ChemComm

Dynamic covalent templated-synthesis of [*c*2]daisy chains

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SUPPORTING INFORMATION

Revised Version

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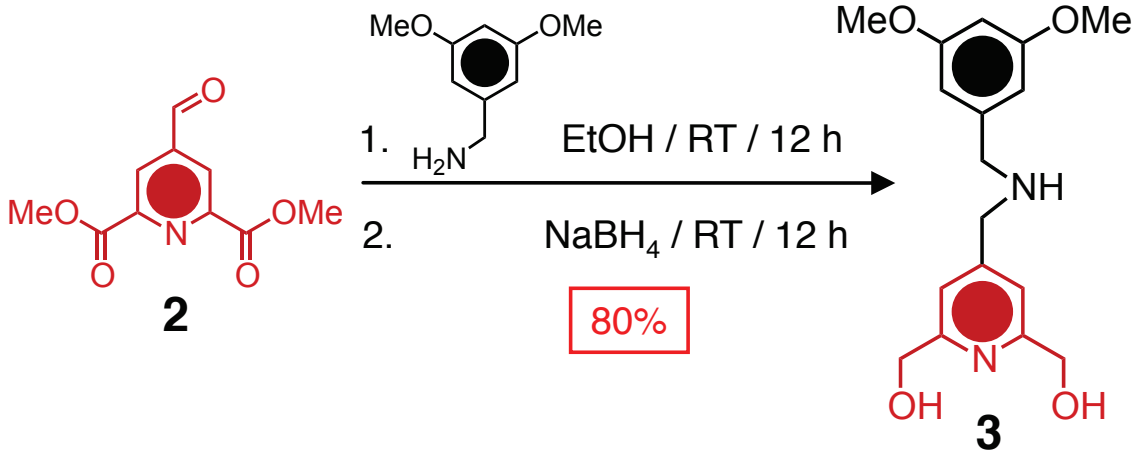
1. General Methods

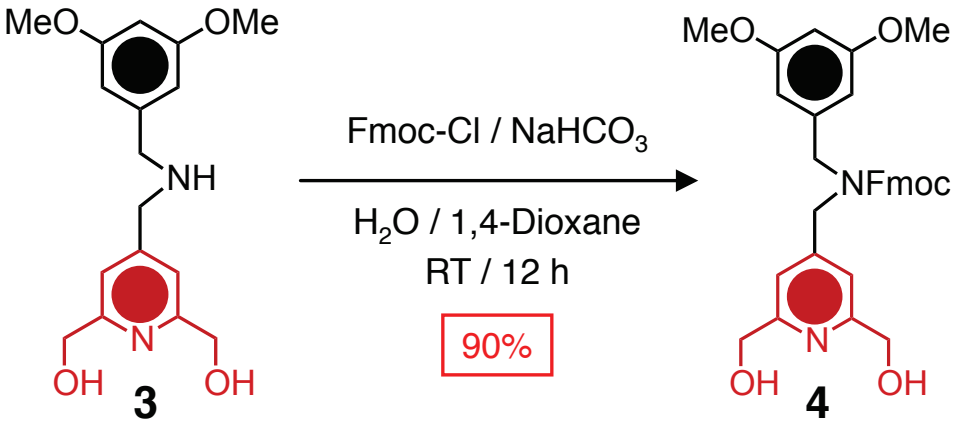
Compounds **1**[S1], **2**[S1], and **M**[S2] were synthesized following the procedures reported in the literature. Anhydrous CH_2Cl_2 was obtained from a SC Water USA Glass Contous Seca Solvent System. Anhydrous EtOH and anhydrous Et_3N were purchased from Aldrich and handled under an atmosphere of dry nitrogen. $CDCl_3$ and CD_3CN were obtained from Aldrich and used without further purification. All other reagents were purchased from commercial sources and used without further purification. All reactions were carried out under an atmosphere of dry nitrogen and anyhrous solvents were used, unless otherwise stated. Reactions were monitored by thin layer chromatography using Merck TLC Silica gel 60 F_{254} and the plates were inspected by 254 nm UV light and/or 2,4-DNP, iodine, and $KMNO_4$ stains. Flash column chromatography was performed over Merck Silica gel 60F (230-400 mesh ASTM). Analytical high performance liquid chromatography (HPLC) were performed on reversed phase HPLC (RP-HPLC) instruments, using C_{18} columns and a binary solvent system, i.e., MeCN and H_2O with 0.1% (v / v) trifluoroacetic acid. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker ARX-500 (operating at 500 MHz for ^1H NMR and 125 MHz for ^{13}C NMR) spectrometer in $CDCl_3$ and CD_3CN. All spectra were recorded at 25°C and coupling constants (*J* values) are given in Hz. Chemical shifts are given in parts per million (ppm). Abbreviations used to define multiplicities are as follows: s = singlet; d = doublet; t = triplet; q = quarter; m = multiplet; br = broad. ESI-Mass spectra were recorded on a Thermo Finnigan LCQ Advantage mass spectrometer. High-resolution mass spectra were measured on an Agilent (Wilmington, DE) 6210 TOF-LC/MS mass spectrometer.

2. Synthesis



Scheme S1. Synthesis of compound **3**

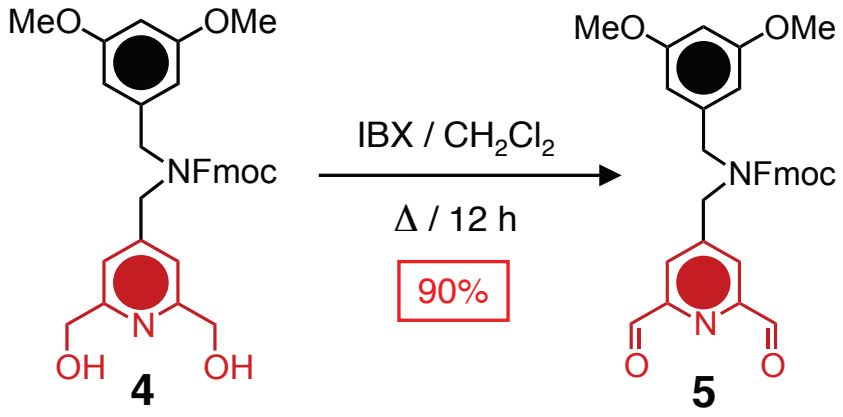
3: Compound **2** (8.96 mmol, 2 g) and 3,5-dimethoxybenzyl amine (8.96 mmol, 1.50 g) were added to a 250 mL round-bottomed flask containing EtOH (100 mL) and the resulting solution was stirred for 24 h at room temperature. $NaBH_4$ (18 mmol, 0.67 g) was added and the reaction mixture was stirred for additional 24 h before H_2O (1 mL) and K_2CO_3 (1 g) were added to quench reduction. Solvent was removed *in vacuo* and the residue was taken up in H_2O (100 mL), extracted with EtOAc (3 x 100 mL), and the combined extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, CH_2Cl_2/MeOH, 95:5) to afford **3** as a colorless viscous oil (2.28 g, 80%). ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ 7.20 (s, 2H), 6.50 (d, J = 2.1 Hz, 2H), 6.37 (t, J = 2.2 Hz, 1H), 4.75 (s, 4H), 3.85 (s, 2H), 3.80 (s, 6H), 3.76 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, 298 K): δ 160.9, 158.5, 151.2, 142.1, 118.5, 106.0, 98.9, 64.4, 55.4, 53.4, 51.8. MS (ESI): *m/z* Calcd for $[M + H]^+$: 319.17; found: 319.50.



