Supporting Information

Catalytic amide allylation of α–ketoesters: extremely highly enantioselective synthesis of ester functionalised α–methylene–γ–butyrolactones

Masaki Takahashi,[†] Yusuke Murata,[‡] Masahiro Ishida,[†] Fumitoshi Yagishita,[§] Masami Sakamoto,[§] Tetsuya Sengoku,[†] and Hidemi Yoda[†,‡]*

†Department of Applied Chemistry, Graduate School of Engineering, Shizuoka University, Johoku 3–5–1, Naka–ku, Hamamatsu 432–8561, Japan

‡Graduate School of Science and Technology, Shizuoka University, Johoku 3–5–1, Naka–ku, Hamamatsu, 432–8561, Japan

§Department of Applied Chemistry and Biotechnology, Graduate School of Engineering, Chiba University, Yayoi–cho 1–33, Inage–ku, Chiba, 263–8522, Japan

E–mail: tchyoda@ipc.shizuoka.ac.jp.

The following data are included in this material:

Experimental procedures and characterization data	S2─S17
References	S17
HPLC chromatographic data	S18─S33
Copies of ^{1}H and ^{13}C NMR spectra	S34─S69

Experimental procedures and characterization data

General methods

All solvents and reagents were used without further purification unless otherwise stated. $In(OTf)_3$, MS3Å, and *p*-toluenesulfonic acid monohydrate (PTSA) were dried at 140, 180, and 90 ˚C for 1, 3, and 1 h under reduced pressure (ca. 1.0 Torr) prior to use, respectively. MeCN was purified by simple distillation at atmospheric pressure and then dried with MS3Å prior to each experiment. 1,2-Dichloroethane (DCE) and tetrahydrofuran (THF) were dried over MS4Å and sodium wire prior to use, respectively. The ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra operating at the frequencies of 300 and 75 MHz, respectively, were recorded in chloroform–*d* ($CDCl_3$) unless otherwise noted. Chemical shifts are reported in parts per million (ppm) relative to TMS and the solvent used as internal standards, and the coupling constants are reported in hertz (Hz). Optical rotations were measured in 1 dm path length cell of 2 mL capacity at a wavelength of 589 nm. Reactions were monitored by thin layer chromatography (TLC) using Merck TLC silica gel $60F_{254}$, visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid in ethanol followed by heating. Column chromatography was performed using silica gel 60N (spherical neutral) from Kanto Chemical Co. and eluting with the indicated solvent system.

Synthesis and characterization of stannylated reagent 2c

To a solution of *N*–(*p*–anis)methacrylamide (1.09 g, 5.70 mmol) in anhydrous THF (57 mL) was added potassium *t*–butoxide (*t*BuOK, 1.60 g, 14.3 mmol), and the resulting mixture was cooled to

–78 °C. After the mixture was stirred at this temperature under nitrogen atmosphere for 1 h, *n*–butyllithium (*n*BuLi, 1.55 M hexane solution, 8.5 mL, 13 mmol) was added to give a suspension. This reaction mixture was kept at –78 °C for an additional 10 min, and tributyltin chloride (nBu$_3$SnCl, 2.23 g, 6.84 mmol) was injected consecutively into the suspension. After stirring for an additional 1 h, the reaction was quenched by addition of saturated aqueous NH_4Cl (20 mL) at –78 °C, and the reaction mixture was then warmed to room temperature. The solvent was removed under reduced pressure, and the resulting residue was extracted with ethyl acetate (50 mL), washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to provide a crude residue. The crude residue was purified by column chromatography on 10% w/w anhydrous K_2CO_3–silica gel[1] (eluent: hexane/AcOEt = 25/1-20/1) to give **2c** (925 mg, 1.93 mmol, 34%) as a white solid. R_f = 0.43 (silica gel, hexane/AcOEt = 8/1); mp 35–36 °C; IR (KBr): 3227 (N–H), 2923 (C–H), 1643 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51 (brs, 1H, N*H*), 7.43 (d, *J* = 9.0 Hz, 2H, Ar*H*), 6.85 (d, *J* = 9.0 Hz, 2H, Ar*H*), 5.31 (s, 1H, CH_2), 5.13 (s, 1H, CH_2), 3.78 (s, 3H, CH_3), 2.01 (s, 2H, CH_2), 1.49 (m, 6H, CH_2), 1.29 (m, 6H, CH_2), 0.91 (m, 6H, CH_2), 0.87 (t, *J* = 7.2 Hz, 9H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.7 (*C*), 156.7 (*C*), 147.8 (*C*), 131.3 (*C*), 122.1 (*C*H), 114.4 (*C*H), 111.2 (*C*H_2), 55.6 (*C*H_3), 29.2 (*C*H_2), 27.5 (*C*H_2), 15.9 (*C*H_2), 13.8 (*C*H_3), 10.1 (*C*H_2). Anal. Calcd for $C_{23}H_{39}NO_2Sn$: C, 57.52; H, 8.19; N, 2.92. Found: C, 57.52; H, 8.17; N, 2.86.

Synthesis and characterization of stannylated reagent 2h

To a solution of *N*–(*p*-chlorophenyl)methacrylamide (500 mg, 2.58 mmol) in anhydrous THF (25

mL) was added potassium *t*–butoxide (*t*BuOK, 724 mg, 6.45 mmol), and the resulting mixture was cooled to –78 °C. After the mixture was stirred at this temperature under nitrogen atmosphere for 1 h, *n*–butyllithium (*n*BuLi, 1.60 M hexane solution, 3.7 mL, 5.9 mmol) was added to give a suspension. This reaction mixture was kept at –78 °C for an additional 10 min, and tributyltin chloride (nBu$_3$SnCl, 1.06 g, 3.09 mmol) was injected consecutively into the suspension. After stirring for an additional 15 min, the reaction was quenched by addition of saturated aqueous NH_4Cl (20 mL) at –78 °C, and the reaction mixture was then warmed to room temperature. The solvent was removed under reduced pressure, and the resulting residue was extracted with ethyl acetate (40 mL), washed with brine (25 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to provide a crude residue. The crude residue was purified by column chromatography on 10% w/w anhydrous K_2CO_3–silica gel[1] (eluent: hexane/AcOEt = 30/1) to give **2h** (84.0 mg, 0.173 mmol, 7%) as a brown solid. R_f = 0.53 (silica gel, hexane/AcOEt = 8/1); mp 33–34 °C; IR (KBr): 3276 (N–H), 2922 (C–H), 1650 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57 (brs, 1H, N*H*), 7.49 (d, J = 9.0 Hz, 2H, Ar*H*), 7.28 (d, J = 9.0 Hz, 2H, Ar*H*), 5.32 (s, 1H, CH_2), 5.17 (s, 1H, CH_2), 2.00 (s, 2H, CH_2), 1.49 (m, 6H, CH_2), 1.28 (m, 6H, CH_2), 0.90 (m, 6H, CH_2), 0.87 (t, J = 7.5 Hz, 9H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.8 (*C*), 147.7 (*C*), 136.8 (*C*), 129.4 (*C*), 129.3 (*C*H), 121.4 (*C*H), 111.7 (*C*H_2), 29.2 (*C*H_2), 27.5 (*C*H_2), 15.9 (*C*H_2), 13.8 (*C*H_3), 10.1 (*C*H_2). Anal. Calcd for $C_{22}H_{36}ClNOSn$: C, 54.52; H, 7.49; N, 2.89. Found: C, 54.55; H, 7.41; N, 2.95.

General procedure for the asymmetric amide allylation of α–ketoesters with 2.

All the experiments for the asymmetric amide allylation of α-ketoesters with **2** were carried out as described in the following typical procedure. For example, the reaction of methyl benzoylformate (**1a**) with *N*−(*p*−tolyl)−β−amido allylstannane (**2a**) in the presence of 10 mol % of [In((*S*,*S*)−Ph−pybox)$(OTf)_3$] (entry 1 in Table 1) was exemplified as follows.

Synthesis and characterization of allylated product 3a

To the suspension of indium trifluoromethanesulfonate ($In(OTf)_3$, 12.2 mg, 0.0217 mmol) and MS3Å (109 mg) in anhydrous MeCN (0.43 mL), which was degassed by at least three freeze-pump-thaw cycles, was added (*S*,*S*)−Ph−pybox (16.0 mg, 0.0434 mmol) at room temperature under argon atmosphere, and the resulting mixture was stirred for 1 h. After addition of **1a** (35.6 mg, 0.217 mmol), the resulting mixture was stirred at this temperature for an additional 30 min. Then, **2a** (121 mg, 0.260 mmol) was added and the reaction mixture was stirred at room temperature for an additional 18 h. The reaction was then quenched by addition of saturated aqueous $NaHCO_3$ (10 mL), and the resulting mixture was extracted with ethyl acetate (30 mL), washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give a crude residue. The crude residue was purified by column chromatography on 10% w/w anhydrous K_2CO_3–silica gel[1] (eluent: hexane/AcOEt = 2/1) to give **3a** (72.9 mg, 0.215 mmol, 99%, 99% ee) as a white solid. R_f = 0.53 (silica gel, hexane/AcOEt = 1/1); mp 117–119 °C; $[\alpha]_D^{25}$ –26.9 (*c* 0.850, $CHCl_3$); IR (KBr): 3294 (N–H), 3137 (O–H), 1725 (C=O), 1645 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.50 (brs, 1H, N*H*), 7.63 (m, 2H, Ar*H*), 7.41 (d, *J* = 8.4 Hz, 2H, Ar*H*), 7.39–7.25 (m, 3H, Ar*H*), 7.11 (d, *J* = 8.4 Hz,

2H, Ar*H*), 5.91 (s, 1H, CH_2), 5.41 (s, 1H, O*H*), 5.35 (s, 1H, CH_2), 3.76 (s, 3H, CH_3), 3.35 (d, J = 13.5 Hz, 1H, CH_2), 3.04 (d, J = 13.5 Hz, 1H, CH_2), 2.30 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6 (*C*), 168.0 (*C*), 141.2 (*C*), 140.5 (*C*), 135.5 (*C*), 134.4 (*C*), 129.7 (*C*H), 128.6 (*C*H), 128.3 (*C*H), 125.8 (*C*H), 125.0 (*C*H_2), 120.4 (*C*H), 79.2 (*C*), 53.3 (*C*H_3), 42.7 (*C*H_2), 21.0 (*C*H_3). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.40; H, 6.23; N, 4.20. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IF column (hexane/EtOH = 80/20), flow rate 0.5 mL/min, t_R (major) = 24.9 min, t_R (minor) = 20.5 min.

Characterization of allylated product 3b

This compound was obtained (61.3 mg, 0.188 mmol, 99%, 98% ee) as a white solid. R_f = 0.53 (silica gel, hexane/AcOEt = 1/1); mp 147–148 °C; $[\alpha]_D^{25}$ –17.2 (*c* 1.42, $CHCl_3$); IR (KBr): 3306 (N–H), 3239 (O–H), 1727 (C=O), 1648 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.57 (brs, 1H, N*H*), 7.66–7.62 (m, 2H, Ar*H*), 7.56–7.52 (m, 2H, Ar*H*), 7.40–7.28 (m, 5H, Ar*H*), 7.11 (m, 1H, Ar*H*), 5.96 (s, 1H, CH_2), 5.38 (s, 1H, CH_2), 5.19 (s, 1H, O*H*), 3.78 (s, 3H, CH_3), 3.37 (d, J = 14.1 Hz, 1H, CH_2), 3.07 (d, J = 14.1 Hz, 1H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6 (*C*), 167.9 (*C*), 141.0 (*C*), 140.5 (*C*), 138.1 (*C*), 129.2 (*C*H), 128.6 (*C*H), 128.4 (*C*H), 125.8 (*C*H), 125.4 (*C*H_2), 124.7 (*C*H), 120.3 (*C*H), 79.3 (*C*), 53.5 (*C*H_3), 42.5 (*C*H_2). Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.15; H, 5.89; N, 4.30. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IF column (hexane/EtOH = 80/20), flow rate 0.5 mL/min, t_R (major) = 20.0 min, t_R (minor) = 18.1 min.

Characterization of allylated product 3c

This compound was obtained (84.9 mg, 0.239 mmol, 99%, 99% ee) as a white solid. R_f = 0.40 (silica gel, hexane/AcOEt = 1/1); mp 95–97 °C; $[\alpha]_D^{25}$ –29.6 (*c* 4.19, $CHCl_3$); IR (KBr): 3318 (N–H), 3220 (O–H), 1727 (C=O), 1639 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.54 (brs, 1H, N*H*), 7.64–7.60 (m, 2H, Ar*H*), 7.43 (d, *J* = 9.0 Hz, 2H, Ar*H*), 7.38–7.29 (m, 3H, Ar*H*), 6.83 (d, *J* = 9.0 Hz, 2H, Ar*H*), 5.89 (s, 1H, CH_2), 5.56 (s, 1H, O*H*), 5.33 (s, 1H, CH_2), 3.77 (s, 3H, CH_3), 3.74 (s, 3H, CH_3), 3.34 (d, *J* = 14.1 Hz, 1H, CH_2), 3.03 (d, *J* = 14.1 Hz, 1H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6 (*C*), 168.1 (*C*), 156.8 (*C*), 141.2 (*C*), 140.3 (*C*), 131.1 (*C*), 128.5 (*C*H), 128.2 (*C*H), 125.8 (*C*H), 124.9 (*C*H_2), 122.2 (*C*H), 114.3 (*C*H), 79.2 (*C*), 55.6 (*C*H_3), 53.3 (*C*H_3), 42.7 (*C*H_2). Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.70; H, 5.97; N, 4.17. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IF column (hexane/EtOH = 70/30), flow rate 0.5 mL/min, t_R (major) = 30.7 min, t_R (minor) = 22.6 min.

Characterization of allylated product 3d

This compound was obtained (88.1 mg, 0.231 mmol, 98%, 98% ee) as a white solid. R_f = 0.63 (silica gel, hexane/AcOEt = 1/1); mp 166–168 °C; $[\alpha]_D^{23}$ –24.0 (*c* 0.465, $CHCl_3$); IR (KBr): 3293 (N–H), 3175 (O–H), 2957 (C–H), 1729 (C=O), 1641 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.40 (brs, 1H, N*H*), 7.65–7.63 (m, 2H, Ar*H*), 7.47–7.28 (m, 7H, Ar*H*), 5.92 (s, 1H, CH_2), 5.37 (s, 1H, CH_2), 5.28 (s, 1H, O*H*), 3.79 (s, 3H, CH_3), 3.37 (d, *J* = 14.4 Hz, 1H, CH_2), 3.06 (d, *J* = 14.4 Hz, 1H, CH_2),

1.30 (s, 9H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.7 (*C*), 167.9 (*C*), 147.9 (*C*), 141.2 (*C*), 140.6 (*C*), 135.4 (*C*), 128.6 (*C*H), 128.3 (*C*H), 126.1 (*C*H), 125.8 (*C*H), 125.0 (*C*H_2), 120.2 (*C*H), 79.3 (*C*), 53.4 (*C*H_3), 42.7 (*C*H_2), 34.5 (*C*), 31.5 (*C*H_3). Anal. Calcd for $C_{23}H_{27}NO_4$: C, 72.42; H, 7.13; N, 3.67. Found: C, 72.45; H, 7.15; N, 3.66. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IA column (hexane/EtOH = 70/30), flow rate 0.5 mL/min, t_R (major) = 20.1 min, t_R (minor) = 15.5 min.

Characterization of allylated product 3e

This compound was obtained (64.3 mg, 0.171 mmol, 99%, 93% ee) as a colorless oil. R_f = 0.53 (silica gel, hexane/AcOEt = 1/1); $[\alpha]_D^{23}$ –19.2 (*c* 1.10, $CHCl_3$); IR (NaCl): 3474 (N–H), 3276 (O–H), 1730 (C=O), 1659 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.87 (brs, 1H, N*H*), 7.87–7.80 (m, 3H, Ar*H*), 7.68–7.62 (m, 3H, Ar*H*), 7.51–7.27 (m, 6H, Ar*H*), 6.02 (s, 1H, CH_2), 5.37 (s, 1H, CH_2), 5.31 (s, 1H, O*H*), 3.75 (s, 3H, CH_3), 3.39 (d, *J* = 14.1 Hz, 1H, CH_2), 3.10 (d, *J* = 14.1 Hz, 1H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6 (*C*), 168.7 (*C*), 141.1 (*C*), 140.3 (*C*), 134.3 (*C*), 132.7 (*C*), 128.9 (*C*H), 128.6 (*C*H), 128.3 (*C*H), 127.6 (*C*), 126.5 (*C*H), 126.17 (*C*H), 126.14 (*C*H), 125.9 (*C*H), 125.8 (*C*H), 125.5 (*C*H_2), 121.3 (*C*H), 121.2 (*C*H), 79.3 (*C*), 53.4 (*C*H_3), 42.7 (*C*H_2). Anal. Calcd for $C_{23}H_{21}NO_4$: C, 73.58; H, 5.64; N, 3.73. Found: C, 73.60; H, 5.80; N, 3.96. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 70/30), flow rate 0.5 mL/min, t_R (major) = 19.1 min, t_R (minor) = 14.1 min.

Characterization of allylated product 3f

This compound was obtained (67.1 mg, 0.210 mmol, 98%, 96% ee) as a white solid. R_f = 0.47 (silica gel, hexane/AcOEt = 1/1); mp 66–67 °C; $[\alpha]_D^{25}$ –31.9 (*c* 1.29, $CHCl_3$); IR (KBr): 3349 (N–H), 3096 (O–H), 2870 (C–H), 1742 (C=O), 1651 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.65–7.60 (m, 2H, Ar*H*), 7.38–7.25 (m, 3H, Ar*H*), 6.31 (brt, 1H, N*H*), 6.12 (s, 1H, O*H*), 5.63 (s, 1H, CH_2), 5.24 (s, 1H, CH_2), 3.74 (s, 3H, CH_3), 3.27 (d, *J* = 13.5 Hz, 1H, CH_2), 3.25 (t, *J* = 7.2 Hz, 2H, CH_2), 2.96 (d, *J* = 13.5 Hz, 1H, CH_2), 1.52 (quint., *J* = 7.2 Hz, 2H, CH_2), 1.38–1.24 (m, 4H, CH_2), 0.90 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.7 (*C*), 170.6 (*C*), 141.7 (*C*), 140.3 (*C*), 128.4 (*C*H), 128.0 (*C*H), 125.8 (*C*H), 123.3 (*C*H_2), 78.9 (*C*), 53.1 (*C*H_3), 43.3 (*C*H_2), 40.1 (*C*H_2), 29.2 (*C*H_2), 29.1 (*C*H_2), 22.4 (*C*H_2), 14.1 (*C*H_3). Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.75; H, 8.05; N, 4.36. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 80/20), flow rate 0.5 mL/min, t_R (major) = 19.9 min, t_R (minor) = 15.9 min.

Characterization of allylated product 3g

This compound was obtained (55.9 mg, 0.171 mmol, 98%, 96% ee) as a white solid. R_f = 0.53 (silica gel, hexane/AcOEt = 1/1); mp 127–128 °C; $[\alpha]_D^{25}$ –30.3 (*c* 1.35, $CHCl_3$); IR (KBr): 3339 (N–H), 3124 (O–H), 2889 (C–H), 1736 (C=O), 1639 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.66–7.62 (m, 2H, Ar*H*), 7.37–7.25 (m, 3H, Ar*H*), 6.21 (s, 1H, O*H*), 6.01 (brs, 1H, N*H*), 5.55 (s, 1H, CH_2), 5.22 (s, 1H, CH_2), 3.74 (s, 3H, CH_3), 3.28 (d, *J* = 14.1 Hz, 1H, CH_2), 2.92 (d, *J* = 14.1 Hz, 1H, CH_2), 1.36

(s, 9H, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.8 (*C*), 170.4 (*C*), 141.9 (*C*), 141.4 (*C*), 128.4 (*C*H), 127.9 (*C*H), 125.9 (*C*H), 122.4 (*C*H$_2$), 78.8 (*C*), 53.0 (*C*H$_3$), 51.8 (*C*), 43.3 (*C*H$_2$), 28.7 (*C*H$_3$). Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.75; H, 7.90; N, 4.94. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IF column (hexane/EtOH = 90/10), flow rate 0.5 mL/min, t_R (major) = 19.7 min, t_R (minor) = 25.9 min.

Characterization of allylated product 3h

This compound was obtained (77.0 mg, 0.214 mmol, 98%, 97% ee) as a white solid. R_f = 0.57 (silica gel, hexane/AcOEt = 1/1); mp 85–87 °C; $[\alpha]_D^{26}$ –13.8 (*c* 2.49, $CHCl_3$); IR (KBr): 3304 (N–H), 3123 (O–H), 1727 (C=O), 1648 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.82 (brs, 1H, N*H*), 7.64–7.60 (m, 2H, Ar*H*), 7.50 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.40–7.24 (m, 5H, Ar*H*), 5.99 (s, 1H, C*H*$_2$), 5.37 (s, 1H, C*H*$_2$), 5.08 (s, 1H, O*H*), 3.78 (s, 3H, C*H*$_3$), 3.35 (d, *J* = 14.4 Hz, 1H, C*H*$_2$), 3.07 (d, *J* = 14.4 Hz, 1H, C*H*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.5 (*C*), 167.7 (*C*), 140.8 (*C*), 140.1 (*C*), 136.8 (*C*), 129.6 (*C*), 129.2 (*C*H), 128.7 (*C*H), 128.5 (*C*H), 126.0 (*C*H$_2$), 125.7 (*C*H), 121.5 (*C*H), 79.4 (*C*), 53.5 (*C*H$_3$), 42.3 (*C*H$_2$). Anal. Calcd for $C_{19}H_{18}ClNO_4$: C, 63.43; H, 5.04; N, 3.89. Found: C, 63.49; H, 5.18; N, 3.90. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IF column (hexane/EtOH = 80/20), flow rate 0.5 mL/min, t_R (major) = 20.0 min, t_R (minor) = 17.3 min.

Characterization of allylated product 3i

This compound was obtained (92.0 mg, 0.213 mmol, 97%, 98% ee) as a colorless oil. R_f = 0.53 (silica

gel, hexane/AcOEt = 1/1); $[\alpha]_D^{25}$ –20.9 (*c* 2.85, $CHCl_3$); IR (NaCl): 3474 (N–H), 3298 (O–H), 2837 (C–H), 1732 (C=O), 1649 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.47 (brs, 1H, N*H*), 7.63–7.59 (m, 2H, Ar*H*), 7.42 (d, *J* = 9.0 Hz, 2H, Ar*H*), 7.36–7.23 (m, 8H, Ar*H*), 6.83 (d, *J* = 9.0 Hz, 2H, Ar*H*), 5.81 (s, 1H, CH_2), 5.35 (s, 1H, O*H*), 5.21 (s, 1H, CH_2), 5.17 (s, 2H, CH_2), 3.76 (s, 3H, CH_3), 3.32 (d, *J* = 14.4 Hz, 1H, CH_2), 3.05 (d, *J* = 14.4 Hz, 1H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.0 (*C*), 167.8 (*C*), 156.8 (*C*), 141.1 (*C*), 140.2 (*C*), 135.2 (*C*), 131.2 (*C*), 128.84 (*C*H), 128.79 (*C*H), 128.6 (*C*H), 128.5 (*C*H), 128.3 (*C*H), 125.9 (*C*H), 125.1 (*C*H_2), 122.1 (*C*H), 114.3 (*C*H), 79.2 (*C*), 68.2 (*C*H_2), 55.6 (*C*H_3), 42.5 (*C*H_2). Anal. Calcd for $C_{26}H_{25}NO_5$: C, 72.37; H, 5.84; N, 3.25. Found: C, 72.02; H, 5.81; N, 3.34. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 70/30), flow rate 0.5 mL/min, t_R (major) = 21.0 min, t_R (minor) = 15.6 min.

Characterization of allylated product 3j

This compound was obtained (54.7 mg, 0.142 mmol, 96%, 97% ee) as a white solid. R_f = 0.53 (silica gel, hexane/AcOEt = 1/1); mp 98–99 °C; $[\alpha]_D^{29}$ –6.36 (*c* 3.17, $CHCl_3$); IR (KBr): 3455 (N–H), 3283 (O–H), 2885 (C–H), 1742 (C=O), 1651 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.68 (brs, 1H, N*H*), 7.67–7.63 (m, 2H, Ar*H*), 7.46 (d, *J* = 9.0 Hz, 2H, Ar*H*), 7.39–7.26 (m, 3H, Ar*H*), 6.85 (d, *J* = 9.0 Hz, 2H, Ar*H*), 6.00 (s, 1H, CH_2), 5.38 (s, 1H, CH_2), 5.07 (sept, *J* = 6.3 Hz, 1H, C*H*), 4.98 (s, 1H, O*H*), 3.79 (s, 3H, CH_3), 3.33 (d, *J* = 14.4 Hz, 1H, CH_2), 3.08 (d, *J* = 14.4 Hz, 1H, CH_2), 1.30 (d, *J* = 6.3 Hz, 3H, CH_3), 1.21 (d, *J* = 6.3 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.7 (*C*), 167.4 (*C*), 156.7

(*C*), 141.2 (*C*), 140.4 (*C*), 131.5 (*C*), 128.5 (*C*H), 128.3 (*C*H), 125.8 (*C*H), 125.5 (*C*H_2), 121.9 (*C*H), 114.3 (*C*H), 79.0 (*C*), 71.2 (*C*H), 55.6 (*C*H_3), 42.2 (*C*H_2), 21.8 (*C*H_3), 21.6 (*C*H_3). Anal. Calcd for $C_{22}H_{25}NO_5$: C, 68.91; H, 6.57; N, 3.65. Found: C, 68.91; H, 6.61; N, 3.59. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 80/20), flow rate 0.5 mL/min, t_R (major) = 26.4 min, t_R (minor) = 20.2 min.

Characterization of allylated product 3k

This compound was obtained (29.0 mg, 0.0989 mmol, 72%, 99% ee) as a white solid. R_f = 0.23 (silica gel, hexane/AcOEt = 1/1); mp 94–95 °C; $[\alpha]_D^{26}$ +42.9 (*c* 2.04, $CHCl_3$); IR (KBr): 3327 (N–H), 3220 (O–H), 1733 (C=O), 1642 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.69 (brs, 1H, N*H*), 7.46 (d, *J* = 9.0 Hz, 2H, Ar*H*), 6.85 (d, *J* = 9.0 Hz, 2H, Ar*H*), 6.02 (s, 1H, CH_2), 5.44 (s, 1H, CH_2), 4.69 (s, 1H, O*H*), 3.78 (s, 3H, CH_3), 3.76 (s, 3H, CH_3), 2.89 (d, *J* = 14.1 Hz, 1H, CH_2), 2.73 (d, *J* = 14.1 Hz, 1H, CH_2), 1.50 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.5 (*C*), 167.3 (*C*), 156.8 (*C*), 140.9 (*C*), 131.3 (*C*), 124.9 (*C*H_2), 122.0 (*C*H), 114.3 (*C*H), 75.7 (*C*), 55.6 (*C*H_3), 52.9 (*C*H_3), 42.8 (*C*H_2), 26.4 (*C*H_3). Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.38; H, 6.50; N, 4.73. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IF column (hexane/EtOH = 70/30), flow rate 0.5 mL/min, t_R (major) = 37.5 min, t_R (minor) = 22.3 min.

