

Stereoselective approach to conjugated enone oximes from aliphatic nitro compounds and sulfur ylides

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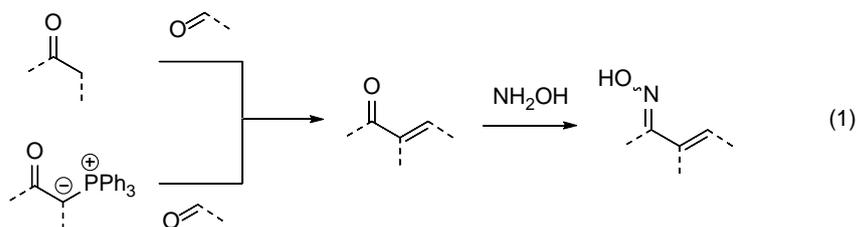
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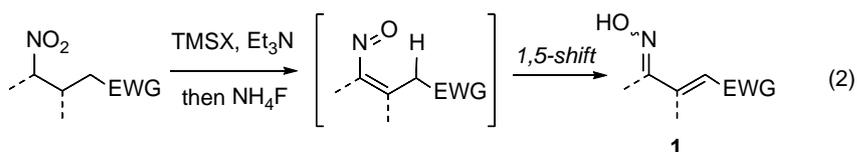
Methods for preparation of enone oximes

The synthesis of enoximes is typically performed by the oximation of the corresponding α,β -unsaturated carbonyl compounds (Scheme S1, eqn. (1)).^[S1] Another method reported by Ioffe et al relies on the silylation of nitro compounds bearing an electron-withdrawing (EWG) group at the γ -position (Scheme S1, eqn. (2)).^[S2] In the present paper, a conceptually novel approach to enoximes **1** from nitro compounds via double silylation to *N,N*-bis(silyloxy)enamines **2** followed by reaction with an ester-stabilized sulfur ylide is reported (Scheme S1, eqn. (3)).

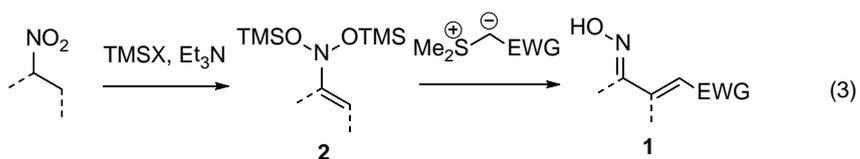
Oximation of α,β -unsaturated carbonyl compounds



Redox silylation of functionalized nitro compounds (Ioffe et al)



Reaction of *N,N*-bis(silyloxy)enamines with ylides (this work)



Scheme S1.

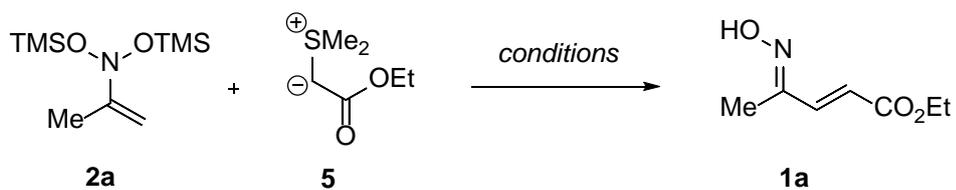
General experimental

All reactions were carried out in oven-dried (150°C) glassware. NMR spectra were recorded at room temperature with residual solvents peaks as an internal standard. Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Peaks in FT-IR spectra data are reported in cm^{-1} with the following relative intensities: s (strong), m (medium), w (weak), br (broad), sh (shoulder). HRMS were measured on electrospray ionization (ESI) instrument with a time-of-flight (TOF) detector. Column chromatography was performed using silica gel 40-60 μm 60A with hexane/ethyl acetate mixtures as eluents. Analytical thin-layer chromatography was performed on silica gel plates with QF-254. Visualization was accomplished with UV light and or solution of p-anisaldehyde/ H_2SO_4 in ethanol.

CH_2Cl_2 , 1,2-dichloroethane, triethylamine and MeCN were distilled from CaH_2 ; DMF was distilled from CaH_2 under reduced pressure. THF, dioxane and Et_2O were distilled from LiAlH_4 . Hexanes, cyclohexane, toluene, methanol and ethyl acetate were distilled without drying agents.

Previously described *N,N*-bis(siloxy)enamines **2a**,^[S3] **2b**,^[S4] **2c**,^[S5] **2d**,^[S5] **2e**,^[S6] **2f**,^[S3] **2g**,^[S3] **2h**^[S7] and **2i**^[S8] were prepared from corresponding aliphatic nitro compounds in accordance with literature procedures. Ylide **5** was prepared using previously described protocol.^[S9] Cyclic *N*-alkoxy,*N*-siloxyenamine **2j** was prepared via a multi-step sequence described ref.^[S10]

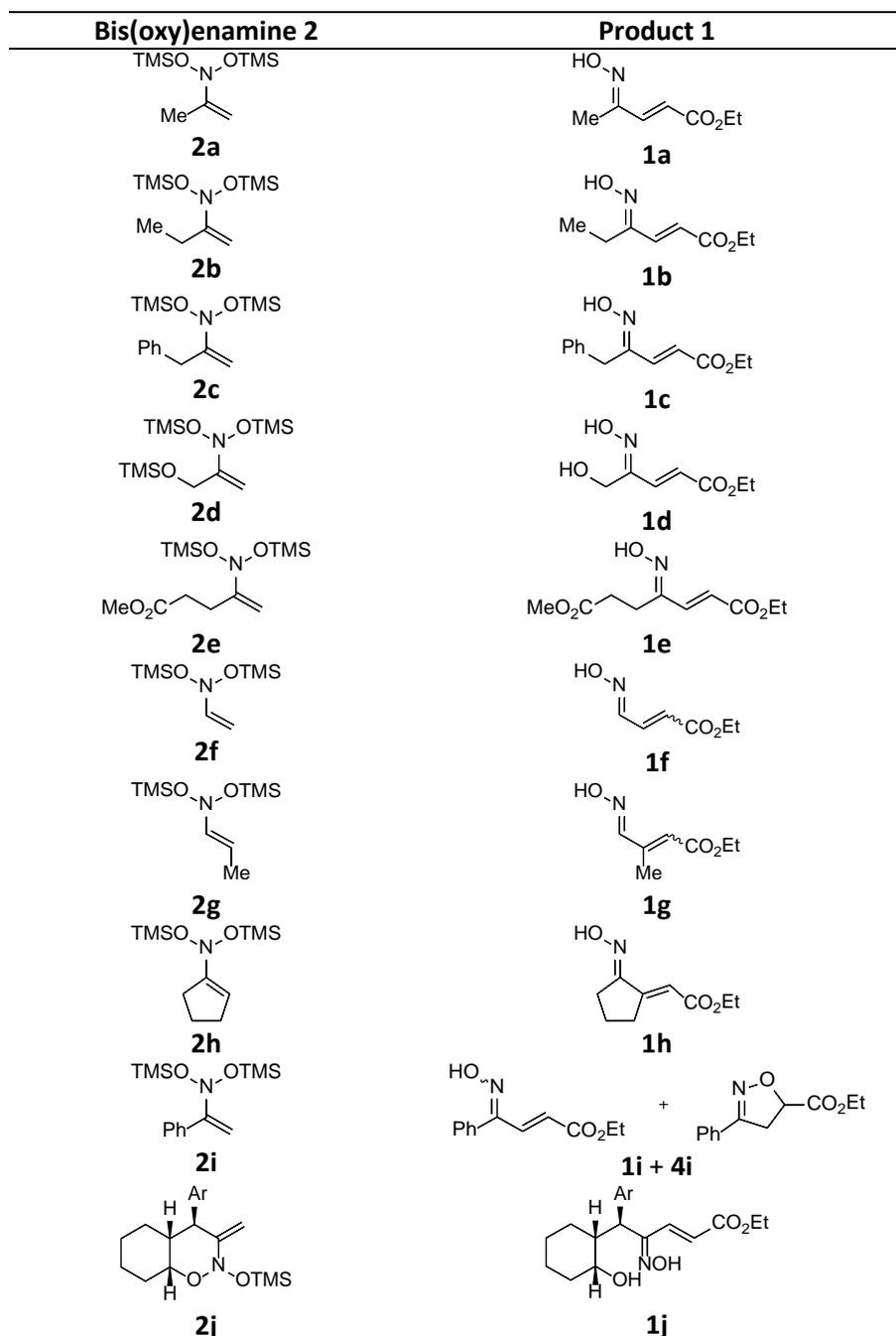
Detailed optimization of reaction conditions



Entry	Solvent	Ratio 2a/5	Concentration	Time	T	Additive	Yield of 1a, % ^a
1	DCM	1 : 1	0.5 M	24 h	rt	none	40
2	DCM	1 : 1	0.5 M	2 h	rt	none	34
3	CHCl ₃	1 : 1	0.5 M	24 h	rt	none	38
4	MeCN/DCM	1 : 1	0.5 M	24 h	rt	none	30
5	toluene/DCM	1 : 1	0.5 M	24 h	rt	none	33
6	cyclohexane/DCM	1 : 1	0.5 M	24 h	rt	none	36
7	AcOEt/DCM	1 : 1	0.5 M	24 h	rt	none	36
8	DMF/DCM	1 : 1	0.5 M	24 h	rt	none	31
9	Et ₂ O/DCM	1 : 1	0.5 M	24 h	rt	none	49
10	Et ₂ O/DCM	1 : 1	0.1 M	24 h	rt	none	16
11	THF/DCM	1 : 1	0.5 M	24 h	rt	none	42
12	dioxane/DCM	1 : 1	0.5 M	24 h	rt	none	33
13	1,2-DCE	1 : 1	0.5 M	2 h	80 °C	none	46
14	1,2-DCE	1 : 1	0.5 M	2 h	80 °C	Et₃N (20 mol%)	60
15	1,2-DCE	1 : 1.5	0.5 M	2 h	80 °C	Et ₃ N (20 mol%)	57
16	1,2-DCE	1.5 : 1.0	0.5 M	2 h	80 °C	Et ₃ N (20 mol%)	48
17	toluene	1 : 1	0.5 M	2 h	80 °C	Et ₃ N (20 mol%)	46
18	dioxane	1 : 1	0.5 M	2 h	80 °C	Et ₃ N (20 mol%)	41
19	heptane	1 : 1	0.5 M	2 h	80 °C	Et ₃ N (20 mol%)	38

^a Yields were determined by ¹H NMR with internal standard (trichloroethylene).

Structures of initial *N,N*-bis(oxy)enamines **2** and corresponding enoximes **1**

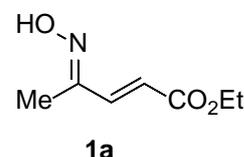


Procedures and products characterization

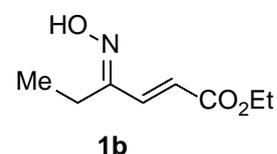
General procedure for preparation of enoximes 1 (procedure i). To a stirred 1M solution of ylide **5** (2 mL, 2.0 mmol) in 1,2-dichloroethane were consequently added triethylamine (0.056 mL, 0.4 mmol) and 1M solution of *N,N*-bis(siloxy)enamine **2** (2 mL, 2 mmol) in 1,2-dichloroethane. The mixture was heated to gentle reflux with stirring for 2 h. Then, volatiles were removed under reduced pressure. To the residue, methanol (10 mL) and NH_4F (0.074 g, 2.0 mmol) were added. After stirring for 15 min at room temperature, the mixture was concentrated under reduced pressure. The residue was subjected to a column chromatography on silica gel (eluent hexane/ethyl acetate mixtures) to give the desired enoxime **1**.

General procedure for preparation of enoximes 1 (procedure ii). To a stirred 1M solution of ylide **5** (2 mL, 2.0 mmol) in dichloromethane were consequently added triethylamine (0.056 mL, 0.4 mmol) and 1M solution of *N,N*-bis(siloxy)enamine **2** (2 mL, 2 mmol) in diethyl ether. The mixture was stirred at room temperature for 24 h. Then, volatiles were removed under reduced pressure. To the residue, methanol (10 mL) and NH_4F (0.074 g, 2.0 mmol) were added. After stirring for 15 min at room temperature, the mixture was concentrated under reduced pressure. The residue was subjected to a column chromatography on silica gel (eluent hexane/ethyl acetate mixtures) to give the desired enoxime **1**.

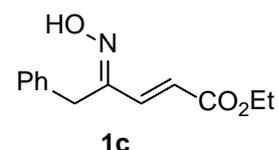
Ethyl (2E,4E)-4-(hydroxyimino)pent-2-enoate (1a).^[S1b] Yield: 57 % (procedure i). White solid. Mp 94 – 95 °C. R_f = 0.45 (hexanes/EtOAc, 3:1). Single isomer. ^1H NMR (300 MHz, CDCl_3) δ 8.83 (br s, 1H, NOH), 7.33 (d, J = 16.1 Hz, 1H, =CH), 6.20 (d, J = 16.1 Hz, 1H, =CH), 4.25 (q, J = 7.1 Hz, 2H, CH_2CH_3), 2.04 (s, 3H, CH_3), 1.32 (t, J = 7.1 Hz, 3H, CH_2CH_3). ^{13}C NMR (75 MHz, JMOD, CDCl_3) δ 166.6 (C=O), 155.4 (C=N), 141.5 (=CH), 123.1 (=CH), 61.0 (CH_2CH_3), 14.3 (CH_3), 9.8 (CH_2CH_3). Anal. Calcd. for $\text{C}_7\text{H}_{11}\text{NO}_3$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.76; H, 7.22; N, 8.78.



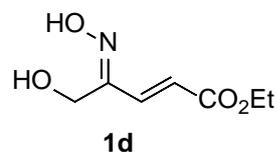
Ethyl (2E,4E)-4-(hydroxyimino)hex-2-enoate (1b). Yield: 51 % (procedure i). White solid. Mp 64 – 67 °C. R_f = 0.44 (hexanes/EtOAc, 3:1). Single isomer. ^1H NMR (300 MHz, CDCl_3) δ 8.93 (br s, 1H, NOH), 7.25 (d, J = 16.2 Hz, 1H, =CH), 6.22 (d, J = 16.2 Hz, 1H, =CH), 4.25 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 2.56 (q, J = 7.6 Hz, 2H, CH_2CH_3), 1.32 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.11 (t, J = 7.6 Hz, 3H, CH_2CH_3). ^{13}C NMR (75 MHz, JMOD, CDCl_3) δ 166.6 (C=O), 160.1 (C=N), 140.5 (=CH), 122.7 (=CH), 61.0 (OCH_2), 17.7 (CH_2), 14.3 (CH_3), 10.7 (CH_3). FT-IR (KBr, cm^{-1}): 3259 (s, br), 2976 (m), 2880 (w), 1684 (s), 1453 (m), 1397 (m), 1369 (m), 1309 (s), 1290 (s), 1252 (m), 1231 (m), 1184 (w), 1044 (m), 998 (s), 983 (s), 879 (w), 752 (w), 737 (w), 650 (w), 604 (w), 520 (w). Anal. Calcd. for $\text{C}_8\text{H}_{13}\text{NO}_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 55.96; H, 7.55; N, 8.06.



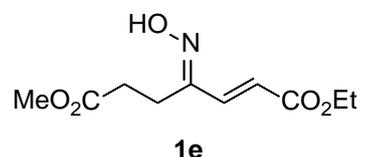
Ethyl (2E,4E)-4-(hydroxyimino)-5-phenylpent-2-enoate (1c). Yield: 28 % (procedure *i*). White solid. Mp 97 – 99 °C. R_f = 0.34 (hexanes/EtOAc, 3:1). Single isomer. ^1H NMR (300 MHz, CDCl_3) δ 9.73 (s, 1H, NOH), 7.42 (d, J = 16.2 Hz, 1H, =CH), 7.35 – 7.21 (m, 5H, Ph), 6.27 (d, J = 16.2 Hz, 1H, =CH), 4.25 (q, J = 7.1 Hz, 2H, CH_2), 3.99 (s, 2H, CH_2), 1.32 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C NMR (76 MHz, DEPT135, CDCl_3) δ 166.5 (C=O), 156.9 (C=N), 140.8 (=CH), 135.8 (*i*-Ph), 128.8, 128.5, 126.7 and 123.8 (o,m,p-Ph, =CH), 61.1 (OCH_2), 30.3 (CH_2), 14.3 (CH_3). FT-IR (KBr, cm^{-1}): 3385 (s, br), 3032 (w), 1692 (s), 1640 (m), 1495 (w), 1453 (w), 1369 (m), 1308 (m), 1279 (m), 1192 (m), 998 (m, sh), 884 (w), 867 (w), 731 (w), 699 (w), 684 (w), 638 (w), 622 (w). HRMS calcd for $[\text{M}+\text{H}]^+$ ($\text{C}_{13}\text{H}_{16}\text{NO}_3^+$) 234.1125, found 234.1132. Anal. Calcd. for $\text{C}_{13}\text{H}_{15}\text{NO}_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.92; H, 6.44; N, 5.83.



