Rapid synthesis of 1,7-bis(*t*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane (DO2A-*t*-Bu ester)

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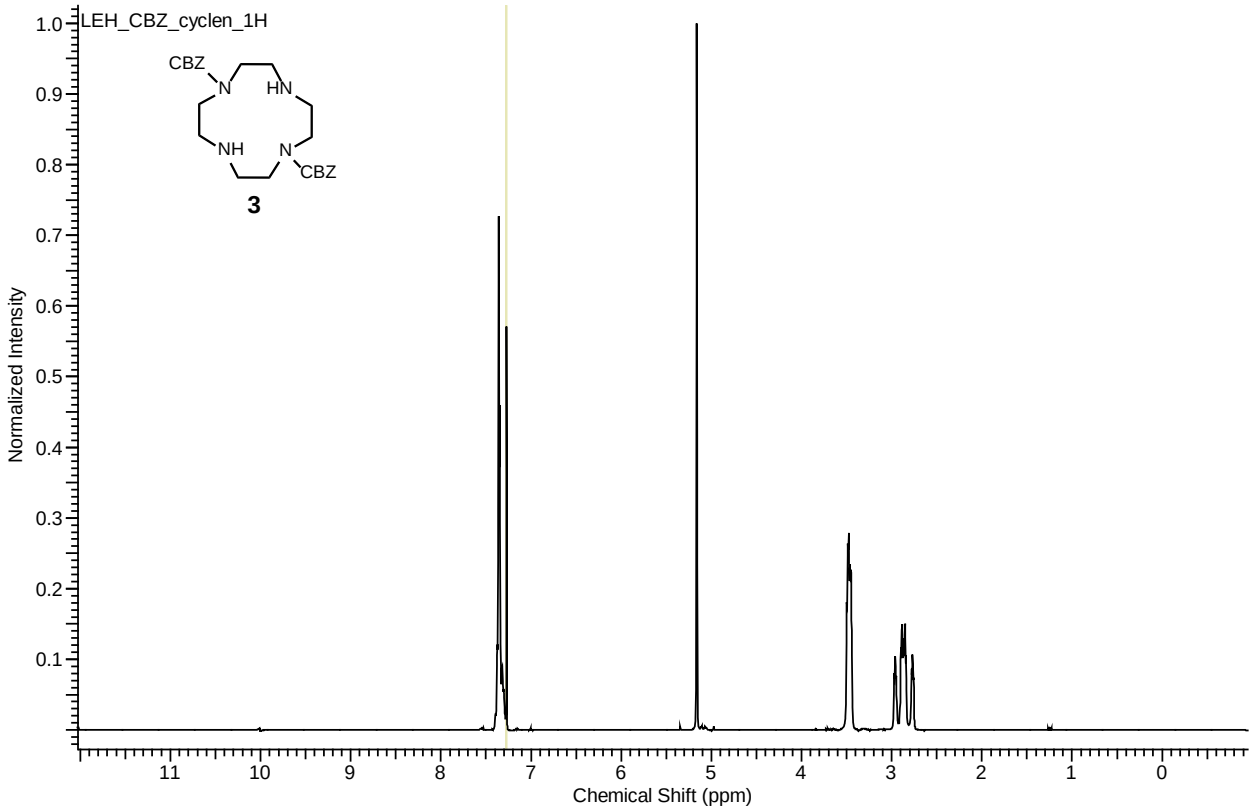
Detailed Experimental Procedures:

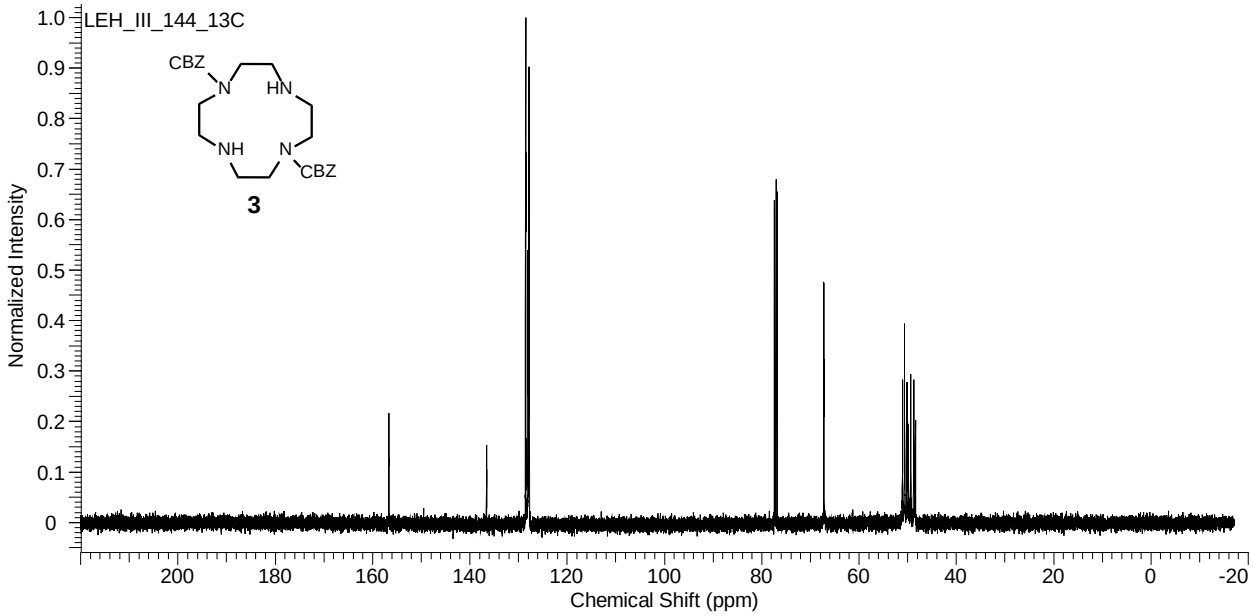
Materials. Commercially available chemicals were of reagent-grade purity and were used without further purification. Microwave irradiation was performed using a CEM MARS 5 microwave (400 W) with internal fiber-optic temperature probe. Water was purified using an Elga Purelab Ultra SC MK2 water purification system. Flash chromatography was performed using silica gel 60, 230–400 mesh. Analytical thin-layer chromatography (TLC) was carried out on TLC plates precoated with silica gel 60 F_{254} (250 μm layer thickness). Visualization of TLC plates was accomplished with a UV lamp and staining with I_2. ^{1}H- and ^{13}C-NMR spectra were obtained at 400 MHz for ^{1}H and 101 MHz for ^{13}C. Chemical shifts were referenced to residual $CHCl_3$ in $CDCl_3$: 7.27 ppm (δ) for ^{1}H and δ 77.0 for ^{13}C. ^{1}H-NMR multiplicities are reported as follows: "s" = singlet, "t" = triplet, "dt" = doublet of triplets, "m" = multiplet, and "br" = broad. Italicized elements are those that are responsible for the shift. Chemical shifts were assigned using distortionless enhancement by polarization transfer, correlation spectroscopy, and heteronuclear multiple quantum coherence spectra. High resolution electrospray ionization mass (HRESIMS) were obtained on an electrospray time-of-flight high-resolution mass spectrometer.

