Supporting Information

Rationalizing the F…S Interaction Discovered within a Tetrafluorophenylazido-containing Bola-Phospholipid

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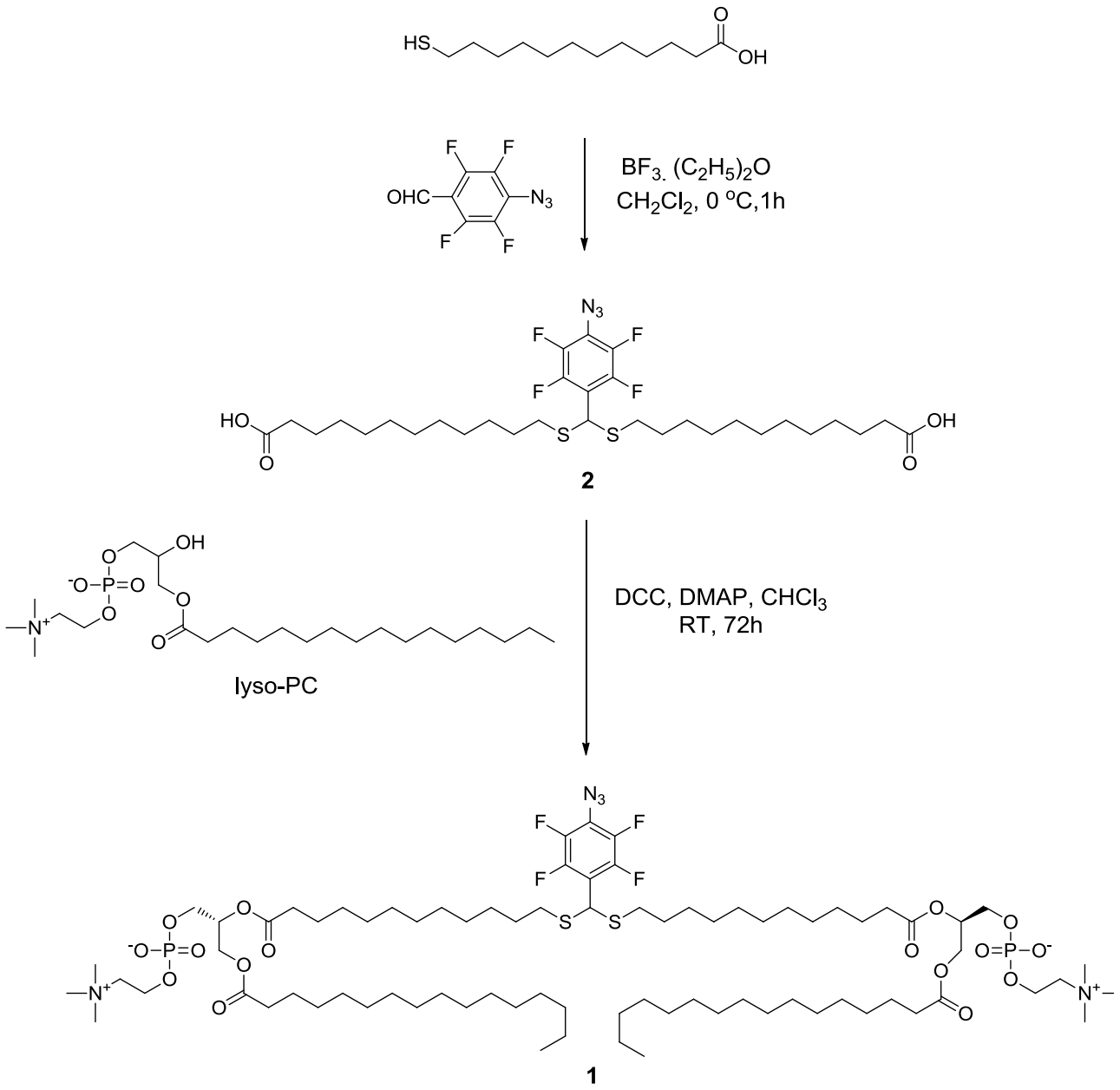
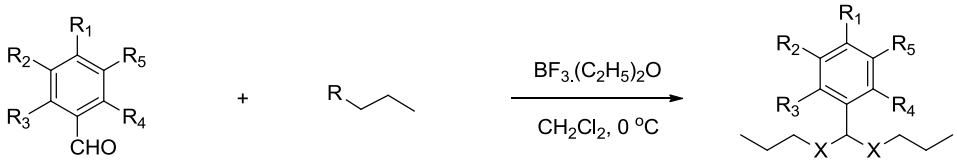
Scheme S1. Synthesis of **1** was following the protocol described in the literature.[1]



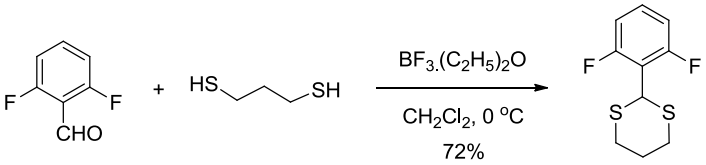
Scheme S2. Synthesis of model compounds **3-9**. A) Synthesis of **3-6**; B) Synthesis of **7**; C) Synthesis of **8**; D) Synthesis of **9**.

A



3: $R_1 = N_3$, $R_2 = R_3 = R_4 = R_5 = F$, X = S (74%)
4: $R_1 = N_3$, $R_2 = R_3 = R_4 = R_5 = F$, X = O (40%)
5: $R_1 = H$, $R_2 = R_5 = F$, $R_3 = R_4 = H$, X = S (89%)
6: $R_1 = R_2 = R_5 = H$, $R_3 = R_4 = F$, X = S (67%)

B



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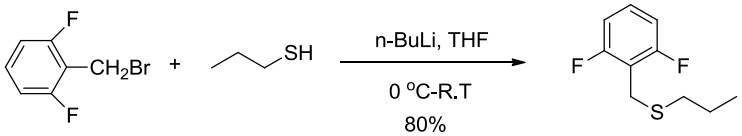
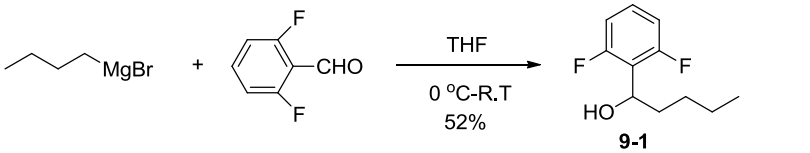
C

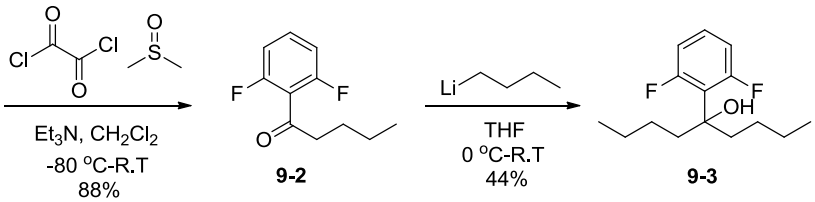


8

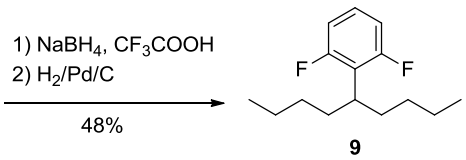
D



9-1



9-2 **9-3**



9

Figure S1. *Ab initio* optimized geometry of compounds **6** (A) and **9** (B). Atom color code: C, gray; F, cyan; S, yellow, H, white.

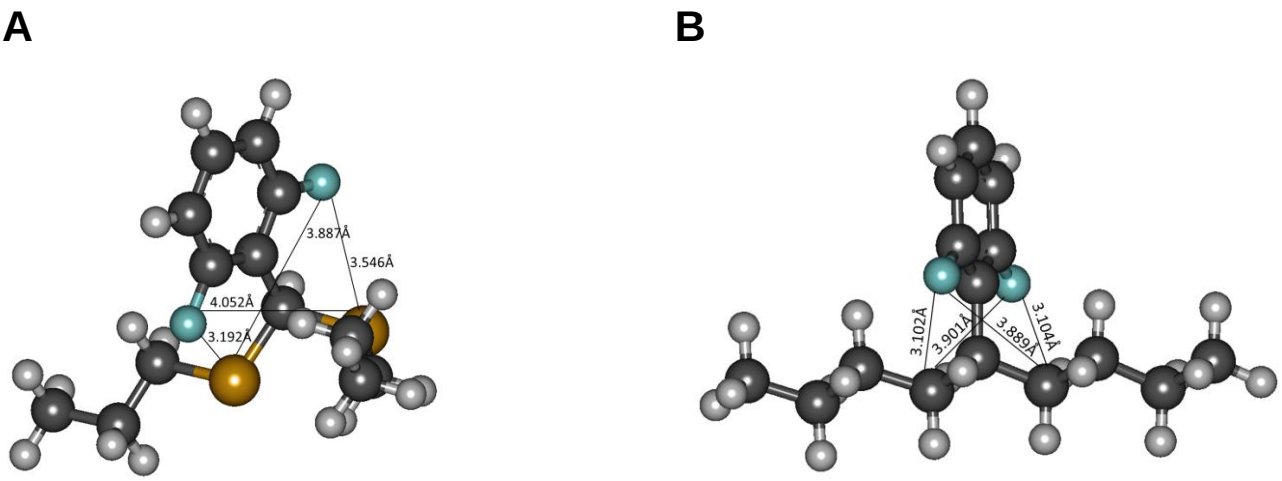


Figure S2. Distances of intra- and intermolecular F…S interactions found in CCDC (sum of van der Waals radii of F and S is 3.27Å). The survey was restricted to the contacts between F and divalent S and the diagram was created by ConQuest v.1.13 using Vista v.2.1. Criteria: distances ≤ 3.27Å, R < 0.05, not disordered, no ions, no powder, only organics, inter- and intramolecular contacts. For the survey on intramolecular interaction, only contacts with minimal 3 bonds between F and S were included to avoid counting cases in which the F and S atoms are close together for topological reasons. Therefore totally 500 structures were found in such case which contain 406 examples for intramolecular F…S interaction and 94 for intermolecular interactions.

