

Electronic Supplementary Information for:

Efficient Multigram Synthesis of the Repeating Unit of Gallic Acid-Triethylene Glycol Dendrimers

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Materials and methods. 2-[2-(2-Chloroethoxy)ethoxy]ethanol (**2**), methyl gallate (**6**), and NaN_3 were purchased from Wako. Thionyl chloride was purchased from Acros Organics. 18-crown-6 (18C6), benzyltriethylammonium chloride (BTEAC), and 4-dimethylaminopyridine (DMAP) were purchased from Sigma-Aldrich. Amberlite IR-120 was obtained from Fluka. All other reagents were of analytical grade. All solvents were HPLC grade, purchased from Scharlab and used without further purification. Water was of Mili-Q grade. Automated column chromatography was performed on a MPLC Teledyne ISCO CombiFlash RF – 200 psi with RediSep Rf normal-phase 330 g silica columns. NMR spectra were recorded on a Bruker DPX 250 MHz and Varian Mercury 300 MHz spectrometers. Chemical shifts are reported in ppm (δ units) downfield from internal tetramethylsilane (CDCl_3) or the HOD solvent peak (D_2O). Mass spectra were collected on a Termo Finnigan Trace-DSQ quadrupole/electronic impact spectrometer (EI-MS) and on a Bruker Microtof/time-of-flight mass spectrometer (ESI-MS). FT-IR spectra were recorded on a Bruker IFS-66v (neat samples, CsI window) and on a Varian 670-IR equipped with a Varian 610-IR microscope and a PIKE universal diamond ATR sampling accessory.

Working with Azides – WARNING! Since the first reports on the CuAAC reaction by the groups of Meldal, and Fokin and Sharpless in 2002,¹ the appearance of NaN_3 and organic azides in synthesis has exponentially increased to the point of us forgetting a prevailing earlier azidophobia. Indeed, as mentioned by Fokin and Sharpless in their seminal work, the success of CuAAC lays on the extraordinary stability of azides toward H_2O , O_2 , and the majority of organic synthesis conditions.¹ Nevertheless, one must take into consideration some general safety issues because of the potential explosive nature of some azides under certain circumstances.

Thus, whereas ionic azides such as NaN_3 are relatively stable, organic and heavy metal azides are thermally decomposable and in part explosive classes of compounds.² For organic azides to

be manipulable or non-explosive, the “Smith’s rules” must be followed: i) the number of nitrogen atoms (N_N) must not exceed that of carbon (N_C), and ii) $(N_C + N_O)/N_N \geq 3$.^{2,3} All organic azides in this report and GATG dendrimers follow these rules and have proven to be stable in our hands.

NaN_3 is toxic [LD_{50} oral (rats) = 27 mg/Kg] and can be absorbed through the skin.² It is not explosive except when heated near its decomposition temperature ($275\text{ }^\circ\text{C}$)² and does not form explosive compounds when dissolved in water.⁴ However, in reaction with Brønsted acids, the highly toxic and potentially explosive hydrazoic acid (HN_3) is released (volatile liquid, Bp $37\text{ }^\circ\text{C}$). Besides its toxicity, the danger associated with NaN_3 is its ability to form highly explosive azides (under pressure or shock) when reacted with heavy metals such as Pb, Cu, Zn, Cd, or Ni.⁴ The same applies to HN_3 vapors into contact with heavy metals or their salts.² Accordingly, NaN_3 should never be flushed down the drain to avoid incidents by reaction with Pb or Cu in drain lines. In addition, metal items used to handle NaN_3 , including spatulas should be avoided. Caution must be also taken to avoid accumulation of heavy metal azides on the metal components of diverse laboratory equipment, including rotary evaporators and freeze-dryers.² It has been reported that NaN_3 and polymer-bound azide reagents form explosive di- and triazidomethane in contact with CH_2Cl_2 and CHCl_3 at rt, respectively.⁵ Therefore, contact of NaN_3 with these solvents must be avoided.⁶ NaN_3 reacts also vigorously with CS_2 , Br_2 , HNO_3 , and dimethyl sulfate.²