Scheme S2. Synthesis of compound **4**

4: A solution of 9-fluorenylmethyl chloroformate (Fmoc-Cl) (7.54 mmol, 1.95 g) in 1,4-dioxane (20 mL) was added to a solution of **3** (6.28 mmol, 2 g) in 1,4-dioxane (10 mL) and 10% $Na_2CO_{3(aq)}$ (20 mL). The mixture was stirred at room temperature for 16 h, poured into H_2O (250

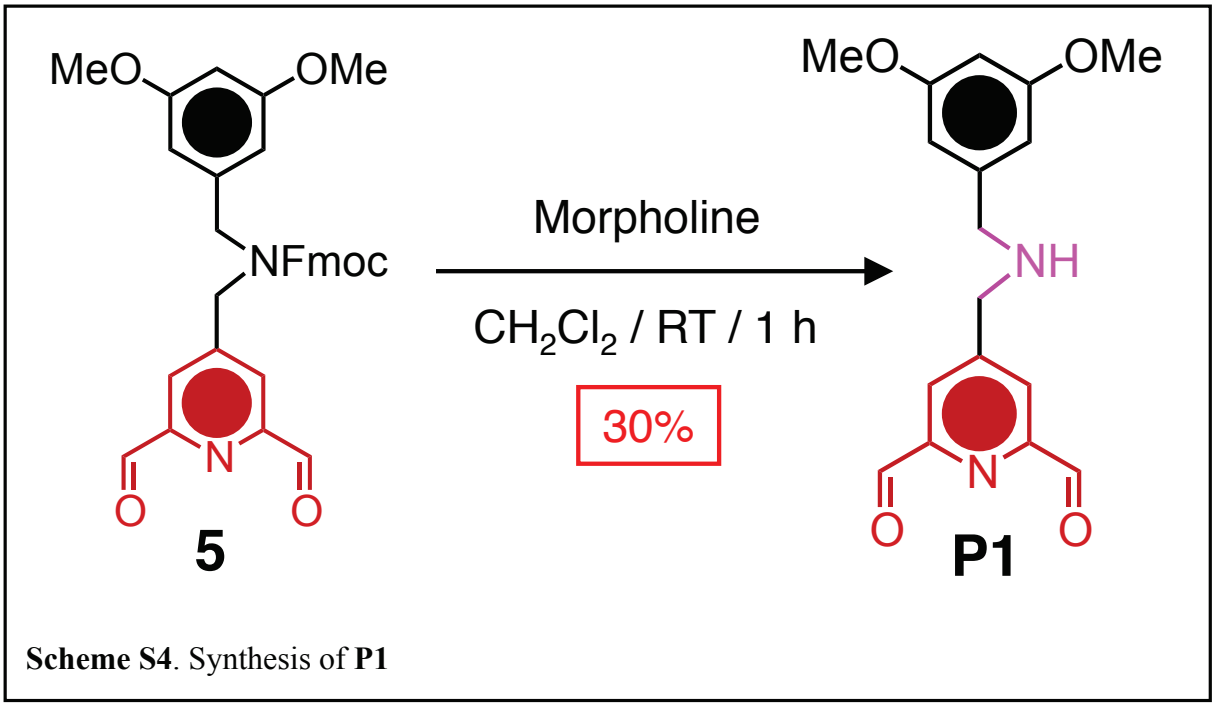
mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, CH_2Cl_2/MeOH, 98:2) to afford **4** as a slightly yellow oil (3.05 g, 90%). Because of the restricted rotation about amide bond in the structure, all protons and carbons exhibit two different signals. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ 7.75 (d, J = 7.5 Hz, 2H), 7.65 (d, J = 7.5 Hz, 2H), 7.50 (d, J = 7.5 Hz, 2H), 7.32–7.42 (m, 6H), 7.19–7.27 (m, 4H), 7.00 (s, 2H), 6.75 (s, 2H), 6.39 (s, 1H), 6.37 (s, 1H), 6.33 (s, 2H), 6.25 (s, 2H), 4.74 (s, 4H), 4.69 (s, 4H), 4.61 (d, J = 5.3 Hz, 2H), 4.55 (d, J = 6.5 Hz, 2H), 4.47 (s, 2H), 4.40 (s, 2H), 4.36 (s, 2H), 4.26 (t, J = 6.5 Hz, 1H), 4.19 (br, s, 3H), 3.75 (br, s, 12H). ^{13}C NMR (125 MHz, $CDCl_3$, 298 K): δ 161.2, 161.0, 159.0, 158.9, 156.4, 148.6, 148.4, 143.7, 141.3, 139.0, 127.8, 127.7, 127.1, 125.0, 124.5, 124.0, 118.0, 117.0, 106.2, 105.3, 99.3, 99.2, 68.1, 67.4, 64.4, 64.3, 60.5, 55.4, 50.8, 50.2, 49.3, 48.5, 47.2, MS (ESI): *m/z* Calcd for $[M + H]^+$: 541.23; found: 541.52.



Scheme S3. Synthesis of compound **5**

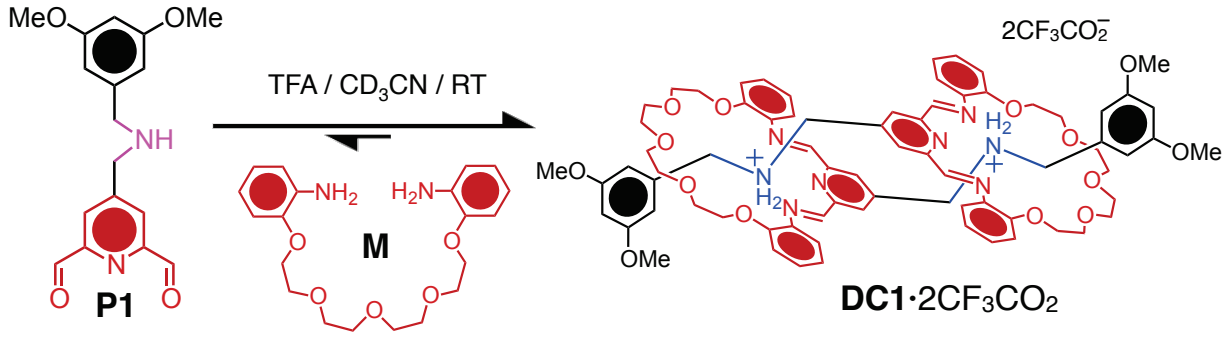
5: Compound **4** (5.54 mmol, 3 g) and IBX (22.16 mmol, 6.20 g) were added to a 250 mL round-bottomed flask containing CH_2Cl_2 (150 mL) and the resulting suspension was heated under reflux until TLC analysis indicated that **4** had been consumed. The reaction mixture was cooled

to room temperature and filtered through celite. H_2O (250 mL) was added to the filtrate and extracted with CH_2Cl_2 (3 x 100 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, CH_2Cl_2) to afford **5** as a slightly yellow solid (2.68 g, 90%). Because of the restricted rotation about amide bond in the structure, all protons and carbons exhibit two different signals. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ 10.2 (s, 2H), 10.1 (s, 2H), 7.95 (s, 2H), 7.65 (d, J = 7.5 Hz, 2H), 7.45–7.55 (m, 6H), 7.40 (m, 4H), 7.15–7.3 (m, 6H), 6.40 (s, 1H), 6.32 (s, 1H), 6.25 (s, 2H), 6.22 (s, 2H), 4.72 (d, J = 4.4 Hz, 2H), 4.62 (s, 2H), 4.56 (d, J = 6.6 Hz, 2H), 4.42 (s, 4H), 4.28 (t, J = 6.4 Hz, 1H), 4.10 (m, 1H), 4.07 (s, 2H), 3.72 (br, s, 12H). ^{13}C NMR (125 MHz, $CDCl_3$, 298 K): δ 191.2, 161.3, 161.1, 156.1, 153.2, 152.9, 150.5, 143.6, 1435, 141,3, 141.1, 138.5, 127.8, 127.6, 127.2, 127.1, 124.9, 124.1, 123.9, 122.5, 120.1, 119.8, 106.2, 105.4, 99.5, 99.4, 68.4, 66.9, 55.3, 51.6, 50.9, 49.4, 48.6, 47.2, 47.1. MS (ESI): *m/z* Calcd for $[M + H]^+$: 537.20; found: 537.52.



