Supporting Information

Synthesis of 2-Alkyl- and 2-Carboxy-*p-tert*-butylcalix[4]arenes via the Lithiation of Tetramethoxy-*p-tert*-butylcalix[4]arene

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1. **Experimental Details. Synthesis and characterization (^{1}H, ^{13}C{^{1}H}, combustion analysis, HRMS, IR)**
2. **2D-NOESY spectrum for 4-Me**

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1. Experimental Details

General Considerations. Reactions were carried out under a dry nitrogen or argon atmosphere using standard Schlenk techniques in flame-dried or oven dried glassware. Tetrahydrofuran (Aldrich, Fisher) was dried over and distilled from sodium and benzophenone. Methylene chloride, chloroform and methanol (Fisher) were used as received. *n*-Butyl lithium was obtained from Aldrich as a 1.6 M solution in hexane whose concentration was checked periodically by titration of salicylaldehyde phenylhydrazone.[1] Tetramethylethylenediamine(TMEDA), MeI, EtI, $PhCH_2Br$, and *p*-bromobenzylbromide were obtained from commercial suppliers (Aldrich, Fisher) and used as received. Tetramethoxy-*p-tert*-butylcalix[4]arene (**1**) was prepared according to a literature procedure.[2] Routine ^{1}H and ^{13}C{^{1}H} NMR spectra were obtained at 300 MHz and 75 MHz repectively using a Bruker AC-300 FT-NMR spectrometer interfaced to a Techmagnetics Tecmag MacSpect 3 controller. Spectra taken in $CDCl_3$ were referenced to residual $CHCl_3$ (^{1}H δ 7.26 ppm, ^{13}C δ 77.00 ppm) while spectra taken in a $CDCl_3/CD_3CN$ mixture were referenced to internal $SiMe_4$ (for ^{1}H spectra) and $CDCl_3$ (as δ 77.00 ppm for ^{13}C spectra). Two-dimensional NMR spectra (NOESY) were obtained using a Bruker DRX-400 spectrometer. Infrared spectra were recorded with a Bruker Vector 22 using a Pike Technologies horizontal ATR attachment. Combustion analyses were performed by Robertson Microlit

Laboratories (Madison, NJ). Samples for combustion analysis were dried to constant weight and analyzed with a combustion aid present. Melting points were determined on samples in sealed, evacuated capillaries using a Thomas Hoover Unimelt capillary melting point apparatus and are uncorrected.

25,26,27,28-Tetramethoxy-2-methyl-5,11,17,23-tetrakis(1,1-dimethylethyl)calix[4]arene (3-Me). A 250 mL Schlenk flask was charged with calixarene **1** (2.146 g, 3.04 mmol) and THF (50 mL) was added via syringe to yield a colorless solution. To a second 250 mL Schlenk flask was added 100 mL THF and TMEDA (2.8 mL, 2.16 g, 18.3 mmol). After this solution was cooled to –78 °C, ^{n}BuLi (8.6 mL, 1.6 M, 13.8 mmol) in hexanes was added. After 30 minutes, the room temperature solution of **1** was added to this solution via cannula and the resulting solution took on a pale red color that became intensely dark red as the solution was allowed to warm to room temperature. After this solution had stood 1 h at room temperature, methyl iodide (1.5 mL, 3.4 g, 24.3 mmol) was added via syringe. The color of the solution immediately became yellow and shortly thereafter a precipitate began to form. After 5 min, all volatiles were removed under reduced pressure. The residue was partitioned between 2 M HCl (200 mL) and methylene chloride (250 mL). The organic layer was washed with H_2O (3 × 150 mL), dried over $MgSO_4$ and evaporated under reduced pressure to afford a yellow solid. Recrystallization from methanol gave 2 crops of microcrystalline solid totaling 1.653 g (75%).

For **3**-Me: HRMS (M+Na) calc 741.4859 found 741.4852, Δ 0.9 ppm; mp 195–197 °C; IR (cm^{-1}) 2959, 2932, 2905, 2867, 2819, 1602, 1584, 1480, 1461, 1431, 1392, 1361, 1298, 1284, 1245, 1204, 1174, 1122, 1023, 944, 871, 796, 750, 738, 698, 642.

