Synthesis of Quaternary Amino Acids Bearing a (2'Z)-Fluorovinyl α-Branch: Potential PLP Enzyme Inactivators.

David B. Berkowitz,* Roberto de la Salud-Bea and Wan-Jin Jahng

Department of Chemistry, University of Nebraska, Lincoln, NE 68588-0304

dbb@unlserve.unl.edu

SUPPORTING INFORMATION

General. All reactions were conducted under argon atmosphere using oven-dried glassware. Methylene chloride and diisopropylamine were distilled from CaH_2. THF and Et_2O were distilled from sodium benzophenone ketyl. HMPA was distilled from Na under reduced pressure. Methanol was distilled from Mg. Flash chromatography was performed using Merck silica gel 60 (230-400 mesh). ^1H NMR spectra were recorded on a Bruker-DRX-Avance-400, 500 or 600-GE, Nicolet-360 or Omega-300 instrument with chemical shifts reported relative to residual $CHCl_3$ (7.25 ppm). Proton-decoupled ^{13}C NMR spectra were acquired on a Bruker-DRX-Avance-400 or 500 or GE Omega-300 instrument with chemical shifts reported relative to $CDCl_3$ (77.0 ppm). ^{19}F NMR spectra were recorded on a Bruker-DRX-Avance-400, 500 or 600 or GE Omega-300 instrument with chemical shifts reported relative to the internal (capillary) standard trifluoroacetic acid (-76.5 ppm). Infrared spectra were obtained using an Analect RFX-65 FTIR spectrometer. Mass spectra were acquired at the Nebraska Center for Mass Spectrometry (University of Nebraska-Lincoln). Elemental analyses were carried out by M-H-W Laboratories (Phoenix, AZ).

Preparation of the α–Vinylaspartate & α-Vinyl-*m*-Tyrosine Educts

Note: These two educts were obtained using the racemic version of our dianionic dienolate alkylation chemistry (This approach was also recently employed by the Columbo group for the synthesis of (±)-α-vinylphenylalanine).[1]

(±)-Methyl N- Benzoyl-α-vinyl-(3'-*O*-*tert*-butyldimethylsilyloxy)-*m*-tyrosinate (4c). To a solution of diisopropylamine (98 μL, 0.7 mmol) and HMPA (360 μL) in THF (3 mL) at –78 ºC was added n-butyllithium (0.47 mL, 1.5 M in n-hexane). The resulting solution was stirred for 20 min at 0 ºC and then cooled to –78 ºC. Then methyl 2-(N-benzoyl)amino-(2Z)-butenoate[2] (139 mg, 0.64 mmol) in THF (5 mL) at –78 ºC was added

via cannula, followed by butyllithium (0.85 mL, 1.5 M in n-hexane). The resulting deep-red solution was stirred for 5 min at –78 ºC followed by the addition of 3'(*tert*-butyldimethylsilyloxy)benzyl bromide[3] (417 mg, 1.46 mmol) in THF (1 mL) at –78 ºC via cannula. After 1 h, the reaction was quenched by addition of NH_4Cl (sat.) in water, extracted with ether, washed the organic phase with brine and dried over Na_2SO_4, evaporated and chromatographed (100→90% hexane/EtOAc) to give **4c** (195 mg, 70%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.09 (s, 9H), 3.35 (d, *J* = 13.5 Hz, 1H), 3.82 (s, 3H), 3.83 (d, *J* = 13.6 Hz), 5.30 (d, *J* = 10.3 Hz, 1H), 5.32 (d, *J* = 17.1, 1H), 6.17 (dd, *J* = 10.6, 17.3, 1 H), 6.57 (m, 1H), 6.67(dd, *J* = 8, 8.1, 2H), 7.02 (s, 1H), 7.05 (t, *J* = 8, 1H), 7.40 (t, *J* = 7.37, 2H), 7.47 (m, 1H), 7.72 (d, *J* = 8, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.5, 18.1, 25.6, 40.0, 53.1, 65.7, 116.3, 118.8, 121.8, 123.0, 127.0, 128.6, 129.2, 131.7, 134.6, 136.3, 137.2, 155.5, 166.3, 172.3; IR (film) 3366, 1743, 1667 cm^{-1}; HRMS (FAB) Calcd for $(M+H)^+$ 440.2258 Found 440.2271.

(±)-α,β-Dimethyl N-Benzoyl-α-vinylaspartate (**4f**). To a solution of methyl 2-(N-benzoyl)amino-(2Z)-butenoate[2] (500 mg, 2.29 mmol) and HMPA (1.2 mL, 6.9 mmol) in THF (6.3 mL) at -78 ºC, was added LiHMDS (8.0 mL of a 1 M solution in hexanes, 8.0 mmol). After warming to 0 ºC for 1 h, and cooling again to -78 ºC, a solution of methyl 2-bromoacetate (1.05 g, 6.90 mmol) in THF (1.7 mL) at –78 ºC was added via cannula. The reaction was warmed to 0 ºC and stirred at this temperature until starting material was consumed (3.5 h). Workup as for **4c** and SiO_2 chromatography (100→75% hexane/EtOAc) gave **4f** (360 mg, 53%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.22 (d, *J* = 17 Hz, 1H), 3.78 (d, *J* = 17 Hz, 1H), 3.63 (s, 3H), 3.82 (s, 3H), 5.30 (d, *J* = 10.5 Hz, 1H), 5.33 (d, *J* = 17 Hz, 1H), 6.06 (dd, *J* = 10.6, 17 Hz, 1H), 7.42 (m, 2H), 7.50 (m, 1H), 7.63 (s, 1H), 7.81 (d, *J* = 8, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 38.7, 51.8, 53.4, 62.0, 116.9, 127.1, 128.6, 131.8, 134.1, 135.1, 166.1, 170.9, 171.7, 174.8; IR (film) 3400, 1738, 1656 cm^{-1}; HRMS (FAB) Calcd for (M+H)+ 292.1107 Found 292.1176.

General Procedure A1 – Vinyl AA Ozonolysis (DMS Ozonide Reduction)

(±)-Methyl N-Benzoyl-α-formylalaninate (5a). Methyl N-benzoyl-α-vinylalaninate (**4a**)[4] (233 mg, 1.00 mmol) was dissolved in 10 mL of CH_2Cl_2 and cooled to –78 ºC. Ozone was bubbled through the solution until a blue color persisted and starting material was consumed. After purging excess ozone with an oxygen stream, dimethyl sulfide (220 μL, 3.00 mmol) was added at rt and stirring continued for 10 h. The volatiles were then distilled and the crude aldehyde was purified by SiO_2 flash chromatography (100→70% hexane/EtOAc) to give **5a** (204 mg, 87%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.79 (s, 3H), 3.82 (s, 3H), 7.34 (bs, 1H), 7.44 (m, 2H), 7.52 (m, 1H), 7.82 (m, 2H), 9.63 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.0, 53.7, 67.0, 127.3, 128.7, 132.3, 132.7, 166.6, 169.2, 193.2; IR (film) 3322, 1735, 1636 cm^{-1}; HRMS (FAB) Calcd for $(M+H)^+$ 236.0845 Found 236.0927.

General Procedure A2 – Vinyl AA Ozonolysis (Zn/HOAc Ozonide Reduction)

(±)-Methyl N-Benzoyl-α-formylphenylalaninate (5b). Methyl N-benzoyl-α-vinylphenylalaninate (**4b**)[4] (322 mg, 1.04 mmol) was dissolved in 10 mL of CH_2Cl_2 and treated with ozone as in General Procedure A1. The resulting ozonide solution was added dropwise into refluxing 50% AcOH (aq, 40 mL) and zinc (300 mg). After 1h the reaction mixture was poured into ether (30 mL) and saturated $NaHCO_3$(aq). Following further extraction with ether (30 mL x 2), the combined ether extracts were dried ($MgSO_4$), filtered, evaporated, and chromatographed (20% EtOAc/hexane) to give **5b** (301 mg, 93%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.70 (d, *J* = 7.25 Hz, 2H), 3.80 (s, 3H), 7.03 (s, 1H), 7.23 (s, 5H), 7.45 (m, 2H), 7.53 (m, 1H), 7.74 (d, *J* = 7.25 Hz, 2H), 9.66 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 37.0, 53.4, 71.8, 126.9, 127.01, 127.34, 128.34, 128.5, 128.6, 129.5, 129.6, 129.6, 132.2, 132.6, 134.1, 166.6, 167.4, 192.3.; IR (film) 1729, 1647, cm^{-1}; HRMS (FAB) Calcd for $(M+H)^+$ 312.1236 Found 312.1245.

(±)-Methyl N-Benzoyl-α-formyl-(3'-*O*-*tert*-butyldimethylsilyl)-*m*-tyrosinate (5c). From **4c** (396 mg, 0.90 mmol), following General Procedure A2, and SiO_2 chromatorgraphy (20% EtOAc/hexane), was obtained **5c** (263 mg, 66%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.90 (s, 9H), 3.64 (br s, 2H), 3.81 (s, 3H), 6.51 (s, 1H), 6.61 (m, 1H), 6.69 (m, 1H), 7.08 (m, 1H), 7.18 (br s, 1H), 7.42 (m, 2H), 7.51 (m, 1H), 7.75 (m, 2H), 9.64 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.7, -4.6, -3.9, 25.4, 25.5, 36.9, 53.2, 121.3, 121.5, 122.6, 127.1, 127.2, 127.3, 127.4, 128.6, 128.7, 128.7, 129.3, 129.5, 132.3, 132.4, 171.3; IR (film) 1737, 1732 cm^{-1}; HRMS (FAB) Calcd for $(M+H)^+$ 442.2050 Found 442.2058.

(±)-Methyl N-Benzoyl-α-formyl-3',4'-bis(*tert*-butyldimethylsilyloxy)phenylalaninate (5d). From from **4d**[4] (1.15 g, 2.02 mmol), following General Procedure A2, and chromatography (20% EtOAc/hexane) was obtained **5d** (1.14 g, 99%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.16 (s, 6H), 0.89 (s, 9H), 0.95 (s, 9H), 3.58 (br s, 2H), 3.80 (s, 3H), 6.50 (s, 1H), 6.69(m, 2H), 7.17 (s, 1H), 7.42(m, 2H), 7.53 (m, 1H), 7.73 (m, 2H), 9.65 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.3, -4.2, -4.1, -4.0, 18.2, 18.4, 25.6, 25.7, 25.9, 36.6, 53.5, 71.8, 121.0, 122.5, 122.7, 127.0, 127.2, 128.5, 128.6, 128.7, 132.2, 132.7, 146.4, 146.9, 166.6, 167.6, 192.6; IR (film) 1732, 1661 cm^{-1}; Anal. Calcd for $C_{30}H_{45}NO_6Si_2$ (571.87): C, 63.01; H, 7.93, N, 2.45 Found: C, 62.86; H,7.79;N, 2.49.

(±)-Methyl Nα,Nε-Dibenzoyl-α-formyllysinate (5e). From **4e**[5] (356 mg, 0.90 mmol), following General Procedure A2, and purifying the crude aldehyde with SiO_2 chromatography (20% EtOAc/hexane), was obtained **5e** (302 mg, 84%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (m, 1 H), 1.38 (m, 1H), 1.58 (m, 2H), 2.27 (t, *J* = 8.70 Hz, 2H), 3.32 (m, 1H), 3.46 (m, 1H), 3.76 (s, 3H), 6.86 (bs, 1H), 7.33 (m, 4H), 7.43 (m, 2H), 7.71 9m, 2H), 7.89 (m, 2H), 7.97 (bs, 1H), 9.77 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.2, 29.4, 30.8, 38.2 53.1, 69.7, 126.9, 127.5, 128.4, 131.4, 132.0, 132.5, 167.3, 168.5, 169.2, 194.6 ; IR (film) 1730, 1637 cm^{-1}; HRMS (FAB) Calcd for $(M+H)^+$ 397.1763 Found 397.1772.

(±)-α,β-Dimethyl N-Benzoyl-α-formylaspartate (5f). From **4f** (208 mg, 0.70 mmol), General Procedure A1 and subsequent column chromatography (20% EtOAc/hexane) gave **5f** (129 mg, 65%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.43 (d, *J* = 18 Hz, 1H), 3.62 (d, *J* = 18 Hz, 1H), 3.66 (s, 3H), 3.83 (s, 3H), 7.47 (t, *J* = 8 Hz, 2H), 7.56 (m, 1H), 7.74, (bs, 1H), 7.83 (d, J = 7 Hz, 2H), 9.46 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 36.2, 52.2, 54.0, 69.2, 127.3, 128.8, 132.3, 132.5, 166.6, 166.7, 170.9, 190.6; IR (film) 3397, 1733, 1654 cm^{-1}; HRMS (FAB) Calcd for $(M+H)^+$ 294.0978 Found 294.0977.

General Procedure B (McCarthy Fluoromethylenation)

(±)-Methyl N-Benzoyl-α-(E)-(2'-fluoro-2'-benzenesulfonyl)vinylalaninate (7a). To a solution of diethyl α-fluoro-α-(phenylsulfonyl)methylphosphonate[5] (McCarthy's reagent, 49 mg, 0.16 mmol) in the THF (1 mL) at –78 °C was added LiHMDS (1 M in THF, 158 μL, 0.16 mmol) and the temperature maintained for 30 min. Then **5a** (34 mg, 0.14 mmol) in THF (0.5 mL) was added, via cannula, and the dry ice bath removed. After stirring overnight at rt, **5a** had been consumed and TLC indicated considerable product formation. The reaction was quenched with NH_4Cl (sat'd, aq) and the product extracted with ether (3 x 15 mL). The combined organics were dried ($MgSO_4$), filtered, evaporated, and chromatographed (20% EtOAc/hexane) to give **7a** (41.3 mg, 74%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.83 (s, 3H), 3.80 (s, 3H), 6.97 (d, *J* = 34 Hz, 1H), 7.07 (s, 1H), 7.38 (m, 2H), 7.51 (m, 3H), 7.65 (m, 3H), 7.93 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.6, 24.1, 24.2, 54.1, 57.7, 119.1, 127.4, 129.0, 129.8, 132.4, 133.6, 134.8, 166.7, 172.1; ^{19}F NMR (470 MHz, $CDCl_3$) δ -94.01 (d, *J* = 34 Hz); IR (film) 1743, 1643 cm^{-1}; Anal. Calcd for $C_{19}H_{18}NSO_5F$ (391.42): C, 58.30; H, 4.64; N, 3.58 Found: C, 58.15; H, 4.61; N, 3.52.

(±)-Methyl N-Benzoyl-α-(E)-(2'-fluoro-2'-benzenesulfonyl)vinylphenylalaninate (7b). Following General Procedure B, from McCarthy's reagent[5] (86 mg, 0.28 mmol), LiHMDS (279 μl, 0.28 mmol) and **5b** (79 mg, 0.25 mmol) in was obtained **7b** (52 mg, 44%), following chromatography (10% EtOAc/hexane): ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.38 (d, *J* = 13.5 Hz, 1H), 3.82 (s, 3H), 3.89 (d, *J* = 13.5 Hz, 1H), 6.90 (d, *J* = 33 Hz, 1H), 7.00 (m, 2H), 7.01 (s, 1H), 7.22 (m, 3H), 7.38 (m, 2H), 7.49 (m, 1H), 7.56 (m, 4H), 7.65 (m, 1H), 7.95 (d, *J* = 8, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.15, 41.24, 53.51, 61.56, 118.01, 126.88, 127.61, 127.73, 128.38, 128.56, 128.61, 128.66, 129.26, 129.37, 129.51, 129.78, 131.89, 133.57, 133.94, 134.45, 136.94, 136.97, 152.56, 154.97, 166.27, 170.18; ^{19}F NMR (470 MHz, $CDCl_3$) δ -121.73 (d, *J* = 34 Hz); IR (film) 1743, 1659 cm^{-1}; HRMS (FAB) Calcd for $(M+H)^+$ 468.1281 Found 468.1270.

(±)-Methyl N-Benzoyl-α-(E)-(2'-fluoro-2'-benzenesulfonyl)vinyl-(3''-O-*tert*-butyldimethylsilyl)-*m*-tyrosinate (7c). Following General Procedure B, from McCarthy's reagent[5] (46 mg, 0.15 mmol), LiHMDS (180 μl, 0.18 mmol) and **5c** (50 mg, 0.11 mmol) was obtained **7c** (37.1 mg, 55%), following chromatography (20% EtOAc/hexane): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.89 (s, 9H), 3.32 (d, *J* =

13.5 Hz, 1H), 3.81 (s, 3H), 3.86 (d, *J* = 13.5 Hz, 1H), 6.50 (m, 1H), 6.57 (d, *J* = 8 Hz, 1H), 6.69 (dd, *J* = 2,8, 1H), 6.87 (d, *J* = 33 Hz, 1H), 7.04 (m, 1H), 7.07 (bs, 1H), 7.53 (m, 8H), 7.95 (d, *J* = 8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -4.6, 25.5, 25.6, 25.6, 37.7, 41.0, 52.4, 53.5, 61.5, 118.2, 119.3, 121.7, 122.3, 122.8, 126.9, 127.0, 128.6, 128.7, 128.8, 129.4, 129.8, 129.4, 129.5, 129.5, 131.9, 133.6, 134.4, 135.5, 137.0, 152.6, 155.8, 166.2, 170.2; ^{19}F NMR (470 MHz, $CDCl_3$) δ -121.63 (d, *J* = 34 Hz); IR (film) 1746, 1662 cm^{-1}; HRMS (FAB) Calcd for $(M+H)^+$ 604.2177 Found 604.2162.

(±)-Methyl N-Benzoyl-α-(E)-(2'-fluoro-2'-benzenesulfonyl)vinyl-[3'',4''-bis-(*tert*-butyldimethylsilyloxy)]phenylalaninate (7d). Following General Procedure B, from McCarthy's reagent[5] (46 mg, 0.14 mmol), LiHMDS (180 μl, 0.18 mmol) and **5d** (65 mg, 0.11 mmol) was obtained **7d** (47 mg, 57 %) after chromatography (20% EtOAc/hexene): ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.15 (s, 6H), 0.88 (s, 9H), 0.94 (s, 9H), 3.27 (d, *J* = 14 Hz, 1H), 3.77 (d, *J* = 14 Hz, 1H),3.80 (s, 3H), 6.45 (m, 1H), 6.50 (s, 1H), 6.66 (d, *J* = 8 Hz, 1H), 6.88 (d, *J* = 33 Hz, 1 H), 7.07 (s, 1H), 7.35 (t, *J* = 8 Hz, 2H), 7.7.46 (m, 1H), 7.54 (m, 4H) 7.64 (m, 1H), 7.95 (d, *J* = 8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.19, -4.16, -4.06, -4.03, 18.3, 18.5, 25.8, 25.9, 40.8, 53.6, 61.5, 118.4, 121.0, 122.6, 122.9, 127.0, 128.6, 128.7, 129.4, 131.9, 133.6, 134.5, 136.9, 146.62, 146.8, 152.1, 155.1 166.1, 170.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ –121.97(d, *J* = 33 Hz); IR (film) 1746, 1667 cm^{-1}; Anal Calcd for $C_{37}H_{50}NO_7FSi_2S$ (728.05): C, 61.04; H, 6.92; N,1.92 Found: C, 60.98, H, 7.12; N, 1.76.

(±)-Methyl Nα,Nε-Dibenzoyl-α-(E)-(2'-fluoro-2'-benzenesulfonyl)vinyllysinate (7e). Following General Procedure B, from McCarthy's reagent[5] (98 mg, 0.32 mmol), LiHMDS (318 μl, 0.30 mmol) and **5e** (115 mg, 0.30 mmol) was obtained gave **7e** (98 mg, 61%), following flash chromatography (20% EtOAc/hexene): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (m, 1H), 1.49 (m, 1H), 1.58 (m, 1H) 1.81 (m, 1H), 2.17 (m, 1H), 2.47 (m, 1H), 6.42 (br s, 1H), 6.62 (br s, 1H), 7.01 (d, *J* = 33 Hz, 1H), 7.26-7.93 (m, 15H); ^{19}F NMR (470 MHz, $CDCl_3$) δ -122.81 (d, *J* = 34 Hz); IR (film) 1742, 1642 cm^{-1}; HRMS (FAB, 3-NOBA) Calcd for $C_{29}H_{29}N_2O_6SFNa$ $(M+Na)^+$ 575.1628 Found 575.1618.

(±)-α,β-Dimethyl N-Benzoyl-α-(E)-(2'-fluoro-2'-benzenesulfonyl)vinylaspartate (7f). Following General Procedure B, from McCarthy's reagent[5] (145 mg, 0.47 mmol), LiHMDS (0.60 mL, 0.60 mmol) and **5f** (115 mg, 0.39 mmol) was obtained **7f** (73 mg, 41%), after chromatography (100→30% hexane/EtOAc): ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.22 (d, *J* = 16 Hz, 1H), 3.62 (s, 3H), 3.69 (d, *J* = 16 Hz, 1H), 3.83 (s, 3H), 6.69 (d, *J* = 33 Hz, 1H), 7.41 (m, 2H), 7.50 (m, 3H), 7.68 (m, 4H), 7.92 (d, *J* = 8 Hz, 2H); ^{13}C NMR (600 MHz, $CDCl_3$) δ 39.4, 52.2, 54.0, 58.4, 116.0, 127.1, 128.7, 128.7, 129.4, 132.1, 133.2, 134.9, 166.2, 170 ; ^{19}F NMR (376 MHz, $CDCl_3$) –121.12 (d, *J* = 33 Hz); IR (film) 1750, 1671 cm^{-1}; $(M+H)^+$ 450.1024 Found 450.1026.

General Procedure C (Sulfone ⇒ Stannane Interchange)

(±)-Methyl N-Benzoyl-α-(E)-[2'-fluoro-2'-(tri-*n*-butyl)stannyl]vinylalaninate (9a).

To a solution of **7a** (41 mg, 0.10 mmol) in benzene (1 mL) was bubbled argon for 2 min followed by the addition of tributyltin hydride (64 mg, 0.20 mmol) and AIBN (2.0 mg, 0.01 mmol) under Ar atmosphere. The reaction was heated under reflux for 24 h, evaporated and chromatographed (100→90% hexane/EtOAc) to give **9a** (45 mg, 80%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (m, 9H), 0.99 (m, 6H), 1.30 (m, 6H), 1.50 (m, 6H), 1.81 (s, 3H), 3.78 (s, 3H) 5.38 (d, *J* = 56 Hz, 1H), 7.40 (m, 2H), 7.46 (d, *J* = 7 Hz, 1H), 7.49 (bs, 1H), 7.77 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.7, 10.1, 13.5, 13.6, 24.3, 26.8, 27.0, 27.2, 28.6, 28.7, 28.8, 52.9, 57.9, 58.0, 124.2, 124.2, 127.0, 127.1, 128.4, 131.4, 134.6, 165.9, 172.2, 173.9, 174.7; ^{19}F NMR (470 MHz, $CDCl_3$) -94.99 (d, *J* = 55 Hz); IR (film) 1741, 1525 cm^{-1}; Anal. Calcd for $C_{25}H_{40}NO_3FSn$ (540.29): C, 55.58; H, 7.46; N, 2.59 Found: C, 54.85; H, 7.34; N, 2.54.

