Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Asymmetric Total Synthesis and Antidepressant Activity of (−)-Sila-mesembranol Bearing a Silicon Stereocenter

Gan Luo,[a†] Lingmin Chen,[b†] Yi Li,[a] Yu Fan,[a] Duyang Wang,[a] Yufan Yang,[a] Lu Gao,[a] Ruotian Jiang[b]* and Zhenlei Song *[a]

[a]*Key Laboratory of Drug-Targeting and Drug Delivery System of the Education Ministry and Sichuan Province, Sichuan Engineering Laboratory for Plant-Sourced Drug and Sichuan Research Center for Drug Precision Industrial Technology, West China School of Pharmacy, Sichuan University, Chengdu, 610041, China.*

[b]*Laboratory of Anesthesia and Critical Care Medicine, Department of Anesthesiology, National-Local Joint Engineering Research Center of Translational Medicine of Anesthesiology, West China Hospital of Sichuan University, Chengdu, Sichuan,610000, China.*

[†]These authors contributed equally to this work.

*Corresponding authors: ruotianjiang@scu.edu.cn; zhenleisong@scu.edu.cn

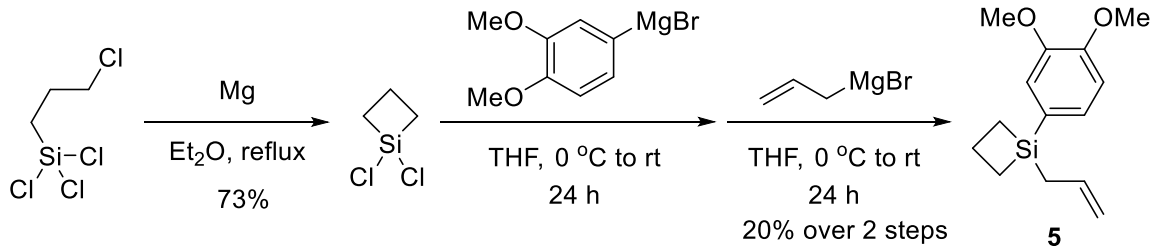
Table of Contents

1. General Methods

Commercial reagents were used without any purification. $[Pd(allyl)Cl]_2$, $[Ir(cod)Cl]_2$ and $[Rh(CH_2CH_2)_2Cl]_2$ was purchased from Acros Scientific. All reactions were performed using common anhydrous, inert atmosphere techniques. Reactions were monitored by TLC which was performed on glass-backed silica plates (purchased from Yantai Jiangyou Silica Gel Development Co. Ltd.) and visualized using UV, $KMnO_4$ stains, $H_3PO_4 \cdot 12MoO_3$/EtOH stains. Column chromatography was performed using silica gel (200-300 or 300-400 mesh, purchased from Yantai Jiangyou Silica Gel Development Co. Ltd.) or Al_2O_3 (200-300 mesh, purchased from Chengdu Huaxia Chemical Reagent Co., Ltd.) eluting with EtOAc/petroleum ether or CH_2Cl_2/MeOH. Preparative TLC separations were performed using Kangbino 48-75 Å SiO_2. Melting point were recorded at WRX-4 Melting-point Apparatus (purchased from Shanghai Yice Apparatus & Equipments Co. Lit.). ^{1}H NMR spectra were recorded at 400 MHz (Varian or Bruker) and 600 MHz (Agilent), ^{13}C NMR spectra were recorded at 100 MHz (Bruker) and 150 MHz (Bruker) and ^{29}Si NMR spectra were recorded at 79 MHz (Bruker) and 119 MHz (Bruker) using $CDCl_3$ (except where noted) with TMS or residual solvent as standard. All coupling constants (*J* values) were reported in hertz (Hz). Multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), triplet (t), quartet (q), and multiplet (m). Infrared spectra were obtained using PerkinElmer Spectrum Two FTIR Spectrometer. High-resolution mass spectral analyses performed on Waters Q-TOF. Specific optical rotation was measured on PL341 Polarimeter (PerkinElmer). Enantiomeric excess was determined by HPLC (Agilent Technologies: 1260 Infinity II) analysis on a Daicel Chiralpak® AD-H column or Daicel Chiralpak® OD-H column. CH_3CN, DMF, CH_2Cl_2, and Et_3N were distilled from CaH_2. Toluenen, Et_2O and THF were distilled from sodium. All spectral data obtained for new compounds are reported here.

2. Experimental Procedures and Spectral Data of Products

2.1. Synthesis of Silacyclobutane 5



Magnesium powder (10 g, 417 mmol) and iodine crystals (50 mg) in dry Et_2O (300 mL) was placed in a 500 mL three-neck round bottomed flask with a reflux condenser. To the above refluxed mixture was added a solution of (3-chloropropyl)-trichlorosilane (27 g, 127 mmol) in dry Et_2O (30 mL) over 2 h via a syringe pump. After stirring for 24 h, an additional dry Et_2O (150 mL) was added. The reaction was stirred for 3 days before cooling to room temperature. The magnesium chloride and excess magnesium were removed via suction filtration through a large sintered-glass funnel. The filter cake was washed with dry Et_2O (500 mL). The combined filtrates were concentrated under reduced pressure to afford the residue, which was distillation to give 1,1-dichlorosiletane[1] (13.2 g, 73% yield) as a clear colorless or slightly pink (trace iodine) liquid.

1. S. E. Denmark, B. D. Griedel, D. M. Coe and M. E. Schnute, *J. Am. Chem. Soc.*, **1994**, *116*, 7026-7043.

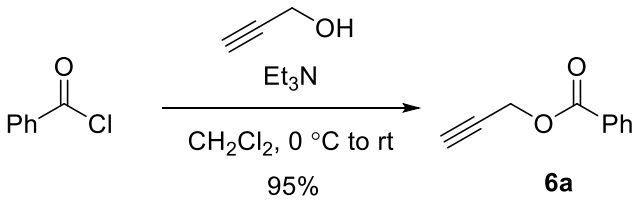
- ^{1}H NMR (400 MHz, Chloroform-*d*) δ 2.17 – 2.08 (m, 2H), 1.93 (t, *J* = 8.6 Hz, 4H).

Magnesium powder (1.72 g, 72 mmol) and iodine crystals (10 mg) in dry THF (30 mL) was placed in a 100 mL three-neck round bottomed flask with a reflux condenser. To the above mixture was added a solution of 4-bromoveratrole (5.27 g, 24 mmol) in dry THF (20 mL) dropwise over 20 min. The resulting mixture was stirred at room temperature for 30 min. and was static standby. The clear liquid of the above Grignard reagent was added to a solution of 1,1-dichlorosiletane (4.0 g, 28.3 mmol) in dry THF (50 mL) at 0 °C over 2 h. After stirring at room temperature for 24 h, allyl magnesium bromide (28 mL, 28 mmol, 1.0 M in Et_2O) was added at 0 °C. The resulting mixture was stirred at room temperature for 24 h before quenching with sat. aq. NH_4Cl (50 mL) and extracting with EtOAc (3 × 30 mL). The combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (eluent: petroleum ether/EtOAc = 100/1) to afford **5** as a colorless oil. (1.8 g, 20% yield).

- ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.18 (d, *J* = 7.7 Hz, 1H), 7.09 (s, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 5.97 – 5.86 (m, 1H), 5.02 – 4.93 (m, 2H), 3.91 (d, *J* = 7.0 Hz, 6H), 2.16 (p, *J* = 8.3 Hz, 2H), 2.02 (d, *J* = 8.0 Hz, 2H), 1.26 (t, *J* = 8.3 Hz, 4H).
- ^{13}C NMR (100 MHz, Chloroform-*d*) δ 150.3, 148.6, 133.7, 128.5, 126.9, 115.8, 114.0, 111.0, 55.8, 55.7, 22.9, 18.0, 12.9.
- ^{29}Si NMR (119 MHz, Chloroform-d) δ 10.72.
- IR (neat) cm^{-1} 2998, 2959, 2927, 2823, 1579, 1507, 1462, 1253, 1234, 1141, 1108, 1027.
- HRMS (MALDI, m/z) calcd for $C_{14}H_{20}O_2Si$ $(M+Na)^+$: 271.1125, found 271.1118.

2.2. Synthesis of Propargyl Ester Derivatives 6

Preparation of 6a[2]

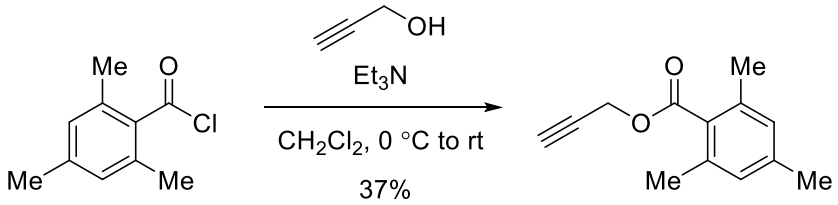


To a solution of prop-2-yn-1-ol (560 mg, 10.0 mmol), Et_3N (1.51 g, 15.0 mmol) in CH_2Cl_2 (30 mL) was added benzoyl chloride (1.68 g, 12.0 mmol) at 0 °C. The resulting mixture was stirred at room temperature until the starting material was completely consumed (monitored by TLC analysis). The reaction mixture was quenched with sat. aq. NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (eluent: petroleum ether/EtOAc = 100/1) to afford **6a** as a colorless oil (1.52 g, 95% yield).

- ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.07 (d, *J* = 7.4 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 4.92 (d, *J* = 2.5 Hz, 2H), 2.52 (t, *J* = 2.5 Hz, 1H).

Preparation of 6b

2. M. Cloutier, M. Roudias, and J. F. Paquin, *Org. Lett.* **2019**, *21*, 3866−3870.

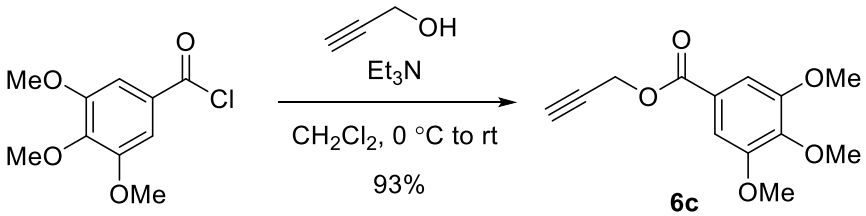


6b

To a solution of prop-2-yn-1-ol (560 mg, 10.0 mmol), Et_3N (1.51 g, 15.0 mmol) in CH_2Cl_2 (30 mL) was added 2,4,6-trimethylbenzoyl chloride (2.19 g, 12.0 mmol) at 0 °C. The resulting mixture was stirred at room temperature until the starting material was completely consumed (monitored by TLC analysis). The reaction was quenched with sat. aq. NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (eluent: petroleum ether/EtOAc = 100/1) to afford **6b** as a white solid. (0.75 g, 37% yield).

- m.p. 36.3-37.2 °C.
- ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.85 (s, 2H), 4.90 (d, *J* = 2.5 Hz, 2H), 2.50 (t, *J* = 2.5 Hz, 1H), 2.31 (s, 6H), 2.28 (s, 3H).
- ^{13}C NMR (100 MHz, Chloroform-*d*) δ 169.2, 139.7, 135.5, 129.8, 128.4, 77.6, 75.0, 52.0, 21.1, 19.7.
- IR (neat) cm^{-1} 3288, 2924, 1728, 1611, 1434, 1258, 1165, 1073, 975, 950.
- HRMS (MALDI, m/z) calcd for $C_{13}H_{14}O_2$ $(M+Na)^+$: 225.0886, found 225.0896.

Preparation of 6c

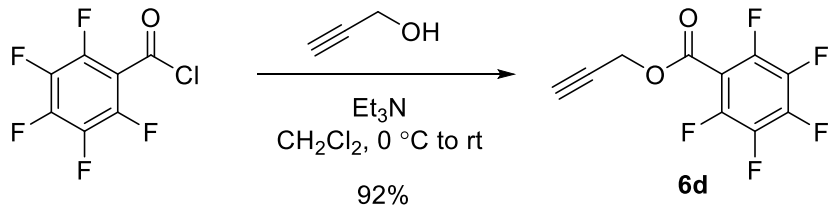


6c

To a solution of prop-2-yn-1-ol (560 mg, 10.0 mmol), Et_3N (1.51 g, 15.0 mmol) in CH_2Cl_2 (30 mL) was added 3,4,5-trimethoxybenzoyl chloride (2.76 g, 12.0 mmol) at 0 °C. The resulting mixture was stirred at room temperature until the starting material was completely consumed (monitored by TLC analysis). The reaction was quenched with sat. aq. NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (eluent: petroleum ether/EtOAc = 100/1) to afford **6c** as a white solid. (2.32 g, 93% yield).

- m.p. 88.0-89.8 °C.
- ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.32 (s, 2H), 4.91 (d, *J* = 2.5 Hz, 2H), 3.91 (s, 9H), 2.52 (t, *J* = 2.4 Hz, 1H).
- ^{13}C NMR (100 MHz, Chloroform-*d*) δ 165.4, 152.9, 142.5, 124.3, 107.0, 77.7, 75.0, 60.9, 56.2, 52.5.
- IR (neat) cm^{-1} 3263, 2941, 1716., 1589, 1503, 1459, 1415, 1330, 1215, 1123, 998.
- HRMS (MALDI, m/z) calcd for $C_{13}H_{14}O_5$ $(M+Na)^+$: 273.0733, found 273.0730.

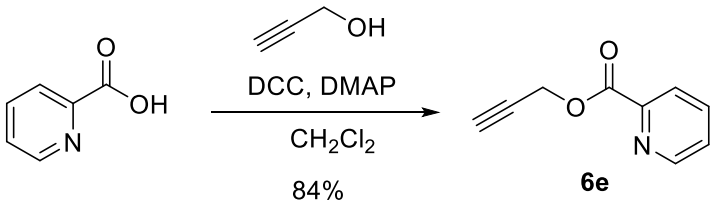
Preparation of 6d



To a solution of prop-2-yn-1-ol (560 mg, 10.0 mmol), Et_3N (1.51 g, 15.0 mmol) in CH_2Cl_2 (30 mL) was added pentafluorobenzoyl chloride (2.76 g, 12.0 mmol) slowly at 0 °C. The resulting mixture was stirred at room temperature until the starting material was completely consumed (monitored by TLC analysis). The reaction was quenched with sat. aq. NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (eluent: petroleum ether/EtOAc = 100/1) to afford **6d** as a colorless oil (2.3 g, 92% yield).

- ^{1}H NMR (400 MHz, Chloroform-d) δ 4.96 (d, *J* = 2.5 Hz, 2H), 2.58 (t, *J* = 2.5 Hz, 1H).
- ^{13}C NMR (100 MHz, Chloroform-d) δ 158.3, 147.9 – 146.3 (m), 145.5 – 143.2 (m), 142.6 – 141.4 (m), 139.9 – 138.2 (m), 137.3 – 135.2 (m), 109.1 – 106.7 (m), 76.2, 76.2, 53.9.
- IR (neat) cm^{-1} 3307, 2922, 1743, 1653, 1524, 1499, 1327, 1216, 1006, 938.

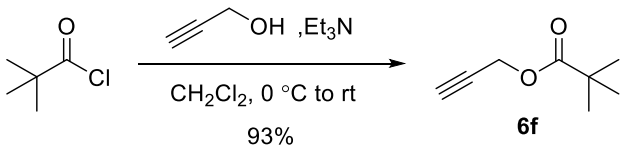
Preparation of 6e[3]



To a solution of 2-picolinic acid (1.23 g, 10 mmol), prop-2-yn-1-ol (560 mg, 10 mmol) in dry CH_2Cl_2 (30 mL) were added DCC and DMAP at room temperature. The resulting mixture was stirred at room temperature until the starting material was completely consumed (monitored by TLC analysis). The reaction was quenched with sat. aq. NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (eluent: petroleum ether/EtOAc = 100/1) to afford **6e** as a colorless oil (1.35 g, 84% yield).

- ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.74 – 8.71 (m, 1H), 8.13 – 8.10 (m, 1H), 7.84 – 7.79 (m, 1H), 7.48 – 7.44 (m, 1H), 4.96 – 4.95 (m, 2H), 2.50 – 2.49 (m, 1H).

Preparation of 6f[4]

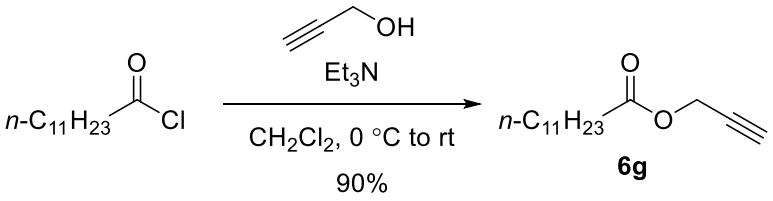


3. S. Gaspa, A. Porcheddu and L. D. Luca, *Org. Lett.* **2015**, *17*, 3666–3669.
4. T. Achard, A. Lepronier, Y. Gimbert, H. Clavier, L. Giordano, A. Tenaglia and G. Buono, *Angew. Chem. Int. Ed*. **2011,** *50*, 3552 –3556.

To a solution of prop-2-yn-1-ol (560 mg, 10.0 mmol), Et_3N (1.51 g, 15.0 mmol) in CH_2Cl_2 (30 mL) was added pivCl (1.44 g, 12.0 mmol) slowly at 0 °C. The resulting mixture was stirred at room temperature until the starting material was completely consumed (monitored by TLC analysis). The reaction was quenched with sat. aq. NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (eluent: petroleum ether/EtOAc = 100/1) to afford **6f** as a colorless oil. (1.3 g, 93% yield).

- ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.66 (d, *J* = 2.6 Hz, 2H), 2.44 (t, *J* = 2.4 Hz, 1H), 1.22 (s, 9H).

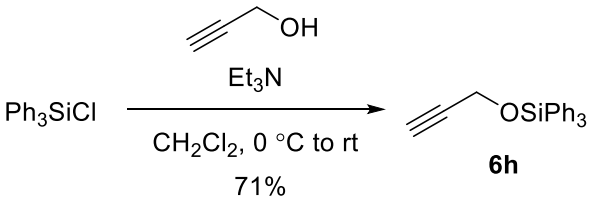
Preparation of 6g[5]



To a solution of prop-2-yn-1-ol (560 mg, 10.0 mmol), Et_3N (1.51 g, 15.0 mmol) in CH_2Cl_2 (30 mL) was added lauroyl chloride (2.62 g, 12.0 mmol) slowly at 0 °C. The resulting mixture was stirred at room temperature until the starting material was completely consumed (monitored by TLC analysis). The reaction was quenched with sat. aq. NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (eluent: petroleum ether/EtOAc = 100/1) to afford **6g** as a colorless oil. (2.14 g, 90% yield).

- ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.67 (d, *J* = 2.5 Hz, 2H), 2.46 (t, *J* = 2.5 Hz, 1H), 2.35 (t, *J* = 7.5 Hz, 2H), 1.67 – 1.60 (m, 2H), 1.33 – 1.28 (m, 16H), 0.87 (t, *J* = 6.7 Hz, 3H).

Preparation of 6h



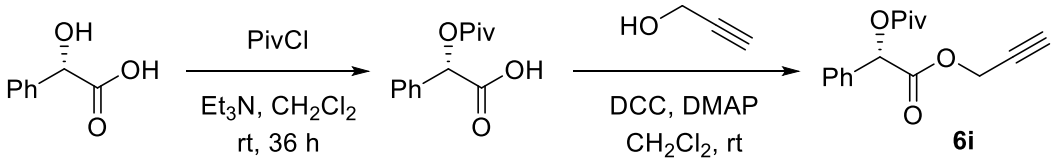
To a solution of prop-2-yn-1-ol (560 mg, 10.0 mmol), Et_3N (1.51 g, 15.0 mmol) in CH_2Cl_2 (30 mL) was added Ph_3SiCl (1.8 g, 12.0 mmol) slowly at 0 °C. The resulting mixture was stirred at room temperature until the starting material was completely consumed (monitored by TLC analysis). The reaction was quenched with sat. aq. NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (eluent: petroleum ether/EtOAc = 100/1) to afford **6h** as a white solid (1.2 g, 71% yield).

- m.p. 65.8-66.8 °C.
- ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.67 – 7.65 (m, 6H), 7.47 – 7.37 (m, 9H), 4.44 (d, *J* = 2.4 Hz, 2H), 2.37 (t, *J* = 2.4 Hz, 1H).
- ^{13}C NMR (100 MHz, Chloroform-*d*) δ 135.4, 133.3, 130.2, 127.9, 81.6, 73.5, 52.3.

5. S. Quader, S. E. Boyd, I. D. Jenkins and T. A.Houston, *J. Org. Chem*, **2007**, *72*, 1962-1979.

- IR (neat) cm^{-1} 3292, 2922, 1428, 1115, 1079, 998.
- HRMS (MALDI, m/z) calcd for $C_{21}H_{18}OSi$ $(M+Na)^+$: 337.1019, found 337.1018.

Preparation of 6i

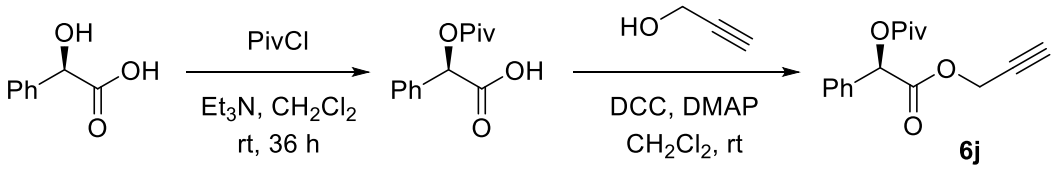


95% over 2 steps

To a solution of (*S*)-(+)-mandelic acid (1.82 g, 12 mmol) in CH_2Cl_2 was added PivCl (1.81 g, 15 mmol) at room temperature. The resulting mixture was stirred for 36 h to afford the crude Piv-protected (*S*)-(+)-mandelic acid. To a solution of the above crude Piv-protected (*S*)-(+)-mandelic acid and prop-2-yn-1-ol (560 mg, 10 mmol) in CH_2Cl_2 (30 mL) was added DCC and DMAP at room temperature. The resulting mixture was stirred at room temperature until the starting material was completely consumed (monitored by TLC analysis). The reaciton was quenched with sat. aq. NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (eluent: petroleum ether/EtOAc = 30/1) to afford **6i** as a colorless oil (2.6 g, 95% yield overall 2 steps).

- $[\alpha]^{25}_D$ = +80.8 (*c* = 0.7, $CHCl_3$).
- ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.50 – 7.48 (m, 2H), 7.41 – 7.38 (m, 3H), 5.92 (s, 1H), 4.70 (d, *J* = 2.5 Hz, 2H), 2.44 (t, *J* = 2.5 Hz, 1H), 1.29 (s, 9H).
- ^{13}C NMR (100 MHz, Chloroform-*d*) δ 177.7, 168.1, 133.4, 129.1, 128.7, 127.4, 76.6, 75.5, 74.0, 52.9, 38.7, 27.0.
- IR (neat) cm^{-1} 3290, 2975, 1761, 1735, 1139, 1048.
- HRMS (MALDI, m/z) calcd for $C_{16}H_{18}O_4$ $(M+Na)^+$: 297.1097, found 297.1103.

Preparation of 6j

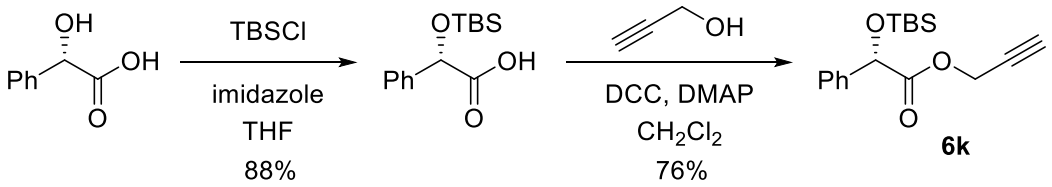


94% over 2 steps

To a solution of (*R*)-(-)-mandelic acid (1.82 g, 12 mmol) in CH_2Cl_2 was added PivCl (1.81 g, 15 mmol) at room temperature. The resulting mixture was stirred for 36 h to afford the crude Piv-protected (*R*)-(-)-mandelic acid. To a solution of the crude Piv-protected (*R*)-(-)-mandelic acid and prop-2-yn-1-ol (560 mg, 10 mmol) in CH_2Cl_2 (30 mL) were added DCC and DMAP at room temperature. The resulting mixture was stirred at room temperature until the starting material was completely consumed (monitored by TLC analysis). The reaction was quenched with sat. aq. NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (eluent: petroleum ether/EtOAc = 30/1) to afford **6j** as a colorless oil. (2.56 g, 94% yield overall 2 steps).

- $[\alpha]^{25}_D$ = -80.1 (*c* = 0.7, $CHCl_3$).
- ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.50 – 7.48 (m, 2H), 7.41 – 7.37 (m, 3H), 5.92 (s, 1H), 4.69 (d, *J* = 2.5 Hz, 2H), 2.44 (t, *J* = 2.5 Hz, 1H), 1.30 (s, 9H).
- ^{13}C NMR (100 MHz, Chloroform-*d*) δ 177.7, 168.1, 133.5, 129.1, 128.7, 127.4, 76.7, 75.5, 74.0, 52.9, 38.7, 27.0.
- IR (neat) cm^{-1} 3289, 2974, 1767, 1733, 1135.
- HRMS (MALDI, m/z) calcd for $C_{16}H_{18}O_4$ $(M+Na)^+$: 297.1097, found 297.1089

Preparation of 6k

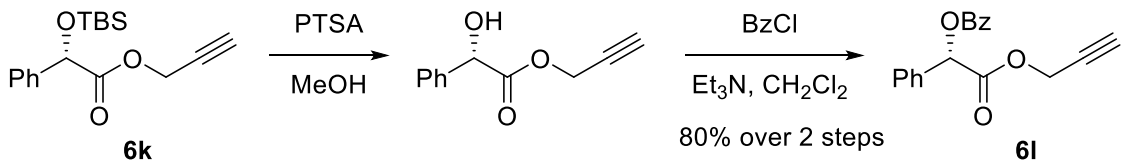


To a solution of (*S*)-(+)-mandelic acid (1.52 g, 10 mmol) in THF (30 mL) were added imidazole (1.62 g, 24 mmol) and TBSCl (3.01 g, 20.0 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min and at room temperature for another 12 h. The heterogeneous mixture was filtered and concentrated under reduced pressure. The resulting residue was dissolved in aq. NaOH (1.0 M, 30 mL) and stirred for 1.5 h. The reaction was diluted with H_2O (30 mL) and extracted with Et_2O (2×30 mL). The aqueous phase was acidified with 10% aq. HCl until a pH of 3.5. The resulting mixture was subsequently extracted with Et_2O (3×30 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the crude TBS-protect (*S*)-(+)-mandelic acid as a colorless solid (2.32 g, 88%).

To a solution of the crude TBS-protect (*S*)-(+)-mandelic acid (1.33 g, 5.0 mmol) and prop-2-yn-1-ol (280 mg, 5.0 mmol) in CH_2Cl_2 (20 mL) were added DCC and DMAP at room temperature. The resulting mixture was stirred at room temperature until the starting material was completely consumed (monitored by TLC analysis). The reaction was quenched with sat. aq. NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (eluent: petroleum ether/EtOAc = 30/1) to afford **6k** as a colorless oil. (1.15 g, 76% yield).

- $[\alpha]^{25}_D$ = +29.6 (*c* = 0.7, $CHCl_3$).
- ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.50 – 7.46 (m, 2H), 7.38 – 7.28 (m, 3H), 5.28 (s, 1H), 4.73 – 4.62 (m, 2H), 2.44 (t, *J* = 2.5 Hz, 1H), 0.93 (s, 9H), 0.13 (s, 3H), 0.05 (s, 3H).
- ^{13}C NMR (100 MHz, Chloroform-*d*) δ 171.3, 138.6, 128.3, 128.2, 126.4, 77.1, 75.1, 74.2, 52.4, 25.7, 18.3, -5.1, -5.2.
- IR (neat) cm^{-1} 3293, 2953, 2931, 2888, 2858, 1762, 1740, 1471, 1256, 1122, 1071, 996.
- HRMS (MALDI, m/z) calcd for $C_{17}H_{24}O_3Si$ $(M+Na)^+$: 327.1389, found 327.1392.

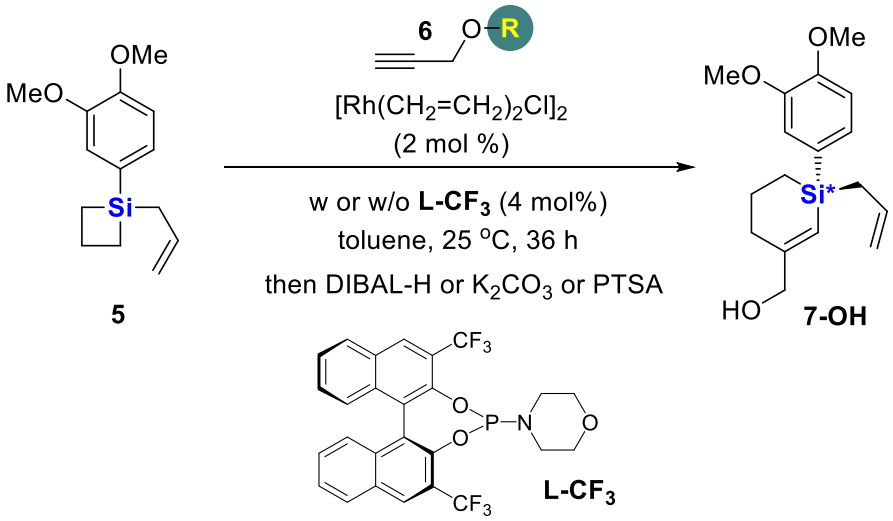
Preparation of 6l



To a solution of **6k** (1.52 g, 5.0 mmol) in MeOH (20 mL) was added *p*-toluenesulfonic acid (86 mg, 0.5 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min. The reaction was quenched with sat. aq. $NaHCO_3$ (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. To a solution of the resulting crude hydroxy ester and Et_3N (1.53 g, 15 mmol) in CH_2Cl_2 (30 mL) was added benzoyl chloride (913 mg, 6.5 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 4 h. The reaction was quenched with sat. aq. NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (eluent: petroleum ether/EtOAc = 30/1) to afford **6l** as a colorless oil. (1.28 g, 80% yield).

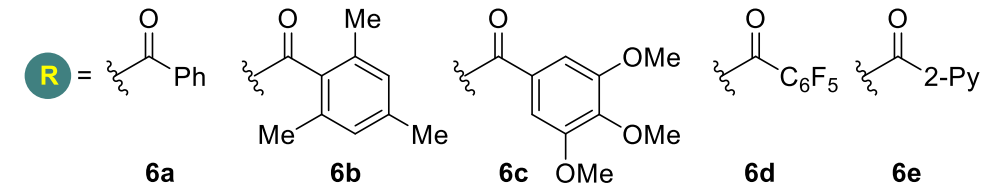
- $[\alpha]^{25}_D$ = +51.5 (*c* = 0.7, $CHCl_3$).
- ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.14 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.61 – 7.57 (m, 3H), 7.48 – 7.40 (m, 5H), 6.21 (s, 1H), 4.82 – 4.69 (m, 2H), 2.46 (t, *J* = 2.5 Hz, 1H).
- ^{13}C NMR (100 MHz, Chloroform-*d*) δ 168.1, 165.8, 133.5, 133.4, 130.0, 129.4, 129.1, 128.9, 128.4, 127.7, 75.5, 74.6, 53.0.
- IR (neat) cm^{-1} 3291, 2922, 1759, 1720, 1317, 1203.
- HRMS (MALDI, m/z) calcd for $C_{18}H_{14}O_4$ $(M+Na)^+$: 317.0784, found 317.0788.

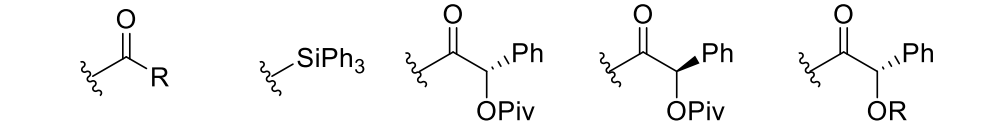
2.3. Screening of Ring Expansion Conditions



entry	**6**	**L-CF$_3$**	**7-OH** (%)[b,c]	**7-OH** (*er*)[d]
1	**6a**	w	75	90:10
2	**6b**	w	57	80:20
3	**6c**	w	N. D.	N. D.
4	**6d**	w	40	85:15
5	**6e**	w	N. R.	N. D.
6	**6f**	w	74	90:10
7	**6g**	w	60	85:15
8	**6h**	w	68	80:20

9	**6i**	w/o	74	50:50
10	**6i**	w	74	90:10 (≥ 99.5:0.5[e])
11	**6j**	w	74	85:15
12	**6k**	w	76	90:10
13	**6l**	w	71	88:12



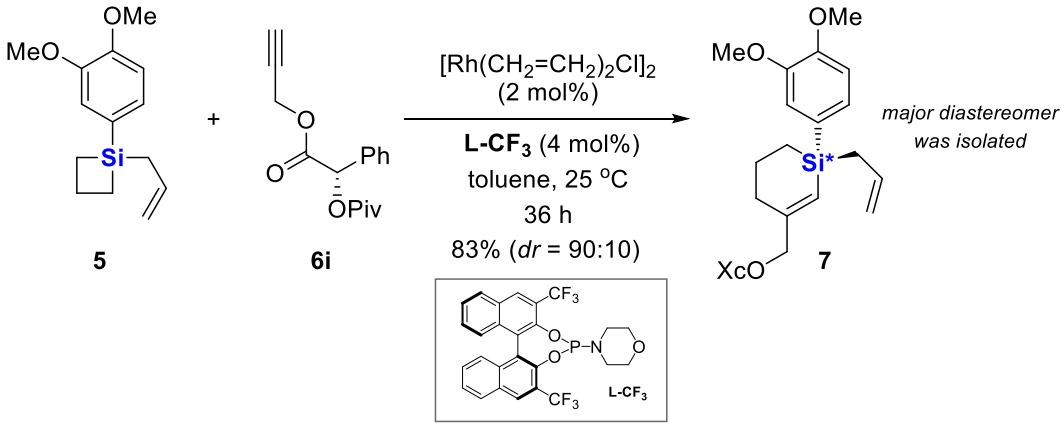


6f (R = *t*-Bu) **6h** **6i** **6j** **6k** (R = Si*t*-BuMe$_2$)
6g (R = *n*-$C_{11}H_{23}$) **6l** (R = Ph)

[a] Reaction conditions: **5** (0.2 mmol), **6** (0.2 mmol), [Rh(CH_2=CH_2)$_2$Cl]$_2$ (2 mol%), L-CF_3 (4 mol%) in toluene, 25 °C, 36 h, then DIBAL-H for entries 1-7, PTSA for entry 8, K_2CO_3/MeOH for entries 9-13. [b] The *R*-configuration at Si was determined according to our previous work. [c] Isolated yields [d] Determined by HPLC analysis using a chiral stationary phase. [e] The *er* value of **7-OH** obtained from the separated major diastereomer.

2.4. Synthesis of (-)-Sila-Mesembranol (4•HOAc)

Preparation of 7

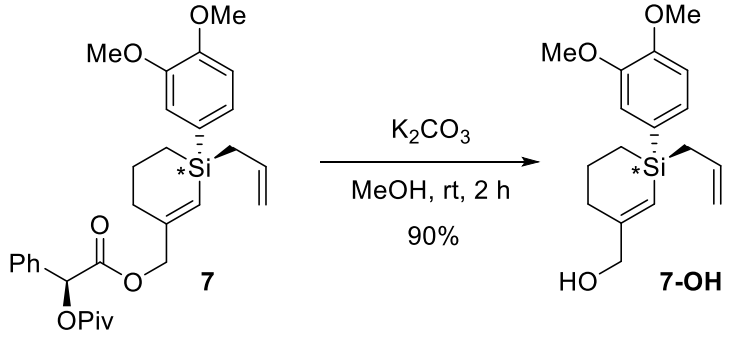


A solution of [Rh(CH_2=CH_2)$_2$]$_2$ (19 mg, 0.004 mmol) and **L-CF$_3$** (51 mg, 0.008 mmol) in toluene (12 mL) was stirred 10 min at room temperature before adding **5** (600 mg, 2.42 mmol) and **6i** (663 mg, 2.42 mmol) subsequently. The reaction mixture was stirred at room temperature for 36 h and concentrated under reduced pressure. The crude products were purified by silica gel column chromatography (gradient eluent: petroleum ether/EtOAc = 50:1→30:1) to afford **7** as a colorless oil (1.01 g, 83% yield, *dr* = 90:10). Further separation by silica gel column chromatography

(gradient eluent: petroleum ether/EtOAc = 50:1→40:1) to afforded the desired major diastereomer of **7** as a colorless oil (563 mg, 45% yield, *dr* ≥ 95:5).

- R*f* = 0.3 (petroleum ether/EtOAc = 10:1). (note: Two diastereomers in TLC overlap as one spot. The major isomer flows out during silica gel column chromatography, indicating it is slightly less polar than the minor one)
- $[\alpha]^{25}_{D}$ = +14.75 (*c* = 0.8, $CHCl_3$).
- ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.49 (dd, *J* = 6.7, 3.0 Hz, 2H), 7.34 – 7.32 (m, 3H), 6.99 (dd, *J* = 7.9, 1.5 Hz, 1H), 6.92 (d, *J* = 1.4 Hz, 1H), 6.88 (d, *J* = 7.9 Hz, 1H), 5.94 (s, 1H), 5.75 – 5.68 (m, 1H), 5.53 (s, 1H), 4.88 – 4.82 (m, 2H), 4.63 (dd, *J* = 13.9, 1.5 Hz, 1H), 4.48 (dd, *J* = 14.0, 1.5 Hz, 1H), 3.89 (s, 6H), 1.97 – 1.94 (m, 2H), 1.80 – 1.75 (m, 4H), 1.29 (s, 9H), 0.85 (dd, *J* = 7.8, 5.5 Hz, 2H).
- ^{13}C NMR (100 MHz, Chloroform-*d*) δ 177.8, 168.5, 155.1, 150.0, 148.5, 134.3, 134.1, 129.0, 128.7, 128.0, 127.4, 127.4, 117.6, 116.5, 113.7, 110.9, 74.2, 69.7, 55.9, 55.7, 38.7, 30.3, 27.0, 21.8, 20.9, 9.0.
- ^{29}Si NMR (119 MHz, Chloroform-d) δ -21.55.
- IR (neat) cm^{-1} 2929, 1736, 1588, 1509, 1252, 1143.
- HRMS (MALDI, m/z) calcd for $C_{30}H_{38}O_6Si$ $(M+Na)^+$: 545.2330, found 545.2338.

