Electronic Supplementary Material (ESI) for ChemComm.

Isothiourea-Catalyzed Formal Enantioselective Conjugate Addition of Benzophenone Imine Derivatives to β-Fluorinated α,β-Unsaturated Esters

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1. GENERAL EXPERIMENTAL

Reactions involving moisture sensitive reagents were carried out in flame-dried glassware under an inert atmosphere (N_2) using standard vacuum line techniques. Anhydrous solvents (CH_2Cl_2) were obtained after passing through an alumina column (Mbraun SPS-800). Petrol is defined as petroleum ether 40–60 C. All other solvents and commercial reagents were used as received without further purification unless otherwise stated.

Room temperature (rt) refers to 20–25 C.

Under reduced pressure refers to the use of either a Büchi Rotavapor R-200 with a Büchi V-491 heating bath and Büchi V-800 vacuum controller, a Büchi Rotavapor R-210 with a V-491 heating bath and Büchi V-850 vacuum controller, a Heidolph Laborota 4001 with vacuum controller, an IKA RV10 rotary evaporator with a IKA HB10 heating bath and ILMVAC vacuum controller, or IKA RV10 rotary evaporator with a IKA HB10 heating bath and Vacuubrand CVC3000 vacuum controller. Rotary evaporator condensers are fitted to Julabo FL Recirculating Coolers filled with ethylene glycol and set to –6 C.

Analytical thin layer chromatography was performed on pre-coated aluminium plates (Kieselgel 60 F254 silica) and visualisation was achieved using ultraviolet light (254 nm). Manual column chromatography was performed in glass columns fitted with porosity 3 sintered discs over Keiselgel 60 silica using the solvent system stated. Automated chromatography was performed on a Biotage Isolera Four running Biotage OS578 with a UV/Vis detector using the method stated and cartridges filled with Keiselgel 60 silica.

Melting points were recorded on an Electrothermal 9100 melting point apparatus, (dec) refers to decomposition.

Optical rotations were measured on a Perkin Elmer Precisely/Model-341 polarimeter operating at the sodium D line with a 100 mm path cell at 20 °C.

HPLC analyses were obtained on either a Shimadzu HPLC consisting of a DGU-$20A_5$ degassing unit, LC-20AT liquid chromatography pump, SIL-20AHT autosampler, CMB-20A communications bus module, SPD-M20A diode array detector and a CTO-20A column oven or a Shimadzu HPLC consisting of a DGU-$20A_{5R}$ degassing unit, LC-20AD liquid chromatography pymp, SIL-20AHT autosampler, SPD-20A UV/Vis detector and a CTO-20A column oven. Separation was achieved using DAICEL CHIRALPAK AD-H column using the method stated. HPLC traces of enantiomerically enriched compounds were compared with authentic racemic spectra.

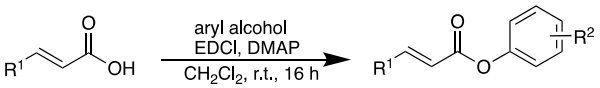
Infrared spectra were recorded on a Shimadzu IRAffinity-1 Fourier transform IR spectrophotometer fitted with a Specac Quest ATR accessory (diamond puck). Spectra were recorded of either thin films or solids, with characteristic absorption wavenumber (ν_{max}) reported in cm^{-1}.

^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were acquired on either a Bruker AV300 with a BBFO probe (^{1}H 300 MHz; $^{13}C\{^{1}H\}$ 75 MHz), a Bruker AV400 with a BBFO probe (^{1}H 400 MHz; $^{13}C\{^{1}H\}$ 101 MHz), a Bruker AVII 400 with a BBFO probe (^{1}H 400 MHz; $^{13}C\{^{1}H\}$ 101 MHz), a Bruker AVIII-HD 500 with a SmartProbe BBFO+ probe (^{1}H 500 MHz, $^{13}C\{^{1}H\}$ 126 MHz), a Bruker AVIII 500 with a CryoProbe Prodigy BBO probe (^{1}H 500 MHz, $^{13}C\{^{1}H\}$ 126 MHz), or a Bruker AVIII-HD 700 with a CryoProbe Prodigy TCI probe (^{1}H 700 MHz, $^{13}C\{^{1}H\}$ 176 MHz) in the deuterated solvent stated. All chemicals shifts are quoted in parts per million (ppm) relative to the residual solvent peak. All coupling constants, *J*, are quoted in Hz. Multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and multiples of thereof. The abbreviation Ar denotes aromatic and app denotes apparent. NMR peak assignments were confirmed using 2D ^{1}H correlated spectroscopy (COSY), 2D ^{1}H nuclear Overhauser effect spectroscopy (NOESY), 2D ^{1}H–^{13}C heteronuclear multiple-bond correlation spectroscopy (HMBC), and 2D ^{1}H–^{13}C heteronuclear single quantum coherence (HSQC) where necessary.

Mass spectrometry (*m/z*) data were acquired by nanospray ionisation (NSI) at the University of St Andrews Mass Spectrometry Facility ([A] quoted).

2. GENERAL PROCEDURES

General Procedure A1: *Synthesis of α,β-Unsaturated Aryl Esters*



The appropriate amount of α,β-unsaturated acid (1.0 equiv.) was charged in to a flame-dried flask with the appropriate amount of alcohol (1.5 equiv.), EDCI (2.0 equiv.), and DMAP (0.1 equiv.), in CH_2Cl_2 (0.15 M) at room temperature. The resulting solution was stirred for 16 h at room temperature and then concentrated *in vacuo*. The resulting oil was dissolved in EtOAc (100 mL) and washed with aqueous citric acid (10% *w/v*, 3 × 50 mL), dried over anhydrous $MgSO_4$, and concentrated in *vacuo*. The residue was then purified by flash silica column chromatography under the conditions specified to afford the final product.

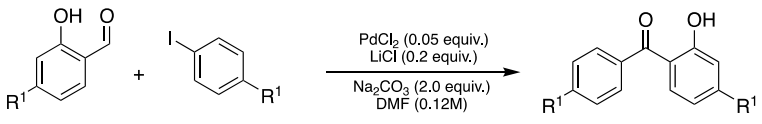
General Procedure A2:

The appropriate amount of carboxylic acid (1.0 equiv.) was dissoleved in CH_2Cl_2 (0.33 M) and added with oxalyl chloride (1.0 equiv) and a few drops of DMF were added. The mixture was then stirred for 1 hour at room temperature. Diisopropylethylamine (2.0 equiv.) and the requisite aryl alcohol (1.0 equiv.) were then added and stirred overnight at room temperature. The mixture was then concentrated *in vacuo* and the residue was purified by column chromatography under the conditions specified to afford the final product.

General Procedure A3:

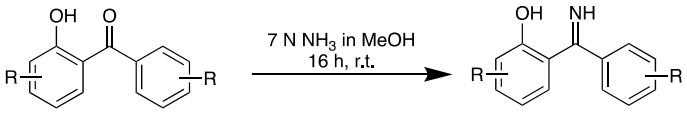
The appropriate amount of the corresponding carboxylic acid (1.0 equiv.) in CH_2Cl_2 (0.1 M) was added with the appropriate aryl alcohol (1.1 equiv.), DCC (1.1 equiv.), and DMAP (0.2 equiv.) at 0 ºC. The mixture was then stirred for 12 hours at room temperature. The mixture was then filtered and concentrated under vacuo. The residue was purified by column chromatography under the conditions specified to afford the final product.

General Procedure B: *Synthesis of 2-Hydroxybenzophenone compounds*



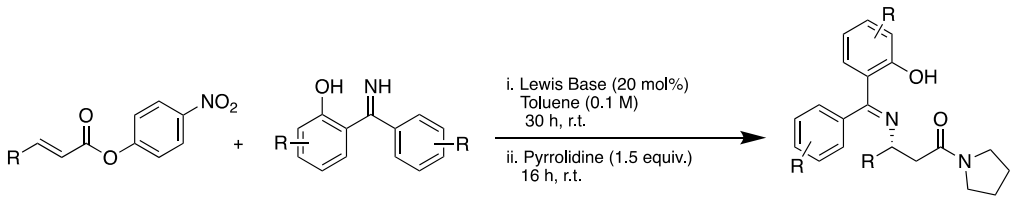
The appropriate amount of 2-hydroxybenzaldehyde derivative (1.0 equiv.), $PdCl_2$ (0.05 equiv.), LiCl (0.2 equiv.), Na_2CO_3 (2.0 equiv.) and DMF (0.12 M) were charged into a round-bottom flask under N_2 atmosphere. The reaction mixture was then heated to 120 ºC, the requisite iodobenzene derivative (2.0 equiv.) was added and the reaction was stirred for 16 h – 20 h. The reaction mixture was added to EtOAc (20 mL), extracted with brine (3 × 20 mL). dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was then purified by flash silica column chromatography under the conditions specified to afford the final product.

General Procedure C: *Synthesis of 2-Hydroxybenzophenone Imines*



The appropriate amount of 2-hydroxybenzophenone derivative (1.0 equiv.) was charged with NH_3 (7 N in MeOH) (5.0 equiv.) and the reaction mixture stirred for 6 h – 20 h at room temperature then concentrated *in vacuo*. The residue was purified by flash silica column chromatography under the conditions specified to afford the final product.

General Procedure D: *Synthesis of β-Amino Substituted Amides*

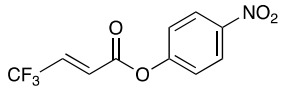


The requisite α,β-Unsaturated aryl ester (1.0 equiv.), 2-hydroxybenzophenone imine (2.0 equiv.), and isothiourea catalyst (20 mol%) were reacted in toluene (0.1 M) were stirred for 30 h at room temperature. The appropriate nucleophile (1.5 equiv.) was added, and the reaction stirred for 16 h at room temperature. The mixture was then concentrated *in vacuo* to give the crude material, which was purified by flash column chromatography under the conditions specified to afford the final product.

3. PREPARATION OF STARTING MATERIALS

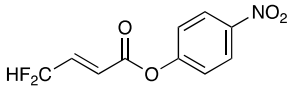
3.1 Data for α,β-Unsaturated Aryl Esters

4-Nitrophenyl (*E*)-4,4,4-trifluorobut-2-enoate (4)



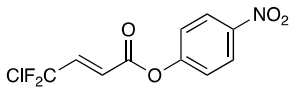
Following **General Procedure A1,** (*E*)-4,4,4-trifluorobut-2-enoic acid (759 mg, 5.40 mmol), 4-nitrophenol (1.13 g, 8.10 mmol), EDCI (2.08 g, 10.8 mmol), DMAP (66.5 mg, 0.540 mmol), and CH_2Cl_2 (40 mL) was stirred at rt for 16 h, purified by flash column chromatography (4:1 Petrol:EtOAc) to give the titled compound (477 mg, 32%) as a colourless crystaline solid. **mp** 86 – 88 ºC (Lit. **mp** 93 – 95ºC)[1]; **IR** ν_{max} (ATR) 3091 (Ar-H), 1739 (C=O), 1132 (C-F); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 6.75 (1H, dq, $^3J_{HH}$ = 15.8, $^4J_{HF}$ = 1.9, CH=C*H*COOPNP), 7.05 (1H, dq, $^3J_{HH}$ = 15.8, $^3J_{HF}$ = 6.4, CF_3C*H*=CH), 7.39 (2H, m, C(2, 6)Ar*H*), 8.35 (2H, m, C(3, 5)Ar*H*); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) , δ_F: -65.7. Spectroscopic data in agreement with the literature.[1]

4-Nitrophenyl (*E*)-4,4-difluorobut-2-enoate



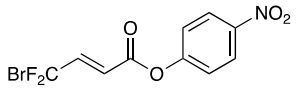
Following **General Procedure A1,** (*E*)-4,4difluorobut-2-enoic acid (759 mg, 5.40 mmol), 4-nitrophenol (1.13 g, 8.10 mmol), EDCI (2.08 g, 10.8 mmol), DMAP (66.5 mg, 0.540 mmol), and CH_2Cl_2 (40 mL) was stirred at rt for 16 h, purified by flash column chromatography (4:1 Petrol:EtOAc) to give the title compound (394 mg, 30%) as a colourless crystaline solid. **mp** 74 – 76 ºC (Lit. **mp** 74 – 76 ºC)[1]; **IR** ν_{max} (ATR) 3118 (Ar-H), 1735 (C=O), 1531 (N-O), 1487 (C=C), 1342 (C-F); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 6.36 (1H, tdd, $^2J_{HF}$ = 54.5, $^3J_{HH}$ = 3.8, $^4J_{HH}$ =1.1, -CF_2*H*), 6.55 (1H, dtd, $^3J_{HH}$ = 15.9, $^4J_{HF}$ = 5.9, $^4J_{HH}$ = 1.1, CF_2HCH=C*H*), 7.08 (1H, dtd, $^3J_{HH}$ = 15.9, $^3J_{HF}$ = 10.3, $^3J_{HH}$ = 3.8, CF_2HC*H*=CH), 7.38 (2H, m, C(2,6)Ar*H*), 8.33 (2H, m, C(3,5)Ar*H*); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) , δ_F: -116.9. Spectroscopic data in agreement with the literature.[1]

4-Nitrophenyl (*E*)-3-chloro-4,4-difluorobut-2-enoate



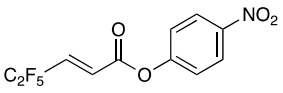
Following **General Procedure A1,** (*E*)-4-chloro-4,4difluorobut-2-enoic acid (759 mg, 5.40 mmol), 4-nitrophenol (1.13 g, 8.10 mmol), EDCI (2.08 g, 10.8 mmol), DMAP (66.5 mg, 0.540 mmol), and CH_2Cl_2 (40 mL) was stirred at rt for 16 h, purified by flash chromatography (4:1 Petrol:EtOAc) to give the title compound (394 mg, 30%) as a colorless crystal solid. **mp** 74 – 76 ºC (Lit. **mp** 74 – 76ºC)[1]; **IR** ν_{max} (ATR) 3118 (Ar-H), 1735 (C=O), 1531 (N-O), 1487 (C=C), 1342 (C-F); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 6.63 (1H, dt, $^3J_{HH}$ = 15.5, $^4J_{HF}$ = 1.8, C*H*=CHCF$_2$Cl), 7.19 (1H, dt, $^3J_{HH}$ = 15.6, $^3J_{HF}$ = 9.0, CF$_2$ClC*H*=CH), 7.39 (2H, m, C(2,6)Ar*H*), 8.35 (2H, m, C(3,5)Ar*H*); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) , δ_F: -54.5. Spectroscopic data in agreement with the literature.[1]

4-Nitrophenyl (*E*)-3-chloro-4,4-difluorobut-2-enoate



Following **General Procedure A2,** (*E*)-4-bromo-4,4difluorobut-2-enoic acid (523 mg, 2.6 mmol), oxalyl chloride (223 µL, 2.6 mmol), and few drops of DMF in CH_2Cl_2 (0.33 M) was stirred for 1 hour. Then, 4-Nitrophenol (362 mg, 2.6 mmol), ^{i}Pr$_2$NEt (905 µL, 5.2 mmol) was added and the reaction was stirred at rt for 16 h, then purified by flash column chromatography (5:1 Petrol:EtOAc) to give the title compound (432 mg, 52%) as a white crystalline solid. **mp** 78 – 80ºC (Lit. **mp** 79 – 80ºC)[1]. **IR** ν_{max} (ATR) 3118 (Ar-H), 1735 (C=O), 1531 (N-O), 1487 (C=C), 1342 (C-F); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 6.54 (1H, dt, $^3J_{HH}$ = 15.6, $^4J_{HF}$ = 1.8, C*H*=CHCF$_2$Cl), 7.23 (1H, m, CF$_2$BrC*H*=CH), 7.39 (2H, m, C(2,6)Ar*H*), 8.35 (2H, m, C(3,5)Ar*H*). **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) , δ_F: -50.6. Spectroscopic data in agreement with the literature.[1]

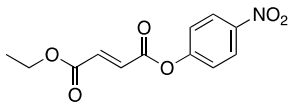
4-Nitrophenyl (*E*)-4,4,5,5,5-pentafluoropent-2-enoate



Following **General Procedure A2,** (*E*)-4,4,5,5,5-pentafluoropent-2-enoic acid (610 mg, 3.2 mmol), oxalyl chloride (275 µL, 3.2 mmol), and few drops of DMF in CH_2Cl_2 (0.33 M) was stirred for 1 hour. Then, 4-Nitrophenol (446 mg, 3.2 mmol), ^{i}Pr$_2$NEt (1.12 mL, 6.4 mmol) was added and the reaction was stirred at rt for 16 h, then purified by flash column chromatography (2:1 Petrol:EtOAc) to give the title compound (800 mg, 80%) as a yellow oil. . **IR** ν_{max} (ATR) 3118 (Ar-H), 1735 (C=O), 1487 – 1531 (C=C), 1342 (C-F); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 6.81 (1H, d, $^3J_{HH}$ = 15.8 C*H*=CHC$_2$F$_5$), 7.05 (1H, m, C$_2$F$_5$C*H*=CH), 7.39 (2H, m, C(2,6)Ar*H*),

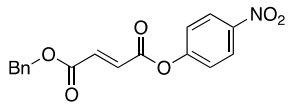
8.35 (2H, m, C(3,5)Ar*H*). **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) , δ_F: -84.4, -117.4. Spectroscopic data in agreement with the literature.[1]

Ethyl (4-nitrophenyl) fumarate



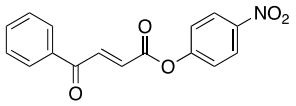
Following **General Procedure A1,** (*E*)-4-ethoxy-4-oxobut-2-enoic acid (1.44 g, 10 mmol), 4-nitrophenol (2.08 g, 15 mmol), EDCI (3.83 g, 20 mmol), DMAP (122 mg, 1 mmol), and 80 mL CH_2Cl_2 was stirred at rt for 16 h and gave the titled compound (889 mg, 34%) as a white solid. **mp** 68 – 69 ºC (Lit. **mp** 67 – 68 ºC)[1]; **IR** ν_{max} (ATR) 3072 (Ar-H), 1716 (C=O), 1514 (N-O), 1489 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 1.35 (3H, t, $^{3}J_{HH}$ = 7.1, OCH_2CH_3), 4.32 (2H, q, $^{3}J_{HH}$ = 7.1, OCH_2CH_3), 7.05 (2H, m, C*H*=C*H*), 7.36 (2H, m, C(2,6)Ar*H*), 8.31 (2H, m, C(3,5)Ar*H*). Spectroscopic data in agreement with the literature.[2]

Benzyl (4-nitrophenyl)fumarate



Following **General Procedure A3,** (*E*)-4-(benzyloxy)-4-oxobut-2-enoic acid (645 mg, 3.13 mmol), 4-nitrophenol (440 mg, 3.16 mmol), DCC (0.710 g, 3.44 mmol), DMAP (76 mg, 0.63 mmol), and 3 mL CH_2Cl_2 was stirred at rt for 12 h and gave the titled compound (0.607 g, 59%) as a white solid. **mp** 74 – 75 ºC (Lit. **mp** 74 – 76 ºC)[2] ; **IR** ν_{max} (ATR) 3078 (Ar-H), 1716 – 1737 (C=O), 1517 (N-O), 1490 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 5.29 (2H, s, CO_2-C*H*$_2$-C_6H_5), 7.22 (2H, m, C*H*=C*H*), 7.35 (2H, m, C(2,6)Ar*H*-NO_2), 7.41 (5H, m, CO_2-CH_2-Ar*H*), 8.30 (2H, m, C(3,5)Ar*H*-NO_2). Spectroscopic data in agreement with the literature.[2]

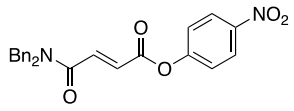
4-Nitrophenyl (*E*)-4-oxo-4-phenylbut-2-enoate



Following **General Procedure A2,** (*E*)-4-oxo-4-phenylbut-2-enoic acid (0.44 g, 2.5 mmol), oxalyl chloride (0.21 mL, 2.5 mmol), and few drops of DMF in CH_2Cl_2 (0.33 M) was stirred for 1 hour. Then, 4-nitrophenol (0.34 g, 2.5 mmol), $^{i}Pr_2NEt$ (0.87 mL, 5.0 mmol) was added and stirred at rt for 16 h and gave the titled product as a yellow solid (0.15 g, 20%). **mp** 127 - 129 ºC (Lit. **mp** 128 – 129 ºC)[3]; **IR** ν_{max} (ATR) 3080 (Ar-H), 1747 (C=O), 1521 (N-O), 1489 (C=C);

^{1}H NMR (400 MHz, $CDCl_3$), δ_H: 7.10 (1H, d, $^3J_{HH}$ = 16.6, C*H*=CH-CO-Ph), 7.40 (2H, m, C(2,6)Ar*H*-NO_2), 7.56 (2H, m, C(3,5)Ar*H*), 7.67 (1H, m, C(4)Ar*H*), 8.05 (2H, m, C(2,6)Ar*H*), 8.13 (1H, d, $^3J_{HH}$ = 16.6 CH=C*H*-CO-Ph), 8.33 (2H, m, C(3,5)Ar*H*-NO_2). Spectroscopic data in agreement with the literature.[3]

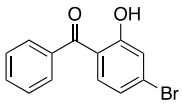
4-Nitrophenyl (*E*)-4-(dibenzylamino)-4-oxobut-2-enoate



Following **General Procedure A3,** (*E*)-4-(dibenzylamino)-4-oxobut-2-enoic acid (2.08 g, 7.04 mmol), 4-nitrophenol (1.0 g, 7.18 mmol), DCC (1.74 g, 8.44 mmol), DMAP (172 mg, 01.41 mmol), and 7 mL CH_2Cl_2 was stirred at rt for 12 h and gave the titled compound (2.20 g, 75%) as an orange solid. **mp** 62 – 65 ºC (Lit. **mp** 62 – 64ºC)[1]; **IR** ν_{max} (ATR) 3030 (Ar-H), 1741 (C=O), 1587 (N-O), 1440 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 5.29 (2H, s, CO_2-C*H*$_2$-C_6H_5), 7.22 (2H, m, C*H*=C*H*), 7.35 (2H, m, C(2,6)Ar*H*-NO_2), 7.41 (5H, m, CO_2-CH_2-Ar*H*), 8.30 (2H, m, C(3,5)Ar*H*-NO_2). Spectroscopic data in agreement with the literature.[1]

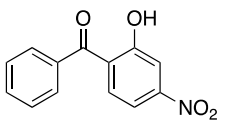
3.2 Data for Benzophenone Derivatives

(4-Bromo-2-hydroxyphenyl)(phenl)methanone



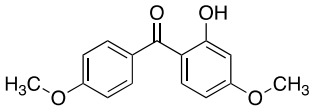
Following **General Procedure B,** 4-bromo-2-hydroxybenzaldehye (289.4 mg, 1.2 mmol), Iodobenzene (266 µL, 2.4 mmol), $PdCl_2$ (10.6 mg, 0.06 mmol), LiCl (10.2 mg, 0.24 mmol), Na_2CO_3 (254.4 mg, 2.4 mmol), DMF (10 mL) were stirred at 120 ºC for 16 hours, then purified by flash column chromatography (2:1 Petrol:EtOAc) to give the title compound (269.5 mg, 72%) as a pale yellow liquid. **IR** ν_{max} (ATR): 3005 (OH), 2843 (Ar-H), 1629 (C=O), 1440 (C=C), ; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.02 (1H, dd, $^3J_{HH}$ = 8.5, $^4J_{HH}$ = 1.9, C(5)Ar*H*OH-Br), 7.28 (1H, d, $^4J_{HH}$ = 1.9, C(3)Ar*H*OH-Br), 7.46 (1H, d, $^3J_{HH}$ = 8.6, C(6)Ar*H*OH-Br), 7.52 (2H, t, $^3J_{HH}$ = 7.5, C(3,5)Ar*H*), 7.60 (1H, m, C(4)Ar*H*), 7.66 (2H, m, C(2,6)Ar*H*), 12.1 (1H, s, O*H*). Spectroscopic data in agreement with literature.[4]

(2-Hydroxy-4-nitrophenyl)(phenyl)methanone



Following **General Procedure B,** 2-hydroxy-4-nitrobenzaldehye (200.6 mg, 1.2 mmol), Iodobenzene (266 µL, 2.4 mmol), $PdCl_2$ (10.6 mg, 0.06 mmol), LiCl (10.2 mg, 0.24 mmol), Na_2CO_3 (254.4 mg, 2.4 mmol), DMF (10 mL) were stirred at 120 ºC for 6 hours, then purified by flash column chromatography (20:1 Petrol:EtOAc then flush with EtOAc) to give the title compound (66.3 mg, 23%) as a pale yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.59 (2H, dd, $^3J_{HH}$ = 8.3, $^3J_{HH}$ = 6.9 Hz, C(3,5)Ar*H*), 7.68 (1H, m, C(4)Ar*H*), 7.73 (3H, m, C(1,2)Ar*H* and C(5)Ar*H*OH-NO_2), 7.83 (1H, d, C(6)Ar*H*OH-NO_2), 7.94 (1H, d, $^4J_{HH}$ = 2.2, C(3)Ar*H*OH-NO_2), 12.01 (1H, s, O*H*). Spectroscopic data in agreement with the literature.[4]

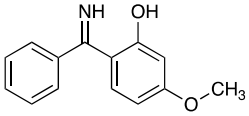
(2-Hydroxy-4-methoxyphenyl)(4-methoxyphenyl)methanone



Following **General Procedure B,** 2-hydroxy-4-methoxybenzaldehye (182.6 mg, 1.2 mmol), 1-iodo-4-methoxybenzene (561.7 µL, 2.4 mmol), $PdCl_2$ (10.6 mg, 0.06 mmol), LiCl (10.2 mg, 0.24 mmol), Na_2CO_3 (254.4 mg, 2.4 mmol), DMF (10 mL) were stirred at 120 º C for 6 hours, then purified by flash column chromatography (2:1 Petrol:EtOAc then flush with EtOAc) to give the title compound (223.8 mg, 72%) as a pale yellow solid. **mp** 108 – 110 ºC (Lit. **mp** 110–112 ºC)[5] ; **IR** ν_{max} (ATR): 3005 (OH), 2843 (Ar-H), 1629 (C=O), 1440 (C=C), 1270 (C-O-CH_3) ; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 3.87 (3H, s, ArH-OCH_3), 3.89 (3H, s, ArHOH-OCH_3), 6.42 (1H, dd, $^3J_{HH}$ = 8.9 Hz, $^4J_{HH}$ = 2.6 Hz, C(5)Ar*H*OH-OCH_3), 6.52 (1H, d, $^4J_{HH}$ = 2.6 Hz, C(3)Ar*H*OH-OCH_3), 6.99 (2H, m, C(3,5)Ar*H*-OCH_3), 7.56 (1H, d, $^3J_{HH}$ = 8.9 Hz, C(6)Ar*H*OH-OCH_3), 7.66 (2H, m, C(2,6)Ar*H*-OCH_3), 12.69 (1H, s, O*H*). Spectroscopic data in agreement with the literature. [5,6]

3.3 Data for Benzophenone Imine Derivatives

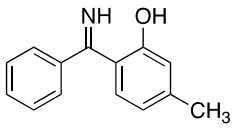
2-(Imino(phenyl)methyl)-5-methoxyphenol (3)



Following **General Procedure C,** (2-hydroxy-4-methoxyphenyl)(phenyl)methanone (685 mg, 3 mmol), and 7N NH_3 in MeOH (2.14 mL, 15 mmol) stirred at rt for 16 hours, and purified by flash column chromatography (2:1 Petrol:EtOAc) to give gave the titled compound (0.31 g, 45%) as a yellow solid. **mp** 123 – 126 ºC; **IR** ν_{max} (ATR): 2932 (N-H), 1608 (C=N), 1423 – 1447

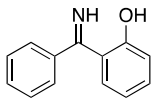
(C=C), 1277 (C-O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 3.84 (3H, s, OC*H*$_3$), 6.23 (1H, m, C(4)Ar*H*OH-OCH_3), 6.45 (1H, s, C(6)Ar*H*OH-OCH_3), 7.06 (1H, d, $^3J_{HH}$ = 9.1 Hz, C(3)Ar*H*OH-OCH_3), 7.49 (5H, m, Ar*H*), 8.18 (1H, s, N*H*), 15.07 (1H, s, O*H*). Spectroscopic data in agreement with the literature.[7]

2-(Imino(phenyl)methyl)-5-methylphenol



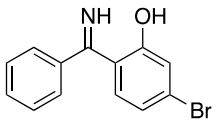
Following **General Procedure C,** (2-hydroxy-4-methylphenyl)(phenyl)methanone (318.4 mg, 1.5 mmol), and 7N NH_3 in MeOH (1.07 mL, 7.5 mmol) stirred at rt for 16 hours, and purified by flash column chromatography (2:1 Petrol:EtOAc) to give gave the titled compound (237.1 mg, 75%) as a yellow solid. **mp** 66 – 70 ºC (Lit. **mp** 69 ºC)[8]; **IR** ν_{max} (ATR): 2845 (N-H), 1616 (C=N), 1429 – 1493 (C=C), 1083 (Ar-CH_3) ; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 2.36 (3H, s, C*H*$_3$), 6.57 (1H, d, $^3J_{HH}$ = 8.0 Hz, C(5)Ar*H*OH-CH_3), 6.88 (1H, s, C(3)Ar*H*OH-CH_3), 7.09 (1H, d, $^3J_{HH}$ = 8.0 Hz, C(6)Ar*H*OH-CH_3), 7.42 (2H, d, $^3J_{HH}$ = 5.5 Hz, C(2,6)Ar*H*), 7.51 (3H, m, C(3,4,5)Ar*H*), 9.14 (1H, s, N*H*), 14.74 (1H, s, O*H*). Spectroscopic data in agreement with the literature.[8]

2-(Imino(phenyl)methyl)phenol

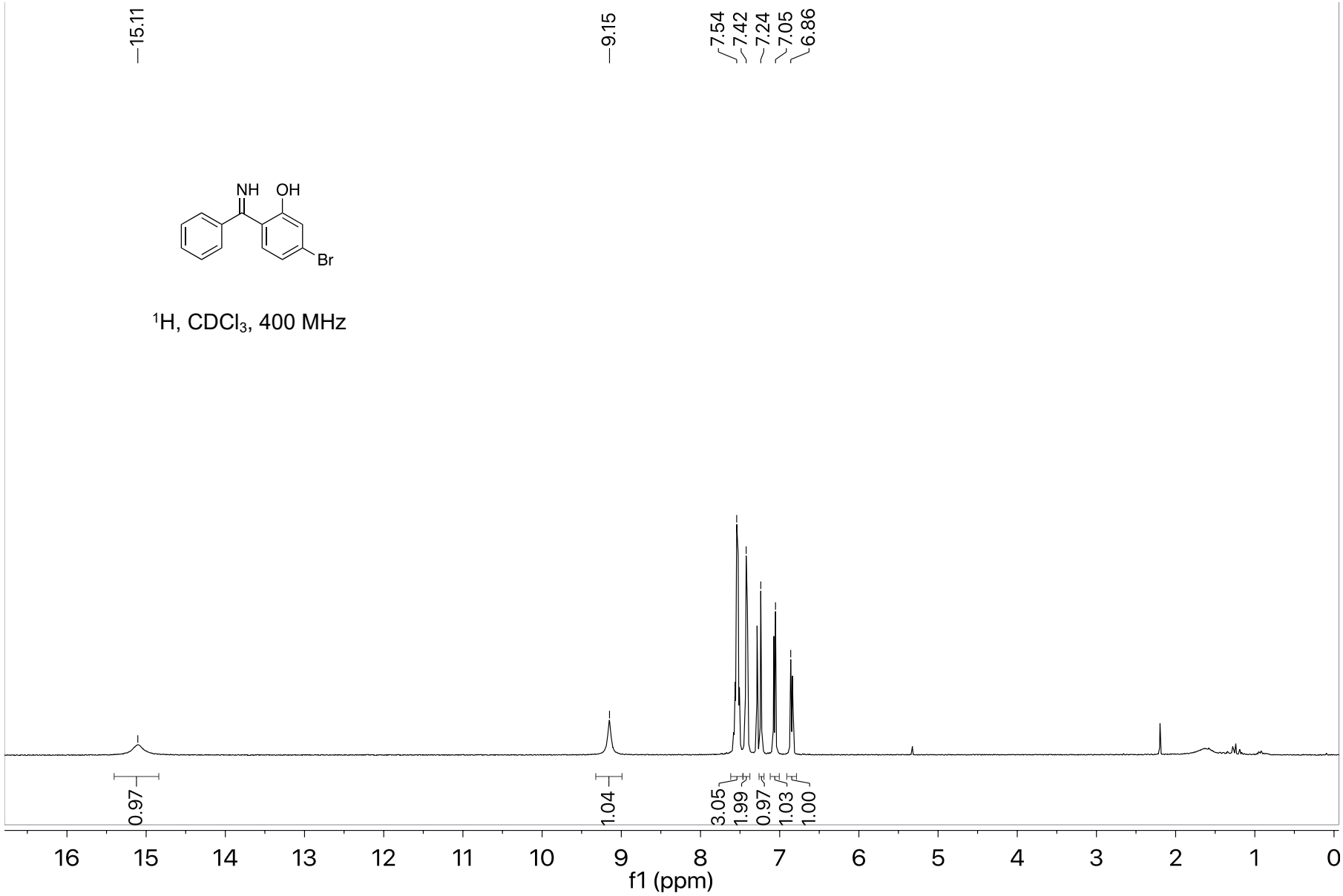


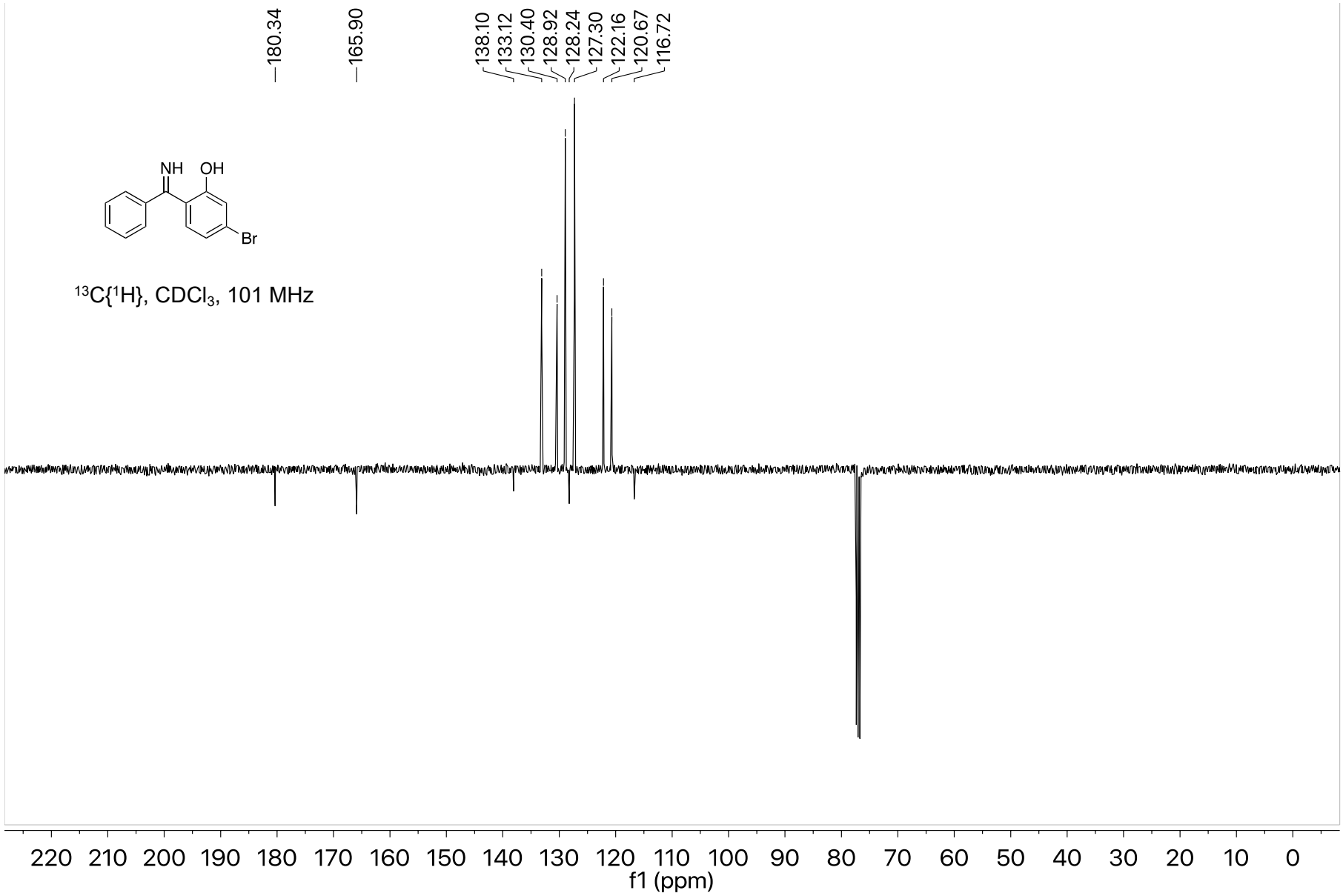
Following **General Procedure C,** (2-hydroxyphenyl)(phenyl)methanone (198 mg, 1 mmol), and 7N NH_3 in MeOH (717.7 µL, 5 mmol) stirred at rt for 16 hours gave the titled compound (153.4 mg, 78%) as a yellow solid. **mp** 82 – 84 ºC (Lit. **mp** 94 – 97 ºC)[9] ; **IR** ν_{max} (ATR): 2826 (N-H), 1589 (C=N), 1462-1508 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 6.79 (1H, dd, $^3J_{HH}$ = 8.2, $^4J_{HH}$ = 1.2, HN=C(3)Ar*H*OH), 7.14 (1H, dd, $^3J_{HH}$ = 8.4, $^4J_{HH}$ = 1.21, C(5)Ar*H*OH), 7.24 (1H, dd, $^3J_{HH}$ = 8.0, $^4J_{HH}$ = 1.7, C(4)Ar*H*OH), 7.41 (1H, dd, $^3J_{HH}$ = 8.6, $^4J_{HH}$ = 1.7, C(6)Ar*H*OH), 7.46 (2H, m, HN=CAr*H*), 7.53 (3H, m, HN=CAr*H*), 9.67 (1H, s, N-*H*), 14.26 (1H, bs, O*H*). Spectroscopic data in agreement with the literature. [7,8,9]

5-Bromo-2-(imino(phenyl)methyl)phenol

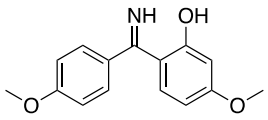


Following **General Procedure C,** 2-(imino(phenyl)methyl)-5-methylphenol (260.3 mg, 0.8 mmol), and 7N NH_3 in MeOH (600 µL, 4.2 mmol) stirred at rt for 16 hours, purified by flash chromatography (2:1 Petrol:EtOAc) to give gave the titled compound (169.7 mg, 65%) as a yellow solid. **mp** 115 – 117 º C; **IR** ν_{max} (ATR): 3038 – 3057 (OH), 1587 (C=N), 1487 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 2.20 (3H, s, ArOH-Br), 6.98 (2H, m, C(3,6)Ar*H*OH-CH_3), 7.20 (1H, d, $^3J_{HH}$ = 8.5 Hz, C(4)Ar*H*OH-CH_3), 7.42 (2H, m, C(2,6)Ar*H*), 7.51 (3H, m, C(3,4,5)Ar*H*), 9.32 (1H, s, N*H*), 14.45 (1H, bs, O*H*). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_H: 116.7 (*C*(1)ArOH-Br), 120.7 (*C*(5)ArOH-Br), 122.2 (*C*(3)ArOH-Br), 127.3 (*C*(2,6)Ar), 128.4 (*C*(4)ArOH-Br), 128.9 (*C*(3,5)ArOH-Br), 130.4 (*C*(4)ArOH-Br), 128. (*C*(4)Ar), 133.1 (*C*(6)ArOH-Br), 138.1 (*C*(1)Ar), 165.9 (*C*(2)ArOH-Br), 180.3 (*C*=N); **HRMS** (NSI$^+$) $C_{13}H_{10}BrNO$ ([M+H$^+$]) requires 276.0019, found 276.0012 (-2.5 ppm).

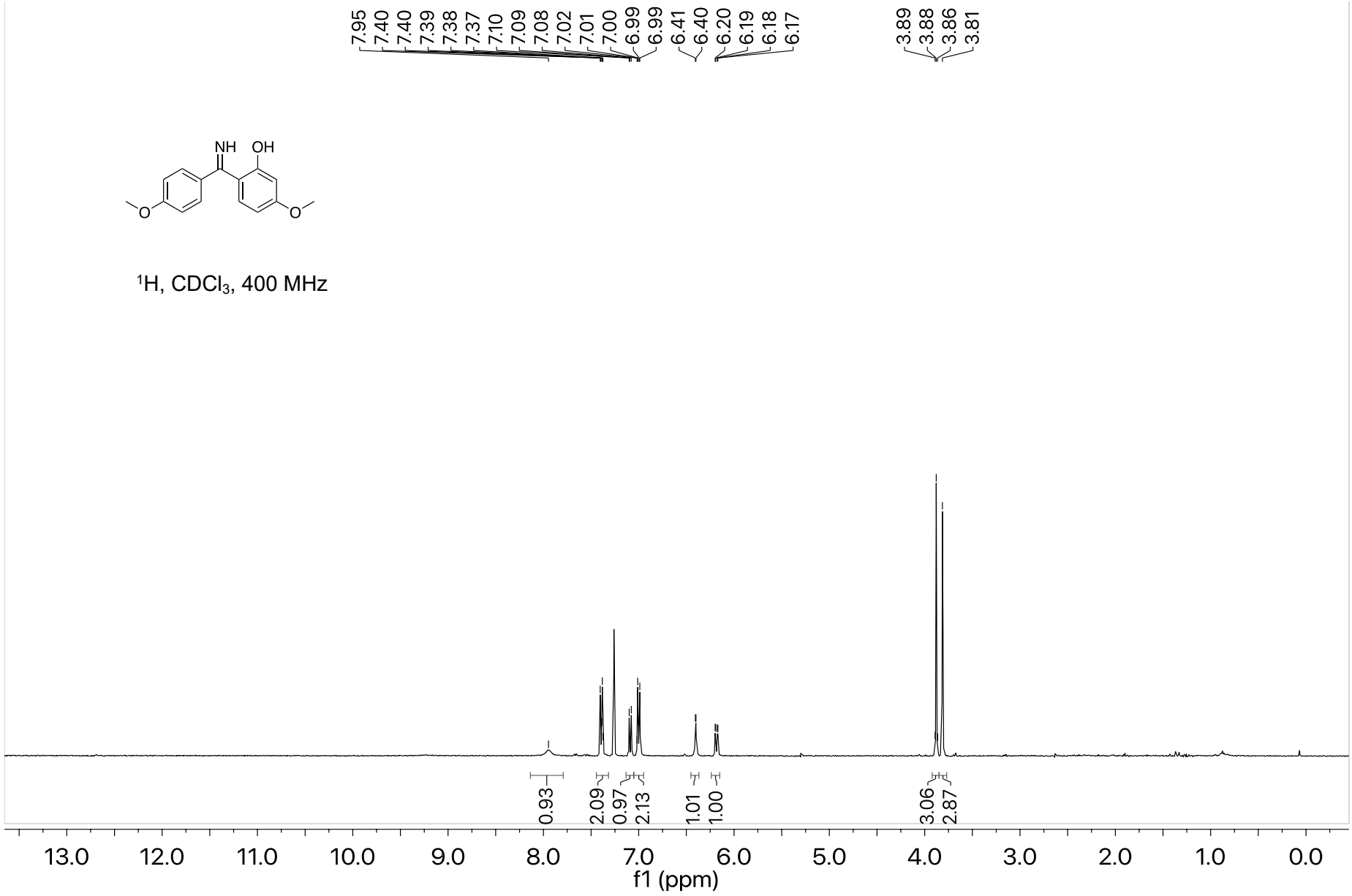

15.11
9.15
7.54
7.42
7.24
7.05
6.86
NH
OH
Br
1H, CDCl3, 400 MHz
0.97
1.04
3.05
1.99
0.97
1.03
1.00
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


180.34
165.90
138.10
133.12
130.40
128.92
128.24
127.30
122.16
120.67
116.72
NH
OH
Br
13C{1H}, CDCl3, 101 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

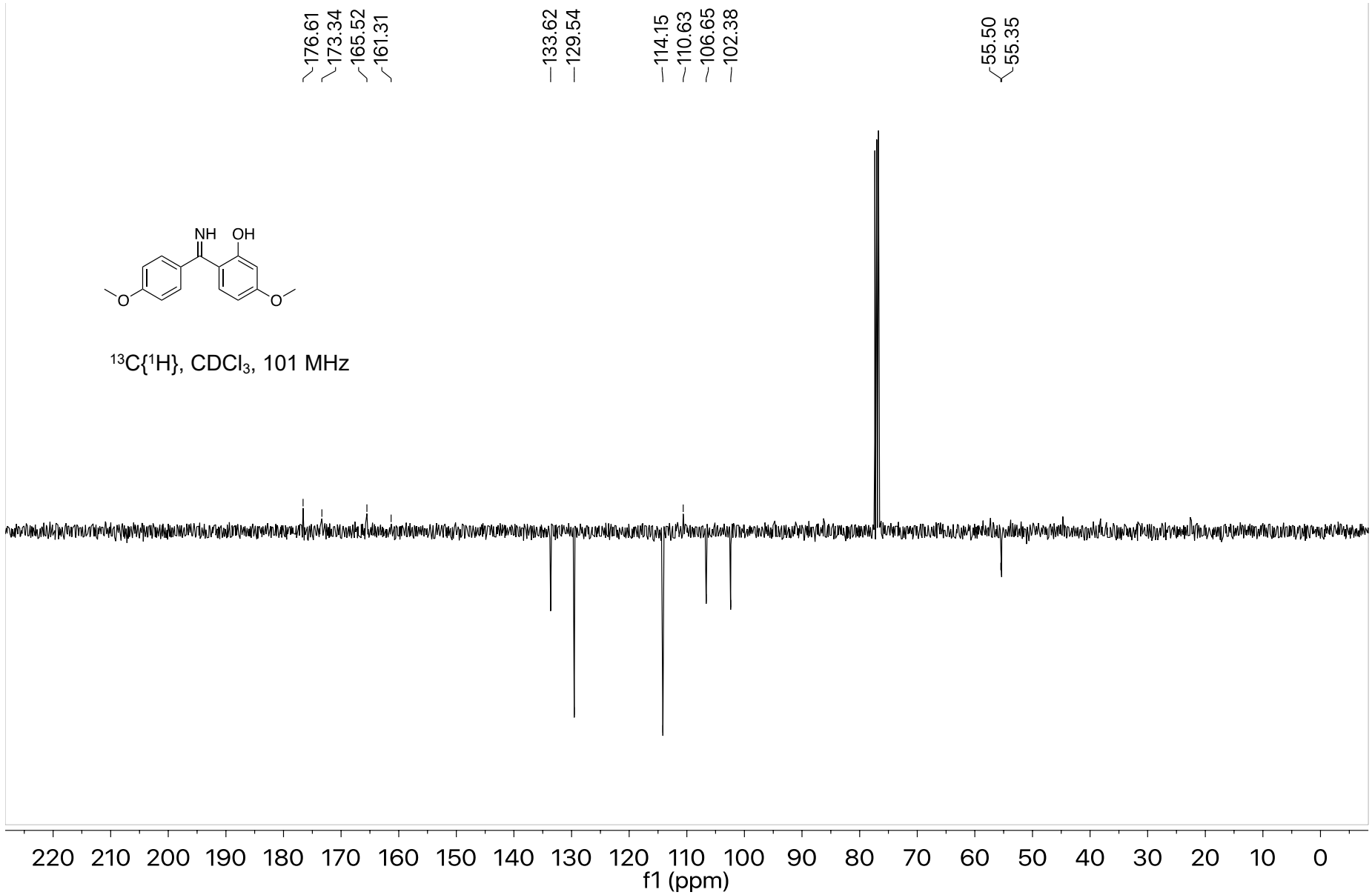
2-(Imino(4-methoxyphenyl)methyl)-5-methoxyphenol



Following **General Procedure C**, (2-hydroxy-4-methoxyphenyl)(4-methoxyphenyl)methanone (136.4 mg, 0.53 mmol), and 7N NH_3 in MeOH (0.38 mL, 2.65 mmol) stirred at rt for 16 hours, and purified by flash column chromatography (2:1 Petrol:EtOAc then flushed with EtOAc) to give gave the titled compound (95.7 mg, 14%) as a yellow oil. **IR** ν_{max} (ATR): 2963 (Ar-H), 1608 (C=N), 1456 (C=C), 1219 – 1254 (C-O-CH_3); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 3.84 (3H, s, ArHOH-OC*H*$_3$), 3.90 (3H, s, ArH-OC*H*$_3$), 6.21 (1H, dd, $^3J_{HH}$ = 9.1 Hz, $^4J_{HH}$ = 2.5 Hz, C(5)Ar*H*OH-OCH_3), 6.43 (1H, d, $^4J_{HH}$ = 2.5 Hz, C(3)Ar*H*OH-OCH_3), 7.02 (2H, d, $^3J_{HH}$ = 8.7 Hz, C(3,5)Ar*H*-OCH_3), 7.11 (1H, d, $^3J_{HH}$ = 9.1, C(6)Ar*H*OH-OCH_3), 7.42 (2H, d, $^3J_{HH}$ = 8.7 Hz, C(2,6)Ar*H*-OCH_3), 7.96 (1H, s, N*H*), 15.07 (1H, s, O*H*). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_{Cl}: 55.4 (ArHOH-O*C*H_3), 55.5 (ArH-O*C*H_3), 102.4 (*C*(3)ArHOH-OCH_3), 106.7 (*C*(5)ArHOH-OCH_3), 110.6 (*C*(1)ArHOH-OCH_3), 114.2 (*C*(3,5)ArH-OCH_3), 129.5 (*C*(1,2,6)ArH-OCH_3), 133.6 (*C*(6)ArHOH-OCH_3), 161.3 (*C*(4)ArH-OCH_3), 165.5 (*C*(4)ArHOH-OCH_3), 173.3 (*C*(2)ArHOH-OCH_3), 176.6 (*C*=N); **HRMS** (NSI^+) $C_{15}H_{15}NO_3$ ([M+H$^+$]) requires 258.1125, found 258.1117 (-3.1 ppm).

