Supplementary Materials For

Synthesis of Large Dendrimers with the Dimensions of Small Viruses

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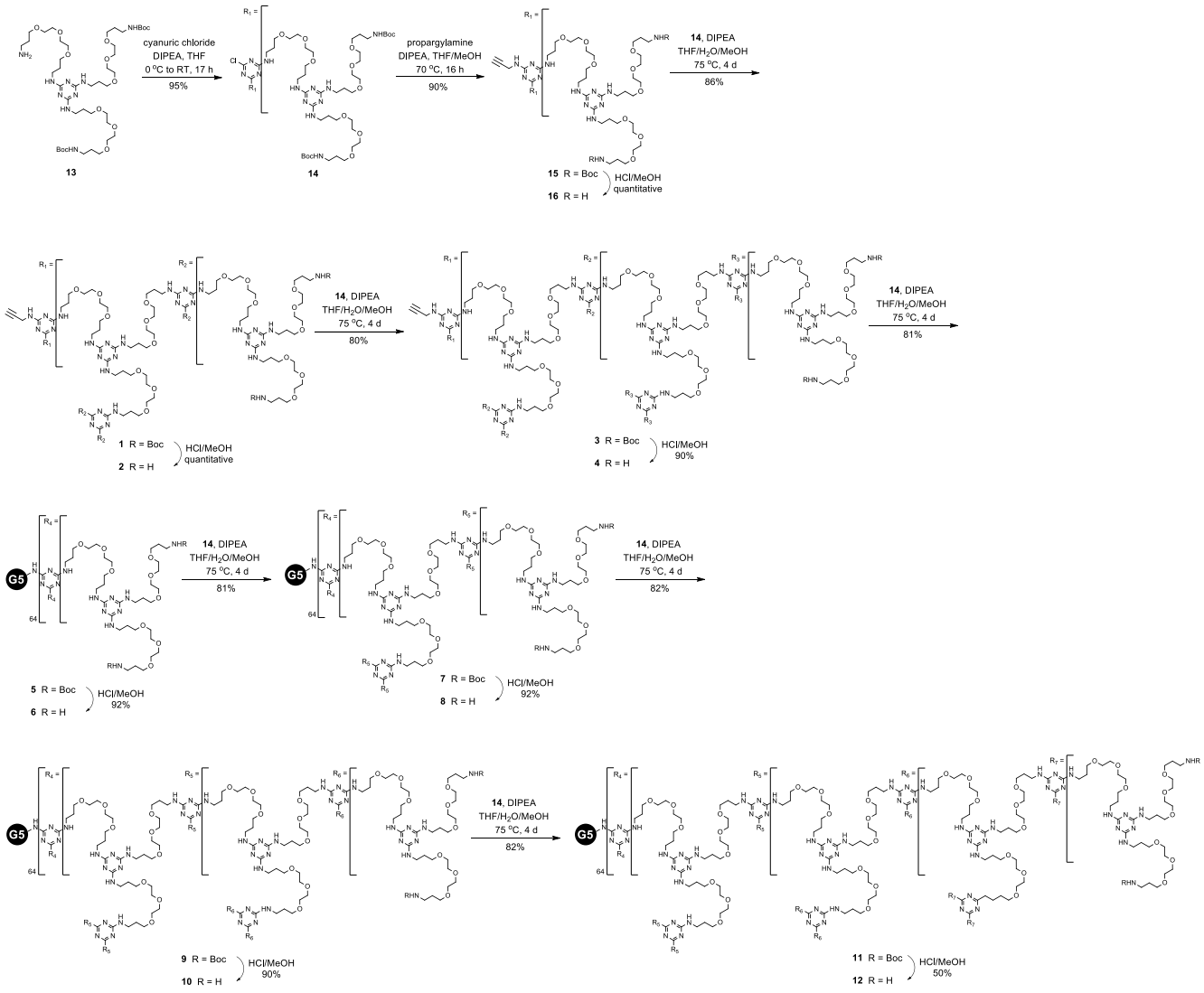
General Synthetic Procedures

All chemicals were purchased from Aldrich and Acros and used without further purification. All solvents were ACS grade and used without further purification. HPLC was carried out using an Agilent Technologies 1260 Infinity system and an Agilent Technologies 1260 Infinity DAD detector. NMR spectra were recorded on a Mercury 300 MHz spectrometer in $CDCl_3$. All mass spectral analyses were carried out by an Agilent Technologies 6224 TOF LC/MS system.

Scheme S1. Synthesis of the Dendrimers



Details of Synthetic Procedures

Compound 1 (Boc-protected G3). A solution of **14** (1.20 g, 0.61 mmol), **16** (0.12 g, 0.074 mmol), and DIPEA (0.30 mL, 1.71 mmol) in THF (3 mL), methanol (0.3 mL), and H_2O (0.3 mL) was stirred at 75 °C in a capped vessel

for 4 d. The solution was evaporated under vacuum. The residue was dissolved in dichloromethane, washed with brine, dried over $MgSO_4$, filtered, and evaporated under vacuum. The crude product was purified by silica gel chromatography (from EA:DCM:MeOH = 6:6:1 to DCM:MeOH = 7:1) to give **1** (0.60 g, 86%) as a white wax. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.05 (br, 2H, HC≡CC**H$_2$**), 3.51-3.29 (m, 448H, C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**, C_3N_3-NHC**H$_2$**CH_2CH_2O), 3.08 (br m, 32H, BocNHC**H$_2$**), 2.17 (br, 1H, **H**C≡CCH_2), 1.69-1.60 (m, 120H, OCH_2C**H$_2$**CH_2), 1.31 (s, 144H, C(C**H$_3$**)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7 (**C**$_3$N$_3$), 155.9 (**C**O), 81.1 (not found, HC≡**C**CH_2), 78.6 (**C**$(CH_3)_3$), 70.5 (not found, H**C**≡CCH_2), 70.4 (O**C**H_2**C**H_2O), 70.0 (two lines, O**C**H_2**C**H_2O), 69.3 (CH_2CH_2**C**H_2O), 69.1 (CH_2CH_2**C**H_2O), 69.0 (CH_2CH_2**C**H_2O), 38.3 (**C**$H_2CH_2CH_2$O), 37.8 (**C**$H_2CH_2CH_2$O), 30.1 (not found, HC≡C**C**H_2), 29.5 (NHCH_2**C**H_2CH_2O), 28.3 (C(**C**$H_3)_3$); MS (ESI-TOF) calcd for $C_{428}H_{808}N_{106}O_{122}$ 9386.03, found 9395.31 $(M + H)^+$.

Compound 2 (deprotected G3). A solution of **1** (0.27 g, 0.029 mmol) in concentrated HCl (2 mL) and methanol (4 mL) was stirred for 16 h at room temperature and then evaporated under vacuum. The residue was dissolved in chloroform, washed with 5 M NaOH (aq), dried over $MgSO_4$, filtered, and evaporated under vacuum to give **2** (0.22 g, quantitative) as a white wax. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.12 (br, 2H, HC≡CC**H$_2$**), 3.60-3.38 (m, 448H, C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**, C_3N_3-NHC**H$_2$**CH_2CH_2O), 2.78 (br, 32H, OCH_2CH_2C**H$_2$**NH_2), 2.22 (br, 1H, **H**C≡CCH_2), 1.78-1.69 (m, 120H, OCH_2C**H$_2$**CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1 (**C**$_3$N$_3$), 81.1 (not found, HC≡**C**CH_2), 70.6 (O**C**H_2**C**H_2O), 70.5 (H**C**≡CCH_2), 70.3 (O**C**H_2**C**H_2O), 70.2 (O**C**H_2**C**H_2O) 69.5 (CH_2CH_2**C**H_2O), 69.4 (CH_2CH_2**C**H_2O), 69.3 (CH_2CH_2**C**H_2O), 39.6 (**C**$H_2CH_2CH_2$O), 38.1 (**C**$H_2CH_2CH_2$O), 32.9 (OCH_2**C**$H_2CH_2NH_2$), 30.1 (not found, HC≡C**C**H_2), 29.7 (NHCH_2**C**H_2CH_2O); MS (ESI-TOF) calcd for $C_{348}H_{680}N_{106}O_{90}$ 7785.19, found 7789.62 $(M + H)^+$.

Compound 3 (Boc-protected G5). A solution of **14** (1.0 g, 0.50 mmol), **2** (0.11 g, 0.014 mmol), and DIPEA (0.30 mL, 1.71 mmol) in THF (5 mL), methanol (0.5 mL), and H_2O (0.5 mL) was stirred at 75 ^{o}C in a capped vessel for 4 d. The solution was evaporated under vacuum. The residue was dissolved in dichloromethane, washed with brine, dried over $MgSO_4$, filtered, and evaporated under vacuum. The crude product was dissolved in dichloromethane and precipitated by adding diethyl ether. The precipitation step was repeated until macromonomer **14** was completely removed, which was monitored by thin layer chromatography (DCM:MeOH = 14:1). The pure product **3** (0.44 g, 80%) was obtained as a white wax. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.05 (not found, 2H, HC≡CC**H$_2$**), 3.53-3.32 (m, 1888H, C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**, C_3N_3-NHC**H$_2$**CH_2CH_2O), 3.11 (br m, 128H, BocNHC**H$_2$**), 2.17 (not found, 1H, **H**C≡CCH_2), 1.72-1.63 (m, 504H, OCH_2C**H$_2$**CH_2), 1.33 (s, 576H, C(C**H$_3$**)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1 (br, **C**$_3$N$_3$), 156.0 (**C**O), 81.1 (not found, HC≡**C**CH_2), 78.7 (**C**$(CH_3)_3$), 70.5 (not found, H**C**≡CCH_2), 70.4 (O**C**H_2**C**H_2O), 70.1 (three lines, O**C**H_2**C**H_2O), 69.4 (CH_2CH_2**C**H_2O), 69.1 (CH_2CH_2**C**H_2O), 38.4 (**C**$H_2CH_2CH_2$O), 38.0 (**C**$H_2CH_2CH_2$O), 30.1 (not found, HC≡C**C**H_2), 29.4 (NHCH_2**C**H_2CH_2O), 28.4 (C(**C**$H_3)_3$); MS (ESI-TOF) calcd for $C_{1772}H_{3352}N_{442}O_{506}$ 38925.0, found 38952.4 $(M + H)^+$.

Compound 4 (deprotected G5). A solution of **3** (0.40 g, 0.0103 mmol) in concentrated HCl (3 mL) and methanol (6 mL) was stirred for 16 h at room temperature and then evaporated under vacuum. The residue was dissolved in chloroform, washed with 5 M NaOH (aq), dried over $MgSO_4$, filtered, and evaporated under vacuum to give **4** (0.30 g, 90%) as a white wax. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.12 (not found, 2H, HC≡CC**H$_2$**), 3.55-3.34 (m, 1888H, C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**, C_3N_3-NHC**H$_2$**CH_2CH_2O), 2.71 (br, 128H, OCH_2CH_2C**H$_2$**NH_2), 2.22 (not found, 1H, **H**C≡CCH_2), 1.75-1.62 (m, 504H, OCH_2C**H$_2$**CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0 (**C**$_3$$N_3$), 81.1 (not found, HC≡**C**CH_2), 70.5 (H**C**≡CCH_2, O**C**H$_2$**C**H_2O), 70.2 (O**C**H$_2$**C**H_2O), 69.4 (CH_2CH_2**C**H_2O), 69.2 (CH_2CH_2**C**H_2O), 39.5 (**C**$H_2CH_2CH_2O$), 38.0 (**C**$H_2CH_2CH_2O$), 33.3 (OCH_2**C**$H_2CH_2NH_2$), 30.1 (not found, HC≡C**C**H_2), 29.6 ($NHCH_2$**C**H_2CH_2O); MS (ESI-TOF) calcd for $C_{1452}H_{2840}N_{442}O_{378}$ 32521.7, not found.

Compound 5 (Boc-protected G7). A solution of **14** (1.0 g, 0.504 mmol), **4** (0.10 g, 3.07 μmol), and DIPEA (0.30 mL, 1.71 mmol) in THF (5 mL), methanol (0.5 mL), and H_2O (0.5 mL) was stirred at 75 °C in a capped vessel for 4 d. The solution was evaporated under vacuum. The residue was dissolved in dichloromethane, washed with brine, dried over $MgSO_4$, filtered, and evaporated under vacuum. The crude product was dissolved in dichloromethane and precipitated by adding diethyl ether. The precipitation step was repeated until macromonomer **14** was completely removed, which was monitored by thin layer chromatography (DCM:MeOH = 14:1). The pure product **5** (0.39 g, 81%) was obtained as a white wax. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.05 (not found, 2H, HC≡CC**H$_2$**), 3.58-3.36 (m, 7648H, C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**, C_3N_3-NHC**H$_2$**CH_2CH_2O), 3.16 (br m, 512H, BocNHC**H$_2$**), 2.17 (not found, 1H, **H**C≡CCH_2), 1.76-1.67 (m, 2040H, OCH_2C**H$_2$**CH_2), 1.37 (s, 2304H, C(C**H$_3$**)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9 (**C**$_3$$N_3$), 156.1 (**C**O), 81.1 (not found, HC≡**C**CH_2), 78.8 (**C**$(CH_3)_3$), 70.6 (O**C**H$_2$**C**H_2O), 70.5 (not found, H**C**≡CCH_2), 70.3 (O**C**H$_2$**C**H_2O), 70.2 (two lines, O**C**H$_2$**C**H_2O), 69.5 (CH_2CH_2**C**H_2O), 69.3 (CH_2CH_2**C**H_2O), 69.2 (CH_2CH_2**C**H_2O), 38.5 (**C**$H_2CH_2CH_2O$), 38.1 (**C**$H_2CH_2CH_2O$), 30.1 (not found, HC≡C**C**H_2), 29.6 ($NHCH_2$**C**H_2CH_2O), 28.5 (C(**C**$H_3)_3$); MS (ESI-TOF) calcd for $C_{7148}H_{13528}N_{1786}O_{2042}$ 157081.0, not found.

Compound 6 (deprotected G7). A solution of **5** (0.34 g, 2.16 μmol) in concentrated HCl (4 mL) and methanol (8 mL) was stirred for 16 h at room temperature and then evaporated under vacuum. The residue was dissolved in chloroform, washed with 5 M NaOH (aq), dried over $MgSO_4$, filtered, and evaporated under vacuum to give **6** (0.26 g, 92%) as a white wax. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.12 (not found, 2H, HC≡CC**H$_2$**), 3.57-3.34 (m, 7648H, C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**, C_3N_3-NHC**H$_2$**CH_2CH_2O), 2.72 (t, *J* = 6.6, 512H, OCH_2CH_2C**H$_2$**NH_2), 2.22 (not found, 1H, **H**C≡CCH_2), 1.75-1.63 (m, 2040H, OCH_2C**H$_2$**CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1 (**C**$_3$$N_3$), 81.1 (not found, HC≡**C**CH_2), 70.6 (O**C**H$_2$**C**H_2O), 70.5 (H**C**≡CCH_2, O**C**H$_2$**C**H_2O), 70.2 (O**C**H$_2$**C**H_2O), 70.1 (O**C**H$_2$**C**H_2O), 69.4 (CH_2CH_2**C**H_2O), 69.3 (CH_2CH_2**C**H_2O), 69.2 (CH_2CH_2**C**H_2O), 39.5 (**C**$H_2CH_2CH_2O$), 38.0 (**C**$H_2CH_2CH_2O$), 33.4 (OCH_2**C**$H_2CH_2NH_2$), 30.1 (not found, HC≡C**C**H_2), 29.6 ($NHCH_2$**C**H_2CH_2O); MS (ESI-TOF) calcd for $C_{5868}H_{11480}N_{1786}O_{1530}$ 131467.5, not found.

Compound 7 (Boc-protected G9). A solution of **14** (1.0 g, 0.504 mmol), **6** (0.10 g, 0.76 μmol), and DIPEA (0.30 mL, 1.71 mmol) in THF (5 mL), methanol (0.5 mL), and H_2O (0.5 mL) was stirred at 75 ^oC in a capped vessel for 4 d. The solution was evaporated under vacuum. The residue was dissolved in dichloromethane, washed with brine, dried over $MgSO_4$, filtered, and evaporated under vacuum. The crude product was dissolved in dichloromethane and precipitated by adding diethyl ether. The precipitation step was repeated until macromonomer **14** was completely removed, which was monitored by thin layer chromatography (DCM:MeOH = 14:1). The pure product **7** (0.39 g, 81%) was obtained as a white wax. ^1H NMR (300 MHz, $CDCl_3$) δ 4.05 (not found, 2H, HC≡CC**H$_2$**), 3.58-3.36 (m, 30688H, C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**, C_3N_3-NHC**H$_2$**CH_2CH_2O), 3.16 (br m, 2048H, BocNHC**H$_2$**), 2.17 (not found, 1H, **H**C≡CCH_2), 1.76-1.67 (m, 8184H, OCH_2C**H$_2$**CH_2), 1.38 (s, 9216H, C(C**H$_3$**)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9 (**C**$_3$N$_3$), 156.1 (**C**O), 81.1 (not found, HC≡**C**CH_2), 78.8 (**C**$(CH_3)_3$), 70.6 (O**C**H_2**C**H_2O), 70.5 (not found, H**C**≡CCH_2), 70.3 (O**C**H_2**C**H_2O), 70.2 (O**C**H_2**C**H_2O), 69.5 (CH_2CH_2**C**H_2O), 69.3 (CH_2CH_2**C**H_2O), 69.2 (CH_2CH_2**C**H_2O), 38.5 (**C**$H_2CH_2CH_2$O), 38.1 (**C**$H_2CH_2CH_2$O), 30.1 (not found, HC≡C**C**H_2), 29.6 (NHCH_2**C**H_2CH_2O), 28.5 (C(**C**$H_3)_3$); MS (ESI-TOF) calcd for $C_{28652}H_{54232}N_{7162}O_{8186}$ 629704.8, not found.

Compound 8 (deprotected G9). A solution of **7** (0.33 g, 0.524 μmol) in concentrated HCl (4 mL) and methanol (8 mL) was stirred for 16 h at room temperature and then evaporated under vacuum. The residue was dissolved in chloroform, washed with 5 M NaOH (aq), dried over $MgSO_4$, filtered, and evaporated under vacuum to give **8** (0.255 g, 92%) as a white wax. ^1H NMR (300 MHz, $CDCl_3$) δ 4.12 (not found, 2H, HC≡CC**H$_2$**), 3.58-3.36 (m, 30688H, C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**, C_3N_3-NHC**H$_2$**CH_2CH_2O), 2.73 (t, *J* = 6.6, 2048H, OCH_2CH_2C**H$_2$**NH_2), 2.22 (not found, 1H, **H**C≡CCH_2), 1.76-1.65 (m, 8184H, OCH_2C**H$_2$**CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3 (**C**$_3$N$_3$), 81.1 (not found, HC≡**C**CH_2), 70.6 (two lines, O**C**H_2**C**H_2O), 70.5 (not found, H**C**≡CCH_2), 70.2 (two lines, O**C**H_2**C**H_2O), 69.4 (CH_2CH_2**C**H_2O), 69.3 (two lines, CH_2CH_2**C**H_2O), 39.6 (**C**$H_2CH_2CH_2$O), 38.1 (**C**$H_2CH_2CH_2$O), 33.3 (OCH_2**C**$H_2CH_2NH_2$), 30.1 (not found, HC≡C**C**H_2), 29.7 (NHCH_2**C**H_2CH_2O); MS (ESI-TOF) calcd for $C_{23532}H_{46040}N_{7162}O_{6138}$ 527251.1, not found.

Compound 9 (Boc-protected G11). A solution of **14** (1.0 g, 0.504 mmol), **8** (0.10 g, 0.19 μmol), and DIPEA (0.30 mL, 1.71 mmol) in THF (5 mL), methanol (0.5 mL), and H_2O (0.5 mL) was stirred at 75 ^oC in a capped vessel for 4 d. The solution was evaporated under vacuum. The residue was dissolved in dichloromethane, washed with brine, dried over $MgSO_4$, filtered, and evaporated under vacuum. The crude product was dissolved in dichloromethane and precipitated by adding diethyl ether. The precipitation step was repeated until macromonomer **14** was completely removed, which was monitored by thin layer chromatography (DCM:MeOH = 14:1). The pure product **9** (0.39 g, 82%) was obtained as a white wax. ^1H NMR (300 MHz, $CDCl_3$) δ 4.05 (not found, 2H, HC≡CC**H$_2$**), 3.61-3.39 (m, 122848H, C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**, C_3N_3-NHC**H$_2$**CH_2CH_2O), 3.19 (br m, 8192H, BocNHC**H$_2$**), 2.17 (not found, 1H, **H**C≡CCH_2), 1.80-1.71 (m, 32760H, OCH_2C**H$_2$**CH_2), 1.41 (s, 36864H,

C(C**H$_3$**)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0 (**C**$_3$N$_3$), 156.1 (**C**O), 81.1 (not found, HC≡**C**CH$_2$), 78.9 (**C**(CH$_3$)$_3$), 70.6 (O**C**H$_2$**C**H$_2$O), 70.5 (not found, H**C**≡CCH$_2$), 70.3 (two lines, O**C**H$_2$**C**H$_2$O), 70.2 (O**C**H$_2$**C**H$_2$O), 69.6 (CH$_2$CH$_2$**C**H$_2$O), 69.3 (two lines, CH$_2$CH$_2$**C**H$_2$O), 38.5 (**C**H$_2$CH$_2$CH$_2$O), 38.1 (**C**H$_2$CH$_2$CH$_2$O), 30.1 (not found, HC≡C**C**H$_2$), 29.7 (NHCH$_2$**C**H$_2$CH$_2$O), 28.5 (C(**C**H$_3$)$_3$); MS (ESI-TOF) calcd for $C_{114668}H_{217048}N_{28666}O_{32762}$ 2520199.9, not found.

Compound 10 (deprotected G11). A solution of **9** (0.33 g, 0.131 μmol) in concentrated HCl (4 mL) and methanol (8 mL) was stirred for 16 h at room temperature and then evaporated under vacuum. The residue was dissolved in chloroform, washed with 5 M NaOH (aq), dried over $MgSO_4$, filtered, and evaporated under vacuum to give **10** (0.25 g, 90%) as a white wax. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.12 (not found, 2H, HC≡CC**H$_2$**), 3.60-3.38 (m, 122848H, C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**, C$_3$N$_3$-NHC**H$_2$**CH$_2$CH$_2$O), 2.76 (t, *J* = 6.6, 8192H, OCH$_2$CH$_2$C**H$_2$**NH$_2$), 2.22 (not found, 1H, **H**C≡CCH$_2$), 1.78-1.67 (m, 32760H, OCH$_2$C**H$_2$**CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1 (**C**$_3$N$_3$), 81.1 (not found, HC≡**C**CH$_2$), 70.7 (O**C**H$_2$**C**H$_2$O), 70.5 (not found, H**C**≡CCH$_2$), 70.3 (two lines, O**C**H$_2$**C**H$_2$O), 69.5 (CH$_2$CH$_2$**C**H$_2$O), 69.3 (CH$_2$CH$_2$**C**H$_2$O), 39.7 (**C**H$_2$CH$_2$CH$_2$O), 38.1 (**C**H$_2$CH$_2$CH$_2$O), 33.5 (OCH$_2$**C**H$_2$CH$_2$NH$_2$), 30.1 (not found, HC≡C**C**H$_2$), 29.8 (NHCH$_2$**C**H$_2$CH$_2$O); MS (ESI-TOF) calcd for $C_{94188}H_{184280}N_{28666}O_{24570}$ 2110385.2, not found.

Compound 11 (Boc-protected G13). A solution of **14** (0.70 g, 0.353 mmol), **10** (0.070 g, 0.033 μmol), and DIPEA (0.20 mL, 1.14 mmol) in THF (4 mL), methanol (0.4 mL), and H_2O (0.4 mL) was stirred at 75 °C in a capped vessel for 4 d. The solution was evaporated under vacuum. The residue was dissolved in dichloromethane, washed with brine, dried over $MgSO_4$, filtered, and evaporated under vacuum. The crude product was dissolved in dichloromethane and precipitated by adding diethyl ether. The precipitation step was repeated until macromonomer **14** was completely removed, which was monitored by thin layer chromatography (DCM:MeOH = 14:1). The pure product **11** (0.275 g, 82%) was obtained as a white wax. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.05 (not found, 2H, HC≡CC**H$_2$**), 3.59-3.39 (m, 491488H, C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**, C$_3$N$_3$-NHC**H$_2$**CH$_2$CH$_2$O), 3.17 (br, 32768H, BocNHC**H$_2$**), 2.17 (not found, 1H, **H**C≡CCH$_2$), 1.78 (br, 131064H, OCH$_2$C**H$_2$**CH$_2$), 1.39 (s, 147456H, C(C**H$_3$**)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4 (br, **C**$_3$N$_3$), 156.1 (**C**O), 81.1 (not found, HC≡**C**CH$_2$), 78.9 (**C**(CH$_3$)$_3$), 70.6 (O**C**H$_2$**C**H$_2$O), 70.5 (not found, H**C**≡CCH$_2$), 70.3 (O**C**H$_2$**C**H$_2$O), 70.2 (O**C**H$_2$**C**H$_2$O), 69.6 (CH$_2$CH$_2$**C**H$_2$O), 69.2 (CH$_2$CH$_2$**C**H$_2$O), 38.5 (**C**H$_2$CH$_2$CH$_2$O), 38.2 (**C**H$_2$CH$_2$CH$_2$O), 30.1 (not found, HC≡C**C**H$_2$), 29.6 (NHCH$_2$**C**H$_2$CH$_2$O), 28.5 (C(**C**H$_3$)$_3$); MS (ESI-TOF) calcd for $C_{458732}H_{868312}N_{114682}O_{131066}$ 10082180.6, not found.

