Oxygen-to-Oxygen Silyl Migration of Alpha-Siloxy Sulfoxides and Oxidation-triggered Allicin Formation

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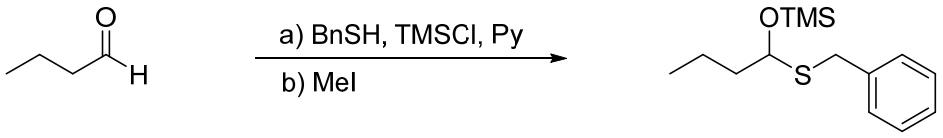
Materials and Methods. All commercially obtained reagents were used as received unless otherwise stated. All reactions were performed at room temperature (approximately 21°C) unless stated otherwise. All flash chromatography was performed using 230-400 mesh silica gel. All ^{1}H NMR spectra were obtained from Varian (600 MHz and 400 MHz) or Bruker (600 MHz and 400 MHz) spectrometers. All ^{1}H NMR spectra are reported relative to the residual solvent signal (δ 7.26 for $CDCl_3$). All ^{13}C NMR spectra were obtained from Varian (151 MHz and 101 MHz) or Bruker (151 MHz and 101 MHz) spectrometers. All ^{13}C NMR spectra are reported relative to the residual solvent signal (δ 77.16 for $CDCl_3$) High resolution mass spectra were obtained using an Agilent 6530 (Q-TOF) LC-MS in $^{+}$ESI mode. EI spectra were obtained using an Agilent 5977A GC-MS. Low resolution ESI (+/-) mass spectra were obtained using either Thermo LXQ linear ion trap LC-MS or Thermo LCQ Deca XP Max LC-MS. HPLC was performed using an Agilent 1260 Infinite LC system with diode array detector (λ = 254 nm and 214 nm).

Experimental Procedures:

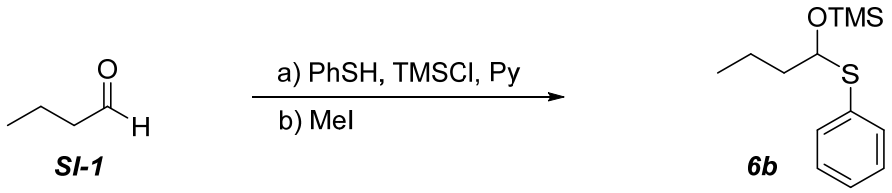
1. General Procedure 1 for Synthesis of alpha-siloxysulfides



SI-1 ***6a***

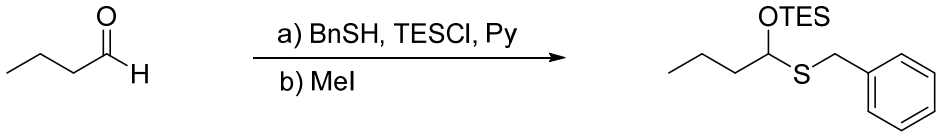
Compound **6a**. A 10 mL flame-dried round-bottom flask was charged with dry pyridine (4.0 mL), followed by addition of butyraldehyde (9.6 mmol, 0.87 mL, 1.2 eq) before cooling to 0°C. After addition of TMSCl (11.2 mmol, 1.42 mL, 1.4 eq), benzyl mercaptan (8.0 mmol, 0.94 mL, 1.0 eq) was diluted with pyridine (1 mL) and added dropwise. The reaction was stirred for 30 minutes at 0°C, then for 18 hours at room temperature. MeI (16.0 mmol, 0.99 mL, 2.0 eq) was added to the flask and stirred for 2 hours. Two yellow liquid phases appeared, and the bottom phase was discarded. (Note: The reaction may also present itself as a yellow liquid with abundant yellow precipitate, in which case the precipitate was filtered and discarded. MeI was added to quench residual thiol and facilitate purification). The liquid was concentrated in vacuo and crude oil purified by flash chromatography (15% ethyl acetate/hexanes), yielding **6a** as a clear/colorless oil. (1.31 g, 4.9 mmol, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.18 (m, 5H), 4.81 (t, *J* = 6.4 Hz, 1H), 3.81 (s, 2H), 1.86 – 1.64 (m, 2H), 1.40 (tdd, *J* = 14.1, 7.7, 1.1 Hz, 2H), 0.88 (t, *J* = 7.4 Hz, 3H), 0.17 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.7, 129.1, 128.6, 127.0, 78.6, 41.0, 33.3, 19.5, 13.8, 0.7; MS-EI *m/z*: $[M\text{-}CH_3]^+$ $C_{13}H_{21}OSSi$ calcd 253.1, found 253; $[M\text{-}TMS]^+$ $C_{11}H_{15}OS$ calcd 195.1, found 195; $[M]^+$ $C_{14}H_{24}OSSi$ calcd 268.1, found 268. Note: for some reason, these α-siloxysulfide compounds (**6a-d** and **17a-c**) appear to be unstable under mass analysis. We have tried different ionization methods (ESI, EI, APCI, MALDI) to obtain their parent MS and HRMS. We were only able to obtain a few parent MS using EI. For each

compound we observed strong fragment MS peaks under EI. Nevertheless, their NMR data and derivatization confirmed their structural identity.



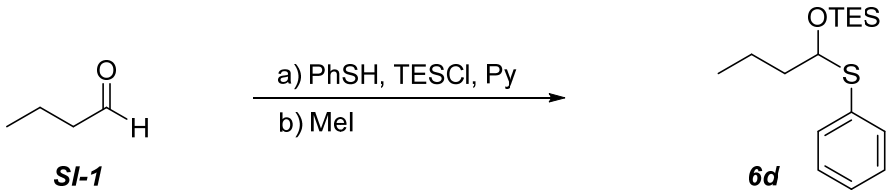
SI-1 ***6b***

Compound **6b**. Clear/colorless oil, 1.95 g, 7.7 mmol, 96%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 – 7.48 (m, 2H), 7.33 – 7.26 (m, 3H), 5.09 (t, *J* = 6.3 Hz, 1H), 1.75 (m`, 2H), 1.53 – 1.38 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H), 0.04 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 134.0, 134.0, 128.8, 127.7, 82.6, 41.0, 19.6, 13.8, 0.3; MS-EI *m/z*: $[M]^{\cdot+}$ $C_{13}H_{22}OSSi$ calcd 254.1, found 254; $[M\text{-}CH_3]^+$ $C_{12}H_{19}OSSi$ calcd 239.1, found 239; $[M\text{-}TMS]^+$ $C_{10}H_{13}OS$ calcd 181.1, found 181.



SI-1 ***6c***

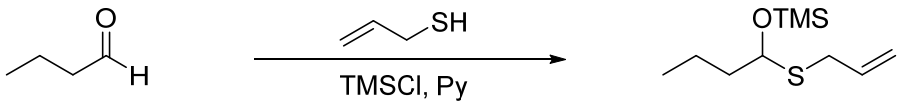
Compound **6c**. Clear/colorless oil, 2.0 g, 6.4 mmol, 80%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (d, *J* = 7.3 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.23 (t, *J* = 7.2 Hz, 1H), 4.82 (t, *J* = 6.4 Hz, 1H), 3.83 (s, 2H), 1.77 (dtd, *J* = 40.0, 13.9, 7.6 Hz, 2H), 1.42 (h, *J* = 7.5 Hz, 2H), 0.99 (t, *J* = 8.0 Hz, 9H), 0.89 (t, *J* = 7.4 Hz, 3H), 0.67 (q, *J* = 7.9 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 138.7, 129.1, 128.5, 126.9, 78.6, 41.3, 32.9, 19.5, 13.9, 7.0, 5.2; MS-EI *m/z*: $[M]^+$ $C_{17}H_{30}OSSi$ calcd 310.2, found 310; $[M\text{-}TES]^+$.$C_{11}H_{15}OS$ calcd 195.1, found 195.



SI-1 ***6d***

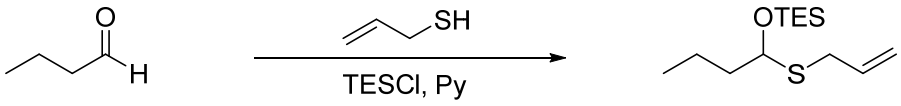
Compound **6d**. Clear/colorless oil, 1.54 g, 5.2 mmol, 66%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.45 (m, 2H), 7.35 – 7.21 (m, 3H), 5.10 (t, *J* = 6.3 Hz, 1H), 1.83 – 1.66 (m, 2H), 1.54 – 1.39 (m, 2H), 0.99-0.85 (m, 12H), 0.58 (q, *J* = 7.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.0, 133.7, 128.8, 127.5, 82.4, 41.1, 19.6, 13.9, 6.9, 5.0; MS-EI *m/z*: $[M\text{-}TES]^+$ $C_{10}H_{13}OS$ calcd 181.1, found 181.

2. General Procedure 2 for Synthesis of alpha-siloxysulfides



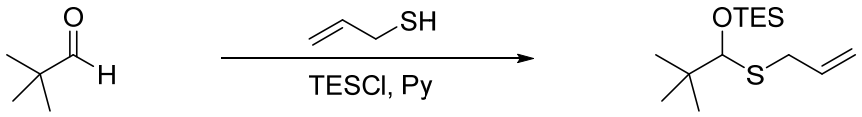
SI-1 ***17a***

Compound **17a**. A 10 mL flame-dried round-bottom flask was charged with dry pyridine (4.0 mL), followed by addition of butyraldehyde (9.6 mmol, 0.87 mL, 1.2 eq) before cooling to 0°C. After addition of TMSCl (11.2 mmol, 1.41 mL, 1.4 eq), allyl mercaptan (≥ 70% pure, 8.0 mmol, 0.94 mL, 1.0 eq) was diluted with pyridine (1 mL) and added dropwise. The reaction was stirred for 30 minutes at 0°C, then for 18 hours at room temperature. The white precipitate was filtered and discarded. The liquid was concentrated in vacuo and crude oil purified by flash chromatography (10% dichloromethane/hexanes), yielding **17a** as a somewhat volatile clear/colorless oil. (0.70 g, 3.2 mmol, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (ddt, *J* = 16.9, 10.0, 6.7 Hz, 1H), 5.16 (dq, *J* = 17.0, 1.4 Hz, 1H), 5.07 (dd, *J* = 10.0, 1.4 Hz, 1H), 4.84 (t, *J* = 6.3 Hz, 1H), 3.31 – 3.16 (m, 2H), 1.84-1.64 (m, 2H), 1.48-1.35 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H), 0.17 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.1, 116.8, 78.2, 41.1, 32.0, 19.5, 13.9, 0.7; MS-EI *m/z*: $[M\text{-}CH_3]^+$ $C_9H_{19}OSSi$ calcd 203.1, found 203; $[M\text{-}TMS]^+$ $C_7H_{13}OS$ calcd 145.1, found 145.



SI-1 ***17b***

Compound **17b**. Clear/colorless oil, 1.13 g, 4.3 mmol, 54%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.92-5.82 (m, 1H), 5.16 (d, *J* = 17, 1H), 5.06 (d, J = 11, 1H), 4.84 (t, *J* = 6.3 Hz, 1H), 3.32-3.19 (m, 2H), 1.85-1.68 (m, 2H), 1.49-1.38 (m , 2H), 0.99 (t, *J* = 8.0 Hz, 9H), 0.92 (t, *J* = 7.4 Hz, 3H), 0.67 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 135.3, 116.6, 78.4, 41.5, 31.7, 19.5, 13.9, 7.0, 5.3; MS-EI *m/z*: $[M\text{-}TES]^+$ $C_7H_{13}OS$ calcd 145.1, found 145.



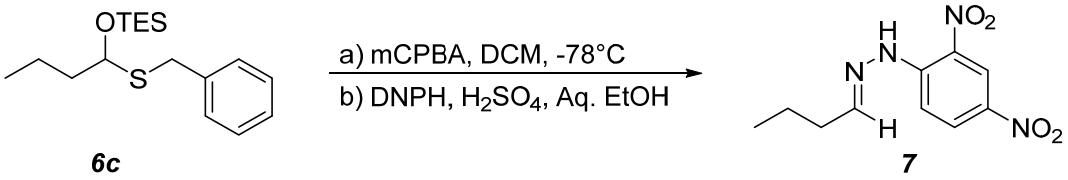
SI-2 ***17c***

Compound **17c**. Clear/colorless oil, 1.5 g, 5.4 mmol, 67%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93 – 5.75 (m, 1H), 5.13 (dq, *J* = 17.0, 1.4 Hz, 1H), 5.10 – 5.04 (m, 1H), 4.45 (s, 1H), 3.25 (dt, *J* = 7.1, 1.1 Hz, 2H), 1.06 – 0.92 (m, 18H), 0.76 – 0.59 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.3, 116.8, 89.2, 39.1, 35.2, 26.4, 7.1, 5.4; MS-EI *m/z*: $[M\text{-}TES]^+$ $C_8H_{15}OS$ calcd 159.1; found 159; $[M\text{-}CH_3]^+$ $C_{13}H_{27}OSSi$ calcd 259.1, found 259.

Stability studies of alpha-siloxysulfides

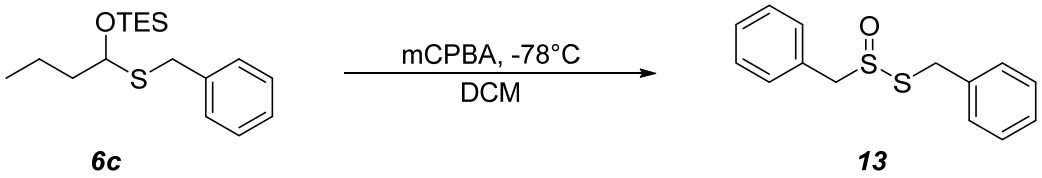
Each alpha-siloxysulfide substrate (**6a-d**) was dissolved in 1:1 of THF/buffers (pH 5~9) and stored at rt. Their degradation was monitored by TLC. After 24 hours the materials were extracted by DCM and analyzed by NMR. No significant decomposition was noted as all materials were recovered >95%.

3. Identification of silyl migration reaction products



6c ***7***

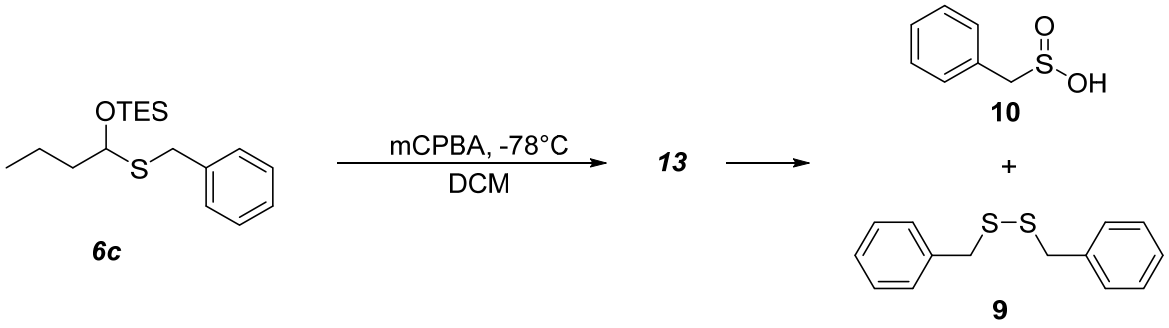
Compound **7**. A 100 mL round-bottom flask was charged with 38 mL dichloromethane and **6c** (1.20 mmol, 0.373 g, 1.0 eq) prior to evacuation with argon and cooling to -78°C. mCPBA (~70% pure, 1.08 mmol, 0.266 g, 0.9 eq) dissolved in 10 mL dichloromethane was then added by syringe pump over 30 minutes and reaction stirred for 3 hours at -78°C. The reaction was warmed to room temperature and stirred for 1 hour with a solution of 2,4-dinitrophenylhydrazine (1.44 mmol, 0.36 g, 1.2 eq) dissolved in H_2SO_4 (1.5 mL), H_2O (2.5 mL), and 95% EtOH (7.5 mL). It was then diluted with dichloromethane (20 mL) and organic phase washed (1x, 15 mL, 1M H_2SO_4) and (3x, 15 mL, sat. $NaHCO_3$) and (1x, 10 mL, brine) and dried with $MgSO_4$. After filtration and concentration in vacuo, the crude material was purified by flash chromatography (10% ethyl acetate/hexanes) to yield **7** as an orange solid (1.1 mmol, 0.27 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.02 (br s, 1H), 9.13 (d, *J* = 2.6 Hz, 1H), 8.30 (dd, *J* = 9.6, 2.6 Hz, 1H), 7.93 (d, *J* = 9.6 Hz, 1H), 7.54 (t, *J* = 5.4 Hz, 1H), 2.42 (td, *J* = 7.4, 5.4 Hz, 2H), 1.71 – 1.61 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H).[1]



6c ***13***

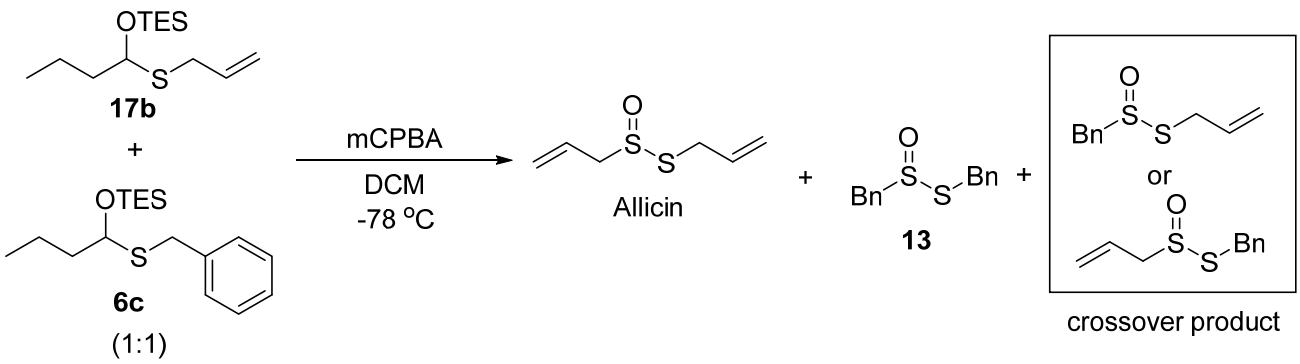
Compound **13**. A 100 mL round-bottom flask was charged with 38 mL dichloromethane and **6c** (1.20 mmol, 0.373 g, 1.0 eq) prior to cooling to -78°C. mCPBA (~70% pure, 1.08 mmol, 0.266 g, 0.9 eq) dissolved in 10 mL dichloromethane was then added by syringe pump over 30 minutes. The reaction stirred for 3 hours at -78°C before warming and addition of saturated $Na_2S_2O_3$ (10 mL). The organic phase was washed (3x, 15 mL, sat. $NaHCO_3$) and (1x, 10 mL,

brine), dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography (100% dichloromethane) to yield **13** as a white solid (0.11 g, 0.4 mmol, 80%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 – 7.24 (m, 10H), 4.36 – 4.24 (m, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 136.8, 130.5, 130.1, 129.3, 129.0, 128.9, 127.9, 62.4, 36.3; HRMS ($^+$ESI in ACN) calcd for $C_{14}H_{15}OS_2^+$ $[M+H]^+$ 263.0559, found 263.0572.[2]



Compounds **9 & 10**. A 25 mL two-neck round-bottom flask was sealed and evacuated with argon. It was charged with dichloromethane (6 mL) and **6c** (0.2 mmol, 0.054 g, 1.0 eq) prior to cooling to -78°C. mCPBA (~70% pure, 0.18 mmol, 0.044 g, 0.9 eq) dissolved in 2 mL dichloromethane was added by syringe pump over 30 minutes, followed by stirring for 3 hours at -78°C. The reaction was warmed to room temperature for 48 hours prior to EI-GCMS and $^-$ESI-MS analysis. Compound **10** $^-$ESI-MS $[M-H]^-$ $C_7H_7O_2S$ calcd 155.0, found 155. Compound **9** EI-GCMS *m/z* $[M]^+$ $C_{14}H_{14}S_2$ calcd 246.0, found 246 (NIST spectral match).