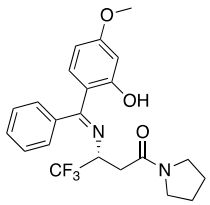


^{1}H, $CDCl_3$, 400 MHz

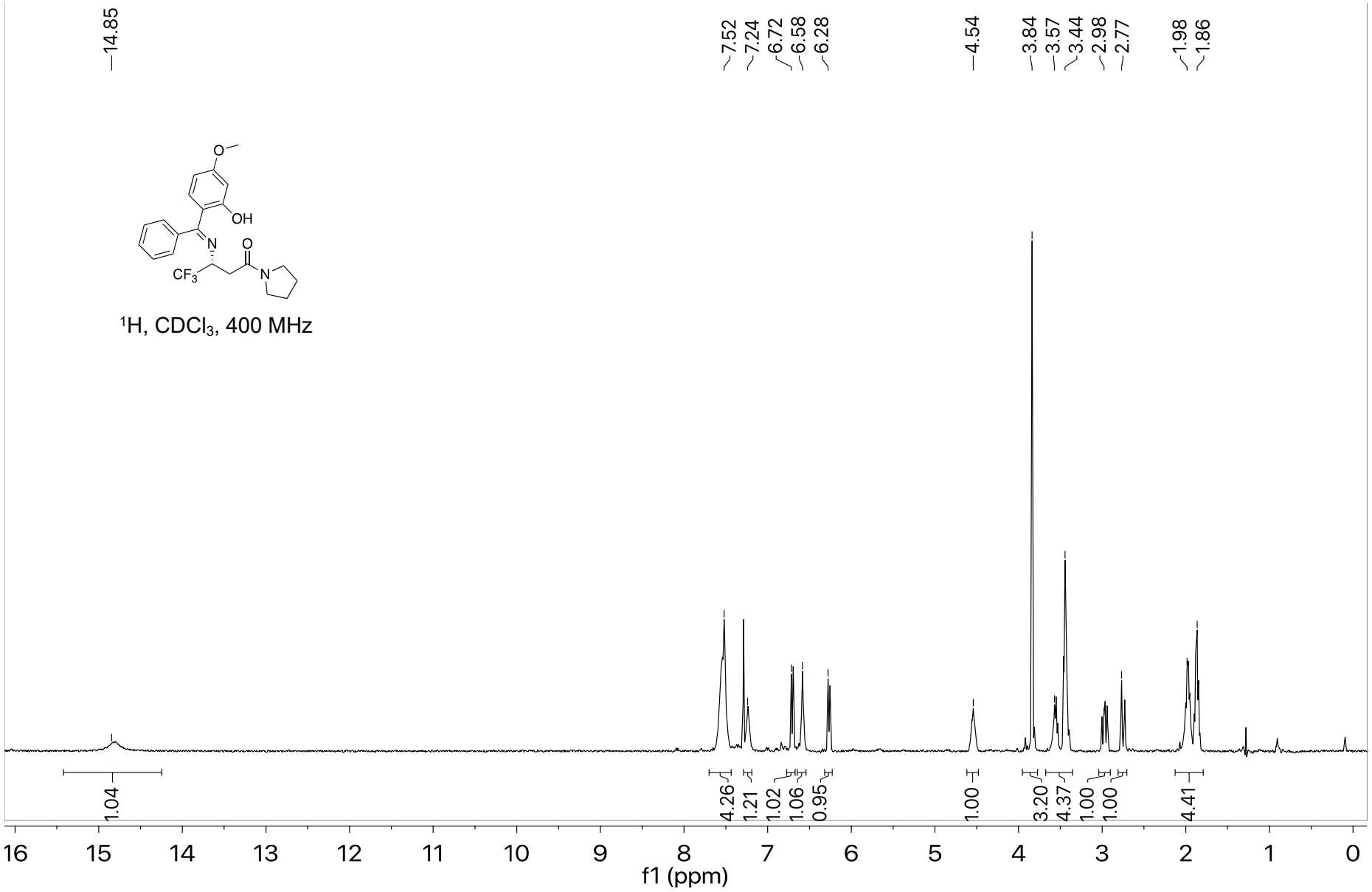

176.61
173.34
165.52
161.31
133.62
129.54
114.15
110.63
106.65
102.38
55.50
55.35
NH
OH
O
O
$^{13}C\{^{1}H\}$, $CDCl_3$, 101 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

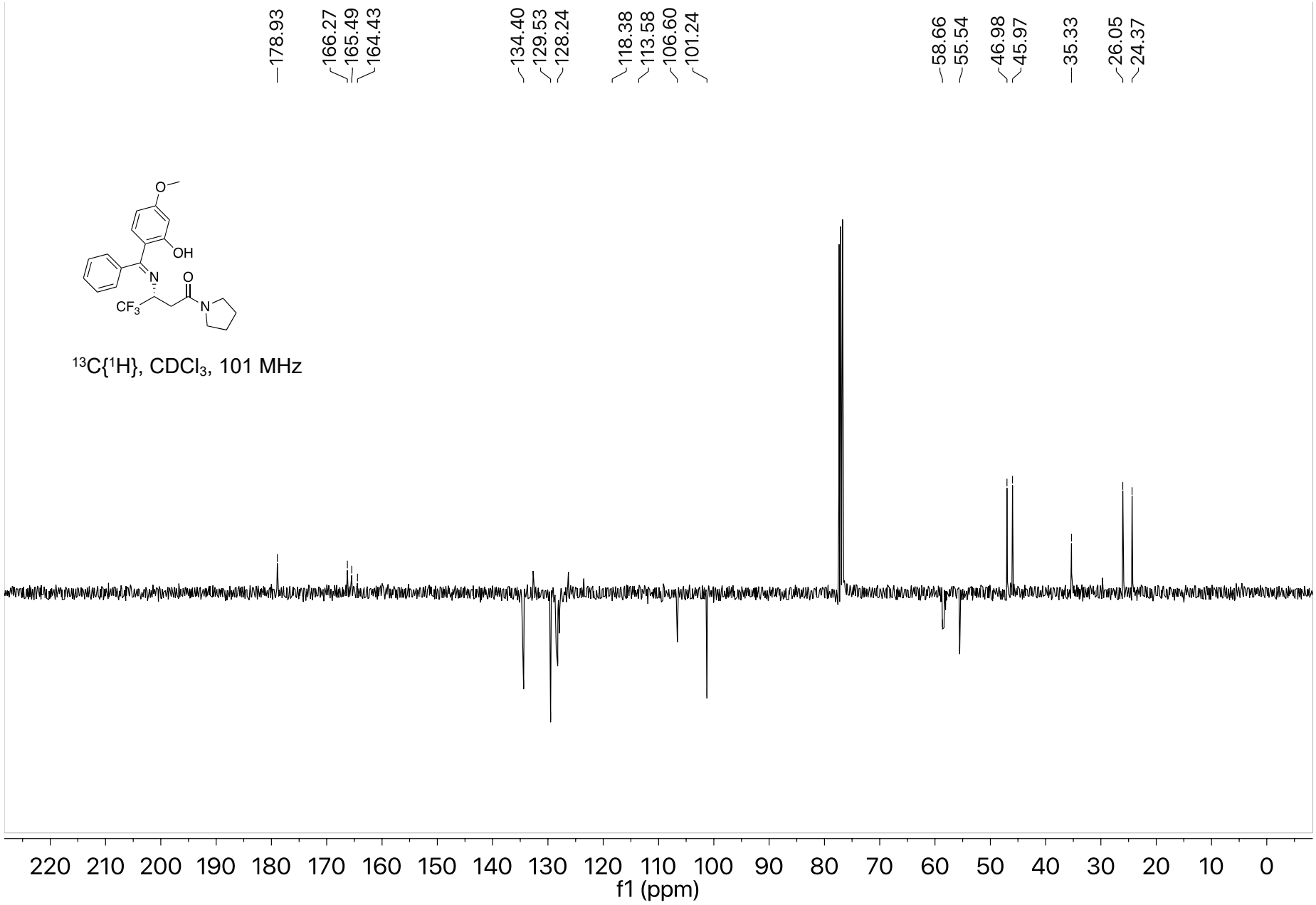
4. PRODUCTS

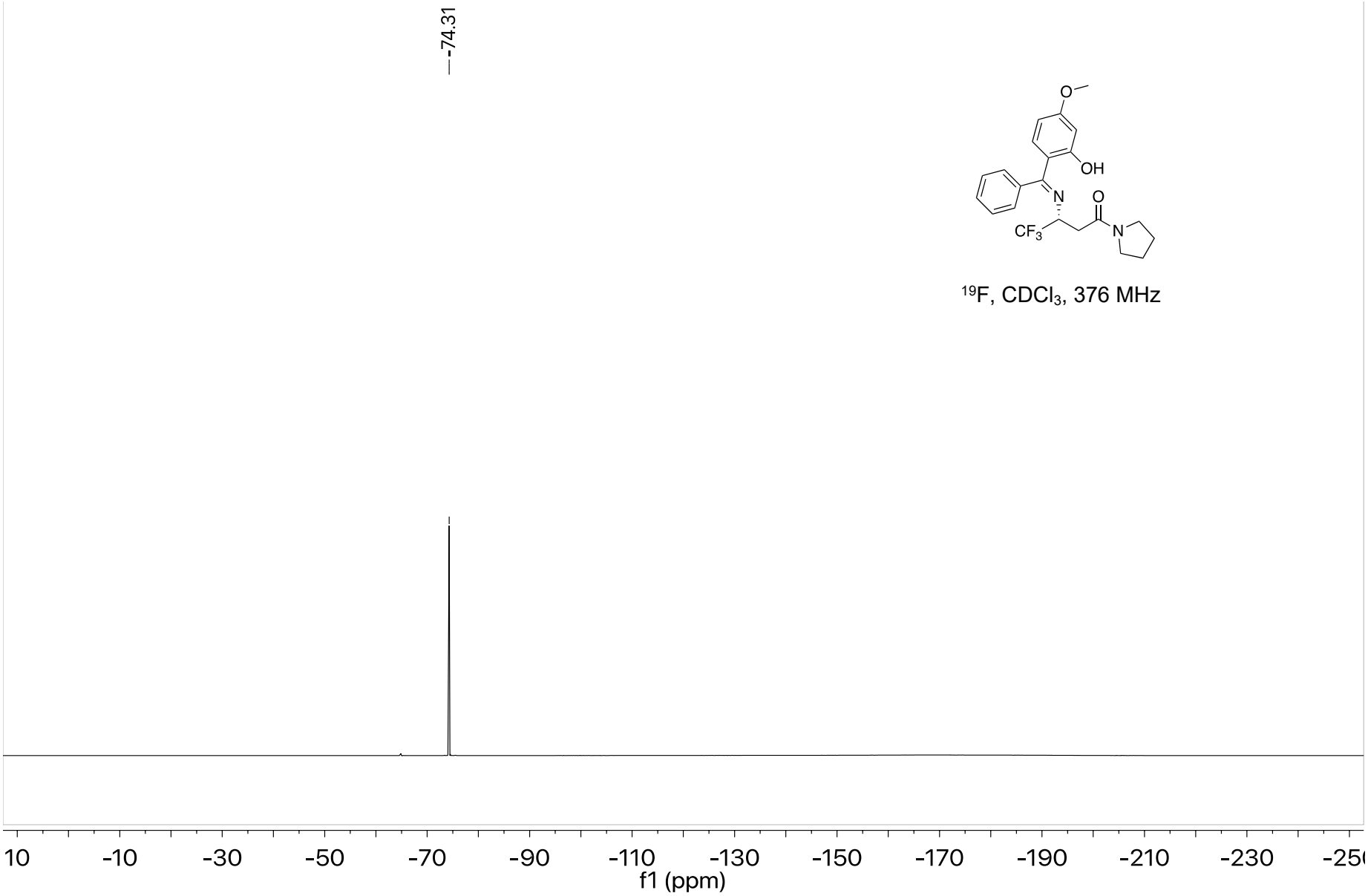
(*R*)-4,4,4-Trifluoro-3-(((2-hydroxy-4-methoxyphenyl)(phenyl)methylene)amino)-1-(pyrrolidin-1-yl)butan-1-one (5)



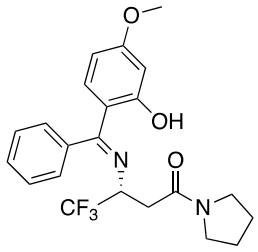
Following **General Procedure D,** 4-nitrophenyl (*E*)-4,4,4,-trifluorobut-2-enoate (26.1 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (45.4 mg, 0.2 mmol), (*R*)-(+)-BTM (5.1 mg, 0.02mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Pyrrolidine was added (12.5 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was purified by flash column chromatography Hexane:EtOAc (4:1) (R_f = 0.20) to give the titled compound (29.8 mg, 70%) as a yellow oil. $[\alpha]_D^{20}$ +95.5 (*c* = 0.87, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(*R*): 19.1 min, t_R(*S*): 25.3 min, 95:5 er; **IR** ν_{max} (ATR), 2976 (Ar-H), 1624 (C=O), 1605 (C=N), 1444 – 1454 (C=C), 1276 (C-O-CH_3), 1261 (CF_3); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.86 – 1.98 (4H, m, NC(2)H_2C(3)*H_2*C(4)*H_2*C(5)H_2), 2.75 (1H, dd, $^3J_{HH}$ = 15.4, $^4J_{HF}$ = 3.0, COC(2)*H_A*H_B), 2.98 (1H, dd, $^3J_{HH}$ = 15.2, $^4J_{HF}$ = 10.0, COC(2)H_A*H_B*), 3.44 – 3.57 (4H, m, NC(2)*H_2*C(3)H_2C(4)H_2C(5)*H_2*), 3.84 (3H, s, OC*H_3*), 4.54 (1H, m, COC$H_A$$H_B$C*H*), 6.28 (1H, dd, $^3J_{HH}$ = 9.0, N=CC(5)Ar*H*OH-OCH_3), 6.58 (1H, s, N=CC(3)Ar*H*OH-OCH_3), 6.72 (1H, dd, $^3J_{HH}$ = 8.9, N=CC(6)Ar*H*OH-OCH_3), 7.24 (1H, m, N=CC(4)Ar*H*), 7.52 (4H, m, N=CC(2,3,5,6)Ar*H*), 14.8 (1H, s, N=CC(2)ArO*H*-OCH_3); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -74.31 (-C*F_3*) ; **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 24.4 (NC(2)H_2*C*(3)H_2C(4)H_2C(5)H_2), 26.1 (NC(2)H_2C(3)H_2*C*(4)H_2C(5)H_2), 35.3 (C=O*C*$H_A$$H_B$$CF_3$), 45.9 (N*C*(2)$H_2$C(3)$H_2$C(4)$H_2$C(5)$H_2$), 47.0 (NC(2)$H_2$C(3)$H_2$C(4)$H_2$*C*(5)$H_2$), 55.54 (O*C*$H_3$), 58.7 (q, $^2J_{CF}$ = 28.3, C=O$CH_A$$H_B$*C*(3)H$CF_3$), 101.2 (N=C*C*(3)ArOH-$OCH_3$), 106.6 (N=C*C*(5)ArOH-$OCH_3$), 114.28 (N=C*C*(1)ArOH-OCH_3), 118.4 (*C*F_3), 128.2 (N=C*C*(2,3,5,6)ArH), 129.5 (N=C*C*(4)Ar), 134.4 (N=C*C*(1)Ar), 164.4 (N=C*C*(2)ArOH-OCH_3), 165.5 (*C*=N), 166.3 (N=C*C*(4)ArOH-OCH_3), 178.9 (*C*=O). **HRMS** (NSI$^+$) $C_{21}H_{23}F_3N_2O_3^+$ ([M+H]$^+$) requires 421.1734, found 421.1729 (-1.2 ppm).


14.85
7.52
7.24
6.72
6.58
6.28
4.54
3.84
3.57
3.44
2.98
2.77
1.98
1.86
O
OH
N
O
CF3
N
1H, CDCl3, 400 MHz
1.04
4.26
1.21
1.02
1.06
0.95
1.00
3.20
4.37
1.00
1.00
4.41
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


178.93
166.27
165.49
164.43
134.40
129.53
128.24
118.38
113.58
106.60
101.24
58.66
55.54
46.98
45.97
35.33
26.05
24.37
O
OH
N
O
CF3
N
13C{1H}, CDCl3, 101 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

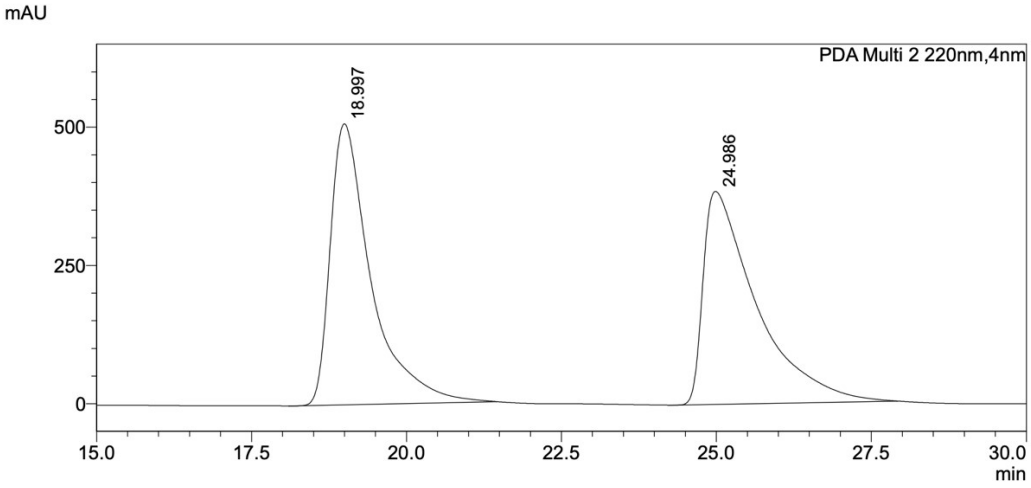

-74.31
O
OH
N
O
CF3
N
19F, CDCl3, 376 MHz
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
-230
f1 (ppm)

HPLC Data for **((*R*)-4,4,4-trifluoro-3-(((2-hydroxy-4-methoxyphenyl)(phenyl)methylene)amino)-1-(pyrrolidin-1-yl)butan-1-one**: Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 220 nm, 30 °C) t_R(*R*): 19.1 min, t_R(*S*): 25.3 min, 95:5 er.

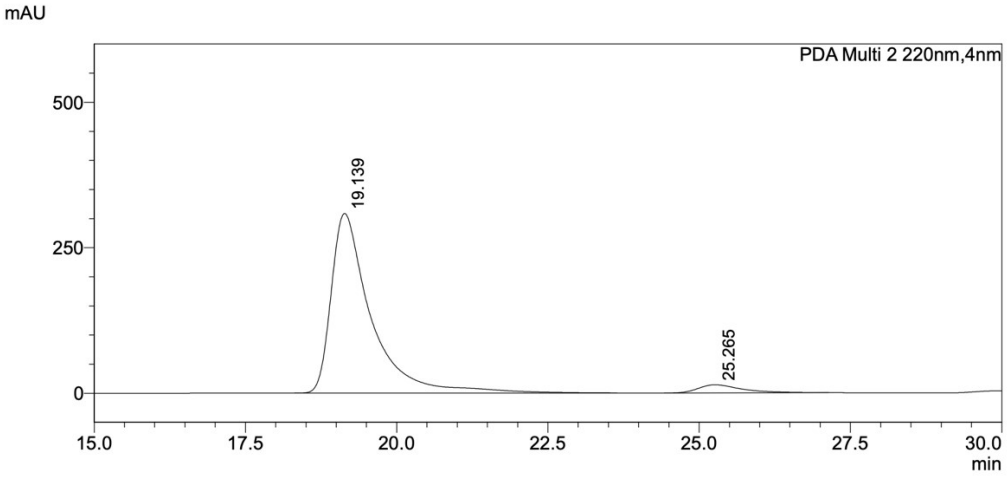


PDA Ch2 220nm

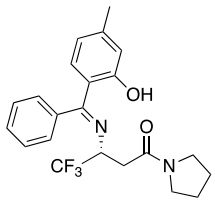
Peak#	Ret. Time	Area%
1	18.997	50.330
2	24.986	49.670
Total		100.000



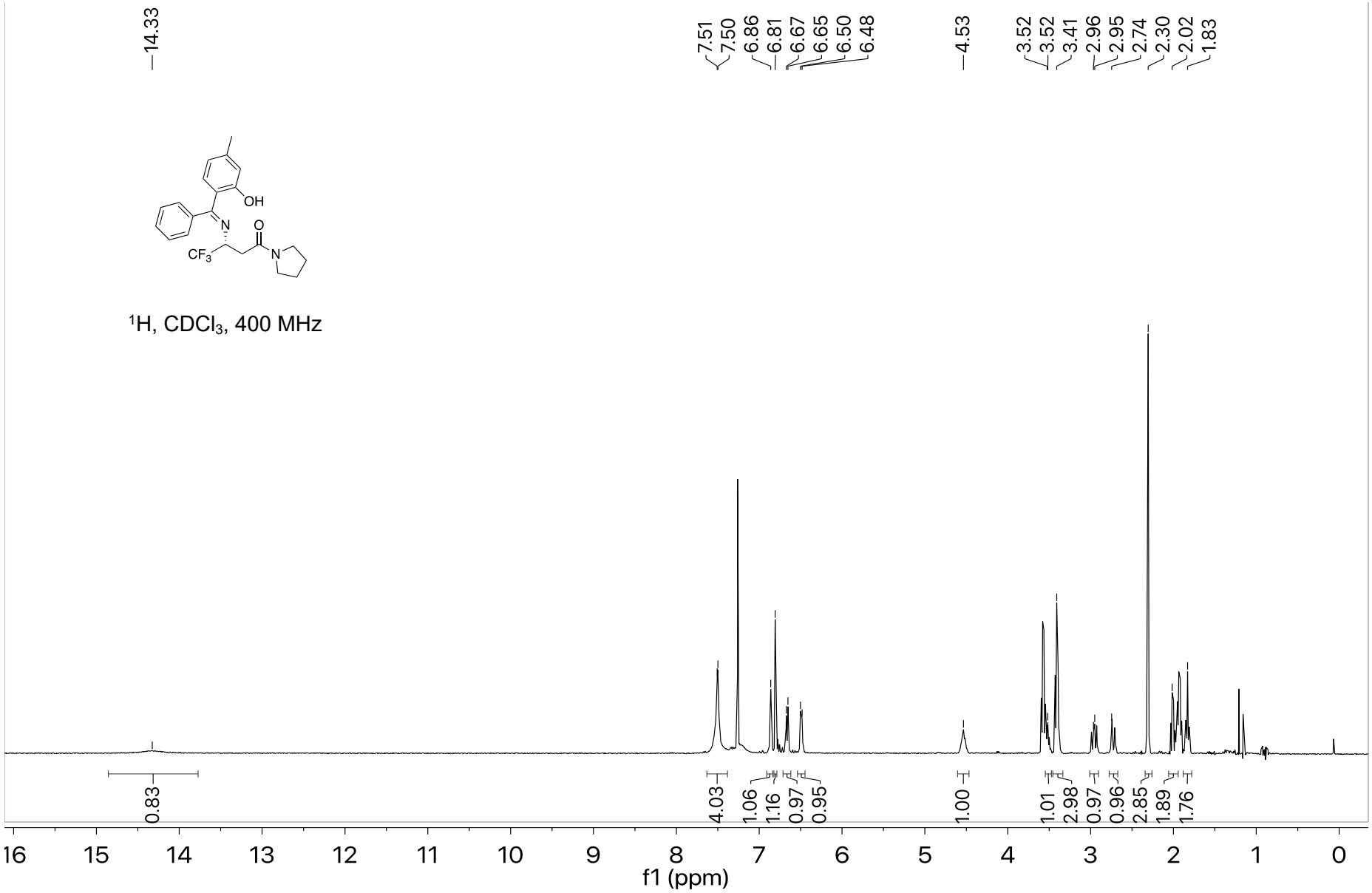
Peak#	Ret. Time	Area%
1	19.139	95.369
2	25.265	4.631
Total		100.000

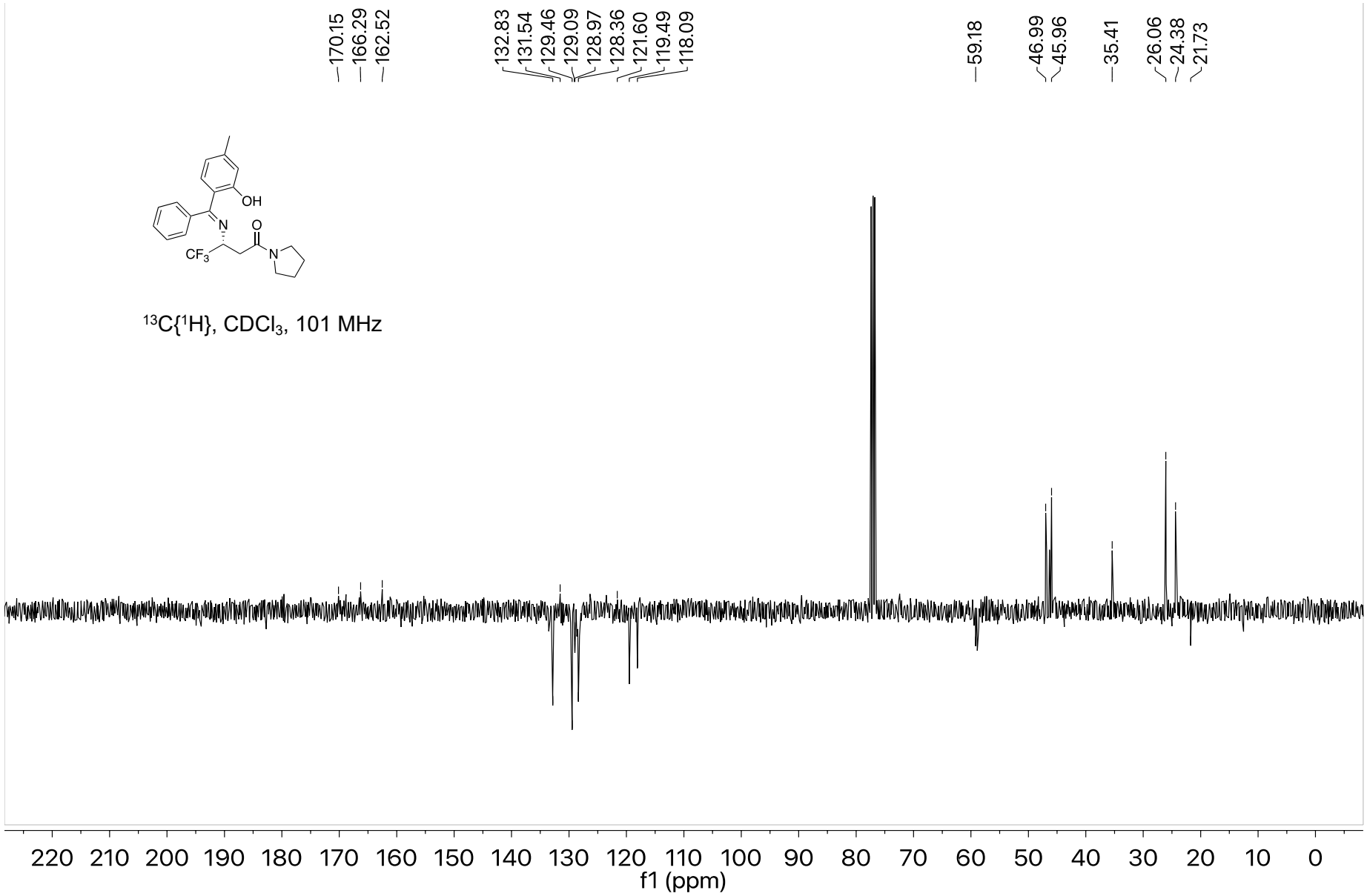


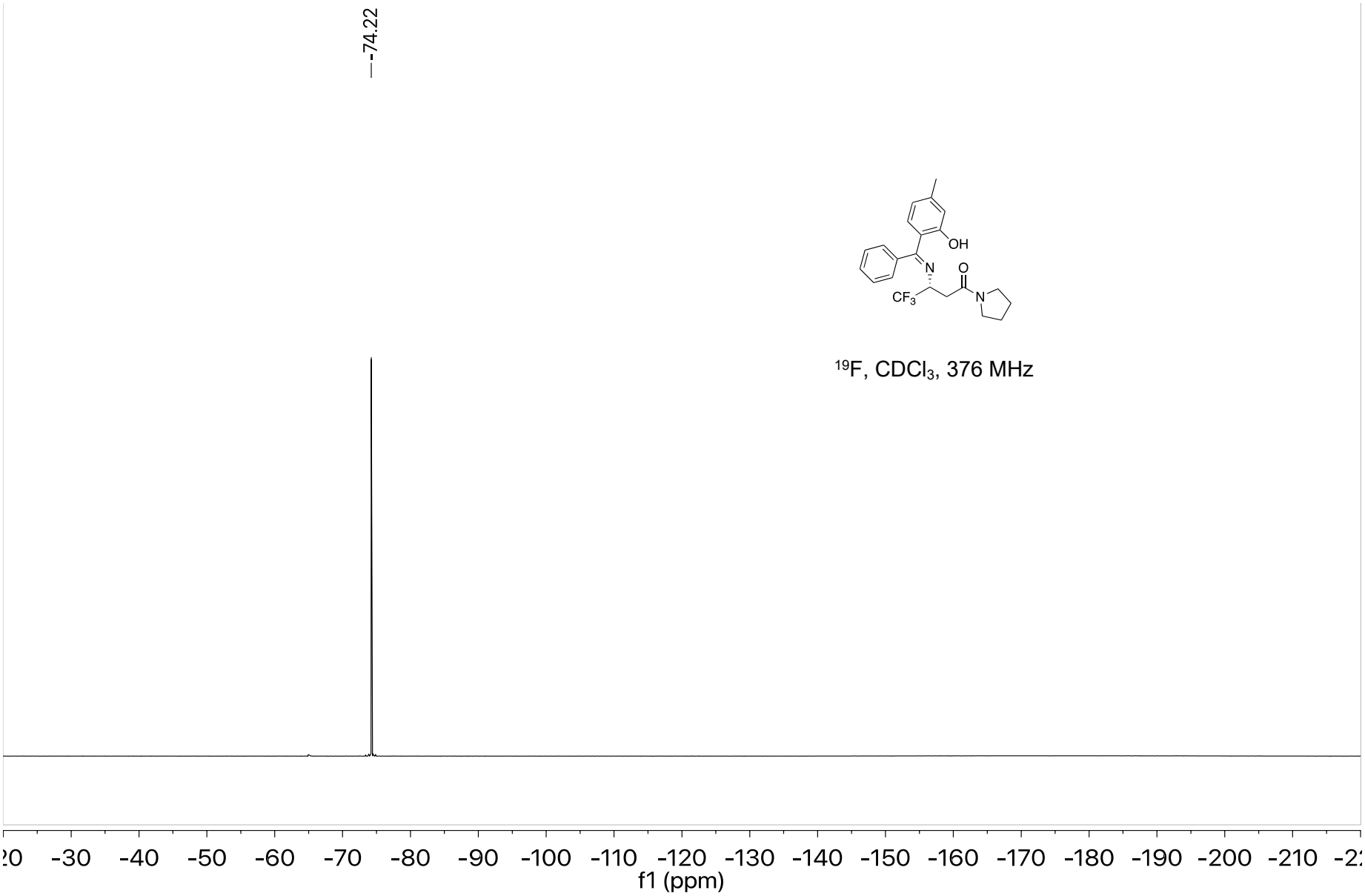
(*R*)-4,4,4-Trifluoro-3-(((2-hydroxy-4-methylphenyl)(phenyl)methylene)amino)-1-(pyrrolidin-1-yl)butan-1-one (9)



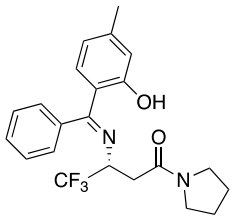
Following **General Procedure D,** 4-nitrophenyl (*E*)-4,4,4,-trifluorobut-2-enoate (26.1 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methylphenol (42.2 mg, 0.2 mmol), (*R*)-(+)-BTM (5.1 mg, 0.02 mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Pyrrolidine was then added (12.5 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was purified by flash column chromatography Hexane:EtOAc (2:1) (R_f =0.53) to give the titled compound (49%, 19.8 mg) as a yellow oil. $[\alpha]_D^{20}$ +48.8 (*c* = 0.40, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak AD-H (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*R*): 12.7 min, t_R(*S*): 15.2 min, 96:4 er; **IR** ν_{max} (ATR), 2976 (Ar-H), 1624 (C=O), 1595 (C=N), 1446 (C=C), 1261 (C-F); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.83 – 2.02 (4H, m, NC(2)H_2C(3)H_2C(4)H_2C(5)H_2), 2.30 (3H, s, CH_3), 2.74 (1H, dd, $^3J_{HH}$ = 15.5, $^4J_{HF}$ = 2.9, COC(2)$H_A$$H_B$), 2.95 (1H, dd, $^3J_{HH}$ = 15.5, $^4J_{HF}$ = 9.6, COC(2)$H_A$$H_B$), 3.41 – 3.52 (4H, m, N=C(2)H_2C(3)H_2C(4)H_2C(5)H_2), 4.53 (1H, m, COC$H_A$$H_B$C*H*), 6.49 (1H, dd, $^3J_{HH}$ = 8.2, N=CC(5)Ar*H*OH-CH_3), 6.66 (1H, s, N=CC(6)Ar*H*OH-CH_3), 6.81 (1H, m, N=CC(4)Ar*H*), 6.86 (1H, m, N=CC(3)Ar*H*OH-CH_3), 7.50 (4H, m, N=CC(2,3,5,6)Ar*H*), 14.33 (1H, s, N=CC(2)ArO*H*); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -74.22 (-CF_3); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 21.7 (ArOH-CH_3), 24.4 (NC(2)H_2C(3)H_2C(4)H_2C(5)H_2), 26.1 (NC(2)H_2C(3)H_2C(4)H_2C(5)H_2), 35.4 (C=OC$H_A$$H_B$$CF_3$), 46.0 (NC(2)$H_2$C(3)$H_2$C(4)$H_2$C(5)$H_2$), 47.0 (NC(2)$H_2$C(3)$H_2$C(4)$H_2$C(5)$H_2$), 59.2 (q, $^2J_{CF}$ = 27.3, C=OC$H_A$$H_B$C(3)H$CF_3$), 118.1 (N=CC(3)ArOH-$CH_3$), 119.5 (N=CC(5)ArOH-$CH_3$), 121.60 (N=CC(1)ArOH-$CH_3$), 128.4 (N=CC(3,5)Ar), 129.0 (N=CC(4)Ar), 129.1 (CF_3), 129.5 (N=CC(2,6)Ar), 129.5 (N=CC(4)Ar), 131.5 (N=CC(1)Ar), 132.8 (N=CC(6)ArOH-CH_3), 162.5 (N=CC(2)ArOH-CH_3), 166.3 (C=O), 170.2 (C=N). **HRMS** (NSI$^+$) $C_{22}H_{23}F_3N_2O_2^+$ ([M+H]$^+$) requires 405.1785, found 405.1774 (-2.7 ppm).


14.33
7.51
7.50
6.86
6.81
6.67
6.65
6.50
6.48
4.53
3.52
3.52
3.41
2.96
2.95
2.74
2.30
2.02
1.83
OH
N
O
CF3
N
1H, CDCl3, 400 MHz
0.83
4.03
1.06
1.16
0.97
0.95
1.00
1.01
2.98
0.97
0.96
2.85
1.89
1.76
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


170.15
166.29
162.52
132.83
131.54
129.46
129.09
128.97
128.36
121.60
119.49
118.09
59.18
46.99
45.96
35.41
26.06
24.38
21.73
OH
N
O
CF3
N
13C{1H}, CDCl3, 101 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

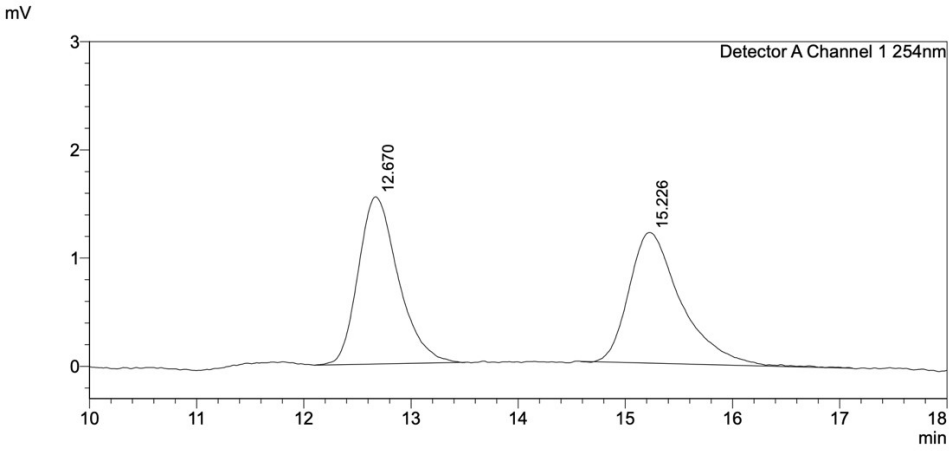

-74.22
OH
N
O
CF3
N
^{19}F, $CDCl_3$, 376 MHz
-30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

HPLC Data for **(*R*)-4,4,4-trifluoro-3-(((2-hydroxy-4-methylphenyl)(phenyl)methylene)amino)-1-(pyrrolidin-1-yl)butan-1-one**: Chiralpak AD-H (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*R*): 12.7 min, t_R(*S*): 15.2 min, 96:4 er.

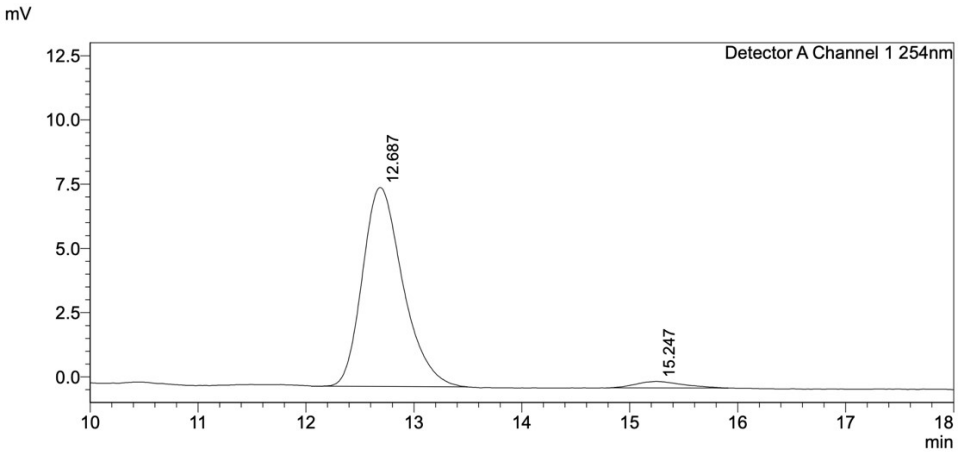


Detector A Channel 1 254nm

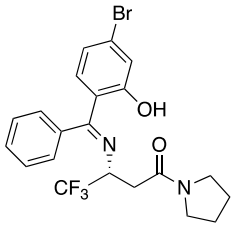
Peak#	Ret. Time	Area%
1	12.670	49.583
2	15.226	50.417
Total		100.000



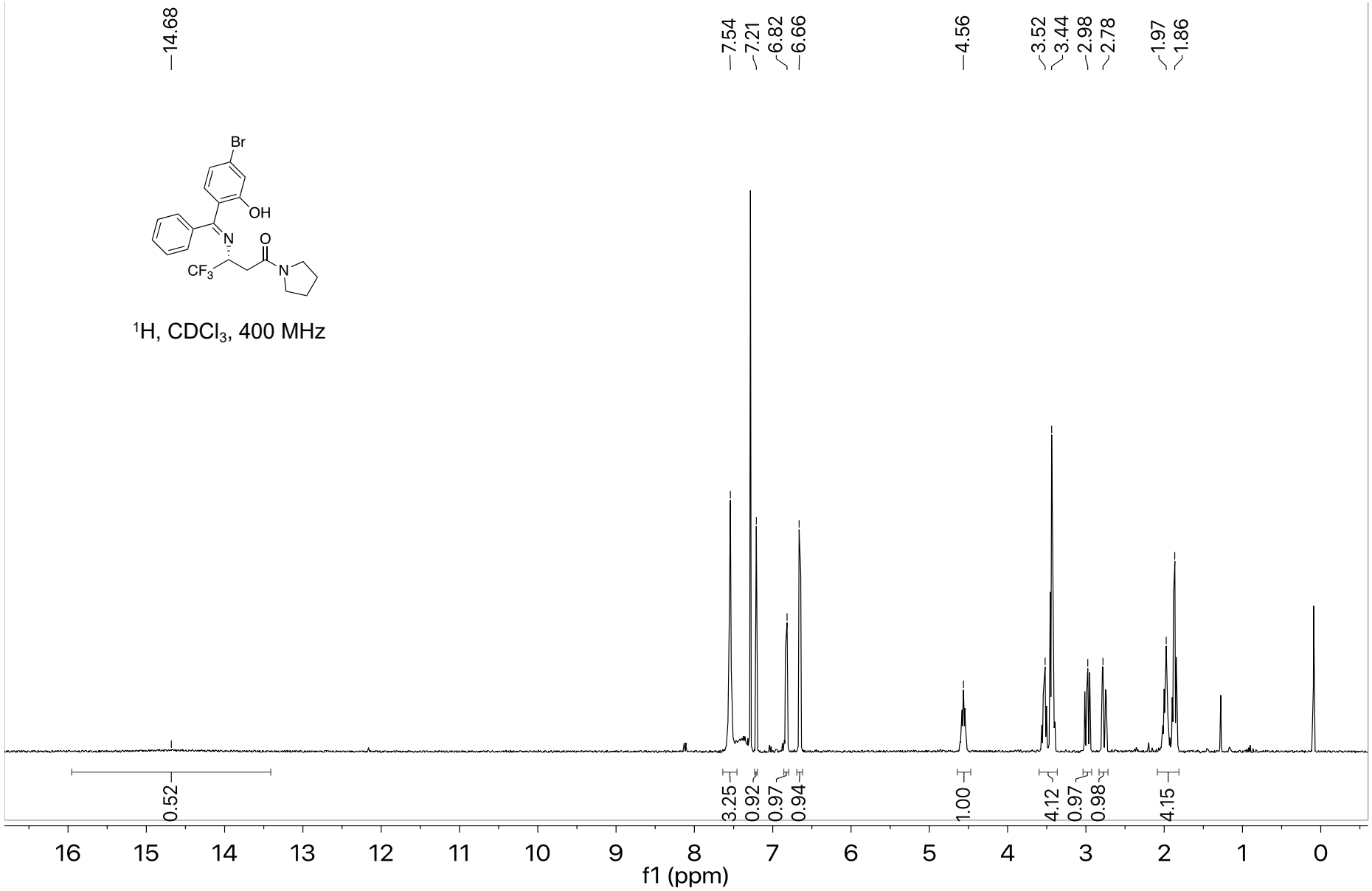
Peak#	Ret. Time	Area%
1	12.687	96.390
2	15.247	3.610
Total		100.000

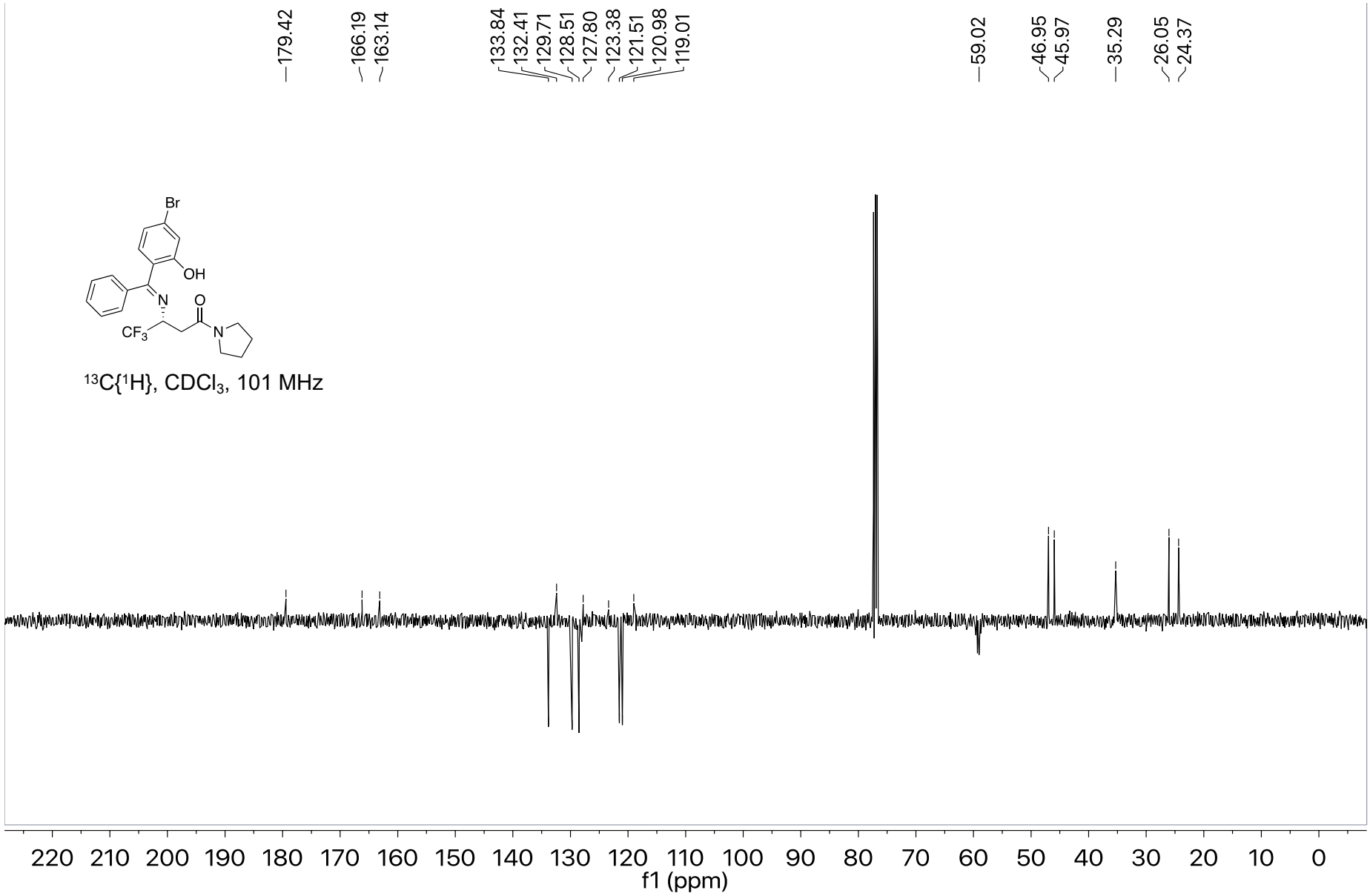


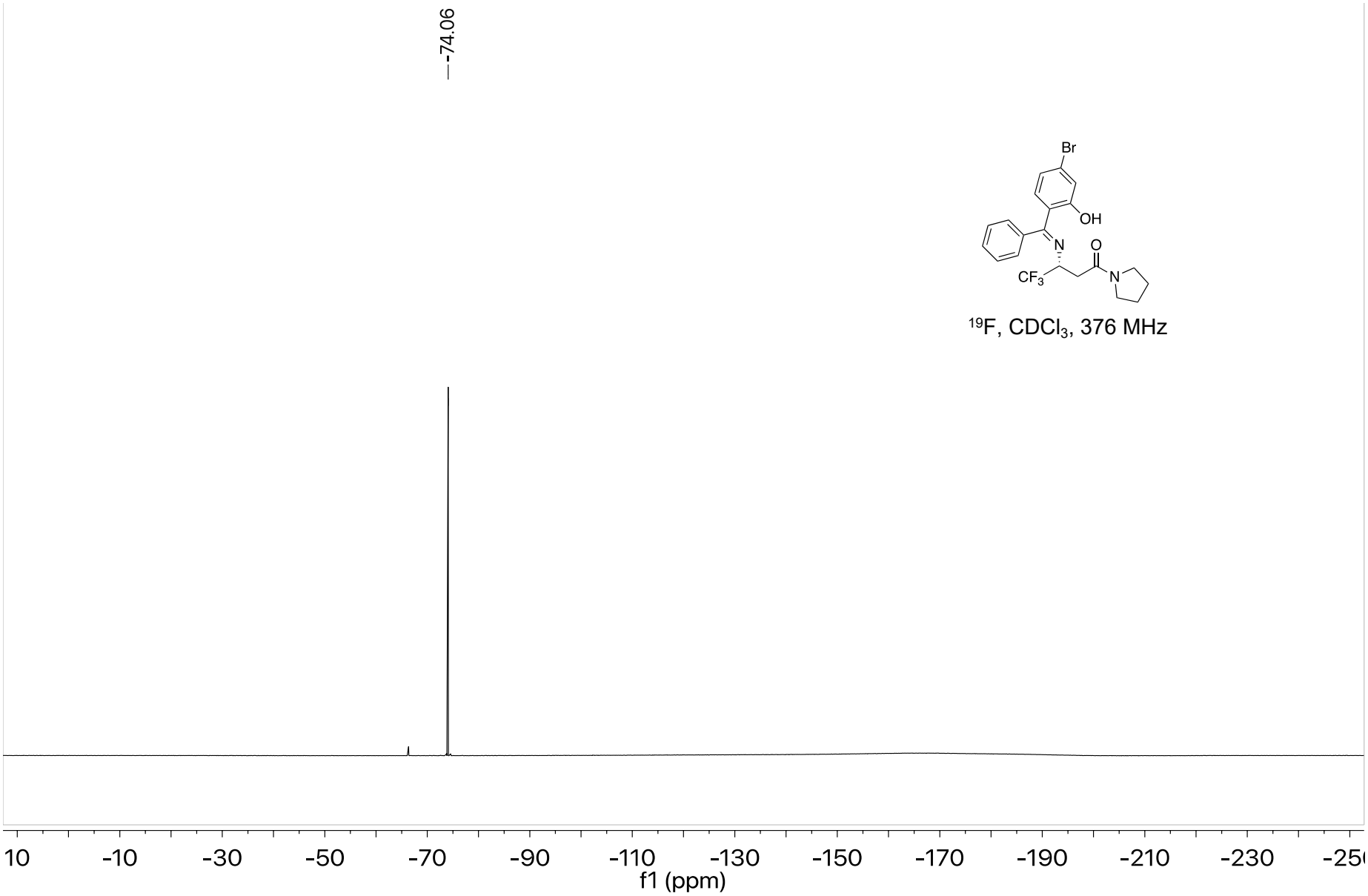
(*R*)-3-(((4-Bromo-2-hydroxyphenyl)(phenyl)methylene)amino)-4,4,4-trifluoro-1-(pyrrolidin-1-yl)butan-1-one (10)



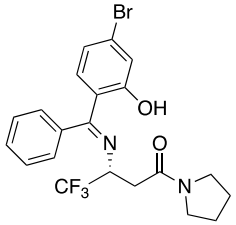
Following **General Procedure C,** 4-nitrophenyl (*E*)-4,4,4,-trifluorobut-2-enoate (26.1 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (45.4 mg, 0.2 mmol), (*R*)-(+)-BTM (5.1 mg, 0.02mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Pyrrolidine was then added (12.5 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was then purified by flash column chromatography Hexane:EtOAc (2:1) (R_f = 0.20) to give the titled compound (11.3 mg, 24%) as a yellow oil. $[\alpha]_D^{20}$ +33.2 (*c* = 0.37, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak ID (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*R*): 15.0 min, t_R(*S*): 20.7 min, 96:4 er; **IR** ν_{max} (ATR), 2974 (Ar-H), 1625 (C=O), 1595 (C=N), 1448 (C=C), 1288 (C-O-CH_3), 1259 (C-F); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.86 – 1.97 (4H, m, NC(2)H_2C(3)*H_2*C(4)*H_2*C(5)H_2), 2.77 (1H, dd, $^3J_{HH}$ = 15.5, $^4J_{HF}$ = 2.9, COC(2)*H_A*H_B), 2.98 (1H, dd, $^3J_{HH}$ = 15.6, $^4J_{HF}$ = 9.7, COC(2)H_A*H_B*), 3.44 – 3.52 (4H, m, NC(2)*H_2*C(3)H_2C(4)H_2C(5)*H_2*), 4.56 (1H, m, COC$H_A$$H_B$C*H*), 6.65 (1H, d, $^3J_{HH}$ = 8.6, N=CC(6)Ar*H*OH-Br), 6.82 (1H, dd, $^3J_{HH}$ = 8.6, $^4J_{HH}$ = 1.9, N=CC(5)Ar*H*OH-Br), 7.21 (1H, d, $^4J_{HH}$ = 1.9, N=CC(3)Ar*H*OH-Br), 7.52 (5H, m, N=CC(2,3,4,5,6)Ar*H*), 14.7 (1H, s, N=CC(2)ArO*H*-Br); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -74.06 (-C*F_3*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 24.4 (NC(2)H_2*C*(3)H_2C(4)H_2C(5)H_2), 26.1 (NC(2)H_2C(3)H_2*C*(4)H_2C(5)H_2), 35.3 (C=O*C*$H_A$$H_B$$CF_3$), 46.0 (N*C*(2)$H_2$C(3)$H_2$C(4)$H_2$C(5)$H_2$), 47.0 (NC(2)$H_2$C(3)$H_2$C(4)$H_2$*C*(5)$H_2$), 59.0 (q, $^2J_{CF}$ = 29.3, C=O$CH_A$$H_B$*C*(3)H$CF_3$), 119.0 (*C*(4)ArOH-Br), 120.9 (*C*(3)ArOH-Br), 121.5 (*C*(5)ArOH-Br), 123.4 (*C*F_3), 127.8 (*C*(1)ArOH-Br), 128.5 (*C*(2,3,5,6)Ar), 129.7 (*C*(1)Ar), 132.4 (*C*(1)Ar), 133.8 (*C*(4)Ar), 163.1 (*C*(2)ArOH-Br), 166.19 (*C*=O), 179.4 (*C*=N). **HRMS** (NSI$^+$) $C_{21}H_{20}BrF_3N_2O_2^+$ ([M+H]$^+$) requires 469.0733, found 469.0727 (-1.3 ppm).