Compound 12 (deprotected G13). A solution of **11** (0.12 g, 0.0119 μmol) in concentrated HCl (3 mL) and methanol (6 mL) was stirred for 16 h at room temperature and then evaporated under vacuum. The residue was dissolved in chloroform, washed with 5 M NaOH (aq), dried over $MgSO_4$, filtered, and evaporated under vacuum to give **12** (50 mg, 50%) as a white wax. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.12 (not found, 2H, HC≡CC**H$_2$**), 3.62-3.40 (m, 491488H, C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**, C$_3$N$_3$-NHC**H$_2$**CH$_2$CH$_2$O), 2.78 (br, 32768H, OCH$_2$CH$_2$C**H$_2$**NH$_2$),

2.22 (not found, 1H, **H**C≡CCH$_2$), 1.80-1.71 (br m, 131064H, OCH$_2$C**H$_2$**CH$_2$); ^{13}C NMR (75 MHz, CDCl$_3$) δ 166.2 (**C**$_3$N$_3$), 81.1 (not found, HC≡**C**CH$_2$), 70.8 (O**C**H$_2$**C**H$_2$O), 70.7 (O**C**H$_2$**C**H$_2$O), 70.5 (not found, H**C**≡CCH$_2$), 70.4 (O**C**H$_2$**C**H$_2$O), 70.3 (O**C**H$_2$**C**H$_2$O), 69.6 (CH$_2$CH$_2$**C**H$_2$O), 69.4 (two lines, CH$_2$CH$_2$**C**H$_2$O), 39.7 (**C**H$_2$CH$_2$CH$_2$O), 38.2 (**C**H$_2$CH$_2$CH$_2$O), 33.5 (OCH$_2$**C**H$_2$CH$_2$NH$_2$), 30.1 (not found, HC≡C**C**H$_2$), 29.8 (NHCH$_2$**C**H$_2$CH$_2$O); MS (ESI-TOF) calcd for $C_{376812}H_{737240}N_{114682}O_{98298}$ 8442921.6, not found.

Compound 13. Cyanuric chloride (1.70 g, 9.22 mmol) was added to an ice-bath cooled solution of *N*-Boc-4,7,10-trioxa-1,13-tridecanediamine (5.80 g, 18.10 mmol) and DIPEA (4.0 mL, 22.8 mmol) in THF (40 mL). The solution was stirred for 1 h at 0 ^{o}C, warmed to room temperature, and then stirred for 16 h. After addition of a solution of 4,7,10-trioxa-1,13-tridecanediamine (14.0 g, 63.5 mmol) and DIPEA (3.0 mL, 17.1 mmol) in methanol (10 mL), the reaction solution was stirred for an additional 16 h at 70 ^{o}C and evaporated under vacuum. The residue was dissolved in dichloromethane, washed with brine, dried over MgSO$_4$, filtered, and evaporated under vacuum. The crude product was purified by silica gel chromatography (DCM:MeOH = 10:1 with 1% NH$_4$OH) to give **13** (7.6 g, 88%) as a clear oil. ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.67-3.34 (m, 42H, C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**, C$_3$N$_3$-NHC**H$_2$**CH$_2$CH$_2$O), 3.17 (m, 4H, BocNHC**H$_2$**), 2.79 (t, *J* = 6.6, 2H, OCH$_2$CH$_2$C**H$_2$**NH$_2$), 1.83-1.67 (m, 12H, OCH$_2$C**H$_2$**CH$_2$), 1.39 (s, 18H, C(C**H$_3$**)$_3$); ^{13}C NMR (75 MHz, CDCl$_3$) δ 166.0 (**C**$_3$N$_3$), 156.2 (**C**O), 78.9 (**C**(CH$_3$)$_3$), 70.6 (O**C**H$_2$**C**H$_2$O), 70.3 (O**C**H$_2$**C**H$_2$O), 70.2 (two lines, O**C**H$_2$**C**H$_2$O), 69.6 (CH$_2$CH$_2$**C**H$_2$O), 69.4 (CH$_2$CH$_2$**C**H$_2$O), 39.6 (**C**H$_2$CH$_2$CH$_2$O), 38.5 (**C**H$_2$CH$_2$CH$_2$O), 38.2 (**C**H$_2$CH$_2$CH$_2$O), 32.6 (OCH$_2$**C**H$_2$CH$_2$NH$_2$), 29.7 (NHCH$_2$**C**H$_2$CH$_2$O), 28.5 (C(**C**H$_3$)$_3$); MS (ESI-TOF) calcd for $C_{43}H_{85}N_9O_{13}$ 935.6267, found 936.6595 $(M + H)^+$.

Compound 14 (macromonomer). Cyanuric chloride (0.46 g, 2.49 mmol) was added to an ice-bath cooled solution of **13** (4.70 g, 5.02 mmol) and DIPEA (2.0 mL, 11.4 mmol) in THF (40 mL). The solution was stirred for 1 h at 0 ^{o}C, warmed to room temperature, and then stirred for an additional 16 h. After concentration under vacuum, the residue was dissolved in dichloromethane, washed with brine, dried over MgSO$_4$, filtered, and evaporated under vacuum. The crude product was purified by silica gel chromatography (DCM:MeOH = 14:1) to give **14** (4.68 g, 95%) as a clear oil. ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.64-3.41 (m, 88H, C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**, C$_3$N$_3$-NHC**H$_2$**CH$_2$CH$_2$O), 3.20 (br m, 8H, BocNHC**H$_2$**), 1.83-1.70 (m, 24H, OCH$_2$C**H$_2$**CH$_2$), 1.42 (s, 36H, C(C**H$_3$**)$_3$); ^{13}C NMR (75 MHz, CDCl$_3$) δ 165.9 (**C**$_3$N$_3$), 165.6 (**C**$_3$N$_3$), 156.1 (**C**O), 78.8 (**C**(CH$_3$)$_3$), 70.5 (O**C**H$_2$**C**H$_2$O), 70.2 (two lines, O**C**H$_2$**C**H$_2$O), 69.5 (CH$_2$CH$_2$**C**H$_2$O), 69.3 (CH$_2$CH$_2$**C**H$_2$O), 38.4 (**C**H$_2$CH$_2$CH$_2$O), 38.1 (**C**H$_2$CH$_2$CH$_2$O), 29.6 (NHCH$_2$**C**H$_2$CH$_2$O), 28.4 (C(**C**H$_3$)$_3$); MS (ESI-TOF) calcd for $C_{89}H_{168}ClN_{21}O_{26}$ 1982.2158, found 1983.1606 $(M + H)^+$.

Compound 15 (Boc-protected G1). A solution of propargylamine (0.10 g, 1.82 mmol), **14** (0.20 g, 0.10 mmol), and DIPEA (0.20 mL, 1.14 mmol) in THF (1 mL) and methanol (0.1 mL) was stirred at 70 ^{o}C in a capped vessel for 16 h. The solution was evaporated under vacuum. The residue was dissolved in dichloromethane, washed with brine (pH 5), dried over MgSO$_4$, filtered, and evaporated under vacuum. The crude product was purified by silica

gel chromatography (DCM:MeOH = 10:1) to give **15** (0.18 g, 90%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.07 (br, 2H, HC≡CC**H$_2$**), 3.61-3.34 (m, 88H, C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**, C_3N_3-NHC**H$_2$**CH_2CH_2O), 3.12 (br m, 8H, BocNHC**H$_2$**), 2.17 (br, 1H, **H**C≡CCH_2), 1.74-1.62 (m, 24H, OCH_2C**H$_2$**CH_2), 1.34 (s, 36H, C(C**H$_3$**)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4 (br, **C**$_3$N$_3$), 156.0 (**C**O), 81.1 (HC≡**C**CH_2), 78.7 (**C**$(CH_3)_3$), 70.7 (H**C**≡CCH_2), 70.5 (O**C**H_2**C**H_2O), 70.2 (O**C**H_2**C**H_2O), 70.1 (O**C**H_2**C**H_2O) 69.4 (CH_2CH_2**C**H_2O), 69.1 (CH_2CH_2**C**H_2O), 38.4 (**C**$H_2CH_2CH_2O$), 38.0 (**C**$H_2CH_2CH_2O$), 30.1 (HC≡C**C**H_2), 29.5 ($NHCH_2$**C**H_2CH_2O), 28.4 (C(**C**$H_3)_3$); MS (ESI-TOF) calcd for $C_{92}H_{172}N_{22}O_{26}$ 2001.2813, found 2002.2499 $(M + H)^+$.

Compound 16 (deprotected G1). A solution of **15** (0.15 g, 0.075 mmol) in concentrated HCl (0.5 mL) and methanol (1.0 mL) was stirred for 16 h at room temperature and then evaporated under vacuum. The residue was dissolved in chloroform, washed with 5 M NaOH (aq), dried over $MgSO_4$, filtered, and evaporated under vacuum to give **16** (0.12 g, quantitative) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.09 (br, 2H, HC≡CC**H$_2$**), 3.57-3.35 (m, 88H, C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**, C_3N_3-NHC**H$_2$**CH_2CH_2O), 2.76 (br, 8H, OCH_2CH_2C**H$_2$**NH_2), 2.18 (br, 1H, **H**C≡CCH_2), 1.77-1.64 (m, 24H, OCH_2C**H$_2$**CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0 (**C**$_3$N$_3$), 81.1 (HC≡**C**CH_2), 70.5 (H**C**≡CCH_2, O**C**H_2**C**H_2O), 70.2 (O**C**H_2**C**H_2O), 70.1 (two lines, O**C**H_2**C**H_2O) 69.4 (CH_2CH_2**C**H_2O), 69.2 (two lines, CH_2CH_2**C**H_2O), 39.4 (**C**$H_2CH_2CH_2O$), 38.0 (**C**$H_2CH_2CH_2O$), 32.4 (OCH_2**C**$H_2CH_2NH_2$), 30.1 (HC≡C**C**H_2), 29.6 ($NHCH_2$**C**H_2CH_2O); MS (ESI-TOF) calcd for $C_{72}H_{140}N_{22}O_{18}$ 1601.0716, found 1602.0498 $(M + H)^+$.

Spectra of Compounds

Sample Name	boc16g3-5	**Position**	P1-A1	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	-1	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	All Ions Missed
Data Filename	boc16g3-6.d	**ACQ Method**		**Comment**		**Acquired Time**	3/28/2012 11:21:14

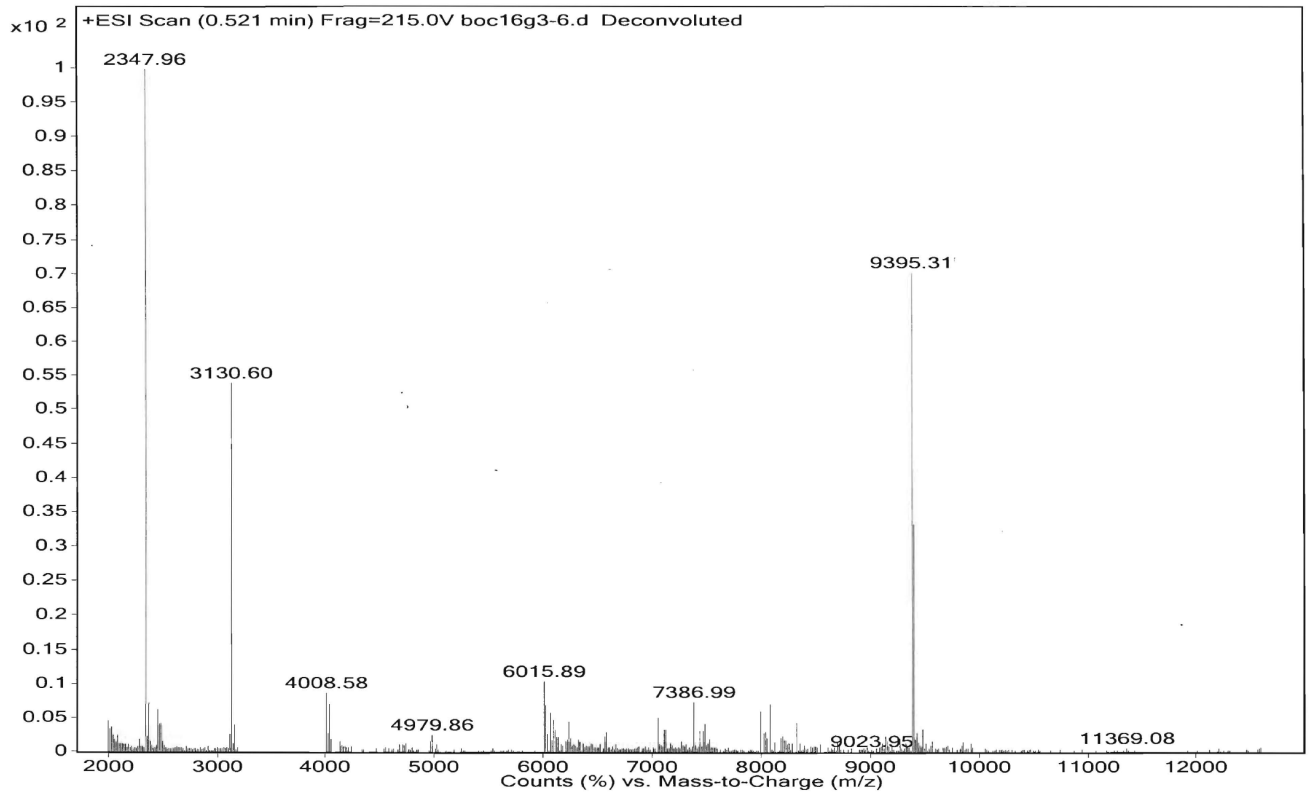


Figure S1. ESI-TOF mass spectrum of **1** (Boc-protected G3)**.**

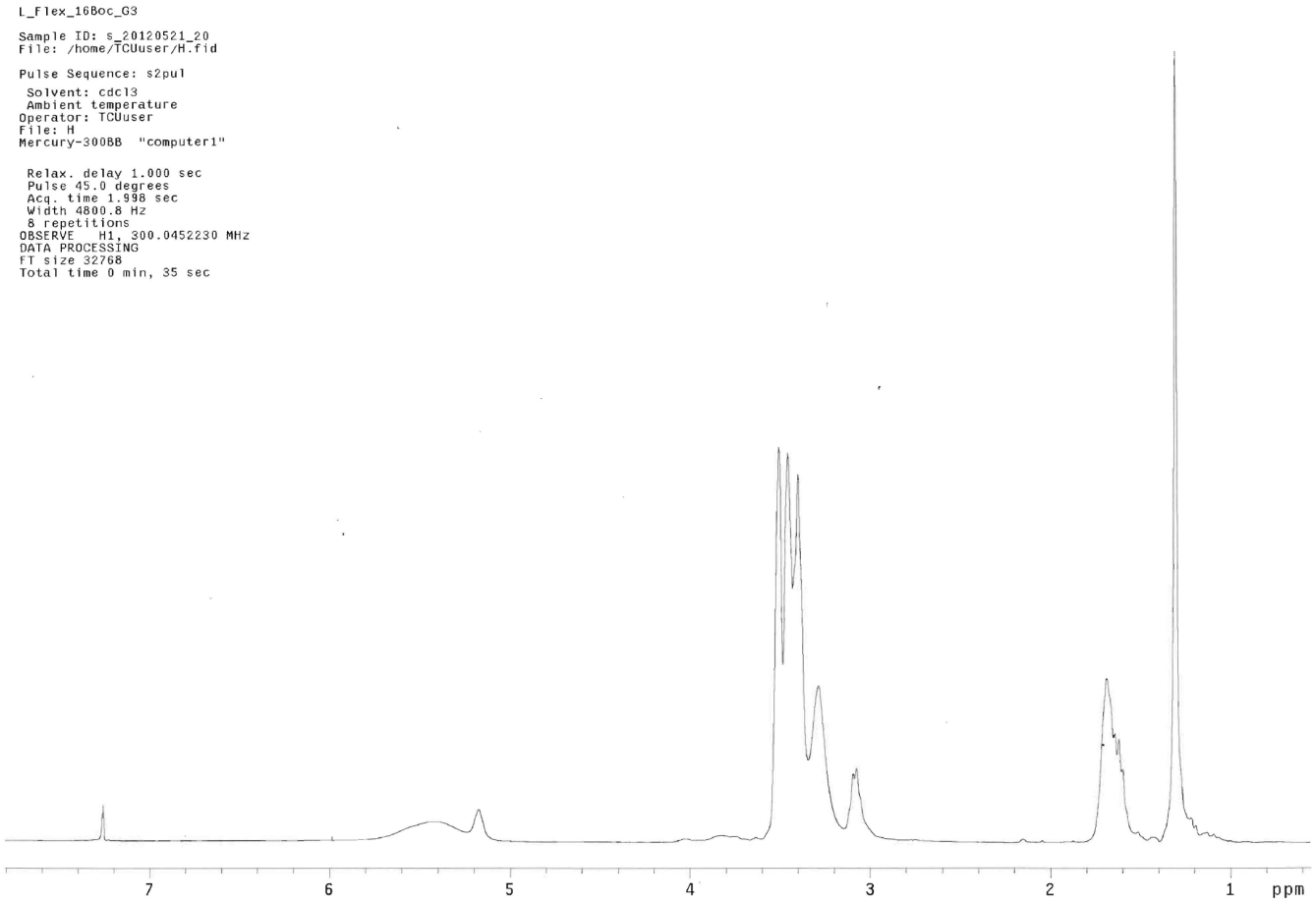


Figure S2. ^{1}H NMR spectrum of **1** (Boc-protected G3, 300 MHz, $CDCl_3$).

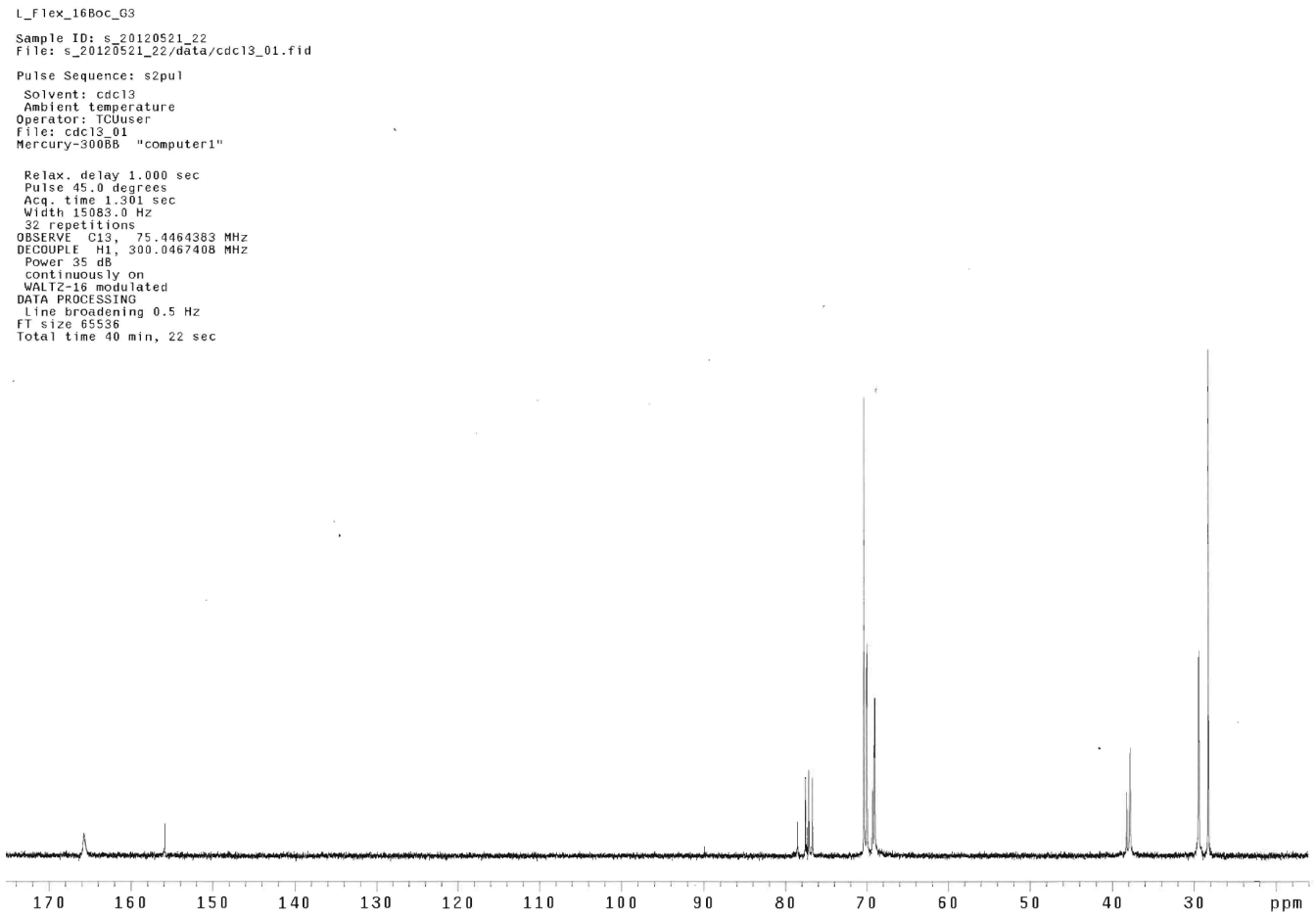


Figure S3. ^{13}C NMR spectrum of **1** (Boc-protected G3, 75 MHz, $CDCl_3$).

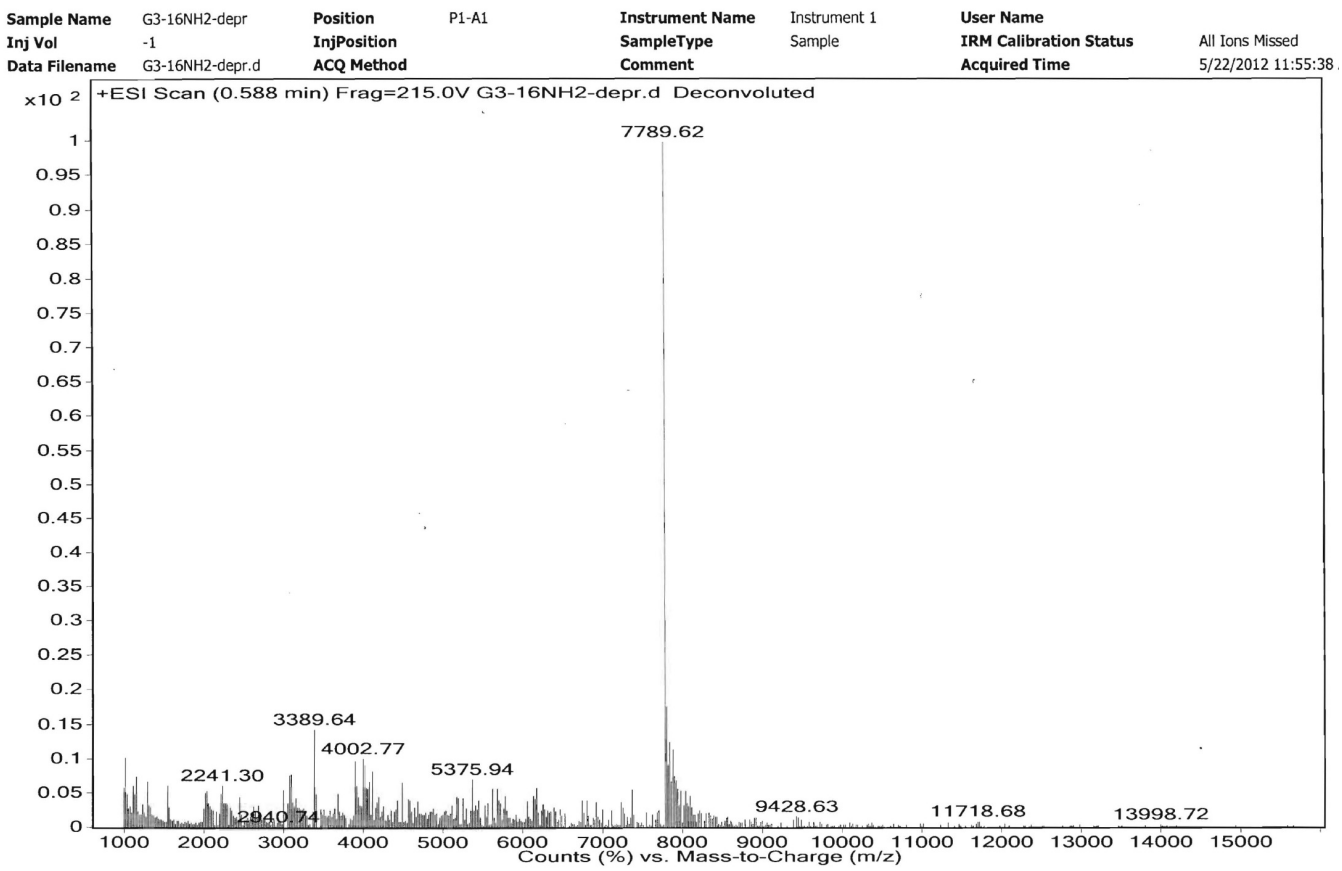


Figure S4. ESI-TOF mass spectrum of **2** (deprotected G3)**.**

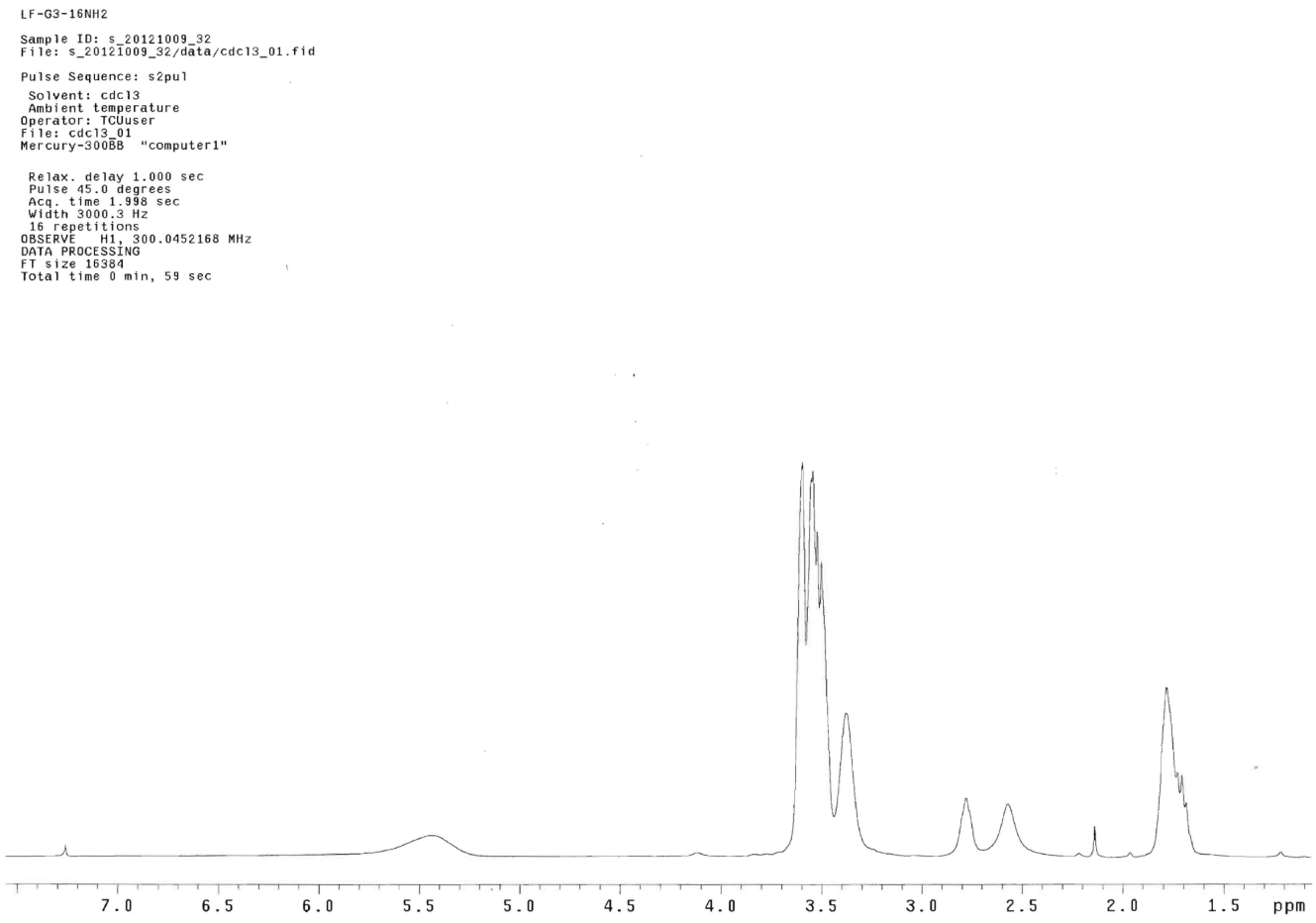


Figure S5. ^{1}H NMR spectrum of **2** (deprotected G3, 300 MHz, $CDCl_3$).

