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SUPPORTING INFORMATION

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Title: Control of Oligomerization and Oxidation Steps in the Synthesis of Tris(pentafluorophenyl)corrole
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General Information

Unless stated otherwise, reactions were performed in ambient atmosphere. High-resolution mass spectra (HRMS) were obtained on Agilent 6200 Series LC-TOF with an Agilent G1978A Multimode source for mixed multimode ionization (MMI) or electrospray ionization (ESI). High-throughput reaction screens were carried out on a Freeslate (Santa Clara, CA) Core Module 2 robotic system. Chiral chromatographic separations of the diastereomers of oligomers **4-7** were conducted using a Thar analytical SFC system using a Mettler-Toledo column compartment at 40 °C and an Agilent 1200 series G1315B diode-array detector using isopropanol/CO_2 and two 4.6 x 250 mm Chiralcel® AD-H columns. ^{1}H NMR was carried out on a Varian 600 MHz spectrometer with shifts reported in parts per million (ppm). Pentafluorobenzaldehyde was purchased from Synquest Laboratories. Pyrrole and trifluoroacetic acid were purchased from Sigma Aldrich and was freshly distilled prior to each use. The Trifluoroacetic acid (TFA) solution in dichloromethane was prepared freshly prior to each use. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was purchased from Ark Pharm Inc. Unless otherwise mentioned, all other materials were used as received.

Representative Screening Results from the Optimization of Oligomerization and Oxidation Steps:

Screening experiments of pyrrole:aldehyde ratio, TFA catalyst concentration, solvent and temperature were prepared using the Freeslate Core Module 2 on a scale of 1 mmol and the crude reaction mixtures were analyzed by LCMS at multiple timepoints. Using the measured relative molar response factors at 254 nM of 1.0, 2.2, 3.5, 5.1, 6.7, 8.4 for the purified compounds **4-9**, respectively, the UV integrations for each oligomer were converted to the per cent of theoretical yield of each oligomer. A representative optimization for pyrrole:aldehyde molar ratio is shown in Figure 1 below. Optimization experiments for the DDQ oxidation step were conducted in a similar fashion using 4,4'-di-*tert*-butylbiphenyl as an internal standard. In practice, the optimum number of equivalents of DDQ and the yield of **1** were dependent on the composition of **4-10** present in the oligomer sample subject to oxidation with the best results obtained when oligomer **4** was present in lesser amounts. A representative optimization for the molar ratio of DDQ:starting aldehyde on the mixture of **4-10** is shown in Figure 2 below.

Figure 1: HPLC % Yield of **4-10** vs. Pyrrole Equivalents.

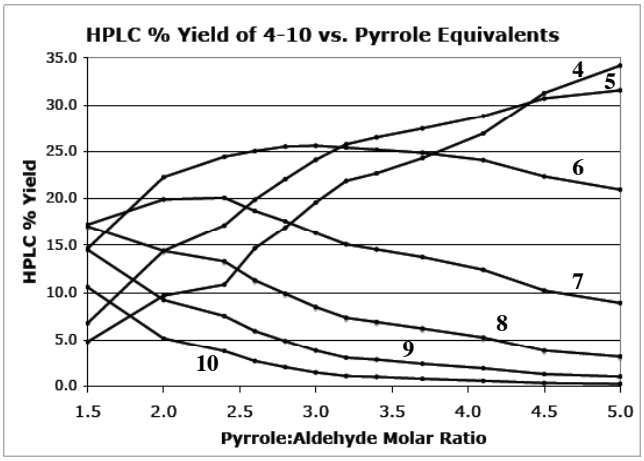
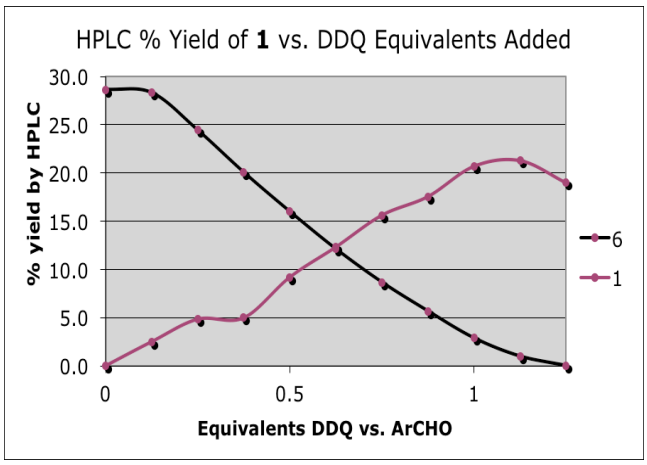


Figure 2: HPLC % Yield of **1** vs. DDQ equivalents (see procedure on page S6).



Procedure for the preparation and preparative HPLC separation of compounds 4-10:

To a 20 mL scintillation vial with stirbar was added a solution of pentafluorobenzaldehyde (1.50 g, 7.65 mmol, 1.0 equiv.) in dichloromethane (2.25 mL) followed by pyrrole (2.25 mL, 2.18 g, 32.4 mmol, 4.2 equiv.). The mixture was cooled to 15 °C and a solution of 1:19 v/v trifluoroacetic acid in dichloromethane (75 µL, .05 mmol, 0.006 equiv.) was added. After stirring for 10 minutes at 15 - 20 °C, an additional 75 µL of the trifluoroacetic acid solution was added and the mixture was allowed to stir at room temperature for 20 minutes.

The reaction mixture was directly purified by reversed phase preparative HPLC (in 12 injections of 500 µL each) on a 30 x 250 mm XDB-C18 column (5 µM particle size) using an Agilent 1200 preparative HPLC with a flow rate of 50 mL/min (85-100% acetonitrile/water) and UV detection at 254 nM. The fractions containing compounds **4-10** were separately collected in ice-cooled receivers and rotary evaporated to dryness. Care was taken to minimize exposure to air and light during the handling and storage of **4-10**. After dissolving in ether, the products were transferred to individual vials and evaporated to afford the pure compounds **4-10** which were pumped under high vacuum for 4 hours.

2,2'-((perfluorophenyl)methylene)bis(1H-pyrrole)

C_4H_4N-$CH(C_6F_5)$-C_4H_4N (**4)** was obtained as an off-white solid (478 mg, 20.0% yield). ^{1}H NMR (600 MHz, CD_2Cl_2): δ 8.20 (br s, 2H), 6.73 (dt, 2H, J = 1.5, 2.7 Hz), 6.14 (q, 2H, J = 3.0 Hz), 6.01 (t, 2H, J = 3.2 Hz), 5.91 (s, 1H). HR(ESI)-MS (M-H) (M = $C_{15}H_9F_5N_2$): Calcd 311.0602, obsd 311.0587.

2,5-bis((perfluorophenyl)(1H-pyrrol-2-yl)methyl)-1H-pyrrole

C_4H_4N-$[CH(C_6F_5)$-$C_4H_3N]$-$CH(C_6F_5)$-C_4H_4N (**5)** was obtained as an orange viscous liquid (393 mg, 18.4% yield). ^{1}H NMR (600 MHz, CD_2Cl_2): δ 8.20 (br s, 2H), 8.07 and 8.04 (pair of s, 1H, dl and meso), 6.72 (q, 2H, J = 2.3 Hz), 6.11 (m, 2H), 5.96 (s, 2H), 5.92 (t, 2H, J = 2.4 Hz), 5.84 (s, 2H). HR(ESI)-MS (M-H) (M = $C_{26}H_{13}F_{10}N_3$): Calcd 556.0866, obsd 556.0851.

5,5'-((perfluorophenyl)methylene)bis(2-((perfluorophenyl)(1H-pyrrol-2-yl)methyl)-1H-pyrrole)

C_4H_4N-$[CH(C_6F_5)$-$C_4H_3N]_2$-$CH(C_6F_5)$-C_4H_4N (**6)** was obtained as a yellow powder (459 mg, 22.4% yield). ^{1}H NMR (600 MHz, CD_2Cl_2): δ 8.20 (br s, 2H), 8.00 – 8.10 (m, 2H), 6.73 (m, 2H), 6.12 (m, 2H), 5.96 (m, 2H), 5.86-5.91 (m, 4H), 5.84 (s, 2H), 5.78 and 5.77 (pair of s, 1H). HR(ESI)-MS (M-H) (M = $C_{37}H_{17}F_{15}N_4$): Calcd 801.1130, obsd 801.1110.

