Supplementary Material (ESI) for Chemical Communications

Supporting Information

"Clickable", Polymerized Liposomes as a Versatile and Robust Platform for Rapid Optimization of Their Peripheral Compositions

Amit Kumar,[a] Uriel J. Erasquin,[a] Guoting Qin,[a,b] King Li,[b] Chengzhi Cai*[a]

[a]Department of Chemistry, University of Houston, Houston, TX 77204, USA.

[b]Department of Radiology, The Methodist Hospital Research Institute, Houston, TX *77030, USA*

Fax: 1 713 743 2709; Tel: 1 713 743 2710; E-mail: cai@uh.edu

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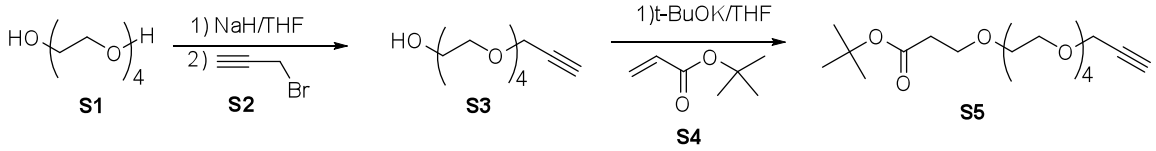
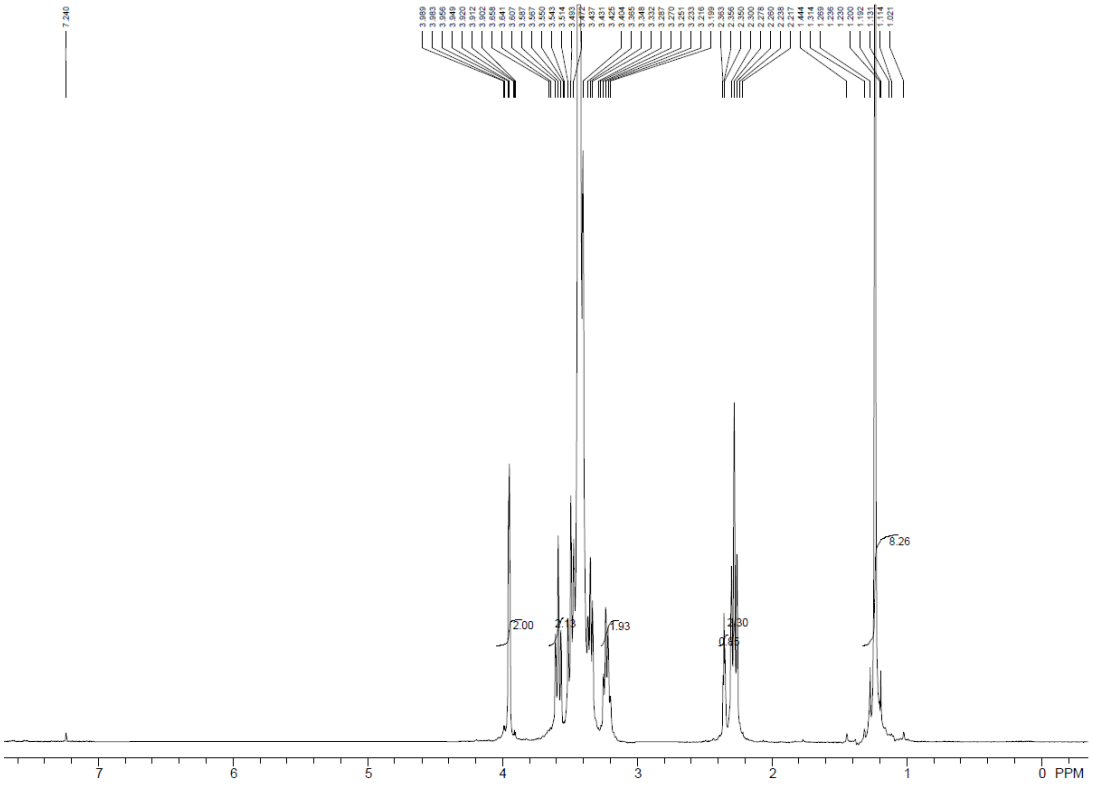
A. Synthesis

General: Air sensitive reactions were performed under a nitrogen atmosphere using Schlenk technique. **S4** and **S7** were purchased from Sigma-Aldrich (St. Louis, MO), **S16** from Thermo-Scientific (Pittsburgh, PA), **S14** from Quanta BioDesign Ltd. (Powell, OH), **S9, 2** from Avanti Polar Lipids Inc. (Alabaster, Al) and **S1** from Alfa Aesar (Ward Hill, MA), and used without further purification. Flash chromatography was carried out on silica gel (60Å, Sorbent Technologies). All ^{1}H and ^{13}C-NMR spectra were recorded in GE QE-300 in $CDCl_3$ (Cambridge Isotope Laboratories Inc.) using residual protons in the solvent as an internal standard. Mass spectroscopy (MS) measurements were carried out using electrospray ionization (ESI) technique on Deca XP Plus from Thermo Finnigan.