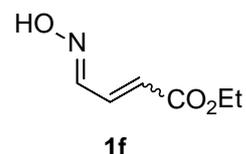
Ethyl (2E,4Z)-5-hydroxy-4-(hydroxyimino)pent-2-enoate (1d). Yield: 49 % (procedure *i*). White solid. Mp 112 – 114 °C. R_f = 0.51 (hexanes/EtOAc, 1:1). Single isomer. ^1H NMR (300 MHz, DMSO-d_6) δ 7.11 (d, J = 16.2 Hz, 1H, =CH), 6.47 (d, J = 16.2 Hz, 1H, =CH), 5.27 – 5.05 (br s, 1H, OH), 4.37 (s, 2H, CH_2), 4.15 (q, J = 7.1 Hz, 2H, CH_2CH_3), 3.16 (s, 1H, OH), 1.22 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C NMR (76 MHz, DEPT135, DMSO-d_6) δ 166.1 (C=O), 156.2 (C=N), 139.7 (=CH), 122.0 (=CH), 60.3 (CH_2), 52.9 (CH_2), 14.2 (CH_3). FT-IR (KBr, cm^{-1}): 3341 (s, br), 3226 (s, br), 3173 (s, br), 3035 (w), 2897 (m, br), 1685 (s), 1636 (m), 1458 (w), 1371 (m), 1331 (m), 1318 (m), 1273 (m), 1201 (s), 1095 (w), 1026 (m), 987 (s), 884 (w), 871 (w), 795 (m), 743 (w), 636 (w), 606 (m). Anal. Calcd. for $\text{C}_7\text{H}_{11}\text{NO}_4$: C, 48.55; H, 6.40; N, 8.09. Found: C, 48.42; H, 6.48; N, 7.93.



Ethyl (2E,4E)-6-acetoxy-4-(hydroxyimino)hex-2-enoate (1e). Yield: 37 % (procedure *i*). Yellowish oil. R_f = 0.42 (hexanes/EtOAc, 2:1). Single isomer. ^1H NMR (300 MHz, CDCl_3) δ 9.93 – 9.65 (br s, 1H, NOH), 7.31 (d, J = 16.2 Hz, 1H, =CH), 6.26 (d, J = 16.2 Hz, 1H, =CH), 4.25 (q, J = 7.1 Hz, 2H, CH_2), 3.69 (s, 3H, OCH_3), 2.84 (dd, J = 8.9, 7.0 Hz, 2H, $\text{CH}_2\text{-CH}_2$), 2.56 (dd, J = 8.9, 7.0 Hz, 2H, $\text{CH}_2\text{-CH}_2$), 1.31 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C NMR (76 MHz, DEPT135, CDCl_3) δ 173.0 (C=O), 166.5 (C=O), 157.1 (C=N), 140.4 (=CH), 123.0 (=CH), 61.1 (OCH_2), 52.0 (OCH_3), 30.2 and 19.9 ($\text{CH}_2\text{-CH}_2$), 14.3 (CH_3). HRMS Calcd for $[\text{M}+\text{H}]^+$ ($\text{C}_{10}\text{H}_{16}\text{NO}_5^+$) 230.1023, found 230.1025. Anal. Calcd. for $\text{C}_{10}\text{H}_{15}\text{NO}_5$: C, 52.40; H, 6.60; N, 6.11. Found: C, 52.38; H, 6.73; N, 6.00.



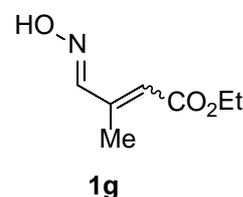
Ethyl (2E,4E)- and (2Z,4E)-4-(hydroxyimino)but-2-enoates (1f). Yield: 9 % (procedure *i*), 18 % (procedure *ii*). White solid. Mp 65 – 67 °C. R_f = 0.4 (hexanes/EtOAc, 3:1). Mixture of *E/Z*-isomers with respect to C=C bond, ratio (2E,4E)-**1f**/(2Z,4E)-**1f** = 8 : 1. Major isomer (2E,4E)-**1f**: ^1H NMR (300 MHz, CDCl_3) δ 9.52 – 9.41 (br s, 1H, NOH), 7.88 (d, J = 10.2 Hz, 1H, N=CH), 7.33 (dd, J = 15.8, 10.2 Hz, 1H, N=CH-CH=CH), 6.18 (d, J = 15.8 Hz, 1H, N=CH-CH=CH), 4.26 (q, J = 7.1 Hz, 2H, CH_2), 1.32 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C NMR (76 MHz, DEPT135, HSQC, CDCl_3) δ 166.3 (C=O), 149.6 (C=N), 137.5 (N=CH-CH=CH), 127.4 (N=CH-CH=CH), 61.2 (CH_2), 14.3 (CH_3). Minor isomer (2Z,4E)-**1f**: ^1H NMR (300 MHz, CDCl_3) δ 9.52 – 9.41 (br s, 1H, NOH), 8.93 (d, J = 10.4 Hz, 1H, N=CH), 6.65 (dd, J = 11.7, 10.4 Hz, 1H, N=CH-CH=CH), 6.04 (dd, J = 11.7 Hz, 1H, N=CH-CH=CH), 4.26 (q, J = 7.1 Hz, 2H, CH_2), 1.32 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C NMR (76 MHz,



DEPT135, HSQC, CDCl₃) δ 165.6 (C=O), 149.0 (C=N), 136.7 (N=CH-CH=CH), 123.8 (N=CH-CH=CH), 60.9 (CH₂), 14.3 (CH₃). Anal. Calcd. for C₆H₉NO₃: C, 50.35; H, 6.34; N, 9.79. Found: C, 50.35; H, 6.08; N, 9.75.

Ethyl (2E,4E)- and (2Z,4E)-4-(hydroxyimino)-3-methylbut-2-enoates (1g).^[S11] Yield: 55 % (procedure *ii*).

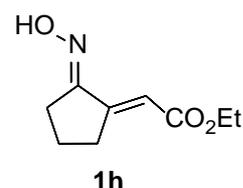
Colorless oil. R_f = 0.47 (hexanes/EtOAc, 3:1). Mixture of *E/Z*-isomers with respect to C=C bond, ratio (2E,4E)-**1g**/(2Z,4E)-**1g** = 2 : 1. Major isomer (2E,4E)-**1g**: ¹H NMR (300 MHz, CDCl₃) δ 9.04 (br s, 1H, NOH), 7.74 (d, *J* = 0.8 Hz, 1H, N=CH), 5.93 (qd, *J* = 1.6, 0.8 Hz, 1H, =CH), 4.20 (q, *J* = 7.1 Hz, 2H, CH₂), 2.29 (d, *J* = 1.6 Hz, 3H, CH₃), 1.29 (t, *J* = 7.1 Hz, 3H, CH₂CH₃). ¹³C NMR (75 MHz, DEPT135, HSQC, CDCl₃) δ 166.4 (C=O), 153.3 (C=N), 147.7 (=C), 124.4 (=CH), 60.5 (CH₂), 14.3 (CH₂CH₃), 13.1 (CH₃).



Characteristic 2D NOESY correlations: N=CH/=CH. Minor isomer (2Z,4E)-**1g**: ¹H NMR (300 MHz, CDCl₃) δ 9.07 (d, *J* = 0.9 Hz, 1H, N=CH), 8.96 (br s, 1H, NOH), 5.96 (qd, *J* = 1.4, 0.9 Hz, 1H, =CH), 4.18 (q, *J* = 7.1 Hz, 2H, CH₂), 2.03 (d, *J* = 1.4 Hz, 3H, CH₃), 1.28 (t, *J* = 7.1 Hz, 3H, CH₂CH₃). ¹³C NMR (75 MHz, DEPT135, HSQC, CDCl₃) δ 165.6 (C=O), 149.6 (C=N), 145.9 (=C), 122.7 (=CH), 60.6 (CH₂), 19.5 (CH₃), 14.3 (CH₂CH₃). Characteristic 2D NOESY correlations: CH₃/=CH. Anal. Calcd. for C₇H₁₁NO₃: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.68; H, 7.34; N, 8.52.

Ethyl (E)-2-((E)-2-(hydroxyimino)cyclopentylidene)acetate (1h). Yield: 43 % (procedure *ii*). White solid.

Mp 123 – 125 °C. R_f = 0.59 (hexanes/EtOAc, 2:1). ¹H NMR (300 MHz, CDCl₃) δ 9.30 – 9.12 (br m, 1H, NOH), 6.52 (t, *J* = 2.7 Hz, 1H, =CH), 4.20 (q, *J* = 7.1 Hz, 2H, OCH₂), 3.00 (td, *J* = 7.6, 2.7 Hz, 2H, CH₂C=C), 2.63 (t, *J* = 7.6 Hz, 2H, CH₂C=N), 1.87 (p, *J* = 7.6 Hz, 2H, CH₂CH₂CH₂), 1.29 (t, *J* = 7.1 Hz, 3H, CH₃). ¹³C NMR (76 MHz, CDCl₃) δ 167.3 (C=O), 162.3 and 154.7 (=C and C=N), 112.1 (=CH), 60.5 (OCH₂), 32.1 (CH₂), 27.1 (CH₂), 22.0 (CH₂), 14.4 (CH₃). FT-IR (KBr, cm⁻¹): 3388 (s, br), 3268 (s, br), 2984

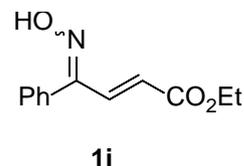


(w), 1676 (s), 1647 (s), 1455 (m), 1372 (w), 1301 (s), 1278 (s), 1057 (s), 974 (w), 939 (m), 907 (m), 759 (w), 707 (w). HRMS calcd for [M+H]⁺ (C₉H₁₄NO₃⁺) 184.0968, found 184.0975. Anal. Calcd. for C₉H₁₃NO₃: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.06; H, 7.23; N, 7.63.

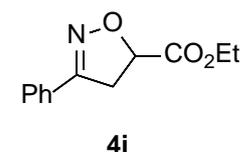
Reaction of *N,N*-bis(oxy)enamine **2i with ylide **5**.** To a stirred 1M solution of ylide **5** (1.45 mL, 1.45 mmol) in dichloromethane were consequently added triethylamine (0.04 mL, 0.29 mmol) and 1M solution of *N,N*-bis(siloxy)enamine **2** (1.45 mL, 1.45 mmol) in diethyl ether. The mixture was stirred at room temperature for 24 h. Then, volatiles were removed under reduced pressure. To the residue, methanol (10 mL) and NH₄F (54 mg, 1.45 mmol) were added. After stirring for 15 min at room temperature, the mixture was concentrated under reduced pressure. The residue was subjected to a column chromatography on silica gel (eluent hexane/ethyl acetate mixtures) to give 235 mg of an unseparable mixture of enoxime **1i** (yield: 32 %) and isoxazoline **4i** (yield: 42 %) (ratio **4i/1i** = 1.3 : 1). **Separation of enoxime **1i** and isoxazoline **4i**.** The mixture of **1i** and **4i** (125 mg, 0.57 mmol) was dissolved in dichloromethane (0.25 mL). *Tert*-Butyldimethylsilyl chloride (87 mg, 0.57 mmol) and triethylamine (0.08 mL, 0.57 mmol) were added at room temperature under argon atmosphere and the mixture was kept overnight. The resulting mixture was concentrated in vacuum and the residue was subjected to a column chromatography on silica gel (eluent hexane → hexane/ethyl acetate 40 : 1 → 20 : 1 → 10 : 1 → 7 : 1) to give two fractions. The less polar fraction contained TBS ether of enoxime **1i** (50 mg, yield 61 %),

the slow-moving fraction contained isoxazoline **4i** (30 mg). TBS ether of enoxime **1i** (50 mg, 0.15 mmol) was dissolved in methanol (5 mL) and NH_4F (7 mg, 0.19 mmol) was added at room temperature. The solution was kept at this temperature for 72 h, then volatiles were removed in vacuum. The residue was subjected to a column chromatography on silica gel (eluent hexane/ethyl acetate 10 : 1 \rightarrow 7 : 1 \rightarrow 5 : 1 \rightarrow 3 : 1) to give 31 mg (94 %) of enoxime **1i**.

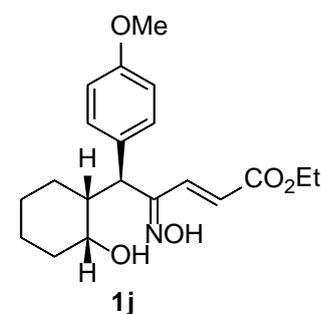
Ethyl (2E,4Z)- and (2E,4E)-4-(hydroxyimino)-4-phenylbut-2-enoates (1i).^[S1b] Yield: 32 % (in mixture with **4i**). White solid. Mp 76 – 78 °C. R_f = 0.42 (hexanes/EtOAc, 2:1). Mixture of *E/Z*-isomers with respect to C=N bond, ratio (2E,4Z)-**1i**/(2E,4E)-**1i** = 13 : 1. Major isomer (2E,4Z)-**1i**: ^1H NMR (300 MHz, CDCl_3) δ 9.09 – 8.90 (br s, 1H, NOH), 7.58 (d, J = 15.9 Hz, 1H, =CH), 7.53 – 7.43 and 7.34 – 7.26 (2m, 3H and 2H, o,m,p-Ph), 5.88 (d, J = 15.9 Hz, 1H, =CH), 4.24 (q, J = 7.1 Hz, 2H, CH_2), 1.30 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, DEPT135, CDCl_3) δ 166.4 (C=O), 157.8 (C=N), 141.4 (=CH), 133.4 (i-Ph), 129.5, 128.7, 128.5 and 126.2 (o,m,p-Ph and =CH), 61.0 (CH_2), 14.3 (CH_3). Minor isomer (2E,4E)-**1i**: ^1H NMR (300 MHz, CDCl_3 , characteristic signals) δ 9.30 – 9.15 (br s, 1H, NOH), 8.12 (d, J = 16.4 Hz, 1H, =CH), 6.18 (d, J = 16.4 Hz, 1H, =CH). HRMS calcd for $[\text{M}+\text{H}]^+$ ($\text{C}_{12}\text{H}_{14}\text{NO}_3^+$) 220.0968, found 220.0976.



Ethyl 3-phenyl-4,5-dihydroisoxazole-5-carboxylate (4i).^[S12] Yield: 42 % (in mixture with **1i**). Yellowish oil. R_f = 0.42 (hexanes/EtOAc, 2:1). ^1H NMR (300 MHz, CDCl_3) δ 7.73 – 7.59 and 7.53 – 7.31 (2 m, 2H and 3H, o,m,p-Ph), 5.14 (dd, J = 10.3, 8.1 Hz, 1H, CH), 4.24 (q, J = 7.0 Hz, 2H, OCH_2), 3.68 – 3.57 (m, 2H, CH_2), 1.30 (t, J = 7.0 Hz, 3H, CH_3). NMR spectrum is in agreement with previously published data.^[S12]

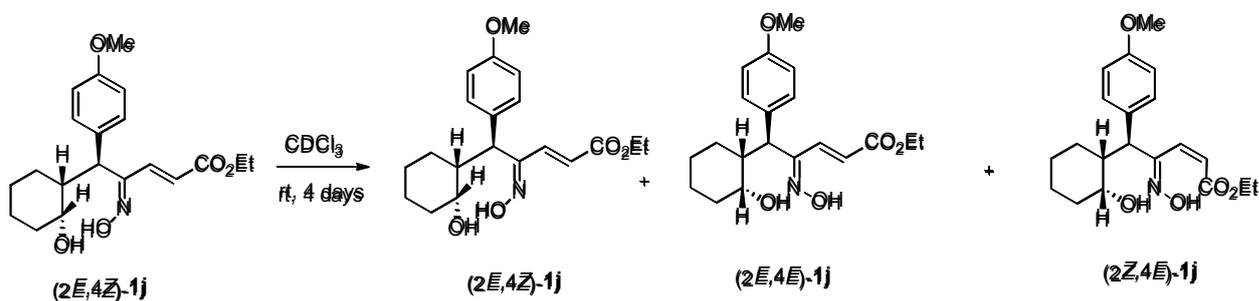


Ethyl (S*)-5-((1R*,2R*)-2-hydroxycyclohexyl)-4-(4-methoxyphenyl)pent-2-enoate (1j). To a stirred 1M solution of ylide **5** (1.25 mL, 1.25 mmol) in dichloromethane were consequently added 1M solution of *N,N*-bis(siloxy)enamine **2** (1.25 mL, 1.25 mmol) in diethyl ether and triethylamine (0.035 mL, 0.25 mmol). The mixture was stirred at room temperature for 24 h. Then, volatiles were removed under reduced pressure. To the residue, methanol (10 mL) and NH_4F (0.046 g, 1.25 mmol) were added. After stirring for 15 min at room temperature, the mixture was concentrated under reduced pressure. The residue was subjected to a column chromatography on silica gel (eluent hexane/ethyl acetate mixtures) to give 221 mg (49 %) of enoxime **1j** as yellowish oil. R_f = 0.23 (hexanes/EtOAc, 2:1). Mixture of *E/Z*-isomers with respect to C=N bond, ratio (2E,4Z)-**1j**/(2E,4E)-**1j** = 10 : 1. Major isomer (2E,4Z)-**1j**: ^1H NMR (300 MHz, COSY, HSQC, CDCl_3) δ 10.84 – 9.97 (br s, 1H, NOH), 7.15 (d, J = 8.7 Hz, 2H, 2 CH_{Ar}), 6.84 (d, J = 8.7 Hz, 2H, 2 CH_{Ar}), 6.11 (d, J = 12.1 Hz, 1H, =CH), 5.85 (d, J = 12.1 Hz, 1H, =CH), 4.57 (d, J = 12.0 Hz, 1H, CH-Ar), 4.11 (q, J = 7.2 Hz, 2H, OCH_2), 4.09 (m, 1H, CH-O), 3.78 (s, 3H, OCH_3), 3.64 – 3.49 (m, 1H, OH), 2.02 – 1.89, 1.74 – 1.55, 1.51 – 1.33 and 1.28 – 1.17 (4 m, 2H, 2H, 4H and 1H, CH and 4 CH_2), 1.21 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C NMR (76 MHz, DEPT135, HSQC, HMBC, CDCl_3) δ 166.9 (C=O), 158.6 and 156.9 (C=N and C_{Ar} -O), 132.0 (=CH), 130.5 (2 CH_{Ar}), 129.8 (C_{Ar}), 125.2 (=CH), 114.1 (2 CH_{Ar}), 67.0 (CH-OH), 61.0 (OCH_2), 55.3 (OCH_3), 44.8 (CH-Ar), 42.8 (CH), 32.8 (CH_2), 26.2 (CH_2), 24.4 (CH_2), 19.9 (CH_2), 14.1 (CH_3). Characteristic