General procedure for lactonisation

All the experiments for lactonisation of allylated products **3** were carried out as described in the

following typical procedure. For example, the reaction of allylated product **3c** was exemplified as follows.

Synthesis and characterization of lactone 4a

To a solution of **3c** (49.3 mg, 0.139 mmol, 99% ee) in anhydrous DCE (2.8 mL) was added *p*−toluenesulfonic acid (PTSA; 26.3 mg, 0.153 mmol) at room temperature, and the resulting mixture was warmed to 50 °C. After stirring at this temperature for 11 h, the reaction mixture was cooled down to room temperature, and the solvent was then removed under reduced pressure to provide a crude residue. The crude residue was purified by column chromatography on silica gel (eluent: hexane/toluene/AcOEt = 0/1/0 to 4/0/1) to give **4a** (31.6 mg, 0.136 mmol, 98%, 99% ee) as a white solid. R_f = 0.43 (silica gel, hexane/AcOEt = 2/1); mp 75–76 °C; $[\alpha]_D^{27}$ –39.0 (*c* 1.87, $CHCl_3$); IR (KBr): 1776 (C=O), 1735 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.54–7.49 (m, 2H, Ar*H*), 7.44–7.33 (m, 3H, Ar*H*), 6.30 (t, *J* = 2.4 Hz, 1H, CH_2), 5.72 (t, *J* = 2.4 Hz, 1H, CH_2), 3.85 (dt, *J* = 2.4, 17.1 Hz, 1H, CH_2), 3.75 (s, 3H, CH_3), 3.26 (dt, *J* = 2.4, 17.1 Hz, 1H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1 (*C*), 168.6 (*C*), 138.7 (*C*), 132.9 (*C*), 129.1 (*C*H), 129.0 (*C*H), 125.2 (*C*H), 123.8 (*C*H_2), 84.1 (*C*), 53.6 (*C*H_3), 39.6 (*C*H_2). Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.19; H, 5.18. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IE column (hexane/EtOH = 80/20), flow rate 0.5 mL/min, t_R (major) = 20.4 min, t_R (minor) = 17.9 min.

Characterization of lactone 4b

This compound was obtained (40.5 mg, 0.131 mmol, 99%, 98% ee) as a white solid. R_f = 0.50 (silica gel, hexane/AcOEt = 2/1); mp 40–41 °C; $[\alpha]_D^{29}$ –22.0 (*c* 2.35, $CHCl_3$); IR (KBr): 1777 (C=O), 1745 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.52–7.46 (m, 2H, Ar*H*), 7.41–7.34 (m, 3H, Ar*H*), 7.32–7.26 (m, 3H, Ar*H*), 7.21–7.15 (m, 2H, Ar*H*), 6.27 (t, *J* = 2.7 Hz, 1H, CH_2), 5.68 (t, *J* = 2.7 Hz, 1H, CH_2), 5.18 (d, *J* = 12.6 Hz, 1H, CH_2), 5.13 (d, *J* = 12.6 Hz, 1H, CH_2), 3.80 (dt, *J* = 2.7, 17.1 Hz, 1H, CH_2), 3.25 (dt, *J* = 2.7, 17.1 Hz, 1H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3 (*C*), 168.6 (*C*), 138.5 (*C*), 135.1 (*C*), 132.9 (*C*), 129.1 (*C*H), 128.9 (*C*H), 128.8 (*C*H), 128.6 (*C*H), 128.0 (*C*H), 125.4 (*C*H), 123.7 (*C*H_2), 84.1 (*C*), 68.1 (*C*H_2), 39.3 (*C*H_2). Anal. Calcd for $C_{19}H_{16}O_4$: C, 74.01; H, 5.23. Found: C, 74.02; H, 5.28. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IE column (hexane/EtOH = 80/20), flow rate 0.5 mL/min, t_R (major) = 19.9 min, t_R (minor) = 18.6 min.

Characterization of lactone 4c

This compound was obtained (41.8 mg, 0.161 mmol, 97%, 97% ee) as a colorless oil. R_f = 0.53 (silica gel, hexane/AcOEt = 2/1); $[\alpha]_D^{27}$ –18.9 (*c* 2.09, $CHCl_3$); IR (NaCl): 1780 (C=O), 1735 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.53–7.49 (m, 2H, Ar*H*), 7.43–7.32 (m, 3H, Ar*H*), 6.29 (t, *J* = 2.7 Hz, 1H, CH_2), 5.71 (t, *J* = 2.7 Hz, 1H, CH_2), 5.02 (sept, *J* = 6.3 Hz, 1H, C*H*), 3.80 (dt, *J* = 2.7, 17.1 Hz, 1H, CH_2), 3.25 (dt, *J* = 2.7, 17.1 Hz, 1H, CH_2), 1.21 (d, *J* = 6.3 Hz, 3H, CH_3), 1.18 (d, *J* = 6.3 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.0 (*C*), 168.8 (*C*), 138.8 (*C*), 133.2 (*C*), 129.0 (*C*H), 128.9 (*C*H), 125.3 (*C*H), 123.5 (*C*H_2), 84.2 (*C*), 70.8 (*C*H), 39.5 (*C*H_2), 21.55 (*C*H_3), 21.46 (*C*H_3). Anal.

Calcd for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20. Found: C, 69.21; H, 6.16. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IE column (hexane/EtOH = 80/20), flow rate 0.5 mL/min, t_R (major) = 16.1 min, t_R (minor) = 13.9 min.

Characterization of lactone 4d

This compound was obtained (13.0 mg, 0.0763 mmol, 86%, 99% ee) as a pale yellow oil. R_f = 0.50 (silica gel, hexane/AcOEt = 1/1); $[\alpha]_D^{26}$ –5.02 (*c* 0.625, $CHCl_3$); IR (NaCl): 1775 (C=O), 1747 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.29 (t, *J* = 2.7 Hz, 1H, C*H*$_2$), 5.69 (t, *J* = 2.7 Hz, 1H, C*H*$_2$), 3.79 (s, 3H, C*H*$_3$), 3.25 (dt, *J* = 2.7, 17.4 Hz, 1H, C*H*$_2$), 2.85 (dt, *J* = 2.7, 17.4 Hz, 1H, C*H*$_2$), 1.69 (s, 3H, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2 (*C*), 169.2 (*C*), 133.6 (*C*), 123.3 (*C*H$_2$), 81.0 (*C*), 53.2 (*C*H$_3$), 38.8 (*C*H$_2$), 24.4 (*C*H$_3$). Anal. Calcd for $C_8H_{10}O_4$: C, 56.47; H, 5.92. Found: C, 56.46; H, 5.86. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IE column (hexane/EtOH = 80/20), flow rate 0.5 mL/min, t_R (major) = 20.3 min, t_R (minor) = 23.7 min.

General procedure for the transformations of 3i and 3j into (*S*)−3c.

The experiments for the transformations **3i** and **3j** into (*S*)−**3c** were carried out as described in the following typical procedure. The transformation of **3i** was exemplified as follows.

Transformation of 3i into (*S*)−3c.

To a solution of **3i** (16.8 mg, 0.0389 mmol, 98% ee) in a mixture of THF and water (1/1, 0.39 mL)

was added lithium hydroxide monohydrate ($LiOH·H_2O$; 16.3 mg, 0.389 mmol) at room temperature, and the resulting mixture was stirred for 1 h. The reaction was then quenched by addition of a saturated solution of aqueous citric acid (20 mL), and the resulting mixture was extracted with DCM (30 mL×3), dried over Na_2SO_4, filtered, and concentrated in vacuo to provide a crude carboxylic acid (17.8 mg) as a yellow oil. To a solution of this product (17.8 mg) in anhydrous DMF (0.078 mL) was added sodium bicarbonate ($NaHCO_3$; 32.7 mg, 0.389 mmol) and iodomethane (MeI; 54.9 mg, 0.389 mmol) at room temperature, and the resulting mixture was stirred for 14 h. Then, the reaction mixture was subjected to column chromatography on silica gel (eluent: hexane/AcOEt = 2/1) to give (*S*)−**3c** (10.9 mg, 0.0307 mmol, 79% from **3i**, 97% ee) as a white solid. Structural confirmation of this product, which was obtained by the ^{1}H NMR analysis, ensured the success in the above sequential transformation. The assignment of the product stereochemistry was made by comparison of the chiral HPLC profile with that of the authentic sample of (*S*)−**3c**. By following the procedure described above, whereby the hydrolysis and esterification steps required longer reaction times of 19 and 21 h, respectively, **3j** (52.0 mg, 0.136 mmol, 97% ee) could also be transformed into (*S*)−**3c** (30.4 mg, 0.0855 mmol, 63% from **3i**, 97% ee). The assignment of the product stereochemistry was made by the same operation as described above.

Transformation of 3k into (*R*)−4d′

To a solution of **3k** (40.7 mg, 0.139 mmol, 91% ee) in EtOH (1.2 mL) was added *p*−toluenesulfonic acid monohydrate (PTSA; 79.1 mg, 0.416 mmol) at room temperature, and the resulting mixture was

warmed to 60 °C. After stirring at this temperature for 4 h, the reaction mixture was cooled down to room temperature, and the solvent was then removed under reduced pressure to provide a crude residue. The crude residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2) to give (*R*)−**4d′** (13.4 mg, 0.0723 mmol, 53%, 71% ee) as a pale yellow oil. R_f = 0.50 (silica gel, CH_2Cl_2); $[\alpha]_D^{26}$ –15.4 (*c* 0.670, EtOH); IR (NaCl): 3020 (C–H), 1773 (C=O), 1740 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.28 (dt, *J* = 2.7, 3.0 Hz, 1H, C*H*$_2$), 5.67 (dt, *J* = 2.7, 3.0 Hz, 1H, C*H*$_2$), 4.24 (q, *J* = 7.2 Hz, 2H, C*H*$_2$), 3.24 (dt, *J* = 2.7, 17.4 Hz, 1H, C*H*$_2$), 2.83 (dt, *J* = 2.7, 17.4 Hz, 1H, C*H*$_2$), 1.68 (s, 3H, C*H*$_3$), 1.29 (t, *J* = 7.2 Hz, 3H, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.7 (*C*), 169.3 (*C*), 133.8 (*C*), 123.2 (*C*H$_2$), 81.1 (*C*), 62.5 (*C*H$_2$), 38.8 (*C*H$_2$), 24.4 (*C*H$_3$), 14.1 (*C*H$_3$). Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.88; H, 6.54. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IE column (hexane/EtOH = 80/20), flow rate 0.5 mL/min, t_R (major) = 18.1 min, t_R (minor) = 20.3 min. The assignment of the product stereochemistry was made by comparison of the observed optical rotation with that reported in the literature.[2]

References

[1] D. C. Harrowven, D. P. Curran, S. L. Kostiuk, I. L. Wallis–Guy, S. Whiting, K. J. Stenning, B. Tang, E. Packard, L. Nanson, *Chem. Commun.* **2010**, *46*, 6335–6337.

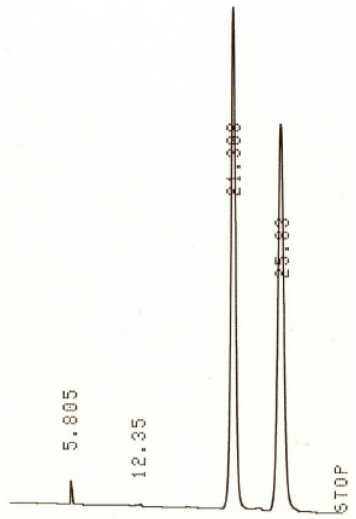
[2] G. Pitacco, A. Sessanta o Santi, E. Valentin, *Tetrahedron: Asymmetry*, **2000**, *11*, 3263−3267.

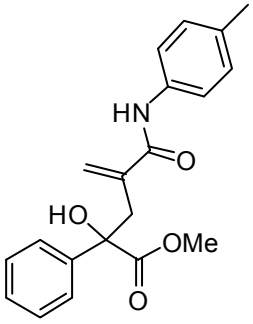
HPLC chromatographic data

HPLC Chromatographic Conditions

Column: Daicel CHIRALPAC® IF (ϕ 0.46 cm, L 25 cm); Eluent: *n*–hexane/EtOH = 80/20; Flow rate: 0.5 mL/min; UV detection: 254 nm

Racemic standard of **3a**

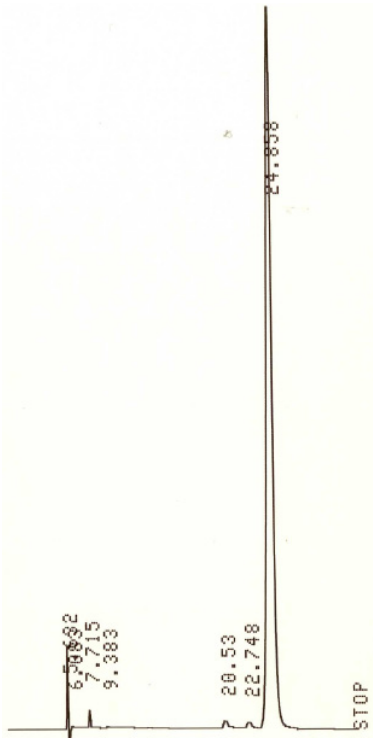


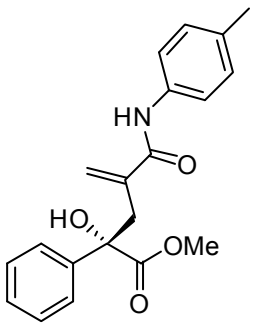


3a

TIME	AREA	MK	IDNO	CONC
5.805	2943			0.8634
12.35	504			0.1479
21.308	167757			49.2105
25.83	169692			49.7781
TOTAL	340897			100

Enantiomerically enriched (*S*)–**3a** (99% ee)



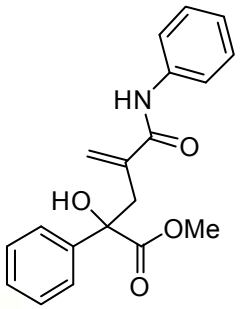


(*S*)-**3a**

TIME	AREA	MK	IDNO	CONC
5.632	10784			3.3595
6.083	7094			2.2099
7.715	1869			0.5821
9.383	395			0.1232
20.53	2139			0.6663
22.748	2063			0.6426
24.858	296645			92.4164
TOTAL	320987			100

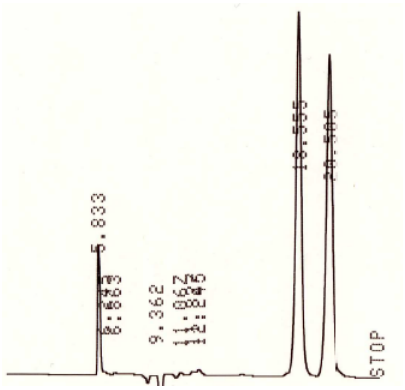
HPLC Chromatographic Conditions

Column: Daicel CHIRALPAC® IF (ϕ 0.46 cm, L 25 cm); Eluent: *n*–hexane/EtOH = 80/20; Flow rate: 0.5 mL/min; UV detection: 254 nm.



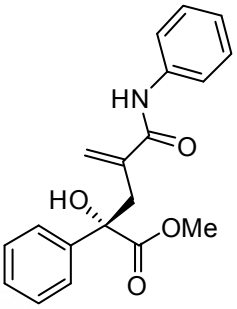
3b

Racemic standard of **3b**

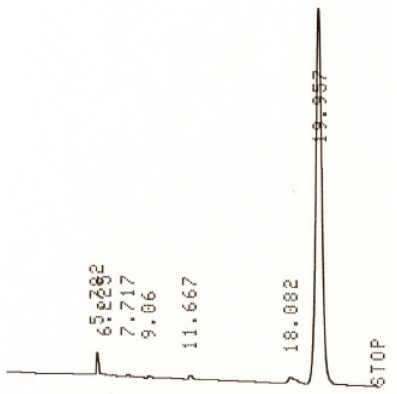


TIME	AREA	MK	IDNO	CONC
5.833	16494			6.7429
6.245	305	V		0.1248
6.863	363			0.1484
9.362	21197			8.6656
11.067	792			0.3238
11.827	801			0.3273
12.245	1384	V		0.5656
18.555	101730			41.5876
20.505	101550			41.5141
TOTAL	244615			100

Enantiomerically enriched (*S*)–**3b** (98% ee)



(*S*)-**3b**

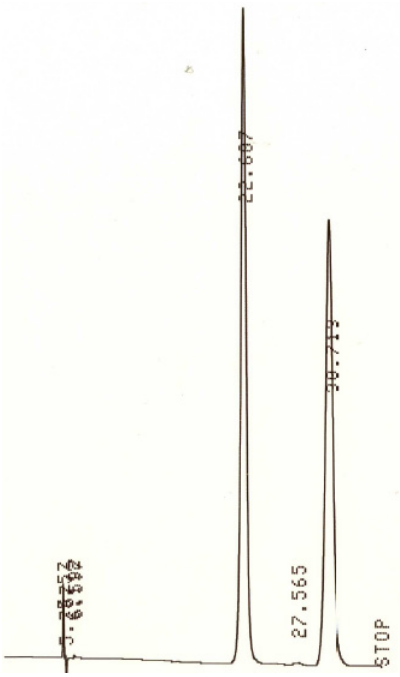


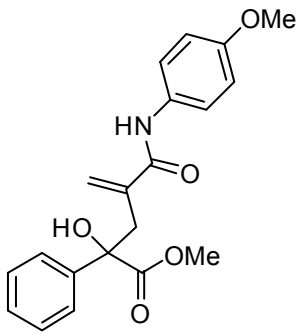
TIME	AREA	MK	IDNO	CONC
5.782	2444			2.0541
6.225	113			0.0948
7.717	458			0.3847
9.06	363			0.3052
11.667	701			0.5889
18.082	894			0.7515
19.957	113990			95.8207
TOTAL	118962			100

HPLC Chromatographic Conditions

Column: Daicel CHIRALPAC® IF (ϕ 0.46 cm, L 25 cm); Eluent: *n*–hexane/EtOH = 70/30; Flow rate: 0.5 mL/min; UV detection: 254 nm.

Racemic standard of **3c**

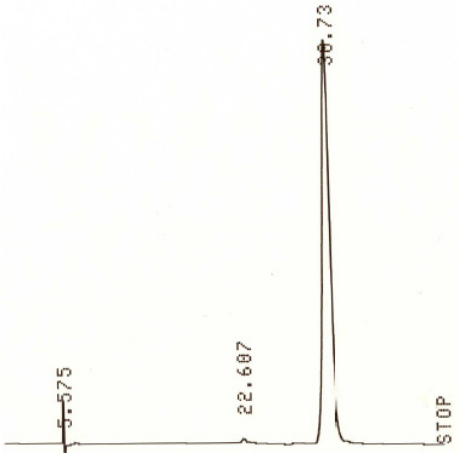


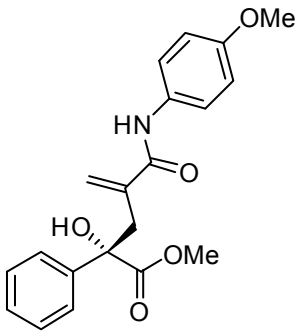


3c

TIME	AREA	MK	IDNO	CONC
5.57	5698			1.0853
5.767	741			0.1411
6.112	6595			1.2562
6.597	905	V		0.1723
22.607	254887			48.5481
27.565	1041			0.1983
30.713	255153			48.5987
TOTAL	525019			100

Enantiomerically enriched (*S*)–**3c** (99% ee)





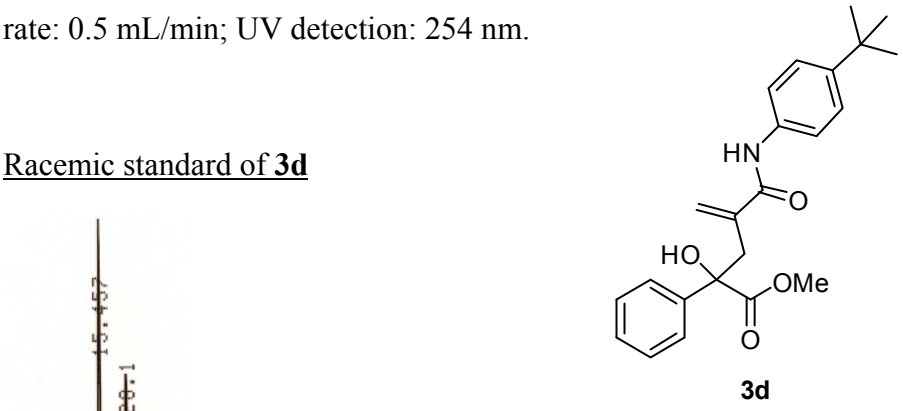
(*S*)-**3c**

TIME	AREA	MK	IDNO	CONC
5.575	4165			1.7815
22.607	1148			0.4912
30.73	228463			97.7272
TOTAL	233776			100

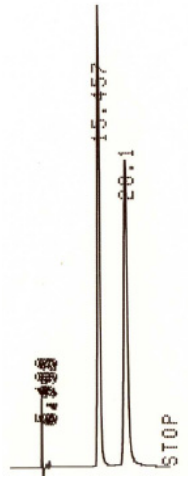
HPLC Chromatographic Conditions

Column: Daicel CHIRALPAC® IA (ϕ 0.46 cm, L 25 cm); Eluent: *n*–hexane/EtOH = 70/30; Flow rate: 0.5 mL/min; UV detection: 254 nm.

Racemic standard of **3d**

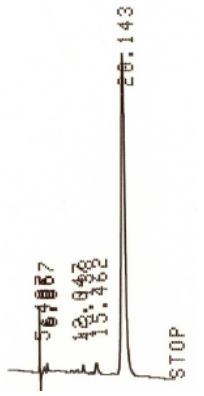


3d

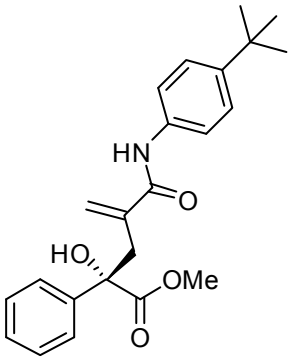


TIME	AREA	MK	IDNO	CONC
5.482	7446			2.5113
6.003	9892			3.3364
6.245	5590	V		1.8854
6.552	985	V		0.3323
6.733	1814	V		0.6117
15.457	135203			45.6022
20.1	135554			45.7206
TOTAL	296483			100

Enantiomerically enriched (*S*)–**3d** (98% ee)



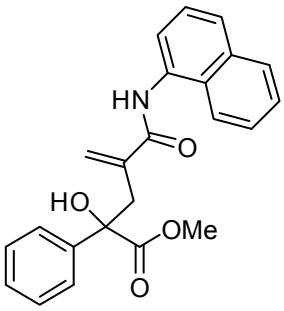
TIME	AREA	MK	IDNO	CONC
5.487	7107			3.9475
6.067	9795			5.44
6.25	6807	V		3.7808
6.8	2981	V		1.6555
12.047	798			0.4431
13.138	1673			0.9294
15.462	3348			1.8597
20.143	147539			81.944
TOTAL	180049			100



(*S*)-**3d**

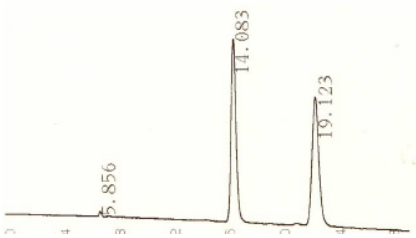
HPLC Chromatographic Conditions

Column: Daicel CHIRALPAC® IC (ϕ 0.46 cm, L 25 cm); Eluent: *n*–hexane/EtOH = 70/30; Flow rate: 0.5 mL/min; UV detection: 254 nm.

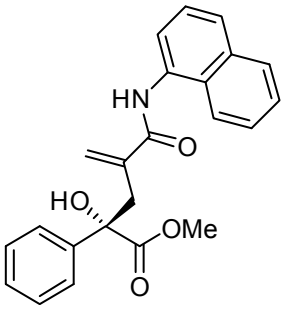


3e

Racemic standard of **3e**

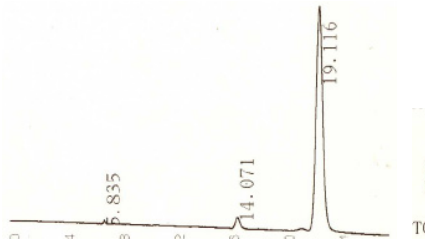


TIME	AREA	HEIGHT	MK	IDNO	CONC
5.856	611	57			0.7528
14.083	40468	1933			49.8245
19.123	40141	1363			49.4227
TOTAL	81220	3353			100



(*S*)-**3e**

Enantiomerically enriched (*S*)–**3e** (93% ee)

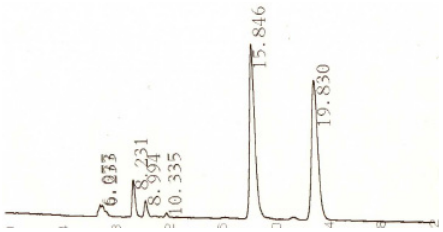


TIME	AREA	HEIGHT	MK	IDNO	CONC
5.835	326	44			0.451
14.071	2540	122			3.5151
19.116	69400	2362			96.0339
TOTAL	72266	2529			100

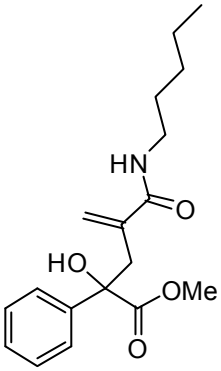
HPLC Chromatographic Conditions

Column: Daicel CHIRALPAC® IC (ϕ 0.46 cm, L 25 cm); Eluent: *n*–hexane/EtOH = 80/20; Flow rate: 0.5 mL/min; UV detection: 254 nm.

Racemic standard of **3f**

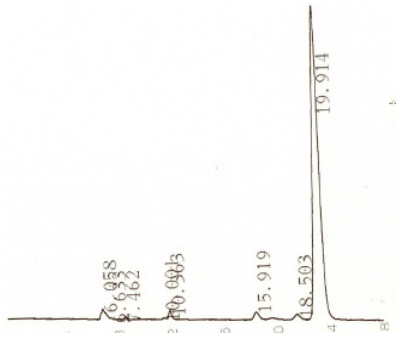


TIME	AREA	HEIGHT	MK	IDNO	CONC
6.077	1430	126			1.4748
6.233	2095	119	V		2.1609
8.231	5283	401			5.4494
8.994	2441	176			2.5183
10.335	522	43			0.5384
15.846	42372	1863			43.7077
19.83	42801	1492			44.1506
TOTAL	96944	4220			100

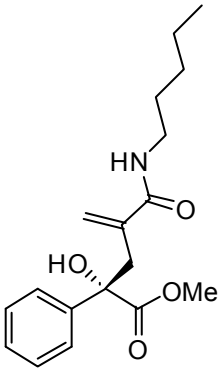


3f

Enantiomerically enriched (*S*)–**3f** (96% ee)



TIME	AREA	HEIGHT	MK	IDNO	CONC
6.058	2498	115			2.3648
6.633	161	14	V		0.1519
7.462	297	27			0.2814
10.001	176	17			0.167
10.363	1408	105	V		1.3327
15.919	1825	84			1.7281
18.503	1521	60			1.4396
19.914	97746	3381			92.5345
TOTAL	105632	3803			100

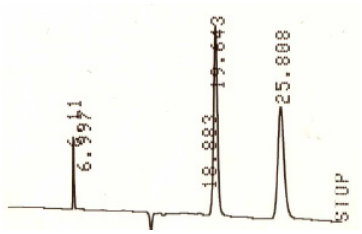


(*S*)-**3f**

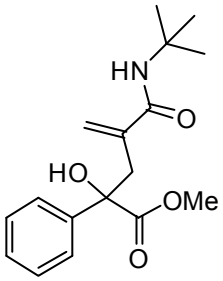
HPLC Chromatographic Conditions

Column: Daicel CHIRALPAC® IF (ϕ 0.46 cm, L 25 cm); Eluent: *n*–hexane/EtOH = 90/10; Flow rate: 0.5 mL/min; UV detection: 254 nm.

