then purified by a silica column with PE/EA (v/v = 1/1) as the eluent to afford the product 3d (17.7g, 75%). \(^1\)H NMR spectrum (400 MHz, DMSO-d_6), \(\delta\) (ppm): 7.23(s, 1H), 6.73(t, 1H), 4.33(t, 2H), 3.65(t, 2H), 3.53-3.49(m, 18H), 3.37(t, 3H), 3.06(q, 2H), 2.57(s, 3H), 2.21(s, 3H), 1.99(t, 3H), 1.44(s, 6H), 1.37(s, 9H), 0.79(s, 9H), -0.07(s, 6H). \(^{13}\)C NMR (101 MHz, DMSO-d_6), \(\delta\) (ppm): 156.05, 152.87, 144.17, 142.39, 141.02, 138.01, 134.17, 128.78, 78.02, 70.32, 70.28, 70.22, 70.00, 69.66, 69.07, 68.44, 60.37, 45.30, 39.96, 31.08, 28.69, 26.19, 25.01, 18.24, 16.78, -5.09. HRMS (ESI): m/z calculated for C_{37}H_{66}N_{12}NaO_{13}Si [M + Na\(^+\)] 797.4226, found 797.4226.

Compound 3e: Compound 3d (17.7g, 22.9 mmol) was dissolved in methanol (230 mL) and Amberlyst 15 (14.75 g, 80.15 mmol) was added. The reaction was performed at room temperature for 1 h. The reaction mixture was filtered and concentrated. The crude product was dissolved in DMF (150 mL) and then Celite 545RV (60.27 g) and Pyridinium dichromate (60.27 g, 160.3 mmol) were added. After reacting at room temperature for overnight, 150 mL diethyl ether is added to the system. After filtering the mixture by diatomite, pH of the filtrate was tuned to 3 by adding 1M
HCl aqueous solution. After washed by water twice, the filtrate was concentrated and purified by a silica column with PE/EA (v/v = 2/3) as the eluent to afford the product 3e (9.05 g, 58.6%). $^1$H NMR (400 MHz, DMSO-d$_6$), δ ppm: 7.07 (s, 1H), 6.76 (t, 1H), 4.58 (t, 1H), 3.52 – 3.47 (m, 18H), 3.43 – 3.34 (m, 4H), 3.05 (q, 2H), 2.84 (s, 2H), 2.49 (s, 3H), 2.21 (d, 3H), 1.38 (d, 15H). $^{13}$C NMR (101 MHz, DMSO-d$_6$), δ (ppm): 166.37, 162.78, 156.06, 142.44, 139.43, 139.02, 130.07, 129.59, 128.58, 78.04, 72.83, 70.31, 70.27, 70.22, 69.99, 69.55, 60.70, 44.01, 36.24, 31.23, 28.69, 27.27, 22.99, 16.23. HRMS (ESI): m/z calculated for C$_{31}$H$_{50}$N$_2$NaO$_4$ [M + Na$^+$] 697.3154, found 697.3154.

**Compound 3f:** To a stirred solution of compound 3e (9.05 g, 13.4 mmol) in THF (65 mL), pentafluorophenol (3.70 g, 20.1 mmol), EDC•HCl (5.15 g, 26.8 mmol) and DMAP (0.33 g, 2.68 mmol) were added. After performing the reaction at room temperature for overnight, the reaction mixture was concentrated and purified by a silica column with PE/EA (v/v = 1/2) as the eluent to afford compound 3f (7.88 g, 70%). $^1$H NMR (400 MHz, DMSO-d$_6$), δ ppm: 7.26(s, 1H), 6.75(t, 1H), 4.37(m, 2H), 3.67(m, 2H), 3.54-3.48(m, 16H), 3.38-3.35 (m, 4H), 3.06(q, 2H), 2.61(s, 3H), 2.22(s, 3H), 1.58(s, 6H),1.37(s, 9H). $^{13}$C NMR (101 MHz, DMSO-d$_6$), δ (ppm): 167.55, 156.06, 152.77, 143.94, 142.02, 140.99, 136.59, 134.39, 129.32, 78.03, 70.26, 70.21, 69.98, 69.64, 69.20, 68.46, 65.39, 46.52, 39.54, 30.14, 28.67, 24.92, 16.87, 15.62. HRMS (ESI): m/z calculated for C$_{37}$H$_{49}$F$_5$N$_2$NaO$_4$ [M + Na$^+$] 863.2996, found 863.2969.

**M2:** Compound 3f (7.88 g, 9.4 mmol) was dissolved in a mixed solution of DCM (48 mL) and TFA (48 mL). The reaction was performed at room temperature for 30 minutes and then concentrated. The residue was dissolved in DCM (200 mL), which was then dropwise added to a large amount of DCM (1.2 L) containing TEA (11.4 g, 112.8 mmol) at room temperature in 3 h by a syringe pump. After that, the solvent was removed and the residue was purified by a silica
column with DCM/MA (v/v = 20/1) as the eluent to afford the M2 (4.1 g, 78.7%). $^{1}$H NMR (400 MHz, DMSO-d$_6$) (Figure S2A), δ (ppm): 7.75(t, 1H), 7.20(s, 1H), 4.33(m, 2H), 3.67(t, 2H), 3.56-3.48(m, 16H), 3.37 (m, 2H), 3.13(q, 2H), 2.59(m, 5H), 2.22(s, 3H), 1.46(s, 6H). $^{13}$C NMR (101 MHz, DMSO-d$_6$) (Figure S2B), δ (ppm): 170.26, 152.90, 143.89, 142.48, 140.83, 138.71, 134.01, 128.54, 70.50, 70.45, 70.38, 70.19, 69.66, 69.24, 68.5, 47.79, 39.75, 39.00, 30.59, 25.16, 16.92. HRMS (ESI): m/z calculated for C$_{26}$H$_{40}$N$_2$NaO$_{11}$ [M + Na$^+$] 579.2524, found 579.2524.