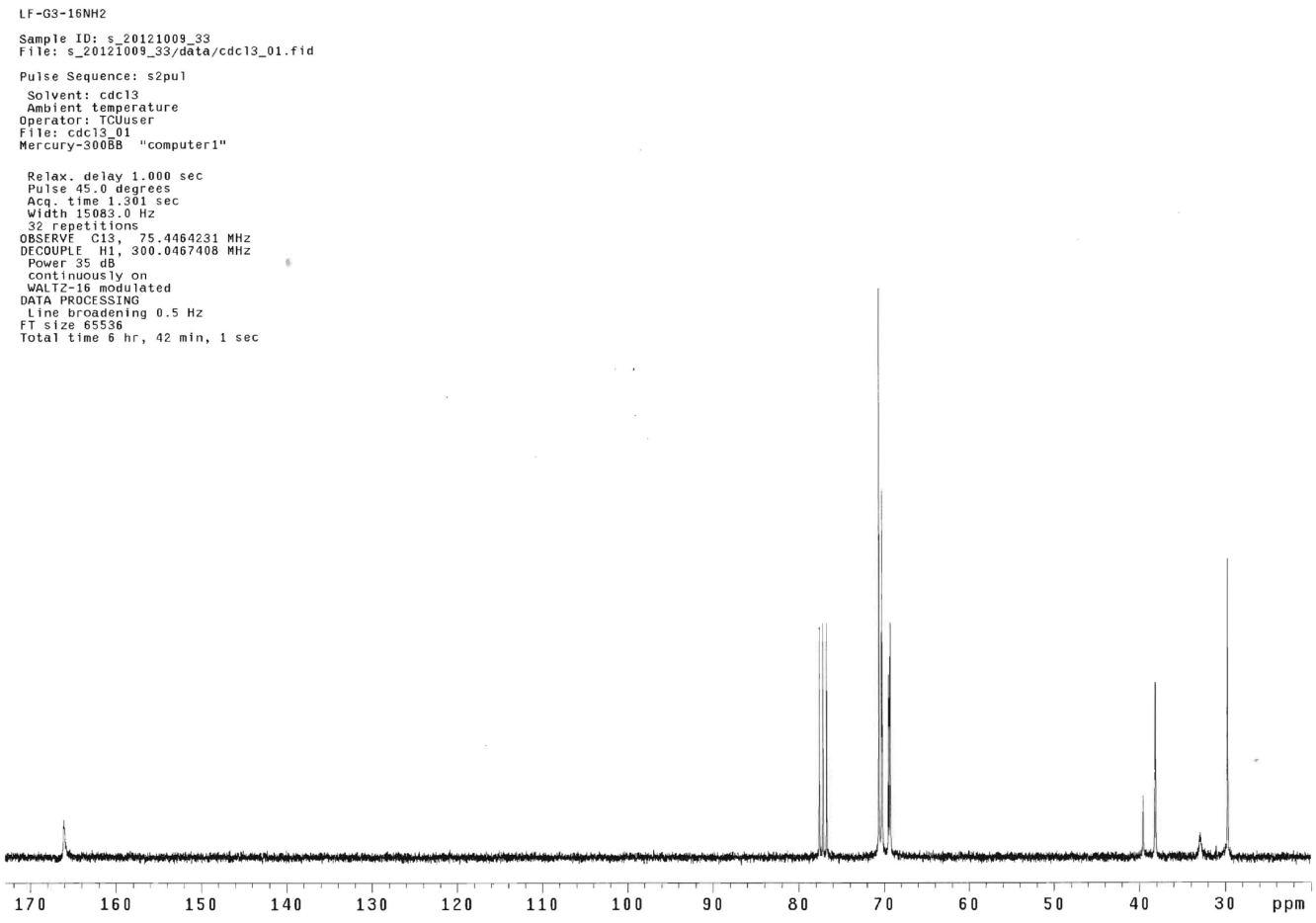


Figure S6. ^{13}C NMR spectrum of **2** (deprotected G3, 75 MHz, $CDCl_3$).

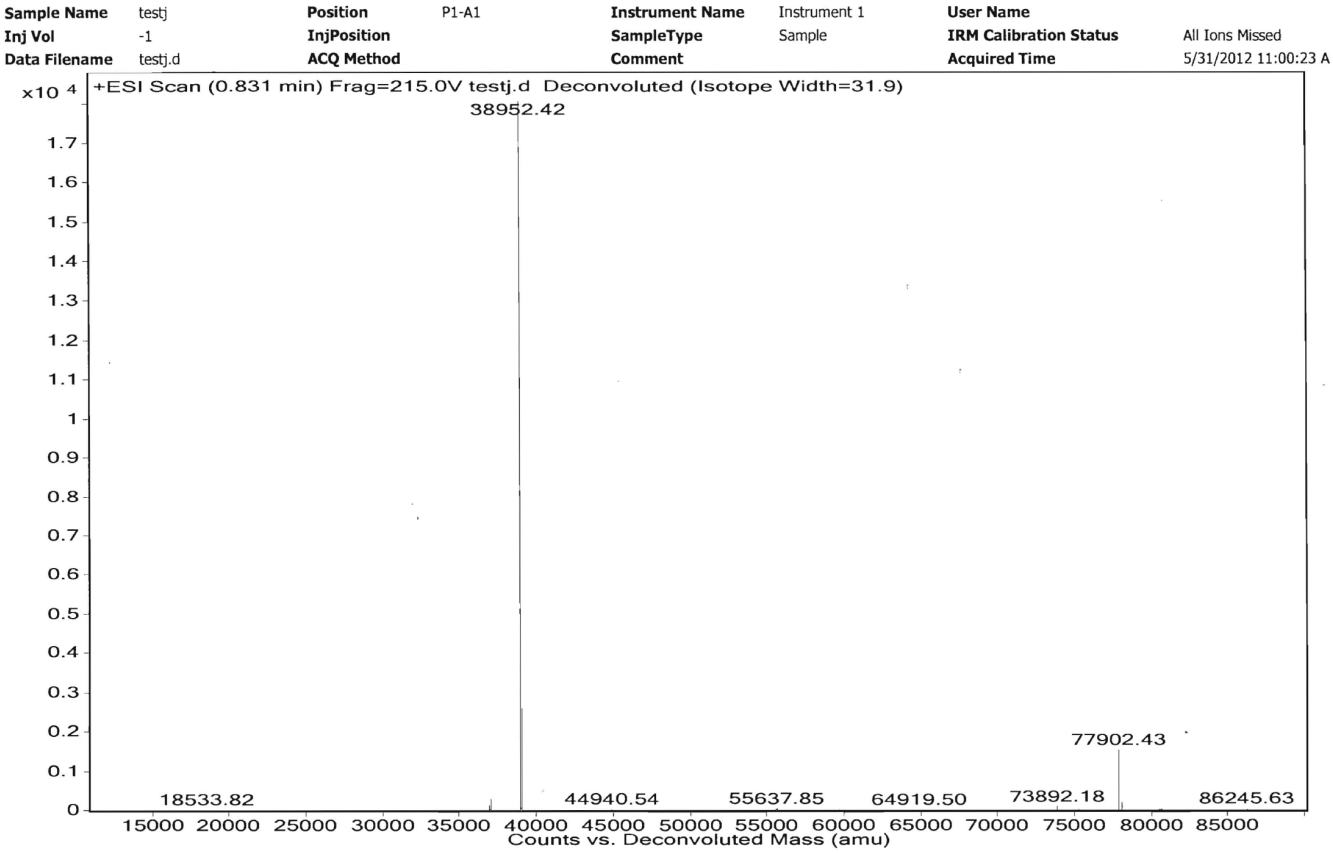


Figure S7. ESI-TOF mass spectrum of **3** (Boc-protected G5)**.** The peak at 77902 is attributed to noncovalent dimer seen in the deconvolution, and not a synthetic impurity.

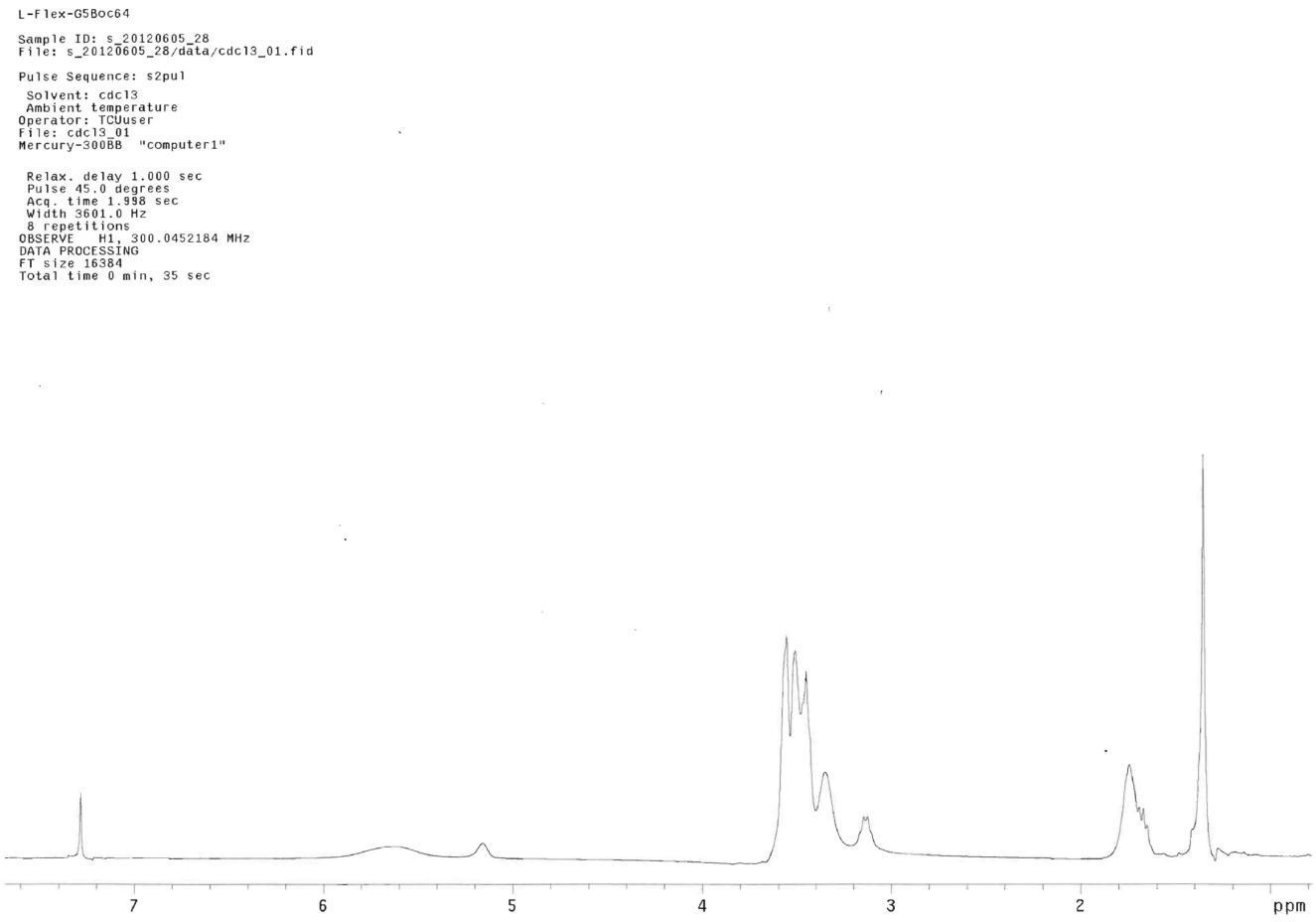


Figure S8. ^{1}H NMR spectrum of **3** (Boc-protected G5, 300 MHz, $CDCl_3$).

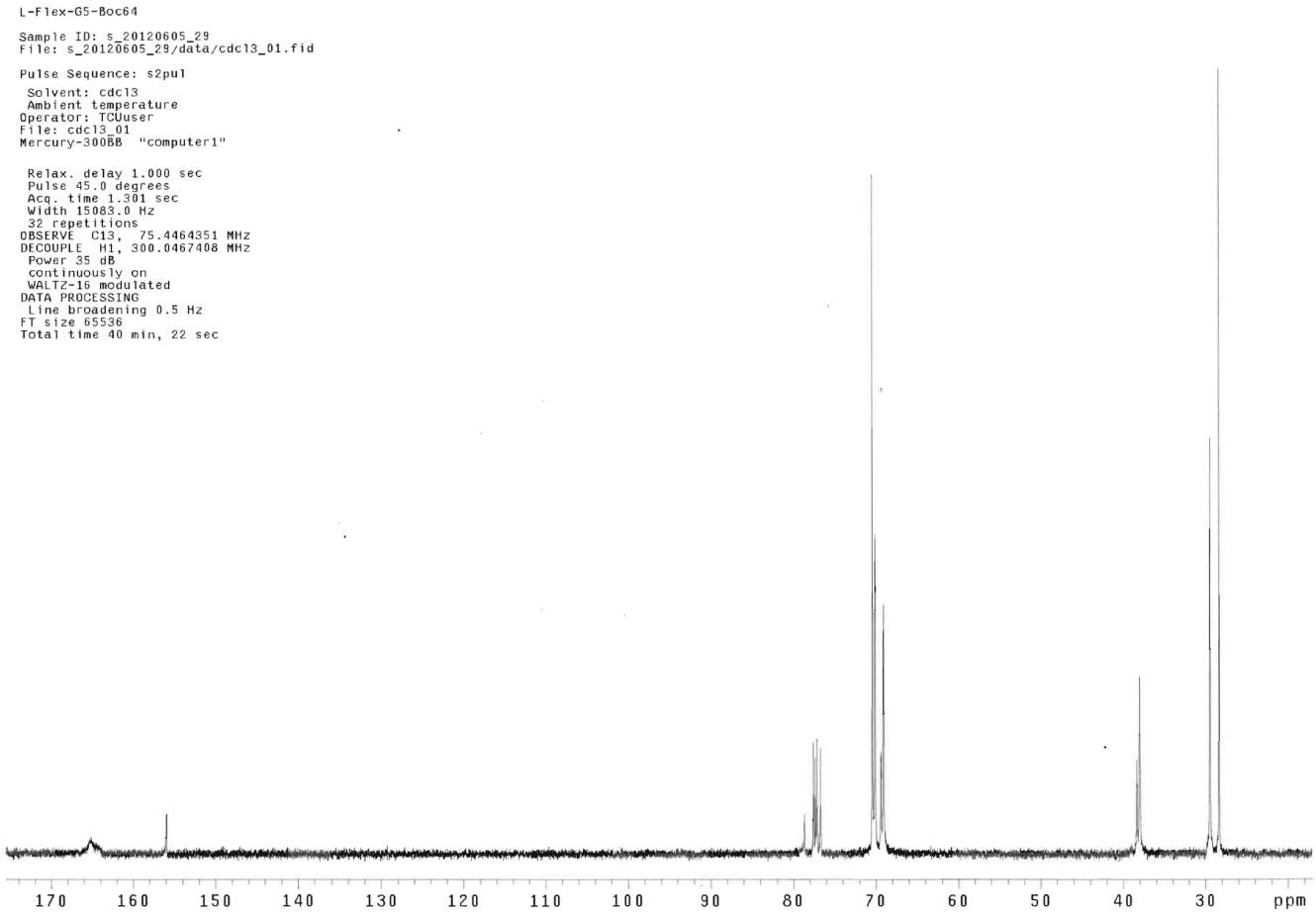


Figure S9. ^{13}C NMR spectrum of **3** (Boc-protected G5, 75 MHz, $CDCl_3$).

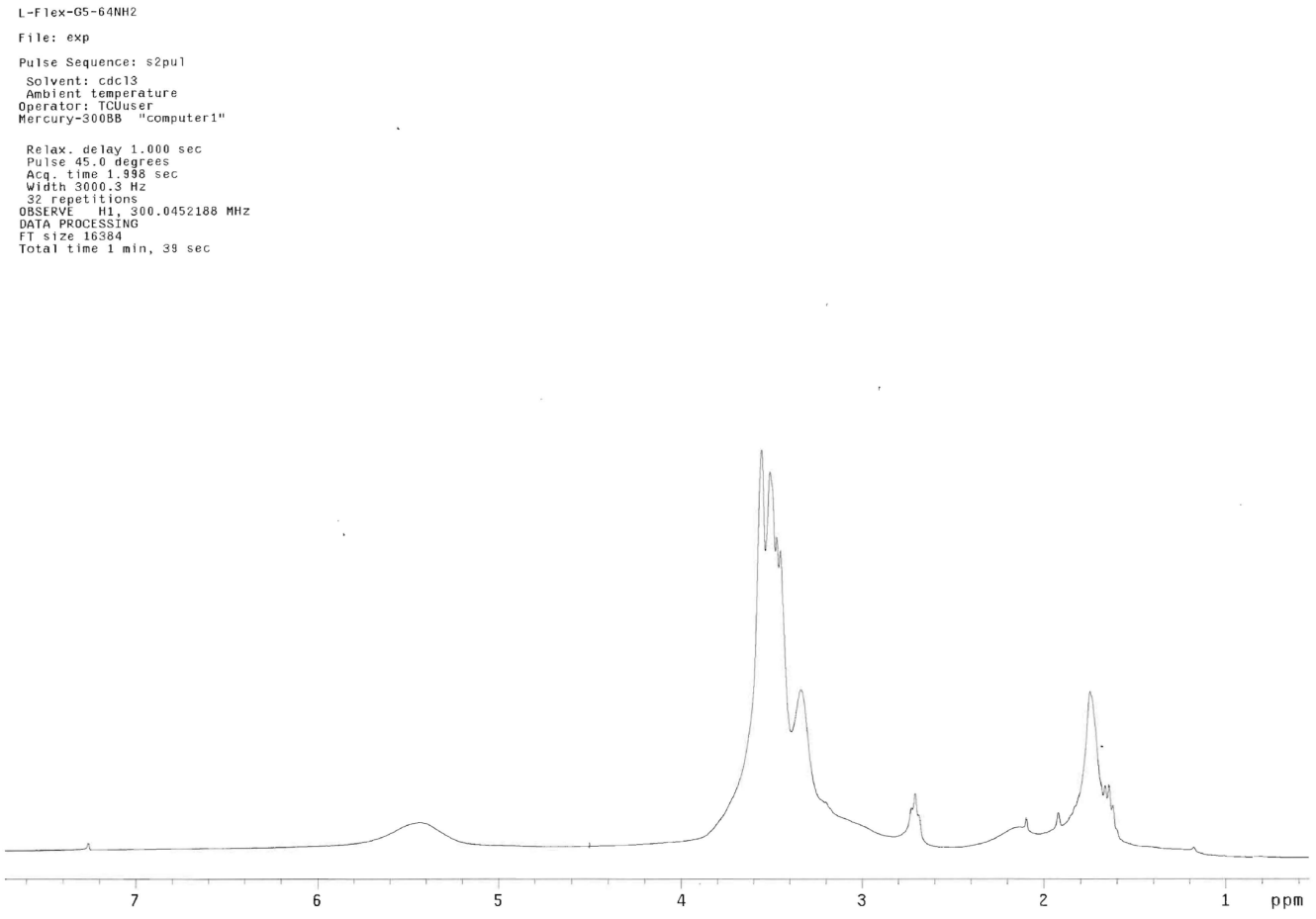


Figure S10. ^{1}H NMR spectrum of **4** (deprotected G5, 300 MHz, $CDCl_3$).

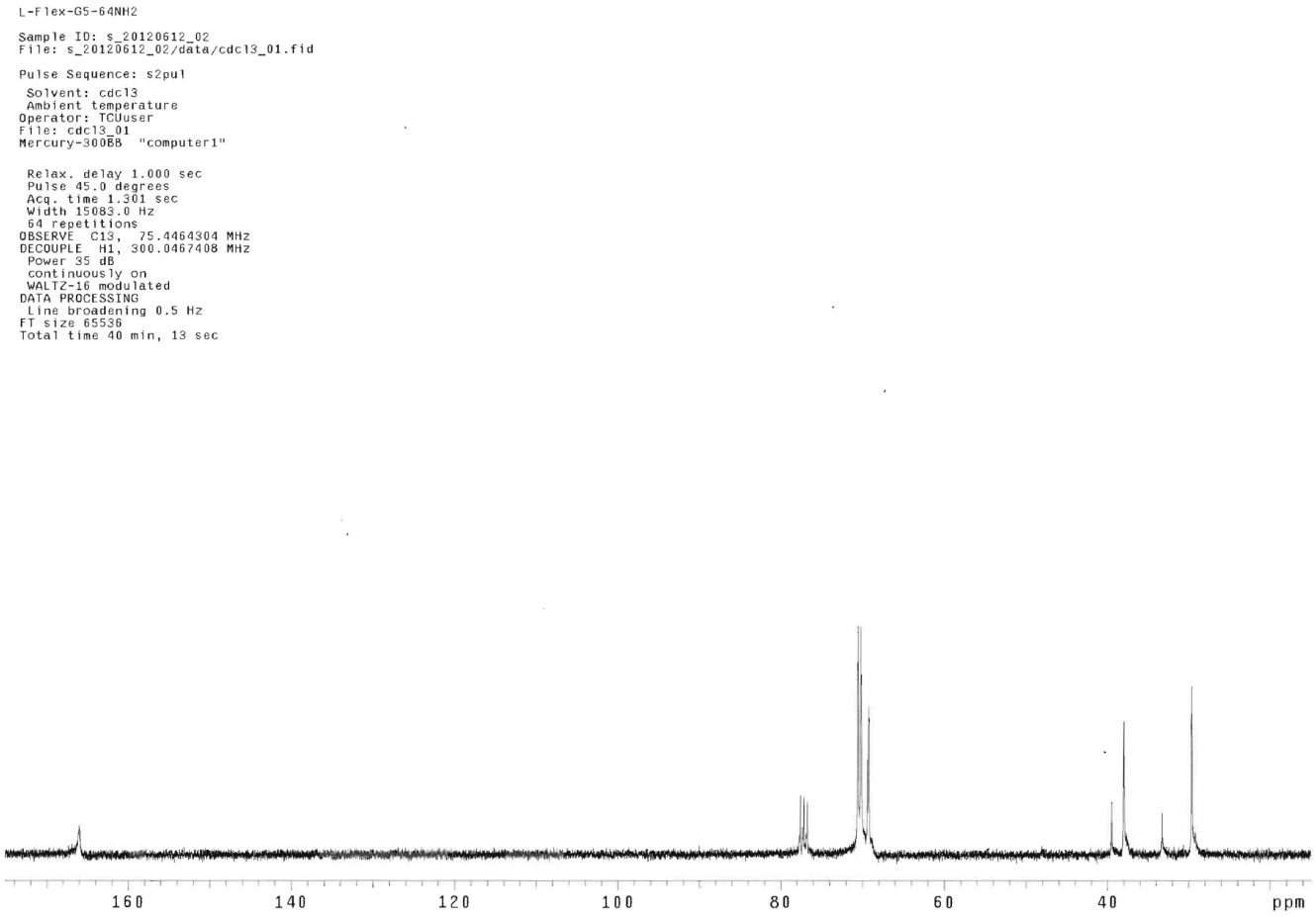


Figure S11. ^{13}C NMR spectrum of **4** (deprotected G5, 75 MHz, $CDCl_3$).

