SUPPORTING INFORMATION

Synthesis, Radio-Synthesis and *in vitro* Evaluation of Terminally Fluorinated Derivatives of HU-210 and HU-211 as Novel Candidate PET Tracers

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General Information

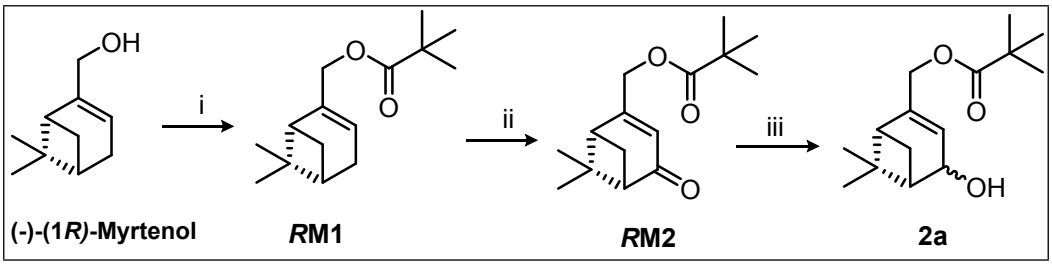
^{1}H (400.13 MHz), ^{13}C (100.58 MHz) and ^{19}F (376.45 MHz) NMR spectra were recorded on a Bruker ADVANCE III spectrometer. For ^{1}H NMR spectra the solvent resonance was employed as the internal standard ($CDCl_3$ δ = 7.26, CD_3OD δ = 3.31). ^{13}C NMR spectra were recorded with complete proton decoupling, and the solvent resonance was employed as the internal standard ($CDCl_3$, δ = 77.0, CD_3OD δ = 49.00). All chemical shifts (δ) are expressed in parts per million and coupling constant (*J*) are given in Hertz. HPLC-MS experiments were performed on an Agilent Technologies 1200 Series HPLC system equipped with a DAD and a 6120 MS detector composed by an ESI ionization source and a Single Quadrupole mass selective detector. Specific optical rotation measurements were performed on an AA-65 Angular Scale automatic polarimeter (Optical Activity Limited) with a 1dm cell at the sodium D line. All reactions were carried out in oven- or flame-dried glassware under nitrogen atmosphere, unless stated otherwise. All commercially available reagents were used as received. Reactions were magnetically stirred and monitored by TLC on silica gel (60 F254 pre-coated glass plates, 0.25 mm thickness). Visualization was accomplished by irradiation with a UV lamp and/or staining with a ceric ammonium molibdate or $KMnO_4$ solution. Flash chromatography was performed on silica gel (60 Å, particle size 0.040–0.062 mm). Yields refer to chromatographically and spectroscopically pure compounds, unless stated otherwise.

HPLC analyses of radioactive compounds were performed using a Shimadzu HPLC system equipped with a SPD-M20A Prominence DAD UV detector and NaI radio-detector (Berthold Technologies). Semi-prep HPLC purification of radioactive compounds were performed using a lead shielded Shimadzu semiprep HPLC system equipped with a SPD-M20A Prominence DAD UV detector and NaI radio-detector (Berthold Technologies).

RadioTLC were performed using a Raytest miniGITA RadioTLC scanner. The dose calibrators used to measure doses were CAPINTEC CRC 15R and CAPINTEC CRC 15PET.

[^{18}F]-Fluoride was produced on a cyclotron by proton bombardment of 97% enriched [^{18}O]H_2O (Cambridge Isotope Laboratories, Inc.) by the $^{18}O(p,n)^{18}F$ nuclear reaction. The silver target (1.1ml) was pressurised to 600psi and irradiated with 11MeV protons produced by the CTI/SIEMENS RDS-111 cyclotron at the John Mallard Scottish PET Centre in Aberdeen. Irradiation with a beam current of 29 μA for 7 minutes was typically used (3.9 GBq). At the end of bombardment (EOB) the target was unloaded within 5 min using argon gas.

Synthetic Procedures and Compounds Characterisations



(1R,5S)-2-[(2,2-dimethylpropoxy)methyl]-6,6-dimethylbicyclo[3.1.1]hept-2-ene (RM1)[1,2]

To a solution of a commercially available (1*R*,5*S*)-myrtenol (5.0 g, 32.8 mmol, 1 eq, ≥95% *ee*) in DCM (30 mL) and pyridine (30 mL) at 0°C was added dropwise trimethylacetyl chloride (5 mL, 41.0 mmol, 1.3 eq). The reaction was stirred for 4 h at 0°C, diethyl ether (100 mL) was added and the mixture was washed with 10% aqueous hydrochloric acid, saturated aqueous bicarbonate solution, brine, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (Hexane/ EtOAc 1:1) to give compound ***RM1*** (6.4 g, 83%) as a colorless oil.

R_f 0.40 (Hexane/EtOAc 1:1).

$[\alpha]_D^{27}$: -30 (*c* = 1.6 $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87 (s, 3 H), 1.17-1.22 (m, 2 H), 1.22 (s, 9 H), 1.31 (s, 3 H), 2.13 (dd, 2H, *J* = 1.3, 5.6 Hz), 2.31 (q, 2H, *J* = 18.0 Hz), 2.42 (dt, 2H, *J* = 5.6, 8.7 Hz), 4.44 (ddd, 1H, *J* = 1.6, 3.2, 12.5 Hz), 4.49 (ddd, 1H, *J* = 1.6, 3.2, 12.5 Hz), 5.57 (dq, 1 H, *J* = 1.4, 4.4 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.1, 26.1, 27.2 (x 3 C), 31.2, 31.4, 38.0, 38.8, 40.7, 43.5, 66.7, 121.0, 143.3, 178.1.

MS (ESI) for $C_{15}H_{25}O_2$: *m*/*z* calculated 237.2 $[M+H]^+$; *m*/*z* found (relative intensity) 237.2 $[M+H]^+$ (100).

(1R,5S)-4-[(2,2-dimethylpropoxy)methyl]-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (RM2)[1,2]

To a suspension of chromium trioxide (16.8 g, 168.0 mmol, 12 eq) in dry DCM (130 mL) at -20°C was added 3,5-dimethylpyrazole (16.1 g, 168.0 mmol, 12 eq) in small portions. After stirring for 15 min a solution of ***RM1*** (3.3 g, 14.0 mmol, 1 eq) in dichloromethane (35 mL) was added and the mixture was stirred at -20°C for 4 h. Aqueous sodium hydroxide solution (5 M, 15 mL) was added and the mixture was stirred at 0°C for 1 h. The organic phase was separated, washed with 10% aqueous HCl, brine, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (Hexane/ EtOAc 8:2) to give compound ***RM2*** (1.8 g, 50%) as a colorless oil.

R_f 0.42 (Hexane/EtOAc 8:2).

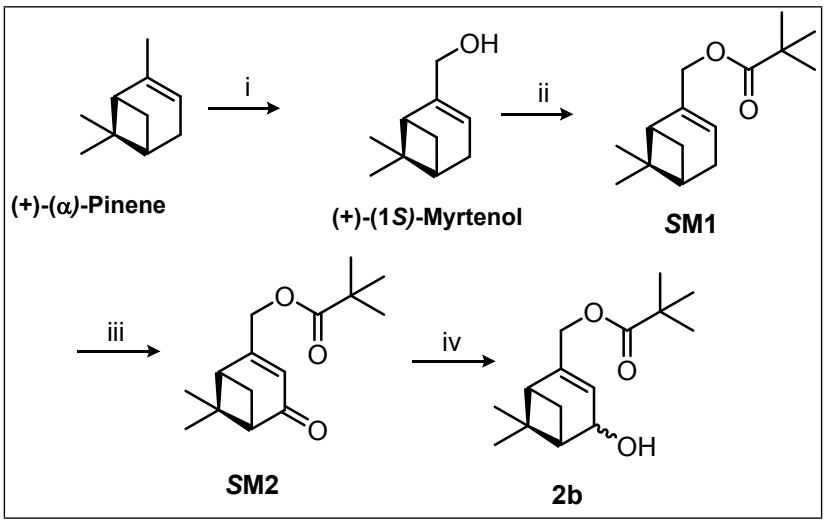
$[\alpha]_D^{27}$: -150 (*c* = 1.4 $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.05 (s, 3 H), 1.27 (s, 9 H), 1.54 (s, 3 H), 2.16 (d, 1 H, *J* = 9.3 Hz), 2.46 (td, 1 H, *J* = 1.4, 5.9 Hz), 2.72 (td, 1 H, *J* = 1.7, 5.9 Hz), 2.89 (dt, 2 H, *J* = 5.5, 9.3 Hz), 4.71 (dd, 1H, *J* = 1.9, 16.6 Hz), 4.76 (dd, 1H, *J* = 1.9, 16.6 Hz), 5.89 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.0, 26.4, 27.1 (x 3 C), 38.7, 40.6, 45.3, 53.9, 58.0, 63.9, 119.1, 165.9, 172.2, 202.3.

MS (ESI) for $C_{15}H_{22}O_3$: *m*/*z* calculated 251.2 $[M+H]^+$; *m*/*z* found (relative intensity) 251.2 $[M+H]^+$ (100).

(1R,5S)-4-[(2,2-dimethylpropoxy)methyl]-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-ol (2a)[1,2]
To a solution of ketone ***R*M2** (500 mg, 2.0 mmol, 1 eq) in dry THF (4 mL) at 0°C was added lithium tri-*tert*-butoxyaluminium hydride (508 mg, 2.0 mmol, 1 eq). The mixture was allowed to warm to room temperature and stirred for a further 4 h. The reaction was quenched with saturated aqueous ammonium chloride solution (5 mL) and extracted with diethyl ether. The combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (Hexane/ EtOAc 8:2) to give alcohol **2a** (454 mg, 90%, diastereomeric mixture) as a colorless oil.
R_f 0.40 (Hexane/EtOAc 8:2).
$[\alpha]_D^{27}$: 0 (*c* = 1.0 $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.11 (s, 3 H), 1.24 (s, 9 H), 1.38 (s, 3 H), 1.59 (bs, OH), 2.13 (t, 1 H, *J* = 5.2 Hz), 2.36 (ddd, 1 H, *J* = 2.6, 5.7, 8.1 Hz), 2.54 (dt, 1 H, *J* = 5.8, 9.2 Hz), 4.52 (m, 3 H), 5.68 (bs, 1 H).
^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.9, 26.7, 27.2 (x 3 C), 35.6, 38.8, 38.9, 44.0, 48.3, 65.8, 72.0, 122.3, 145.1, 178.2.
MS (ESI) for $C_{15}H_{24}O_3$: *m*/*z* calculated 253.2 $[M+H]^+$; *m*/*z* found (relative intensity) 253.2 $[M+H]^+$ (100).



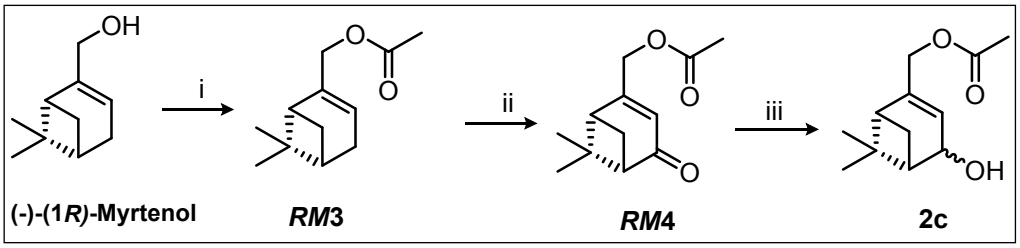
(+)-(1S)-Myrtenol[2,3]
A solution of selenium dioxide (2.4g, 22.0 mmol, 0.6 eq) in ethanol (36 mL) was added over a period of 1h to **(+)-α-pinene** (5.0 g, 36.7 mmol, 1 eq, ≥99 % *ee*). The mixture was heated to 75°C and was stirred for 2 h. The mixture was cooled, the precipitate of selenium was filtered off, and the filtrate was evaporated under reduced pressure to remove volatile products. The crude mixture was added under stirring to a solution of $NaBH_4$ in (138.8 mg, 3.67 mmol, 0.1 eq) in ethanol (70 mL) and the mixture was stirred for 1 h. A saturated aqueous solution of NH_4Cl was added and the mixture was extracted with diethyl ether (3 x 50 mL). The organic phase was washed with water, dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The resulting **(+)-(1*S*)-Myrtenol** was used crude, without further purification.
MS (ESI) for $C_{10}H_{16}O$: *m*/*z* calculated 153.1 $[M+H]^+$; *m*/*z* found (relative intensity) 153.1 $[M+H]^+$ (100).

***[(1S,5R)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl]methyl 2,2-dimethylpropanoate (S*M1)** [1,2]
To a solution of crude (+)-(1*S*)-Myrtenol (1 g, 6.6 mmol, 1 eq) in DCM (6 mL) and pyridine (6 mL) at 0°C was added dropwise trimethylacetyl chloride (1 mL, 8.2 mmol, 1.3 eq). The reaction was stirred for 4 h at 0°C, diethyl ether (20 mL) was added and the mixture was washed with 10% aqueous hydrochloric acid, saturated aqueous bicarbonate solution, brine, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (Hexane/ EtOAc 1:1) to give compound ***S*M1** (935 mg, 60%) as a colorless oil.
R_f 0.40 (Hexane/EtOAc 1:1).
$[\alpha]_D^{27}$: +31 (*c* = 1.6 $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.82 (s, 3 H), 1.19 (m, 2 H), 1.17 (s, 9 H), 1.26 (s, 3 H), 2.20 (dd, 2H, *J* = 1.3, 5.6 Hz), 2.33 (q, 2H, *J* = 18.0 Hz), 2.38 (dt, 2H, *J* = 5.6, 8.7 Hz), 4.39 (ddd, 1H, *J* = 1.6, 3.2, 12.5 Hz), 4.45 (ddd, 1H, *J* = 1.6, 3.2, 12.5 Hz), 5.52 (dq, 1 H, *J* = 1.4, 4.4 Hz).
^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.1, 26.1, 27.2 (x 3 C), 31.2, 31.4, 38.0, 38.8, 40.7, 43.5, 66.7, 121.0, 143.3, 178.1.
MS (ESI) for $C_{15}H_{25}O_2$: *m*/*z* calculated 237.2 $[M+H]^+$; *m*/*z* found (relative intensity) 237.2 $[M+H]^+$ (100).

***[(1S,5R)-6,6-dimethyl-4-oxobicyclo[3.1.1]hept-2-en-2-yl]methyl 2,2-dimethylpropanoate (S*M2)**[1,2]
To a suspension of chromium trioxide (2.4 g, 24.0 mmol, 12 eq) in dry DCM (20 mL) at -20°C was added 3,5-dimethylpyrazole (2.3 g, 24.0 mmol, 12 eq) in small portions. After stirring for 15 min a solution of ***S*M1** (500 mg, 2.0 mmol, 1 eq) in dichloromethane (5 mL) was added and the mixture was stirred at -20°C for 4 h. Aqueous sodium hydroxide solution (5 M, 5 mL) was added and the mixture was stirred at 0°C for 1 h. The organic phase was separated, washed with 10% aqueous HCl, brine, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (Hexane/ EtOAc 8:2) to give compound ***S*M2** (240 mg, 48%) as a colorless oil.
R_f 0.42 (Hexane/EtOAc 8:2).
$[\alpha]_D^{27}$: +152 (*c* = 1.5 $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.05 (s, 3 H), 1.27 (s, 9 H), 1.54 (s, 3 H), 2.15 (d, 1 H, *J* = 9.3 Hz), 2.46 (td, 1 H, *J* = 1.4, 5.9 Hz), 2.72 (td, 1 H, *J* = 1.7, 5.9 Hz), 2.89 (dt, 2 H, *J* = 5.5, 9.3 Hz), 4.72 (dd, 1H, *J* = 1.9, 16.6 Hz), 4.75 (dd, 1H, *J* = 1.9, 16.6 Hz), 5.89 (m, 1 H).
^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.0, 26.4, 27.1 (x 3 C), 38.7, 40.6, 45.3, 53.9, 58.0, 63.9, 119.1, 165.9, 172.2, 202.3.
MS (ESI) for $C_{15}H_{22}O_3$: *m*/*z* calculated 251.2 $[M+H]^+$; *m*/*z* found (relative intensity) 251.2 $[M+H]^+$ (100).

[(1S,5R)-4-hydroxy-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl]methyl 2,2-dimethylpropanoate (2b)
To a solution of ketone ***S*M2** (250 mg, 1.0 mmol, 1 eq) in dry THF (2 mL) at 0°C was added lithium tri-*tert*-butoxyaluminium hydride (254 mg, 1.0 mmol, 1 eq). The mixture was allowed to warm to room temperature and stirred for a further 4 h. The reaction was quenched with saturated aqueous ammonium chloride solution (2.5 mL) and extracted with diethyl ether. The combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (Hexane/ EtOAc 8:2) to give alcohol **2b** (229 mg, 91%, diastereomeric mixture) as a colorless oil.

R_f 0.40 (Hexane/EtOAc 8:2).
$[\alpha]_D^{27}$: 0 (c = 1.2 $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.03 (s, 3 H), 1.16 (s, 9 H), 1.31 (s, 3 H), 2.05 (t, 1 H, J = 5.2 Hz), 2.27 (ddd, 1 H, J = 2.6, 5.7, 8.1 Hz), 2.37 (bs, OH), 2.44 (dt, 1 H, J = 5.8, 9.2 Hz), 4.40-4.43 (m, 3 H), 5.61 (bs, 1 H).
^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.9, 26.7, 27.2 (x 3 C), 35.6, 38.8, 38.9, 44.0, 48.3, 65.8, 72.0, 122.3, 145.1, 178.2.
MS (ESI) for $C_{15}H_{24}O_3$: m/z calculated 253.2 $[M+H]^+$; m/z found (relative intensity) 253.2 $[M+H]^+$ (100).



(1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl]methyl acetate(R*M3*)
To a solution of a commercially available (1*R*,5*S*)-myrtenol (2.0 g, 13.16 mmol, 1 eq, ≥95% *ee*) in DCM 10 mL) was added dropwise acetic anhydride (1.37 mL, 14.47 mmol, 1.1 eq), Et_3N (7.3 mL, 52.63 mmol, 4 eq) and DMAP (112 mg, 0.92 mmol, 0.07 eq). The reaction was stirred for 2 h at room temperature. The mixture was washed with 10% aqueous hydrochloric acid, saturated aqueous bicarbonate solution, brine, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (Hexane/ EtOAc 1:1) to give compound ***R*M3** (2.1 g, 80%) as a colorless oil.
R_f 0.41 (Hexane/EtOAc 1:1).
$[\alpha]_D^{27}$: -53 (c = 1.8 $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.69 (s, 3 H), 1.05 (d, 1H, J = 8.7 Hz), 1.15 (s, 3 H), 1.88 (s, 3 H), 1.98 (d, 2H, J = 4.9 Hz), 2.14 (q, 2H, J = 17.9 Hz), 2.26 (d, 1H, J = 2.7 Hz), 4.26 (d, 1H, J = 12.6 Hz), 4.32 (d, 1H, J = 12.6 Hz), 5.41 (bs, 1 H).
^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.6, 20.8, 25.9, 31.1, 31.3, 37.8, 40.6, 43.4, 66.6, 121.0, 142.9, 170.3.
MS (ESI) for $C_{12}H_{19}O_2$: m/z calculated 195.1 $[M+H]^+$; m/z found (relative intensity) 195.1 $[M+H]^+$ (100).

(1R,5S)-6,6-dimethyl-4-oxobicyclo[3.1.1]hept-2-en-2-yl]methyl acetate (R*M4*)[4]
To a solution of ***R*M3** (1.0 g, 5.1 mmol, 1 eq, in *n*-butyl butanoate (10 mL) at -20°C diacetoxyiodobenzene (4.8 g, 15.3 mmol, 3 eq) and K_2CO_3 (350 mg, 2.5 mmol, 0.5 eq) were added. The mixture was vigorously stirred and a solution of *tert*-butyl hydroperoxide (3.6 mL, 18.4 mmol, 4 eq) was added dropwise over 30 minutes. The resulting solution was stirred for 8 hours at -20°C then was allowed to warm to room temperature, filtered to remove the solid and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (Hexane/ EtOAc 8:2) to give compound ***R*M4** (319 mg, 30%) as a colorless oil.
R_f 0.38 (Hexane/EtOAc 8:2).

$[\alpha]_D^{27}$: -146 (c = 1.0 $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.03 (s, 3 H), 1.53 (s, 3 H), 2.13 (m, 1 H), 2.15 (s, 3 H), 2.36 (td, 1 H, J = 1.3, 5.9 Hz), 2.71 (td, 1 H, J = 1.7, 5.9 Hz), 2.88 (dt, 1 H, J = 5.5, 9.3 Hz), 4.69 (dd, 1H, J = 1.9, 16.6 Hz), 4.78 (dd, 1H, J = 1.9, 16.6 Hz), 5.88 (m, 1 H).
^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.5, 21.9, 26.4, 40.7, 45.3, 54.1, 58.0, 64.0, 119.3, 165.7, 170.0, 202.7.
MS (ESI) for $C_{12}H_{16}O_3$: m/z calculated 209.1 $[M+H]^+$; m/z found (relative intensity) 209.1 $[M+H]^+$ (100).

(1R,5S)-4-hydroxy-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl]methyl acetate(2c)[1,2]

To a solution of ketone ***R*M4** (305 mg, 1.46 mmol, 1 eq) in dry THF (6 mL) at 0°C was added lithium tri-*tert*-butoxyaluminium hydride (599 mg, 2.2 mmol, 1.5 eq). The mixture was allowed to warm to room temperature and stirred for a further 4 h. The reaction was quenched with saturated aqueous ammonium chloride solution (5 mL) and extracted with diethyl ether. The combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (Hexane/ EtOAc 8:2) to give alcohol **2c** (158 mg, 75%, diastereomeric mixture) as a colorless oil.
R_f 0.35 (Hexane/EtOAc 7:3).
$[\alpha]_D^{27}$: 0 (c = 1.1 $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.05 (s, 3 H), 1.34 (m, 1 H), 1.36 (s, 3 H), 1.76 (bs, OH), 2.06 (s, 3H) 2.10 (m, 1 H), 2.31 (m, 1H), 2.50 (ddd, 1 H, J = 5.4, 6.2, 9.2 Hz), 4.49 (m, 3 H), 5.65 (bs, 1 H).
^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.9, 22.7, 26.7, 35.8, 38.9, 44.1, 48.4, 65.8, 73.0, 122.3, 145.1, 178.8.
MS (ESI) for $C_{12}H_{19}O_3$: m/z calculated 210.1 $[M+H]^+$; m/z found (relative intensity) 210.1 $[M+H]^+$ (100).

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3 I. A. Dvornikova, L. L. Frolova, A. V. Kuchin, I. P. Beletskaya, *Russ. J. Org. Chem.,* 2007, **43**, 352-358.
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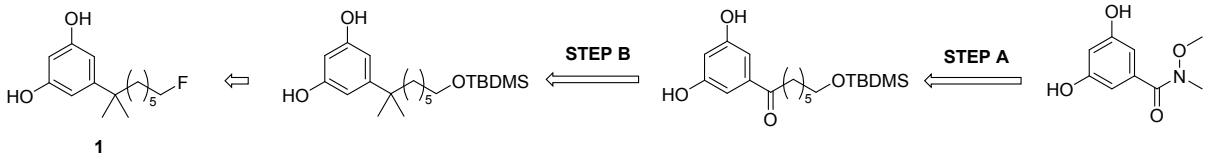
Synthesis of 1: Unsuccessful Approaches

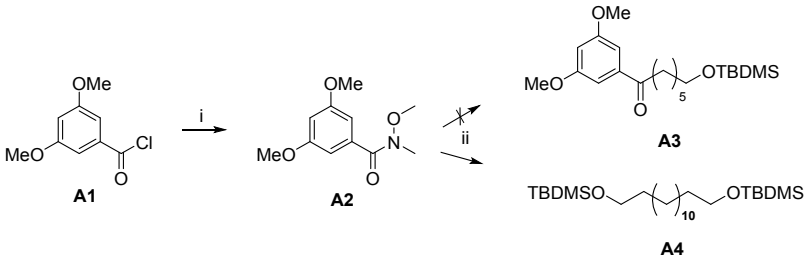
The first retrosynthetic approach to the fluorinated building block **1** (**Scheme S1**) was initially based on two steps: the insertion of the alkyl side chain (**A**) and the introduction of the *gem*-dimethyl group (**B**).



Scheme S1 First retrosynthetic approach to **1**

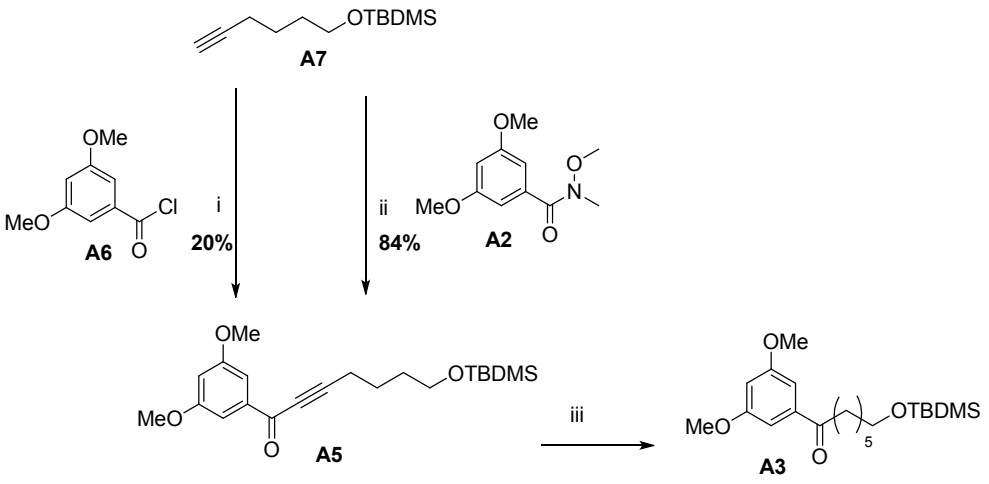
Step A: insertion of the alkyl side chain

In our first synthetic attempt (**Scheme S2**) the commercially available 3,5-dimethoxybenzoyl chloride **A1** was transformed into the corresponding Weinreb amide **A2** which was directly subjected to the reaction with the appropriate Grignard reagent (prepared from the 6-*tert*-butyldimethylsilyl hexyl bromide). Unfortunately, despite the different conditions tried, we were unable to isolate the desired ketone **A3** whereas we obtained only the by-product **A4** derived from the undesired Wurtz coupling.[5]



Scheme S2 *Reagents and conditions*: (i) *N*-methoxymethylamine hydrochloride, TEA, DCM, 0°C, on, 90%, (ii) 6-tert-butyldimethylsilyl hexyl bromide, Mg(0), THF, 0°C, 6 h.

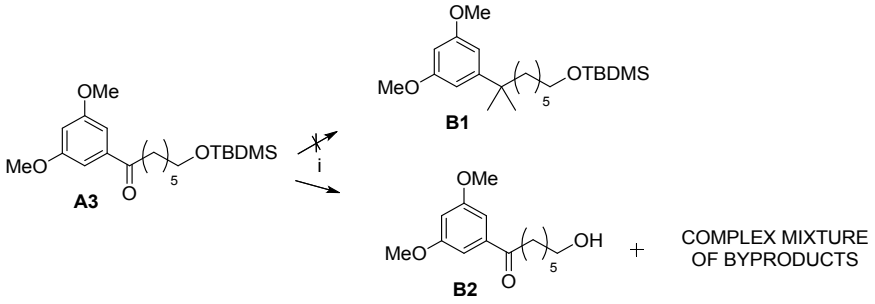
We, therefore, changed strategy, planning to synthesize the saturated ketone **A5** (**Scheme S3**) and then to hydrogenate it into the target compound **A3**. We explored both the Sonogashira reaction and the direct addition of terminal alkyne. Unfortunately, the palladium catalyzed cross coupling between the acetyl chloride **A6** and the TBDMS-protected alkyne **A7** gave unsatisfactory yields (20%) while the direct alkylation of the Weinreb amide **A2** with the same alkyne **A7** by means of *n*BuLi, occurred in good yield (80%).



Scheme S3 *Reagents and conditions*: (i) CuI (2%), $PdCl_2(PPh_3)_2$ (0.4%), TEA, rt, 12h, 20%; (ii) *n*BuLi, THF, -78 °C, 3h, 84%; (iii) 10% Pd, EtOAc, H_2, rt, 2h, 95%.

Step B: insertion of the of the gem-dimethyl group

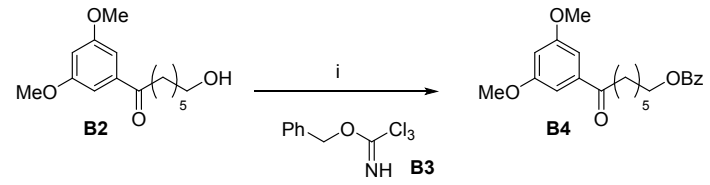
In order to insert the *gem*-dimethyl moiety in **A3** to give the target **B1** we opted for the Reetz reaction, inspired by the various successful examples present in the literature on similar substrates (**Scheme S4**). Unfortunately, **A3** proved to be unsuitable for this procedure.



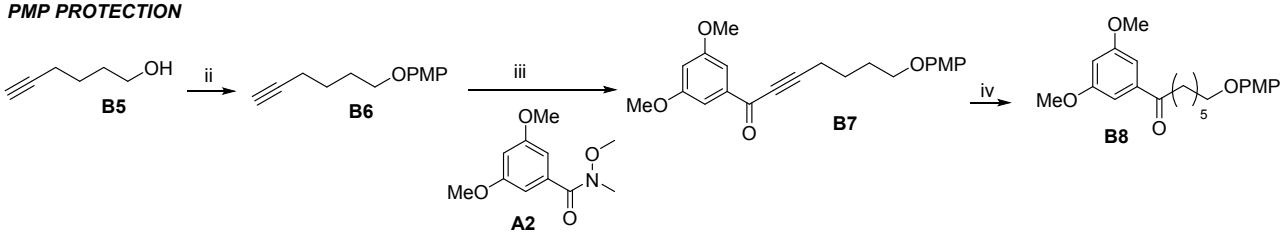
Scheme S4 *Reagents and conditions*: (i) $TiCl_4$, $Zn(CH_3)_2$, DCM, -30 °C to rt, 6 h (and plenty of other different conditions).

In fact, despite countless attempts using different reaction temperatures, organozinc reagents, solvents, Lewis acids and reaction times, we were able to isolate only complex mixtures of products and the undesired alcohol **B2**. We then decided to change the protecting group on the terminal OH trying both the benzyl and the PMP group that are known to tolerate acidic conditions[6] (**Scheme S5**).

BENZYL PROTECTION



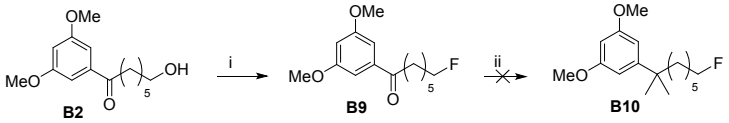
PMP PROTECTION



Scheme S5 *Reagents and conditions*: (i) CF_3SO_3H, DCM, rt, 3h, 90%; (ii) 4-methoxyphenol, PPh_3, DIAD, THF, rt, 2h, 70%; (iii) *n*BuLi, THF, -78 °C, 3h, 85%; (iv) 10% Pd, EtOAc, H_2, rt, 3h, 95%.

The benzyl group was introduced by means of the reaction between alcohol **B2** and the freshly synthesised[7] benzyl trichloroacetimi date **B3**, to give compound **B4**.
The PMP group was introduced on the alcohol **B5** by means of the Mitsunobu reaction, subsequently, the resulting alkyne **B6**, was subjected to the coupling with the Weinreb amide **A2** in order to give ketone **B7** which was hydrogenated to provide the saturated compound **B8**. Unfortunately, even in this case, the Reetz reaction both using **B4** and **B8** failed and the alcohol **B2** was the only isolated product.

At this point we decided to invert the synthetic pathways (**Scheme S6**), introducing the terminal fluorine atom before the *gem*-dimethyl group, in order to perform the Reetz reaction on the fluorinated derivative **B9**.
Even if the fluorination reaction occurred in excellent yields and we were able to obtain compound **B9** effectively, the subsequent Reetz reaction once again did not work. Even in this scenario, performing the Reetz reaction under different conditions did not lead to the formation of the desired molecule **B10** but only to a complex mixture of cyclic and linear products.



Scheme S6 *Reagents and conditions*: (i) DAST, THF, 2h, 84%; (ii) $TiCl_4$, $Zn(CH_3)_2$, DCM, -30 °C to rt, 6 h (and plenty of other different conditions).

Conclusion

Due to the inability to introduce the geminal dimethyl function employing the Reetz reaction we decided to change our retrosynthetic approach as described in the main paper.

5 C. J. Baylis, S. W. D. Odle, J. H. P. Tyman, *J. Chem. Soc., Perkin Trans.*, 1981, **24**, 132-141.
6 T. W. Green, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, Wiley-Interscience, New York, 1999, **76-86**, 708-711.
7 L. E. Overman, *J. Am Chem Soc,* 1976, 2901-2910.

Chiral HPLC Purification of (-)-(*R*,*R*)-HU-210F and (+)-(*S*,*S*)-HU-211F

The determination of the enantiomeric purity of the cannabinoids mimics (-)-(*R,R*)-**HU-210F** and (+)-(*S,S*)-**HU-211F** was performed by HPLC. The compounds were first injected separately into the HPLC, then together as a mixture, in order to establish the retention time of each enantiomer and confirm the separation of the two peaks and thus the efficiency of the analytical method.