1,7-bis(benzyloxycarbonyl)-1,4,7,10-tetraazacyclododecane (3). Benzyl chloroformate (2.05 equiv, 0.850 mL, 5.95 mmol) was added dropwise to a solution of cyclen (0.4989 g, 2.902 mmol) in $CHCl_3$ (26 mL) under an atmosphere of argon. The resulting reaction mixture was stirred for 100 min at 60 °C and resulted in the formation of a white precipitate. Solvent was removed under reduced pressure, and the resulting white solid was washed with Et_2O (45 mL). The solid was dissolved in an aqueous solution of NaOH (3 M, 20 mL) and extracted with DCM (3 × 20 mL). Extracts were combined and dried over Na_2SO_4. Solvent was removed under reduced pressure, and the resulting oil was purified using silica gel chromatography [5:2 MeOH/NH_4OH (30% aq)] to yield 1.15 g (90%) of **3** as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.42–7.28 (m, 10H, C_6H_5), 5.16 (s, 4H, OCH_2), 3.56–3.40 (m, 8H, NCH_2), 2.96 (t, J = 4.7 Hz, 2H, NCH_2), 2.87 (dt, J = 4.9 and 14.7 Hz, 4H, NCH_2), 2.77 (t, J = 4.7 Hz, 2H, NCH_2); ^{13}C NMR (101 MHz, $CDCl_3$, δ) 156.6, 136.5, 128.5 (CH), 127.8 (CH), 127.7 (CH), 67.4 (OCH_2), 51.0 (NCH_2), 50.6 (NCH_2), 50.1 (NCH_2), 49.8 (NCH_2), 49.3 (NCH_2), 48.6 (NCH_2), 48.3 (NCH_2); HRESIMS (m/z): $[M + H]^+$ calcd for $C_{24}H_{33}N_4O_4$, 441.2502; found, 441.2494; TLC R_f = 0.21 [5:2 MeOH/NH_4OH (30% aq)].

1,7-bis(benzyloxycarbonyl)-4,10-bis(*t*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane (4). To a solution of **3** (0.747 g, 1.70 mmol) dissolved in CH_3CN (12 mL) was added DIEA (20 equiv, 5.94 mL, 34.1 mmol) followed by *t*-Bu bromoacetate (2 equiv, 0.50 mL, 3.4 mmol). The reaction mixture was stirred for 30 min at reflux. Solvent was removed under reduced pressure, resulting in a light orange oil and a white precipitate. The oil was dissolved in Et_2O (15 mL) and washed with H_2O (3 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to yield 0.96 g (85%) of **4** as a light orange oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.42–7.28 (m, 10H, C_6H_5), 5.12 (s, 4H, CH_2), 3.56–3.05 (m, 12H, CH_2), 2.87 (brs, 8H, NCH_2), 1.42 (s, 18H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$, δ) 170.5, 156.4, 136.8 (CH), 128.4 (CH), 127.8 (CH), 80.9, 66.9 (CH_2), 56.0 (br, CH_2), 54.3 (br, NCH_2), 46.7 (br, NCH_2), 28.1 (CH_3); HRESIMS (m/z): $[M + H]^+$ calcd for $C_{36}H_{53}N_4O_8$, 669.3863; found, 669.3845.

1,7-bis(*t*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane (1). To a solution of **4** (0.2321 g, 0.3470 mmol) in *i*-PrOH (8 mL) was added 10% Pd/C (20 wt %, 0.0464 g, 0.0436 mmol) and ammonium formate (46 equiv, 0.9987 g, 15.81 mmol). The mixture was heated for 10 min at 80 °C in the microwave (ramp time of 1.5 min and cool down time of 5 min). Pd/C was removed by filtration, and the solvent was removed under reduced pressure. The resulting white solid was dissolved in NaOH (5 M, 5 mL) and extracted with $CHCl_3$ (3 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to yield 0.118 g (85%) of **1** as a light yellow oil that became an off-white solid upon exposure to air. ^{1}H NMR (400 MHz, $CDCl_3$, δ) 3.31 (s, 4H, OCCH_2), 2.82 (brs, 8H, CH_2CH_2), 2.63 (t, J = 4.9 Hz, 8H, CH_2CH_2), 1.45 (s, 18H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$, δ) 171.0, 81.0, 57.2 (OCCH_2), 52.0 (CH_2CH_2), 46.0 (CH_2CH_2), 28.2 (CH_3); HRESIMS (*m*/*z*): $[M + H]^+$ calcd for $C_{20}H_{41}N_4O_4$, 401.3128; found, 401.3142.