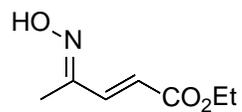
2D NOESY correlations: =CH/CH_{Ar}, CH-Ar/CH_{Ar}. Minor isomer (2E,4E)-**1j**: ¹H NMR (300 MHz, COSY, HSQC, CDCl₃, selected signals) δ 8.86 – 8.65 (br s, 1H, NOH), 7.07 (d, J = 8.7 Hz, 2H, 2 CH_{Ar}), 6.84 (d, J = 8.7 Hz, 2H, 2 CH_{Ar}), 6.32 (d, J = 12.1 Hz, 1H, =CH), 5.88 (d, J = 12.1 Hz, 1H, =CH), 4.56 (br m, 1H, CH-O), 4.19 (q, J = 7.2 Hz, 2H, OCH₂), 3.59 (d, J = 11.1 Hz, 1H, CH-Ar), 2.14 – 2.07 (m, 1H, CH), 1.27 (t, J = 7.2 Hz, 3H, CH₃). ¹³C NMR (76 MHz, DEPT135, HSQC, HMBC, CDCl₃) δ 166.0 (C=O), 159.2 and 156.5 (C=N and C_{Ar}-O), 140.4 (=CH), 129.9 (2 CH_{Ar}), 129.7 (C_{Ar}), 122.0 (=CH), 114.0 (2 CH_{Ar}), 65.7 (CH-O), 61.3 (OCH₂), 55.3 (OCH₃), 52.0 (CH-Ar), 43.7 (CH), 32.9 (CH₂), 26.1 (CH₂), 24.4 (CH₂), 20.0 (CH₂), 14.0 (CH₃). Characteristic 2D NOESY correlations: CH-Ar/CH_{Ar}. Exchange correlations in 2D NOESY: =CH(2E,4Z)/=CH(2E,4E). HRMS calcd for [M+Na]⁺ (C₂₀H₂₇NO₅Na⁺) 384.1781, found 384.1776.

Upon storage in CDCl₃ solution at rt for 4 days enoxime (2E,4Z)-**1j** underwent isomerization to give a mixture containing (2E,4Z)-**1j**, (2E,4E)-**1j** and (2Z,4E)-**1j** in 2.2 : 1.0 : 1.7 ratio. Isomer (2Z,4E)-**1j**: ¹H NMR (300 MHz, COSY, HSQC, CDCl₃, selected signals) δ 8.82 – 8.62 (br s, 1H, NOH), 7.20 (d, J = 8.8 Hz, 2H, 2 CH_{Ar}), 6.92 (d, J = 9.8 Hz, 1H, =CH), 6.87 (d, J = 8.8 Hz, 2H, 2 CH_{Ar}), 6.55 (d, J = 9.8 Hz, 1H, =CH), 4.10 (m, 1H, CH-O), 3.94 (d, J = 11.4 Hz, 1H, CH-Ar), 3.79 (s, 3H, OCH₃), 3.72 (q, J = 7.0 Hz, 2H, OCH₂), 2.30 – 2.18 (m, 1H, CH), 2.13 (br m, 1H, OH), 2.03 – 1.90, 1.88 – 1.80, 1.74 – 1.05 and 0.96 – 0.86 (4 m, 1H, 1H, 5H and 1H, 4 CH₂), 1.24 (t, J = 7.0 Hz, 3H, CH₃). ¹³C NMR (76 MHz, DEPT135, HSQC, CDCl₃, selected signals) δ 163.0 (C=O), 157.1 and 156.5 (C=N and C_{Ar}-O), 134.2 (=CH), 130.4 (2 CH_{Ar}), 129.9 (C_{Ar}), 125.4 (=CH), 114.6 (2 CH_{Ar}), 66.6 (CH-O), 58.4 (OCH₂), 55.2 (OCH₃), 50.9 (CH-Ar), 43.0 (CH), 33.4 (CH₂), 25.6 (CH₂), 24.4 (CH₂), 19.6 (CH₂), 18.3 (CH₃). Characteristic 2D NOESY correlations: =CH/=CH, CH-Ar/CH_{Ar}.



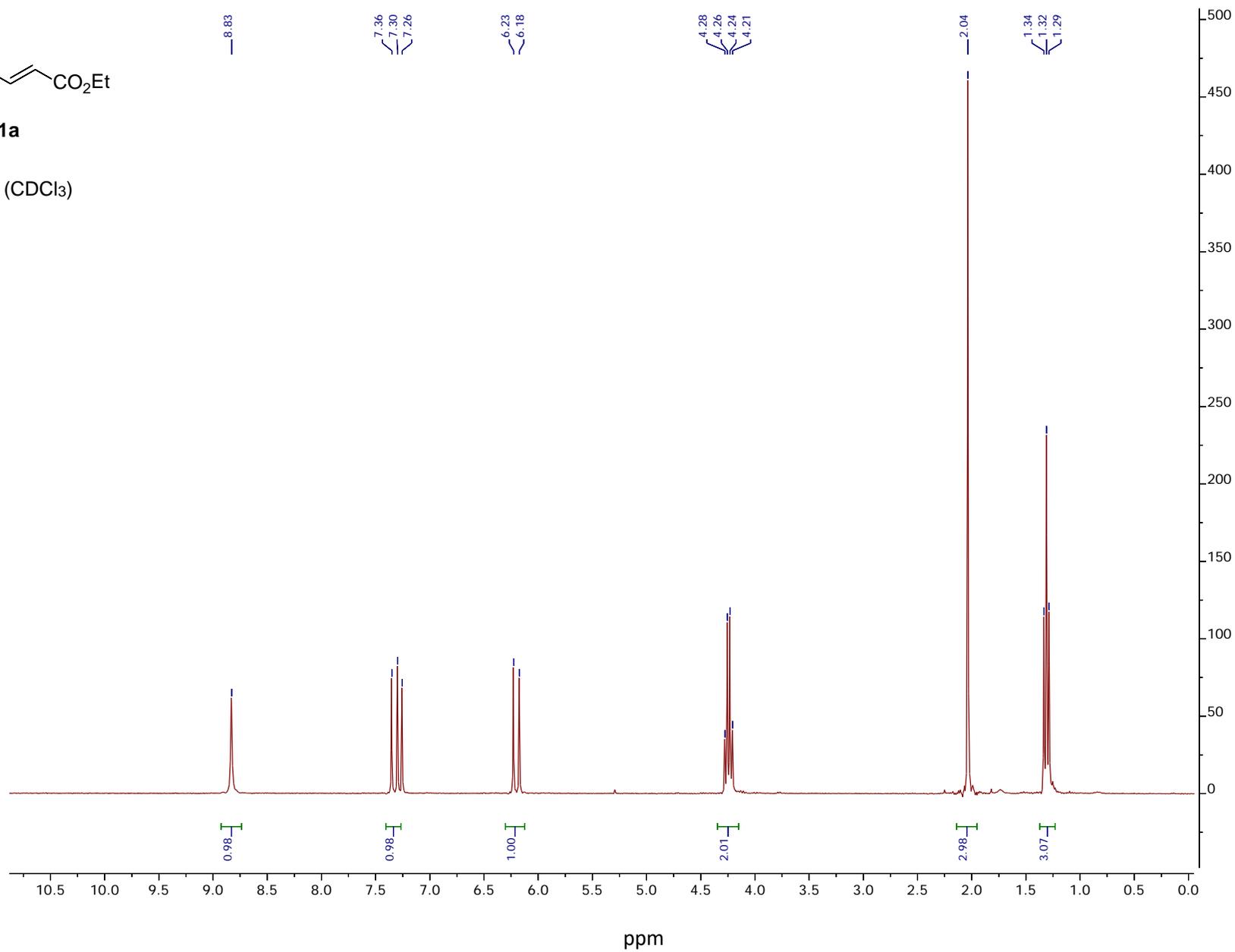
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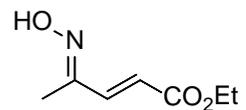
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1a

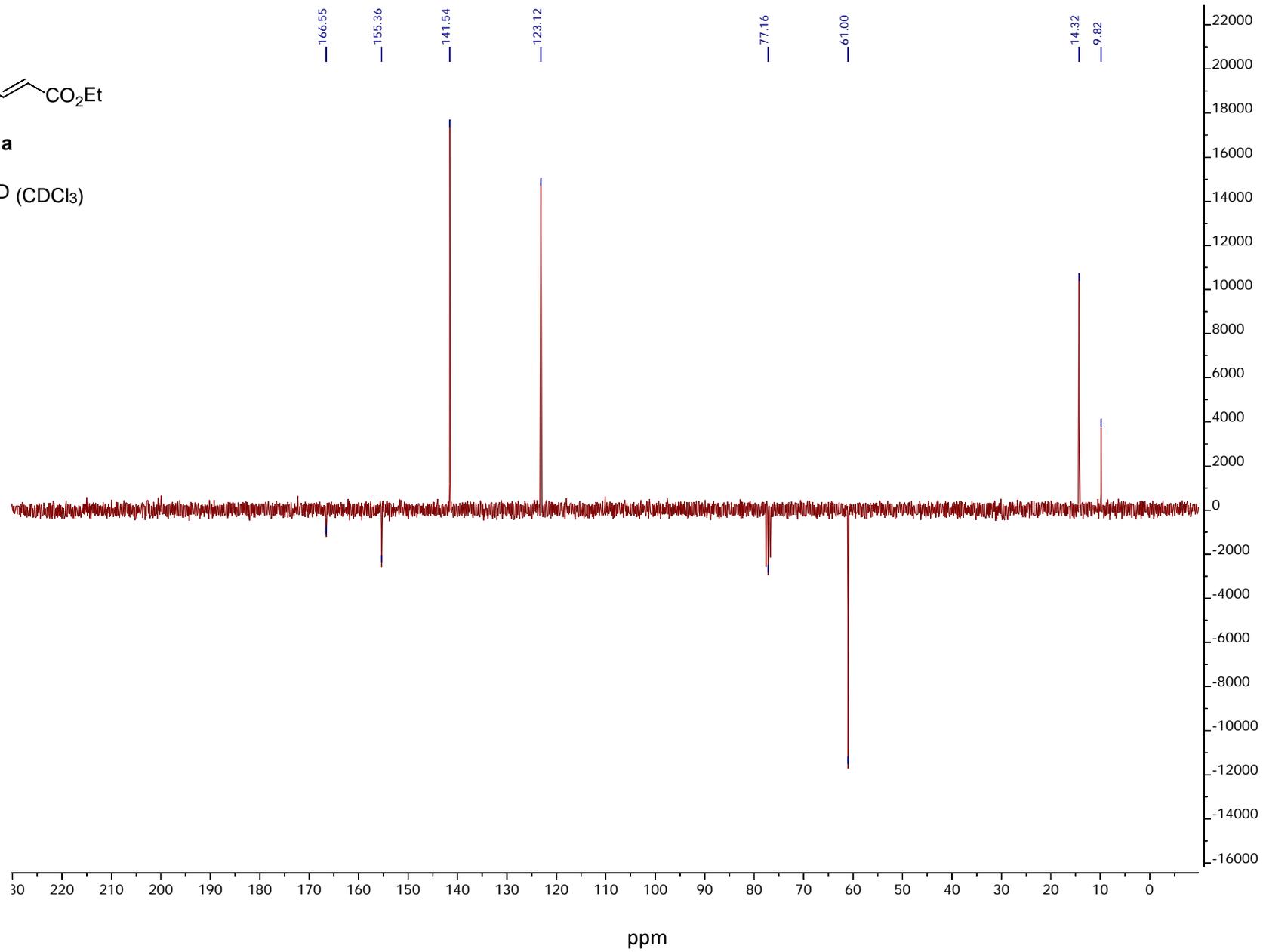
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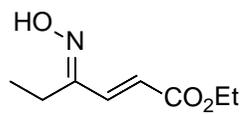




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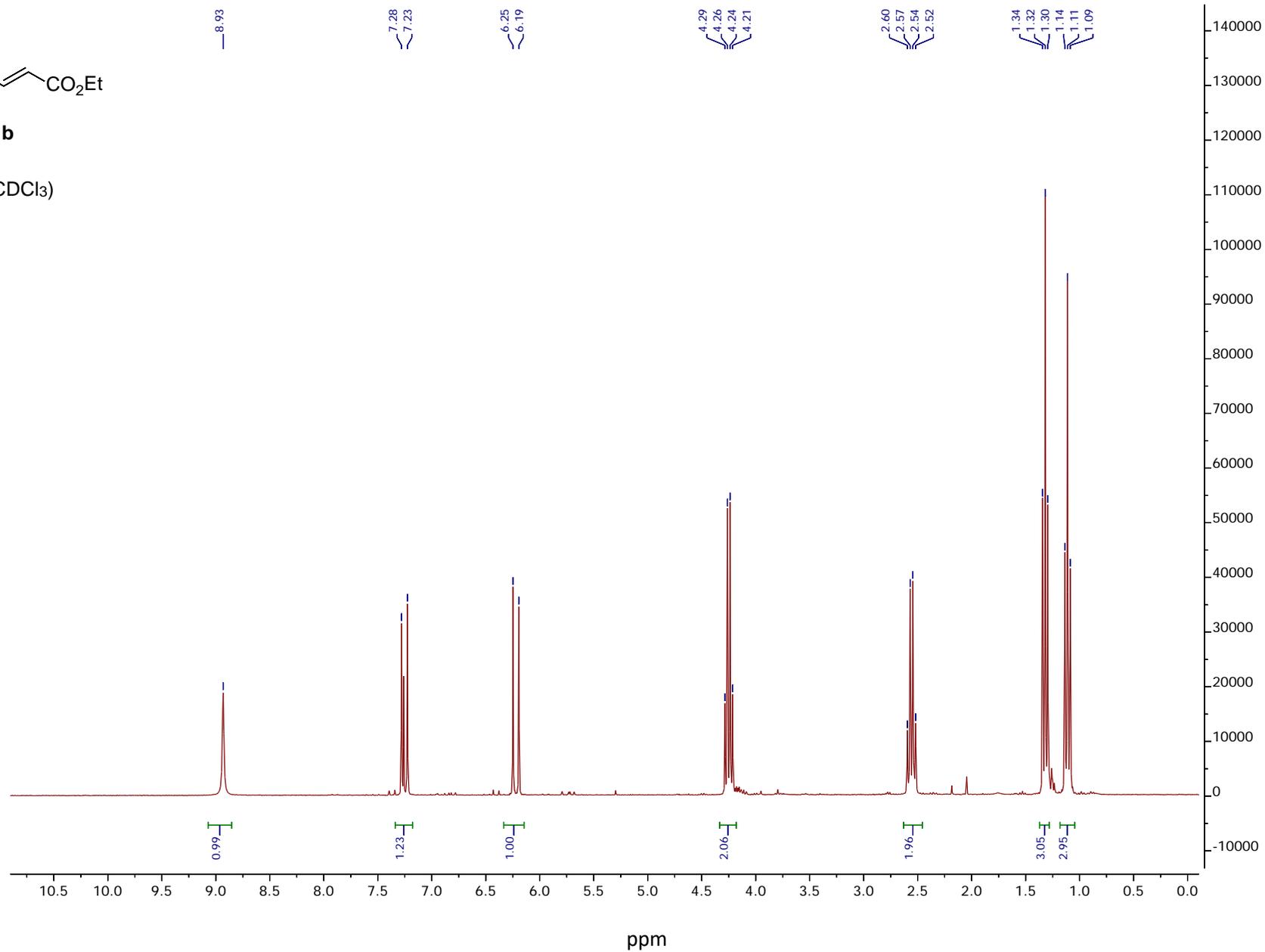
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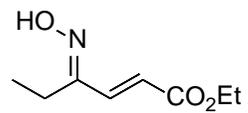