14.68
7.54
7.21
6.82
6.66
4.56
3.52
3.44
2.98
2.78
1.97
1.86
Br
OH
N
O
CF3
N
1H, CDCl3, 400 MHz
0.52
3.25
0.92
0.97
0.94
1.00
4.12
0.97
0.98
4.15
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


179.42
166.19
163.14
133.84
132.41
129.71
128.51
127.80
123.38
121.51
120.98
119.01
59.02
46.95
45.97
35.29
26.05
24.37
Br
OH
N
O
CF3
N
13C{1H}, CDCl3, 101 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

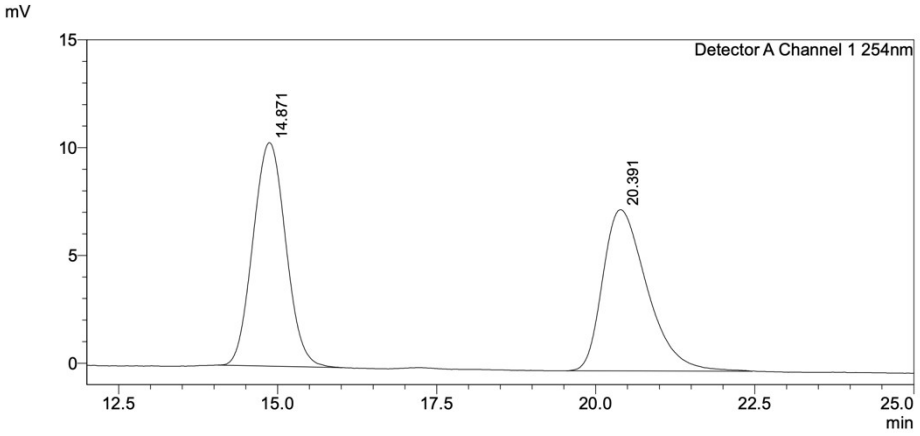

-74.06
Br
OH
N
O
CF3
N
19F, CDCl3, 376 MHz
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
-230
f1 (ppm)

HPLC Data for **(*R*)-3-(((4-bromo-2-hydroxyphenyl)(phenyl)methylene)amino)-4,4,4-trifluoro-1-(pyrrolidin-1-yl)butan-1-one**: Chiralpak ID (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*R*): 15.0 min, t_R(*S*): 20.7 min, 96:4 er.

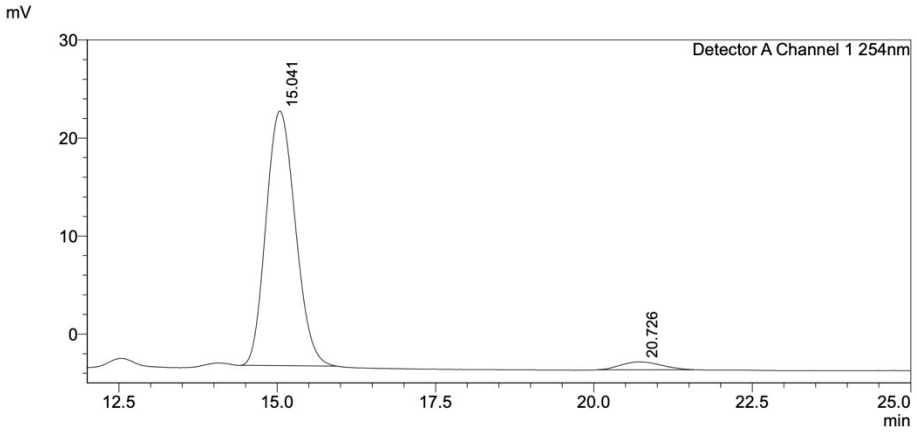


Detector A Channel 1 254nm

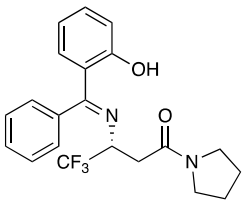
Peak#	Ret. Time	Area%
1	14.871	50.674
2	20.391	49.326
Total		100.000



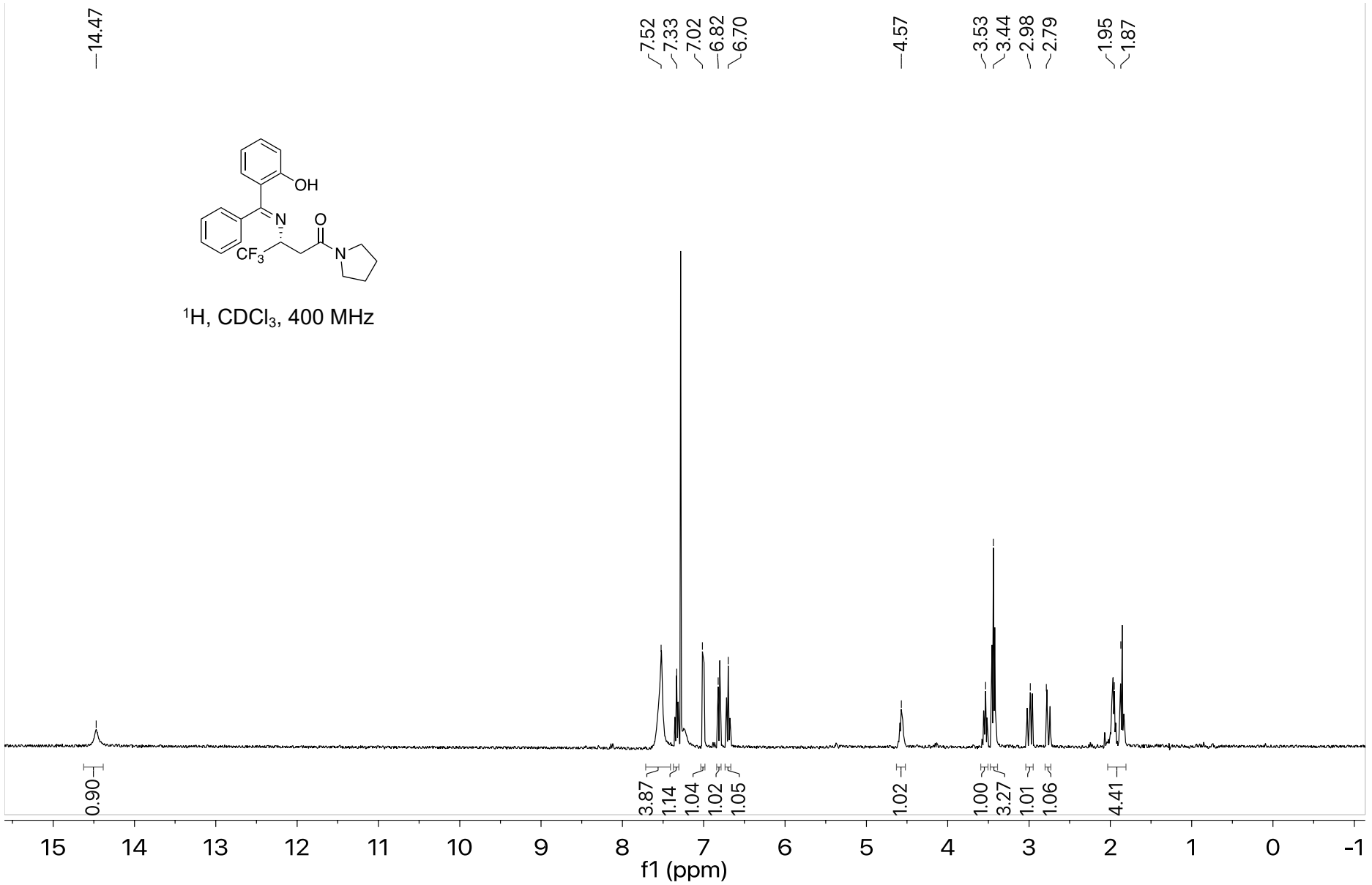
Peak#	Ret. Time	Area%
1	15.041	95.912
2	20.726	4.088
Total		100.000

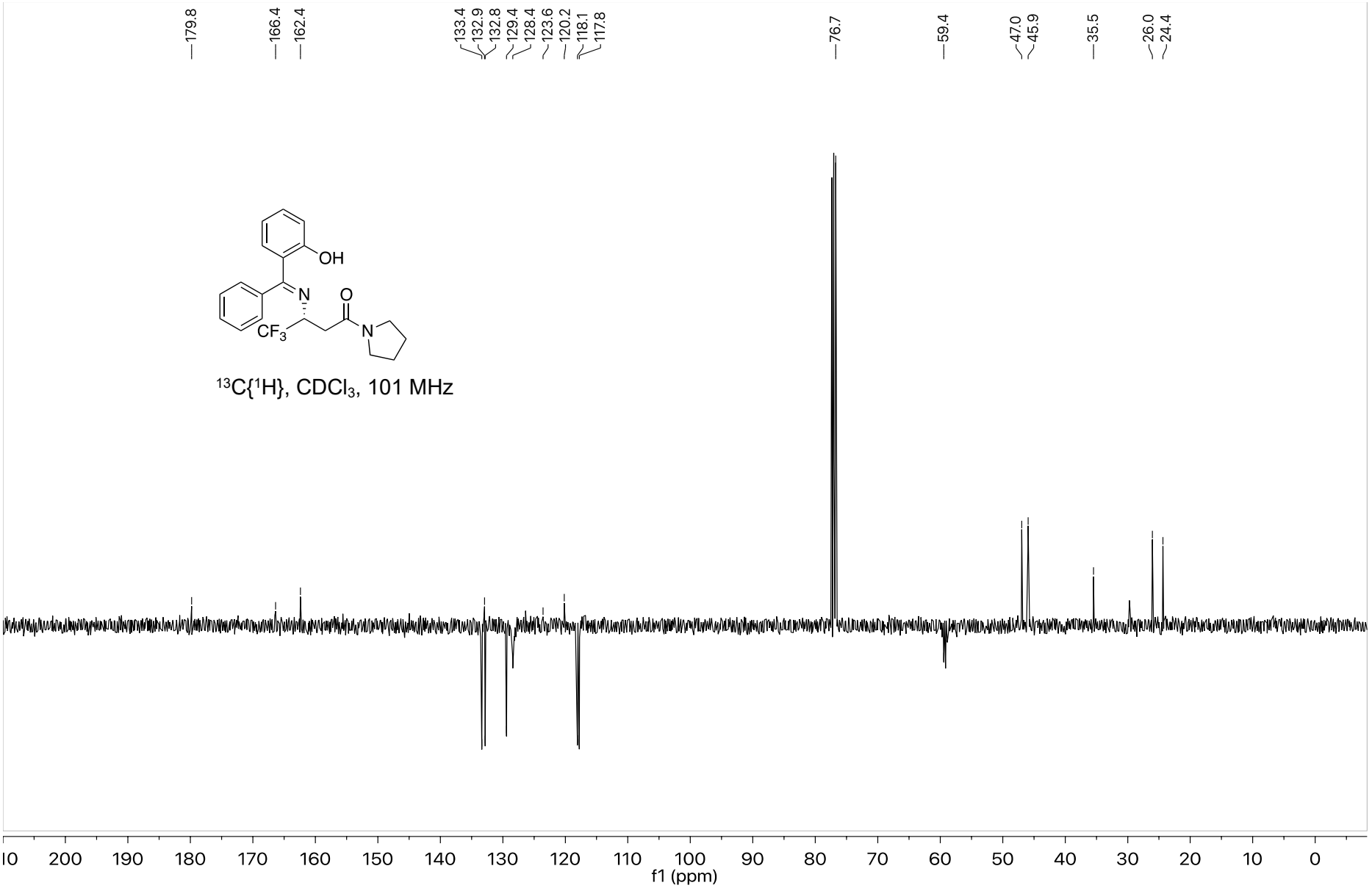


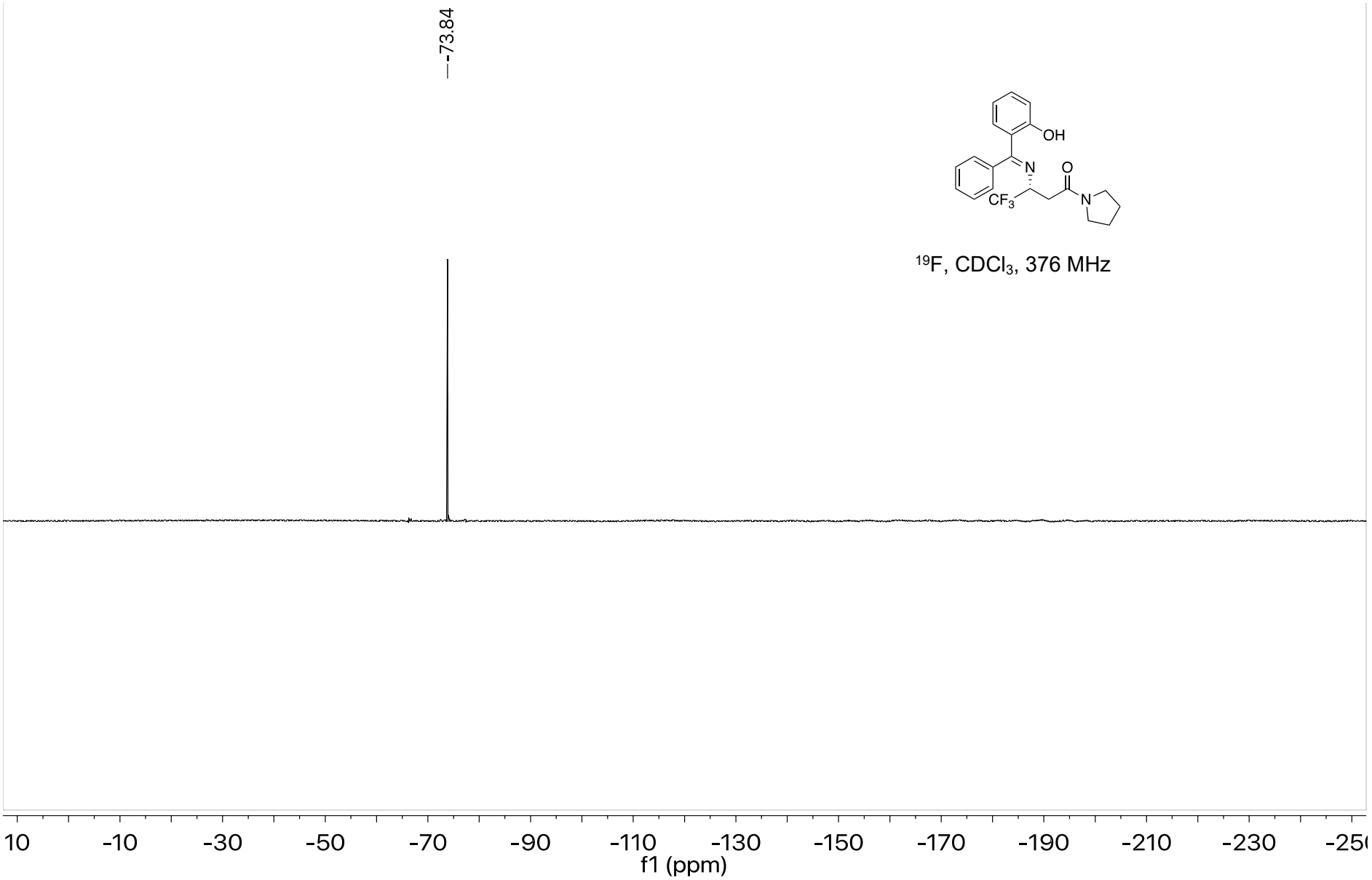
(*R*)-4,4,4-Trifluoro-3-(((2-hydroxyphenyl)(phenyl)methylene)amino)-1-(pyrrolidine-1-yl)butan-1-one (11)



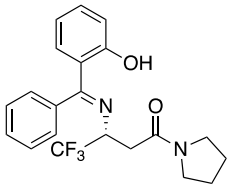
Following **General Procedure D,** 4-nitrophenyl (*E*)-4,4,4,-trifluorobut-2-enoate (26.1 mg, 0.1 mmol), 2-(imino(phenyl)methyl)phenol (39.4 mg, 0.2 mmol), (*R*)-(+)-BTM (5.1 mg, 0.02 mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Pyrrolidine was added (12.5 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was purified by Biotage® Isolera™ 4[SNAP Ultra 10g, 75 mLmin^{-1}, Petrol:EtOAc (100:0 2CV, 100:0 to 80:20 1 CV, 80:20 25 CV) to give the titled compound (14.0 mg, 36%) as a yellow oil. $[\alpha]_D^{20}$ +35.02 (*c* 1.9, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak AD-H (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(*S*): 11.9 min, t_R(*R*): 17.2 min, 96:4 er; **IR** ν_{max} (ATR), 2926 (Ar-H), 1647 (C=O), 1609 (C=N), 1447 (C=C), 1261 (C-F); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.87 – 1.95 (4H, m, NC(2)H_2C(3)H_2C(4)H_2C(5)H_2), 2.79 (1H, dd, $^3J_{HH}$ = 15.4, $^4J_{HF}$ = 3.0, COC(2)H_AH_B), 2.98 (1H, dd, $^3J_{HH}$ = 15.4, $^4J_{HF}$ = 9.6, COC(2)H_AH_B), 3.44 – 3.53 (4H, m, NC(2)H_2C(3)H_2C(4)H-$_2$C(5)H_2), 4.57 (1H, m, COCH_AH$_B$C*H*), 6.70 (1H, ddd, $^3J_{HH}$ = 8.1, $^3J_{HH}$ = 7.1, $^4J_{HH}$ = 1.2, N=CC(5)Ar*H*OH), 6.82 (1H, dd, $^3J_{HH}$ = 8.0, $^4J_{HH}$ = 1.7, N=CC(6)Ar*H*OH), 7.02 (1H, dd, $^3J_{HH}$ = 8.4, $^4J_{HH}$ = 1.2, N=CC(3)Ar*H*OH), 7.33 (1H, ddd, $^3J_{HH}$ = 8.8, $^3J_{HH}$ = 7.2, $^4J_{HH}$ = 1.7, N=CC(4)Ar*H*OH), 7.52 (5H, m, N=CC(2,3,4,5,6)Ar*H*), 14.47 (1H, s, N=CC(2)ArO*H*); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -73.84; **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 24.4 (NC(2)H_2*C*(3)H_2C(4)H_2C(5)H_2), 26.0 (NC(2)H_2C(3)H_2*C*(4)H_2C(5)H_2), 35.5 (C=O*C*H$_A$H$_B$CF_3), 45.9 (N*C*(2)H_2C(3)H_2C(4)H_2C(5)H_2), 47.0 (NC(2)H_2C(3)H_2C(4)H_2*C*(5)H_2), 59.4 (q, $^2J_{CF}$ = 28.5, C=OCH$_A$H$_B$*C*(3)HCF_3), 117.7 (N=C*C*(3)ArOH), 118.1 (N=C*C*(5)ArOH), 120.2 (*C*F_3), 123.6 (N=C*C*(1)Ar), 128.4 (N=C*C*(3,5)Ar), 129.4 (N=C*C*(2,4,6)Ar), 132.8 (N=C*C*(6)ArOH), 132.9 (N=C*C*(1)ArOH), 133.4 (N=C*C*(4)ArOH), 162.4 (N=C*C*(2)ArOH), 166.4 (*C*=O), 179.8 (*C*=N). **HRMS** (NSI$^+$) $C_{21}H_{21}F_3N_2O_2^+$ ([M+H]$^+$) requires 391.1628, found 391.1622 (-1.6 ppm).


14.47
7.52
7.33
7.02
6.82
6.70
4.57
3.53
3.44
2.98
2.79
1.95
1.87
OH
N
O
CF3
N
1H, CDCl3, 400 MHz
0.90
3.87
1.14
1.04
1.02
1.05
1.02
1.00
3.27
1.01
1.06
4.41
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


179.8
166.4
162.4
133.4
132.9
132.8
129.4
128.4
123.6
120.2
118.1
117.8
76.7
59.4
47.0
45.9
35.5
26.0
24.4
OH
N
O
CF3
N
13C{1H}, CDCl3, 101 MHz
f1 (ppm)

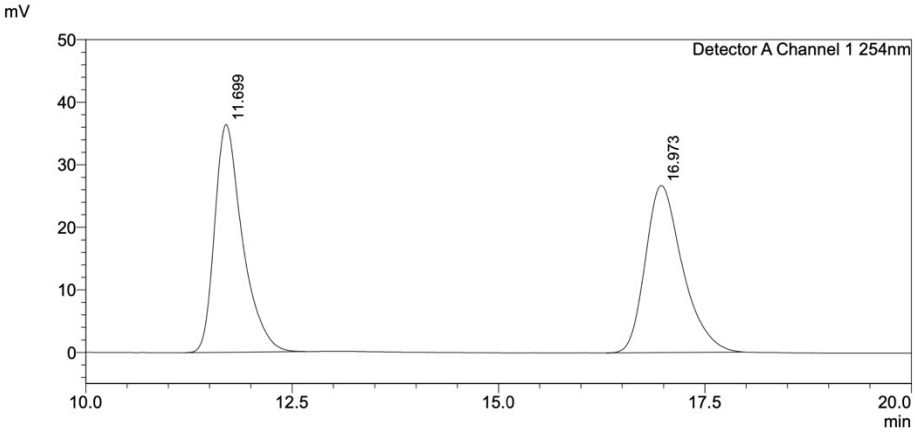

-73.84
OH
N
O
CF3
N
19F, CDCl3, 376 MHz
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
-230
f1 (ppm)

HPLC Data for **(*R*)-4,4,4-trifluoro-3-(((2-hydroxyphenyl)(phenyl)methylene)amino)-1-(pyrrolidine-1-yl)butan-1-one**: Chiralpak AD-H (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(*S*): 11.9 min, t_R(*R*): 17.2 min, 96:4 er.

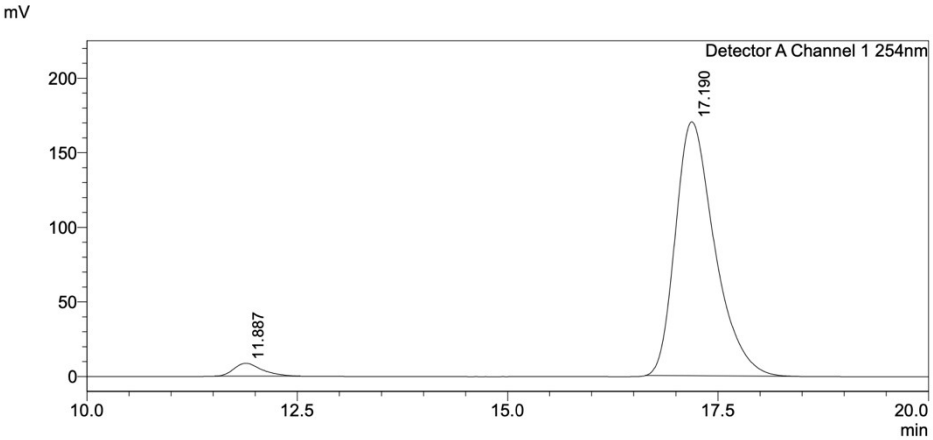


Detector A Channel 1 254nm

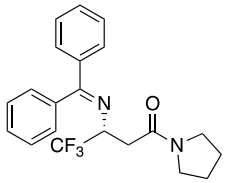
Peak#	Ret. Time	Area%
1	11.699	50.474
2	16.973	49.526
Total		100.000



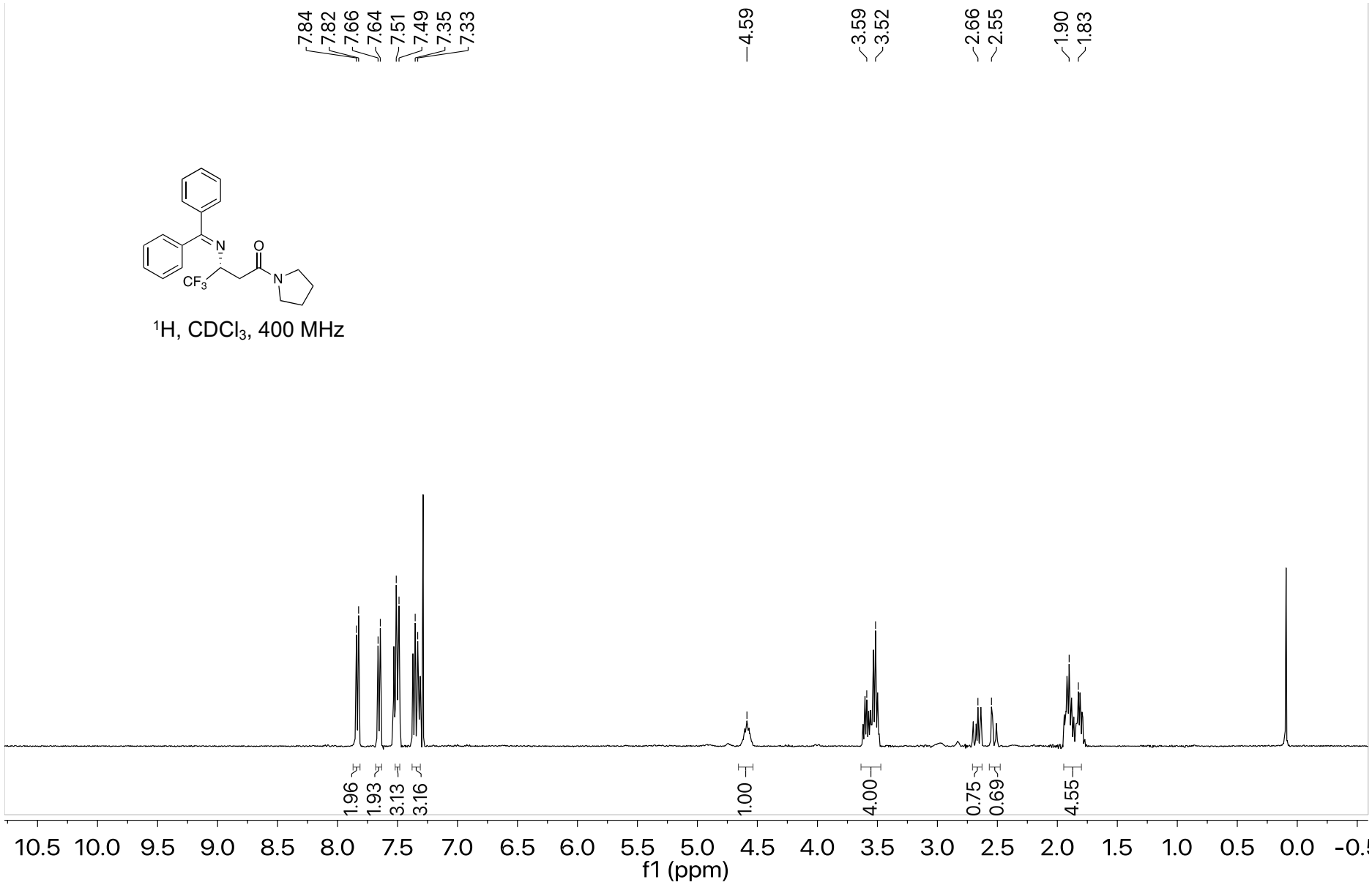
Peak#	Ret. Time	Area%
1	11.887	3.510
2	17.190	96.490
Total		100.000

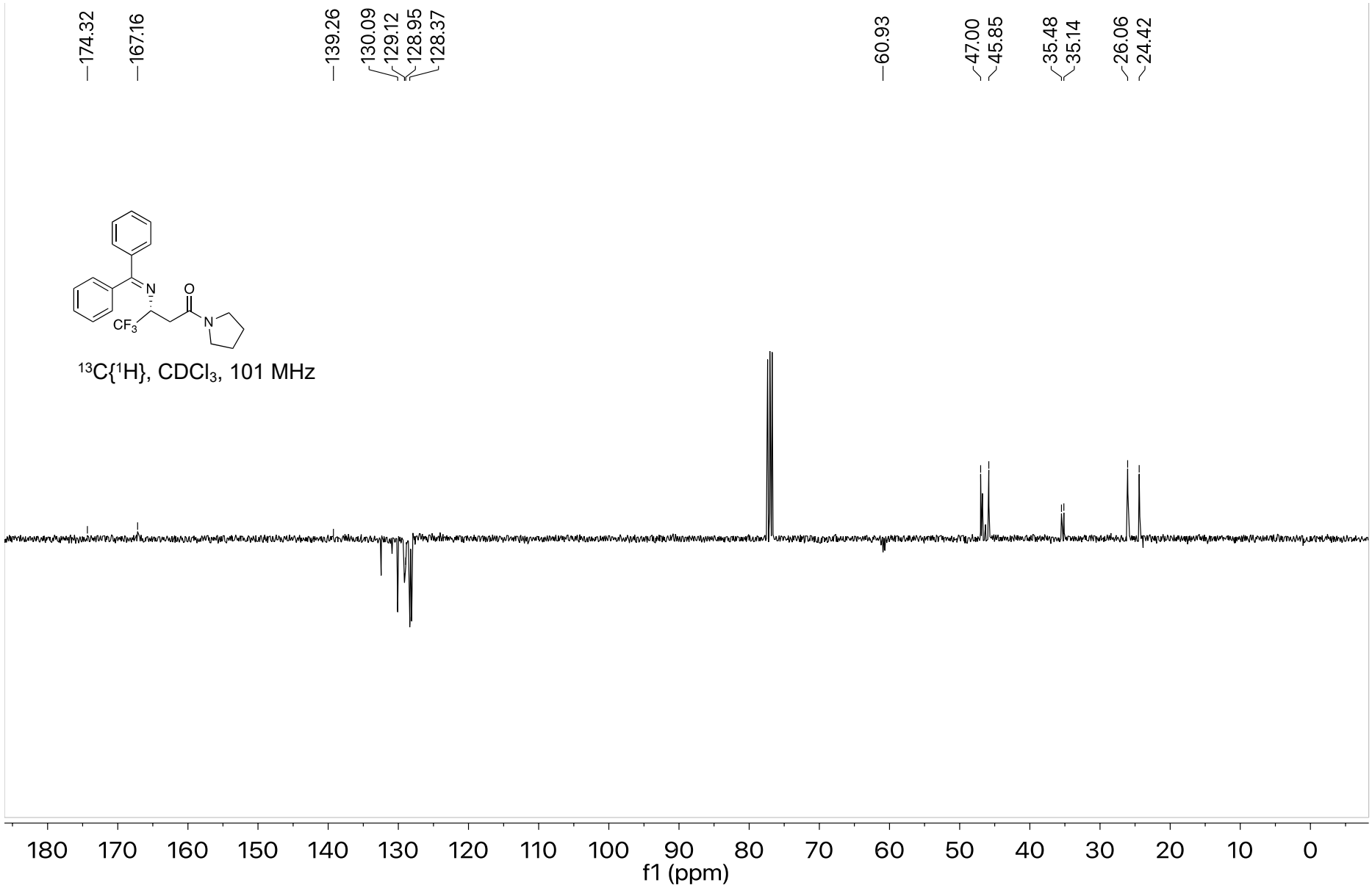


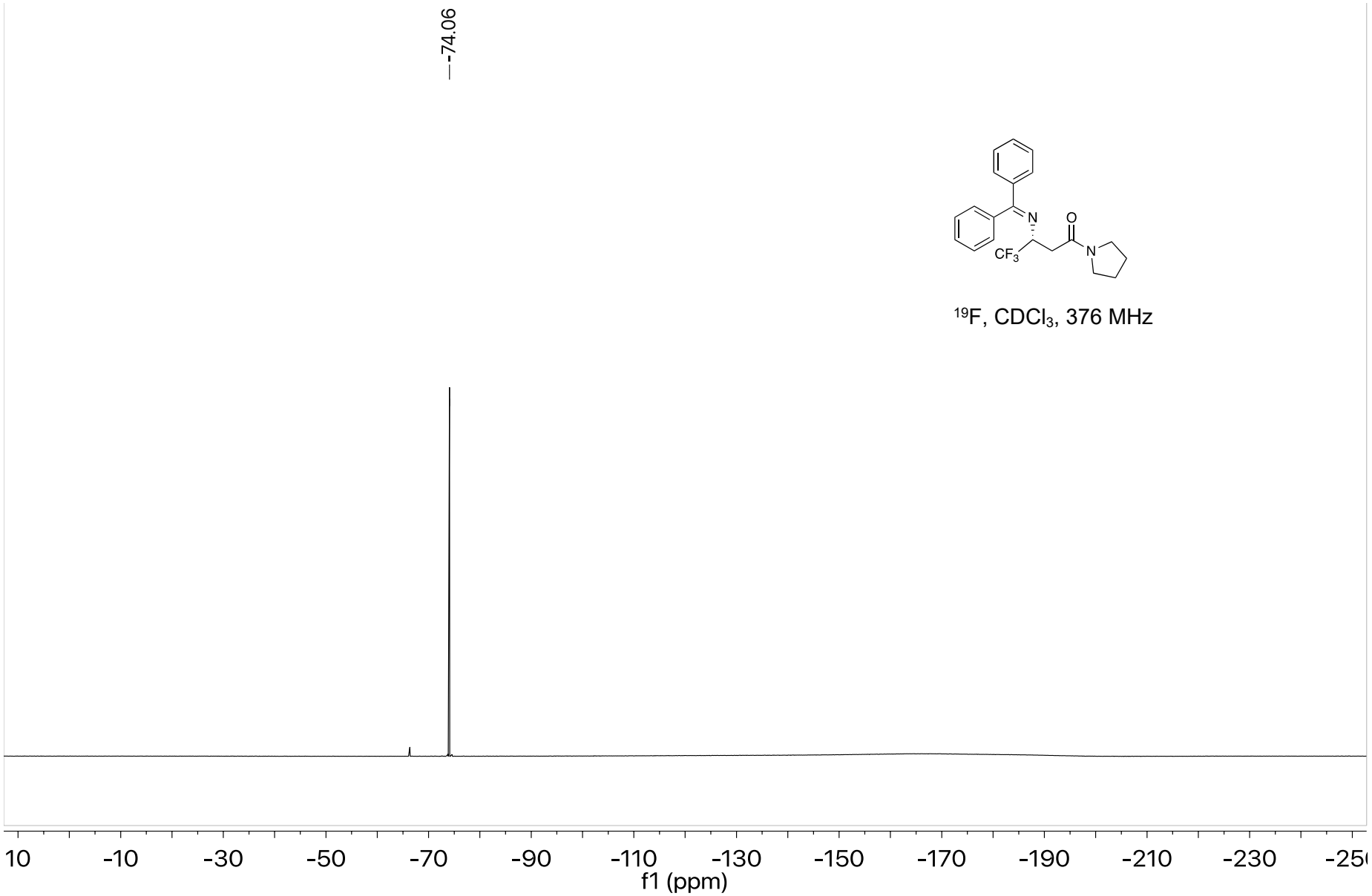
(*R*)-3-((Diphenylmethylene)amino)-4,4,4-trifluoro-1-(pyrrolidine-1-yl)butan-1-one (12)



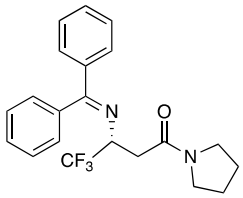
Following **General Procedure D,** 4-nitrophenyl (*E*)-4,4,4,-trifluorobut-2-enoate (26.2 mg, 0.1 mmol), diphenylmethanimine (36.2 mg, 0.2 mmol), (*R*)-(+)-BTM (5.1 mg, 0.02mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Pyrrolidine was added (12.5 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was purified by flash column chromatography Hexane:EtOAc (2:1) (R_f = 0.20) to give the titled compound (15 mg, 40%) as a yellow oil. $[\alpha]_D^{20}$ +35.0 (*c* = 1.9, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak ADH (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 250 nm, 30 °C) t_R(*S*): 6.9 min, t_R(*R*): 13.6 min, 83:17 er; **IR** ν_{max} (ATR), 2976 (Ar-H), 1633 (C=O), 1598 (C=N), 1448 (C=C), 1276 (C-F); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.83 – 1.90 (4H, m, NC(2)H_2C(3)*H*$_2$C(4)*H*$_2$C(5)H_2), 2.69 (1H, dd, $^3J_{HH}$ = 15.7, $^4J_{HF}$ = 2.5, COC(2)*H*$_A$H$_B$), 2.93 (1H, dd, $^3J_{HH}$ = 15.8, $^4J_{HF}$ = 9.6, COC(2)H$_A$*H*$_B$), 3.41 – 3.52 (4H, m, NC(2)*H*$_2$C(3)H$_2$C(4)H$_2$C(5)*H*$_2$), 3.80 (3H, s, C*H*$_3$O-ArOH), 3.86 (3H, s, C*H*$_3$O-Ar), 4.59 (1H, m, COCH$_A$H$_B$C*H*), 7.33 – 7.35 (3H, m, N=CC(3,4,5)Ar$_1$*H*), 7.50 (3H, m, N=CC(3,4,5)Ar$_2$*H*), 7.65 (2H, m, N=CC(2,6)Ar$_1$*H*), 7.83 (2H, m, N=CC(2,6)Ar$_2$*H*); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -74.1 (-C*F*$_3$); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 24.4 – 26.1 (NC(2)H$_2$*C*(3)H$_2$*C*(4)H$_2$C(5)H$_2$), 35.5 (C=O*C*H$_A$H$_B$CF$_3$), 45.9 – 47.0 (N*C*(2)H$_2$C(3)H$_2$C(4)H$_2$*C*(5)H$_2$), 60.7 – 61.21 (q, $^2J_{CF}$ = 28.0, C=OCH$_A$H$_B$*C*(3)HCF$_3$), 128.4 (), 128.95 (), 129.1 (), 130.1 (), 139.3 N=CC(1)Ar), 167.2 (*C*=O), 174.3 (*C*=N). **HRMS** (NSI$^+$) $C_{21}H_{21}F_3N_2O^+$ ([M+H]$^+$) requires 375.1679, found 375.1670 (-2.4 ppm).


7.84
7.82
7.66
7.64
7.51
7.49
7.35
7.33
4.59
3.59
3.52
2.66
2.55
1.90
1.83
N
O
CF3
N
1H, CDCl3, 400 MHz
1.96
1.93
3.13
3.16
1.00
4.00
0.75
0.69
4.55
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

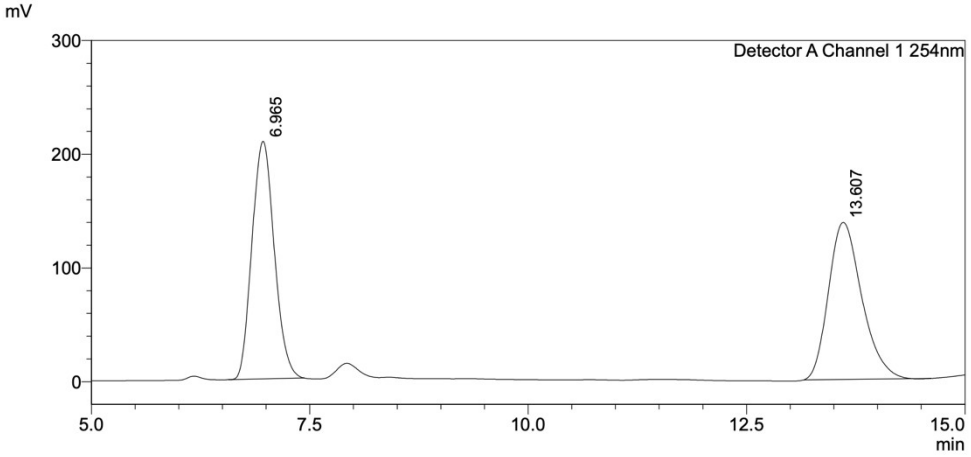

174.32
167.16
139.26
130.09
129.12
128.95
128.37
60.93
47.00
45.85
35.48
35.14
26.06
24.42
N
O
CF3
N
13C{1H}, CDCl3, 101 MHz
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


-74.06
N
O
CF3
N
19F, CDCl3, 376 MHz
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
-230
f1 (ppm)

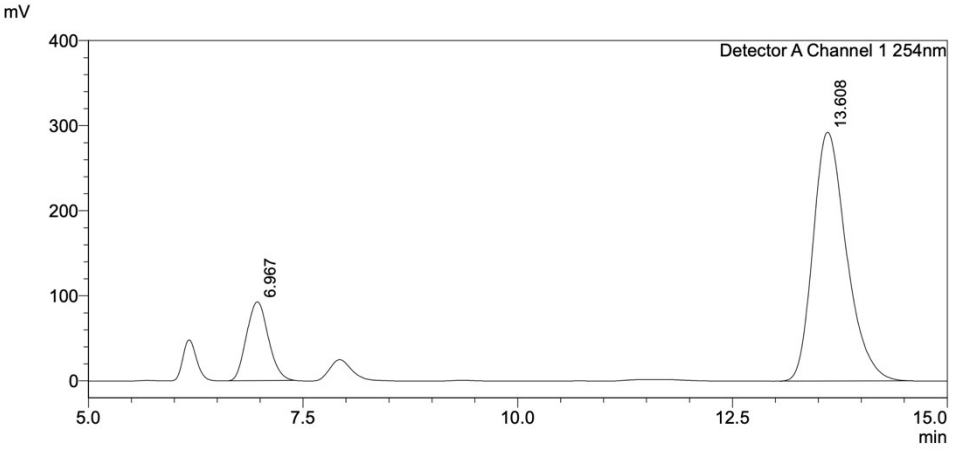
HPLC Data for **(*R*)-3-((diphenylmethylene)amino)-4,4,4-trifluoro-1-(pyrrolidine-1-yl)butan-1-one**: Chiralpak ADH (95:5 Hexane:IPA, flow rate 1 mL•min^{-1}, 250 nm, 30 °C) t_R(*S*): 6.9 min, t_R(*R*): 13.6 min, 83:17 er.