Racemic standard of **3g**

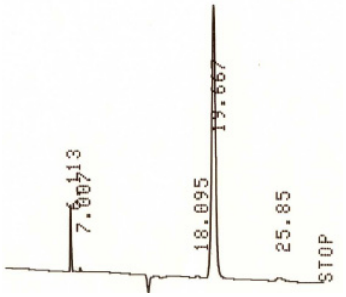


TIME	AREA	MK	IDNO	CONC
6.11	5919			5.3931
6.997	177			0.1615
18.883	73			0.0661
19.643	52265	V		47.6185
25.808	51324			46.7609
TOTAL	109759			100

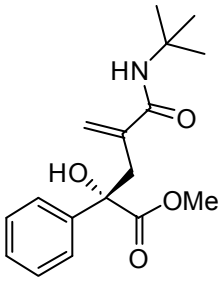


3g

Enantiomerically enriched (*S*)–**3g** (96% ee)



TIME	AREA	MK	IDNO	CONC
6.113	5421			6.535
7.007	442			0.5326
18.095	593			0.7154
19.667	74996			90.4155
25.85	1494			1.8014
TOTAL	82946			100

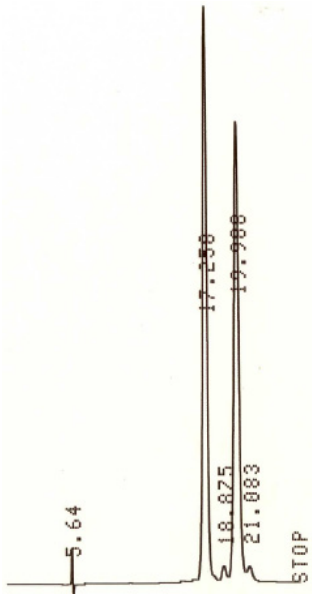


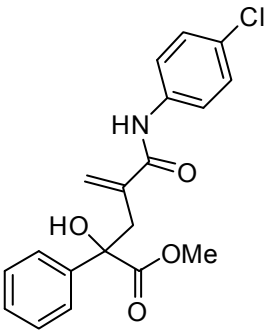
(*S*)-**3g**

HPLC Chromatographic Conditions

Column: Daicel CHIRALPAC® IF (ϕ 0.46 cm, L 25 cm); Eluent: *n*–hexane/EtOH = 80/20; Flow rate: 0.5 mL/min; UV detection: 254 nm.

Racemic standard of **3h**

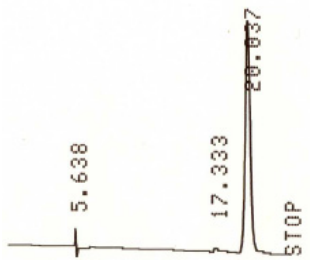




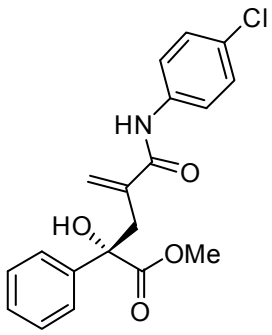
3h

TIME	AREA	MK	IDNO	CONC
5.64	2803			0.9792
17.258	137292			47.9593
18.875	4200	V		1.4672
19.988	136865	V		47.8102
21.083	5107	V		1.7841
TOTAL	286268			100

Enantiomerically enriched (*S*)–**3h** (97% ee)



TIME	AREA	MK	IDNO	CONC
5.638	1470			2.1439
17.333	1023			1.4916
20.037	66088			96.3646
TOTAL	68582			100

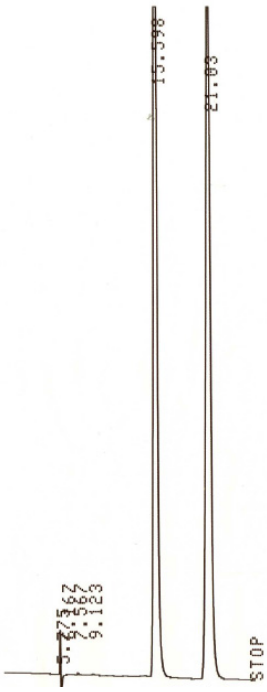


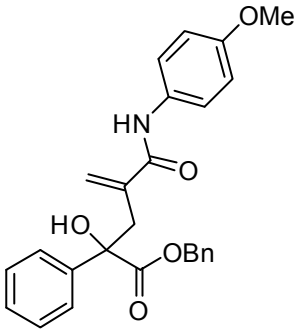
(*S*)-**3h**

HPLC Chromatographic Conditions

Column: Daicel CHIRALPAC® IC (ϕ 0.46 cm, L 25 cm); Eluent: *n*–hexane/EtOH = 70/30; Flow rate: 0.5 mL/min; UV detection: 254 nm.

Racemic standard of **3i**

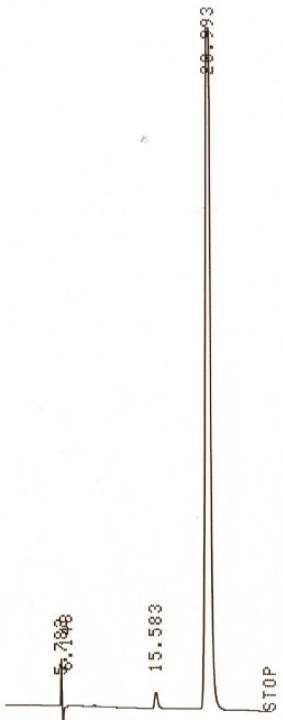


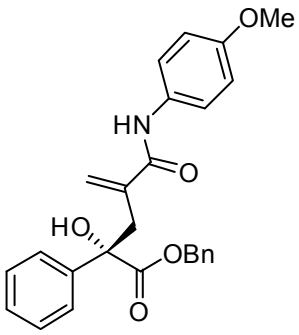


3i

TIME	AREA	MK	IDNO	CONC
5.775	4993			0.8262
6.167	3102			0.5133
7.567	236			0.039
9.123	273			0.0452
15.598	297745			49.2646
21.03	298029			49.3117
TOTAL	604378			100

Enantiomerically enriched (*S*)–**3i** (98% ee)





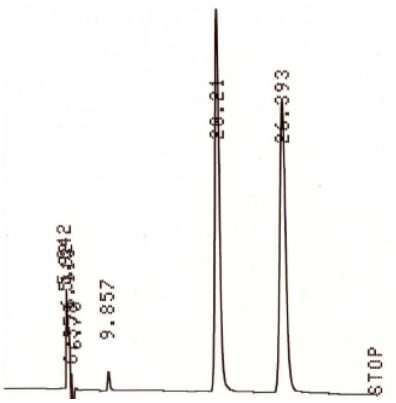
(*S*)-**3i**

TIME	AREA	MK	IDNO	CONC
5.782	6092			1.7619
6.148	3401			0.9837
15.583	4136			1.1961
20.993	332132			96.0582
TOTAL	345761			100

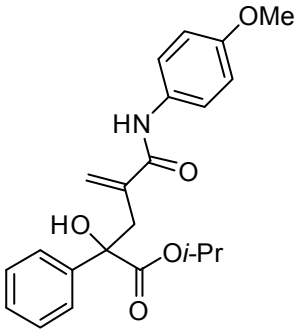
HPLC Chromatographic Conditions

Column: Daicel CHIRALPAC® IC (ϕ 0.46 cm, L 25 cm); Eluent: *n*–hexane/EtOH = 80/20; Flow rate: 0.5 mL/min; UV detection: 254 nm.

Racemic standard of **3j**

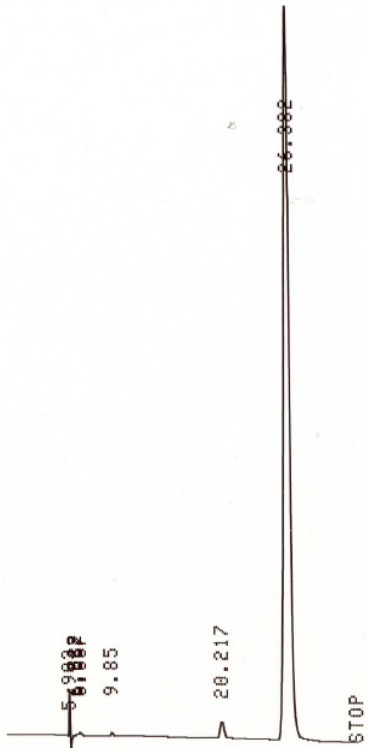


TIME	AREA	MK	IDNO	CONC
5.342	1582			0.567
5.92	12323	V		4.4161
6.113	8028	V		2.877
6.358	1729			0.6198
6.73	3957			1.4179
9.857	2746			0.9841
20.21	124682			44.6826
26.393	123993			44.4356
TOTAL	279039			100

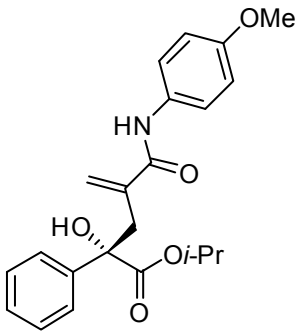


3j

Enantiomerically enriched (*S*)–**3j** (97% ee)



TIME	AREA	MK	IDNO	CONC
5.903	3489			1.0899
6.282	3199			0.9994
6.567	1264	V		0.395
6.867	1637	V		0.5114
9.85	492			0.1538
20.217	5035			1.5728
26.382	305019			95.2777
TOTAL	320137			100

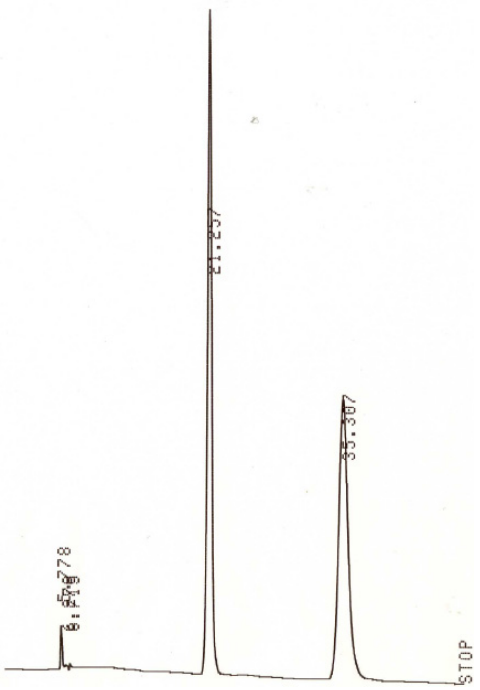


(*S*)-**3j**

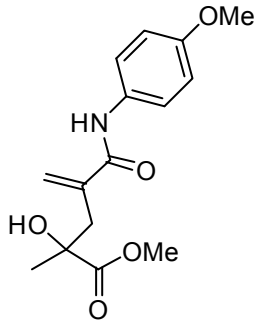
HPLC Chromatographic Conditions

Column: Daicel CHIRALPAC® IF (ϕ 0.46 cm, L 25 cm); Eluent: *n*–hexane/EtOH = 70/30; Flow rate: 0.5 mL/min; UV detection: 254 nm.

Racemic standard of **3k**

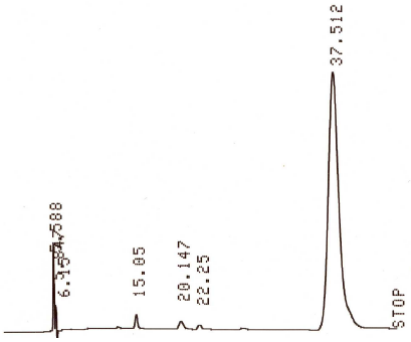


TIME	AREA	MK	IDNO	CONC
5.778	6645			1.3689
6.278	1169	V		0.2408
6.715	619			0.1275
21.257	238344			49.1028
35.307	238621			49.16
TOTAL	485397			100

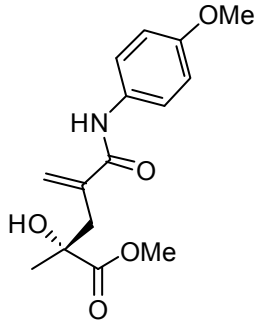


3k

Enantiomerically enriched (*R*)–**3k** (99% ee)



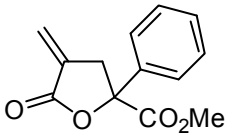
TIME	AREA	MK	IDNO	CONC
5.588	11989			3.7275
5.847	6313	V		1.9628
6.15	3687			1.1464
15.05	3594			1.1174
20.147	3188			0.9913
22.25	1768			0.5498
37.512	291087			90.5049
TOTAL	321626			100



(*R*)-**3k**

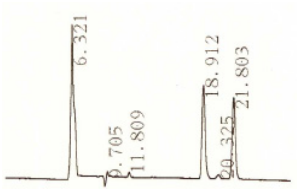
HPLC Chromatographic Conditions

Column: Daicel CHIRALPAC® IE (ϕ 0.46 cm, L 25 cm); Eluent: *n*–hexane/EtOH = 80/20; Flow rate: 0.5 mL/min; UV detection: 254 nm.



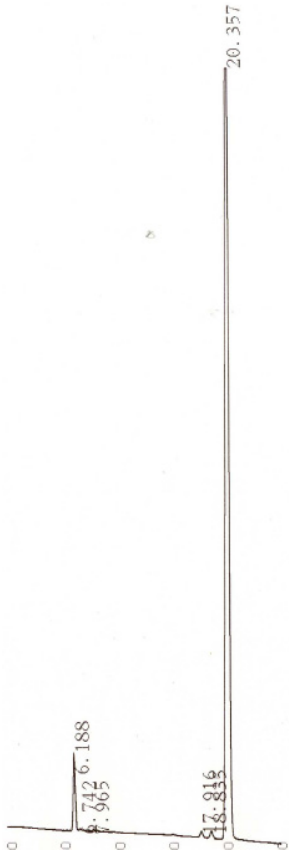
4a

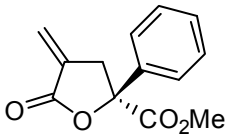
Racemic standard of **4a**



TIME	AREA	HEIGHT	MK	IDNO	CONC
6.321	33896	1635			43.8226
9.705	1778	117			2.2981
11.809	713	55			0.9218
18.912	20572	1002			26.5961
20.325	925	45			1.1955
21.803	19465	874			25.1659
TOTAL	77348	3728			100

Enantiomerically enriched (*S*)–**4a** (99% ee)





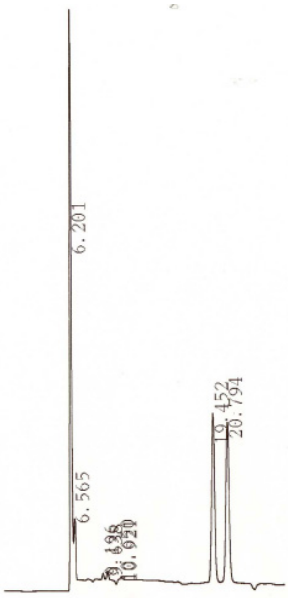
(*S*)-**4a**

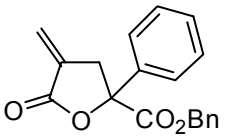
TIME	AREA	HEIGHT	MK	IDNO	CONC
6.188	11036	829			4.5713
6.742	199	18	V		0.0824
7.965	225	23			0.0933
17.916	1085	63			0.4493
18.835	1533	82			0.6351
20.357	227333	10827			94.1686
TOTAL	241411	11842			100

HPLC Chromatographic Conditions

Column: Daicel CHIRALPAC® IE (ϕ 0.46 cm, L 25 cm); Eluent: *n*–hexane/EtOH = 80/20; Flow rate: 0.5 mL/min; UV detection: 254 nm.

Racemic standard of **4b**

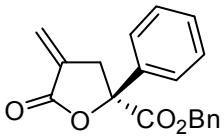




4b

TIME	AREA	HEIGHT	MK	IDNO	CONC
6.201	72384	6244			45.6854
6.565	8424	704	V		5.3167
9.196	832	71			0.5251
9.638	1151	98	V		0.7266
10.65	460	39			0.2906
10.921	835	49	V		0.5273
19.452	37080	1839			23.4034
20.794	37273	1734			23.5249
TOTAL	158440	10777			100

Enantiomerically enriched (*S*)–**4b** (98% ee)



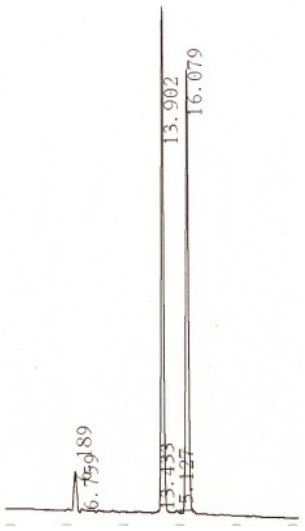
(*S*)-**4b**

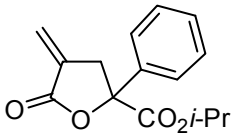
TIME	AREA	HEIGHT	MK	IDNO	CONC
6.191	2873	165			3.597
6.747	238	23			0.2981
9.463	1935	172			2.4221
12.445	4496	320			5.6285
18.599	873	47			1.0934
19.865	69458	3440			86.9609
TOTAL	79872	4166			100

HPLC Chromatographic Conditions

Column: Daicel CHIRALPAC® IE (ϕ 0.46 cm, L 25 cm); Eluent: *n*–hexane/EtOH = 80/20; Flow rate: 0.5 mL/min; UV detection: 254 nm.

Racemic standard of **4c**

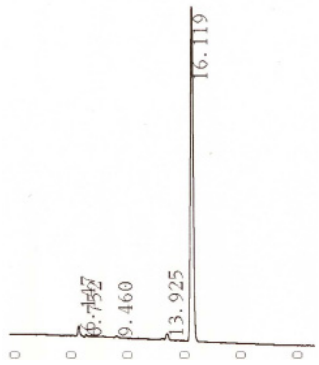


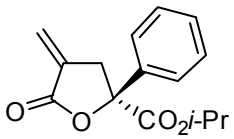


4c

TIME	AREA	HEIGHT	MK	IDNO	CONC
6.189	6845	405			4.3533
6.759	381	37			0.2423
13.433	162	13			0.103
13.902	74514	5064	V		47.3876
15.127	371	23			0.2359
16.079	74970	4455	V		47.6779
TOTAL	157243	9997			100

Enantiomerically enriched (*S*)–**4c** (97% ee)





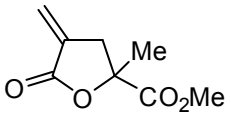
(*S*)-**4c**

TIME	AREA	HEIGHT	MK	IDNO	CONC
6.147	1661	112			2.8194
6.752	324	32			0.5496
9.46	246	18			0.4169
13.925	942	66			1.5983
16.119	55741	3371			94.6158
TOTAL	58913	3599			100

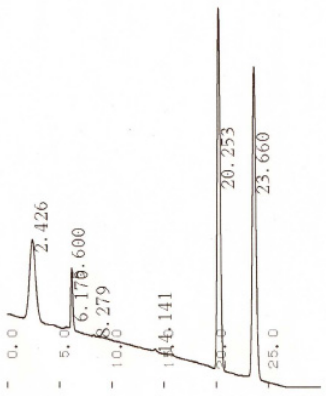
HPLC Chromatographic Conditions

Column: Daicel CHIRALPAC® IE (ϕ 0.46 cm, L 25 cm); Eluent: *n*–hexane/EtOH = 80/20; Flow rate: 0.5 mL/min; UV detection: 230 nm.

Racemic standard of **4d**

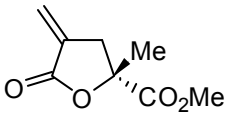


4d



TIME	AREA	HEIGHT	MK	IDNO	CONC
2.426	36617	876			17.7989
5.6	586	20			0.2846
6.17	9482	676	V		4.609
8.279	179	21			0.0869
14.141	395	26			0.1919
20.253	79164	3918			38.4802
23.66	79304	3372			38.5484
TOTAL	205727	8910			100

Enantiomerically enriched (*R*)–**4d** (99% ee)



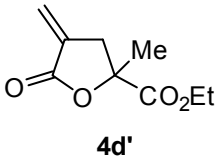
(*R*)-**4d**

TIME	AREA	HEIGHT	MK	IDNO	CONC
6.107	145989	16068			35.6272
6.782	75130	4503	SV		18.3347
7.1	138	24	T		0.0337
8.677	23311	522			5.6888
10.245	425	31			0.1037
10.741	351	24	V		0.0857
14.46	1006	60			0.2456
15.175	1075	64			0.2623
15.796	3629	180	V		0.8856
18.123	394	21			0.0961
20.285	157157	7629			38.3525
23.721	1164	51			0.2841
TOTAL	409769	29177			100

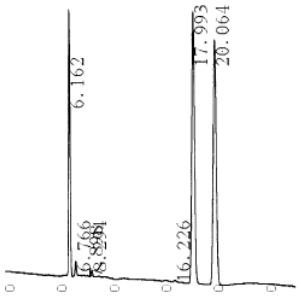
HPLC Chromatographic Conditions

Column: Daicel CHIRALPAC® IE (ϕ 0.46 cm, L 25 cm); Eluent: *n*–hexane/EtOH = 80/20; Flow rate: 0.5 mL/min; UV detection: 230 nm.

Racemic standard of **4d′**

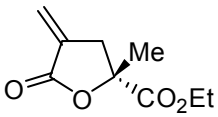


4d'

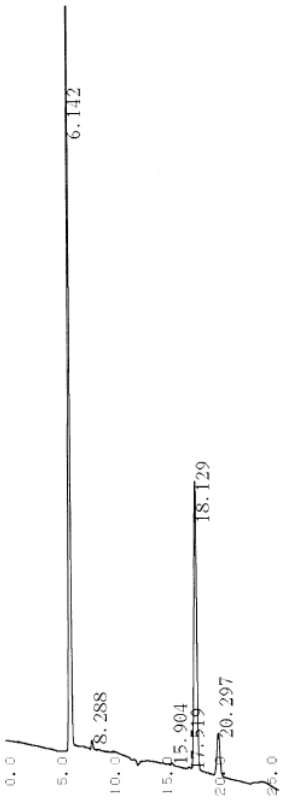


TIME	AREA	HEIGHT	MK	IDNO	CONC
6.162	27660	2900			20.2239
6.766	1543	166			1.1284
7.898	95	12			0.0698
8.294	719	72			0.5259
16.226	224	15			0.1641
17.993	53118	2968			38.8383
20.064	53407	2678			39.0497
TOTAL	136768	8811			100

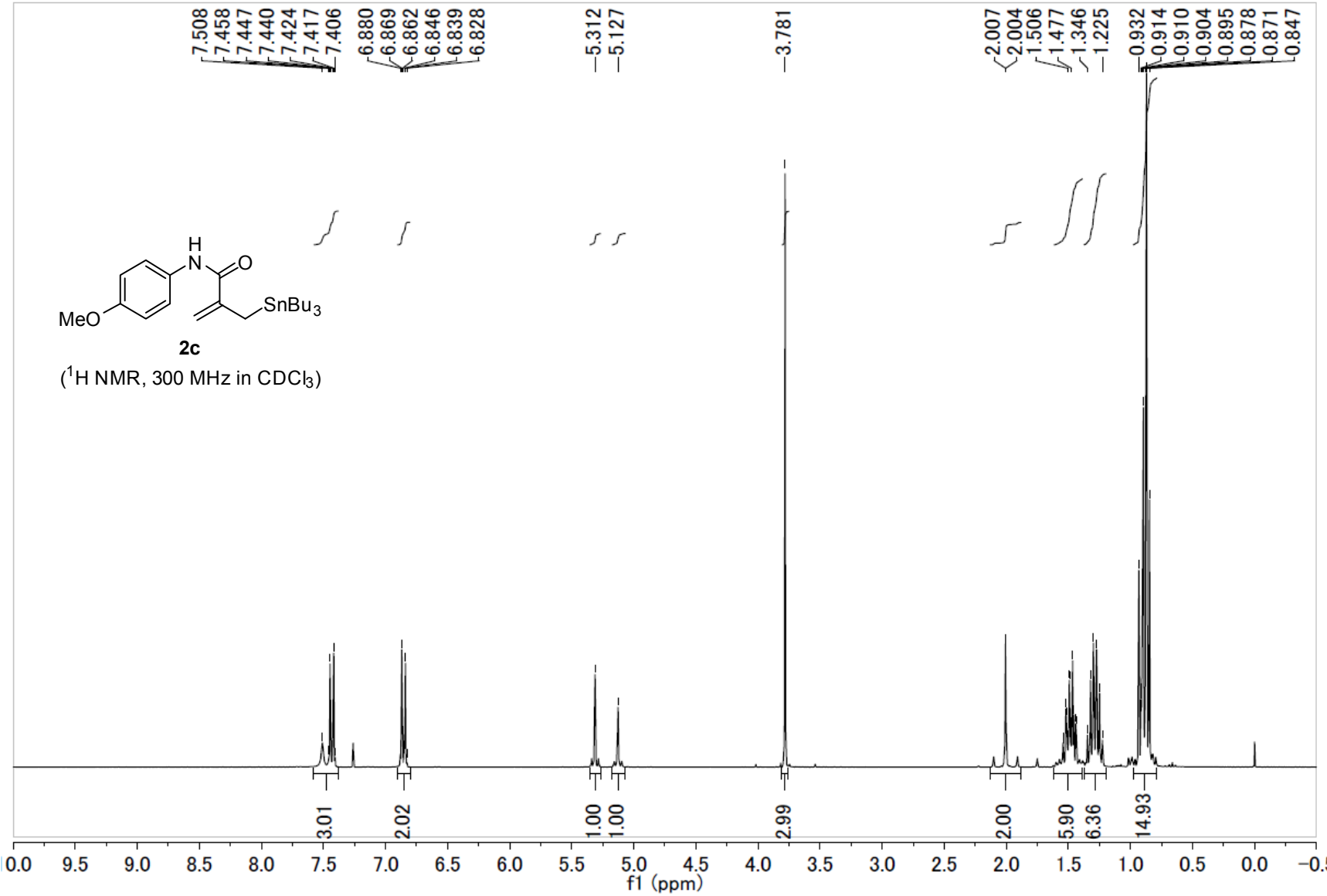
Enantiomerically enriched (*R*)–**4d′** (71% ee)