To a solution of the alkyne **S3**[1] (500 mg, 2.15 mmol) and ^{t}BuOK (12 mg, 0.11 mmol) under nitrogen in dry THF (1.0 mL) was drop-wise added tert-butyl acrylate (**S4**, 358 mg, 2.79 mmol). The mixture was stirred overnight at room temperature. The solution was neutralized with 1 N HCl, mixed with saturated brine solution, and extracted three times with CH_2Cl_2 (25 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent was removed under vacuum affording a crude product, which was purified by flash chromatography (ethyl acetate/methanol 9:1) to give the alkyne **S5** (442 mg, 1.22 mmol, 57%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.95 (t, J = 2.2 Hz, 2H), 3.58 (t, J = 6 Hz, 2H), 3.52-3.29 (m, 14H), 3.23 (t, J = 5.4 Hz, 2H), 2.35 (t, J = 2.2 Hz, 2H), 2.27 (t, J = 5.4 Hz, 2H). 1.23 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.5, 36.7, 58.6, 66.5, 67.2, 70.2, 70.6, 70.7, 70.9, 75.3, 79.9, 80.7, 171.2. MS (ESI) m/z calcd for $C_{18}H_{32}O_7$: 360.2; found: 383.4 ($[M + Na]^+$).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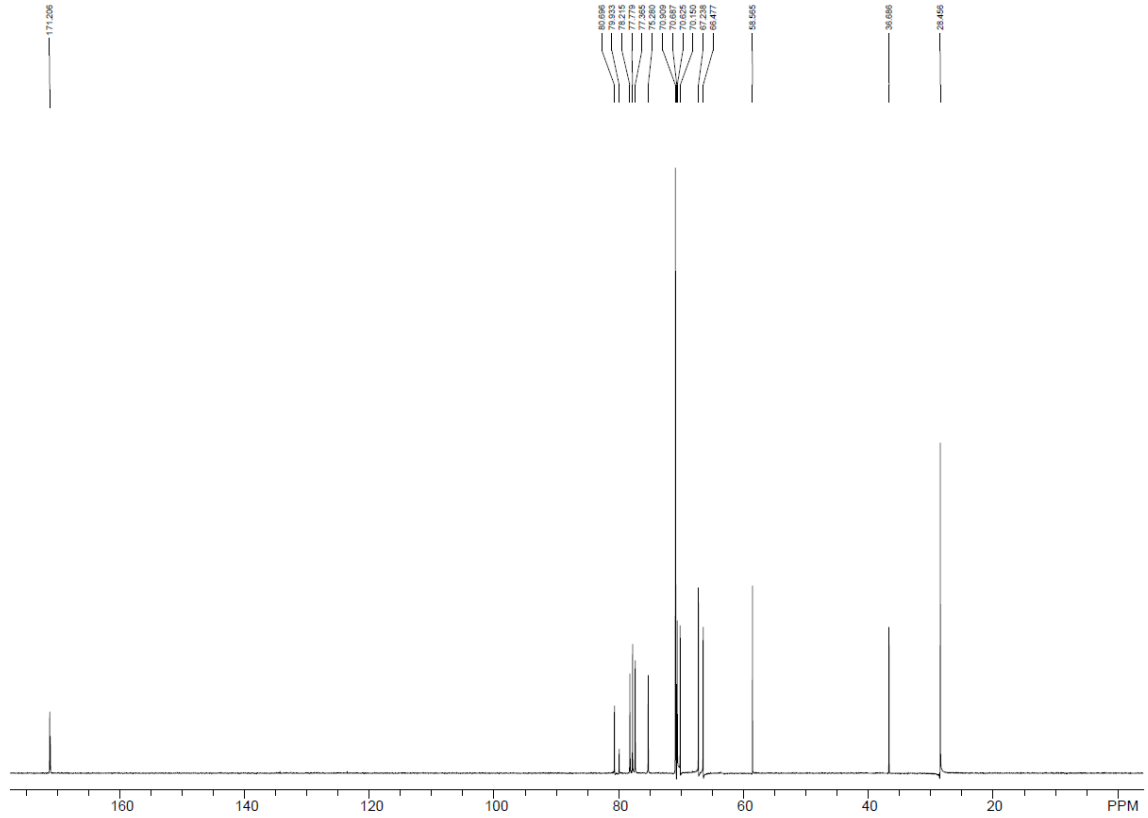
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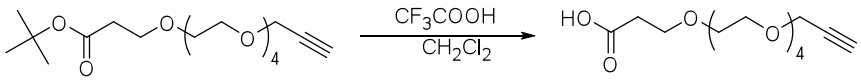
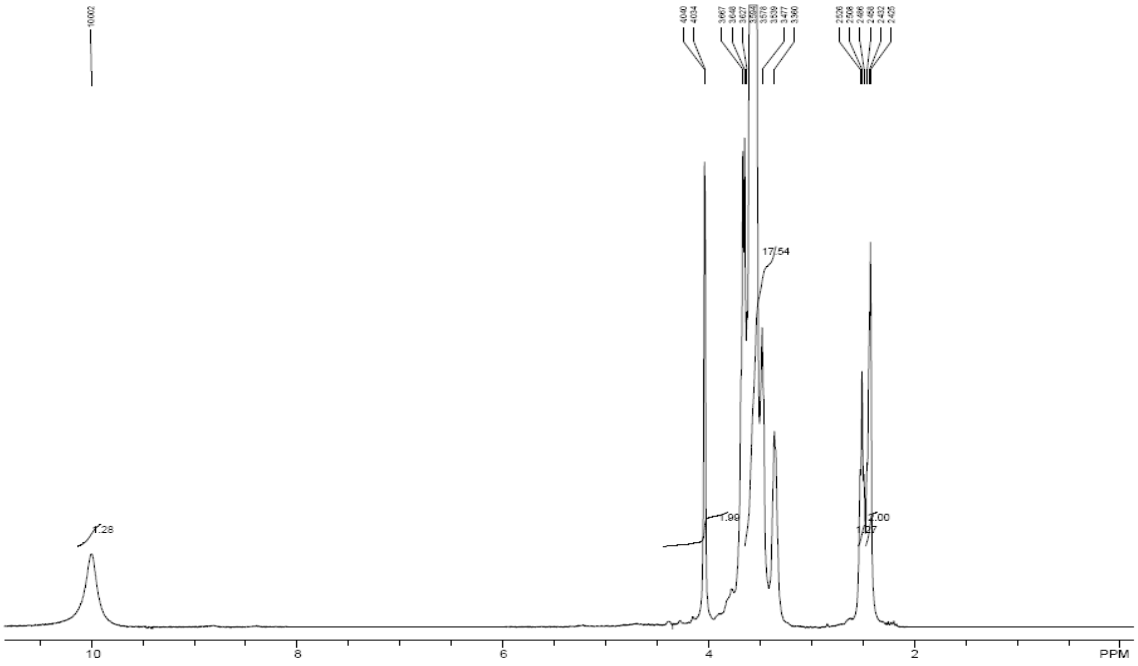
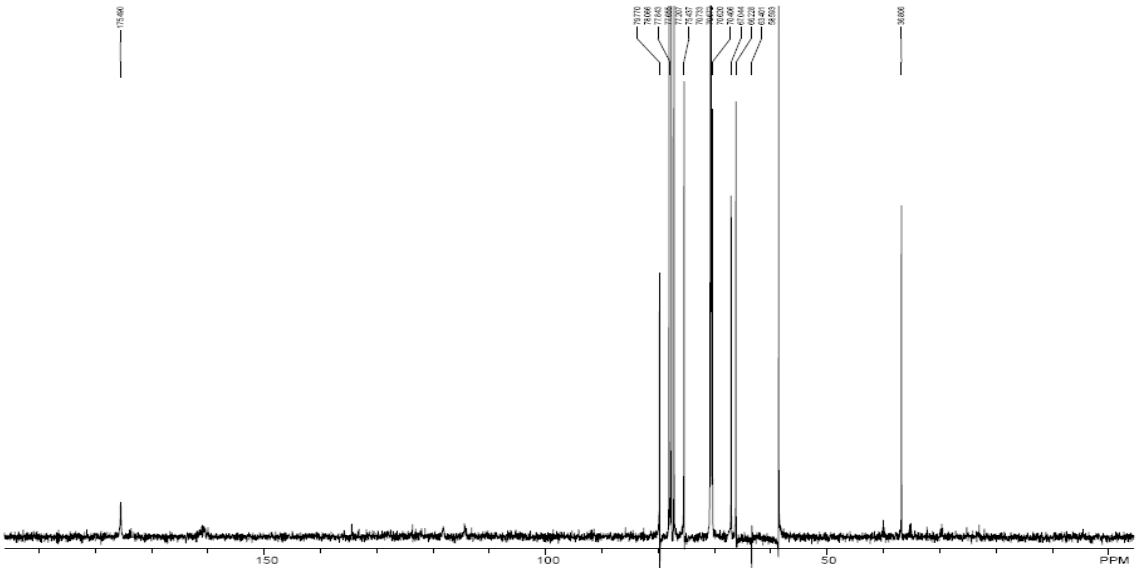
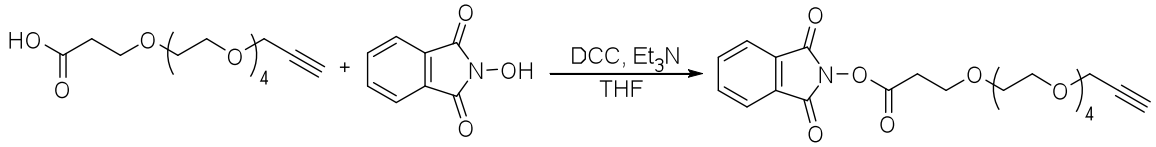


