

## **BVMO-catalysed dynamic kinetic resolution of racemic benzylketones in presence of anion exchange resins**

Cristina Rodríguez,<sup>a</sup> Gonzalo de Gonzalo,<sup>a</sup> Ana Rioz-Martínez,<sup>a</sup> Daniel E. Torres Pazmiño,<sup>b</sup> Marco W. Fraaije<sup>b</sup> and Vicente Gotor<sup>\*,a</sup>

<sup>a</sup> Departamento de Química Orgánica e Inorgánica, Instituto de Biotecnología de Asturias, Universidad de Oviedo, c/ Julián Clavería 8, 33006, Oviedo, Spain.

e-mail: [vgs@fq.uniovi.es](mailto:vgs@fq.uniovi.es)

<sup>b</sup> Laboratory of Biochemistry, Groningen Biomolecular Sciences and Biotechnology Institute, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands.

### Supporting Information

#### **Contents**

1. Characterization data of compounds.....	S2
2. Experimental data.....	S4
3. NMR Spectra.....	S6

## 1. Characterization data of compounds.

**(S)-1-Phenylethyl acetate (1b, colourless oil).** (38.2 mg, 69% yield);  $\delta_{\text{H}}$  (300.13 MHz,  $\text{CDCl}_3$ ,  $\text{Me}_4\text{Si}$ ) 1.56 (3H, d,  $J$  6.6 Hz), 2.10 (3H, s), 5.91 (1H, q,  $J$  6.6 Hz), 7.28-7.39 (5H, m);  $\delta_{\text{C}}$  (75.5 MHz,  $\text{CDCl}_3$ ,  $\text{Me}_4\text{Si}$ ) 20.9, 21.7, 71.8, 125.6, 125.7, 127.4, 128.0, 128.1, 141.2, 169.8;  $m/z$  (APCI<sup>+</sup>) 165 ( $\text{M}+\text{H}^+$ , 100%). Determination of the *ee* by GC analysis: RT $\beta$ DEXse, 70°C (5 min), 1°C/min, 120°C (5 min),  $t_{\text{R}}$  (R) 50.5 min;  $t_{\text{R}}$  (S) 42.9 min.

**(S)-1-(3-Methylphenyl)ethyl acetate (2b, colourless oil).** (32.9 mg, 60% yield);  $\delta_{\text{H}}$  (300.13 MHz,  $\text{CDCl}_3$ ,  $\text{Me}_4\text{Si}$ ) 1.53 (3H, d,  $J$  6.6 Hz), 2.08 (3H, s), 2.36 (3H, s), 5.85 (1H, q,  $J$  6.6 Hz), 7.09-7.25 (4H, m);  $\delta_{\text{C}}$  (75.5 MHz,  $\text{CDCl}_3$ ,  $\text{Me}_4\text{Si}$ ) 21.3, 21.4, 22.1, 72.3, 123.0, 126.7, 128.3, 128.6, 138.1, 141.5, 170.3;  $m/z$  (EI<sup>+</sup>) 178 ( $\text{M}^+$ , 28%), 136 (100%), 117 (91%). Determination of the *ee* by GC analysis: Chirasil DexCB, 70°C, 1°C/min, 120°C (5 min),  $t_{\text{R}}$  (R) 32.7 min;  $t_{\text{R}}$  (S) 29.0 min.

**(S)-1-(3-Trifluoromethylphenyl)ethyl acetate (3b, colourless oil).** (40.3 mg, 75% yield);  $\delta_{\text{H}}$  (300.13 MHz,  $\text{CDCl}_3$ ,  $\text{Me}_4\text{Si}$ ) 1.55 (3H, d,  $J$  6.8), 2.10 (3H, s), 5.91 (1H, q,  $J$  6.6), 7.47- 7.61 (4H, m);  $\delta_{\text{C}}$  (75.5 MHz,  $\text{CDCl}_3$ ,  $\text{Me}_4\text{Si}$ ) 21.2, 22.2, 71.5, 122.7 (d,  $J$  3.76 Hz), 124.0 (d,  $J$  270.6 Hz), 124.6 (d,  $J$  3.6 Hz), 128.9, 129.5, 130.9 (d,  $J$  32.0 Hz), 142.7, 170.1;  $m/z$  (EI<sup>+</sup>) 232 ( $\text{M}^+$ , 11%), 190 (90%). Determination of the *ee* by GC analysis: RT $\beta$ DEXse, 100°C (20 min), 2°C/min, 150°C (5 min),  $t_{\text{R}}$  (R) 22.8 min;  $t_{\text{R}}$  (S) 18.3 min.

**(S)-1-(4-Chlorophenyl)ethyl acetate (4b, yellow pale oil).** (32.6 mg, 60% yield);  $\delta_{\text{H}}$  (300.13 MHz,  $\text{CDCl}_3$ ,  $\text{Me}_4\text{Si}$ ) 1.53 (3H, d,  $J$  6.6 Hz), 2.09 (3H, s), 5.86 (1H, q,  $J$  6.6 Hz), 7.28- 7.36 (4H, m);  $\delta_{\text{C}}$  (75.5 MHz,  $\text{CDCl}_3$ ,  $\text{Me}_4\text{Si}$ ) 21.2, 22.1, 71.5, 127.4, 127.5, 128.6, 128.7, 133.5, 140.1, 170.1;  $m/z$  (ESI<sup>+</sup>) 221 ( $\text{M}+\text{Na}^+$ , 100%). Determination of the *ee* by GC analysis: RT $\beta$ DEXse, 110°C (10 min), 1°C/min, 140°C (5 min),  $t_{\text{R}}$  (R) 38.5 min;  $t_{\text{R}}$  (S) 34.6 min.

**(S)-1-Phenylethyl propionate (5b, colourless oil).** (32.4 mg, 59% yield);  $\delta_{\text{H}}$  (300.13 MHz,  $\text{CDCl}_3$ ,  $\text{Me}_4\text{Si}$ ) 1.06 (3H, t,  $J$  7.4 Hz), 1.45 (3H, d,  $J$  6.6 Hz), 2.22-2.31 (2H, m), 5.81 (1H, q,  $J$  6.6 Hz), 7.17-7.27 (5H, m);  $\delta_{\text{C}}$  (75.5 MHz,  $\text{CDCl}_3$ ,  $\text{Me}_4\text{Si}$ ) 9.0, 22.2, 27.8, 72.0, 126.0, 126.1, 127.7, 128.2, 128.3, 141.8, 173.6;  $m/z$  (APCI<sup>+</sup>) 179 ( $\text{M}+\text{H}^+$ , 100%)..

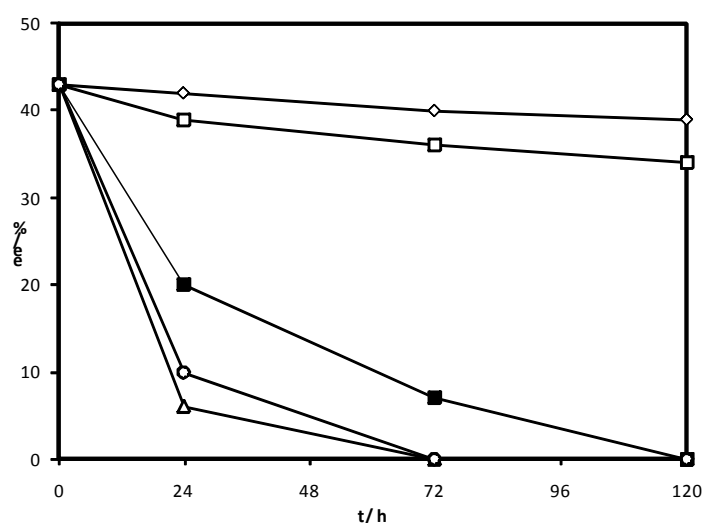
Determination of the *ee* by GC analysis: Rt $\beta$ DEXse, 70 °C (5 min), 3°C/ min, 200 °C (5 min):  $t_R$  (*R*) 29.3 min;  $t_R$  (*S*) 28.9 min.

**(S)-1-Phenylpropyl acetate (6b, colourless oil)**: (34.6 mg, 63% yield);  $\delta_H$  (300.13 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si) 0.88 (3H, t, *J* 7.4 Hz), 1.81-1.95 (2H, m), 2.08 (3H, s), 5.67 (1H, t, *J* 6.9 Hz), 7.28-7.37 (5H, m);  $\delta_C$  (75.5 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si) 9.8, 21.2, 29.2, 77.3, 126.5, 126.6, 127.7, 128.3, 128.4, 140.4, 170.4;  $m/z$  (APCI<sup>+</sup>) 179 (M+H<sup>+</sup>, 100%).  
Determination of the *ee* by GC analysis: Rt $\beta$ DEXse, 110 °C isotherm:  $t_R$  (*R*) 26.6 min;  $t_R$  (*S*) 23.7 min.

**(S)-1-Phenylbutyl propionate (7b, yellow pale oil)**. (20.6 mg, 38% yield);  $\delta_H$  (300.13 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si) 0.85 (3H, t, *J* 7.2 Hz), 1.07 (3H, t, *J* 7.4 Hz), 1.15-1.34 (2H, m), 1.61-1.73 (1H, m), 1.77-1.90 (1H, m), 2.24-2.33 (2H, m), 5.69 (1H, t, *J* 7.0 Hz), 7.20-7.28 (5H, m);  $\delta_C$  (75.5 MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si) 9.1, 13.7, 18.7, 27.8, 38.5, 75.6, 126.4, 126.5, 127.7, 128.2, 128.3, 140.9, 173.7;  $m/z$  (ESI<sup>+</sup>) 229 (M<sup>+</sup>+Na, 100%).  
Determination of the *ee* by GC analysis: Hydrodex  $\beta$ -TBOAc, 50 °C (10 min), 1°C/min, 120°C (5 min):  $t_R$  (*R*) 78.4 min;  $t_R$  (*S*) 78.8 min.

## 2. Experimental data.

Racemisation experiments were performed by dissolving optically active 3-phenylpentan-2-one (*R*)-**1a** (10 mM) isolated from the preparative kinetic resolution of ( $\pm$ )-**1a** performed at pH 8.0 and 20°C with HAPMO, in Tris/HCl buffer containing the anion exchange resins at the selected conditions (pH and temperature). The solution was shaken for different reaction times and aliquots were taken, extracted with ethyl acetate, dried onto Na<sub>2</sub>SO<sub>4</sub> and analyzed by GC in order to determine the enantiomeric excesses. Results are summarized in Figure 1.



**Figure 1.** Racemisation of ketone (*R*)-**1a** (10 mM) when dissolved in different reaction media: Tris/HCl pH 8.0 (◇), Tris/HCl pH 10.0 (□) and Tris/HCl pH 10.0 containing: Amberlite IRA-440C (△), Lewatit MP62 (■) or Dowex MWA-1 (○).

Racemisation is supposed to be a pseudo-first order reaction. Relative initial rate constants ( $k_{rac}$ ) were determined from the enantiomeric excesses of ketone **1a** according to Equation 1:

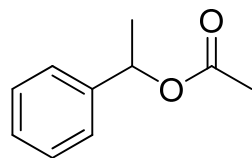
$$ee(t) = ee(0)e^{-2(k_{rac})t}$$

where  $ee(t)$  is the enantiomeric excess of **1a** at the time established,  $ee(0)$  the initial optical purity of **1a**,  $k_{rac}$  is the relative initial racemisation constant and  $t$  is the time of measurement.