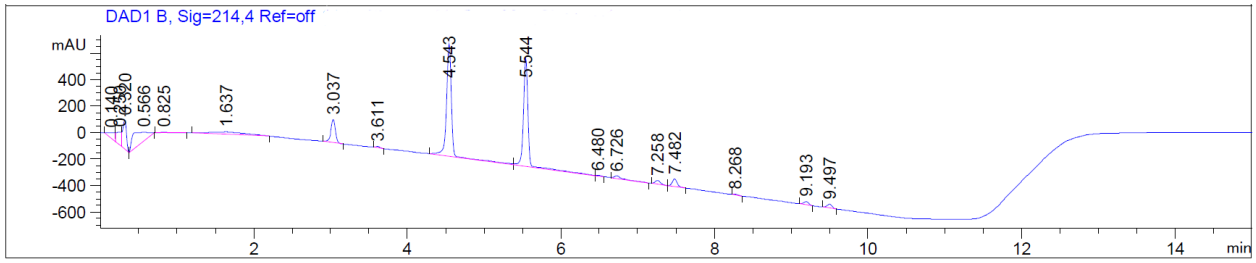
Crossover studies



A 250 mL round-bottom flask was charged with 60 mL DCM, **17b** (1.00 mmol, 0.261 g, 1.0 eq), and **6c** (1.00 mmol, 0.311 g, 1.0 eq) prior to cooling to -78°C. mCPBA (~70% pure, 1.80 mmol, 0.444 g, 1.8 eq) dissolved in 20 mL dichloromethane was then added by syringe pump over 30 minutes. The reaction stirred for 3 hours at -78°C before warming and addition of saturated $Na_2S_2O_3$ (10 mL). The organic phase was washed (3x, 15 mL, sat. $NaHCO_3$) and (1x, 10 mL, brine), dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude material was analyzed by HPLC and HRMS. As shown below, in addition to the two self-condensation products (allicin and **13**), an additional product peak (RT at 4.543 min) was observed. HRMS demonstrated that it was the crossover product.

HPLC was done using a Supelcosil^{TM} LC-18 column (50 x 4.6 mm, 5 µm), ACN/H_2O = 5/95 to 95/5 gradient, flow rate = 2.0 mL/min, l = 214 nm.

HPLC Trace:

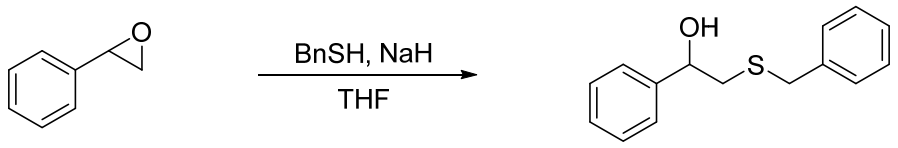


RT 3.037 min, Allicin. HRMS ($^+$ESI) calcd for $C_6H_{11}OS_2^+$ $[M+H]^+$ 163.0246, found 3163.0251.

RT 4.543 min, the crossover thiosulfinates. HRMS ($^+$ESI) calcd for $C_{10}H_{13}OS_2^+$ $[M+H]^+$ 213.0402, found 213.0413.

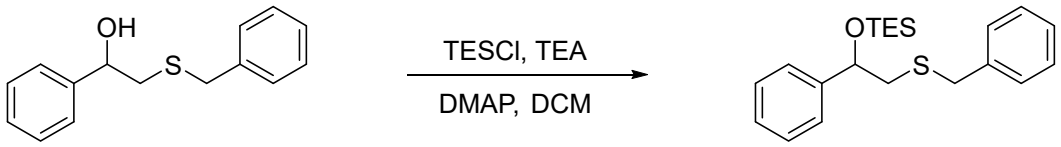
RT 5.544 min, dibenzyl thiosulfinate **13**. HRMS ($^+$ESI) calcd for $C_{14}H_{15}OS_2^+$ $[M+H]^+$ 263.0559, found 263.0571.

4. Synthesis of mechanistically relevant analogs



SI-3 ***SI-4***

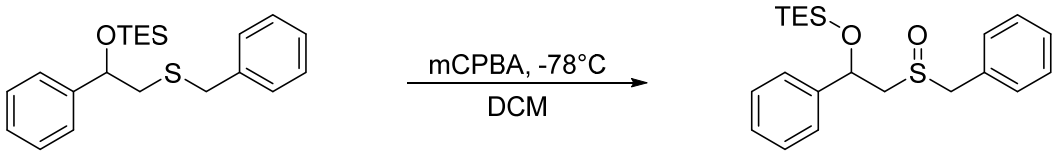
Compound **SI-4**. A 10 mL two-neck flame-dried round-bottom flask was charged with THF (5 mL) and benzyl mercaptan (6.2 mmol, 0.77 g, 2.5 eq). Sodium hydride (excess) was added and stirred for 20 minutes prior to dropwise addition of **SI-3** (2.5 mmol, 0.30 g, 1.0 eq). After stirring for 18 hours, saturated ammonium chloride (5 mL) was added, and the resulting mixture was diluted with ethyl acetate (60 mL), organic phase washed (3x, 10 mL, sat. $NaHCO_3$) and (1x, 10 mL, brine), then dried with $MgSO_4$. Filtration and concentration in vacuo gave the crude material, which was further purified by flash chromatography (10% ethyl acetate/hexanes) to yield **SI-4** as a white solid (1.9 mmol, 0.471 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.03 (m, 14H), 4.64 (dt, *J* = 9.1, 3.3 Hz, 1H), 3.69 (s, 2H), 2.91 (d, *J* = 2.7 Hz, 1H), 2.79 – 2.59 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.6, 138.0, 129.0, 128.7, 128.6, 127.9, 127.3, 125.9, 71.8, 40.9, 36.2; HRMS (ESI) calcd for $C_{15}H_{16}OSNa^+$ $[M+Na]^+$ 267.0820, found 267.0827.[3]



SI-4 ***SI-5***

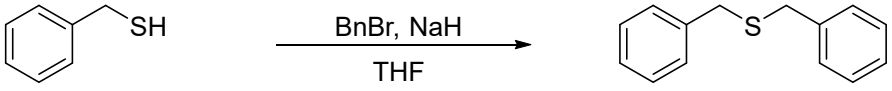
Compound **SI-5**. A 10 mL two-neck flame-dried round-bottom flask was charged with **SI-4** (1.50 mmol, 0.37 g, 1.0 eq) in dichloromethane (5 mL). Triethylamine (1.65 mmol, 0.23 mL, 1.1 eq) and DMAP (0.075 mmol, 0.009 g, 0.05 eq) were added prior to dropwise addition of TESCl (1.50 mmol, 0.25 mL, 1.0 eq). After stirring for 4 hours, the reaction was diluted with dichloromethane (40 mL), washed (3x, 10 mL, sat. Na_2CO_3) and (1x, 10 mL, brine), then dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by flash chroma-

tography (20% dichloromethane/hexanes) to yield **SI-5** as a clear/colorless oil (1.4 mmol, 0.52 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.18 (m, 8H), 4.69 (dd, *J* = 7.4, 5.4 Hz, 1H), 3.59 (q, *J* = 13.3 Hz, 2H), 2.80-2.2.55 (m, 2H), 0.87 (t, *J* = 7.9 Hz, 9H), 0.63 – 0.42 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.3, 138.8, 129.2, 128.6, 128.3, 127.7, 127.1, 126.3, 75.5, 41.4, 37.2, 6.9, 5.0; EI-GCMS *m/z* (in ACN): $[M]^+$ $C_{21}H_{30}OSSi$ calcd 358.2, found 358.



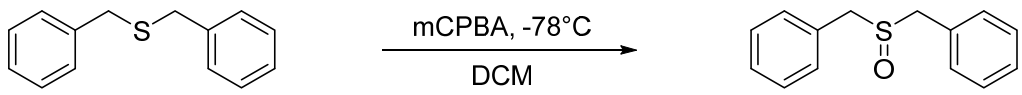
SI-5 ***14***

Compound **14**. A 25 mL round-bottom flask was charged with dichloromethane (6 mL) and **SI-5** (0.20 mmol, 0.072 g, 1.0 eq) prior to cooling to -78°C. mCPBA (~70% pure, 0.18 mmol, 0.043 g, 0.9 eq) dissolved in dichloromethane (2 mL) was then added by syringe pump over 30 minutes. The reaction stirred for 3 hours at -78°C before warming and addition of saturated $Na_2S_2O_3$ (5 mL). The organic phase was diluted with dichloromethane (50 mL), washed (3x, 15 mL, sat. $NaHCO_3$) and (1x, 10 mL, brine), dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography (25% ethyl acetate/hexanes) to yield **14** as a clear/colorless oil (0.15 mmol, 0.055 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.28 (m, 10H), 5.32 (dd, *J* = 9.9, 2.7 Hz, 1H), 4.48 (d, *J* = 13.7 Hz, 1H), 4.21 (d, *J* = 13.7 Hz, 1H), 3.44 (dd, *J* = 15.1, 9.9 Hz, 1H), 2.85 – 2.73 (m, 1H), 0.91 (t, *J* = 7.9 Hz, 9H), 0.66 – 0.47 (m, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 142.1, 131.3, 129.1, 129.0, 128.9, 128.7, 128.6, 126.3, 71.4, 61.1, 59.5, 6.8, 4.9; HRMS (ESI) calcd for $C_{21}H_{31}O_2SSi^+$ $[M+H]^+$ 375.1809, found 375.1821.



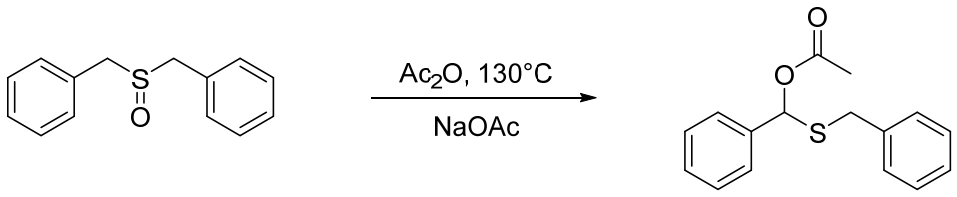
SI-6 ***SI-7***

Compound **SI-7**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.23 (m, 10H), 3.63 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.3, 129.2, 128.6, 127.1, 35.7.[4]



SI-7 ***SI-8***

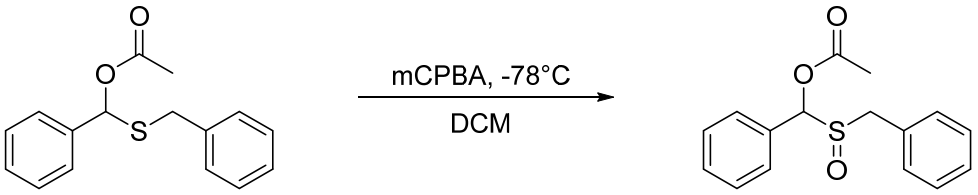
Compound **SI-8**. A 250 mL round-bottom flask was charged with **SI-7** (2.0 mmol, 0.43 g, 1.0 eq) and dichloromethane (60 mL). After cooling the flask to -78°C, a solution of mCPBA (~70% pure, 1.8 mmol, 0.44 g, 0.9 eq) in dichloromethane (20 mL) was added via syringe pump over 30 min. After stirring for 3 hours the reaction was warmed and quenched with a saturated $Na_2S_2O_3$ solution (5 mL). The organic phase was washed (3x, 20mL, sat. $NaHCO_3$) and (1x, 10 mL, brine), dried with $MgSO_4$, filtered, and concentrated in vacuo. The material was quite pure and used without further purification. (white solid) ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 – 7.27 (m, 10H), 3.93 and 3.88 (AB q, J = 13.0, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 130.3, 130.3, 129.1, 128.5, 57.4.[5]



SI-8 ***SI-9***

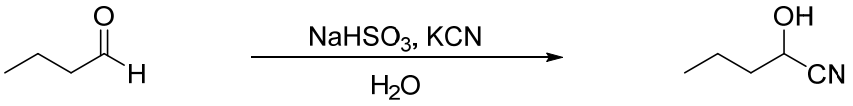
Compound **SI-9**. A round-bottom flask was charged with **SI-8** (0.90 mmol, 0.21 g, 1.0 eq) and freshly distilled acetic anhydride (8 mL). Anhydrous sodium acetate (0.27 mmol, 0.037 g, 0.3 eq) was added to the solution and the reaction heated to reflux for 4 hours. The reaction was then concentrated in vacuo at 75°C and taken up in ethyl acetate (60 mL). The organic phase was then washed (3x, 20 mL, sat. $NaHCO_3$) and (1x, 10 mL, brine). After drying with $MgSO_4$ the organic phase was concentrated in vacuo to yield **SI-9** as a brown oil (0.82 mmol, 0.22 g,

91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.22 (m, 10H), 6.91 (s, 1H), 3.92 and 3.79 (AB q, J = 13.4, 2H), 2.04 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 137.8, 137.8, 129.1, 128.7, 128.7, 128.6, 127.3, 126.5, 79.4, 36.2, 21.2; ESI-MS *m/z* $[M+H]^+$ $C_{16}H_{17}O_2S$ calcd 273.0, found 273; $[M+Na]^+$ $C_{16}H_{16}NaO_2S$ calcd 295.1, found 295.



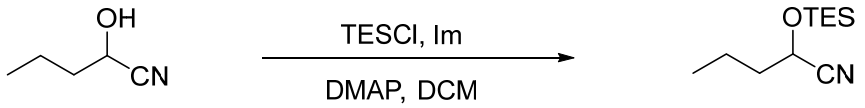
SI-9 ***15***

Compound **15**. A 25 mL round-bottom flask was charged with **SI-9** (0.20 mmol, 0.055 g, 1.0 eq) and dichloromethane (6 mL). After cooling the flask to -78°C, a solution of mCPBA (~70% pure, 0.18 mmol, 0.044 g, 0.9 eq) in dichloromethane (2 mL) was added via syringe pump over 30 min. After 3 hours stirring at -78°C, the reaction was warmed to room temperature and saturated $Na_2S_2O_3$ (5 mL) was added. The organic phase was separated, diluted with dichloromethane (50 mL), and washed (3x, 15 mL, sat. $NaHCO_3$) and (1x, 10 mL, brine). It was then dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography (40% ethyl acetate/hexanes) to yield **15** (0.16 mmol, 0.045 g, 87%) as a mix of diastereomers, appearing as a viscous hazy golden oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.39 (m, 5H), 7.39 – 7.29 (m, 3H), 7.25 – 7.18 (m, 2H), 6.63 – 6.53 (s, 1H), 3.89 – 3.66 (m, 2H), 2.24 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 169.2, 131.3, 130.3, 130.2, 130.2, 130.2, 130.1, 130.1, 130.0, 129.2, 129.1, 128.9, 128.6, 128.5, 128.0, 127.9, 87.0, 86.7, 55.1, 54.7, 20.9, 20.9; HRMS (ESI) calcd for $C_{16}H_{17}O_3S^+$ $[M+H]^+$ 289.0893, found 289.0890.



SI-1 ***SI-10***

Compound **SI-10**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.48 (t, *J* = 6.8 Hz, 1H), 2.70 (s, 1H), 1.95 – 1.75 (m, 2H), 1.54 (h, *J* = 7.4 Hz, 2H), 0.99 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 120.3, 60.9, 37.0, 17.9, 13.4.[6]



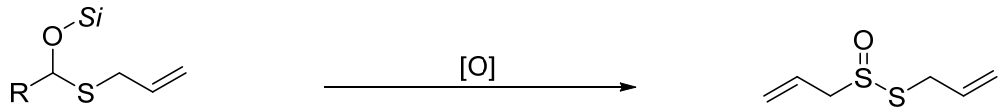
SI-10 ***16***

Compound **16**. A 100 mL two-neck flame-dried round-bottom flask was charged with dichloromethane (60 mL) and **SI-10** (12.0 mmol, 1.00 g, 1.0 eq) before cooling to 0°C. After addition of imidazole (24.0 mmol, 1.63 g, 2.0 eq), DMAP (0.6 mmol, 0.073 g, 0.05 eq), and TESCl (14.4 mmol, 2.17 g, 1.2 eq) the reaction was stirred for 20 min at 0°C followed by 6 hours at 25°C. The organic phase was washed (1x, 30 mL, H_2O) and (1x, 30 mL, brine) then dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude oil was then purified by flash chromatography (5% ethyl acetate/hexanes) to yield **16** as a clear/gold tinted oil (8.8 mmol, 1.87 g, 73%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.43 (t, *J* = 6.5 Hz, 1H), 1.80 – 1.74 (m, 2H), 1.55 – 1.46 (m, 2H), 1.01-0.93 (m, 12H), 0.74 – 0.61 (m, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 120.3, 61.7, 38.6, 18.0, 13.6, 6.7, 4.5; EI-GCMS *m/z* (in ACN): $[M]^+$ $C_{11}H_{23}NOSi$ calcd 213.1, found 213; $[M+H]^+$ $C_{11}H_{24}NOSi$ calcd 214.1, found 214.

