Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

SUPPORTING INFORMATION

Double Asymmetric Intramolecular aza-Michael Reaction: a Convenient Strategy for the Synthesis of Quinolizidine Alkaloids

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Contents

General remarks.

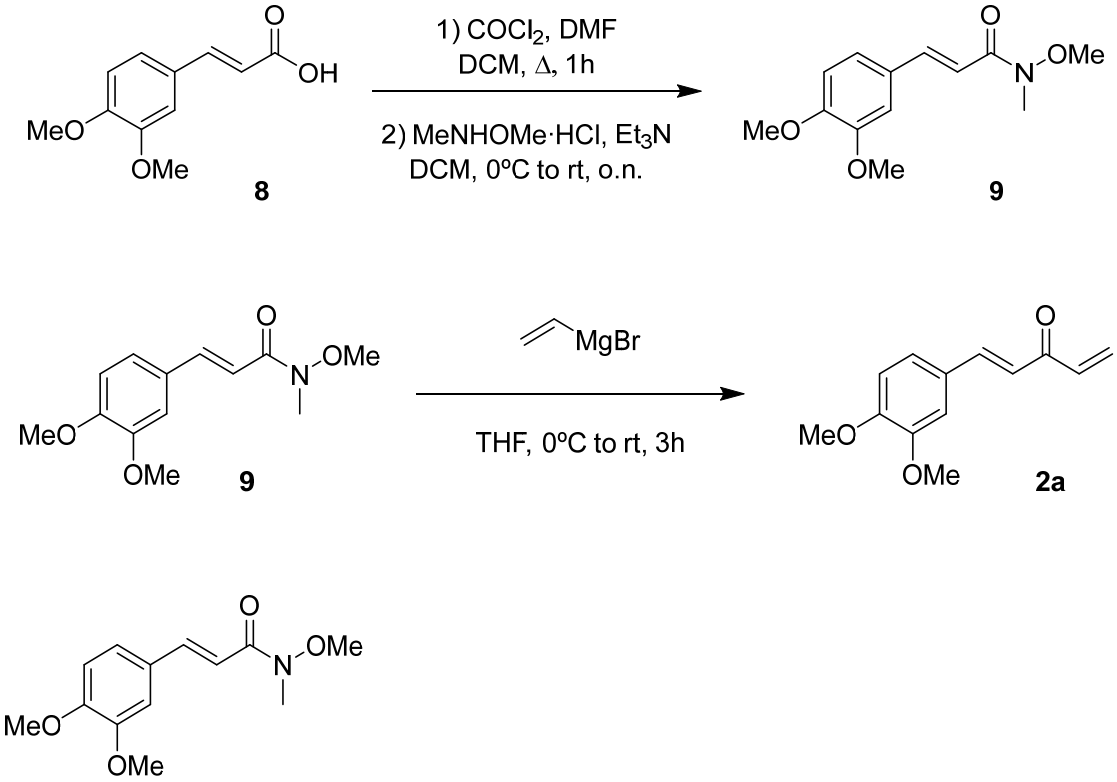
Reactions involving moisture-sensitive chemicals were carried out in flame-dried glassware with magnetic stirring under nitrogen atmosphere. The following solvents were purified prior to use: THF, diethyl ether and toluene were distilled from sodium/benzophenone, CH_2Cl_2 was distilled from calcium hydride. All other solvents and reagents were used as received. The reactions were monitored with the aid of thin-layer chromatography (TLC) on 0.25 mm precoated silica gel plates. Visualization was carried out with UV light and aqueous ceric ammonium molybdate solution, potassium permanganate or vanillin stains. Flash column chromatography was performed with the indicated solvents on silica gel 60 (particle size 0.040-0.063 mm). 1H and 13C NMR spectra were recorded on a 300 MHz or 500MHz spectrometer. Chemical shifts are given in ppm (δ), with reference to the residual proton resonances of the solvents. Coupling constants (J) are given in Hertz (Hz). The letters m, s, d, t, and q stand for multiplet, singlet, doublet, triplet and quartet, respectively. The letters br indicate that the signal is broad. High-resolution mass spectra were carried out on VGmAutospec (VG Analytical, Micromass Instruments) by the Universidad de Valencia Mass Spectrometry Service. The optic rotations were determined using a Perkin Elmer 241 polarimeter, using as radiation source a sodium lamp and spectroscopic graded chloroform for the preparation of the solutions in a cell with a length of 10cm.

The synthesis of starting *N*-sulfinyl amine **1**[1,] and conjugated ketone **2b**[2] was previously described.

[1] Fustero, S.; Monteagudo, S.; Sanchez-Rosello, M.; Flores, S.; Barrio, P.; del Pozo, C.; *Eur. J. Chem.* 2010, **16**, 9835.

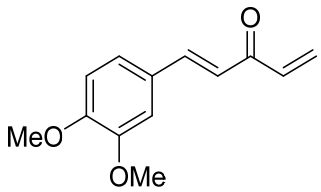
[2] K. D. Ashtekar, X. Ding, E. Toma, W. Sheng, H. Gholami, C. Rahn, P. Reed, B. Borhan, *Org. Lett.* 2016, **18**, 3976.

Synthesis of conjugated ketone 2a



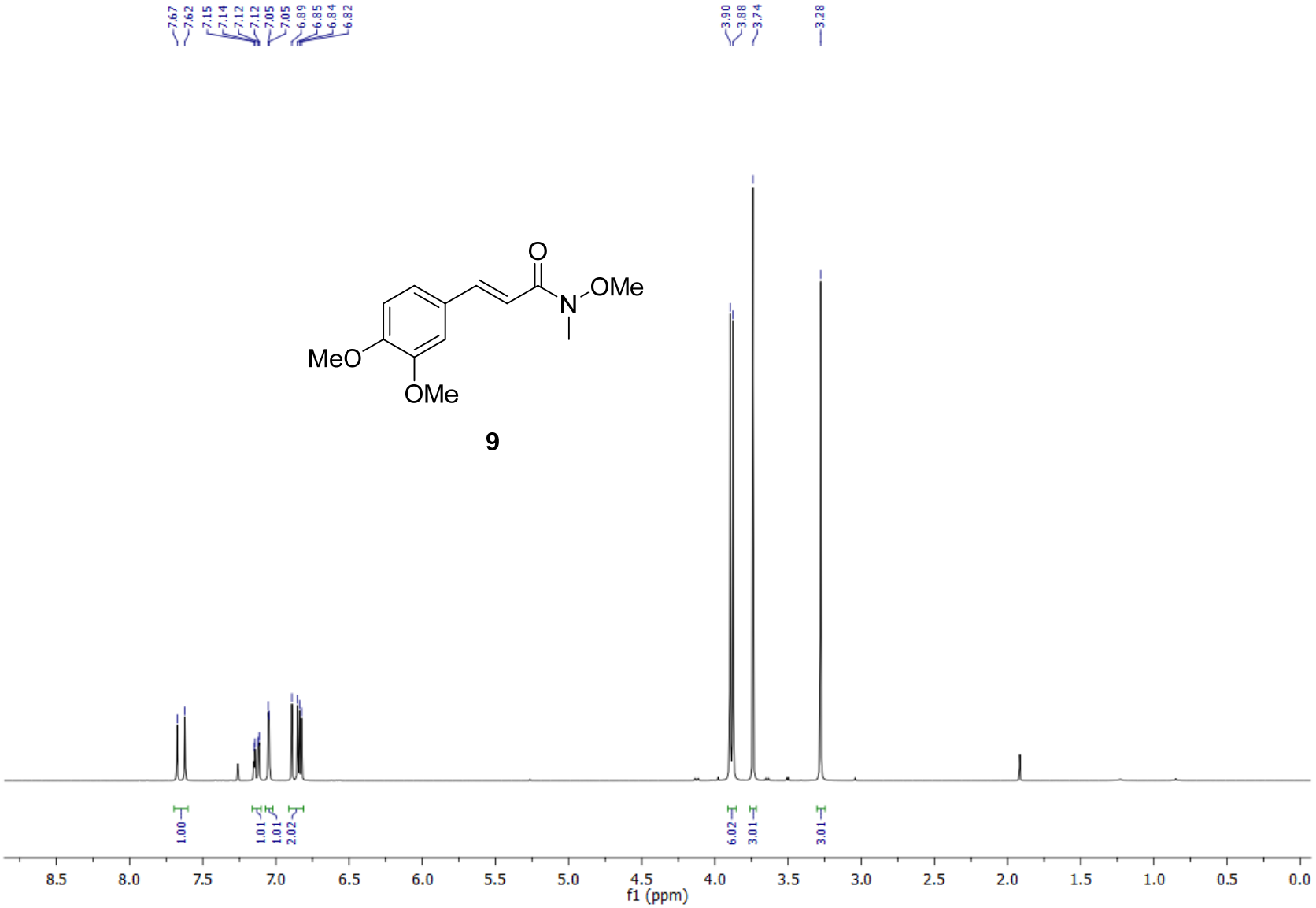
(E)-3-(3,4-dimethoxyphenyl)-N-methoxy-N-methylacrylamide 9

To a stirred solution of carboxylic acid **8** (2.0 g, 9,6 mmol) in DCM (20 mL, 0.5M) at 0°C, oxalyl chloride (3 mL of a 2M solution in DCM, 1.1 equiv) was added dropwise and after adding a couple of DMF drops, the reaction mixture was refluxed for an hour. In a separated flask, MeNHOMe·HCl (1.41 g, 1.5 equiv), DCM (20 mL), and triethylamine (6,7 mL, 5 equiv) were stirred at room temperature for thirty minutes. The reaction mixture was cooled at 0°C in an ice bath and acid chloride previously prepared was added dropwise. The reaction mixture was stirred overnight allowing the temperature to reach room temperature. Once the reaction has finished (monitored by TLC), saturated NH_4Cl solution was added (30 mL) and the mixture was extracted with dichloromethane three times. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated. The crude was recrystalized in hexane:dichloromethane to obtain Weinreb amide **9** (2.11 g, 87% yield) as a pale yellow solid. Mp = 89-91 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): δ 7.65 (d, *J* = 15.7 Hz, 1H), 7.13 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.05 (d, *J* = 2.0 Hz, 1H), 6.87 (d, *J* = 11.6 Hz, 1H), 6.83 (d, *J* = 4.2 Hz, 1H), 3.89 (d, *J* = 5.7 Hz, 6H), 3.74 (s, 3H), 3.28 (s, 3H). ^{13}C NMR (75,5 MHz, $CDCl_3$) δ (ppm): δ 167.3, 150.8, 149.2, 143.5, 128.2, 122.2, 113.6, 111.1, 110.2, 61.9, 56.0, 32.6. HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{13}H_{18}NO_4$: 152.1236; found: 252.1244.



