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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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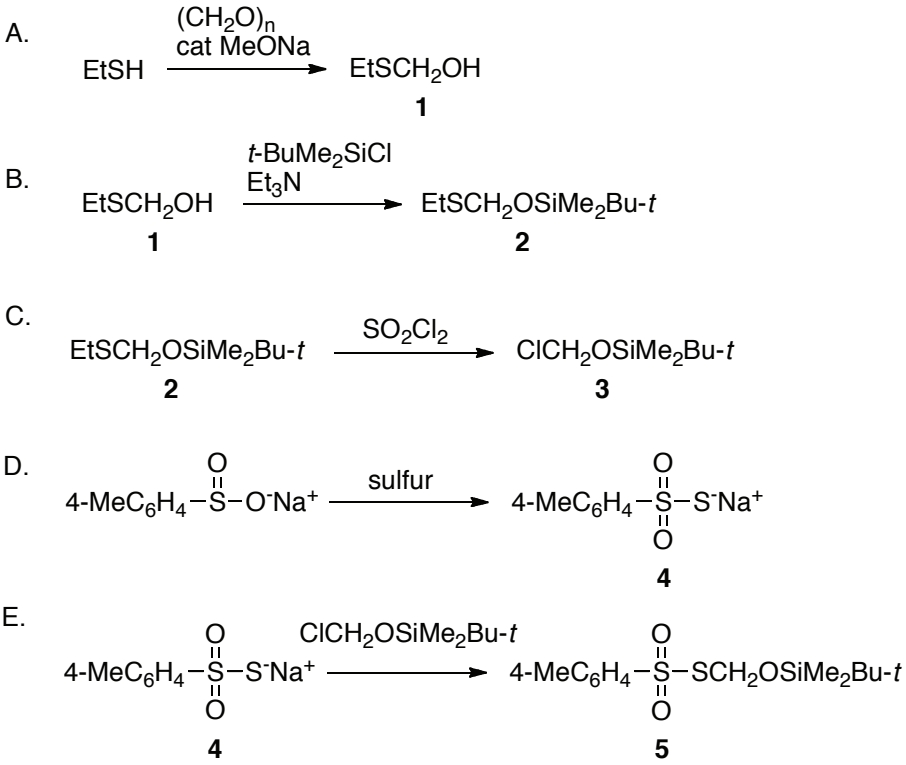
Reagent for Divalent Sulfur Protection: Preparation of 4-Methylbenzenesulfonothioic Acid, *S*-[[[(1,1-Dimethylethyl)-Dimethylsilyl]oxy]methyl] Ester



Submitted by Lihong Wang and Derrick L. J. Clive.[1]
Checked by David Hughes.

1. Procedure

Caution: Steps A and B must be conducted in an efficient fumehood.

A. *(Ethylthio)methanol (**1**).* An oven-dried 250-mL, 3-necked, round-bottomed flask equipped with a PTFE-coated magnetic stirring bar (3 x 1 cm) is fitted with a gas inlet adapter connected to a nitrogen line and a gas bubbler. The other two necks are capped with rubber septa; a thermocouple probe is inserted through one of the septa (Note 1). Paraformaldehyde (5.58 g, 0.186 mol, 1.07 equiv) (Notes 2 and 3) and ethanethiol (12.8 mL, 10.7 g, 0.173 mol, 1.0 equiv) (Note 4) are added to the flask. The mixture is stirred gently (avoid splashing) and cooled in an ice-water bath to 4 °C. A 25% solution of NaOMe in MeOH (0.07 mL, 0.002 equiv) is added through

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one of the septa via a 100 μL syringe over 1 min. The temperature rises to 33 °C over 3 min, then cools to 13 °C over 5 min. The solids completely dissolve (Note 5). The ice-water bath is removed and the solution is stirred at 13–16 °C for 15 min. The pale yellow *(ethylthio)methanol* (***1***) (Note 6) is used immediately in the next step (Note 7).

B. *(1,1-Dimethylethyl)[(ethylthio)methoxy]dimethylsilane* ***(2)***. Dichloromethane (Note 8) (120 mL) is added to the same flask containing neat (ethylthio)methanol from Step A. The stirred solution is cooled in an ice-water bath to 3 °C, then 4-(dimethylamino)pyridine (0.90 g, 7.4 mmol, 0.04 equiv) and triethylamine (21.9 g, 0.22 mol, 1.27 equiv) are added, followed by chloro(1,1-dimethylethyl)dimethylsilane (30.0 g, 0.20 mol, 1.18 equiv), added in 3 portions over 10 min (Note 9). The ice-water bath is replaced with a water bath and the reaction is stirred for 4 h (Note 10). The mixture is transferred to a 1-L separatory funnel using dichloromethane (60 mL) to rinse the flask. The organic layer is washed with water (2 x 100 mL) and saturated aqueous ammonium chloride (100 mL). The organic phase is filtered through a bed of sodium sulfate (50 g) in a medium porosity sintered glass funnel into a 1-L round-bottomed flask, using dichloromethane (2 x 50 mL) to rinse the filter cake. The solution is concentrated by rotary evaporation (70 mmHg, bath temperature 40 °C). The residue is diluted with hexanes (150 mL), transferred to a 1-L separatory funnel, and washed with water (2 x 200 mL) and brine (75 mL). The organic layer is filtered through a bed of sodium sulfate (50 g) in a medium porosity sintered glass funnel into a 500-mL round-bottomed flask, using hexanes (2 x 50 mL) to rinse the filter cake. The solution is concentrated by rotary evaporation (70 mmHg, bath temperature 40 °C) to afford crude **2** (38 g) as an oil. Vacuum distillation (Note 11) provides (1,1-dimethylethyl)[(ethylthio)methoxy]dimethylsilane (**2**) as a colorless liquid (28.0–28.6 g, 78–80 % yield over Steps A and B) (Notes 12 and 13).

> ***WARNING:*** *Chloromethyl ethers are potent carcinogens. The preparation and handling of compound* ***3*** *should be conducted at all times in a hood or ventilated balance enclosure.*

C. *(Chloromethoxy)(1,1-dimethylethyl)dimethylsilane* ***(3)***. An oven-dried 500-mL round-bottomed flask equipped with a PTFE-coated magnetic stirring bar (3 x 1 cm) is capped with a rubber septum pierced with a

nitrogen inlet needle connected to a gas bubbler. A thermocouple thermometer probe is also inserted through the septum (Note 1). (1,1-Dimethylethyl)[(ethylthio)methoxy]dimethylsilane (**2**) (12.1 g, 58.6 mmol, 1.00 equiv) and dichloromethane (120 mL) are added to the flask. The stirred solution is cooled to 2 °C using an ice-water bath. Sulfuryl chloride (8.14 g, 60.3 mmol, 1.03 equiv) (Note 14) is added via a 10 mL syringe over 10 min, keeping the temperature <5 °C. During the addition the reaction mixture turns yellow. After the addition, the ice-bath is removed and the solution is stirred for 20 min (Note 15). The stir bar is removed and the solution is concentrated by rotary evaporation (70 mmHg, bath temperature 40 °C) to afford crude **3** (12.4 g). Vacuum distillation provides (chloromethoxy)(1,1-dimethylethyl)dimethylsilane (**3**) as a slightly yellow liquid (8.41–8.66 g, 80–82 % yield) (Notes 16 and 17).

D. *4-Methylbenzenesulfonothioic acid, sodium salt* (**4**). Sodium *p*-toluenesulfinate monohydrate (Note 18) (25.4 g, 0.13 mol. 1.0 equiv), sulfur (4.54 g, 0.14 mol. 1.09 equiv), ethanol (100 mL) and water (100 mL) are added to a 500-mL round-bottomed flask equipped with a PTFE-coated magnetic stir bar (3 x 1 cm). The flask is lowered into a heating mantle and fitted with a Liebig condenser. The mixture is stirred and warmed to reflux for 8 h (Note 19). After the reaction mixture is cooled to room temperature, the residual sulfur is removed by filtration through a 60-mL medium porosity sintered glass funnel into a 1-L round bottom flask, using water (2 x 20 mL) to wash the reaction flask and the collected solid. The filtrate is concentrated by rotary evaporation (50 °C water bath, 70 mmHg) to wet solids (49 g). The flask is equipped with a PTFE stir bar (3 x 1 cm) and water (40 mL) is added. The slightly hazy mixture is stirred at room temperature for 3 h. The solution, which contains some suspended particles, is filtered into a 500-mL round bottomed flask through pad of pre-wetted Celite (3 g) (Note 20) in a 40-mL medium porosity sintered glass funnel, the flask and Celite pad being rinsed with water (4 x 10 mL). The clear filtrate is concentrated by rotary evaporation (50 °C water bath, 70 mmHg) to provide a wet solid (32 g) (Note 21). The flask is equipped with a PTFE stir bar (3 x 1 cm) and a Liebig condenser. Absolute ethanol (80 mL) is added and the heterogeneous mixture is stirred and warmed to reflux over a 30 min period using a heating mantle. Once the mixture reaches reflux, the heating mantle is removed and the mixture is cooled in air to room temperature over the course of 1 h, then is stirred at room temperature for 3 h. The resulting white solid is collected on a 150-mL medium porosity sintered glass funnel, portions of the filtrate being used to rinse all solids out of the flask. The

filter cake is washed with absolute ethanol (25 mL), air-dried in the funnel by continued suction (ca 1 h) and then dried for 9 h in a vacuum oven (70 mmHg, 50 °C) to afford 4-methylbenzenesulfonothioic acid, sodium salt (22.4–23.4 g, 82–86 %) (Note 22).

