

Facile Synthesis of a Tadpole-shaped Dendrimer Based on Aromatic Polyamides

Yumiko Ito, Isao Washio, and Mitsuru Ueda*

Department of Organic and Polymeric Materials, Graduate School of Science and Engineering, Tokyo

Institute of Technology, 2-12-1, O-okayama, Meguro-ku, Tokyo, 152-8552, Japan

Supporting Information

Synthesis and characterization of protected-monomer (2), protected-dimer (3), dimer (4), protected-tetramer (5), tetramer (6), protected-octamer (7), octamer (8), AB-monomer (1'), protected-monomer (2'), protected-dimer (3'), dimer (4'), protected-tetramer (5'), tetramer (6'), protected-octamer (7'), octamer (8'), protected-hexadecamer (9')

MALDI-TOF-MS spectrum of protected-nonamer 7''

Figure 1S. MALDI-TOF MS spectrum of octamer 8

Figure 2S. MALDI-TOF MS spectrum of protected-nonamer 7''

Preparation of protected-monomer (2). To a solution of 4-(*N*-methylamino)benzoic acid (10.0 g, 66.2 mmol) in THF (100 mL) was added trifluoroacetic anhydride (30.6 g, 146 mmol) at 0 °C under nitrogen. The reaction mixture was stirred at the temperature for 10 min, followed by 25 °C for 3 h. Then, water (100 mL) was added and stirring was continued for 6 h at the temperature °C. The reaction mixture was extracted with diethyl ether, and the organic layer was washed with water several times, dried over MgSO₄, and filtered. The filtrate was evaporated, and the residue was recrystallized from toluene to give a white crystal (94% yield). ¹H NMR (CDCl₃, ppm, 25 °C): δ = 3.42 (s, 3H), 7.39 (d, 2H), 8.21 (d, 2H).

Preparation of protected-dimer (3). Thionyl chloride (5.01 mL, 68.9 mmol) was added to a solution of protected-monomer **2** (16.4 g, 66.3 mmol) in NMP (66 mL) at 0 °C under nitrogen. The solution was stirred at the temperature for 10 min, followed by 25 °C for 30 min. Then, to this solution was added 4-(*N*-methylamino)benzoic acid (10.5 g, 69.6 mmol) and the solution was stirred at the temperature for 1 h. The solution was poured into dilute HCl, and the precipitate was filtered and dried. The crude product was recrystallized from *i*-PrOH and dried under reduced pressure at 100 °C to give white solid (93% yield). ¹H NMR (CDCl₃, ppm, 25 °C): δ = 3.30 (s, 3H), 3.56 (s, 3H), 7.10 (m, 4H), 7.38 (d, 2H), 7.97 (d, 2H).

Preparation of dimer (4). A solution of potassium carbonate (16.6 g, 120 mmol) in water (160 mL) was added to a solution of protected-dimer **3** (15.3 g, 40.0 mmol) in MeOH (160 mL) at 0 °C under nitrogen. The solution was stirred at the temperature for 10 min, followed by 25 °C for 3 h. Then, the solution was diluted with NaCl_{aq}, and the pH of the solution was adjusted around 4.0 using HCl_{aq}. The precipitate was filtered and dried under reduced pressure at 120 °C to give white solid (98% yield). ¹H NMR (DMSO-d₆, 40 °C): δ = 2.62 (s, 3H), 3.35 (s, 3H), 5.99 (s, 1H), 6.32 (d, 2H), 7.05 (d, 2H), 7.18 (d, 2H), 7.80 (d, 2H).

Preparation of protected-tetramer (5). To a solution of protected-dimer **3** (12.1 g, 31.8 mmol) in NMP (50 mL), was added thionyl chloride (2.41 ml, 33.1 mmol) at 0 °C under nitrogen. The reaction mixture was stirred at the temperature for 10 min, followed by 25 °C for 30 min. Then, to this solution

was added dimer **4** (9.32 g, 32.8 mmol) and the resultant solution was stirred at the temperature for 1 h. The solution was poured into dilute HCl, and the precipitate was filtered. The crude product was purified by recrystallization from acetonitrile to give a white crystal (90% yield). ^1H NMR (CDCl_3 , ppm, 25 °C): δ = 3.31 (s, 3H), 3.41 (s, 3H), 3.47 (s, 3H), 3.51 (s, 3H), 6.79 (m, 4H), 7.06 (m, 6H), 7.17 (d, 2H), 7.24 (d, 2H), 7.92 (d, 2H).