Scheme S4. Synthesis of **P1**

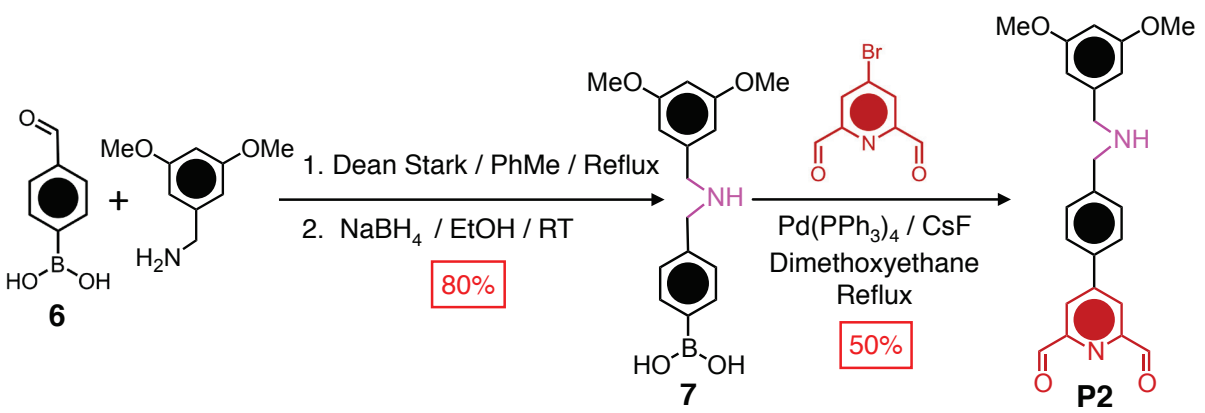
P1: Morpholine (10 mL) was added to a solution of **5** (3.73 mmol, 2 g) in CH_2Cl_2 (20 mL) and the resulting reaction mixture was stirred at room temperature for 1 h, poured into H_2O (100 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, CH_2Cl_2/MeOH, 95:5) to afford **P1** as a colorless oil (0.35 g, 30%). ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ 10.1 (s, 2H), 8.15 (s, 2H), 6.45 (d, J = 2.1 Hz, 2H), 6.30 (t, J = 2.2 Hz, 1H), 3.90 (s, 2H), 3.79 (s, 2H), 3.72 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$, 298 K): δ 192.5, 161.0, 153.1, 152.9, 124.6, 106.0, 99.3, 66.4, 55.4, 53.3, 51.1. MS (ESI): *m/z* Calcd for $[M + H]^+$: 315.13; found: 315.45.



Scheme S5. Synthesis of **DC1**·2CF_3CO_2

DC1·2CF_3CO_2: **P1** (0.016 mmol, 5 mg) and **M** (0.016 mmol, 6 mg) were dissolved in CD_3CN (1 mL) containing an equimolar amount of TFA. The resulting slightly yellow solution was used for characterization. ^{1}H NMR (500 MHz, CD_3CN, 298 K): δ 10.05 (br, s, 4H), 8.4 (s, 4H), 7.95 (s, 4H), 7.35 (t, J = 7.5 Hz, 4H), 7.20 (d, J = 7.5 Hz, 4H), 6.98 (d, J = 7.5 Hz, 4H), 6.80 (d, J = 7.5 Hz, 4H), 6.17 (d, J = 7.5 Hz, 2H), 6.15 (d, J = 7.5 Hz, 4H), 5.00 (m, 4H), 4.65 (m, 4H), 4.35–4.45 (m, 8H), 3.95–4.20 (m, 8H), 3.40–3.80 (m, 16H), 3.30 (s, 12H). ^{13}C NMR (125 MHz, CD_3CN, 298 K): δ 161.5, 160.4, 152.7, 151.6, 140.0, 128.9, 128.6, 121.4, 121.2, 120.5, 112.9,

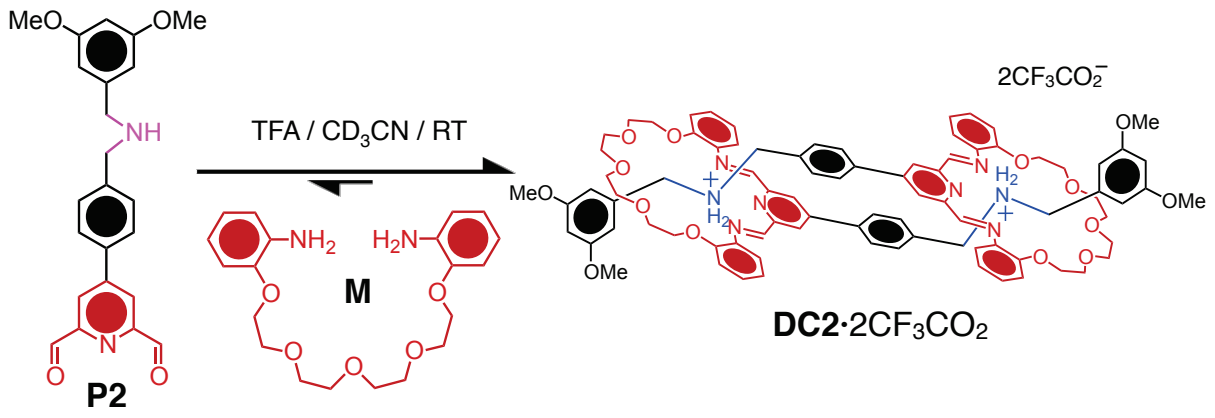
112.1, 106.2, 100.6, 70.2, 69.8, 69.0, 68.5, 68.2, 54.3, 52.2, 49.7. MS (ESI-HRMS): *m/z* Calcd for $[M - 2CF_3CO_2 - H]^+$: 1309.6185; found: 1309.8259. *m/z* Calcd for $[M - 2CF_3CO_2]^{2+}$: 655.3132; found: 655.3133.



Scheme S6. Synthesis of **P2**

P2: Compound **6** (20.0 mmol, 3 g) and 3,5-dimethoxybenzyl amine (20.0 mmol, 3.34 g) were added to a 100 mL round-bottomed flask containing C_6H_6 (50 mL) and the resulting mixture was refluxed in the presence of a Dean-Stark trap for 16 h. Solvent was removed *in vacuo* and the residue was dissolved in anhydrous MeOH, $NaBH_4$ (21 mmol, 0.72 g) was added to this solution and the reaction mixture was stirred for additional 24 h before adding H_2O (1 mL) to quench reduction. Solvent was removed *in vacuo* and the residue was taken up in H_2O (100 mL), extracted with EtOAc (3 x 100 mL), and the combined extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, EtOAc/MeOH, 95:5) to afford **7** as a colorless viscous oil (4.8 g, 80%). ^{1}H NMR (500 MHz, CD_3CN, 298 K): δ 7.75 (d, J = 7.9 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 6.55 (d, J = 2.3 Hz, 2H), 6.47 (t, J = 2.3 Hz, 1H), 6.0 (br, s, 2H), 3.78 (m, 6H), 3.77 (s, 2H), 3.71 (s, 2H). In the next step, **7** (0.66 mmol, 0.2 g), 4-bromo-3,5-diformylpyridine (0.7 mmol, 0.15 mg), and CsF (2 mmol, 0.3 g) were added into 1,2-dimethoxyethane (100 mL) and the resulting mixture was purged with

Argon for 30 min. $Pd(PPh_3)_4$ (0.033 mmol, 0.038 g) was added and the mixture was heated under reflux for 1 h, cooled to room temperature, filtered over Celite and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, CH_2Cl_2/MeOH, 97:3) to obtain **P2** as a colorless viscous oil (0.13 g, 50%). ^{1}H NMR (500 MHz, CD_3CN, 298 K): δ 10.2 (s, 2H), 8.45 (s, 2H), δ 7.75 (d, J = 7.9 Hz, 2H), 7.55 (d, J = 8.0 Hz, 2H), 6.55 (d, J = 2.3 Hz, 2H), 6.40 (t, J = 2.3 Hz, 1H) 3.90 (s, 2H), 3.80 (br, s, 8H). ^{13}C NMR (125 MHz, $CDCl_3$, 298 K): δ 192.7, 160.9, 153.6, 150.7, 129.3, 127.2, 122.7, 106.0, 98.9, 55.4, 53.3, 52.5. MS (ESI): *m/z* Calcd for $[M + H]^+$: 391.43; found: 391.47.



Scheme S7. Synthesis of **DC2**·$2CF_3CO_2$

DC2·2CF_3CO_2: **P2** (0.013 mmol, 5 mg) and **M** (0.013 mmol, 4.8 mg) were dissolved in CD_3CN (1 mL) containing an equimolar amount of TFA and the resulting slightly yellow solution was used for characterization. ^{1}H NMR (500 MHz, CD_3CN, 298 K): δ 10.05 (br, s, 4H), 8.4 (s, 4H), 7.78 (s, 4H), 7.65 (d, J = 7.5 Hz, 4H), 7.38 (t, J = 7.5 Hz, 4H), 7.30 (d, J = 7.5 Hz, 4H), 7.25 (d, J = 7.5 Hz, 4H), 7.05 (d, J = 7.5 Hz, 4H), 6.92 (d, J = 7.5 Hz, 4H), 6.30 (d, J = 7.5 Hz, 4H), 6.15 (d, J = 7.5 Hz, 2H), 4.85 (m, 4H), 4.70 (m, 4H), 4.50–4.60 (m, 8H), 4.05 (br, s, 8H), 3.60–3.70 (m, 8H), 3.40–3.50 (m, 8H), 3.27 (s, 12H). ^{13}C NMR (125 MHz, CD_3CN, 298 K): δ 161.7, 160.4,

152.4, 151.4, 140.4, 136.4, 131.2, 128.5, 128.1, 121.4, 120.6, 112.2, 106.2, 100.7, 71.8, 70.1, 69.8, 68.9, 68.5, 54.2, 51.9, 51.3, 49.1. MS (ESI-HRMS): *m/z* Calcd for $[M–CF_3CO_2]^+$: 1575.6734; found: 1575.6778. *m/z* Calcd for $[M – 2CF_3CO_2 – H]^+$: 1461.6806; found: 1461.6880. *m/z* Calcd for $[M – 2CF_3CO_2]^{2+}$: 731.3440; found: 731.3469.