E. *4-Methylbenzenesulfonothioic acid, S-[[[(1,1-dimethylethyl)-dimethylsilyl]oxy]methyl] ester* (**5**). An oven-dried 250-mL round-bottomed flask equipped with a PTFE-coated magnetic stirring bar (3 x 1 cm) is capped with a rubber septum pierced with a nitrogen inlet needle connected to a gas bubbler. A thermocouple thermometer probe is also inserted through the septum (Note 1). The septum is removed momentarily and 4-methylbenzenesulfonothioic acid, sodium salt (**4**) (5.97 g, 28.4 mmol, 1.03 equiv) and acetonitrile (35 mL) (Note 23) are added and the suspension is stirred. (Chloromethoxy)(1,1-dimethylethyl)dimethylsilane (**3**) (4.96 g, 27.4 mmol, 1.00 equiv) is added via a 10-mL syringe over 1 min (Note 24). The mixture is stirred vigorously for 4 h (Note 25), then the septum is replaced with a 200-mL addition funnel and *t*-butyl methyl ether (140 mL) is added dropwise to the stirred mixture over 15 min. The mixture is filtered through a tightly packed pad of Celite (4 cm in diameter x 2.5 cm in height) (Note 26) in a 40-mL sintered glass funnel into a pre-weighed 500-mL round-bottomed flask, using MTBE (3 x 10 mL) as a rinse of the flask and filter cake. The filtrate is concentrated by rotary evaporation (40 °C bath, 70 mmHg) and dried for 3 h at ambient temperature (70 mmHg) to give *4-methylbenzenesulfonothioic acid, S-[[[(1,1-dimethyl-ethyl)dimethylsilyl]-oxy]methyl] ester* (**5**) as a colorless, viscous oil (9.06 g, 99 %) (Notes 27, 28, and 29).

2. Notes

1. The internal temperature was monitored using a J-Kem Gemini digital thermometer with a Teflon-coated T-Type thermocouple probe (12-inch length, 1/8 inch outer diameter, temperature range –200 to +250 °C). The submitters did not monitor the internal temperature in any of the procedure's steps A-E.

2. The following reagents and solvents were obtained from Sigma-Aldrich and used as received for Step A: paraformaldehyde (powder, 95%), ethanethiol (97%), sodium methoxide (25% wt % solution in MeOH).

3. Paraformaldehyde is added in slight excess with the intention to consume all ethanethiol during the reaction to minimize odors.

4. Ethanethiol was transferred to the flask via a 10 mL graduated glass pipette (2 transfers). After transfer, the pipette was immediately rinsed with bleach.

5. If a portion of the mixture has splashed onto the walls of the flask, the material should be rinsed down by gentle swirling.

6. (Ethylthio)methanol (**1**) has the following physical and spectroscopic properties: FTIR (microscope) υ (cm^{-1}): 3395 br, 2968, 2928, 2873, 1453 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 1.32 (t, J = 7.4 Hz, 3 H), 1.82 (br s, 1 H), 2.73 (q, J = 7.4 Hz, 2 H), 4.74 (s, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 15.2, 24.8, 65.8. Low resolution EI m/z calcd for C_3H_8OS 92, found 92. The submitters determined a purity of 91% by GC/MS (Agilent Technologies 7890 GC with 5975C mass spectrometer; column ZEBRON ZB-5, length 30 m, ID 0.25 mm; film thickness 0.25 μm; initial temperature 35 °C for 2 min, final temperature 290 °C for 2 min; rate of temperature increase 10 °C/min; helium gas; flow 0.6636 mL/min; inlet temperature 200 °C; 50:1 split injection); and 83% by NMR. The checker determined a purity of approximately 85% by ^1H NMR.

7. To minimize odors, it is recommended that the material produced in step A be used directly in Step B using the same flask.

8. The following reagents and solvents were used as received for Step B: dichloromethane (Fisher ACS certified, stabilized), chloro(1,1-dimethylethyl)dimethylsilane (Oakwood Products, Inc., West Columbia, SC), triethylamine (Sigma-Aldrich, 99.5% distilled), hexanes (Fisher, ACS reagent, >98.5%).

9. The temperature rises to 10 °C after the addition.

10. The reaction was monitored by ^1H NMR. A 0.1 mL aliquot of the reaction mixture was quenched into 1 mL $CDCl_3$/1 mL sat. aq. NH_4Cl. The layers were separated, then the $CDCl_3$ layer was concentrated to dryness. The concentrated sample was diluted with $CDCl_3$ for ^1H NMR analysis. Diagnostic peaks: product **2**, δ 4.82 (s, 2H, CH_2); starting material **1**, δ 4.74 (s, 2H, CH_2). Approx 1.5 % unreacted **1** remained at the 3 h sampling point.

11. The checker carried out the distillation in a 100-mL pear-shaped flask equipped with a 1-cm oval PTFE stir bar using a 3-cm Vigreaux column at a pressure of 70 mmHg. Three fractions were collected: fr 1, 80 - 120 °C (2.2 g); fr 2, 125-128 °C (28.6 g); and fr 3, 128-134 °C (3.2g). The pot residue was 1.7 g. By GC analysis (conditions in Note 12), fraction 2 was >98 % pure and fraction 3 was 85 - 90% pure. The yield was based on fraction 2. The submitters carried out the distillation at 4.8 mmHg, 58.5 – 61 °C.

12. *(1,1-Dimethylethyl)[(ethylthio)methoxy]dimethylsilane (**2**)* has the following physical and spectroscopic properties: FTIR (microscope) υ (cm^{-1}): 2957, 2930, 2897, 2858, 1472, 1463 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.13 (s, 6 H), 0.91 (s, 9 H), 1.30 (t, J = 7.4 Hz, 3 H), 2.68 (q, J = 7.4 Hz, 2 H), 4.82 (s, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: –4.8, 15.1, 18.4, 24.8, 26.0, 66.2. GC-MS *m/z* (relative intensity), 149 (92%, M^+ - *t*-Bu), 119 (100%, M^+ – *t*-$BuMe_2$), 91(40%), 89 (61%), 75 (43%), 73 (63%). Purity = 98 % by GC (t_R = 7.5 min; conditions: Agilent DB35MS column; 30 m x 0.25 mm; initial temp 60 °C, ramp at 20 °C/min to 280 °C, hold 15 min).

13. The submitters report the compound is stable at room temperature for at least 1 month when kept in a stoppered flask.

14. The following reagents and solvents were used as received for Step C: dichloromethane (Fisher ACS certified, stabilized,), sulfuryl chloride (Acros, 97%).

15. The temperature rose to 12 °C.

16. The distillation was carried out in a 50-mL pear-shaped flask containing a PTFE-coated oval magnetic stir bar (1 cm) using a 3-cm Vigreaux column at a pressure of 70 mmHg. Three fractions were collected: fr 1, 30–83 °C (1.18 g); fr 2, 83–87 °C (6.89 g); fr 3, 87–88 °C (1.52 g). GC purity (Note 12) was 96.5% for fraction 2 and 94.5% for fraction 3. Fractions 2 and 3 were combined. The submitters reported distillation at 70.0–72.5 °C (26 mmHg).

17. *(Chloromethoxy)(1,1-dimethylethyl)dimethylsilane (**3**)* has the following physical and spectroscopic properties: FTIR (neat film, microscope) υ (cm^{-1}): 2958, 2932, 2901, 2860, 1473, 1464 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.21 (s, 6 H), 0.92 (s, 9 H), 5.61 (s, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: –5.0, 18.0, 25.7, 76.6. GC-MS *m/z* (relative intensity), 125 (9 %, M^+ - *t*-Bu) 123 (24%, M^+ - *t*-Bu), 95 (35 %, M^+ – *t*-$BuMe_2$), 93 (100 %, M^+ – *t*-$BuMe_2$), 73 (25%), 57 (45%). Purity = 96 % by GC (t_R = 5.5 min, conditions in Note 12). The checkers noted the compound decomposes at a rate of 15% per week at room temperature when stored in a glass flask with a glass stopper based on ^1H NMR analysis. In the refrigerator, a small amount of decomposition (2-3%) occurred over a two-week period. When stored in the freezer, no decomposition occurred over a two-week period.

18. The following reagents and solvents were used as received for Step D: *p*-toluenesulfinate hydrate (Acros, 98%), sulfur (Fisher, sublimed powder, ethanol (Sigma-Aldrich, 99.5%), Celite (Sigma-Aldrich, acid-washed).

19. Reaction progress was monitored by ^{1}H NMR as follows. A 0.1 mL reaction aliquot was evaporated to dryness then dissolved in DMSO-d_6. Diagnostic resonances were δ 7.14–7.15 (m, 2 H), 7.61–7.63 (m, 2 H) for product **4** and 7.35–7.37 (m, 2H) for *p*-$TsSO_2Na$. Approximately 1% *p*-$TsSO_2Na$ remained at the 7 h timepoint.

20. The Celite was pre-wetted by filtering 20-mL water through the Celite cake. The hazy filtrate was discarded and the receiving flask rinsed with water prior to filtering the reaction mixture.

