Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Single and dual glycoside clustering round calix[4]arene scaffolds via click thiol-ene coupling and azide-alkyne cycloaddition

Michele Fiore,[a] Angela Chambery,[b] Alberto Marra,[a]* Alessandro Dondoni[a]*
[a] *Dipartimento di Chimica, Laboratorio di Chimica Organica, Università di Ferrara, Via L. Borsari 46, 44100 Ferrara, Italy*
[b] *Dipartimento di Scienze della Vita, II Università di Napoli, Via Vivaldi 43, 81100 Caserta, Italy*

Supplementary Information

Table of contents **page**

General Experimental Section. All moisture-sensitive reactions were performed under a nitrogen atmosphere using oven-dried glassware. Anhydrous solvents were dried over standard drying agents[27] and freshly distilled prior to use. Reactions were monitored by TLC on silica gel 60 F_{254} with detection by charring with sulfuric acid. Flash column chromatography[28] was performed on silica gel 60 (40-63 μm). Optical rotations were measured at 20 ± 2 °C in the stated solvent; $[\alpha]_D$ values are given in deg·mL·g^{-1}·dm^{-1}. ^{1}H NMR (300 and 400 MHz) and ^{13}C NMR spectra (75 MHz) were recorded from $CDCl_3$ solutions at room temperature unless otherwise specified. Peak assignments were aided by ^{1}H-^{1}H COSY and gradient-HMQC experiments. In the ^{1}H NMR spectra reported below, the *n* and *m* values quoted in geminal or vicinal proton-proton coupling constants $J_{n,m}$ refer to the number of the corresponding sugar protons. For accurate mass measurements the compounds were analyzed in positive ion mode by electrospray hybrid quadrupole orthogonal acceleration time-of-flight mass spectrometer (Q-TOF) fitted with a Z-spray electrospray ion source (Waters, Manchester, UK). The capillary source voltage and the cone voltage were set at 3500 V and 35 V, respectively; the source temperature was kept at 80 °C; nitrogen was used as a drying gas at a flow rate of ca. 50 L/h. The time-of-flight analyzer was externally calibrated with NaI from *m/z* 300 to 2000 to yield an accuracy near to 5 ppm. When necessary an internal lock mass was used to further increase the mass accuracy. Accurate mass data were collected by directly infusing samples (10 pmol/μL in 1:1 CH_3CN-H_2O containing 10 mM ammonium formate) into the system at a flow rate of 5 μL/min. The acquisition and data processing were performed with the MassLynx 4.1 software (Waters, Manchester, UK). The monoisotopic masses were calculated according to the reported[29] atomic weights of the elements. The household UVA lamp apparatus was equipped with four 15 W tubes (1.5 x 27 cm each). The commercially available copper(I) iodide (light grey powder) and photoinitiator DPAP (Aldrich 19611-8) were used without further purification. The glycosyl thiol **1a**,[17] sugar azides **10**,[23] **14**,[7a] and calixarenes **2**,[2c] **4**,[18] **6**,[3] were prepared as described.

25,26,27,28-Tetrakis[3-(2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranosyl)propoxy]-calix[4]arene (5). The reaction between the thiol **1** (218 mg, 0.60 mmol) and the calixarene **4** (29 mg, 0.05 mmol) was carried out as described for the preparation of **3** to give, after acetylation of the crude reaction mixture and flash chromatography (from 2:1 to 1:4 cyclohexane-AcOEt), **5** (90 mg, 88%) as a syrup; $[\alpha]_D$ = -35.2 (*c* 1.1, $CHCl_3$). ^{1}H NMR (300 MHz): δ 6.70 (bs, 12H, Ar), 5.23 (dd, 4H, $J_{2,3}$ = 9.3 Hz, $J_{3,4}$ = 9.6 Hz, 4 H-3), 5.10 (dd, 4H, $J_{4,5}$ = 10.0 Hz, 4 H-4), 5.03 (dd, 4H, $J_{1,2}$ = 10.0 Hz, 4 H-2), 4.48 (dd, 4H, 4 H-1), 4.34 and 3.19 (2d, 8H, *J* = 13.5 Hz, 4 ArC*H*$_2$Ar), 4.27 (dd, 4H, $J_{5,6a}$ = 4.5 Hz, $J_{6a,6b}$ = 12.6 Hz, 4 H-6a), 4.09 (dd, 4H, $J_{5,6b}$ = 2.1 Hz, 4 H-6b), 3.98 (t, 8H, *J* =

7.0 Hz, 4 $CH_2CH_2CH_2O$), 3.72 (ddd, 4H, 4 H-5), 2.83 (t, 8H, J = 7.2 Hz, 4 $CH_2CH_2CH_2O$), 2.17 (tt, 8H, J = 7.0, 7.2 Hz, 4 $CH_2CH_2CH_2O$), 2.08, 2.07, 2.05, and 2.03 (4s, 48H, 16 Ac). ^{13}C NMR: δ 170.6 (C), 170.1 (C), 169.4 (C), 169.3 (C), 156.0 (C), 134.7 (C), 128.5 (CH), 128.3 (CH), 122.4 (CH), 83.6 (CH), 75.7 (CH), 73.8 (CH), 73.0 (CH_2), 69.8 (CH), 68.2 (CH), 62.0 (CH_2), 31.1 (CH_2), 30.0 (CH_2), 26.9 (CH_2), 20.7 (CH_3), 20.6 (CH_3). HRMS (ESI/Q-TOF) *m/z* calcd for $(C_{96}H_{128}N_2O_{40}S_4)/2$ $(M+2NH_4)^{2+}$ 1038.3463, found 1038.3513.

5,11,17,23-Tetrakis[3-(2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranosyl)propyl]-25,26,27,28-tetrakis[3-(2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranosyl)propoxy]-calix[4]arene (7). The reaction between the thiol **1** (436 mg, 1.20 mmol) and the calixarene **6** (37 mg, 0.05 mmol) was carried out as described for the preparation of **3** to give, after acetylation of the crude reaction mixture and flash chromatography (3:1 AcOEt-cyclohexane, then AcOEt), **7** (122 mg, 67%) as a white foam; $[\alpha]_D$ = -44.7 (*c* 0.7, $CHCl_3$). ^{1}H NMR (300 MHz): δ 6.40 (s, 8H, Ar), 5.26 (dd, 4H, $J_{2,3}$ = 9.3 Hz, $J_{3,4}$ = 9.5 Hz, 4 H-3), 5.25 (dd, 4H, $J_{2,3}$ = 9.3 Hz, $J_{3,4}$ = 9.5 Hz, 4 H-3), 5.12 (dd, 8H, $J_{4,5}$ = 10.0 Hz, 8 H-4), 5.04 (dd, 8H, $J_{1,2}$ = 10.0 Hz, 8 H-2), 4.56 (dd, 4H, 4 H-1), 4.54 (dd, 4H, 4 H-1), 4.29 (dd, 8H, $J_{5,6a}$ = 4.5 Hz, $J_{6a,6b}$ = 12.5 Hz, 8 H-6a), 4.25 and 3.06 (2d, 8H, J = 13.5 Hz, 4 $ArCH_2Ar$), 4.15 (dd, 4H, $J_{5,6b}$ = 2.0 Hz, 4 H-6b), 4.11 (dd, 4H, $J_{5,6b}$ = 2.0 Hz, 4 H-6b), 3.91 (t, 8H, J = 7.0 Hz, 4 $CH_2CH_2CH_2O$), 3.76 (ddd, 8H, 8 H-5), 2.83 (t, 8H, J = 7.0 Hz, 4 $CH_2CH_2CH_2O$), 2.67-2.56 (m, 8H, 4 $ArCH_2CH_2CH_2$), 2.40-2.32 (m, 8H, 4 $ArCH_2CH_2CH_2$), 2.20-2.13 and 1.78-1.70 (2m, 16H, 4 $CH_2CH_2CH_2O$, 4 $ArCH_2CH_2CH_2$), 2.01, 2.00, and 1.99 (3s, 96H, 32 Ac). ^{13}C NMR: δ 170.6 (C), 170.1 (C), 169.4 (C), 169.3 (C), 154.1 (C), 134.8 (C), 134.3 (C), 128.1 (CH), 83.8 (CH), 83.6 (CH), 75.7 (CH), 73.9 (CH), 73.2 (CH_2), 70.0 (CH), 69.9 (CH), 68.3 (CH), 62.1 (CH_2), 34.1 (CH_2), 31.5 (CH_2), 30.9 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 26.8 (CH_2), 20.7 (CH_3), 20.6 (CH_3). HRMS (ESI/Q-TOF) *m/z* calcd for $(C_{164}H_{224}N_2O_{76}S_8)/2$ $(M+2NH_4)^{2+}$ 1846.5745, found 1846.5741.

5,11,17,23-Tetraallyl-25,26,27,28-tetrapropargyloxy-calix[4]arene (9). To a cooled (0 °C), stirred solution of tetrol **8** (497 mg, 0.85 mmol) in anhydrous DMF (5 mL) was added NaH (408 mg, 10.20 mmol, of a 60% dispersion in oil) and, after 15 min, propargyl bromide (0.76 mL, 10.20 mmol). The mixture was stirred at room temperature overnight, then diluted with CH_3OH (2 mL) and, after 10 min, 1 M phosphate buffer at pH 7 (10 mL) and extracted with Et_2O (2 x 100 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was eluted from a column of silica gel with 1:1 cyclohexane-CH_2Cl_2 to give **9** (475 mg, 76%) as a pale yellow syrup. ^{1}H NMR (300 MHz): δ 6.56 (s, 8H, Ar), 5.80 (ddt, 4H, J = 6.5, 10.0, 16.8 Hz, 4 $CH_2CH{=}CH_2$),

4.96 (ddt, 4H, *J* = 1.2, 2.2, 10.0 Hz, H_{cis} of 4 $CH_2CH=CH_2$), 4.87 (ddt, 4H, *J* = 1.4, 2.2, 16.8 Hz, H_{trans} of 4 $CH_2CH=CH_2$), 4.77 (d, 8H, *J* = 2.5 Hz, 4 $CH_2C\equiv CH$), 4.60 and 3.16 (2d, 8H, *J* = 13.4 Hz, 4 $ArCH_2Ar$), 3.11 (ddd, 8H, *J* = 1.2, 1.4, 6.5 Hz, 4 $CH_2CH=CH_2$), 2.48 (t, 4H, *J* = 2.5 Hz, 4 $CH_2C\equiv CH$). ^{13}C NMR: δ 153.3 (C), 138.0 (CH), 135.1 (C), 134.2 (C), 128.4 (CH), 115.0 (CH_2), 80.7 (CH), 74.5 (C), 61.1 (CH_2), 39.3 (CH_2), 31.9 (CH_2). HRMS (ESI/Q-TOF) *m/z* calcd for $C_{52}H_{52}NO_4$ $(M+NH_4)^+$ 754.3896, found 754.3842.

5,11,17,23-Tetraallyl-25,26,27,28-tetrakis[1-(3,4,5,7-tetra-*O*-acetyl-2,6-anhydro-1-deoxy-D-*glycero*-L-*gluco*-heptitol-1-yl)-1*H*-1,2,3-triazol-4-yl]methoxy-calix[4]arene (11). A mixture of calixarene **9** (44 mg, 0.06 mmol), azide **10** (102 mg, 0.26 mmol), freshly distilled *N,N*-diisopropylethylamine (210 μL, 1.20 mmol), CuI (11.4 mg, 0.06 mmol), and anhydrous toluene (1.2 mL) was sonicated in an ultrasound cleaning bath for 1 min, then magnetically stirred in the dark at room temperature for 26 h, diluted with AcOEt (ca. 20 mL), filtered through a pad of Celite to remove most of the copper salts, and concentrated. A solution of the resulting yellow syrup in pyridine (2 mL) and acetic anhydride (2 mL) was kept at room temperature for 3 h, then concentrated. The residue was eluted from a column of silica gel with 2:1 AcOEt-cyclohexane, then AcOEt, to give **11** (77 mg, 56%) as syrup; $[\alpha]_D$ = +61.6 (*c* 0.8, $CHCl_3$). ^1H NMR (300 MHz): δ 7.95 (s, 4H, 4 H-5 Tr.), 6.45 (bs, 8H, Ar), 5.80 (ddt, 4H, *J* = 6.5, 10.1, 16.8 Hz, 4 $CH_2CH=CH_2$), 5.50 (dd, 4H, $J_{4,5}$ = 3.3 Hz, $J_{5,6}$ = 2.7 Hz, 4 H-5), 5.46 (dd, 4H, $J_{2,3}$ = 4.7 Hz, $J_{3,4}$ = 8.9 Hz, 4 H-3), 5.36 (dd, 4H, 4 H-4), 5.02 and 4.97 (2d, 8H, *J* = 12.5 Hz, 4 $OCH_2Tr.$), 4.98 (ddt, 4H, *J* = 1.5, 2.0, 10.1 Hz, H_{cis} of 4 $CH_2CH=CH_2$), 4.88 (ddt, 4H, *J* = 1.8, 2.0, 16.8 Hz, H_{trans} of 4 $CH_2CH=CH_2$), 4.79 (dd, 4H, $J_{1a,2}$ = 11.5 Hz, $J_{1a,1b}$ = 14.7 Hz, 4 H-1a), 4.68-4.60 (m, 8H), 4.55-4.44 (m, 4H), 4.22 and 2.99 (2d, 8H, *J* = 13.5 Hz, 4 $ArCH_2Ar$), 4.15 (dd, 4H, $J_{6,7a}$ = 7.4 Hz, $J_{7a,7b}$ = 11.6 Hz, 4 H-7a), 4.04 (dd, 4H, $J_{6,7b}$ = 5.5 Hz, 4 H-7b), 3.06 (ddd, 8H, *J* = 1.5, 1.8, 6.5 Hz, 4 $CH_2CH=CH_2$), 2.16, 2.14, 2.06, and 1.90 (4s, 48H, 16 Ac). ^{13}C NMR: δ 170.3 (C), 169.9 (C), 169.7 (C), 153.1 (C), 144.4 (C), 138.1 (CH), 134.7 (C), 133.7 (C), 128.5 (CH), 125.2 (CH), 114.9 (CH_2), 71.0 (CH), 69.0 (CH), 67.7 (CH), 67.2 (CH), 66.5 (CH_2), 60.7 (CH_2), 46.7 (CH_2), 39.3 (CH_2), 31.2 (CH_2), 20.8 (CH_3), 20.6 (CH_3), 20.5 (CH_3). HRMS (ESI/Q-TOF) *m/z* calcd for $(C_{112}H_{134}N_{12}O_{40})/2$ $(M+2H)^{2+}$ 1143.4410, found 1143.4417.