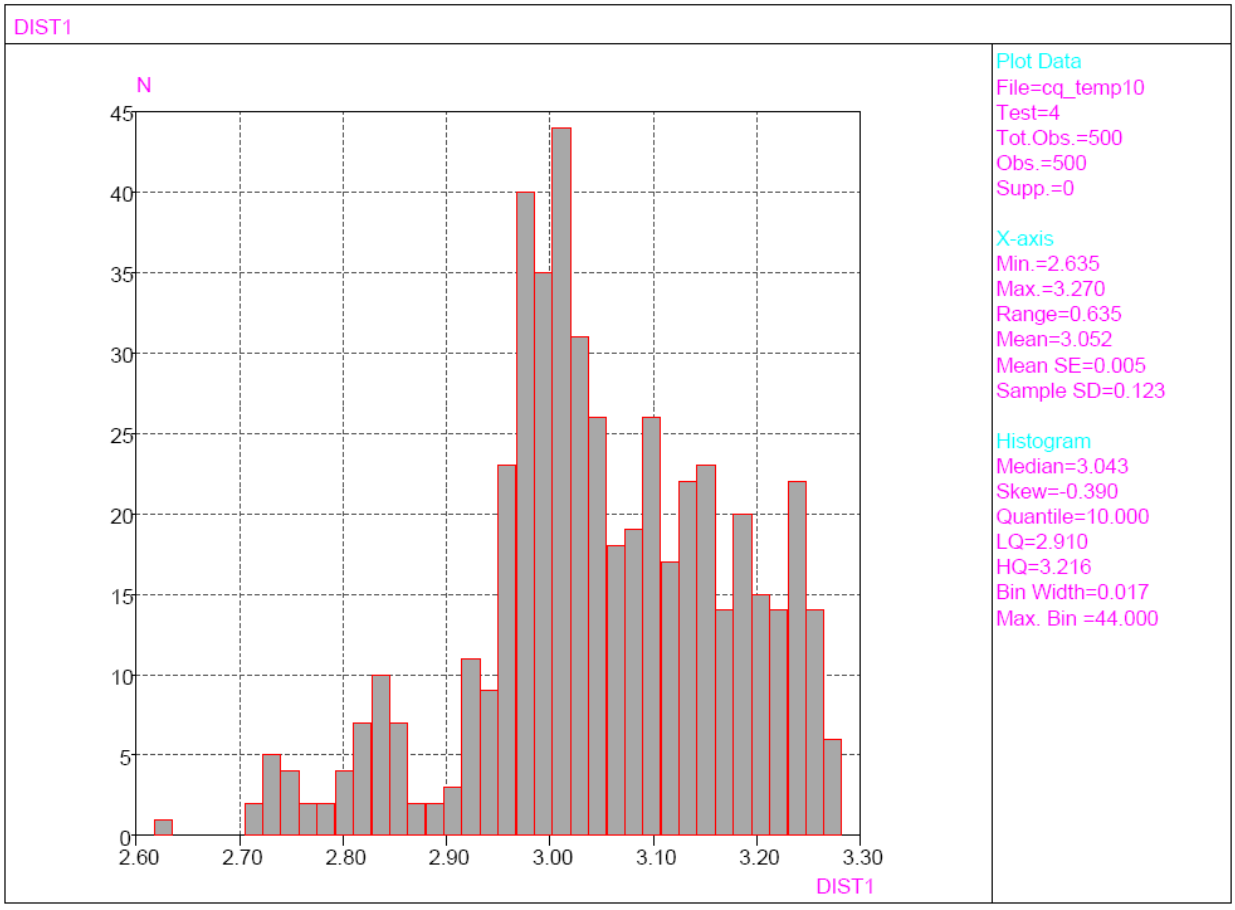


Figure S3. Temperature-dependent ^{19}F NMR spectra of **6** (**A**) and **9** (**B**). The spectra shown within the red dashed frames were those recorded near the corresponding coalescent temperatures.

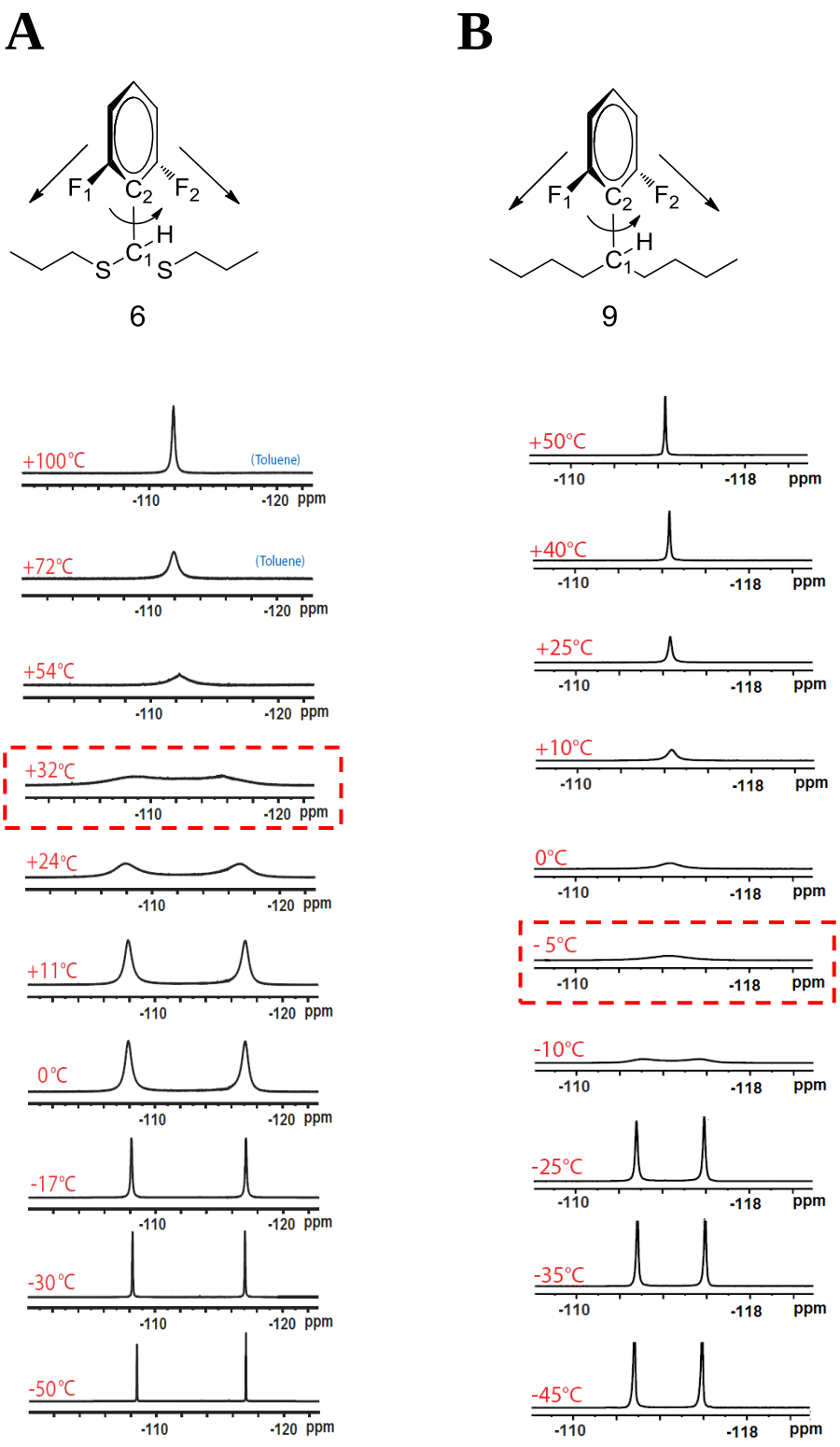


Table S1. Results of the NBO analysis on compounds **6** and **9.**

Compound	ΔE_{del}[a] (kcal/mol)	$\Delta q(\sigma^*_{S-C})$[b] (electron)	$\Delta q(n_F)$[c] (electron)
6	3.5	0.0049	-0.0078
9	1.6	0.0022	-0.044

[a] NBO delocalization energy between the divalent sulfur moiety (**6**) and the C atom of the CH_2 group (**9**) and the fluorine atom [b] Charge increase of the antibonding σ^*_{S-C} (**9**) and σ^*_{C-C} (**6**) orbital due to the orbital interaction between the sulfur (**6**)/carbon (**9**) and the fluorine atoms. [c] Charge decrease of the fluorine n_F orbital due to the orbital interaction between sulfur (**6**)/carbon (**9**) and fluorine interaction

In Table **S1**, the NBO deletion energy (ΔE_{del}) represents the orbital interaction energy between the -S- (or -CH_2-) moiety and the F atom. The values $\Delta q(\sigma^*)$ and $\Delta q(n)$ are the charge increase in the σ^* orbital of a S-C bond due to the S…F interaction formation and the corresponding charge decrease of the fluorine lone pair for **6** and **9**, respectively.

Table S2. Total energies (E) and relative energies (ΔE) corresponding to the global minimum and first lowest local minimum conformations of compounds **6** and **9**.

Compound/Conformer	E (Hartree)			ΔE (kcal/mol)		
	B3LYP	M06-2X	B97D	B3LYP	M06-2X	B97D
6/I	-2936.4366	-2936.2121	-2935.5440	0.00	4.92	5.49
6/II	-2936.4280	-2936.2042	-2935.5303	5.39	1.08	0.16
9	-2690.8657	-2690.7072	-2690.0867	-	0.01	0.07

Further results obtained through DFT calculations on compounds **6** and **9** are summarized in Table S2. We may observed from Table S2 that all three B3LYP, M06-2X, and B97-D methods employed to determine the conformational preferences of these two molecules agree consistently in identifying the global minimum for both **6** and **9**. In particular, for compound **6** the separation between the global energy minimum (i.e., conformer **I**, characterized by an app-gauche arrangement of the thioacetal group) and the first, low-energy local minimum (i.e., conformer **II**, featuring a gauche-gauche conformation of the same group), is rather large (see last three columns in Table S1). Single point energy calculations using the M06-2X/6-311++G** method and performed on the optimized geometries of the most stable conformers obtained at the B3LYP level yield an estimation of the intramolecular F…S interaction energy. The F…S interaction energy in the case of molecule **6** is found to be 4.92 kcal/mol for conformer **I** and 1.08 kcal/mol for conformer **II** respectively. In the case of compound **9** the estimated value of this interaction energy is -0.01 kcal/mol which substantially indicate that an intramolecular F…C interaction between C and F is absent in this molecule, as expected.

As B97D-DFT based calculations include a specific dispersion term in the corresponding energy calculation, we can expect this method to give even a more refined estimation of the F…S intramolecular interaction eventually present in compound **6**. As it may be inferred from the values listed in the last column of Table S1, the explicit inclusion of a dispersion energy contribution

results in a small but significant lowering of the total energy of the global minimum (conformer **I**) with respect to the first local minimum (conformer **II**). This evidence concurs to support the existence of a F…S interaction in compound **6** which, in turn, accounts for the unexpected ^{19}F NMR spectrum observed for this compound.

To further confirm the DFT results obtained for compound **6** discussed above, we decided to run also some Molecular Dynamics (MD) simulations. To the purpose, we resorted to a combination of Single-Coordinate Driving (SCD) with Simulated Annealing (SA) techniques. The starting set of conformers for compound **6** thus consisted of conformer **I** and **II** obtained from the DFT calculations discussed above, while one conformer only was selected for compound **9** was used. Considering compound **6**, after a few pathways were calculated, in both cases the system jumped to the same global minimum, i.e., conformer **I**. The energy barrier found by MD simulations was 12.9 kcal/mol, in excellent agreement with the values estimated from the elaboration of the NMR experimental data. As intuitively expected, in the case of compound **9** the same minimum energy conformer was recovered, for which an energy barrier of 11.6 kcal/mol was obtained, again in agreement with the NMR experiments. Accordingly, we can conclude that the conformational preference for compound **6** is characterized by the presence of a non-negligible F-S intramolecular interaction, which stabilizes an app-gauche conformation of the thioacetal group.

General: The chemical reagents were purchased from Acros, Sigma or Fluka. The ^{1}H NMR, ^{13}C NMR, ^{19}F NMR and ^{31}P NMR spectra were recorded at 300 MHz, 150 MHz, 564.6 MHz and 242.9 MHz respectively, on Varian Mercury-VX300 and Varian Inova-600 spectrometers. Chemical shifts were reported in parts per million (ppm) with TMS as the internal references, CF_3COOH and H_3PO_4 as the external reference. The NMR recordings of phospholipid were performed in $CDCl_3$ with adding two or three drops of CD_3OD to improve NMR resolution. FAB and ESI MS were determined using ZAB-HF-3F or Finnigan LCQ Advantage mass spectrometer. MALDI mass spectra and high resolution mass spectra were obtained by Matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS) using an IonSpec 4.7 Tesla Fourier Transform Mass Spectrometer, with 2,5-dihydroxybenzoic acid (DHB) being the matrix. IR spectra were recorded using an Avatar 360 FT-IR spectrophotometer. UV absorption spectra were recorded using a Perkin Elmer Lambda 35 UV/VIS spectrophotometer. All compounds were purified by performing flash chromatography on silica gel (200-300 mesh).

