

Supporting Information

Synthesis of tri-Arylated Cyclotrimeratrilenes with *ortho*- and *meta*- Extended Functionality.

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EXPERIMENTAL SECTION

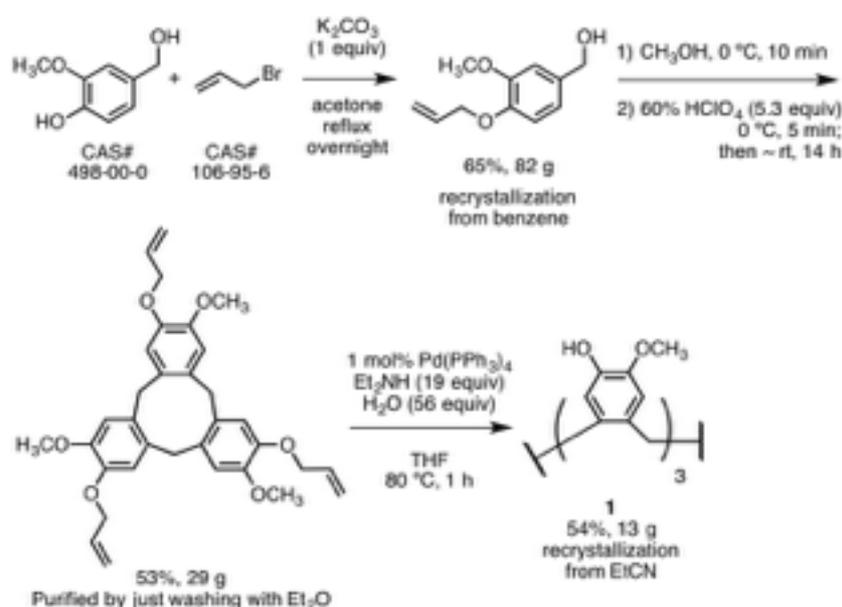
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a) General Information.

All reactions sensitive to air or moisture were carried out under an argon atmosphere and anhydrous conditions unless otherwise noted. Dry solvents were purchased and used without further purification and dehydration. All reagents were purchased and used without further purification. Analytical thin layer chromatography was carried out on Merck silica 60F₂₅₄. Column chromatography was carried out with silica gel 60_N (Kanto Chemical Co.). HRMS were reported on the basis of TOF (time of flight), and EB (double-focusing) techniques. ¹H and ¹³C NMR spectra were recorded with a 5 mm QNP probe at 400 MHz and 100 MHz, respectively. Chemical shifts are reported to residual solvent signals [¹H NMR: CHCl₃ (7.26), C₇H₈ (2.08), C₆H₆ (7.16), CH₂Cl₂ (5.32); ¹³C NMR: CDCl₃ (77.0)]. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br., broad.

b) Scalable & column-free preparation of cyclotriguaiacylene **1**, Scheme 1S.



Scheme 1S Scalable preparation of **1**

(4-(Allyloxy)-3-methoxyphenyl)methanol: Vanillyl alcohol (100 g, 649 mmol) in 1 L flask was totally dissolved in refluxing acetone (150 mL), then allyl bromide (61.8 mL, 714

mmol) and K_2CO_3 (89.7 g, 649 mmol) were added. After 1 h, additional allyl bromide (22.5 mL, 260 mmol) was poured into the flask, and the mixture was further stirred for overnight. Filtration of the resultant reaction mixture through a pad of celite (eluent; CH_2Cl_2) and the following evaporation of the filtrate gave the solid materials. These were dissolved in CH_2Cl_2 and washed with water (20 mL), and dried over Na_2SO_4 , and filtered, and concentrated *in vacuo* to afford 125 g of crude as yellow solid stuff. Recrystallization from freshly distilled benzene (1.0 mL/crude 1 g) afforded 81.3 g (65%) of the desired compound as white solid crystals. The physical data were ensured according to the literature.¹ 1H NMR (400 MHz, $CDCl_3$) 6.94 (s, 1H), 6.86 (s, 1H), 6.85 (s, 1H), 6.08 (ddt, $J = 17.2, 10.4, 5.5$ Hz, 1H), 5.40 (dd, $J = 17.2, 1.4$ Hz, 1H), 5.28 (dd, $J = 10.4, 1.4$ Hz, 1H), 4.63-4.60 (m, 4H), 3.89 (s, 3H), 1.63 (t, $J = 6.0$ Hz, 1H) ppm.

(±)-2,7,12-trimethoxy-3,8,13-tris(2-propenyloxy)-10,15-dihydro-5H-

tribenzo[*a,d,g*]cyclononene: The 1 L three-neck flask charged with a solution of (4-(allyloxy)-3-methoxyphenyl)methanol (60.0 g, 309 mmol) in methanol (288 mL) was dipped in 0 °C ice-bath. To the flask perchloric acid (60%, 155 mL, 1640 mmol) was slowly added over 8 min; then, the mixture was stirred for 5 min, and allowed to warm to ambient temperature. After overnight stirring (> 14 h), the reaction was quenched at 0 °C with addition of cold water (300 mL). The resultant precipitates were filtered, and thoroughly rinsed with water, and dissolved in CH_2Cl_2 (300 mL). The solution was washed with brine, 5% aqueous K_2CO_3 , and brine again, and followed by Na_2SO_4 dry and concentration *in vacuo* to give 35 g of crude products as yellowish white solid materials. A good rinse with diethyl ether (2.0 mL/ crude 1 g) yielded the target trimer molecule in 53% (28.8 g) as white solid stuff. The physical data were ensured

¹ a) Canceill, J.; Collet, A.; Gottarelli, G. *J. Am. Chem. Soc.* **1984**, *106*, 5997-6003; b) Gosse, I.; Dutasta, J.-P.; Perrin, M.; Thozet, A. *New. J. Chem.* **1999**, *23*, 545-548.

according to the literature.²⁵ ¹H NMR (400 MHz, CDCl₃) 6.85 (s, 3H), 6.79 (s, 3H), 6.06 (ddt, *J* = 17.4, 10.5, 5.2 Hz, 3H), 5.37 (dd, *J* = 17.4, 1.4 Hz, 3H), 5.24 (dd, *J* = 10.5, 1.4 Hz, 3H), 4.74 (d, *J* = 13.8 Hz, 3H), 4.64-4.54 (m, 6H), 3.83 (s, 9H), 3.51 (d, *J* = 13.8 Hz, 3H) ppm.

(±)-2,7,12-trihydroxy-3,8,13-trimethoxy-10,15-dihydro-5H-

tribenzo[*a,d,g*]cyclononene: Under an argon atmosphere, the starting triallyl CTV (30.0 g, 56.7 mmol) in 1 L two-neck flask was suspended in THF (200 mL); then, water (57.2 mL, 3180 mmol), diethyl amine (113 mL, 1080 mmol), and Pd(PPh₃)₄ (659 mg, 0.57 mmol) were added. The reaction was conducted at 80 °C for 1 h, and allowed to cool to ambient temperature. After all the volatiles were evaporated the residue was dissolved in acetone (400 mL), which was filtered through a pad of celite and concentrated *in vacuo*. The resultant solid dissolved in acetone (600 mL) was poured into water (1500 mL) with stirring for 30 min, and the precipitates were collected and thoroughly rinsed with water and again dissolved in acetone (600 mL). The acetone solution was dried over Na₂SO₄, filtered, and concentrated *in vacuo* to give a crude product of 26.6 g as a white solid. This was rinsed with EtOAc (5 mL/g), and the following recrystallization from propionitrile (56 mL/g, filtered at the time of heat, then removed 18 mL/g) afforded **1** in 39% yield of 9.06 g as white solid materials of first prisms. The mother liquid was evaporated, and the residue was rinsed with EtOAc, and purified with recrystallization from EtCN to yield **1** in 15% of 3.41 g as white solid materials of second prisms. The physical data were ensured according to the literature.²⁵ ¹H NMR (400 MHz, CDCl₃) 6.88 (s, 3H), 6.79 (s, 3H), 5.39 (s, 3H), 4.71 (d, *J* = 13.8 Hz, 3H), 3.85 (s, 9H), 3.50 (d, *J* = 13.8 Hz, 3H) ppm.

c) Typical procedure for Reaction of 1 with *ortho*-substituted fluoroarenes (Table 1).

Under an argon atmosphere, cyclotriguaiacylene **1** (1.63 g, 4.0 mmol) in a 200 mL two-neck flask was totally dissolved in DMF (40 mL). To the flask was added *ortho*-substituted fluorobenzene (24 mmol) and K₂CO₃ (2.76 g, 20 mmol), and the mixture was conducted at 150 °C (pre-heated oil bath was used) for appropriate reaction time with TLC monitoring. Allowed to cool to ambient temperature, the reaction mixture was filtered through a pad of celite (eluent; toluene) and the filtrate was evaporated off. The resultant stuff was dissolved in CH₂Cl₂ (ca. 120 mL), and washed with water and brine, and dried over Na₂SO₄, filtered, and concentrated *in vacuo* to give a crude product. Purification protocols and analytical data are listed in the section below.

d) Data for novel compounds 2-7.

For the nitro **2 ((±)2,7,12-Tris-(2-nitrophenoxy)-3,8,13-trimethoxy-10,15-dihydro-5H-tribenzo[*a,d,g*]-cyclononene):** The crude product was rinsed with acetonitrile (8.6 mL/g) afforded **2** in 93% yield (2.87 g) as a pure form of white solid material. ¹H NMR (400 MHz, CDCl₃) 7.93 (dd, *J* = 7.4, 1.7 Hz, 3H), 7.39 (ddd, *J* = 7.4, 7.4, 1.7 Hz, 3H), 7.11 (ddd, *J* = 7.4, 7.4, 1.2 Hz, 3H), 7.08 (s, 3 H), 6.84 (s, 3H), 6.81 (dd, *J* = 7.4, 1.2 Hz, 3H), 4.76 (d, *J* = 13.8 Hz, 3H), 3.67 (s, 9H), 3.60 (d, *J* = 13.8 Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) 152.0, 150.4, 142.4, 140.5, 137.7, 134.3, 132.4, 125.9, 123.3, 122.5, 118.7, 114.9, 56.5, 36.6 ppm; MS (ESI) *m/z*: 794 ([M + Na]⁺); IR (neat): 2920, 1601, 1516 (NO₂), 1346 (NO₂), 1273, 741 cm⁻¹; HRMS (ESI) calcd for C₄₂H₃₃N₃O₁₂Na 794.1962 [M + Na]⁺, Found 794.1973; Anal. Calcd for C₄₂H₃₃N₃O₁₂: C, 65.37; H, 4.31; N, 5.44. Found: C, 65.40; H, 4.16; N, 5.27.

For the nitrile **3 ((±)2,7,12-Tris-(2-cyanophenoxy)-3,8,13-trimethoxy-10,15-dihydro-5H-tribenzo[*a,d,g*]-cyclononene):** The crude product was washed with hexane (48.5 mL/g) to afford **3** in 81% (2.32 g) as a pure form of white solid material. ¹H NMR (400

MHz, CDCl₃) 7.62 (dd, $J = 7.5, 1.6$ Hz, 3H), 7.38 (ddd, $J = 7.5, 7.5, 1.6$ Hz, 3H), 7.12 (s, 3H), 7.05 (ddd, $J = 7.5, 7.5, 1.6$ Hz, 3H), 6.88 (s, 3H), 6.65 (dd, $J = 7.5, 1.6$ Hz, 3H), 4.80 (d, $J = 13.8$ Hz, 3H), 3.69 (s, 9H), 3.64 (d, $J = 13.8$ Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) 160.6, 150.7, 141.9, 138.0, 134.3, 133.9, 132.4, 124.0, 122.4, 116.6, 115.6, 115.0, 102.7, 56.5, 36.7 ppm; MS (ESI) m/z : 734 ([M+Na]⁺); IR (neat): 2931, 2225 (CN), 1601, 1481, 1281, 1238, 756 cm⁻¹; HRMS (ESI) calcd for C₄₅H₃₃N₃O₆Na 734.2267 [M + Na]⁺, Found 734.2273; Anal. Calcd for C₄₅H₃₃N₃O₆: C, 75.94; H, 4.67; N, 5.90. Found: C, 75.91; H, 4.65; N, 5.84.

For the aldehyde 4 ((±)-2,7,12-Tris-(2-formyl-phenoxy)-3,8,13-trimethoxy-10,15-dihydro-5H-tribenzo[*a,d,g*]cyclononene): After the reaction in the heat condition was allowed to cool to ambient temperature, the mixture was poured into 1 M aqueous HCl (128 mL) at 0 °C and stirred for 30 min at room temperature. The precipitates was filtered off, and thoroughly rinsed with water (200 mL), and followed by washing with acetonitrile to yield **4** in 91% (2.62 g) as a pure form of white solid materials. ¹H NMR (400 MHz, CDCl₃) 10.59 (s, 3H), 7.91 (dd, $J = 7.8, 1.8$ Hz, 3H), 7.42 (ddd, $J = 7.8, 7.6, 1.8$ Hz, 3H), 7.12 (dd, $J = 7.8, 7.6$ Hz, 3H), 7.04 (s, 3 H), 6.82 (s, 3H), 6.73 (d, $J = 7.8$ Hz, 3H), 4.80 (d, $J = 13.8$ Hz, 3H), 3.67 (s, 9H), 3.62 (d, $J = 13.8$ Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) 190.2, 161.4, 150.8, 143.5, 137.5, 136.2, 132.6, 128.9, 126.5, 123.4, 123.3, 117.4, 115.0, 56.7, 37.0 ppm; MS (ESI) m/z : 743 ([M+Na]⁺); IR (neat): 2858, 1689 (CHO), 1601, 1508, 1450, 1273, 1211, 1080, 868, 760 cm⁻¹; HRMS (ESI) calcd for C₄₅H₃₆O₉Na 743.2252 [M + Na]⁺, Found 743.2257.

For the ester 5 ((±)2,7,12-Tris-(2-methylester-phenoxy)-3,8,13-trimethoxy-10,15-dihydro-5H-tribenzo[*a,d,g*] cyclononene): The crude product was purified with silica-gel column chromatography to give **5** in 19 % yield (461 mg) as a pure form of white needles.

^1H NMR (400 MHz, CDCl_3) 7.88 (dd, $J = 7.8, 1.6$ Hz, 3H), 7.36 (ddd, $J = 7.8, 7.8, 1.6$ Hz, 3H), 7.10 (dd, $J = 7.8, 7.8$ Hz, 3H), 6.87 (s, 3H), 6.80 (d, $J = 7.8$ Hz, 3H), 6.71 (s, 3H), 4.70 (d, $J = 13.8$ Hz, 3H), 3.80 (s, 9H), 3.66 (s, 9H), 3.51 (d, $J = 13.8$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) 166.6, 157.5, 149.8, 144.4, 136.0, 133.5, 132.2, 131.9, 122.8, 122.2, 121.6, 119.0, 114.5, 56.3, 52.4, 36.5 ppm; MS (ESI) m/z : 833 ($[\text{M}+\text{Na}]^+$); IR (neat): 2935, 1713 (CO_2CH_3), 1601, 1477, 1446, 1234, 748 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{48}\text{H}_{42}\text{O}_{12}\text{Na}$ 833.2568 $[\text{M} + \text{Na}]^+$, Found 833.2583; Anal. Calcd for $\text{C}_{48}\text{H}_{42}\text{O}_{12}$: C, 71.10; H, 5.22. Found: C, 71.12; H, 5.20.