2,5-bis((perfluorophenyl)(5-((perfluorophenyl)(1H-pyrrol-2-yl)methyl)-1H-pyrrol-2-yl)methyl)-1H-pyrrole

C_4H_4N-[$CH(C_6F_5)$-C_4H_3N]$_3$-$CH(C_6F_5)$-C_4H_4N (**7)** was obtained as an orange viscous liquid (318 mg, 15.9% yield). ^{1}H NMR (600 MHz, CD_2Cl_2): δ 8.20 (br s, 2H), 8.00 (m, 3H), 6.71 (m, 2H), 6.10 (m, 2H), 5.96 (m, 2H), 5.90 (m, 2H), 5.87 (m, 4H), 5.83 (s, 2H), 5.76 (pair of s, 2H). HR(ESI)-MS (M-H) (M = $C_{48}H_{21}F_{20}N_5$): Calcd 1046.1394, obsd 1046.1395.

5,5'-((perfluorophenyl)methylene)bis(2-((perfluorophenyl)(5-((perfluorophenyl)(1H-pyrrol-2-yl)methyl)-1H-pyrrol-2-yl)methyl)-1H-pyrrole)

C_4H_4N-[$CH(C_6F_5)$-C_4H_3N]$_4$-$CH(C_6F_5)$-C_4H_4N (**8)** was obtained as an orange viscous liquid (162 mg, 8.2% yield). ^{1}H NMR (600 MHz, CD_2Cl_2): δ 8.18 (br s, 2H), 8.03 (m, 4H), 6.71 (m, 2H), 6.10 (m, 2H), 5.95 (m, 2H), 5.89 (m, 2H), 5.87 (m, 6H), 5.83 (s, 2H), 5.76 (m, 3H). HR(ESI)-MS (M-H) (M = $C_{59}H_{25}F_{25}N_6$): Calcd 1291.1658, obsd 1291.1627.

2,5-bis((perfluorophenyl)(5-((perfluorophenyl)(5-((perfluorophenyl)(1H-pyrrol-2-yl)methyl)-1H-pyrrol-2-yl)methyl)-1H-pyrrol-2-yl)methyl)-1H-pyrrole

C_4H_4N-[$CH(C_6F_5)$-C_4H_3N]$_5$-$CH(C_6F_5)$-C_4H_4N (**9)** was obtained as an light brown viscous liquid (85 mg, 4.3% yield). ^{1}H NMR (600 MHz, CD_2Cl_2): δ 8.18 (br s, 2H), 8.02 (m, 5H), 6.70 (m, 2H), 6.09 (m, 2H), 5.95 (m, 2H), 5.89 (m, 2H), 5.87 (m, 8H), 5.83 (s, 2H), 5.76 (br s, 4H). HR(ESI)-MS (M-H) (M = $C_{70}H_{29}F_{30}N_7$): Calcd 1536.1922, obsd 1536.1883.

5,5'-((perfluorophenyl)methylene)bis(2-((perfluorophenyl)(5-((perfluorophenyl)(5-((perfluorophenyl)(1H-pyrrol-2-yl)methyl)-1H-pyrrol-2-yl)methyl)-1H-pyrrol-2-yl)methyl)-1H-pyrrole

C_4H_4N-[$CH(C_6F_5)$-C_4H_3N]$_6$-$CH(C_6F_5)$-C_4H_4N (**10)** was obtained as an light brown viscous liquid (32 mg, 1.8% yield). ^{1}H NMR (600 MHz, CD_2Cl_2): δ 8.18 (br s, 2H), 8.02 (m, 6H), 6.70 (m, 2H), 6.09 (m, 2H), 5.94 (m, 2H), 5.90 (m, 2H), 5.87 (m, 10H), 5.82 (s, 2H), 5.75 (br s, 5H). HR(ESI)-MS (M-H) (M = $C_{81}H_{33}F_{35}N_8$): Calcd 1781.2186, obsd 1781.2135.

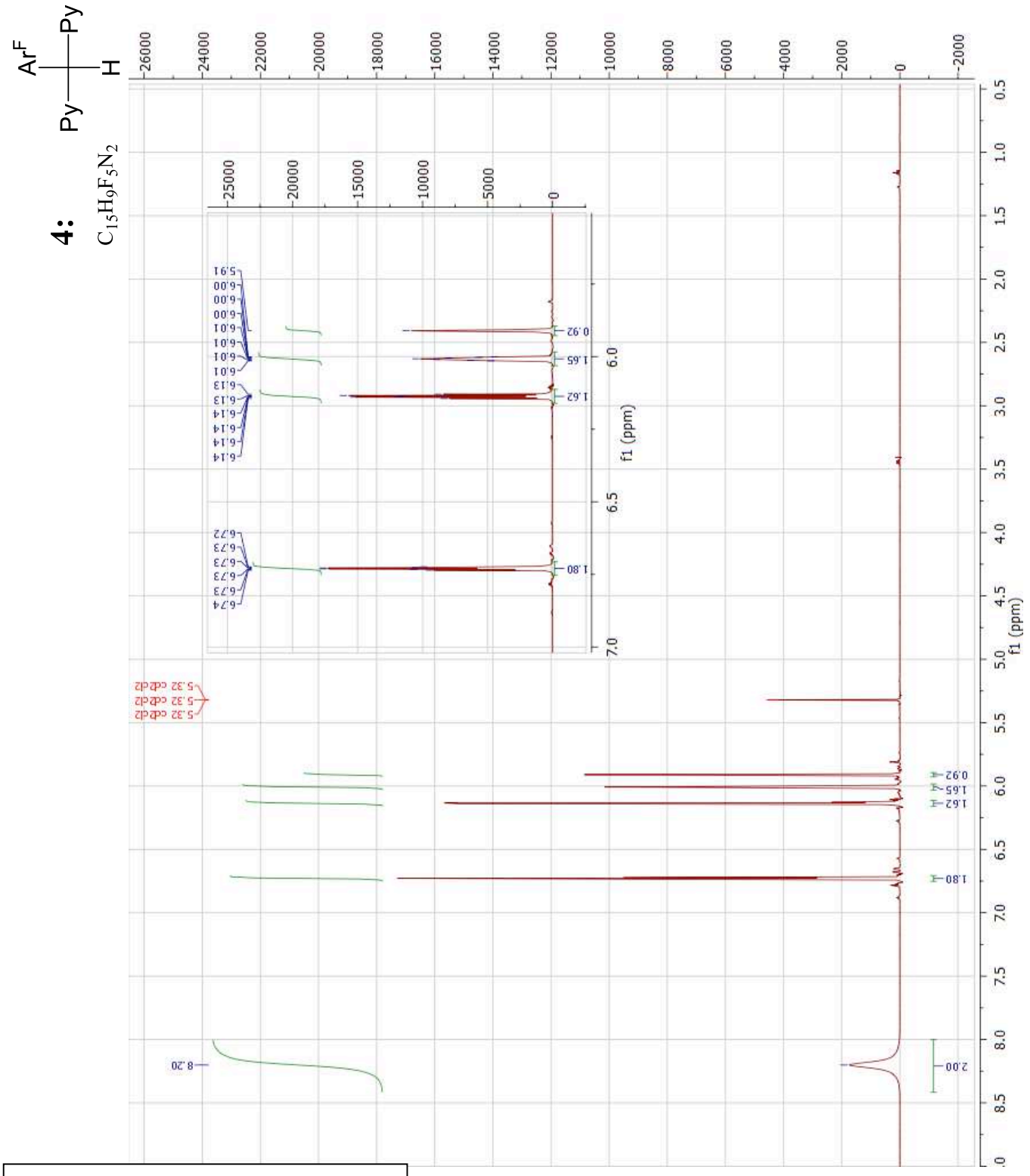
Procedure for the DDQ oxidation of purified oligomer 6:

In a 40 mL scintillation vial with stirbar, a solution of oligomer **6** (364 mg, 0.45 mmol) in 25 mL dichloromethane was treated by the dropwise addition over 10 minutes of a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (341.5 mg, 1.50 mmol, 3.3 equiv.) in 1.5 mL tetrahydrofuran at 15 °C. The reaction was allowed to proceed with stirring at 15 °C for 20 minutes. After filtration of the cold reaction mixture through Celite®, the filtrated was concentrated to dryness. The residue was immediately taken up in 1:3 dichloromethane-hexane and purified by column chromatography on silica using 1:3 dichloromethane-hexanes as eluent. The corrole **1** was obtained as a dark purple powder (305 mg, 84% yield).