2-[2-(2-azidoethoxy)ethoxy]ethanol (3). 2-[2-(2-Chloroethoxy)ethoxy]ethanol (**2**) (153 g, 0.91 mol) was dissolved in H₂O (445 mL) in a round-bottom flask provided with a NaOH drying tube. Then, NaN₃ (117.98 g, 1.81 mol) was added and the reaction mixture was heated at 75 °C while stirring for 48 h. Upon completion of the reaction, the mixture was cooled down to rt. H₂O was evaporated under reduced pressure (20 mm Hg) in a rotary evaporator (bath temperature: 40 °C), and condensed over NaOH pellets (1 g) to trap any HN₃ potentially produced. Additionally, the system was provided with a NaOH tower between the rotary evaporator and the vacuum pump to avoid accumulation of heavy metal azides on metal components. The resulting residue was suspended in Et₂O (2 L) and filtered through a sintered funnel (porosity 5). The filtrate was evaporated to afford **3** (158.60 g, 100%) as a colorless liquid. IR (neat, CsI window): 2869, 2107, 1299, 1123 cm⁻¹. ¹H NMR (250 MHz, CDCl₃, Me₄Si) δ: 3.77-3.60 (m, 10H), 3.41 (t, *J* = 5.0 Hz, 2H). ¹³C NMR (63 MHz, CDCl₃) δ: 72.2, 70.2, 69.9, 69.6, 61.2, 50.2. Elem. Anal. Calcd for C₆H₁₃N₃O₃·0.1H₂O: C, 40.71; H, 7.47; N, 23.74. Found: C, 40.91; H, 7.71; N, 23.46. ESI-HRMS Calcd for C₆H₁₃N₃NaO₃⁺: 198.0849; Found [M + Na]⁺: 198.0842.

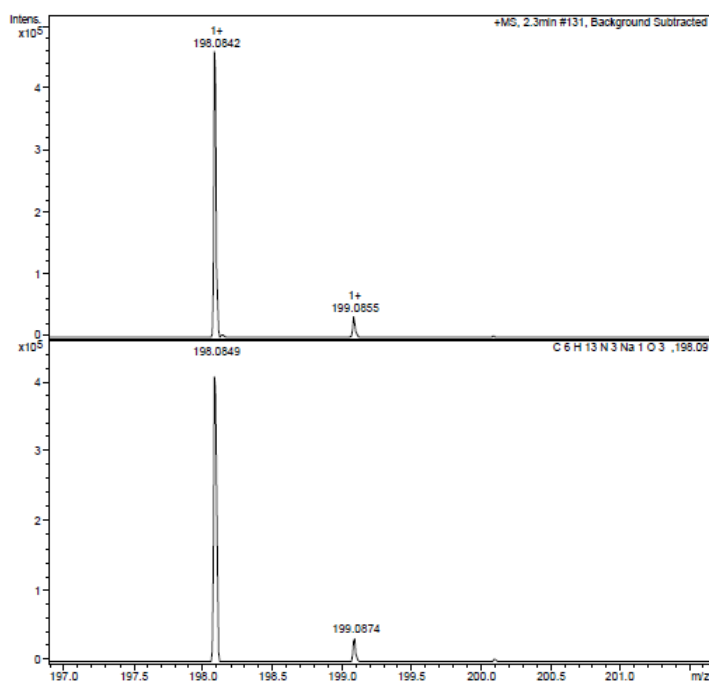


Figure S1. Found and calculated ESI-HRMS of **3**.