The analytical HPLC was performed on an amylose-based analytical chiral column ChiralPak AD-I, 250x4.6mm, 5μm particle size (Daicel Ltd), as mobile phase a mixture of Hexane : IPA (96%-4% v/v) was used, in isocratic condition and with 1mL/min of flow rate (as reported previously for the separation of HU-210 and HU-211).[4]

The analytical HPLC analyses showed that compound (-)-(*R,R*)-**HU-210F** has a retention time of 40.2 minutes and an *ee* of about 97:3 while compound (+)-(*S,S*)-**HU-211F** has a retention time of 27.5 minutes and an *ee* of about 99:1. The enantiomeric excess calculated by HPLC are consistent whit the enantiomeric purity of the commercially available starting materials: for (-)-(*R,R*)-**HU-210F** we started from (1*R*,5*S*)-myrtenol ≥95% *ee* and for (+)-(*S,S*)-**HU-211F** we started from (+)-α-pinene ≥99 % *ee.*

In order to perform the biological tests we decided to purify both the enantiomers *via* HPLC. The HPLC separations were performed on an amylose-based Semi-prep. chiral column ChiralPak AD-I, 250x20mm, 5μm particle size (Daicel Ltd), as mobile phase a mixture of Hexane : IPA (92%-8% v/v) was used, in isocratic condition and with 5mL/min of flow rate.

Using the Semi-prep. conditions (-)-(*R,R*)-**HU-210F** showed a retention time of 14.2 minutes, while (+)-(*S,S*)-**HU-211F** 10.6 minutes. After the separation, an HPLC spectra of the two compounds (and of a mixture of them) were recorded to confirm theirs enantiopiurity.

[4] Patent WO2004050011A2 - High enantiomeric purity dexanabinol for pharmaceutical copositions - Google Patents http://www.google.com/patents/WO2004050011A2?cl=en (accessed Feb 2, 2015).

Radio synthesis of (-)-(*R*,*R*)-[^{18}F]HU210

The radiosynthesis of [^{18}F]HU210F was carried out using a remotely controlled synthesis module Eckert&Ziegler ModularLab synthesizer (Figure S1). Prior to the EOB, vial PO4 was filled with KH_2PO_4 aqueous solution (0.5 mL, 10 mg/mL), and vial K222 was filled with Kryptofix 2.2.2 (15 mg) in dry acetonitrile (1 mL). Vial ACN was filled with 1 mL of dry acetonitrile and vial PREC was filled with precursor 14b (7.7 mg) dissolved in 1 mL of dry acetonitrile.

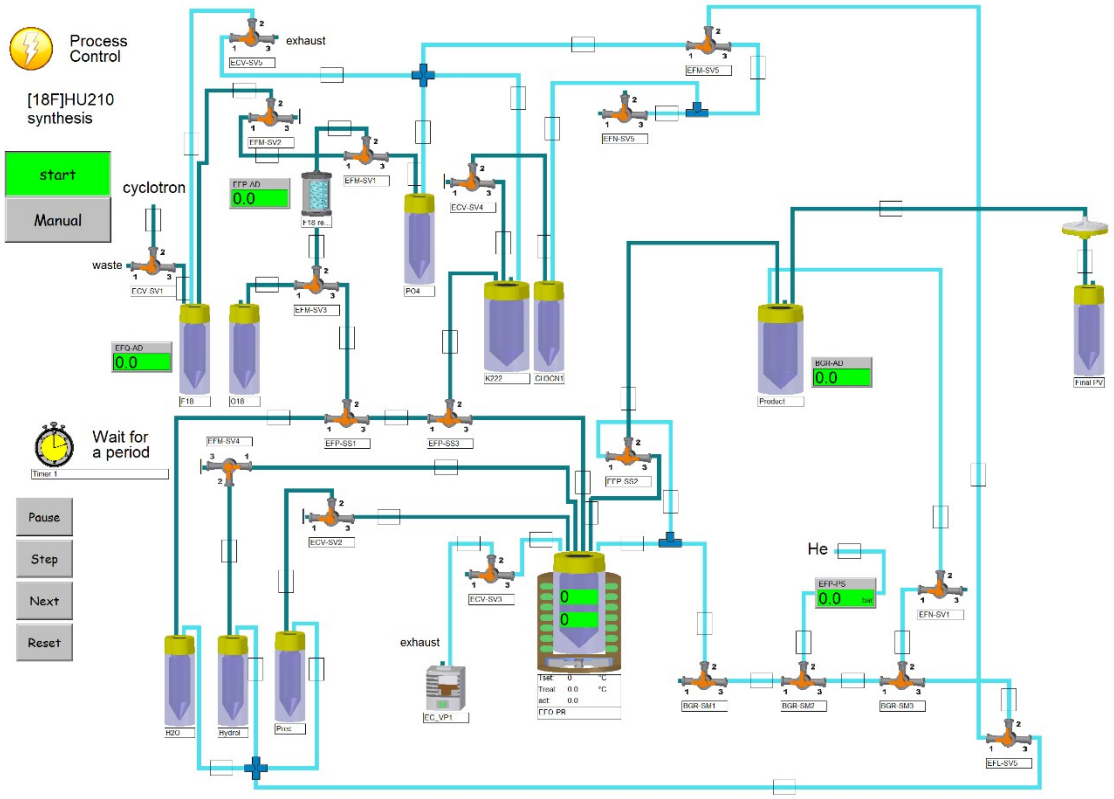
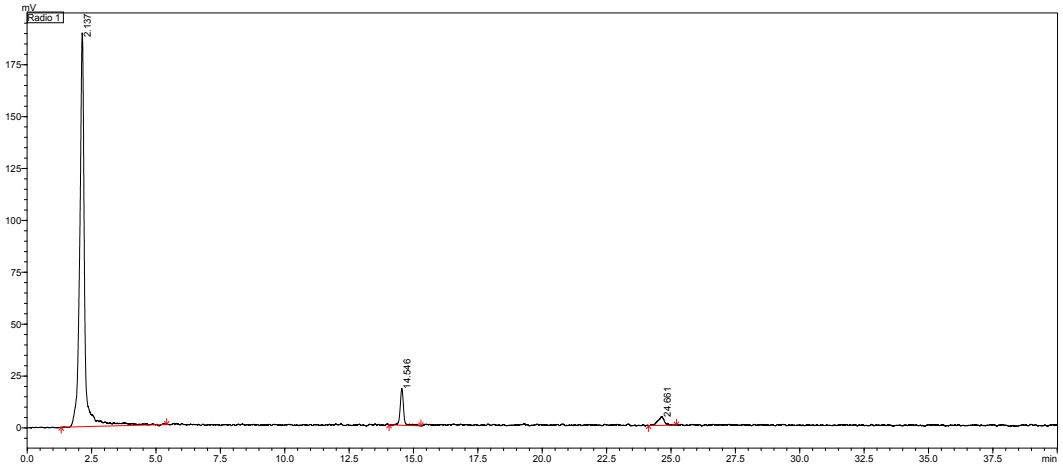


Figure S1. Graphical rappresentation of the Eckert&Ziegler Modular Lab reactor used for the production of **[^{18}F]HU210F**.

After the EOB [^{18}F]-fluoride was unloaded and transferred with argon gas to the synthesis module, which was contained in a lead shielded hot cell. The [^{18}F]-fluoride was subsequently isolated using a CHROMAFIX anion exchange cartridge (Macherey Nagel, Germany) and then eluted into the reaction vessel with the dipotassium hydrogen orthophosphate solution (vial PO4). The solution in vial K222 was added to the reaction vessel and the azeotropic mixture of water and acetonitrile was evaporated under vacuum using a stream of helium. The content of the vial ACN was then added and the mixture was evaporated under vacuum using a stream of helium to ensure formation of the dried complex [K/K222]^{18}F.
Precursor **14b** in vial PREC was then added and the reaction mixture was heated at 100˚C for 15 minutes to produce the fluorinated desired product **[^{18}F]HU210** (Radiochemical conversion by RadioHPLC of 6%, Figure S2).



Peak#	Ret. Time	Area	Height	Name	Area%
1	2.137	2449321	189263	Unreacted [18F]fluoride	91.212
2	14.546	162049	17546	**[^{18}F]HU210**	6.035
3	24.661	73942	4126	Unknown product	2.754
Total		2685311	210935		100.000

Figure S2. Radio-HPLC chromatogram of crude mixture (**[^{18}F]HU210** Rt=14.546 min)

Since precursor **14b (**Rt 16.5 min**)** and desired product (Rt 14.5 min) had a good separation, HPLC purification of the crude mixture was attempted. An aliquot (100 µL, 120 MBq) of the crude mixture was purified by semipreparative HPLC (Phenomenex Luna C18(2) column 10x250 mm 100Å 5 µm, 5 mL/min) using a linear gradient reported in Table S1, affording 4.65 Mbq of **[^{18}F]HU210**; the collected peak was contaminated by approx. 20% of unreacted [^{18}F]fluoride (Figure S3, black trace).

Table S1. Linear gradient for Radio-HPLC analysis and purification

Time [min]	% H_2O	% ACN
0	50	50
15	0	100
30	0	100

Identity of the product was confirmed by comparison with cold reference (Figure S3). (–)-(*R*,*R*)-**[^{18}F]HU210** production was achieved using a non-optimised procedure.

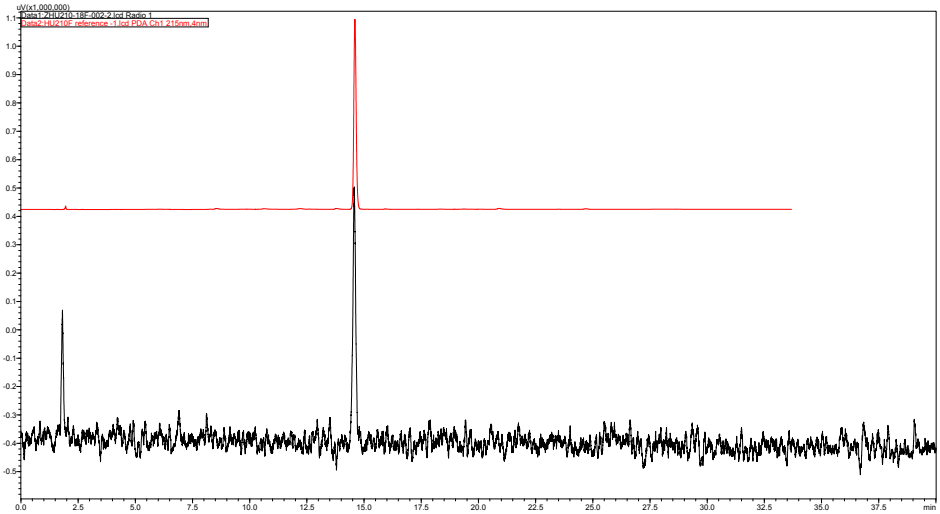
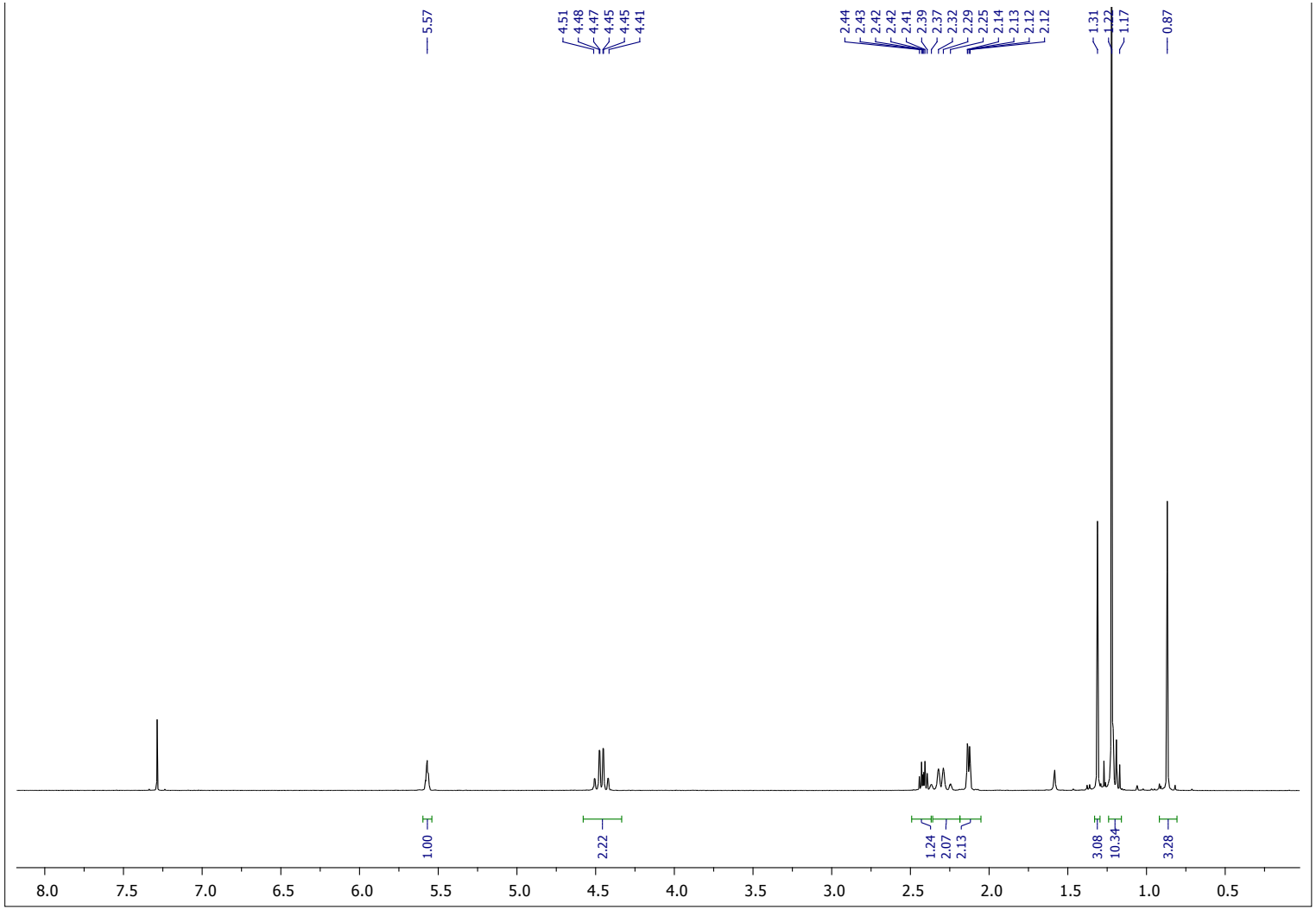
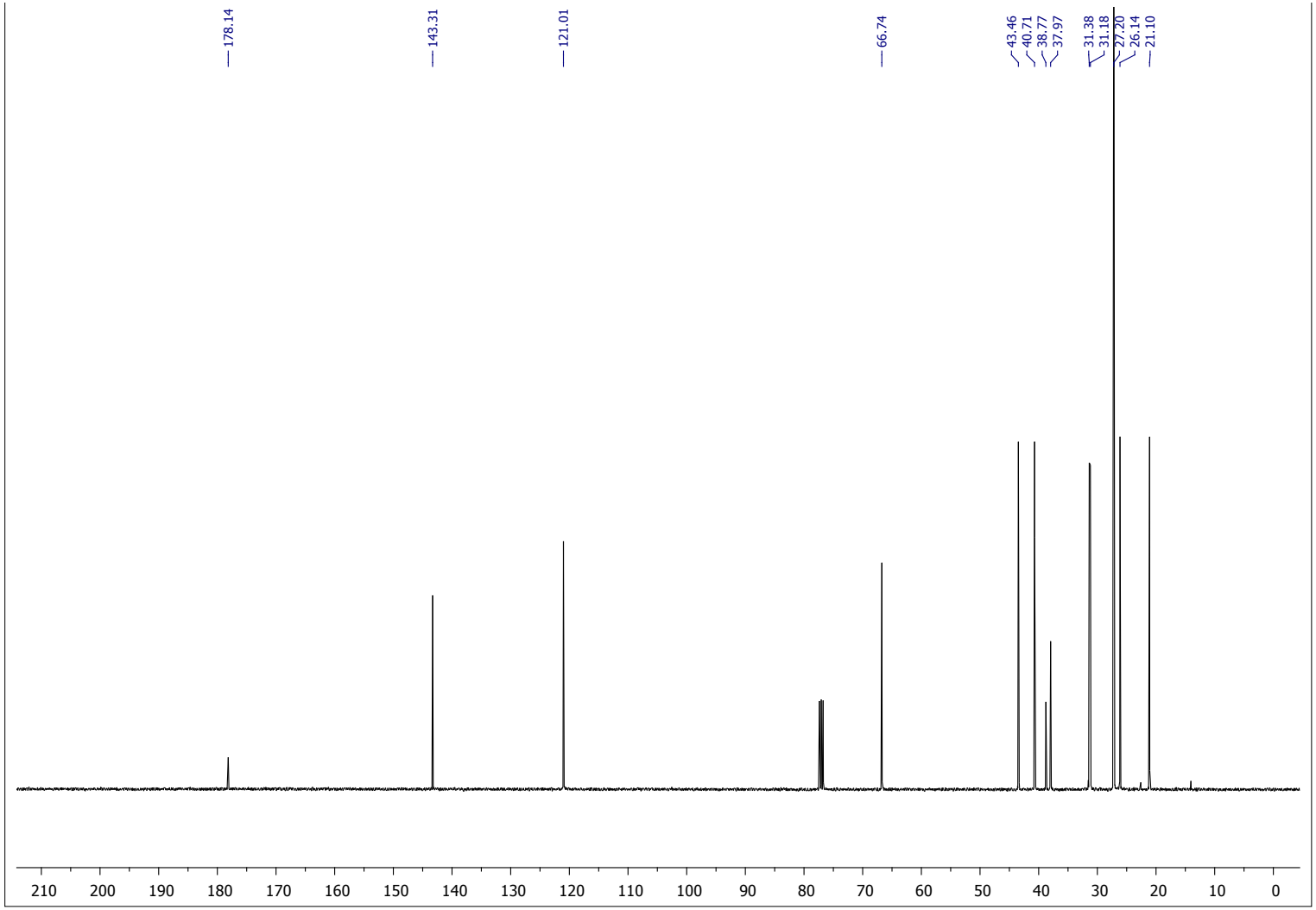


Figure S3. Radio-HPLC chromatogram of purified **[^{18}F]HU210** Rt=14.570 (black trace) and cold reference **HU210F** Rt 14.600 min (red trace)

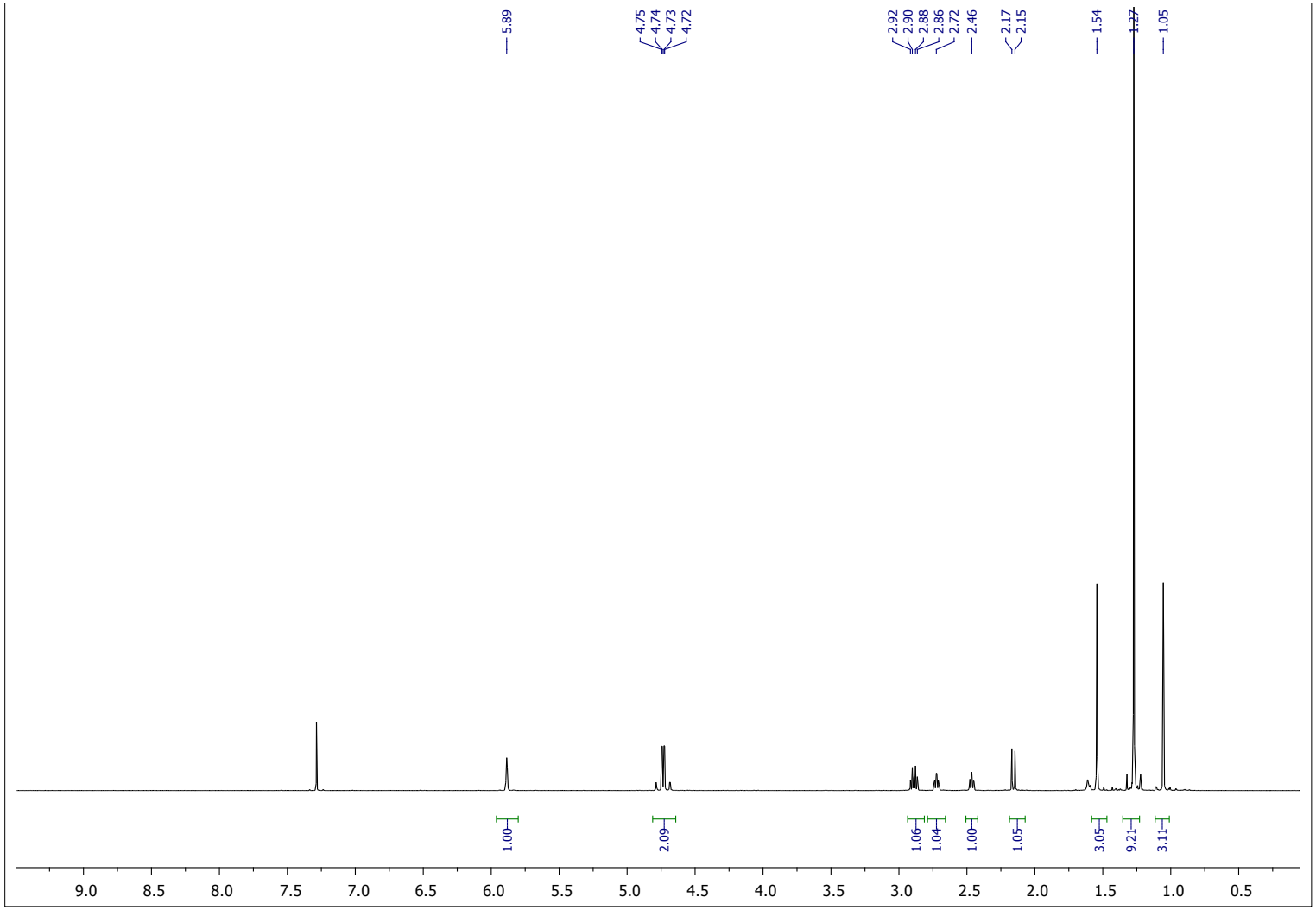
^{1}H NMR of ***R*M1**


5.57
4.51
4.48
4.47
4.45
4.45
4.41
2.44
2.43
2.42
2.42
2.41
2.39
2.37
2.32
2.29
2.25
2.14
2.13
2.12
2.12
1.31
1.22
1.17
0.87
1.00
2.22
1.24
2.07
2.13
3.08
10.34
3.28
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

^{13}C NMR of *R*M1



^{1}H NMR of ***R*M2**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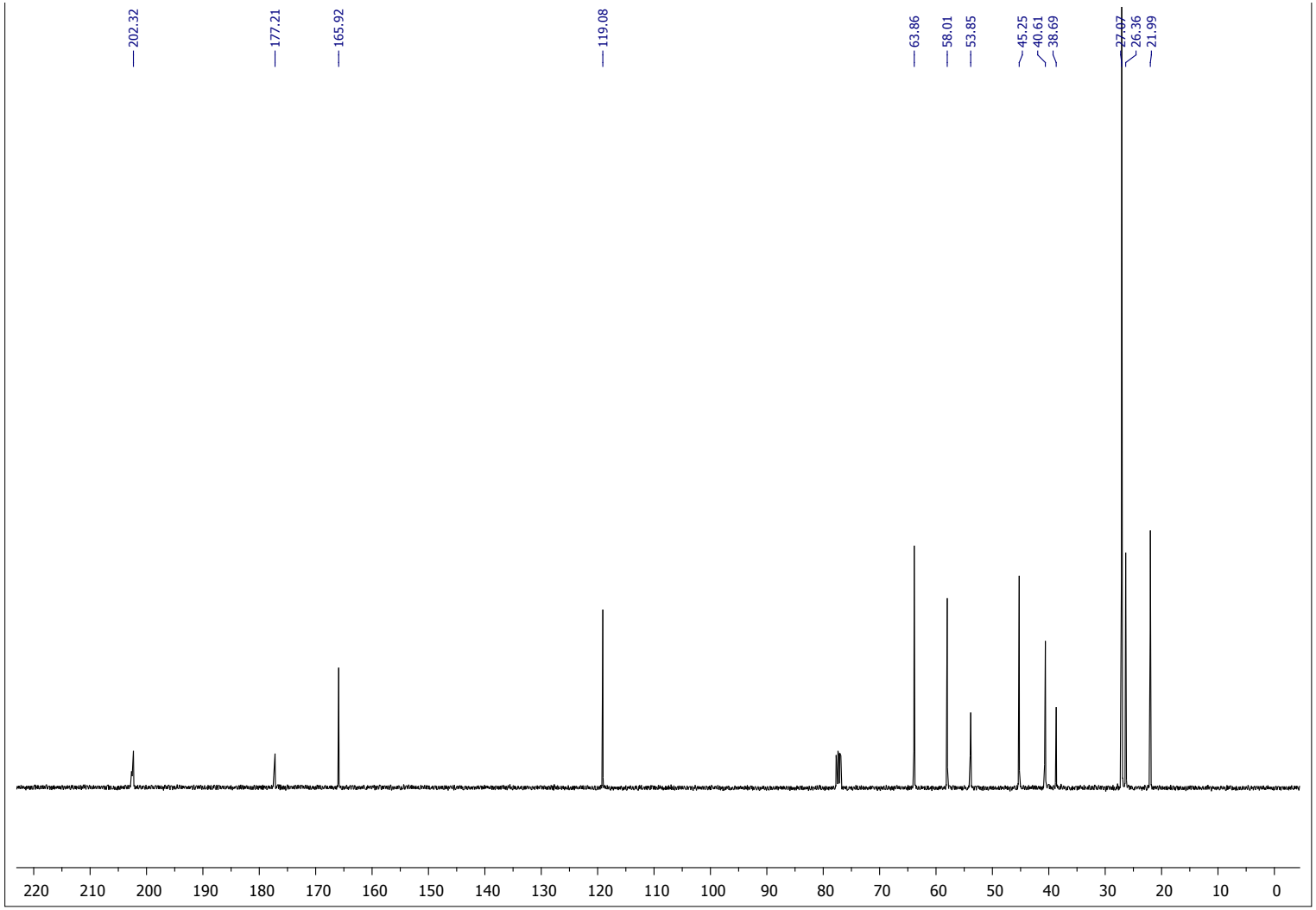
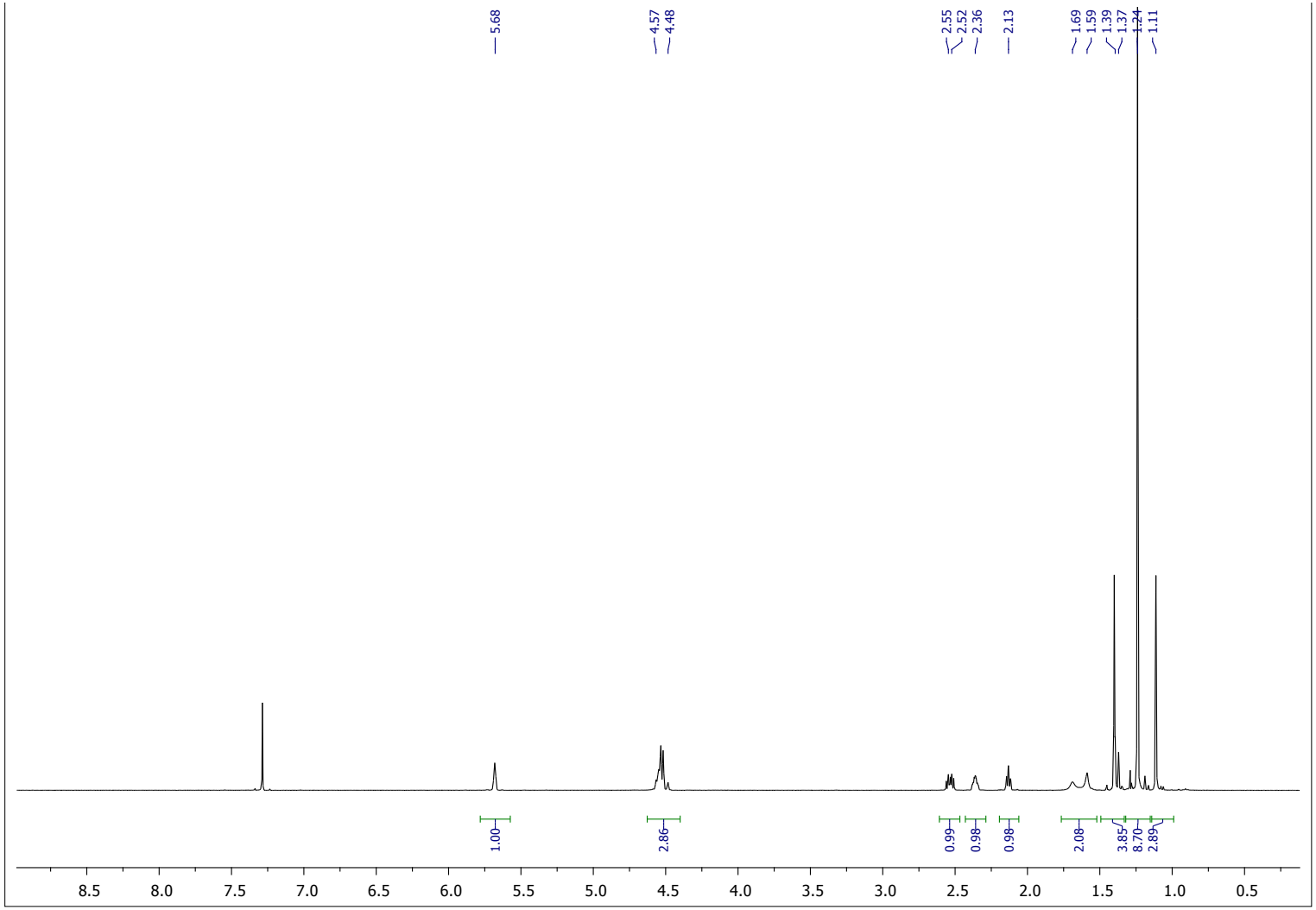
4.75
4.74
4.73
4.72
2.92
2.90
2.88
2.86
2.72
2.46
2.17
2.15
1.54
1.27
1.05
1.00
2.09
1.06
1.04
1.00
1.05
3.05
9.21
3.11
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

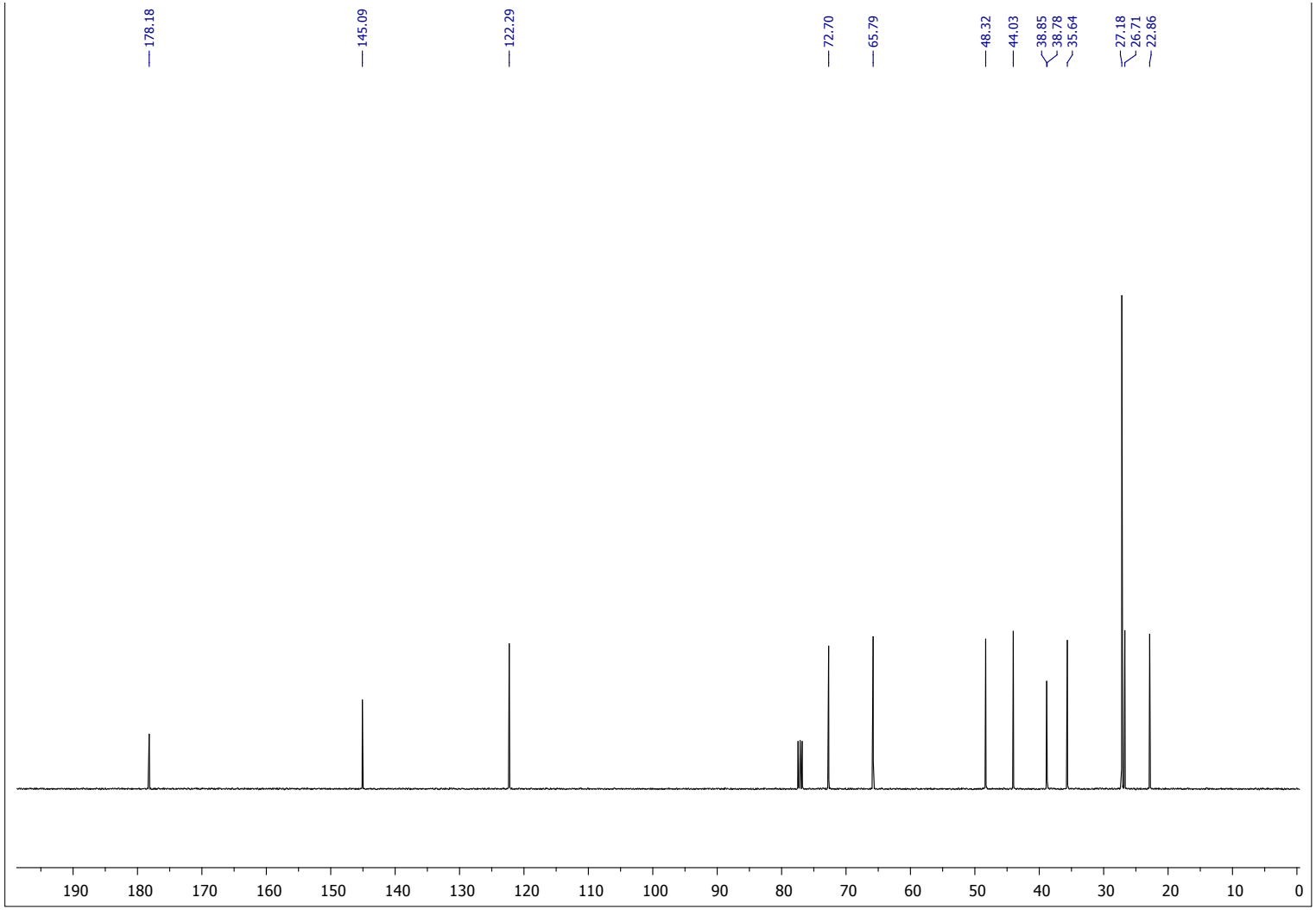
^{13}C NMR of *R*M2



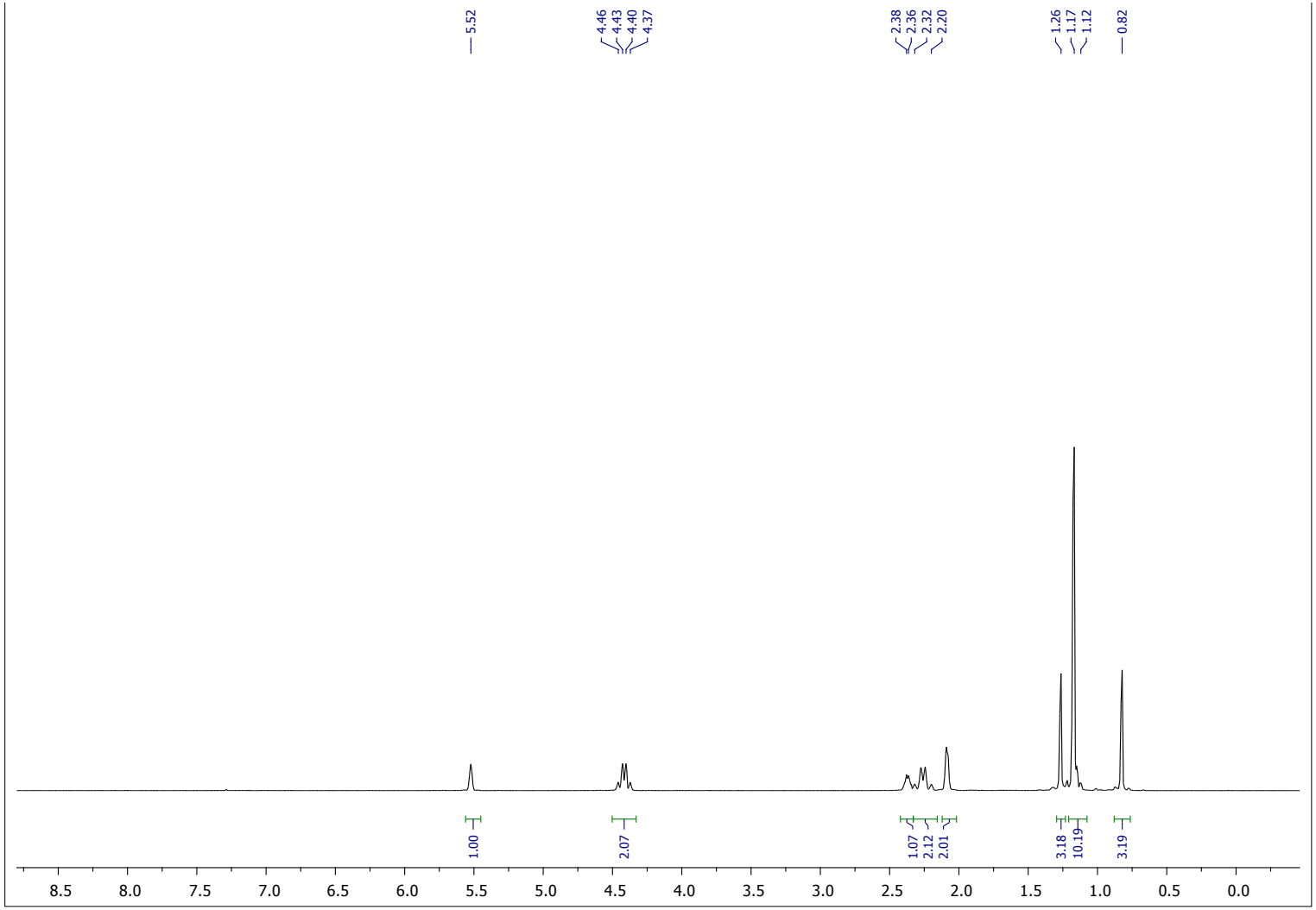
^{1}H NMR of **2a**


5.68
4.57
4.48
2.55
2.52
2.36
2.13
1.69
1.59
1.39
1.37
1.24
1.11
1.00
2.86
0.99
0.98
0.98
2.08
3.85
8.70
2.89
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