(*R*)-**4d'**

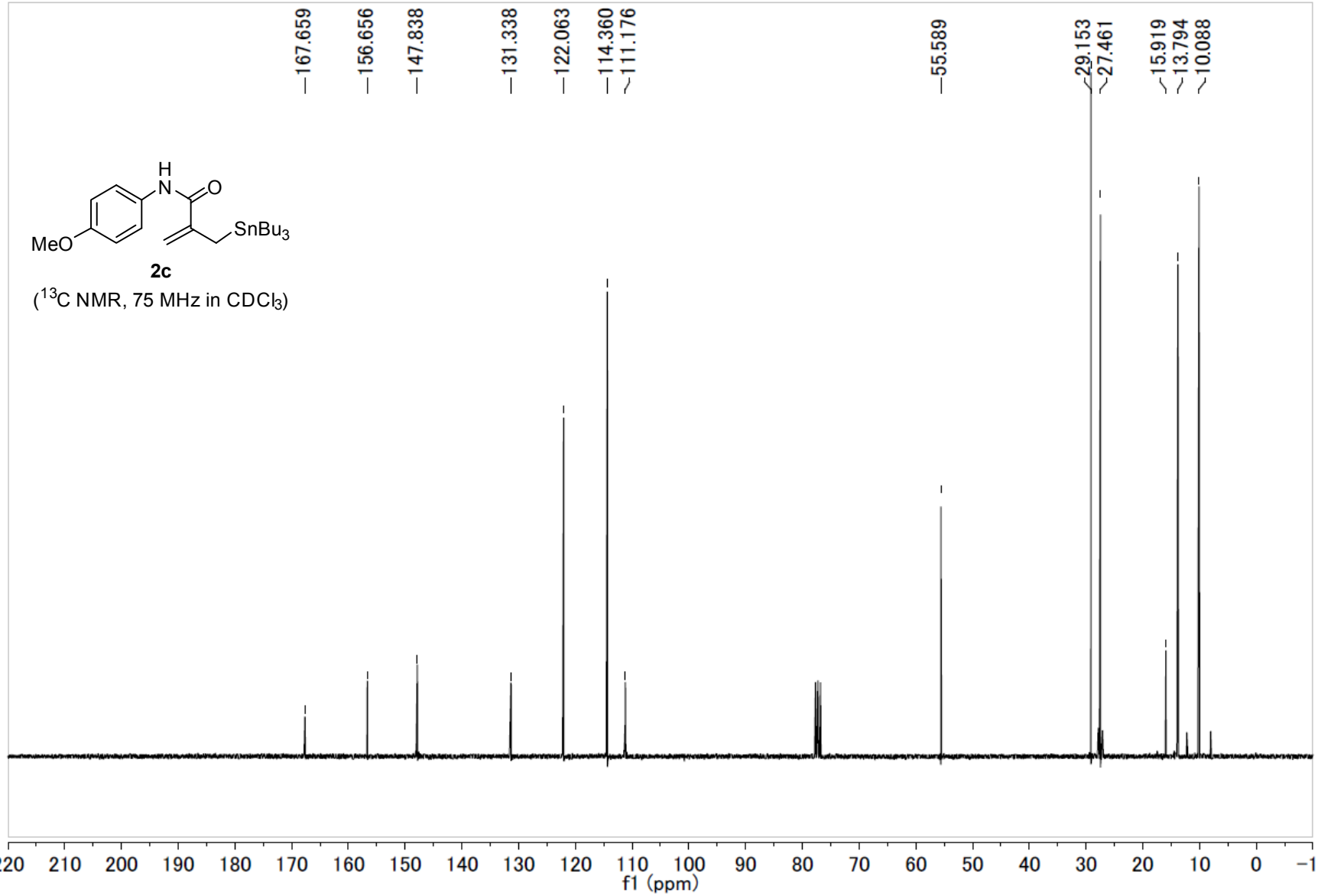


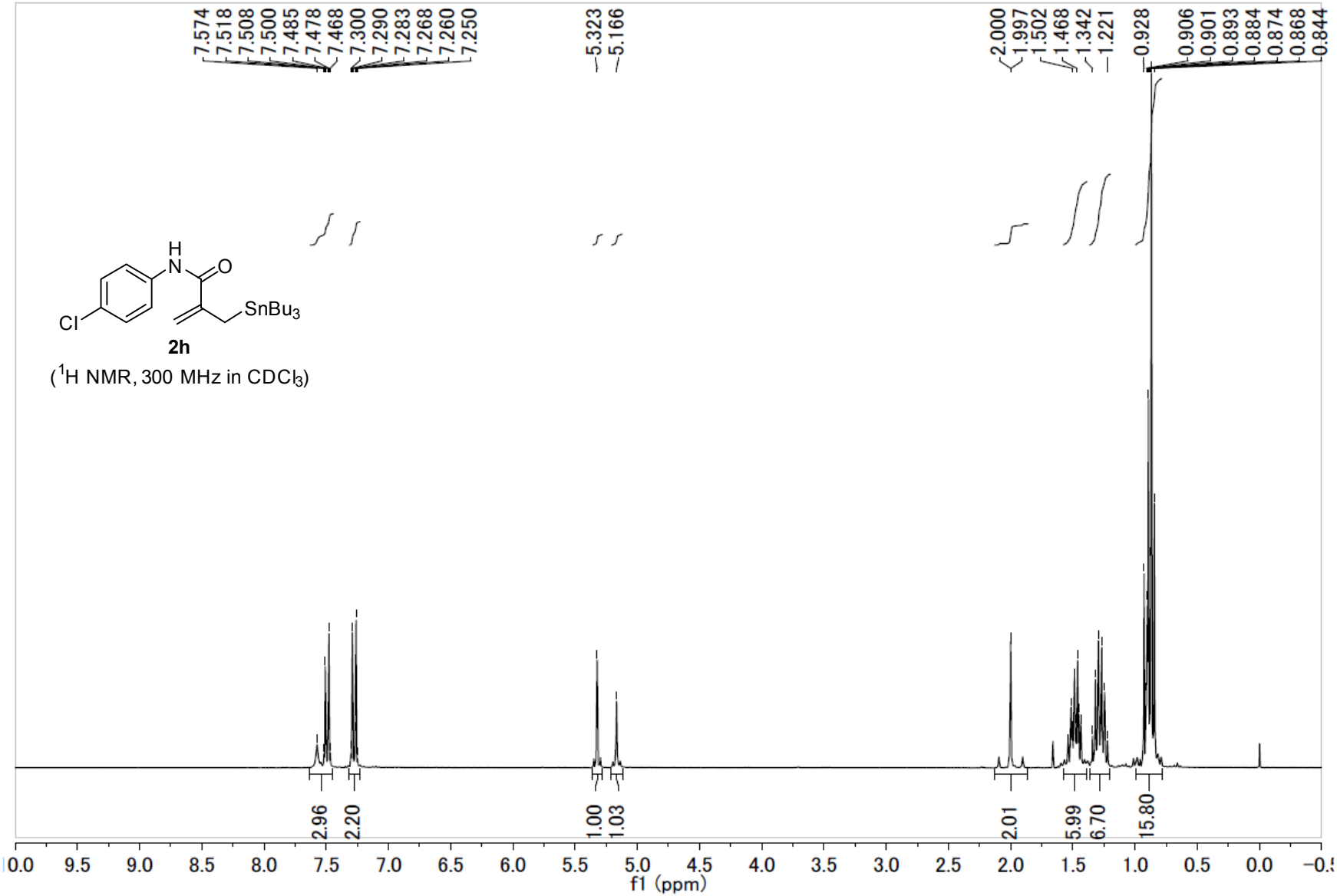
TIME	AREA	HEIGHT	MK	IDNO	CONC
6.142	98386	8470			58.8829
8.288	1157	111			0.6924
15.904	338	24			0.202
17.519	239	19			0.1432
18.129	57300	3151			34.2936
20.297	9668	474			5.786
TOTAL	167087	12249			100

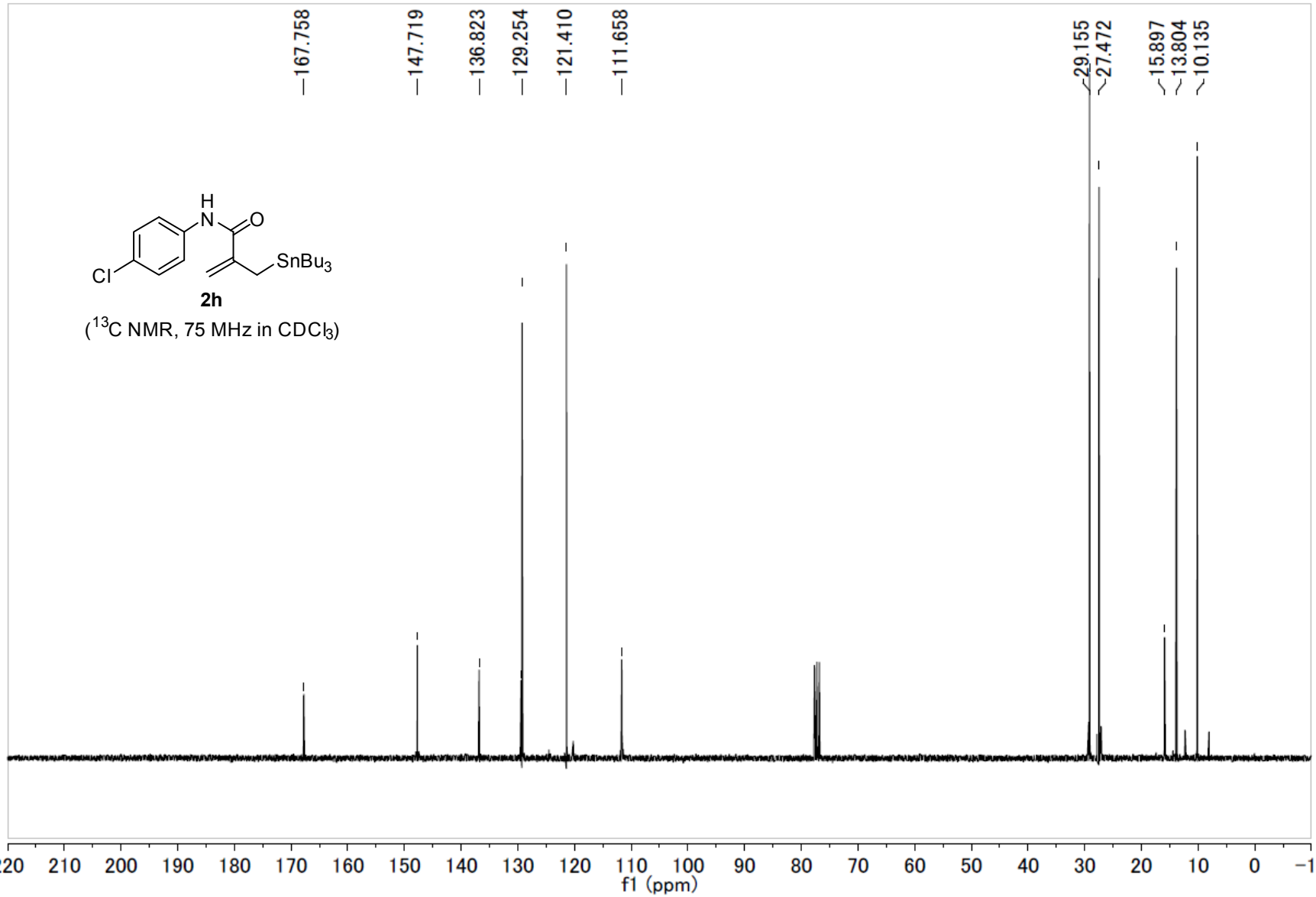


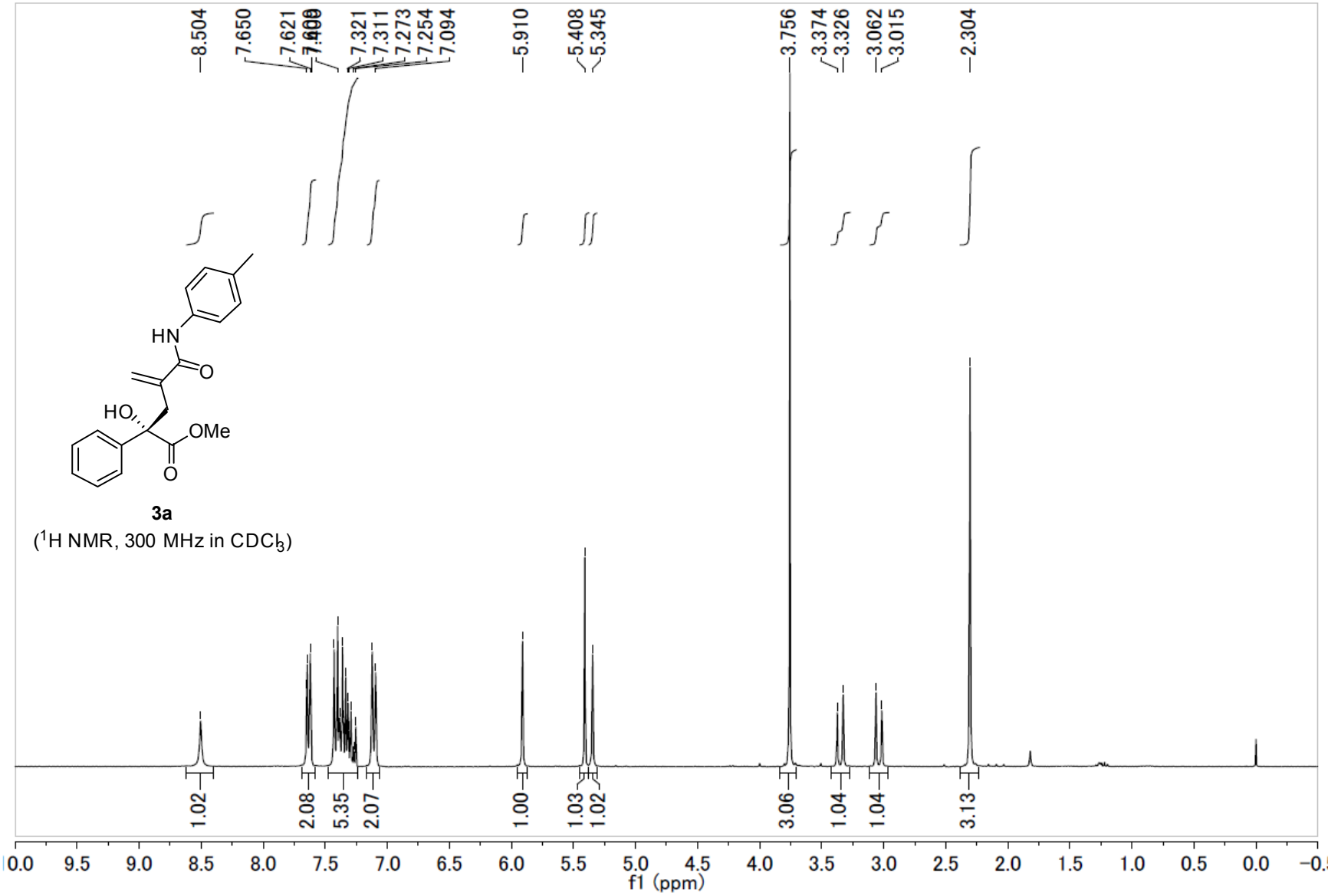
2c

(^{1}H NMR, 300 MHz in $CDCl_3$)


167.659
156.656
147.838
131.338
122.063
114.360
111.176
55.589
29.153
27.461
15.919
13.794
10.088
H
N
O
MeO
SnBu3
2c
(13C NMR, 75 MHz in CDCl3)
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)

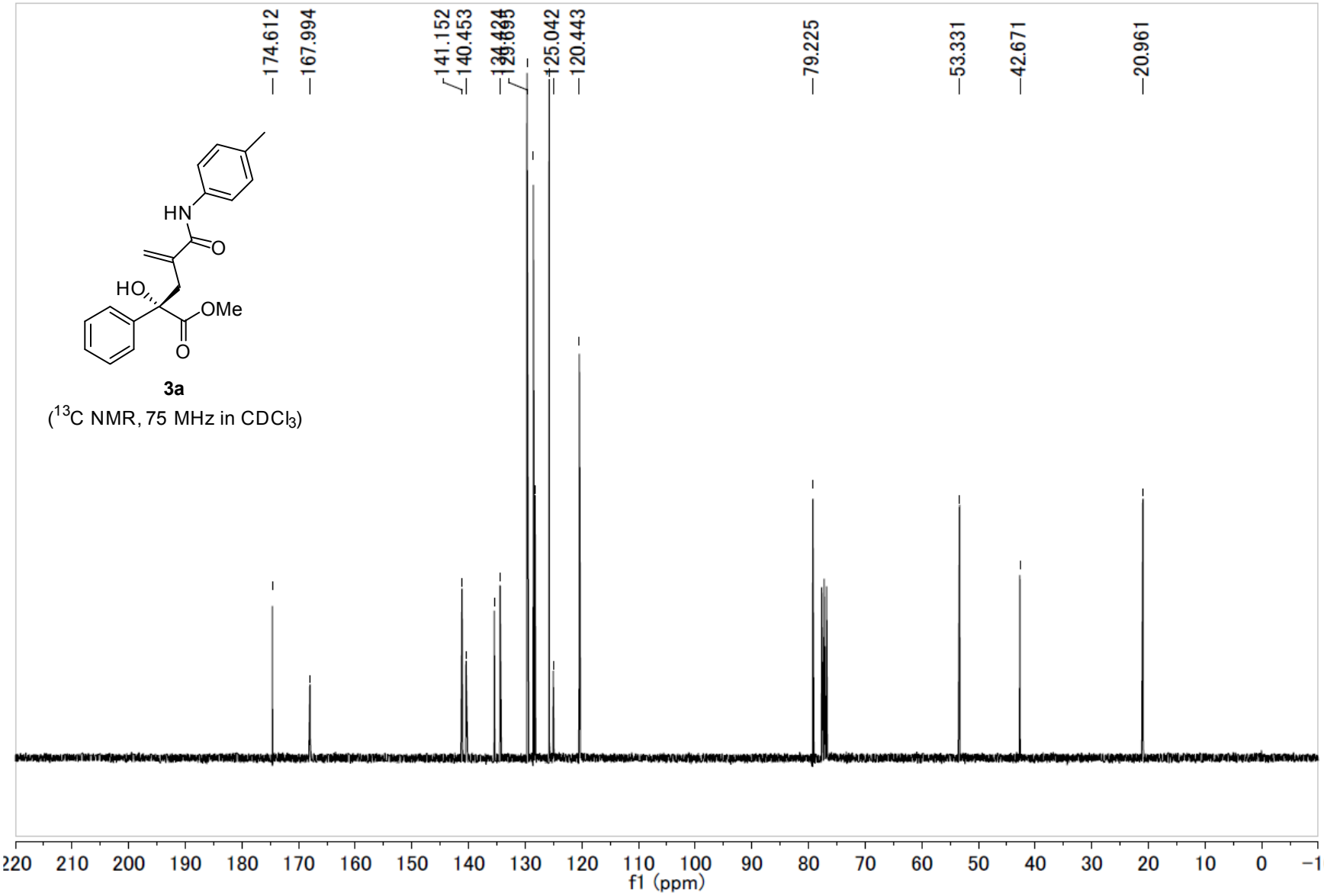

7.574
7.518
7.508
7.500
7.485
7.478
7.468
7.300
7.290
7.283
7.268
7.260
7.250
5.323
5.166
2.000
1.997
1.502
1.468
1.342
1.221
0.928
0.906
0.901
0.893
0.884
0.874
0.868
0.844
H
N
O
Cl
SnBu3
2h
(1H NMR, 300 MHz in CDCl3)
2.96
2.20
1.00
1.03
2.01
5.99
6.70
15.80
f1 (ppm)


167.758
147.719
136.823
129.254
121.410
111.658
29.155
27.472
15.897
13.804
10.135
H
N
O
Cl
SnBu3
2h
(13C NMR, 75 MHz in CDCl3)
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)



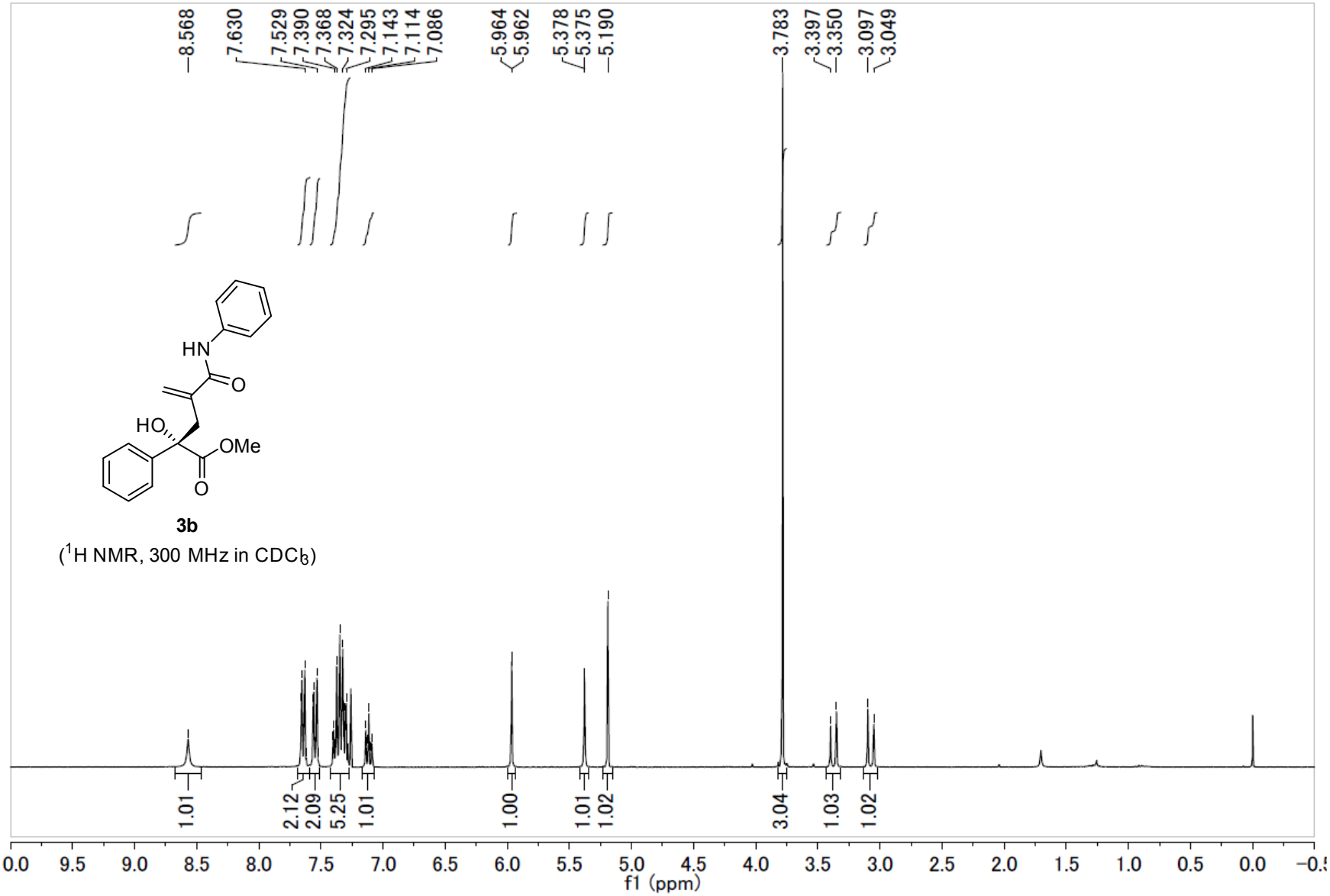
3a

(^{1}H NMR, 300 MHz in $CDCl_3$)



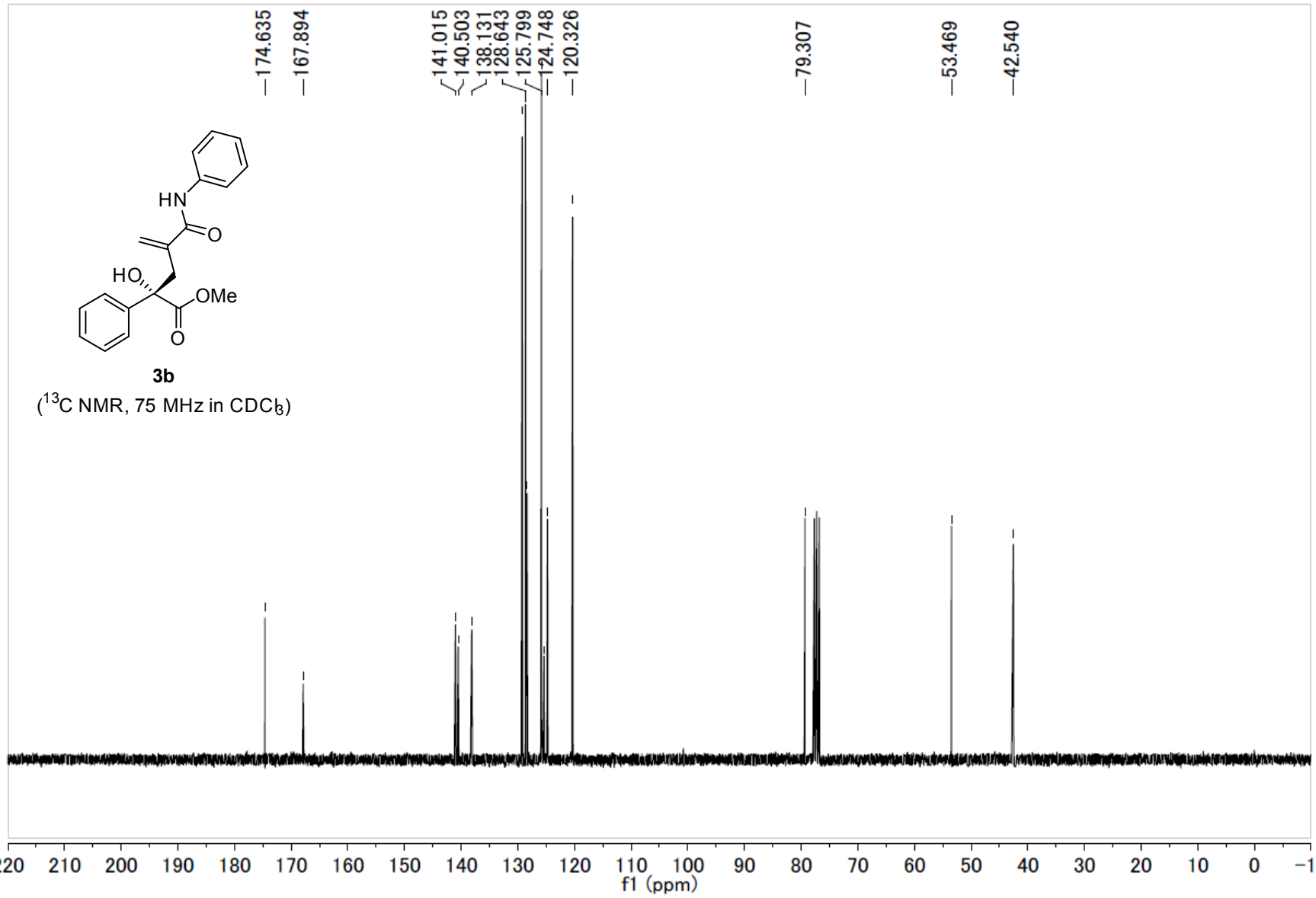
3a

(^{13}C NMR, 75 MHz in $CDCl_3$)