For [**3**-Me-Na$^+$]: ^{1}H NMR ($CDCl_3/CD_3CN$) δ (ppm) 7.30 (d, *J* = 2.2 Hz, 2H, aryl), 7.23 (s, 4H, aryl), 7.21 (d, *J* = 2.6 Hz, 2H, aryl), 4.88 (q, *J* = 7.7 Hz, 1H, CH), 4.27 (d, *J* = 12.4 Hz, 2H, 8,20-H_{ax}), 4.27 (d, *J* = 12.5 Hz, 1H, 14-H_{ax}), 4.13 (s, 6H, OCH_3), 4.12 (s, 6H, OCH_3), 3.46 (d, *J* = 12.5 Hz, 3H, 8,14,20-H_{eq}), 1.73 (d, *J* = 7.7 Hz, 3H, CH_3), 1.21 (s, 18H, ^{t}Bu), 1.22 (s, 18H, ^{t}Bu); ^{13}C NMR ($CDCl_3/CD_3CN$) δ (ppm) 149.9, 149.4, 147.90, 147.89, 138.3, 133.93, 133.88, 133.6, 125.4, 125.3, 124.9, 121.7, 64.2, 63.9, 33.7, 33.5, 30.30, 30.26, 29.1, 29.0, 28.5, 19.2.

2-Ethyl-25,26,27,28-tetramethoxy-5,11,17,23-tetrakis(1,1-dimethylethyl)calix[4]arene (3-Et). A 100 mL Schlenk flask was charged with calixarene **1** (0.705 g, 1.0 mmol) and THF (30 mL) was added to give a colorless solution. Over a 15 s period, a solution of ^{n}BuLi (2.85 mL, 1.6 M, 4.6 mmol) was added which turned the solution cherry red. After 30 min ethyl iodide (0.64 mL, 1.25 g, 8.0 mmol) was added via syringe. Over the next ca. 30 sec the color of the reaction mixture gradually changed to yellow. After 30 minutes all volatile materials were removed under reduced pressure to give a residue that was partitioned between water (30 mL) and methylene chloride (30 mL). The organic layer was extracted with water (2 × 30 mL), then the aqueous extracts were combined and back-extracted with methylene chloride. The organic portions were combined, dried over $MgSO_4$ and evaporated under reduced pressure to yield a solid yellow foam. This substance was recrystallized from methanol to a fine colorless powder collected by filtration in 64% yield (471 mg).

For **3**-Et: HRMS (M+Na) calc 755.5015 found 755.5012, Δ 0.4 ppm; mp 184–186 °C; IR (cm^{-1}) 2955, 2930, 2870, 2821, 1603, 1583, 1480, 1462, 1431, 1392, 1361, 1299, 1285, 1243, 1203, 1173, 1128, 1114, 1099, 1023, 975, 942, 870, 803, 641.

For [**3**-Et-Na^{+}]: ^{1}H NMR ($CDCl_3/CD_3CN$) δ (ppm) 7.23 (d, J = 2.6 Hz, 2H, aryl), 7.23 (s, 4H, aryl), 7.20 (d, J = 2.2 Hz, 2H, aryl), 4.58 (t, J = 8.4 Hz, 1H, CH), 4.28 (d, J = 12.5 Hz, 3H, 8,14,20-H_{ax}), 4.15 (s, 6H, OCH_3), 4.13 (s, 6H, OCH_3), 3.47 (d, J = 12.5 Hz, 2H, 8,20-H_{eq}), 3.46 (d, J = 12.5 Hz, 1H, 14-H_{eq}), 2.19 ("quint", J = 7.7 Hz, 2H, $-CH_2-$), 1.21 (s, 18H, ^{t}Bu), 1.20 (s, 18H, ^{t}Bu), 1.01 (t, J = 7.3 Hz, 3H, $-CH_3$); ^{13}C NMR ($CDCl_3/CD_3CN$) δ (ppm) 149.9, 149.8, 147.80, 147.76, 137.1, 133.79, 133.76, 133.6, 125.2, 124.7, 121.4, 64.0, 63.9, 36.3, 33.6, 33.4, 30.23, 30.18, 29.9, 29.1, 28.9, 12.3.