Preparation of tetramer (6). To a solution of protected-tetramer **5** (8.41 g, 13.0 mmol) in MeOH (52 mL) was added a solution of potassium carbonate (5.39 g, 39.0 mmol) in water (52 ml) at 0 °C under nitrogen. The reaction mixture was stirred at the temperature for 10 min, followed by 25 °C for 30 min. The solution was diluted with NaCl_{aq} , and the pH of the solution was adjusted around 4.0 using HCl_{aq} . The precipitate was filtered and dried under reduced pressure at 120 °C to give white solid (98% yield). ^1H NMR (CDCl_3 , ppm, 25 °C): δ = 2.78 (s, 3H), 3.41 (s, 3H), 3.44 (s, 3H), 3.50 (s, 3H), 5.58 (s, 1H), 6.25 (d, 2H), 6.82 (d, 4H), 6.97 (d, 2H), 7.03 (d, 2H), 7.08 (d, 2H), 7.17 (d, 2H), 7.88 (d, 2H).

Preparation of protected-octamer (7). Thionyl chloride (0.165 mL, 2.27 mmol) was added to a solution of protected-tetramer **5** (1.41 g, 2.18 mmol) in NMP (4.4 mL) at 0 °C under nitrogen. The solution was stirred at the temperature for 10 min, followed by 25 °C for 3 h. To this solution, a solution of tetramer **6** (1.23 g, 2.23 mmol) in NMP (4.4 mL) was added and the resultant solution was stirred at the temperature for 3 h. The solution was poured into dilute HCl. the precipitate was filtered and dried. The crude product was washed with hot MeOH, then filtered and dried under reduced pressure at 120 °C

to give white solid (97% yield). ^1H NMR (CDCl_3 , ppm, 25 °C): δ = 3.29 (s, 3H), 3.35 (s, 3H), 3.37 (s, 3H), 3.41 (s, 6H), 3.43 (s, 3H), 3.46 (s, 3H), 3.48 (s, 3H), 6.70 (d, 2H), 6.73 (d, 2H), 6.76-6.86 (m, 6H), 6.93 (d, 2H), 6.97-7.11 (m, 12H), 7.15 (d, 2H), 7.19 (d, 2H), 7.26 (d, 2H), 7.85 (d, 2H). Anal. Calcd for $\text{C}_{74}\text{H}_{73}\text{F}_3\text{N}_8\text{O}_{10}$: C, 68.82; H, 5.70; N, 8.68. Found: C, 68.64; H, 5.94; N, 8.53.

Preparation of octamer (8). To a solution of protected-octamer **7** (2.03 g, 1.72 mmol) in NMP (17.2 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.785 g, 5.15 mmol) and water (0.1 mL) under nitrogen. The reaction mixture was stirred at 100 °C for 4 h. Then, the resultant solution was diluted with water, and the pH of the solution was adjusted around 4.0 using HCl_{aq} . The precipitate was filtered and dried under reduced pressure at 100 °C to give white solid (94% yield). ^1H NMR (CDCl_3 , ppm, 25 °C): δ = 2.75 (s, 3H), 3.34 (s, 3H), 3.38 (s, 3H), 3.39 (s, 3H), 3.42 (s, 3H), 3.43 (s, 3H), 3.49 (s, 6H), 6.16 (d, 2H), 6.62 (d, 2H), 6.65 (d, 2H), 6.71-6.85 (m, 6H), 6.89 (d, 2H), 6.96-7.08 (m, 14H), 7.15 (d, 2H), 7.87 (d, 2H). Calcd.: $[\text{M}]^+$ m/z = 1083.2. Found: MALDI-TOF-MS: $[\text{M}+\text{H}]^+$ = 1086.8, $[\text{M}+\text{Na}]^+$ = 1108.9.

Preparation of AB-monomer (1'). Ethyl iodide (15.6 g, 100 mol) was added to a solution of 4-aminobenzoic acid (33.0 g, 200 mol) in hexamethylphosphoric triamide (100 mL) at 25 °C under nitrogen. The solution was stirred at 120 °C for 10 h, allowed to cool to 25 °C, and poured into water. The precipitate was filtered, dissolved in MeOH (400 mL) and then precipitated with water (500 mL). The precipitate was collected and dissolved in EtOH (150 mL). To this solution was added potassium

hydroxide (22.0 g, 392 mmol) under nitrogen, and the resultant solution was refluxed for 6 h. The reaction mixture was poured into water, and then the pH of the resulting solution was adjusted around 4.0 using HCl_{aq} . The precipitate was filtered, dried and recrystallized from chloroform to give a slightly yellow crystal (68% yield calculated toward ethyl iodide). ^1H NMR (CDCl_3 , ppm, 25 °C): δ = 1.21 (t, 3H), 3.85 (q, 2H), 7.36 (d, 2H), 8.21 (d, 2H).