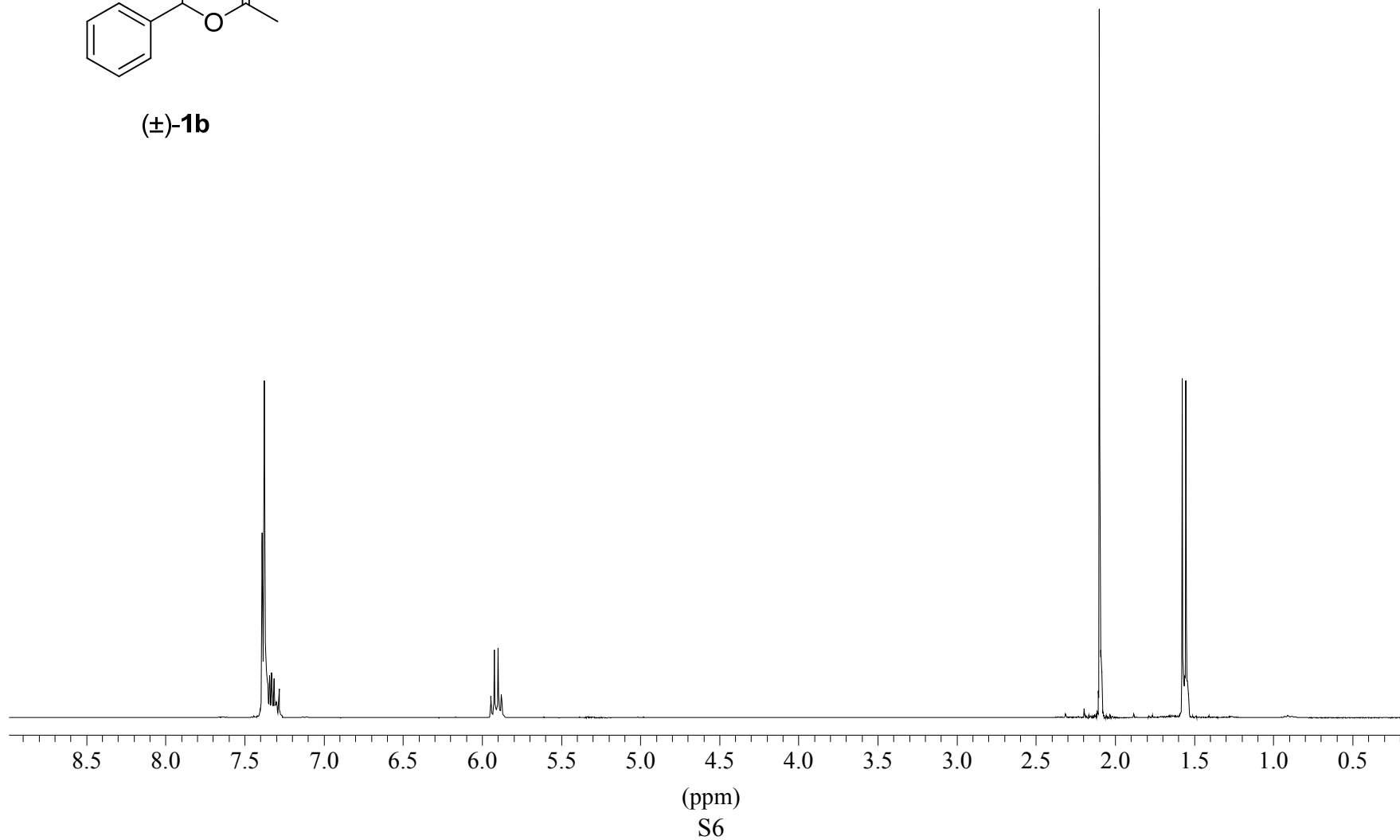
Racemisation studies were also performed with optically pure (*S*)-1-phenylethyl acetate (*S*)-**1b**. This compound was dissolved in Tris/HCl buffer at different reaction conditions (pH and anion exchange resins). The solution was shaken for different reaction times

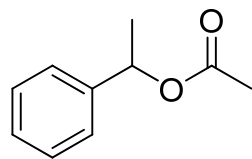
and aliquots were taken, extracted with ethyl acetate, dried onto Na<sub>2</sub>SO<sub>4</sub> and analyzed by GC in order to determine the enantiomeric excesses. No change in optical purity of (*S*)-**1b** was observed after 120 h at all the conditions tested.