3.4 Synthesis of M3

![Chemical reaction diagram showing the synthesis of M3](attachment:image.png)
Scheme S4. Synthesis of M3.

*Compound 4a:* Di-tert-butyl decarbonate (7.32 g, 33.55 mmol) was added to a stirred solution of 6-aminocaproic acid (4.00 g, 30.5 mmol) and 1 M aqueous solution of NaOH (1.22 g, 30.5 mmol) in 1,4-dioxane and water (120 mL, v/v = 2/1) at 0 °C. The reaction mixture was stirred at room temperature for 3 h. The solutions were concentrated under reduced pressure. The basic aqueous residue was washed once with EA (50 mL). The aqueous layer was acidified by 1 M HCl aqueous solution until pH reached 1 and then extracted with EA (3 × 50 mL). The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure to afford compound 4a (7.05 g, 99%). ¹H NMR (400 MHz, DMSO-d₆), δ (ppm): 11.96 (br, 1H), 6.78(t, 1H), 2.88(q, 2H), 2.18(t, 2H), 1.48(m, 2H), 1.42(s, 9H), 1.23(m, 2H). ¹³C NMR (101 MHz, DMSO-d₆), δ (ppm): 174.86, 156.04, 77.75, 34.09, 29.67, 28.73, 26.31, 24.68. HRMS (ESI): m/z calculated for C₁₁H₂₀NO₄ [M-H⁺] 230.1398, found 230.1398.

*Compound 4b:* Compound 4a (7.00 g, 30.3 mmol) was dissolved in THF (120 mL), and then 1,4-butanediol (13.64 g, 151.5 mmol), EDC·HCl (11.64 g, 60.6 mmol) and DMAP (0.74 g, 6.06 mmol) were added. After preforming the reaction at room temperature for overnight, the reaction mixture was concentrated and then purified by a silica column with PE/EA (v/v = 1/1) as the eluent to afford compound 4b (6.95 g, 76%). ¹H NMR (400 MHz, DMSO-d₆), δ (ppm): 6.72(t, 1H), 4.39(t, 1H), 4.01(t, 2H), 3.4(q, 2H), 2.88(q, 2H), 2.26(t, 2H), 1.63-1.41(m, 6H), 1.40-1.32(m, 11H), 1.24(m, 2H). ¹³C NMR (101 MHz, DMSO-d₆), δ (ppm): 173.31, 156.04, 77.75, 64.13, 60.72, 33.97, 29.60, 29.33, 28.72, 26.22, 25.45, 24.67. HRMS (ESI): m/z calculated for C₁₅H₃₀NO₅ [M+H⁺] 304.2118, found 304.2118.

*Compound 4c:* Compound 4b (6.85 g, 22.6 mmol) and glutaric anhydride (3.86 g, 33.9 mmol) were dissolved in DCM (90 mL), to which TEA (5.71 g, 56.5 mmol) was added. The reaction
mixture was performed at room temperature for overnight and concentrated. The crude product was purified by a silica column with PE/EA (v/v = 1/1) as the eluent to afford compound **4c** (9.25 g, 98%). $^1$H NMR (400 MHz, DMSO-$d_6$), δ ppm: 12.07(br, 1H), 6.73(t, 1H), 4.03(q, 4H), 2.89(q, 2H), 2.33(t, 2H), 2.28(m, 4H), 1.75(m, 2H), 1.62(m, 4H), 1.51(m, 2H), 1.43-1.33(m, 11H), 1.25(m, 2H). $^{13}$C NMR (101 MHz, DMSO-$d_6$), δ (ppm): 172.41, 156.06, 77.76, 64.44, 61.92, 57.68, 31.99, 29.82, 29.12, 28.73, 28.54, 26.36, 25.51. HRMS (ESI): m/z calculated for C$_{20}$H$_{34}$NO$_8$ [M - H$^+$] 416.2290, found 416.2290.

**Compound 4d:** To a stirred solution of compound **F** (7.34 g, 20.0 mmol) in THF (85 mL), **4c** (9.16 g, 22.0 mmol), EDC·HCl (7.68 g, 40.0 mmol) and DMAP (0.49 g, 4.0 mmol) were added. After performing the reaction at 50 ℃ for 2 h. The reaction mixture was concentrated and then purified by a silica column with PE/EA (v/v = 5/1) as the eluent to afford compound **4d** (14.25 g, 93%). $^1$H NMR spectrum (400 MHz, DMSO-$d_6$), δ ppm: 7.19(s, 1H), 6.75(t, 1H), 4.03(m, 4H), 3.44(t, 2H), 2.87(q, 2H), 2.60-2.55(m, 5H), 2.40(t, 2H), 2.26(t, 2H), 2.19(s, 3H), 1.97(t, 2H), 1.80(m, 2H), 1.61(m, 4H), 1.50(m, 2H), 1.41(s, 6H), 1.36-1.32(m, 11H), 1.21(m, 2H), 0.79(s, 9H), -0.07(s, 6H). $^{13}$C NMR (101 MHz, DMSO-$d_6$), δ (ppm): 173.26, 172.67, 171.56, 156.02, 144.29, 142.10, 140.90, 138.00, 133.79, 128.45, 77.73, 63.93, 63.71, 60.38, 45.36, 33.94, 33.11, 32.58, 31.29, 29.59, 28.72, 26.22, 26.18, 25.30, 25.07, 24.64, 19.80, 18.24, 16.73, -5.10. HRMS (ESI): m/z calculated for C$_{39}$H$_{67}$N$_2$NaO$_{11}$Si [M + Na$^+$] 789.4328, found 789.4328.