For the pyridine 6: The crude product was washed with EtOAc (38 mL/g) to give 1.34 g of white materials; then, this was recrystallized from acetonitrile (51.1 mL/g, filtered at the time of heating) to yield **6** in 48% (1.2 g) as first crops of white needles. The residual stuff of 678 mg was washed with EtOAc, and recrystallized to afford **6** in 12% yield (323 mg) as second crops of white needles. ^1H NMR (400 MHz, CDCl_3) 8.26 (dd, $J = 5.0, 1.9$ Hz, 3H), 7.96 (dd, $J = 7.6, 1.9$ Hz, 3H), 7.18 (s, 3H), 7.04 (dd, $J = 7.6, 5.0$ Hz, 3H), 6.94 (s, 3 H), 4.82 (d, $J = 13.8$ Hz, 3H), 3.70-3.66 (m, 12H) ppm; ^{13}C NMR (100 MHz, CD_2Cl_2) 164.0, 151.9, 150.7, 143.7, 140.7, 138.4, 132.2, 124.6, 118.3, 115.4, 114.9, 97.1, 56.6, 36.8 ppm; MS (ESI) m/z : 737 ($[\text{M} + \text{Na}]^+$); IR (neat): 2943, 2233 (CN), 1577, 1508, 1427, 1269, 1180, 895, 748 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{42}\text{H}_{30}\text{N}_6\text{O}_6\text{Na}$ 737.2119 $[\text{M} + \text{Na}]^+$, Found 737.2132.

For the pyridine 7: After the reaction in the heat condition was allowed to cool to ambient temperature, the mixture was poured into water (80 mL) and stirred for 30 min at room temperature. The precipitates were suspended and washed with acetonitrile (40 mL), and filtered off. The resultant stuff was recrystallized from acetonitrile (282 mL/g, filtered at the time of heating, then removed 78 mL/g) to give **7** in 75% (1.66 g) as white crystals. ^1H NMR (400 MHz, CDCl_3) 8.34 (dd, $J = 4.5, 1.3$ Hz, 3H), 7.33 (dd, $J = 8.7, 4.5$ Hz, 3H), 7.17

(s, 3H), 7.00 (dd, $J = 8.7, 1.3$ Hz, 3H), 6.91 (s, 3H), 4.82 (d, $J = 13.8$ Hz, 3H), 3.71 (s, 9H), 3.67 (d, $J = 13.8$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, CD_2Cl_2) 158.2, 150.5, 144.6, 140.8, 138.9, 132.6, 128.2, 124.1, 123.6, 123.1, 115.5, 115.0, 56.5, 36.7 ppm; MS (ESI) m/z : 737 ($[\text{M}+\text{Na}]^+$); IR (neat): 2233 (CN), 1570, 1508, 1443, 1180, 1080, 1007 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{42}\text{H}_{30}\text{N}_6\text{O}_6\text{Na}$ 737.2119 $[\text{M} + \text{Na}]^+$, Found 737.2135.

e) Synthesis of *ortho*-amine 8 and *ortho*-ethylamine 9 (Scheme 3(a)).

For 8 ((±)-2,7,12-Tris-(2-aminophenoxy)-3,8,13-trimethoxy-10,15-dihydro-5H-

tribenzo[*a,d,g*]cyclononene): To the nitro **2** (800 mg, 1.0 mmol) suspended in methanol (8 mL) and CH_2Cl_2 (4 mL) were added 10% Pd/C (480 mg, 60 wt%) and NH_4OAc (197 mg, 3.1 mmol), and the reaction vessel was evacuated and fulfilled with gaseous H_2 three times. After the reaction was monitored with TLC for 3 h, the mixture was filtered through a pad of celite. The filtrate was evaporated off, and the residual solid was dissolved in CH_2Cl_2 and washed with water, brine, and dried over Na_2SO_4 to give a crude product of 812 mg. Purification with short-plug column chromatography (SiO_2 , $\text{CHCl}_3/\text{Acetone}$ 9/1) afforded **8** in 93% yield (653) mg. ^1H NMR (400 MHz, CDCl_3) 6.96 (dd, $J = 7.6, 7.5$ Hz, 3H), 6.81 (m, 6H), 6.73 (s, 3H), 6.66 (dd, $J = 7.6, 7.3$ Hz, 3H), 6.62 (s, 3H), 4.65 (d, $J = 13.8$ Hz, 3H), 3.82 (s, 6H), 3.71 (s, 9H), 3.44 (d, $J = 13.8$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) 148.7, 143.8, 143.4, 139.5, 135.2, 132.0, 123.8, 120.0, 117.7, 116.2, 115.4, 114.1, 55.7, 35.0 ppm; MS (ESI) m/z : 704 ($[\text{M} + \text{Na}]^+$); IR (neat): 3444, 3370, 1617, 1500, 1258, 748 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{42}\text{H}_{39}\text{N}_3\text{O}_6\text{Na}$ 704.2731 $[\text{M} + \text{Na}]^+$, Found 704.2725.

For 9 ((±)2,7,12-Tris-(2-ethylamino-phenoxy)-3,8,13-tri-methoxy-10,15-dihydro-5H-

tribenzo[*a,d,g*]cyclononene): To the nitro **2** (200 mg, 0.26 mmol) suspended in methanol (2 mL) and CH_2Cl_2 (1 mL) were added 10% Pd/C (120 mg, 60 wt%) and

NH₄OAc (45 mg, 0.78 mmol), and the reaction vessel was evacuated and fulfilled with gaseous H₂ three times. After the reaction was monitored with TLC for 3 h, acetonitrile (2 mL) was added and overnight stirring was performed. The reaction mixture was filtered through a pad of celite (eluent; acetone), and the filtrate was evaporated off. The residue dissolved in CH₂Cl₂ was washed with water and brine, and dried over Na₂SO₄ to give a yellow solid of 186 mg, which included a mixture of mono-ethyl, and di-ethyl, and tri-ethyl adducts. Thus, the alkylation step was repeated additionally more twice: to the resultant solid was added methanol (2 mL), CH₂Cl₂ (1 mL), 10% Pd/C (120 mg, 60 wt%), and NH₄OAc (45 mg, 0.78 mmol), and the vessel was evacuated and fulfilled with gaseous H₂, and the reaction was conducted at room temperature for overnight. The resultant crude product was finally formed in 179 mg as a yellow solid material. Purification by silica-gel column chromatography (CH₂Cl₂/Acetone 50/1) gave **9** in 50% yield (98 mg) as white solid stuff. ¹H NMR (400 MHz, CDCl₃) 7.01 (ddd, *J* = 7.7, 7.7, 1.4 Hz, 3H), 6.77-6.75 (m, 6 H), 6.71 (dd, *J* = 7.7, 1.4 Hz, 3H), 6.63 (s, 3H), 6.56 (ddd, *J* = 7.7, 7.7, 1.4 Hz, 3H), 4.65 (d, *J* = 13.7 Hz, 3H), 4.19 (brs, 3H), 3.70 (s, 9H), 3.44 (d, *J* = 13.7 Hz, 3H), 3.17 (m, 6H), 1.23 (t, *J* = 7.2 Hz, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) 149.2, 145.2, 143.9, 140.9, 134.8, 132.0, 124.9, 119.3, 119.0, 116.5, 113.8, 111.5, 56.2, 38.5, 36.4, 15.1 ppm; MS (ESI) *m/z*: 788 ([M + Na]⁺); IR (neat): 3399, 2847, 1606, 1505, 1188, 735 cm⁻¹; HRMS (ESI) calcd for C₄₈H₅₁N₃O₆Na 788.3670 [M + Na]⁺, Found 788.3663.

f) Synthesis of *ortho*-benzylamine **10 (Scheme 3(b)).**

To the 200 mL two-neck flask charged with dry THF (48 mL) under an argon atmosphere was added freshly-opened LiAlH₄ (454 mg, 12 mmol) at 0 °C. The nitrile **3** (1.42 g, 2 mmol) was separately and slowly added as a solid state *in ten times*, and the mixture was stirred at room temperature for 3 h with TLC monitoring. The reaction was quenched at 0 °C with ten pieces of ices, and followed by slow addition of 15% aqueous NaOH (10 mL) and

water (20 mL). The mixture was transferred into 500 mL beaker charged with Na₂SO₄ (for smooth removal of LiAlH₄), and filtered, and all the volatiles were evaporated off. The residue was dissolved in CH₂Cl₂ (25 mL), and washed with water and brine, and dried over Na₂SO₄, filtered, and concentrated *in vacuo* to give a crude product to 1.19 g. The crude was suspended in methanol (75.6 mL/g) at room temperature, which was filtered off. The filtrate was concentrated *in vacuo* to afford **10** in 54% yield (779 mg) as a pure form of yellowish white compounds. ¹H NMR (400 MHz, CDCl₃) 7.34 (dd, *J* = 7.4, 1.6 Hz, 3H), 7.13 (ddd, *J* = 7.7, 7.4, 1.6 Hz, 3H), 7.05 (ddd, *J* = 7.4, 7.4, 1.1 Hz, 3H), 6.85 (s, 3H), 6.75 (dd, *J* = 7.7, 1.1 Hz, 3H), 6.70 (s, 3H), 4.72 (d, *J* = 13.7 Hz, 3H), 3.89 (s, 6H), 3.68 (s, 9H), 3.51 (d, *J* = 13.7 Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) 155.6, 149.6, 144.2, 135.5, 131.9, 129.2, 128.1, 123.3, 121.1, 117.2, 114.1, 56.1, 42.5, 36.3 ppm; MS (ESI) *m/z*: 724 ([M+H]⁺); IR (neat): 3371, 2924, 1581 (NH₂), 1485, 1450, 1269, 1215, 748 cm⁻¹; HRMS (ESI) calcd for C₄₅H₄₆N₃O₆ 724.3381 [M + H]⁺, Found 724.3375.

g) Synthesis of *ortho*-benzylalcohol **11** (Scheme 3(c)).

The starting aldehyde **4** (1.0 g, 1.39 mmol) in a 200 mL two-neck flask under an argon atmosphere was suspended in ethanol (20 mL) and CH₂Cl₂ (20 mL), to which NaBH₄ (525 mg, 13.9 mmol) was added at 0 °C. After overnight reaction at ambient temperature, the mixture was observed as a solution state, and concentrated *in vacuo*. To the residue in CH₂Cl₂ (100 mL) was added 3 M aqueous HCl (40 mL) dropwise over 15 min, and the mixture was allowed to warm to room temperature, and transferred into a separatory funnel. The organic phase was washed with water and brine, and dried over Na₂SO₄, and concentrated *in vacuo* to afford a crude product of 1.07 g. Purification with recrystallization from ethanol (9.3 mL/g) afforded **11** in 86% yield (863 mg) as a form of white solid materials. ¹H NMR (400 MHz, CDCl₃) 7.38 (dd, *J* = 7.4, 1.6 Hz, 3H), 7.15 (ddd, *J* = 7.8, 7.4, 1.6 Hz, 3H), 7.05 (ddd, *J* = 7.4, 7.4, 0.9 Hz, 3H), 6.98 (s, 3 H), 6.77 (s, 3H), 6.74 (dd, *J*

= 7.8, 0.9 Hz, 3H), 4.78-4.75 (m, 9H), 3.68 (s, 9H), 3.57 (d, $J = 13.9$ Hz, 3H), 2.61 (t, $J = 6.4$, Hz, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) 156.0, 149.9, 143.8, 136.2, 132.1, 131.3, 129.6, 129.0, 123.4, 122.2, 116.6, 114.2, 61.7, 58.6, 36.5 ppm; MS (ESI) m/z : 749 ($[\text{M}+\text{Na}]^+$); IR (neat): 3564 (OH), 2931, 1585, 1493, 1450, 1269, 1211, 1007, 756 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{45}\text{H}_{42}\text{O}_9\text{Na}$ 749.2721 $[\text{M} + \text{Na}]^+$, Found 749.2749.

h) Synthesis of *ortho*-phenol **12** (Scheme 3(d)).

To the 1 L two-neck flask charged with the starting **4** (2.00 g, 2.77 mmol) in suspension of CH_2Cl_2 (300 mL) was added mCPBA (2.95 g, 11.1 mmol), and the reaction was conducted at 50 °C for 16 h. After allowed to cool to ambient temperature, the mixture was treated with slow addition of saturated aqueous NaHCO_3 (50 mL), and stirred for 30 min, and transferred into a separatory funnel. The organic phase was thoroughly washed three times with saturated aqueous NaHCO_3 , and brine, and dried over Na_2SO_4 , and concentrated *in vacuo* to give an formate of 2.55 g as an orange solid material. This formate was hydrolyzed with 0.5 M aqueous NaOH (120 mL) for overnight, and which was quenched with slow addition of concentrated aq. HCl (15 mL) over 5 min at 0 °C. The mixture was diluted with diethyl ether (20 mL), and the organic layer was washed with satd. aq. NaHCO_3 , (three times, ~ pH 7), and dried over Na_2SO_4 , and concentrated *in vacuo* to give a crude product of 1.75 g. Purification with silica-gel column chromatography ($\text{CH}_2\text{Cl}_2/\text{Acetone}$ 19/1) yielded **12** in 50% (950 mg) as white solid stuff. ^1H NMR (400 MHz, CDCl_3) 7.02-6.99 (m, 6H), 6.92 (s, 3H), 6.88 (dd, $J = 8.0, 1.3$ Hz, 3H), 6.79-6.75 (m, 3H), 6.70 (s, 3H), 5.99 (s, 3H), 4.68 (d, $J = 13.8$ Hz, 3H), 3.73 (s, 9H), 3.50 (d, $J = 13.8$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) 149.5, 148.0, 144.62, 144.60, 135.9, 132.1, 125.2, 120.8, 120.6, 119.2, 116.6, 114.0, 56.2, 36.5 ppm; MS (ESI) m/z : 685 ($[\text{M} + \text{Na}]^+$); IR (neat): 3445 (OH), 1608, 1592, 1256, 1189, 874 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{42}\text{H}_{36}\text{O}_9\text{H}$ 685.2432 $[\text{M} + \text{H}]^+$, Found 685.2407.

i) Synthesis of *meta*-nitro **13 (Table 2).**

To a solution of cyclotriguaiacylene **1** (1.63 g, 4.00 mmol) in DMF (40 mL) were added *meta*-fluoronitrobenzene (2.55 mL, 24.0 mmol) and K₂CO₃ (2.76 g, 20.0 mmol), and the mixture was conducted at 150 °C for more than 21 h with TLC monitoring. After the reaction was allowed to cool to ambient temperature, the mixture was filtered through a pad of celite (eluent; CH₂Cl₂), and the filtrate was concentrated. The residue was dissolved in CH₂Cl₂ (120 mL), and washed with water and brine, and dried over Na₂SO₄, and concentrated *in vacuo* to give a crude product of 3.42 g. The crude was washed with cold acetonitrile (10 mL/g) at 0 °C, and the following recrystallization from propionitrile (100 mL/g - 44 mL/g) yielded **13** in 1.57 g of brown needles (51 %). ¹H NMR (400 MHz, CDCl₃) 7.87 (dd, *J* = 8.2, 2.3 Hz, 3H), 7.68 (dd, *J* = 2.3, 2.3 Hz, 3H), 7.42 (dd, *J* = 8.2, 8.2 Hz, 3H), 7.22 (dd, *J* = 8.2, 2.3 Hz, 3H), 7.10 (s, 3H), 6.89 (s, 3H), 4.84 (d, *J* = 13.8 Hz, 3H), 3.69-3.65 (m, 12H) ppm; ¹³C NMR (100 MHz, CDCl₃) 159.3, 150.6, 149.5, 142.0, 137.9, 132.5, 130.3, 123.8, 122.8, 117.3, 114.9, 111.4, 56.4, 36.8 ppm; MS (ESI) *m/z*: 794 ([M + Na]⁺); IR (neat): 2927, 1612, 1516 (NO₂), 1346, 1215, 1080, 730 cm⁻¹; HRMS (ESI) calcd for C₄₂H₃₃N₃O₁₂Na 794.1956 [M + Na]⁺, Found 794.1982.