21. The crude material contains 3% sodium *p*-toluenesulfinate based on ^{1}H NMR analysis.

22. *4-Methylbenzenesulfonothioic acid, sodium salt* (**4**) has the following physical and spectroscopic properties: IR (KBr) υ (cm^{-1}): 3039, 3023, 2981, 2920, 2861, 1934, 1664, 1596, 1494, 1398 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.30 (s, 3 H), 7.14–7.15 (m, 2 H), 7.61–7.63 (m, 2 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 20.7, 124.0, 128.0, 138.2, 152.6; exact mass (electrospray) *m*/*z* calcd for $C_7H_7O_2S_2$ (M-Na) 186.9893, found 186.9895. The material contained 0.2 wt% water based on Karl Fischer titration. Weight percent purities of 94% and 97% (2 runs) were determined based on quantitative ^{1}H NMR analysis (DMSO-d_6) using dichloroethane as internal standard, based on 2 weighings (samples 30-60 mg each), 4 acquisitions using a pulse delay of 10 seconds, and 8 independent peak integrations. The material with 94 wt% purity was purified by slurrying as follows: Compound **4** (22.6 g) and 95% ethanol (80 mL) were added to a 500-mL round bottomed flask equipped with a PTFE oval-stir bar (3 x 1 cm). The stirred mixture was heated to reflux (remains a slurry) with a heating mantle, then cooled in air with stirring to ambient temperature over 1 h and stirred for an additional 3 h. The material was filtered into a 60-mL sintered glass funnel, washed with absolute ethanol (25 mL), and dried under vacuum (70 mmHg, 50 °C) to afford product (17.9 g, 79% recovery). NMR quantitative assay indicated 98 wt% purity.

23. The following reagents and solvents were used as received for Step E: acetonitrile (Fisher Optima, water content 0.001%), *t*-butyl methyl ether (>98.5%, Sigma-Aldrich), Celite (Sigma-Aldrich, acid-washed).

24. The reaction warms to 27 °C over 10 min, then cools slowly to room temperature over 30 min.

25. The reaction remains heterogeneous throughout. The reaction was monitored by ^{1}H NMR as follows. A 0.1 mL reaction aliquot was added to 1 mL MTBE, filtered, and concentrated to dryness. The sample was dissolved in $CDCl_3$ for analysis. Diagnostic peaks were δ 5.61 (s, 2H) for

unreacted **3** and 5.41 (s, 2H) for product **5**. Less than 1% starting material remained at the 3 h timepoint.

26. The Celite was pre-wetted by filtering 20-mL MTBE through the Celite cake. The filtrate was discarded and the receiving flask rinsed with MTBE prior to filtering the reaction mixture. The submitters used diethyl ether in this experiment instead of MTBE.

27. *4-Methylbenzenesulfonothioic acid, S-[[[(1,1-dimethylethyl)-dimethylsilyl]oxy]methyl] ester* (**5**) has the following physical and spectroscopic properties: mp 33–34 °C (MTBE/hexanes); FTIR (dichloromethane cast film) υ (cm^{-1}): 2955, 2930, 2886, 2858, 1595, 1493, 1472, 1464, 1444 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: –0.03 (s, 6 H); 0.76 (s, 9 H), 2.42 (s, 3 H), 5.41 (s, 2 H), 7.27–7.32 (m, 2 H), 7.84–7.86 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: –5.3, 18.1, 21.8, 25.6, 71.5, 127.3, 129.8, 144.0, 144.6; exact mass (electrospray) *m/z* calcd for $C_{14}H_{24}NaO_3S_2Si$ 355.0828, found 355.0824; GC-MS *m/z* (relative intensity), 275 (6%, M^+ - *t*-Bu), 245 (59%, M^+ – *t*-BuMe_2), 91 (39%), 75 (100%), 73 (30%). Anal. calcd. for $C_{14}H_{24}O_3S_2Si$: C, 50.56; H, 7.27; S, 19.28; found C, 50.44; H, 6.83; S, 19.61. Weight percent purities of 87% and 90% (2 runs) were determined based on quantitative ^{1}H NMR analysis ($CDCl_3$) using dichloroethane as internal standard, as outlined in note 22.

28. A purified sample of **5** was obtained by crystallization as follows: Compound **5** (7.1 g) was dissolved in MTBE (10 mL). Residual solids were removed by filtration through a 0.45 μm PTFE syringe filter (25 mm, Millipore catalog # SLCR025NS) into a 100-mL round-bottomed flask. Hexanes (20 mL) were added and the solution was held in a –20 °C freezer for 20 h. (Obtaining crystals for the first time at small scale required 6 days in the freezer; thereafter, crystallization typically initiated within a few hours). The product was isolated by filtration on a 40-mL sintered glass funnel, using MTBE/hexanes (1:1) (5 mL, –20 °C) as a wash, to provide colorless cubic crystals (4.1 g 59% recovery). Weight percent purities of 97% and 98 % (2 runs) were determined based on quantitative ^{1}H NMR analysis ($CDCl_3$) using dichloroethane as internal standard, as outlined in note 22.

29. The submitters report the compound decomposes on silica gel and on neutral Grade III alumina. The compound has been kept without change (^{1}H NMR) at room temperature for 1 week and is stable in the freezer for at least 2 months.

Handling and Disposal of Hazardous Chemicals

The procedures in this article are intended for use only by persons with prior training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011 www.nap.edu). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In the development and checking of these procedures, every effort has been made to identify and minimize potentially hazardous steps. The Editors believe that the procedures described in this article can be carried out with minimal risk if performed with the materials and equipment specified, and in careful accordance with the instructions provided. However, these procedures must be conducted at one's own risk. *Organic Syntheses, Inc*., its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

3. Discussion

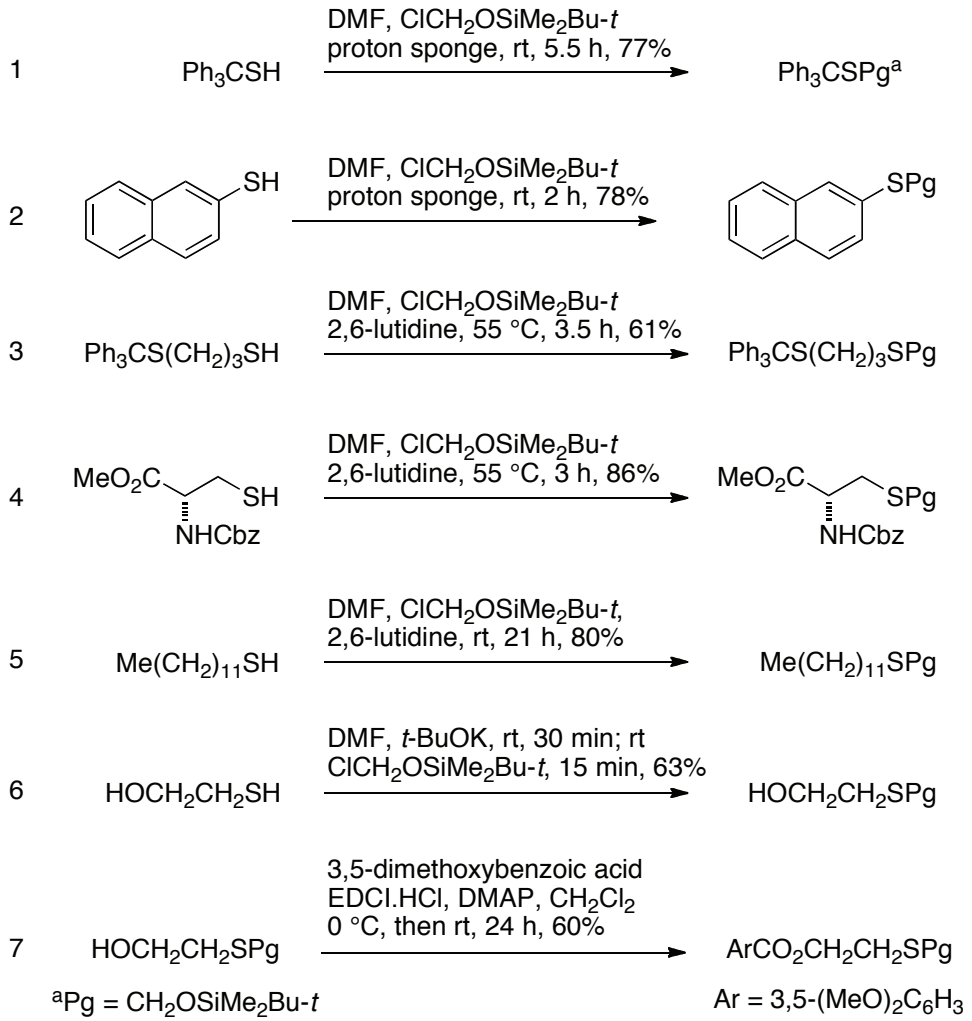
During the course of synthetic studies directed towards the antitumor agent MPC1001,[2] a need arose for a protected bivalent sulfur unit so constituted that it could be introduced by reaction with a carbanion and later dismantled to release a sulfhydryl group under mild conditions. Although numerous sulfur protecting groups are known,[3] our precise requirements prompted us to investigate the CH_2OSiMe_2Bu-*t* group for sulfur protection and the reagent 4-$MeC_6H_4SO_2$-SCH_2OSiMe_2Bu-*t* (**5**) for introducing sulfur protected in this manner.[4] Other sulfonothioic acid esters such as $PhSO_2$-SPh have been used for sulfenylation of carbanions,[5] and the use of a silyl group offered the possibility of controlling the deprotection conditions by changing the substituents on silicon.[6] Although chloromethoxysilanes have been used for protection of alcohols,[7] they do not appear to have been used for sulfur protection.