3. Molecular Modeling

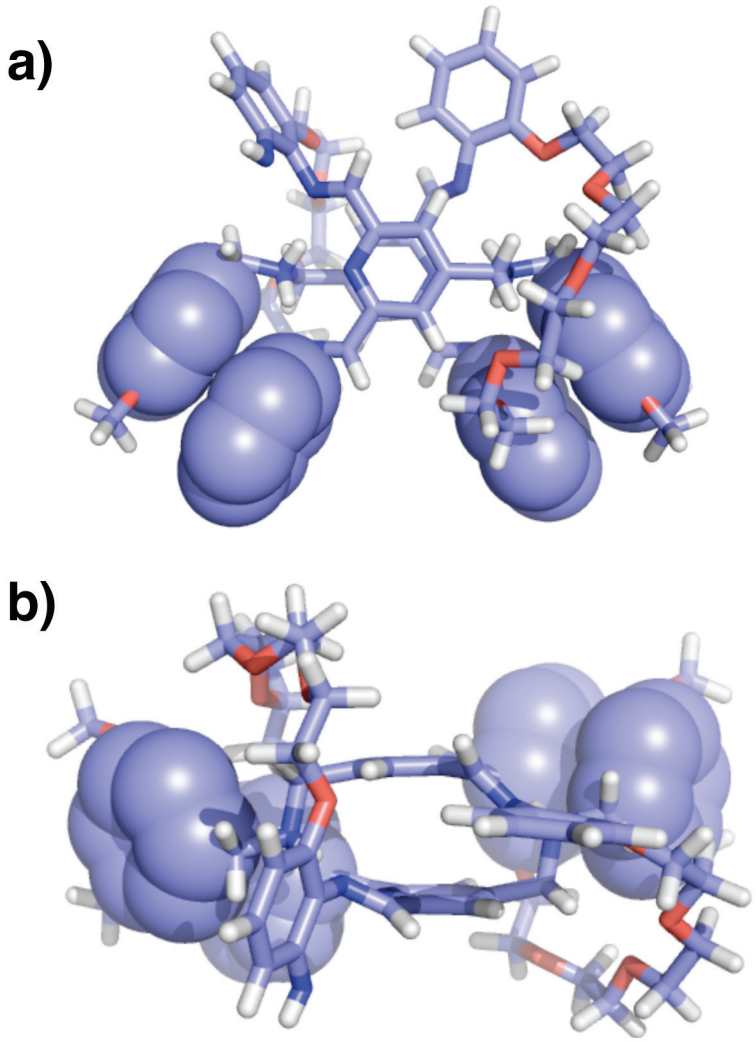


Figure S1: MMF94-minimized (Merck molecular force field (MMFF94) implemented in the molecular modeling software SPARTAN '06[S3]) 3D structures of **DC1**$^{2+}$ showing [π···π] stacking interactions between dimethoxybenzyl stoppers and one of the lateral imino phenyl rings – a) top view, b) side view.

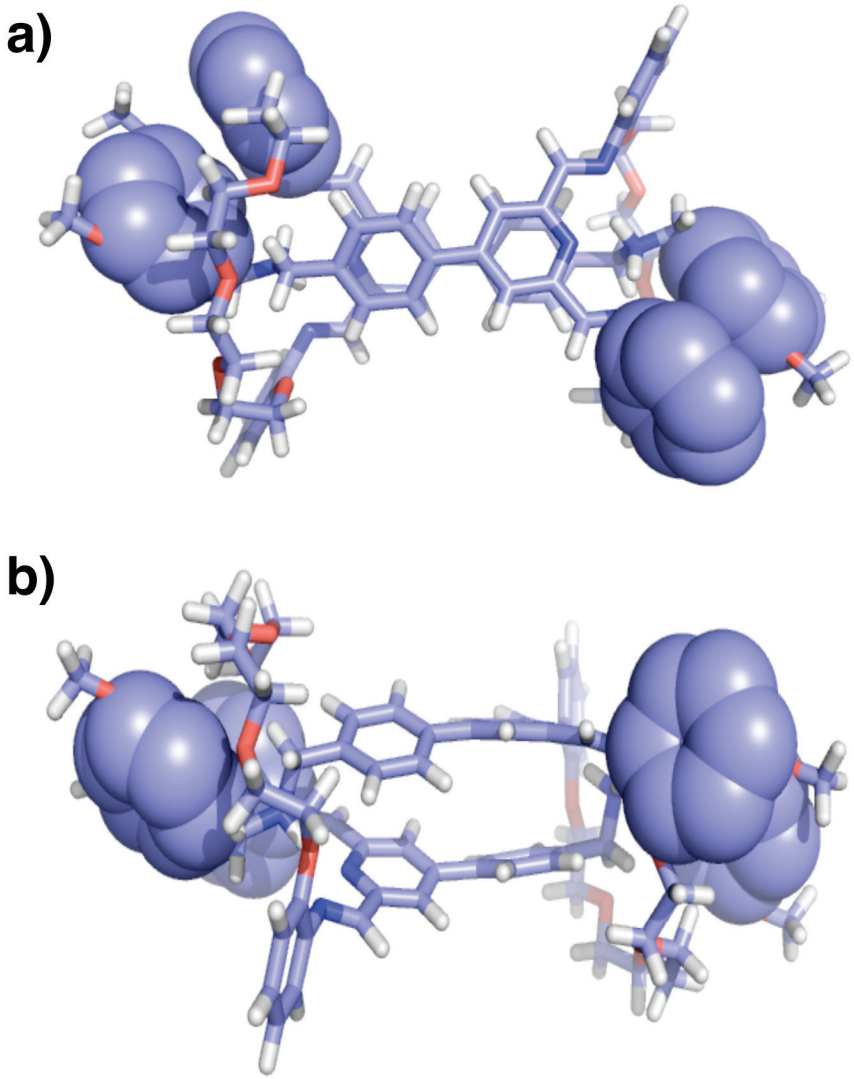


Figure S2: MMF94-minimized (Merck molecular force field (MMFF94) implemented in the molecular modeling software SPARTAN '06[S3]) 3D structures of **DC2**$^{2+}$ showing [π···π] stacking interactions between dimethoxybenzyl stoppers and one of the lateral imino phenyl rings – a) top view, b) side view.

4. References

S1. Tang, R.; Zhao, Q.; Yan, Z. and Luo, Y. *Synth Commun.* **2006**, *36*, 2027–2034.

S2. Sieger, H. and Vögtle, F. *Liebigs Ann*. **1980**, 425–440.

S3. SPARTAN '06, Version 1.1.1, http://wavefun.com.