Preparation of protected-monomer (2'). To a solution of 4-(*N*-ethylamino)benzoic acid (21.4 g, 130 mmol) in THF (200 mL) was added trifluoroacetic anhydride (59.9 g, 285 mmol) at 0 °C under nitrogen. The solution was stirred at the temperature for 10 min, followed by 25 °C for 3 h. Then, to this solution was added water (200 mL) and stirring was continued for 6 h at the temperature. The reaction mixture was extracted with diethyl ether, and the organic layer was washed with water several times, dried over MgSO_4 , and filtered. The filtrate was evaporated, and the residue was recrystallized from toluene to give a white crystal (84% yield). ^1H NMR (CDCl_3 , ppm, 25 °C): δ = 1.21 (t, 3H), 3.85 (q, 2H), 7.36 (d, 2H), 8.21 (d, 2H). Anal. Calcd for $\text{C}_{11}\text{H}_{10}\text{F}_3\text{NO}_3$: C, 50.58; H, 3.86; N, 5.36. Found: C, 50.55; H, 3.94; N, 5.30.

Preparation of protected-dimer (3'). Thionyl chloride (5.01 mL, 68.9 mmol) was added to a solution of protected-monomer 2' (17.3 g, 66.3 mmol) in NMP (66 mL) at 0 °C under nitrogen. The solution was stirred at the temperature for 10 min, and then 25 °C for 30 min. To this solution 4-(*N*-ethylamino)benzoic acid (11.3 g, 68.2 mmol) was added, and stirring was continued for 1 h at the

temperature. The solution was poured into dilute HCl, and the precipitate was filtered and dried. The crude product was recrystallized from toluene to give a white crystal (96% yield). ^1H NMR (CDCl_3 , ppm, 25 °C): δ = 1.10 (t, 3H), 1.26 (t, 3H), 3.72 (q, 2H), 4.06 (q, 2H), 7.04 (d, 2H), 7.10 (d, 2H), 7.37 (d, 2H), 7.97 (d, 2H). Anal. Calcd for $\text{C}_{20}\text{H}_{19}\text{F}_3\text{N}_2\text{O}_4$: C, 58.82; H, 4.69; N, 6.86. Found: C, 58.77; H, 4.79; N, 6.94.

Preparation of dimer (4'). To a solution of protected-dimer **3'** (18.4 g, 45.0 mmol) in MeOH (180 mL) was added a solution of potassium carbonate (18.7 g, 135 mmol) in water (180 mL) at 0 °C under nitrogen. The reaction mixture was stirred at the temperature for 10 min, and followed by 25 °C for 3 h. Then, the resulting solution was diluted with NaCl_{aq} , and the pH of the solution was adjusted around 4.0 using HCl_{aq} . The precipitate was filtered and dried under reduced pressure at 100 °C to give white solid (97% yield). ^1H NMR (CDCl_3 , ppm, 25 °C): δ = 1.21 (t, 3H), 1.23 (t, 3H), 3.10 (q, 2H), 4.02 (q, 2H), 6.32 (d, 2H), 7.12 (d, 2H), 7.17 (d, 2H), 7.97 (d, 2H). Anal. Calcd for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.54; H, 6.67; N, 8.99.

Preparation of protected-tetramer (5') Thionyl chloride (3.01 mL, 41.4 mmol) was added to a solution of protected-dimer **3'** (16.2 g, 39.8 mmol) in NMP (40 mL) at 0 °C under nitrogen. The reaction mixture was stirred at the temperature for 10 min, followed by 25 °C for 30 min. Dimer **4'** (12.8 g, 41.0 mmol) was added to this solution and stirring was continued for 1 h at the temperature. The solution was poured into dilute HCl, and the precipitate was filtered and dried. The crude product was purified by

silica gel column chromatography (gradient elution from diethyl ether to ethyl acetate) to give white solid (82% yield). ^1H NMR (CDCl_3 , ppm, 25 °C): δ = 1.08-1.28 (m, 12H), 3.77 (q, 2H), 3.90 (q, 2H), 3.98 (q, 2H), 4.03 (q, 2H), 6.80 (m, 4H), 7.02 (d, 2H), 7.07 (d, 2H), 7.10 (d, 2H), 7.19 (d, 2H), 7.25 (d, 2H), 7.95 (d, 2H). Anal. Calcd for $\text{C}_{38}\text{H}_{37}\text{F}_3\text{N}_4\text{O}_6$: C, 64.99; H, 5.31; N, 7.97. Found: C, 64.99; H, 5.54; N, 7.84.