(±)-Methyl N-Benzoyl-α-(E)-[2'-fluoro-2'-(tri-*n*-butyl)stannyl]vinylphenylalaninate (9b). Following General Procedure C, from **7b** (52 mg, 0.10 mmol), Bu_3SnH (65 mg, 0.22 mmol) and AIBN (2.0 mg, 0.01mmol), was obtained **9b** (62 mg, 91%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (m, 9H), 1.01 (m, 6H), 1.28 (m, 6H), 1.51 (m, 6H), 3.35 (d, *J* = 14 Hz, 1H), 3.80 (s, 3 H), 3.89 (d, *J* = 13 Hz, 1H), 5.43 (d, *J* = 56 Hz, 1H), 7.05 (m, 2H), 7.18 (m, 3H), 7.36(s, 1H), 7.39 (m, 2H), 7.46 (m, 1H), 7.69 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.1, 13.6, 27.0, 28.7, 40.9, 52.8, 127.0, 128.1, 128.5, 130.0, 131.4, 135.8, 166.1, 172.7, 173.5, 174.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ -93.45 (d, *J* = 55 Hz); IR (film) 1742, 1667 cm^{-1}; HRMS (FAB) Calcd for $(M+H)^+$ 618.2405 Found 618.2407.

(±)-Methyl N-Benzoyl-α-(E)-[2'-fluoro-2'-(tri-*n*-butyl)stannyl]vinyl-(3''-O-*tert*-butyldimethylsilyl)-*m*-tyrosinate (9c). Following General Procedure C, from **7c** (19.3 mg, 0.03 mmol), Bu_3SnH (19 mg, 0.07 mmol) and AIBN (0.5 mg, 0.003 mmol) was obtained **9c** (23.2 mg, 97%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.84-0.92 (m, 18H), 1.01 (m, 6H), 1.30 (m, 6H), 1.50 (m, 6H), 3.27 (d, *J* = 13 Hz, 1H), 3.79 (s, 3H), 3.86 (d, *J* = 14 Hz, 1H), 5.42 (d, *J* = 55 Hz, 1H), 6.53 (s, 1H), 6.63 (m, 2H), 7.02 (m, 1H), 7.38 (m, 2H), 7.41 (s, 1H), 7.45 (m, 1H), 7.71 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ –4.6, 10.2, 13.6, 17.5, 18.0, 25.6, 26.8, 27.3, 28.7, 40.8, 52,8, 61.9, 118.6, 121.9, 123.0, 127.0, 128.48, 128.9, 131.3,137.2, 155.4, 166.0, 172.1 ^{19}F NMR (470 MHz, $CDCl_3$) δ -93.31 (d, *J* = 58 Hz); IR (film) 1743, 1668 cm^{-1}; HRMS (FAB) Calcd for $(M+H)^+$ 748.3219 Found 748.3189.

(±)-Methyl N-Benzoyl-α-(E)-[2'-fluoro-2'-(tri-*n*-butyl)stannyl]vinyl-[3'',4''-bis-(*tert*-butyldimethylsilyloxy)]phenylalaninate (9d). Following General Procedure C, from **7d** (12 mg, 0.02 mmol), Bu_3SnH (14.5 mg, 0.05 mmol) and AIBN (0.5 mg, 0.003 mmol) was obtained **9d** (11.4 mg, 79%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.01 (s, 6H), 0.14 (s, 6H), 0.89 (m, 27H), 1.00 (m, 6H), 1.26 (m, 6H), 1.55 (m, 6H), 3.19 (d, *J* = 14 Hz, 1H), 3.79 (d, *J* = 13 Hz, 1H), 3.78 (s, 3H), 5.42 (d, *J* = 56 Hz, 1H), 6.50 (s, 1H), 6.63 (m, 2H), 7.40 (m, 4H), 7.68 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ –4.3, -4.2, -4.1, 10.1, 13.6, 25.8, 25.9, 27.0, 28.7, 40.5, 52.7, 62.0, 120.5, 122.8, 123.0, 127.1, 128.4, 128.8, 131.3, 135.0, 146.4, 165.8, 172.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ –93.09 (d, *J* = 55 Hz); IR

(film) 1742, 1668 cm^{-1}; HRMS (FAB) Calcd for $(M+H)^+$ 878.4033 Found 878.4026.

(±)-Methyl Nα,Nε-Dibenzoyl-α-(E)-[2'-fluoro-2'-(tri-*n*-butyl)stannyl]vinyllysinate (9e) Following General Procedure C, from **7e** (48 mg, 0.10 mmol), Bu_3SnH (51 mg, 0.20 mmol) and AIBN (2.0 mg, 0.01 mmol) was obtained **9e** (46 mg, 76 %): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (t, *J* = 7.3, 9H), 0.98 (m, 6H), 1.28 (m, 6H), 1.48 (m, 6H), 1.65 (m, 1H), 2.12 (m, 1H), 2.68 (m, 1H), 3.45 (m, 2H), 3.78 (s, 3H), 5.33 (d, *J* = 56 Hz, 1H), 6.2 (bs, 1H), 7.31 (m, 2H), 7.35 (m, 4H), 7.61 (s, 1H), 7.67 (m, 2H), 7.75 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.8, 14.2, 21.5, 27.7, 29.4, 35.6, 39.8, 53.7, 127.5, 127.7, 129.1, 129.2, 131.9, 132.1, 166.7, 168.2, 17.05; ^{19}F NMR (470 MHz, $CDCl_3$) δ -93.04 (d, *J* = 58 Hz); IR (film) 1737, 1643 cm^{-1}; HRMS (FAB, 3-NBA) Calcd for $C_{35}H_{51}N_2O_4FSnNa$ $(M+Na)^+$ 725.2753 Found 725.2753.

(±)-α,β-Dimethyl N-Benzoyl-α-(E)-[2'-fluoro-2'-(tri-*n*-butyl)stannyl]vinylaspartate (9f). Following General Procedure C, from **7f** (70 mg, 0.16 mmol), (159 mg, 0.60 mmol) and AIBN (5.0 mg, 0.03 mmol) was obtained **9f** (47 mg, 50%). In this case only, the chromatography was carried out with a slightly more polar eluent (100→80% hexane/EtOAc): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (t, *J* = 7 Hz, 9H), 1.00 (dd, *J* = 8 Hz, 5H), 1.28 (m, 7H), 1.49 (m, 6H), 3.21 (d, *J* = 16 Hz, 1H), 3.77 (d, *J* = 16 Hz, 1H), 5.22 (d, *J* = 55 Hz, 1H), 7.41 (t, *J* = 8 Hz, 2H), 7.47 (d, *J* = 8 Hz, 1H), 7.77 (d, *J* = 7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.4, 13.7, 27.1, 27.4, 28.9, 29.0, 29.1, 41.6, 51.7, 52.9, 128.5, 128.8, 131.3, 135.9, 163.0, 170.1; ^{19}F NMR (564 MHz, $CDCl_3$) δ –92.80 (d, *J* = 55 Hz); IR (film) 1746, 1667 cm^{-1}; HRMS (FAB, 3-NBA) Calcd for $C_{27}H_{42}NO_5FSn$ $(M+H)^+$ 600.2148 Found 600.2144.

Cross-Coupling Chemistry

(±)-(3Z)-Methyl N-Benzoyl-4-fluoro-2-methyl-3,4-dehydro-homophenylalaninate (11). ***Via Stille Coupling:*** Fluorovinylstannane **9a** (10.2 mg, 19 μmol) was dissolved in THF (0.3 mL) and $Pd(PPh_3)_4$ (1.2 mg, 1.0 μmol), CuI (3.6 mg, 19 μmol) and iodobenzene (3.9 mg, 19 μmol) were added in a glove bag under Ar atmosphere. The reaction was heated at 65 °C for 7 h, after which time TLC clearly indicated product formation. The volatiles were was evaporated and the crude purified by preparative TLC (20% EtOAc/hexane) to give **11** (5.9 mg, 95%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.93 (s, 3H), 3.84 (s, 3H), 6.12 (d, *J* = 39 Hz, 1H), 7.33 (m, 3H), 7.42 (t, *J* = 9 Hz, 2H), 7.48 (s, 1H), 7.50 (m, 3H), 7.80 (d, *J* = 9 Hz, 2H); ^{19}F NMR (470MHz, $CDCl_3$) δ –113.85 (d, *J* = 39 Hz); IR (film) 1743, 1640 cm^{-1}; HRMS (FAB) Calcd for $(M+H)^+$ 328.1350 Found 328.1364.

(±)-(3Z)-Methyl N-Benzoyl-4-fluoro-2-methyl-(3'-*tert*-butyldimethylsilyloxy)-3,4-dehydro-homophenylalaninate (13). From fluorovinylstannane **9a** (10.2 mg, 19 μmol) $Pd(PPh_3)_4$ (1.2 mg, 1.0 μmol), CuI (3.6 mg, 19 μmol) and 4-(*tert*-butylsilyloxy)-iodobenzene[6] (6.4 mg, 19 μmol), after heating for 4 h at 65 °C, and performing prep TLC, as before, was obtained **13** (5.2 mg, 60%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.17 (s,

6H), 0.97 (s, 9H), 1.92 (s, 3H), 3.84 (s, 3H), 6.07 (d, *J* = 39 Hz, 1H), 6.79 (dd, *J* = 2, 8 Hz, 1H), 6.96 (t, *J* = 2 Hz, 1H), 7.15 (m, 2H), 7.44 (m, 4H), 7.80 (d, *J* = 8 Hz, 2H); ^{19}F NMR (470 MHz, $CDCl_3$) δ–113.40 (d, *J* = 39 Hz); IR (film) 1739, 1644 cm^{-1}; HRMS (FAB) Calcd for $(M+H)^+$ 458.2164 Found 458.2149.

(±)-(3E)-Methyl N-Benzoyl-4-fluoro-4-iodo-2-methyl-3,4-dehydro-butyrinate (12). Fluorovinylstannane **9a** (150 mg, 0.30 mmol) was dissolved in Et_2O (2.5 mL) at rt under Ar. I_2 (74 mg, 0.3 mmol) was added in 3 portions for 5 min. After stirring 2 h at rt, the solvent was removed in vacuo, column chromatography performed (20% EtOAc-hexane) to give **12** (97 mg, 92%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.81 (s, 3H), 3.83 (s, 3H), 6.05 (d, *J* = 36 v, 1H), 7.44 (t, *J* = 8.5 Hz, 2H), 7.50 (m, 1H), 7.77 (s, 1H), 7.78 (d, *J* = 8.5 Hz, 2H); ^{19}F NMR (470MHz, $CDCl_3$) δ –63.40 (d, *J* = 36 Hz); IR (film) 1743, 1644 cm^{-1}; HRMS (FAB) Calcd for $(M+H)^+$ 378.0003 Found 378.0010.

(±)-(3Z)-α-Methyl γ-Ethyl N-Benzoyl-4-fluoro-2-methyl-3,4-dehydro-glutamate (10). To a solution of **9a** (31.9 mg, 60 μmol) in toluene (0.5 mL), were added $Cl_2Pd(PPh_3)_2$ (4.0 mg, 6.0 μmol), CuCN (0.5 mg, 6.0 μmol) and ethyl chloroformate (10 mg, 90 μmol) at rt under Ar. After heating at 80 ^{0}C for 7.5 h, the reaction mixture was cooled and washed with 5% KF (aq) and brine. The aqueous phase was extracted further with ether. The combined organics were dried (Na_2SO_4), filtered and evaporated. SiO_2 flash chromatography (20% EtOAc/hexane) gave **10** (13 mg, 68%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.31 (t, *J* = 7, 3H), 1.86 (s, 3H), 3.83 (s, 3H), 4.25 (q, *J* = 7 Hz, 2H), 6.79 (d, *J* = 34 Hz, 1H), 7.42 (m, 2H), 7.49 (m, 1H), 7.77 (d, *J* = 8 Hz, 2H); ^{13}C NMR (600 MHz, $CDCl_3$) δ 14.5, 24.3, 54.0, 57.5, 62.5, 120.3, 120.3, 127.5, 129.0, 133.3, 133.9, 147.0, 148.8, 166.6, 172.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ –123.90 (d, *J* = 34 Hz); IR (film) 1735, 1739, 1636 cm^{-1}; HRMS (FAB) Calcd for $(M+H)^+$ 324.1248 Found 324.1252

(±)-(3Z)-Methyl N-Benzoyl-4-fluoro-2-methyl-3,4-dehydro-norvalinate (14)

Via Pd-Mediated Negishi Coupling: To α-fluorovinyl iodide **12** (10.5 mg, 28 μmol) and $Pd(PPh_3)_4$ (1.7 mg, 1.4 μmol) in Et_2O (0.2 mL) at rt under Ar, was added Me_2Zn (0.23 mL, 39 μmol of a 0.14M solution in 10% toluene/ether), via syringe. After stirring in the dark for 5 h, water was added and the reaction mixture extracted with ether. Following bicarbonate extraction, drying, filtration and evaporation, preparative TLC (40% EtOAc hexane) gave **14** (6.1 mg, 83%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80 (s. 3H), 1.88 (d, *J* = 17 Hz, 3H), 3.81 (s, 3H), 5.25 (d, *J* = 39 Hz, 1H), 7.42 9m, 2H), 7.47 (m, 1H), 7.77 (s, 1H), 7.78 (d, *J* = 8.67 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –95.64 (dq, *J* = 17, 39 Hz); IR (film) 1742, 1635 cm^{-1}; HRMS (FAB) Calcd for $(M+H)^+$ 266.1193 Found 266.1201

(±)-(3Z)-Methyl N-Benzoyl-4-fluoro-2-methyl-3,4-dehydro-norvalinate (14)

Via Ni-Mediated Knochel Coupling: To α-fluorovinyl iodide **12** (7.0 mg, 18.5 μmol) and $Ni(acac)_2$ (1.0 mg, 3.7 μmol) in THF/NMP (2:1 volume ratio, 0.3 mL), under Ar was added acetophenone (2.5 μl). Upon cooling to 0 °C, Me_2Zn (0.27 mL, 37 μmol of a 0.14M solution in 10% toluene/ether) was added, dropwise via syringe. The resulting

reaction mixture was heated to 45 ºC for 6 h, and then quenched at rt by the addition of NH_4Cl (sat'd, aq). Following extraction with ether, washing with brine, and drying, as usual, the crude product was purified by preparative TLC (40% EtOAc/hexane) to give **14** (3.9 mg, 80%).

(±)-(3Z)-Methyl N-Benzoyl-4-fluoro-2-methyl-3,4-dehydro-homophenylalaninate (11). ***Via Suzuki Coupling:*** To α-fluorovinyl iodide **12** (7.2 mg, 19 μmol), phenylboronic acid (3.0 mg, 23 μmol) and $Pd_2(dba)_3$ (1.0 mg, 1.0 μmol) in THF (0.6 mL) under Ar, was added KOH (58 μmol, 11 μl of 5.4 M aq solution), and the reaction stirred at rt for 6.5 h. The volatiles were evaporated and the residue taken up in Et_2O and washed sequentially, with water and brine. Drying (Na_2SO_4), filtration, evaporation and prep TLC (40% EtOAc/hexane) provided **11** (4.9 mg, 79%).

General Procedure D (Global Deprotection)

(±)-(Z)-α-(2'-Fluoro)vinylalanine Hydrochloride (15a). A suspension of **9a** (46.4 mg, 0.1 mmol) in 6 N HCl (2 mL) was refluxed for 17 h. Following sequential extraction with CH_2Cl_2 and EtOAc, the aqueous layer was evaporated, in vacuo, under mild heating (40 ºC) to give **15a** (13.4 mg, 89%): ^{1}H NMR (500 MHz, D_2O) δ 1.73 (s, 3H), 5.21 (dd, *J* = 5, 44 Hz, 1H), 6.77 (dd, *J* = 5, 82 Hz, 1H); ^{19}F NMR (470 MHz, $CDCl_3$) δ -117.85 (dd, *J* = 43, 82 Hz); HRMS (FAB) Calcd for $(M+H)^+$ 134.0617 Found 134.0616.

(±)-(Z)-α-(2'-Fluoro)vinylphenylalanine Hydrochloride (15b). Following General Procedure D, from **9b** (62 mg, 0.10 mmol), after 24 h reflux, was obtained **15b** (21 mg, 85%): ^{1}H NMR (500 MHz, D_2O) δ 3.19 (d, *J* = 14 Hz, 1H), 3.42 (d, *J* = 14 Hz, 1H), 5.32 (dd, *J* = 5, 45 Hz, 1H), 6.76 (dd, *J* = 5, 82 Hz, 1H), 7.33 (m, 2H), 7.45 (m, 3H); ^{13}C NMR (125 MHz, D_2O) δ 43.5, 110.3, 128.8, 129.7, 131.0, 134.4, 150.2, 152.3; ^{19}F NMR (470 MHz, D_2O) δ -116.71 (dd, *J* = 43, 80 Hz); HRMS (FAB) Calcd for $(M+H)^+$ 210.0930 Found 210.0929.

(±)-(Z)-α-(2'-Fluoro)vinyl-*m*-tyrosine Hydrochloride (15c). Following General Procedure D, from **9c** (23.2 mg, 0.030 mmol) after refluxing 24 h, was obtained **15c** (7.0 mg, 88%): ^{1}H NMR (500 MHz, D_2O) δ 3.24 (d, *J* = 14 Hz, 1H), 3.45 (d, *J* = 15 Hz, 1H), 5.36 (dd, *J* = 5, 45 Hz, 1H), 6.75 (d, *J* = 5 Hz, 0.5H), 6.81 (s, 1H), 6.90 (m, *J* = 83, 2.5H) 7.32 (m, 1H); ^{19}F NMR (470MHz, $CDCl_3$) δ -117.09 (dd, *J* = 46, 82 Hz); HRMS (FAB) Calcd for $(M+H)^+$ 226.0879 Found 226.0888.

(±)-(Z)-α-(2'-Fluoro)vinyl-3'',4''-dihydroxyphenylalanine Hydrochloride (15d). Following General Procedure D, from **9d** (47 mg, 0.060 mmol), after 15 h reflux, was obtained **15e** (14 mg, 93%): ^{1}H NMR (500 MHz, D_2O) δ 2.99 (d, *J* = 15 Hz, 1H), 3.41 (d, *J* = 15 Hz, 1H), 5.19 (dd, *J* = 5, 44 Hz, 1H), 6.68 (dd, *J* = 5, 82 Hz, 1H), 6.62 (dd, *J* = 2, 8 Hz, 1H), 6.70 (d, *J* = 2 Hz 1H), 6.79 (d, *J* = 8 Hz, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ –118.24 (dd, *J* = 45, 82 Hz); HRMS (FAB) Calcd for $(M+H)^+$ 242.0829 Found 242.0825.

(±)-(Z)-α-(2'-Fluoro)vinyllysine (15e). General Procedure D was followed, starting

from **9e** (98 mg, 0.14 mmol). After refluxing for 44 h and the usual extractive workup, the crude product was further purified by Dowex 50 cation exchange chromatography (elution with a step gradient: $H_2O \rightarrow 0.65$ N $NH_4OH \rightarrow 1.3$ N NHOH) to give **15e** (17 mg, 63%): ^{1}H NMR (500 MHz, D_2O) δ 1.22 (m, 1H), 1.34 (m, 1H), 1.53 (m, 2H), 1.94 (m, 2H), 2.82 (m, 2H), 5.09 (dd, *J* = 5, 44 Hz, 1H), 6.64 (dd, *J* = 5, 82 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 21.0, 27.3, 36.8, 39.8, 108.5, 126.2, 151.2, 153.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ -117.74 (dd, *J* = 46, 82 Hz); HRMS (FAB) Calcd for $(M+H)^+$ 191.1196 Found 191.1192.

(±)-α-[(2'Z)-Fluorovinyl]aspartate (15f). The same general protocol as for **9e** was followed for **9f** (46 mg (0.08 mmol), though refluxing was limited to 12 h. Extractive workup was followed by further purification with Dowex 50 (elution with a step gradient: $H_2O \rightarrow 0.65$ N NH_4OH) to give **15f** (7.1 mg, 52%): ^{1}H NMR (500 MHz, D_2O) δ 3.02 (dd, *J* = 18, 37 Hz, 2H), 5.02 (dd, *J* = 5, 44 Hz, 1H), 6.66 (dd, *J* = 5, 82 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 40.0, 59.0, 107.6, 150.0, 152.7, 172.8, 174.0; ^{19}F NMR (470 MHz, D_2O) δ –118.32 (dd, *J* = 45, 82 Hz); HRMS (FAB) Calcd for $(M+H)^+$ 178.0516 Found 178.0512.

References for the Supporting Information

[1]Columbo, L.; Di Giacomo, M.; Vinci, V.; Columbo, M.; Manzoni, L.; Scolastico, C. *Tetrahedron* **2003**, *59*, 4501-4513.

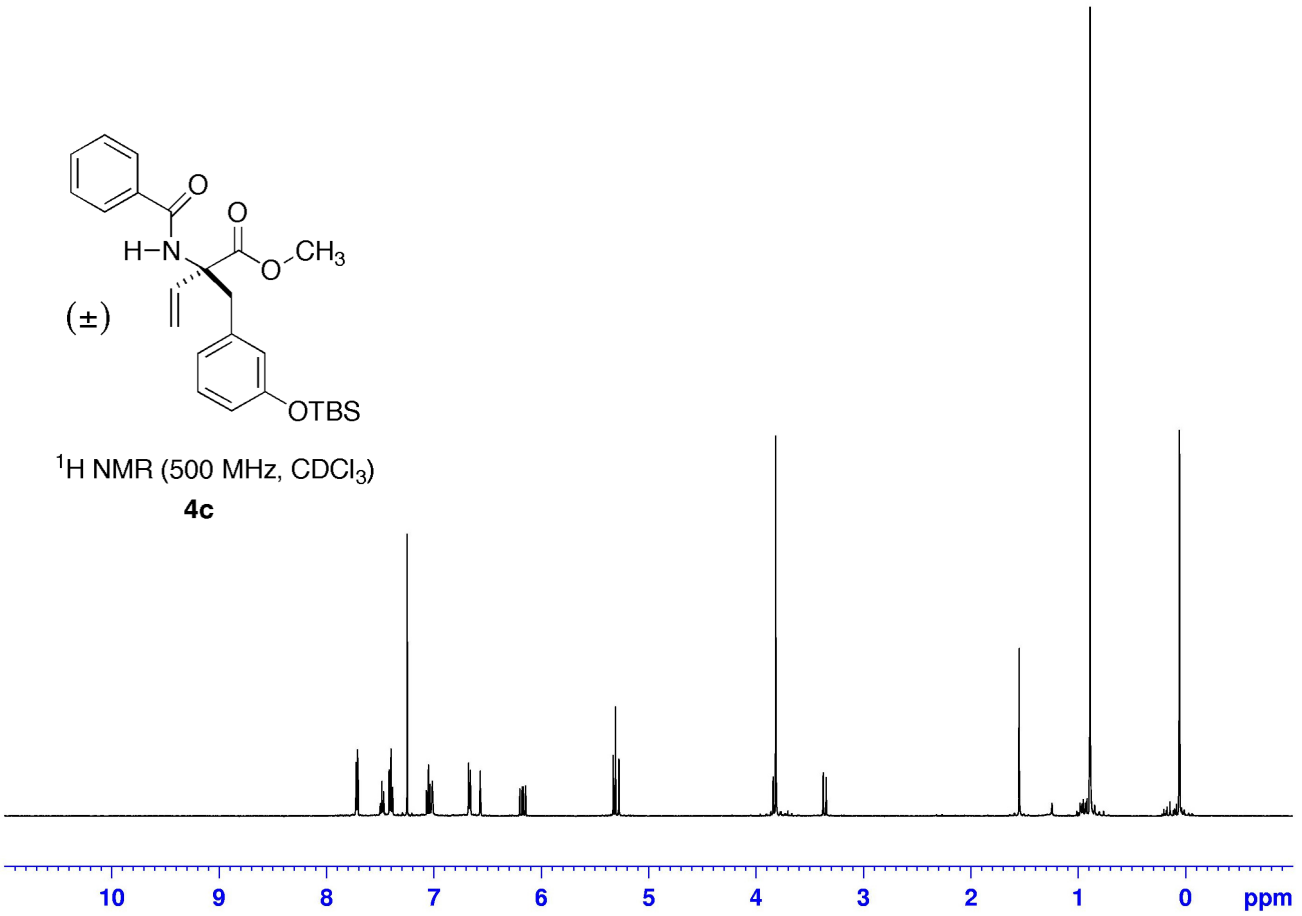
[2]Paradisi, M. P.; Zecchini, G. P. *Tetrahedron*, **1977**, *33*, 1729-1732.