A direct method for preparing reagent (**5**) appeared to be by way of reaction E above, and so we prepared the two components, salt (**4**) and the chloromethoxysilane (**3**). Both were made by the literature methods[8,9] which

are described in detail here. Reaction of the salt with silane (**3**) afforded the desired sulfenylating agent (**5**).

In order to test if the CH_2OSiMe_2Bu-*t* group could indeed serve as an effective form of protection for bivalent sulfur, we treated a number of simple thiols with reagent (**3**) so as to generate the sulfides shown in Table 1.[4] DMF is a satisfactory solvent and proton sponge or 2,6-lutidine gave the best results, depending on the particular case.

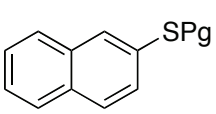
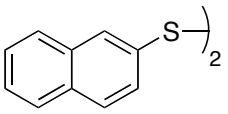
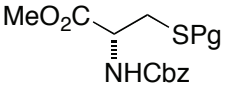
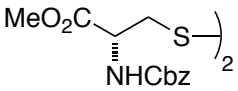
Table 1. Protection of thiols



Several methods for deprotection of the sulfides were examined (Table 2).[4] Treatment with Bu_4NF in THF; Bu_4NF and AcOH in THF, or HF.pyridine in THF were all suitable, and it was usually convenient to oxidize the thiols in situ by addition of iodine. In a few cases the protecting group was removed by reaction with a sulfenyl halide (2-nitro-

benzenesulfenyl chloride, α,α-diphenylbenzenemethanesulfenyl chloride, benzenemethanesulfenyl chloride).

Table 2. Deprotection

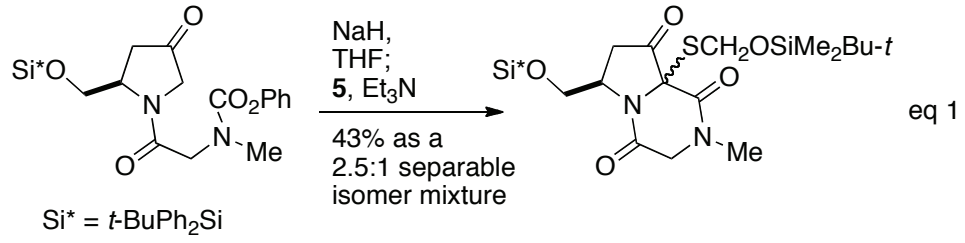
1	Ph_3CSPg[a]	Bu_4NF, THF, -78 °C, 15 min; to -10 °C (ca. 3 min), 68%	Ph_3CSH
2		Bu_4NF, THF, rt, 20 min; I_2, $CDCl_3$, rt, 30 min, 89%	
3	$Ph_3CS(CH_2)_3SPg$	Bu_4NF, AcOH, THF, rt, 40 min; Et_3N, I_2, rt, 3 min, 53%	$Ph_3CS(CH_2)_3S)_2$
4		HF-pyr, THF, rt, 60 min; I_2, rt, 60, 87%	
5	$Me(CH_2)_{11}SPg$	HF-pyr, THF, rt, 50 min; I_2, rt, 12 h, 89%	$Me(CH_2)_{11}S)_2$
6	$ArCO_2CH_2CH_2SPg$ Ar = 3,5-$(MeO)_2C_6H_4$	HF-pyr, THF, rt, 6 h; I_2, rt, 1 min, 91%	$ArCO_2CH_2CH_2S)_2$
7	$Me(CH_2)_{11}SPg$	2-$(O_2N)C_6H_4SCl$, CH_2Cl_2 2,6-lutidine, rt, 20 min, 96%	$Me(CH_2)_{11}SSAr'$ Ar' = 2-$(O_2N)C_6H_4$
8	$Me(CH_2)_{11}SPg$	Ph_3CSSCl, CH_2Cl_2 2,6-lutidine, rt, 1 h, 93%	$Me(CH_2)_{11}SSSCPh_3$
9	$Me(CH_2)_{11}SPg$	BnSCl, CH_2Cl_2 2,6-lutidine, rt, 10 min, 66%	$Me(CH_2)_{11}SSBn$

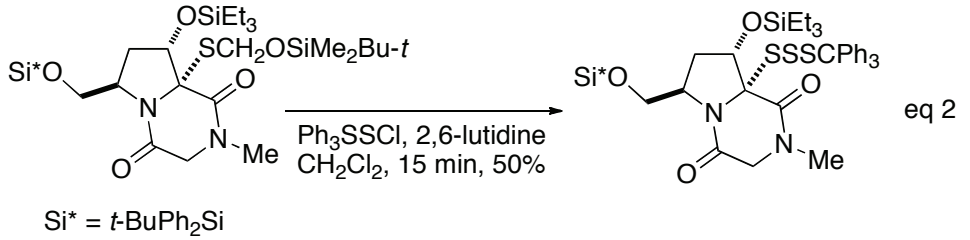
[a]Pg = CH_2OSiMe_2Bu-*t*

The stability of the protecting group was evaluated[4] by exposing *n*-$C_{12}H_{25}SCH_2OSiMe_2Bu$-*t* (**6**) to a variety of conditions. The compound is stable to H_2/Pd/C in methanol-dichloromethane and to H_2/Rh/Al_2O_3/ethyl acetate. An *O*-triethylsilyl ether can be selectively deprotected in the presence of (**6**), using H_2/Pd/C in methanol-dichloromethane. The protecting group appears to survive typical conditions for removal of a Troc group (zinc dust in acetic acid-diethyl ether) and an Fmoc group can be

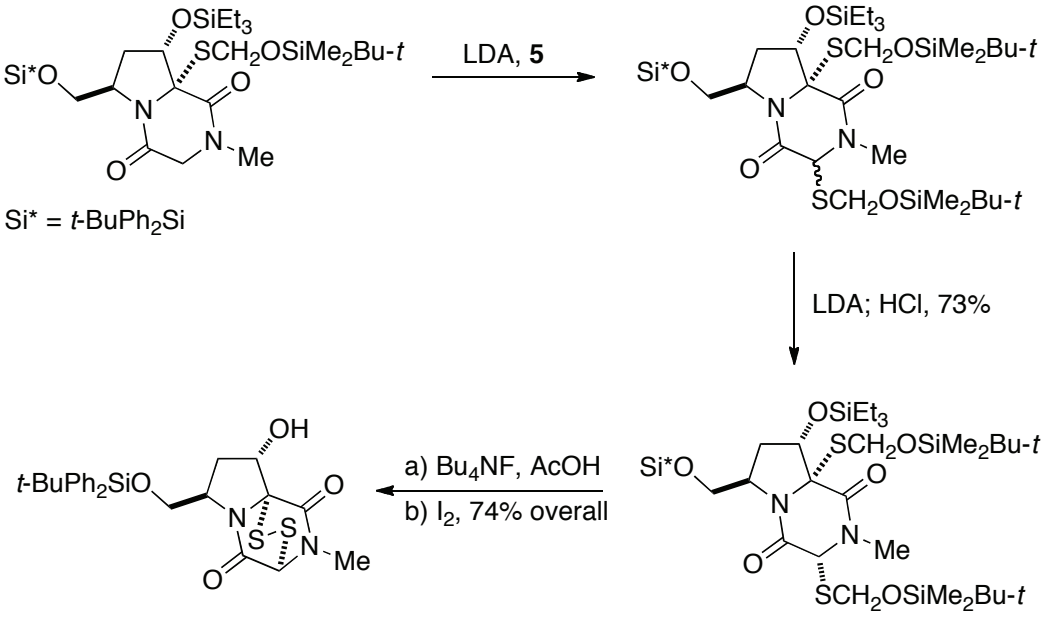
removed in its presence by using piperidine. Hydride reducing agents either have no effect (sodium borohydride) or little effect (lithium aluminum hydride, diisobutylaluminum hydride). $(PhS)_2CH_2$ can be deprotonated with butyllithium with very little decomposition (4%) of the test substrate. Acidic reagents (trifluoroacetic acid, *p*-toluenesulfonic acid hydrate, pyridinium *p*-toluenesulfonate-MeOH, boron trifluoride etherate) are not compatible with the protecting group, except for pyridinium *p*-toluenesulfonate in dichloromethane and exposure to silica gel during chromatography. A primary alcohol can be converted into the corresponding bromide (tetrabromomethane, triphenylphosphine) without affecting the protecting group, but oxidizing agents (pyridinium chlorochromate, Dess-Martin periodinane, 2-iodoxybenzoic acid (IBX), Swern conditions) are not compatible with the protecting group. A primary alcohol can be silylated with triethylsilyl triflate in the presence of (**6**).