5,11,17,23-Tetrakis[3-(2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranosyl)propyl]-25,26,27,28-tetrakis[1-(3,4,5,7-tetra-*O*-acetyl-2,6-anhydro-1-deoxy-D-*glycero*-L-*gluco*-heptitol-1-yl)-1*H*-1,2,3-triazol-4-yl]methoxy-calix[4]arene (12). The reaction between the thiol **1** (67 mg, 0.18

mmol) and the cluster **11** (35 mg, 0.015 mmol) was carried out as described for the preparation of **3** to give, after acetylation of the crude reaction mixture and flash chromatography (AcOEt, then 2:1 AcOEt-acetone), **12** (43 mg, 76%) as a syrup; $[\alpha]_D$ = +20.1 (*c* 0.7, $CHCl_3$). ^{1}H NMR (400 MHz): δ 7.92 (s, 4H, 4 H-5 Tr.), 6.36 (bs, 8H, Ar), 5.48 (dd, 4H, $J_{4,5}$ = 3.1 Hz, $J_{5,6}$ = 2.5 Hz, 4 H-5Gal), 5.43 (dd, 4H, $J_{2,3}$ = 4.7 Hz, $J_{3,4}$ = 9.0 Hz, 4 H-3Gal), 5.36 (dd, 4H, 4 H-4Gal), 5.24 (dd, 4H, $J_{2,3}$ = 9.3 Hz, $J_{3,4}$ = 9.5 Hz, 4 H-3Glc), 5.09 (dd, 4H, $J_{4,5}$ = 10.0 Hz, 4 H-4Glc), 5.02 (dd, 4H, $J_{1,2}$ = 10.0 Hz, 4 H-2Glc), 4.96 and 4.91 (2d, 8H, *J* = 12.5 Hz, 4 OCH_2Tr.), 4.80 (dd, 4H, $J_{1a,2}$ = 11.5 Hz, $J_{1a,1b}$ = 14.5 Hz, 4 H-1aGal), 4.66-4.58 (m, 8H, 4 H-1bGal, 4 H-2Gal), 4.52 (d, 4H, 4 H-1Glc), 4.45 (ddd, 4H, $J_{6,7a}$ = 7.5 Hz, $J_{6,7b}$ = 5.3 Hz, 4 H-6Gal), 4.25 (dd, 4H, $J_{5,6a}$ = 4.6 Hz, $J_{6a,6b}$ = 12.3 Hz, 4 H-6aGlc), 4.17 and 2.92 (2d, 8H, *J* = 13.3 Hz, 4 ArCH_2Ar), 4.13 (dd, 4H, $J_{5,6b}$ = 2.3 Hz, 4 H-6bGlc), 4.12 (dd, 4H, $J_{7a,7b}$ = 11.5 Hz, 4 H-7aGal), 4.00 (dd, 4H, 4 H-7bGal), 3.73 (ddd, 4H, 4 H-5Glc), 2.64-2.50 (m, 8H, 4 $CH_2CH_2CH_2$S), 2.35-2.31 (m, 8H, 4 $CH_2CH_2CH_2$S), 2.12, 2.11, 2.06, 2.04, 2.03, and 2.01 (6s, 96H, 32 Ac), 1.74-1.66 (m, 8H, 4 $CH_2CH_2CH_2$S). ^{13}C NMR: δ 170.6 (C), 170.3 (C), 170.2 (C), 170.0 (C), 169.7 (C), 169.4 (C), 153.2 (C), 144.3 (C), 135.2 (C), 134.7 (C), 128.2 (CH), 128.0 (CH), 125.1 (CH), 83.8 (CH), 77.2 (CH), 75.7 (CH), 73.9 (CH), 71.0 (CH), 70.0 (CH), 69.0 (CH), 68.3 (CH), 67.7 (CH), 67.1 (CH), 62.1 (CH_2), 60.8 (CH_2), 46.7 (CH_2), 34.1 (CH_2), 31.5 (CH_2), 31.4 (CH_2), 29.8 (CH_2), 20.7 (CH_3), 20.6 (CH_3). HRMS (ESI/Q-TOF) *m/z* calcd for $(C_{168}H_{214}N_{12}O_{76}S_4)/2$ $(M+2H)^{2+}$ 1871.6066, found 1871.6040.

5,11,17,23-Tetrakis[3-(1-thio-β-D-glucopyranosyl)propyl]-25,26,27,28-tetrakis[1-(2,6-anhydro-1-deoxy-D-*glycero*-L-*gluco*-heptitol-1-yl)-1*H*-1,2,3-triazol-4-yl]methoxy-calix[4]arene (13). A solution of **12** (37.4 mg, 0.01 mmol) in a 0.2 M solution of NaOMe in MeOH (2 ml, prepared from Na and MeOH immediately before the use) was stirred at room temperature for 3 h in a nitrogen atmosphere (after a few minutes the solution turned turbid), then diluted with H_2O (ca. 0.4 mL), neutralized with Dowex 50X2-400 resin (H^+ form, activated and washed with H_2O and MeOH immediately before the use), and filtered through a sintered glass filter. The resin was washed with MeOH, H_2O, and DMF, and the solution was concentrated. The residue was eluted from a C18 silica gel cartridge with H_2O, then 1:1 H_2O-MeOH, and dried under high vacuum to give **13** (16.1 mg, 67%) as an amorphous solid; $[\alpha]_D$ = +18.3 (*c* 1.0, H_2O). ^{1}H NMR (400 MHz, D_2O) selected data: δ 7.75 (s, 4H, 4 H-5 Tr.), 6.39 (bs, 8H, Ar), 4.96 and 4.90 (2d, 8H, *J* = 12.5 Hz, 4 OCH_2Tr.), 4.32 (d, 4H, $J_{1,2}$ = 10.0 Hz, 4 H-1Glc), 3.13 (dd, 4H, $J_{2,3}$ = 8.7 Hz, 4 H-2Glc), 2.69 (d, 4H, *J* = 12.5 Hz, H_{eq} of 4 ArCH_2Ar), 2.48-2.32 (m, 8H, 4 $CH_2CH_2CH_2$S), 2.24-2.18 (m, 8H, 4 $CH_2CH_2CH_2$S), 1.60-1.50 (m, 8H, 4 $CH_2CH_2CH_2$S). ^{13}C NMR (75 MHz, D_2O): δ 152.6 (C), 144.4 (C), 136.2 (C),

135.4 (C), 135.3 (C), 128.5 (CH), 126.3 (CH), 85.7 (CH), 80.0 (CH), 77.5 (CH), 75.2 (CH), 72.6 (CH), 72.4 (CH), 70.0 (CH), 69.7 (CH), 68.6 (CH), 67.4 (CH), 65.5 (CH_2), 61.1 (CH_2), 60.5 (CH_2), 45.8 (CH_2), 33.2 (CH_2), 31.3 (CH_2), 31.1 (CH_2), 29.6 (CH_2). HRMS (ESI/Q-TOF) *m/z* calcd for ($C_{104}H_{150}N_{12}O_{44}S_4$)/2 $(M+2H)^{2+}$ 1199.4376, found 1199.4346.

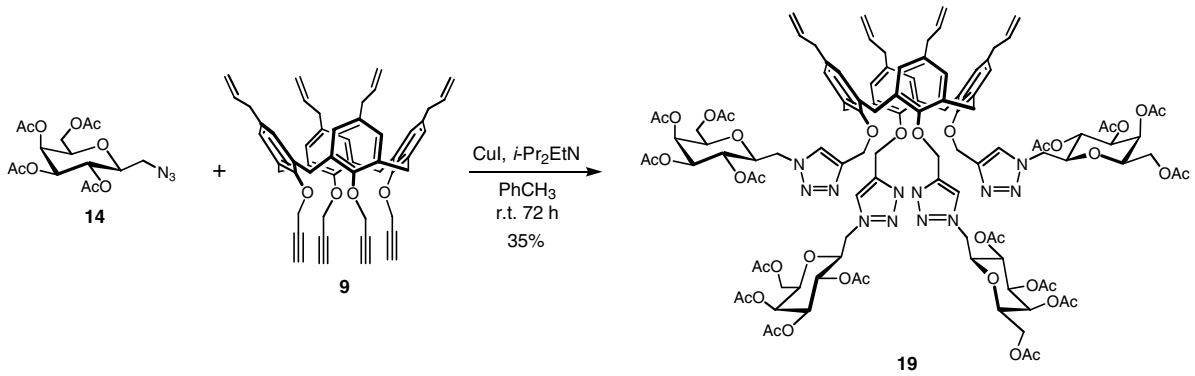
2,6-Anhydro-1-azido-1-deoxy-3,4:5,7-di-*O*-isopropylidene-D-*glycero*-L-*manno*-heptitol (15). A solution of acetylated sugar azide **14** (155 mg, 0.40 mmol) in a 0.2 M solution of NaOMe in MeOH (4 ml, prepared from Na and MeOH immediately before the use) was stirred at room temperature for 1 h in a nitrogen atmosphere, then neutralized with Dowex 50X2-400 resin (H^+ form, activated and washed with H_2O and MeOH immediately before the use), and filtered through a sintered glass filter. The resin was washed with MeOH and H_2O, and the solution was concentrated. To a solution of the crude tetrol and camphorsulfonic acid (ca. 5 mg) in anhydrous DMF (1 mL) was added 2-methoxypropene (190 μL, 2.00 mmol). The solution was kept at room temperature for 50 min, then diluted with Et_3N (0.2 mL) and concentrated. The residue was eluted from a column of silica gel with 1.5:1 cyclohexane-AcOEt (containing 0.5% of Et_3N) to give **15** (96 mg, 80%) as a syrup that became solid upon standing; $[\alpha]_D$ = -4.0 (*c* 0.8, $CHCl_3$). ^{1}H NMR (400 MHz): δ 4.48 (dd, 1H, $J_{4,5}$ = 2.8 Hz, $J_{5,6}$ = 1.5 Hz, H-5), 4.11 (dd, 1H, $J_{6,7a}$ = 2.3 Hz, $J_{7a,7b}$ = 13.0 Hz, H-7a), 3.98 (dd, 1H, $J_{6,7b}$ = 1.7 Hz, H-7b), 3.86 (dd, 1H, $J_{2,3}$ = 9.3 Hz, $J_{3,4}$ = 9.2 Hz, H-3), 3.70 (dt, 1H, $J_{1,2}$ = 4.9 Hz, H-2), 3.53 (dd, 1H, H-4), 3.51 (d, 2H, 2 H-1), 3.32 (ddd, 1H, H-6), 1.48, 1.46, 1.44, and 1.42 (4s, 12H, 4 Me). ^{13}C NMR: δ 110.9 (C), 98.5 (C), 79.8 (C-4), 78.6 (C-2), 70.8 (C-3), 69.2 (C-6), 66.8 (C-5), 63.2 (C-7), 52.2 (C-1), 29.0 (CH_3), 26.6 (CH_3), 26.5 (CH_3), 18.5 (CH_3). HRMS (ESI/Q-TOF) *m/z* calcd for $C_{13}H_{22}N_3O_5$ $(M+H)^+$ 300.1559, found 300.1537.

5,11,17,23-Tetraallyl-25,26,27,28-tetrakis[1-(2,6-anhydro-1-deoxy-3,4:5,7-di-*O*-isopropylidene-D-*glycero*-L-*manno*-heptitol-1-yl)-1*H*-1,2,3-triazol-4-yl]methoxy-calix[4]arene (16). The cyclo-addition between the calixarene alkyne **9** (44 mg, 0.06 mmol) and the sugar azide **15** (79 mg, 0.26 mmol) was carried out as described for the preparation of **11** to give, after a similar workup and purification by flash chromatography (AcOEt, containing 0.5% of Et_3N), **16** (103 mg, 89%) as an amorphous solid; $[\alpha]_D$ = -1.1 (*c* 0.9, $CHCl_3$). ^{1}H NMR (300 MHz): δ 7.90 (s, 4H, 4 H-5 Tr.), 6.44-6.40 (m, 8H, Ar), 5.78 (ddt, 4H, *J* = 6.5, 10.3, 16.8 Hz, 4 CH_2CH=CH_2), 5.12 and 5.04 (2d, 8H, *J* = 12.3 Hz, 4 OCH_2Tr.), 4.95 (ddt, 4H, *J* = 1.4, 2.0, 10.3 Hz, H_{cis} of 4 CH_2CH=CH_2), 4.85 (ddt, 4H, *J* = 1.7, 2.0, 16.9 Hz, H_{trans} of 4 CH_2CH=CH_2), 4.82 (dd, 4H, $J_{1a,2}$ = 1.4 Hz, $J_{1a,1b}$ = 14.5 Hz, 4 H-1a), 4.51 (dd, 4H, $J_{4,5}$ = 2.8 Hz, $J_{5,6}$ = 1.1 Hz, 4 H-5), 4.46 (dd, 4H, $J_{1b,2}$ = 8.5 Hz, 4 H-1b),

4.17 and 2.88 (2d, 8H, J = 13.3 Hz, 4 ArCH_2Ar), 4.07 (dd, 4H, $J_{6,7a}$ = 2.1 Hz, $J_{7a,7b}$ = 13.2 Hz, 4 H-7a), 3.91-3.78 (m, 8H, 4 H-2, 4 H-3), 3.88 (dd, 4H, $J_{6,7b}$ = 1.0 Hz, 4 H-7b), 3.62 (dd, 4H, $J_{3,4}$ = 8.5 Hz, 4 H-4), 3.37 (ddd, 4H, 4 H-6), 3.05 (ddd, 8H, J = 1.4, 1.7, 6.5 Hz, 4 CH_2CH=CH$_2$), 1.50, 1.49, 1.46, and 1.42 (4s, 48H, 16 Me). ^{13}C NMR: δ 153.2 (C), 144.2 (C), 138.1 (CH), 135.0 (C), 134.7 (C), 133.3 (C), 128.2 (CH), 128.1 (CH), 125.3 (CH), 114.8 (CH$_2$), 110.9 (C), 98.3 (C), 79.4 (CH), 77.9 (CH), 70.8 (CH), 68.9 (CH), 66.8 (CH), 66.2 (CH$_2$), 63.1 (CH$_2$), 51.9 (CH$_2$), 39.2 (CH$_2$), 31.5 (CH$_2$), 29.1 (CH$_3$), 26.6 (CH$_3$), 26.4 (CH$_3$), 18.5 (CH$_3$). HRMS (ESI/Q-TOF) *m/z* calcd for ($C_{104}H_{134}N_{12}O_{24}$)/2 $(M+2H)^{2+}$ 967.4817, found 967.4814.

5,11,17,23-Tetrakis[3-(2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranosyl)propyl]-25,26,27,28-tetrakis[1-(2,6-anhydro-1-deoxy-3,4:5,7-di-*O*-isopropylidene-D-*glycero*-L-*manno*-heptitol-1-yl)-1*H*-1,2,3-triazol-4-yl]methoxy-calix[4]arene (17). The reaction between the thiol **1** (219 mg, 0.60 mmol) and the cluster **16** (97 mg, 0.05 mmol) was carried out as described for the preparation of **3** to give, after flash chromatography (AcOEt, then 4:1 AcOEt-acetone), **17** (137 mg, 81%) as a white foam; $[\alpha]_D$ = -23.5 (*c* 0.6, $CHCl_3$). ^{1}H NMR (400 MHz): δ 7.89 (s, 4H, 4 H-5 Tr.), 6.38-6.33 (m, 8H, Ar), 5.23 (dd, 4H, $J_{2,3}$ = 9.5 Hz, $J_{3,4}$ = 9.3 Hz, 4 H-3Glc), 5.09 (dd, 4H, $J_{4,5}$ = 10.2 Hz, 4 H-4Glc), 5.09 and 4.97 (2d, 8H, J = 12.5 Hz, 4 OCH_2Tr.), 5.01 (dd, 4H, $J_{1,2}$ = 10.0 Hz, 4 H-2Glc), 4.79 (dd, 4H, $J_{1a,2}$ = 1.5 Hz, $J_{1a,1b}$ = 14.5 Hz, 4 H-1aGal), 4.52 (d, 4H, 4 H-1Glc), 4.50 (dd, 4H, $J_{4,5}$ = 2.8 Hz, $J_{5,6}$ = 1.1 Hz, 4 H-5Gal), 4.45 (dd, 4H, $J_{1b,2}$ = 8.6 Hz, 4 H-1bGal), 4.26 (dd, 4H, $J_{5,6a}$ = 4.9 Hz, $J_{6a,6b}$ = 12.4 Hz, 4 H-6aGlc), 4.15 and 2.85 (2d, 8H, J = 13.4 Hz, 4 ArCH_2Ar), 4.13 (dd, 4H, $J_{5,6b}$ = 2.3 Hz, 4 H-6bGlc), 4.05 (dd, 4H, $J_{6,7a}$ = 2.0 Hz, $J_{7a,7b}$ = 13.0 Hz, 4 H-7aGal), 3.85 (ddd, 4H, $J_{2,3}$ = 9.4 Hz, 4 H-2Gal), 3.84 (dd, 4H, $J_{6,7b}$ = 1.5 Hz, 4 H-7bGal), 3.79 (dd, 4H, $J_{3,4}$ = 8.8 Hz, 4 H-3Gal), 3.74 (ddd, 4H, 4 H-5Glc), 3.60 (dd, 4H, 4 H-4Gal), 3.36 (ddd, 4H, 4 H-6Gal), 2.60-2.52 (m, 8H, 4 CH$_2$CH$_2$CH_2S), 2.33 (t, 8H, J = 7.5 Hz, 4 CH_2CH$_2$CH$_2$S), 2.06, 2.04, 2.02, and 2.00 (4s, 48H, 16 Ac), 1.73-1.64 (m, 8H, 4 CH$_2$CH_2CH$_2$S), 1.48, 1.46, 1.44, and 1.40 (4s, 48H, 16 Me). ^{13}C NMR: δ 170.5 (C), 170.1 (C), 169.4 (C), 169.3 (C), 153.3 (C), 144.2 (C), 135.0 (C), 134.8 (C), 127.9 (CH), 127.8 (CH), 125.3 (CH), 111.0 (C), 98.4 (C), 83.8 (CH), 79.4 (CH), 77.9 (CH), 75.6 (CH), 73.8 (CH), 70.8 (CH), 70.0 (CH), 68.9 (CH), 68.3 (CH), 66.8 (CH), 66.2 (CH$_2$), 63.1 (CH$_2$), 62.1 (CH$_2$), 52.0 (CH$_2$), 34.0 (CH$_2$), 31.5 (CH$_2$), 31.3 (CH$_2$), 29.8 (CH$_2$), 29.1 (CH$_3$), 26.6 (CH$_3$), 26.5 (CH$_3$), 20.7 (CH$_3$), 20.5 (CH$_3$), 18.5 (CH$_3$). HRMS (ESI/Q-TOF) *m/z* calcd for ($C_{160}H_{214}N_{12}O_{60}S_4$)/2 $(M+2H)^{2+}$ 1695.6473, found 1695.6389.