### 3. NMR Spectra

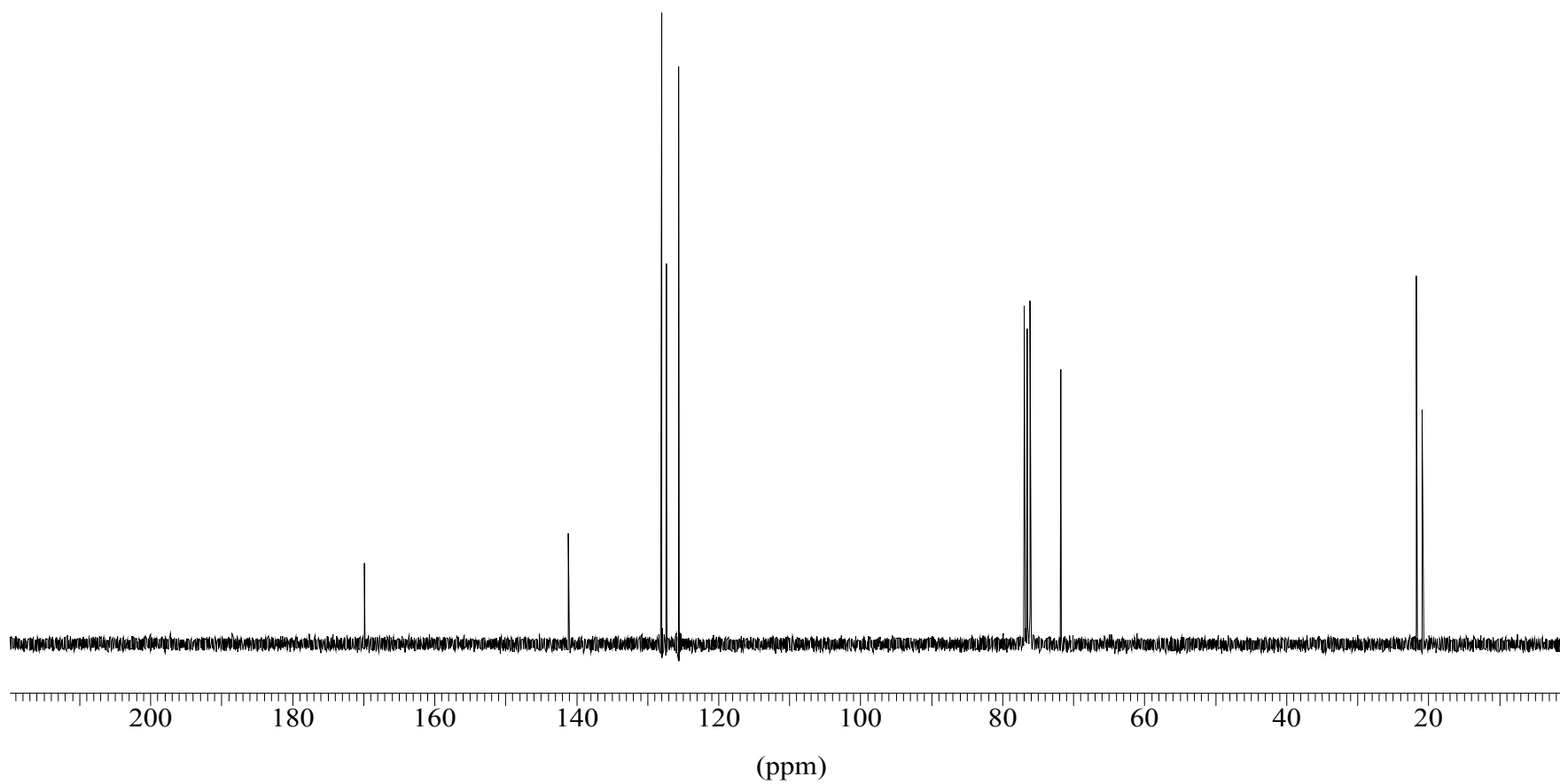


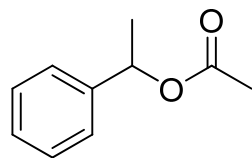
(±)-1b



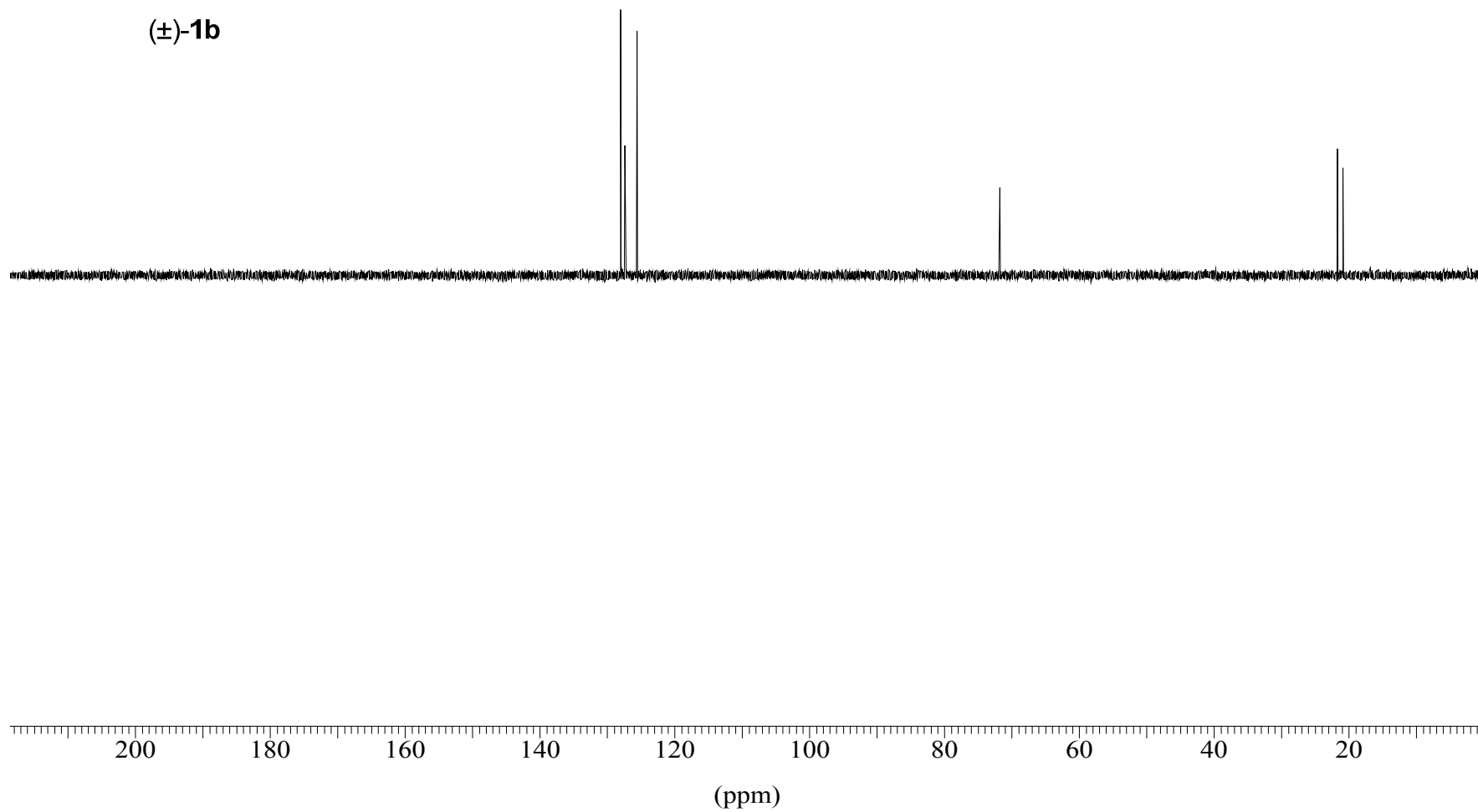


**(±)-1b**

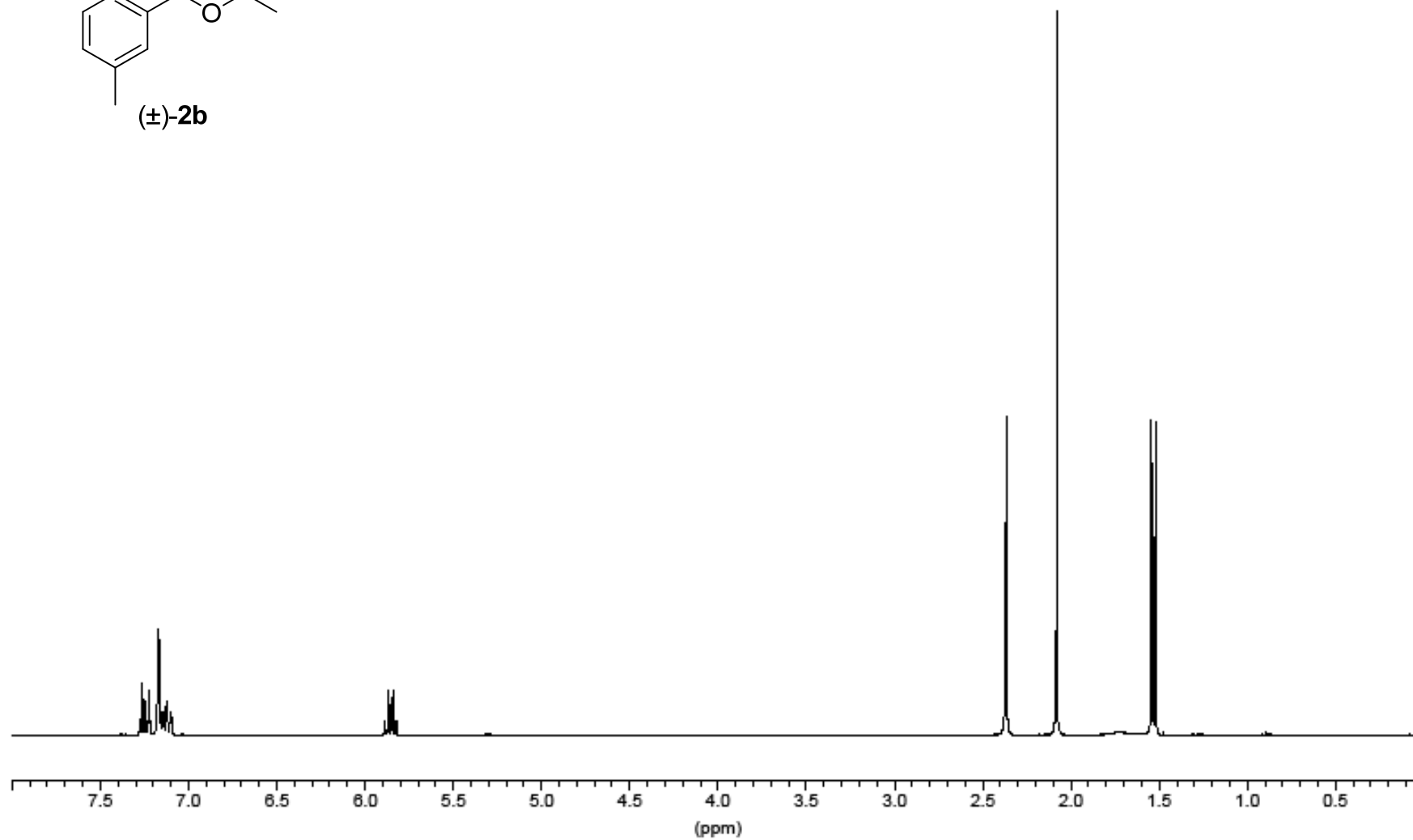
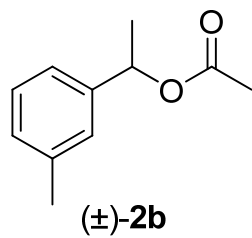


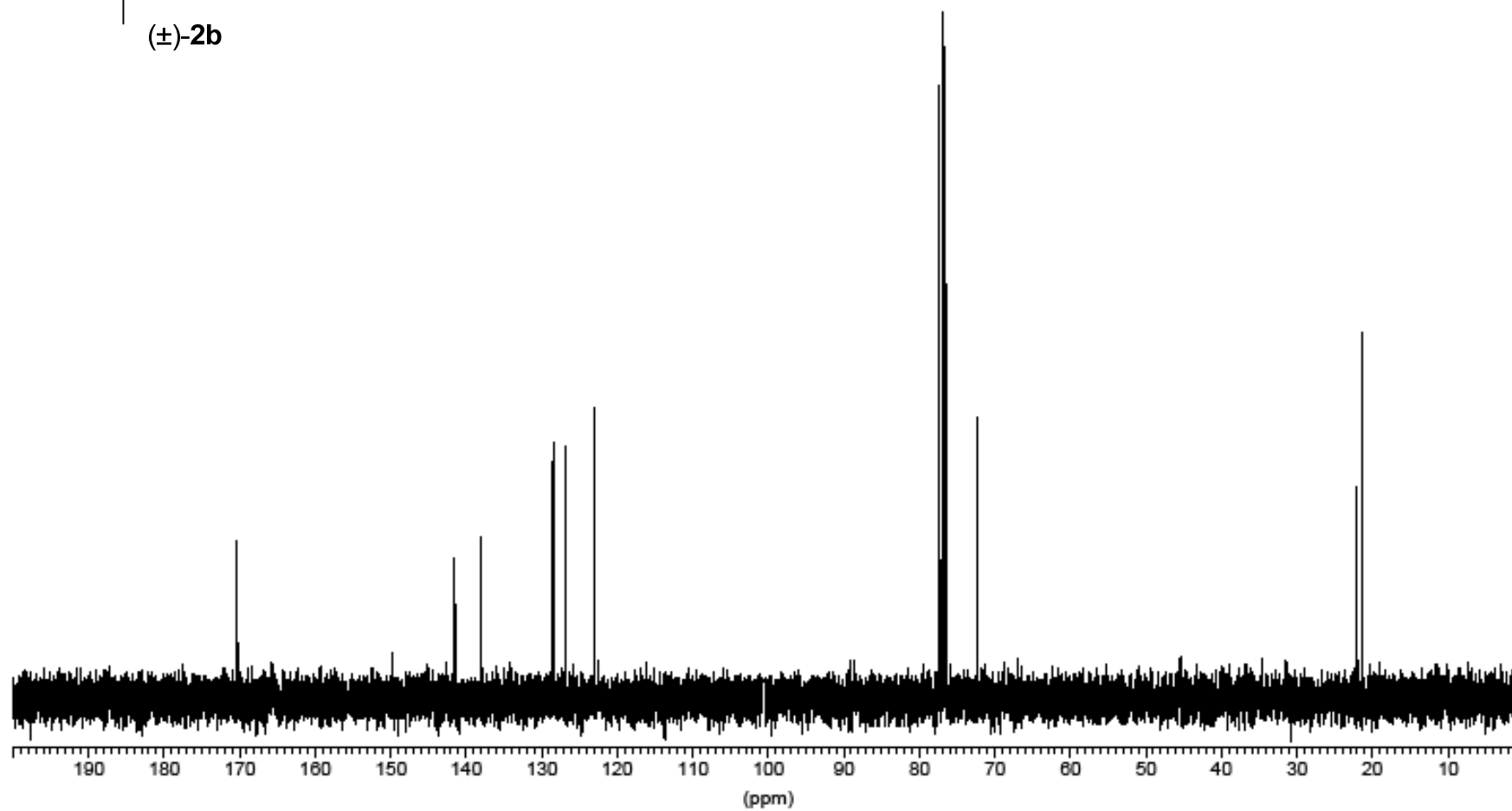
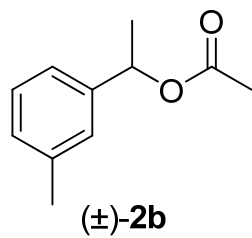


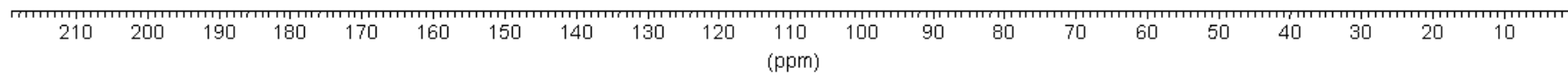
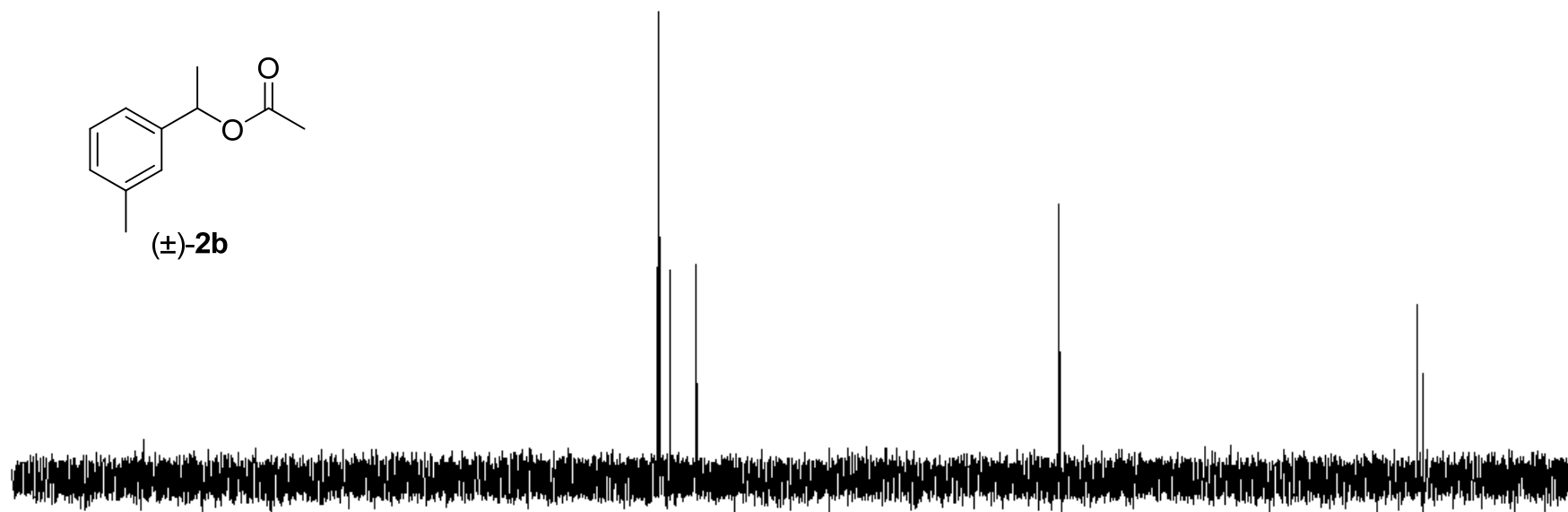
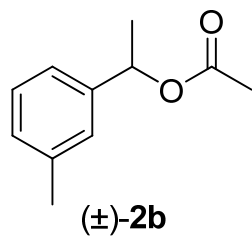
(±)-**1b**