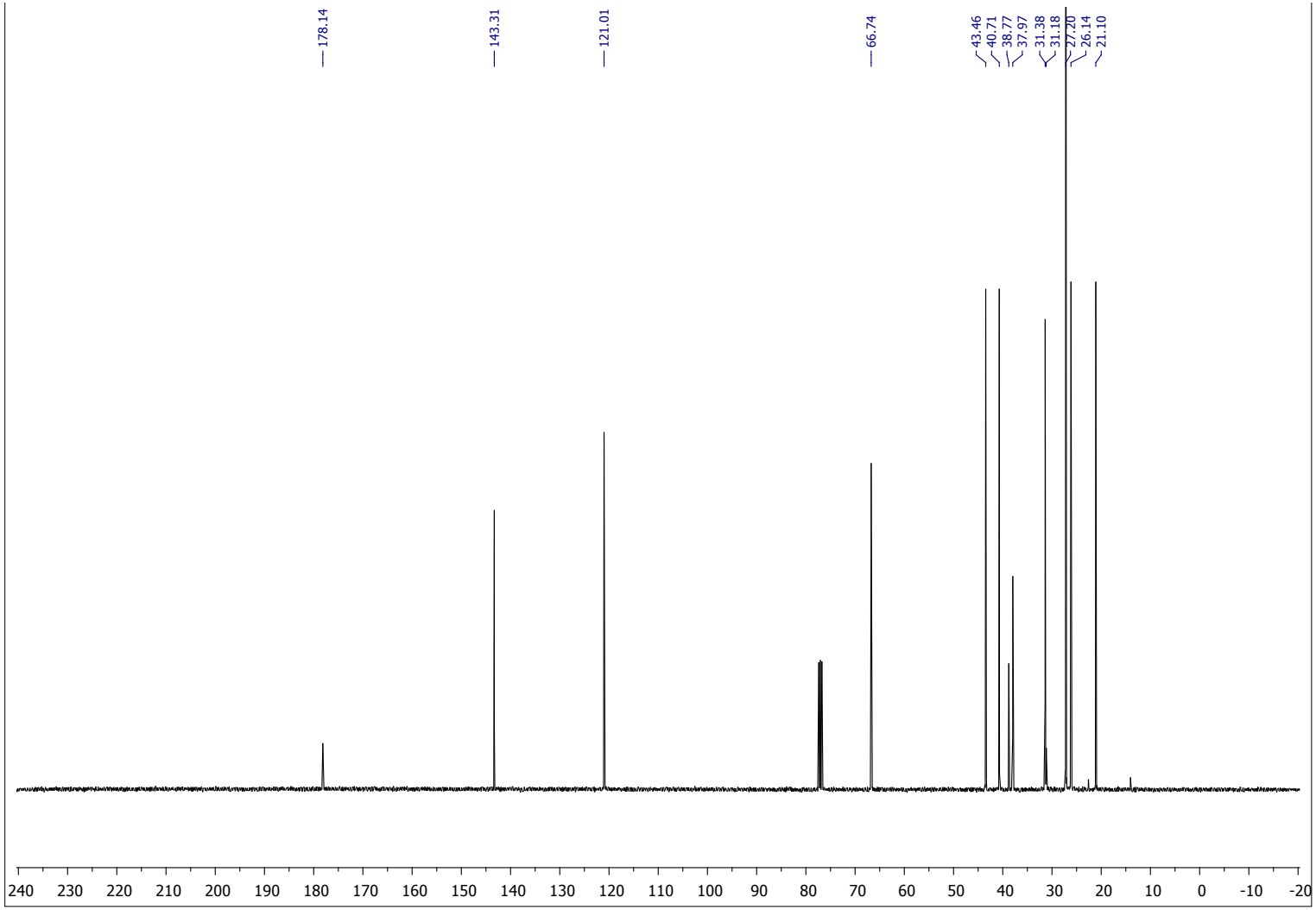
^{13}C NMR of **2a**


178.18
145.09
122.29
72.70
65.79
48.32
44.03
38.85
38.78
35.64
27.18
26.71
22.86
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

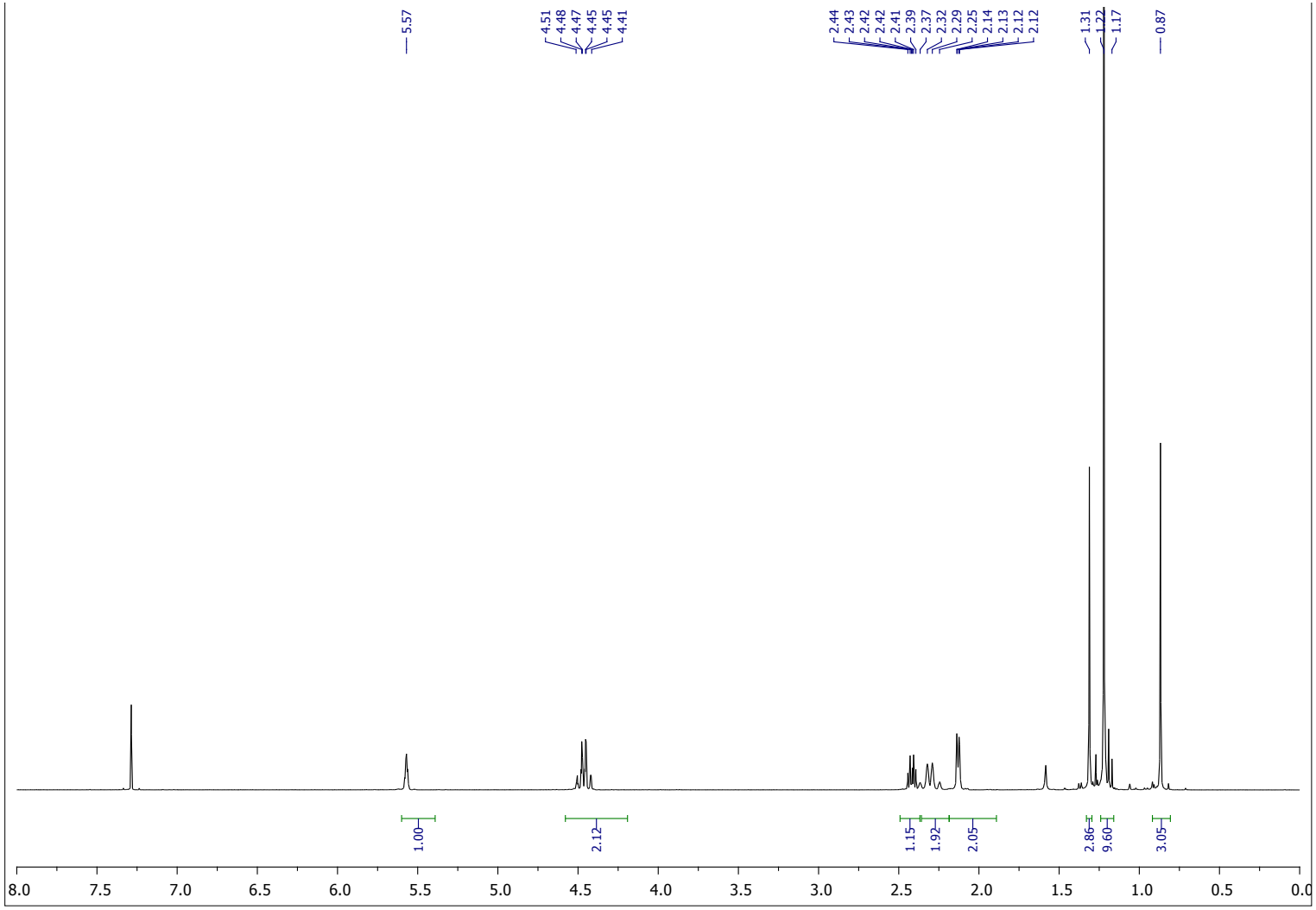
^{1}H NMR of ***S*M1**


5.52
4.46
4.43
4.40
4.37
2.38
2.36
2.32
2.20
1.26
1.17
1.12
0.82
1.00
2.07
1.07
2.12
2.01
3.18
10.19
3.19
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

^{13}C NMR of *S*M1



^{1}H NMR of ***S*M2**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4.51
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4.45
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2.44
2.43
2.42
2.42
2.41
2.39
2.37
2.32
2.29
2.25
2.14
2.13
2.12
2.12
1.31
1.22
1.17
0.87
1.00
2.12
1.15
1.92
2.05
2.86
9.60
3.05
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
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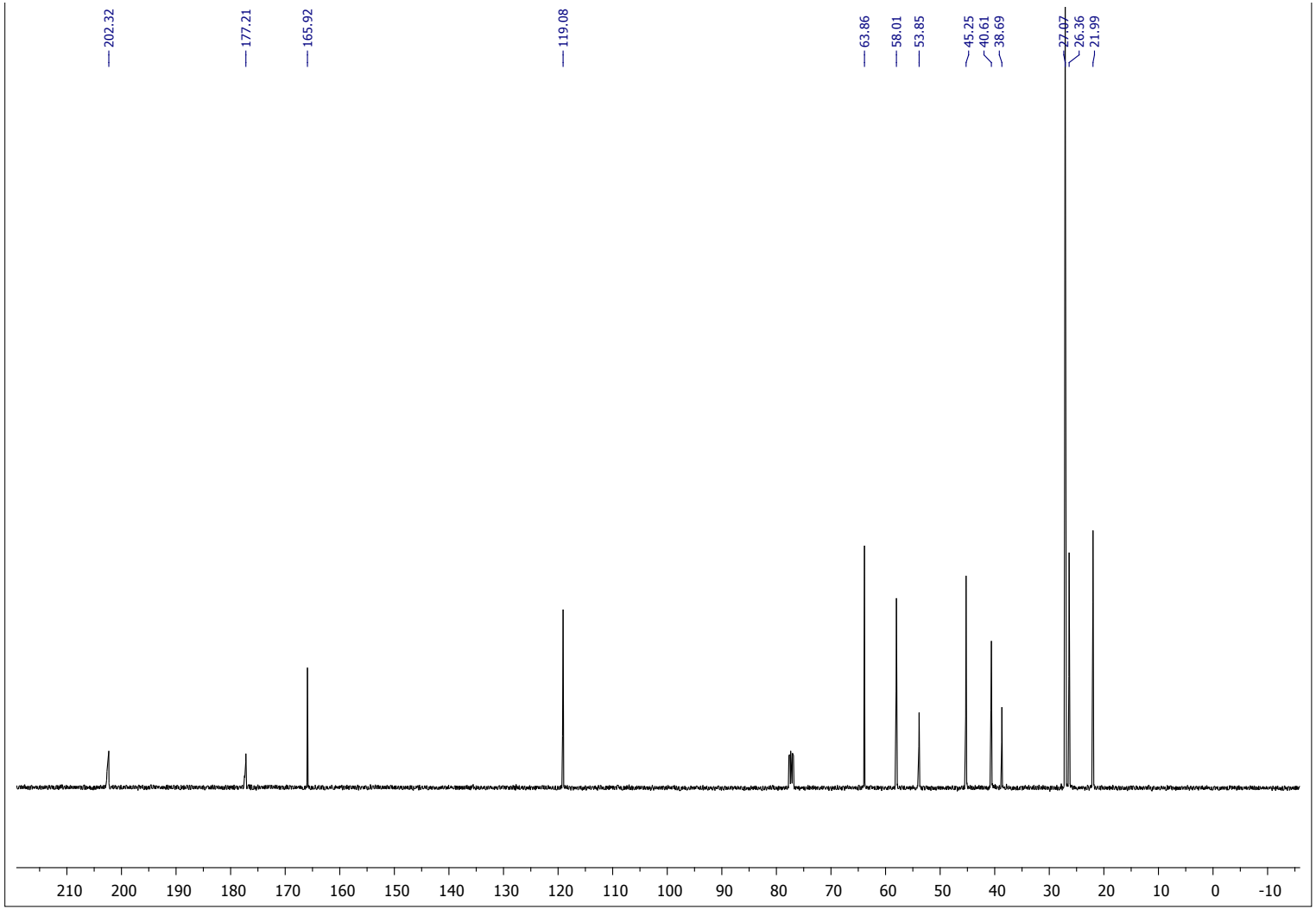
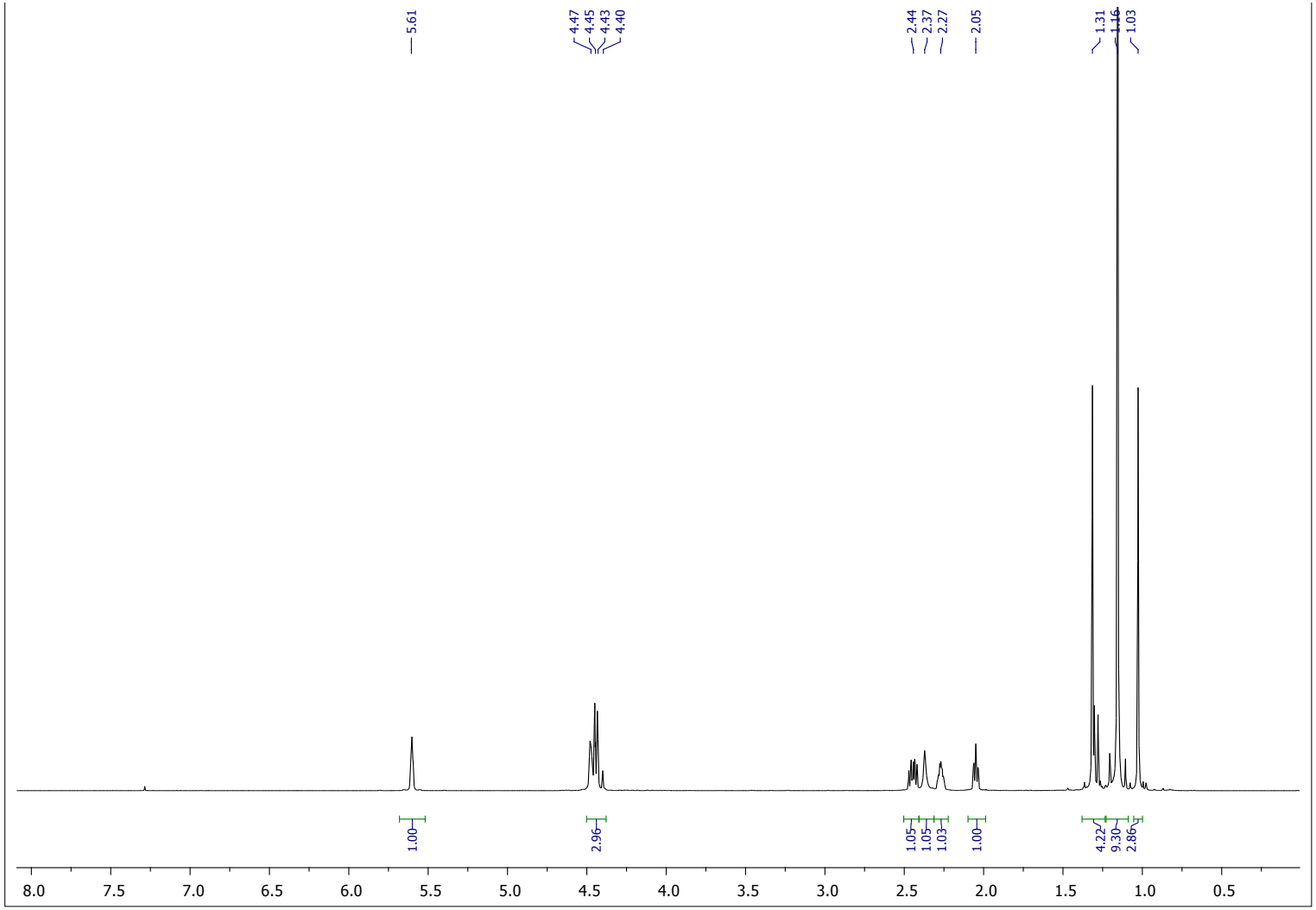
0.0

^{13}C NMR of *SM2*



^{1}H NMR of **2b**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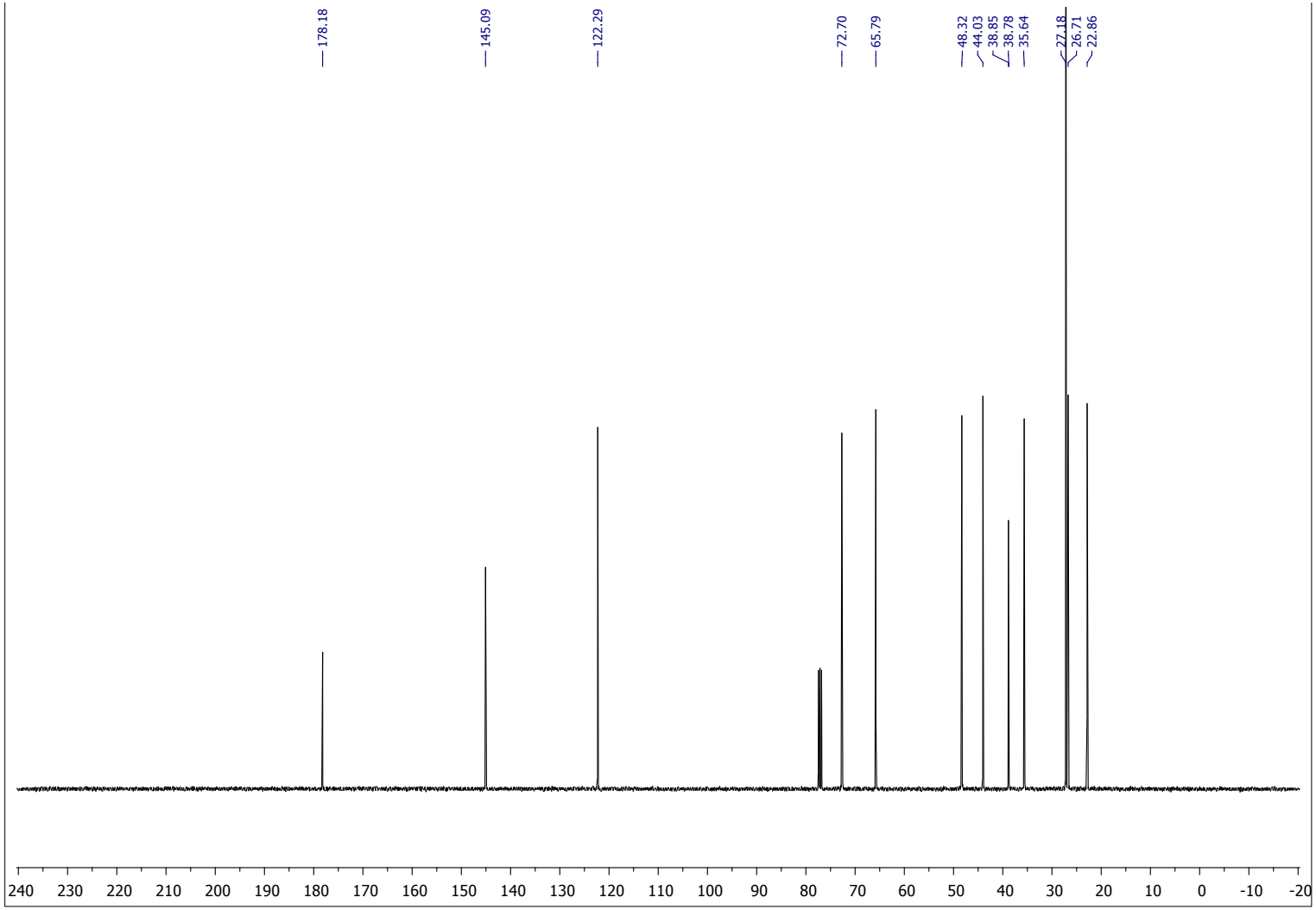
4.47
4.45
4.43
4.40
2.44
2.37
2.27
2.05
1.31
1.16
1.03
1.00
2.96
1.05
1.05
1.03
1.00
4.22
9.30
2.86
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

^{13}C NMR of **2b**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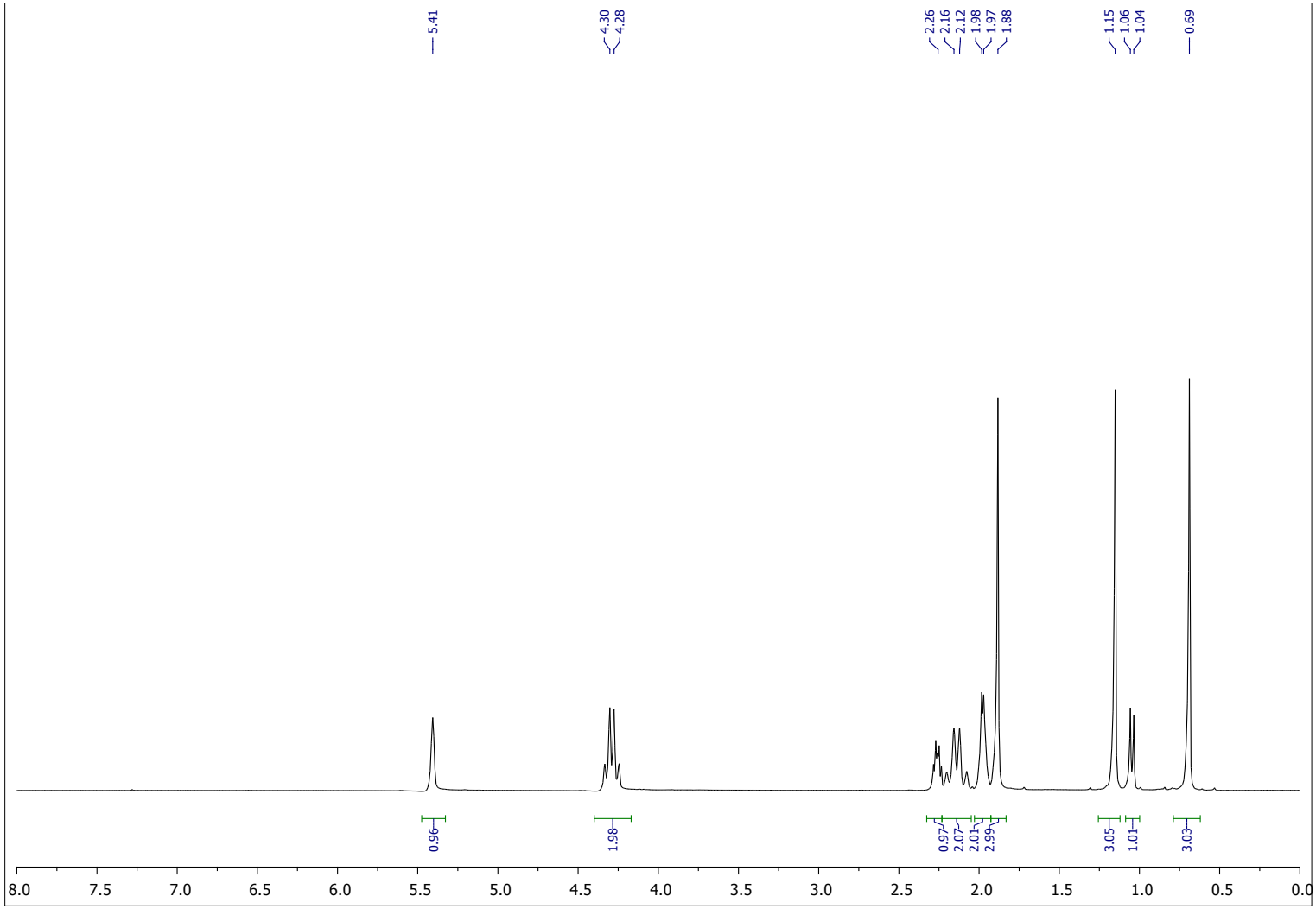
145.09
122.29
72.70
65.79
48.32
44.03
38.85
38.78
35.64
27.18
26.71
22.86
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20

^{1}H NMR of ***R*M3**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2.16
2.12
1.98
1.97
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1.15
1.06
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0.69
0.96
1.98
0.97
2.07
2.01
2.99
3.05
1.01
3.03
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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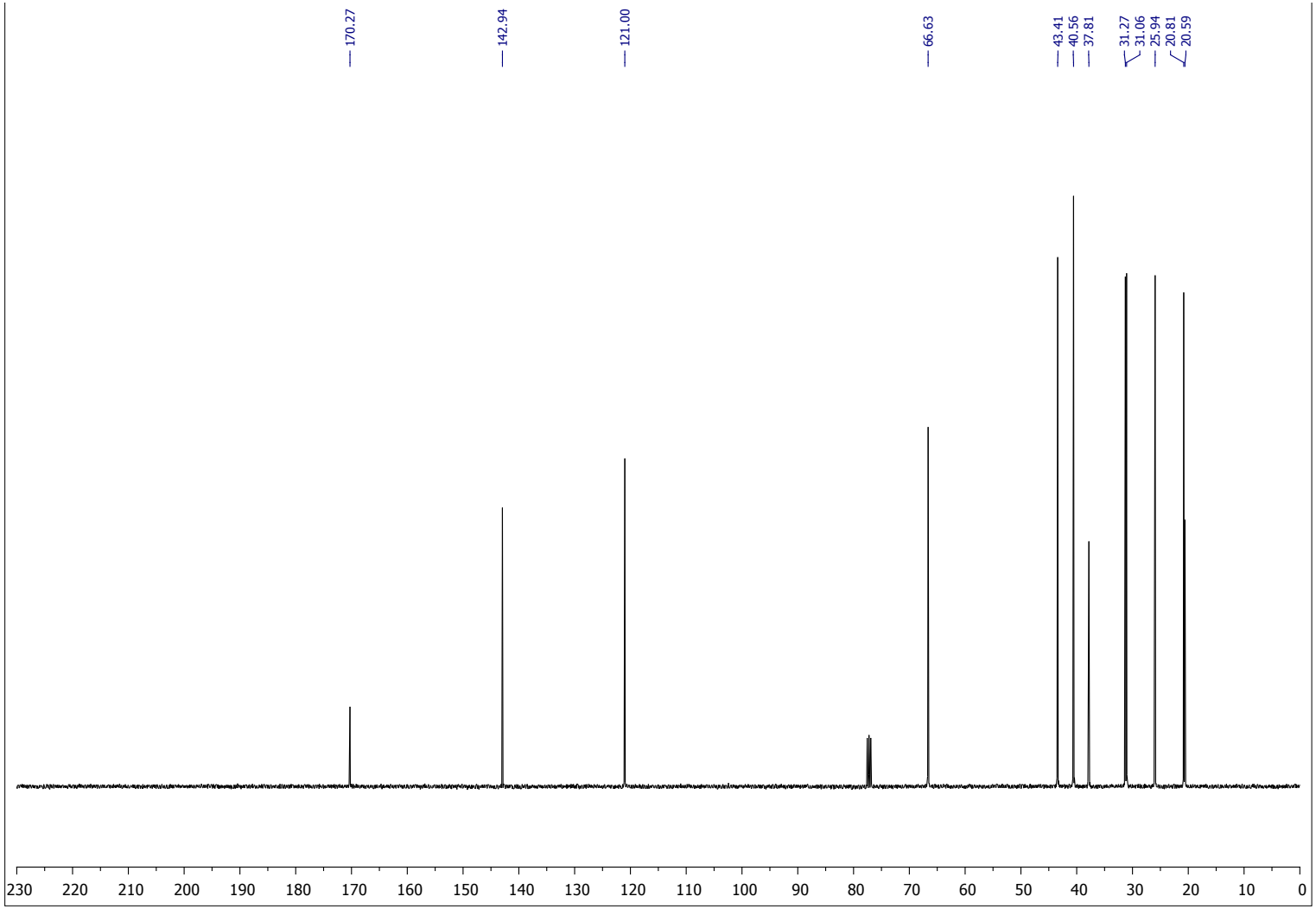
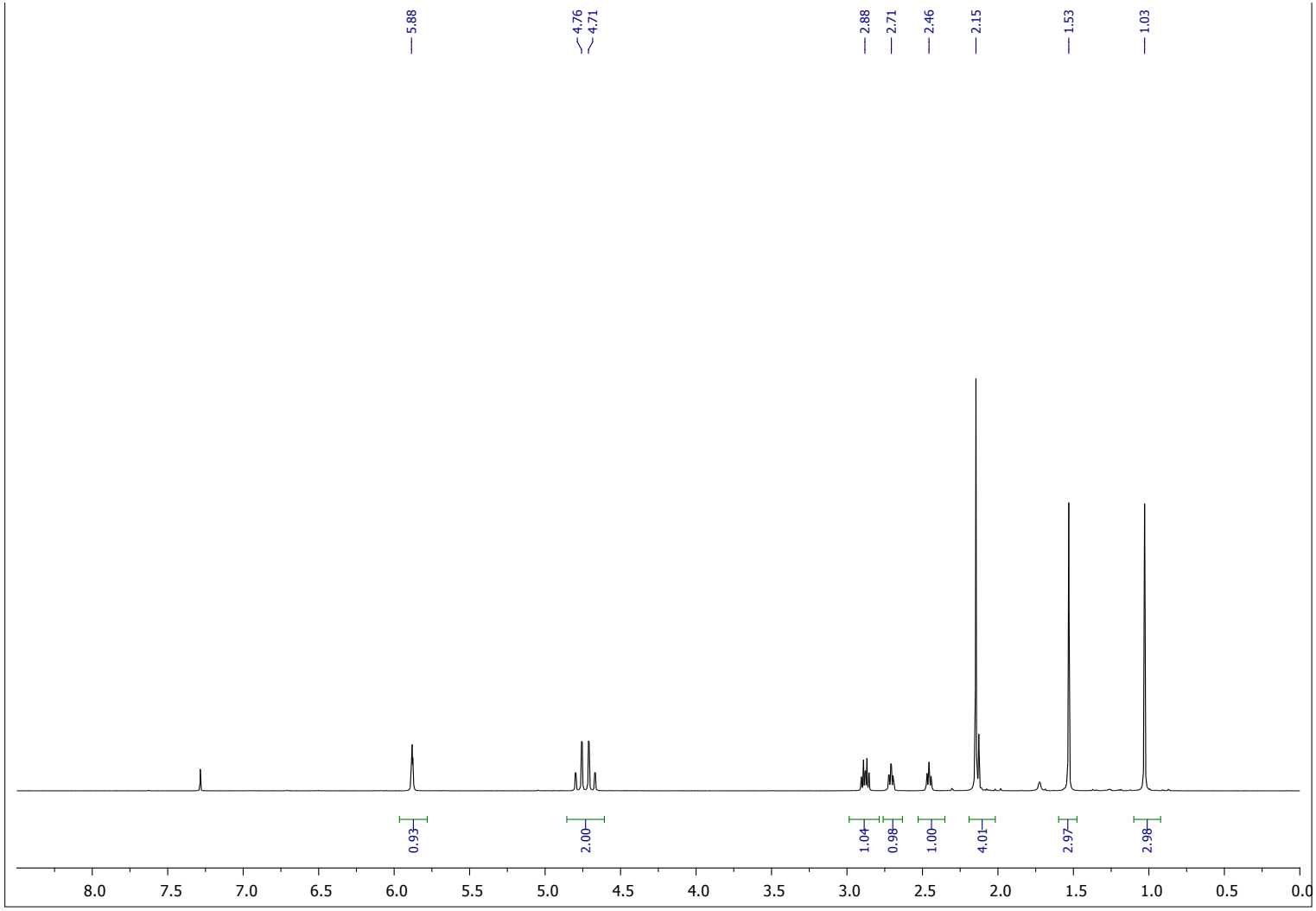
3.0
2.5
2.0
1.5
1.0
0.5
0.0