^{19}F-NMR investigation: All room temperature ^{19}F NMR spectra were recorded on a Varian Inova 600 spectrometer (^{19}F Larmor frequency of 564.6 MHz). The concentration of the product in NMR solvent is about 6mg/mL. Moreover, all the ^{19}F temperature-dependent NMR experiments were recorded on a two frequency channels BRUKER Avance NMR spectrometer (9.4 T magnet) operating at a ^{19}F Larmor frequency of 376 MHz, by using a homemade modified BRUKER Broad Band NMR probe head. All the NMR spectra recorded in the temperature range between -45°C and +54 °C were performed in $CDCl_3$, whereas higher working temperatures (higher than +54°C) were achieved by solubilizing the samples in toluene. The ^{19}F NMR chemical shifts were referenced with respect to $CFCl_3$, and were externally calibrated using an aqueous solution of KF (^{19}F NMR signal

set to -125.3 ppm).

CCDC crystal structure search: The survey was restricted to the contacts between F and divalent S and the diagram was created by ConQuest v.1.13 using Vista v.2.1. All searches were confined to error-free structures. Criteria: distances < 3.27Å = sum of van der Waals radii of F and S; Crystallographic R factor ≤ 0.05, not disordered, no ions, no powder, only organics; inter- and intramolecular contacts were included in the statistics. The survey was restricted to the contacts between F and divalent S. For the survey on intramolecular interaction, only contacts with minimal 3 bonds between F and S were included to avoid counting cases in which the F and S atoms are close together for topological reasons. With these geometric constrains, the CCDC survey were made to determine the frequency with F…S contacts occur. Therefore totally 500 structures were found in such case which contain 406 examples for intramolecular F…S interaction and 94 examples for intermolecular interactions.

Method for *ab* initio molecular orbital (MO) and density functional theory calculations (DFT) calculations: All computational calculations were carried out by using Gaussian 09[2] installed on the MOSE21 cluster at the MOSE-Lab of University of Trieste. The minimum energy conformers of compounds **6** and **9** were identified by changing the dihedral angle along the Ph-CH-S and Ph-CH-CH_2 bonds, respectively, with an interval of 10º at the HF/3-21G(d,p) level. The obtained conformers were then fully optimized at the B3LYP/6-31G(d,p) level.[3,4] To confirm the results obtained at this level, dispersion corrected density functional theory B97D (DFT-D) calculations were also carried out. The density functional used is of the following form:

$$E_{XC} = (1 - a_0)E_X^{LSDA} + a_0 E_X^{HF} + a_X E_X^{B88} + a_C E_{XC}^{LYP} + (1 - a_C)E_C^{vWN} \quad \text{(SI1)}$$

where the energy terms are the Slater exchange, the Hartree-Fock exchange, Becke exchange functional correction, the gradient corrected correlation functional of Lee, Yang, Parr and the local correlation functional of Vosco, Wilk and Nusair.[5] In DFT-D calculations the total dispersion energy is computed as a sum of all possible pair wise atomic contributions and then added to the usual DFT energy. In other words,

$$E_{DFT-D} = E_{KS-DFT} + E_{disp} \qquad \text{(SI2)}$$

where $E_{KS\text{-}DFT}$ is the self-consistent Kohn–Sham energy as obtained from the chosen DF and E_{disp} is an empirical dispersion correction given by:

$$E_{disp} = -S_6 \sum_{i=1}^{N_{at}-1} \sum_{j=i+1}^{N_{at}} \frac{C_6^{ij}}{R_{ij}^{-6}} f_{damp}(R_{ij}) \qquad \text{(SI3)}$$

In Eq. (SI3), N_{at} is the number of atoms in the system, C_6^{ij} denotes the dispersion coefficient for atom pair ij, S_6 is a global scaling factor that only depends on the DF form used, and R_{ij} is an interatomic distance. In order to avoid near-singularities for small R, a damping function f_{damp} must be used, which is given by:

$$f_{damp}(R_{ij}) = \frac{1}{1+e^{-d\left(R_{ij}/R_r-1\right)}} \qquad \text{(SI4)}$$

The constant d in Eq. (SI4) is another scaling parameter, optimized with respect to f_{damp},while R_r is the sum of the atomic van der Waals radii. The C_6^{ij} coefficients in Eq. (SI3) are calculated as the geometric means of the respective atomic values ($C_6^{ij} = \sqrt{C_6^i C_6^j}$). In the present paper, the values of

the van der Waals radii and of the C_6 coefficients employed were taken from the recent work of Grimme.[6]

The contributions of the dispersion term to the DFT energy, gradient and hessian are implemented in the Gaussian suite of programs for quantum chemistry.[2] To account for the dispersion term at the B3LYP level, refined values of the energies for the obtained conformers were also estimated using the M06-2X density functional with 6-311++G** basis set, which is known to be best suited for systems with non-covalent interactions.[7]

The potential energy scans (PES) performed with both theoretical methods yielded three lowest energy structures for both compound **6** and **9**. The molecular geometries at the energy minimum points were then fully optimized without any constraints. The stationary points for the most stable conformers of **6** and **9** were confirmed by the frequency analysis minima with all real frequencies and with no imaginary frequency, implying no transition state. The absence of imaginary frequencies in each of the resulting conformations was used to confirm that both of them correspond to true minima on the potential energy surface.

NBO deletion analysis[8] was performed using the NBO program[9] as link 607 in Gaussian 09 with standard parameters at the HF/6-31G(d,p) level.

Method for MD simulations: The SCD-SA procedure adopted here[10] consists of the following, sequential steps:

1) take the lowest energy conformer (i.e., the current global minimum as predicted from DFT calculations);

2) rotate the critical torsion angle by a predefined step and then constrain the torsion angle at this value;

3) heat the structure slowly from 10 to 50K in 1 ns MD steps, run 1 ns MD trajectory at 50 K, cool the structure back to 10 K in 2 ns MD steps, and then minimize the energy of the structure and store its value;

4) repeat steps 2) and 3). If the energy profile obtained from the previous steps shows a minimum, then go to step 5, otherwise go to step 2);

5) apply the annealing procedure described in step 3) but without any constraints. Store the structure as a new conformer if not previously stored, and store the highest energy structure on the pathway obtained in steps 2)-3) as the transition barrier of the conformational interconversion;

6) repeat steps 2)-5) for all predefined torsions and in both directions of rotation (clockwise and counterclockwise);

7) if any interesting conformation remains, mark it as current global minimum and continue from step 1). Otherwise, stop the procedure.

The necessity to combined two well-known methods to search the conformational space relies on the fact that the SCD method is a systematic tool that gives a complete picture of the conformational space of small-to-medium-sized molecules, including information about conformational interconversions. However, this method may fail for molecules with high steric hindrance, the reason being that a standard minimization routine is not able to relax the molecule extensively. SA is not a systematic method, but it is able to yield highly relaxed molecular geometries, with a notable tendency to converge to the corresponding global minimum. Therefore, it is not suitable to explore the entire conformational space; further, it gives no information about conformational interconversions. The coupling of the two methods thus yield a systematic tool that for a good description of the entire conformational space of molecules, even in the presence of

steric hindrance and/or large molecular dimensions.

Procedure for the preparation of 1-2:

2: The mixture of 4-azidotetrafluorobenzaldehyde (60.7 mg, 0.28 mmol) and the freshly prepared 12-mercaptododecanoic acid (148.0 mg, 0.64 mmol) was dissolved in CH_2Cl_2 and stirred under argon in an ice bath. Then the boron trifluoride etherate solution (105.0 μL, 0.83 mmol) was added to initiate the reaction. When TLC analysis showed the complete disappearance of 4-azidotetrafluorobenzaldehyde, the saturated $NaHCO_3$ solution was added to neutralize the excess Lewis acid (final pH 7-8). Then the aqueous phase was acidified with 6N HCl to pH l and the product was extracted by CH_2Cl_2. The combined extracts were dried with $MgSO_4$ and filtered, and the solvent was evaporated under reduced pressure. Purification is achieved by column silica gel chromatography with CH_2Cl_2/MeOH 20/1, yielding **2** (129.3 mg, 71.4%) as white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.07 (s, 1H, CH), 2.60-2.67 (m, 4H, CH_2), 2.36 (t, 4H, J = 6.8 Hz, CH_2), 1.60-1.64 (m, 8H, CH_2), 1.28 (m, 28H, CH_2); ^{13}C NMR (150 MHz, $CDCl_3$): δ 180.3, 144.4 (d, 2C, $^1J_{CF}$ = 267.0 Hz), 140.5 (d, 2C, $^1J_{CF}$ = 256.8 Hz), 119.1, 116.3 (d, 1C, $^2J_{CF}$ = 14.6 Hz), 42.2, 39.2, 34.1, 33.5, 29.4, 29.3, 29.2, 29.1, 29.0, 28.9, 28.8, 28.5, 24.7; ^{19}F NMR (564.6 MHz, $CDCl_3$): δ -151.8; IR (cm^{-1}): υ 2120.1 ($-N_3$); UV (CH_2Cl_2): λ_{max} = 268 nm, ε_{mol} = 12124.8 $mol^{-1}cm^{-1}$; MS (ESI) *m/z* 664.1 [M-H]; HRMS: calcd. for $C_{31}H_{47}F_4N_3O_4S_2Na^+$ $[M+Na]^+$ 688.2842. Found 688.2863.

1: The mixture of **2** (33.6 mg, 0.05 mmol) and 1-palmitoyl-*sn*-glycero-3-phosphochline (50 mg, 0.1 mmol) was connected to a high vacuum pump for 5 h in order to remove all traces of moisture. A solution of dicyclohexylcarbodiimide (41.5 mg, 0.21 mmol) and N,N-dimethylaminopyridine (24.5 mg, 0.21 mmol) in 5 mL anhydrous $CHCl_3$ freshly distilled from P_2O_5 was added to the above mixture. The flask was then flushed with argon and protected from the light. The reaction mixture

was stirred at room temperature for 72 h. The white solid in the mixture was removed by filtration and the filtrate was concentrated under reduced pressure. The resulting residue was purified by chromatography on silica gel and eluted with CH_2Cl_2/MeOH 10/1, CH_2Cl_2/MeOH 6/1 and CH_2Cl_2/MeOH/H_2O 65/35/2, yielding white waxy **1** (16.4 mg, 20.0%). ^{1}H NMR (600 MHz, $CDCl_3$ + 2 drops CD_3OD): δ 5.22 (m, 1H, CH), 5.07 (s, 1H, CH), 4.39-4.41 (m, 1H, CH_2), 4.25 (m, 2H, CH_2), 4.12-4.15 (m, 1H, CH_2), 3.98-4.00 (m, 4H, CH_2), 3.67 (m, 2H, CH_2), 3.62 (m, 3H, CH_2), 3.23 (s, 18H, CH_3), 2.63-2.64 (m, 4H, CH_2), 2.28-2.38 (m, 8H, CH_2), 1.95-1.96 (m, 2H, CH_2), 1.73-1.81 (m, 8H, CH_2), 1.58-1.61 (m, 16H, CH_2),1.25-1.36 (m, 66H, CH_2), 0.88 (t, 6H, J = 6.9 Hz, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$ + 2 drops CD_3OD): δ 174.1, 173.7, 144.5 (d, 2C, $^1J_{CF}$ = 257.1 Hz), 140.4 (dd, 2C, $^1J_{CF}$ = 261.2 Hz, $^2J_{CF}$ = 24.0 Hz), 119.3, 116.6, 70.5, 66.6, 63.7, 62.9, 59.3, 54.5, 50.1, 42.5, 35.663, 34.381, 34.235, 33.7, 32.7, 32.1, 31.0, 29.8, 29.7, 29.6, 29.5, 29.3, 29.2, 29.0, 28.7, 26.3, 25.7, 25.6, 25.5, 25.0, 24.9, 24.8, 22.8, 14.2; ^{19}F NMR (564.6 MHz, $CDCl_3$ + 2 drops CD_3OD): δ -152.0; ^{31}P NMR (242.9 MHz, $CDCl_3$ + 2 drops CD_3OD): δ 0.24; IR (cm^{-1}): υ 2120.1 ($-N_3$); UV (CH_2Cl_2): λ_{max} = 268 nm, ε_{mol} = 21337.5 $mol^{-1}cm^{-1}$; MS (ESI) *m/z* 1654.9 [M+MeOH].