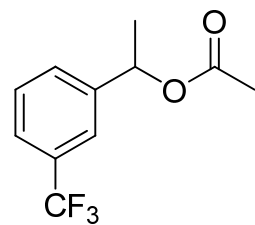




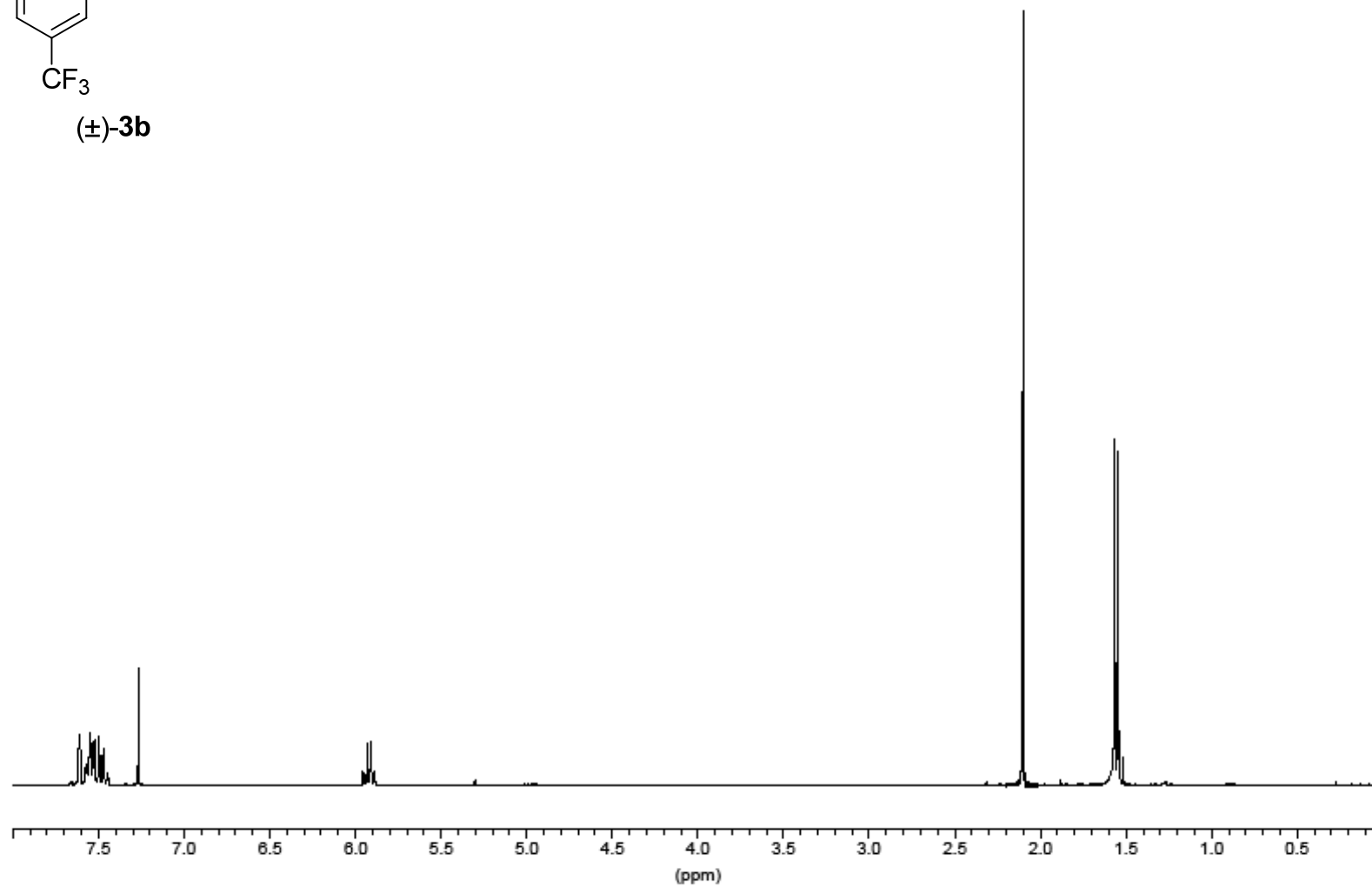


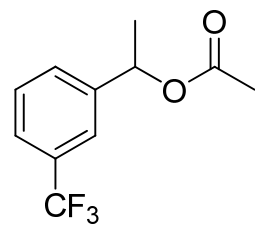




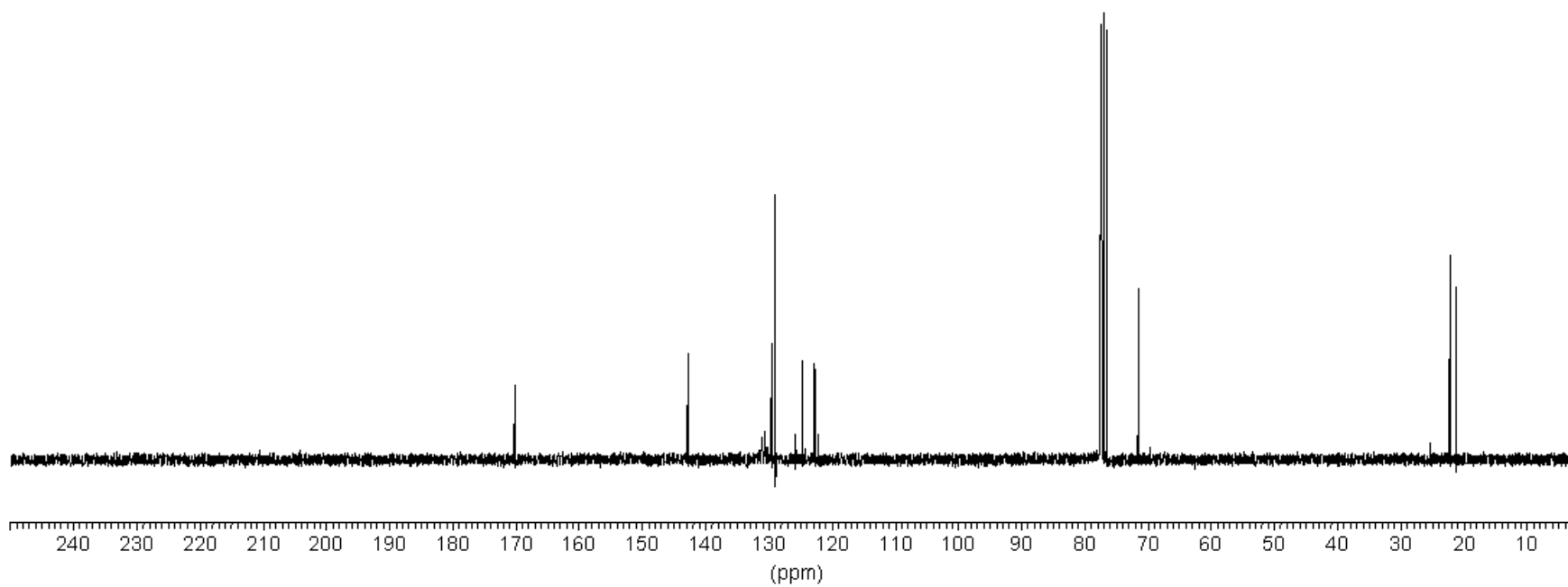


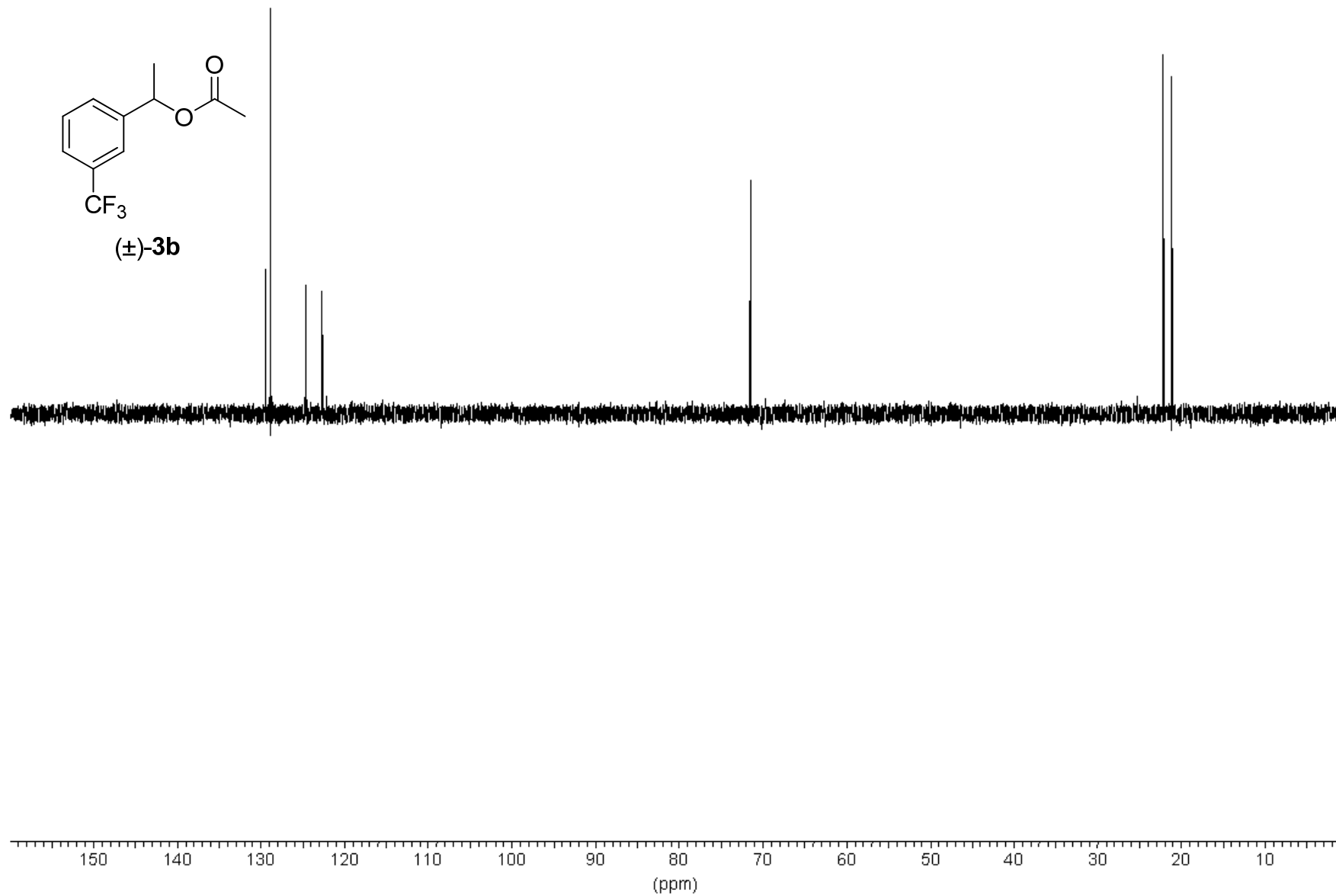
(±)-3b

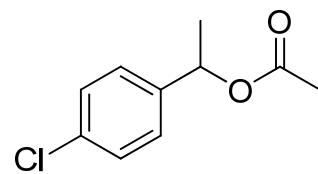