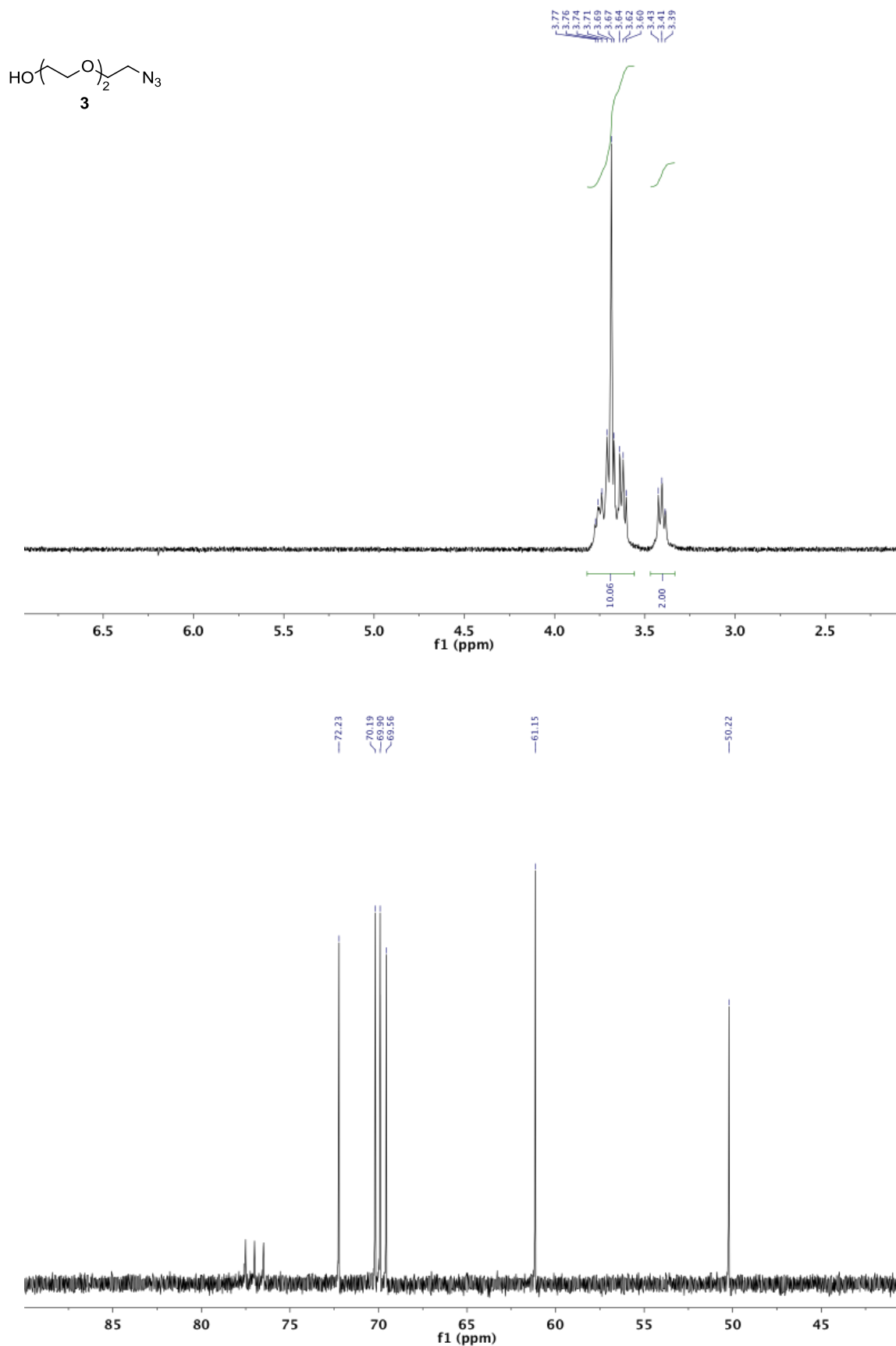


Figure S2. ¹H and ¹³C NMR spectra of **3** in CDCl₃.

1-azido-2-[2-(2-chloroethoxy)ethoxy]ethane (4). A mixture of **3** (158.60 g, 0.90 mol) and benzyltriethylammonium chloride (BTEAC) (0.62 g, 2.71 mmol) was heated at 65 °C in a three-necked round-bottom flask under Ar. Thionyl chloride (132 mL, 1.81 mol) was added dropwise from an addition funnel with pressure-equalization arm, and then the reaction was stirred at 65 °C for 3 h while maintaining a continuous positive Ar flow (to remove HCl generated during the process). After cooling at rt, the excess of thionyl chloride was removed at reduced pressure. The resulting crude product was suspended in phosphate buffer (50 mM, pH 7.0, 1.0 L) and extracted with a mixture EtOAc/hexane (1:1, 1 L). The organic layer was washed with phosphate buffer (50 mM, pH 7.0, 5x1.0 L), dried (Na₂SO₄), and concentrated to give **4** (173.20 g, 99%) as a pale yellow liquid. Work-up with non-buffered aqueous solutions led to the formation of 2-[2-(2-azidoethoxy)ethoxy]ethyl acetate as by-product. IR (ATR): 2867, 2095, 1297, 1114, 664 cm⁻¹. ¹H NMR (300 MHz, CDCl₃, Me₄Si) δ: 3.79-3.62 (m, 10H), 3.39 (t, *J* = 5.0 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃) δ: 70.4, 69.6 (2C), 69.1, 49.7, 42.0. Elem. Anal. Calcd for C₆H₁₂ClN₃O₂: C, 37.22; H, 6.25; N, 21.70. Found: C, 37.04; H, 6.31; N, 22.01. ESI-HRMS Calcd for C₆H₁₂ClN₃NaO₂⁺: 216.0510. Found [M + Na]⁺: 216.0513.