The sulfenylating agent (**5**) has been used to introduce the protected sulfur, as shown in eq 1.[4] Sulfur deprotection is illustrated in eq 2,[10] which represents the result of a single experiment. A more sophisticated use of the sulfenylating agent (**5**) as well as subsequent deprotection in a synthetically complex setting is summarized in Scheme 1.[10]





Scheme 1. Sulfenylation with reagent **5** and deprotection



1. Chemistry Department, University of Alberta, Edmonton, Alberta T6G 2G2, Canada; e-mail: derrick.clive@ualberta.ca. We thank the Natural Sciences and Engineering Research Council of Canada for financial support. L.W. held a Marie Arnold Cancer Research Graduate Scholarship and an Alberta Heritage Foundation for Medical Research Graduate Studentship.

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6. *i*-Pr_3SiOCH_2Cl is commercially available.

7. (a) Gundersen, L.-L.; Benneche, T.; Undheim, K. *Acta. Chem. Scand*. **1989**, *43*, 706–709. (b) EP 1565479B1 (2006). (c) Pitsch, S.; Weiss, P. A.; Jenny, L.; Stutz, A.; Wu, X. *Helv. Chim. Acta* **2001**, *84*, 3773–3795.
8. Harmon, J. P.; Field, L. *J. Org. Chem*. **1986**, *51*, 5235–5240.
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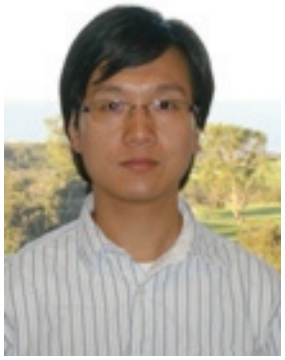
10. Wang, L.; Clive, D. L. J. *Tetrahedron Lett*. **2012**, *53*, 1504–1506.

Appendix
Chemical Abstracts Nomenclature (Registry Number)

(Chloromethoxy)(1,1-dimethylethyl)dimethylsilane; (119451-80-8)
Chloro(1,1-dimethylethyl)dimethylsilane; (18162-48-6)
4-(Dimethylamino)pyridine; (1122-58-3)
(1,1-Dimethylethyl)[(ethylthio)methoxy]dimethylsilane; (119451-79-5)
Ethanethiol; (75-08-1)
(Ethylthio)methanol; (15909-30-5)
4-Methylbenzenesulfonothioic acid, *S*-[[[(1,1-dimethylethyl)dimethylsilyl]-oxy]methyl] ester; (1277170-42-9)
4-Methylbenzenesulfonothioic acid, sodium salt (1:1); (3753-27-3)
Paraformaldehyde; (30525-89-4)
Sodium methoxide; (124-41-4)
Sodium *p*-toluenesulfinate hydrate ($TolSO_2Na \cdot H_2O$); (207801-20-5)
Sulfur; (7704-34-9)
Sulfuryl chloride; (7791-21-5)
Triethylamine; (121-44-8)

Derrick Clive was born in London and was educated at Imperial College where he obtained a B.Sc. (Special) in Chemistry, and then a Ph.D. in Professor Barton's group. Dr. Jack E. Baldwin (now Sir Jack) assisted in the supervision of these postgraduate studies. Derrick then held a postdoctoral position at Harvard in R. B. Woodward's group. In 1975 he joined the Chemistry Department of the University of Alberta, where he is now Professor of Chemistry. He has published over 200 papers on the development of general synthetic methods — involving mainly selenium chemistry and radical cyclization — and on the total synthesis of complex natural products with significant biological properties.



Lihong Wang was born in Zhoushan, Zhejiang Province, and obtained his B.Sc. at Fudan University. He stayed at Fudan University to begin his graduate studies, but moved to the University of Alberta in 2006 for his Ph.D. under the supervision of Professor Clive. Lihong's research has been supported by a number of Scholarships and is in the area of synthetic methodology and natural product synthesis. After obtaining his Ph.D. in 2011 he joined Professor Nicolaou's group at the Scripps Institute as a postdoctoral fellow.

32077-192
crude (ethylthio)methanol
nmr400c h-1
hughesda

NAME	32077-192
EXPNO	4
PROCNO	1
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Time	8.21
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NS	32
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FIDRES	0.195625 Hz
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RG	128
DW	78.000 usec
DE	6.50 usec
TE	300.0 K
D1	0.10000000 sec
TD0	1
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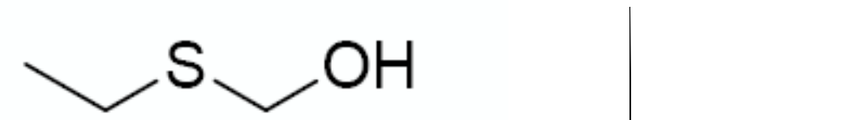
GB	0
PC	1.40



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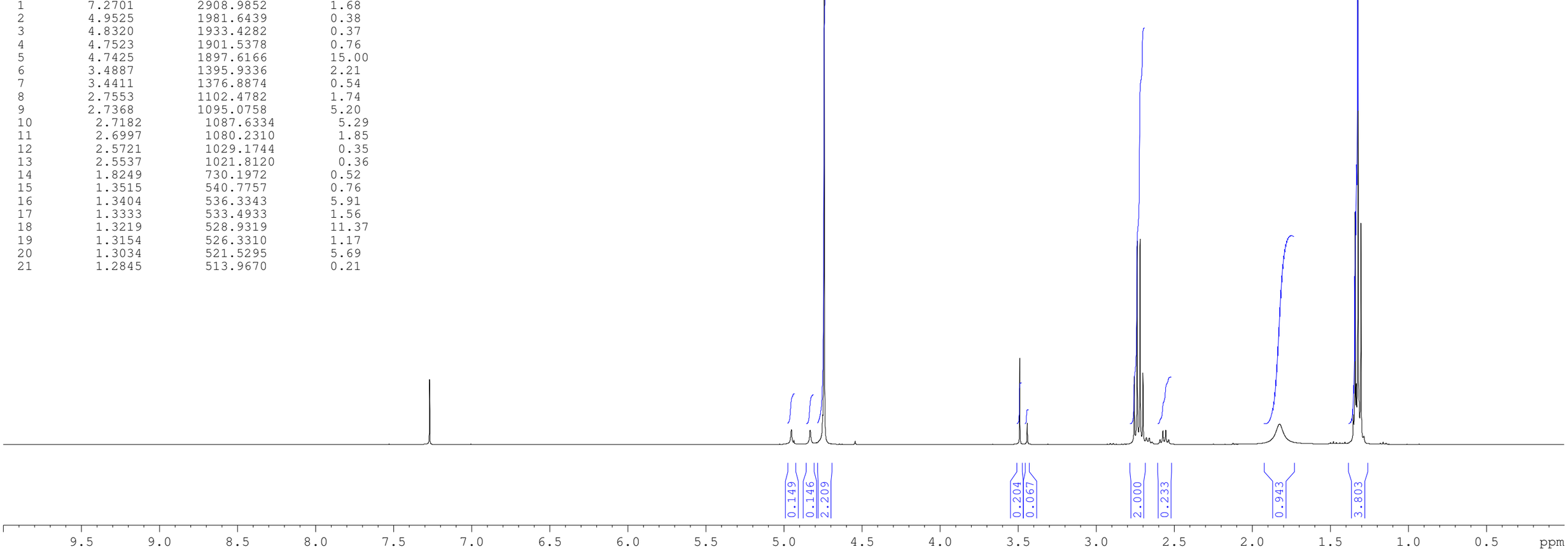
3	4.8320	1933.4282	0.37	
4	4.7523	1901.5378	0.76	
5	4.7425	1897.6166	15.00	
6	3.4887	1395.9336	2.21	
7	3.4411	1376.8874	0.54	
8	2.7553	1102.4782	1.74	
9	2.7368	1095.0758	5.20	
10	2.7182	1087.6334	5.29	
11	2.6997	1080.2310	1.85	
12	2.5721	1029.1744	0.35	
13	2.5537	1021.8120	0.36	
14	1.8249	730.1972	0.52	
15	1.3515	540.7757	0.76	
16	1.3404	536.3343	5.91	
17	1.3333	533.4933	1.56	
18	1.3219	528.9319	11.37	
19	1.3154	526.3310	1.17	
20	1.3034	521.5295	5.69	
21	1.2845	513.9670	0.21	



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crude (ethylthio)methanol
nmr400c c-13
hughesda

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PROCNO                1
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PULPROG         zgdc30
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SOLVENT           CDCl3
NS                  364
DS                    4
SWH           26315.789 Hz
FIDRES         0.401547 Hz
AQ            1.2452340 sec
RG                 8192
DW                19.000 usec
DE                 6.50 usec
TE                300.1 K
D1           0.10000000 sec
D11          0.03000000 sec
TD0                  40

======== CHANNEL f1 ========
NUC1                13C
P1                 8.00 usec
PL1                4.50 dB
SFO1        100.6238364 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                1H
PCPD2              80.00 usec
PL2               120.00 dB
PL12               18.34 dB
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LB                 1.00 Hz
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PC                 1.40
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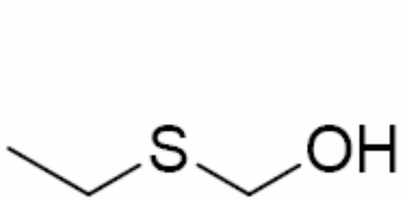