Procedure for the preparation of 3-7: The mixture of 4-azidotetrafluorobenzaldehyde and the corresponding alcohol (or thiol) was dissolved in CH_2Cl_2 and stirred under argon in an ice bath. Then the boron trifluoride etherate solution was added to initiate the reaction. When the TLC analysis showed the complete disappearance of 4-azidotetrafluorobenzaldehyde, the saturated $NaHCO_3$ solution was added to neutralize the excess Lewis acid (final pH 7-8). The product was extracted by ethyl ether. The combined extracts were dried with $MgSO_4$ and filtered, and the solvent was evaporated under reduced pressure. Purification is achieved by column silica gel chromatography yielding the corresponding acetal or thioacetal.

3: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.07 (s, 1H, CH), 2.60-2.66 (m, 4H, CH_2), 1.60-1.67 (m, 4H, CH_2), 0.99 (t, 6H, J = 7.4 Hz, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 143.3 (d, 2C, $^{1}J_{CF}$ = 254.6 Hz), 139.5 (dd, 2C, $^{1}J_{CF}$ = 258.5 Hz, $^{2}J_{CF}$ = 15.5 Hz), 118.1, 115.4 (t, 1C, $^{2}J_{CF}$ = 15.4 Hz), 41.2, 34.5, 21.5, 12.4; ^{19}F NMR (564.6 MHz, $CDCl_3$): δ -135.3 (br), -151.9; IR (cm^{-1}): υ 2119.8 ($-N_3$); UV (CH_2Cl_2): λ_{max} = 266 nm, ε_{mol} = 10754.7 $mol^{-1}cm^{-1}$; MS (FAB) *m/z* 352 [M-H]; HRMS: calcd. for $C_{13}H_{19}F_4N_4S_2^+$ $[M+NH_4]^+$ 371.0987. Found 371.0986.

4: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.68 (s, 1H, CH), 3.61-3.69 (m, 2H, CH_2), 3.41-3.49 (m, 2H, CH_2), 1.58-1.67 (m, 4H, CH_2), 0.92 (t, 6H, J = 7.4 Hz, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 143.7 (d, 2C, $^{1}J_{CF}$ = 250.2 Hz), 139.4 (d, 2C, $^{1}J_{CF}$ = 266.7 Hz), 118.9, 112.5, 95.8, 68.7, 21.8, 9.5; ^{19}F NMR (564.6 MHz, $CDCl_3$): δ -143.2 (dd, 2F, J = 21.2, 10.4 Hz), -152.4 (dd, 2F, J = 20.9, 9.6 Hz); IR (cm^{-1}): υ 2124.4 ($-N_3$); MS (FAB) *m/z* 320 [M-H]; HRMS: calcd. for $C_{13}H_{19}F_4N_4O_2^+$ $[M+NH_4]^+$ 339.1439. Found 339.1436.

5: ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.97-7.04 (m, 2H, ArH), 6.67-6.75 (m, 1H, ArH), 4.79 (s, 1H, CH), 2.44-2.64 (m, 4H, CH_2), 1.52-1.66 (m, 4H, CH_2), 0.97 (t, 6H, J = 7.3 Hz, CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 162.9 (dd, 2C, $^{1}J_{CF}$ = 247.4 Hz, $^{3}J_{CF}$ = 12.7 Hz), 144.9 (t, 1C, $^{3}J_{CF}$ = 8.7 Hz), 110.7 (d, 2C, $^{2}J_{CF}$ = 25.6 Hz), 103.2 (t, 1C, $^{2}J_{CF}$ = 25,3 Hz), 52.4, 34.4, 22.5, 13.5; ^{19}F NMR (235.2 MHz, $CDCl_3$): δ -109.3; HRMS: calcd. for $C_{13}H_{22}F_2NS_2^+$ $[M+NH_4]^+$ 294.1156. Found 294.1156.

6: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18-7.23 (m, 1H, ArH), 6.89 (dd, 2H, $^{3}J_{HF}$ = 8.7 Hz, $^{3}J_{HH}$ = 8.7 Hz, ArH), 5.16 (s, 1H, CH), 2.62 (t, 4H, J = 7.1 Hz, CH_2), 1.55-1.69 (m, 4H, CH_2), 0.97 (t, 6H, J = 6.9 Hz, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 160.6 (m, 2C, $^{1}J_{CF}$ = 233.9 Hz,), 129.2 (dd, 1C, $^{3}J_{CF}$ = 9.9 Hz), 118.3 (dd, 1C, $^{2}J_{CF}$ = 16.4 Hz), 111.9 (br s), 42.4, 35.7, 22.8, 13.7; ^{19}F NMR (564.6 MHz, $CDCl_3$): δ -103.5 (br s), -112.0 (br s); MS (FAB) *m/z* 276 [M]; HRMS: calcd. for $C_{13}H_{18}F_2S_2^+$ $[M]^+$

276.0818. Found 276.0817.

7: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20-7.30 (m, 1H, ArH), 6.90 (dd, 2H, $^{3}J_{HF}$ = 8.7 Hz, $^{3}J_{HH}$ = 8.1 Hz, ArH), 5.63 (t, 1H, J = 2.3 Hz, CH), 3.08-3.16 (m, 2H, CH_2), 2.90-2.97 (m, 2H, CH_2), 2.16-2.21 (m, 1H, CH_2), 1.95-2.09 (m, 1H, CH_2); ^{13}C NMR (150 MHz, $CDCl_3$): δ 161.1 (d, 2C, $^{1}J_{CF}$ = 249.9 Hz), 130.2 (t, 1C, $^{3}J_{CF}$ = 10.2 Hz), 115.2, 112.2 (d, 2C, $^{2}J_{CF}$ = 22.7 Hz), 41.3, 32.8, 25.4; ^{19}F NMR (564.6 MHz, $CDCl_3$): δ -111.4; MS (FAB) *m/z* 232 [M]; HRMS: calcd. for $C_{10}H_{10}F_2S_2^+$ $[M]^+$ 232.0192. Found 232.0198.

Procedure for the preparation of 8: n-butyl lithium (690.0 μL, 1.1 mmol) was dissolved in 8 mL freshly distilled THF and cooled to 0 °C. Then the propanethiol (87.4 μL, 0.97 mmol) was added at 0 °C. The mixture was stirred at room temperature for 20 minutes and the 2,6-difluorobenzyl bromide (190.0 mg, 0.92 mmol) was added. When the TLC analysis showed the complete consumption of 2,6-difluorobenzyl bromide, 6 mL H_2O was added to quench the reaction. Then the THF was removed under reduced pressure and the residue was extracted twice by ethyl ether. The combined extracts were dried with $MgSO_4$ and filtered, and the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel with petroleum ether / ethyl acetate (40/1), yielding **8** (148.3 mg, 80%) in the form of colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.14-7.21 (m, 1H, ArH), 6.88 (dd, 2H, $^{3}J_{HF}$ = 8.1 Hz, $^{3}J_{HH}$ = 7.2 Hz, ArH), 3.75 (s, 2H, CH_2), 2.50 (t, 2H, J = 7.4 Hz, CH_2), 1.56-1.69 (m, 2H, CH_2), 0.97 (t, 3H, J = 7.4 Hz, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 160.6 (dd, 2C, $^{1}J_{CF}$ = 246.9 Hz, $^{3}J_{CF}$ = 7.7 Hz), 128.6 (t, 1C, $^{3}J_{CF}$ = 10.4 Hz), 115.9, 111.5 (d, 2C, $^{2}J_{CF}$ = 25.2 Hz), 34.2, 22.9, 22.8, 13.7; ^{19}F NMR (564.6 MHz, $CDCl_3$): δ -115.6; MS (FAB) *m/z* 201 [M-H]; HRMS: calcd. for $C_{10}H_{13}F_2S^+$ $[M+H]^+$ 203.0701. Found 203.0700.

Procedure for the preparation of 9: The n-butyl-magnesium bromide was prepared by activated magnesium chips (171 mg, 7.0 mmol) and 1-bromobutane (535.5 μL, 4.2 mmol). 2,6-difluorobenzaldehyde (200.0 mg, 1.41 mmol) was dissolved in 2 mL freshly distilled THF and cooled to 0 ºC. Then the n-butyl-magnesium bromide was added at 0 ºC and the mixture was stirred under Ar until the TLC analysis indicated the complete consumption of 2,6-difluorobenzaldehyde. The reaction mixture was cooled to 0 ºC again and 6 mL saturated NH_4Cl solution was added slowly. The organic layer was separated and the water layer was extracted by the ether twice. The combined organic layers were washed by saturated NaCl solution for 2-3 times and dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel with petroleum ether / ethyl acetate (30/1 – 20/1), yielding **9-1** (145.7 mg, 51.9%) in the form of colorless oil. Then the oxalyl chloride (253.6 mg, 2.0 mmol) was dissolved in 3 mL freshly distilled CH_2Cl_2 and cooled to -80 ºC. Then DMSO (212.0 μL, 3.0 mmol) in 3 mL CH_2Cl_2 was added to the solution of the oxalyl chloride in 5 minutes. The reaction mixture was stirred at -80 ºC for 10 minutes. Then **9-1** (80.0 mg, 0.4 mmol) in 3 mL CH_2Cl_2 was added to the above mixture at -80 ºC and the mixture was stirred for 20 minutes. Then the triethylamine (550.0 μL, 4.0 mmol) was added. After being stirred for 30 minutes at -80 ºC, the reaction mixture was stirred at room temperature until the TLC analysis indicated the complete consumption of **9-1**. The 8 mL H_2O was then added and the mixture was stirred for additional 10 minutes. The organic layer was separated and the water layer was extracted by the CH_2Cl_2 twice. The combined organic layers were dried over $MgSO_4$, filtrated and the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel with petroleum ether / ethyl acetate (40/1 – 30/1), yielding **9-2** (69.8 mg, 88.2%) as colorless oil. Then **9-2** (60.0 mg,