5,11,17,23-Tetrakis[3-(1-thio-β-D-glucopyranosyl)propyl]-25,26,27,28-tetrakis[1-(2,6-anhydro-1-deoxy-D-*glycero*-L-*manno*-heptitol-1-yl)-1*H*-1,2,3-triazol-4-yl]methoxy-calix[4]arene (18). A solution of **17** (67.8 mg, 0.02 mmol) in a 0.2 M solution of NaOMe in MeOH (2 ml, prepared from Na and MeOH immediately before the use) was kept at room temperature for 4 h in a nitrogen atmosphere, then diluted with MeOH (4 mL) and stirred with an excess of Dowex 50X2-400 resin (H^+ form, activated and washed with H_2O and MeOH immediately before the use) at room temperature for 15 min to remove the isopropylidene protecting groups. The suspension was filtered through a sintered glass filter, the resin was washed with MeOH, H_2O, and DMF, and the solution was concentrated. The residue was eluted from a C18 silica gel cartridge with H_2O, then 1:1 H_2O-MeOH, and dried under high vacuum to give **18** (40.8 mg, 85%) as an amorphous solid; $[\alpha]_D$ = -24.2 (*c* 1.0, H_2O). ^{1}H NMR (400 MHz, D_2O) selected data: δ 7.80 (s, 4H, 4 H-5 Tr.), 6.45 (s, 8H, Ar), 5.80 (s, 8H, 4 OC*H*$_2$Tr.), 4.33 (d, 4H, $J_{1,2}$ = 9.8 Hz, 4 H-1Glc), 3.81 (dd, 4H, $J_{4,5}$ = 2.2 Hz, $J_{5,6}$ = 0.5 Hz, 4 H-5Gal), 3.75 and 2.71 (2d, 8H, *J* = 13.5 Hz, 4 ArC*H*$_2$Ar), 3.14 (dd, 4H, $J_{2,3}$ = 8.8 Hz, 4 H-2Glc), 2.46 and 2.38 (2dt, 8H, *J* = 7.0, 13.3 Hz, 4 $CH_2CH_2CH_2S$), 2.26 (t, 8H, *J* = 7.3 Hz, 4 $CH_2CH_2CH_2S$), 1.59 (tt, 8H, *J* = 7.0, 7.3 Hz, 4 $CH_2CH_2CH_2S$). ^{13}C NMR (75 MHz, D_2O): δ 152.6 (C), 144.3 (C), 136.2 (C), 135.3 (C), 128.4 (CH), 126.6 (CH), 85.7 (CH), 80.0 (CH), 78.7 (CH), 78.4 (CH), 77.5 (CH), 74.1 (CH), 72.6 (CH), 69.7 (CH), 68.9 (CH), 68.4 (CH), 65.5 (CH_2), 61.1 (CH_2), 60.8 (CH_2), 51.6 (CH_2), 33.2 (CH_2), 31.3 (CH_2), 31.2 (CH_2), 29.5 (CH_2). HRMS (ESI/Q-TOF) *m/z* calcd for $(C_{104}H_{150}N_{12}O_{44}S_4)/2$ $(M+2H)^{2+}$ 1199.4376, found 1199.4346.



5,11,17,23-Tetraallyl-25,26,27,28-tetrakis[1-(3,4,5,7-tetra-*O*-acetyl-2,6-anhydro-1-deoxy-D-*glycero*-L-*manno*-heptitol-1-yl)-1*H*-1,2,3-triazol-4-yl]methoxy-calix[4]arene (19). A mixture of calixarene **9** (52 mg, 0.07 mmol), azide **14** (120 mg, 0.31 mmol), freshly distilled *N,N*-diisopropylethylamine (245 µL, 1.40 mmol), CuI (13.3 mg, 0.07 mmol), and anhydrous toluene (1.4 mL) was sonicated in an ultrasound cleaning bath for 1 min, then magnetically stirred in the dark at

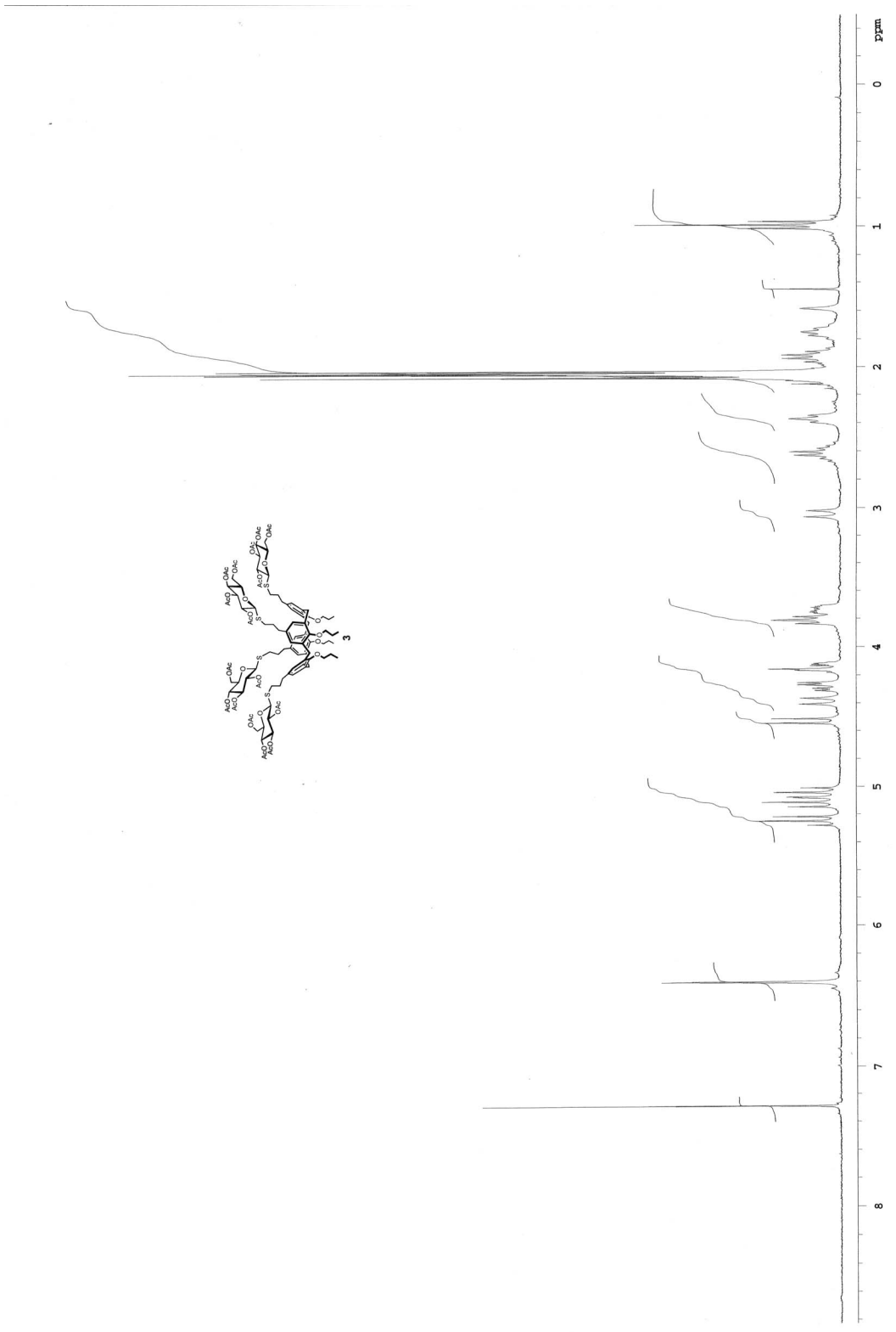
room temperature for 72 h, and concentrated. A solution of the residue in pyridine (2 ml) and acetic anhydride (2 mL) was kept at room temperature for 3 h, then concentrated. A solution of the residue in AcOEt (50 mL) was washed with a 0.05 M aqueous solution of EDTA (3 x 15 mL) and water (10 mL), dried (Na_2SO_4), and concentrated. The residue was eluted from a column of silica gel (AcOEt, then 1.5:1 AcOEt-acetone) to give **19** (56 mg, 35%) as a syrup; $[\alpha]_D$ = +3.8 (*c* 0.8, $CHCl_3$). ^{1}H NMR (300 MHz) selected data: δ 7.80 (s, 4H, 4 H-5 Tr.), 6.47-6.41 (m, 8H, Ar), 5.78 (ddt, 4H, *J* = 6.5, 10.5, 16.7 Hz, 4 CH_2CH=CH_2), 5.45 (bs, 4H, 4 H-5), 4.96 (ddt, 4H, *J* = 1.4, 2.0, 10.5 Hz, H_{cis} of 4 CH_2CH=CH_2), 4.85 (ddt, 4H, *J* = 1.8, 2.0, 16.7 Hz, H_{trans} of 4 CH_2CH=CH_2), 4.37 (dd, 4H, $J_{1b,2}$ = 9.3 Hz, $J_{1a,1b}$ = 14.3 Hz, 4 H-1b), 4.17 and 2.88 (2d, 8H, *J* = 13.5 Hz, 4 ArCH_2Ar), 3.05 (ddd, 8H, *J* = 1.4, 1.8, 6.5 Hz, 4 CH_2CH=CH_2), 2.18, 2.14, 2.02, and 1.97 (4s, 48H, 16 Ac). ^{13}C NMR: δ 170.2 (C), 170.0 (C), 153.0 (C), 144.2 (C), 138.1 (CH), 134.7 (C), 133.7 (C), 128.4 (CH), 128.3 (CH), 125.3 (CH), 115.0 (CH_2), 73.9 (CH), 71.6 (CH), 67.3 (CH), 66.2 (CH_2), 60.9 (CH_2), 51.2 (CH_2), 39.3 (CH_2), 31.3 (CH_2), 20.8 (CH_3), 20.7 (CH_3), 20.6 (CH_3). HRMS (ESI/Q-TOF) *m/z* calcd for $(C_{112}H_{134}N_{12}O_{40})/2$ $(M+2H)^{2+}$ 1143.4410, found 1143.4385.

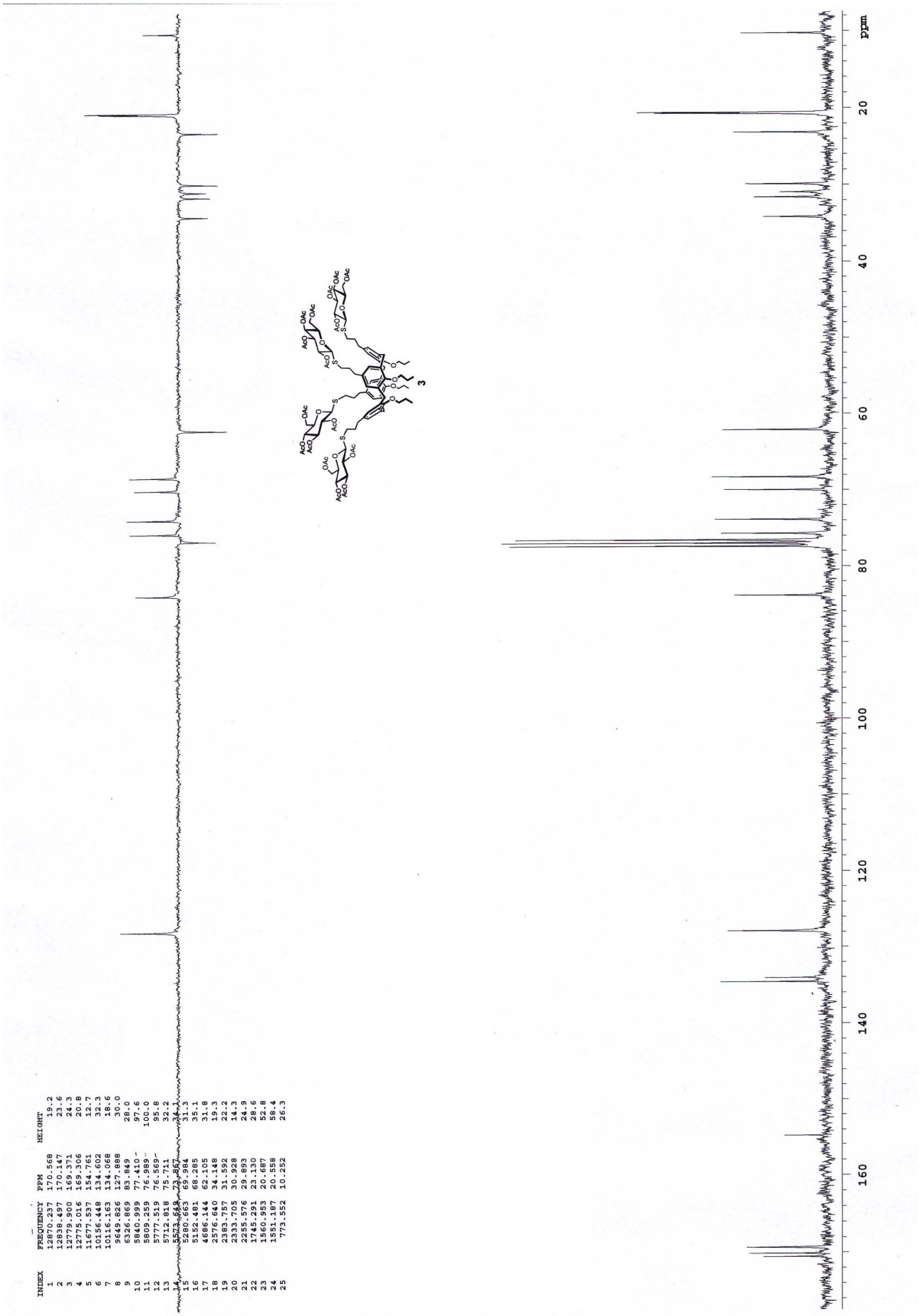
References

27. Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals,* 5th ed., Butterworth-Heinemann, Amsterdam, 2003.