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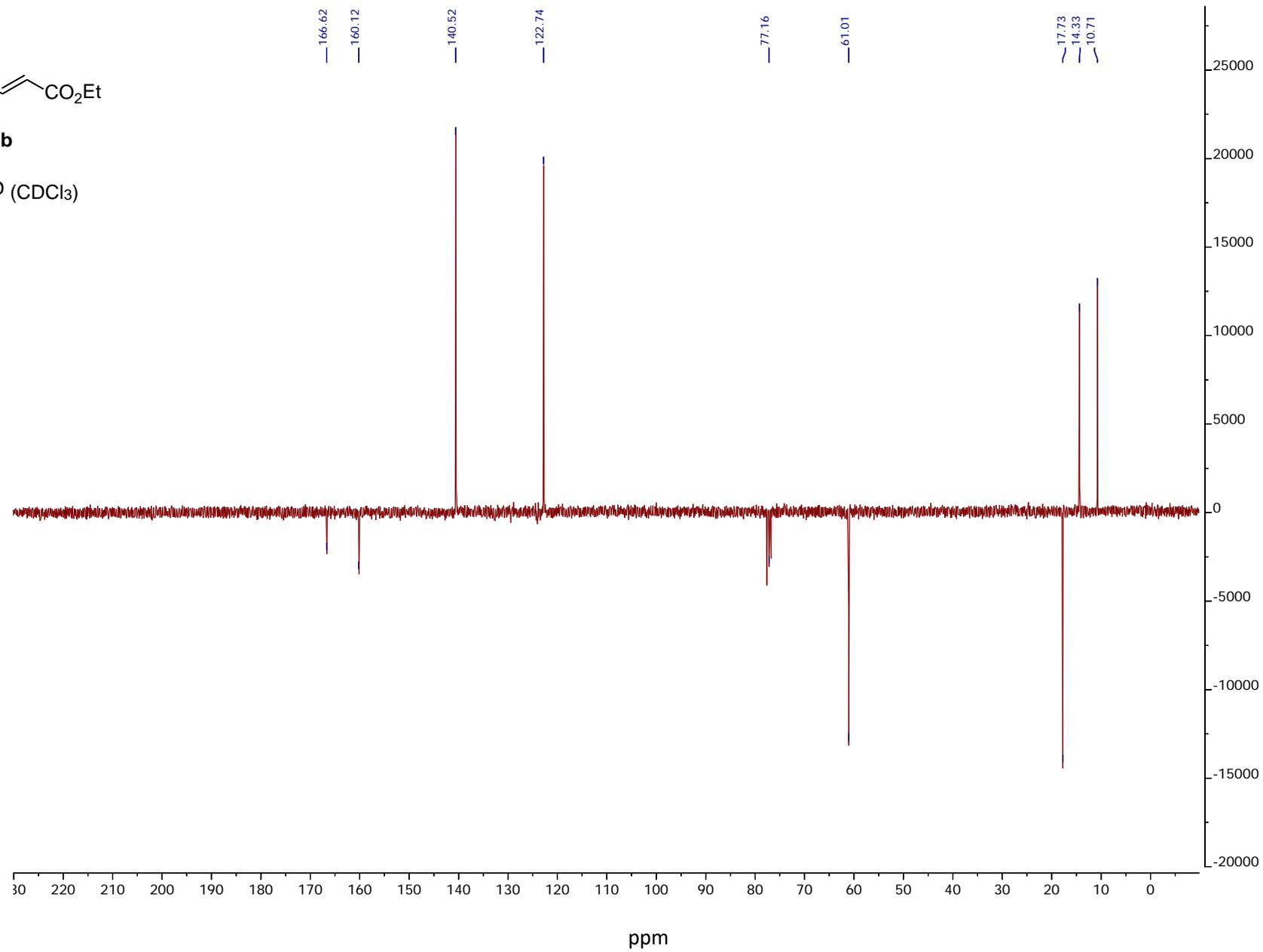
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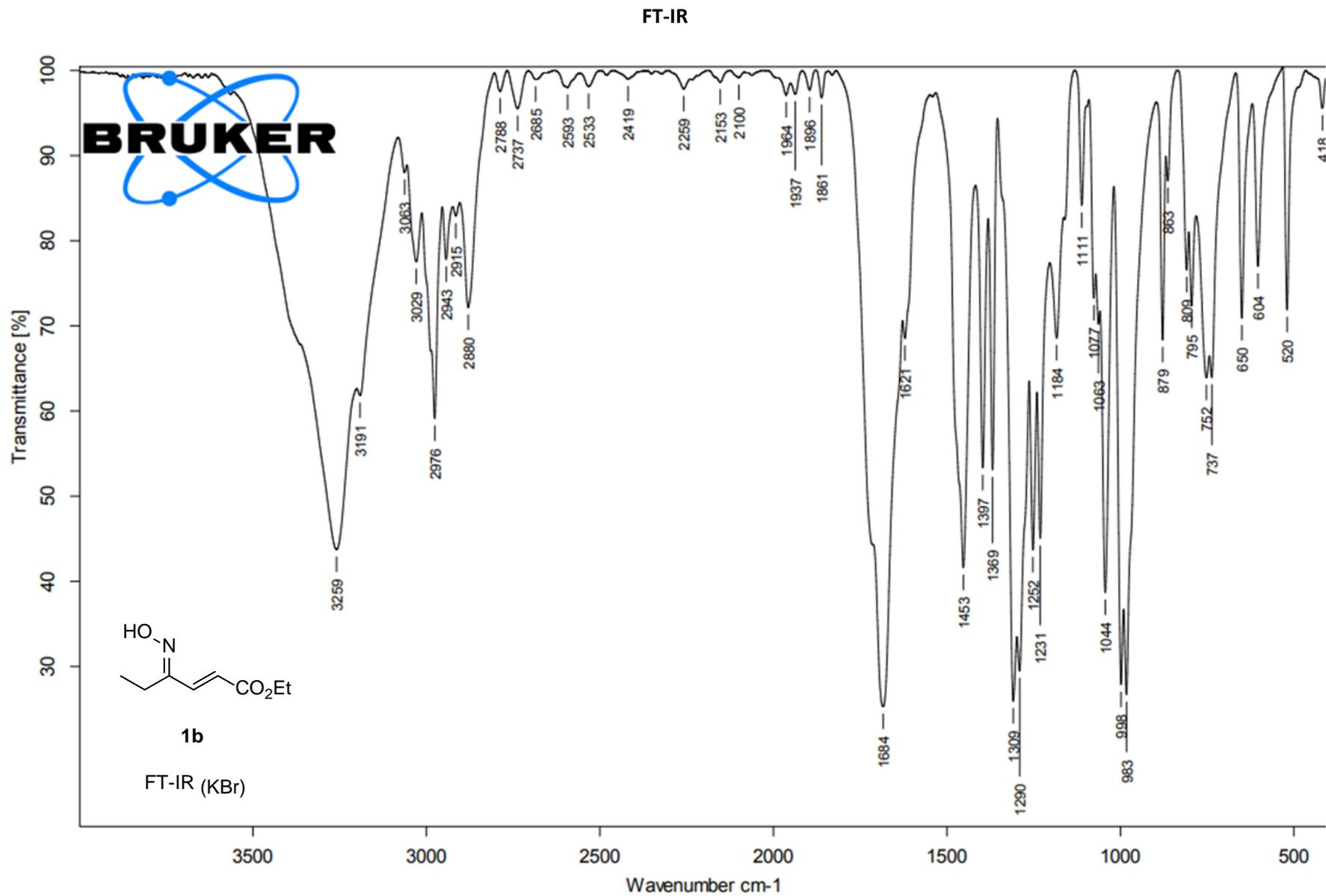


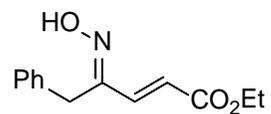


1b

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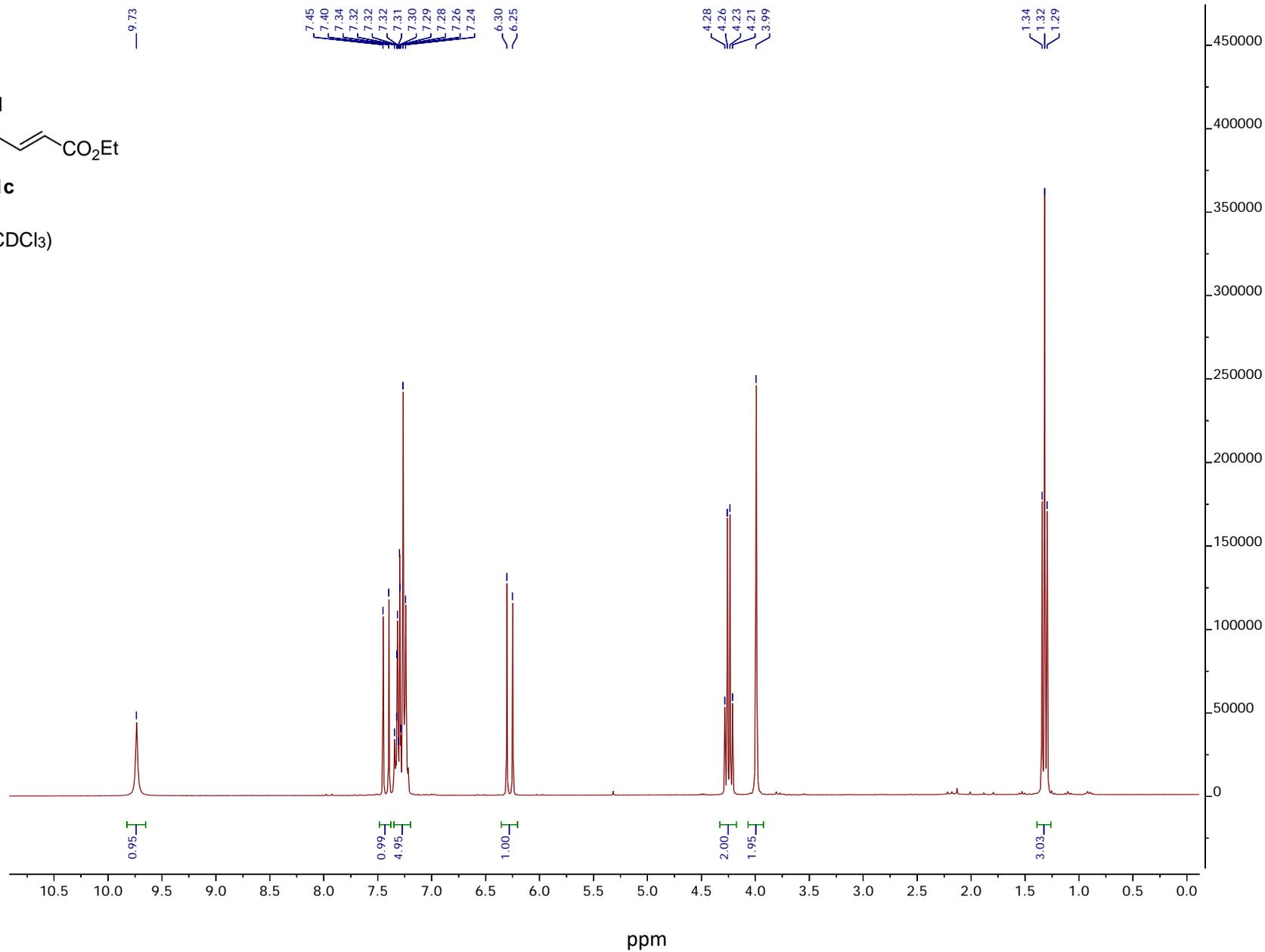


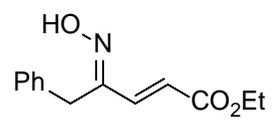




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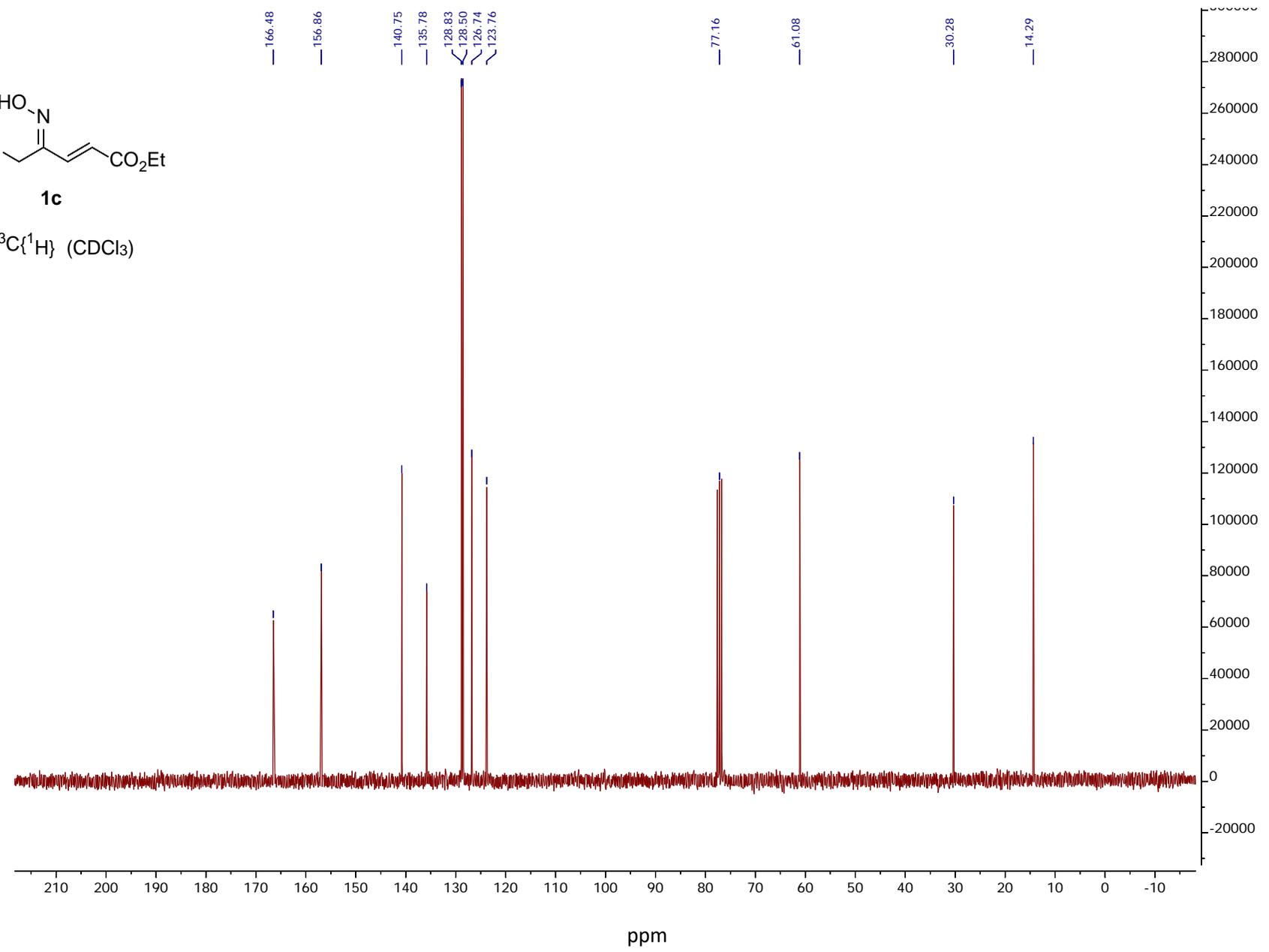
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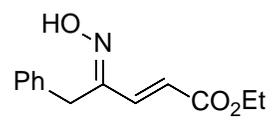




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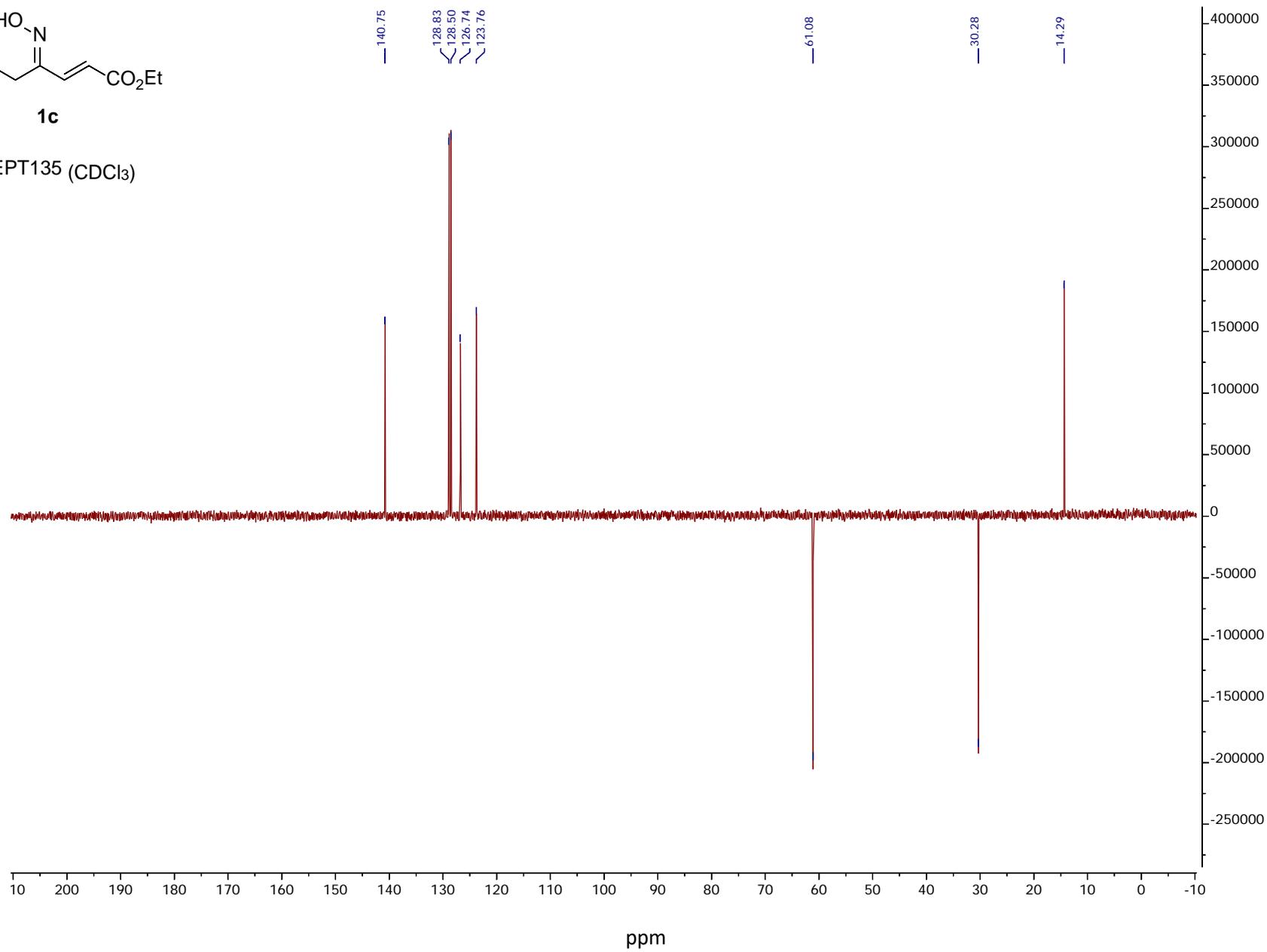
$^{13}\text{C}\{^1\text{H}\}$ (CDCl₃)