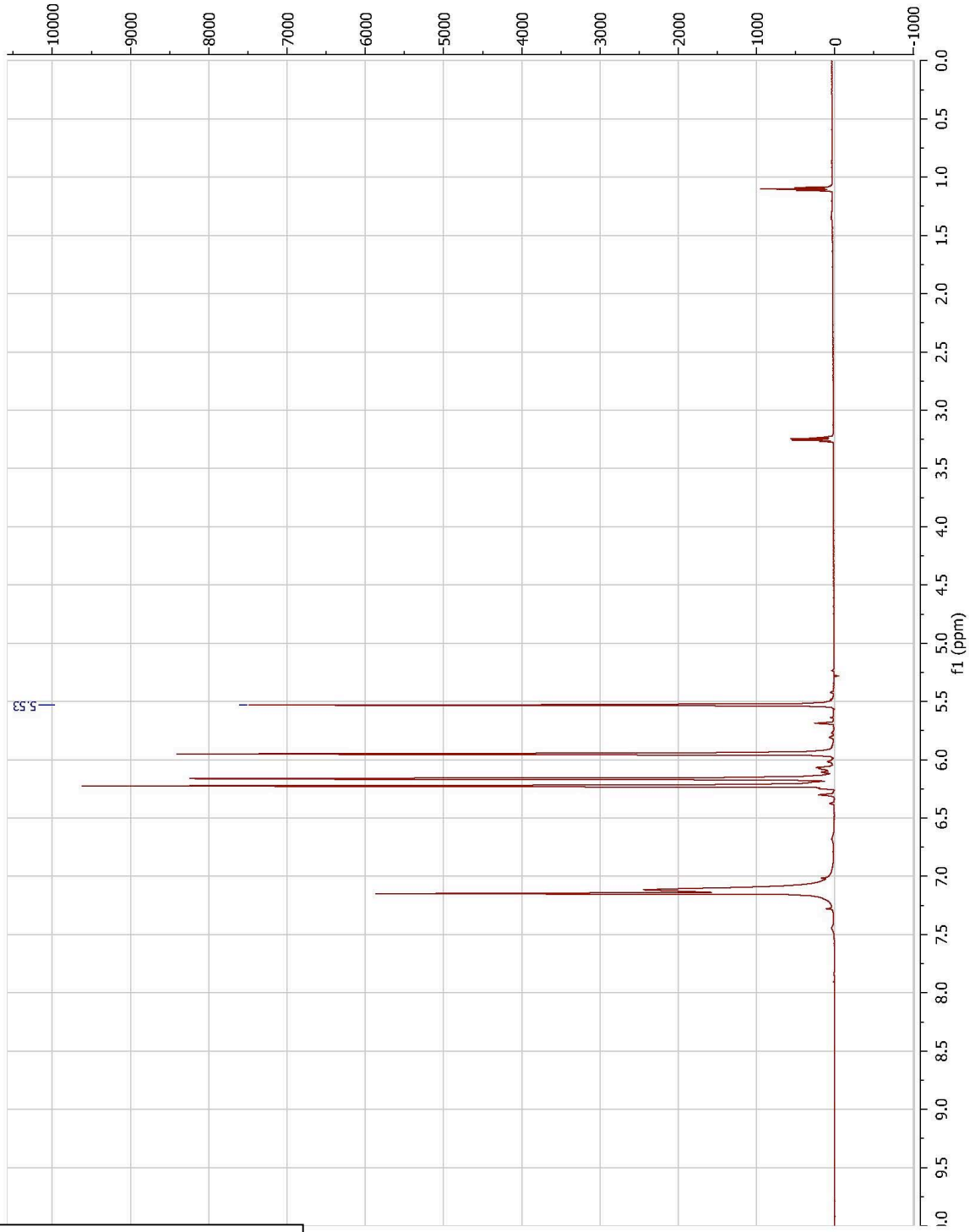
Preparation of Tris(pentafluorophenyl)corrole (1):

To an open 500 mL round-bottomed flask equipped with a stir bar was added pentafluorobenzaldehyde (20.0 g, 0.102 mole), dichloromethane (15 mL) followed by freshly distilled pyrrole (20 mL, 19.3 g, 0.29 mole, 2.8 equiv.). The mixture was placed in an ice-water mixture with stirring and when the internal temperature reached 15 °C, 1.0 mL of a 5% by volume trifluoroacetic acid solution (0.075 g of TFA, 0.65 mmol) in dichloromethane was added in one portion with rapid stirring. After 3 minutes, the solution temperature had risen to 40 °C while stirring in the ice-water bath was continued. (It was found that allowing the temperature to rise in this manner ensured that the reaction mixture remained homogeneous and this procedure produced the most favorable distribution of the oligomers **4-10**.) Once the temperature subsided to 30 °C, an additional 2.0 mL of trifluoroacetic acid solution (0.15 g of TFA, 1.3 mmol) was added and the reaction was removed from the bath and allowed to proceed at room temperature for 30 minutes. The reaction mixture was filtered through anhydrous magnesium sulfate and concentrated to a viscous liquid by rotary evaporation using a vacuum pump at 0.5 torr and 50 °C. Complete removal of excess pyrrole was achieved by dissolving in 50 mL dichloromethane and rotary evaporation a second time. Analysis of the oligomeric mixture by LC-TOF confirmed the presence of oligomers **4-10** in relative contributions shown in Figure 1. Integration of the UV signal (254 nm) of the HPLC chromatogram revealed that the desired peak corresponding to oligomer **6** represented 25.7% of the total integration for the oligomers **4-10**. (Using the measured relative molar response factors at 254 nM of 1.0, 2.2, 3.5, 5.1, 6.7, 8.4 for the purified compounds **4-9**, respectively, we estimated that the mole fraction of the desired oligomer **6** in this mixture was approximately 26% in reasonable agreement with the isolated yield of **6** obtained in the preparative HPLC procedure above.) The mixture of oligomers **4-10** was subject to discoloration by air oxidation and was therefore used without delay.