Stability studies of control compounds (14, 15, 16)

Each control compound was subjected to mCPBA oxidation conditions as described above. The progress of the reaction was monitored by TLC and we did not observe any significant change to the control compound after 3~5 hours. After the reaction, the control compound was recovered (>95%) from the reaction mixture by extraction and confirmed by NMR analysis.

5. Procedures for oxidation-triggered allicin formation



17a: R = nPr, *Si* = TMS
17b: R = nPr, *Si* = TES
17c: R = iBu, *Si* = TES

Allicin

mCPBA Oxidation:

Formation of **Allicin**. A round-bottom flask was charged with **17a** (0.40 mmol, 0.087 g, 1.0 eq) and dichloromethane (12 mL). After cooling the flask to -78°C, a solution of mCPBA (~70% pure, 0.36 mmol, 0.089 g, 0.9 eq) in dichloromethane (4 mL) was added via syringe pump over 30 min. After 3 hours the reaction was warmed to 25°C, quenched with sat. $Na_2S_2O_3$ (5 mL), and diluted with dichloromethane (50 mL). The organic phase was washed (3x, 15 mL, sat. $NaHCO_3$), the resulting aqueous phase extracted (2x, 15 mL, DCM), and the combined organic phases washed (1x, 10 mL, brine). After drying with $MgSO_4$ and concentrating in vacuo, the crude material was purified by flash chromatography (15% ethyl acetate/hexane) to yield **allicin** (0.05 mmol, 0.008 g, 29%) as a clear/light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07 – 5.78 (m, 1H), 5.56 – 5.03 (m, 2H), 4.04 – 3.71 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 133.0, 125.9, 124.2, 119.2, 60.0, 35.2.[2]

Formation of **Allicin**. Substrate **17b**. (0.4 mmol scale, 0.07 mmol, 0.012 g, 40%) and (1.2 mmol scale, 0.35 mmol, 0.056 g, 64%).

Formation of **Allicin**. Substrate **17c**. (0.13 mmol, 0.021 g, 71%).

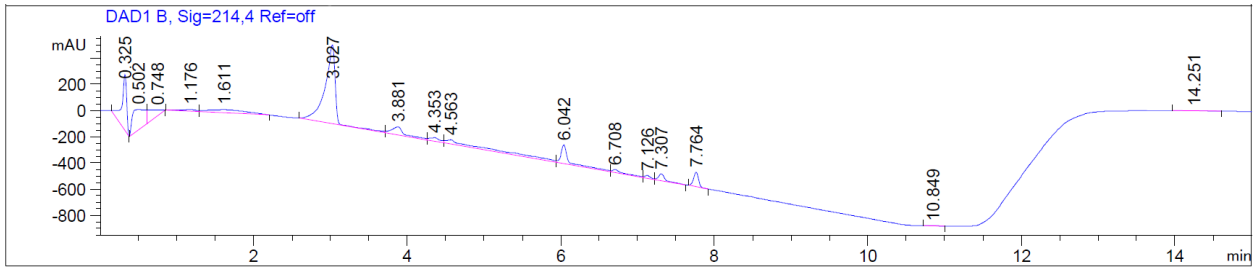
H_2O_2 Oxidation:

Formation of **Allicin**. Two 4 mL vials were charged with H_2O_2 (0.98 M, 1.28 mL, 25.0 eq) and H_2O (0.12 mL). **17a** (0.05 mmol, 0.011 g, 1.0 eq) was dissolved in THF (0.6 mL) and combined with the aq. H_2O_2 to make a H_2O/THF (70/30) solution (2 mL). The vials were sealed and heated to 37°C for 30 min and 4 hours, respectively. The solutions were extracted (3x, 0.7 mL, DCM) and organic phases were dried with $MgSO_4$. After filtration via a 0.2 µm filter the solu-

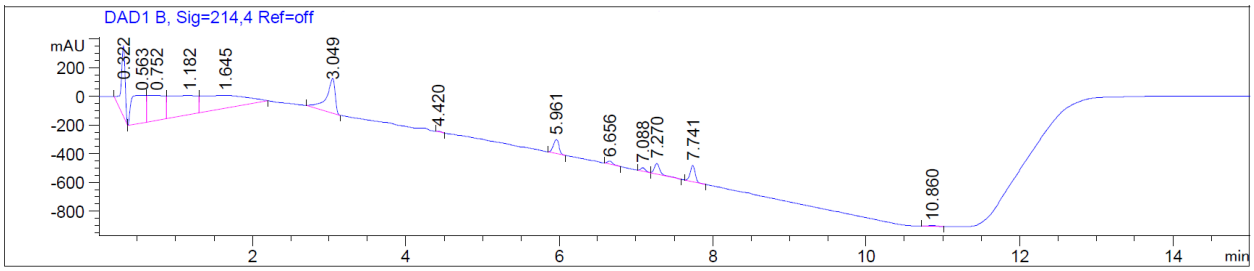
tions were concentrated gently. The crude material was then taken up in acetonitrile (1 mL) and diluted for quantitation by HPLC with external standard to yield **allicin**. The corresponding yields were noted in Table 1. The yields were determined by HPLC using a Supelcosil^{TM} LC-18 column (50 x 4.6 mm, 5 µm), ACN/H_2O = 5/95 to 95/5 gradient, flow rate = 2.0 mL/min, l = 214 nm; t_R = 3.0 min (major). The purified allicin HPLC fraction was collected and confirmed by ESI-MS *m/z* $[M+H]^+$ $C_6H_{11}S_2$ calcd 163.0, found 163.

Reaction:

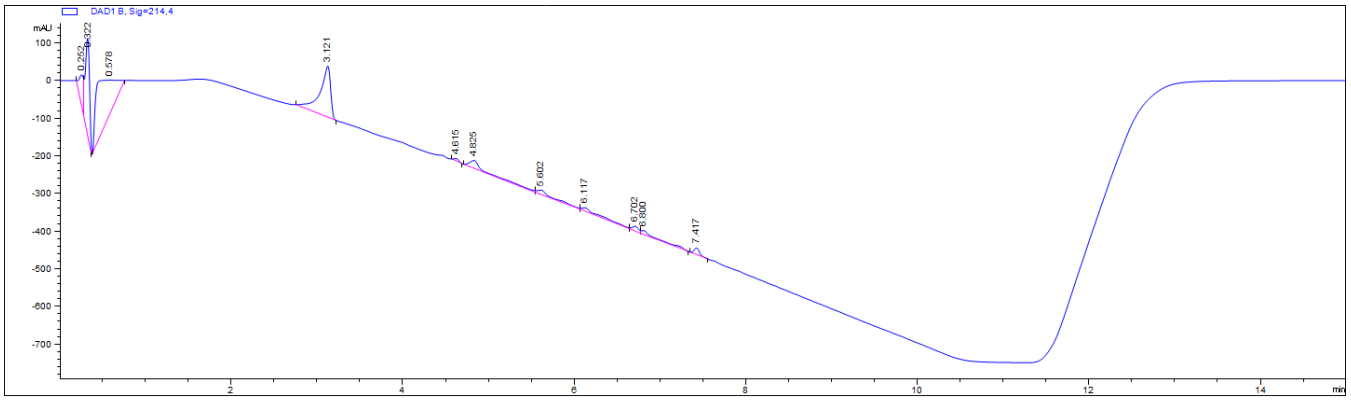
17a with H_2O_2 at 30 min:



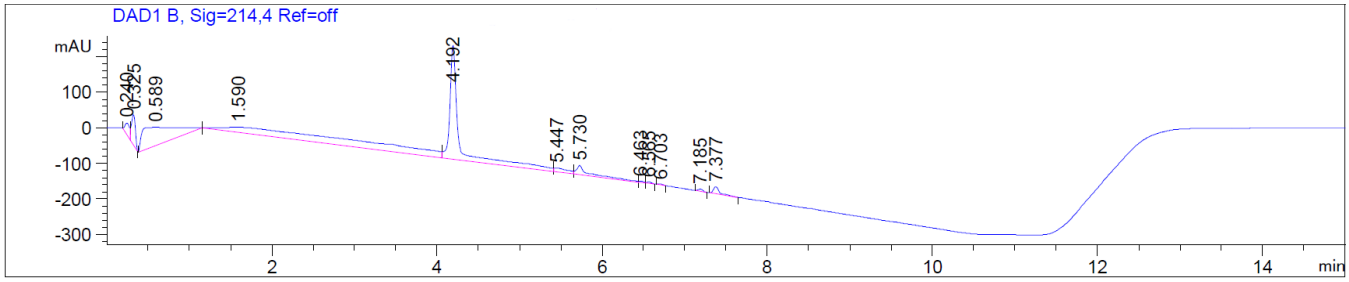
17a with H_2O_2 at 4 hr:



Allicin standard:



Starting material (**17a**) standard:



NaOCl Oxidation:

Formation of **Allicin**. A 4 mL vial was charged with H_2O_2 (0.98 M, 1.28 mL, 25.0 eq) and H_2O (0.12 mL). **17a** (0.05 mmol, 0.011 g, 1.0 eq) was dissolved in THF (0.6 mL) and combined with the aq. H_2O_2 to make a H_2O/THF (70/30) solution (2 mL). The vial was sealed and heated to 37°C for 24 hours and monitored by TLC. The solution was extracted (3x, 0.7 mL, DCM), organic phase then washed (1x, 1 mL, brine) and dried with $MgSO_4$. After filtration via a 0.2 µm filter the solution was concentrated gently. The crude material was then taken up in acetonitrile (1 mL) and diluted for quantitation by HPLC with external standard. No allicin was detected.

MMPP Oxidation:

Formation of **Allicin**. A 10 mL round-bottom flask was charged with **17b** (0.4 mmol, 0.10 g, 1.0 eq), tetrahydrofuran (3.6mL), and H_2O (0.4 mL). The reaction was cooled to 0°C and magnesium monoperoxyphthalate (~80% pure, 0.2 mmol, 0.12 g, 0.5 eq) added portion wise. After 45 minutes the reaction was diluted with ethyl acetate (60 mL). The organic phase was then washed (1x, 10 mL, H_2O) and (3x, 10 mL, sat. $NaHCO_3$). The combined aqueous phase was extracted (3x, 10 mL, EtOAc). The combined organic phase then washed (1x, 10 mL, brine), dried with $MgSO_4$, filtered, and purified by flash chromatography (15% ethyl acetate/hexanes) to yield **allicin** as a clear/light yellow oil (0.14 mmol, 0.024 g, 74%).

$NaIO_4$ Oxidation:

Formation of **Allicin**. A 25 mL round-bottom flask was charged with **17b** (0.4 mmol, 0.10 g, 1.0 eq), methanol (20 mL). The reaction was cooled to 0°C and aq. $NaIO_4$ (0.5 M, 0.4 mmol, 0.8

mL, 1.0 eq) added dropwise. The reaction was monitored by TLC and did not produce **allicin** after 8 hours.

References:

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3. J. Zhu, R. Li, Z. Ge, T. Cheng and R. Li, Chin. J. Chem., 2009, **27**, 791-796.

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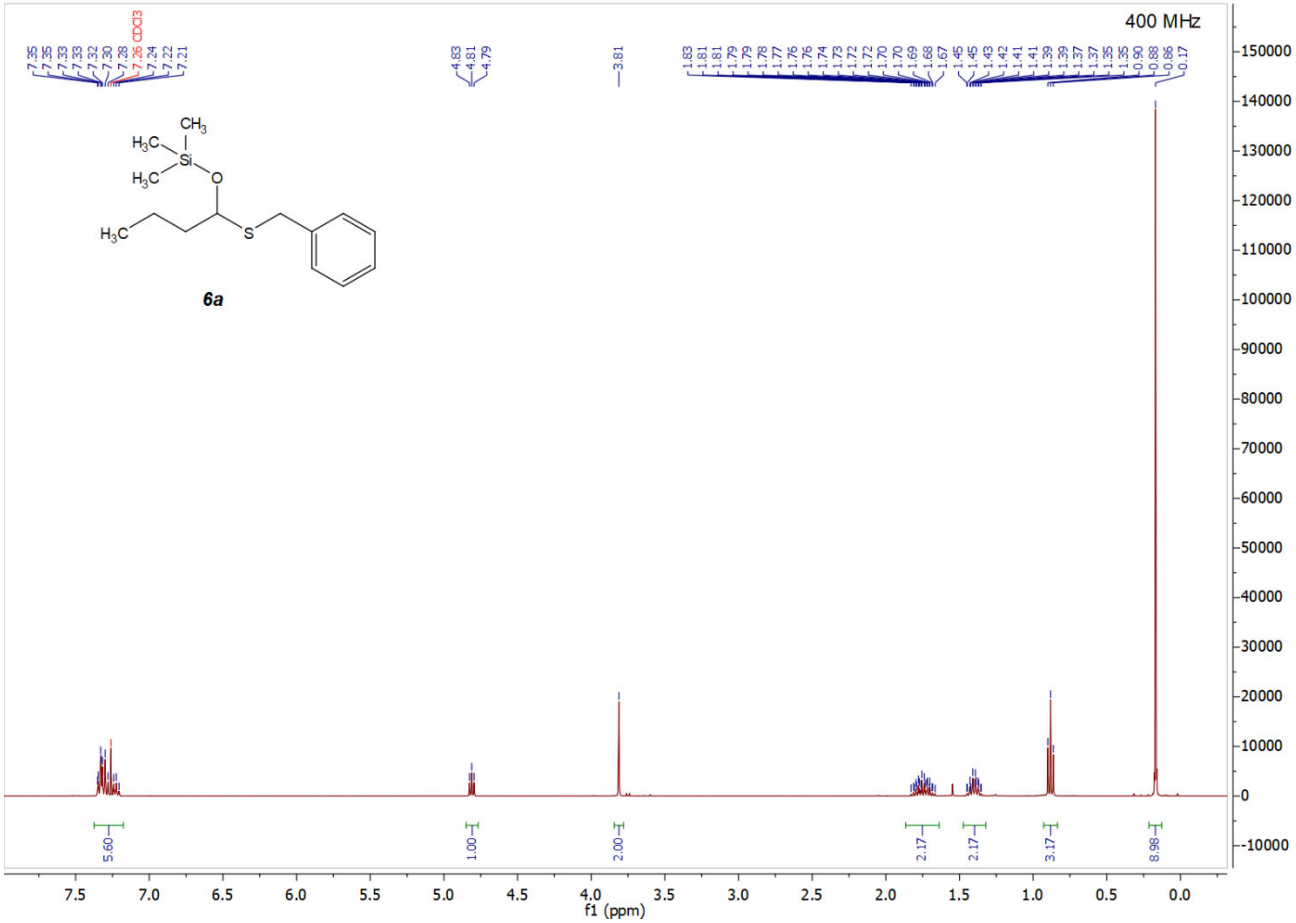
5. C. Boudou, M. Bergès, C. Sagnes, J. Sopková−de Oliveira Santos, S. Perrio and P. Metzner, *J. Org. Chem.*, 2007, **72**, 5403-5406.