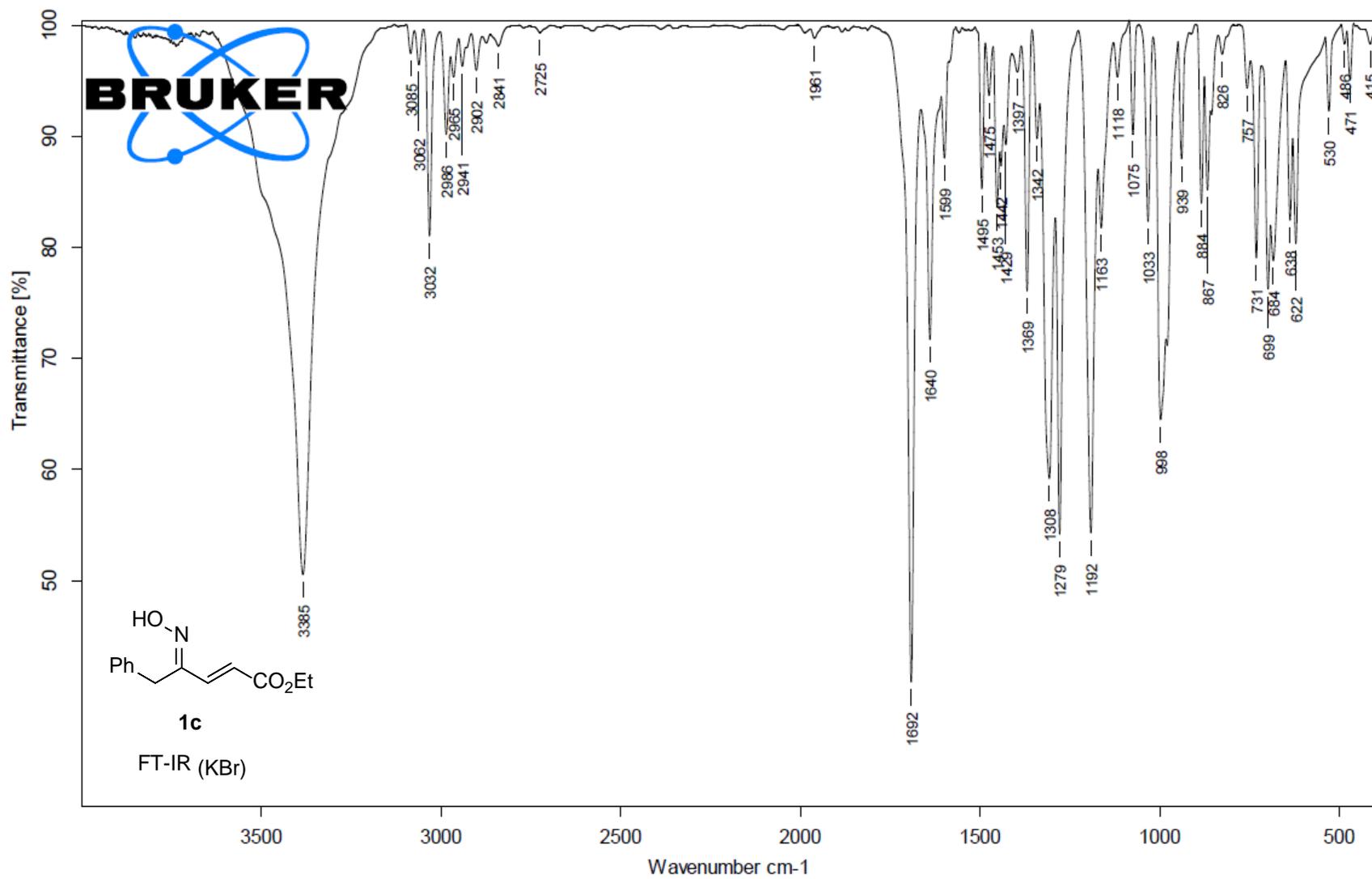


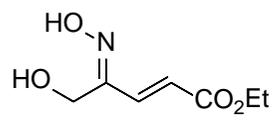
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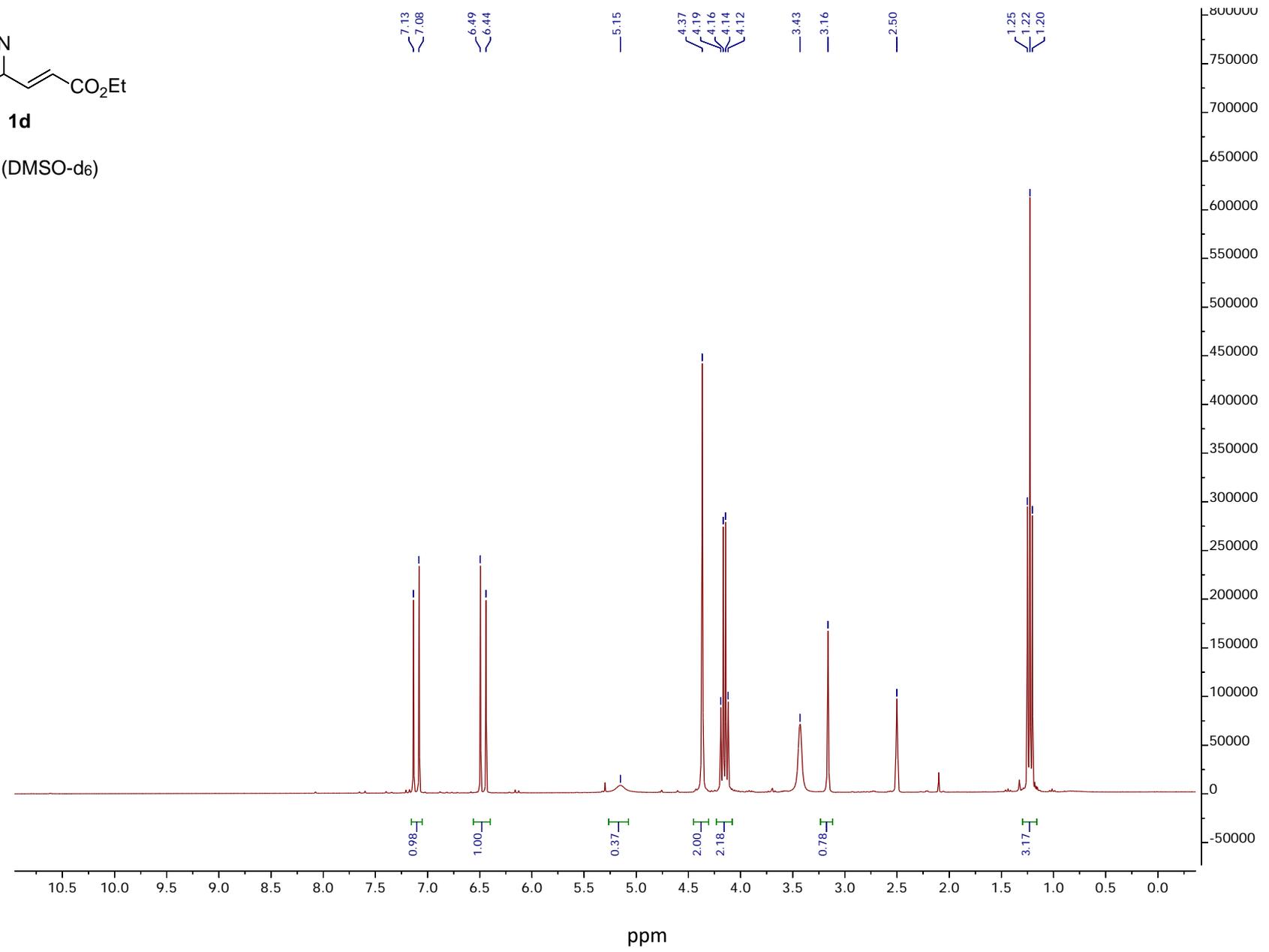
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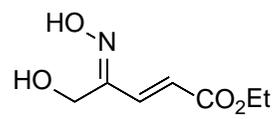




1d

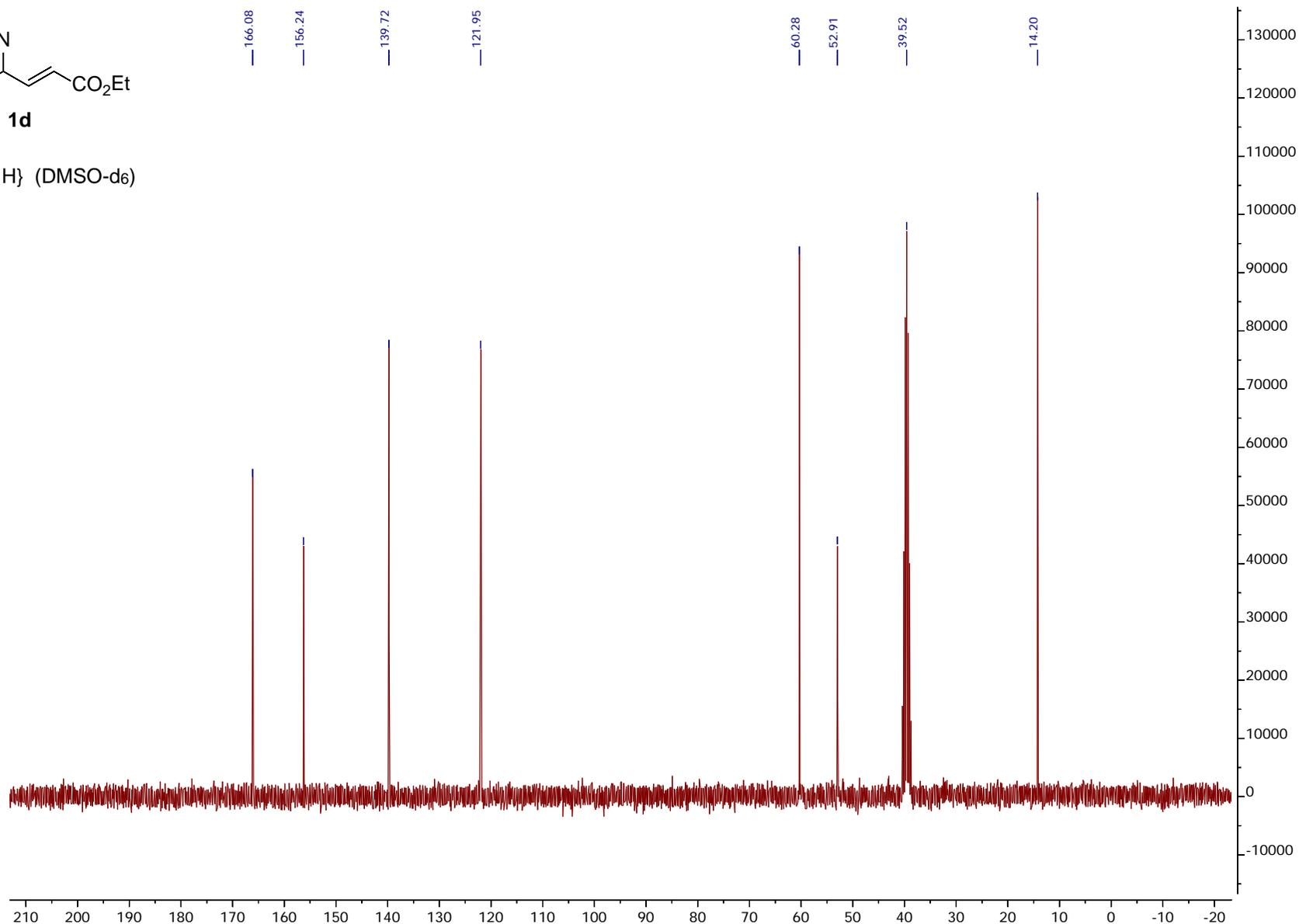
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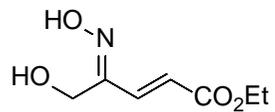
1d

$^{13}\text{C}\{^1\text{H}\}$ (DMSO- d_6)



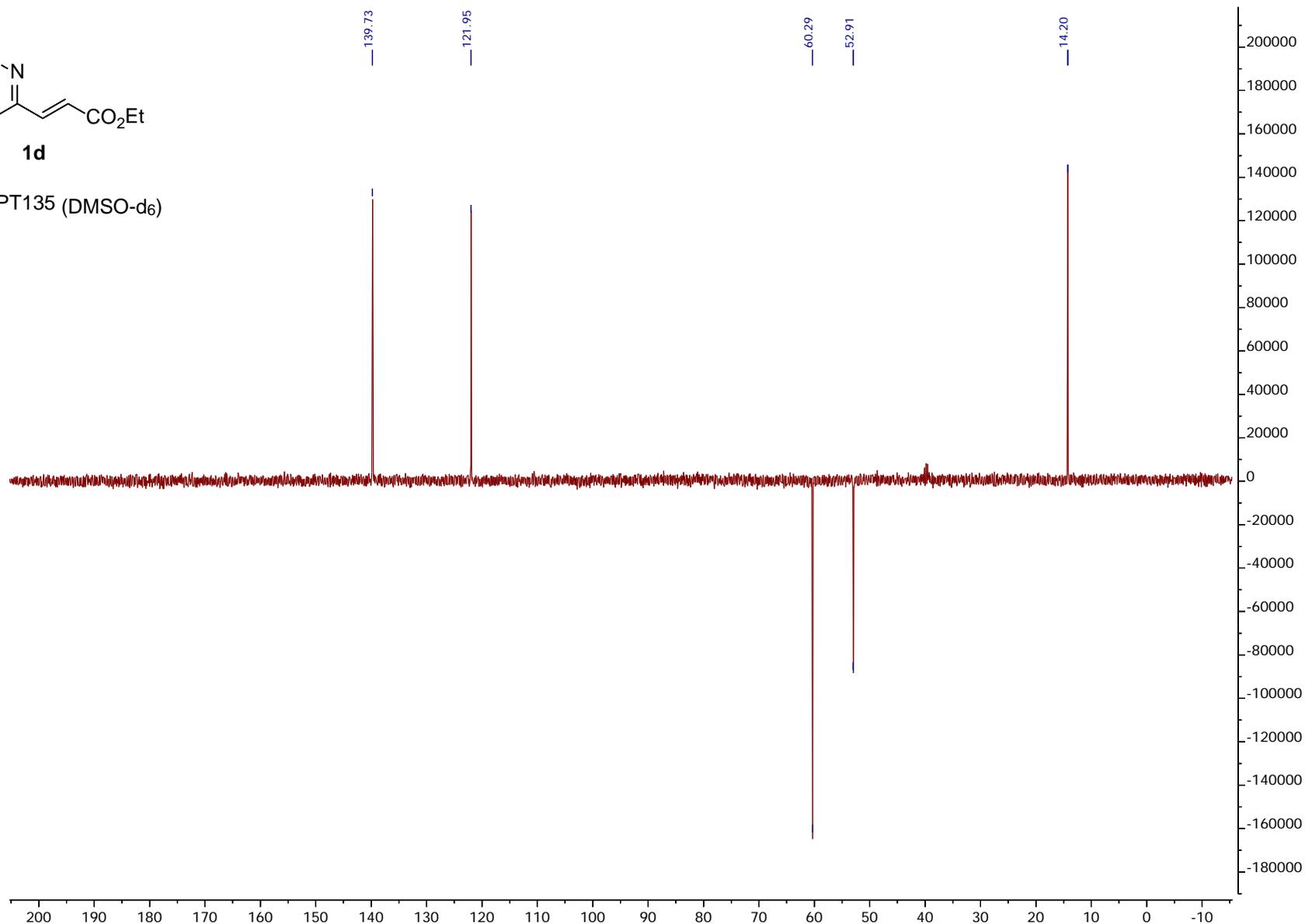
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S22