(E)-1-(3,4-dimethoxyphenyl)penta-1,4-dien-3-one (2a)

To a stirred solution of Weinreb amide **9** (1.41 g, 5,63 mmol) in THF (50 mL, 0,1 M) at 0°C, vynilmagnesium bromide solution (11,3 mL of 1M solution in THF, 2 equiv) was added dropwise. After addition, reaction mixture was stirred for 30 minutes at 0°C, and 2h at room temperature. Once the reaction has finished (monitored by TLC), 3% H_2SO_4 aqueous solution was added (30 mL), and the mixture was extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated. The residue was chromatographed on silica gel, employing hexane:ethyl acetate mixtures (from 2:1 to ethyl acetate), to obtain vynil ketone **2a** as a yellow oil (1.22 g, 99 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): δ 7.64 (d, *J* = 15.9 Hz, 1H), 7.18 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.11 (d, *J* = 2.0 Hz, 1H), 6.90 – 6.84 (m, 2H), 6.73 (dd, *J* = 17.4, 10.6 Hz, 1H), 6.37 (dd, *J* = 17.4, 1.4 Hz, 1H), 5.86 (dd, *J* = 10.6, 1.4 Hz, 1H), 3.93 (d, *J* = 1.8 Hz, 6H). ^{13}C NMR (75,5 MHz, $CDCl_3$) δ (ppm): δ 189.6, 151.6, 149.4, 144.2, 135.5, 128.3, 127.7, 123.4, 122.6, 111.2, 110.0, 56.2, 56.1. HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{13}H_{15}O_3$: 219.1021; found: 219.1014.