5. ^{1}H and ^{13}C NMR Spectra

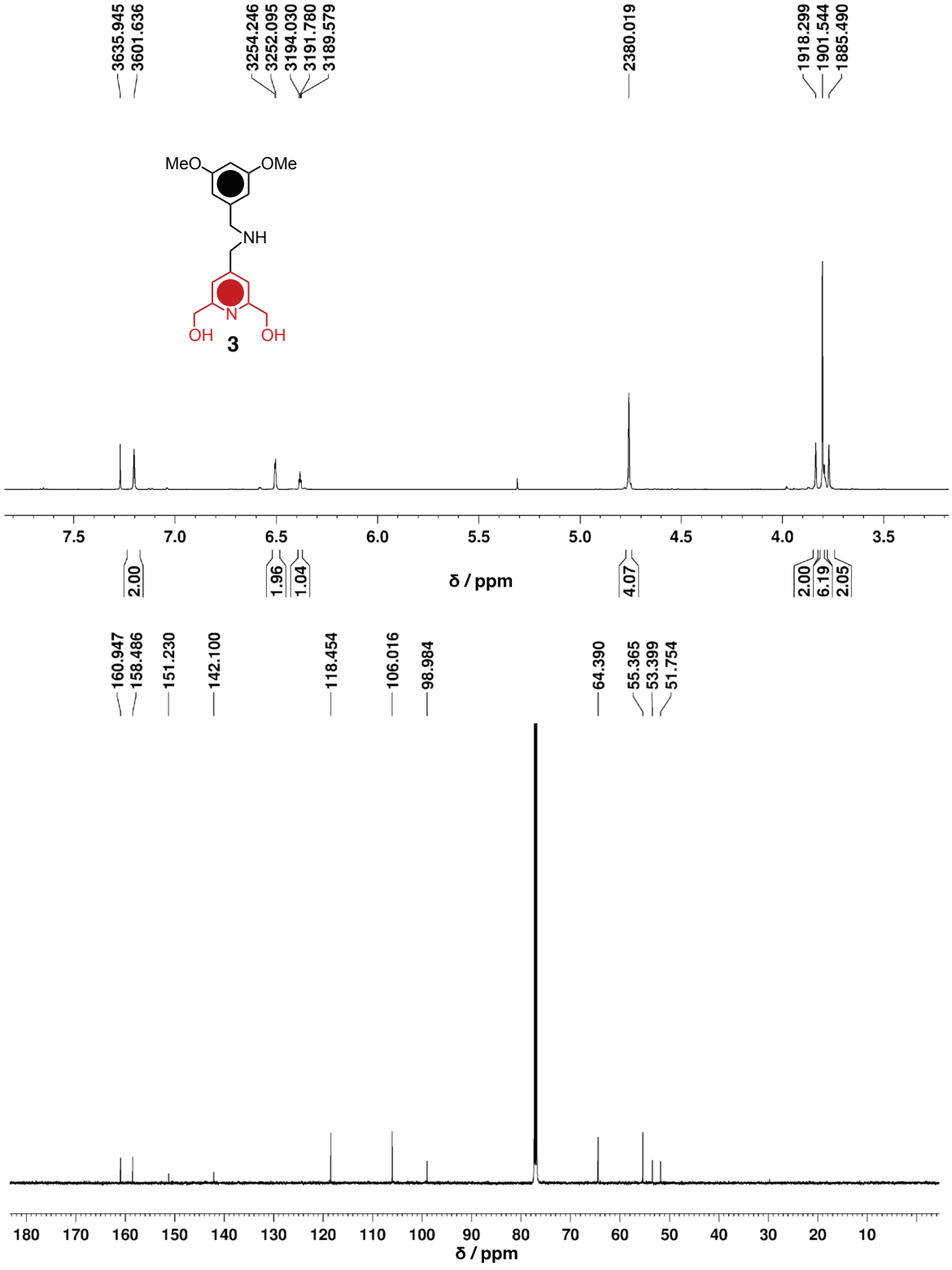


Figure S3: ^{1}H and ^{13}C NMR spectra of compound **3**

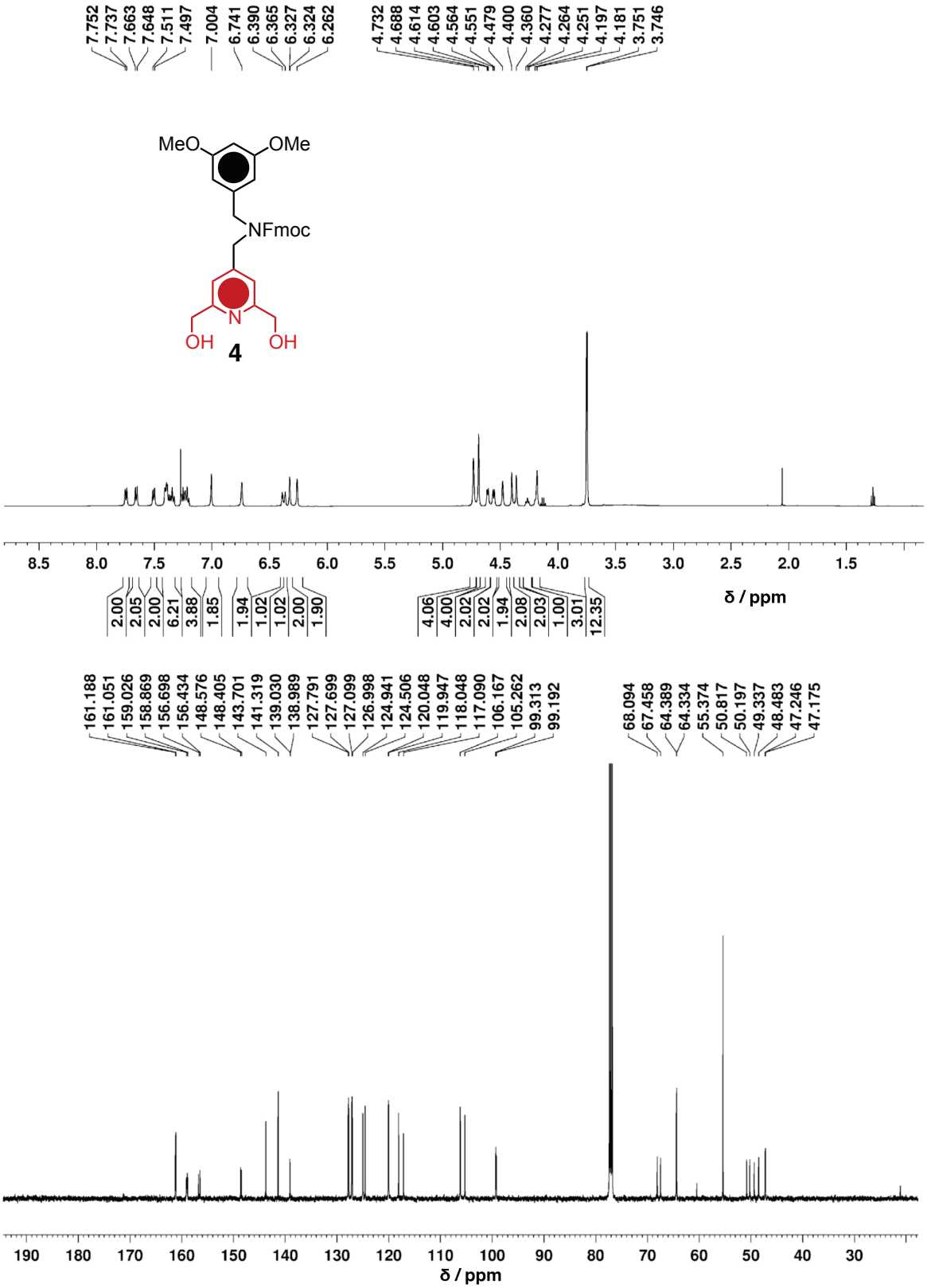


Figure S4: ^{1}H and ^{13}C NMR spectra of compound **4**

