Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

SUPPORTING INFORMATION

Asymmetric Synthesis of γ–Aryl-substituted GABA Derivatives via a Highly Diastereoselective Rh-Catalyzed Boronic Acid Addition at Room Temperature

*P. V. Ramachandran, Wataru Mitsuhashi and Bidyut Biswas

Herbert C. Brown Center for Borane Research, Department of Chemistry, Purdue University, 560 Oval Drive, West Lafayette, IN, USA 47907-2084

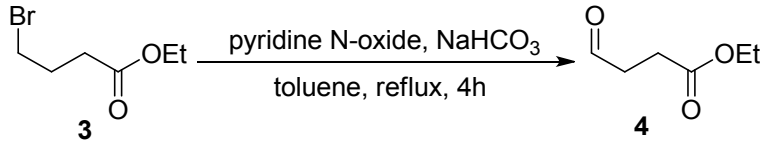
E-Mail: chandran@purdue.edu

Supporting Information Table of Contents

General Supporting Information

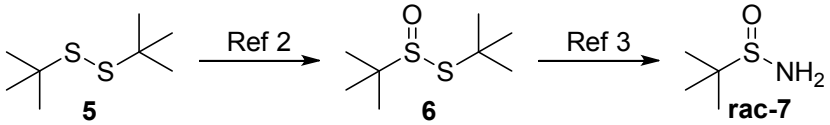
All reagents were purchased from Sigma-Aldrich, Fisher-Acros, Strem Chemical, Oakwood Chemical, or Alfa-Aesar, and were used without further purification unless otherwise noted. All solvents were distilled prior to use unless otherwise noted. All reactions were performed at room temperature and under a nitrogen atmosphere in either flame or oven-dried glassware unless otherwise noted. All TLC analysis was performed using aluminum-backed Thin-Layer Chromatography Plates (Dynamic Absorbent Inc., 200 μm thickness, F-254 Indicator). All solvent systems are given as volume/volume ratios. Flash chromatography was performed using 230-400 mesh, 60Å pore diameter flash chromatography gel. All chromatography elutions were gradient in nature, eluting first with hexanes, followed by incorporating more polar solvents as appropriate. ^{1}H, ^{13}C, and ^{19}F spectra were recorded at room temperature, on Varian INOVA 300 MHz or Bruker400 MHz. Chemical shifts (δ values) are reported in parts per million, and are referenced to tetramethylsilane. ^{19}F NMR is referenced internal to the spectrometer. Data are reported as: δ value, multiplicity, and integration, (s=singlet, d=doublet, t=triplet, q=quartet, p=pentet, h=hextet, br=broad). ^{1}H NMR (and/or ^{19}F NMR) was used as the measurement of dr by comparing the relative integration values of the benzylic or NH protons. Optical rotations were measured on an Autopol III automatic polarimeter, and are reported against the "Sodium D" line at 25 °C ($[\alpha]_D^{25}$).

General Procedure for the Preparation of Sulfinylimine 1



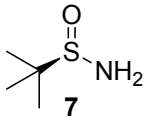
3 4

Ethyl 4-oxobutanoate (4). **4** was synthesized from ethyl 4-bromobutanoate (**3**) by the reported procedure.[1] The product was purified by column chromatography (CH_2Cl_2 to CH_2Cl_2/Et_2O 50:50) on which the crude reaction solution was directly loaded to provide **4** (52% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 1H), 4.15 (q, J = 7.1 Hz, 2H), 2.80 (t, J = 6.6 Hz, 2H), 2.63 (t, J = 6.6 Hz, 2H), 1.27 (t, J = 7.1 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 200.4, 172.6, 61.2, 38.9, 27.0, 14.5.



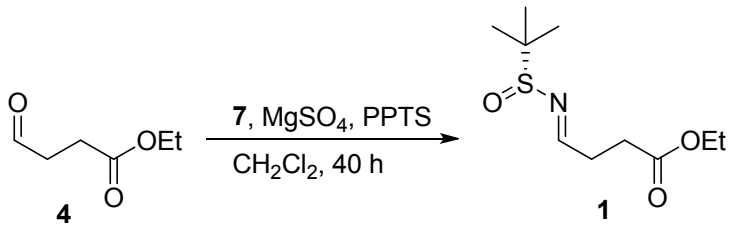
5 6 rac-7

***t*-Butanesulfinamide (rac-7)**. Rac-7 was synthesized by the reported procedures.[2,3] Spectral data is listed below.



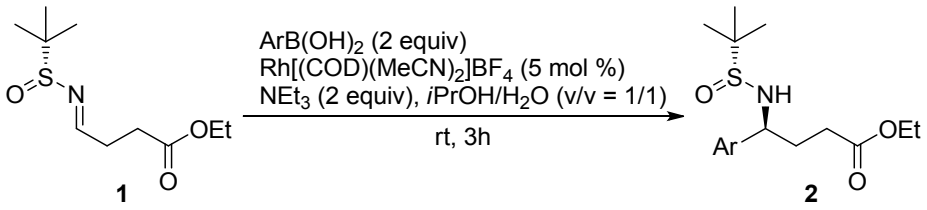
7

(*R*)-*t*-Butanesulfinamide (7). **7** was synthesized by the reported procedure[4] (er 99:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.65 (s, 2H), 1.21 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.8, 22.3. HPLC analysis on a Chiralcel OD-H: 85:15 *n*-hexane/ *i*PrOH, 1.0 mL/min, UV VIS detection at 220 nm, **(*R*)-7**: 18.0 min, **(*S*)-7**: 19.9 min.



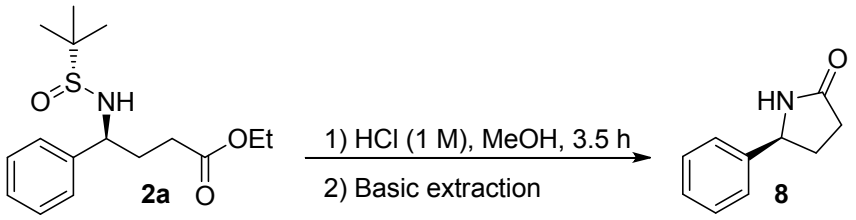
(*R*,*E*)-Ethyl 4[(*t*-butylsulfinyl)imino]butanoate (1). **1** was synthesized by the following procedure[5]: To **7** (327 mg, 2.72 mmol), $MgSO_4$ (2.12 g, 17.7 mmol) and PPTS (34.2 mg, 0.136 mmol) in a round bottom flask, **4** (426 mg, 3.27 mmol) in CH_2Cl_2 (5.5 mL) was added at 0 ºC. After stirring for 40 h at rt, the reaction mixture was filtered through Celite®, concentrated under reduced pressure, and purified via column chromatography (hexane/ethyl acetate 60:40 to 50:50) to provide an analytically pure product **1** (522 mg, 82%). $[\alpha]_D^{25}$ = -168 (c 2.18, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (t, *J* = 2.8 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 2.92 – 2.54 (m, 4H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.18 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 167.3, 60.9, 57.0, 31.3, 29.6, 22.6, 14.6. Mass (ESI+): calc. for $[M+H]^+$ 234.1, found 234.3; for $[M+Na]^+$ 256.1, found 256.2; for $[M+K]^+$ 272.1, found 272.3.

General Procedure for Rh-catalyzed Boronic Acid Addition



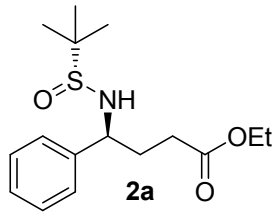
To $ArB(OH)_2$ (0.4 mmol) and $Rh[(COD)(MeCN)_2]BF_4$ (3.8 mg, 0.01 mmol) in a 1 dram vial, **1** (0.2 mmol) in degassed *i*PrOH/H_2O (1 mL, v/v = 1:1) and triethylamine (56 μL, 0.4 mmol) at 0 °C. After stirring for 3 h at rt, the crude product was diluted with water (5 mL) and extracted with EtOAc (3×10 mL). The combined organic layer was then washed with brine (15 mL) and filtered through Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography to provide the addition products **2**.

Preparation of Chiral Lactam 8



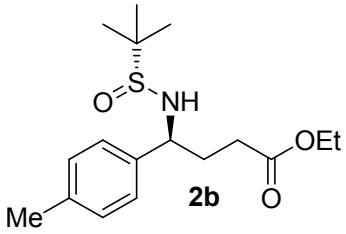
(*S*)-5-phenylpyrrolidin-2-one (8). 8 was synthesized by the following procedure[6]: To **2a** (44.8 mg, 0.144 mmol) in MeOH (1.4 mL) in a round bottom flask, HCl (0.29 mL, 1 M in Et_2O) was added at 0 °C. After stirring for 3.5 h at rt, the reaction mixture was concentrated under reduced pressure, and diluted with 10 mL aqueous HCl (2 M). The aqueous layer was washed with EtOAc (3×5 mL) and basified with 10 mL aqueous NH_3 (2 M)/NH_4Cl (2 M) and 3 mL aqueous NaOH (3 M) was added to obtain pH >11. After 30 mins, the crude product was extracted with CH_2Cl_2 (3×10 mL), and the combined organic layer was washed with 10 mL aqueous HCl (2 M), filtered through Na_2SO_4. The solvent was removed under reduced pressure to provide **8** (21.6 mg, 93 %). $[\alpha]_D^{25}$ = -45 (c 0.81, $CHCl_3$) , (Lit. -51)[7]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 5H), 6.73 (bs, 1H), 4.75 (t, *J* = 7.0 Hz, 1H), 2.65 – 2.48 (m, 1H), 2.48 – 2.31 (m, 2H), 1.95 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.4, 142.3, 128.6, 127.6, 125.4, 58.0, 31.3, 30.3.

Characterization Data



2a

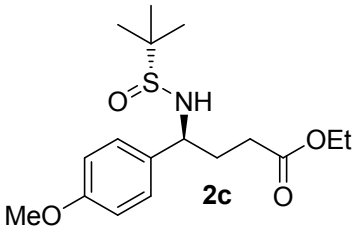
(*S*)-ethyl 4-[(*R*)-1,1-dimethylethylsulfinamido]-4-phenylbutanoate (2a). 77% yield, 97.5:2.5 dr. $[\alpha]_D^{25}$ = -121 (c 0.86, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.26 (m, 5H), 4.43 (td, *J* = 6.8, 2.7 Hz, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.79 (d, *J* = 2.7 Hz, 1H), 2.39 – 2.07 (m, 4H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.19 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 141.0, 128.3, 127.5, 127.3, 60.5, 58.7, 55.5, 33.2, 30.7, 22.5, 14.1. Mass (ESI+): calc. for $[M+H]^+$ 312.2, found 312.2; for $[M+Na]^+$ 334.2, found 334.3.



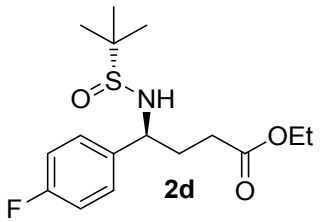
2b

(*S*)-ethyl 4-[(*R*)-1,1-dimethylethylsulfinamido]-4-(4-methylphenyl)butanoate (2b). 81% yield, 97:3 dr. $[\alpha]_D^{25}$ = -82.9 (c 2.43, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 – 7.04 (m, 4H), 4.37 (dt, *J* = 6.8, 2.7 Hz, 1H), 4.07 (q, *J* = 7.2 Hz, 2H), 3.75 (d, *J* = 2.7 Hz, 1H), 2.32 (s, 3H), 2.28 – 2.00 (m, 4H), 1.22 (d, *J* = 7.2 Hz, 3H), 1.17 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 137.8,

137.2, 129.0, 127.2, 60.5, 58.3, 55.4, 33.2, 30.7, 22.5, 21.1, 14.1. Mass (ESI+): calc. for $[M+H]^+$ 326.2, found 326.1; for $[M+Na]^+$ 348.2, found 348.2.

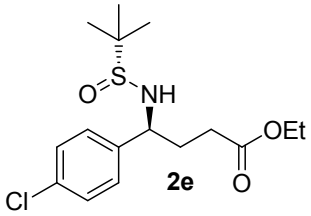


(*S*)-ethyl 4-[(*R*)-1,1-dimethylethylsulfinamido]-4-(4-methoxyphenyl)butanoate (2c). 64% yield, 96:4 dr. $[\alpha]_D^{25}$ = -78.6 (c 1.66, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.46 – 4.31 (m, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 3.73 (d, *J* = 2.1 Hz, 1H), 2.33 – 2.02 (m, 4H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.18 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2, 159.2, 133.0, 128.7, 113.9, 60.6, 58.1, 55.5, 55.2, 33.3, 30.8, 22.6, 14.2. Mass (ESI+): calc. for $[M+Na]^+$ 364.2, found 364.1; for $[M+K]^+$ 380.1, found 380.0.



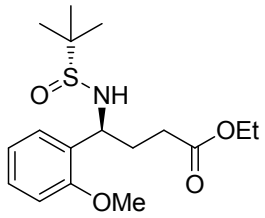
(*S*)-ethyl 4-[(*R*)-1,1-dimethylethylsulfinamido]-4-(4-fluorophenyl)butanoate (2d). 49% yield (63% yield on the basis of recovered starting material), 97:3 dr. $[\alpha]_D^{25}$ = -82.7 (c 1.48, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.20 (m, 2H), 7.03 (m, 2H), 4.43 (m, 1H), 4.10 (q, *J* = 7.2 Hz, 2H), 3.81 (s, 1H), 2.40 – 2.18 (m, 2H), 2.18 – 2.00 (m, 2H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.19 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2, 162.3 (d, *J* = 246.1 Hz), 137.0, 129.2 (d, *J* = 8.1 Hz),

115.5 (d, J = 21.5 Hz), 60.7, 58.0, 55.6, 33.3, 30.7, 22.6, 14.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ -115.71. Mass (ESI+): calc. for $[M+H]^+$ 330.2, found 330.1; for $[M+Na]^+$ 352.1, found 352.2; $[M+K]^+$ 368.1, found 368.1.