6. N. P. Chandia, J. C. Canales, I. Azocar, S. Vanlaer, V. G. Pawar, W. M. De Borggraeve, J. Costamagna and W. Dehaen, *Synth. Commun.*, 2009, **39**, 927-939.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4.79
3.81
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H3C
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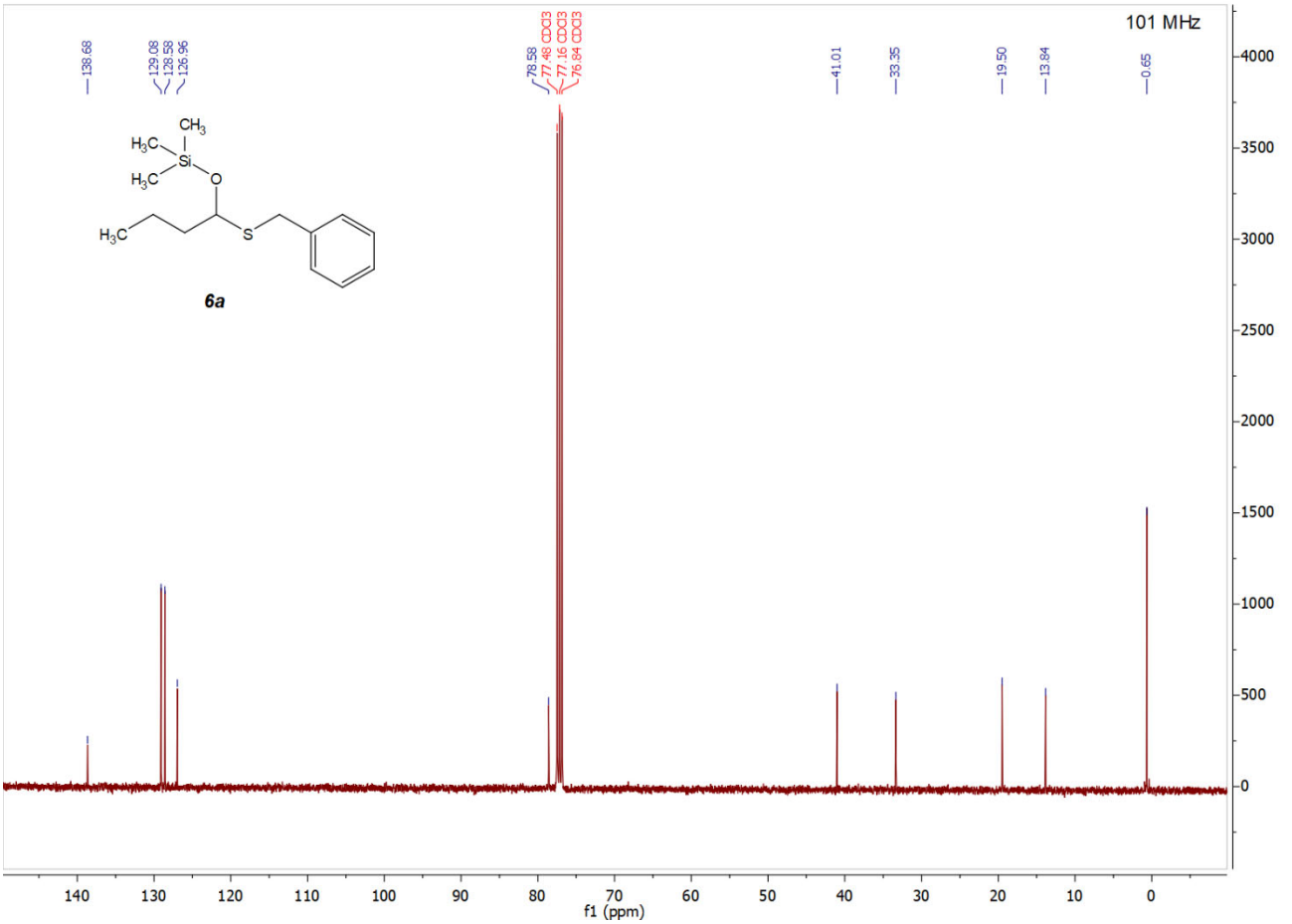
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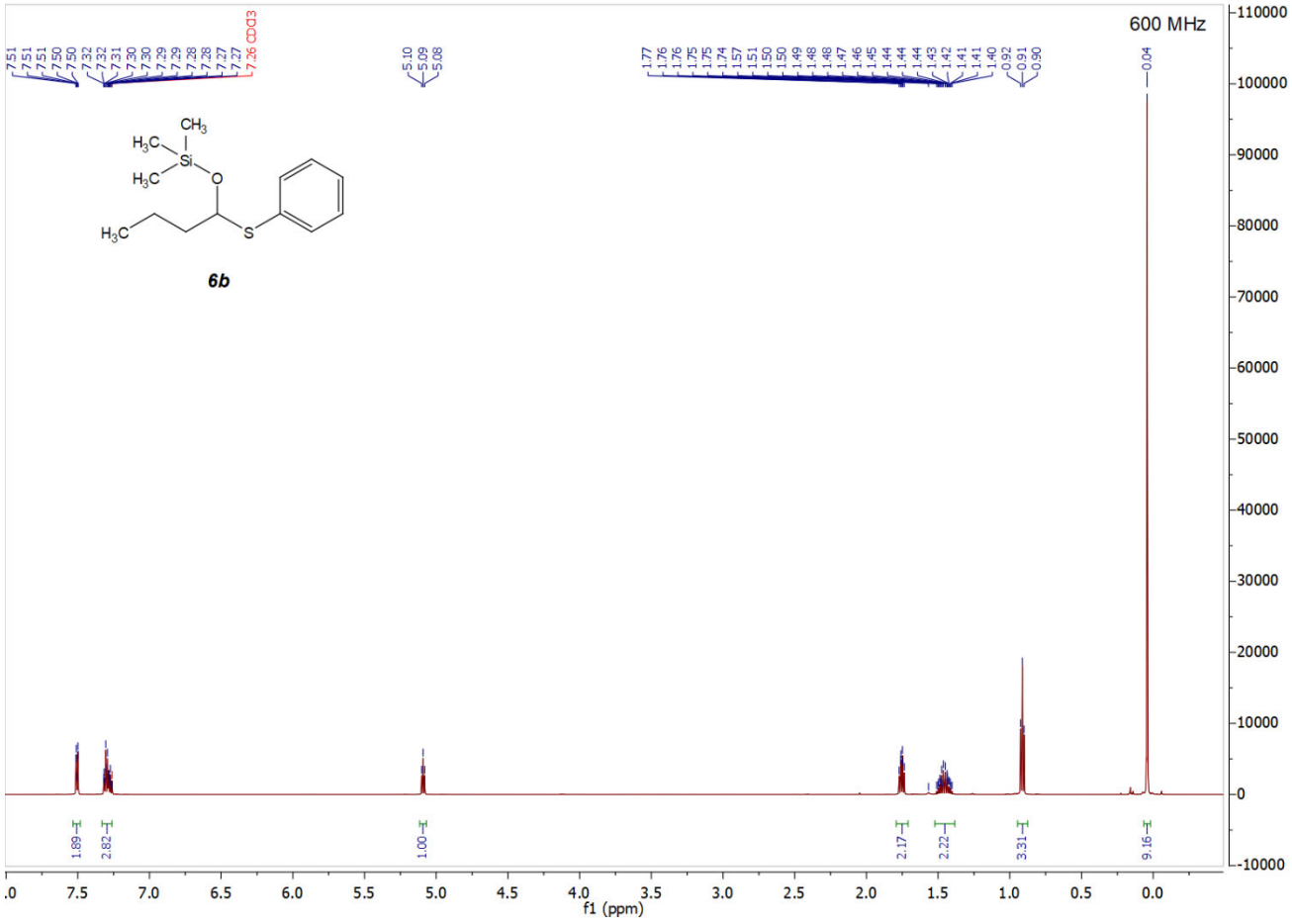
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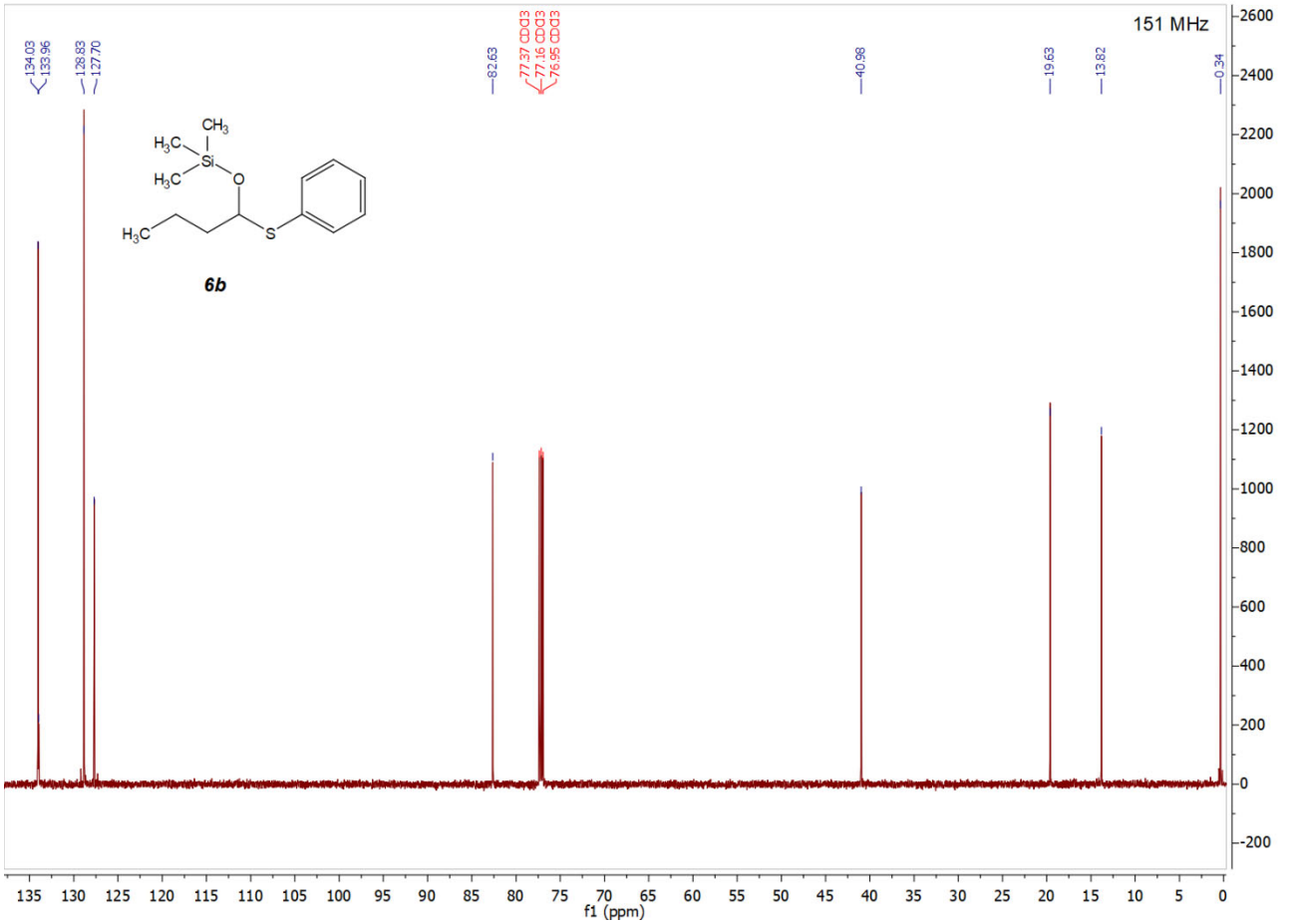
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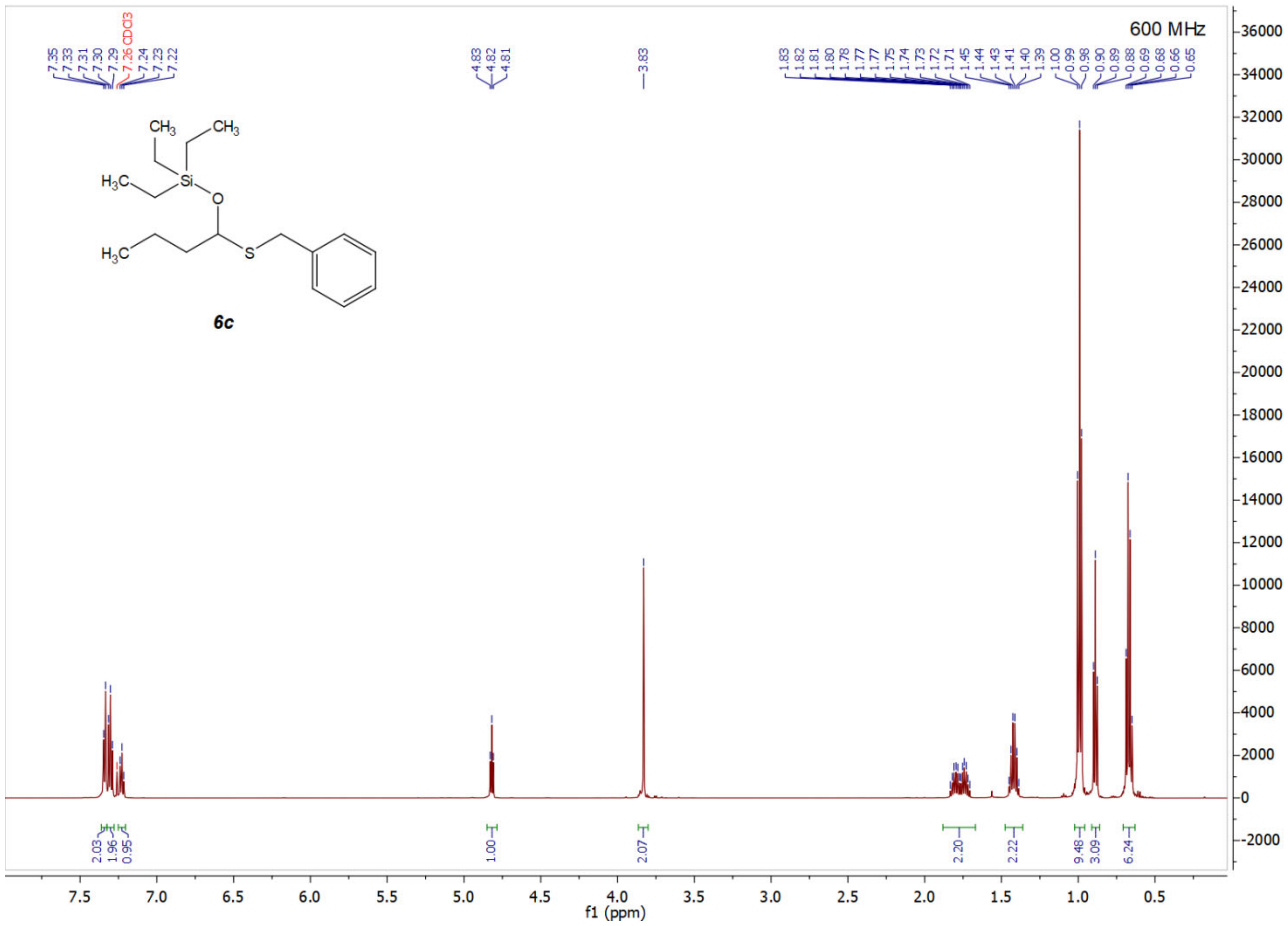
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0.66