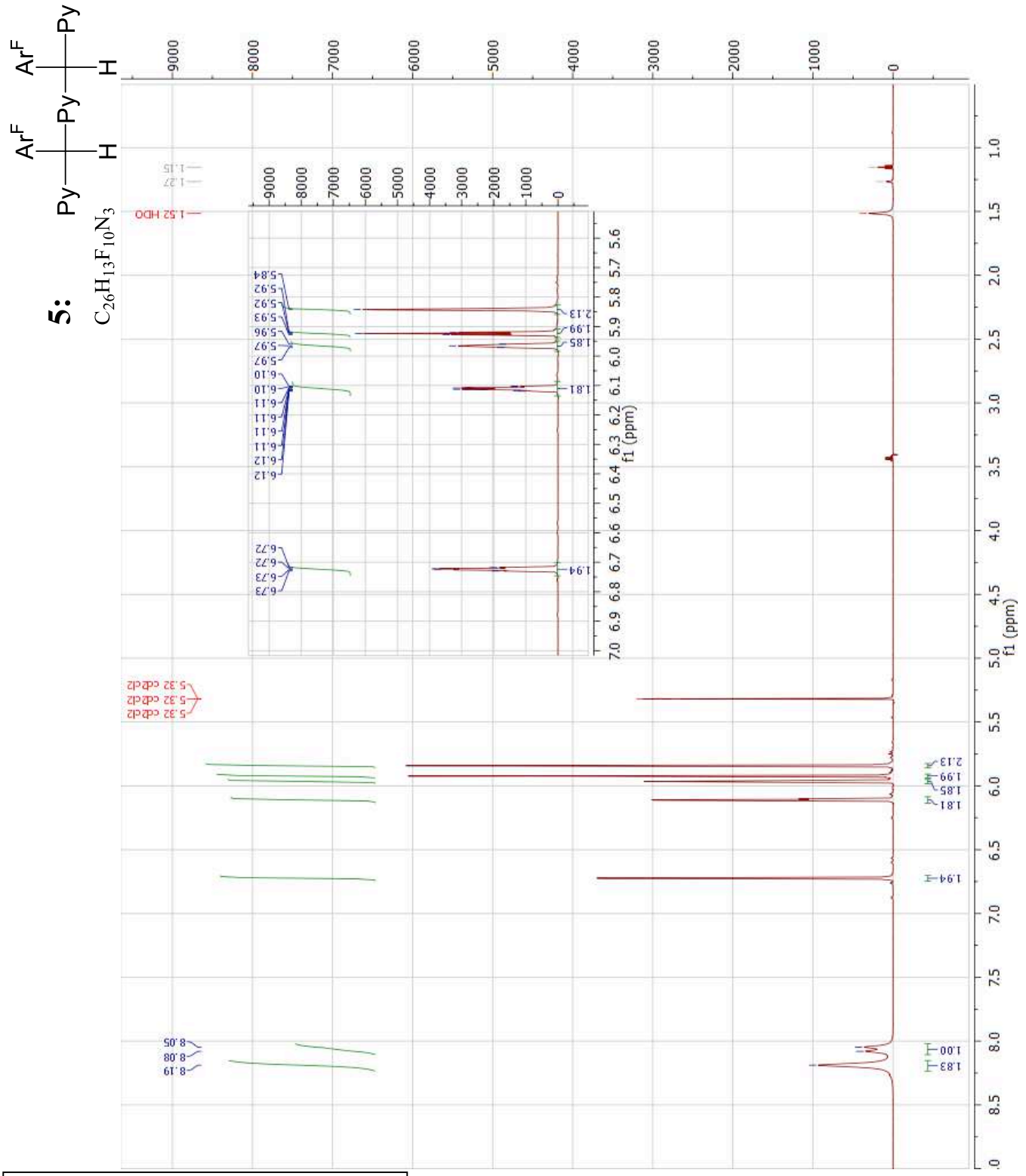
The crude mixture of **4**-**10** was dissolved in dichloromethane (4000 mL), transferred to a 5L round bottomed flask with stirbar and cooled to 5 °C using an ice-water mixture. A solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (22.7 g, 0.100 mole, 1.00 equiv. based on starting aldehyde) in tetrahydrofuran (200 mL) was added dropwise with stirring over 40 minutes while the reaction mixture was maintained at 5 °C. After completion of the addition (the complete consumption of **6** and the generation of **1** in the reaction mixture could be monitored by LCMS), the reaction mixture was stirred at room temperature for 6 hours. The resulting product mixture was then concentrated to a volume of 400 mL, diluted with 400 mL hexane and filtered to remove the hydroquinone byproduct. After rotary evaporation, the material was dissolved in dichloromethane (100 mL) with heating until dissolved and flash silica gel (120 g) was added followed by hexane (300 mL). The warm mixture was loaded without delay onto a column of 1200g flash (40-60 uM) silica gel prepared with 1:3 dichloromethane-hexanes. Upon elution of the column with 1:3 dichloromethane-hexane as eluant, the strongly colored corrole-containing fraction was concentrated. [It was desirable to efficiently separate the less polar orange contaminant (described and characterized by Gross[3]) during this chromatography procedure in order to ensure the successful purification of **1** by recrystallization.] The crude corrole **1** was dissolved in dichloromethane (120 mL) with heating and hexane was added (180 mL). The mixture was heated to evaporate about half of the dichloromethane from the mixture inducing the crystallization of a significant portion of the product. After cooling the mixture to 0 °C, the first crop of **1** was collected by filtration and washing with cold hexane (3.75 g, 13.9% yield). The filtrate was combined with mixed fractions from the first column chromatography and repurified by column chromatography to afford, after recrystallization, an additional crop of **1** (0.83 g, 3.1% yield). The combined yield of tris(pentafluorophenyl)corrole (**1**) was 4.58 g, (17.0% yield). ^{1}H NMR (600 MHz, CD_2Cl_2): δ 9.17 (d, 2H, J = 3.5 Hz), 8.83 (d, 2H, J = 3.5 Hz), 8.61-8.66 (m, 4H). HR(ESI)-MS (M+H) (M = $C_{37}H_{11}F_{15}N_4$): Calcd 797.0817, obsd 797.0825.



