Supporting Information

Highly Enantioselective Addition of Dimethylzinc to Fluorinated Alkyl Ketones, and the Mechanism Behind It

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1. General information

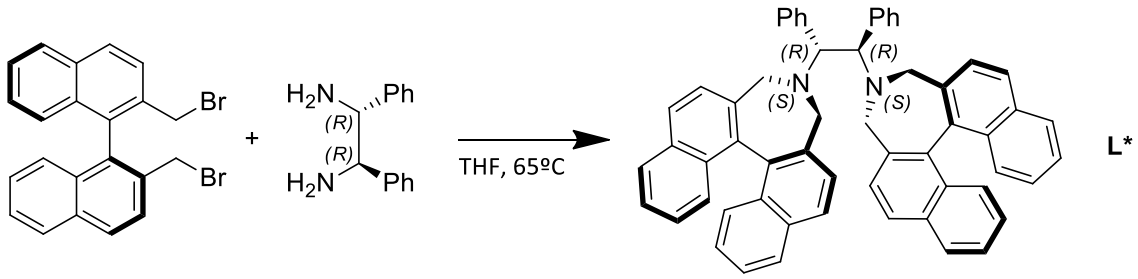
All reactions were carried out under nitrogen atmosphere using Schlenk–tube techniques. Dichloromethane and tetrahydrofuran were obtained oxygen– and water–free from an SPS PS–MD–5 solvent purification apparatus. Toluene was dried over sodium and distilled. Dimethylzinc solutions (0.5 M in dichloromethane o toluene) were prepared from pure $ZnMe_2$ purchased from Strem. Fluorinated ketones were purchased from commercial sources (Fluorochem or Apollo Scientific) and used without further purification.

^{1}H, $^{13}C\{^{1}H\}$ and ^{19}F NMR spectra were recorded on Bruker AV–400 and/or Varian Inova 500–MR instruments. Chemical shifts (in δ units, parts per million) were referenced to the residual solvent peaks (^{1}H, $^{13}C\{^{1}H\}$) or internal $CFCl_3$ (^{19}F). Coupling constants *J* and variation of frequencies $\Delta\nu$ (AB spin systems) are given in hertz. The following abbreviations are used to describe peak patterns when appropriate: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sept (septuplet), m (multiplet), br (broad) and AB (AB spin system). Mass spectra were recorded using an Agilent Technologies 5973 Network apparatus.

Purification of reaction solutions were carried out by flash chromatography using silica gel (silica gel 60, 230–400 mesh, Merk). Enantiomeric excesses (ee) were determinated by gas chromatography (GC) or high–pressure liquid chromatography (HPLC) analysis. Chiral GC analyses were performed on an Agilent chromatograph, equipped with a flame ionization detector (FID). LIPODEX–E (30 m × 0.25 mm ; DF = 0.25 µm) capillary column was used with helium as the carrier gas in a constant flow 1 ml/min. The injector was operated in the splitless (1/20) mode at 200 °C and the detector at 250 °C. Chiral HPLC analyses were performed on a Agilent HPLC system using ChiralPack–AD column or Lux–amyl–1_002–CH1. The GC and the HPLC traces of the product were compared to those of the corresponding racemic samples prepared through the *Grignard reaction* by addition of MeMgBr to the corresponding ketone.

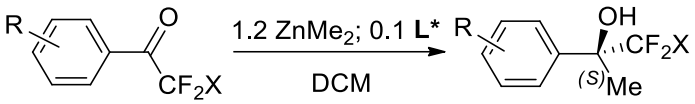
2. Preparation of L*

A solution of (1*R*,2*R*)–1,2–diphenylethane–1,2–diamine (1.0 g, 4.71 mmol, 1 eq), (*S*)–2,2'–bis(bromomethyl)–1,1'–binaphthalene (4.35 g, 9.89 mmol, 2.1 eq) and trimethylamine (2.6 mL, 1.91 g, 18.84 mmol, 4 eq) in anhydrous THF (50 mL) was stirred at 65 °C under nitrogen atmosphere. After 48 h, the suspension obtained was filtered over silica to remove $NHEt_3Br$ and the solution was concentrated under reduced pressure. The residue was purified by crystallization in dichloromethane/acetone to afford **L*** (3.08 g, 4.0 mmol, 85% yield).

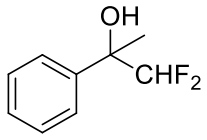


3. General procedure for the catalytic enantioselective addition of $ZnMe_2$ to ketones

In a typical procedure, The ketone (0.42 mmol, 1 eq) was added to a previously prepared solution containing 0.5 M ZnMe2 in dichloromethane (1 mL, 0.5 mmol, 1.2 eq) and L* (0.042 mmol, 0.01 eq) in a 25 mL screw tap Schlenk and immersed in a –85 °C bath of isopropanol. After addition of the ketone, the reaction was placed in an isopropanol bath with the temperature regulated by a cryoprobe.



After the corresponding reaction time, the mixture was carefully hydrolysed with 2 M HCl (5 mL). The organic layer (DCM) was separated and an aliquot was taken to determine by ^{19}F NMR spectroscopy and chiral gas chromatography or HPLC the conversion and enantiomeric. The aqueous layer was extracted with OEt_2 (2 X 5 mL). This OEt_2 solution was added to the dichloromethane solution, whereupon a white precipitate, corresponding to Zn salts containing the ligand **L*** was formed. The DCM+OEt_2 solution, containing the alcohol, was dried over $MgSO_4$, filtered, and concentrated by passing airflow until ca. 4 mL. The solution was then filtered through a silica gel column to remove the salt derived from the ligand. Removal of the solvent by airflow gave the corresponding alcohol. The yield of the reaction was measured by weighing (60-95%).

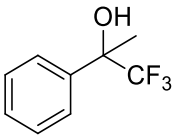


1,1–difluoro–2–phenylpropan–2–ol (**1b**)

Starting from **1a** (52 µL, 65.1 mg, 0.42 mmol) and following the general procedure described above (–30 °C, 24 h), compound **1b** (52.0 mg, 73%) was obtained as a colorless oil. The conversion observed by ^{19}F NMR was > 99%. In these conditions, the compound was obtained with a 89:11 enantiomeric ratio determined by HPLC using Chiralpak–AD column [hexane/isopropanol (95:5), 1 mL/min]: t_{mayor} = 8.381 min, t_{minor} = 9.136 min.

^{1}H NMR (499.72 MHz, $CDCl_3$, 298 K): δ 7.53 (m, 2H, *o*–C*H*), 7.40 (m, 2H, *m*–C*H*), 7.35 (m, 1H, *p*–C*H*), 5.73 (dd, $J_{H–F}$ = 56.8, 56.1 Hz, 1H, C*H*F_2), 2.53 (br, 1H, O*H*), 1.66 (t, $J_{H–F}$ = 1.6, 3H, CH_3). **^{19}F NMR (470.15 MHz, $CDCl_3$, 298 K):** δ –129.6 and –130.3 (*AB*X system, J_{AB} = 277.0 Hz, $J_{H–F}$ = 56.8, 56.1 Hz, 2F, CHF_2). **^{13}C{^{1}H} NMR (125.67 MHz, $CDCl_3$, 298 K)**: δ 140.5 (dd, $J_{C–F}$ = 2.1, 1.1 Hz, C_{arom}–COH), 128.5 (s, *m*–*C*H), 128.2 (s, *p*–*C*H), 125.8 (t, $J_{C–F}$ = 1.1 Hz, *o*–*C*H), 117.0 (t, $J_{C–F}$ = 249.2 Hz, *C*HF_2), 74.3 (t, $J_{C–F}$ = 22.0 Hz, *C*OH), 22.4 (t, $J_{C–F}$ = 2.6 Hz, *C*H_3).

MS: calculated mass for $C_9H_{10}F_2O$: 172.07; measured mass: 172.04

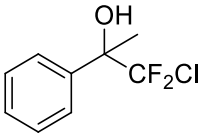


1,1,1–trifluoro–2–phenylpropan–2–ol (**2b**)

Starting from **2a** (57 µL, 72.6 mg, 0.42 mmol) and following the general procedure described above (–30 °C, 24 h), compound **2b** (74.2 mg, 94%) was obtained as a colorless oil. The conversion observed by ^{19}F NMR was > 99%. In these conditions, the compound was obtained with a 96:4 enantiomeric ratio determined by GC using LIPODEX–E capillary column [T_0 = 100 °C; t_0 = 15 min; *ramp* = 20 °C /min; T_f = 120 °C; t_f = 10 min]: t_{mayor} = 18.985 min, t_{minor} = 19.684 min.

^{1}H NMR (400.14 MHz, $CDCl_3$, 298 K): δ 7.59 (m, 2H, *o*–C*H*), 7.45–7.35 (m, 3H, *p*–C*H* + *m*–C*H*), 2.38 (s, 1H, O*H*), 1.80 (s, 3H, CH_3). **^{19}F NMR (376.51 MHz, $CDCl_3$, 298 K):** δ –81.00 (s, 3F, CF_3). **^{13}C{^{1}H} NMR (100.62 MHz, $CDCl_3$, 298 K)**: δ 138.6 (s, C_{arom}–COH), 128.7 (s, *p*–*C*H), 128.5 (s, *m*–*C*H), 126.2 (s, *o*–*C*H), 125.8 (q, $J_{C–F}$ = 285.2 Hz, *C*F_3), 75.0 (q, $J_{C–F}$ = 29.2 Hz, *C*OH), 23.9 (s, *C*H_3).

MS: calculated mass for $C_9H_9F_3O$: 190.06; measured mass: 190.02

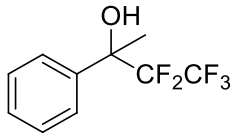


1–chloro–1,1–difluoro–2–phenylpropan–2–ol (**3b**)

Starting from **3a** (60 µL, 79.4 mg, 0.42 mmol) and following the general procedure described above (–30 °C, 24 h), compound **3b** (80.4 mg, 93%) was obtained as a colorless oil. The conversion observed by ^{19}F NMR was > 99%. In these conditions, the compound was obtained with a 99:1 enantiomeric ratio determined by GC using LIPODEX–E capillary column [isotherm conditions, T = 110 °C; *t* = 40 min]: t_{mayor} = 29.146 min, t_{minor} = 31.035 min.

^{1}H NMR (499.72 MHz, $CDCl_3$, 298 K): δ 7.61 (m, 2H, *o*–C*H*), 7.33–7.45 (m, 3H, *p*–C*H* + *m*–C*H*), 3.03 (br, 1H, O*H*), 1.85 (s, 3H, CH_3). **^{19}F NMR (470.15 MHz, $CDCl_3$, 298 K):** δ –64.2 and –64.6 (*AB* system, J_{AB} = 164.0 Hz, Δν = 198.8 Hz, 2F, $CClF_2$). **^{13}C{^{1}H} NMR (125.67 MHz, $CDCl_3$, 298 K)**: δ 139.0 (s, C_{arom}–COH), 131.7 (t, $J_{C–F}$ = 301.1 Hz, $CClF_2$), 128.6 (s, *p*–*C*H), 128.2 (s, *m*–*C*H), 126.6 (t, $J_{C–F}$ = 1.6 Hz, *o*–*C*H), 78.4 (t, $J_{C–F}$ = 24.9 Hz, *C*OH), 24.5 (t, $J_{C–F}$ = 1.6 Hz, *C*H_3).

MS: calculated mass for $C_9H_9ClF_2O$: 206.03; measured mass: 206.00

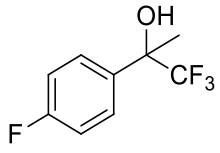


1,1,1,2,2–pentafluoro–3–phenylbutan–3–ol (**4b**)

Starting from **4a** (68 µL, 93.4 mg, 0.42 mmol) and following the general procedure described above (–30 °C, 24 h), compound **4b** (78.7 mg, 79%) was obtained as a colorless oil. The conversion observed by ^{19}F NMR was 87%. In these conditions, the compound was obtained with a 100:0 enantiomeric ratio determined by GC using LIPODEX–E capillary column [isotherm conditions, T = 100 °C; *t* = 30 min]: t_{mayor} = 22.882 min, t_{minor} = 23.705 min.

^{1}H NMR (499.72 MHz, $CDCl_3$, 298 K): δ 7.58 (m, 2H, *o*–C*H*), 7.35–7.43 (m, 3H, *p*–C*H* + *m*–C*H*), 2.43 (br, 1H, O*H*), 1.83 (s, 3H, CH_3). **^{19}F NMR (470.15 MHz, $CDCl_3$, 298 K):** δ –77.97 (s, 3F, CF_2CF_3), –121.5 and –123.0 (*AB* system, J_{AB} = 277.5 Hz, Δν = 686.4 Hz, 2F, CF_2CF_3). **^{13}C{^{1}H} NMR (125.67 MHz, $CDCl_3$, 298 K)**: δ 138.7 (dd, $J_{C–F}$ = 1.9, 0.7 Hz, C_{arom}–COH), 128.7 (s, *p*–*C*H), 128.4 (s, *m*–*C*H), 126.2 (t, $J_{C–F}$ = 1.5 Hz, *o*–*C*H), 119.4 (qt, $J_{C–F}$ = 288.1, 36.6 Hz, CF_2CF_3), 114.5 (tq, $J_{C–F}$ = 261.9, 34.6, CF_2CF_3), 75.2 (t, $J_{C–F}$ = 23.8 Hz, *C*OH), 24.8 (tq, $J_{C–F}$ = 3.3, 1.6 Hz , *C*H_3).

MS: calculated mass for $C_{10}H_9F_5O$: 240.06; measured mass: 239.00



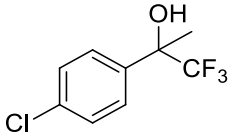
1,1,1–trifluoro–2–(4–fluorophenyl)propan–2–ol (**5b**)

Starting from **5a** (80.0 mg, 0.42 mmol) and following the general procedure described above (–30 °C, 24 h), compound **5b** (72.6 mg, 84%) was obtained as a colorless oil. The conversion observed by ^{19}F NMR was > 99%. In these conditions, the compound was obtained with a 96:4

enantiomeric ratio determined by GC using LIPODEX–E capillary column [isotherm conditions, T = 110 °C; *t* = 30 min]: t_{mayor} = 14.347 min, t_{minor} = 15.829 min.

^{1}H NMR (499.72 MHz, $CDCl_3$, 298 K): δ 7.56 (m, 2H, *o*–C*H*), 7.08 (m, 2H, *m*–C*H*), 2.40 (s, 1H, O*H*), 1.78 (q, $J_{H–F}$ = 1.0 Hz, 3H, CH_3). **^{19}F NMR (470.15 MHz, $CDCl_3$, 298 K):** δ –81.29 (s, 3F, CF_3), –113.70 (tt, $J_{F–H}$ = 8.4, 5.3 Hz, 1F, *p*–C*F*). **^{13}C{^{1}H} NMR (125.67 MHz, $CDCl_3$, 298 K)**: δ 163.0 (d, $J_{C–F}$ = 247.8 Hz, *p*–*C*F), 134.2 (d, $J_{C–F}$ = 3.2 Hz, C_{arom}–COH), 128.2 (dq, $J_{C–F}$ = 8.3, 1.4 Hz, *o*–*C*H), 125.6 (q, $J_{C–F}$ = 285.1 Hz, *C*F_3), 115.4 (d, $J_{C–F}$ = 21.5 Hz, *m*–*C*H), 74.7 (q, $J_{C–F}$ = 29.4 Hz, *C*OH), 24.2 (q, $J_{C–F}$ = 1.1 Hz, *C*H_3).

MS: calculated mass for $C_9H_8F_4O$: 208.05; measured mass: 208.03

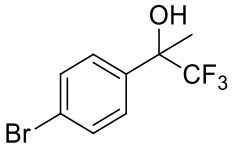


1,1,1–trifluoro–2–(4–chlorophenyl)propan–2–ol (**6b**)

Starting from **6a** (80.0 mg, 0.42 mmol) and following the general procedure described above (–30 °C, 24 h), compound **6b** (73.5 mg, 79%) was obtained as a colorless oil. The conversion observed by ^{19}F NMR was > 99%. In these conditions, the compound was obtained with a 95:5 enantiomeric ratio determined by GC using LIPODEX–E capillary column [T_0 = 100 °C; t_0 = 15 min; *ramp* = 5 °C /min; T_f = 120 °C; t_f = 25 min]: t_{mayor} = 38.221 min, t_{minor} = 40.589 min.

^{1}H NMR (499.72 MHz, $CDCl_3$, 298 K): δ 7.52 (m, 2H, *o*–C*H*), 7.37 (m, 2H, *m*–C*H*), 2.39 (s, 1H, O*H*), 1.77 (q, $J_{H–F}$ = 1.1 Hz, 3H, CH_3). **^{19}F NMR (470.15 MHz, $CDCl_3$, 298 K):** δ –81.17 (s, 3F, CF_3). **^{13}C{^{1}H} NMR (125.67 MHz, $CDCl_3$, 298 K)**: δ 136.9 (s, *p*–*C*Cl), 134.9 (s, C_{arom}–COH), 128.6 (s, *m*–*C*H), 127.6 (q, $J_{C–F}$ = 1.3 Hz, *o*–*C*H), 125.5 (q, $J_{C–F}$ = 285.3 Hz, *C*F_3), 74.7 (q, $J_{C–F}$ = 29.6 Hz, *C*OH), 24.1 (q, $J_{C–F}$ = 1.1 Hz, *C*H_3).

MS: calculated mass for $C_9H_8ClF_3O$: 224.02; measured mass: 223.97



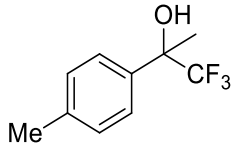
1,1,1–trifluoro–2–(4–bromophenyl)propan–2–ol (**7b**)

Starting from **7a** (105.4 mg, 0.42 mmol) and following the general procedure described above (–30 °C, 24 h), compound **7b** (100.1 mg, 89%) was obtained as a colorless oil. The conversion

observed by ^{19}F NMR was > 99%. In these conditions, the compound was obtained with a 94:6 enantiomeric ratio determined by GC using LIPODEX–E capillary column [T_0 = 100 °C; t_0 = 15 min; *ramp* = 5 °C /min; T_f = 120 °C; t_f = 30 min]: t_{mayor} = 24.782 min, t_{minor} = 30.139 min.

^{1}H NMR (499.72 MHz, $CDCl_3$, 298 K): δ 7.40 (m, 2H, *o*–C*H*), 7.47 (m, 2H, *m*–C*H*), 2.87 (s, 1H, O*H*), 1.70 (s, 3H, CH_3). **^{19}F NMR (470.15 MHz, $CDCl_3$, 298 K):** δ –80.94 (s, 3F, CF_3). **^{13}C{^{1}H} NMR (125.67 MHz, $CDCl_3$, 298 K)**: δ 137.5 (s, C_{arom}–COH), 131.6 (s, *m*–*C*H), 128.0 (s, *o*–*C*H), 125.4 (q, $J_{C–F}$ = 285.2 Hz, *C*F_3), 123.1 (s, *p*–*C*Br), 74.8 (q, $J_{C–F}$ = 29.4, Hz, *C*OH), 23.7 (s, *C*H_3).

MS: calculated mass for $C_9H_8BrF_3O$: 267.97; measured mass: 267.96

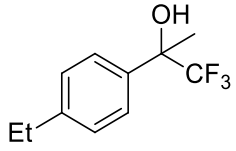


1,1,1–trifluoro–2–(4–methylphenyl)propan–2–ol (**8b**)

Starting from **8a** (63 µL, 78.4 mg, 0.42 mmol) and following the general procedure described above (–30 °C, 24 h), compound **8b** (68.3 mg, 80%) was obtained as a colorless oil. The conversion observed by ^{19}F NMR was > 99%. In these conditions, the compound was obtained with a 94:6 enantiomeric ratio determined by GC using LIPODEX–E capillary column [T_0 = 100 °C; t_0 = 15 min; *ramp* = 20 °C /min; T_f = 120 °C; t_f = 30 min]: t_{mayor} = 21.472 min, t_{minor} = 22.905 min.

^{1}H NMR (499.72 MHz, $CDCl_3$, 298 K): δ 7.46 (m, 2H, *o*–C*H*), 7.21 (m, 2H, *m*–C*H*), 2.40 (s, 1H, O*H*), 2.37 (s, 3H, C_{arom}–CH_3), 1.77 (s, 3H, CH_3). **^{19}F NMR (470.15 MHz, $CDCl_3$, 298 K):** δ –81.09 (s, 3F, CF_3). **^{13}C{^{1}H} NMR (125.67 MHz, $CDCl_3$, 298 K)**: δ 138.4 (s, *p*–*C*Me), 135.5 (s, C_{arom}–COH), 129.0 (s, *m*–*C*H), 125.9 (q, $J_{C–F}$ = 1.2 Hz, *o*–*C*H), 125.6 (q, $J_{C–F}$ = 285.2 Hz, *C*F_3), 74.7 (q, $J_{C–F}$ = 29.2 Hz, *C*OH), 23.8 (q, $J_{C–F}$ = 1.1 Hz, *C*H_3), 21.0 (s, *p*–C*C*H_3).

MS: calculated mass for $C_{10}H_{11}F_3O$: 204.08; measured mass: 204.05



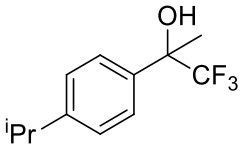
1,1,1–trifluoro–2–(4–ethylphenyl)propan–2–ol (**9b**)

Starting from **9a** (70 µL, 84.2 mg, 0.42 mmol) and following the general procedure described above (–30 °C, 24 h), compound **9b** (69.0 mg, 76%) was obtained as a colorless oil. The

conversion observed by ^{19}F NMR was > 99%. In these conditions, the compound was obtained with a 94:6 enantiomeric ratio determined by GC using LIPODEX–E capillary column [isotherm conditions, T = 110 °C; *t* = 40 min]: t_{mayor} = 28.928 min, t_{minor} = 32.128 min.

^{1}H NMR (499.72 MHz, $CDCl_3$, 298 K): δ 7.49 (m, 2H, *o*–C*H*), 7.24 (m, 2H, *m*–C*H*), 2.67 (q, $J_{H–H}$ = 7.6, 2H, CH_2CH$_3$), 2.46 (s, 1H, O*H*), 1.78 (q, $J_{H–F}$ = 1.1 Hz, 3H, CH_3), 1.25 (t, $J_{H–H}$ = 7.6 Hz, 3H, CH$_2$CH_3). **^{19}F NMR (470.15 MHz, $CDCl_3$, 298 K):** δ –81.04 (s, 3F, CF_3). **^{13}C{^{1}H} NMR (125.67 MHz, $CDCl_3$, 298 K)**: δ 144.7 (s, *p*–*C*Et), 135.7 (s, C_{arom}–COH), 127.8 (s, *m*–*C*H), 125.9 (q, $J_{C–F}$ = 1.2 Hz, *o*–*C*H), 125.6 (q, $J_{C–F}$ = 285.3 Hz, *C*F$_3$), 74.7 (q, $J_{C–F}$ = 29.2 Hz, *C*OH), 28.4 (s, *C*H$_2$CH$_3$), 23.8 (q, $J_{C–F}$ = 1.1, *C*H$_3$), 15.3 (s, CH$_2$*C*H$_3$).

MS: calculated mass for $C_{11}H_{13}F_3O$: 218.09; measured mass: 218.10

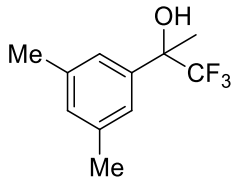


1,1,1–trifluoro–2–(4–isopropylphenyl)propan–2–ol (**10b**)

Starting from **10a** (78 µL, 90.1 mg, 0.42 mmol) and following the general procedure described above (–30 °C, 24 h), the conversion to **10b** observed by ^{19}F NMR was < 2%. In this case, it was necessary to increasing the temperature (25ºC, 24h) in order to get the compound **10b** (93,4 mg, 97%) as a colorless oil. The conversion observed by ^{19}F NMR was 76%. In these new conditions, the compound was obtained with a 73:27 enantiomeric ratio determined by GC using LIPODEX–E capillary column [isotherm conditions, T = 110 °C; *t* = 50 min]: t_{mayor} = 34.040min, t_{minor} = 36.731 min.

^{1}H NMR (499.72 MHz, $CDCl_3$, 298 K): δ 7.49 (m, 2H, *o*–C*H*), 7.24 (m, 2H, *m*–C*H*), 2.93 (sp, $J_{H–H}$ = 6.9 Hz, C*H*(CH$_3$)$_2$), 2.39 (s, 1H, O*H*), 1.77 (s, 3H, CH_3), 1.26 (d, $J_{H–H}$ = 6.9 Hz, 6H, CH(CH_3)$_2$). **^{19}F NMR (470.15 MHz, $CDCl_3$, 298 K):** δ –80.90 (s, 3F, CF_3). **^{13}C{^{1}H} NMR (125.67 MHz, $CDCl_3$, 298 K)**: δ 149.3 (s, *p*–*C*^{i}Pr), 135.8 (s, C_{arom}–COH), 126.4 (s, *m*–*C*H), 125.9 (q, $J_{C–F}$ = 1.3 Hz, *o*–*C*H), 125.6 (q, $J_{C–F}$ = 285.2 Hz, *C*F$_3$), 74.7 (q, $J_{C–F}$ = 29.1 Hz, *C*OH), 33.7 (s, *C*H(CH$_3$)$_2$), 23.8 (q, $J_{C–F}$ = 1.1, *C*H$_3$), 23.8 (s, CH(*C*H$_3$)$_2$).

MS: calculated mass for $C_{12}H_{15}F_3O$: 232.11; measured mass: 232.06

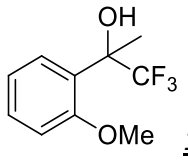


1,1,1–trifluoro–2–(3,5–dimethylphenyl)propan–2–ol (**11b**)

Starting from **11a** (71 µL, 84.2 mg, 0.42 mmol) and following the general procedure described above (–30 °C, 24 h), compound **11b** (72.2 mg, 79%) was obtained as a colorless oil. The conversion observed by ^{19}F NMR was > 99%. In these conditions, the compound was obtained with a 98:2 enantiomeric ratio determined by GC using LIPODEX–E capillary column [isotherm conditions, T = 110 °C; *t* = 30 min]: t_{mayor} = 21.014 min, t_{minor} = 22.092 min.

^{1}H NMR (499.72 MHz, $CDCl_3$, 298 K): δ 7.18 (s, 2H, *o*–C*H*), 7.02 (m, 1H, *p*–C*H*), 2.46 (s, 1H, O*H*), 2.36 (q, $J_{H–F}$ = 0.6 Hz, 6H, CH_3), 1.77 (q, $J_{H–F}$ = 1.1 Hz, 3H, CH_3). **^{19}F NMR (470.15 MHz, $CDCl_3$, 298 K):** δ –81.19 (s, 3F, CF_3). **^{13}C{^{1}H} NMR (125.67 MHz, $CDCl_3$, 298 K)**: δ 138.5 (s, C_{arom}–COH), 138.0 (s, *m*–*C*Me), 130.3 (s, *p*–*C*H), 125.7 (q, $J_{C–F}$ = 285.3 Hz, *C*F_3), 123.8 (q, $J_{C–F}$ = 1.2 Hz, *o*–*C*H), 74.9 (q, $J_{C–F}$ = 29.1 Hz, *C*OH), 24.1 (q, $J_{C–F}$ = 1.3 Hz, *C*H_3), 21.6 (s, *m*–C*C*H_3).

MS: calculated mass for $C_{11}H_{13}F_3O$: 218.09; measured mass: 218.02

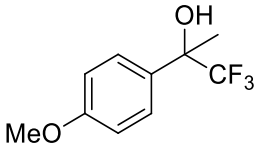


1,1,1–trifluoro–2–(2–methoxyphenyl)propan–2–ol (**12b**)

Starting from **12a** (64 µL, 85.0 mg, 0.42 mmol) and following the general procedure described above (–30 °C, 24 h), compound **12b** (32.1 mg, 32%) was obtained as a colorless oil. The conversion observed by ^{19}F NMR was 64%. In these conditions, the compound was obtained with a 42:58 enantiomeric ratio determined by GC using LIPODEX–E capillary column [isotherm conditions, T = 110 °C; *t* = 30 min]: t_{minor} = 20.676 min, t_{mayor} = 21.698 min.

^{1}H NMR (499.72 MHz, $CDCl_3$, 298 K): δ 7.30–7.40 (m, 2H), 6.97–7.07 (m, 2H), 6.13 (s, 1H, O*H*), 3.93 (s, 3H, OCH_3), 1.79 (s, 3H, CH_3). **^{19}F NMR (470.15 MHz, $CDCl_3$, 298 K):** δ –81.43 (s, 3F, CF_3). **^{13}C{^{1}H} NMR (125.67 MHz, $CDCl_3$, 298 K)**: δ 158.2 (s, *o*–*C*OMe), 130.4 (s, *p*–*C*H), 129.5 (q, $J_{C–F}$ = 1.0 Hz, *o*–*C*H), 126.1 (q, $J_{C–F}$ = 287.2 Hz, *C*F_3), 125.9 (s, C_{arom}–COH), 121.7 (s, *m*–*C*H), 112.6 (s, *m*–*C*H), 76.4 (q, $J_{C–F}$ = 29.6 Hz, *C*OH), 56.3 (s, OCH_3), 22.5 (q, $J_{C–F}$ = 1.6 Hz, *C*H_3).

MS: calculated mass for $C_{10}H_{11}F_3O_2$: 220.07; measured mass: 220.05

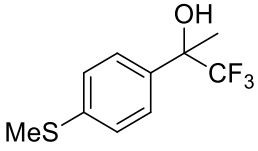


1,1,1–trifluoro–2–(4–methoxyphenyl)propan–2–ol (**13b**)

Starting from **13a** (62 µL, 85.0 mg, 0.42 mmol) and following the general procedure described above (–30 °C, 24 h), compound **13b** (65 mg, 71%) was obtained as a colorless oil. The conversion observed by ^{19}F NMR was < 99%. In these conditions, the compound was obtained with a **92:8** enantiomeric ratio determined by HPLC using Lux–amyl–1_002–CH1 column [hexane/isopropanol (98:2), 1.0 mL/min]: τ_{major} = 23.550 min, τ_{minor} = 25.042 min.

^{1}H NMR (499.72 MHz, $CDCl_3$, 298 K): δ 7.18 (m, 2H, *o*–C*H*), 6.92 (m, 2H, *m*–C*H*), 3.82 (s, 3H, OCH_3), 2.46 (s, 1H, O*H*), 1.77 (q, $J_{H–F}$ = 1.1 Hz, 3H, CH_3). **^{19}F NMR (470.15 MHz, $CDCl_3$, 298 K):** δ –81.64 (s, 3F, CF_3). **^{13}C{^{1}H} NMR (125.67 MHz, $CDCl_3$, 298 K)**: δ 159.7 (s, *p*–*C*OMe), 130.9 (s, C_{arom}–COH), 127.6 (q, $J_{C–F}$ = 1.1 Hz, *o*–*C*H), 125.8 (q, $J_{C–F}$ = 285.2 Hz, *C*F_3), 113.7 (s, *m*–*C*H), 74.6 (q, $J_{C–F}$ = 29.2 Hz, *C*OH), 55.4 (s, O*C*H_3), 23.8 (q, $J_{C–F}$ = 1.2 Hz, *C*H_3).

MS: calculated mass for $C_{10}H_{11}F_3O_2$: 220.07; measured mass:220.05

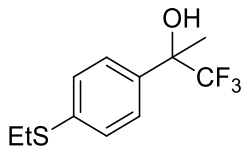


1,1,1–trifluoro–2–(4–(methylthio)methylphenyl)propan–2–ol (**14b**)

Starting from **14a** (91.7 mg, 0.42 mmol) and following the general procedure described above (–30 °C, 24 h), compound **14b** (72.4 mg, 74%) was obtained as a colorless oil. The conversion observed by ^{19}F NMR was > 99%. In these conditions, the compound was obtained with a 91:9 enantiomeric ratio determined by GC using LIPODEX–E capillary column [T_0 = 130 °C; t_0 = 20 min; *ramp* = 10 °C /min; T_f = 140 °C; t_f = 20 min]: t_{mayor} = 36.232 min, t_{minor} = 37.381 min.

^{1}H NMR (499.72 MHz, $CDCl_3$, 298 K): δ 7.49 (m, 2H, *o*–C*H*), 7.31 (m, 2H, *m*–C*H*), 2.52 (s, 1H, O*H*), 2.50 (s, 3H, SCH_3), 1.76 (s, 3H, CH_3). **^{19}F NMR (470.15 MHz, $CDCl_3$, 298 K):** δ –81.07 (s, 3F, CF_3). **^{13}C{^{1}H} NMR (125.67 MHz, $CDCl_3$, 298 K)**: δ 139.3 (s, *p*–*C*SMe), 135.1 (s, C_{arom}–COH), 126.5 (s, *m*–*C*H), 126.1 (s, *o*–*C*H), 125.5 (q, $J_{C–F}$ = 285.3 Hz, *C*F_3), 74.6 (q, $J_{C–F}$ = 29.3 Hz, *C*OH), 23.7 (s, *C*H_3), 15.4 (s, S*C*H_3).

MS: calculated mass for $C_{10}H_{11}F_3OS$: 236.05; measured mass: 236.04



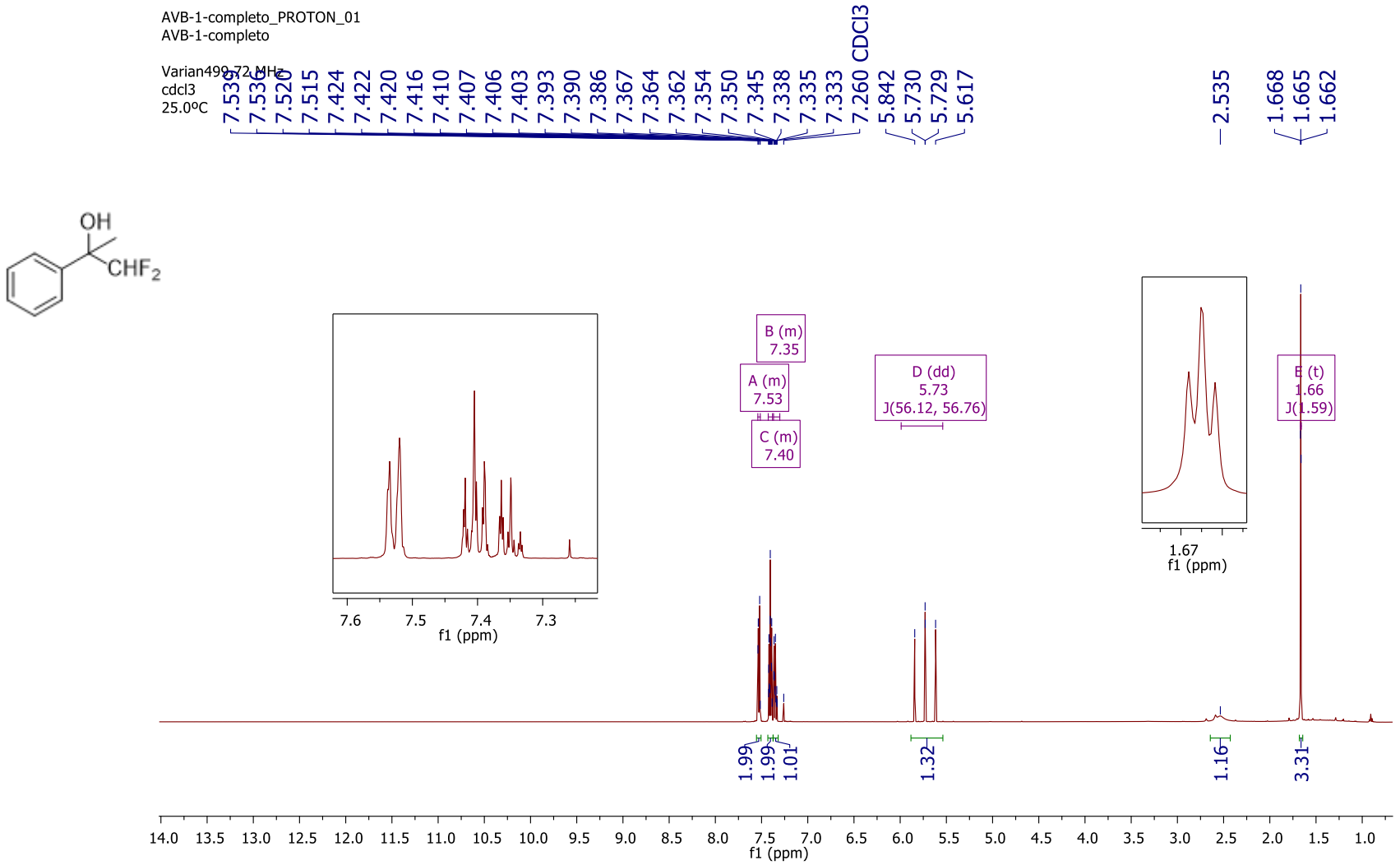
1,1,1–trifluoro–2–(4–(ethylthio)phenyl)propan–2–ol (**15b**)

Starting from **15a** (97.6 mg, 0.42 mmol) and following the general procedure described above (–30 °C, 24 h), compound **15b** (68.3 mg, 66%) was obtained as a colorless oil. The conversion observed by ^{19}F NMR was > 99%. In these conditions, the compound was obtained with a 7:93 enantiomeric ratio determined by HPLC using Chiralpak–AD column [hexane/isopropanol (97:3), 1 mL/min]: t_{minor} = 9.754 min, t_{mayor} = 10.887 min

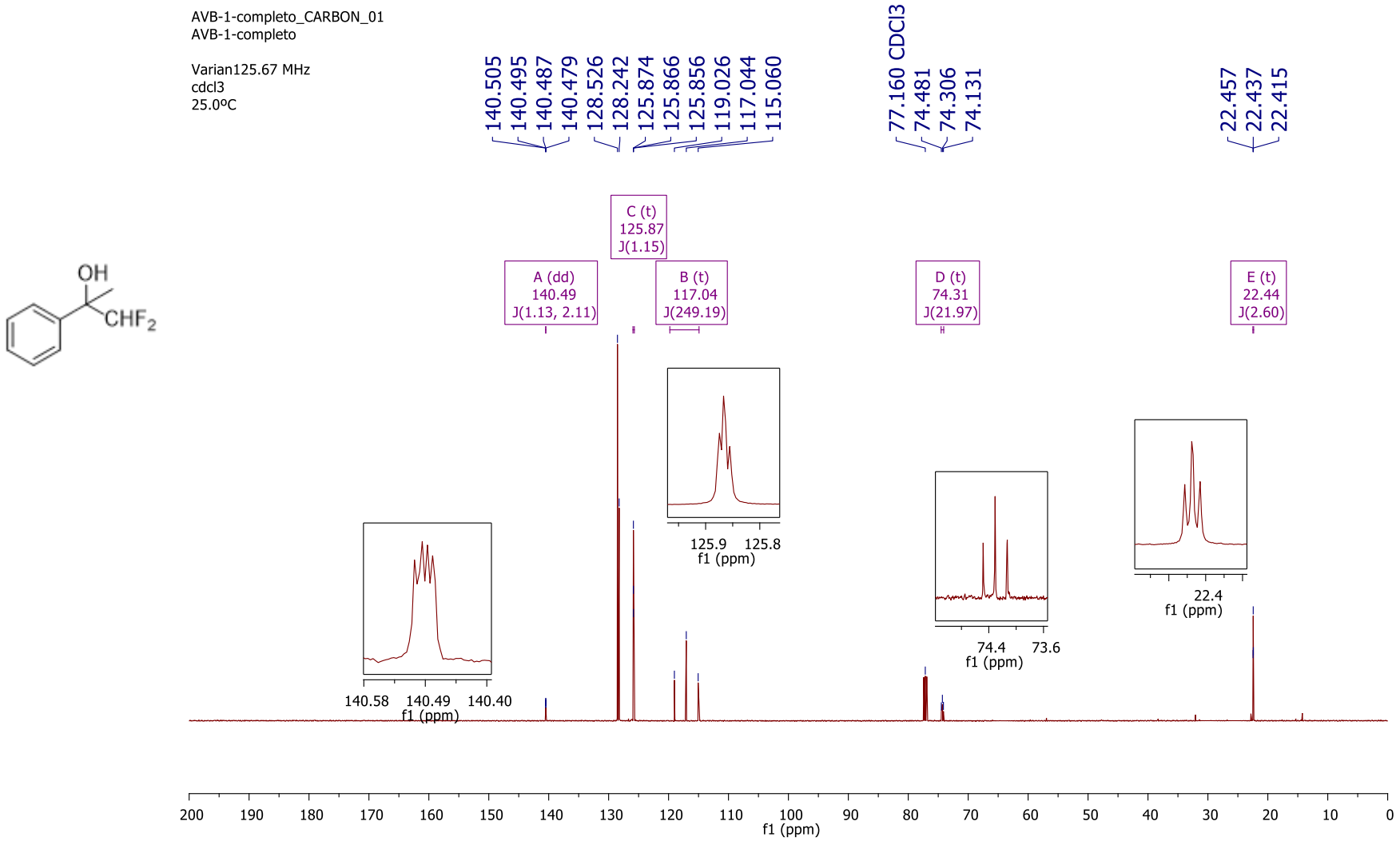
^{1}H NMR (499.72 MHz, $CDCl_3$, 298 K): δ 7.48 (m, 2H, *o*–C*H*), 7.31 (m, 2H, *m*–C*H*), 3.0 (q, $J_{H–H}$ = 7.4, 2H SC*H*$_2$CH$_3$), 2.16 (s, 1H, O*H*), 1.75 (s, 3H, C*H*$_3$), 1.33 (t, $J_{H–H}$ = 7.4, 3H, SCH$_2$C*H*$_3$). **^{19}F NMR (470.15 MHz, $CDCl_3$, 298 K):** δ –81.05 (s, 3F, C*F*$_3$). **^{13}C{^{1}H} NMR (125.67 MHz, $CDCl_3$, 298 K)**: δ 137.6 (s, *p*–*C*SEt), 135.7 (s, *C*$_{arom}$–COH), 128.0 (s, *m*–*C*H), 126.6 (q, $J_{C–F}$ = 1.2 Hz, *o*–*C*H), 125.5 (q, $J_{C–F}$ = 285.3 Hz, *C*F$_3$), 74.6 (q, $J_{C–F}$ = 29.3 Hz, *C*OH), 27.1 (s, S*C*H$_2$CH$_3$), 23.7 (s, *C*H$_3$), 14.2 (s, SCH$_2$*C*H$_3$).

MS: calculated mass for $C_{11}H_{13}F_3OS$: 250.06; measured mass: 250.06

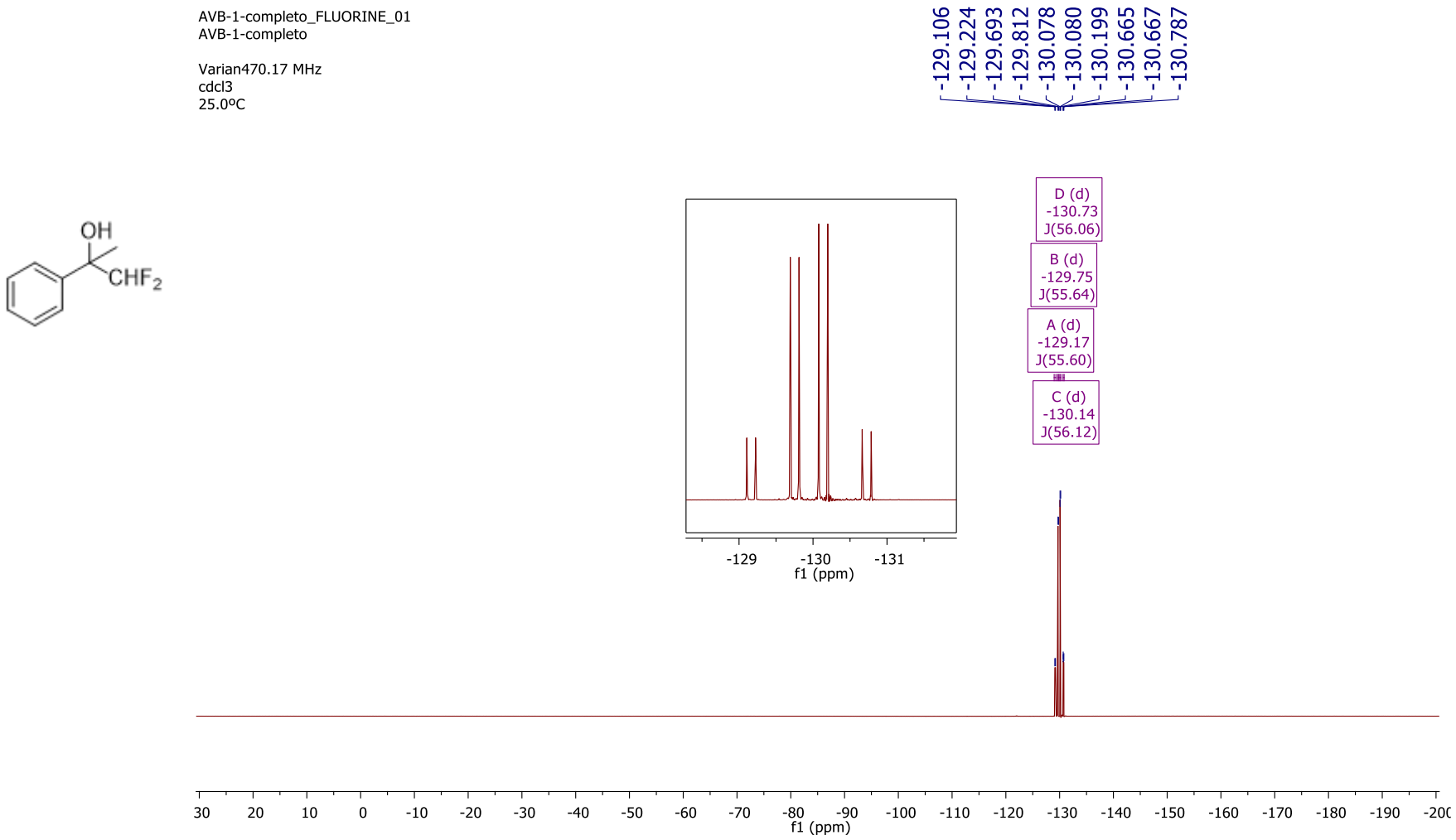
4. NMR spectra of the fluoroalkyl alcohols



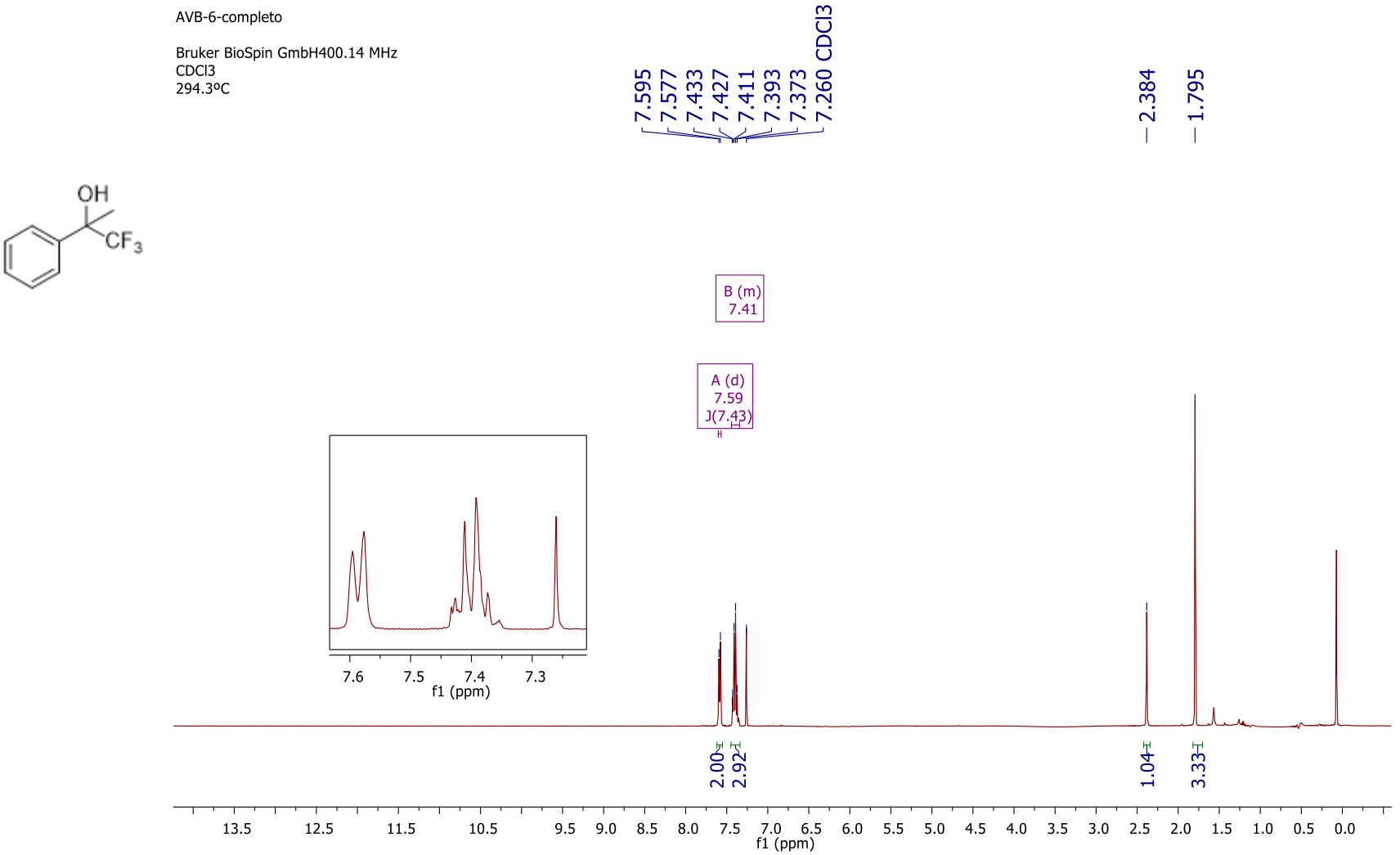
S 1. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) of **1b**



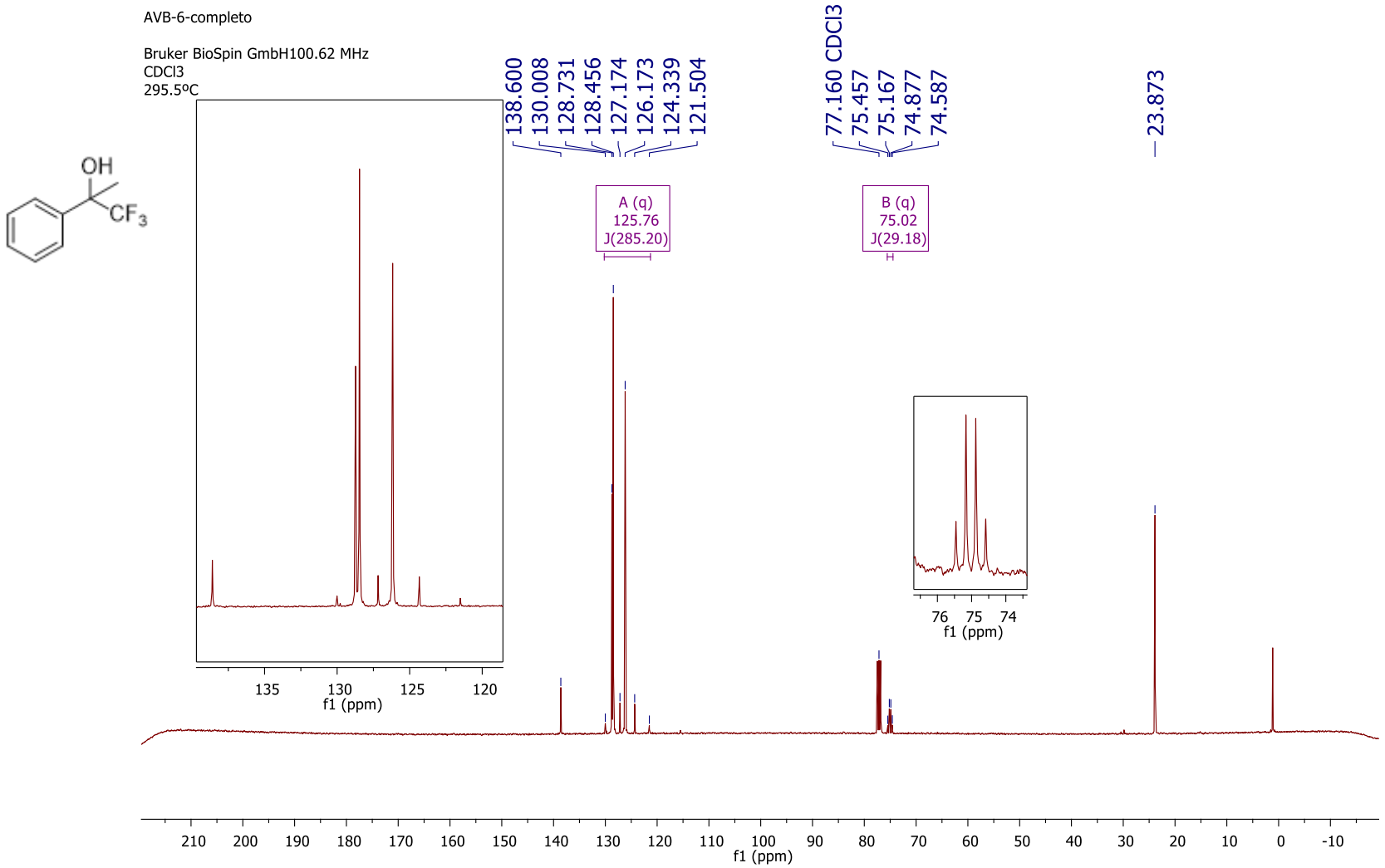
S 2. $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$, 298 K) of **1b**.



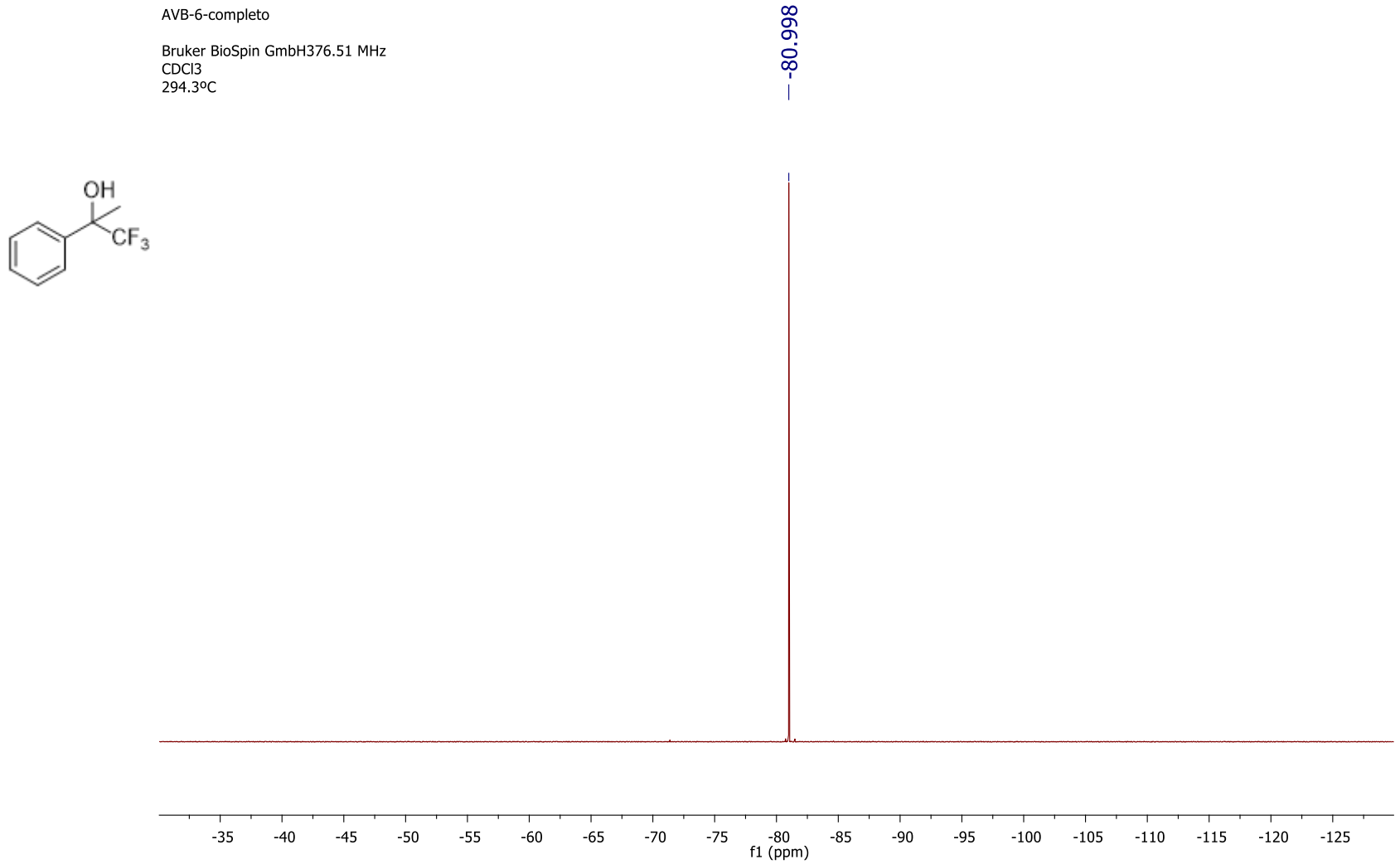
S 3. ^{19}F NMR (470 MHz, $CDCl_3$, 298 K) of **1b**



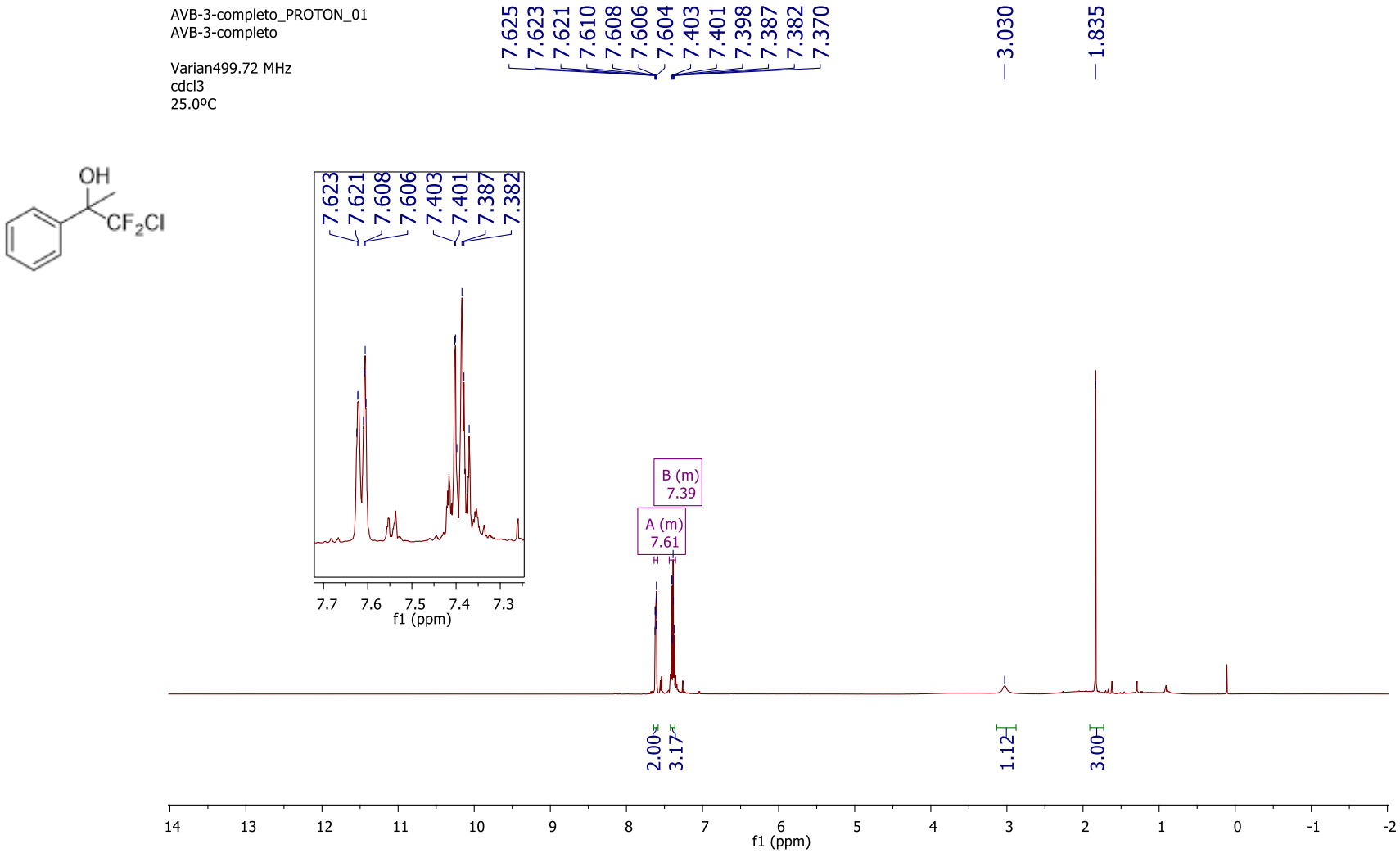
S 4. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) of **2b**.