2e

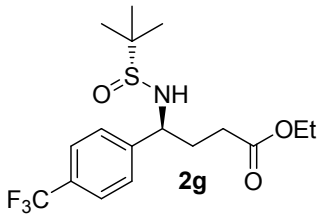
(*S*)-ethyl 4-[(*R*)-1,1-dimethylethylsulfinamido]-4-(4-chlorophenyl)butanoate (2e). 43% yield, (53% on the basis of recovered starting material), 97:3 dr. $[\alpha]_D^{25}$ = -82.4 (c 1.19, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 8.5 Hz, 2H), 7.24 (d, J = 8.5 Hz, 2H), 4.42 (td, J = 6.9, 2.5 Hz, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.85 (d, J = 2.2 Hz, 1H), 2.39 – 2.19 (m, 2H), 2.19 – 2.00 (m, 2H), 1.24 (t, J = 7.2 Hz, 3H), 1.19 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 139.8, 133.4, 128.8, 128.7, 60.7, 58.0, 55.5, 33.0, 30.6, 22.5, 14.1. Mass (ESI+): calc. for $[M+Na]^+$ 368.1, found 368.2; $[M+K]^+$ 384.1, found 384.1.



2f

(*S*)-ethyl 4-[(*R*)-1,1-dimethylethylsulfinamido]-4-(2-methoxyphenyl)butanoate (2f). 28% yield, (52% yield on the basis of recovered starting material), 97:3 dr. $[\alpha]_D^{25}$ = -56.9 (c 0.93, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.20 (m, 2H), 7.00 – 6.76 (m, 2H), 4.73 (m, 1H),

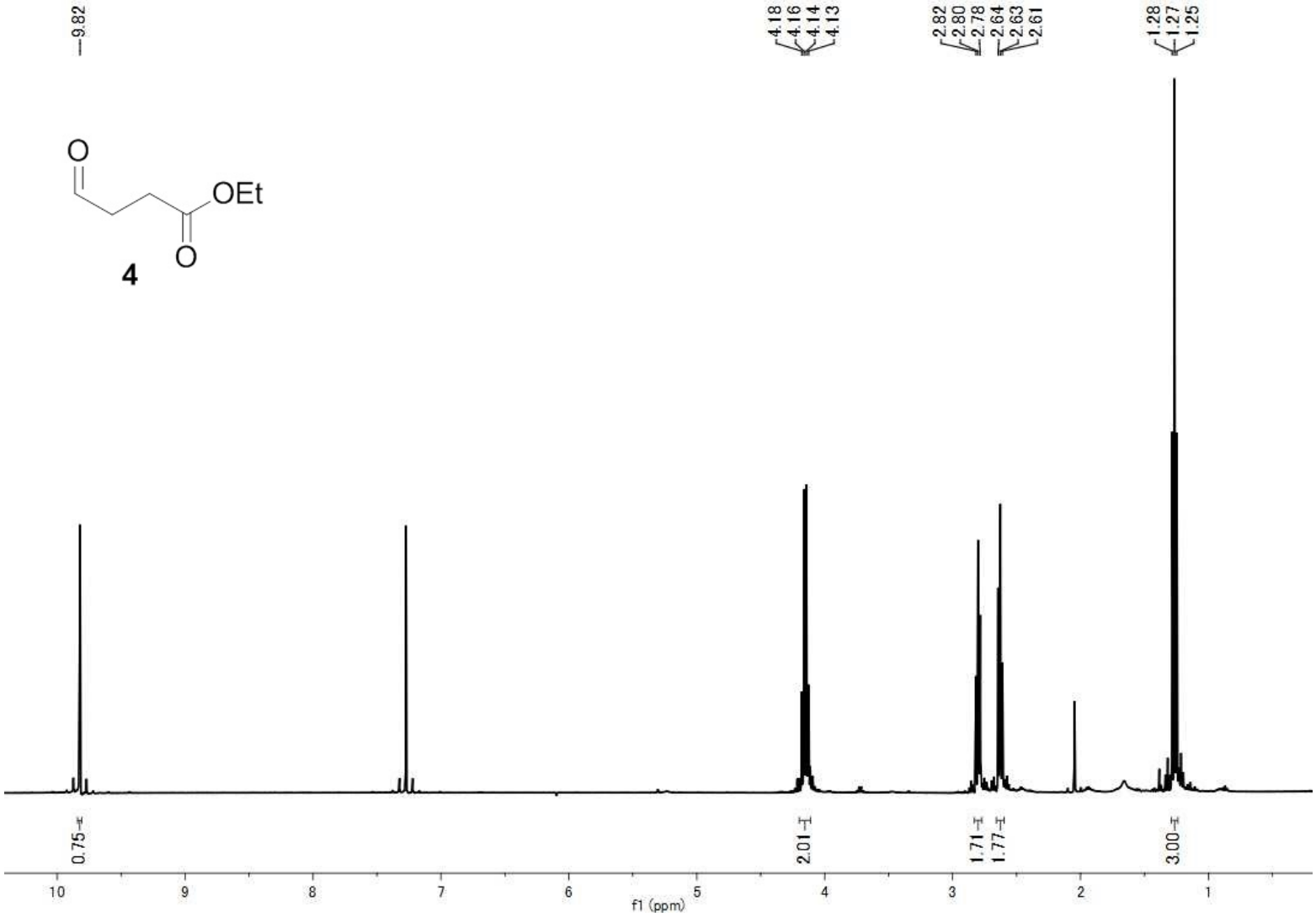
4.10 (t, J = 7.1 Hz, 2H), 3.83 (s, 3H), 2.50 – 2.02 (m, 4H), 1.23 (t, J = 7.1 Hz, 3H), 1.17 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 156.6, 129.5, 128.3, 127.8, 120.3, 110.5, 60.4, 55.6, 55.2, 55.1, 31.8, 31.0, 22.5, 14.2. Mass (ESI+): calc. for $[M+Na]^+$ 364.2, found 364.3; $[M+K]^+$ 380.1, found 380.1.



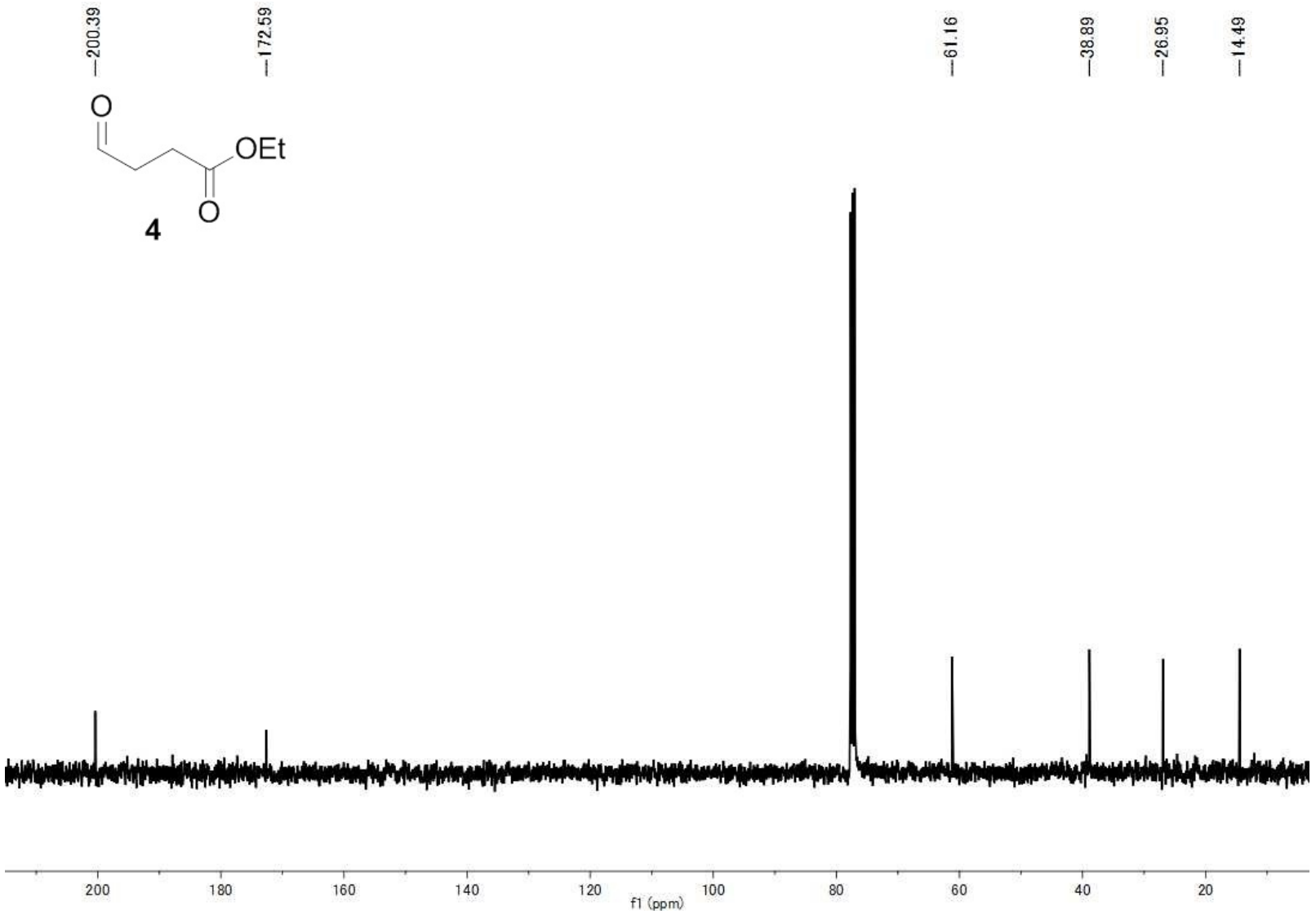
2g

(*S*)-ethyl 4-[(*R*)-1,1-dimethylethylsulfinamido]-4-(4-trifluoromethylphenyl)butanoate (2g).

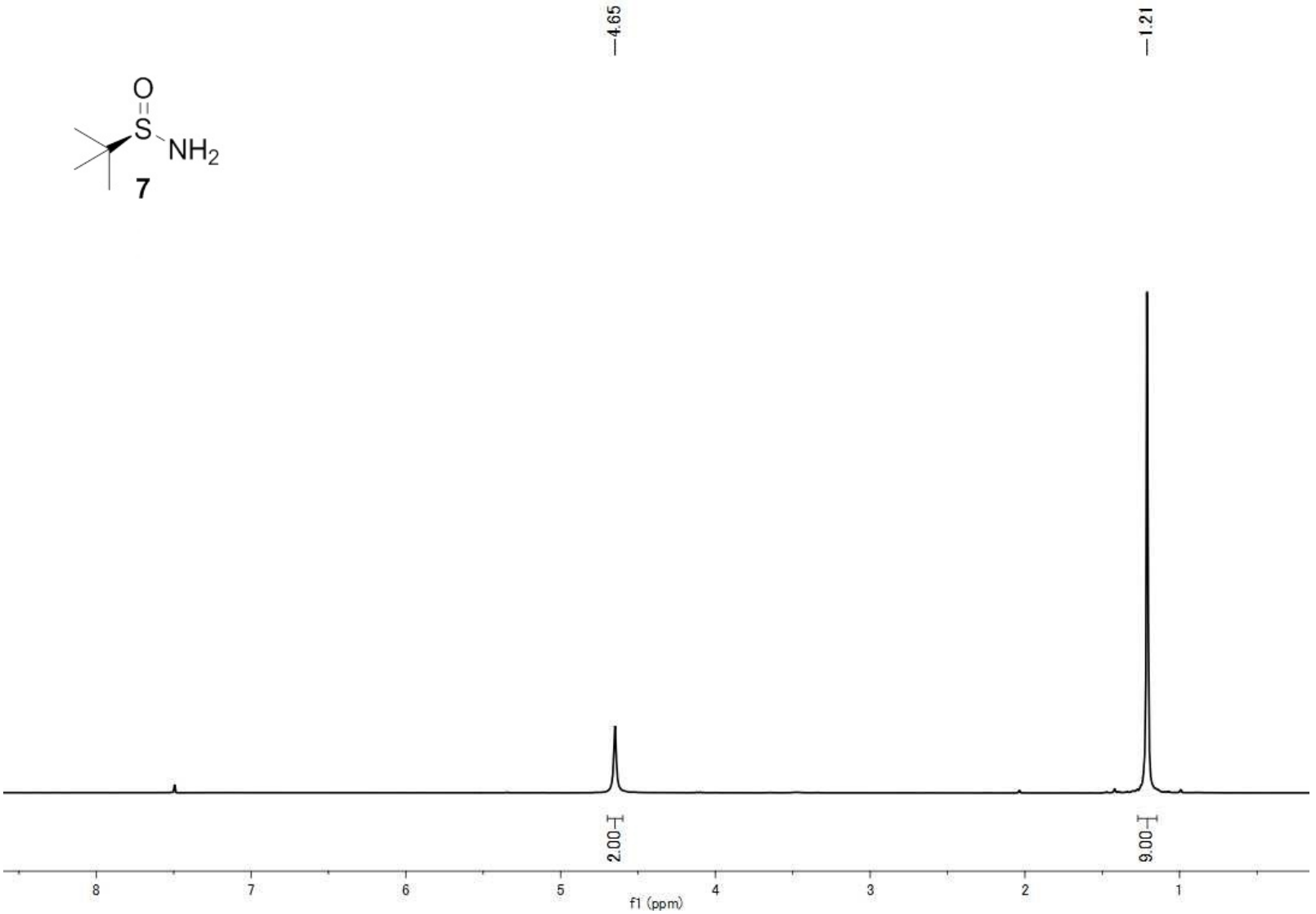
21% yield, (54% yield on the basis of recovered starting material), 97:3 dr. $[\alpha]_D^{25}$ = -74.2 (c 0.75, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.1 Hz, 2H), 7.44 (d, J = 8.1 Hz, 2H), 4.52 (td, J = 6.8, 2.6 Hz, 1H), 4.11 (q, J = 7.2 Hz, 2H), 4.05 – 3.92 (m, 1H), 2.45 – 2.23 (m, 2H), 2.13 (m, 2H), 1.24 (t, J = 7.2 Hz, 3H), 1.21 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2, 145.7, 130.1 (q, J = 32.7 Hz), 127.9, 125.6 (d, J = 3.5 Hz), 122.7, 60.9, 58.4, 55.8, 33.1, 30.7, 22.6, 14.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ -64. Mass (ESI+): calc. for $[M]^+$ 381.2, found 381.0; $[M+Na]^+$ 402.1, found 402.3.