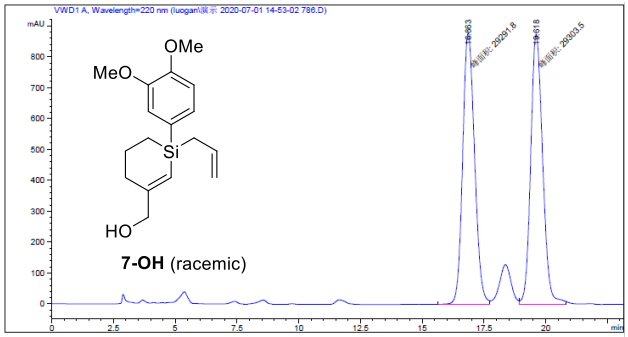
Preparation of 7-OH



To a solution of **7** (52 mg, 0.1 mmol) in MeOH (1.0 mL) was added K_2CO_3 (28 mg, 0.2 mmol) at room temperature. The mixture was stirred at room temperature for 2 h before diluting with EtOAc (5 mL) and H_2O (20 mL). The aqueous phase extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (gradient eluent: petroleum ether/EtOAc = 4/1~2/1) to afford **7-OH** as a colorless oil (27 mg, 90% yield). The *er* was determined on Daicel Chiralcel OD-H column with hexane/2-propanol = 95/5, flow = 1.0 mL/min. Retention times: 16.8 min [minor enantiomer], 19.5 min [major enantiomer]. *er* = 99.5:0.5).

- $[\alpha]^{25}_{D}$ = -30.16 (*c* = 0.38, $CHCl_3$).
- ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.09 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.01 (d, *J* = 1.5 Hz, 1H), 6.89 (d, *J* = 7.9 Hz, 1H), 5.87 (s, 1H), 5.83 – 5.76 (m, 1H), 4.91 – 4.83 (m, 2H), 4.07 (s, 2H), 3.88 (d, *J* = 6.1 Hz, 6H), 2.08 – 2.05 (m, 2H), 1.89 – 1.82 (m, 4H), 0.95 (t, *J* = 6.6 Hz, 2H).
- ^{13}C NMR (100 MHz, Chloroform-*d*) δ 161.6, 150.0, 148.5, 134.5, 128.5, 127.4, 116.4, 113.6, 113.5, 110.9, 68.2, 55.9, 55.6, 30.5, 22.2, 21.1, 9.3.
- ^{29}Si NMR (119 MHz, Chloroform-d) δ -18.84.

- IR (neat) cm^{-1} 3392, 2997, 2913, 2851, 1617, 1588, 1508, 1462, 1389, 1251, 1232, 1144, 1105, 1026.
- HRMS (MALDI, m/z) calcd for $C_{17}H_{24}O_3Si$ $(M+H)^+$: 305.1567, found 305.1567.

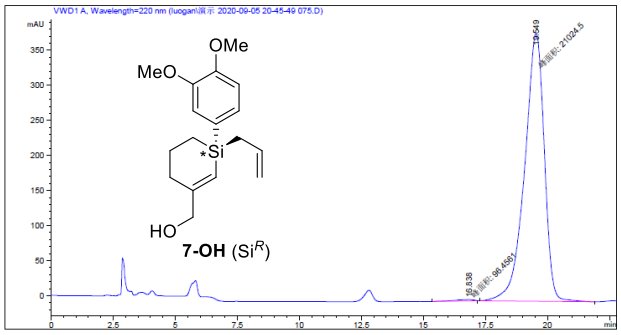


面积百分比报告

排序 : 信号
乘积因子 : 1.0000
稀释因子 : 1.0000
内标使用乘积因子和稀释因子

信号 1: VWD1 A, Wavelength=220 nm

峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	16.863	MF	0.5562	2.92918e4	877.70160	49.9901
2	19.618	MF	0.5591	2.93035e4	873.53949	50.0099



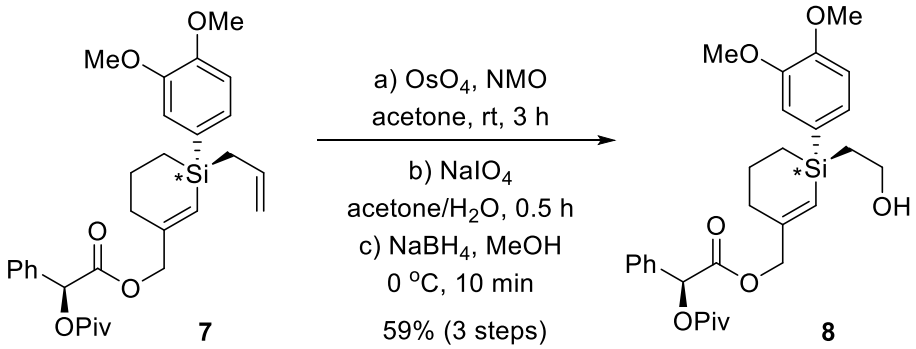
面积百分比报告

排序 : 信号
乘积因子 : 1.0000
稀释因子 : 1.0000
内标使用乘积因子和稀释因子

信号 1: VWD1 A, Wavelength=220 nm

峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	16.838	MM	0.8945	96.45609	1.79717	0.4567
2	19.549	MM	0.9169	2.10245e4	382.15466	99.5433

Preparation of 8



A solution of **7** (2.0 g, 3.83 mmol), NMO (672 mg, 5.75 mmol) and OsO_4 (3.8 mL, 5.0 mg/mL in water) in acetone (50 mL) was stirred at room temperature for 3 h. The resulting mixture was diluted with EtOAc (30 mL) and H_2O (100 mL). The aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure, affording the crude diol, which was used in the next step without purification.

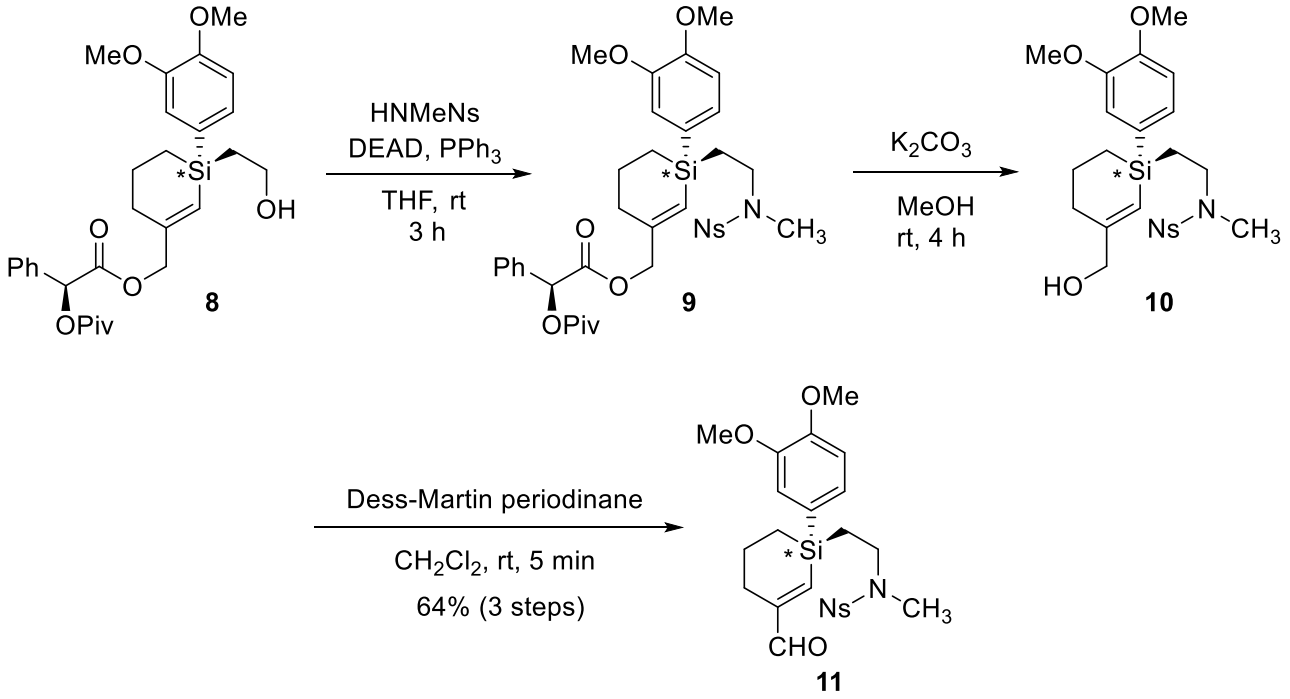
A solution of the above crude diol and $NaIO_4$ (1.62 g, 7.66 mmol) in acetone/H_2O (2:1, 45 mL) was stirred at room temperature for 30 min. The reaction was diluted with EtOAc (30 mL) and H_2O (100 mL). The aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure, affording the crude aldehyde, which was used in the next step without purification.

To a solution of the above crude aldehyde in MeOH (10 mL) was added $NaBH_4$ (145.5 mg, 3.83 mmol) slowly at 0 °C. The mixture was stirred at 0 °C for 10 min. before diluting with EtOAc

(20 mL) and H_2O (50 mL). The aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (gradient eluent: petroleum ether/EtOAc = 4/1~2/1) to afford **8** as a colorless oil (1.19 g, 59% yield over 3 steps).

- $[\alpha]^{25}_D$ = +16.68 (*c* = 3.25, $CHCl_3$).
- ^{1}H NMR (600 MHz, Chloroform-d) δ 7.48 (s, 2H), 7.34 (s, 3H), 7.01 (d, *J* = 7.8 Hz, 1H), 6.93 (s, 1H), 6.88 (d, *J* = 7.9 Hz, 1H), 5.93 (s, 1H), 5.55 (s, 1H), 4.59 (d, *J* = 14.2 Hz, 1H), 4.50 (d, *J* = 14.2 Hz, 1H), 3.89 (s, 6H), 3.69 (t, *J* = 8.3 Hz, 2H), 1.96 (t, *J* = 6.0 Hz 2H), 1.80 – 1.75 (m, 2H), 1.47 (brs, 1H), 1.29 (s, 9H), 1.25 – 1.18 (m, 2H), 0.92 – 0.87 (m, 1H), 0.85 – 0.80 (m, 1H).
- ^{13}C NMR (100 MHz, Chloroform-d) δ 177.9, 168.5, 155.1, 150.2, 148.7, 134.1, 129.1, 128.7, 128.1, 127.4, 127.4, 117.4, 116.6, 111.1, 74.3, 69.5, 59.7, 56.0, 55.7, 38.8, 30.3, 27.0, 20.9, 19.5, 9.9.
- ^{29}Si NMR (119 MHz, Chloroform-d) δ -18.78.
- IR (neat) cm^{-1} 3524, 2924, 1736, 1588, 1509, 1251, 1143, 1028.
- HRMS (MALDI, m/z) calcd for $C_{39}H_{38}O_7Si$ $(M+Na)^+$: 549.2279, found 549.2280.

Preparation of 11



To a solution of **8** (1.0 g, 1.9 mmol), *N*-methyl-2-nitrobenzenesulfonamide (452 mg, 2.1 mmol) and PPh_3 (996 mg, 3.8 mmol) in dry THF (30 mL) was added diethyl azodicarboxylate (496 mg, 2.85 mmol) in dry THF (1.0 mL) dropwise at room temperature. The resulting mixture was stirred at room temperature for 3 h before removing THF. The residue was purified by silica gel flash column chromatography (eluent: petroleum ether/EtOAc = 3/1) to afford a crude **9**, which was used in next step directly.

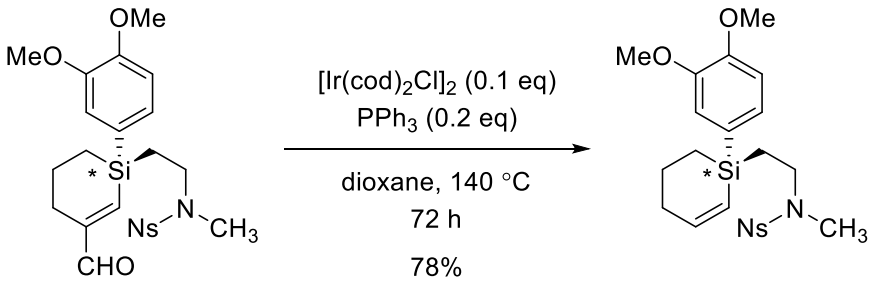
To a solution of the crude **9** in MeOH (30 mL) was added K_2CO_3 (524 mg, 3.8 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h before diluting with

EtOAc (30 mL) and H_2O (100 mL) The aqueous was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The crude allylic alcohol **10** was used in the next step without purification.

To a solution of the above crude alcohol **10** and $NaHCO_3$ (817 mg, 9.5 mmol) in CH_2Cl_2 (20 mL) was added Dess-Martin periodinane (1.2 g, 2.85 mmol) slowly at 0 °C. The resulting mixture was stirred at room temperature for 5 min. The reaction was quenched with sat. aq. $Na_2S_2O_3$ (50 mL). The aqueous phase extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (gradient eluent: petroleum ether/EtOAc = 5/1~3/1) to afford **11** as a light yellow oil (591 mg, 62% yield over 3 steps).

- $[\alpha]^{25}_D$ = -41.78 (*c* = 0.9, $CHCl_3$)
- ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.49 (s, 1H), 7.91 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.68 – 7.63 (m, 2H), 7.62 – 7.58 (m, 1H), 7.07 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.02 (s, 1H), 6.99 (s, 1H), 6.92 (d, *J* = 7.9 Hz, 1H), 3.90 (d, *J* = 8.0 Hz, 7H), 3.38 – 3.34 (m, 2H), 2.86 (s, 3H), 2.42 – 2.36 (m, 2H), 1.90 – 1.88 (m, 2H), 1.37 – 1.25 (m, 2H), 1.13 – 1.07 (m, 1H), 1.05 – 1.01 (m, 1H).
- ^{13}C NMR (100 MHz, Chloroform-*d*) δ 194.8, 159.5, 150.9, 149.2, 148.2, 144.4, 133.4, 132.4, 131.4, 130.8, 127.6, 124.9, 124.1, 116.3, 111.5, 56.1, 55.8, 46.4, 33.6, 25.9, 20.5, 13.5, 9.5.
- ^{29}Si NMR (119 MHz, Chloroform-d) δ -16.56.
- IR (neat) cm^{-1} 2932, 1685, 1587, 1544, 1509, 1463, 1373, 1348, 1253, 1235, 1163, 1147, 1108, 1024.
- HRMS (MALDI, m/z) calcd for $C_{23}H_{28}N_2O_7SSi$ $(M+Na)^+$: 527.1284, found 527.1285.

Preparation of 12



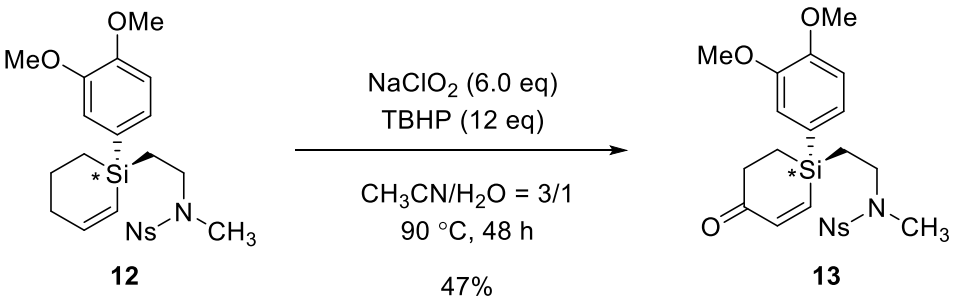
11 **12**

A solution of **11** (755 mg, 1.5 mmol), $[Ir(cod)_2Cl]_2$ (101 mg, 0.15 mmol) and PPh_3 (79 mg, 0.3 mmol) in dioxane (50 mL) was heated to 140 °C slowly and maintained at this temperature for 72 h. After removing the solvent under reduce pressure, the residue was purified by silica gel flash column chromatography (gradient eluent: petroleum ether/EtOAc = 8/1~4/1) to afford **12** as a light yellow oil (560 mg, 78% yield).

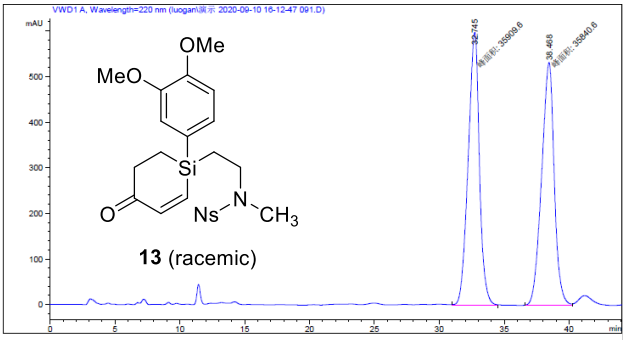
- $[\alpha]^{25}_D$ = -28.2 (*c* = 1.8, $CHCl_3$).
- ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.88 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.68 – 7.57 (m, 3H), 7.06 (dd, *J* = 7.8, 1.4 Hz, 1H), 6.98 (s, 1H), 6.95 (dt, *J* = 9.1, 5.1 Hz, 1H), 6.88 (d, *J* = 7.8 Hz, 1H), 5.83 (d, *J* = 14.1 Hz, 1H), 3.88 (d, *J* = 7.4 Hz, 6H), 3.36 – 3.31 (m, 2H), 2.86 (s, 3H), 2.22 – 2.18 (m, 2H), 1.84 – 1.78 (m, 2H), 1.25 – 1.19 (m, 2H), 0.96 – 0.90 (m, 2H).
- ^{13}C NMR (100 MHz, Chloroform-*d*) δ 152.5, 150.2, 148.8, 148.1, 133.2, 132.6, 131.4, 130.7, 127.6, 127.3, 124.0, 121.9, 116.3, 111.1, 55.9, 55.7, 46.7, 33.4, 30.8, 20.8, 13.8, 9.7.
- ^{29}Si NMR (119 MHz, Chloroform-d) δ -19.37.

- IR (neat) cm^{-1} 2935, 1669, 1588, 1544, 1510, 1373, 1253, 1235, 1161, 1109, 1024, 968.
- HRMS (MALDI, m/z) calcd for $C_{22}H_{28}N_2O_6SSi$ $(M+Na)^+$: 499.1335, found 499.1316.

Preparation of 13



A solution of **12** (250 mg, 0.52 mmol) and *tert*-butyl hydroperoxide (810 mg, 70% in water, 6.3 mmol) and $NaClO_2$ (189 mg, 2.1 mmol) in CH_3CN/H_2O (3:1, 15 mL) was stirred at 90 °C for 48 h. The resulting mixture was diluted with EtOAc (10 mL) and H_2O (20 mL). The aqueous phase extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (gradient eluent: petroleum ether/EtOAc = 5/1~2/1) to afford **13** as a light yellow oil (120 mg, 47% yield). The *er* was determined on Daicel Chiralcel AD-H column with hexane/2-propanol = 90/10, flow = 1.0 mL/min. Retention times: 31.9 min [major enantiomer], 37.0 min [minor enantiomer]. *er* = 98.5:1.5

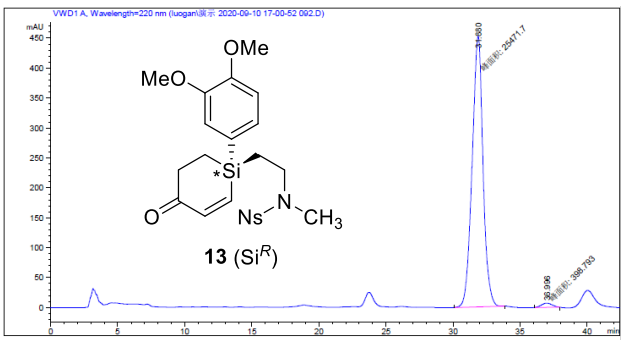


面积百分比报告

排序 : 信号
乘积因子 : 1.0000
稀释因子 : 1.0000
内标使用乘积因子和稀释因子

信号 1: VWD1 A, Wavelength=220 nm

峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	32.745	MM	1.0022	3.59096e4	597.20337	50.0481
2	38.468	MM	1.1242	3.58406e4	531.34607	49.9519



面积百分比报告

排序 : 信号
乘积因子 : 1.0000
稀释因子 : 1.0000
内标使用乘积因子和稀释因子

信号 1: VWD1 A, Wavelength=220 nm

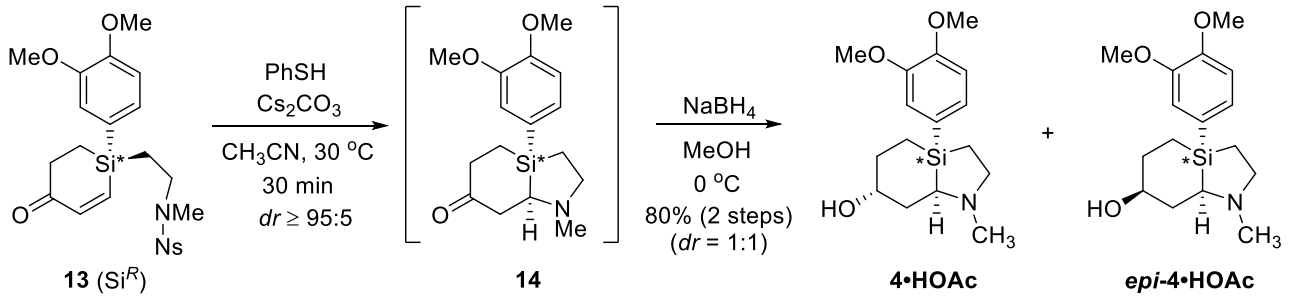
峰 #	保留时间 [min]	类型	峰宽 [min]	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	31.880	MM	0.9389	2.54717e4	452.14996	98.4585
2	36.996	MM	0.9283	398.79285	7.15986	1.5415

- $[\alpha]^{25}_D$ = -28.86 (*c* = 0.7, $CHCl_3$).
- ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.92 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.67 (ddd, *J* = 9.5, 7.4, 1.7 Hz, 2H), 7.60 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.14 (d, *J* = 14.5 Hz, 1H), 7.09 (dd, *J* = 7.9, 1.5 Hz, 1H),

7.00 (d, *J* = 1.4 Hz, 1H), 6.93 (d, *J* = 7.9 Hz, 1H), 6.83 (d, *J* = 14.5 Hz, 1H), 3.91 (d, *J* = 5.1 Hz, 6H), 3.41 – 3.37 (m, 2H), 2.86 (s, 3H), 2.75 – 2.70 (m, 2H), 1.41 – 1.24 (m, 4H);

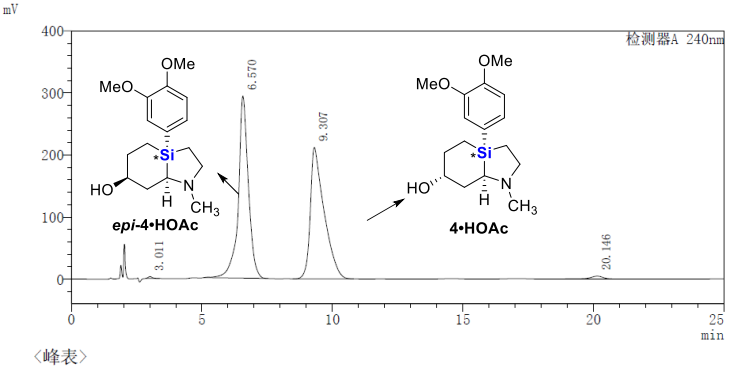
- ^{13}C NMR (100 MHz, Chloroform-d) δ 201.5, 151.1, 149.2, 148.2, 148.0, 144.5, 133.5, 132.2, 131.5, 130.8, 127.7, 124.1, 123.2, 116.2, 111.5, 56.1, 55.8, 46.2, 36.0, 33.6, 12.8, 7.9.
- ^{29}Si NMR (119 MHz, Chloroform-d) δ -19.26.
- IR (neat) cm^{-1} 2930, 1717, 1588, 1543, 1509, 1463, 1364, 1252, 1234, 1162, 1145, 1108, 1025.
- HRMS (MALDI, m/z) calcd for $C_{22}H_{26}N_2O_7SSi$ $(M+Na)^+$: 513.1128, found 513.1132.

***Preparation of (-)-Sila-mesembranol* (4•HOAc)**



13 (Si^R) **14** **4•HOAc** ***epi*-4•HOAc**

To a solution of **13** (25 mg, 0.05 mmol) in CH_3CN (1 mL) was added Cs_2CO_3 (49 mg, 0.15 mmol) and thiophenol (11 mg, 0.1 mmol) at room temperature. The reaction was sirred at 30 °C for 30 min. The mixture was filtered through a pad of cilite and washed with EtOAc. Removal of CH_3CN under reduced pressure to afforded the crude **14**. To a solution of **14** in MeOH (1 mL) was added $NaBH_4$ (2 mg, 0.05 mmol) at 0 °C. The reaction was stirred at 0 °C for 10 min. before quenching with sat. aq. $NaHCO_3$ and extracting with EtOAc (3 × 20 mL). The combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by neutral Aluminum Oxide to afford a mixture of **4** and ***epi*-4** as a yellow oil (12 mg, 80% yield, *dr* = 1:1). The 1:1 mixture of **4** and ***epi*-4** (100 mg) was further purified by Pre-HPLC [Gemini C_{18} (150×4.6 mm), H_2O/MeOH/HOAc = 90/10/0.05, flow = 1.0 mL/min] to afford pure 4•HOAc (Retention times: 9.3 min, 32 mg, 32%) and pure *epi*-4•HOAc (Retention times: 6.6 min, 42 mg, 42%) as a colorless oil.



〈峰表〉

检测器A 240nm

峰号	保留时间	化合物名	面积	面积%
1	3.011		32126	0.202
2	6.570		7906835	49.770
3	9.307		7788833	49.027
4	20.146		158902	1.000
总计			15886696	100.000

(-)-sila-mesembranol•HOAc (4•HOAc):

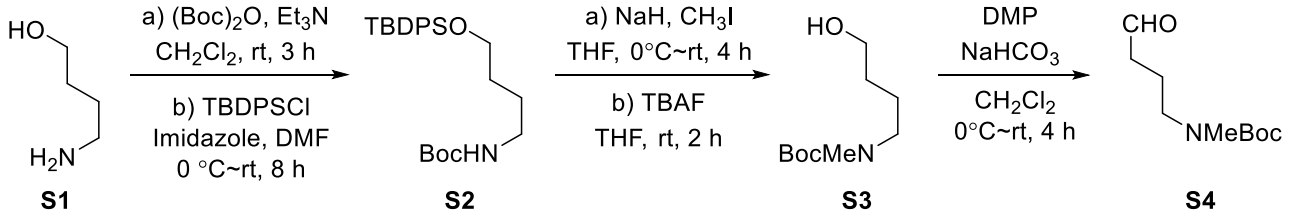
- $[\alpha]^{25}_D$ = -6.7 (*c* = 0.75, $CHCl_3$).
- ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.15 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.02 (d, *J* = 1.4 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 4.15 (t, *J* = 5.0 Hz, 1H), 3.90 (d, *J* = 8.1 Hz, 6H), 3.42 (ddd, *J* = 10.5, 8.0, 2.3 Hz, 1H), 2.55 – 2.52 (m, 1H), 2.46 (s, 3H), 2.32 – 2.28 (m, 1H), 2.27 – 2.22 (m, 1H), 1.82 (t, *J* = 3.5 Hz, 1H), 1.66 – 1.60 (m, 2H), 1.33 – 1.27 (m, 2H), 1.17 – 1.11 (m, 2H).
- ^{13}C NMR (150 MHz, Chloroform-d) δ 150.9, 149.0, 127.4, 125.2, 116.0, 111.3, 68.3, 58.5, 56.0, 55.7, 52.8, 41.9, 30.9, 29.6, 11.3, 3.3.
- ^{29}Si NMR (79 MHz, Chloroform-d) δ 1.91.
- IR (neat) cm^{-1} 3356, 2920, 2849, 1588, 1509, 1462, 1389, 1310, 1253, 1234, 1145, 1068, 1025.
- HRMS (MALDI, m/z) calcd for $C_{16}H_{25}NO_3Si$ $(M+H)^+$: 308.1682, found 308.1678.

***epi*-(-)-sila-mesembranol•HOAc (*epi*-4•HOAc):**

- $[\alpha]^{25}_D$ = -1.0 (c = 0.7, $CHCl_3$).
- ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.14 (dd, *J* = 7.8, 1.2 Hz,1H), 7.03 (d, *J* = 1.4 Hz, 1H), 6.92 (d, *J* = 7.8 Hz, 1H), 3.96 (t, *J* = 10.2 Hz 1H), 3.90 (d, *J* = 6.4 Hz, 6H), 3.58 (t, *J* = 9.7 Hz, 1H), 2.55 (s, 3H), 2.52 – 2.47 (m, 1H), 2.37 (d, *J* = 14.5 Hz, 1H), 2.20 (dd, *J* = 12.1, 6.0 Hz, 1H), 2.11 (d, *J* = 4.4 Hz, 1H), 1.82 – 1.77 (m, 1H), 1.66 – 1.61 (m, 1H), 1.35 – 1.30 (m, 1H), 1.25 – 1.16 (m, 2H), 1.14 – 1.07 (m, 1H).
- ^{13}C NMR (100 MHz, Chloroform-*d*) δ 151.0, 149.0, 127.5, 124.3, 116.1, 111.4, 68.0, 58.2, 56.0, 55.8, 53.6, 41.5, 35.5, 32.2, 10.3, 7.5.
- ^{29}Si NMR (79 MHz, Chloroform-d) δ 2.26.
- HRMS (MALDI, m/z) calcd for $C_{16}H_{25}NO_3Si$ $(M+H)^+$: 308.1682, found 308.1684.

2.5. Synthesis of (-)-Mesembranol (1•HOAc)

***Preparation of S4*[6]**



To a solution of 4-aminobutan-1-ol (8.7 g, 97 mmol) and Et_3N (11.7 g, 116 mmol) in CH_2Cl_2 (100 mL) was added a solution of $(Boc)_2O$ (21.4 g, 97 mmol) in CH_2Cl_2 (20 mL) dropwise at room temperature. The mixture was stirred 3 h at room temperature before quenching with sat. aq. NH_4Cl and extracting with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude alcohol. To a solution of the crude alcohol in DMF (120 mL) was added imidazole (8.6 g, 126 mmol) and TBDPSCl (18.3 g, 97 mmol) at 0 °C. The mixture was stirred at room temperature for 8 h before quenching with sat. aq. NH_4C and extracting with EtOAc (3 × 50 mL). The combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (gradient eluent: petroleum ether/EtOAc = 10/1~5/1) to afford **S2** as a colorless oil (42.7 g, 99%).

6. H. Zhu, J. G. Wickenden, N. E. Campbell, J. C. T. Leung, K. M. Johnson and G. M. Sammis, *Org. Lett.,* **2009**, *11*, 2019–2022.

- ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.67 (dd, *J* = 7.5, 1.8 Hz, 4H), 7.43 – 7.36 (m, 6H), 4.61 (brs, 1H), 3.68 (q, *J* = 4.9, 4.2 Hz, 2H), 3.12 (d, *J* = 6.1 Hz, 2H), 1.57 (t, *J* = 3.3 Hz, 4H), 1.45 (s, 9H), 1.05 (s, 9H).

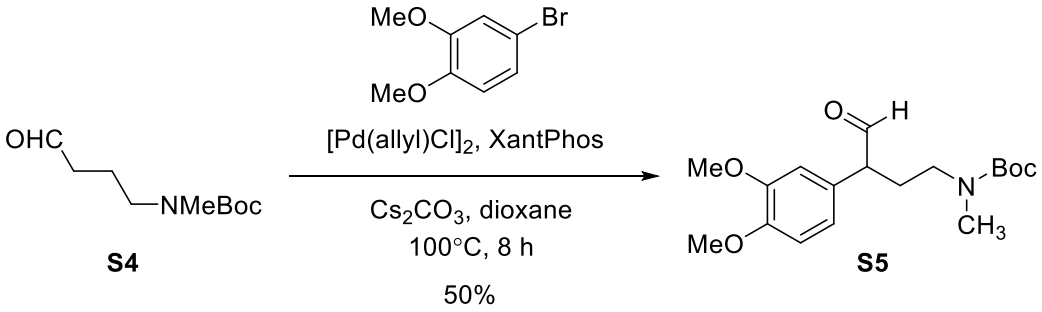
To a solution of **S2** (42.7 g, 97 mmol) in THF (200 mL) was added NaH (5.84 g, 146 mmol) slowly at 0 °C. The mixture was stirred at 0 °C for 1 h before adding a solution of CH_3I (18.0 g, 126 mmol) in THF (20 mL) was added at room temperature. The reaction was stirred for 4 h and quenched with sat. aq. NH_4Cl and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude *N*-Me product. To a solution of the crude *N*-Me product in THF (420 mL) was added TBAF (31.6 g, 121 mmol) at room temperature. The reaction was stirred for 2 h before quenching with sat. aq. NH_4Cl and extracting with EtOAc (3 × 50 mL). The combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (gradient eluent: petroleum ether/EtOAc = 5/1~2/1) to afford **S3** as a colorless oil (16.4 g, 99%).

- ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.64 – 3.60 (m, 2H), 3.20 (t, *J* = 6.9 Hz, 2H), 2.80 (s, 3H), 2.16 (brs, 1H), 1.60 – 1.42 (m, 4H), 1.42 (s, 9H).

To a solution of **S3** (6.4 g, 31.5 mmol) in CH_2Cl_2 (70 mL) were added $NaHCO_3$ (13.2 g, 157.5 mmol) and DMP (16.0 g, 37.8 mmol) slowly at 0 °C. The mixture was stirred at room temperature for 4 h before quenching with sat. aq. $Na_2S_2O_3$ and extracting with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (gradient eluent: petroleum ether/EtOAc = 10/1~4/1) to afford **S4** as a colorless oil (6.0 g, 95%).

- ^{1}H NMR (400 MHz, Chloroform-d) δ 9.75 (t, *J* = 1.5 Hz, 1H), 3.22 (t, *J* = 7.0 Hz, 2H), 2.81 (s, 3H), 2.43 (td, *J* = 7.2, 1.4 Hz, 2H), 1.85 – 1.77 (m, 2H), 1.42 (s, 9H).

Preparation of S5[7]

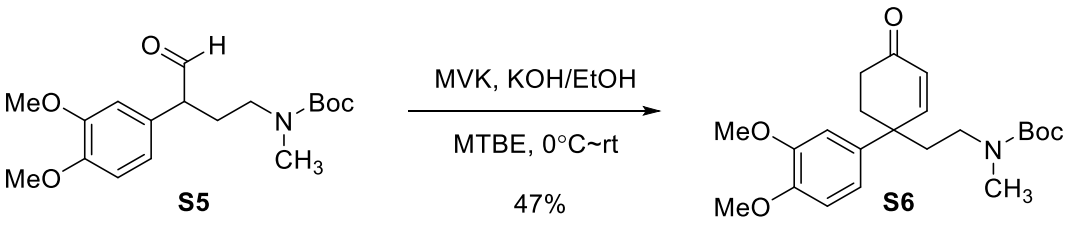


A mixture of **S4** (3.47 g, 16.0 mmol), 4-bromoveratrole (4.8 g, 24 mmol), Cs_2CO_3 (7.3 g, 22.4 mmol), $[Pd(allyl)Cl]_2$ (88 mg, 0.24 mmol), XantPhos (416 mg, 0.72 mmol) and H_2O (26 mg, 0.8 mmol) in dioxane (80 mL) was heated at 100 °C for 8 h under Ar. The mixture was cooled down to room temperature and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (gradient eluent: petroleum ether/EtOAc = 10/1~6/1) to afford **S5** as a light yellow oil (2.71 g, 50% yield).

- ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.61 (d, *J* = 1.4 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.73 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.65 (s, 1H), 3.85 (d, *J* = 1.3 Hz, 6H), 3.45 (s, 1H), 3.29 – 3.15 (m, 2H), 2.79 (s, 3H), 2.33 – 2.77 (m, 1H), 1.86 – 1.79 (m, 1H), 1.41 (s, 9H).

7. A. Bokka, J. X. Mao, J. Hartung, S. R. Martinez, J. A. Simanis, K. Nam, J. Jeon and X. Q. Shen, *Org. Lett.*, **2018**, *20*, 5158-5162.

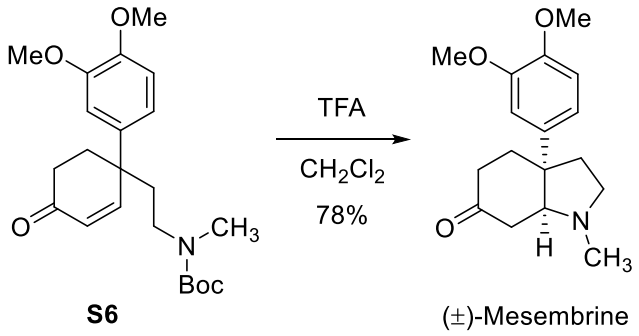
Preparation of S6



To a solution of **S5** (1.75 g, 5.19 mmol) and MVK (363 mg, 5.19 mmol) in MTBE (15 mL) was added a freshly prepared solution of KOH in EtOH (116 μL, 2 g/10 mL, 2.1 mmol) dropwise at 0 °C under Ar. The mixture was stirred at 0 °C for 2 h and at room temperature for 2 h. The mixture was diluted with MTBE (25 mL) and washed with sat. aq. NH_4Cl and sat. aq. NaCl. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (gradient eluent: petroleum ether/EtOAc = 10/1~3/1) to afford **S6** as a colorless oil (950 mg, 47% yield).