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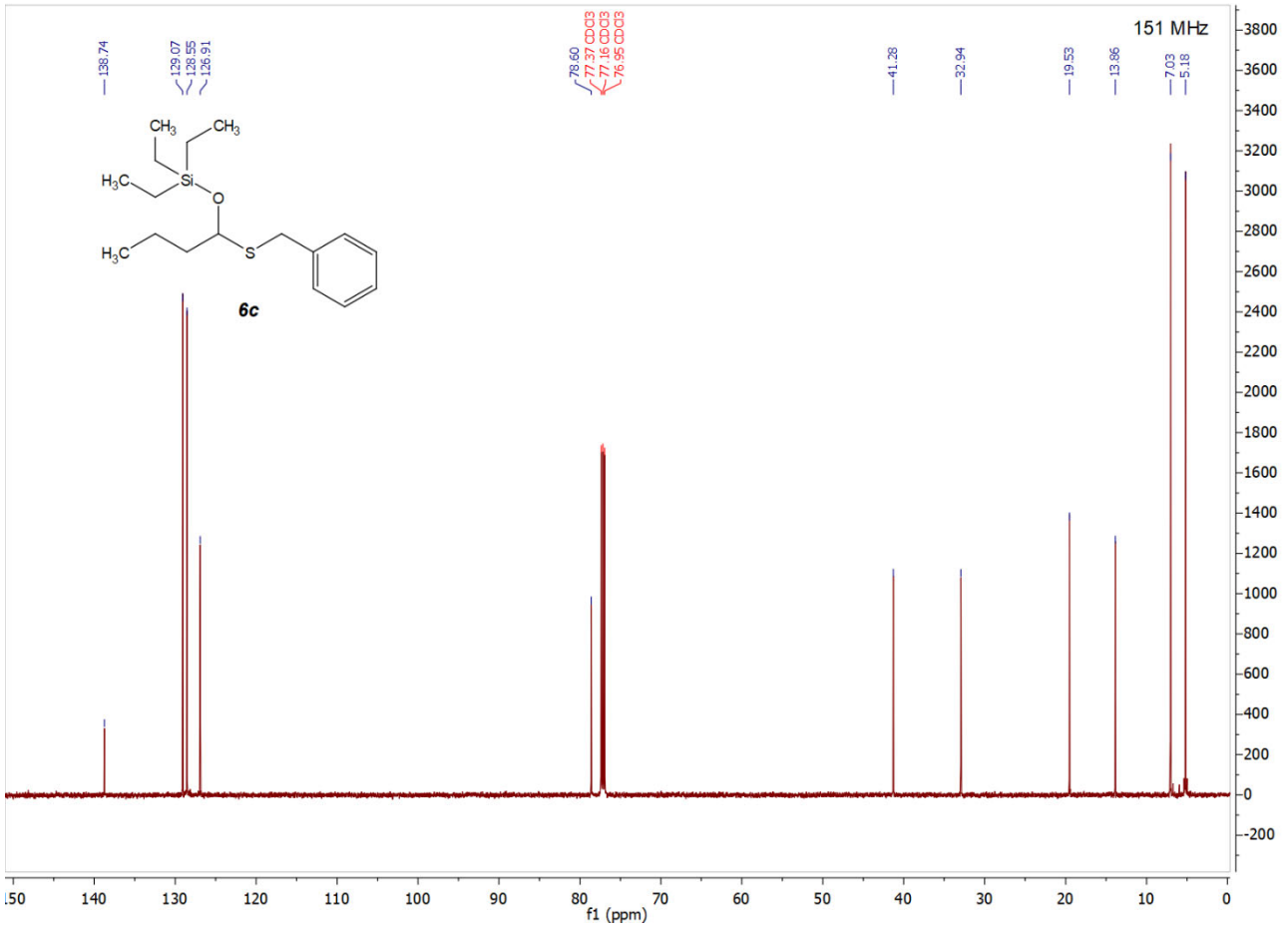
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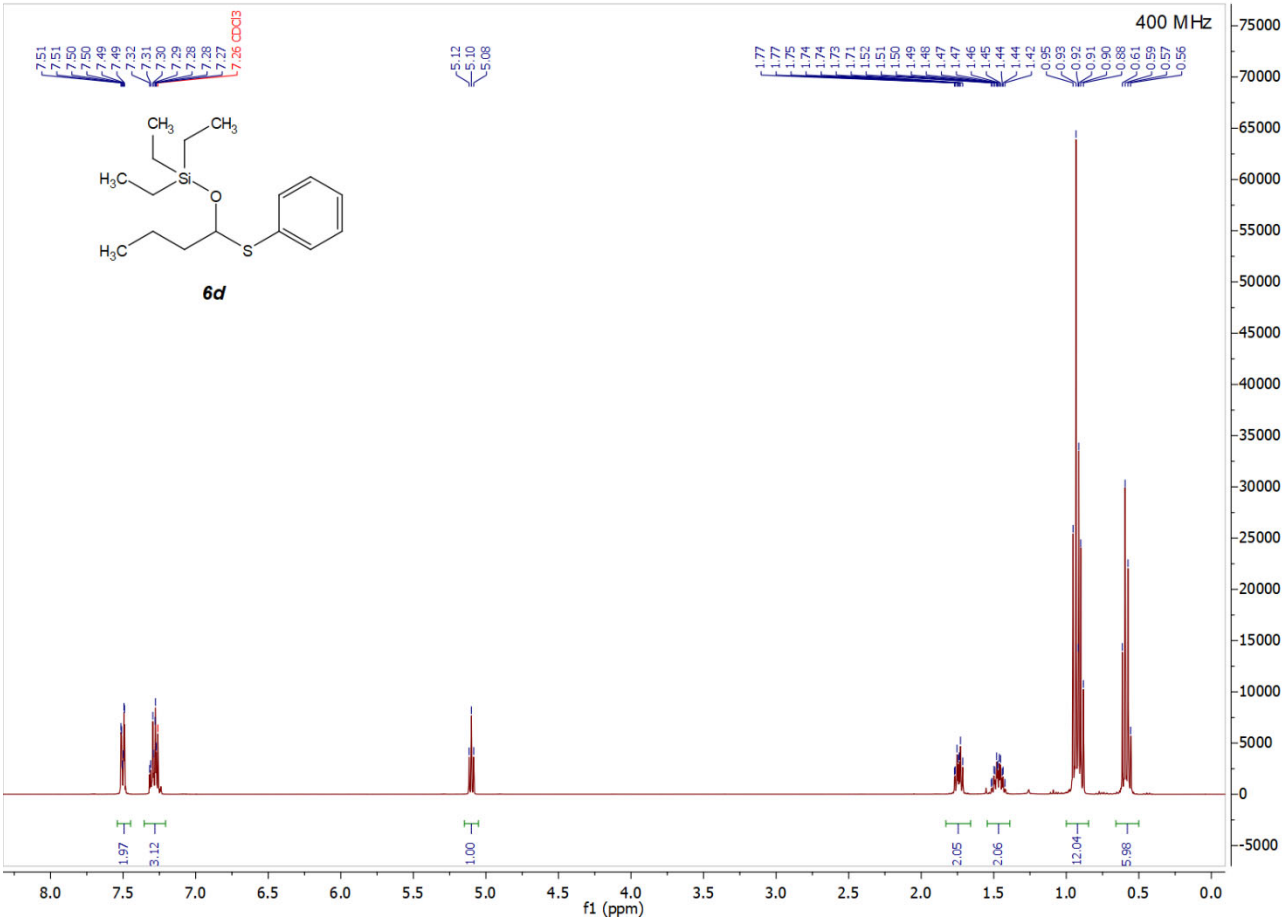
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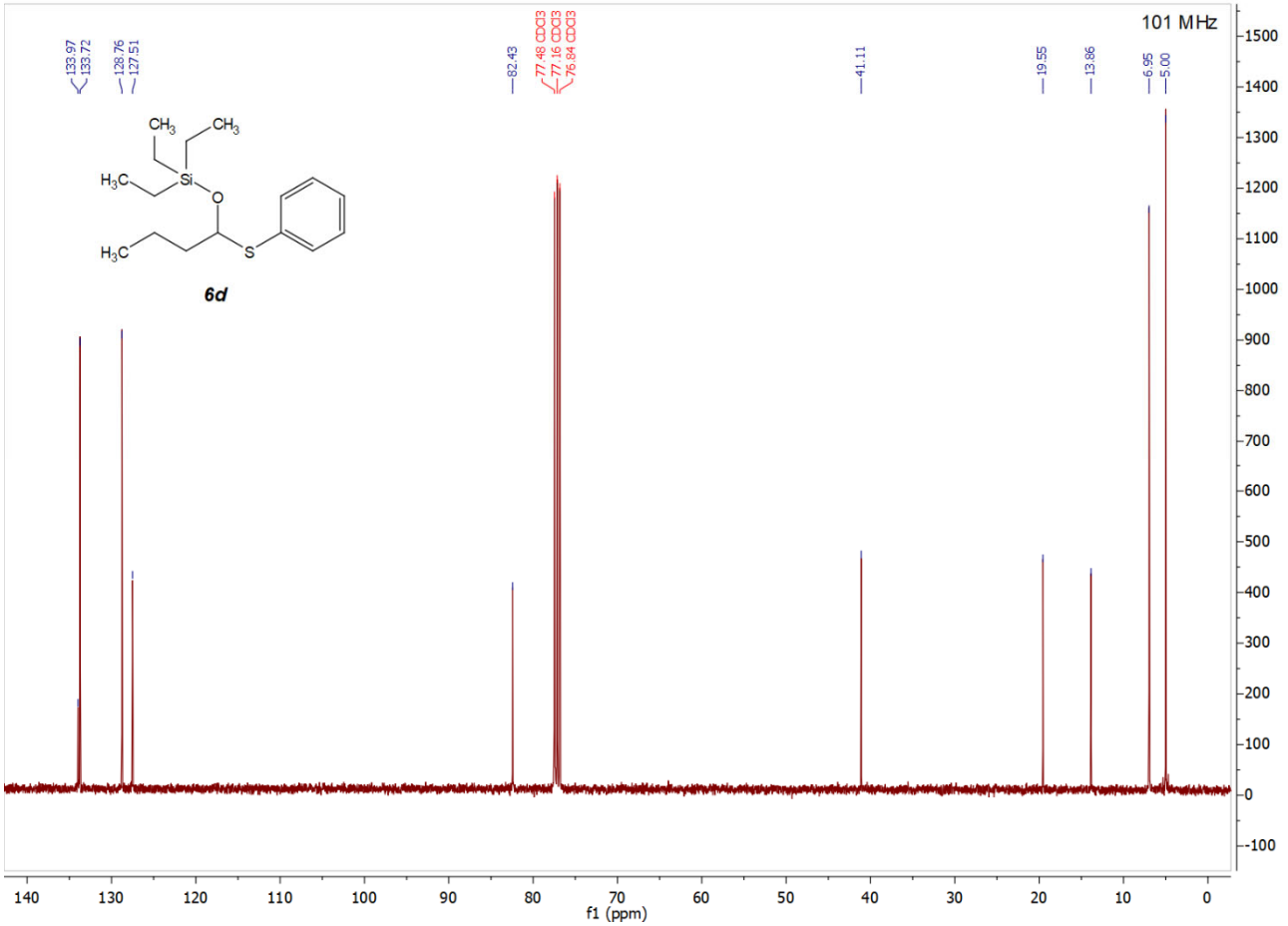
f1 (ppm)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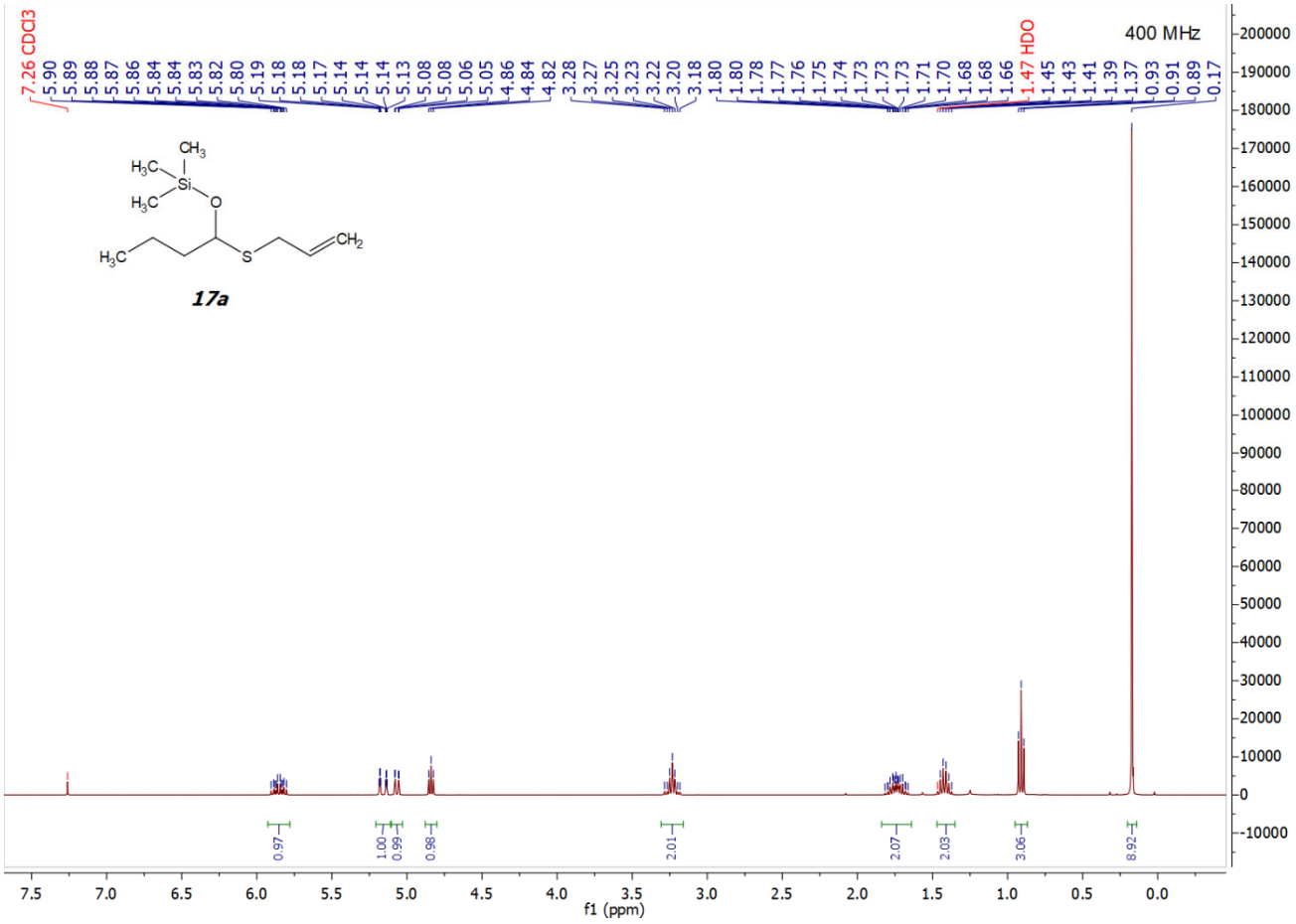
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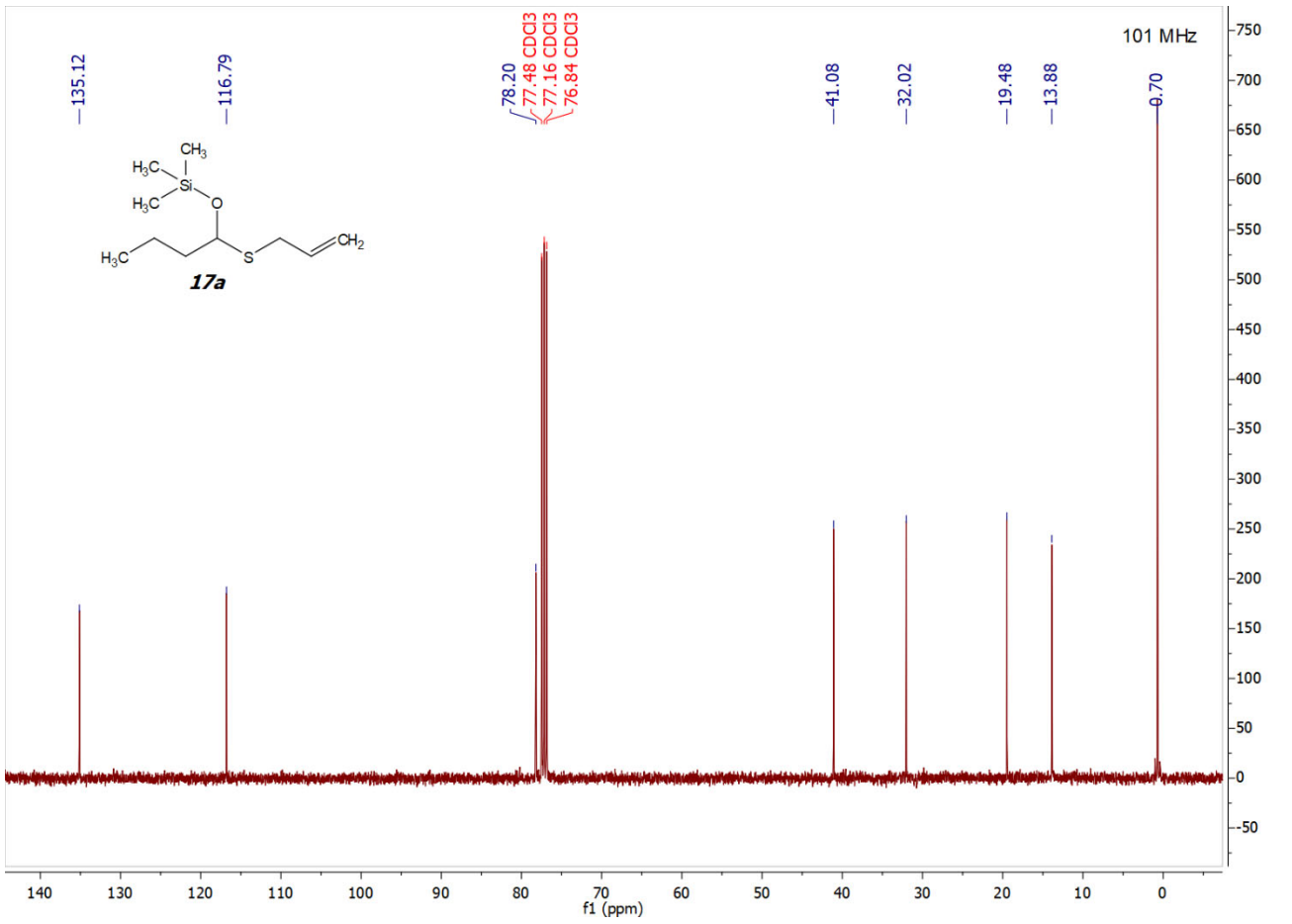
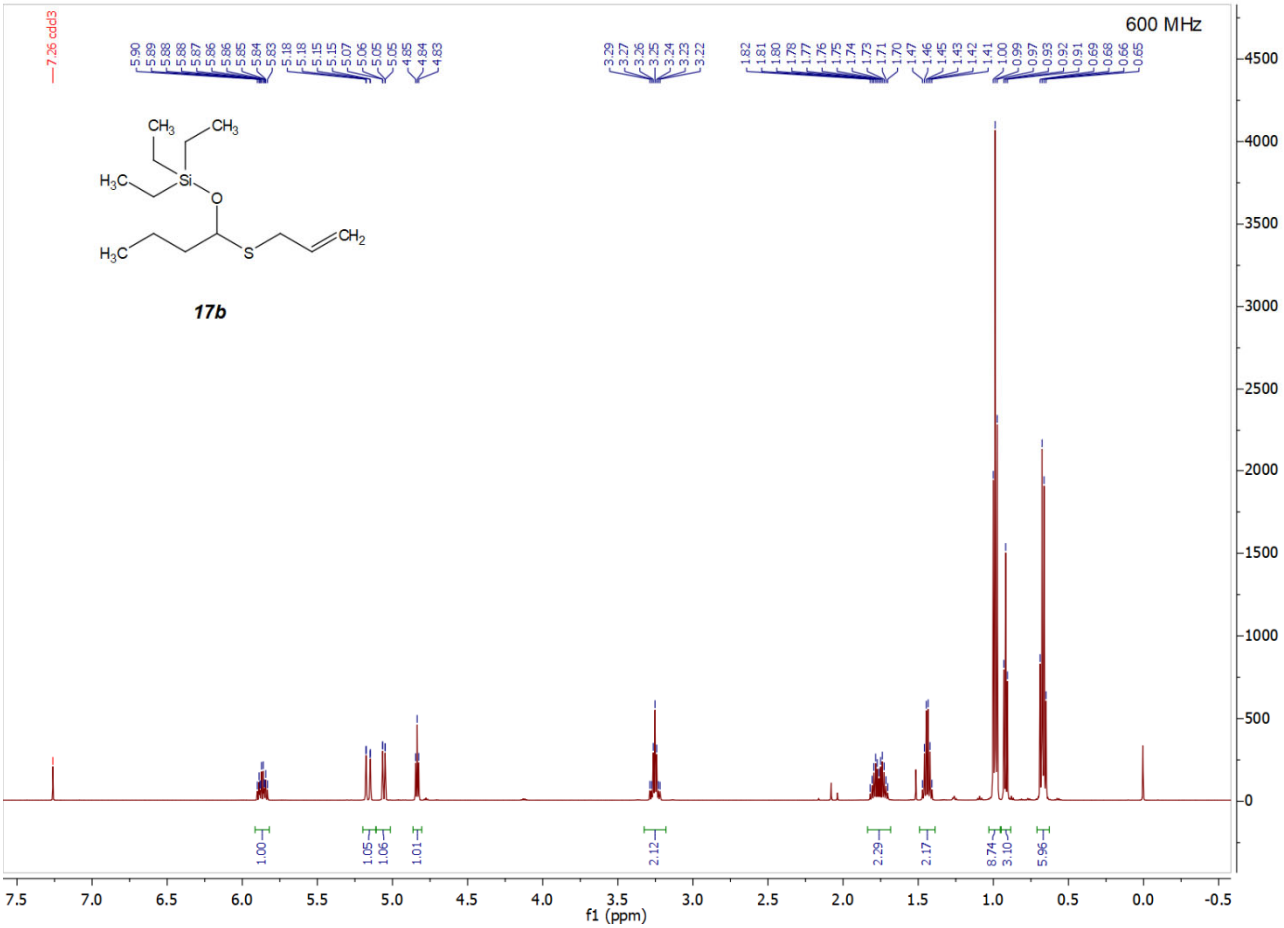
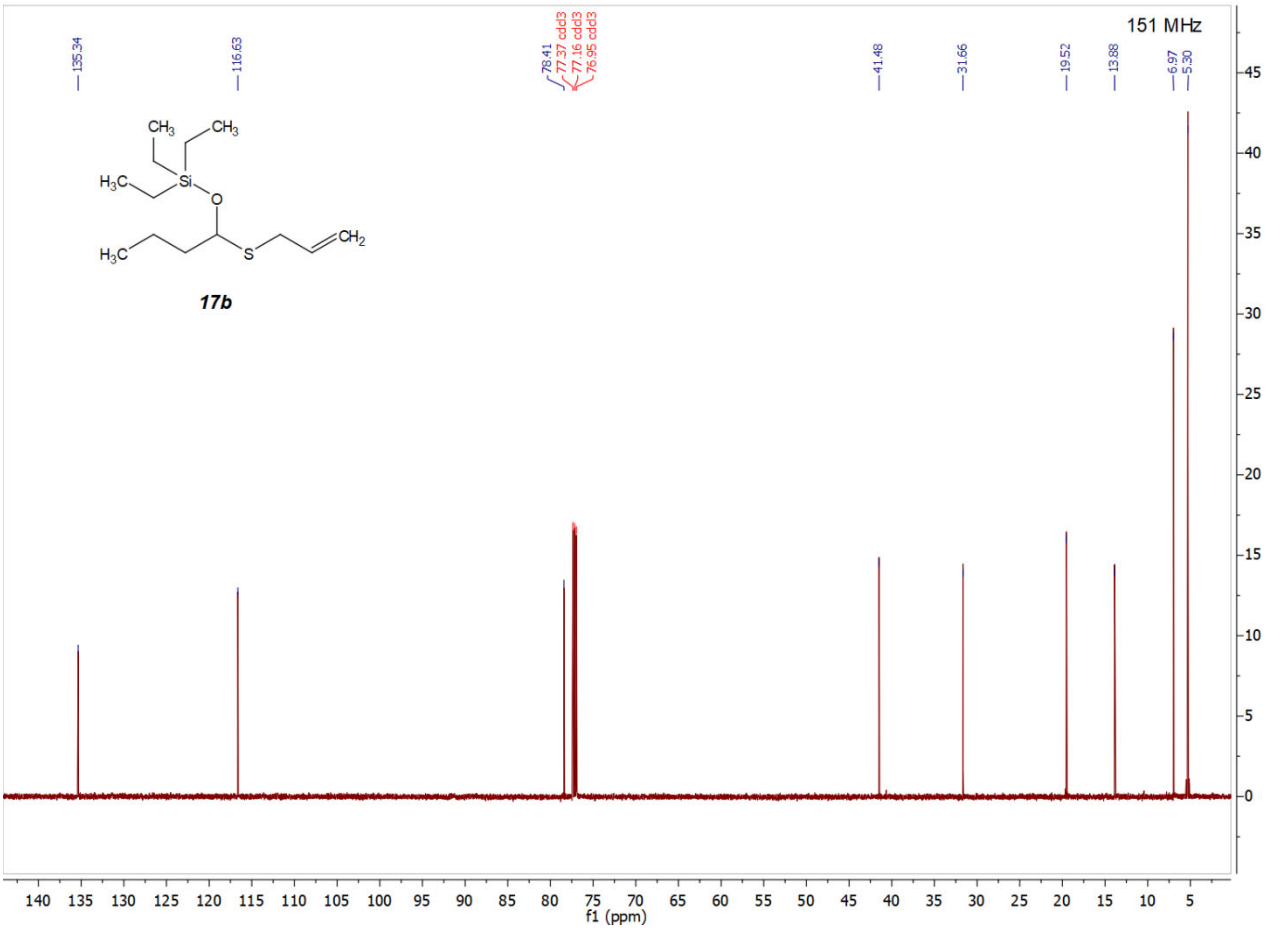
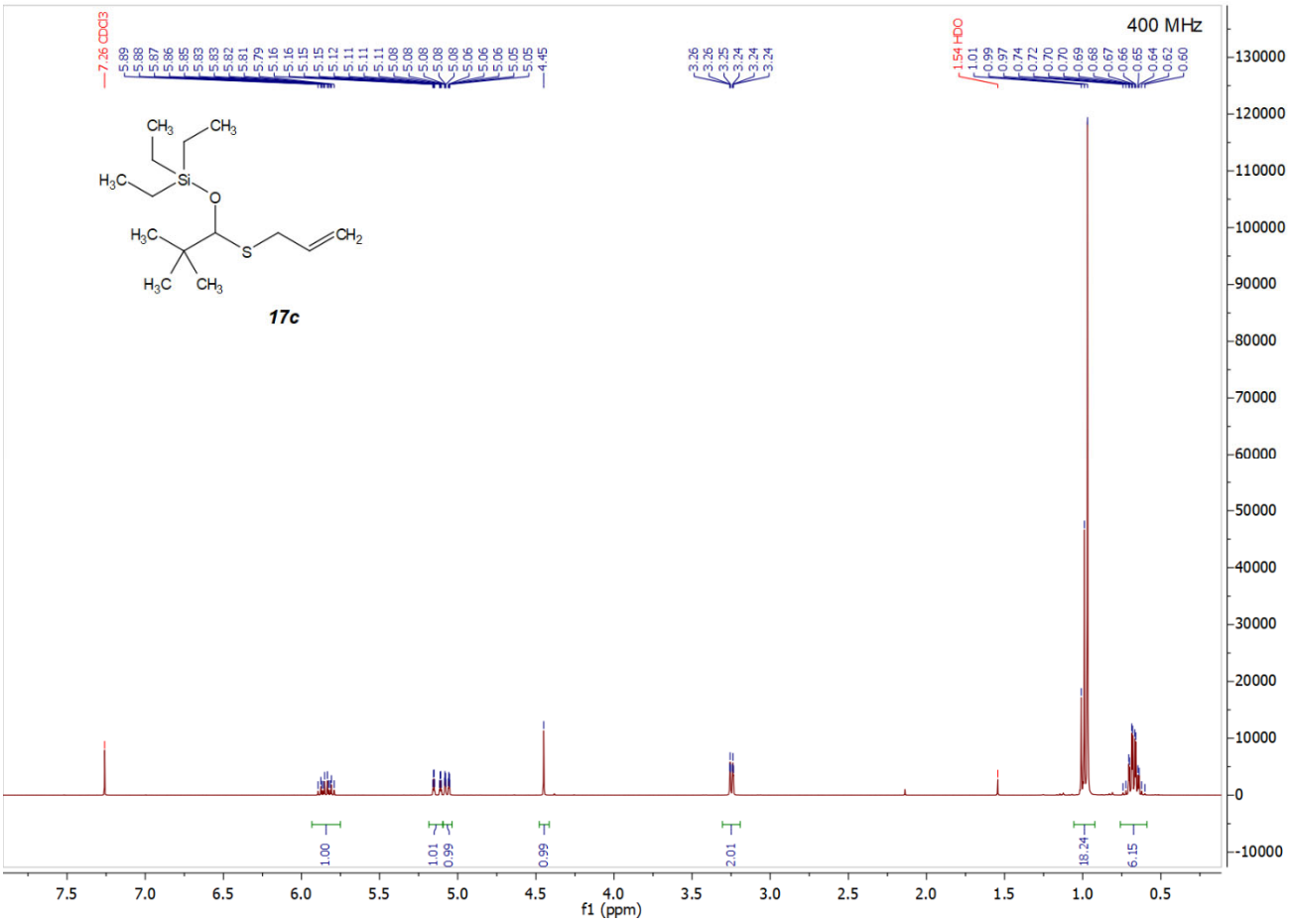
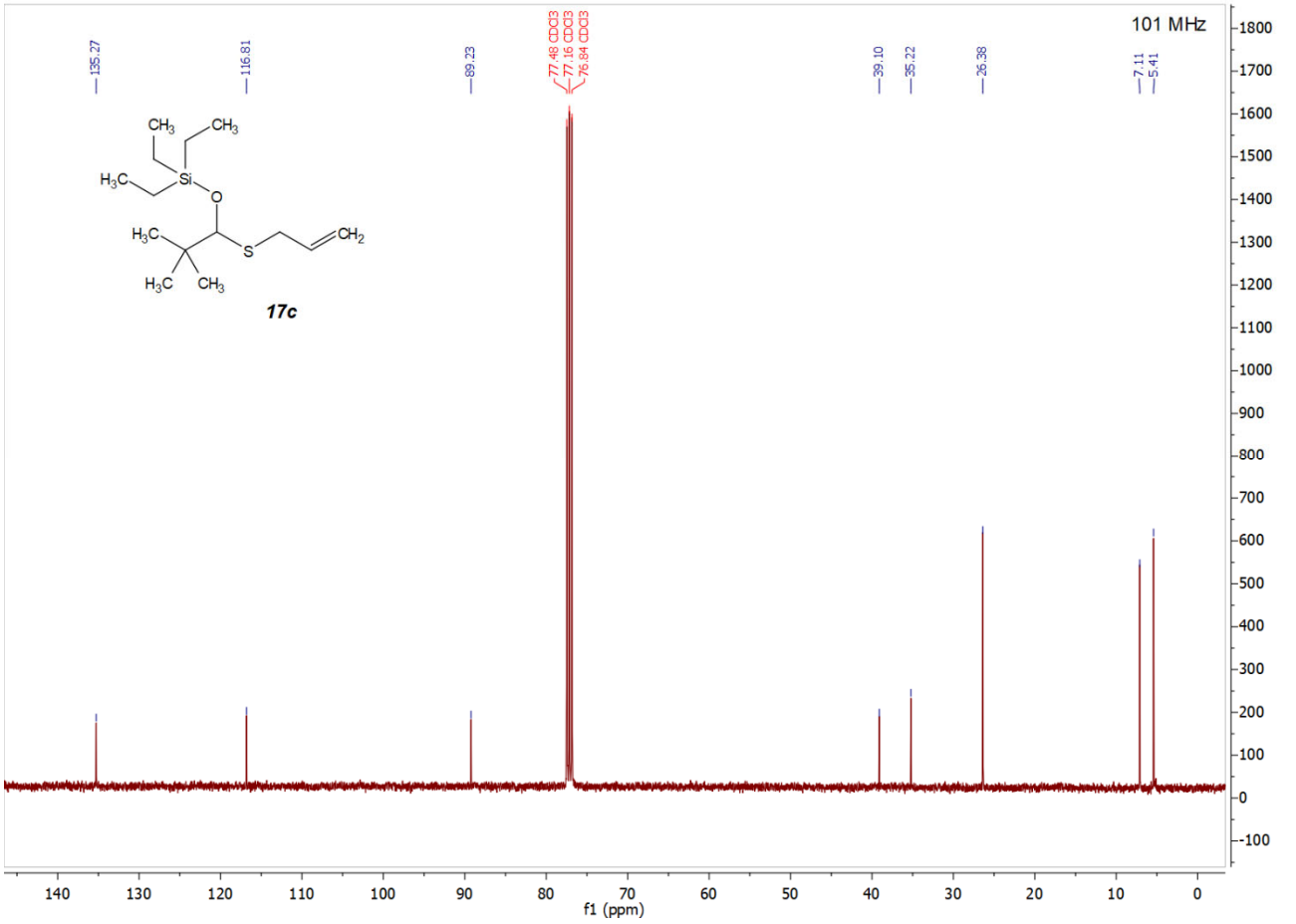
17a
f1 (ppm)