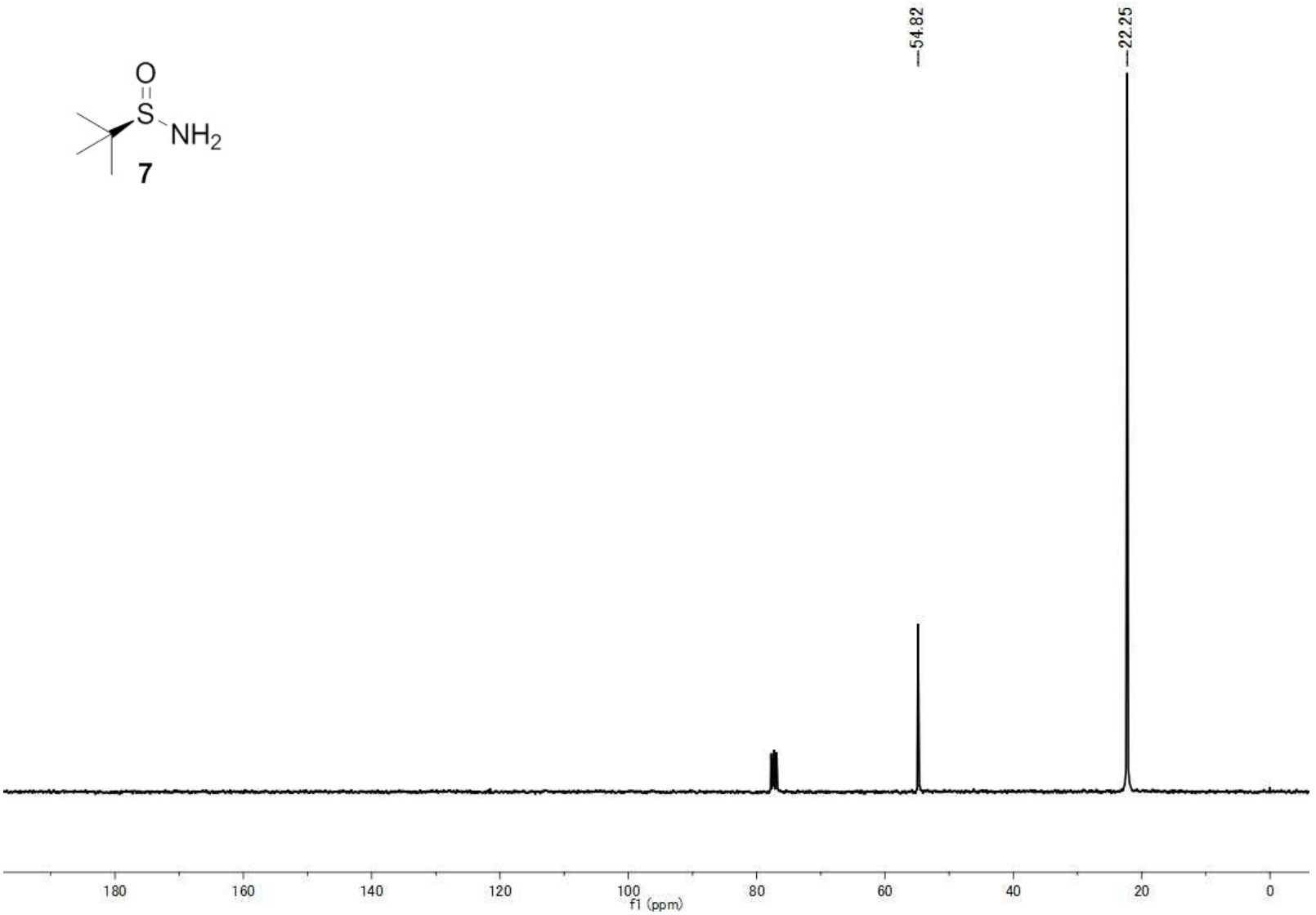
^{1}H NMR (400 MHz, $CDCl_3$) Ethyl 4-oxobutanoate (**4**)



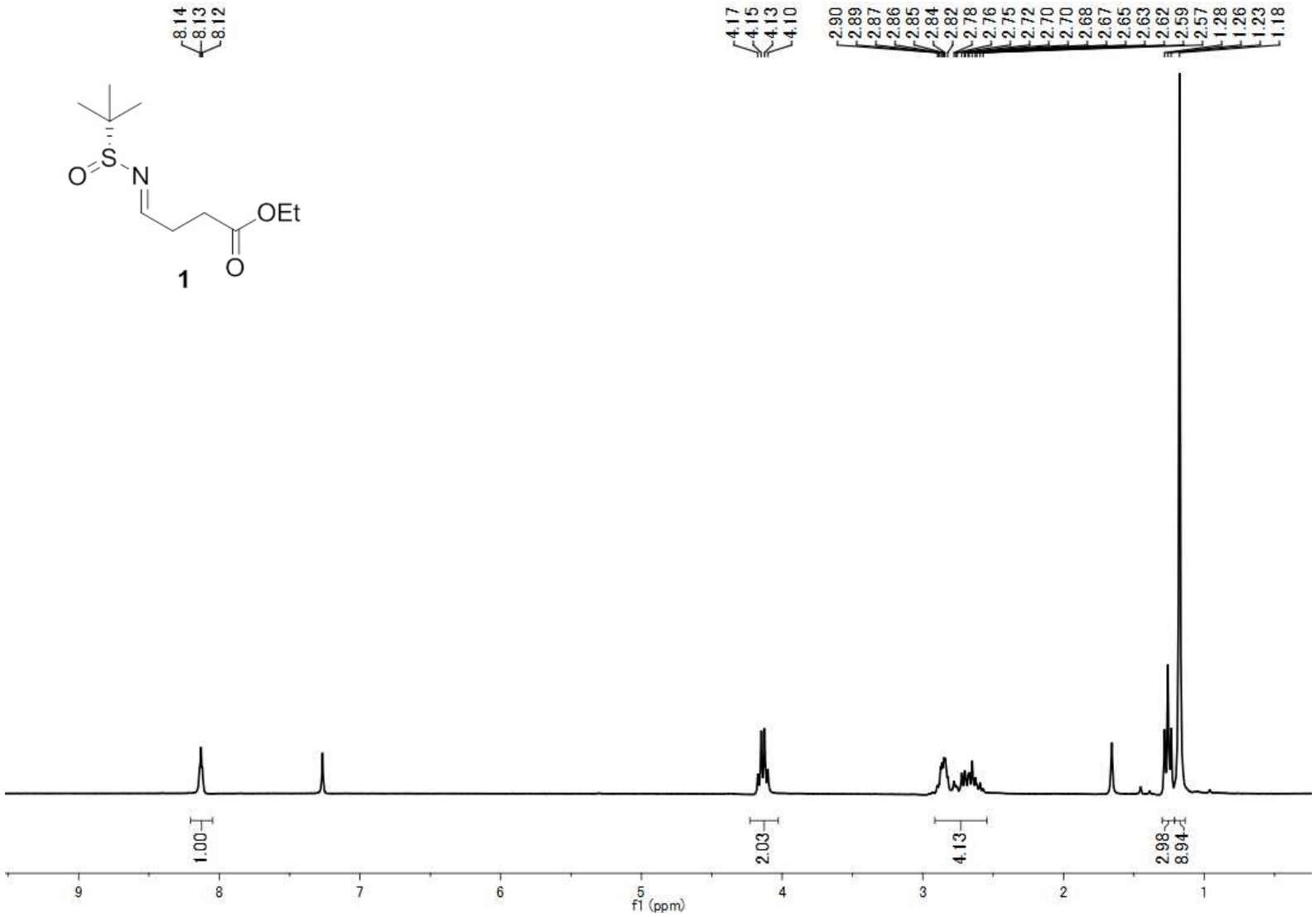
^{13}C NMR (101 MHz, $CDCl_3$) Ethyl 4-oxobutanoate (**4**)



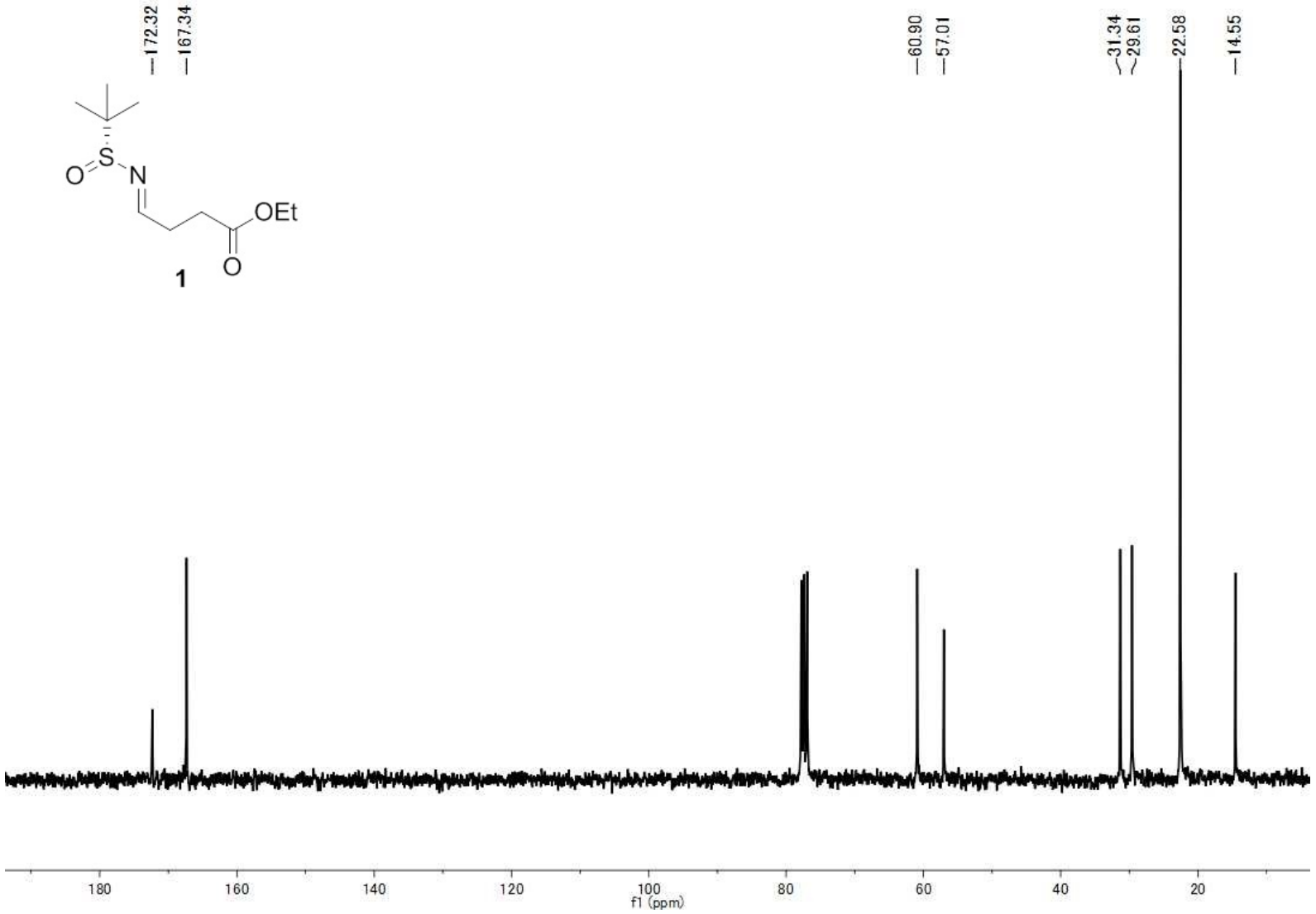
^{1}H NMR (300 MHz, $CDCl_3$) (*R*)-*t*-Butanesulfinamide (**7**)



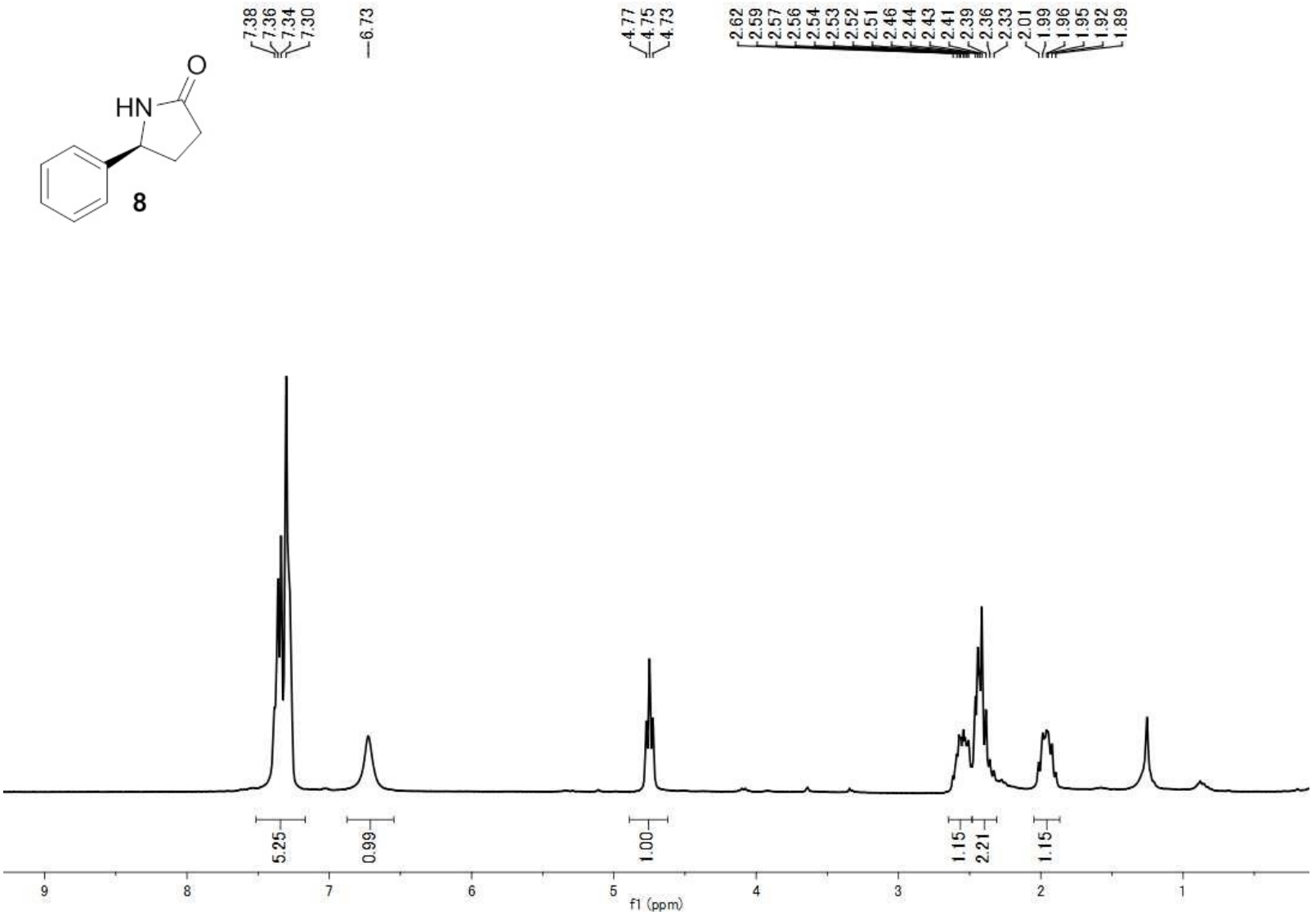
^{13}C NMR (75 MHz, $CDCl_3$) (*R*)-*t*-Butanesulfinamide (**7**)