**Compound 4e:** Compound **4d** (14 g, 18.18 mmol) was dissolved in methanol (90 mL) and Amberlyst 15 (11.71 g, 63.63 mmol) was added. After performing the reaction at room temperature for 1 h, the reaction mixture was filtered and concentrated. The crude product was dissolved in DMF (90 mL) and then celite 545RV (47.85 g) and pyridinium dichromate (47.85 g, 127.3 mmol) were added. After reacting at room temperature for overnight, diethyl ether (90 mL) is added to
the system. The mixture was filtered by diatomite, then water (100 mL) was added to the filtrate. The aqueous layer was acidified by 1 M HCl aqueous solution until pH reached 2. The layers were separated and the organic layer was washed by water (2×100 mL). Then the organic layer was concentrated under reduced pressure and purified by a silica column with PE/EA (v/v = 1/2) as the eluent to afford the product 4e (6.66 g, 55%). $^1$H NMR (400 MHz, DMSO-d$_6$), δ ppm: 12.09(s, 1H), 7.07(s, 1H), 6.74(t, 1H), 4.04(m, 4H), 2.87(m, 2H), 2.52(s, 3H), 2.34(t, 2H), 2.29-2.20(m, 9H), 1.75(m, 2H), 1.61(m, 4H), 1.51(m, 2H), 1.40-1.33(m, 17H), 1.20(m, 2H). $^{13}$C NMR (101 MHz, DMSO-d$_6$), δ (ppm): 174.47, 173.00, 166.37, 156.04, 142.42, 139.42, 130.06, 129.57, 128.57, 77.77, 63.84, 63.73, 44.00, 35.69, 33.92, 33.12, 29.60, 28.72, 27.26, 26.21, 25.28, 24.65, 23.00, 20.42, 16.23. HRMS (ESI): m/z calculated for C$_{33}$H$_{50}$N$_2$NaO$_{13}$ [M + Na$^+$] 689.3256, found 689.3256.

Compound 4f: To a stirred solution of compound 4e (6.5 g, 9.8 mmol) in THF (50 mL), pentafluorophenol (2.70 g, 14.7 mmol), EDC·HCl (3.76 g, 19.6 mmol) and DMAP (0.24 g, 1.96 mmol) were added and the reaction was performed at room temperature for overnight. The reaction mixture was concentrated and then purified by a silica column with PE/EA (v/v = 2/1) as the eluent to afford compound 4f (5.83 g, 72%). $^1$H NMR (400 MHz, DMSO-d$_6$), δ ppm: 7.21(s, 1H), 6.72(t, 1H), 4.30(m, 4H), 3.34(t, 2H), 2.87(m, 2H), 2.65(t, 2H), 2.60(s, 2H), 2.41(t, 2H), 2.26(t, 2H), 2.20(s, 3H), 1.83(m, 2H), 1.61(m, 4H), 1.56(s, 6H), 1.49(m, 2H), 1.40-1.31 (m, 11H), 1.21 (m, 2H). $^{13}$C NMR (101 MHz, DMSO-d$_6$), δ (ppm): 173.27, 172.69, 171.63, 167.58, 156.03, 143.99, 141.73, 140.82, 136.77, 133.97, 128.94, 77.73, 63.93, 63.69, 46.77, 33.91, 32.99, 32.55, 30.23, 29.59, 28.69, 26.21, 25.28, 24.98, 24.63, 19.76, 16.78. HRMS (ESI): m/z calculated for C$_{39}$H$_{40}$F$_5$N$_2$NaO$_{12}$ [M + Na$^+$] 855.3098, found 855.3098.
**M3**: Compound 4f (5.71 g, 6.86 mmol) was dissolved in a mixed solution of DCM (35 mL) and TFA (35 mL). The reaction was performed at room temperature for 30 minutes and then concentrated. The residue was dissolved in DCM (140 mL), which was then dropwise added to a large amount of DCM (915 mL) containing TEA (17.07 g, 170 mmol) at room temperature in 3 h by a syringe pump. After that, the solvent was removed and the residue was purified by a silica column with PE/EA (v/v = 1/1) as the eluent to afford the M3 (3.50 g, 94%). $^1$H NMR (400 MHz, DMSO-d$_6$), $\delta$ (ppm): 7.60(t, 1H), 7.15(s, 1H), 4.06(m, 4H), 2.94(m, 2H), 2.60-2.53(m, 7H), 2.41(t, 2H), 2.24(t, 2H), 2.19(s, 3H), 1.83(m, 2H), 1.65(m, 4H), 1.51(m, 2H), 1.45(s, 6H), 1.30(m, 2H), 1.21(m, 2H). $^{13}$C NMR (101 MHz, DMSO-d$_6$), $\delta$ (ppm): 173.21, 172.66, 171.53, 169.94, 144.01, 142.10, 140.74, 138.61, 133.56, 128.15, 63.99, 63.81, 48.23, 39.57, 38.26, 34.08, 33.13, 32.78, 30.85, 29.02, 26.01, 25.69, 25.23, 25.08, 24.64, 19.83, 16.83. HRMS (ESI): m/z calculated for C$_{28}$H$_{40}$N$_2$NaO$_9$ [M + Na$^+$] 571.2626, found 571.2626.

**3.5 Synthesis of M4**
Scheme S5. Synthesis of M4.

**Compound 5a:** To a stirred solution of 2,2-dimethyl-4-oxo-3,8,11,14-tetraoxa-5-azahexadecan-16-oic acid (10.00 g, 32.5 mmol) in DCM (130 mL), EDC·HCl (7.49 g, 39.0 mmol), HOBt (5.27
g, 39.0 mmol), DIPEA (6.29 g, 48.8 mmol) and L-valine methylester hydrochloride (5.45 g, 32.5 mmol) were added at 0 °C. After performing the reaction at room temperature for overnight, the reaction mixture was washed by water (3 × 90 mL). The organic phase was dried over anhydrous MgSO₄ and concentrated, then purified by a silica column with DCM/MeOH (v/v = 50/1) as the eluent to afford compound 5a (12.98 g, 95%). ¹H NMR (400 MHz, DMSO-d₆), δ (ppm): 7.71 (d, 1H), 6.72 (d, 1H), 4.24 (d, 1H), 3.96 (s, 2H), 3.65 (s, 3H), 3.63–3.49 (m, 8H), 3.37 (t, 2H), 3.06 (m, 2H), 2.08 (m, 1H), 1.37 (s, 9H), 0.87 (d, 6H). ¹³C NMR (101 MHz, DMSO-d₆), δ (ppm): 172.23, 170.03, 156.04, 78.03, 70.78, 70.22, 70.02, 69.94, 69.90, 69.65, 57.27, 52.26, 30.40, 28.68, 19.39, 18.61. HRMS (ESI): m/z calculated for C₁₉H₃₆N₂NaO₈ [M + Na⁺] 443.2364, found 443.2364.