1d

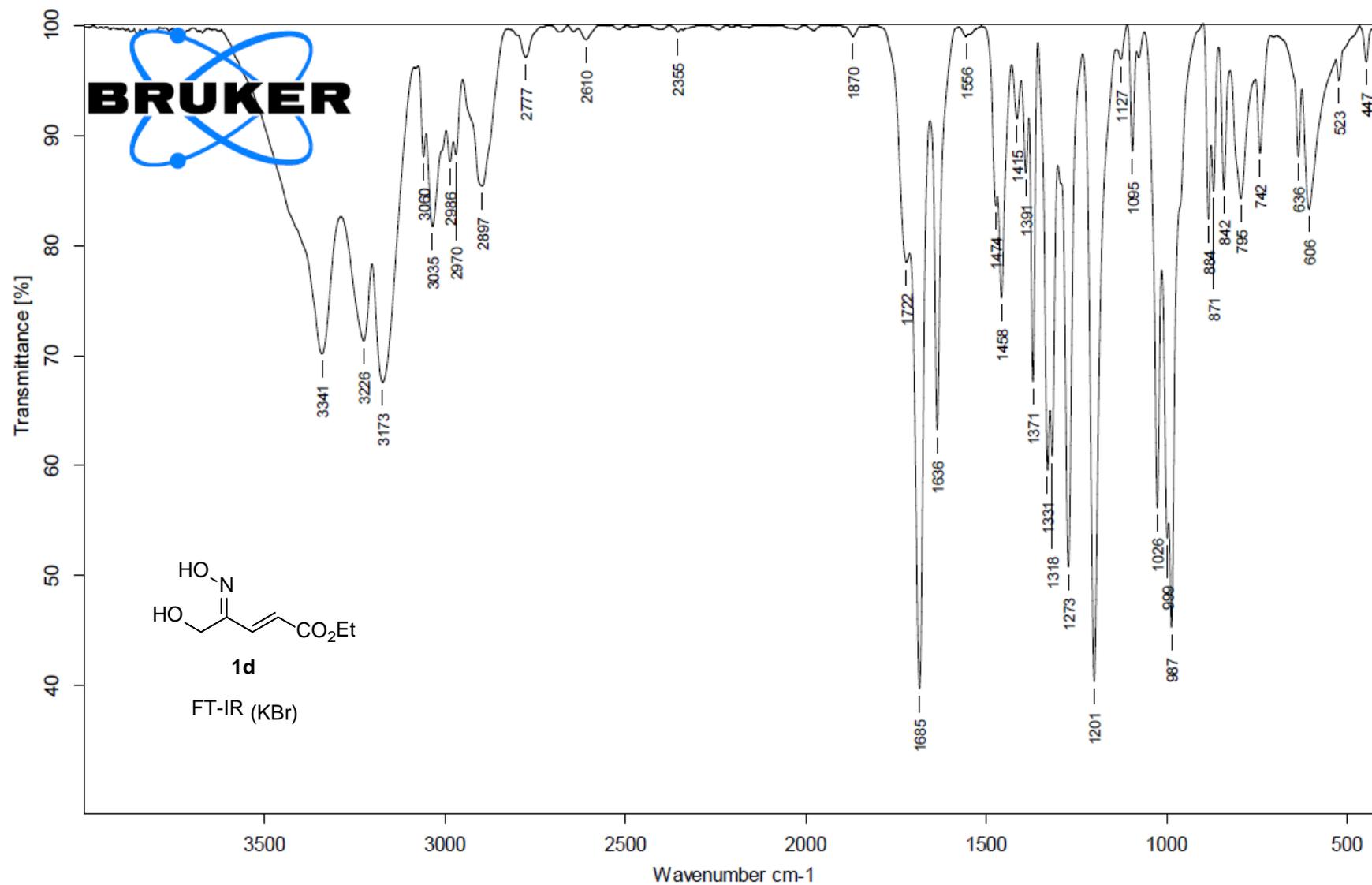
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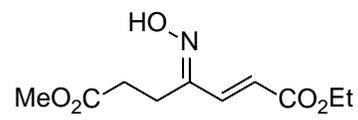


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S23

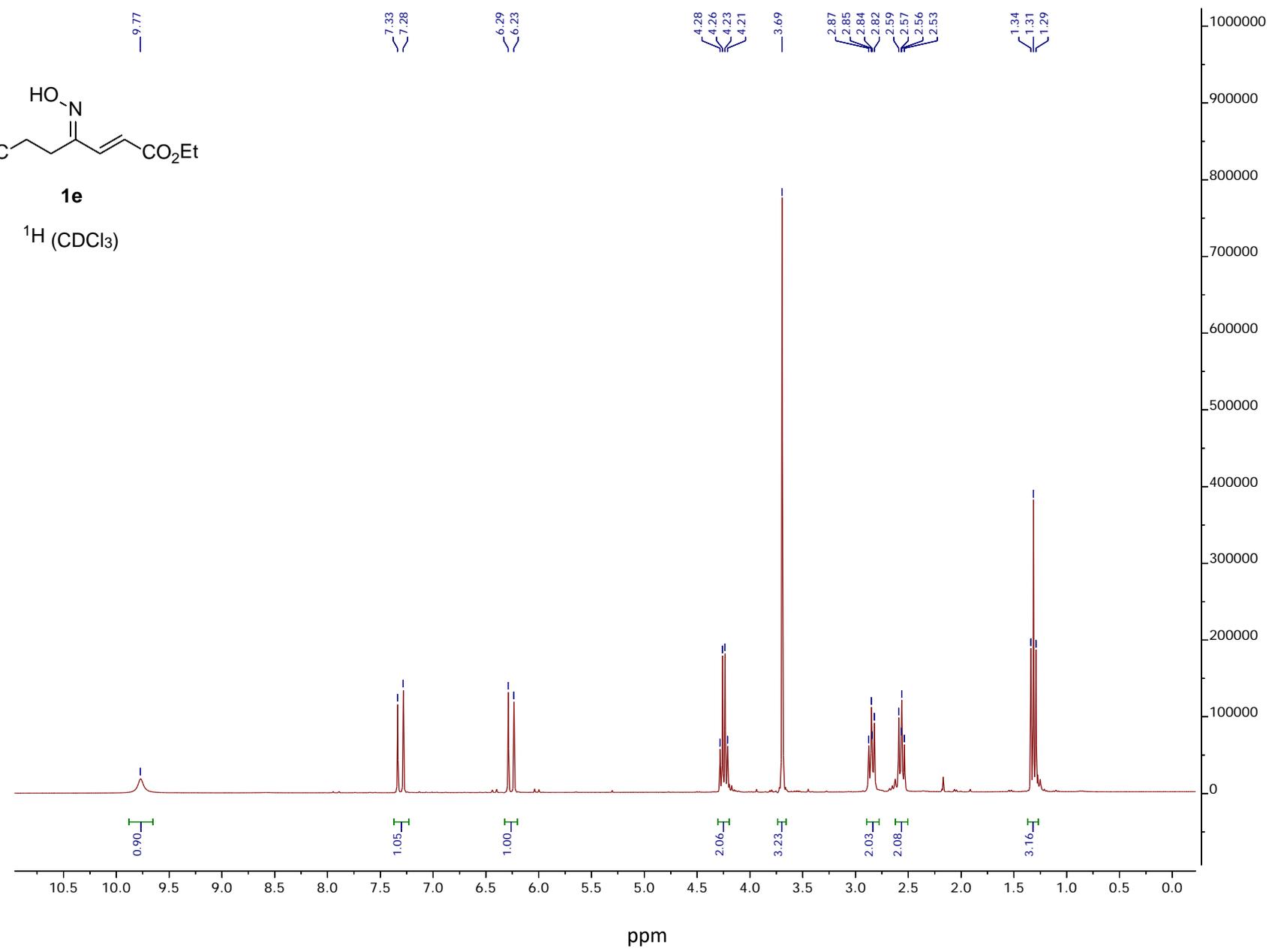
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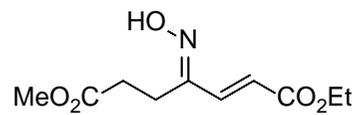




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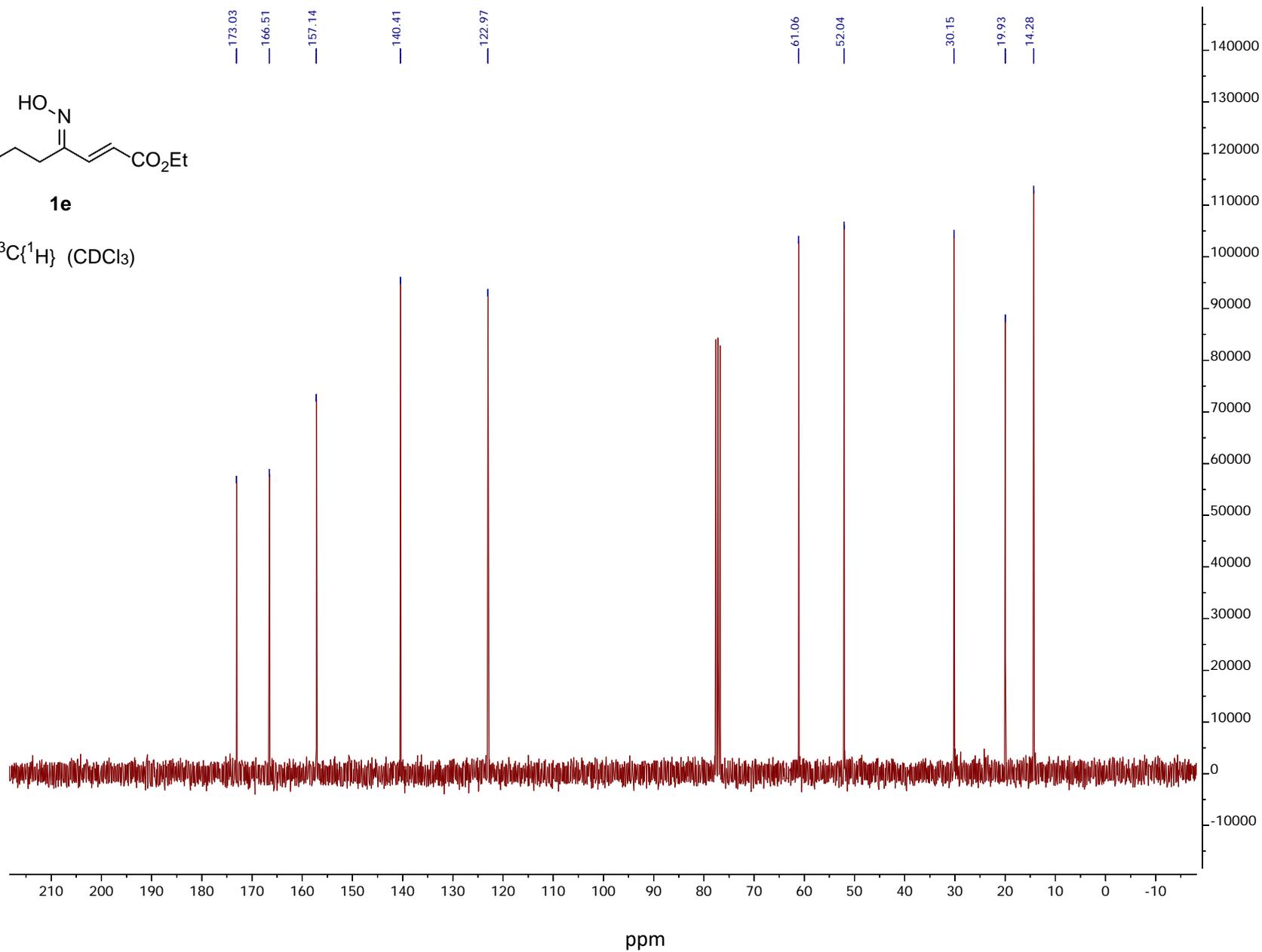
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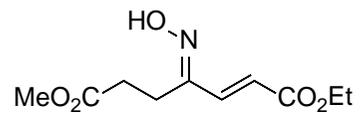




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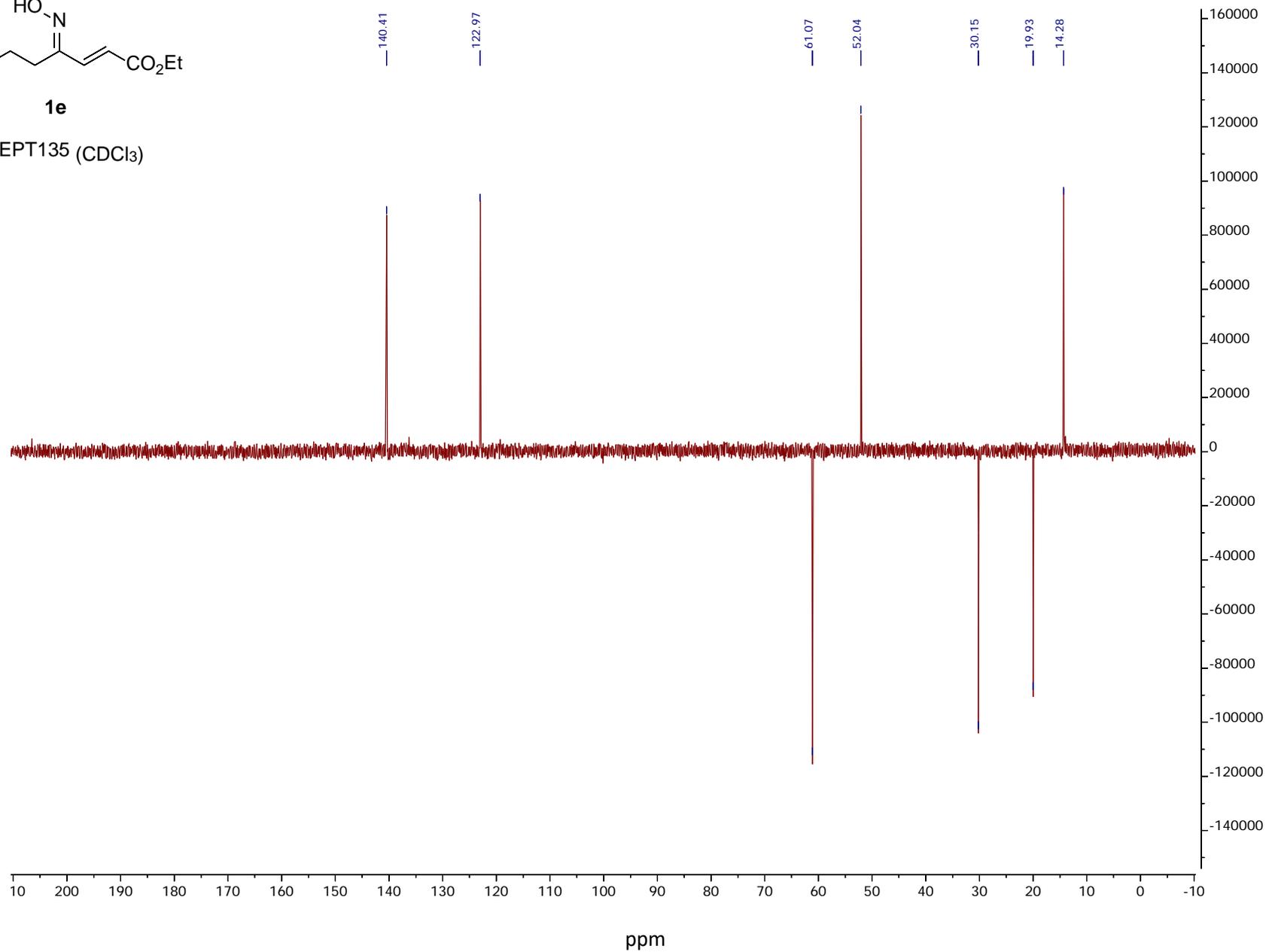
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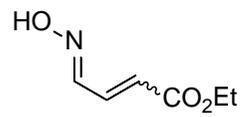