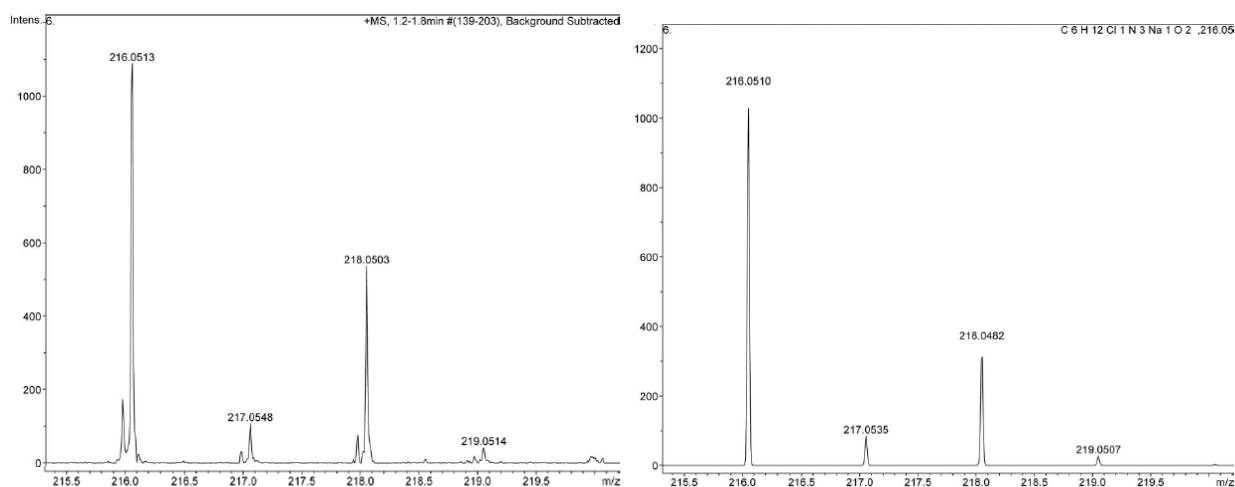


Figure S3. Found and calculated ESI-HRMS of **4**.