2-Benzyl-25,26,27,28-tetramethoxy-5,11,17,23-tetrakis(1,1-dimethylethyl)calix[4]arene (3-CH_2Ph). Prepared in the same manner as **3**-Et from **1** (705 mg, 1.0 mmol), butyl lithium (2.85 mL, 1.6 M, 4.5 mmol), and benzyl bromide (0.95 mL, 1.37 g, 8.0 mmol). After workup, the product was recrystallized from methanol to yield 2 crops of **3**-CH_2Ph (572 mg, 72%).

For **3**-CH_2Ph : HRMS (M+Na) calc 817.5172 found 817.5178, Δ 0.7 ppm; mp 168–173; IR (cm^{-1}) 2953, 2931, 2904, 2866, 2819, 1602, 1584, 1480, 1461, 1431, 1392, 1361, 1285, 1267, 1245, 1204, 1174, 1119, 1076, 1021, 950, 870, 809, 796, 751, 738, 698, 643, 624.

For [**3**-CH$_2$Ph-Na$^+$]: ^{1}H NMR (CDCl$_3$/CD$_3$CN) δ (ppm) 7.46 (d, *J* = 2.2 Hz, 2H, aryl), 7.22 (s, 4H, aryl), 7.21–7.10 (m, 7H, aryl), 4.86 (t, *J* = 8.1 Hz, 1H, CH), 4.24 (d, *J* = 12.5 Hz, 1H, 14-H$_{ax}$), 4.20 (d, *J* = 12.4 Hz, 2H, 8,20-H$_{ax}$), 4.11 (s, 6H, OCH$_3$), 3.77 (s, 6H, OCH$_3$), 3.46 (d, *J* = 7.3 Hz, 2H, –C$\underline{H}_2$Ph), 3.44 (d, *J* = 12.5 Hz, 1H, 8,20-H$_{eq}$) , 3.43 (d, *J* = 12.1 Hz, 2H, 14-H$_{eq}$), 1.26 (s, 18H, ^{t}Bu), 1.20 (s, 18H, ^{t}Bu)); ^{13}C NMR (CDCl$_3$/CD$_3$CN) δ (ppm) 149.8, 149.7, 147.83, 147.79, 139.5, 136.6, 133.82, 133.80, 133.7, 128.5, 127.5, 125.5, 125.3, 125.0, 122.2, 63.9, 63.7, 39.3, 38.1, 33.7, 33.5, 30.3, 30.2, 29.1, 28.9.

2-Carboxy-25,26,27,28-tetramethoxy-5,11,17,23-tetrakis(1,1-dimethylethyl)calix[4]arene (3-COOH). Prepared in the same manner as **3**-Me from **1** (2148 mg, 3.05 mmol), butyl lithium (8.6 mL, 1.6 M, 13.7 mmol), and TMEDA (2.76 mL, 2.13 g, 18.3 mmol). Excess solid CO$_2$ was added directly to the reaction mixture as coarse chunks under an argon counterflow. The color of the solution immediately became yellow and after 5 min all volatiles were removed under reduced pressure. The residue was partitioned between 2 M HCl (30 mL) and methylene chloride (30 mL). The organic layer was washed with 2 M hydrochloric acid (2 × 30 mL), water (1 × 30 mL), dried over MgSO$_4$ and evaporated under reduced pressure to afford a colorless solid. Recrystallization from methanol/water gave a microcrystalline solid weighing 1.718 g (75%).

For **3**-COOH: HRMS (M+Na) calc 771.4601 found 771.4628, Δ 3.5 ppm; mp 267–269 °C; IR (cm^{-1}) 2954, 2905, 2869, 2825, 1707, 1602, 1585, 1482, 1462, 1434, 1409, 1393, 1362, 1299, 1277, 1262, 1244, 1216, 1204, 1173, 1120, 1105, 1020, 1004, 973, 953, 942, 872, 810, 797, 770, 737, 709, 695, 635.

