

Supporting Information

Role of Polar Solvents for the Synthesis of Pillar[6]arenes

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Experimental Section:

General experimental methods: ¹H NMR spectra were determined on a Bruker 400 (400 MHz) spectrometer as solutions in CDCl₃. Chemical shifts are expressed in parts per million (δ) and are referenced to tetramethyl silane (TMS) as internal standard and the signals were reported as s (singlet), d (doublet), t (triplet), m (multiplet) and coupling constants *J* were given in Hz. ¹³C NMR spectra were recorded at 100 MHz in CDCl₃ solution. ESI-HRMS data were collected at Bruker MicrOTOF-Q II Instrument. MALDI-TOF data were obtained on Bruker Ultraflex III MALDI-TOF instrument using 4-nitroaniline or matrixes. Melting points were determined using the Boetius Block apparatus. All organic solvents were purified and dried in accordance with standard procedures before use. Additional control of the purity of compounds and monitoring of the reaction were carried out by thin-layer chromatography using Silica G, 200 μm plates, UV 254. Commercially available substrates were freshly distilled before the reaction. Solvents, reagents and chemicals were purchased from Aldrich, Fluka, Merck, SRL, Spectrochem and Process Chemicals and used as received without additional purification. The spectral data of all the synthesized products (**2a-2d**) are consistent with our previously reported method.¹

General procedure for the synthesis of 1,4-dialkoxybenzenes:

1,4-Dialkoxybenzenes were synthesized by the reported method.² The adequate amounts of hydroquinone, TBAB and KOH were mixed at room temperature. The appropriate alkyl halide was then added and the reaction mixture was heated to 60-80 °C in an oil bath for the required time. The crude mixture was extracted with diethyl ether (50 mL). Filtration and evaporation of the solvent afforded the pure 1,4-dialkoxybenzene.

For 1,4-diethoxybenzene: 3 Equiv. of ethyl iodide, 9 mol% of TBAB and 2.5 equiv. of KOH were used with respect to hydroquinone. The reaction mixture was heated at 60 °C for 24 h.

For 1,4-dipropoxybenzene: 3 Equiv. of *n*-propyl bromide, 9 mol% of TBAB and 2.5 equiv. of KOH were used with respect to hydroquinone. The reaction mixture was heated at 70 °C for 5 h.

For 1,4-dibutoxybenzene: 2.5 Equiv. of *n*-butyl bromide, 9 mol% of TBAB and 2.5 equiv. of KOH were used with respect to hydroquinone. The reaction mixture was heated at 80 °C for 4 h.

For 1,4-diheptyloxy benzene: 2.5 Equiv. of heptyl iodide, 9 mol% of TBAB and 2.5 equiv. of KOH were used with respect to hydroquinone. The reaction mixture was heated at 80 °C for 4 h.

For 1,4-di-*tert*-butyloxycarbonylmethoxy benzene: 2.5 Equiv. of *tert*-butyl bromoacetate, 9 mol% of TBAB and 2.5 equiv. of KOH were used with respect to hydroquinone. The reaction mixture was heated at 80 °C for 4 h.

General procedure for the synthesis of per-alkylated pillar[6]arenes (2a-2f) in presence of H₂SO₄:

To a solution of the appropriate 1,4-dialkoxy benzene (2 mmol) in 2 mL of acetonitrile, paraformaldehyde (124 mg, 4 mmol) was added. The reaction mixture was stirred for 5 minutes. Then conc. H₂SO₄ (32 μL, 30 mol%) was added to that reaction mixture and stirred at room temperature for 5 minutes. After that 5 mL of ethanol was poured into the reaction mixture. The resulting precipitate was filtered off, washed two-three times with ethanol, dried and purified by column chromatography [silica gel, hexane/ethyl acetate 30:1 (v/v)] to result in analytically pure per-alkylated pillar[6]arenes **2**.

1,4-Bis(ethoxy)pillar[6]arene (2a):¹ To a solution of 1,4-diethoxy benzene (0.33 g, 2 mmol) in 2 mL of acetonitrile, paraformaldehyde (124 mg, 4 mmol) was added. The reaction mixture was stirred for 5 minutes. Then conc. H₂SO₄ (32 μL, 30 mol%) was added to that reaction mixture and stirred at room temperature for 5 minutes. After that 5 mL of ethanol was poured into the reaction mixture. The resulting precipitate was filtered off, washed two-three times with ethanol, dried and purified by column chromatography [silica gel, hexane/ethyl acetate 30:1 (v/v)] to result in analytically pure 1,4-bis(ethoxy)pillar[6]arene (**2a**) as a white solid. Yield 71%, mp. 171-173 °C (Lit.¹ 170-172 °C); ¹H NMR (CDCl₃, 400 MHz): δ 6.67 (s, 12H, phenyl protons), 3.90-3.85 (m, 36H, methylene protons and methylene bridges), 1.31 (t, *J* = 6.7 Hz, 36H, methyl protons); ¹³C NMR (CDCl₃, 100 MHz): δ 150.7, 128.1, 115.0 (C of phenyl), 64.4 (C of oxymethylene groups), 29.7 (C of methylene bridge), 15.1 (C of methyl groups). Calcd. For C₆₆H₈₄O₁₂: m/z = 1068.60; Found: m/z = 1086.63 [M+NH₄]⁺. Anal. Calcd for C₆₆H₈₄O₁₂: C, 74.13; H, 7.92%. Found: C, 73.97; H, 8.05%. HPLC Retention time = 22.7 min.

1,4-Bis(propoxy)pillar[6]arene (2b):¹ To a solution of 1,4-dipropoxy benzene (0.39 g, 2 mmol) in 2 mL of acetonitrile, paraformaldehyde (124 mg, 4 mmol) was added. The reaction mixture was stirred for 5 minutes. Then conc. H₂SO₄ (32 μL, 30 mol%) was added to that reaction mixture and stirred at room temperature for 5 minutes. After that 5 mL of ethanol was poured into the reaction mixture. The resulting precipitate was filtered off, washed two-three times with ethanol, dried and purified by column chromatography [silica gel, hexane/ethyl acetate 30:1 (v/v)] to result in analytically pure 1,4-bis(propoxy)pillar[6]arene (**2b**) as a white solid. Yield 70%, mp. 118-120 °C (Lit.¹ 121-123 °C); ¹H NMR (CDCl₃, 400 MHz): δ 6.67 (s, 12H, phenyl

protons), 3.90 (s, 12H, methylene bridges), 3.77 (t, $J = 6.48$ Hz, 24H, $-\text{OCH}_2\text{CH}_2\text{CH}_3$), 1.75-1.70 (m, 24H, $-\text{OCH}_2\text{CH}_2\text{CH}_3$), 0.97 (t, $J = 7.4$ Hz, 36H, methyl protons); ^{13}C NMR (CDCl_3 , 100 MHz): δ 150.6, 128.0, 114.7 (C of phenyl), 70.3 (C of oxymethylene groups), 30.8 (C of methylene bridge), 22.8 (C of methylene groups), 10.5 (C of methyl groups). ESI-HRMS: Calcd. for $\text{C}_{78}\text{H}_{108}\text{O}_{12}$ $m/z = 1236.78$, found 1254.82 $[\text{M}+\text{NH}_4]^+$. Anal. Calcd for $\text{C}_{78}\text{H}_{108}\text{O}_{12}$: C, 75.69; H, 8.80%; Found: C, 75.77; H, 8.68%.