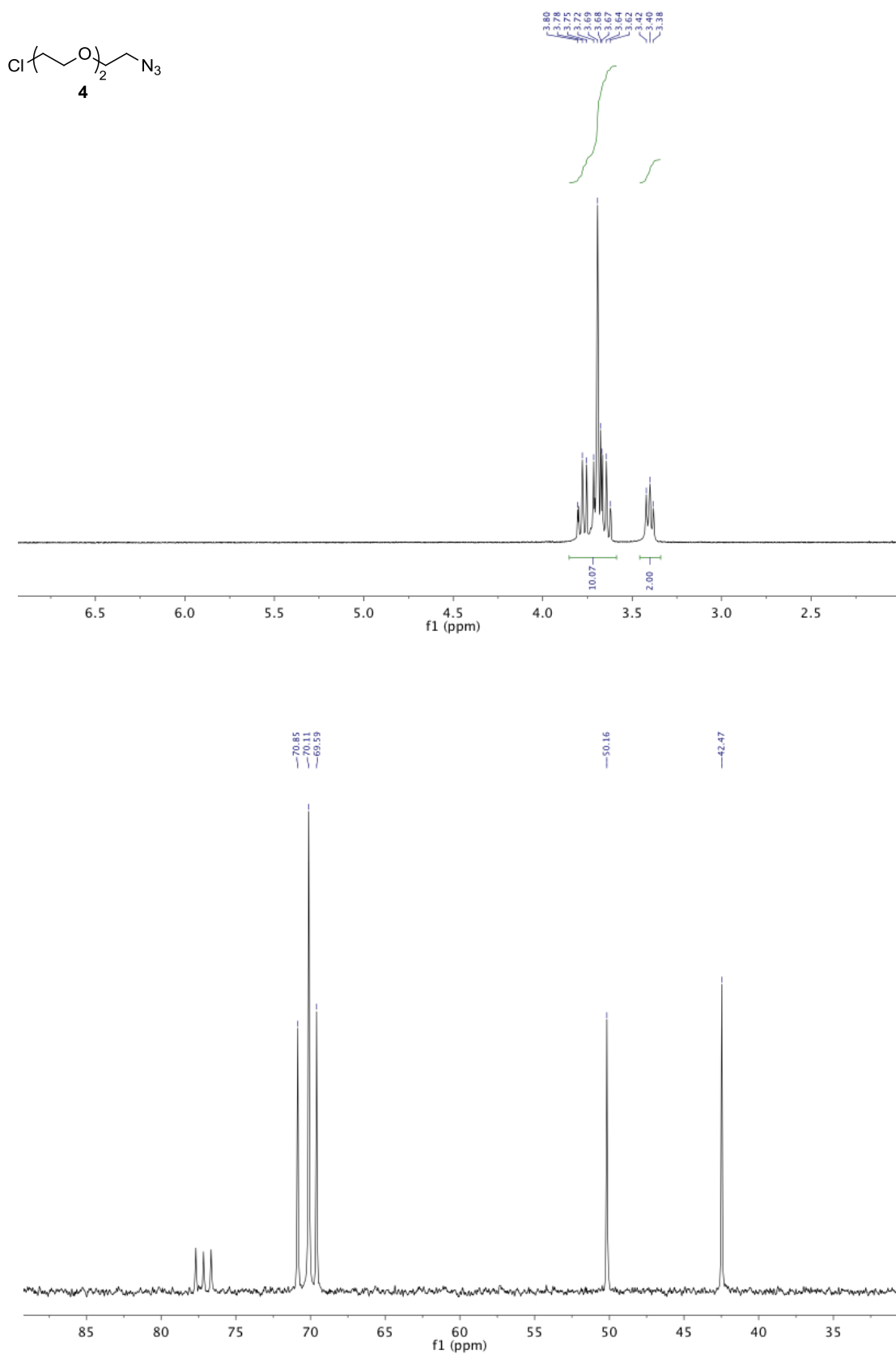


Figure S4. ¹H and ¹³C NMR spectra of **4** in CDCl₃.

Methyl 3,4,5-tri-{2-[2-(2-azidoethoxy)ethoxy]ethyl}benzoate (7). Methyl gallate **6** (44.10 g, 0.23 mol), dry K_2CO_3 (324.35 g, 2.35 mol), and 18-crown-6 (6.20 g, 0.02 mol) were sequentially added to a solution of **4** (140.00 g, 0.71 mol) in DMF (470.0 mL) under Ar. Then, the reaction mixture was heated at 80 °C for 32 h under mechanical stirring. After cooling down to rt, the solvent was evaporated and the resulting crude product was filtered through a pad of basic alumina (350 g; eluent gradient from hexane to acetone) to remove solid residues. The filtrate was concentrated and the resulting residue was separated in five equal portions and purified by an automated MPLC (eluent gradient from hexane to acetone, 30 min) to yield **7** (130.27 g, 87%) as a pale yellow oil. IR (neat, CsI window): 2928, 2871, 2105, 1718, 1122 cm^{-1} . 1H NMR (300 MHz, $CDCl_3$, Me_4Si) δ : 7.30 (s, 2H), 4.26-4.19 (m, 6H), 3.89-3.66 (m, 27H), 3.39 (t, $J = 5$ Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ : 166.0, 151.8, 142.0, 124.5, 108.4, 71.9, 70.3, 70.2, 70.1, 69.5, 69.2, 68.4, 51.6, 50.1. Elem. Anal. Calcd for $C_{26}H_{41}N_9O_{11}$: C, 47.63; H, 6.30; N, 19.23. Found: C, 47.42; H, 6.70; N, 19.02. EI-HRMS: Calcd for $C_{26}H_{41}N_9O_{11}^+$: 655.2926; Found $[M]^+$: 655.2928.

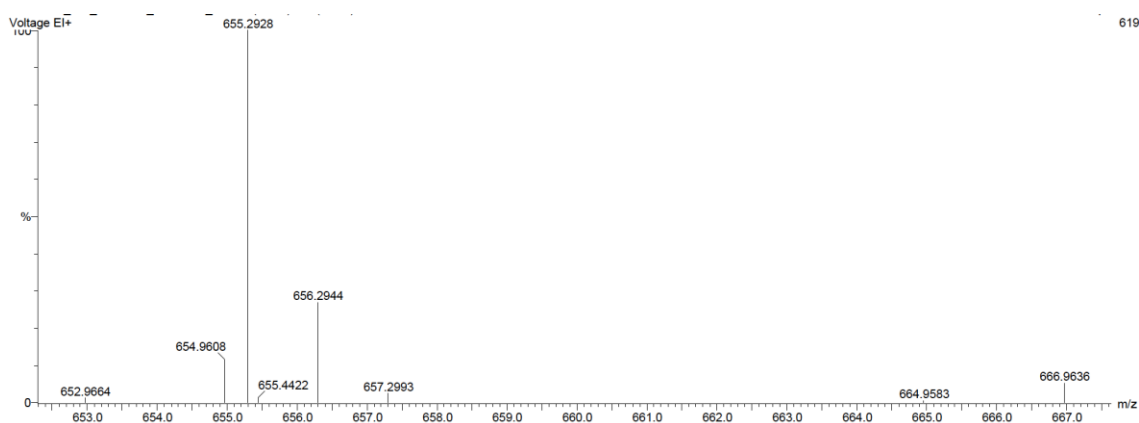


Figure S5. EI-HRMS of **7**.