j) Synthesis of *meta*-ethylamine **14 (Scheme 4(a)).**

To the nitro **13** (1.6 g, 2.07 mmol) suspended in methanol (16 mL) and CH₂Cl₂ (4 mL) were added 10% Pd/C (960 mg, 60 wt%) and NH₄OAc (392 mg, 6.21 mmol), and the reaction vessel was evacuated and fulfilled with gaseous H₂ three times. After the reaction was monitored with TLC for 4 h, additional CH₂Cl₂ (4 mL) was poured and further stirring for 4 h was performed. Acetonitrile (16 mL) for ethylation was added and overnight stirring (> 11h) was performed. The reaction mixture was filtered through a pad of celite (eluent; acetone), and the filtrate was evaporated off. The residue dissolved in CH₂Cl₂ was washed with

water and brine, and dried over Na₂SO₄ to give a brown solid of 1.32 g, which included a mixture of mono-ethyl, and di-ethyl, and tri-ethyl adducts at this time. Thus, the alkylation step was repeated additionally more twice: to the resultant solid were added methanol (16 mL), CH₂Cl₂ (8 mL), 10% Pd/C (960 mg, 60 wt%), and NH₄OAc (392 mg, 6.21 mmol), and the vessel was evacuated and fulfilled with gaseous H₂, and the reaction was conducted at room temperature for more than 11 h. The resultant crude product was finally formed in 1.12 g as a brownish white solid. Purification by silica-gel column chromatography (CH₂Cl₂/Acetone 50/1) gave **14** in 47% yield (746 mg) as white solid stuff. ¹H NMR (400 MHz, CDCl₃) 7.04 (dd, *J* = 8.7, 8.7 Hz, 3H), 6.92 (s, 3H), 6.72 (s, 3H), 6.30 (dd, *J* = 8.7, 0.8 Hz, 3H), 6.26-6.24 (m, 6H), 4.70 (d, *J* = 13.8 Hz, 3H), 3.71 (s, 9H), 3.57 (brs, 3H), 3.50 (d, *J* = 13.8 Hz, 3H), 3.09 (q, *J* = 7.1 Hz, 6H), 1.21 (t, *J* = 7.1 Hz, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) 159.0, 150.3, 149.8, 144.6, 135.4, 132.0, 130.2, 121.4, 114.2, 107.8, 106.9, 102.8, 56.4, 38.7, 36.6, 15.1 ppm; MS (ESI) *m/z*: 788 ([M + Na]⁺); IR (neat): 3381(NH), 2850, 1604, 1506, 1277, 1187 cm⁻¹; HRMS (ESI) calcd for C₄₈H₅₁N₃O₆Na 788.3670 [M + Na]⁺, Found 788.3691.

k) Synthesis of amphoteric 15 (Scheme 4(b)).

To the 100 mL two-neck flask charged with **13** (500 mg, 0.65 mmol) in dry toluene (30 mL) was added BBr₃ (1 M CH₂Cl₂ solution, 3.89 mL) dropwise over 7 min, and the reaction was conducted at 90 °C for 2 h with TLC monitoring. The reaction was quenched with slow addition of methanol (15 mL), and all the volatiles were evaporated off. The residue was dissolved in EtOAc (40 mL), and washed with water and brine, and dried over Na₂SO₄, filtered, and concentrated *in vacuo* to give a crude product of 610 mg. Purification by silica-gel column chromatography (CH₂Cl₂/Acetone 50/1) yield the corresponding the nitro-phenol compound in 235 mg (50%) of brown solid materials. ¹H NMR (400 MHz, CDCl₃) 7.96 (dd, *J* = 8.2, 2.3 Hz, 3H), 7.82 (dd, *J* = 2.3, 2.3 Hz, 3H), 7.52 (dd, *J* = 8.2, 8.2 Hz,

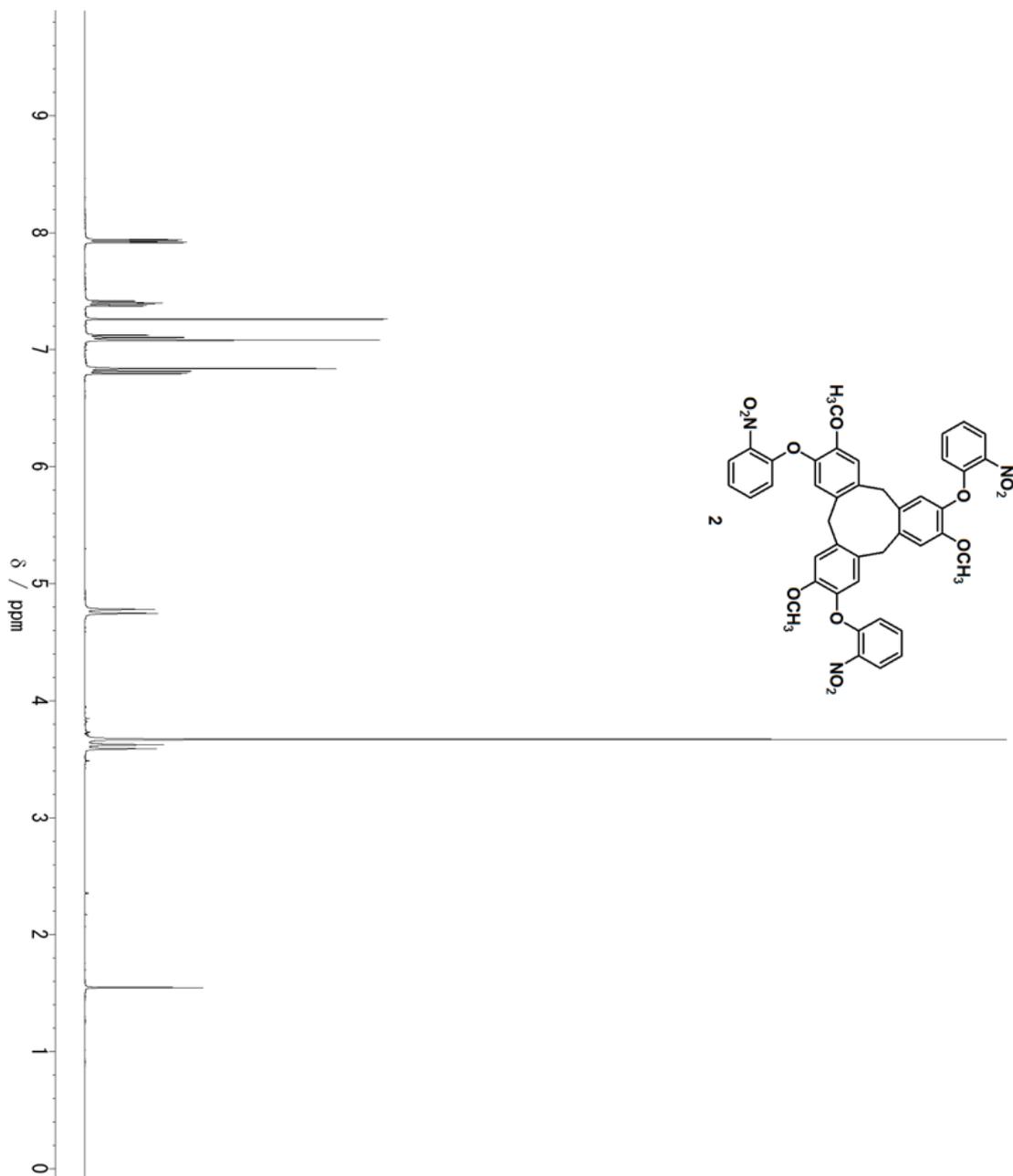
3H), 7.36 (dd, $J = 8.2, 2.3$ Hz, 3H), 6.99 (s, 3H), 6.89 (s, 3H), 5.22 (s, 3H), 4.72 (d, $J = 13.8$ Hz, 3H), 3.56 (d, $J = 13.8$ Hz, 3H) ppm.

To a solution of this nitro-phenol compounds (553 mg, 0.76 mmol) in methanol (24 mL) and CH_2Cl_2 (8 mL) were added 10% Pd/C (221 mg, 40 wt%) and NH_4OAc (175 mg, 2.27 mmol), and the vessel was evacuated and fulfilled with gaseous H_2 three times. After 2 h stirring at room temperature, the mixture was filtered through a pad of celite (eluent; acetone), and the filtrate was evaporated off. The residue was dissolved in EtOAc (40 mL), and washed with water and brine, and dried over Na_2SO_4 , filtered, and concentrated *in vacuo* to give a crude product of 498 mg. Purification of reprecipitation from EtOAc (5 mL/g)/Hexane (40 mL/g) afforded **15** in 396 mg (82%) of light dark white solid materials. ^1H NMR (400 MHz, Acetone- d_6) 7.92 (s, 3H), 7.07 (s, 3H), 7.01 (s, 3H), 6.93 (dd, $J = 8.0, 8.0$ Hz, 3H), 6.32 (dd, $J = 8.0, 2.4$ Hz, 3H), 6.14 (dd, $J = 2.4, 2.4$ Hz, 3H), 6.10 (dd, $J = 8.0, 2.4$ Hz, 3H), 4.80 (d, $J = 13.5$ Hz, 3H), 4.67 (brs, 6H), 3.59 (d, $J = 13.5$ Hz, 3H) ppm; ^1H NMR (400 MHz, DMSO- d_6) 9.18 (s, 3H), 6.97 (s, 3H), 6.91 (s, 3H), 6.87 (dd, $J = 8.0, 8.0$ Hz, 3H), 6.16 (dd, $J = 8.0, 2.2$ Hz, 3H), 5.99 (dd, $J = 8.0, 2.2$ Hz, 3H), 5.95 (dd, $J = 2.2, 2.2$ Hz, 3H), 5.08 (brs, 6H), 4.67 (d, $J = 13.4$ Hz, 3H), 3.48 (d, $J = 13.4$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, Acetone- d_6) 160.2, 150.8, 148.7, 142.3, 138.0, 132.5, 130.6, 123.7, 119.0, 109.3, 105.8, 103.0, 36.2 ppm; ^{13}C NMR (100 MHz, DMSO- d_6) 159.3, 150.0, 148.1, 140.6, 137.1, 130.9, 129.5, 123.6, 118.2, 107.5, 103.5, 100.7, 34.9 ppm; MS (MALDI) m/z : 640 ($[\text{M}+\text{H}]^+$); IR (neat): 3366, 1586, 1489, 1281, 1177, 1147, 958, 856 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{39}\text{H}_{33}\text{N}_3\text{O}_6\text{Na}$ 662.2262 $[\text{M} + \text{Na}]^+$, Found 662.2274.

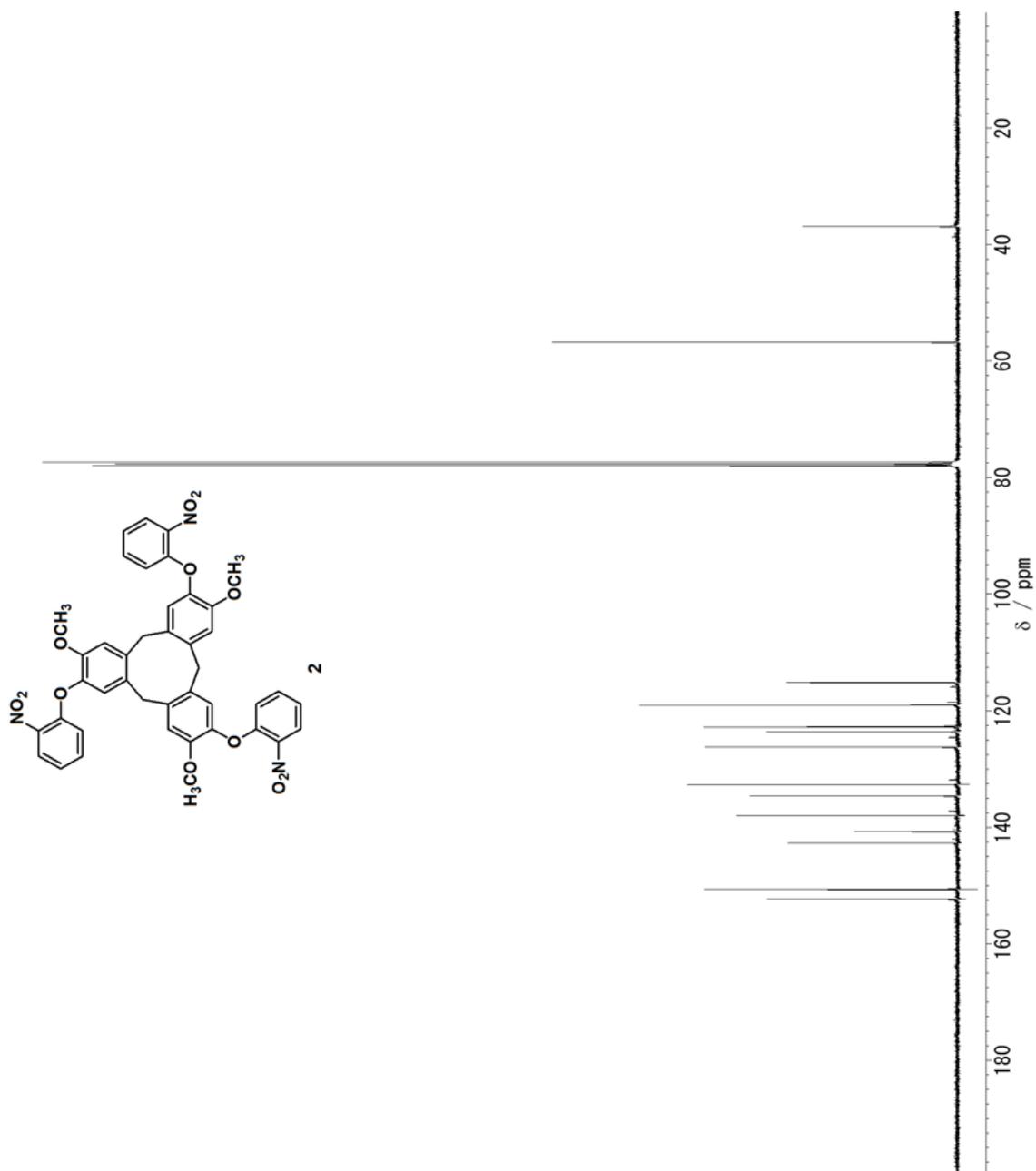
I) All spectra of ^1H NMR and ^{13}C NMR for new compounds.