[3]Meanwell, N. A.; Rosenfeld, M. J.; Trehan, A. K.; Romine, J. L.; Wright, J. J. K.; Brassard, C. L.; Buchanan, J. O.; Federici, M. E.; Fleming, J. S.; Gamberdella, M.; Zavoico, G. B.; Seiler, S. M. *J. Med. Chem.* **1992**, *35*, 3498-3512.

[4]Pedersen, M. L.; Berkowitz, D. B. *J. Org. Chem.* **1993**, *58*, 6966-6975.

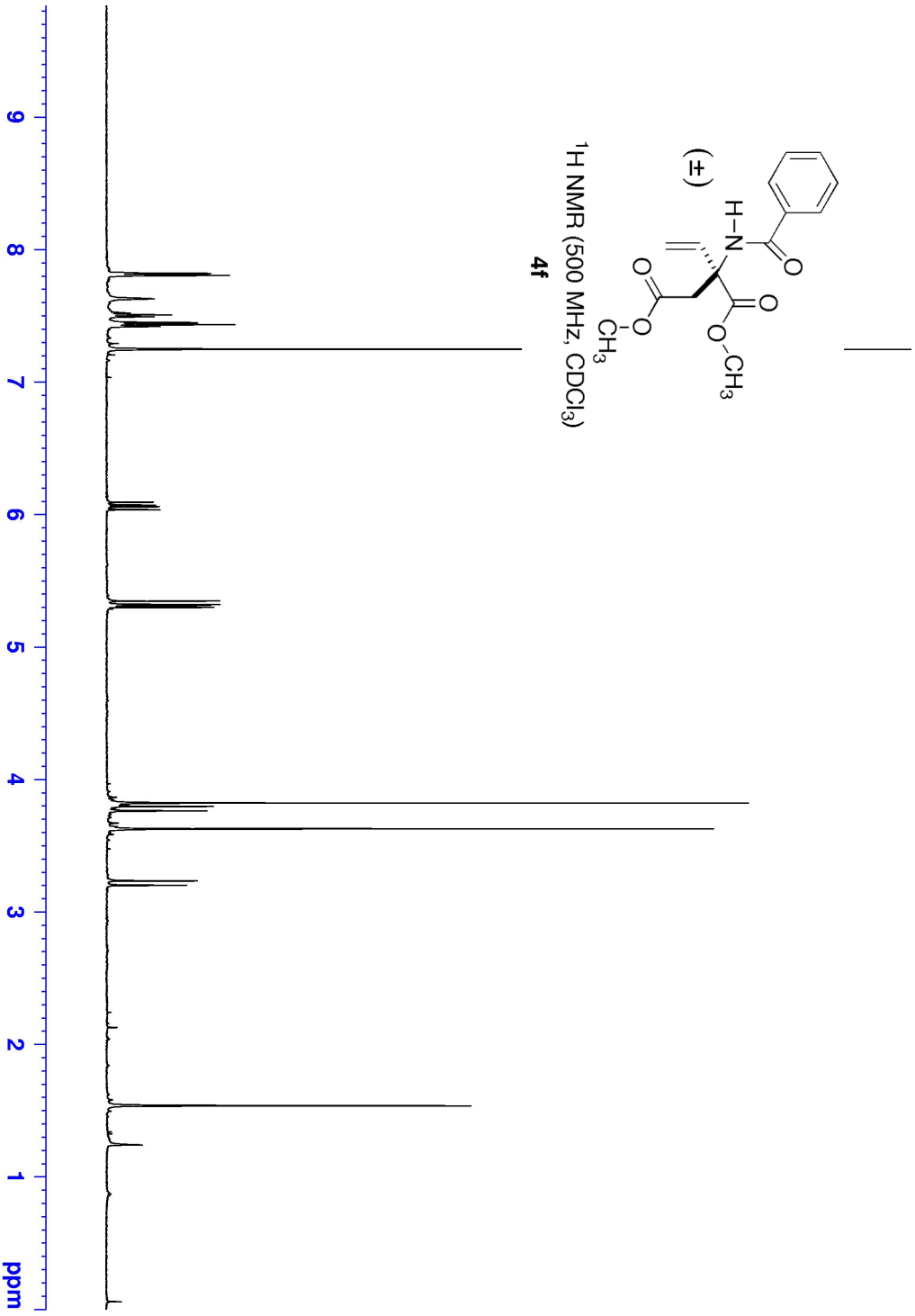
[5]Berkowitz, D. B.; Bose, M.; Asher, N. G. *Org. Lett.* **2001**, *3*, 2009-2012.

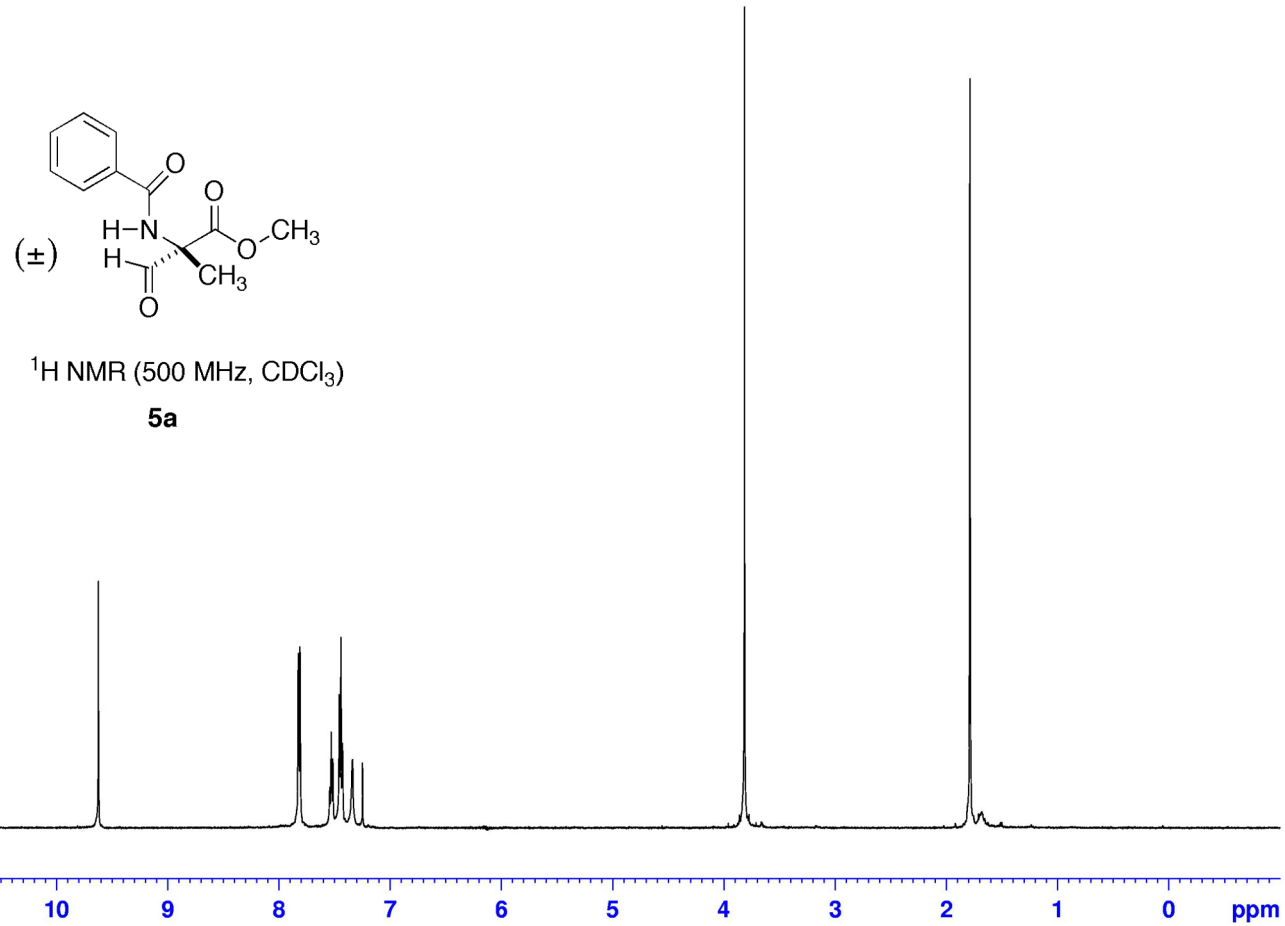
[6]Figadere, B.; Norman, A. W.; Henry, H. L.; Koeffler, H. P.; Zhou, J.-Y.; Okamura., W. H. *J. Med. Chem*, **1991**, *34*, 2452-2463.



^{1}H NMR (500 MHz, $CDCl_3$)

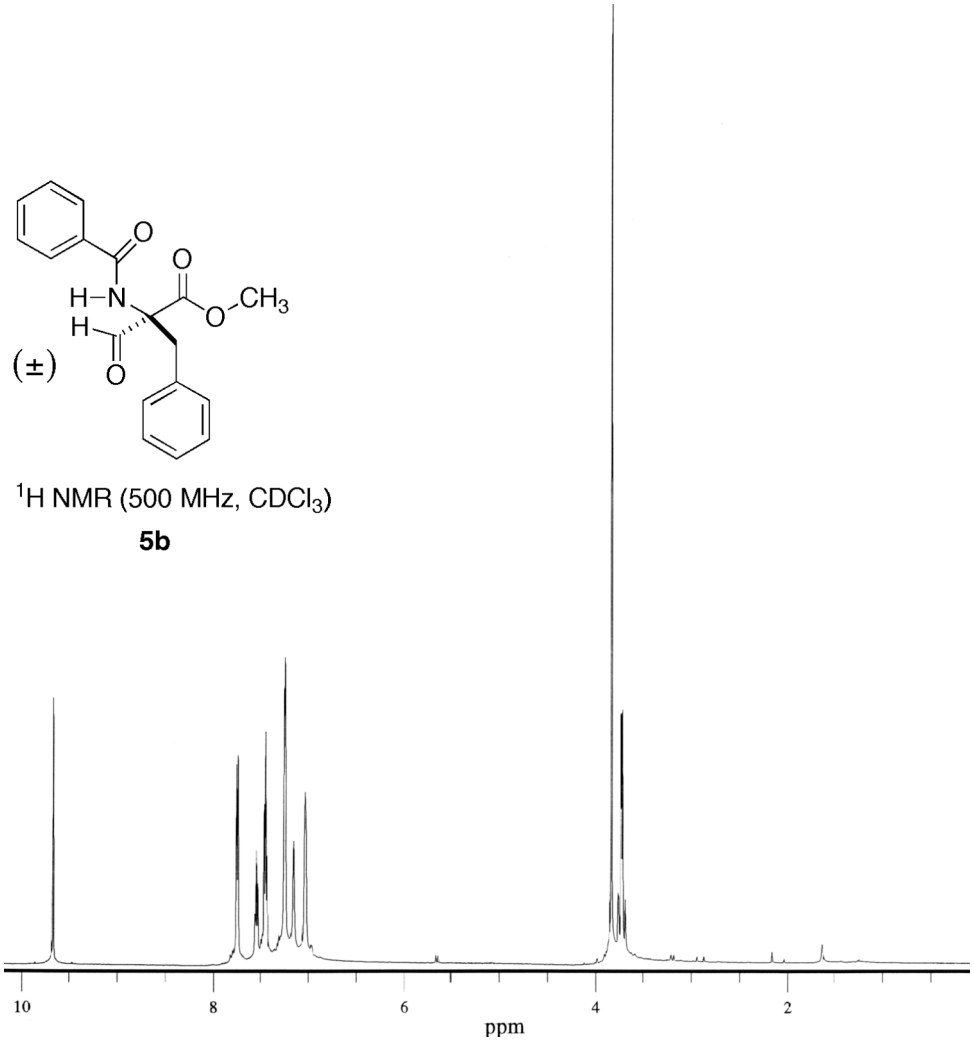
4c


(±)
H–N
O
O
O
O
O
CH3
CH3
1H NMR (500 MHz, CDCl3)
4f
9
8
7
6
5
4
3
2
1
ppm



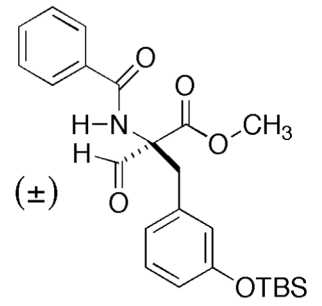
^{1}H NMR (500 MHz, $CDCl_3$)

5a



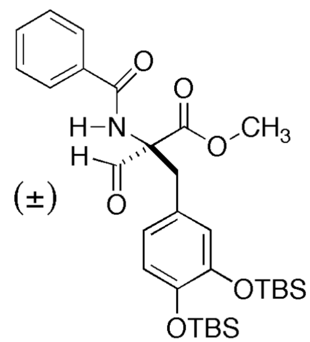
^{1}H NMR (500 MHz, $CDCl_3$)

5b



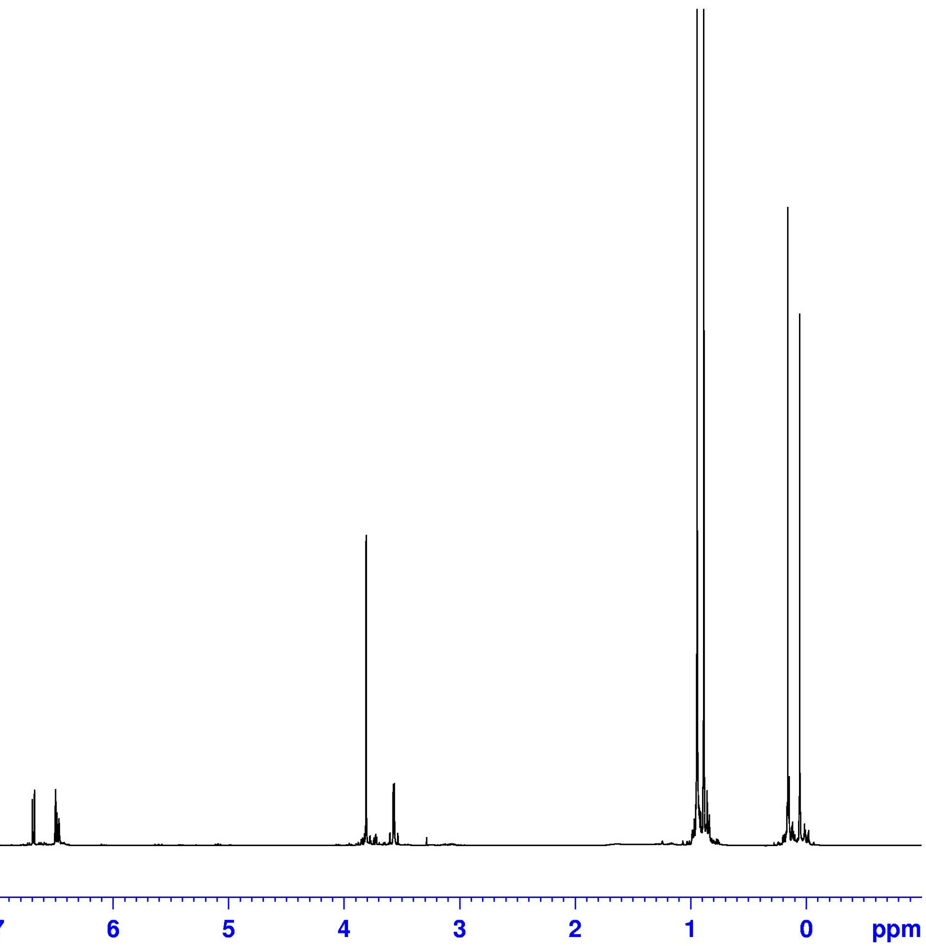
^{1}H NMR (500 MHz, $CDCl_3$)

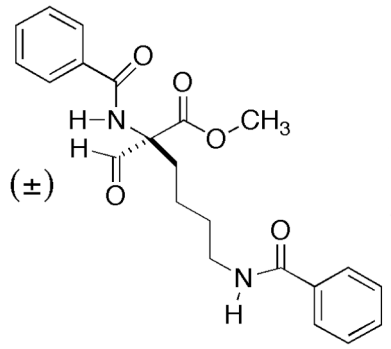
5c



^{1}H NMR (500 MHz, $CDCl_3$)