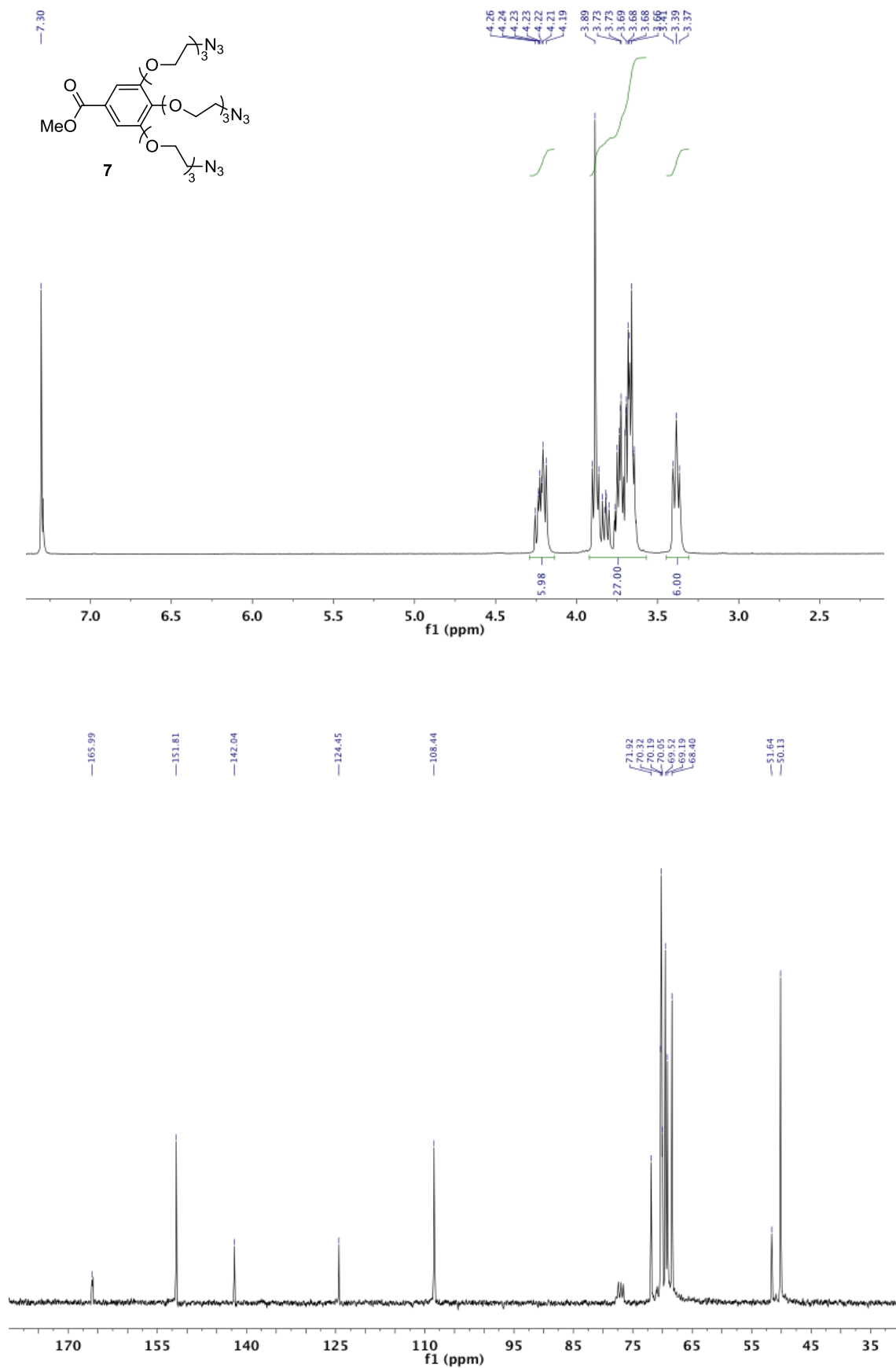


Figure S6. ^1H and ^{13}C NMR spectra of **7** in CDCl_3 .