**Compound 5b:** Compound 5a (12.85 g, 30.6 mmol) in a mixed solution of THF and water (120 mL, v/v = 2/1), LiOH (1.35 g, 61.2 mmol) was added at 0 °C and the reaction was performed at room temperature for 1 h. The reaction mixture was acidified until pH = 2 by 1M HCl aqueous solution and then diluted by EA. The organic layer was separated and the aqueous layer was extracted by EA (3 × 40 mL). The combined organic phase was dried over anhydrous MgSO₄ and concentrated. To the residue in DCM (120 mL) was added EDC·HCl (7.05 g, 36.7 mmol), HOBt (4.96 g, 36.7 mmol), DIPEA (5.92 g, 45.9 mmol), and L-alanine methyl ester hydrochloride (4.48 g, 32.1 mmol) at 0 °C. After performing the reaction at room temperature for overnight, the reaction mixture was washed by water (3 × 80 mL). The organic phase was dried over anhydrous MgSO₄ and concentrated, then purified by a silica column with DCM/MeOH (v/v = 40/1) as the eluent to afford compound 5b (11.27 g, 75%). ¹H NMR (400 MHz, DMSO-d₆), δ (ppm): 8.53 (d, 1H), 7.41 (d, 1H), 6.72 (t, 1H), 4.35–4.17 (m, 2H), 3.93 (s, 2H), 3.69–3.44 (m, 11H), 3.37 (t, 2H), 3.05 (q, 2H), 2.04–1.92 (m, 1H), 1.37 (s, 9H), 1.28 (d, 3H), 0.95–0.76 (m, 6H). ¹³C NMR (101 MHz, DMSO-d₆), δ (ppm): 13C NMR (101 MHz, DMSO-d₆), δ (ppm): 172.23, 170.03,
Compound 5c: Compound 5b (11.10 g, 22.6 mmol) was dissolved in a mixed solution of THF and water (90 mL, v/v = 2/1), to which LiOH (1.35 g, 61.2 mmol) was added at 0 °C. The reaction was performed at room temperature for 1 h. The reaction mixture was acidified until pH = 2 by 1 M HCl aqueous solution and diluted by EA. The organic layer was separated and the aqueous layer was extracted by EA (3 × 30 mL). The organic phase was combined, dried over anhydrous MgSO₄, and concentrated. The residue was redissolved in DCM (90 mL) and then EDC·HCl (5.21 g, 27.1 mmol), HOBt (3.66 g, 27.1 mmol), DIPEA (4.37 g, 33.9 mmol) and glycine methyl ester hydrochloride (2.91 g, 23.7 mmol) were added at 0°C. After performing the reaction at room temperature for overnight, the reaction mixture was washed by water (3 × 60 mL). The organic phase was dried over anhydrous MgSO₄ and concentrated, then purified by a silica column with DCM/MeOH (v/v = 30/1) as the eluent to afford compound 5c (11.08 g, 90%).

1H NMR (400 MHz, DMSO-d₆), δ ppm: 8.40 – 8.12 (m, 2H), 7.45 (dd, 1H), 6.71 (t, 1H), 4.42 – 4.17 (m, 2H), 4.03 – 3.70 (m, 4H), 3.70 – 3.44 (m, 11H), 3.37 (t, 2H), 3.06 (q, 2H), 2.07 – 1.89 (m, 1H), 1.37 (s, 9H), 1.22 (dd, 3H), 0.95 – 0.70 (m, 6H). 13C NMR (101 MHz, DMSO-d₆), δ (ppm): 173.04, 170.67, 170.64, 169.40, 156.04, 78.03, 70.81, 70.24, 70.18, 70.05, 69.96, 69.64, 57.02, 55.37, 52.13, 48.30, 48.24, 40.98, 31.45, 28.68, 19.66, 19.57, 18.61, 18.34. HRMS (ESI): m/z calculated for C₂₄H₄₄N₄NaO₁₀ [M + Na⁺] 571.2950, found 571.2950.

Compound 5d: Compound 5c (10.85 g, 19.9 mmol) was dissolved in a mixed solution of THF and water (80 mL, v/v = 2/1), to which LiOH (0.86 g, 39.8 mmol) was added at 0°C. The reaction was performed at room temperature for 1 h. The reaction mixture was acidified by 1M HCl
aqueous solution to pH = 2 and then diluted by EA. The organic layer was separated and the aqueous layer was extracted by EA (3 × 25 mL). The organic phase was dried over anhydrous MgSO₄ and concentrated. The residue was redissolved in DMF (80 mL), then compound F (8.07 g, 22.0 mmol), EDC·HCl (4.58 g, 23.9 mmol) and DMAP (0.61 g, 5.0 mmol) were added. After performing the reaction at 50°C for 2h, the reaction mixture was concentrated and then purified by a silica column with DCM/MeOH (v/v = 30/1) as the eluent to afford compound 4d (13.00 g, 74%). ¹H NMR spectrum (400 MHz, DMSO-d₆), δ ppm: 8.51 (q, 1H), 8.25 (d, 1H), 7.41 (d, 1H), 7.20 (s, 1H), 6.71 (t, 1H), 4.44 – 4.20 (m, 2H), 4.12 (d, 1H), 3.93 (s, 3H), 3.55 (dd, 8H), 3.40 (dt, 4H), 3.05 (q, 2H), 2.56 (s, 3H), 2.19 (s, 3H), 2.05 – 1.89 (m, 3H), 1.42 (d, 6H), 1.37 (s, 10H), 1.22 (d, 3H), 0.90 – 0.70 (m, 16H), -0.07 (s, 6H). ¹³C NMR (101 MHz, DMSO-d₆), δ (ppm): 173.18, 170.64, 169.37, 168.93, 156.03, 140.67, 133.94, 78.01, 70.81, 70.24, 70.20, 70.06, 69.97, 69.65, 60.43, 56.95, 48.26, 45.36, 41.17, 31.48, 31.29, 28.69, 26.20, 25.00, 19.69, 18.68, 18.32, 18.25, 16.80, -5.08. HRMS (ESI): m/z calculated for C₄₂H₇₃N₅O₁₃Si [M + Na⁺] 906.4866, found 906.4866.