- ^{1}H NMR (400 MHz, Chloroform-d) δ 7.09 (brs, 1H), 6.82 (s, 3H), 6.17 (d, *J* = 10.2 Hz, 1H), 3.87 (d, *J* = 4.0 Hz, 6H), 3.17 (brs, 1H), 3.01 (brs, 1H), 2.77 (s, 3H), 2.39 – 2.32 (m, 1H), 2.28 – 2.19 (m, 3H), 2.14 – 2.07 (m, 1H), 2.03 – 1.96 (m, 1H), 1.42 (s, 9H).

Preparation of (-)-Mesembrine

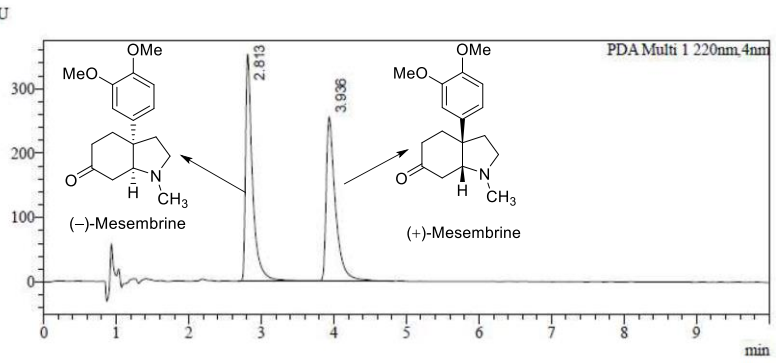


To a solution of **S6** (950 mg, 2.44 mmol) in CH_2Cl_2 (30 mL) was added TFA (10 mL) at room temperature. The mixture was stirred for 2 h before neutralized wiht sat. aq. $NaHCO_3$ and extracting with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (gradient eluent: CH_2Cl_2/MeOH = 50/1~30/1) to afford a racemic mesembrine as a colorless oil (550 mg, 78% yield). Then chiral preparation to afford (-)-mesembrine (Retention times:2.8 min, 246 mg) and (+)-mesembrine (Retention times: 3.9 min, 253 mg) (Daicel Chiralcel IG-H, eluent: 0.2% DEA/EtOH:CO_2 = 18:82, flow = 1.0 mL/min).

- ^{1}H NMR (400 MHz, Chloroform-d) δ 6.93 – 6.88 (m, 2H), 6.83 (d, *J* = 8.3 Hz, 1H), 3.88 (d, *J* = 8.3 Hz, 6H), 3.12 (ddd, *J* = 9.3, 7.7, 3.0 Hz, 1H), 2.94 (t, *J* = 3.6 Hz, 1H), 2.63 – 2.54 (m, 2H), 2.47 – 2.38 (m, 1H), 2.35 – 2.28 (m, 4H), 2.23 – 2.05 (m, 5H).

Sample Name : LG-09
Project ID :
Batch : 20210122.lcb
Vial : 1-29
Injection Volume : 1 uL
Method : C4_MD_20%_1mL.lcm
Additive : EtOH+0.2%DEA
Data Acquired : 2021/1/22 14:42:07 Acquired by : xh.zhang
Data File : C:\LabSolutions\Data\2021\202101\20210122\SFC LG-09 C4 MD 20% 1mL 02.lcd

<Chromatogram>



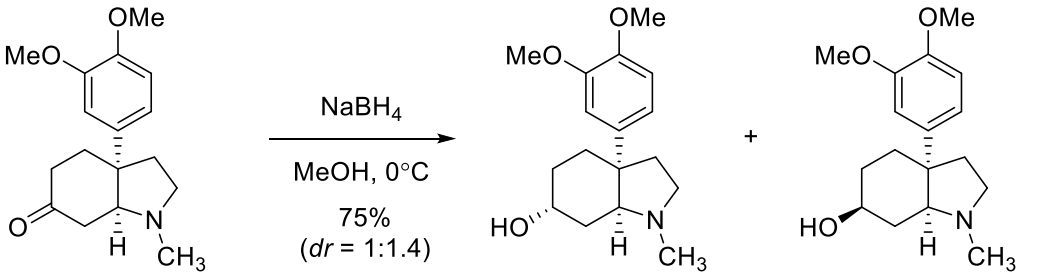
<Chromatogram Peak Table>

Peak Table

PDA Ch1 220nm

Peak	Ret. Time	Area	Height	Tailing Factor	Resolution	Area%
1	2.813	2360120	352189	2.151	--	51.179
2	3.936	2251372	254085	2.013	5.895	48.821
总计		4611492	606274			100.000

Synthesis of (-)-Mesembranol (1•HOAc)[8]



(-)-mesembrine **(-)-mesembranol** ***epi*-(-)-mesembranol**

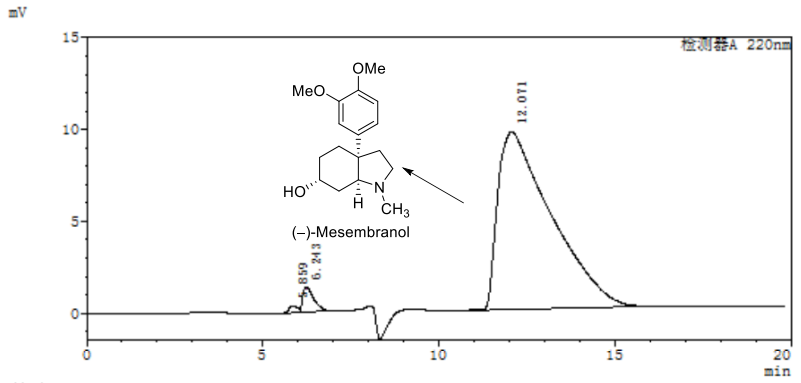
To a solution of (-)-mesembrine (80 mg, 0.28 mmol) in 4.0 mL MeOH was added $NaBH_4$ (11 mg, 0.28 mmol) at 0 °C. The mixture was stirred for 30 min at 0 °C before quenching with sat. aq. $NaHCO_3$ and extracting with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (eluent: CH_2Cl_2 /MeOH/NH_3•H_2O = 100/10/0.25) to afford *epi*-(-)-mesembranol as a colorless oil (35 mg, 44% yield, CH_2Cl_2/MeOH/NH_3•H_2O = 100/10/0.25, R_f = 0.6) and (-)-mesembranol as a white solid (25 mg, 31%, CH_2Cl_2 /MeOH/NH_3•H_2O = 100/10/0.25, R_f = 0.3). The ^1H, ^{13}C NMR spectra of (-)-mesembranol and *epi*-(-)-mesembranol are identical to those reported.[8] Then (-)-mesembranol (20 mg) purified by Pre-HPLC (H_2O/MeOH/HOAc = 75/25/0.1) to afford **1•HOAc** (Retention times: 12.1 min, 15 mg) as a colorless oil.

8. Y. Sasano, S. Nagasawa, M. Yamazaki, M. Shibuya, J. Park and Y. Iwabuchi, *Angew. Chem. Int. Ed.*, **2014**, *53*, 3236-3240.

<样品信息>

仪器名称	: Shimadzu LC-20AR
检测器	: Shimadzu SPD-20A
样品名	: LG
数据文件名	: 20201021-002.lcd
方法文件名	: LG.lcm
分析日期	: 2020/10/21 13:40:12
进样体积	: 100 uL
分析者	: WYN

<色谱图>



<峰表>

检测器A 220nm

峰号	保留时间	化合物名	面积	面积%
1	5.859		5995	0.564
2	6.243		29851	2.810
3	12.071		1026600	96.626
总计			1062446	100.000

(-)-mesembranol

- ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.91 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.87 (d, *J* = 2.2 Hz, 1H), 6.81 (d, *J* = 8.4 Hz, 1H), 4.02 – 3.94 (m, 1H), 3.87 (d, *J* = 7.1 Hz, 6H), 3.20 (td, *J* = 9.2, 4.6 Hz, 1H), 2.73 (t, *J* = 3.2 Hz, 1H), 2.35 (s, 3H), 2.26 (ddd, *J* = 11.0, 9.6, 6.7 Hz, 1H), 2.19 – 2.14 (m, 1H), 2.04 (dd, *J* = 9.1, 3.4 Hz, 2H), 1.94 – 1.86 (m, 1H), 1.83 – 1.72 (m, 2H), 1.55 – 1.48 (m, 1H), 1.23 – 1.17 (m, 1H).

***epi*-(-)-mesembranol**

- ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.90 – 6.86 (m, 2H), 6.81 (d, *J* = 8.2 Hz, 1H), 3.93 (t, *J* = 3.2 Hz, 1H), 3.88 (d, *J* = 7.0 Hz, 6H), 3.41 – 3.35 (m, 1H), 2.90 (t, *J* = 3.2 Hz, 1H), 2.48 (s, 3H), 2.41 – 2.27 (m, 2H), 2.16 (dd, *J* = 14.9, 2.7 Hz, 1H), 1.96 – 1.90 (m, 2H), 1.88 – 1.83 (m, 1H), 1.72 (dt, *J* = 13.6, 3.1 Hz, 1H), 1.64 (dt, *J* = 14.9, 3.0 Hz, 1H), 1.45 – 1.37 (m, 1H).

(-)-mesembranol•HOAc (1•HOAc):

- $[\alpha]^{25}_{D}$ = -16.9 (*c* = 0.85, $CHCl_3$).
- ^{1}H NMR (600 MHz, Chloroform-d) δ 6.87 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.84 (d, *J* = 2.3 Hz, 1H), 6.81 (d, *J* = 8.4 Hz, 1H), 4.07 – 4.02 (m, 1H), 3.87 (d, *J* = 10.2 Hz, 6H), 3.46 –3.42 (m, 1H), 2.96 (t, *J* = 3.5 Hz, 1H), 2.46 (s, 3H), 2.43 – 2.38 (m, 1H), 2.24 – 2.20 (m, 1H), 2.07 – 1.97 (m, 5H), 1.92 – 1.87 (m, 1H), 1.76 – 1.73 (m, 1H), 1.62 (ddd, *J* = 14.6, 10.8, 4.1 Hz, 1H), 1.22 – 1.17 (m, 2H).
- ^{13}C NMR (100 MHz, Chloroform-d) δ 148.8, 147.2, 138.4, 118.5, 110.8, 110.3, 70.4, 66.1, 56.0, 55.8, 53.9, 47.1, 40.9, 39.6, 34.3, 32.6, 31.9.

3. Study on the antidepressant activity of (-)-sila-mesembranol•HOAc (4•HOAc) and (-)-mesembranol•HOAc (1•HOAc):

Animals. Male C57BL/6 mice（4-12 weeks）were used in these studies. All procedures performed on mice were approved by the Animal Research Committee at the West China Hospital of Sichuan University (protocol2018159A). Mice were housed under standard conditions with a 12-h light–dark cycle, and provided with ad libitum access to water and food except when food/water deprivation was part of the experimental protocol.

Drug administration. (-)-sila-mesembranol•HOAc (**4•HOAc**) and (-)-mesembranol•HOAc (**1•HOAc**) were dissolved in 20% sulfobutylether-β-cyclodextrin. For the in vivo study, (-)-sila-mesembranol•HOAc (**4•HOAc**) and (-)-mesembranol•HOAc (**1•HOAc**) were intraperitoneally administered to mice at a dose of 10 mg kg-1. The vehicle, 20% sulfobutylether-β-cyclodextrin, was administered to control mice. The drugs were all administered 30 min before the behavioral experiments. For the electrophysiological study, (-)-sila-mesembranol•HOAc (**4•HOAc**) (10 μM) were loaded by bath application.

Animal models of lipopolysaccharide-induced depression. Mice were administered an intraperitoneal injection of lipopolysaccharide (LPS) at a dose of 1 mg kg-1. Animals in the vehicle control group were administered the same volume of saline. Behavioral tests were carried out at 24h after LPS or saline administration.

Animal models of chronic mild stress (CMS). After a two-week acclimation period, male C57BL/6 mice (8 weeks) were individually housed and subjected to various, randomly scheduled, low-intensity stressors 3 times a day for 4 weeks. No same stressor was applied for two consecutive days. The stressors included the following: (1) food and water deprivation for 12 h, (2) absence of sawdust in cage for 12 h, (3) moistened sawdust with water for 24 h, (4) tail nipping (1 cm from the tip of the tail) 5min, (5) physical restraint for 2 h, (6) forced swimming at 6 °C for 10 min, (7) 45° cage-tilt along the vertical axis for 12 h, (8) overnight illumination, (9) stroboscopic illumination for 12 h, and (10) lights-off for 12h during daylight phase. The control mice were standard housed and had no contact with these stressed mice.

Sucrose preference test (SPF). Mice were housed in individual cages. After 24 h of water and food deprivation, mice were free access to two bottles containing of 1% sucrose solution and of water for 2 h. The volumes of consumed sucrose solution and water were recorded and the sucrose preference was calculated as follows: sucrose preference (%) = sucrose consumption/(water + sucrose consumption) *100%.

Tail suspension test (TST). Mice were suspended individually by the tail with adhesive tape (60 cm above the floor) for 6 min. The tape was placed 1 cm from the tip of the tail. During the test, the mice were videotaped, and the duration of immobility was determined over the last 5 min of the test by an experienced observer blind to the experimental design.

Forced swimming test (FST). Mice were placed individually in a glass cylinder (diameter: 12 cm; height: 15 cm) containing 12 cm of water maintained at 25±1 *°C*. Mice were placed into the water for 6 min. The water was changed after each test in order to eliminate odors. During the test, the mice were videotaped, and the duration of immobility was determined over the last 4 min of the test by an experienced observer blind to the experimental design. Mice were judged to be immobile when they remained floating motionless in the water without struggling, making only slight movements to keep the head above water.

Spontaneous locomotor activity. Spontaneous locomotor activity was tested using a spontaneous activity assessment device (TAIMENG, China) equipped with infrared detectors to detect the horizontal and vertical activities. Each mouse was place in one testing chamber allowing for free activity for 6 min, and the number of activities (horizontally) and standings (vertically) during the last 5 min of the test was recorded automatically.

C-Fos immunohistochemistry. Mice were euthanized with 100 mg/kg pentobarbital and subsequently underwent transcardial perfusion with phosphate-buffered saline (PBS) followed by 10% formalin. Brains were extracted and placed in 10% formalin at 4 ℃ for another 24 h, and then embedded in 30% sucrose at 4 ℃ for 2 d. Coronal sections (30 μm thick) were cut on a freezing microtome. For immunohistochemistry, Coronal sections were rinsed three times (10 min each) in PBS, incubated in 0.5% Triton X-100 for 30 min at 37 ℃, and blocked with 10% normal goat serum (NGS) for 1 h at 37 ℃. Then sections were incubated with rabbit anti-c-Fos (1:2000, Sigma) antibody solution containing 0.02% Triton X-100, and 5% NGS at 4 ℃ overnight. Thereafter, sections were rinsed three times (10 min each) with PBS and incubated with goat anti-rabbit 555-conjugated secondary antibody (1:500, Abcam) solution containing 5% NGS for 2 h at room temperature. After nucleus labeling with DAPI, slides were cover-slipped with anti-fade solution, and imaged with exactly the same protocol. Positive cell counting was performed using Image J.

Electrophysiology. Acute slices were prepared as previously described[9]. Layer II/III pyramidal neurons in anterior cingulate cortex in slices were visualized with infrared optics on an upright microscope (BX51WI, Olympus). Miniature excitatory postsynaptic currents (mEPSCs) were recorded at a holding potential of -70 mV in the presence of TTX (300nM) and picrotoxin(100μM) using a Multiclamp 700A(Molecular Devices). Recordings were filtered at 2 KHz, digitized at 10 KHz and acquired with Digidata 1440A (Molecular Devices). mEPSCs were collected for 3-5 min for each cell. The recording pipettes (3-4 MΩ) were pulled from borosilicate glass on a Brown Flaming puller (Model P2000, Sutter Instruments). The intracellular solution in the patch pipette contained the following (in mM): 130 KCl, 2 NaCl, 10 HEPES, 5 EGTA, 2 Mg-ATP, 0.5 $CaCl_2$, pH adjusted to 7.3 with KOH. Cells were excluded from analysis if initial access resistances were >20 MΩ, or changed by >20% during the recording. Analysis was carried out by using Mini Analysis Program (version 6.0.3; Synaptosoft, Leonia, NJ). The current threshold for event detection was set at 8pA.

Statistics. Data were expressed as mean ± S.E.M. and analyzed using Origin 9 software. When comparing two data sets, unpaired two-tailed Student's t-test were performed for parametric data, and two-tailed Mann–Whitney were performed for nonparametric data. For data with more than two groups, one-way ANOVA test followed by post hoc Tukey test were used for parametric data. Significance was defined as $P < 0.05$.

4•HOAc inhibits glutamatergic transmission in the anterior cingulate cortex. To identify the brain region targeted by **4•HOAc**, the sila-analogue was intraperitoneally injected into healthy, untreated mice and the following brain regions related to depression were stained for c-Fos, an indicator of cell activation: prefrontal cortex, anterior cingulate cortex, amygdala, hippocampus,

9. R. T. Jiang, B. Diaz-Castro, L. L. Looger, B. S. Khakh, *J Neurosci.* **2016**, *36*, 3453–3470.

lateral habenula, and dorsal raphe nucleus.[10][27] The strong increase of the number of c-Fos+ cells after **4•HOAc** injection was only observed in the anterior cingulate cortex (Figs S-1A and S-1B), suggesting that this is one of the primary brain regions targeted by **4•HOAc**.

Excessive glutamate release has been associated with the pathogenesis of depression and the mechanism of antidepressants.[11][28] *Sceletium tortuosum* extractions have also been shown to inhibit *alpha*-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid (AMPA) receptor-mediated transmission.[12][29] Therefore, here, we performed patch–clamp electrophysiological experiments on acute brain slices to measure AMPA receptor-mediated miniature excitatory postsynaptic currents (mEPSCs) in the pyramidal neurons of the anterior cingulate cortex in the absence and presence of **4•HOAc**. The mEPSC frequency decreased after **4•HOAc** application, whereas the mEPSC amplitude was not affected (Figs S-1C–E), suggesting that **4•HOAc** may inhibit glutamate release *via* a presynaptic mechanism.

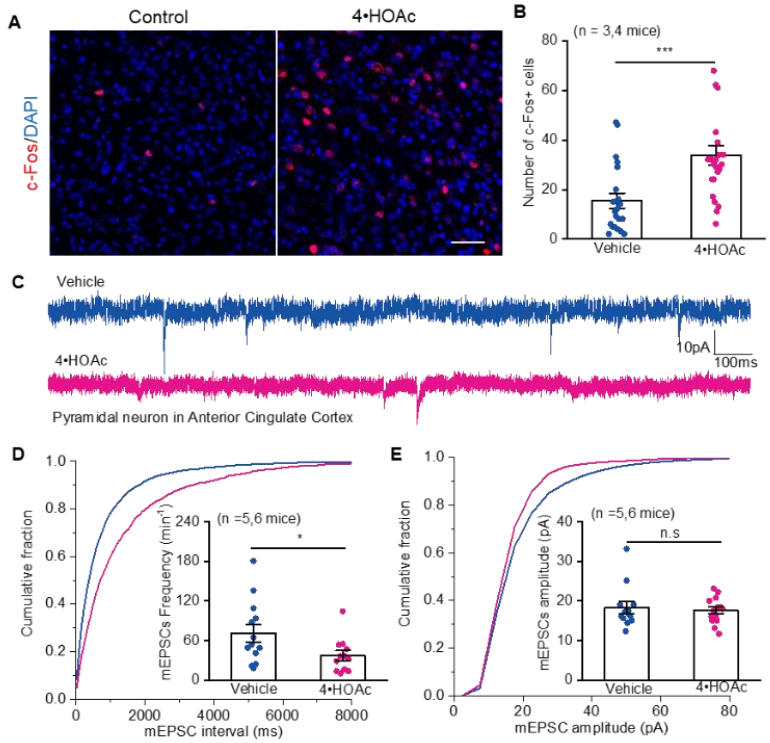


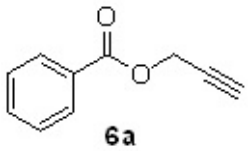
Fig S-1. Effects of (−)-sila-mesembranol (**4•HOAc**) on c-Fos activation and synaptic transmission in the anterior cingulate cortex. (**A**) Representative immunofluorescence images of c-Fos staining in the anterior cingulate cortex. Scale bar: 50 μm. (**B**) Number of c-Fos+ cells in the anterior cingulate cortex (two-tailed Mann–Whitney test, Z = −3.45). (**C**) Representative AMPA receptor-mediated miniature excitatory postsynaptic currents (mEPSCs) in the pyramidal neurons of the anterior cingulate cortex. (**D**) Cumulative distribution and average mEPSC frequency (two-tailed Mann–Whitney test, Z = 2.04). (**E**) Cumulative distribution and average mEPSC amplitude (two-tailed Mann–Whitney test, Z = −0.07). $^{*}P < 0.05$; n.s., not significant. Data are shown as mean ± SEM. DAPI: 4′,6-diamidino-2-phenylindole.

10 (a) K. A. Michelsen, J. Prickaerts, H. W. M. Steinbusch, *Prog Brain Res*. **2008**, *172*, 233-264; (b) V. Fasick, R. N. Spengler, S. amankan, N. D, Nader, T. A. Ignatowski, *Neurosci Biobehav Rev*. **2015**, *53*, 139-159; (c) J. S. Seo, P. Zhong, A. Liu, Z. Yan, P. Greengard, Mol Psychiatry. 2018, 23, 1113-1119.

11 (a) K. Hashimoto, A. Sawa, M. Iyo, *Biol Psychiatry*. **2007**, *62*, 1310-1316; (b) K. Hashimoto, *Prog Neuropsychopharmacol Biol Psychiatry.* **2011**, *35*, 1558-1568.

12 W. Dimpfel, R. Franklin, N. Gericke, L. Schombert, *J Ethnopharmacol*. **2018**, *223*, 135-141.

LG-09-O_H1_CDCl3_2021-2-2.220.fid



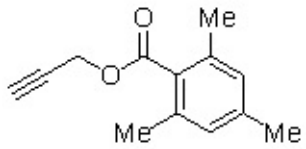
6a

8.080
8.062
7.592
7.574
7.555
7.465
7.446
7.427
7.260
4.927
4.921
2.529
2.523
2.517

2.08
1.07
2.14
2.13
1.00

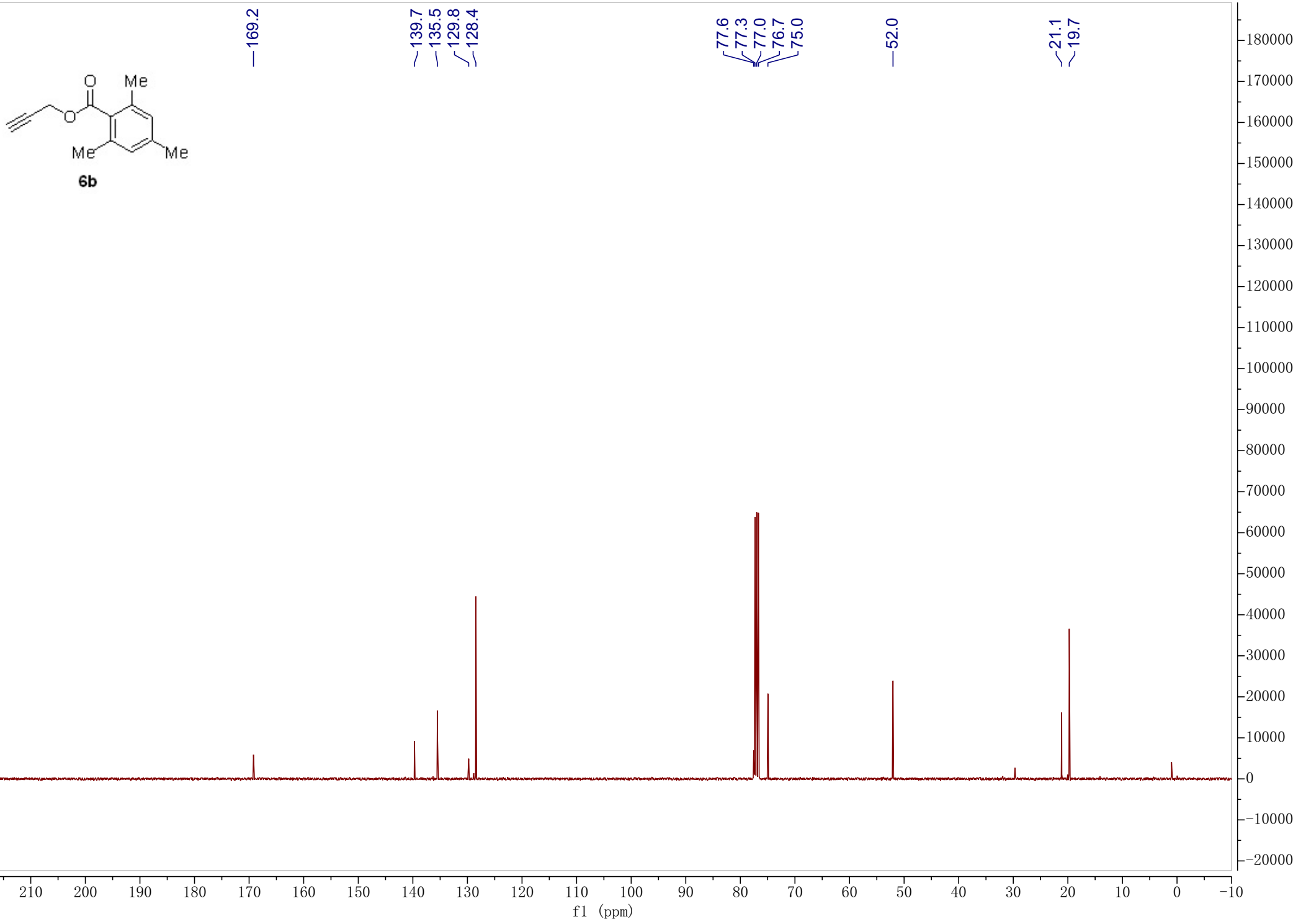
f1 (ppm)