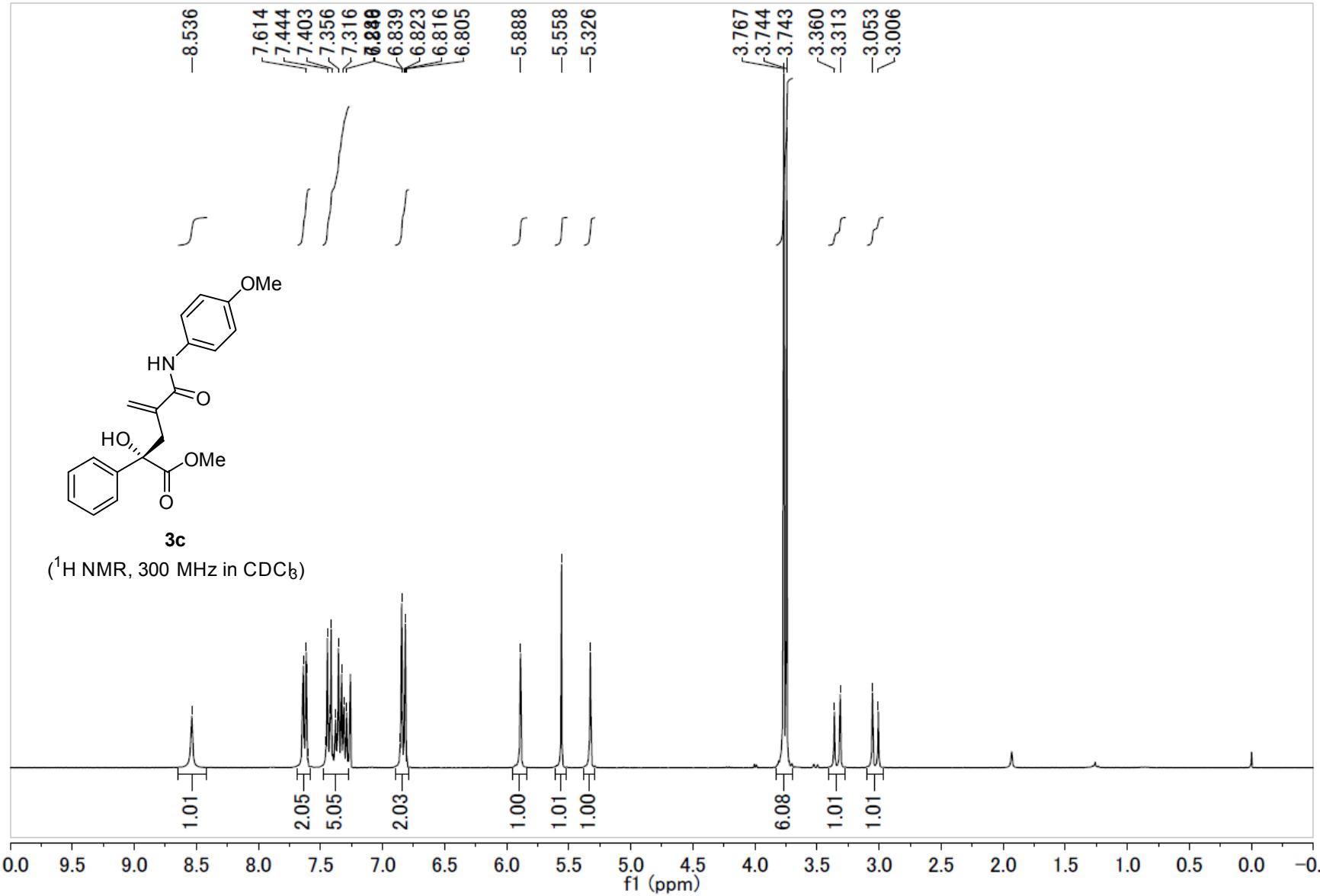
3b

(^{1}H NMR, 300 MHz in $CDCl_3$)



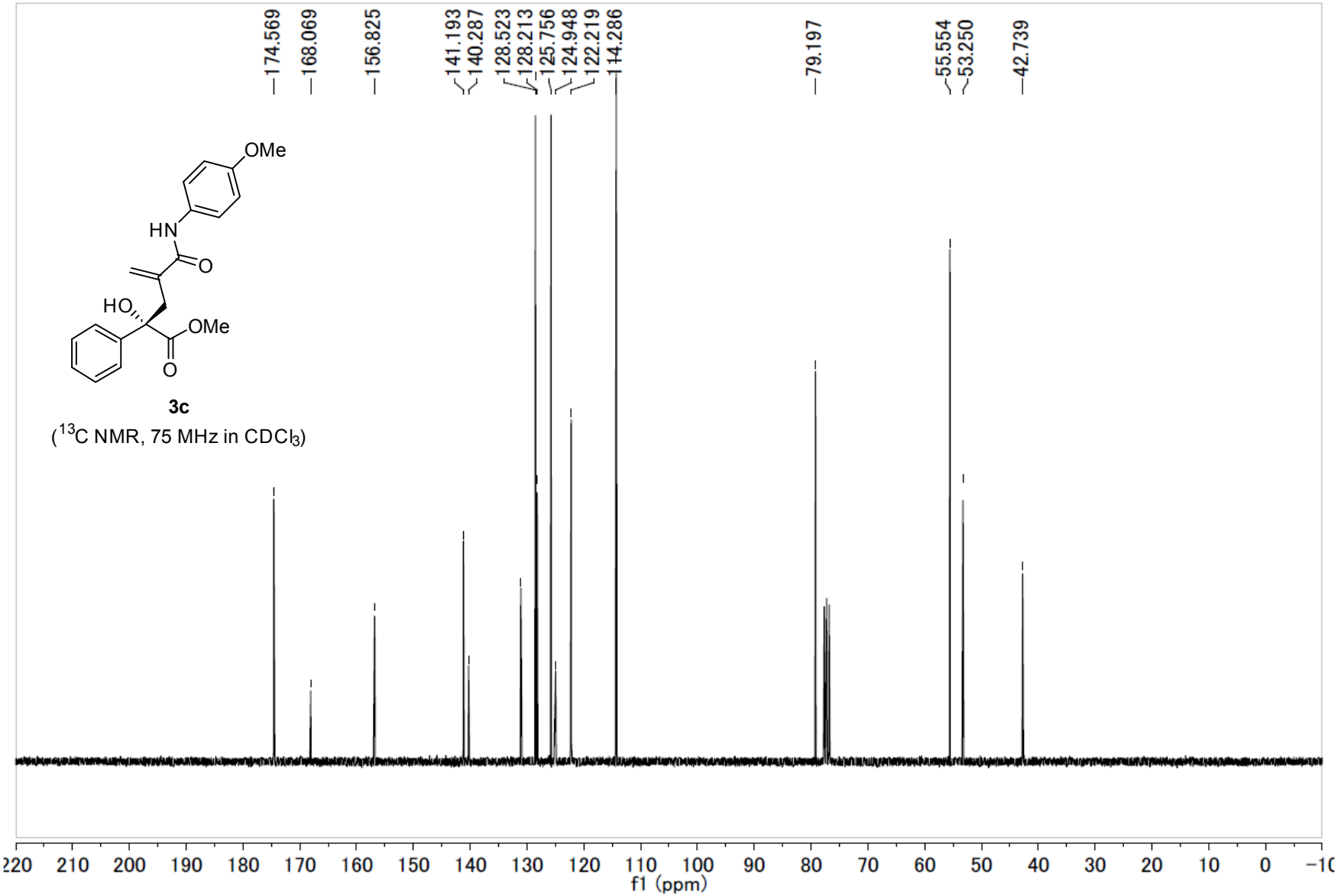
3b

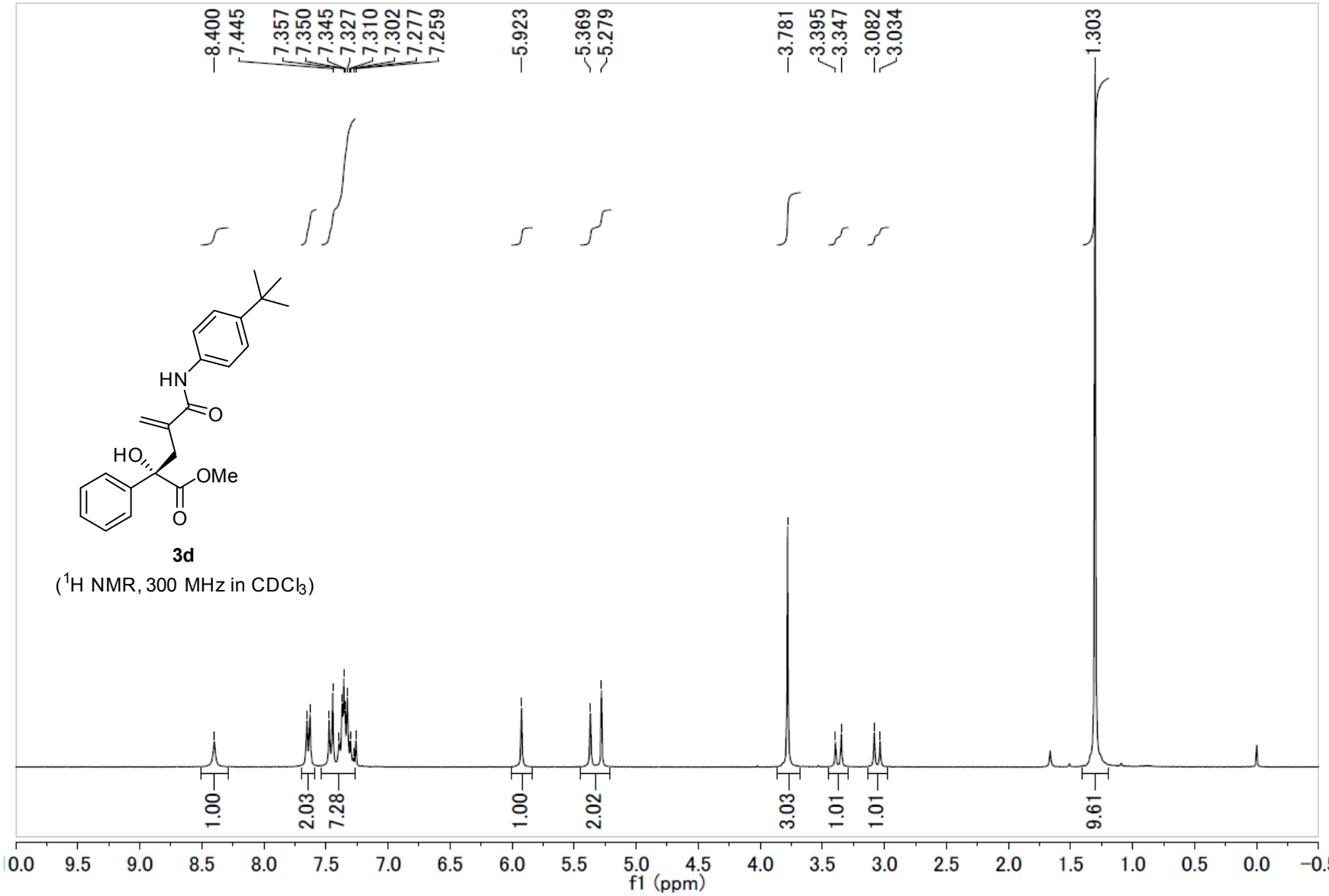
(^{13}C NMR, 75 MHz in $CDCl_3$)



3c

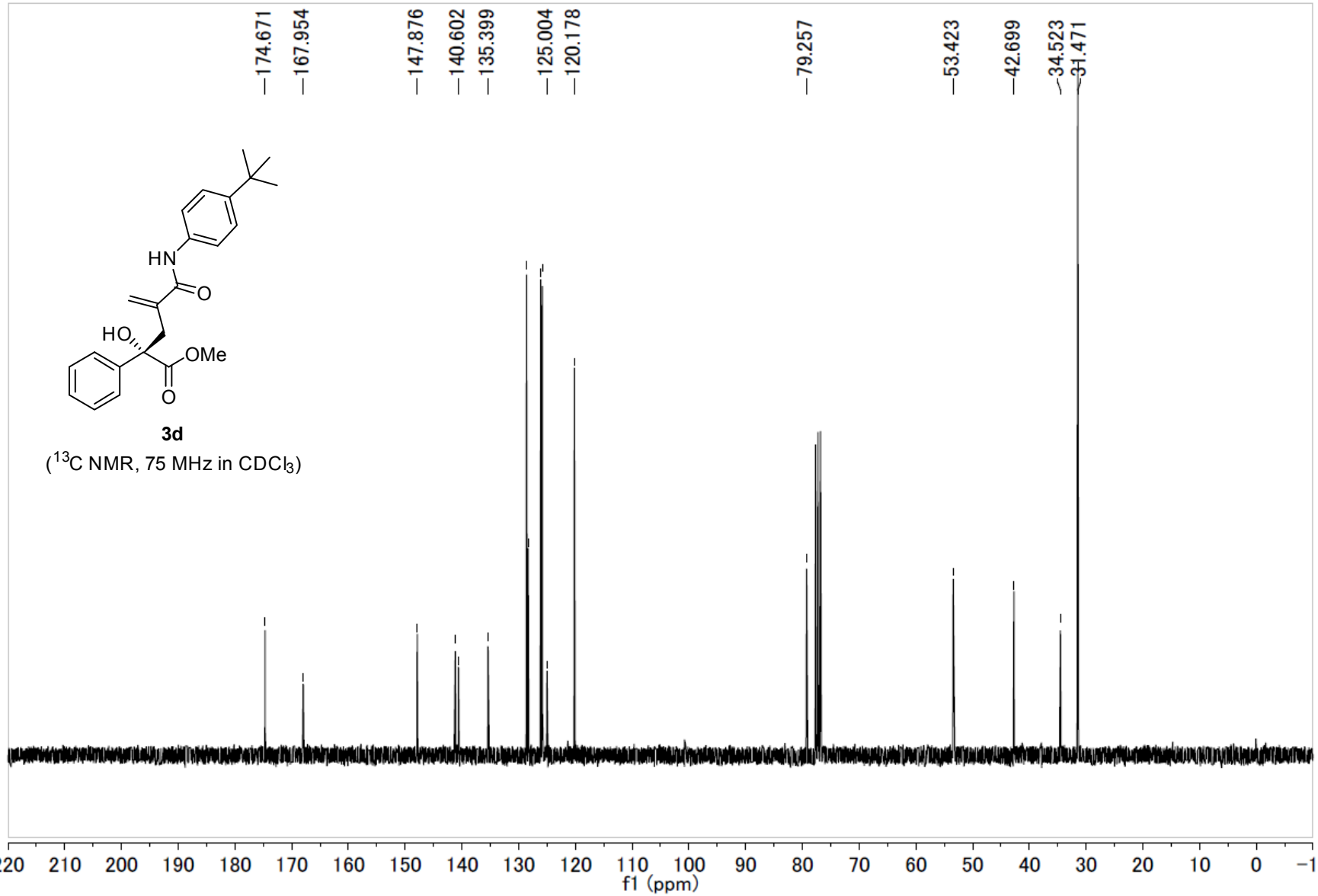
(^{1}H NMR, 300 MHz in $CDCl_3$)

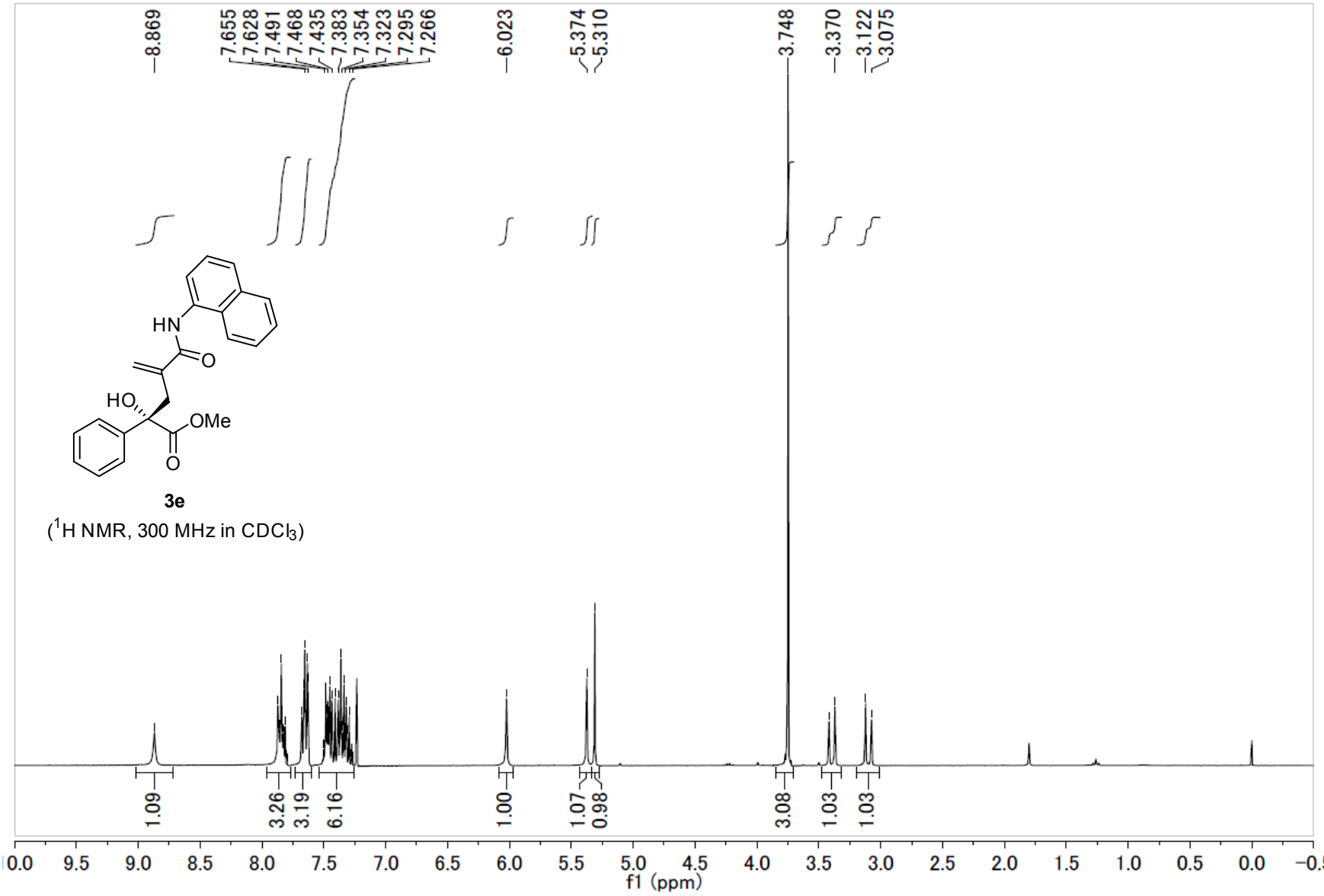

174.569
168.069
156.825
141.193
140.287
128.523
128.213
125.756
124.948
122.219
114.286
79.197
55.554
53.250
42.739
OMe
HN
O
HO
OMe
O
3c
(13C NMR, 75 MHz in CDCl3)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



3d

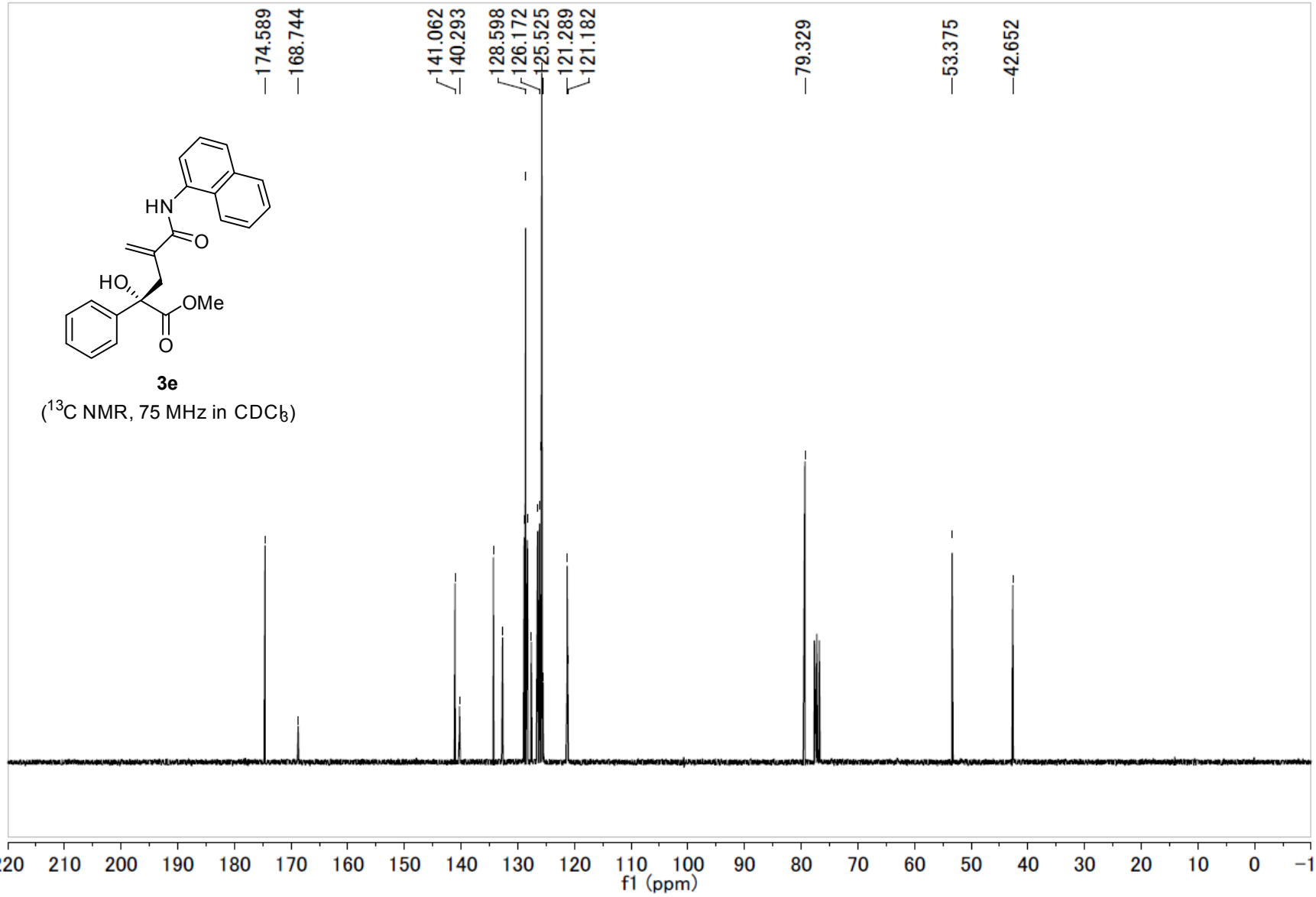
(^{1}H NMR, 300 MHz in $CDCl_3$)

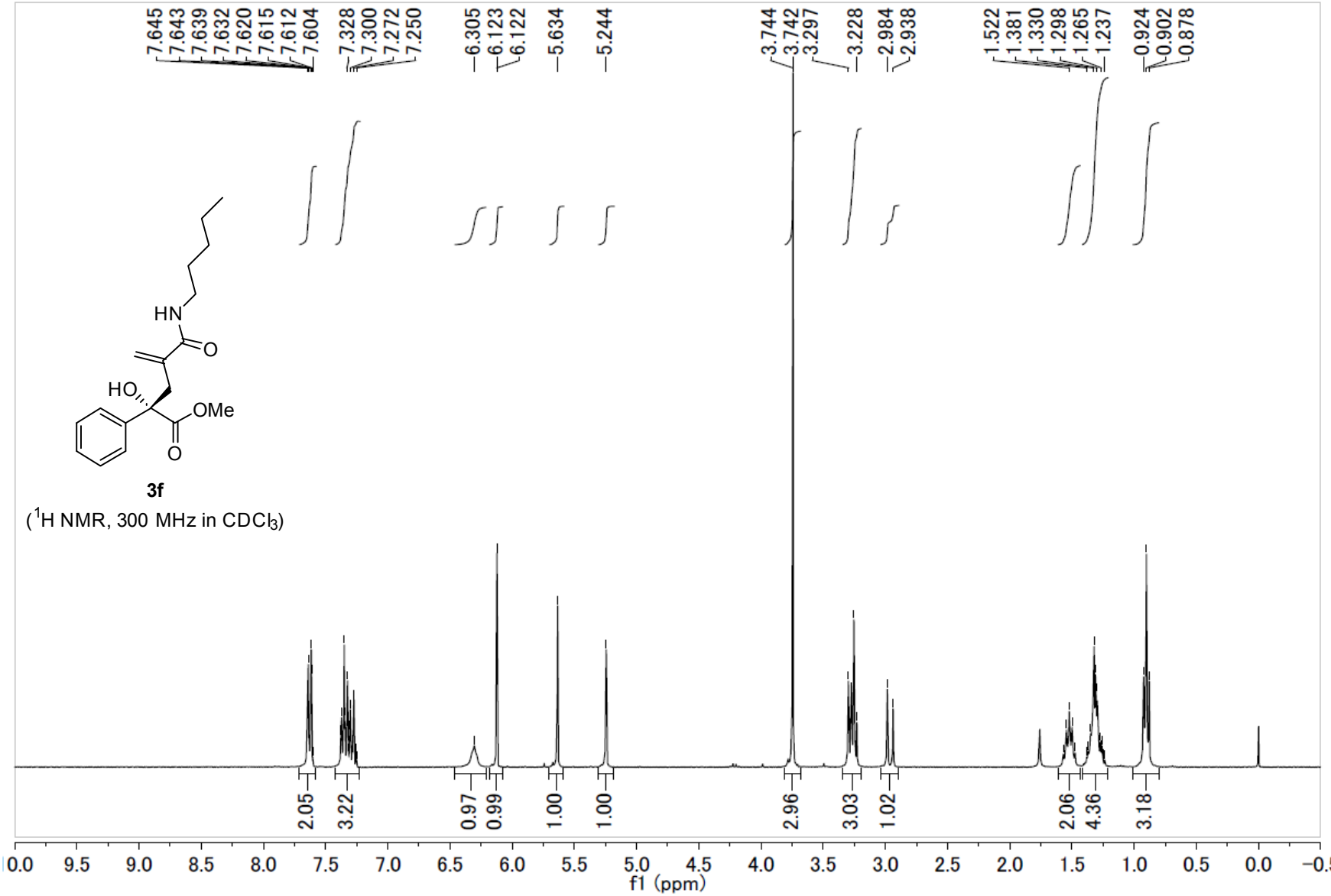

174.671
167.954
147.876
140.602
135.399
125.004
120.178
79.257
53.423
42.699
34.523
31.471
HN
O
HO
OMe
O
3d
(13C NMR, 75 MHz in CDCl3)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