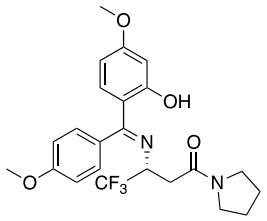
Peak#	Ret. Time	Area%
1	6.965	50.463
2	13.607	49.537
Total		100.000



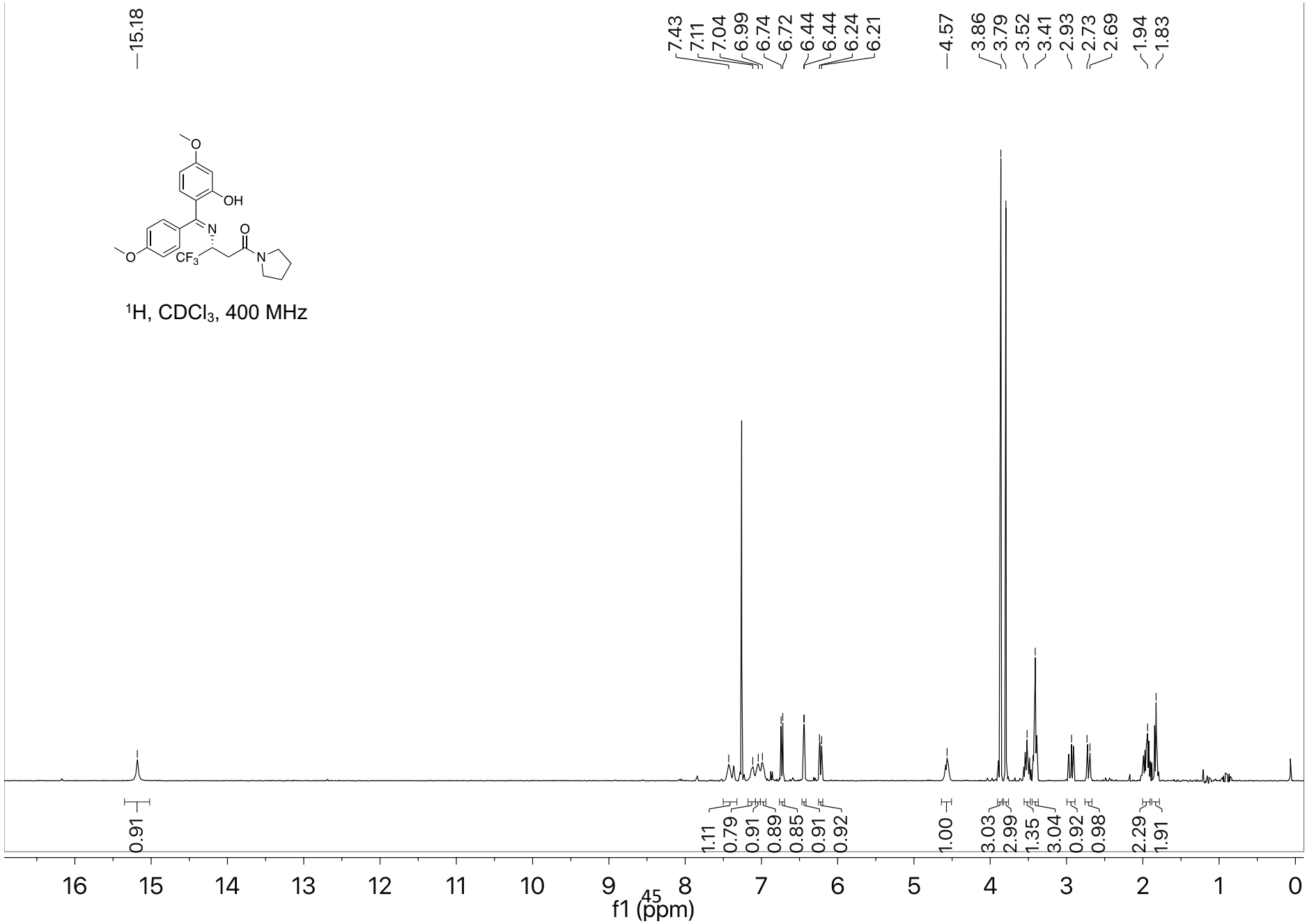
Peak#	Ret. Time	Area%
1	6.967	17.136
2	13.608	82.864
Total		100.000

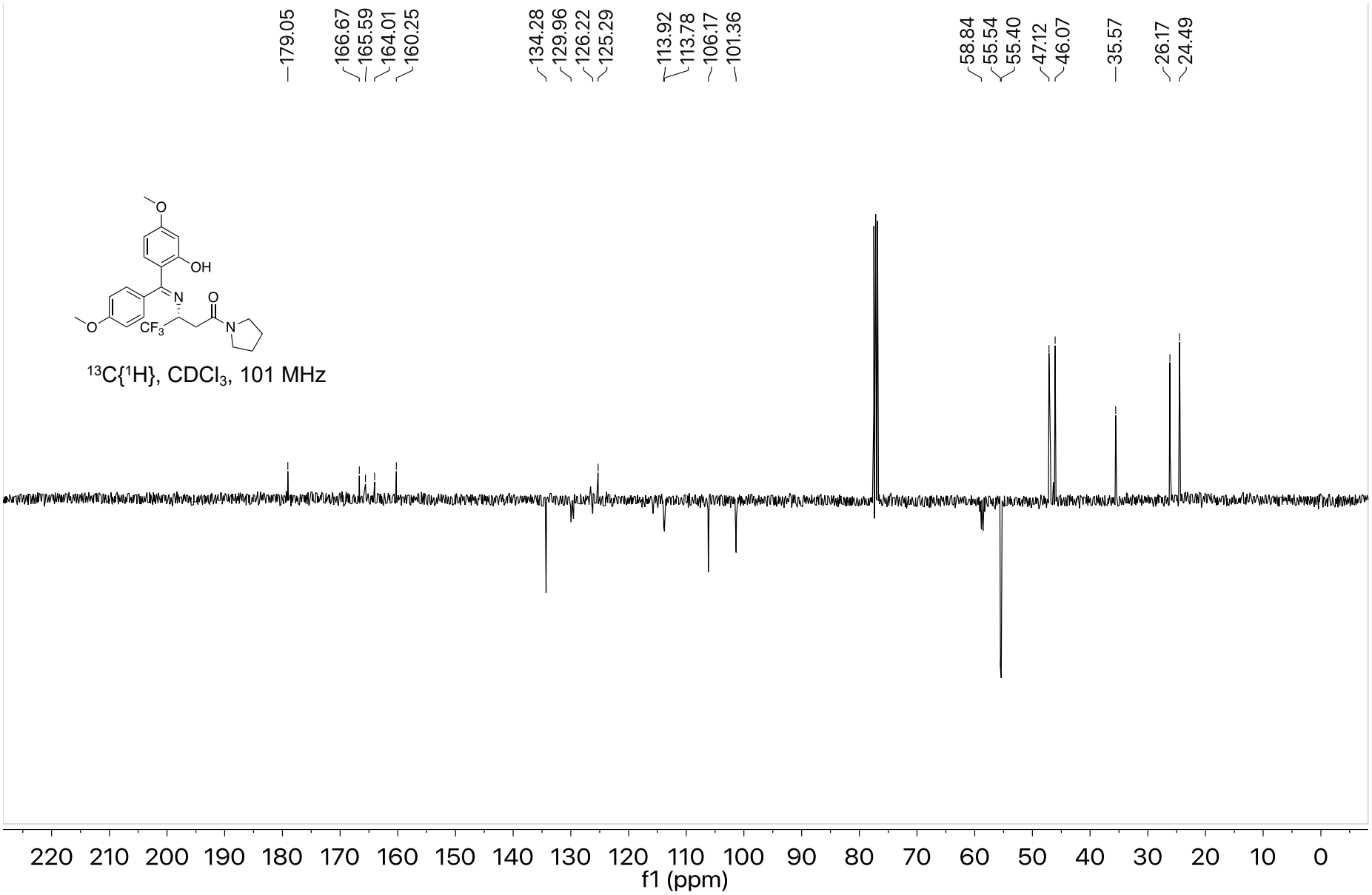


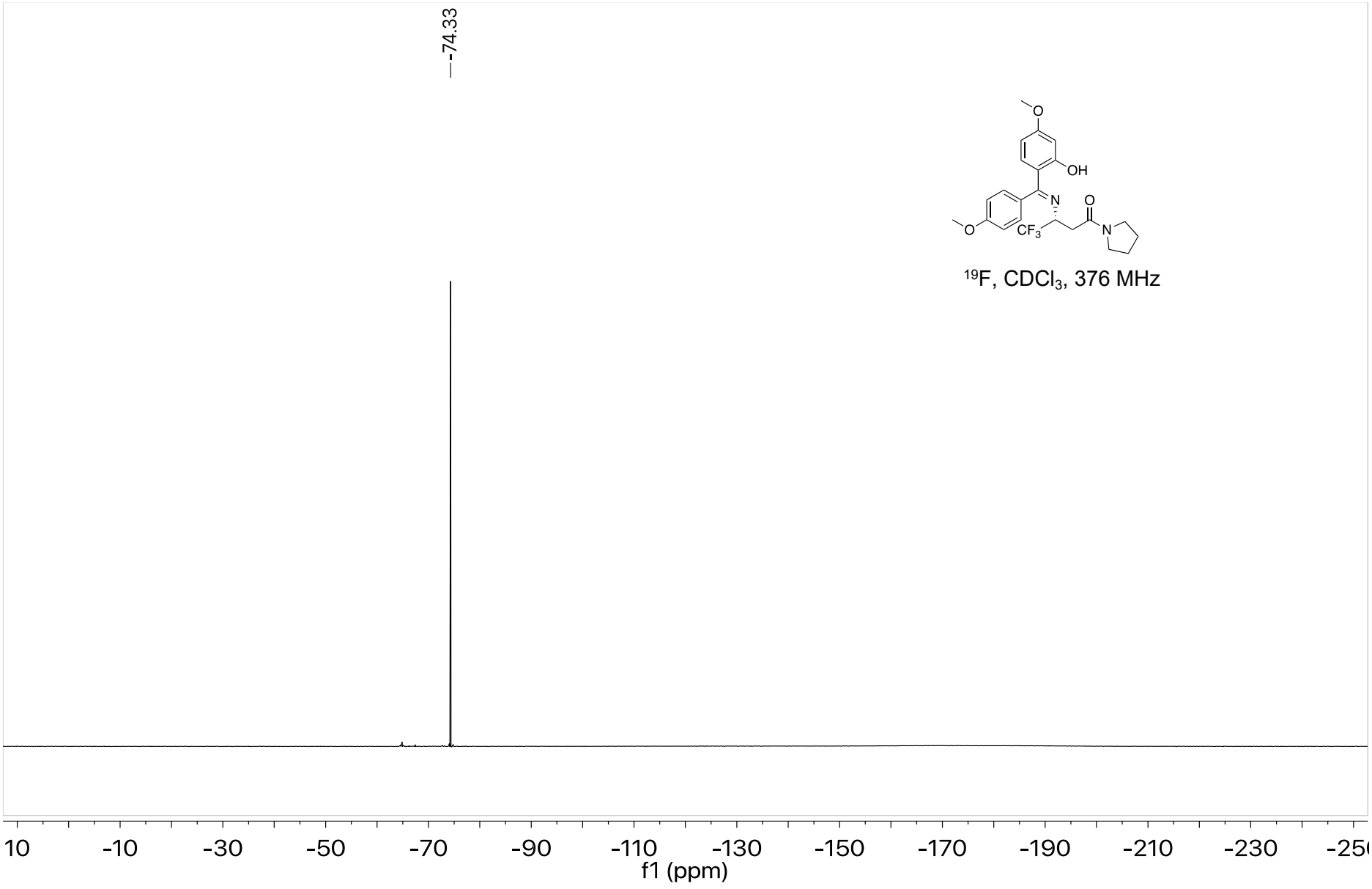
(*R*)-4,4,4-Trifluoro-3-(((2-hydroxy-4-methoxyphenyl)(4-methoxyphenyl)methylene) amino)-1-(pyrrolidin-1-yl)butan-1-one (13)



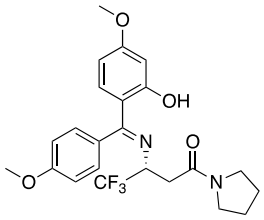
Following **General Procedure C,** 4-nitrophenyl (*E*)-4,4,4,-trifluorobut-2-enoate (26.1 mg, 0.1 mmol), 2-(imino(4-methoxyphenyl)methyl)-5-methoxyphenol (51.5 mg, 0.2 mmol), (*R*)-(+)-BTM (5.1 mg, 0.02mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Pyrrolidine (12.5 µL, 0.15 mmol) and stirred at rt for 16 hrs. The crude mixture was purified by flash column chromatography Hexane:EtOAc (2:1) (R_f = 0.21) to give the titled compound (18 mg, 41%) as a yellow oil. $[\alpha]_D^{20}$ +57.1 (*c* = 0.92, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 220 nm, 30 °C) t_R(*S*): 31.5 min, t_R(*R*): 39.9 min, 95:5 er; **IR** ν_{max} (ATR), 2970 (Ar-H), 1621 (C=O), 1593 (C=N), 1442 (C=C), 1342 (C-O-CH_3), 1247 (C-F); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.83 – 1.94 (4H, m, NC(2)H_2C(3)*H*$_2$C(4)*H*$_2$C(5)H_2), 2.69 (1H, dd, $^3J_{HH}$ = 15.5, $^4J_{HF}$ = 2.9, COC(2)*H*$_A$H$_B$), 2.93 (1H, dd, $^3J_{HH}$ = 15.6, $^4J_{HF}$ = 9.7, COC(2)H$_A$*H*$_B$), 3.41 – 3.52 (4H, m, NC(2)*H*$_2$C(3)H$_2$C(4)H$_2$C(5)*H*$_2$), 3.80 (3H, s, C*H*$_3$O-ArOH), 3.86 (3H, s, C*H*$_3$O-Ar), 4.56 (1H, m, COCH$_A$H$_B$C*H*), 6.22 (1H, dd, $^3J_{HH}$ = 8.95, $^4J_{HH}$ = 2.43 N=CC(5)Ar*H*OH-OCH$_3$), 6.44 (1H, d, $^3J_{HH}$ = 2.58, N=CC(3)Ar*H*OH-OCH$_3$), 6.73 (1H, d, $^3J_{HH}$ = 9.00, N=CC(6)Ar*H*OH-OCH$_3$), 7.05 (2H, m, N=CC(2,6)Ar*H*-OCH$_3$), 7.40 (2H, m, N=CC(3,4)Ar*H*-OCH$_3$), 15.2 (1H, s, N=CC(2)ArO*H*-OCH$_3$); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -66.22, -74.11, -74.33 (-C*F*$_3$); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 24.5 – 26.2 (NC(2)H$_2$*C*(3)H$_2$*C*(4)H$_2$C(5)H$_2$), 35.6 (C=O*C*H$_A$H$_B$CF$_3$), 46.1 – 47.1 (N*C*(2)H$_2$C(3)H$_2$C(4)H$_2$*C*(5)H$_2$), 47.0 (NC(2)H$_2$C(3)H$_2$C(4)H$_2$*C*(5)H$_2$), 55.4 (*C*H$_3$O-ArOH), 55.5 (*C*H$_3$O-Ar), 58.3 – 59.1 (q, $^2J_{CF}$ = 28.6, C=OCH$_A$H$_B$*C*(3)HCF$_3$), 101.36 (*C*(3)ArOH-OCH$_3$), 106.17 (*C*(5)ArOH-OCH$_3$), 113.9 (*C*(1)ArOH-OCH$_3$, *C*(2,6)Ar-OCH$_3$), 125.29 (*C*(1)Ar-OCH$_3$), 126.22 (*C*F$_3$), 129.6 – 129.9 (*C*(3,5)Ar-OCH$_3$), 134.3 (*C*(6)ArOH-OCH$_3$), 160.3 (*C*(4)Ar-OCH$_3$), 164.0 (*C*(4)ArOH-OCH$_3$), 165.6 (*C*(2)ArOH-OCH$_3$), 166.7 (*C*=O), 179.0 (*C*=N). **HRMS** (NSI$^+$) $C_{23}H_{25}F_3N_2O_4^+$ ([M+H]$^+$) requires 451.1839, found 451.1827 (-2.7ppm).


15.18
7.43
7.11
7.04
6.99
6.74
6.72
6.44
6.44
6.24
6.21
4.57
3.86
3.79
3.52
3.41
2.93
2.73
2.69
1.94
1.83
O
OH
N
O
O
CF3
N
1H, CDCl3, 400 MHz
0.91
1.11
0.79
0.91
0.89
0.85
0.91
0.92
1.00
3.03
2.99
1.35
3.04
0.92
0.98
2.29
1.91
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


179.05
166.67
165.59
164.01
160.25
134.28
129.96
126.22
125.29
113.92
113.78
106.17
101.36
58.84
55.54
55.40
47.12
46.07
35.57
26.17
24.49
OH
N
O
O
CF3
N
13C{1H}, CDCl3, 101 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

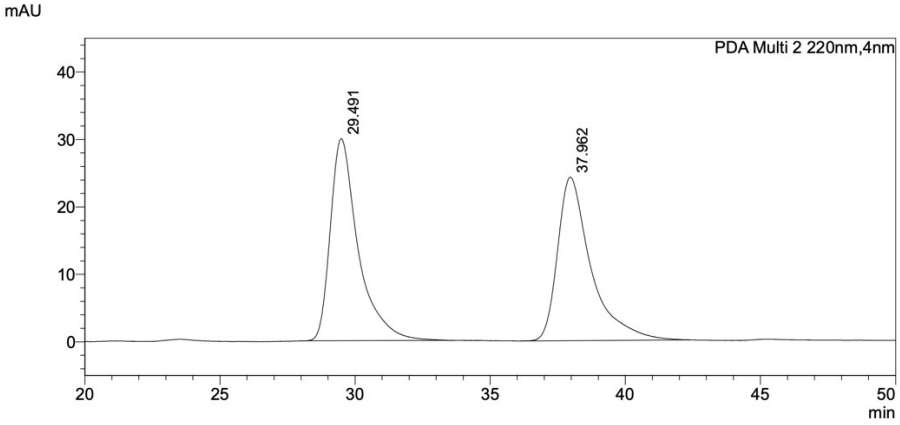

-74.33
OH
N
O
O
O
CF3
N
19F, CDCl3, 376 MHz
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
-230
f1 (ppm)

HPLC Data for **((*R*,*E*)-4,4,4-trifluoro-3-(((2-hydroxy-4-methoxyphenyl)(4-methoxyphenyl)methylene)amino)-1-(pyrrolidin-1-yl)butan-1-one**: Chiralpak ID (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 220 nm, 30 °C) t_R(*S*): 31.5 min, t_R(*R*): 39.9 min, 95:5 er.

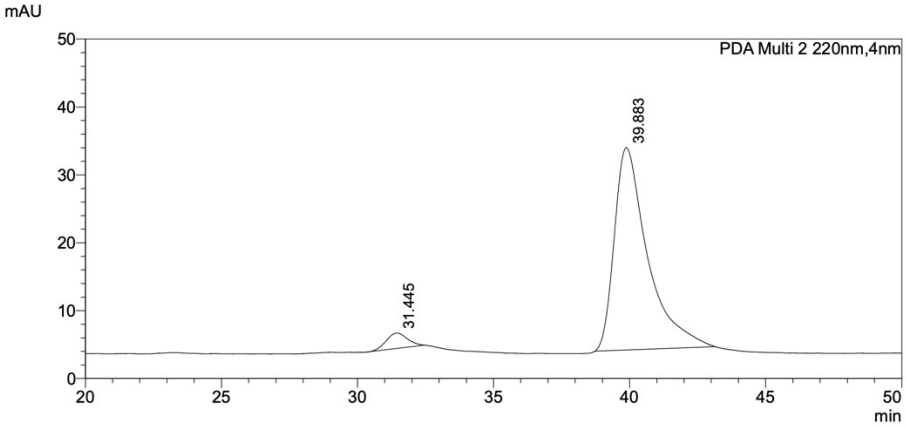


PDA Ch2 220nm

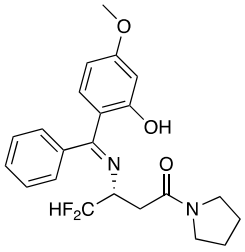
Peak#	Ret. Time	Area%
1	29.491	50.834
2	37.962	49.166
Total		100.000



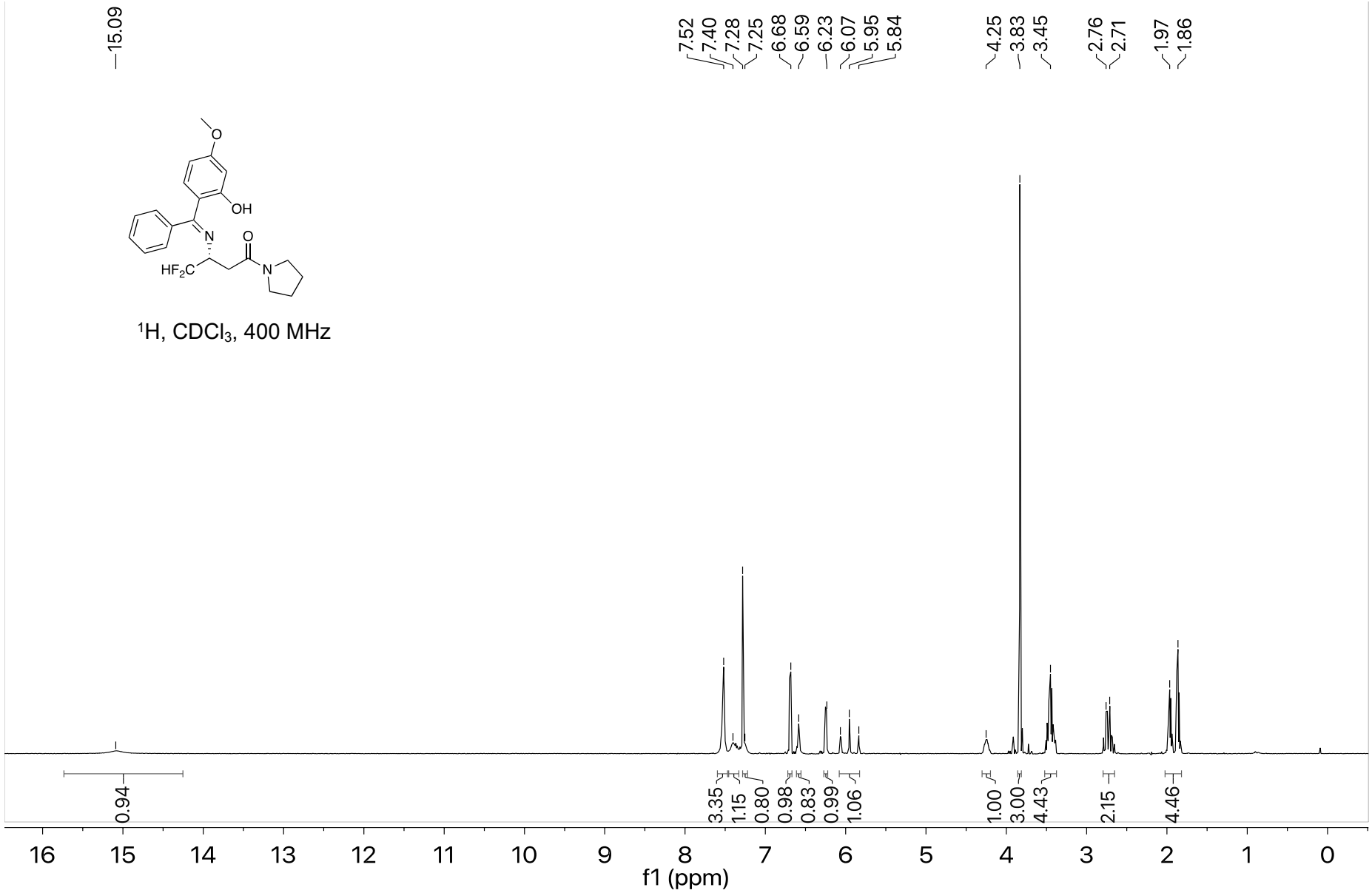
Peak#	Ret. Time	Area%
1	31.445	4.658
2	39.883	95.342
Total		100.000

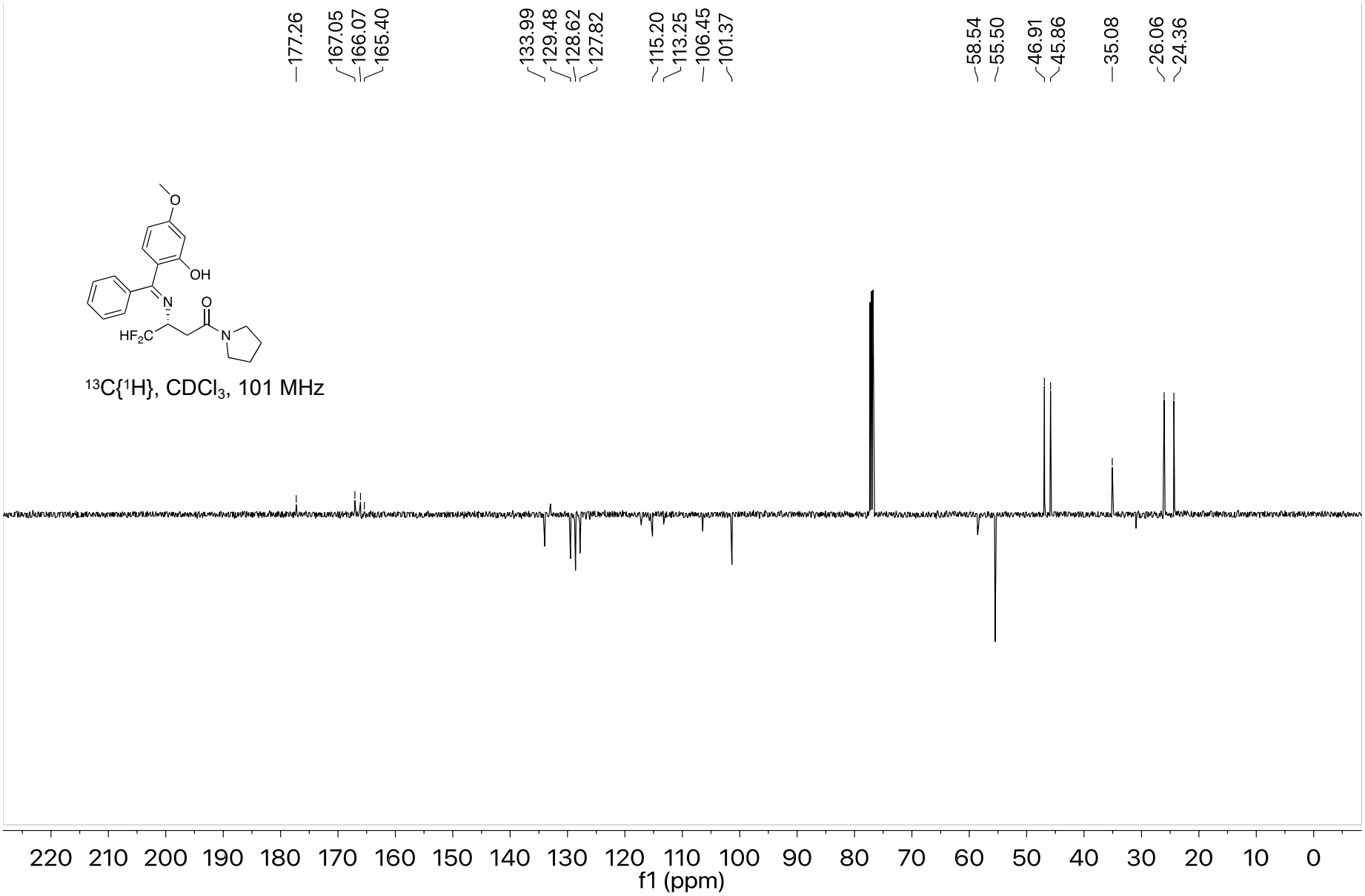


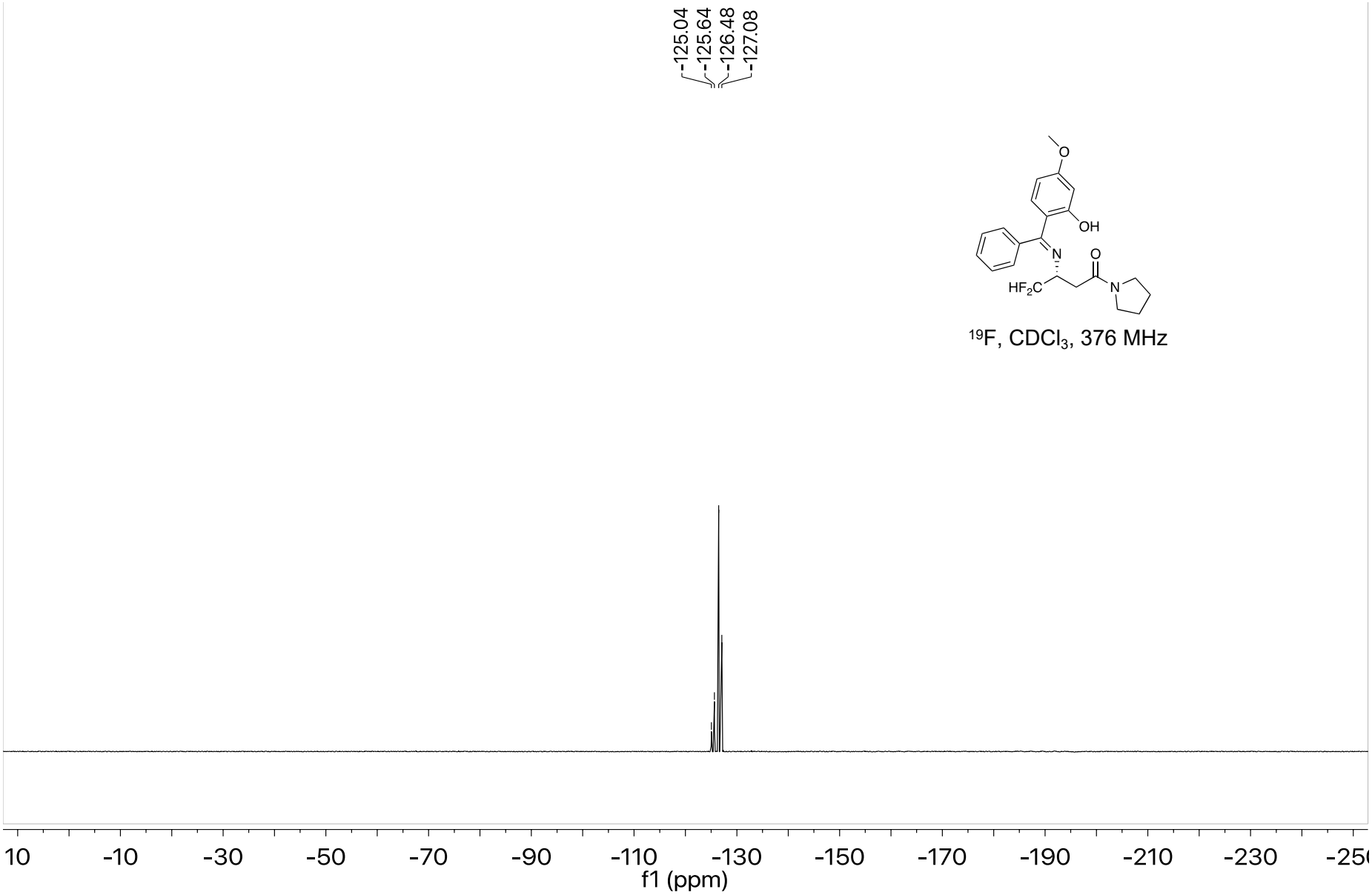
(*R*)-4,4-Difluoro-3-(((2-hydroxy-4-methoxyphenyl)methylene)amino)-1-(pyrrolidin-1-yl)butan-1-one (14)



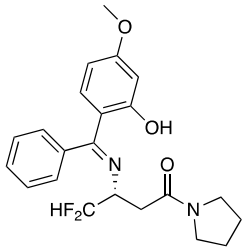
Following **General Procedure D,** 4-nitrophenyl (*E*)-4,4-difluorobut-2-enoate (24.3 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (45.4 mg, 0.2 mmol), (*R*)-(+)-BTM (5.1 mg, 0.02mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Pyrrolidine was added (12.5 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was purified by flash column chromatography Hexane:EtOAc (1:1) (R_f = 0.24) to give the titled compound (16.0 mg, 40%) as a yellow oil. $[\alpha]_D^{20}$+23.8 (*c* = 0.72, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IB (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 220 nm, 30 °C) t_R(*S*): 48.5 min, t_R(*R*): 52.1 min, 97:3 er.; **IR** ν_{max} (ATR), 2976 (Ar-H), 1622 (C=O), 1595 (C=N), 1444 (C=C), 1259 (C-F); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.86 – 1.96 (4H, m, NC(2)H_2C(3)*H_2*C(4)*H_2*C(5)H_2), 2.72 – 2.74 (2H, qd, $^3J_{HH}$ = 15.7, $^4J_{HH}$ = 3.0, COC(2)*$H_A H_B$*), 3.45 (4H, m, NC(2)*H_2*C(3)H_2C(4)H-$_2$C(5)*H_2*), 3.82 (3H, s, ArOH-OC*H_3*), 4.24 (1H, m, COCH_AH$_B$C*H*), 5.94 (1H, td, $^2J_{HF}$ = 55.8, $^4J_{HH}$ = 3.0, CF_2*H*), 6.23 (1H, dd, $^3J_{HH}$ = 9.0, $^4J_{HH}$ = 2.5, N=CC(5)Ar*H*OH-OCH_3), 6.52 (1H, s, N=CC(3)Ar*H*OH-OCH_3), 6.68 (1H, d, $^3J_{HH}$ = 9.0, N=CC(6)Ar*H*OH-OCH_3), 7.45 (5H, m, N=CC(2,3,4,5,6)Ar*H*), 15.3 (1H, s, N=CC(2)ArHO*H*-OCH_3). **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -125.3 (d, $^2J_{FF}$ = 282.1, -C*F*$_A$F$_B$H), -126.8 (d, $^2J_{FF}$ = 282.0, -CF$_A$*F*$_B$H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 24.4 (NC(2)H_2*C*(3)H_2C(4)H_2C(5)H_2), 26.1 (NC(2)H_2C(3)H_2*C*(4)H_2C(5)H_2), 35.1 (C=O*C*H$_A$H$_B$CF$_3$), 45.9 (N*C*(2)H_2C(3)H_2C(4)H_2C(5)H_2), 46.9 (NC(2)H_2C(3)H_2C(4)H_2*C*(5)H_2), 55.0 (-O*C*H$_3$), 58.7 – 59.9 (q, $^2J_{CF}$ = 29.3, C=OCH$_A$H$_B$*C*(3)HCF$_3$), 101.4 (*C*(3)ArOH-OCH_3), 106.5 (*C*(5)ArOH-OCH_3), 113.3 (*C*(1)ArOH-OCH_3), 115.20 (-*C*F$_2$H), 127.8 (*C*(1,2,6)Ar), 128.6 (*C*(3,4,5)Ar), 133.99 (*C*(6)ArOH-OCH_3), 165.4 (*C*(2)ArOH-OCH_3), 166.1 (*C*(4)ArOH-OCH_3), 167.1 (*C*=O), 177.3 (*C*=N). **HRMS** (NSI$^+$) $C_{22}H_{25}F_2N_2O_3^+$ ([M+H]$^+$) requires 403.1828, found 403.1822 (-1.5ppm).


15.09
7.52
7.40
7.28
7.25
6.68
6.59
6.23
6.07
5.95
5.84
4.25
3.83
3.45
2.76
2.71
1.97
1.86
O
OH
N
O
HF2C
N
1H, CDCl3, 400 MHz
0.94
3.35
1.15
0.80
0.98
0.83
0.99
1.06
1.00
3.00
4.43
2.15
4.46
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


177.26
167.05
166.07
165.40
133.99
129.48
128.62
127.82
115.20
113.25
106.45
101.37
58.54
55.50
46.91
45.86
35.08
26.06
24.36
O
OH
N
O
HF2C
N
13C{1H}, CDCl3, 101 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

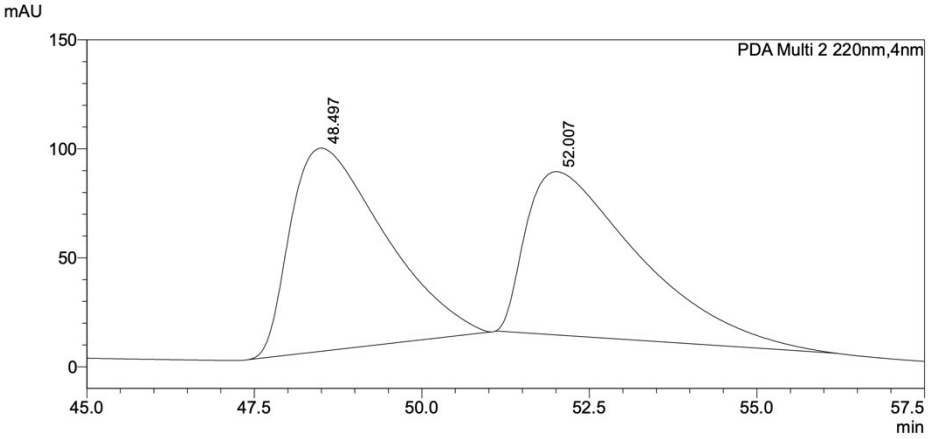

-125.04
-125.64
-126.48
-127.08
O
OH
N
O
HF2C
N
19F, CDCl3, 376 MHz
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
-230
f1 (ppm)

HPLC Data for ***R*)-4,4-difluoro-3-(((2-hydroxy-4-methoxyphenyl)methylene)amino)-1-(pyrrolidin-1-yl)butan-1-one**: Chiralpak IB (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 220 nm, 30 °C) t_R(*S*): 48.5 min, t_R(*R*): 52.1 min, 97:3 er.



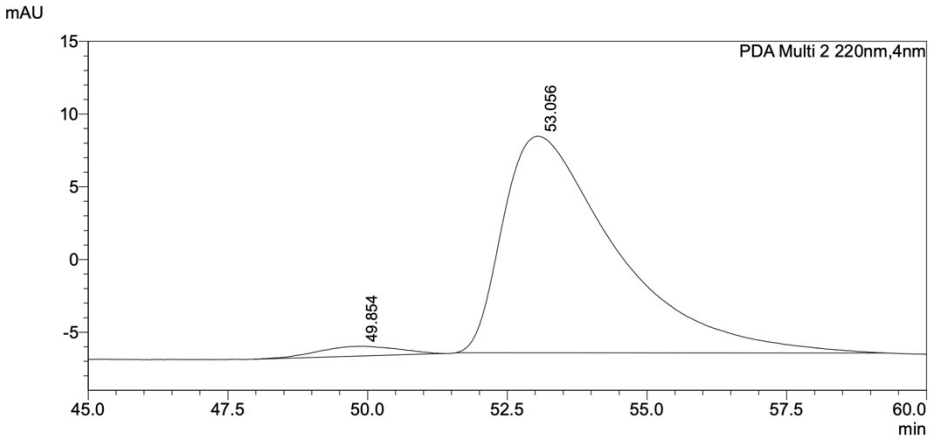
PDA Ch2 220nm

Peak#	Ret. Time	Area%
1	48.497	50.706
2	52.007	49.294
Total		100.000

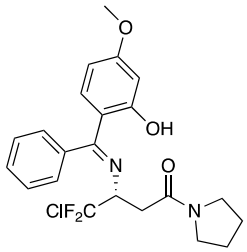


PDA Ch2 220nm

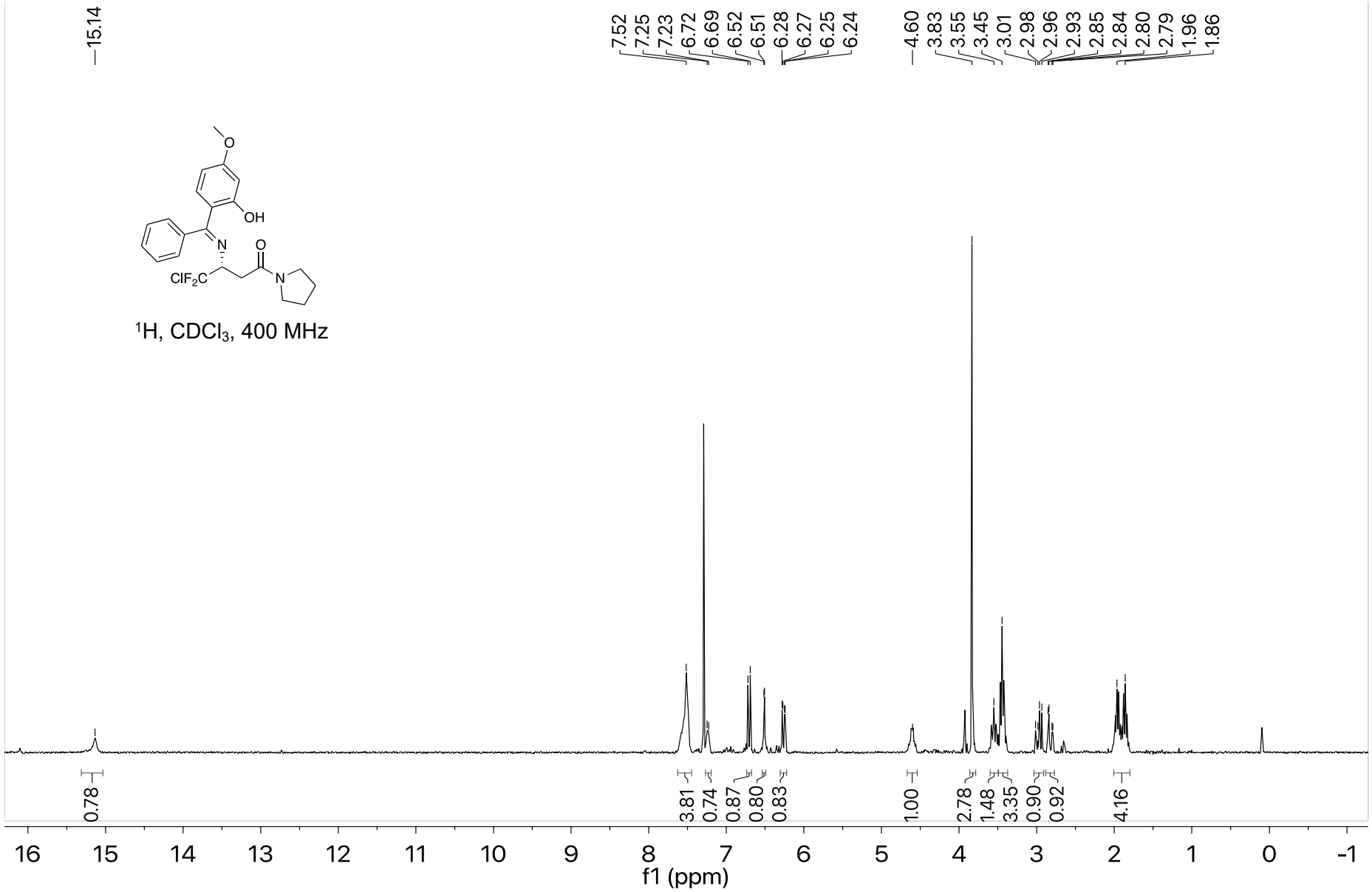
Peak#	Ret. Time	Area%
1	49.854	3.115
2	53.056	96.885
Total		100.000

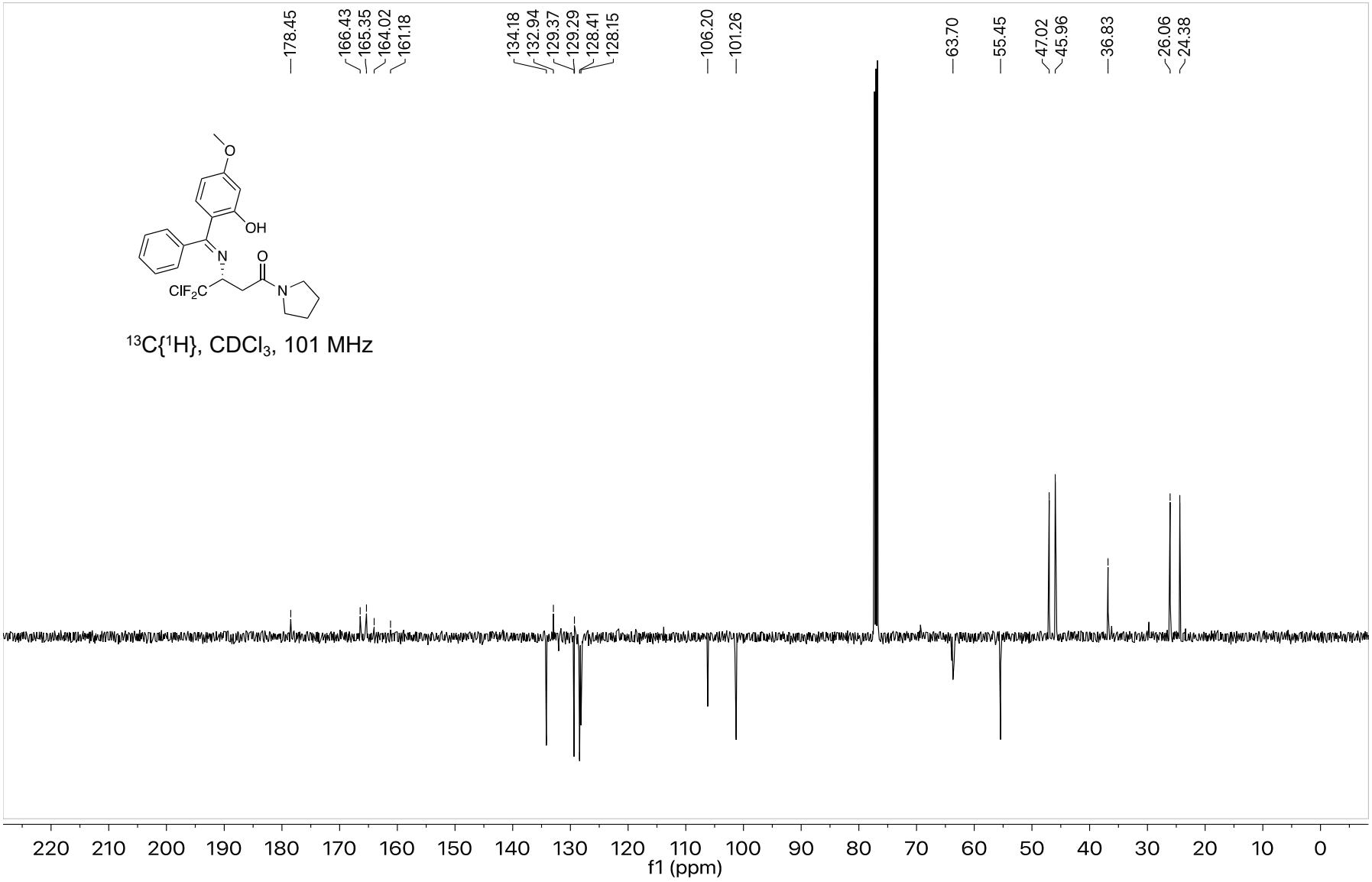


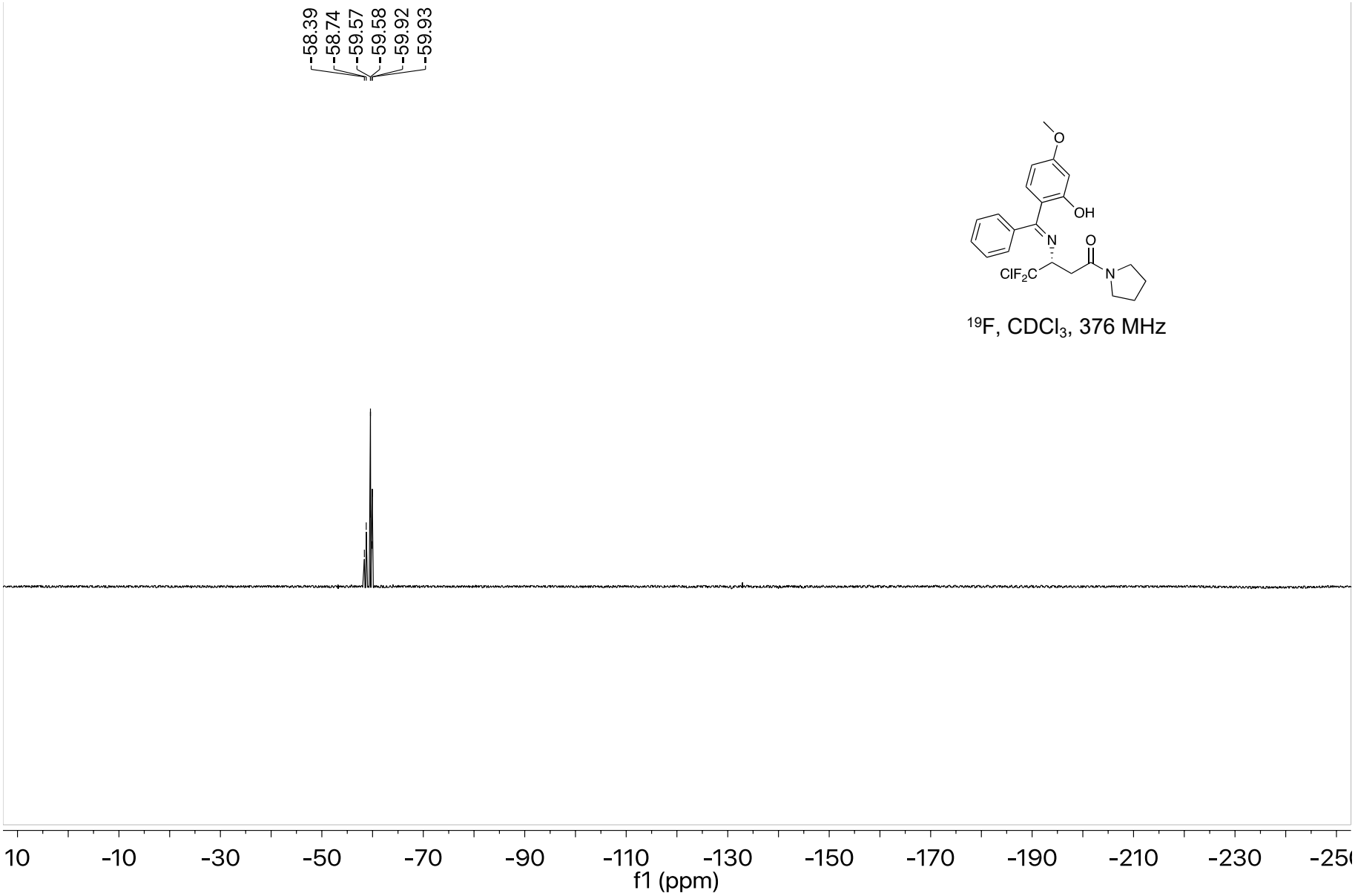
(*R*)-4-Chloro-4,4-difluoro-3-(((2-hydroxy-4-methoxyphenyl)methylene)amino)-1-(pyrrolidin-1-yl)butan-1-one (15)



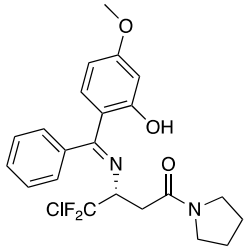
Following **General Procedure D,** 4-nitrophenyl (*E*)-4-chloro-4,4-difluorobut-2-enoate (27.8 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (45.4 mg, 0.2 mmol), (*R*)-(+)-BTM (5.1 mg, 0.02mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Pyrrolidine was added (12.5 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was then purified by flash column chromatography Hexane:EtOAc (1:1) (R_f = 0.16) to give the titled compound (31.9 mg, 73%) as a yellow oil. $[\alpha]_D^{20}$ +9.60 (*c* = 1.60, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(*S*): 22.0 min, t_R(*R*): 29.0 min, 96:4 er; **IR** ν_{max} (ATR), 2974 (Ar-H), 1635 (C=O), 1593 (C=N), 1444 (C=C), 1263 (C-F); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.86 – 1.96 (4H, m, NC(2)H_2C(3)*H_2*C(4)*H_2*C(5)H_2), 2.82 (1H, dd, $^3J_{HH}$ = 15.1, $^4J_{HH}$ = 3.2, COC(2)*H_A*H_B), 2.97 (1H, dd, $^3J_{HH}$ = 15.1, $^4J_{HH}$ = 9.2, COC(2)H_A*H_B*) 3.50 (4H, m, NC(2)*H_2*C(3)H_2C(4)H_2C(5)*H_2*), 3.83 (3H, s, ArOH-OC*H_3*), 4.60 (1H, m, COC$H_A$$H_B$C*H*), 6.26 (1H, dd, $^3J_{HH}$ = 9.0, $^4J_{HH}$ = 2.5, N=CC(5)Ar*H*OH-OCH_3), 6.51 (1H, d, $^4J_{HH}$ = 2.3, N=CC(3)Ar*H*OH-OCH_3), 6.71 (1H, d, $^3J_{HH}$ = 9.0, N=CC(6)Ar*H*OH-OCH_3), 7.24 (1H, N=CC(4)Ar*H*), 7.52 (4H, m, N=CC(2,3,5,6)Ar*H*), 15.1 (1H, s, N=CC(2)ArHO*H*-OCH_3). **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -58.6 (d, $^2J_{FF}$ = 164.8, -C*F_A*F_BCl), -59.8 (dd, $^2J_{FF}$ = 164.8, $^3J_{HF}$ = 2.8, CF_A*F_B*Cl); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 24.4 (NC(2)H_2*C*(3)H_2C(4)H_2C(5)H_2), 26.1 (NC(2)H_2C(3)H_2*C*(4)H_2C(5)H_2), 36.8 (C=O*C*$H_A$$H_B$$CF_3$), 46.0 (N*C*(2)$H_2$C(3)$H_2$C(4)$H_2$C(5)$H_2$), 47.0 (NC(2)$H_2$C(3)$H_2$C(4)$H_2$*C*(5)$H_2$), 55.45 (-O*C*$H_3$), 63.5 – 63.9 (q, $^2J_{CF}$ = 20.2, C=O$CH_A$$H_B$*C*(3)H$CF_2$Cl), 101.3 (N=C*C*(3)ArOH-OCH_3), 106.2 (N=C*C*(5)ArOH-OCH_3), 128.1 (N=C*C*(4)Ar), 128.4 (N=C*C*(2,6)Ar), 129.3 (*C*F_2-Cl), 129.4 (N=C*C*(3,5)Ar), 132.9 (N=C*C*(1)Ar), 134.2 (N=C*C*(6)ArOH-OCH_3), 161.2 (N=C*C*(2)ArOH-OCH_3), 164.0 (N=C*C*(1)ArOH-OCH_3), 165.4 (N=C*C*(4)ArOH-OCH_3), 166.4 (*C*=O), 178.4 (*C*=N). **HRMS** (NSI$^+$) $C_{22}H_{23}ClF_2N_2O_3^+$ ([M+H]$^+$) requires 437.1438, found 437.1429 (-2.1 ppm).