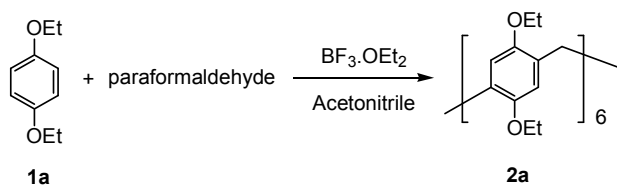
1,4-Bis(butoxy)pillar[6]arene (2c):¹ To a solution of 1,4-dibutoxy benzene (0.44 g, 2 mmol) in 2 mL of acetonitrile, paraformaldehyde (124 mg, 4 mmol) was added. The reaction mixture was stirred for 5 minutes. Then conc. H_2SO_4 (32 μL , 30 mol%) was added to that reaction mixture and stirred at room temperature for 5 minutes. After that 5 mL of ethanol was poured into the reaction mixture. The resulting precipitate was filtered off, washed two-three times with ethanol, dried and purified by column chromatography [silica gel, hexane/ethyl acetate 30:1 (v/v)] to result in analytically pure 1,4-bis(butoxy)pillar[6]arene (**2c**) as a white solid. Yield 66%, mp. 92-93 °C (Lit.¹ 90-92 °C); ^1H NMR (CDCl_3 , 400 MHz): δ 6.67 (s, 12H, phenyl protons), 3.87 (s, 12H, methylene bridges), 3.81 (t, $J = 8.96$ Hz, 24H, $-\text{OCH}_2\text{CH}_2-$), 1.73-1.67 (m, 24H, $-\text{OCH}_2\text{CH}_2-$), 1.46-1.40 (m, 24H, $-\text{OCH}_2\text{CH}_2\text{CH}_2-$), 0.91 (t, $J = 7.36$ Hz, 36H, methyl protons); ^{13}C NMR (CDCl_3 , 100 MHz): δ 150.8, 128.2, 114.9 (C of phenyl), 68.7 (C of oxymethylene groups), 31.9 (C of methylene groups), 31.0 (C of methylene bridge), 19.5 (C of methylene groups), 14.0 (C of methyl groups). ESI-HRMS: Calcd. for $\text{C}_{90}\text{H}_{132}\text{O}_{12}$ $m/z = 1404.97$, found 1423.01 $[\text{M}+\text{NH}_4]^+$. Anal. Calcd for $\text{C}_{90}\text{H}_{132}\text{O}_{12}$: C, 76.88; H, 9.46%; Found: C, 77.07; H, 9.22%.

1,4-Bis(heptyloxy)pillar[6]arene (2d):¹ To a solution of 1,4-diheptyloxy benzene (0.61 g, 2 mmol) in 2 mL of acetonitrile, paraformaldehyde (124 mg, 4 mmol) was added. The reaction mixture was stirred for 5 minutes. Then conc. H_2SO_4 (32 μL , 30 mol%) was added to that reaction mixture and stirred at room temperature for 5 minutes. After that 5 mL of ethanol was poured into the reaction mixture. The resulting precipitate was filtered off, washed two-three times with ethanol, dried and purified by column chromatography [silica gel, hexane/ethyl acetate 30:1 (v/v)] to result in analytically pure 1,4-bis(heptyloxy)pillar[6]arene (**2d**) as a white solid. Yield 61%, mp. 104-106 °C (Lit.¹ 105-107 °C); ^1H NMR (CDCl_3 , 400 MHz): δ 6.67 (s, 12H, phenyl protons), 3.86 (s, 12H, methylene bridges), 3.80 (t, $J = 6.44$ Hz, 24H, $-\text{OCH}_2\text{CH}_2-$), 1.73-1.67 (m, 24H, $-\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$), 1.31-1.27 (m, 96H, $-\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$), 0.87 (t, $J = 6.28$ Hz, 36H, methyl protons); ^{13}C NMR (CDCl_3 , 100 MHz): δ 150.7, 128.1, 114.8 (C of phenyl), 68.9 (C of oxymethylene groups), 31.9, 29.8 (C of methylene groups), 29.2 (C of methylene bridges), 29.2, 26.2, 22.7 (C of methylene groups), 14.1 (C of methyl groups). Anal.

Calcd. For $C_{126}H_{204}O_{12}$: C, 79.19; H, 10.76%; Found: C, 79.13; H, 10.70%. MALDI-TOF Calcd. For $C_{126}H_{204}O_{12}$: $m/z = 1910.54$; Found: $m/z = 1911.9$ $[M+H]^+$.

***tert*-Butyloxycarbonylmethoxy-substituted Pillar[6]arene (2f):** To a solution of 1,4-di-*tert*-butyloxycarbonylmethoxy benzene (0.68 g, 2 mmol) in 2 mL of acetonitrile, paraformaldehyde (124 mg, 4 mmol) was added. The reaction mixture was stirred for 5 minutes. Then conc. H_2SO_4 (32 μ L, 30 mol%) was added to that reaction mixture and stirred at room temperature for 5 minutes. After that 5 mL of methanol was poured into the reaction mixture. The resulting precipitate was filtered off, washed two-three times with methanol, dried and purified by column chromatography [silica gel, hexane/ethyl acetate 30:1 (v/v)] to result in analytically pure pillar[6]arene (2f) as a white solid. Yield 42%, mp. 160-162 $^{\circ}C$; 1H NMR ($CDCl_3$, 400 MHz): δ 6.84 (s, 12H, phenyl protons), 4.88 (s, 24H, $-OCH_2CO-$), 3.89 (s, 12H, methylene bridges), 1.28 (s, 108H, methyl protons); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.0 (C of carbonyl groups), 153.6, 129.1, 114.6 (C of phenyl), 81.2 (C of oxymethylene groups), 69.5 (*tertiary* carbons), 29.6 (C of methylene bridges), 28.1 (C of methyl groups). Anal. Calcd. For $C_{114}H_{156}O_{36}$: C, 65.13; H, 7.48%; Found: C, 65.02 H, 7.32%.

Table 1. Optimization of the reaction conditions in presence of $BF_3 \cdot OEt_2$ ^[a]



Entry	Amount of PF used (equiv.)	Amount of $BF_3 \cdot OEt_2$	Time (min) ^[b]	Yields (%) ^[c]
1	2	1 equiv.	5	42
2	3	1 equiv.	10	60
3	3	1 equiv.	15	67
4	3	0.5 equiv.	15	46
5	3	1 equiv.	20	68

^[a] All reactions were carried out on 2 mmol scale in 2 mL of acetonitrile. ^[b] Time was counted after addition of the catalyst. ^[c] Yields after washing with ethyl alcohol. PF = Paraformaldehyde.

Typical procedure for the synthesis of pillar[6]arene 2a in presence of BF₃·OEt₂:

Paraformaldehyde (186 mg, 6 mmol) was added to a solution of 1,4-diethoxybenzene (332 mg, 2 mmol) in acetonitrile (2 mL) and stirred for 5 min at room temperature for dissolving the reactants in solvent. Then BF₃·OEt₂ (0.25 mL, 2 mmol) was added to the solution, and the mixture was stirred at room temperature for 15 min. After that 5 mL of ethanol was poured into the reaction mixture. The resulting precipitate was filtered off, washed two-three times with ethanol, dried and purified by column chromatography [silica gel, hexane/ethyl acetate 30:1 (v/v)] to result in analytically pure per-alkylated pillar[6]arene **2a**.