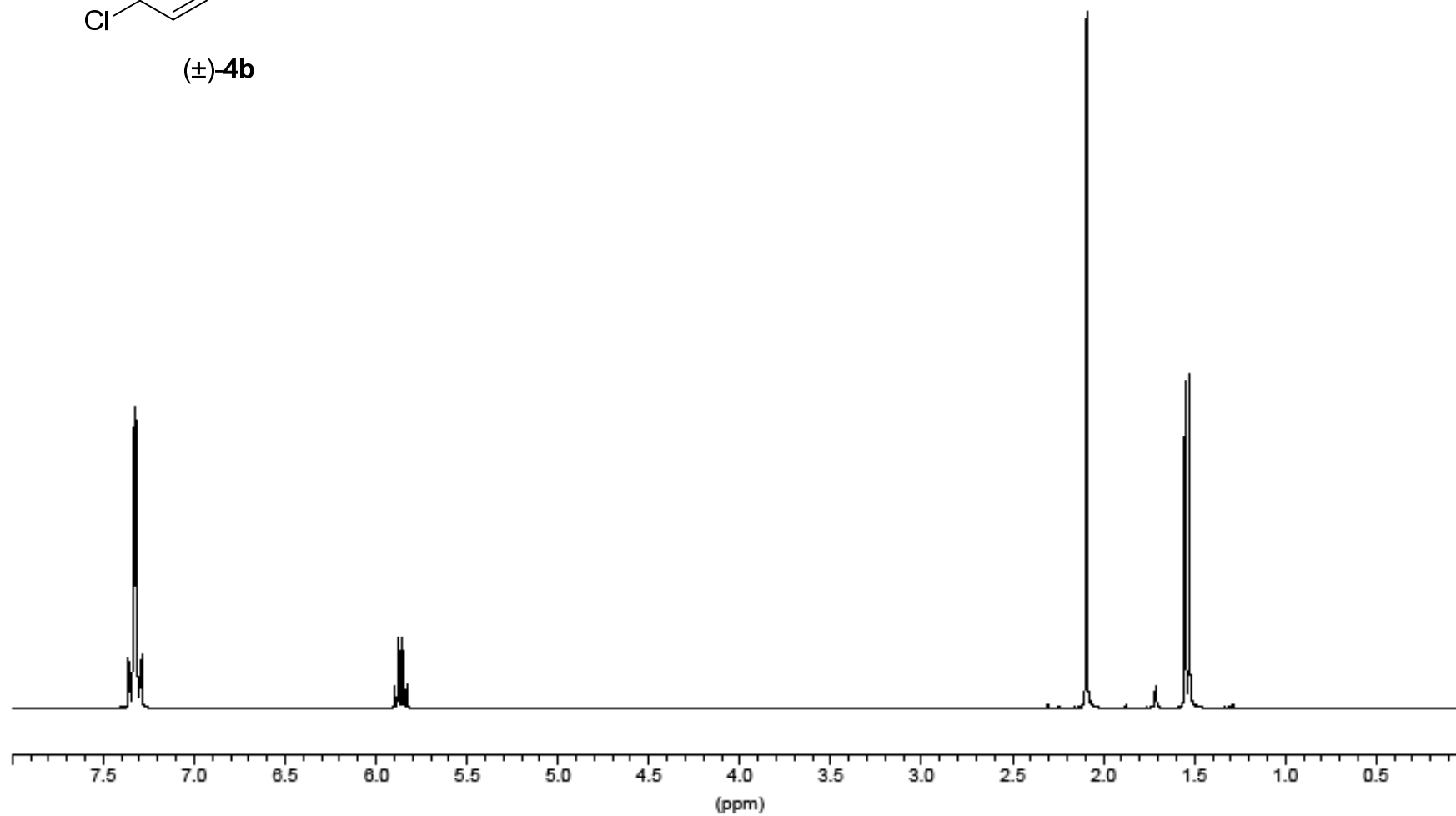
(±)-3b

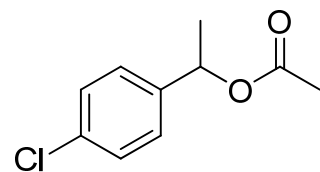




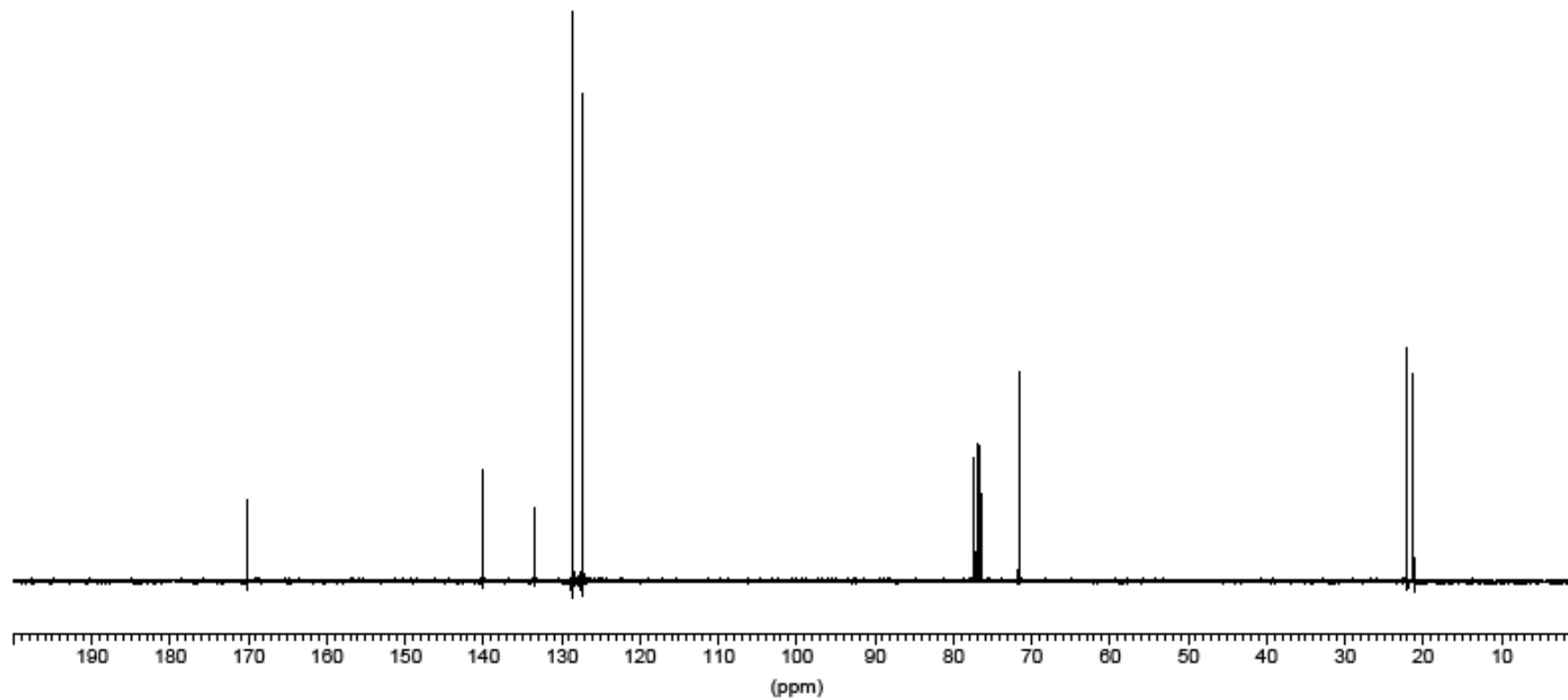


(±)-4b

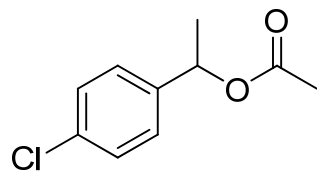




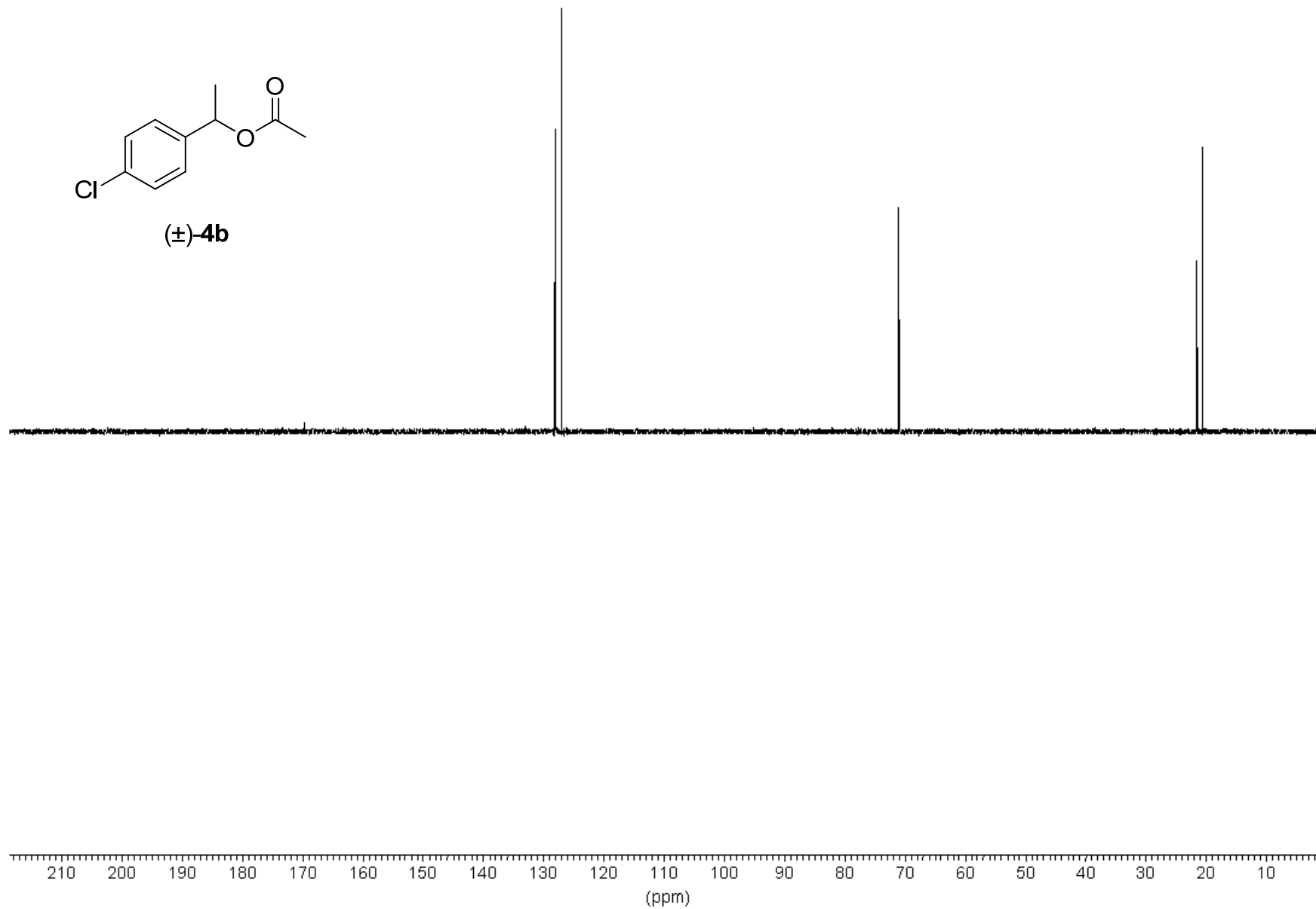
(±)-4b