**Compound 5e:** Compound 5d (12.50 g, 14.2 mmol) was dissolved in methanol (55 mL) and Amberlyst 15 (9.14 g, 49.7 mmol) was added. After performing the reaction for 1h, the reaction mixture was filtered and concentrated. The crude product was dissolved in DMF (55 mL) and then Celite 545RV (37.37 g) and pyridinium dichromate (37.37 g, 99.4 mmol) were added. After reacting overnight at room temperature, diethyl ether (55 mL) is added to the system. The mixture was filtered by diatomite, then water (80 mL) was added to the filtrate. The aqueous layer was acidified by aqueous 1 M HCl aqueous solution until pH = 2. The organic layer was separated, washed by water (2×80 mL) and then concentrated. The crude product was purified by a silica column with DCM/MeOH (v/v = 20/1) as the eluent to afford the product 5e (4.65 g, 42%)
containing a small amount of by-products (ca. 30% molar content), which cannot be separated by silica column. The contaminated product 5e was then used directly in the next reaction step to synthesize compound 5f.

**Compound 5f**: To a stirred solution of contaminated compound 5e (4.00 g, 5.13 mmol) in THF (50 mL), pentafluorophenol (1.42 g, 7.70 mmol), EDC·HCl (1.97 g, 10.26 mmol) and DMAP (0.16 g, 1.28 mmol) were added. After performing the reaction at room temperature for overnight, the reaction mixture was concentrated and then purified by a silica column with DCM/MeOH (v/v = 30/1) as the eluent to afford compound 5f (2.43 g, 50%).

$^1$H NMR (400 MHz, DMSO-d$_6$), δ ppm: 8.60 (t, 1H), 8.29 (d, 1H), 7.42 (d, 1H), 7.22 (s, 1H), 4.44 – 4.20 (m, 2H), 4.05 (d, 2H), 3.93 (s, 2H), 3.67 – 3.40 (m, 10H), 3.37 (d, 2H), 3.04 (q, 2H), 2.59 (s, 3H), 2.20 (s, 3H), 1.55 (s, 6H), 1.36 (s, 10H), 1.22 (d, 3H), 0.82 (dd, 6H). $^{13}$C NMR (101 MHz, DMSO-d$_6$), δ (ppm): 173.51, 170.67, 169.40, 168.91, 167.93, 156.04, 143.48, 141.92, 134.14, 129.00, 78.02, 70.81, 70.23, 70.19, 70.05, 69.96, 69.63, 56.96, 48.22, 47.27, 41.28, 39.18, 31.46, 30.04, 28.66, 24.98, 19.65, 18.57, 18.29, 16.83. HRMS (ESI): m/z calculated for C$_{42}$H$_{56}$F$_5$NS$_5$NaO$_{14}$ [M + Na$^+$] 972.3636, found 972.3636.

**M4**: Compound 5f (2.00 g, 2.11 mmol) was dissolved in a mixed solution of DCM (15 mL) and TFA (6 mL). The reaction was performed at room temperature for 30 minutes and then concentrated. The residue was dissolved in DCM (42 mL), which was then dropwise added to a large amount of DCM (280 mL) containing TEA (0.71 g, 7.03 mmol) at room temperature in 3 h by a syringe pump. After that, the solvent was removed and the residue was purified by a silica column with PE/EA (v/v = 1/1) as the eluent to afford the M4 (0.58 g, 42%).

$^1$H NMR (400 MHz, DMSO-d$_6$), δ (ppm): 8.62 (t, 1H), 8.21 (d, 1H), 7.55 (d, 1H), 7.30 (s, 1H), 7.15 (s, 1H), 4.36 (p, 1H), 4.23 (dd, 1H), 4.18 – 3.83 (m, 4H), 3.69 – 3.42 (m, 8H), 3.10 (m, 2H), 2.61 (d, 4H), 2.44 (d, 1H), 2.21 (s, 3H), 2.02 (m, 1H), 1.47 (d, 6H), 1.27 (d, 3H), 0.87 (dd, 6H). $^{13}$C NMR (101 MHz,
DMSO-d$_6$), $\delta$ (ppm): 173.57, 170.78, 170.44, 169.70, 168.62, 143.53, 142.66, 140.77, 138.97, 133.83, 128.61, 71.02, 70.43, 69.95, 69.91, 69.86, 69.41, 57.56, 55.37, 48.43, 47.82, 41.68, 39.46, 38.81, 31.44, 31.25, 31.22, 25.53, 19.79, 18.68, 18.47, 17.14. HRMS (ESI): m/z calculated for C$_{31}$H$_{47}$N$_5$NaO$_{11}$ [M + Na$^+$] 688.3164, found 688.3164.

4. Homopolymerization

4.1 General polymerization procedure

Scheme S6. ROP of macrocyclic monomers.

Hexylamine was used as initiator for all polymerization reactions. After dissolving monomer in designed solvent with designed initial monomer concentration and feed ratio, hexylamine was added to initiate the polymerization at designed temperature. The polymerization aliquots were taken at the designed reaction time for in-situ $^1$H NMR analysis to determine monomer conversion and for GPC analysis to determine $M_n$ and $D$. The resultant polymer could be purified by precipitation.