For [**3**-COOH-Na$^+$]: ^{1}H NMR (CDCl$_3$/CD$_3$CN) δ (ppm) 7.51 (d, *J* = 2.2 Hz, 2H, aryl), 7.29 (d, *J* = 2.2 Hz, 2H, aryl), 7.24 (s, 4H, aryl), 5.71 (s, 1H, CH), 4.28 (d, *J* = 12.5 Hz, 2H, 8,20-H$_{ax}$), 4.26 (d, *J* = 12.1 Hz, 1H, 14-H$_{ax}$), 4.19 (s, 6H, OCH$_3$), 4.14 (s, 6H, OCH$_3$), 3.49 (d, *J* = 12.5 Hz, 2H, 8,20-H$_{eq}$), 3.47 (d, *J* = 12.5 Hz, 1H, 14-H$_{eq}$), 1.21 (s, 18H, ^{t}Bu), 1.20 (s, 18H, ^{t}Bu); ^{13}C NMR (CDCl$_3$/CD$_3$CN) δ (ppm) 171.7, 149.9, 149.6, 148.0, 133.9, 133.79, 133.76, 132.3, 126.1, 125.43, 125.36, 123.7, 64.5, 63.9, 39.8, 33.7, 33.6, 30.3, 29.2, 29.0.

2-(*p*-Bromobenzyl)-25,26,27,28-tetramethoxy-5,11,17,23-tetrakis(1,1-dimethylethyl)-calix[4]arene (3-CH$_2$Ar^{Br}). Prepared in the same manner as **3**-Et from **1** (707 mg, 1.0 mmol), butyl lithium (2.9 mL, 1.6 M, 4.5 mmol), and a solution of *para*-bromobenzyl bromide (308 mg, 1.23 mmol) in 8 mL THF.

After workup, the product was recrystallized from methanol/chloroform to yield 528 mg of **3**-CH_2Ar^{Br} (60%).

For **3**-CH_2Ar^{Br}: HRMS (M+Na) calc 895.4277 found 895.4272, Δ 0.6 ppm; mp 243–245 °C; IR (cm^{-1}) 2954, 2931, 2905, 2867, 2819, 1602, 1584, 1480, 1461, 1431, 1392, 1361, 1285, 1245, 1204, 1174, 1120, 1076, 1021, 950, 870, 809, 796, 751, 738, 698, 644, 623, 602.

For [**3**-CH_2Ar^{Br}-Na^+]: ^1H NMR ($CDCl_3/CD_3CN$) δ (ppm) 7.43 (d, *J* = 2.2 Hz, 2H, aryl), 7.34 (d, *J* = 8.1 Hz, 2H, aryl), 7.22 (s, br, 6H, aryl), 7.08 (d, *J* = 8.4 Hz, 2H, aryl), 4.83 (t, *J* = 8.1 Hz, 1H, aryl), 4.24 (d, *J* = 12.5 Hz, 1H, 14-H_{ax}), 4.20 (d, *J* = 12.4 Hz, 2H, 8,20-H_{ax}), 4.11 (s, 6H, OCH_3), 3.81 (s, 6H, OCH_3), 3.44 (“d”, *J* = 10.3 Hz, 5H, –$C\underline{H}_2Ar$, 8,14,20-H_{eq}), 1.25 (s, 18H, ^tBu), 1.20 (s, 18H, ^tBu). ^{13}C NMR ($CDCl_3/CD_3CN$) δ (ppm) 149.8, 149.7, 147.92, 147.88, 138.7, 136.3, 133.9, 133.84, 133.79, 130.4, 125.3, 122.1, 63.9, 63.8, 38.5, 37.9, 33.8, 33.5, 30.3, 30.2, 29.1, 28.9.