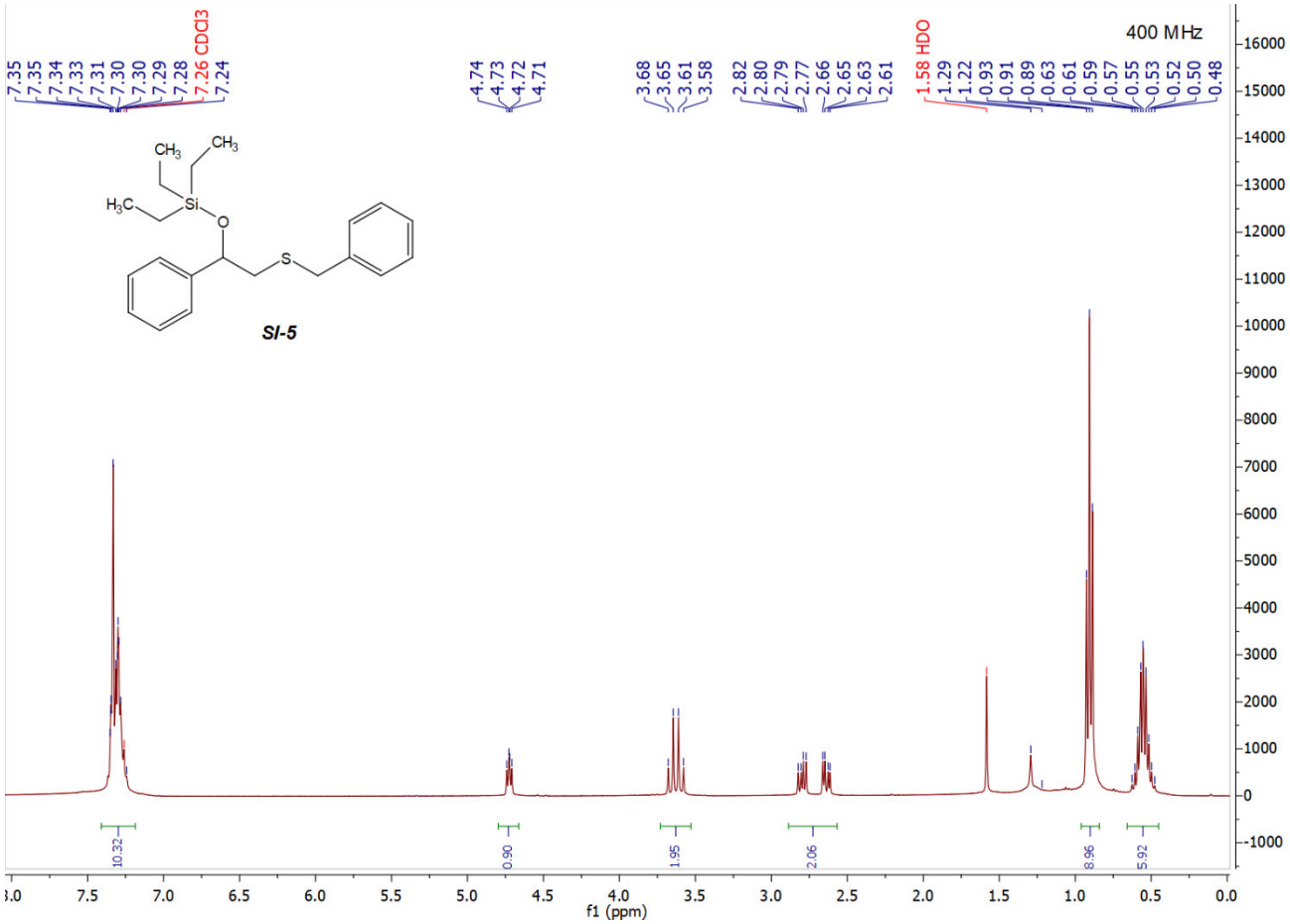

101 MHz
135.12
116.79
78.20
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
41.08
32.02
19.48
13.88
0.70
17a
f1 (ppm)

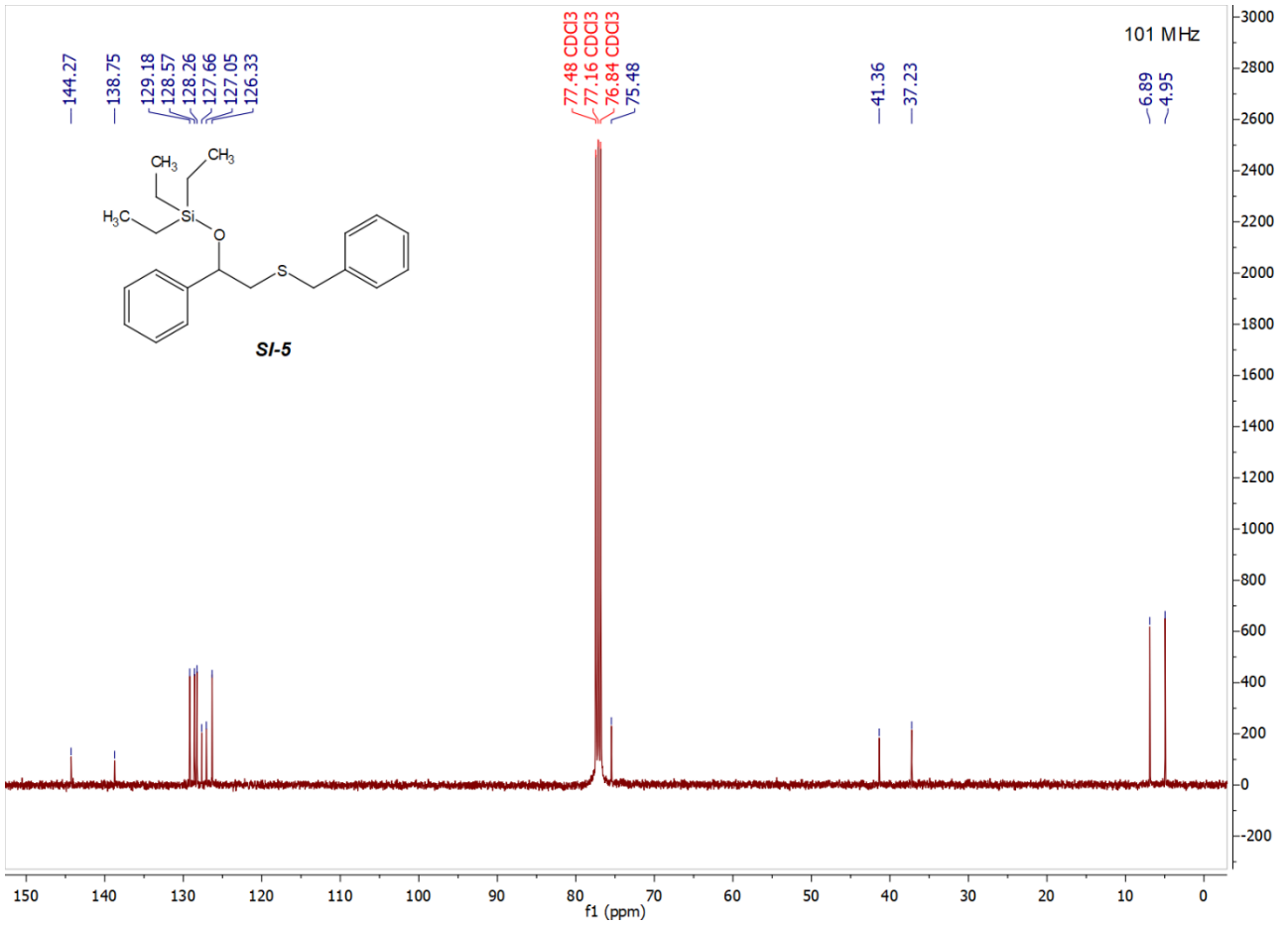

600 MHz
7.26 cdd3
5.90
5.89
5.88
5.88
5.87
5.86
5.86
5.85
5.84
5.83
5.18
5.18
5.15
5.15
5.07
5.06
5.05
5.05
4.85
4.84
4.83
3.29
3.27
3.26
3.25
3.24
3.23
3.22
1.82
1.81
1.80
1.78
1.77
1.76
1.75
1.74
1.73
1.71
1.70
1.47
1.46
1.45
1.43
1.42
1.41
1.00
0.99
0.97
0.93
0.92
0.91
0.69
0.68
0.66
0.65
CH3
CH3
H3C
Si
O
H3C
S
CH2
17b
1.00
1.05
1.06
1.01
2.12
2.29
2.17
8.74
3.10
5.96
f1 (ppm)