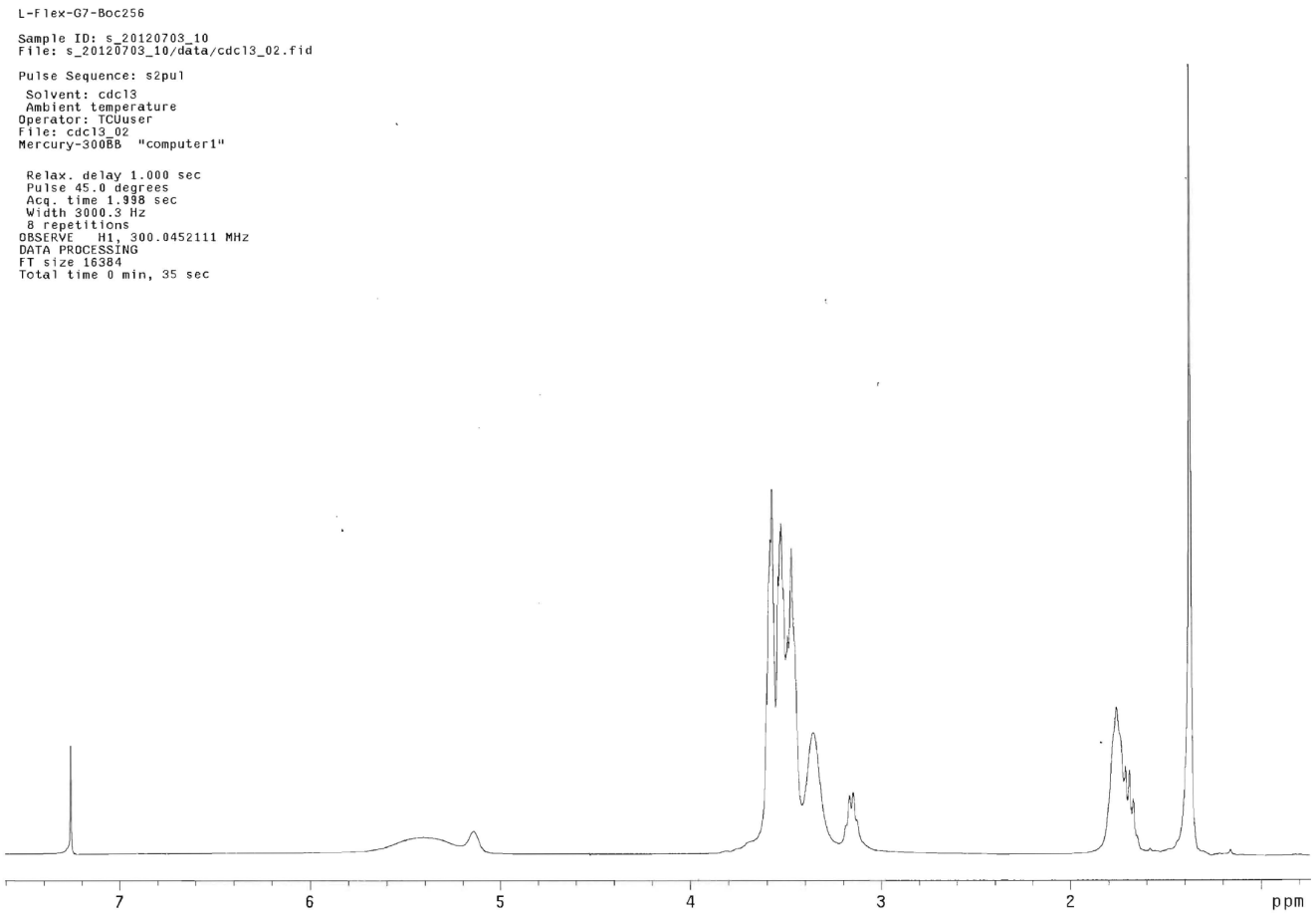


Figure S12. ^{1}H NMR spectrum of **5** (Boc-protected G7, 300 MHz, $CDCl_3$).

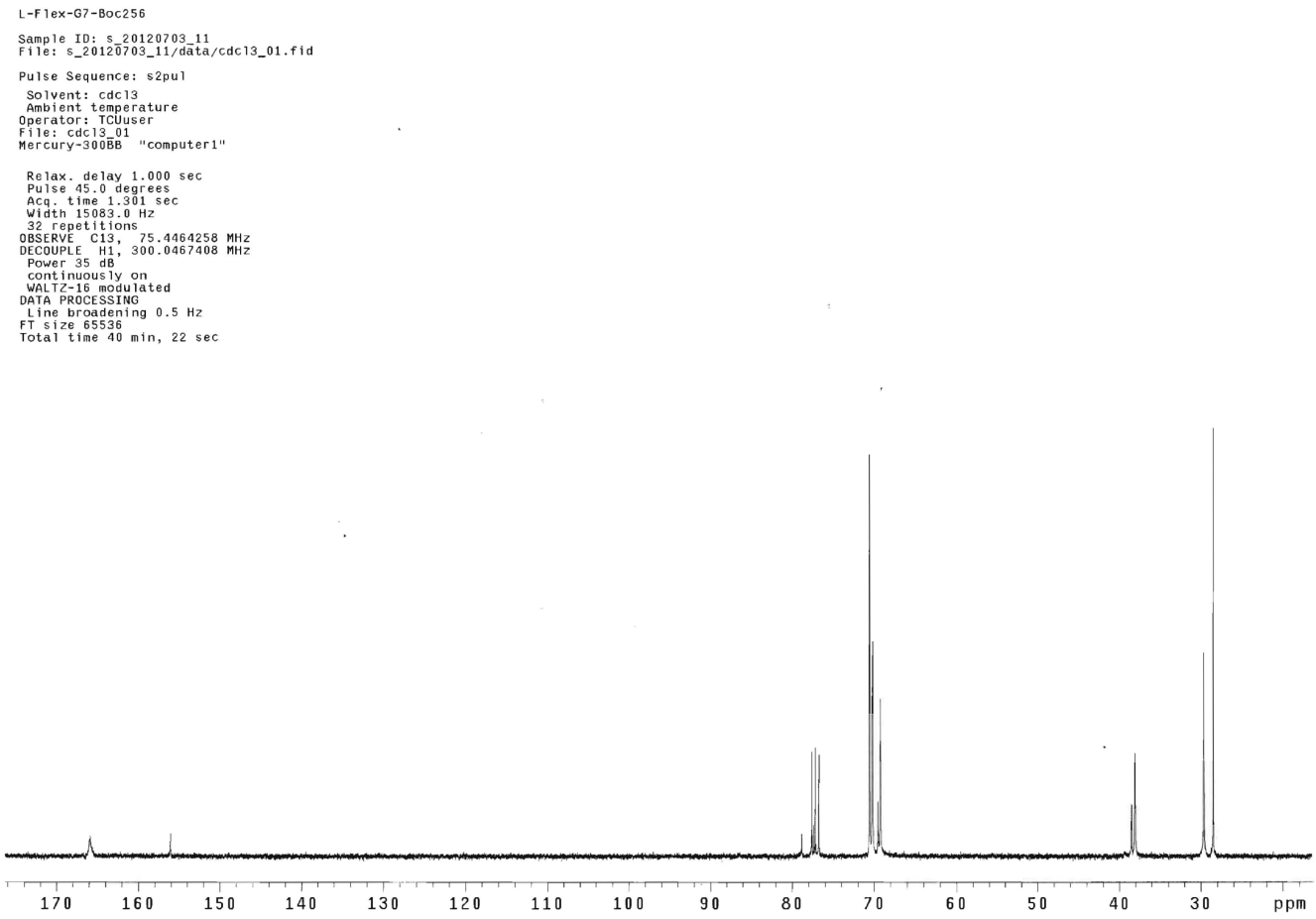


Figure S13. ^{13}C NMR spectrum of **5** (Boc-protected G7, 75 MHz, $CDCl_3$).

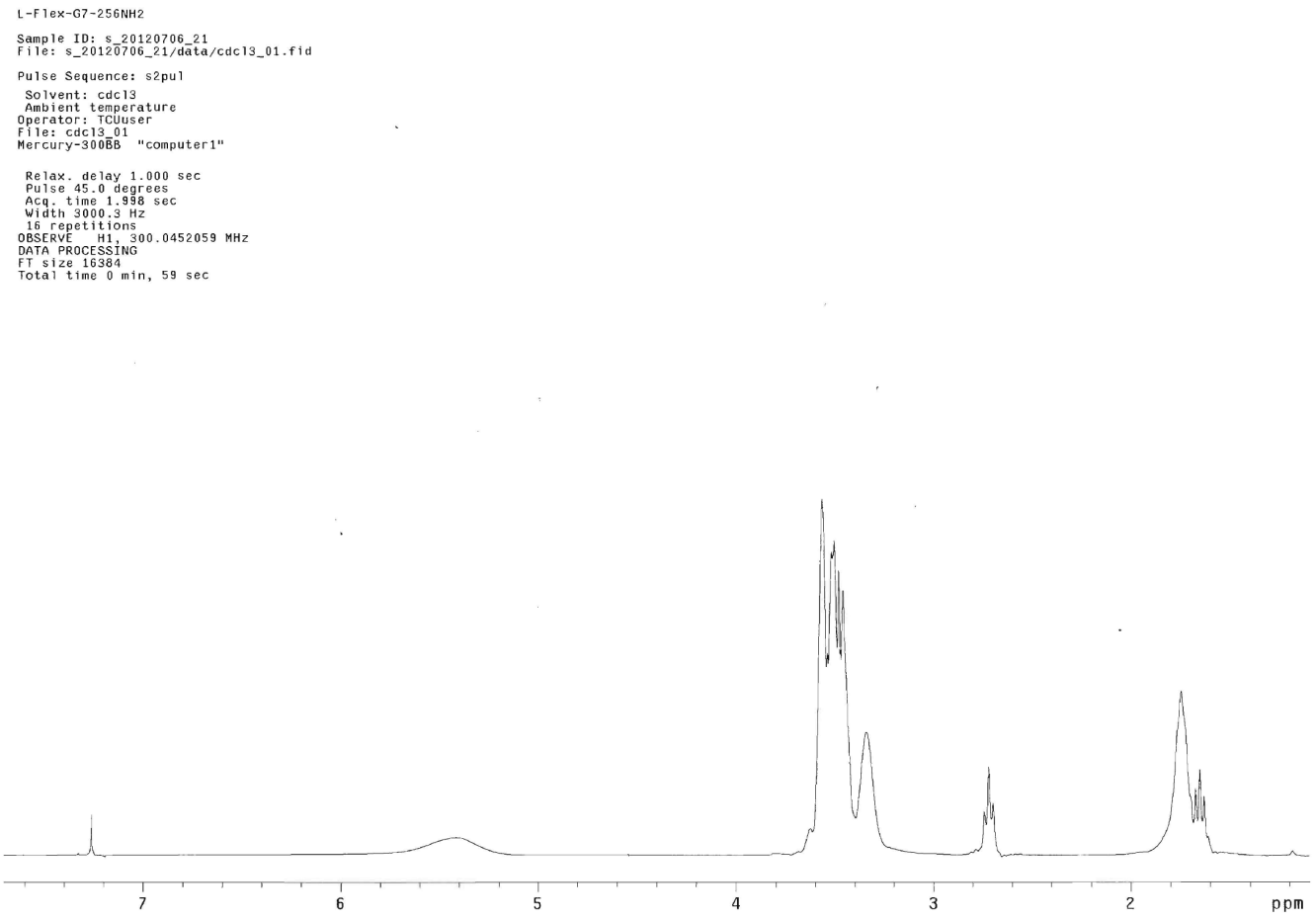


Figure S14. ^{1}H NMR spectrum of **6** (deprotected G7, 300 MHz, $CDCl_3$).

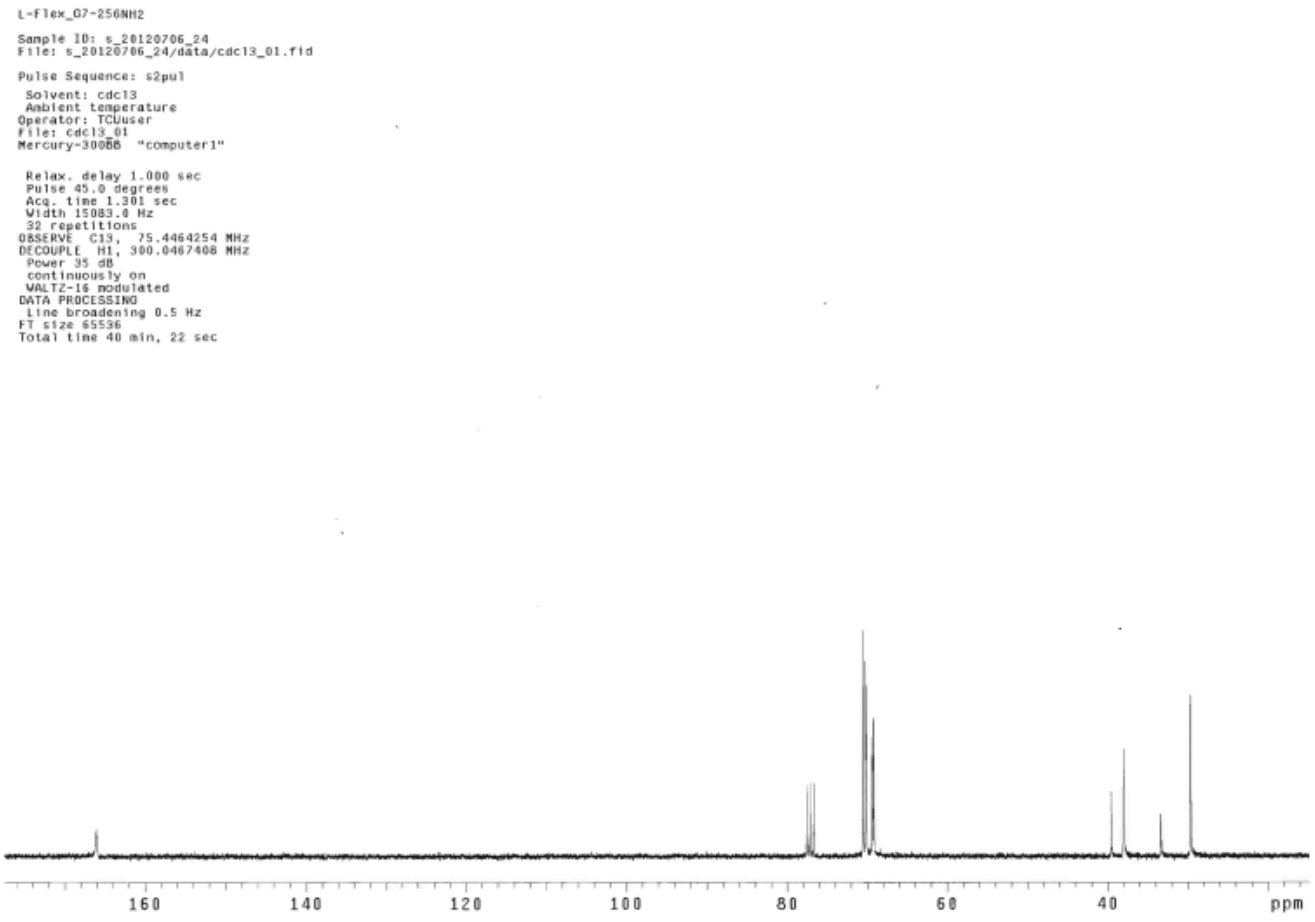


Figure S15. ^{13}C NMR spectrum of **6** (deprotected G7, 75 MHz, $CDCl_3$).

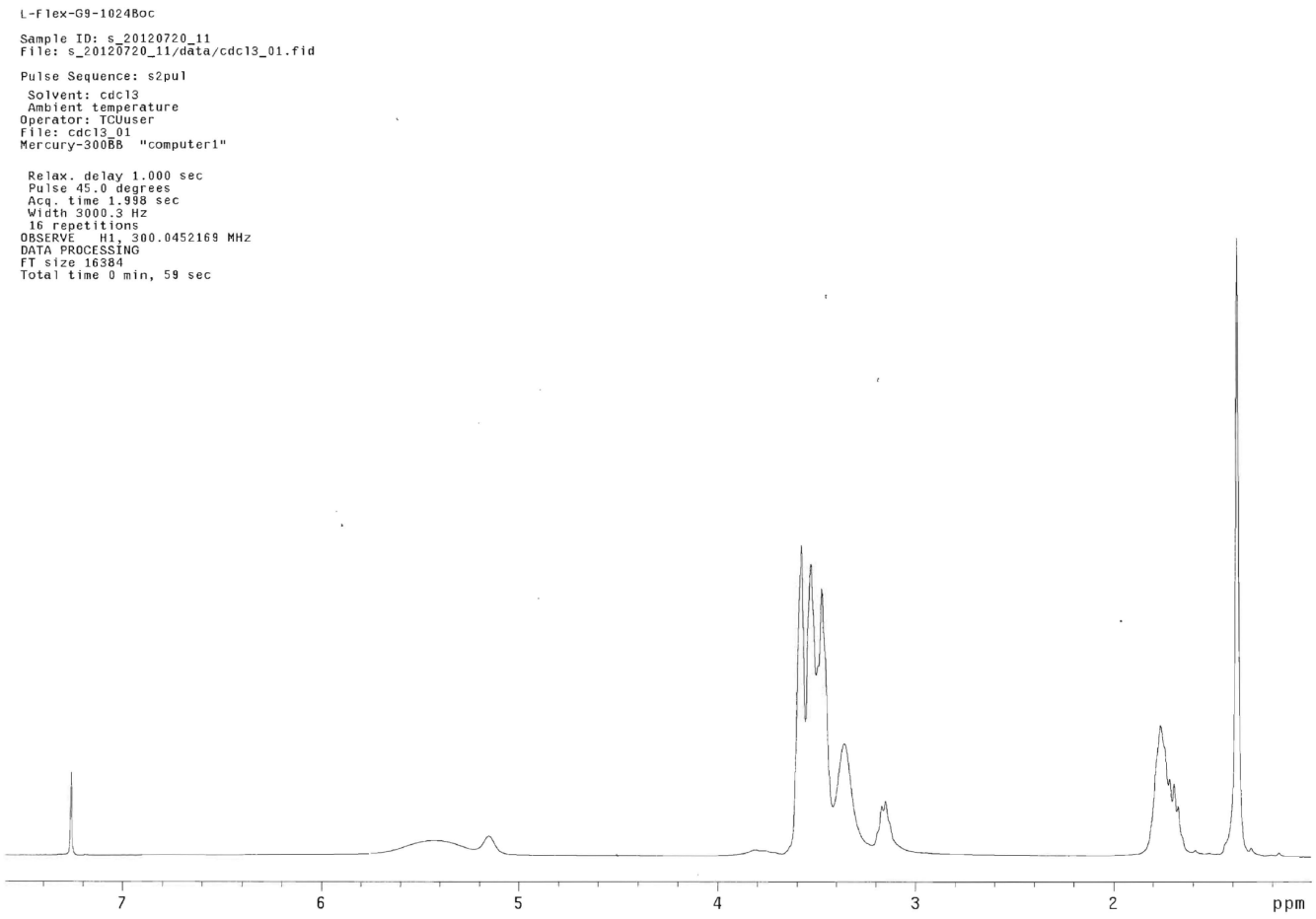


Figure S16. ^{1}H NMR spectrum of **7** (Boc-protected G9, 300 MHz, $CDCl_3$).

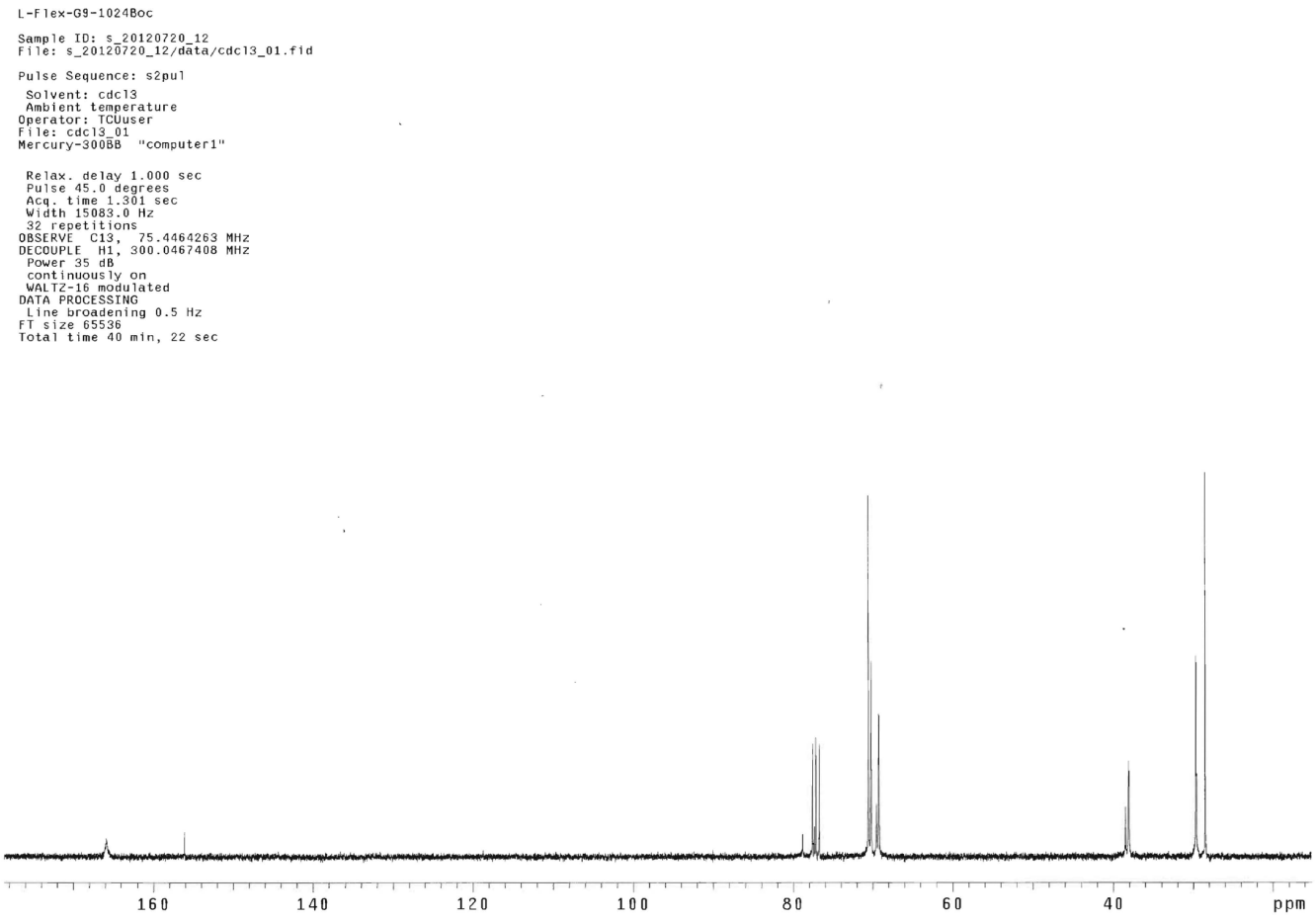


Figure S17. ^{13}C NMR spectrum of **7** (Boc-protected G9, 75 MHz, $CDCl_3$).

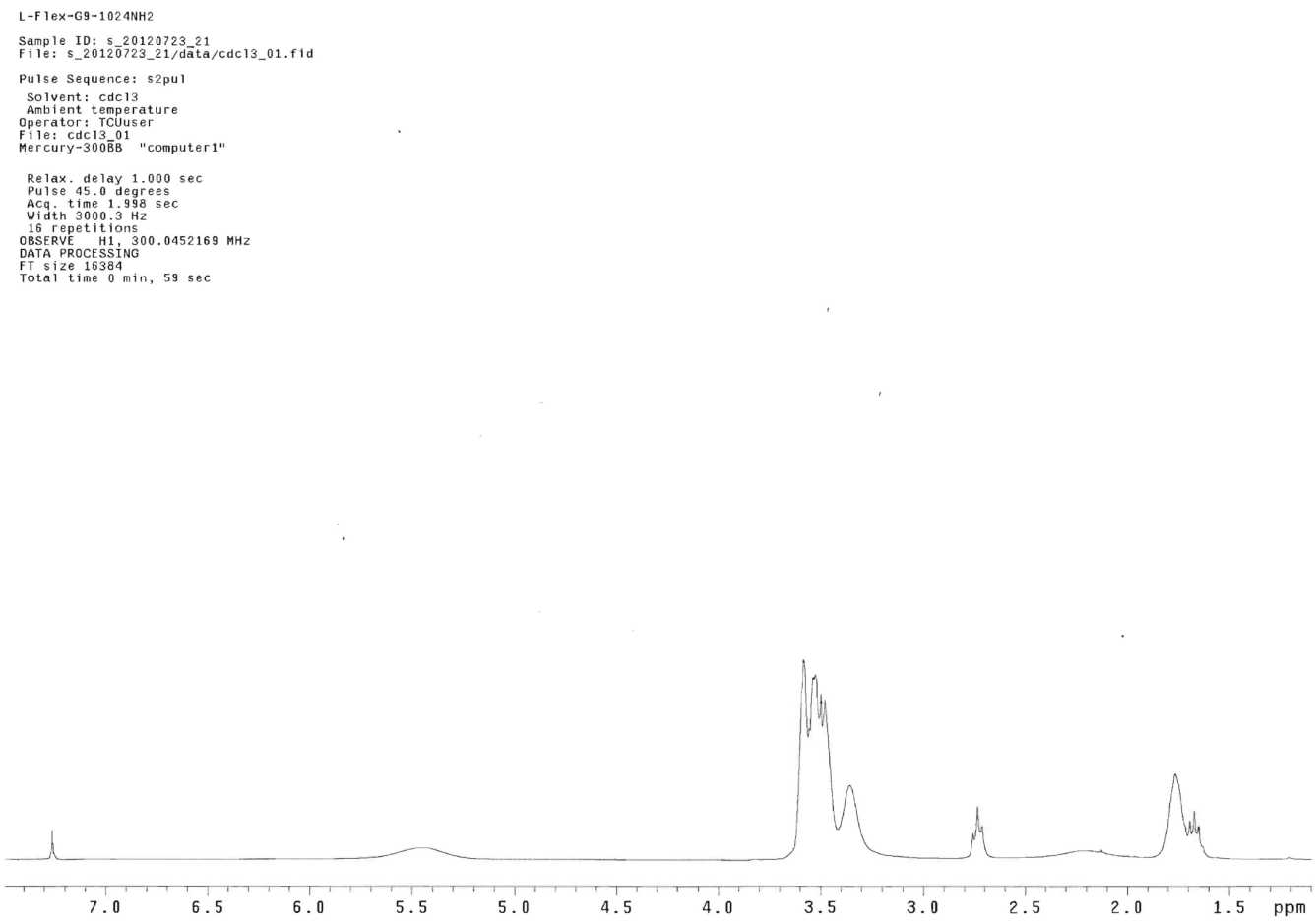


Figure S18. ^{1}H NMR spectrum of **8** (deprotected G9, 300 MHz, $CDCl_3$).