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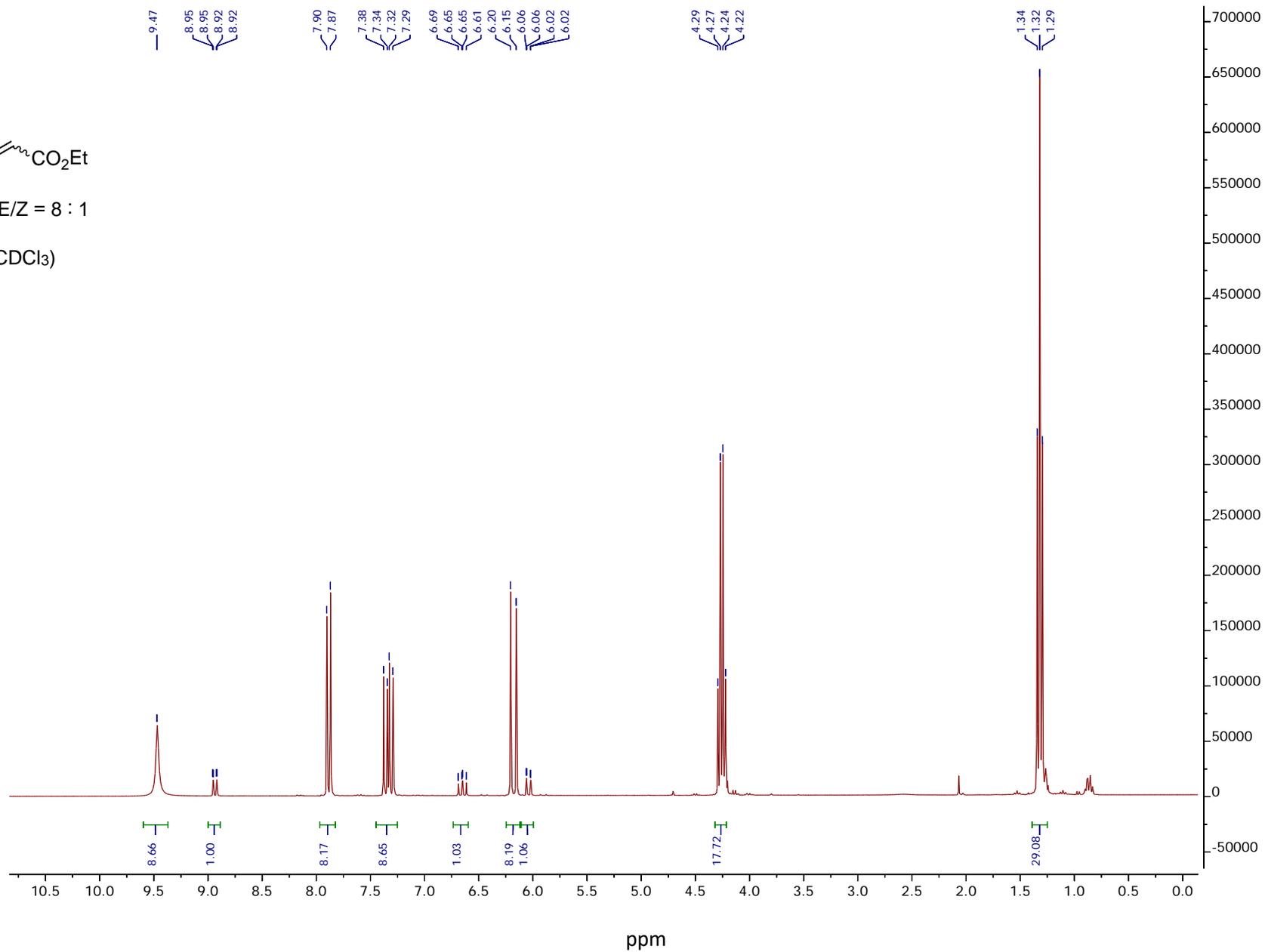
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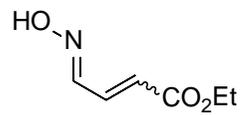




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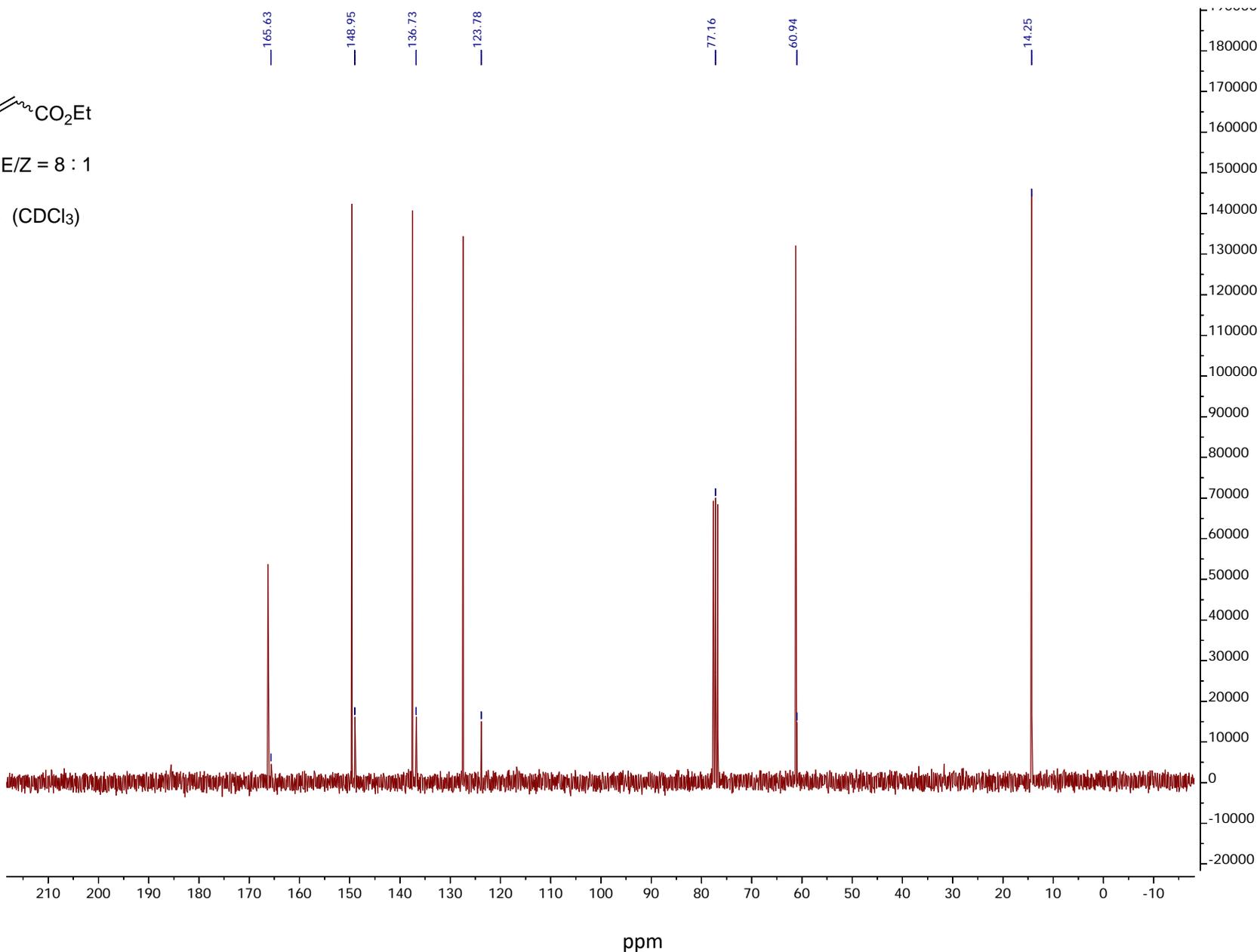
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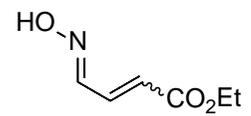




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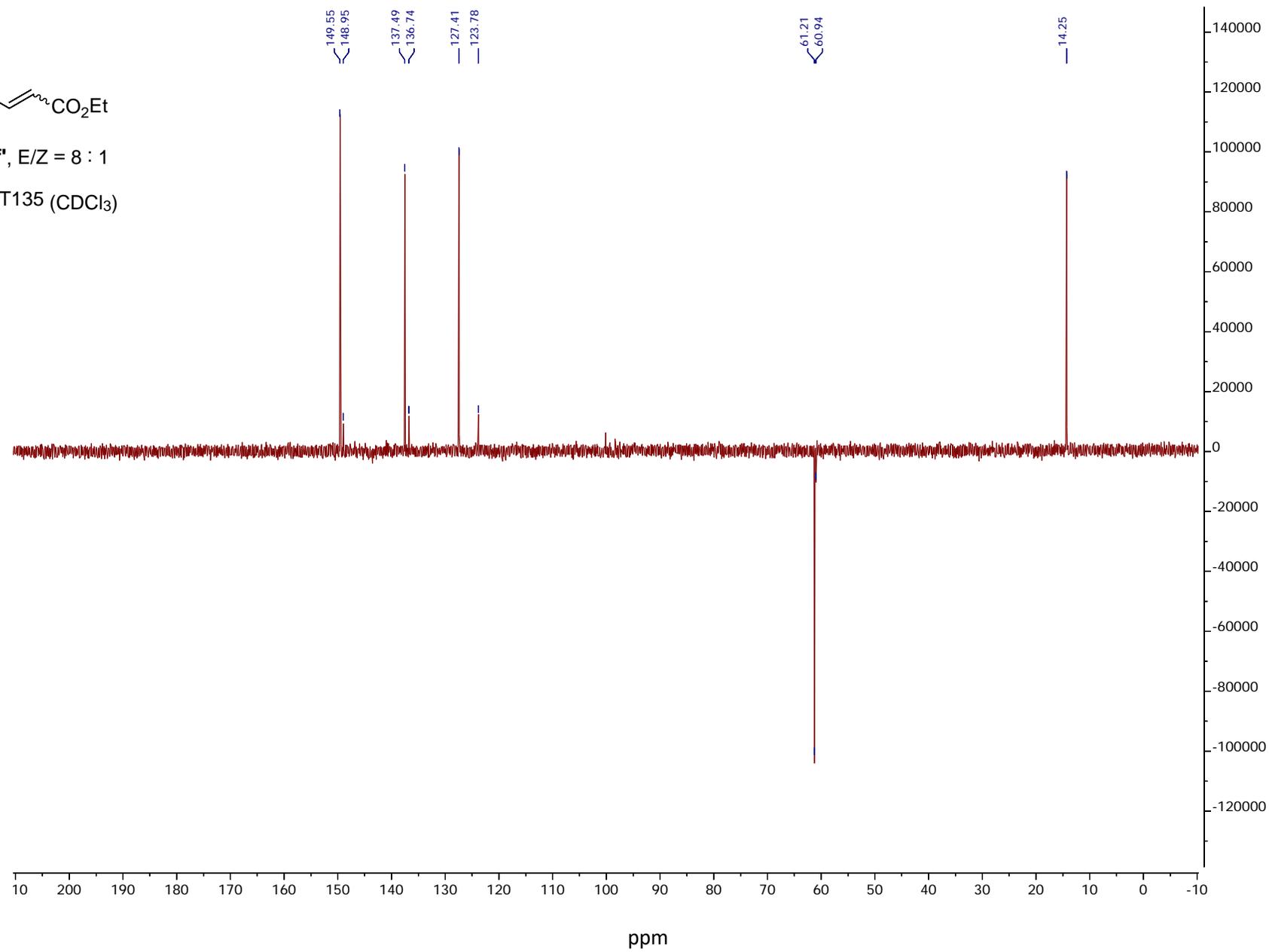
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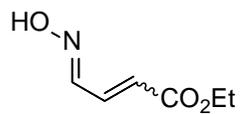




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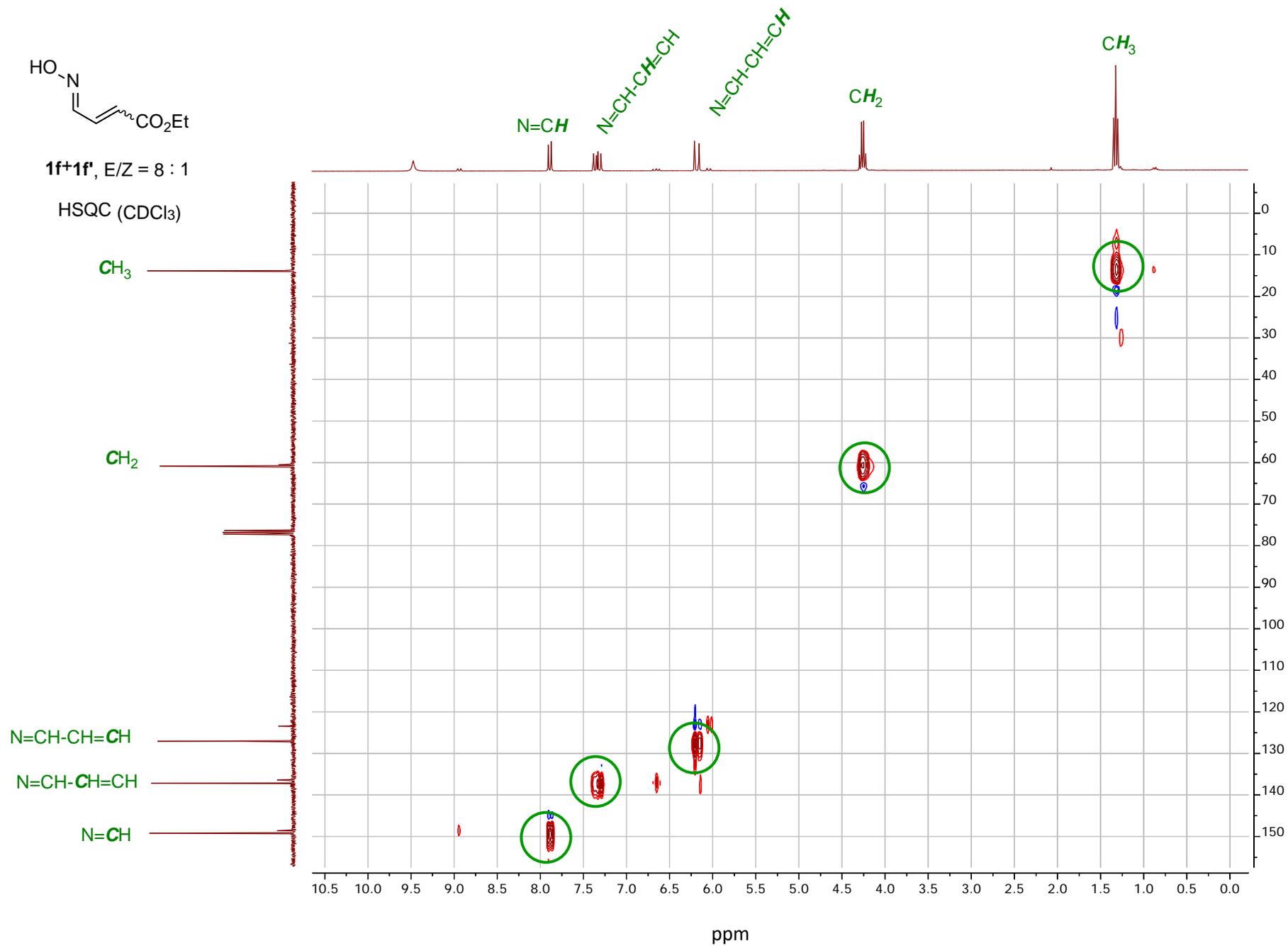
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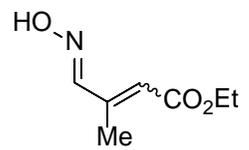




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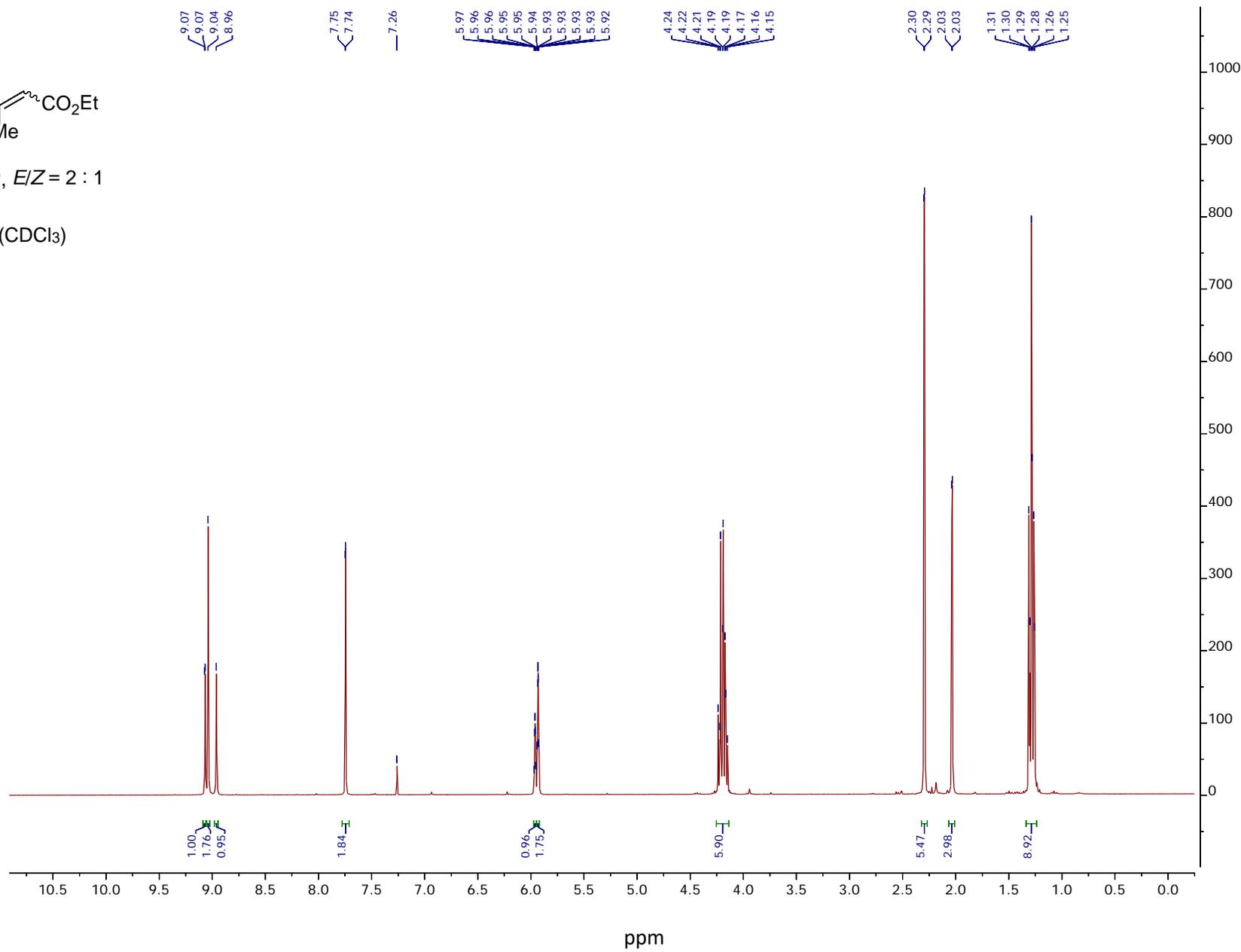
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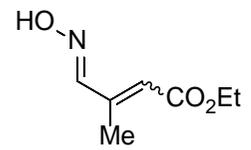