Compound 2

^1H NMR spectrum in CDCl_3

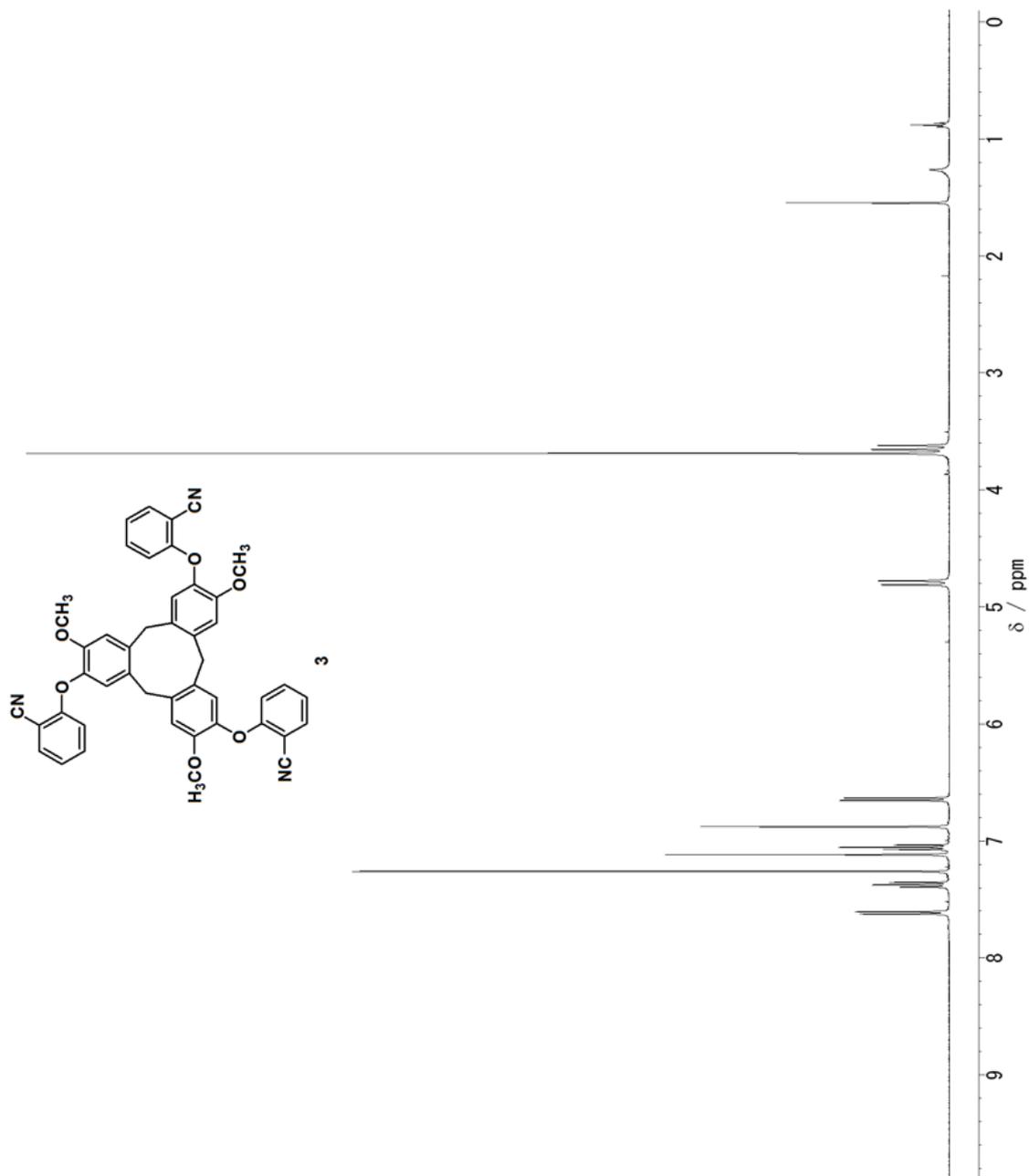


Compound 2
¹³C NMR spectrum in CDCl₃



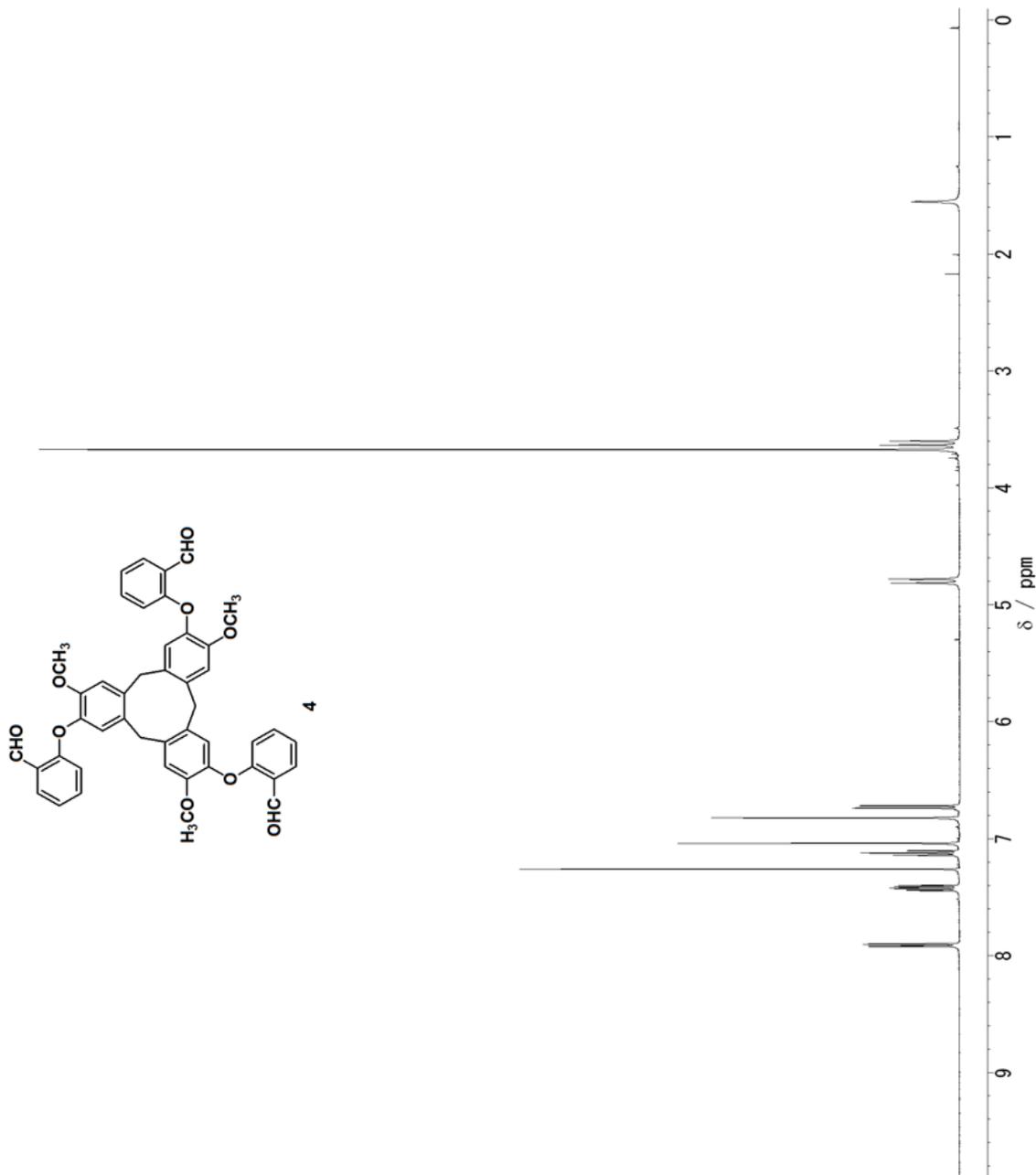
Compound 3

^1H NMR spectrum in CDCl_3

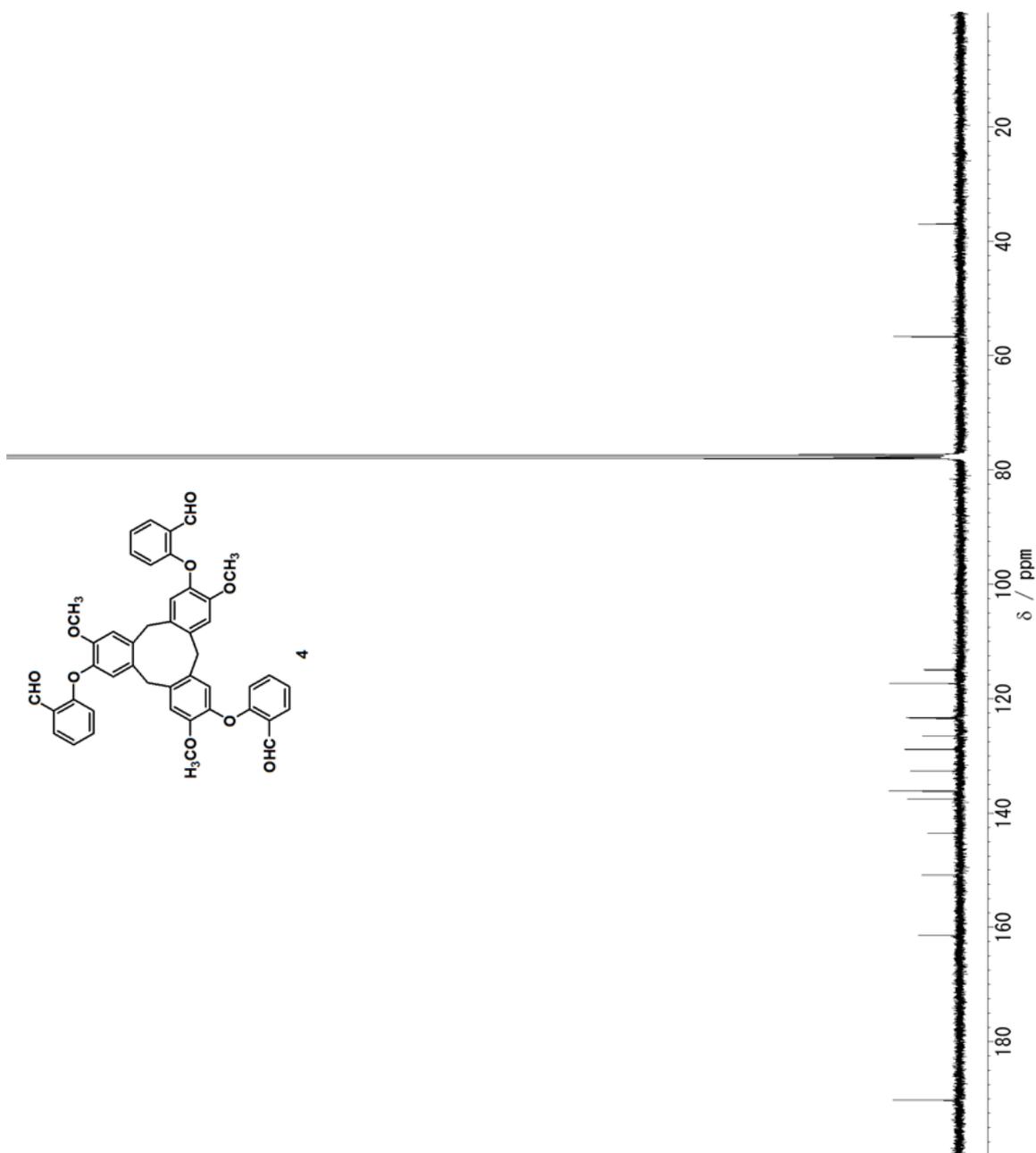


Compound 4

¹H NMR spectrum in CDCl₃

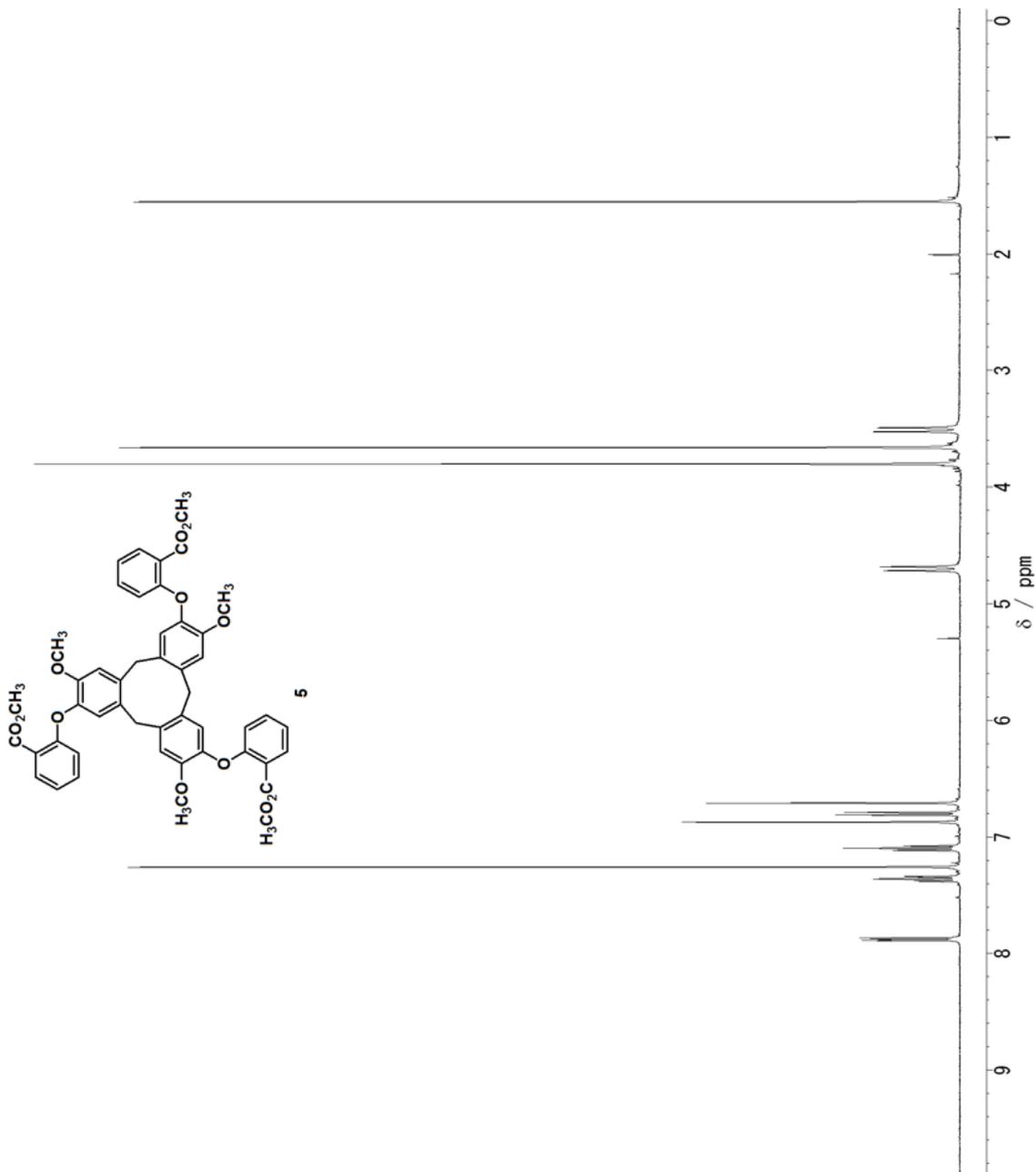


Compound 4
¹³C NMR spectrum in CDCl₃



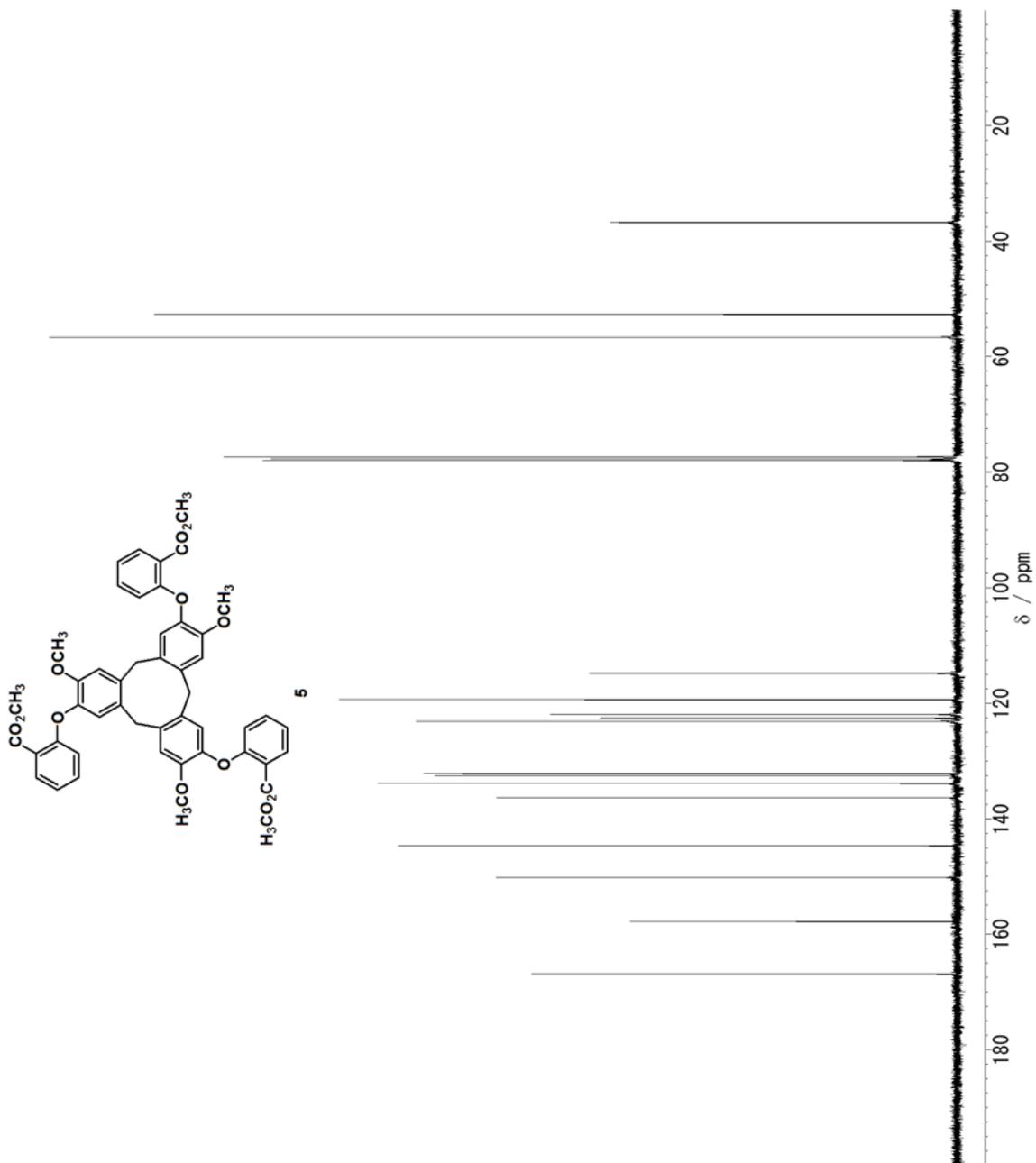
Compound 5

¹H NMR spectrum in CDCl₃