4.2 Polymerization of M1 for evaluating its polymerization kinetics
Scheme S7. ROP of M1.

**M1 polymerization with $[\text{M1}]_0/[\text{I}]_0=25:1$:** In a 2 mL Agilent injection bottle, M1 (82.5 mg, 0.15 mmol) and hexylamine (0.606 mg, 6 μmol) were dissolved in 0.1 mL solvent (anisole, DMSO, DMF, toluene, or chlorobenzene). The polymerization was performed at the designed temperature of 70 °C, 90 °C, or 110 °C. The polymerization aliquots were taken at the designed reaction time for in-situ $^1$H NMR analysis to determine M1 conversion and for GPC analysis to determine $M_{n,GPC}$ and $D$.

**M1 polymerization with $[\text{M1}]_0/[\text{I}]_0=50:1$:** In a 2 mL Agilent injection bottle, M1 (82.5 mg, 0.15 mmol) and hexylamine (0.303 mg, 3 μmol) were dissolved in 0.15 mL anisole. The polymerization was performed at 90 °C. Polymerization aliquots were taken at the designed reaction time for in-situ $^1$H NMR analysis to determine M1 conversion and for GPC analysis to determine $M_{n,GPC}$ and $D$.

**M1 polymerization with $[\text{M1}]_0/[\text{I}]_0=100:1$:** In a 2 mL Agilent injection bottle, M1 (82.5 mg, 0.15 mmol) and hexylamine (0.1515 mg, 1.5 μmol) were dissolved in 0.15 mL anisole. The polymerization was performed at 90 °C. Polymerization aliquots were taken at the designed reaction time for in-situ $^1$H NMR analysis to determine M1 conversion and for GPC analysis to determine $M_{n,GPC}$ and $D$.

4.3 Polymerization of M2 for evaluating its polymerization kinetics
**Scheme S8. ROP of M2.**

*M2 polymerization with *[M1]*₀/[I]₀=25:1*: In a 2 mL Agilent injection bottle, **M2** (83.4 mg, 0.15 mmol) and hexylamine (0.606 mg, 6 μmol) were dissolved in 0.1 mL anisole. The polymerization was performed at 90 °C. Polymerization aliquots were taken at the designed reaction time for in-situ ¹H NMR analysis to determine **M2** conversion and for GPC analysis to determine *M*_n,GPC and *D*.

**4.4 Polymerization of M3 for evaluating its polymerization kinetics**

**Scheme S9. ROP of M3.**

*M3 polymerization with *[M3]*₀/[I]₀=25:1*: In a 2 mL Agilent injection bottle, **M3** (82.2 mg, 0.15 mmol) and hexylamine (0.606 mg, 6 μmol) were dissolved in 0.1 mL DMF. The polymerization was performed at 90 °C. Polymerization aliquots were taken at the designed
reaction time for in-situ \(^1\)H NMR analysis to determine M3 conversion and for GPC analysis to determine \(M_{n,GPC}\) and \(D\).

4.5 Polymerization of M4 for evaluating its polymerization kinetics

\[ \text{Scheme S10. ROP of M4.} \]

**M4 polymerization with \([M4]_0/[I]_0=25:1:**  In a 2 mL Agilent injection bottle, M4 (99.3 mg, 0.15 mmol) and hexylamine (0.606 mg, 6 \(\mu\)mol) were dissolved in 0.1 mL DMF. The polymerization was performed at 90 °C. Polymerization aliquots were taken at the designed reaction time for in-situ \(^1\)H NMR analysis to determine M4 conversion and for GPC analysis to determine \(M_{n,GPC}\) and \(D\).

5. Preparation of diblock copolymer

5.1 Preparation of P1\(_{25-}\)-b-P3\(_{20}\) by sequential monomer addition
In a 2 mL Agilent injection bottle, \( \text{M1} \) (82.5 mg, 0.15 mmol) and hexylamine (0.606 mg, 6 μmol) were dissolved in 0.1 mL DMF. The polymerization of \( \text{M1} \) was performed in DMF at 90 °C for 3 h. In this condition, \(^1\text{H-NMR} \) analysis shows \( \text{M1} \) conversion reached above 99.0%. GPC analysis produced \( M_{n,\text{GPC}} = 27400 \) and \( D = 1.04 \) for \( \text{P1}_{25}-\text{NH}_2 \). Then, \( \text{M3} \) (82.2 mg, 0.15 mmol) was added directly into the polymerization solution to extend the polymer chain by polymerizing \( \text{M2} \). The polymerization reaction was further performed at 90 °C for another 10 h. In this condition, \(^1\text{H-NMR} \) analysis shows \( \text{M2} \) conversion reached 78.8%. GPC analysis produced \( M_{n,\text{GPC}} = 44700 \) and \( D = 1.06 \) for the resultant \( \text{P1}_{25}-\text{P3}_{20} \).

5.2 Preparation of \( \text{P1}_{22}-b-\text{PEG}_{45} \) by copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) click reaction

5.2.1 Synthesis of alkyne-functionalized \( p \)-nitrophenol activated carbonate X
Scheme S12. Synthesis of compound X.

4-Pentyn-1-ol (0.54 g, 6 mmol) was dissolved in DCM (20 mL) and 4-nitrophenyl chloroformate (1 g, 5 mmol) was added. Then TEA (0.61 g, 6 mmol) in DCM (5 mL) was added dropwise under ice bath. The reaction was performed at room temperature for 2 h. After that, the solution was washed by water and with brine, then dried over anhydrous MgSO$_4$. The organic phase was concentrated and purified by a silica column with PE/EA (v/v = 10/1) as the eluent to afford the Compound 1 (0.94 g, 75.5%). $^1$H NMR (400 MHz, DMSO-d$_6$), $\delta$ (ppm): 8.32 (m, 2H), 7.58 (m, 2H), 4.32 (t, 2H), 2.86 (t, 1H), 2.30 (m, 2H), 1.88 (m, 2H). $^{13}$C NMR (101 MHz, DMSO-d$_6$), $\delta$ (ppm): 155.78, 152.47, 145.62, 125.82, 123.06, 83.64, 72.24, 27.40, 14.83. HRMS (ESI): m/z calculated for C$_{12}$H$_{11}$NNaO$_5$ [M + Na$^+$] 272.0529, found 272.0529.