15.14
7.52
7.25
7.23
6.72
6.69
6.52
6.51
6.28
6.27
6.25
6.24
4.60
3.83
3.55
3.45
3.01
2.98
2.96
2.93
2.85
2.84
2.80
2.79
1.96
1.86
O
OH
N
O
ClF2C
N
1H, CDCl3, 400 MHz
0.78
3.81
0.74
0.87
0.80
0.83
1.00
2.78
1.48
3.35
0.90
0.92
4.16
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


178.45
166.43
165.35
164.02
161.18
134.18
132.94
129.37
129.29
128.41
128.15
106.20
101.26
63.70
55.45
47.02
45.96
36.83
26.06
24.38
O
OH
N
O
ClF2C
N
13C{1H}, CDCl3, 101 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

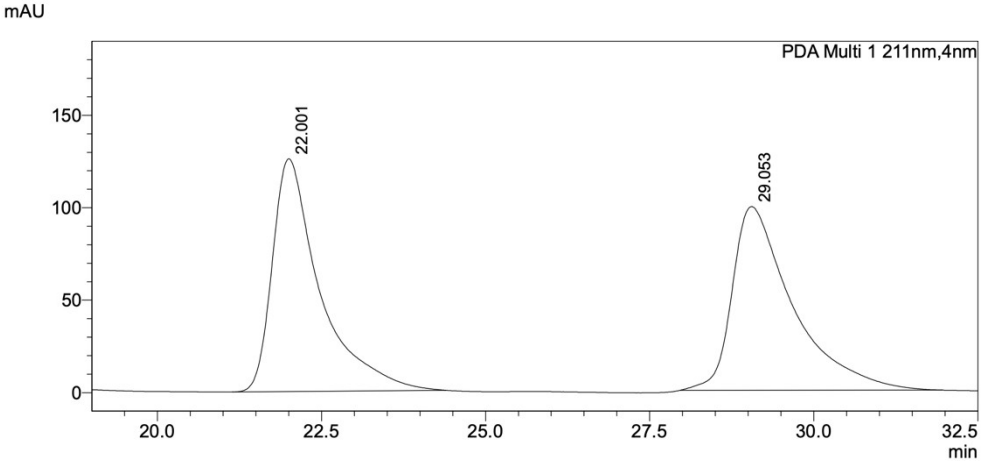

-58.39
-58.74
-59.57
-59.58
-59.92
-59.93
O
OH
N
O
ClF2C
N
19F, CDCl3, 376 MHz
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
-230
f1 (ppm)

HPLC Data for **(*R*)-4-chloro-4,4-difluoro-3-(((2-hydroxy-4-methoxyphenyl)methylene) amino)-1-(pyrrolidin-1-yl)butan-1-one**: Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(*S*): 22.0 min, t_R(*R*): 29.0 min, 96:4 er.



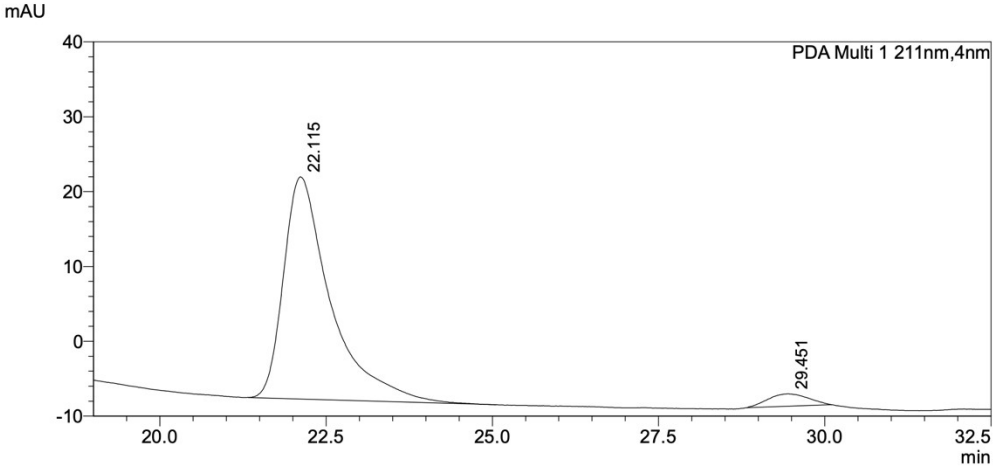
PDA Ch1 211nm

Peak#	Ret. Time	Area%
1	22.001	49.069
2	29.053	50.931
Total		100.000

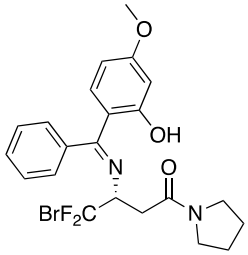


PDA Ch1 211nm

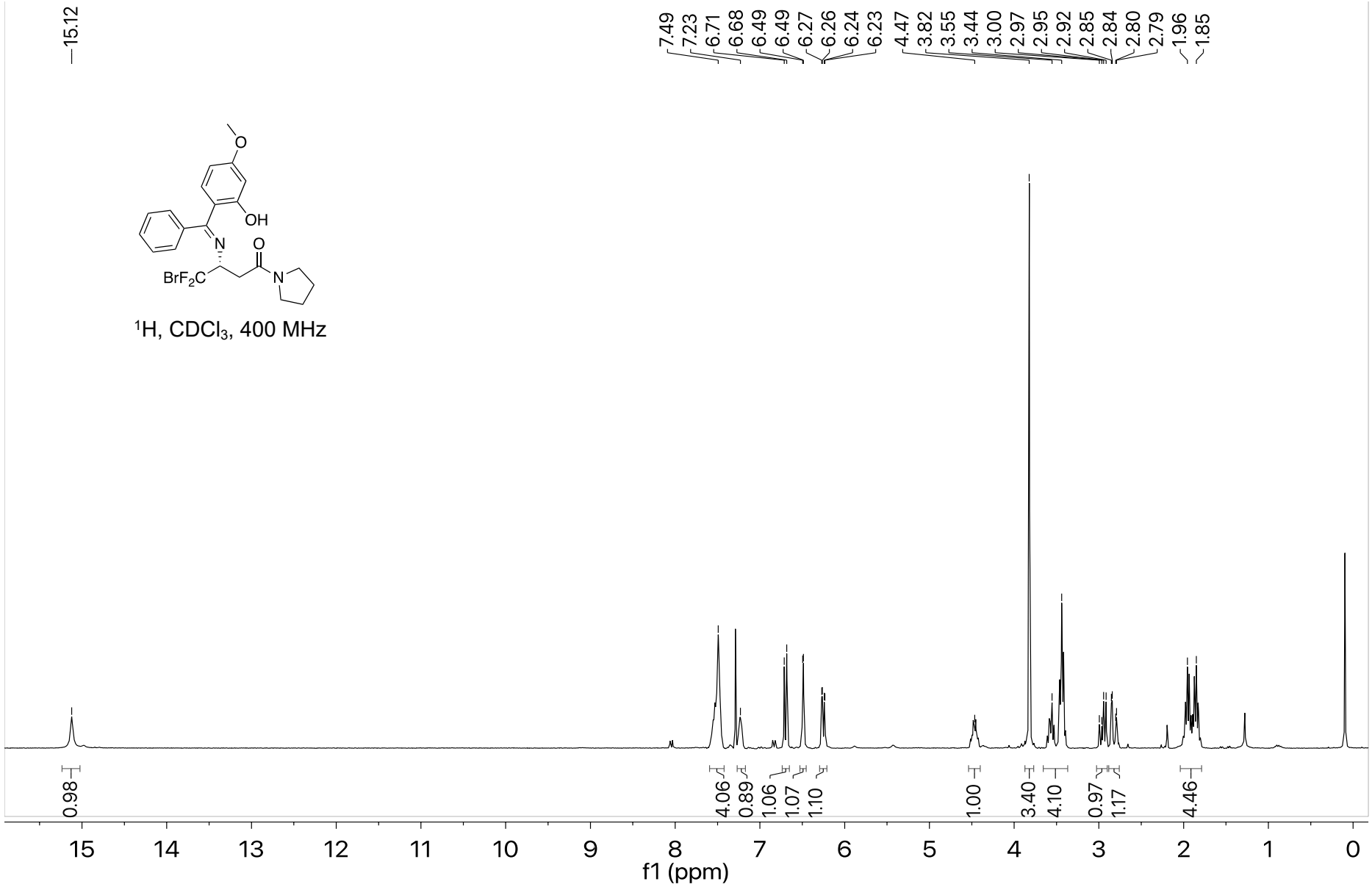
Peak#	Ret. Time	Area%
1	22.115	95.637
2	29.451	4.363
Total		100.000

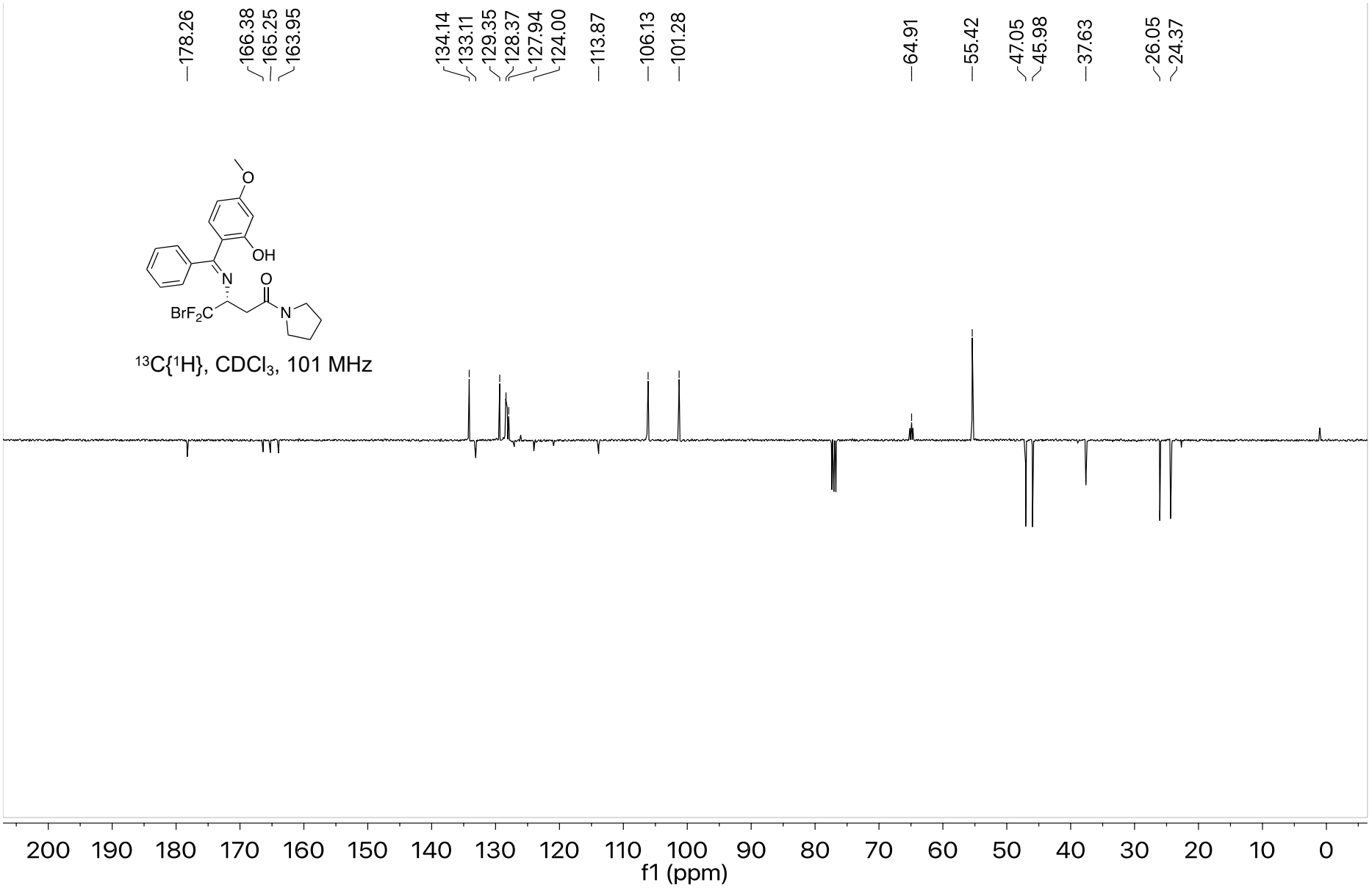


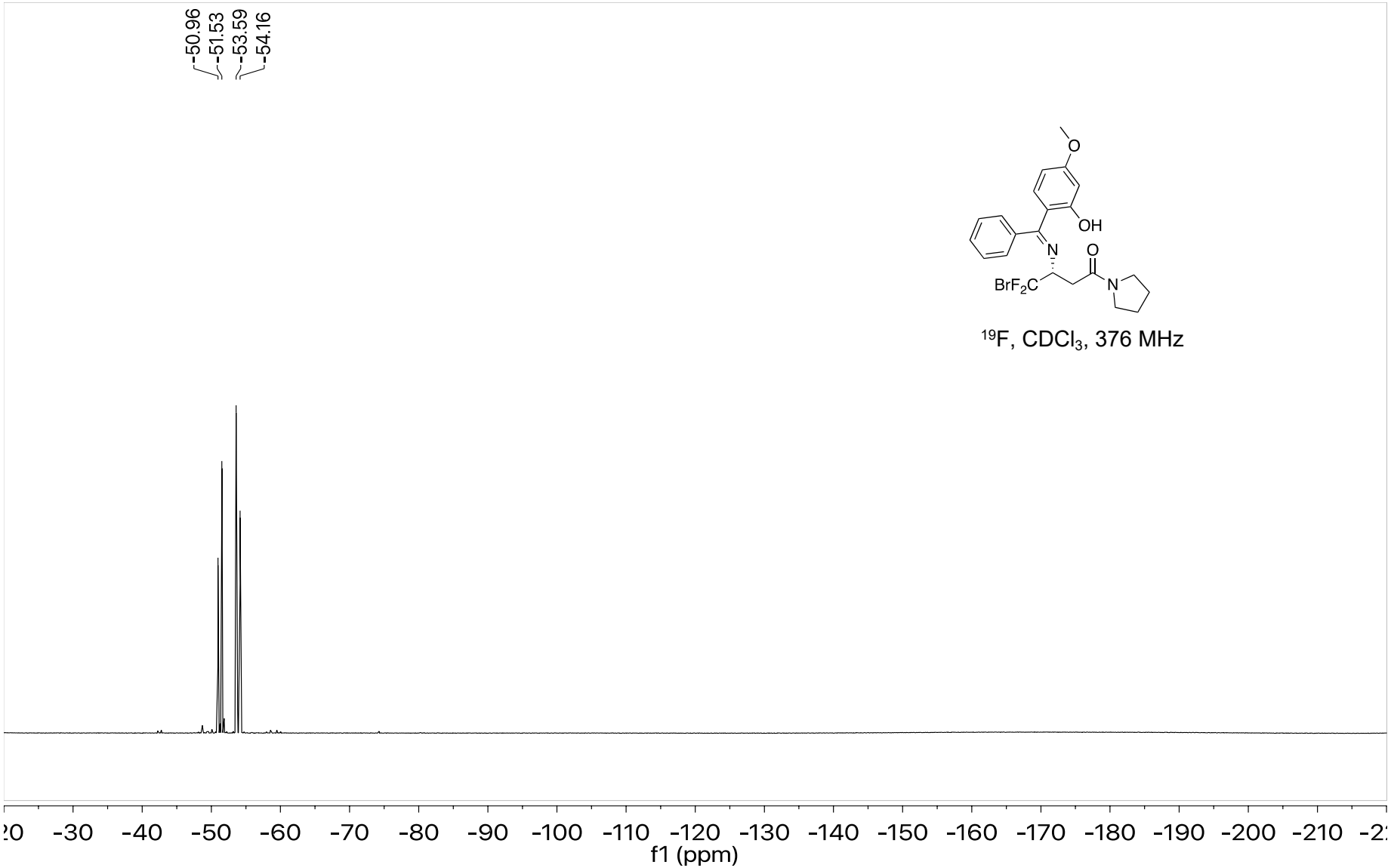
(*R*)-4-Bromo-4,4-difluoro-3-(((2-hydroxy-4-methoxyphenyl)methylene)amino)-1-(pyrrolidin-1-yl)butan-1-one (16)



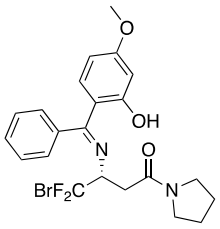
Following **General Procedure C,** 4-nitrophenyl (*E*)-4-Bromo-4,4-difluorobut-2-enoate (32.2 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (45.4 mg, 0.2 mmol), (*R*)-(+)-BTM (5.1 mg, 0.02mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Pyrrolidine was added (12.5 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was then purified by flash column chromatography Hexane:EtOAc (2:1) (R_f = 0.24) to give the titled compound (34.6 mg, 72%) as a yellow oil. $[\alpha]_D^{20}$ +70.8 (*c* = 0.67, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak OD-H (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C), t_R(*R*): 13.5 min, t_R(*S*): 18.7 min, 96:4 er; **IR** ν_{max} (ATR), 2970 (Ar-H), 1637 (C=O), 1591 (C=N), 1442 (C=C), 1261 (C-F); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.84 – 1.95 (4H, m, NC(2)H_2C(3)*H_2*C(4)*H_2*C(5)H_2), 2.82 (1H, dd, $^2J_{HH}$ = 15.1, $^3J_{HH}$ = 3.2, COC(2)*H_A*H_B), 2.95 (1H, dd, $^2J_{HH}$ = 15.1, $^3J_{HH}$ = 9.0, COC(2)H_A*H_B*) 3.44 – 3.56 (4H, m, NC(2)*H_2*C(3)H_2C(4)H_2C(5)*H_2*), 3.82 (3H, s, ArOH-OC*H_3*), 4.46 (1H, $^3J_{HH}$ = 9.0, $^3J_{HH}$ = 3.3, , $COCH_AH_BCH$), 6.25 (1H, dd, $^3J_{HH}$ = 8.9, $^4J_{HH}$ = 2.6, N=CC(5)Ar*H*OH-OCH_3), 6.48 (1H, d, $^4J_{HH}$ = 2.6, N=CC(3)Ar*H*OH-OCH_3), 6.70 (1H, d, $^3J_{HH}$ = 9.0, N=CC(6)Ar*H*OH-OCH_3), 7.23 (1H, m, N=CC(4)Ar*H*), 7.50 (4H, m, N=CC(2,3,5,6)Ar*H*), 15.1 (1H, s, N=CC(2)ArHO*H*-OCH_3). **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -51.2 (d, $^2J_{FF}$ = 160.2, -C*F_A*F_BBr), -53.9 (d, $^2J_{FF}$ = 160.1, -CF_A*F_B*Br); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 24.4 (NC(2)H_2*C*(3)H_2C(4)H_2C(5)H_2), 26.1 (NC(2)H_2C(3)H_2*C*(4)H_2C(5)H_2), 37.6 (C=O*C*$H_A$$H_B$$CF_3$), 46.0 (N*C*(2)$H_2$C(3)$H_2$C(4)$H_2$C(5)$H_2$), 47.0 (NC(2)$H_2$C(3)$H_2$C(4)$H_2$*C*(5)$H_2$), 55.4 (-O*C*$H_3$), 64.7 – 65.1 (q, $^2J_{CF}$ = 22.5, C=OCH_AH_B*C*(3)HCF_2Cl), 101.3 (N=C*C*(3)ArOH-OCH_3), 106.2 (N=C*C*(5)ArOH-OCH_3), 113.9 (N=C*C*(1)ArOH-OCH_3), 124.0 (CF_2Br), 127.9 (N=C*C*(4)Ar), 128.4 (N=C*C*(3,5)Ar), 129.4 (N=C*C*(2,6)Ar), 133.1 (N=C*C*(1)Ar), 134.1 (N=C*C*(6)ArOH-OCH_3), 164.0 (N=C*C*(4)ArOH-OCH_3), 165.3 (N=C*C*(2)ArOH-OCH_3), 166.4 (*C*=O), 178.4 (*C*=N). **HRMS** (NSI$^+$) $C_{22}H_{24}BrF_2N_2O_3^+$ ([M+H]$^+$) requires 481.3378, found 481.0933 (-0.60 ppm).


15.12
7.49
7.23
6.71
6.68
6.49
6.49
6.27
6.26
6.24
6.23
4.47
3.82
3.55
3.44
3.00
2.97
2.95
2.92
2.85
2.84
2.80
2.79
1.96
1.85
O
OH
N
O
BrF2C
N
1H, CDCl3, 400 MHz
0.98
4.06
0.89
1.06
1.07
1.10
1.00
3.40
4.10
0.97
1.17
4.46
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


178.26
166.38
165.25
163.95
134.14
133.11
129.35
128.37
127.94
124.00
113.87
106.13
101.28
64.91
55.42
47.05
45.98
37.63
26.05
24.37
O
OH
N
O
BrF2C
N
13C{1H}, CDCl3, 101 MHz
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

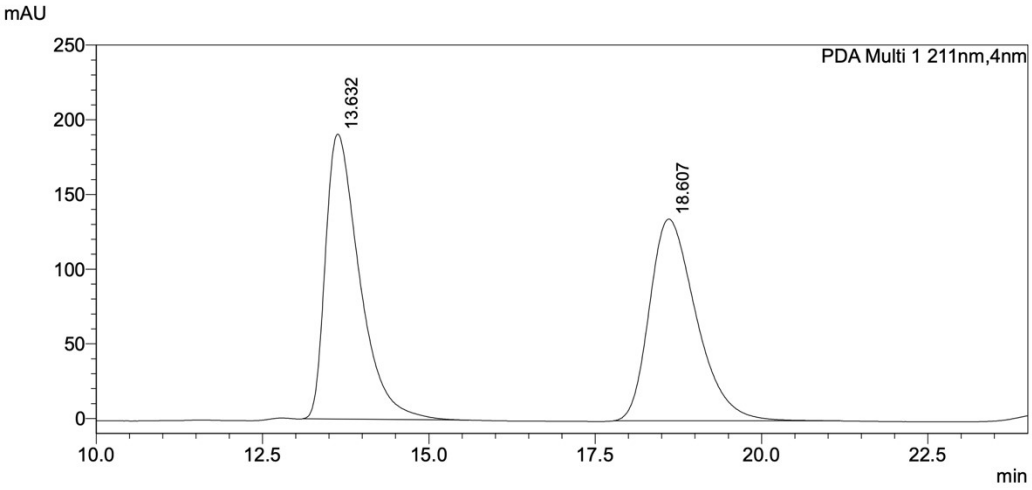

-50.96
-51.53
-53.59
-54.16
O
OH
N
O
N
BrF2C
19F, CDCl3, 376 MHz
-30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

HPLC Data for **(*R*)-4-Bromo-4,4-difluoro-3-(((2-hydroxy-4-methoxyphenyl)methylene) amino)-1-(pyrrolidin-1-yl)butan-1-one**: Chiralpak OD-H (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C), t_R(*R*): 13.5 min, t_R(*S*): 18.7 min, 96:4 er.



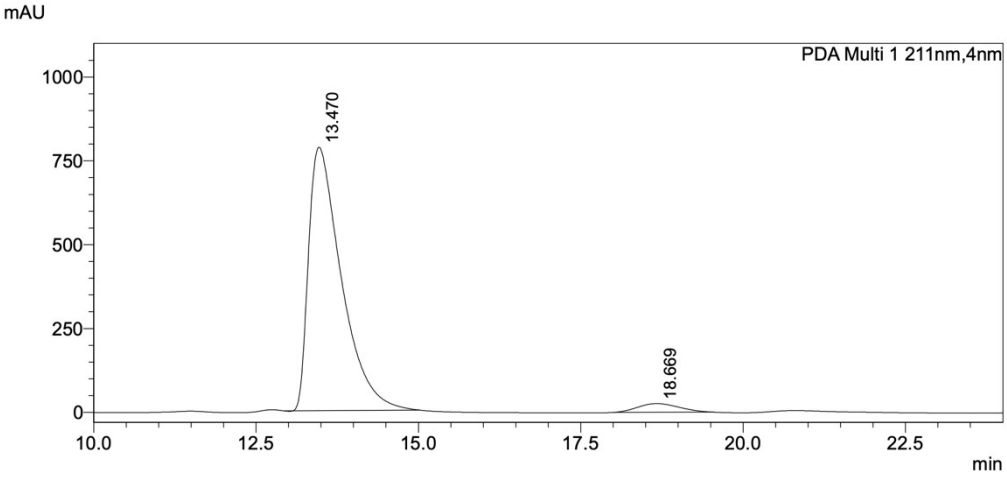
PDA Ch1 211nm

Peak#	Ret. Time	Area%
1	13.632	50.731
2	18.607	49.269
Total		100.000

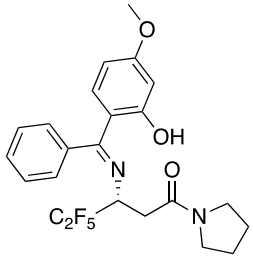


PDA Ch1 211nm

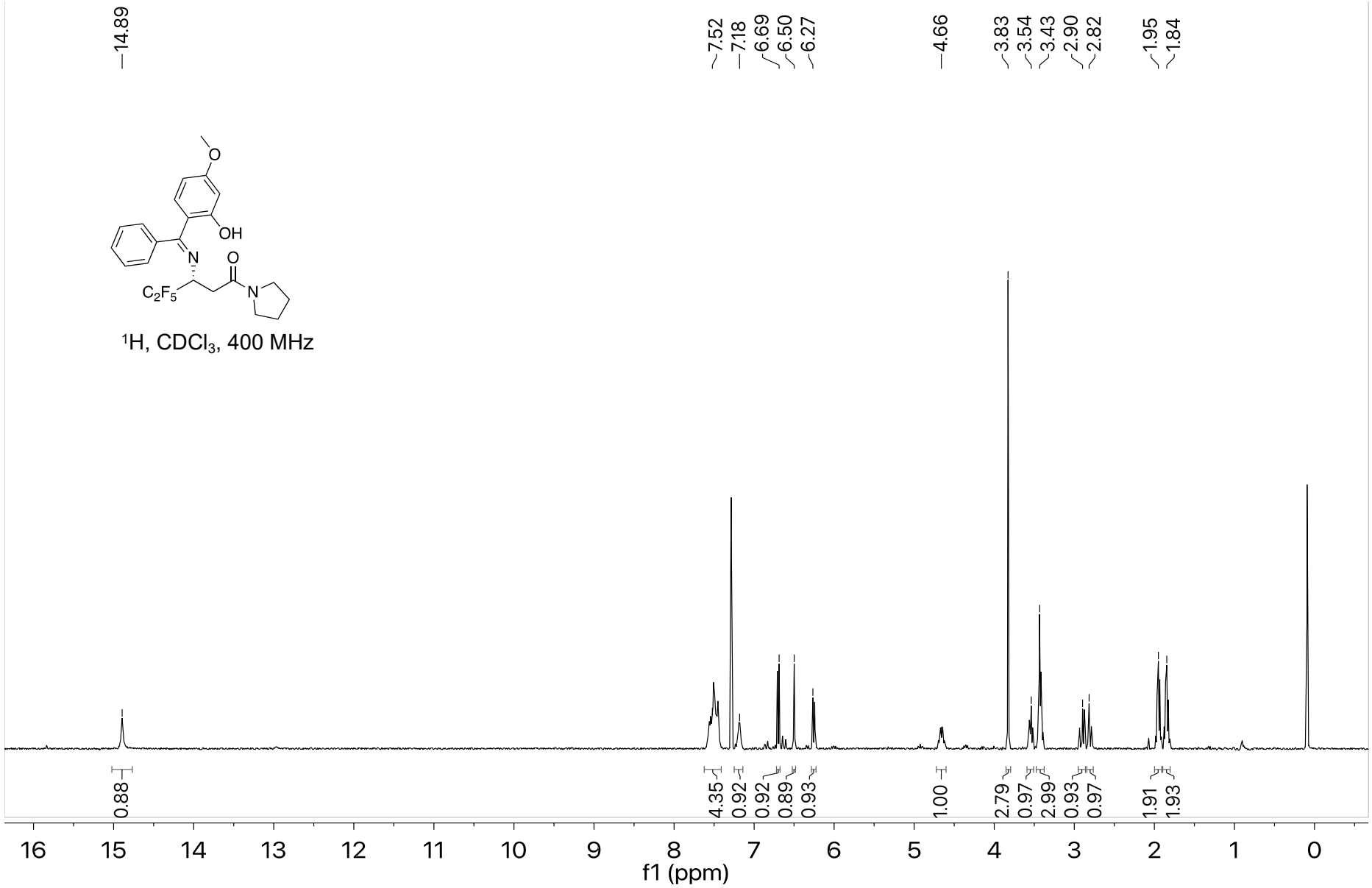
Peak#	Ret. Time	Area%
1	13.470	95.989
2	18.669	4.011
Total		100.000

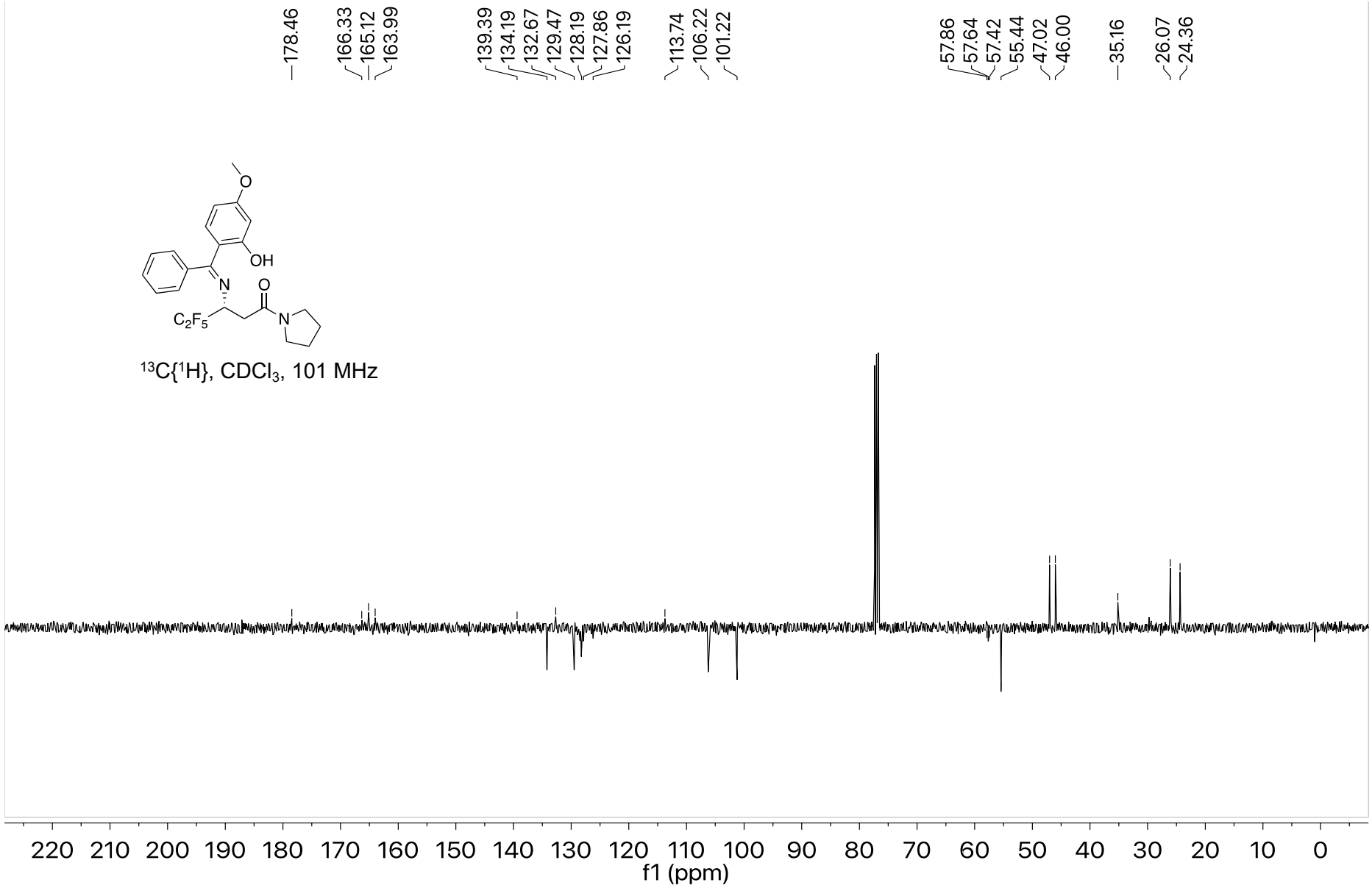


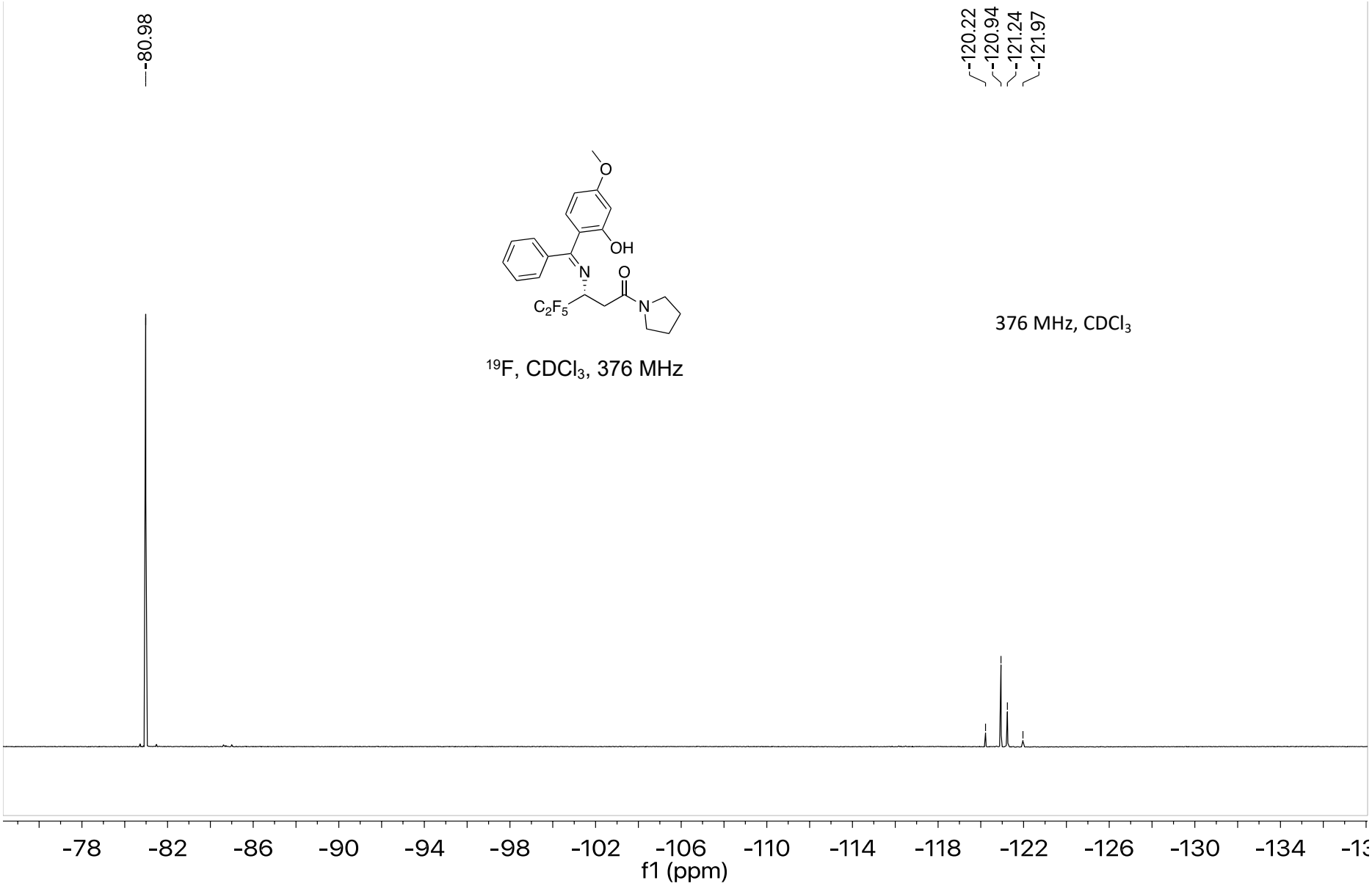
(*R*)-4,4,5,5,5-Pentafluoro-3-(((2-hydroxy-4-methoxyphenyl)methylene)amino)-1-(pyrrolidine-1-yl)pentan-1-one (17)



Following **General Procedure D,** 4-nitrophenyl (*E*)-4,4,5,5,5-pentafluoroppentan-2-enoate (31.1 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (45.4 mg, 0.2 mmol), (*R*)-(+)-BTM (5.1 mg, 0.02mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Pyrrolidine was added (12.3 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was then purified by flash column chromatography Hexane:EtOAc (2:1) (R_f = 0.20) to give the titled compound (38.1 mg, 81%) as a yellow oil. $[\alpha]_D^{20}$ +95.2 (*c* = 0.31, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(*R*): 13.9 min, t_R(*S*): 20.6 min, 97:3 er; **IR** ν_{max} (ATR), 2974 (Ar-H), 1622 (C=O), 1593 (C=N), 1445 – 1456 (C=C), 1207 (C_2F_5); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.84 – 1.95 (4H, m, N NC(2)H_2C(3)*H*$_2$C(4)*H*$_2$C(5)H_2), 2.82 (1H, dd, $^2J_{HH}$ = 15.1, $^3J_{HH}$ = 3.9, O=CC(2)*H*$_A$H$_B$), 2.90 (1H, dd, , $^2J_{HH}$ = 15.1, $^3J_{HH}$ = 8.8, O=CC(2)H$_A$*H*$_B$), 3.43 – 3.54 (4H, m, NC(2)*H*$_2$C(3)H$_2$C(4)H$_2$C(5)*H*$_2$), 3.83 (3H, s, -OC*H*$_3$), 4.66 (1H, m, O=CCH$_A$H$_B$C(3)*H*), 6.27 (1H, dd, $^3J_{HH}$ = 8.9, $^4J_{HH}$ = 2.2, N=CC(5)Ar*H*OH-OCH$_3$), 6.50 (1H, d, $^4J_{HH}$ = 2.4, N=CC(3)Ar*H*OH-OCH$_3$), 6.69 (1H, d, $^3J_{HH}$ = 9.0, N=CC(6)Ar*H*OH-OCH$_3$), 7.18 (1H, m, N=CC(2)Ar*H*), 7.52 (4H, m, N=CC(3,4,5,6)Ar*H*), 14.9 (1H, s, -O*H*). **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F -80.9 (-CF$_A$F$_B$C*F*$_3$), -120.6 (d, $^2J_{FF}$ = 272.9, -C*F*$_A$F$_B$CF$_3$), -121.2 (d, $^2J_{FF}$ = 272.9, -CF$_A$*F*$_B$CF$_3$); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 24.4 – 26.1 (NC(2)H_2*C*(3)H_2*C*(4)H_2C(5)H_2), 35.2 (O=C*C*(2)H$_A$H$_B$), 46.0 – 47.0 (N*C*(2)H_2C(3)H-$_2$C(4)H_2*C*(5)H_2), 55.4 (-O*C*H$_3$), 57.9 (t, $^2J_{CF}$ = 22.2, O=CCH$_A$H$_B$*C*(3)H), 101.2 (N=C*C*(3)ArOH-OCH$_3$), 106.22 (N=C*C*(5)ArOH-OCH$_3$), 113.7 (N=C*C*(1)ArOH-OCH$_3$), 126.2 (N=C*C*(1)Ar), 127.9 (N=C*C*(2,6)Ar), 129.5 (N=C*C*(3,4,5)Ar), 132.7 (-*C*F$_2$CF$_3$), 134.2 (N=C*C*(6)ArOH-OCH$_3$), 139.4 (-CF$_2$*C*F$_3$), 163.7 (N=C*C*(2)ArOH-OCH$_3$), 165.1 (N=C*C*(4)ArOH-OCH$_3$), 166.3 (*C*=O), 178.5 (*C*=N). **HRMS** (NSI$^+$) $C_{23}H_{23}F_5N_2O_3^+$ ([M+H]$^+$) requires 471.1702, found 471.1690 (-2.5 ppm).

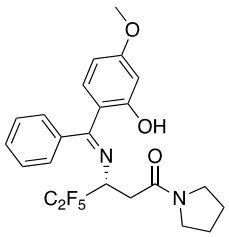

14.89
7.52
7.18
6.69
6.50
6.27
4.66
3.83
3.54
3.43
2.90
2.82
1.95
1.84
O
OH
N
O
C2F5
N
1H, CDCl3, 400 MHz
0.88
4.35
0.92
0.92
0.89
0.93
1.00
2.79
0.97
2.99
0.93
0.97
1.91
1.93
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


178.46
166.33
165.12
163.99
139.39
134.19
132.67
129.47
128.19
127.86
126.19
113.74
106.22
101.22
57.86
57.64
57.42
55.44
47.02
46.00
35.16
26.07
24.36
O
OH
N
O
C2F5
N
13C{1H}, CDCl3, 101 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



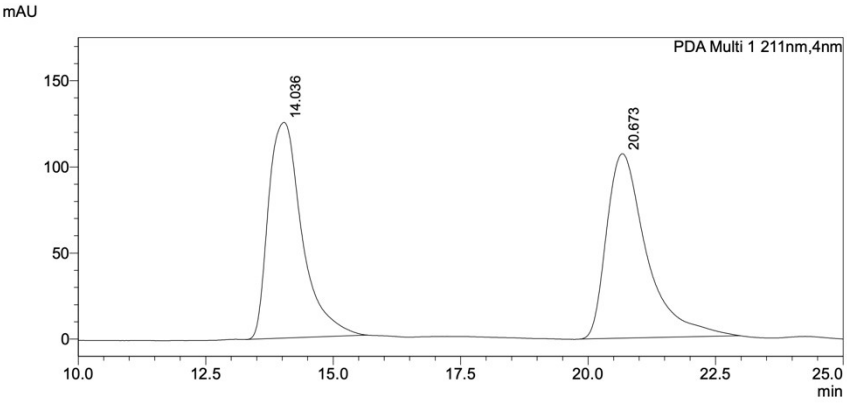
^{19}F, $CDCl_3$, 376 MHz

HPLC Data for **(*R*)-4,4,4-trifluoro-3-(((2-hydroxy-4-methoxyphenyl)methylene)amino)-1-(piperidin-1-yl)butan-1-one**: Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(*R*): 13.9 min, t_R(*S*): 20.6 min, 97:3 er.