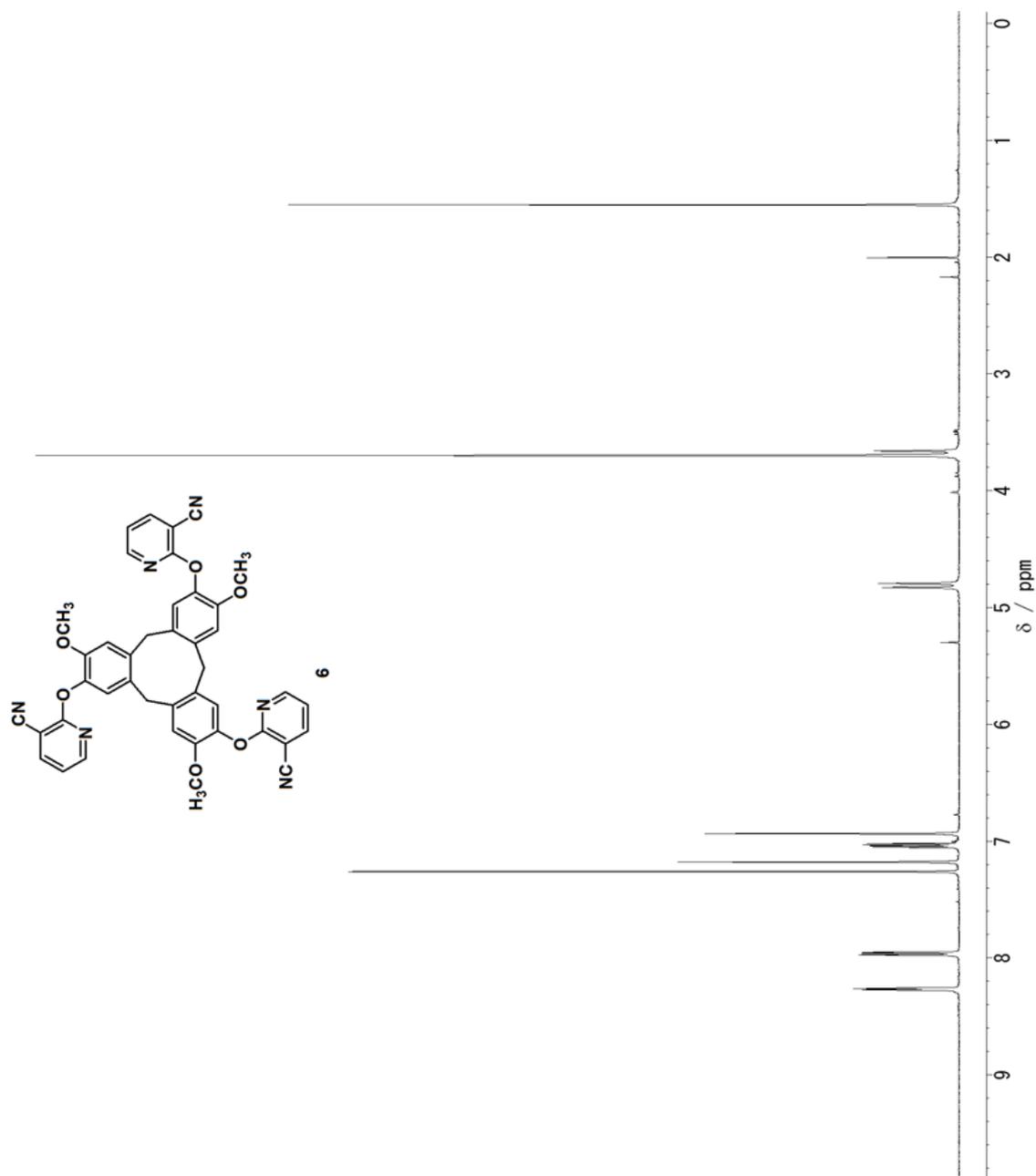


Compound 5

^{13}C NMR spectrum in CDCl_3

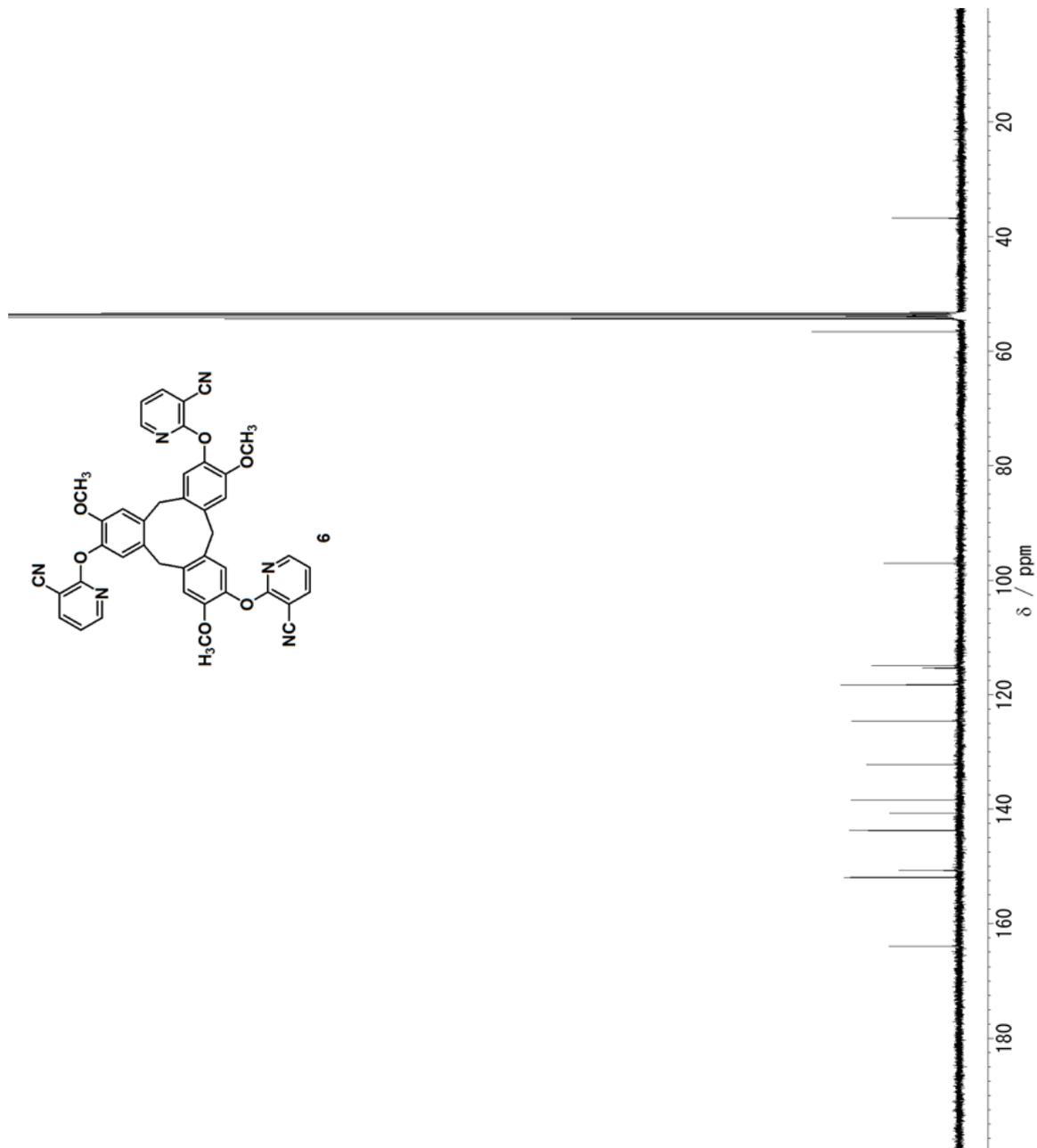


Compound 6
¹H NMR spectrum in CDCl₃



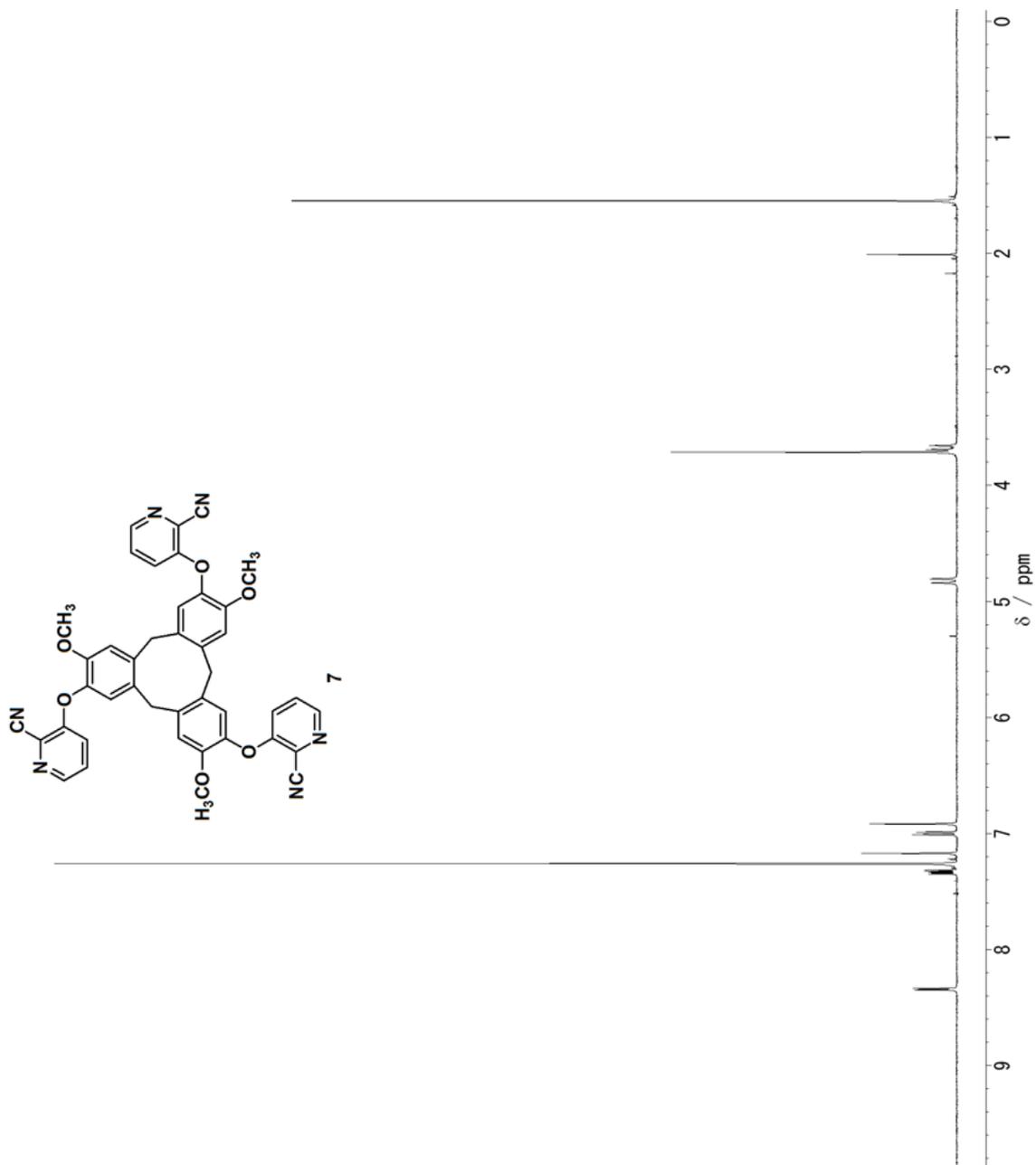
Compound 6

¹³C NMR spectrum in CD₂Cl₂



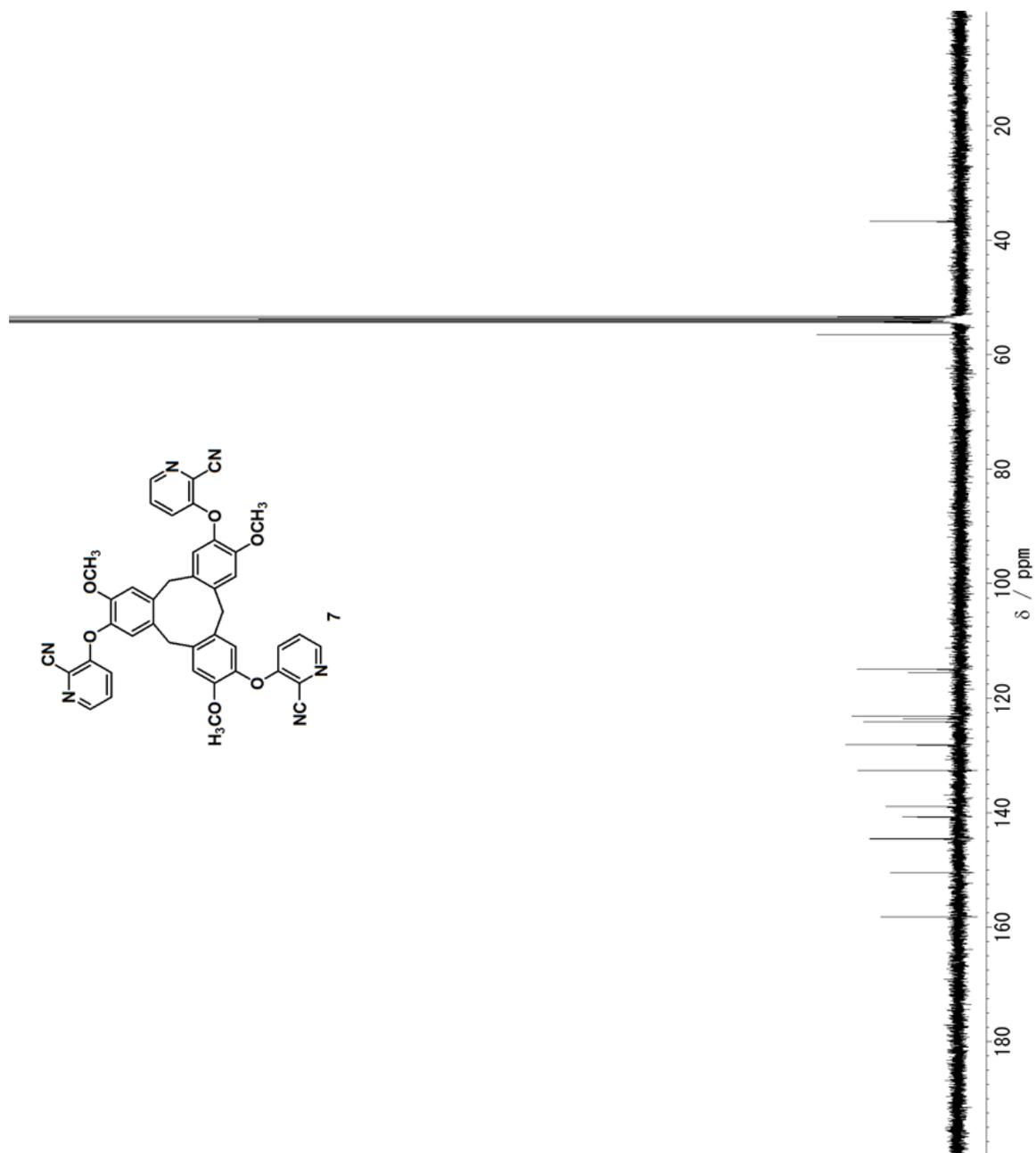
Compound 7

¹H NMR spectrum in CDCl₃



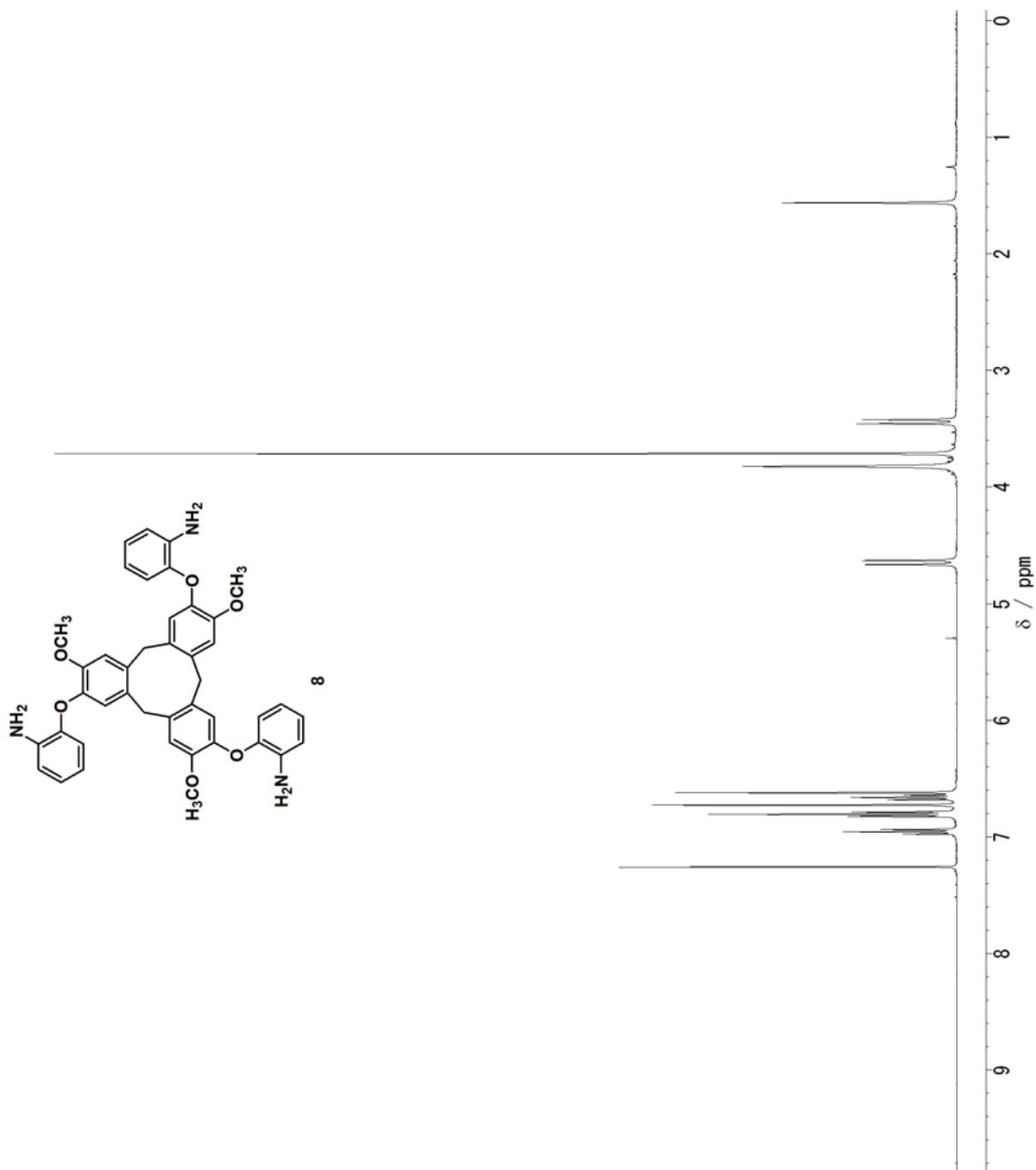
Compound 7

¹³C NMR spectrum in CD₂Cl₂

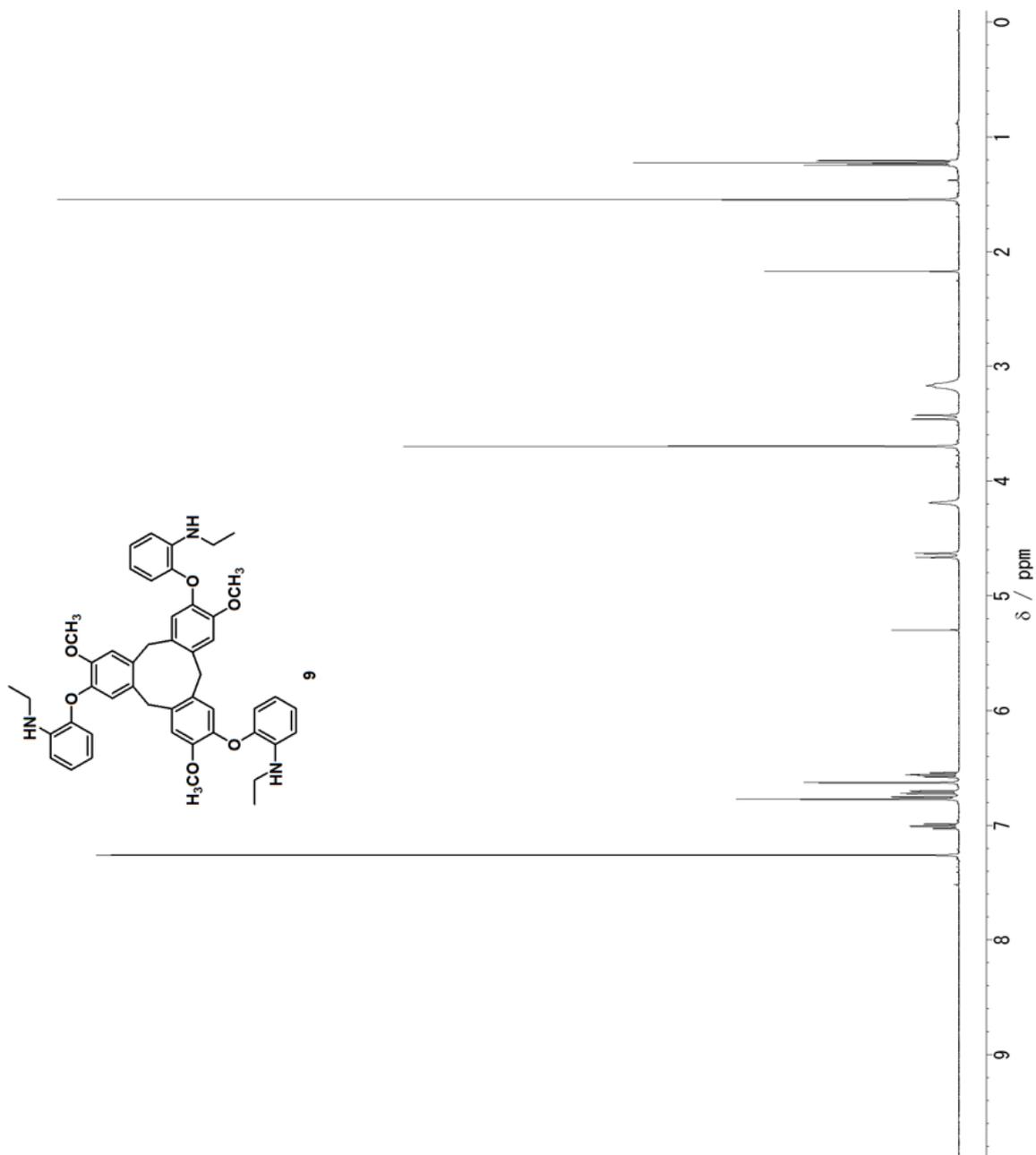