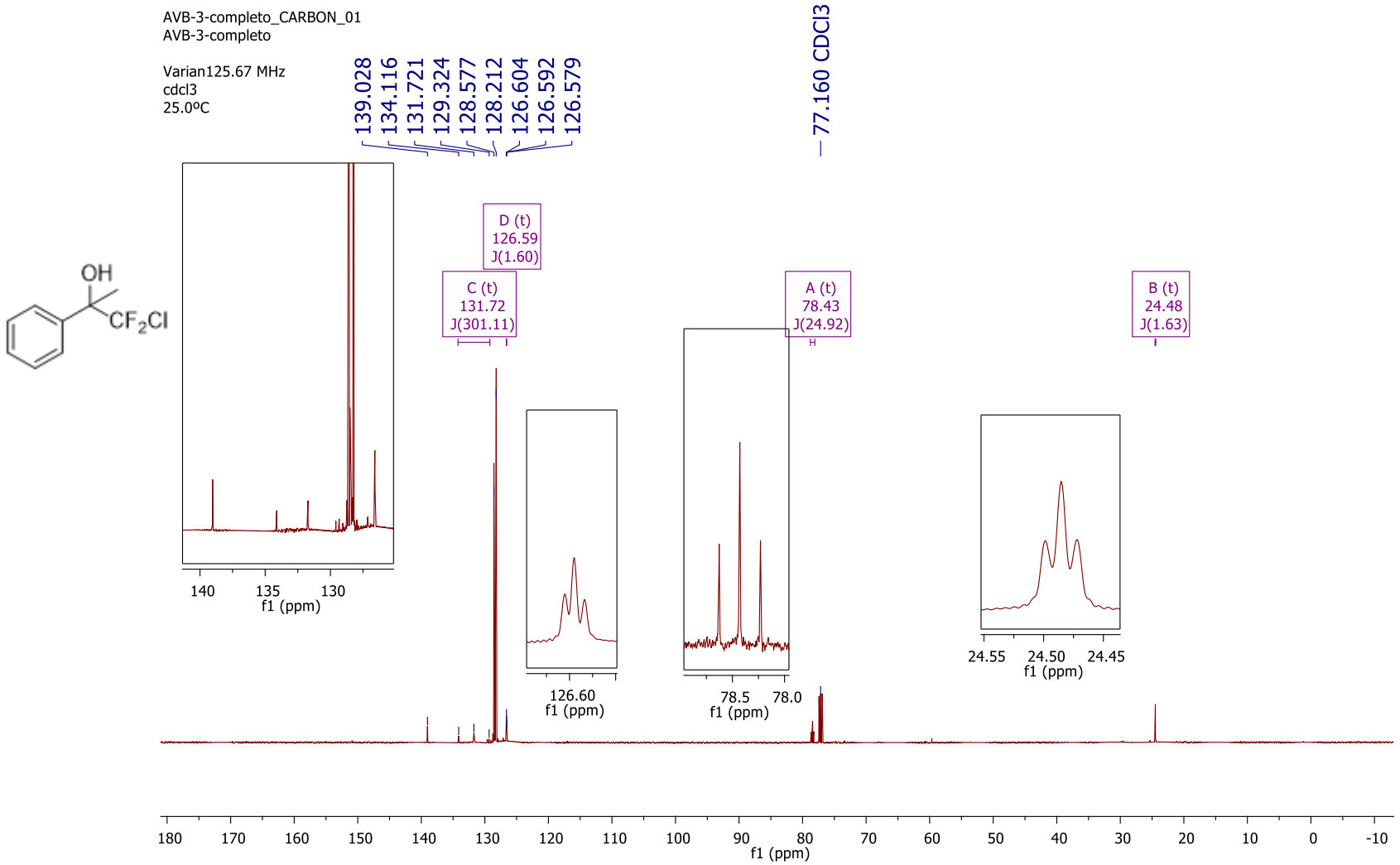
S 5. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 298 K) of **2b**.



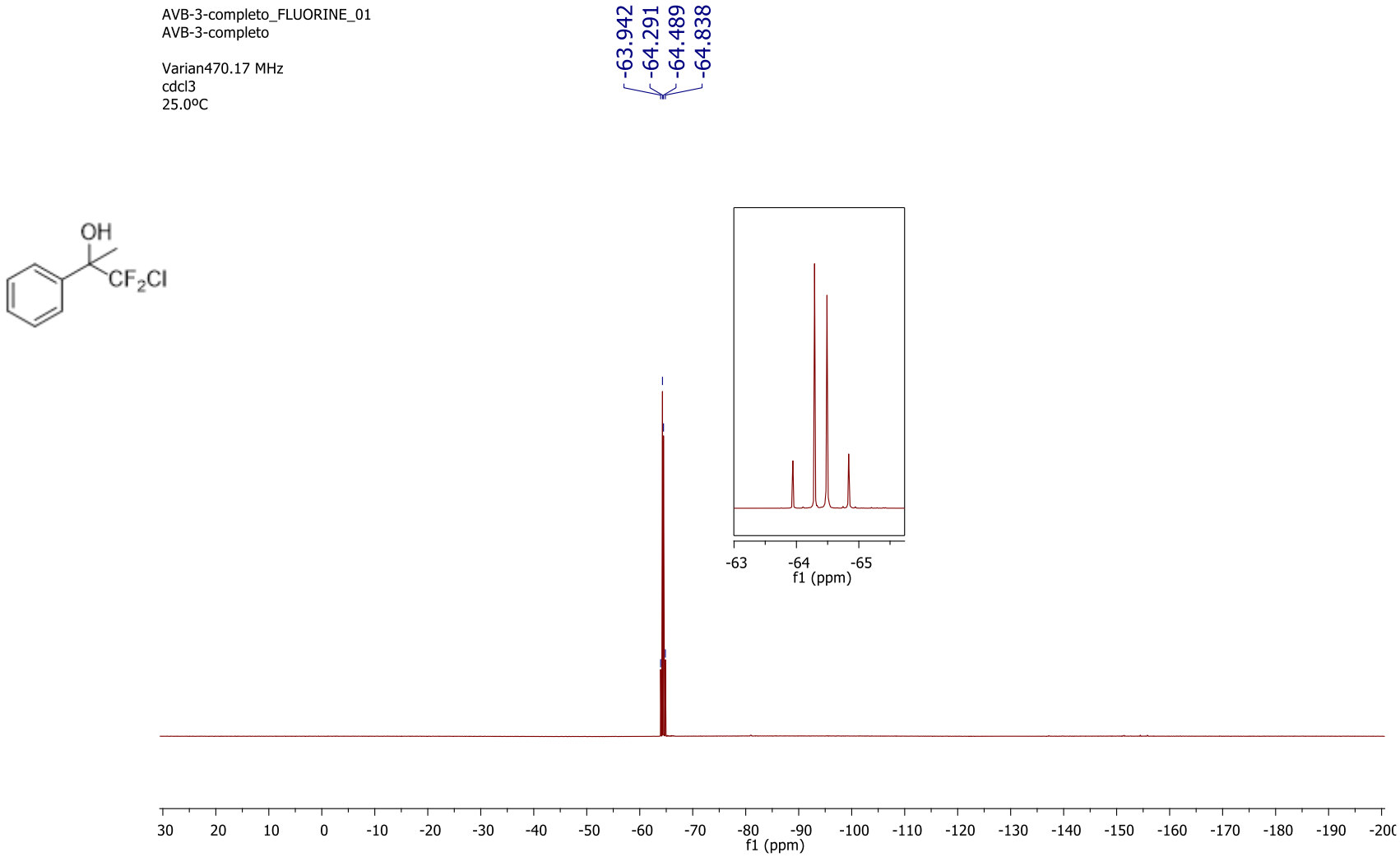
S 6. ^{19}F NMR (376 MHz, $CDCl_3$, 298 K) of **2b**.



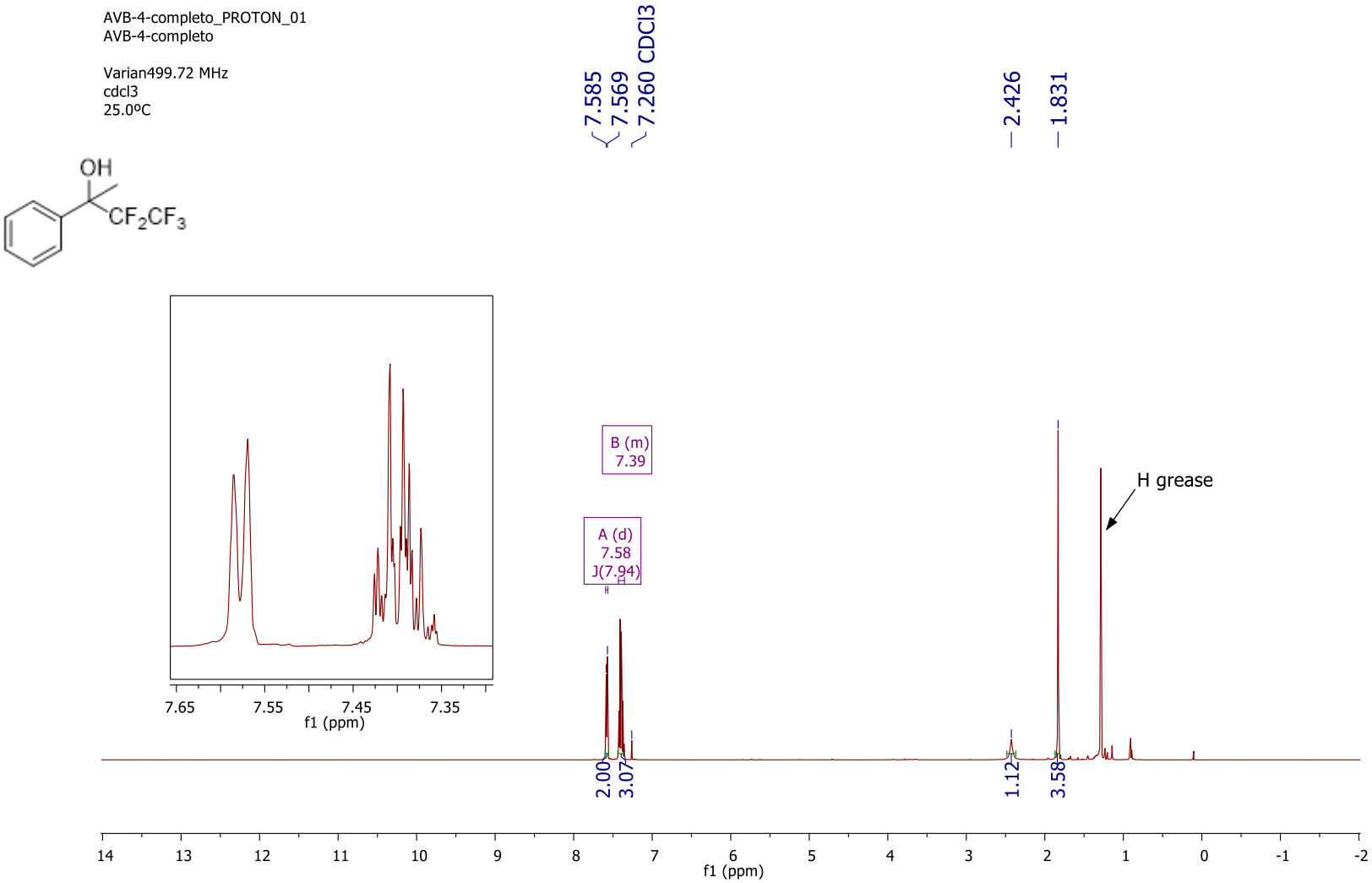
S 7. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) of **3b**



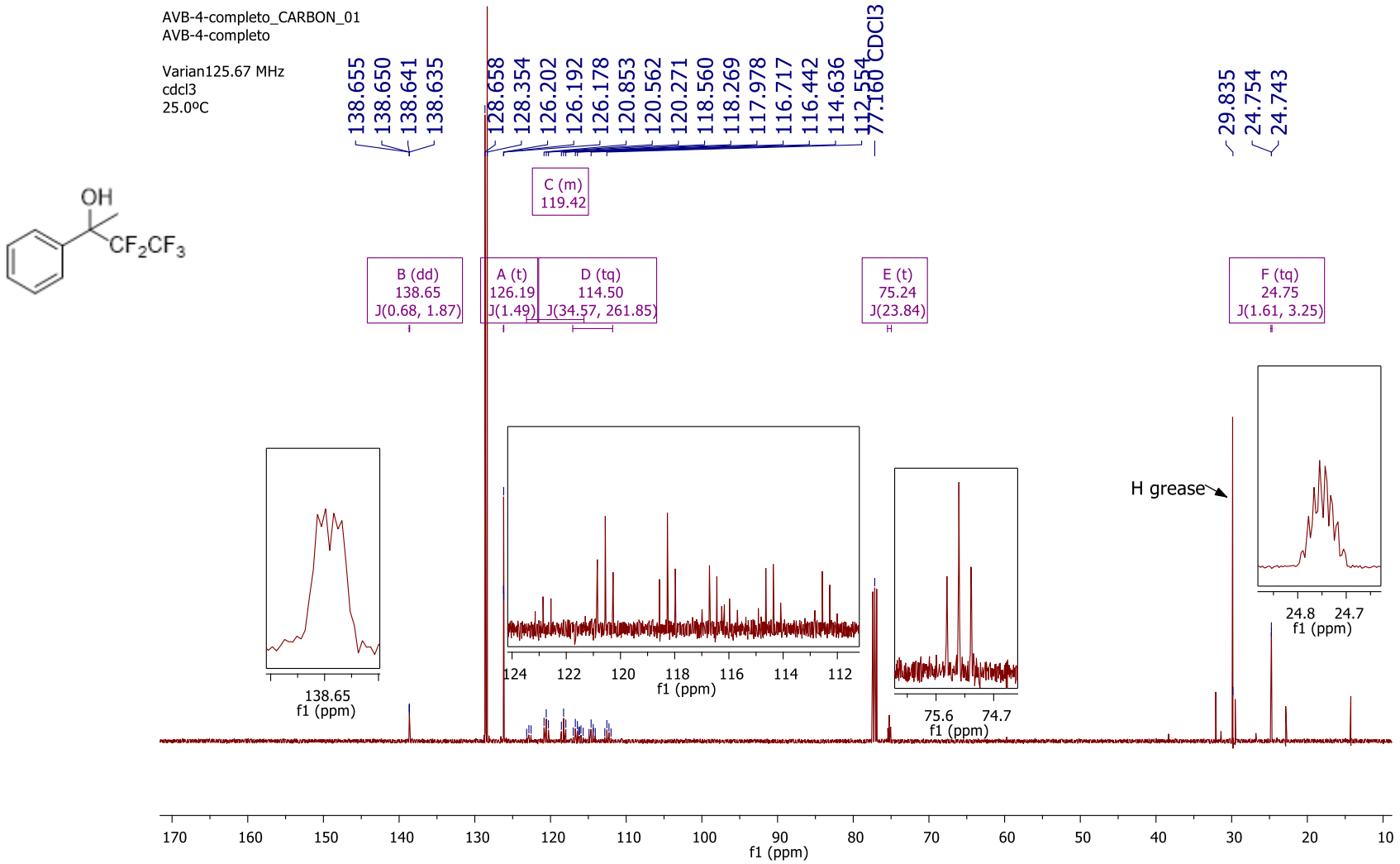
S 8. $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$, 298 K) of **3b**.



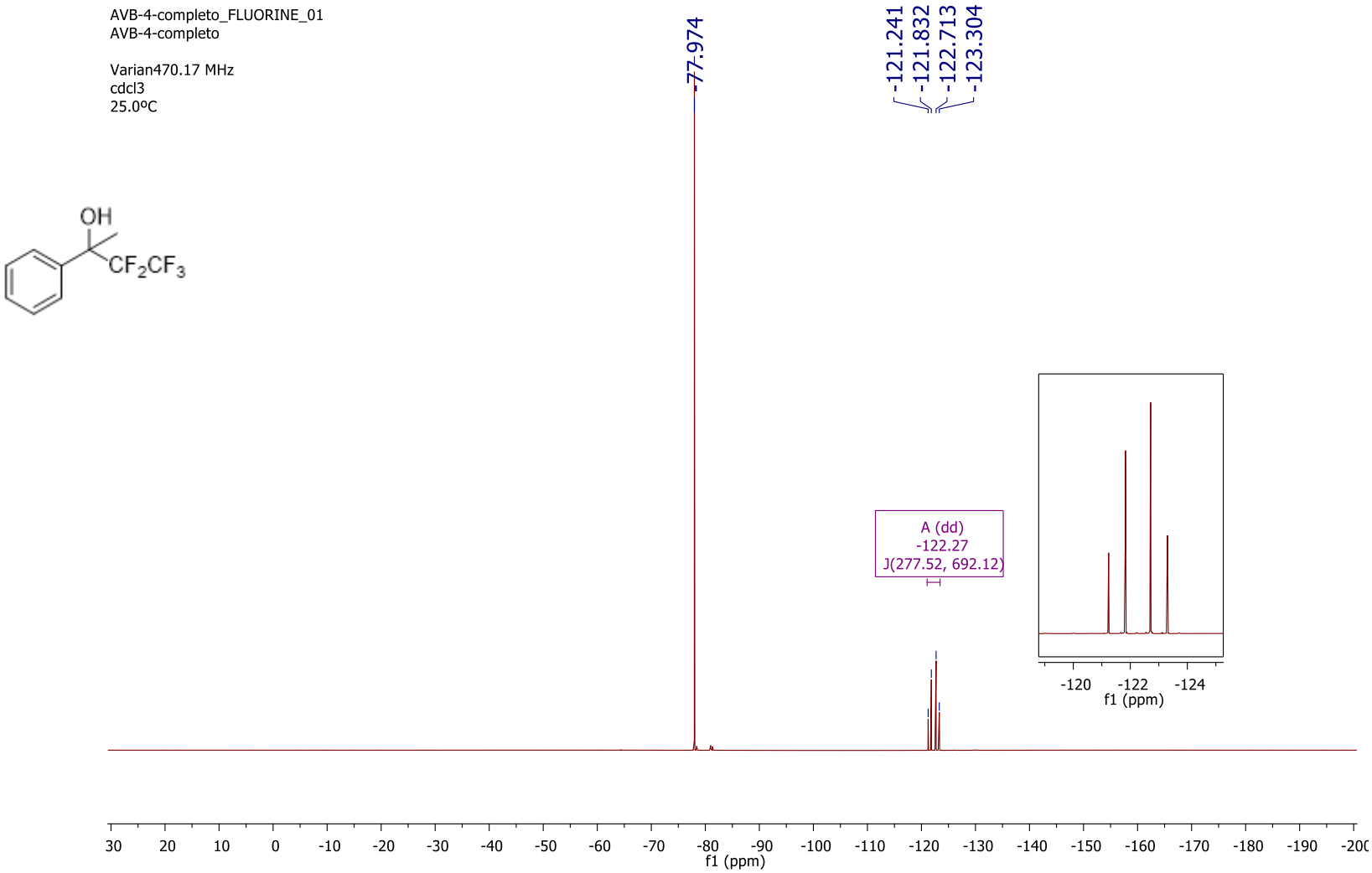
S 9. ^{19}F NMR (470 MHz, $CDCl_3$, 298 K) of **3b**



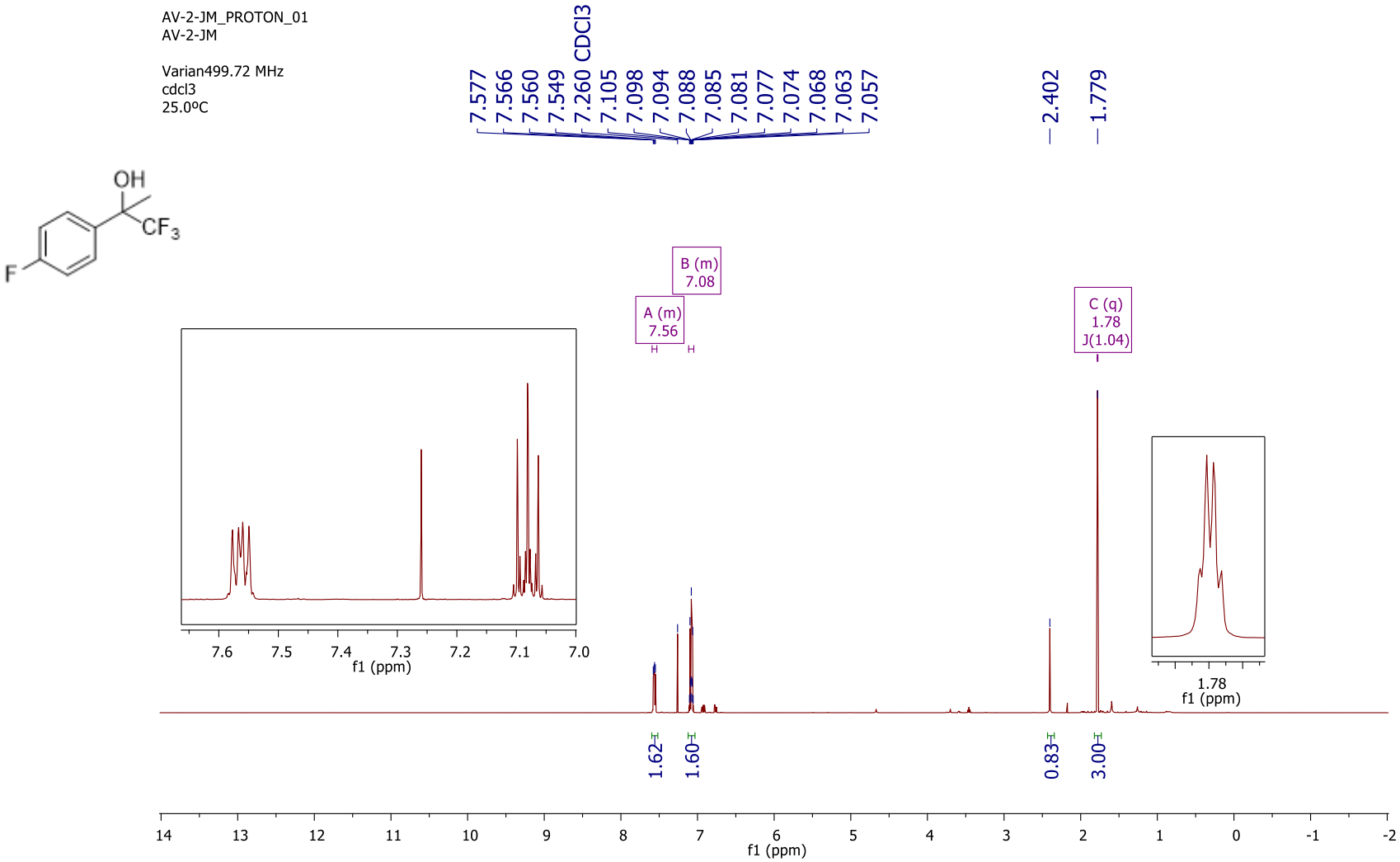
S 10. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) of **4b**



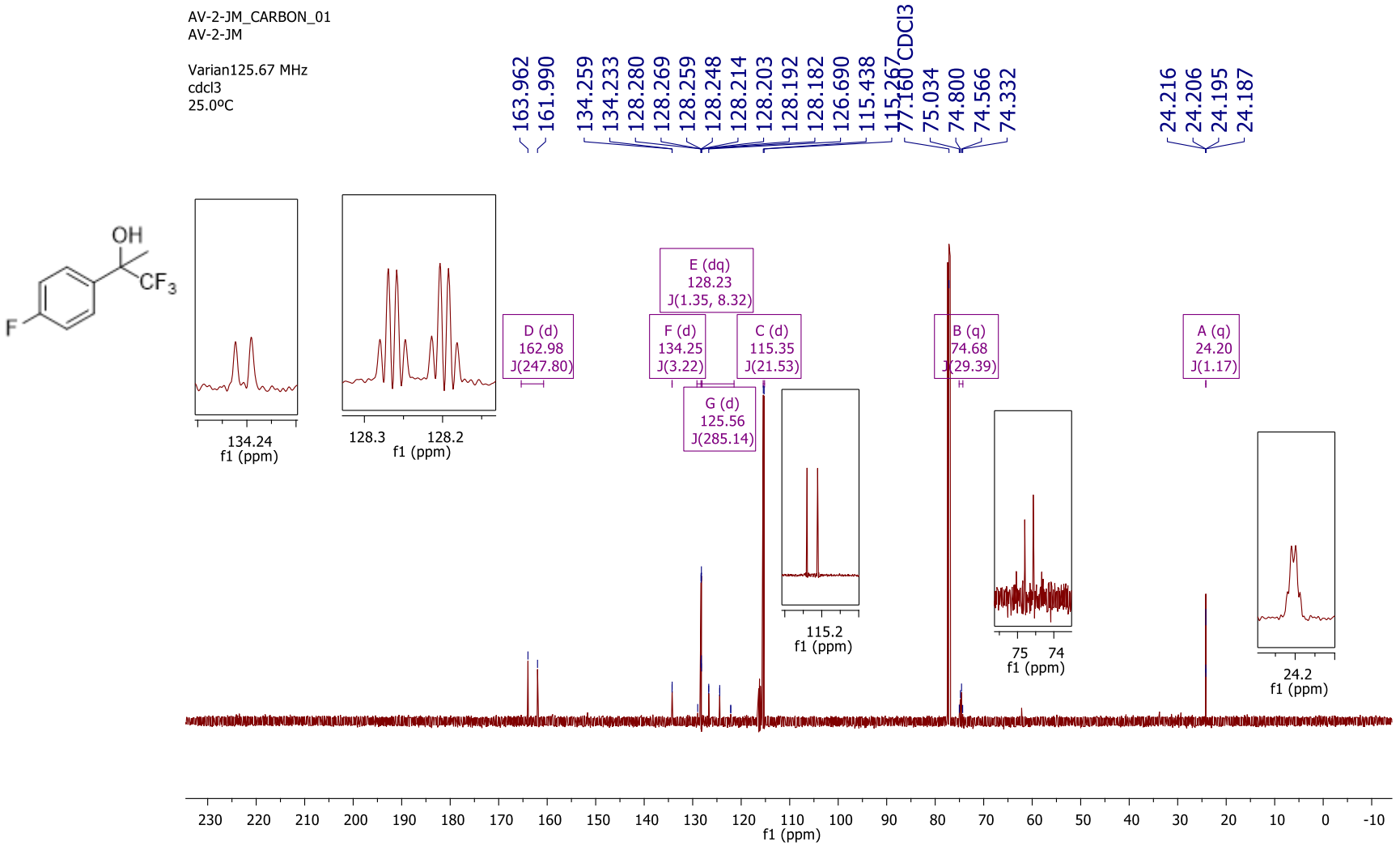
S 11. $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$, 298 K) of **4b**



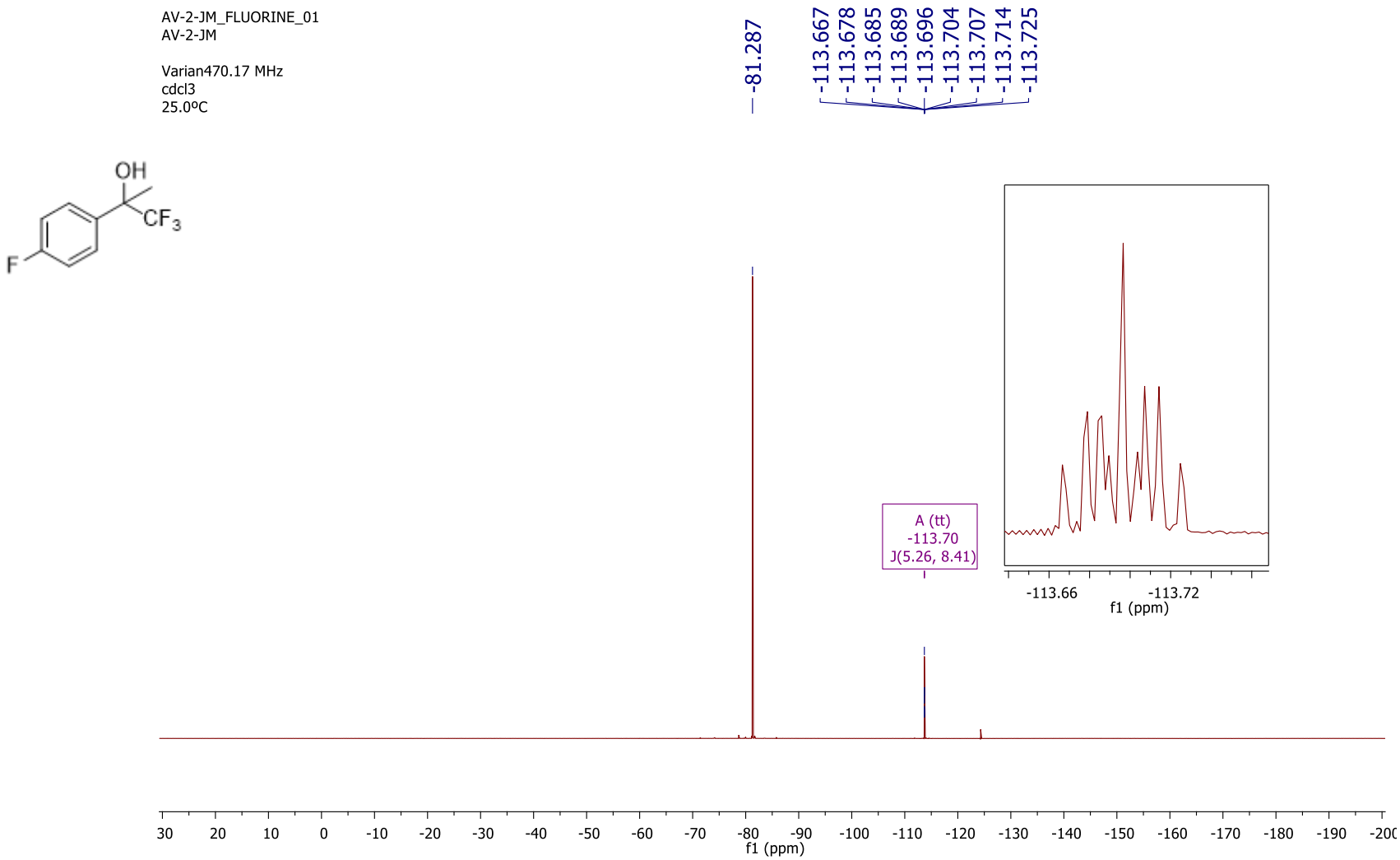
S 12. ^{19}F NMR (470 MHz, $CDCl_3$, 298 K) of **4b**



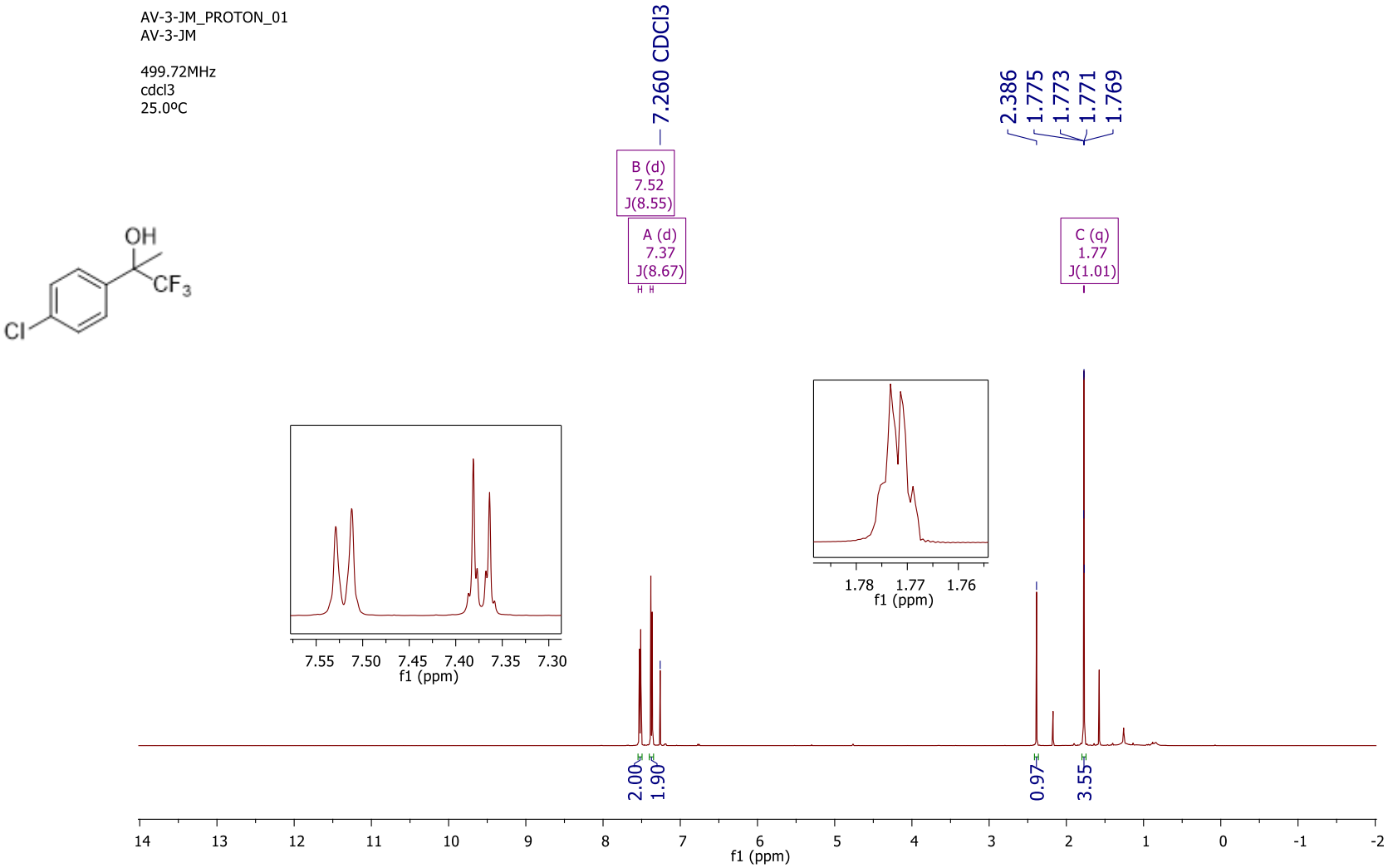
S 13. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) of **5b**



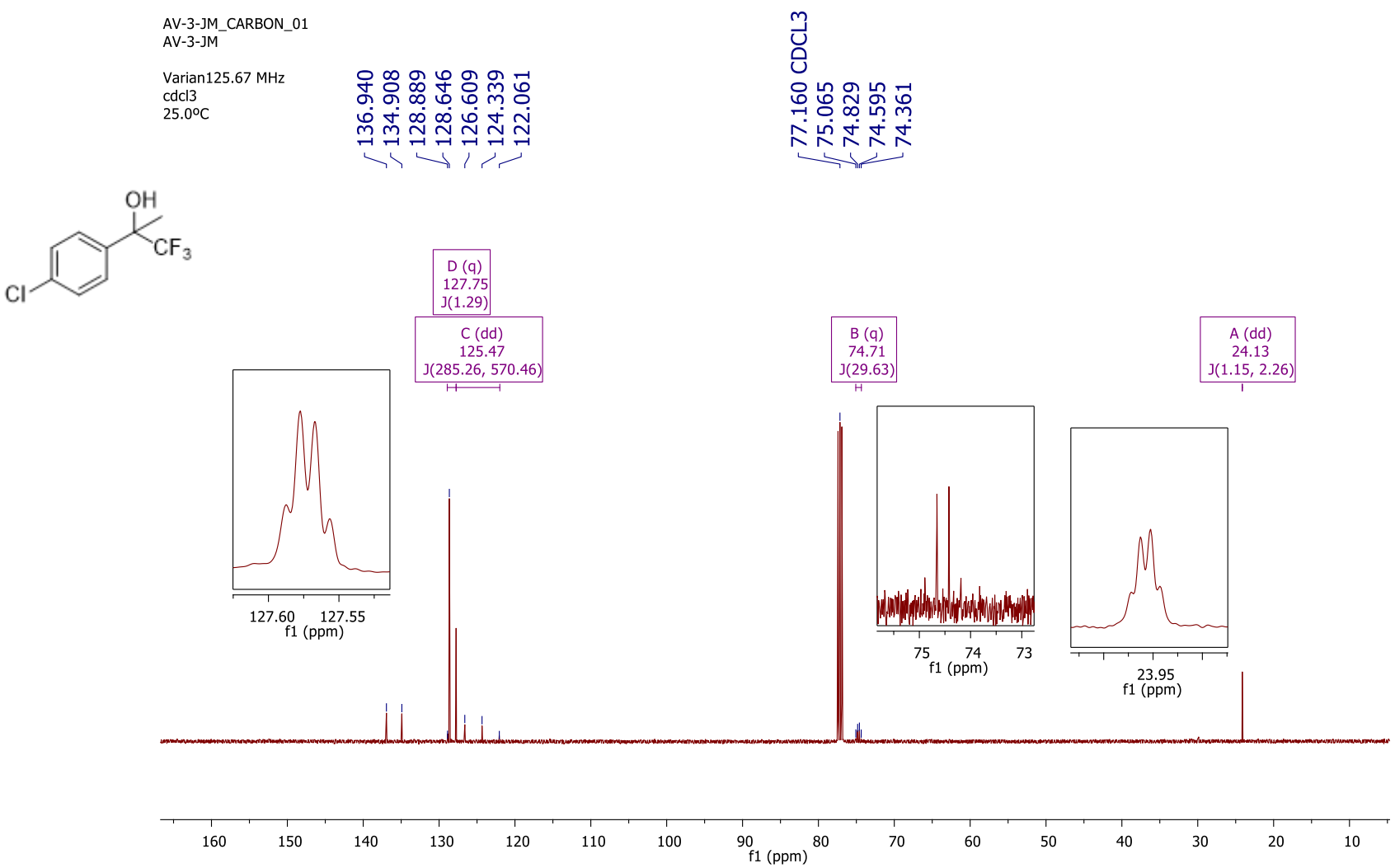
S 14. $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$, 298 K) of **5b**



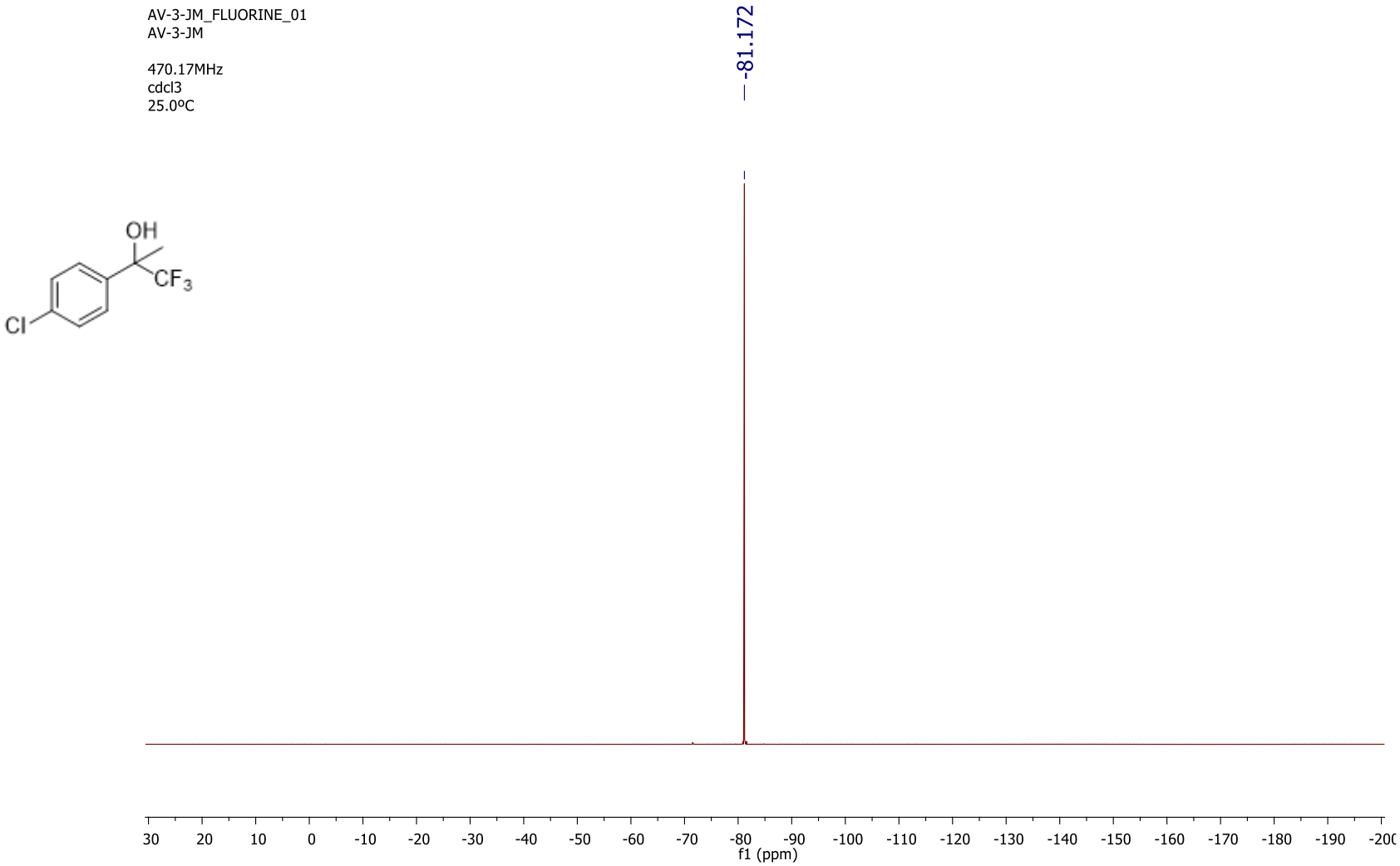
S 15. ^{19}F NMR (470 MHz, $CDCl_3$, 298 K) of **5b**



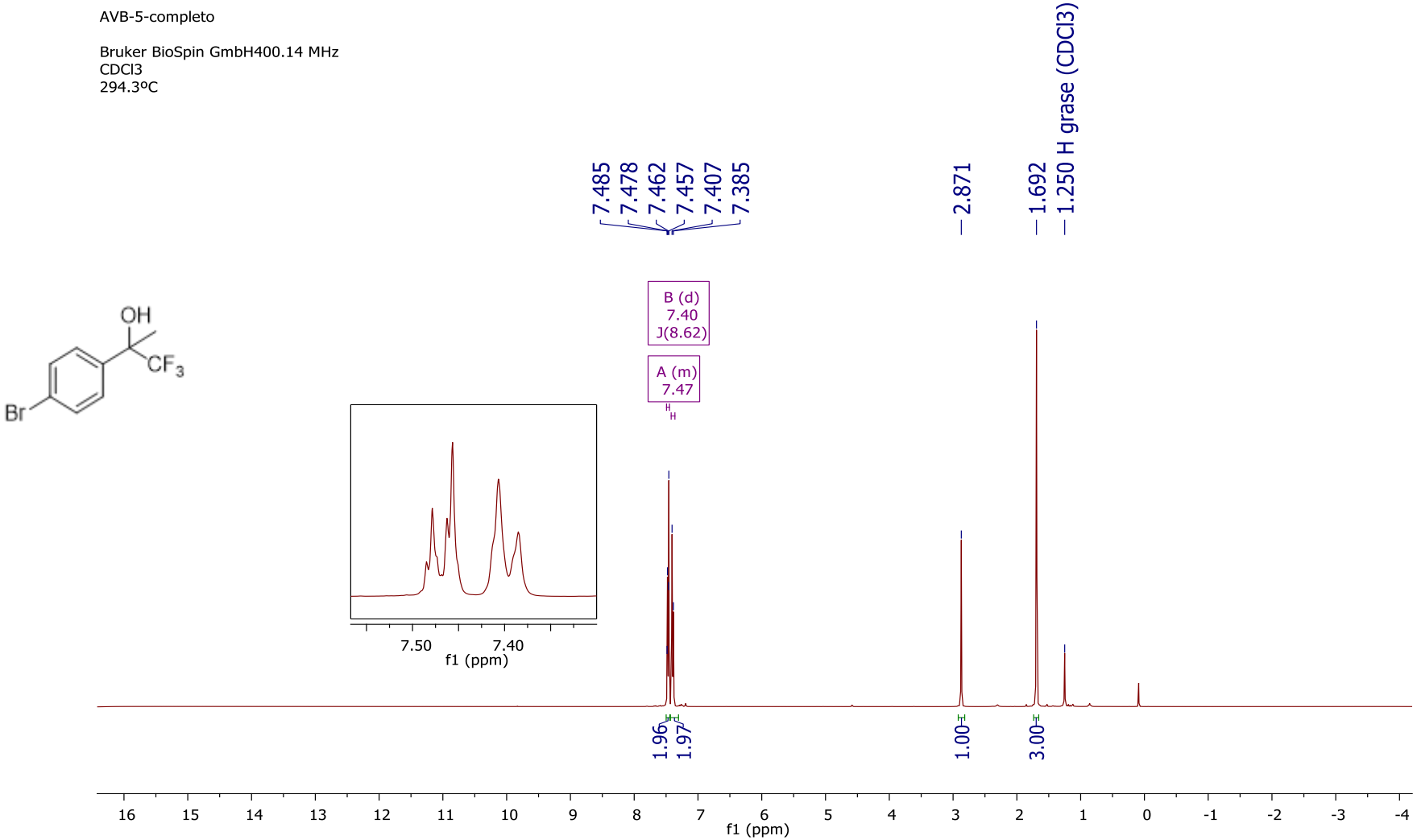
S 16. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) of **6b**



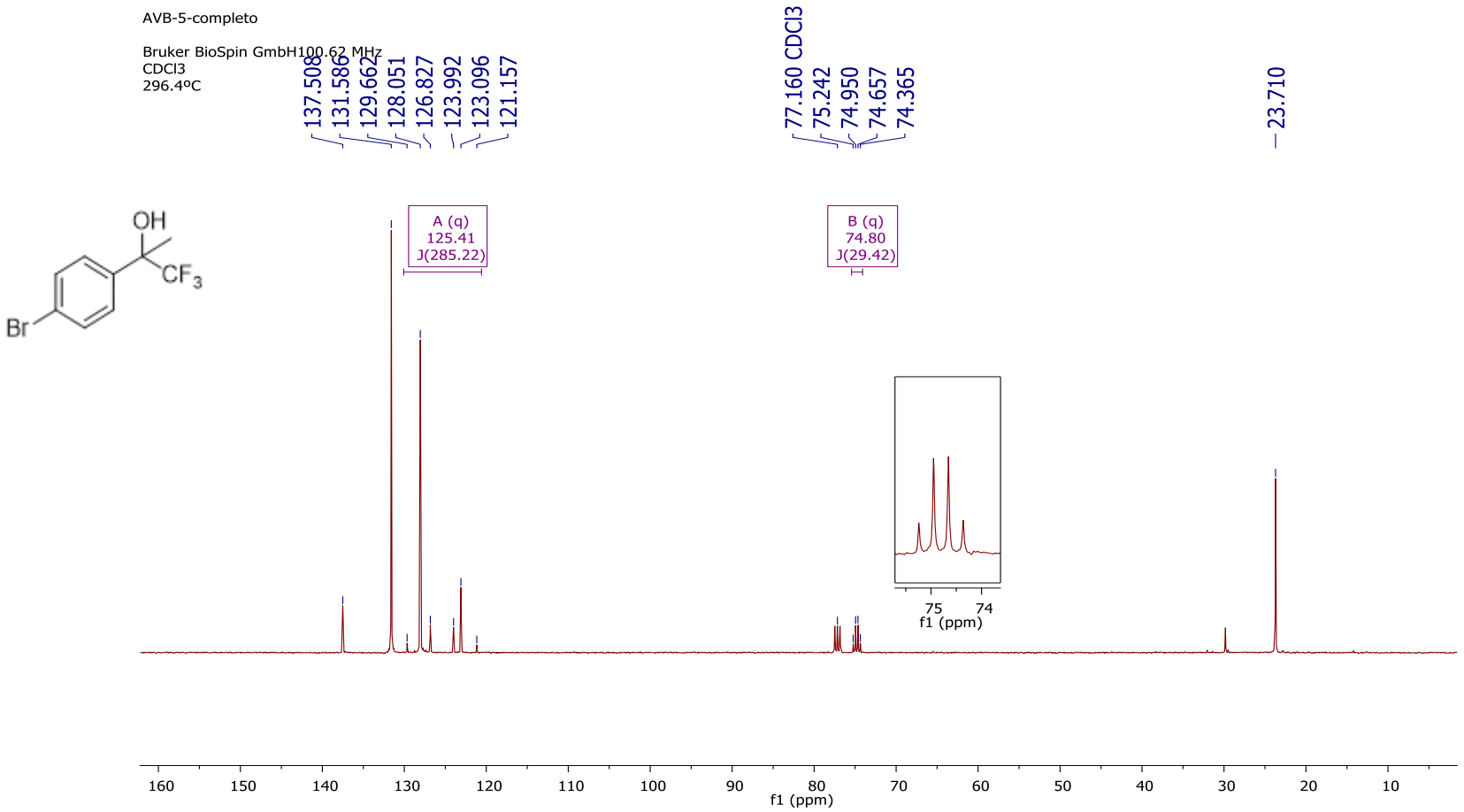
S 17. $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$, 298 K) of **6b**



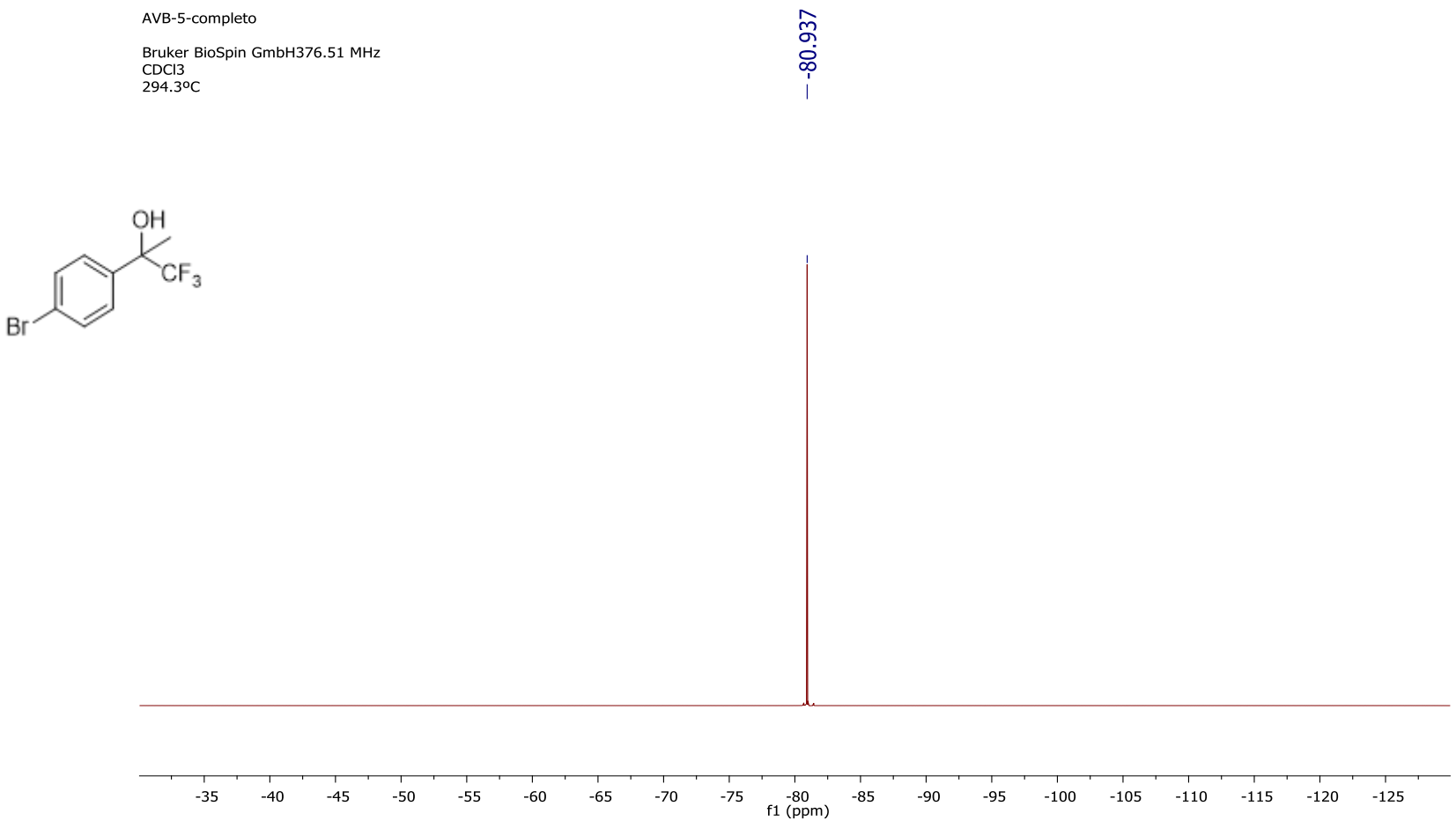
S 18. ^{19}F NMR (470 MHz, $CDCl_3$, 298 K) of **6b**



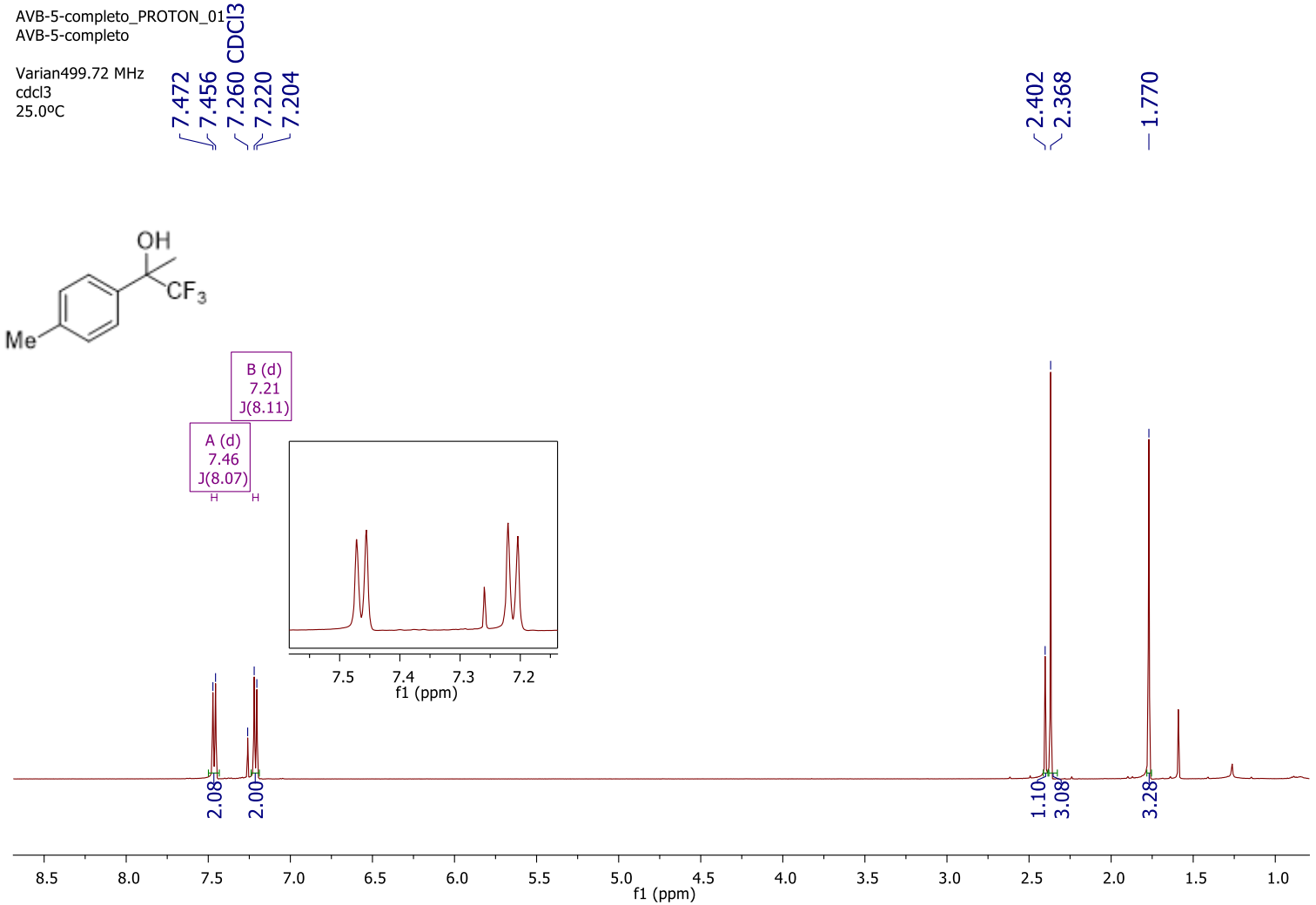
S 19. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) of **7b**



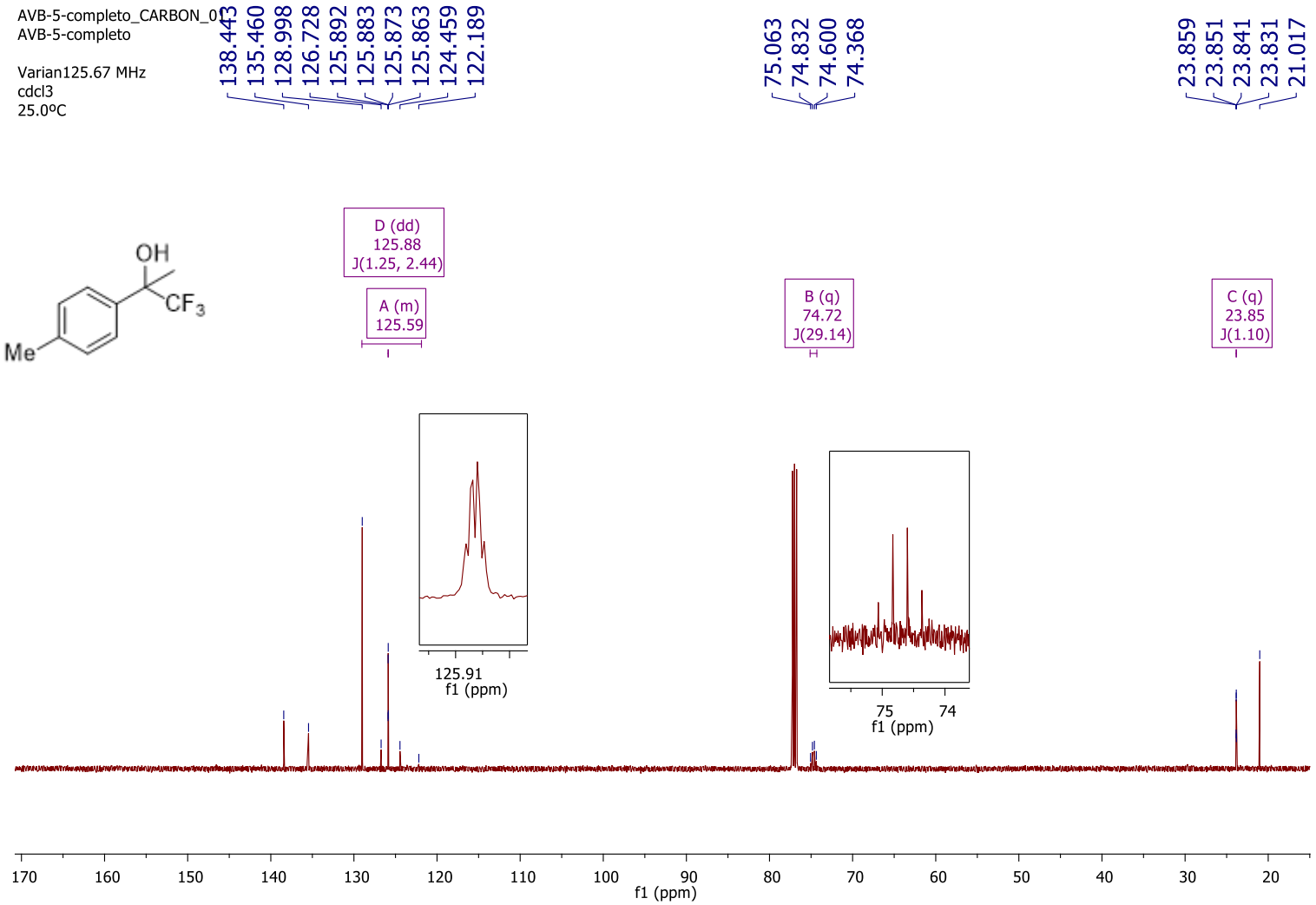
S 20. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 298 K) of **7b**



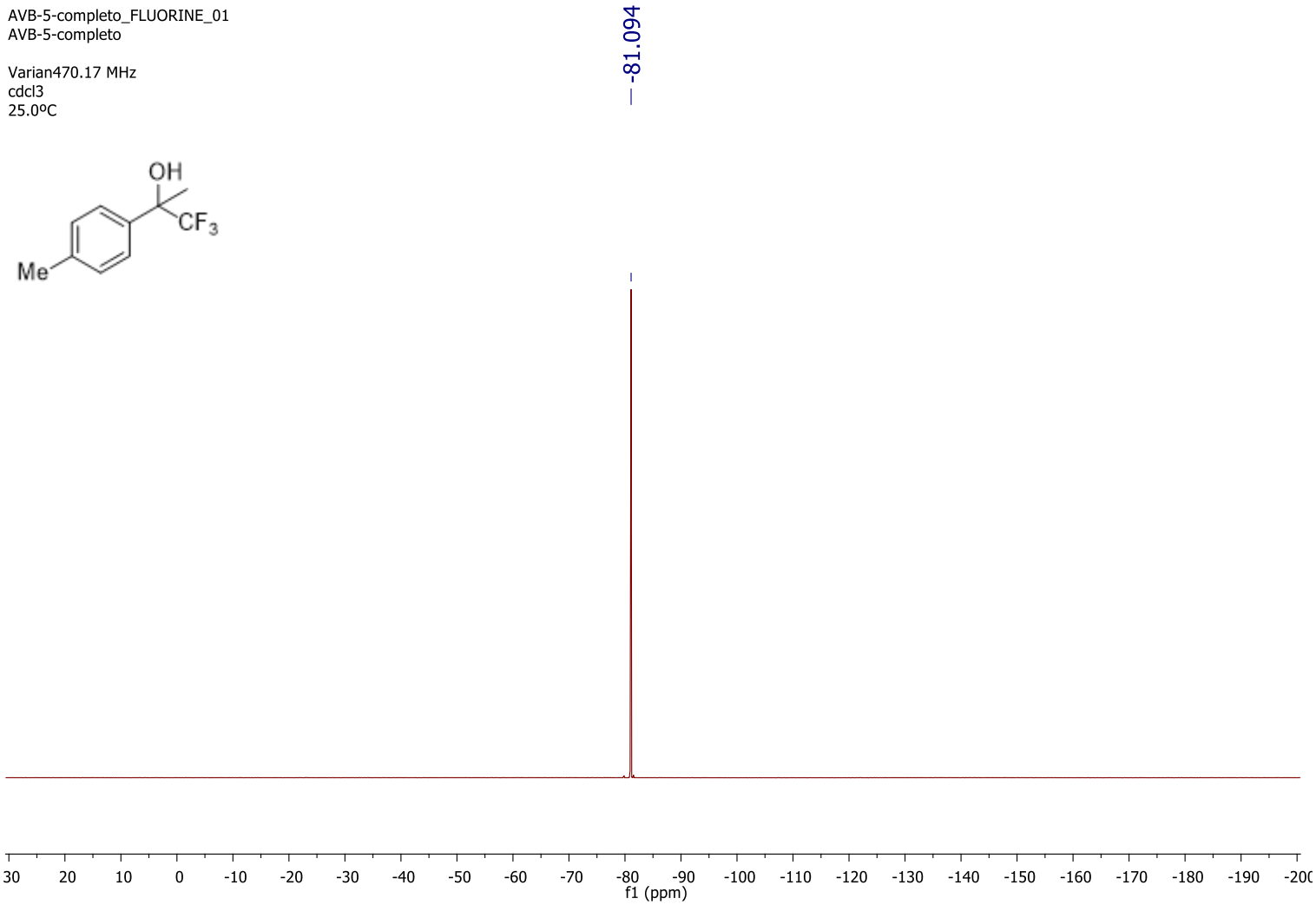
S 21. ^{19}F NMR (376 MHz, $CDCl_3$, 298 K) of **7b**



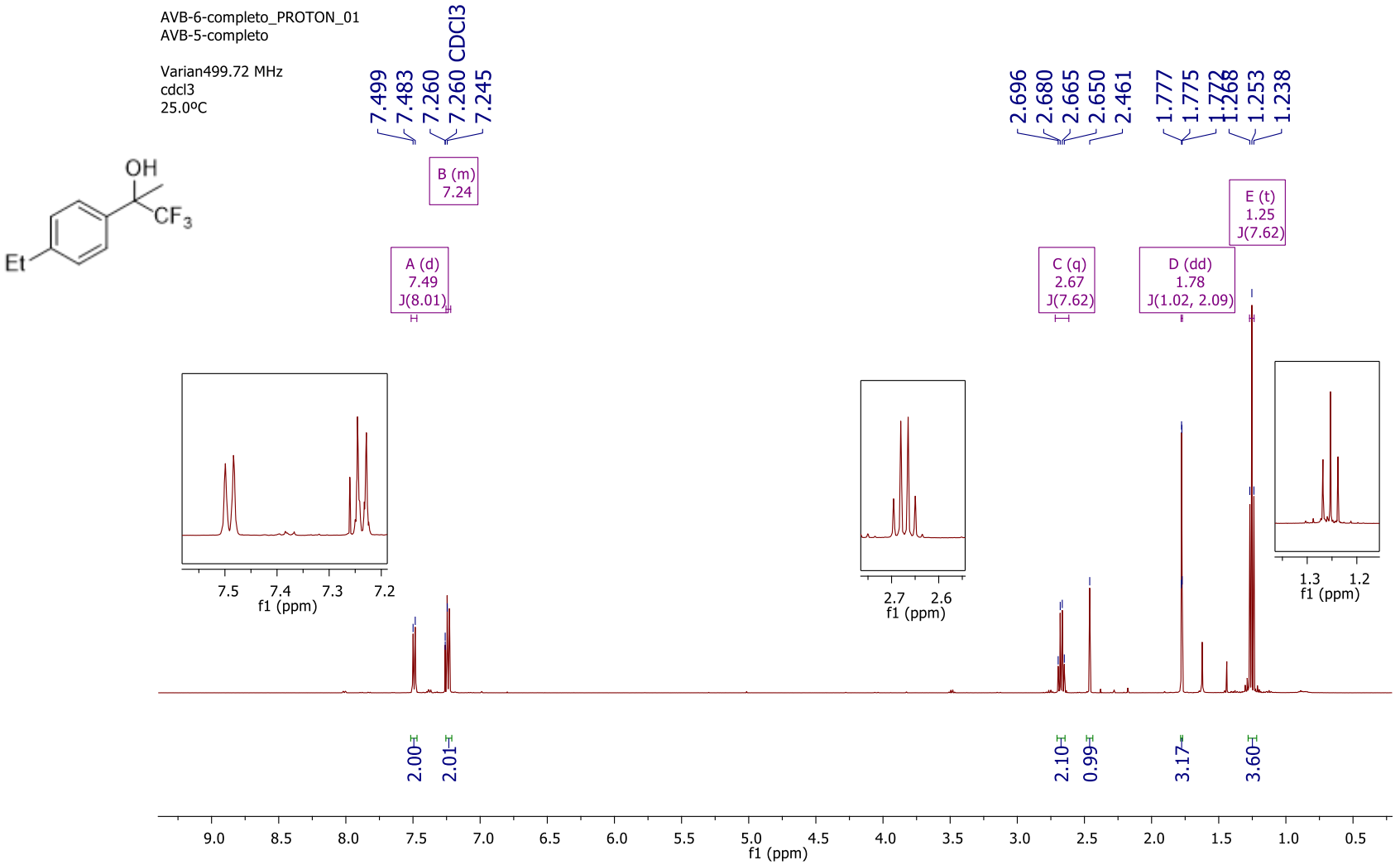
S 22. ^{11}H NMR (500 MHz, $CDCl_3$, 298 K) of **8b**.