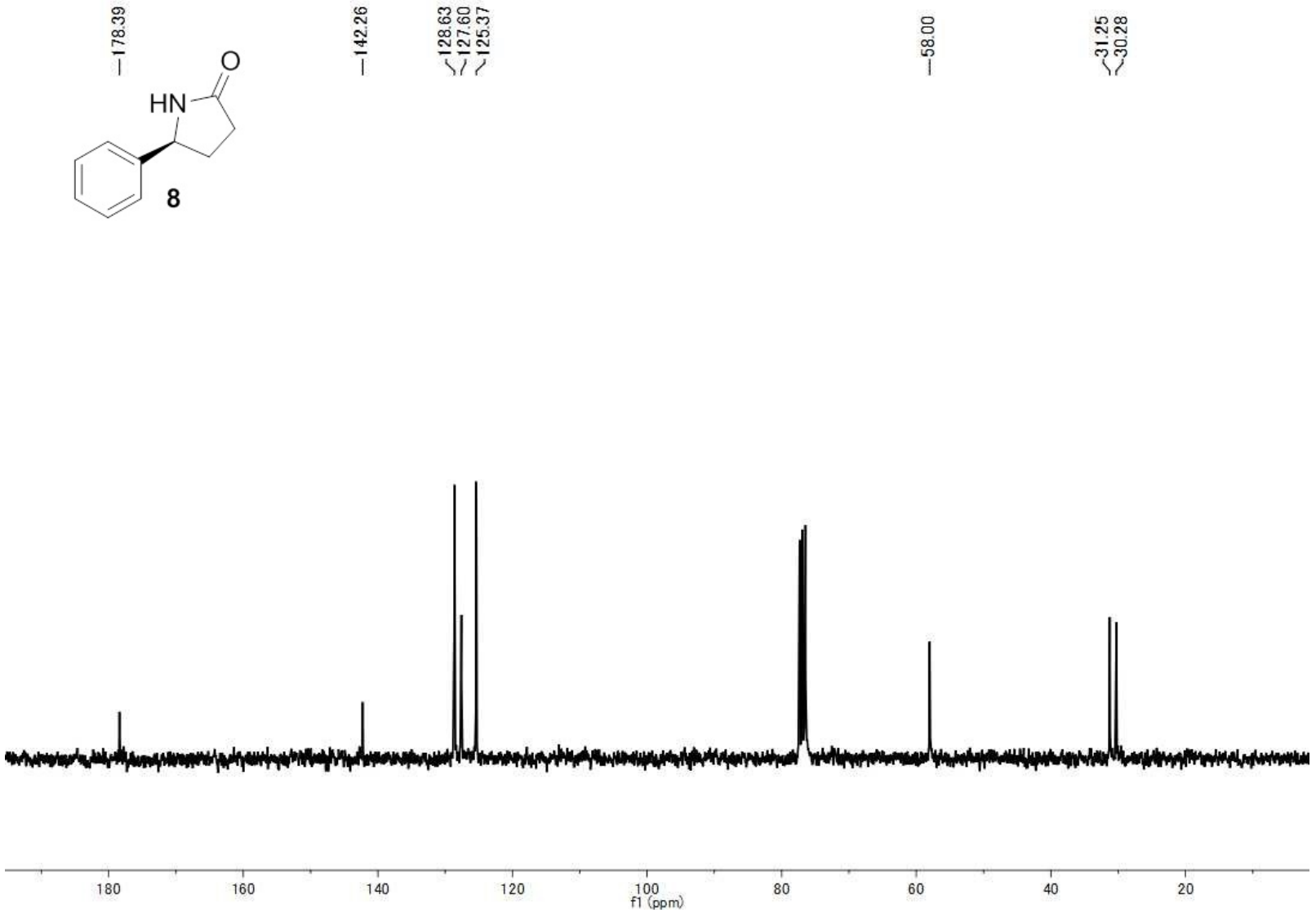
^{1}H NMR (300 MHz, $CDCl_3$) (*R*,*E*)-Ethyl 4[(*t*-butylsulfinyl)imino]butanoate (**1**)



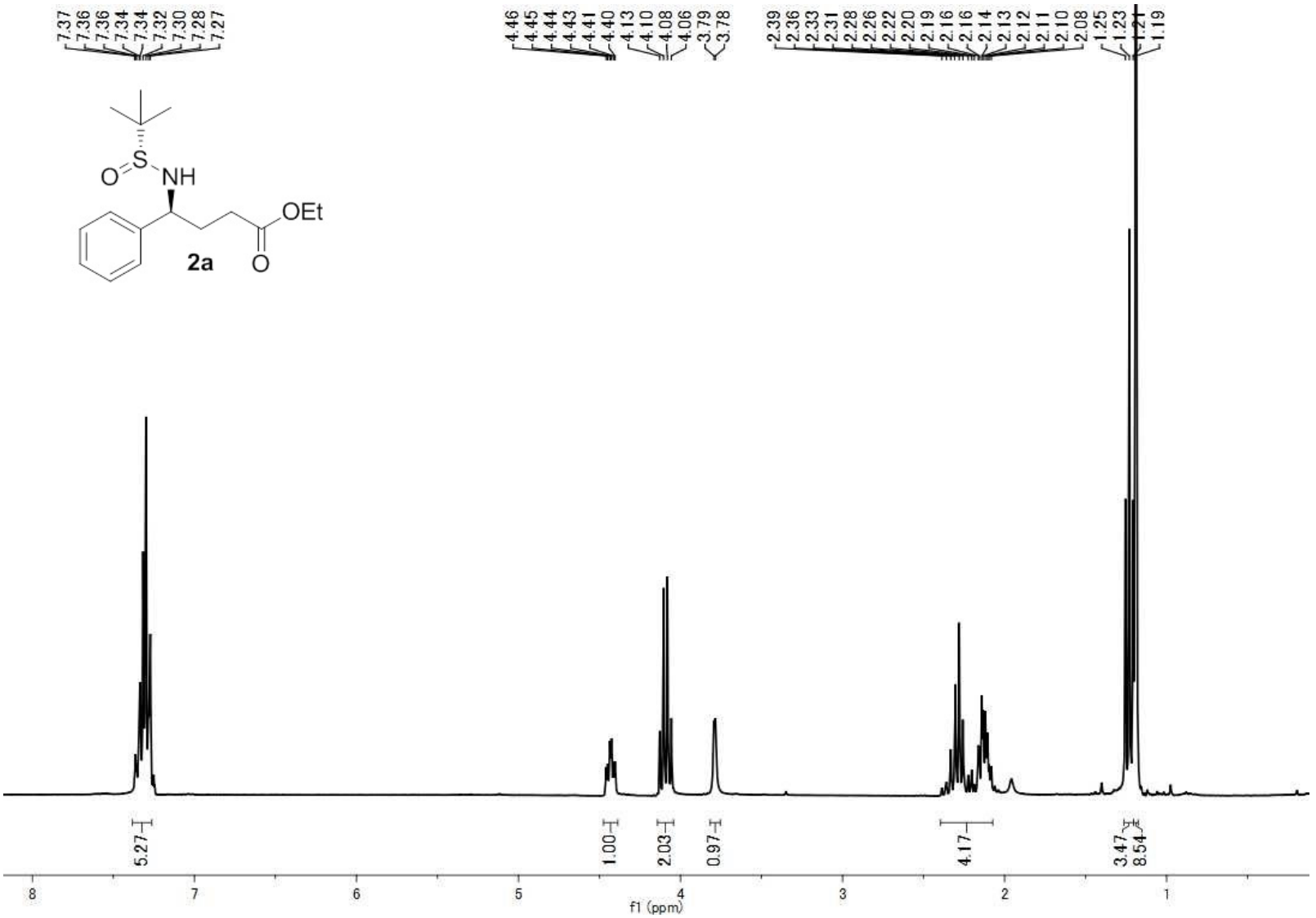
^{13}C NMR (75 MHz, $CDCl_3$) (*R*,*E*)-Ethyl 4[(*t*-butylsulfinyl)imino]butanoate (**1**)



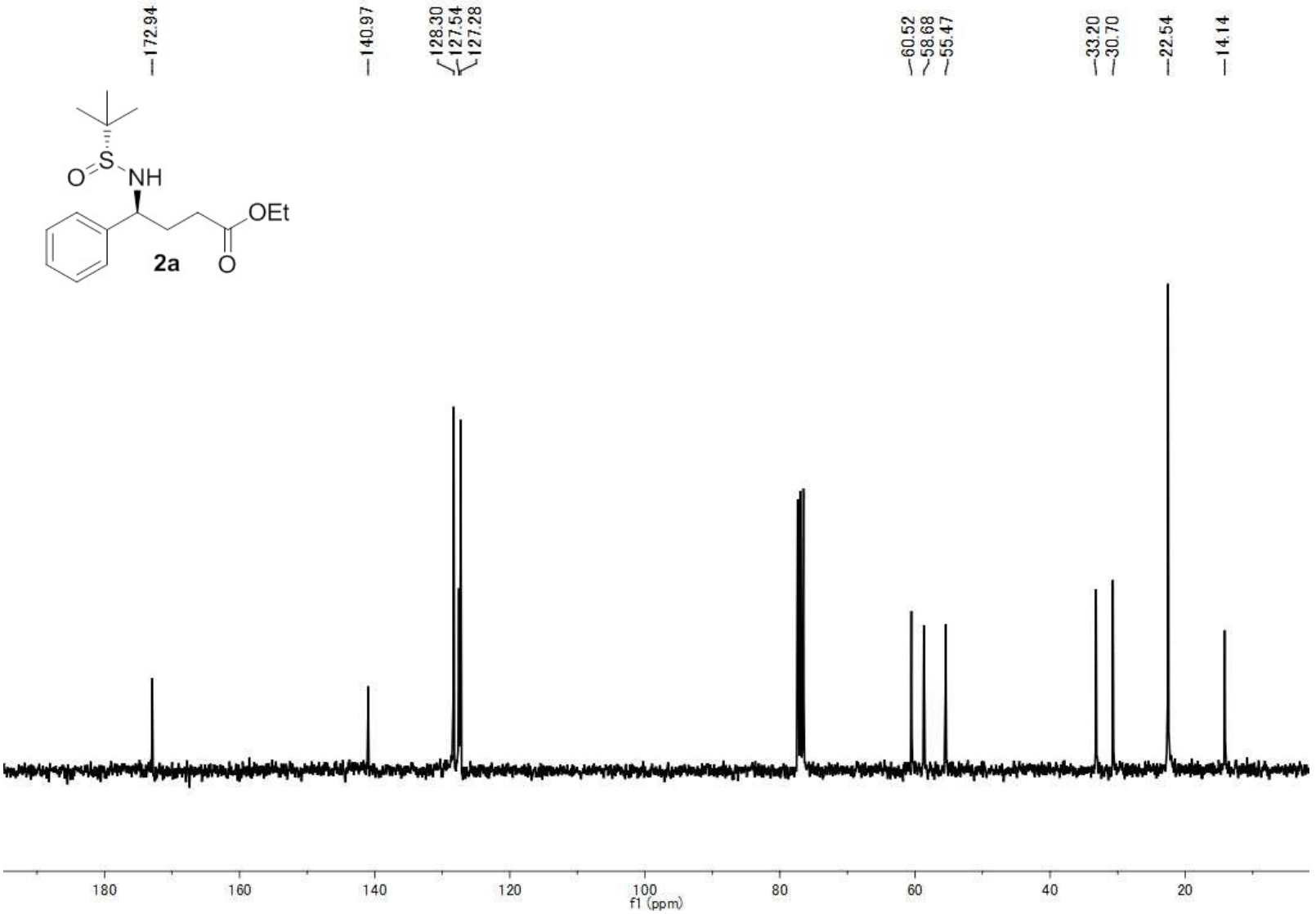
^{1}H NMR (300 MHz, $CDCl_3$) (*S*)-5-phenylpyrrolidin-2-one (**8**)