S5 **S6**

To a solution of the alkyne **S5** (150 mg, 0.42 mmol) under nitrogen in dry CH_2Cl_2 (1 mL) was added drop-wise trifluoroacetic acid (1 mL). The mixture was stirred for 4 hours at room temperature. The solvent was removed under vacuum affording the acid **S6** in quantitative yields. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.99 (s, 1H), 4.03 (t, J = 2.2 Hz, 2H), 3.82-3.26 (m, 18H), 2.49 (t, J = 2.2 Hz, 2H), 2.41(t, J = 5.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ175.5, 79.8, 75.4, 70.7, 70.6, 70.4, 67.0, 66.2, 63.4, 58.6, 36.8. MS (ESI) m/z calcd for $C_{14}H_{24}O_7$: 304.1; found: 327.4 ($[M + Na]^+$).

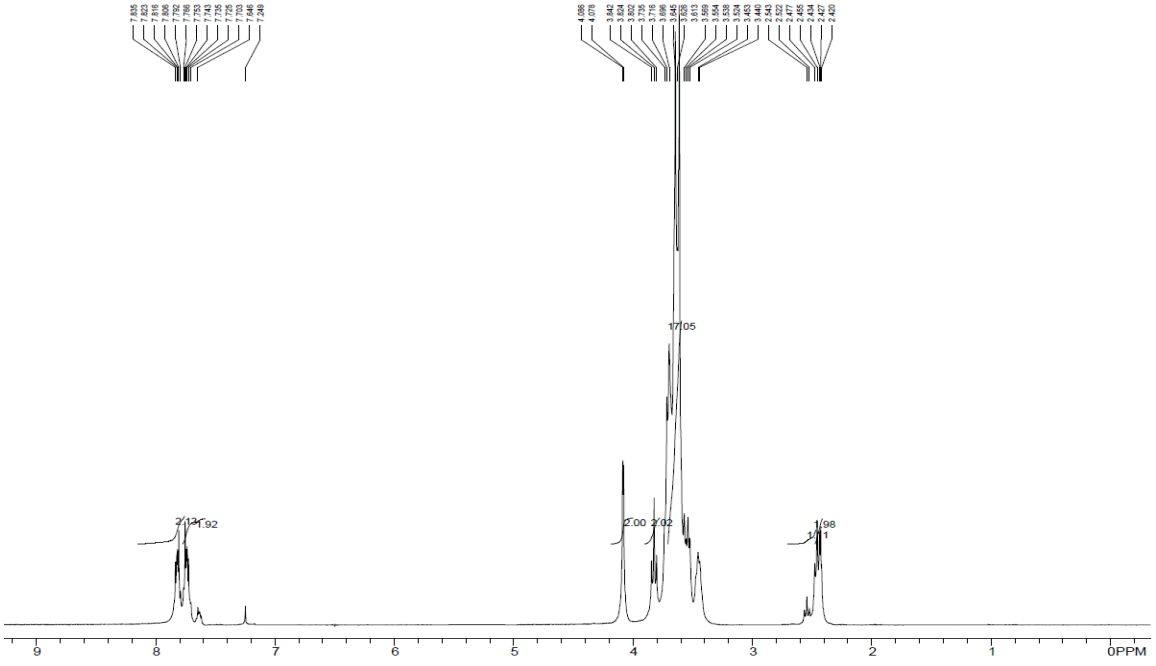


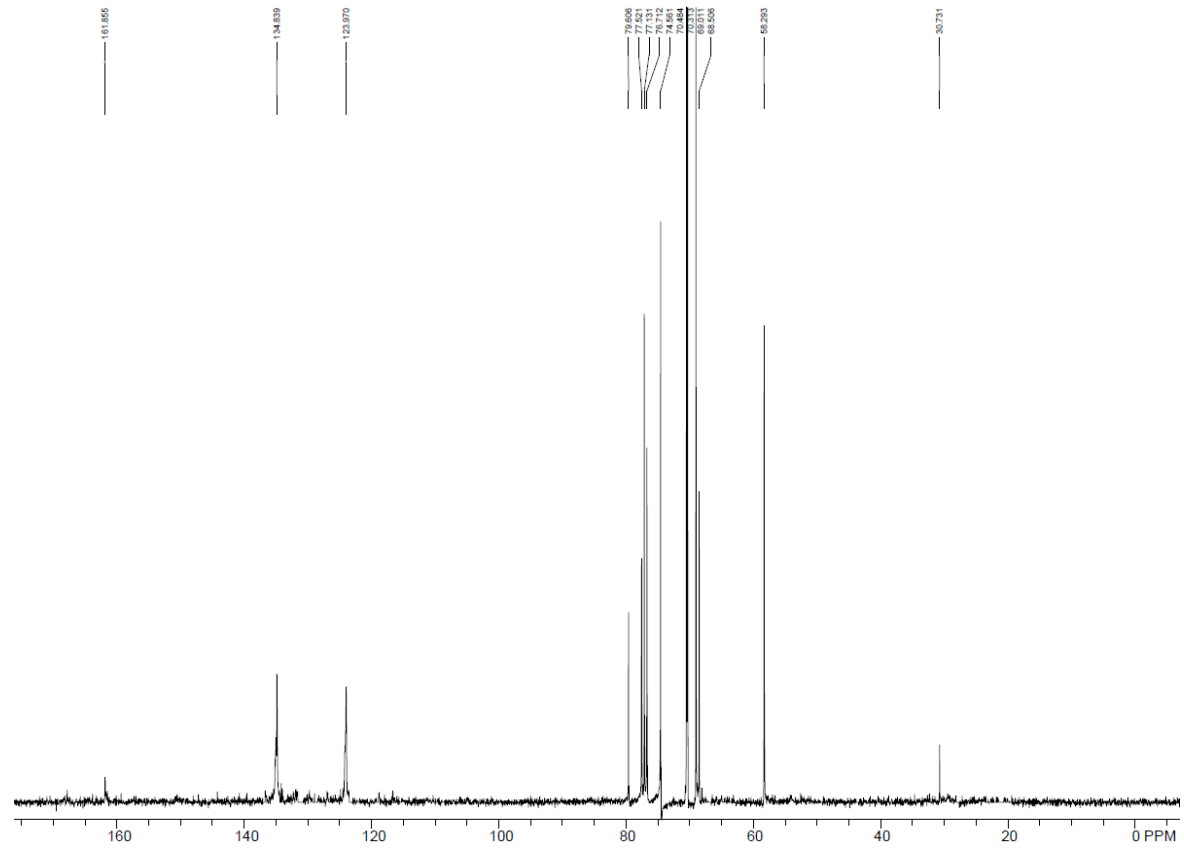


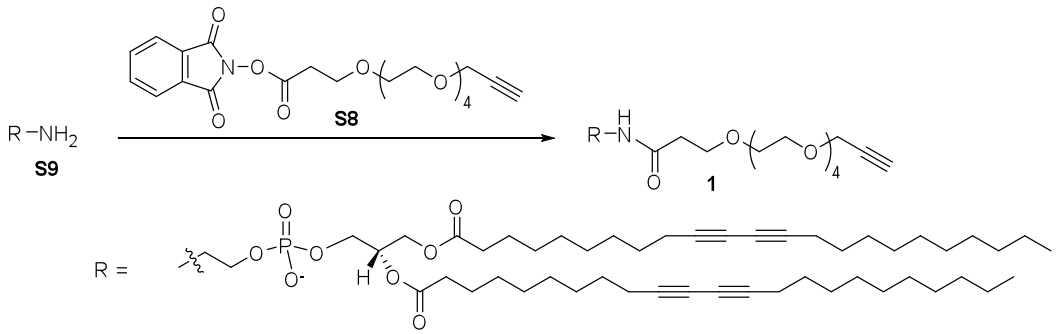


S6 **S7** **S8**

Et_3N (59 µL, 0.43 mmol), and DCC (89 mg, 0.43 mmol) were added to a solution of the acid **S6** (100 mg, 0.33 mmol) in THF (1 mL). A solution of **S7** (70 mg, 0.43 mmol) in THF (1 mL) was added, and the reaction mixture was stirred at room temperature for 12 h. The solution was filtered and the solvent was removed in vacuo, the residue was purified by flash chromatography (ethyl acetate/methanol 9:1) to give **S8** (104 mg, 0.23 mmol, 70%) as a colorless semisolid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90-7.75 (m, 2 H), 7.77 -7.70 (m, 2 H), 4.08 (t, J = 2.2 Hz, 2H), 3.82 (t, 2 H, J = 5.4 Hz) 3.76-3.37 (m, 16 H), 3.57-3.27 (m, 2 H), 2.42-2.48 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ161.9, 134.8, 123.9, 79.6, 74.6, 70.7, 70.6, 70.4, 69.0, 68.5, 58.2, 30.7. MS (ESI) m/z calcd for $C_{22}H_{27}NO_9$: 449.2; found: 472.3 ([M + Na]$^+$).