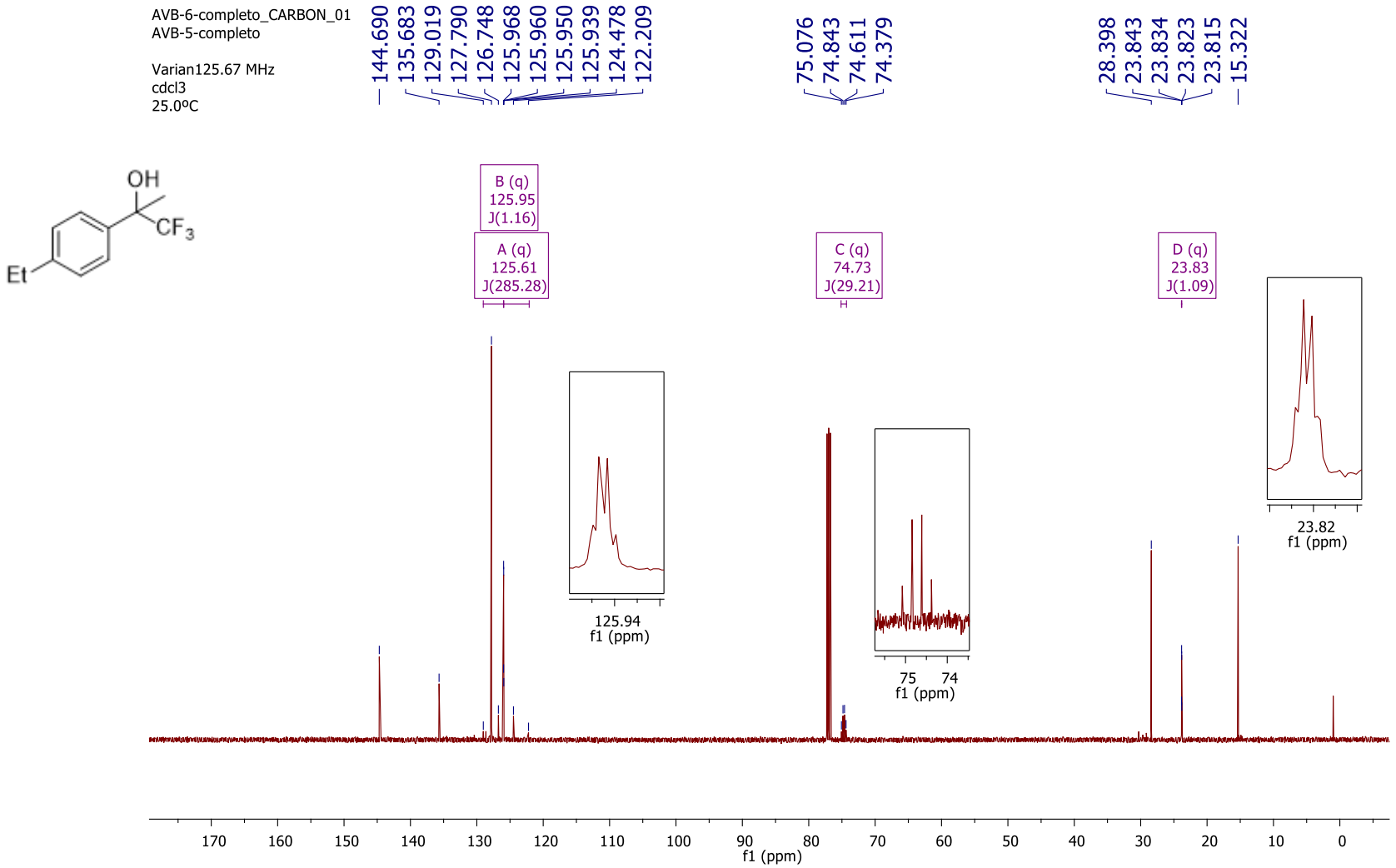
S 23. $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$, 298 K) of **8b**.



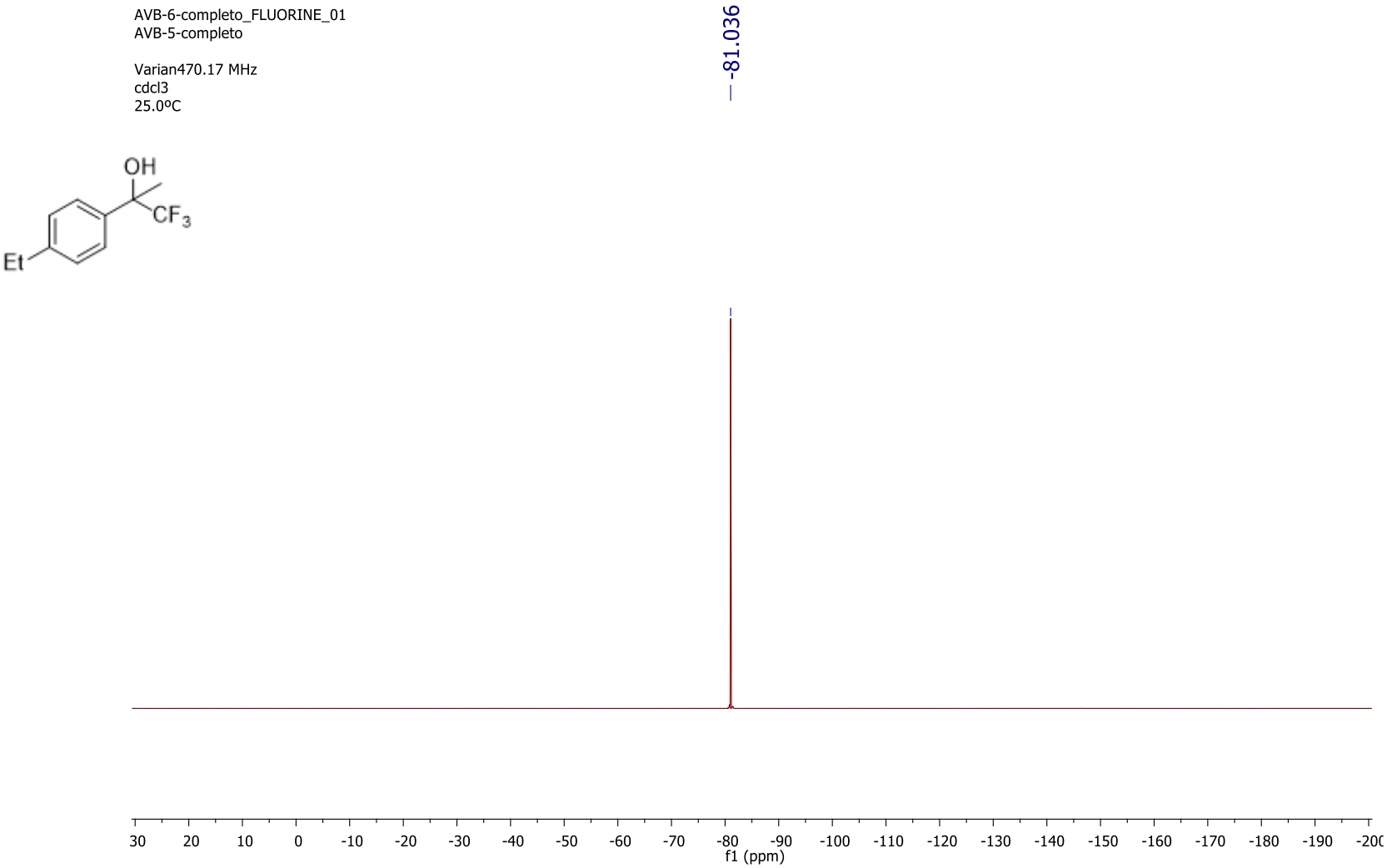
S 24. ^{19}F NMR (470 MHz, $CDCl_3$, 298 K) of **8b**



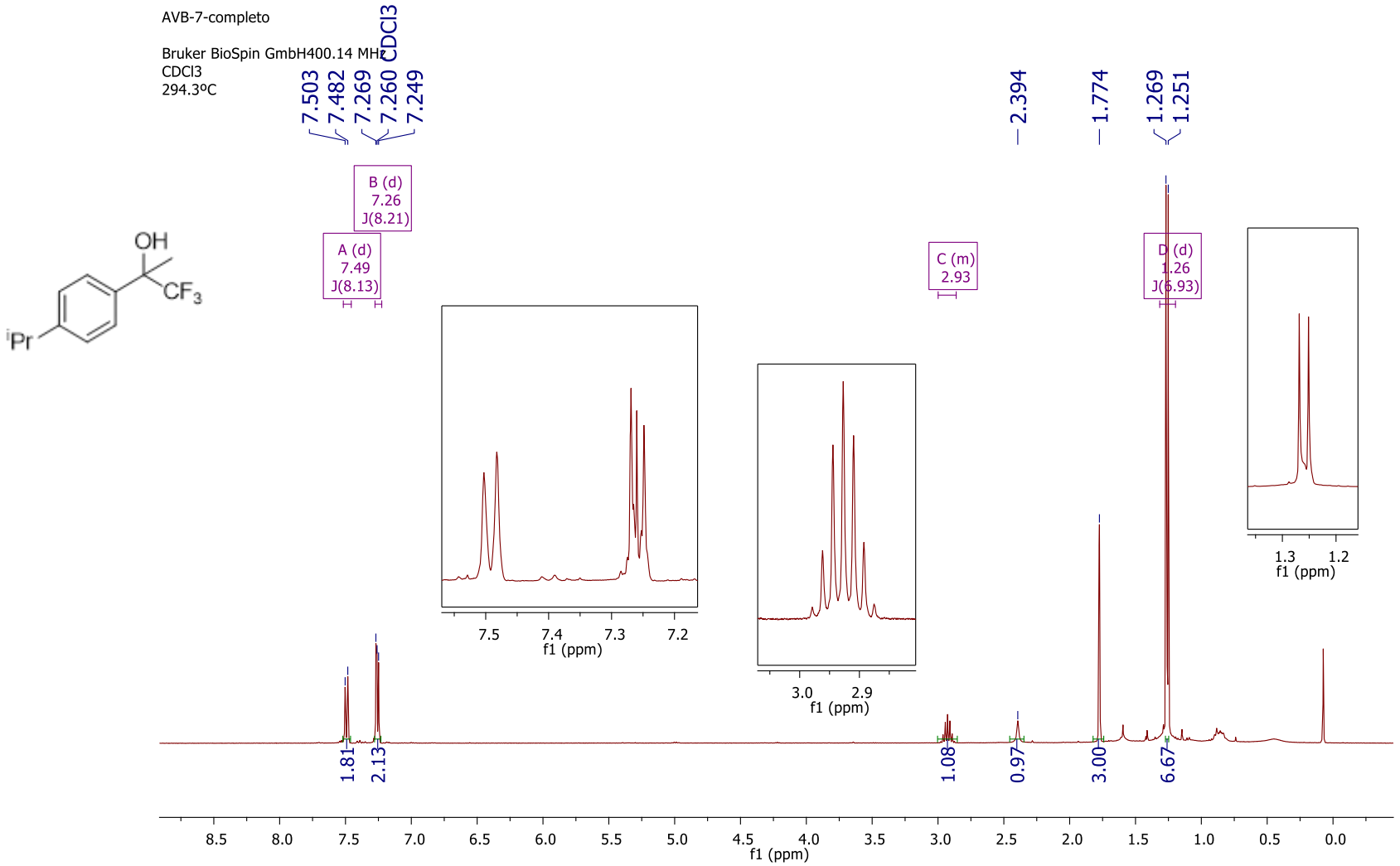
S 25. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) of **9b**



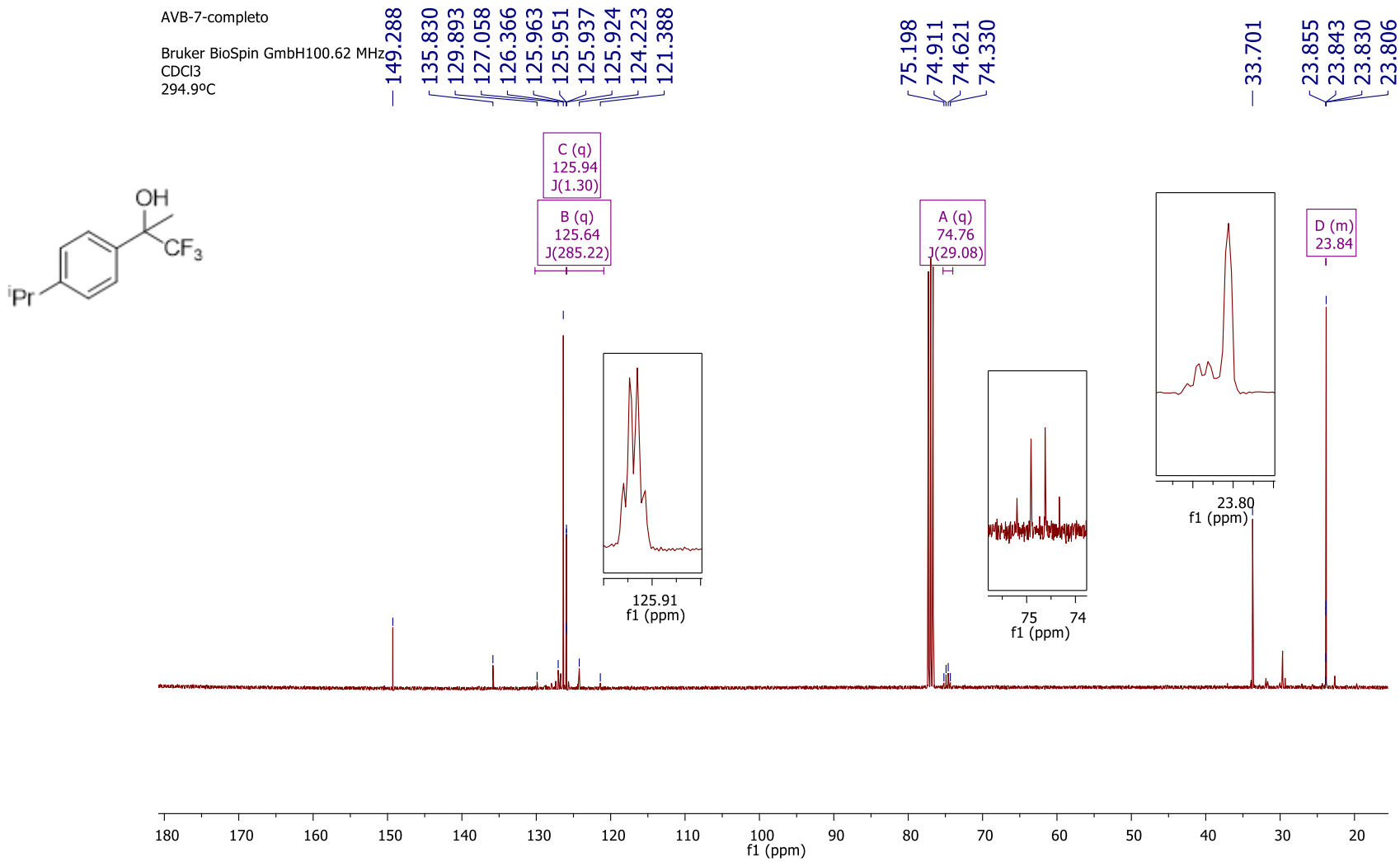
S 26. $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$, 298 K) of **9b**



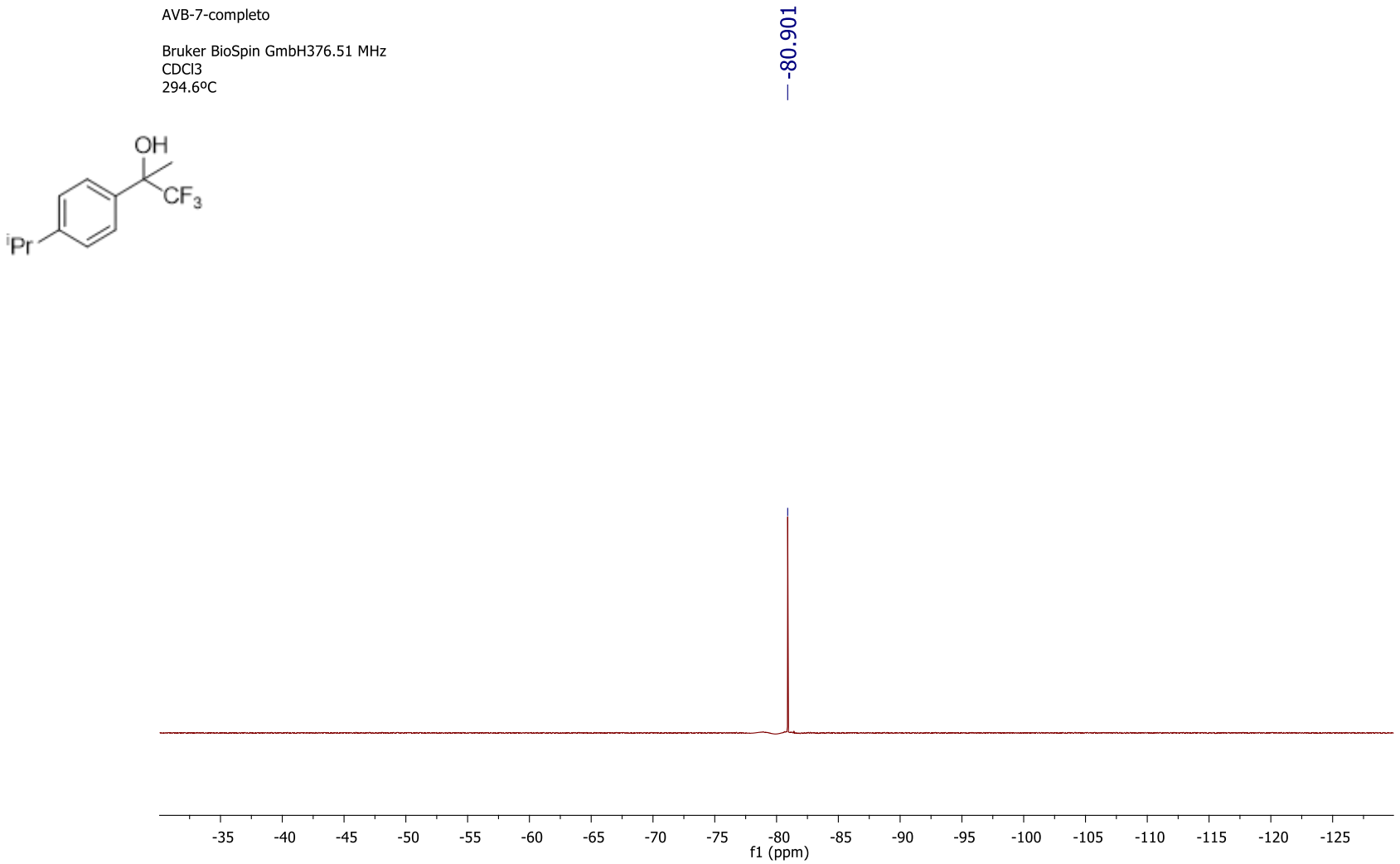
S 27. ^{19}F NMR (470 MHz, $CDCl_3$, 298 K) of **9b**.



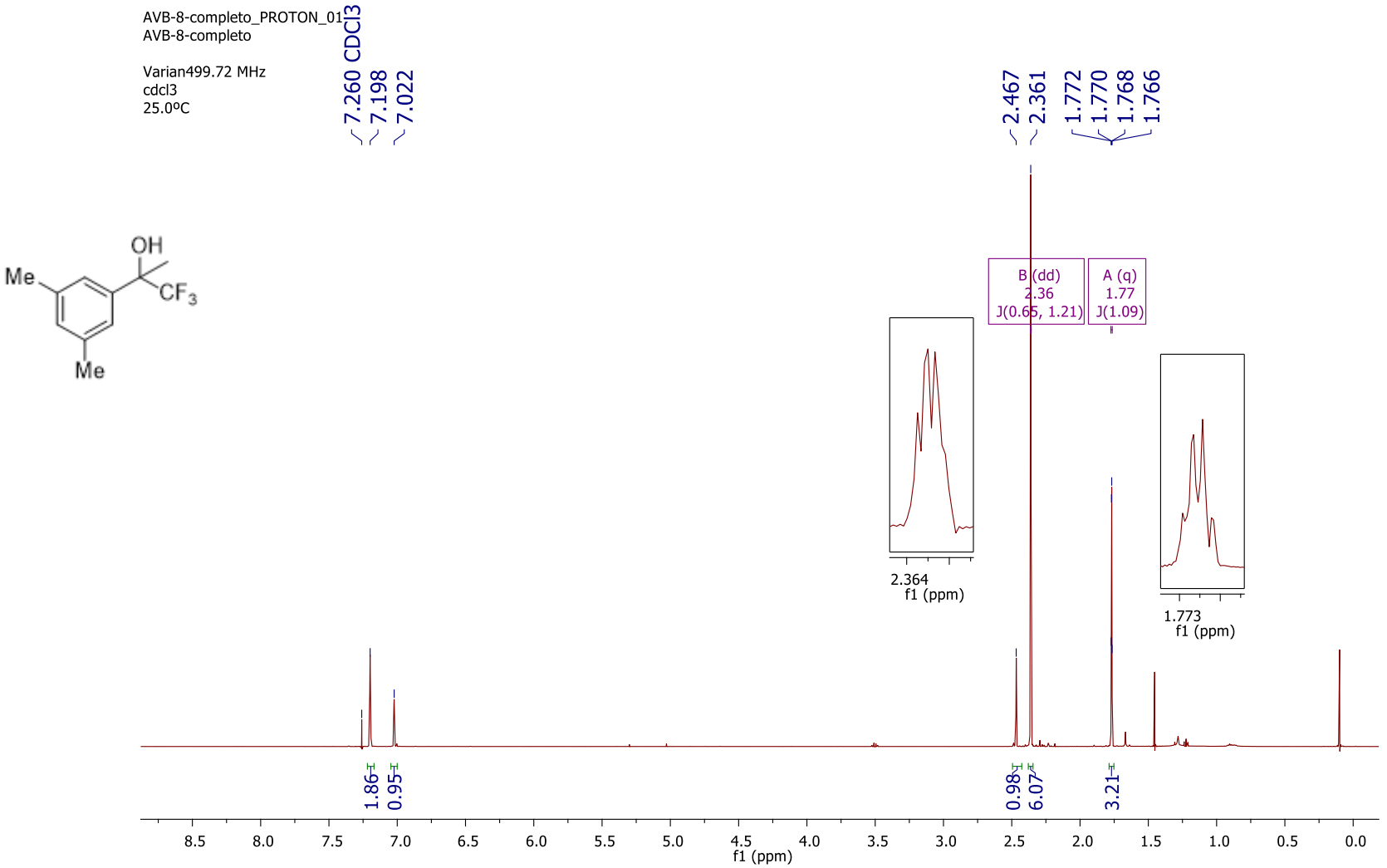
S 28. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) of **10b**



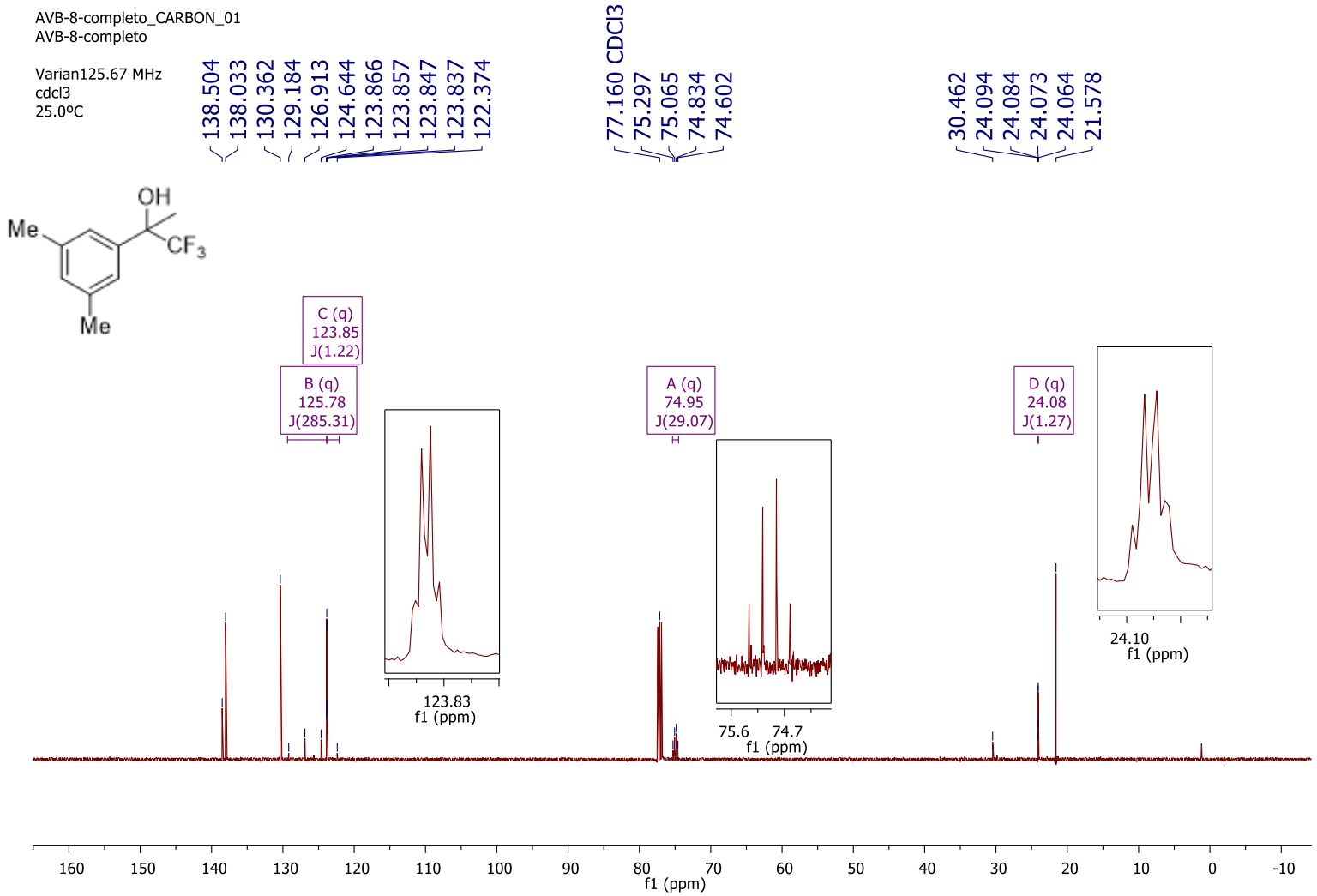
S 29. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 298 K) of **10b**.



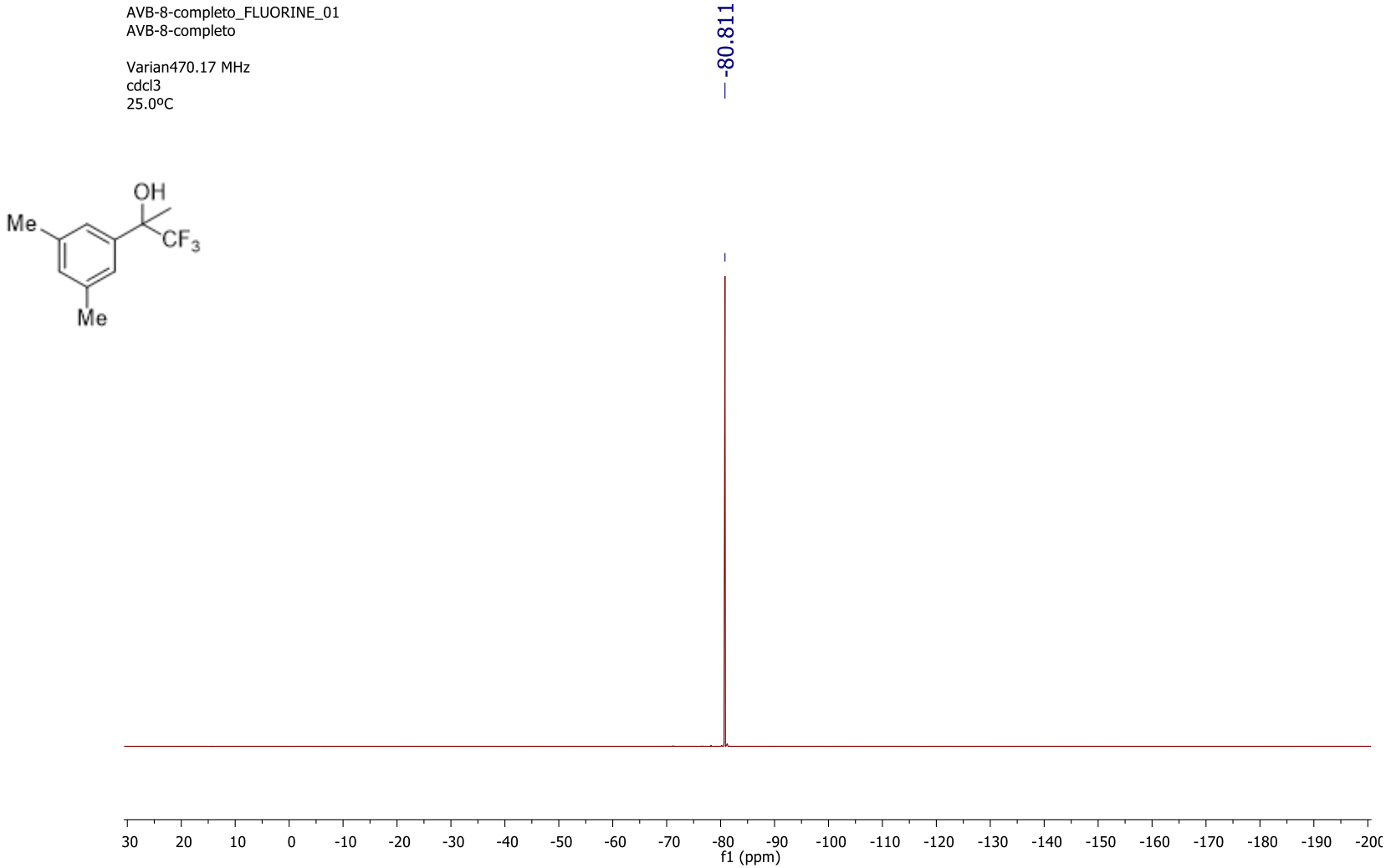
S 30. ^{19}F NMR (376 MHz, $CDCl_3$, 298 K) of **10b**



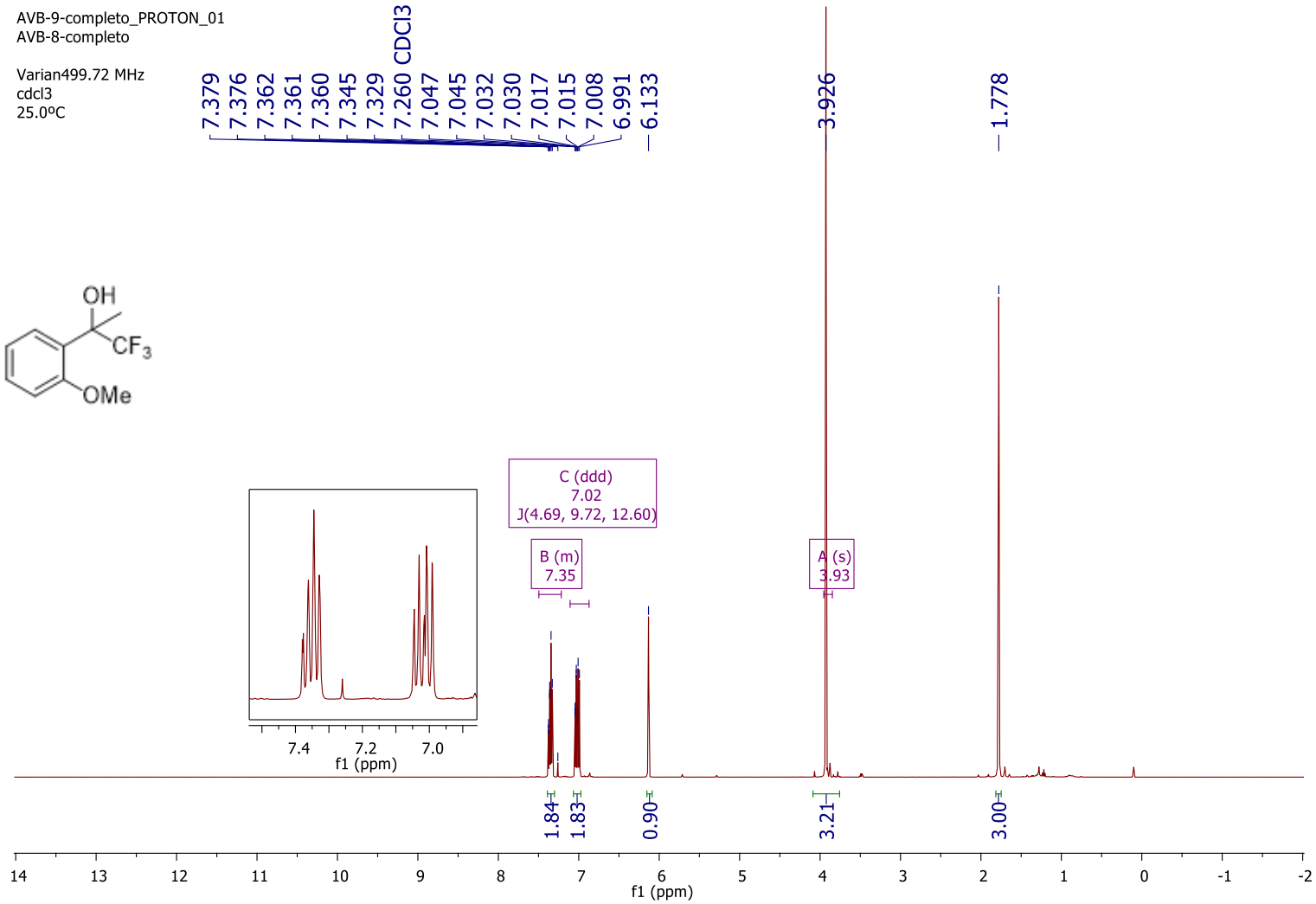
S 31. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) of **11b**.



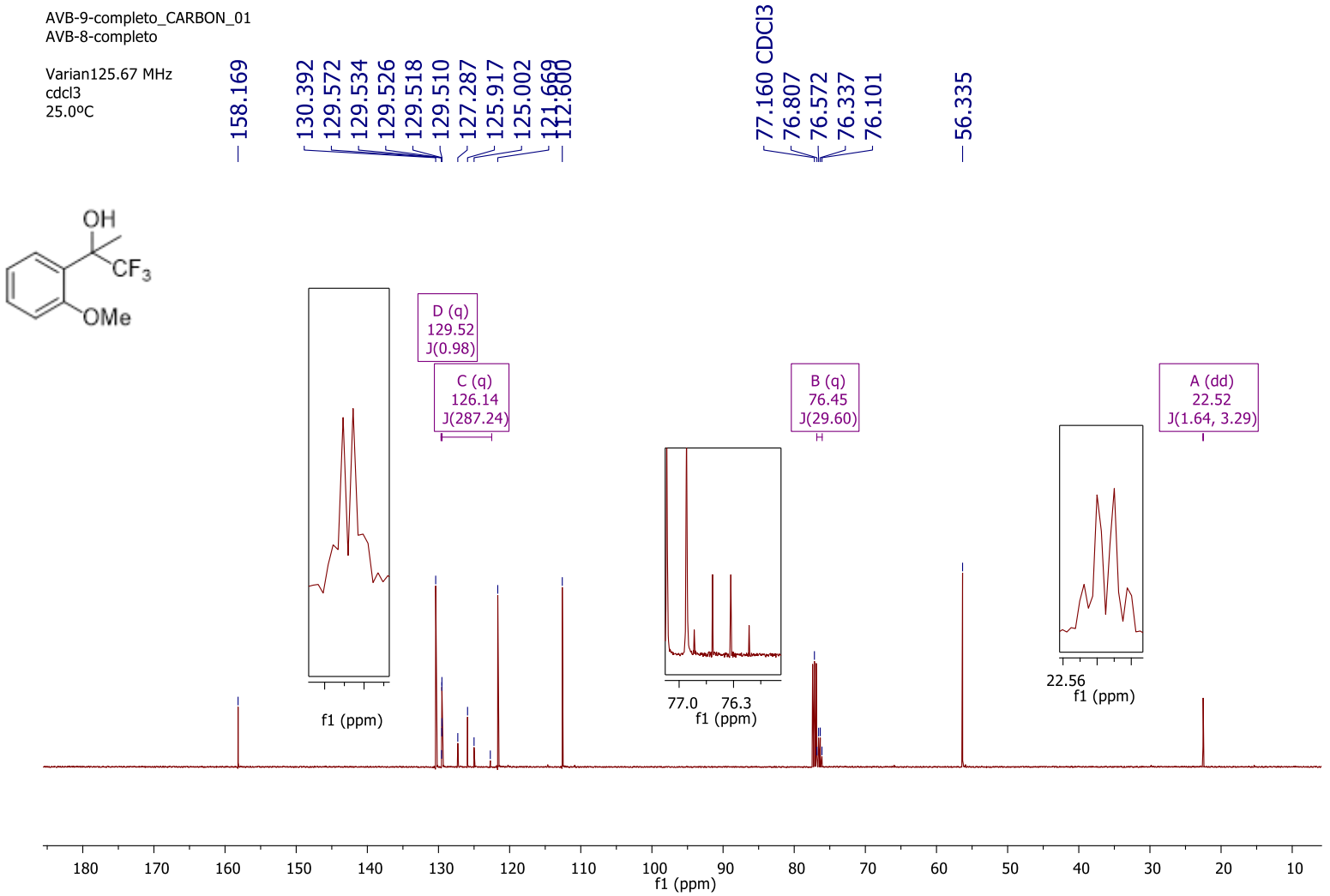
S 32. $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$, 298 K) of **11b**.



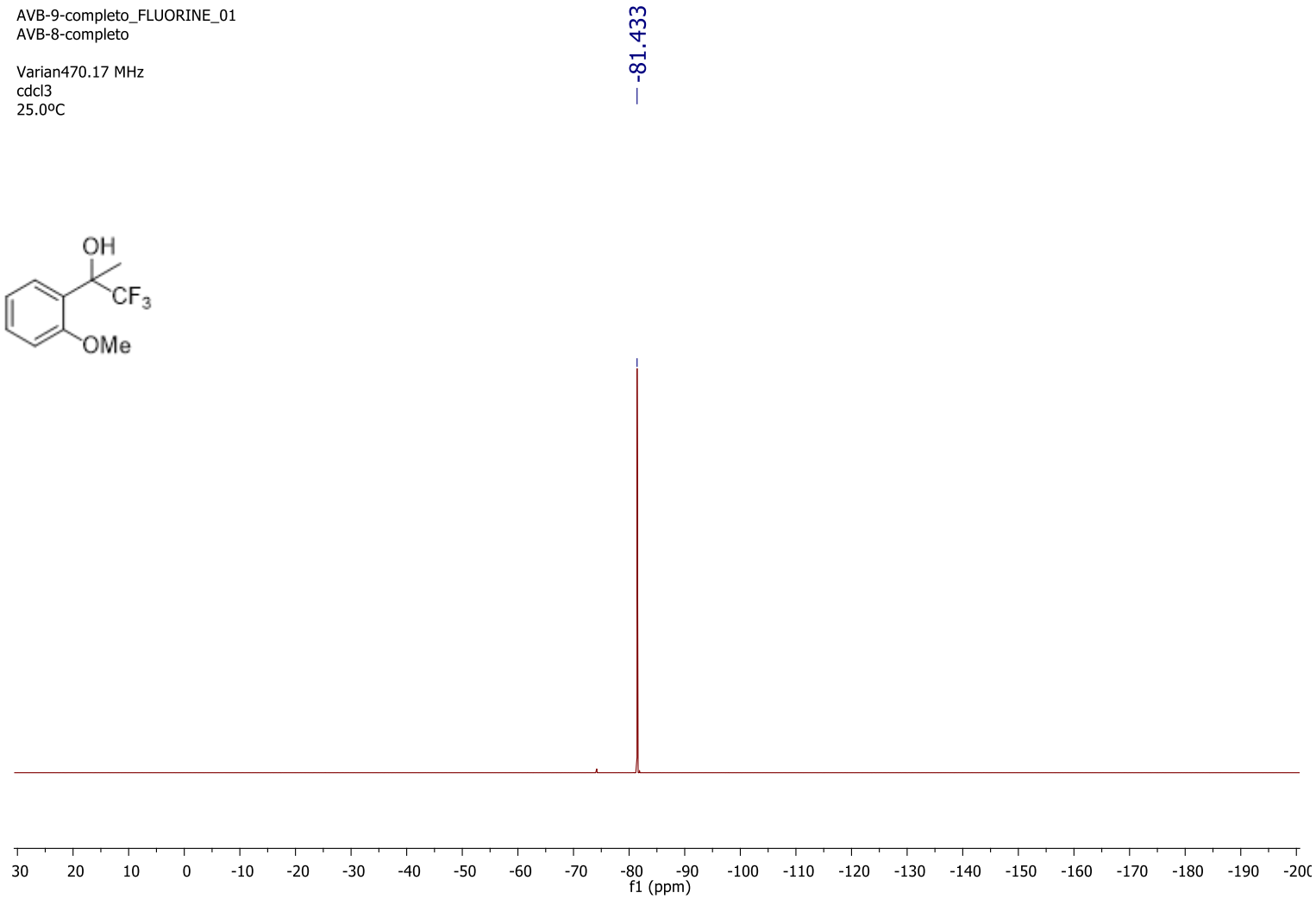
S 33. ^{19}F NMR (470MHz, $CDCl_3$, 298 K) of **11b**



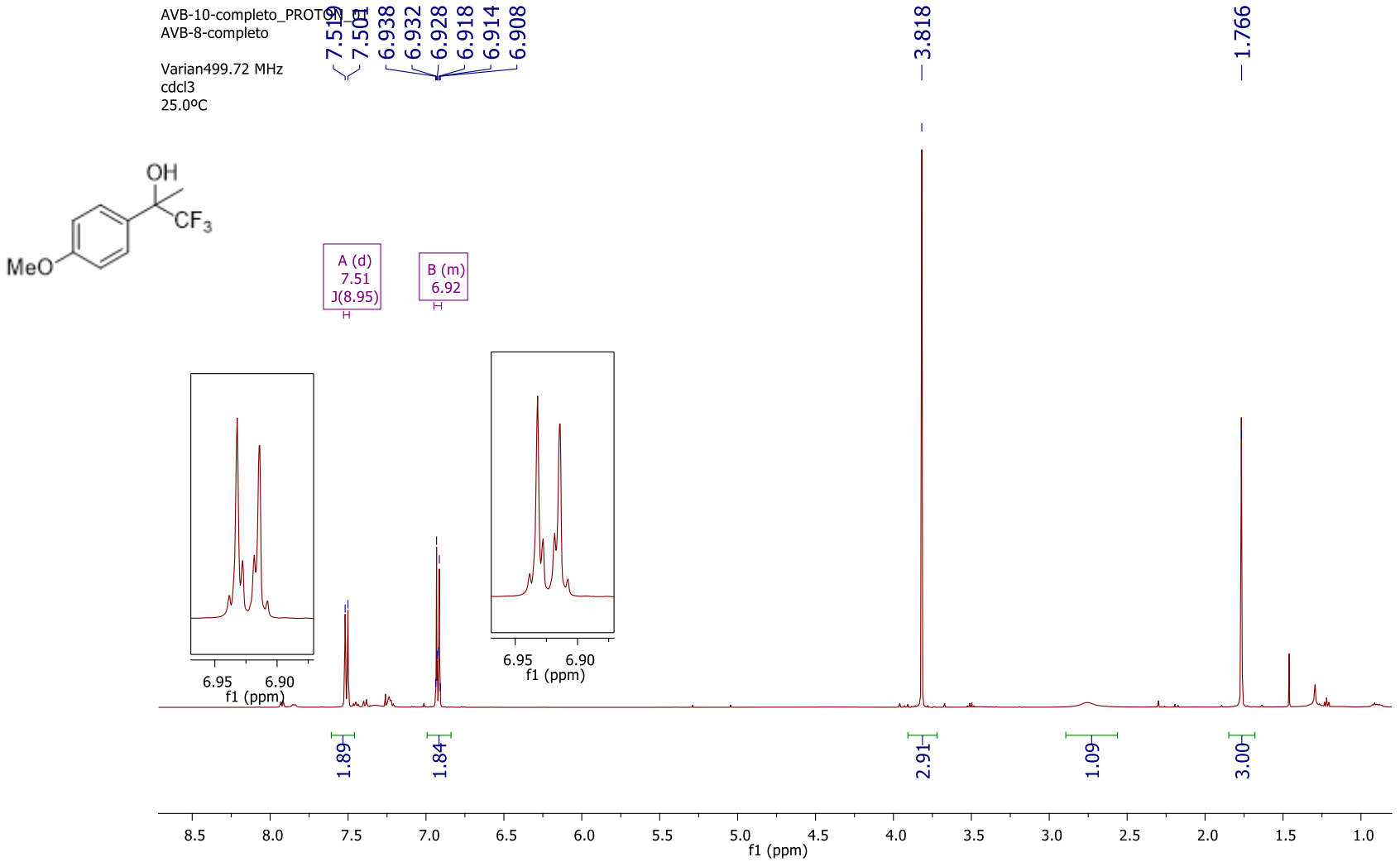
S 34. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) of **12b**



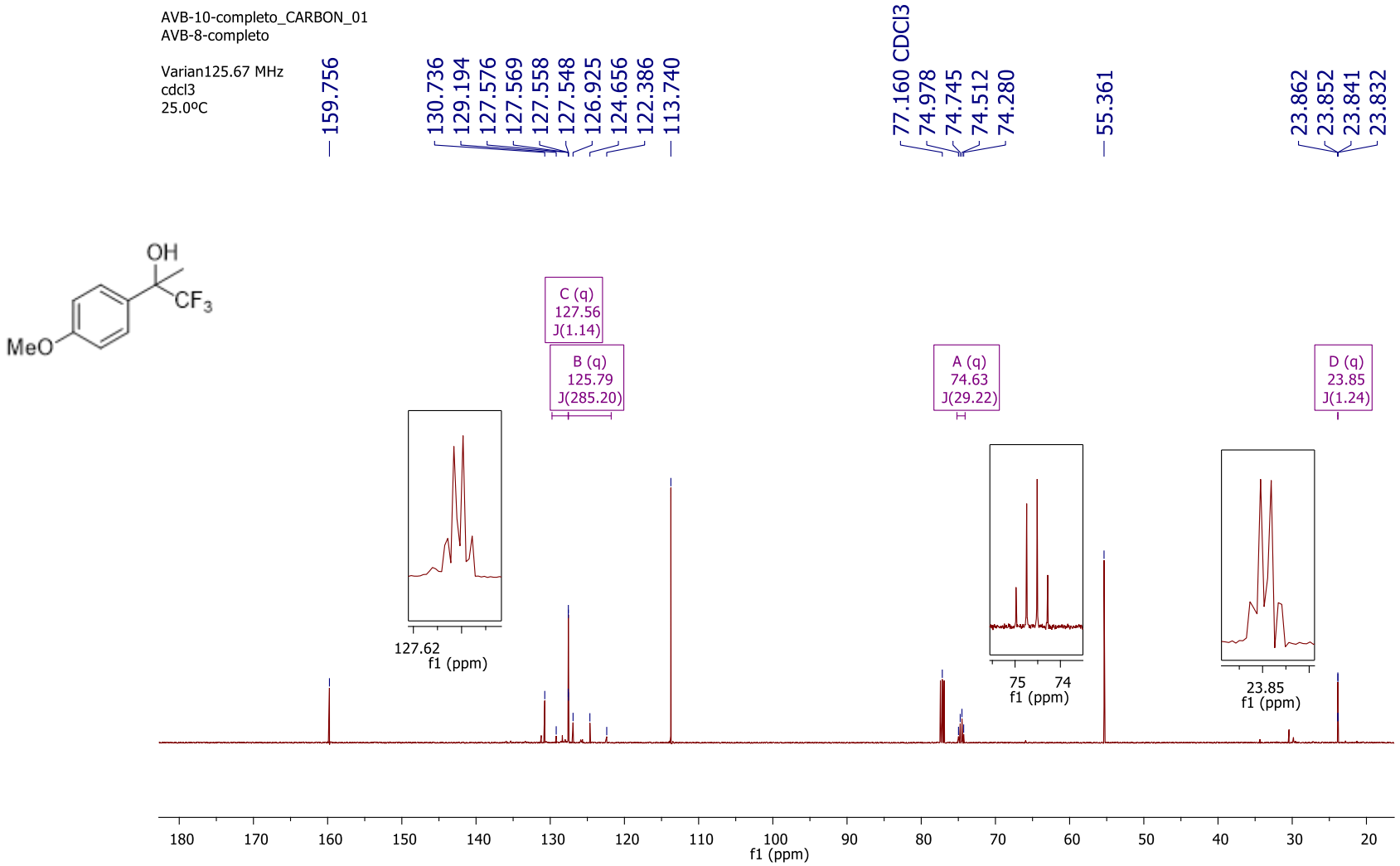
S 35. $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$, 298 K) of **12b**



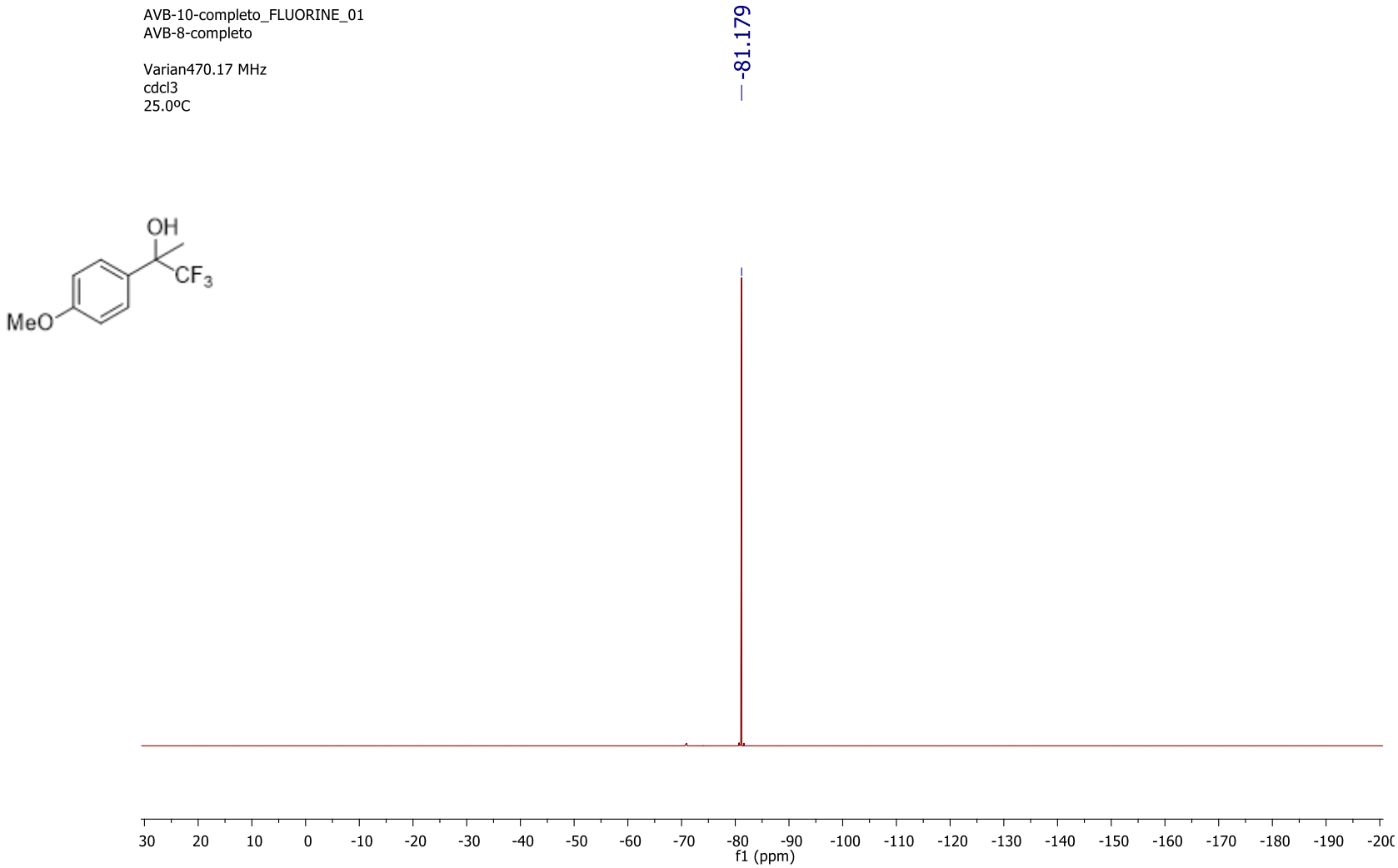
S 36. ^{19}F NMR (470 MHz, $CDCl_3$, 298 K) of **12b**