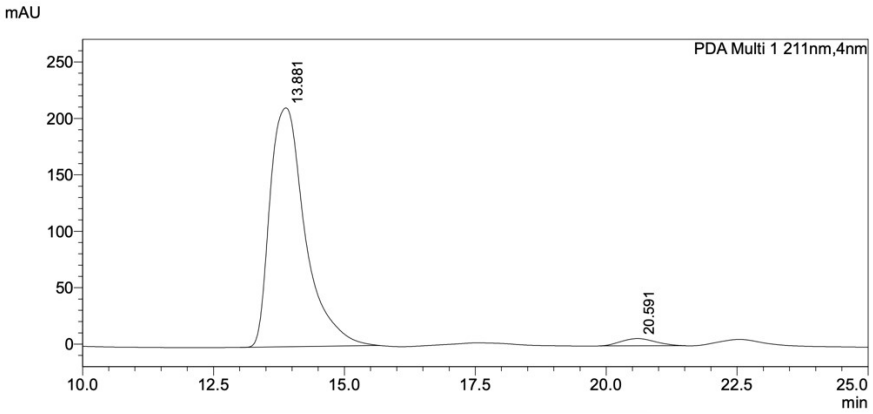
PDA Ch1 211nm

Peak#	Ret. Time	Area%
1	14.036	49.567
2	20.673	50.433
Total		100.000

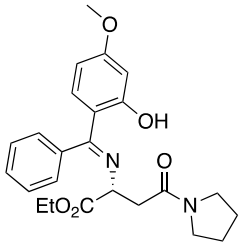


PDA Ch1 211nm

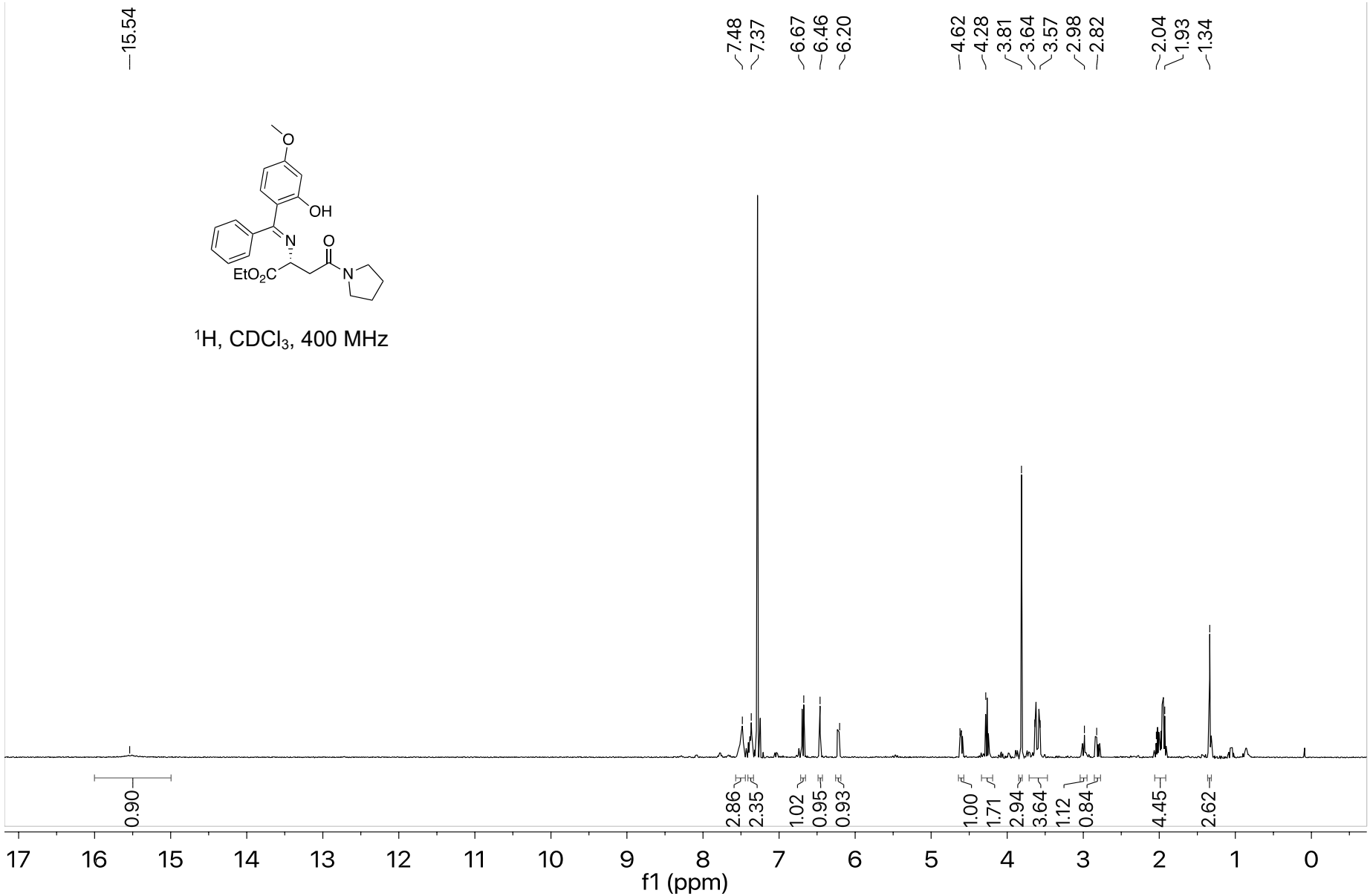
Peak#	Ret. Time	Area%
1	13.881	97.105
2	20.591	2.895
Total		100.000

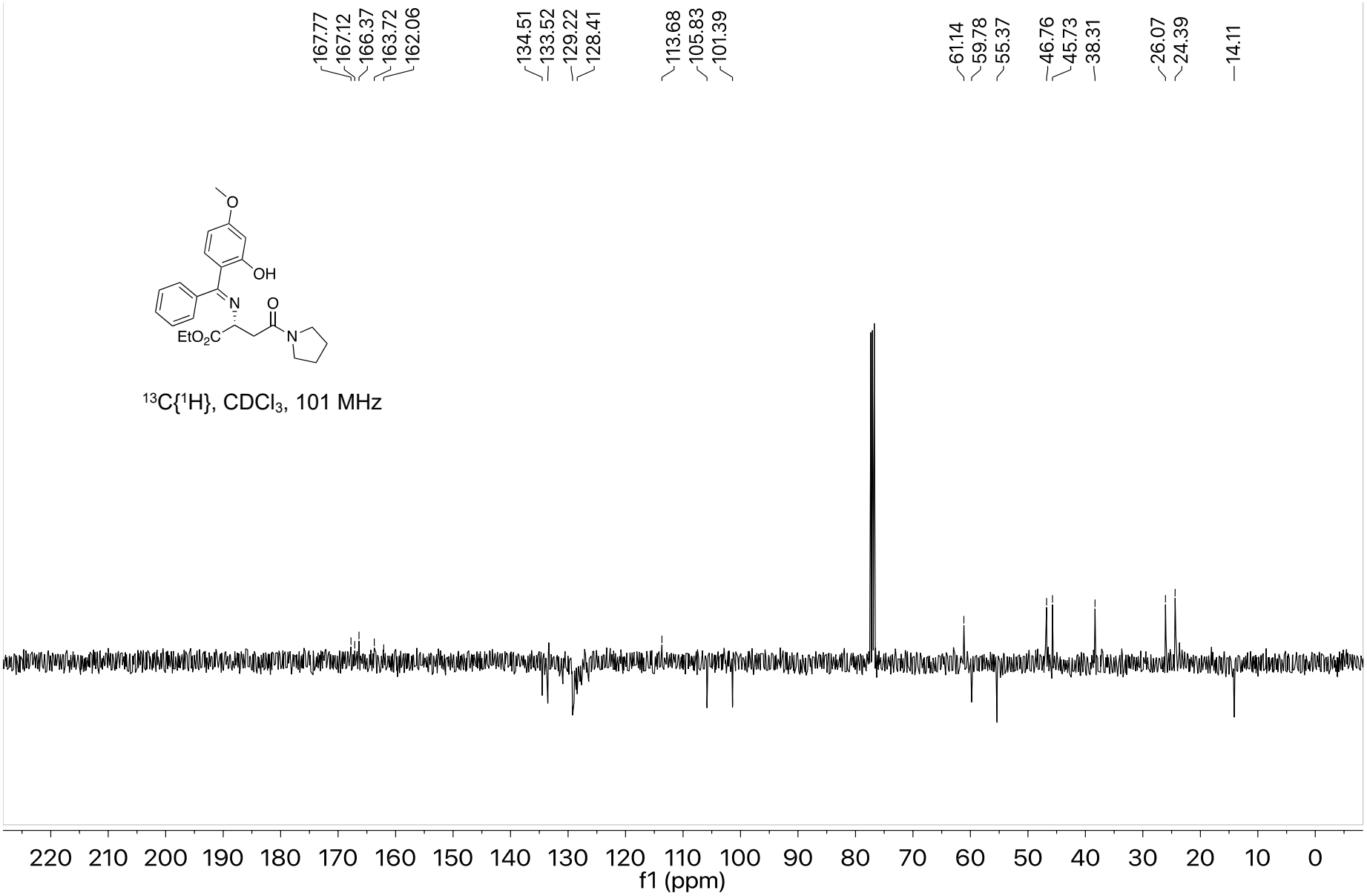


Ethyl (*R*)-2-(((2-hydroxy-4-methoxyphenyl)methylene)amino)-4-oxo-4-(pyrrolidin-1-yl)butanoate (18)

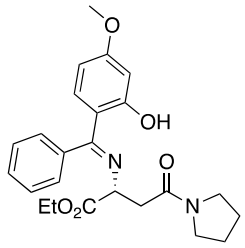


Following **General Procedure D,** ethyl (4-nitrophenyl)fumarate (26.3 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (45.4 mg, 0.2 mmol), (*R*)-(+)-BTM (5.1 mg, 0.02mmol), and toluene (0.1 M) was stirred at 40 º C for 30 hrs. Pyrrolidine was added (12.5 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was then purified by flash column chromatography with 5% MeOH in CH_2Cl_2 (R_f = 0.20) to give the titled compound (8.5 mg, 20%) as a yellow oil. $[\alpha]_D^{20}$ +2.94 (*c* = 1.10, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 270 nm, 30 °C) t_R(*S*): 34.5 min, t_R(*R*): 44.7 min, 96:4 er; **IR** ν_{max} (ATR), 2970 (Ar-H), 1637 (C=O), 1591 (C=N), 1442 (C=C), 1261 (CF_2Br); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.34 (3H, t, $^3J_{HH}$ = 7.1, $CO_2CH_2CH_3$), 1.93 – 2.04 (4H, m, NC(2)H_2C(3)H_2C(4)H_2C(5)H_2), 2.82 (1H, dd, $^2J_{HH}$ = 15.7, $^3J_{HH}$ = 7.7, COC(2)H_AH_B), 2.98 (1H, dd, $^2J_{HH}$ = 15.8, $^3J_{HH}$ = 5.6, COC(2)H_AH_B) 3.57 – 3.64 (4H, m, NC(2)H_2C(3)H_2C(4)H-$_2$C(5)H_2), 3.81 (3H, s, ArOH-OCH_3), 4.28 (2H, q, $^3J_{HH}$ = 7.1, $CO_2CH_2CH_3$), 4.62 (1H, dd, $^3J_{HH}$ = 7.6, $^3J_{HH}$ = 5.6, , $COCH_AH_BCH$), 6.20 (1H, dd, $^3J_{HH}$ = 8.9, $^4J_{HH}$ = 2.6, N=CC(5)Ar*H*OH-OCH_3), 6.46 (1H, d, $^4J_{HH}$ = 2.6, N=CC(3)Ar*H*OH-OCH_3), 6.67 (1H, d, $^3J_{HH}$ = 9.0, N=CC(6)Ar*H*OH-OCH_3), 7.37 (1H, m, N=CC(4)Ar*H*), 7.48 (4H, m, N=CC(2,3,5,6)Ar*H*), 15.5 (1H, s, N=CC(2)ArHO*H*-OCH_3). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 14.1 ($CO_2CH_2CH_3$), 24.4 (NC(2)H_2C(3)H_2C(4)H_2C(5)H_2), 26.1 (NC(2)H_2C(3)H_2C(4)H_2C(5)H_2), 38.3 (C=OCH_AH_BCHCO-$_2$Et), 45.7 (N*C*(2)H_2C(3)H_2C(4)H_2C(5)H_2), 46.8 (NC(2)H_2C(3)H_2C(4)H_2*C*(5)H_2), 55.4 (-OCH_3), 59.8 ($CHCO_2CH_2CH_3$), 61.1 ($CO_2CH_2CH_3$), 101.4 (N=C*C*(3)ArOH-OCH_3), 105.8 (N=C*C*(5)ArOH-OCH_3), 113.7 (N=C*C*(1)ArOH-OCH_3), 128.4 (N=C*C*(2,6)Ar), 129.22 (N=C*C*(3,4,5)Ar), 133.5 (N=C*C*(6)ArOH-OCH_3), 134.5 (N=C*C*(1)Ar), 162.1 (N=C*C*(2)ArOH-OCH_3), 163.7 (N=C*C*(4)ArOH-OCH_3), 166.4 (*C*=O$CH_AH_BCHCO_2Et$), 167.1 (C=O$CH_AH_BCHCO_2Et$), 167.8 (*C*=N). **HRMS** (NSI$^+$) $C_{24}H_{28}N_2O_5^+$ ([M+H]$^+$) requires 425.2071, found 425.2063 (-1.9 ppm).


15.54
7.48
7.37
6.67
6.46
6.20
4.62
4.28
3.81
3.64
3.57
2.98
2.82
2.04
1.93
1.34
O
OH
N
O
EtO2C
N
1H, CDCl3, 400 MHz
0.90
2.86
2.35
1.02
0.95
0.93
1.00
1.71
2.94
3.64
1.12
0.84
4.45
2.62
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

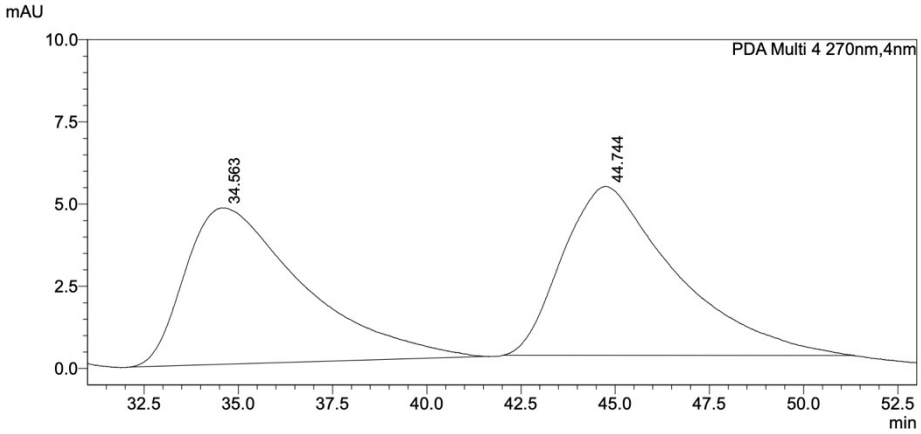

167.77
167.12
166.37
163.72
162.06
134.51
133.52
129.22
128.41
113.68
105.83
101.39
61.14
59.78
55.37
46.76
45.73
38.31
26.07
24.39
14.11
O
OH
N
O
EtO2C
N
13C{1H}, CDCl3, 101 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

HPLC Data for **Ethyl (*R*)-2-(((2-hydroxy-4-methoxyphenyl)methylene)amino)-4-oxo-4-(pyrrolidin-1-yl)butanoate**: Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 270 nm, 30 °C) t_R(*S*): 34.5 min, t_R(*R*): 44.7 min, 96:4 er.



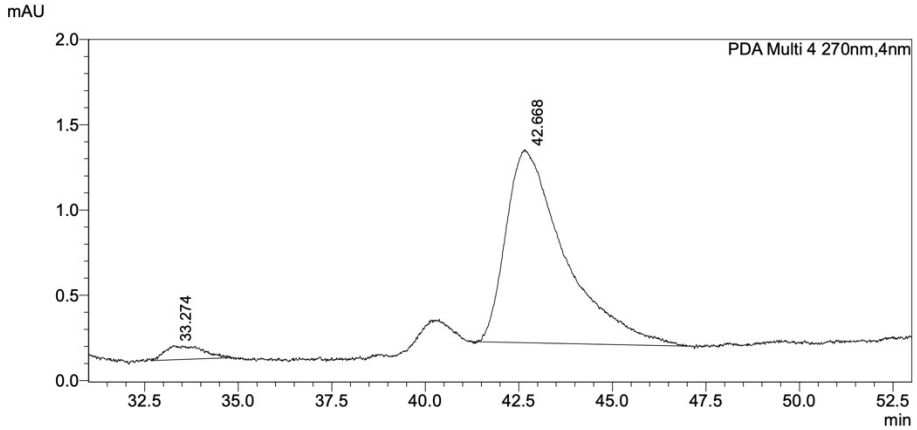
PDA Ch4 270nm

Peak#	Ret. Time	Area%
1	34.563	49.047
2	44.744	50.953
Total		100.000

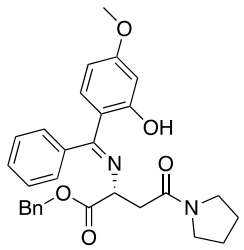


PDA Ch4 270nm

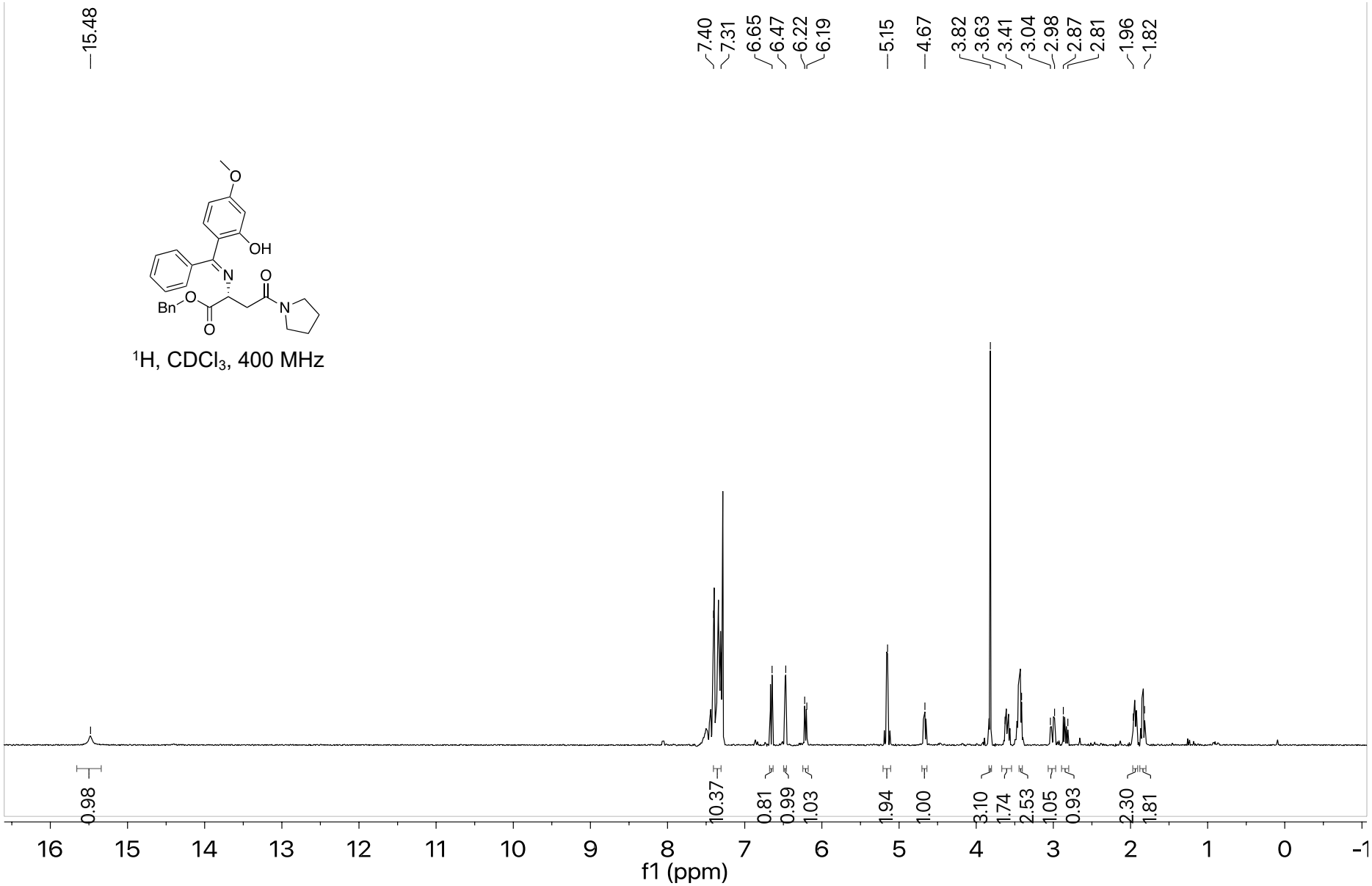
Peak#	Ret. Time	Area%
1	33.274	4.323
2	42.668	95.677
Total		100.000

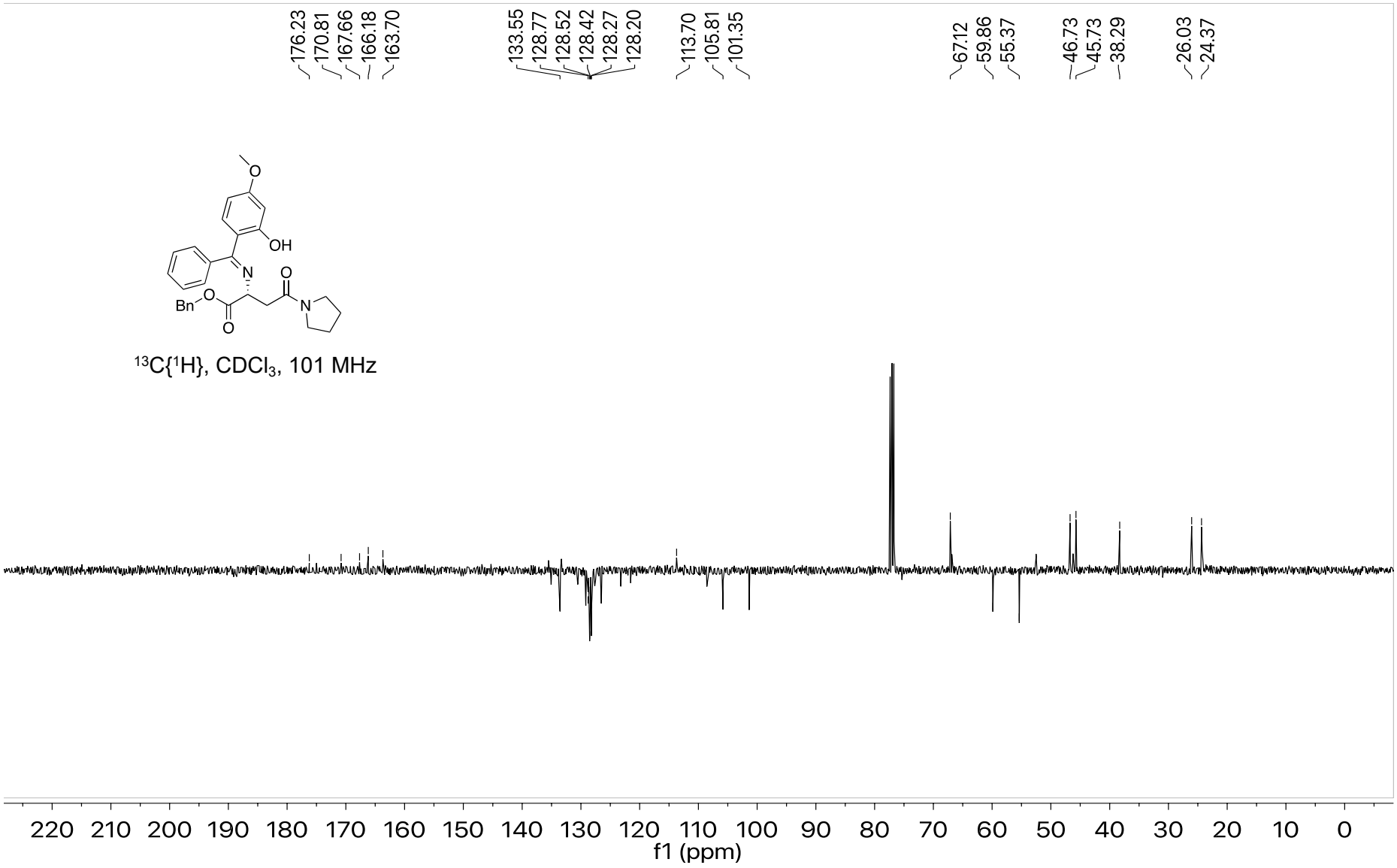


Benzyl (*R*)-2-(((2-hydroxy-4-methoxyphenyl)(phenyl)methylene)amino)-4-oxo-4-(pyrrolidin-1-yl)butanoate (19)

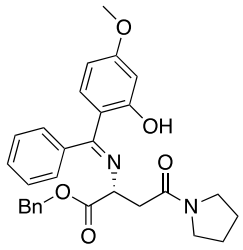


Following **General Procedure D,** Benzyl (4-nitrophenyl)fumarate (32.7 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (45.4 mg, 0.2 mmol), (*R*)-(+)-BTM (5.1 mg, 0.02mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Pyrrolidine was added (12.3 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was then purified by flash column chromatography with 5% MeOH in CH_2Cl_2 (R_f = 0.42) to give the titled compound (9.7 mg, 20%) as a yellow oil. $[\alpha]_D^{20}$ +2.71 (*c* = 2.9, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(*R*): 35.0 min, t_R(*S*): 44.7 min, 87:13 er; **IR** ν_{max} (ATR), 2970 (Ar-H), 1736 (CO_2Bn), 1639 (C=O), 1593 (C=N), 1443 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.80 – 1.98 (4H, m, NC(2)H_2C(3)*H*$_2$C(4)*H*$_2$C(5)H_2), 2.84 (1H, dd, $^2J_{HH}$ = 15.8, $^3J_{HH}$ = 7.7, O=CC(2)*H*$_A$H$_B$), 3.01 (1H, dd, $^2J_{HH}$ = 15.8, $^3J_{HH}$ = 5.6, O=CC(2)H$_A$*H*$_B$), 3.40 – 3.64 (4H, m, NC(2)*H*$_2$C(3)H$_2$C(4)H$_2$C(5)*H*$_2$), 3.82 (3H, s, -OC*H*$_3$), 4.67 (1H, dd, $^3J_{HH}$ = 7.5, $^3J_{HH}$ = 5.5, O=CCH$_A$H$_B$C(3)*H*), 5.17 (2H, m, CO_2C*H*$_2$Ph), 6.21 (1H, dd, $^3J_{HH}$ = 8.9, $^4J_{HH}$ = 2.6, N=CC(5)Ar*H*OH-OCH$_3$), 6.47 (1H, dd, $^4J_{HH}$ = 2.6, N=CC(3)Ar*H*OH-OCH$_3$), 6.66 (1H, d, $^3J_{HH}$ = 8.9, N=CC(6)Ar*H*OH-OCH$_3$), 7.30 – 7.46 (10H, m, N=CC(2,3,4,5,6)Ar*H* & CO_2CH_2C(2,3,4,5,6)Ar*H*), 15.5 (1H, bs, -O*H*). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 24.4 – 26.0 (NC(2)H$_2$*C*(3)H$_2$*C*(4)H$_2$C(5)H$_2$), 38.3 (O=C*C*(2)H$_A$H$_B$), 45.7 – 46.7 (N*C*(2)H$_2$C(3)H$_2$C(4)H$_2$*C*(5)H$_2$), 55.4 (-O*C*H$_3$), 59.9 (O=CCH$_A$H$_B$*C*(3)H), 67.1 (CO_2*C*H$_2$Ph), 101.4 (N=C*C*(3)ArOH-OCH$_3$), 105.8 (N=C*C*(5)ArOH-OCH$_3$), 113.7 (N=C*C*(1)ArOH-OCH$_3$), 128.2 (N=C*C*(2,6)Ar), 128.3 (N=C*C*(1,3,5)Ar & CO_2CH_2*C*(1)Ar), 128.4 (N=C*C*(4)Ar), 128.5 (CO_2CH_2*C*(3,5)Ar), 128.8 (CO_2CH_2*C*(4)Ar), 133.6 (N=C*C*(6)ArOH-OCH$_3$), 163.7 (N=C*C*(4)ArOH-OCH$_3$), 166.2 (N=C*C*(2)ArOH-OCH$_3$), 167.7 (*C*=O-pyrrolidinyl), 170.8 (*C*O_2CH_2Ph), 176.2 (*C*=N). **HRMS** (NSI$^+$) $C_{29}H_{30}N_2O_5^+$ ([M+H]$^+$) requires 487.2228, found 487.2222 (-1.2 ppm).


15.48
7.40
7.31
6.65
6.47
6.22
6.19
5.15
4.67
3.82
3.63
3.41
3.04
2.98
2.87
2.81
1.96
1.82
OH
N
O
Bn
O
O
N
O
^{1}H, CDCl$_3$, 400 MHz
0.98
10.37
0.81
0.99
1.03
1.94
1.00
3.10
1.74
2.53
1.05
0.93
2.30
1.81
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

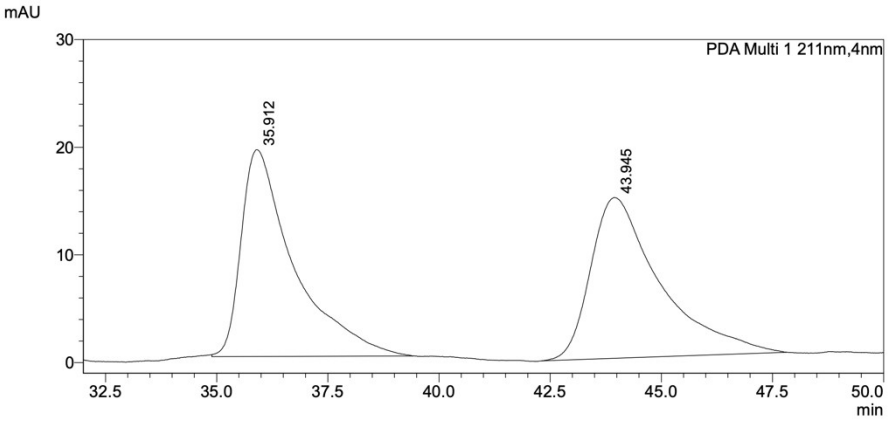

176.23
170.81
167.66
166.18
163.70
133.55
128.77
128.52
128.42
128.27
128.20
113.70
105.81
101.35
67.12
59.86
55.37
46.73
45.73
38.29
26.03
24.37
O
OH
N
O
Bn
O
O
N
13C{1H}, CDCl3, 101 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

HPLC Data for **Benzyl (*R*)-2-(((2-hydroxy-4-methoxyphenyl)(phenyl)methylene)amino)-4-oxo-4-(pyrrolidin-1-yl)butanoate**: Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(*R*): 35.0 min, t_R(*S*): 44.7 min, 87:13 er.



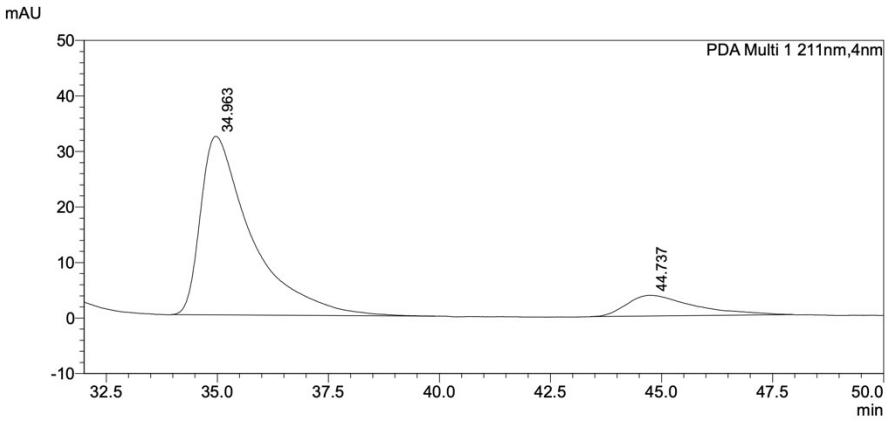
PDA Ch1 211nm

Peak#	Ret. Time	Area%
1	35.912	49.442
2	43.945	50.558
Total		100.000

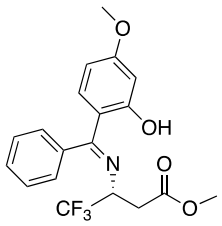


PDA Ch1 211nm

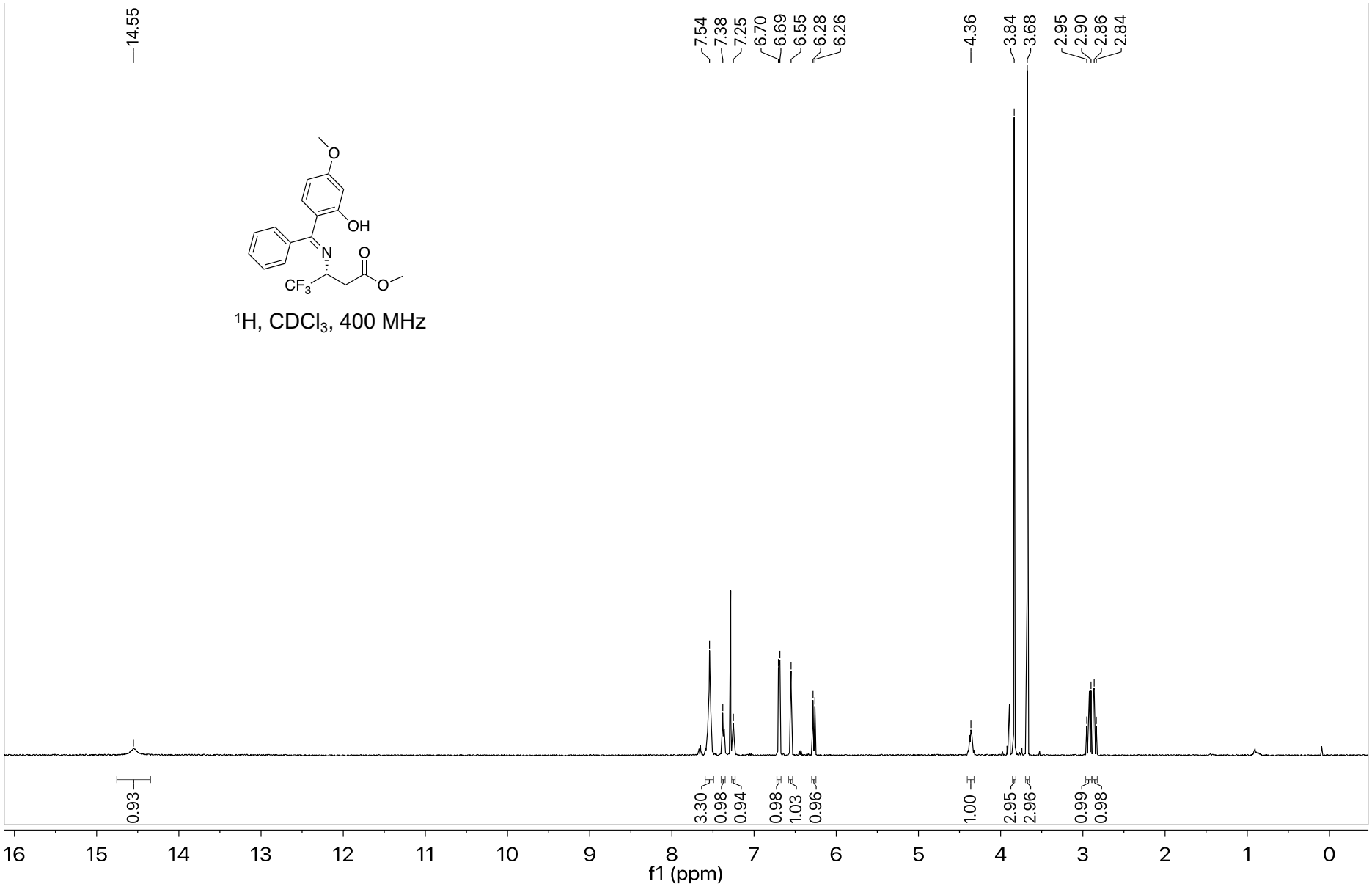
Peak#	Ret. Time	Area%
1	34.963	86.658
2	44.737	13.342
Total		100.000

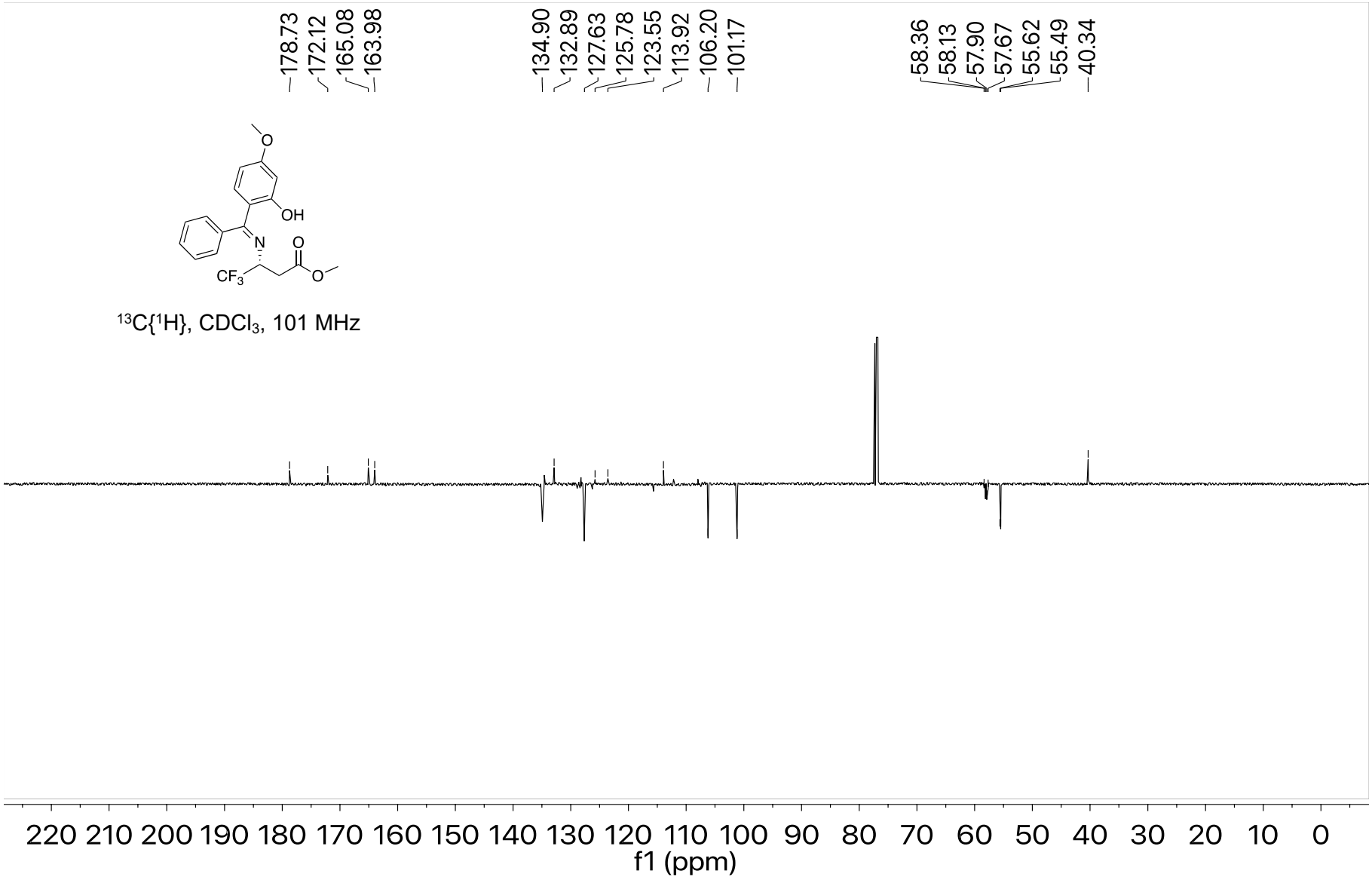


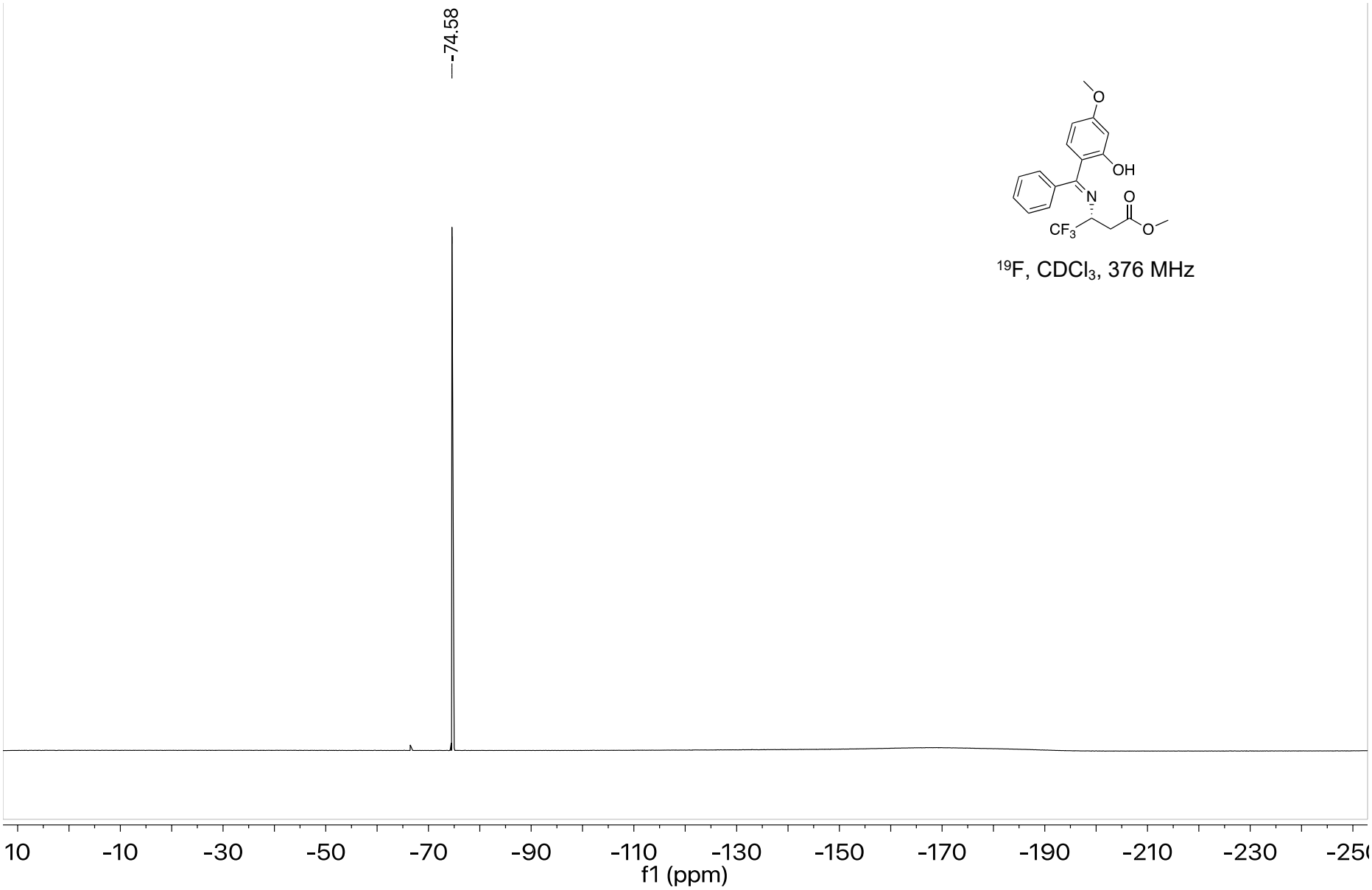
Methyl (*R*)-4,4,4-trifluoro-3-(((2-hydroxy-4-methoxyphenyl)(phenyl)methylene) amino)butanoate (20)



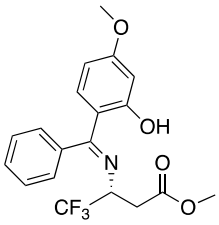
Following **General Procedure D,** 4-nitrophenyl (*E*)-4,4,4-trifluorobut-2-enoate (26.1 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (45.4 mg, 0.2 mmol), (*R*)-(+)-BTM (5.1 mg, 0.02mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Methanol (12.5 µL, 0.15 mmol) and DMAP (2.5 mg, 20 mol%) was added and the reaction was stirred at rt for 16 hrs. The crude mixture was then purified by flash column chromatography (10:1 Petrol:Ethyl acetate) (R_f = 0.13) to give the titled compound (24.4 mg, 64 %) as a yellow oil. $[\alpha]_D^{20}$ +91.9 (*c* = 0.36, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak AD-H (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(*R*): 5.92 min, t_R(*S*): 9.13 min, 97: 3 er; **IR** ν_{max} (ATR), 2957 (Ar-H), 1743 (C=O), 1593 – 1605 (C=N), 1442 (C=C), 1261 (CF_3); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 2.84 – 2.86 (1H, dd, $^2J_{HH}$ = 16.3, $^3J_{HH}$ = 3.7, COC(2)H_AH_B), 2.90 – 2.95 (1H, dd, $^2J_{HH}$ = 16.3, $^3J_{HH}$ = 9.2, COC(2)H_AH_B), 3.68 (3H, s, CO_2CH_3), 3.84 (3H, s, ArOH-OCH_3), 4.36 (1H, m, $COCH_AH_BC(3)H$), 6.26 – 6.28 (1H, dd, $^3J_{HH}$ = 9.0, $^4J_{HH}$ = 2.6, N=CC(5)Ar*H*OH-OCH_3), 6.55 – 6.56 (1H, d, $^4J_{HH}$ = 2.6, N=CC(3)Ar*H*OH-OCH_3), 6.69 – 6.73 (1H, d, $^3J_{HH}$ = 9.0, N=CC(6)Ar*H*OH-OCH_3), 7.26 (1H, m, N=CC(2)Ar*H*), 7.37 (1H, m, N=CC(6)Ar*H*), 7.55 (3H, m, N=CC(3,4,5)Ar*H*), 14.6 (1H, s, -O*H*); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$): -74.58 (-CF_3); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 40.3 (CO*C*(2)$H_AH_BCHCF_3$), 55.9 (CO_2CH_3), 57.7 (ArOH-OCH_3), 58.0 (q, $^3J_{CF}$ = 28.9, $COCH_AH_BCHCF_3$), 101.2 (N=C*C*(3)ArOH-OCH_3), 106.2 (N=C*C*(5)ArOH-OCH_3), 113.9 (N=C*C*(1)ArOH-OCH_3), 123.6 (N=C*C*(1)Ar), 125.8 (-*C*F_3), 127.6 (N=C*C*(2,6)Ar), 132.9 (N=C*C*(3,4,5)Ar), 134.9 (N=C*C*(6)ArOH-OCH_3), 163.9 (N=C*C*(2)ArOH-OCH_3), 165.1 (N=C*C*(4)ArOH-OCH_3), 172.1 (*C*O_2CH_3), 178.8 (*C*=N); **HRMS** (NSI$^+$) $C_{19}H_{18}F_3NO_4^+$ ([M+H]$^+$) requires 382.1261, found 382.1255 (-1.6 ppm).


14.55
7.54
7.38
7.25
6.70
6.69
6.55
6.28
6.26
4.36
3.84
3.68
2.95
2.90
2.86
2.84
O
OH
N
O
CF3
O
1H, CDCl3, 400 MHz
0.93
3.30
0.98
0.94
0.98
1.03
0.96
1.00
2.95
2.96
0.99
0.98
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


178.73
172.12
165.08
163.98
134.90
132.89
127.63
125.78
123.55
113.92
106.20
101.17
58.36
58.13
57.90
57.67
55.62
55.49
40.34
O
OH
N
O
CF3
O
13C{1H}, CDCl3, 101 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

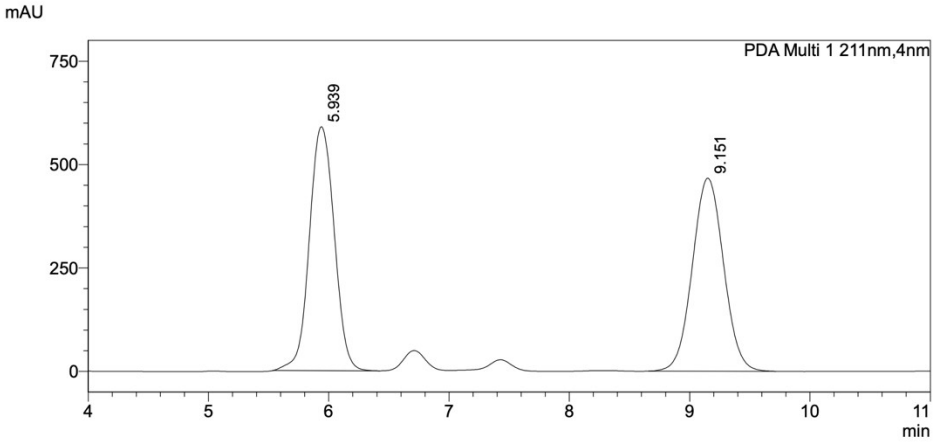

-74.58
O
OH
N
O
CF3
O
19F, CDCl3, 376 MHz
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
-230
f1 (ppm)

HPLC Data for **methyl (*R*,*E*)-4,4,4-trifluoro-3-(((2-hydroxy-4-methoxyphenyl)(phenyl)methylene)amino)butanoate**: Chiralpak AD-H (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(*R*): 5.92 min, t_R(*S*): 9.13 min, 97:3 er.