Compound 8

¹H NMR spectrum in CDCl₃

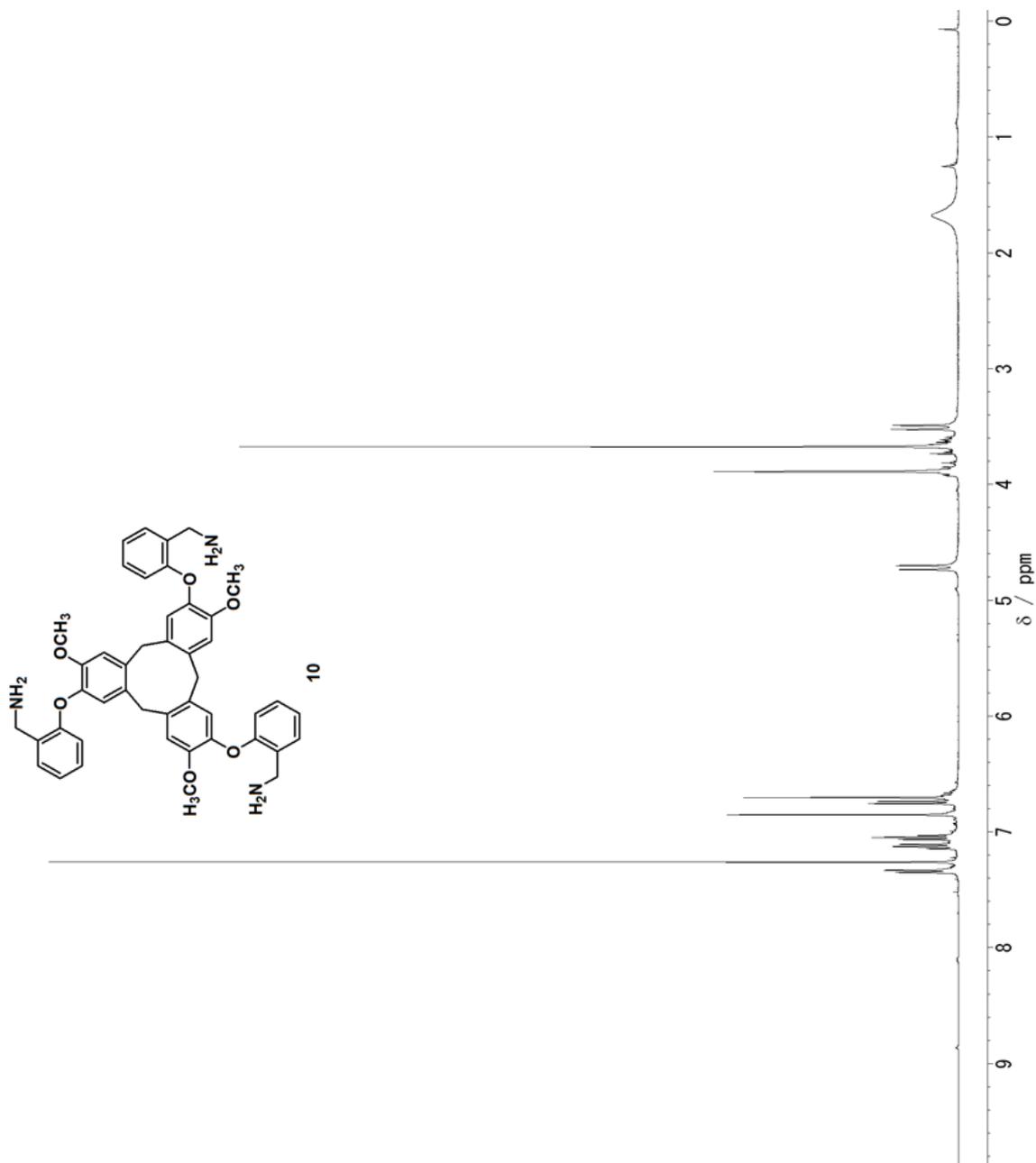


Compound 9
¹H NMR spectrum in CDCl₃



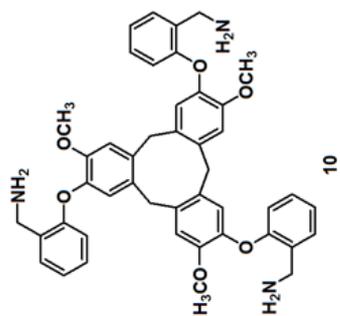
Compound 10

¹H NMR spectrum in CDCl₃

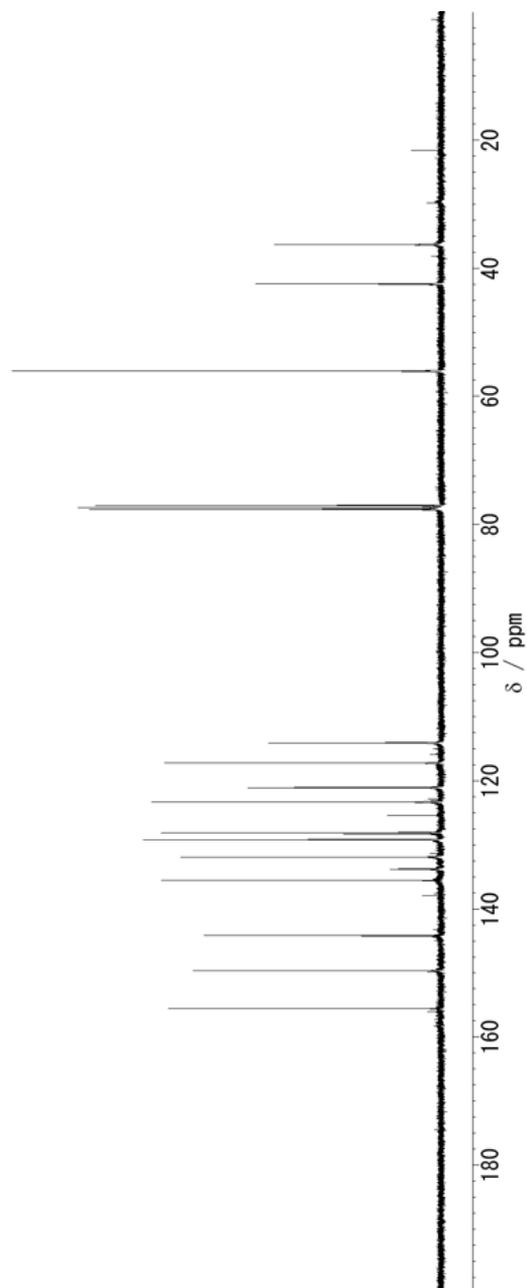


Compound 10

¹³C NMR spectrum in CDCl₃

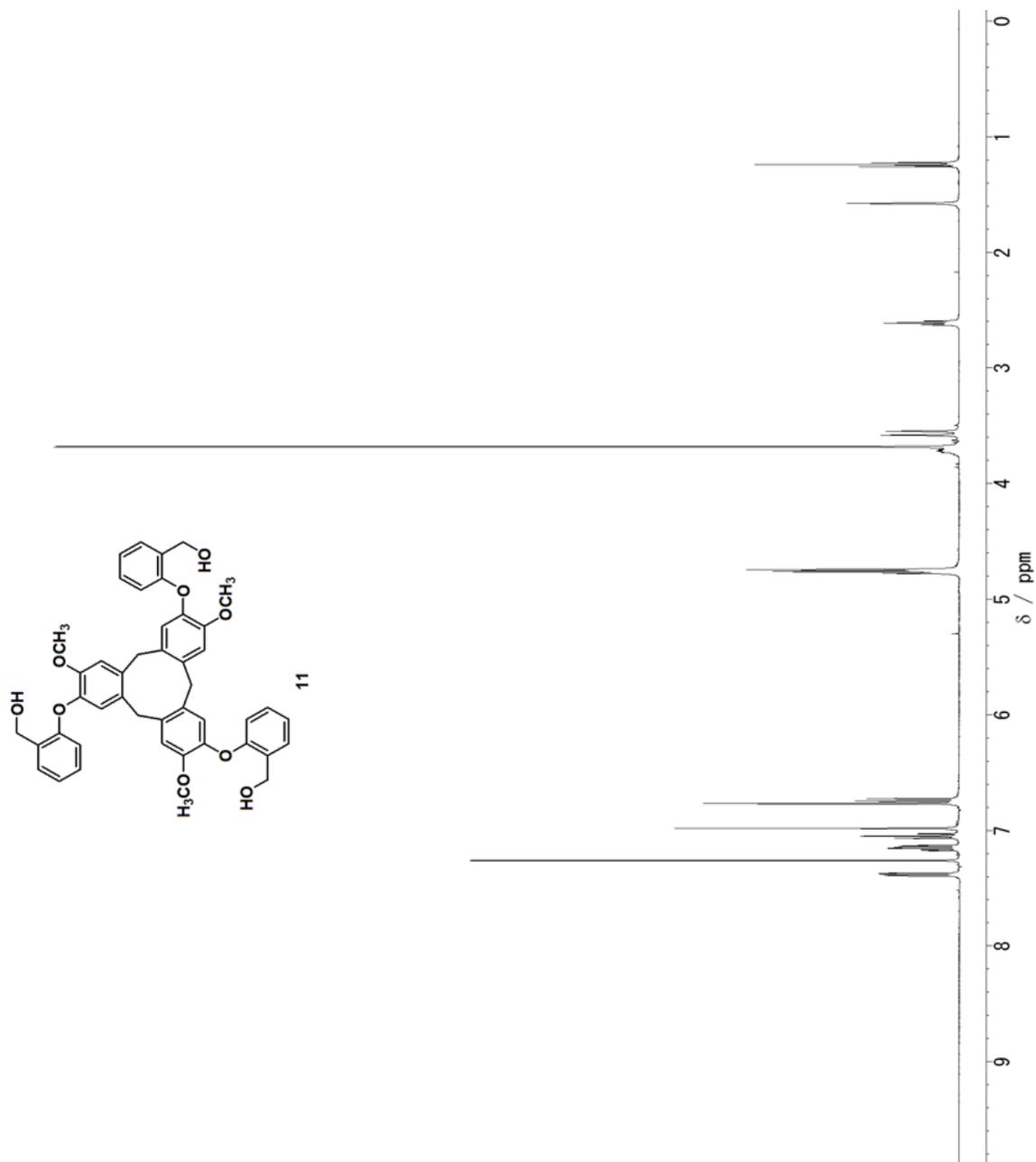


10



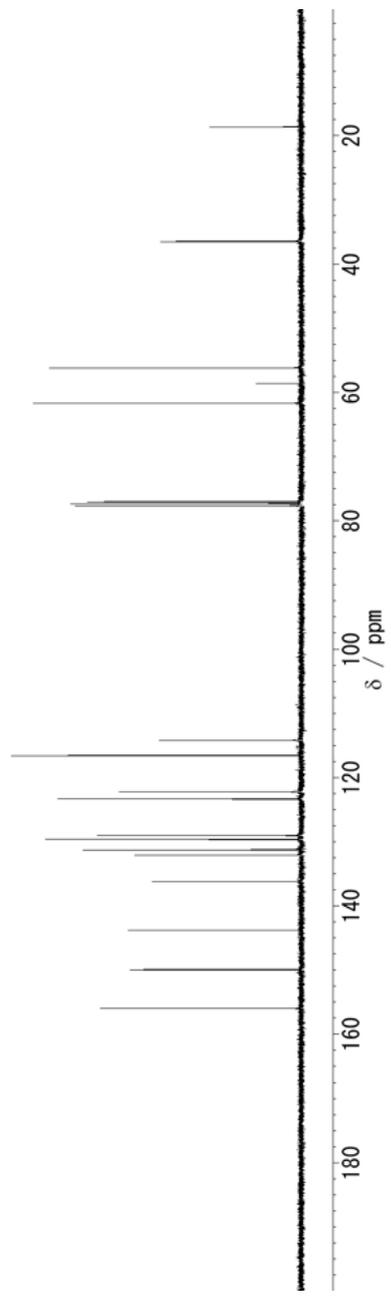
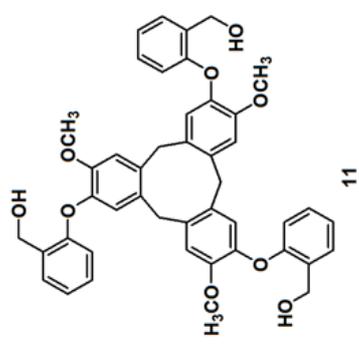
Compound 11