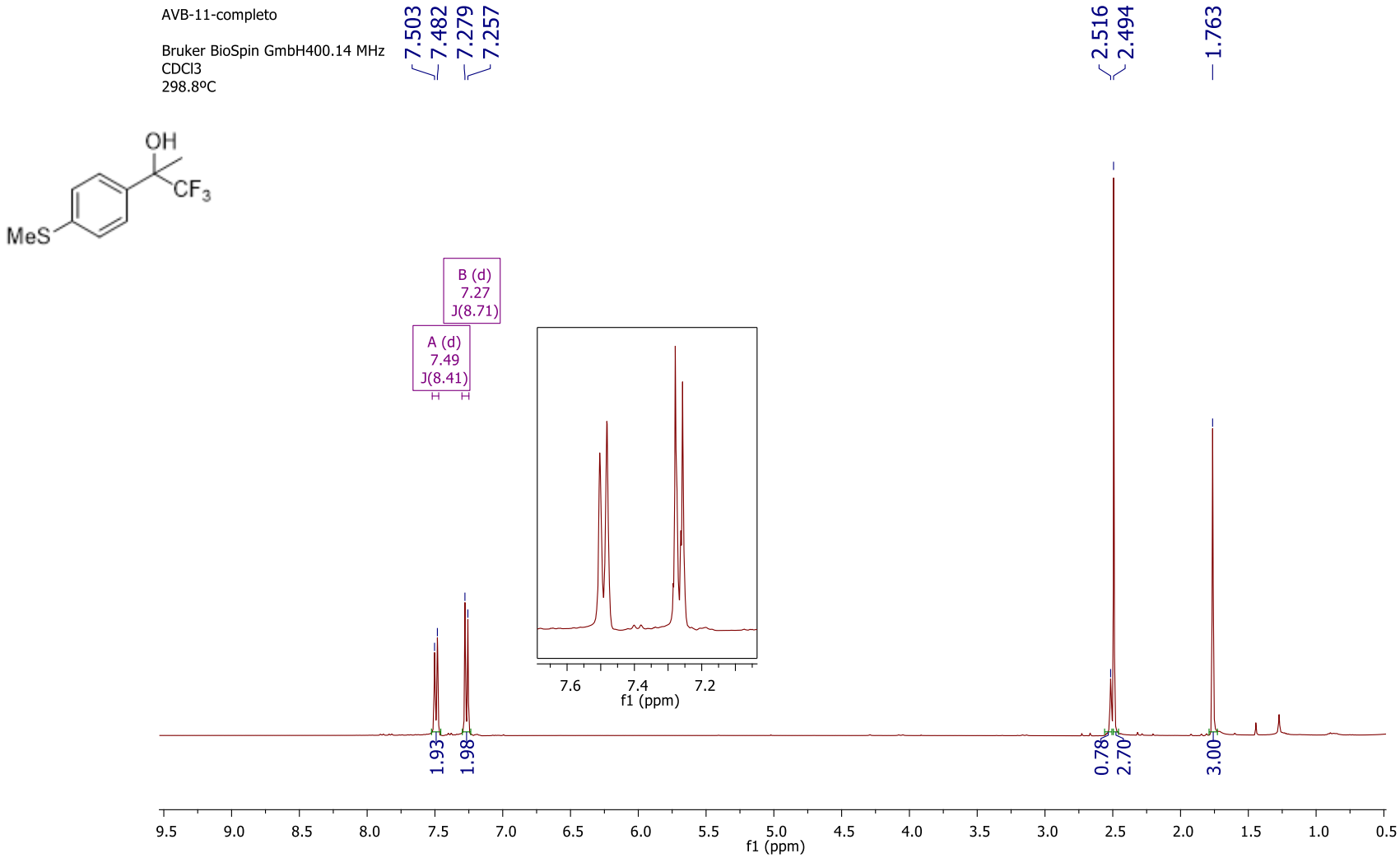
S 37. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) of **13b**



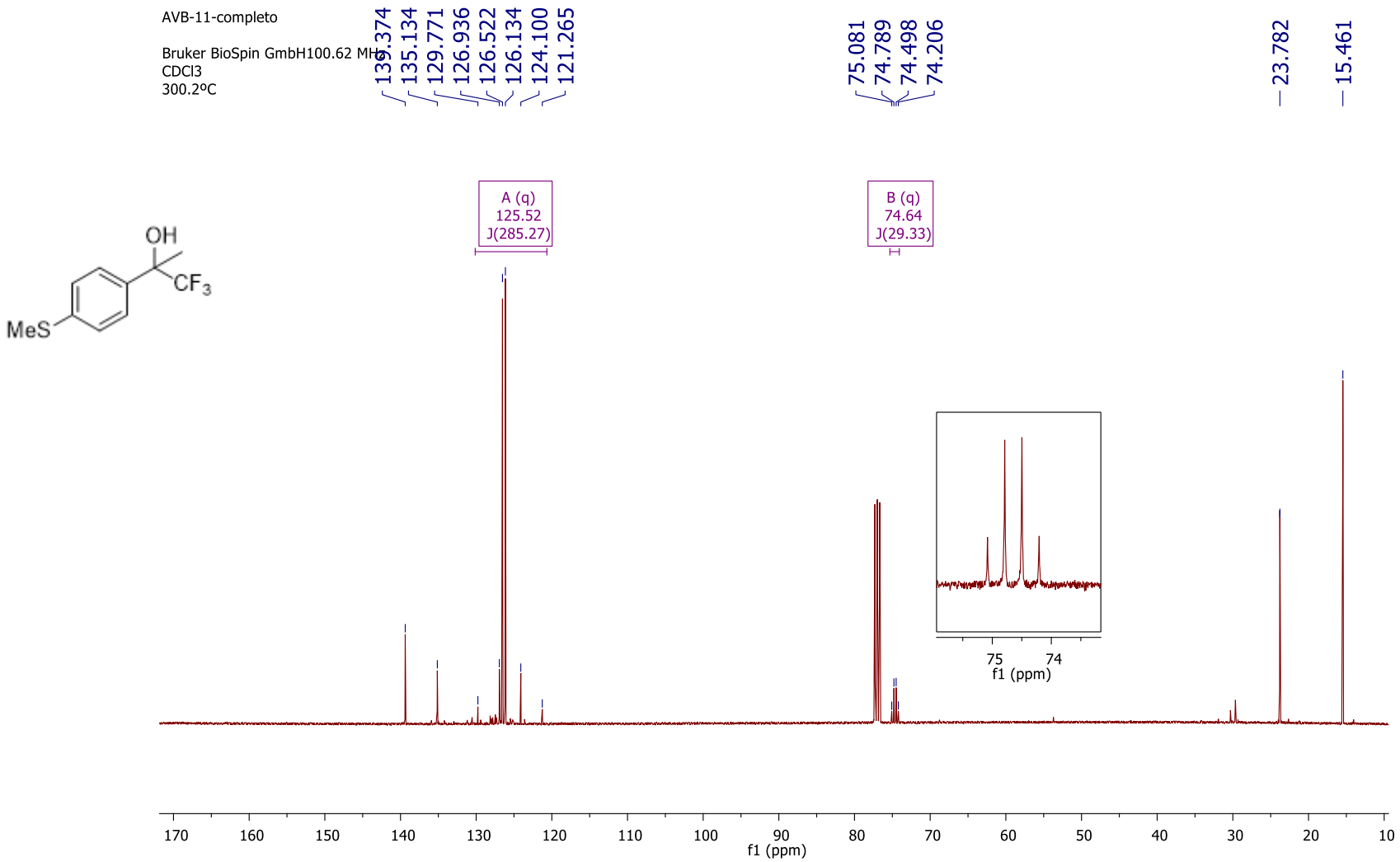
S 38. $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$, 298 K) of **13b**



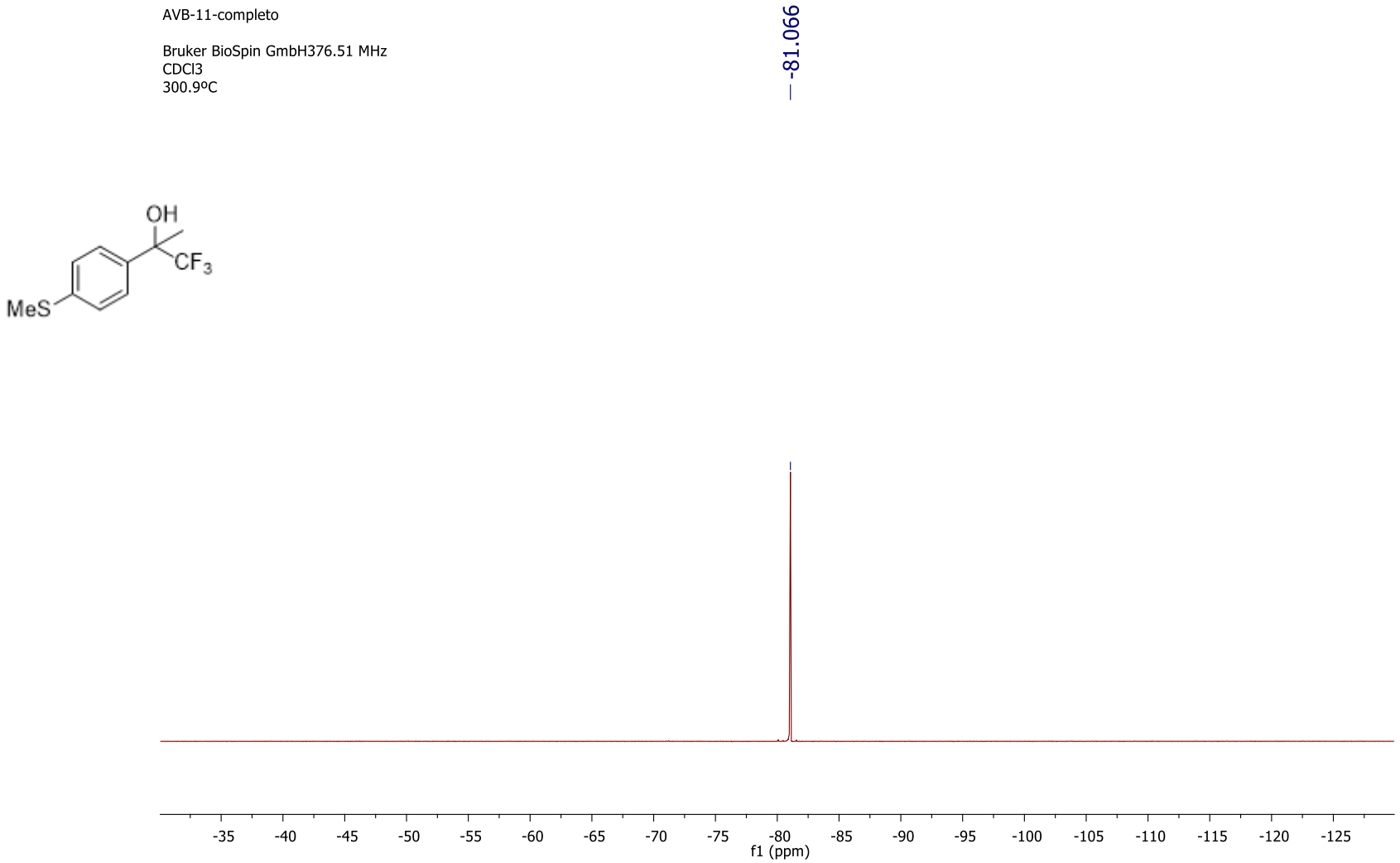
S 39. ^{19} F NMR (470 MHz, $CDCl_3$, 298 K) of **13b**



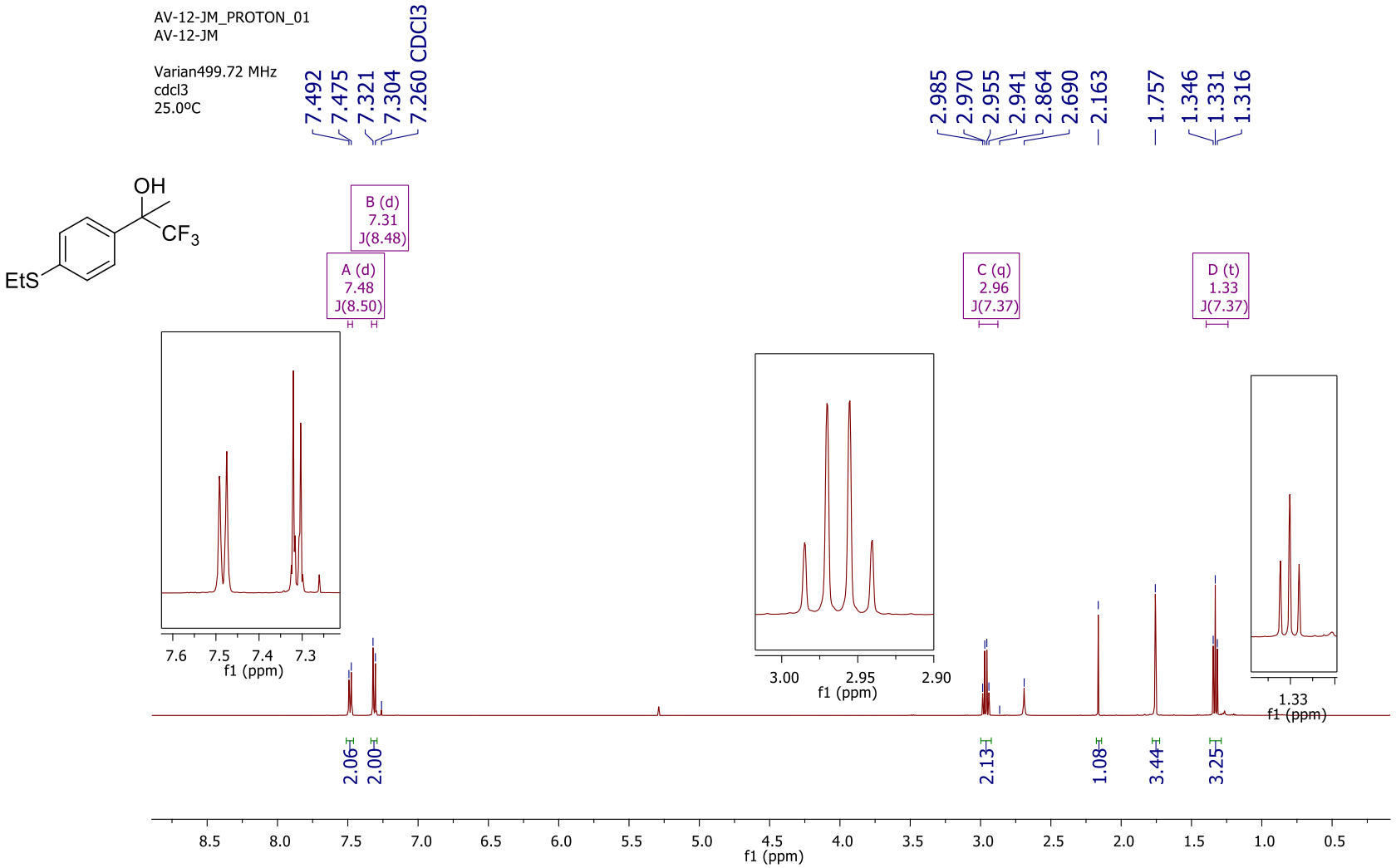
S 40. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) of **14b**



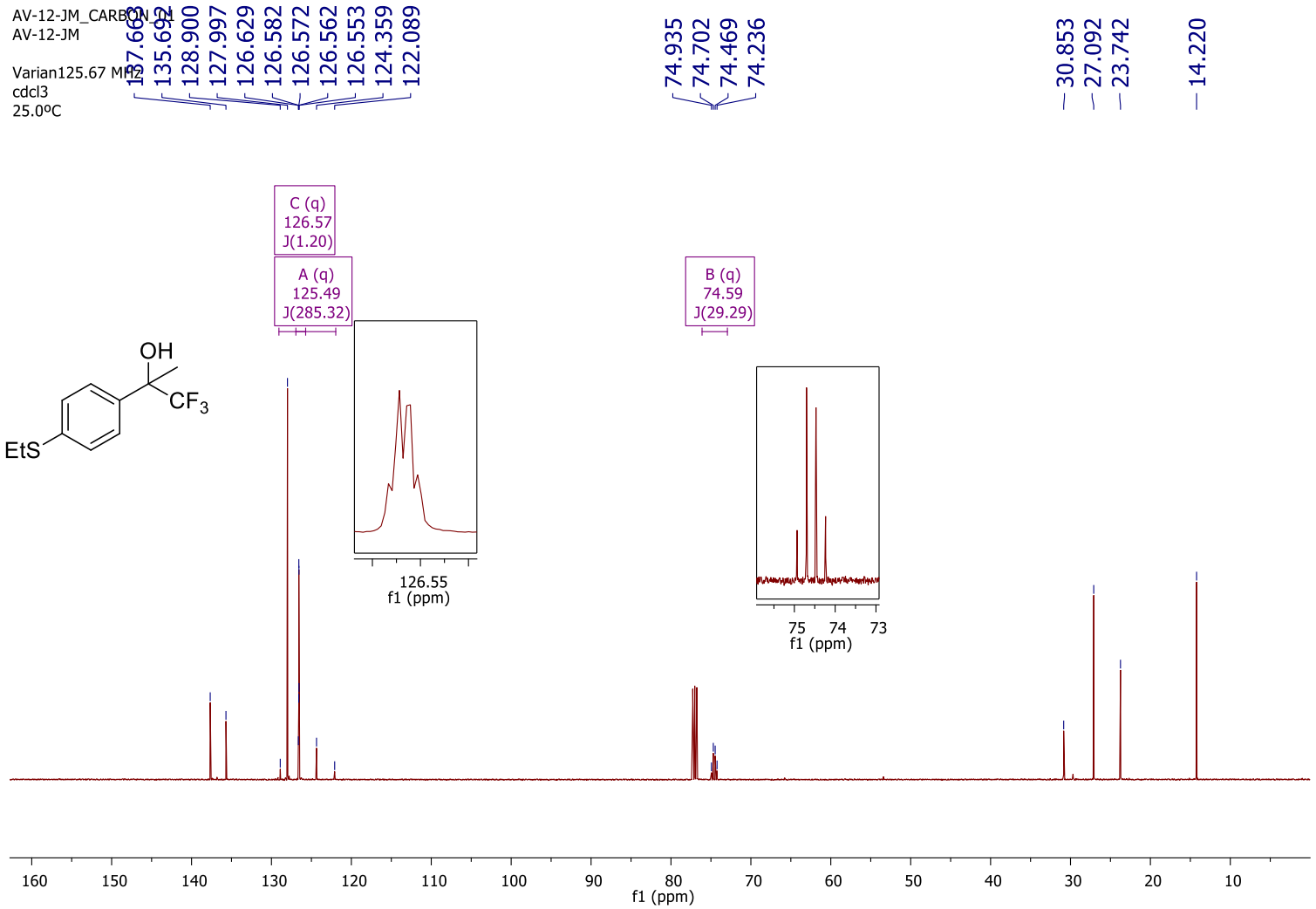
S 41. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 298 K) of **14b**



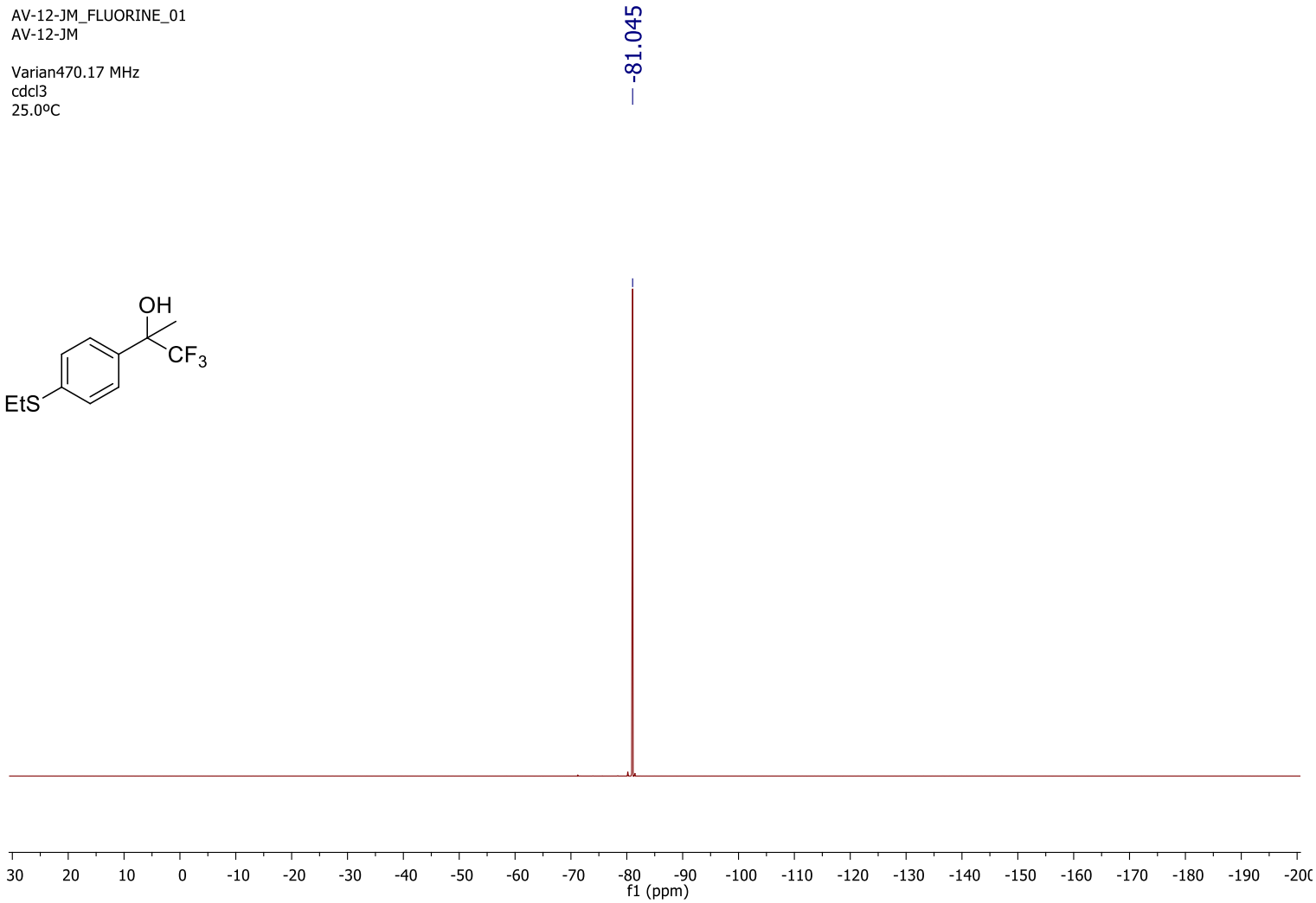
S 42. ^{19} F NMR (376 MHz, $CDCl_3$, 298 K) of **14b**



S 43. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) of **15b**

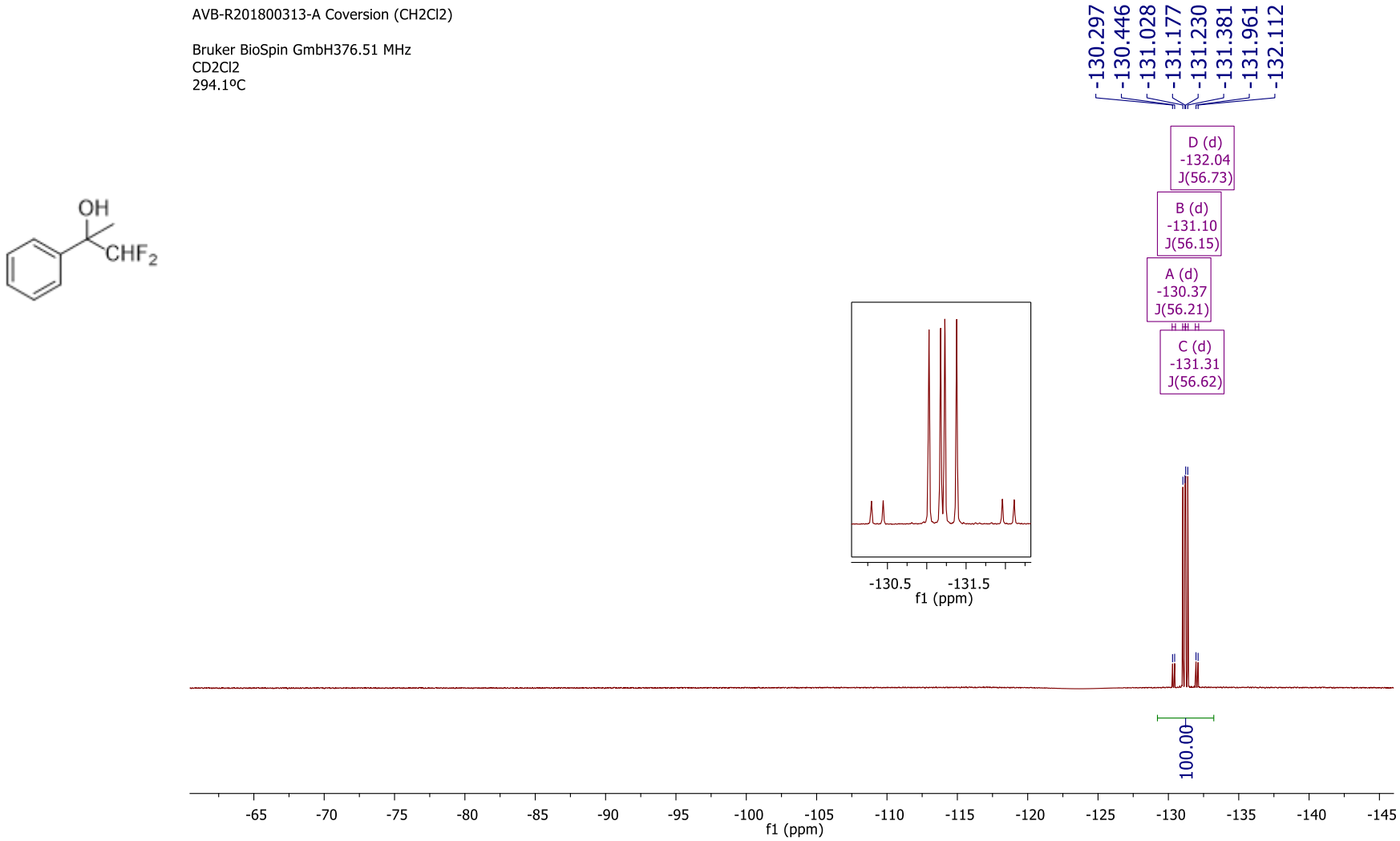


S 44. $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$, 298 K) of **15b**

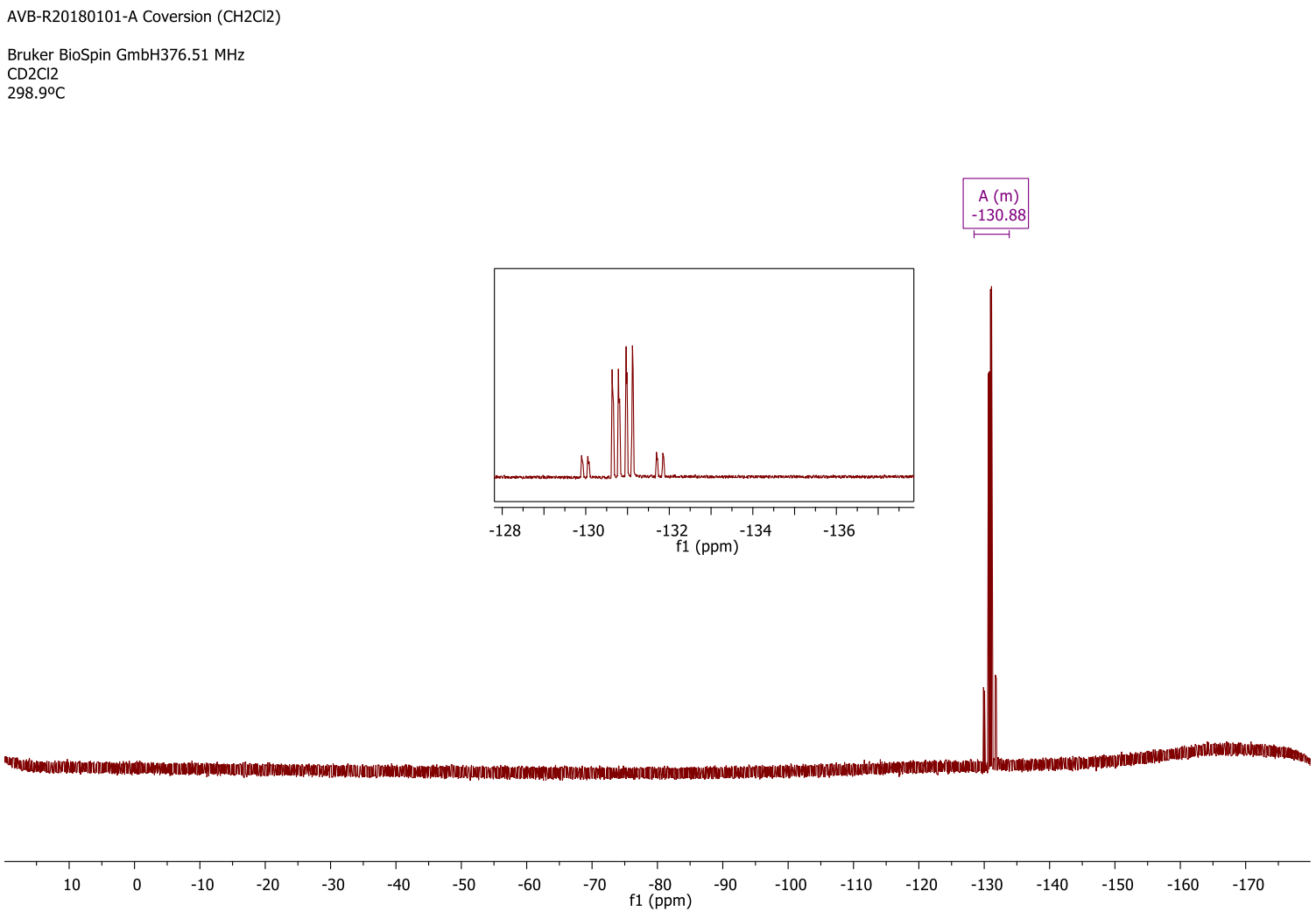


S 45. ^{19} F NMR (470 MHz, $CDCl_3$, 298 K) of **15b**

5. Results of enantioselective addition of $ZnMe_2$ to (T)FAKs in toluene and in DCM. The conversions (^{19}F NMR integration) and enantiomeric excesses (chiral GC or HPLC analysis) of the products (C6H4R)C(CF2X)(Me)(OH) are presented.



S 46. ^{19}F NMR (376 MHz, CH_2Cl_2, 298 K) from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **1a** in DCM at –30 °C.



S 47. ^{19}F NMR (376 MHz, CH_2Cl_2, 298 K) from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **1a** in toluene at –30 °C.

Data File C:\CHEM32\1\DATA\C18034\ANDREA_JM 2018-03-15 14-16-26\A RAC.D
Sample Name: A RAC

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Acq. Operator   : marta                          Seq. Line :   2
Acq. Instrument : LC-PREP                         Location : Vial 2
Injection Date  : 3/15/2018 2:33:17 PM                 Inj :   1
                                                  Inj Volume : 1 µl
Acq. Method     : C:\CHEM32\1\DATA\C18034\ANDREA_JM 2018-03-15 14-16-26\ANDREA_JM.M
Last changed    : 3/15/2018 2:16:24 PM by marta
Analysis Method : C:\CHEM32\1\METHODS\ACHETATO.M
Last changed    : 3/15/2018 6:12:46 PM by marta
                  (modified after loading)
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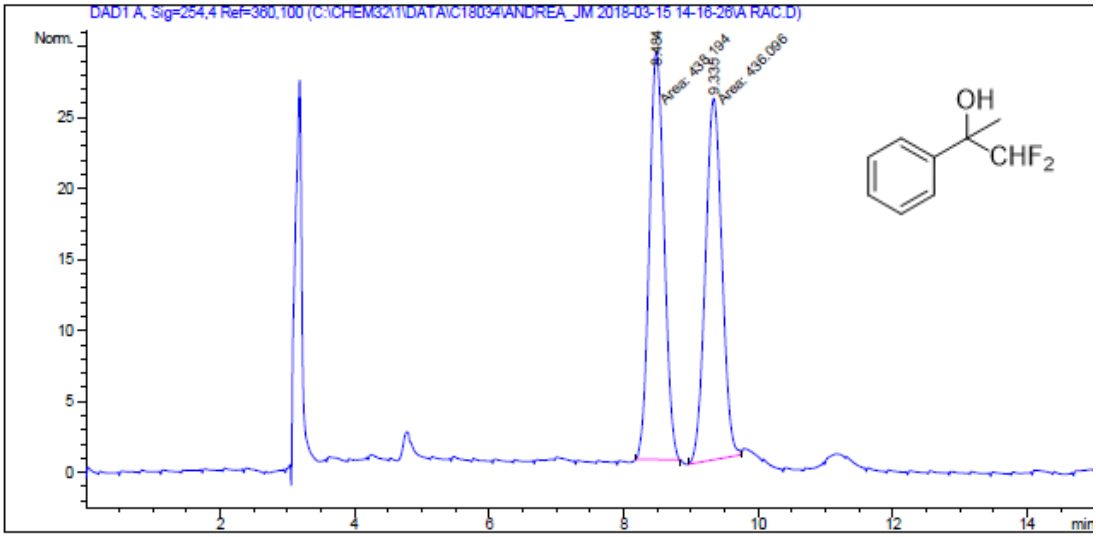


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==================================================================
                        Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   8.484 MM    0.2540  438.19418   28.75208  50.1200
   2   9.335 MM    0.2850  436.09644   25.50593  49.8800

Totals :                   874.29062   54.25801
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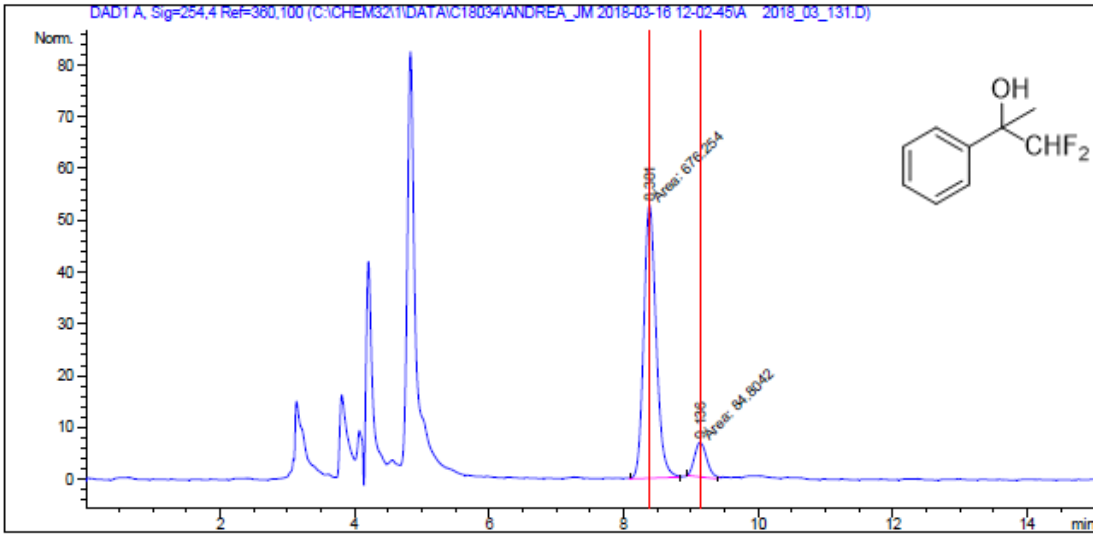
S 48. Enantiomeric resolution by chiral HPLC from racemic compound **1a**.

Data File C:\CHEM32\1\DATA\C18034\ANDREA_JM 2018-03-16 12-02-45\A 2018_03_131.D
Sample Name: A 2018_03_13

Acq. Operator : marta Seq. Line : 2
Acq. Instrument : LC-PREP Location : Vial 2
Injection Date : 3/16/2018 12:35:46 PM Inj : 1
Inj Volume : 1 µl
Acq. Method : C:\CHEM32\1\DATA\C18034\ANDREA_JM 2018-03-16 12-02-45\ANDREA_JM.M
Last changed : 3/15/2018 6:29:04 PM by marta
Analysis Method : C:\CHEM32\1\METHODS\ACHETATO.M
Last changed : 3/16/2018 1:55:59 PM by marta
(modified after loading)



Area Percent Report

Sorted By : Signal
Multiplier: : 1.0000
Dilution: : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.381	MM	0.2135	676.25415	52.80120	88.8571
2	9.136	MM	0.2095	84.80417	6.74575	11.1429
Totals :				761.05832	59.54695	

S 49. Enantiomeric resolution by HPLC from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **1a** in DCM at –30 °C.

```
Data File C:\CHEM32\1\DATA\ANDREA\ANDREA_JM 2018-05-15 13-24-45\A -601.D
Sample Name: A -T

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Acq. Instrument : LC-PREP                        Location : Vial 2
Injection Date  : 5/15/2018 2:07:48 PM               Inj :   1
                                                 Inj Volume : 1 µl
Acq. Method     : C:\CHEM32\1\DATA\ANDREA\ANDREA_JM 2018-05-15 13-24-45\ANDREA_JM.M
Last changed    : 5/15/2018 1:24:44 PM by marta
Analysis Method : C:\CHEM32\1\METHODS\ANDREA_JM.M
Last changed    : 5/15/2018 1:24:44 PM by marta
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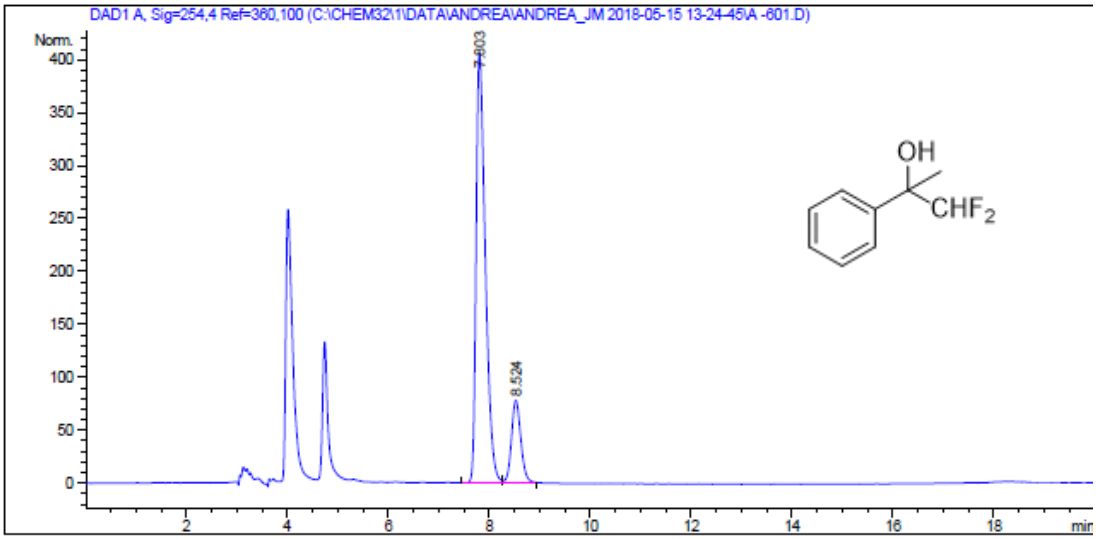


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==================================================================
                      Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   7.803 BV    0.1916 5141.78564  406.31320  83.6057
   2   8.524 VB    0.1958 1008.25836   77.99348  16.3943

Totals :                  6150.04401  484.30668


LC-PREP 7/4/2018 11:27:58 AM marta                          Page   1 of 2
```
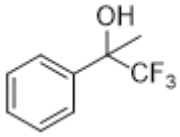
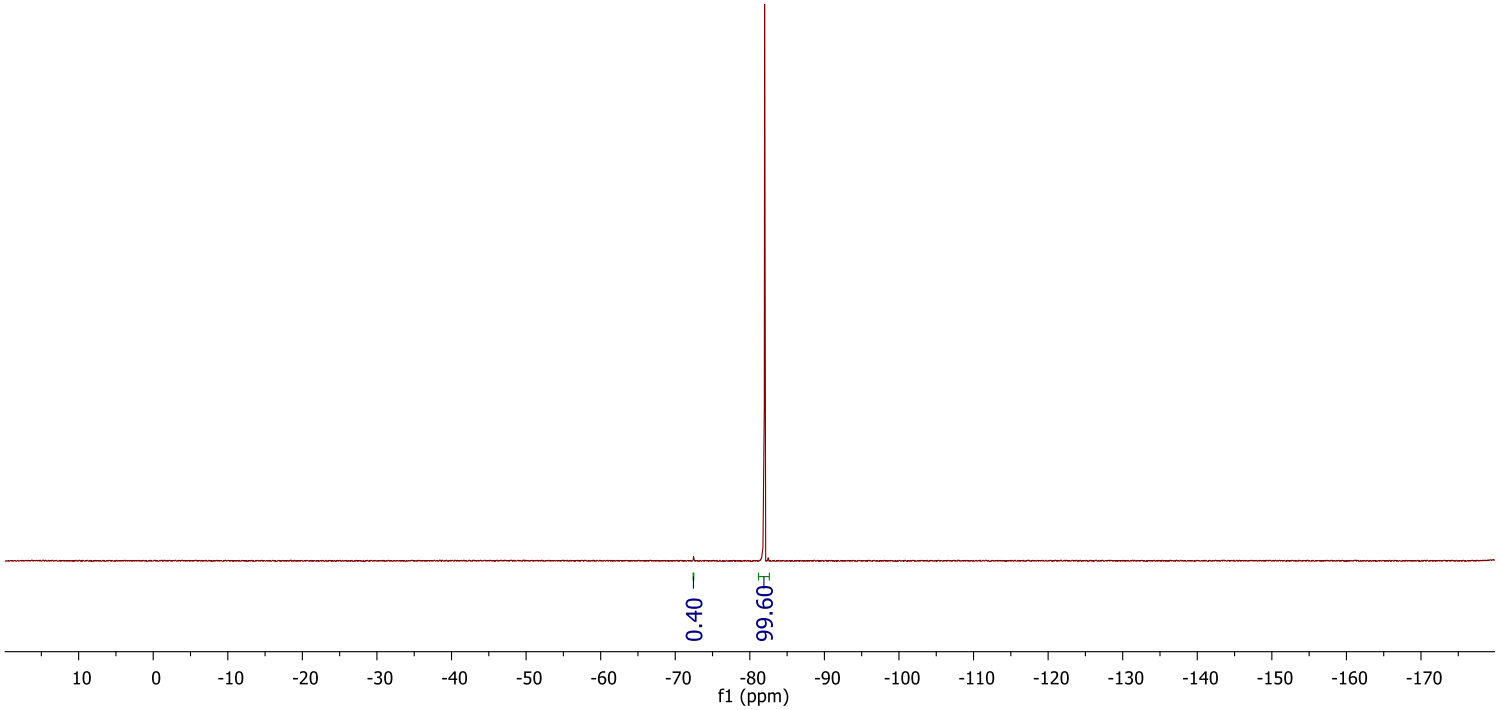

S 50. Enantiomeric resolution by HPLC from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **1a** in toluene at –30 °C

AVB-R201800313-B Coversion (CH2Cl2)

Bruker BioSpin GmbH376.51 MHz
CD2Cl2
294.1ºC

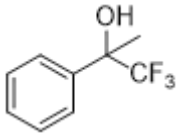


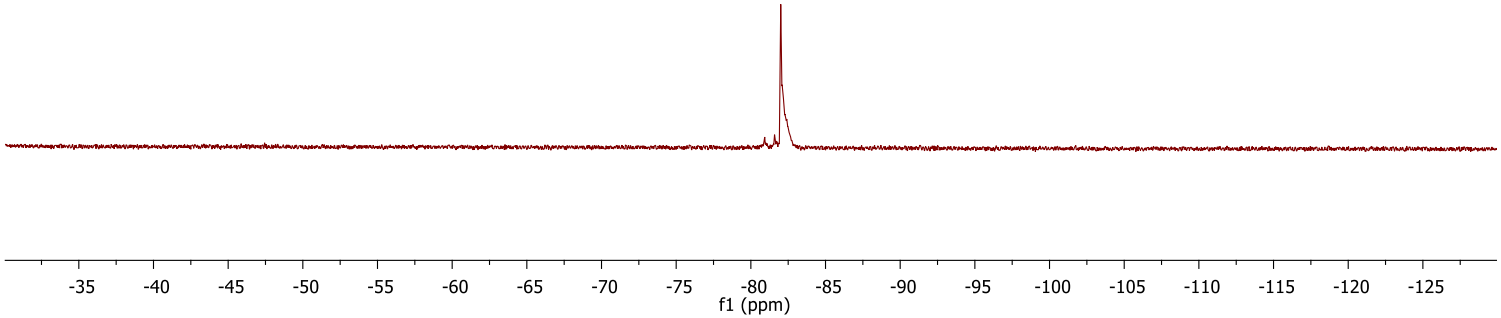


S 51. ^{19}F NMR (376 MHz, CH_2Cl_2, 298 K) from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **2a** in DCM at –30 °C.

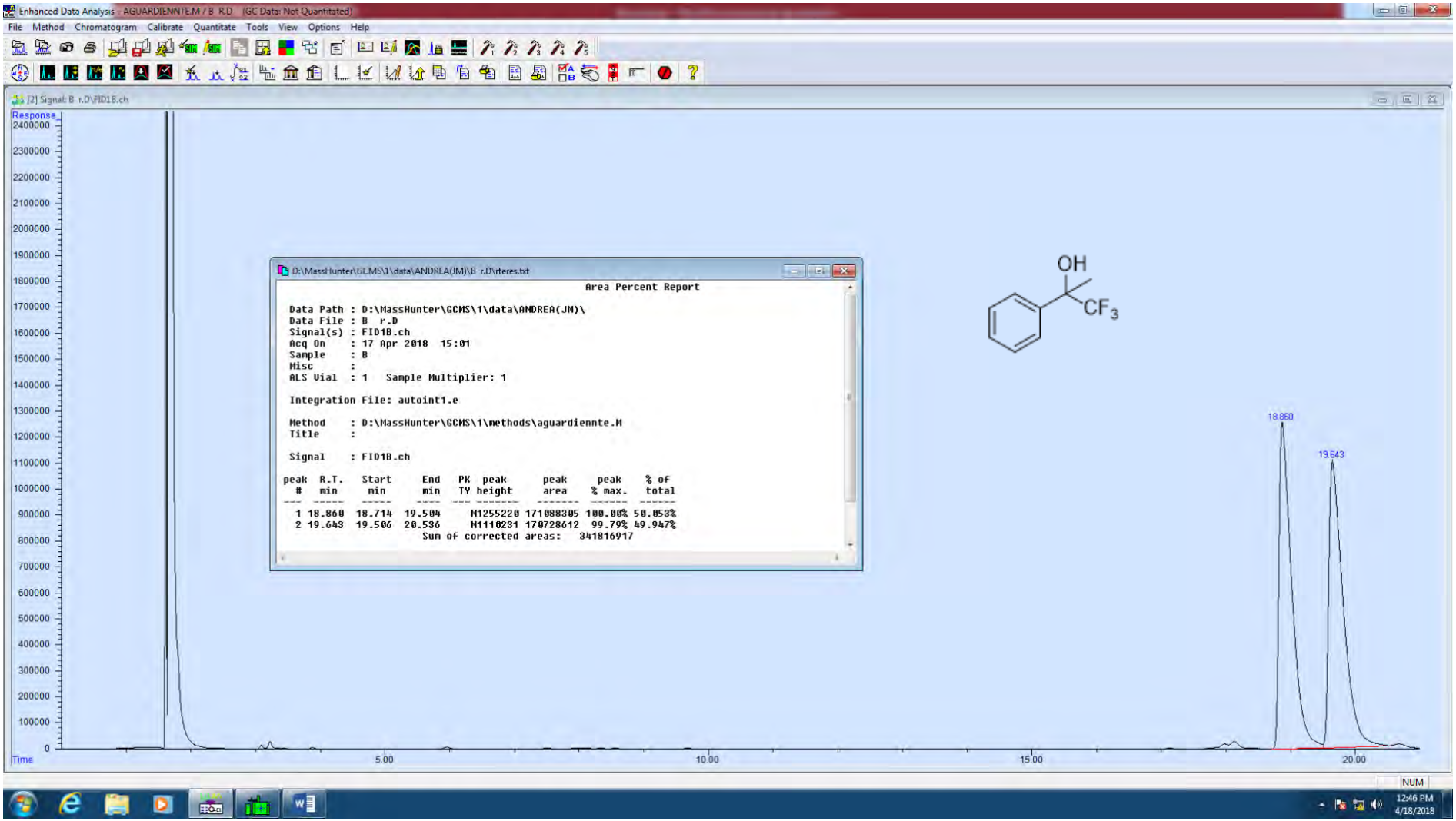
AVB-R20180501-B Coversion (CH2Cl2)

Bruker BioSpin GmbH376.51 MHz
CD2Cl2
294.7°C

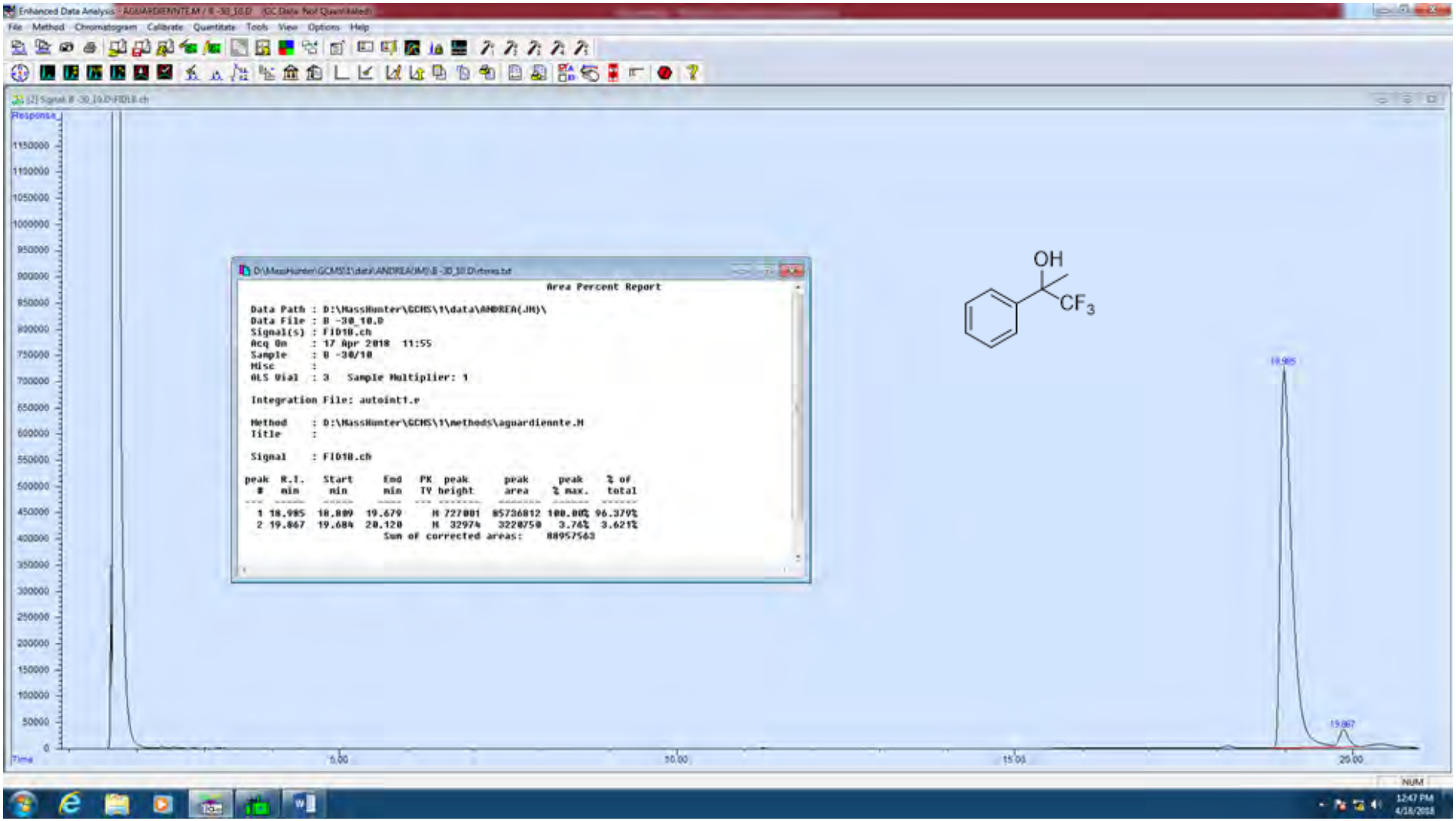




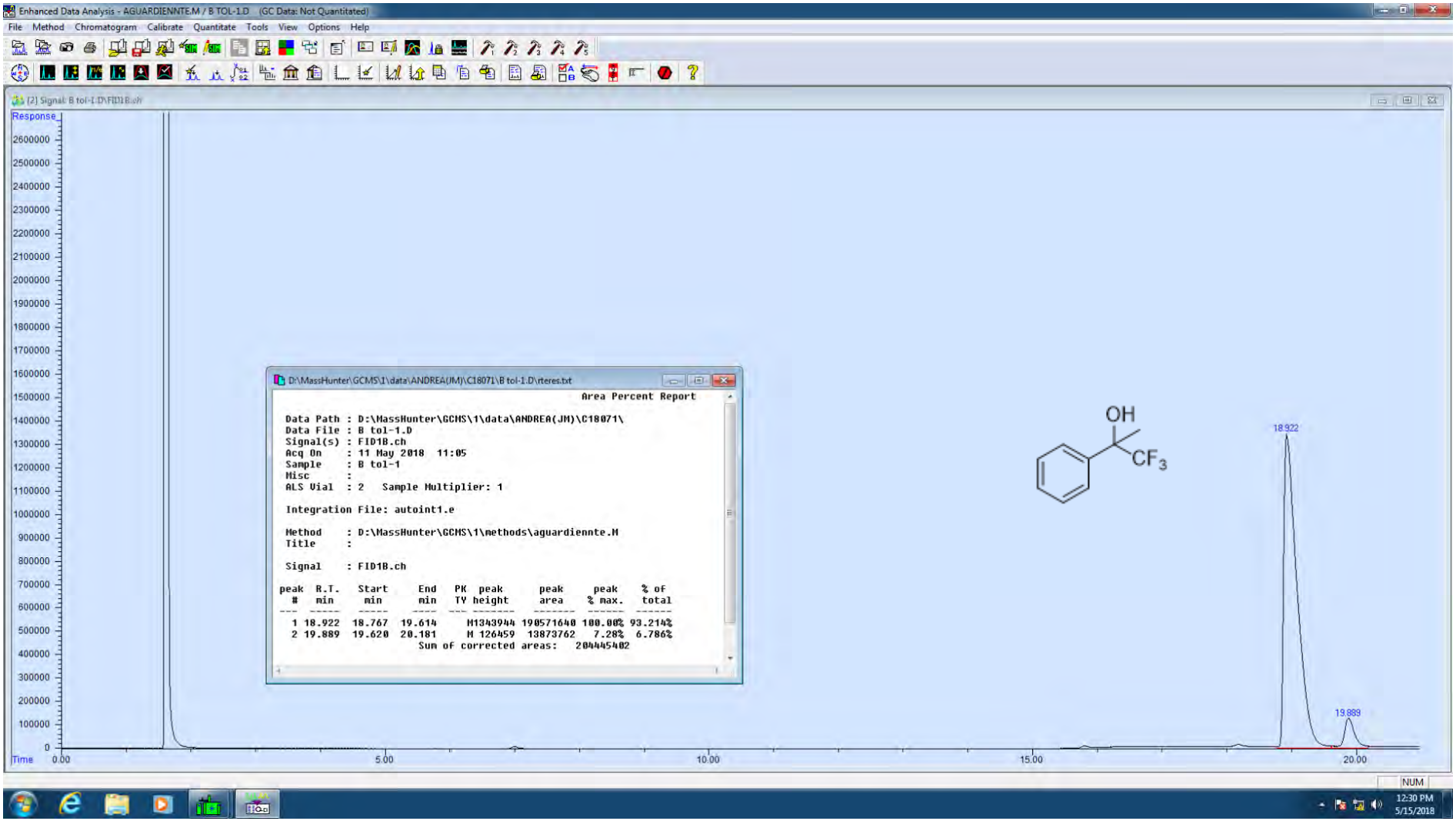
S 52. ^{19}F NMR (376 MHz, CH_2Cl_2, 298 K) from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **2a** in toluene at –30 °C.



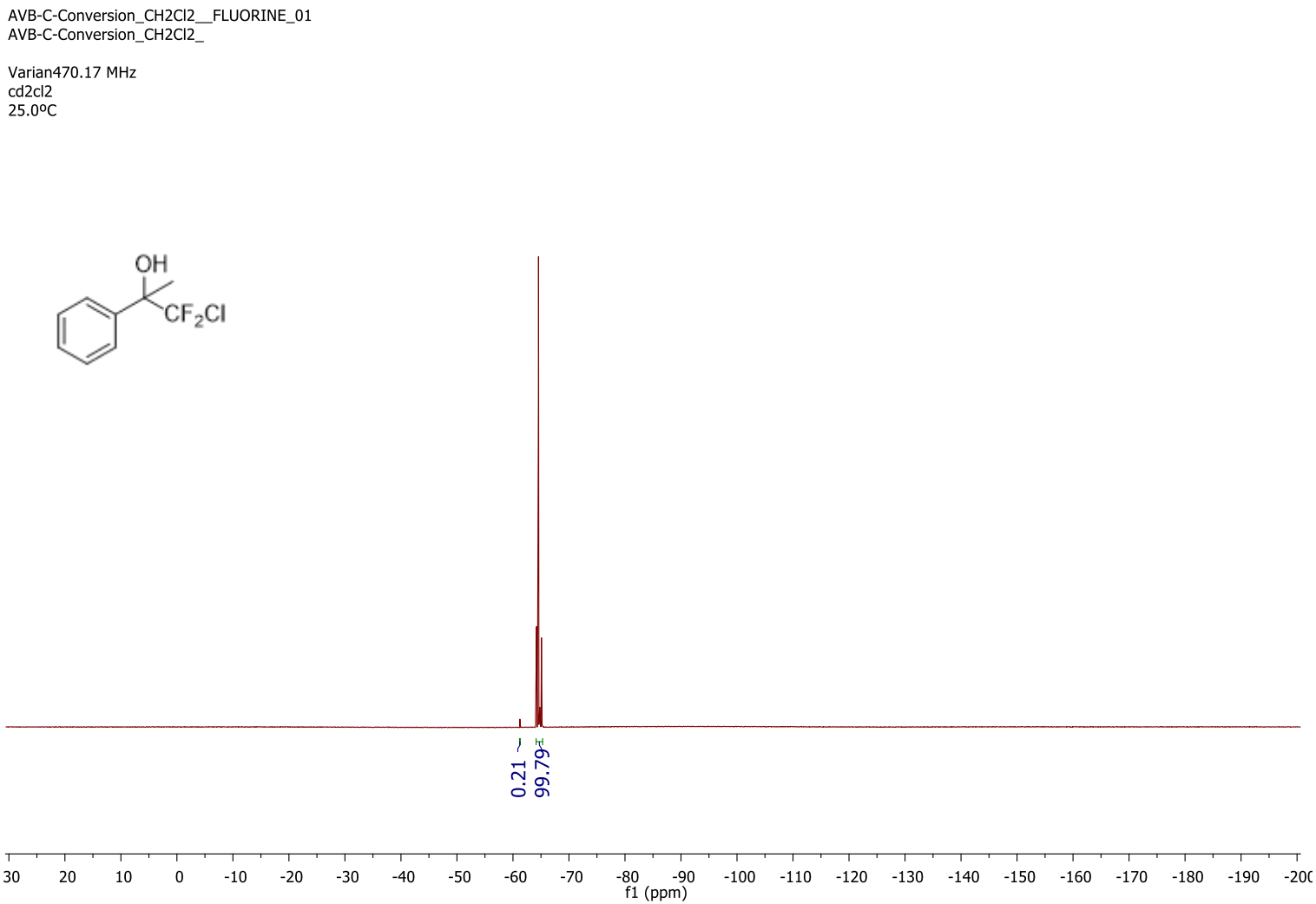
S 53. Enantiomeric resolution by chiral GC from racemic compound **2a**.