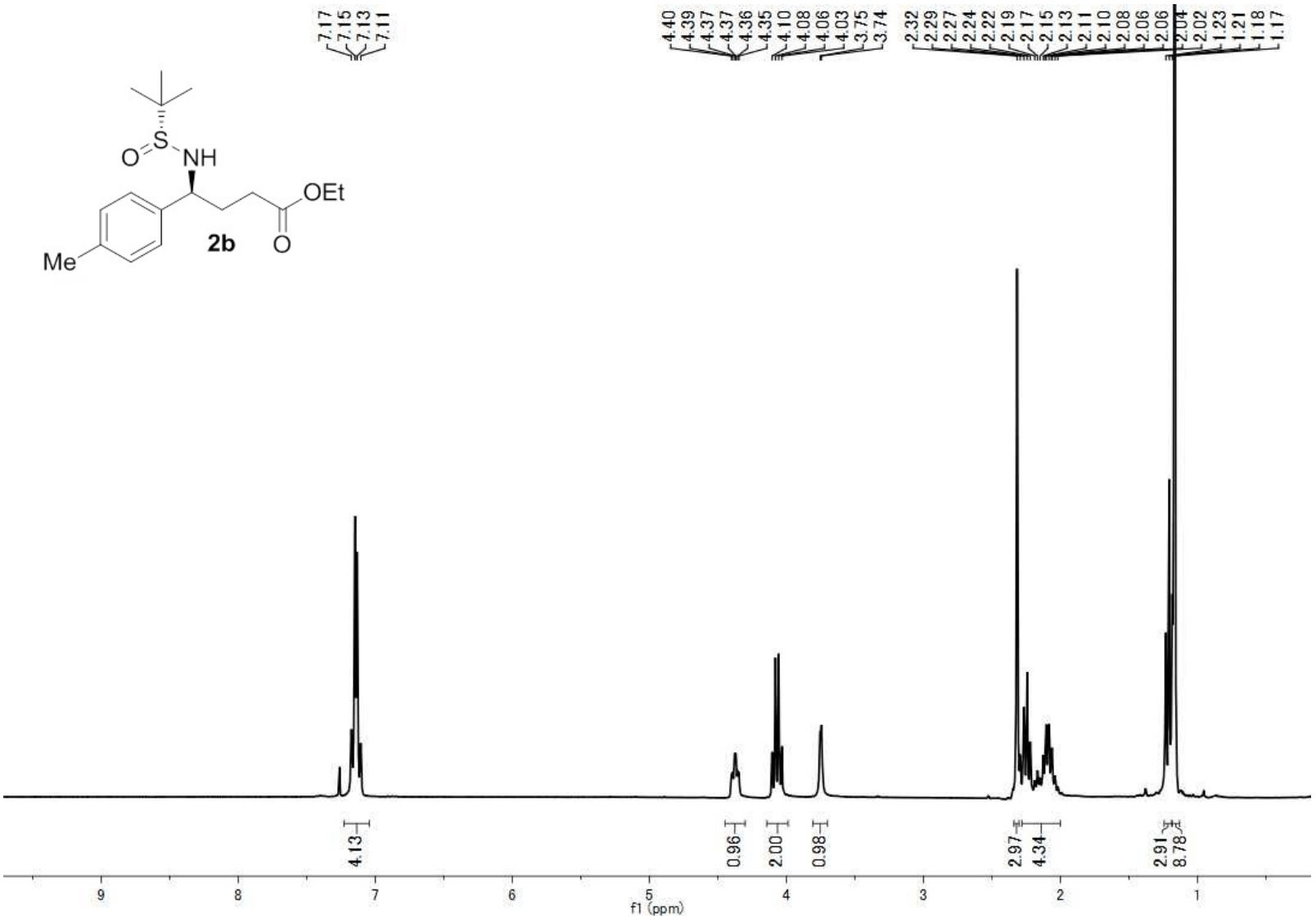
^{13}C NMR (75 MHz, $CDCl_3$) (*S*)-5-phenylpyrrolidin-2-one (**8**)



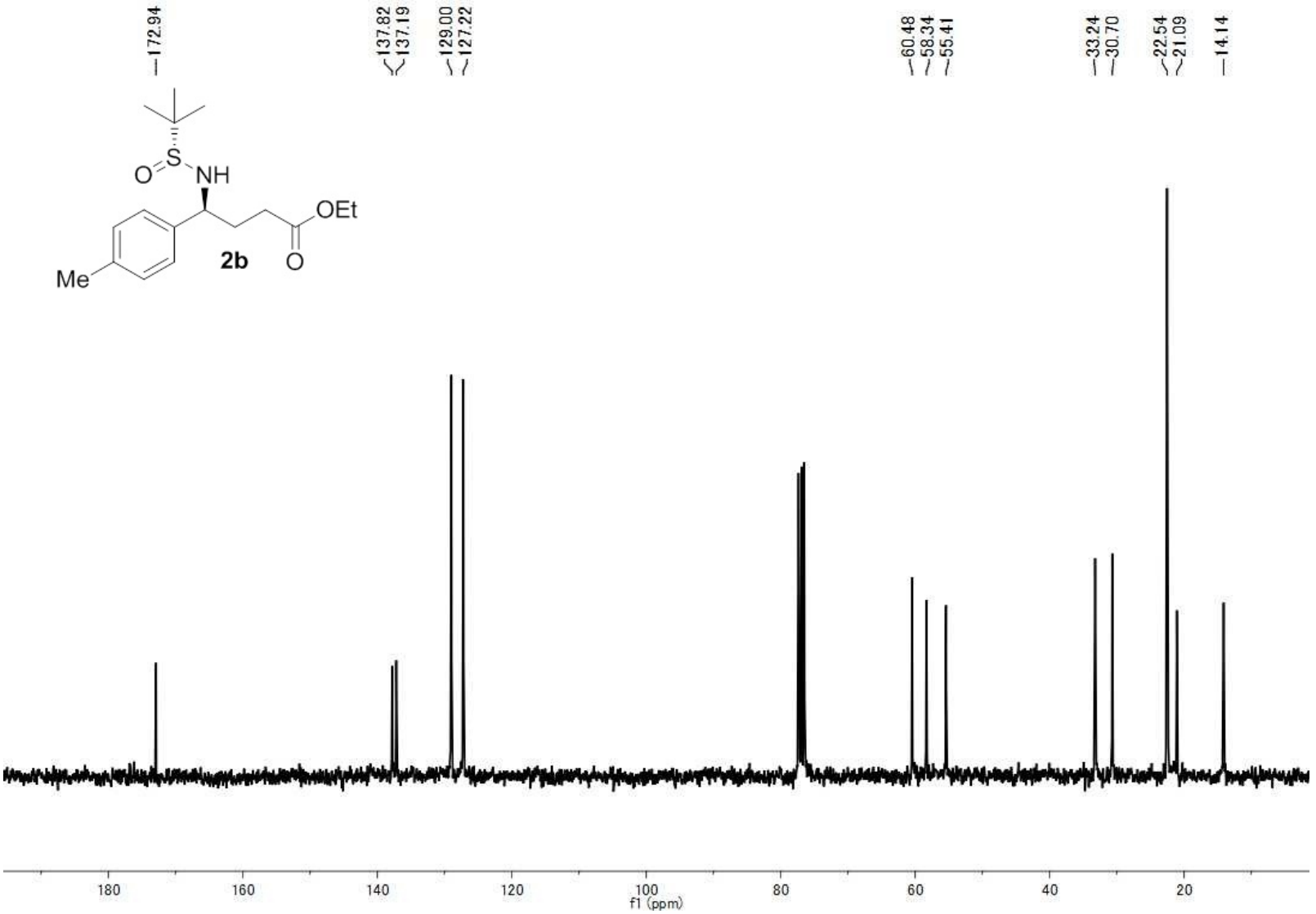
^{1}H NMR (300 MHz, $CDCl_3$) (*S*)-ethyl 4-[(*R*)-1,1-dimethylethylsulfinamido]-4-phenylbutanoate (**2a**)



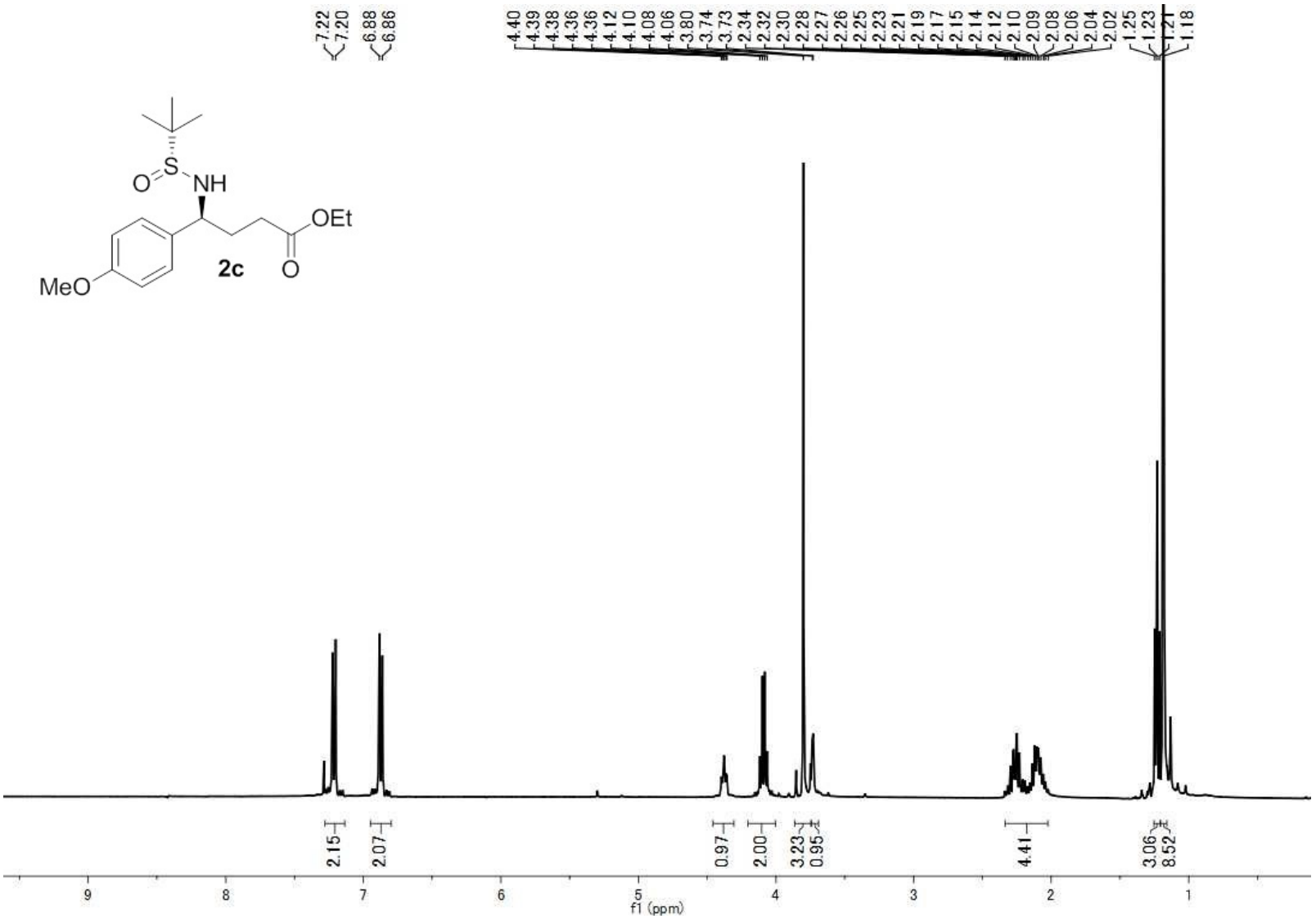
^{13}C NMR (75 MHz, $CDCl_3$) (*S*)-ethyl 4-[(*R*)-1,1-dimethylethylsulfinamido]-4-phenylbutanoate (**2a**)



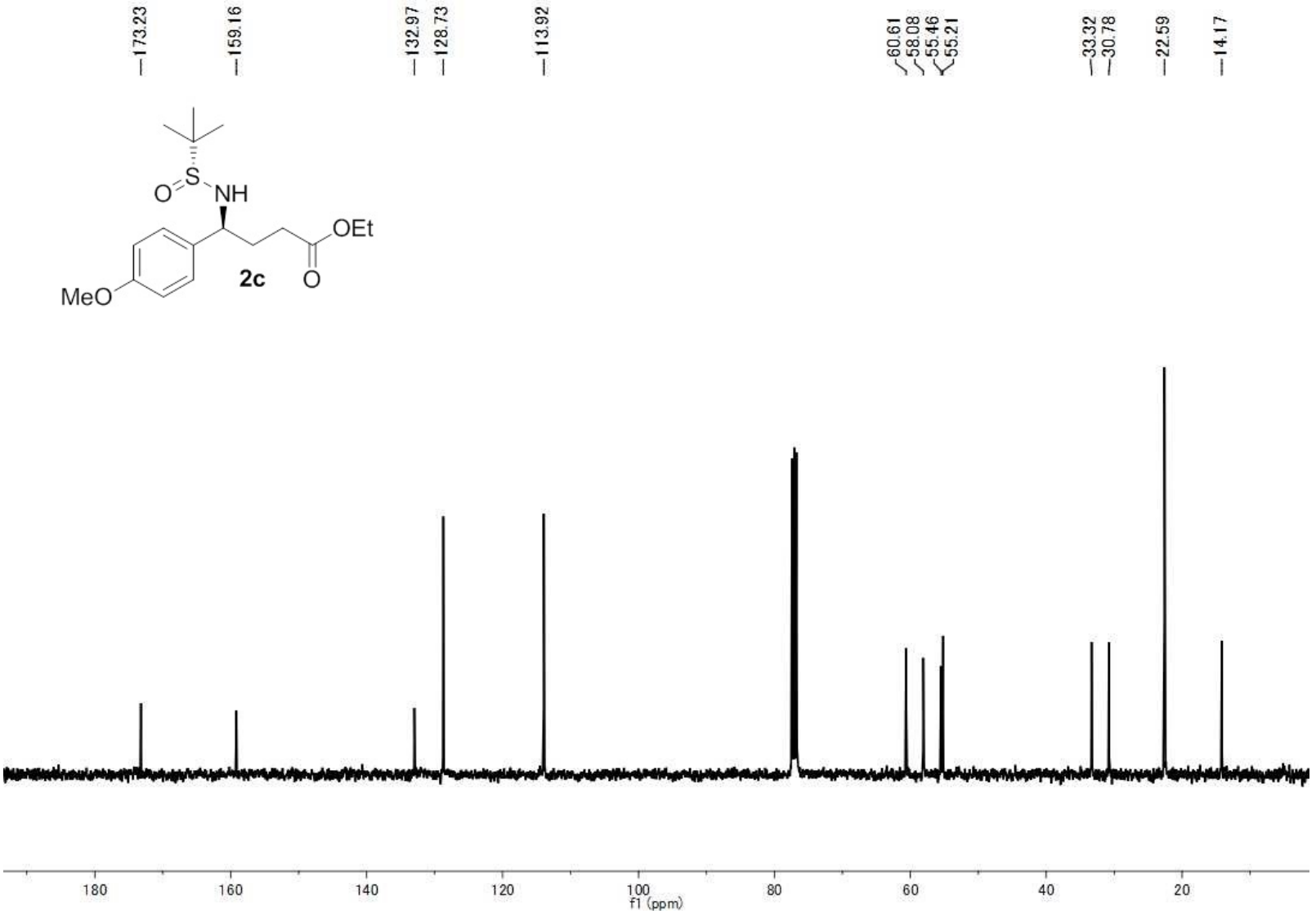
^{1}H NMR (300 MHz, $CDCl_3$) (*S*)-ethyl 4-[(*R*)-1,1-dimethylethylsulfinamido]-4-(4-methylphenyl)butanoate (**2b**)