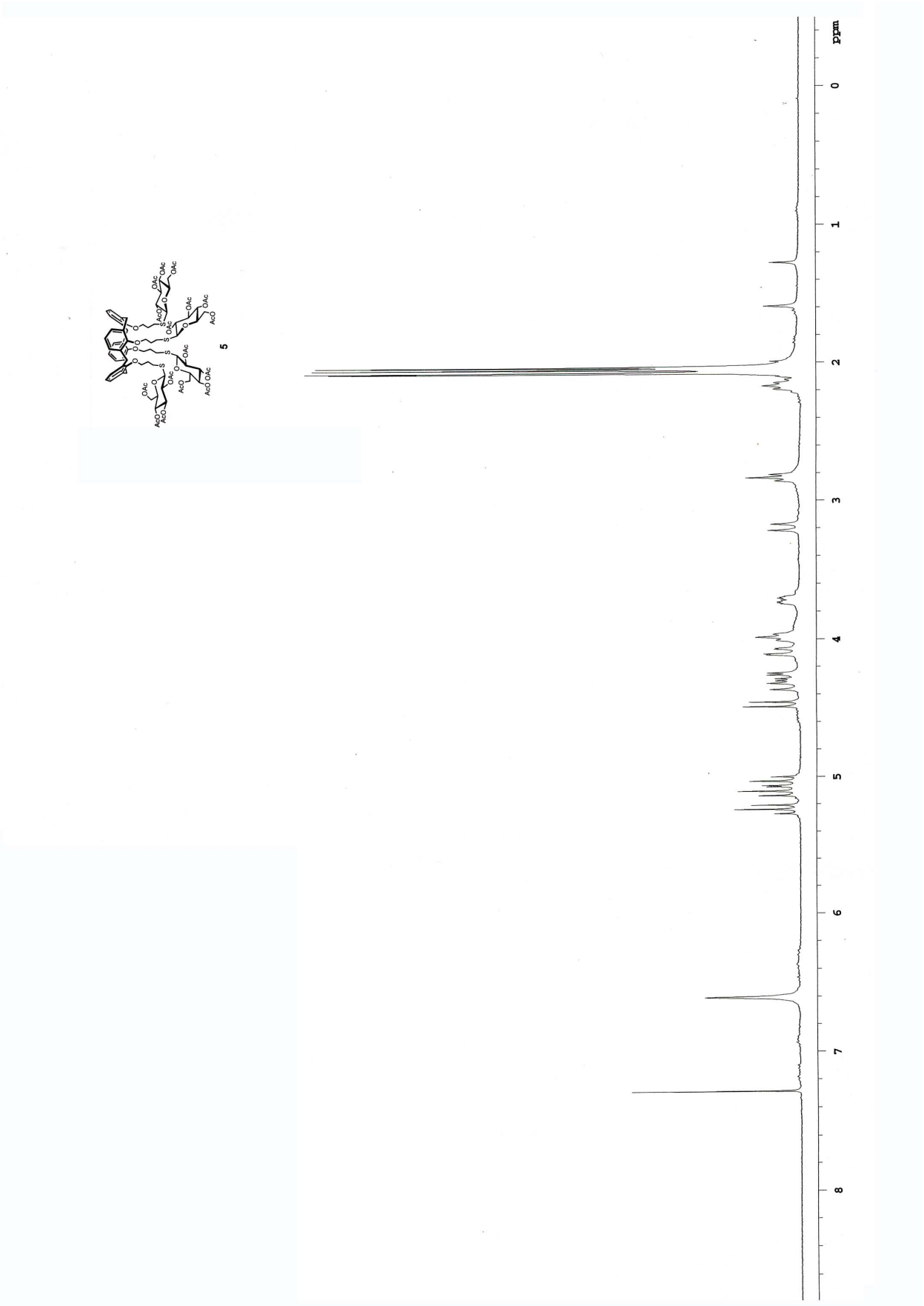
28. W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.* 1978, **43**, 2923-2925.

29. *Pure & Appl. Chem*. 1991, **63**, 975-990.

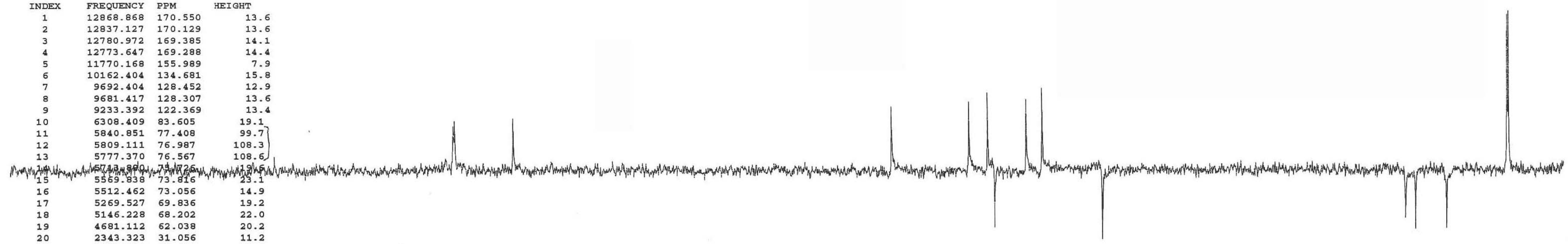

3
ppm
0
1
2
3
4
5
6
7
8

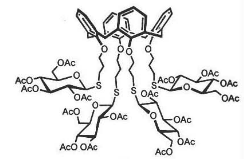


INDEX	FREQUENCY	PPM	HEIGHT
1	12870.237	170.568	19.2
2	12838.497	170.147	23.6
3	12779.900	169.371	24.3
4	12775.016	169.306	20.8
5	11677.537	154.761	12.7
6	10156.448	134.602	32.3
7	10116.163	134.068	18.6
8	9649.826	127.888	30.0
9	6326.869	83.849	28.0
10	5840.999	77.410	97.6
11	5809.259	76.989	100.0
12	5777.519	76.569	95.8
13	5712.818	75.711	32.2
14	5703.668	75.587	34.1
15	5290.663	69.984	31.3
16	5152.481	68.285	35.1
17	4696.144	62.105	31.8
18	2576.640	34.148	19.3
19	2393.757	31.592	22.2
20	2238.705	29.893	14.3
21	1745.291	23.130	24.9
22	1560.851	20.687	52.8
23	1551.187	20.558	58.4
24	773.552	10.252	26.3

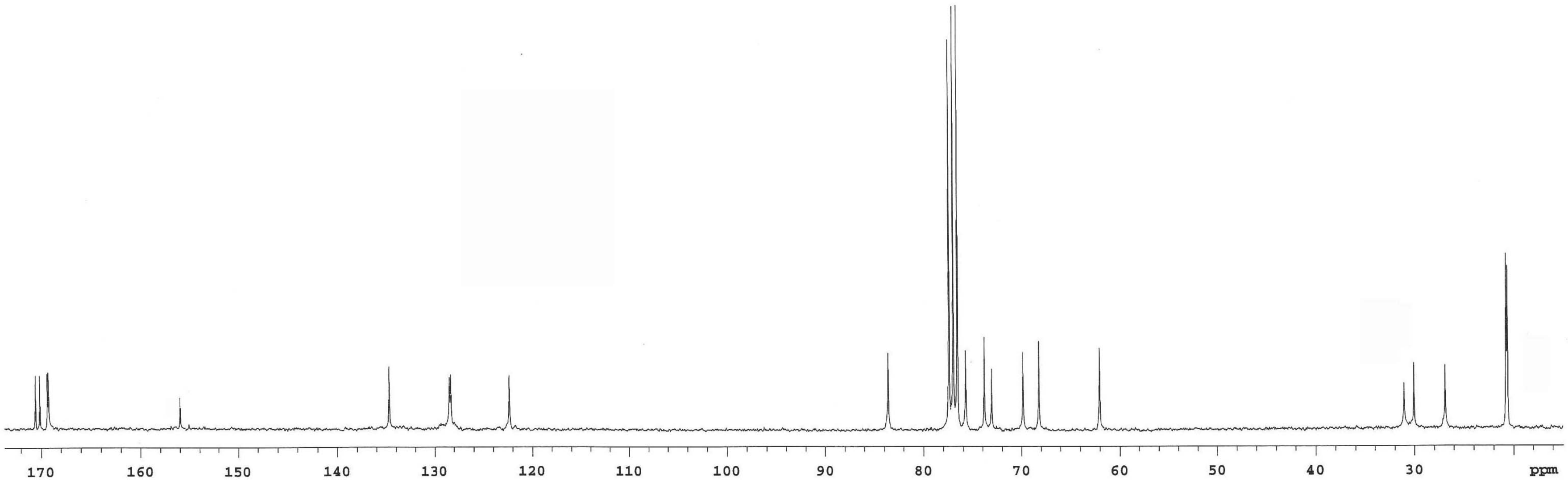


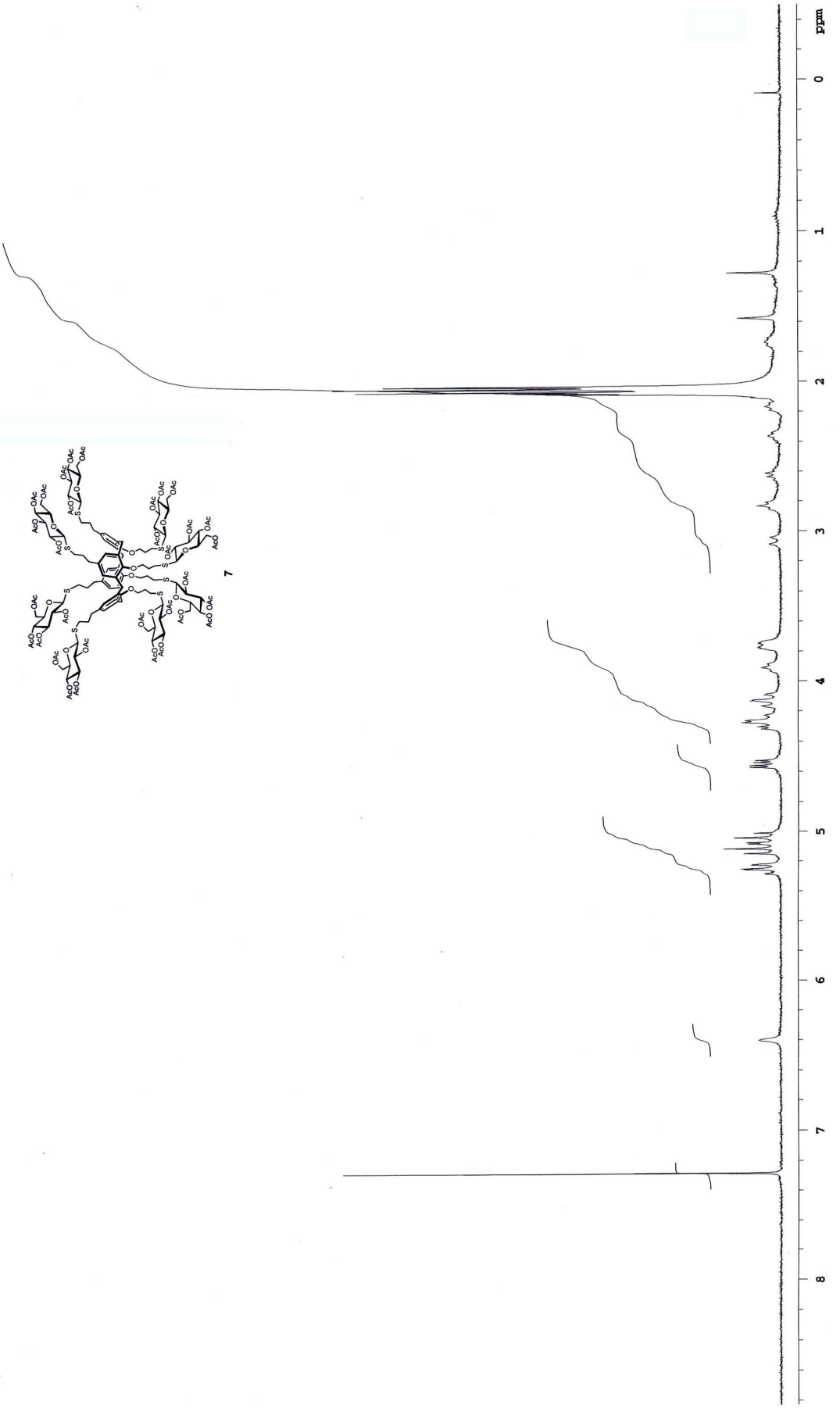
INDEX	FREQUENCY	PPM	HEIGHT
1	12868.868	170.550	13.6
2	12837.127	170.129	13.6
3	12780.972	169.385	14.1
4	12773.647	169.288	14.4
5	11770.168	155.989	7.9
6	10162.404	134.681	15.8
7	9692.404	128.452	12.9
8	9681.417	128.307	13.6
9	9233.392	122.369	13.4
10	6308.409	83.605	19.1
11	5840.851	77.408	99.7
12	5809.111	76.987	108.3
13	5777.370	76.567	108.6
14	5713.880	75.726	19.6
15	5569.838	73.816	23.1
16	5512.462	73.056	14.9
17	5269.527	69.836	19.2
18	5146.228	68.202	22.0
19	4681.112	62.038	20.2
20	2343.323	31.056	11.2
21	2266.414	30.037	16.3
22	2027.141	26.865	15.8
23	1563.246	20.718	44.3
24	1553.480	20.588	41.1