^{13}C NMR of *R*M3



^{1}H NMR of ***R*M4**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1.00
4.01
2.97
2.98
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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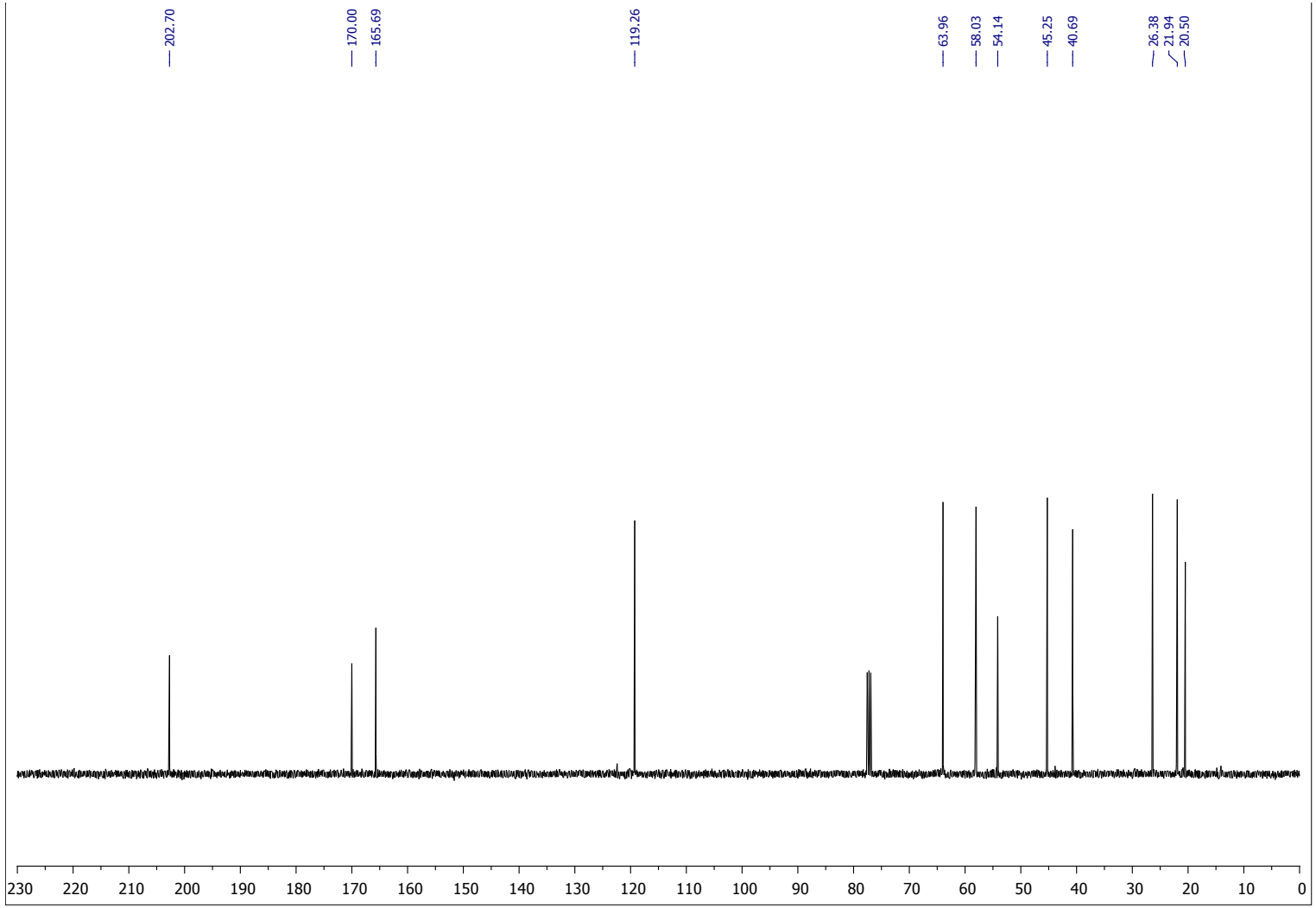
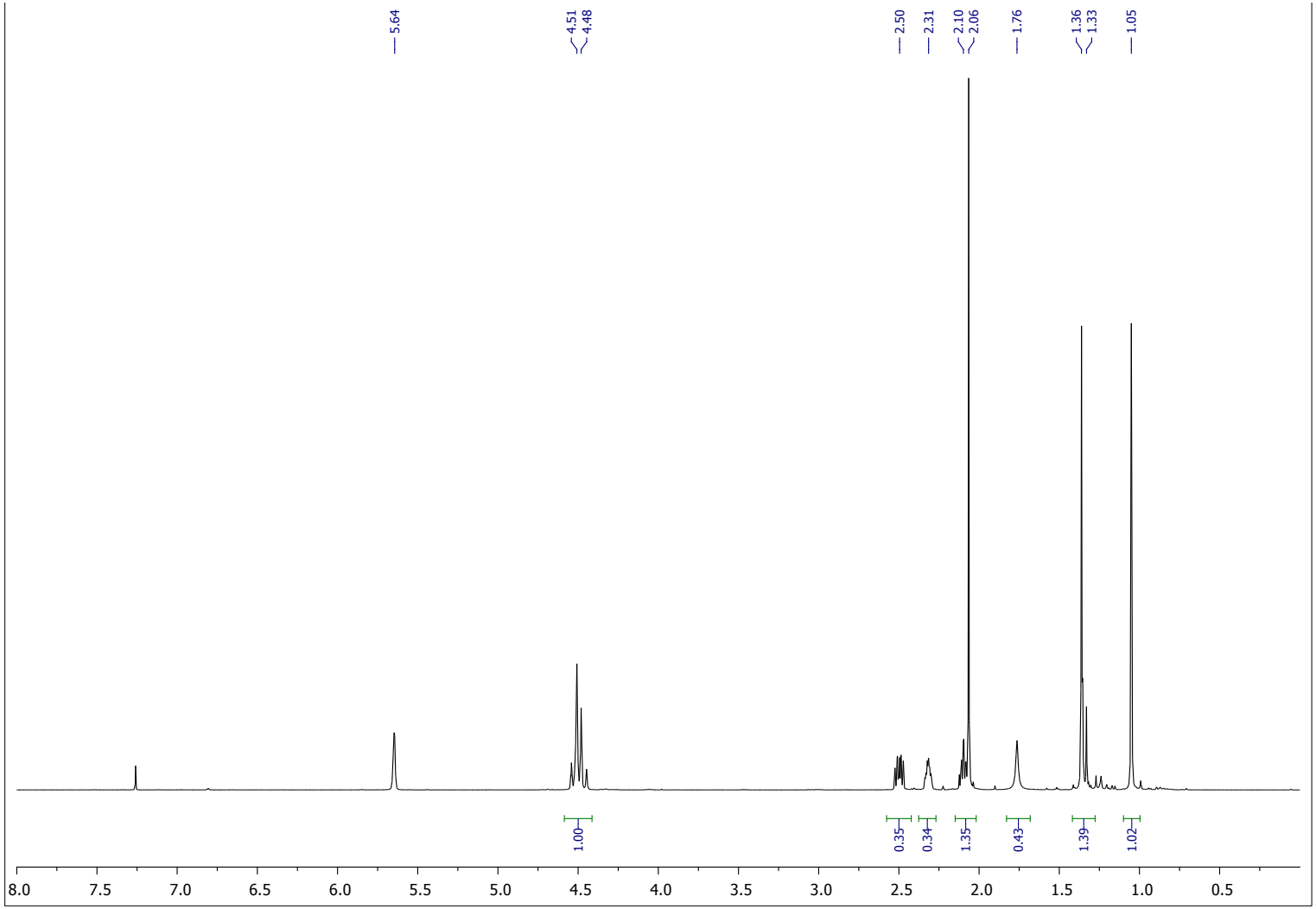
3.0
2.5
2.0
1.5
1.0
0.5
0.0

^{13}C NMR of ***R*M4**



^{1}H NMR of **2c**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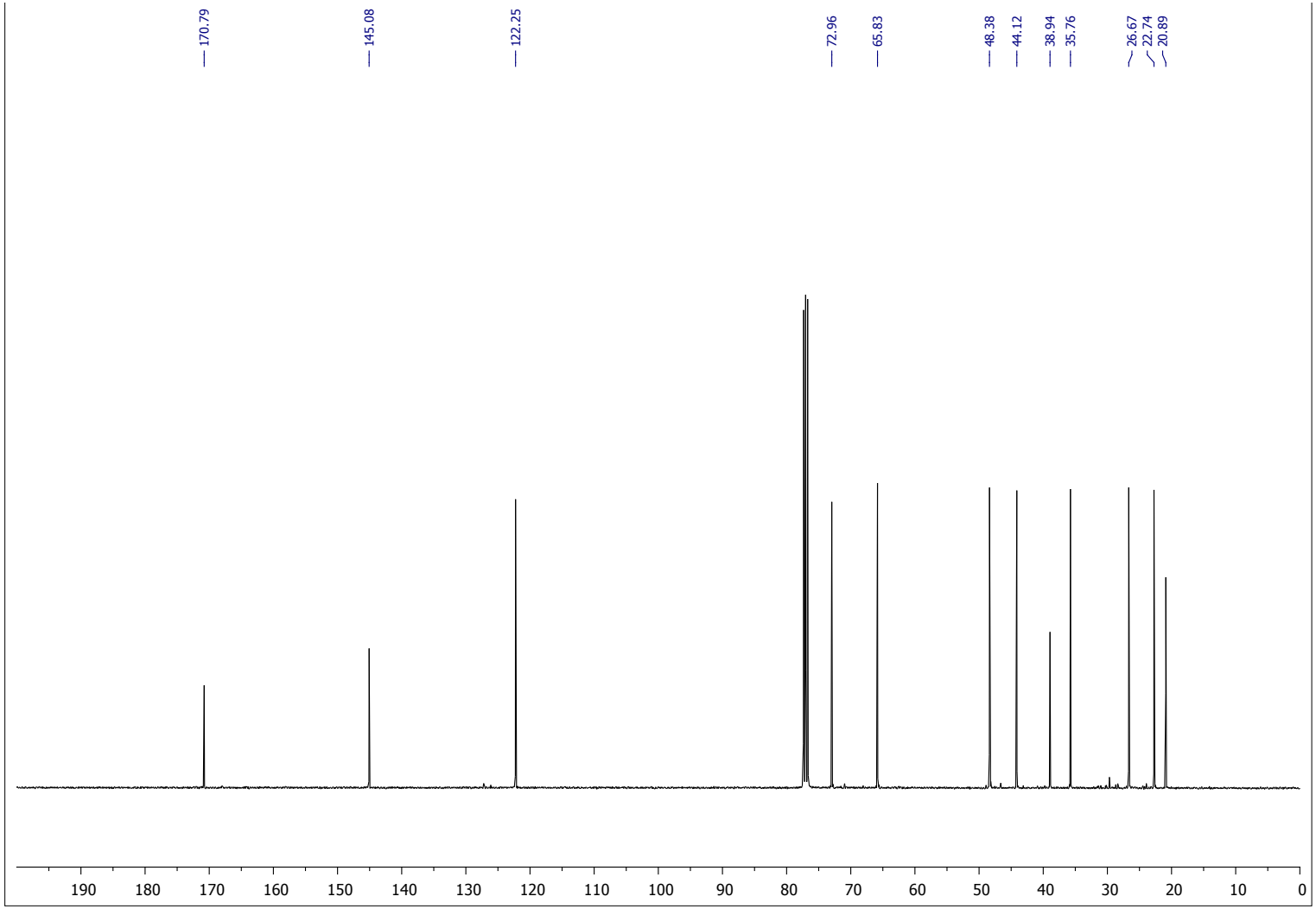
4.51
4.48
2.50
2.31
2.10
2.06
1.76
1.36
1.33
1.05
1.00
0.35
0.34
1.35
0.43
1.39
1.02
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

^{13}C NMR of **2c**


170.79
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72.96
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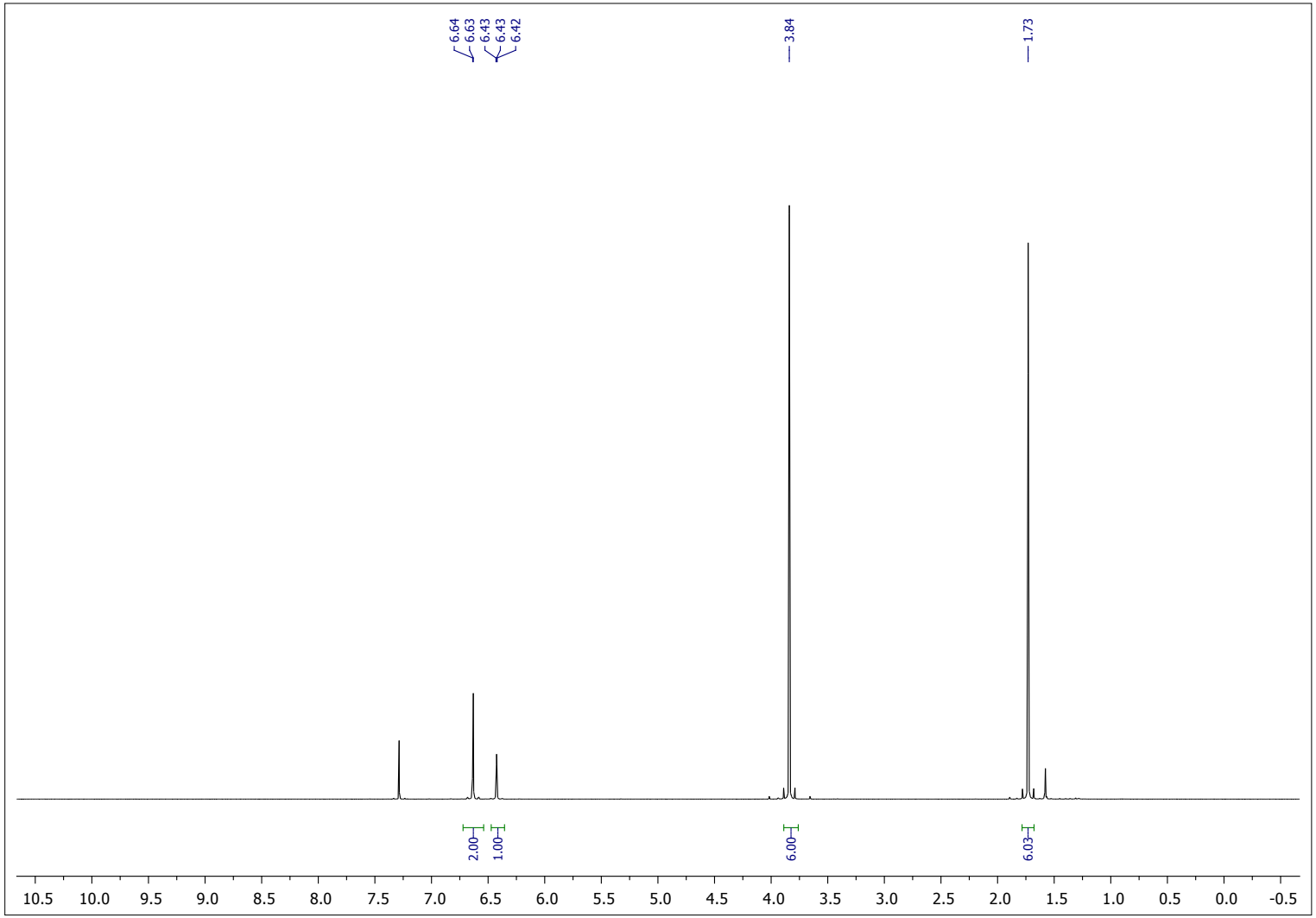
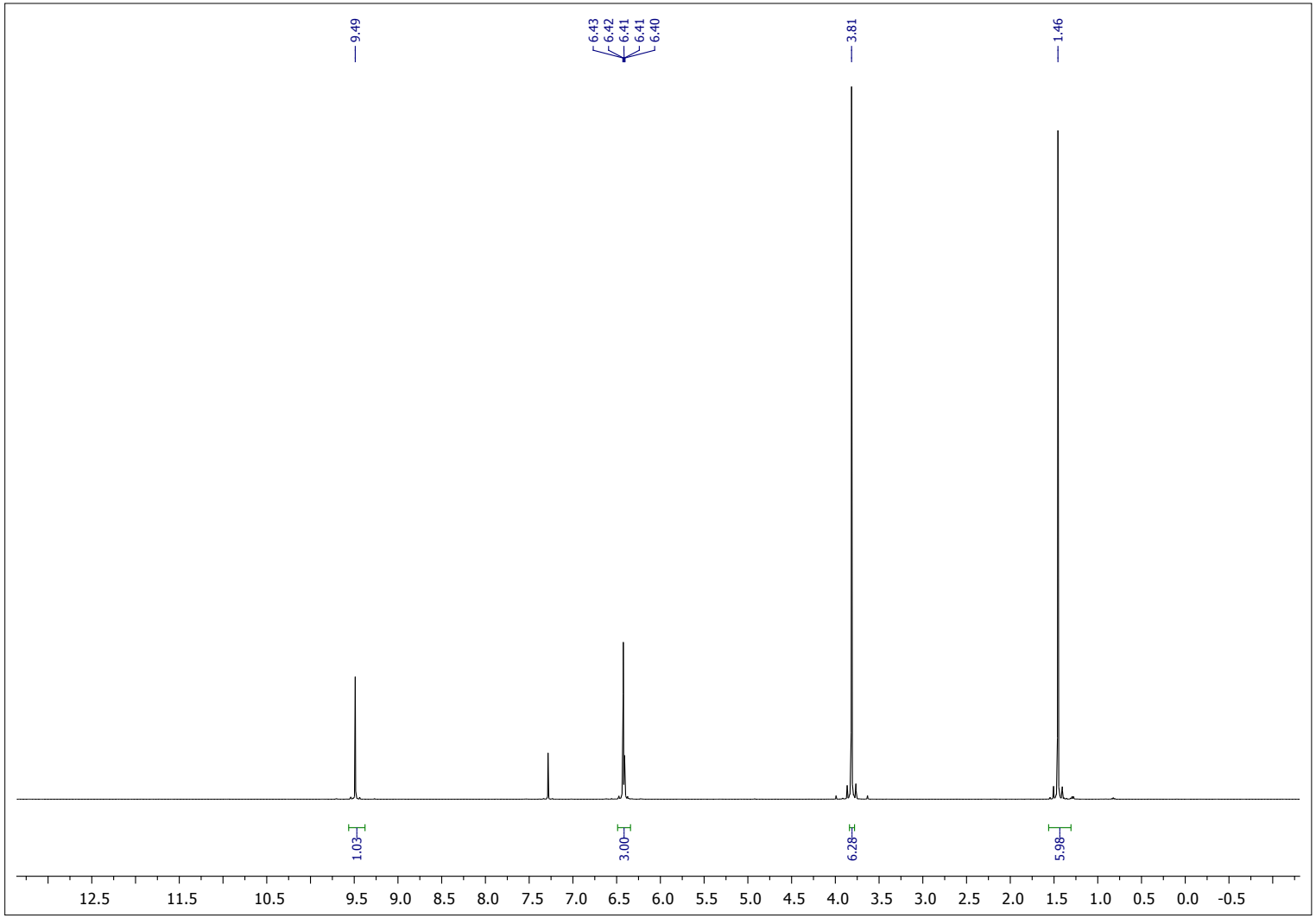
48.38
44.12
38.94
35.76
26.67
22.74
20.89
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

^{1}H NMR of **4**


6.64
6.63
6.43
6.43
6.42
3.84
1.73
2.00
1.00
6.00
6.03
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 -0.5

^{1}H NMR of **5**


9.49
6.43
6.42
6.41
6.41
6.40
3.81
1.46
1.03
3.00
6.28
5.98
12.5
11.5
10.5
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
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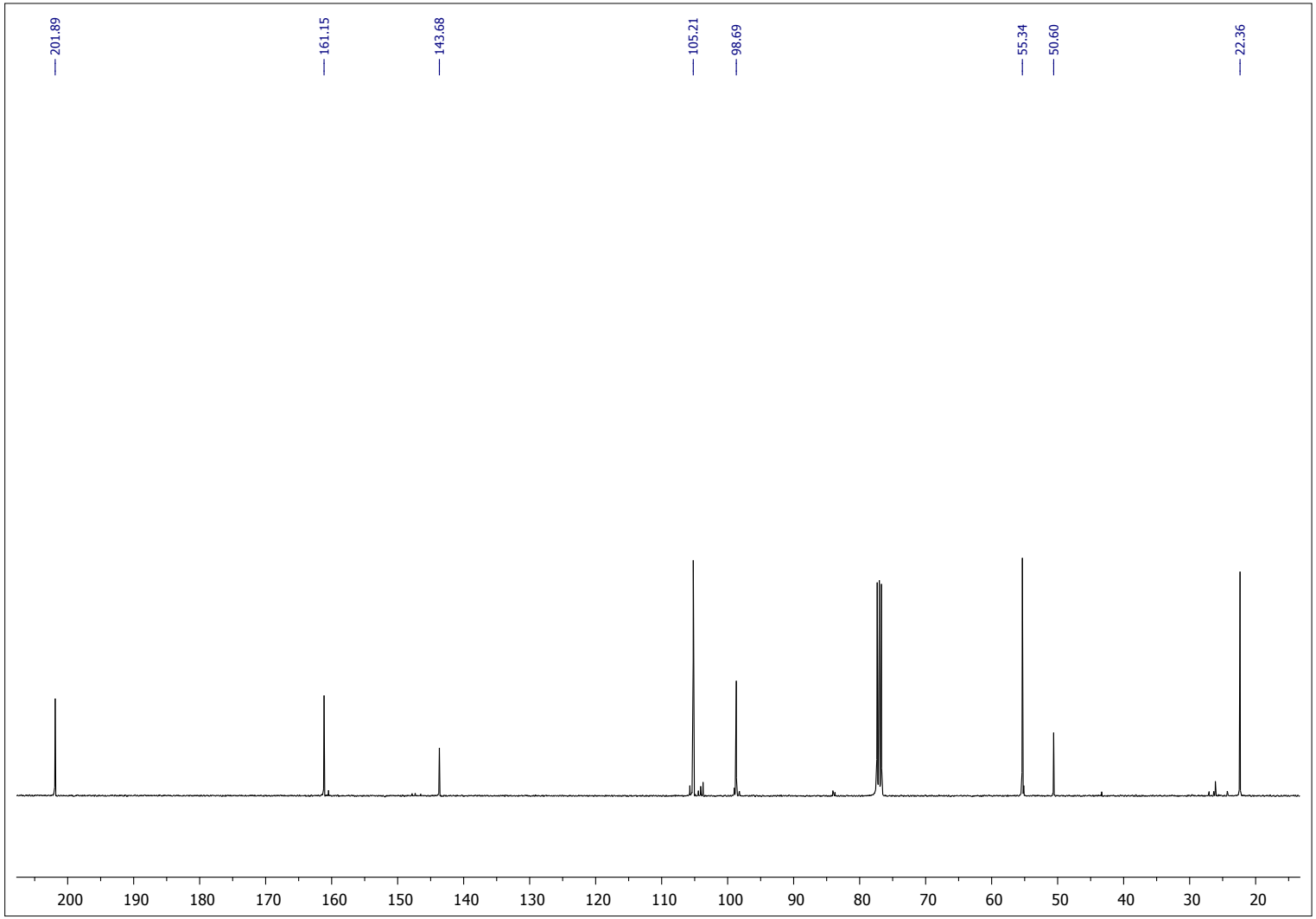
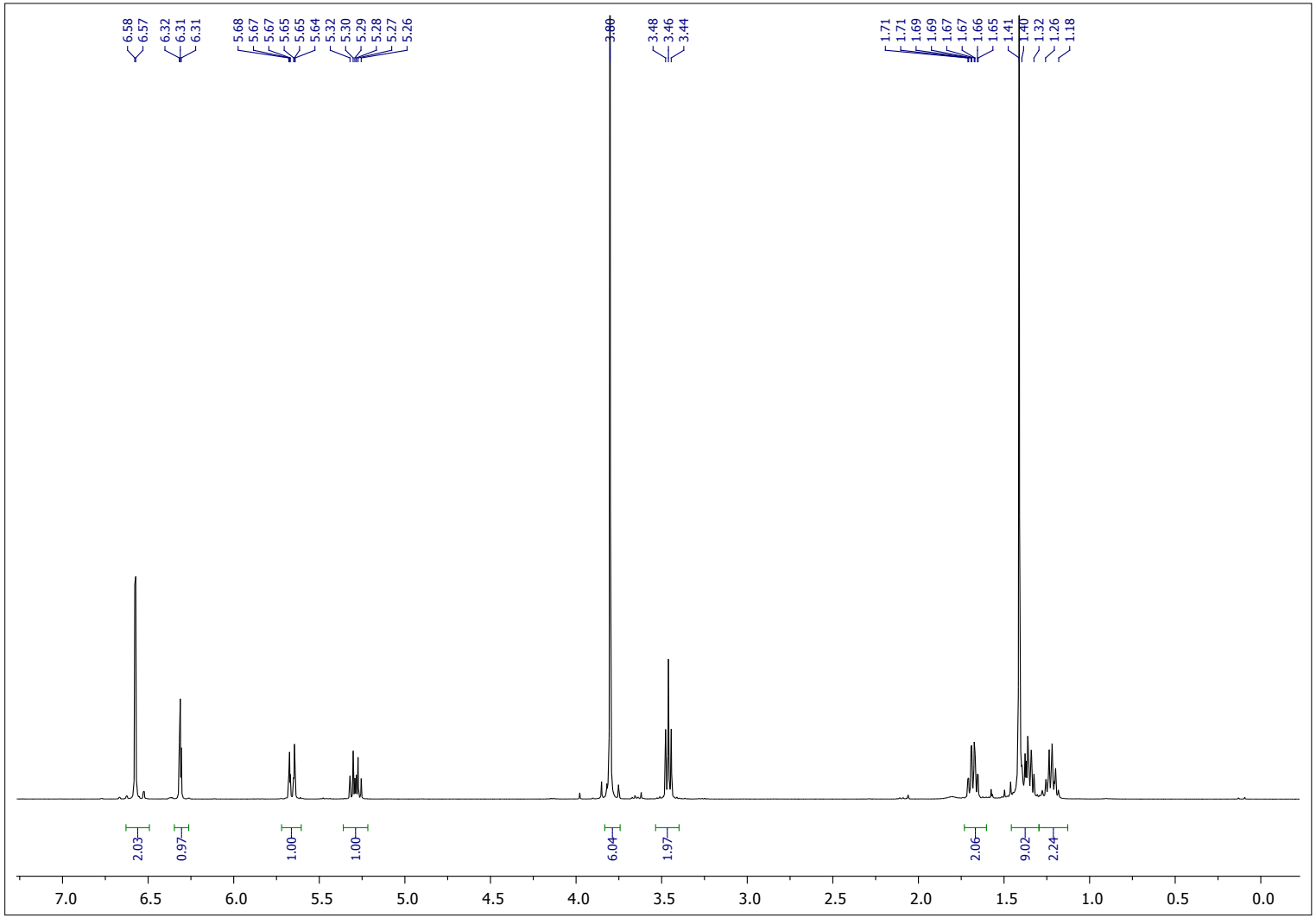
1.5
1.0
0.5
0.0
-0.5

^{13}C NMR of **5**


201.89
161.15
143.68
105.21
98.69
55.34
50.60
22.36
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20

^{1}H NMR of **7**


6.58
6.57
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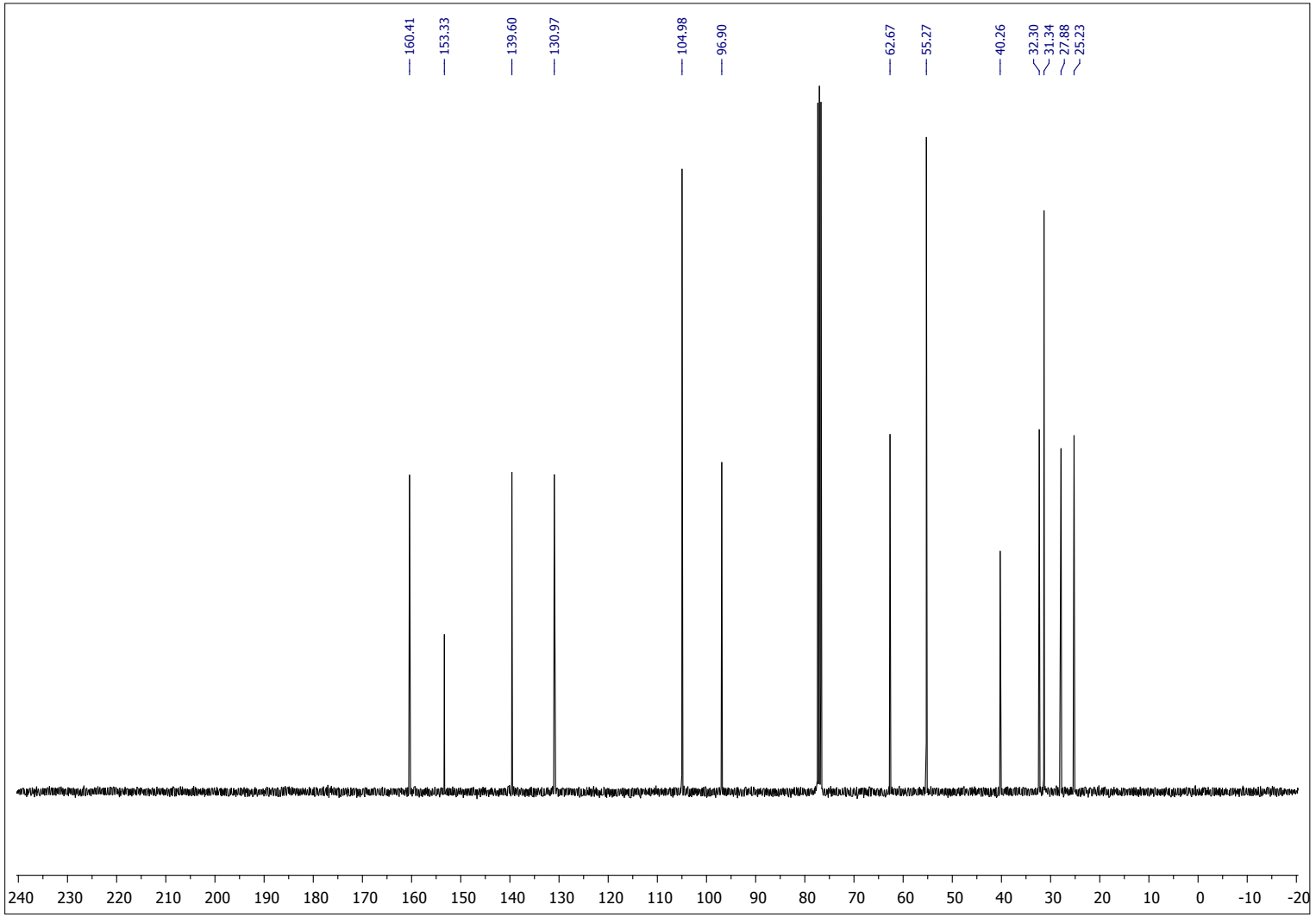
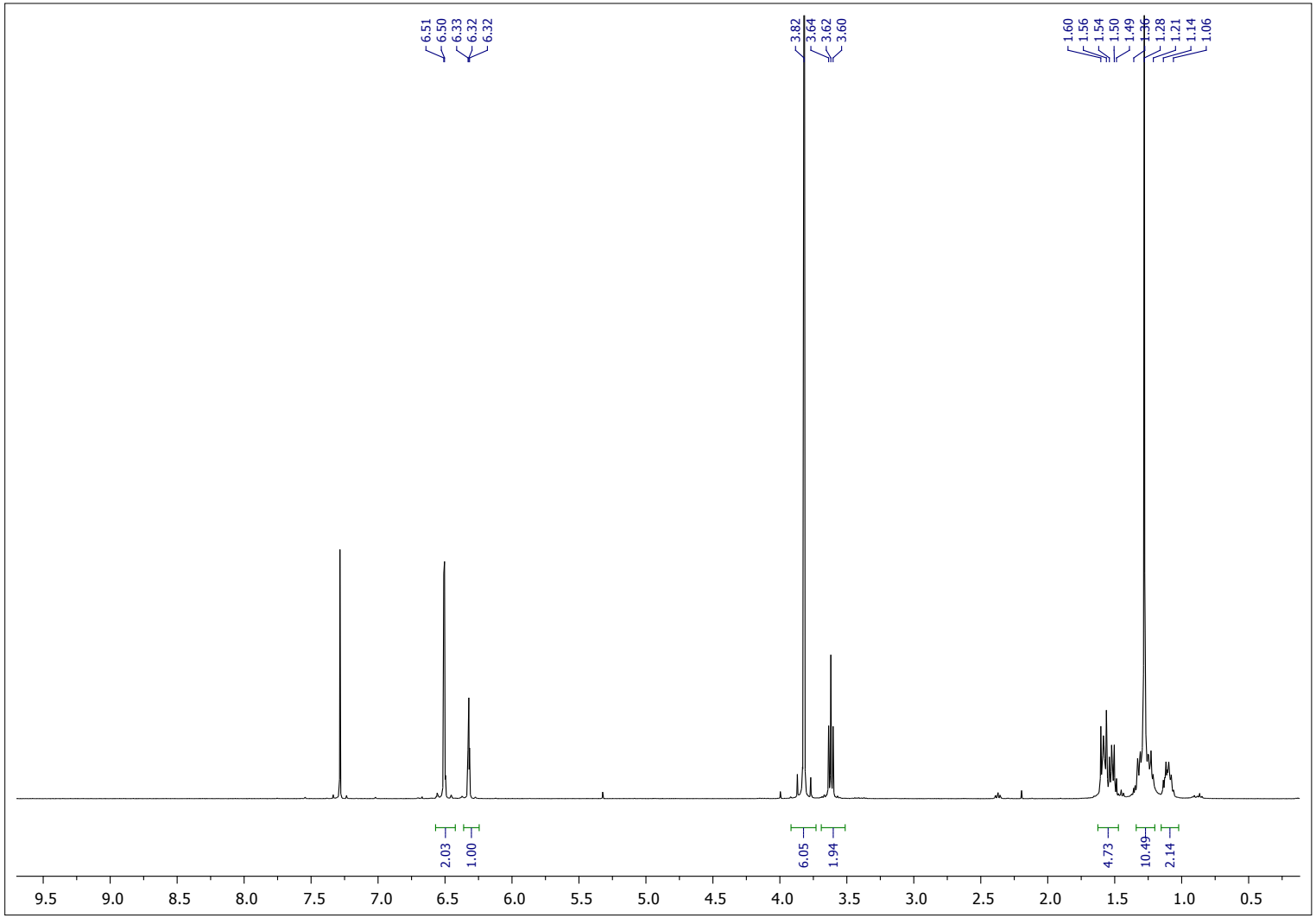
6.31
6.31
5.68
5.67
5.67
5.65
5.65
5.64
5.32
5.30
5.29
5.28
5.27
5.26
3.48
3.46
3.44
1.71
1.71
1.69
1.69
1.67
1.67
1.66
1.65
1.41
1.40
1.32
1.26
1.18
2.03
0.97
1.00
1.00
6.04
1.97
2.06
9.02
2.24
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