3e

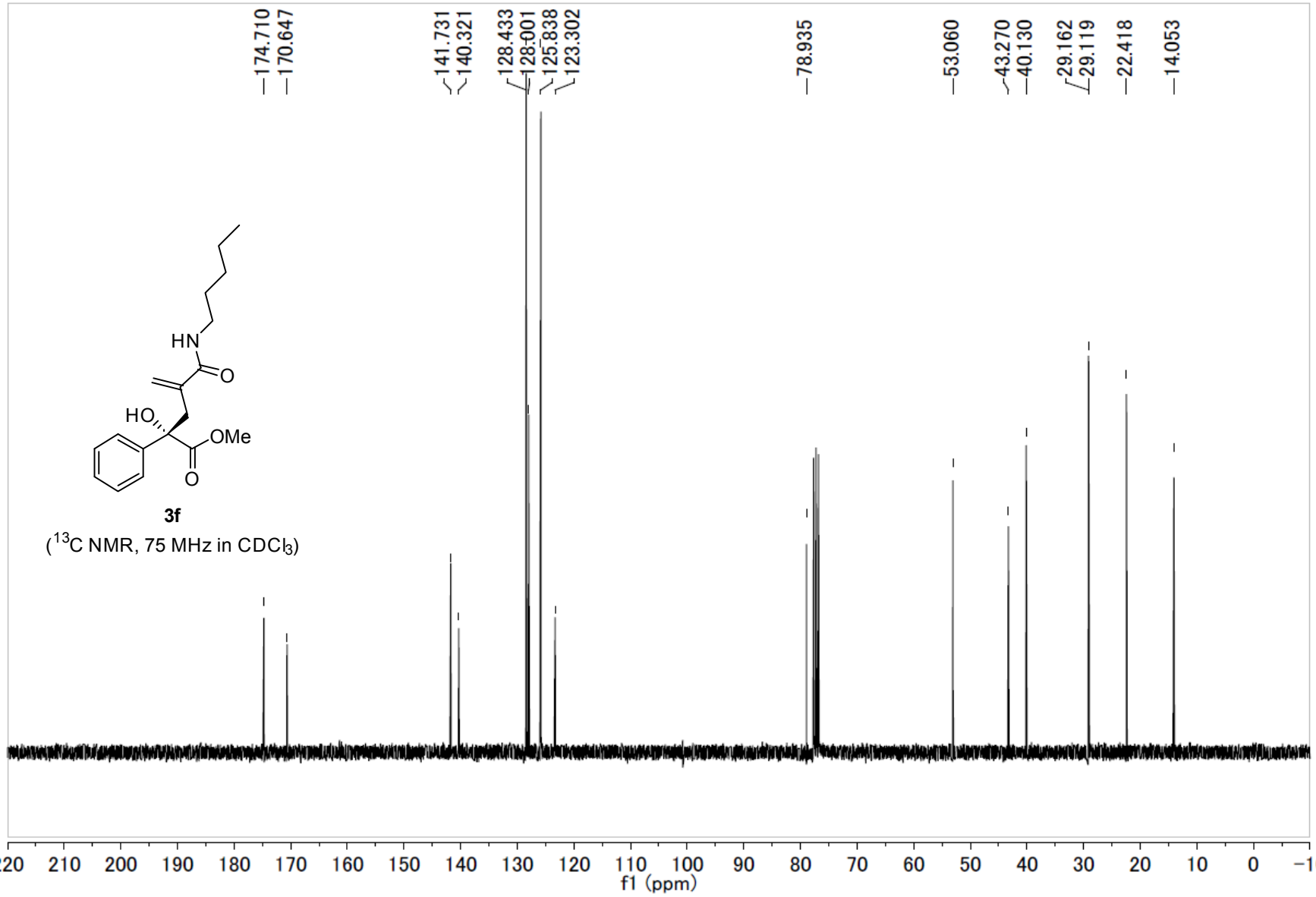
(^{1}H NMR, 300 MHz in $CDCl_3$)

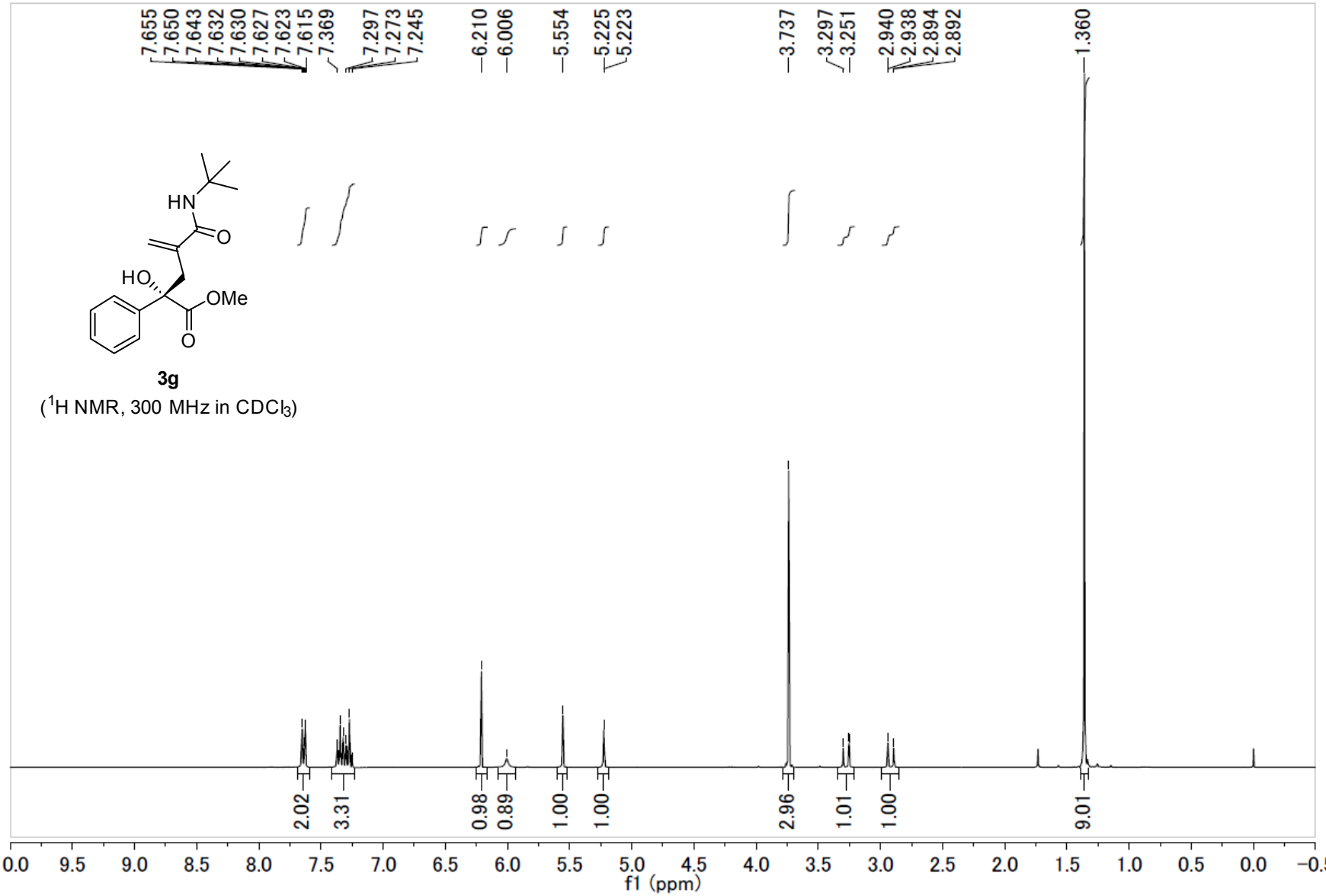

174.589
168.744
141.062
140.293
128.598
126.172
125.525
121.289
121.182
79.329
53.375
42.652
HN
O
HO
OMe
O
3e
(13C NMR, 75 MHz in CDCl3)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)



3f

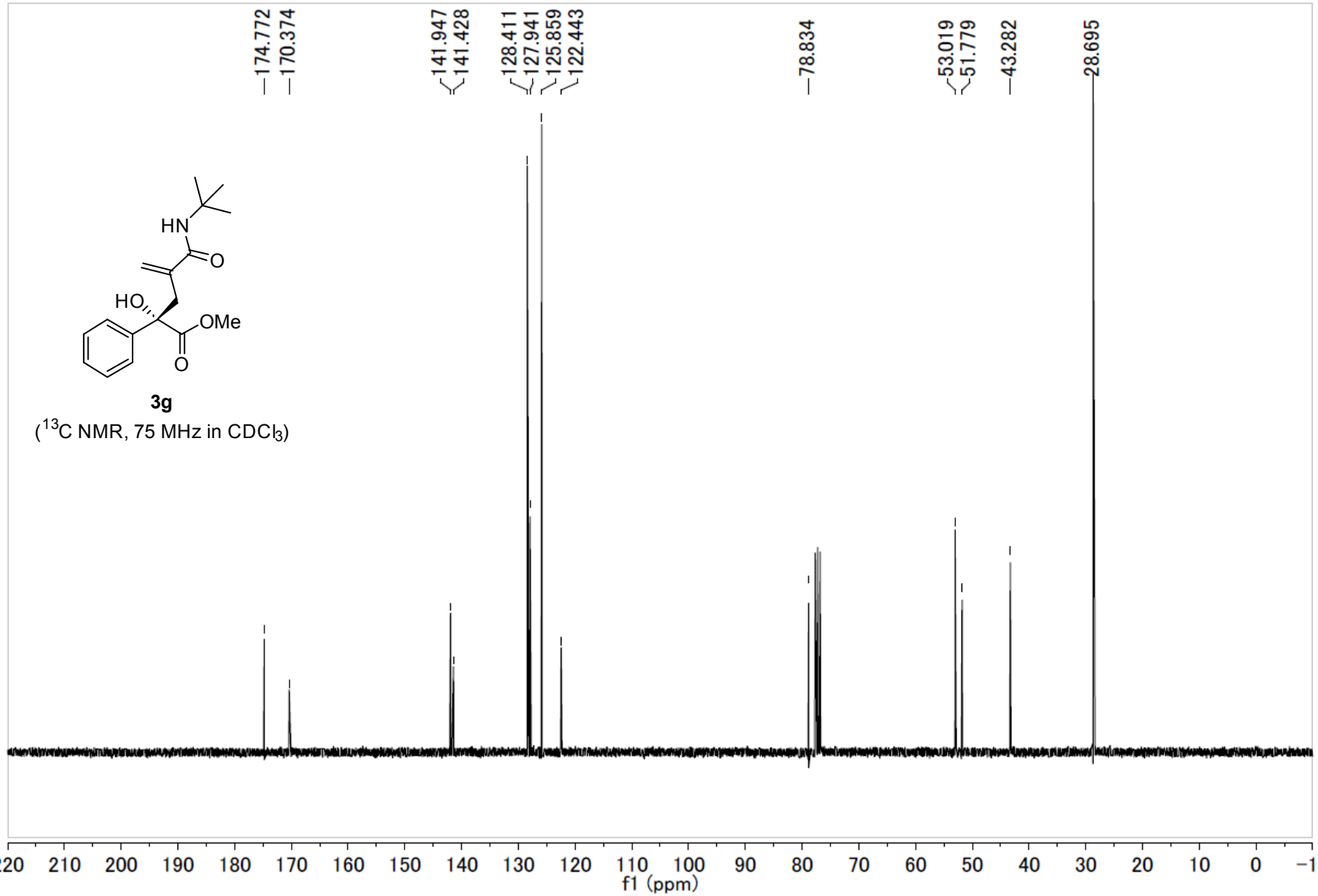
(^{1}H NMR, 300 MHz in $CDCl_3$)


174.710
170.647
141.731
140.321
128.433
128.001
125.838
123.302
78.935
53.060
43.270
40.130
29.162
29.119
22.418
14.053
HN
O
HO
OMe
O
3f
(13C NMR, 75 MHz in CDCl3)
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)



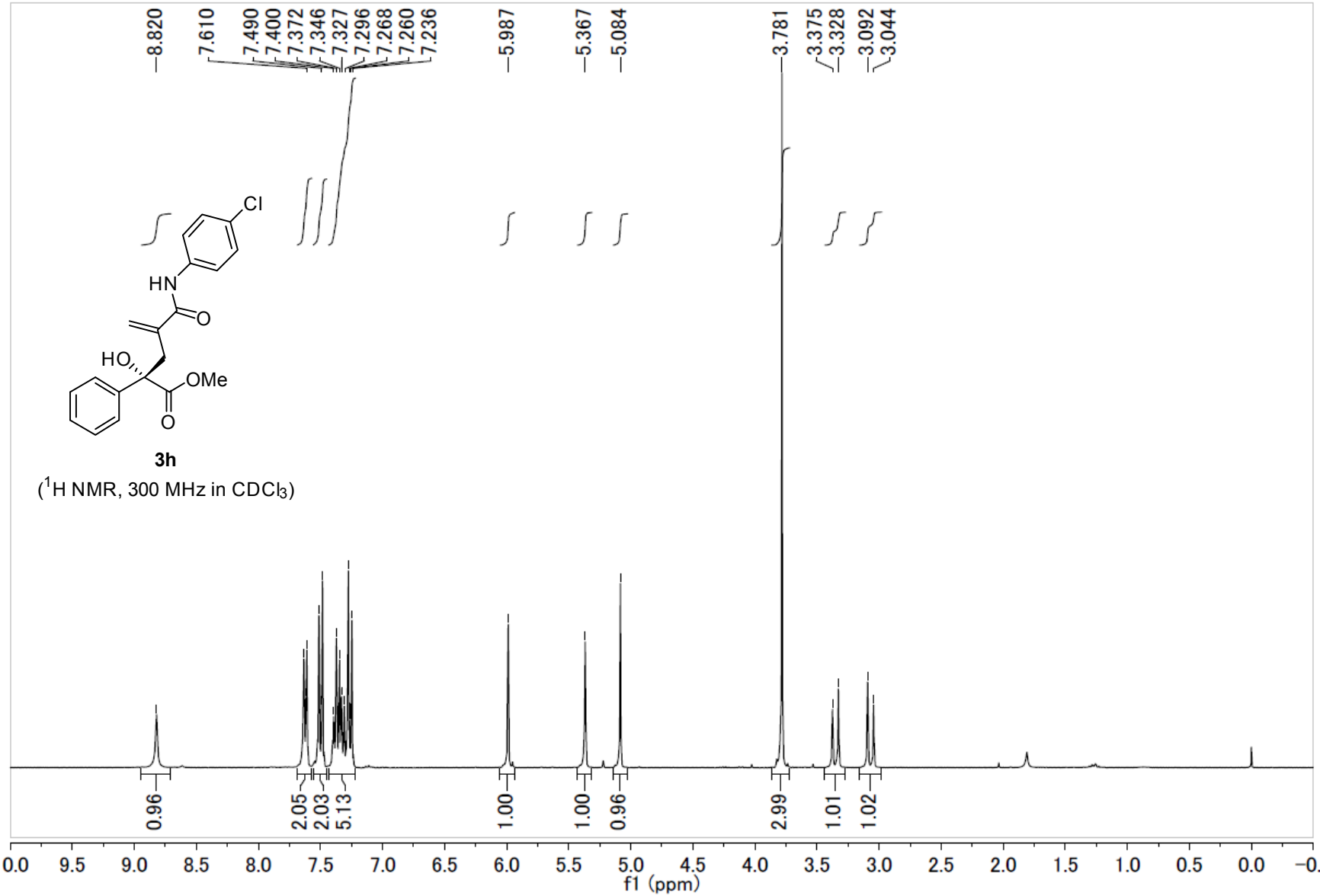
3g

(^{1}H NMR, 300 MHz in $CDCl_3$)



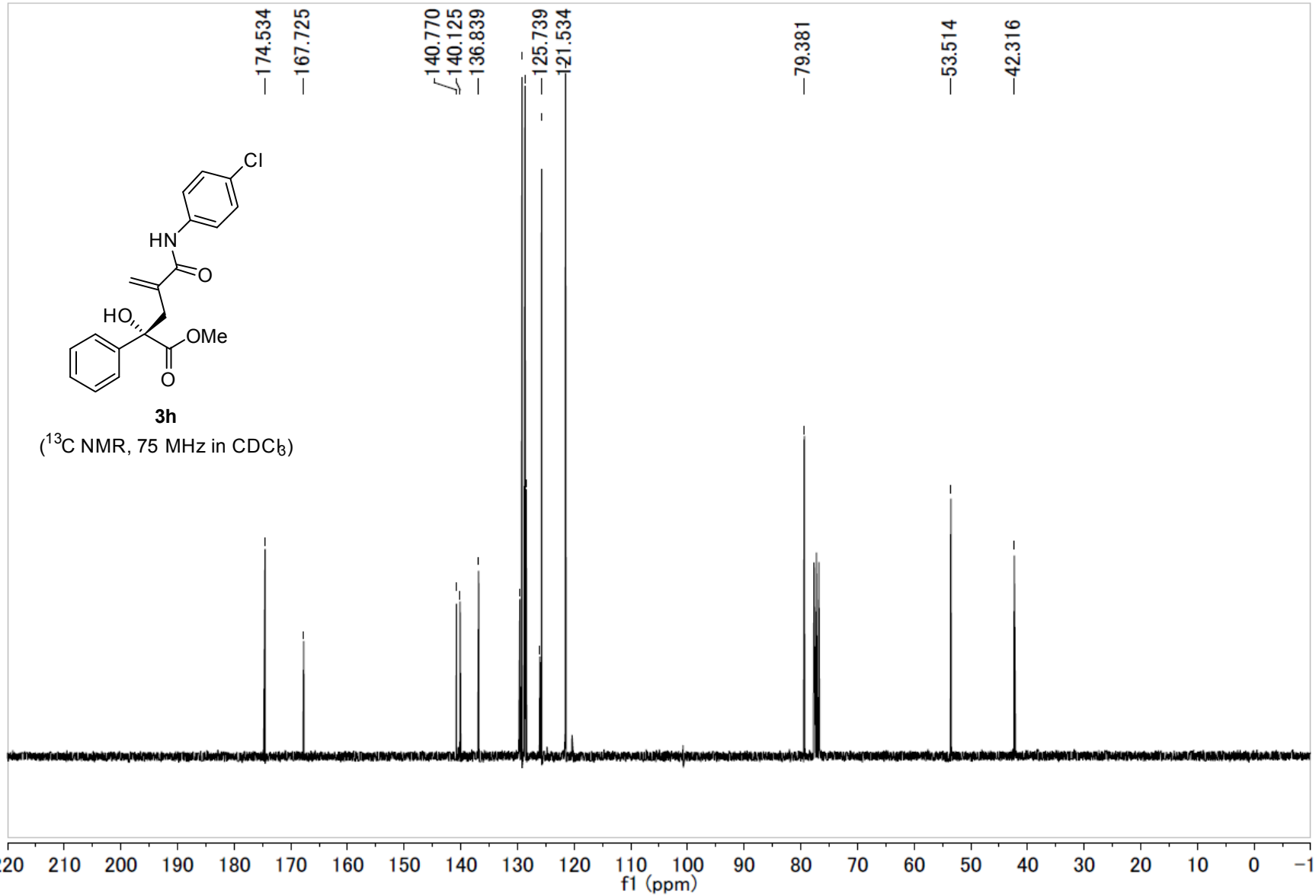
3g

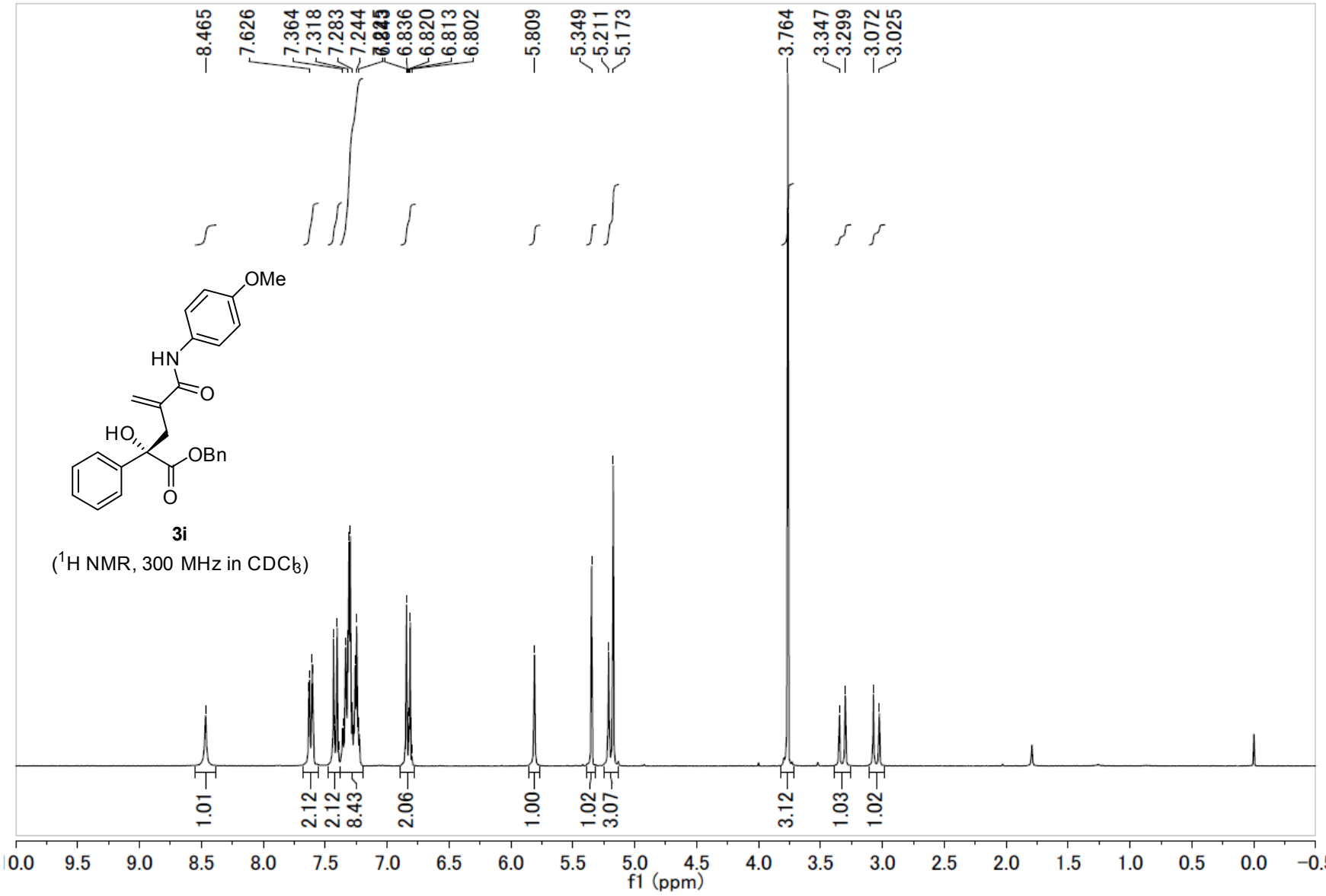
(^{13}C NMR, 75 MHz in $CDCl_3$)



3h

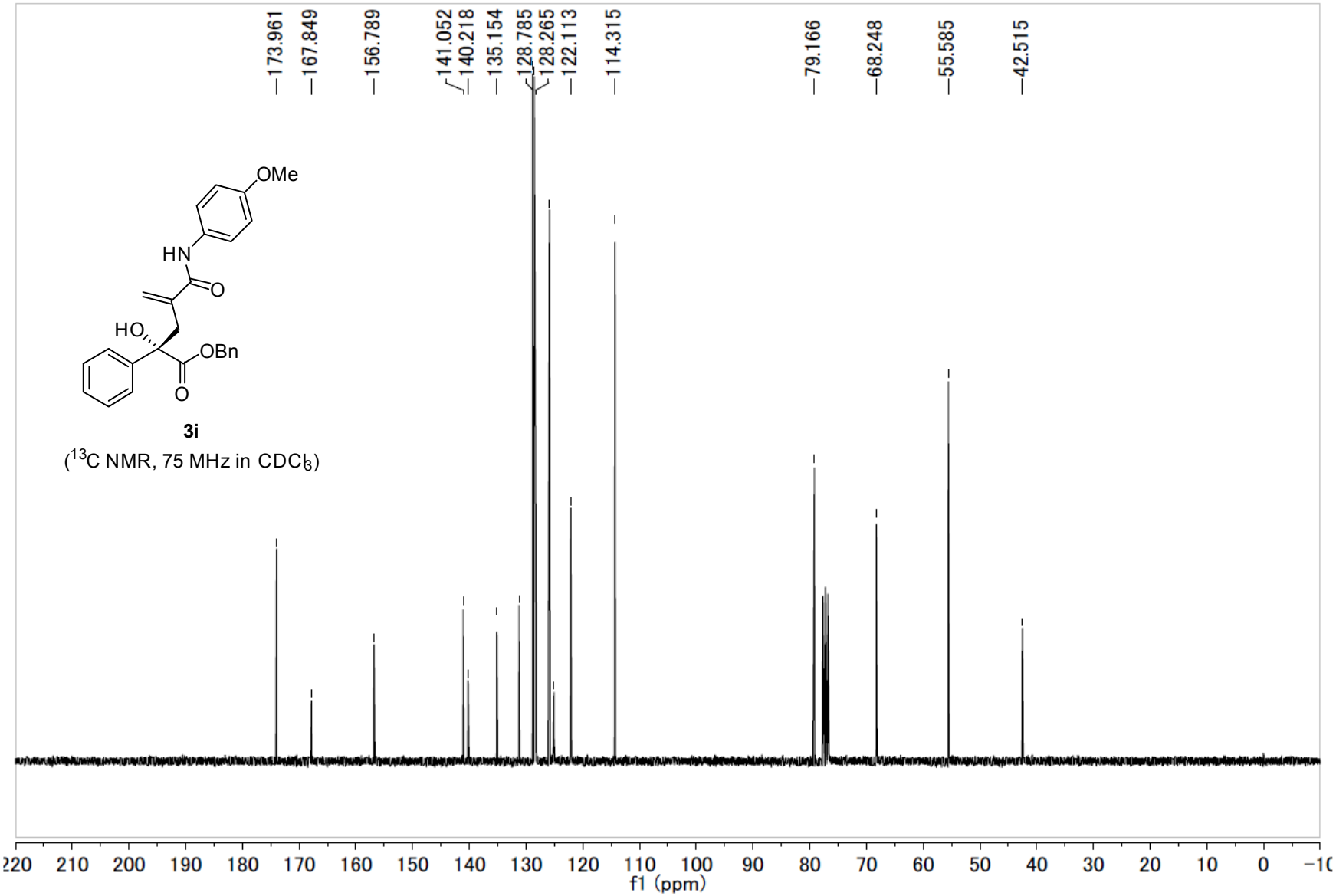
(^{1}H NMR, 300 MHz in $CDCl_3$)