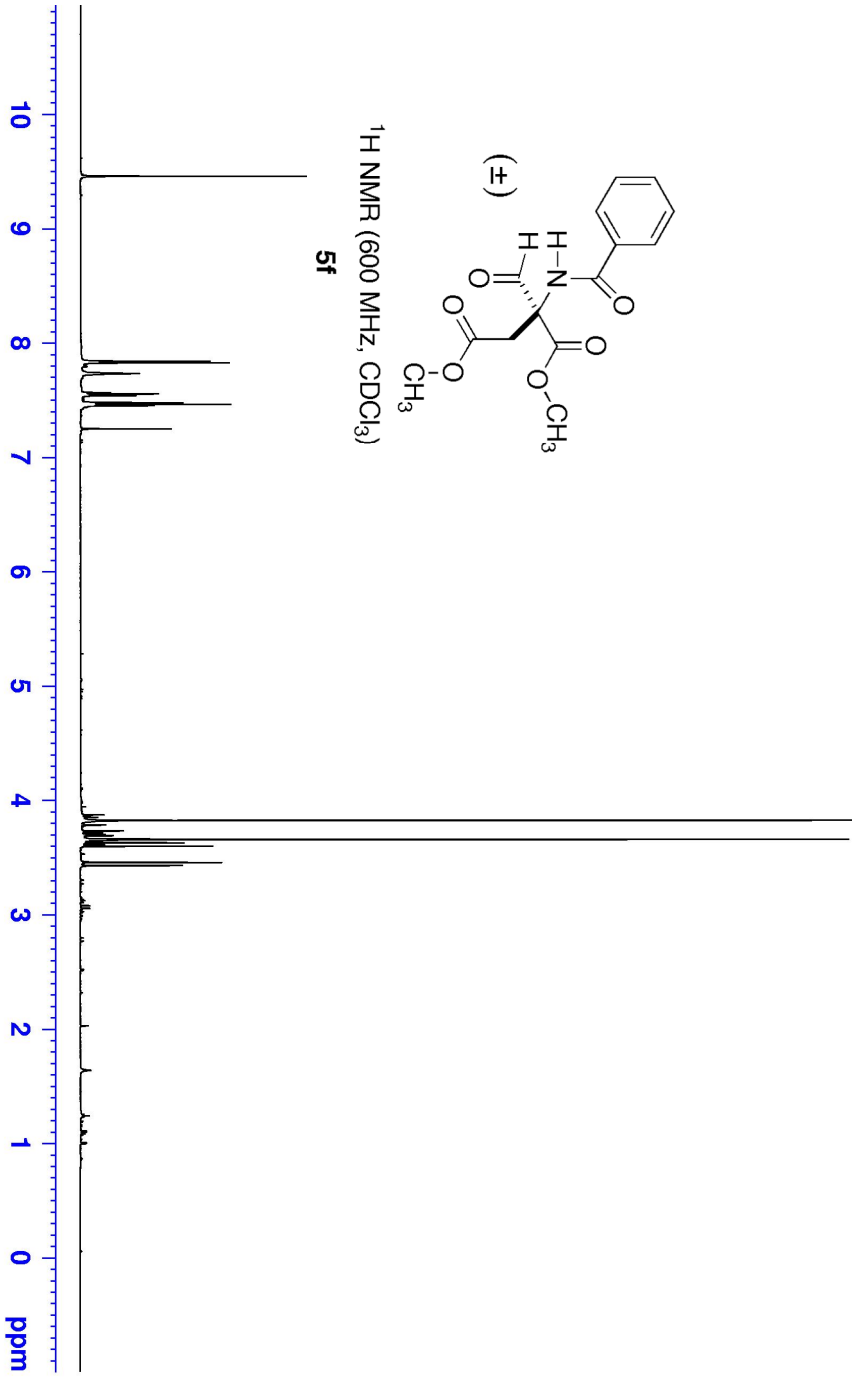
5d

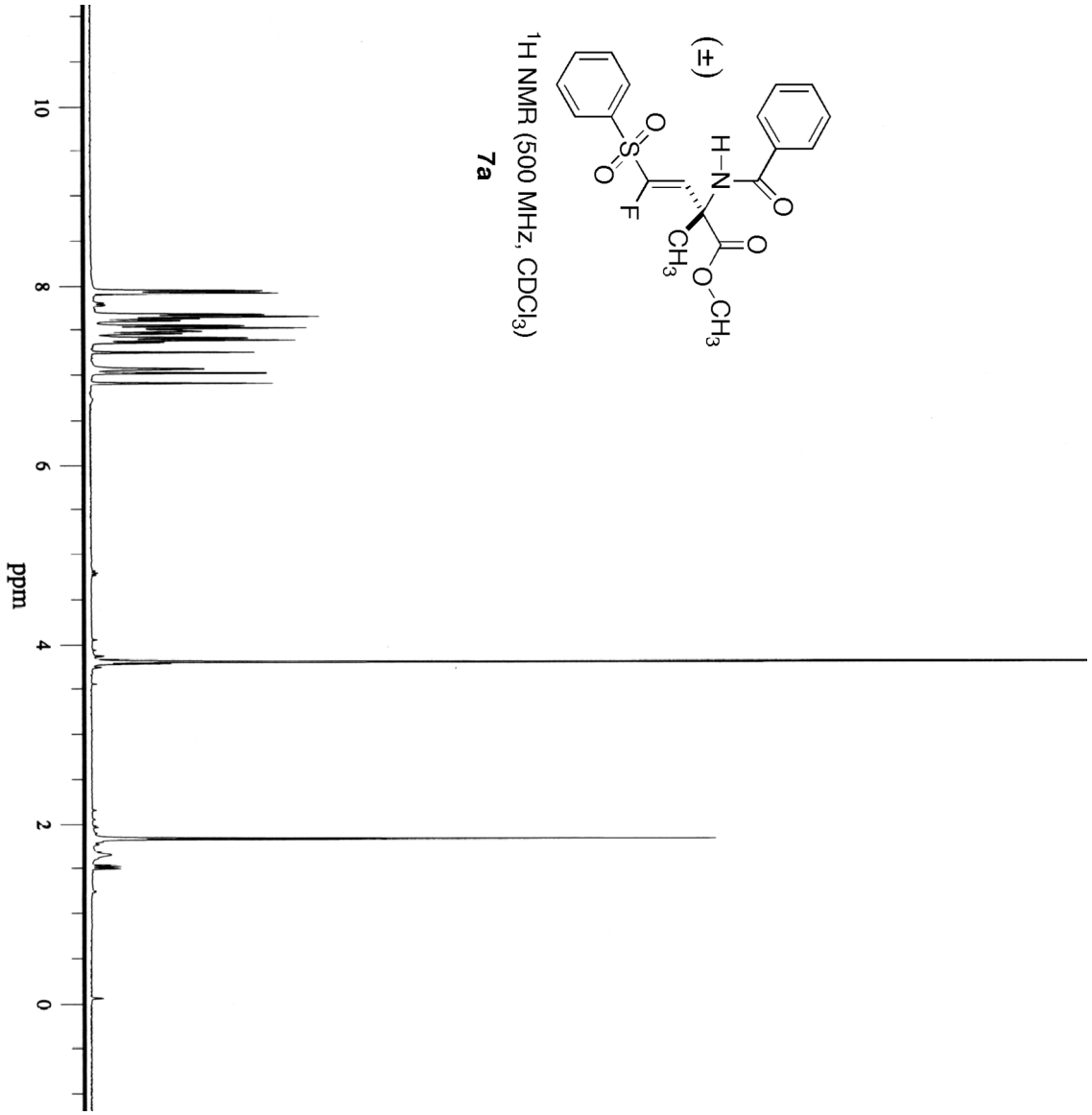


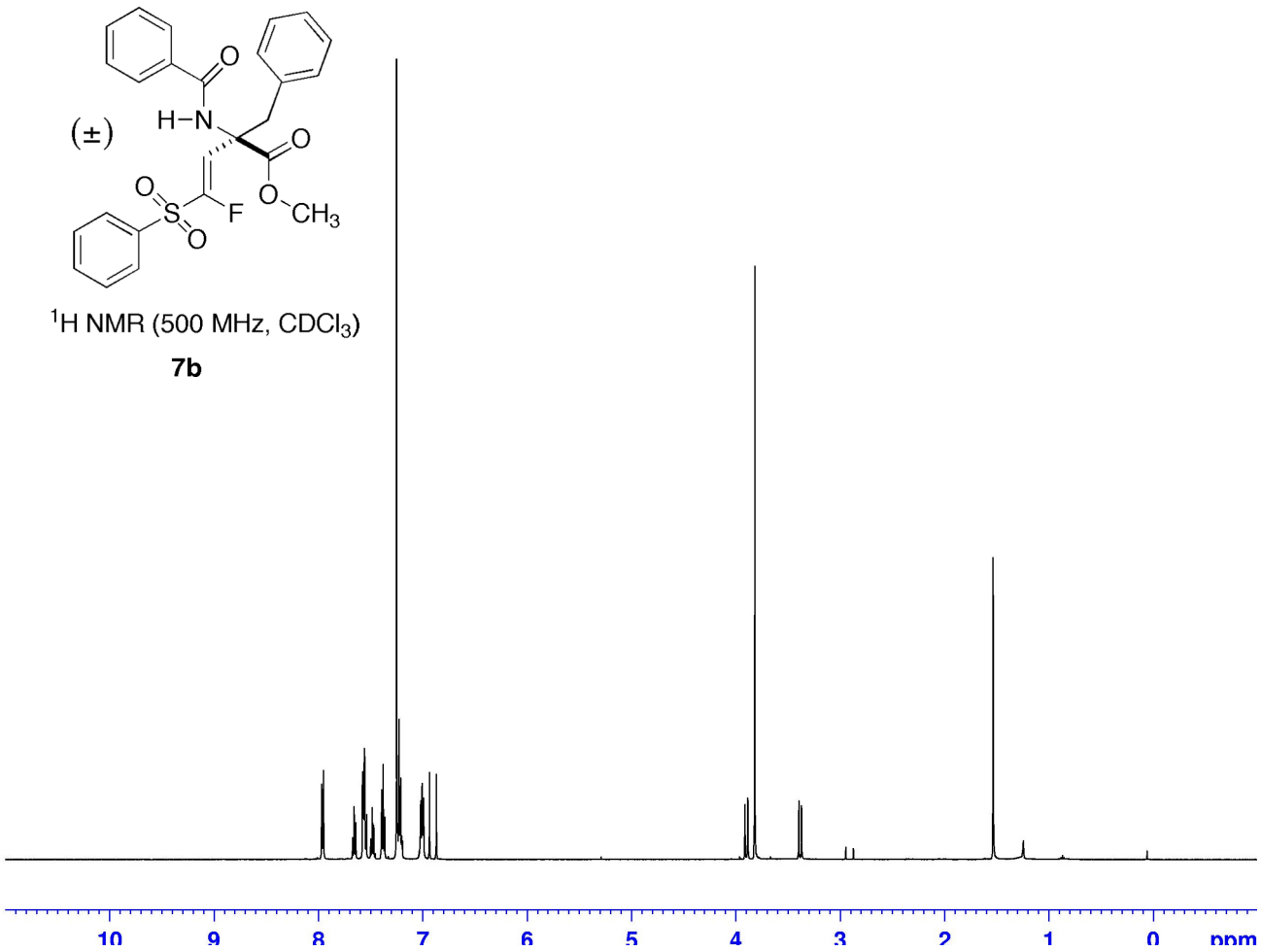


^{1}H NMR (300 MHz, $CDCl_3$)

5e

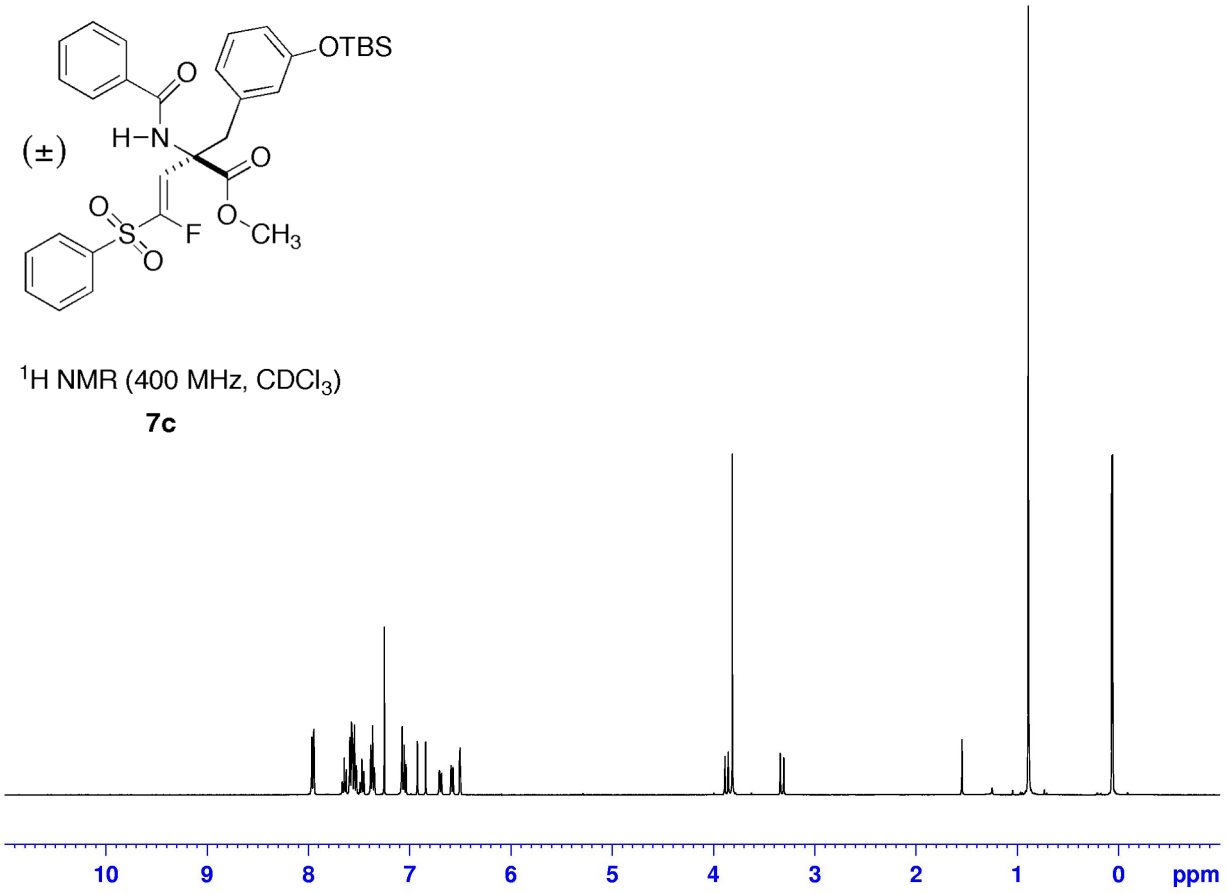

(±)
H–N
H
O
O
O
O
O–CH3
O
CH3
1H NMR (600 MHz, CDCl3)
5f
10
9
8
7
6
5
4
3
2
1
0
ppm


(±)
H–N
O
O
O
S
O
F
CH3
O
CH3
1H NMR (500 MHz, CDCl3)
7a
ppm
10
8
6
4
2
0



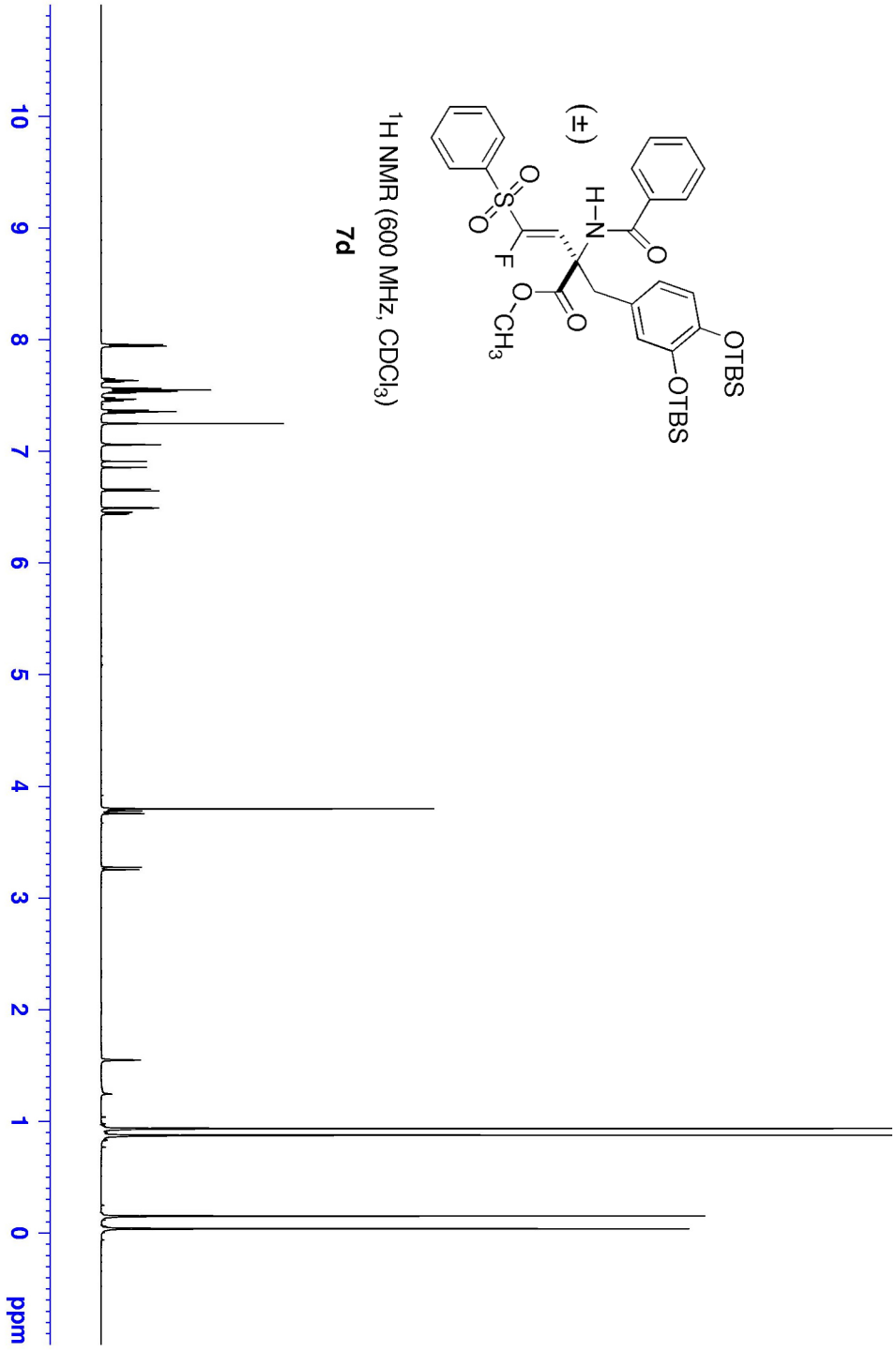
^{1}H NMR (500 MHz, $CDCl_3$)

7b



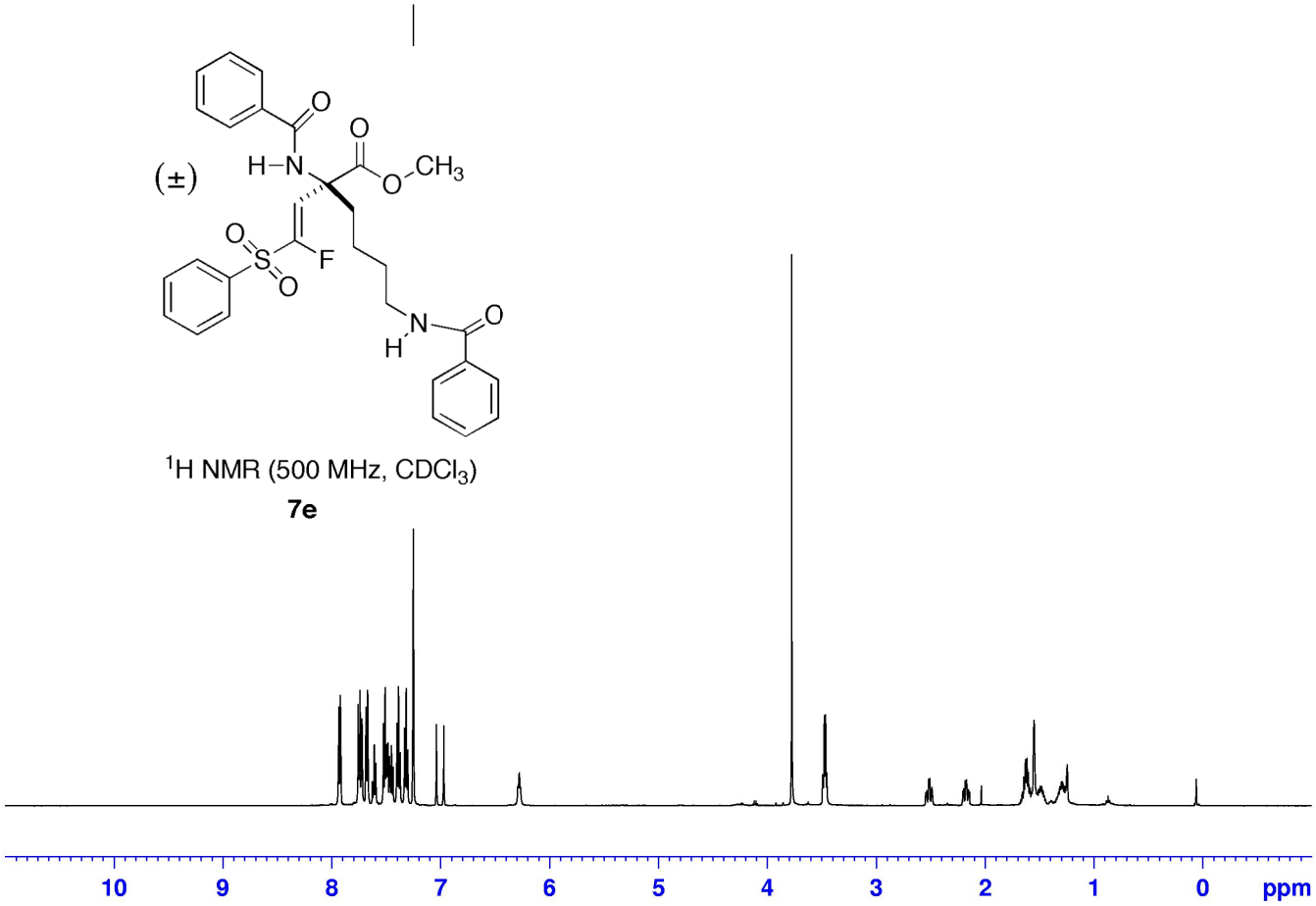
^{1}H NMR (400 MHz, $CDCl_3$)

7c



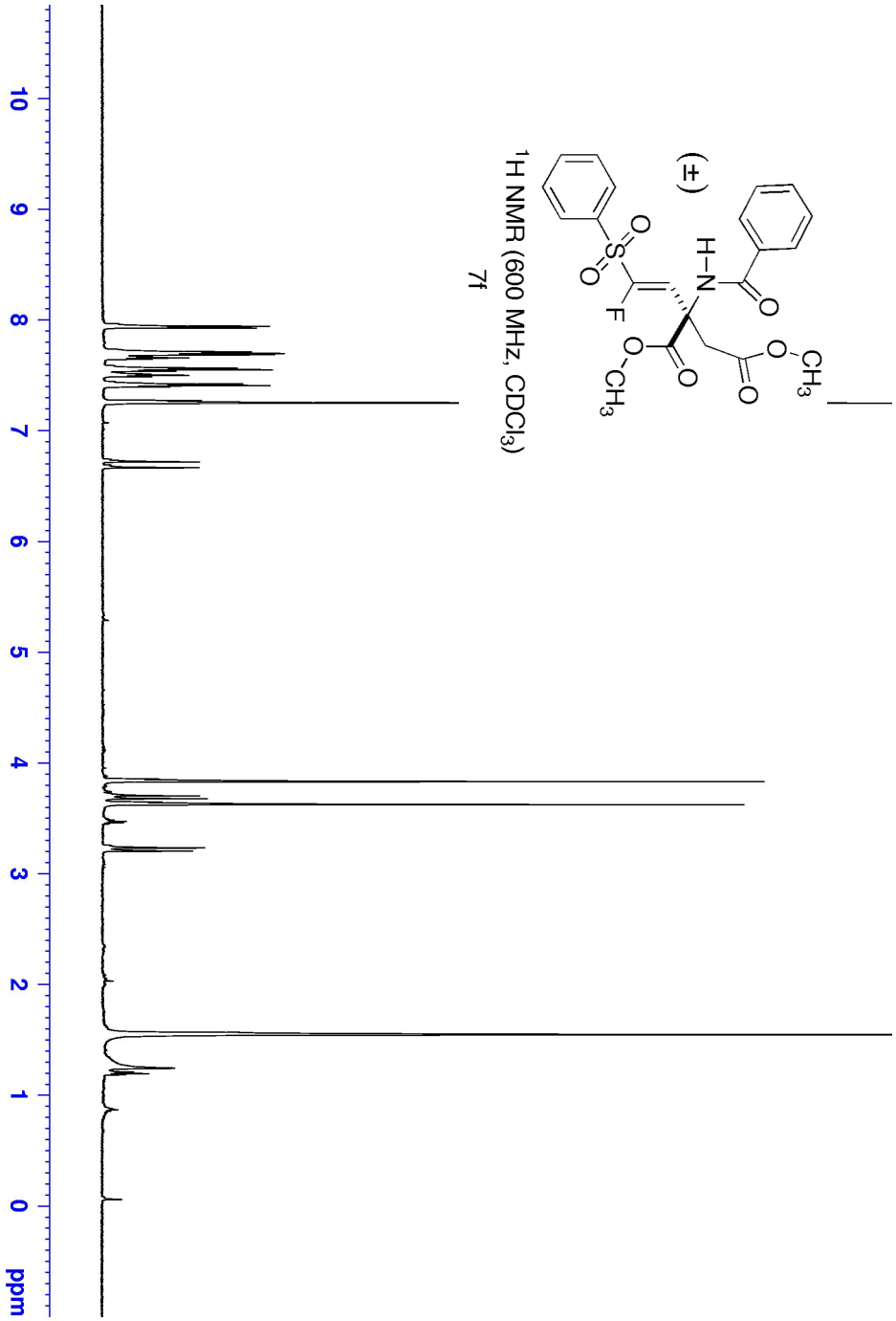
^{1}H NMR (600 MHz, $CDCl_3$)