32077-192
EtSCH2OTBS Distilled
Fr 2
nmr500c h-1
hughesda

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PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	32
DS	4
SWH	13020.833 Hz
FIDRES	0.198682 Hz
AQ	2.5166707 sec
RG	90.5
DW	38.400 usec
DE	6.50 usec
TE	300.0 K
D1	0.10000000 sec
TD0	1

======== CHANNEL f1 ========

NUC1	1H
P1	12.00 usec
PL1	-4.00 dB
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SI	32768
SF	500.1300082 MHz
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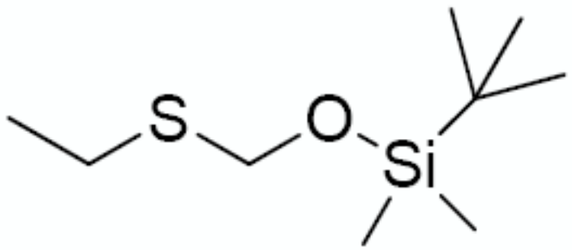
SSB	0
LB	0.30 Hz
GB	0
PC	1.40



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4	2.6857	1343.1992
5	2.6707	1335.6972
6	2.6560	1328.3453
7	1.3175	658.9213
8	1.3025	651.4193
9	1.2878	644.0674
10	0.9539	477.0740
11	0.9221	461.1699
12	0.9195	459.8695
13	0.9139	457.0688
14	0.9078	454.0180
15	0.1347	67.3675
16	0.1288	64.4167
17	0.1224	61.2159
18	0.1052	52.6137

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EXPNO                11
PROCNO                1
Date_          20120522
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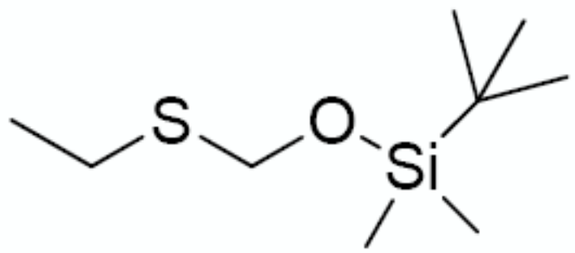
PROBHD   5 mm QNP 1H/13
PULPROG            zgdc
TD               131072
SOLVENT           CDCl3
NS                 257
DS                   4
SWH            40322.582 Hz
FIDRES          0.307637 Hz
AQ             1.6253552 sec
RG                8192
DW               12.400 usec
DE                6.50 usec
TE               300.0 K
D1           0.10000000 sec
D11          0.03000000 sec
TD0                 40

======== CHANNEL f1 ========
NUC1               13C
P1                2.50 usec
PL1               0.00 dB
SFO1        125.7703648 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                1H
PCPD2             80.00 usec
PL2              120.00 dB
PL12              11.50 dB
SFO2        500.1325007 MHz
SI                65536
SF          125.7577617 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```



32077-192
EtSCH2OTBS Distilled
Fr 2
nmr500c c-13
hughesda

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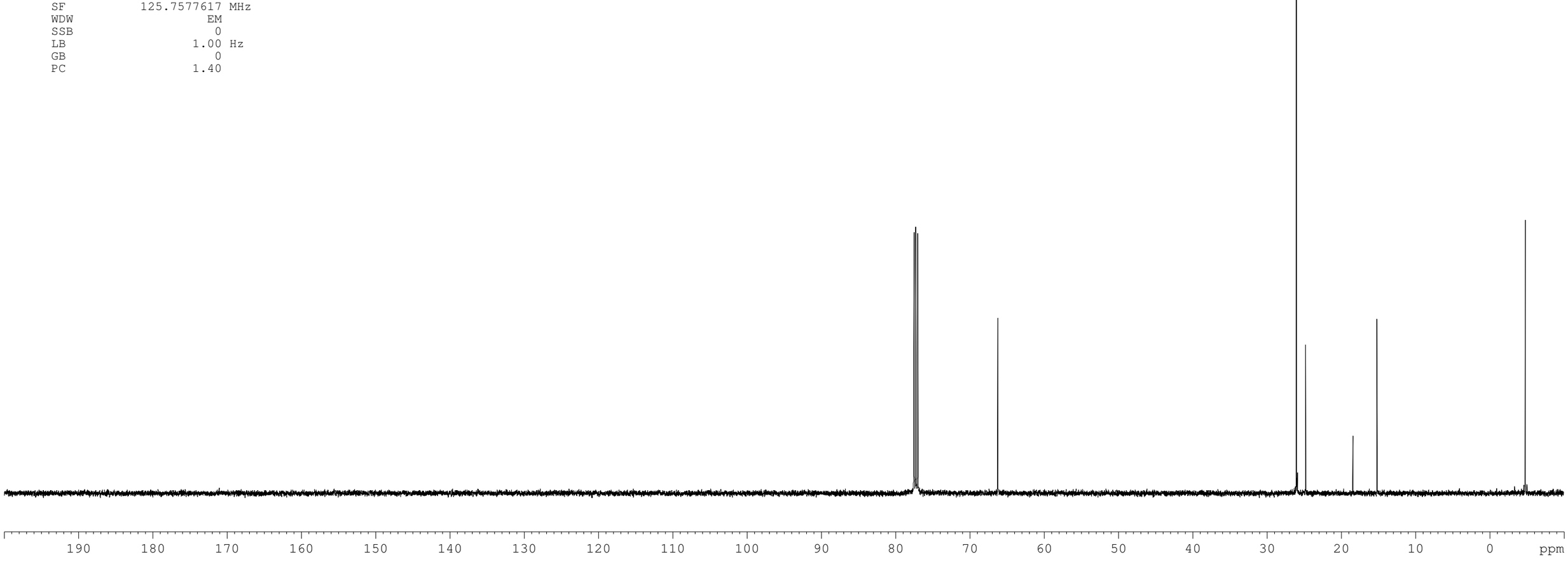
77.23
76.98
66.20
26.01
24.77
18.39
15.14
-4.84



32077-194
distilled, fr 2
nmr500c h-1
hughesda
hughesda

```
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EXPNO                 1
PROCNO                1
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Time              14.44
INSTRUM           spect
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PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                   32
DS                    4
SWH           13020.833 Hz
FIDRES         0.198682 Hz
AQ            2.5166707 sec
RG                  181
DW                38.400 usec
DE                 6.50 usec
TE                300.0 K
D1           0.10000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                 1H
P1                12.00 usec
PL1               -4.00 dB
SFO1        500.1330885 MHz
SI                32768
SF          500.1300083 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
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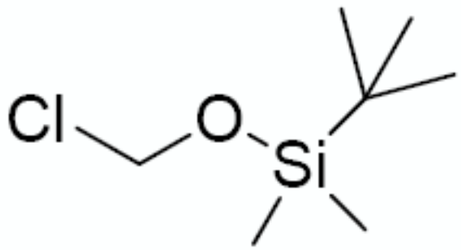

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5	0.9237	461.9701
6	0.9178	459.0193
7	0.2148	107.4279
8	0.2086	104.3271
9	0.2022	101.1263

```
NAME          32077-194
EXPNO                 2
PROCNO                1
Date_          20120526
Time              14.51
INSTRUM           spect
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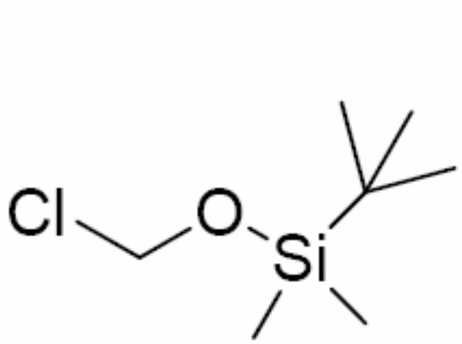
PULPROG            zgdc
TD               131072
SOLVENT           CDCl3
NS                 1014
DS                    4
SWH           40322.582 Hz
FIDRES         0.307637 Hz
AQ            1.6253552 sec
RG                 8192
DW                12.400 usec
DE                 6.50 usec
TE                300.0 K
D1           0.10000000 sec
D11          0.03000000 sec
TD0                  40

======== CHANNEL f1 ========
NUC1                13C
P1                 2.50 usec
PL1                0.00 dB
SFO1        125.7703648 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                1H
PCPD2              80.00 usec
PL2               120.00 dB
PL12               11.50 dB
SFO2        500.1325007 MHz
SI                 65536
SF          125.7577618 MHz
WDW                   EM
SSB                    0
LB                1.00 Hz
GB                     0
PC                1.40
```



32077-194
distilled fr 2
ClCH2OTBS
nmr500c c-13
hughesda

32077-193
recrystallized
nmr500c h-1
hughesda