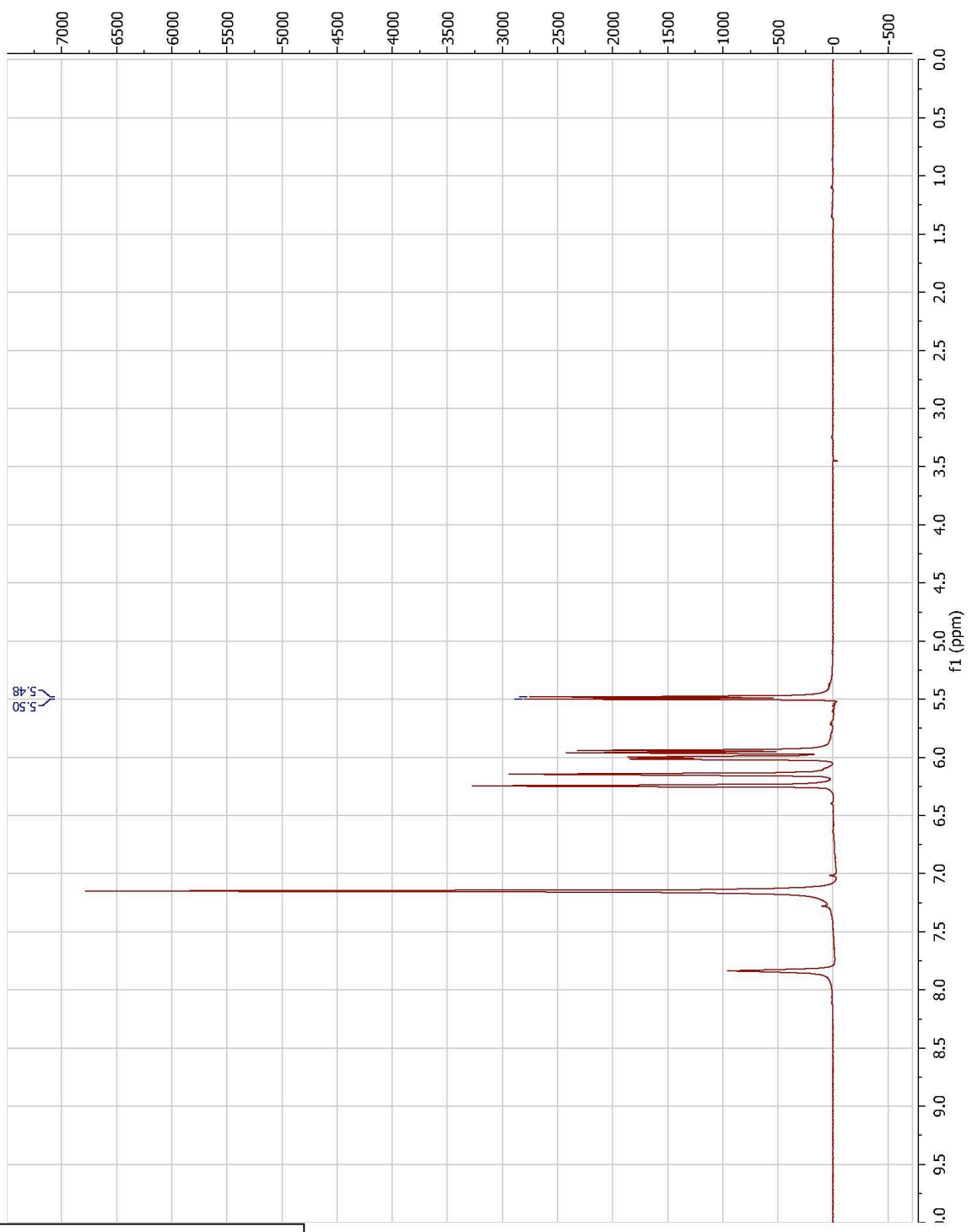
^{1}H NMR of **4** in CD_2Cl_2



^{1}H NMR of **4** in C_6D_6



^{1}H NMR of **5** in CD_2Cl_2



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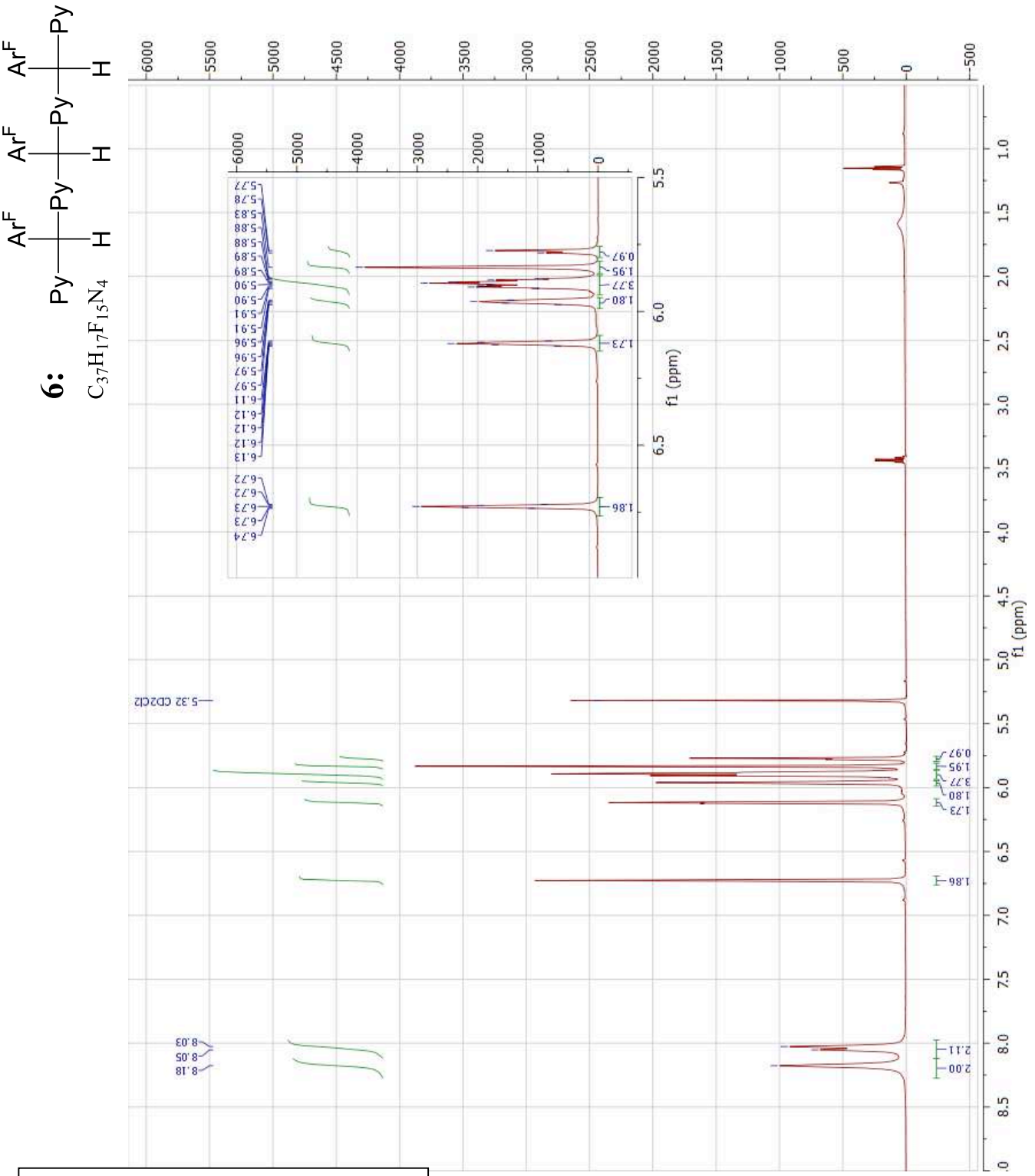

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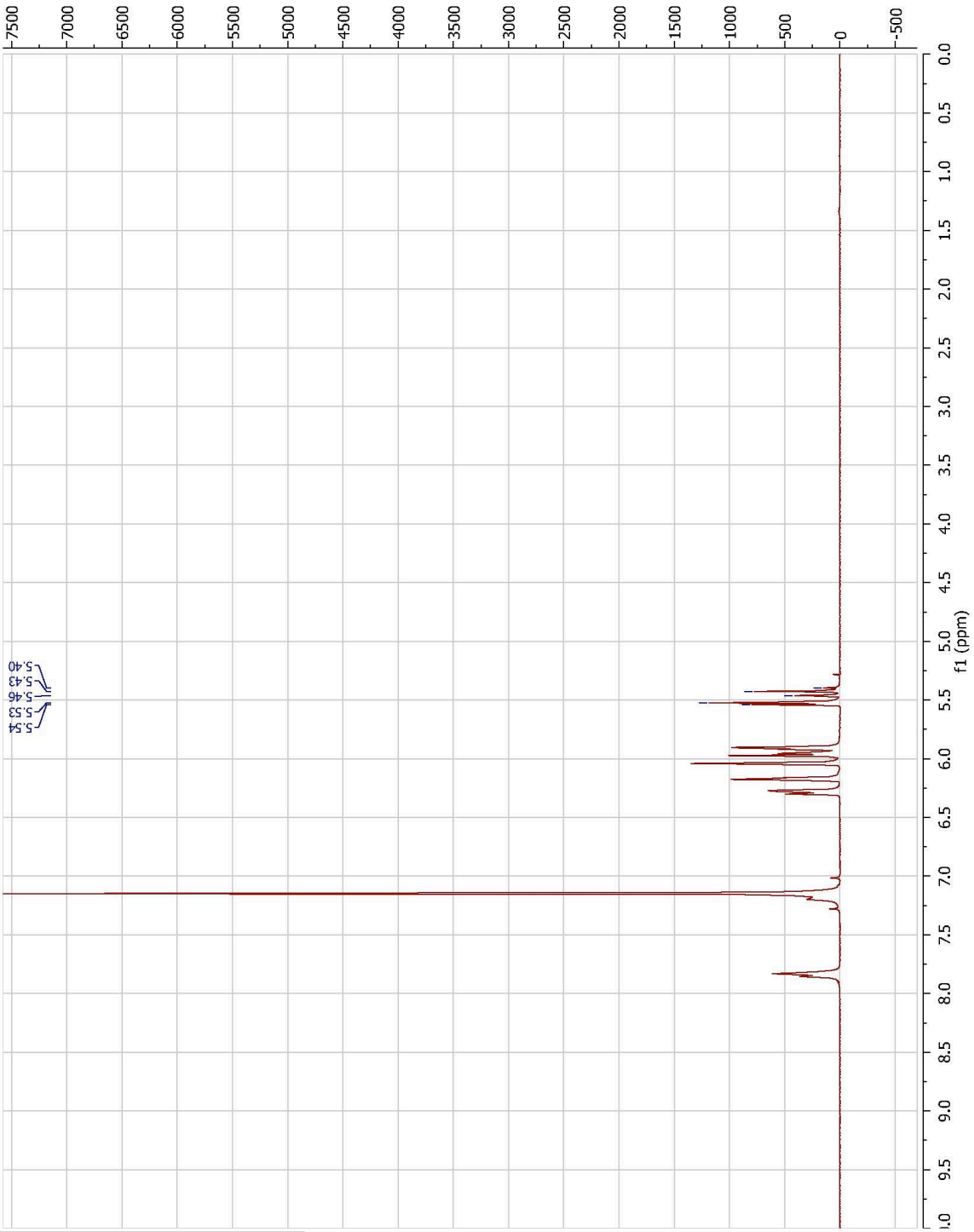

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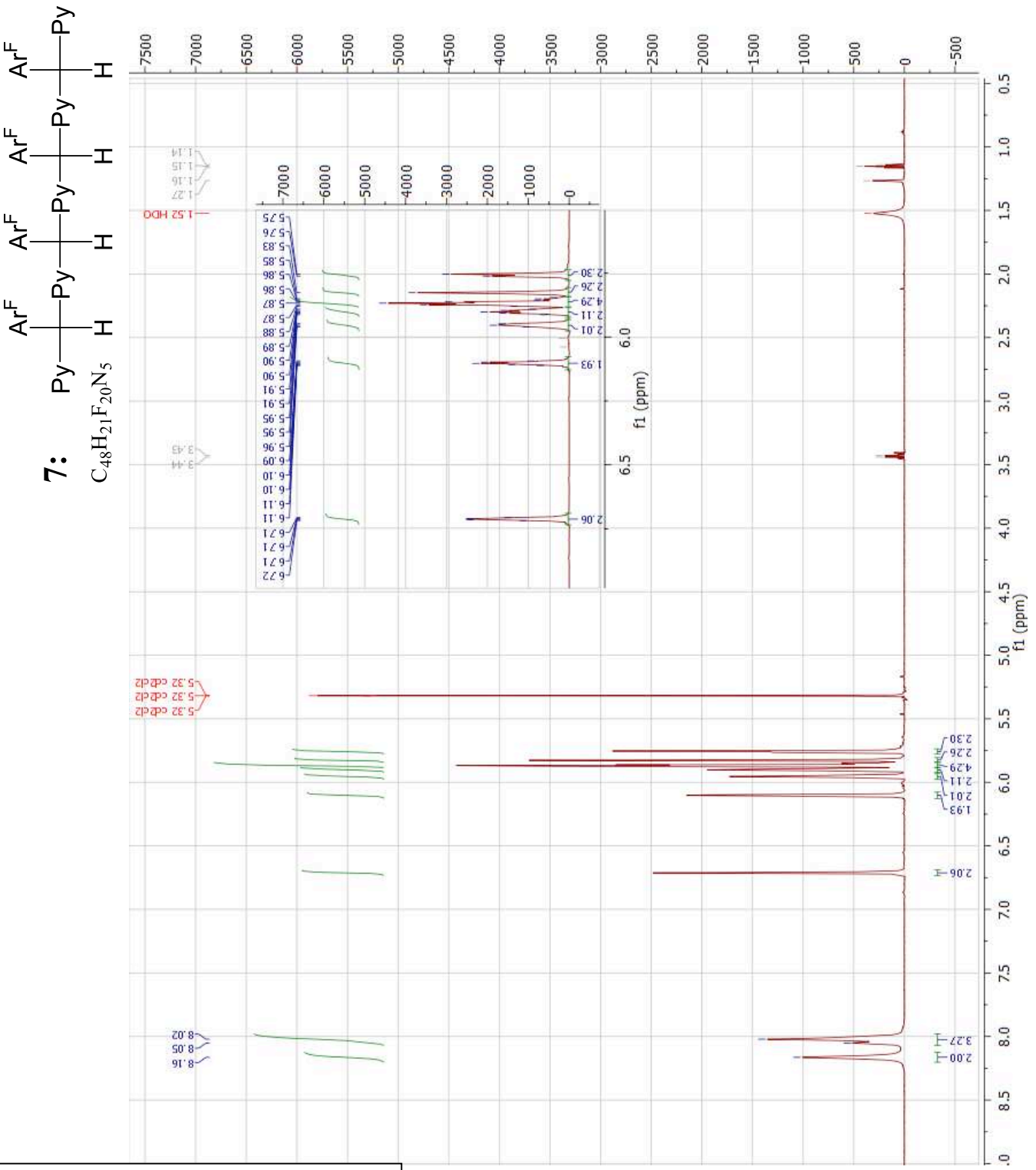