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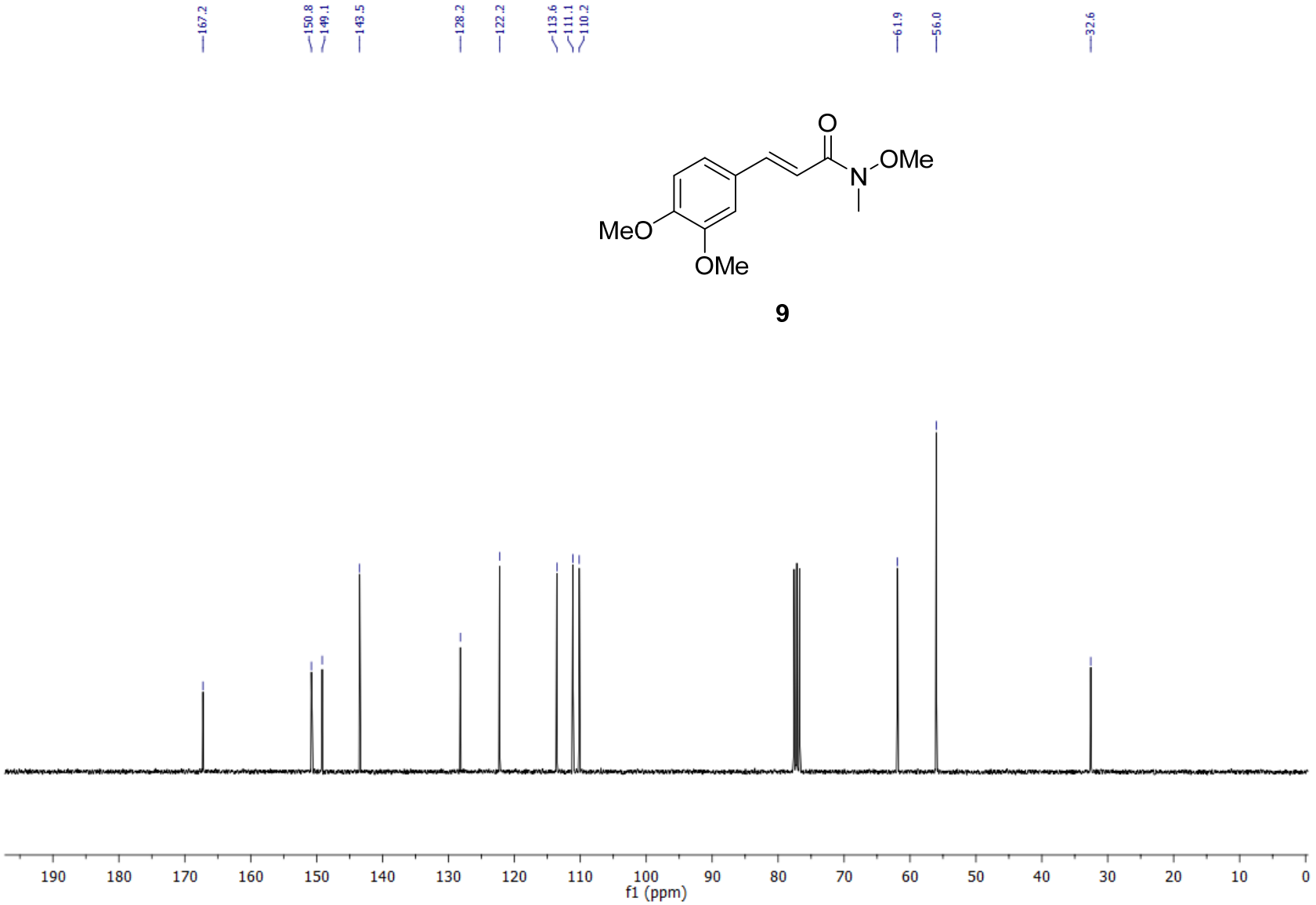
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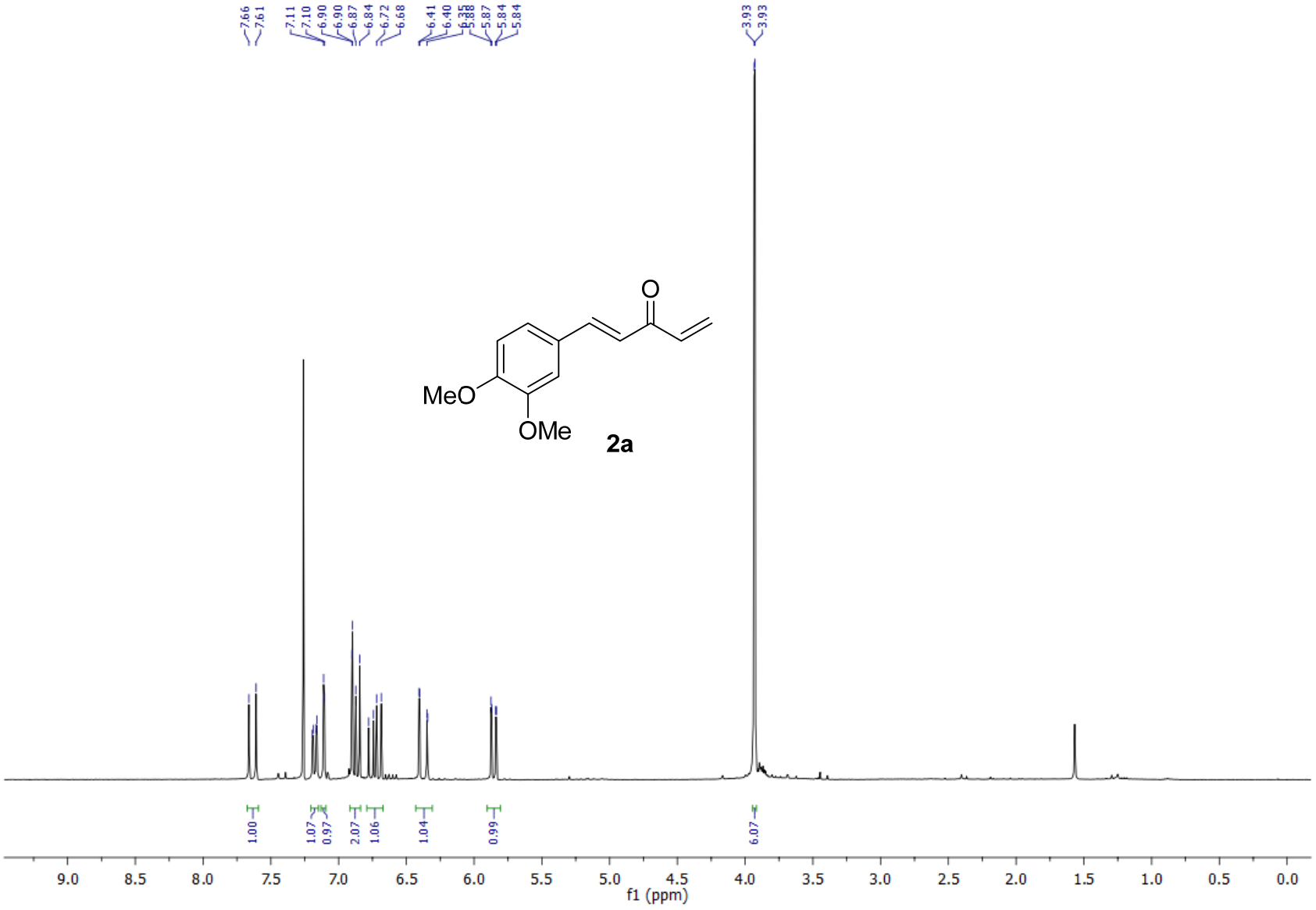
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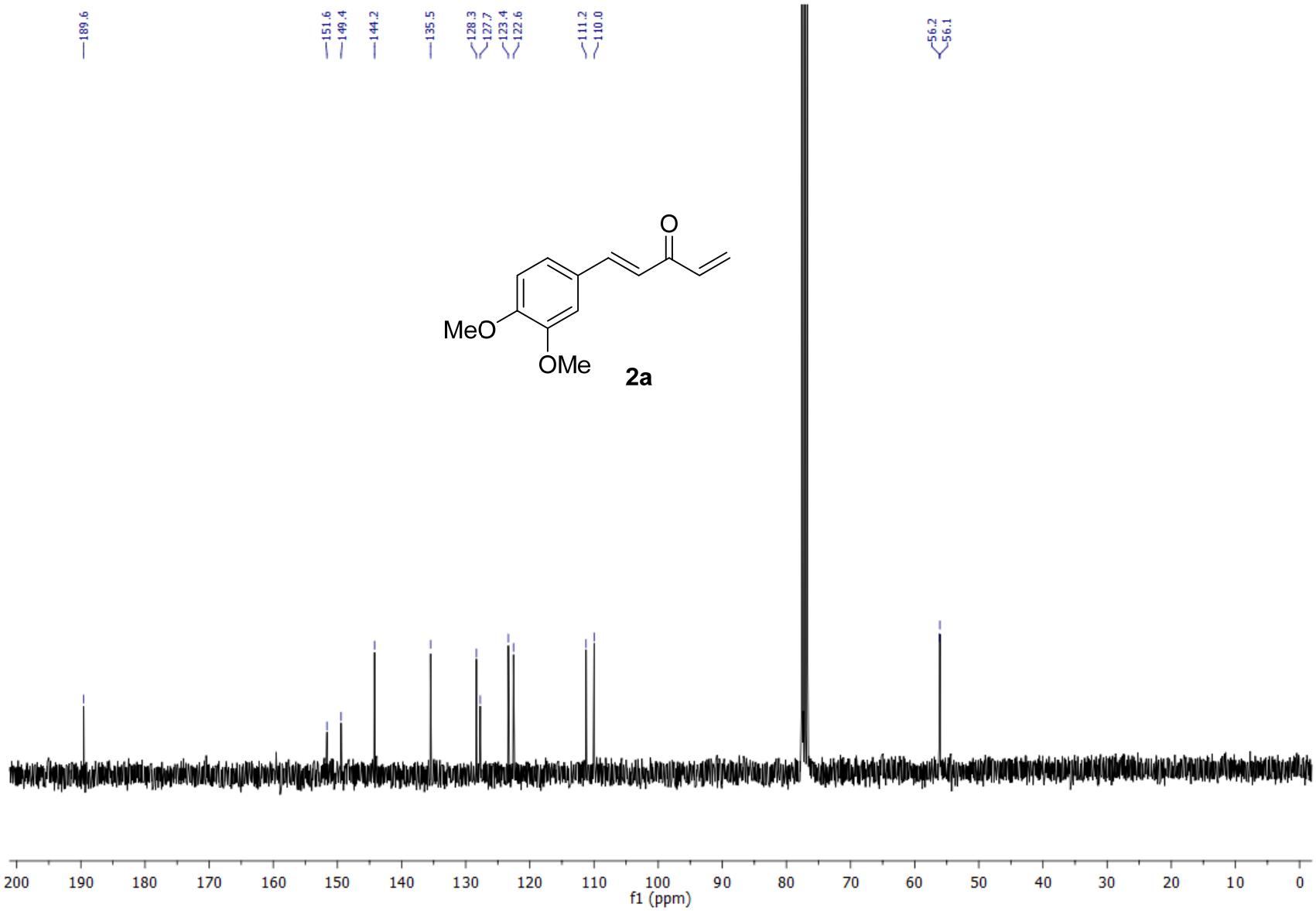
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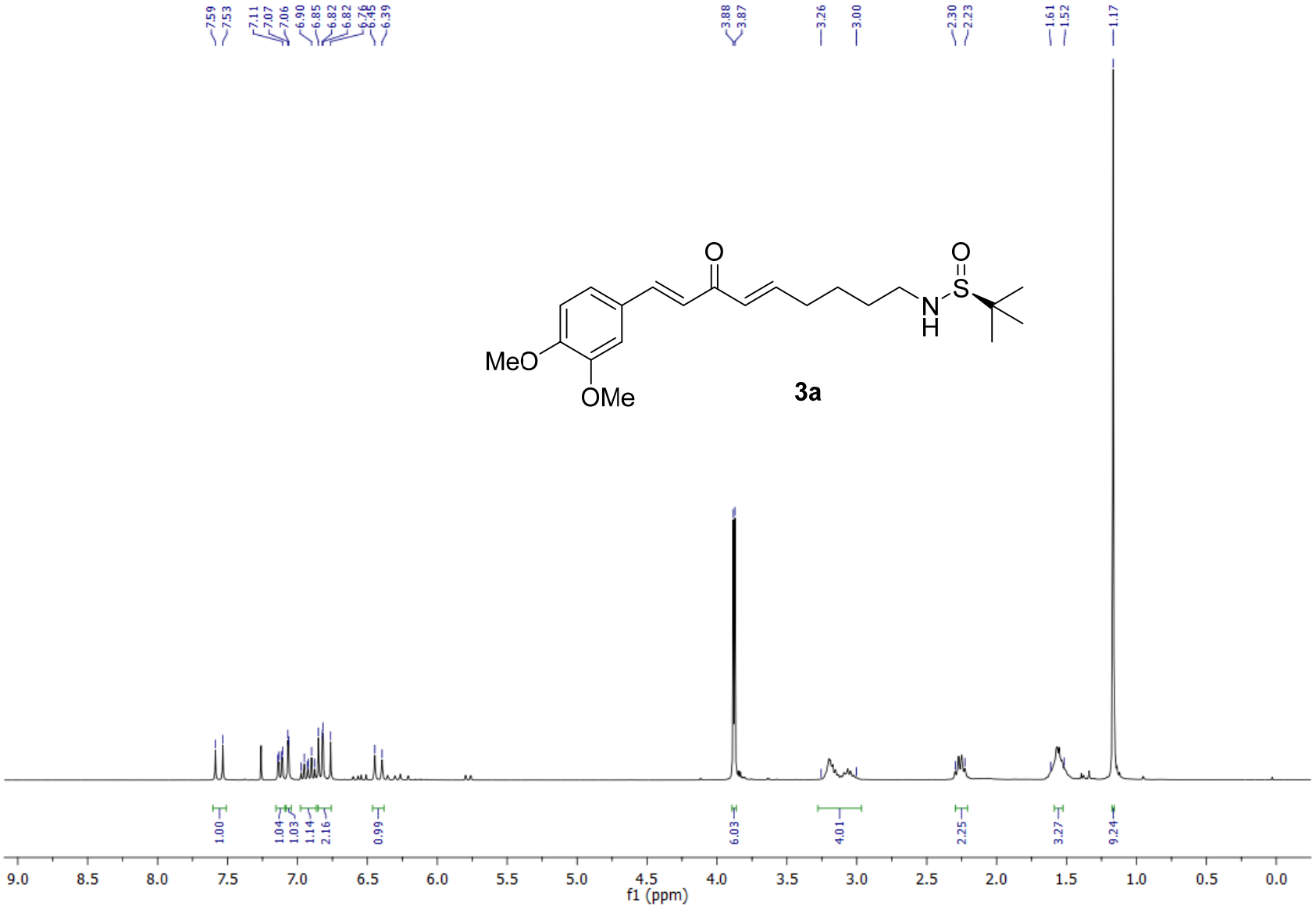
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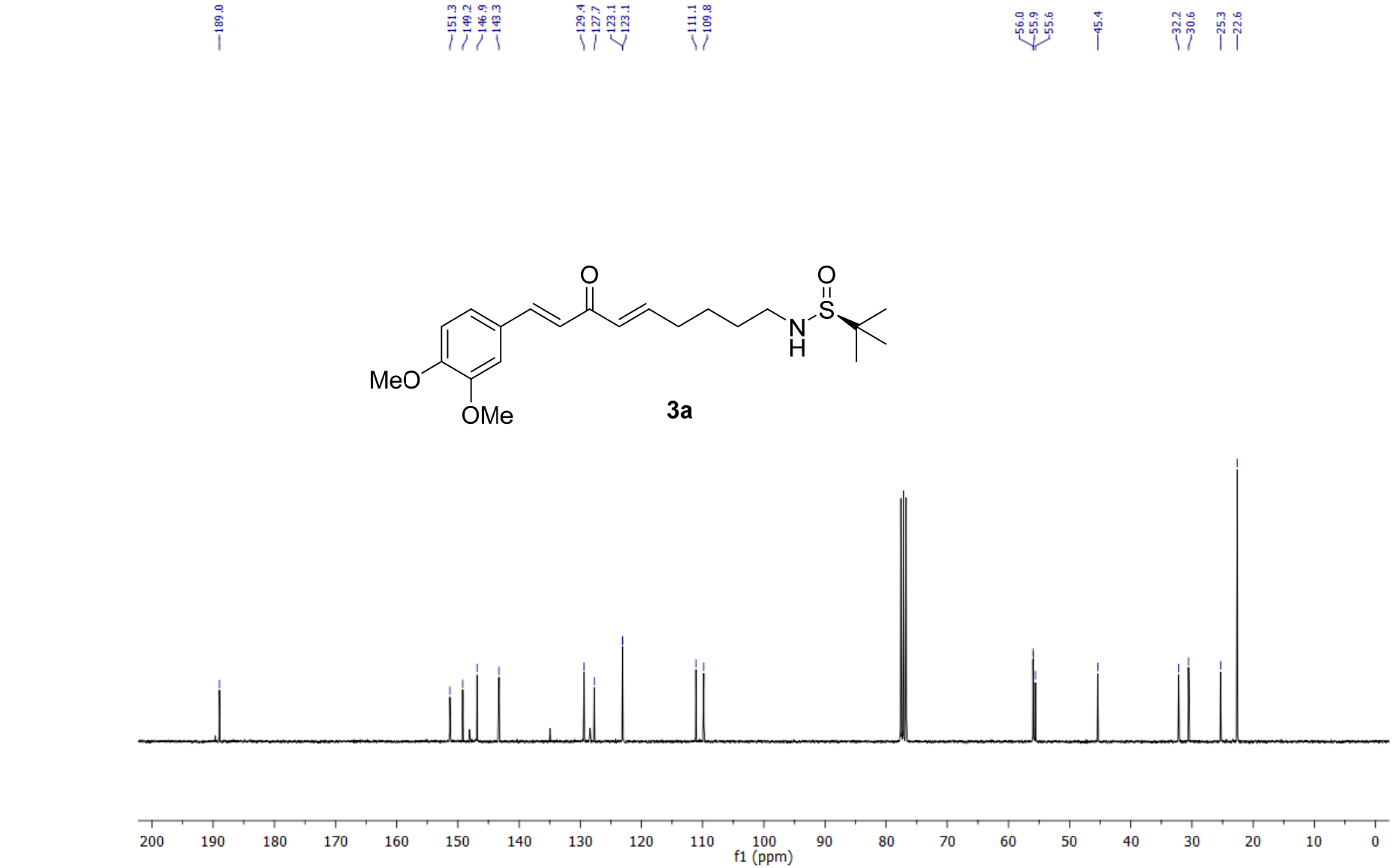