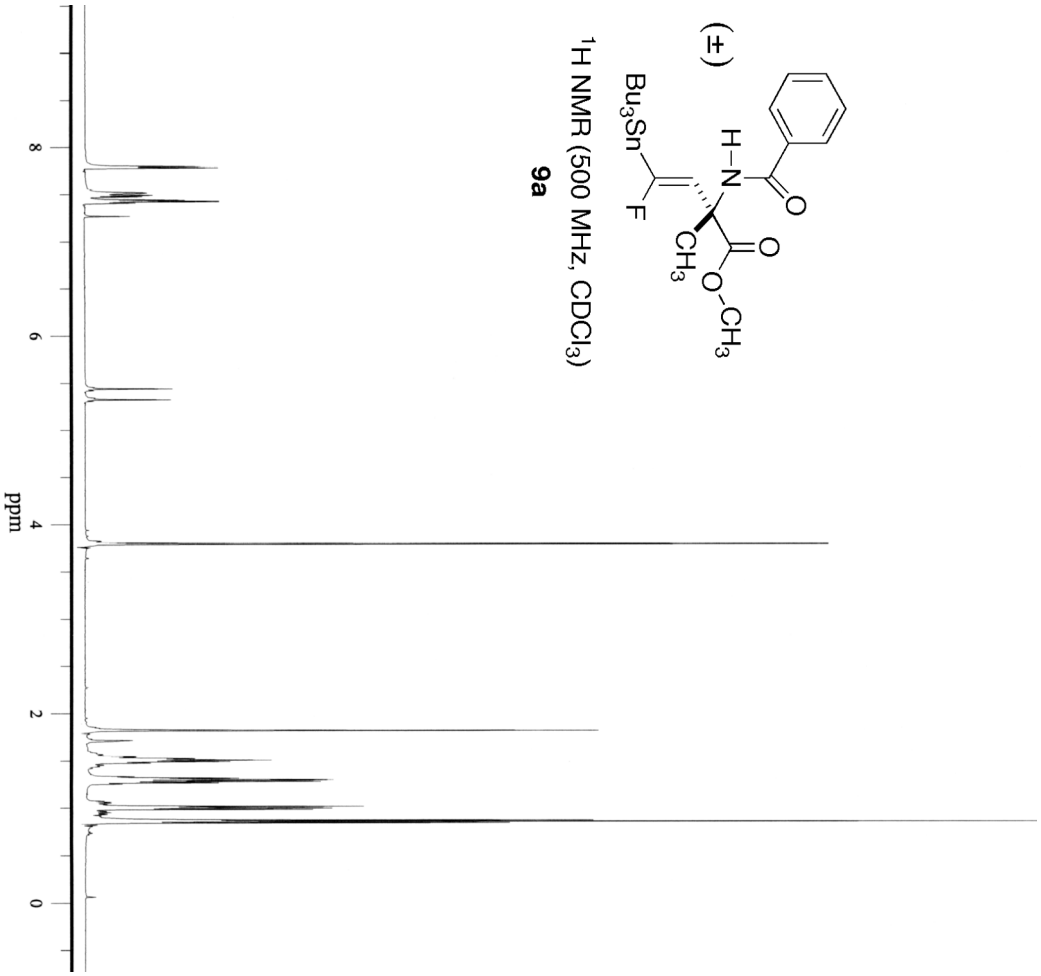
7d

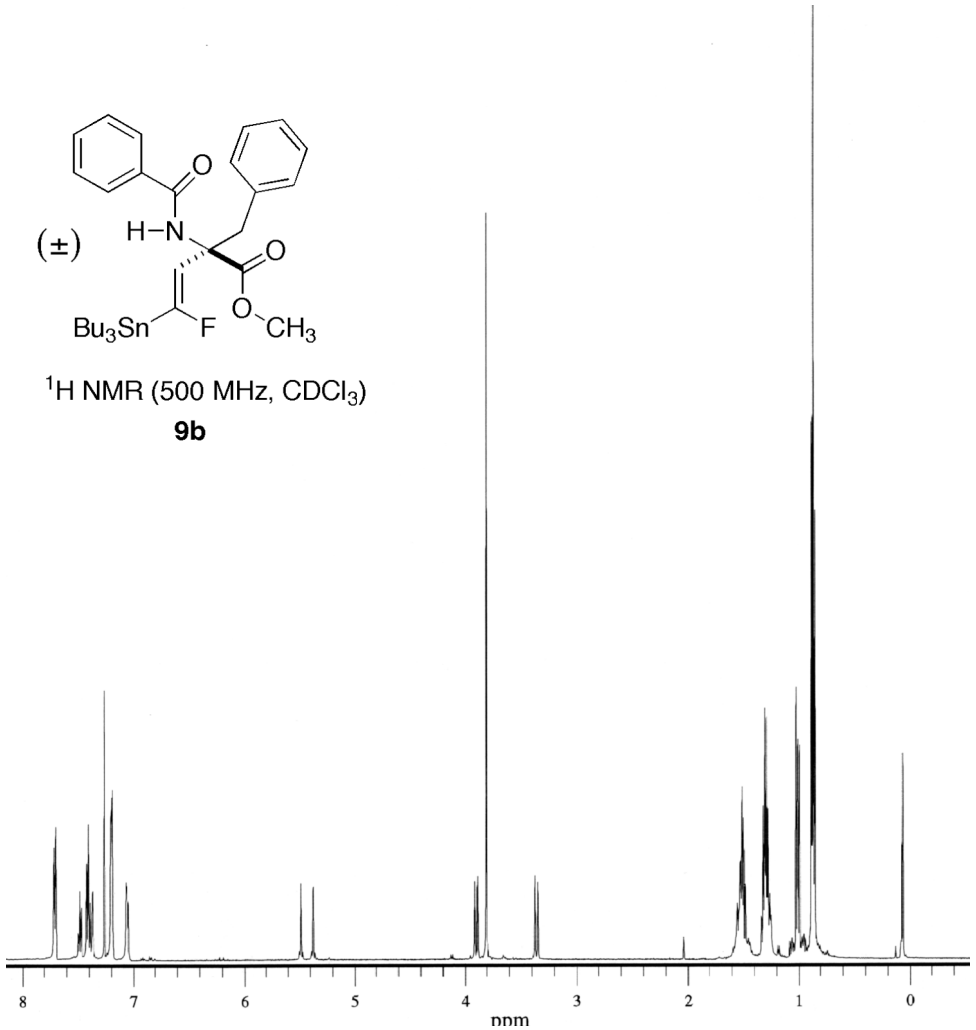


^{1}H NMR (500 MHz, $CDCl_3$)

7e

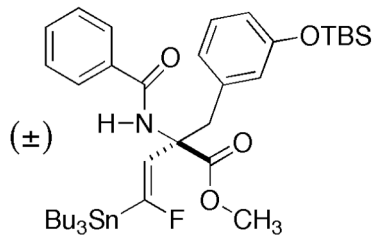

(±)
H–N
O
S
O
F
O
CH3
O
CH3
O
O
O
CH3
1H NMR (600 MHz, CDCl3)
7f
10
9
8
7
6
5
4
3
2
1
0
ppm


(±)
H–N
O
O
O–CH3
CH3
Bu3Sn
F
1H NMR (500 MHz, CDCl3)
9a
ppm
8
6
4
2
0



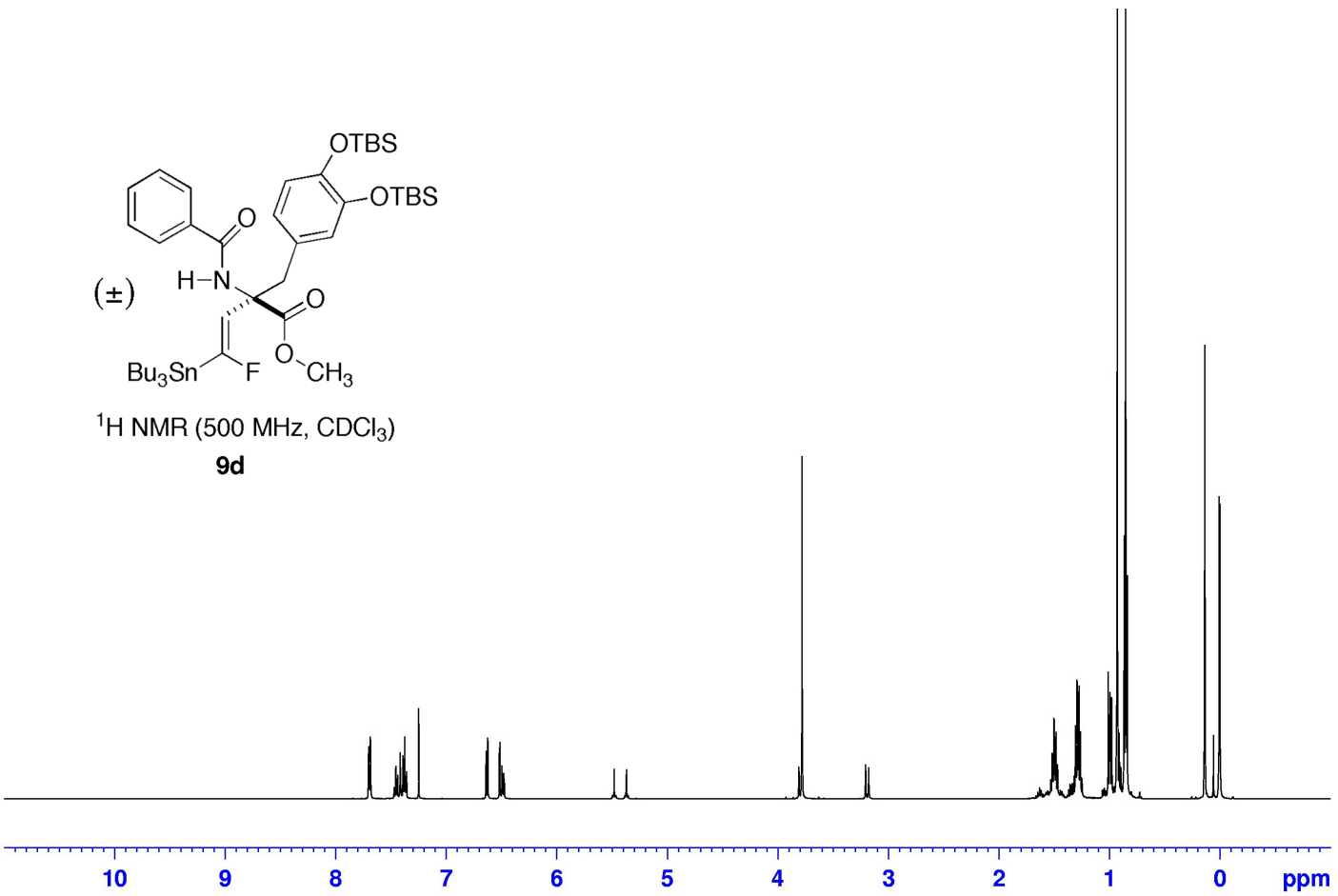
^{1}H NMR (500 MHz, $CDCl_3$)

9b



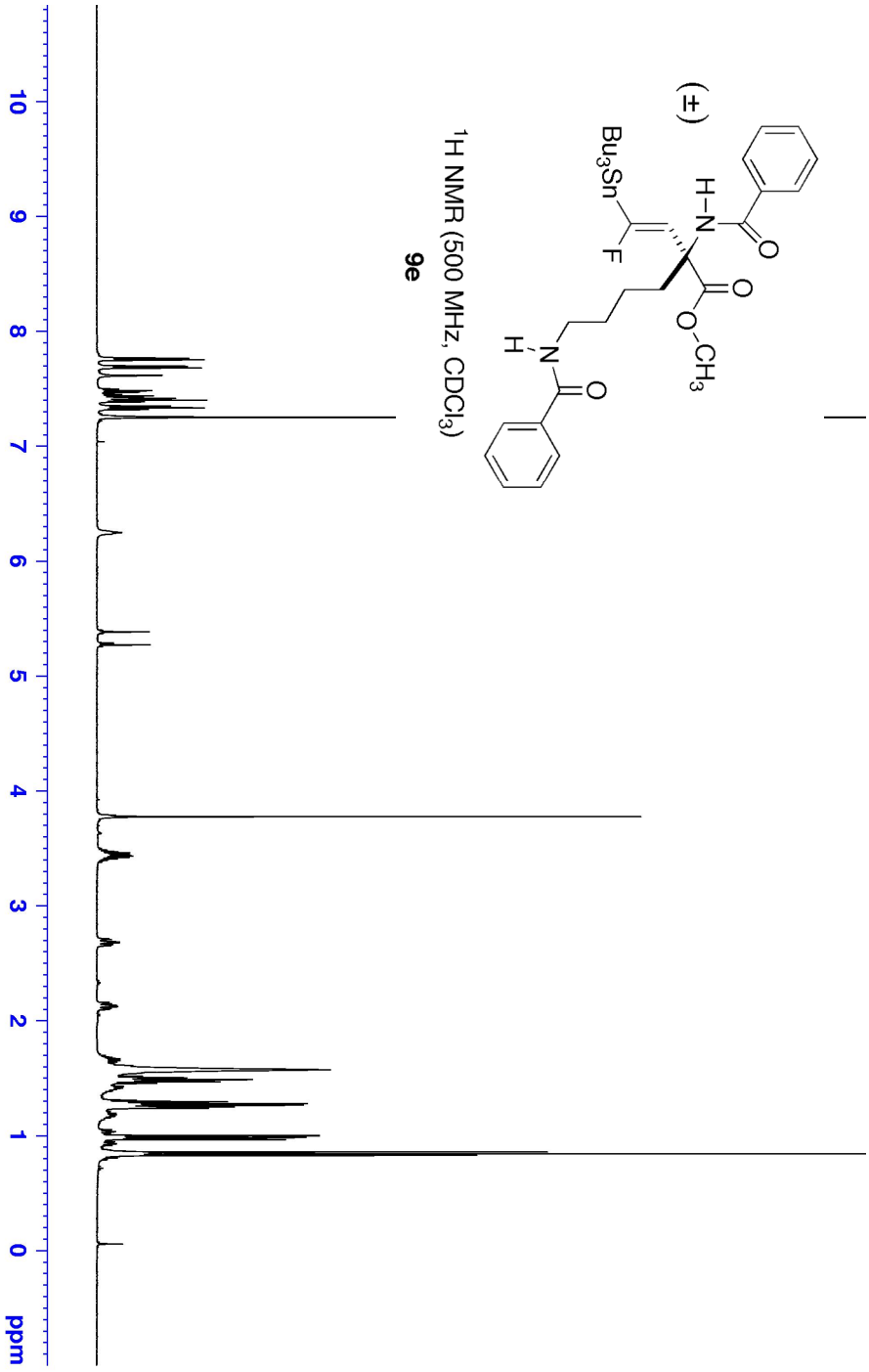
^{1}H NMR (500 MHz, $CDCl_3$)

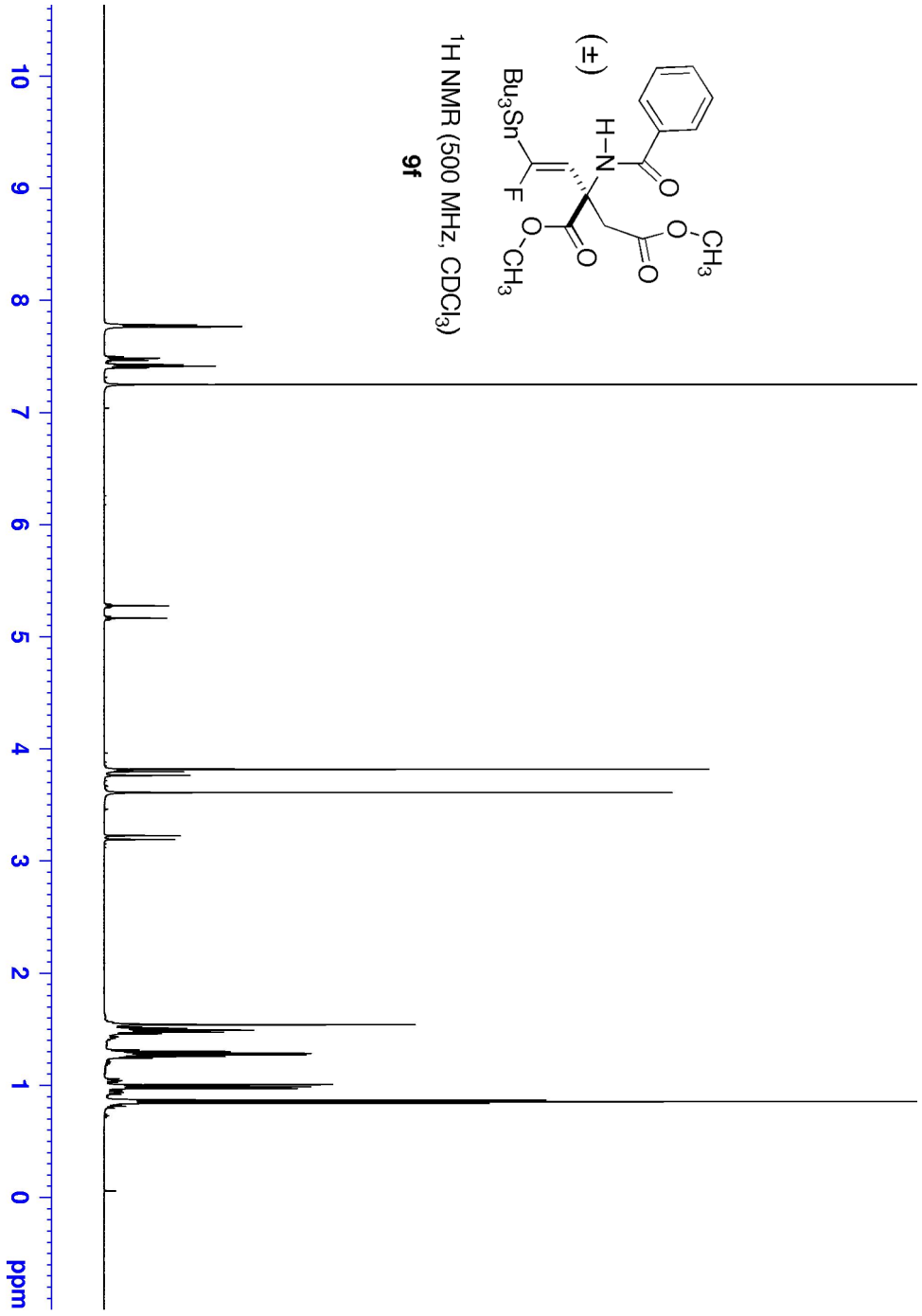
9c

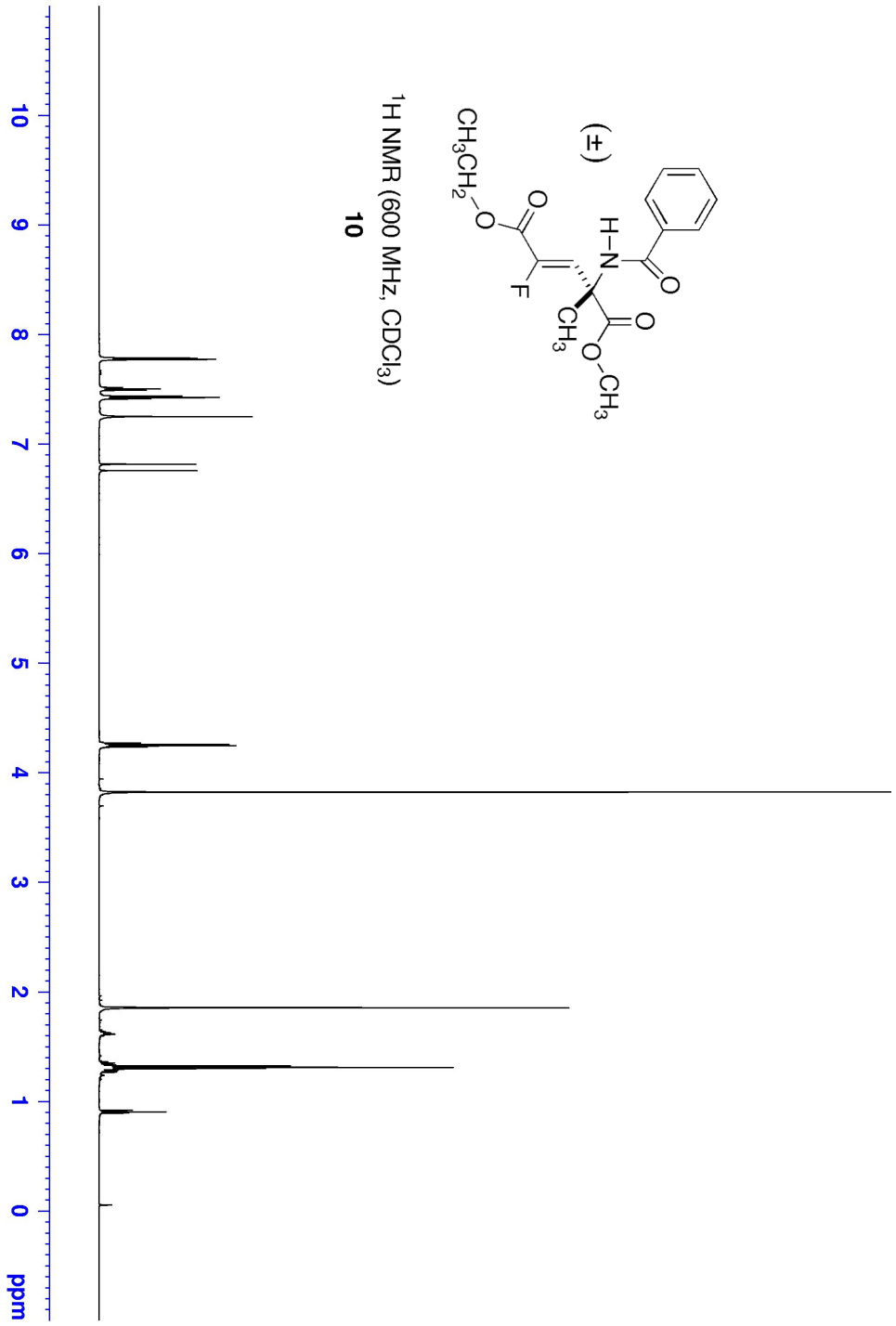


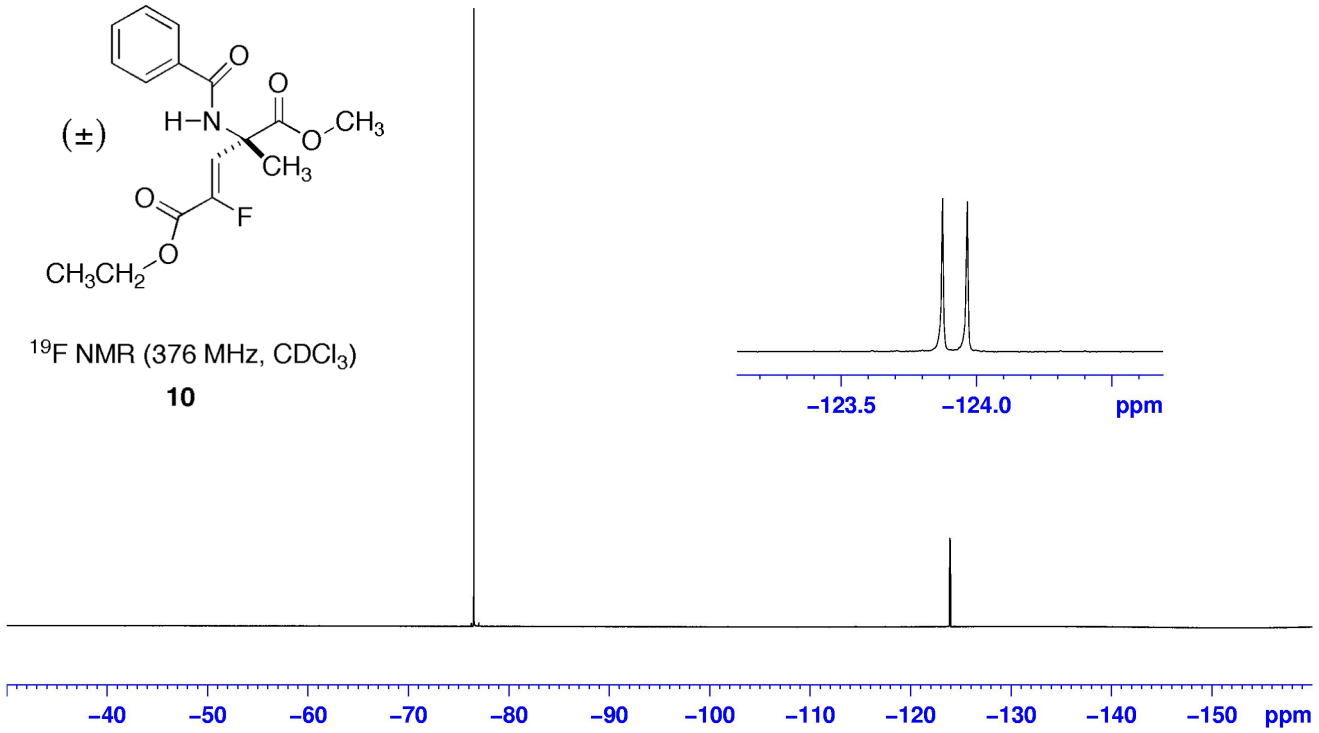
^{1}H NMR (500 MHz, $CDCl_3$)