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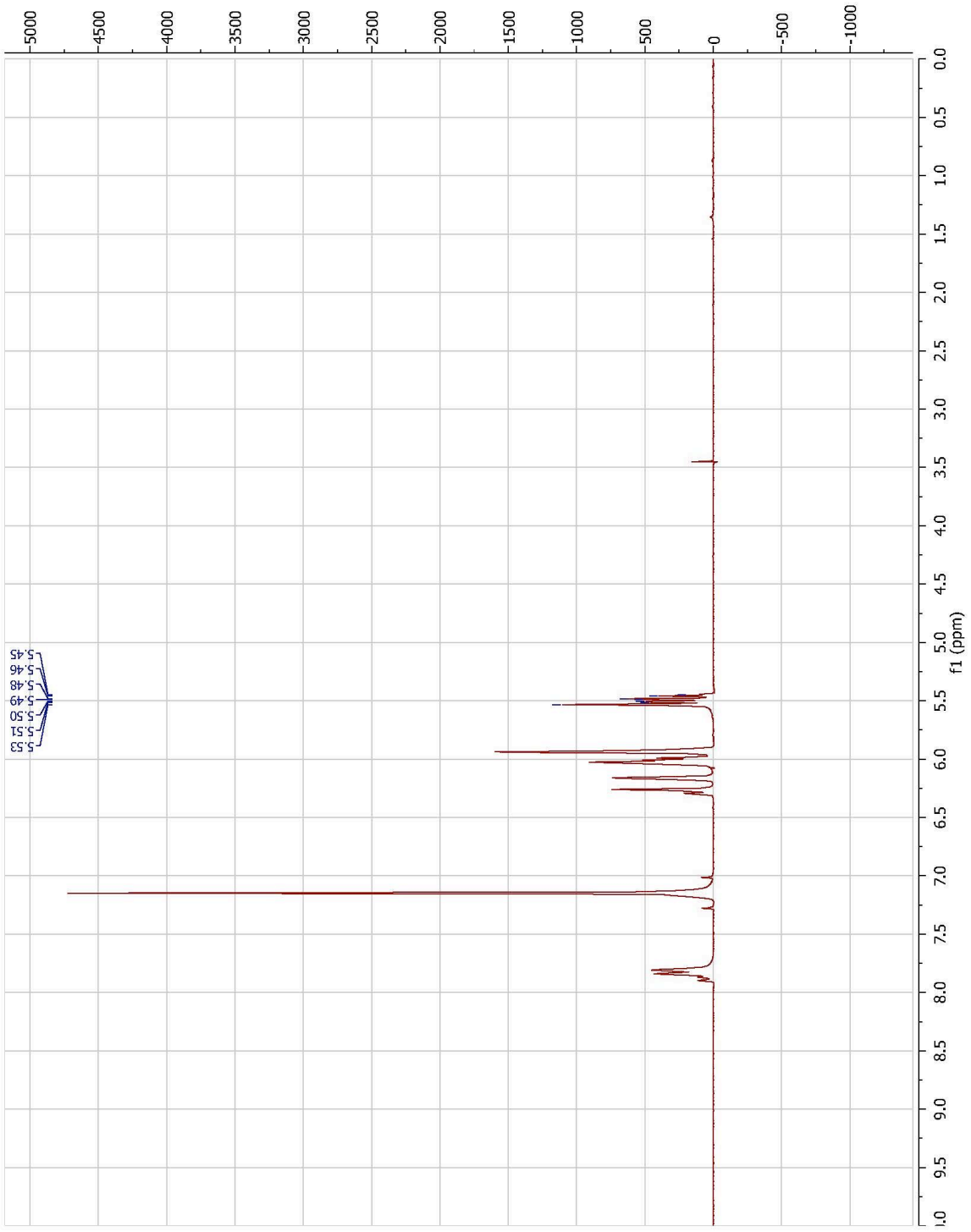