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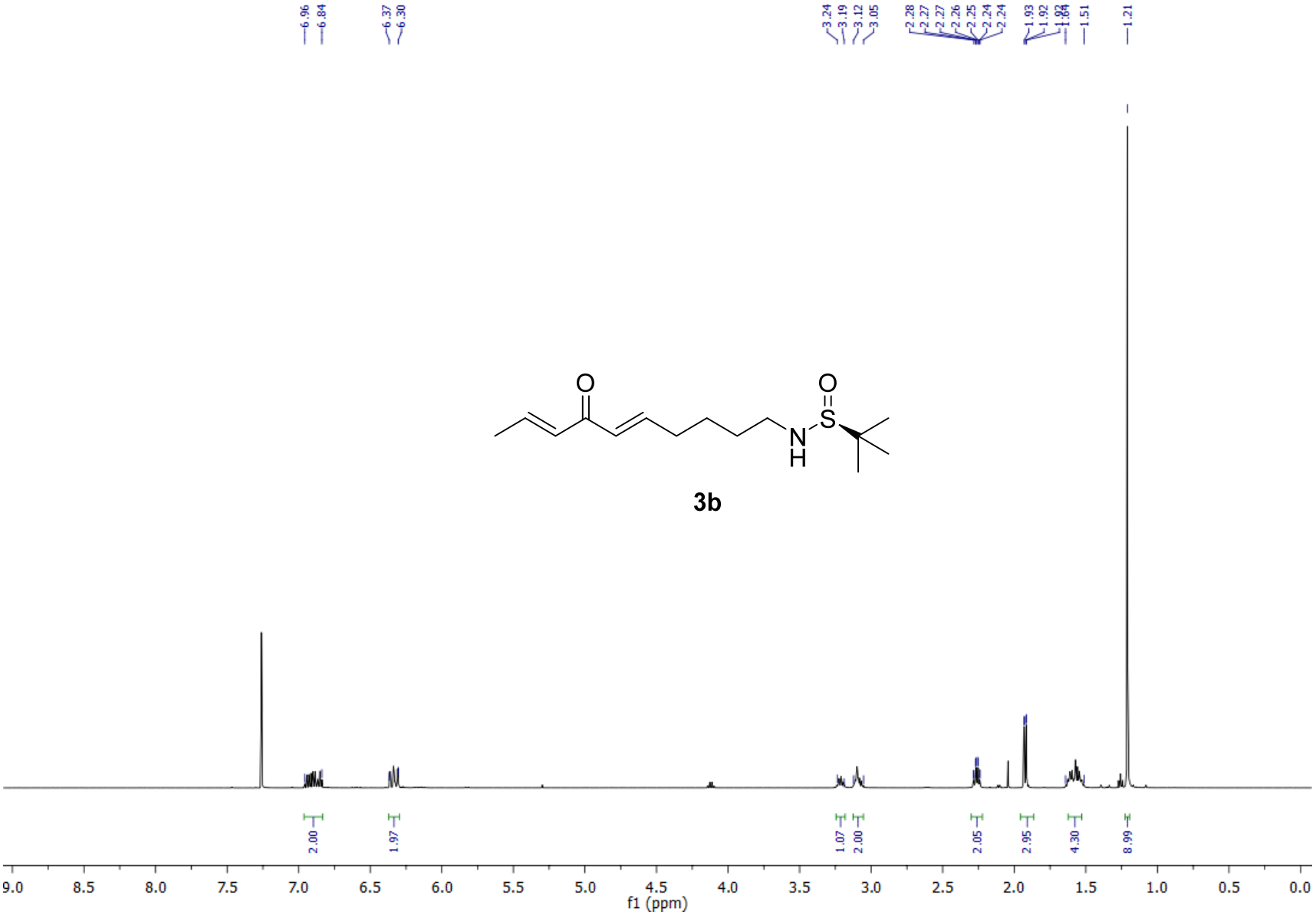
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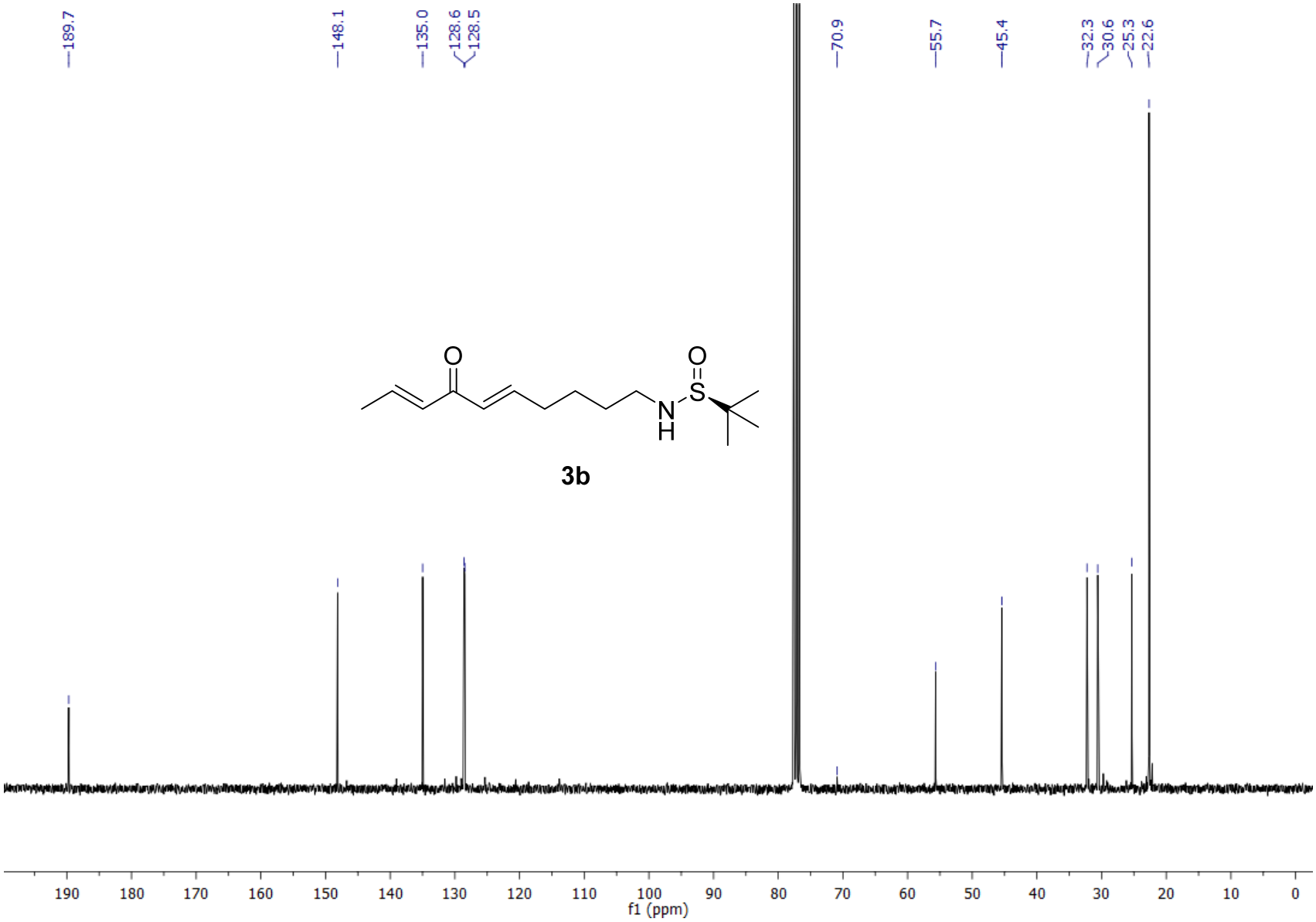
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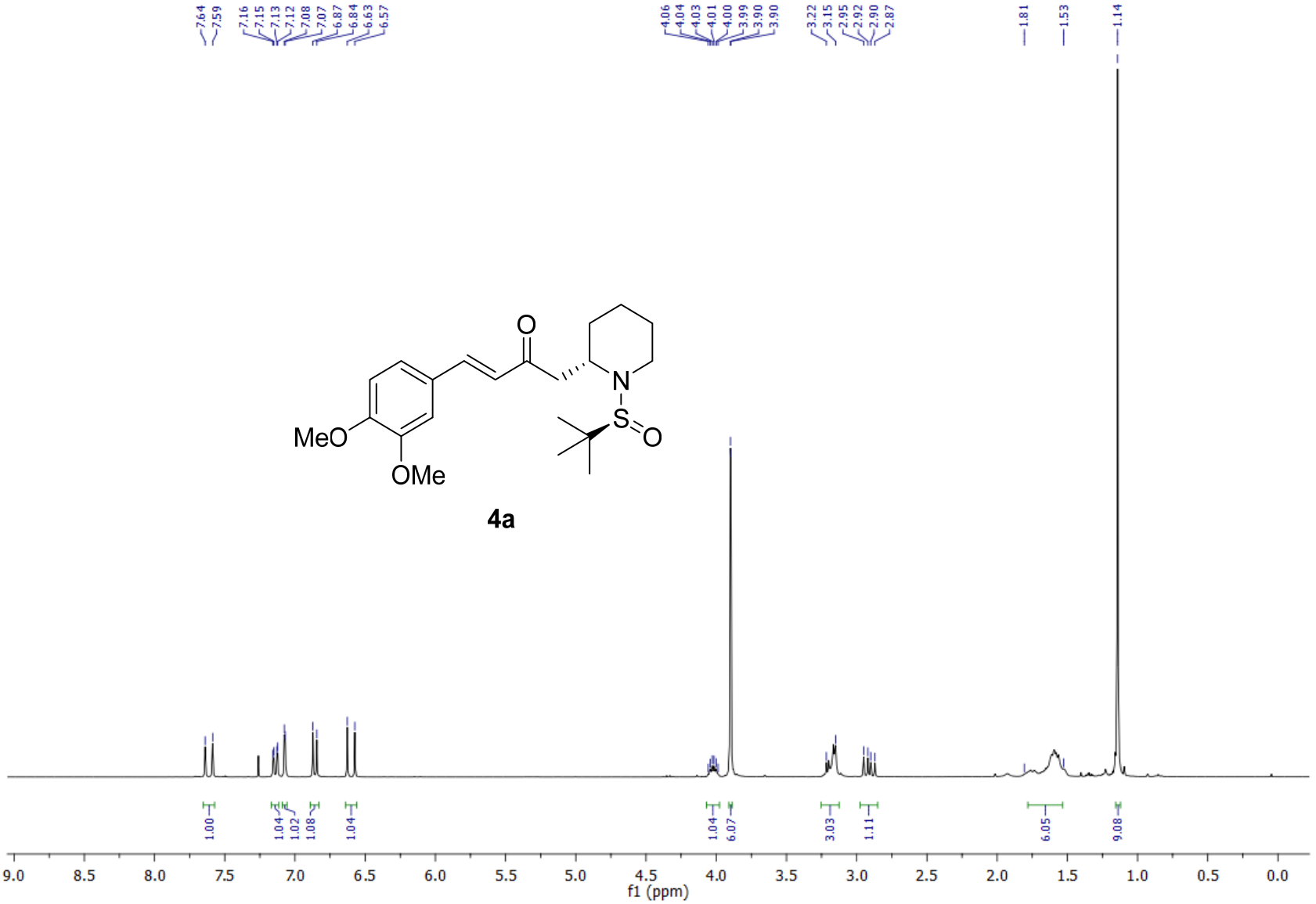
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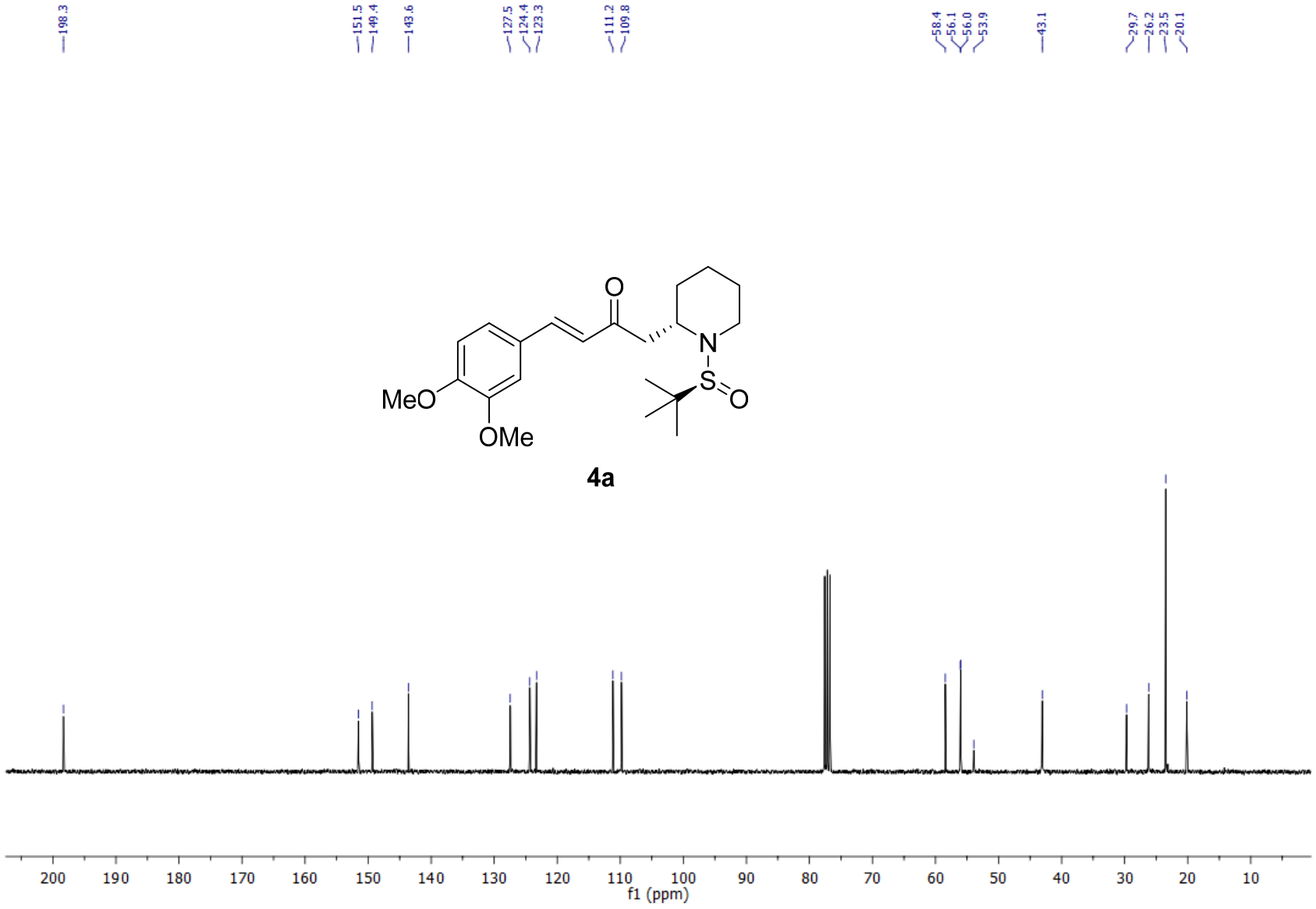