LG-mes-1-CDCL3-H1-2021-1-26.10.fid

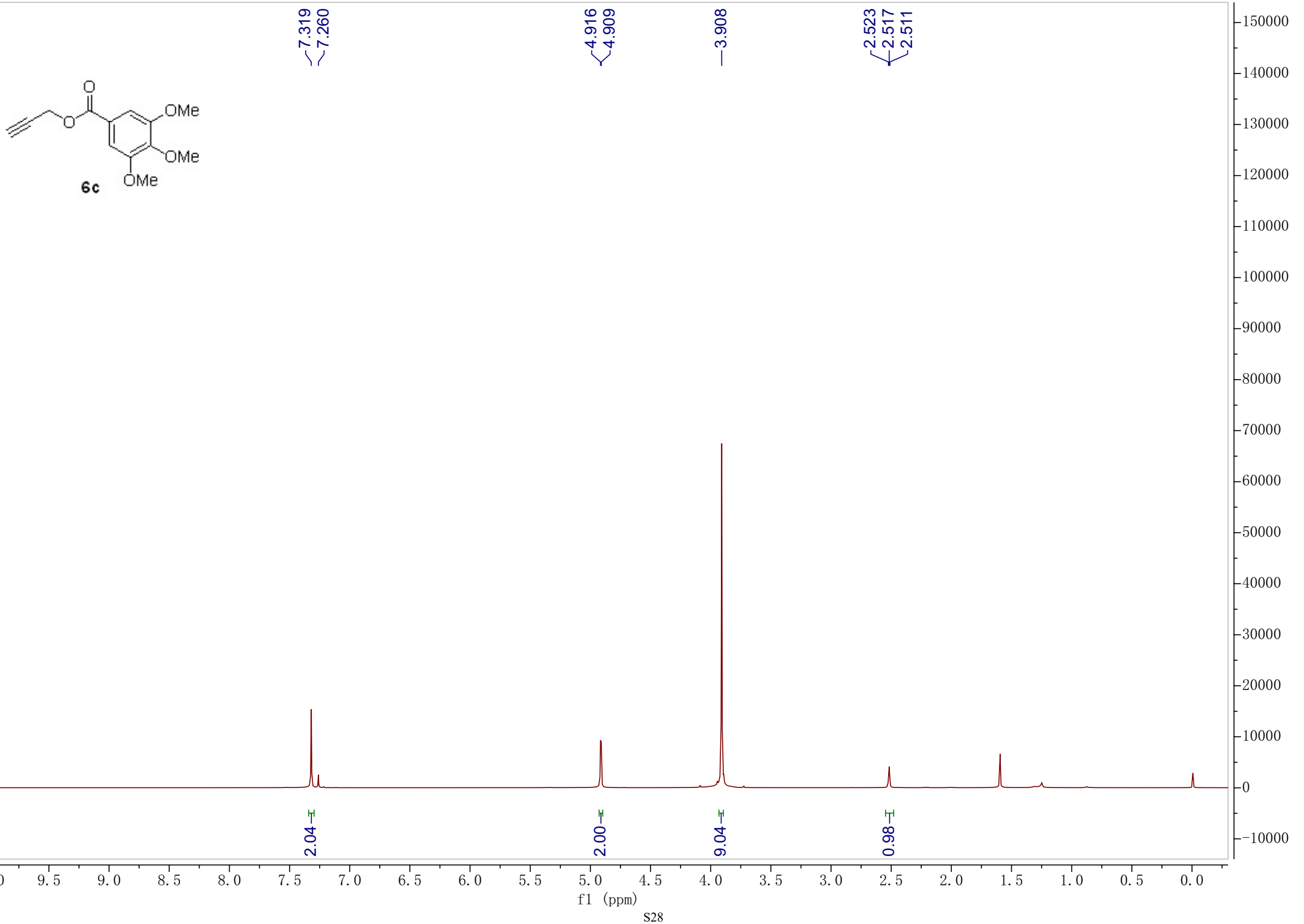


6b

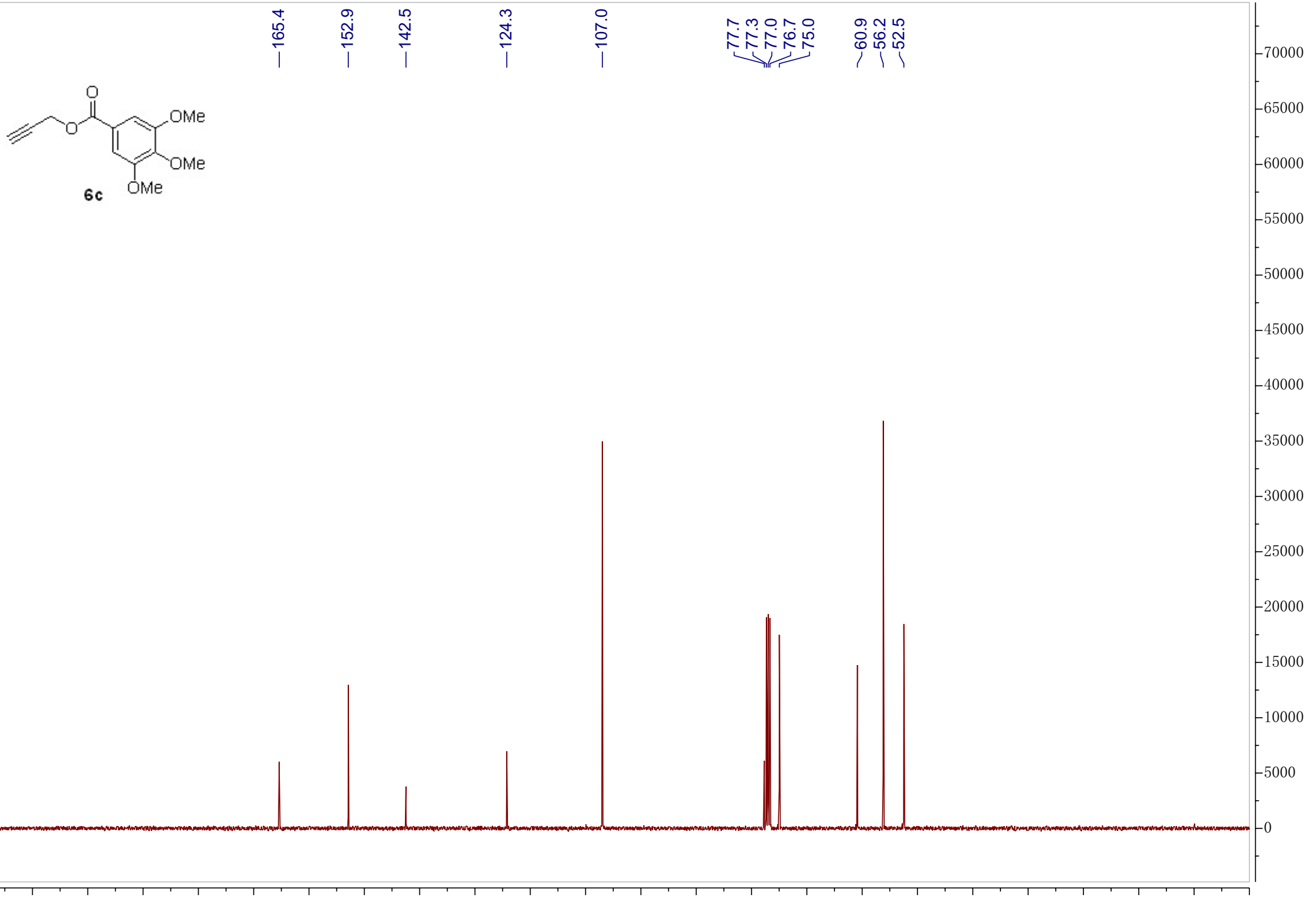
LG-Mes-1-CDCL3-C13-2021-1-26.10.fid



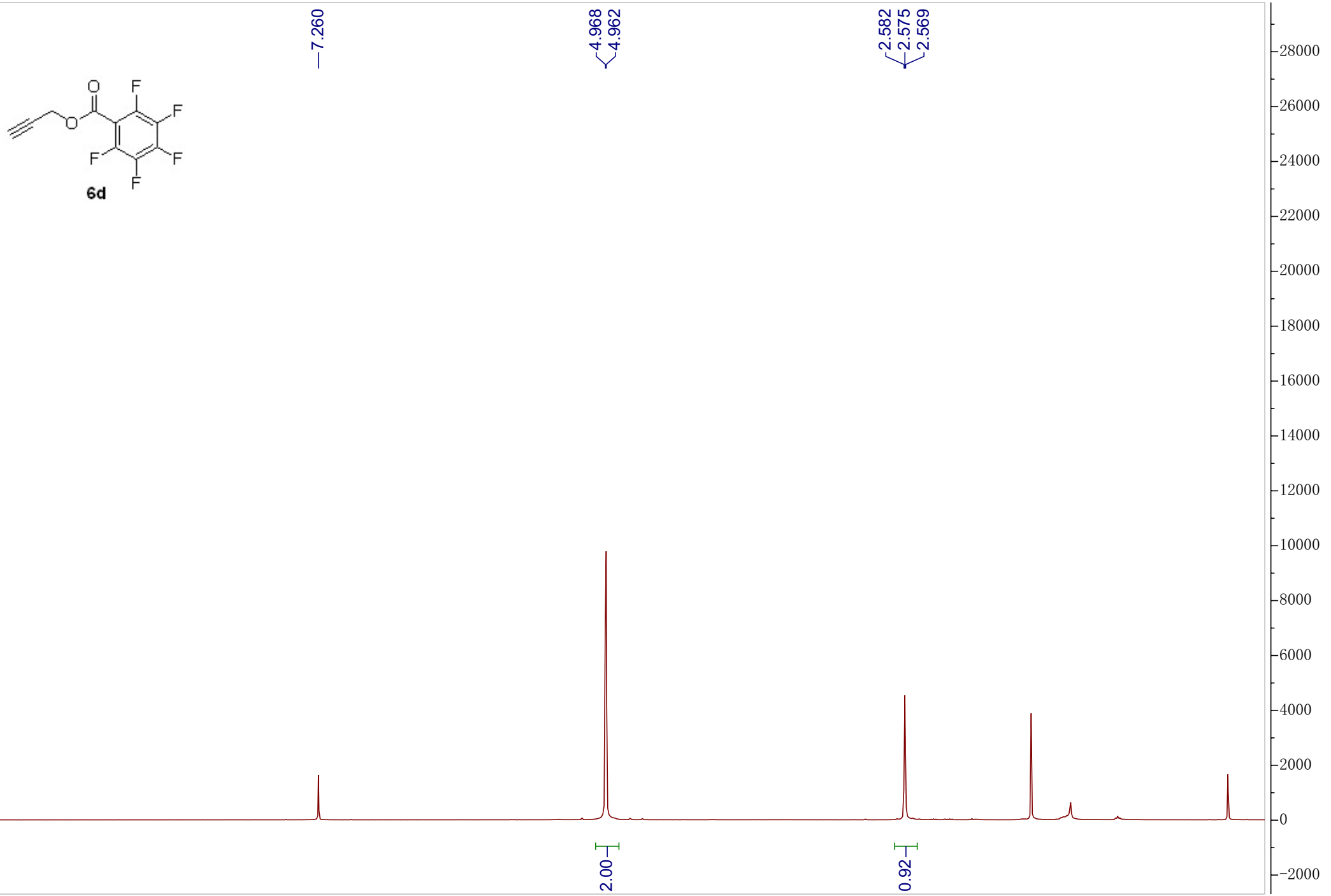
YYY-01-57_H1_CDCl3_2020-7-7.50.fid



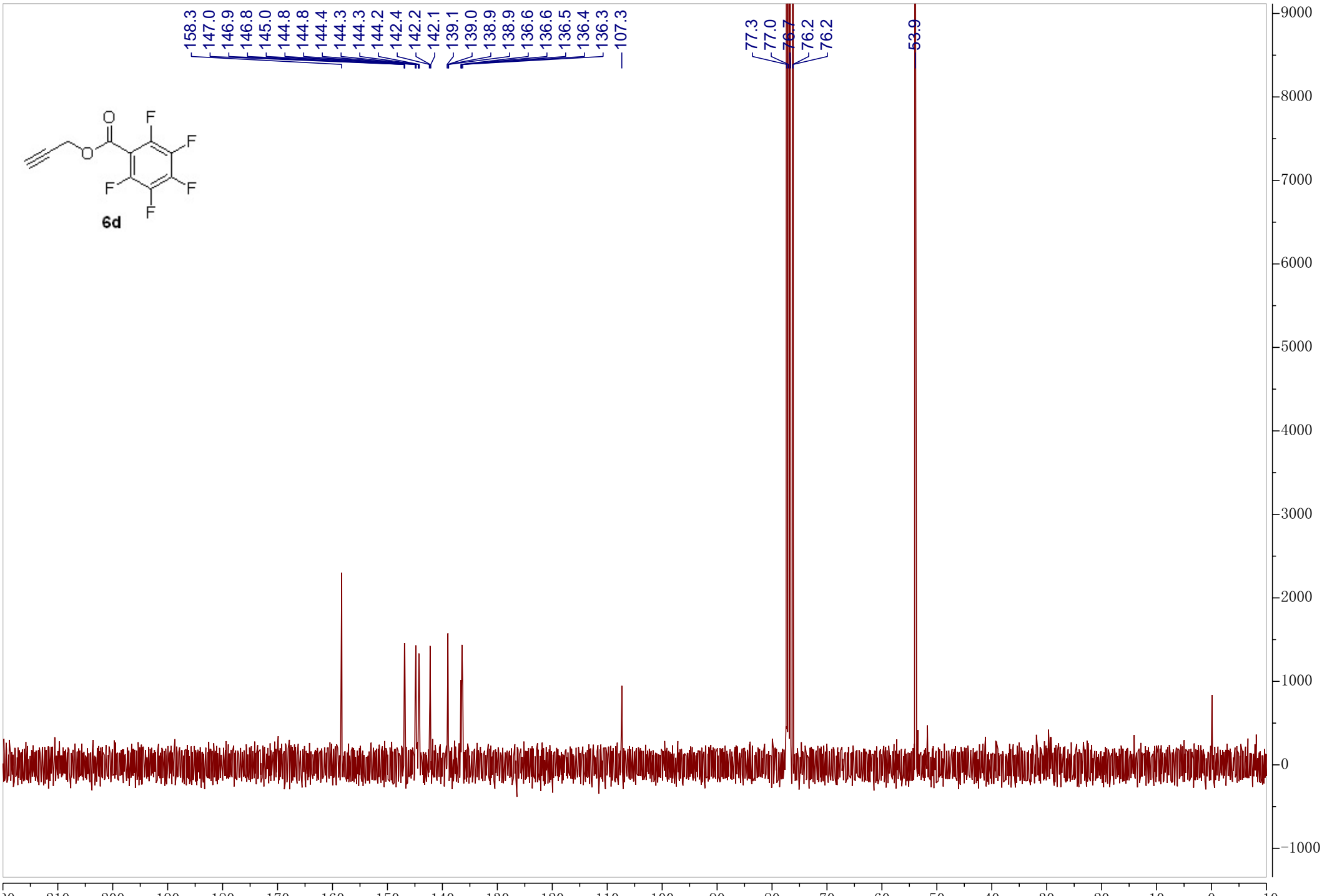
YYY-01-57-CDCL3-C13-2020-9-17.10.fid —



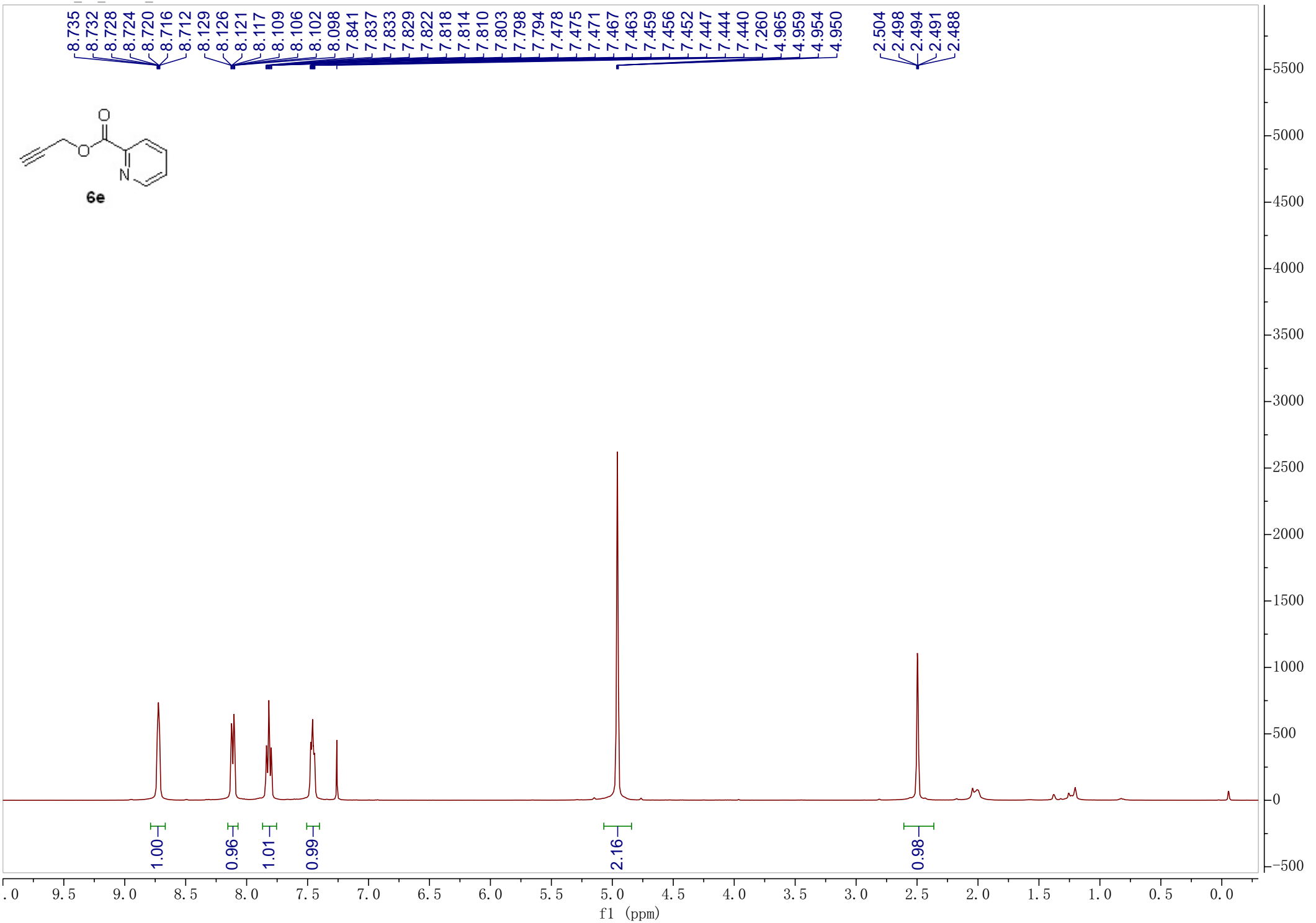
YYY-01-56_H1_CDCl3_2020-7-7.40.fid



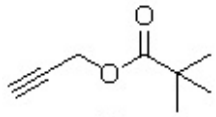
YYY-01-56-CDCL3-C13-2020-9-17.10.fid



YYY-01-72_H1_CDCl3_2020-7-13.260.fid

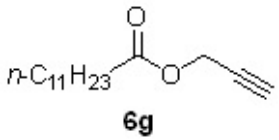


YYY-01-58_H1_CDCl3_2020-7-7.60.fid



6f

YYY-01-55_H1_CDCl3_2020-7-7.30.fid



6g

7.260

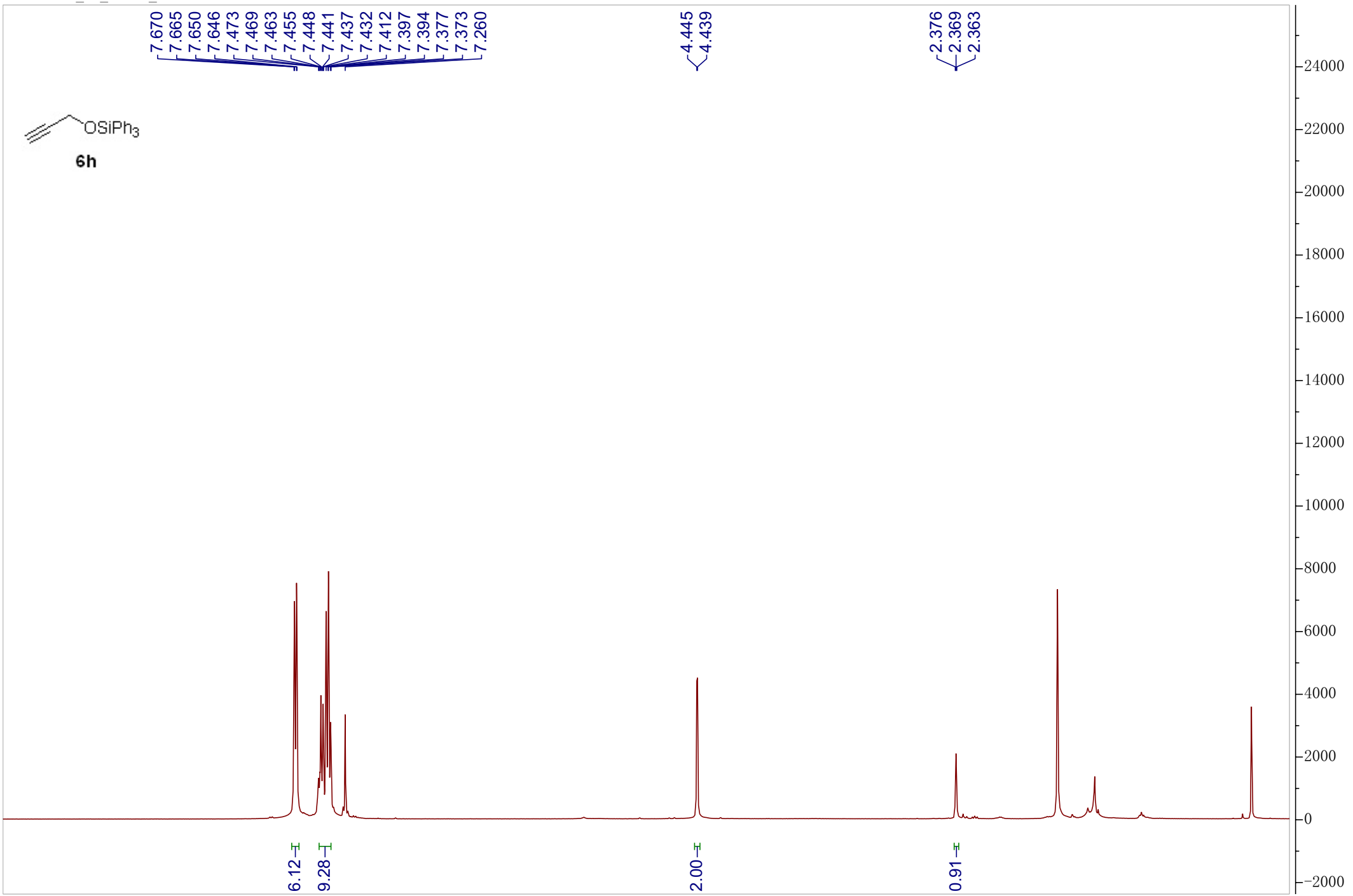
4.674
4.668

2.465
2.459
2.452
2.364
2.345
2.326
1.670
1.652
1.634
1.616
1.597
1.582
1.331
1.312
1.296
1.282
1.253
0.891
0.875
0.858

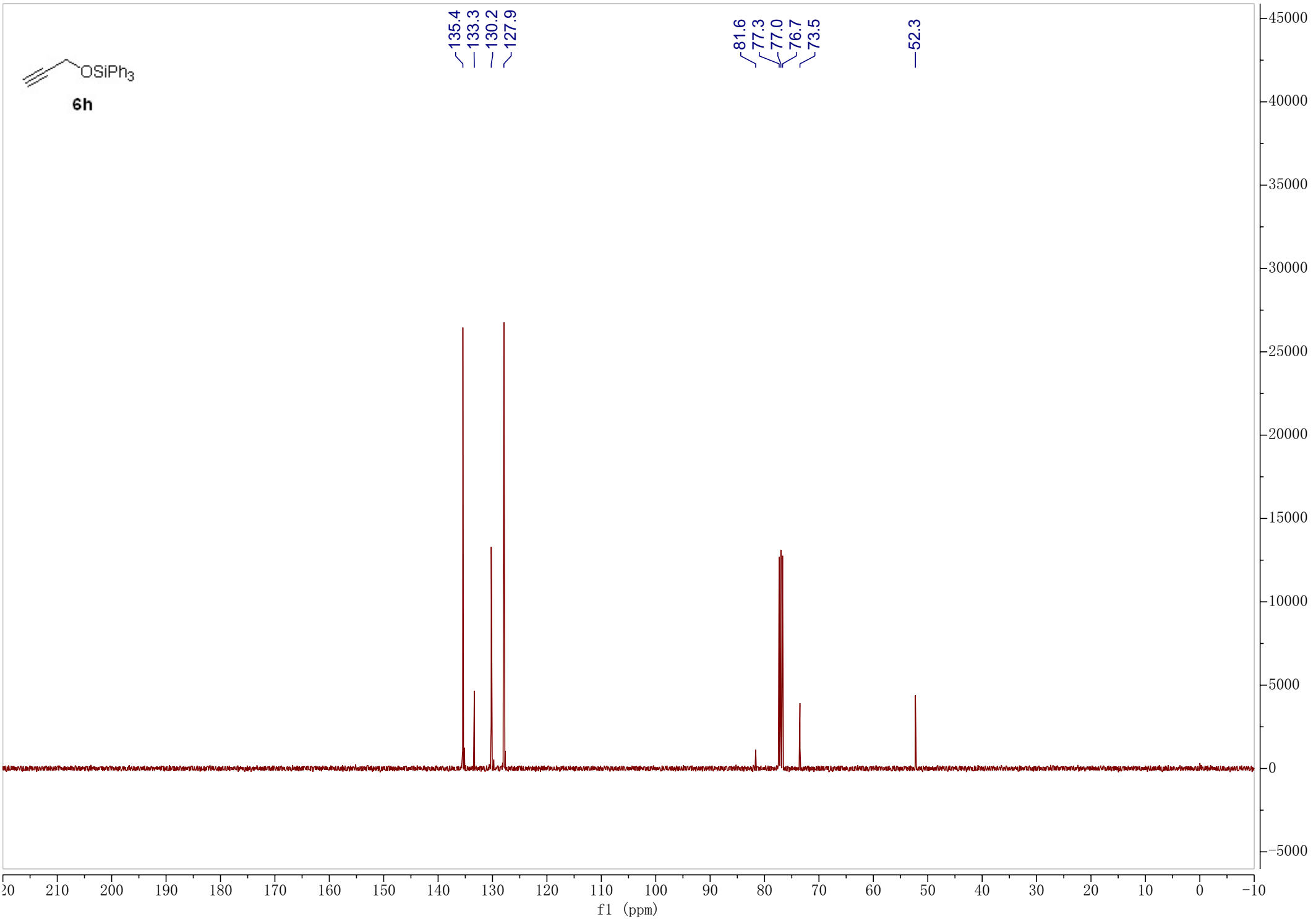
2.00
0.88
2.11
2.27
16.13
3.25

f1 (ppm)

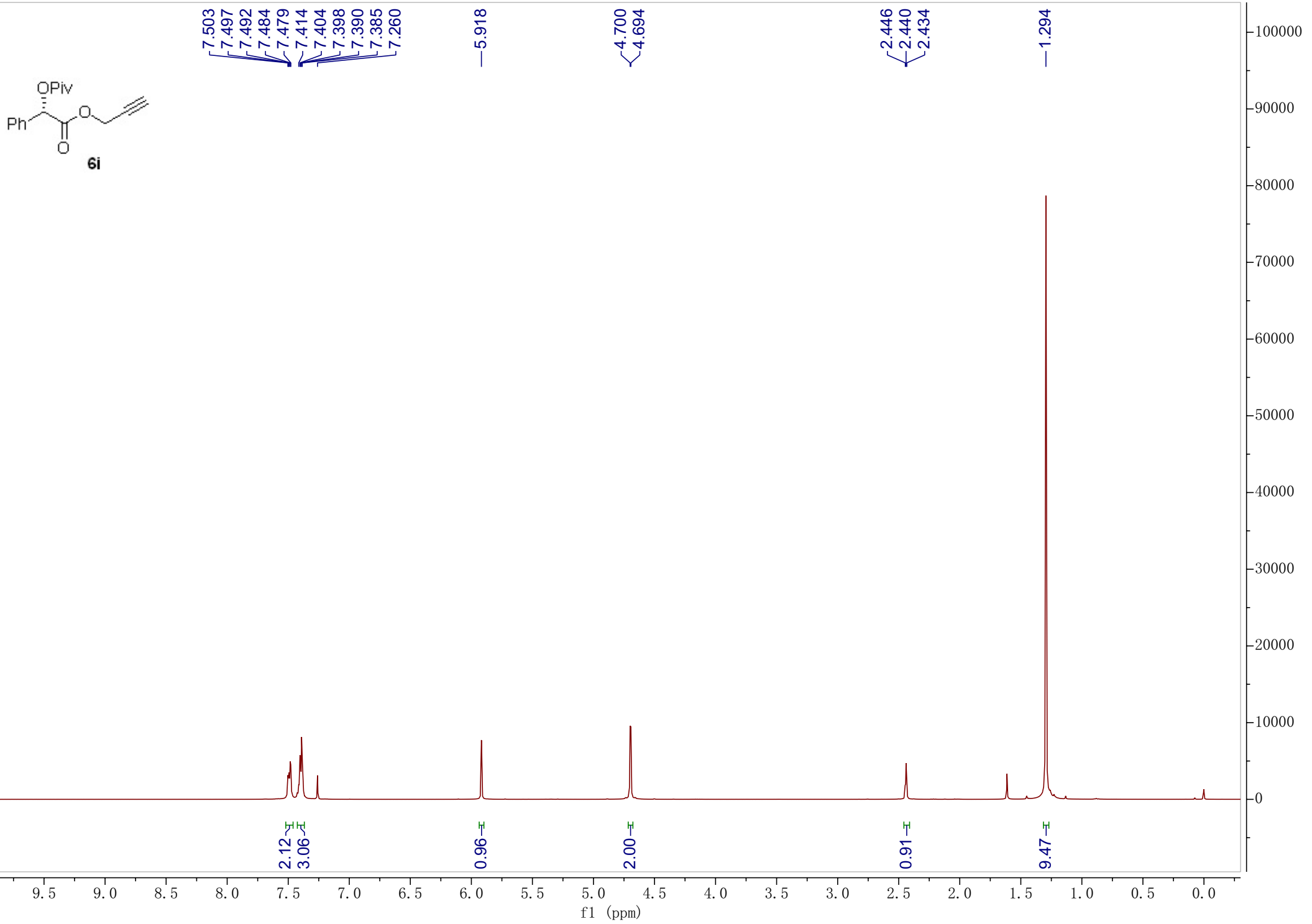
YYY-01-52_H1_CDCl3_2020-7-7.20.fid



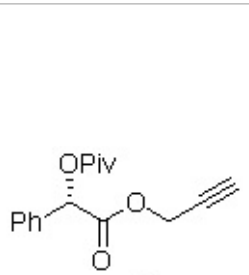
YYY-01-52-CDCL3-C13-2020-9-17.10.fid



YYY-01-65_H1_CDCl3_2020-7-7.80.fid



YYY-01-65-CDCL3-C13-2020-9-17.10.fid —

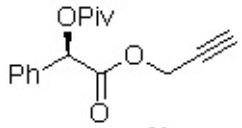


6i

177.7
168.1
133.4
129.1
128.7
127.4
77.3
77.0
76.7
76.6
75.5
74.0
52.9
38.7
27.0

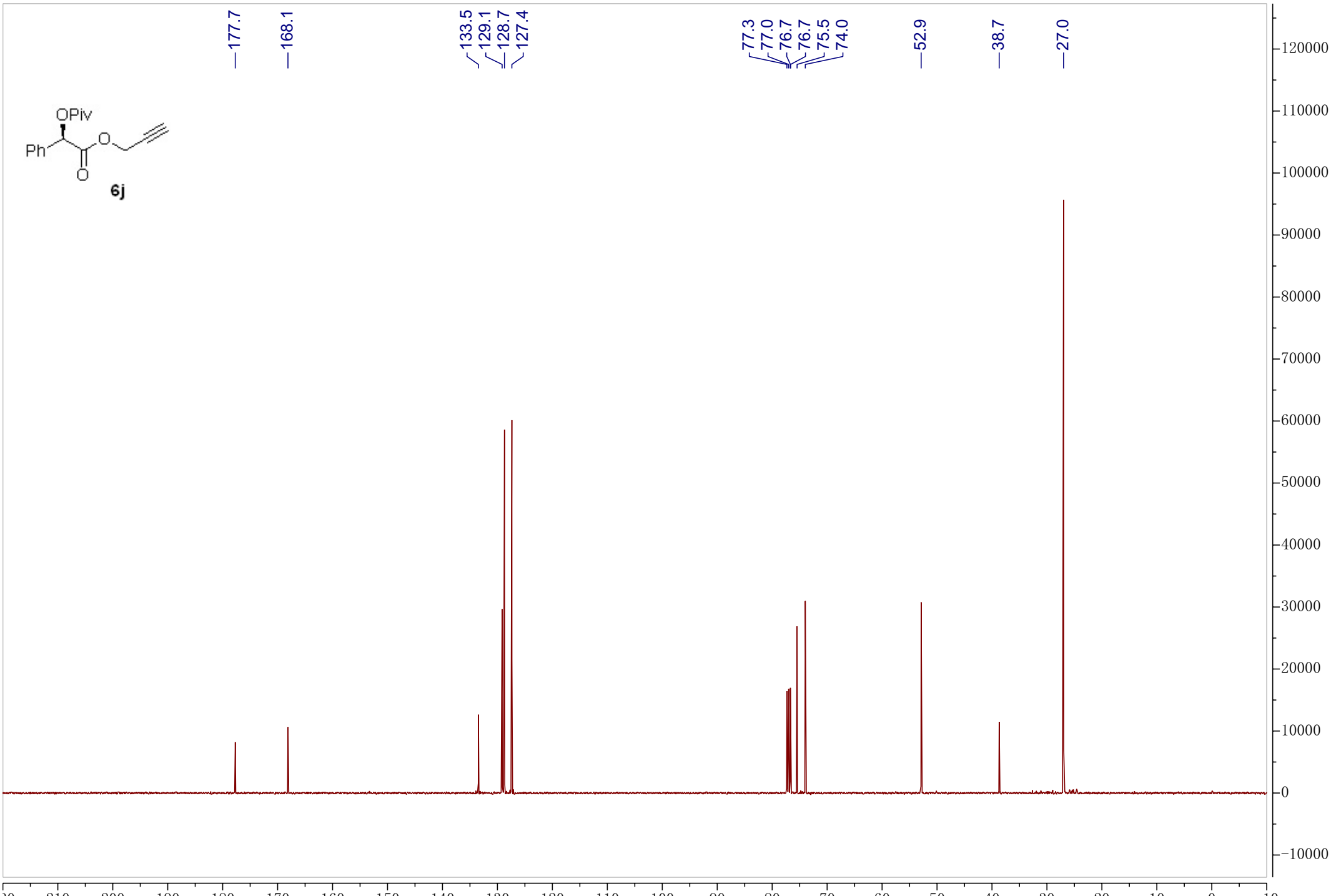
f1 (ppm)

YYY-02-04_H1_CDCl3_2020-9-24.80.fid

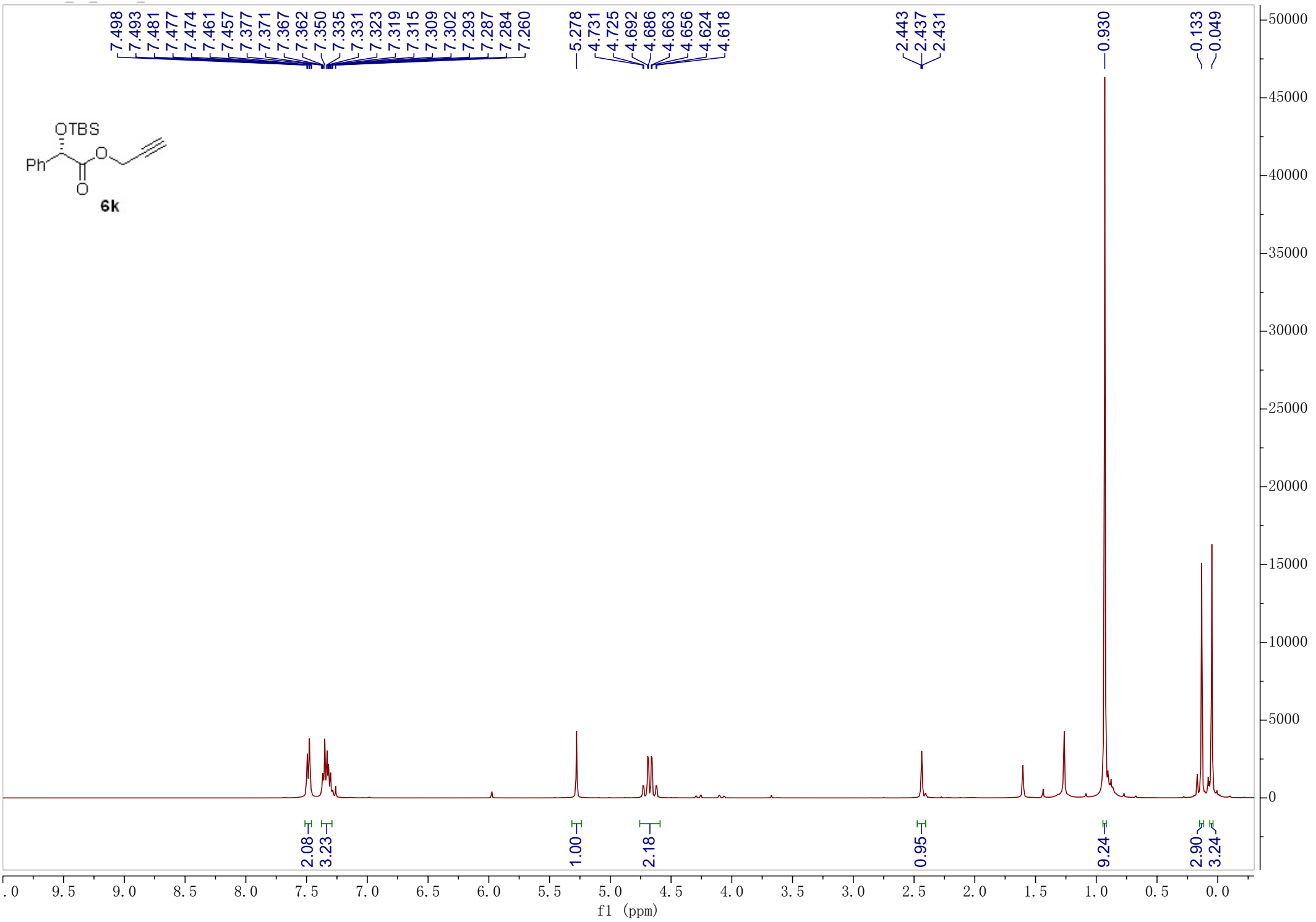


6j

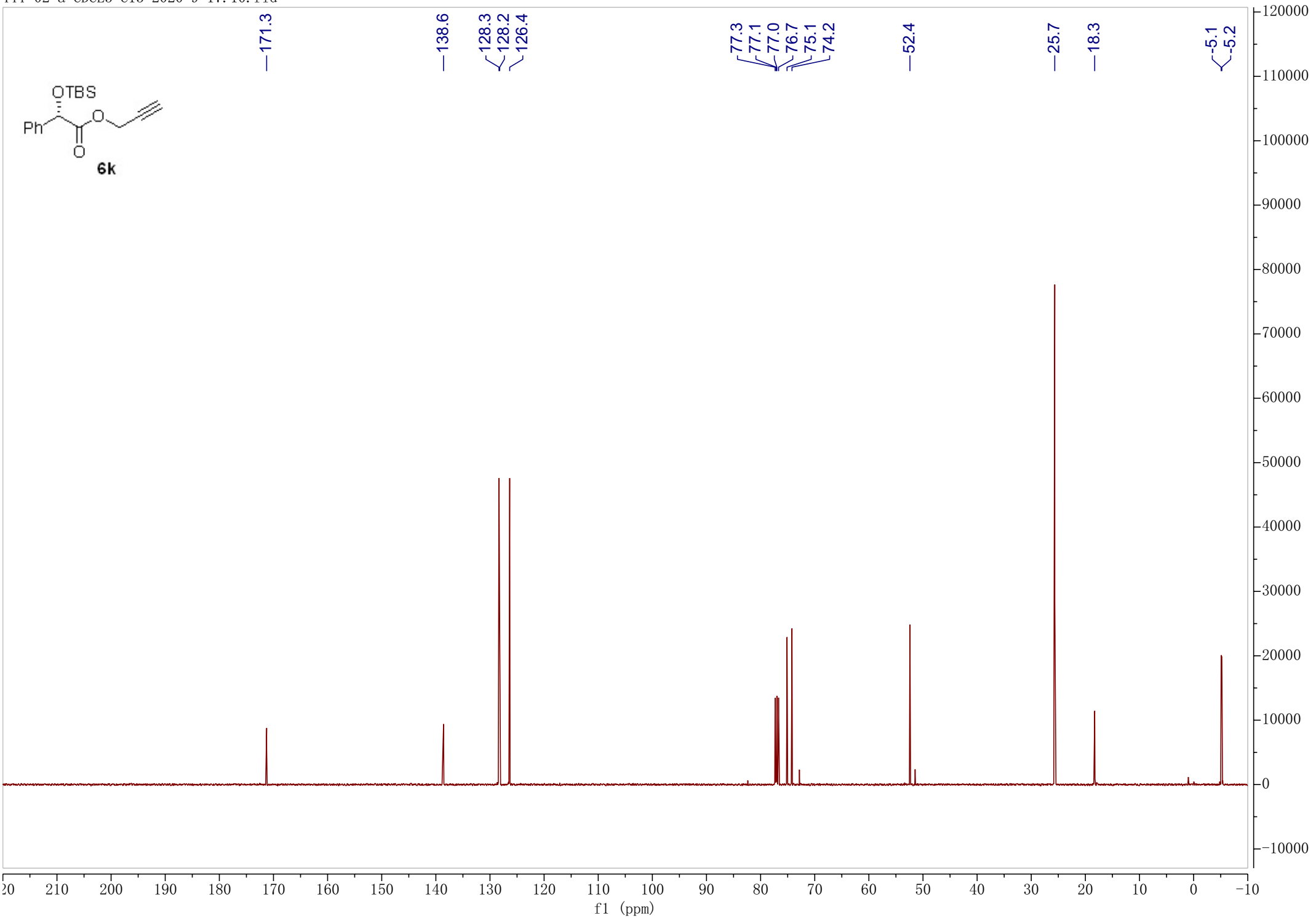
YYY-02-04-CDCL3-C13-2020-9-17.10.fid



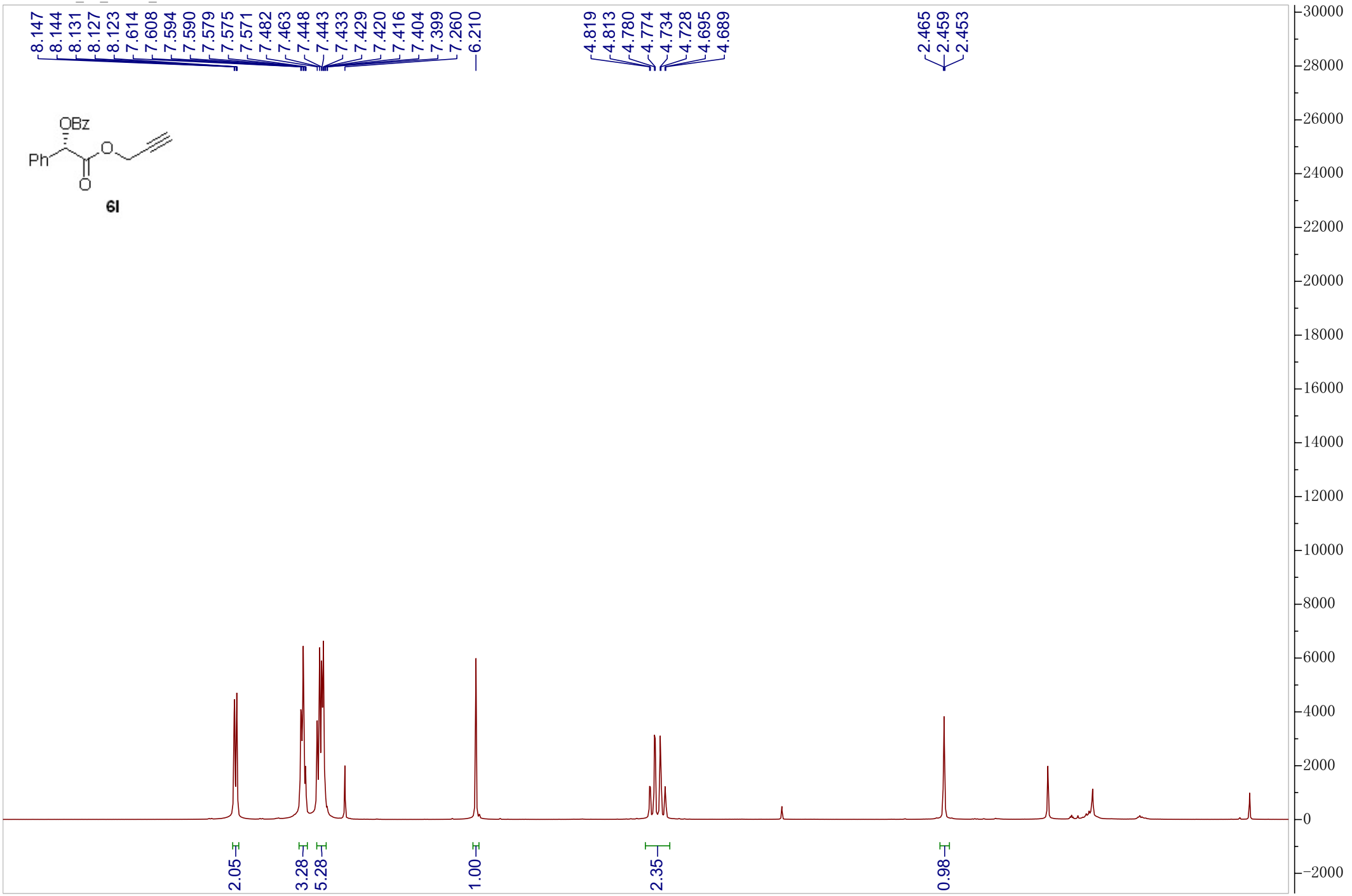
LY-02-13_H1_CDCl3_2020-8-6.90.fid



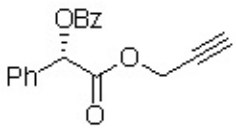
YYY-02-a-CDCL3-C13-2020-9-17.10.fid



YYY-02-45_H1_CDCl3_2020-9-18.70.fid



YYY-02-45-CDCL3-C13-2020-9-17.10.fid



6l

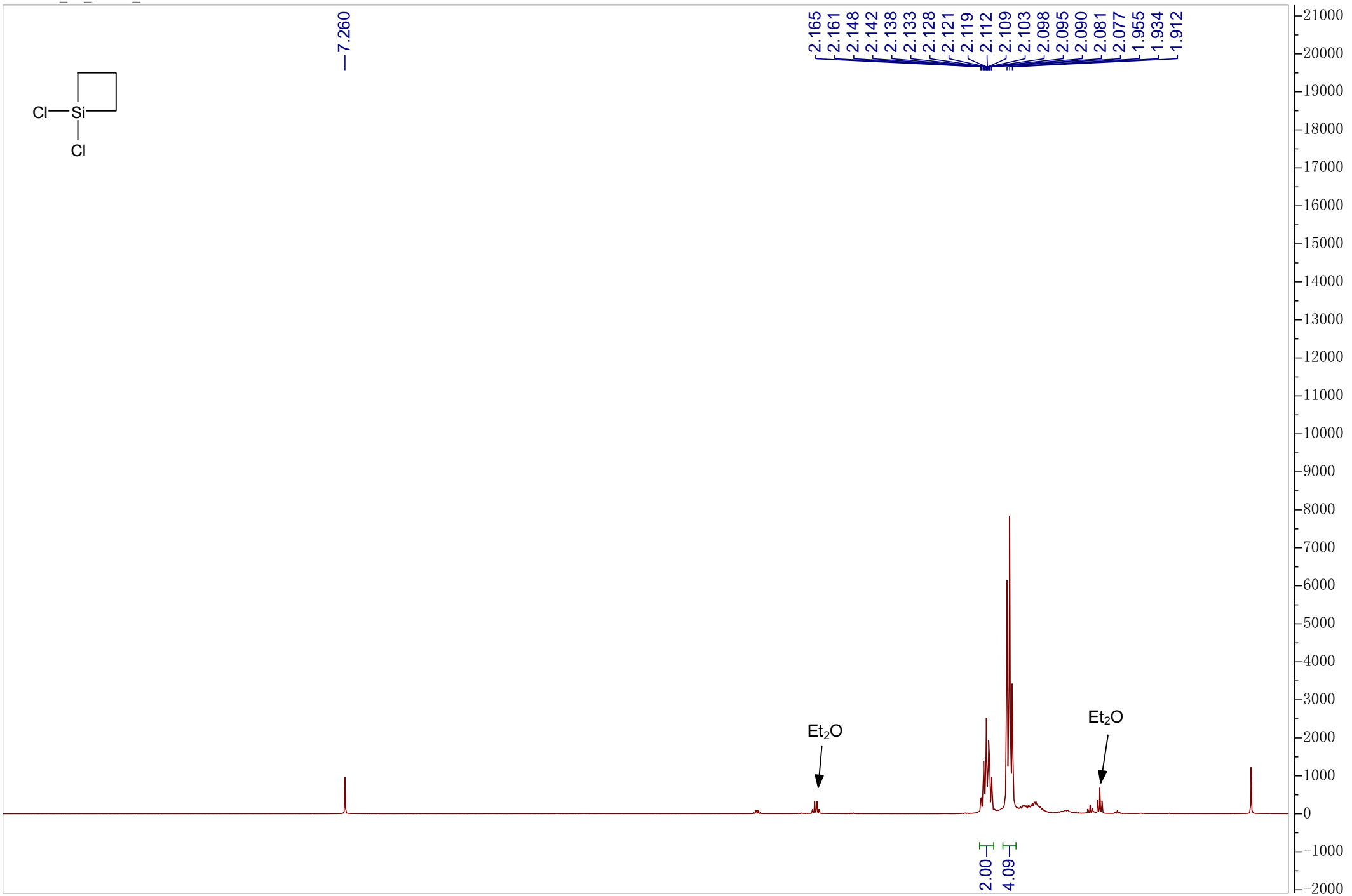
168.1
165.8
133.5
133.4
130.0
129.4
129.1
128.9
128.4
127.7
77.3
77.0
76.7
75.5
74.6
53.0