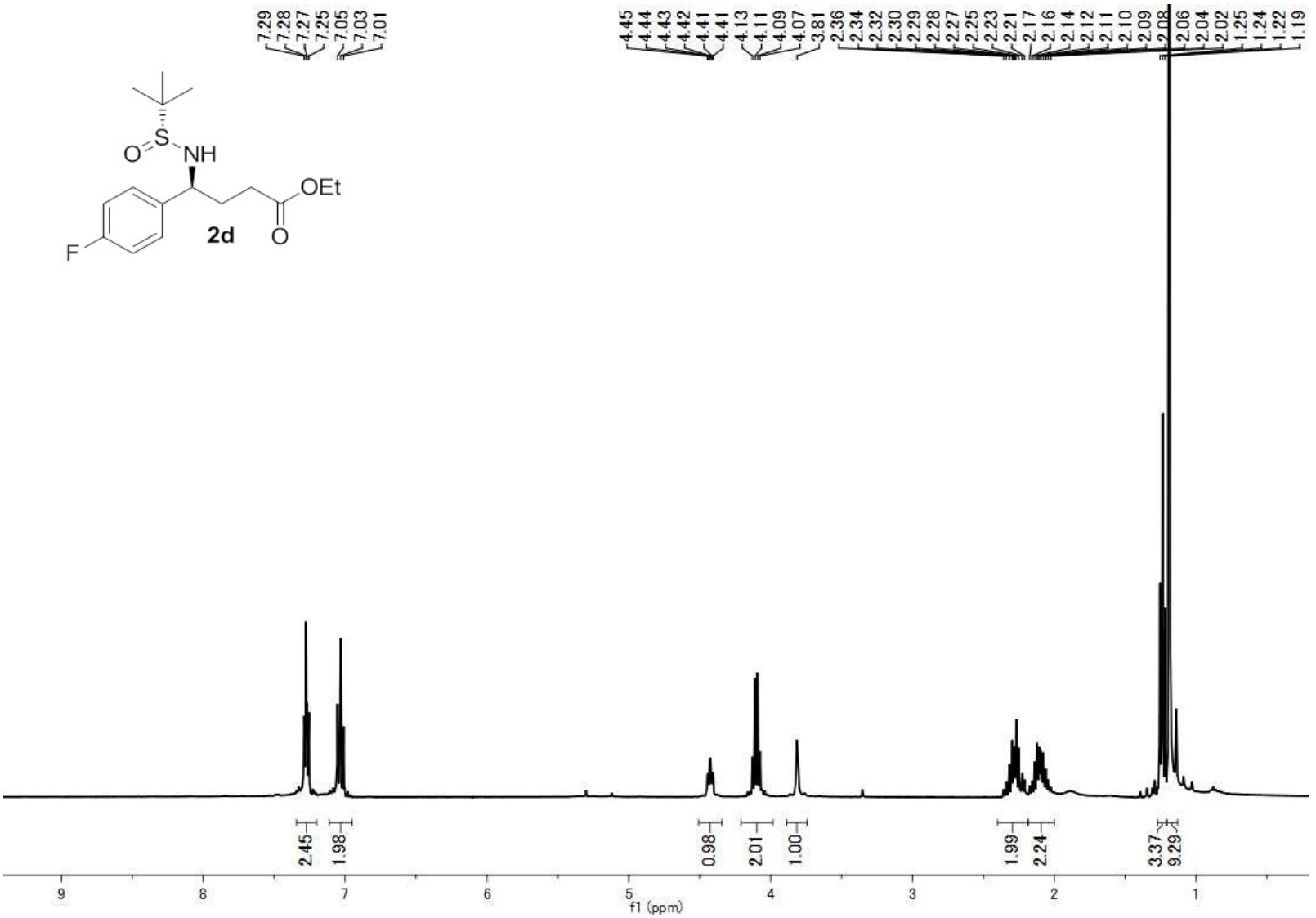
^{13}C NMR (75 MHz, $CDCl_3$) (*S*)-ethyl 4-[(*R*)-1,1-dimethylethylsulfinamido]-4-(4-methylphenyl)butanoate (**2b**)



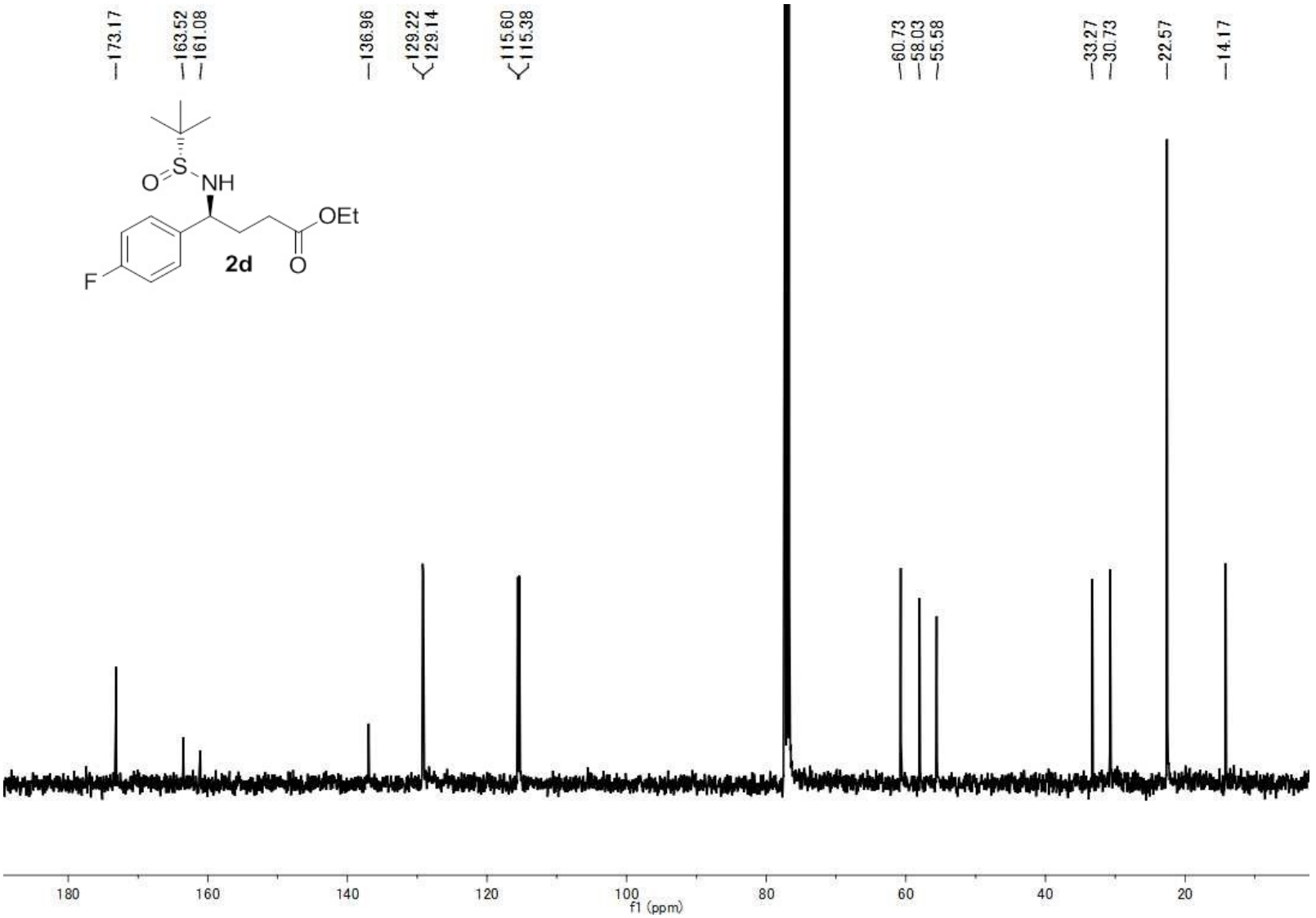
^{1}H NMR (400 MHz, $CDCl_3$) (*S*)-ethyl 4-[(*R*)-1,1-dimethylethylsulfinamido]-4-(4-methoxyphenyl)butanoate (**2c**)



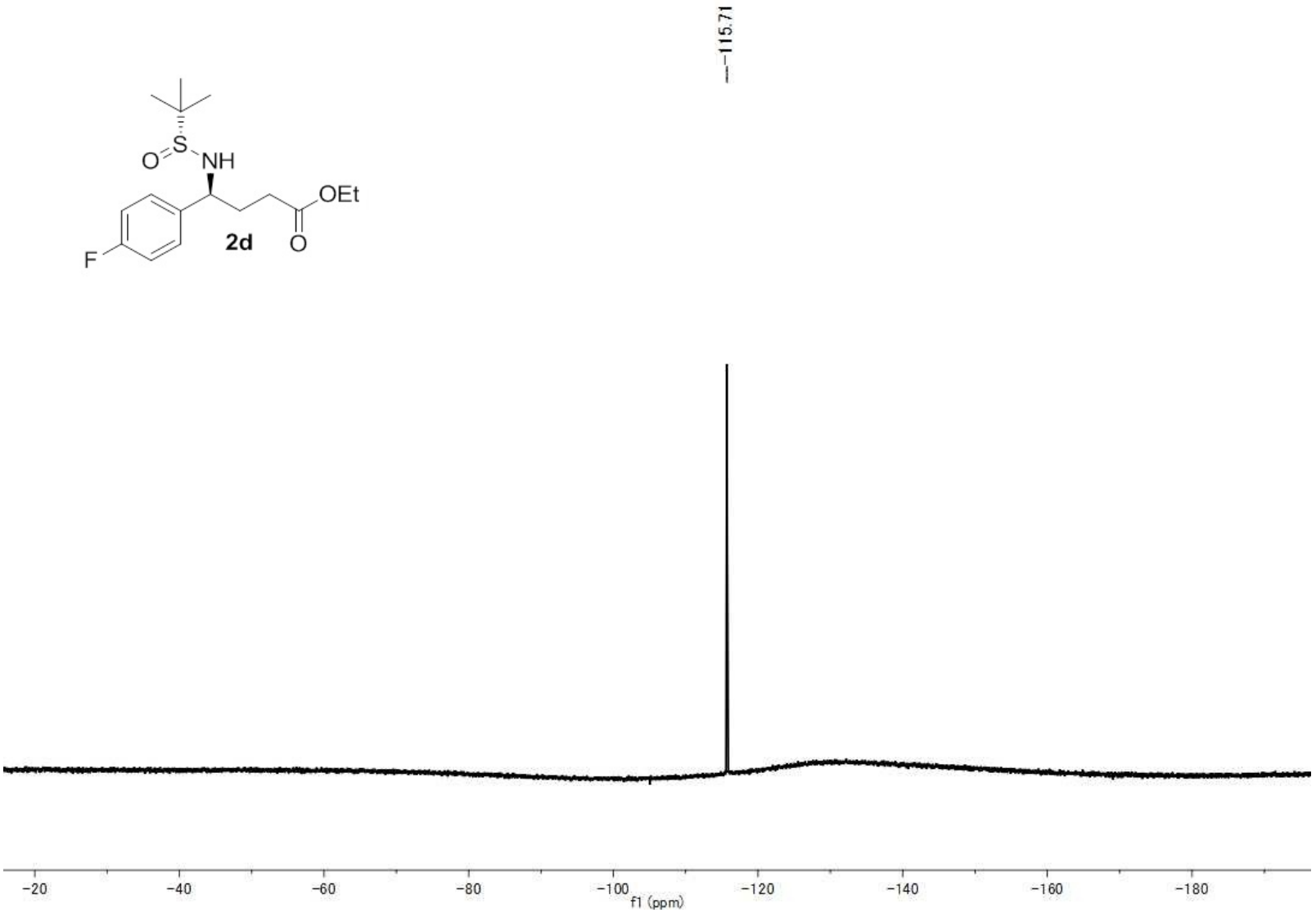
^{13}C NMR (101 MHz, $CDCl_3$) (*S*)-ethyl 4-[(*R*)-1,1-dimethylethylsulfinamido]-4-(4-methoxyphenyl)butanoate (**2c**)