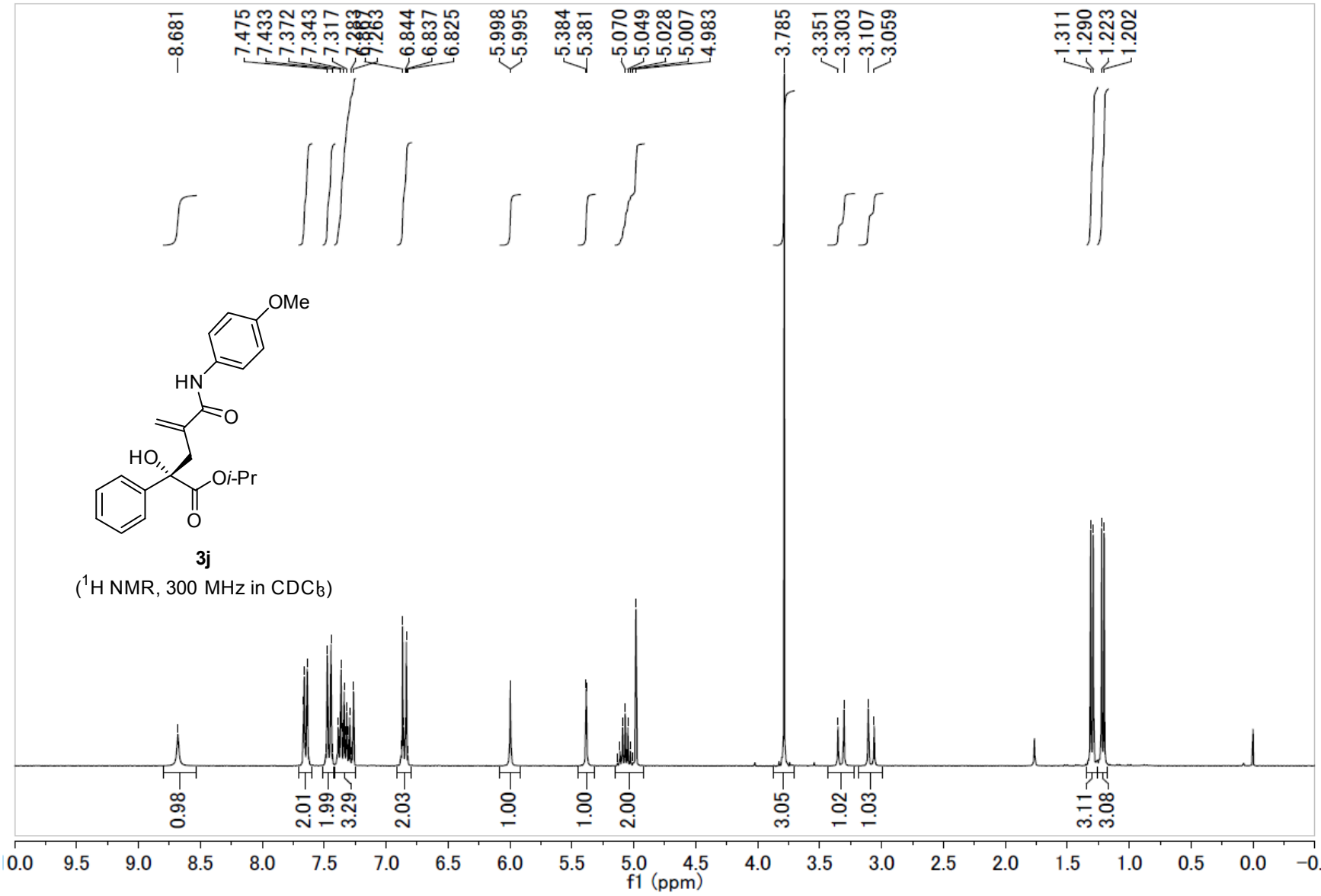

174.534
167.725
140.770
140.125
136.839
125.739
121.534
79.381
53.514
42.316
Cl
HN
O
HO
OMe
O
3h
(13C NMR, 75 MHz in CDCl3)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



3i

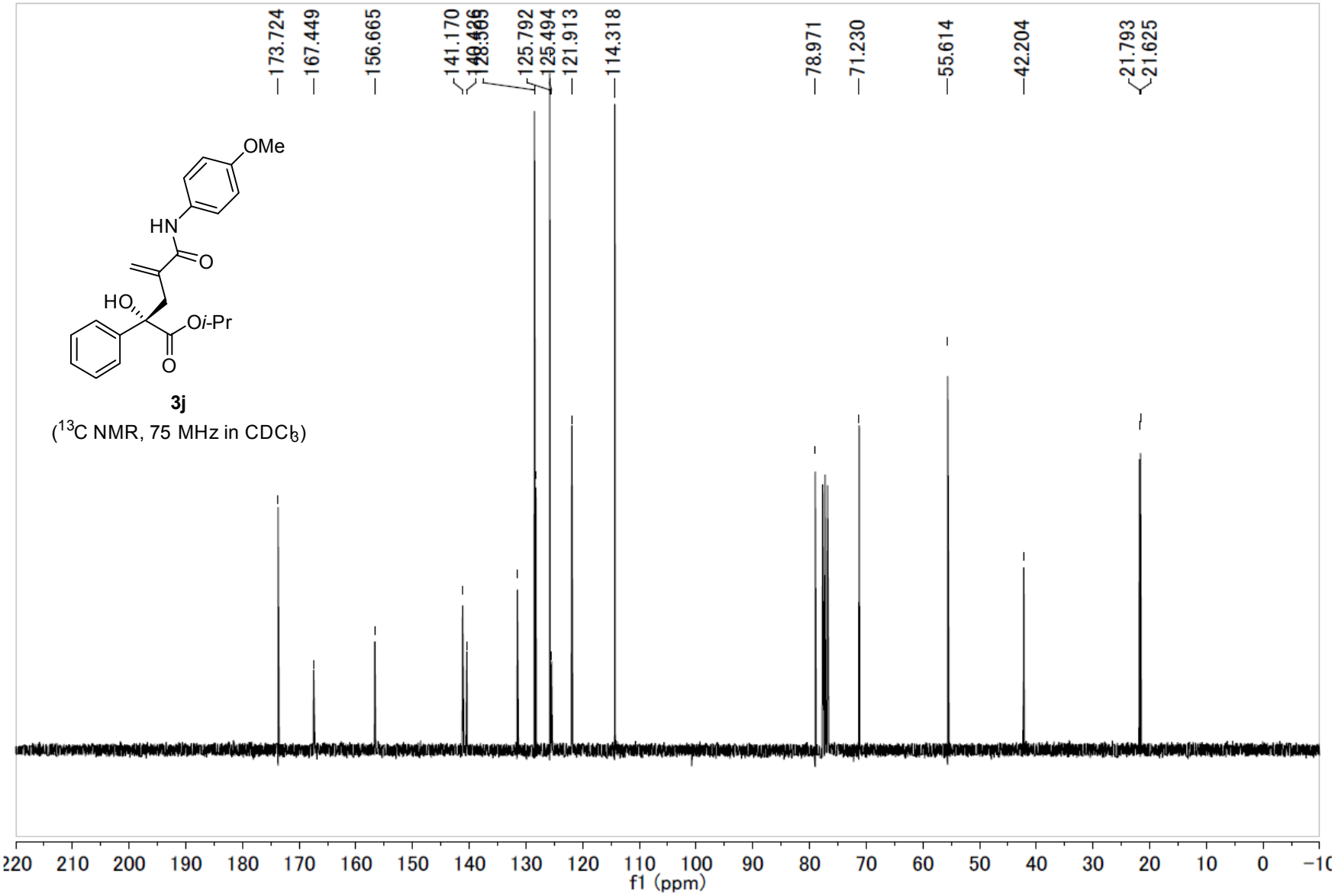
(^{1}H NMR, 300 MHz in $CDCl_3$)


173.961
167.849
156.789
141.052
140.218
135.154
128.785
128.265
122.113
114.315
79.166
68.248
55.585
42.515
OMe
HN
O
HO
OBn
O
3i
(13C NMR, 75 MHz in CDCl3)
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)



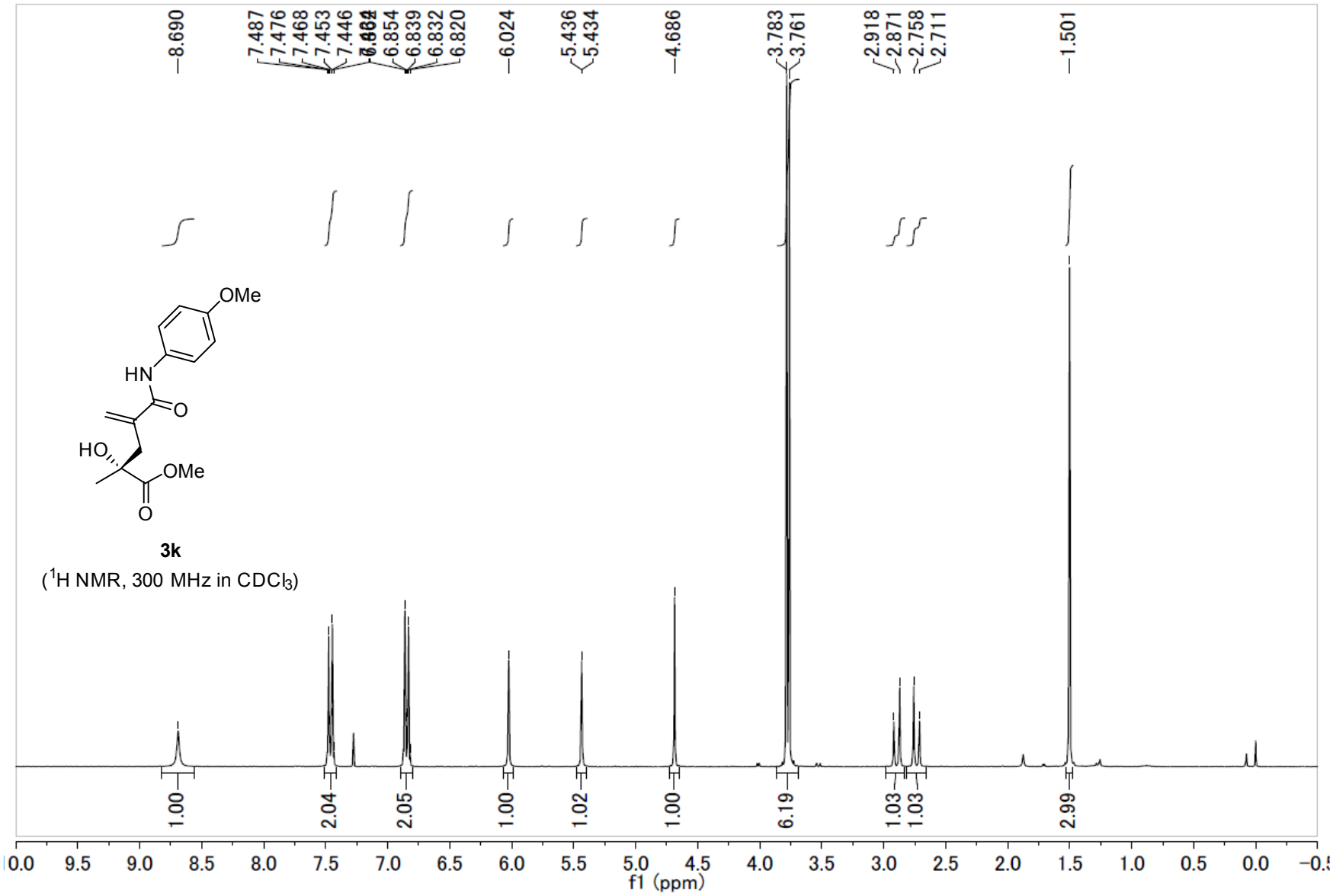
3j

(^{1}H NMR, 300 MHz in $CDCl_3$)



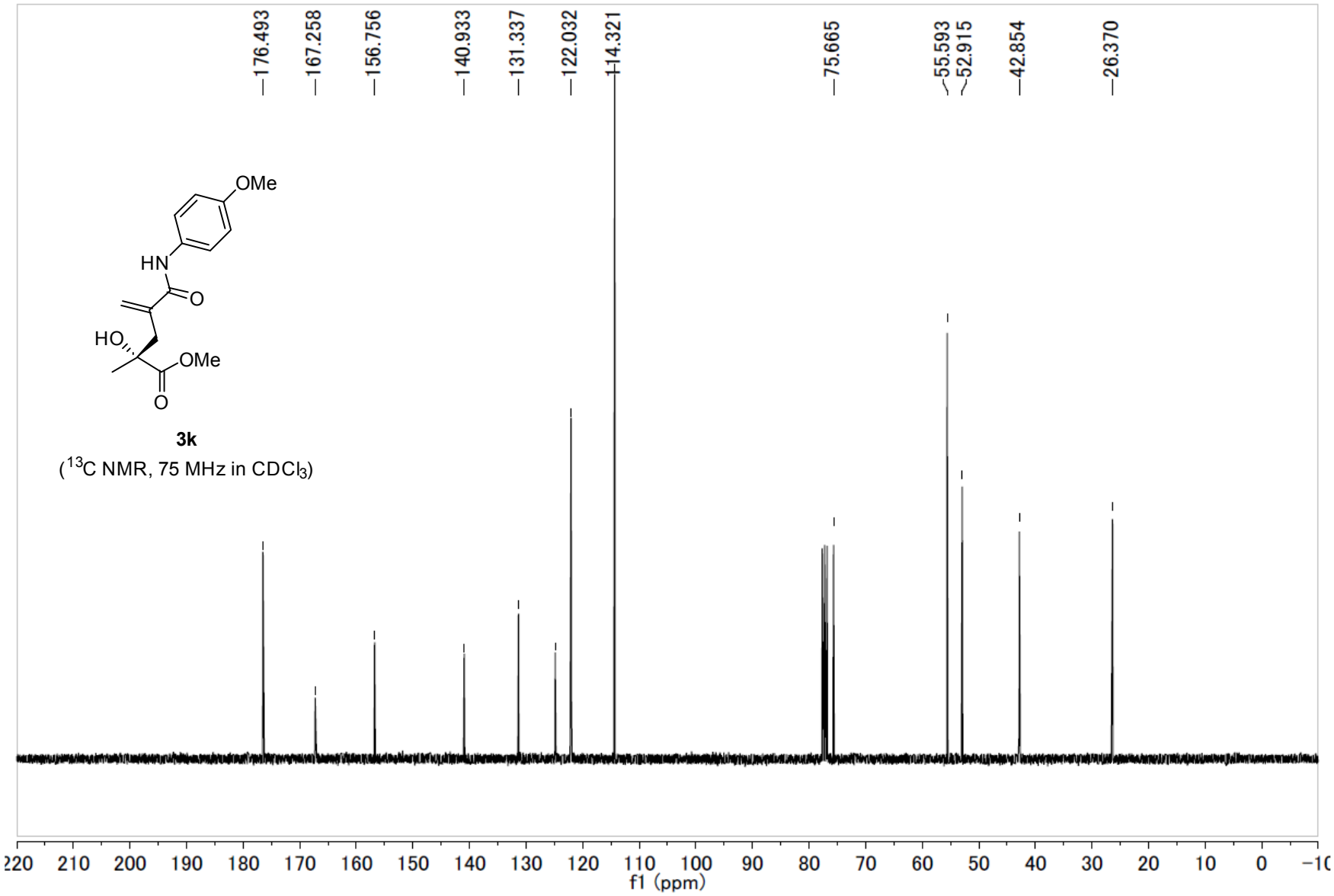
3j

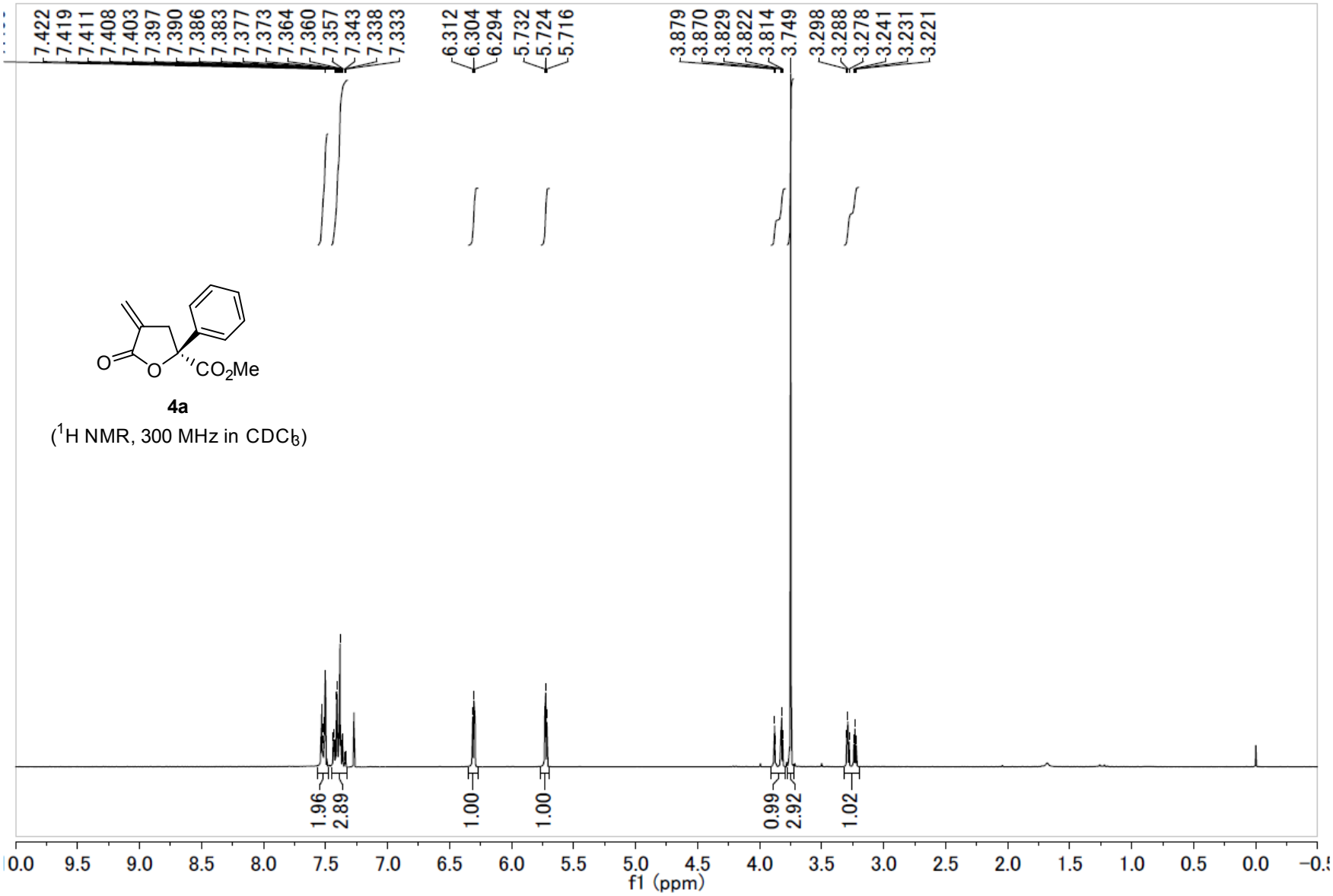
(^{13}C NMR, 75 MHz in $CDCl_3$)



3k

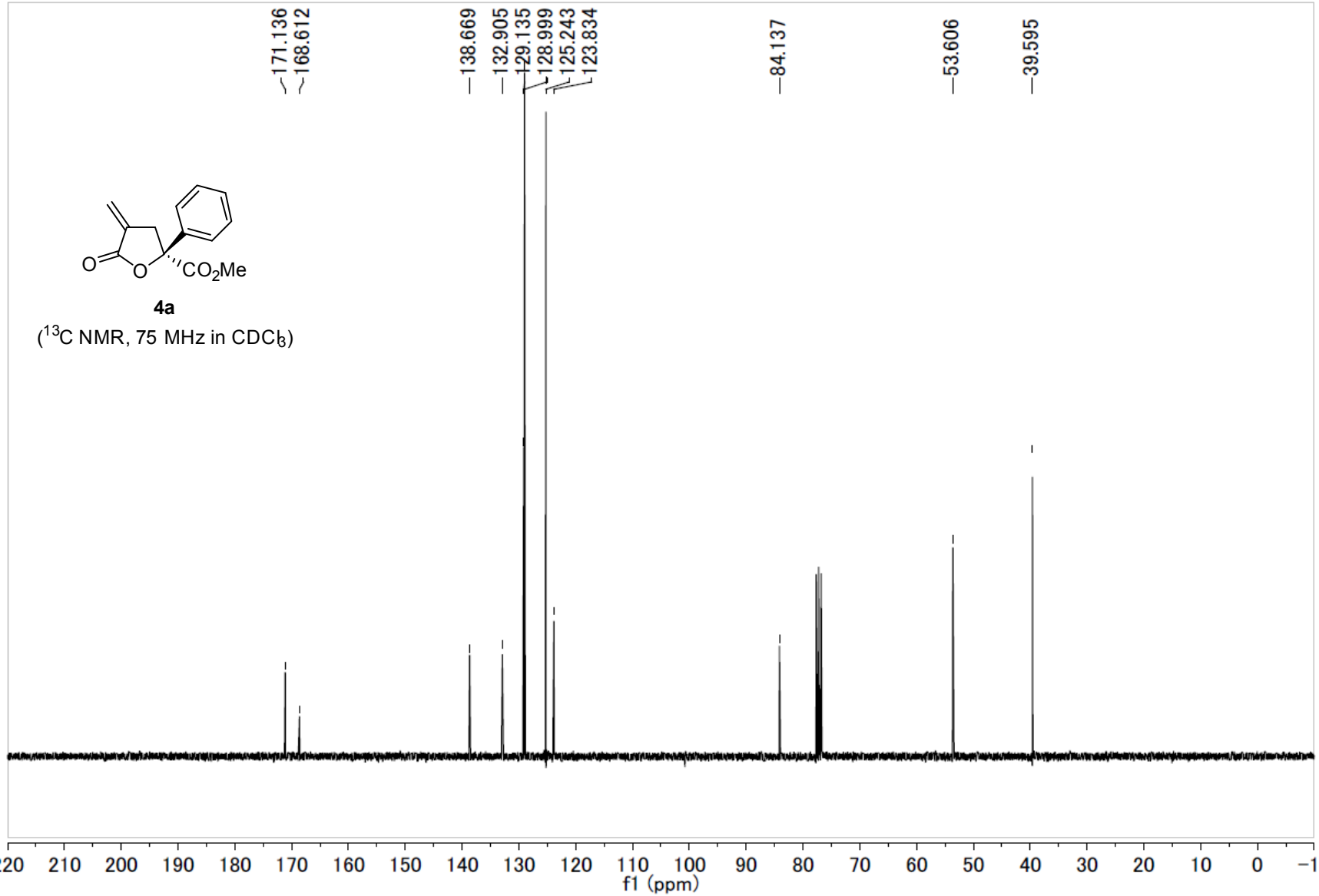
(^{1}H NMR, 300 MHz in $CDCl_3$)


176.493
167.258
156.756
140.933
131.337
122.032
114.321
75.665
55.593
52.915
42.854
26.370
OMe
HN
O
HO
OMe
O
3k
(^{13}C NMR, 75 MHz in $CDCl_3$)
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)



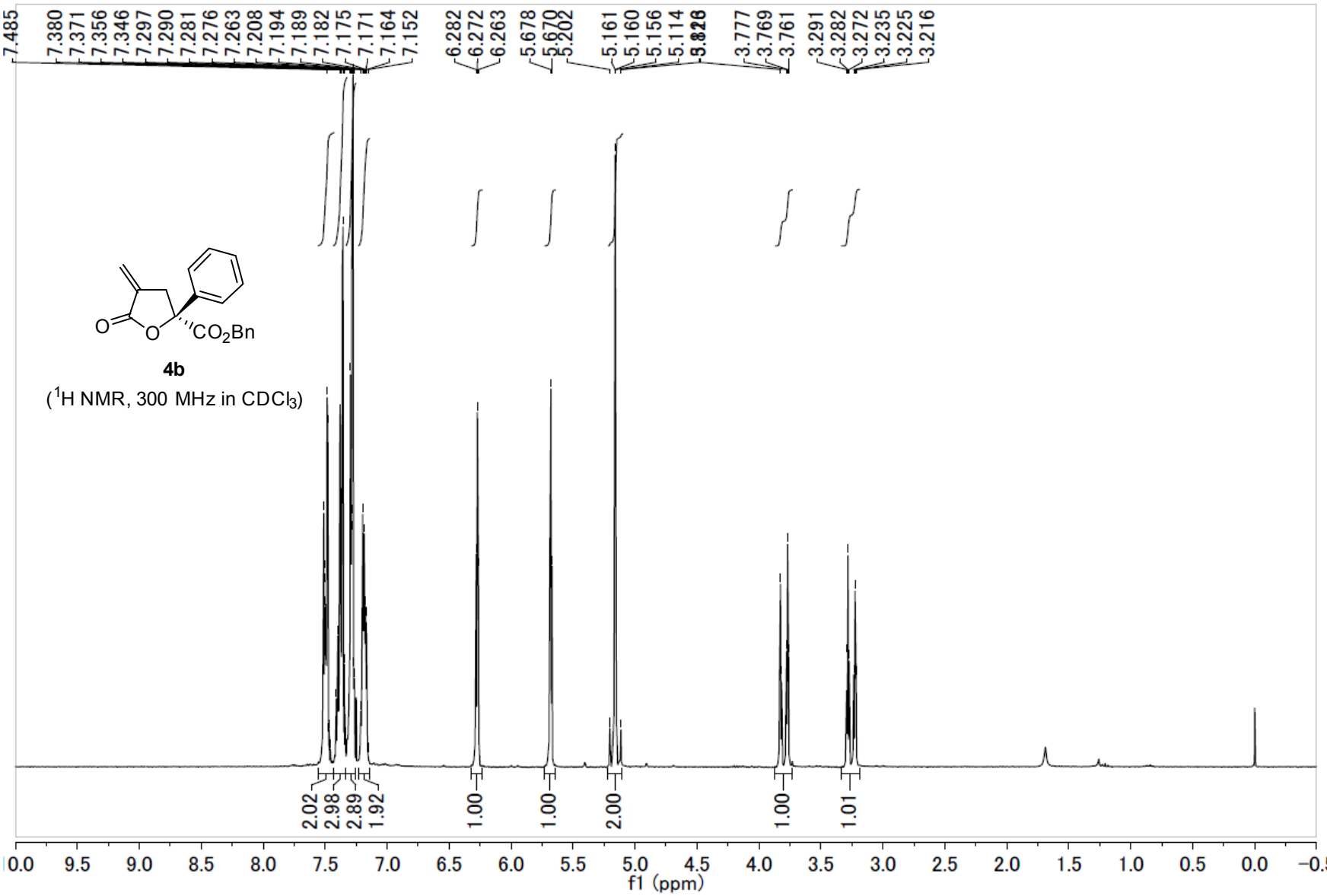
4a

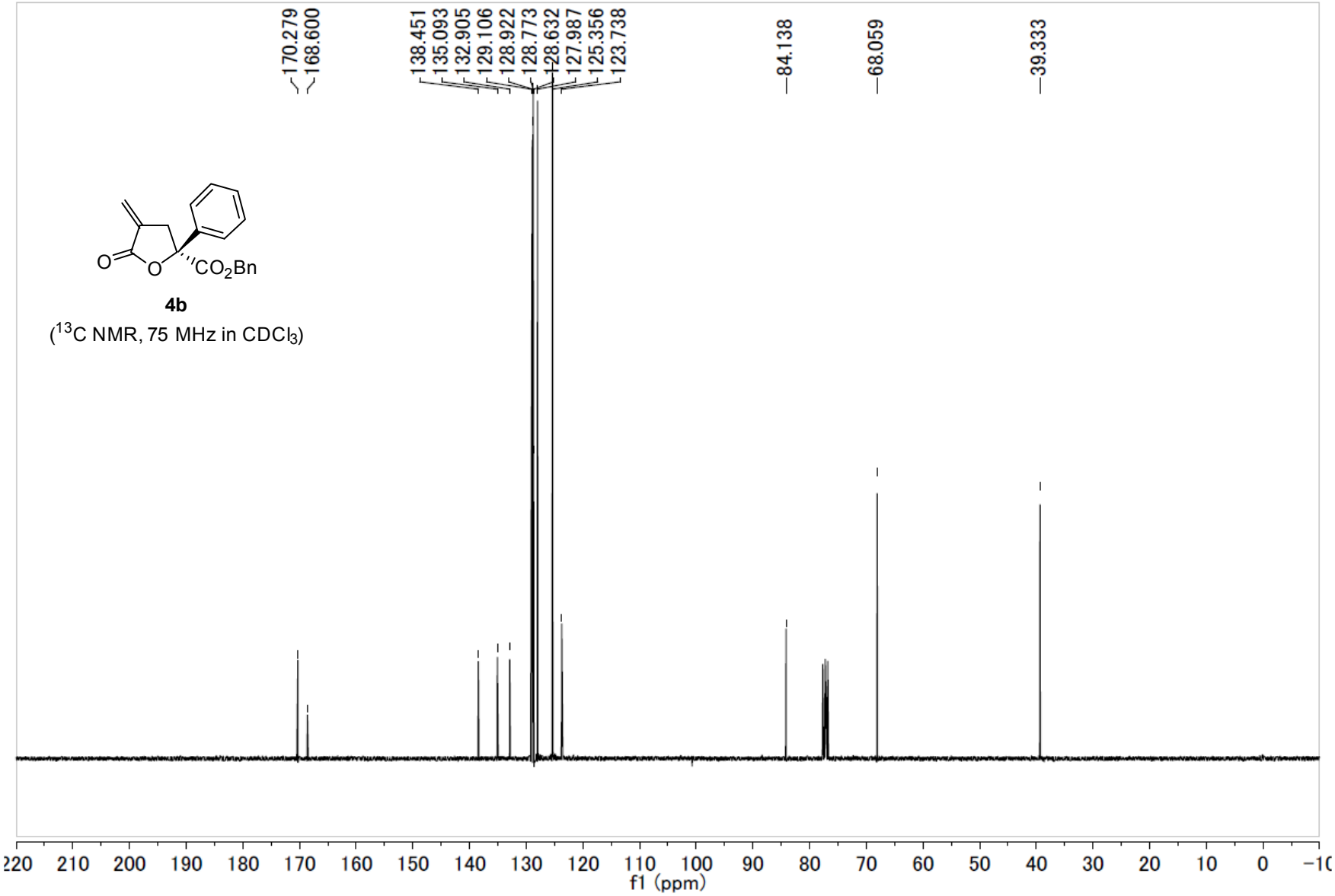
(^{1}H NMR, 300 MHz in $CDCl_3$)