Preparation of tetramer (6'). To a solution of protected-tetramer **5'** (6.00 g, 8.54 mmol) in MeOH (50 mL) was added a solution of potassium carbonate (3.54 g, 25.6 mmol) in water (50 mL) at 0 °C under nitrogen. The reaction mixture was stirred at the temperature for 10 min, followed by 25 °C for 6 h. Then, the resulting solution was diluted with NaCl_{aq} , and the pH of the solution was adjusted around 4.0 using HCl_{aq} . The precipitate was filtered and dried under reduced pressure at 100 °C to give white solid (99% yield). ^1H NMR (CDCl_3 , ppm, 25 °C): δ = 1.13 (m, 6H), 1.23 (m, 6H), 3.10 (q, 2H), 3.89 (q, 2H), 3.93 (q, 2H), 4.00 (q, 2H), 6.22 (d, 2H), 6.80 (d, 2H), 6.81 (d, 2H), 6.97 (d, 2H), 7.00 (d, 2H), 7.07 (d, 2H), 7.17 (d, 2H), 7.87 (d, 2H).

Preparation of protected-octamer (7'). Thionyl chloride (0.765 ml, 10.5 mmol) was added to a solution of protected-tetramer **5'** (7.12 g, 10.1 mmol) in NMP (10 mL) at 0 °C under nitrogen. The solution was stirred at the temperature for 10 min, followed by 25 °C for 30 min. To this solution a solution of tetramer **6'** (6.21 g, 10.2 mmol) in NMP (10 mL) was added and the resultant solution was stirred at the temperature for 3 h. Then, the reaction mixture was poured into dilute HCl, the precipitate

was filtered and dried. The crude product was recrystallized from ethyl acetate to give a white crystal (85% yield). $^1\text{H NMR}$ (CDCl_3 , ppm, 25 °C): $\delta = 1.05\text{-}1.25$ (m, 24H), 3.73 (q, 2H), 3.80-4.05 (m, 14H), 6.66-6.85 (m, 10H), 6.91 (d, 2H), 6.95-7.11 (m, 12H), 7.15 (d, 2H), 7.21 (d, 2H), 7.26 (d, 2H), 7.85 (d, 2H). Anal. Calcd for $\text{C}_{74}\text{H}_{73}\text{F}_3\text{N}_8\text{O}_{10}$: C, 68.82; H, 5.70; N, 8.68. Found: C, 68.64; H, 5.94; N, 8.53.

Preparation of octamer (8'). To a solution of protected-octamer **7'** (5.00 g, 3.87 mmol) in NMP (15 mL) was added hydrazine monohydrate (0.582 g, 11.6 mmol) under nitrogen. The solution was stirred at 25 °C for 10 h. Then, the resulting solution was diluted with water, and the pH of the solution was adjusted around 4.0 using HCl_{aq} . The precipitate was filtered and dried under reduced pressure at 100 °C to give white solid (97% yield). $^1\text{H NMR}$ (CDCl_3 , ppm, 25 °C): $\delta = 1.06\text{-}1.28$ (m, 24H), 3.09 (q, 2H), 3.78-4.05 (m, 14H), 6.16 (d, 2H), 6.64 (d, 2H), 6.67 (d, 2H), 6.73-6.89 (m, 8H), 6.95-7.12 (m, 14H), 7.16 (d, 2H), 7.88 (d, 2H).