Typical procedure for the synthesis of 2,5-diethoxybenzyl alcohol (4a):

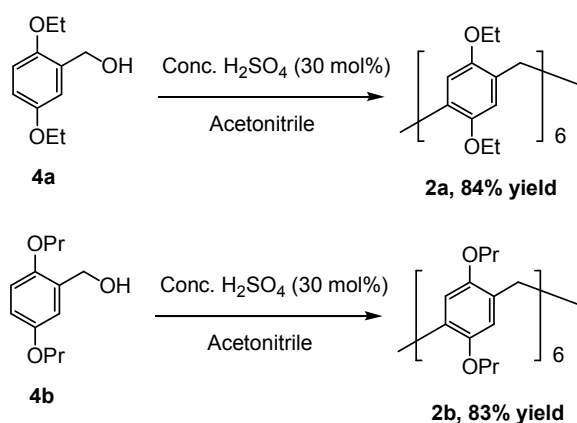
In a typical procedure a mixture of 1,4-diethoxy benzene (1.66 g, 10 mmol), paraformaldehyde (3 g, 100 mmol), H₂SO₄ (20 mg), and DDQ (4.54 g, 20 mmol) was stirred in 10 mL acetonitrile for 5 h at 80 °C. The reaction mixture was cooled to room temperature. The obtained precipitate was filtered off and washed with ethyl acetate. The crude product from the filtrate was purified by column chromatography (eluent: hexane/ethyl acetate) to get the corresponding 2,5-diethoxybenzaldehyde. The product was dissolved in 10 mL of MeOH. 1.5 equiv. of NaBH₄ was added by portion to that solution and stirred for 5 h. After evaporation of the solvent 20 mL of ethyl acetate and 5 mL of water were added. Then the combined organic layer was dried over anhydrous Na₂SO₄. Evaporation of solvent furnished the pure product **4a**.

Same procedure was followed in case of **4b**.

General procedure for the synthesis of **2a** from **4a**:

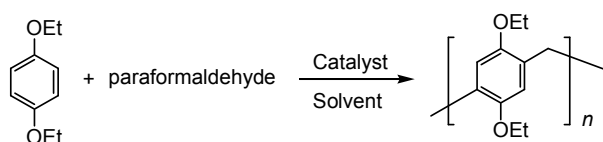
To a solution of **4a** (392 mg, 2 mmol) in acetonitrile (2 mL) conc. H₂SO₄ (32 μ L, 30 mol%) was added and stirred for 5 min at room temperature. After that 5 mL of ethanol was poured into the reaction mixture. The resulting precipitate was filtered off, washed two-three times with ethanol, dried and purified by column chromatography [silica gel, hexane/ethyl acetate 30:1 (v/v)] to result in analytically pure per-alkylated pillar[6]arene **2a**.

Same procedure was followed for the synthesis of **2b** from **4b**, where **4b** was taken as starting material instead of **4a**.



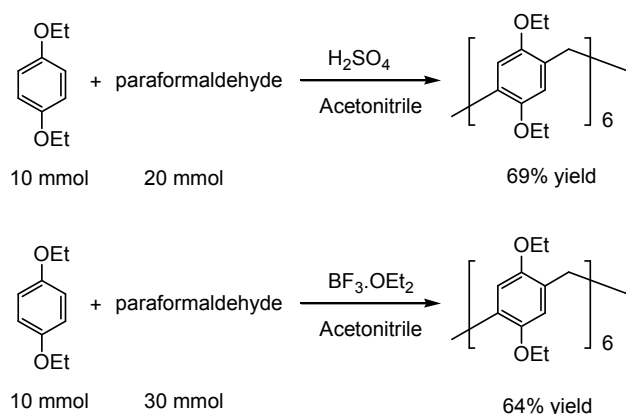
Scheme 1. Synthesis of **2a** & **2b** from **4a** & **4b** respectively.

Table 2. Solvent controlled synthesis of Pillar[*n*]arenes:^[a]



Entry	Catalyst	Solvents (2 mL)	Yields of Pillar[5]arene (%)	Yields of Pillar[6]arene (%)
1	H ₂ SO ₄ (30 mol%)	1,2-DCE	0	Traces
2	H ₂ SO ₄ (30 mol%)	Acetonitrile	0	71
3	H ₂ SO ₄ (30 mol%)	1,2-DCE & Acetonitrile (1:1)	0	68
4 ^[b]	BF ₃ .OEt ₂ (1 equiv.)	1,2-DCE	15	0
5	BF ₃ .OEt ₂ (1 equiv.)	Acetonitrile	Traces	67
6	BF ₃ .OEt ₂ (1 equiv.)	1,2-DCE & Acetonitrile (1:1)	Traces	63

^[a] All reactions were carried out on 2 mmol scale. ^[b] Typical Ogoshi's procedure. (Ref. 3)



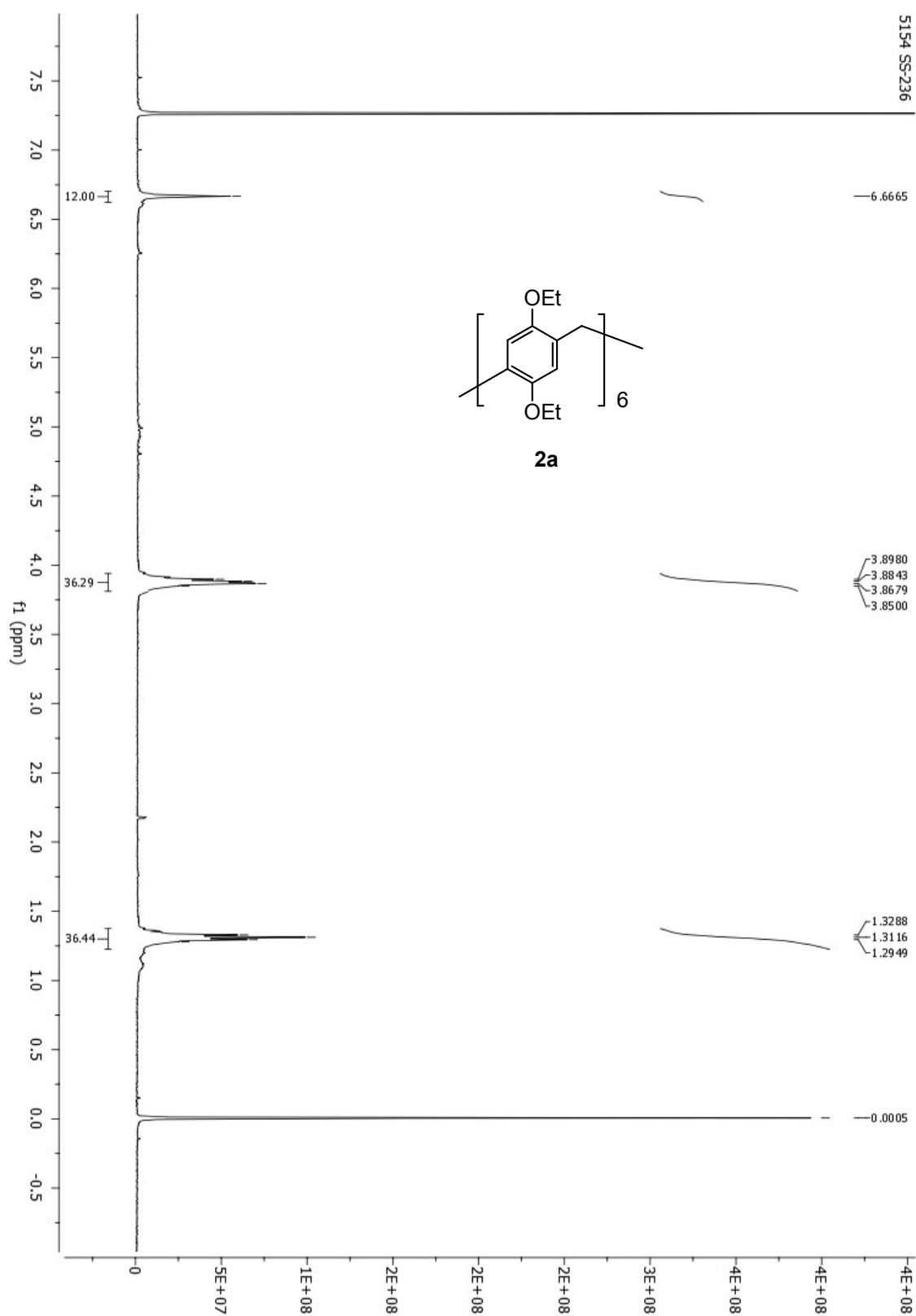
Scheme 2. Gram scale synthesis

Typical procedure for the synthesis of 2a on gram scale:

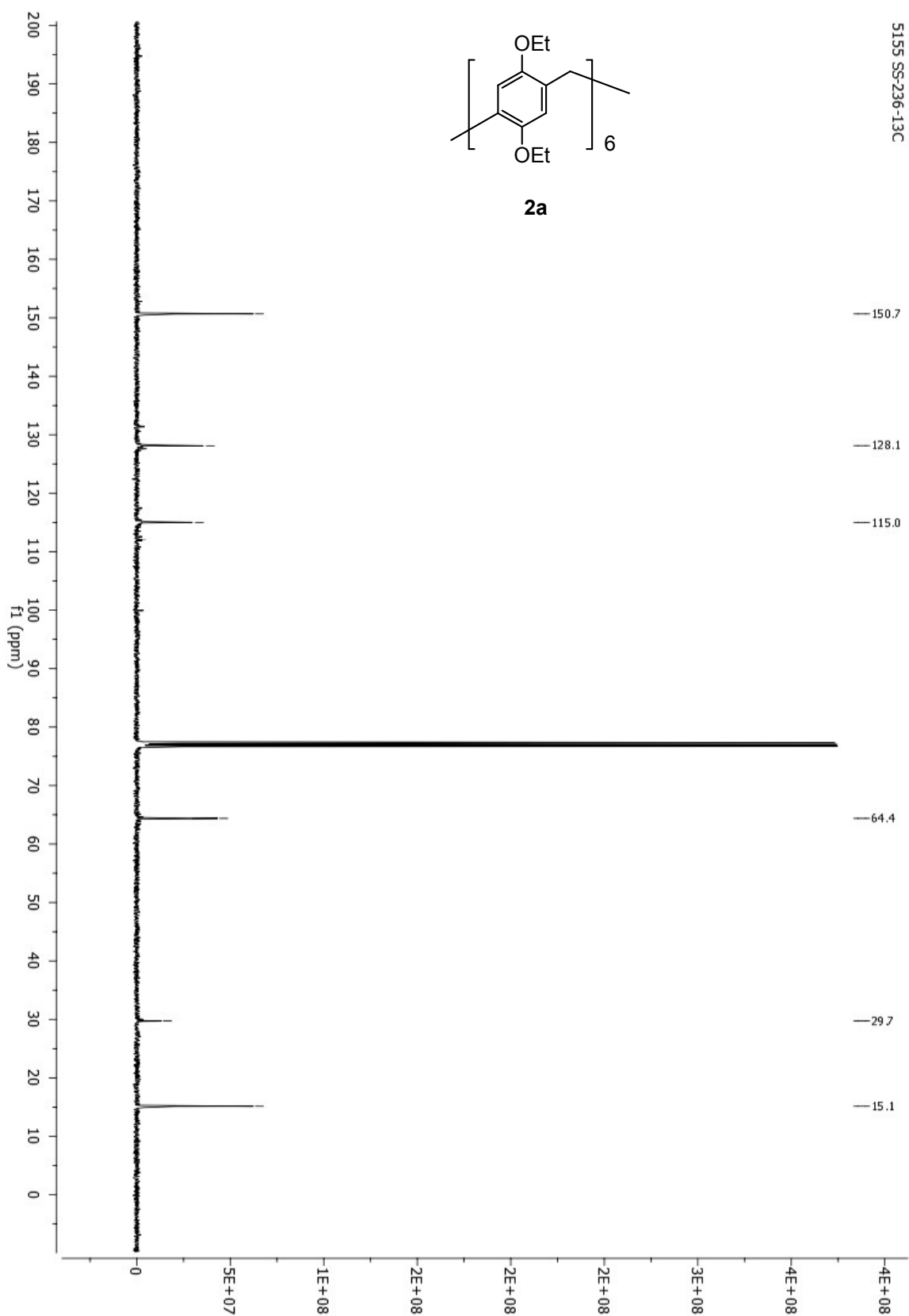
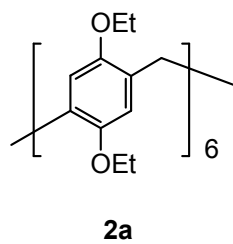
Using H_2SO_4 . To a solution of the appropriate 1,4-diethoxy benzene **1a** (1.66 g, 10 mmol) in 10 mL of acetonitrile, paraformaldehyde (0.62 g, 20 mmol) was added. The reaction mixture was stirred for 10 minutes. Then conc. H_2SO_4 (160 μL , 30 mol%) was added to that reaction mixture and stirred at room temperature for 5 minutes. After that 20 mL of ethanol was poured into the reaction mixture. The resulting precipitate was filtered off, washed two-three times with ethanol, dried and purified by column chromatography [silica gel, hexane/ethyl acetate 30:1 (v/v)] to result in analytically pure per-alkylated pillar[6]arene **2a**.