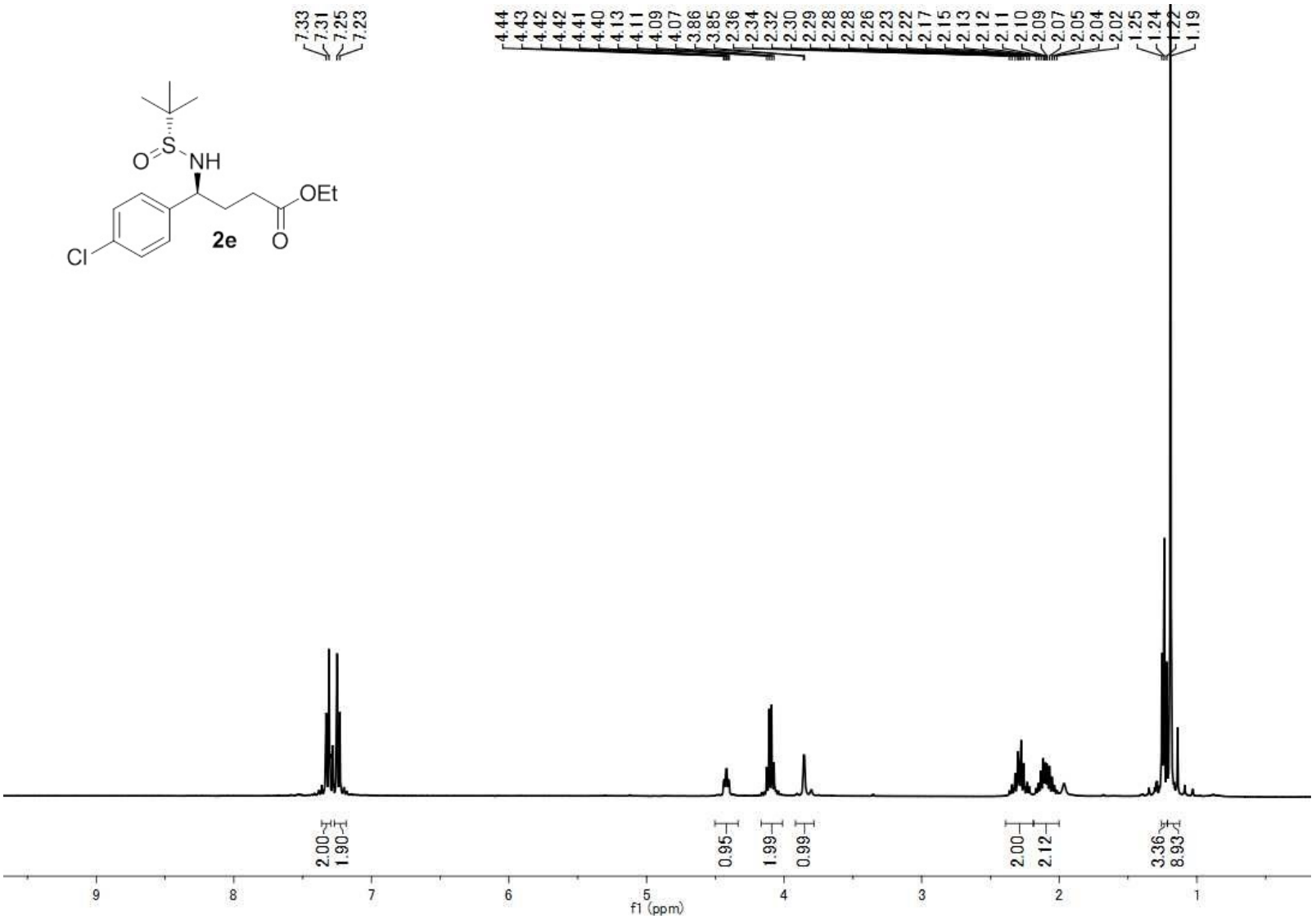
^{1}H NMR (400 MHz, $CDCl_3$) (*S*)-ethyl 4-[(*R*)-1,1-dimethylethylsulfinamido]-4-(4-fluorophenyl)butanoate (**2d**)



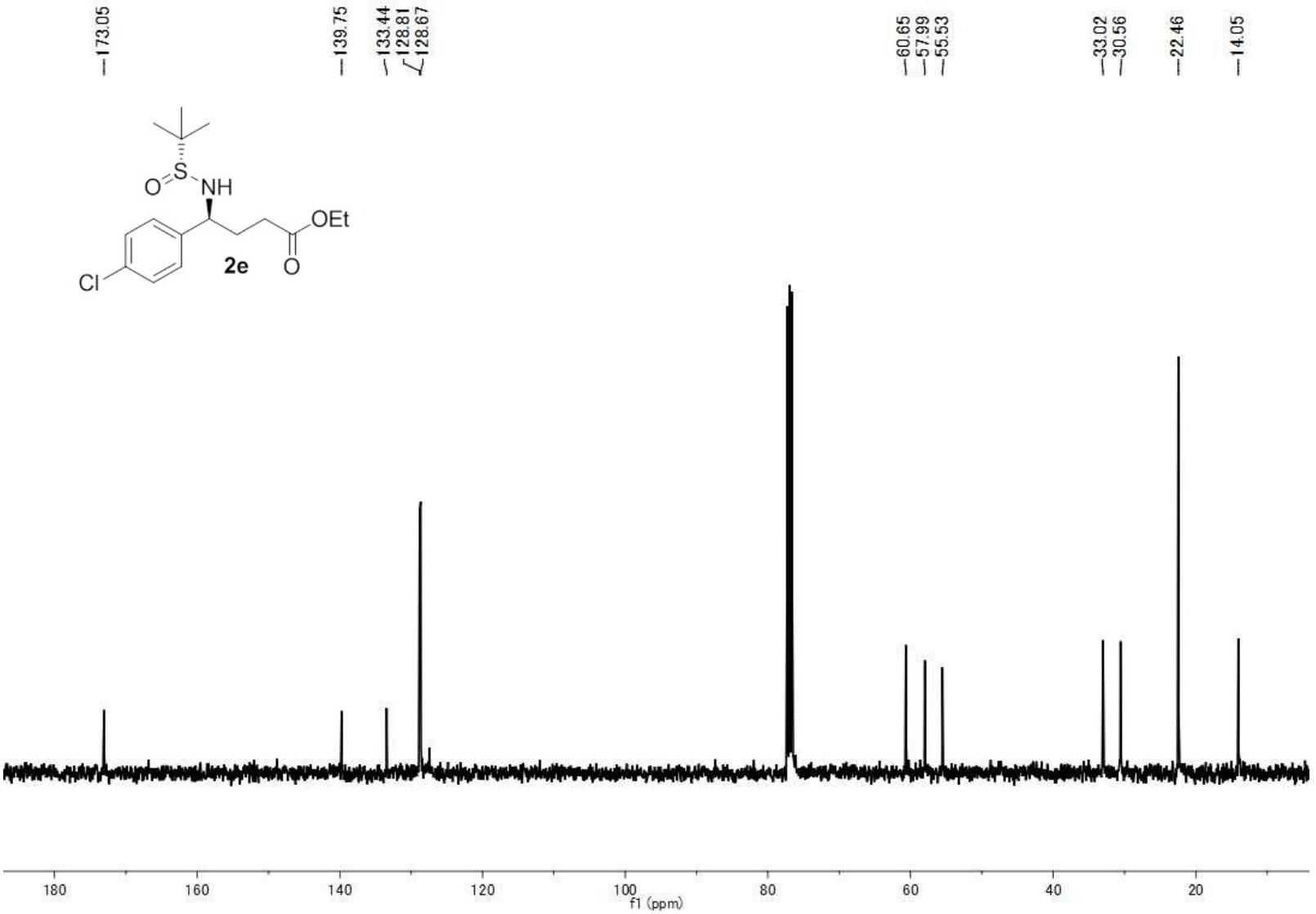
^{13}C NMR (101 MHz, $CDCl_3$) (*S*)-ethyl 4-[(*R*)-1,1-dimethylethylsulfinamido]-4-(4-fluorophenyl)butanoate (**2d**)



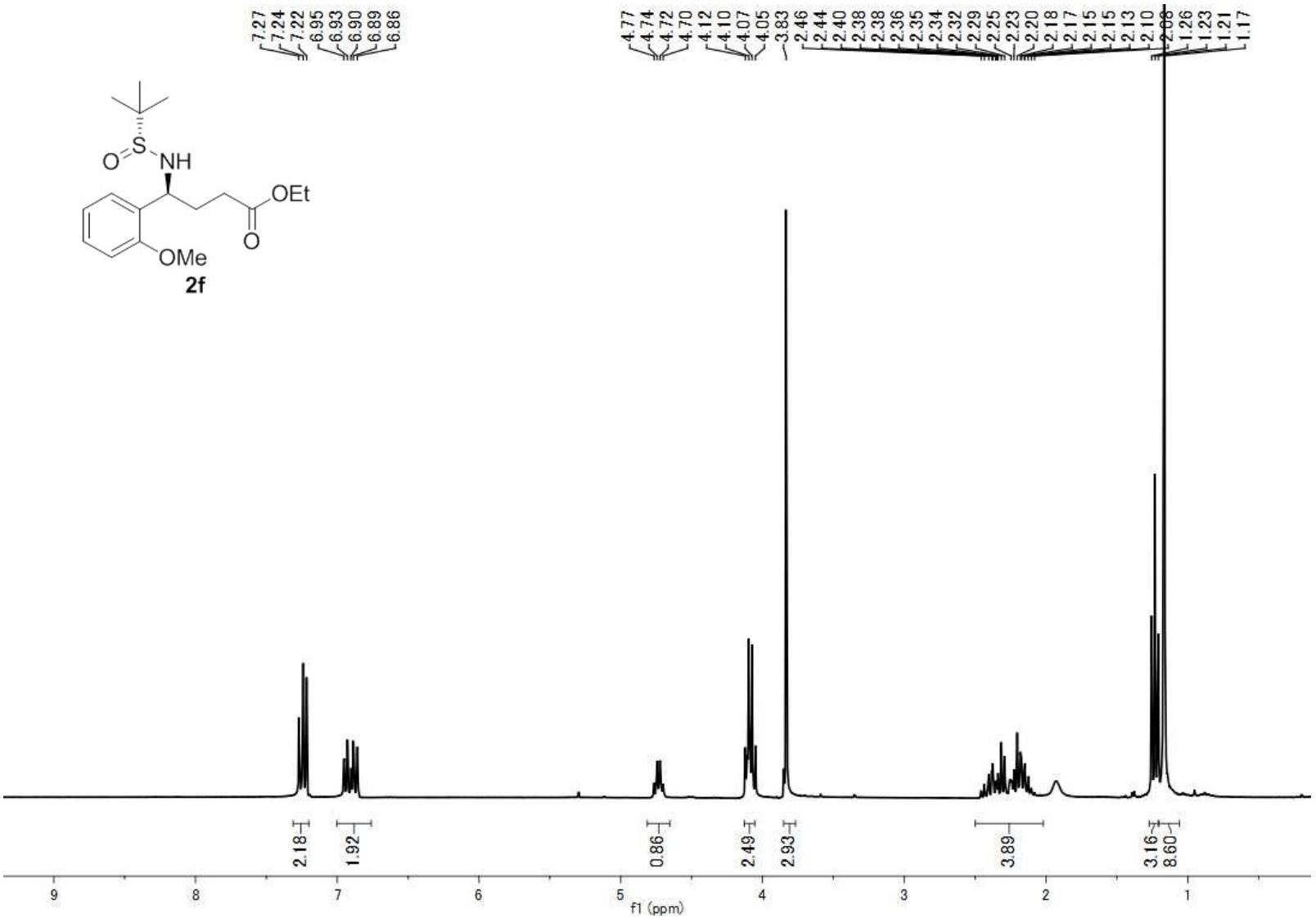
^{19}F NMR (282 MHz, $CDCl_3$) (*S*)-ethyl 4-[(*R*)-1,1-dimethylethylsulfinamido]-4-(4-fluorophenyl)butanoate (**2d**)



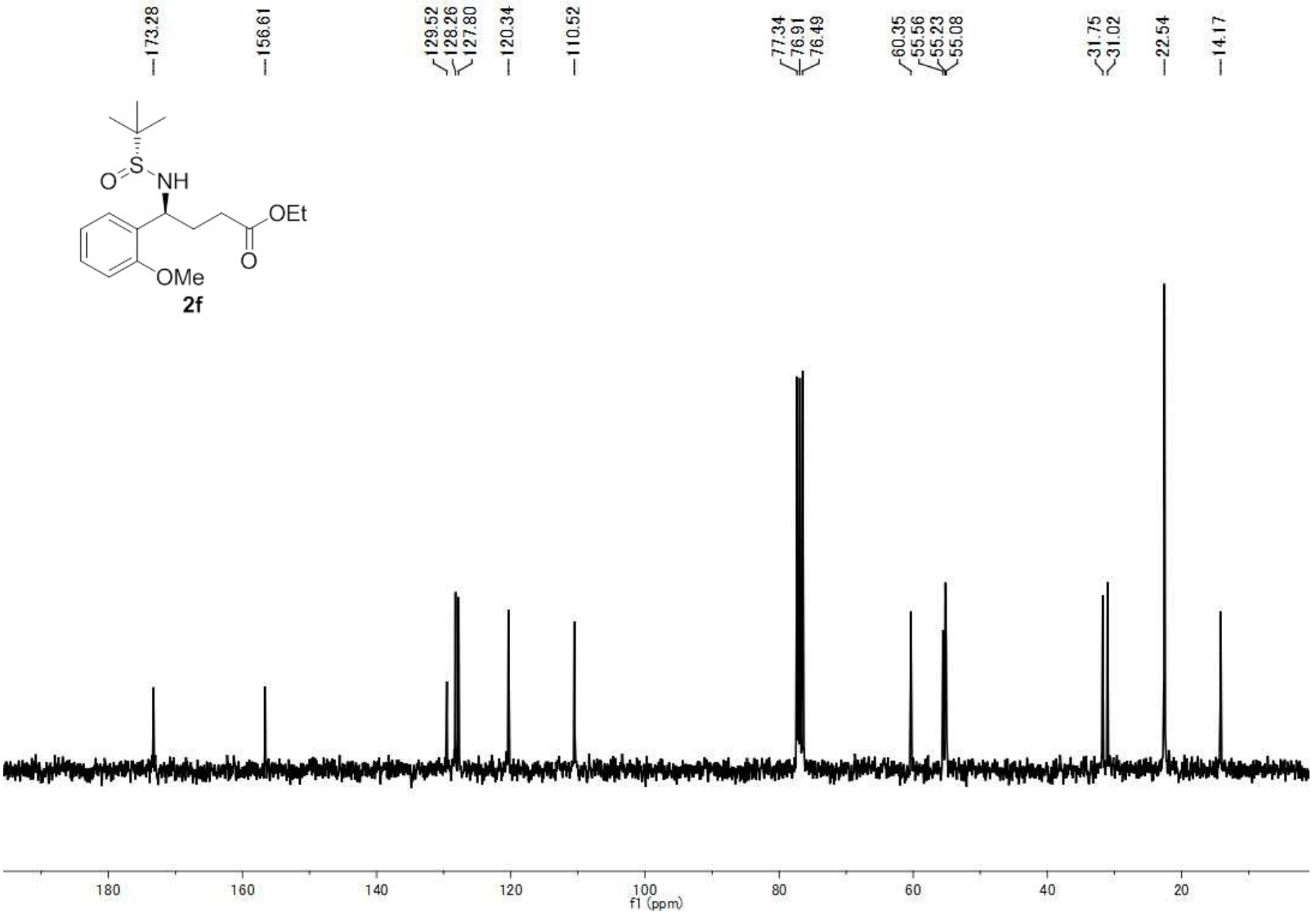
^{1}H NMR (400 MHz, $CDCl_3$) (*S*)-ethyl 4-[(*R*)-1,1-dimethylethylsulfinamido]-4-(4-chlorophenyl)butanoate (**2e**)