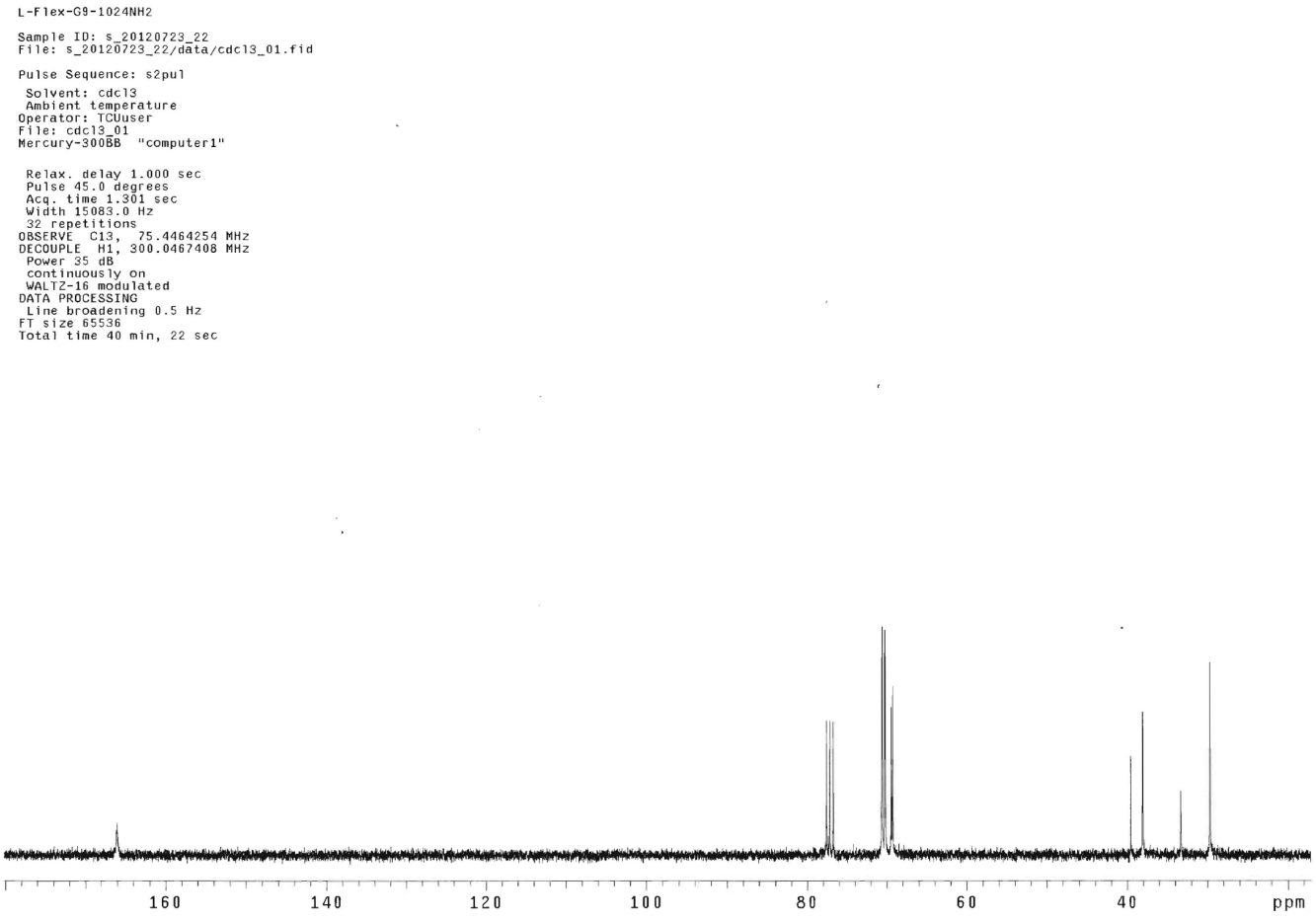


Figure S19. ^{13}C NMR spectrum of **8** (deprotected G9, 75 MHz, $CDCl_3$).

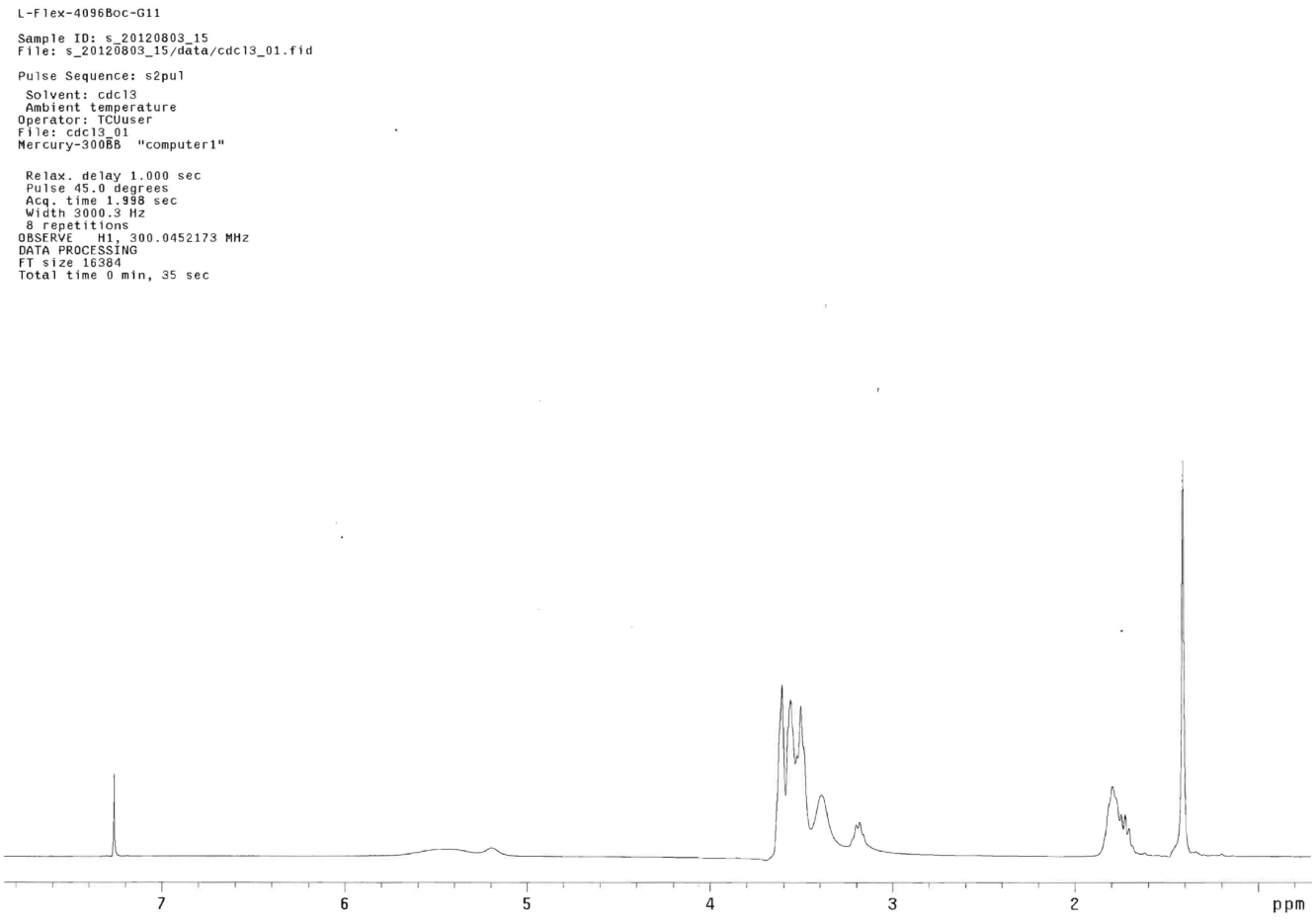


Figure S20. ^{1}H NMR spectrum of **9** (Boc-protected G11, 300 MHz, $CDCl_3$).

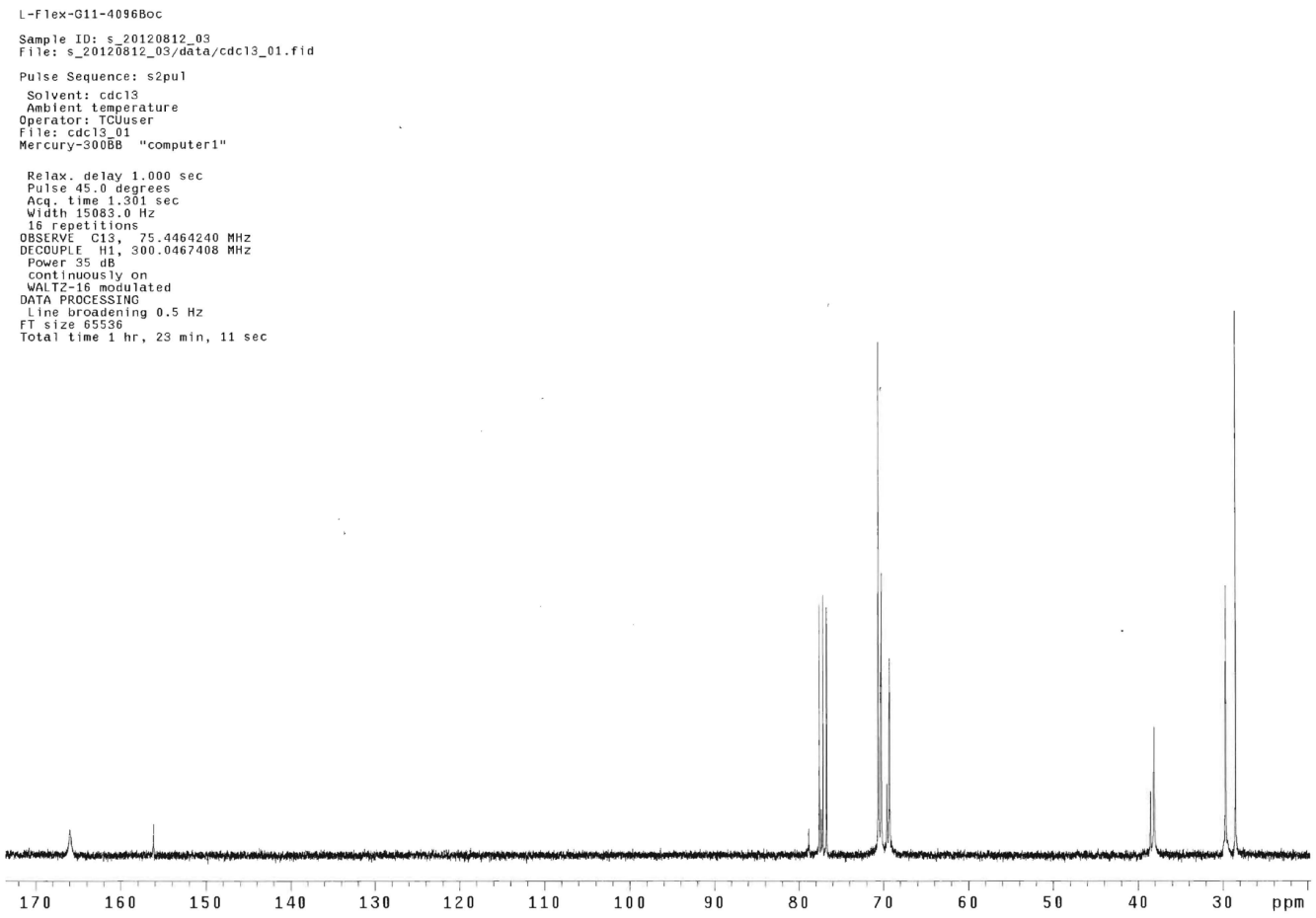


Figure S21. ^{13}C NMR spectrum of **9** (Boc-protected G11, 75 MHz, $CDCl_3$).

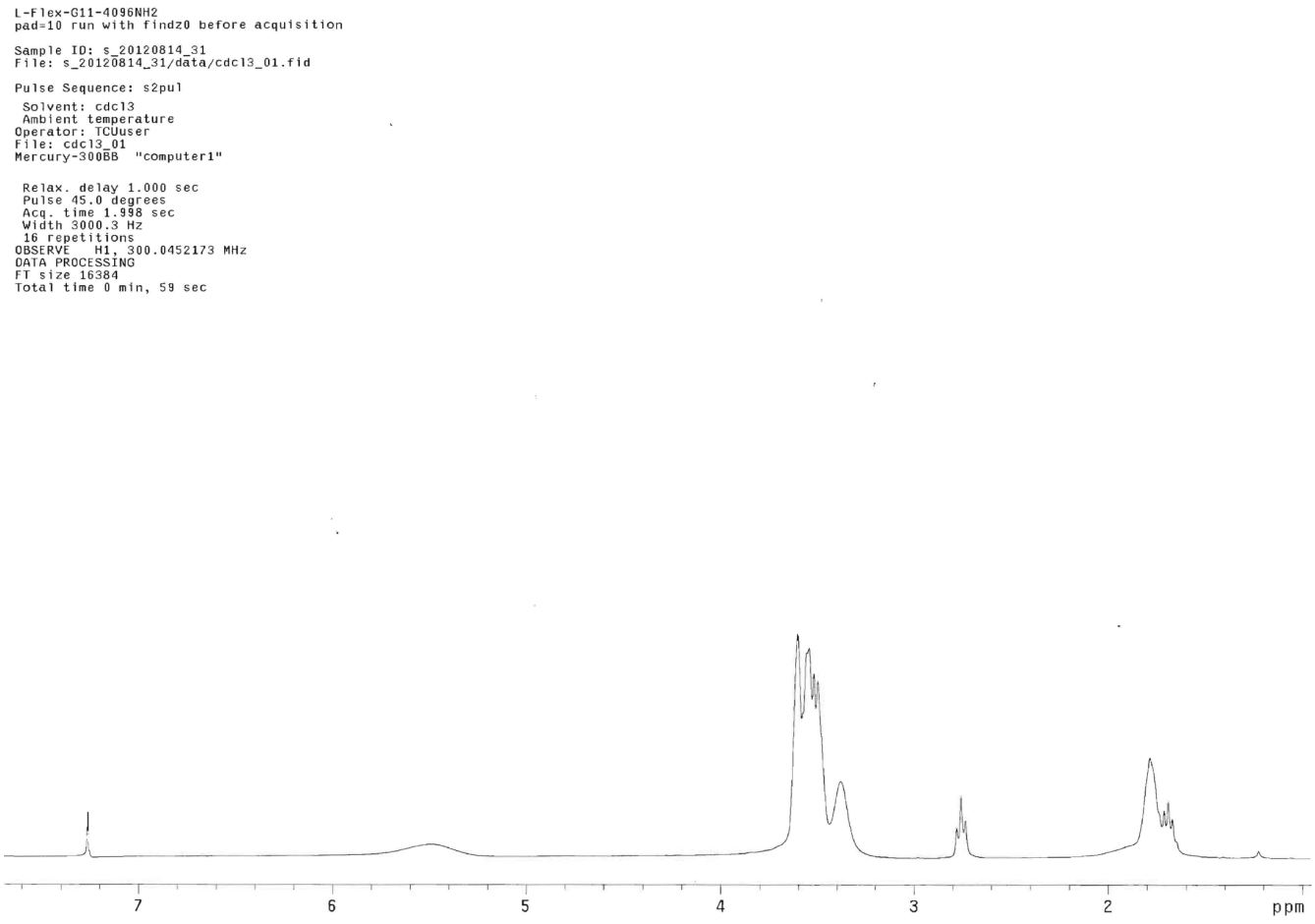


Figure S22. ^{1}H NMR spectrum of **10** (deprotected G11, 300 MHz, $CDCl_3$).

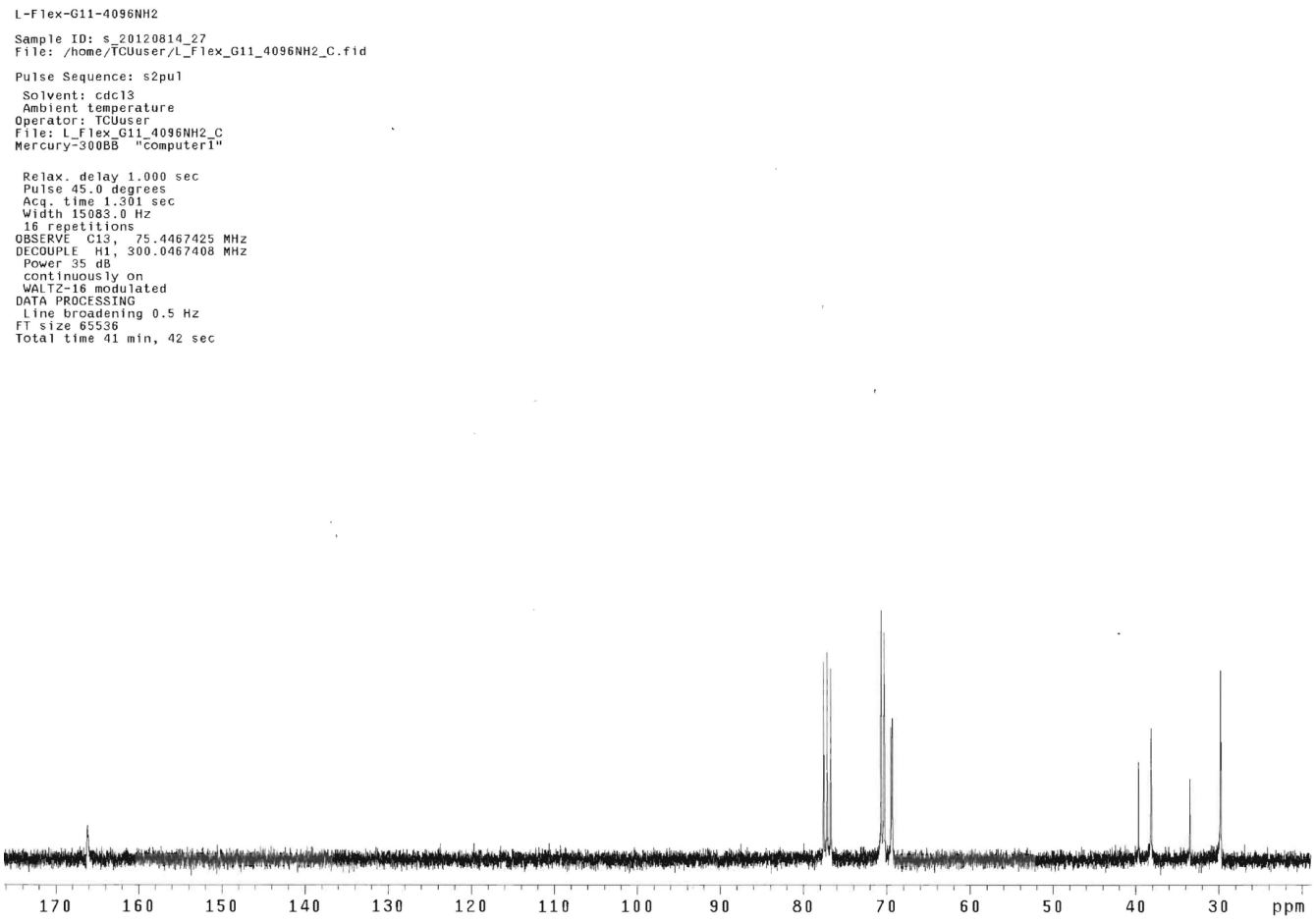


Figure S23. ^{13}C NMR spectrum of **10** (deprotected G11, 75 MHz, $CDCl_3$).

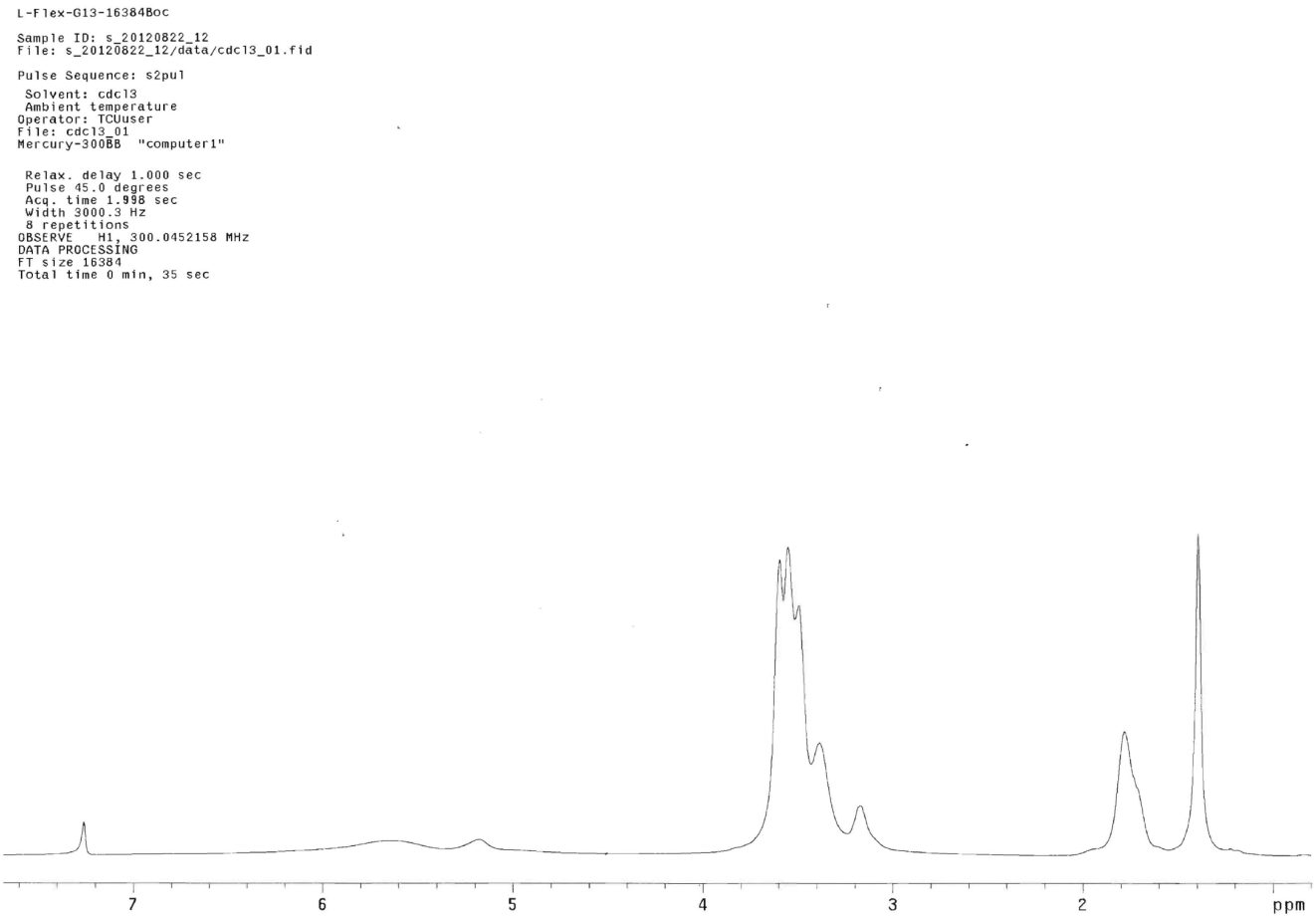


Figure S24. ^{1}H NMR spectrum of **11** (Boc-protected G13, 300 MHz, $CDCl_3$).

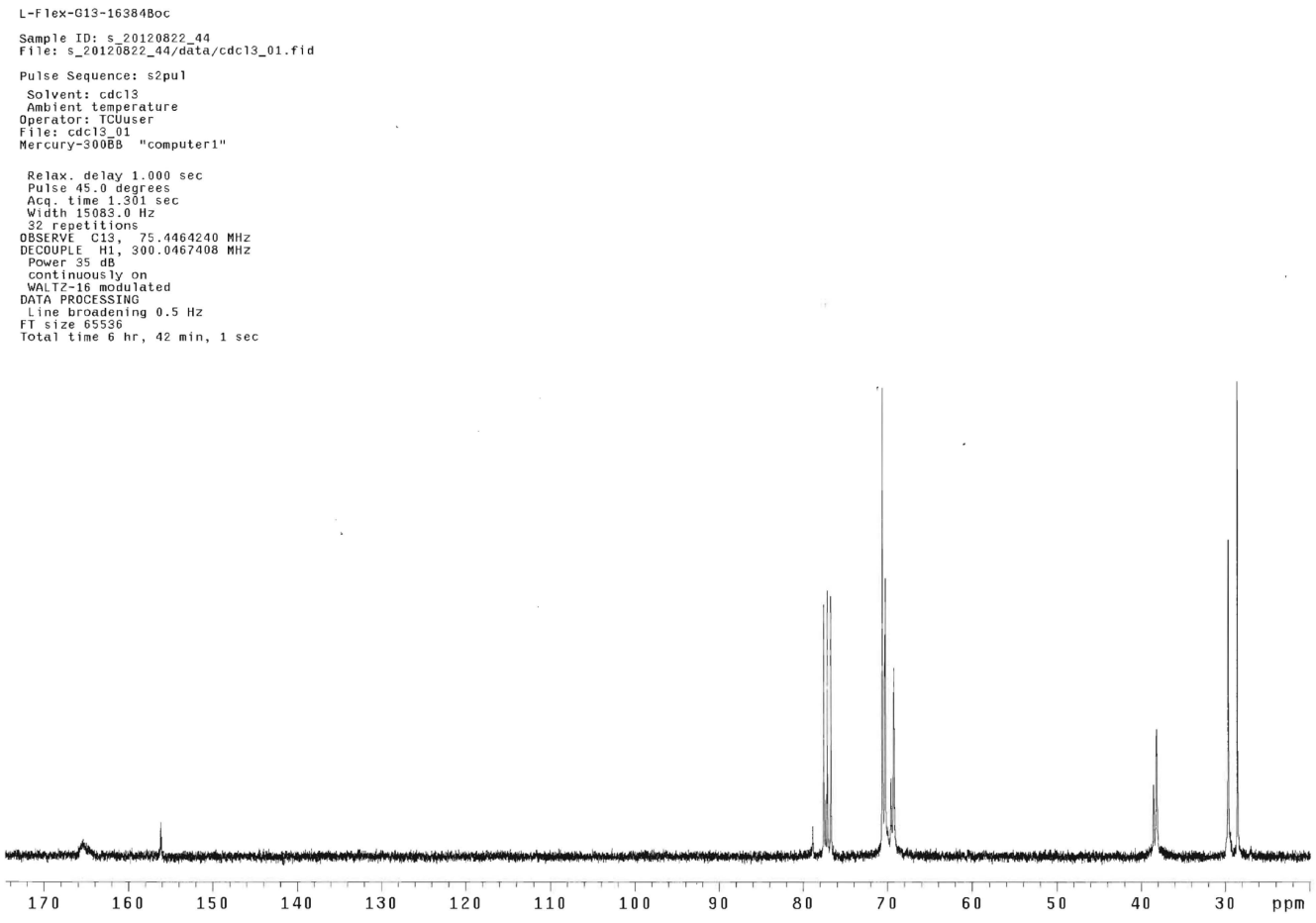


Figure S25. ^{13}C NMR spectrum of **11** (Boc-protected G13, 75 MHz, $CDCl_3$).