^{13}C NMR of **7**


160.41
153.33
139.60
130.97
104.98
96.90
62.67
55.27
40.26
32.30
31.34
27.88
25.23
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20

^{1}H NMR of **8**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6.50
6.33
6.32
6.32
3.82
3.64
3.62
3.60
1.60
1.56
1.54
1.50
1.49
1.36
1.28
1.21
1.14
1.06
2.03
1.00
6.05
1.94
4.73
10.49
2.14
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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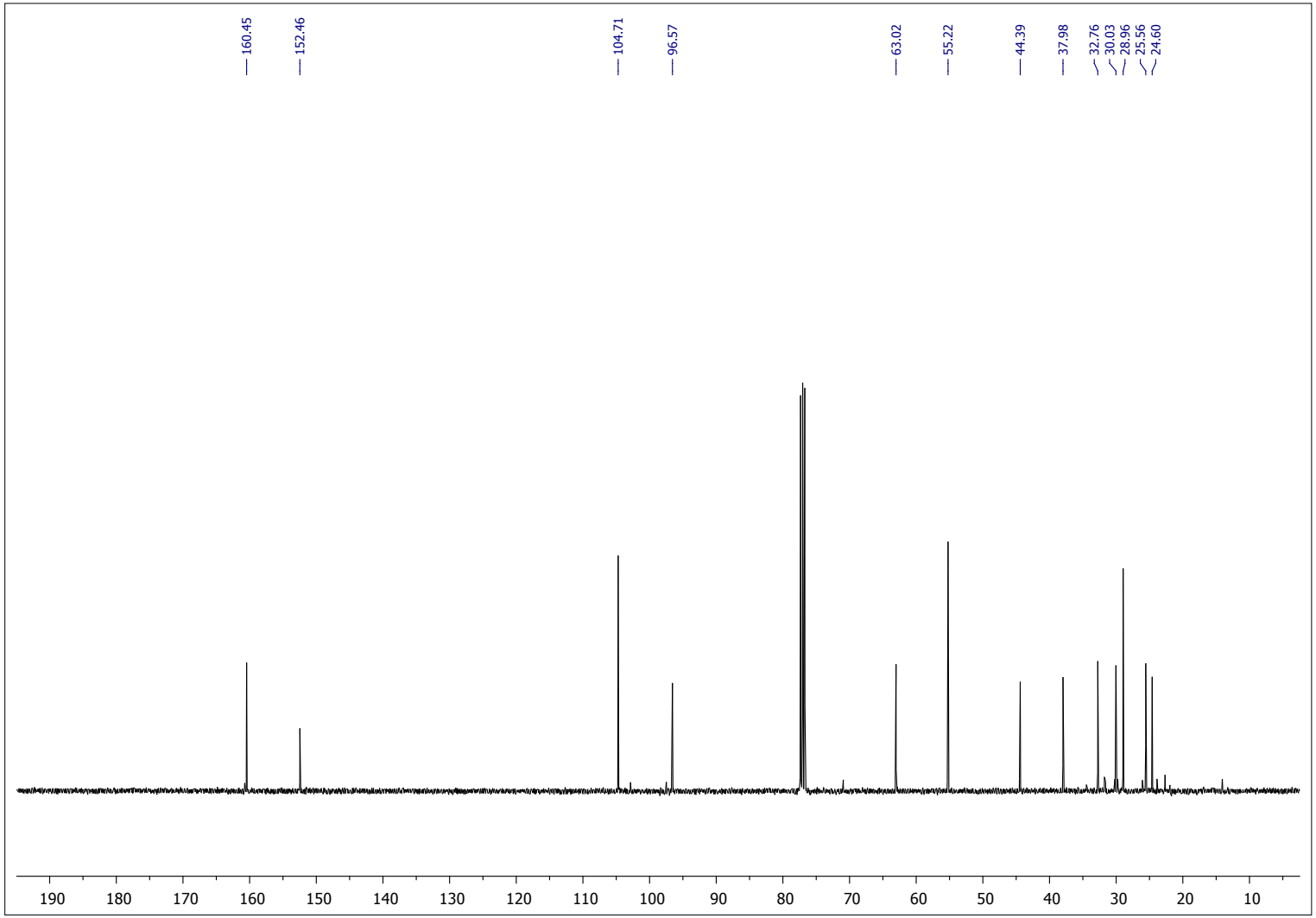
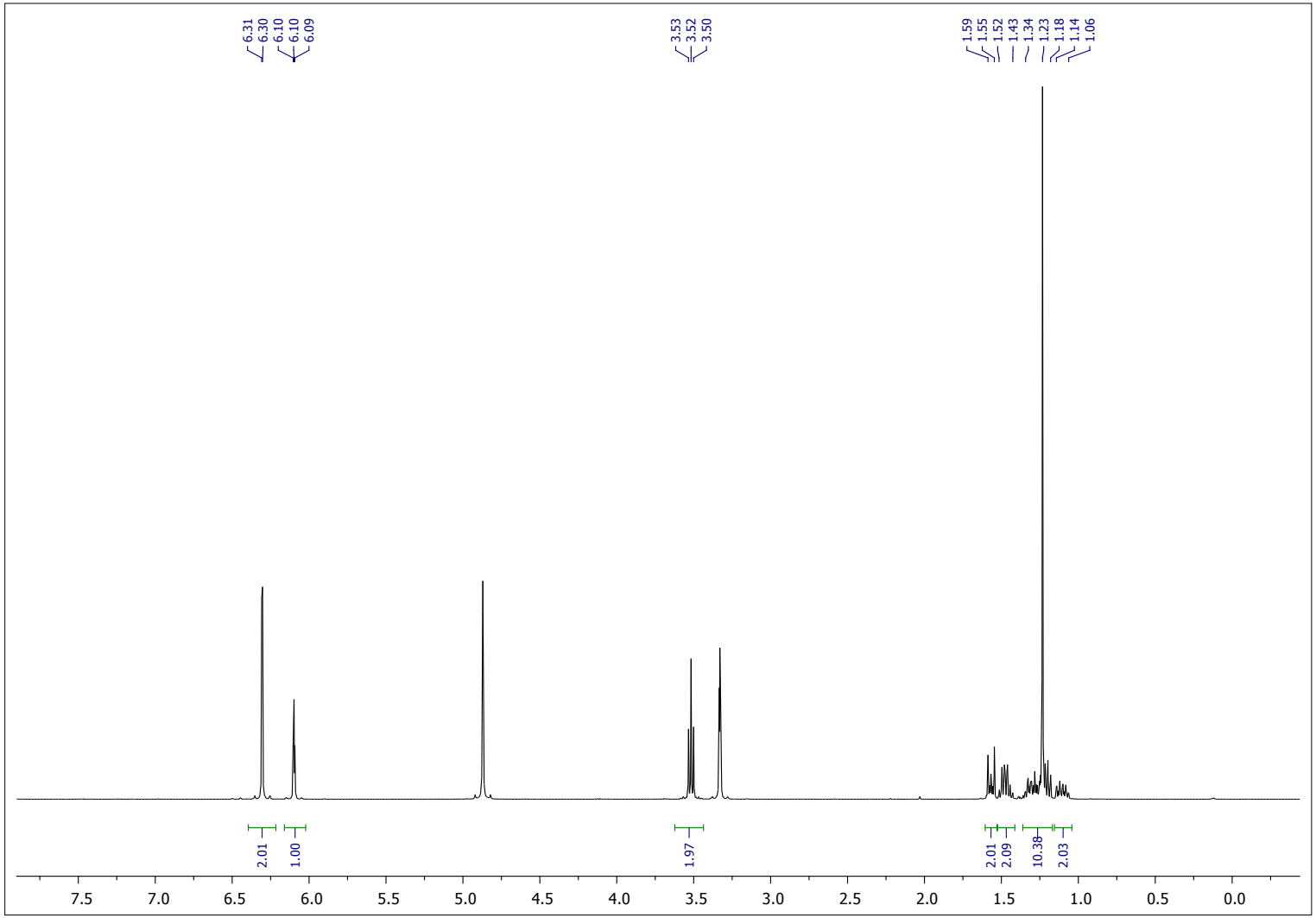
3.5
3.0
2.5
2.0
1.5
1.0
0.5

^{13}C NMR of **8**


160.45
152.46
104.71
96.57
63.02
55.22
44.39
37.98
32.76
30.03
28.96
25.56
24.60
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

^{1}H NMR of **9**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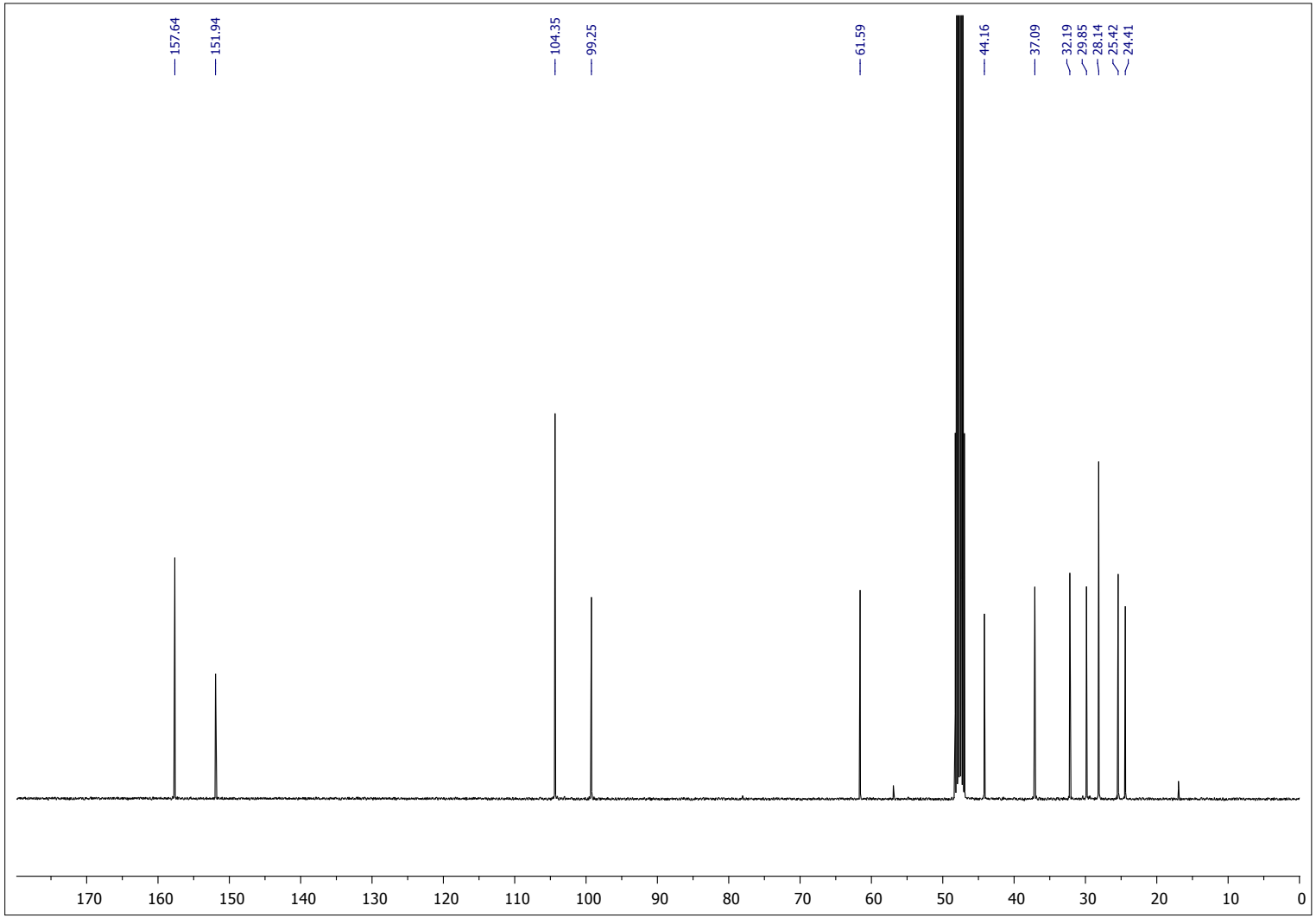
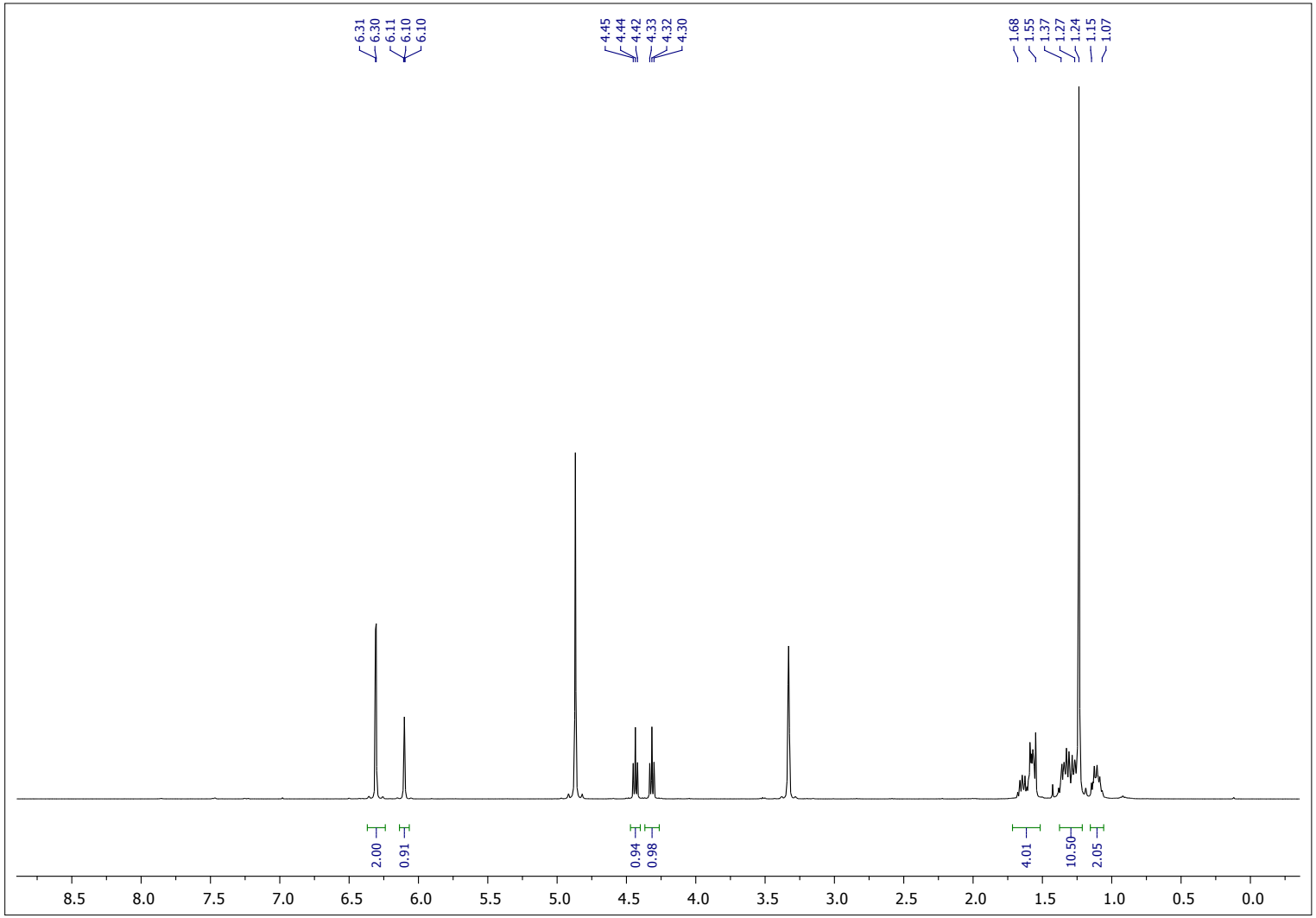
6.30
6.10
6.10
6.09
3.53
3.52
3.50
1.59
1.55
1.52
1.43
1.34
1.23
1.18
1.14
1.06
2.01
1.00
1.97
2.01
2.09
10.38
2.03
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

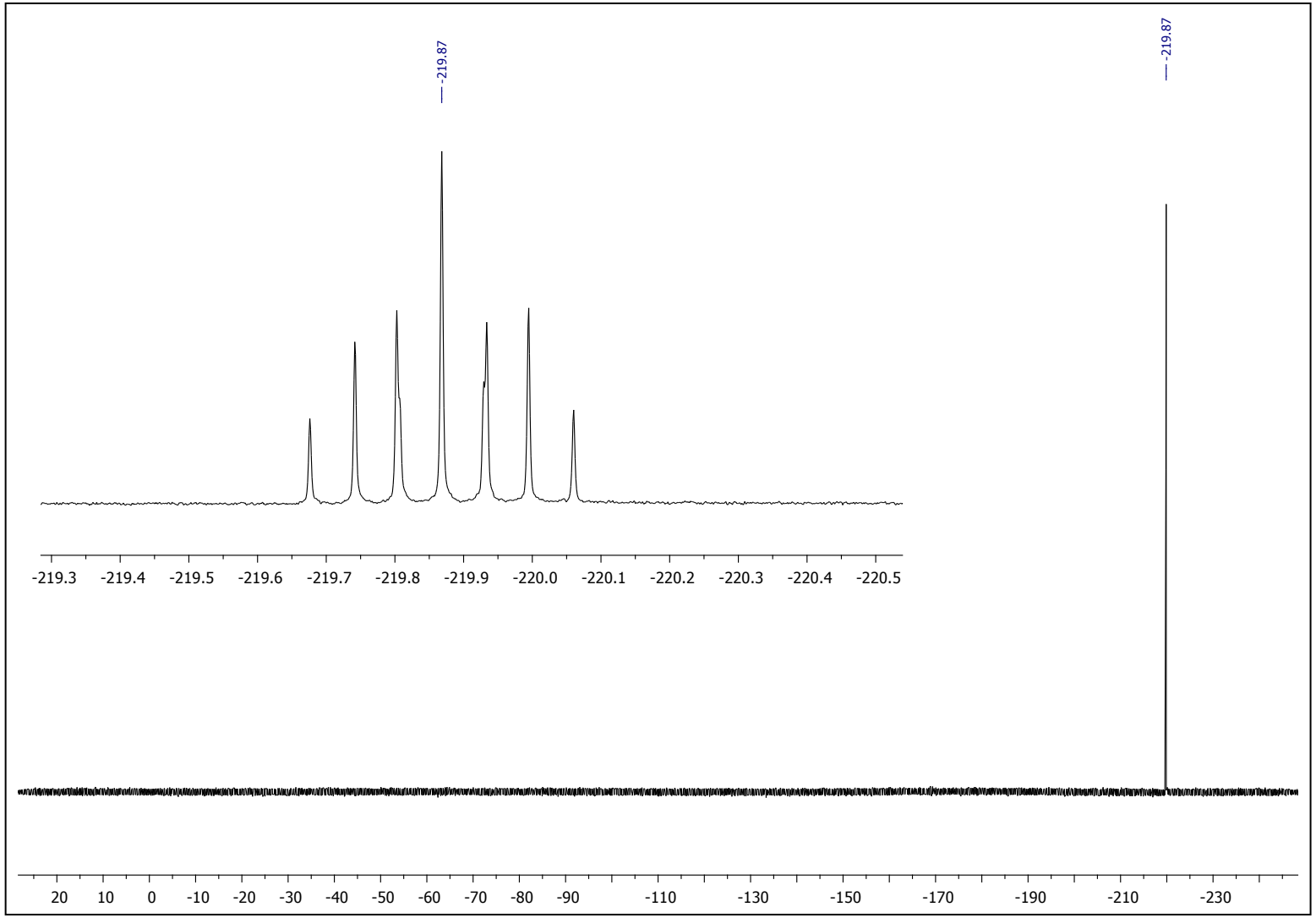
^{13}C NMR of **9**


157.64
151.94
104.35
99.25
61.59
44.16
37.09
32.19
29.85
28.14
25.42
24.41
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

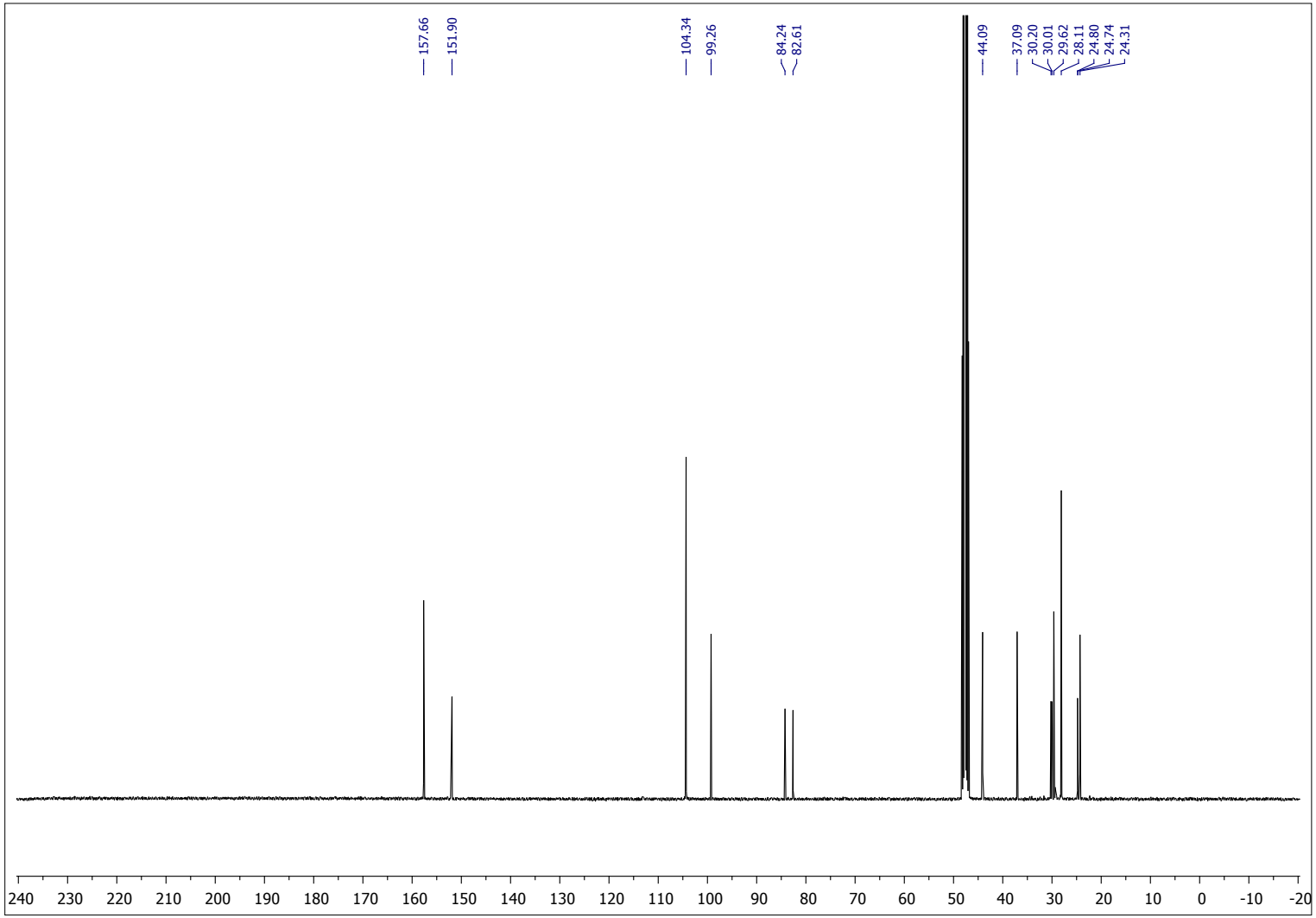
^{1}H NMR of **1**


6.31
6.30
6.11
6.10
6.10
4.45
4.44
4.42
4.33
4.32
4.30
1.68
1.55
1.37
1.27
1.24
1.15
1.07
2.00
0.91
0.94
0.98
4.01
10.50
2.05
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

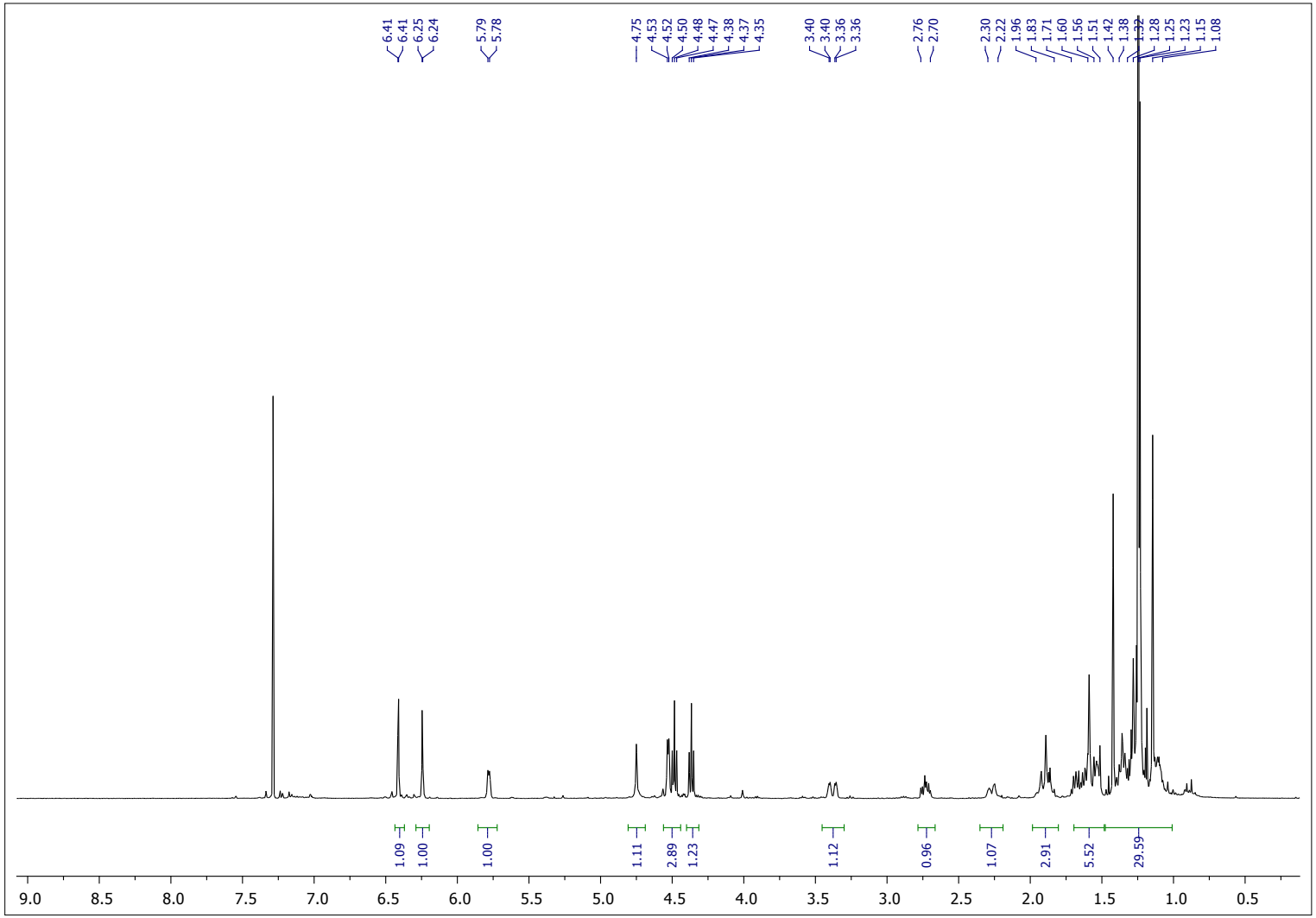
^{19}F NMR of **1**


-219.87
-219.87
-219.3
-219.4
-219.5
-219.6
-219.7
-219.8
-219.9
-220.0
-220.1
-220.2
-220.3
-220.4
-220.5
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-110
-130
-150
-170
-190
-210
-230

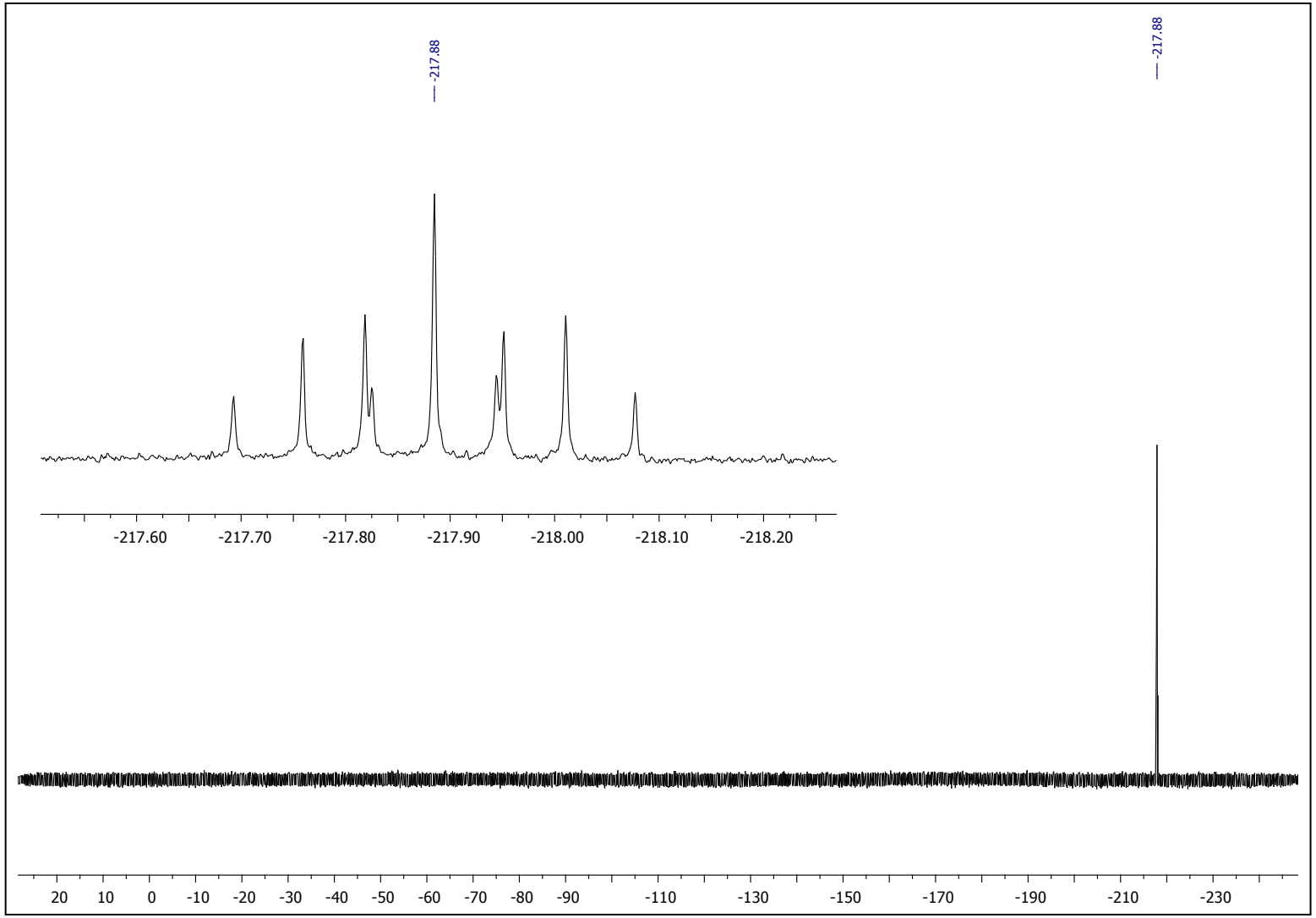
^{13}C NMR of **1**


157.66
151.90
104.34
99.26
84.24
82.61
44.09
37.09
30.20
30.01
29.62
28.11
24.80
24.74
24.31
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20