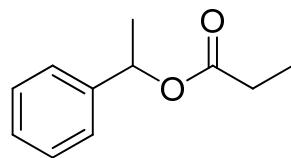




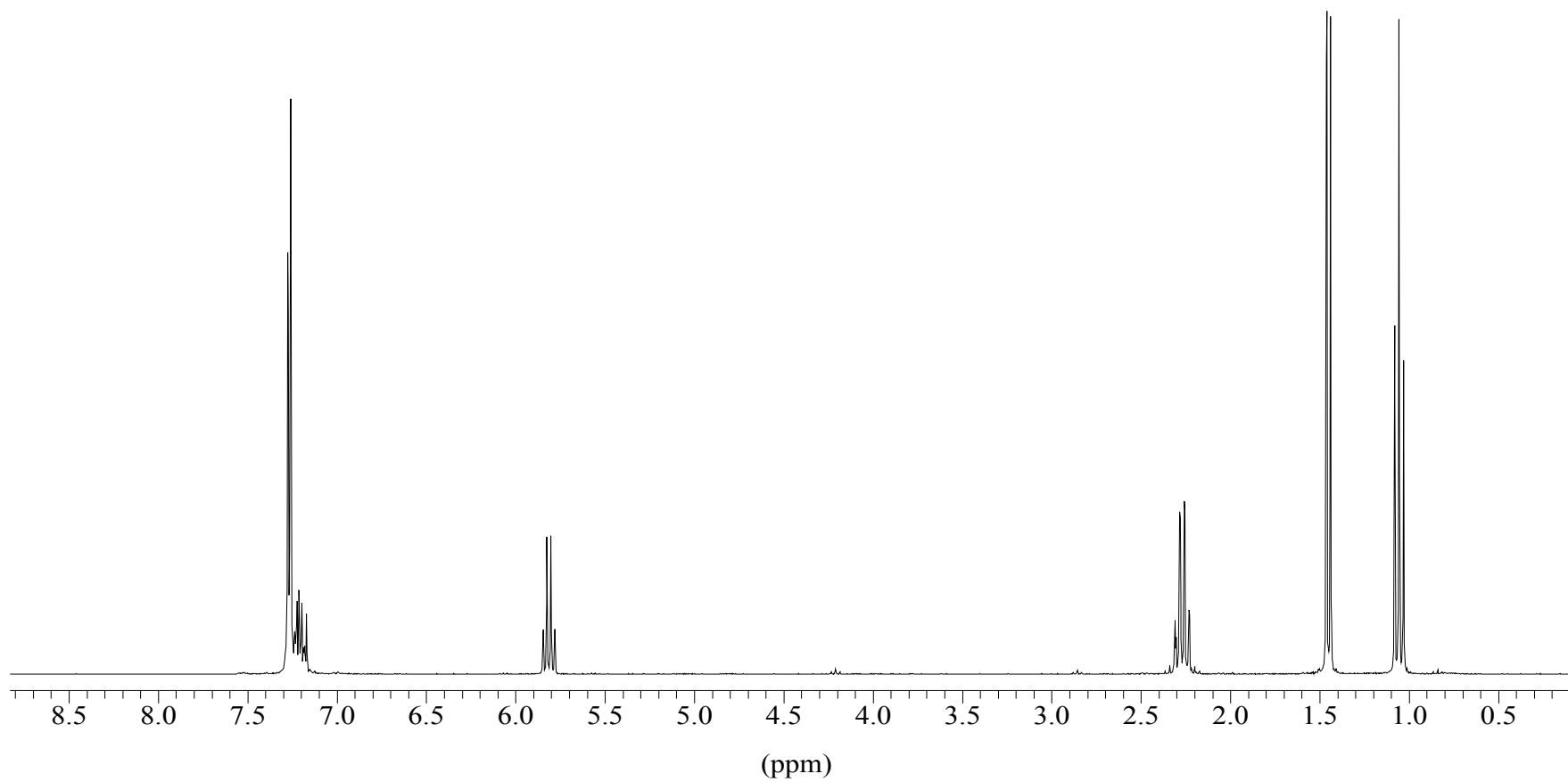


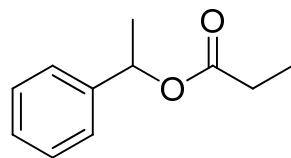
(±)-4b



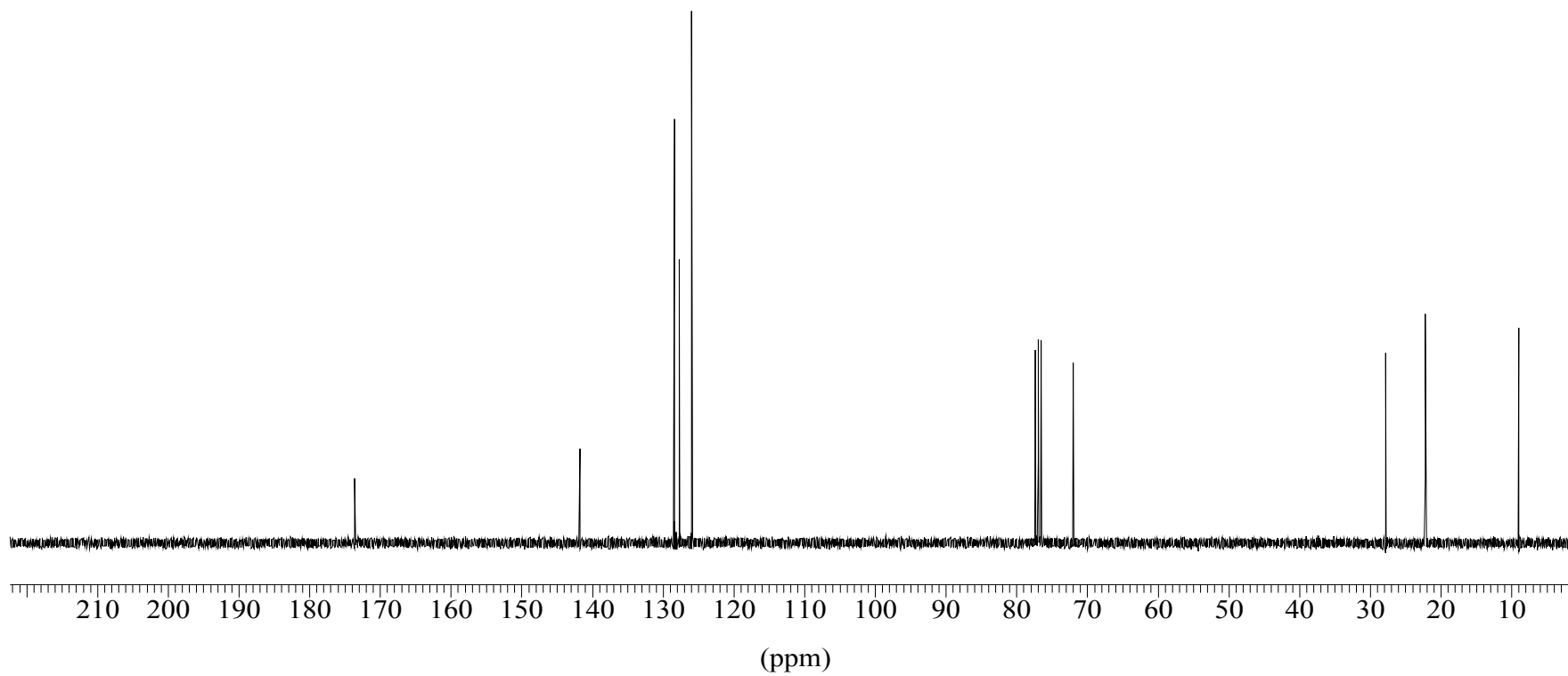


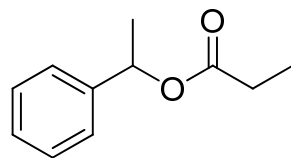
**(±)-5b**



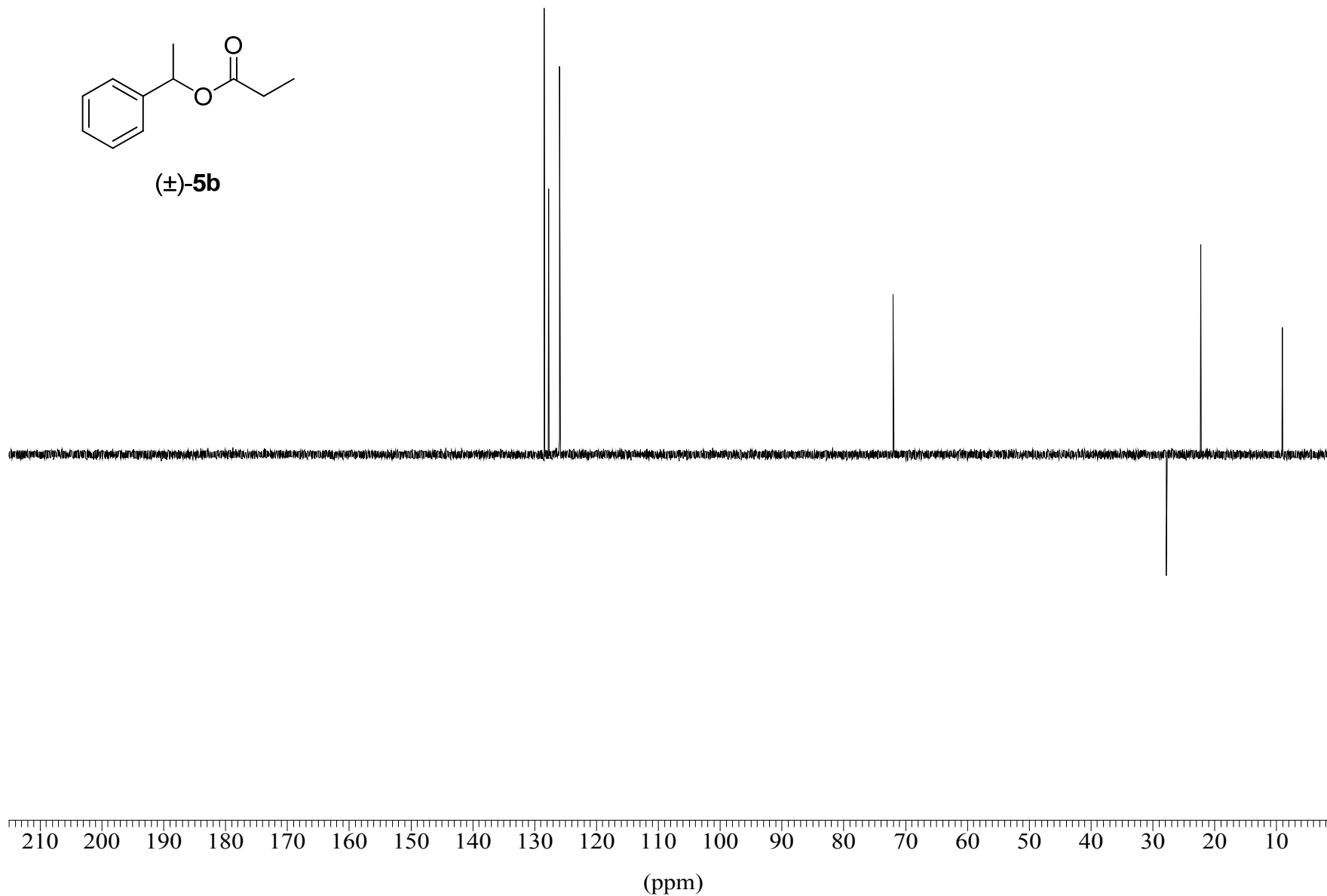