25,26,27,28-Tetrahydroxy-2-methyl-5,11,17,23-tetrakis(1,1-dimethylethyl)calix[4]arene (4-Me). Prepared in the same manner as **3**-Et from **1** (705 mg, 1.0 mmol), butyl lithium (2.85 mL, 1.6 M, 4.5 mmol), and methyl iodide (0.5 mL, 1.14 g, 8.0 mmol). After workup the crude **3**-Me was dissolved in CH_2Cl_2 (30 mL) under argon and the resulting solution was cooled to –78 °C. A 1.0 M solution of BBr_3 in CH_2Cl_2 (6.5 mL, 6.5 mmol) was added via syringe. The reaction mixture was held at –78 °C for 45 min then allowed to warm to room temperature. The reaction mixture was treated with saturated sodium bicarbonate (2 × 30 mL) and water (2 × 30 mL), dried over $MgSO_4$ and concentrated under reduced pressure to a black solid which was recrystallized from $CHCl_3$/methanol to give sparkling white microcrystals (455 mg, 68%).

For **4**-Me: ^1H NMR ($CDCl_3$) δ (ppm) 10.33 (s, 4H), 7.17 (d, *J* = 2.2 Hz, 2H), 7.07 (d, *J* = 2.2 Hz, 2H), 7.05 (d, *J* = 2.2 Hz, 2H), 7.01 (d, *J* = 2.2 Hz, 2H), 4.74 (q, *J* = 7.3 Hz, 1H, CH), 4.26 (d, *J* = 13.9 Hz, 1H, 14-H_{ax}), 4.25 (d, *J* = 13.9 Hz, 2H, 8,20-H_{ax}), 3.50 (d, *J* = 13.9 Hz, 3H, 8,14,20-H_{eq}), 1.72 (d, *J* = 7.3 Hz, 3H, CH_3), 1.22 (s, 18H, ^tBu), 1.21 (s, 18H, ^tBu); ^{13}C NMR ($CDCl_3$) δ (ppm) 146.71, 146.20, 144.23, 144.21, 132.00, 127.72, 127.50, 127.21, 125.88, 125.86, 125.21, 121.56, 34.25, 34.07, 32.74, 31.46(br), 29.68, 18.57; Anal. Calcd for $C_{45}H_{58}O_4$: C, 81.53; H, 8.82. Found: C, 81.40; H, 8.74; IR (cm^{-1}) 3119, 3025, 2960, 2905, 2868, 1755, 1601, 1478, 1430, 1393, 1362, 1286, 1256, 1243, 1199, 1161, 1128, 1110, 1064, 940, 911, 871, 857, 813, 780, 747, 722, 705, 626, 605.

2-Ethyl-25,26,27,28-tetrahydroxy-5,11,17,23-tetrakis(1,1-dimethylethyl)calix[4]arene (4-Et). Prepared in a manner similar to the preparation of **3**-Me from calixarene **1** (705 mg, 1.0 mmol), TMEDA (0.9 mL, 0.7 g, 6.0 mmol), and ethyl iodide (0.64 mL, 1.25 g, 8.0 mmol). After workup the crude **3**-Et was dissolved in CH_2Cl_2 (30 mL) under argon and the resulting solution was cooled to –78 °C. A 1.0 M solution of BBr_3 in CH_2Cl_2 (6.5 mL, 6.5 mmol) was added via syringe. The reaction mixture was held at –78 °C for 45 min then allowed to warm to room temperature. The reaction mixture was treated with saturated sodium bicarbonate (2 × 30 mL) and water (2 × 30 mL), dried over $MgSO_4$ and concentrated under reduced pressure to a black solid which was recrystallized from $CHCl_3$/methanol to give sparkling white microcrystals (483 mg, 66%).