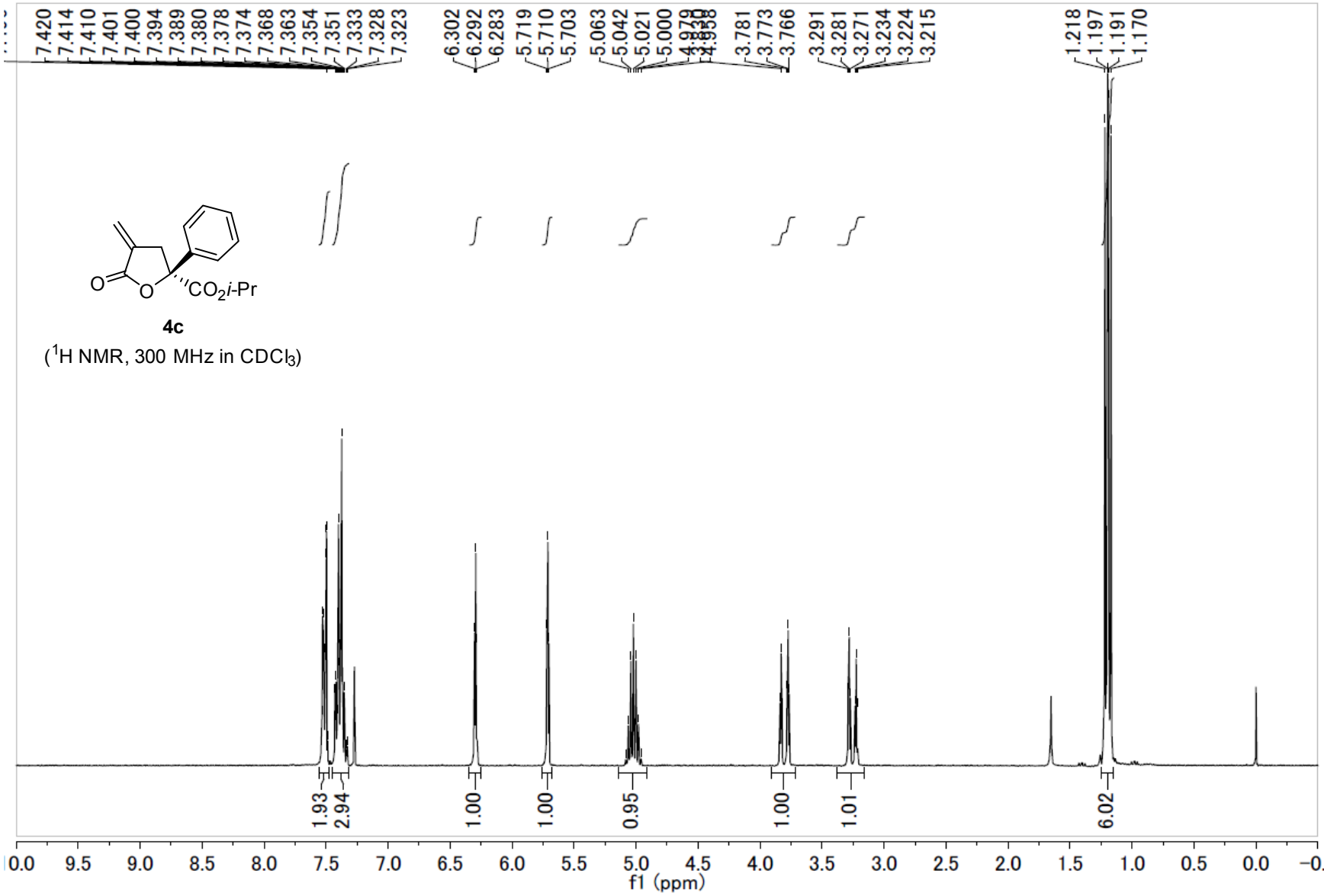


4a

(^{13}C NMR, 75 MHz in $CDCl_3$)

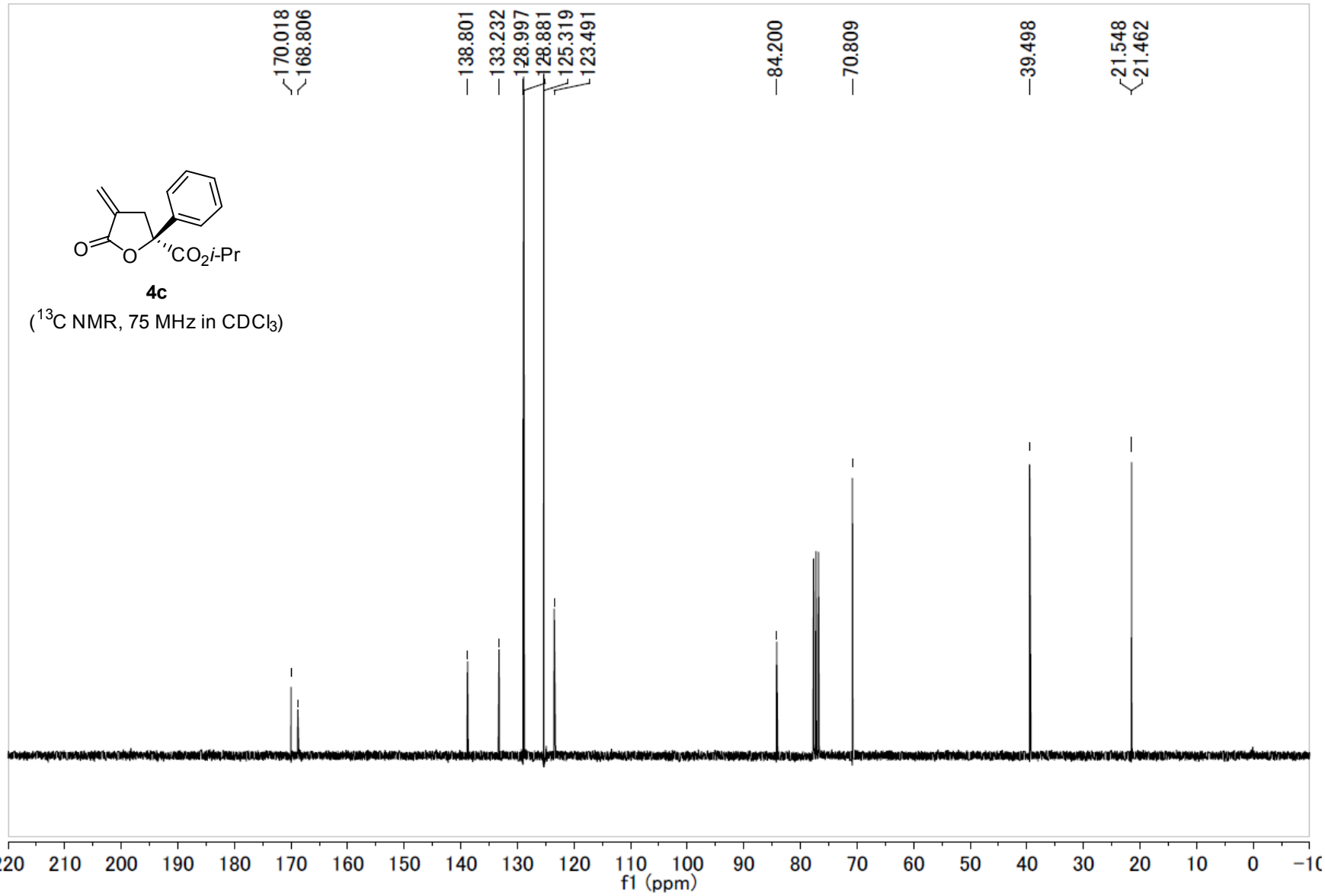

7.485
7.380
7.371
7.356
7.346
7.297
7.290
7.281
7.276
7.263
7.208
7.194
7.189
7.182
7.175
7.171
7.164
7.152
6.282
6.272
6.263
5.678
5.670
5.202
5.161
5.160
5.156
5.114
3.777
3.769
3.761
3.291
3.282
3.272
3.235
3.225
3.216
O
O
CO2Bn
4b
(1H NMR, 300 MHz in CDCl3)
2.02
2.98
2.89
1.92
1.00
1.00
2.00
1.00
1.01
f1 (ppm)

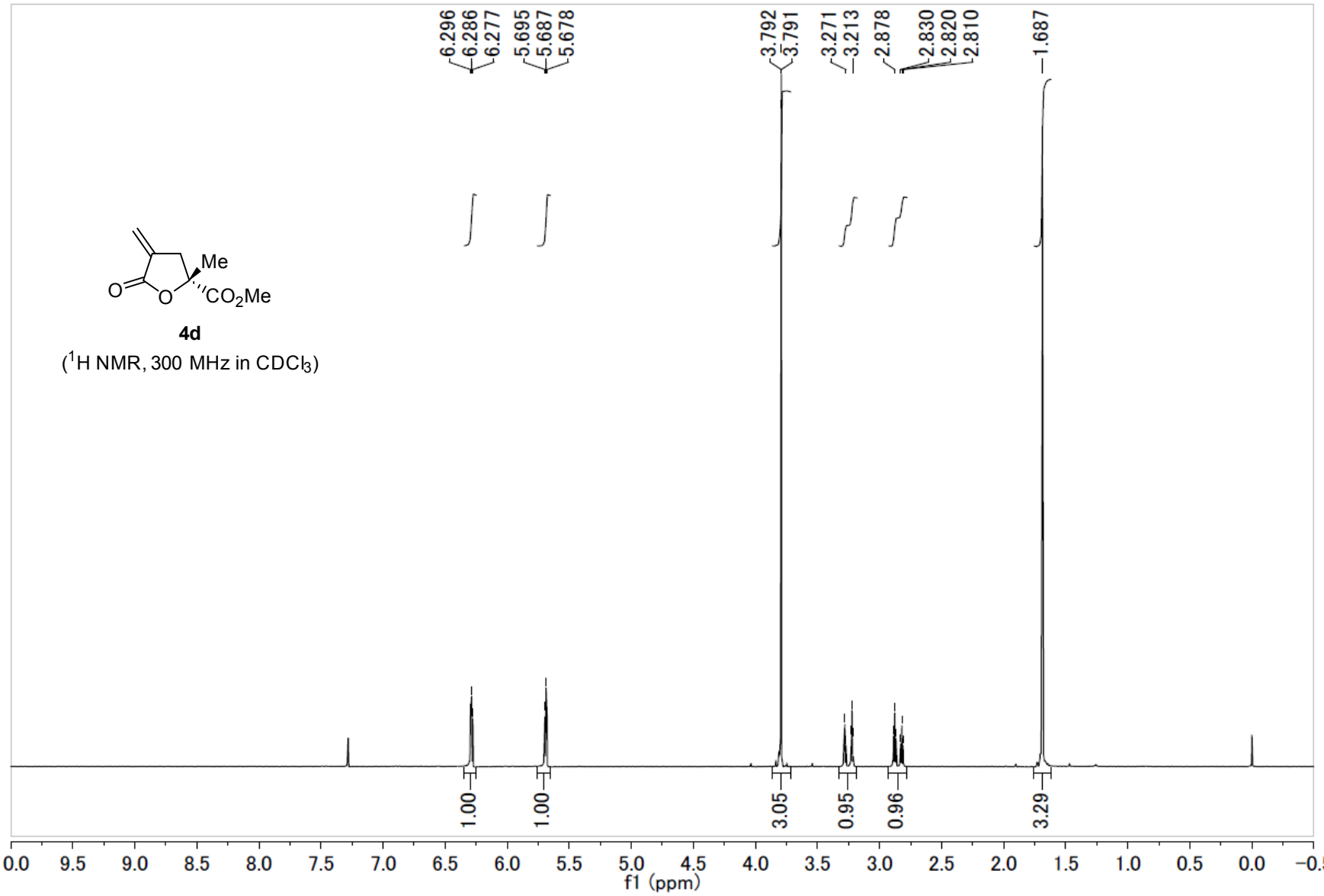

170.279
168.600
138.451
135.093
132.905
129.106
128.922
128.773
128.632
127.987
125.356
123.738
84.138
68.059
39.333
O
O
CO2Bn
4b
(13C NMR, 75 MHz in CDCl3)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)

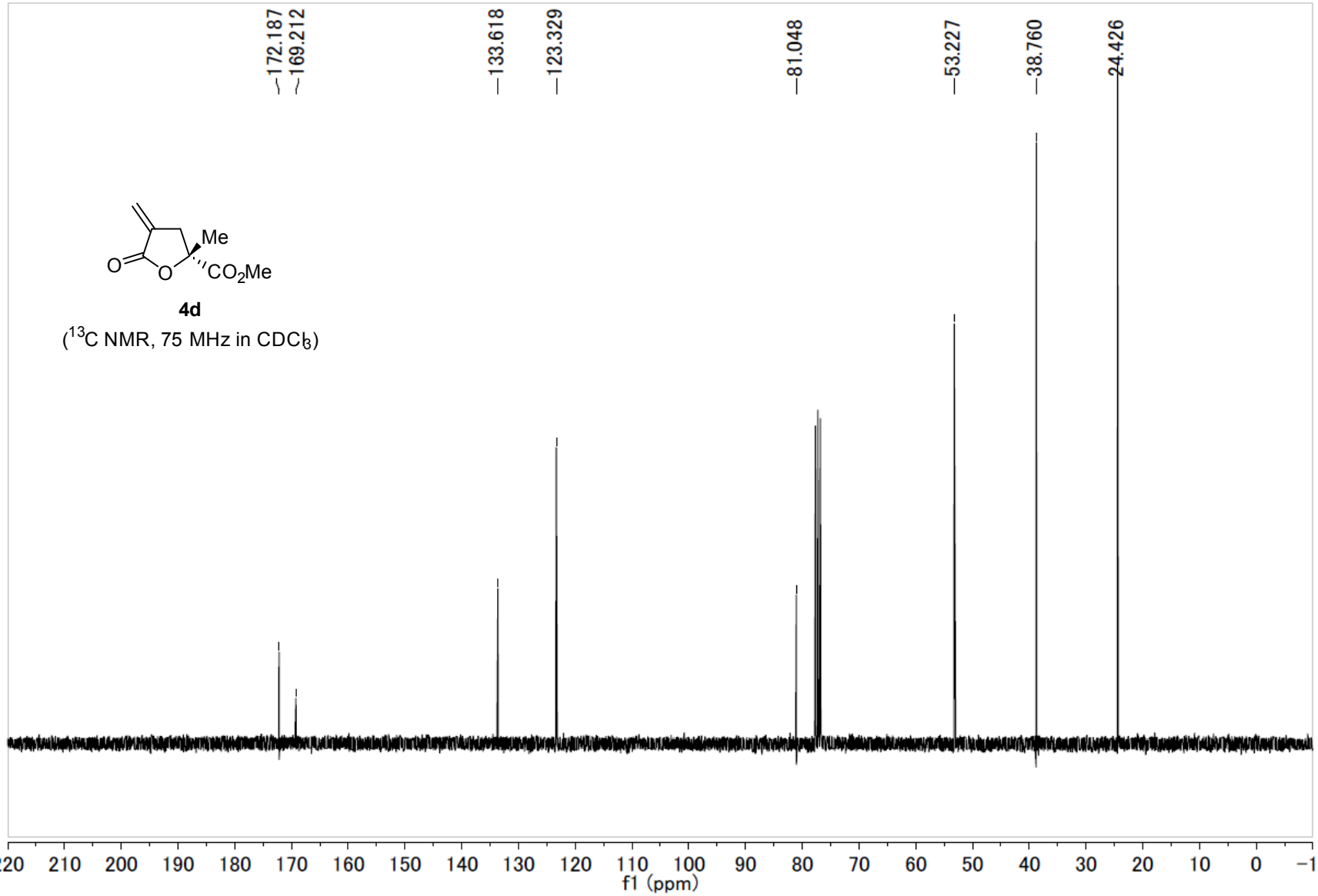


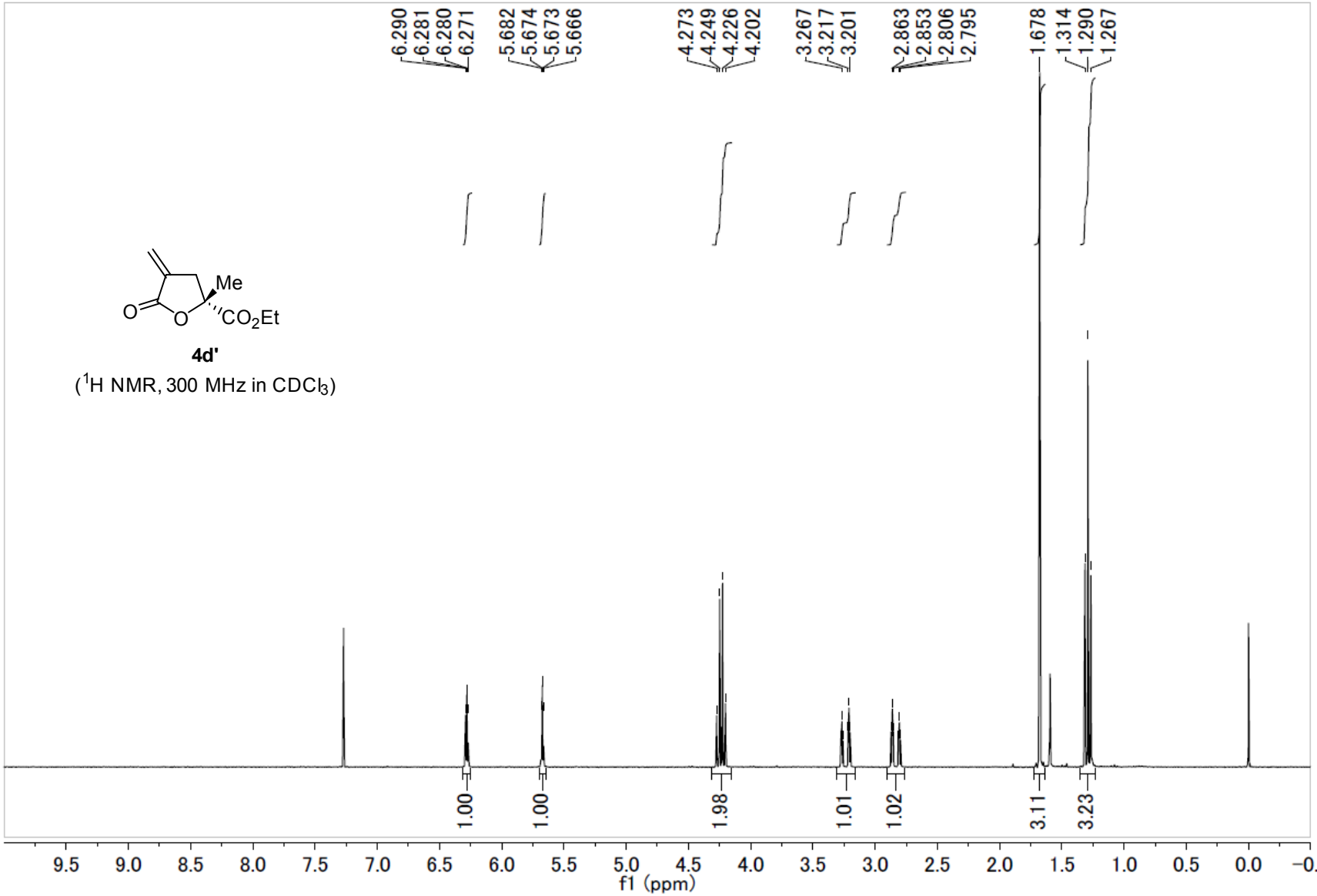
4c

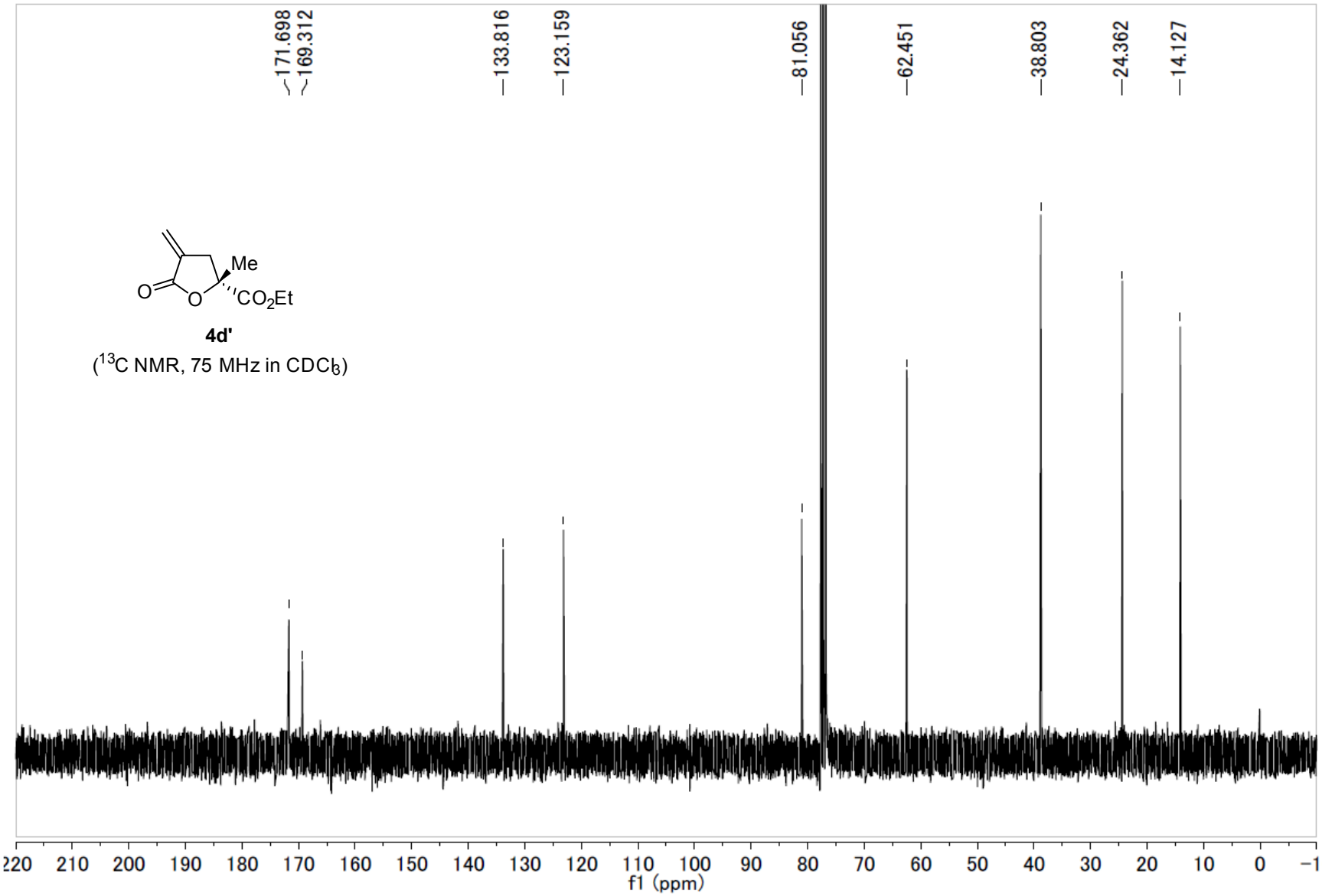
(^{1}H NMR, 300 MHz in $CDCl_3$)


170.018
168.806
138.801
133.232
128.997
128.881
125.319
123.491
84.200
70.809
39.498
21.548
21.462
O
O
CO2i-Pr
4c
(13C NMR, 75 MHz in CDCl3)
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)


6.296
6.286
6.277
5.695
5.687
5.678
3.792
3.791
3.271
3.213
2.878
2.830
2.820
2.810
1.687
Me
O
O
CO2Me
4d
(1H NMR, 300 MHz in CDCl3)
1.00
1.00
3.05
0.95
0.96
3.29
f1 (ppm)


172.187
169.212
133.618
123.329
81.048
53.227
38.760
24.426
Me
O
O
CO2Me
4d
(13C NMR, 75 MHz in CDCl3)
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)


6.290
6.281
6.280
6.271
5.682
5.674
5.673
5.666
4.273
4.249
4.226
4.202
3.267
3.217
3.201
2.863
2.853
2.806
2.795
1.678
1.314
1.290
1.267
Me
O
O
CO2Et
4d'
(1H NMR, 300 MHz in CDCl3)
1.00
1.00
1.98
1.01
1.02
3.11
3.23
f1 (ppm)


171.698
169.312
133.816
123.159
81.056
62.451
38.803
24.362
14.127
Me
O
O
CO2Et
4d'
(13C NMR, 75 MHz in CDCl3)
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)