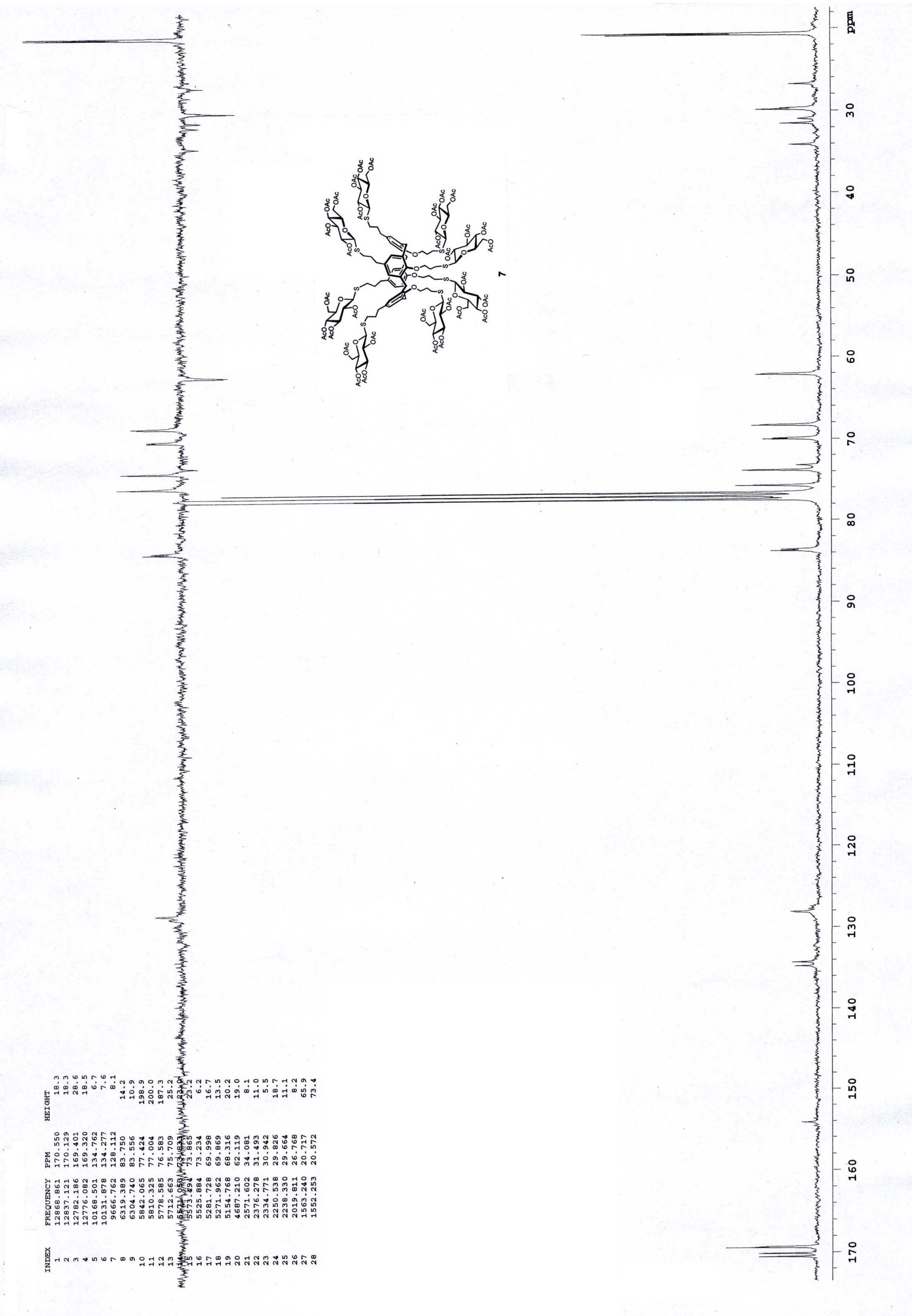


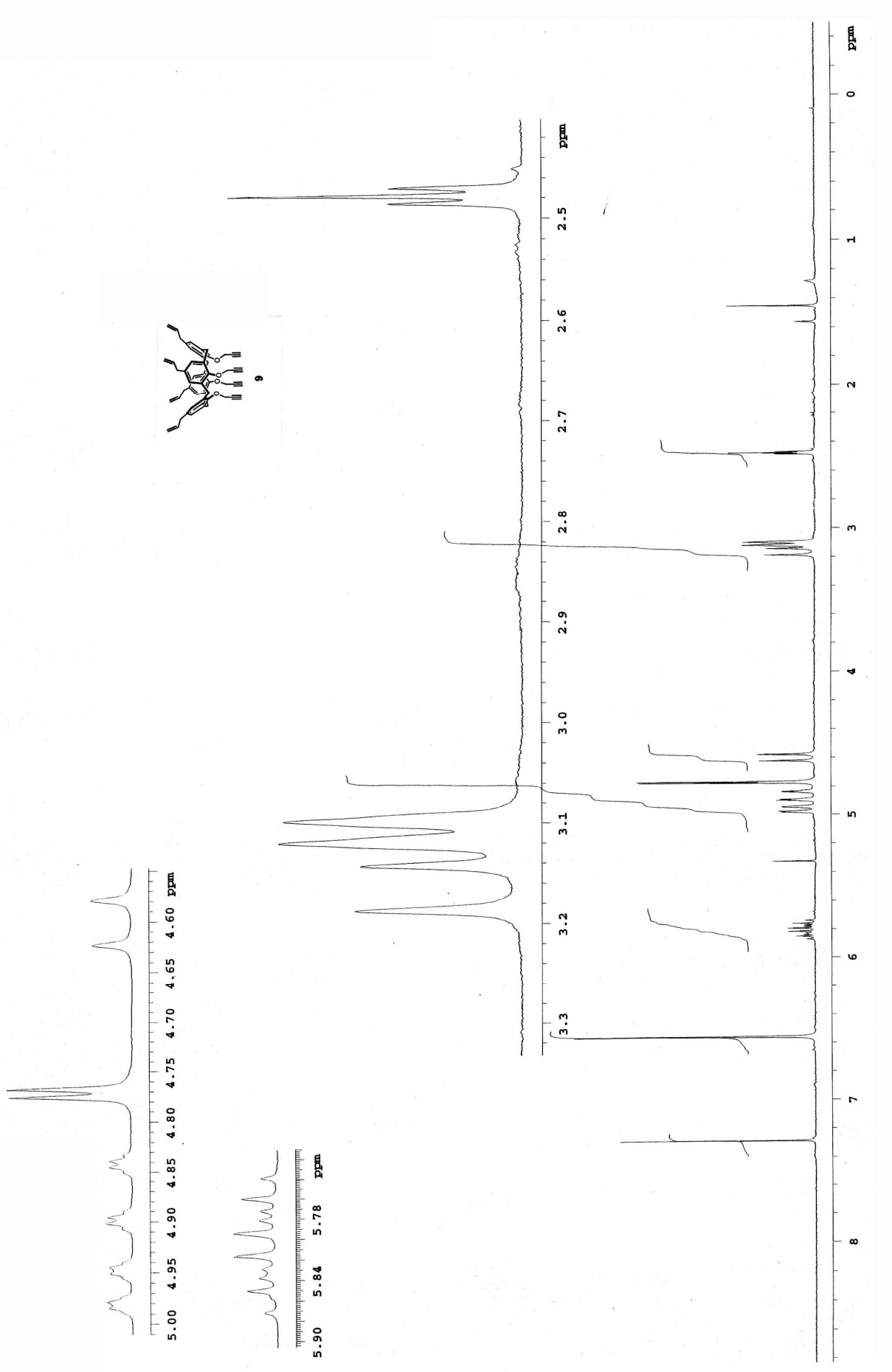


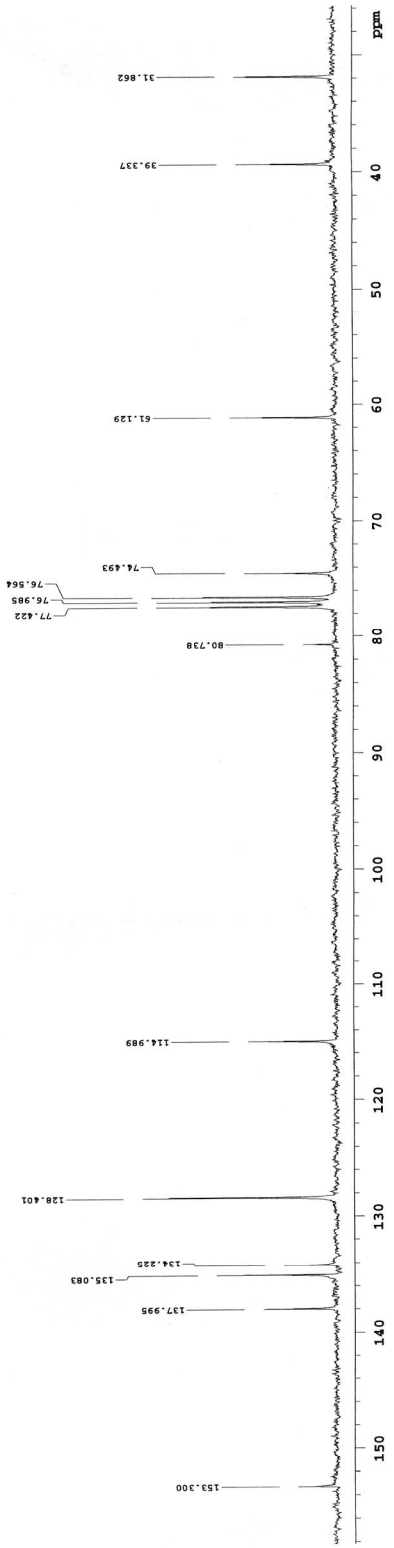
5

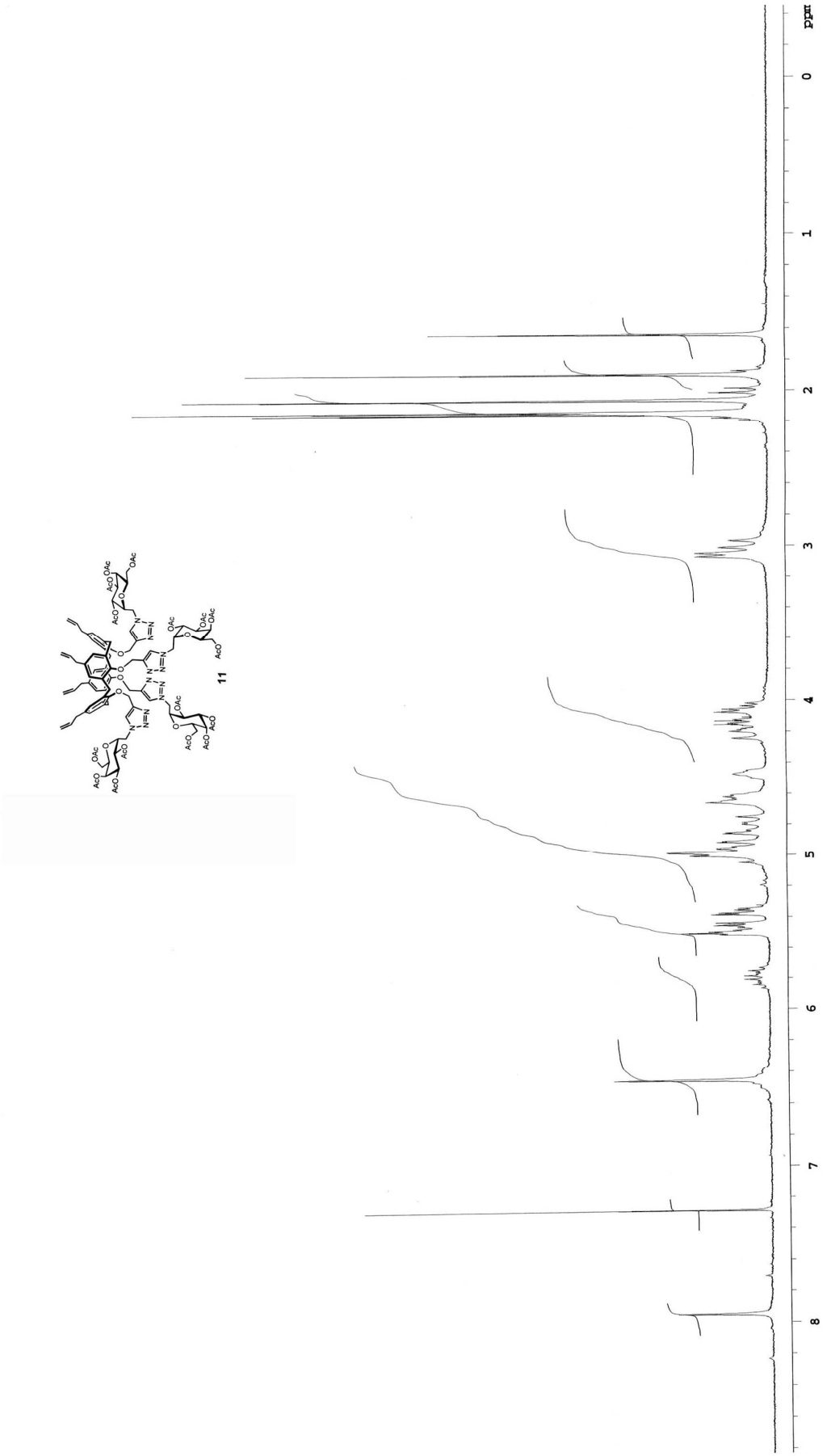




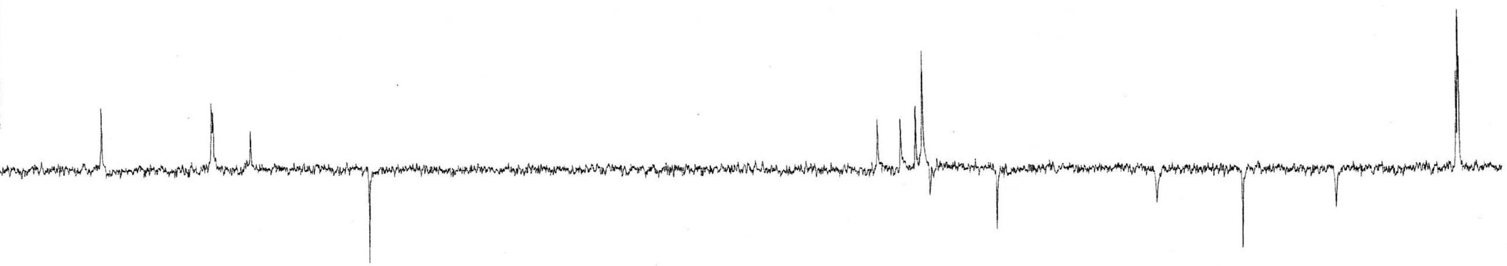

INDEX FREQUENCY PPM HEIGHT
1 12868.861 170.550 18.3
2 12837.121 170.129 18.3
3 12782.186 169.401 28.6
4 12776.082 169.320 18.5
5 10168.501 134.762 6.7
6 10131.878 134.277 7.6
7 9666.762 128.112 8.1
8 6319.389 83.750 14.2
9 6304.740 83.556 10.9
10 5842.065 77.424 198.9
11 5810.325 77.004 200.0
12 5778.585 76.583 187.3
13 5712.663 75.709 25.2
14 5571.058 73.833 23.0
15 5573.494 73.865 23.2
16 5525.884 73.234 6.2
17 5281.728 69.998 16.7
18 5271.962 69.869 13.5
19 5154.768 68.316 20.2
20 4687.210 62.119 19.0
21 2571.602 34.081 8.1
22 2376.278 31.493 11.0
23 2334.771 30.942 5.5
24 2250.538 29.826 18.7
25 2238.330 29.664 11.1
26 2019.811 26.768 8.2
27 1563.240 20.717 65.9
28 1552.253 20.572 73.4
7
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 ppm