For **4**-Et: ^{1}H NMR ($CDCl_3$) δ (ppm) 10.30 (s, 4H), 7.10 (d, *J* = 2.2 Hz, 2H), 7.08 (d, *J* = 2.6 Hz, 2H), 7.05 (d, *J* = 2.6 Hz, 2H), 6.99 (d, *J* = 2.2 Hz, 2H), 4.39 (t, *J* = 7.7 Hz, 1H), 4.26 (d, *J* = 13.6 Hz , 1H, 14-H_{ax}), 4.25 (d, *J* = 13.9 Hz, 2H, 8,20-H_{ax}), 3.50 (d, *J* = 13.9 Hz, 3H, 8,14,20-H_{eq}), 2.23 ("quintet", *J* = 7.3 Hz, 2H, $–CH_2–$), 1.22 (s, 18H), 1.20 (s, 18H), 0.96 (t, *J* = 7.3 Hz, 3H, $–CH_3$); ^{13}C NMR ($CDCl_3$) δ (ppm) 146.72, 144.24, 144.16, 130.97, 127.73, 127.45, 127.14, 125.88, 125.84, 125.05, 121.73, 37.67, 34.21, 34.06, 32.78, 32.74, 31.45, 31.27, 25.40, 12.81; Anal. Calcd for $C_{46}H_{60}O_4$: C, 81.61; H, 8.93. Found: C, 81.42; H, 8.89; IR (cm^{-1}) 3137, 2953, 2904, 2866, 1602, 1479, 1392, 1362, 1297, 1286, 1256, 1240, 1200, 1160, 1131, 1112, 942, 888, 873, 846, 818, 806, 780, 759, 745, 720, 708, 668, 604.

2-Benzyl-25,26,27,28-tetrahydroxy-5,11,17,23-tetrakis(1,1-dimethylethyl)calix[4]arene (4-CH_2Ph). Prepared in a manner similar to the preparation of **3**-Me from calixarene **1** (709 mg, 1.0 mmol), TMEDA (0.9 mL, 0.7 g, 6.0 mmol), butyl lithium (3.9 mL, 1.2 M, 4.7 mmol), and benzyl bromide (0.95 mL, 0.66 g, 8.0 mmol). After workup the crude **3**-CH_2Ph was dissolved in CH_2Cl_2 (30 mL) under argon and the resulting solution was cooled to –78 °C. A 1.0 M solution of BBr_3 in CH_2Cl_2 (6.5 mL, 6.5 mmol) was added via syringe. The reaction mixture was held at –78 °C for 45 min then allowed to warm to room temperature. The reaction mixture was treated with saturated sodium bicarbonate (2 × 30 mL) and water

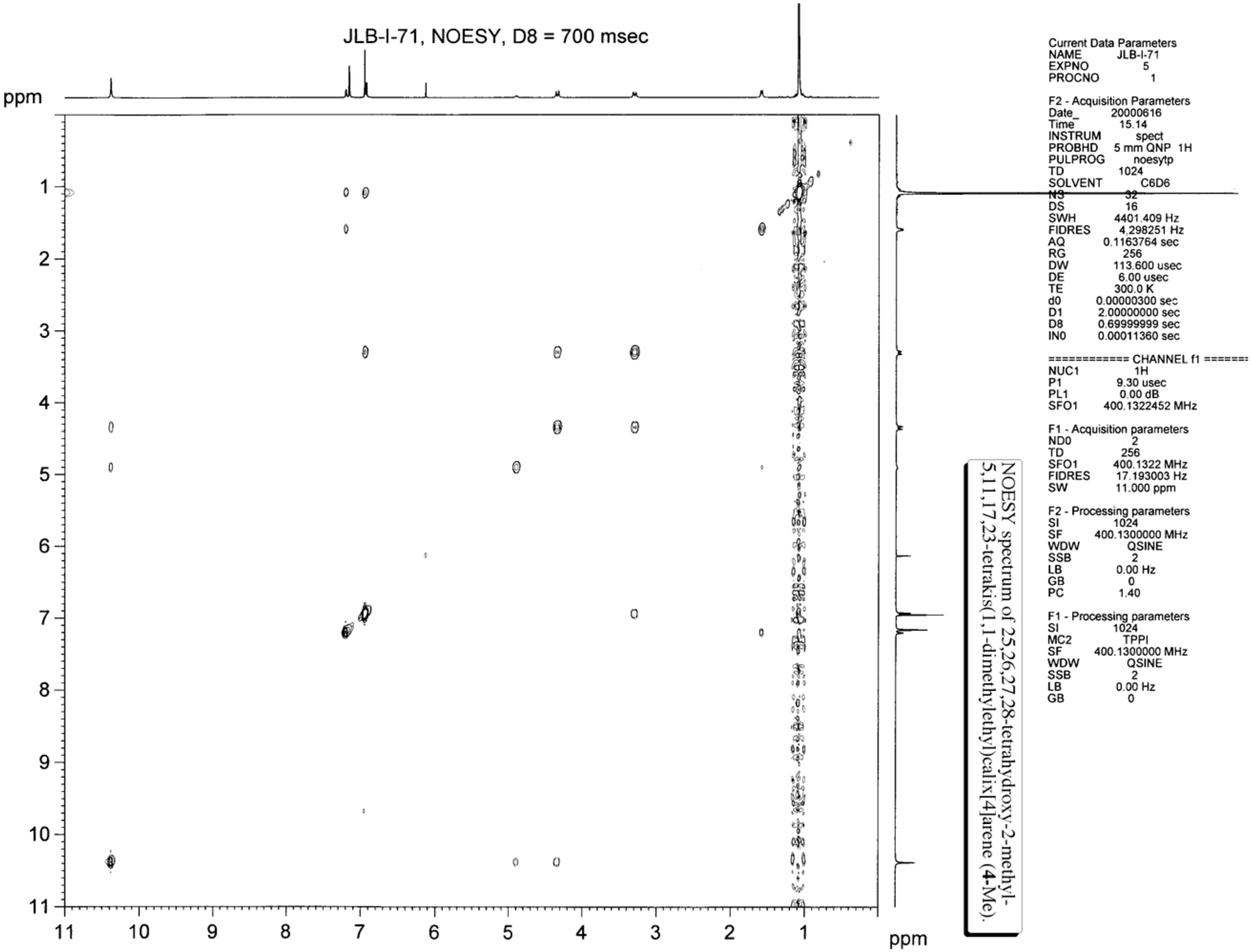
(2 × 30 mL), dried over $MgSO_4$ and concentrated under reduced pressure to a black solid which was recrystallized from $CHCl_3$/methanol to give sparkling white microcrystals (462 mg, 62%).