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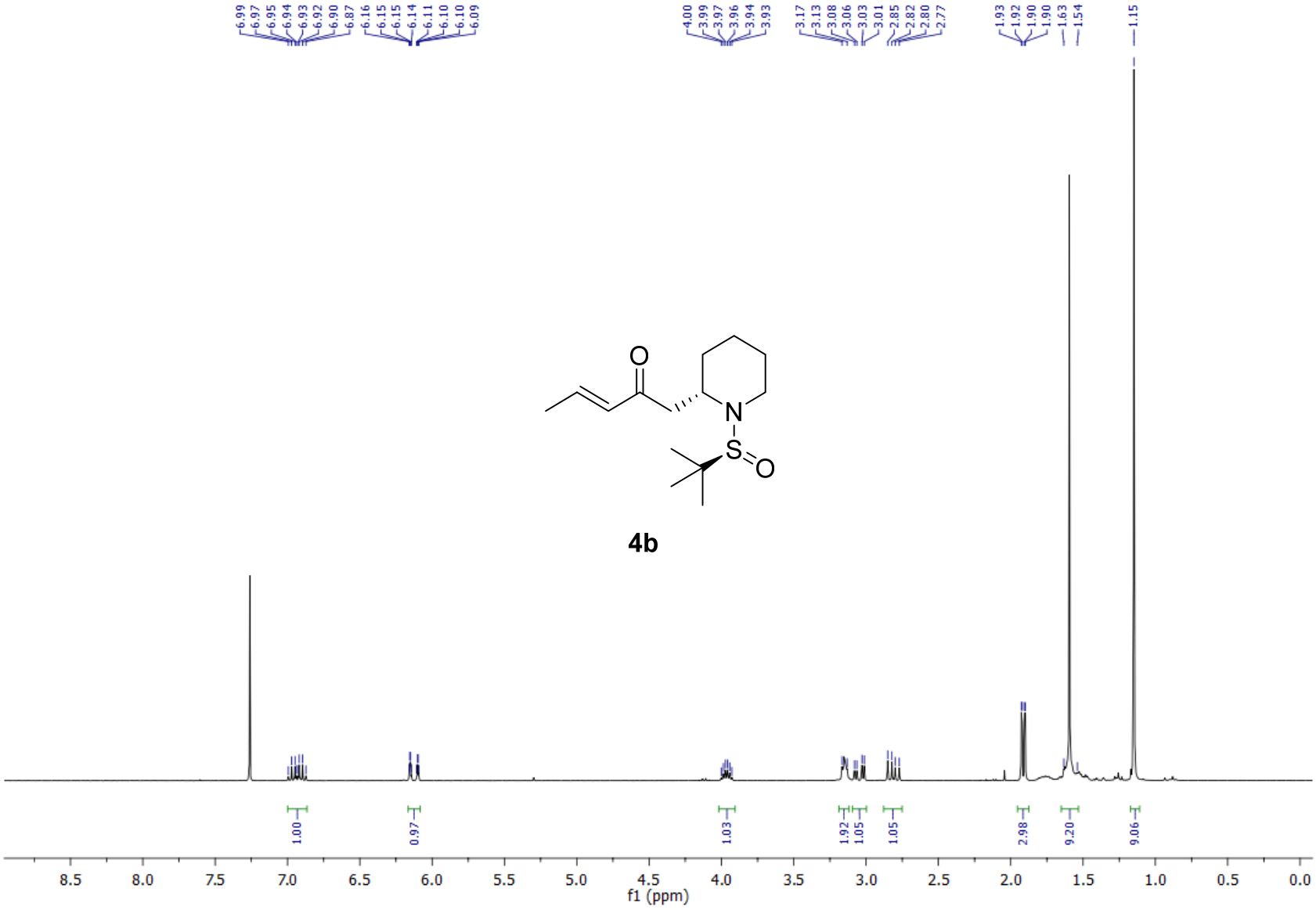
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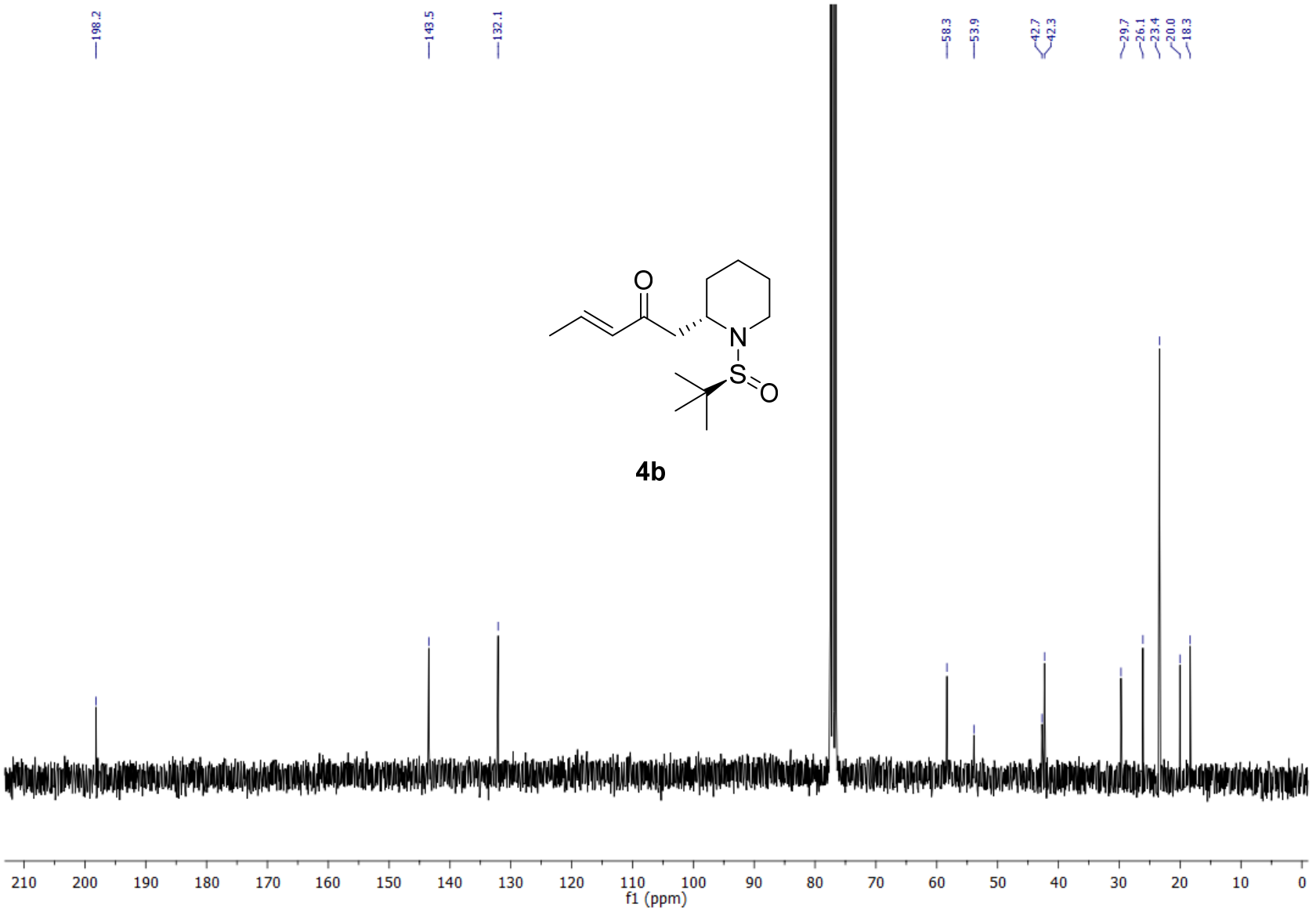
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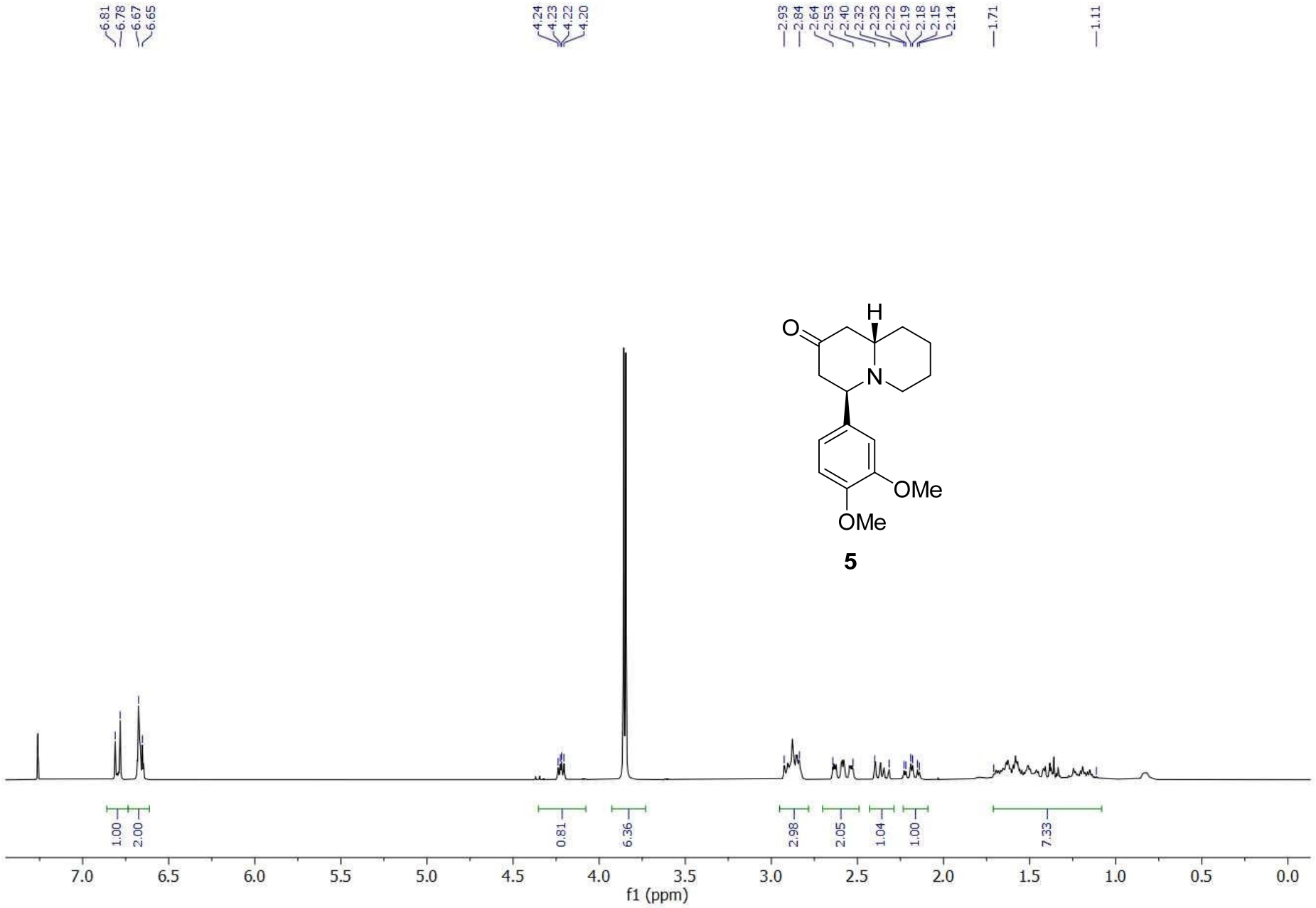
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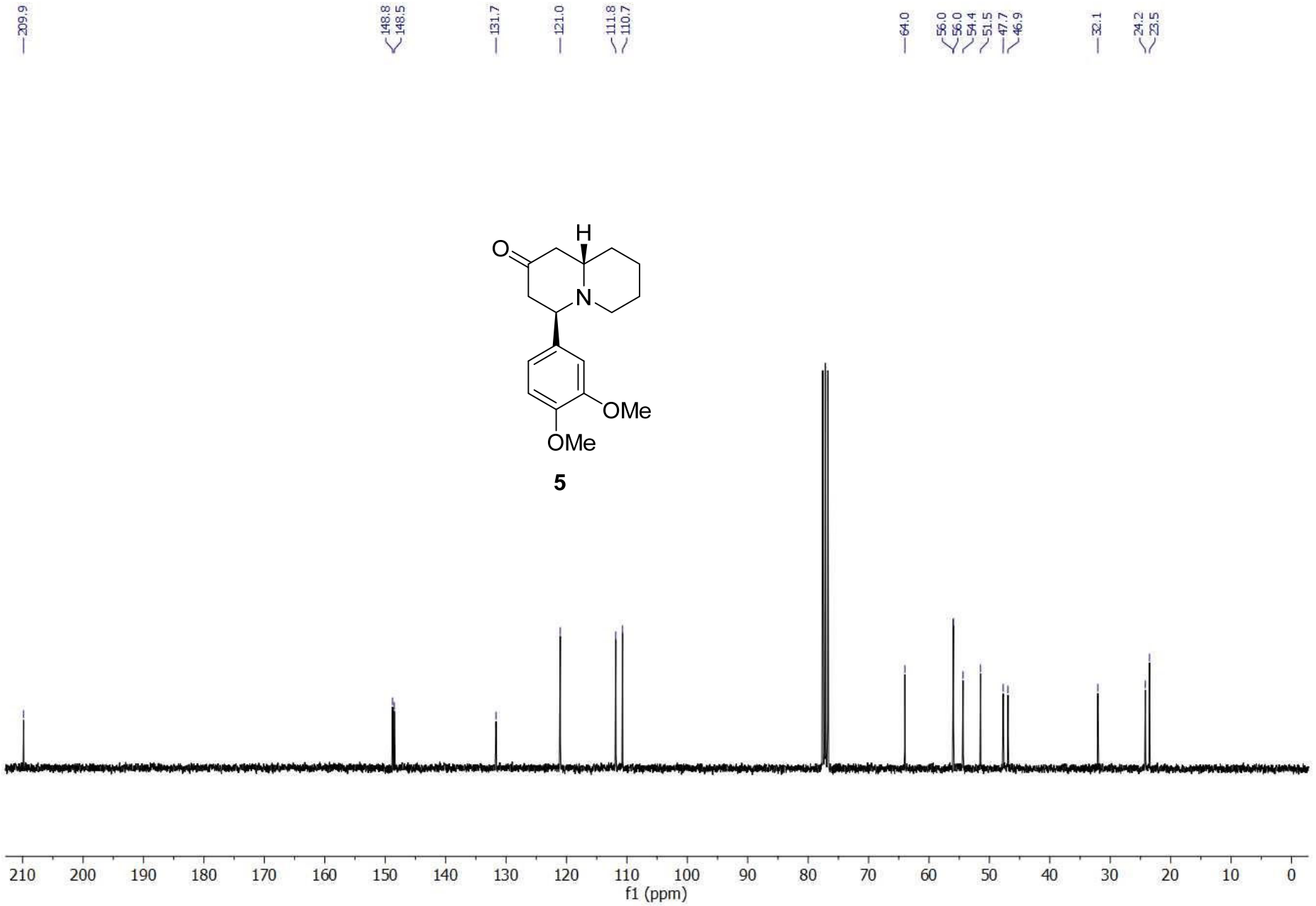
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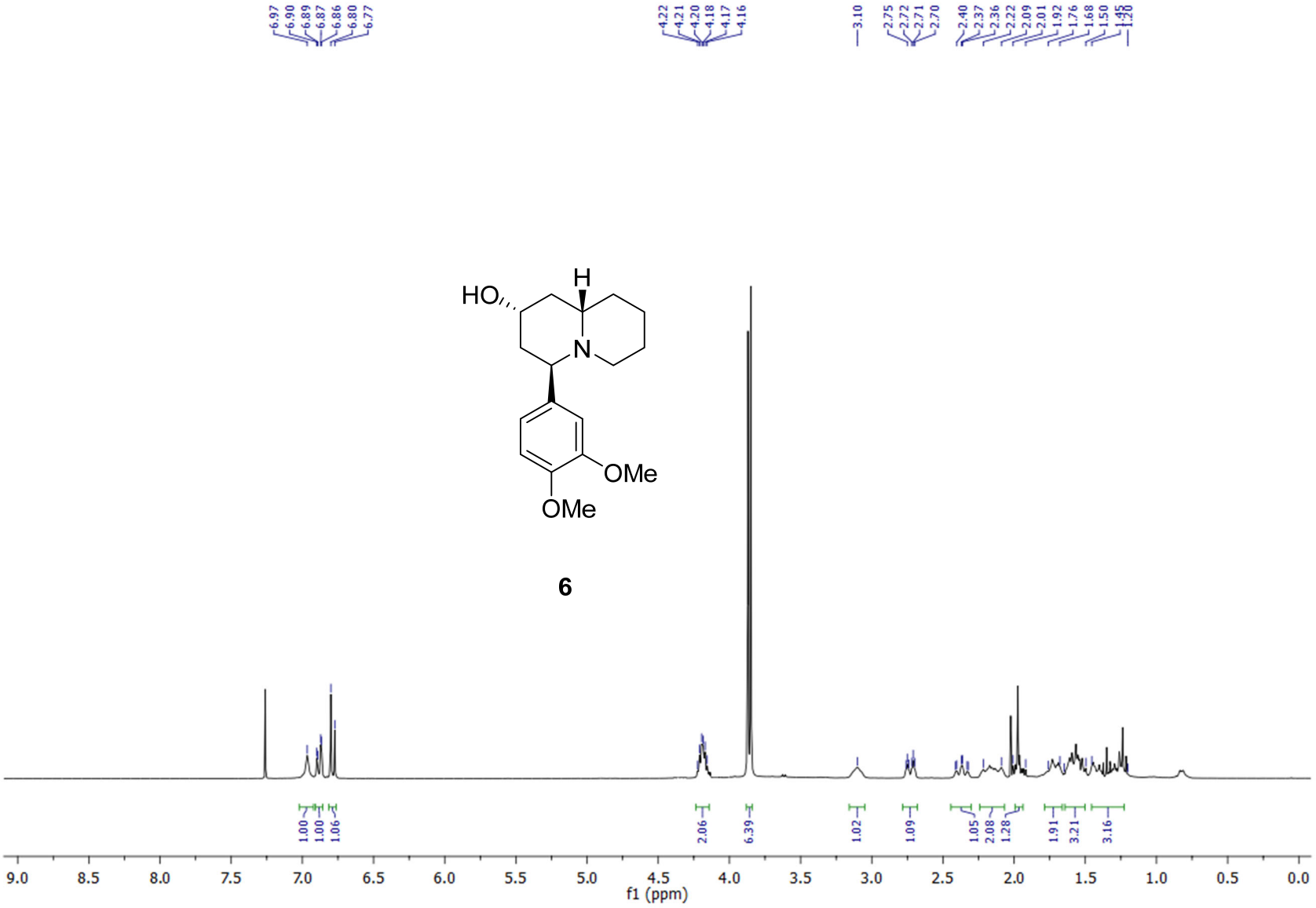