5.2.2 Synthesis of PEG$_{45}$-N$_3$$^{[1]}$

Scheme S13. Synthesis of PEG$_{45}$-N$_3$.

PEG$_{45}$-OTS: PEG$_{45}$-OH (1 g, 0.5 mmol) was dissolved in DCM (5 mL) and NaOH aqueous solution (30%, 10 mL) was added. After stirring the mixture for 15 minutes, TsCl (1.6 g, 16.84 mmol) in DCM (5 mL) was added dropwise. The reaction was performed at room temperature for 24 h. After that, the organic phase was separated, washed by water (2×10 mL), and dried over anhydrous MgSO$_4$. Next, the organic phase was concentrated and frozen to 0°C. While stirring,
excess diethyl ether was added to the concentrate slowly. After 1 h, white solid was filtered and washed with diethyl ether (2×10 mL). The product PEG₄₅-OTs (0.99 g, 91.7%) was used without further purification. ¹H NMR (400 MHz, DMSO-d₆), δ (ppm): 7.48(dd, 2H), 7.12(dd, 2H), 3.68-3.38(m, 170H), 3.24(s, 3H), 2.29(s, 3H).

PEG₄₅-N₃: PEG₄₅-OTs (0.97 g, 0.45mmol) and NaN₃ (0.23 g, 3.6 mmol) were sequentially added to DMF (2.5 mL) and the reaction system was stirred for 36 h at 50 °C. After diluting the reaction solution in DCM (20 mL), filtration was used to remove excess NaN₃. After concentrating the filtrate, the product PEG₄₅-N₃ (0.72 g, 78.5%) was collected by precipitation in diethyl ether. ¹H NMR (400 MHz, CDCl₃), δ (ppm): 3.69-3.54(m, 170H), 3.40-3.38(m, 5H), 1.72(s, 4H).

5.2.3 Synthesis of P1₂₂-yne

![Scheme S14. Synthesis of P1₂₂-yne.](image)

In a 2 mL Agilent injection bottle, M1 (198 mg, 0.36 mmol) and hexylamine (1.45 mg, 14.4 μmol) were dissolved in 0.24 mL anisole. In this condition, [M1]₀/[hexamine]₀ and [M1]₀ were calculated as 25/1 and 1.5 M, respectively. The polymerization was performed at 90 °C for 1.75 h to reach a M1 conversion of 90% determined by ¹H-NMR characterization. Compound 1 (358.6 mg, 1.44 mmol) and DIPEA (46.44 mg, 0.36 mmol) were then added to the polymerization solution to terminate the reaction. The end-group modification reaction was performed at 90 °C for another
6 h. The pure P122-yne (90 mg, 91.5%) was obtained by precipitation in Et₂O twice. GPC analysis produced $M_{n,GPC} = 26500$ and $D = 1.04$.

5.2.4 Synthesis of P122-b-PEG₄₅ by CuAAC click reaction

PEG₄₅-N₃ (18 mg, 8.8 μmol), P122-yne (40 mg, 5.9 μmol), and PMDETA (10 mg, 59 μmol) were dissolved in DCM (0.2 mL) in a 5 mL Schlenk tube. After three freeze-evacuate-thaw cycles, CuBr (8.4 mg, 59 μmol) was added to the mixture under N₂. The reaction was performed at room temperature overnight and then quenched by exposing to air. The reaction mixture was precipitated in a mixed solvent of diethyl ether/methanol (v/v = 8/1) to remove the excess PEG₄₅-N₃ and other small molecules, producing pure P122-b-PEG₄₅ (38 mg) with a yield of 77%. GPC analysis produced $M_{n,GPC} = 30000$ and $D = 1.04$.

6. Polymer degradation

6.1 Degradation of P1₂₂
Scheme S16. Degradation of P1$_{22}$.

P1$_{22}$-yne (20 mg, 3.0 μmol) was dissolved in a mixed solution of DCM and MeOH (2 mL, v/v = 9/1), to which TBD (5.6 mg, 40 μmol, 0.3 equiv/ester) was added. The degradation reaction was performed at room temperature. At the given time, the reaction aliquots (0.5 mL) were quenched by adding AcOH (1.2 μL, 2 equiv/TBD) and then concentrated. The resultant crude products were then directly characterized by GPC and $^1$H-NMR.

6.2 Degradation of P3$_{22}$

6.2.1 Synthesis of P3$_{22}$

Scheme S17. Synthesis of P3$_{22}$-yne.

In a 2 mL Agilent injection bottle, M3 (137 mg, 0.25 mmol) and hexylamine (1.01 mg, 10.0 μmol) were dissolved in 0.167 mL DMF. In this condition, [M3]/[hexamine] and [M3]$_0$ were calculated as 25/1 and 1.5 M, respectively. The polymerization was performed at 90 °C for 10 h.
to reach a \textbf{M3} conversion of 86.5\% determined by \textsuperscript{1}H-NMR characterization. Compound 1 (311 mg, 1.25 mmol) and DIPEA (32.3 mg, 0.25 mmol) were then added to the polymerization solution to terminate the reaction. The end-group modification reaction was performed at 90 °C for another 6 h. The pure P3\textsubscript{22} (57 mg, 93\%) was obtained by precipitation in Et\textsubscript{2}O twice. GPC analysis produced $M_{n,GPC} = 25400$ and $D = 1.06$.

**6.2.22 Degradation of P3\textsubscript{22}**

![Scheme S18. Degradation of P3\textsubscript{22}.

P3\textsubscript{22} (20 mg, 3 \textmu mol) was dissolved in a mixed solution of DCM and MeOH (2 mL, v/v = 9/1), to which TBD (5.4 mg, 38.8 \textmu mol, 0.3 equiv/ester) was added. At the given time, the reaction aliquots were quenched by adding AcOH (1.1 \textmu L, 2 equiv/TBD) and then concentrated. The crude products were then directly characterized by GPC and \textsuperscript{1}H-NMR.