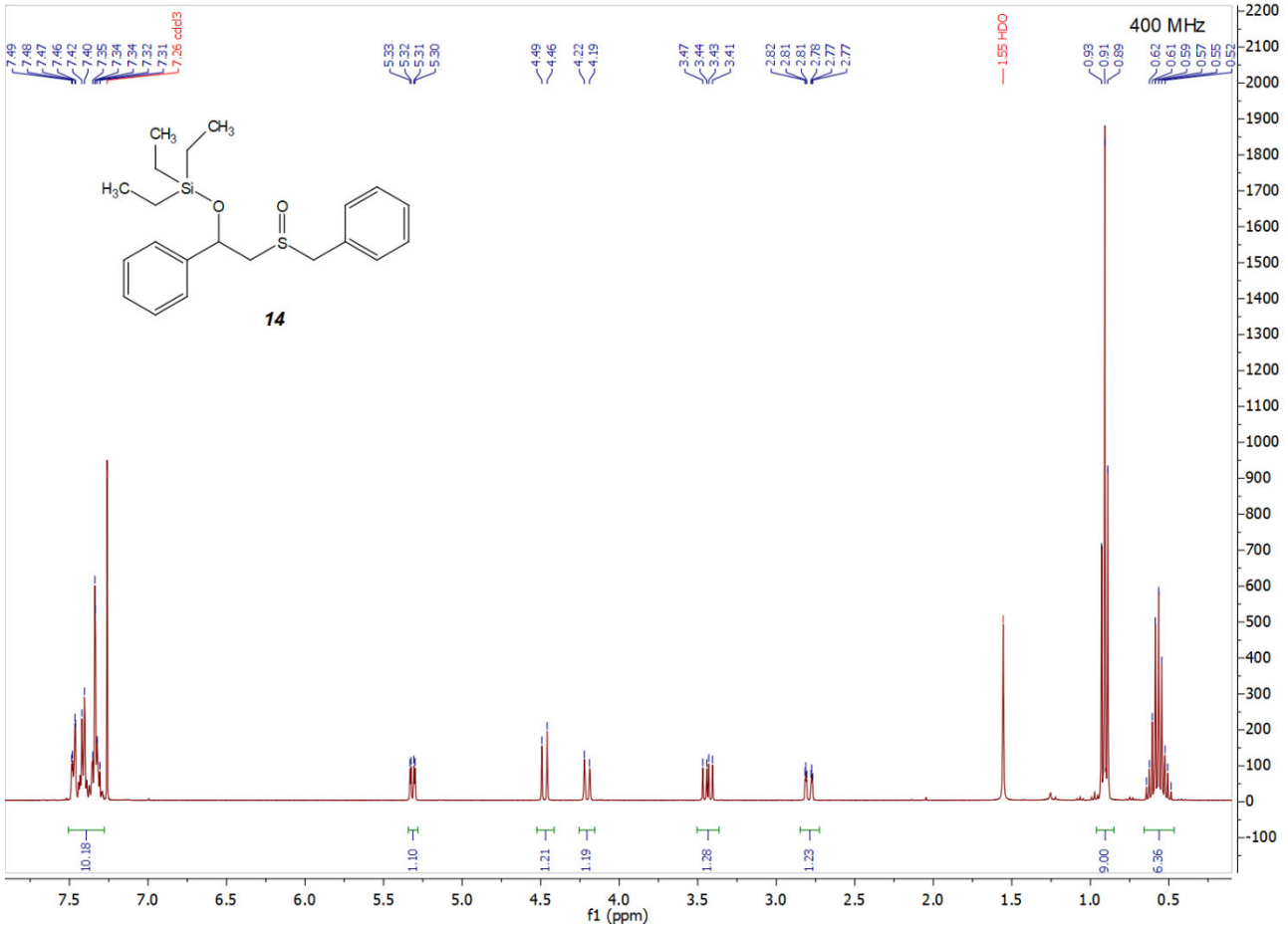

151 MHz
135.34
116.63
78.41
77.37 cdd3
77.16 cdd3
76.95 cdd3
41.48
31.66
19.52
13.88
6.97
5.30
CH3
CH3
H3C
Si
O
H3C
S
CH2
17b
f1 (ppm)

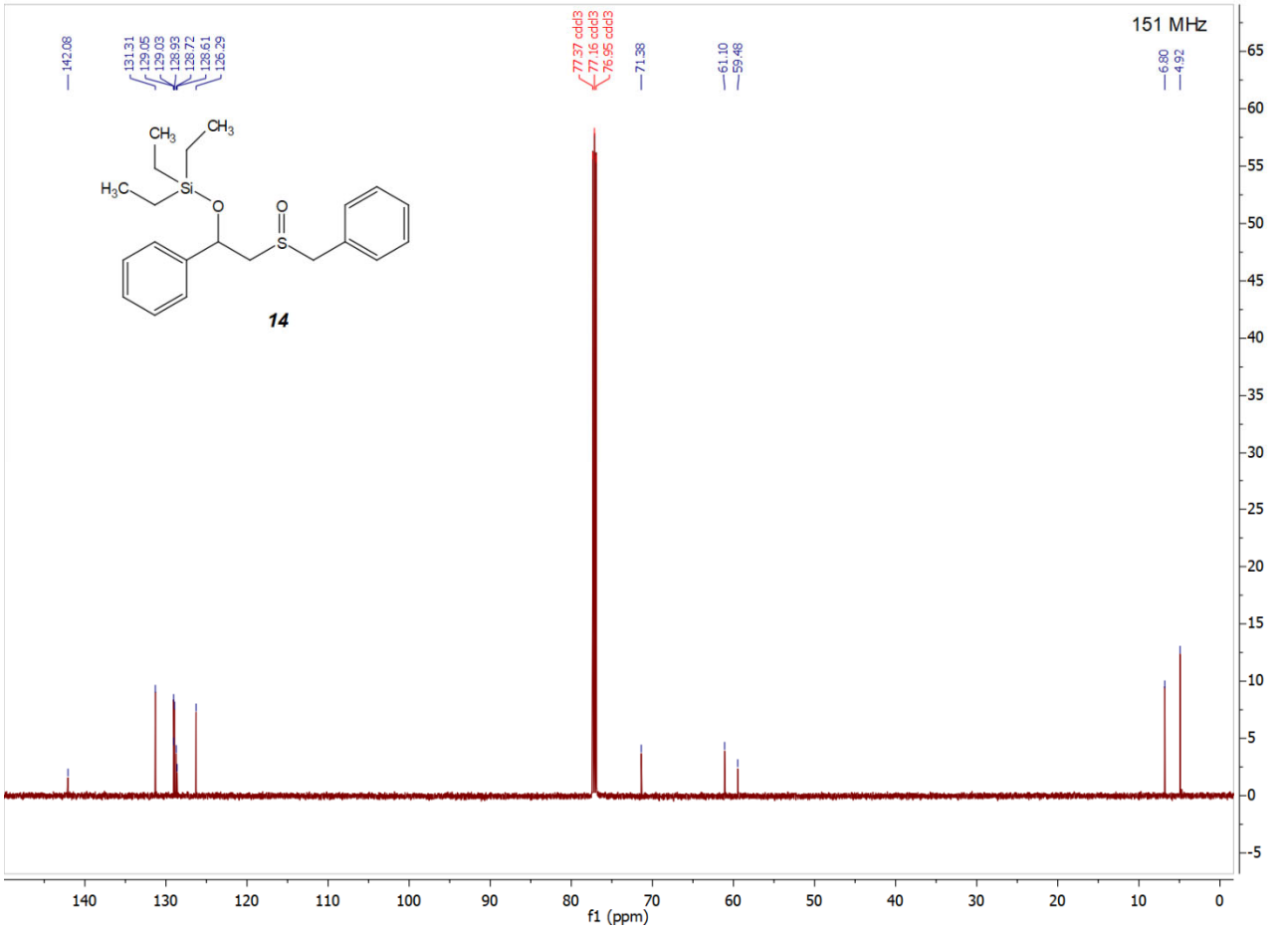

400 MHz
7.26 CDCl3
5.89
5.88
5.87
5.86
5.85
5.83
5.83
5.82
5.81
5.79
5.16
5.16
5.15
5.15
5.12
5.11
5.11
5.11
5.08
5.08
5.08
5.08
5.08
5.06
5.06
5.06
5.05
5.05
4.45
3.26
3.26
3.25
3.24
3.24
3.24
1.54 HDO
1.01
0.99
0.97
0.74
0.72
0.70
0.70
0.69
0.68
0.67
0.66
0.65
0.64
0.62
0.60
17c
1.00
1.01
0.99
0.99
2.01
18.24
6.15
f1 (ppm)

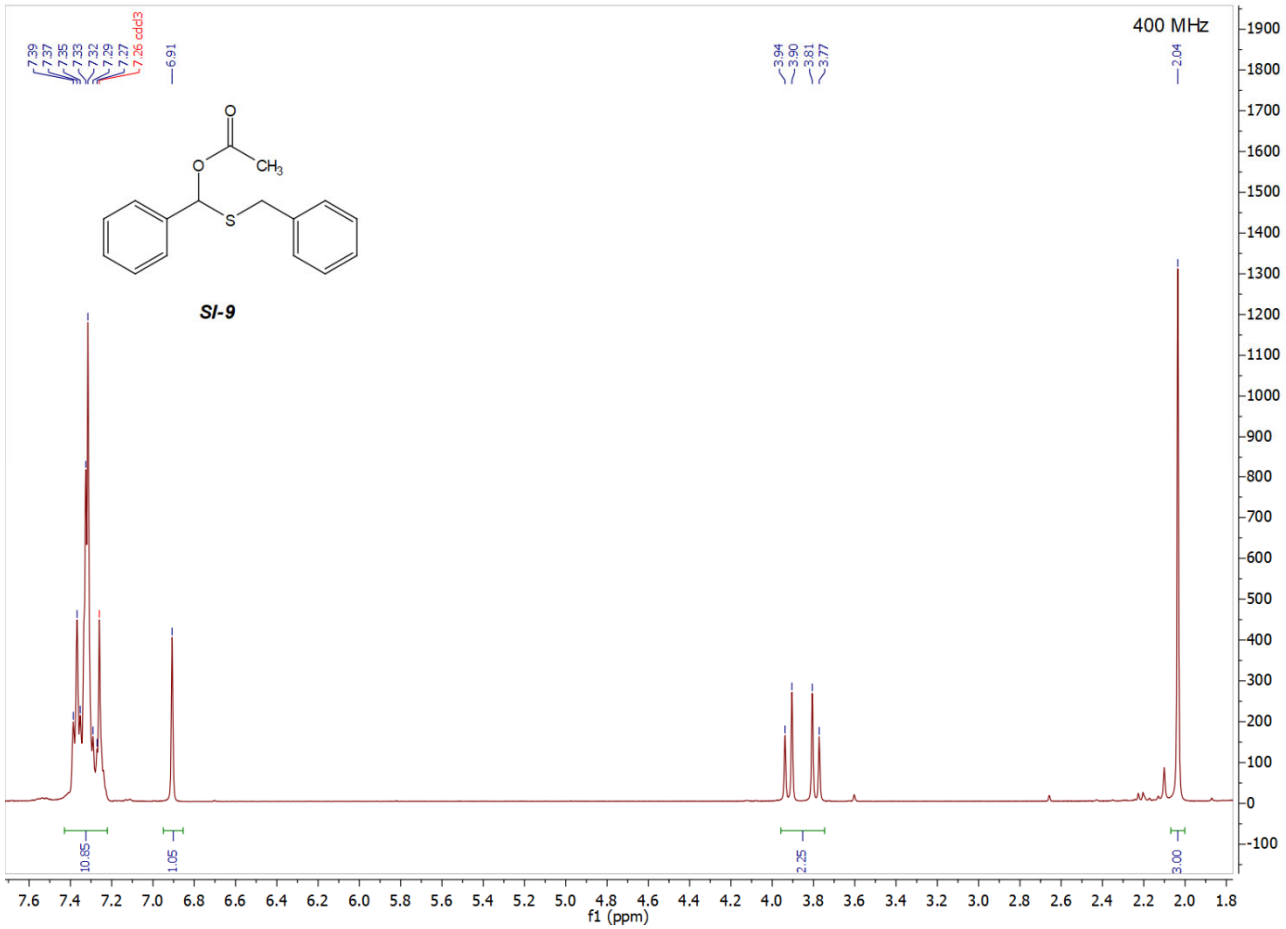

101 MHz
135.27
116.81
89.23
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
39.10
35.22
26.38
7.11
5.41
17c
f1 (ppm)

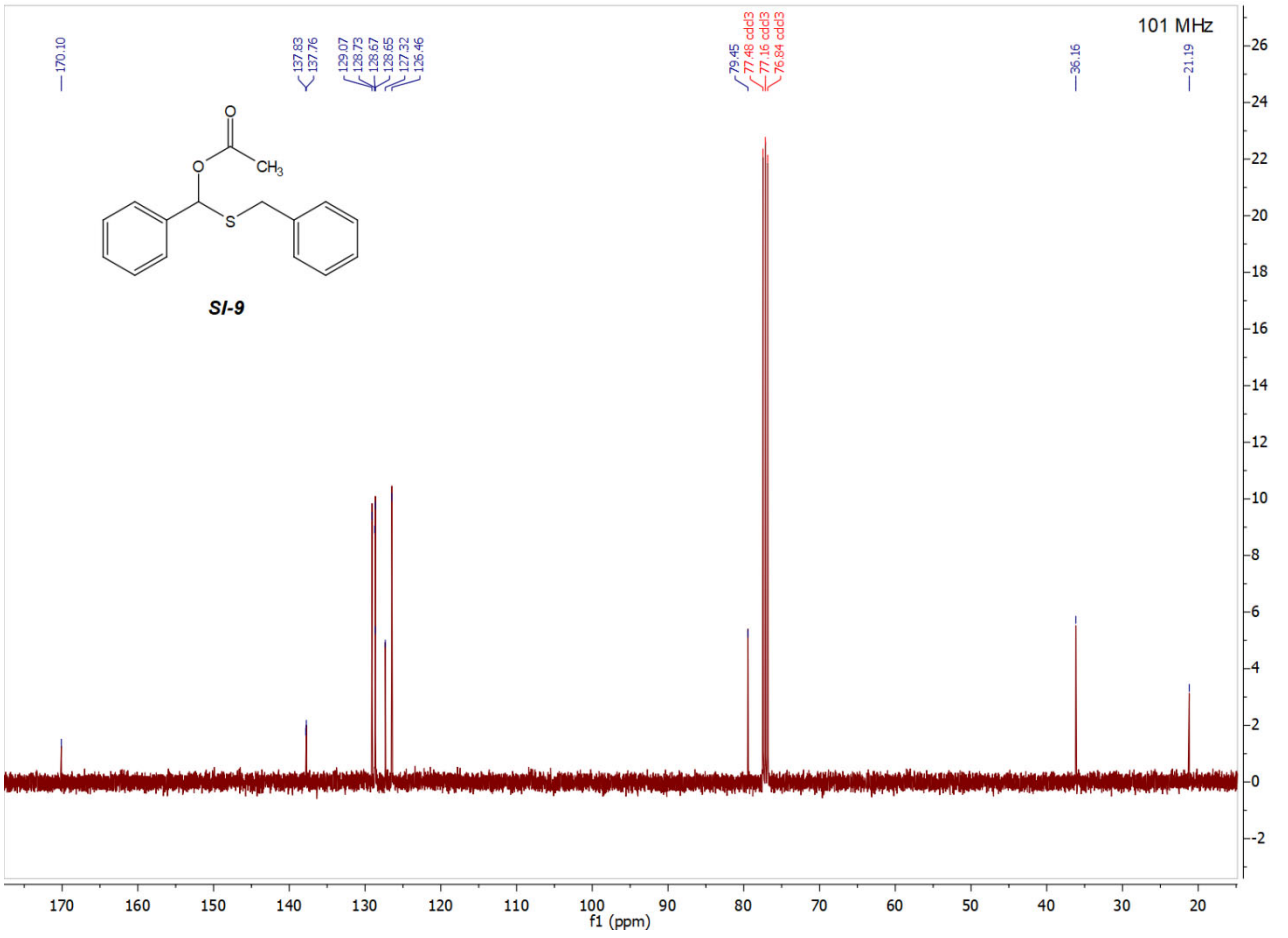

400 MHz
7.35
7.35
7.34
7.33
7.31
7.30
7.30
7.29
7.28
7.26 CDCl3
7.24
4.74
4.73
4.72
4.71
3.68
3.65
3.61
3.58
2.82
2.80
2.79
2.77
2.66
2.65
2.63
2.61
1.58 HDO
1.29
1.22
0.93
0.91
0.89
0.63
0.61
0.59
0.57
0.55
0.53
0.52
0.50
0.48
CH3
CH3
H3C
Si
O
S
SI-5
10.32
0.90
1.95
2.06
8.96
5.92
f1 (ppm)

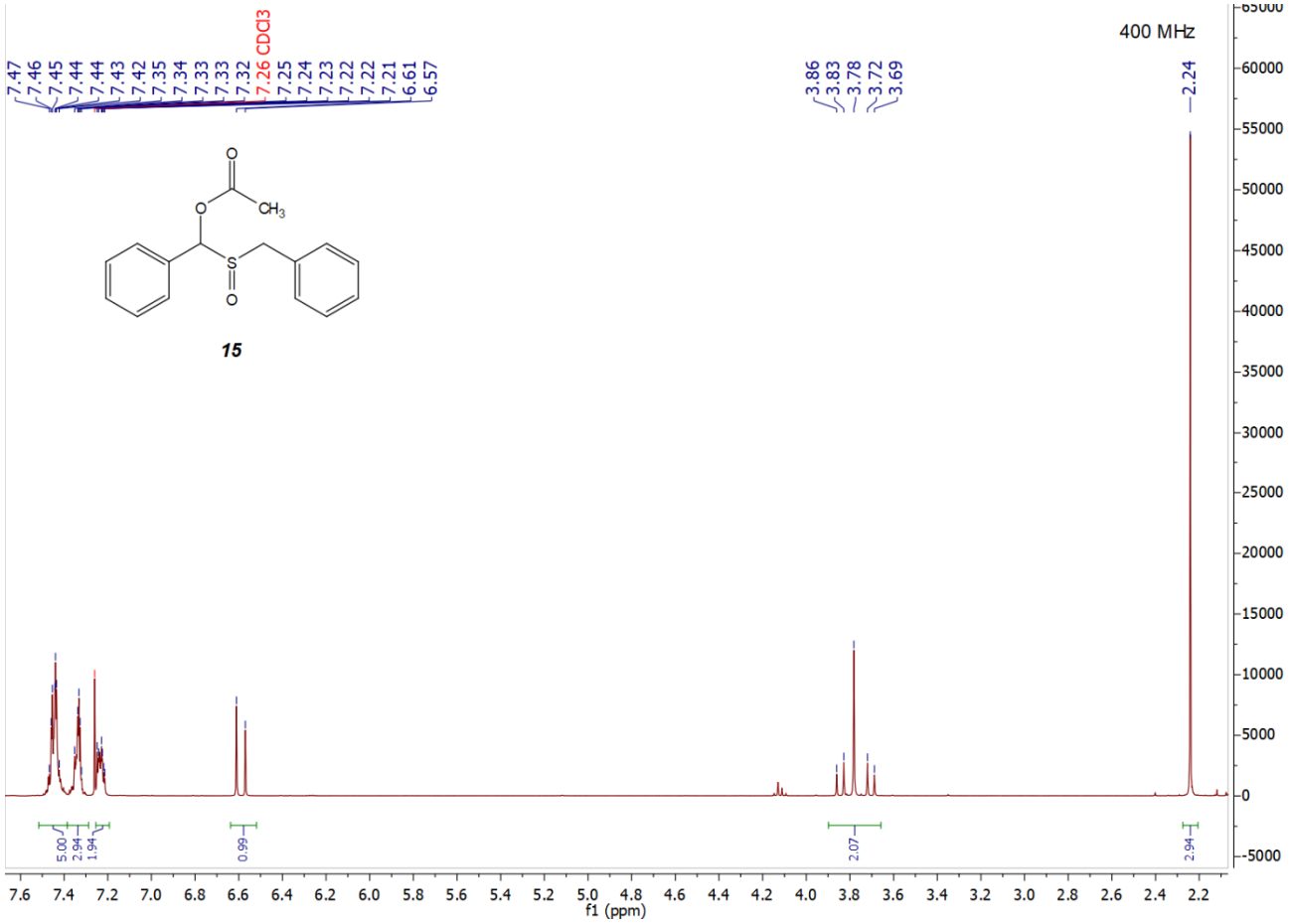

101 MHz
144.27
138.75
129.18
128.57
128.26
127.66
127.05
126.33
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
75.48
41.36
37.23
6.89
4.95
CH3
CH3
H3C
Si
O
S
SI-5
f1 (ppm)