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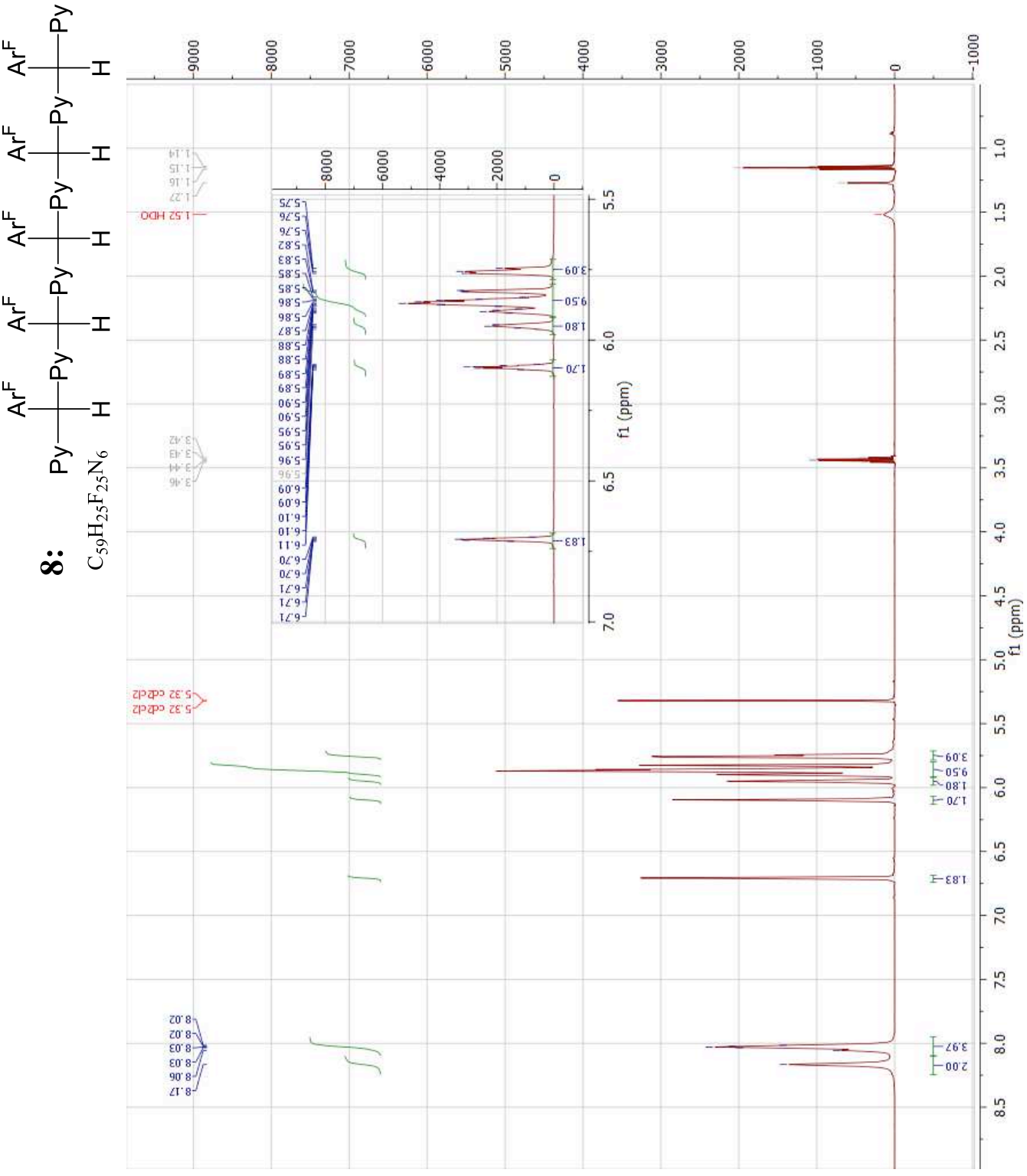
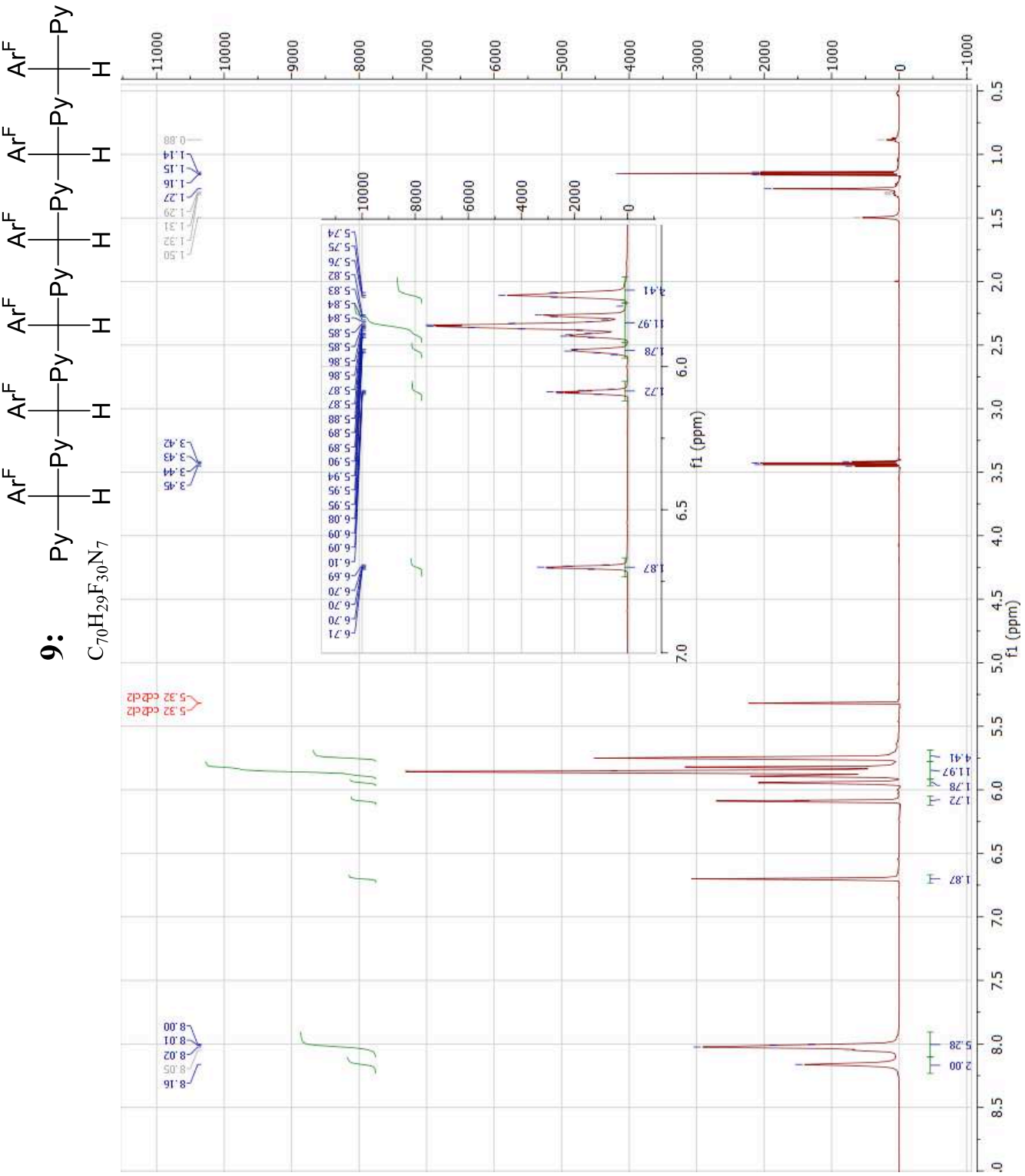
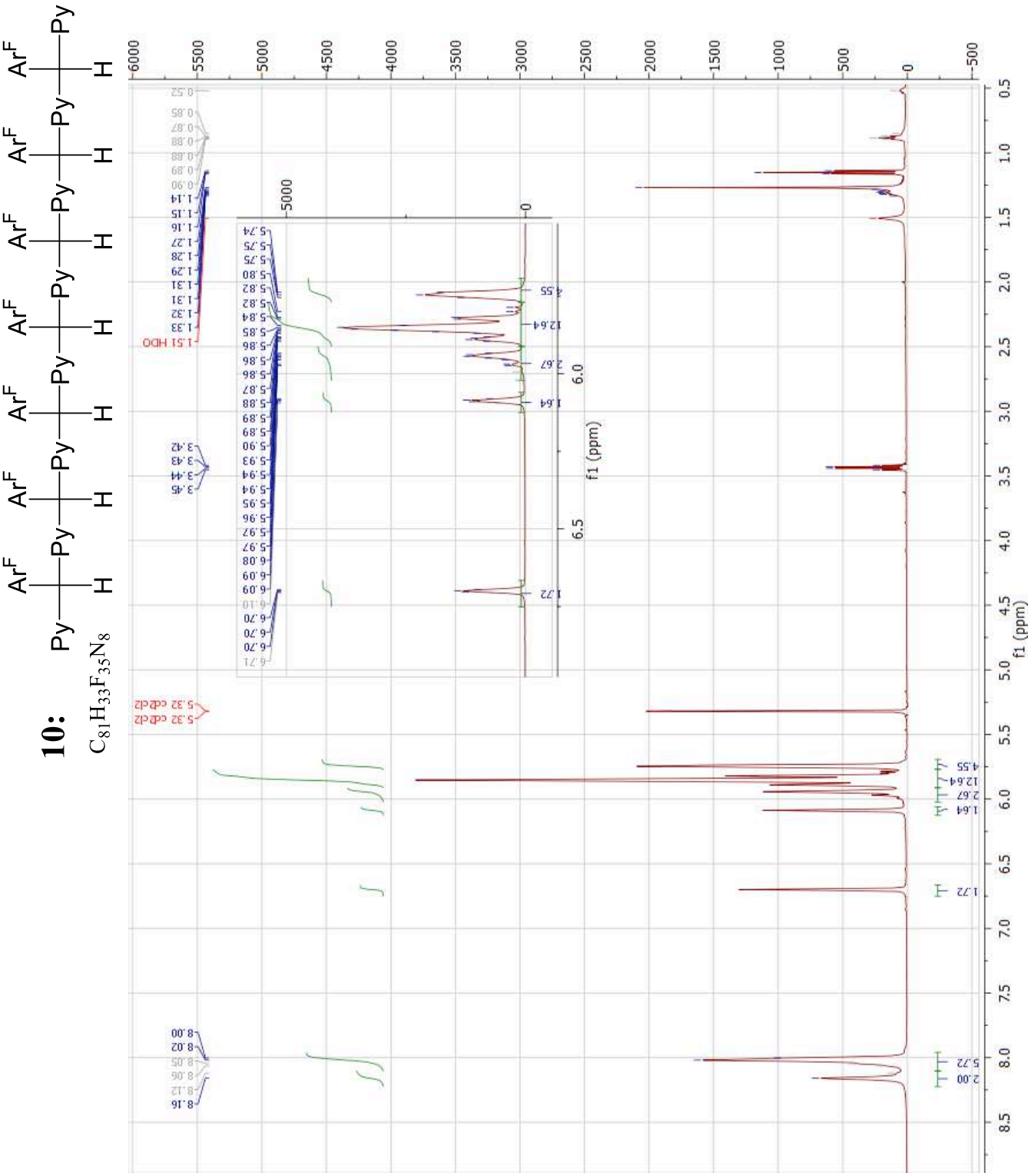