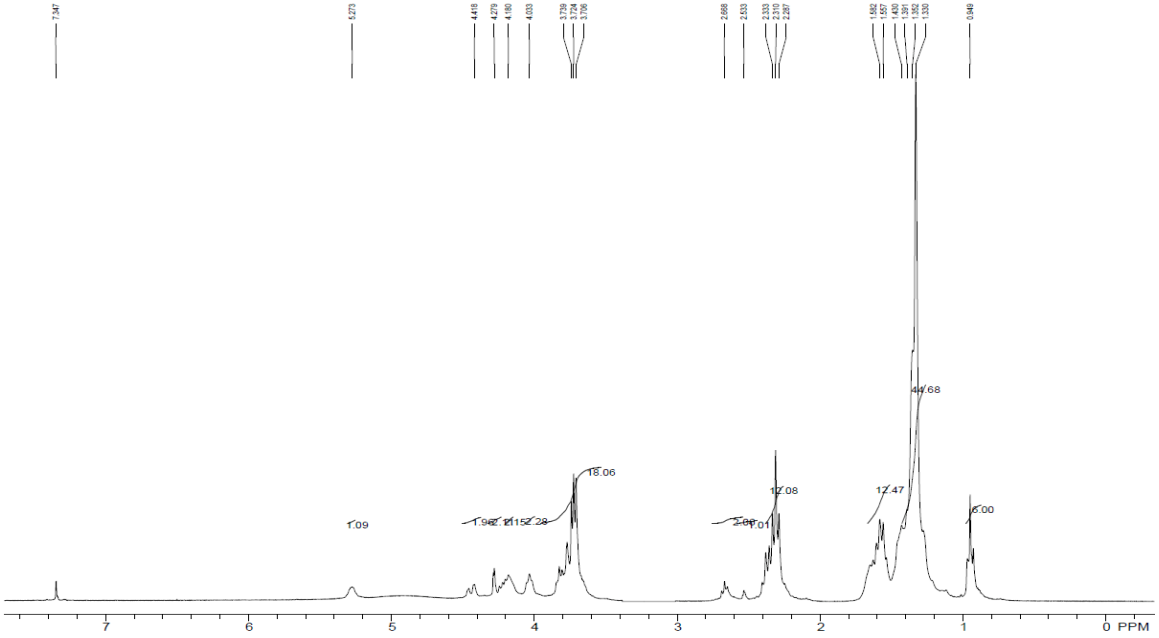


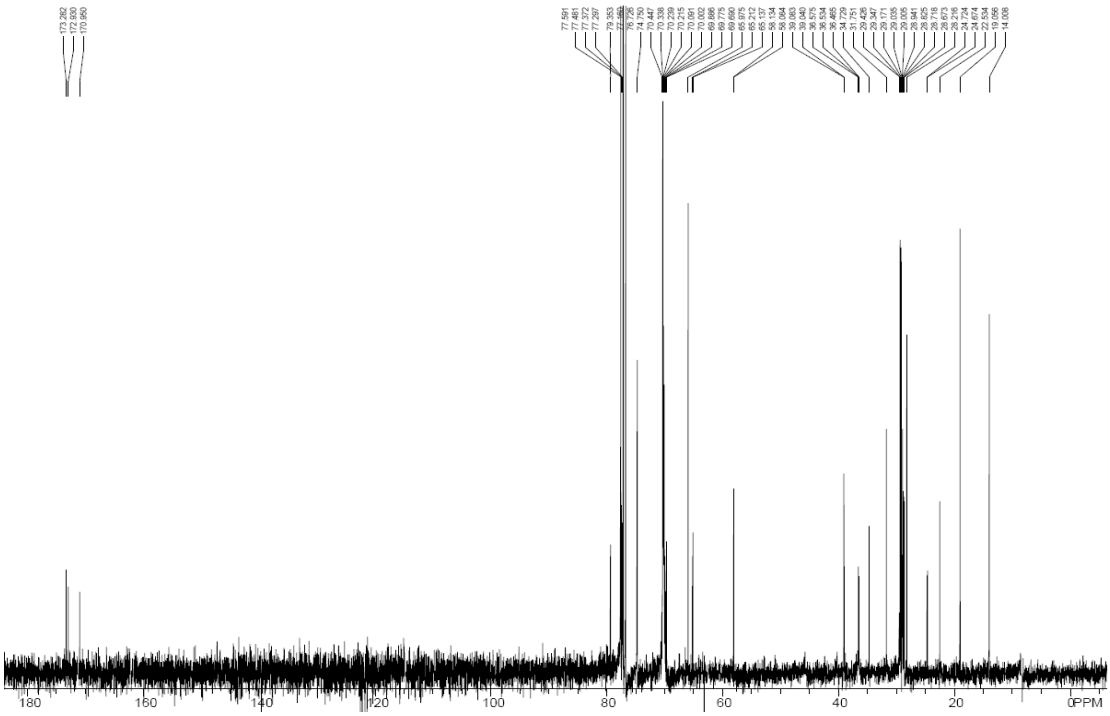


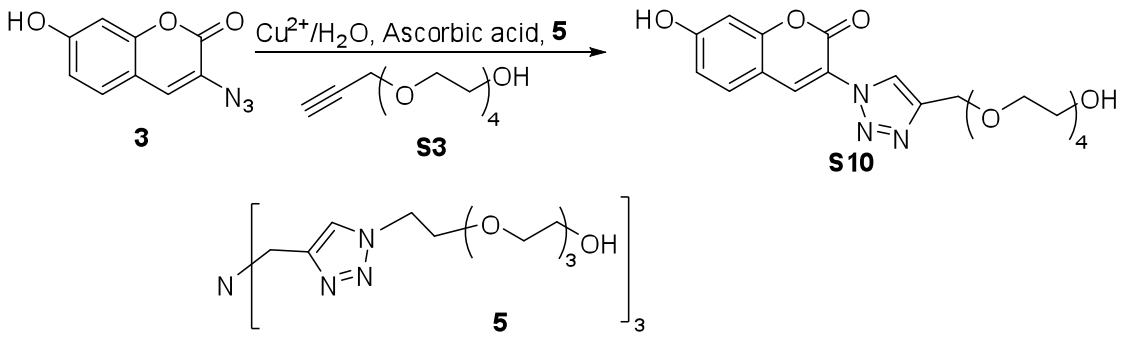


To a solution of the amine **S9** (50 mg, 0.06 mmol) and triethylamine (17 µL, 0.12 mmol) in dry $CHCl_3$ (1 mL) at 0 ˚C under nitrogen was drop-wise added **S8** (35 mg, 0.09 mmol) dissolved in dry $CHCl_3$ (1 mL). After being stirred for 1.5 h at 0 ˚C, the solution was allowed to warm up and stirred overnight at room temperature. Saturated aqueous NH_4Cl (3 mL) was added, and the mixture was extracted three times with $CHCl_3$. The combined organic layers were washed with water, brine, and dried over Na_2SO_4. The solvent was removed under vacuum affording a crude product, which was purified by flash chromatography (chloroform) to