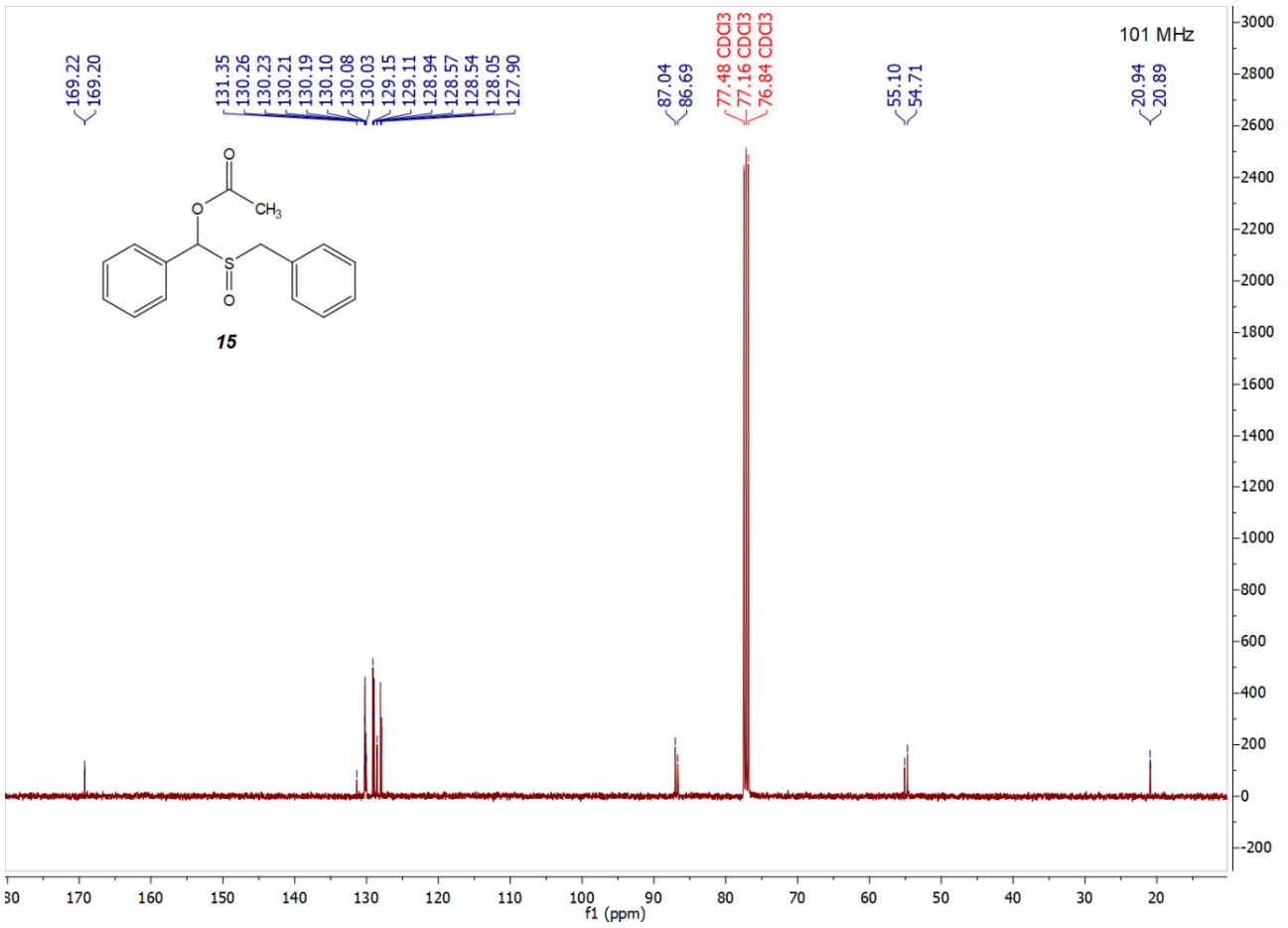

400 MHz
14
f1 (ppm)

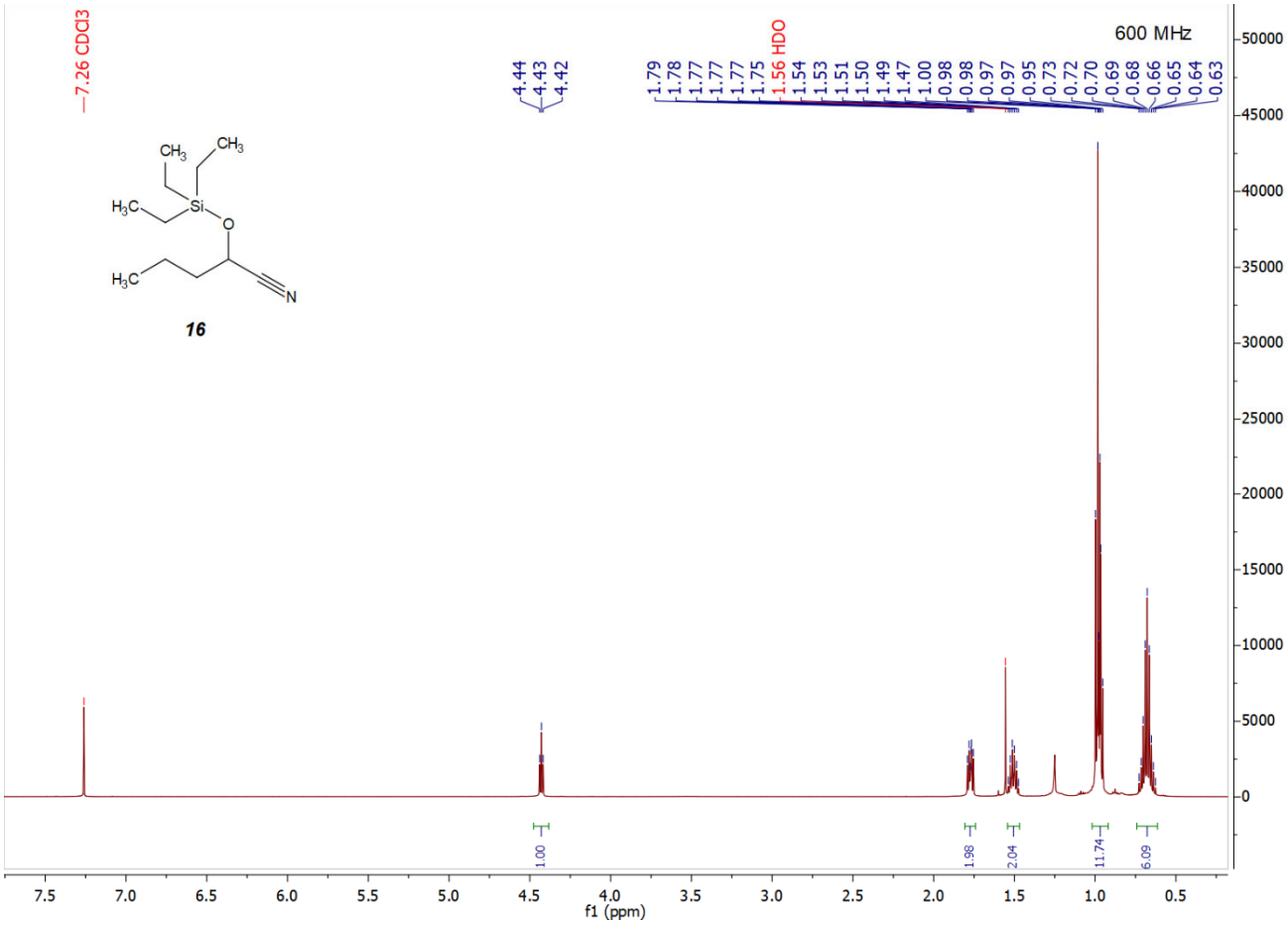

151 MHz
14
f1 (ppm)

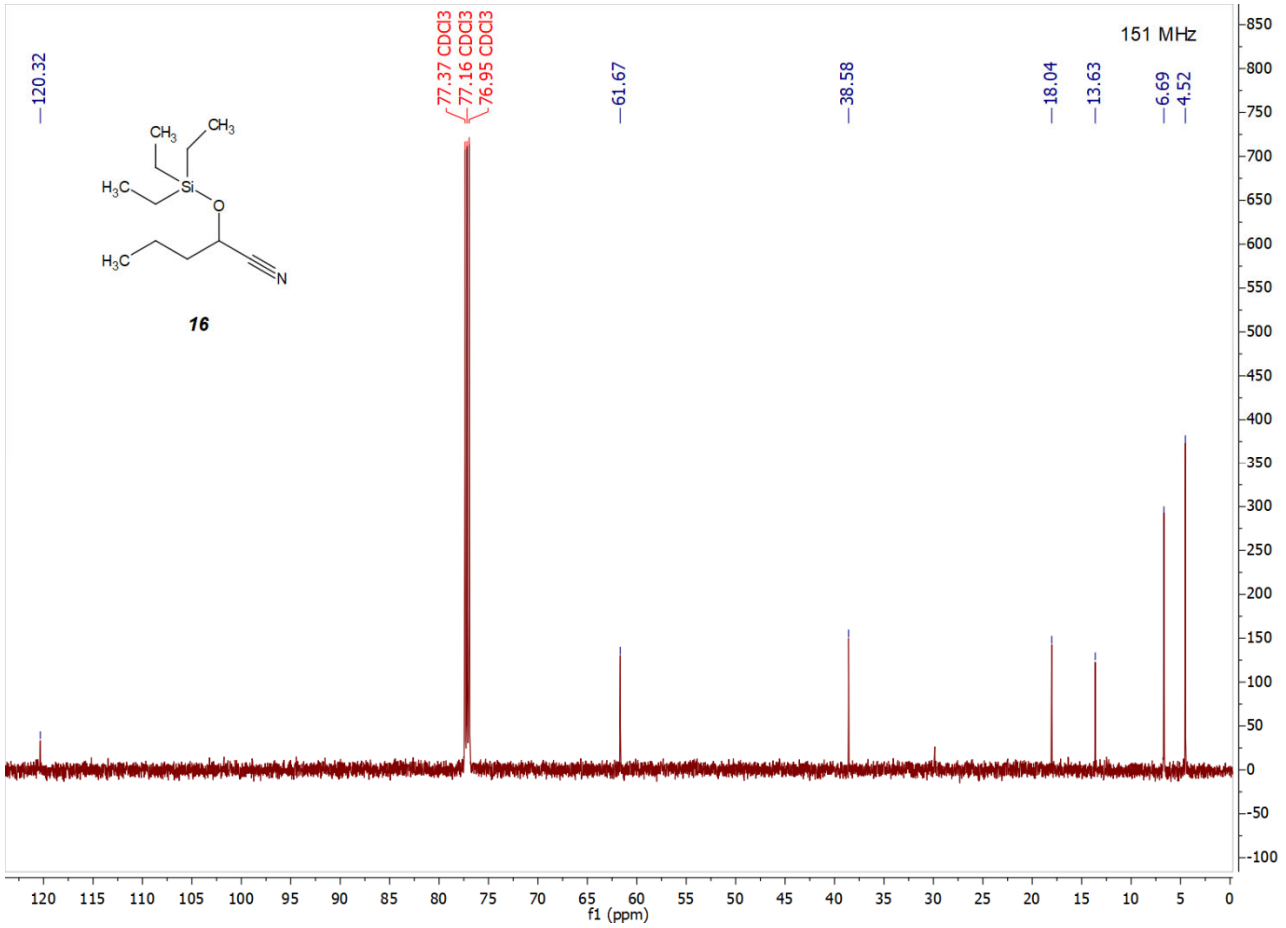

400 MHz
7.39
7.37
7.35
7.33
7.32
7.29
7.27
7.26 cdcl3
6.91
3.94
3.90
3.81
3.77
2.04
SI-9
10.85
1.05
2.25
3.00
f1 (ppm)

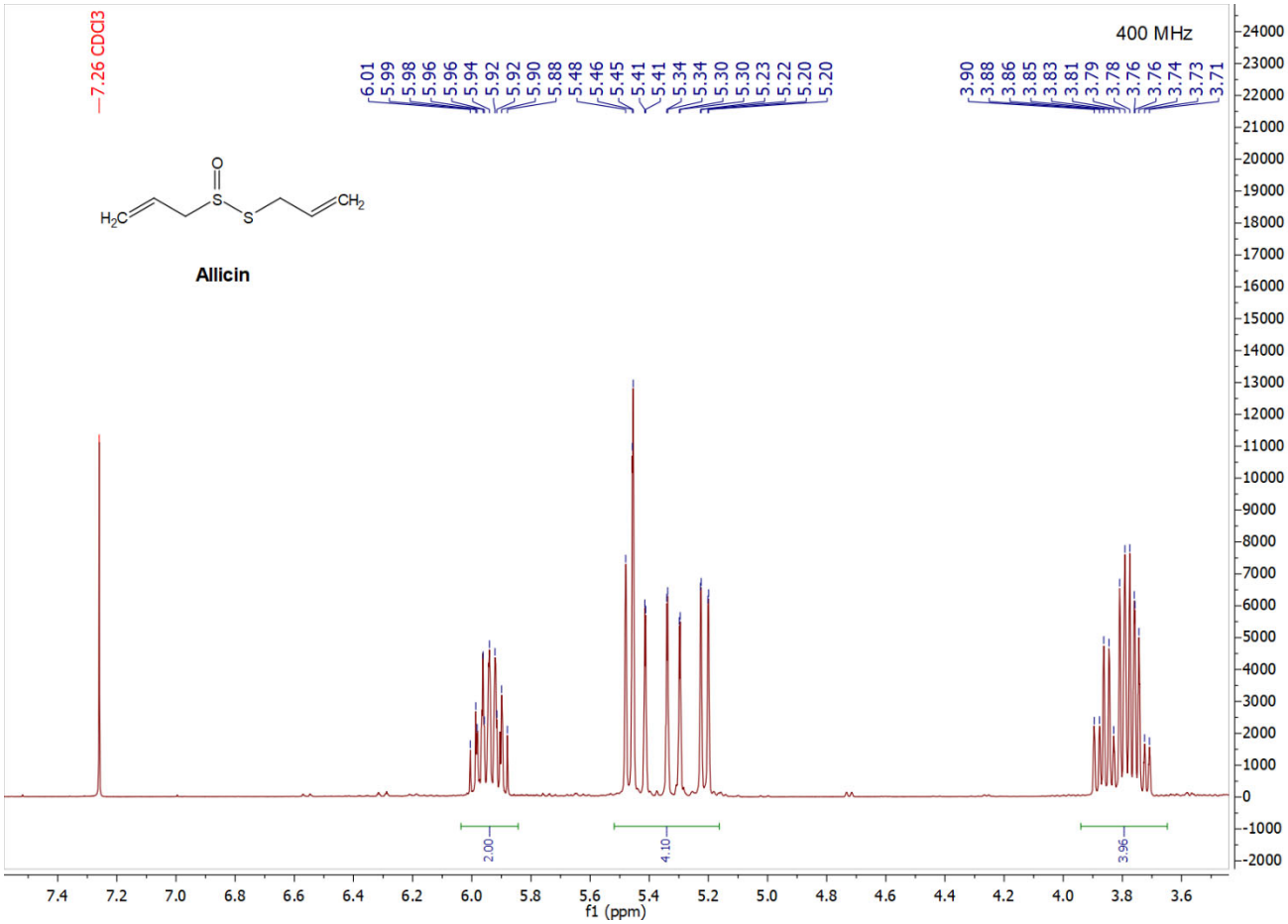

101 MHz
170.10
137.83
137.76
129.07
128.73
128.67
128.65
127.32
126.46
79.45
77.48 cdcl3
77.16 cdcl3
76.84 cdcl3
36.16
21.19
SI-9
f1 (ppm)


400 MHz
7.47
7.46
7.45
7.44
7.44
7.43
7.42
7.35
7.34
7.33
7.33
7.32
7.26 CDCl3
7.25
7.24
7.23
7.22
7.22
7.21
6.61
6.57
3.86
3.83
3.78
3.72
3.69
2.24
5.00
2.94
1.94
0.99
2.07
2.94
f1 (ppm)


101 MHz
169.22
169.20
131.35
130.26
130.23
130.21
130.19
130.10
130.08
130.03
129.15
129.11
128.94
128.57
128.54
128.05
127.90
87.04
86.69
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
55.10
54.71
20.94
20.89
f1 (ppm)


7.26 CDCl3
600 MHz
4.44
4.43
4.42
1.79
1.78
1.77
1.77
1.77
1.75
1.56 HDO
1.54
1.53
1.51
1.50
1.49
1.47
1.00
0.98
0.97
0.97
0.95
0.73
0.72
0.70
0.69
0.68
0.66
0.65
0.64
0.63
16
1.00
1.98
2.04
11.74
6.09
f1 (ppm)


120.32
77.37 CDCl3
77.16 CDCl3
76.95 CDCl3
61.67
38.58
18.04
13.63
6.69
4.52
151 MHz
16
f1 (ppm)


7.26 CDCl3
400 MHz
6.01
5.99
5.98
5.96
5.96
5.94
5.92
5.92
5.90
5.88
5.48
5.46
5.45
5.41
5.41
5.34
5.34
5.30
5.30
5.23
5.22
5.20
5.20
3.90
3.88
3.86
3.85
3.83
3.81
3.79
3.78
3.76
3.76
3.74
3.73
3.71
O
S
S
H2C
CH2
Allicin
2.00
4.10
3.96
f1 (ppm)