0.32 mmol) was dissolved in 3 mL freshly distilled THF and cooled to 0 ºC. The n-butyl lithium (620.0 μL, 0.98 mmol) in 3 mL was added slowly to the solution of **9-2**. The reaction mixture was stirred at 0 ºC for 10 minutes and then the reaction continued at 25 ºC until the TLC analysis indicated the complete consumption of **9-2**. Then 3 mL NH_4Cl and 2 mL H_2O were added to the reaction system. After separating the organic layers, the water layer was extracted by ether twice. The combined organic layers were dried over $MgSO_4$, filtrated and the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel with petroleum ether / ethyl acetate (40/1), yielding **9-3** (33.8 mg, 43.6%) as colorless oil. $NaBH_4$ (17.8 mg, 0.46 mmol) was dissolved in 0.5 mL CF_3COOH and stirred at room temperature for 30 minutes. Then **9-3** (20.0 mg，0.08 mmol) in 2.5 mL CH_2Cl_2 was added to the above solution and the reaction mixture was stirred at room temperature until the TLC analysis indicated the complete consumption of **9-3**. Then the reaction was quenched by the saturated Na_2CO_3 solution (final pH 8-9). The product was extracted by ether for three times. The combined extracts were dried over $MgSO_4$, filtrated and the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel with petroleum ether, yielding the alkene precursor of **9** (14.7 mg) as colorless oil which were the mixture of two alkene cistransisomer. The alkene precursors were dissolved in 3 mL MeOH and the reaction solution was stirred under H_2 in the presence of Pd/C. When the TLC analysis indicated the completed consumption of the alkene precursor, the Pd/C was filtrated and the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel with petroleum ether, yielding **9** (9.0 mg, 48.4%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.06-7.13 (m, 1H, ArH), 6.81 (dd, 2H, $^3J_{HF}$ = 9.0 Hz, $^3J_{HH}$ = 8.7 Hz, ArH), 3.01-3.07 (m, 1H, -C*H*-), 1.59-1.81 (m, 4H, CH_2), 1.02-1.37 (m, 8H, CH_2), 0.83 (t, 6H, *J* =

7.4 Hz, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 162.2 (dd, 2C, $^1J_{CF}$ = 244.7 Hz, $^3J_{CF}$ = 9.0 Hz), 127.3, 121.0, 118.3 (d, 2C, $^2J_{CF}$ = 23.4 Hz), 35.8, 34.1, 30.5, 22.8, 14.2; ^{19}F NMR (564.6 MHz, $CDCl_3$): δ -113.8; MS (ESI) *m/z* 240 [M]; HRMS: calcd. for $C_{15}H_{22}F_2^+$ $[M]^+$ 240.1690. Found 240.1694.

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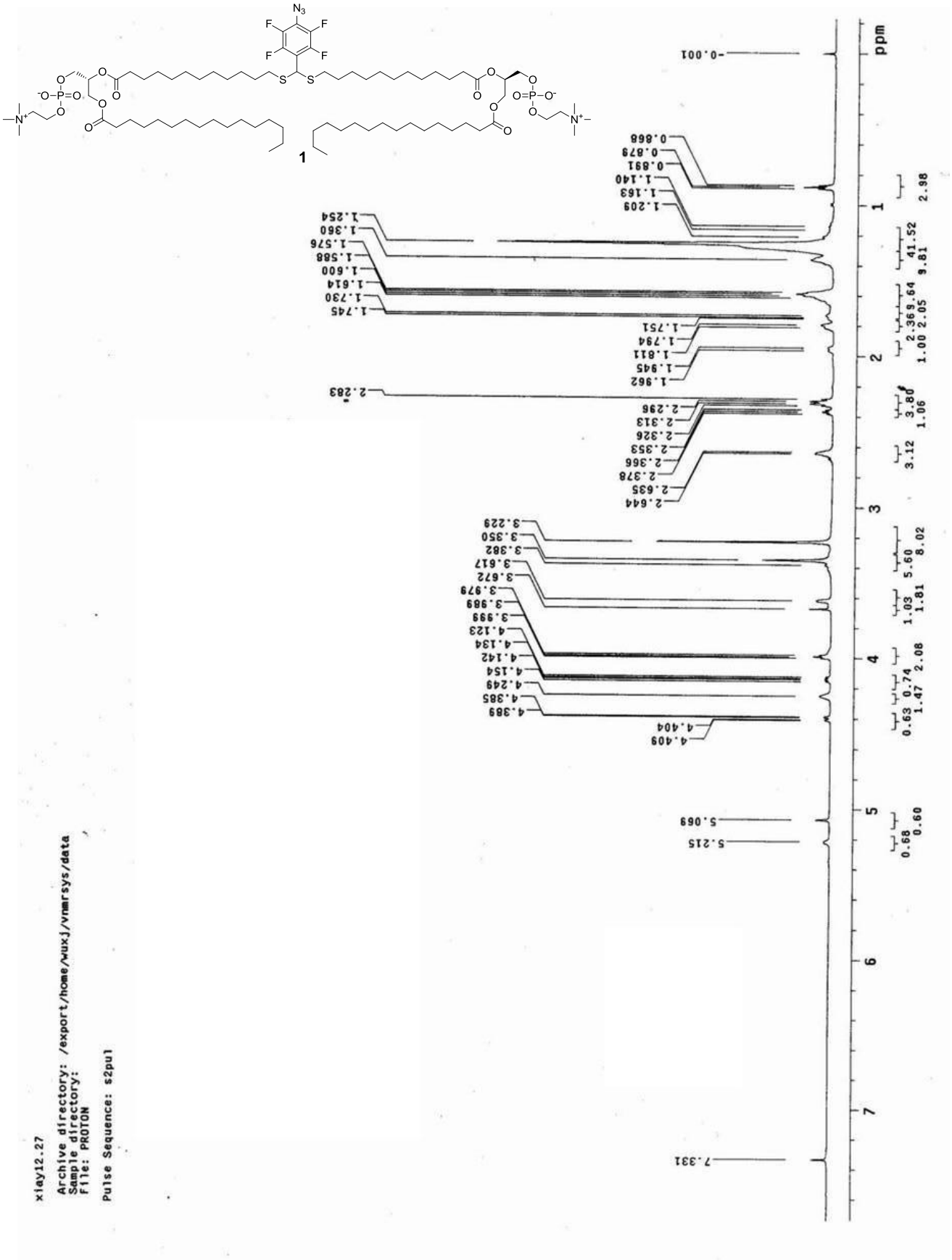
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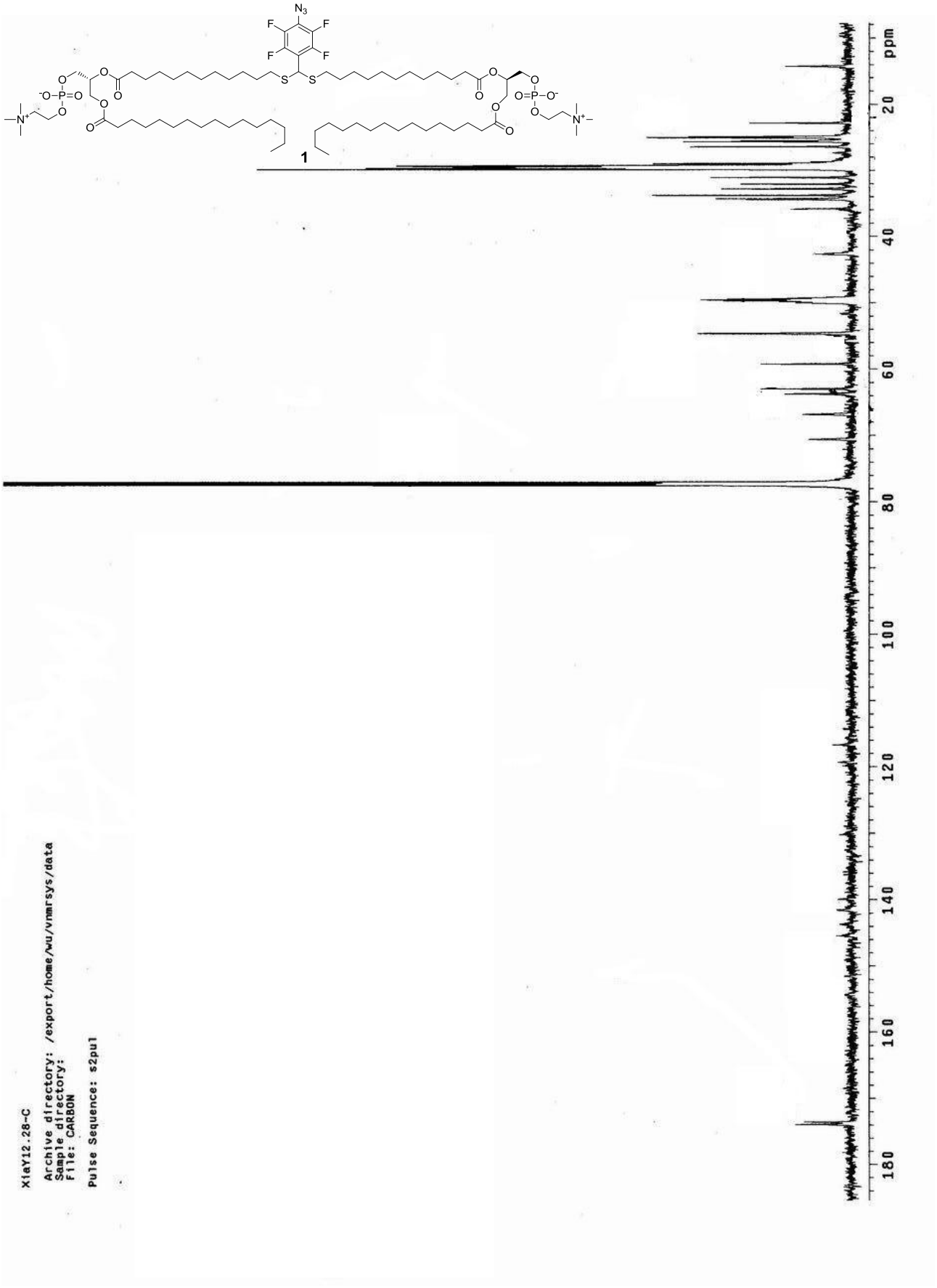
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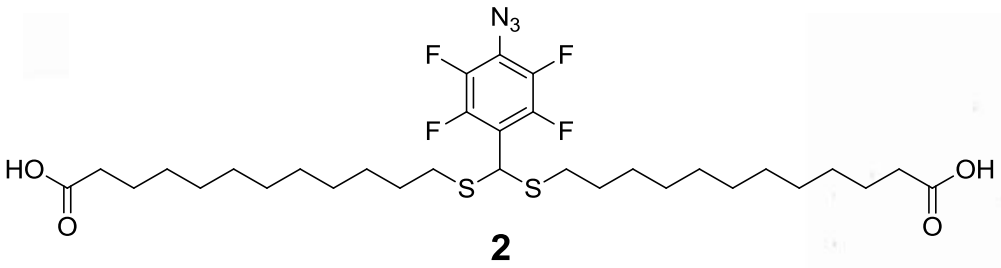