^{1}H NMR of **8** in CD_2Cl_2



^{1}H NMR of **9** in CD_2Cl_2



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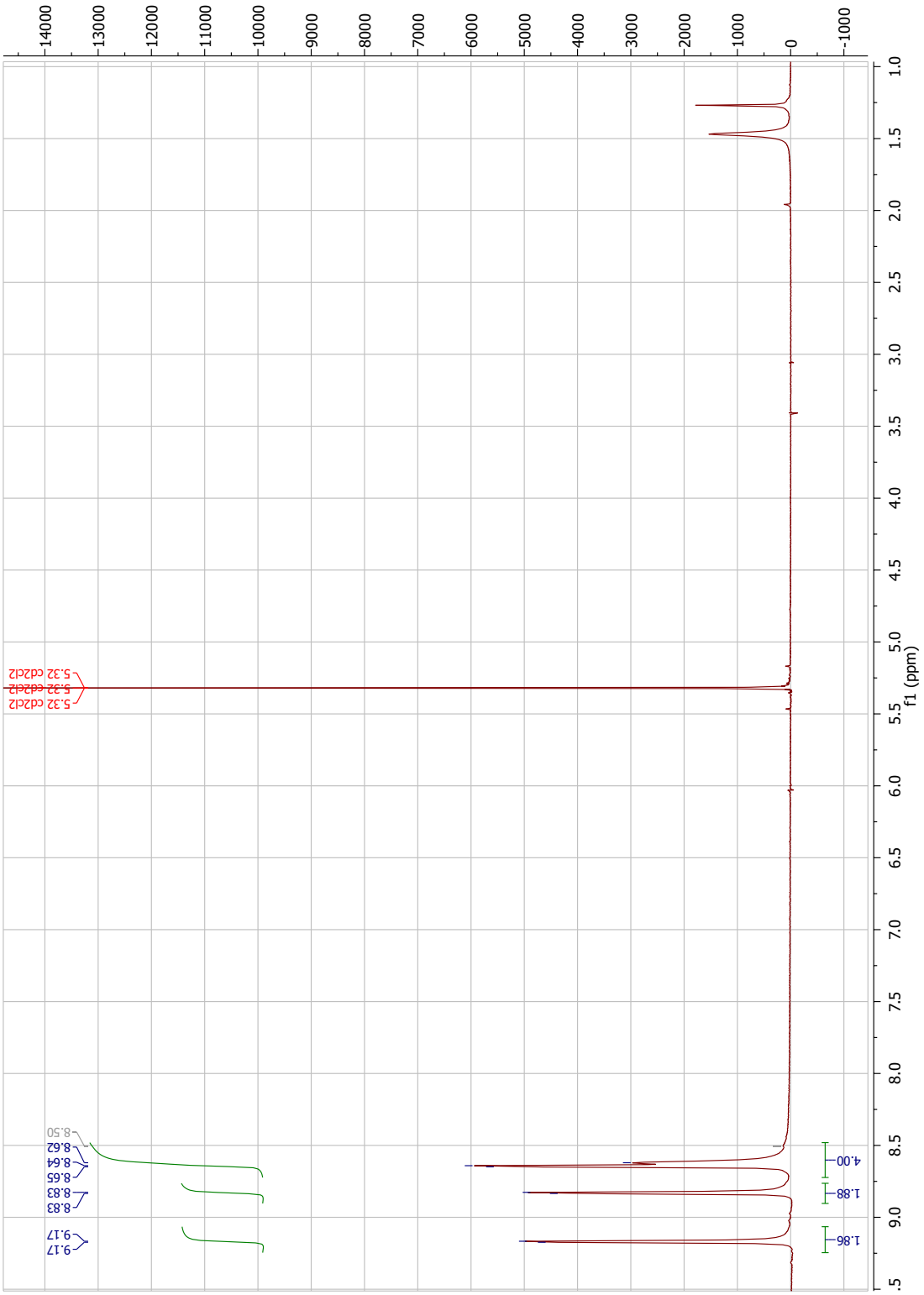
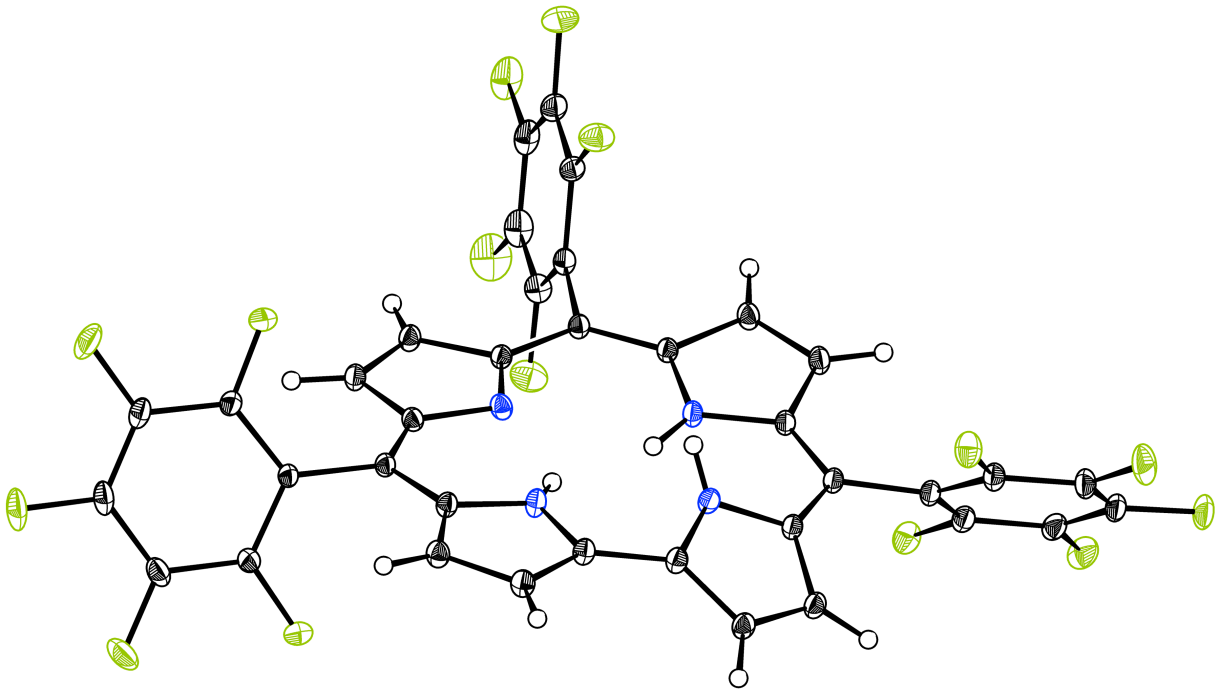


^{1}H NMR of **1** in CD_2Cl_2

X-Ray Structure Determination

Diffraction data (ω-and ϕ-scans) were collected on a Bruker AXS KAPPA APEX II diffractometer using an APEX II CCD detector with Triumph graphite monochromated Mo K_α fine-focus sealed tube radiation (λ = 0.71073 Å) equipped with an Oxford 700 Cryostream low-temperature cooler set to 100 K. The structure was solved by direct methods using SHELXT[i] and refined against F^2 on all data by full-matrix least squares with SHELXL[1] using OLEX2[2].

Compound A14375 crystallizes in the monoclinic space group $P2_1/c$ (#14) as large (several mm in length) purplish-red crystals with a metallic luster. The asymmetric unit consists of one corrole and two acetone solvent molecules. Except for the minor orientation of one disordered perfluorophenyl group, all non-hydrogen atoms were refined anisotropically. The central pentafluorophenyl group is disordered 92:08 by an ~4° tilt parallel to the plane of the phenyl ring. The minor component was refined isotropically and restrained to have the same geometry as the major component. One of the two acetones is disordered 80:20 over two positions. There may be some small disorder in the other as well. All hydrogen atoms on the corrole were located in difference maps and freely refined. The methyl groups on the solvent acetone molecules were refined as rotating groups with U_{iso} values 1.5 times the U_{eq} of the bonded atom. There is a hydrogen bond from a pyrrole nitrogen to one acetone oxygen. The out of pyrrole plane distances for the hydrogens H1, H2, and H4 are 0.37, 0.09, and 0.10Å respectively. The angles between the pyrrole planes (N1-N2, N2-N3, N3-N4, N4-N1 respectively) are 157.0, 167.2, 6.6, and 25.5°. The overall conformation of the corrole is similar to that in a structure of an *m*-xylene solvate reported by Gross[3] in which the hydrogen parameters were not refined.



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