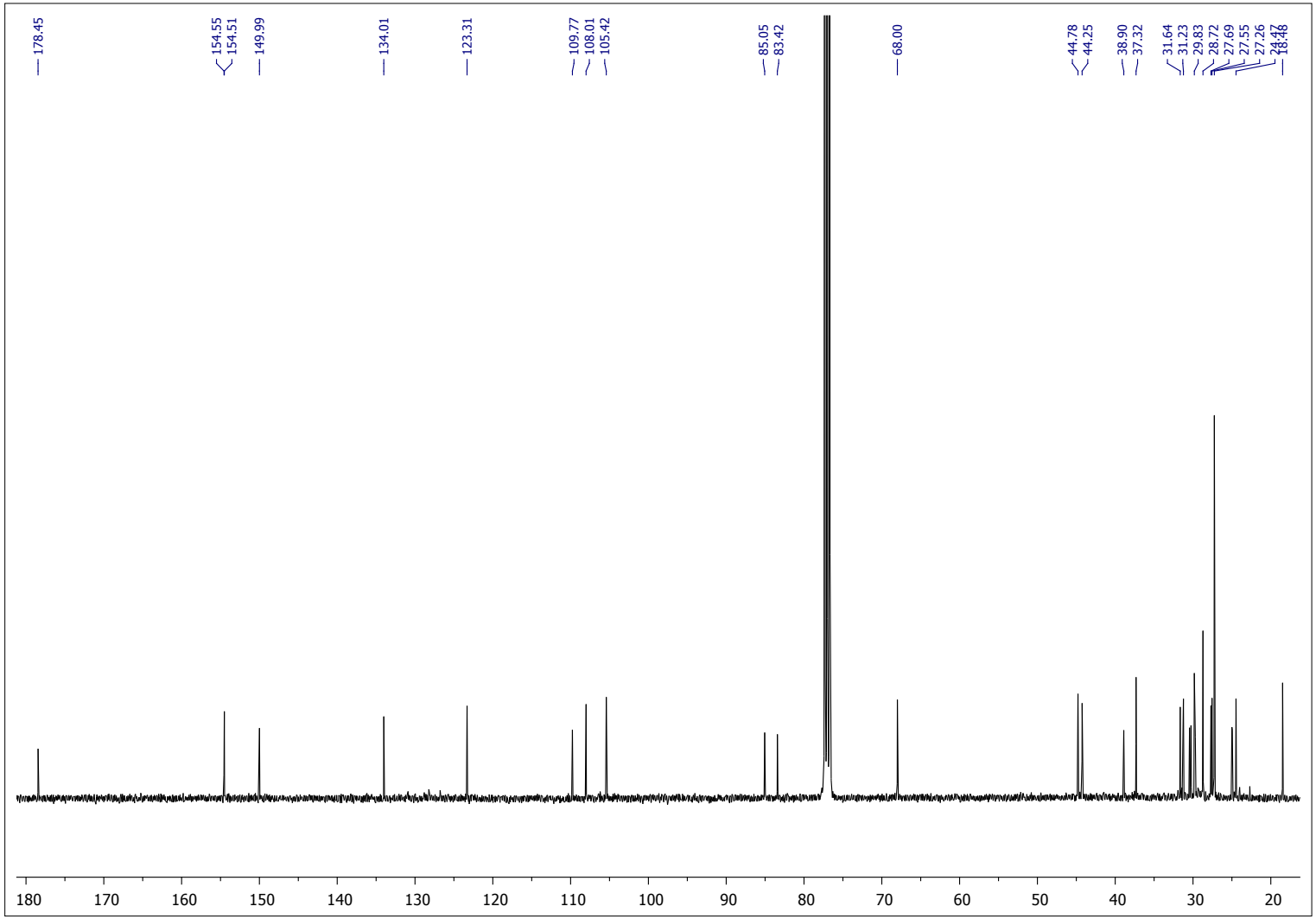
^{1}H NMR of **10a**


6.41
6.41
6.25
6.24
5.79
5.78
4.75
4.53
4.52
4.50
4.48
4.47
4.38
4.37
4.35
3.40
3.40
3.36
3.36
2.76
2.70
2.30
2.22
1.96
1.83
1.71
1.60
1.56
1.51
1.42
1.38
1.32
1.28
1.25
1.23
1.15
1.08
1.09
1.00
1.00
1.11
2.89
1.23
1.12
0.96
1.07
2.91
5.52
29.59
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

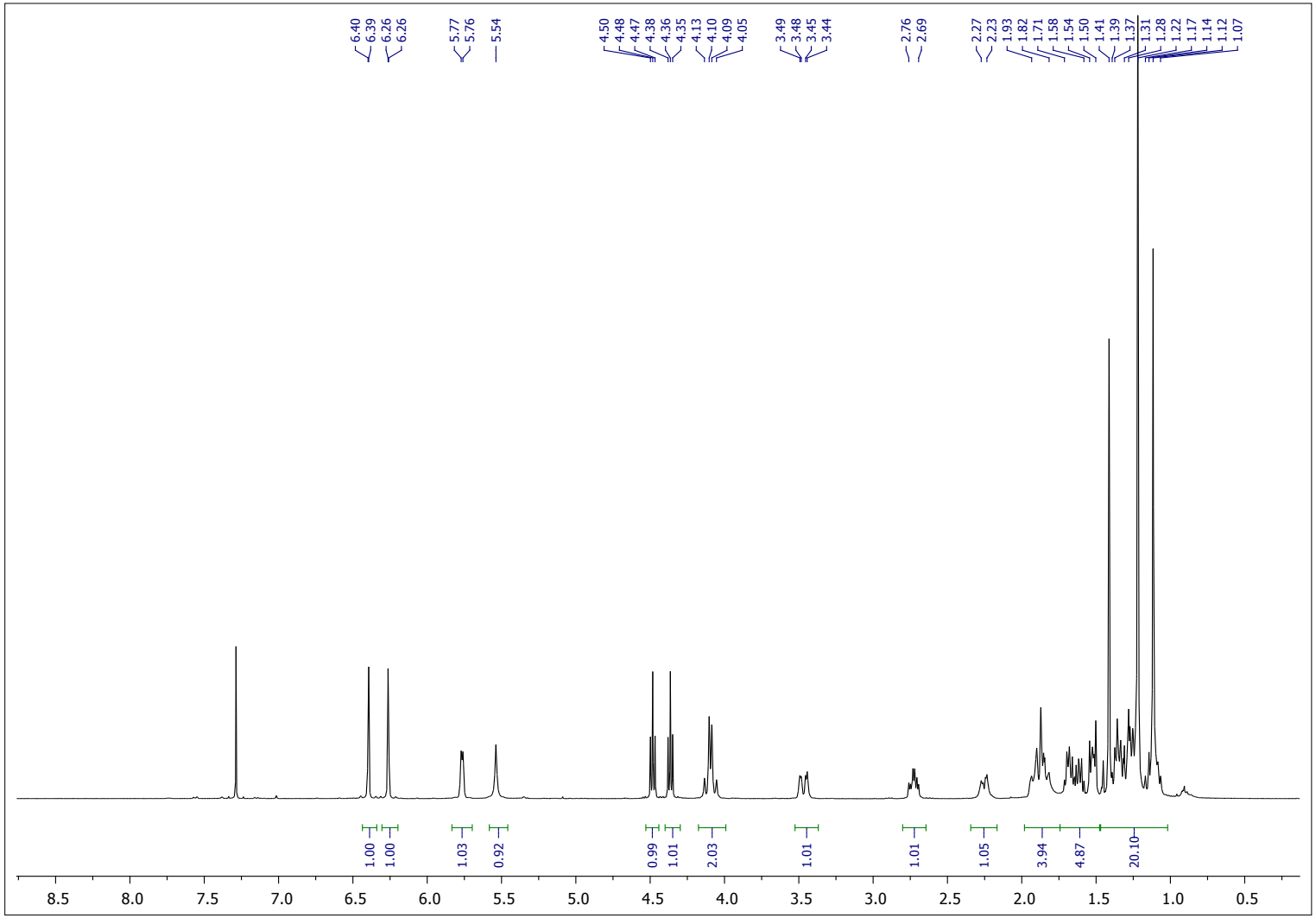
^{19}F NMR of **10a**



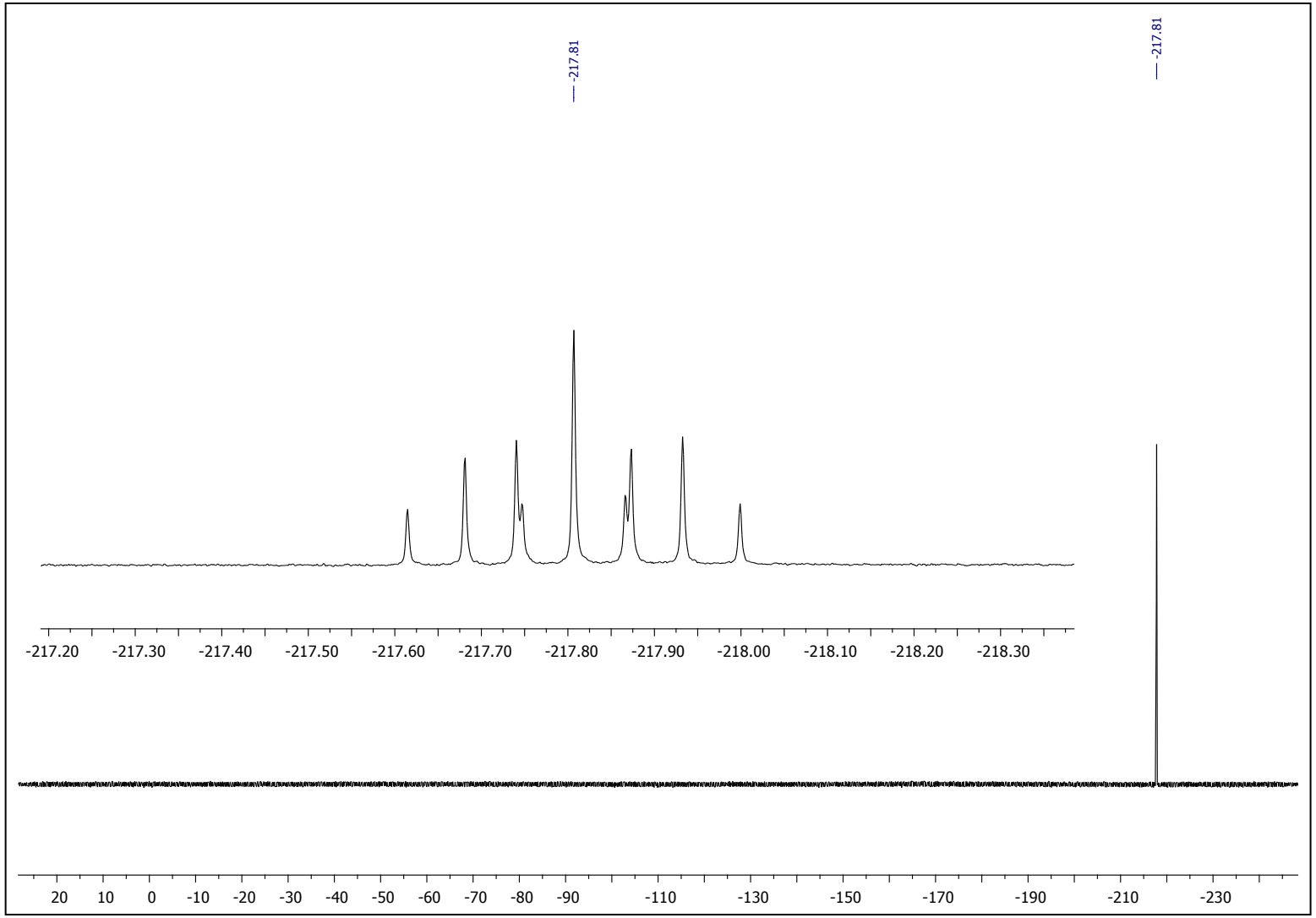
^{13}C NMR of **10a**



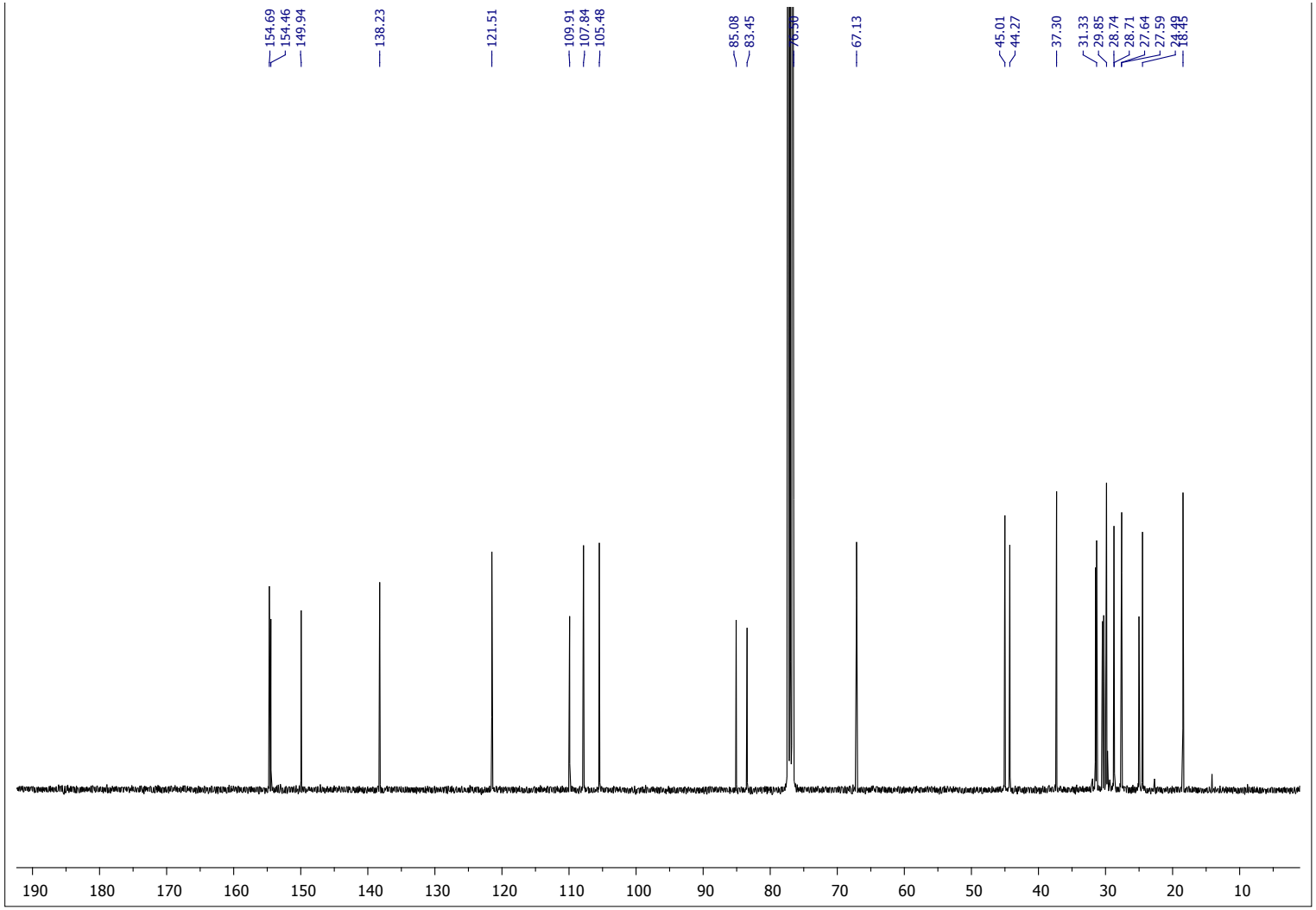
^{1}H NMR of (-)-(*R,R*)-**HU210F**



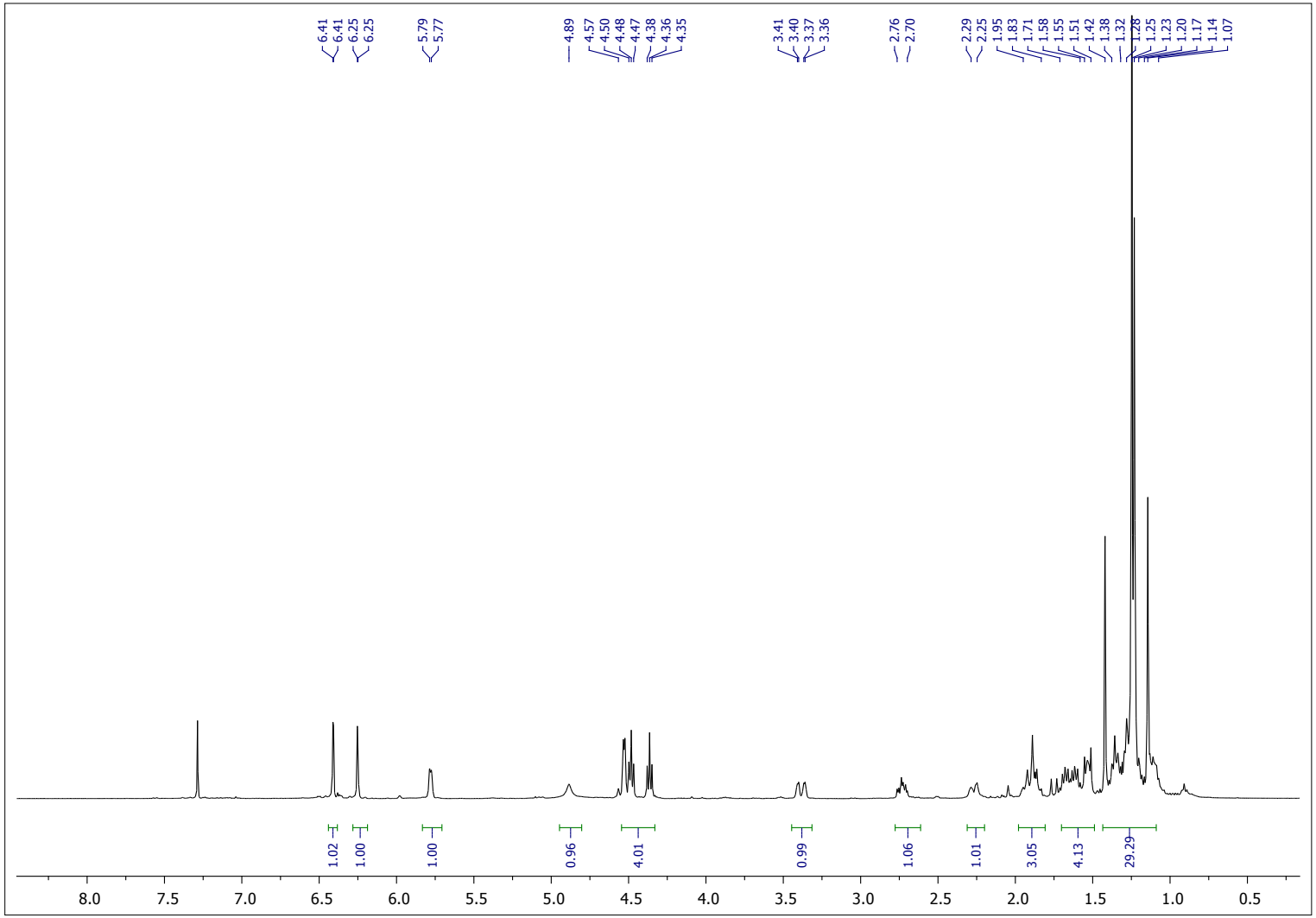
^{19}F NMR of (-)-(*R,R*)-**HU210F**



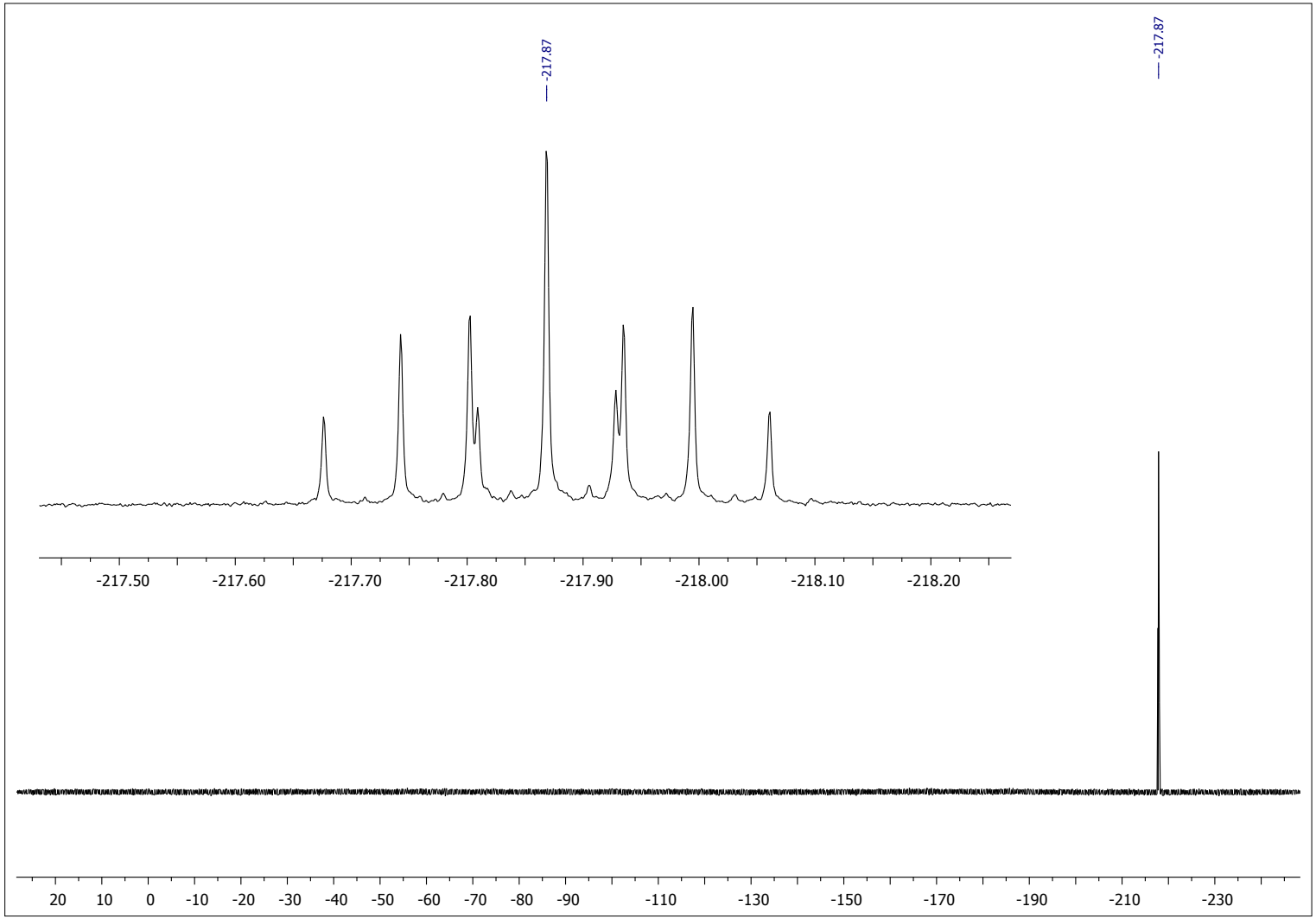
^{13}C NMR of (-)-(*R,R*)-**HU210F**



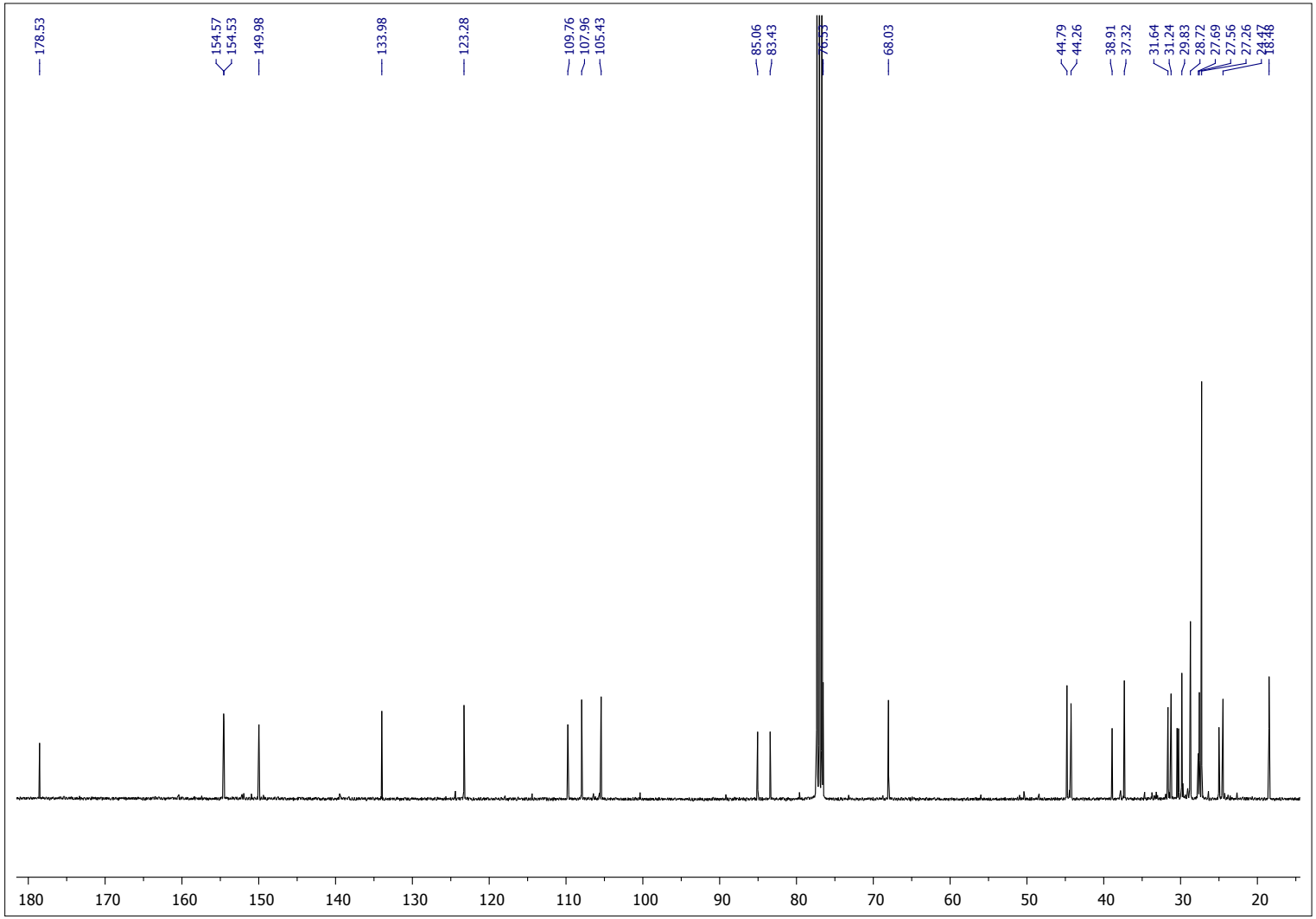
^{1}H NMR of **10b**


6.41
6.41
6.25
6.25
5.79
5.77
4.89
4.57
4.50
4.48
4.47
4.38
4.36
4.35
3.41
3.40
3.37
3.36
2.76
2.70
2.29
2.25
1.95
1.83
1.71
1.58
1.55
1.51
1.42
1.38
1.32
1.28
1.25
1.23
1.20
1.17
1.14
1.07
1.02
1.00
1.00
0.96
4.01
0.99
1.06
1.01
3.05
4.13
29.29
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