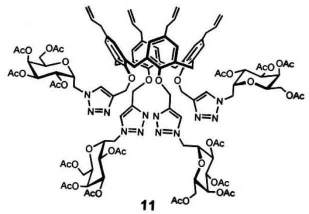




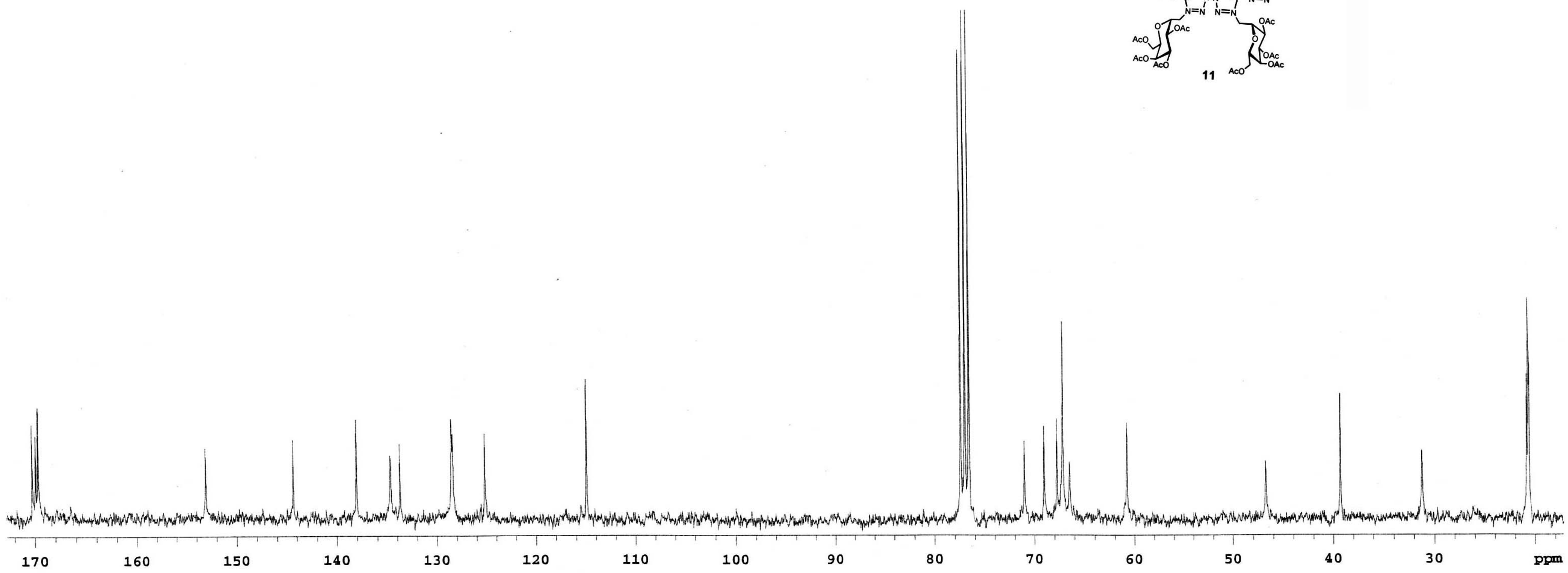


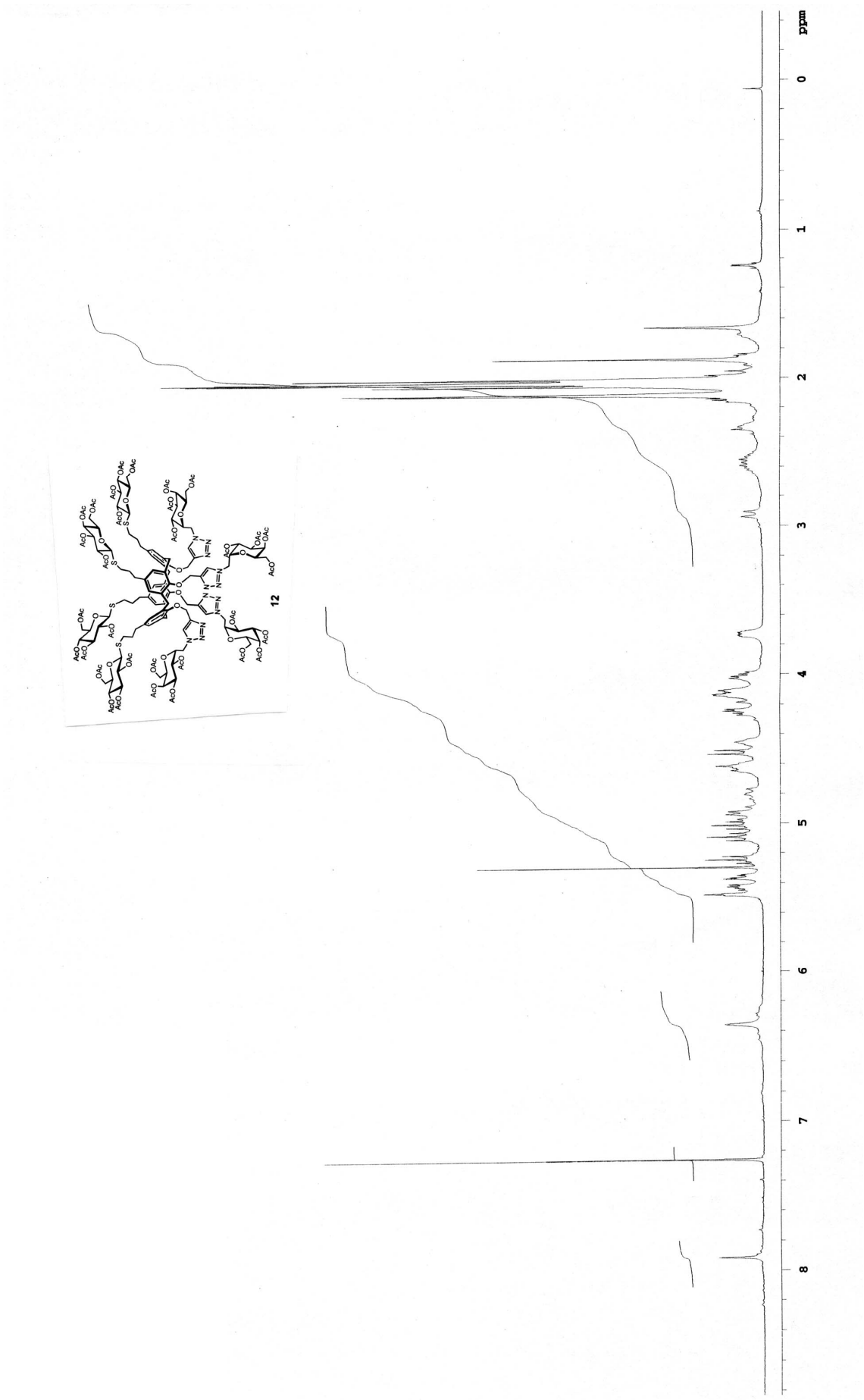
INDEX	FREQUENCY	PPM	HEIGHT
1	12848.695	170.282	23.5
2	12823.059	169.943	20.6
3	12805.968	169.716	27.9
4	11549.787	153.068	17.5
5	10891.788	144.348	19.7
6	10416.906	138.054	24.8
7	10164.205	134.705	15.7
8	10092.179	133.750	18.6
9	9697.868	128.525	24.8
10	9443.946	125.160	21.1
11	8673.635	114.951	34.8
12	5841.431	77.416	119.2
13	5809.691	76.995	129.2
14	5777.951	76.575	129.3
15	5358.003	71.009	19.0
16	5207.848	69.019	22.8
17	5110.185	67.725	24.7
18	5067.458	67.158	49.5
19	5017.406	66.495	13.7
20	4582.810	60.735	23.8
21	3526.837	46.741	14.0
22	2964.058	39.282	31.2
23	2354.890	31.209	16.6
24	1568.710	20.790	35.9
25	1557.723	20.644	55.3
26	1550.398	20.547	42.0