**References:**

Figure S1. $^1$H NMR (A) and $^{13}$C NMR (B) spectra of macrocyclic monomer M1 in DMSO-d$_6$. 
Figure S2. $^1$H NMR (A) and $^{13}$C NMR (B) spectra of macrocyclic monomer M2 in DMSO-d$_6$. 
Figure S3. $^1$H NMR (A) and $^{13}$C NMR (B) spectra of macrocyclic monomer M3 in DMSO-d$_6$. 
Figure S4. $^1$H NMR (A) and $^{13}$C NMR (B) spectra of macrocyclic monomer M4 in DMSO-d$_6$. 
Figure S5. $^1$H NMR of spectra (in CDCl$_3$) of M1 (A), crude polymerization solution of M1 after 2.75 h reaction (B), and the detached compound C during polymerization collected by simply
evaporating the crude ethyl ether solution of P1 precipitate (C). M1 conversion was calculated by 
\[
\frac{(\text{Area}(H_{f,a,c,r})-\text{Area}(H_a))}{(\text{Area}(H_{f,a,c,r})+\text{Area}(H_a)+\text{Area}(H_c))}
\]
in Figure B.

**Figure S6.** GPC curves of the polymerization aliquots for preparing P1 with varied reaction time using different [M1]/[hexamine]₀ values of 25/1 (A), 50/1 (B), and 100/1 (C). The polymerizations were performed in anisole at 90 °C using [M1]₀ = 1.5 M (A) or 1 M (B and C).
Figure S7. GPC curves of the polymerization aliquots with varied reaction time (A, C, E, G) and dependence of $M_n$ and $D$ on M1 conversion (B, D, F, H) for preparing P1 in different solvents of DMSO (A, B), DMF (C, D), chlorobenzene (E, F), and toluene (G, H). The polymerizations were performed at 90 °C using $[M1]_0 = 1.5$ M and $[M1]_0/[hexamine]_0 = 25/1$. 
Figure S8. GPC curves of the polymerization aliquots with varied reaction time (A, C), dependence of $M_{n,GPC}$ and $D$ on M1 conversion (B, D), and dependence of $\ln([M]_0/[M]_t)$ on reaction time (E) for preparing P1 at different temperature of 70 (A, B) and 110 °C (C, D). The polymerizations were performed at in anisole using $[M1]_0 = 1.5$ M and $[M1]_0/[\text{hexamine}]_0 = 25/1$. 
Figure S9. GPC curves of the polymerization aliquots with varied reaction time (A, C), dependence of $M_{n, GPC}$ and $D$ on $M1$ conversion (B, D), and dependence of $\ln([M]_0/[M]_t)$ on reaction time (E) for preparing $P1$ using different $[M1]_0$ values of 0.2 (A, B) and 0.5 M (C, D). The polymerizations were performed at 90 °C in anisole using $[M1]_0/[\text{hexamine}]_0 = 25/1$. 
Figure S10. GPC curves of the polymerization aliquots with varied reaction time for polymerizing M2 (A), M3 (B), and M4 (C). The polymerizations were performed at 90 °C using [M]₀/[hexamine]₀ = 25/1 and [M]₀ = 1.5 M, where anisole was used as solvent for polymerizing M2 and DMF was used as solvent for polymerizing M3 and M4.
Figure S11. Kinetic plots of $\ln([M]_0/[M]_t)$ versus reaction time for the syntheses of P1, P2, P3, and P4, where the polymerizations were all performed at 90 °C using $[M]_0$/[hexamine]$_0 = 25/1$ and $[M]_0 = 1.5$ M. Anisole was used as solvent for polymerizing M1 and M2, while DMF was used as solvent for polymerizing M3 and M4.
**Figure S12.** $^1$H NMR spectra (in DMSO-d$_6$) of M1 (A) and the crude polymerization solution of M1 with 3 h reaction (B). The nearly quantitative M1 conversion was indicated by the disappearance of its characteristic peaks a, b, and m in Figure B.
Figure S13. $^1$H NMR spectra (in DMSO-$d_6$) of M1 (A) and the crude polymerization solution of M3 in 10 h (B). M3 conversion was calculated by $\text{Area}(H_k)/(\text{Area}(H_k)+\text{Area}(H_{k'}))$ in Figure B.
**Figure S14.** $^1$H NMR spectra (in DMSO-d$_6$) of P1$_{22}$-yne (A) and the resultant block copolymer P1$_{22}$-b-PEG$_{45}$ (B).
Figure S15. $^1$H NMR spectra (in DMSO-d$_6$) of P1$_{22}$ (A) and the crude degraded products without purification (B). The complete degradation of P1$_{22}$ was indicated by the disappearance of its characteristic peak f in Figure B.
Figure S16. $^1$H NMR spectra (in DMSO-d$_6$) of P3$_{22}$ (A) and the crude degraded products without purification (B). The complete degradation of P3$_{22}$ was indicated by the disappearance of its characteristic peaks d and e in Figure B.
Table S1. GPC measurement of P1–P4.

<table>
<thead>
<tr>
<th>polymer</th>
<th>$M_n,\text{GPC}$ (g/mol)</th>
<th>$D$</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1$_{24}$</td>
<td>26500</td>
<td>1.03</td>
</tr>
<tr>
<td>P1$_{48}$</td>
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</tr>
<tr>
<td>P2$_{24}$</td>
<td>25900</td>
<td>1.05</td>
</tr>
<tr>
<td>P3$_{24}$</td>
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<td>1.10</td>
</tr>
<tr>
<td>P4$_{24}$</td>
<td>22700</td>
<td>1.05</td>
</tr>
</tbody>
</table>

Molecular weights ($M_n,\text{GPC}$) and dispersities ($D$) determined by gel permeation chromatography (GPC) in DMF using polystyrene standards for calibration.