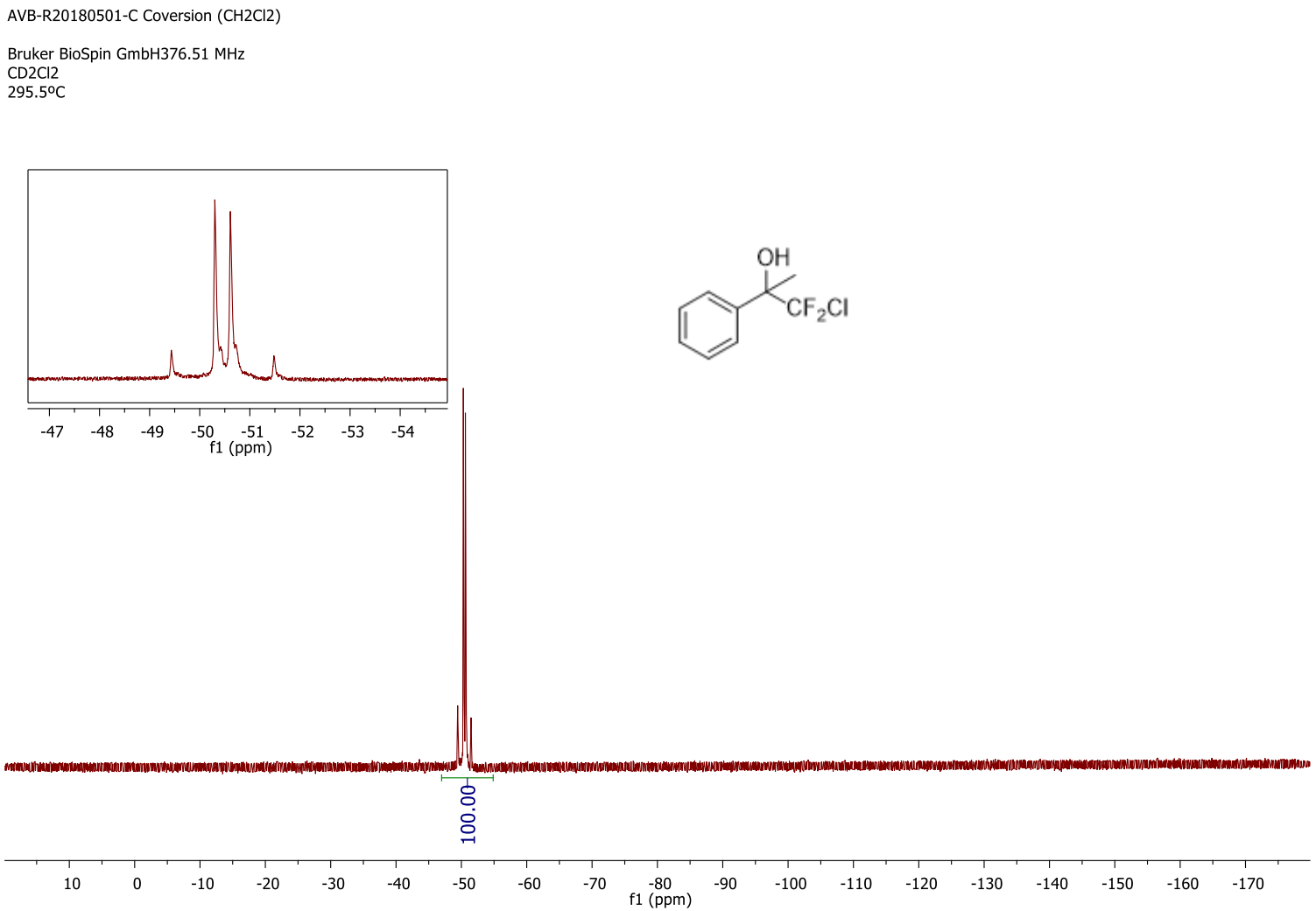
S 54. Enantiomeric resolution by GC from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **2a** in DCM at –30 °C.



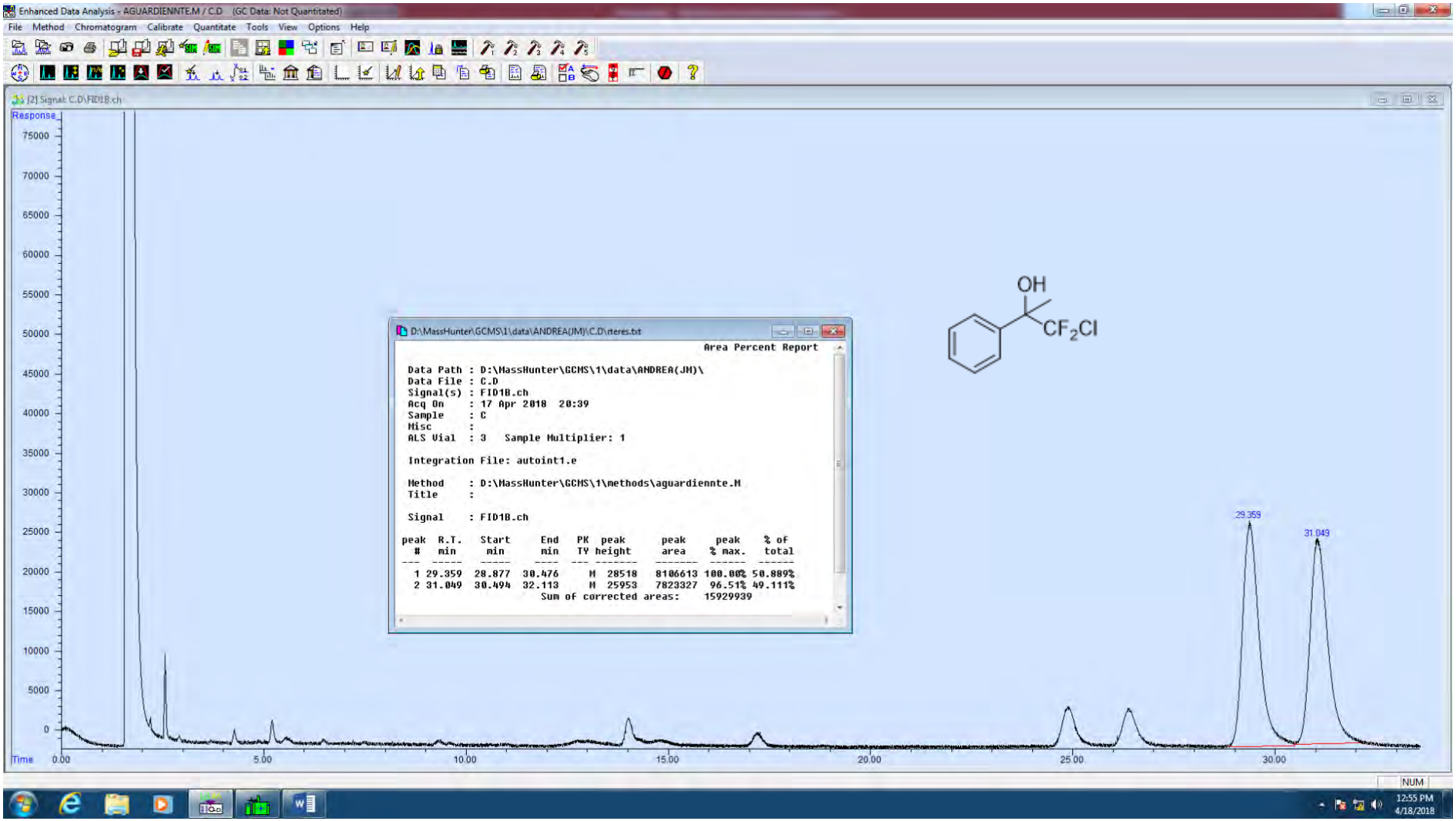
S 55. Enantiomeric resolution by GC from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **2a** in toluene at –30 °C



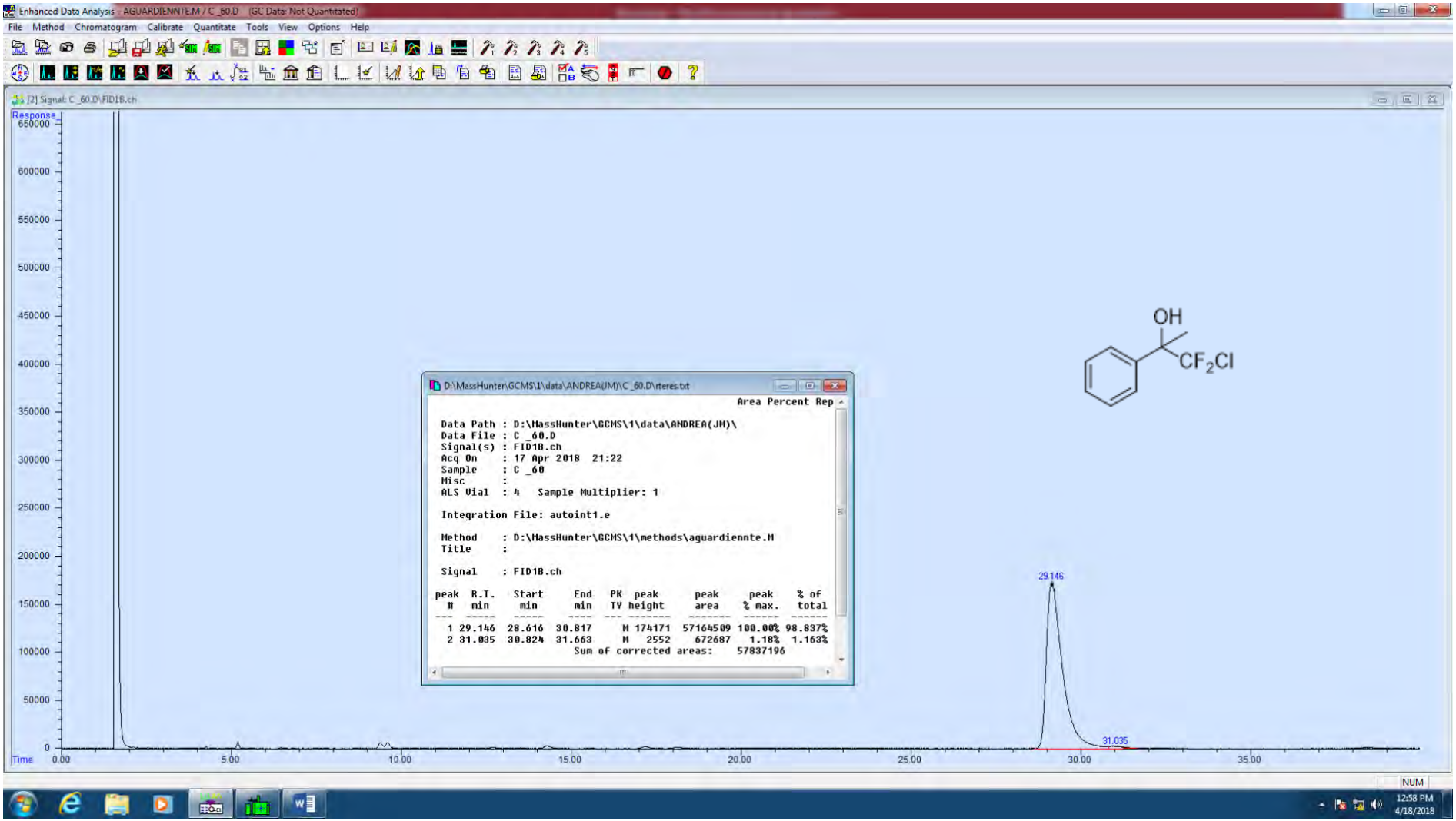
S 56. ^{19}F NMR (470 MHz, CH_2Cl_2, 298 K) from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **3a** in DCM at –30 °C.



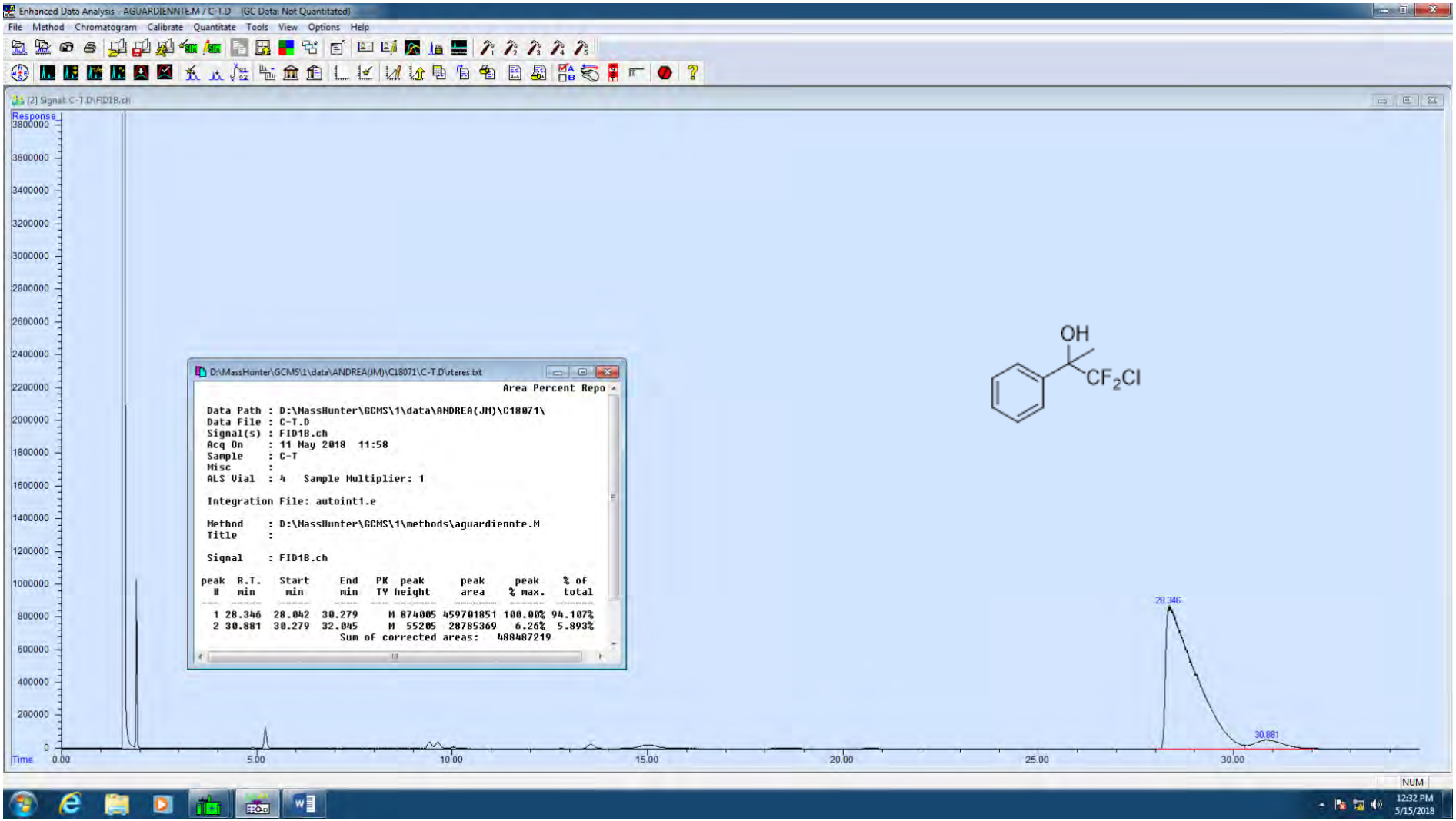
S 57. ^{19}F NMR (376 MHz, CH_2Cl_2, 298 K) from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **3a** in toluene at –30 °C.



S 58. Enantiomeric resolution by chiral GC from racemic compound **3b**.



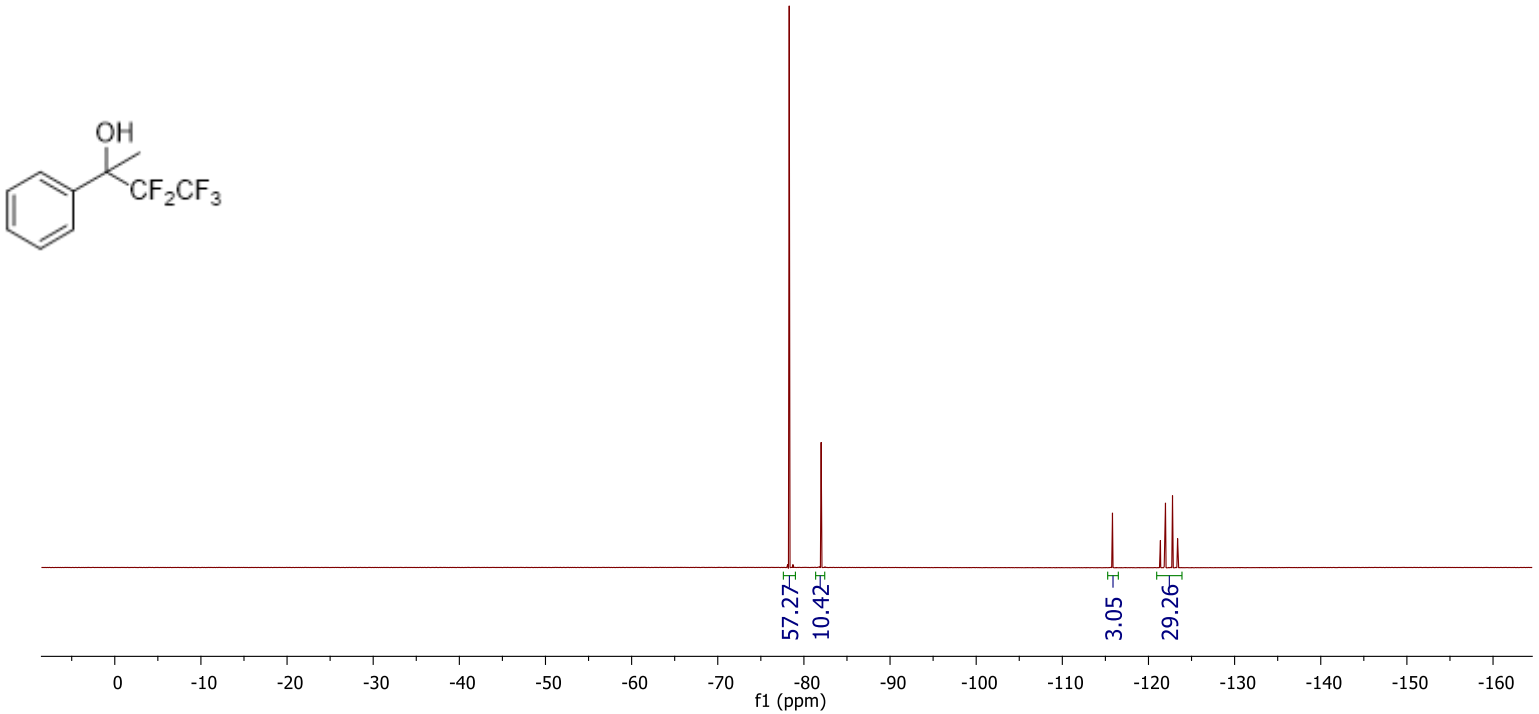
S 59. Enantiomeric resolution by GC from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **3a** in DCM at –30 °C.



S 60. Enantiomeric resolution by GC from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **3a** in toluene at –30 °C.

AVB-D-Conversion_CH2Cl2__FLUORINE_01
AVB-C-Conversion_CH2Cl2_

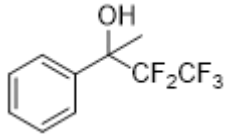
Varian470.17 MHz
cd2cl2
25.0ºC

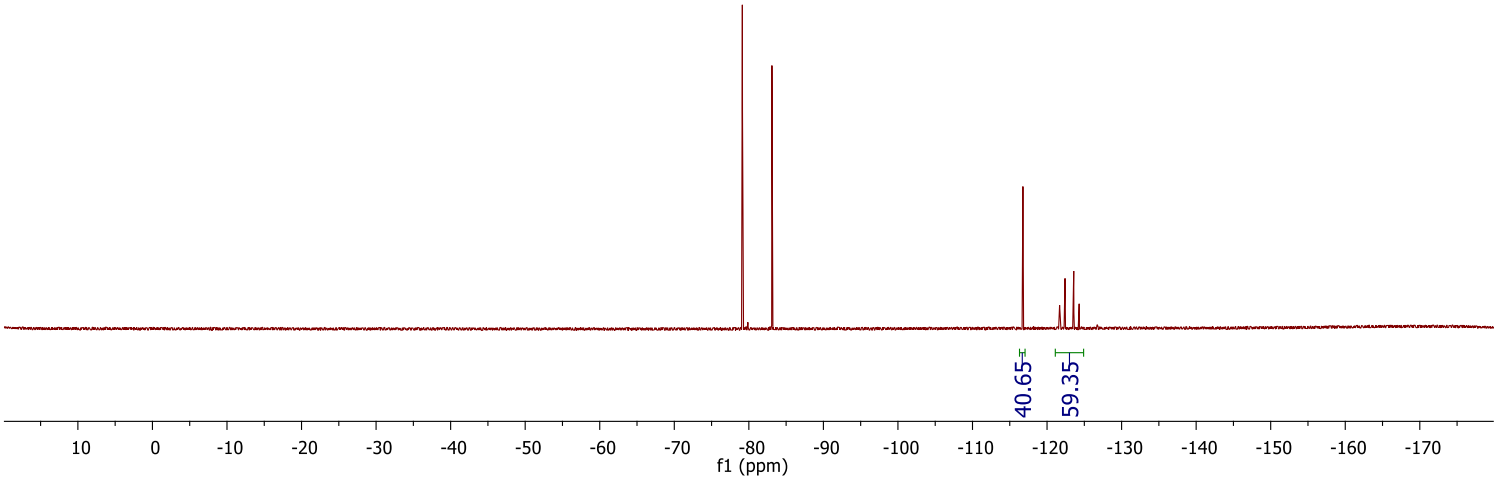


S 61. ^{19}F NMR (470 MHz, CH_2Cl_2, 298 K) from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **4a** in DCM at –30 °C.

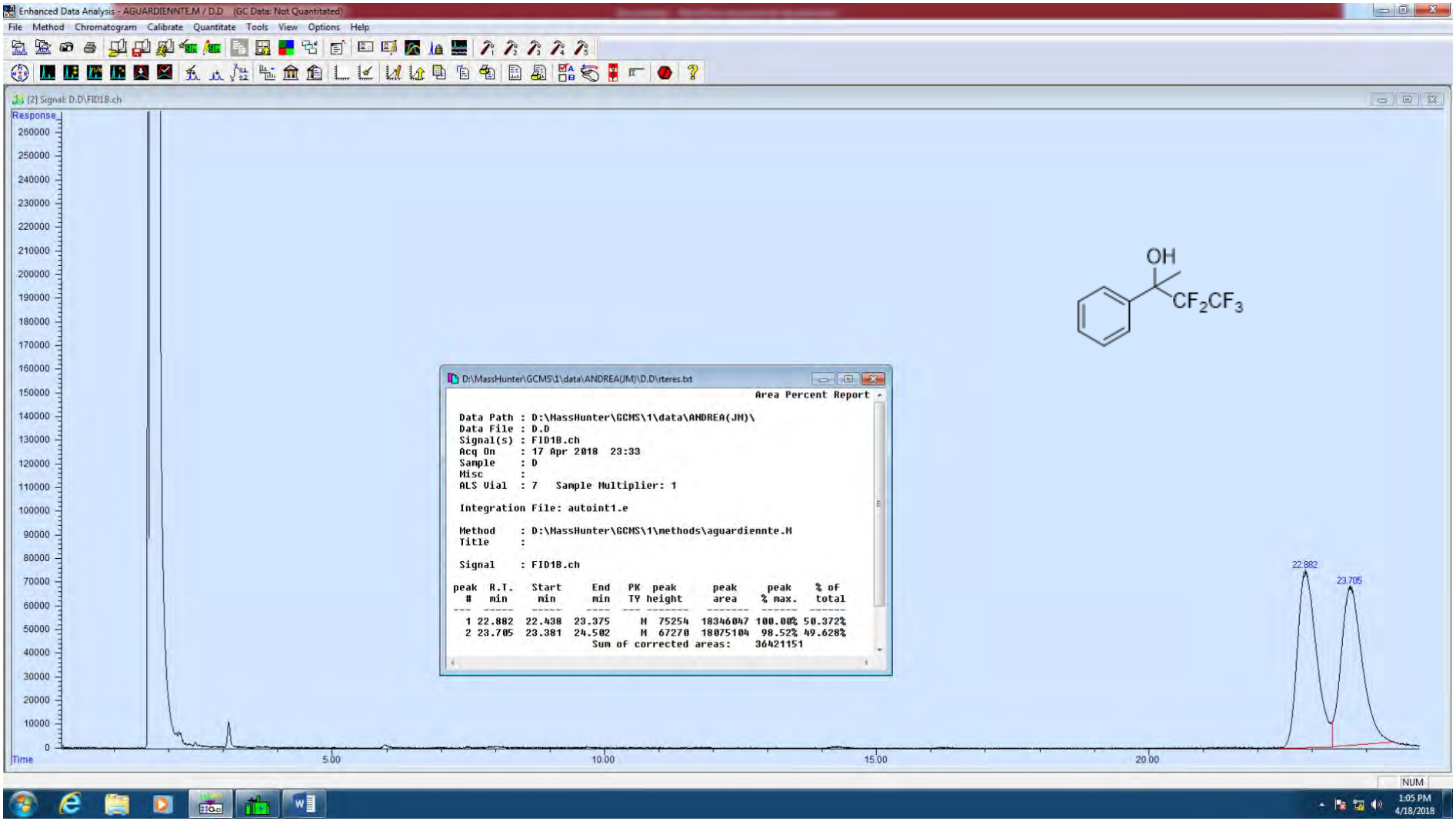
AVB-R20180101-D Coversion (CH2Cl2)

Bruker BioSpin GmbH376.51 MHz
CD2Cl2
298.5ºC

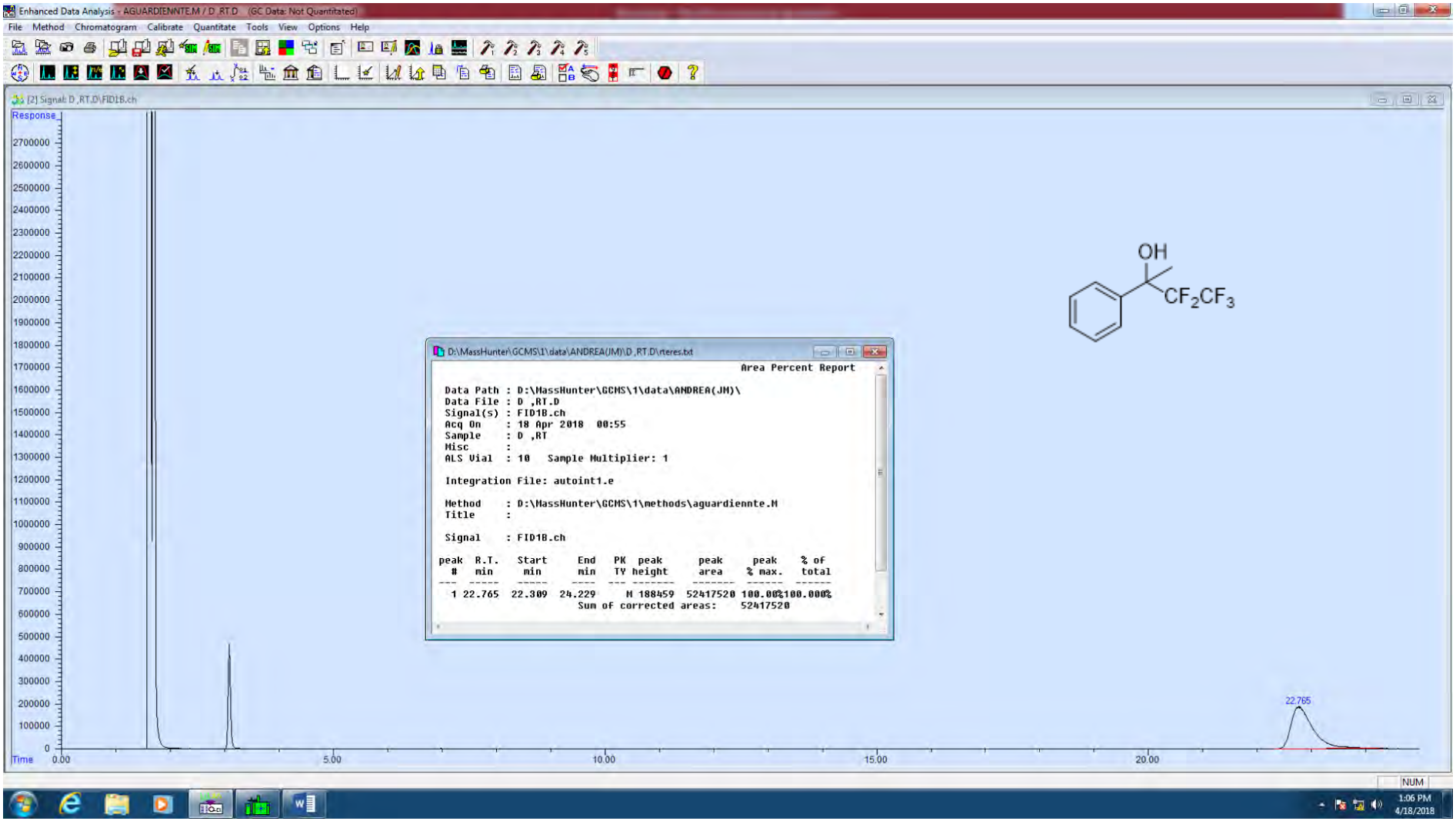




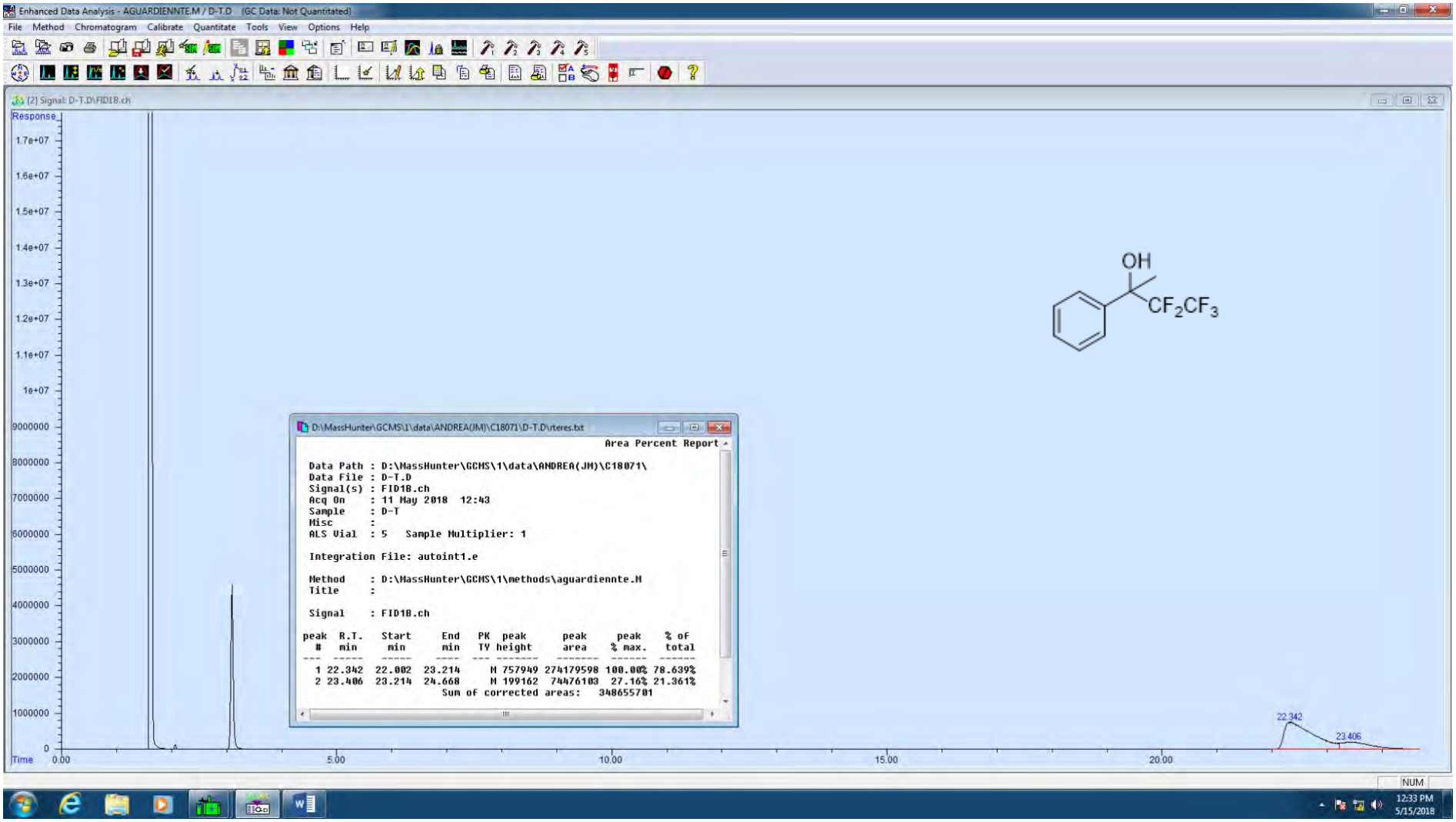
S 62. ^{19}F NMR (376 MHz, CH_2Cl_2, 298 K) from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **4a** in toluene at –30 °C.



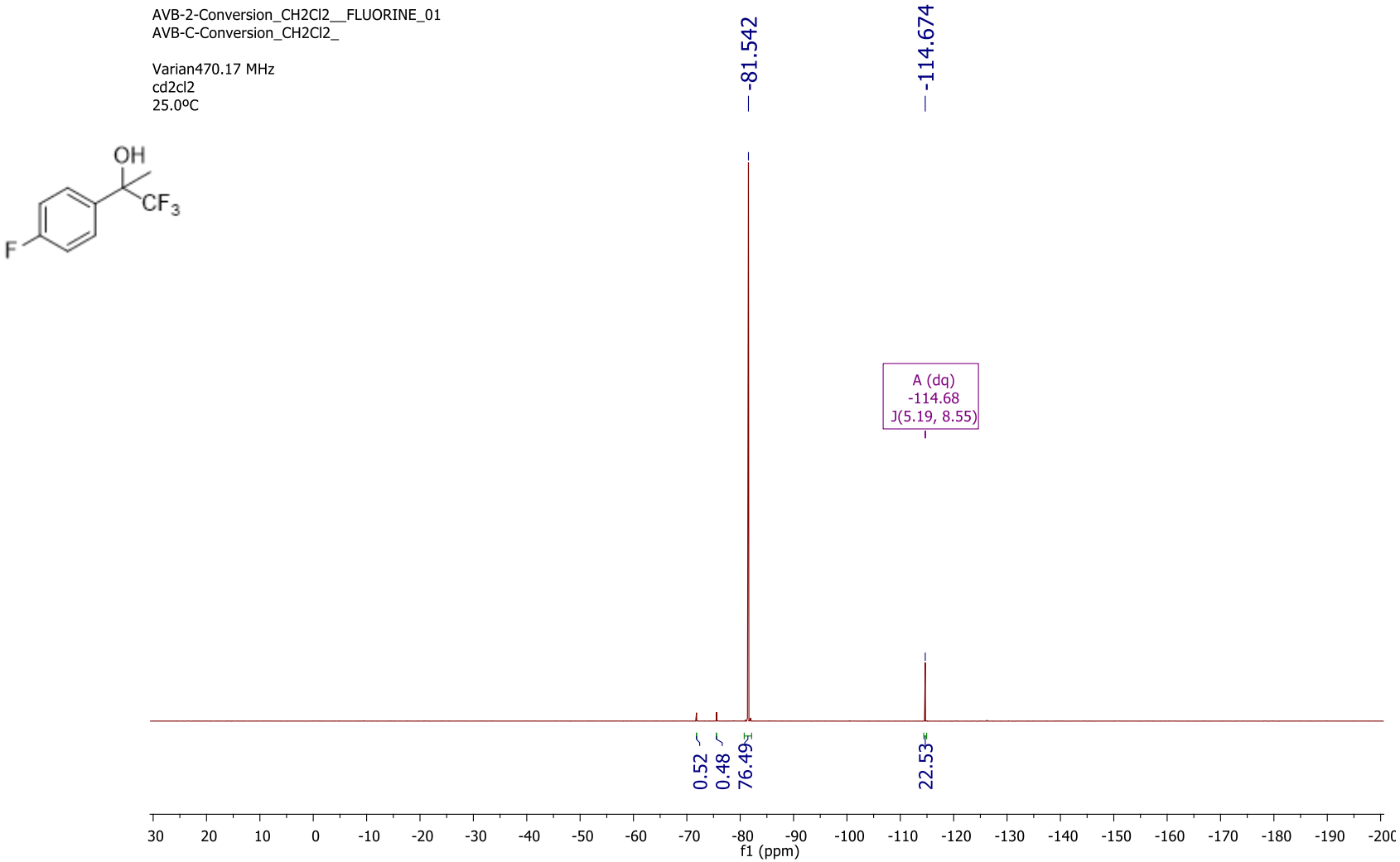
S 63. Enantiomeric resolution by chiral GC from racemic compound **4b**.



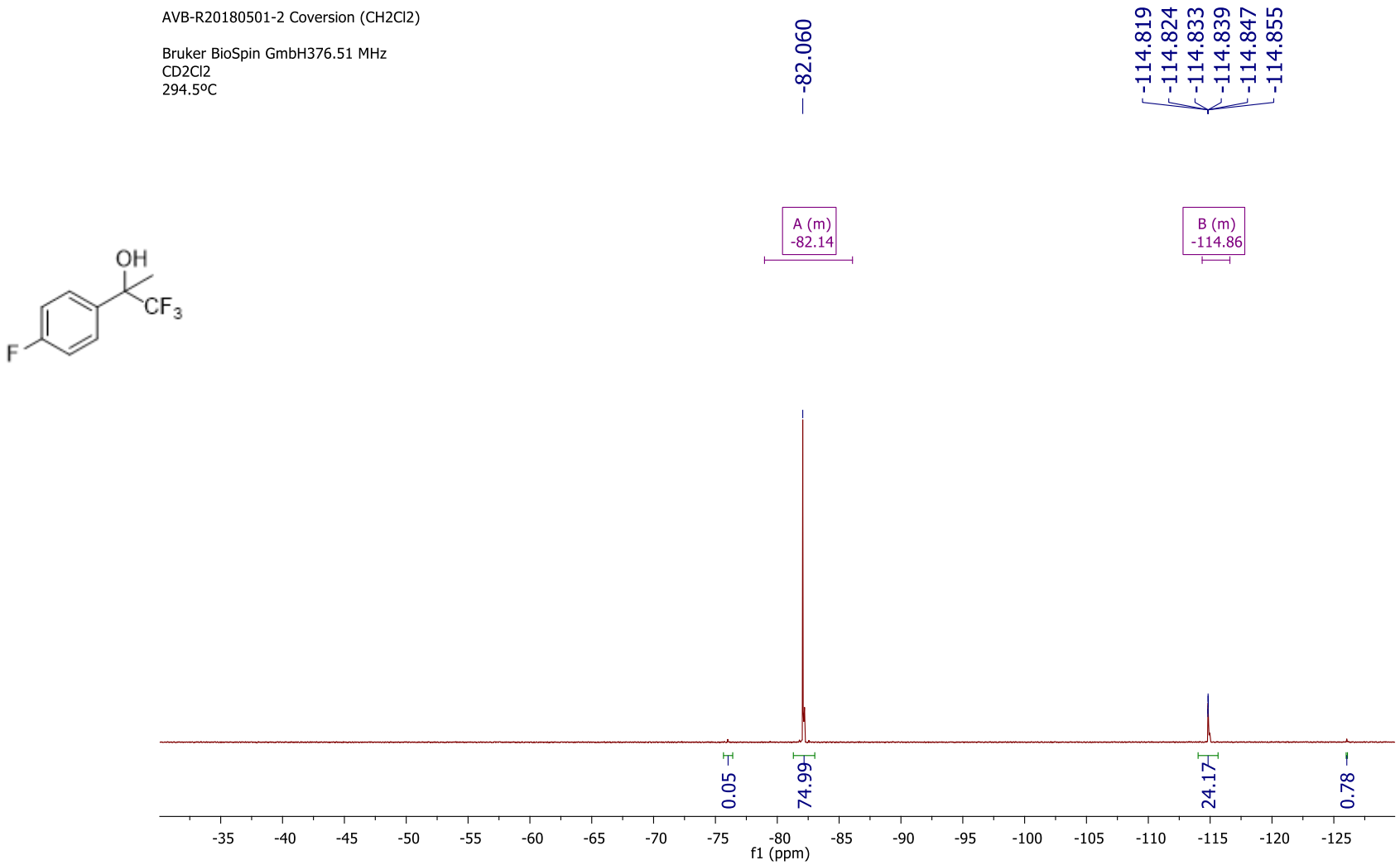
S 64. Enantiomeric resolution by GC from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **4a** in DCM at –30 °C.



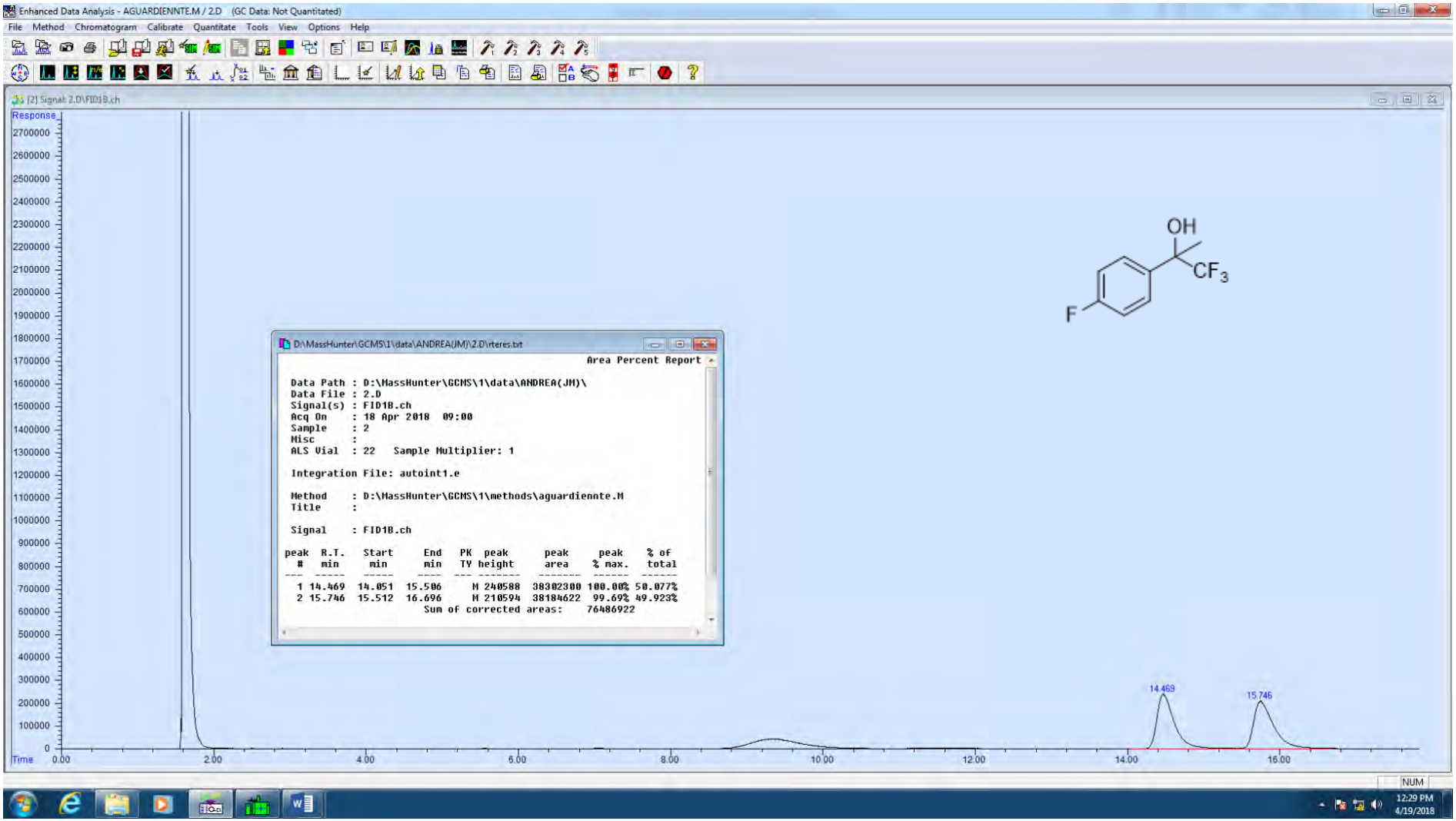
S 65. Enantiomeric resolution by GC from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **4a** in toluene at –30 °C.



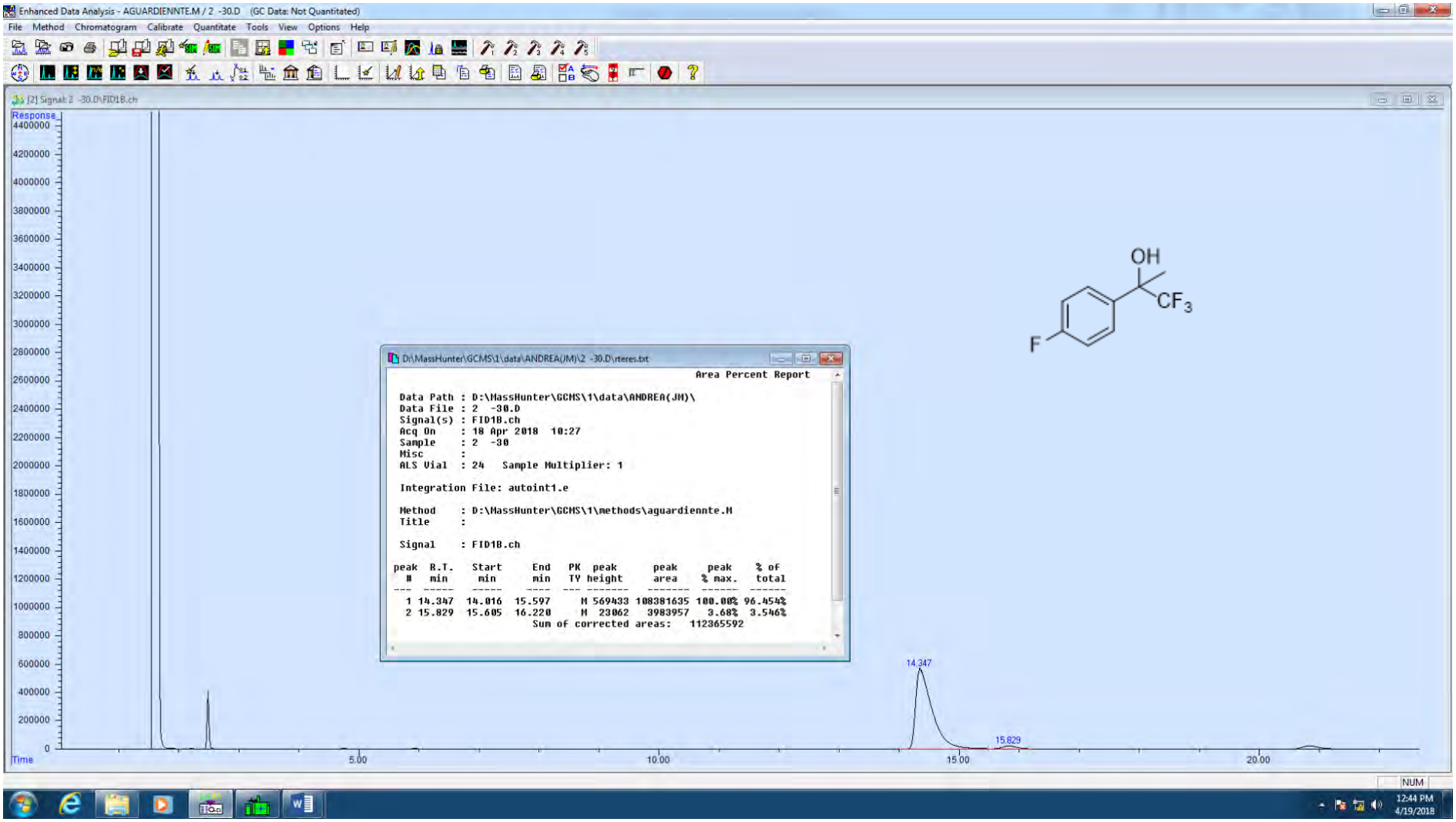
S 66. ^{19}F NMR (376 MHz, CH_2Cl_2, 298 K) from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **5a** in DCM at –30 °C.



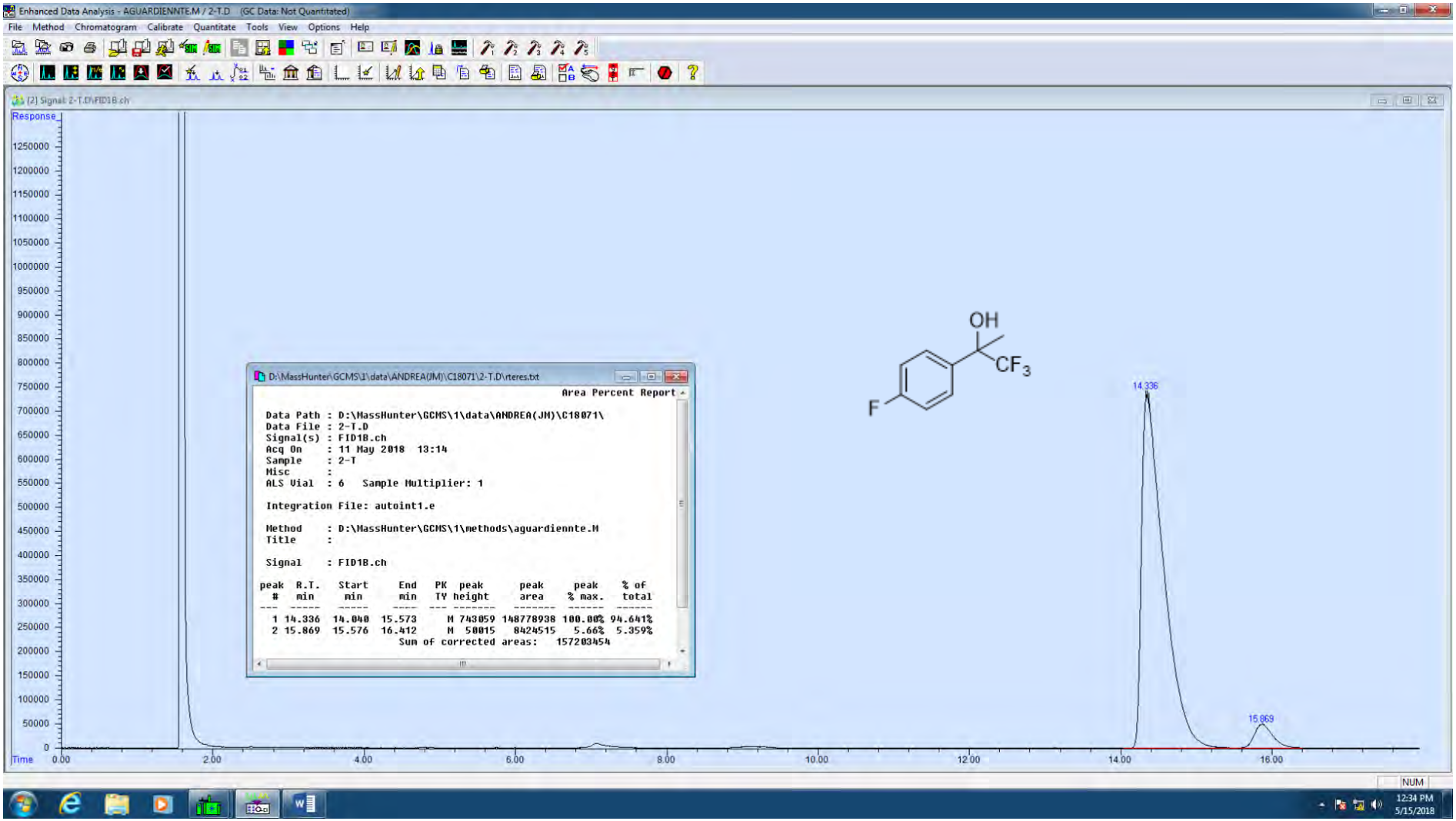
S 67. ^{19}F NMR (376 MHz, CH_2Cl_2, 298 K) from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **5a** in toluene at –30 °C.



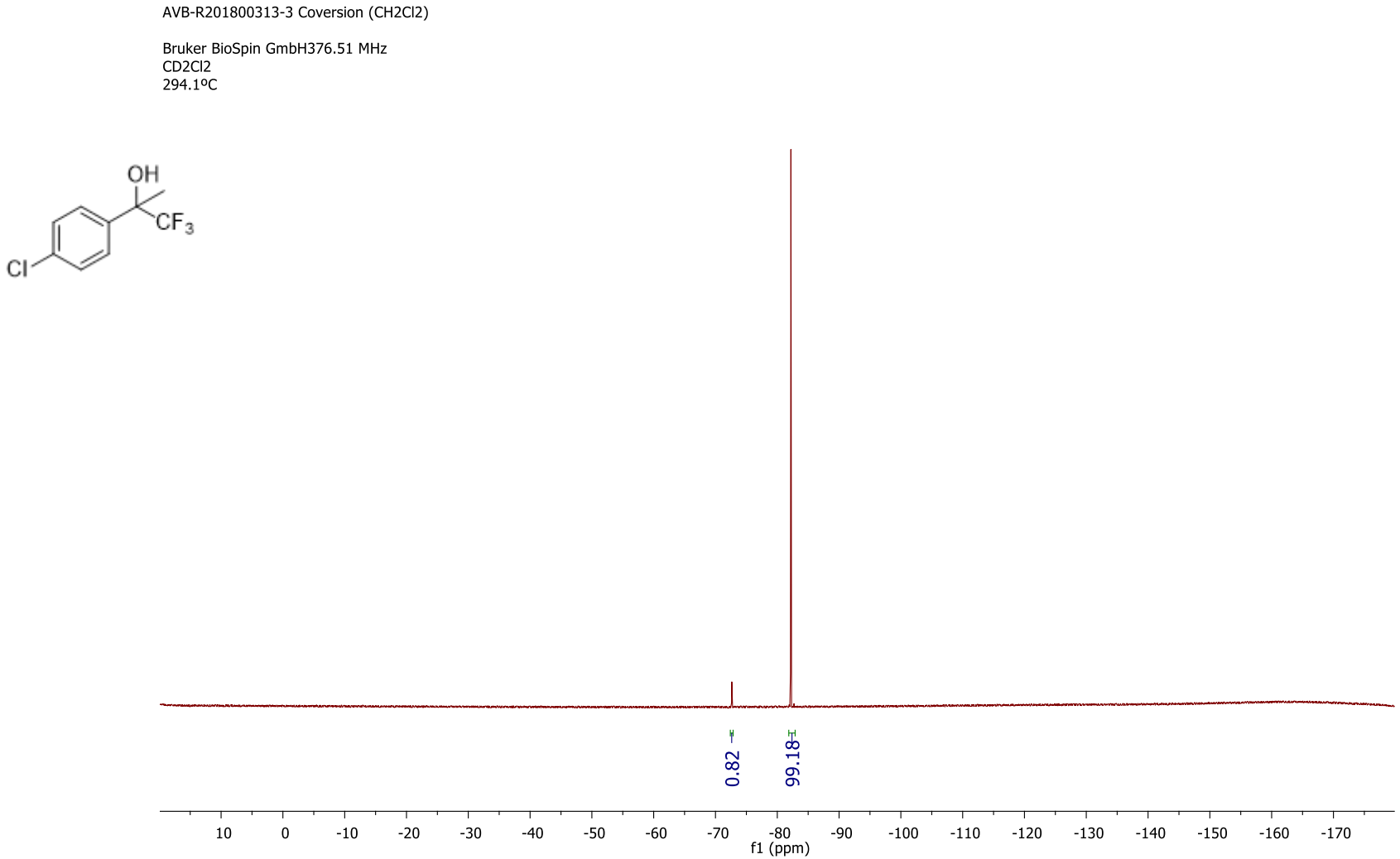
S 68. Enantiomeric resolution by chiral GC from racemic compound **5b**.



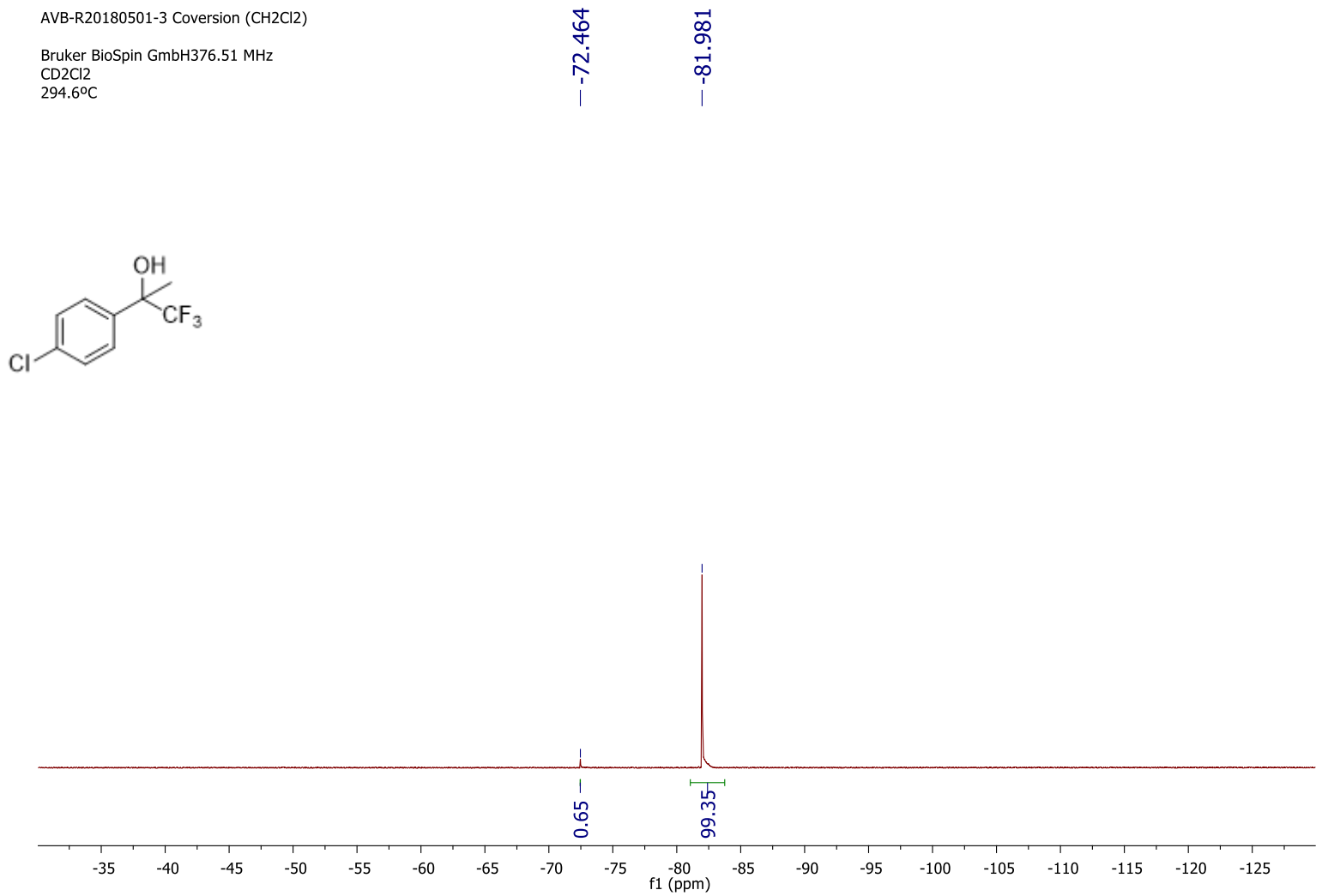
S 69. Enantiomeric resolution by GC from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **5a** in DCM at –30 °C.