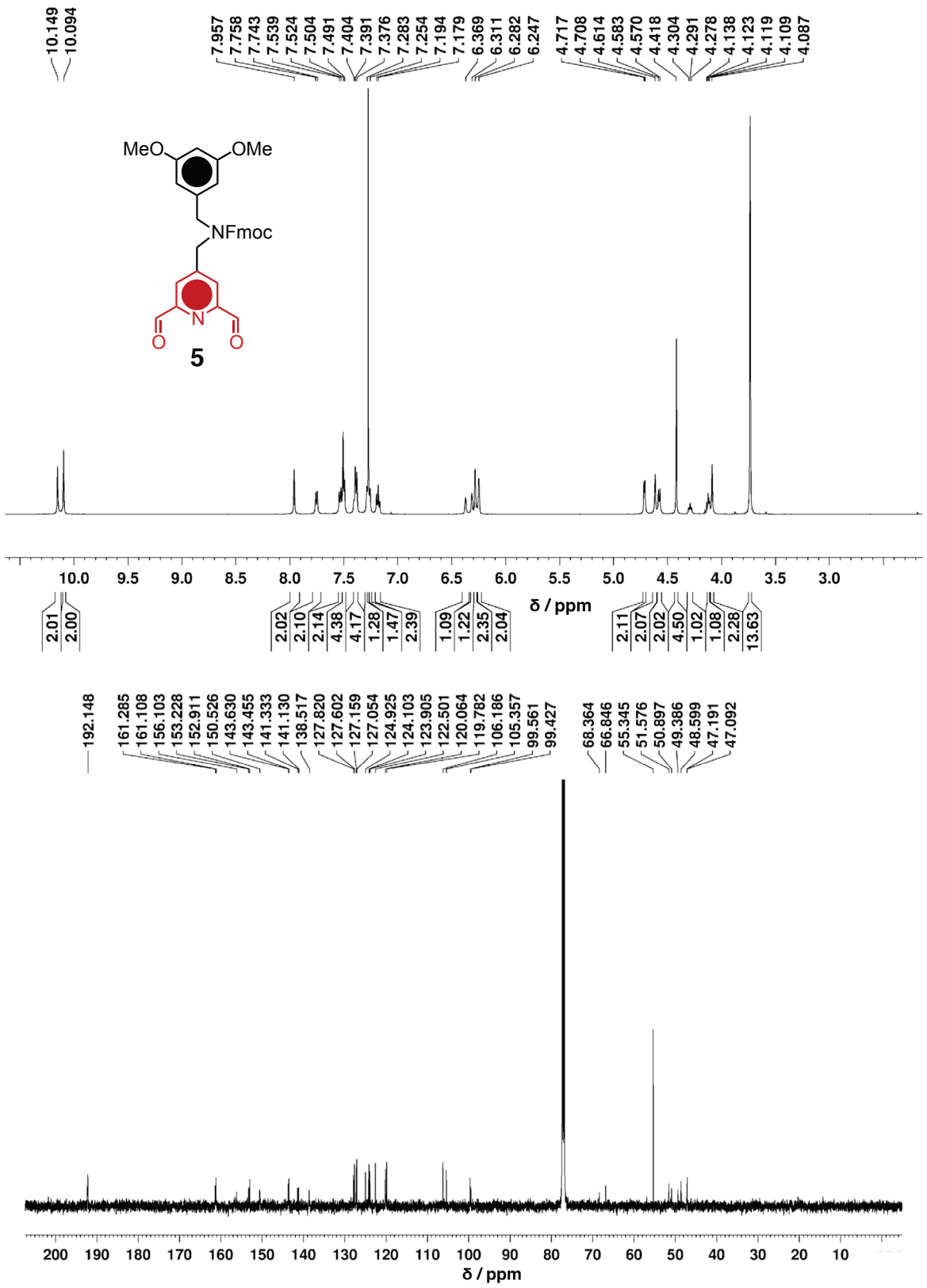


Figure S5: ^{1}H and ^{13}C NMR spectra of compound **5**

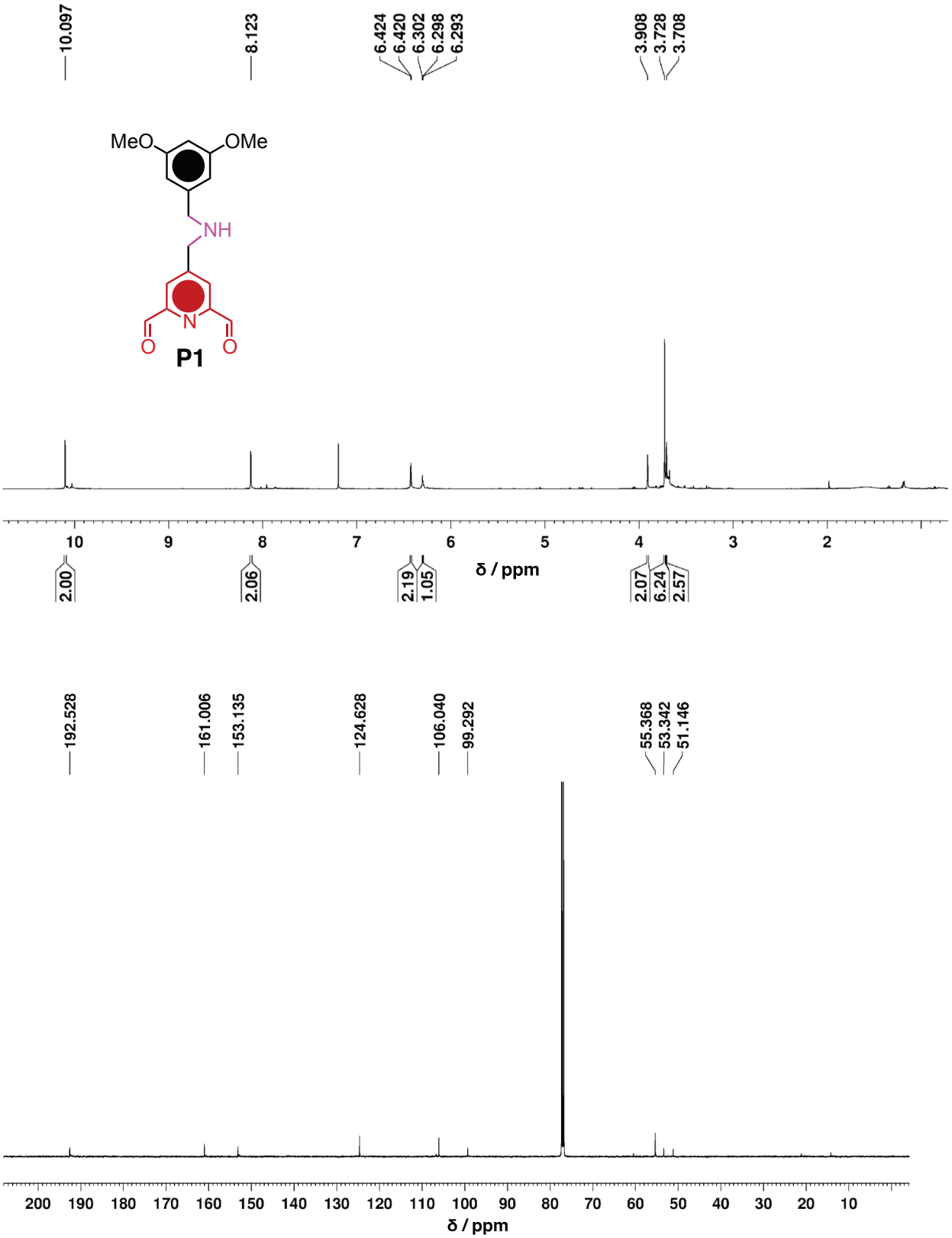


Figure S6: ^{1}H and ^{13}C NMR spectra of **P1**

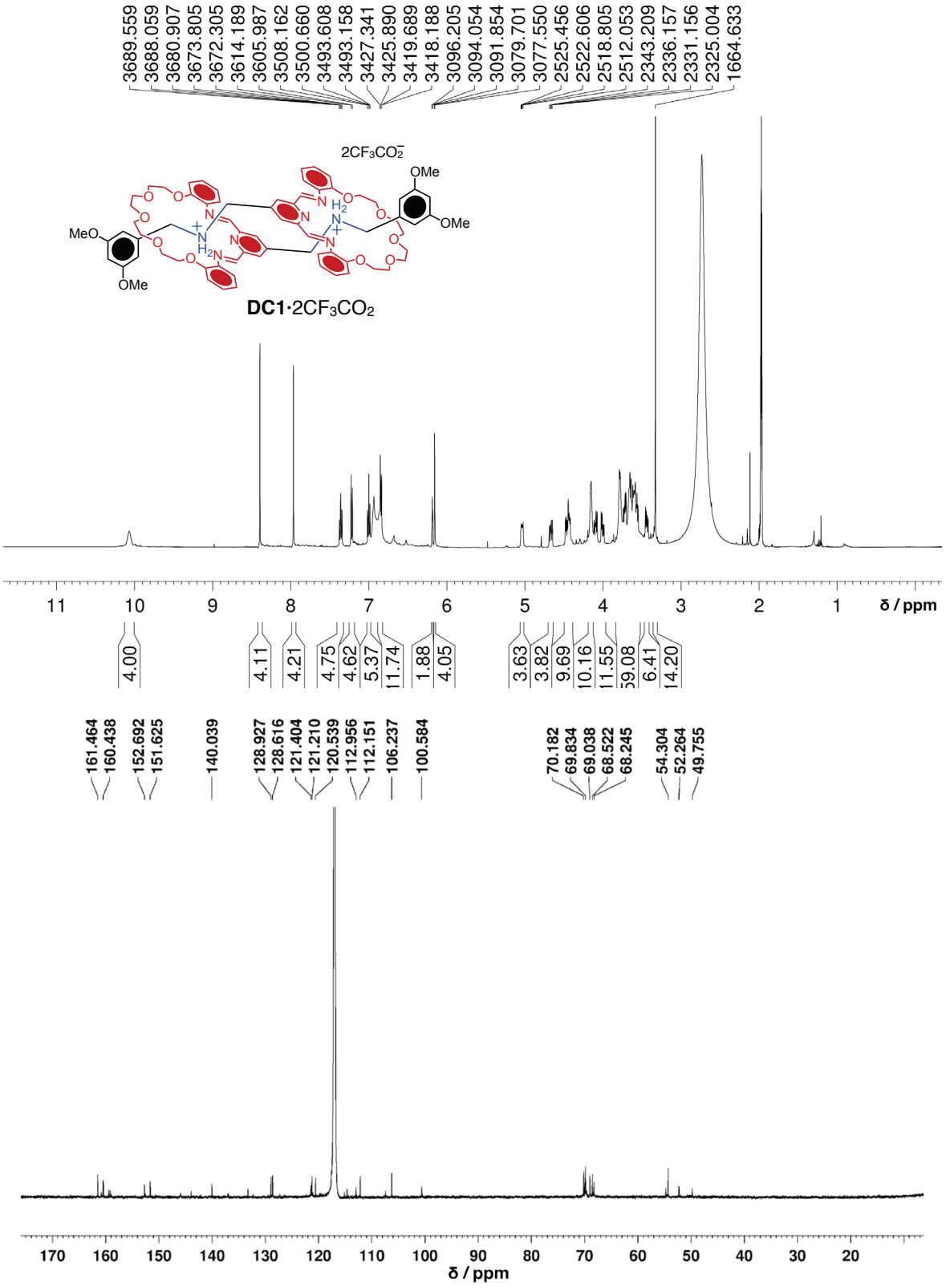


Figure S7: ^{1}H and ^{13}C NMR spectra of **DC1**·$2CF_3CO_2$