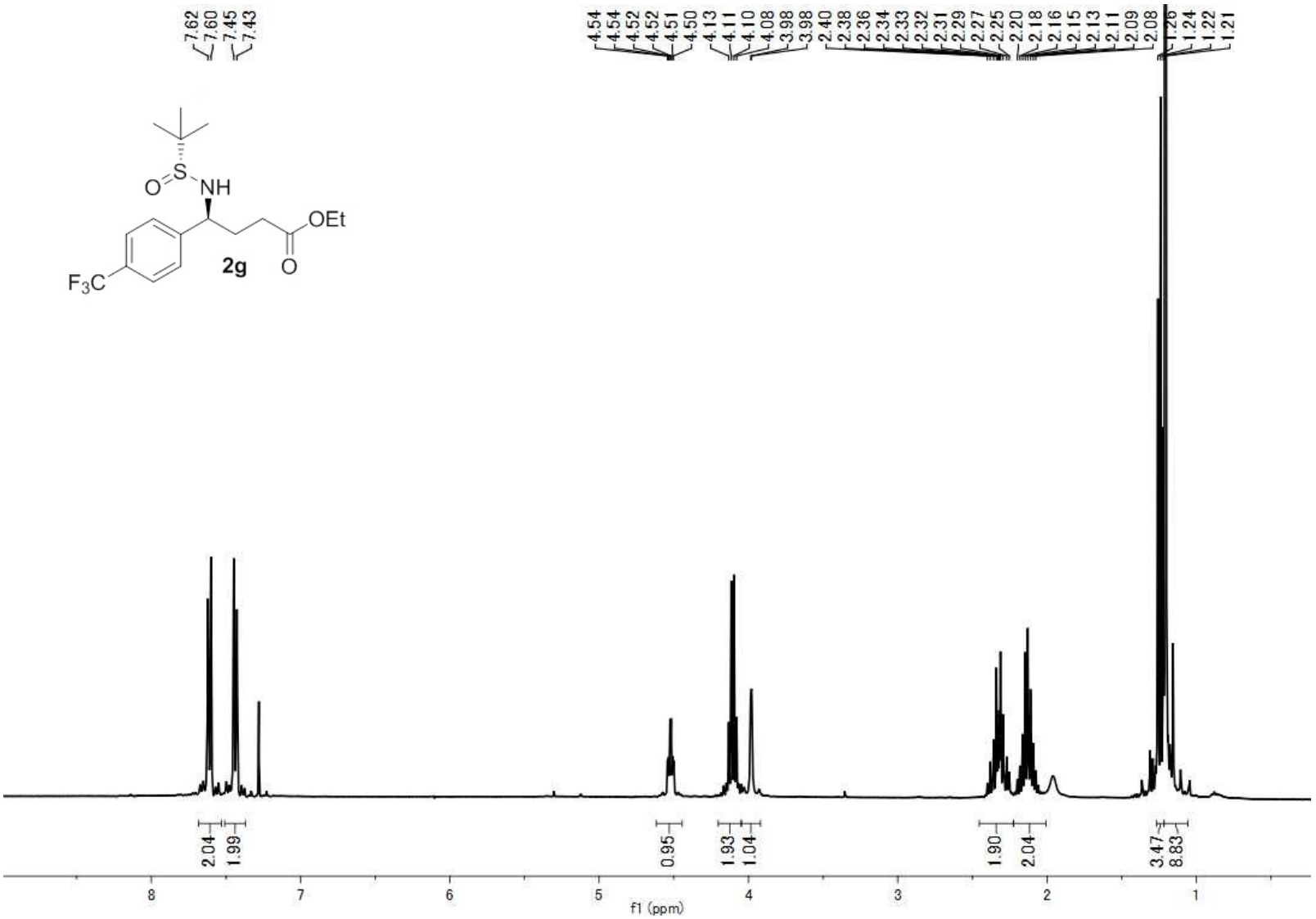
^{13}C NMR (101 MHz, $CDCl_3$) (*S*)-ethyl 4-[(*R*)-1,1-dimethylethylsulfinamido]-4-(4-chlorophenyl)butanoate (**2e**)



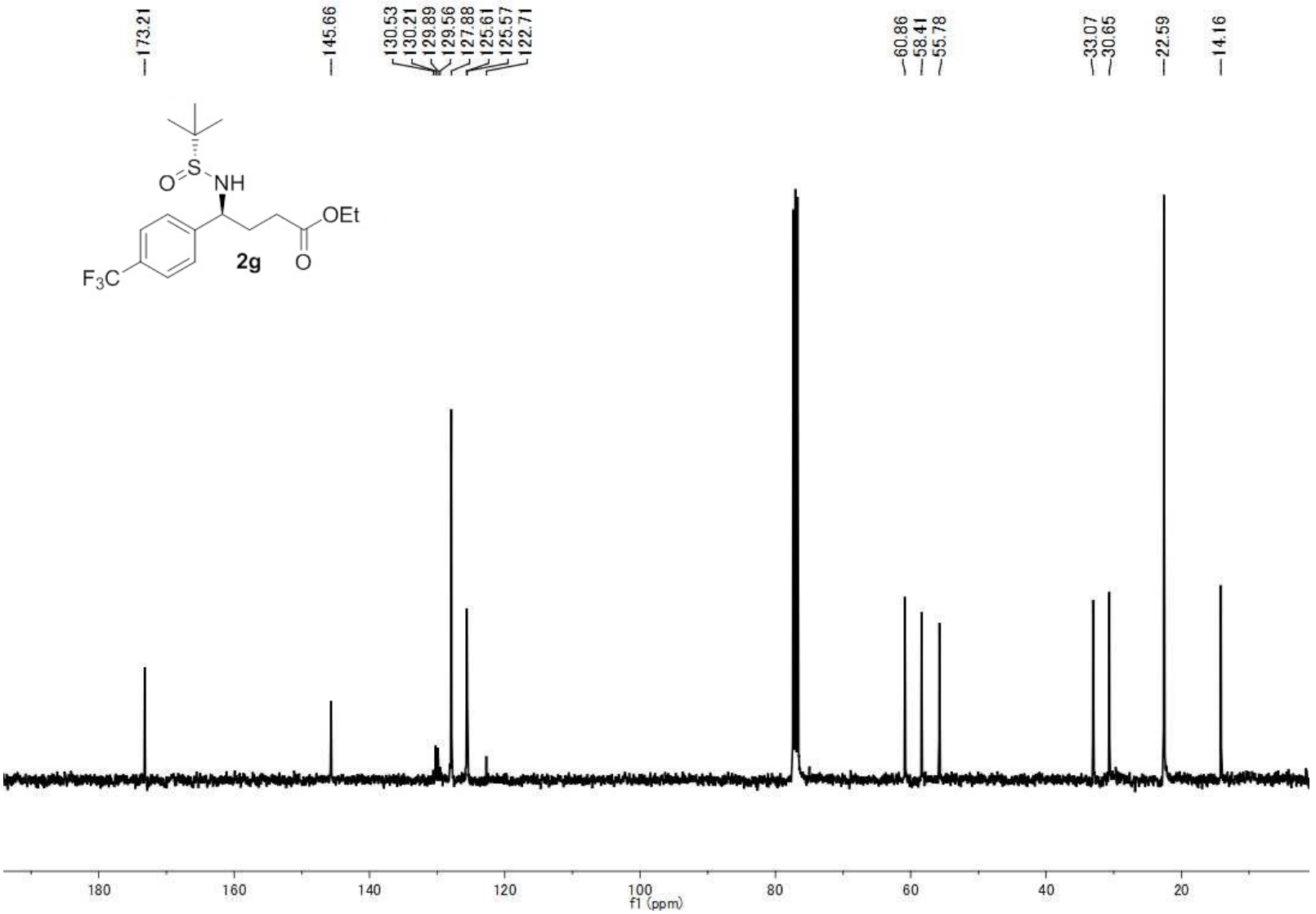
^{1}H NMR (300 MHz, $CDCl_3$) (*S*)-ethyl 4-[(*R*)-1,1-dimethylethylsulfinamido]-4-(2-methoxyphenyl)butanoate (**2f**)



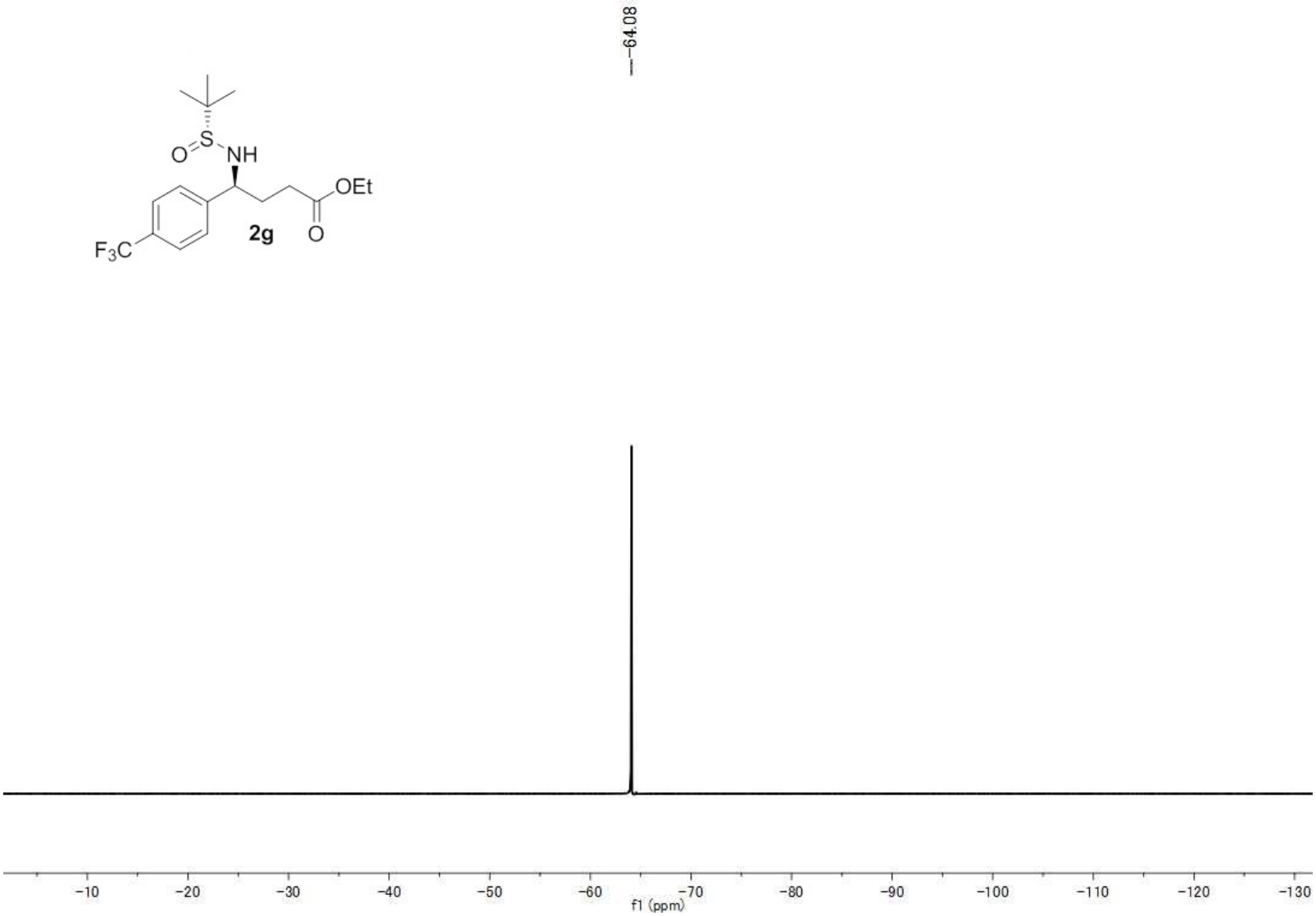
^{13}C NMR (75 MHz, $CDCl_3$) (*S*)-ethyl 4-[(*R*)-1,1-dimethylethylsulfinamido]-4-(2-methoxyphenyl)butanoate (**2f**)



^{1}H NMR (400 MHz, $CDCl_3$) (*S*)-ethyl 4-[(*R*)-1,1-dimethylethylsulfinamido]-4-(4-trifluoromethyophenyl)butanoate (**2g**)



^{13}C NMR (101 MHz, $CDCl_3$) (*S*)-ethyl 4-[(*R*)-1,1-dimethylethylsulfinamido]-4-(4-trifluoromethyophenyl)butanoate (**2g**)



^{19}F NMR (376 MHz, $CDCl_3$) (*S*)-ethyl 4-[(*R*)-1,1-dimethylethylsulfinamido]-4-(4-trifluoromethyophenyl)butanoate (**2g**)

References

1) G. Fournet, G. Balme, J. J. Barieux and J. Gore, *Tetrahedron*, 1988, **44**, 5821.

2) T. Netscher and H. Prinzbach, *Synthesis*, 1987, 683.

3) D. A. Cogan, G. Liu, K. Kim, B. J. Backes and J. A. Ellman, J. Am. Chem. Soc., 1988, 120, 8011.

4) Z. S. Han, A. M. Meyer, Y. Xu, Y. Zhang, R. Busch, S. Shen, N. Grinberg, B. Z. Lu, D. Krishnamurthy and C. H. Senanayake, *J. Org. Chem.*, 2011, **76**, 5480.

5) G. Liu, D. A. Cogan, T. D. Owens, T. P. Tang and J. A. Ellman, *J. Org. Chem.*, 1999, **64**, 1278.

6) D. Guijarro, Ó. Pabl and M. Yus, *J. Org. Chem.*, 2013, **78**, 3647.

7) P. Camps, T. Gómez, D. Muñoz-Torrero, J. Rull, L. Sánchez, F. Boschi, M. Comes-Franchini, A. Ricci, T. Calvet, M. Font-Bardia, E. De Clercq and L. Naesens, *J. Org. Chem.*, 2008, **73**, 6657.