55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0

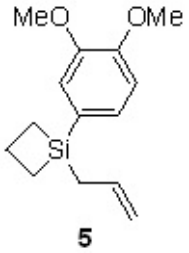
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

f1 (ppm)

LG-07-0_H1_CDCl3_2020-3-31.20.fid

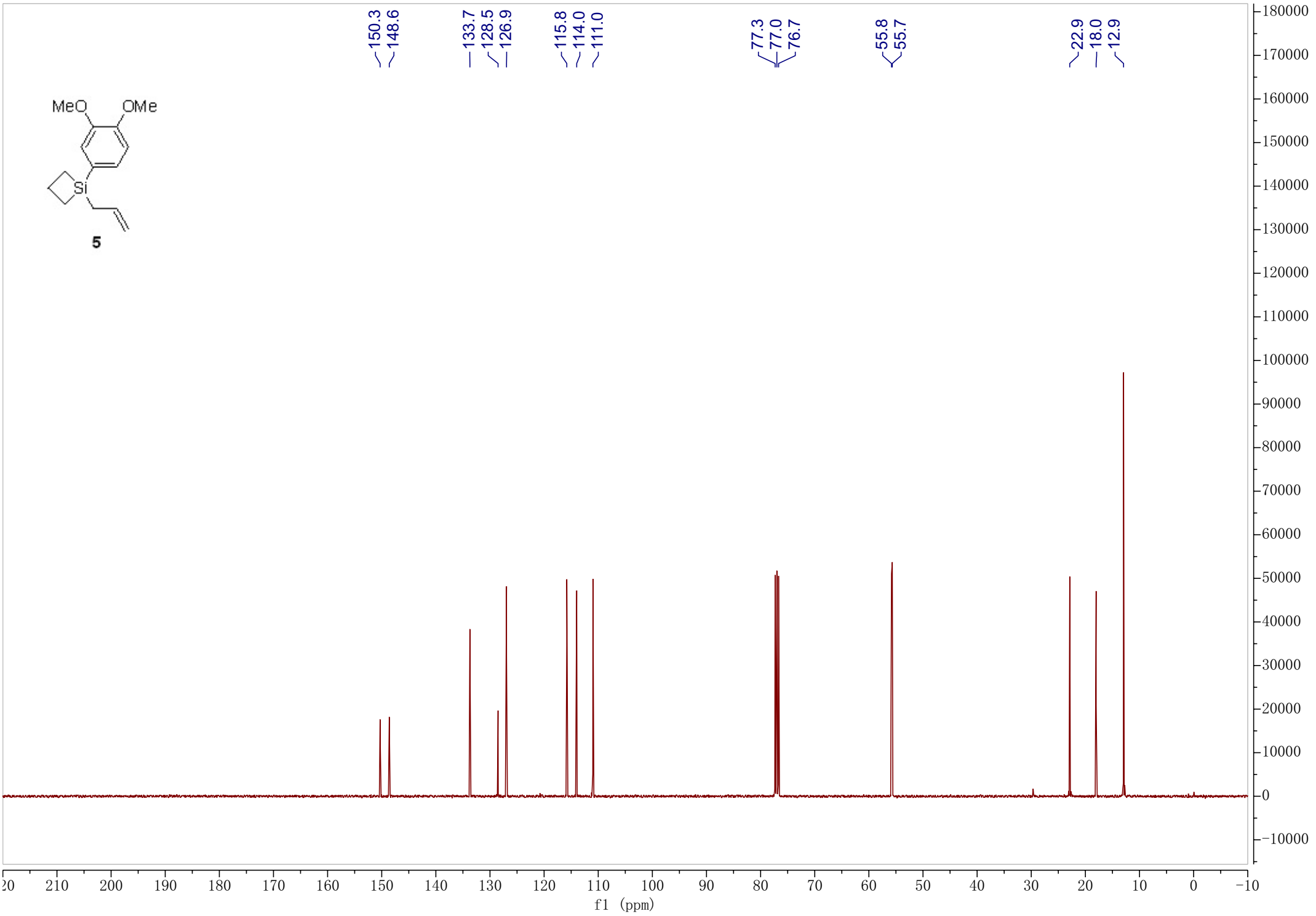


LG-07-29_H1_CDCl3_2020-4-17.20.fid

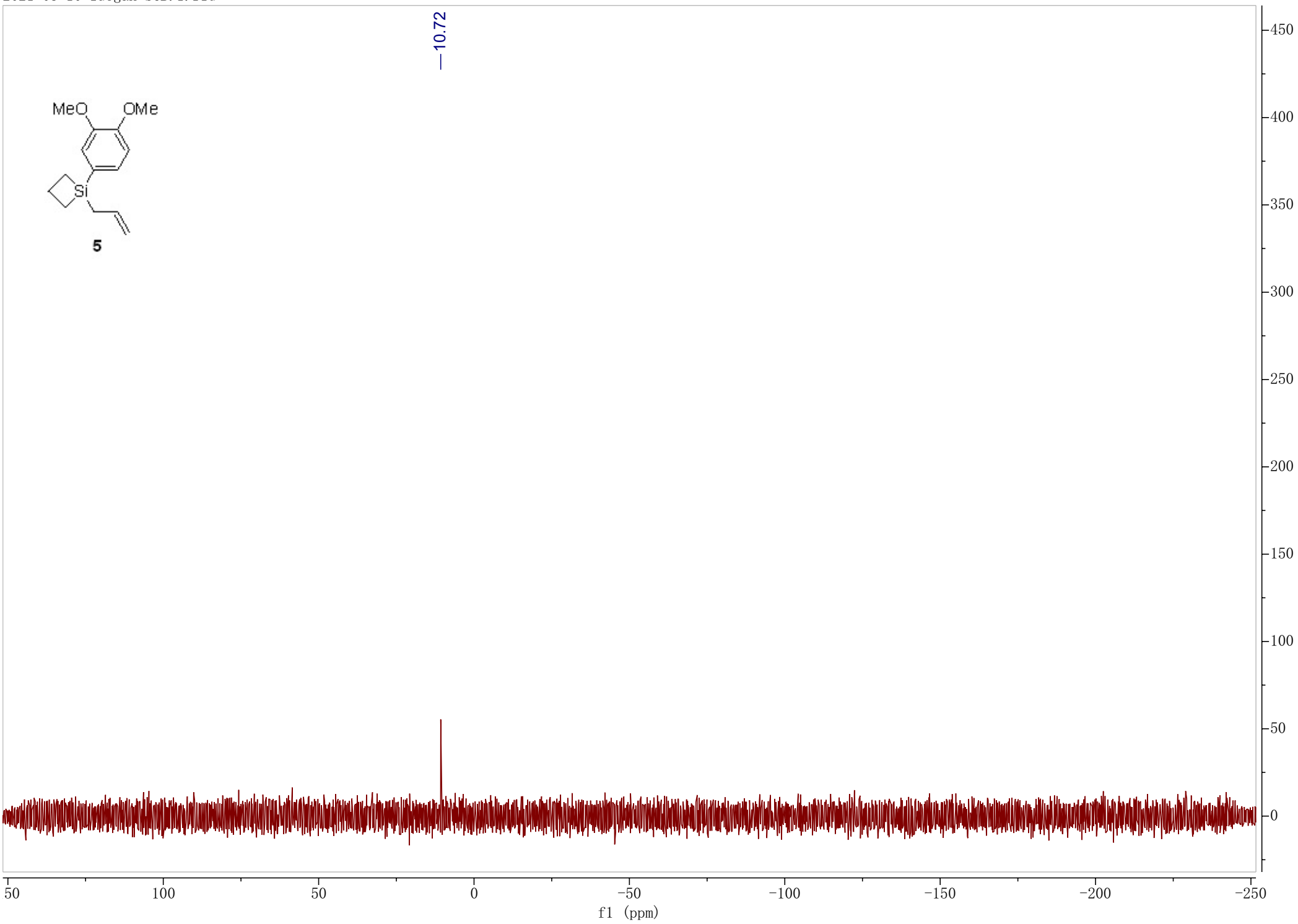


5

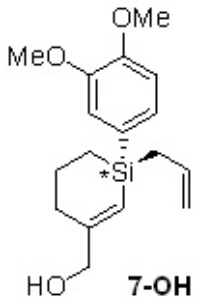
LG-07-29-CDCL3-C13-2020-4-17.10.fid —



2021-03-10 luogan-SCB.1.fid —

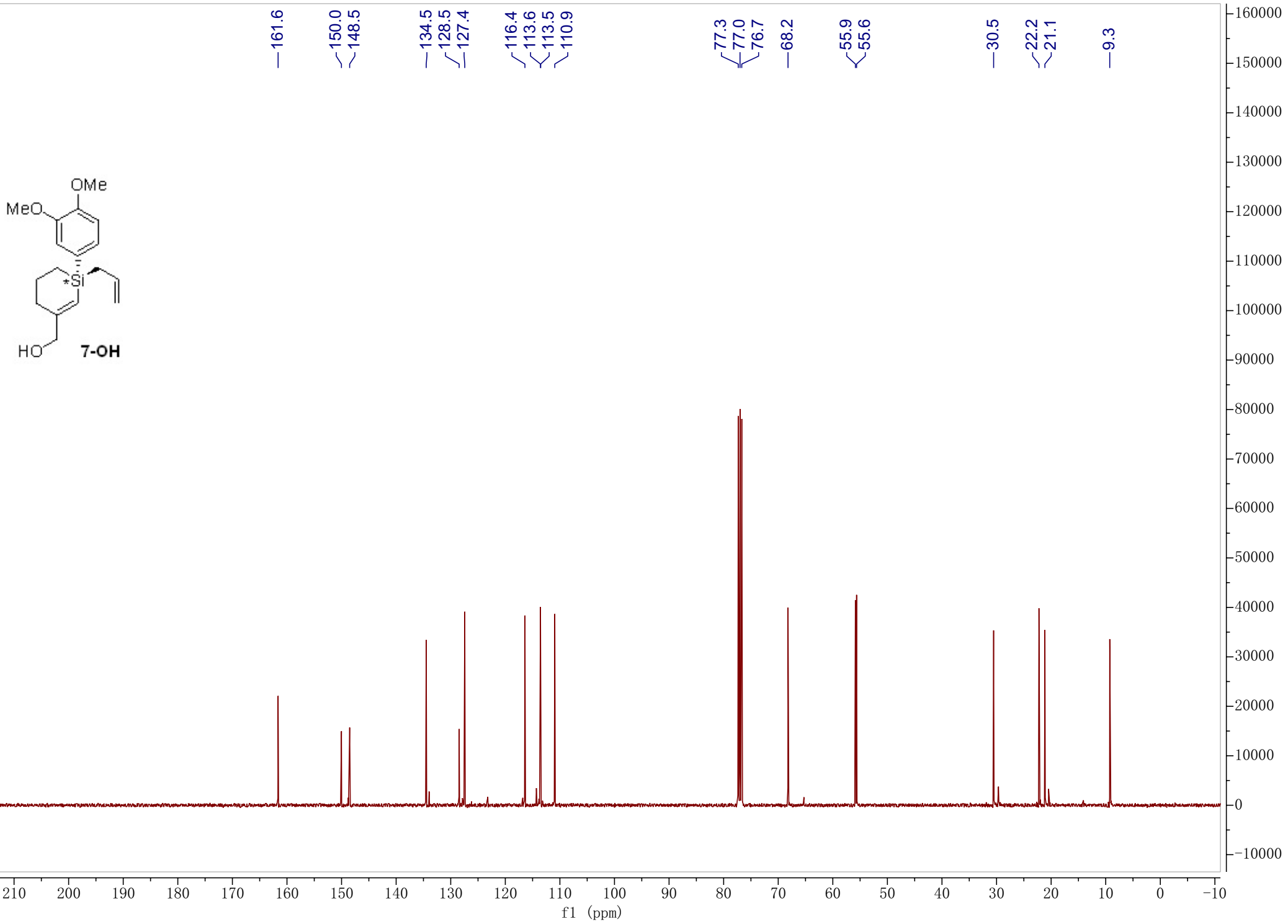


LG-07-92-CDCL3-H1-2020-7-8.10.fid

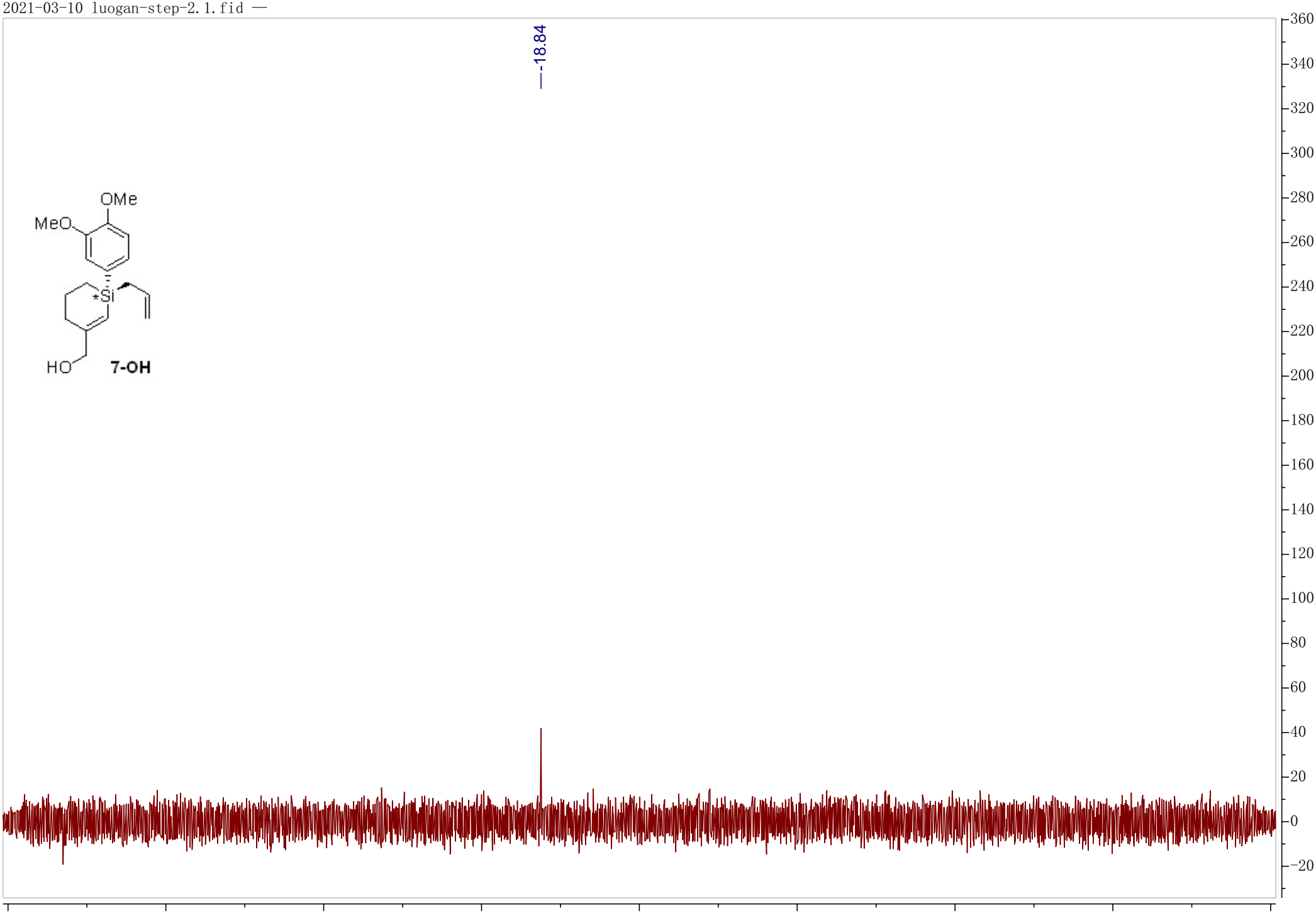


7-OH

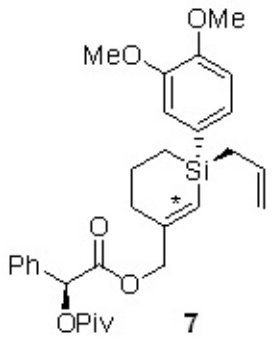
LY-02-36-CDCL3-C13-2020-9-10.10.fid



2021-03-10 luogan-step-2.1.fid



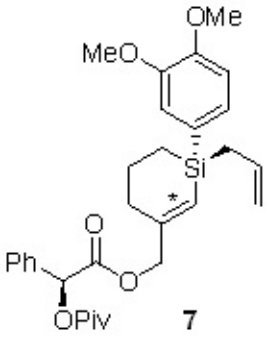
LY-02-34-CDCL3-H1-2020-8-21.10.fid



7

f1 (ppm)

LY-02-34-CDCL3-C13-2020-8-21.10.fid

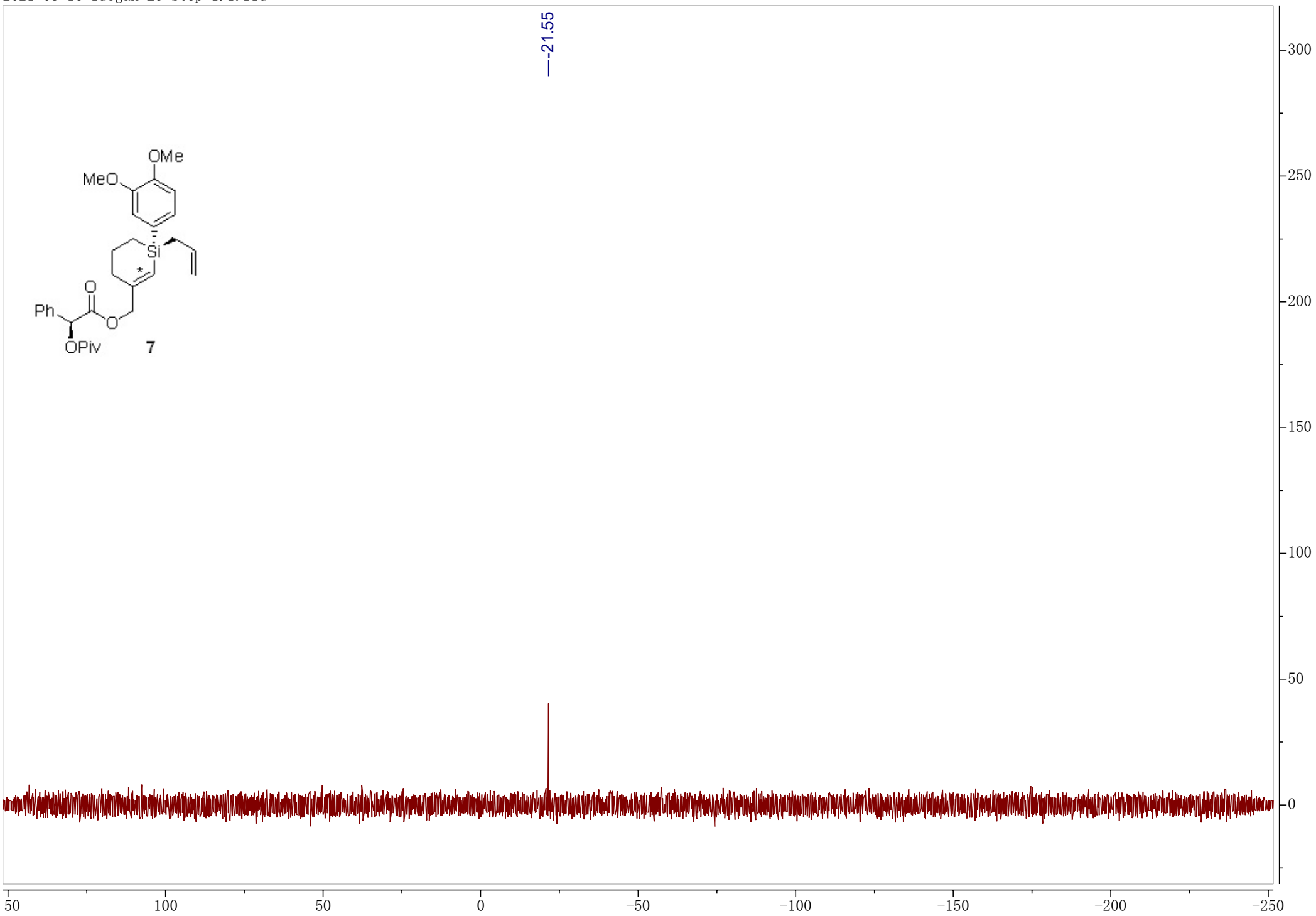


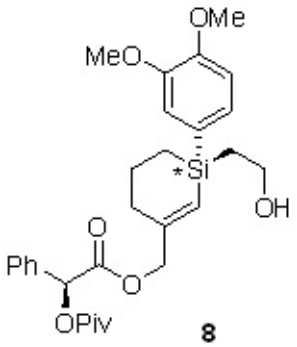
7

177.8 168.5 155.1 150.0 148.5 134.3 134.1 129.0 128.7 128.0 127.4 127.4 117.6 116.5 113.7 110.9 77.3 77.0 76.7 74.2 69.7 55.9 55.7 38.7 30.3 27.0 21.8 20.9 9.0

f1 (ppm)

2021-03-16 luogan-LG-step-1.1.fid —

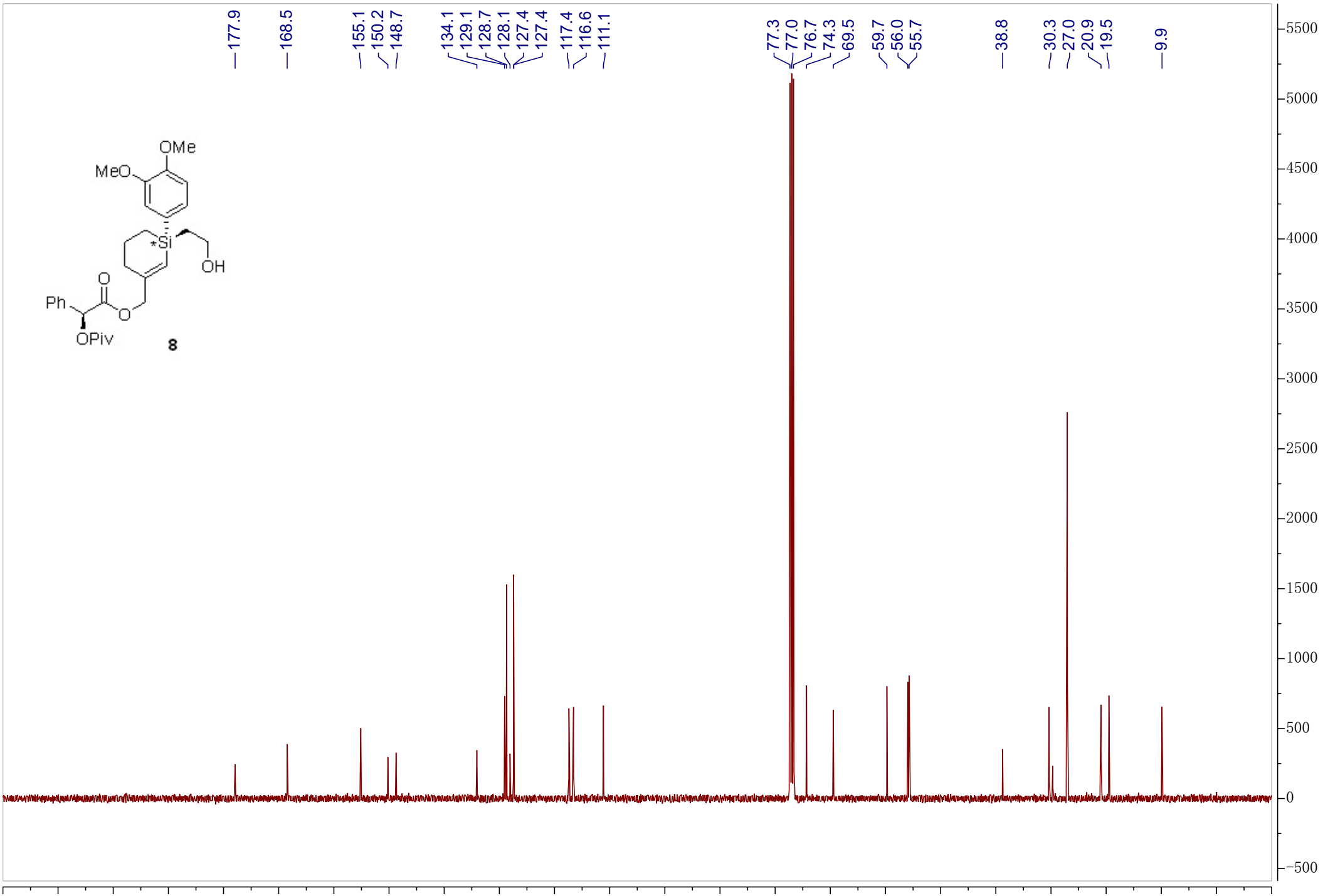



OMe
MeO
*Si
OH
O
Ph
O
OPiv

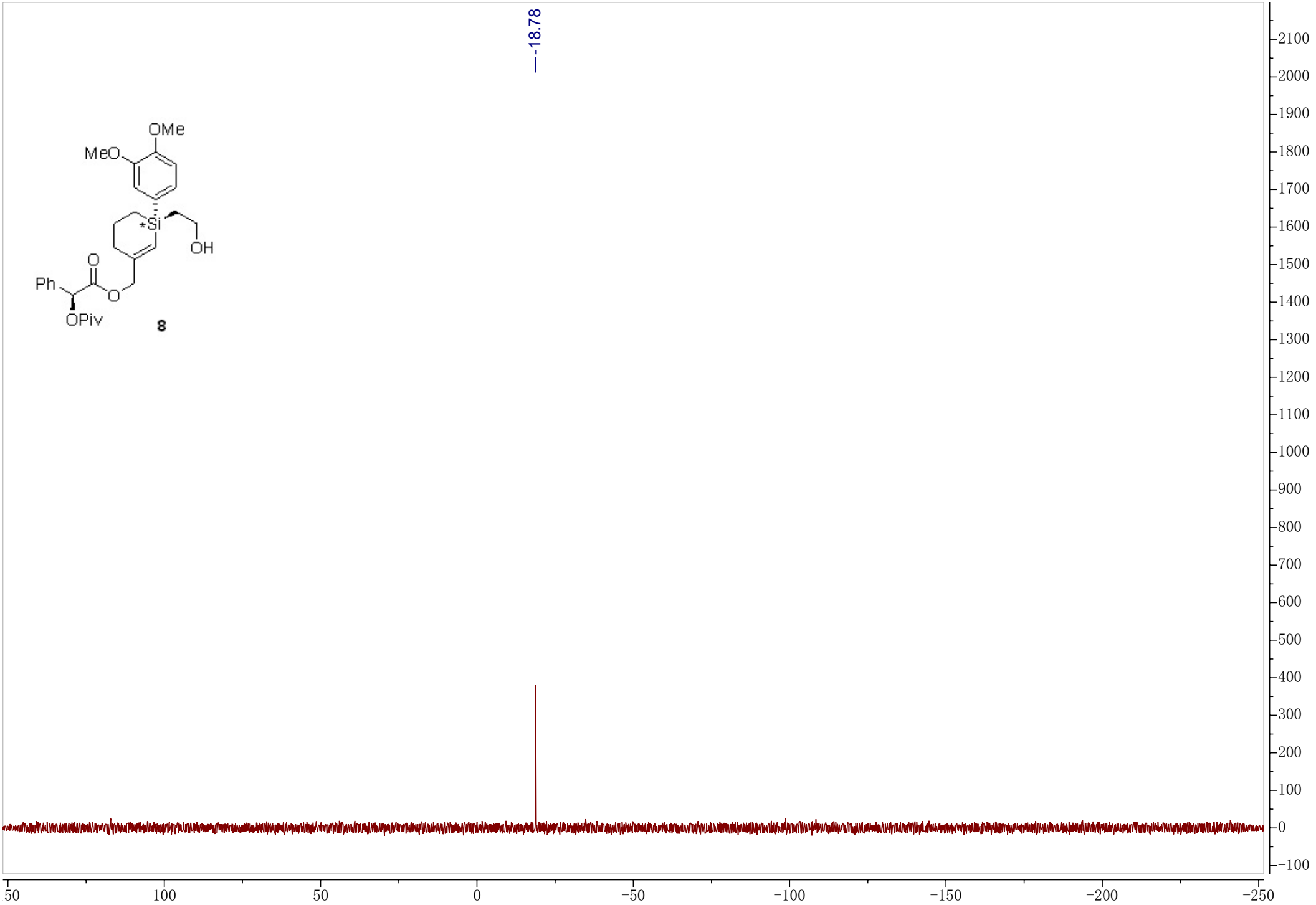
8

7.483
7.338
7.260
7.016
7.003
6.933
6.890
6.877
5.933
5.552
4.602
4.578
4.514
4.490
3.890
3.701
3.687
3.673
1.977
1.967
1.957
1.800
1.792
1.785
1.778
1.769
1.746
1.474
1.461
1.287
1.253
1.224
1.212
1.206
1.199
1.192
1.179
0.912
0.902
0.894
0.887
0.878
0.871
0.848
0.841
0.831
0.824
0.817
0.806
2.09
2.99
0.96
0.98
1.01
0.96
0.99
1.00
1.00
5.95
2.08
1.98
1.99
0.97
9.20
2.04
1.31
1.19
f1 (ppm)

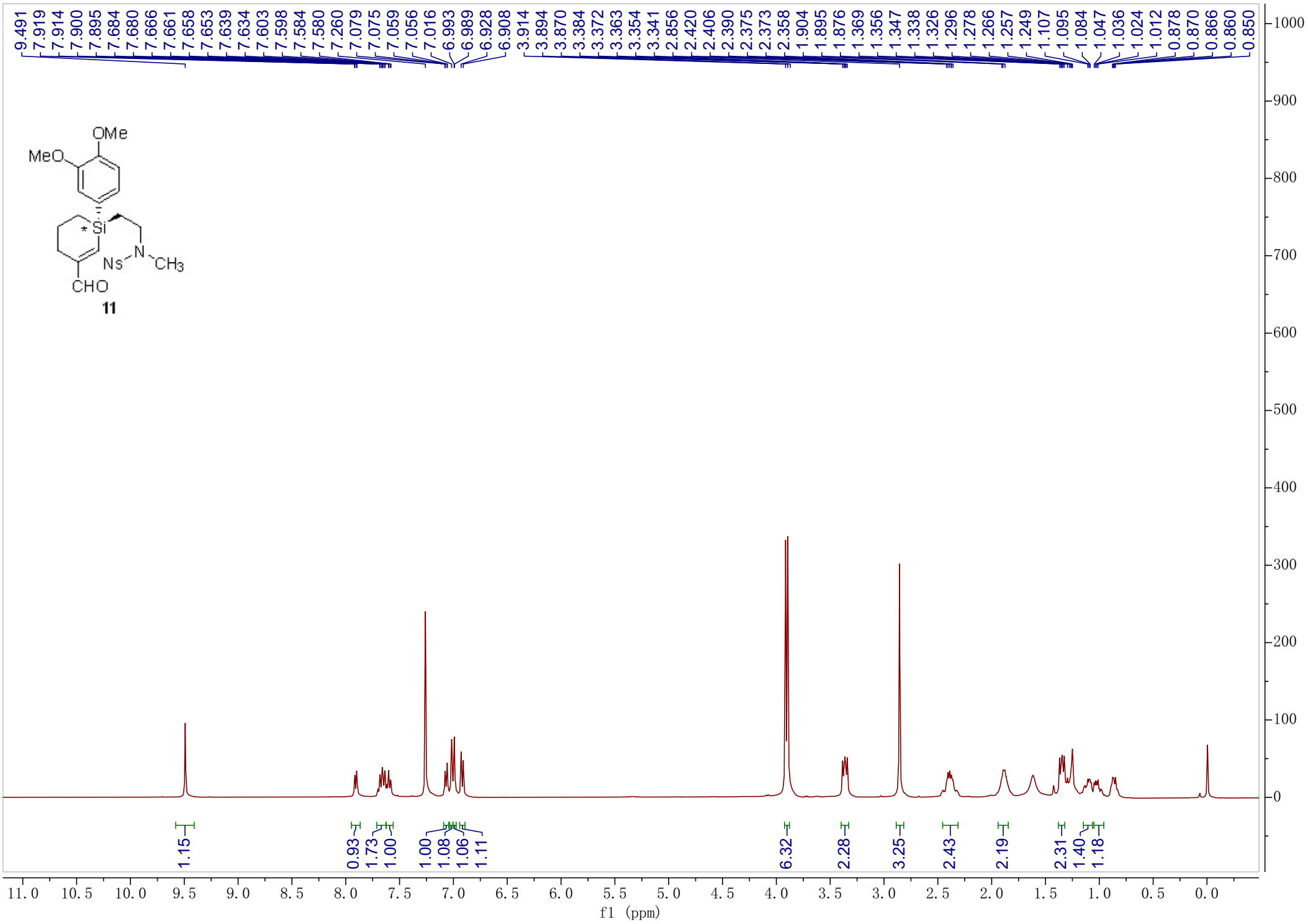
LG-07-108-CDCL3-C13-2020-8-24.10.fid



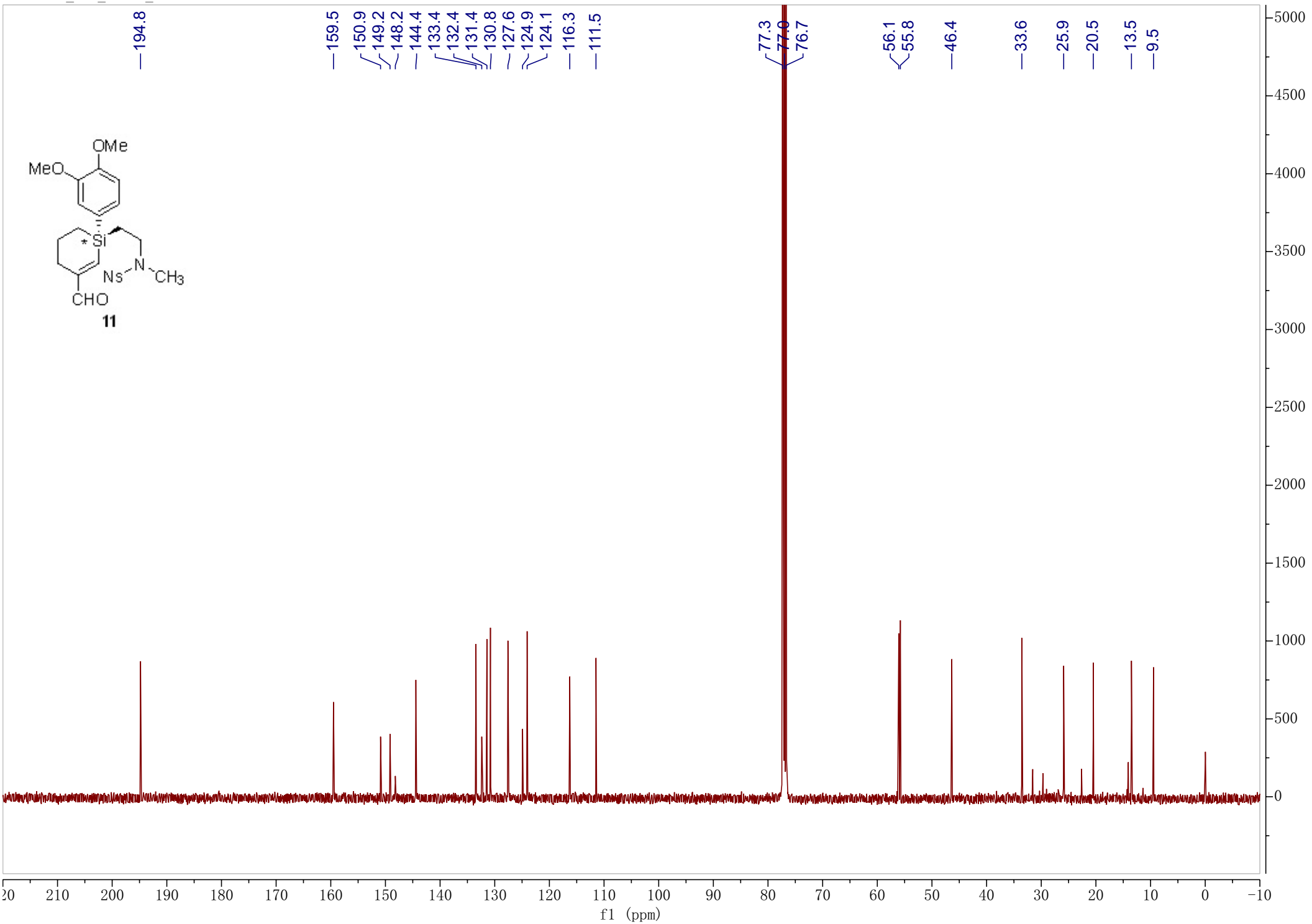
Desktop/2021-03-12 luogan-step-3 —



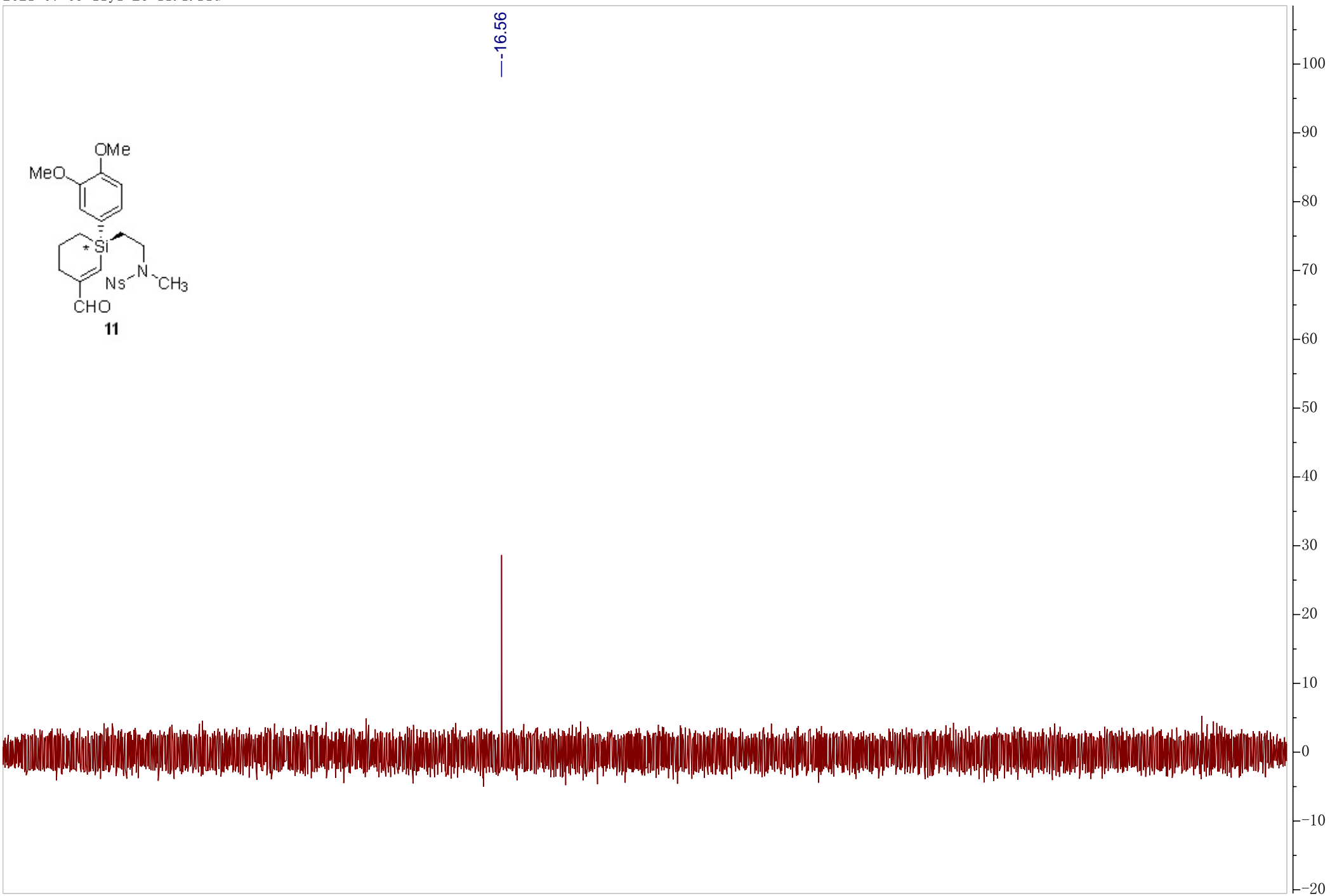
LG-04-92-CDCL3-H1-2019-4-19 — LG-04-92-CDCL3-H1-2019-4-19 —