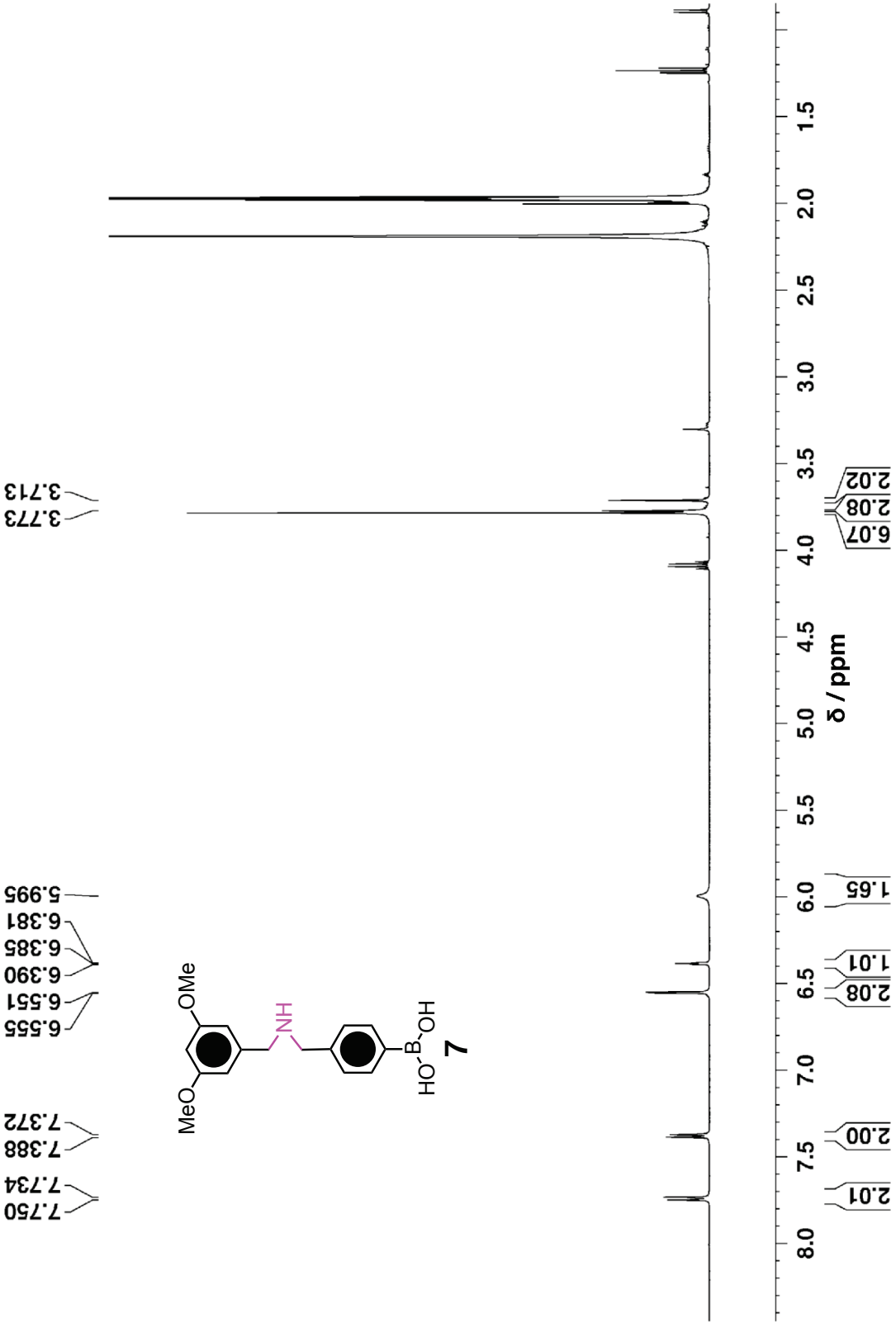


Figure S8: ^{1}H NMR spectrum of compound **7**

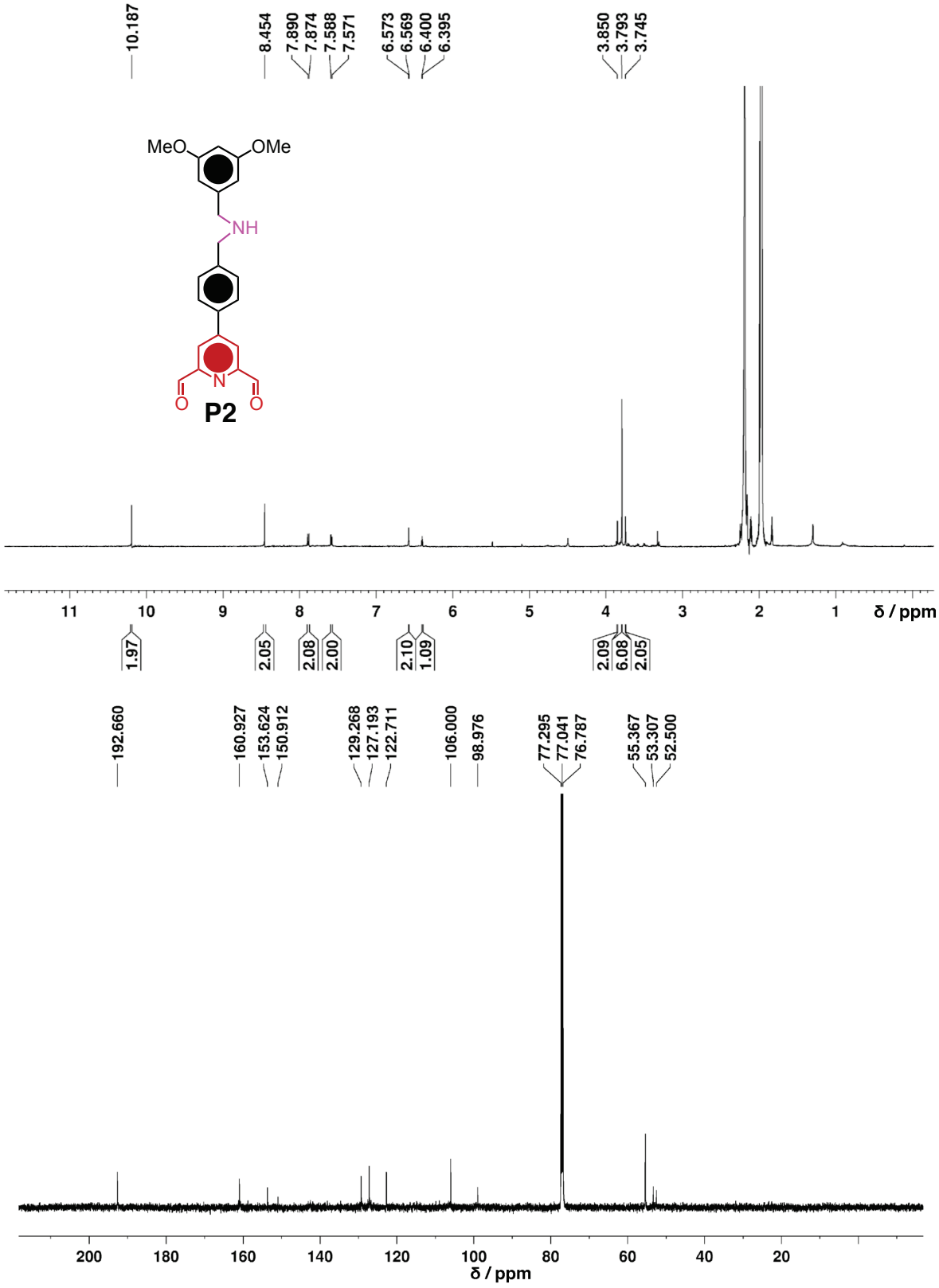


Figure S9: ^{1}H and ^{13}C NMR spectra of **P2**

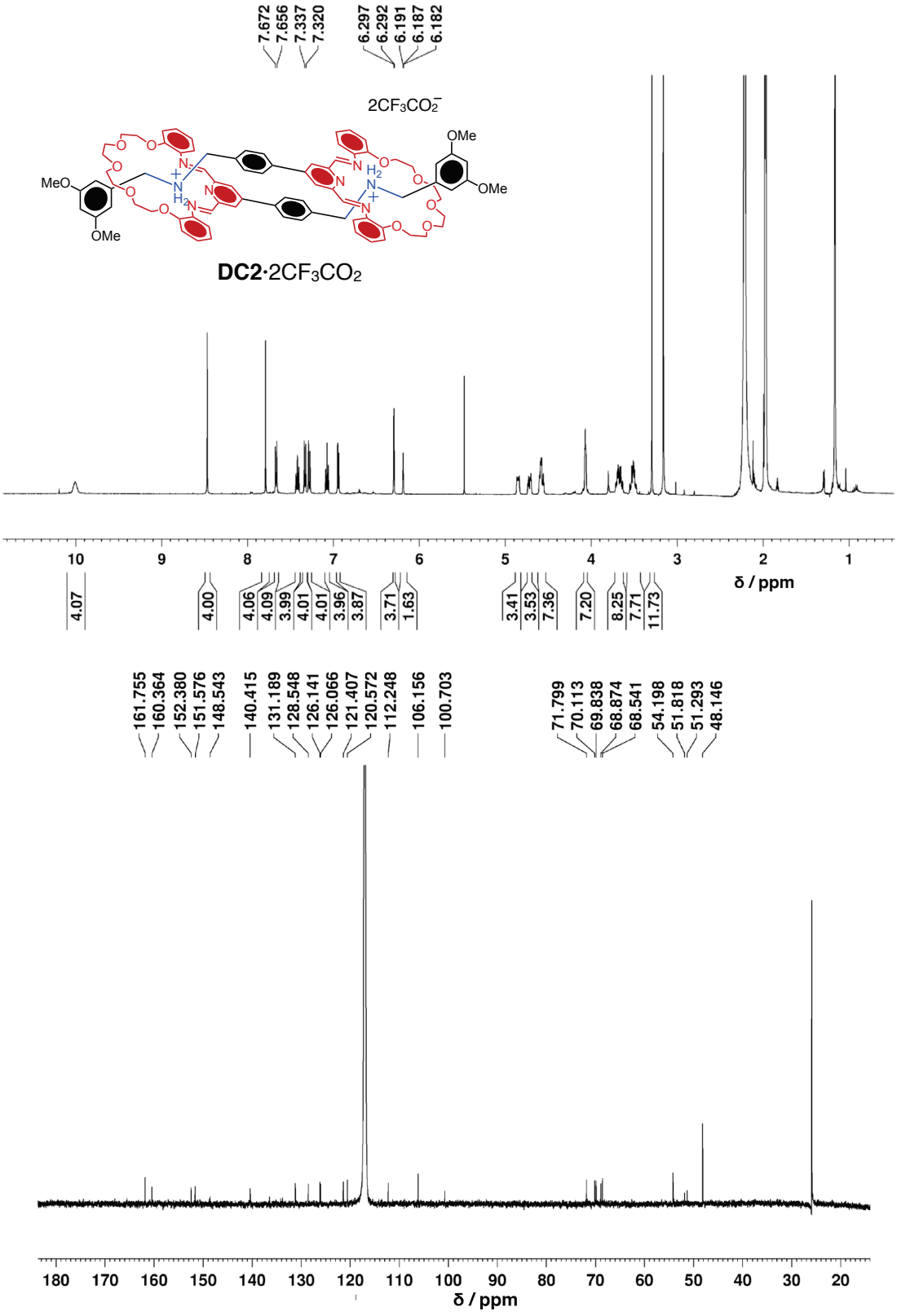