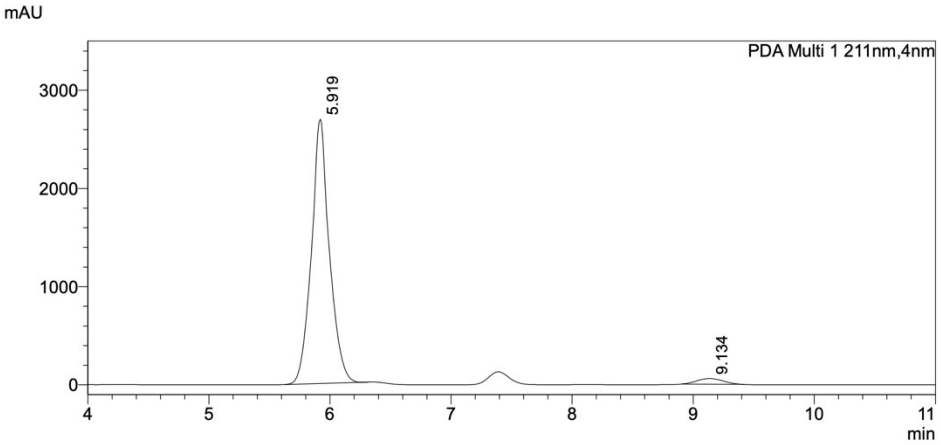
PDA Ch1 211nm

Peak#	Ret. Time	Area%
1	5.939	50.188
2	9.151	49.812
Total		100.000

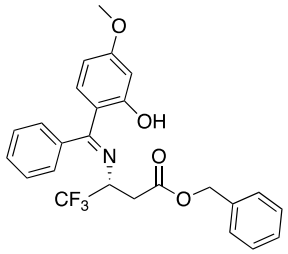


PDA Ch1 211nm

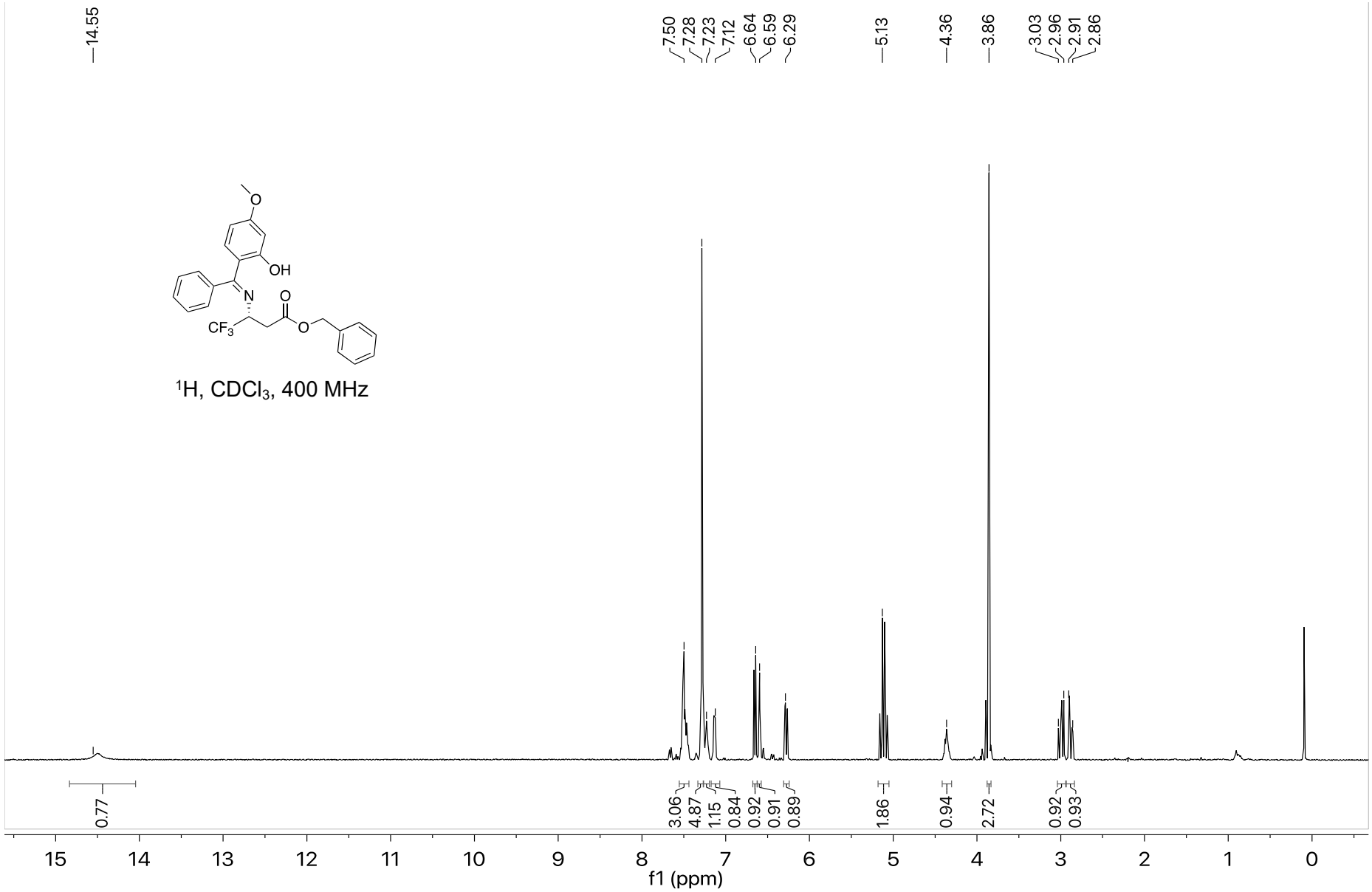
Peak#	Ret. Time	Area%
1	5.919	96.965
2	9.134	3.035
Total		100.000

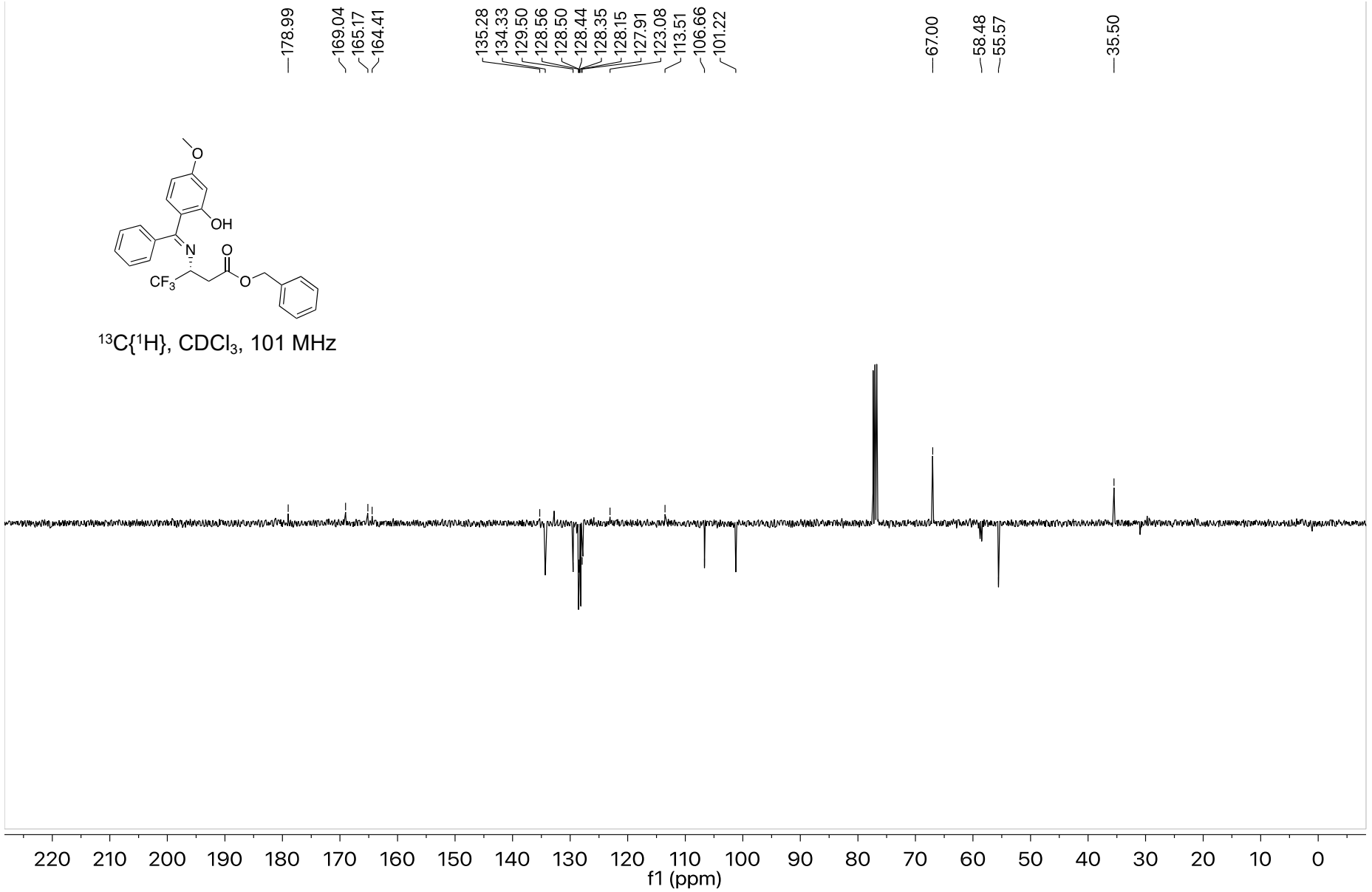


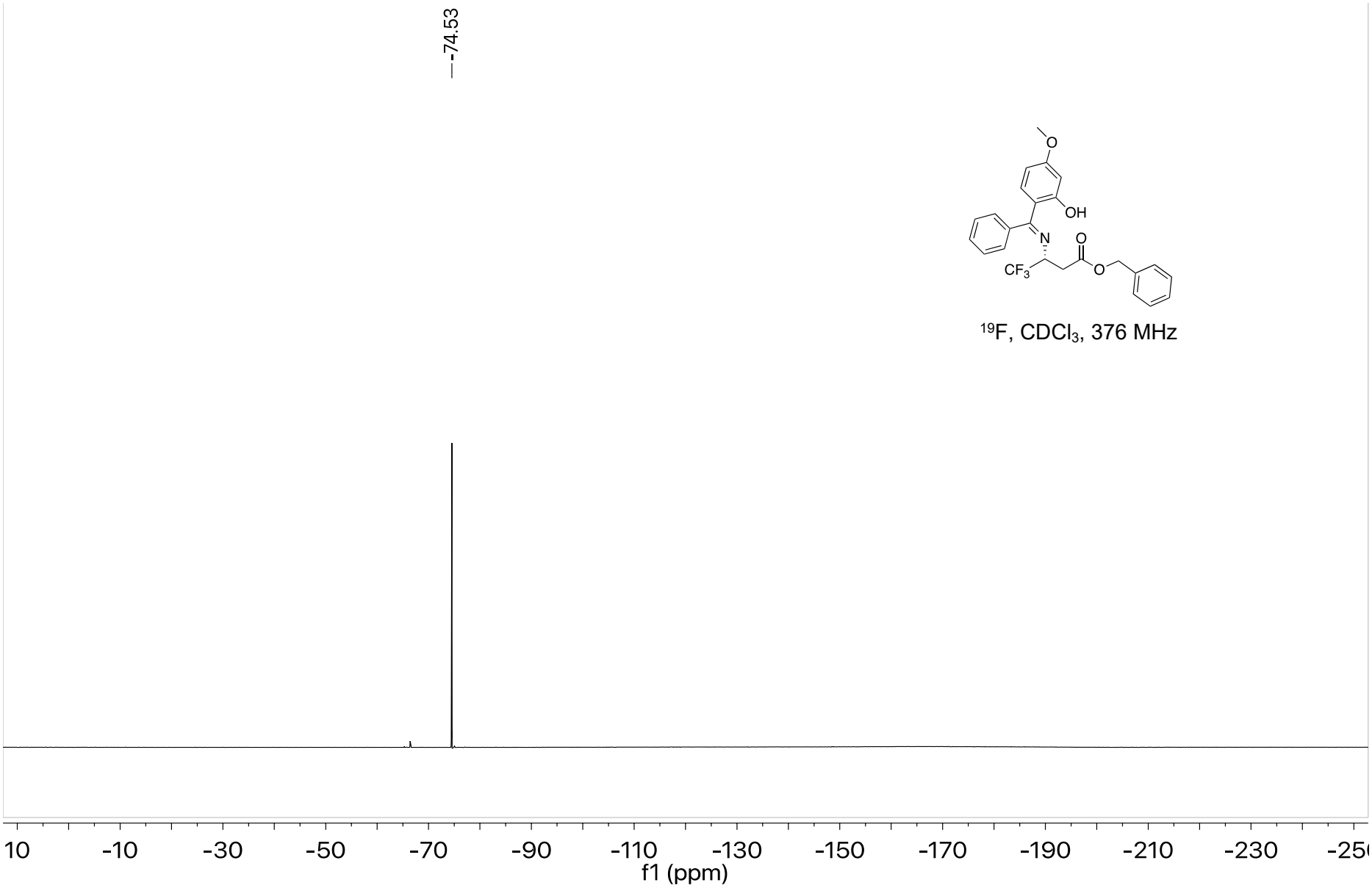
Benzyl (*R*)-4,4,4-trifluoro-3-(((2-hydroxy-4-methoxyphenyl)(phenyl)methylene)amino) butanoate (21)



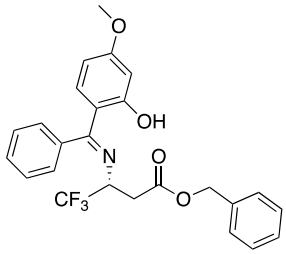
Following **General Procedure D,** 4-nitrophenyl (*E*)-4,4,4-trifluorobut-2-enoate (26.1 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (45.4 mg, 0.2 mmol), (*R*)-(+)-BTM (5.1 mg, 0.02mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Benzylalcohol (12.5 µL, 0.15 mmol) and DMAP (2.5 mg, 20 mol%) was added and the reaction was stirred at rt for 16 hrs. The crude mixture was then purified by flash column chromatography (10:1 Petrol:Ethyl acetate) (R_f = 0.33) to give the titled compound (19.3 mg, 42%) as a yellow oil. $[\alpha]_D^{20}$ +78.4 (*c* = 0.45, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak AD-H (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(*R*): 8.13 min, t_R(*S*): 10.8 min, 96:4 er; **IR** ν_{max} (ATR), 2933 (Ar-H), 1741 (C=O), 1593 – 1616 (C=N), 1444 (C=C), 1261 (CF_3); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 2.86 – 2.91 (1H, dd, $^2J_{HH}$ = 15.9, $^3J_{HH}$ = 3.6, COC(2)H_AH_B), 2.96 – 3.03 (1H, dd, $^2J_{HH}$ = 16.0, $^3J_{HH}$ = 9.5, COC(2)H_AH_B), 3.86 (3H, s, ArOH-OCH_3), 4.36 (1H, m, COCH_AH_BC(3)*H*), 5.12 (2H, m, CO_2CH_2Ph), 6.28 (1H, dd, $^3J_{HH}$ = 9.0, $^4J_{HH}$ = 2.5, N=CC(5)Ar*H*OH-OCH_3), 6.60 (1H, d, $^4J_{HH}$ = 2.5, N=CC(3)Ar*H*OH-OCH_3), 6.65 (1H, d, $^3J_{HH}$ = 9.0, N=CC(6)Ar*H*OH-OCH_3), 7.13 – 7.23 (2H, m, N=CC(2,6)Ar*H*), 7.28 (5H, m, CO_2CH_2C(2,3,4,5,6)Ar*H*), 7.49 (3H, m, N=CC(3,4,5)Ar*H*), 14.5 (1H, bs, -O*H*); **^{19}F NMR (376 MHz)**: -74.5 (-CF_3); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 33.5 (CO*C*(2)H_AH_BCHCF_3), 55.6 (-O*C*H_3), 58.5 (COCH_AH_BC*H*CF_3), 67.0 (CO_2*C*H_2Ph), 101.2 (N=C*C*(3)ArOH-OCH_3), 106.7 (N=C*C*(5)ArOH-OCH_3), 113.5 (N=C*C*(1)ArOH-OCH_3), 123.1 (-*C*F_3),127.9 (N=C*C*(1)Ar), 128.2 (N=C*C*(2,6)Ar), 128.3 (CO_2CH_2*C*(2,6)Ar), 128.4 – 128.5 (CO_2CH_2*C*(3,4,5)Ar), 128.6 (N=C*C*(3,4,5)Ar), 134.3 (N=C*C*(6)ArOH-OCH_3), 135.3 (CO_2CH_2*C*(1)Ar), 164.4 (N=C*C*(2)ArOH-OCH_3), 165.2 (N=C*C*(3)ArOH-OCH_3), 169.0 (*C*=O), 179.0 (*C*=N). **HRMS** (NSI$^+$) $C_{25}H_{23}F_3NO_4^+$ ([M+H]$^+$) requires 458.1574, found 458.1563 (-2.4 ppm).


14.55
7.50
7.28
7.23
7.12
6.64
6.59
6.29
5.13
4.36
3.86
3.03
2.96
2.91
2.86
O
OH
N
O
CF3
O
1H, CDCl3, 400 MHz
0.77
3.06
4.87
1.15
0.84
0.92
0.91
0.89
1.86
0.94
2.72
0.92
0.93
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


178.99
169.04
165.17
164.41
135.28
134.33
129.50
128.56
128.50
128.44
128.35
128.15
127.91
123.08
113.51
106.66
101.22
67.00
58.48
55.57
35.50
O
OH
N
O
CF3
O
13C{1H}, CDCl3, 101 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

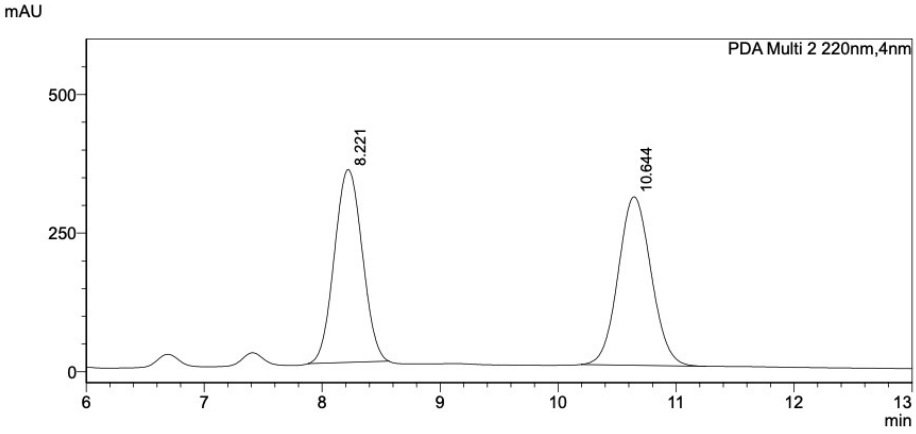

-74.53
O
OH
N
O
CF3
O
19F, CDCl3, 376 MHz
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
-230
f1 (ppm)

HPLC Data for **Benzyl (*R*)-4,4,4-trifluoro-3-(((2-hydroxy-4-methoxyphenyl)(phenyl)methylene)amino)butanoate**: Chiralpak AD-H (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(*R*): 8.13 min, t_R(*S*): 10.8 min, 96:4 er.



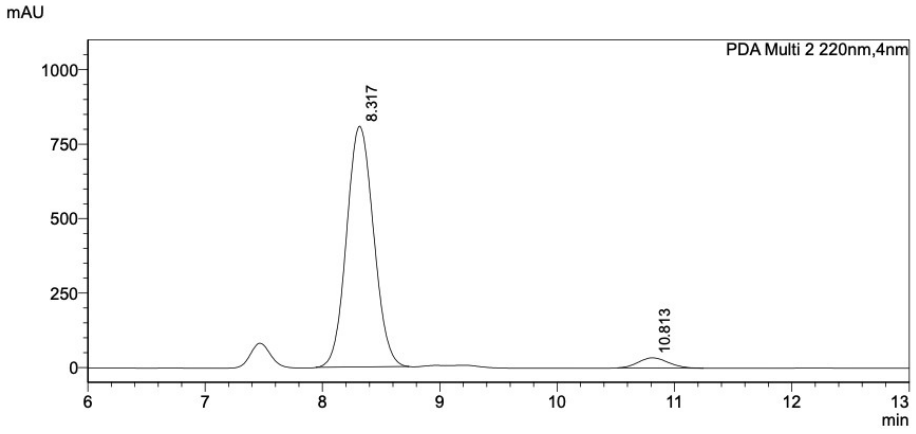
PDA Ch2 220nm

Peak#	Ret. Time	Area%
1	8.221	49.242
2	10.644	50.758
Total		100.000

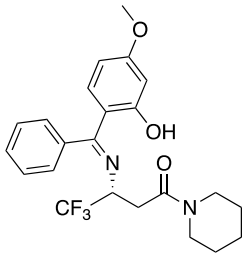


PDA Ch2 220nm

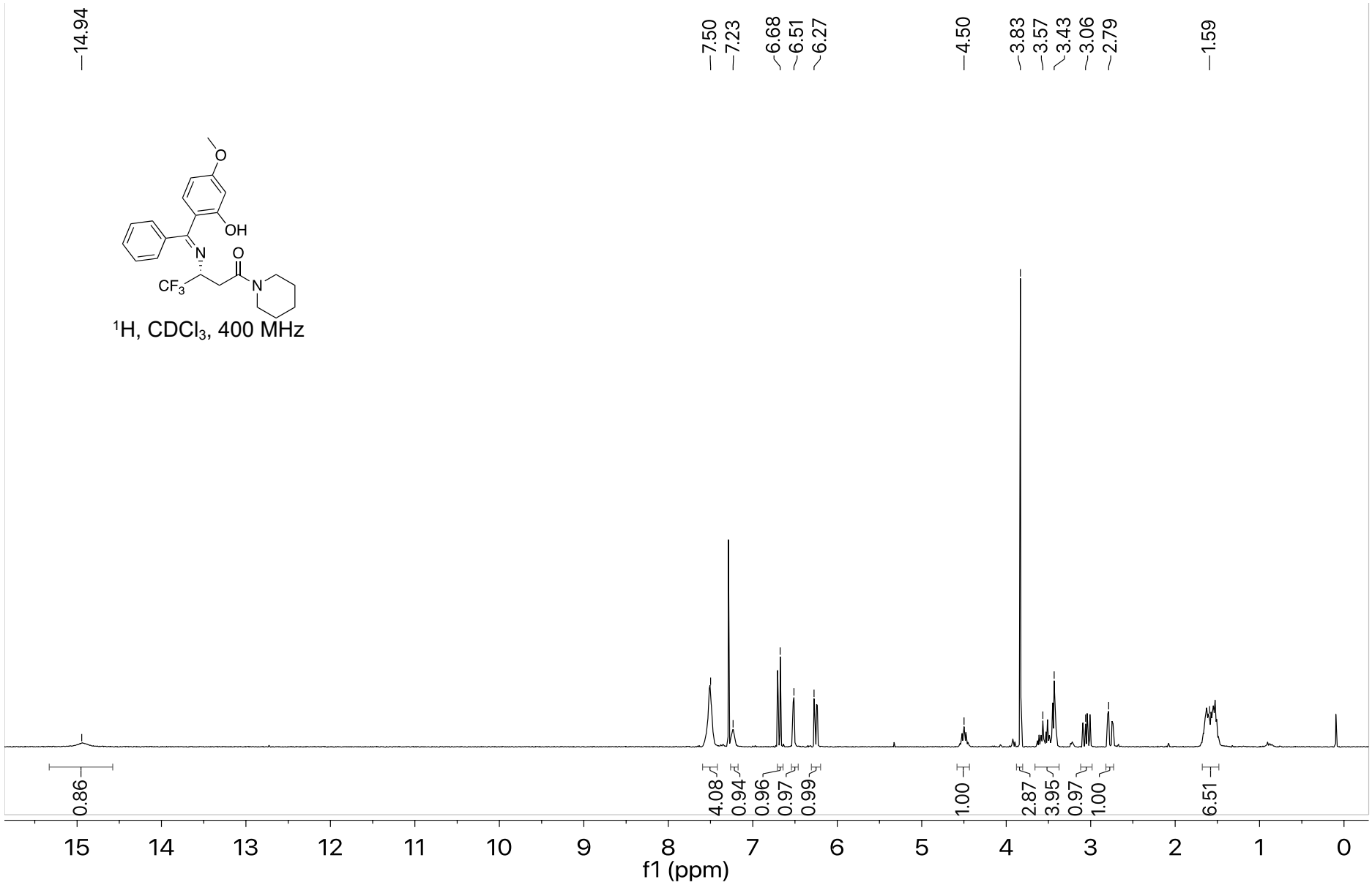
Peak#	Ret. Time	Area%
1	8.317	95.555
2	10.813	4.445
Total		100.000

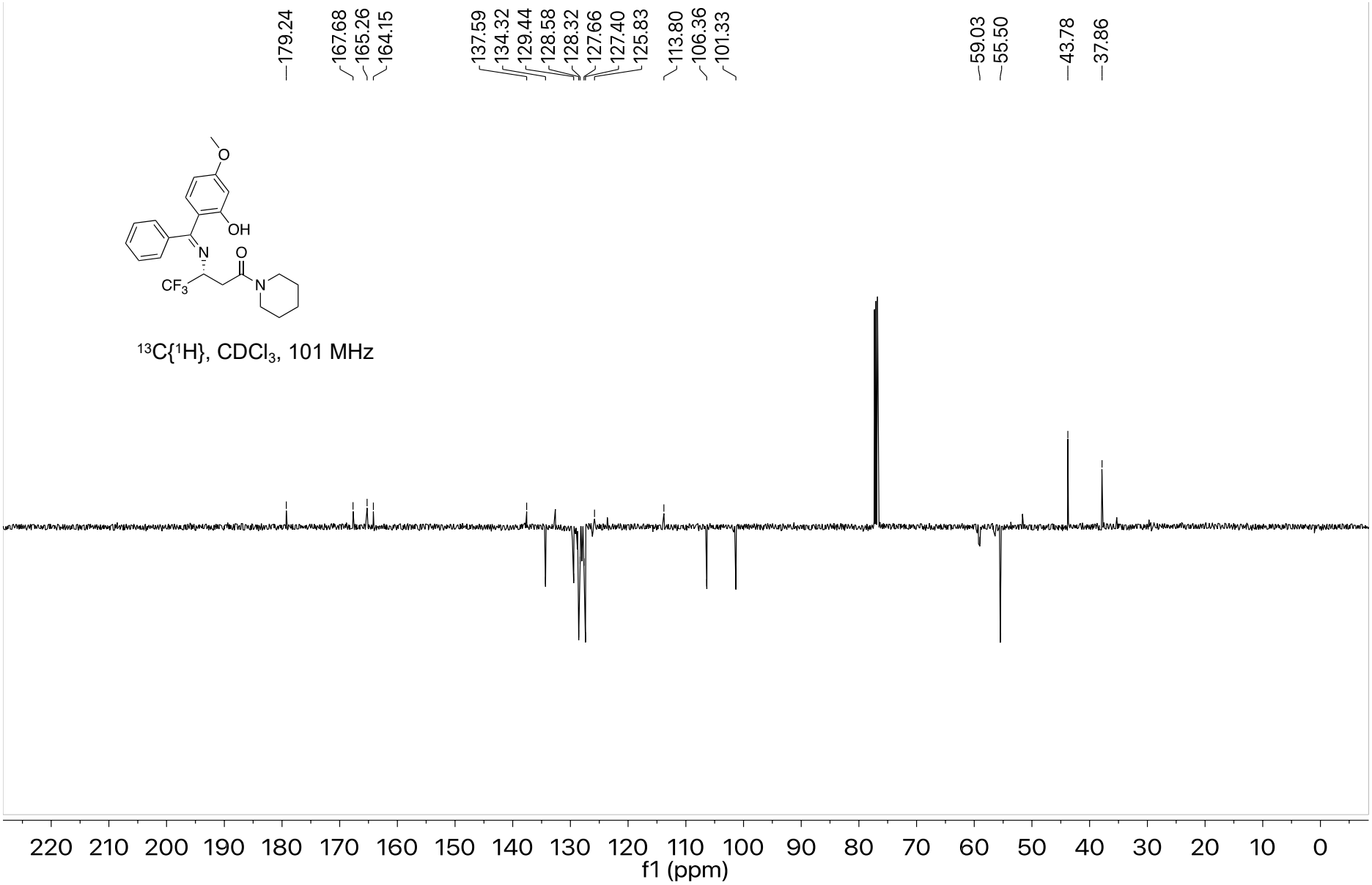


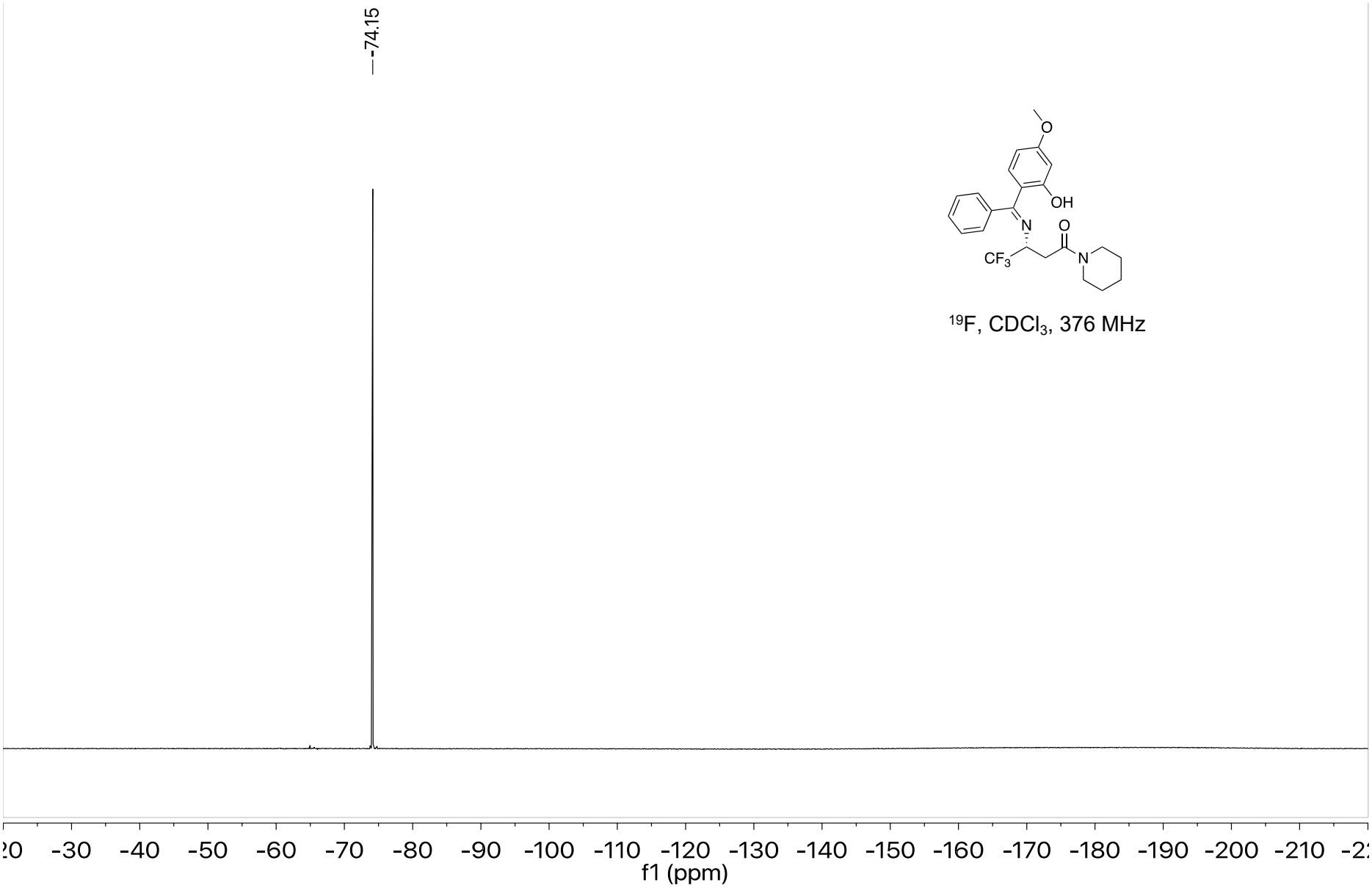
(*R*)-4,4,4-trifluoro-3-(((2-hydroxy-4-methoxyphenyl)methylene)amino)-1-(piperidin-1-yl)butan-1-one (22)



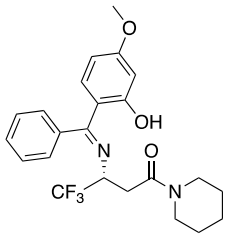
Following **General Procedure D,** 4-nitrophenyl (*E*)-4,4,4-difluorobut-2-enoate (26.1 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (45.4 mg, 0.2 mmol), (*R*)-(+)-BTM (5.1 mg, 0.02mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Piperidine was added (14.8 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was then purified by flash column chromatography Hexane:EtOAc (4:1) (R_f = 0.21) to give the titled compound (23.0 mg, 53%) as a yellow oil. $[\alpha]_D^{20}$ +89.0 (*c* = 0.50, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak AD-H (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 220 nm, 30 °C) t_R(*S*): 12.2 min, t_R(*R*): 16.3 min, 96:4 er; **IR** ν_{max} (ATR), 2941 (Ar-H), 1620 (C=O), 1593 (C=N), 1445 (C=C), 1259 (CF_3); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.59 (6H, m, NC(2)H_2C(3)*H*$_2$C(4)*H*-$_2$C(5)*H*$_2$C(6)H_2), 2.79 (1H, dd, $^2J_{HH}$ = 15.4, $^3J_{HH}$ = 3.0, O=CC(2)*H*$_A$H$_B$), 3.06 (1H, dd, $^2J_{HH}$ = 15.4, $^3J_{HH}$ = 9.5, O=CC(2)H$_A$*H*$_B$), 3.43 – 3.57 (4H, m, NC(2)*H*$_2$C(3)H$_2$C(4)H$_2$C(5)H$_2$C(6)*H*$_2$), 3.83 (3H, s, -OC*H*$_3$), 4.50 (1H, m, O=CCH$_A$H$_B$C(3)*H*), 6.27 (1H, dd, $^3J_{HH}$ =9.0, $^4J_{HH}$ = 2.6, N=CC(5)Ar*H*OH-OCH$_3$), 6.51 (1H, d, $^4J_{HH}$ = 2.6, N=CC(3)Ar*H*OH-OCH$_3$), 6.68 (1H, d, $^3J_{HH}$ = 9.0, N=CC(6)Ar*H*OH-OCH$_3$), 7.23 (1H, s, N=CC(2)Ar*H*), 7.50 (4H, m, N=CC(3,4,5,6)Ar*H*), 14.9 (1H, s, -O*H*). **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -74.15 (-C*F*$_3$); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 37.9 (O=C*C*(2)H$_A$H$_B$), 43.9 (NH*C*H$_2$Ph), 55.5 (-O*C*H$_3$), 58.8 – 59.4 (q, $^2J_{CF}$ = 23.3 O=CCH$_A$H$_B$*C*(3)H), 101.3 (N=C*C*(3)ArOH-OCH$_3$), 106.4 (N=C*C*(5)ArOH-OCH$_3$), 113.8 (N=C*C*(1)ArOH-OCH$_3$), 125.8 (-*C*F$_3$), 127.4 (NHCH$_2$*C*(3,4,5)Ph), 127.6 (N=C*C*(2,6)ArH), 128.3 (NHCH$_2$*C*(2,6)Ph), 128.5 (N=C*C*(1)Ar), 129.4 (NHCH$_2$*C*(1)Ph), 164.2 (N=C*C*(2)ArOH-OCH$_3$), 165.3 (N=C*C*(4)ArOH-OCH$_3$), 167.8 (*C*=O), 179.2 (*C*=N). **HRMS** (NSI$^+$) $C_{23}H_{25}F_3N_2O_4^+$ ([M+H]$^+$) requires 435.1890, found 435.1878 (-2.8 ppm).


14.94
7.50
7.23
6.68
6.51
6.27
4.50
3.83
3.57
3.43
3.06
2.79
1.59
O
OH
N
O
CF3
N
1H, CDCl3, 400 MHz
0.86
4.08
0.94
0.96
0.97
0.99
1.00
2.87
3.95
0.97
1.00
6.51
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


179.24
167.68
165.26
164.15
137.59
134.32
129.44
128.58
128.32
127.66
127.40
125.83
113.80
106.36
101.33
59.03
55.50
43.78
37.86
O
OH
N
O
CF3
N
13C{1H}, CDCl3, 101 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

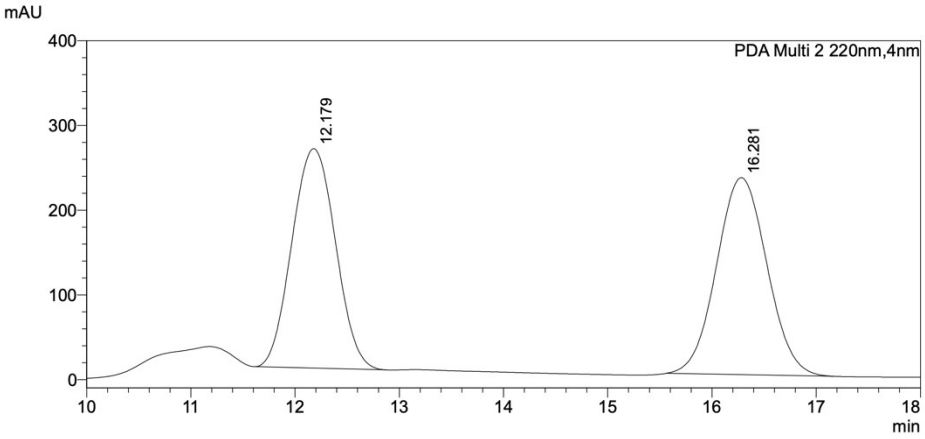

-74.15
O
OH
N
O
CF3
N
19F, CDCl3, 376 MHz
-30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

HPLC Data for **(*R*)-4,4,4-trifluoro-3-(((2-hydroxy-4-methoxyphenyl)methylene)amino)-1-(piperidin-1-yl)butan-1-one**: Chiralpak AD-H (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 220 nm, 30 °C) t_R(*R*): 12.2 min, t_R(*S*): 16.3 min, 96:4 er.



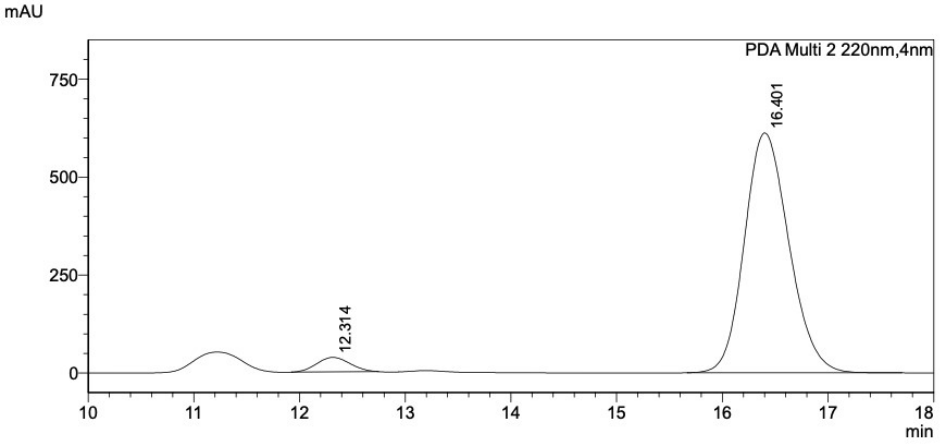
PDA Ch2 220nm

Peak#	Ret. Time	Area%
1	12.179	49.056
2	16.281	50.944
Total		100.000

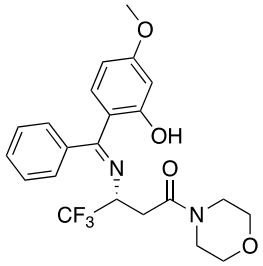


PDA Ch2 220nm

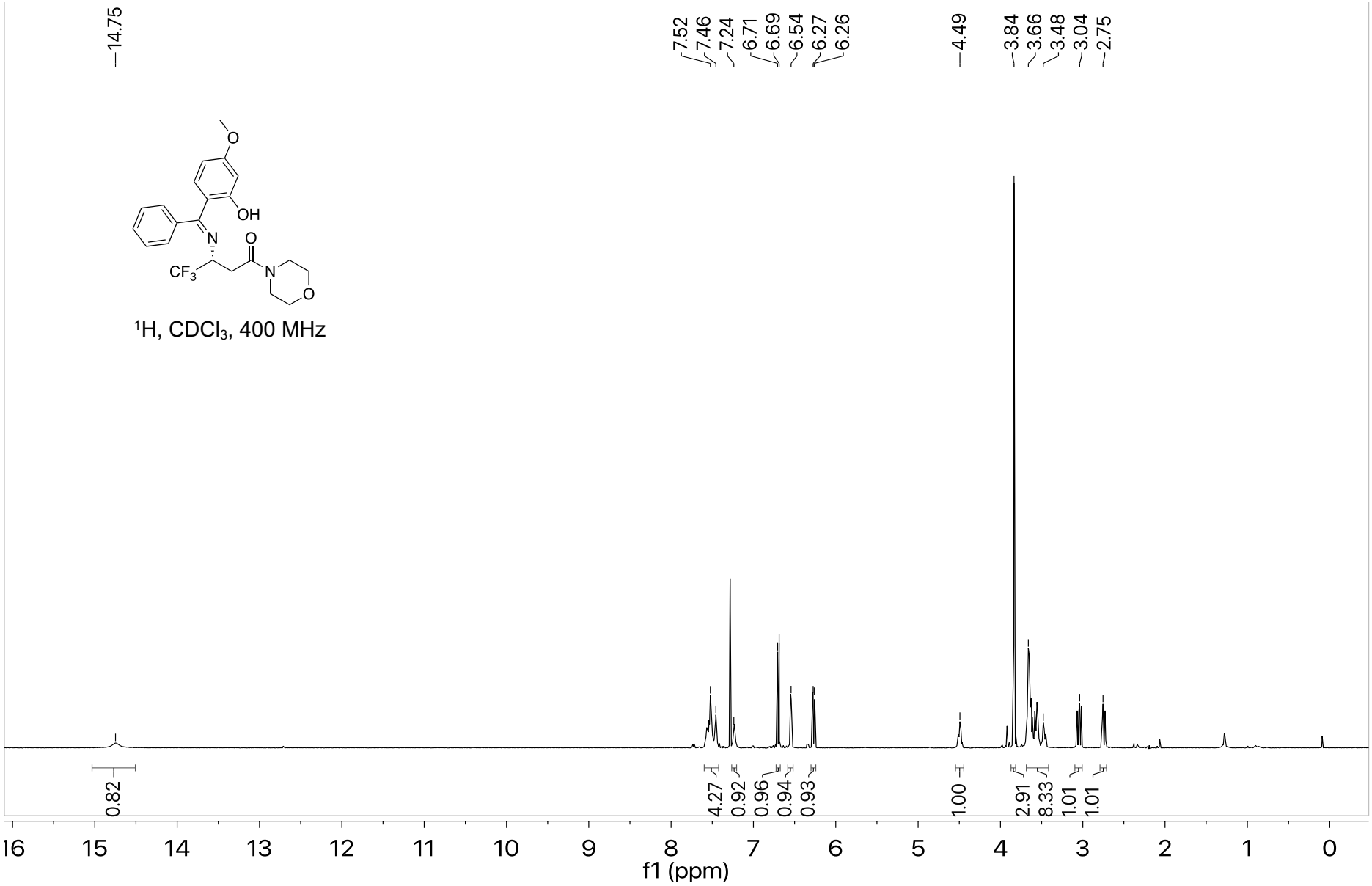
Peak#	Ret. Time	Area%
1	12.314	4.349
2	16.401	95.651
Total		100.000

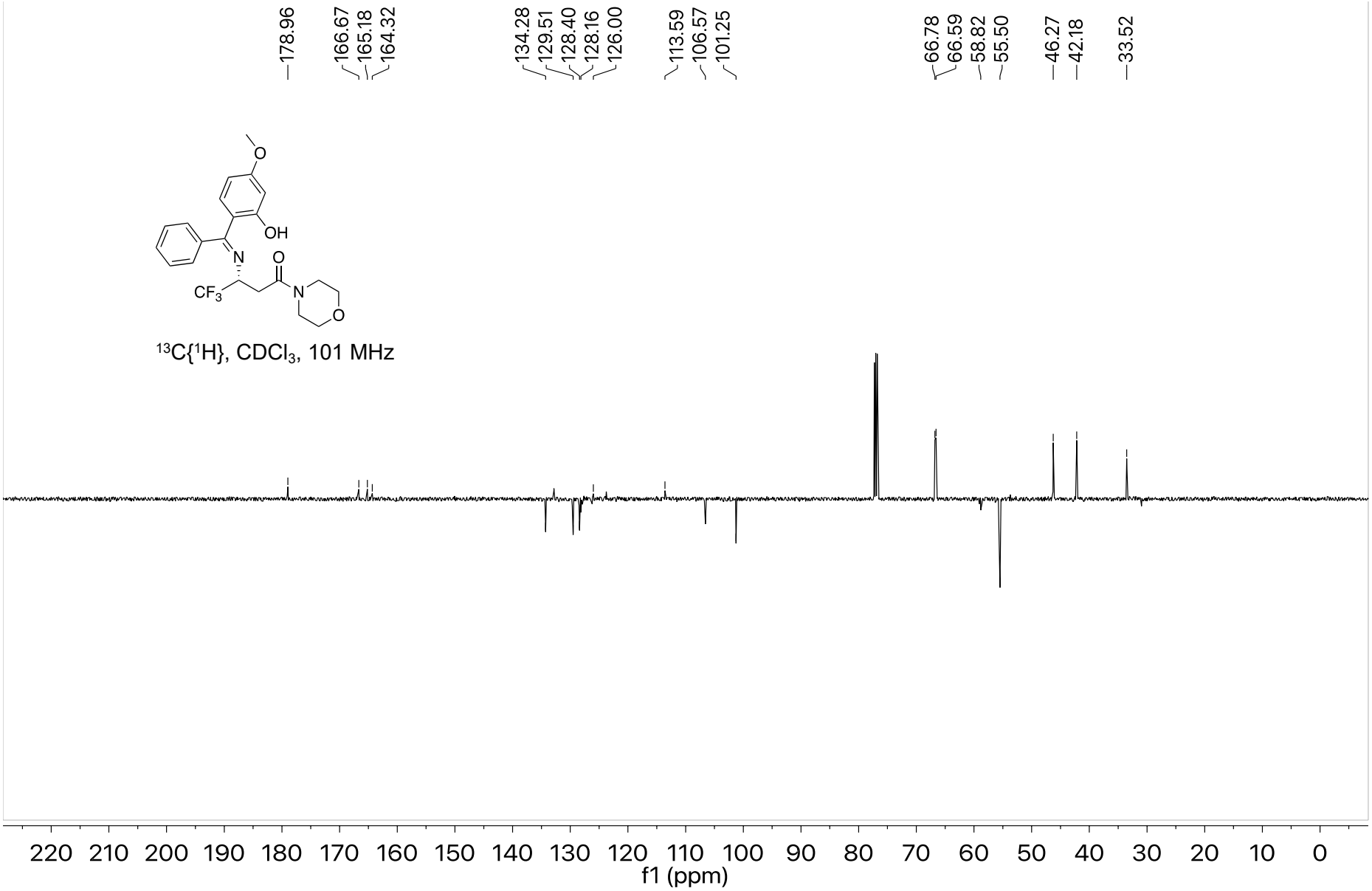


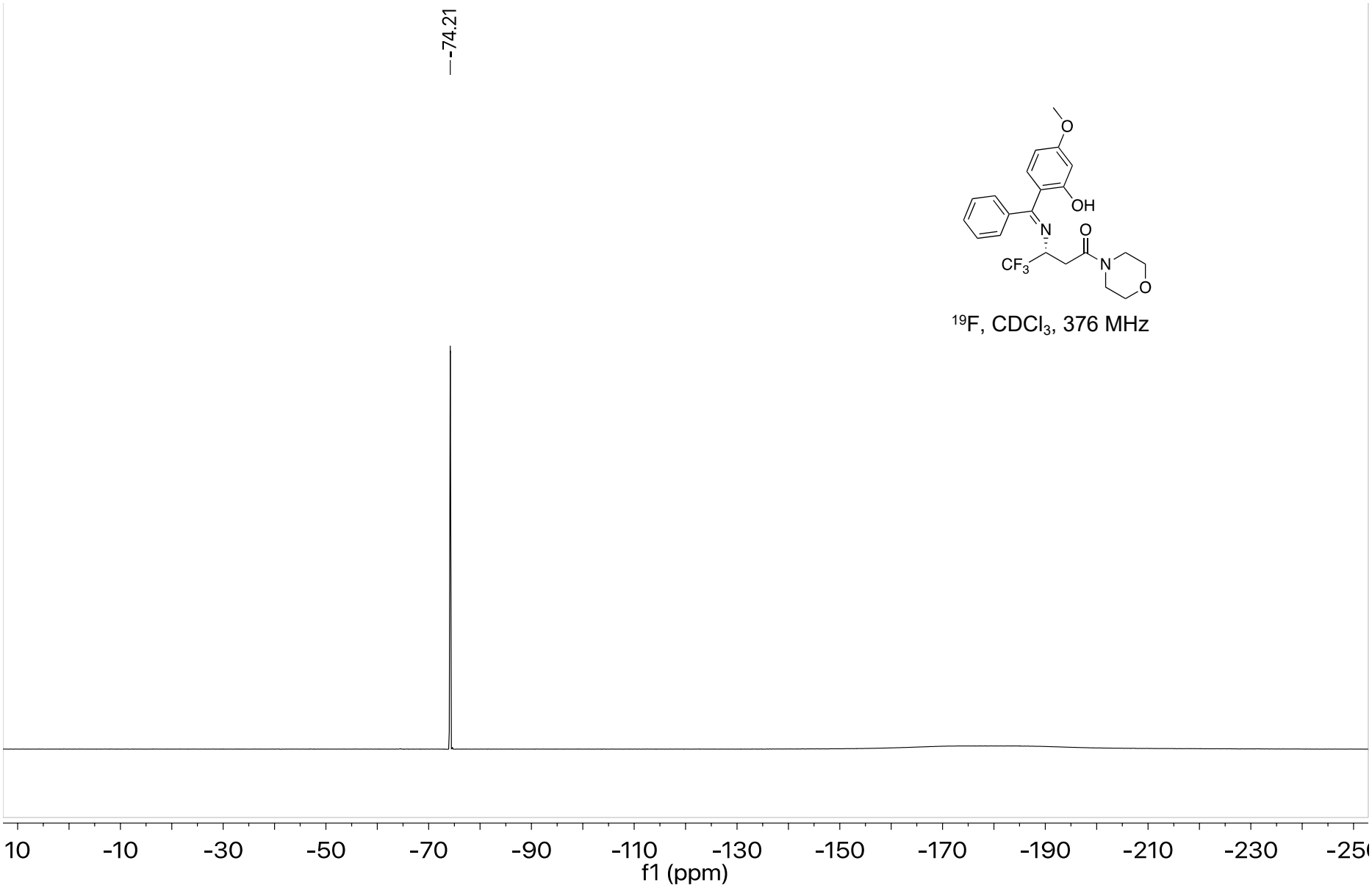
(*R*)-4,4,4-trifluoro-3-(((2-hydroxy-4-methoxyphenyl)methylene)amino)-1-morpholinobutan-1-one (23)



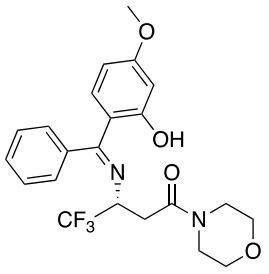
Following **General Procedure D,** 4-nitrophenyl (*E*)-4,4,4-difluorobut-2-enoate (26.1 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (45.4 mg, 0.2 mmol), (*R*)-(+)-BTM (5.1 mg, 0.02mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Morpholine was added (12.9 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was then purified by flash column chromatography Hexane:EtOAc (2:1) (R_f = 0.19) to give the titled compound (22.6 mg, 52%) as a yellow oil. $[\alpha]_D^{20}$ +86.0 (*c* = 0.45, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak OD-H (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 220 nm, 30 °C) t_R(*R*): 14.7 min, t_R(*S*): 20.1 min, 96:4 er; **IR** ν_{max} (ATR), 2990 (Ar-H), 1645 (C=O), 1593 (C=N), 1444 (C=C), 1259 (CF_3); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 2.74 (1H, dd, $^2J_{HH}$ = 15.4, $^3J_{HH}$ = 2.9, O=CC(2)H_AH_B), 3.04 (1H, dd, $^2J_{HH}$ = 15.3, $^3J_{HH}$ = 9.67, O=CC(2)H_AH_B), 3.48 – 3.66 (8H, m, NC(2)H_2C(3)H_2C(5)H_2C(6)H_2O), 3.84 (3H, s, -OCH_3), 4.49 (1H, m, COCH_AH_BC*H*), 6.47 (1H, dd, $^3J_{HH}$ = 9.0, $^4J_{HH}$ = 2.6, N=CC(5)Ar*H*OH-OCH_3), 6.55 (1H, d, $^4J_{HH}$ = 2.6, N=CC(3)Ar*H*OH-OCH_3), 6.70 (1H, d, $^3J_{HH}$ = 9.0, N=CC(6)Ar*H*OH-OCH_3), 7.23 (1H, m, N=CC(2)Ar*H*), 7.46 – 7.52 (4H, m, N=CC(3,4,5,6)Ar*H*), 14.75 (1H, s, -O*H*). **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -74.21 (-CF_3); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 33.5 (O=C*C*(2)H_AH_B), 42.2 – 46.3 (N*C*(2)H_2C(3)H_2C(5)H_2*C*(6)H_2O), 55.5 (-O*C*H_3), 58.8 (q, $^2J_{CF}$ = 22.9, C=OCH_AH_B*C*(3)HCF_3), 66.6 – 66.8 (NC(2)H_2*C*(3)H_2*C*(5)H_2C(6)H_2O), 101.3 (N=C*C*(3)ArOH-OCH_3), 106.6 (N=C*C*(5)ArOH-OCH_3), 113.6 (N=C*C*(1)ArOH-OCH_3), 126.0 (-*C*F_3), 128.2 (N=C*C*(1)Ar), 128.4 (N=C*C*(2,6)Ar), 129.5 (N=C*C*(3,4,5)Ar), 134.3 (N=C*C*(6)ArOH-OCH_3), 164.3 (N=C*C*(4)ArOH-OCH_3), 165.2 (N=C*C*(2)ArOH-OCH_3), 166.7 (*C*=O), 179.0 (*C*=N). **HRMS** (NSI$^+$) $C_{22}H_{23}F_3N_2O_4^+$ ([M+H]$^+$) requires 437.1683, found 437.1673 (-2.3 ppm).