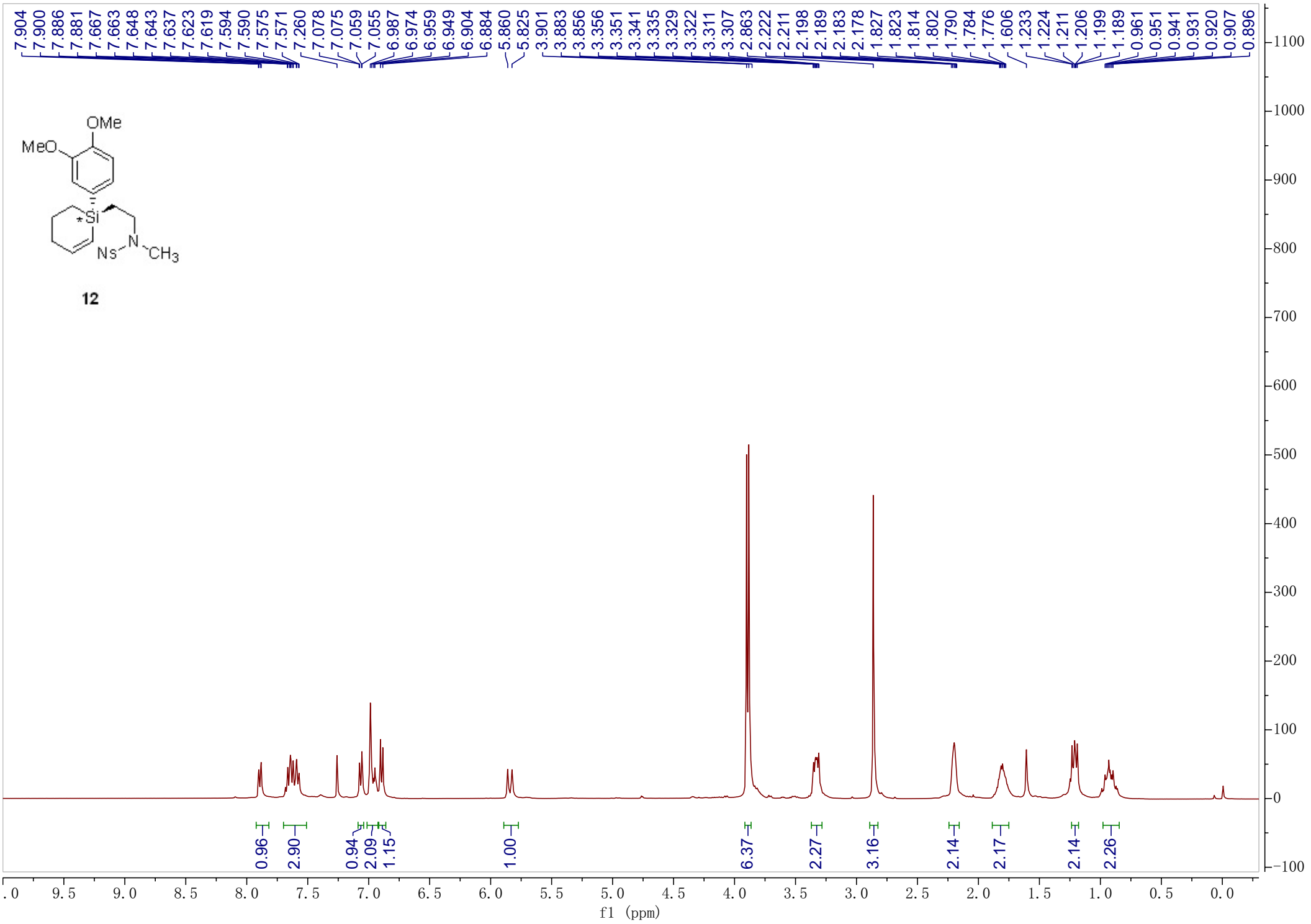


LG-04-92_C13_CDCl3_2019-4-19.10.fid

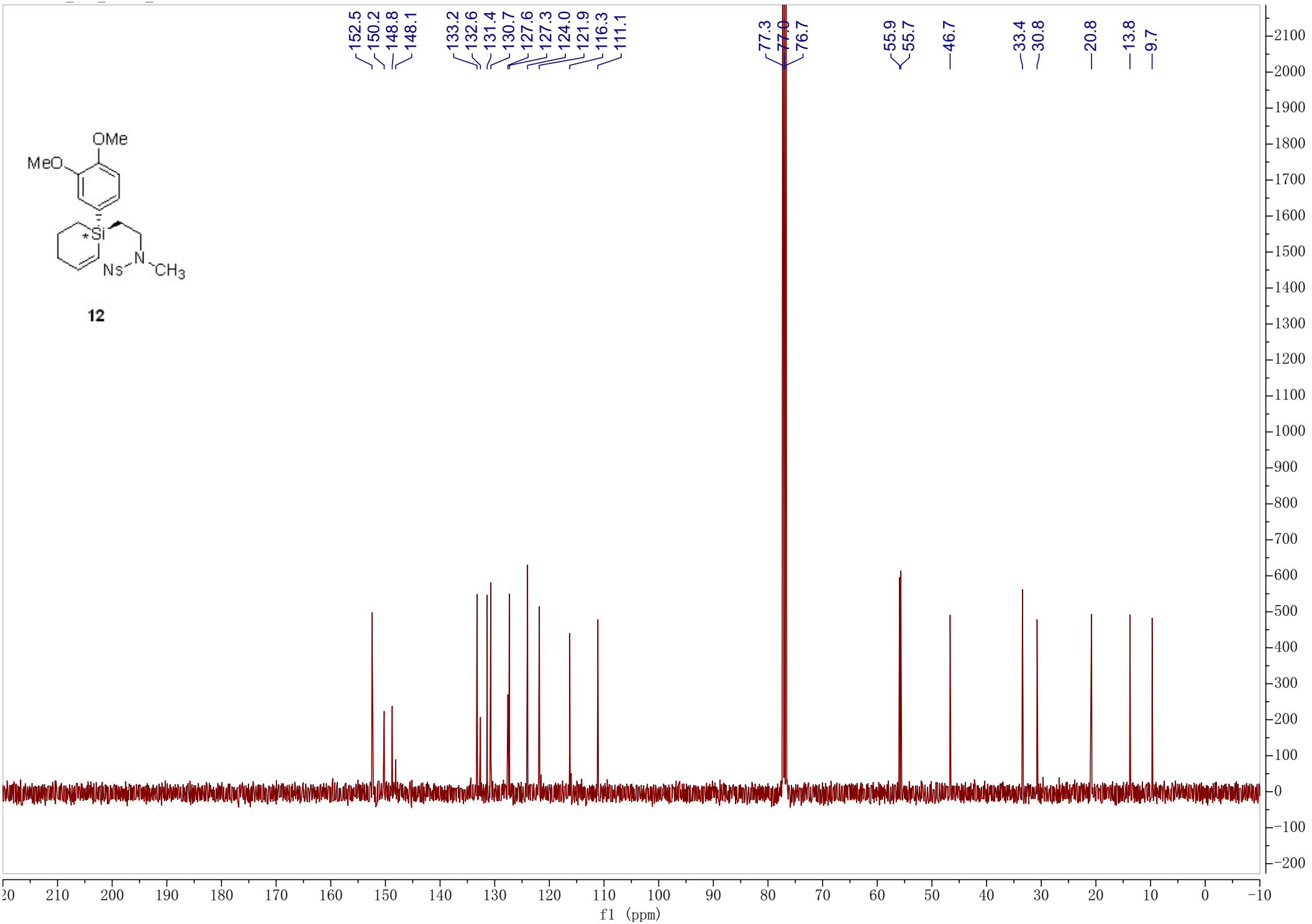


2021-07-09 liyi-LG-11.1.fid

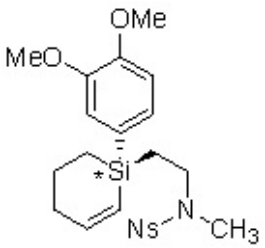



7.904
7.900
7.886
7.881
7.667
7.663
7.648
7.643
7.637
7.623
7.619
7.594
7.590
7.575
7.571
7.260
7.078
7.075
7.059
7.055
6.987
6.974
6.959
6.949
6.904
6.884
5.860
5.825
3.901
3.883
3.856
3.356
3.351
3.341
3.335
3.329
3.322
3.311
3.307
2.863
2.222
2.211
2.198
2.189
2.183
2.178
1.827
1.823
1.814
1.802
1.790
1.784
1.776
1.606
1.233
1.224
1.211
1.206
1.199
1.189
0.961
0.951
0.941
0.931
0.920
0.907
0.896
OMe
MeO
*Si
Ns
N
CH3
12
0.96
2.90
0.94
2.09
1.15
1.00
6.37
2.27
3.16
2.14
2.17
2.14
2.26
f1 (ppm)

LG-04-32_C13_CDCl3_2019-1-15.10.fid

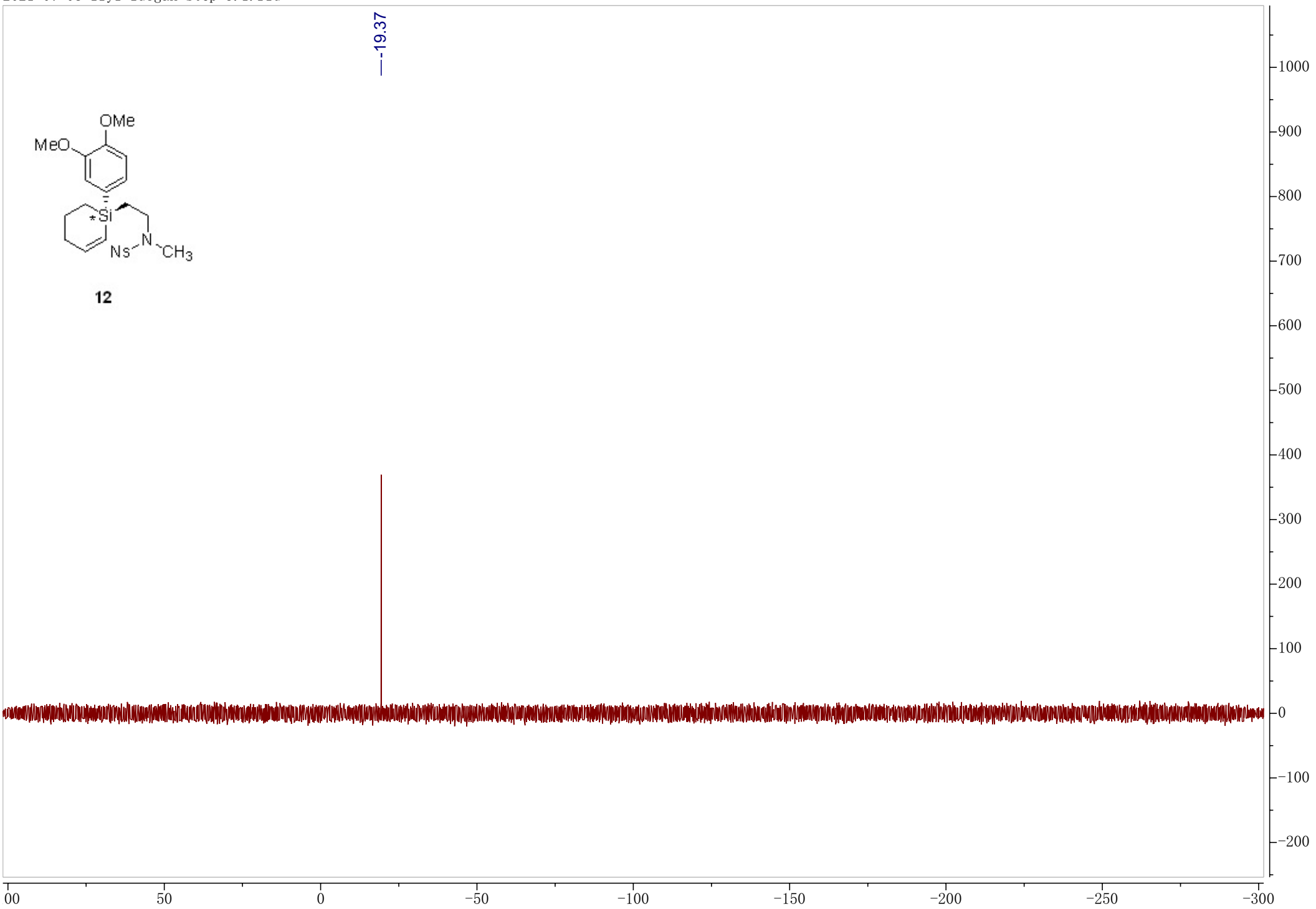


LG-04-32_DEPT135_CDCl3_2019-1-16 — LG-04-32 DEPT135 CDCl3 2019-1-16 —

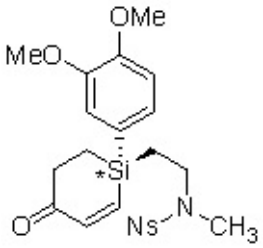


12

2021-07-08 liyi-luogan-step-5.1.fid —

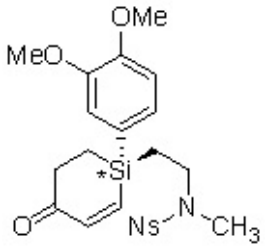


LG-04-58_H1_CDCl3_2019-2-25.20.fid



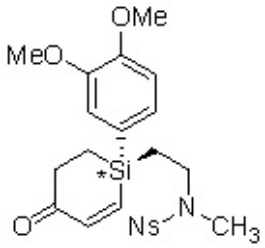
13

LG-04-61_C13_CDCl3_2019-3-13.10.fid



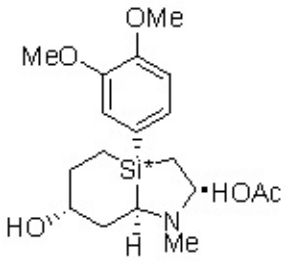
13

2021-03-12 luogan-step-6.1.fid



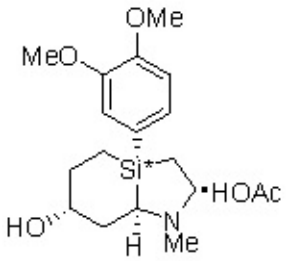
13

LG-Si-TM_H1_CDCl3_2021-3-10 — LG-Si-TM H1 CDCl3 2021-3-10 —

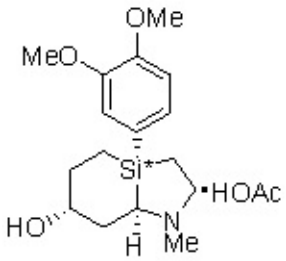


4•HOAc

LG-09-7M_C13_CDCl3_2021-1-15 — LG-09-7M C13 CDCl3 2021-1-15 —



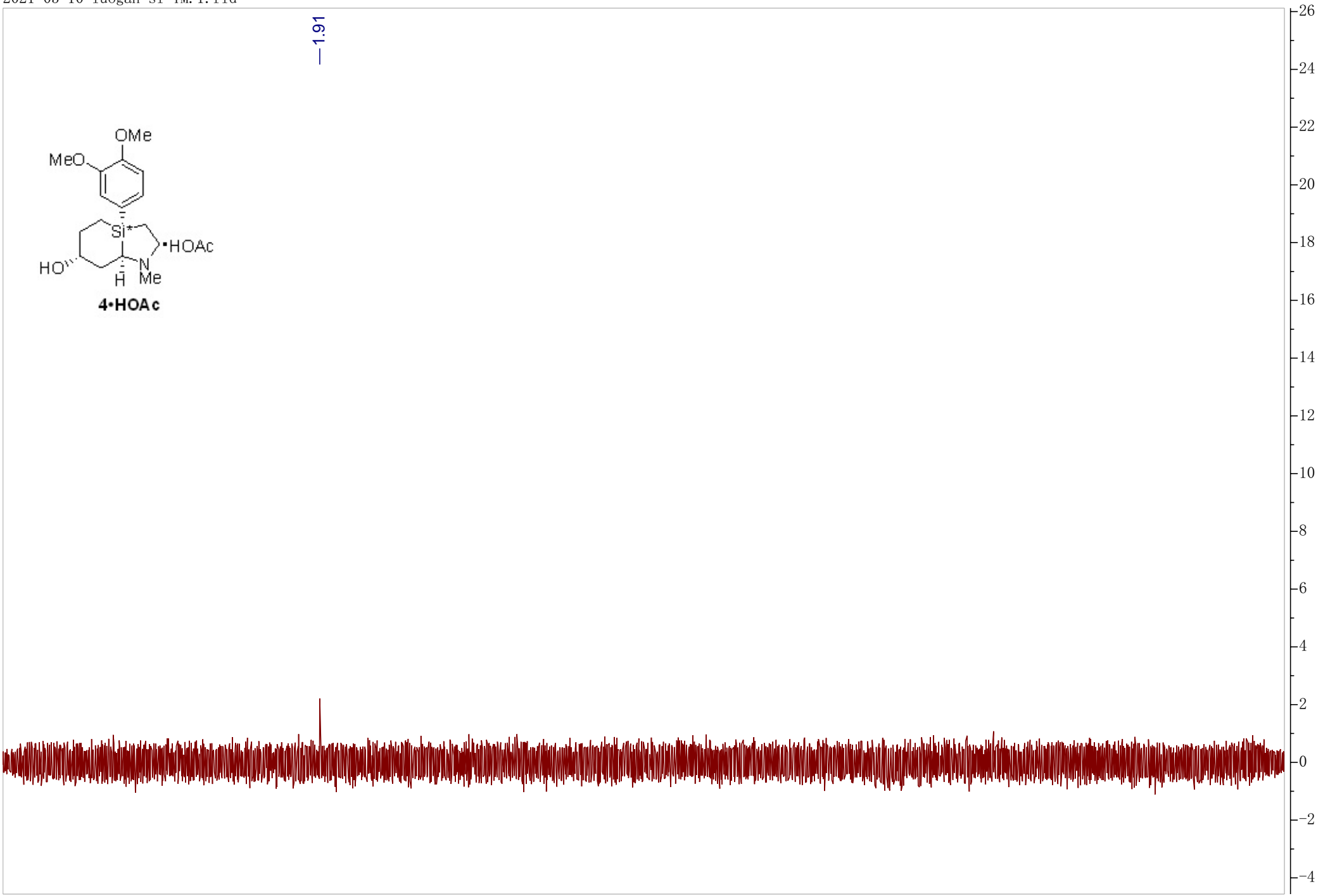
4•HOAc

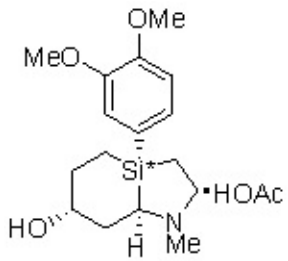

OMe
MeO
Si
HOAc
HO
N
H
Me

4•HOAc

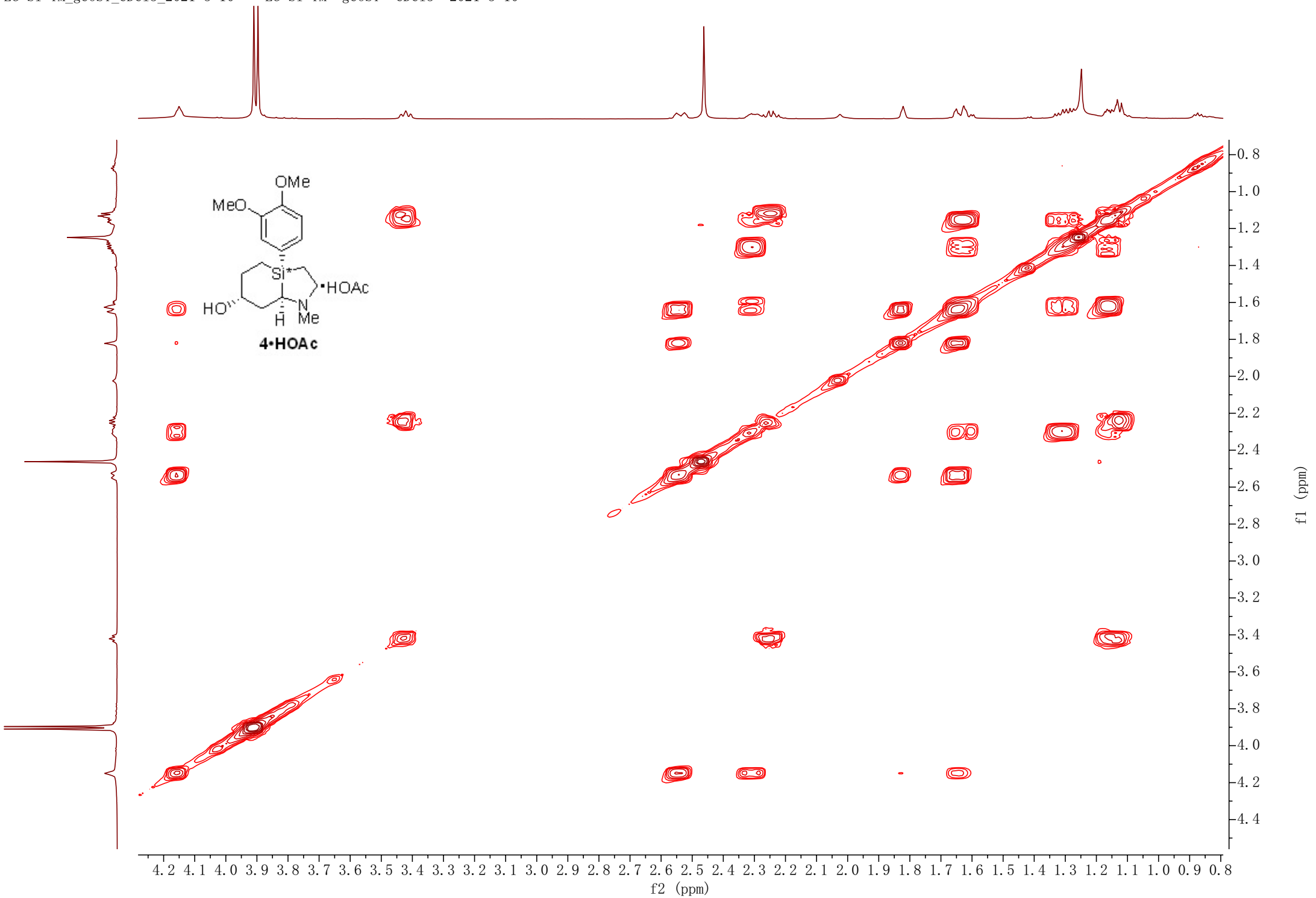
127.5
116.2
111.3
69.0
58.7
56.0
55.8
52.7
42.0
30.8
29.9
11.5
3.6
f1 (ppm)

2021-03-10 luogan-si-TM.1.fid

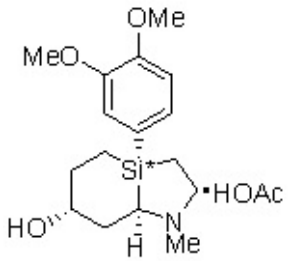




4•HOAc


LG-Si-TM_gCOSY_CDCl3_2021-3-10 — LG-Si-TM gCOSY CDCl3 2021-3-10 —
OMe
MeO
Si
HOAc
HO
N
H
Me
4•HOAc
f2 (ppm)
f1 (ppm)

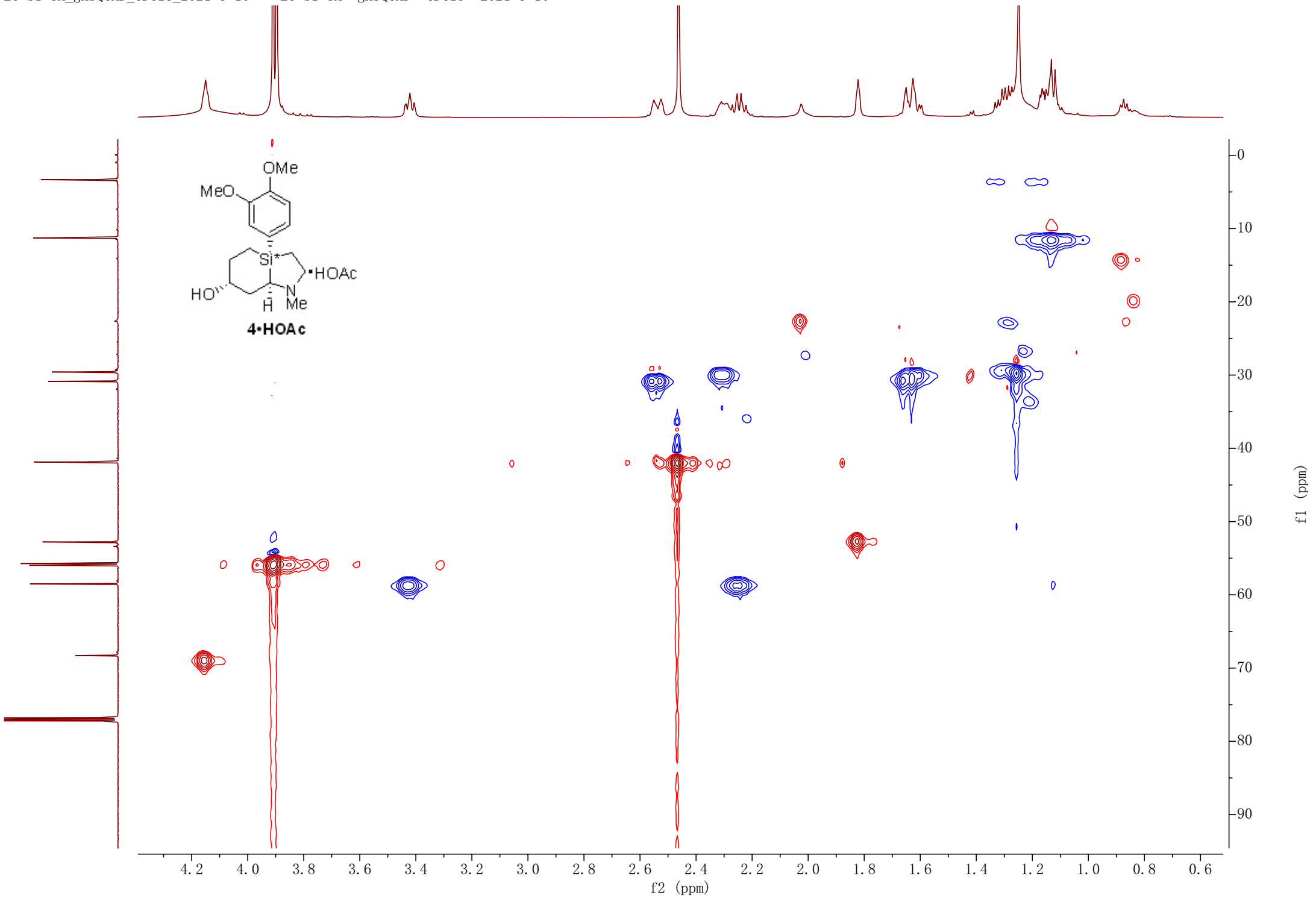
LG-Si-TM_gHSQCAD_CDCl3_2021-3-10 — LG-Si-TM gHSQCAD CDCl3 2021-3-10 —

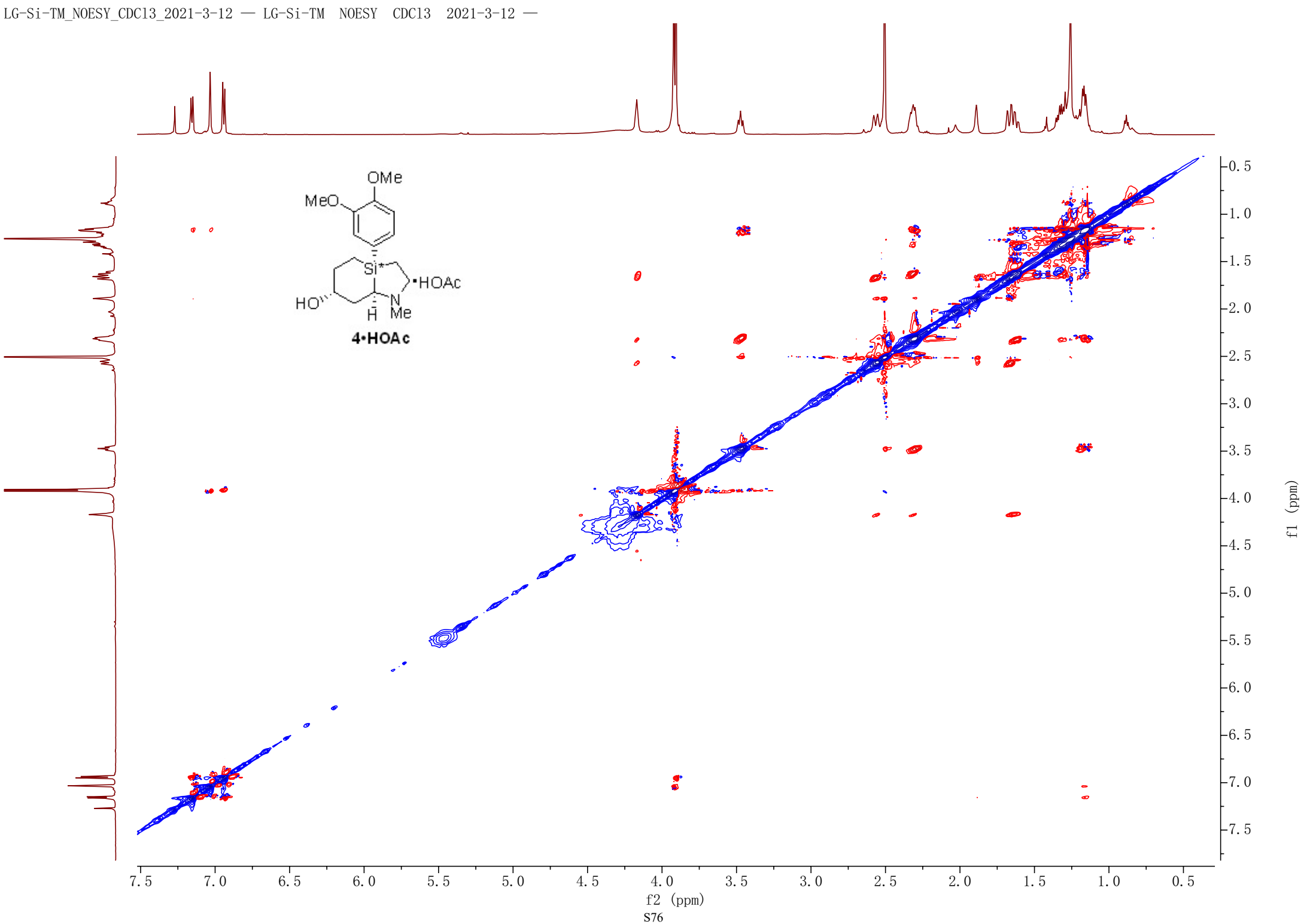


4•HOAc

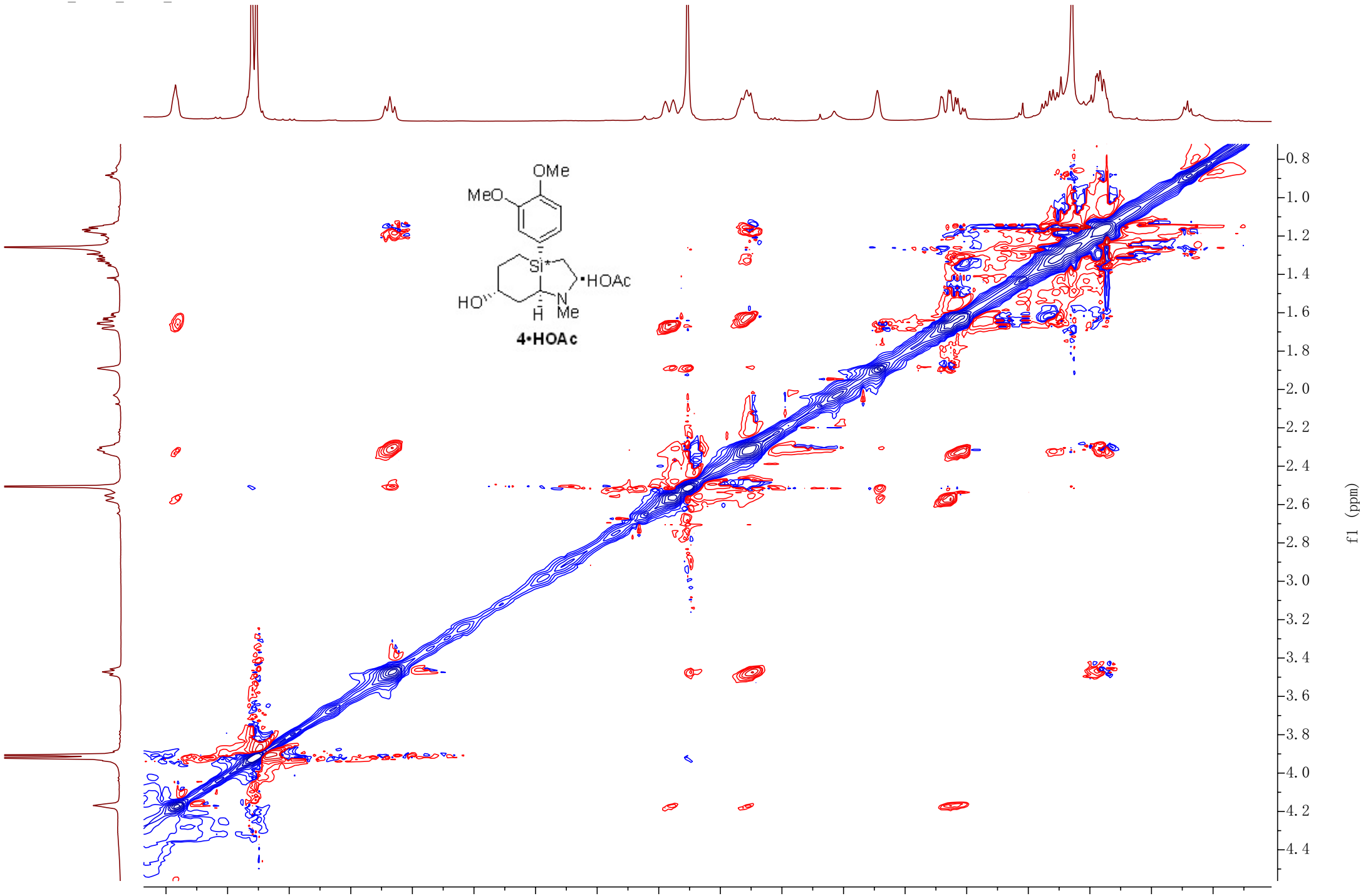
f2 (ppm)

f1 (ppm)