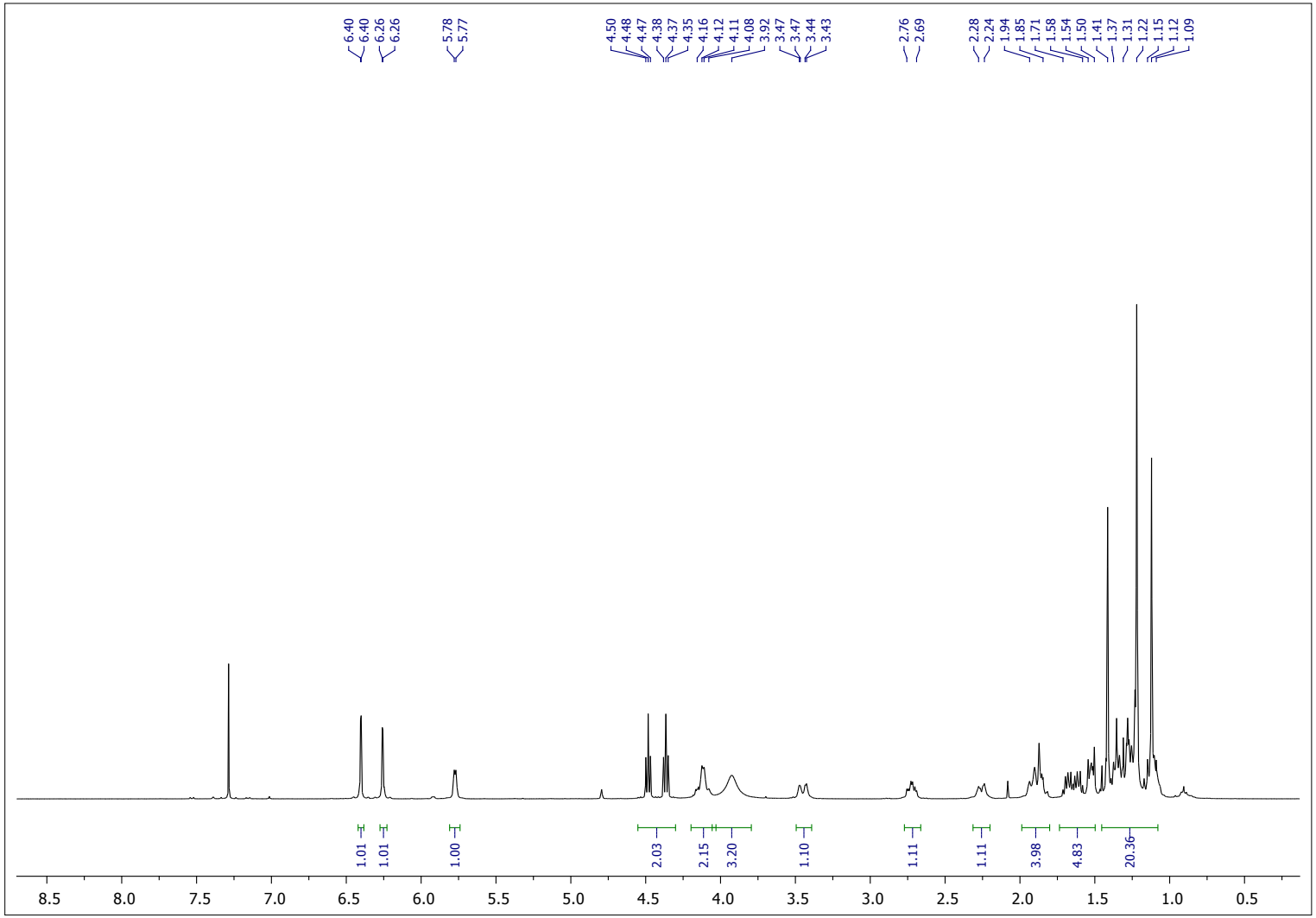
^{19}F NMR of **10b**



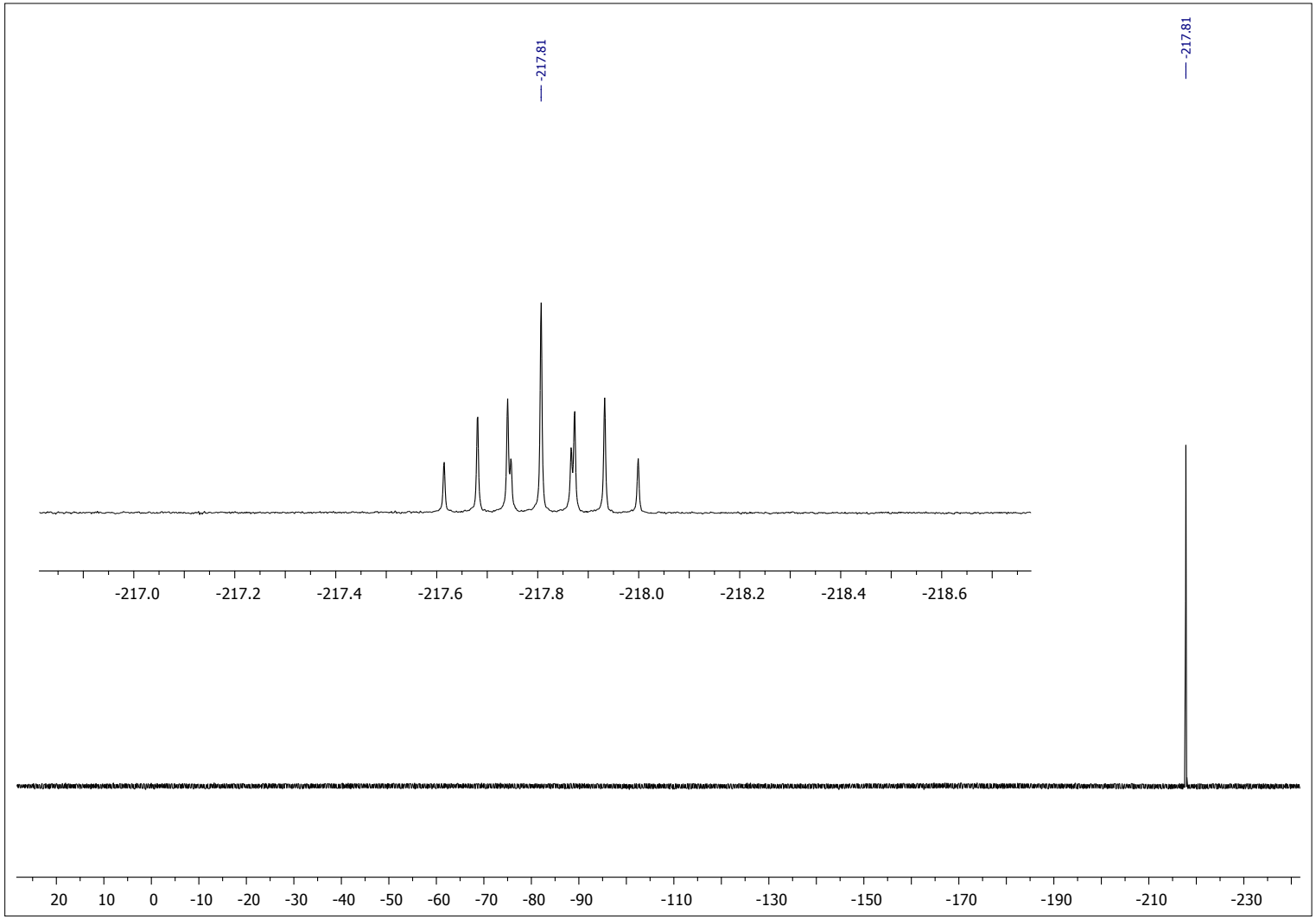
^{13}C NMR of **10b**



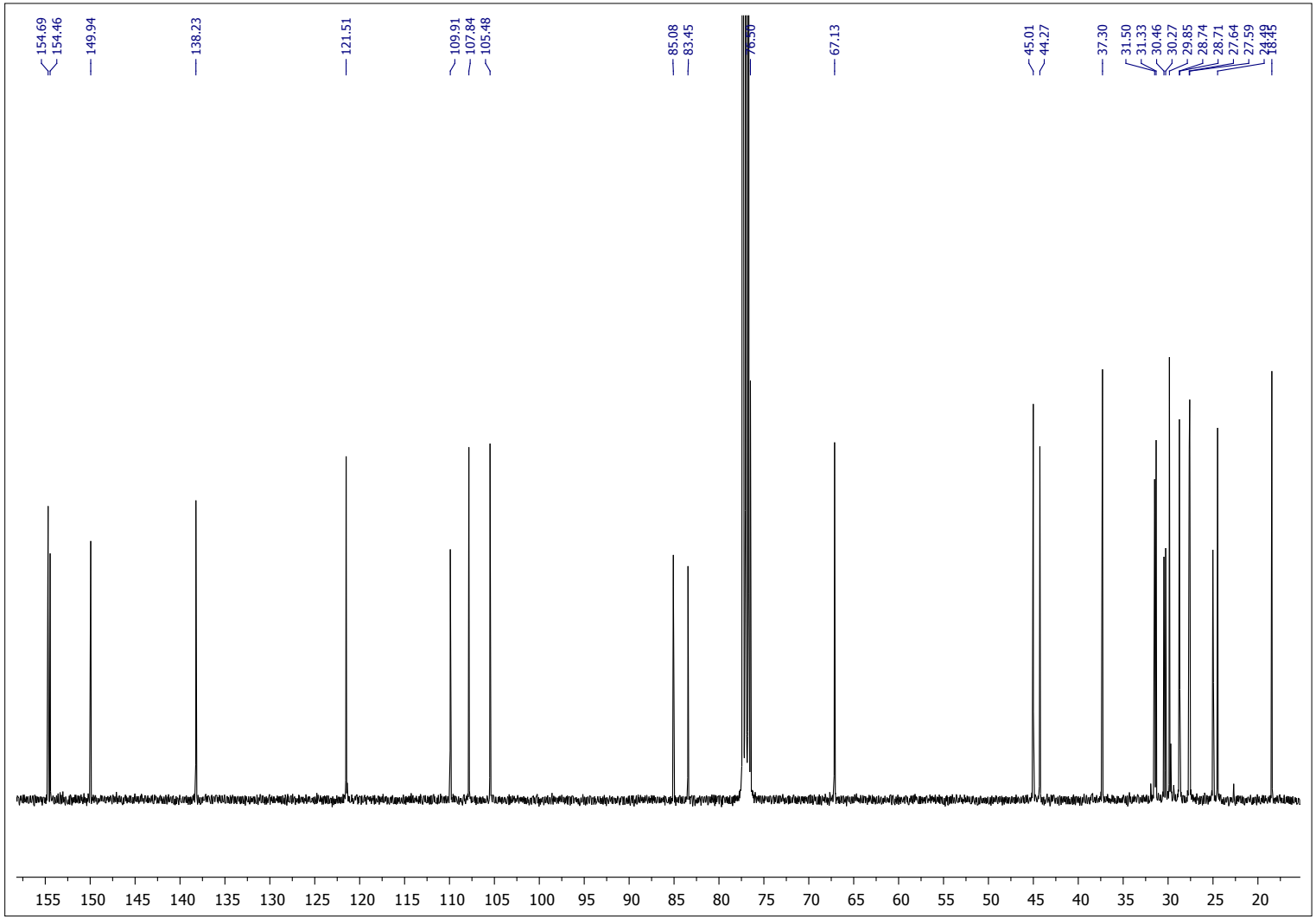
^{1}H NMR of (+)-(*S,S*)-**HU211F**



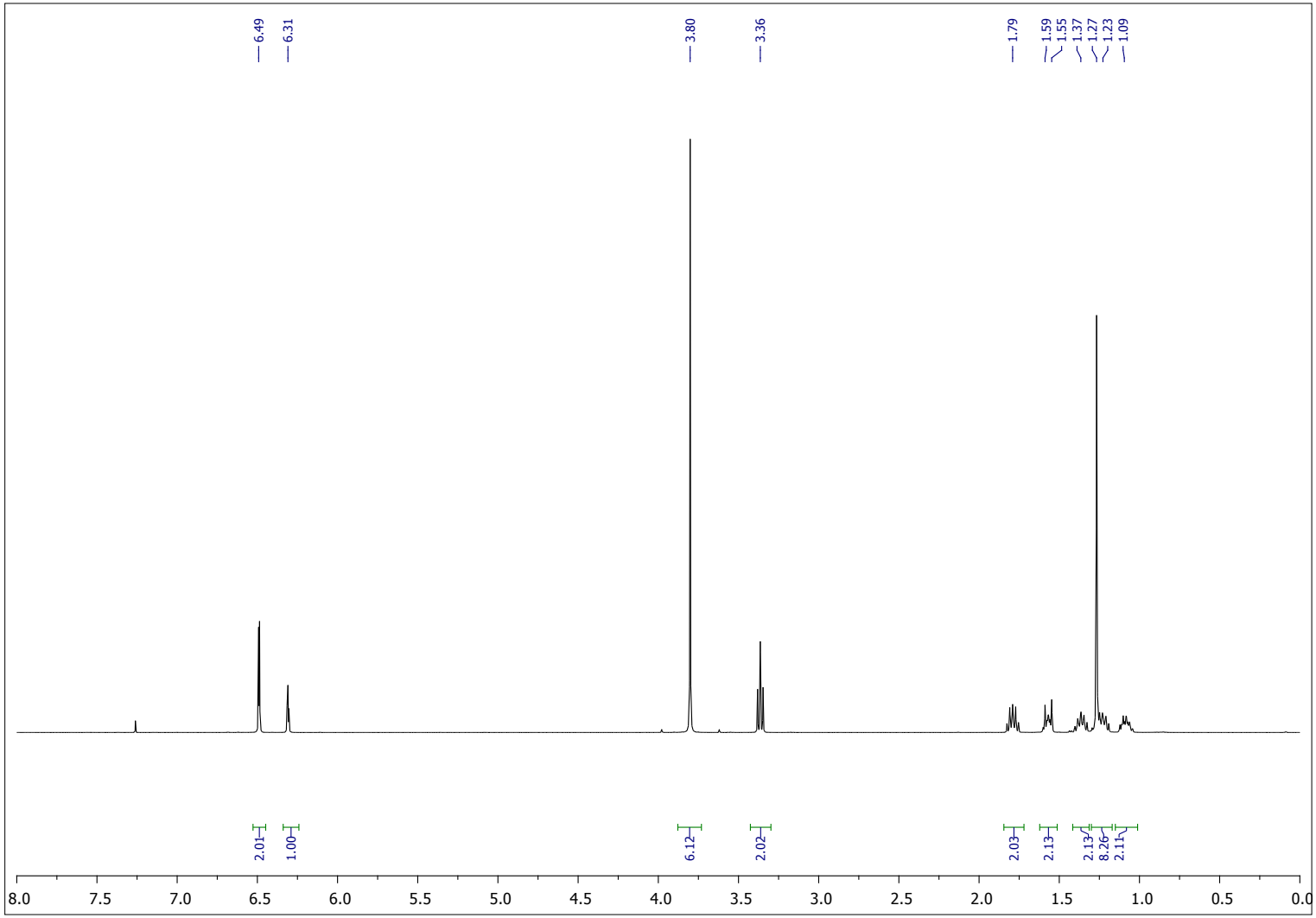
^{19}F NMR of (+)-(*S,S*)-**HU211F**



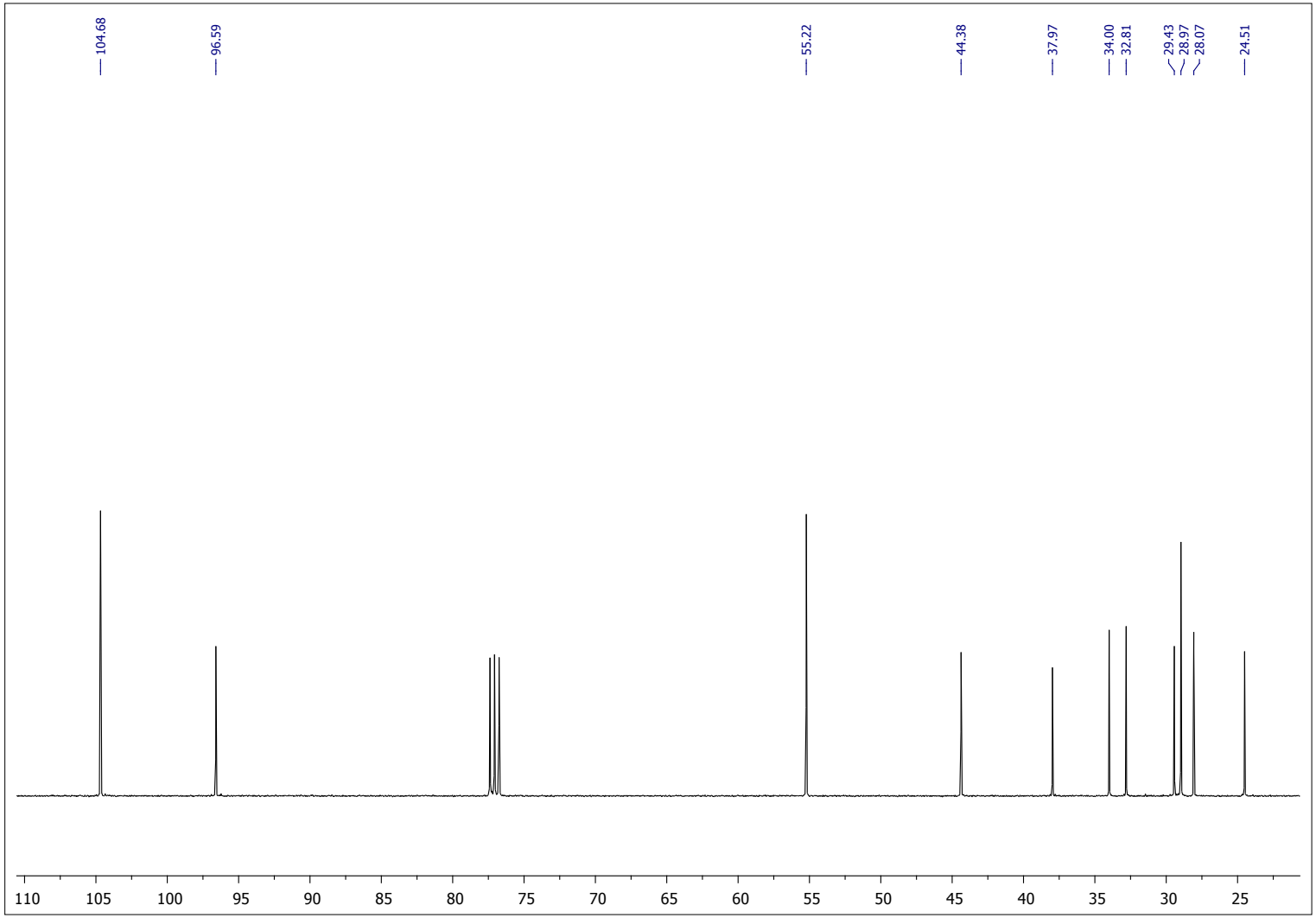
^{13}C NMR of **(+)-(*S*,*S*)-HU211F**



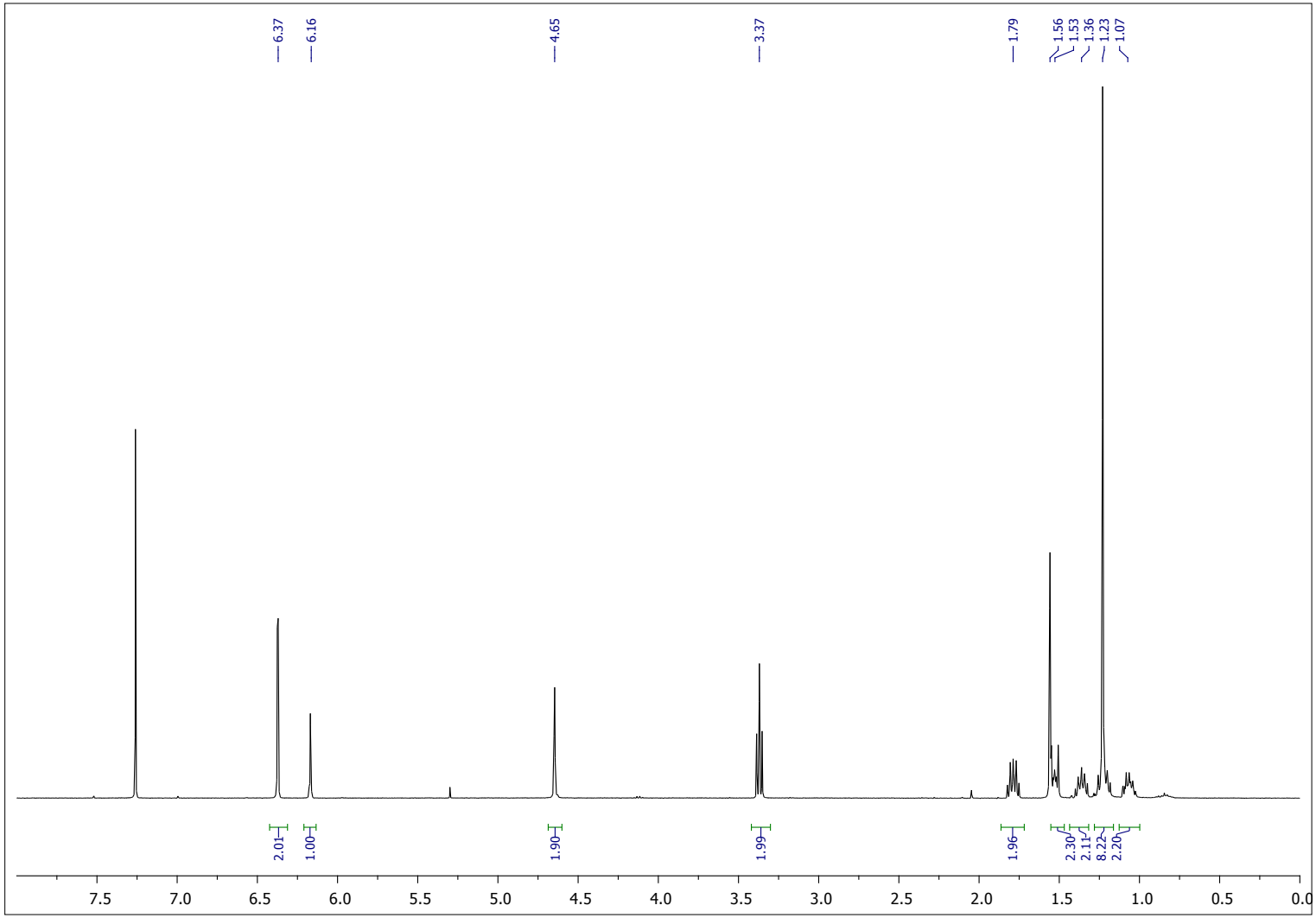
^{1}H NMR of **11**


6.49
6.31
3.80
3.36
1.79
1.59
1.55
1.37
1.27
1.23
1.09
2.01
1.00
6.12
2.02
2.03
2.13
2.13
8.26
2.11
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

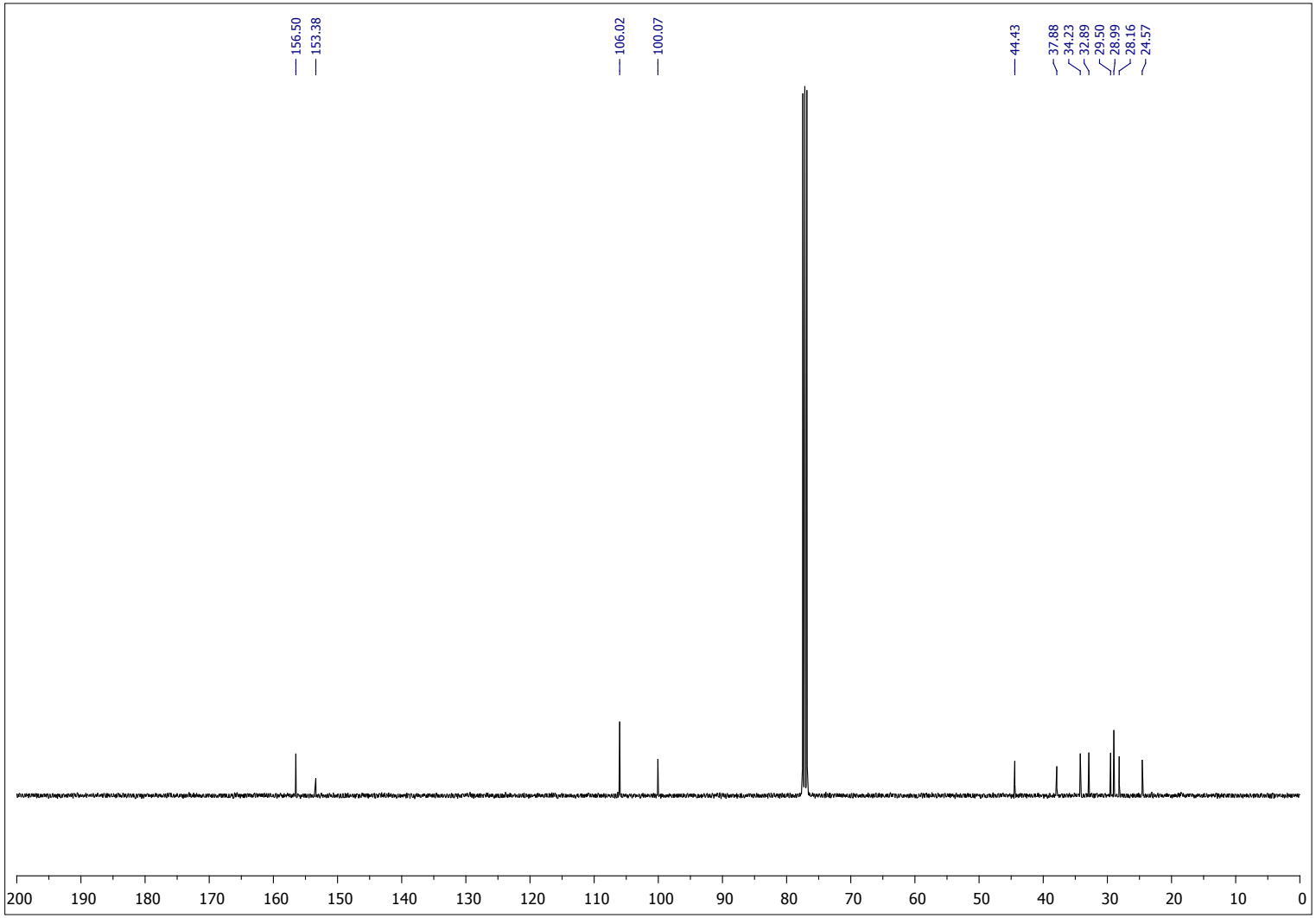
^{13}C NMR of **11**


104.68
96.59
55.22
44.38
37.97
34.00
32.81
29.43
28.97
28.07
24.51
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25

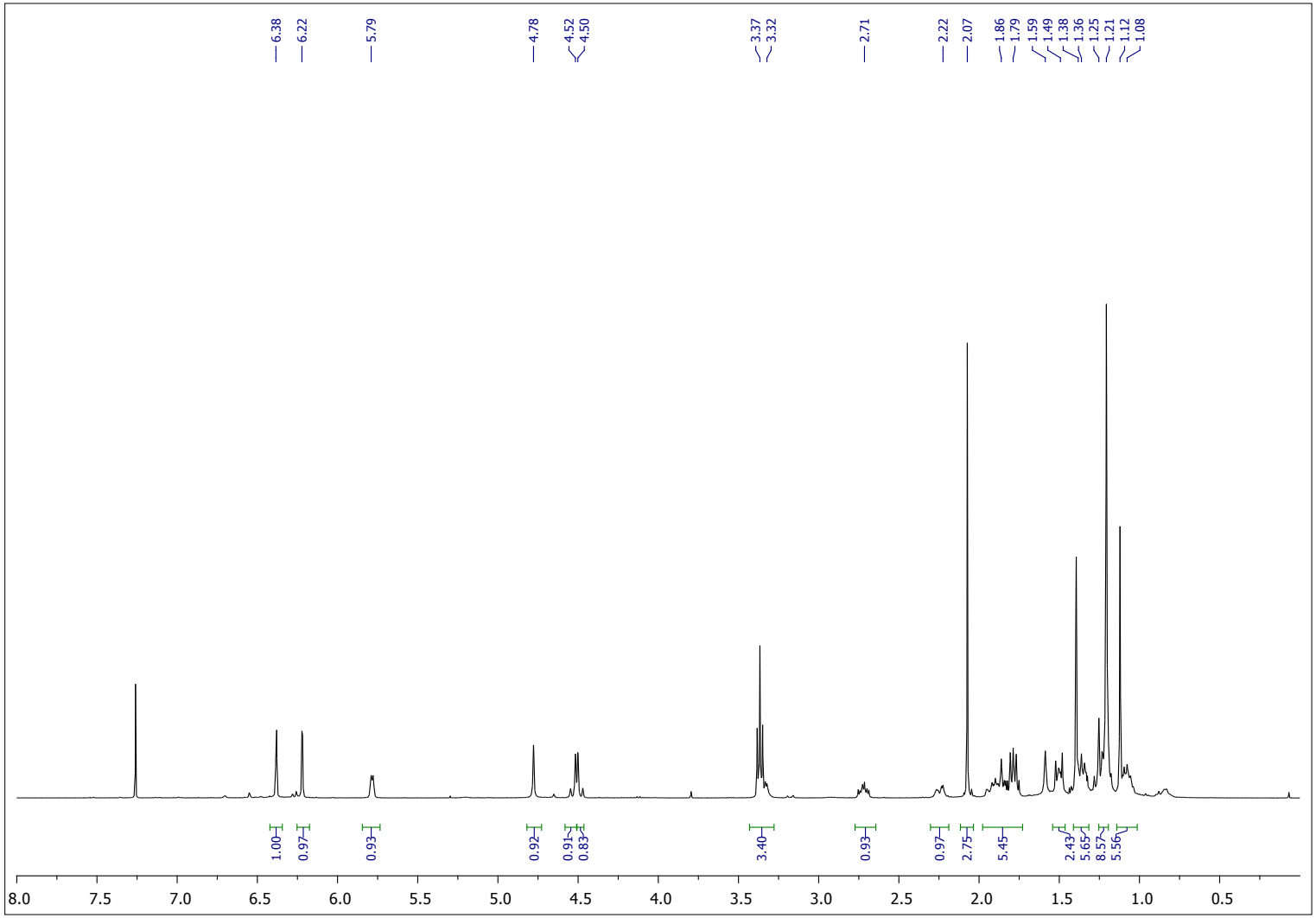
^{1}H NMR of **12**


6.37
6.16
4.65
3.37
1.79
1.56
1.53
1.36
1.23
1.07
2.01
1.00
1.90
1.99
1.96
2.30
2.11
8.22
2.20
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

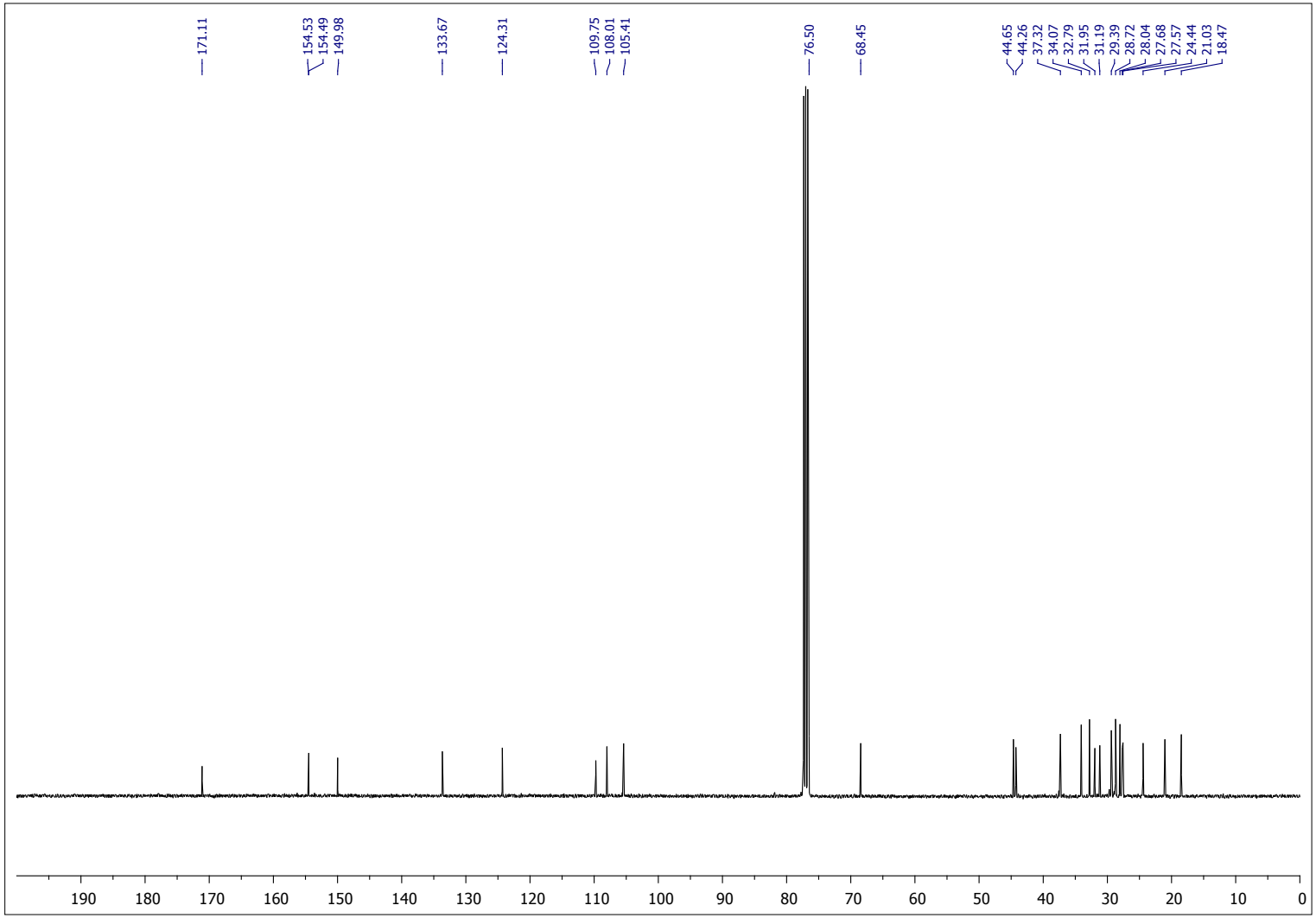
^{13}C NMR of **12**


156.50
153.38
106.02
100.07
44.43
37.88
34.23
32.89
29.50
28.99
28.16
24.57
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

^{1}H NMR of **13**


6.38
6.22
5.79
4.78
4.52
4.50
3.37
3.32
2.71
2.22
2.07
1.86
1.79
1.59
1.49
1.38
1.36
1.25
1.21
1.12
1.08
1.00
0.97
0.93
0.92
0.91
0.83
3.40
0.93
0.97
2.75
5.45
2.43
5.65
8.57
5.56
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

^{13}C NMR of **13**


171.11
154.53
154.49
149.98
133.67
124.31
109.75
108.01
105.41
76.50
68.45
44.65
44.26
37.32
34.07
32.79
31.95
31.19
29.39
28.72
28.04
27.68
27.57
24.44
21.03
18.47
190
180
170
160
150
140
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110
100
90
80
70
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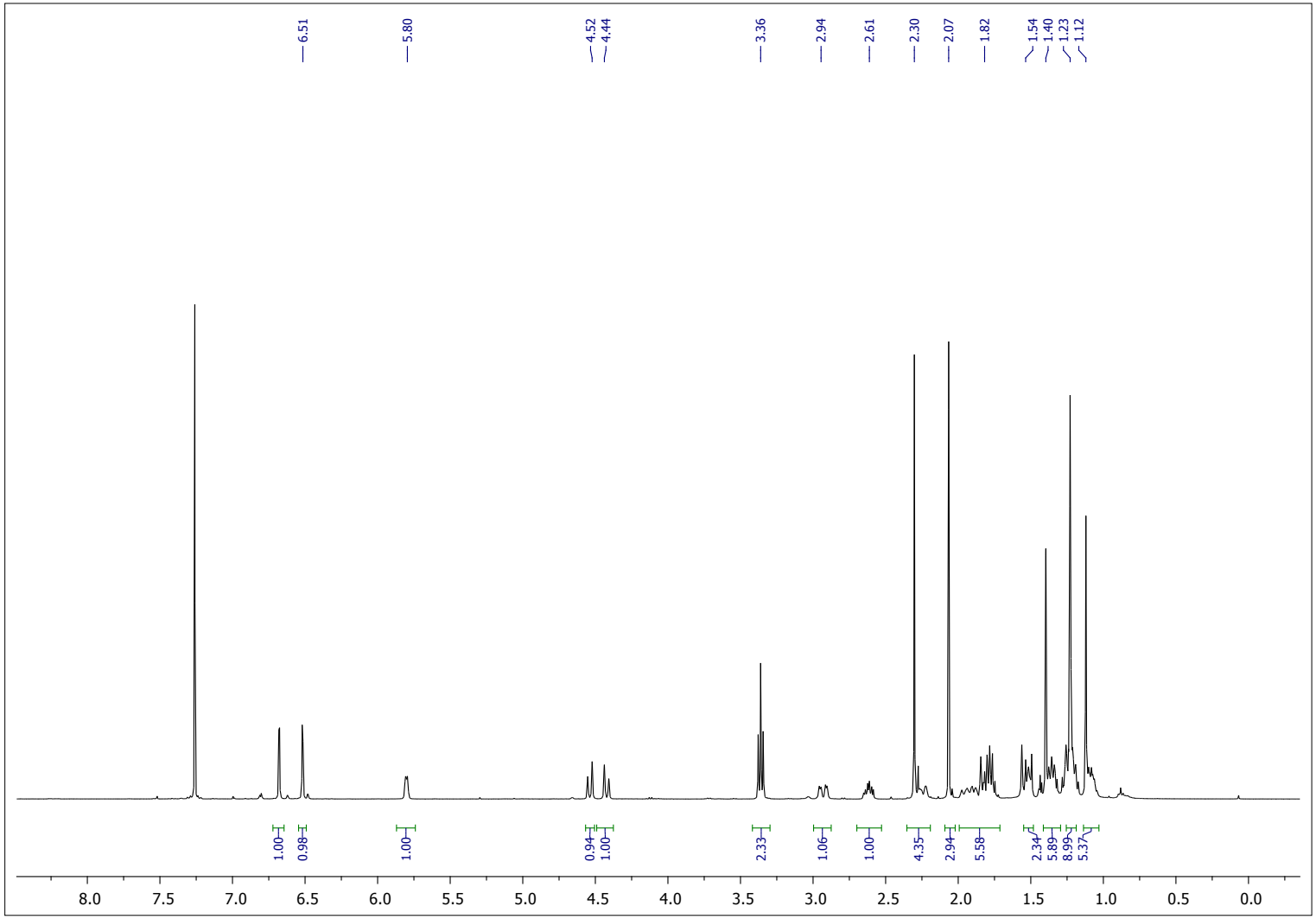
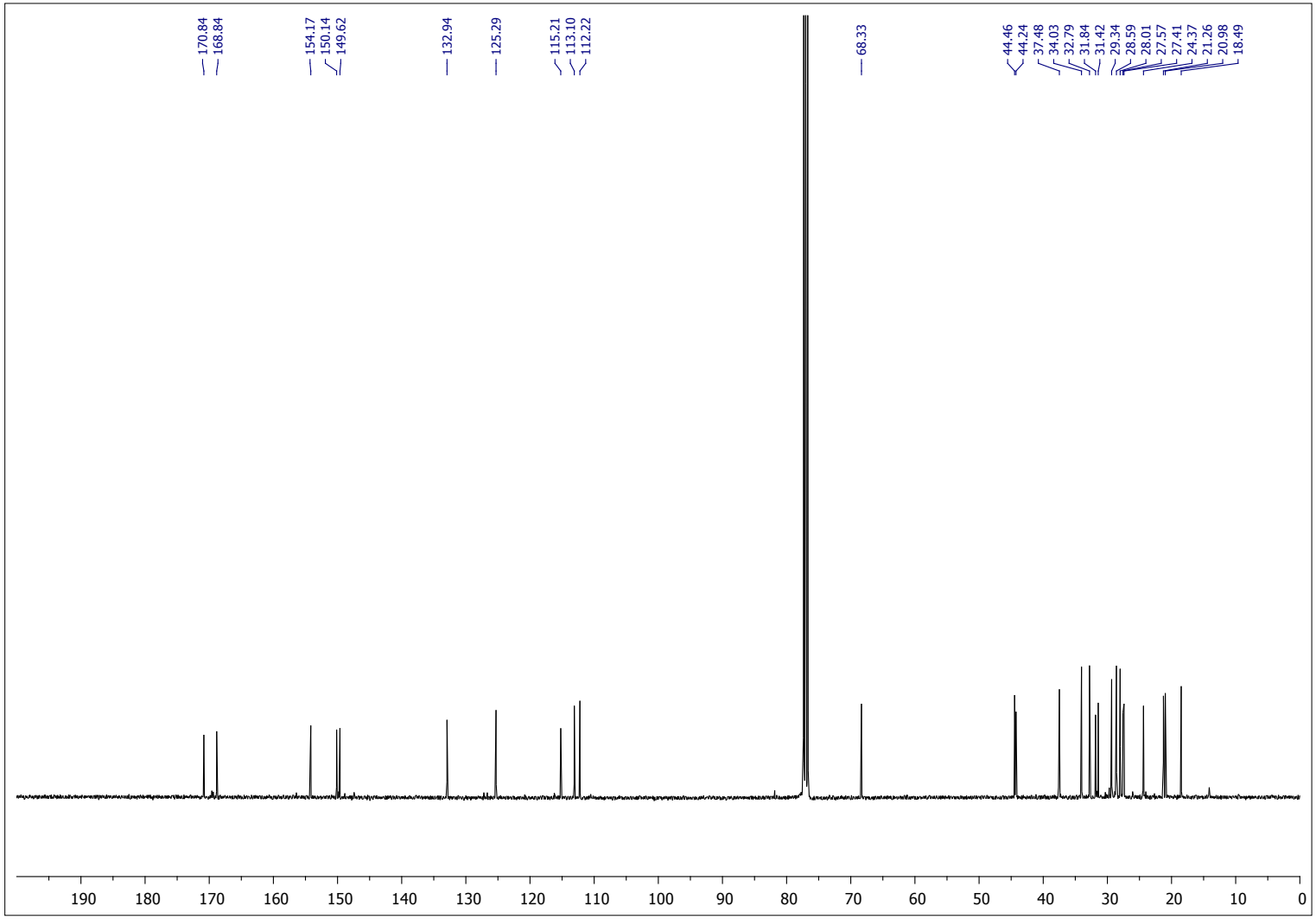
50
40
30
20
10
0