14.75
7.52
7.46
7.24
6.71
6.69
6.54
6.27
6.26
4.49
3.84
3.66
3.48
3.04
2.75
O
OH
N
O
CF3
N
O
1H, CDCl3, 400 MHz
0.82
4.27
0.92
0.96
0.94
0.93
1.00
2.91
8.33
1.01
1.01
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


178.96
166.67
165.18
164.32
134.28
129.51
128.40
128.16
126.00
113.59
106.57
101.25
66.78
66.59
58.82
55.50
46.27
42.18
33.52
O
OH
N
O
CF3
N
O
13C{1H}, CDCl3, 101 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

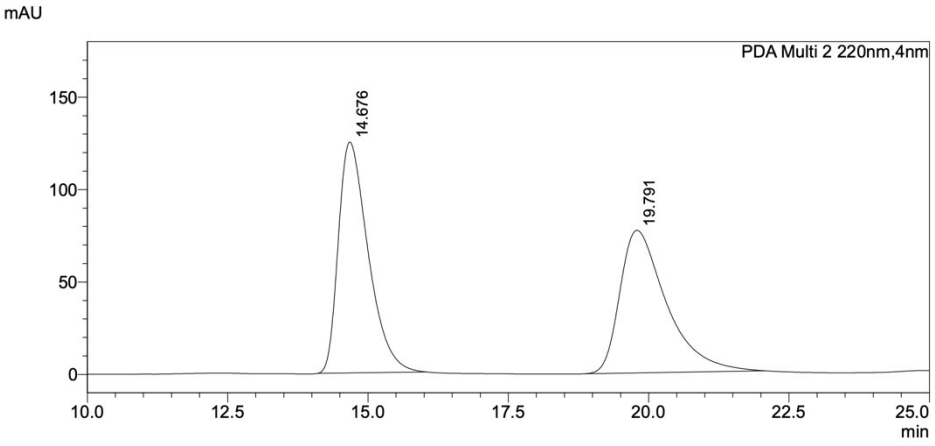

-74.21
O
OH
N
O
CF3
N
O
19F, CDCl3, 376 MHz
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
-230
f1 (ppm)

HPLC Data for **(*R*)-4,4,4-trifluoro-3-(((2-hydroxy-4-methoxyphenyl)methylene)amino)-1-morpholinobutan-1-one**: Chiralpak OD-H (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 220 nm, 30 °C) t_R(*R*): 14.7 min, t_R(*S*): 20.1 min, 96:4 er.



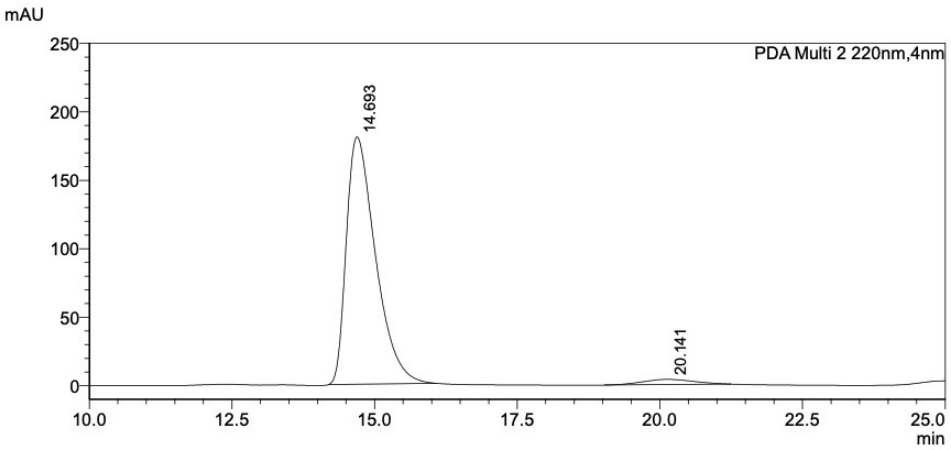
PDA Ch2 220nm

Peak#	Ret. Time	Area%
1	14.676	50.978
2	19.791	49.022
Total		100.000

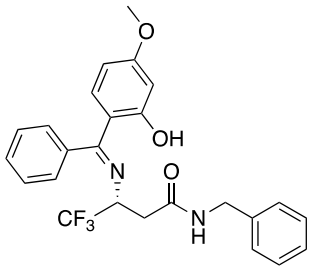


PDA Ch2 220nm

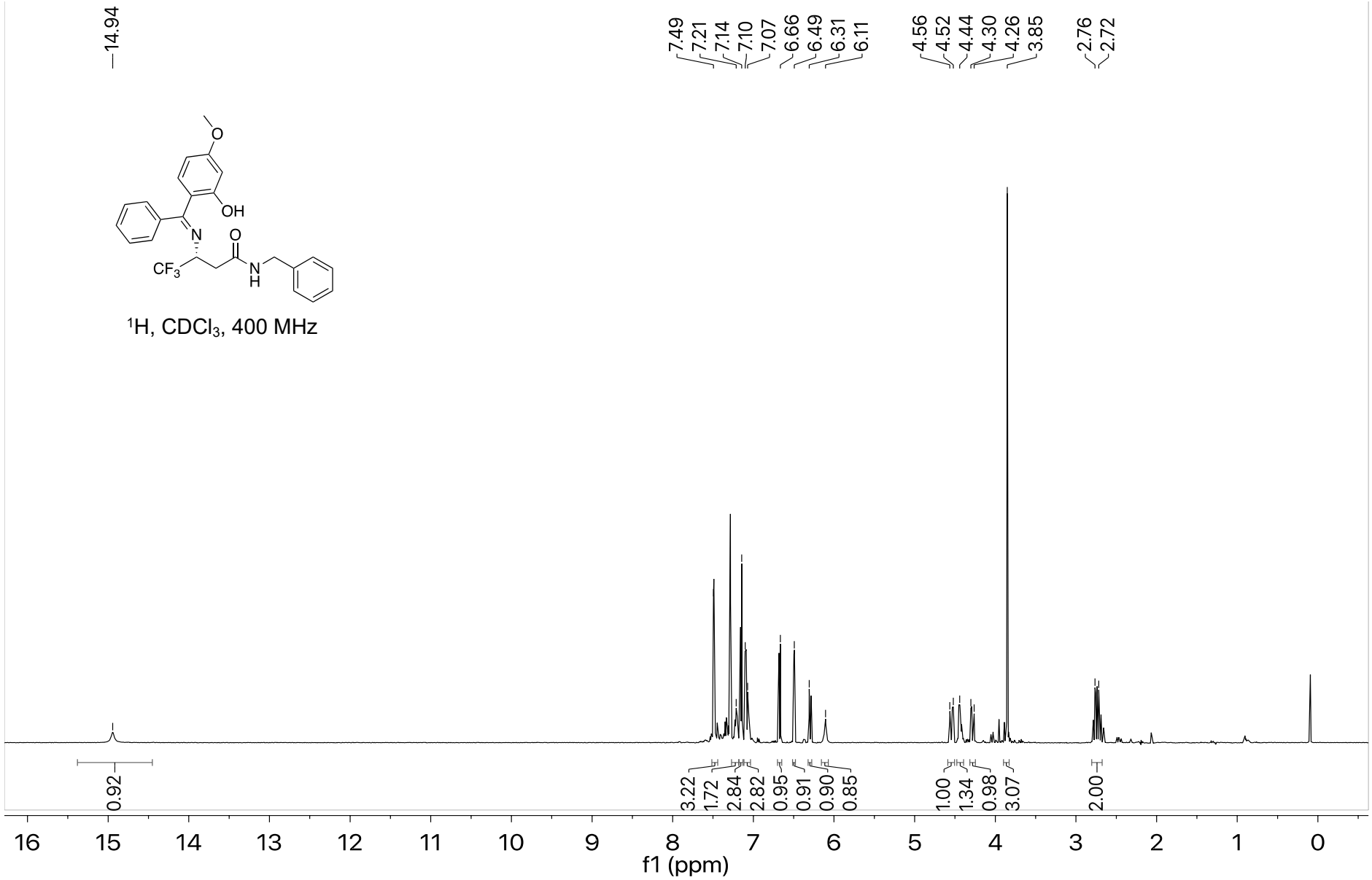
Peak#	Ret. Time	Area%
1	14.693	96.435
2	20.141	3.565
Total		100.000

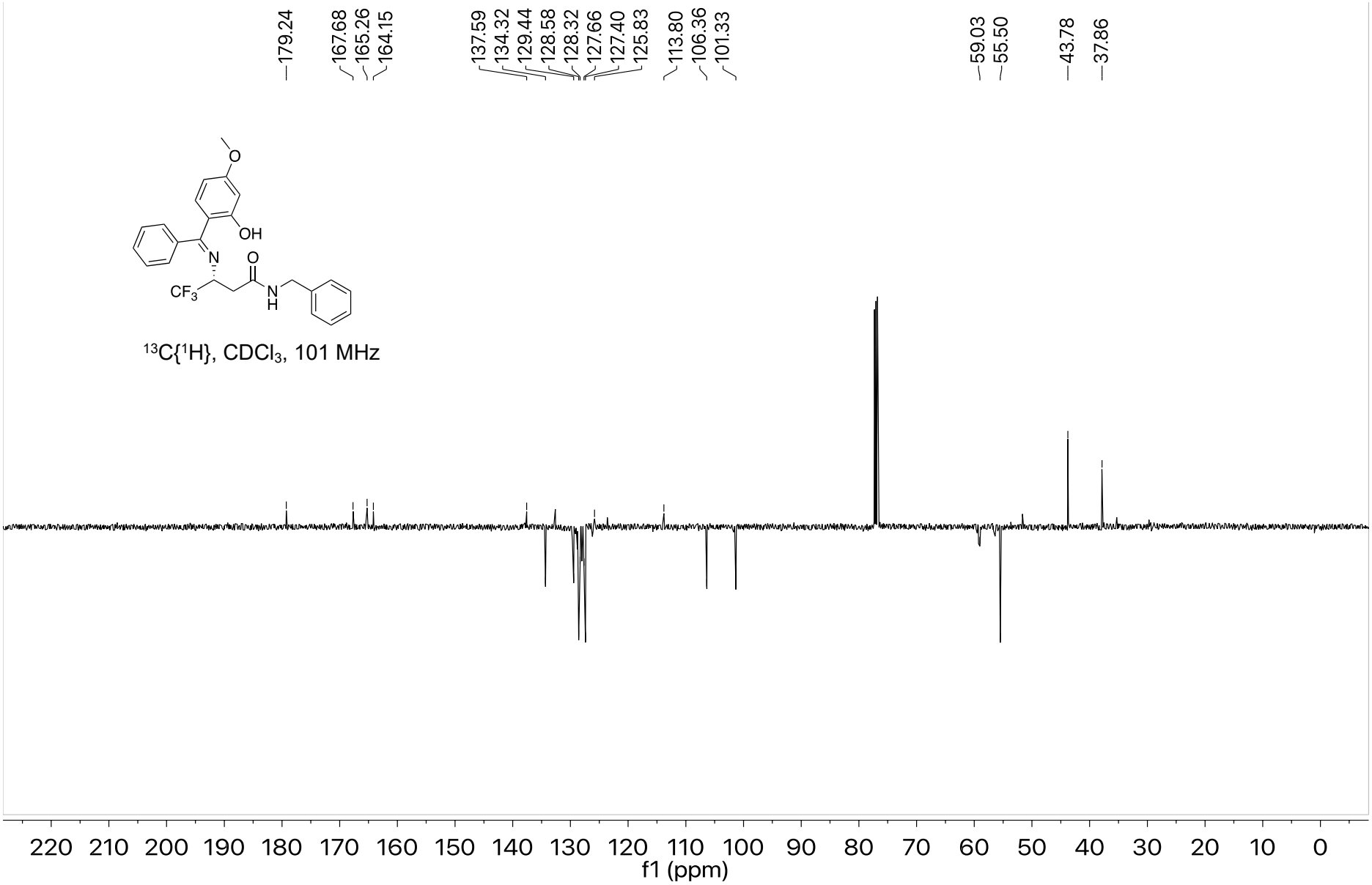


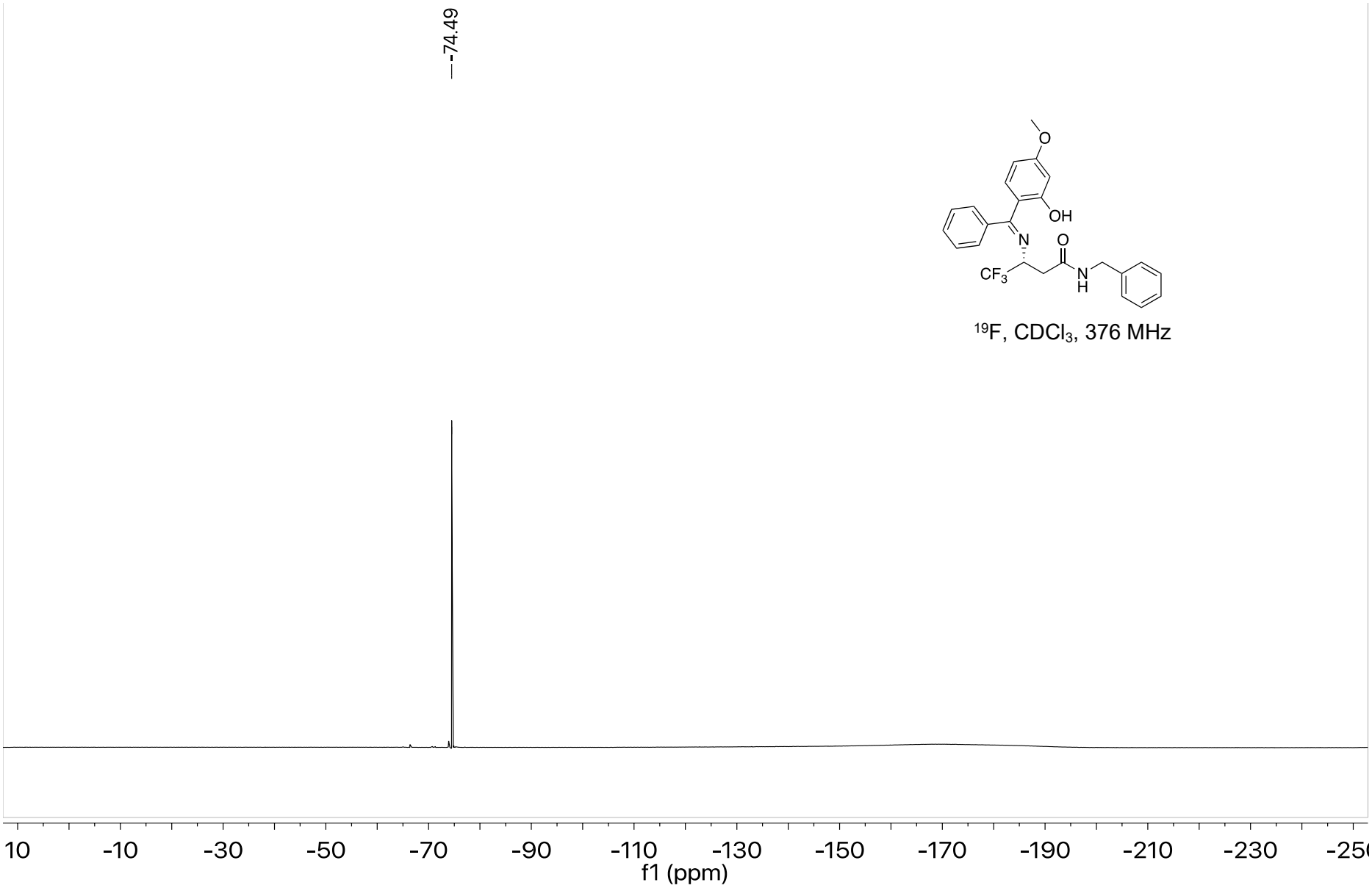
(*R*)-*N*-Benzyl-4,4,4-trifluoro-3-(((2-hydroxy-4-methoxyphenyl)methylene)amino) Butanamide (24)



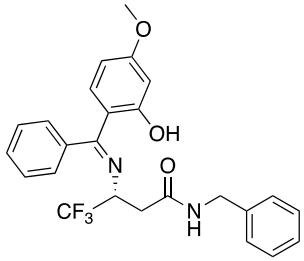
Following **General Procedure D,** 4-nitrophenyl (*E*)-4,4,4-difluorobut-2-enoate (26.1 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (45.4 mg, 0.2 mmol), (*R*)-(+)-BTM (5.1 mg, 0.02mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Benzylamine was added (16.4 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was then purified by flash column chromatography Hexane:EtOAc (4:1) (R_f = 0.18) to give the titled compound (23.8 mg, 52%) as a yellow oil. $[\alpha]_D^{20}$ +108.8 (*c* = 0.51, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak OD-H (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 220 nm, 30 °C) t_R(*S*): 13.0 min, t_R(*R*): 14.9 min, 97:3 er; **IR** ν_{max} (ATR), 2956 (Ar-H), 1743 (O=CNHBn) 1604 (C=O), 1595 (C=N), 1442 (C=C), 1261 (CF_3); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 2.72 – 2.76 (2H, m, O=CC(2)H_AH_B), 3.85 (3H, s, -OCH_3), 4.26 – 4.30 (1H, dd, $^2J_{HH}$ = 15.0, $^3J_{HH}$ = 5.3, O=CCH_AH$_B$Ph), 4.43 (1H, m, O=CCH$_A$H$_B$C(3)*H*), 4.52 – 4.56 (1H, dd, $^2J_{HH}$ = 15.-, $^3J_{HH}$ = 6.4, O=CCH$_A$$H_B$Ph), 6.11 (1H, d, $^3J_{HH}$ = 6.4, O=CN*H*), 6.31 (1H, dd, $^3J_{HH}$ = 9.0, $^4J_{HH}$ = 2.6, N=CC(5)Ar*H*OH-OCH$_3$), 6.49 (1H, d, $^4J_{HH}$ = 2.6, N=CC(3)Ar*H*OH-OCH$_3$), 6.67 (1H, d, $^3J_{HH}$ = 9.0, N=CC(6)Ar*H*OH-OCH$_3$), 7.07 – 7.10 (2H, m, NHCH$_2$C(2,6)Ar*H*), 7.14 (3H, m, NHCH$_2$C(3,4,5)Ar*H*), 7.21 (2H, m, N=CC(2,6)Ar*H*), 7.49 (3H, m, N=CC(3,4,5)Ar*H*), 14.9 (1H, s, -O*H*). **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -74.49 (-CF_3); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 37.9 (O=C*C*(2)H_AH_B), 43.9 (NH*C*H$_2$Ph), 55.5 (-O*C*H$_3$), 58.8 – 59.4 (q, $^2J_{CF}$ = 23.3 O=CCH$_A$H$_B$*C*(3)H), 101.3 (N=C*C*(3)ArOH-OCH$_3$), 106.4 (N=C*C*(5)ArOH-OCH$_3$), 113.8 (N=C*C*(1)ArOH-OCH$_3$), 125.8 (-*C*F$_3$), 127.4 (NHCH$_2$*C*(3,4,5)Ph), 127.7 (N=C*C*(2,6)ArH), 128.3 (NHCH$_2$*C*(2,6)Ph), 128.6 (N=C*C*(1)Ar), 129.4 (N=C*C*(3,4,5)Ar), 134.2 (N=C*C*(6)ArOH-OCH$_3$), 137.6 (NHCH$_2$*C*(1)Ph), 164.2 (N=C*C*(2)ArOH-OCH$_3$), 165.3 (N=C*C*(4)ArOH-OCH$_3$), 167.8 (*C*=O), 179.2 (*C*=N). **HRMS** (NSI$^+$) $C_{25}H_{23}F_3N_2O_4^+$ ([M+H]$^+$) requires 457.1734, found 457.1724 (-2.2 ppm).


14.94
7.49
7.21
7.14
7.10
7.07
6.66
6.49
6.31
6.11
4.56
4.52
4.44
4.30
4.26
3.85
2.76
2.72
O
OH
N
O
CF3
N
H
1H, CDCl3, 400 MHz
0.92
3.22
1.72
2.84
2.82
0.95
0.91
0.90
0.85
1.00
1.34
0.98
3.07
2.00
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


179.24
167.68
165.26
164.15
137.59
134.32
129.44
128.58
128.32
127.66
127.40
125.83
113.80
106.36
101.33
59.03
55.50
43.78
37.86
O
OH
N
O
CF3
N
H
13C{1H}, CDCl3, 101 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

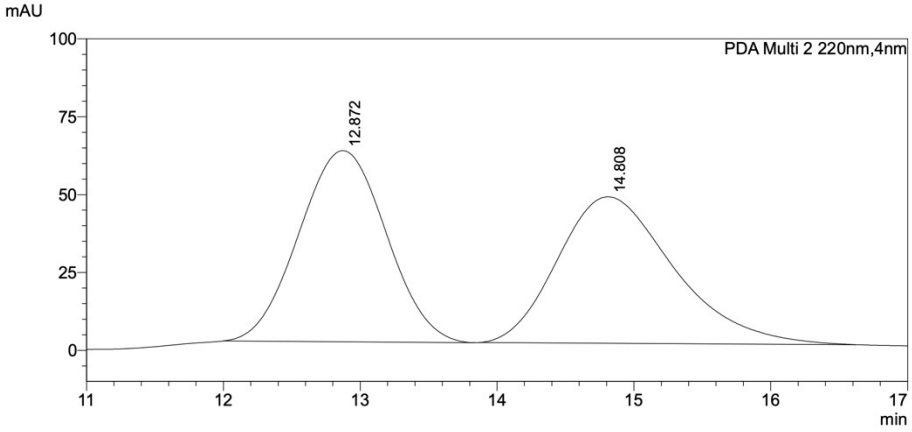

-74.49
O
OH
N
O
CF3
N
H
19F, CDCl3, 376 MHz
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
-230
f1 (ppm)

HPLC Data for **(*R*)-*N*-benzyl-4,4,4-trifluoro-3-(((2-hydroxy-4-methoxyphenyl)methylene)amino)butanamide**: Chiralpak OD-H (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 220 nm, 30 °C) t_R(*R*): 13.0 min, t_R(*S*): 14.9 min, 97:3 er.



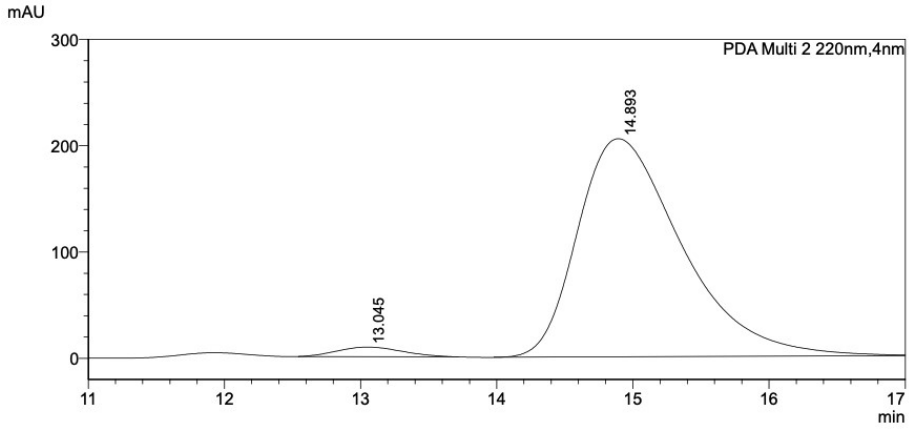
PDA Ch2 220nm

Peak#	Ret. Time	Area%
1	12.872	49.509
2	14.808	50.491
Total		100.000



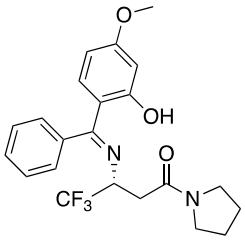
PDA Ch2 220nm

Peak#	Ret. Time	Area%
1	13.045	2.651
2	14.893	97.349
Total		100.000



5. GRAM SCALE SYNTHESIS

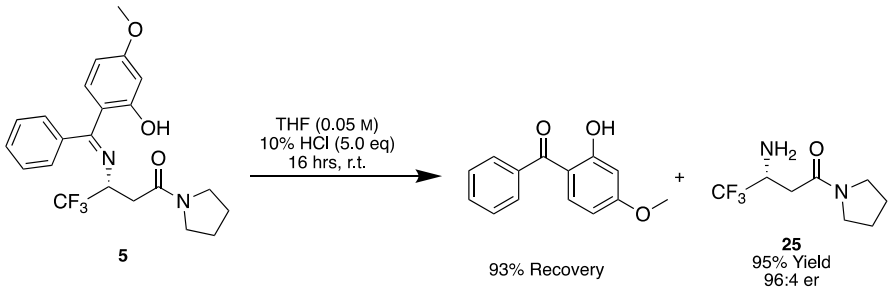
(*R*)-4,4,4-trifluoro-3-(((2-hydroxy-4-methoxyphenyl)(phenyl)methylene)amino)-1-(pyrrolidin-1-yl)butan-1-one (5)



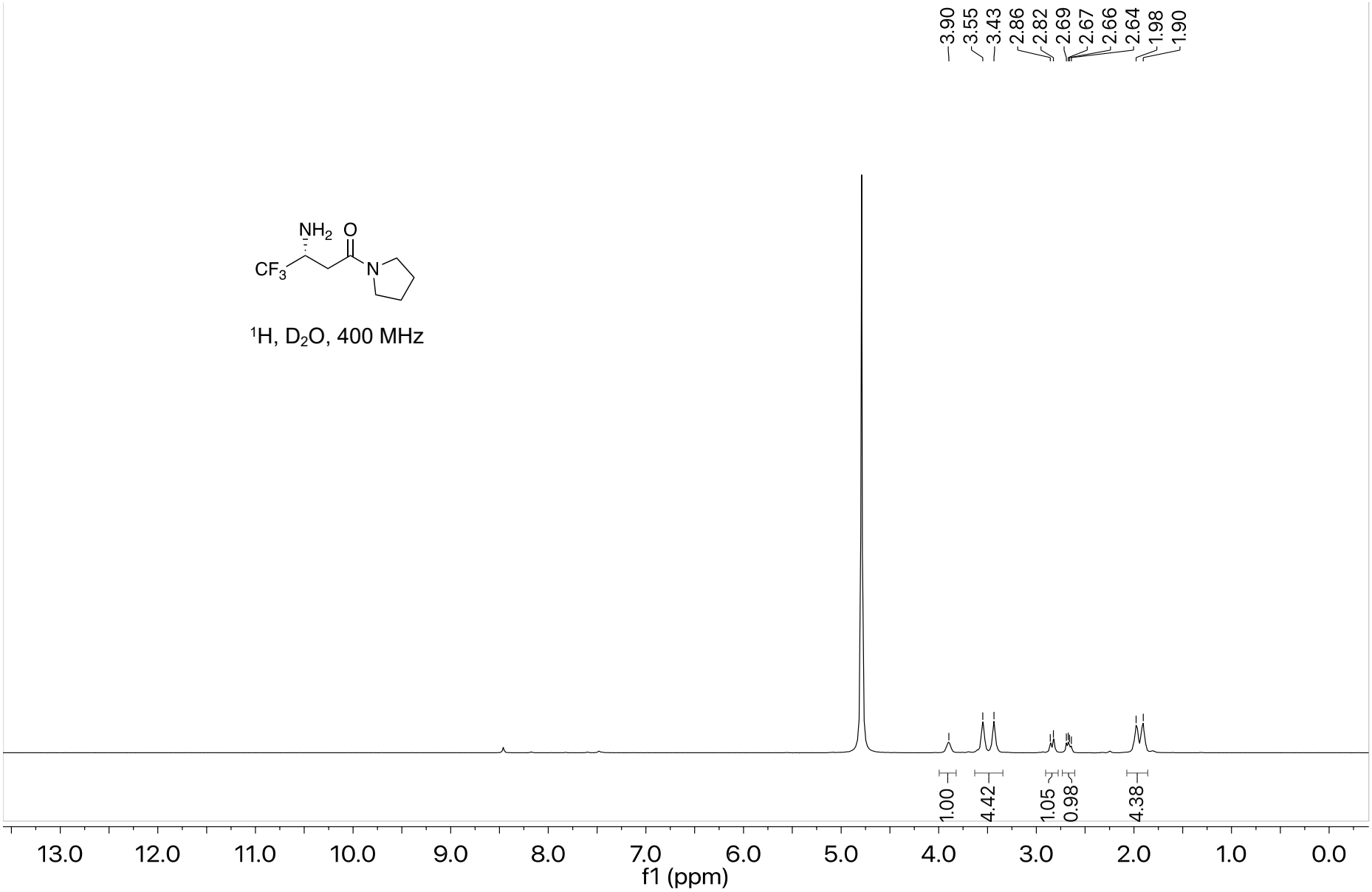
Following **General Procedure D,** 4-nitrophenyl (*E*)-4,4,4,-trifluorobut-2-enoate (1.436 g, 5.5 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (2.50 g, 11.0 mmol), (*R*)-(+)-BTM (277.6 mg, 1.1 mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Pyrrolidine was added (678 µL, 8.25 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was then purified by flash column chromatography Hexane:EtOAc (4:1) (R_f = 0.20) to give the titled compound (1.55 g, 67%) as a yellow oil. $[\alpha]_D^{20}$ +95.5 (*c* = 0.87, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(*R*): 19.1 min, t_R(*S*): 25.3 min, 95:5 er; **IR** ν_{max} (ATR), 2976 (Ar-H), 1624 (C=O), 1605 (C=N), 1444 – 1454 (C=C), 1276 (C-O-CH_3), 1261 (CF_3); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.86 – 1.98 (4H, m, NC(2)H_2C(3)*H_2*C(4)*H_2*C(5)H_2), 2.75 (1H, dd, $^3J_{HH}$ = 15.4, $^4J_{HF}$ = 3.0, COC(2)*H_A*H_B), 2.98 (1H, dd, $^3J_{HH}$ = 15.2, $^4J_{HF}$ = 10.0, COC(2)H$_A$*H_B*), 3.44 – 3.57 (4H, m, NC(2)*H_2*C(3)H_2C(4)H_2C(5)*H_2*), 3.84 (3H, s, OC*H_3*), 4.54 (1H, m, COCH$_A$H$_B$C*H*), 6.28 (1H, dd, $^3J_{HH}$ = 9.0, N=CC(5)Ar*H*OH-OCH_3), 6.58 (1H, s, N=CC(3)Ar*H*OH-OCH_3), 6.72 (1H, dd, $^3J_{HH}$ = 8.9, N=CC(6)Ar*H*OH-OCH_3), 7.24 (1H, m, N=CC(4)Ar*H*), 7.52 (4H, m, N=CC(2,3,5,6)Ar*H*), 14.8 (1H, s, N=CC(2)ArO*H*-OCH_3); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -74.31 (-C*F_3*) ; **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 24.4 (NC(2)H_2*C*(3)H_2C(4)H_2C(5)H_2), 26.1 (NC(2)H_2C(3)H_2*C*(4)H_2C(5)H_2), 35.3 (C=O*C*H$_A$H$_B$$CF_3$), 45.9 (N*C*(2)$H_2$C(3)$H_2$C(4)$H_2$C(5)$H_2$), 47.0 (NC(2)$H_2$*C*(3)$H_2$C(4)$H_2$*C*(5)$H_2$), 55.54 (O*C*$H_3$), 58.7 (q, $^2J_{CF}$ = 28.3, C=OCH$_A$H$_B$*C*(3)HCF_3), 101.2 (N=C*C*(3)ArOH-OCH_3), 106.6 (N=C*C*(5)ArOH-OCH_3), 114.28 (N=C*C*(1)ArOH-OCH_3), 118.4 (*C*F_3), 128.2 (N=C*C*(2,3,5,6)ArH), 129.5 (N=C*C*(4)Ar), 134.4 (N=C*C*(1)Ar), 164.4 (N=C*C*(2)ArOH-OCH_3), 165.5 (*C*=N), 166.3 (N=C*C*(4)ArOH-OCH_3), 178.9 (*C*=O). **HRMS** (NSI$^+$) $C_{21}H_{23}F_3N_2O_3^+$ ([M+H]$^+$) requires 421.1734, found 421.1729 (-1.2 ppm).

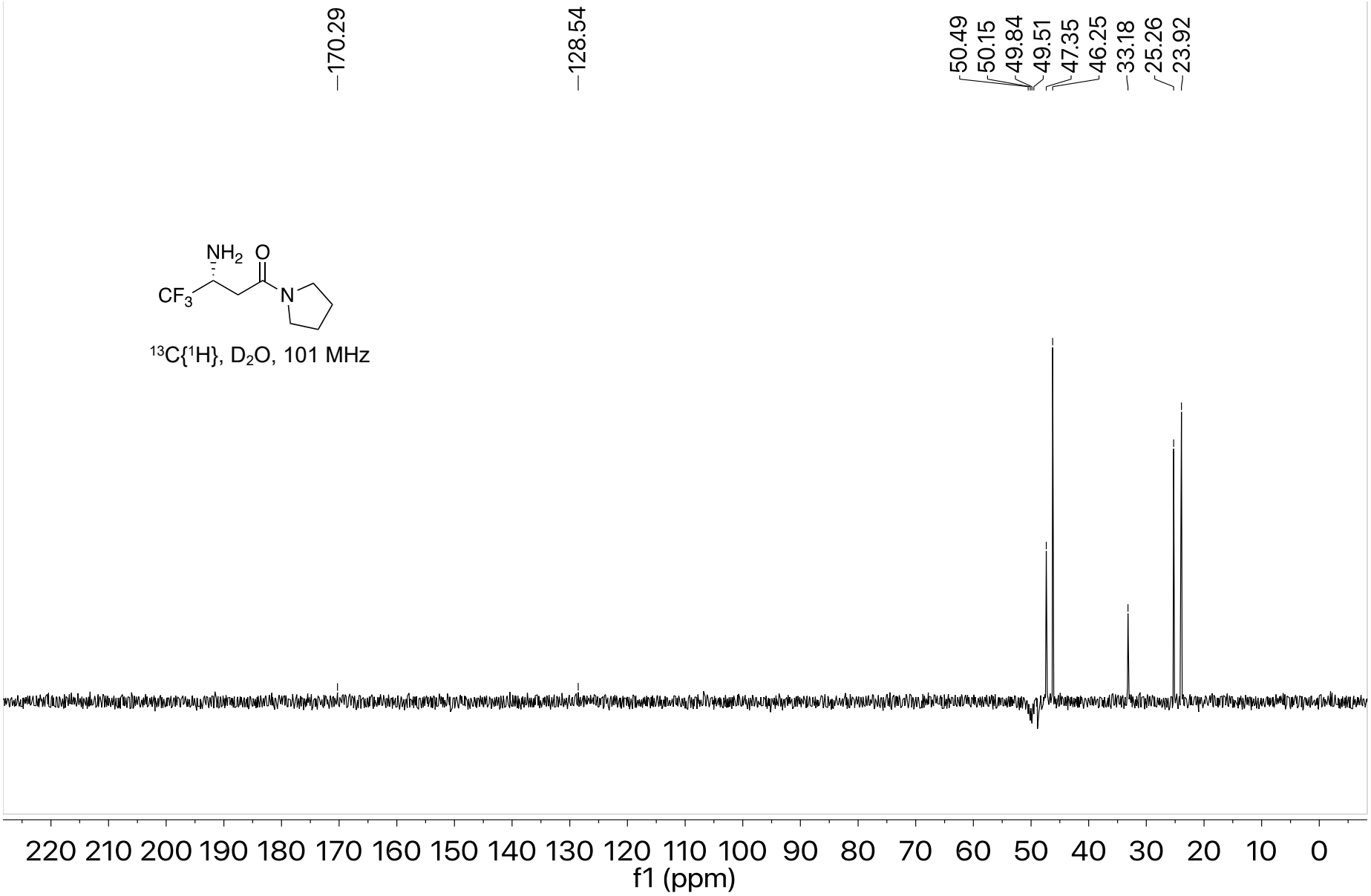
6. HYDROLYSIS OF PRODUCT 5

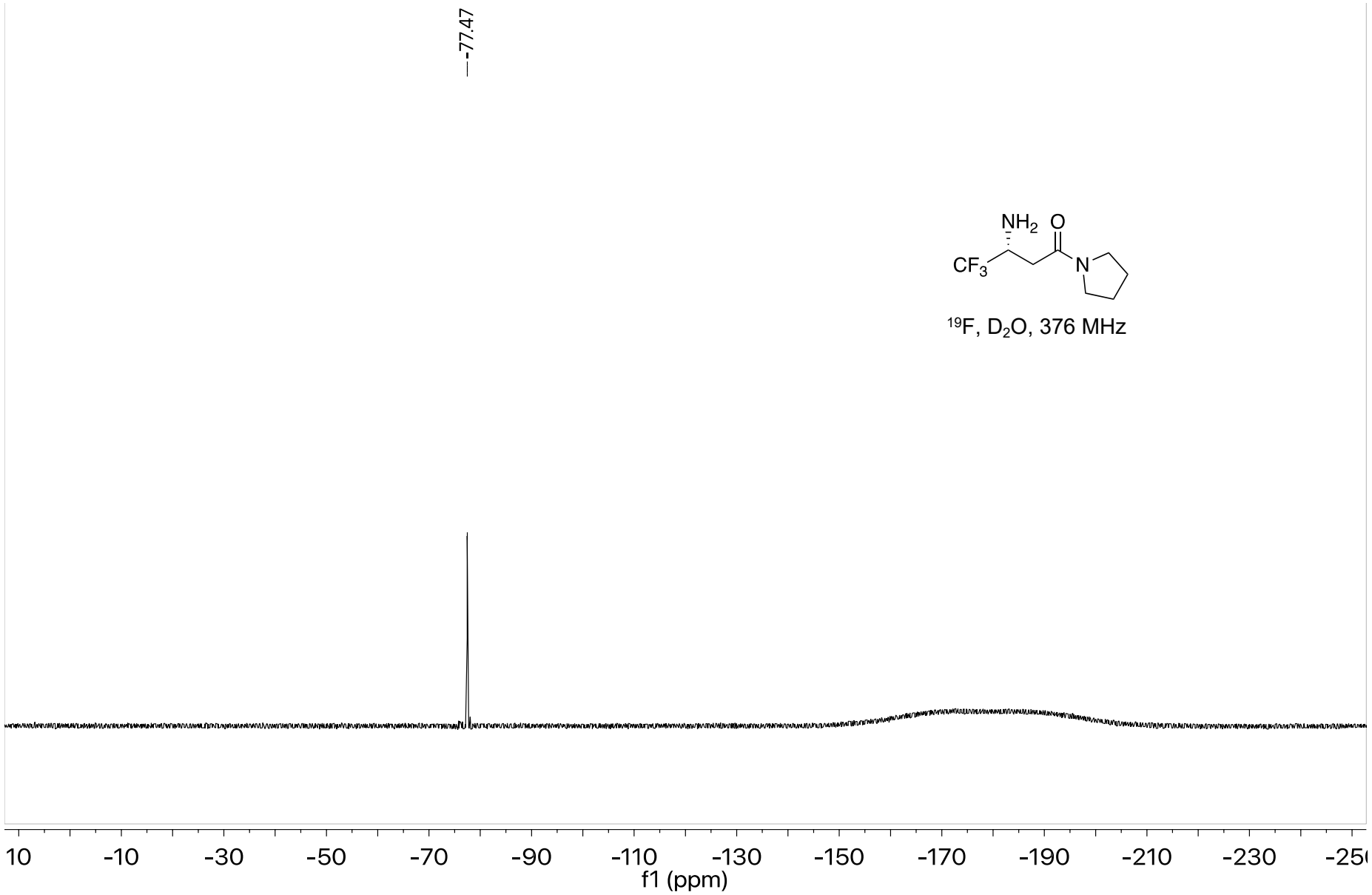
(*R*)-3-amino-4,4,4-trifluoro-1-(pyrrolidin-1-yl)butan-1-one (25)



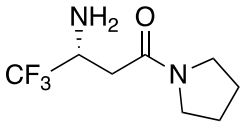
Compound **5** (292 mg, 0.7 mmol), THF (0.05 M), and 10% HCl (1.1 mL, 3.45 mmol) was stirred at room temperature for 16 hrs. The crude mixture was purified by flash column chromatography MeOH to give the titled compound **25** (138 mg, 95% yield) as an off-white solid. $[\alpha]_D^{20}$ +96.1 (*c* = 0.84, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak ADH (85:15 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(*S*): 12.9 min, t_R(*R*): 18.3 min, 96:4 er; **IR** ν_{max} (ATR), 3116 (NH_2), 2981 (Ar-H), 1715 (C=O), 1618 (Amide stretch), 1390 (C=C), 1296 (CF_3); **^{1}H NMR** (400 MHz, D_2O) δ_H: 1.90 – 1.98 (4H, m, NC(2)H_2C(3)*H_2*C(4)*H_2*C(5)H_2), 2.64 – 2.69 (1H, dd, $^2J_{HH}$ = 16.8, $^3J_{HH}$ = 9.4, COC(2)*H_A*H_BCHCF_3), 2.82 – 2.86 (1H, dd, $^2J_{HH}$ = 15.9, $^3J_{HH}$ = 3.4, COC(2)H_A*H_B*CHCF_3), 3.43 – 3.55 (4H, m, NC(2)*H_2*C(3)H_2C(4)H_2C(5)*H_2*), 3.90 (1H, s, COC$H_A$$H_B$C*H*C$F_3$). **^{19}F{^{1}H} NMR** (376 MHz, D_2O), δ_F: -77.47 (-C*F_3*); **^{13}C{^{1}H} NMR** (101 MHz, D_2O) δ_C: 23.9 – 25.2 (N*C*(2)H_2C(3)H_2C(4)H_2*C*(5)H_2), 33.2 (CO*C*$H_A$$H_BCHCF_3$), 46.3 – 47.4 (NC(2)$H_2$*C*(3)$H_2$*C*(4)$H_2$C(5)$H_2$), 50.0 (q, $^2J_{CF}$ = 33.0, COC$H_A$$H_B$*C*HC$F_3$), 128.5 (-*C*$F_3$), 170.3 (*C*=O). **HRMS** (NSI$^+$) $C_8H_{14}F_3N_2O^+$ ([M+H]$^+$) requires 211.1053, found 211.1047 (-2.8 ppm).


3.90
3.55
3.43
2.86
2.82
2.69
2.67
2.66
2.64
1.98
1.90
NH2
O
CF3
N
1H, D2O, 400 MHz
1.00
4.42
1.05
0.98
4.38
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)


170.29
128.54
50.49
50.15
49.84
49.51
47.35
46.25
33.18
25.26
23.92
NH2
O
CF3
N
13C{1H}, D2O, 101 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

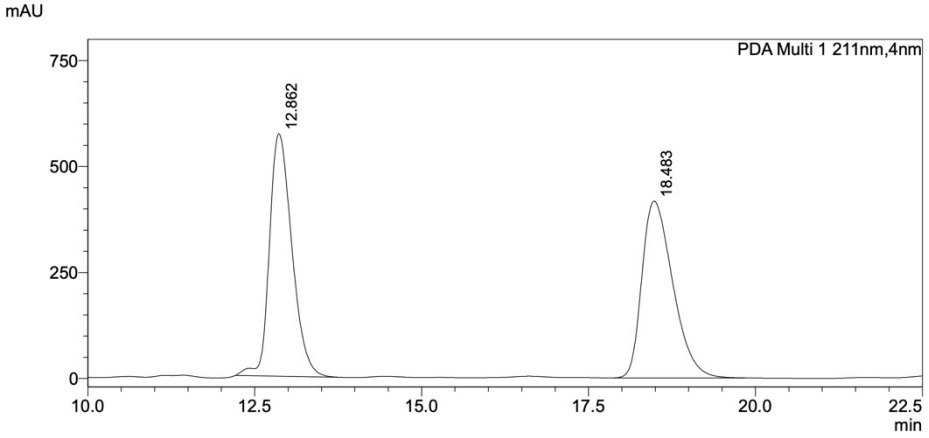

-77.47
NH2
O
CF3
N
19F, D2O, 376 MHz
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
-230
f1 (ppm)

HPLC Data for **(*R*)-3-amino-4,4,4-trifluoro-1-(pyrrolidin-1-yl)butan-1-one (25)**: Chiralpak ADH (85:15 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(*S*): 12.9 min, t_R(*R*): 18.3 min, 96:4 er.



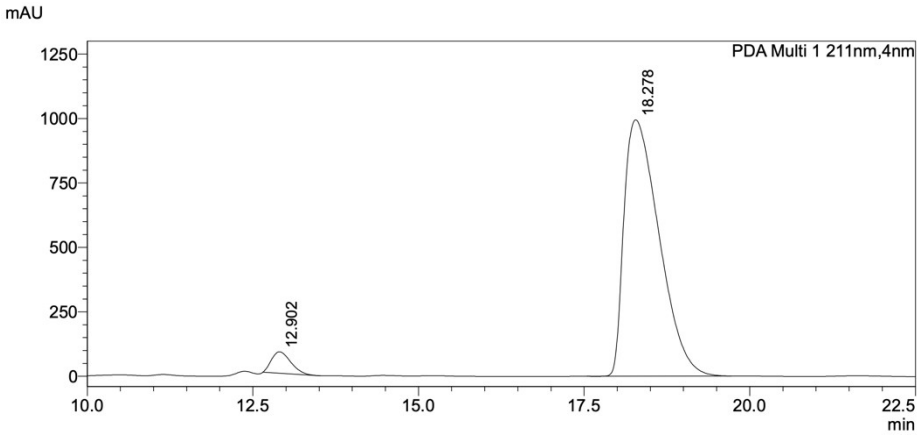
PDA Ch1 211nm

Peak#	Ret. Time	Area%
1	12.862	49.955
2	18.483	50.045
Total		100.000



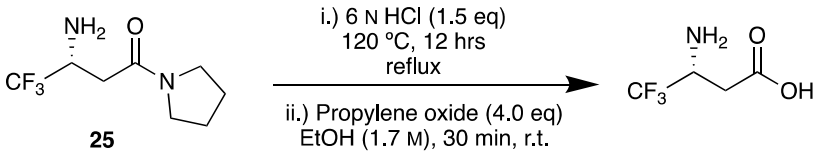
PDA Ch1 211nm

Peak#	Ret. Time	Area%
1	12.902	4.405
2	18.278	95.595
Total		100.000



7. ABSOLUTE CONFIGURATION: HYDROLYSIS OF PRODUCT 25

(*R*)-3-amino-4,4,4-trifluorobutanoic acid



Compound **25** (41.3 mg, 0.2 mmol) was added with 6 N HCl (0.4 mL) stirred at 120 °C for 12 hrs. The crude mixture was then dried to obtain a crude beige solid. The crude solid was then added with dried EtOH (1.7 M) and propylene oxide (56 µL, 0.8 mmol) and the reaction mixture was stirred for 30 minutes. The mixture was then concentrated under vacuo and the crude solid was then washed with propanol to obtain the solid product (12.7 mg, 40% yield) as an off-white solid **mp** 173–175 ºC; $[\alpha]_D^{20}$ +17.9 (*c* = 1.27, 6N HCl) (literature $[\alpha]_D^{25}$ +24.4 (*c* = 1.05, 6N HCl))[10]; **IR** ν_{max} (ATR), 3387 (NH_2), 3045 (OH) 1615 (C=O), 1430 (CH_2 bend), 1296 (CF_3); **^{1}H NMR** (400 MHz, CD_3OD) δ_H: 2.50 (1H, m, COC(2)H_AH_BCHCF$_3$), 2.74 (1H, m, COC(2)H-$_AH_B$CHCF$_3$), 3.94 (1H, m, COCH$_A$H$_B$C*H*CF$_3$). **^{19}F{^{1}H} NMR** (400 MHz, CD_3OD), δ_F: -77.9 (-CF_3). Data in agreement with literature.[10]

8. REFERENCES

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