3,4,5-tris{2-[2-(2-azidoethoxy)ethoxy]ethoxy}benzoic acid (1). aq KOH (435 mL, 1M, 2.2 equiv) was added to a solution of **7** (130.27 g, 0.20 mol) in MeOH (875 mL). The resulting mixture was refluxed for 3 h and then was allowed to reach rt. Neutralization with Amberlite IR-120, followed by filtration (sintered funnel) and evaporation, afforded pure acid **1** (126.98 g, 100%) as a colorless oil. IR (neat, CsI window): 2929, 2872, 2106, 1717, 1121 cm^{-1} . ^1H NMR (300 MHz, CDCl_3 , Me_4Si) δ : 10.41 (br s, 1H), 7.36 (s, 2H), 4.29-4.20 (m, 6H), 3.75-3.65 (m, 24H), 3.39 (t, $J = 5$ Hz, 6H). ^{13}C NMR (75 MHz, CDCl_3) δ : 169.6, 151.9, 142.6, 124.1, 109.0, 72.1, 70.5, 70.3, 70.2, 69.7, 69.4, 68.5, 50.3. Elem. Anal. Calcd for $\text{C}_{25}\text{H}_{39}\text{N}_9\text{O}_{11}$: C, 46.80; H, 6.13; N, 19.65. Found: C, 46.72; H, 6.51; N, 19.50. EI-HRMS: Calcd for $\text{C}_{25}\text{H}_{39}\text{N}_9\text{O}_{11}^+$: 641.2769; Found $[\text{M}]^+$: 641.2766. Gel permeation chromatography (GPC) of **1** was performed on an Agilent 1100 series separation module using a PSS SDV pre-column ($5\mu\text{m}$, 8×50 mm), a PSS SDV Linear S column ($5\mu\text{m}$, 8×300 mm), and a PSS SDV Lux Linear M column ($5\mu\text{m}$, 8×300 mm) with an Agilent 1100 series refractive index (RI) detector. THF was used as eluent at 0.5 mL/min. A solution of **1** in THF (5 mg/mL) was used and filtered through $0.45\mu\text{m}$ before injection.

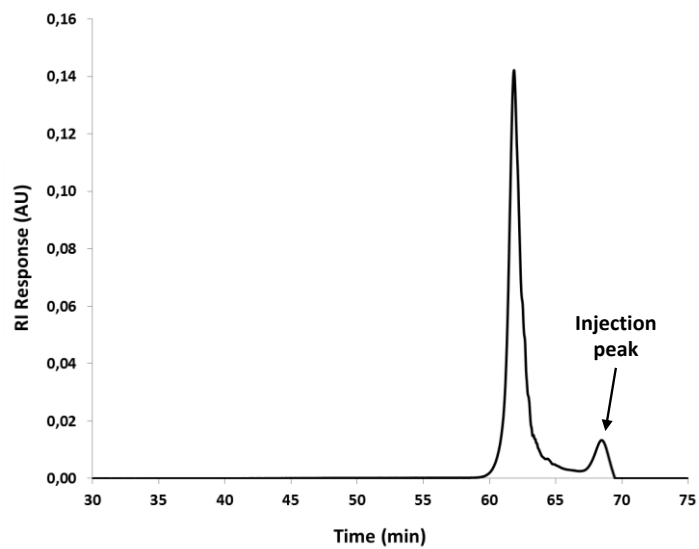


Figure S7. GPC elugram of **1** (THF).

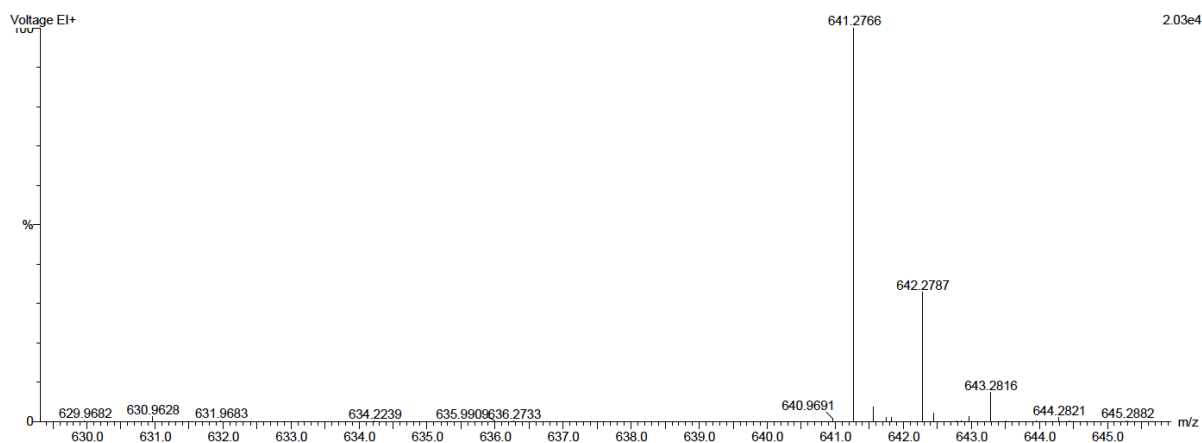


Figure S8. EI-HRMS of **1**.