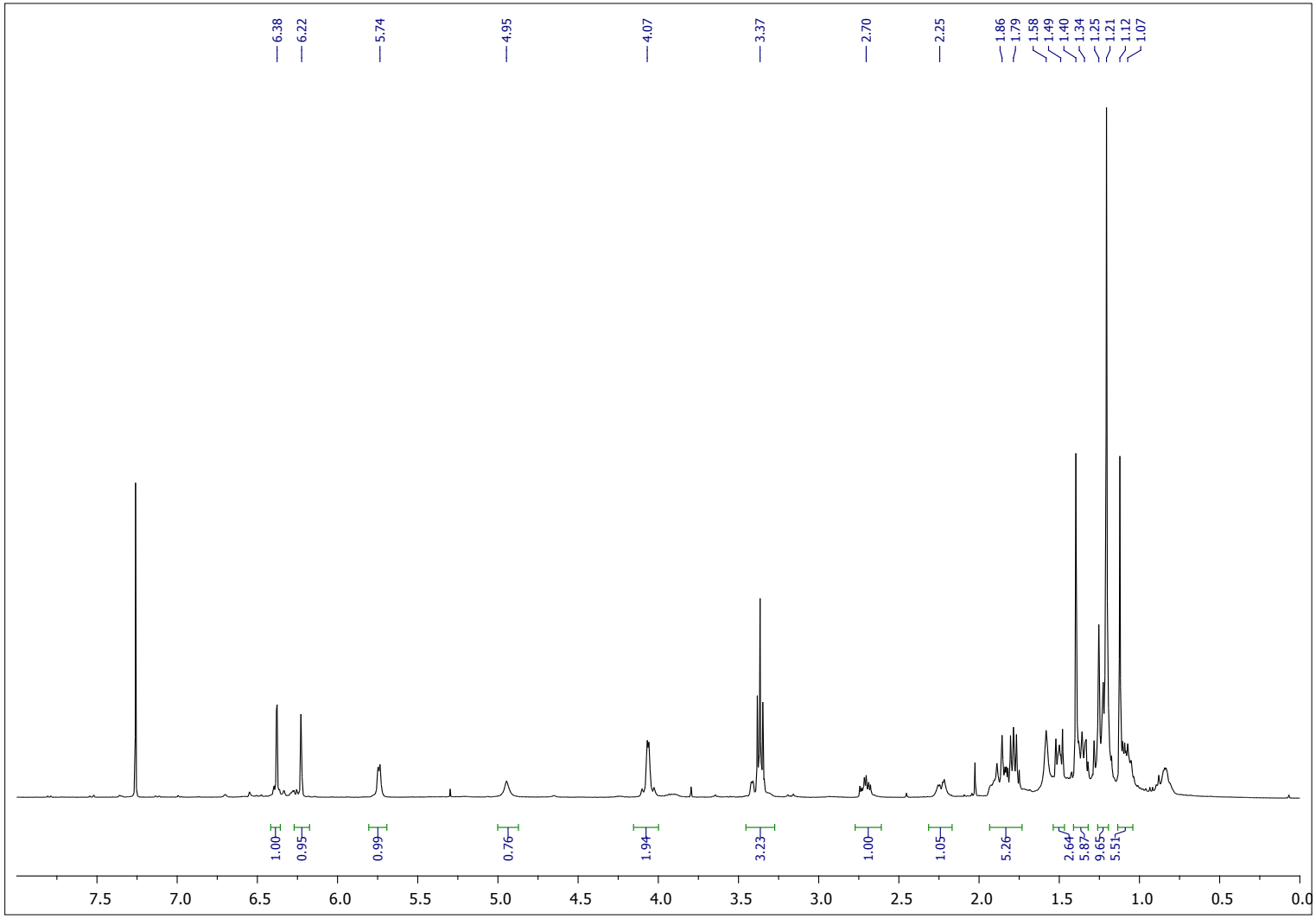
^{1}H NMR of **14a**


6.51
5.80
4.52
4.44
3.36
2.94
2.61
2.30
2.07
1.82
1.54
1.40
1.23
1.12
1.00
0.98
1.00
0.94
1.00
2.33
1.06
1.00
4.35
2.94
5.58
2.34
5.89
8.99
5.37
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

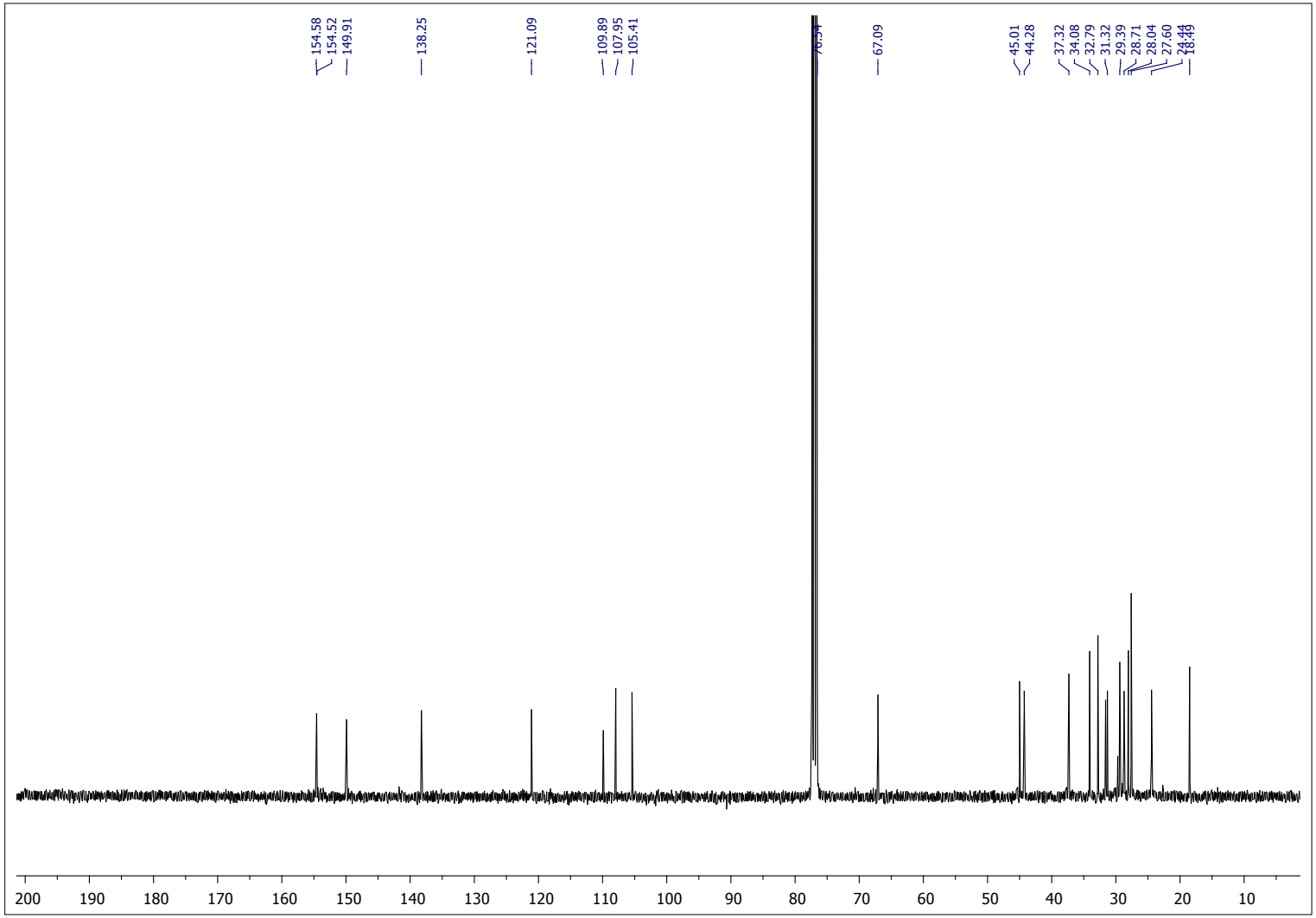
^{13}C NMR of **14a**



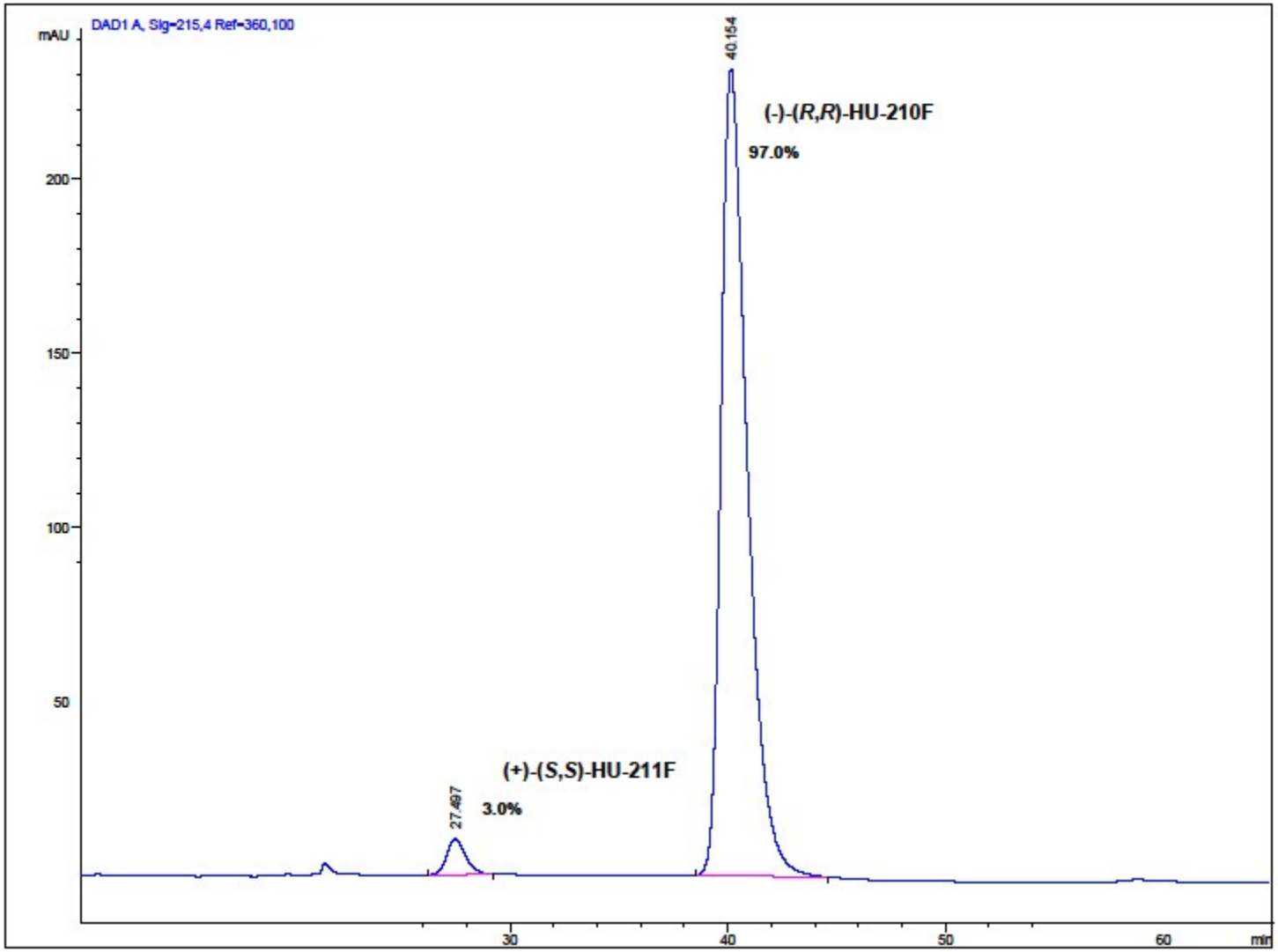
^{1}H NMR of **14b**


6.38
6.22
5.74
4.95
4.07
3.37
2.70
2.25
1.86
1.79
1.58
1.49
1.40
1.34
1.25
1.21
1.12
1.07
1.00
0.95
0.99
0.76
1.94
3.23
1.00
1.05
5.26
2.64
5.87
9.65
5.51
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

^{13}C NMR of **14b**

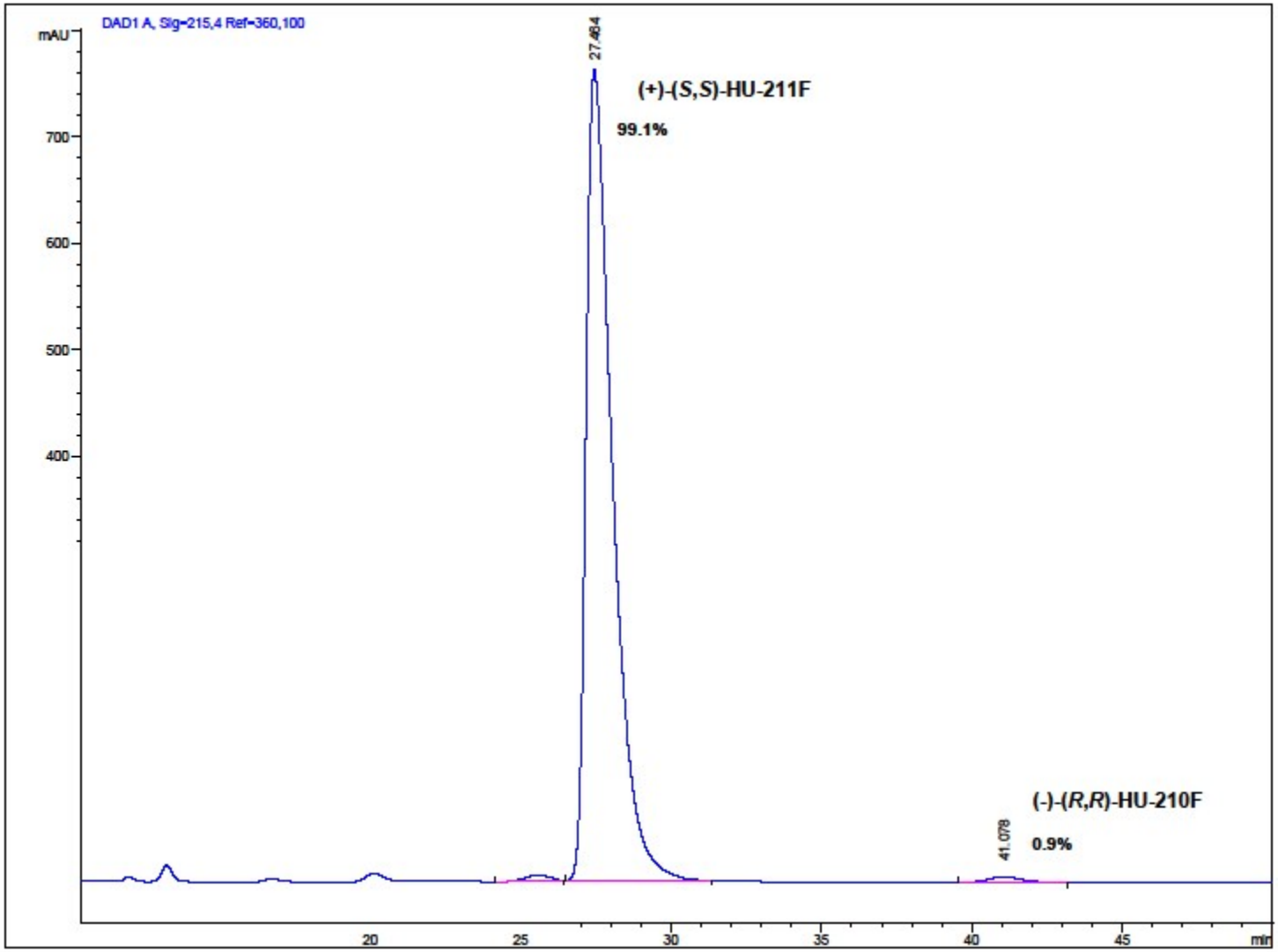


(-)-(*R,R*)-HU-210F Before Purification



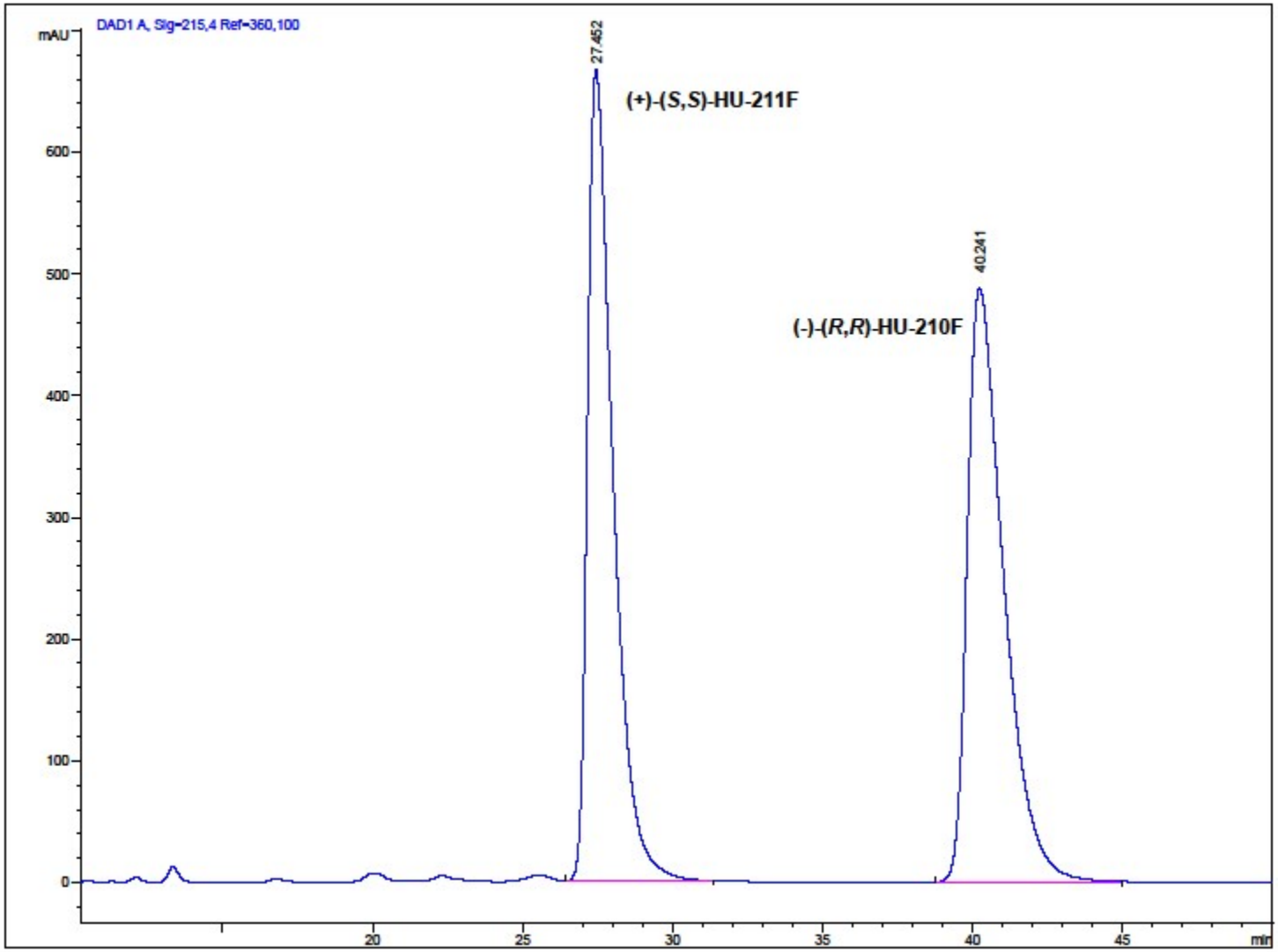
ChiralPak AD-I, 250x4.6mm, 5µm; Hexane : IPA (96:4); isocratic condition;1mL/min.

(+)-(*S*,*S*)-HU-211F Before Purification



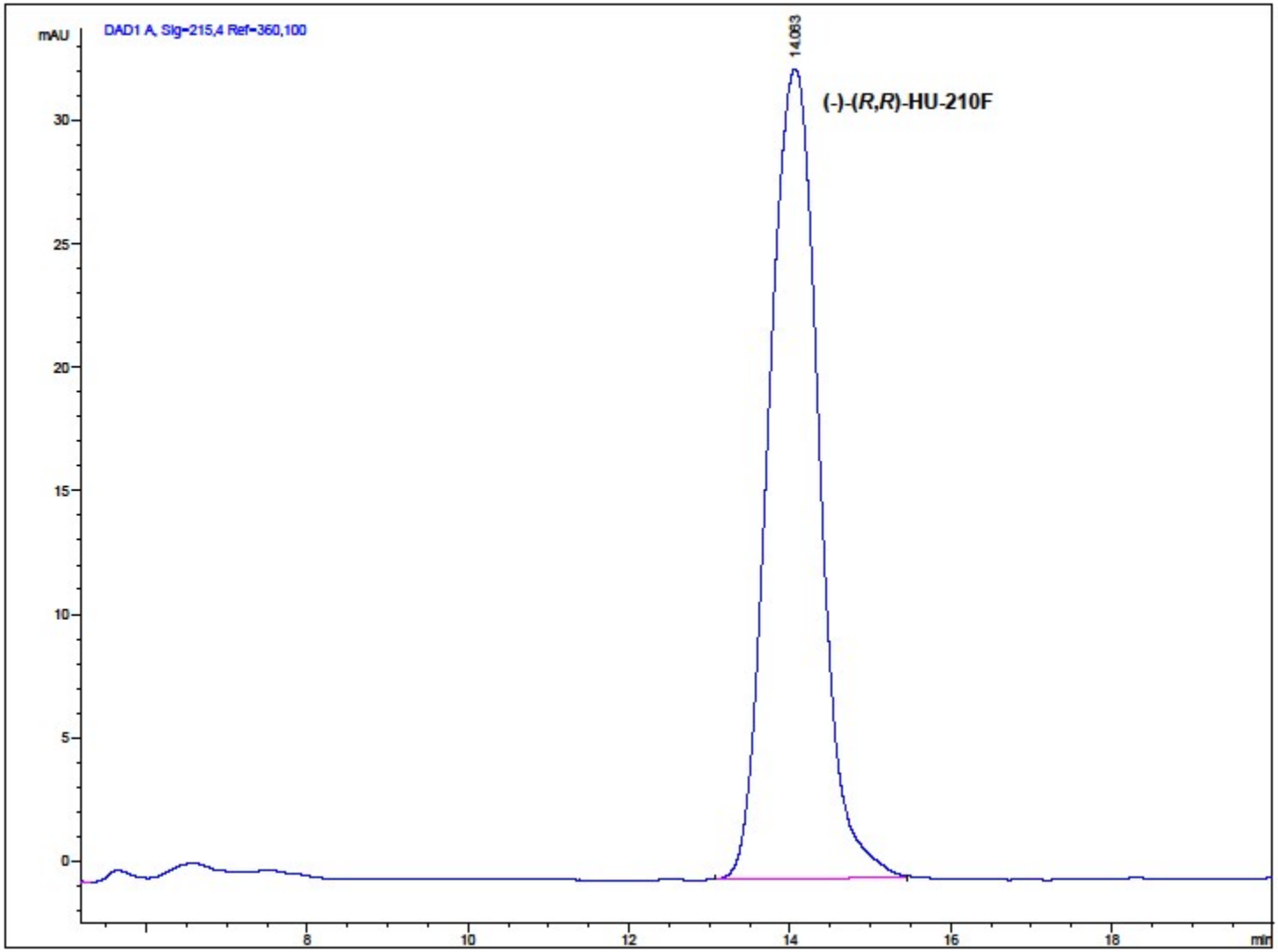
ChiralPak AD-I, 250x4.6mm, 5μm; Hexane : IPA (96:4); isocratic condition;1mL/min.

(-)-(*R*,*R*)-HU-210F+ (+)-(*S*,*S*)-HU-211F Before Purification



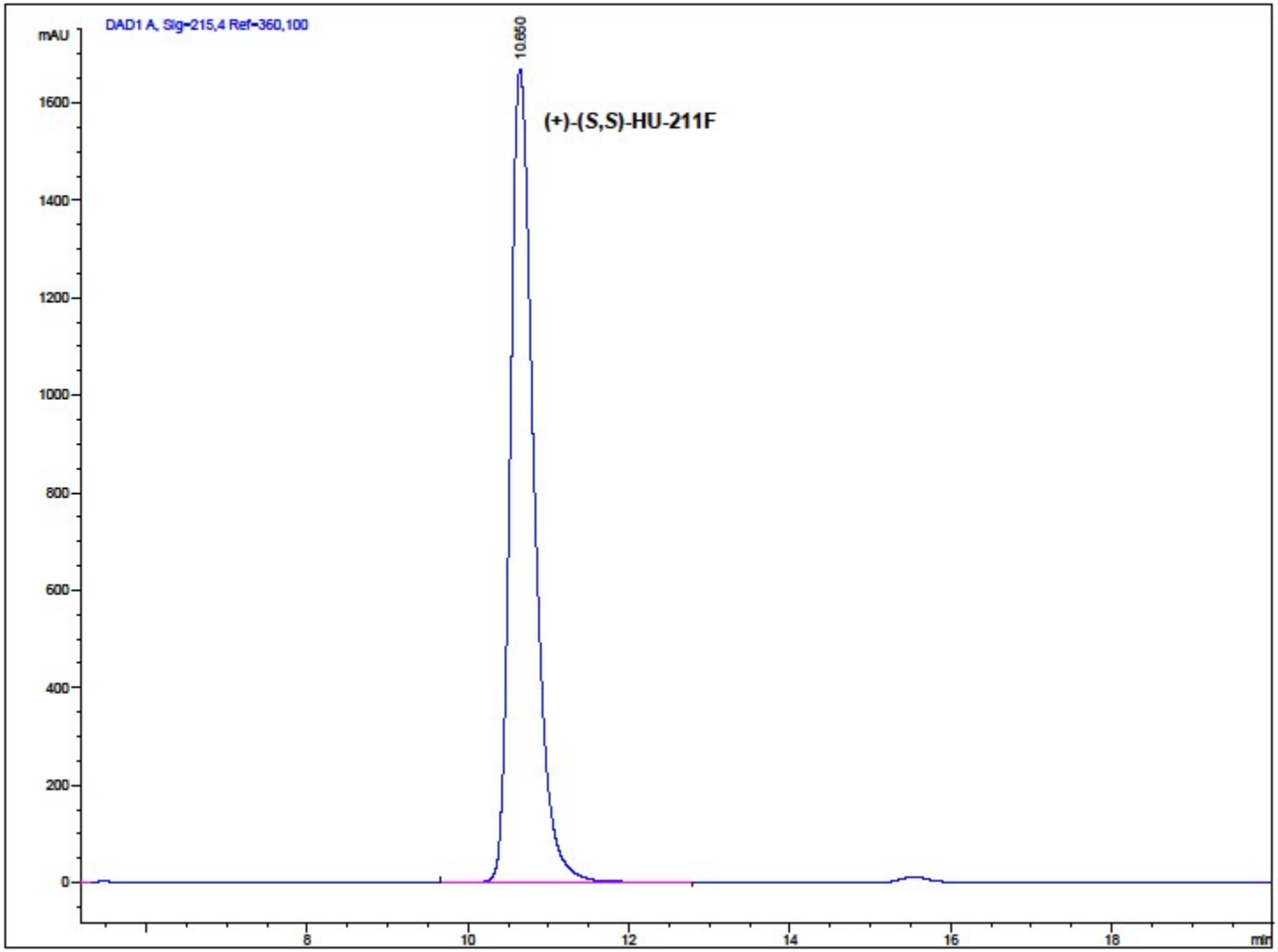
ChiralPak AD-I, 250x4.6mm, 5μm; Hexane : IPA (96:4); isocratic condition;1mL/min.

(-)-(*R*,*R*)-HU-210F After Purification



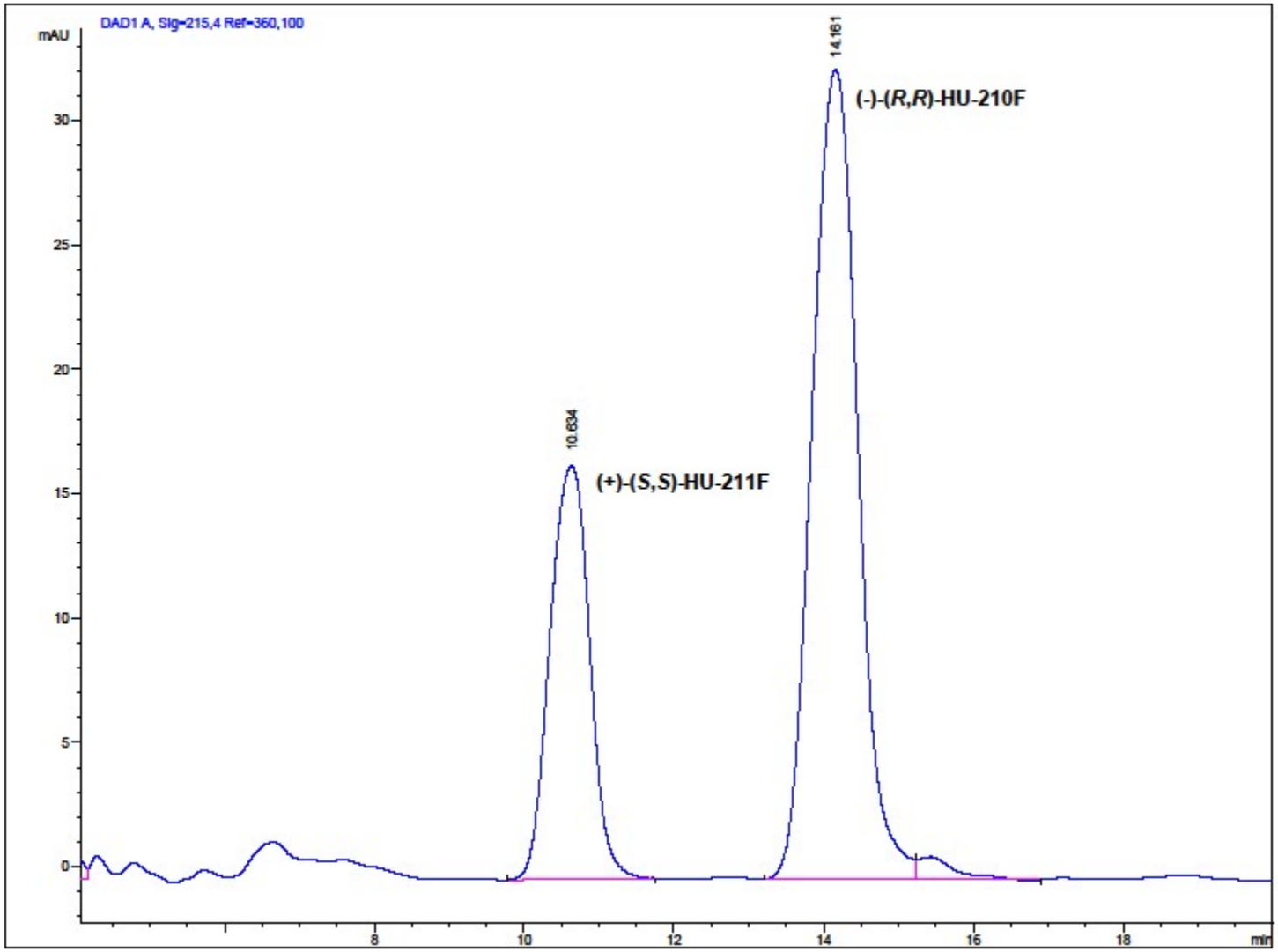
ChiralPak AD-I Semi-prep. 250x20mm, 5μm; Hexane : IPA (92:8); isocratic condition; 5mL/min.

(+)-(*S*,*S*)-HU-211F After Purification



ChiralPak AD-I Semi-prep. 250x20mm, 5μm; Hexane : IPA (92:8); isocratic condition; 5mL/min.

(-)-(*R*,*R*)-HU-210F + (+)-(*S*,*S*)-HU-211F After Purification



ChiralPak AD-I Semi-prep. 250x20mm, 5μm; Hexane : IPA (92:8); isocratic condition; 5mL/min.