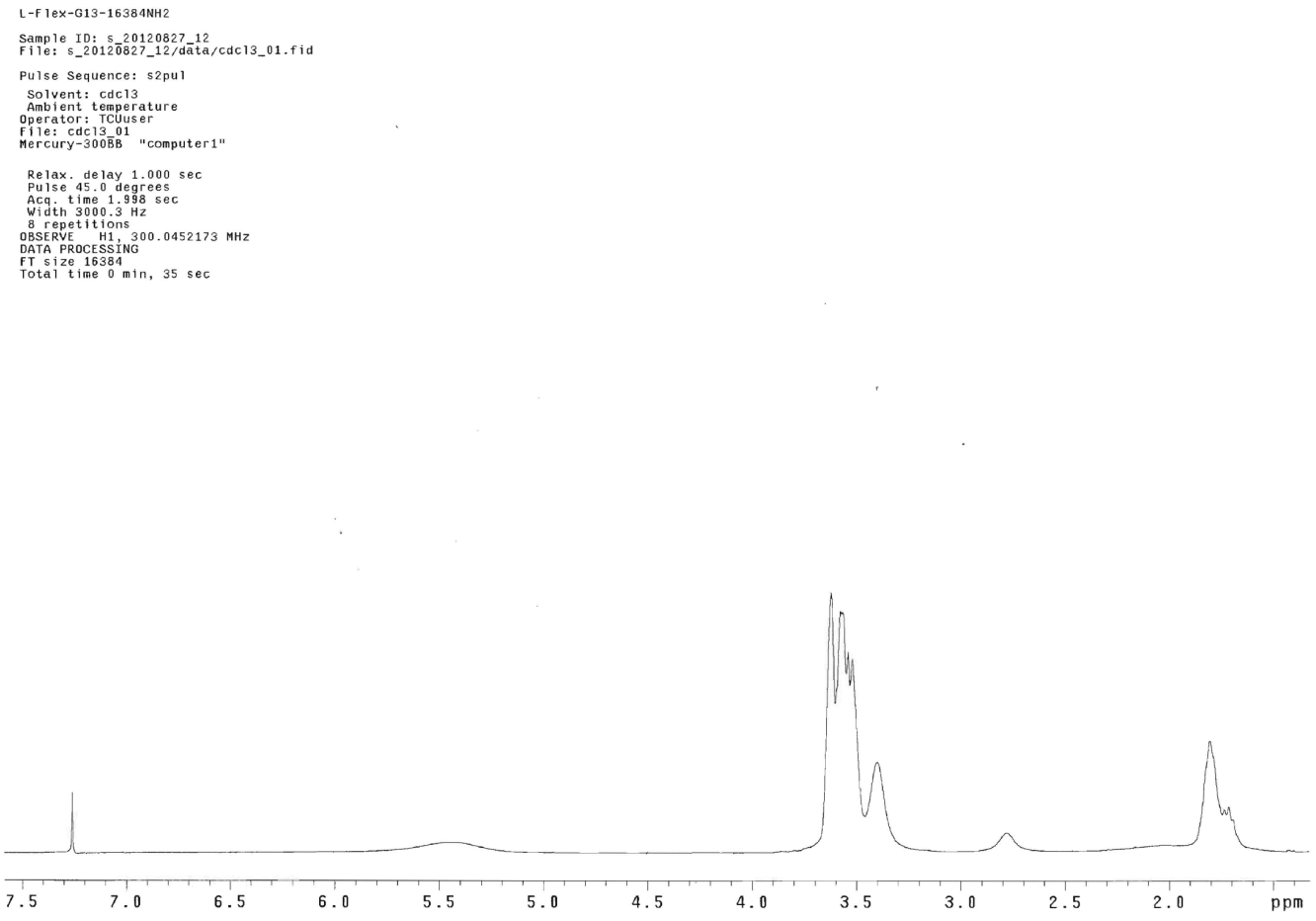


Figure S26. ^{1}H NMR spectrum of **12** (deprotected G13, 300 MHz, $CDCl_3$).

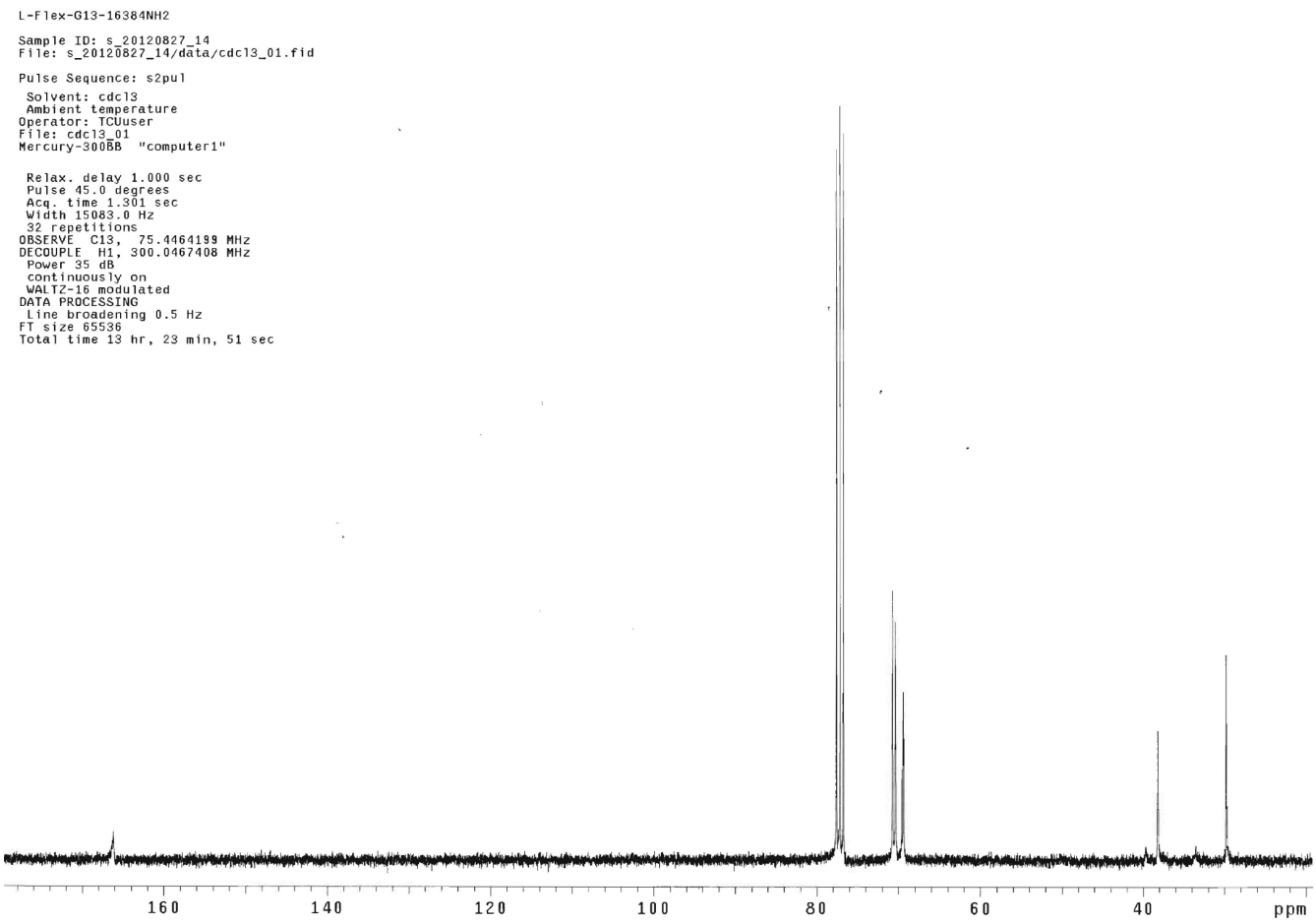


Figure S27. ^{13}C NMR spectrum of **12** (deprotected G13, 75 MHz, $CDCl_3$).

Sample Name	Bis(mbocTODA)triazin	**Position**	P1-A1	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	-1	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	All Ions Missed
Data Filename	Bis(mbocTODA)triazin	**ACQ Method**		**Comment**		**Acquired Time**	3/8/2012 3:08:31 PM

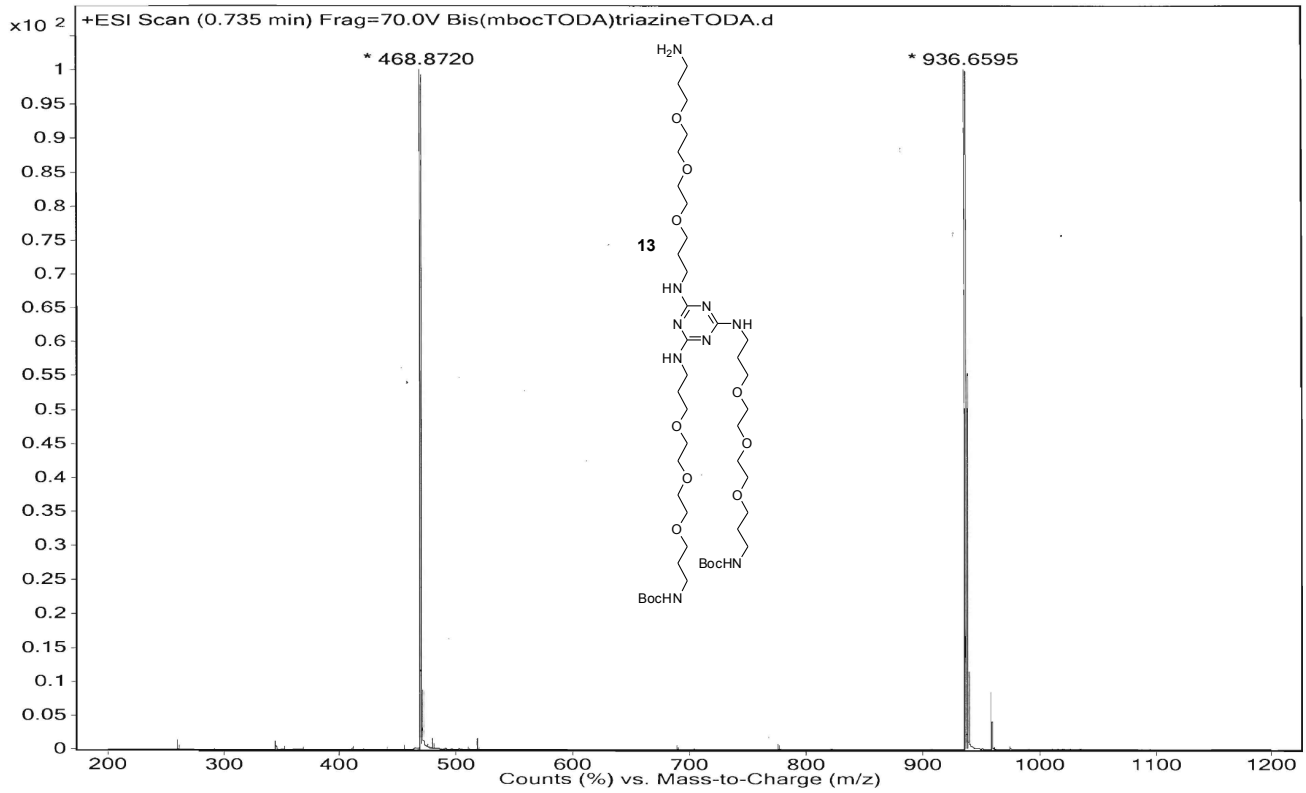


Figure S28. ESI-TOF mass spectrum of **13**.

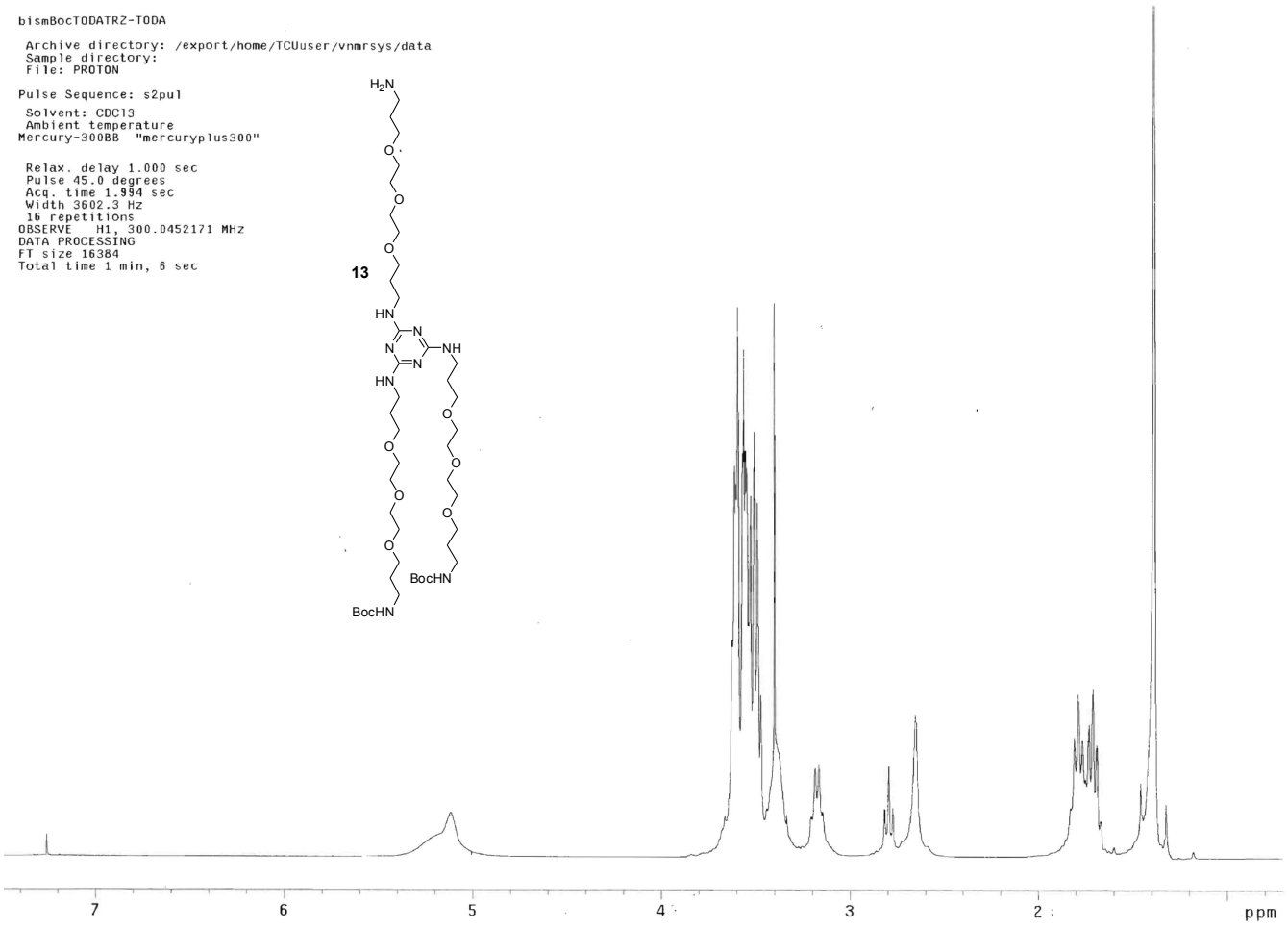


Figure S29. ^{1}H NMR spectrum of **13** (300 MHz, $CDCl_3$).

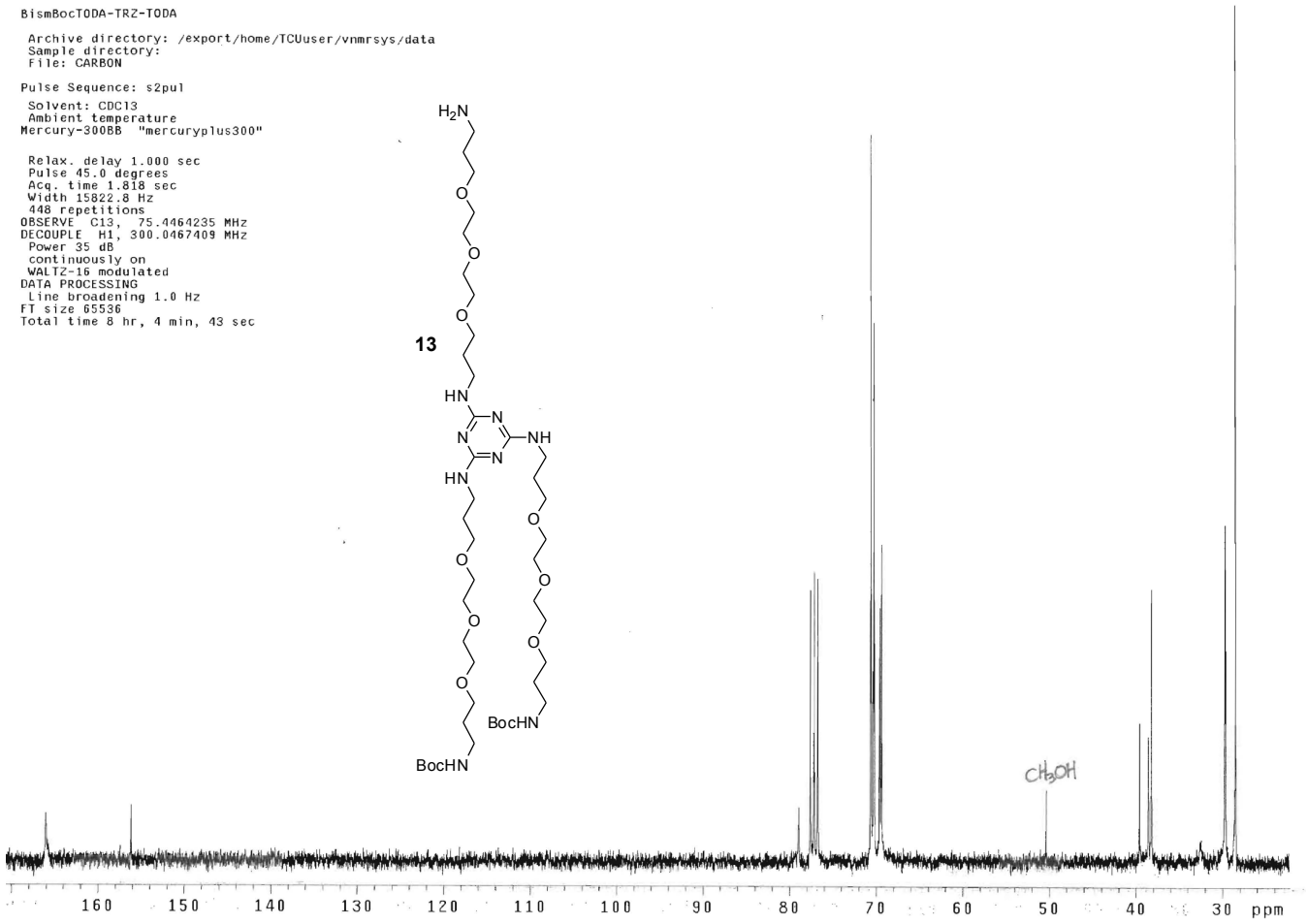


Figure S30. ^{13}C NMR spectrum of **13** (75 MHz, $CDCl_3$).

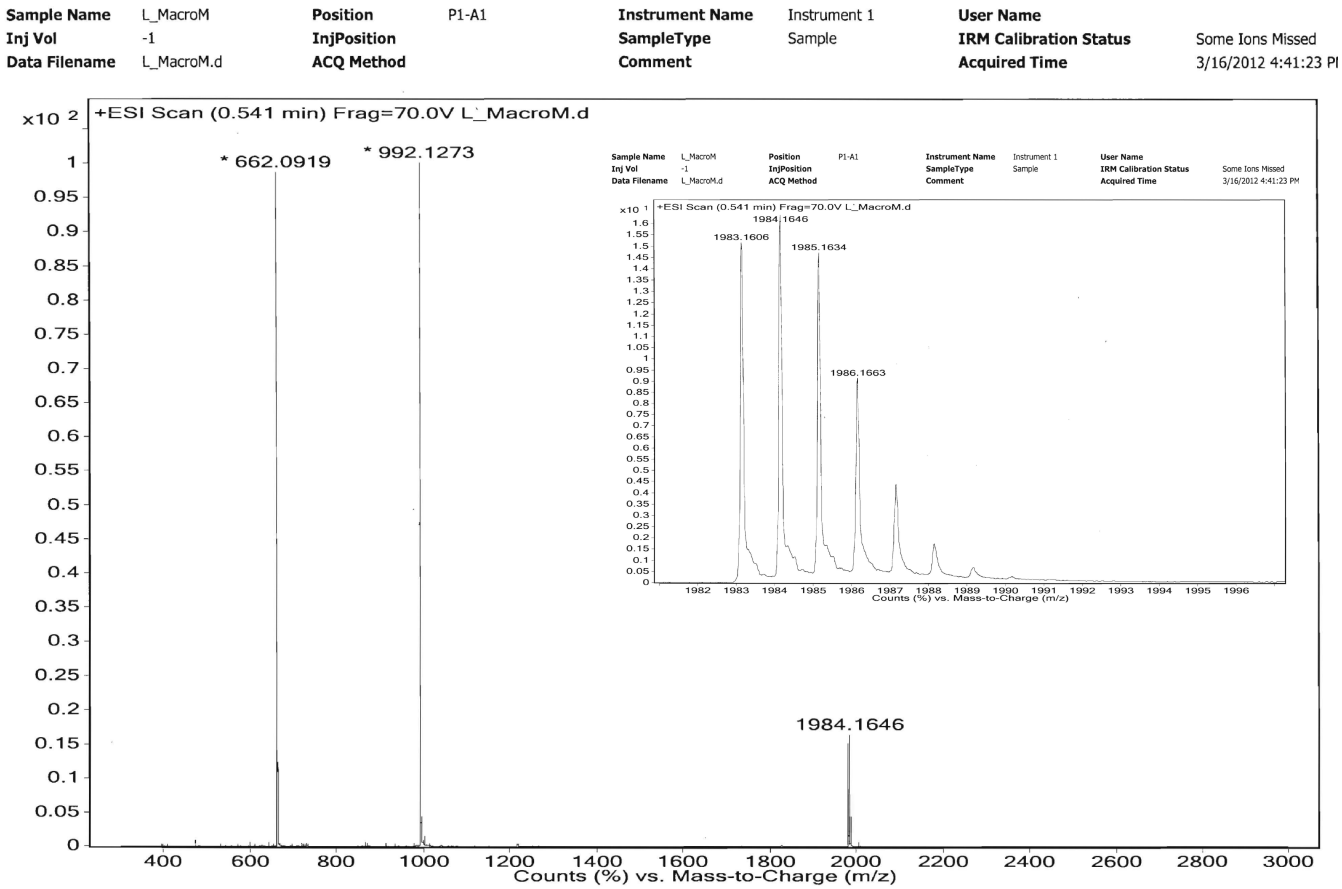
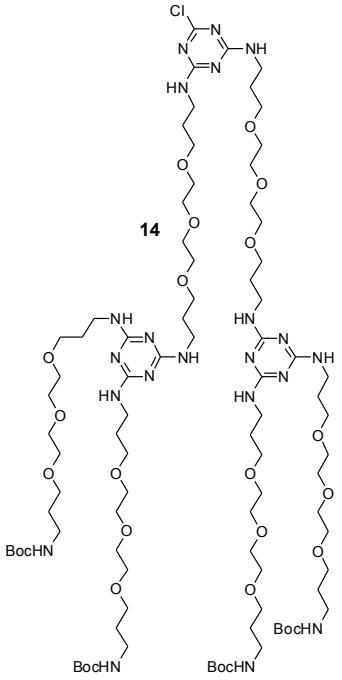


Figure S31. ESI-TOF mass spectrum of **14** (macromonomer)**.**



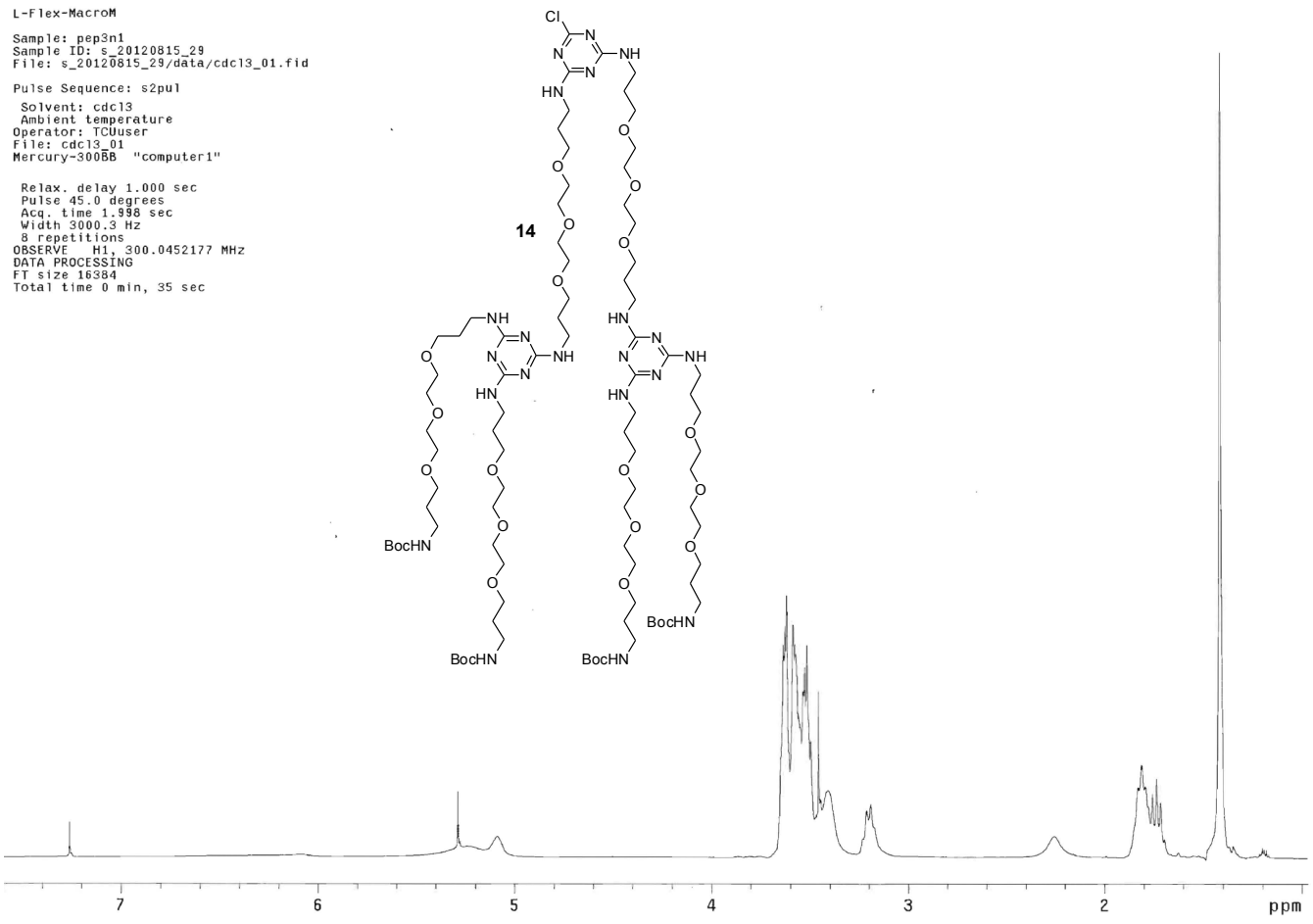


Figure S32. ^{1}H NMR spectrum of **14** (macromonomer, 300 MHz, $CDCl_3$).