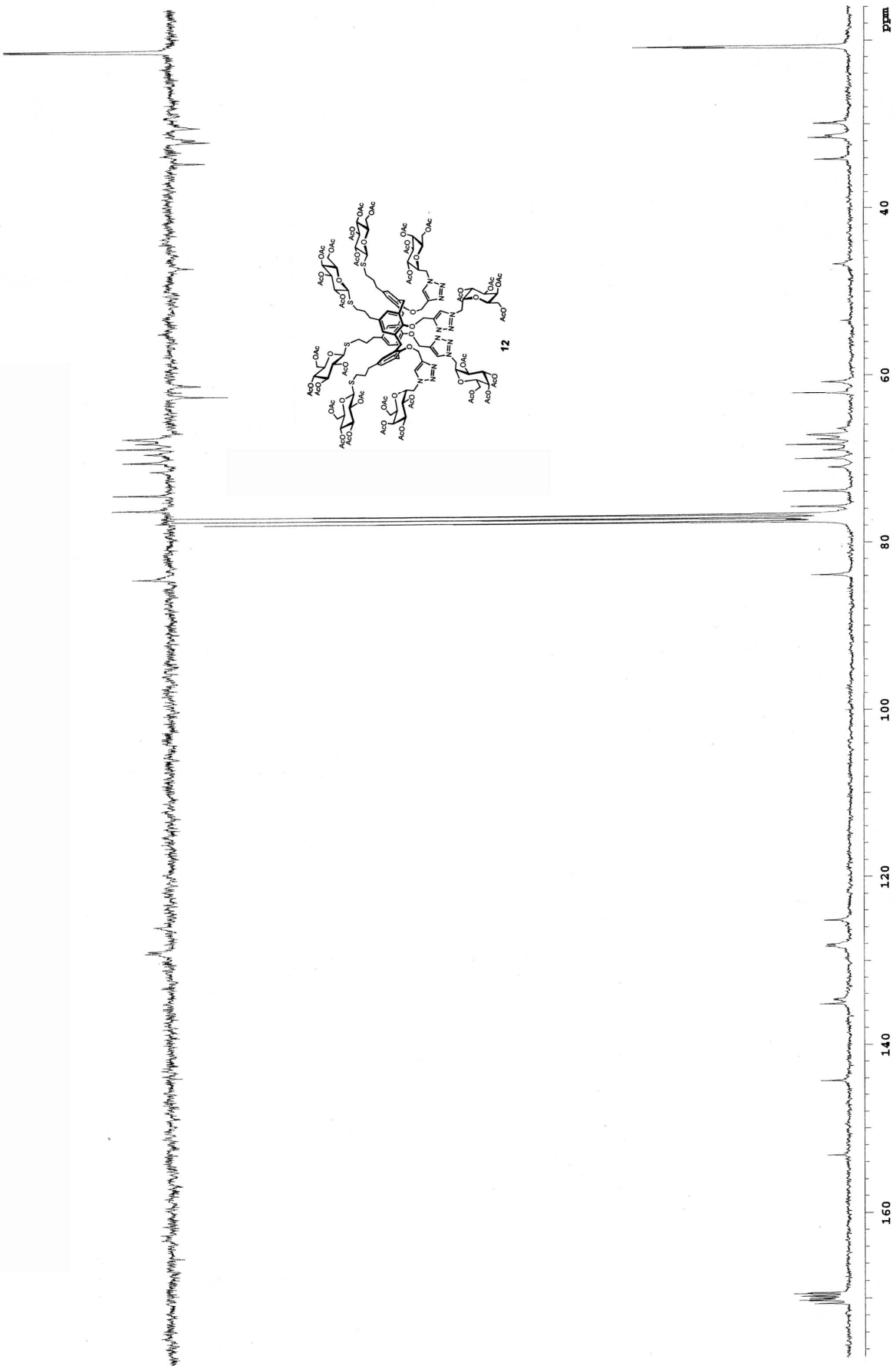


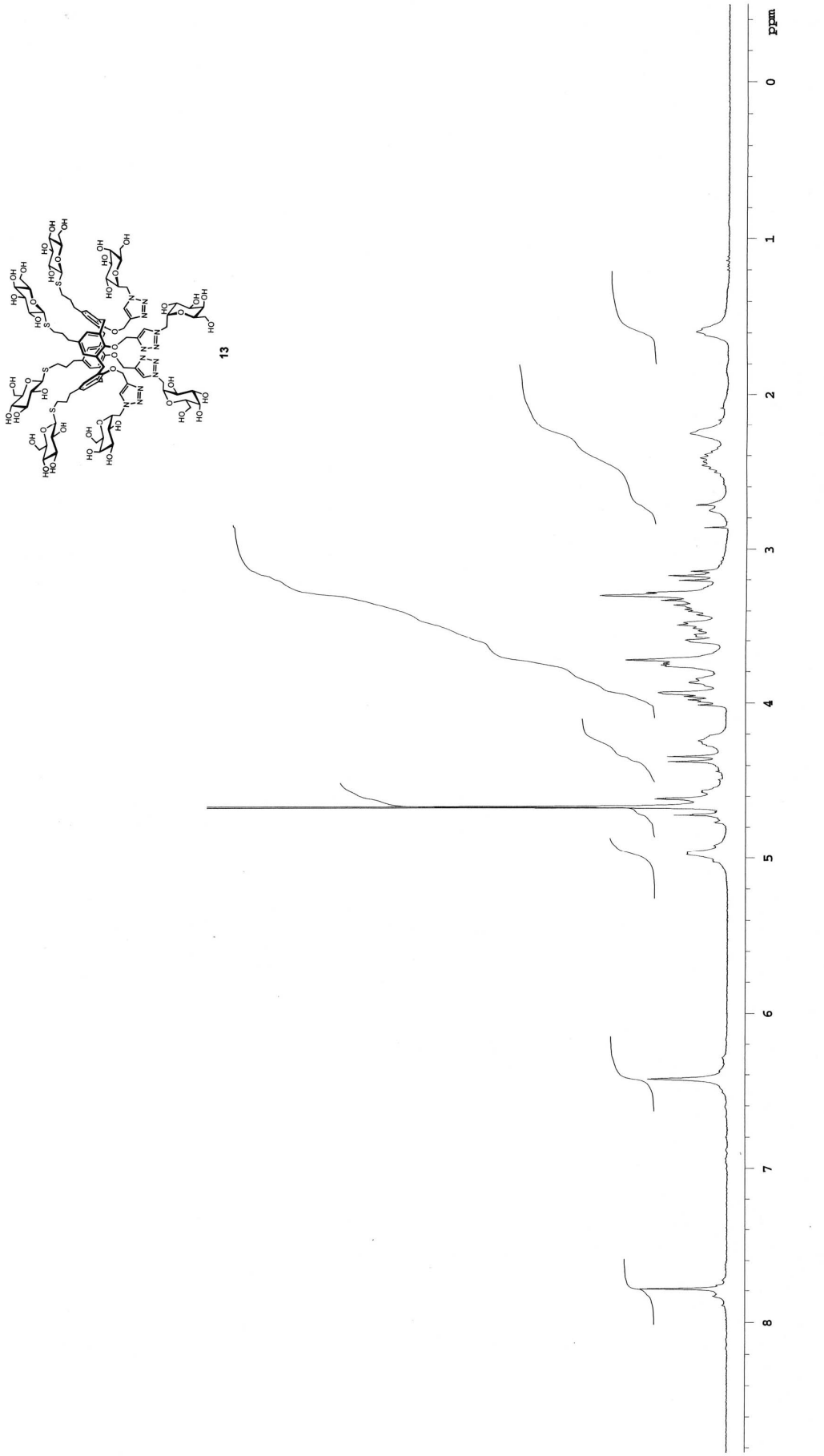


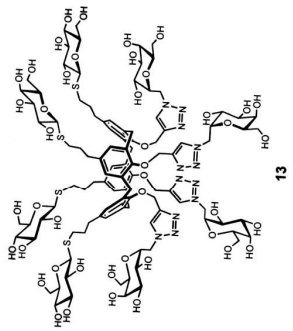
11



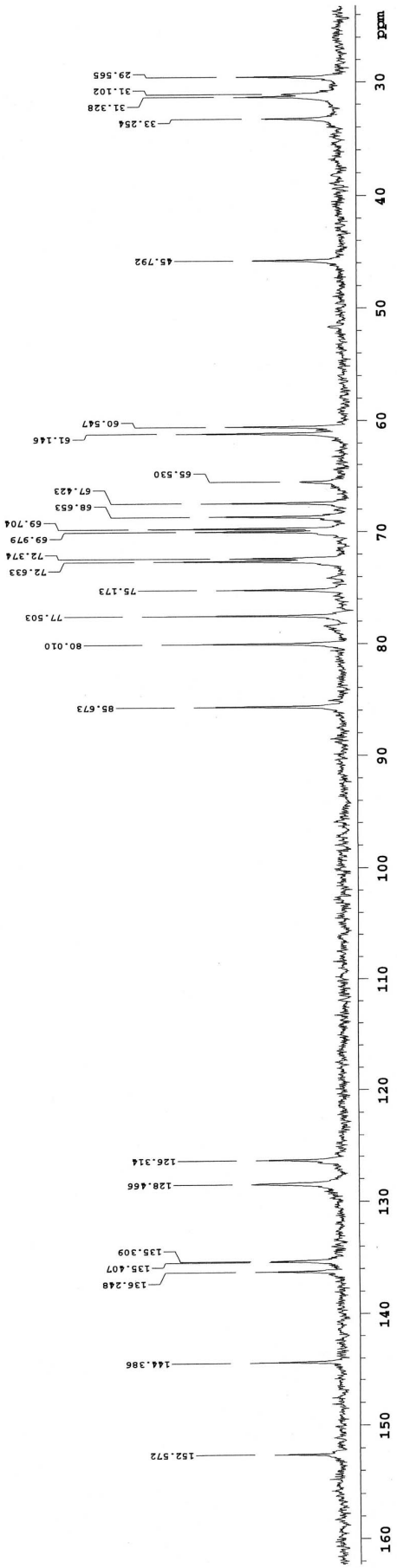


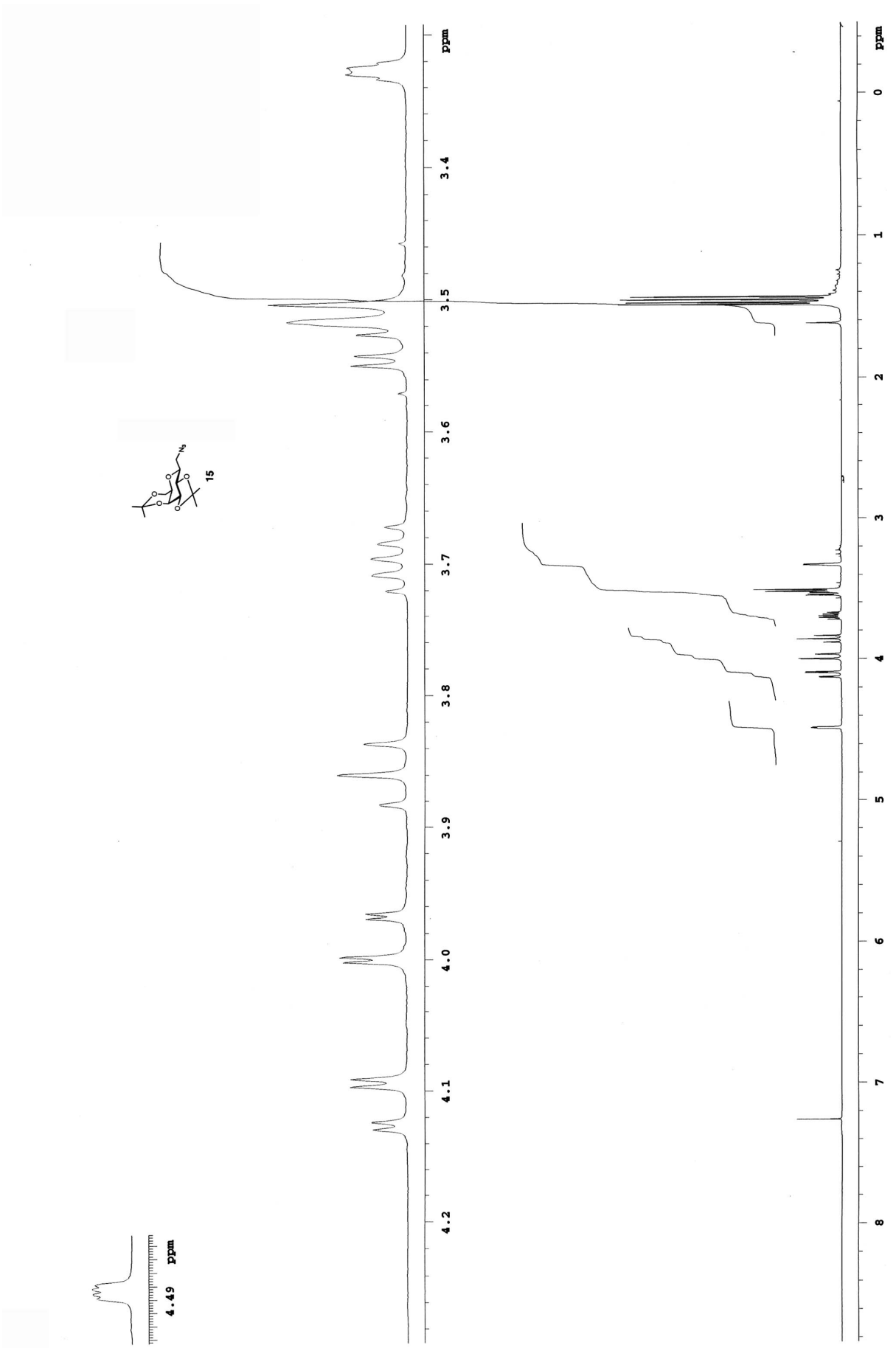


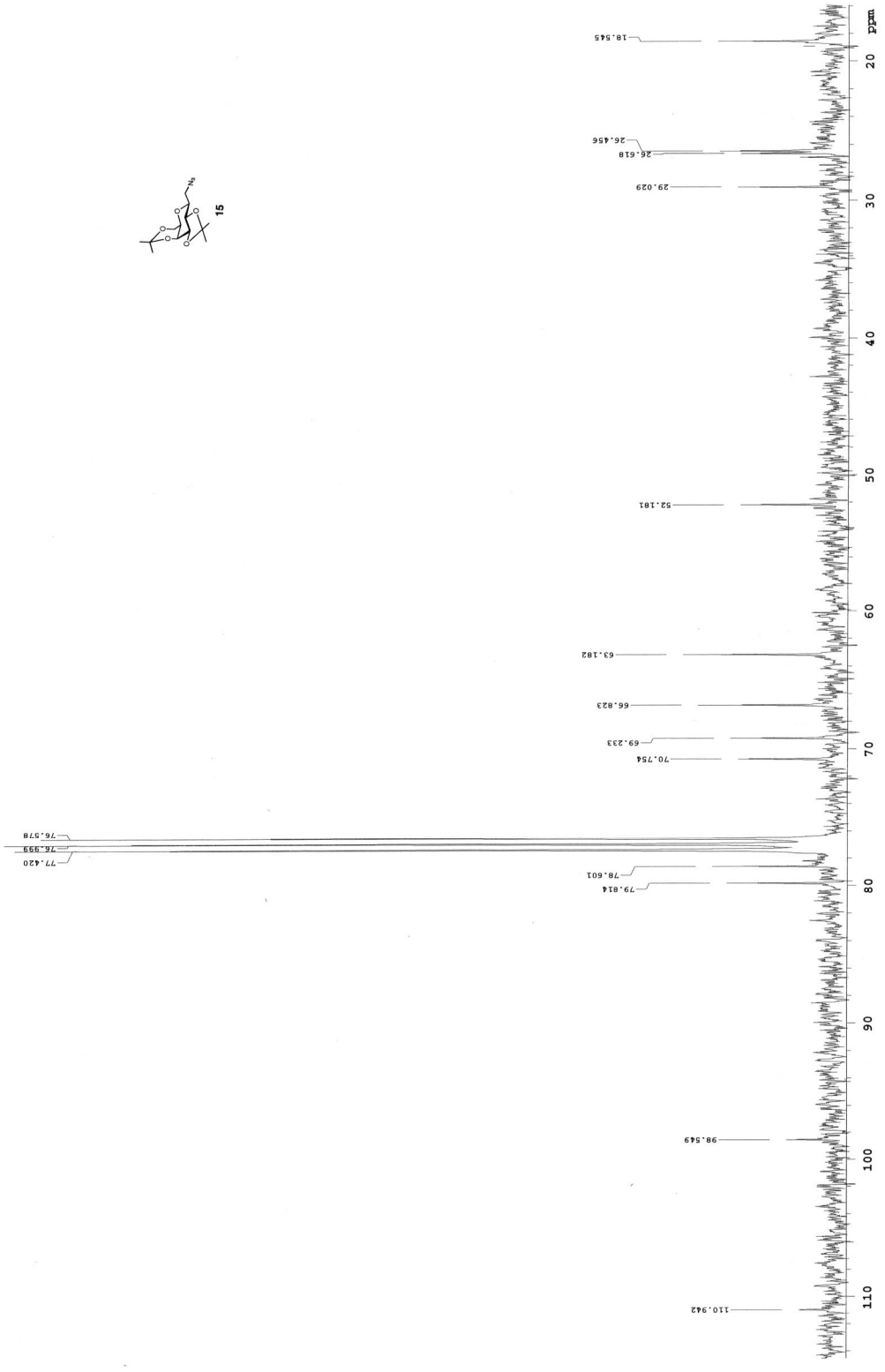


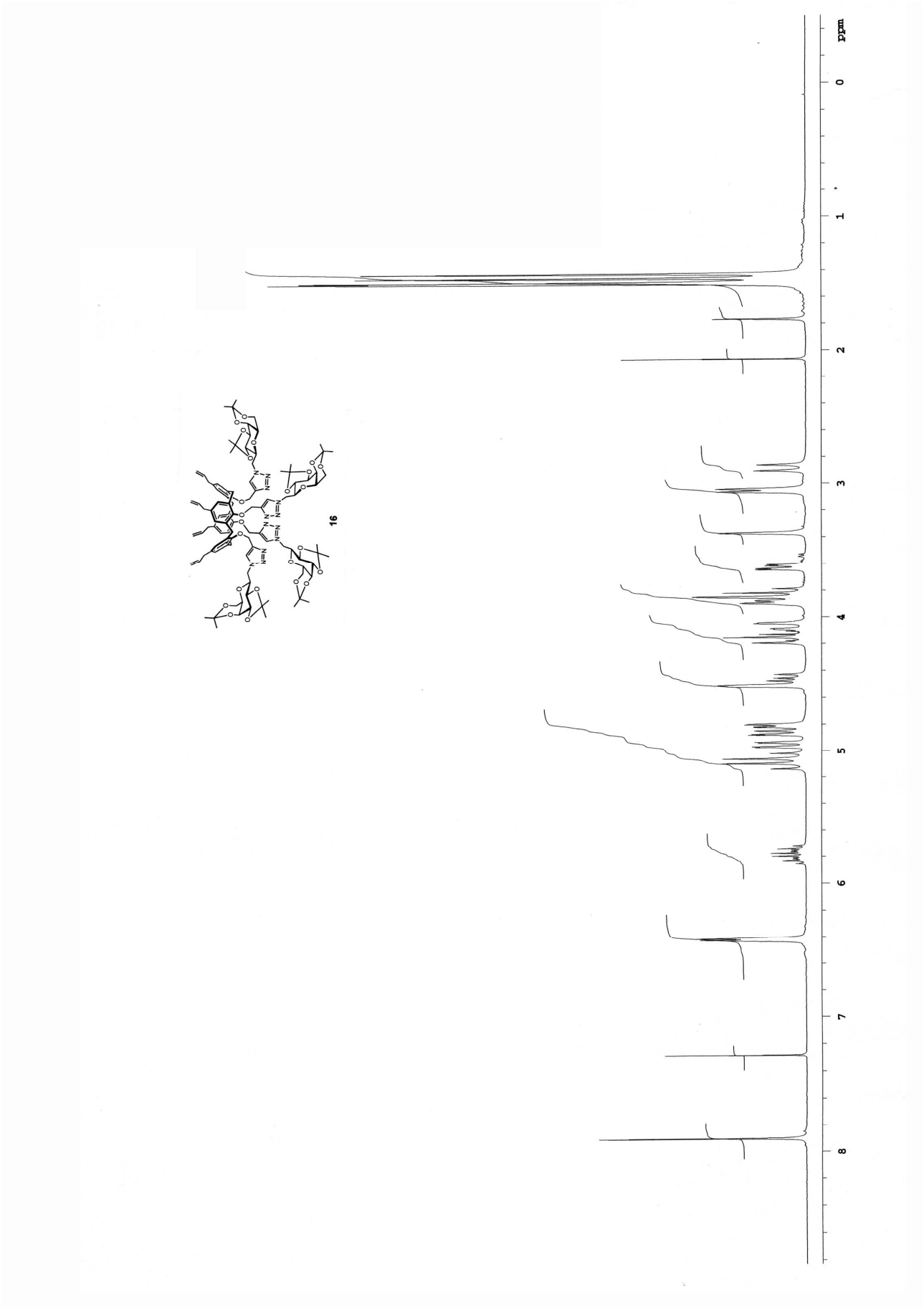


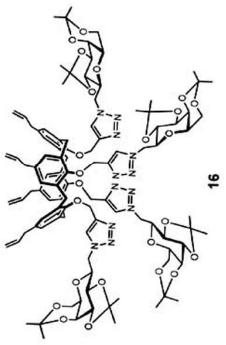
13

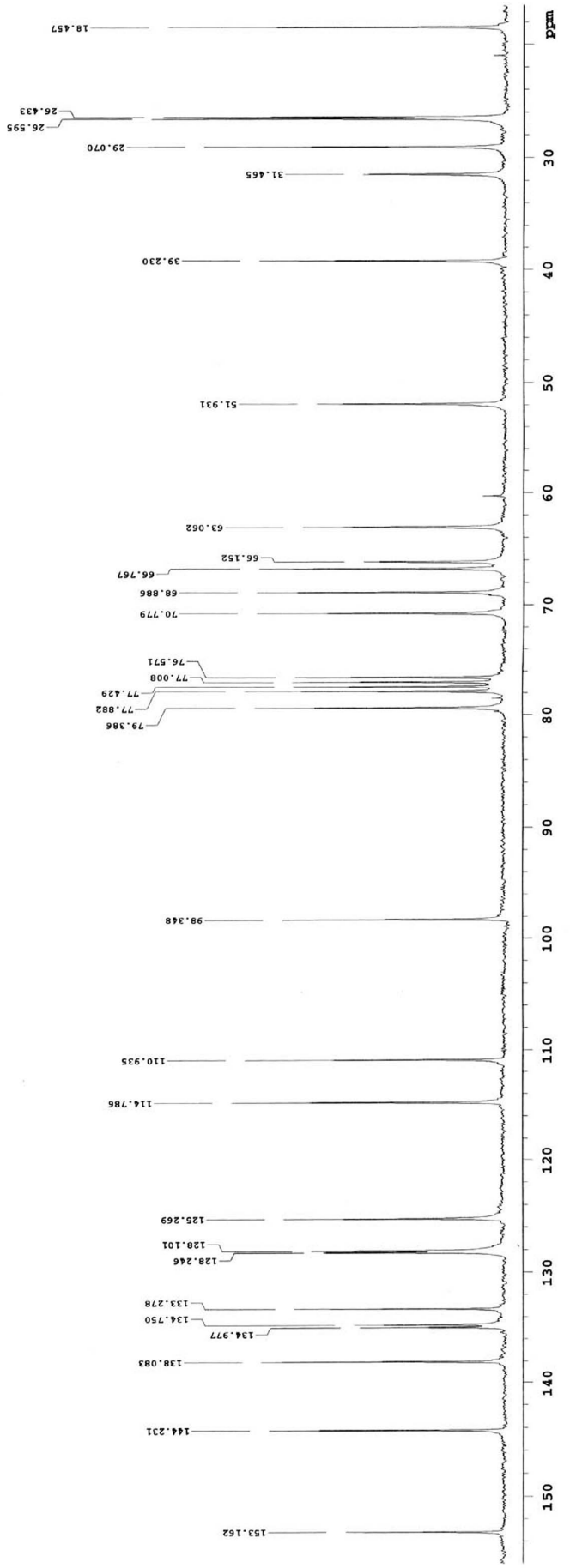

29.565
31.102
31.328
33.254
45.792
60.547
61.146
65.530
67.423
68.653
69.704
69.979
72.374
72.633
75.173
77.503
80.010
85.673
126.314
128.466
135.309
135.407
136.248
144.386
152.572
ppm