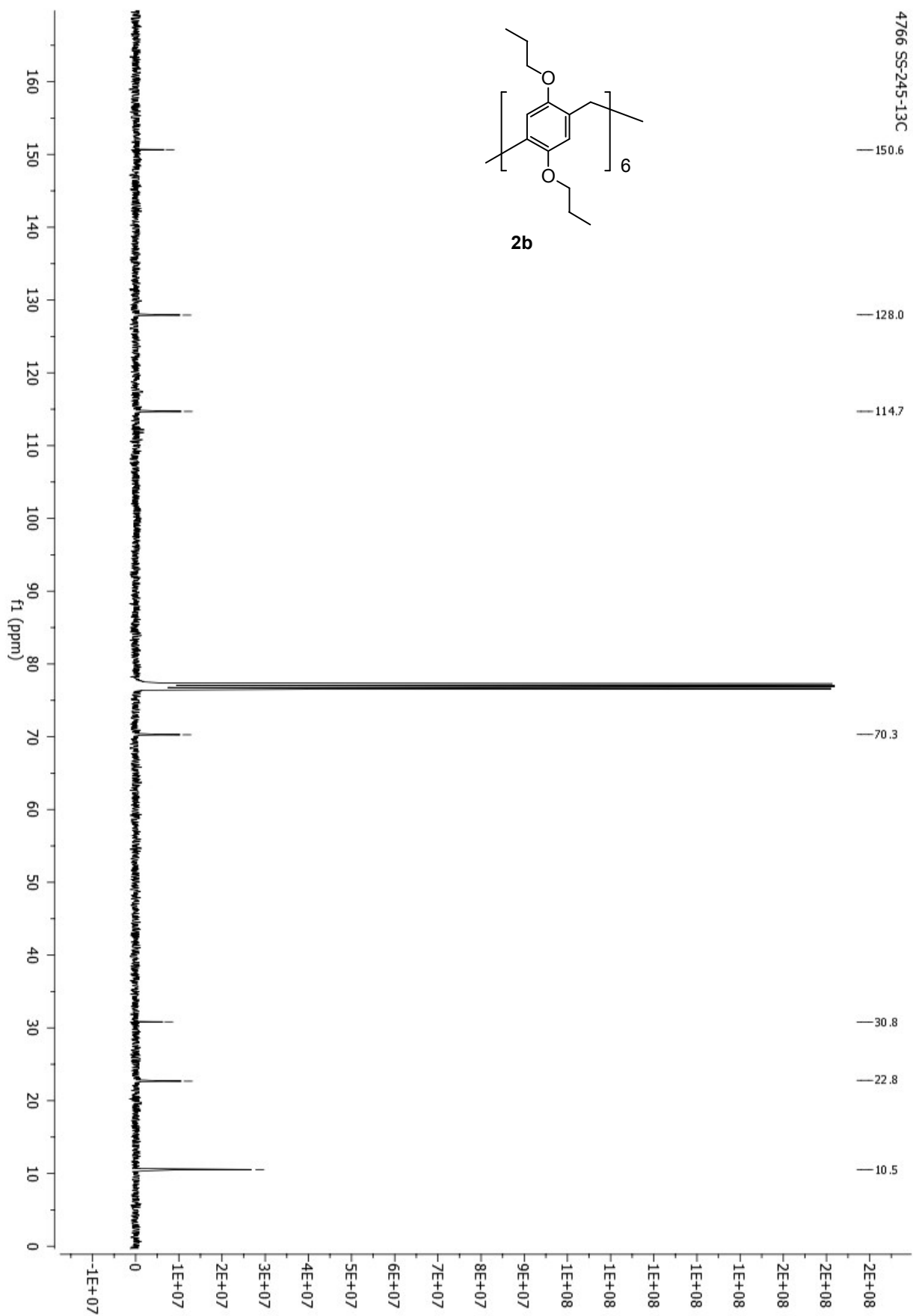
Using $\text{BF}_3 \cdot \text{OEt}_2$. To a solution of the appropriate 1,4-diethoxy benzene **1a** (1.66 g, 10 mmol) in 10 mL of acetonitrile, paraformaldehyde (0.93 g, 30 mmol) was added. The reaction mixture was stirred for 10 minutes. Then $\text{BF}_3 \cdot \text{OEt}_2$ (1.25 mL, 10 mmol) was added to that reaction mixture and stirred at room temperature for 5 minutes. After that 20 mL of ethanol was poured into the reaction mixture. The resulting precipitate was filtered off, washed two-three times with ethanol, dried and purified by column chromatography [silica gel, hexane/ethyl acetate 30:1 (v/v)] to result in analytically pure per-alkylated pillar[6]arenes **2a**.

1,4-Bis(ethoxy)pillar[6]arene (2a):