¹H NMR spectrum in CDCl₃



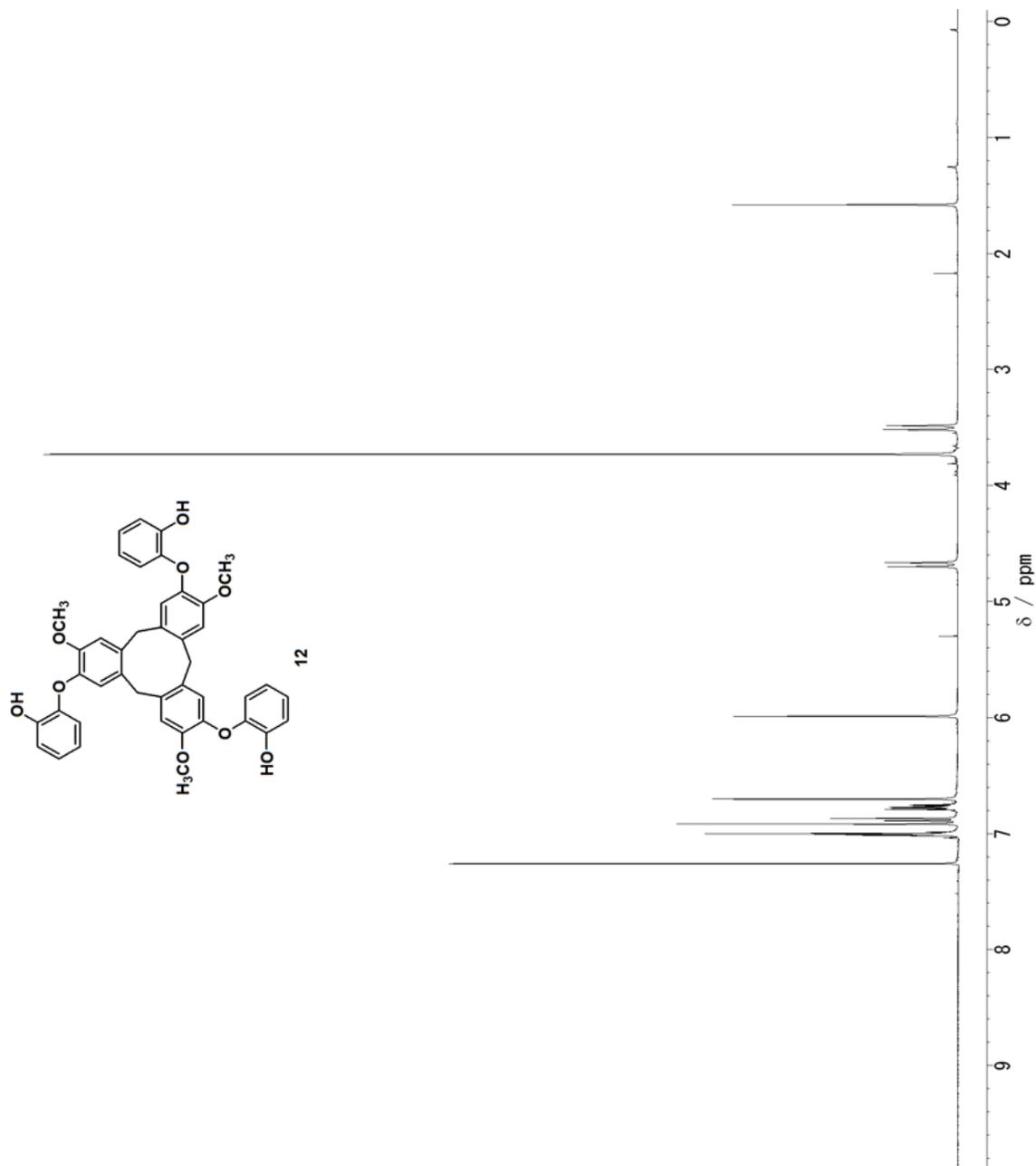
Compound 11

¹³C NMR spectrum in CDCl₃



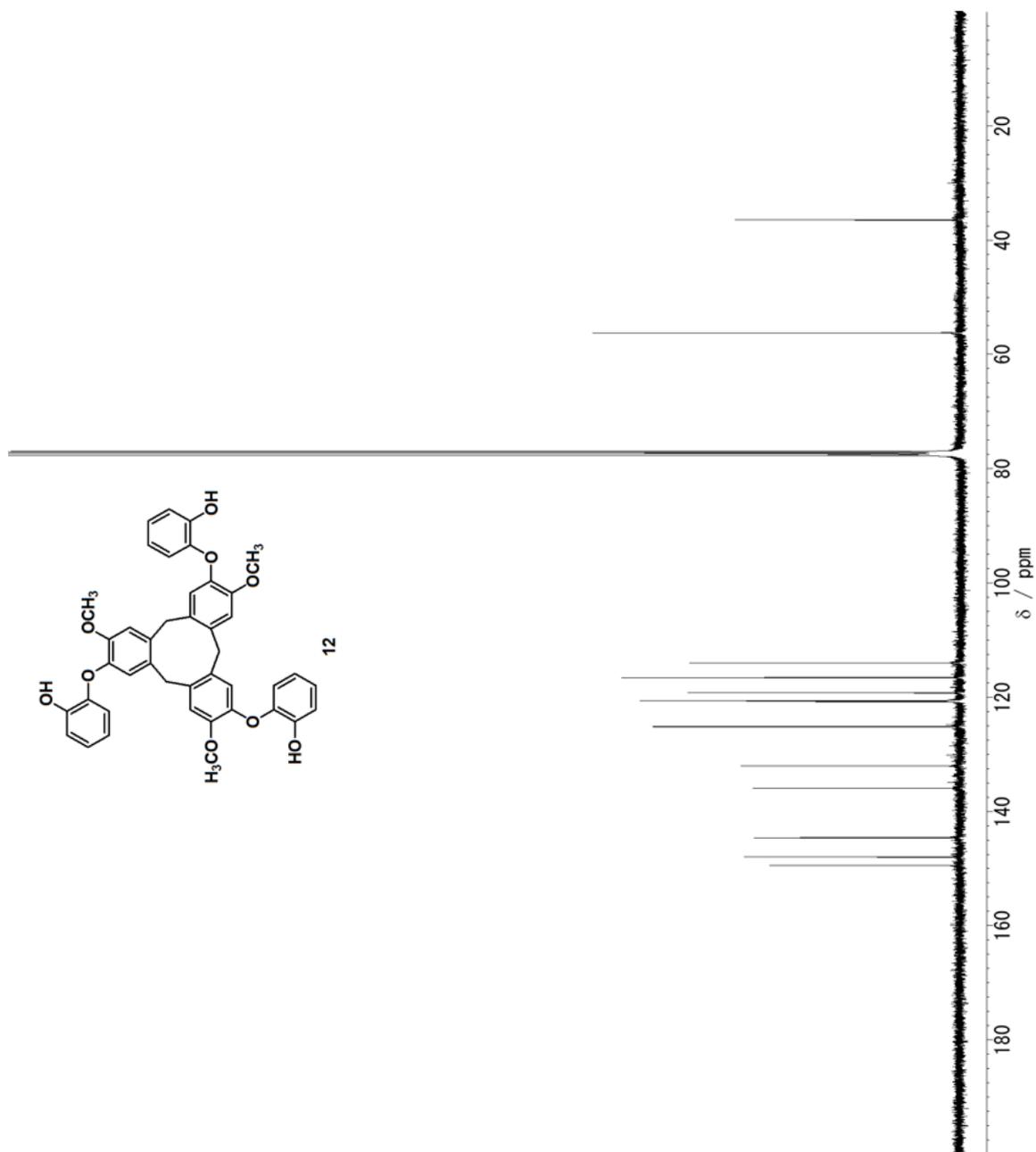
Compound 12

¹H NMR spectrum in CDCl₃



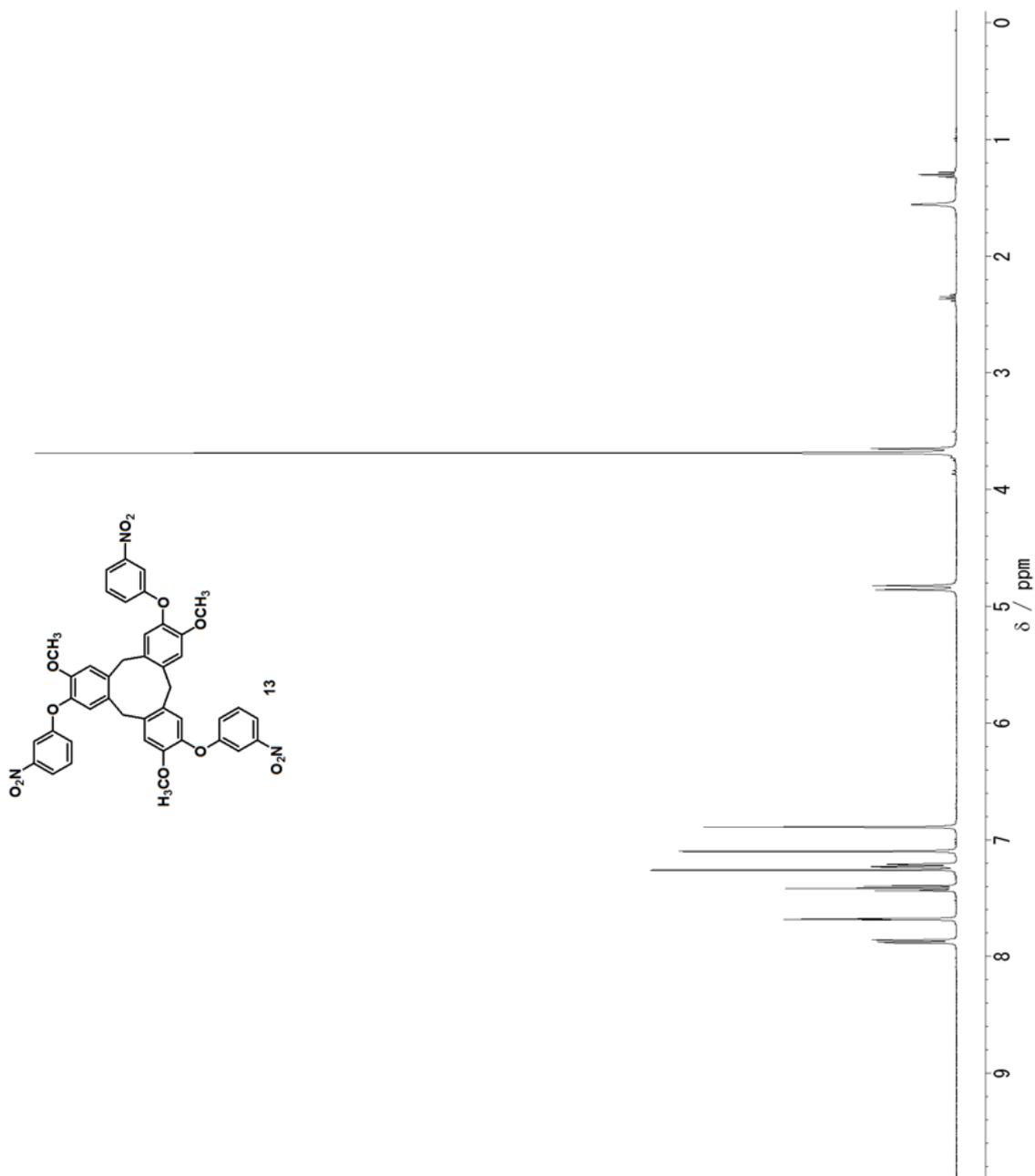
Compound 12

¹³C NMR spectrum in CDCl₃



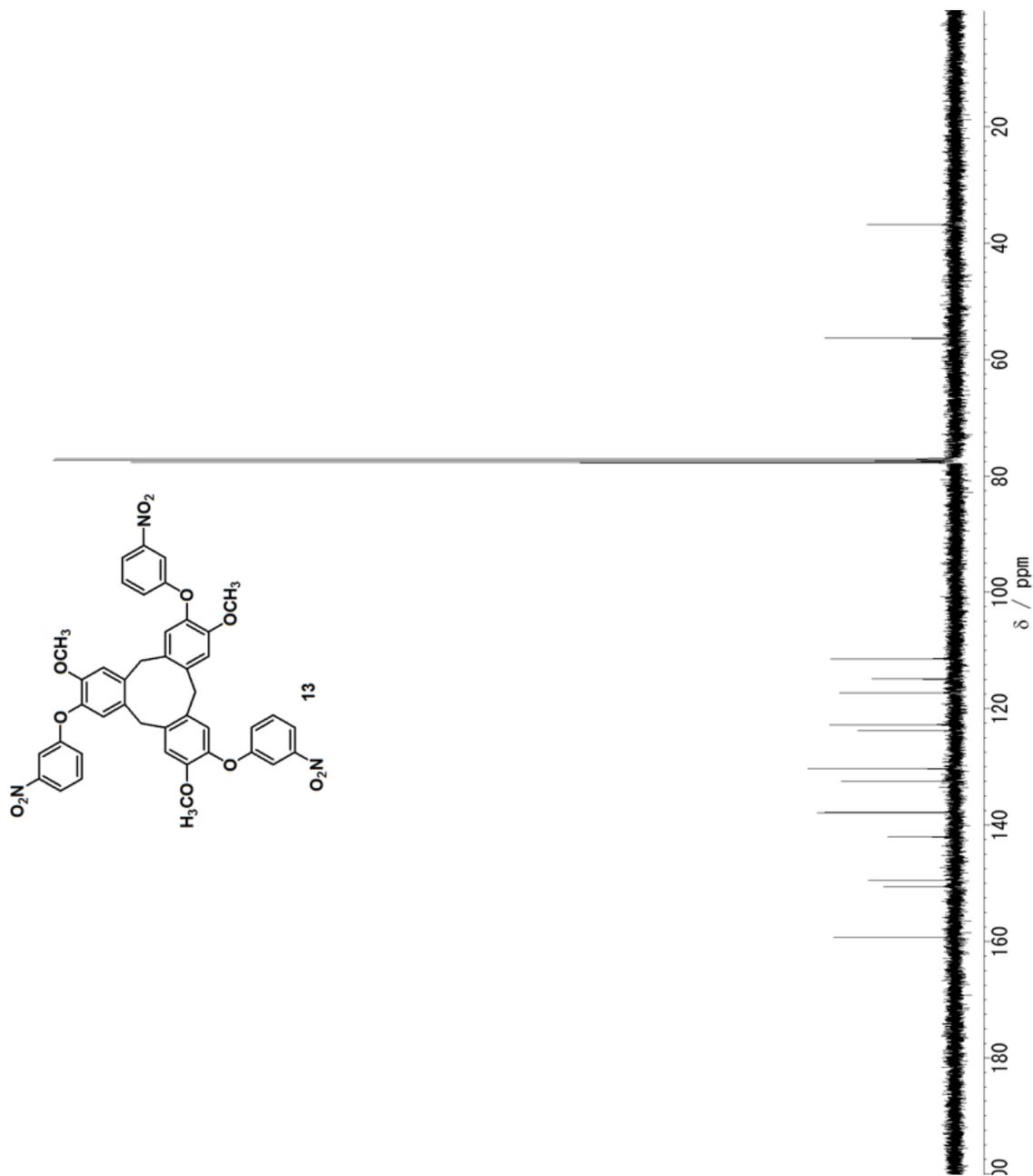
Compound 13

¹H NMR spectrum in CDCl₃