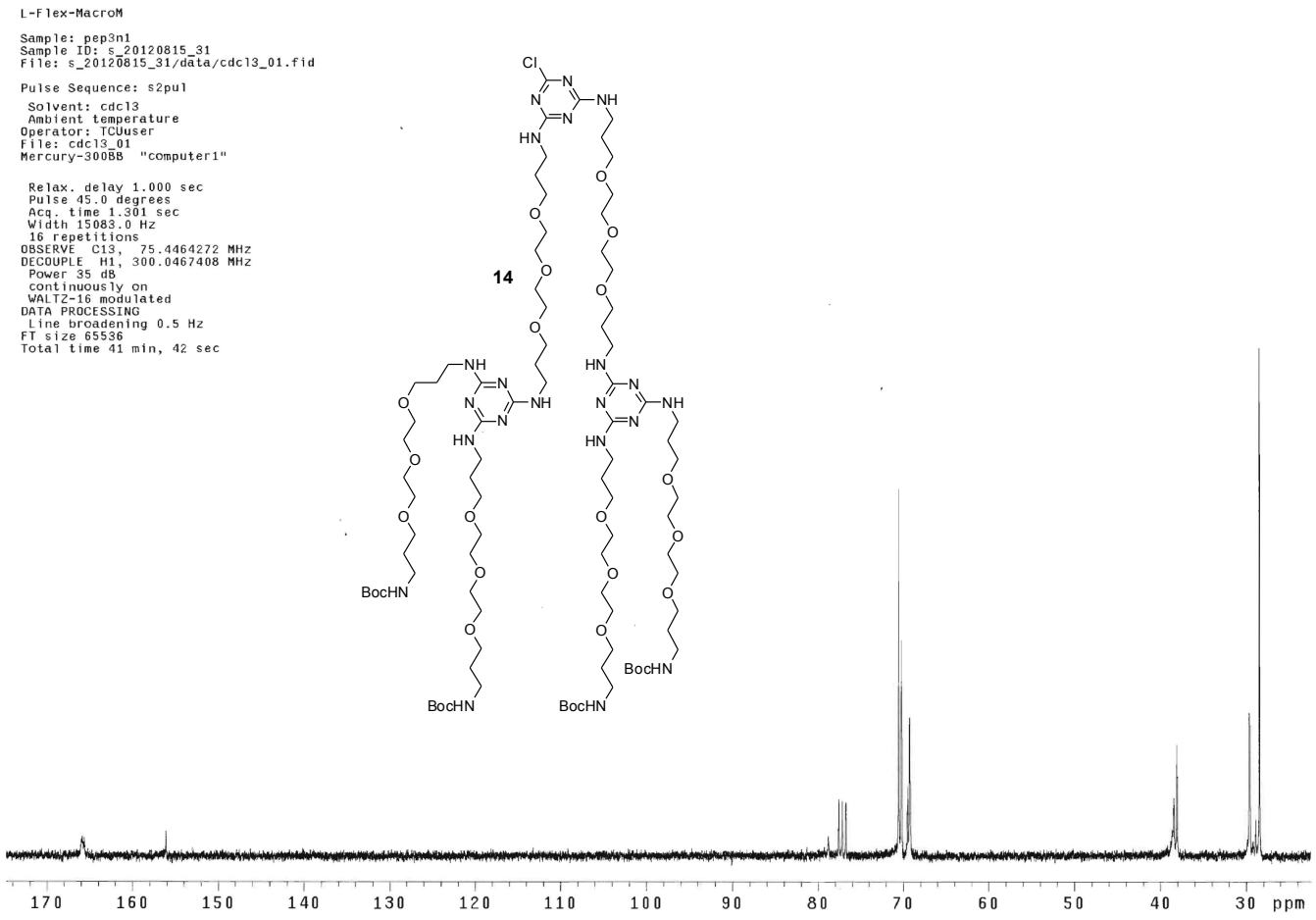


Figure S33. ^{13}C NMR spectrum of **14** (macromonomer, 75 MHz, $CDCl_3$).

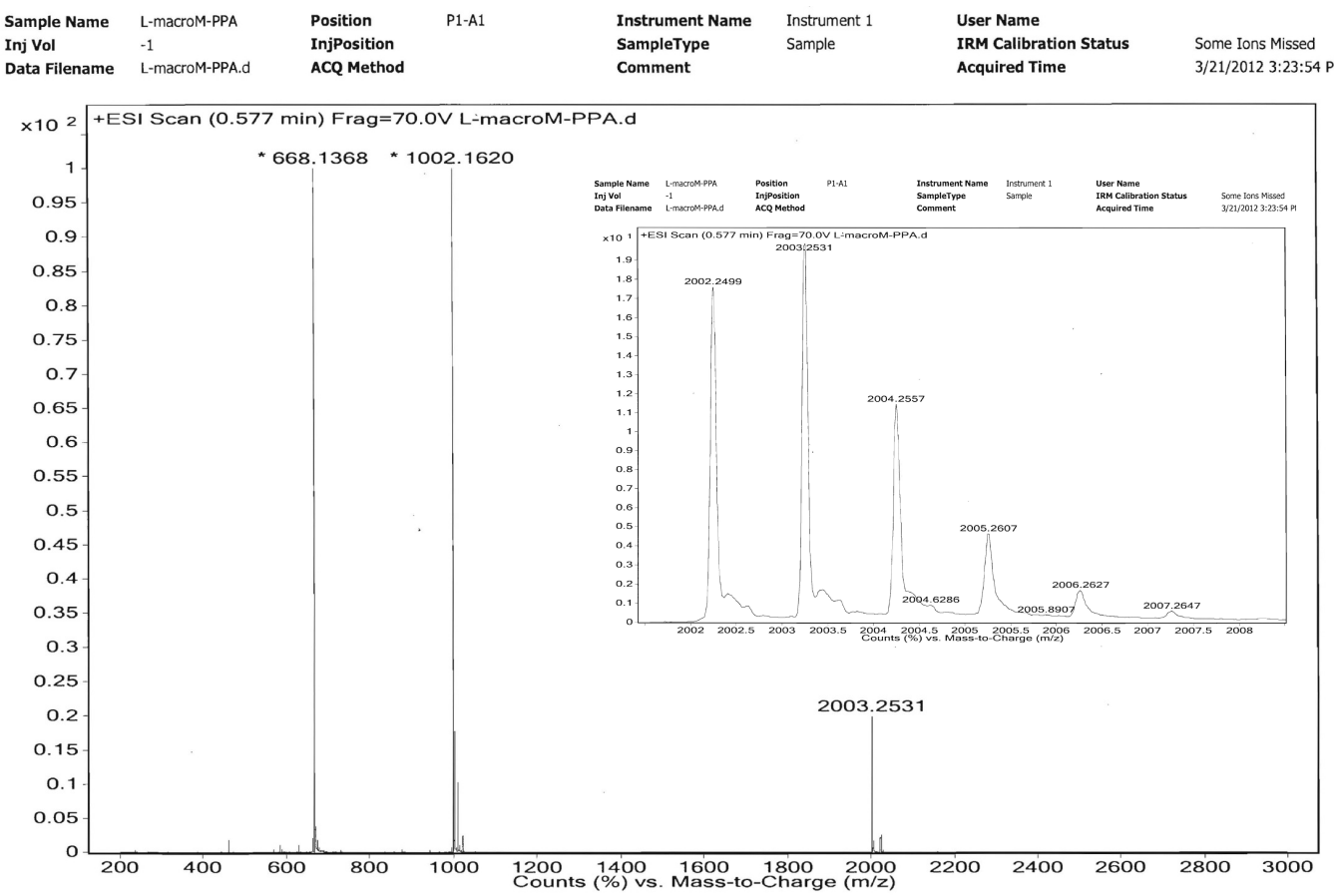
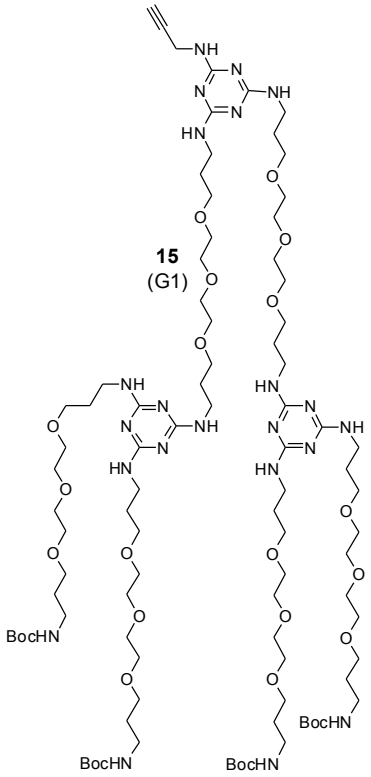


Figure S34. ESI-TOF mass spectrum of **15** (Boc-protected G1).



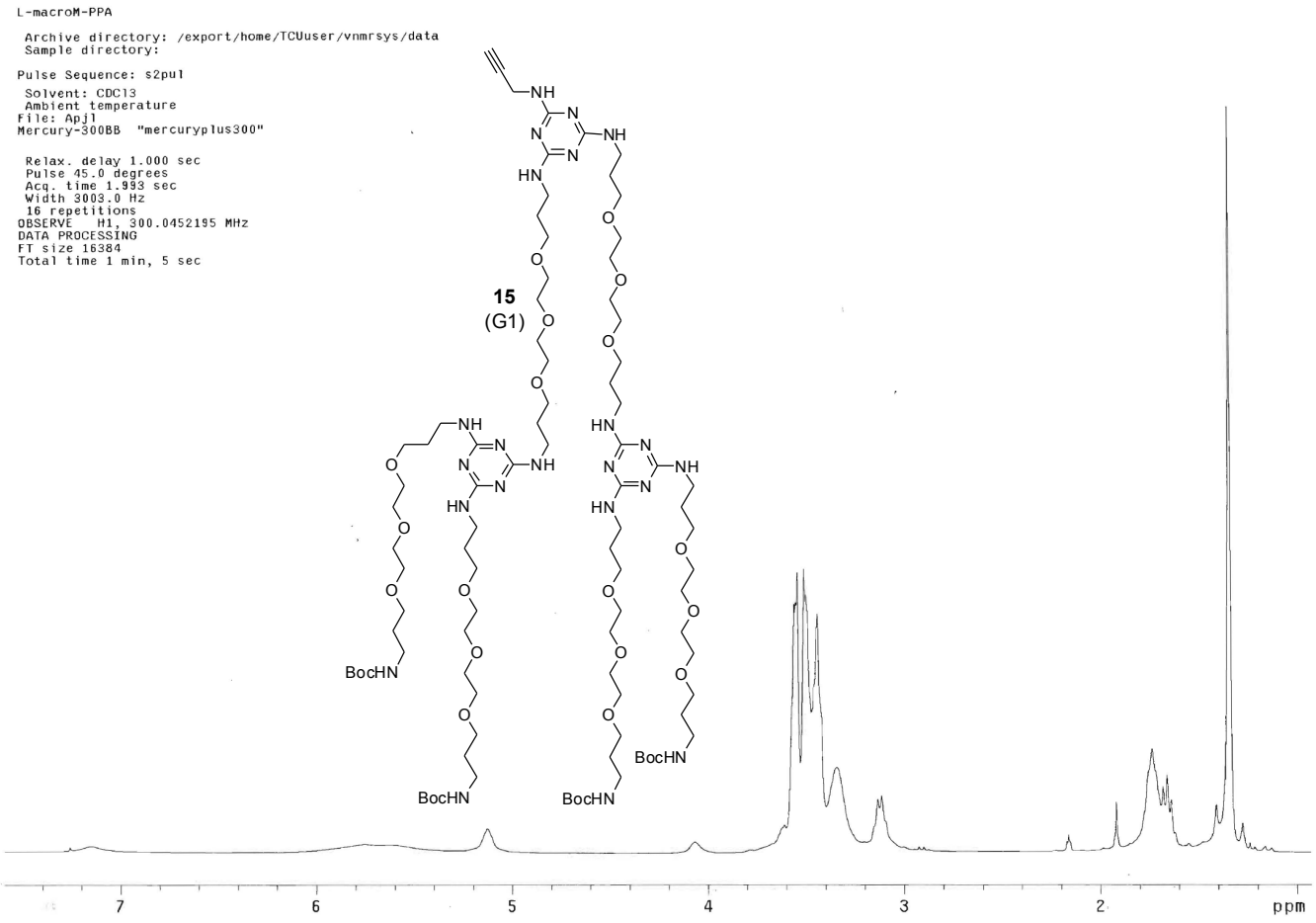


Figure S35. ^{1}H NMR spectrum of **15** (Boc-protected G1, 300 MHz, $CDCl_3$).

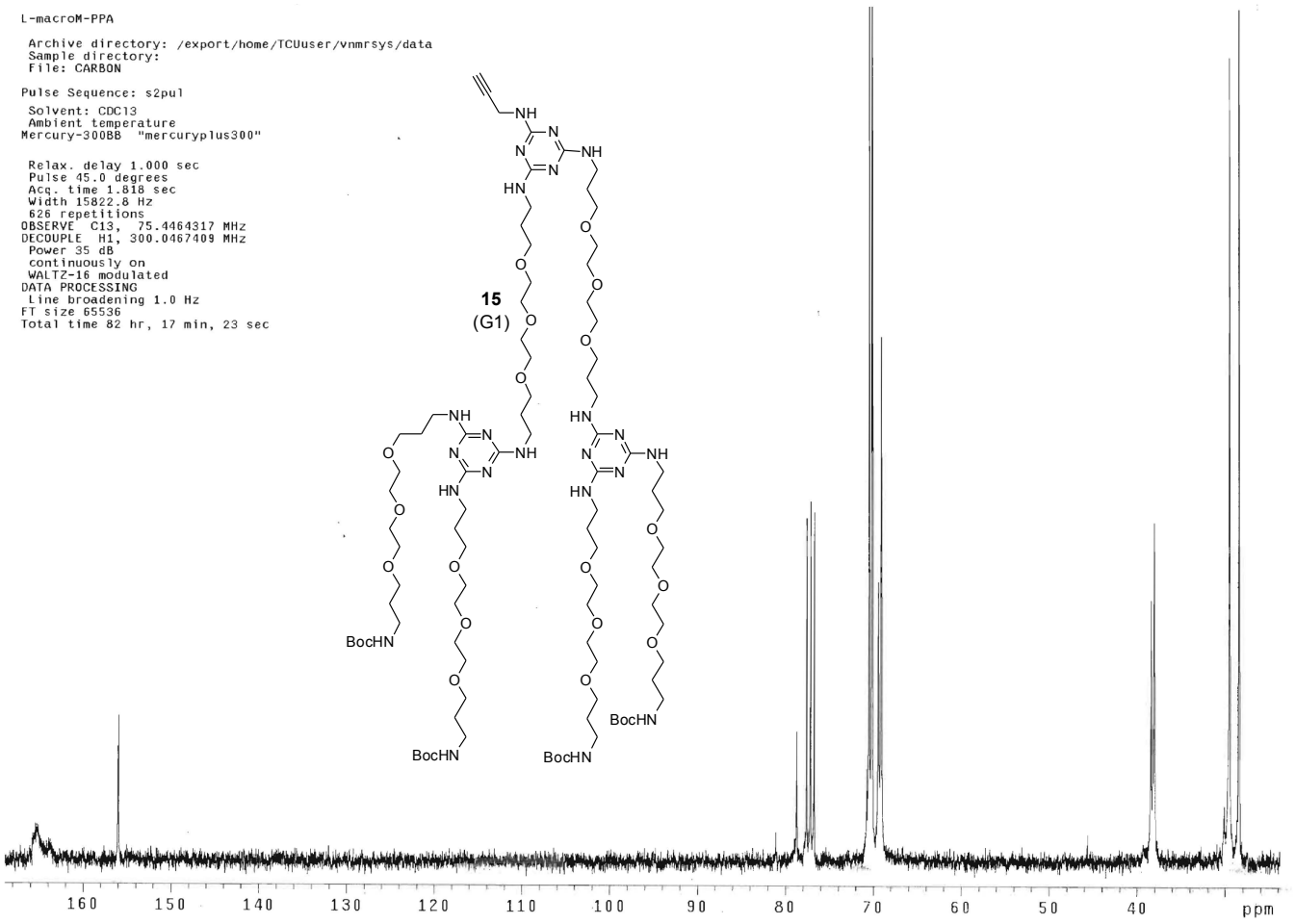


Figure S36. ^{13}C NMR spectrum of **15** (Boc-protected G1, 75 MHz, $CDCl_3$).

Sample Name	L-macroM-PPA-Dep	**Position**	P1-A1	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	-1	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Some Ions Missed
Data Filename	L-macroM-PPA-Dep.d	**ACQ Method**		**Comment**		**Acquired Time**	3/23/2012 10:07:42 A

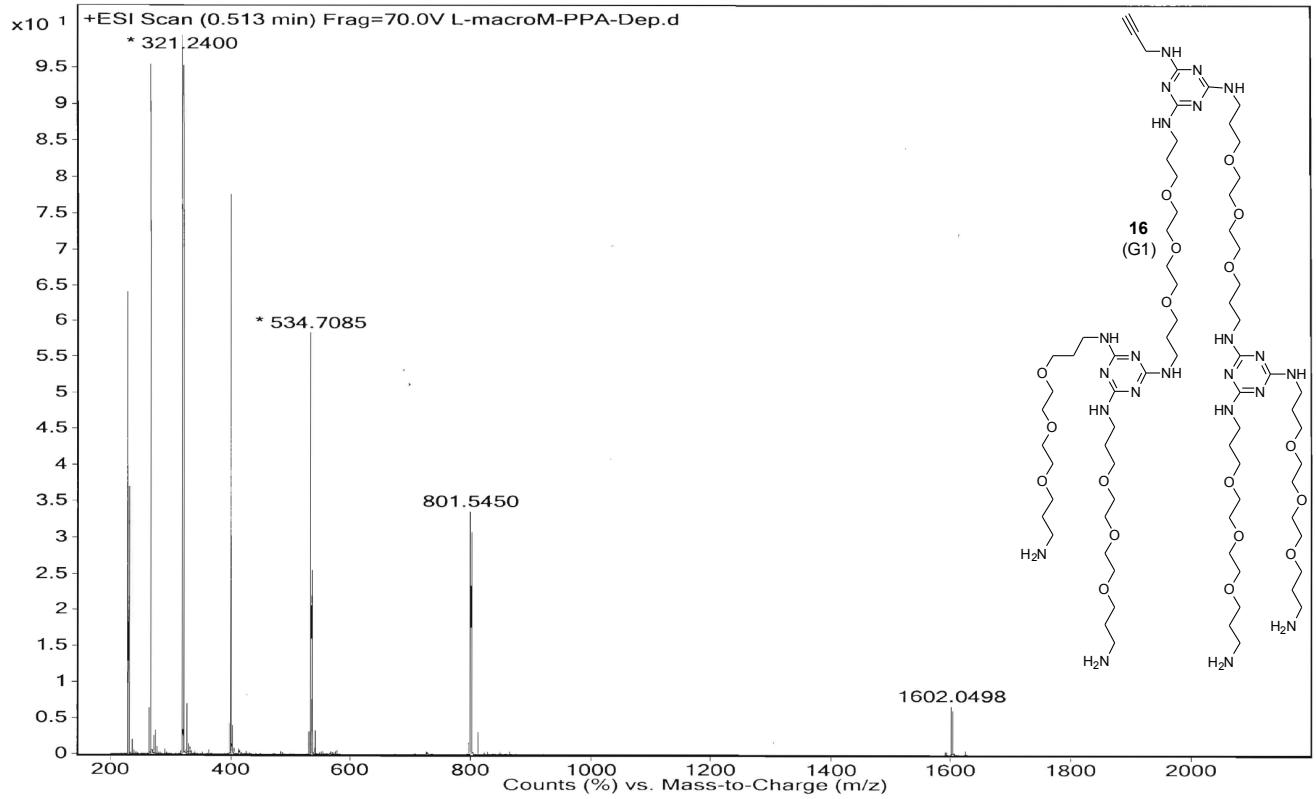


Figure S37. ESI-TOF mass spectrum of **16** (deprotected G1)**.**

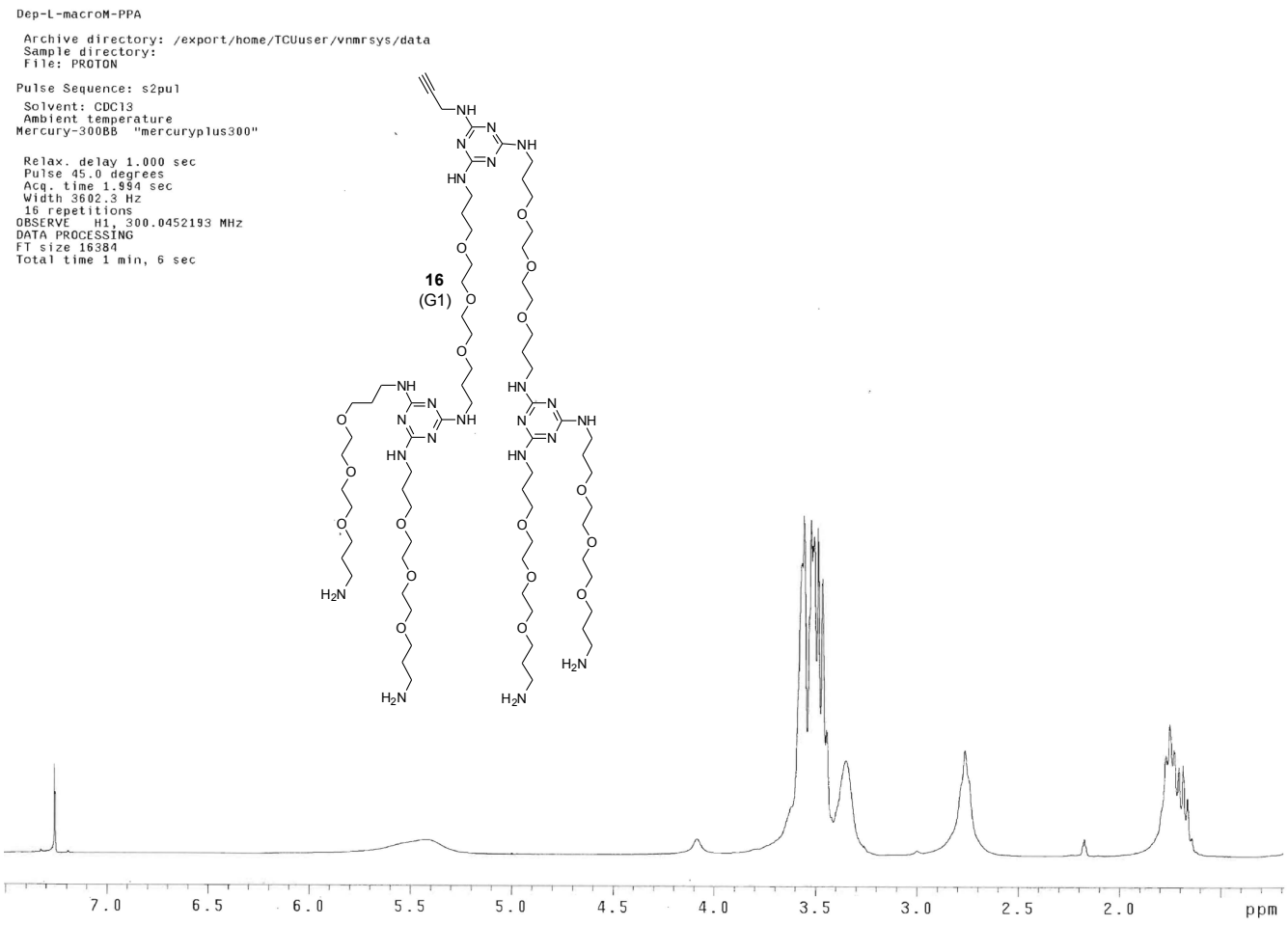


Figure S38. ^{1}H NMR spectrum of **16** (deprotected G1, 300 MHz, $CDCl_3$).

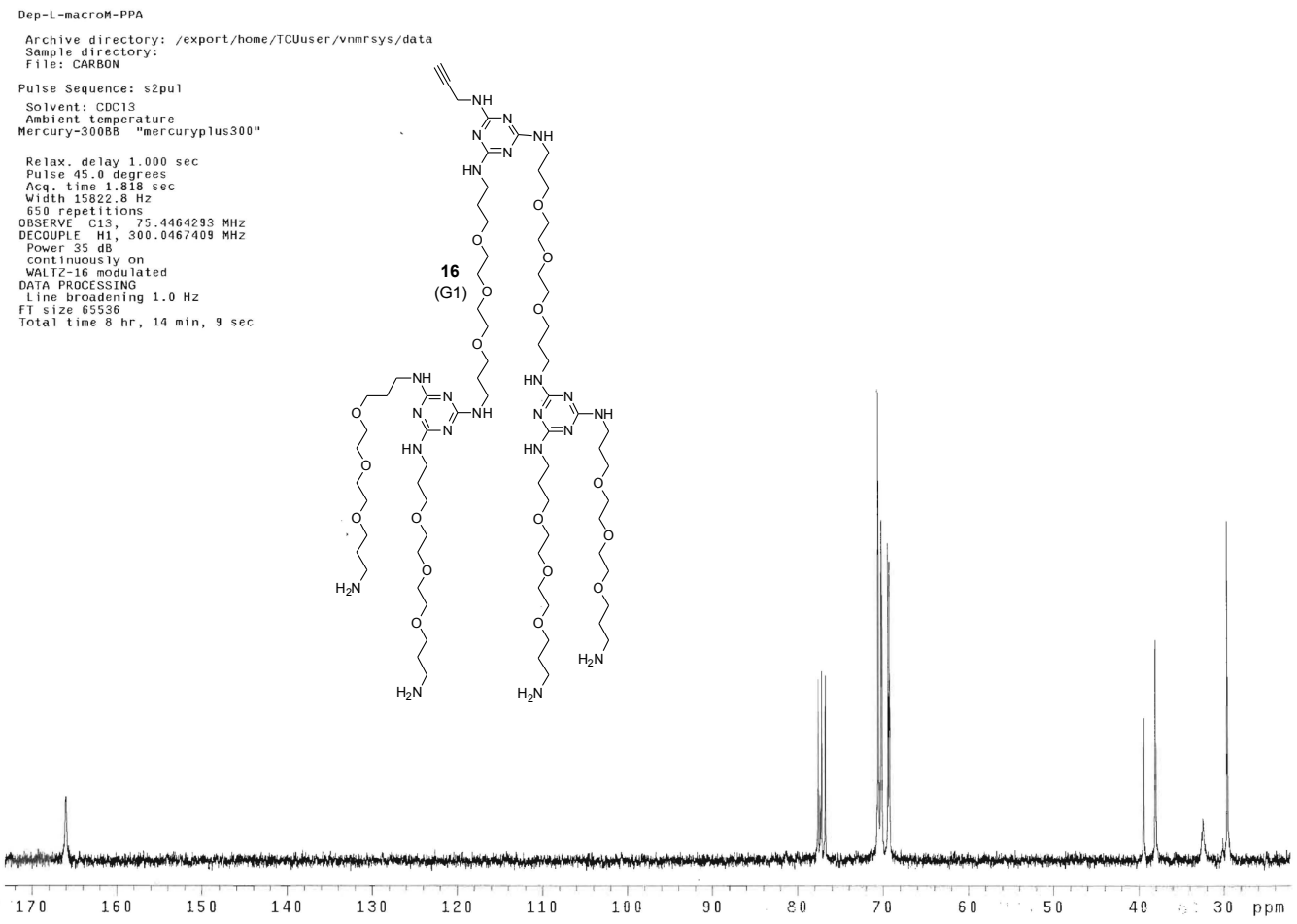


Figure S39. ^{13}C NMR spectrum of **16** (deprotected G1, 75 MHz, $CDCl_3$).