give the alkyne **1** (53 mg, 0.05 mmol, 77%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.27 (m, 1H), 4.50-4.35 (m, 2H), 4.34-4.25 (m, 2H), 4.25-4.10 (m, 2 H), 4.03 (t, 2 H, J = 5.4 Hz), 3.90-3.40 (m, 18H), 2.67 (t, 2 H, J = 5.4

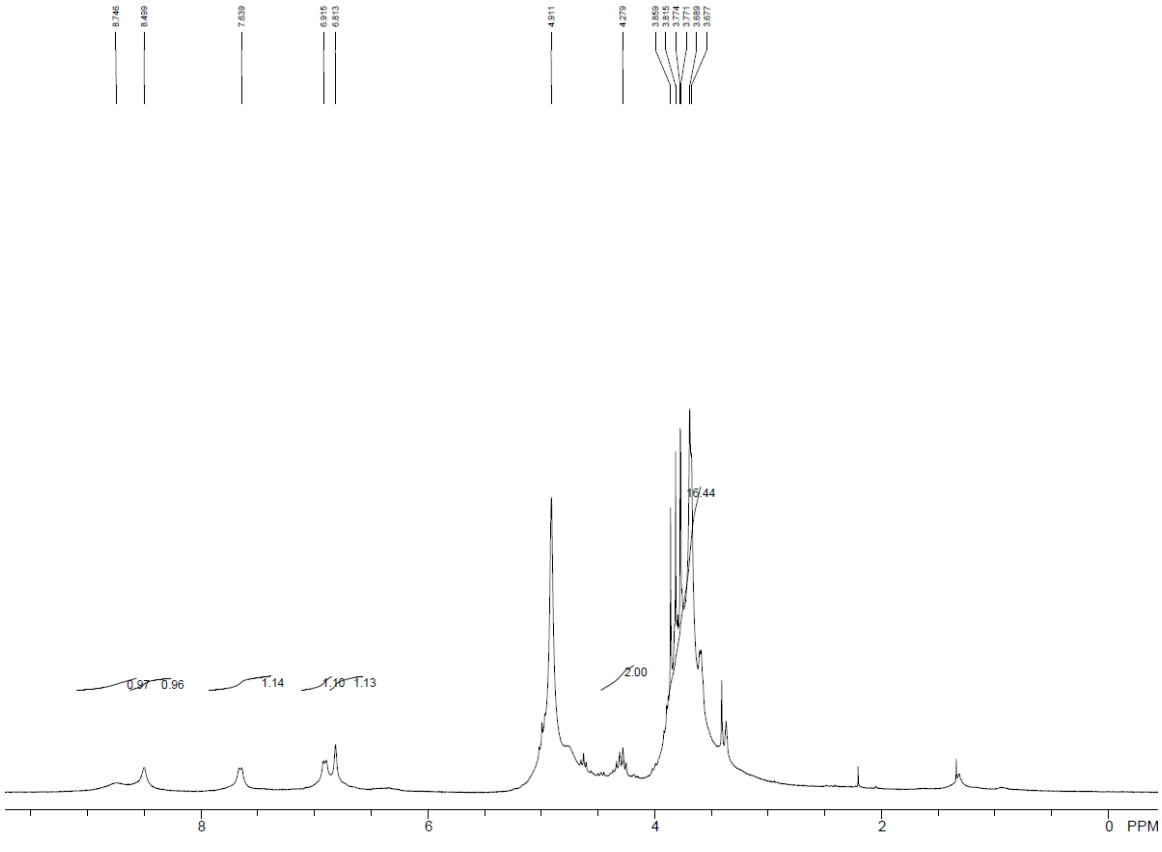
Hz), 2.53 (t, 1 H, J = 2.2 Hz), 2.46-2.05 (m, 12H), 1.75-1.50 (m, 12H), 1.50-1.20 (m, 44H), 0.95 (t, 6 H, J = 5.4 Hz) ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.3, 172.9, 170.9, 79.3, 74.8, 70.4, 70.3, 70.2, 70.1, 70.0, 69.9, 69.8, 69.7, 65.9, 65.2, 56.1, 39.0, 36.5, 34.7, 31.7, 29.4, 29.3, 29.2, 29.1, 29.0, 28.9, 28.8, 28.7, 28.6, 28.5, 28.4, 28.3, 28.2, 24.7, 22.5, 19.1, 14.0. MS (ESI) m/z calcd for $(C_{65}H_{107}NO_{14}P)^-$: 1156.7; found: 1180.9 ($[M + Na + H]^+$).