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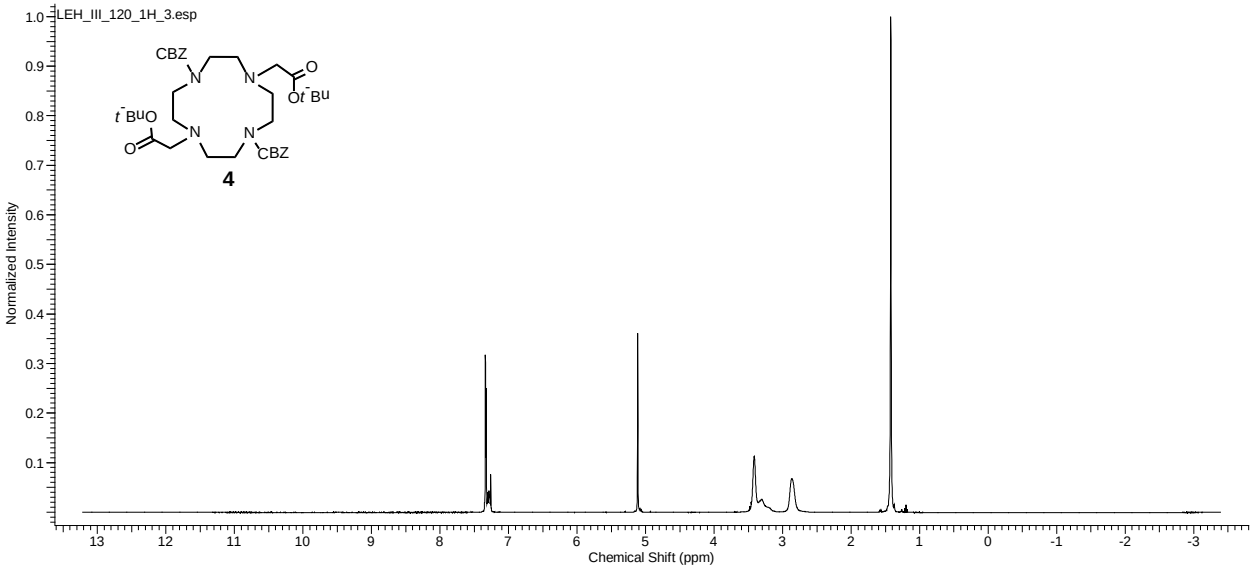
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