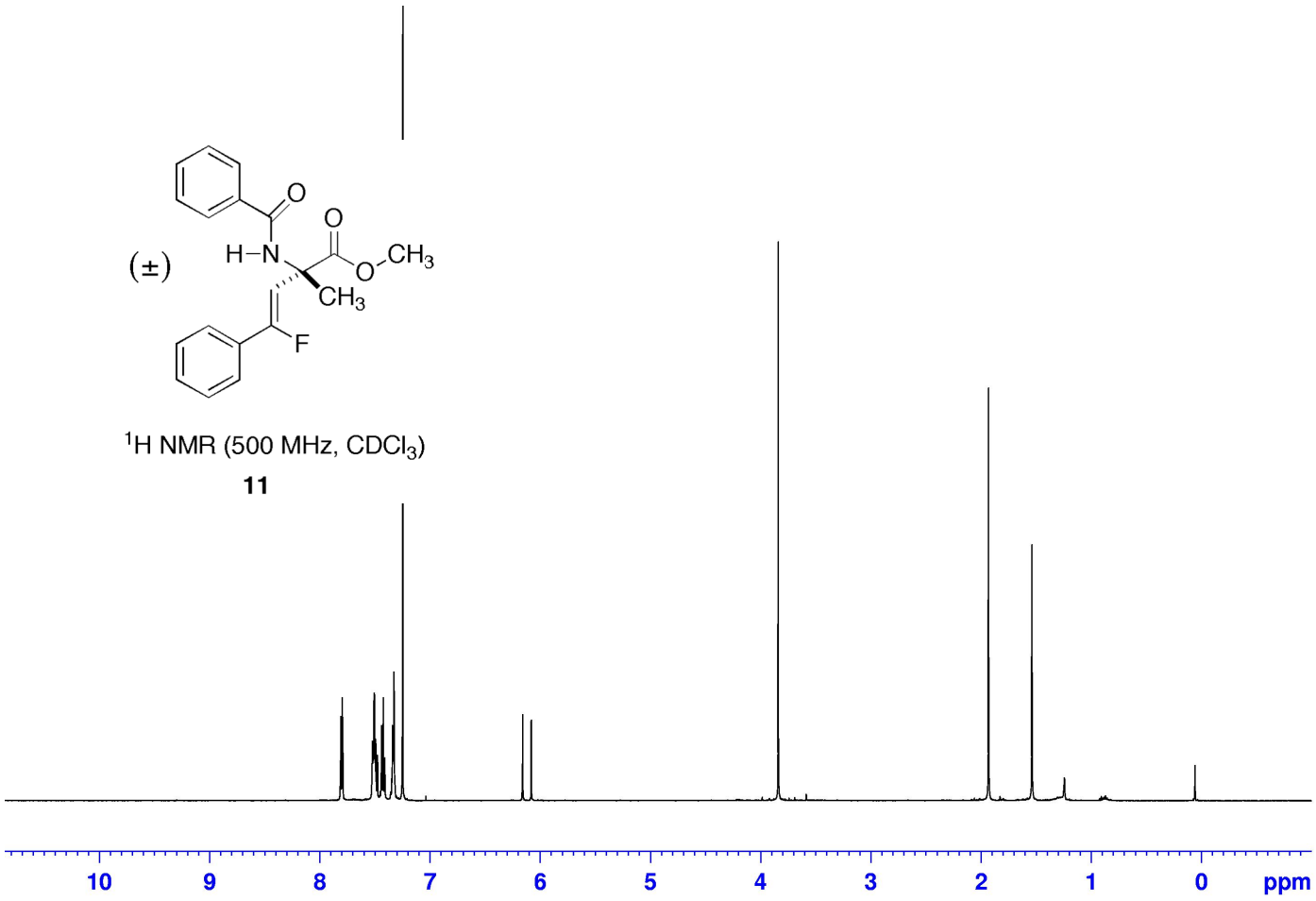
9d


(±)
Bu3Sn
F
H–N
O
O
O–CH3
H
N
O
1H NMR (500 MHz, CDCl3)
9e
10
9
8
7
6
5
4
3
2
1
0
ppm


(±)
Bu3Sn
F
H–N
O
O
O
O
CH3
O
CH3
1H NMR (500 MHz, CDCl3)
9f
10
9
8
7
6
5
4
3
2
1
0
ppm

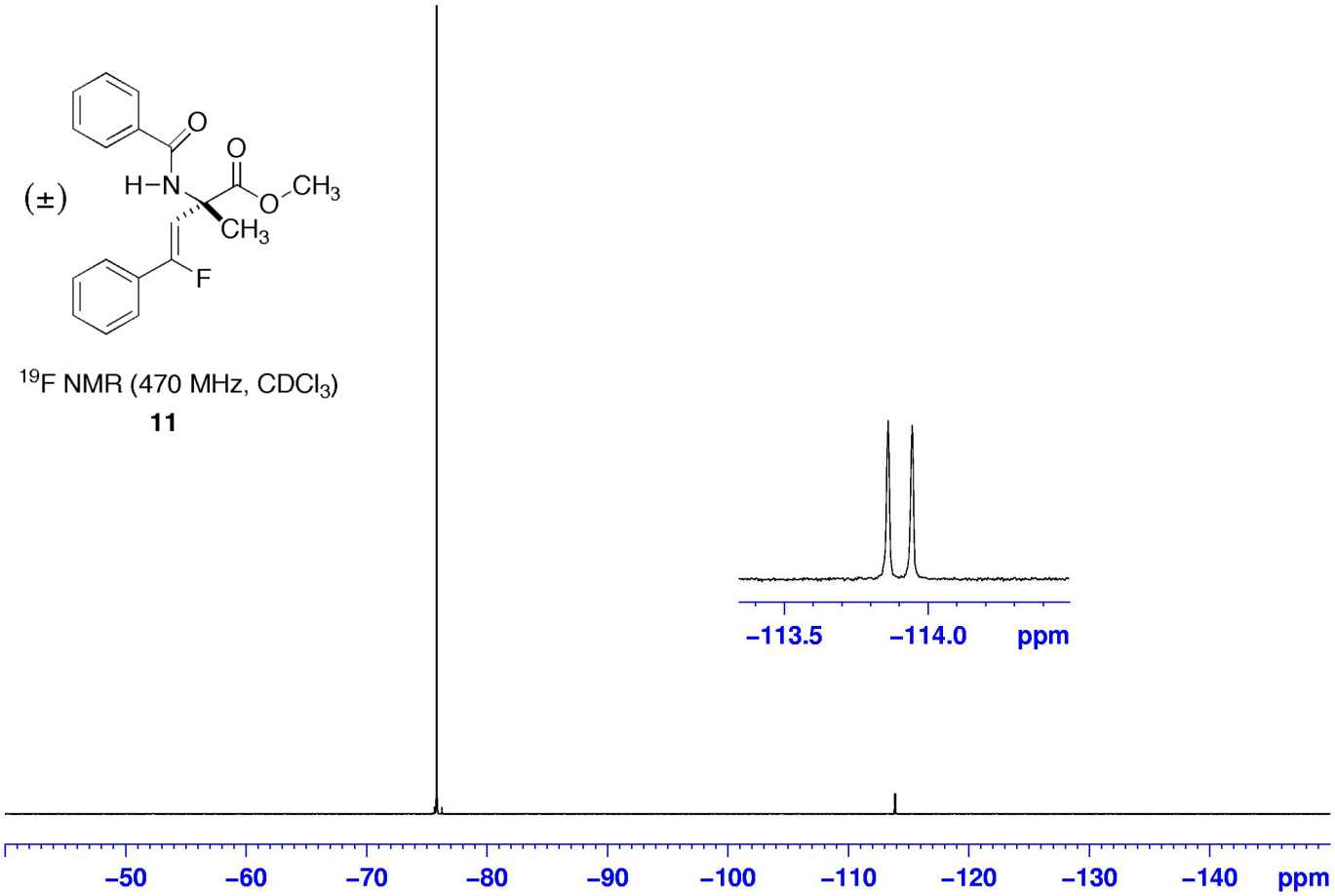

(±)
H–N
O
O
O
O–CH3
CH3
F
CH3CH2–O
1H NMR (600 MHz, CDCl3)
10
10
9
8
7
6
5
4
3
2
1
0
ppm


(±)
H–N
O
O
O
CH3
CH3
O
F
O
CH3CH2
19F NMR (376 MHz, CDCl3)
10
–123.5
–124.0
ppm
–40
–50
–60
–70
–80
–90
–100
–110
–120
–130
–140
–150
ppm



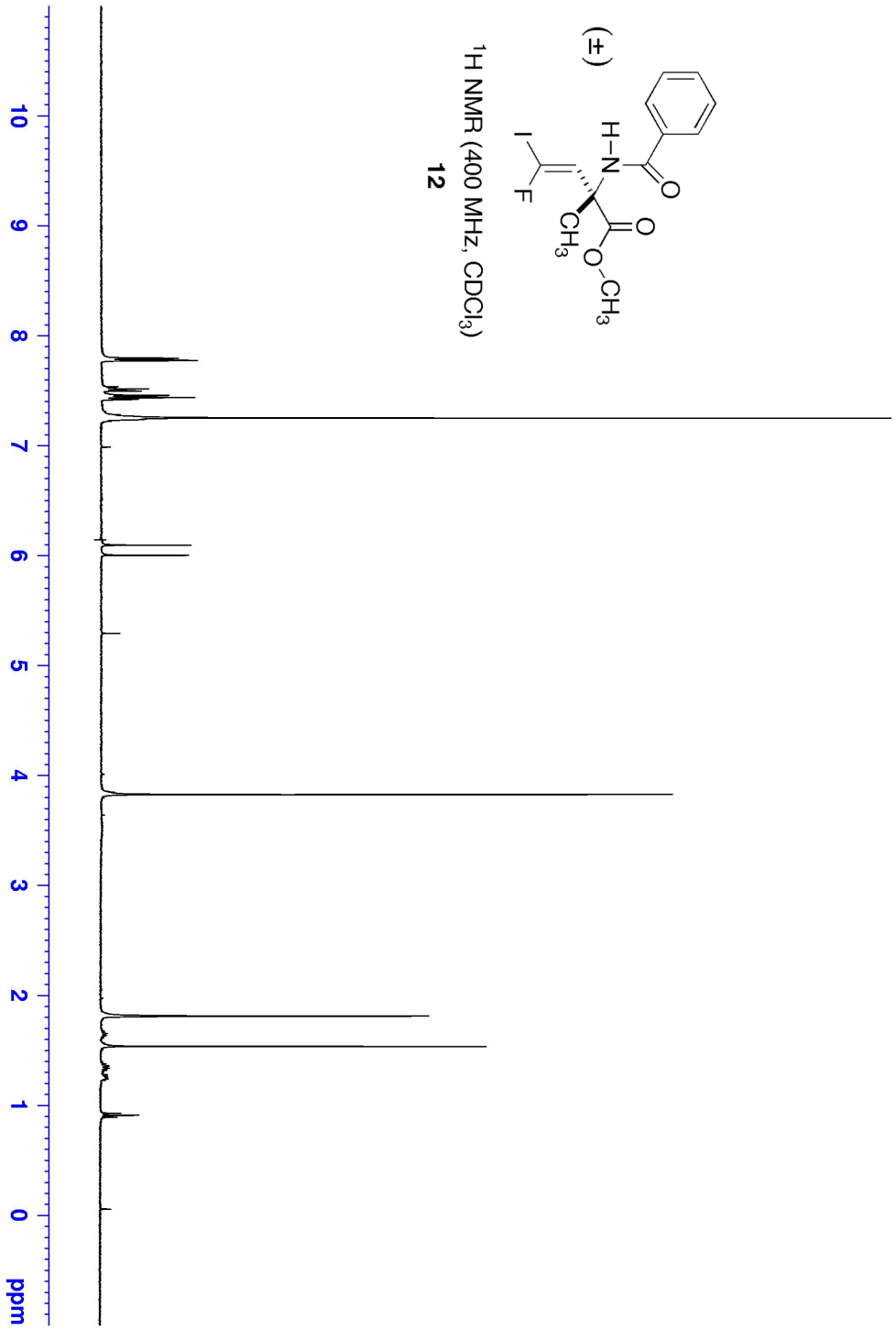
^{1}H NMR (500 MHz, $CDCl_3$)

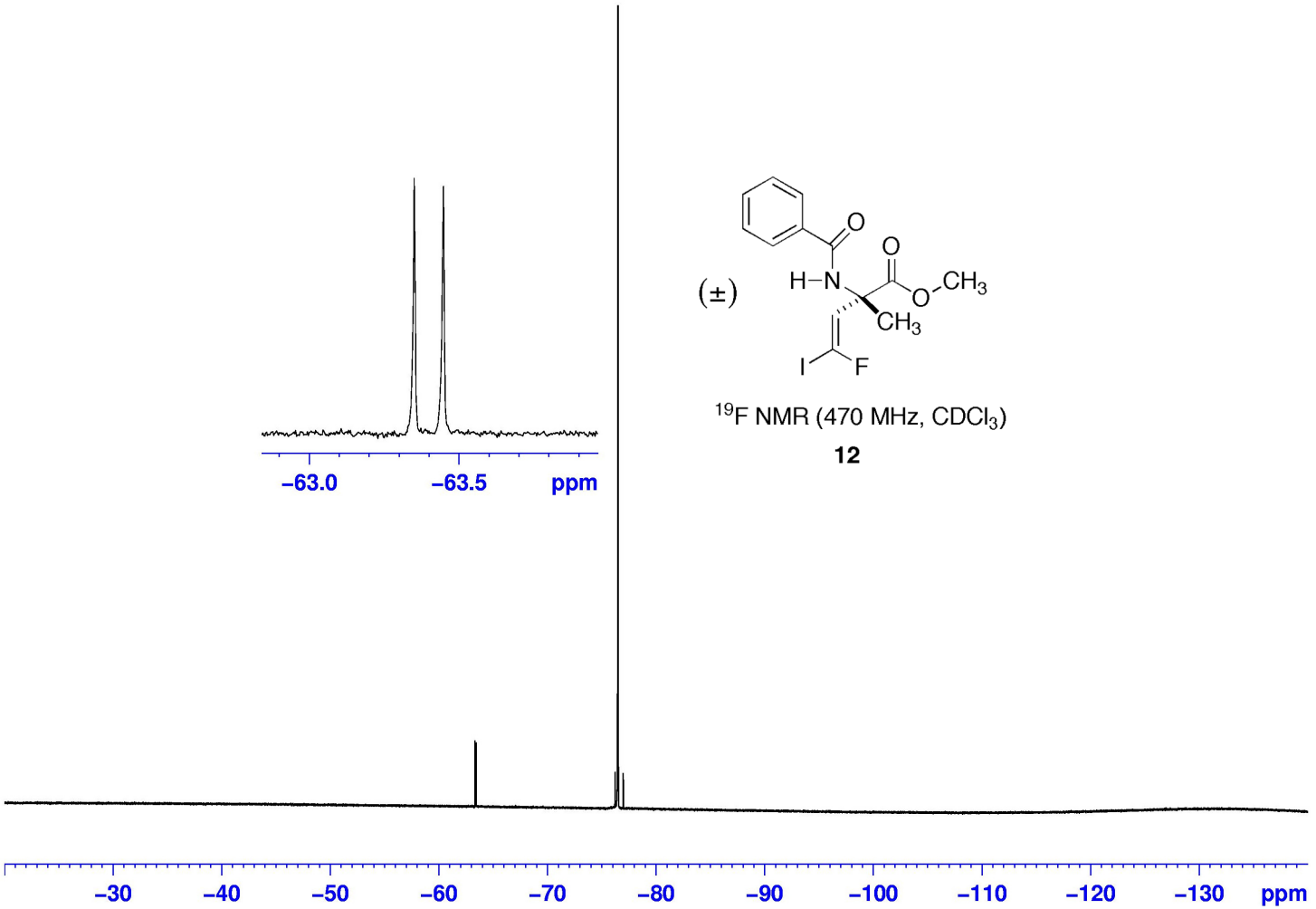
11

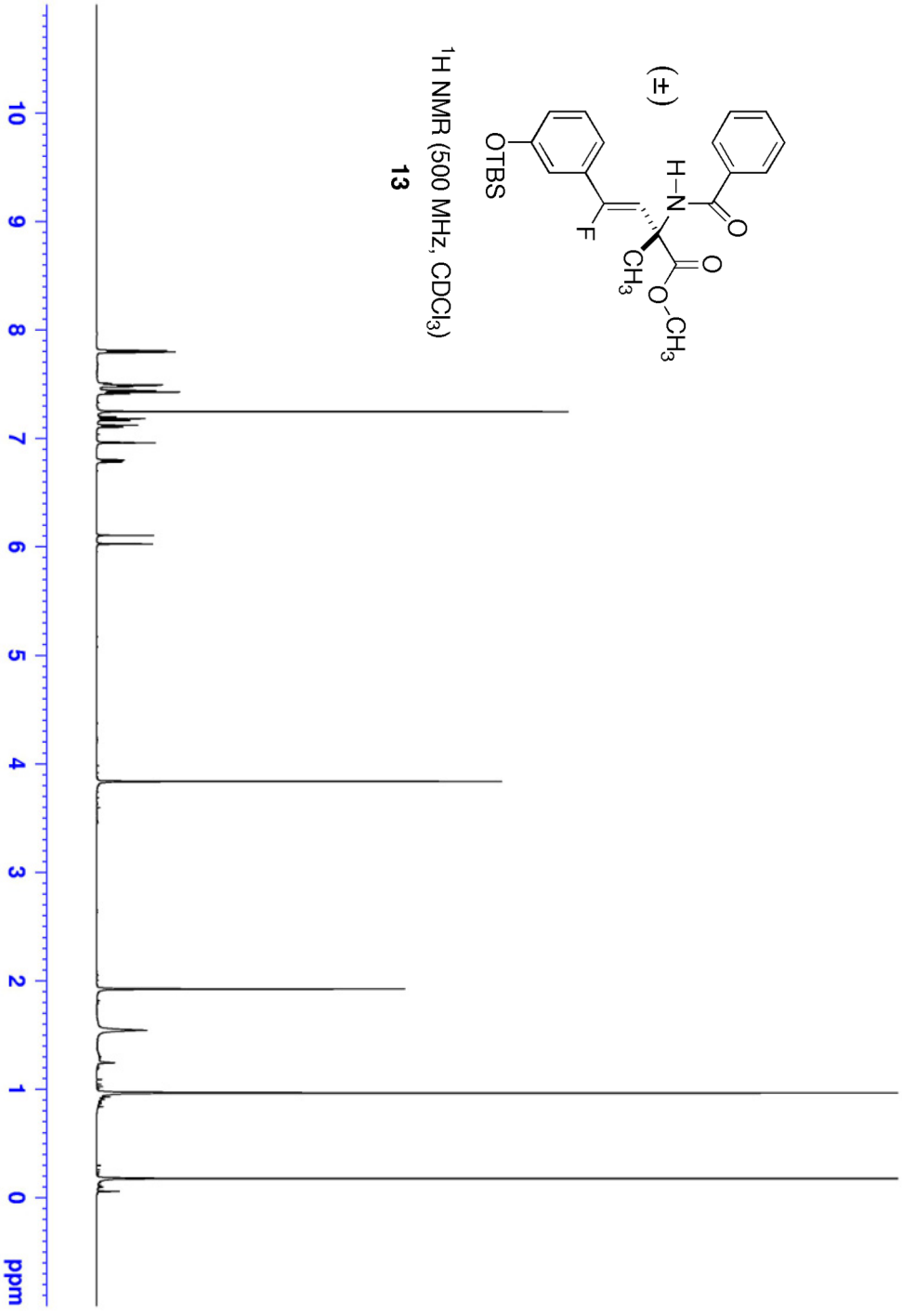


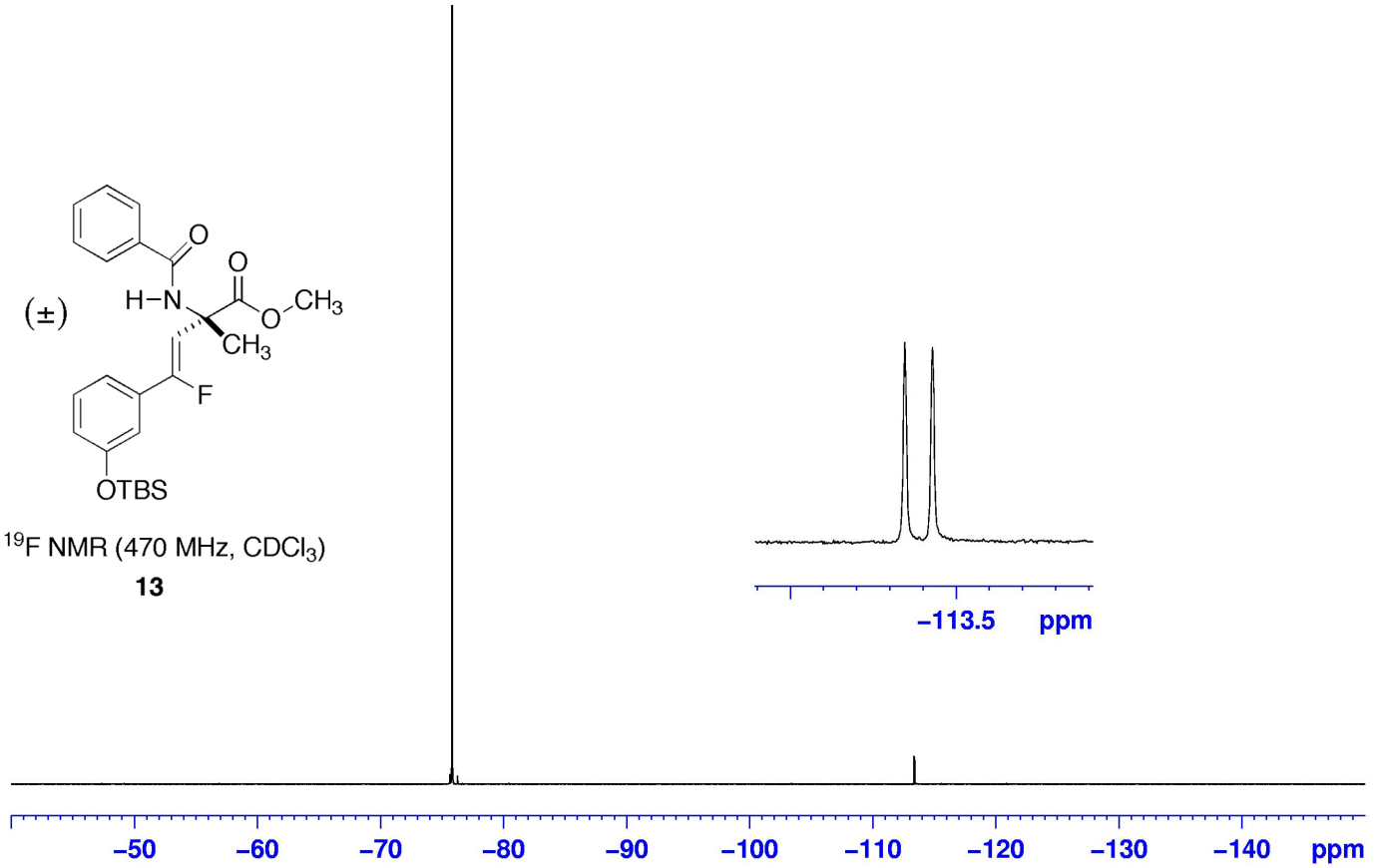
^{19}F NMR (470 MHz, $CDCl_3$)