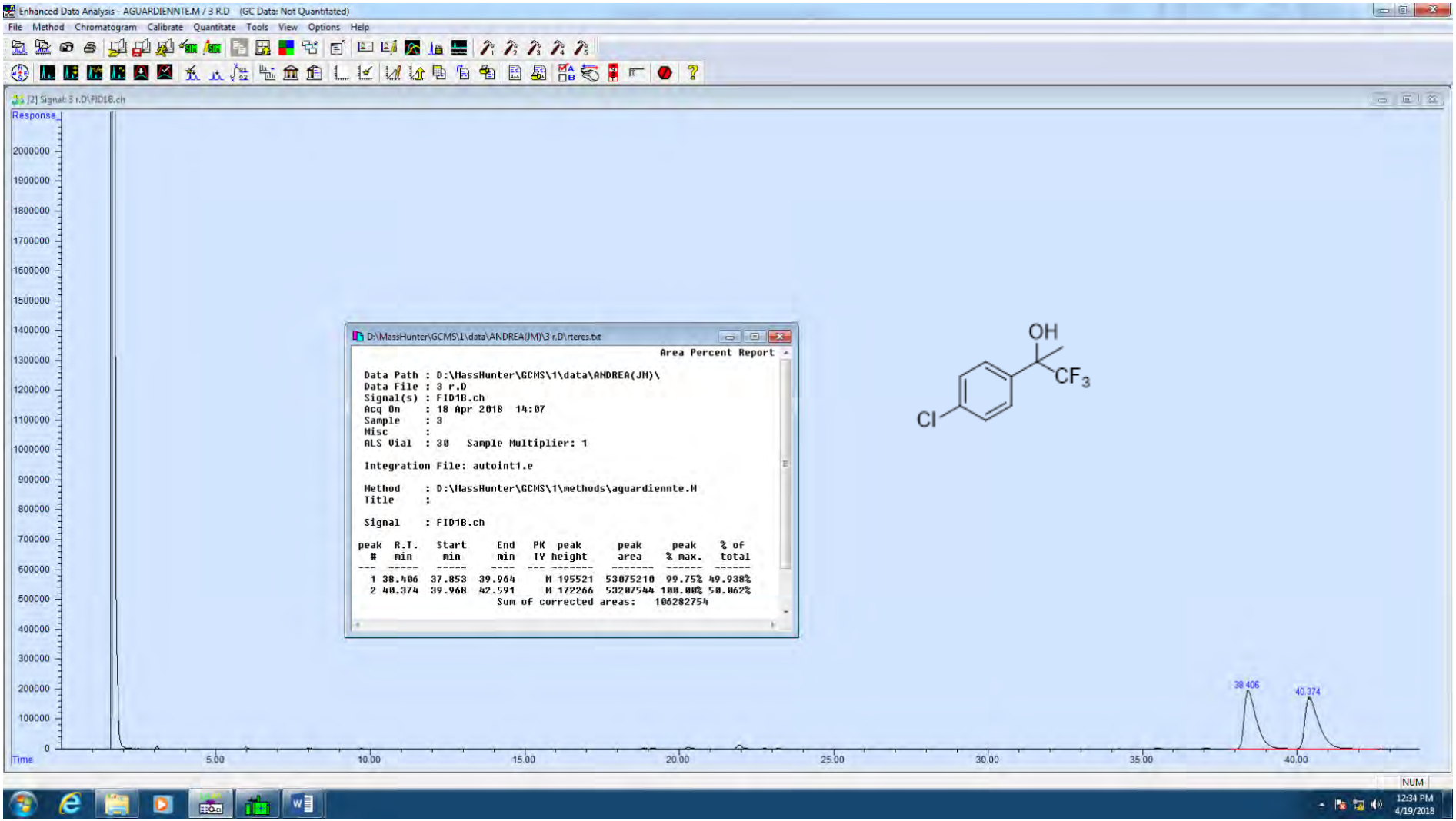
S 70. Enantiomeric resolution by GC from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **5a** in toluene at –30 °C.



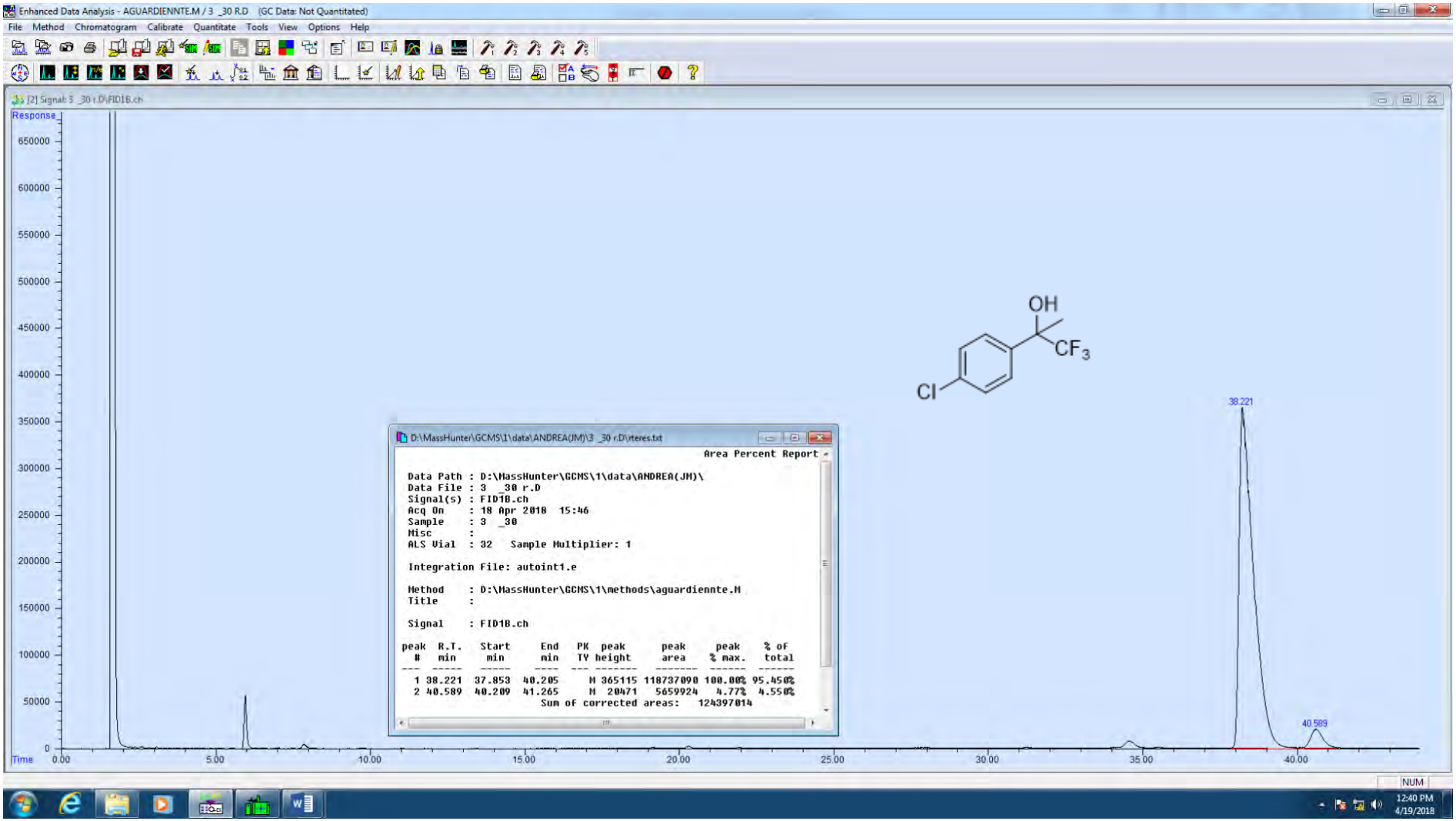
S 71. ^{19}F NMR (376 MHz, CH_2Cl_2, 298 K) from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **6a** in DCM at –30 °C.



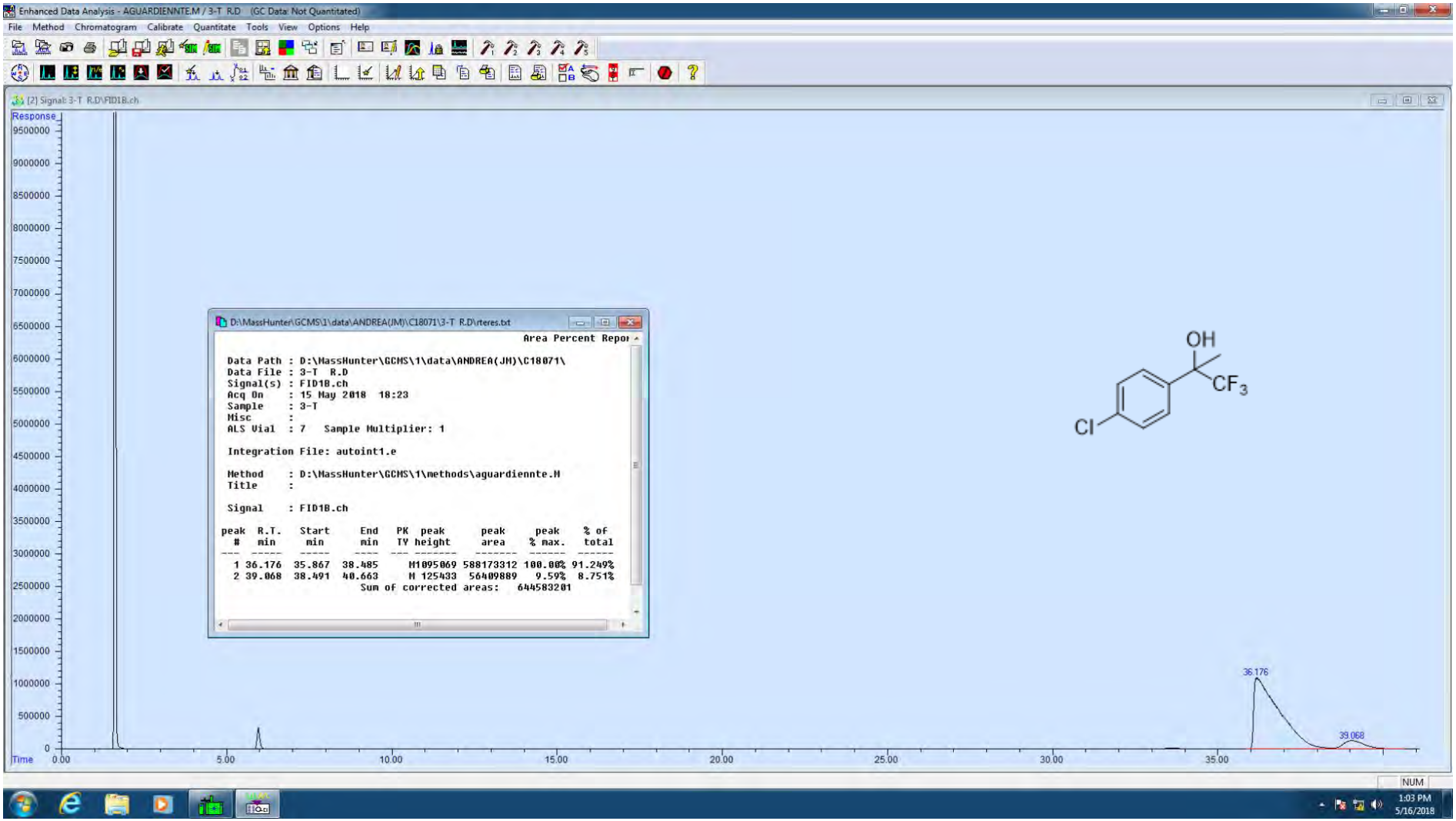
S 72. ^{19}F NMR (376 MHz, CH_2Cl_2, 298 K) from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **6a** in Toluene at –30 °C.



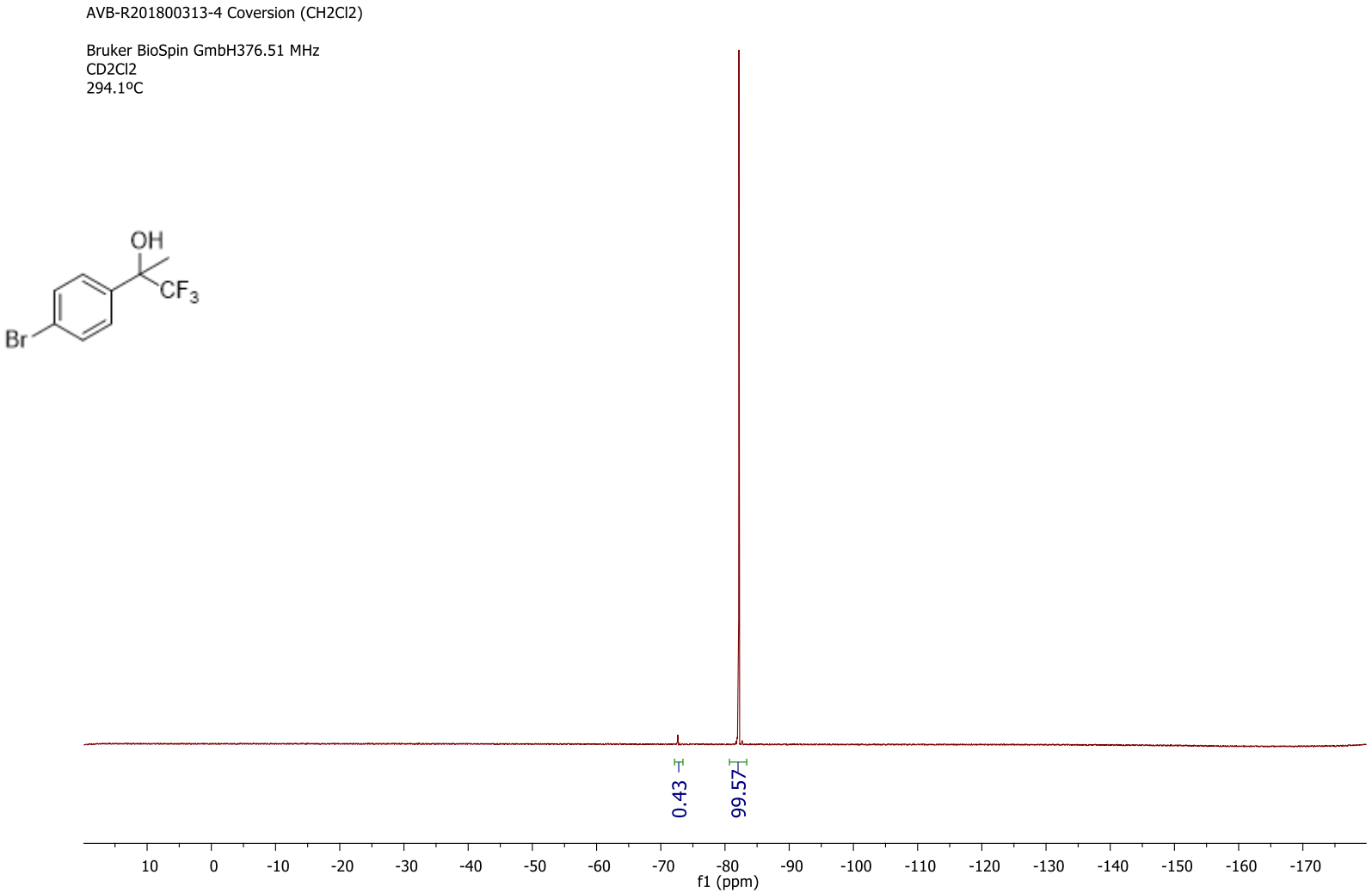
S 73. Enantiomeric resolution by chiral GC from racemic compound **6b**.



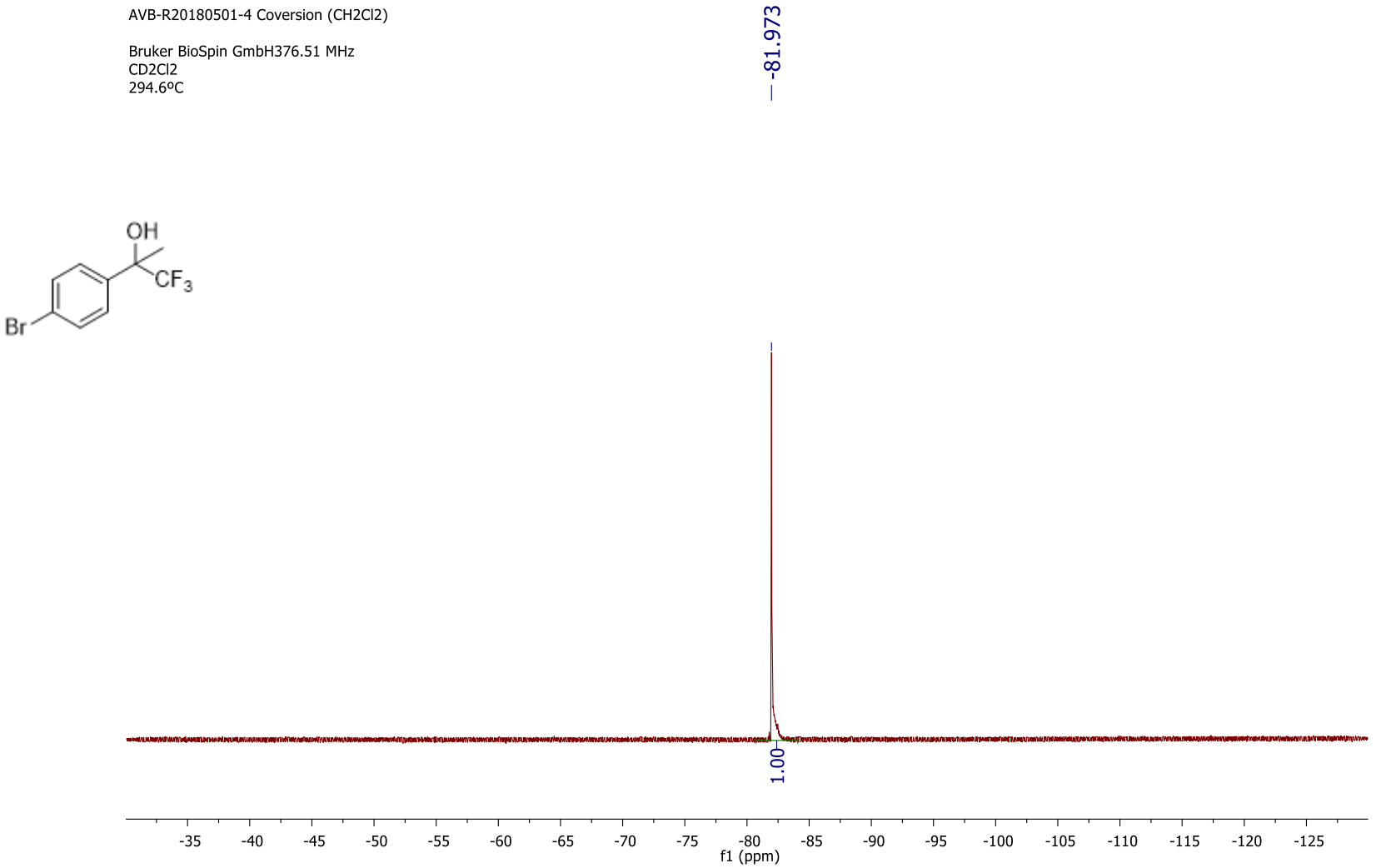
S 74. Enantiomeric resolution by GC from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **6a** in DCM at –30 °C.



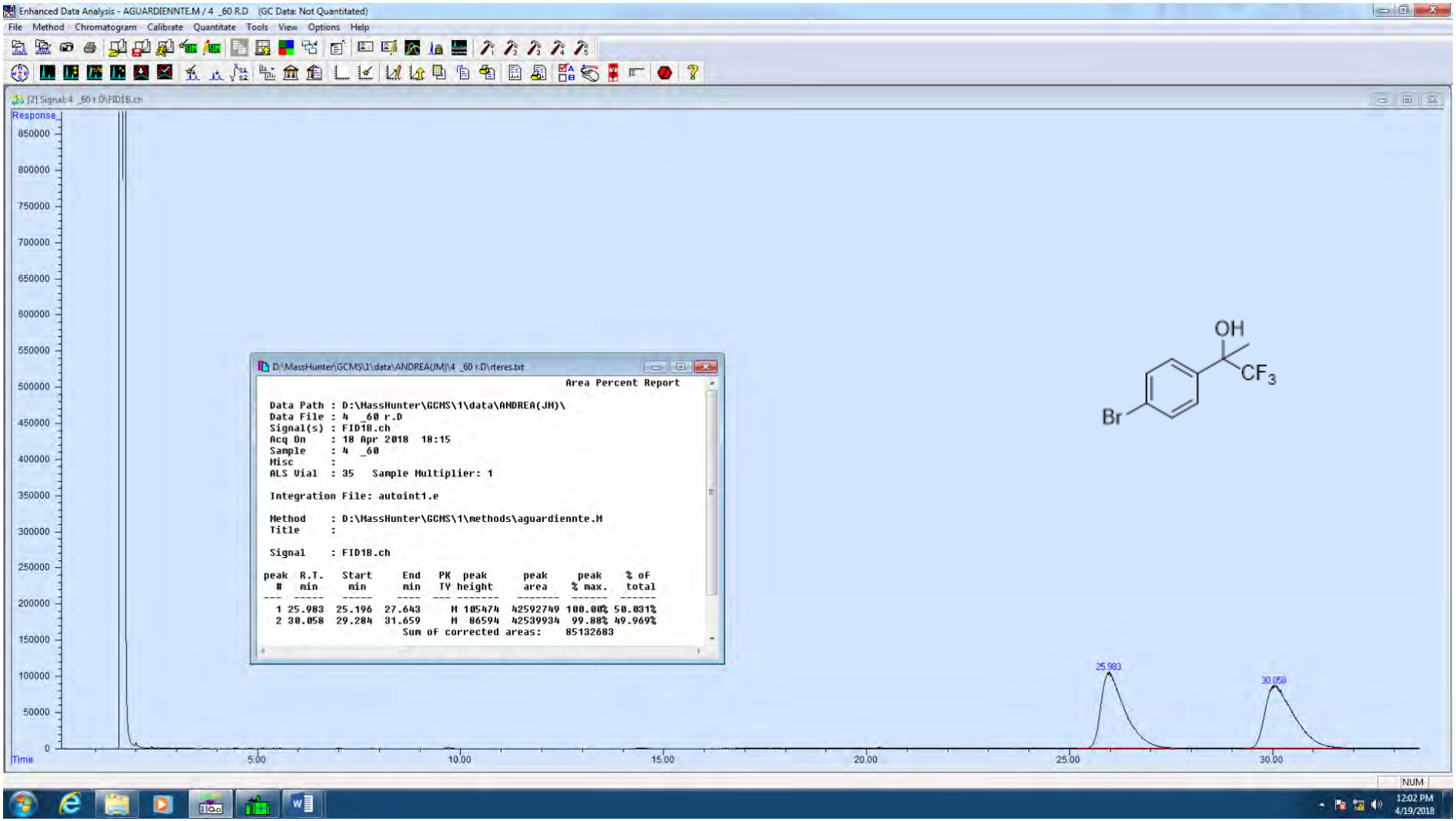
S 75. Enantiomeric resolution by GC from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **6a** in toluene at –30 °C.



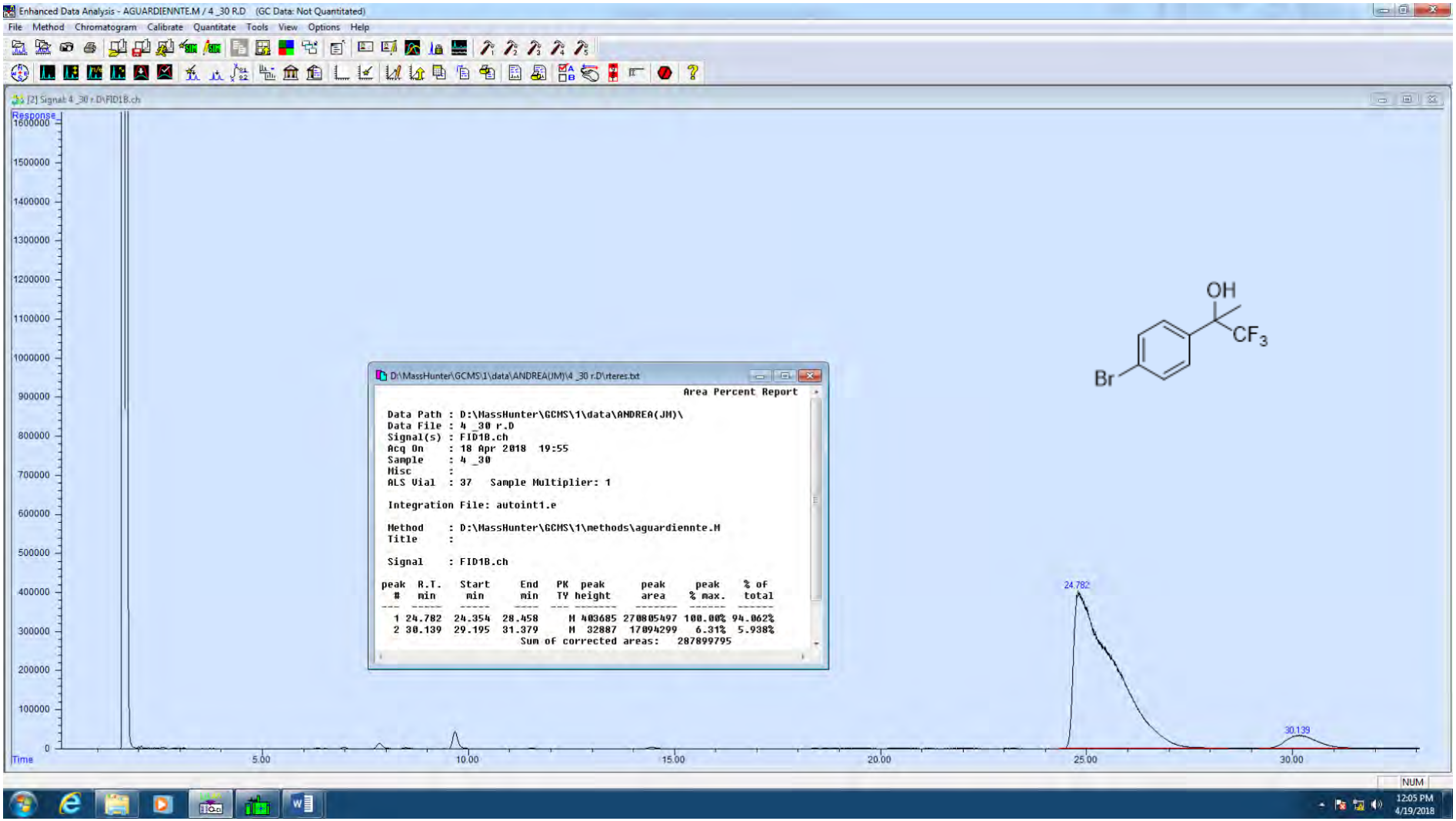
S 76. ^{19}F NMR (376 MHz, CH_2Cl_2, 298 K) from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **7a** in DCM at –30 °C.



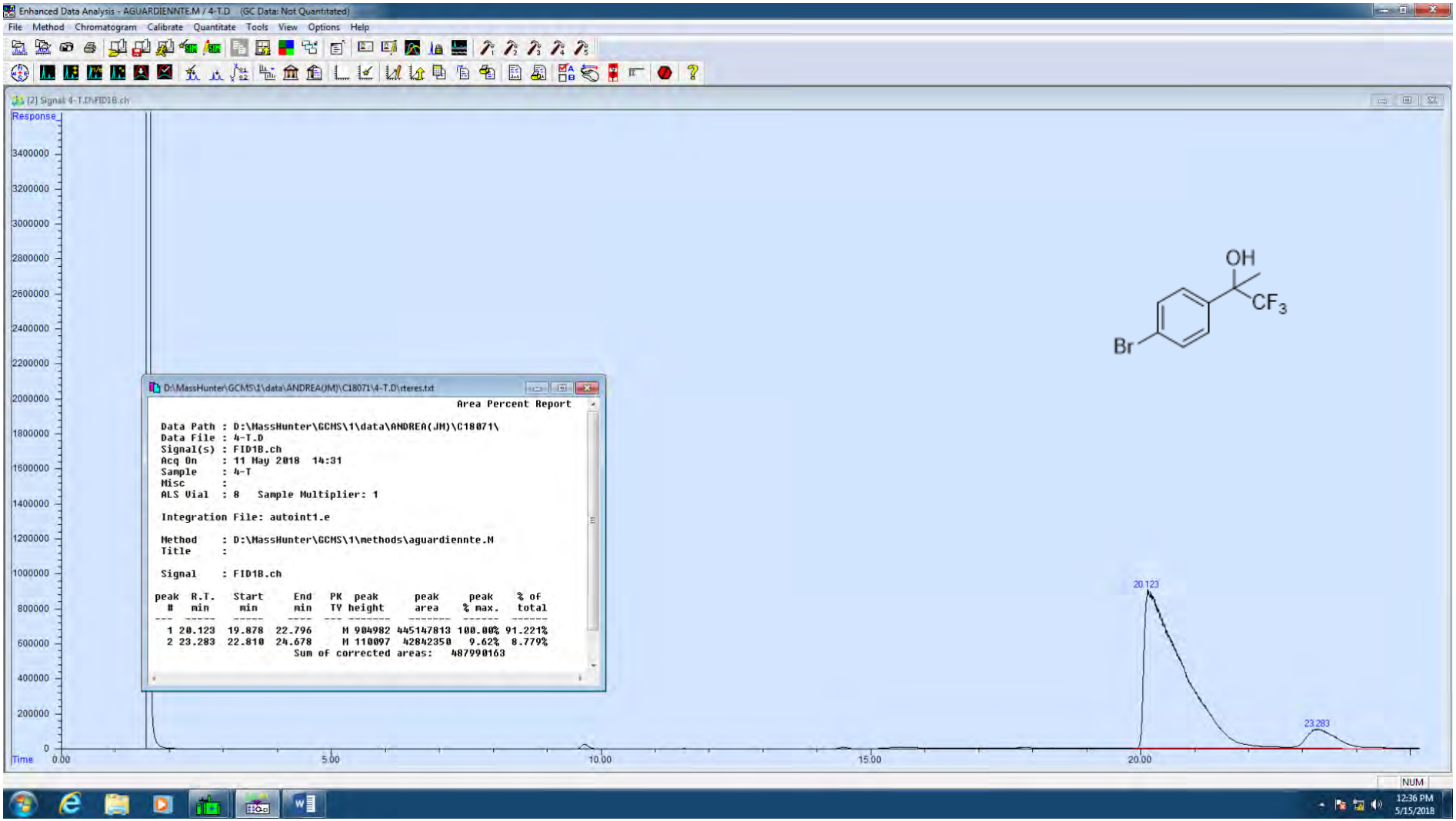
S 77. ^{19}F NMR (376 MHz, CH_2Cl_2, 298 K) from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **7a** in toluene at –30 °C.



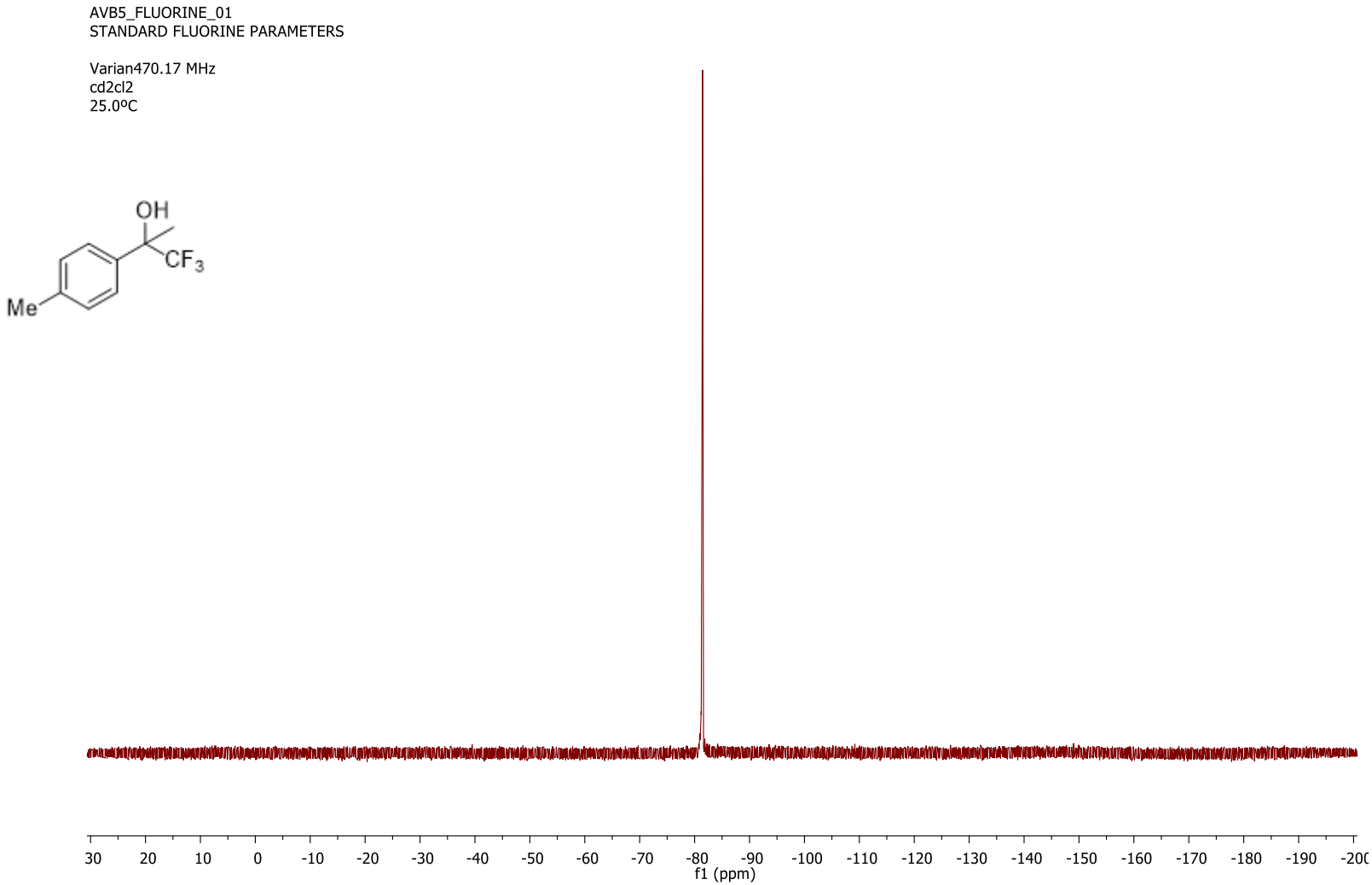
S 78. Enantiomeric resolution by chiral GC from racemic compound **7b.**



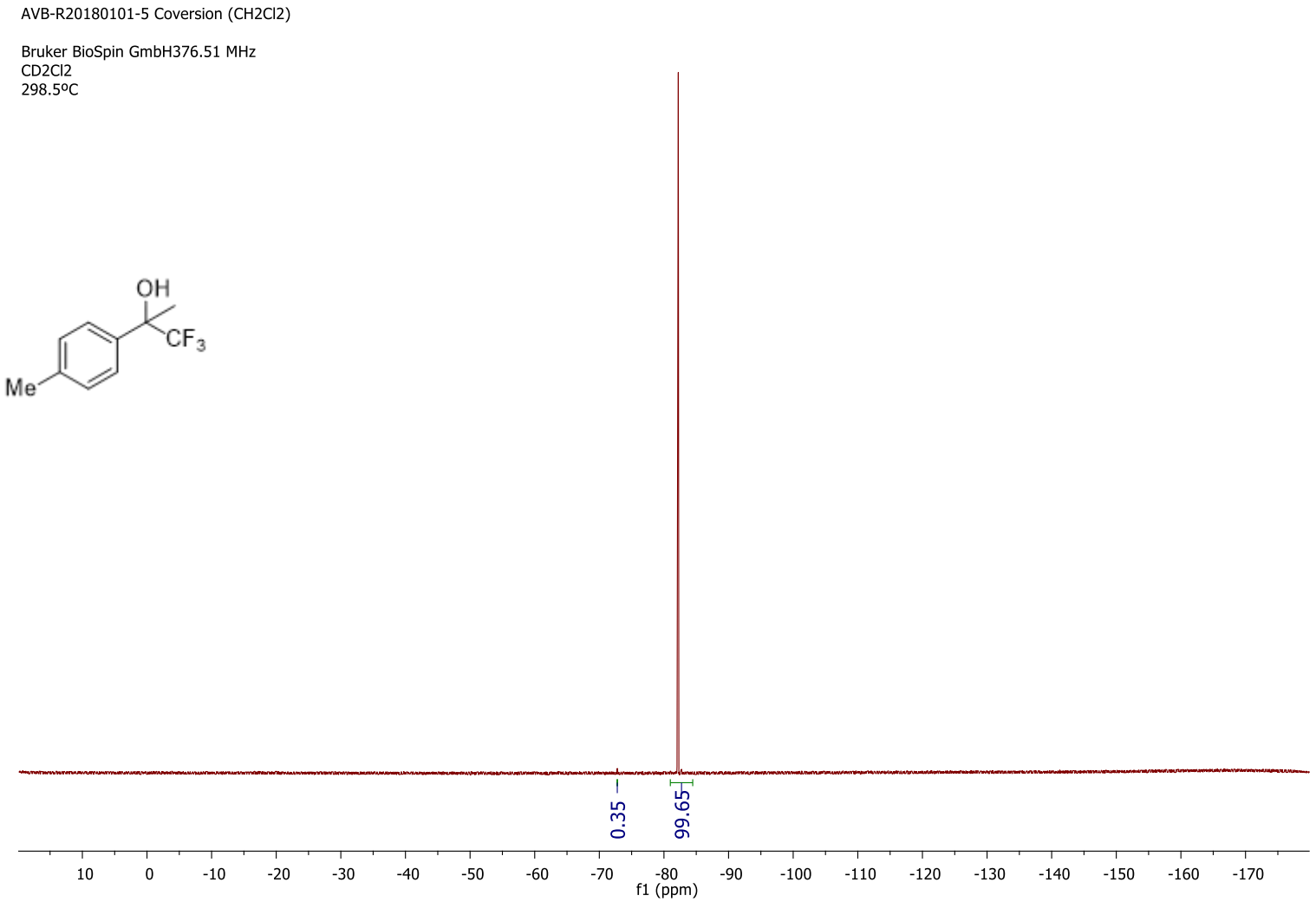
S 79. Enantiomeric resolution by GC from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **7a** in DCM at –30 °C.



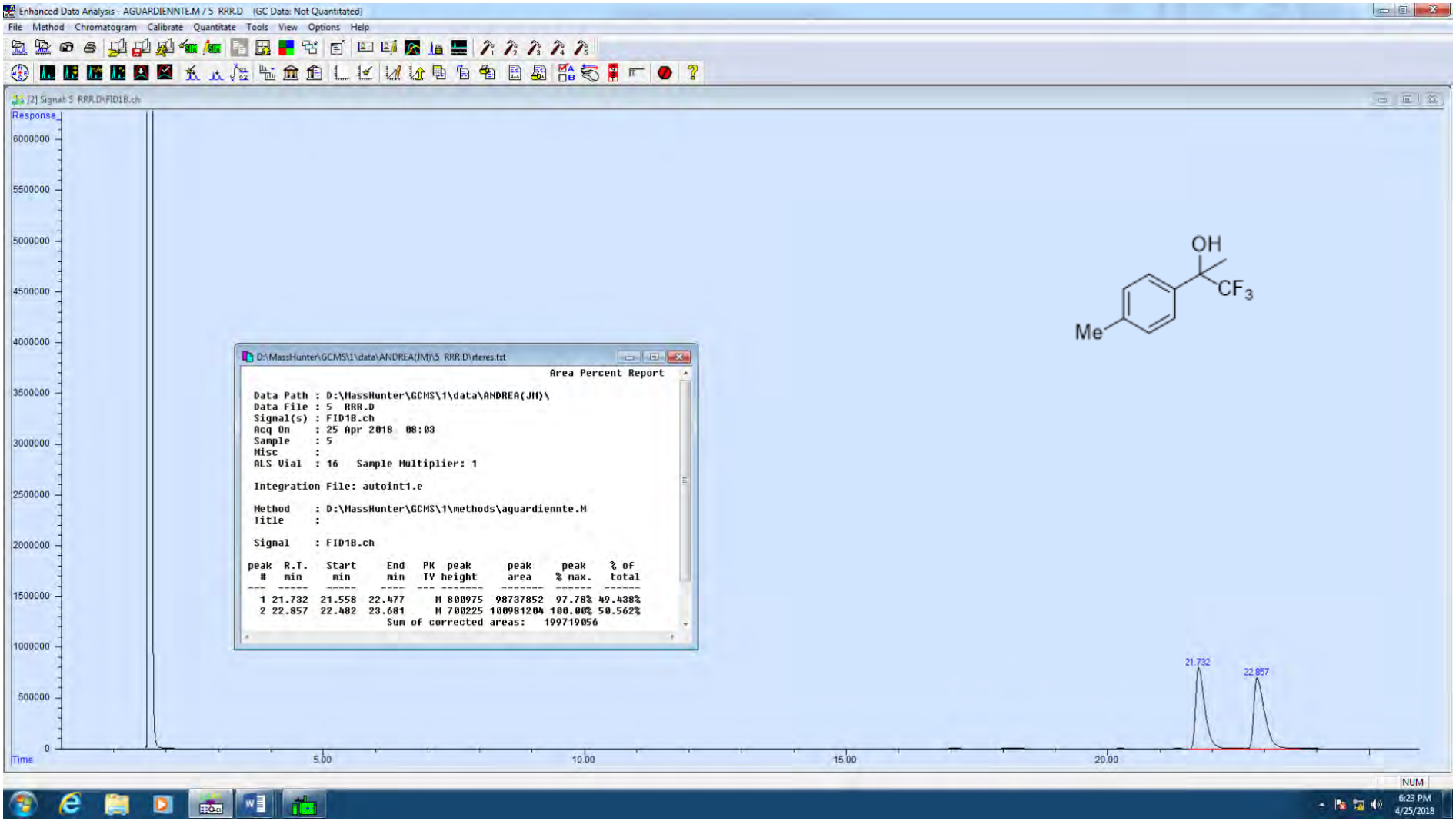
S 80. Enantiomeric resolution by GC from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **7a** in toluene at –30 °C.



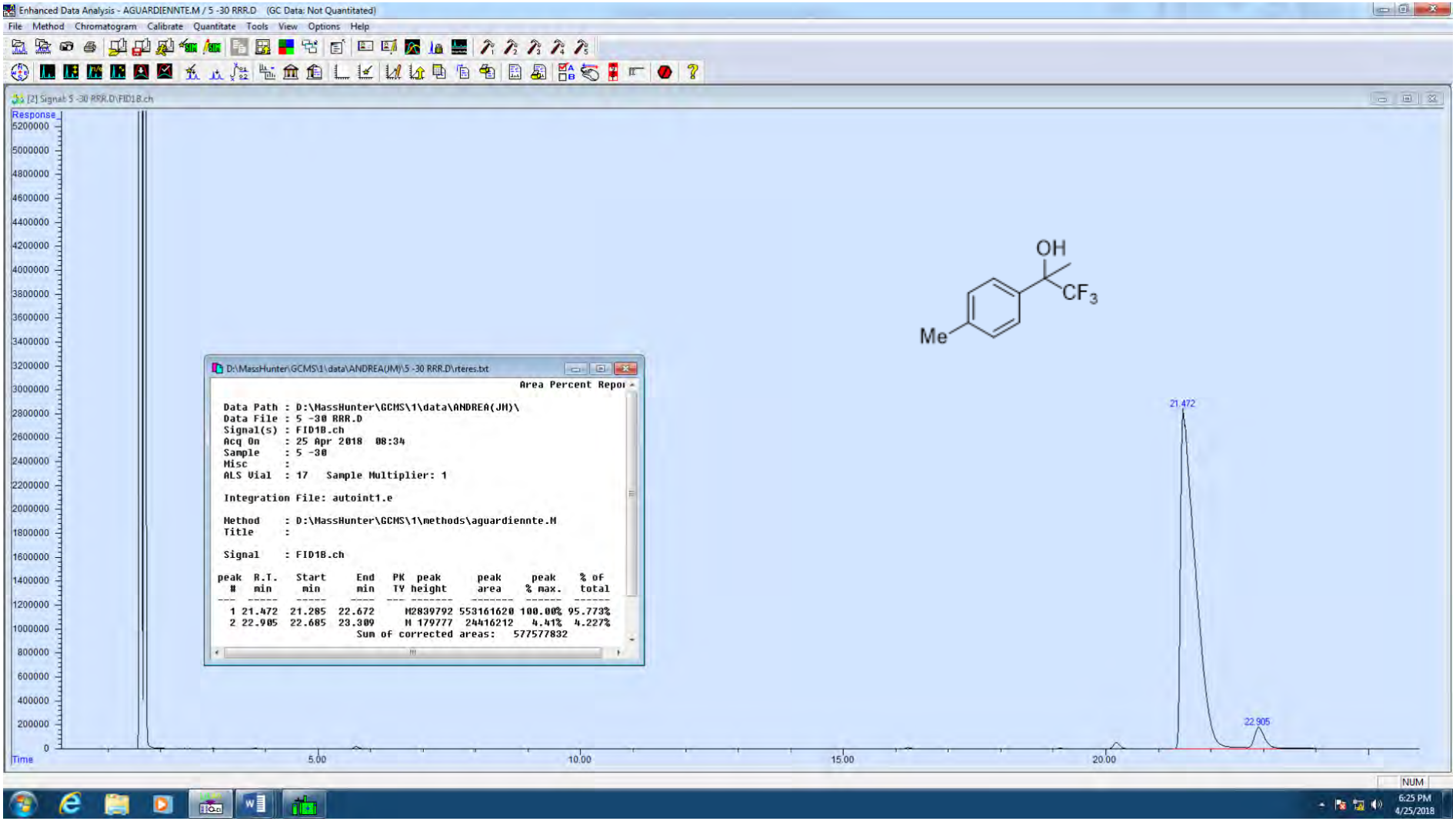
S 81. ^{19}F NMR (470 MHz, CH_2Cl_2, 298 K) from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **8a** in DCM at –30 °C.



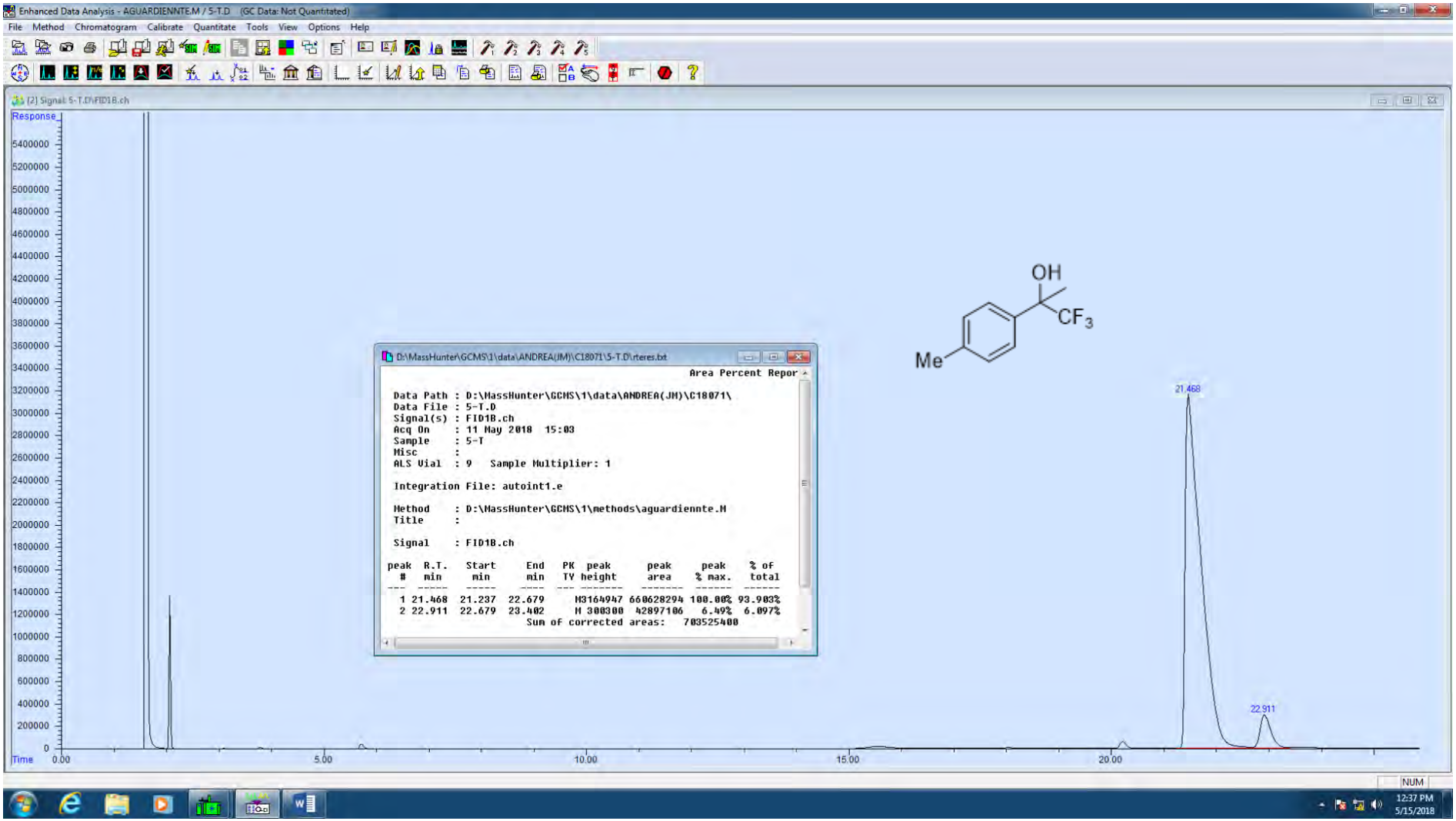
S 82. ^{19}F NMR (376 MHz, CH_2Cl_2, 298 K) from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **8a** in toluene at –30 °C.



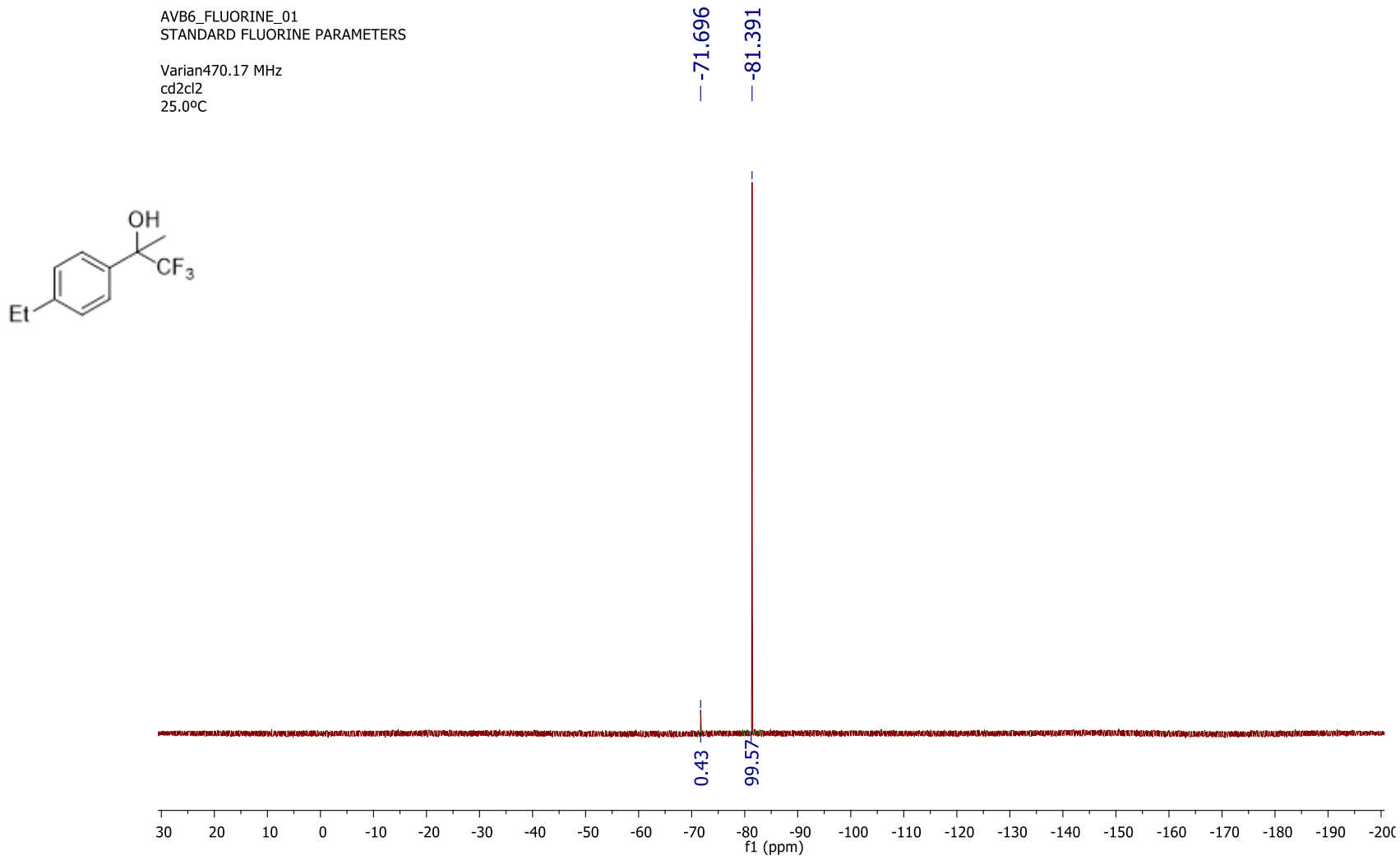
S 83. Enantiomeric resolution by chiral GC from racemic compound **8a.**



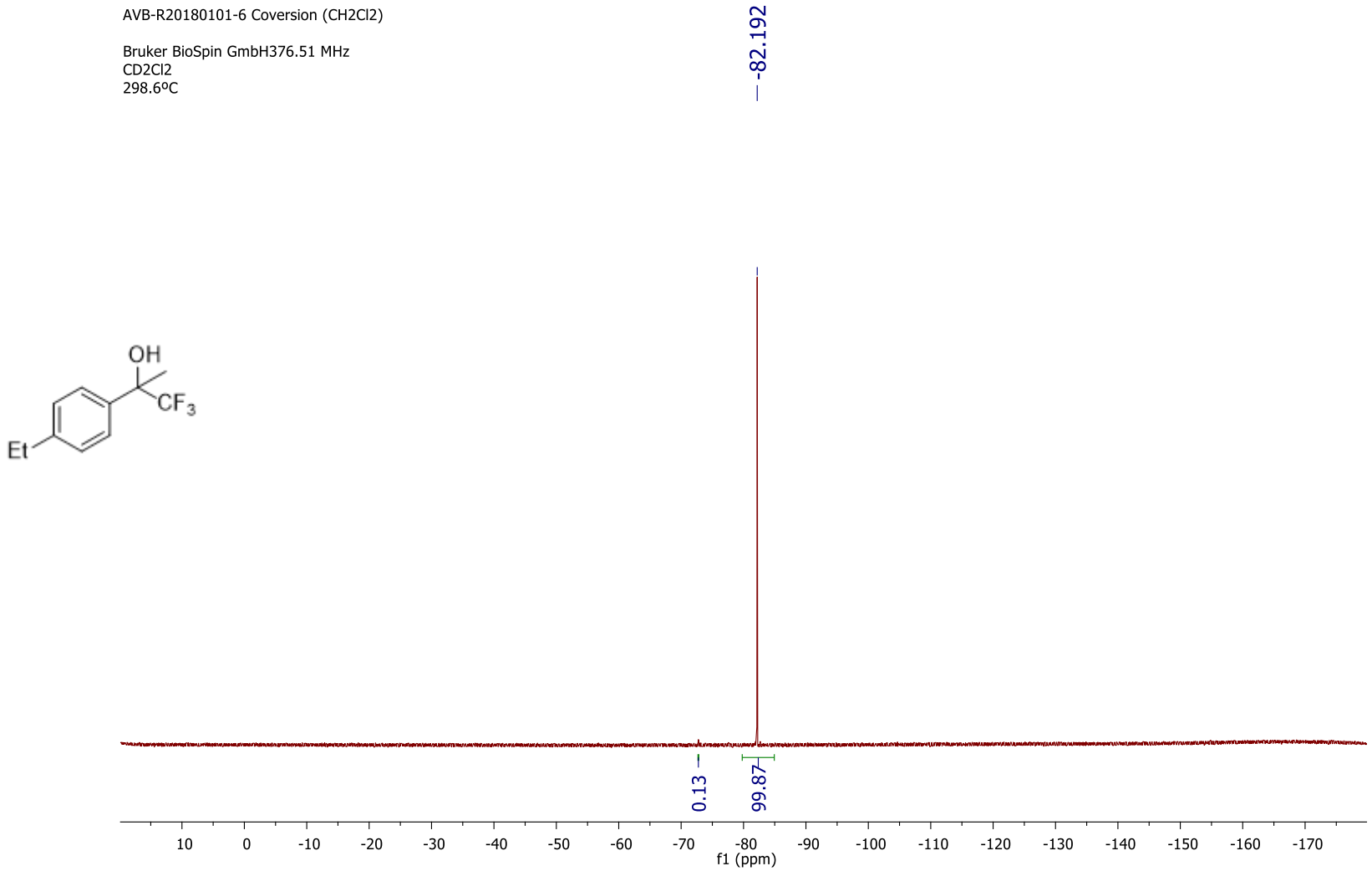
S 84. Enantiomeric resolution by GC from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **8a** in DCM at –30 °C.



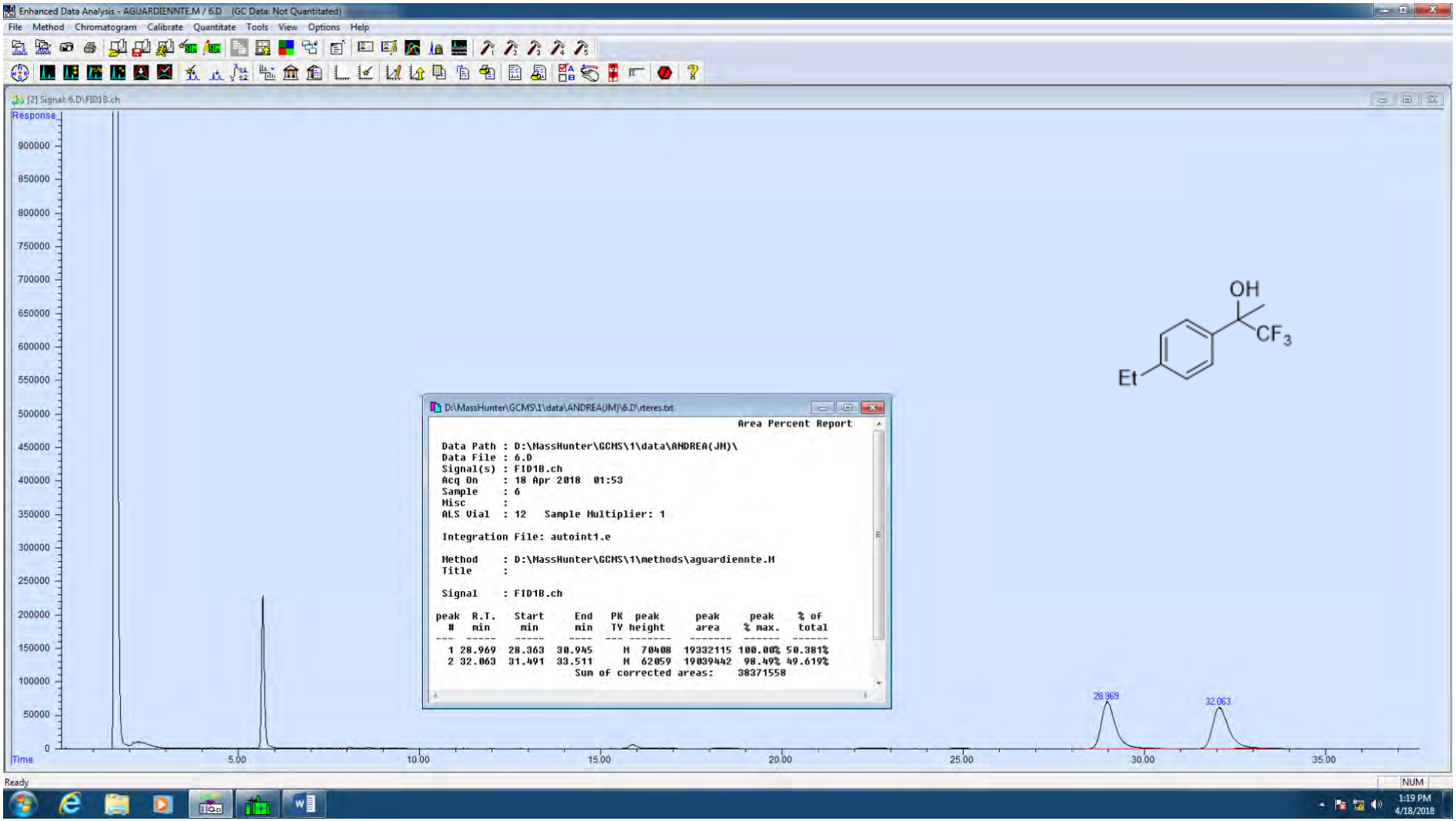
S 85. Enantiomeric resolution by GC from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **8a** in toluene at –30 °C.