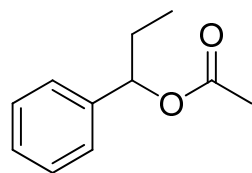
(±)-5b



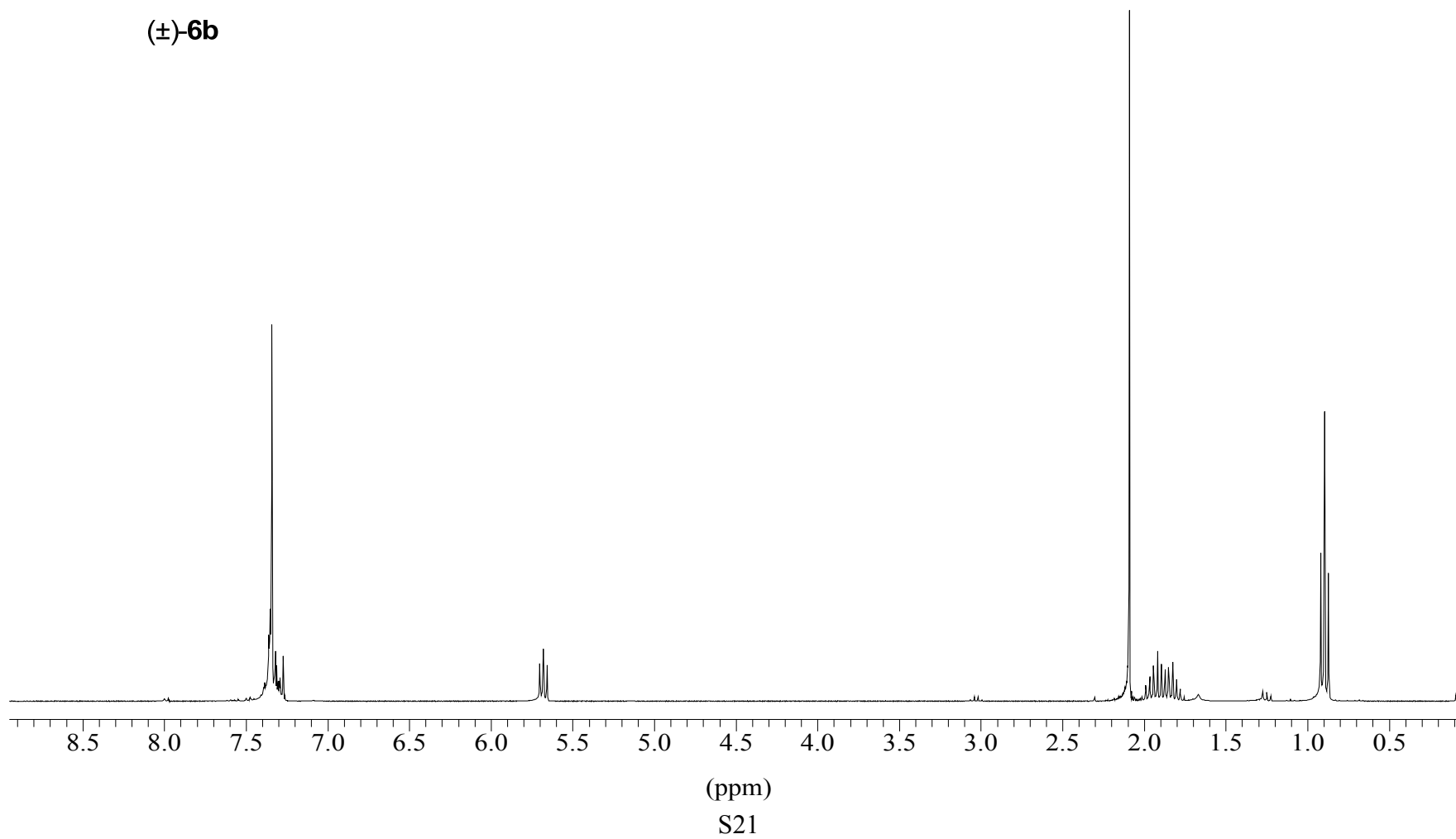


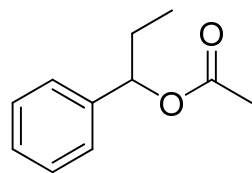
(±)-5b



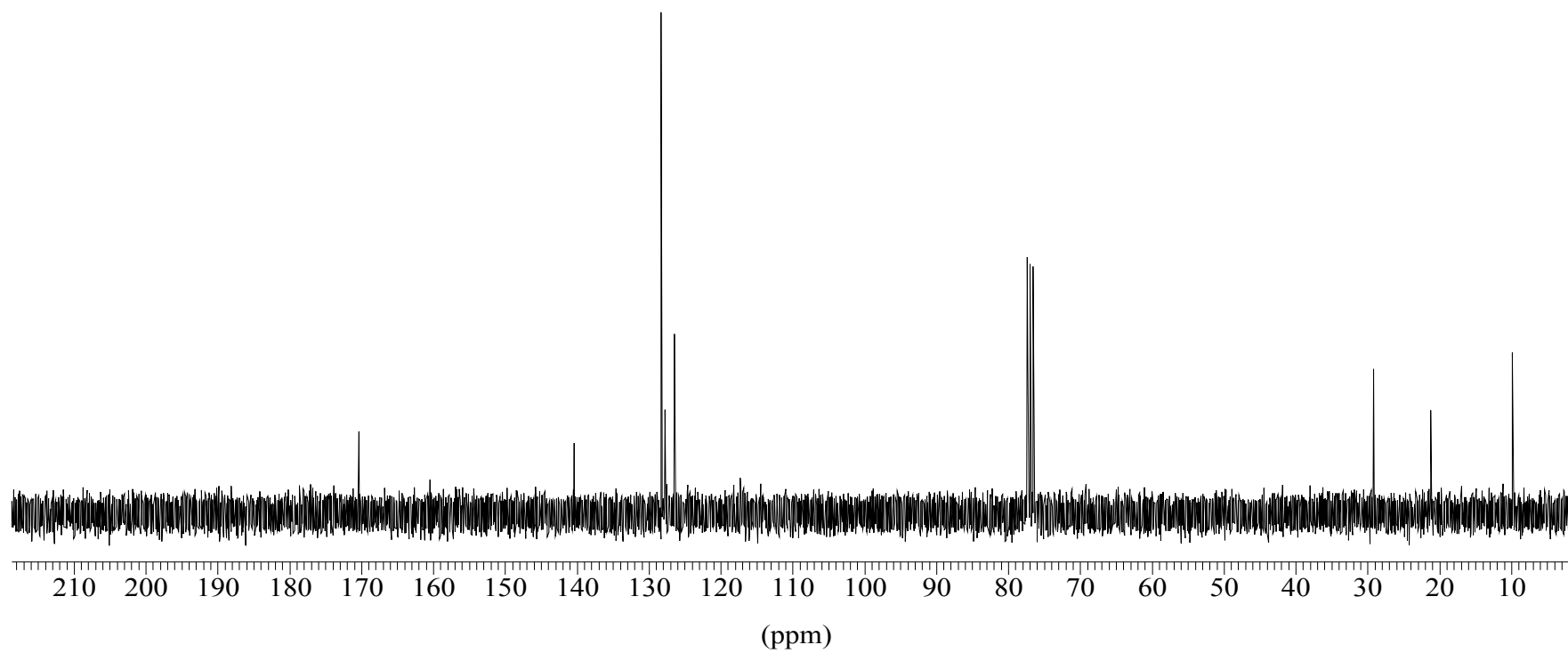


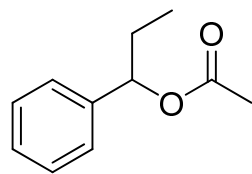
(±)-6b