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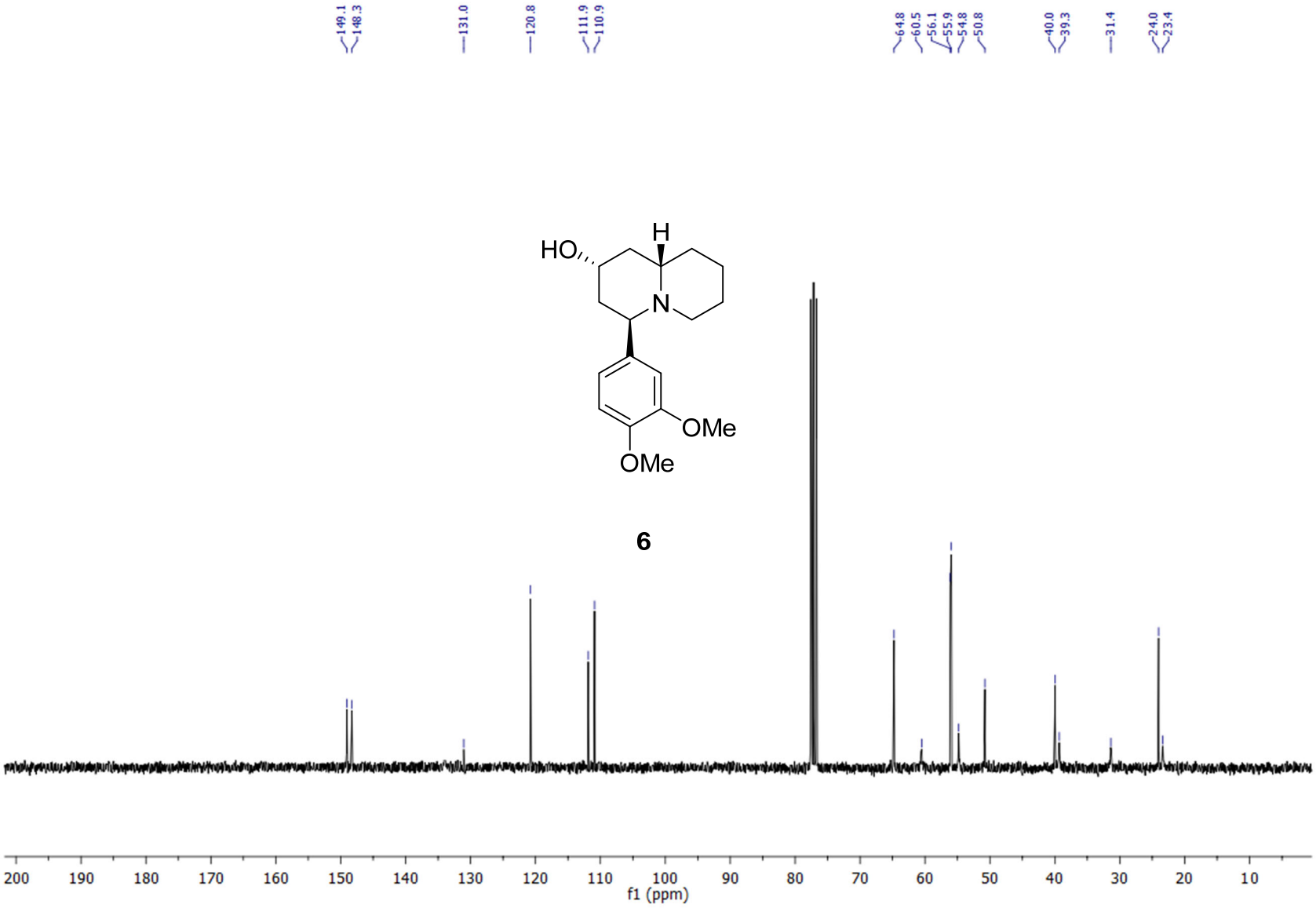
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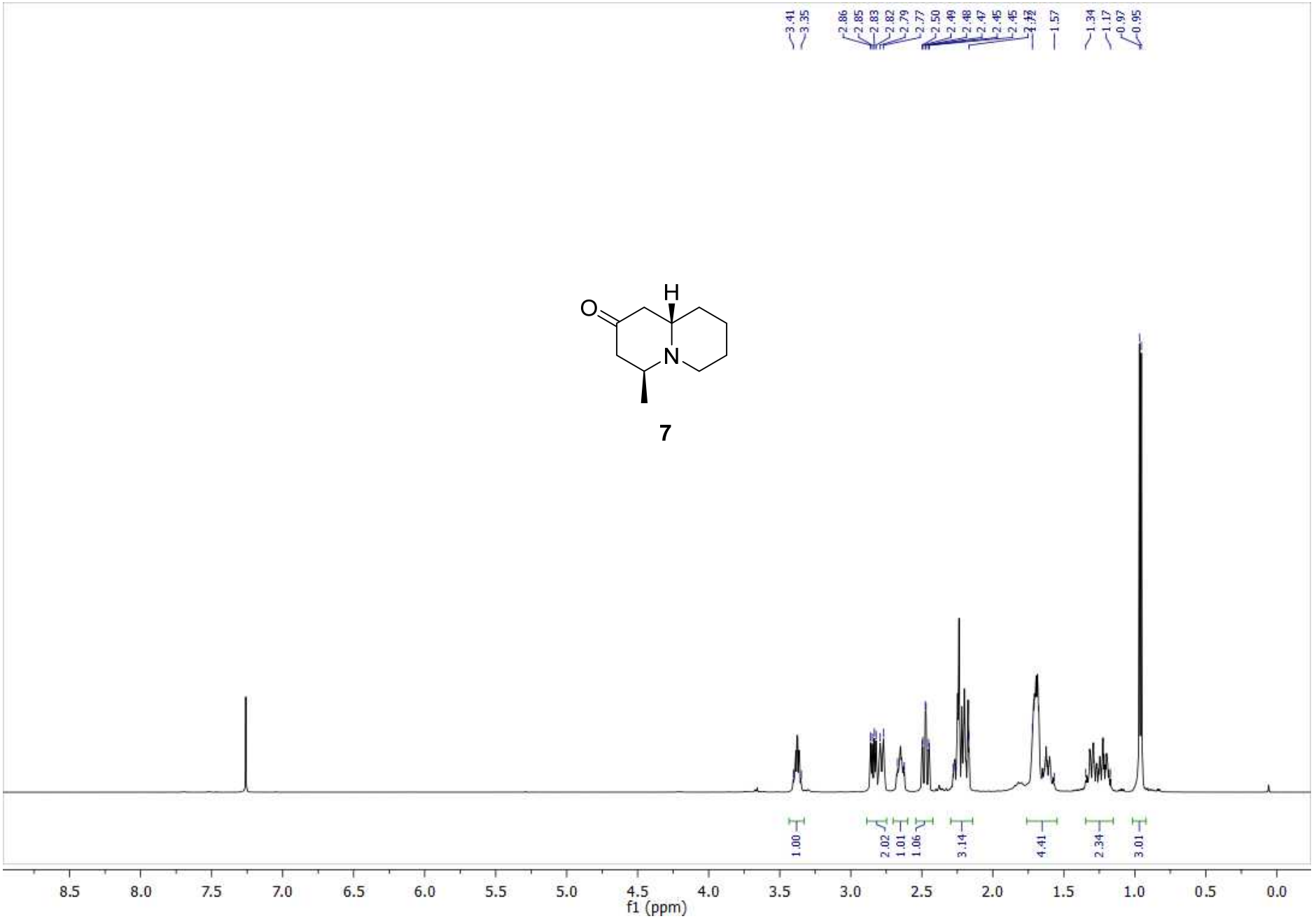
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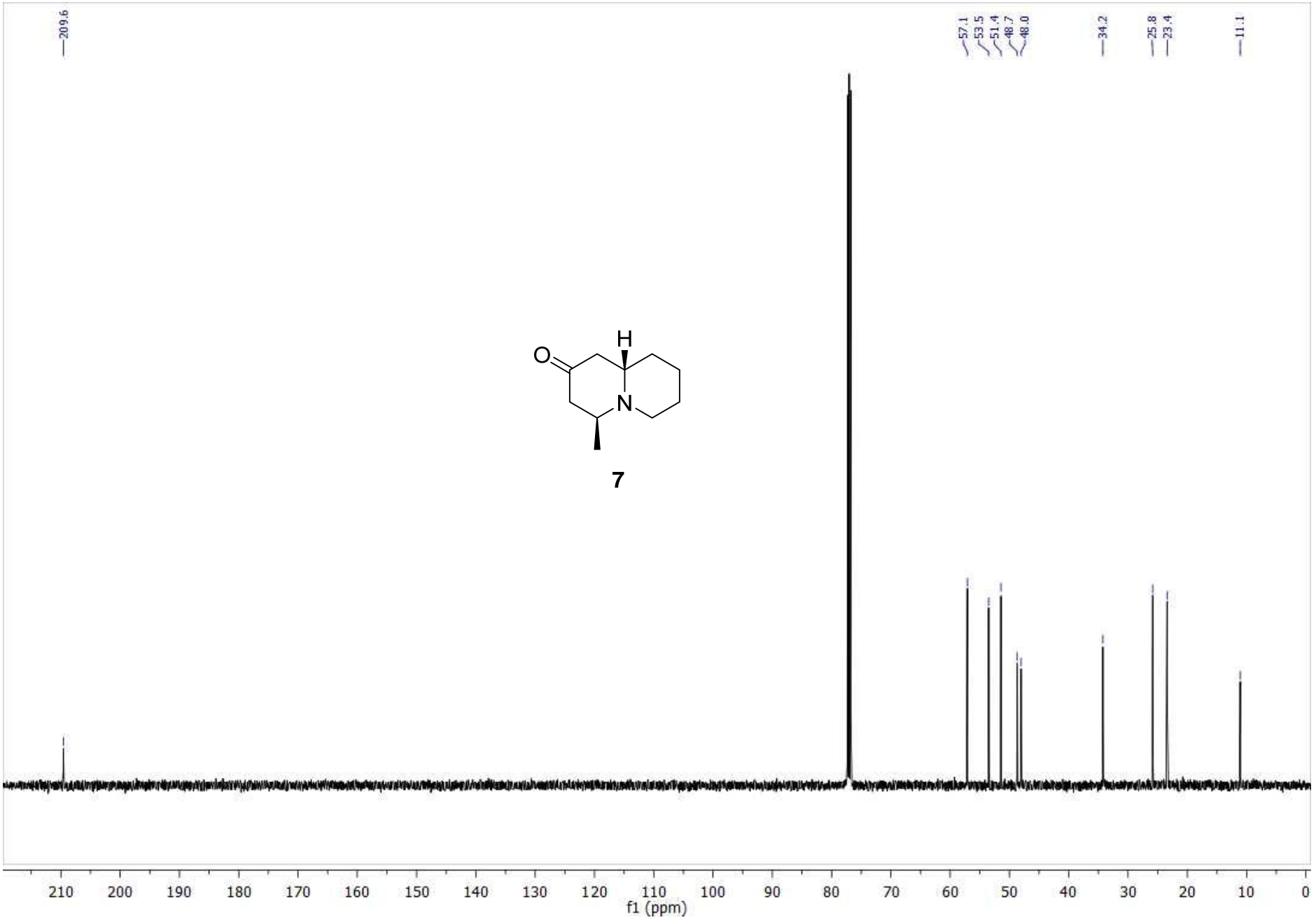
f1 (ppm)

7


209.6
57.1
53.5
51.4
48.7
48.0
34.2
25.8
23.4
11.1
O
H
N
7
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)