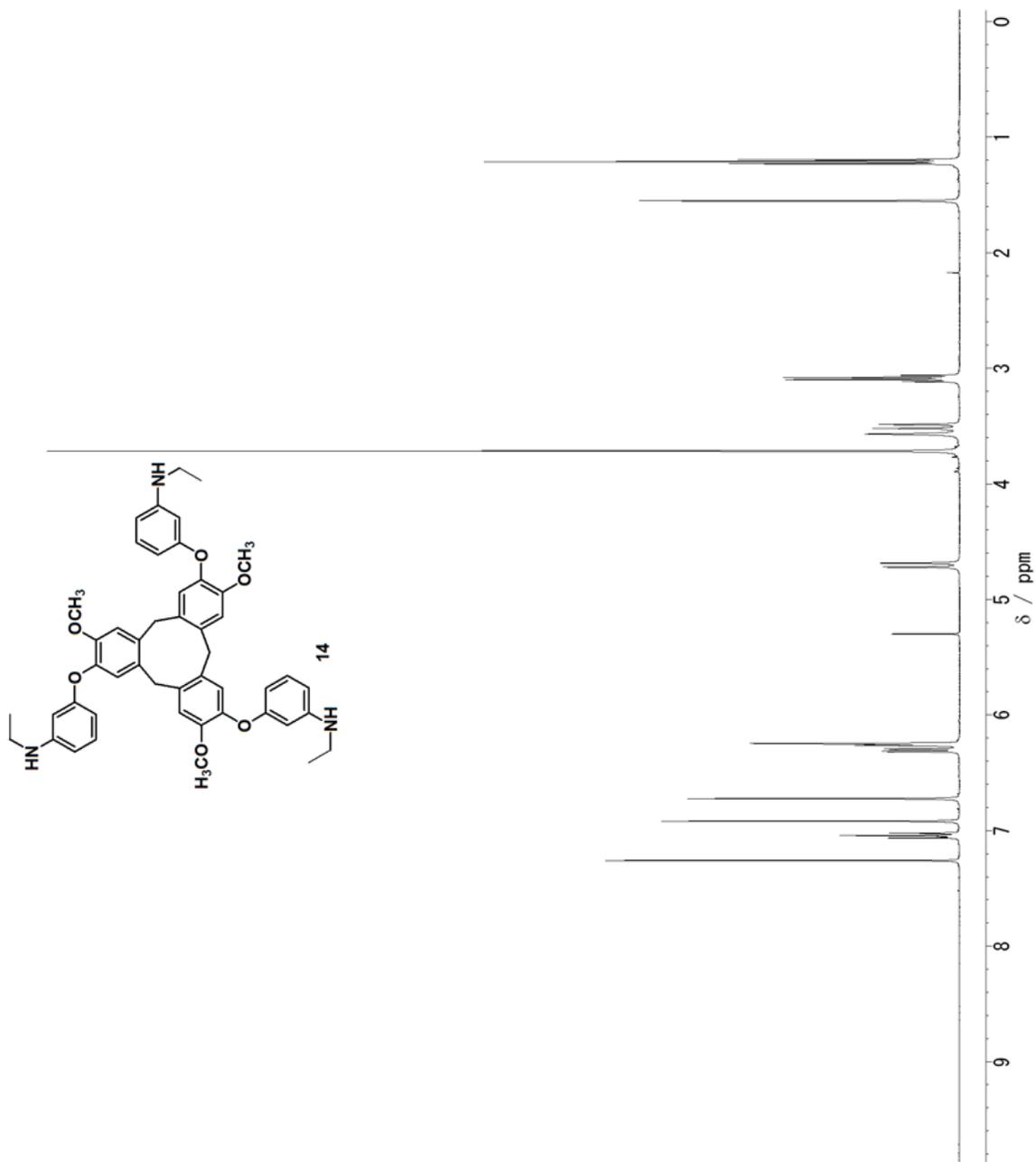
Compound 13

¹³C NMR spectrum in CDCl₃



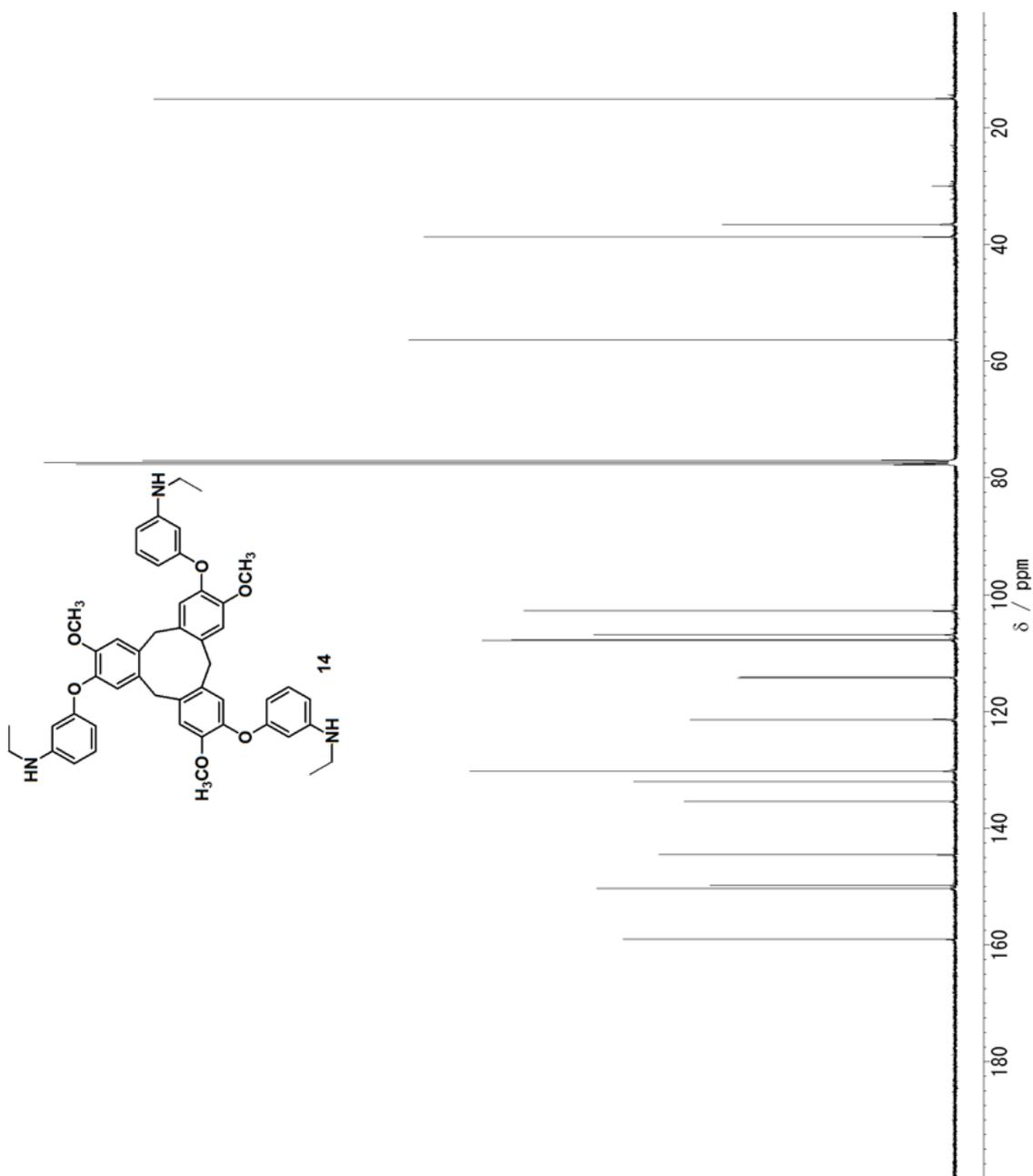
Compound 14

¹H NMR spectrum in CDCl₃



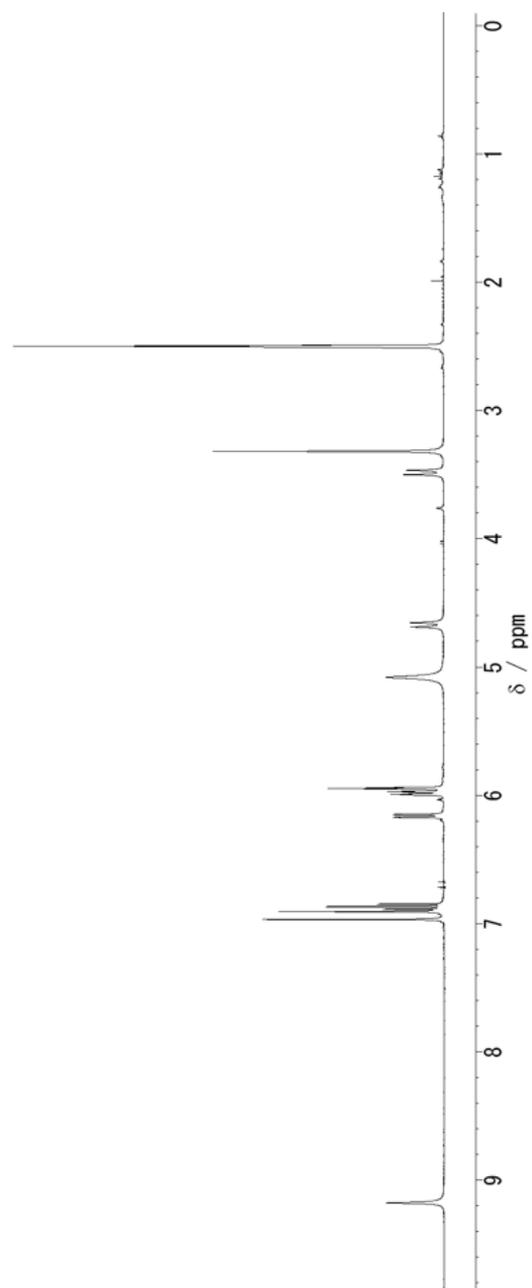
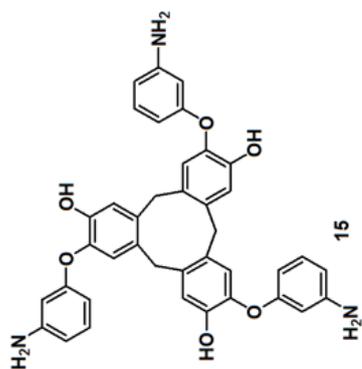
Compound 14

¹³C NMR spectrum in CDCl₃



Compound 15

¹H NMR spectrum in (CD₃)₂SO



Compound 15

^{13}C NMR spectrum in $(\text{CD}_3)_2\text{SO}$