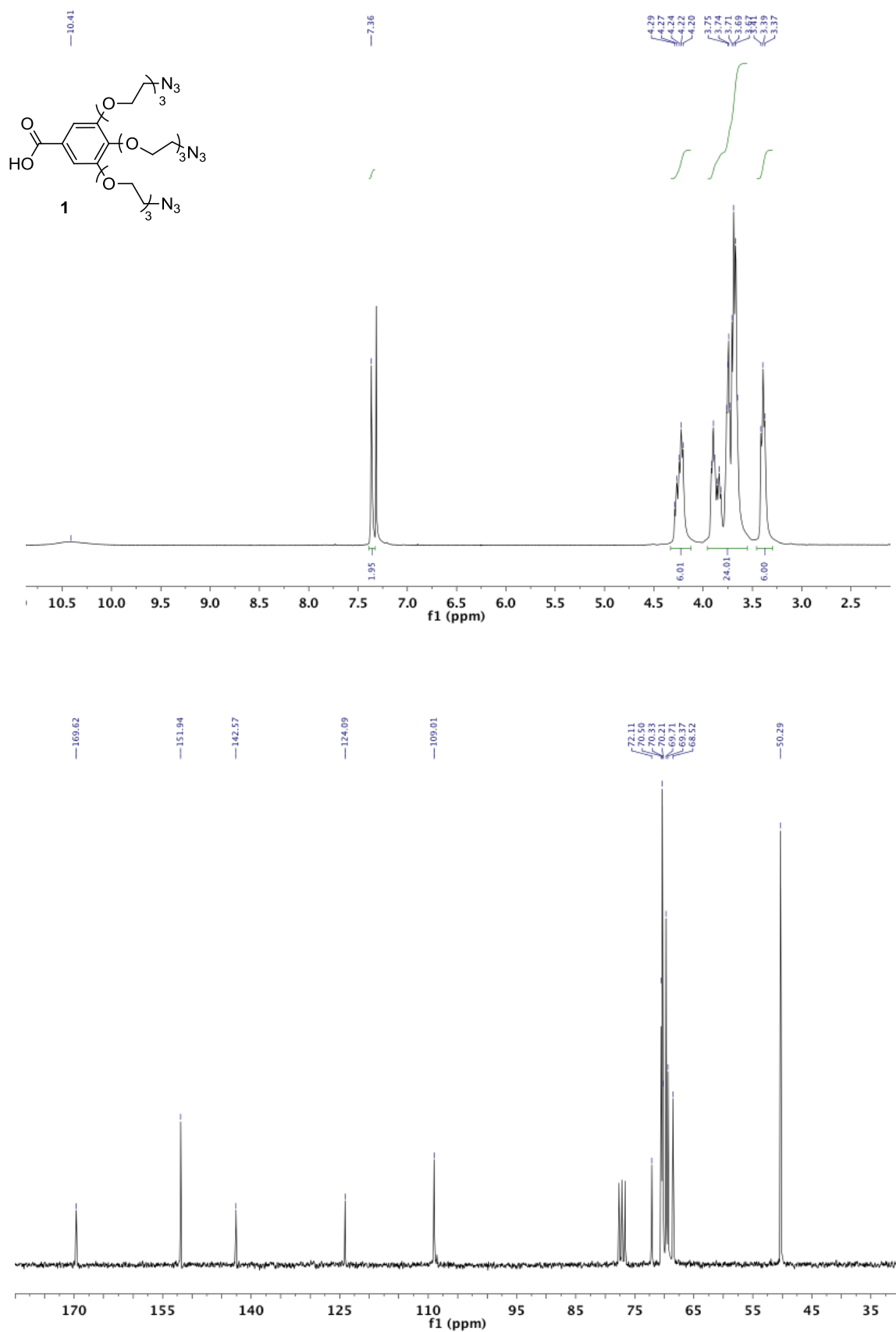


Figure S9. ¹H and ¹³C NMR spectra of **1** in CDCl₃.

References

(1) (a) Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952. (b) Wu, P.; Fokin, V. V. *Aldrichimica Acta* **2007**, *40*, 7. (c) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596. (d) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057.

(2) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188, and references therein.

(3) Similarly, the “rule of six” indicates that six carbons (or other atoms of about the same size) per azide provides sufficient dilution to render an organic azide relatively safe. See: Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004 and references therein.

(4) Aliaga, C. *Chemical Safety: Sodium Azide Hazards*, *Chem. Eng. News* **2010**, *88*, 4.

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