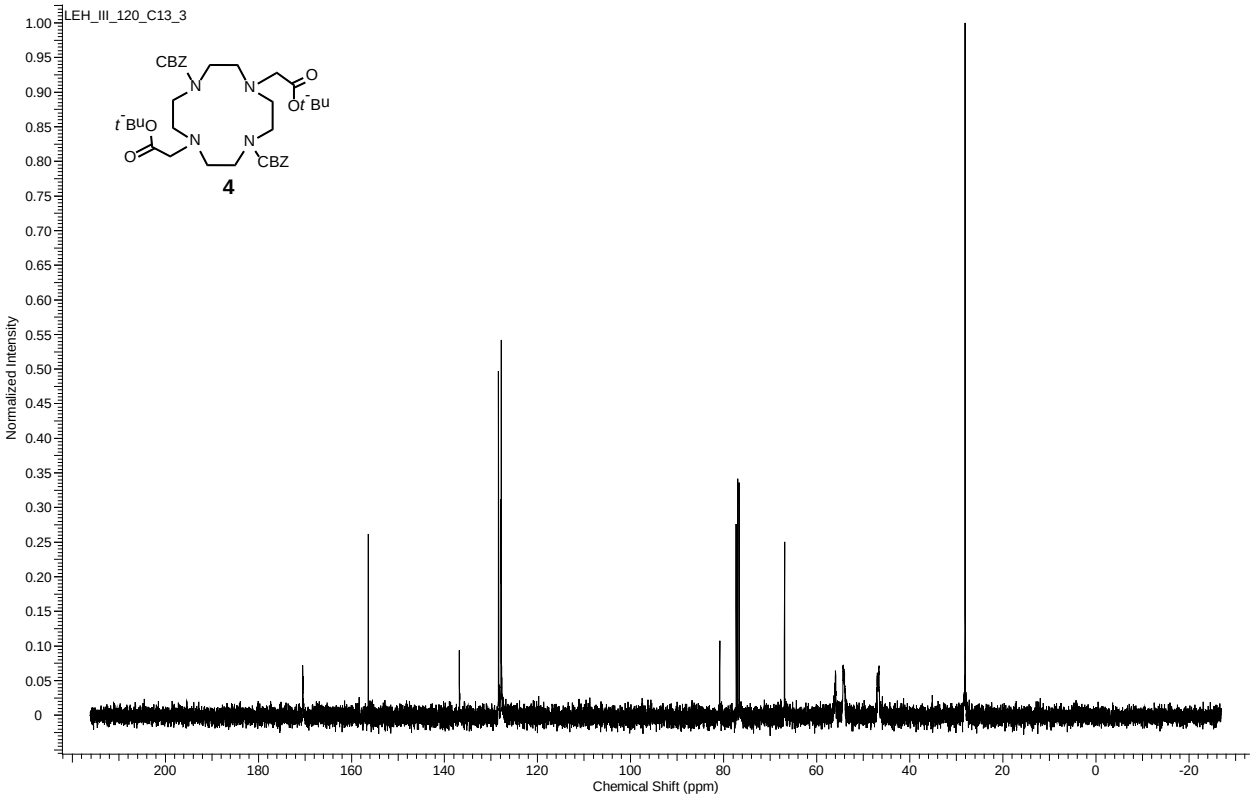
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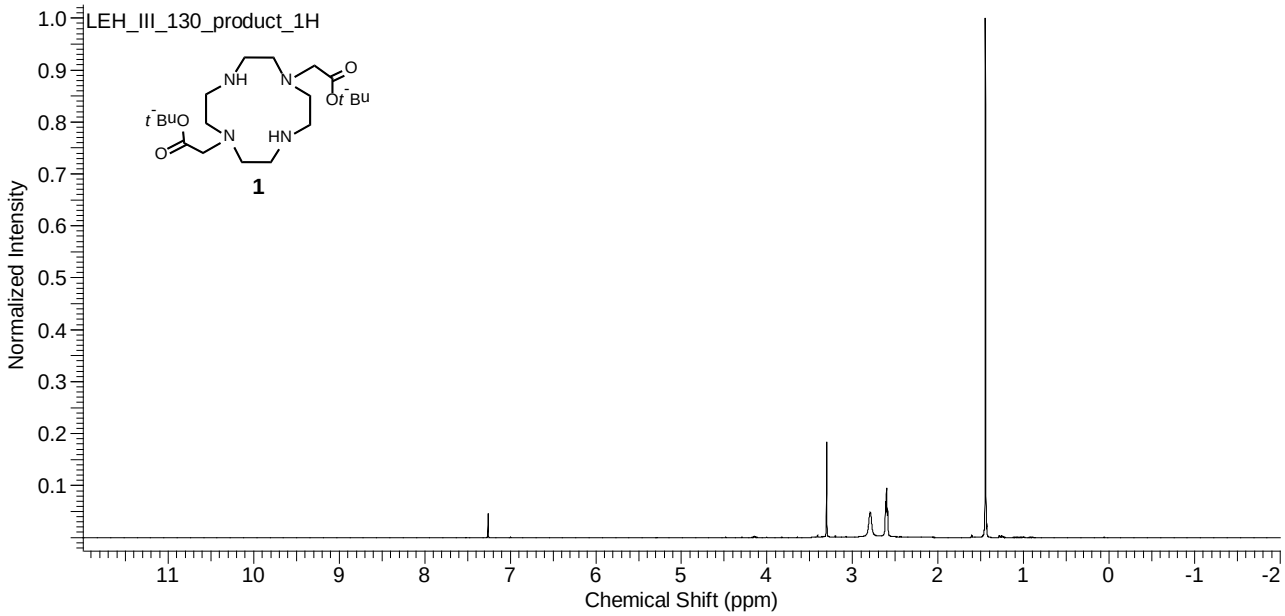