```
NAME          32077-193
EXPNO                 5
PROCNO                1
Date_          20120529
Time               8.24
INSTRUM           spect
PROBHD   5 mm QNP 1H/13
PULPROG            zg30
TD                65536
SOLVENT            DMSO
NS                   32
DS                    4
SWH           13020.833 Hz
FIDRES         0.198682 Hz
AQ            2.5166707 sec
RG                  362
DW                 38.400 usec
DE                  6.50 usec
TE                 300.0 K
D1           0.10000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                  1H
P1                 12.00 usec
PL1                -4.00 dB
SFO1        500.1330885 MHz
SI                 32768
SF          500.1300053 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
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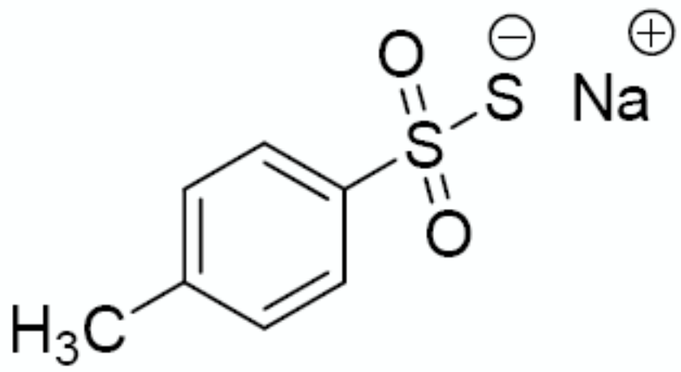

Peak	?(F1) [ppm]	?(F1) [Hz]
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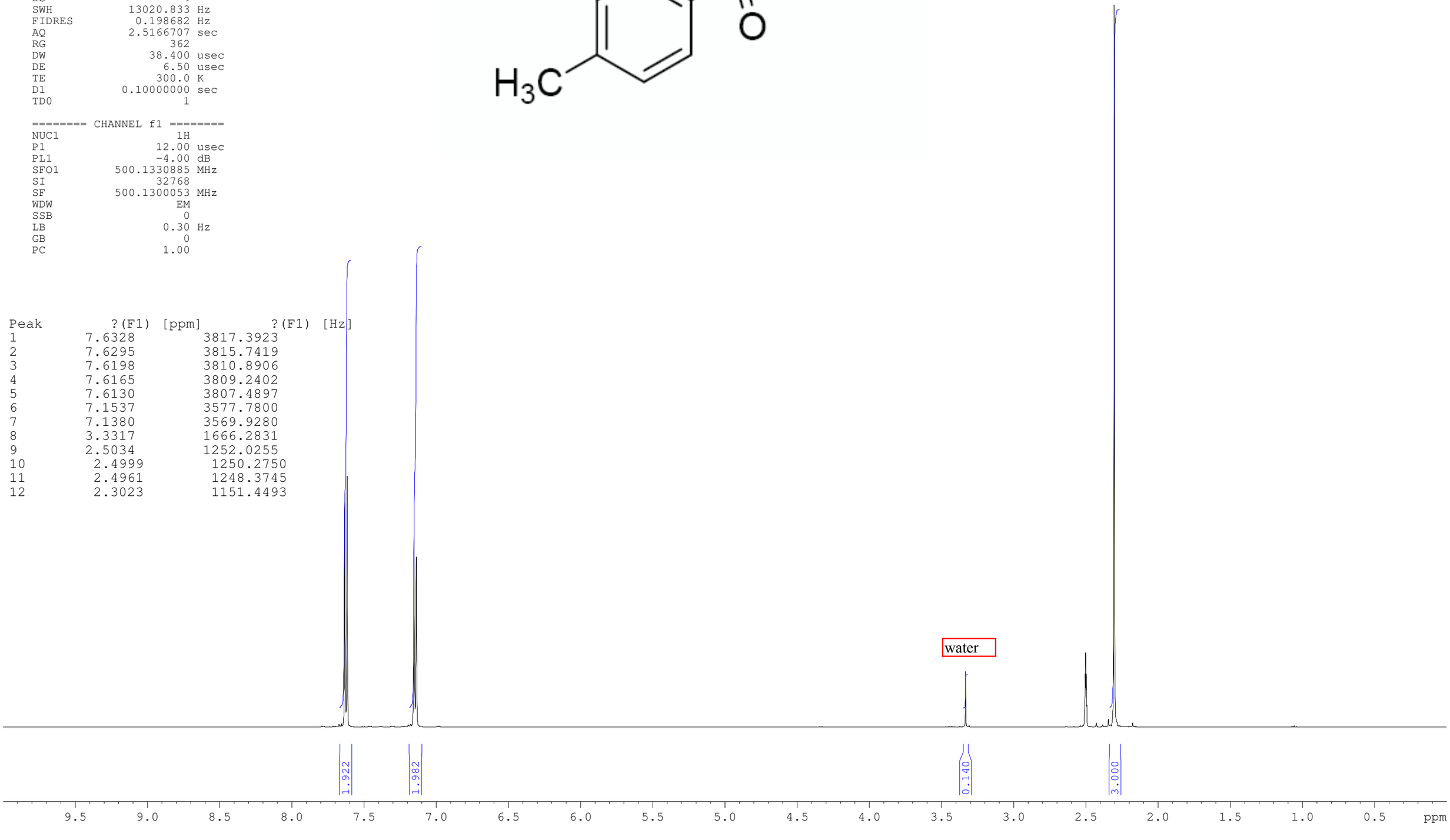
2	7.6295	3815.7419
3	7.6198	3810.8906
4	7.6165	3809.2402
5	7.6130	3807.4897
6	7.1537	3577.7800
7	7.1380	3569.9280
8	3.3317	1666.2831
9	2.5034	1252.0255
10	2.4999	1250.2750
11	2.4961	1248.3745
12	2.3023	1151.4493



32077-193
recrystallized
nmr500c c-13
hughesda

NAME	32077-193
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PROCNO	1
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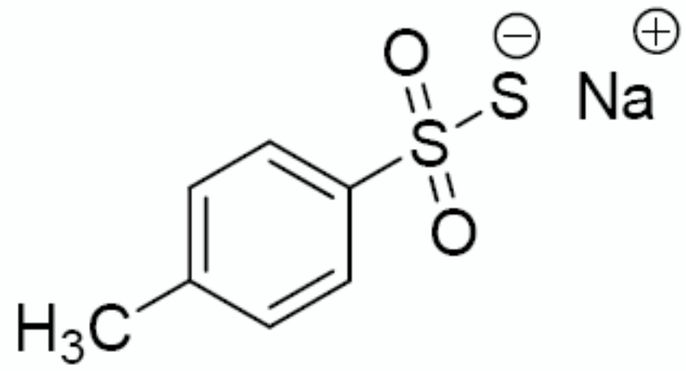
Time	8.29
INSTRUM	spect
PROBHD	5 mm QNP 1H/13
PULPROG	zgdc
TD	131072
SOLVENT	DMSO
NS	322
DS	4
SWH	40322.582 Hz
FIDRES	0.307637 Hz
AQ	1.6253552 sec
RG	8192
DW	12.400 usec
DE	6.50 usec
TE	300.1 K
D1	0.10000000 sec
D11	0.03000000 sec
TD0	40
======== CHANNEL f1 ========	
NUC1	13C
P1	2.50 usec
PL1	0.00 dB
SFO1	125.7703648 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	120.00 dB
PL12	11.50 dB
SFO2	500.1325007 MHz
SI	65536
SF	125.7578533 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40



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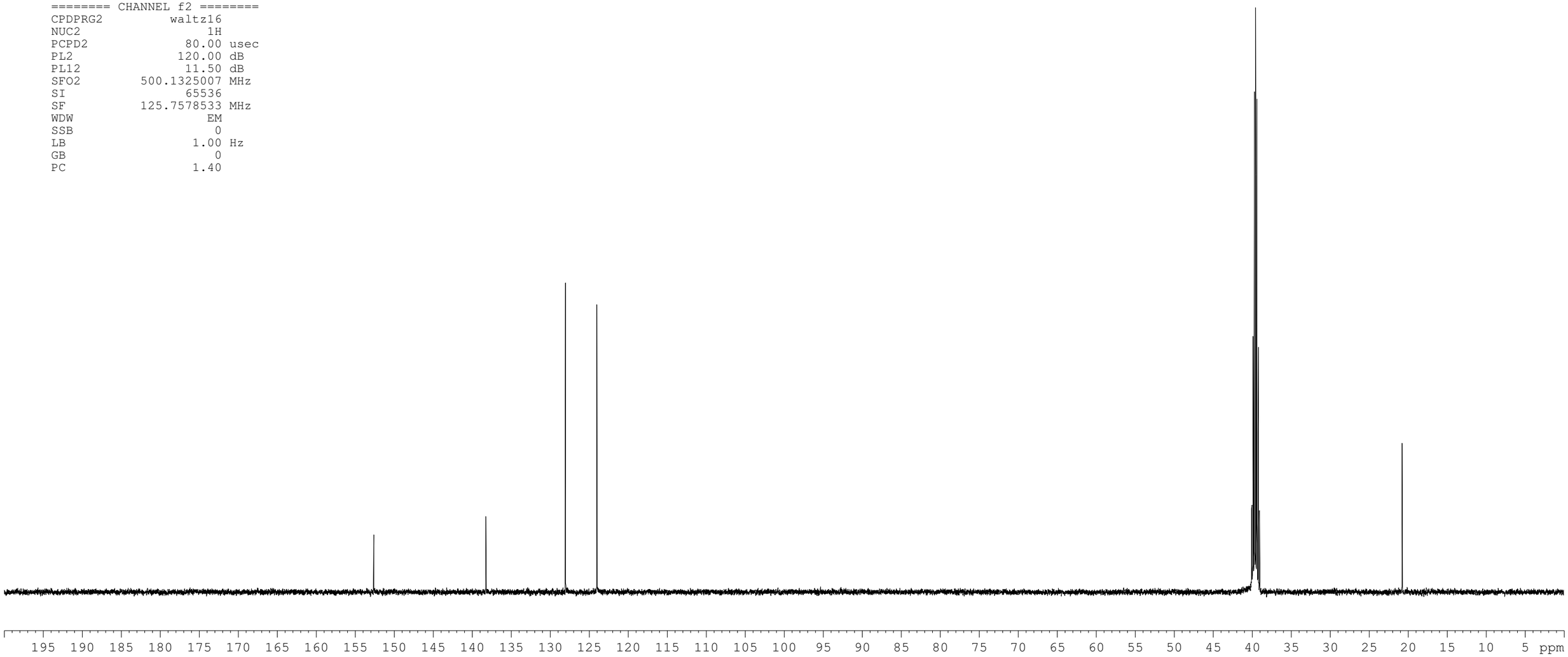
40.01 39.84 39.68 39.51 39.34 39.17 39.01