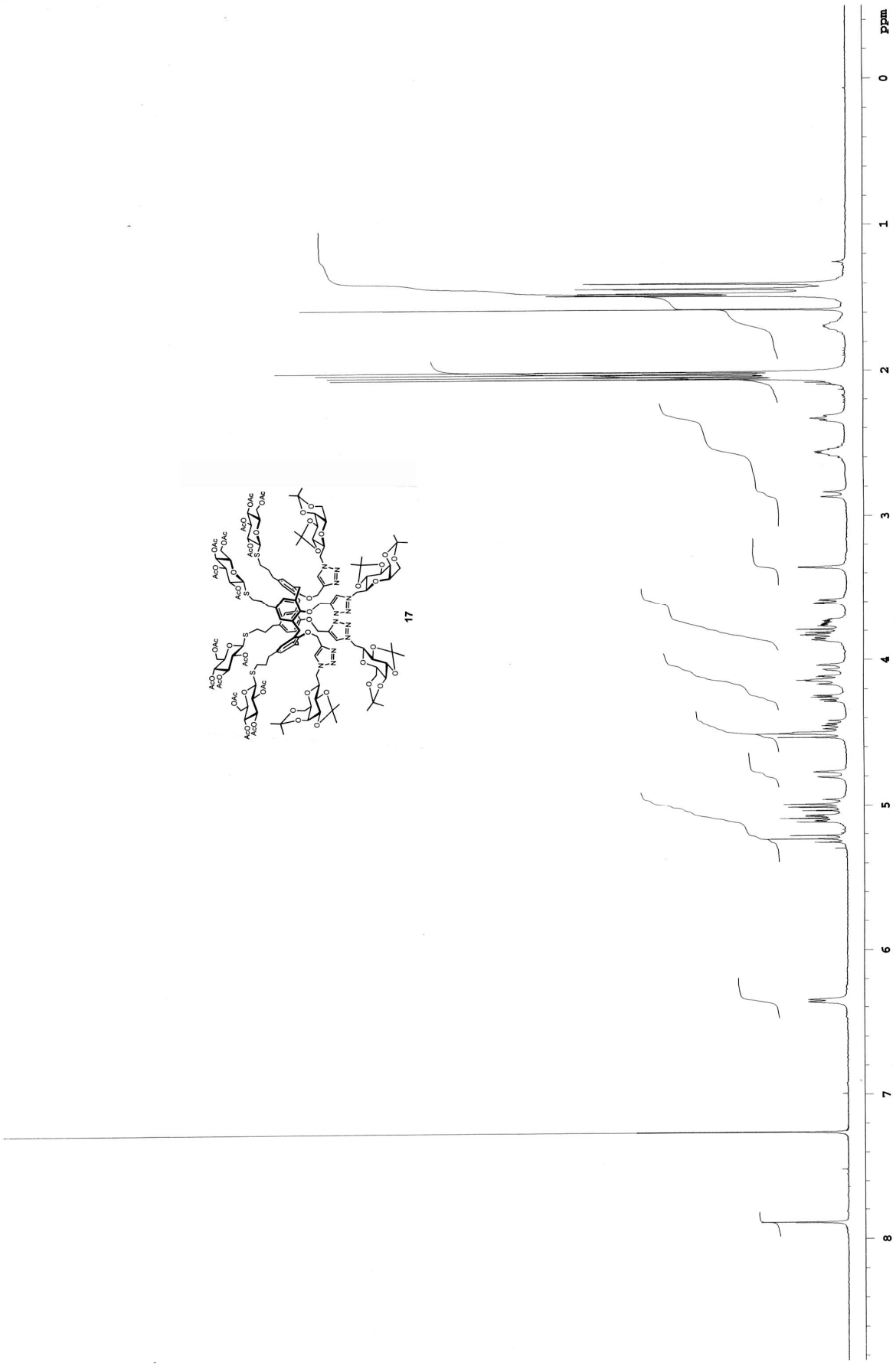


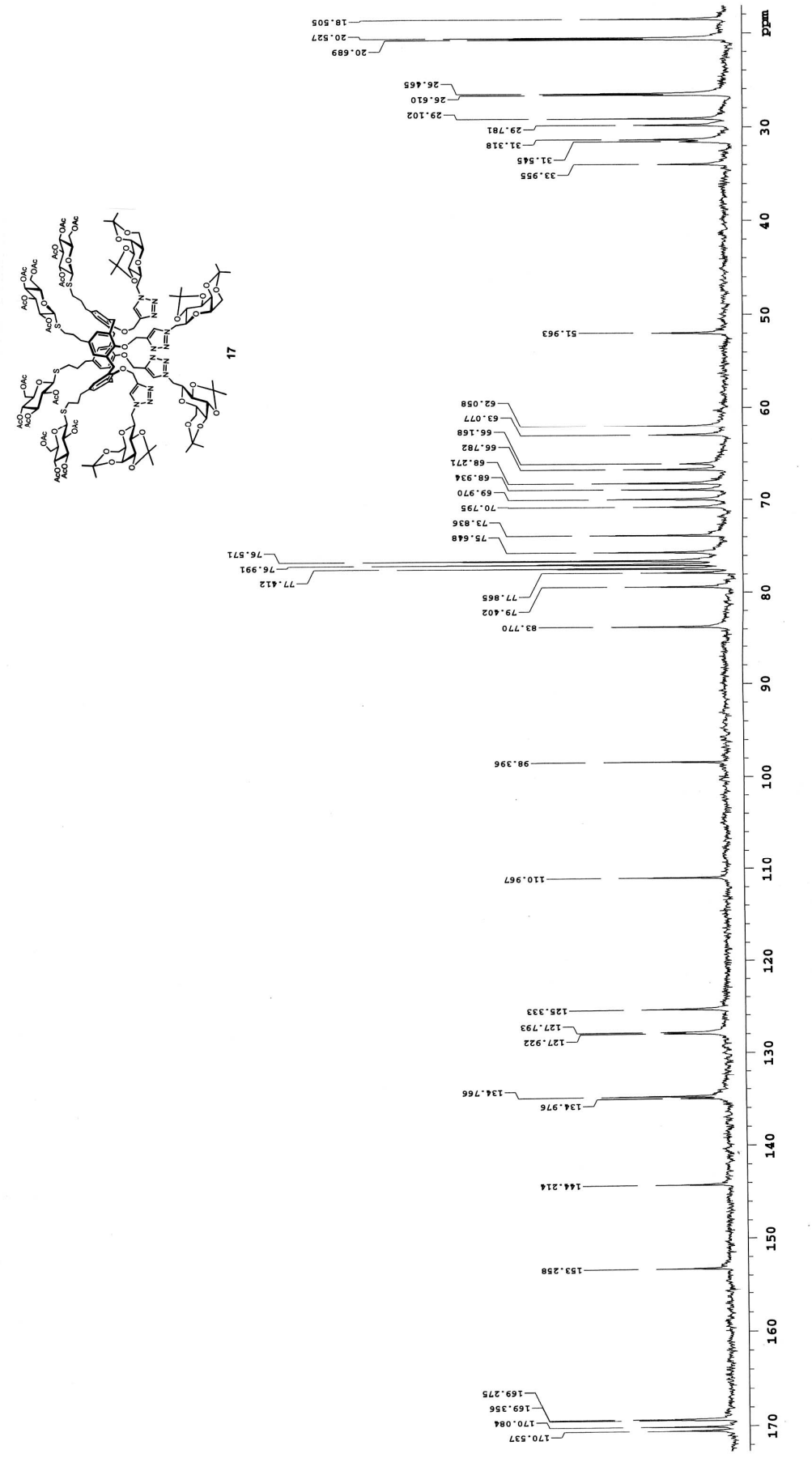

15
18.545
26.456
26.618
29.029
52.181
63.182
66.823
69.233
70.754
76.578
76.999
77.420
78.601
79.814
98.549
110.942
ppm
20
30
40
50
60
70
80
90
100
110

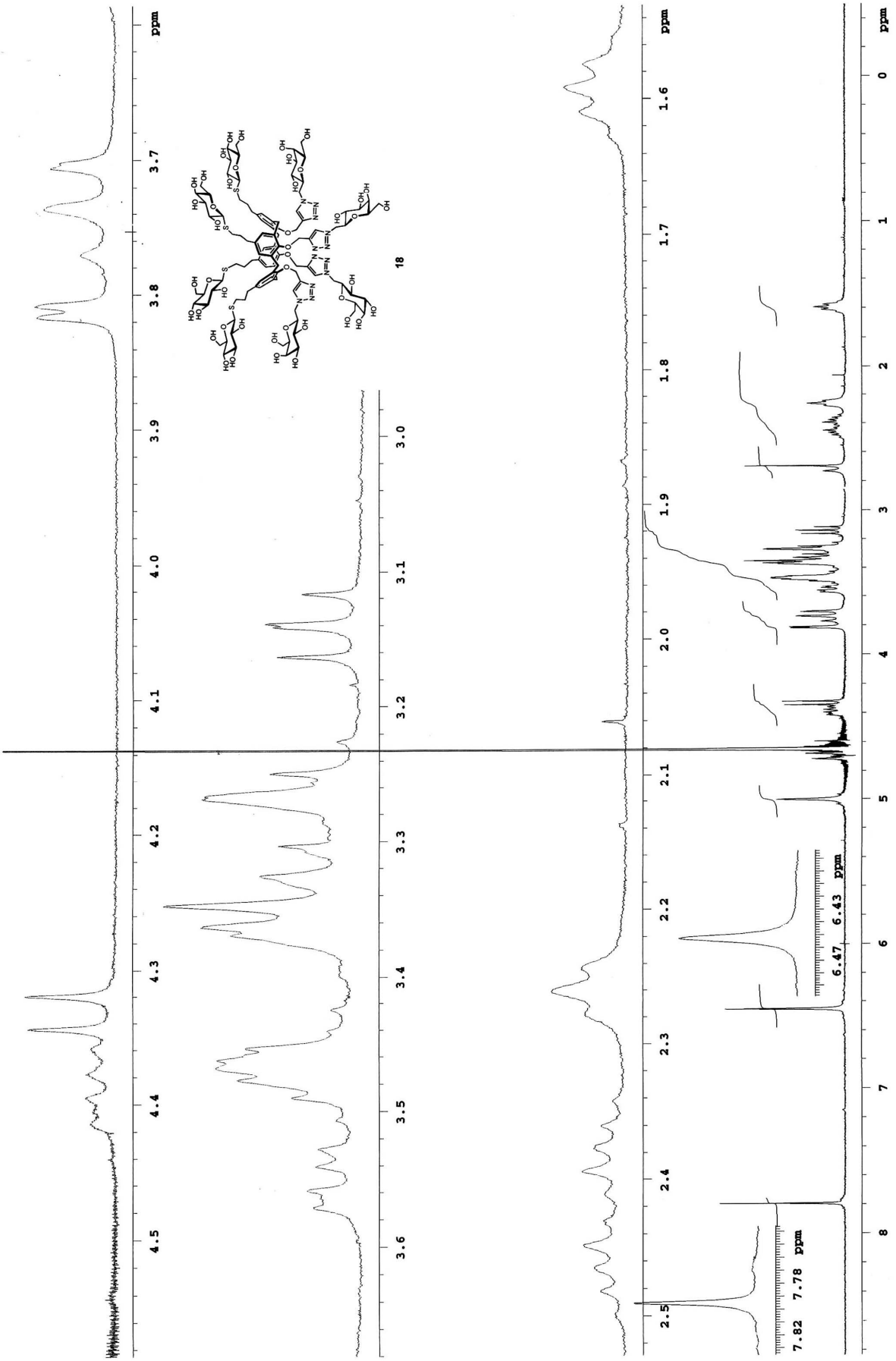


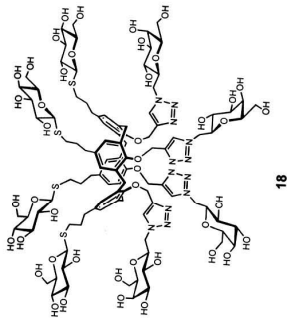

16


18.457
26.433
26.595
29.070
31.465
39.230
51.931
63.062
66.152
66.767
68.886
70.779
76.571
77.008
77.429
77.882
79.386
98.348
110.935
114.786
125.269
128.101
128.246
133.278
134.750
134.977
138.083
144.231
153.162
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150

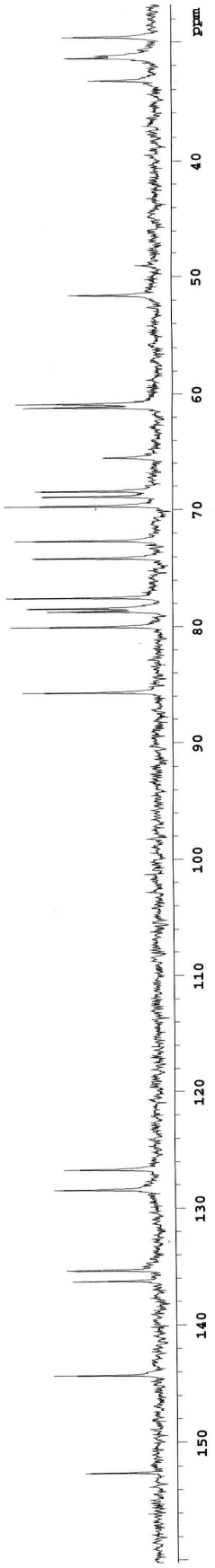

17
ppm
0
1
2
3
4
5
6
7
8

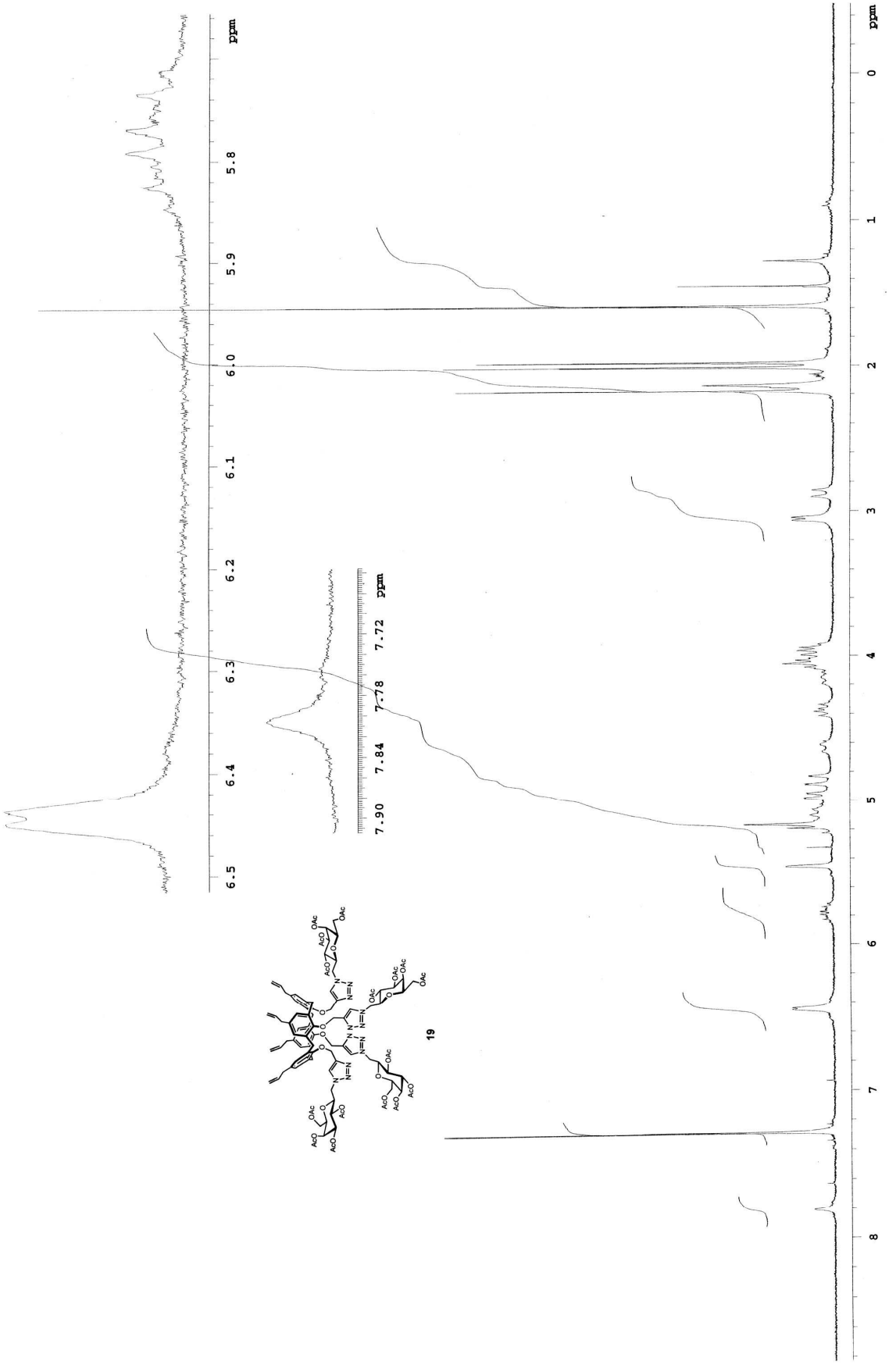



ppm
7.82 7.78 ppm
6.47 6.43 ppm



18




ppm
5.8
5.9
6.0
6.1
6.2
6.3
6.4
6.5
7.72
7.78
7.84
7.90
ppm
0
1
2
3
4
5
6
7
8
ppm
19