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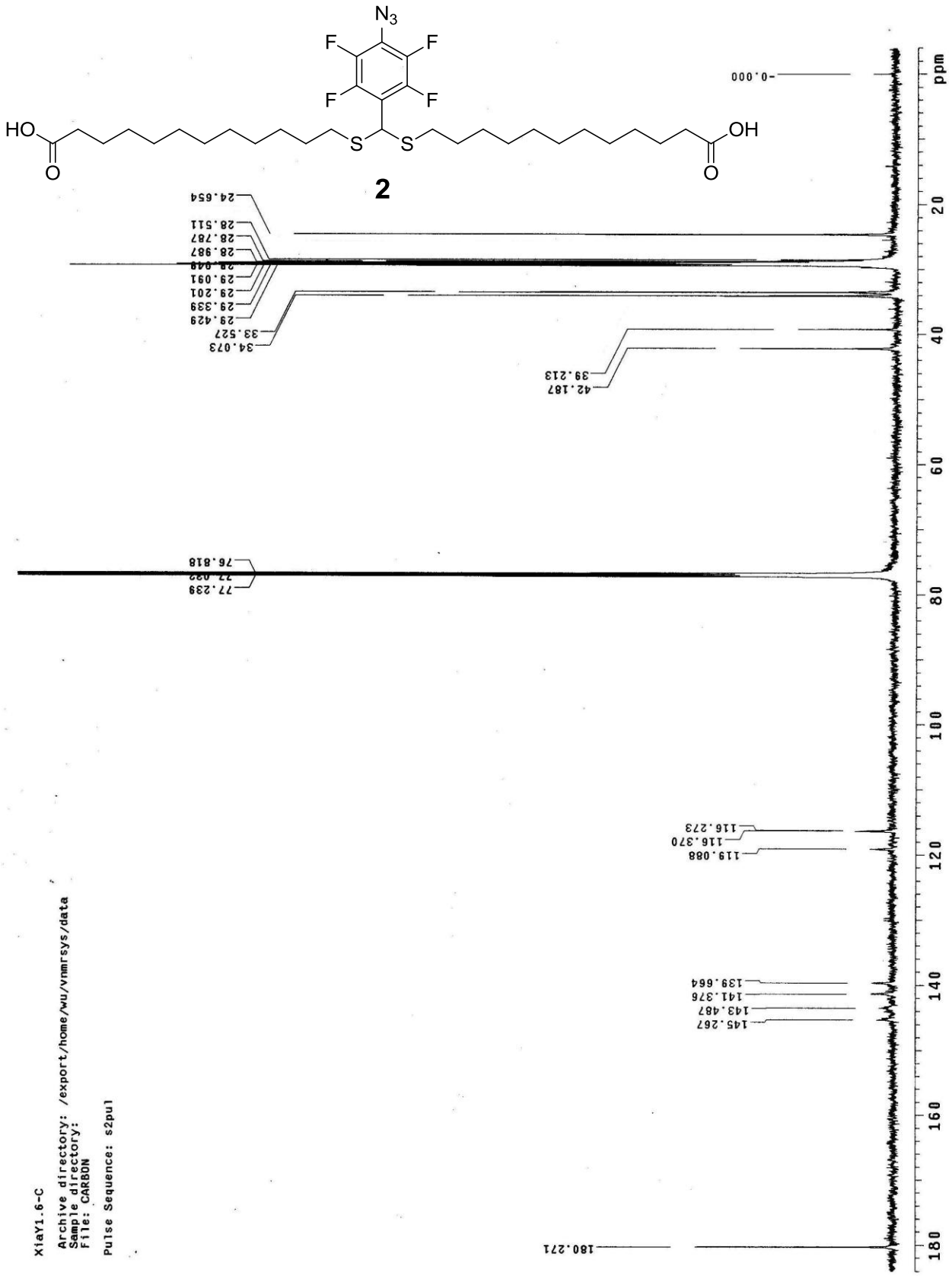

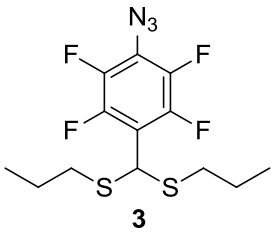
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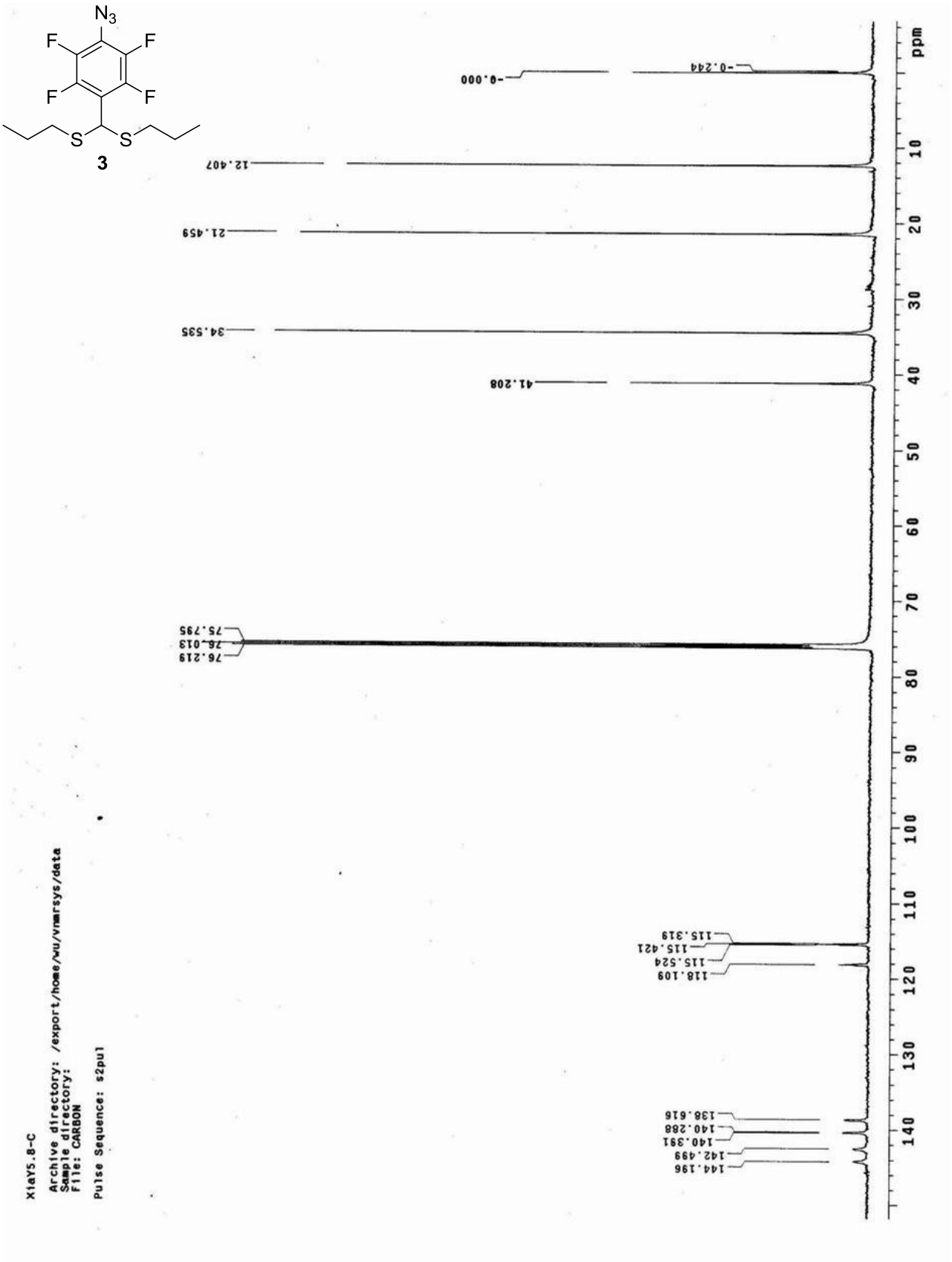
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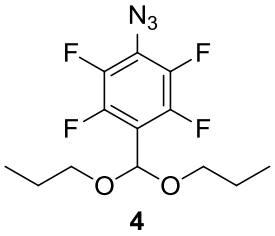
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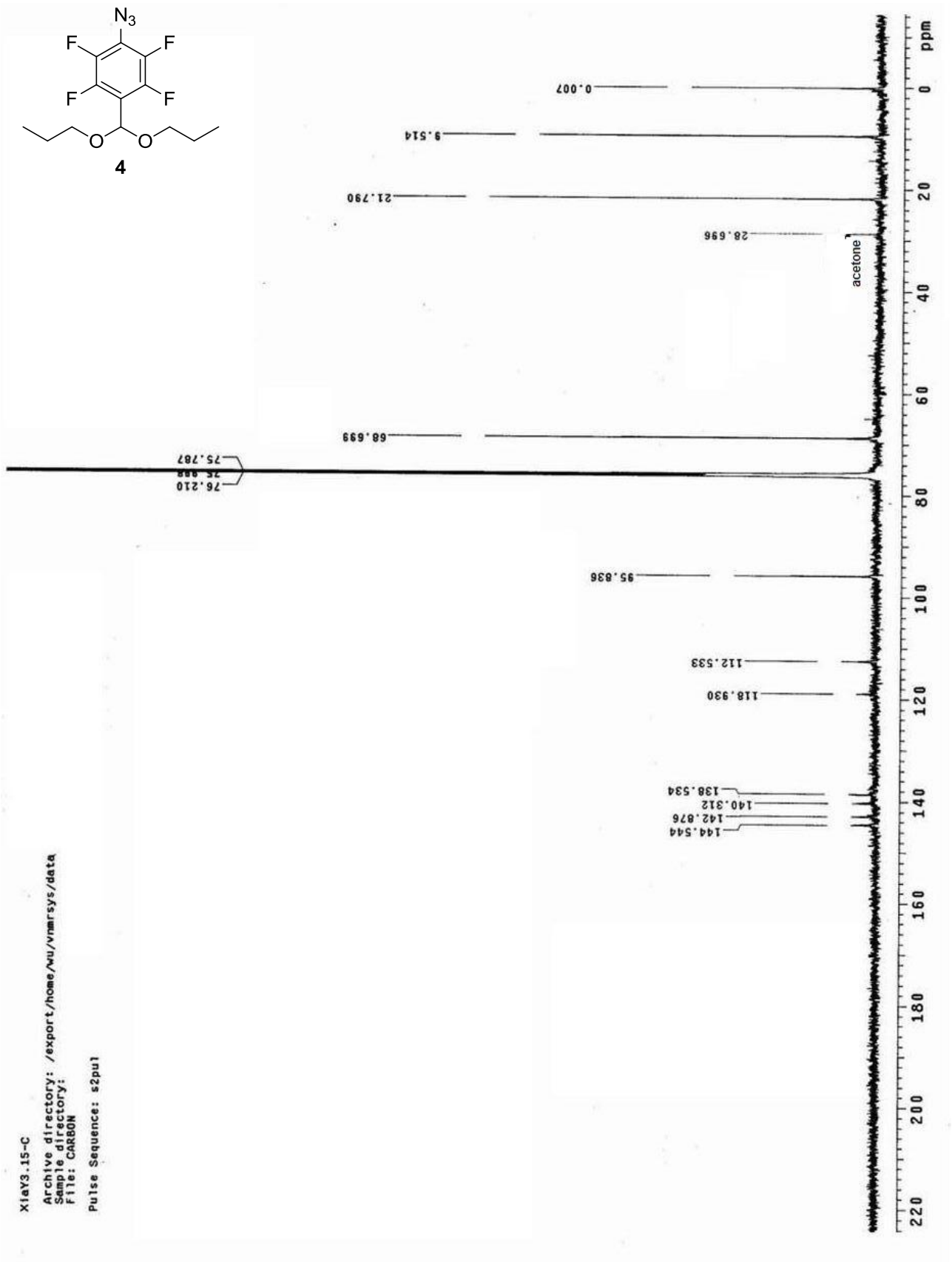
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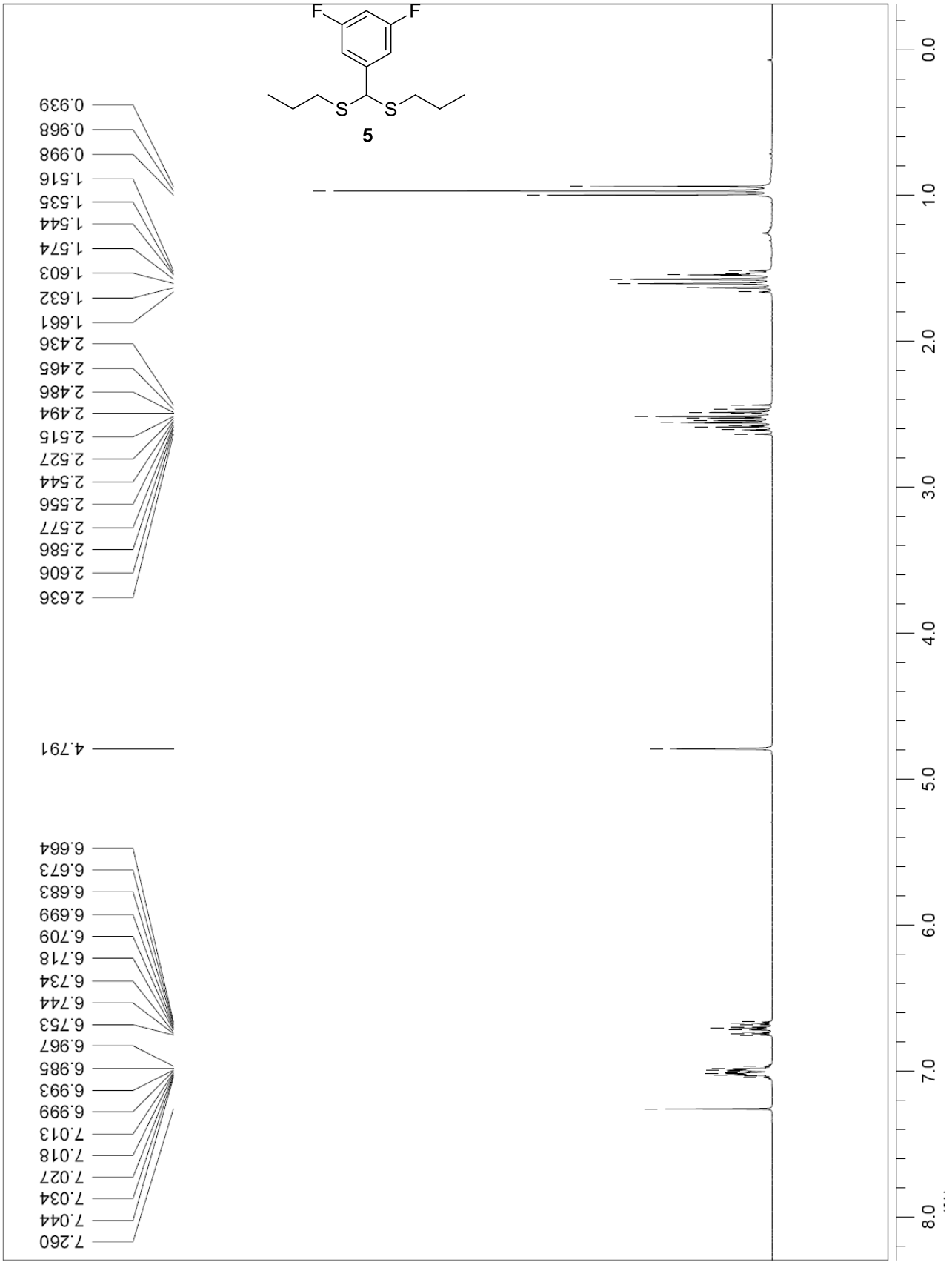
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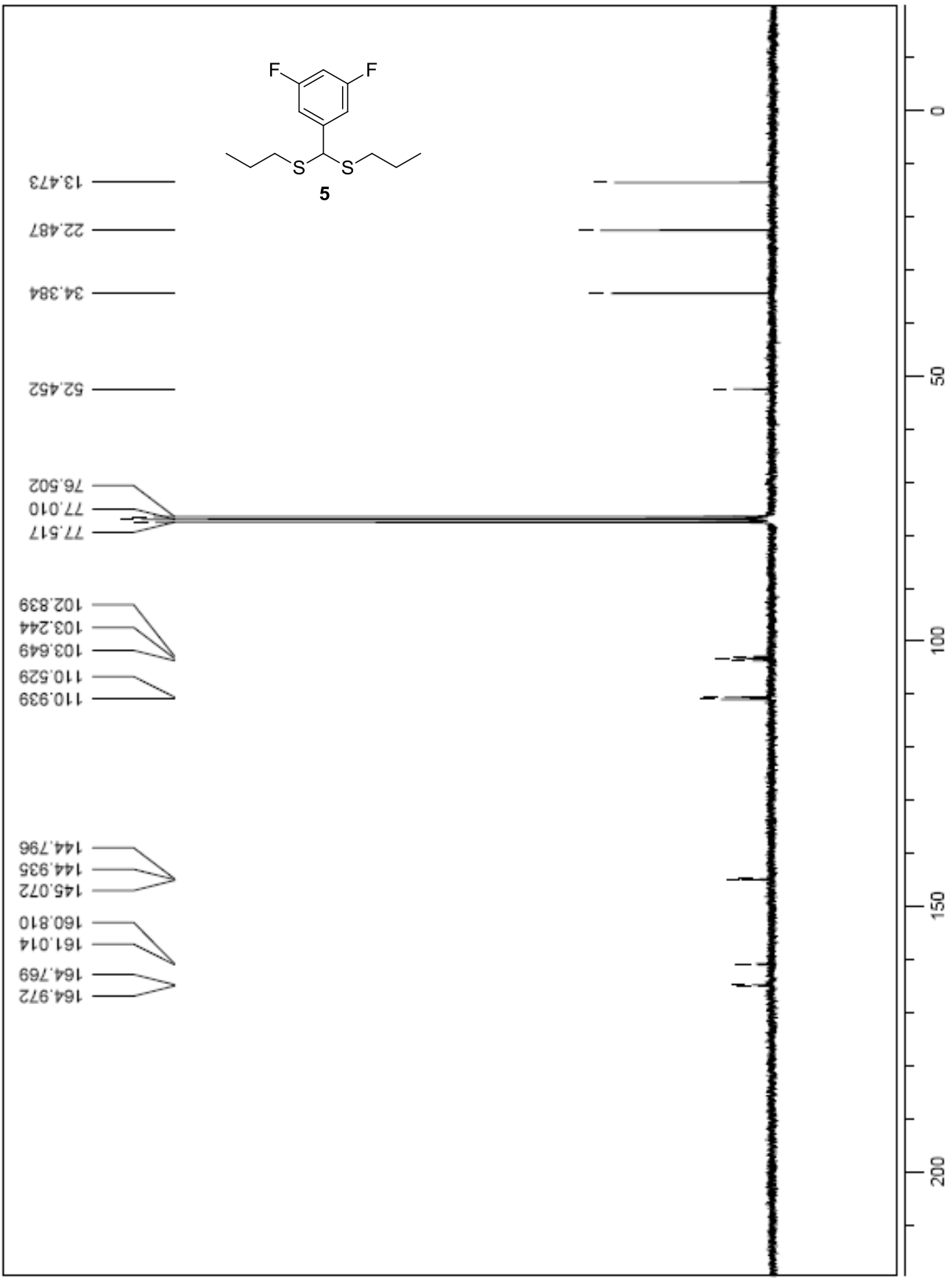