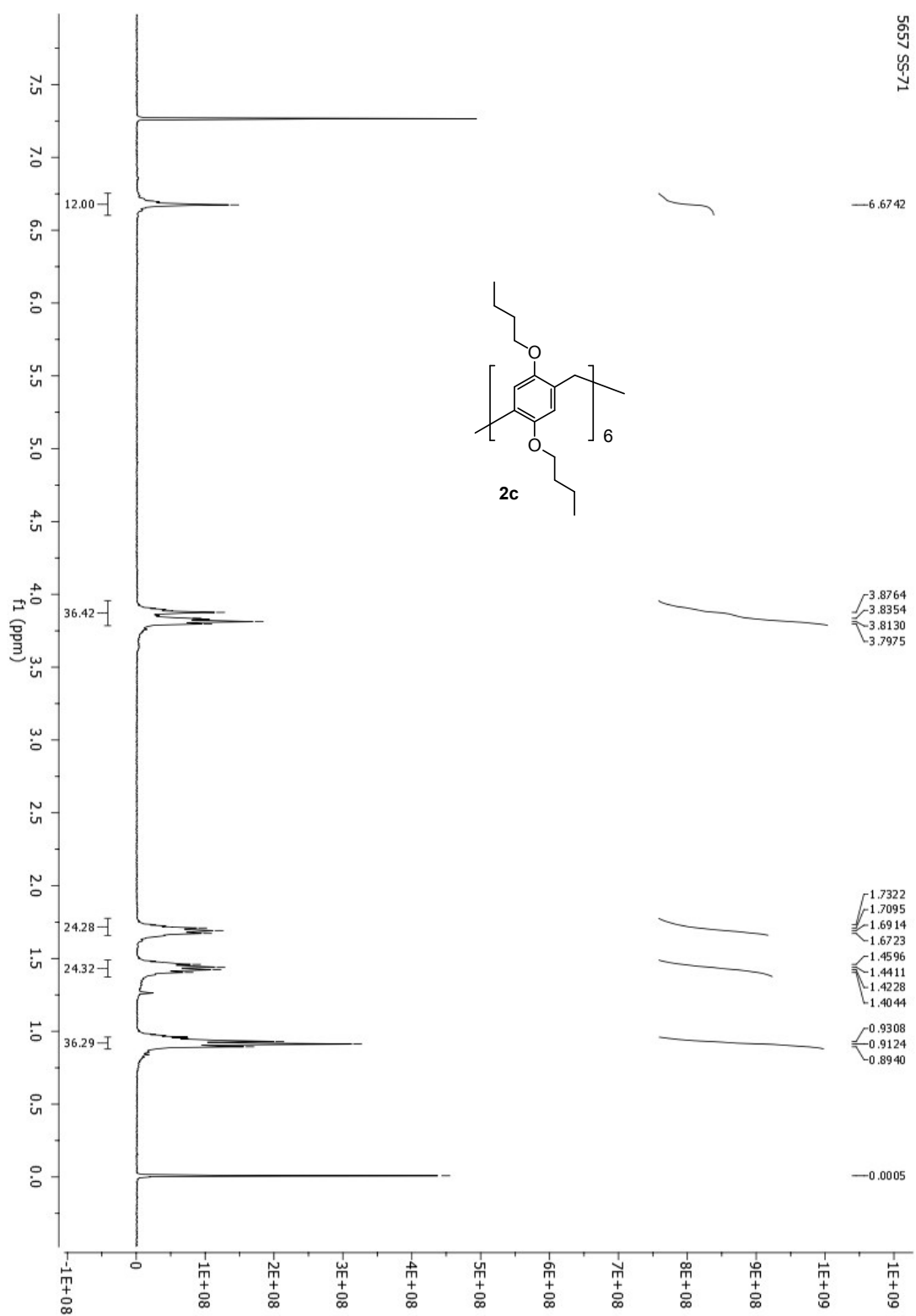


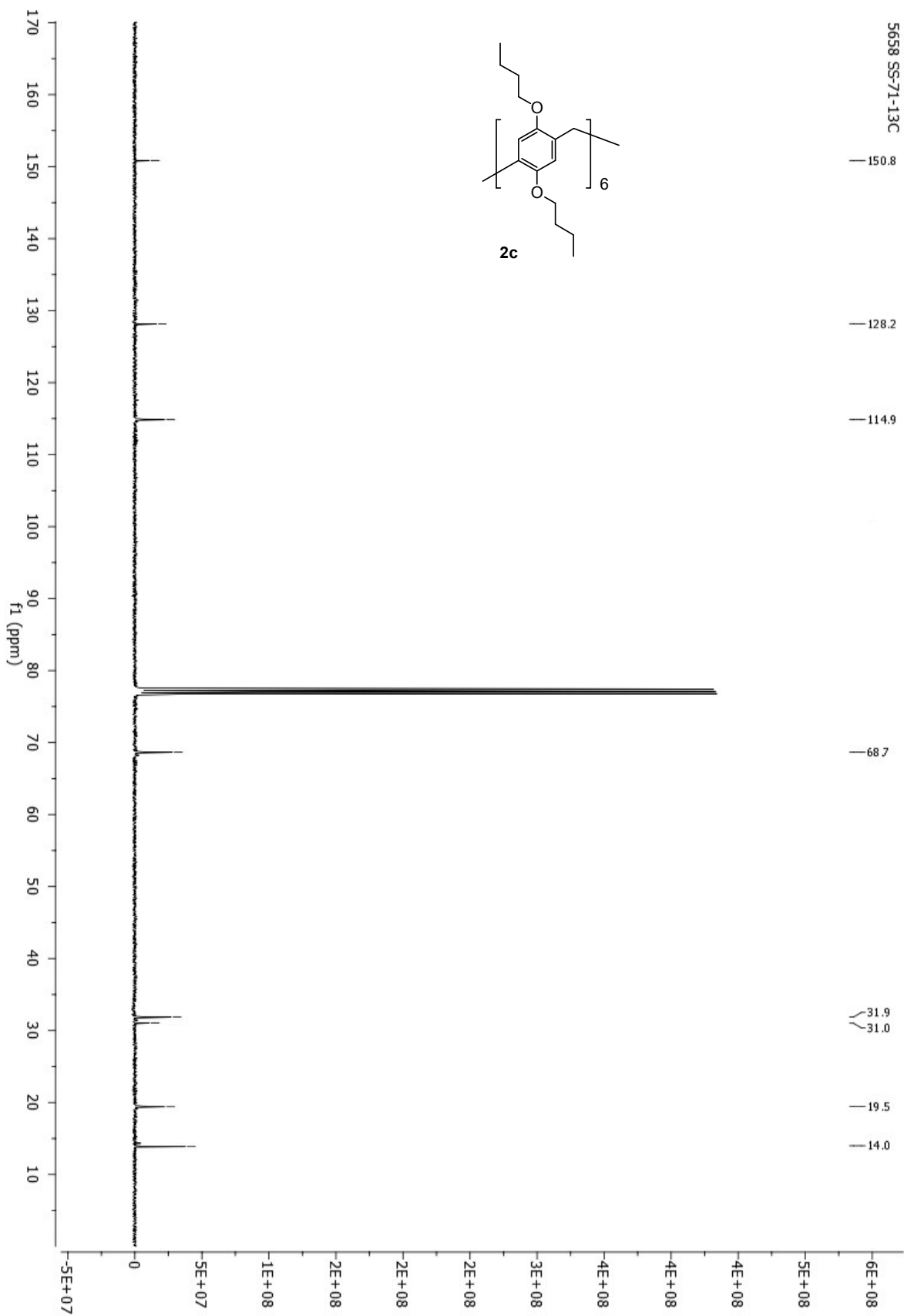
5155 SS-236-13C



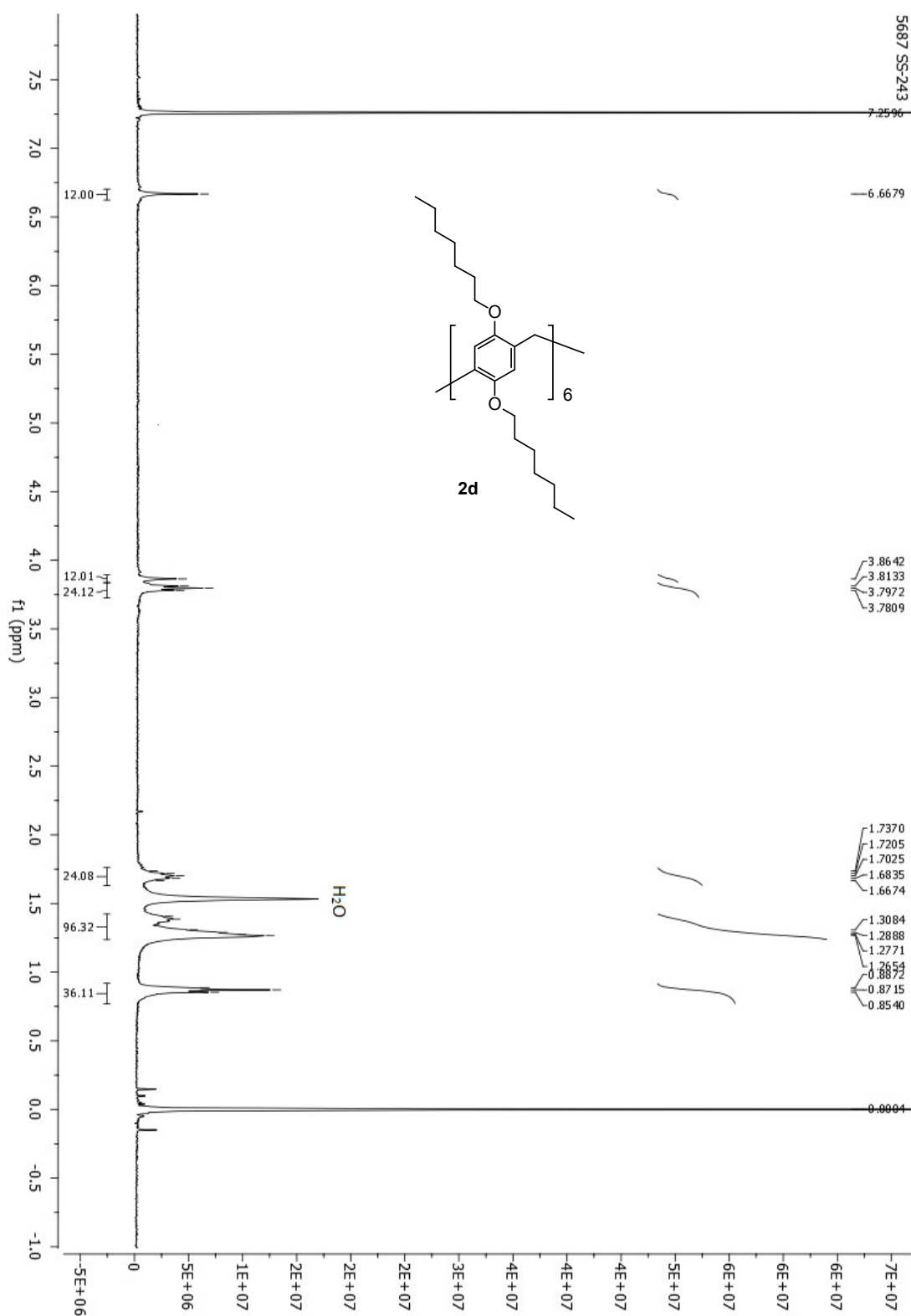


1,4-Bis(butoxy)pillar[6]arene (2c):