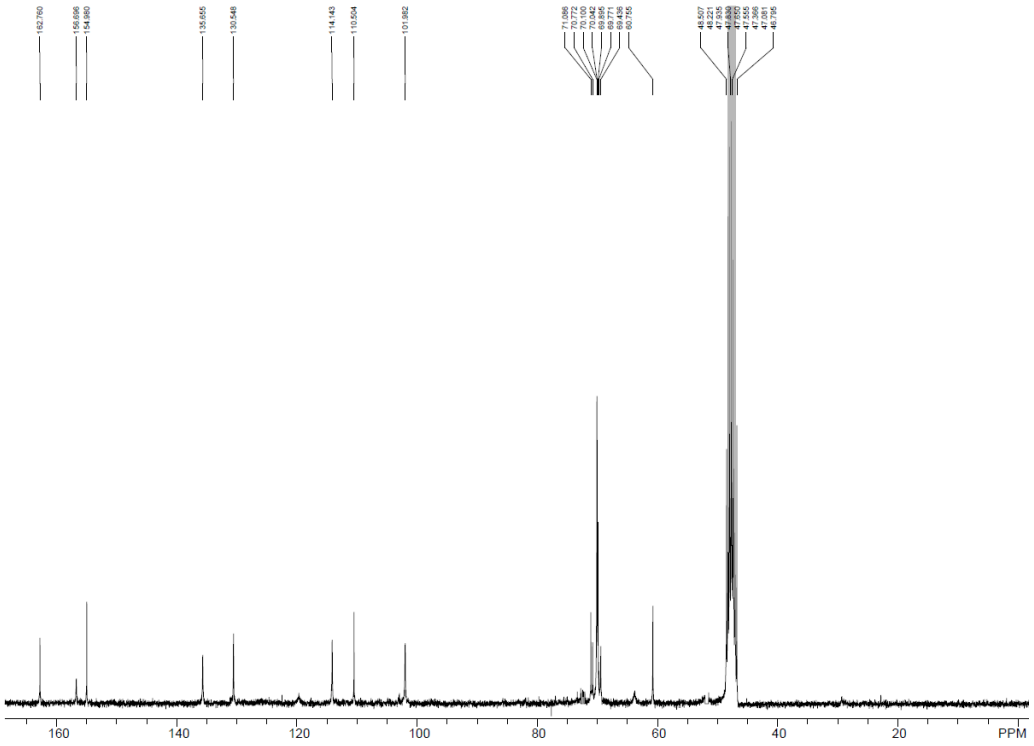


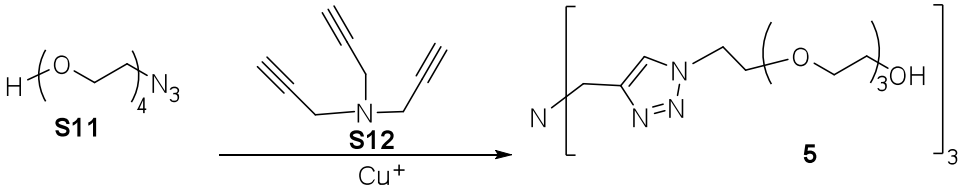




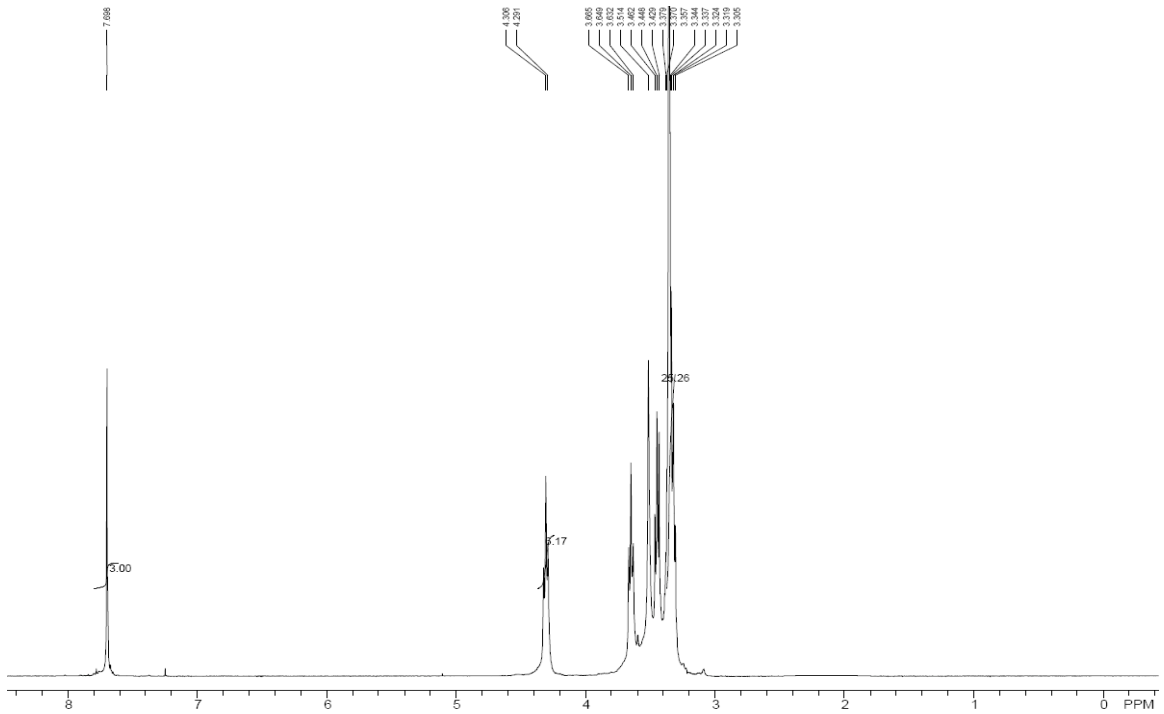
To a stirred solution of **3**[2] (500 mg, 2.46 mmol) in H_2O (2.0 mL) was treated sequentially with the alkyne **S3** (600 mg, 2.58 mmol), ascorbic acid (114 mg, 650 μmol), $CuSO_4$ (20.8 mg, 130 μmol) and ligand **5** (309 mg, 260 μmol). After the mixture was stirred at room temperature for 6 hours, the solvent was evaporated, and the residue was purified by flash chromatography (ethyl acetate/methanol 9:1) to give **S10** (0.86 g, 1.96 mmol, 80%) as a light brown viscous liquid. ^{1}H NMR (300 MHz, CD_3COCD_3): δ 8.75 (s, 1 H), 8.42 (s, 1 H), 7.60 (d, 1 H, J = 7.1 Hz), 6.89 (d, 1 H, J = 7.1 Hz), 6.79 (s, 1 H), 4.27 (m, 2 H), 4.06-3.42 (m, 16 H); ^{13}C NMR (75 MHz, CD_3OD): δ 162.8, 156.7, 154.9, 135.7, 130.5, 114.1, 110.5, 101.9, 71.1, 70.8, 70.1, 70.0, 69.9, 69.8, 69.4, 60.6; MS (ESI) *m*/*z* calcd for $C_{12}H_{24}N_4O_4$: 435.1; found: 458.3 ($[M + Na]^+$).