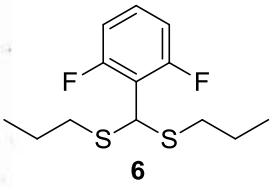
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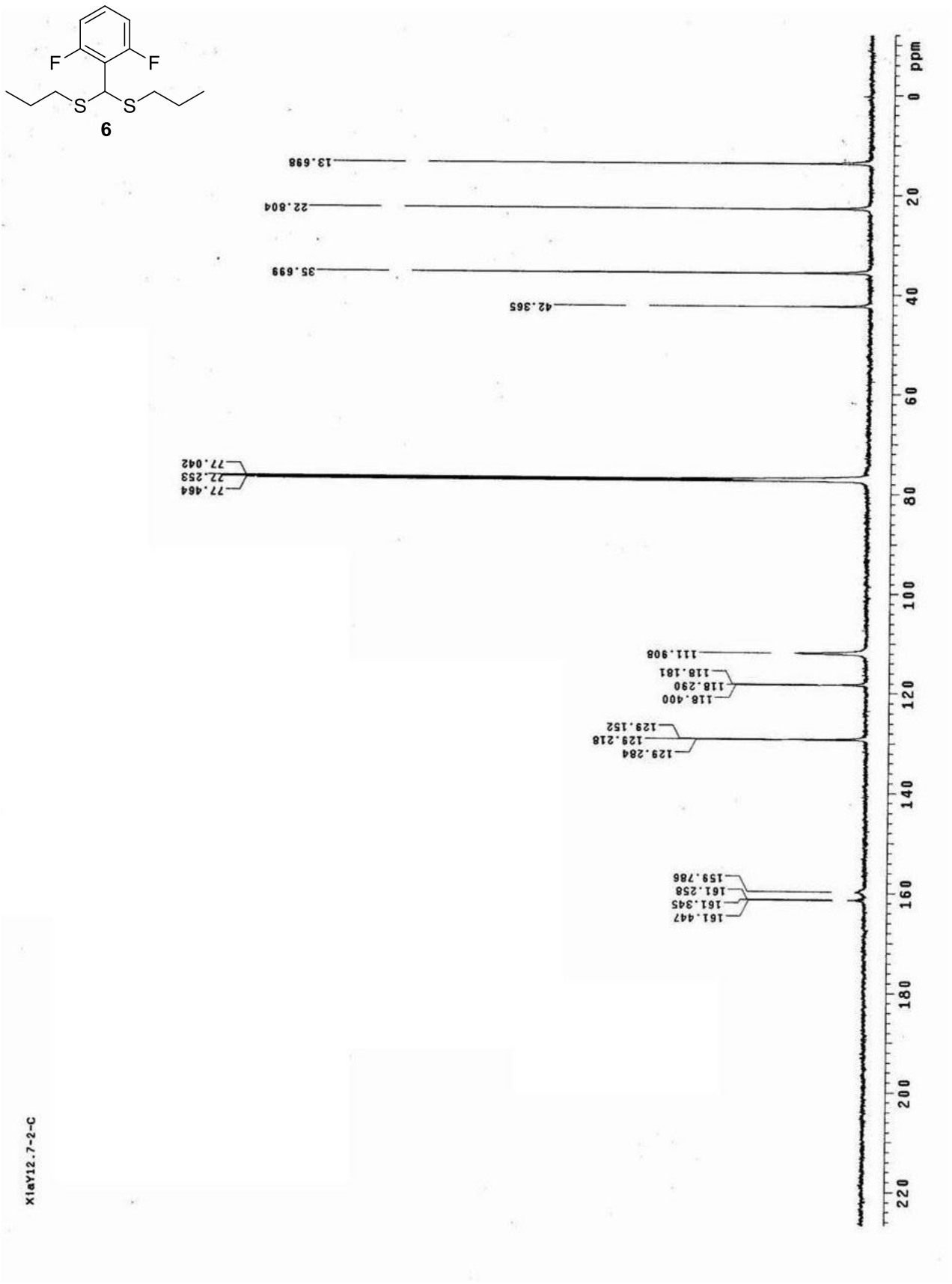