Figure S10: ^{1}H and ^{13}C NMR spectra of **DC2**·$2CF_3CO_2$

6. Analytical High Performance Liquid Chromatography

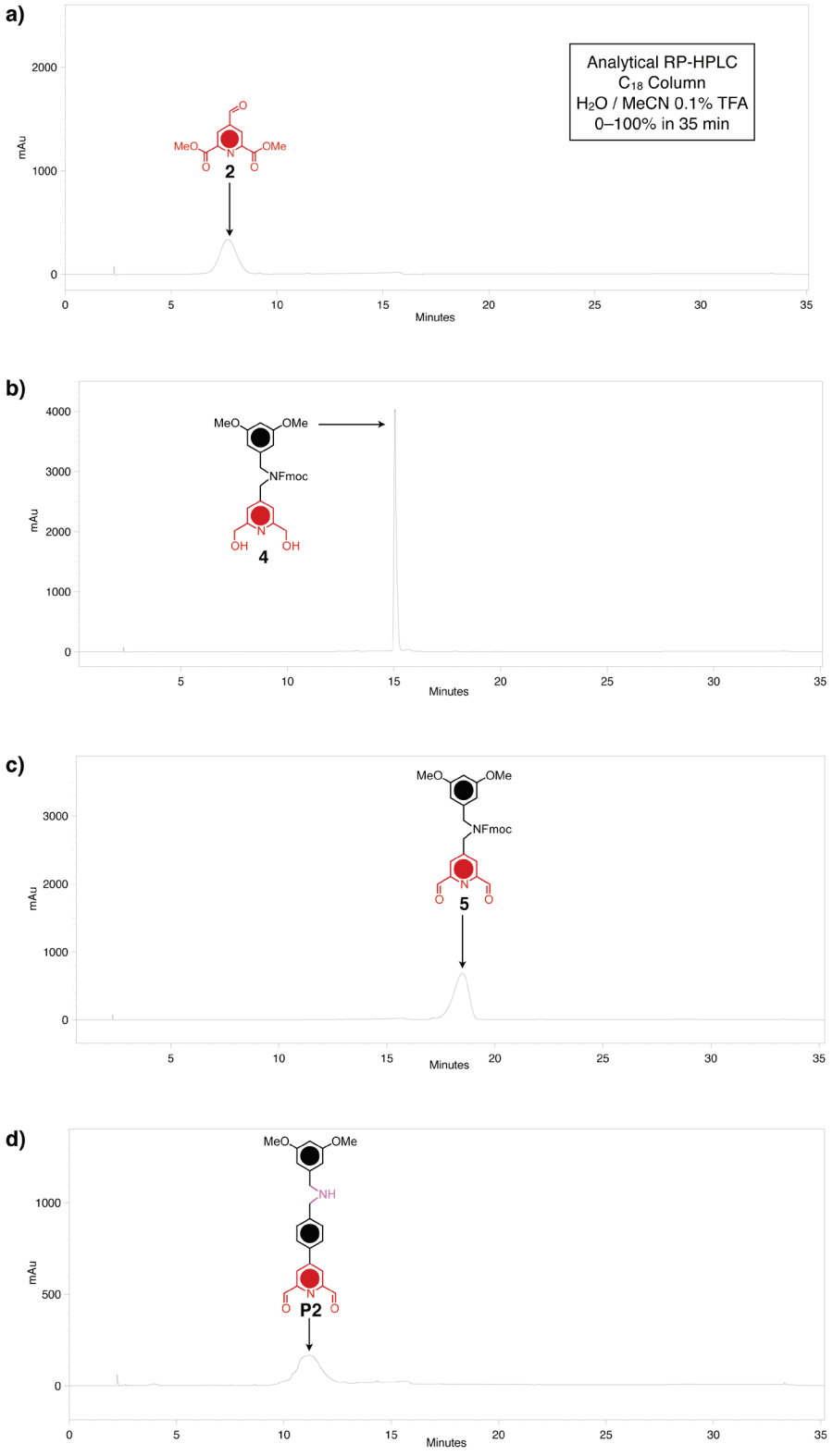


Figure S11: Analytical RP-HPLC of a) **2**, b) **4**, c) **5**, and d) **P2**; Abs @ 270 nm.