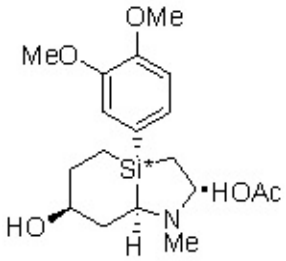

LG-Si-TM_gHSQCAD_CDCl3_2021-3-10 — LG-Si-TM gHSQCAD CDCl3 2021-3-10 —
OMe
MeO
Si
HOAc
HO
N
H
Me
4•HOAc
f2 (ppm)
f1 (ppm)


LG-Si-TM_NOESY_CDCl3_2021-3-12 — LG-Si-TM NOESY CDCl3 2021-3-12 —
OMe
MeO
Si
HO
N
H
Me
•HOAc
4•HOAc
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)
f1 (ppm)

LG-Si-TM_NOESY_CDCl3_2021-3-12 — LG-Si-TM NOESY CDCl3 2021-3-12 —

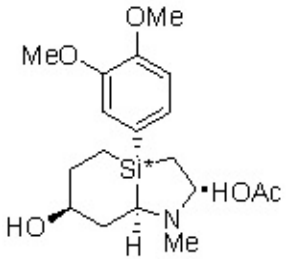


LG-si-epi_H1_CDCl3_2021-3-15 — LG-si-epi H1 CDCl3 2021-3-15 —



***epi*-4•HOAc**

LG-07-epi-CDCL3-C13-2020-9-7.10.fid

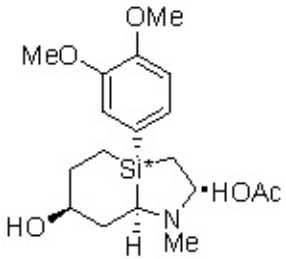


***epi*-4•HOAc**

151.0
149.0
127.5
124.3
116.1
111.4
77.3
77.0
76.7
68.0
58.2
56.0
55.8
53.6
41.5
35.5
32.2
10.3
7.5

f1 (ppm)

LG-si-epi_DEPT135_CDCl3_2021-3-16 — LG-si-epi DEPT135 CDCl3 2021-3-16 —



***epi*-4•HOAc**

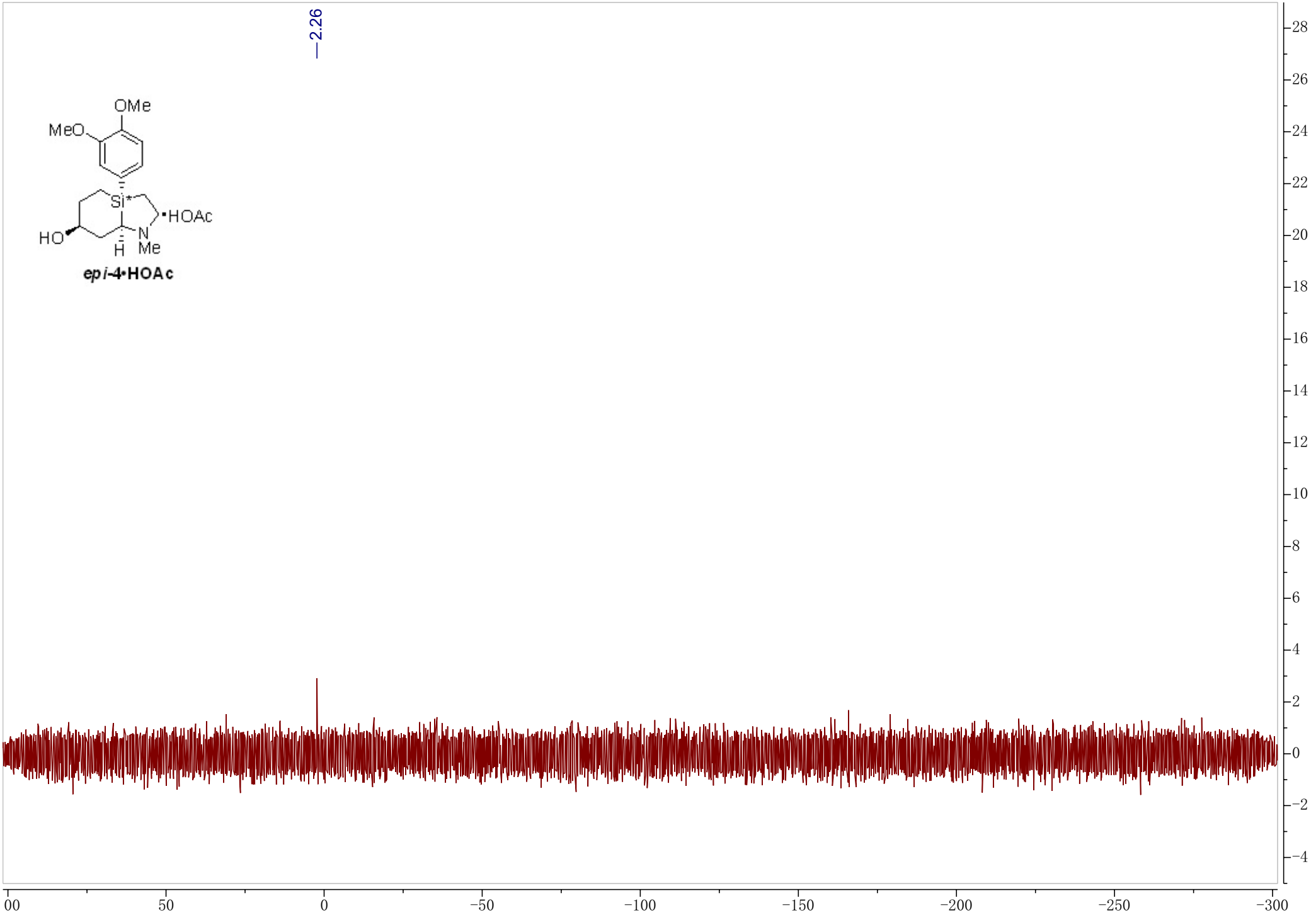
127.5
116.2
111.4
67.8
58.4
56.0
55.8
53.6
41.6
35.7
32.4
10.4
7.6

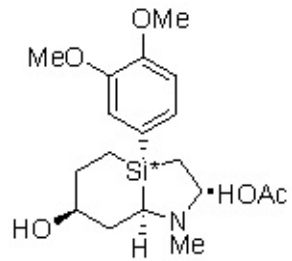
600
500
400
300
200
100
0
−100
−200
−300
−400

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10

f1 (ppm)

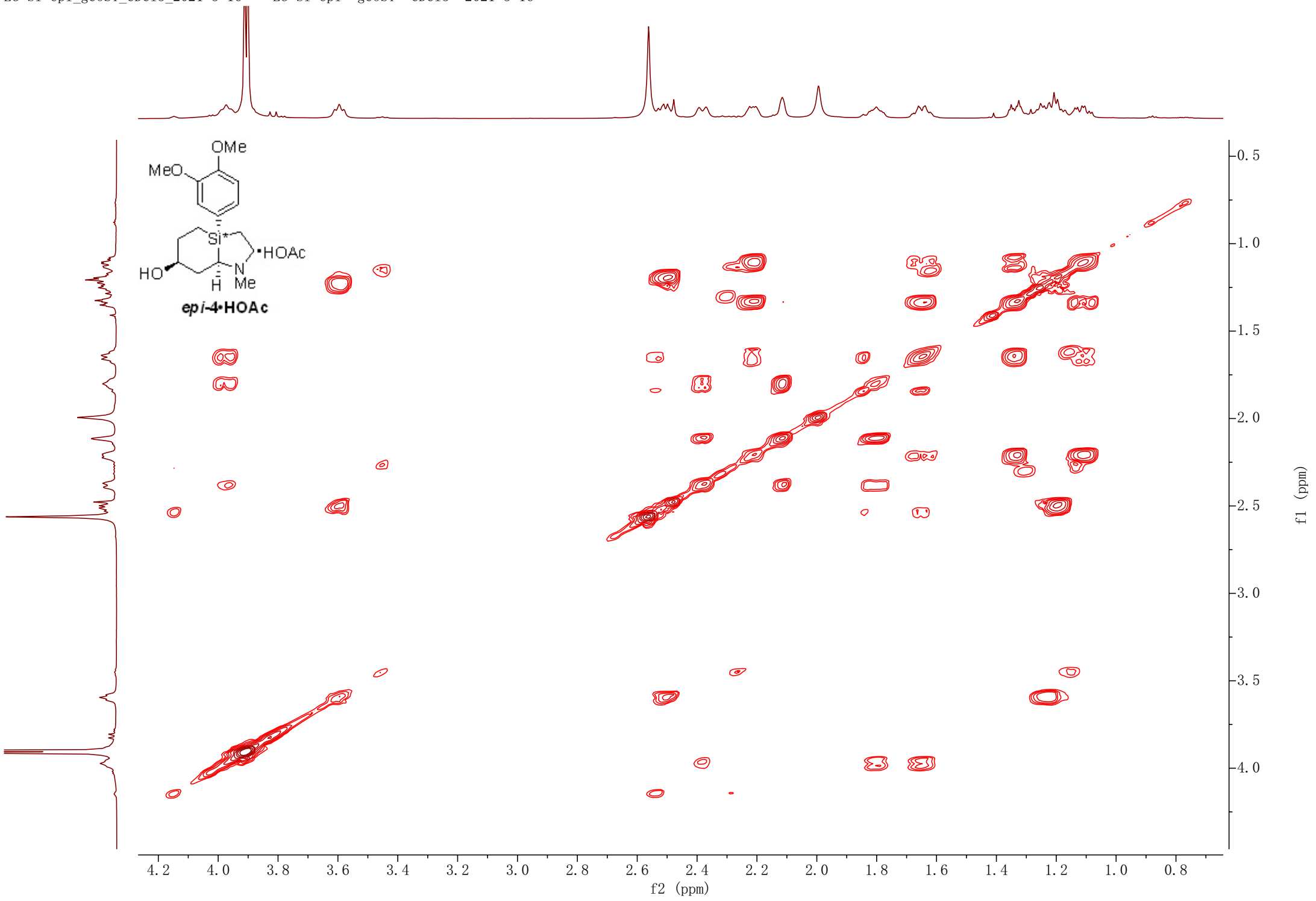
2020-09-04 zhousong-ig-07-epi.1.fid —



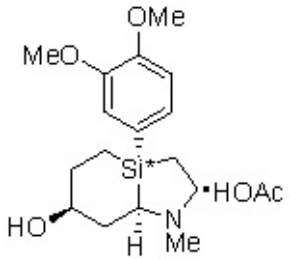

OMe
MeO
Si
HOAc
HO
N
H
Me

epi-4•HOAc

7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)
f1 (ppm)


LG-si-epi_gCOSY_CDCl3_2021-3-16 — LG-si-epi gCOSY CDCl3 2021-3-16 —
OMe
MeO
Si
•HOAc
HO
N
H
Me
epi-4•HOAc
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
f2 (ppm)
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
f1 (ppm)

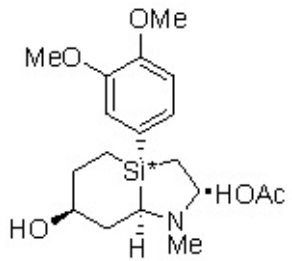
LG-si-epi_gHSQCAD_CDCl3_2021-3-16 — LG-si-epi gHSQCAD CDCl3 2021-3-16 —



***epi*-4•HOAc**

f2 (ppm)

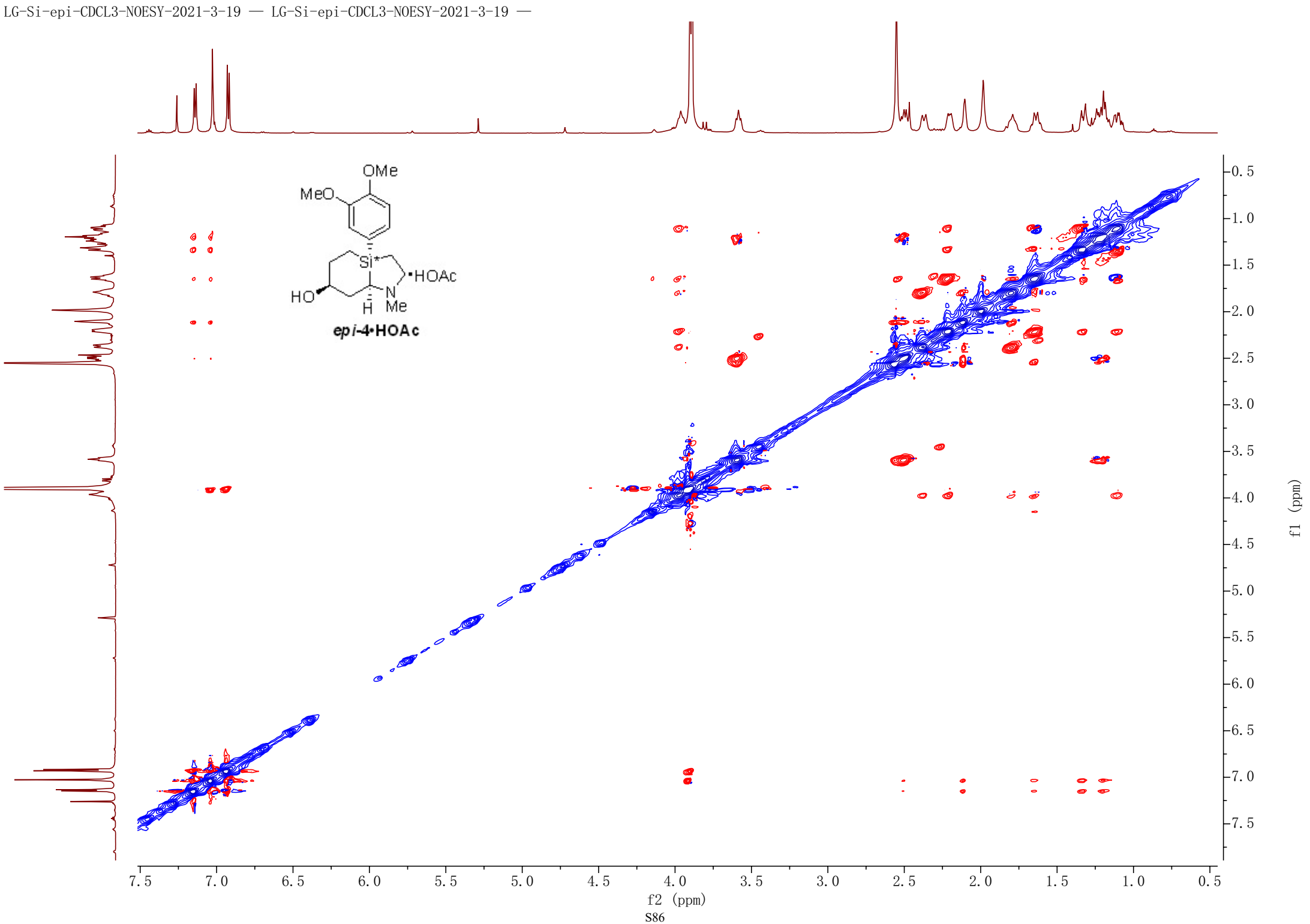
f1 (ppm)

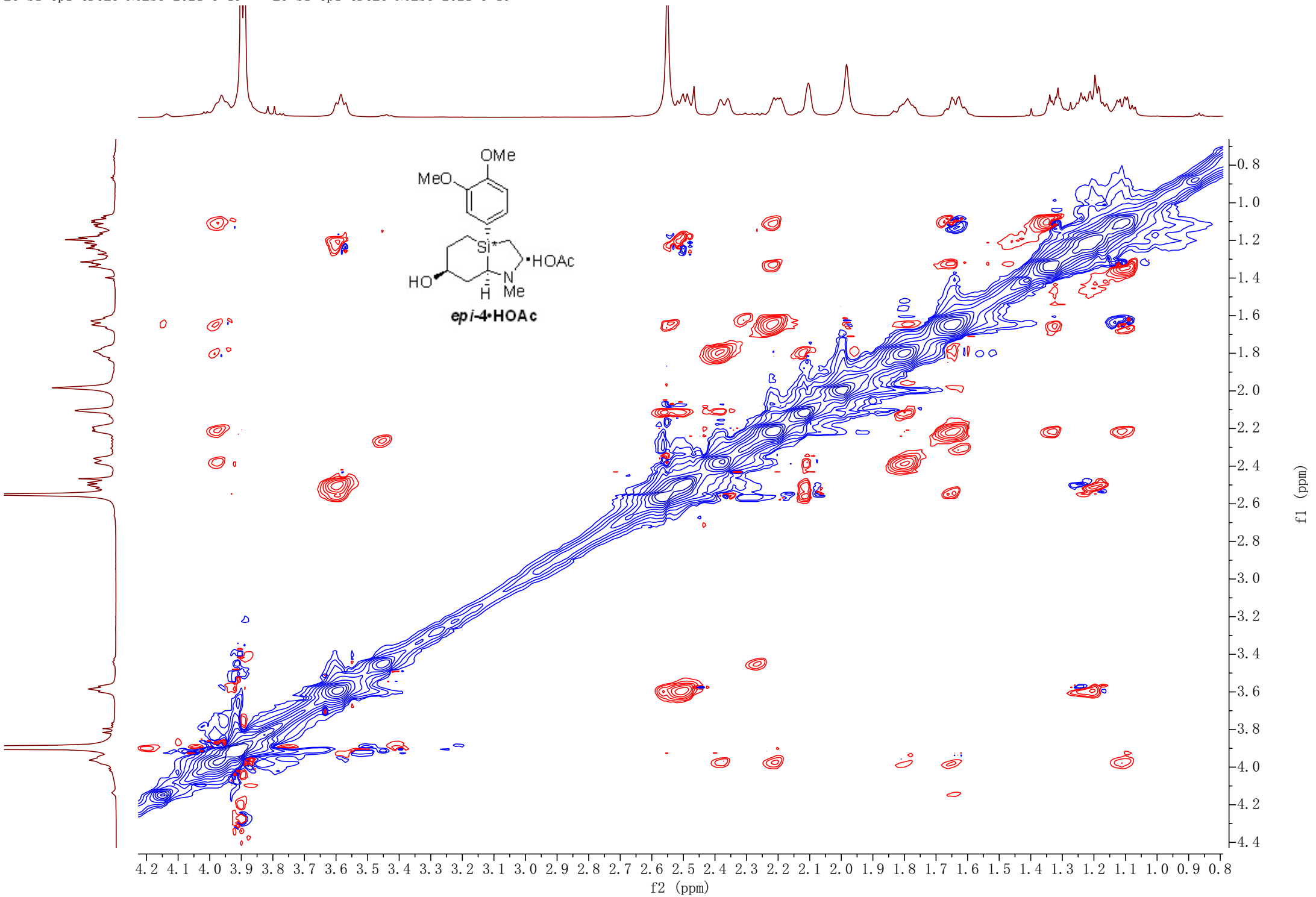


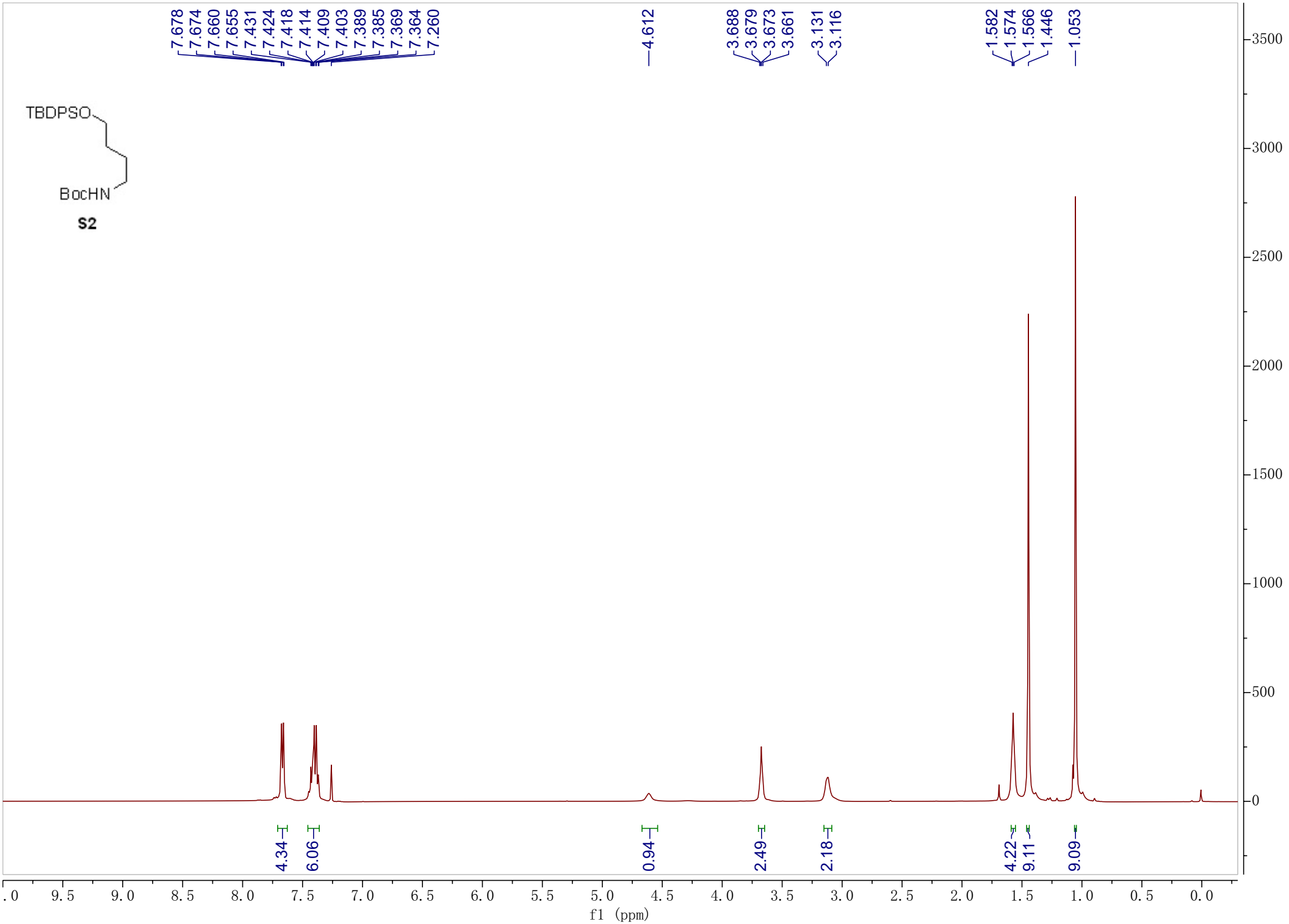
epi-4•HOAc

f2 (ppm)

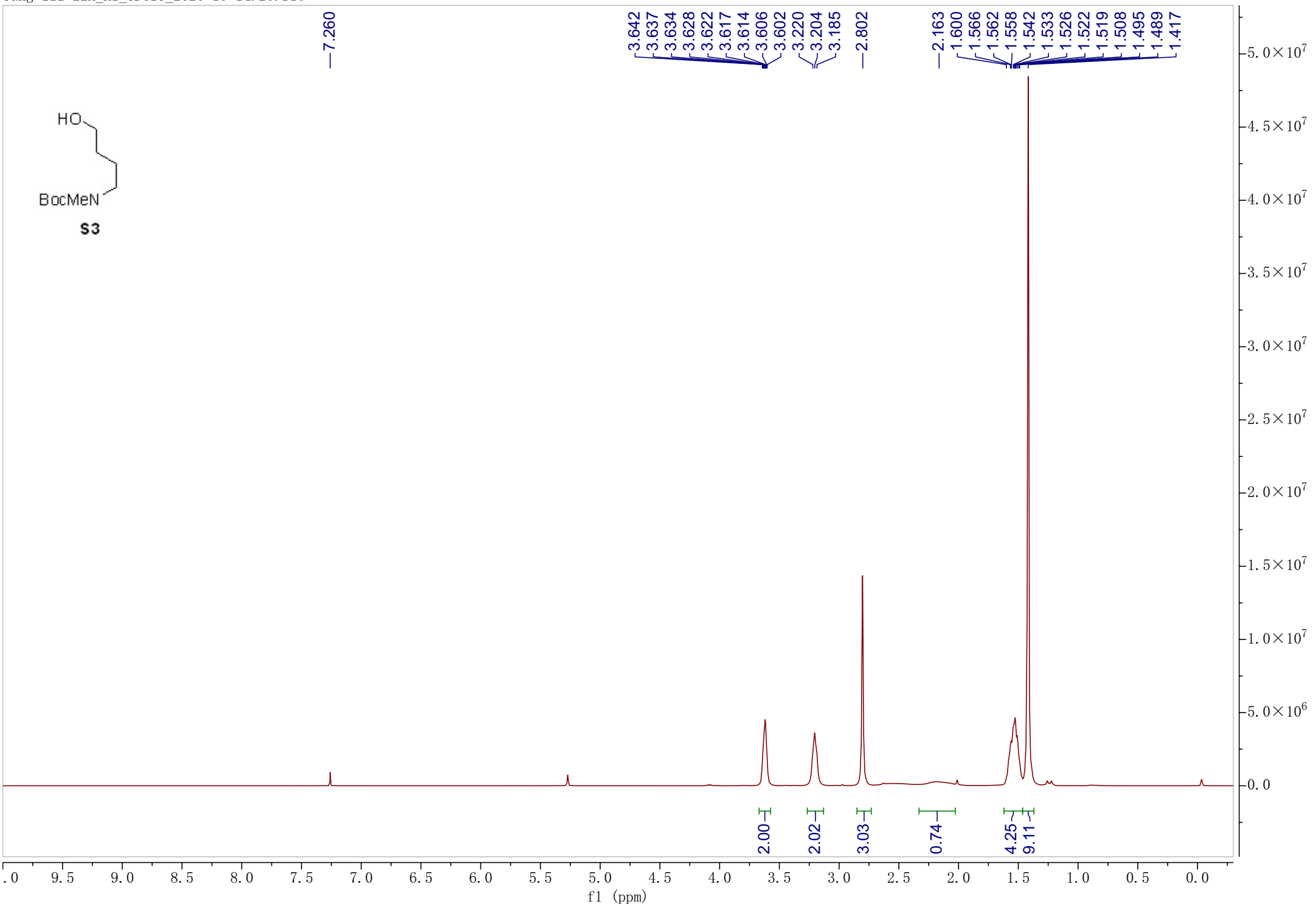
f1 (ppm)

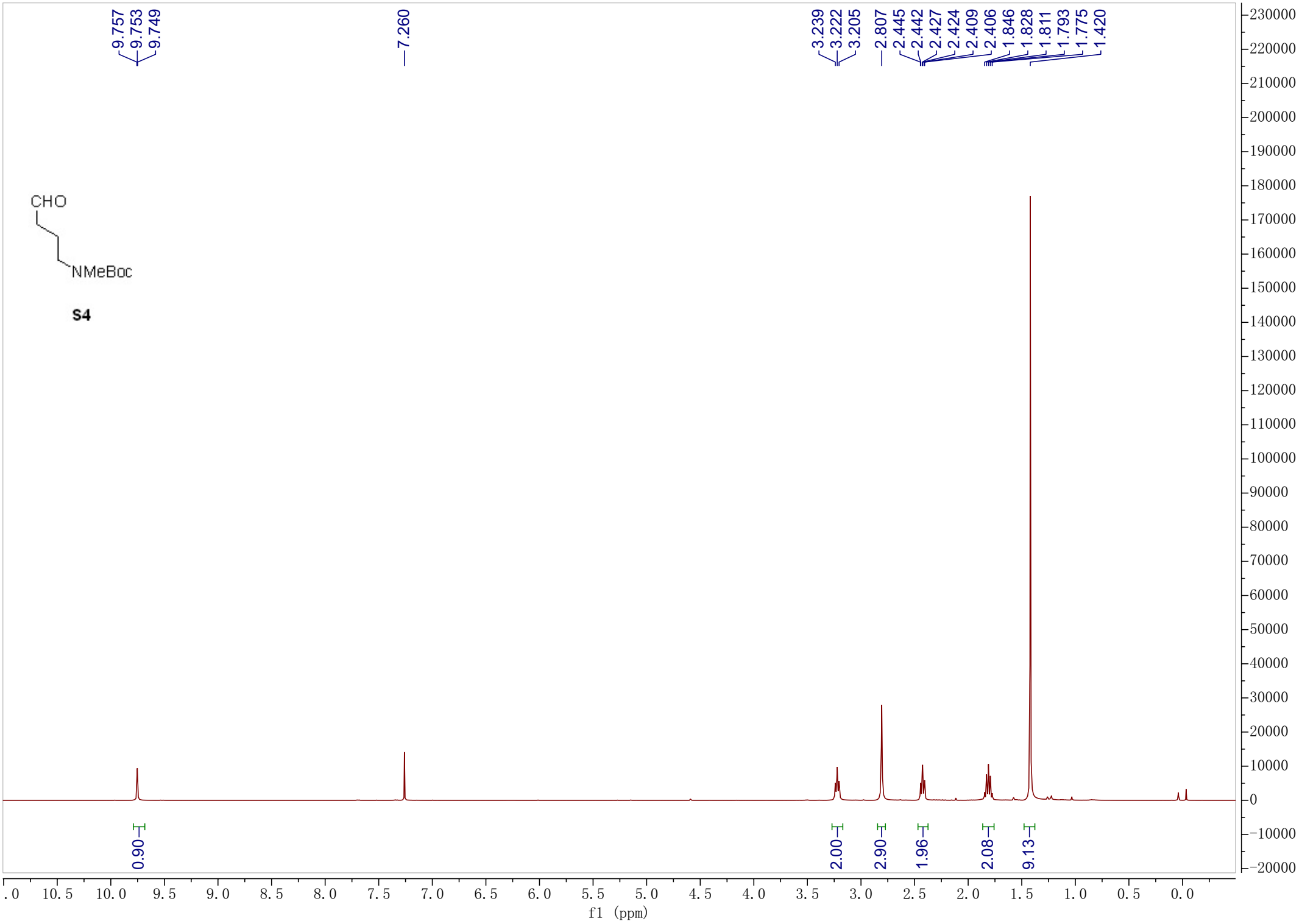

LG-Si-epi-CDCL3-NOESY-2021-3-19 — LG-Si-epi-CDCL3-NOESY-2021-3-19 —
OMe
MeO
Si
HOAc
HO
N
H
Me
epi-4•HOAc
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)
f1 (ppm)


LG-Si-epi-CDCL3-NOESY-2021-3-19 — LG-Si-epi-CDCL3-NOESY-2021-3-19 —
OMe
MeO
Si
HOAc
HO
N
H
Me
epi-4•HOAc
f2 (ppm)
f1 (ppm)

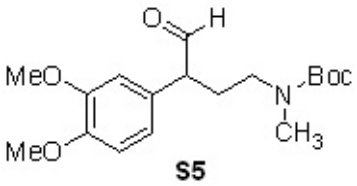

7.678
7.674
7.660
7.655
7.431
7.424
7.418
7.414
7.409
7.403
7.389
7.385
7.369
7.364
7.260
4.612
3.688
3.679
3.673
3.661
3.131
3.116
1.582
1.574
1.566
1.446
1.053
TBDPSO
BocHN
S2
4.34
6.06
0.94
2.49
2.18
4.22
9.11
9.09
f1 (ppm)

Yang-III-22A_H1_CDCl3_2020-10-14.20.fid

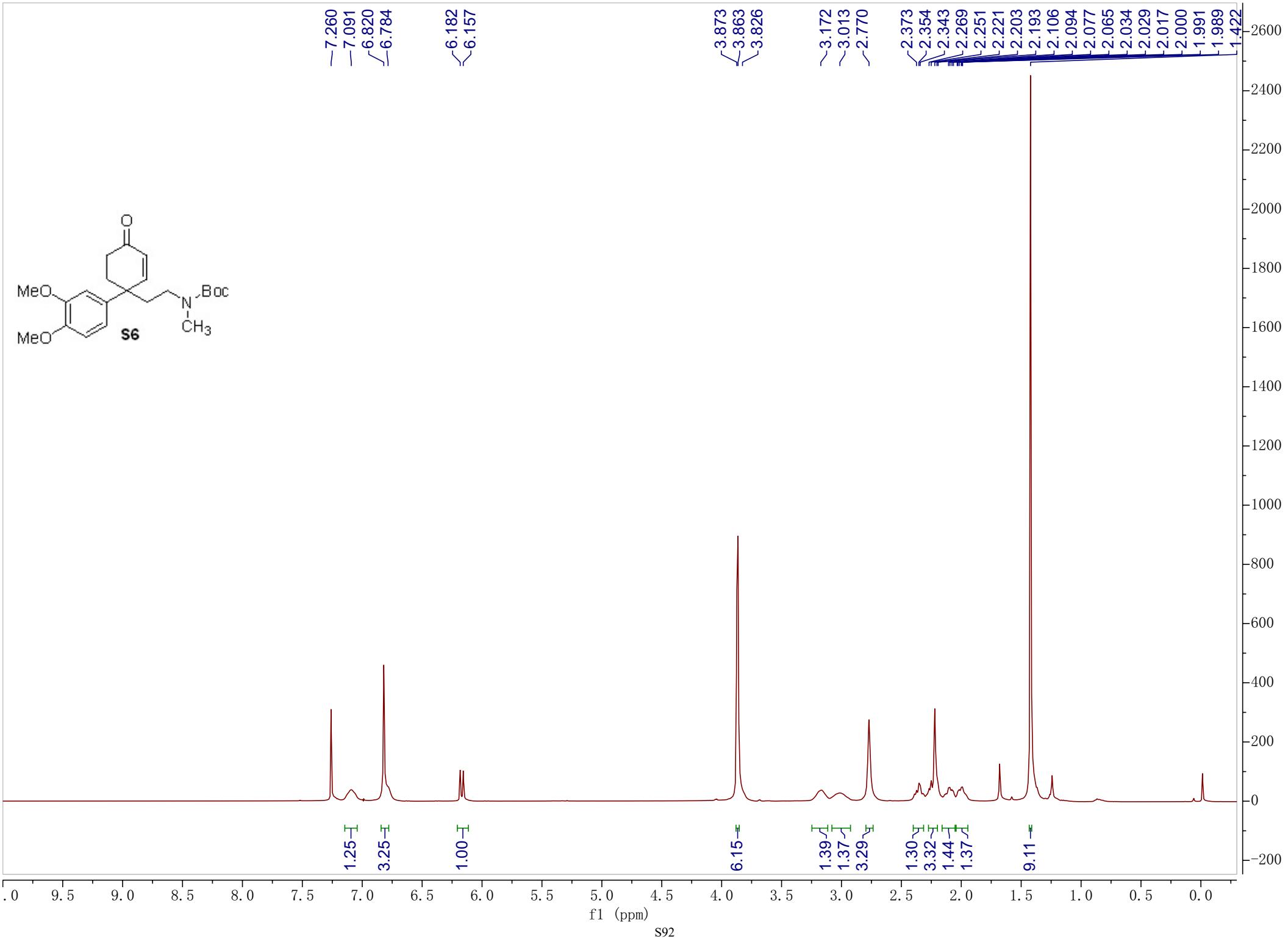


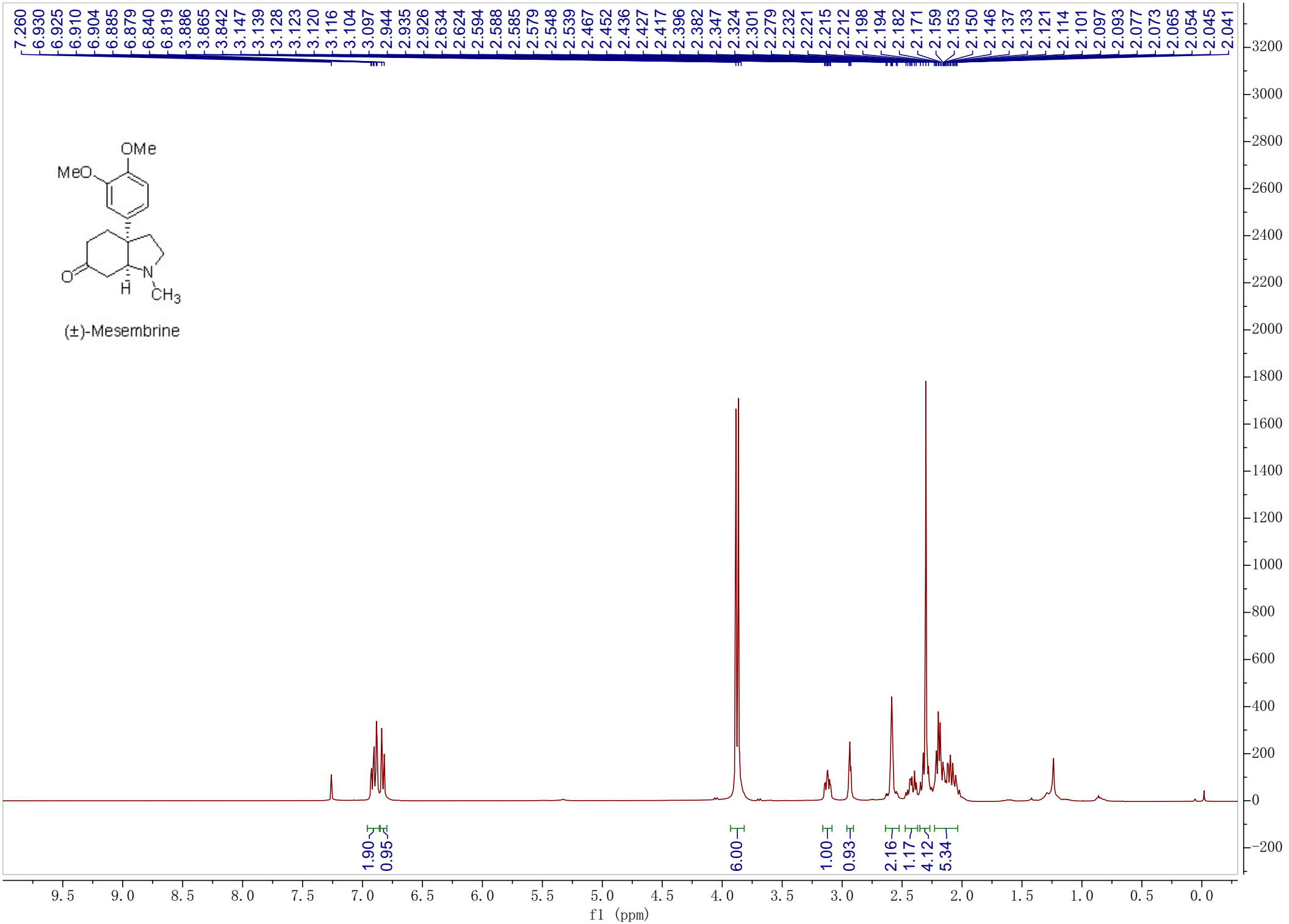

9.757
9.753
9.749
7.260
3.239
3.222
3.205
2.807
2.445
2.442
2.427
2.424
2.409
2.406
1.846
1.828
1.811
1.793
1.775
1.420
CHO
NMeBoc
S4
0.90
2.00
2.90
1.96
2.08
9.13
f1 (ppm)