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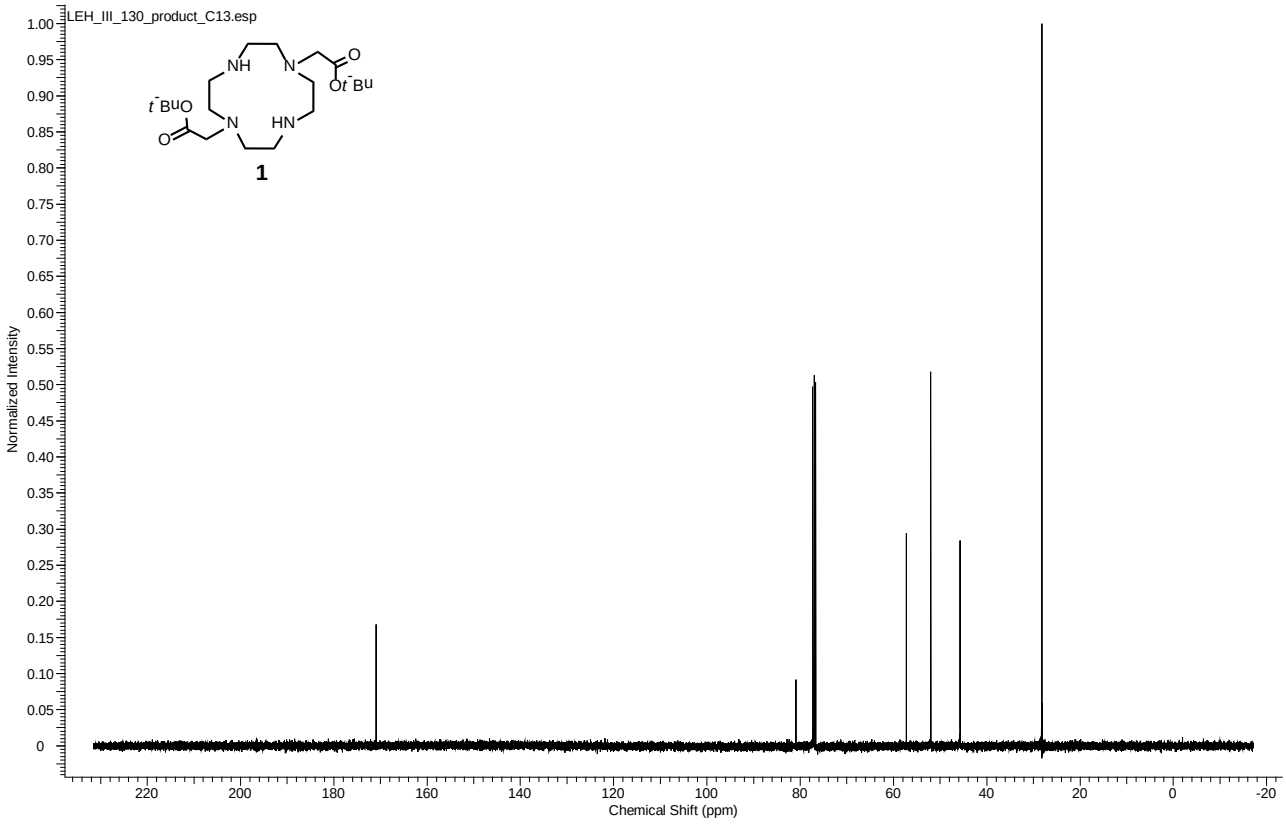
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