20.72



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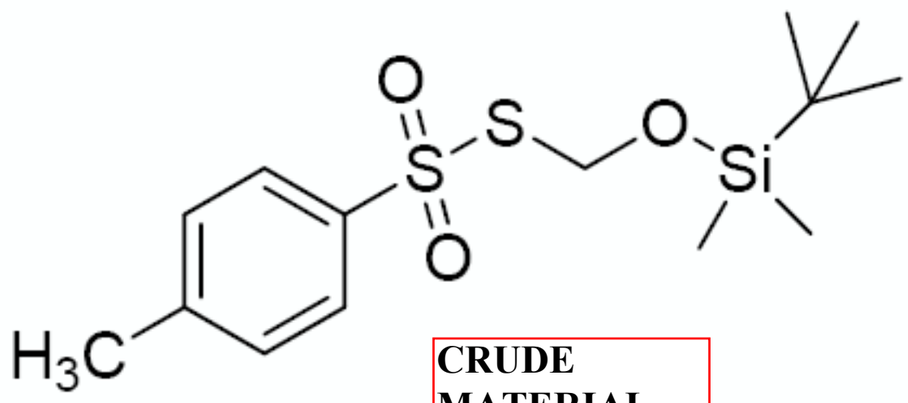
Time	14.59
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	32
DS	2
SWH	6410.256 Hz
FIDRES	0.195625 Hz
AQ	2.5559540 sec
RG	114
DW	78.000 usec
DE	6.50 usec
TE	300.0 K
D1	0.10000000 sec
TD0	1

======== CHANNEL f1 ========

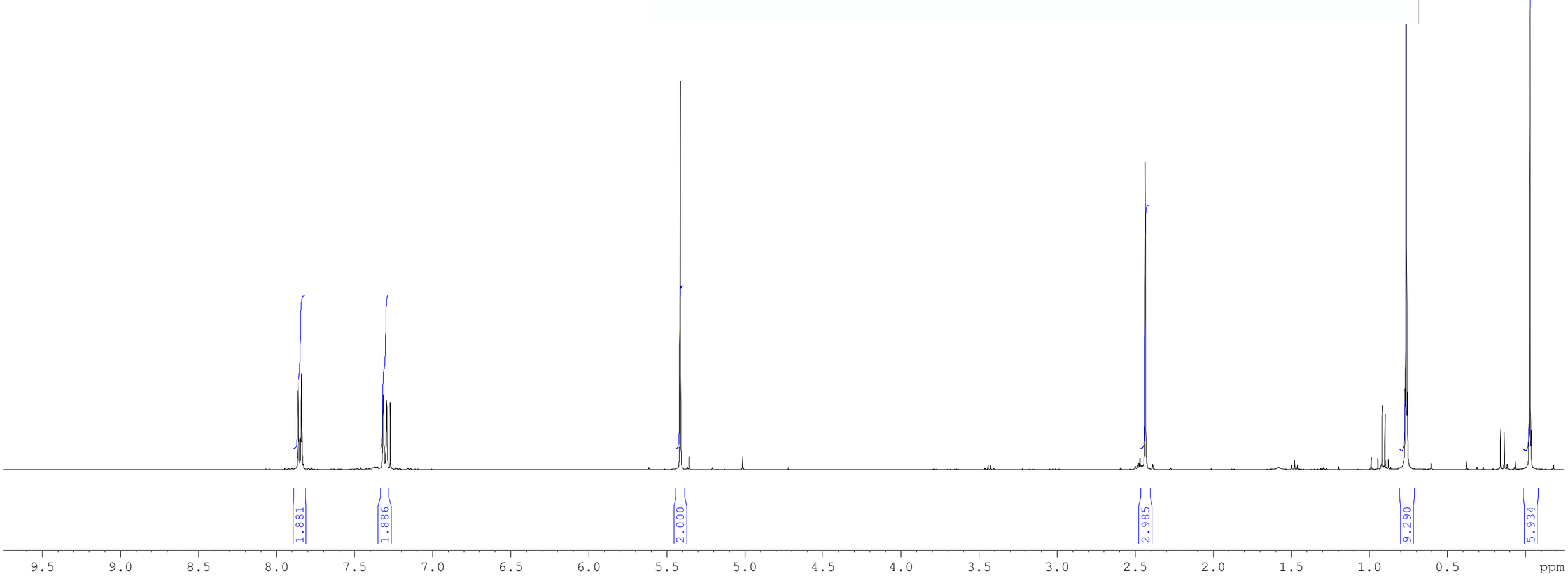
NUC1	1H
P1	10.40 usec
PL1	0.00 dB
SFO1	400.1324710 MHz
SI	32768
SF	400.1300054 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

Peak	?(F1) [ppm]	?(F1) [Hz]	Intensity [rel]	Annotation
1	7.8612	3145.5020	0.80	
2	7.8402	3137.0993	0.86	
3	7.3157	2927.2311	0.68	
4	7.2957	2919.2285	0.62	
5	7.2944	2918.7083	0.55	
6	7.2701	2908.9852	0.61	
7	5.4138	2166.2238	3.55	
8	2.4342	973.9965	2.74	
9	0.9177	367.1993	0.57	
10	0.8981	359.3568	0.49	
11	0.7698	308.0201	0.73	
12	0.7623	305.0191	15.00	
13	0.7548	302.0181	0.69	
14	0.1588	63.5406	0.36	
15	0.1346	53.8575	0.35	
16	-0.0226	-9.0429	0.42	
17	-0.0303	-12.1239	10.93	
18	-0.0382	-15.2850	0.36	

32077-197
isolated and vacuum dried
nmr400c h-1
hughesda

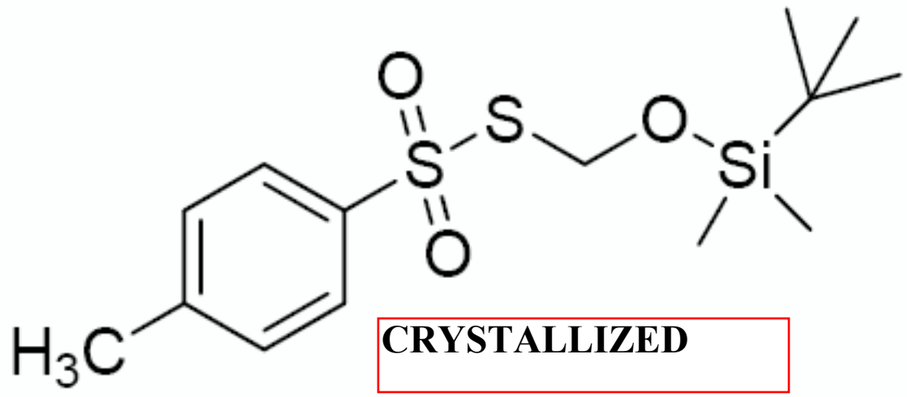


CRUDE MATERIAL



32077-200
recryst from MTBE
nmr500c h-1
hughesda

NAME	32077-200
EXPNO	10
PROCNO	1
Date_	20120707
Time	8.05
INSTRUM	spect
PROBHD	5 mm QNP 1H/13
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	32
DS	4
SWH	13020.833 Hz
FIDRES	0.198682 Hz
AQ	2.5166707 sec
RG	90.5
DW	38.400 usec
DE	6.50 usec
TE	300.0 K
D1	0.10000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	12.00 usec
PL1	-4.00 dB
SFO1	500.1330885 MHz
SI	32768
SF	500.1300082 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00



CRYSTALLIZED

Peak	?(F1) [ppm]	?(F1) [Hz]	Intensity [abs]
1	7.8535	3927.7710	31160953.00
2	7.8501	3926.0706	10519502.00
3	7.8403	3921.1693	11895955.00
4	7.8367	3919.3688	31209633.00
5	7.8328	3917.4183	5068397.00
6	7.3099	3655.9003	24609565.00
7	7.2938	3647.8483	25872015.00
8	7.2701	3635.9952	3944909.00
9	5.4093	2705.3533	136863886.00
10	2.4295	1215.0659	105994808.00
11	0.7985	399.3538	4472616.00
12	0.7643	382.2494	33620975.00
13	0.7587	379.4486	480559328.00
14	0.7527	376.4479	25913614.00
15	-0.0276	-13.8036	18696702.00
16	-0.0337	-16.8544	232446207.00
17	-0.0400	-20.0052	13034602.00