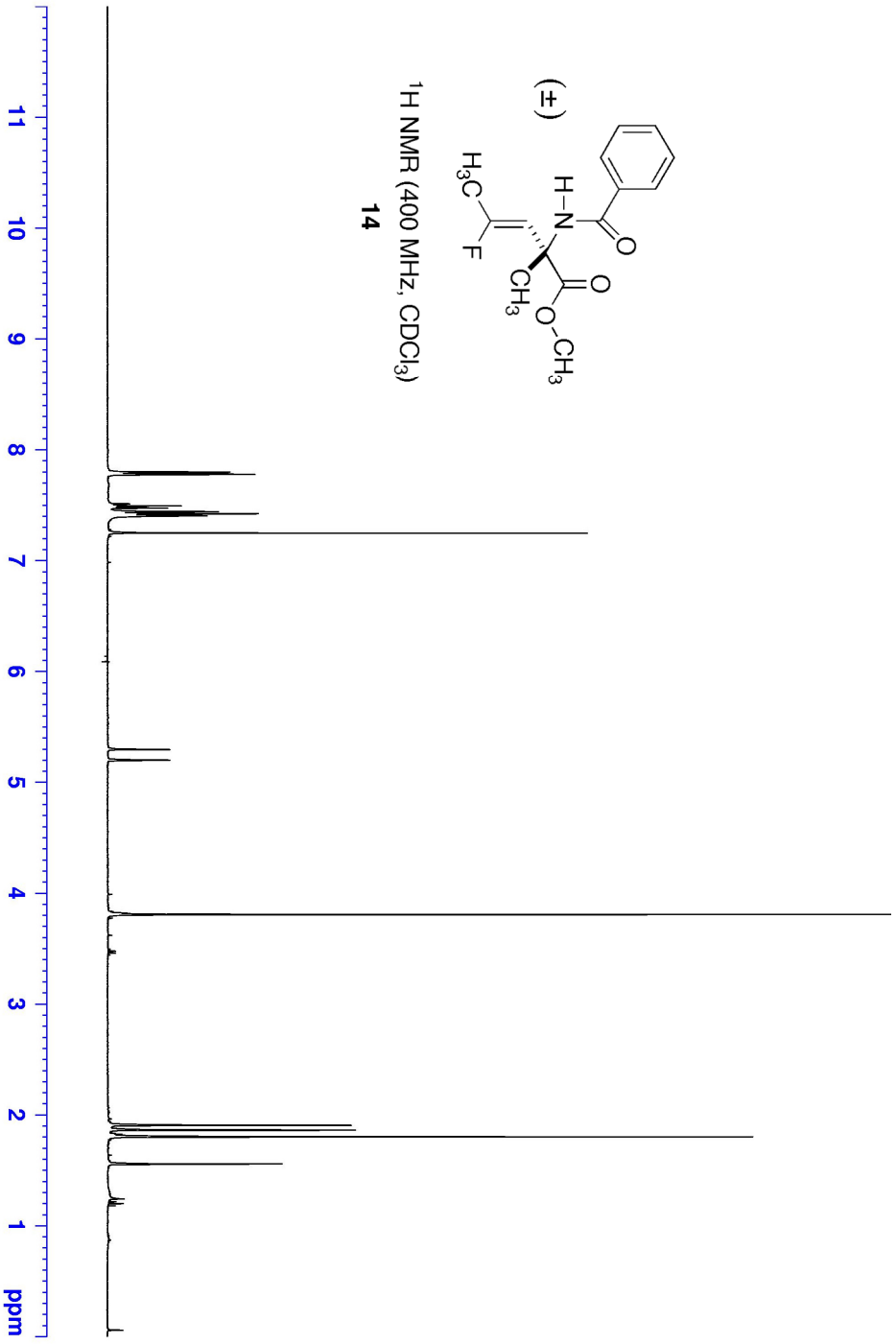
11

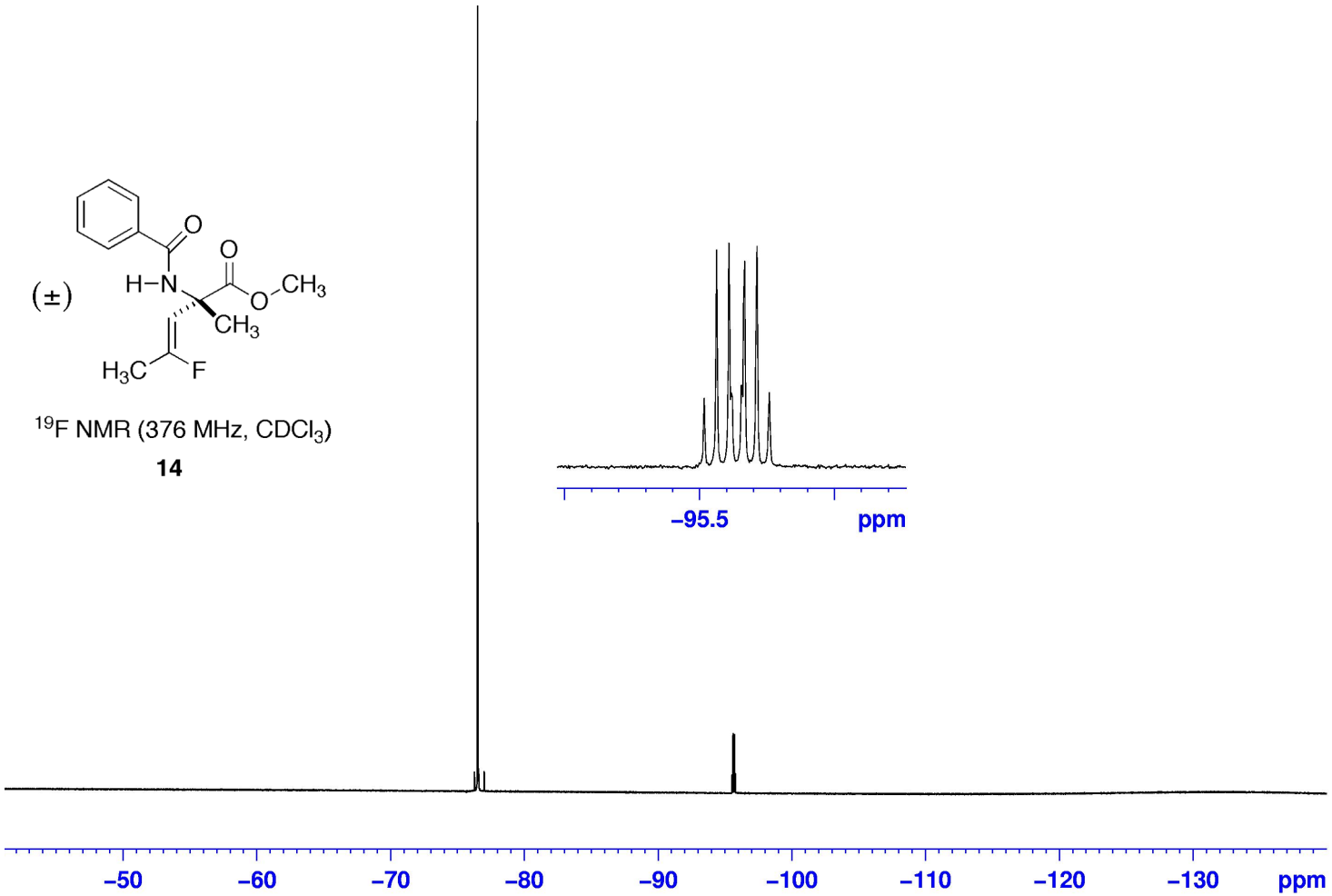

(±)
H–N
O
O
O
CH3
CH3
I
F
1H NMR (400 MHz, CDCl3)
12
10
9
8
7
6
5
4
3
2
1
0
ppm

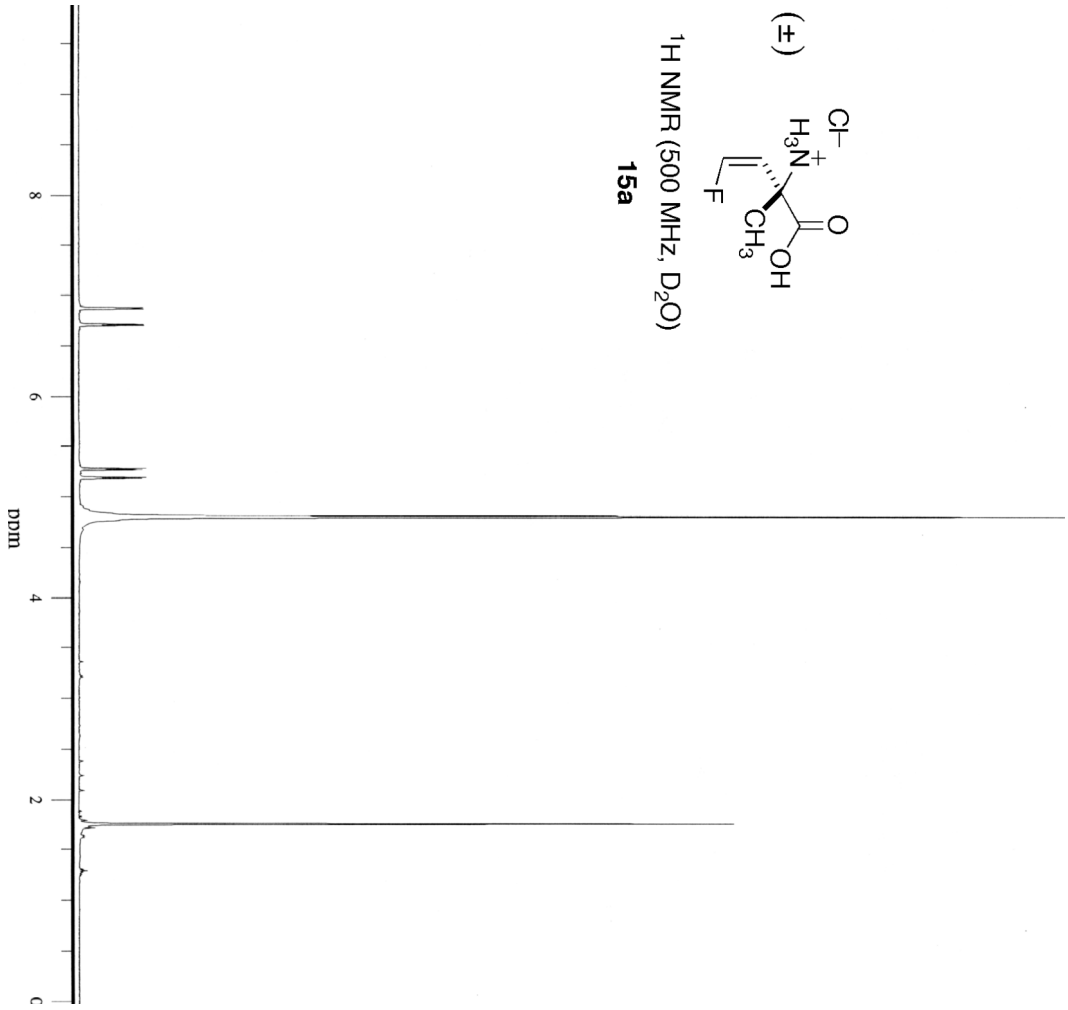

(±)
H–N
O
O
O
CH3
CH3
I
F
19F NMR (470 MHz, CDCl3)
12
–63.0
–63.5
ppm
–30
–40
–50
–60
–70
–80
–90
–100
–110
–120
–130
ppm


(±)
H–N
O
O
O
CH3
CH3
F
OTBS
1H NMR (500 MHz, CDCl3)
13
10
9
8
7
6
5
4
3
2
1
0
ppm

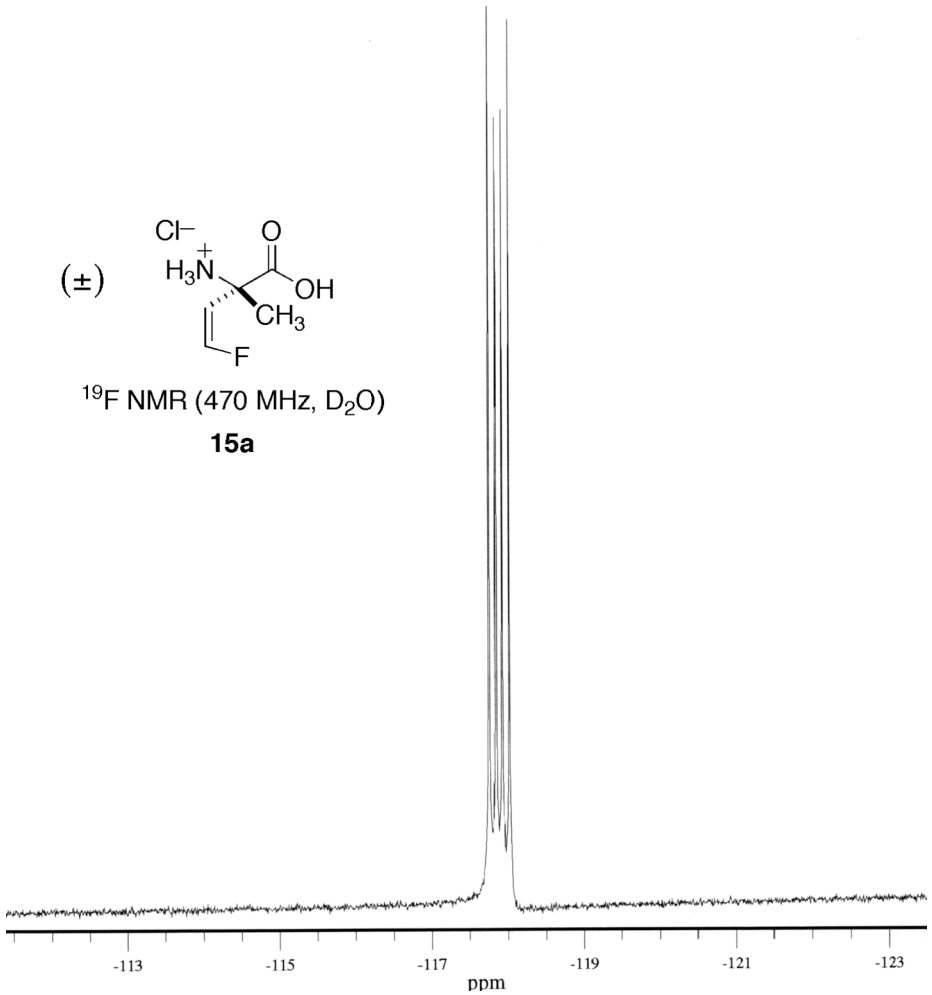

(±)
H–N
O
O
O
CH3
CH3
F
OTBS
19F NMR (470 MHz, CDCl3)
13
–113.5 ppm
–50 –60 –70 –80 –90 –100 –110 –120 –130 –140 ppm

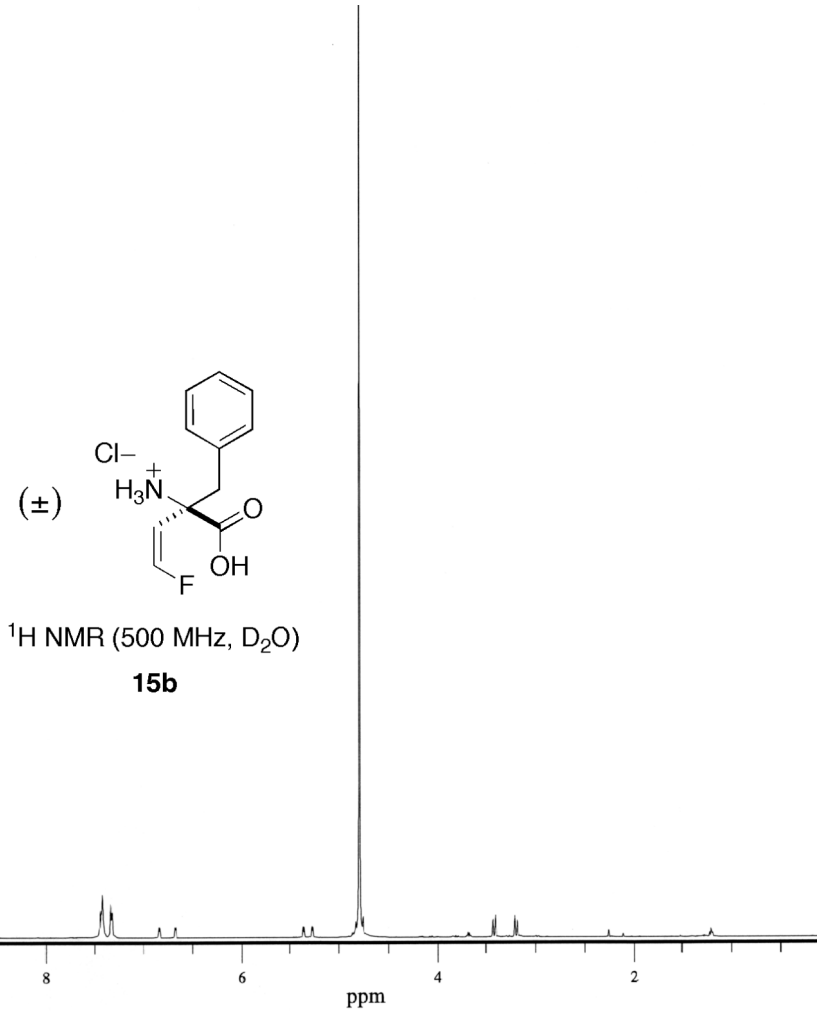

(±)
H–N
O
O
O
CH3
CH3
H3C
F
1H NMR (400 MHz, CDCl3)
14
11
10
9
8
7
6
5
4
3
2
1
ppm


(±)
H–N
O
O
O
CH3
CH3
H3C
F
19F NMR (376 MHz, CDCl3)
14
–95.5
ppm
–50
–60
–70
–80
–90
–100
–110
–120
–130
ppm



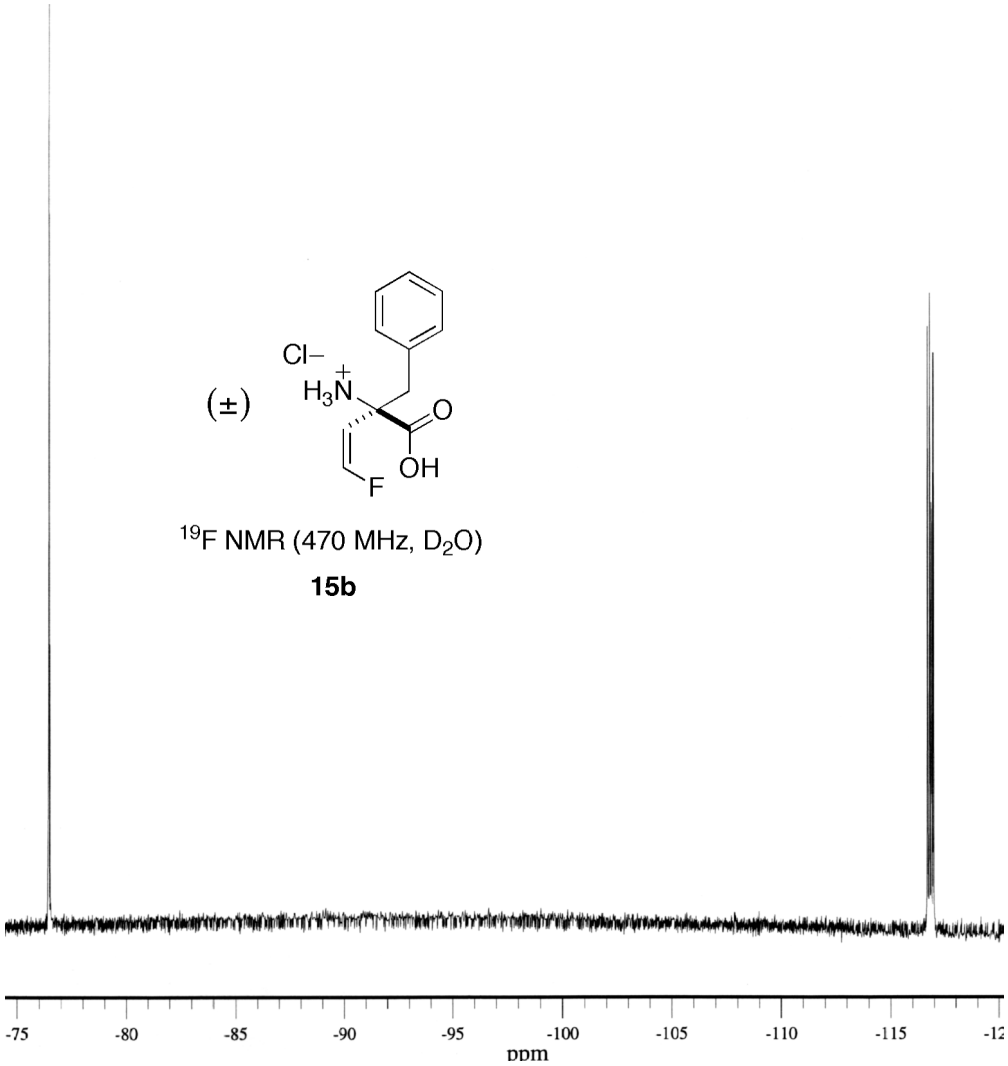
s


(±)
Cl–
O
H3N+
OH
CH3
F
19F NMR (470 MHz, D2O)
15a
-113
-115
-117
-119
-121
-123
ppm



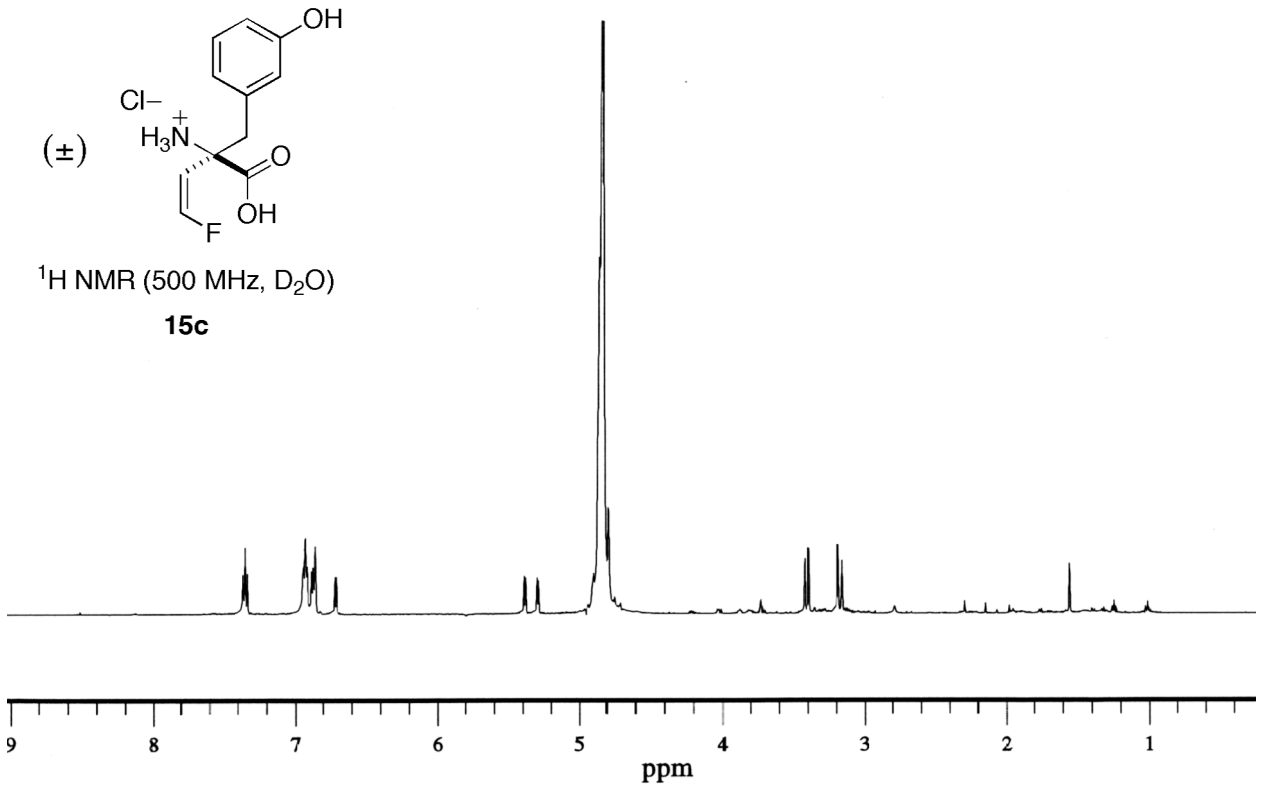
^{1}H NMR (500 MHz, D_2O)