Preparation of protected-hexadecamer (9'). Thionyl chloride (60.0 μl , 0.826 mmol) was added to a solution of protected-octamer **7'** (1.03 g, 0.794 mmol) in NMP (2.7 mL) at 25 °C under nitrogen. The reaction mixture was stirred for 10 min, followed by 40 °C for 9 h. To this solution, a solution of octamer **8'** (0.959 g, 0.802 mmol) in NMP (1 mL) was added under nitrogen, and the resultant solution was stirred at the temperature for 4 h, followed by 60 °C for 2 h. Then, the reaction mixture was poured into MeOH and the precipitate was filtered and dried. The crude product was washed with hot MeOH/EtOH (1/1 volume ratio) to give white solid (82% yield). $^1\text{H NMR}$ (CDCl_3 , ppm, 25 °C): $\delta =$

1.05-1.28 (m, 48H), 3.75 (q, 2H), 3.78-4.05 (m, 30H), 6.66-6.92 (m, 28H), 6.94-7.20 (m, 32H), 7.26 (d, 2H), 7.86 (d, 2H). Calcd.: $[M]^+$ $m/z = 2468.8$. Found: MALDI-TOF-MS: $[M+Na]^+ = 2495.5$, $[M+K]^+ = 2515.5$.

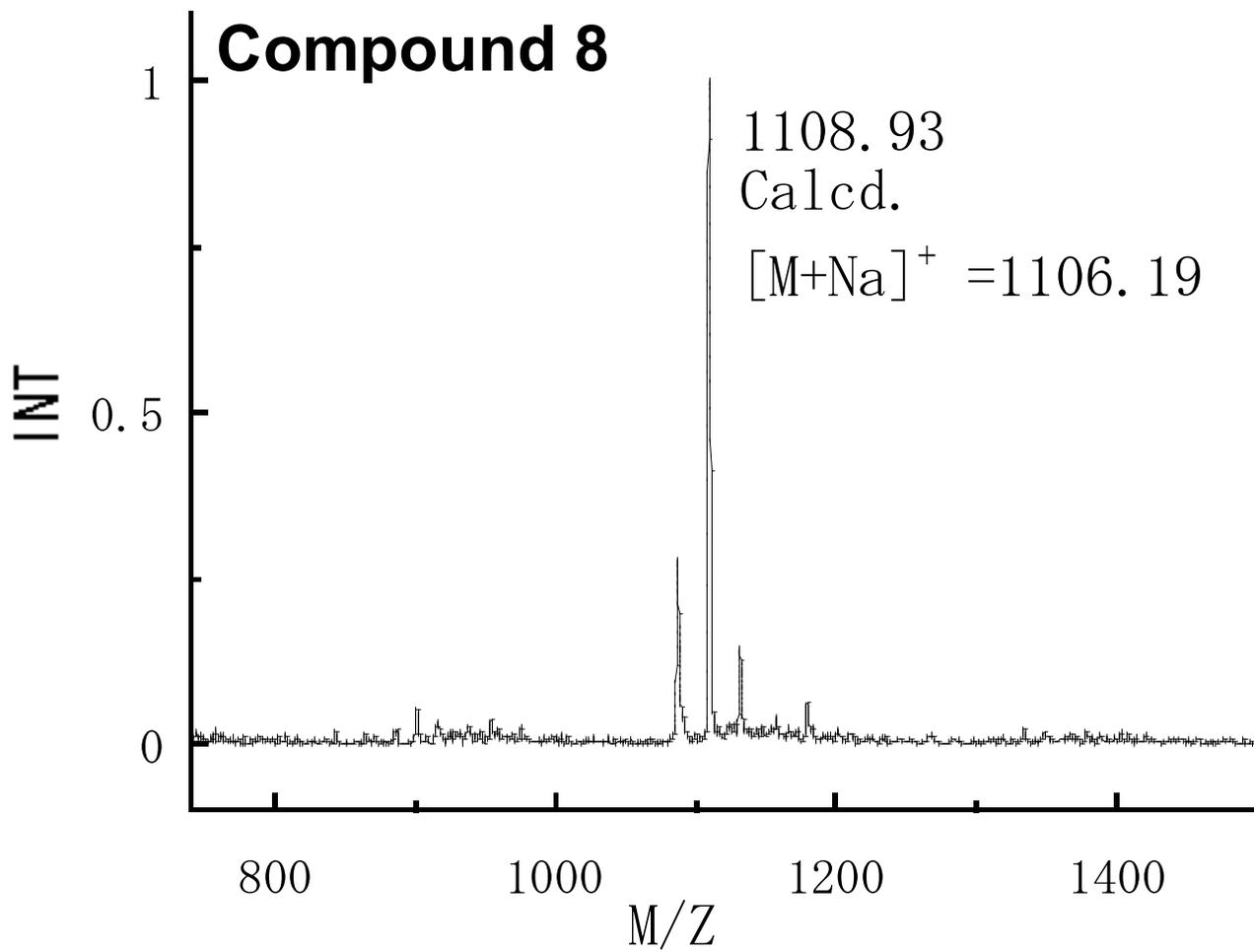


Figure 1S. MALDI-TOF MS spectrum of octamer 8

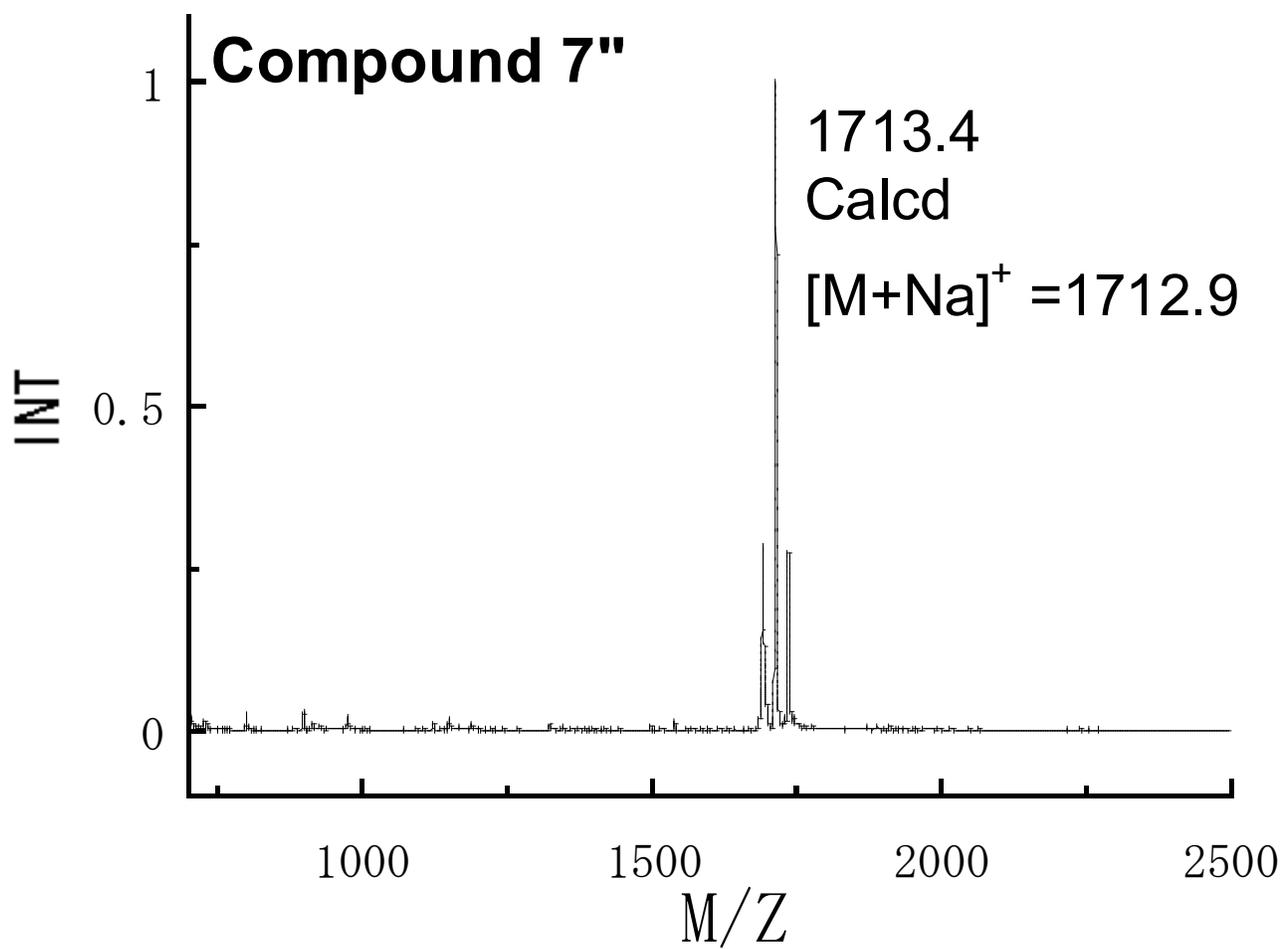


Figure 2S. MALDI-TOF MS spectrum of protected-nonamer 7''