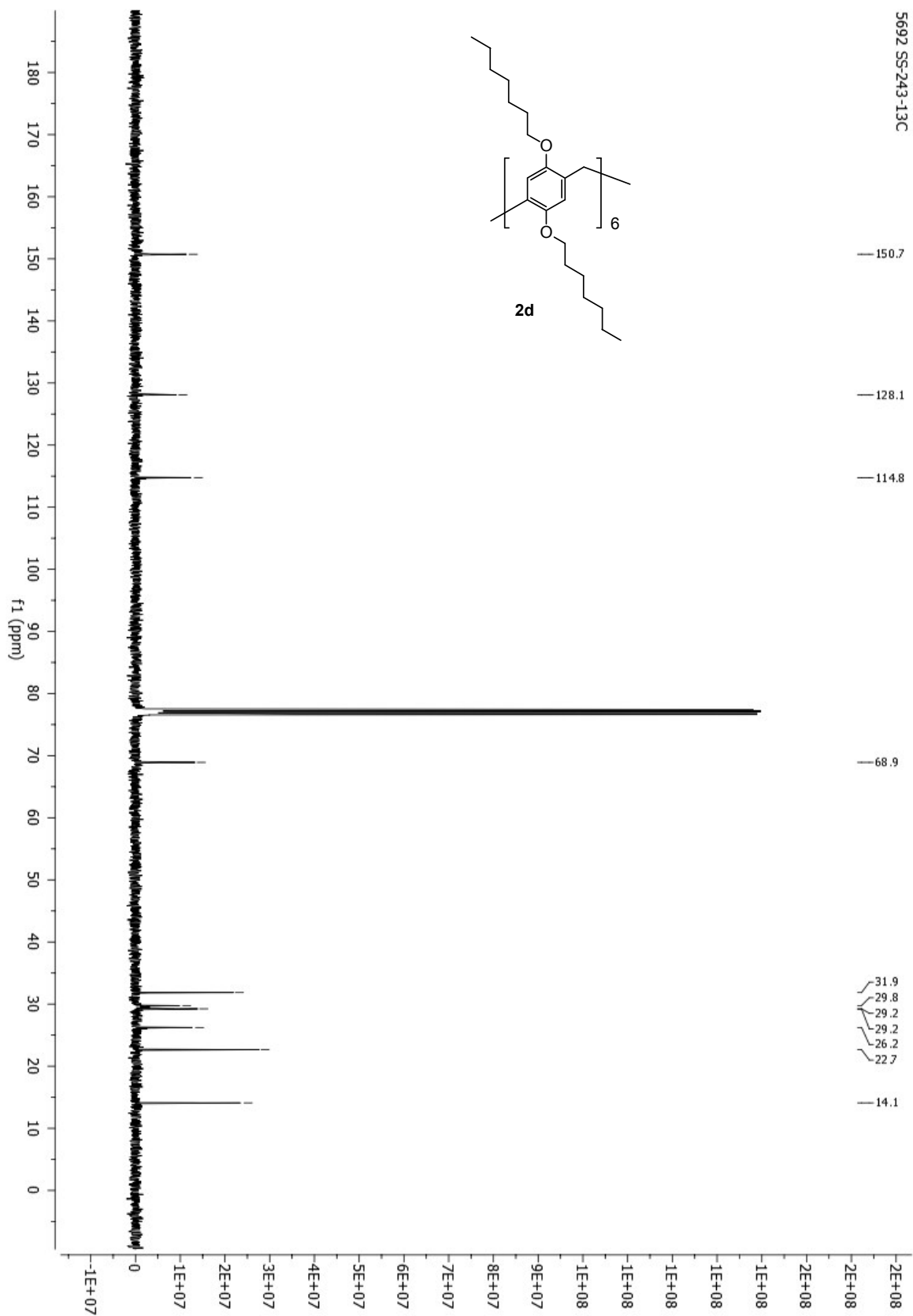




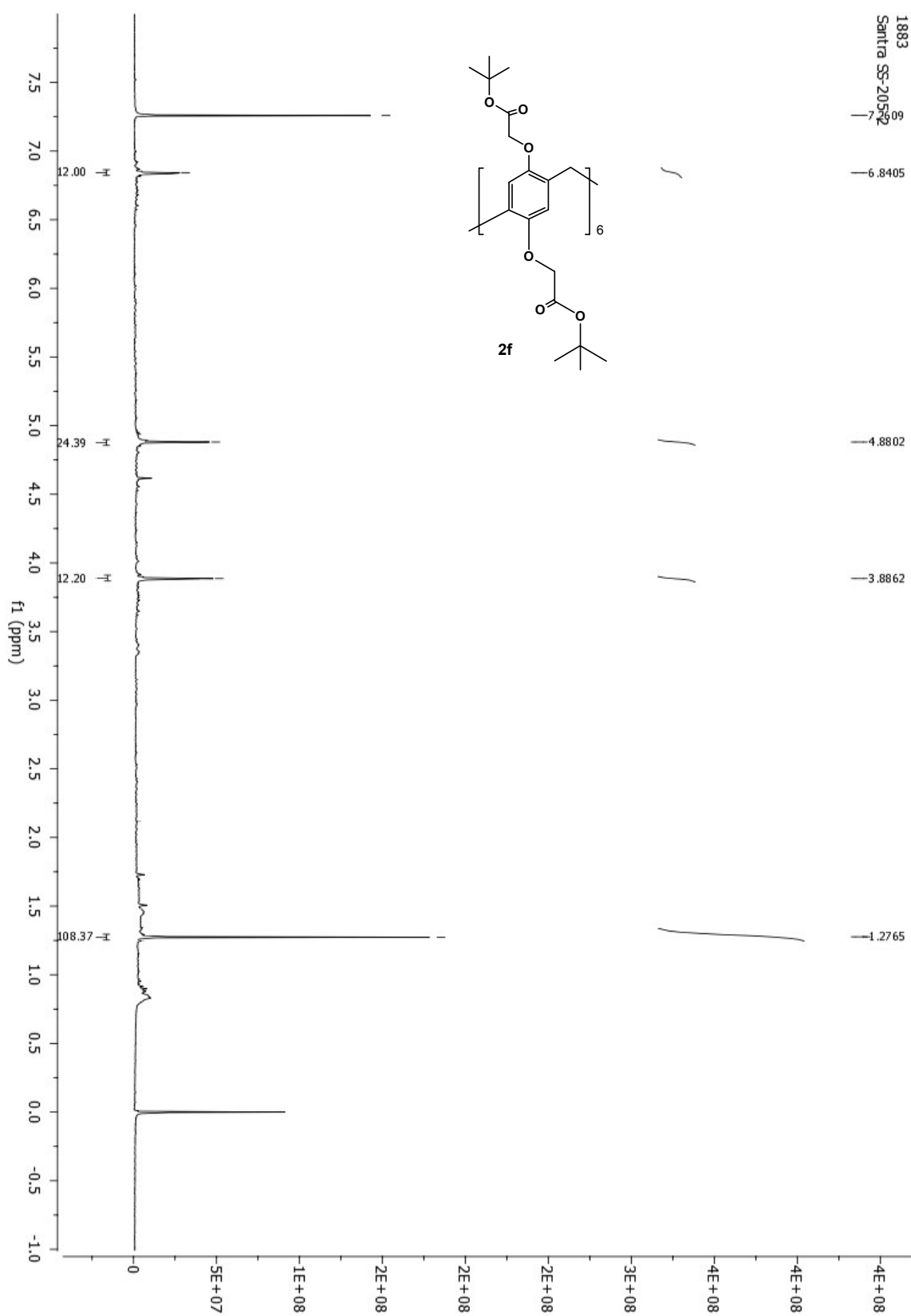
1,4-Bis(heptyloxy)pillar[6]arene (2d):