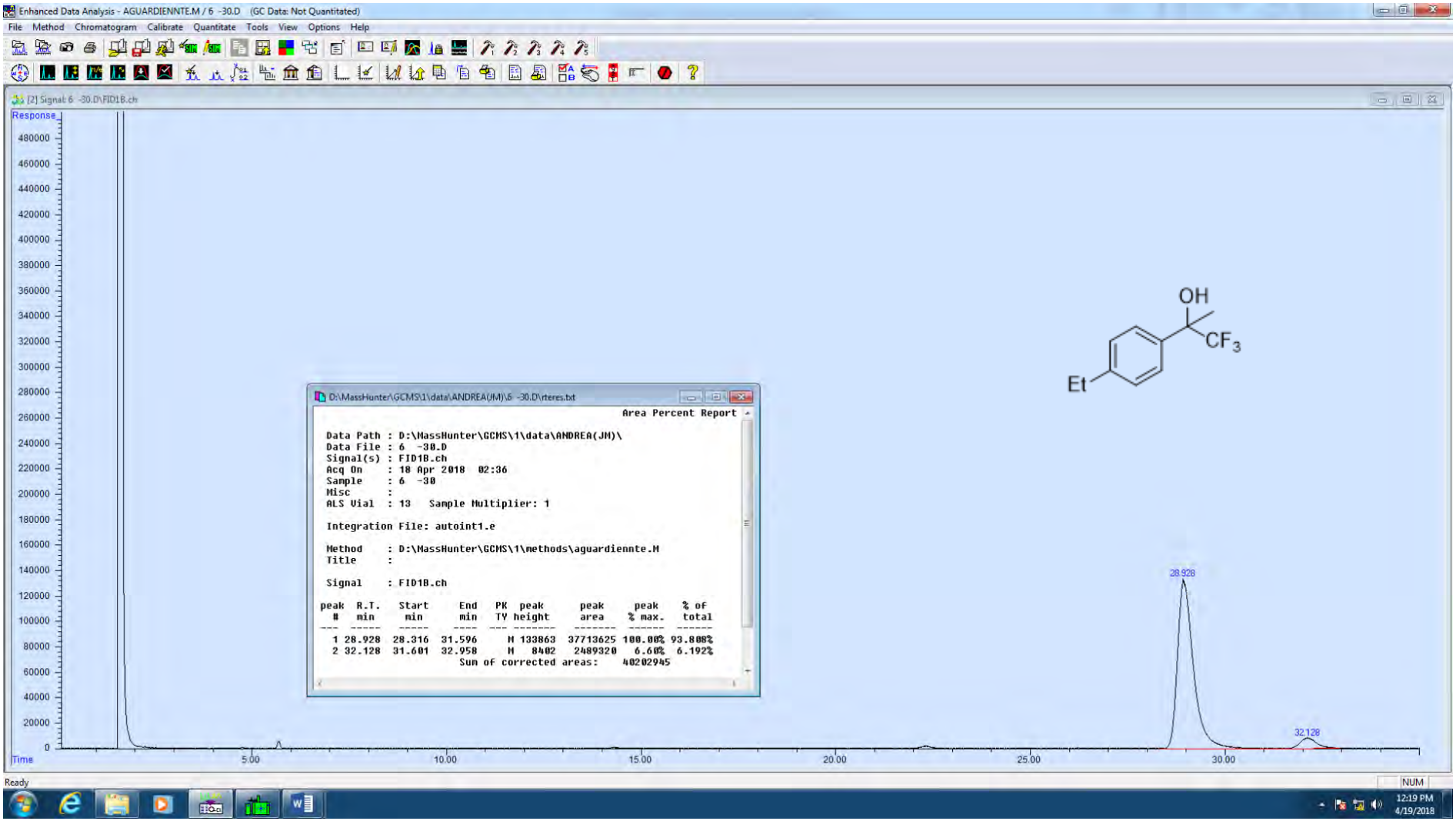
S 86. ^{19}F NMR (470 MHz, CH_2Cl_2, 298 K) from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **9a** in DCM at –30 °C.



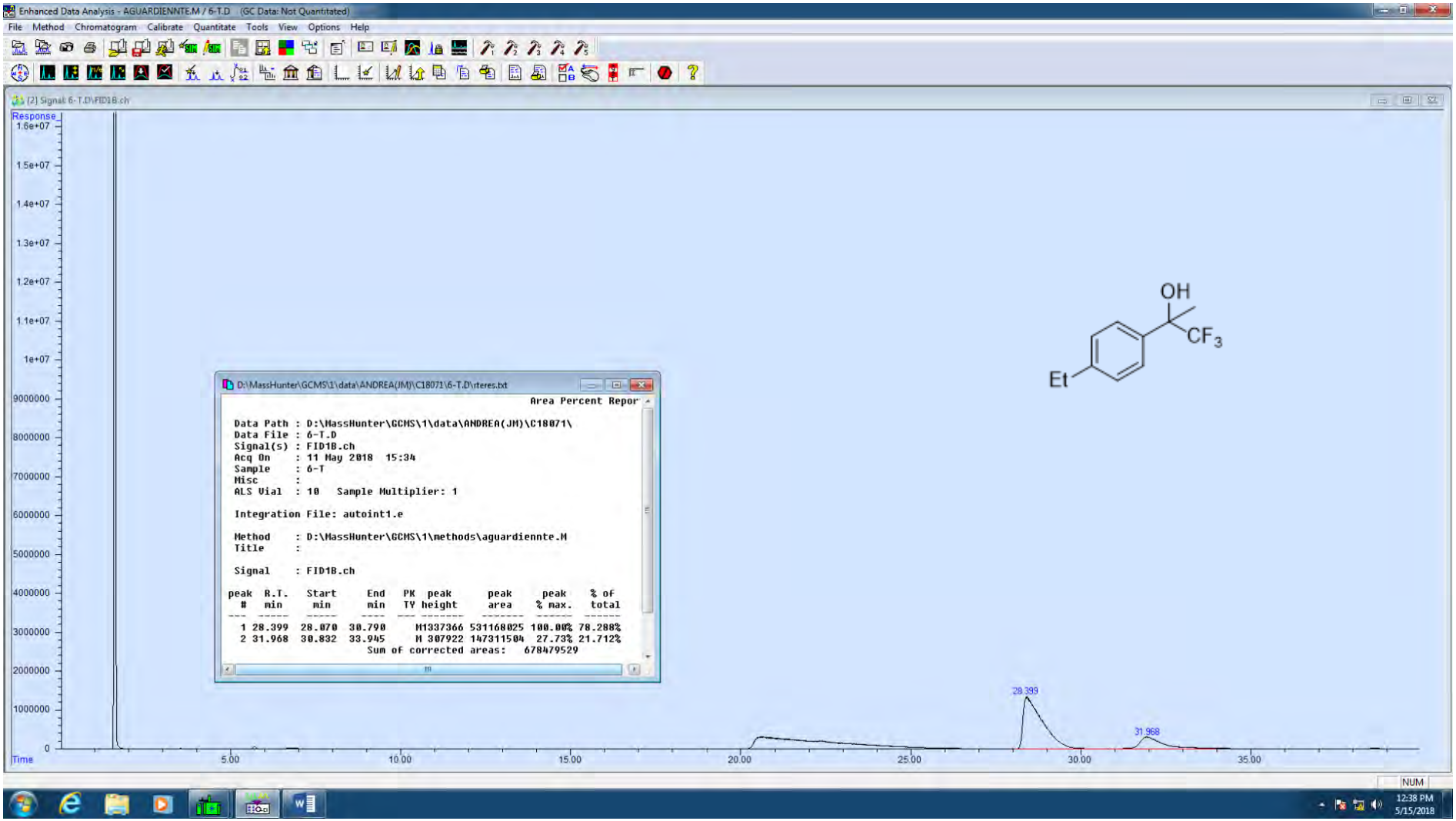
S 87. ^{19}F NMR (376 MHz, CH_2Cl_2, 298 K) from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **9a** in toluene at –30 °C.



S 88. Enantiomeric resolution by chiral GC from racemic compound **9b**.



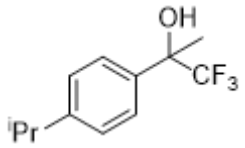
S 89. Enantiomeric resolution by GC from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **9a** in DCM at –30 °C.

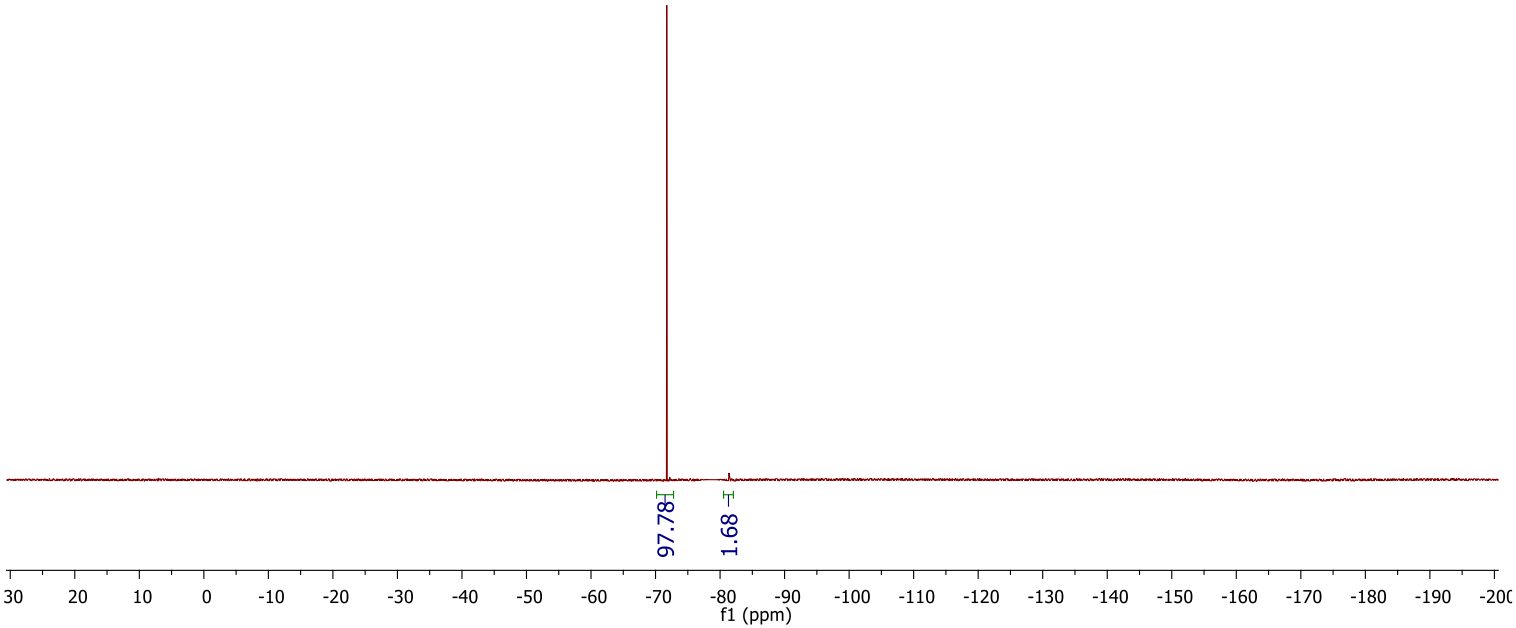


S 90. Enantiomeric resolution by GC from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **9a** in toluene at –30 °C.

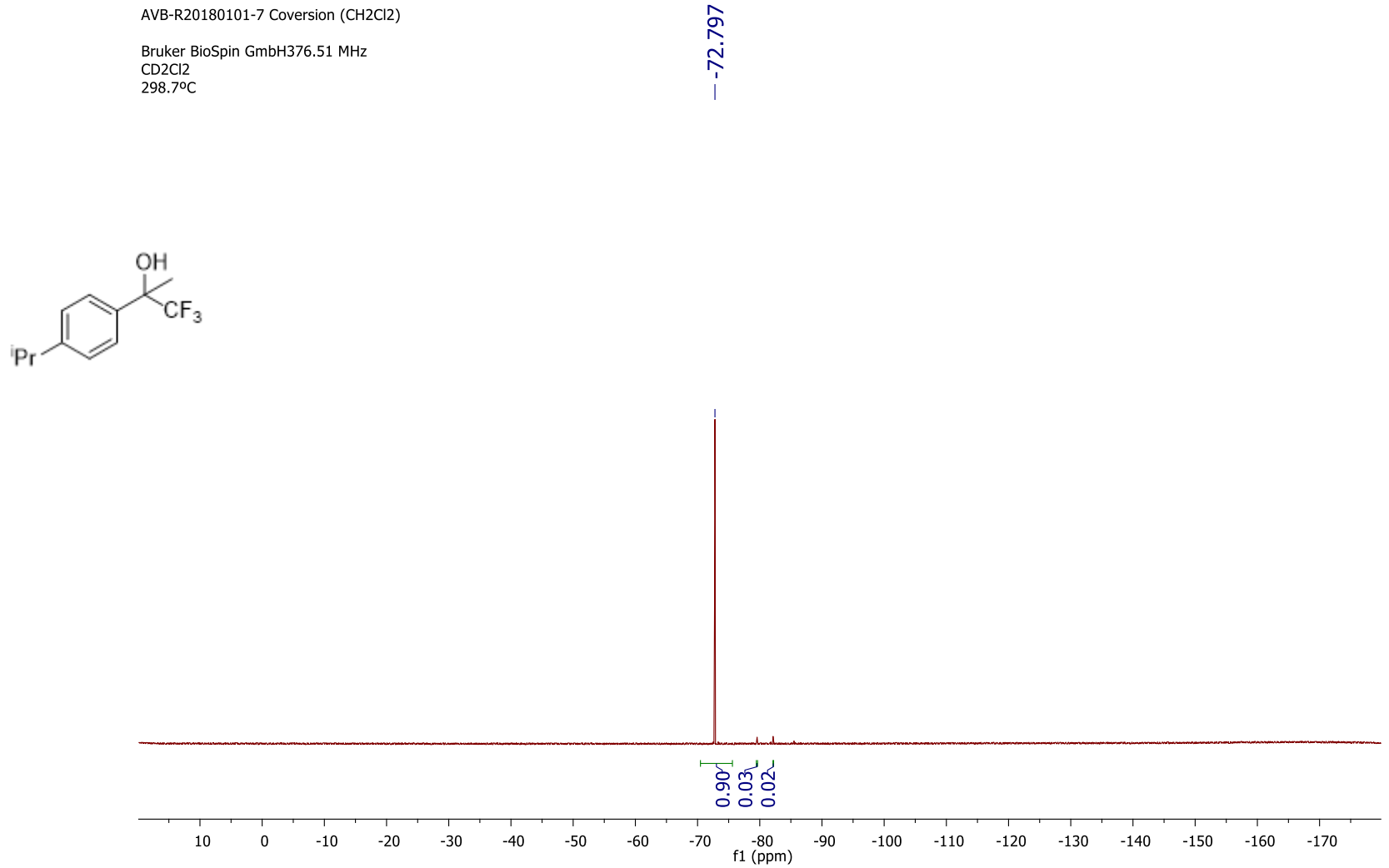
AVB7_FLUORINE_01
STANDARD FLUORINE PARAMETERS

Varian470.17 MHz
cd2cl2
25.0ºC

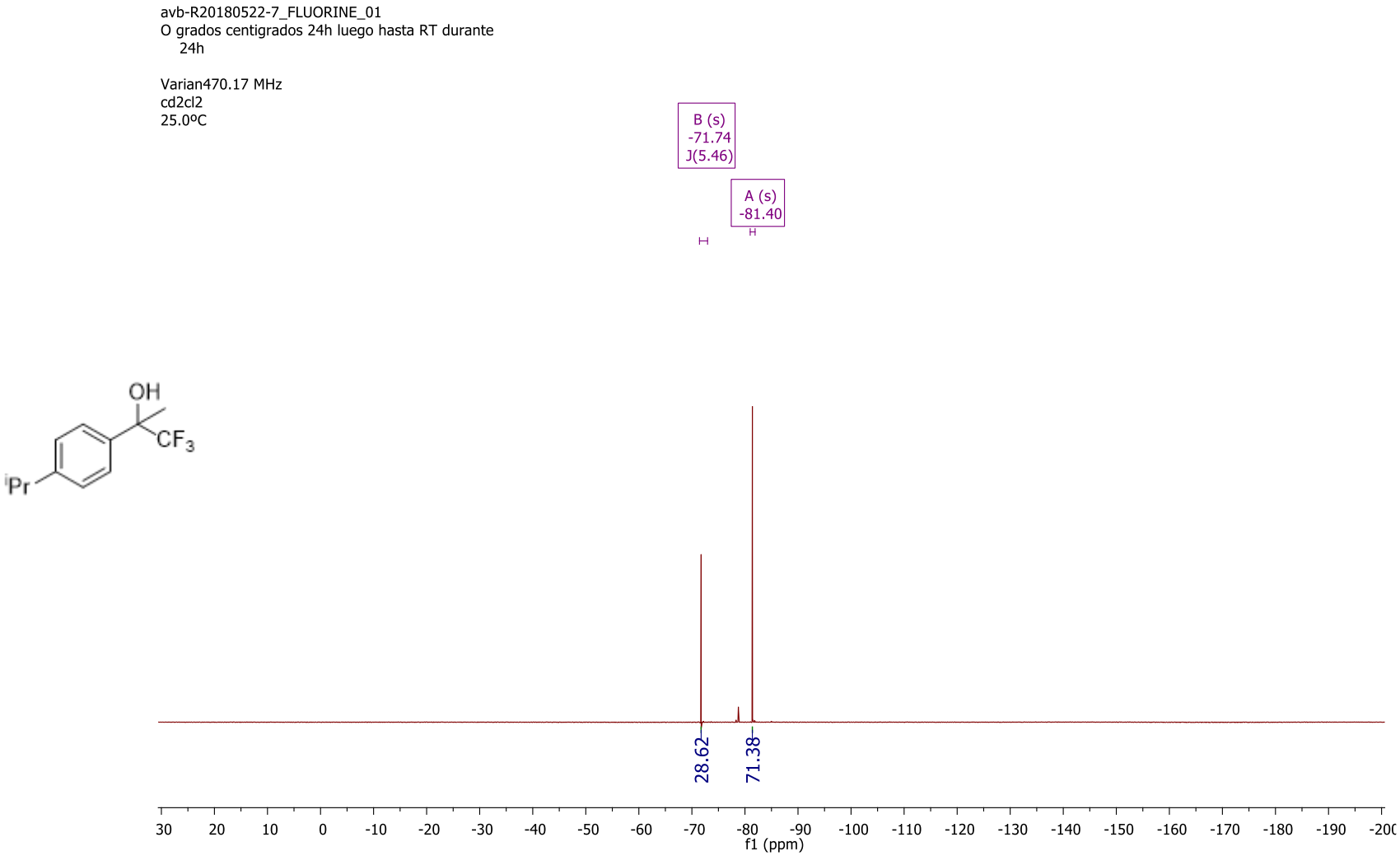




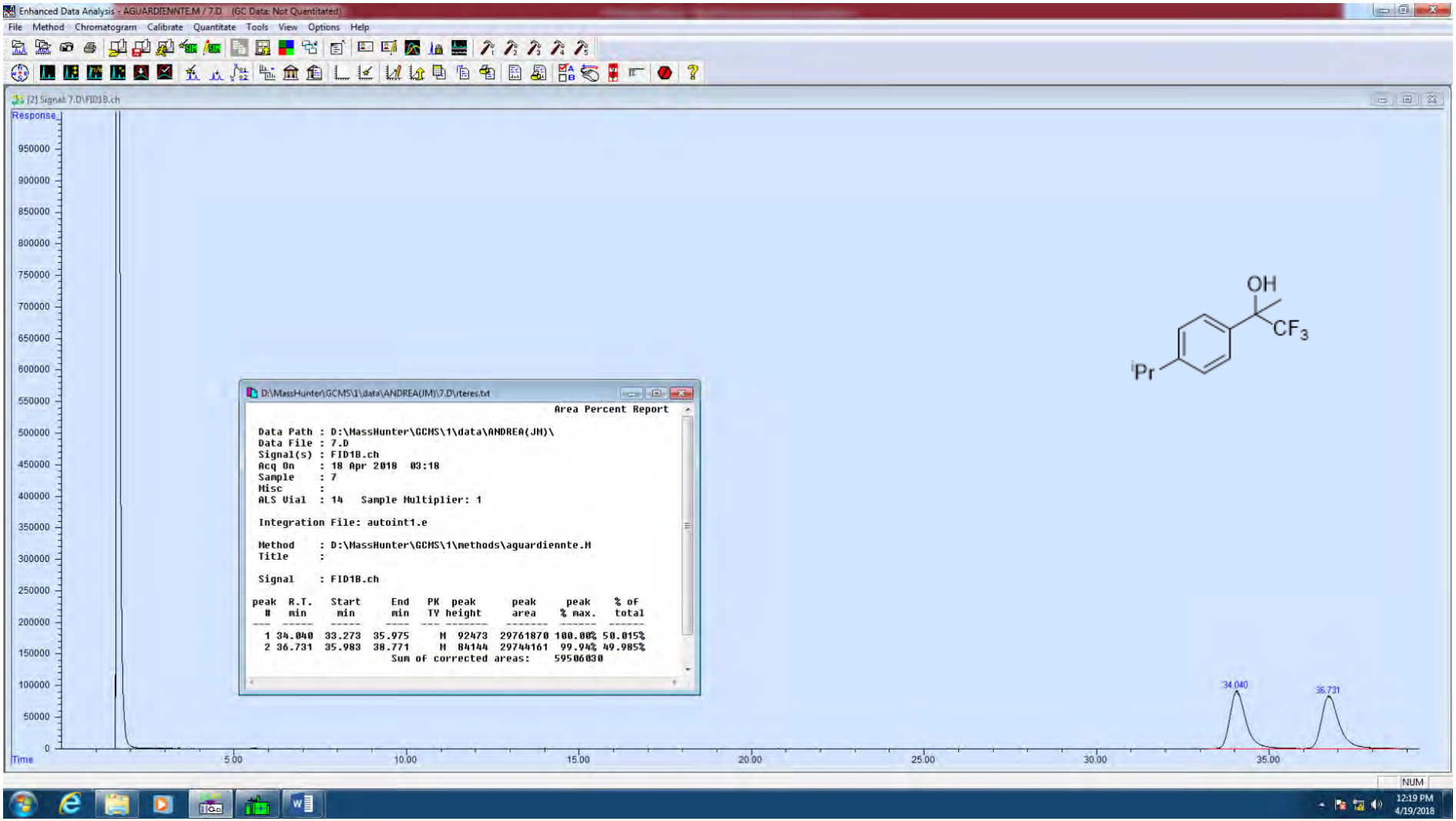
S 91. ^{19}F NMR (470 MHz, CH_2Cl_2, 298 K) from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **9a** in DCM at –30 °C.



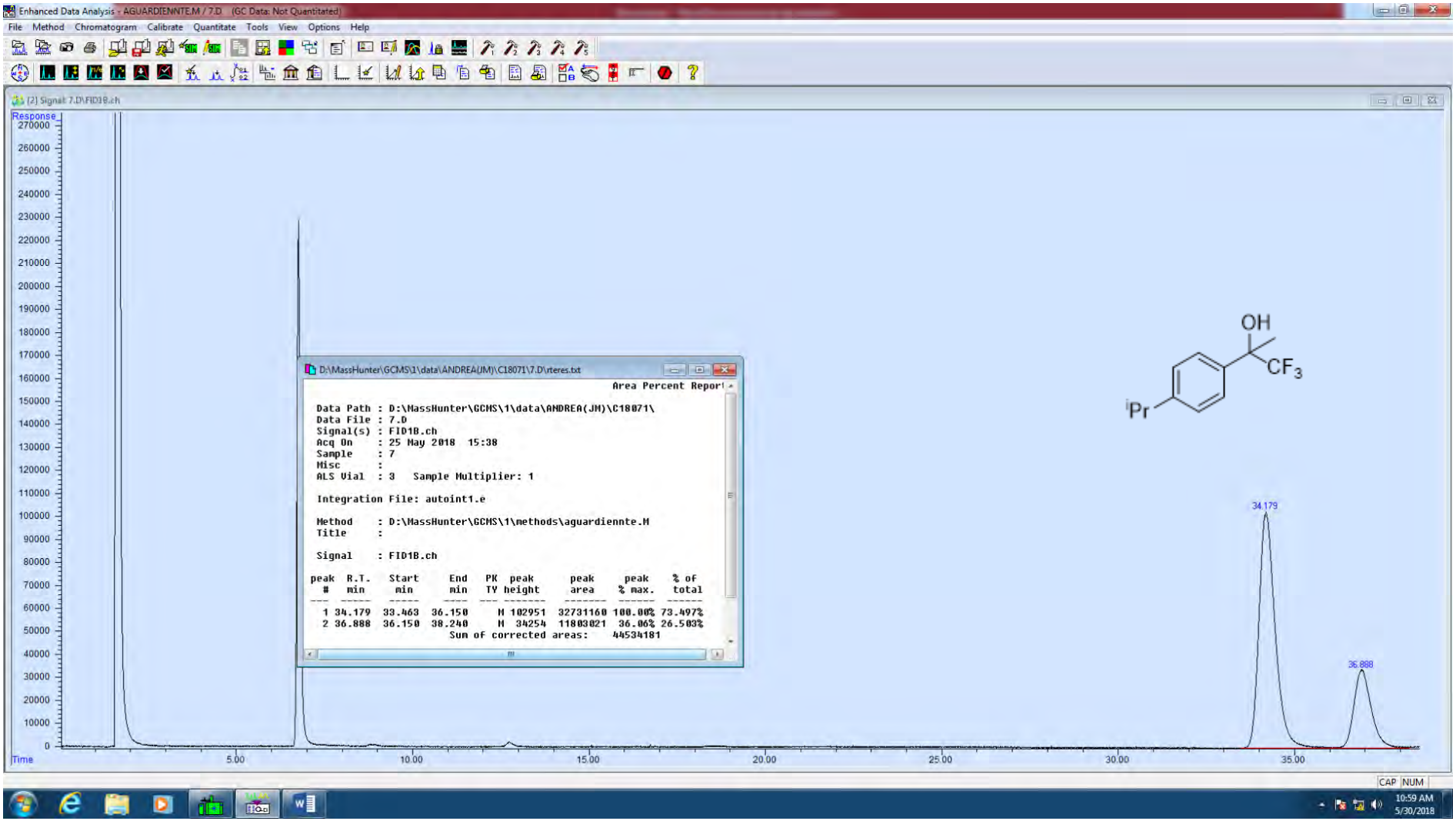
S 92. ^{19}F NMR (376 MHz, CH_2Cl_2, 298 K) from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **9a** in toluene at –30 °C.



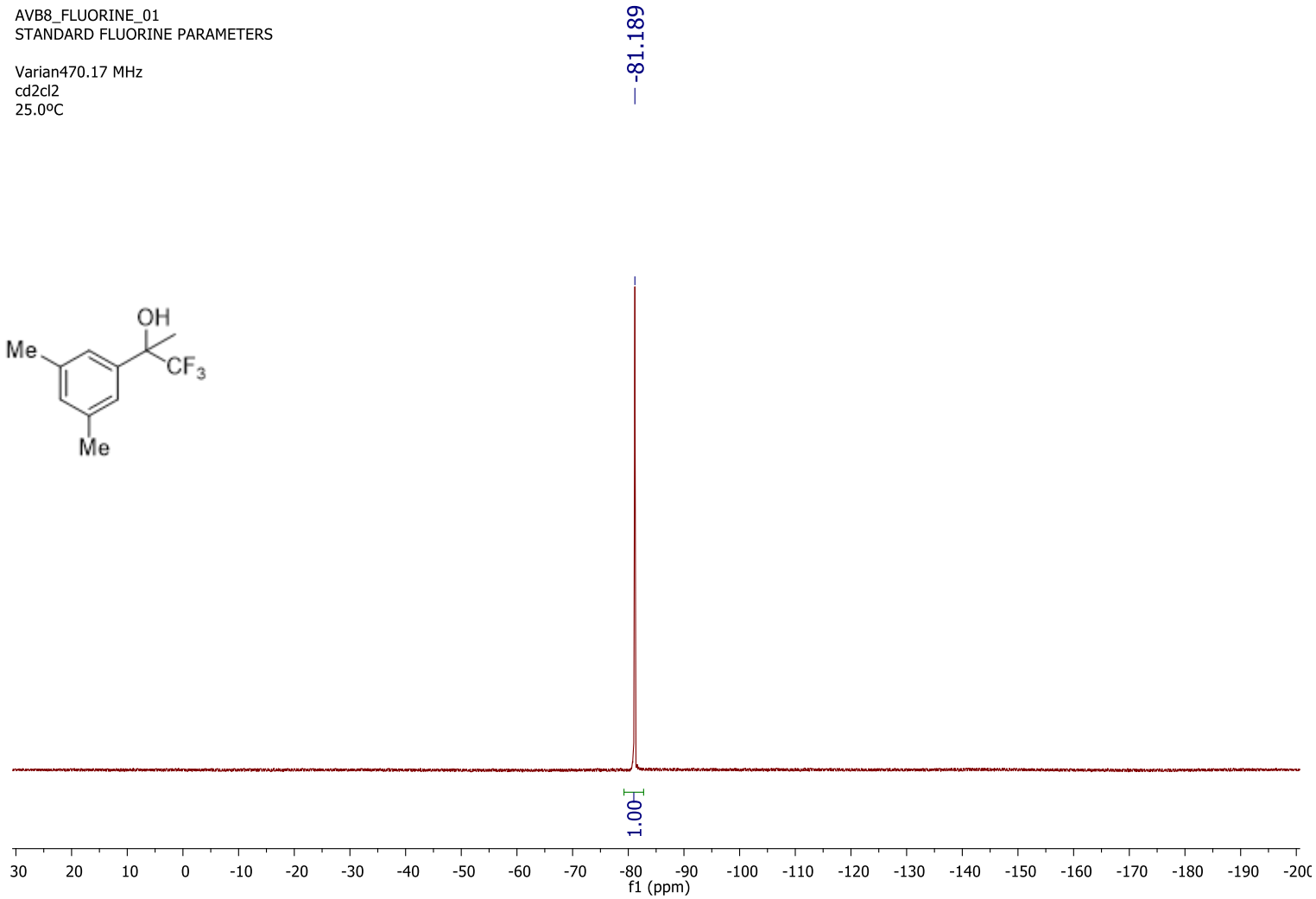
S 93. ^{19}F NMR (470 MHz, CH_2Cl_2, 298 K) from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **10a** in DCM at 25 °C.



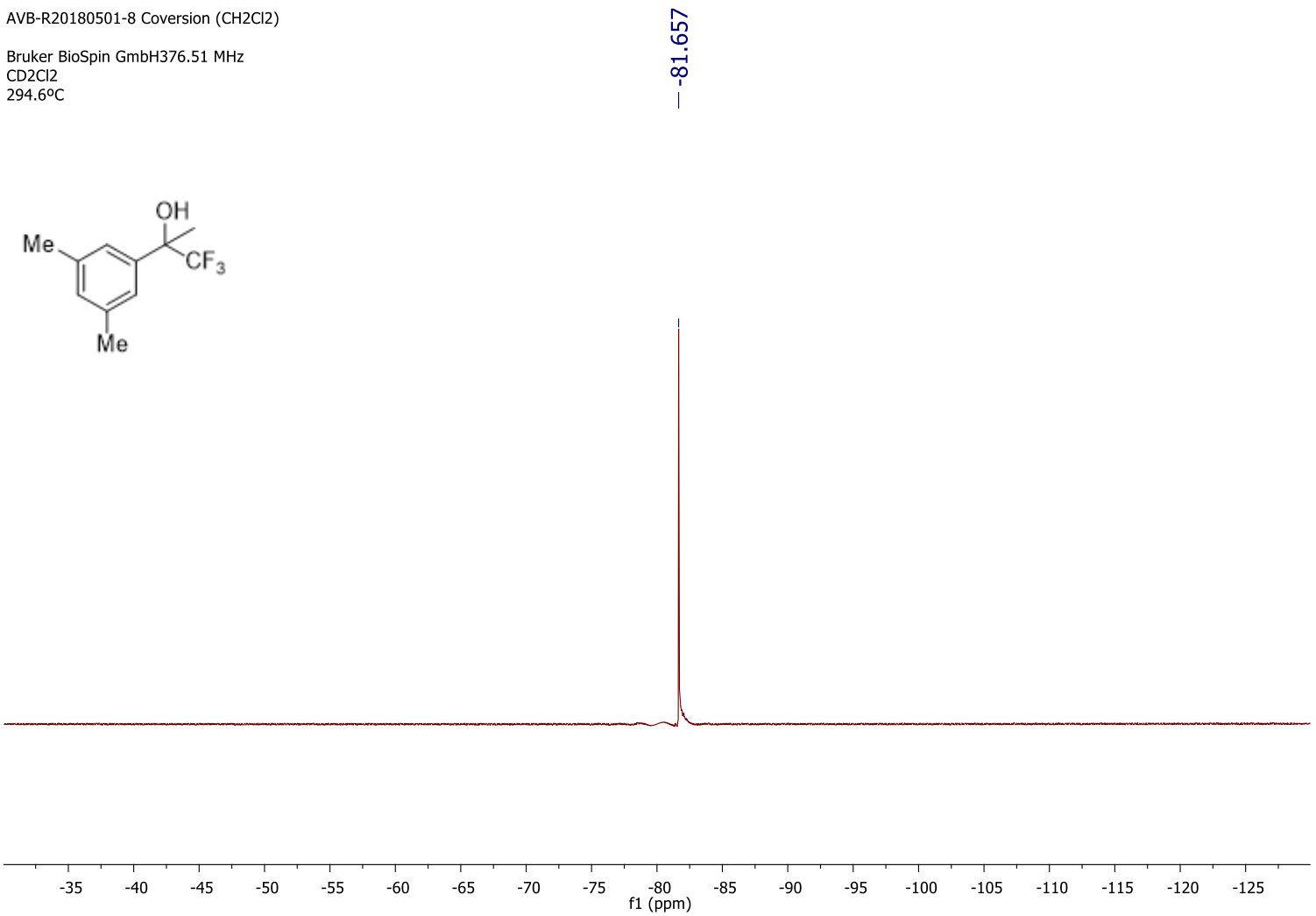
S 94. Enantiomeric resolution by chiral GC from racemic compound **10b**.



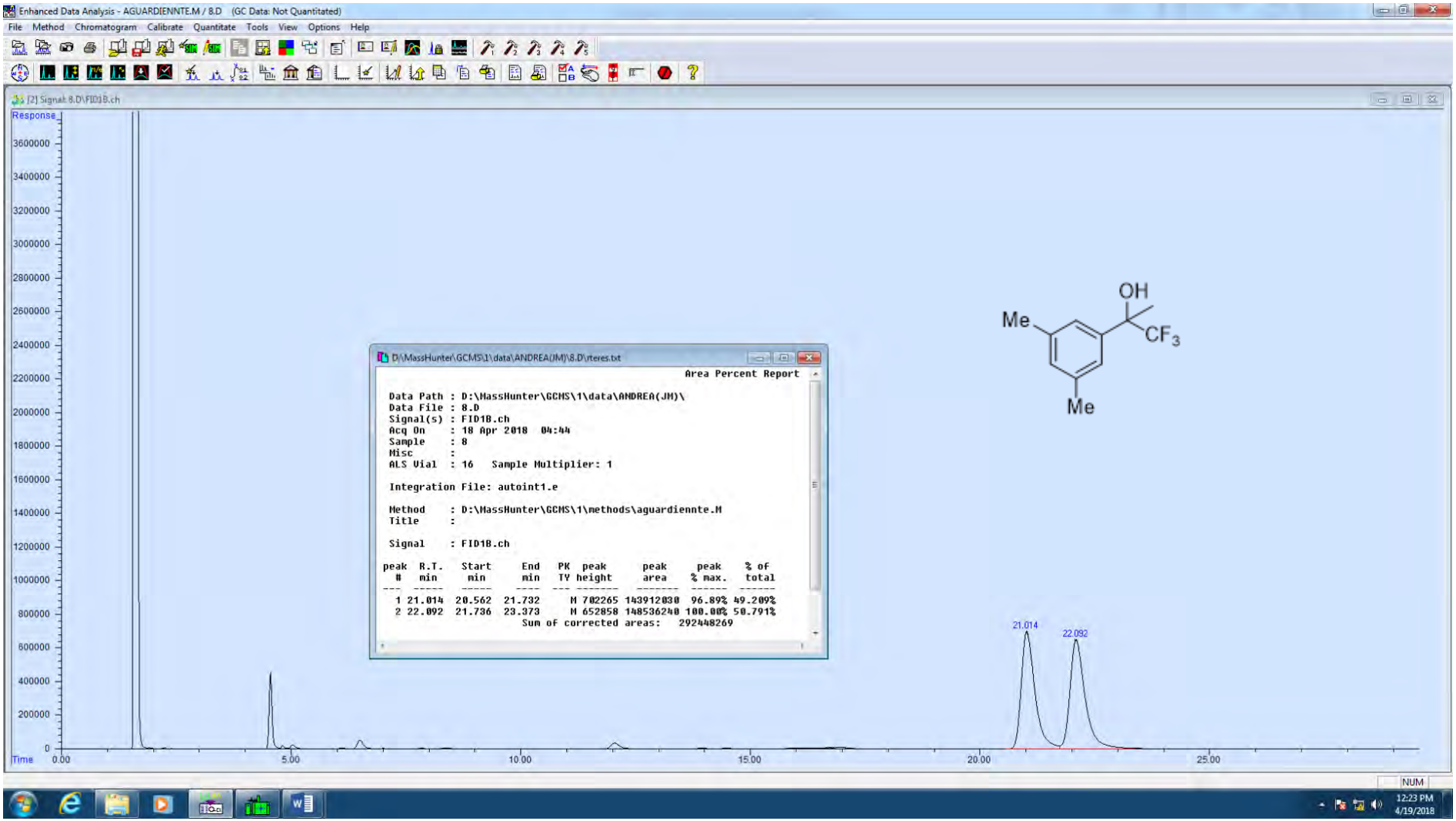
S 95. Enantiomeric resolution by GC from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **10a** in DCM at 25 °C



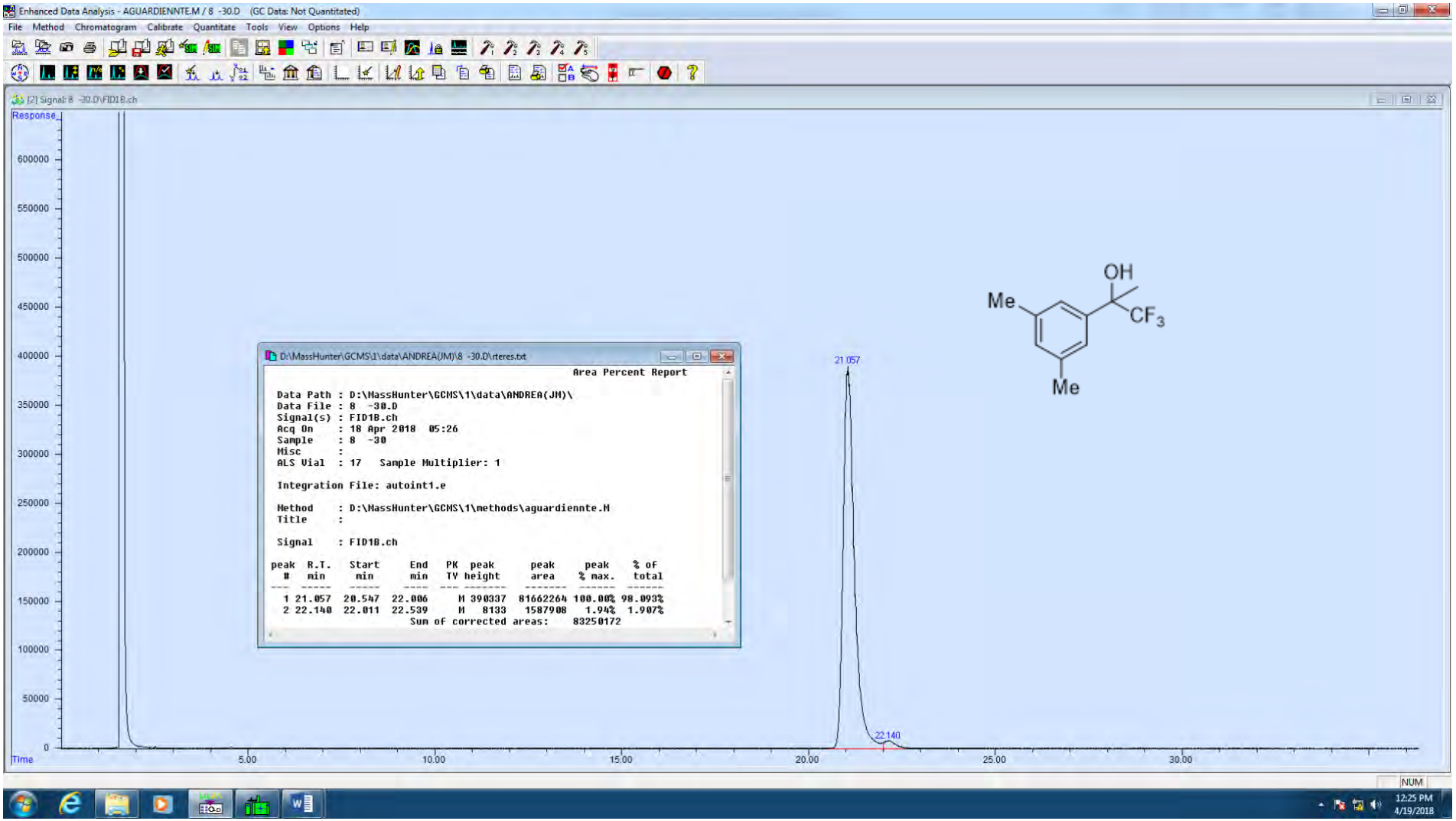
S 96. ^{19}F NMR (470 MHz, CH_2Cl_2, 298 K) from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **11a** in DCM at –30 °C.



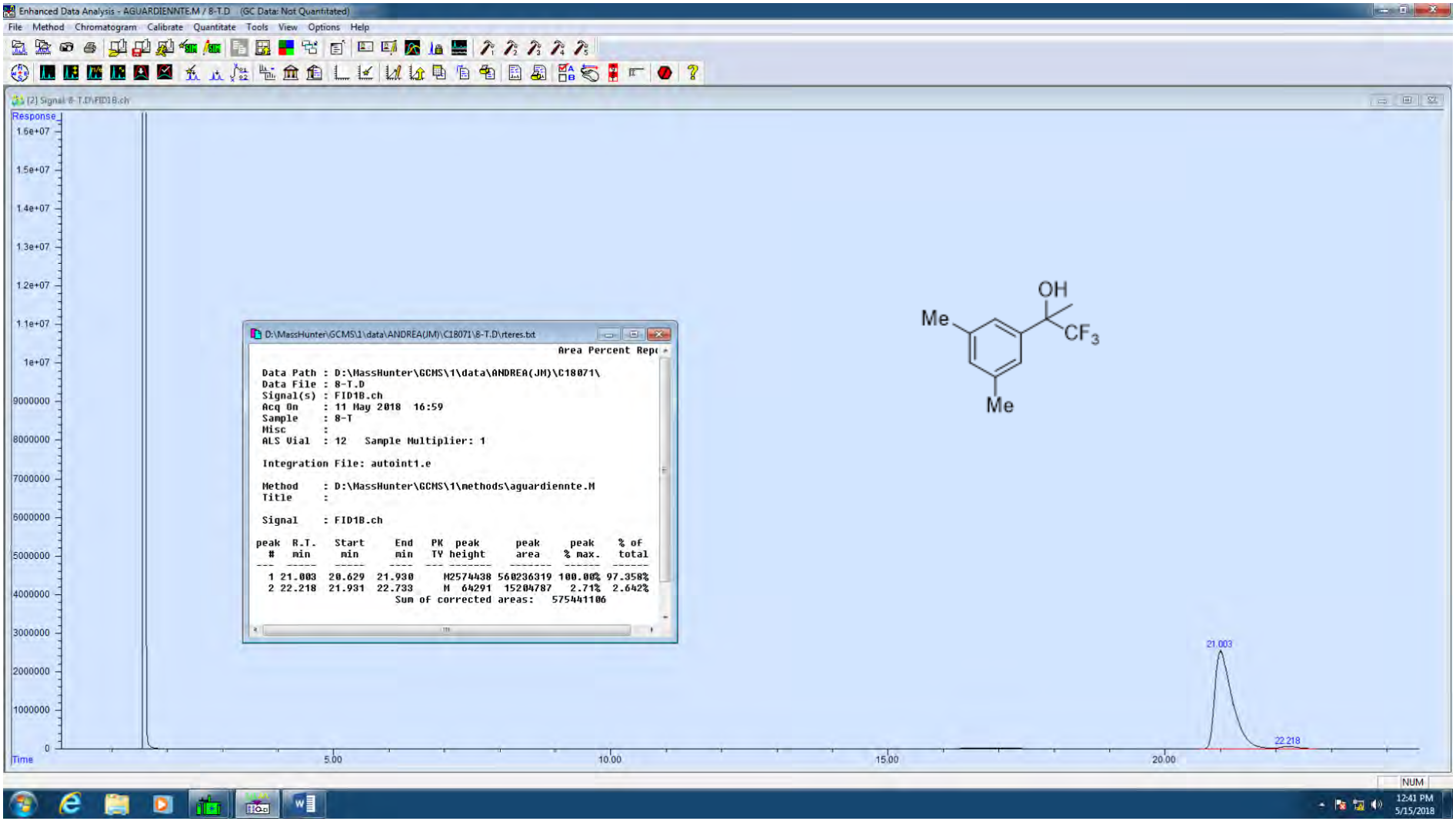
S 97. ^{19}F NMR (470 MHz, CH_2Cl_2, 298 K) from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **11a** in toluene at –30 °C.



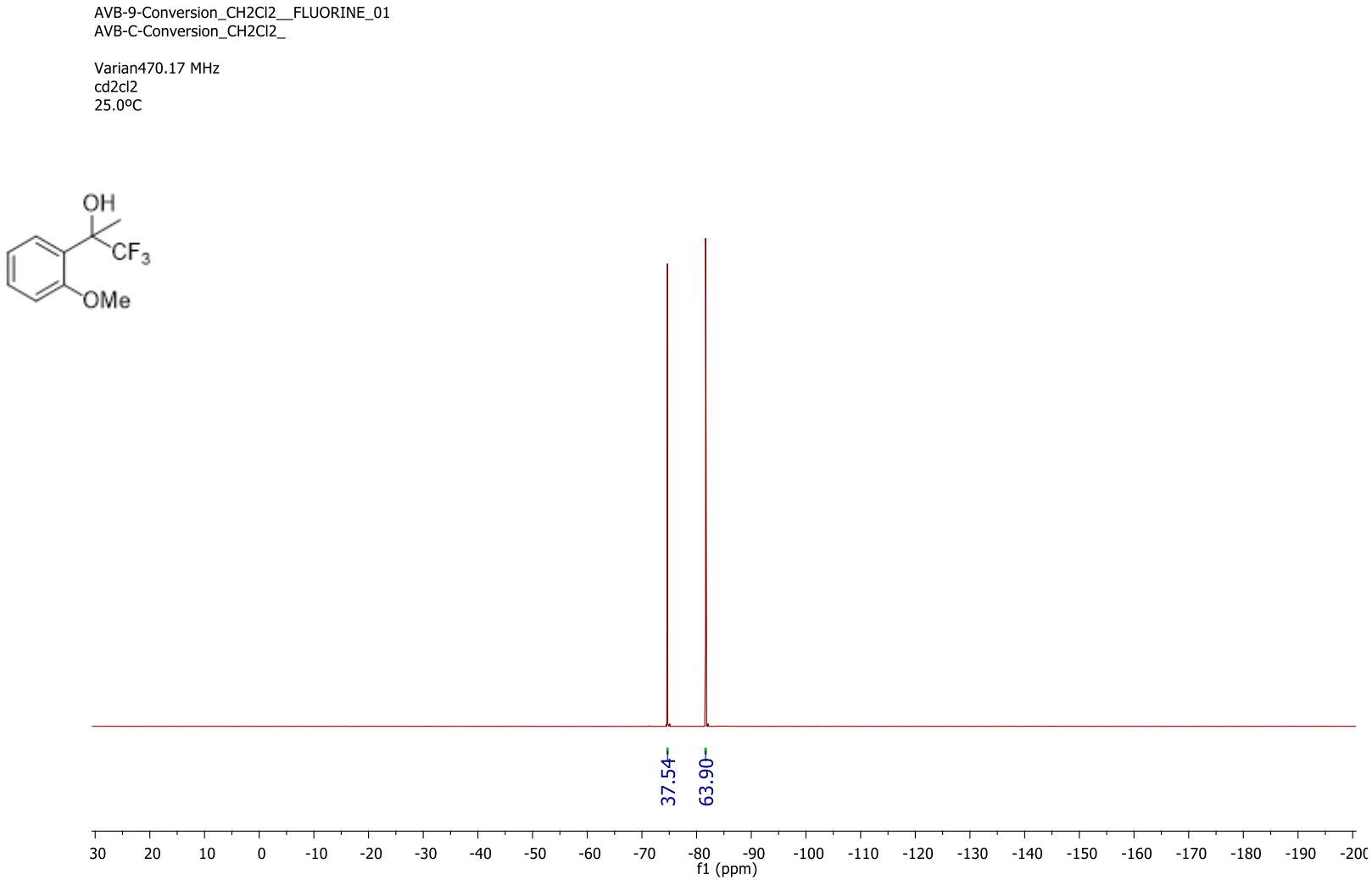
S 98. Enantiomeric resolution by chiral GC from racemic compound **11b**.



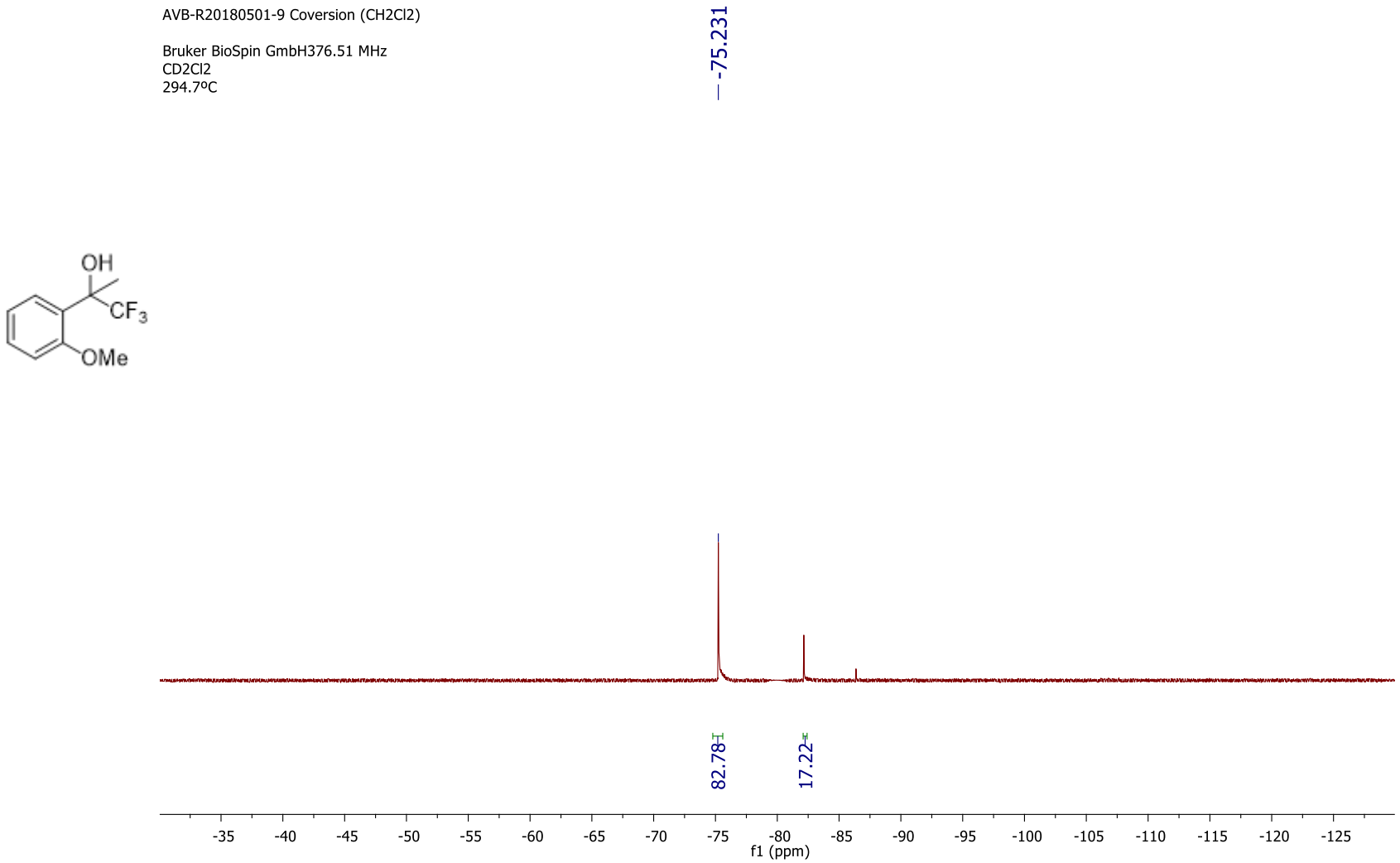
S 99. Enantiomeric resolution by GC from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **11a** in DCM at –30 °C.



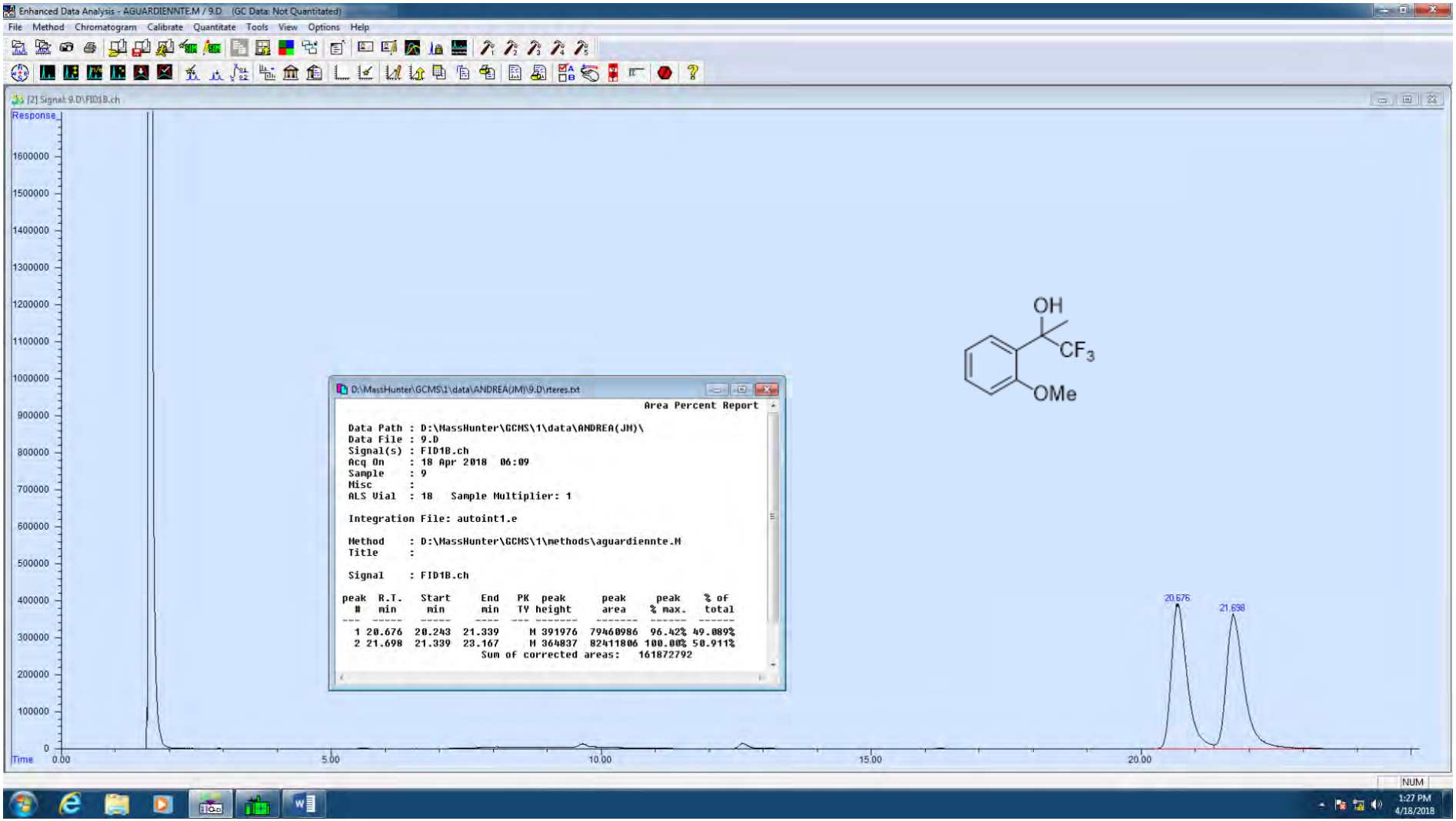
S 100. Enantiomeric resolution by GC from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **11a** in toluene at –30 °C.



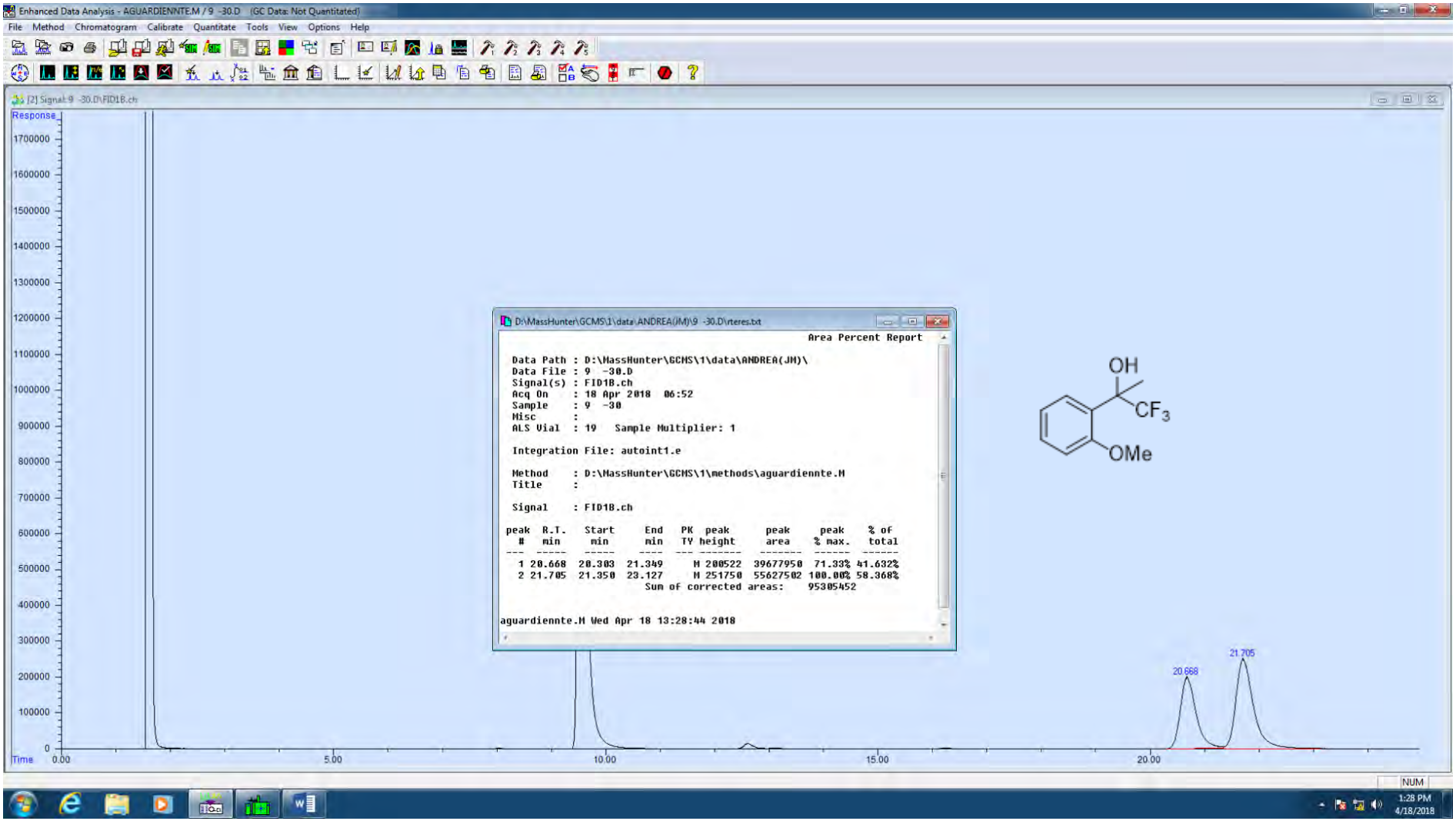
S 101. ^{19}F NMR (470 MHz, CH_2Cl_2, 298 K) from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **12a** in DCM at –30 °C.