For **4**-CH_2Ph: ^{1}H NMR ($CDCl_3$) δ (ppm) 10.26 (s, 4H), 7.25–7.11 (m, 7H), 7.06 (d, J = 2.2 Hz, 2H), 7.04 (d, J = 2.6 Hz, 2H), 6.97 (d, J = 2.2 Hz, 2H), 4.92 (t, J = 8.1 Hz, 1H, CH), 4.25 (d, J = 13.6 Hz, 1H, 14-46H_{ax}), 4.20 (d, J = 13.6 Hz, 2H, 8,20-H_{ax}) , 3.53 (d, J = 8.1 Hz, 2H, –CH_2–), 3.49 (d, J = 13.6 Hz, 1H, 14-H_{eq}), 3.46 (d, J = 13.6 Hz, 2H, 8,20-H_{eq}), 1.22 (s, 18H), 1.21 (s, 18H); ^{13}C NMR ($CDCl_3$) δ (ppm) 146.69, 146.49, 144.18, 144.08, 140.04, 130.45, 128.88, 128.15, 127.66, 127.44, 127.22, 125.96, 125.88, 125.84, 125.24, 122.08, 38.39, 37.35, 34.23, 34.06, 32.77, 32.71, 31.45; Anal. Calcd for $C_{51}H_{62}O_4$: C, 82.89; H, 8.45. Found: C, 82.57; H, 8.39; IR (cm^{-1}) 3170, 3058, 3027, 2956, 2904, 2865, 1604, 1482, 1461, 1392, 1361, 1300, 1285, 1242, 1202, 1156, 1122, 1110, 946, 870, 814, 783, 740, 720, 695, 676, 647, 627, 604.

References:

(1) Love, B. E.; Jones, E. G. *J. Org. Chem.* **1999**, *64*, 3755-3756.

(2) Arduini, A.; Casnati, A. In *Macrocycle Synthesis. A Practical Approach*; Parker, D., Ed.; Oxford University Press: New York, 1996, p 145-173.



NOESY spectrum of 25,26,27,28-tetrahydroxy-2-methyl-5,11,17,23-tetrakis(1,1-dimethylethyl)calix[4]arene (**4**-Me).