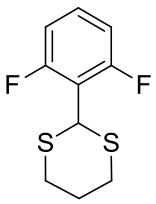
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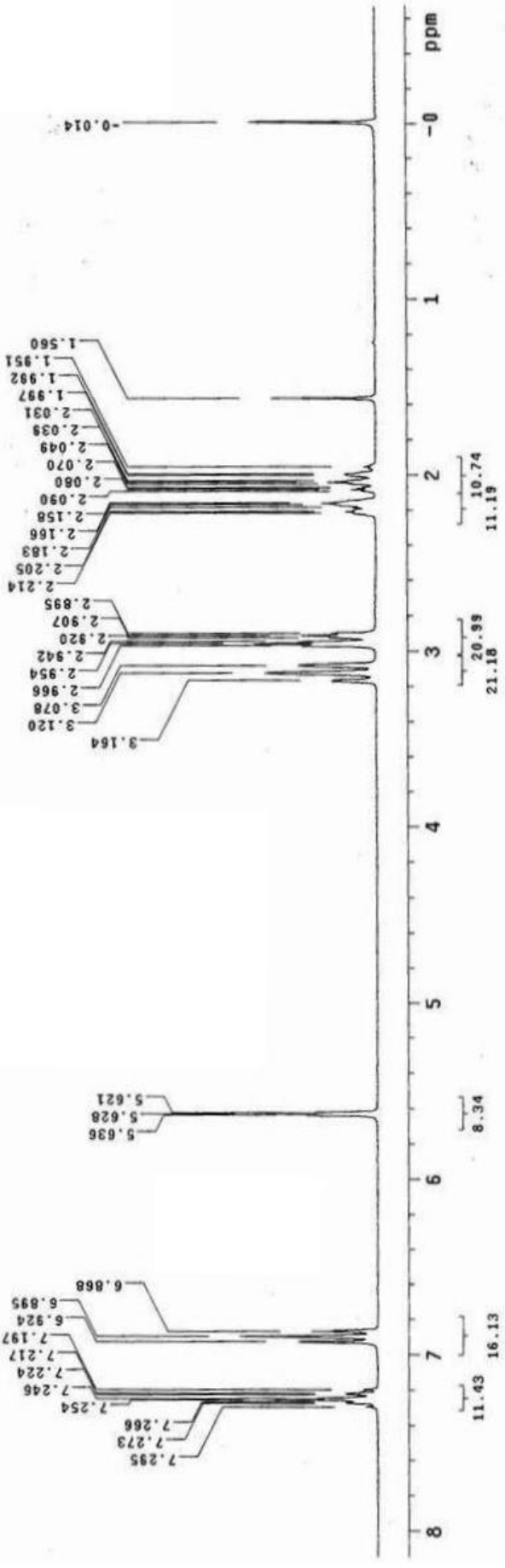
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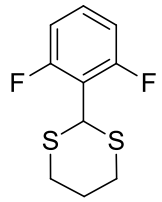
F
F
S
S

7

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32.798
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77.268
77.478
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112.315
115.272
130.154
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160.296
161.962
ppm
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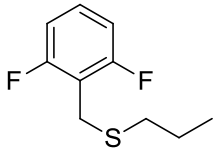
40
60
80
100
120
140
160
ZhuRZ12.12-C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F
S

8

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1.613
1.637
1.662
1.686
2.472
2.496
2.521
3.751
6.855
6.882
6.906
7.145
7.165
7.191
7.213
7.260
ppm
0
1
2
3
4
5
6
7
8
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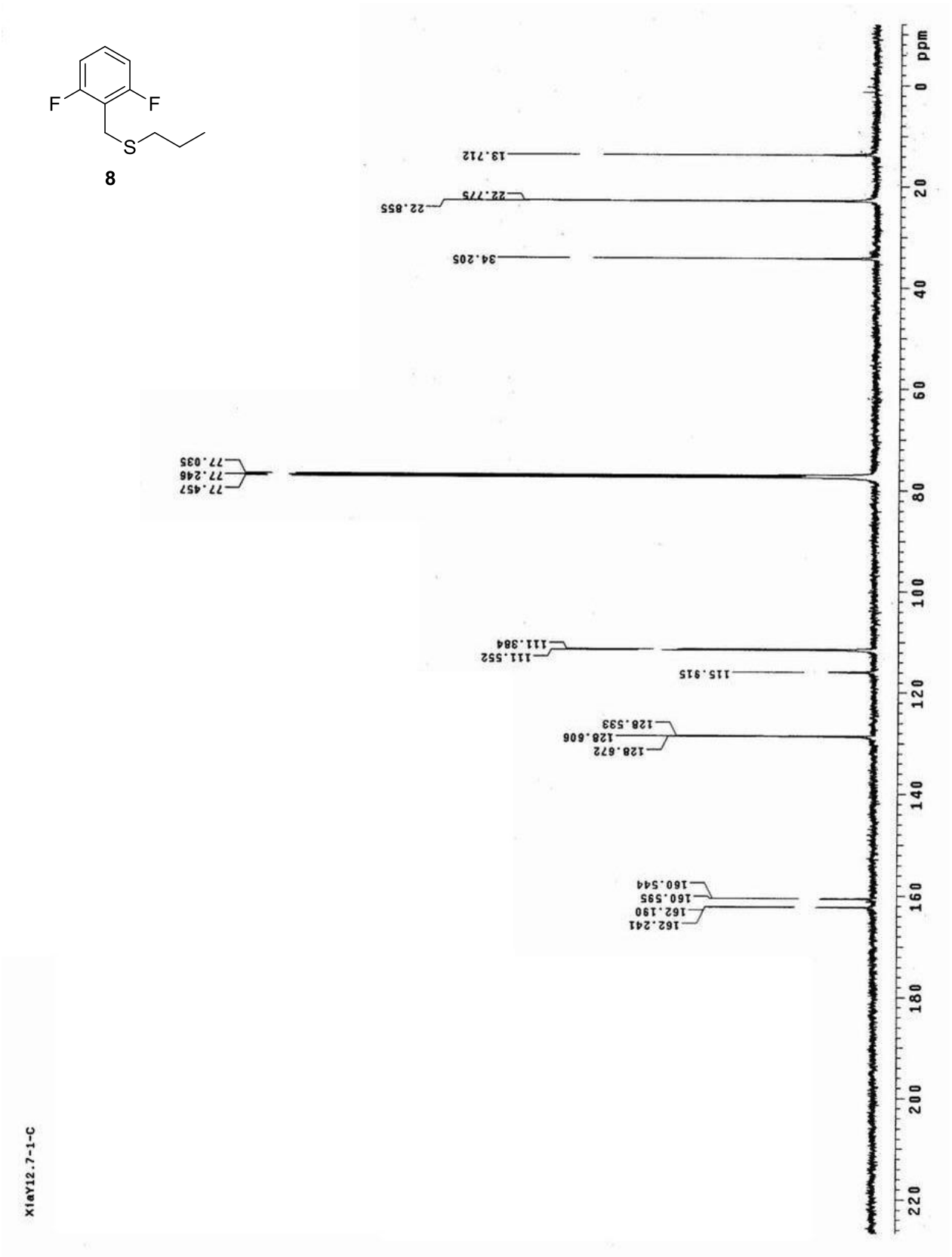
18.09
17.08
17.52
14.22
7.28
xiayi2.7-1


F
F
S
8
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22.855
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77.457
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111.552
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128.606
128.672
160.544
160.595
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40
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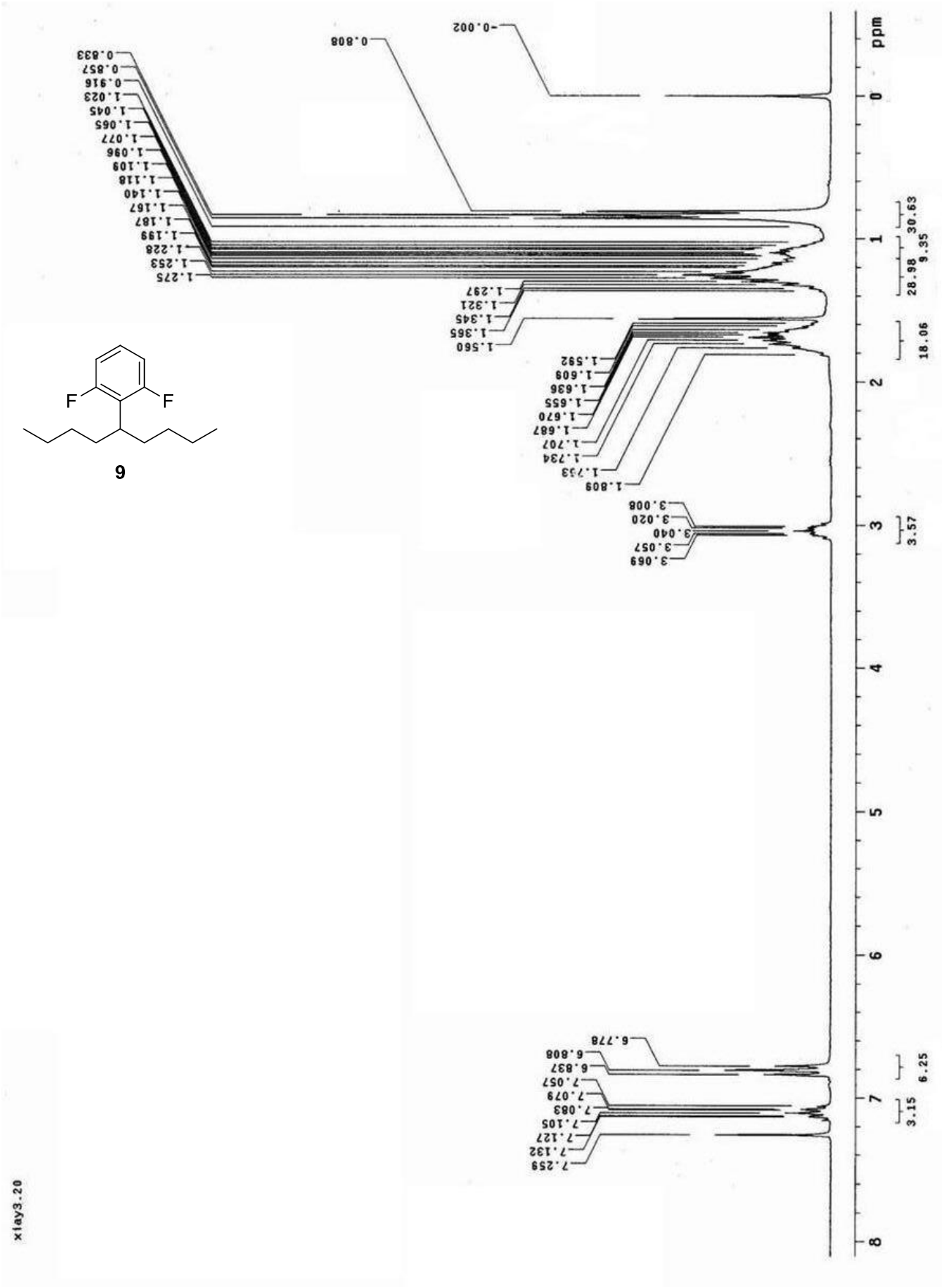
160
180
200
220
X1aY12.7-1-C


F
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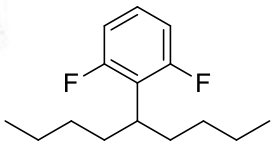
ppm
xlay3.20


F
F

9

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77.427
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127.256
161.329
161.392
162.963
163.020
ppm
20
40
60
80
100
120
140
160
X1aY3.26-C