LG-08-72_H1_CDCl3_2020-12-18.10.fid

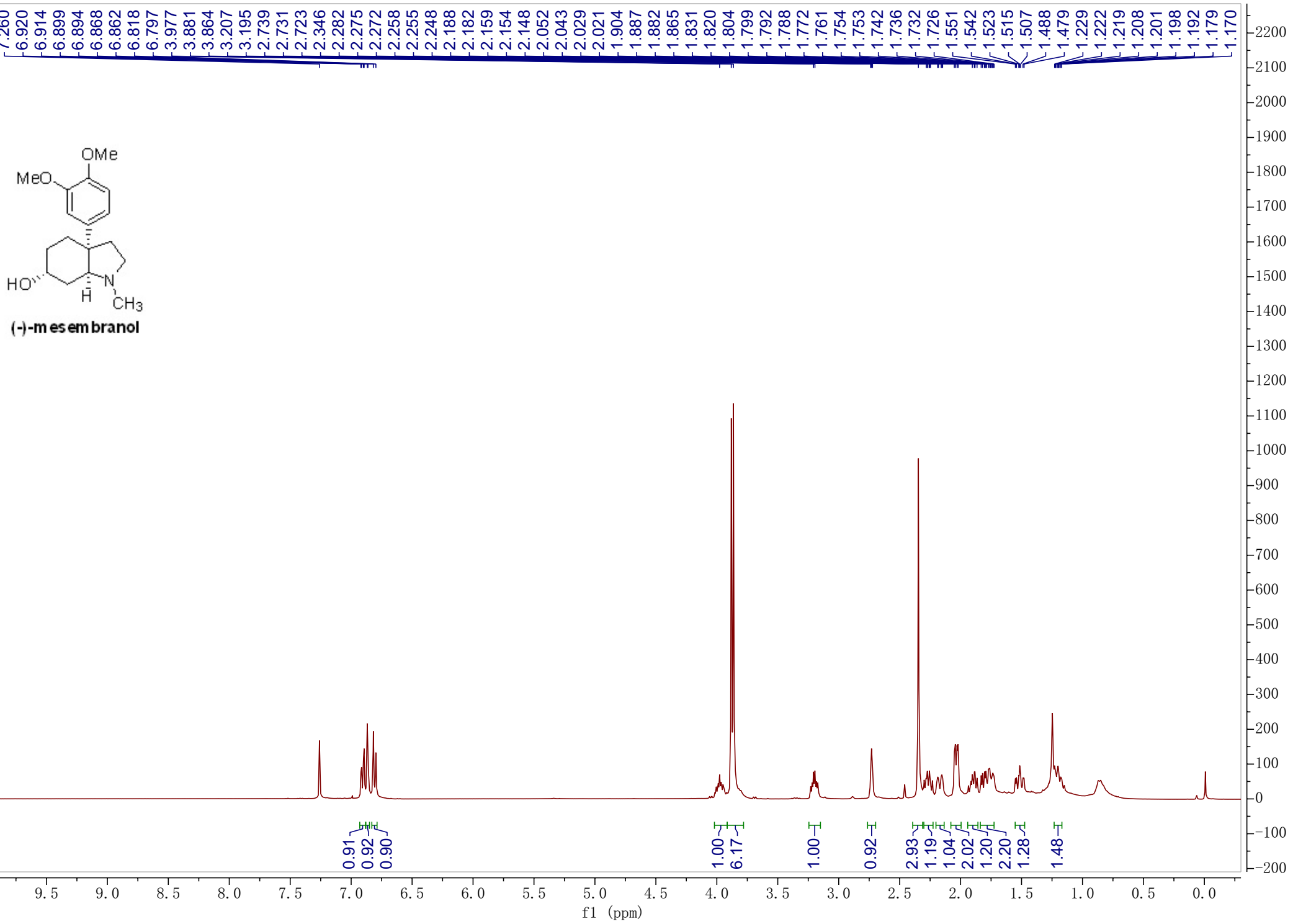


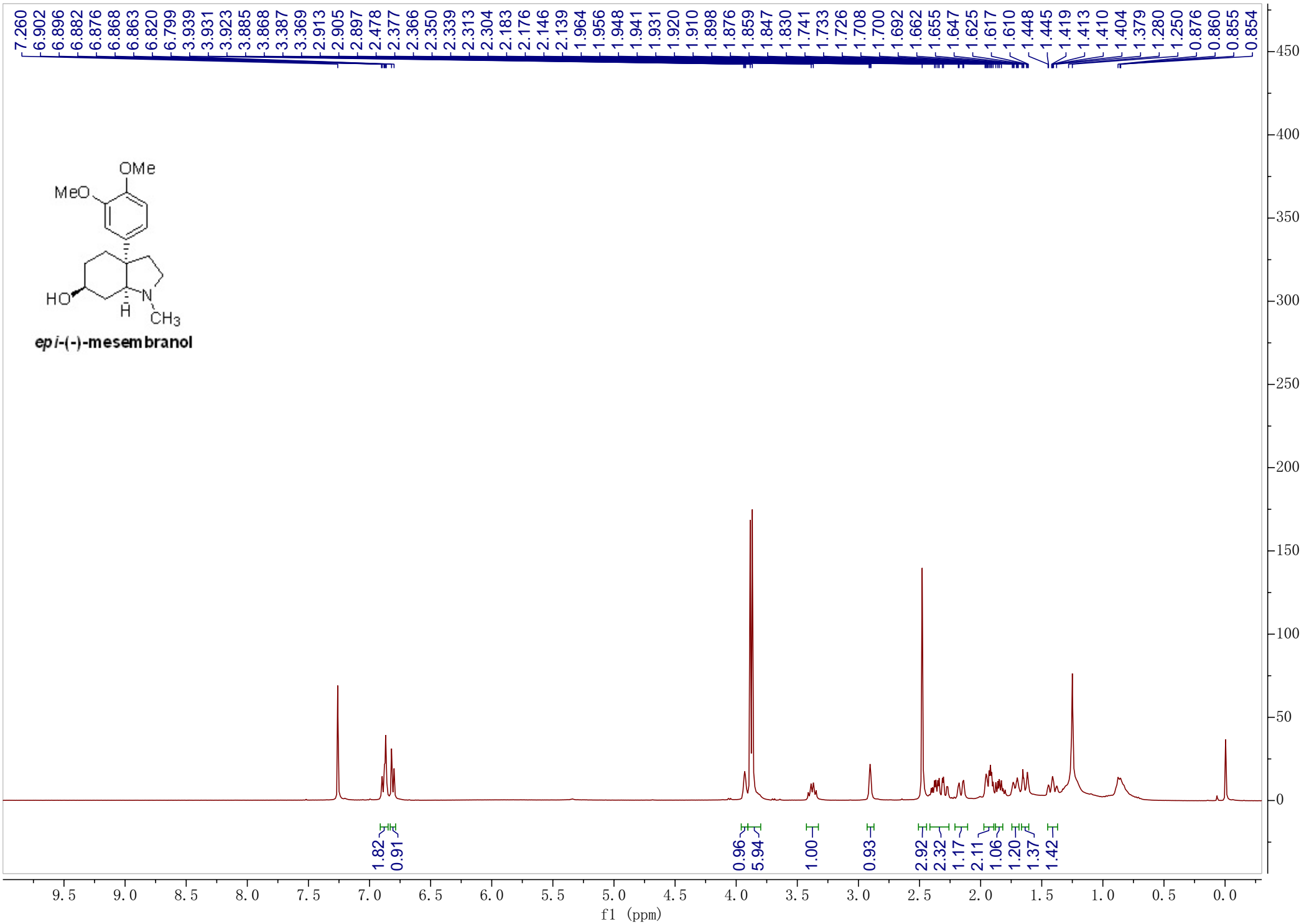
S5


7.260
7.091
6.820
6.784
6.182
6.157
3.873
3.863
3.826
3.172
3.013
2.770
2.373
2.354
2.343
2.269
2.251
2.221
2.203
2.193
2.106
2.094
2.077
2.065
2.034
2.029
2.017
2.000
1.991
1.989
1.422
MeO
MeO
Boc
N
CH3
O
S6
1.25
3.25
1.00
6.15
1.39
1.37
3.29
1.30
3.32
1.44
1.37
9.11
f1 (ppm)

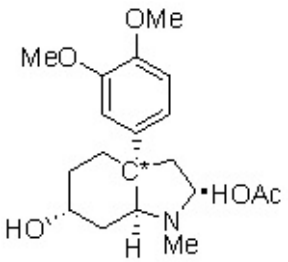

7.260 6.930 6.925 6.910 6.904 6.885 6.879 6.840 6.819 3.886 3.865 3.842 3.147 3.139 3.128 3.123 3.120 3.116 3.104 3.097 2.944 2.935 2.926 2.634 2.624 2.594 2.588 2.585 2.579 2.548 2.539 2.467 2.452 2.436 2.427 2.417 2.396 2.382 2.347 2.324 2.301 2.279 2.232 2.221 2.215 2.212 2.198 2.194 2.182 2.171 2.159 2.153 2.150 2.146 2.137 2.133 2.121 2.114 2.101 2.097 2.093 2.077 2.073 2.065 2.054 2.045 2.041
OMe
MeO
O
H
N
CH3
(±)-Mesembrine
1.90
0.95
6.00
1.00
0.93
2.16
1.17
4.12
5.34
f1 (ppm)

FY-03-69D-CDCL3-H1-2019-5-23 — FY-03-69D-CDCL3-H1-2019-5-23 —



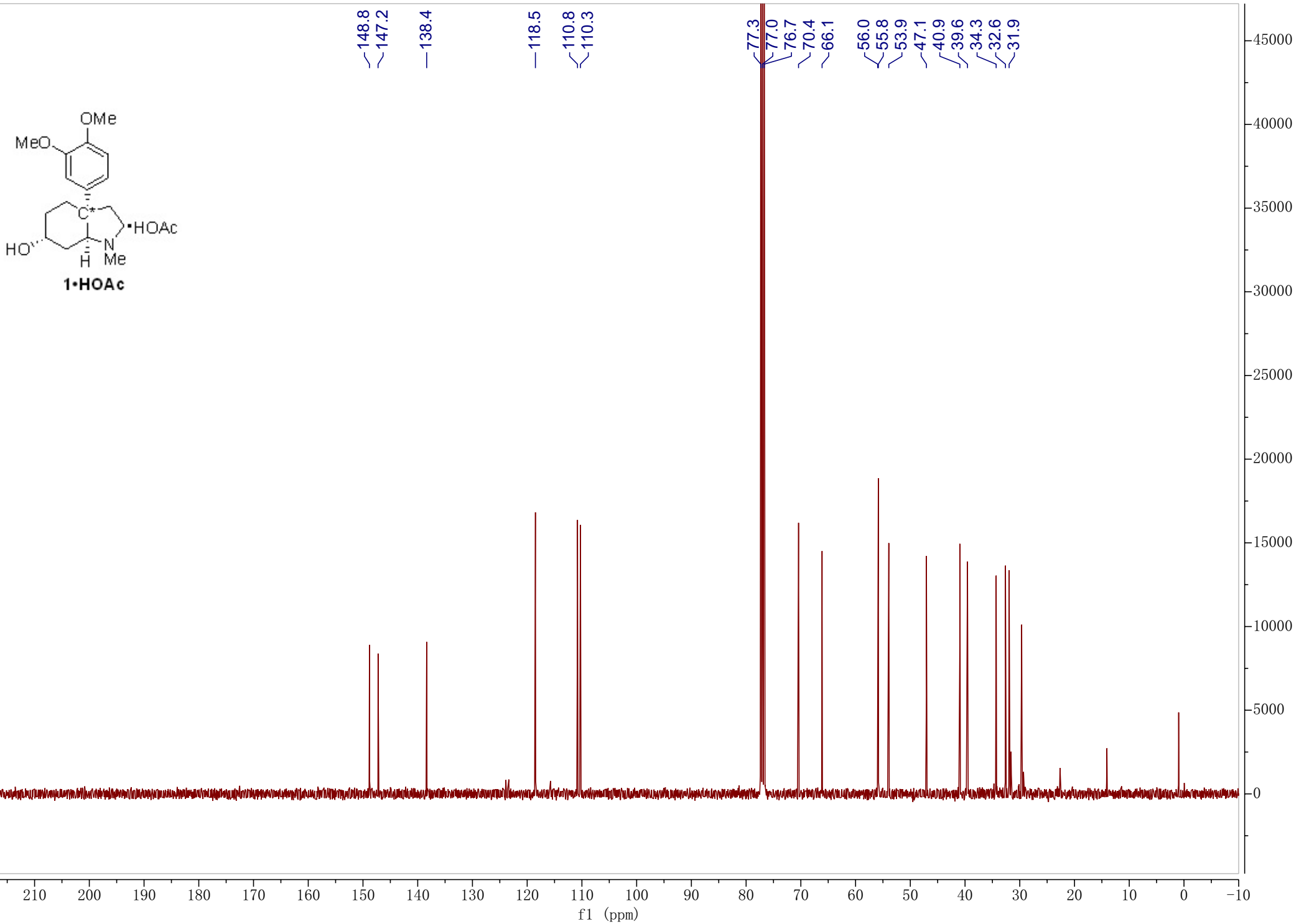

7.260
6.902
6.896
6.882
6.876
6.868
6.863
6.820
6.799
3.939
3.931
3.923
3.885
3.868
3.387
3.369
2.913
2.905
2.897
2.478
2.377
2.366
2.350
2.339
2.313
2.304
2.183
2.176
2.146
2.139
1.964
1.956
1.948
1.941
1.931
1.920
1.910
1.898
1.876
1.859
1.847
1.830
1.741
1.733
1.726
1.708
1.700
1.692
1.662
1.655
1.647
1.625
1.617
1.610
1.448
1.445
1.419
1.413
1.410
1.404
1.379
1.280
1.250
0.876
0.860
0.855
0.854
OMe
MeO
HO
H
N
CH3
epi-(-)-mesembranol
1.82
0.91
0.96
5.94
1.00
0.93
2.92
2.32
1.17
2.11
1.06
1.20
1.37
1.42
f1 (ppm)

LG-C-TM_H1_CDCl3_2021-3-9 — LG-C-TM H1 CDCl3 2021-3-9 —

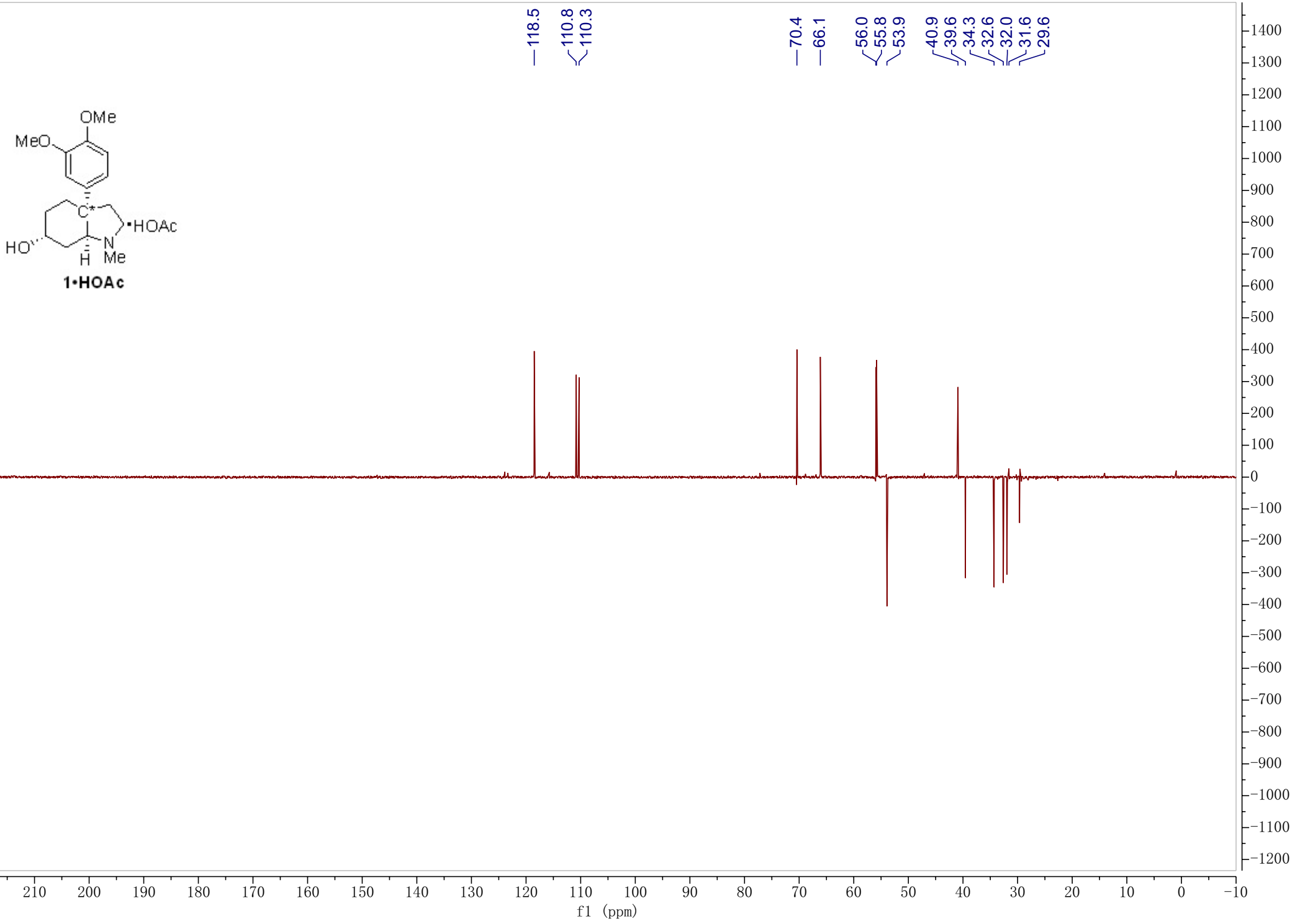


1•HOAc

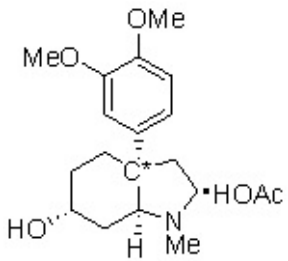
LG-C-TM-CDCL3-C13-2021-3-9.10.fid



LG-C-TM_DEPT135_CDCl3_2021-3-9 — LG-C-TM DEPT135 CDCl3 2021-3-9 —



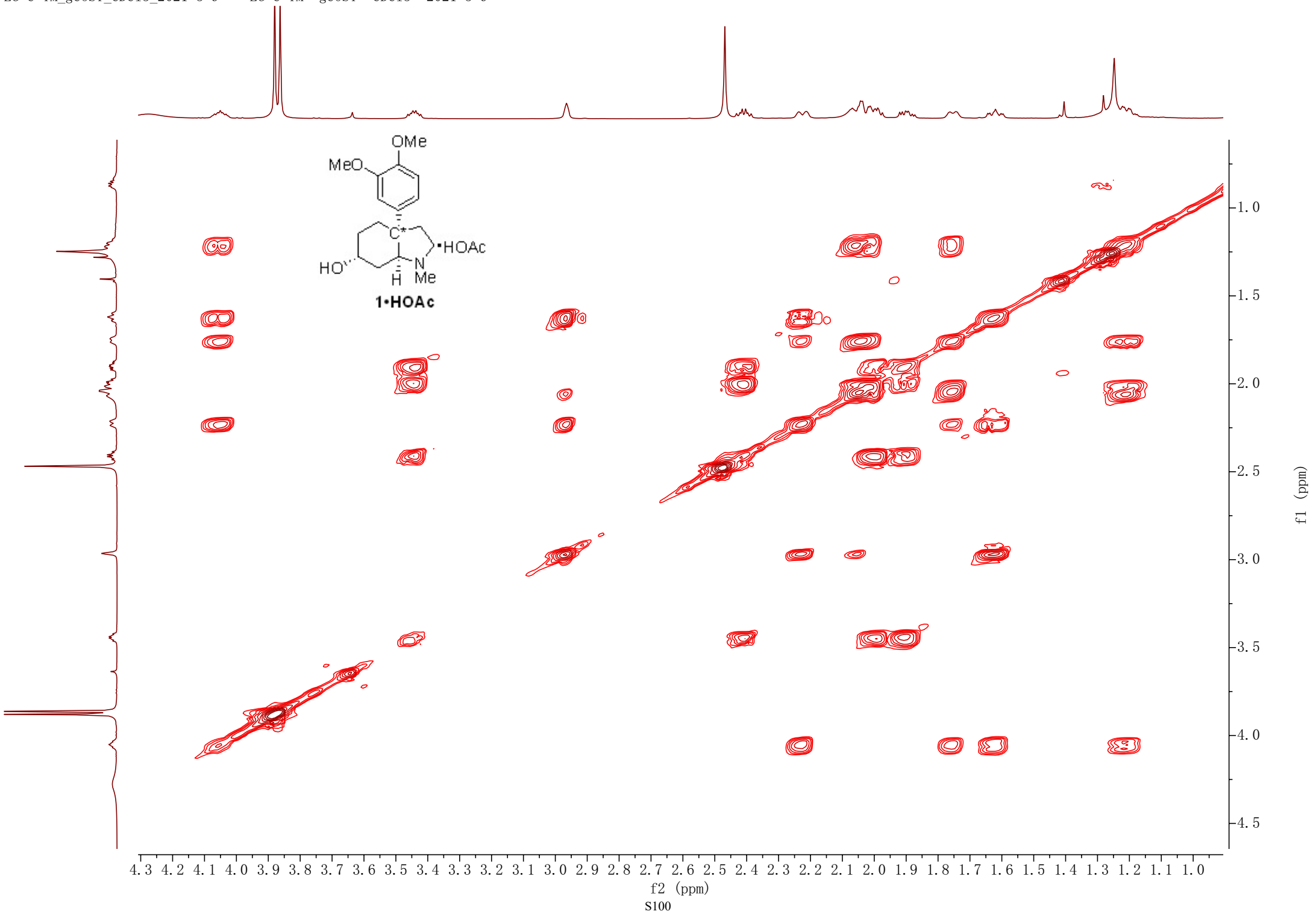
LG-C-TM_gCOSY_CDCl3_2021-3-9 — LG-C-TM gCOSY CDCl3 2021-3-9 —

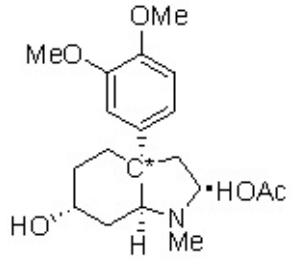


1•HOAc

f2 (ppm)

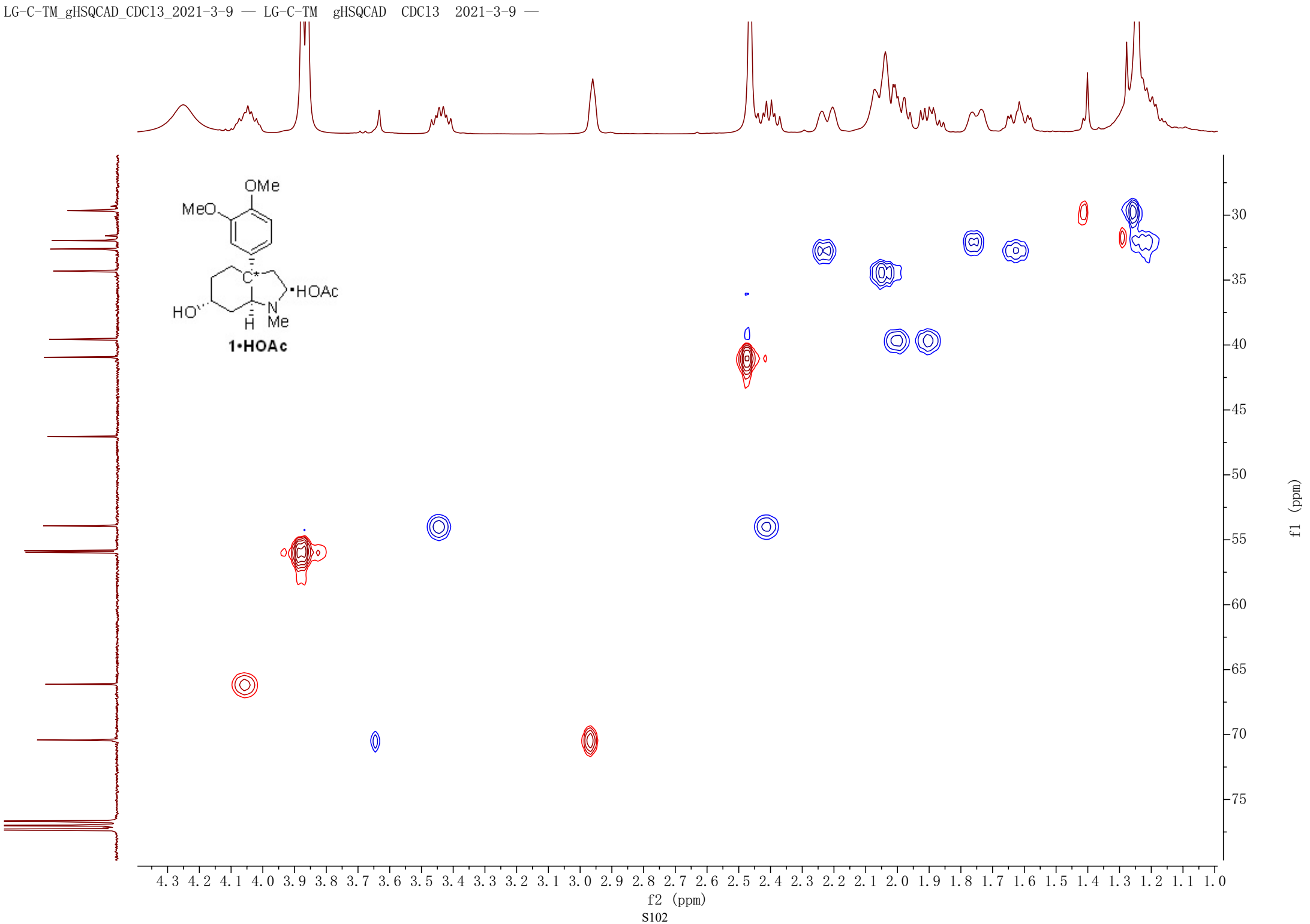
f1 (ppm)

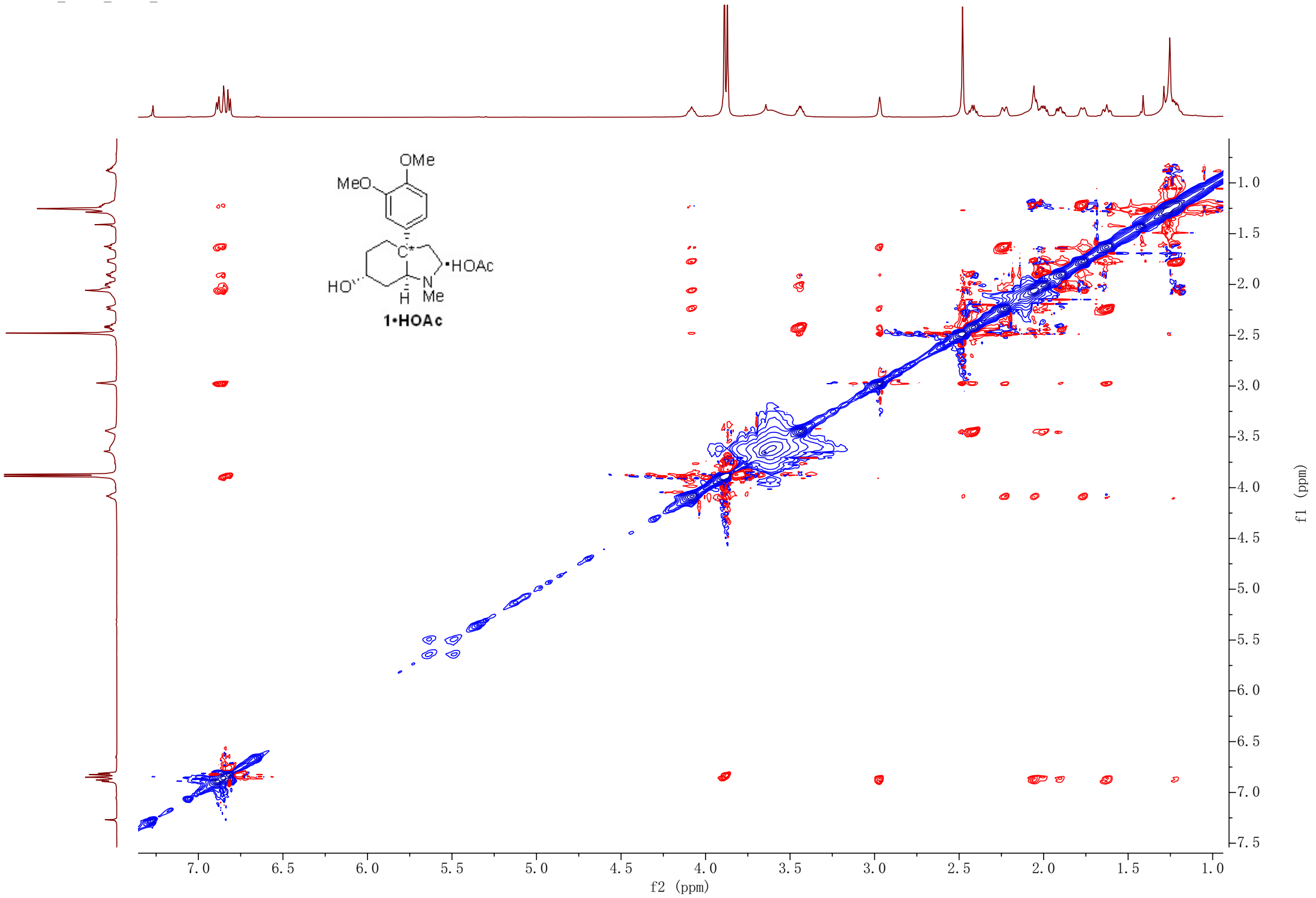

LG-C-TM_gCOSY_CDCl3_2021-3-9 — LG-C-TM gCOSY CDCl3 2021-3-9 —
OMe
MeO
HO
HOAc
N
Me
H
1•HOAc
f2 (ppm)
f1 (ppm)

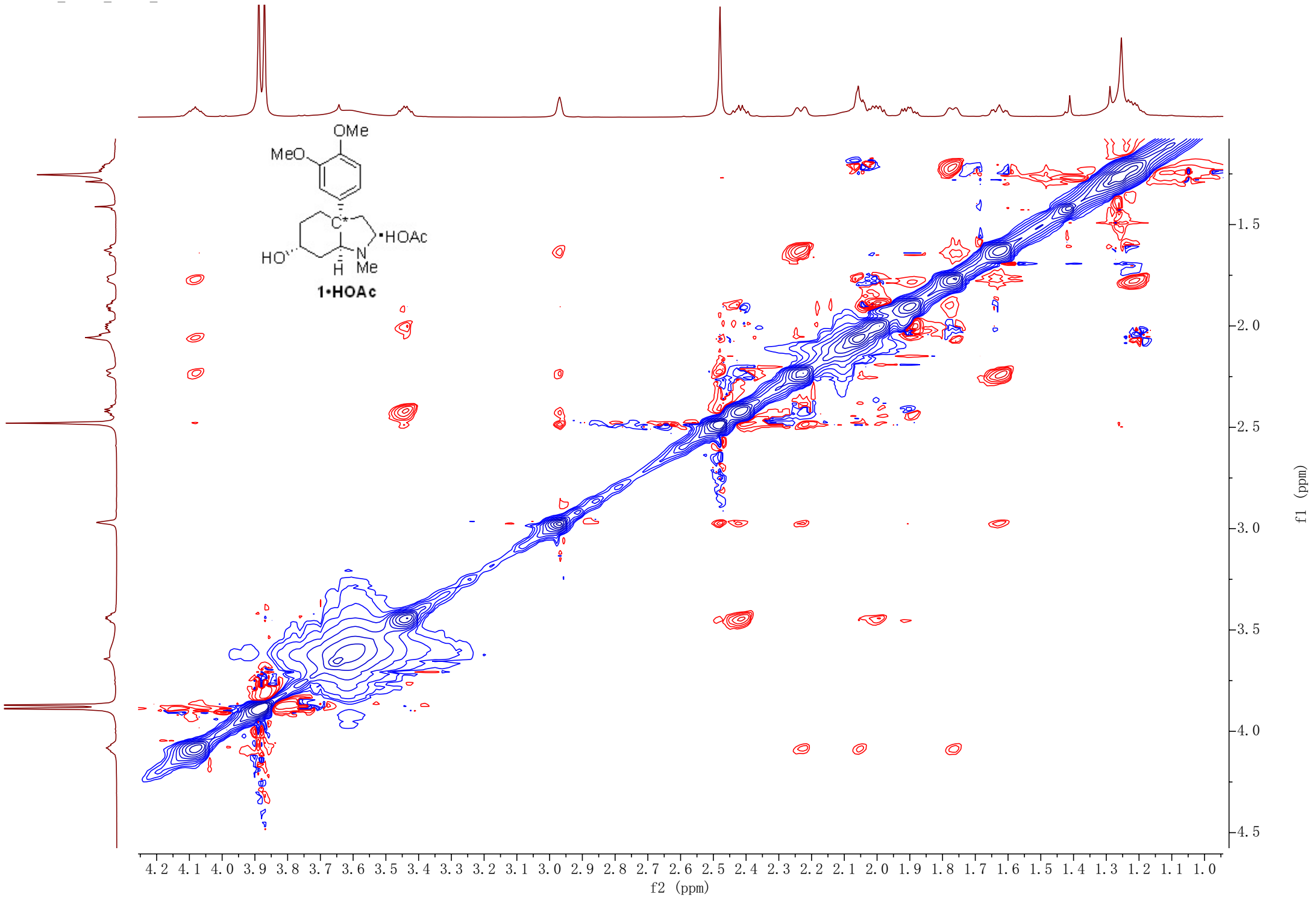

OMe
MeO
C*
•HOAc
HO
N
H
Me

1•HOAc

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)
30
40
50
60
70
80
90
100
110
120
130
140
150
f1 (ppm)


LG-C-TM_gHSQCAD_CDCl3_2021-3-9 — LG-C-TM gHSQCAD CDCl3 2021-3-9 —
OMe
MeO
HO
HOAc
N
Me
H
1•HOAc
30
35
40
45
50
55
60
65
70
75
f1 (ppm)
4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0
f2 (ppm)


LG-C-TM_NOESY_CDCl3_2021-3-11 — LG-C-TM NOESY CDCl3 2021-3-11 —
OMe
MeO
HO
HOAc
N
Me
H
1•HOAc
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)
f1 (ppm)


LG-C-TM_NOESY_CDCl3_2021-3-11 — LG-C-TM NOESY CDCl3 2021-3-11 —
OMe
MeO
HO
HOAc
N
Me
H
1•HOAc
f2 (ppm)
f1 (ppm)