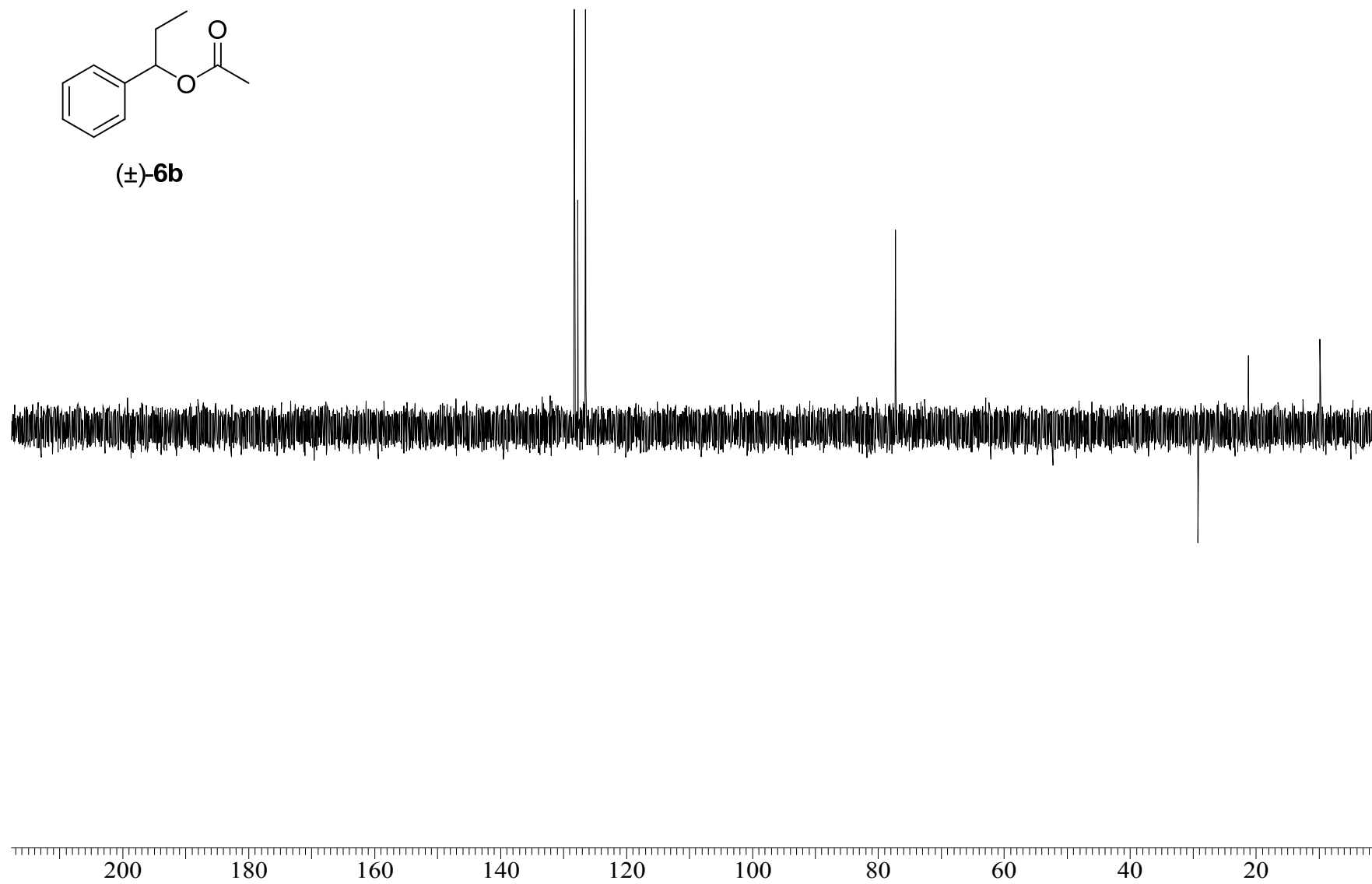


(±)-6b

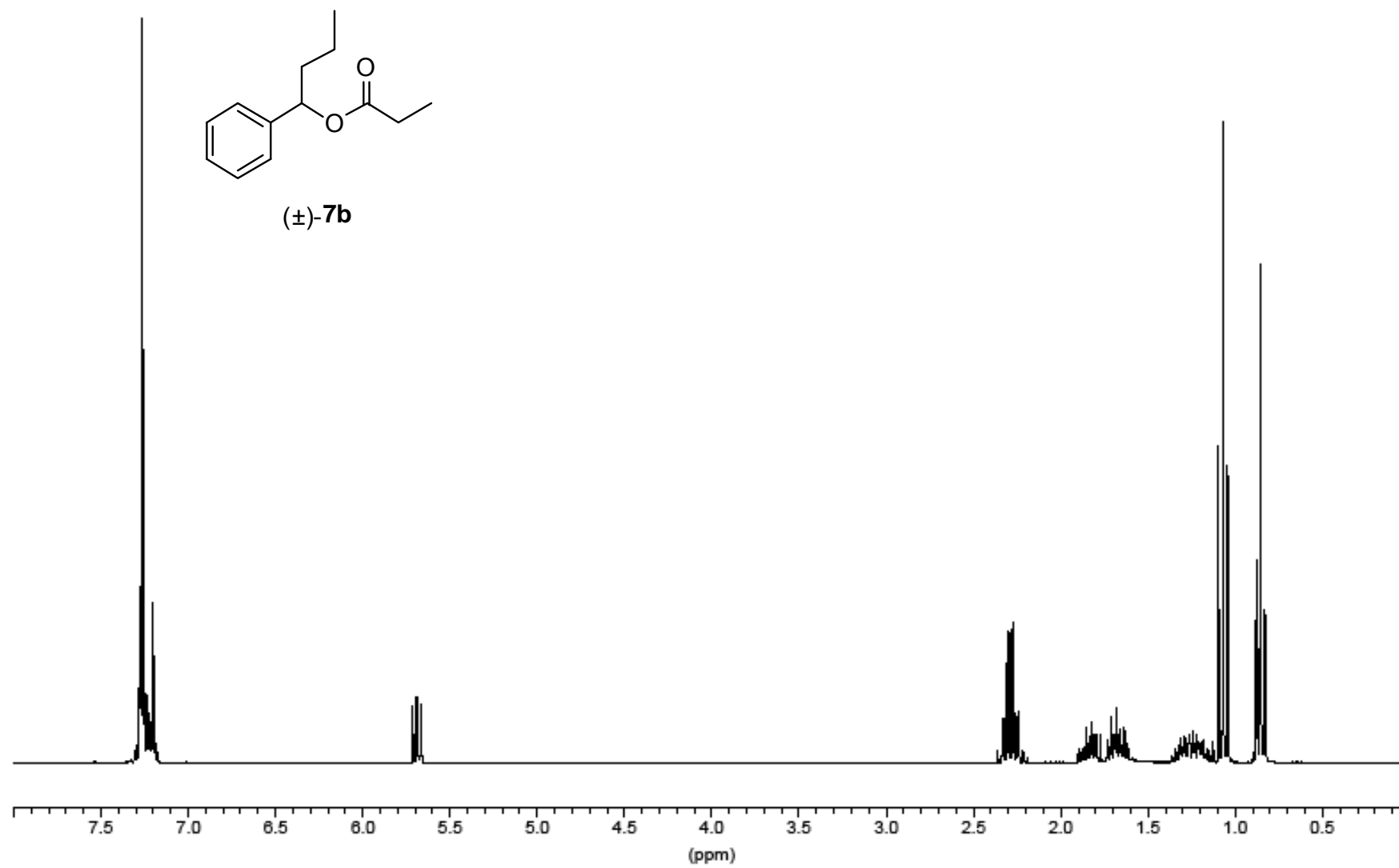




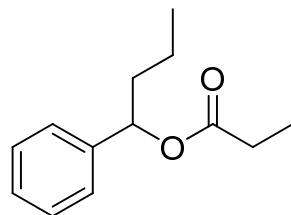
(±)-**6b**



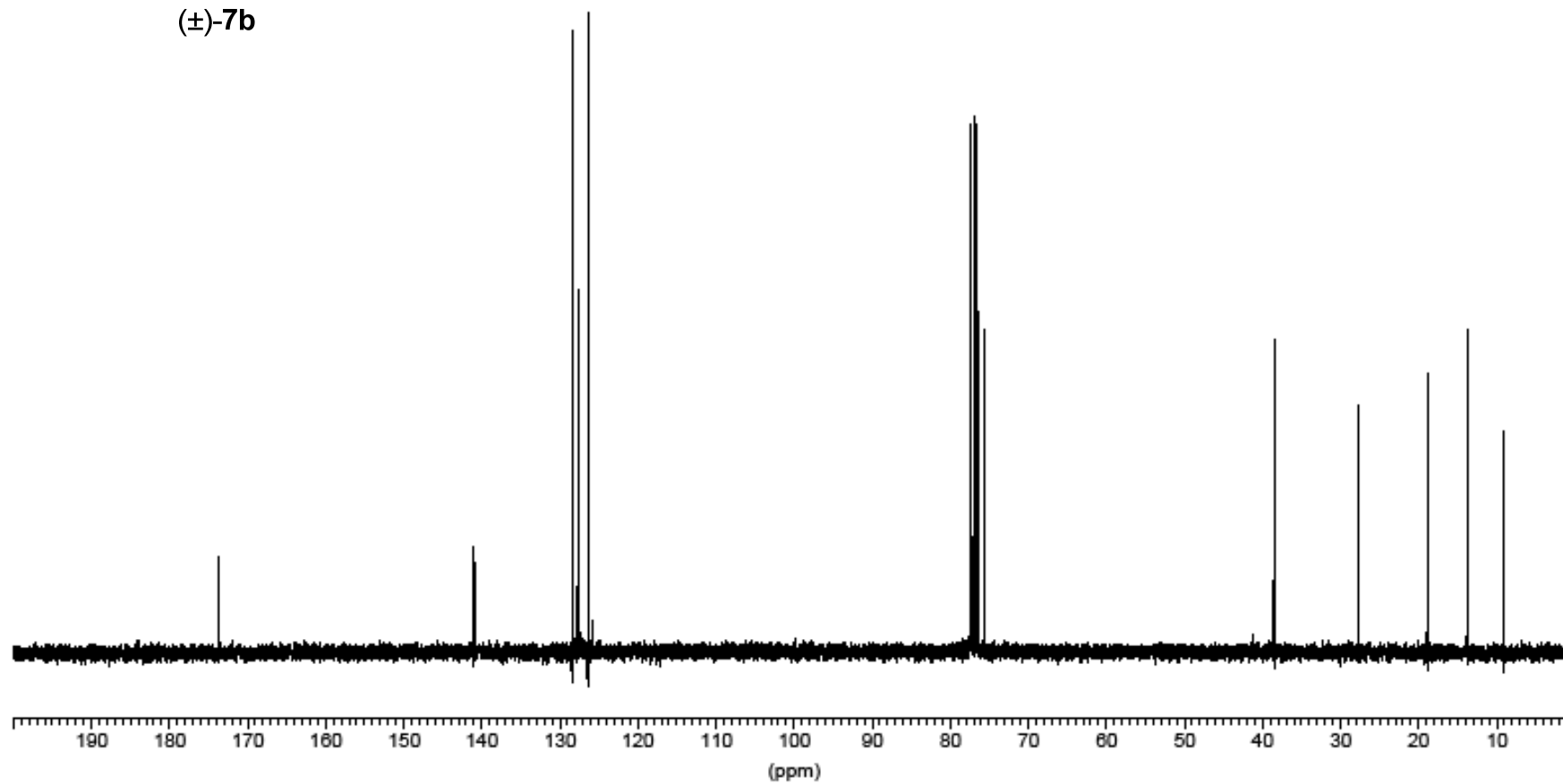
(ppm)  
S23

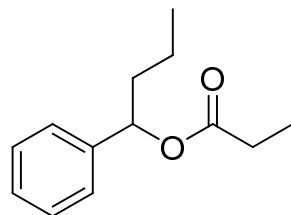






(±)-7b





(±)-7b