To a stirred solution of tripropargylamine (**S12**, 250 mg; 1.91 mmol) in CH_3CN (2.5 mL) was treated sequentially with the azide **S11**[3] (1.50 g, 6.87 mmol), 2,6-lutidine (735 mg, 6.87 mmol), and $Cu(MeCN)_4PF_6$ (27.7 mg, 0.07 mmol). After the mixture was stirred at room temperature for 24 hours, the solvent was evaporated, and the residue was purified by flash chromatography (ethyl acetate/methanol 9:1) to give **5** (0.93 g, 1.18 mmol, 62%) as a light brown viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$): 7.69 (s, 3 H), 4.30 (t, 6 H, J = 5.0 Hz), 3.64 (t, 6 H, J = 5.0 Hz), 3.46 (s, 6 H), 3.44 (t, 6 H, J = 5.0 Hz), 3.37-3.30 (m, 30 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.6, 124.4, 72.3, 70.2, 70.0, 69.2, 61.1, 49.6, 47.2; MS (ESI) m/z calcd for $C_{33}H_{60}N_{10}O_{12}$: 788.4; found: 811.4 ($[M + Na]^+$).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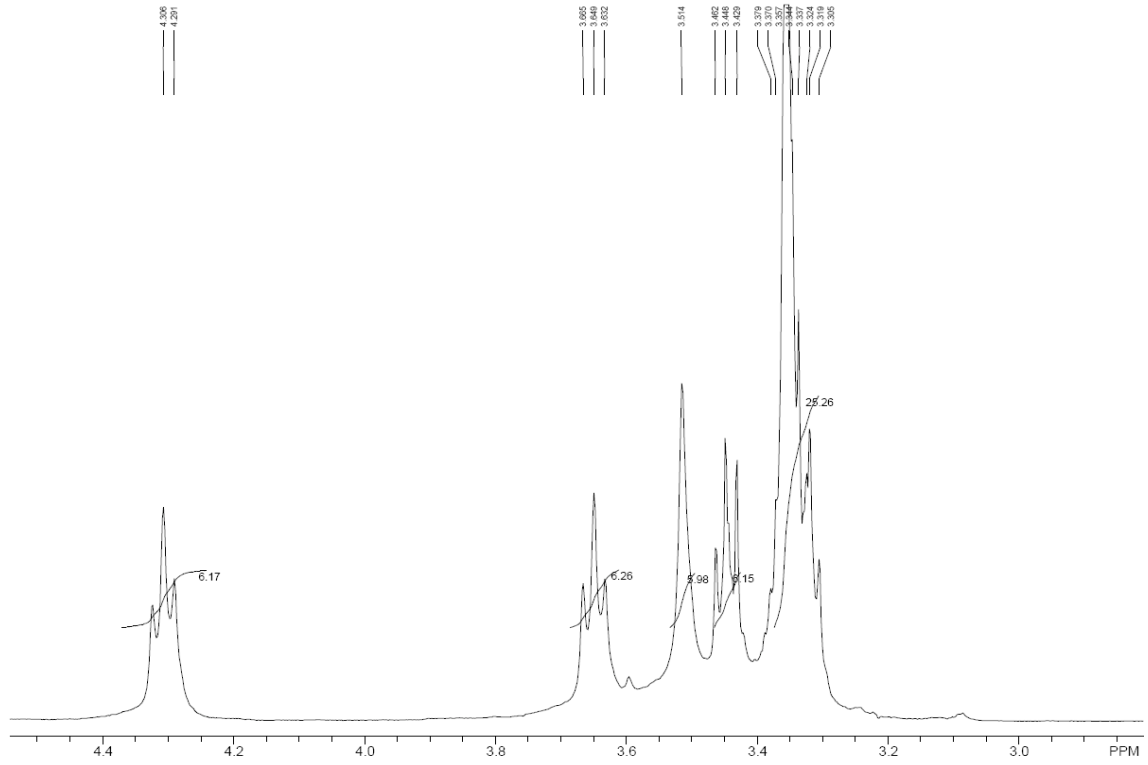
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