NMR Analysis

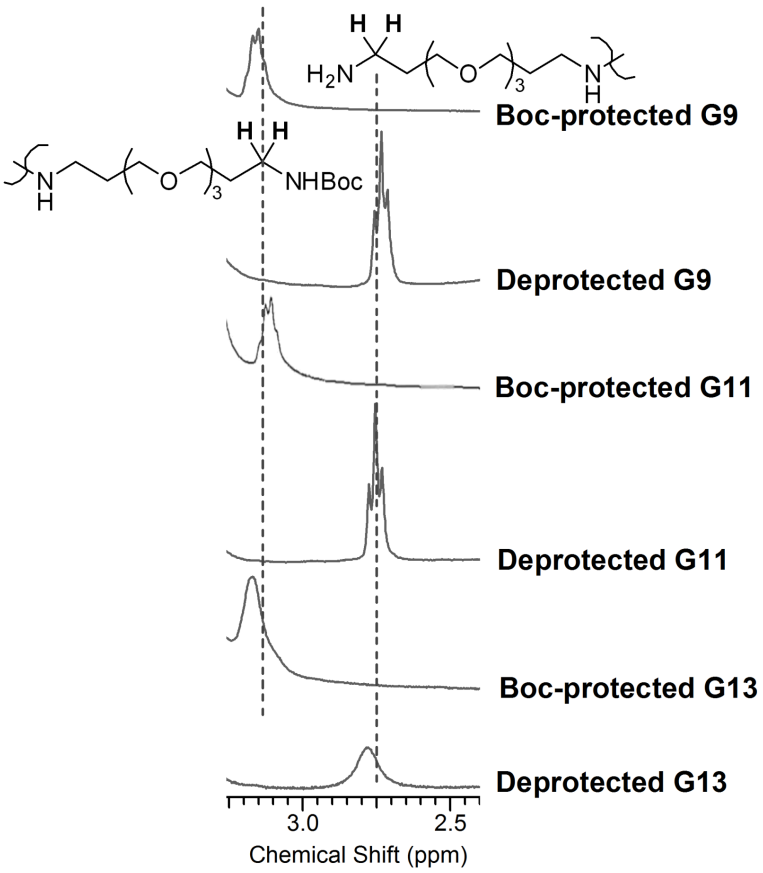


Figure S40. ^{1}H NMR Spectra of the large generation dendrimers (G9-G13) display the finger print region for monitoring the reiterative addition and deprotection: The vicinal proton signals of NHBoc groups appear around at 3.2 ppm, while the vicinal proton signals of NH_2 groups appear around at 2.75 ppm.

HPLC Analysis

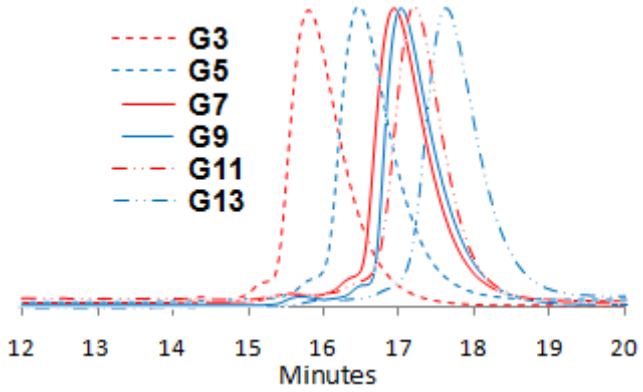


Figure S41. HPLC traces of the dendrimers (G3-G13). For analytic HPLC of the dendrimers, a ZORBAX 300SB-C8 column (1.0 x 150 mm, 3.5 µm) was used with a gradient elution: 70% A to 30% A over 20 min and then keep 30% A (A = water with 0.1% TFA, B = acetonitrile with 0.1% TFA) with a flow rate of 80 µL/min. UV detection was performed at 230 nm.

Transmission Electron Microscopy

***Experimental*.** Transmission electron microscopy micrographs (TEM) were recorded on a Tecnai 12 Bio Twin instrument operating at a 120 kV accelerating voltage . Samples (dendrimer: 1 mg mL^{-1} in Milli-Q water, CCMV: 50 mg L^{-1} in 10 mM NaAc, 1 mM EDTA, 1 mM NaN_3, pH 5) were prepared on formvar carbon-coated copper grids by placing a 3 μL drop of the sample solution on the grid. The sample drop was left standing for 1 min after which time the excess solution was blotted away with filter paper. Samples were negatively stained by applying 3 μL of stain (0.5% uranyl acetate in Milli-Q water) onto the grid and removing the excess stain with filter paper after 15 s. The samples were dried under air flow for at least 5 min before imaging.

Cryo-TEM samples were prepared from the same aqueous (dendrimer) or buffer (virus) solutions. Prior to sample deposition the TEM grids (Quantifoil R 3.5/1, holey carbon film, Cu 200 mesh) were treated with Gatan Solarus 950 plasma system. 3 μL of sample was placed on the grid, which was consecutively blotted for 1-2 s (100 % relative humidity, -2 mm blot offset), with Fei Vitrobot Mk3 followed by immediate vitrification with a mixture of liquid ethane and propane (~1:1) at –180 °C. Vitrified samples were cryo-transferred to the microscope. Images were obtained with a JEOL JEM-3200 FSC field emission cryo electron microscope operating at a 300 kV accelerating voltage and specimen temperature of 86 K.

Dynamic Light Scattering

Measurements of dynamic light scattering (DLS) were performed at 25.0 ± 0.1 ^{o}C. All dendrimer samples were filtered through a 0.2 mm filter (Anotop 10, Whatman) and placed in a test tube. The experiments were performed on a light scattering apparatus built using the following main components: He-Ne laser (35 mW, 632.8 nm, Coherent Radiation), manual goniometer and thermostat (Photocor Instruments), multi-tau correlator, APD detector and software (PD4042, Precision Detectors).[1,2] All measurements were performed at a scattering angle of 90°. The dynamic-light-scattering correlation functions were analyzed using a regularization algorithm (Precision Deconvolve 32, Precision Detectors). Light-scattering distributions were bimodal. The calculated *z*-average diffusion coefficient, D, corresponds to the peak at low apparent radii (fast diffusion mode).[2,3] For dilute solutions, diffusion coefficient values can be converted into the corresponding hydrodynamic radius, R_{h}, using the Stokes-Einstein equation: $R_{\mathrm{h}} = k_{\mathrm{B}}T/(6\pi\eta D)$ for a sphere,[4] where k_{B} is the Boltzmann constant, $T = 298.2\,\mathrm{K}$ the absolute temperature, and η the corresponding viscosity of water. The viscosity value of water, $\eta = 0.890\times10^{-3}\,\mathrm{kg\,m^{-1}s^{-1}}$,[5] was used to calculate R_{h}.

For **G9** and **G11**, DLS measurements were performed in phosphate buffered saline (PBS) solutions. For **G13**, filtering of phosphate buffered saline solutions virtually removed all dendrimer material. Thus, DLS measurements were performed in NaCl 0.01 M and water. Our results are summarized in **Table S1**. Representative light-scattering distributions for G9,G11 and G13 are shown in **Figure S42.**

Table S1. Diffusion coefficients and calculated hydrodynamic radii. [a] concentration values do not take into account dendrimer material removed by filtering. [b] errors are standard deviations. [c] pH≈7.4

Sample description [a]	$D/10^{-9}\mathrm{m^2s^{-1}}$	R_h/nm
G3 3.9 g/L in PBS	0.124±0.01 [b]	-
G3 7.0 g/L in PBS	0.117±0.01	-
G3 9.0 g/L in PBS	0.112±0.01	-
G3 0.0 g/L in PBS [c]	0.132±0.01	1.85±0.02
G5 4.9 g/L in PBS	0.0614±0.006	3.99±0.04
G7 1.0 g/L in PBS	0.0358±0.002	6.85±0.03
G9 1.0 g/L in PBS	0.0229±0.003	10.7±0.2
G11 0.48 g/L in PBS	0.0168±0.002	14.6±0.2
G13 0.25 g/L in NaCl 0.01 M [d]	0.0162±0.005	15.1±0.4
G13 0.11 g/L in water [d]	0.0187±0.003	-
G13 0.40 g/L in water [d]	0.0207±0.006	-
G13 2.0 g/L in water [d]	0.0317±0.033	-

Comments. Diffusion coefficients of **G13** in water were found to be higher than that in NaCl 0.01 M. This can be explained by considering dendrimer charge. In the absence of electrostatic screening, dendrimer diffusion coefficients are expected to be higher than their intrinsic Brownian mobilities.[6] Thus, the Stokes-Einstein equation was not applied in this case.

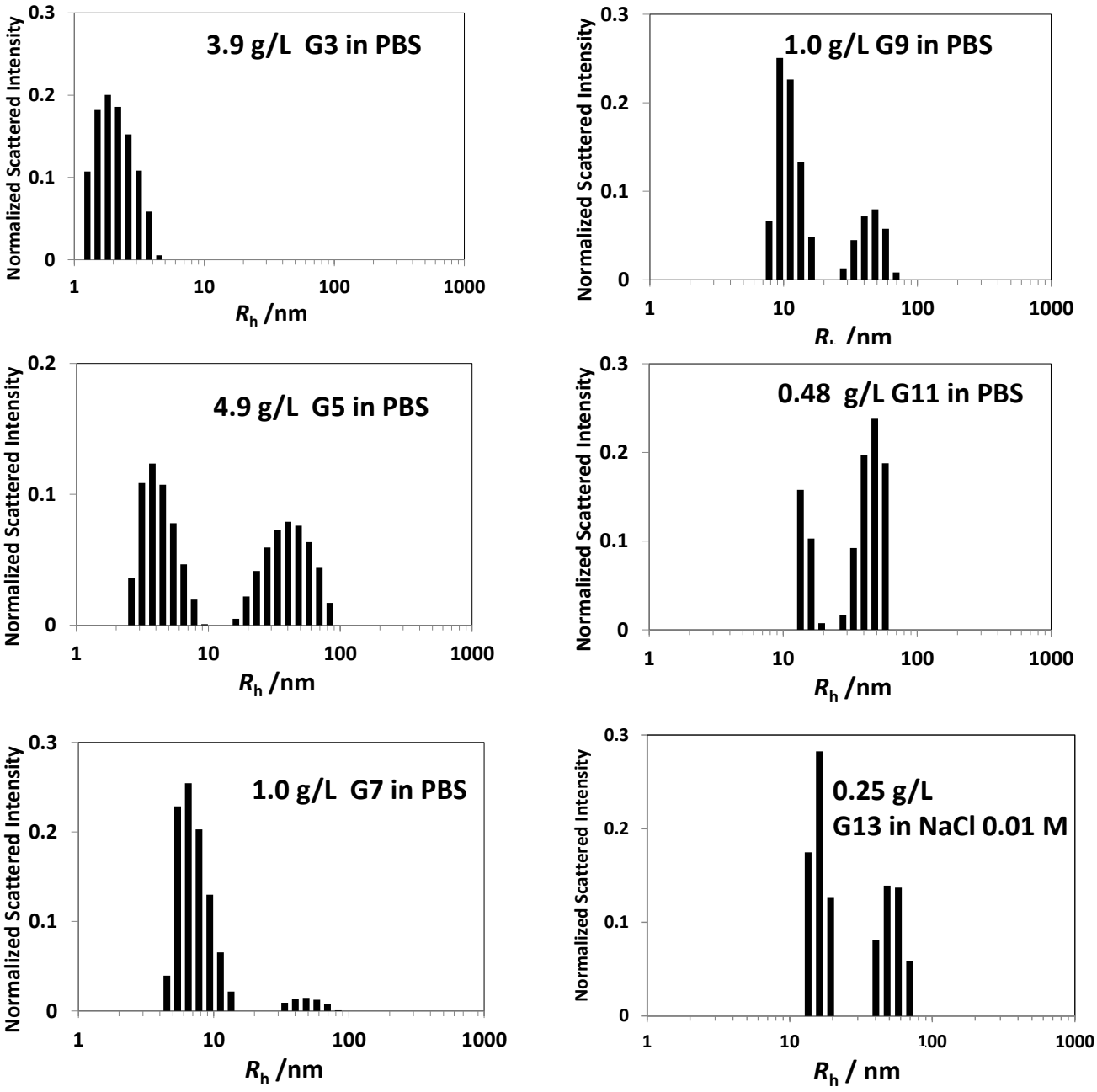


Figure S42. Normalized scattered-intensity distributions.

References

1 Lomakin, A.; Teplow, D.B.; Benedek, G.B. *Meth. Mol. Biol.* **2005**, *299*, 153–174.
2 Zhang H.; Annunziata**,** O. , *J. Phys. Chem. B* ***2005***, ***112***, 3633-3643.
3 Schmitz, K. S. *Introduction to Dynamic Light Scattering by Macromolecules* (Academic Press, San Diego, 1990), pp 77-98.
4 Tanford, C. *Physical Chemistry of Macromolecules*; Wiley: New York, 1961, p. 356.
5 Kestin, J.; Sokolov, M.; Wakeham, W.A. *J. Phys. Chem. Ref. Data* **1978**, *7*, 941-948.
6 Schmitz, K. S. *Introduction to Dynamic Light Scattering by Macromolecules* (Academic Press, San Diego, 1990), pp 205-214.

ATOMIC FORCE MICROSCOPY

Sample Preparation. For AFM analysis on air, **G13** dendrimers (2 mg/ml water solution filtered through the 0.2 µm filter (Whatman GD/X))) were dropped (5 µl) on freshly cleaved circular mica disc (diameter 1 cm) and solution was let to evaporate at ambient conditions (30 min.). Samples for liquid AFM were prepared by drop casting of **G13** solution (15 µl) of the same composition on mica disc fixed in liquid measurement cell. After 10 minutes of incubation (without drying) the surface of mica was gently layered with 1ml of ultrapure (Milli-Q) water and AFM analysis performed.

AFM analysis. Atomic force microscopy analysis was performed with an AFM Integra Probe Nanolaboratory (NT-MDT, Russia). Analysis of dry samples was performed in semi-contact mode with a 100×100 µm closed-loop scanner (scanning by sample). Samples were analyzed by high accuracy noncontact composite (HA_NC) ETALON silicon tip cantilevers (NT-MDT, Russia) with a typical resonant frequency of 280 kHz, a tip radius of 10 nm and a force constant of 11.5 N/m in air, and at ambient temperature and humidity. Analysis of hydrated **G13** was performed in liquid cell (total volume 1ml) fixed on 100×100 µm closed-loop scanner (scanning by sample) in soft contact mode AFM. Triangular silicon nitride cantilevers (NanoAndMore Inc.) with tip radius bellow 10 nm and force constant 0.08 N/m were used. A scan rate of 0.5–1 Hz was used for the best resolution. Data were collected from at least three different samples, with two different tips and in a minimum of 10 different positions on each sample.

Image processing and height (Z_{max}) analysis. The images were analyzed by Scanning Probe Image Processor software (Image Metrology A/S, Denmark). Raw images were corrected for the tilting of the sample stage and zero leveled based on the dominant height value in the distribution histogram. No other image filtering was used. Objects (at least 100 entities) were analyzed for the Z_{max} (the maximum Z value of all points inside the shape contour) by threshold method using embedded grain analysis module and values obtained presented as height distribution histogram.

Comments. Liquid AFM analysis is very precise method suitable to measure the diameter (Z_{max} value) of symmetric (spherical) hydrated nanoobjects as are dendrimers. The important prerequisite for such analysis in liquid is the immobilization of sample on atomically flat surface. Fortunately, the **G13** triazine dendrimers are positively charged at neutral pH and therefore able to be immobilized electrostatically on negatively charged mica surface. AFM analysis of the hydrated dendrimers revealed the predominant presence (≈ 66%) of subpopulation of **G13** with dimensions within the

interval 29-36 nm (see histogram **Fig S43**) with average Z_{max} = 31.5 +/- 1.9 nm (n = 93)). Although there were present also other subpopulations of dendrimers in lower range than expected (lower or incomplete generations), their overall percentage is much lower compared to largest subpopulation in histogram. Based on the HPLC, the purity of sample has been predicted more than 95%. We therefore expect that the presence of **G13** (largest subpopulation) will be significantly higher than ≈ 66% as obtained from AFM analysis. **G13** tend to aggregate compared to lower generations (as observed by DLS). This aggregation is further increased during the AFM sample preparation (preconcentration step on mica surface). The relative proportion of **G13** could be underestimated compared to its presence in solution due to aggregation.

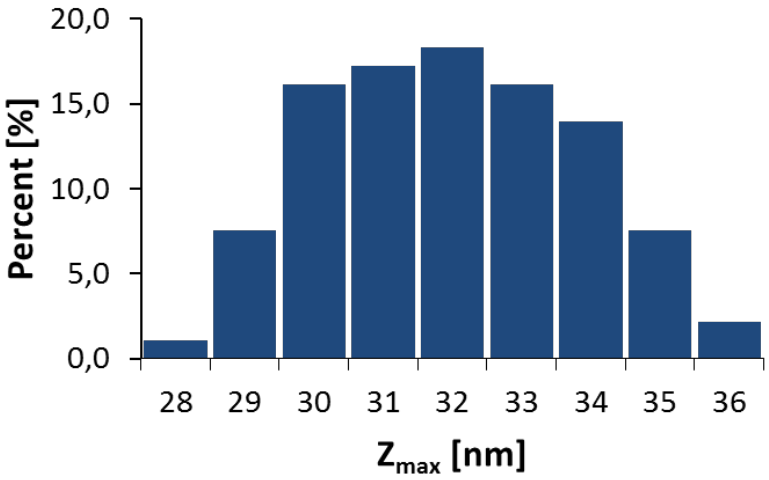


Fig. S43. Histogram of Z_{max} distributions (n = 93) of **G13** dendrimers as obtained by AFM in liquid

Fig. S45 shows AFM analysis of G13 on air (dry sample). Based on the cross section profile and histogram is apparent, that the desiccation process leads to significant changes in volume and Z_{max} values of dendrimers, absorbed electrostatically on the surface of mica. Since the diameter of the dendrimers measured on dry samples by TEM is approx. 25-30 nms (measured at x-y scale), we may assume that the dendrimer shrinks predominantly in the Z-scale (average final value 9.8 +/- 1.9 nm) towards the mica surface resulting in disc shape. Volume and Z_{max} changes can be explained by gradual loss of water molecules during the drying process and possibly also by attractive forces between the negatively charged mica and positively charged amino groups of dendrimer which may deform the expected spherical shape of **G13**. The partial aggregation of **G13** observed on **Fig. S44** is the most probably the result of the preconcentration of dendrimers on mica surface during the drying process. The extent of the volume changes observed suggests natural high hydration state of internal space of dendrimer.

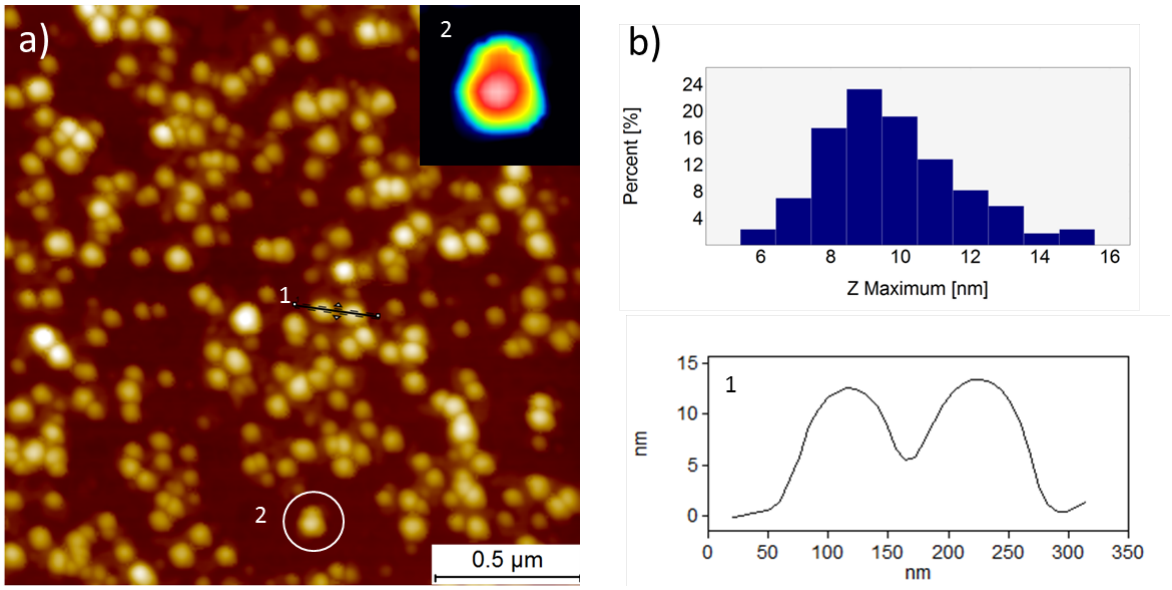


Figure S44. Atomic force microscopy (AFM) analysis of **G13** on air (dry sample). a) **G13** imaged on mica surface. Cross section profile (average of 3 lines) of two dendrimers (marked 1) is shown on the right panel. Inset: close view of **G13** dendrimer marked by cycle (numbered 2) in the lower part of the image (image size 200 × 200 nm). b) histogram of Z_{max} values obtained from AFM analysis.

Computation

Experimental. The molecular models for the whole dendrimer series were constructed and parametrized according to a validated procedure.[S1-S3] The dendrimers were built iteratively in consecutive generations from **G1** to **G13** by using the Material Studio software (Accelrys, San Diego, CA, USA). Each built generation underwent to preliminary gas-phase minimization and short molecular dynamics (MD) simulation in order to relax the structure and to eliminate bad contacts within the dendritic scaffold before growing with the next generation. For the larger generations – i.e., **G9**, **G11** and **G13** – this procedure was extremely delicate and time consuming, since complexity increases exponentially with the dendritic generation. For this reason, it has been very hard to obtain an atomistic model for **G13**, which required many steps of minimizations and of MD simulations with increasing temperature and time step. In particular, T was increased from 0 to 1000 K and then the system was cooled down again to 300 K, with increasing time step from 0.5 to 2 femtoseconds (fs) due to high atom velocity in the earlier steps of this phase. The final **G13** model, subject of this study, is composed by different residues – a central (COR) core unit, the repetitive units that compose the flexible branches (BRA) and the terminal groups which constitute the dendrimer's surface (END). **G13** has 16384 surface groups bearing primary amino-groups that at neutral pH (≈7.4) are assumed to be protonated. The entire parametrization, simulation work and data analysis were carried out using the AMBER 12 suite of programs.[S4] The partial charges for all of the non-standard residues that constitute **G13** were obtained using the AM1-BCC[S5] calculation method within the *antechamber*[S6] module of AmberTools 12 (AMBER 12). Parameters and force field types were assigned consistently with the "general AMBER force field (GAFF)" (*gaff.dat*)[S7] – such parameters already demonstrated to be well-consistent for the parameterization and the simulation of dendrimers[S1-S2,S8] and dendrons.[S3,S9]

***Comments*.** Due to the enormous size of the atomistic model of **G13** (1343416 atoms), for this generation it was not possible to run a molecular dynamics (MD) simulation in explicit solvent, as the number of water molecules introduced in the system largely exceed the maximum size limit that it is currently possible to

simulate. Even the use of a simplified coarse-grained (CG) model to decrease the system size was not practicable in this case. In fact, first, CG models that account the presence of explicit solvent did not allow for the size reduction necessary to run the simulation – the system was still too large. Secondly, regarding the CG simulation of **G13** in absence of explicit solvent, a very coarse model would have been necessary to reduce substantially the size of **G13** to make the use of a CG model convenient. This was incompatible with the highly flexible branches that compose the dendritic scaffold. In fact, the approximation the linear monomers of **G13** into a single, or two-bound beads would not reproduce correctly the flexibility of the molecule nor the surface roughness and irregularity. For this reason, a fully atomistic MD simulation of **G13** was conducted *in vacuum* to obtain a single-molecule view of this large dendrimer. **G13** was initially minimized and then preliminary 100 ps of MD simulation a 1 fs time step were run at 300 K of temperature. **G13** was then equilibrated for 4 ns at 300K, using a time step of 2 fs, the Langevin thermostat and a 12 Å cutoff. The SHAKE algorithm was used on the bonds involving Hydrogen atoms.[S10] The reduced simulation time was sufficient to obtain a molecular picture of the dendrimer, as **G13** reached rapidly the equilibrium due to the high structural crowding and rigidity. Size (radius of gyration) and radial distribution functions (RDF) for **G13** were extracted from the equilibrated phase of the MD trajectories using the *ptraj* module within AMBER 12.

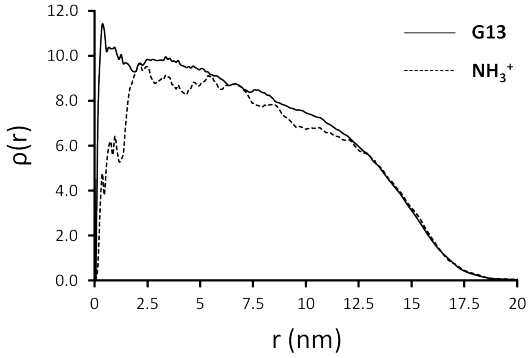


Figure S45. Radial distribution function of **G13** showing peripheral amine groups reveal extensive backfolding. observed.

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