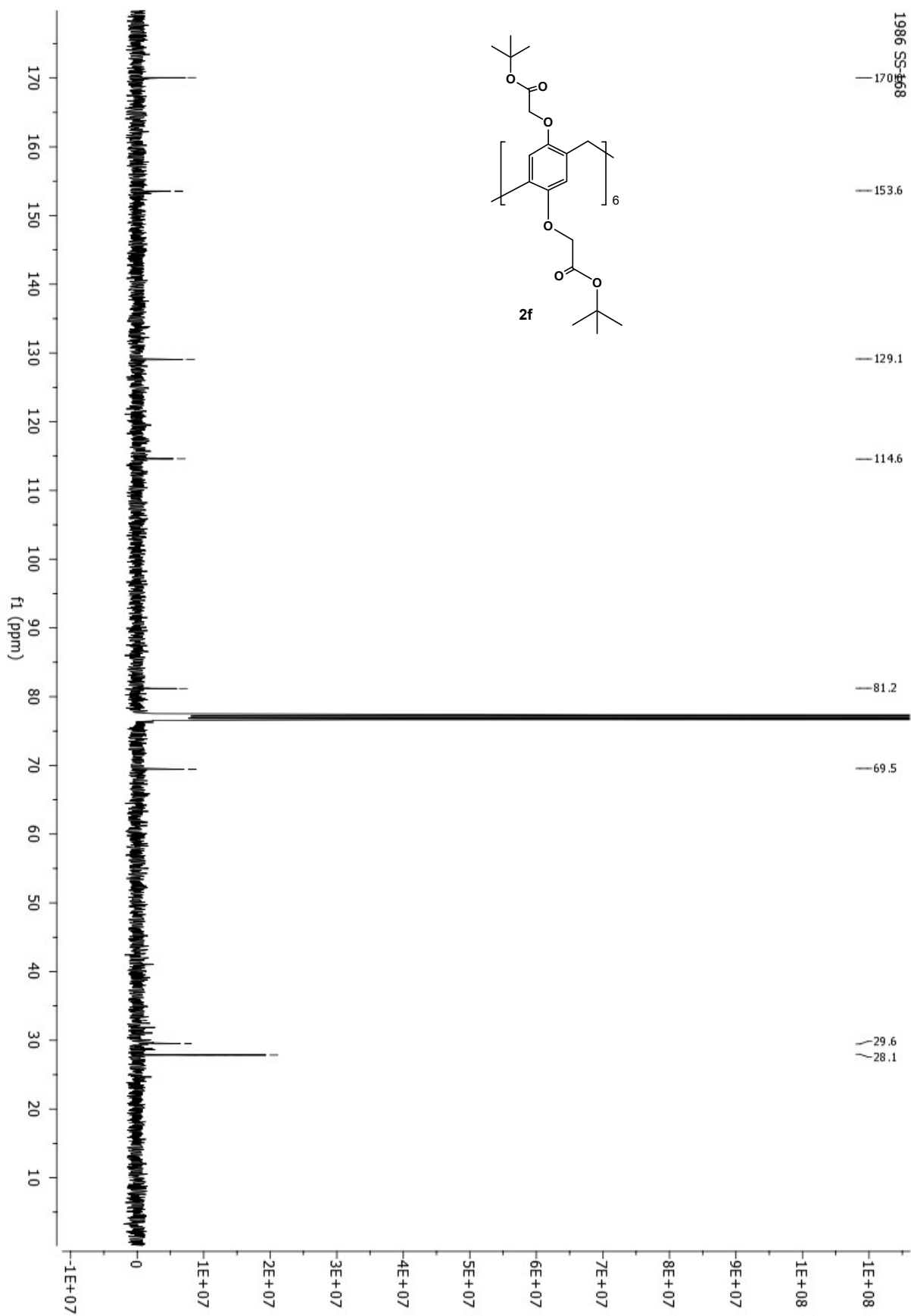


5692 SS-243-13C



Tert-Butyloxycarbonylmethoxy-substituted Pillar[6]arene (2f):





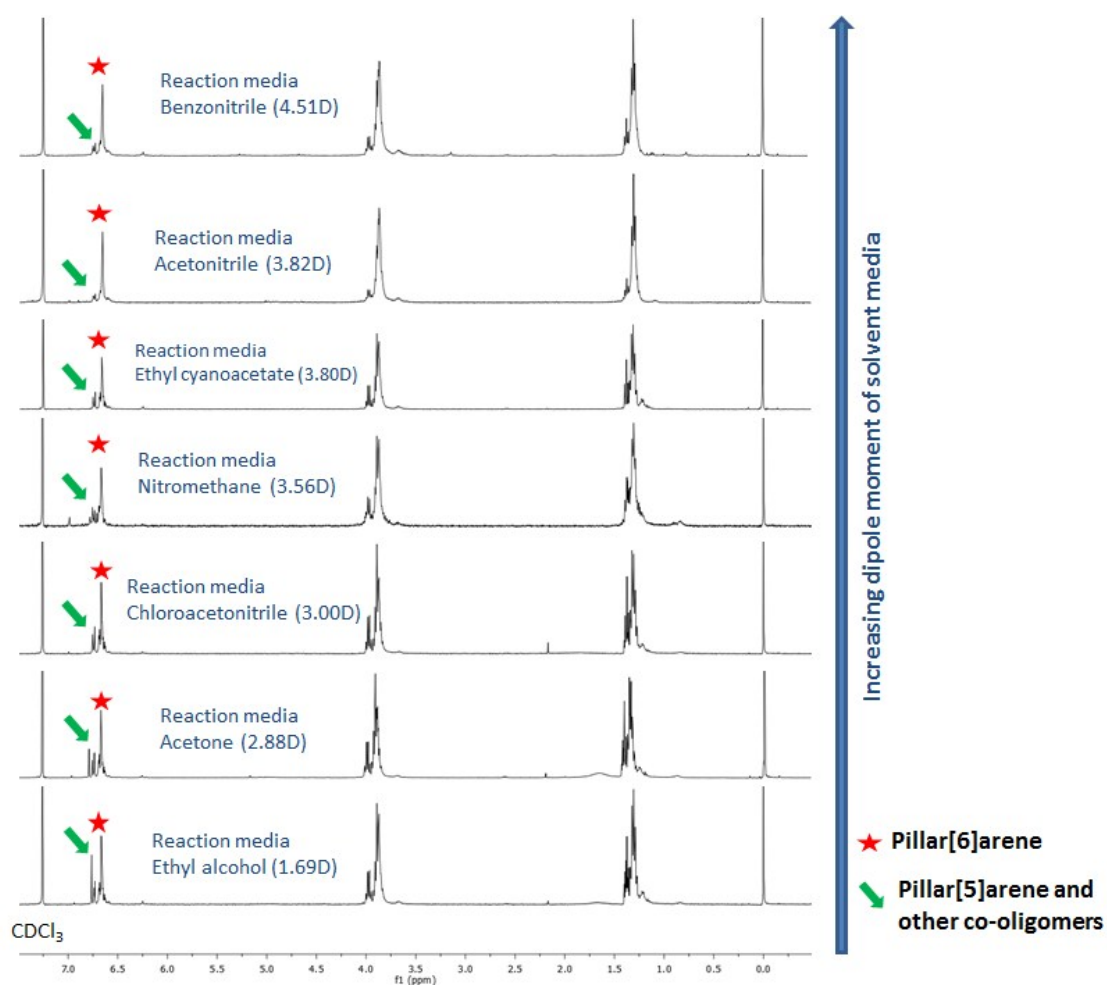


Fig. 1 Comparison of ¹H NMR spectra (run in CDCl₃) of crude product (**2a**) in different solvent media.

References:

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