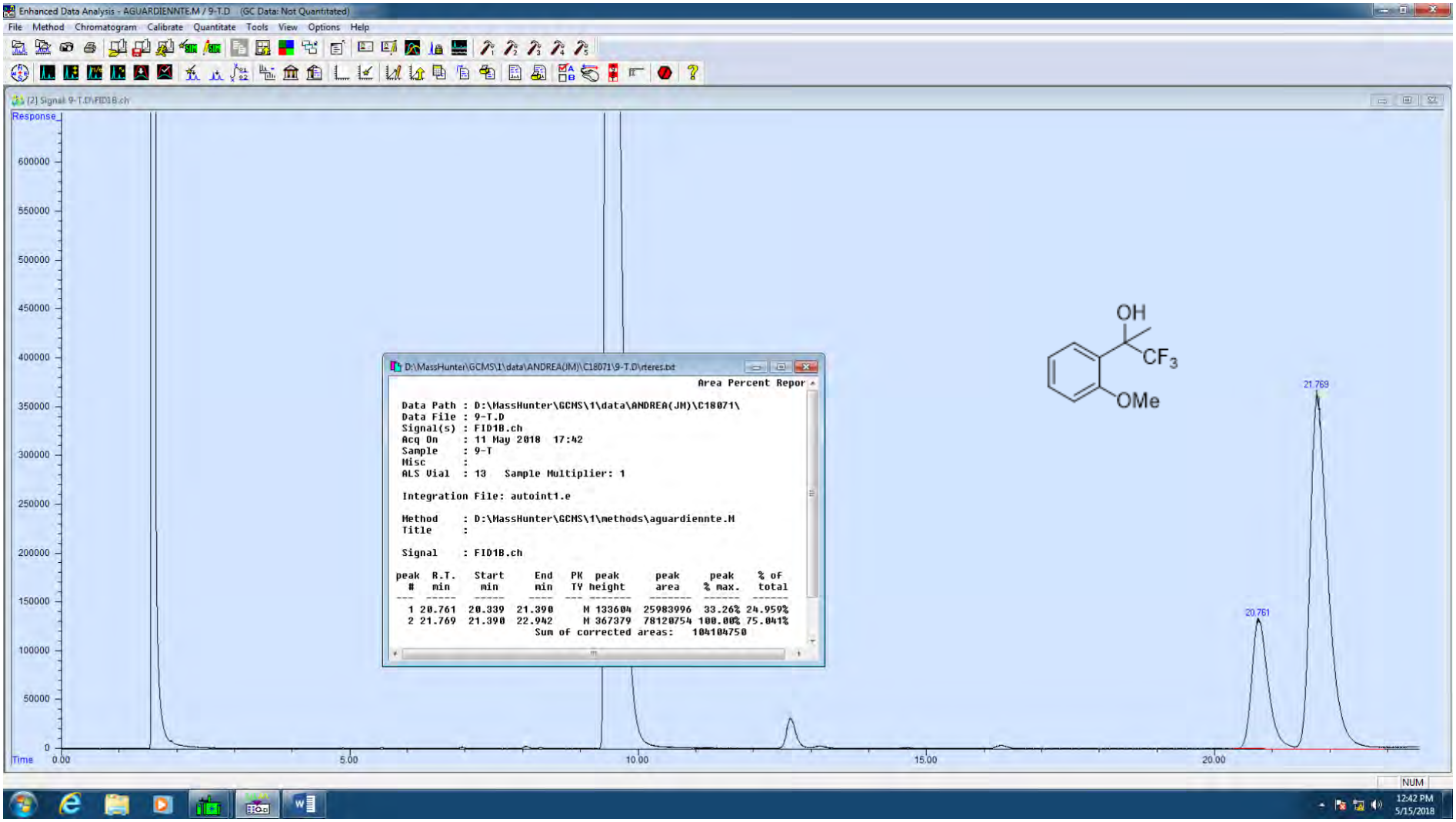
S 102. ^{19}F NMR (376 MHz, CH_2Cl_2, 298 K) from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **12a** in toluene at –30 °C.



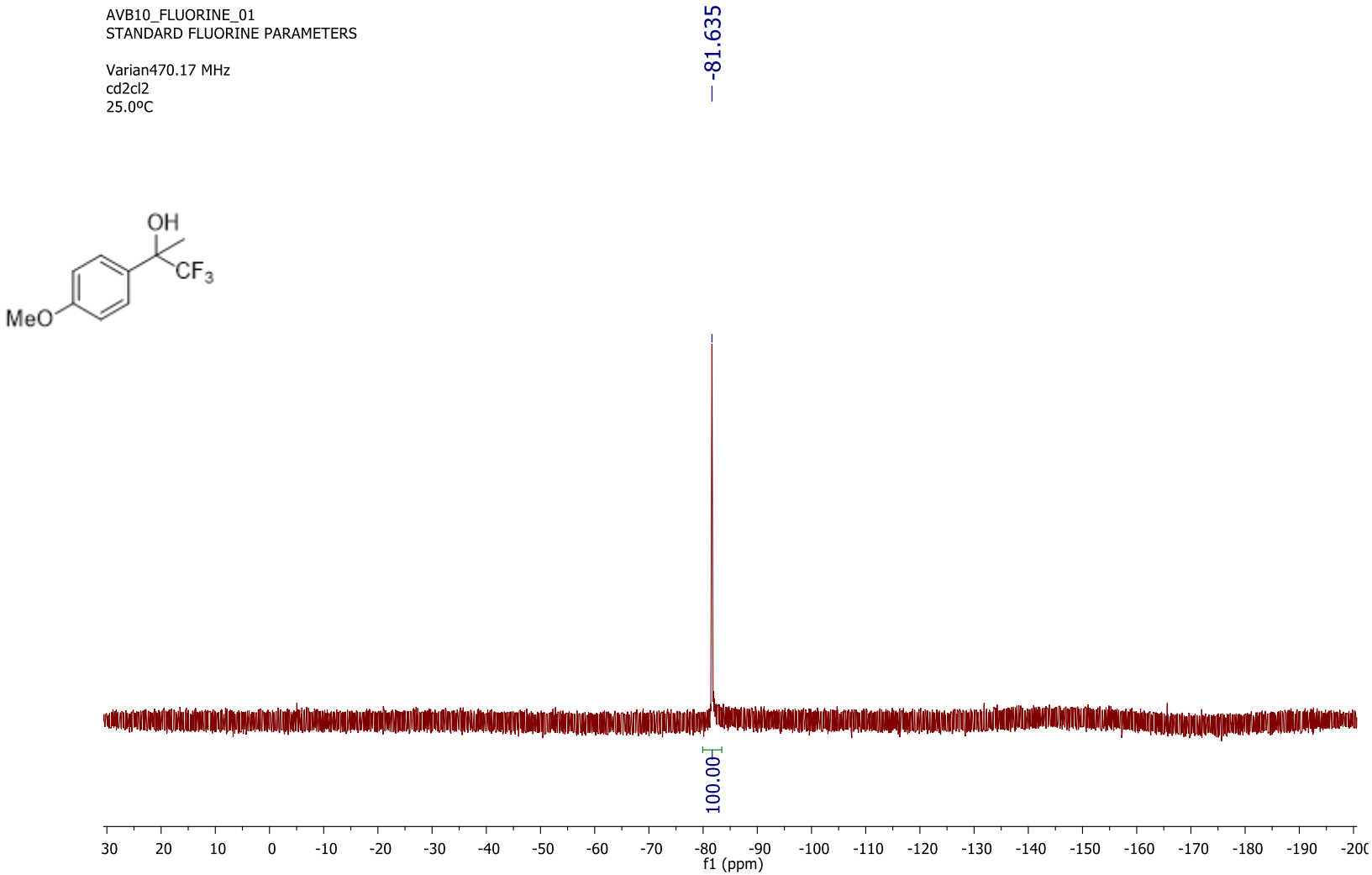
S 103. Enantiomeric resolution by chiral GC from racemic compound **12b.**



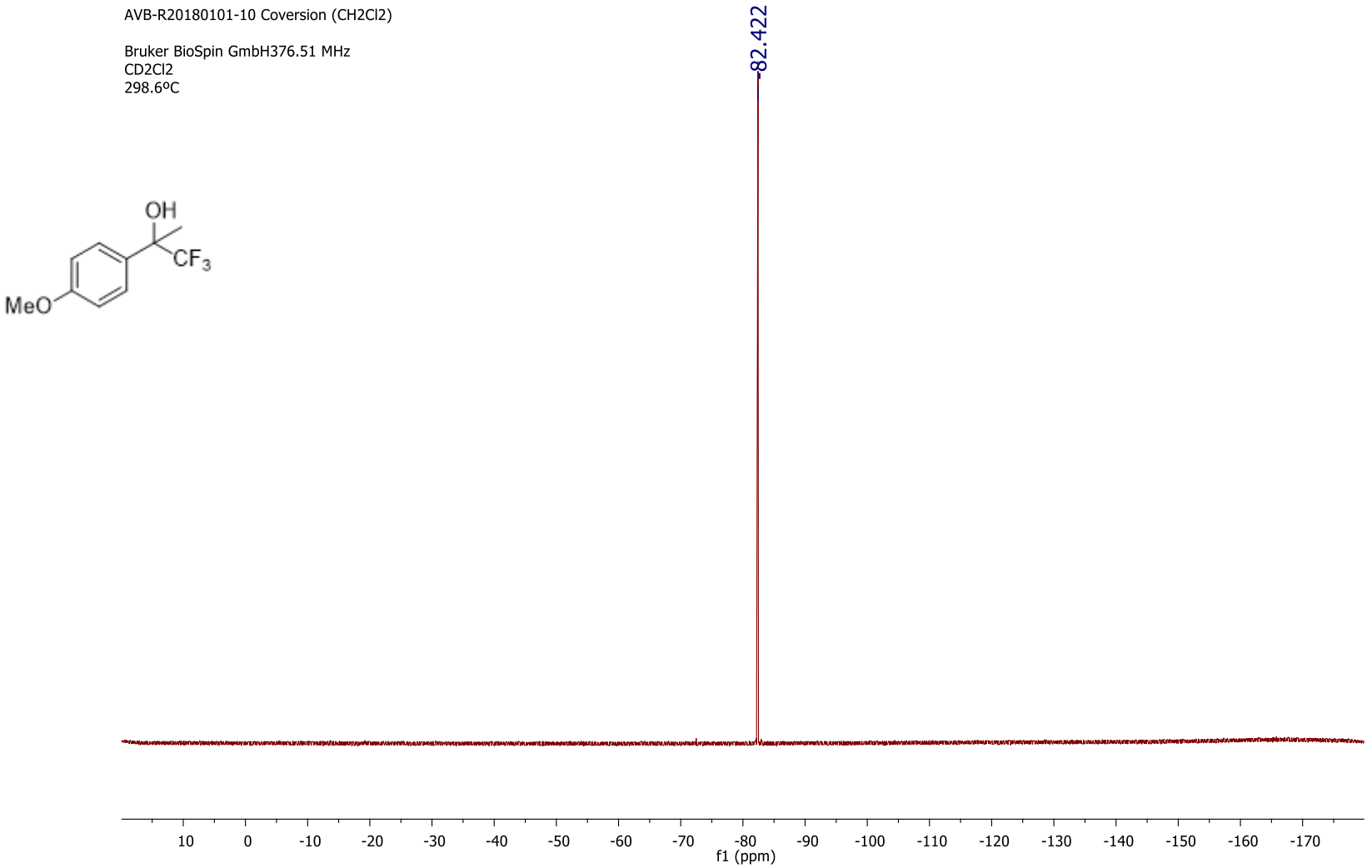
S 104. Enantiomeric resolution by GC from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **12a** in DCM at –30 °C.



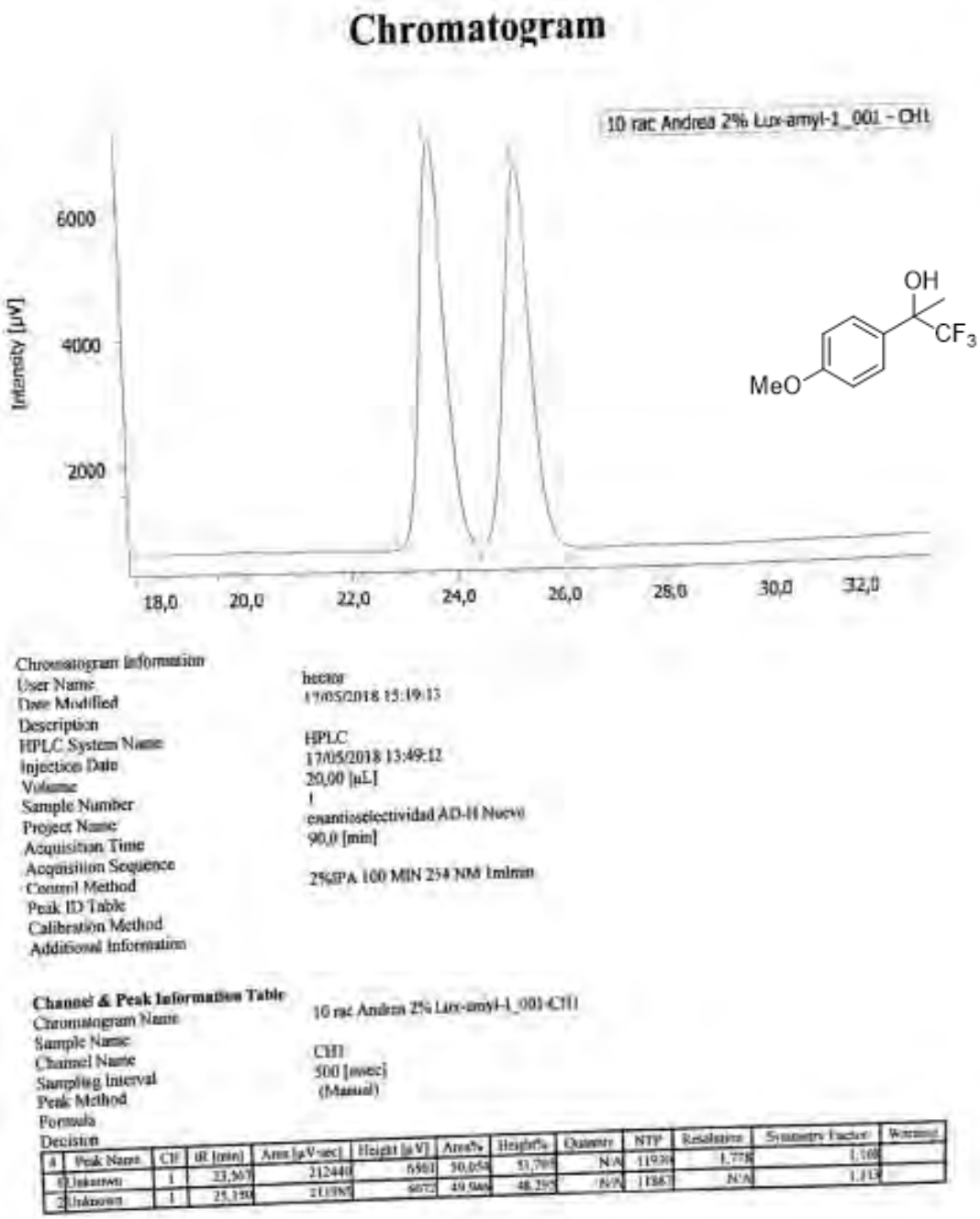
S 105. Enantiomeric resolution by GC from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **12a** in toluene at –30 °C.



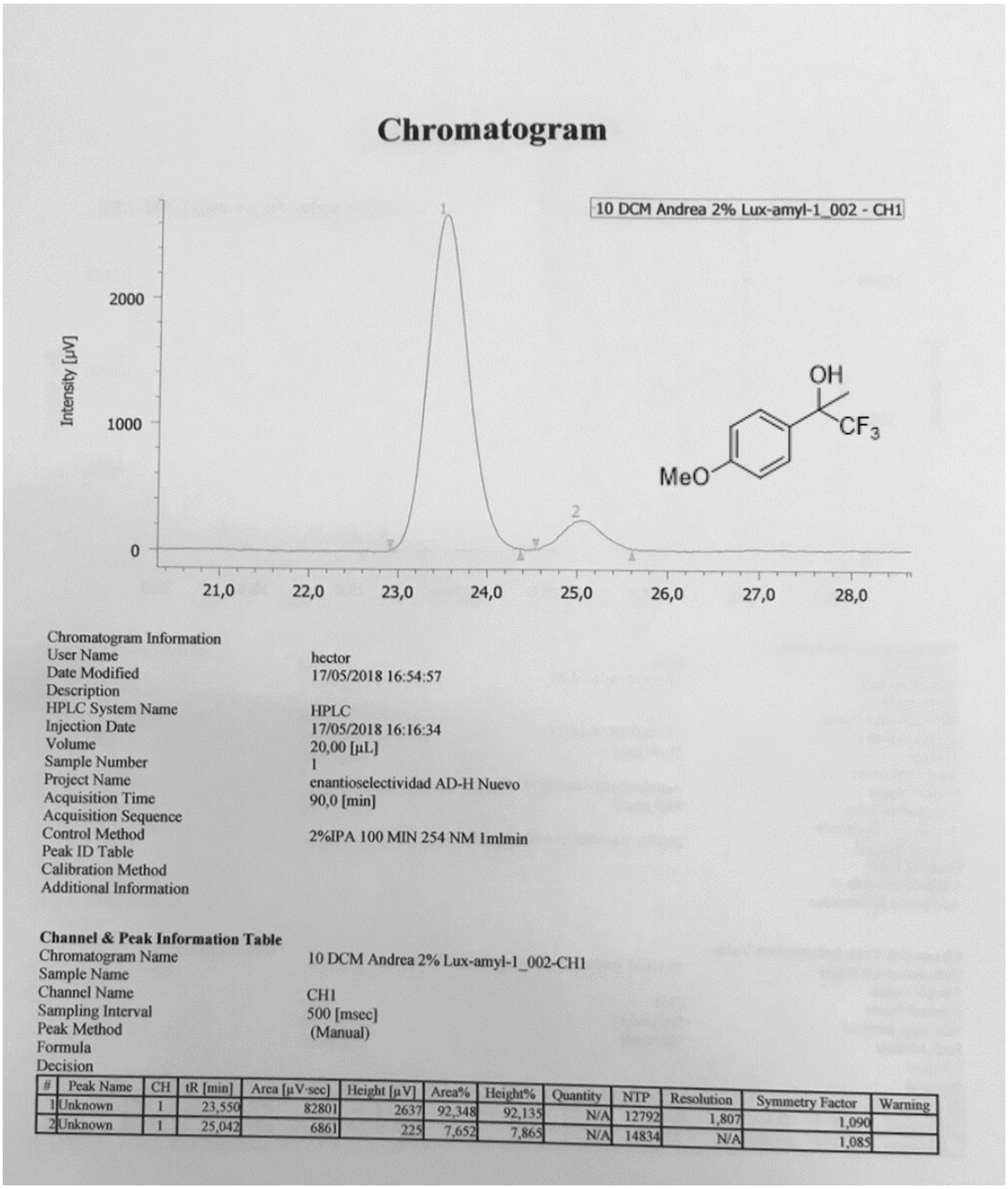
S 106. ^{19}F NMR (470 MHz, CH_2Cl_2, 298 K) from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **13a** in DCM at –30 °C.



S 107. ^{19}F NMR (376 MHz, CH_2Cl_2, 298 K) from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **13a** in toluene at –30 °C.



S 108. Enantiomeric resolution by chiral HPLC from racemic compound **13a**



Chromatogram Information

User Name	hector
Date Modified	17/05/2018 16:54:57
Description	
HPLC System Name	HPLC
Injection Date	17/05/2018 16:16:34
Volume	20,00 [µL]
Sample Number	1
Project Name	enantioselectividad AD-H Nuevo
Acquisition Time	90,0 [min]
Acquisition Sequence	
Control Method	2%IPA 100 MIN 254 NM 1mlmin
Peak ID Table	
Calibration Method	
Additional Information	

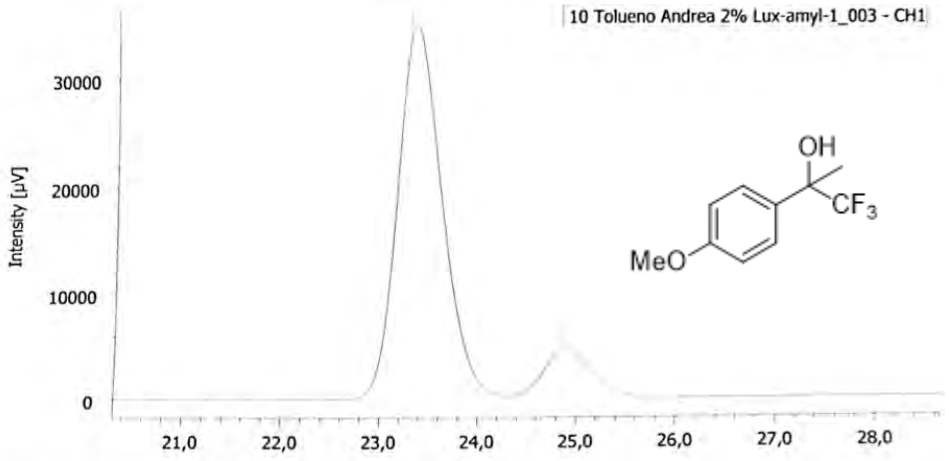
Channel & Peak Information Table

Chromatogram Name	10 DCM Andrea 2% Lux-amyl-1_002-CH1
Sample Name	
Channel Name	CH1
Sampling Interval	500 [msec]
Peak Method	(Manual)
Formula	
Decision	

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	1	23,550	82801	2637	92,348	92,135	N/A	12792	1,807	1,090	
2	Unknown	1	25,042	6861	225	7,652	7,865	N/A	14834	N/A	1,085	

S 109. Enantiomeric resolution by HPLC from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **13a** in DCM at –30 °C.

Chromatogram



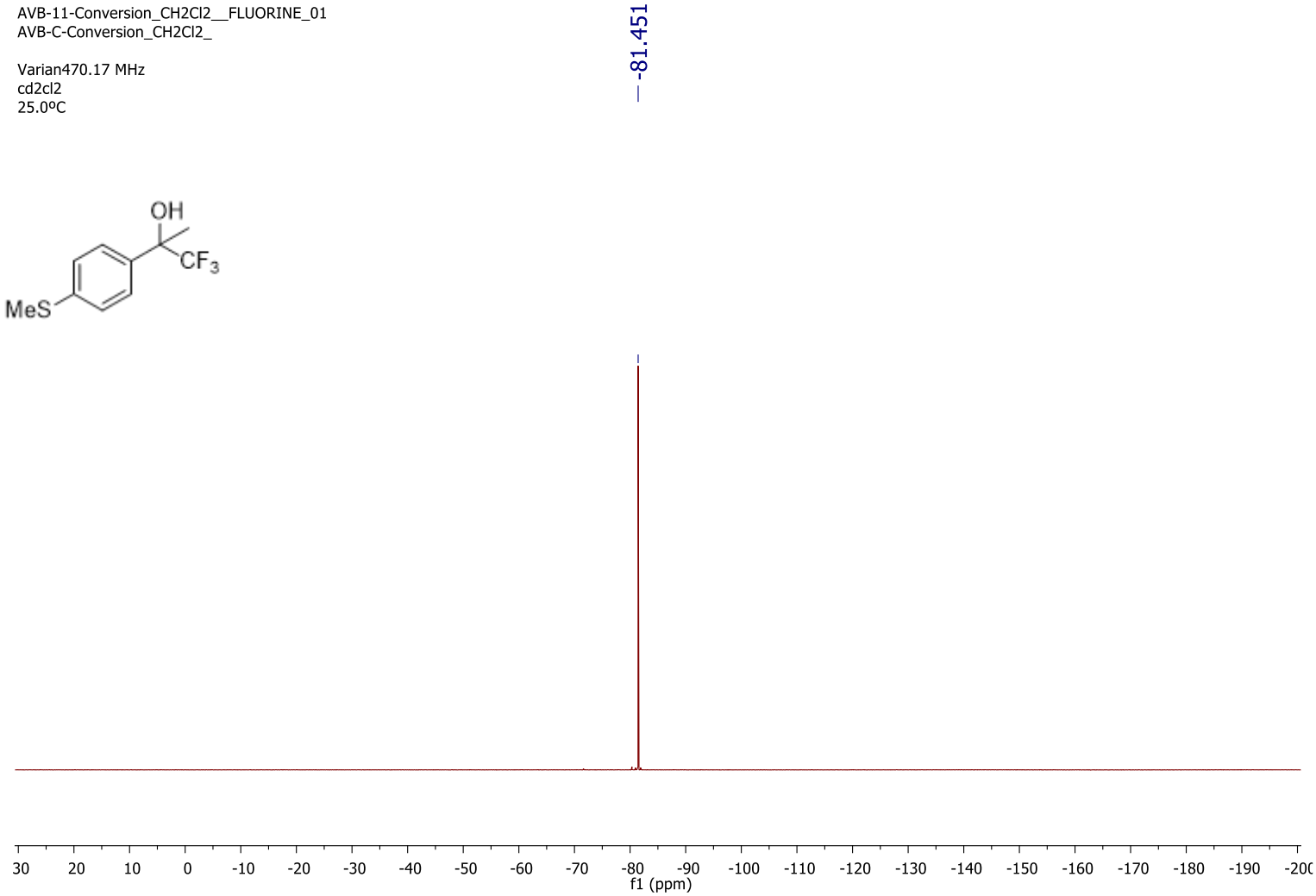
Chromatogram Information	
User Name	hector
Date Modified	17/05/2018 17:41:04
Description	
HPLC System Name	HPLC
Injection Date	17/05/2018 16:57:07
Volume	20,00 [µL]
Sample Number	1
Project Name	enantioselectividad AD-H Nuevo
Acquisition Time	90,0 [min]
Acquisition Sequence	
Control Method	2%IPA 100 MIN 254 NM 1mlmin
Peak ID Table	
Calibration Method	
Additional Information	

Channel & Peak Information Table

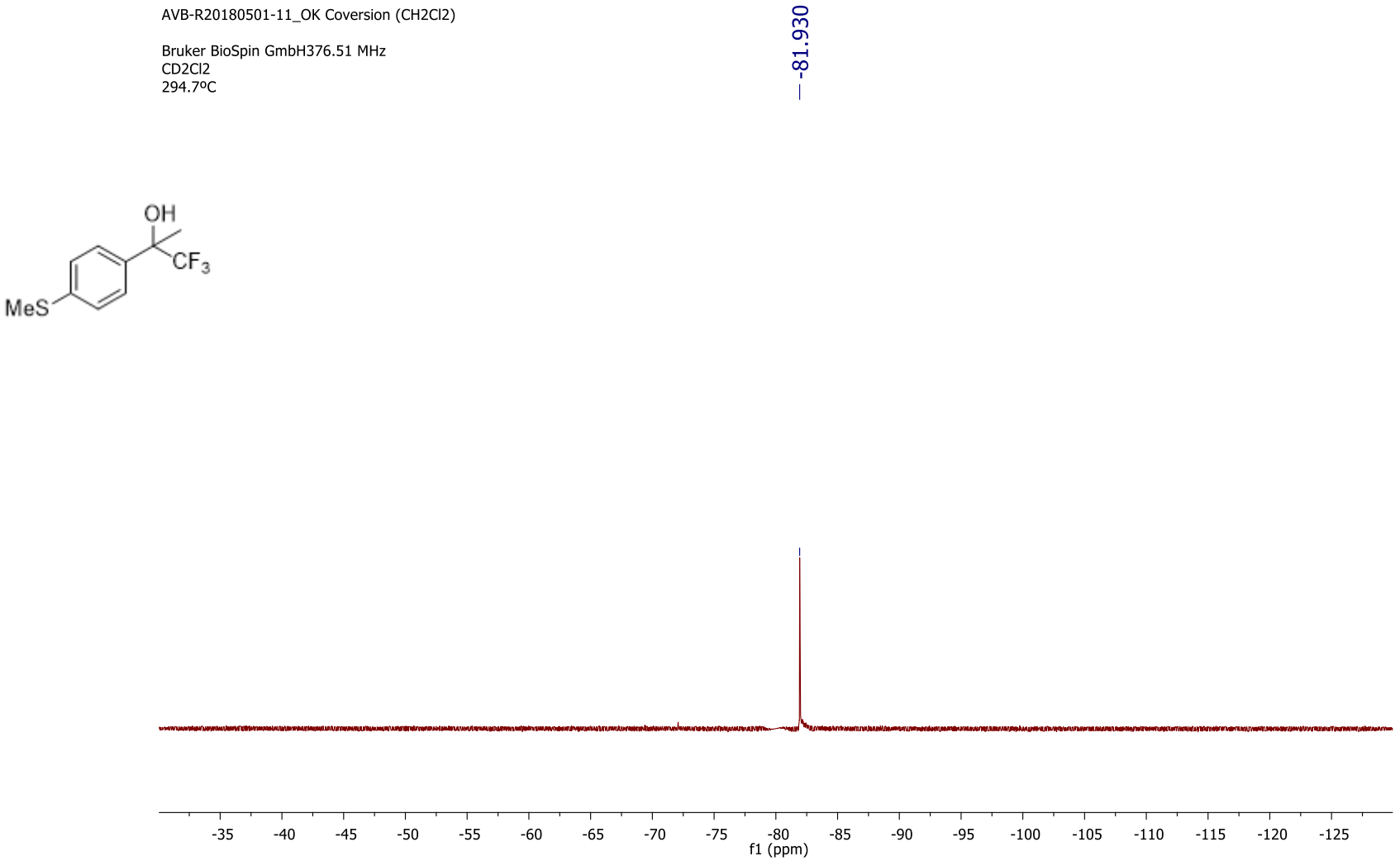
Chromatogram Name	10 Tolueno Andrea 2% Lux-amyl-1_003-CH1
Sample Name	
Channel Name	CH1
Sampling Interval	500 [msec]
Peak Method	(Manual)
Formula	
Decision	

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	1	23,383	1085742	34471	88,004	88,400	N/A	12691	1,791	1,196	
2	Unknown	1	24,908	148003	4523	11,996	11,600	N/A	12903	N/A	1,126	

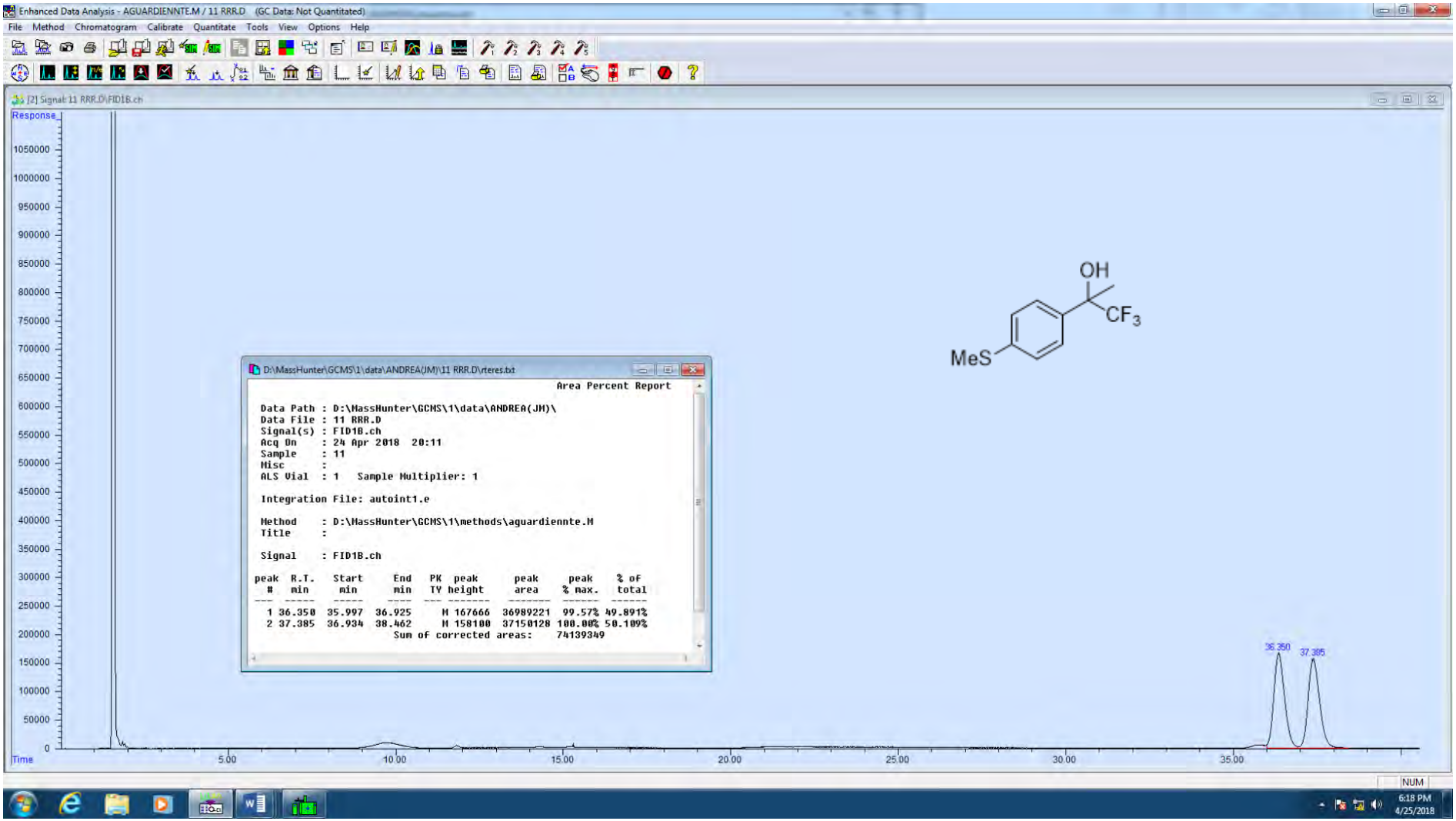
S 110. Enantiomeric resolution by HPLC from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **13a** in toluene at –30 °C.



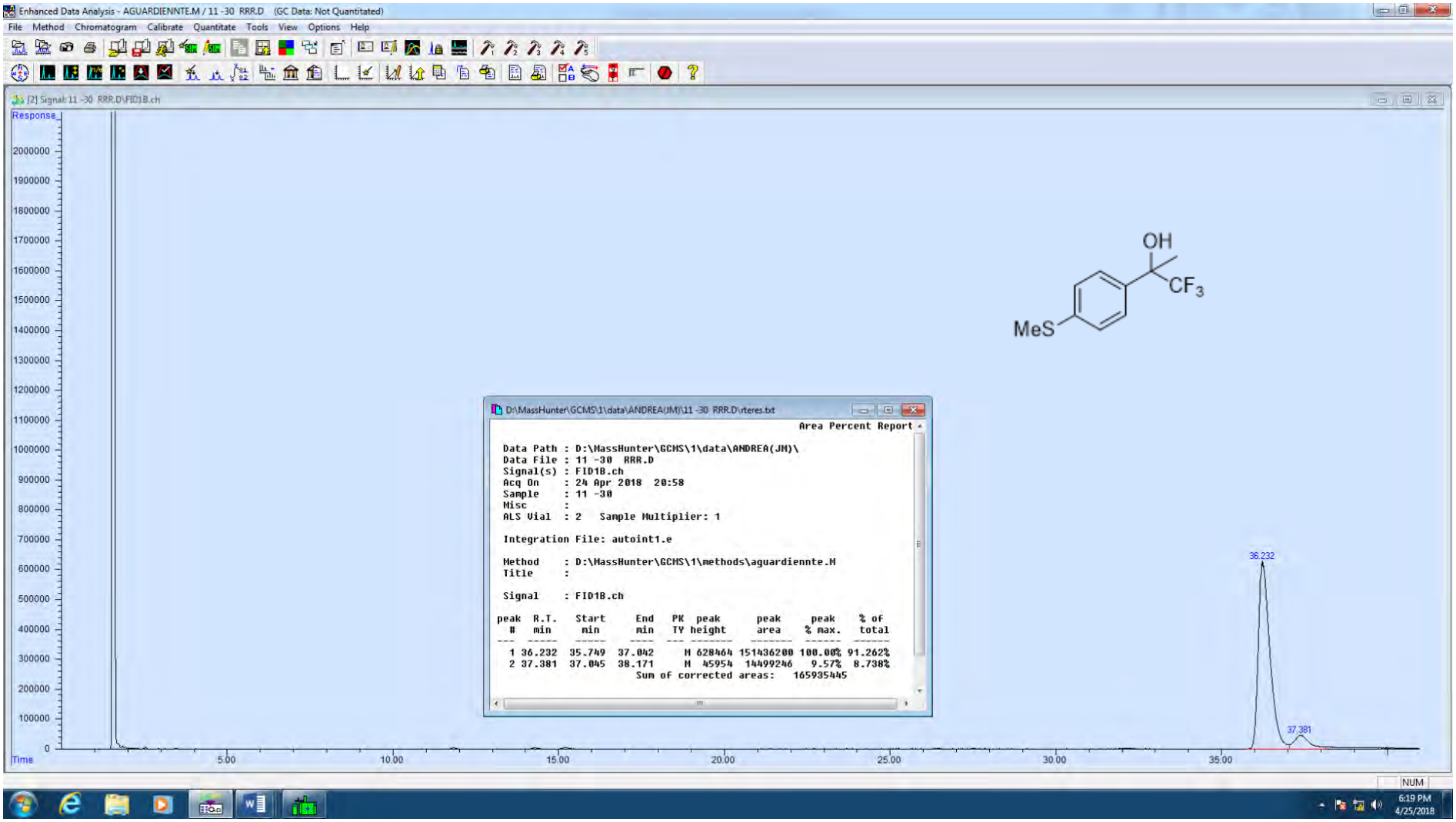
S 111. ^{19}F NMR (470 MHz, CH_2Cl_2, 298 K) from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **14a** in DCM at –30 °C.



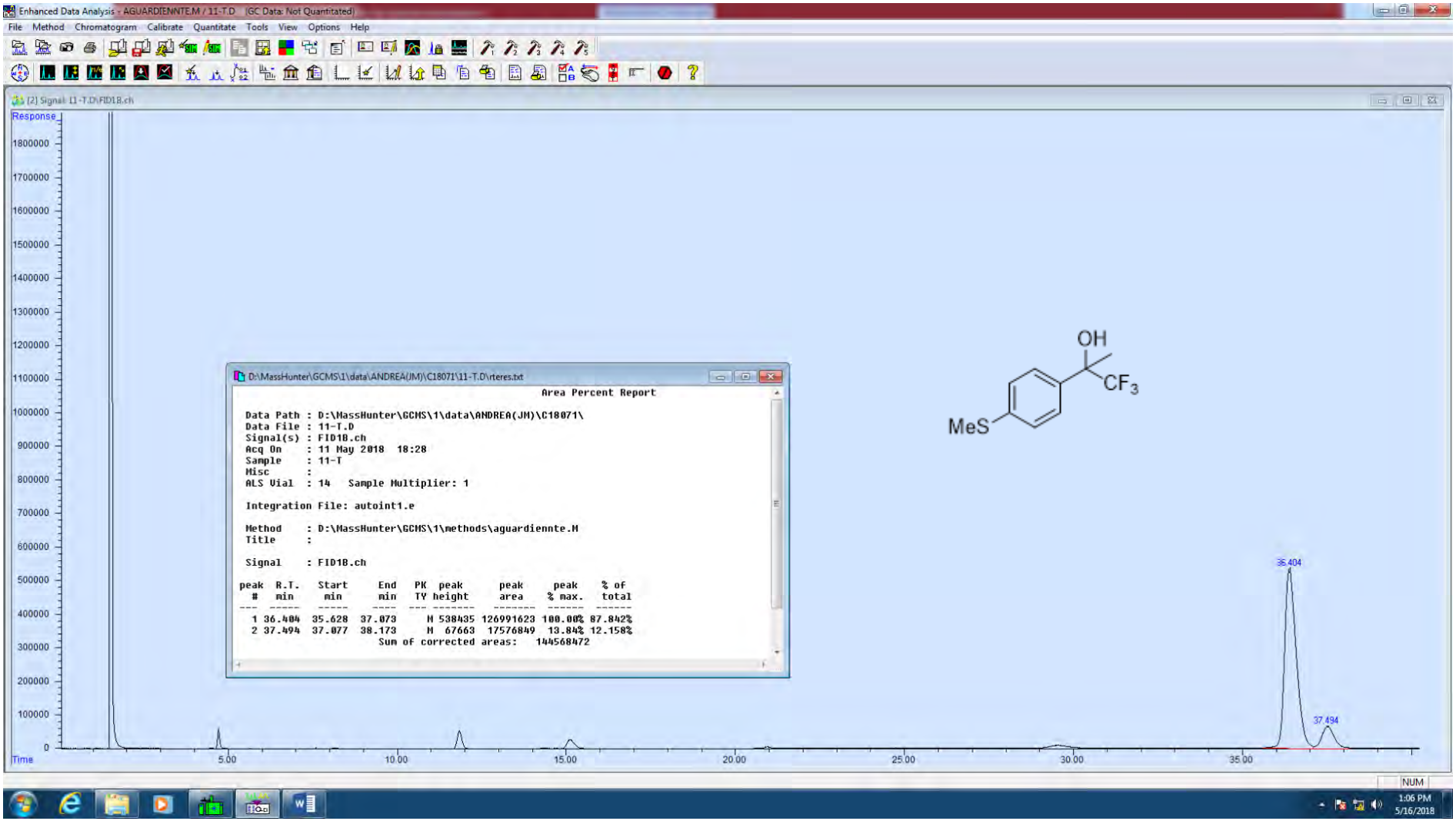
S 112. ^{19}F NMR (376 MHz, CH_2Cl_2, 298 K) from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **14a** in toluene at –30 °C.



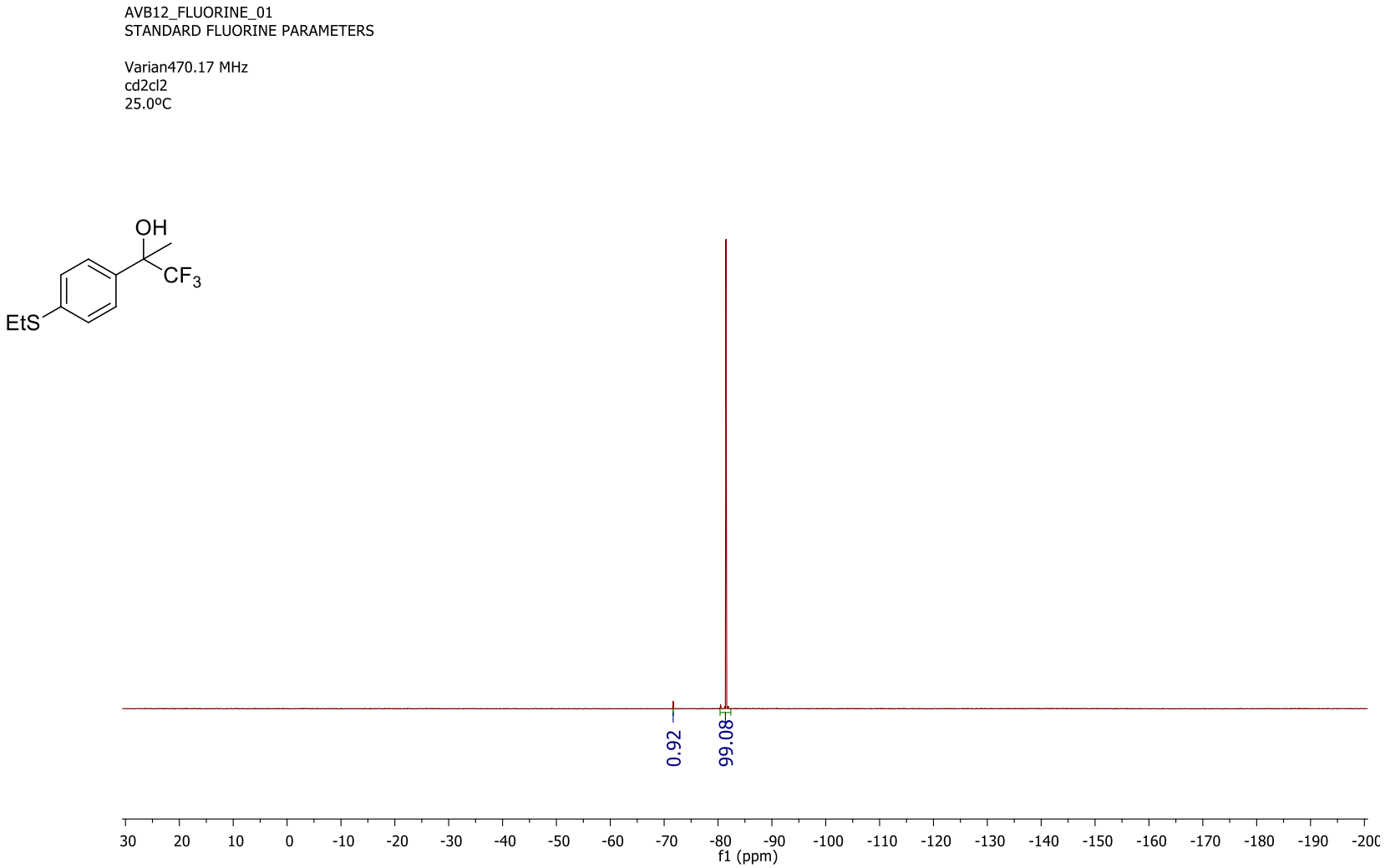
S 113. Enantiomeric resolution by chiral GC from racemic compound **14b**



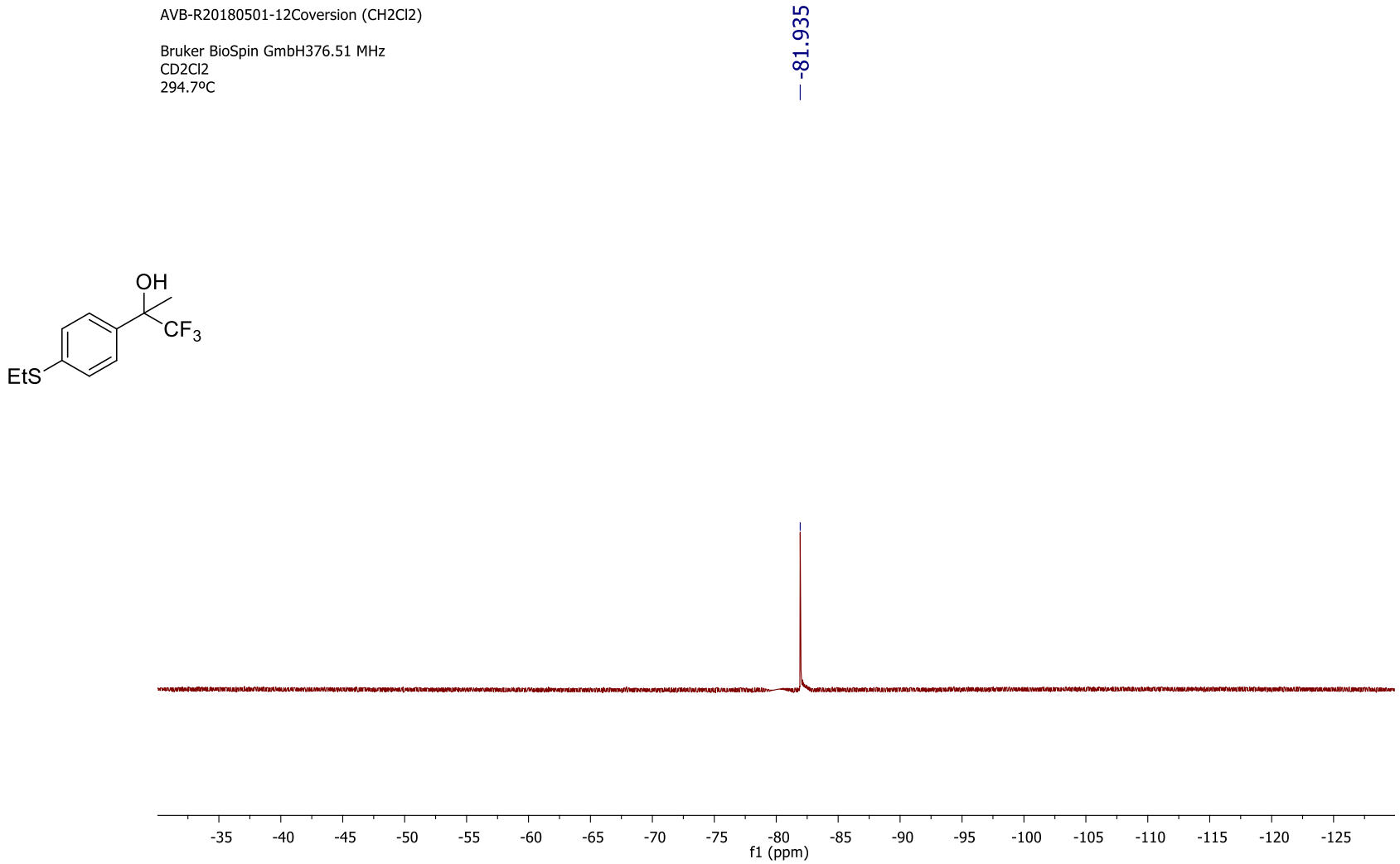
S 114. Enantiomeric resolution by GC from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **14a** in DCM at –30 °C.



S 115. Enantiomeric resolution by GC from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **14a** in toluene at –30 °C.



S 116. ^{19}F NMR (470 MHz, CH_2Cl_2, 298 K) from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **15a** in DCM at –30 °C.



S 117. ^{19}F NMR (376 MHz, CH_2Cl_2, 298 K) from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **15a** in toluene at –30 °C.

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Data File C:\CHEM32\1\DATA\C18034\ANDREA_JM 2018-03-15 14-16-26\12.D
Sample Name: 12

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Acq. Operator   : marta                          Seq. Line :   1
Acq. Instrument : LC-PREP                        Location : Vial 1
Injection Date  : 3/15/2018 2:17:13 PM               Inj :   1
                                                 Inj Volume : 1 µl
Acq. Method     : C:\CHEM32\1\DATA\C18034\ANDREA_JM 2018-03-15 14-16-26\ANDREA_JM.M
Last changed    : 3/15/2018 2:16:24 PM by marta
Analysis Method : C:\CHEM32\1\METHODS\ACHETATO.M
Last changed    : 3/15/2018 6:12:46 PM by marta
                  (modified after loading)
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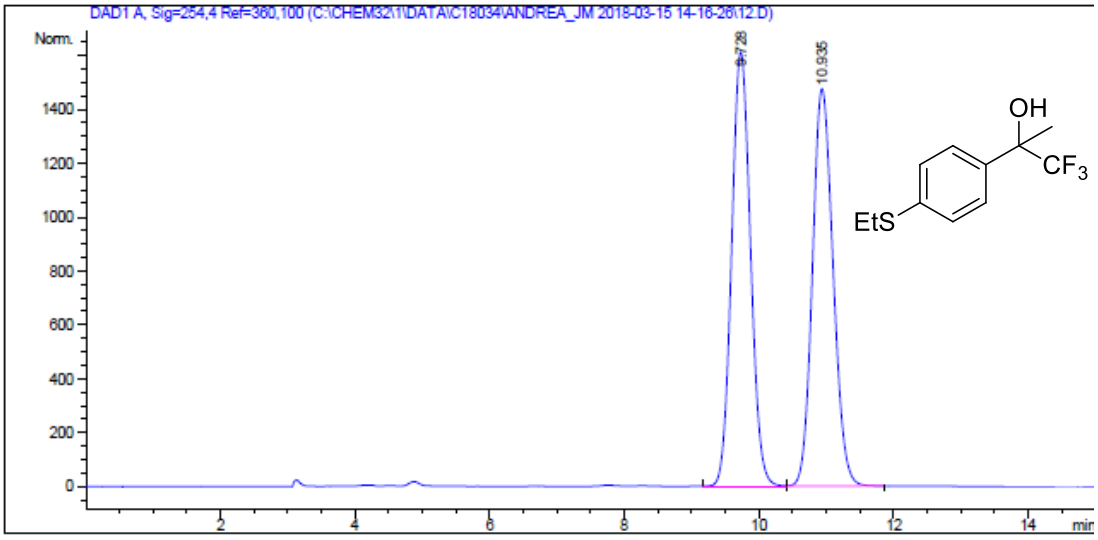


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======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   9.728 VV    0.3055 3.14189e4  1611.02014  49.9550
   2  10.935 VB    0.3320 3.14756e4  1475.04163  50.0450

Totals :                  6.28945e4  3086.06177

LC-PREP 3/15/2018 6:13:26 PM marta                          Page   1 of 2
```

S 118. Enantiomeric resolution by chiral HPLC from racemic compound **15a**.

```
Data File C:\CHEM32\1\DATA\C18034\ANDREA_JM 2018-03-26 18-30-43\12   2018_03_182.D
Sample Name: 12   2018_03_18

    ======================================================================
    Acq. Operator   : marta                          Seq. Line :   1
    Acq. Instrument : LC-PREP                        Location : Vial 21
    Injection Date  : 3/26/2018 6:47:36 PM               Inj :   2
                                                   Inj Volume : 1 µl
    Acq. Method     : C:\CHEM32\1\DATA\C18034\ANDREA_JM 2018-03-26 18-30-43\ANDREA_JM.M
    Last changed    : 3/20/2018 12:48:21 PM by marta
    Analysis Method : C:\CHEM32\1\METHODS\ACHETATO.M
    Last changed    : 3/26/2018 6:13:38 PM by marta
                      (modified after loading)
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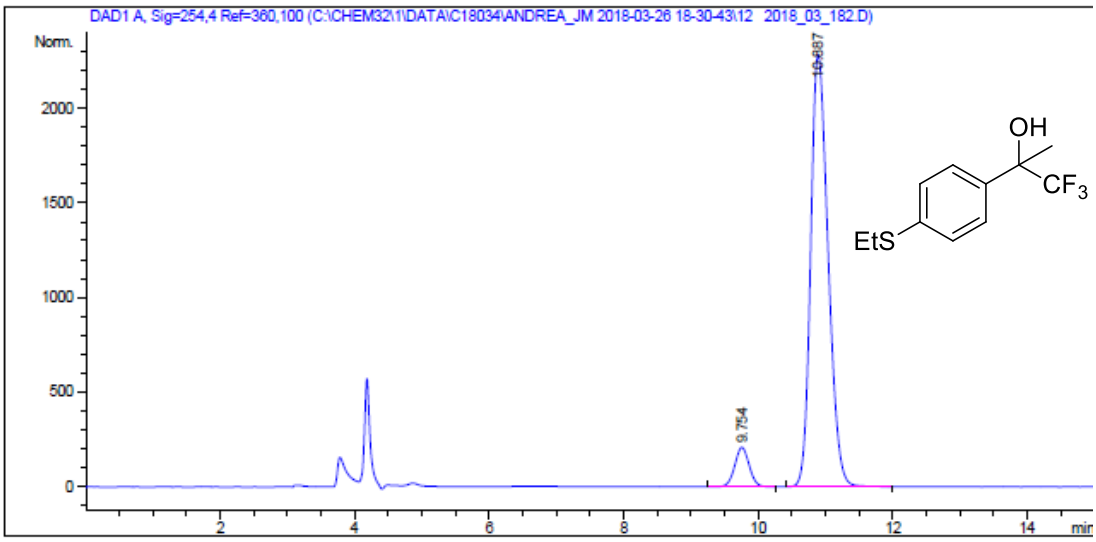


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    ======================================================================
                            Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier:                   :      1.0000
    Dilution:                     :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 A, Sig=254,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1   9.754 BB    0.2318 3097.00952  207.88104   7.0097
       2  10.887 BB    0.2781 4.10846e4  2281.71021  92.9903

LC-PREP 3/26/2018 9:09:33 PM marta                          Page   1 of 2
```

S 119. Enantiomeric resolution by HPLC from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **15a** in DCM at –30 °C.

Data File C:\CHEM32\1\DATA\ANDREA\ANDREA_JM 2018-05-15 13-24-45\A RAC1.D
Sample Name: 12-T

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==================================================================
Acq. Operator   : marta                          Seq. Line :   1
Acq. Instrument : LC-PREP                         Location : Vial 1
Injection Date  : 5/15/2018 1:25:32 PM                 Inj :   1
                                                 Inj Volume : 1 µl
Acq. Method     : C:\CHEM32\1\DATA\ANDREA\ANDREA_JM 2018-05-15 13-24-45\ANDREA_JM.M
Last changed    : 5/15/2018 1:24:44 PM by marta
Analysis Method : C:\CHEM32\1\METHODS\ANDREA_JM.M
Last changed    : 5/15/2018 1:24:44 PM by marta
Sample Info     : HEXANO/IPA 95/5
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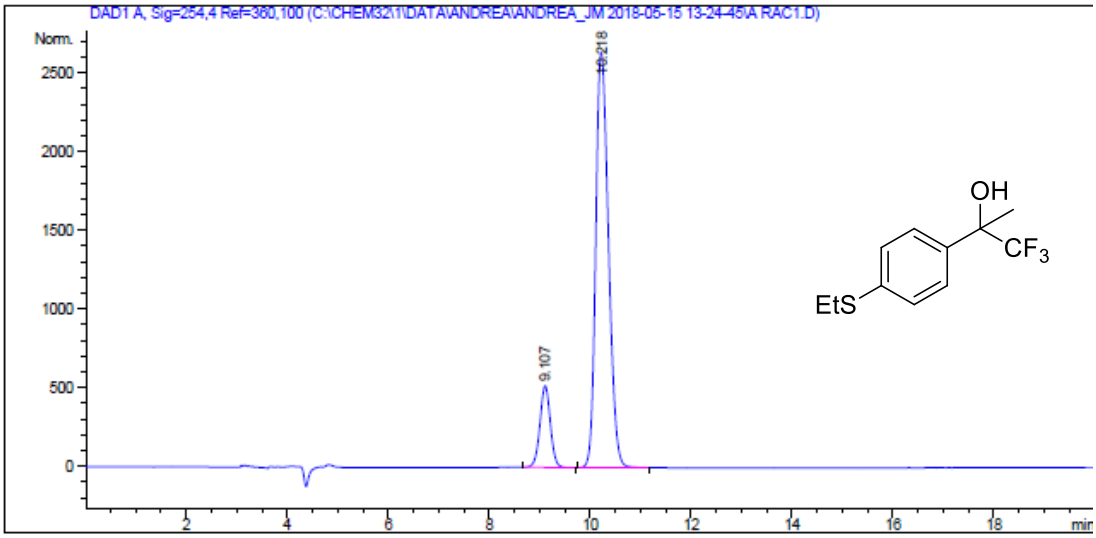


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==================================================================
                        Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   9.107 BB    0.2228 7514.91797  519.44397  13.9960
   2  10.218 BB    0.2723 4.61783e4  2637.01953  86.0040
```


S 120. Enantiomeric resolution by HPLC from the organic layer after the hydrolysis of enantioselective addition of $ZnMe_2$ to TFMK **15a** in toluene at –30 °C.