15b



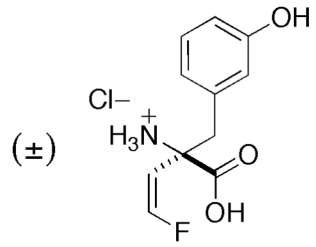
^{19}F NMR (470 MHz, D_2O)

15b



^{1}H NMR (500 MHz, D_2O)

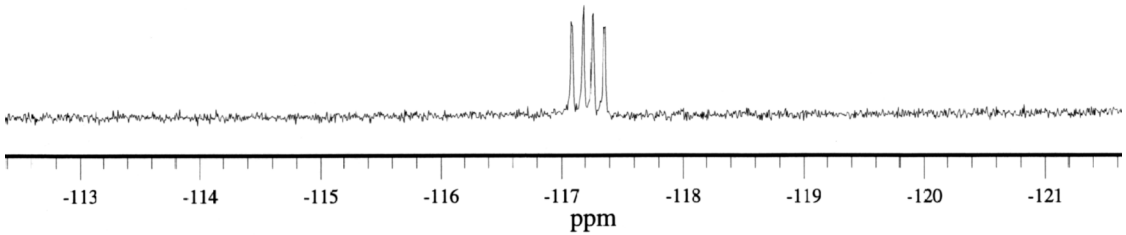
15c

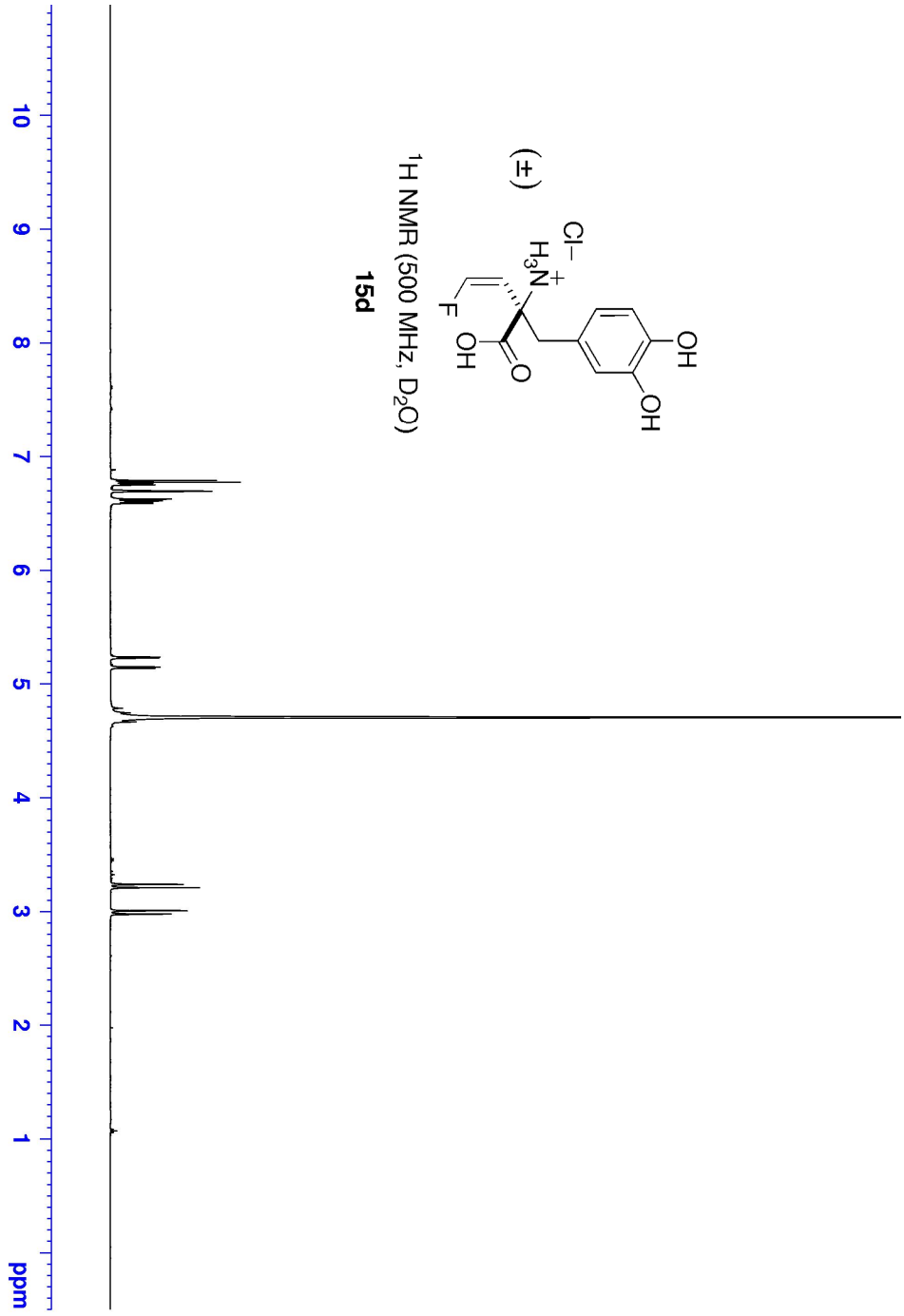


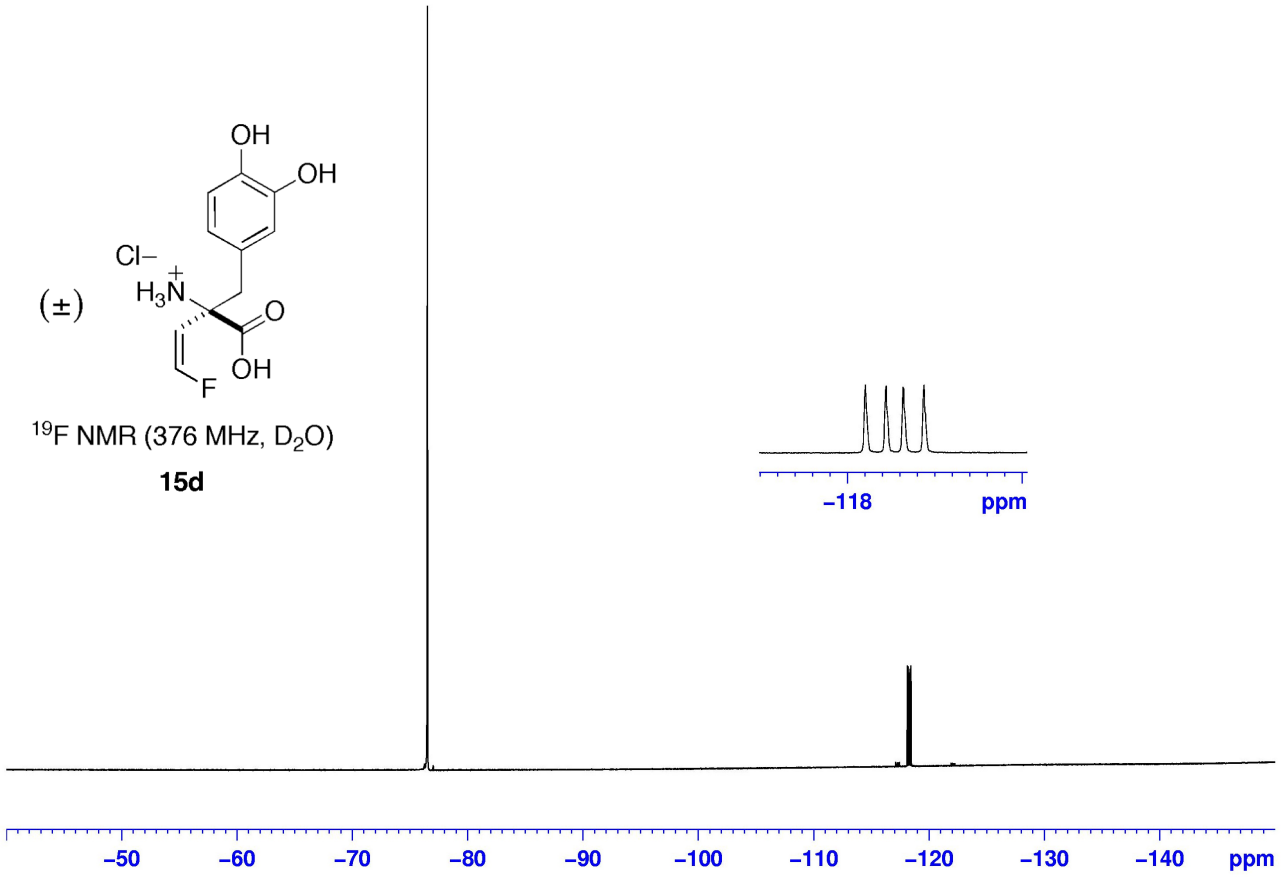
(±)

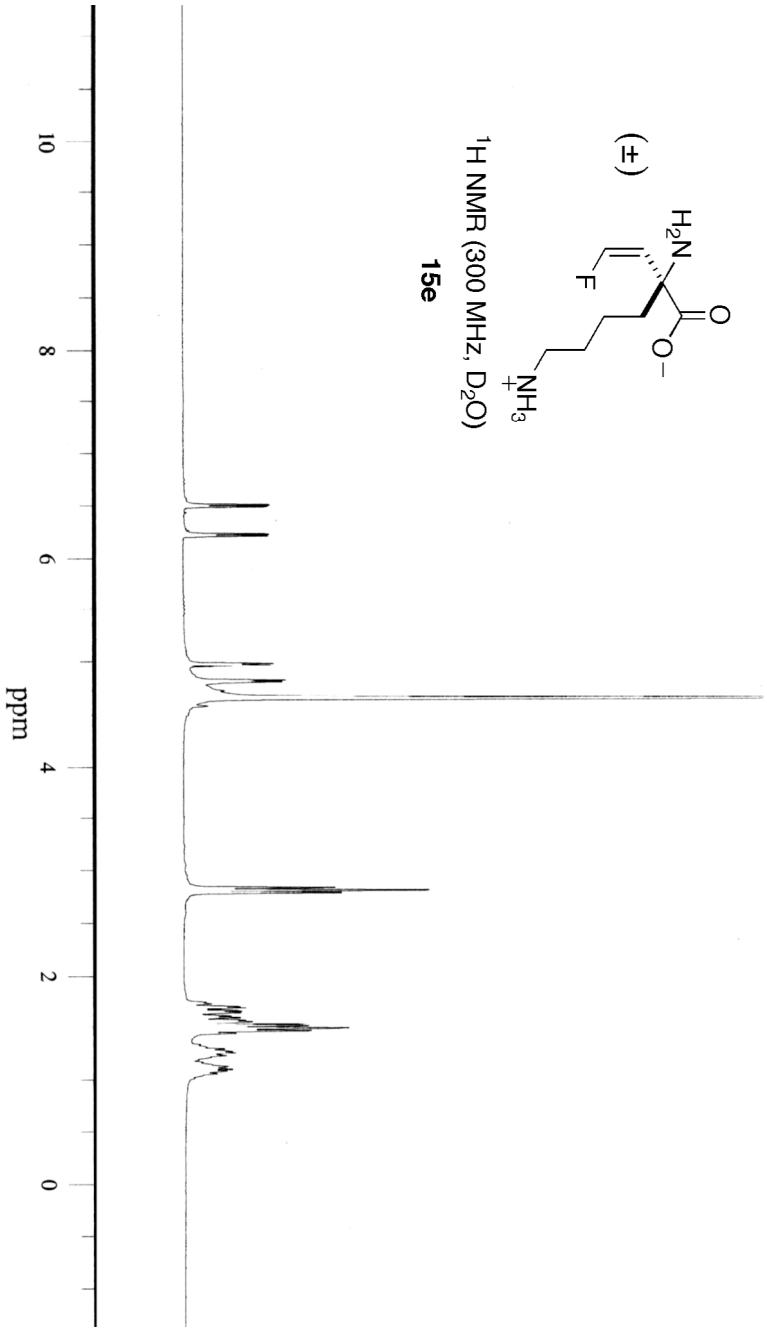
^{19}F NMR (470 MHz, D_2O)

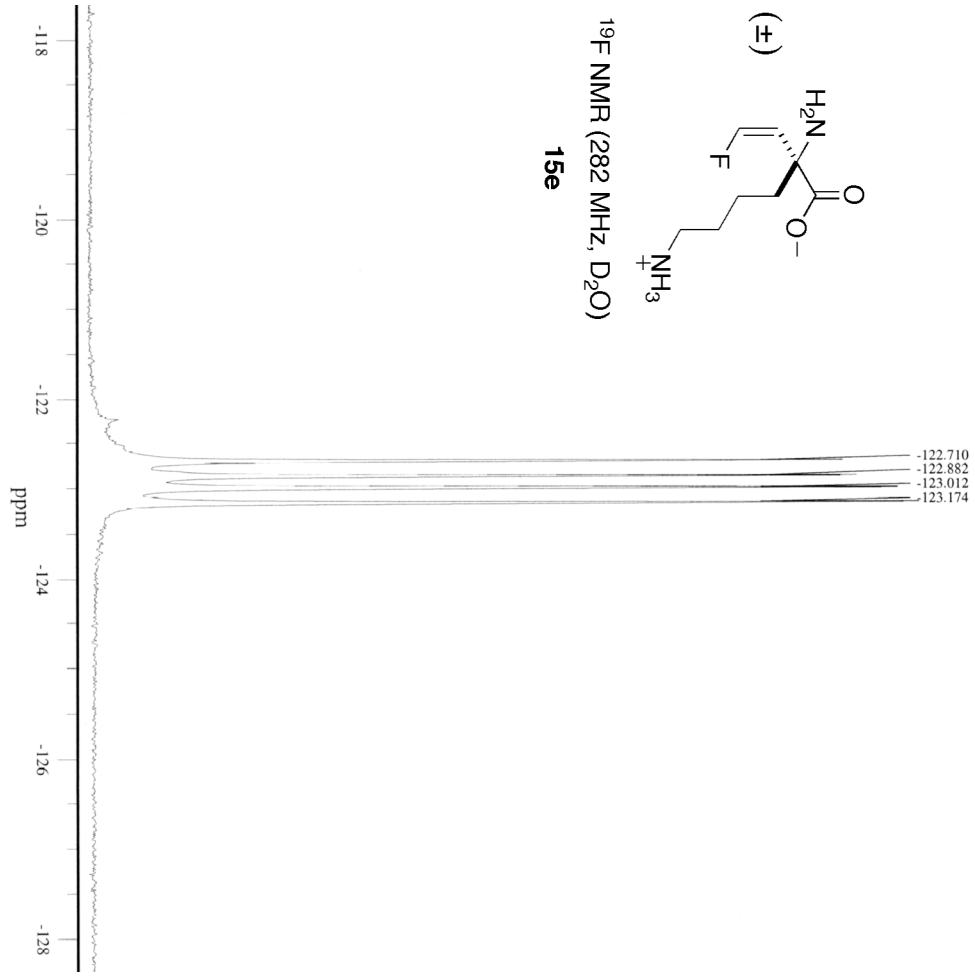
15c

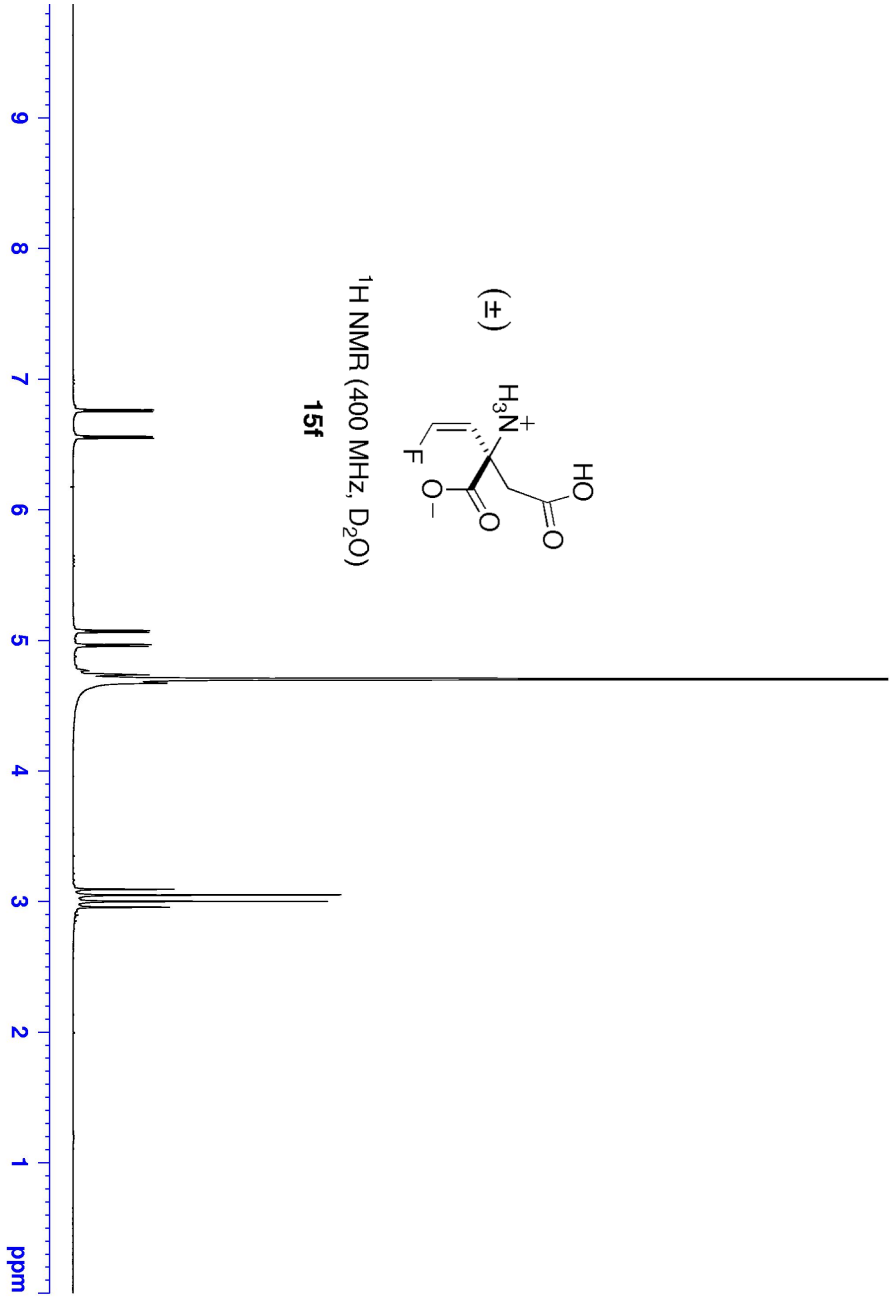


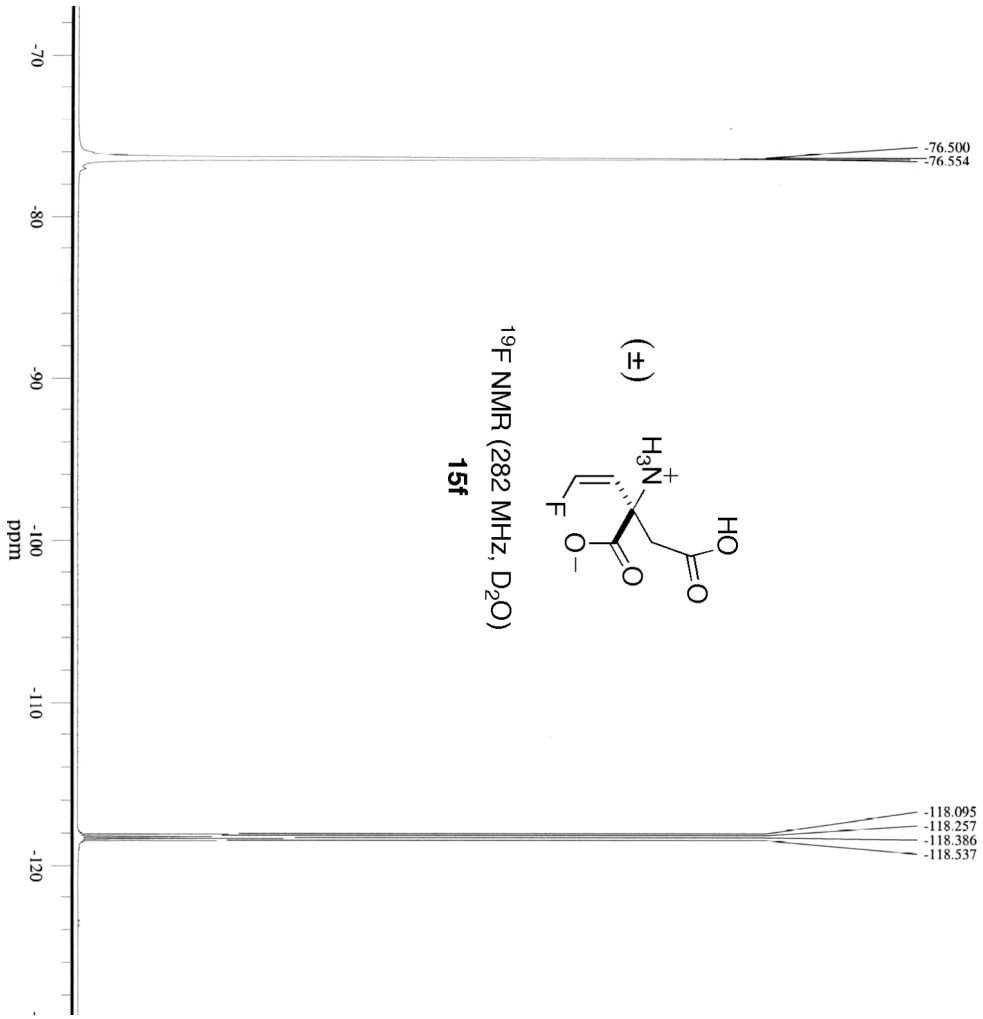

(±)
Cl–
H3N+
F
OH
O
OH
OH
1H NMR (500 MHz, D2O)
15d
10
9
8
7
6
5
4
3
2
1
ppm


OH
OH
Cl–
H3N+
(±)
O
OH
F
19F NMR (376 MHz, D2O)
15d
–118
ppm
–50
–60
–70
–80
–90
–100
–110
–120
–130
–140
ppm


(±)
H2N
F
O
O−
+NH3
1H NMR (300 MHz, D2O)
15e
10
8
6
4
2
0
ppm


(±)
H2N
F
O
O−
NH3+
19F NMR (282 MHz, D2O)
15e
-122.710
-122.882
-123.012
-123.174
-118
-120
-122
-124
-126
-128
ppm


(±)
^{1}H NMR (400 MHz, D_2O)
15f
ppm



^{19}F NMR (282 MHz, D_2O)

15f

(±)