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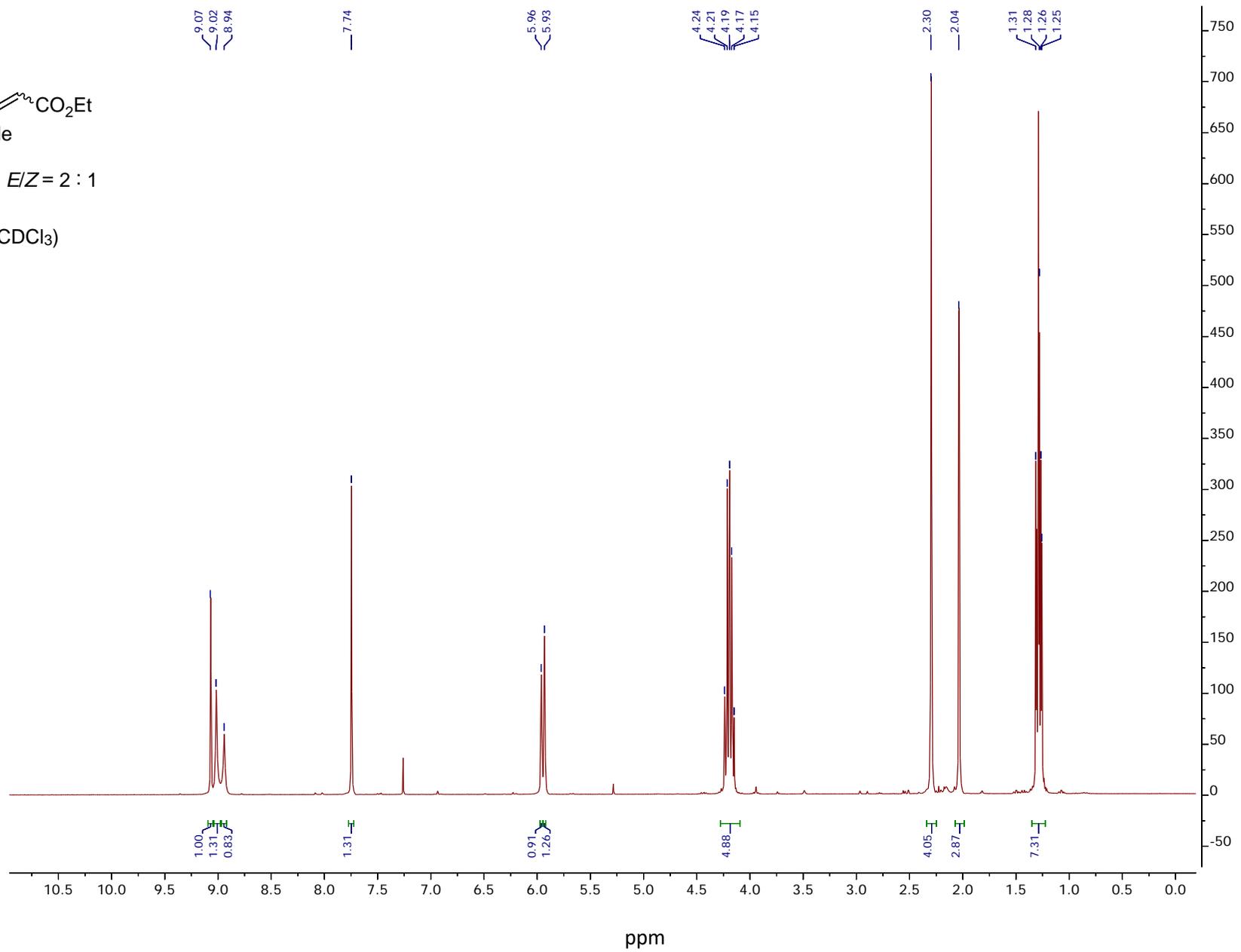
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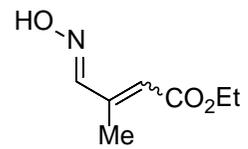




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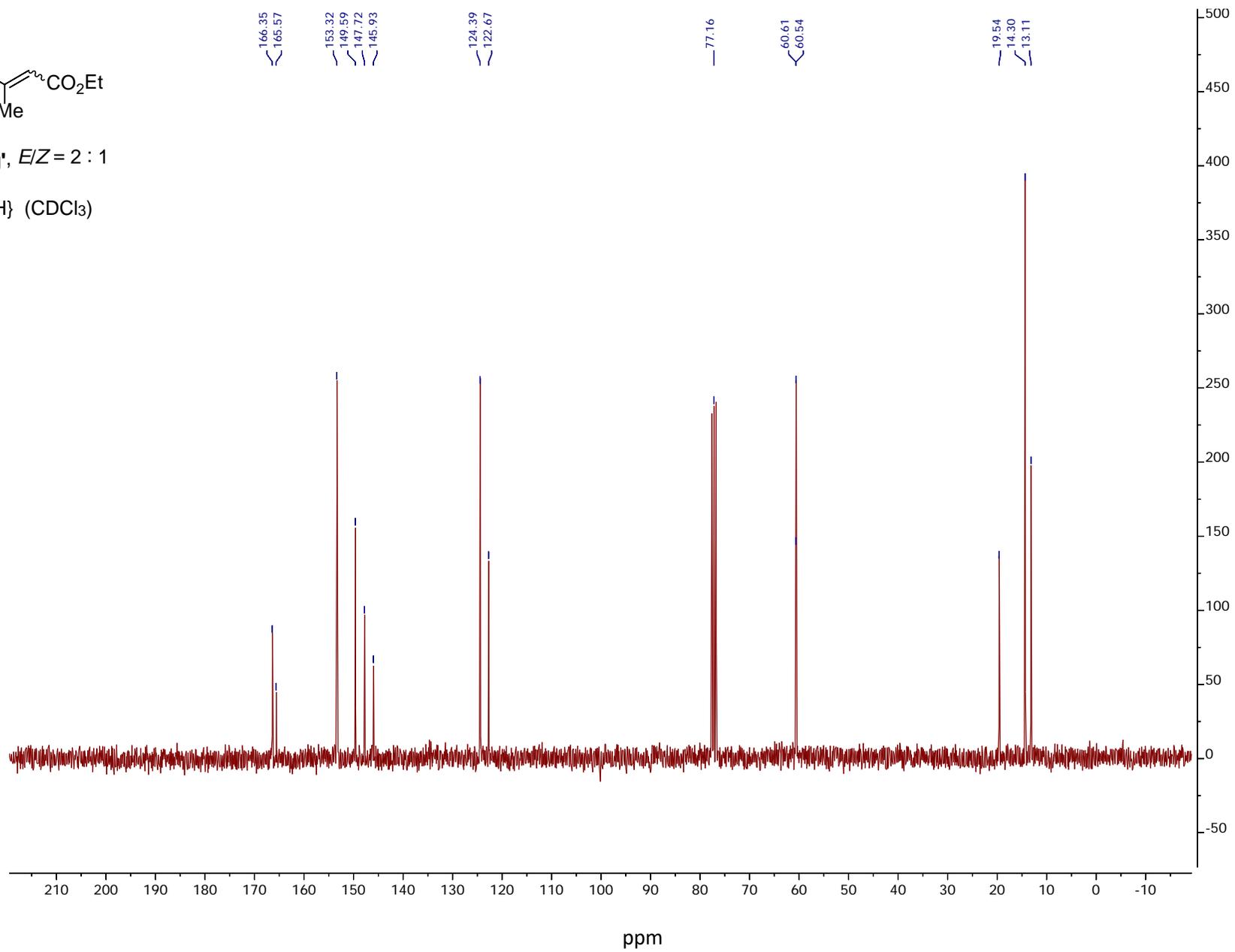
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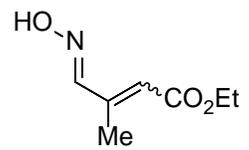




1g+1g', *EZ* = 2 : 1

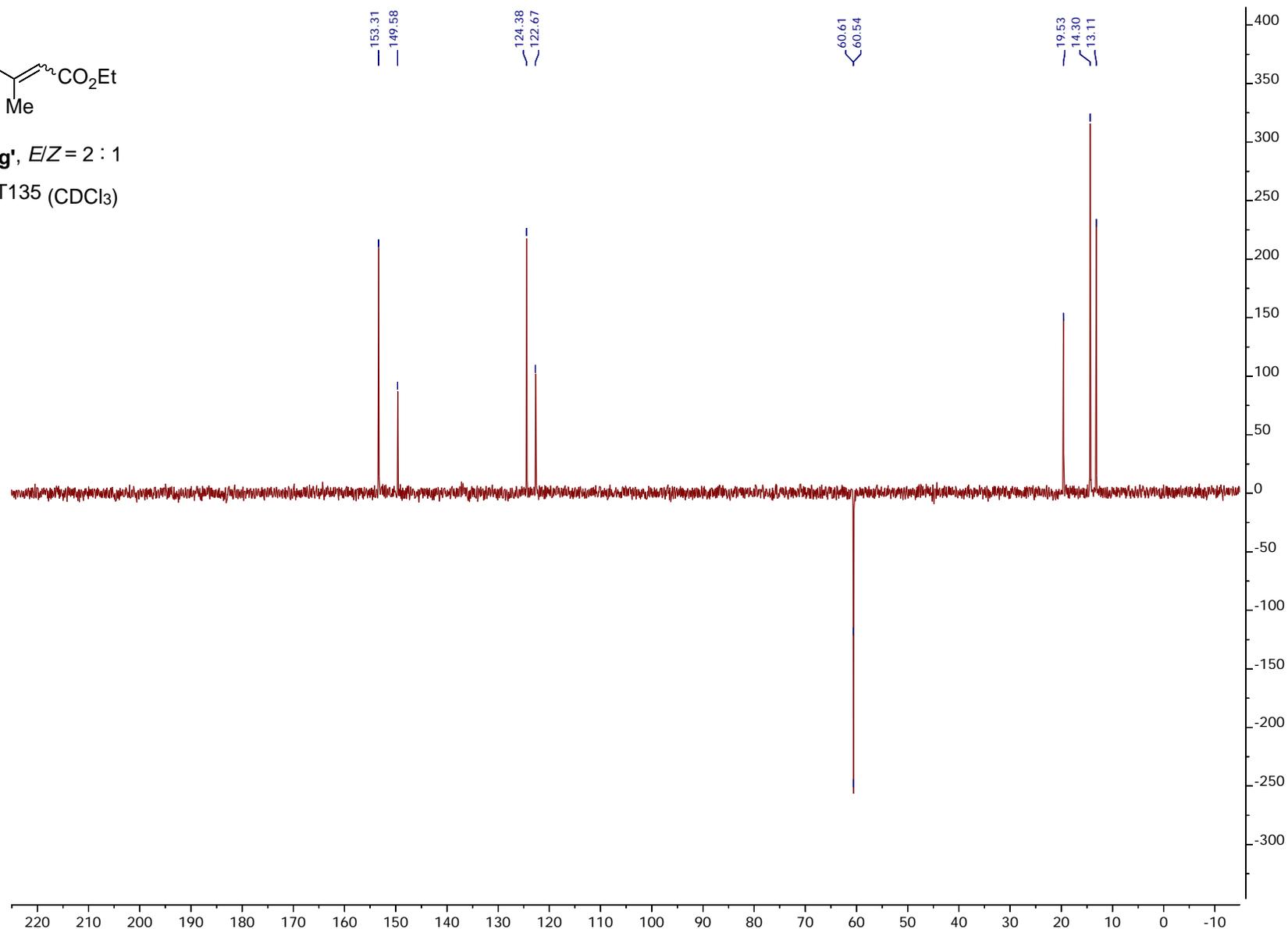
¹³C{¹H} (CDCl₃)





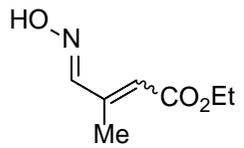
1g+1g', *E/Z* = 2 : 1

DEPT135 (CDCl₃)



ppm

S35



1g+1g', E/Z = 2 : 1

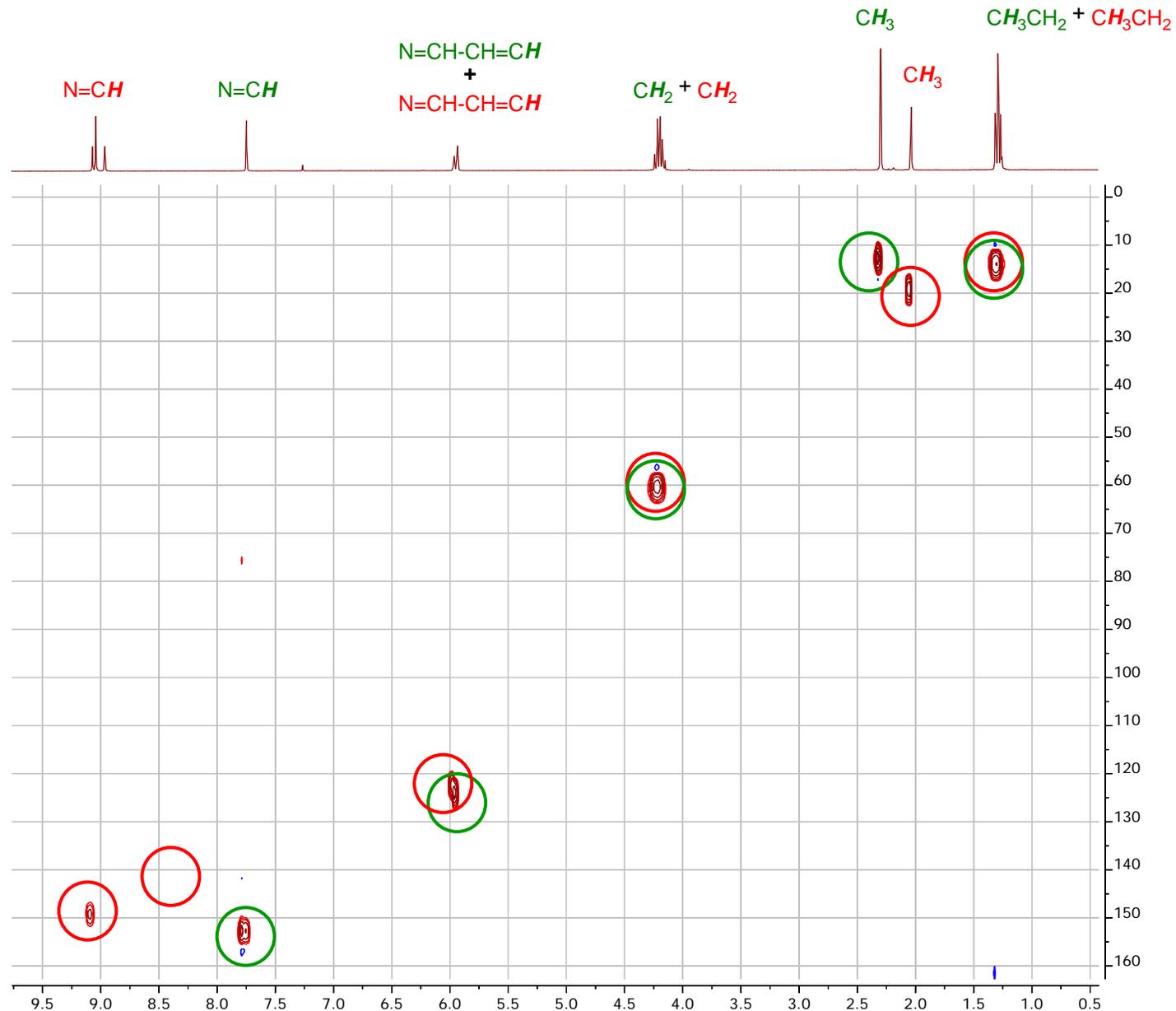
HSQC (CDCl₃)

CH₃CH₂ + CH₃CH₂
 CH₃

CH₂ + CH₂

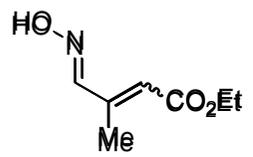
N=CH-CH=CH
 N=CH-CH=CH

N=CH
 N=CH



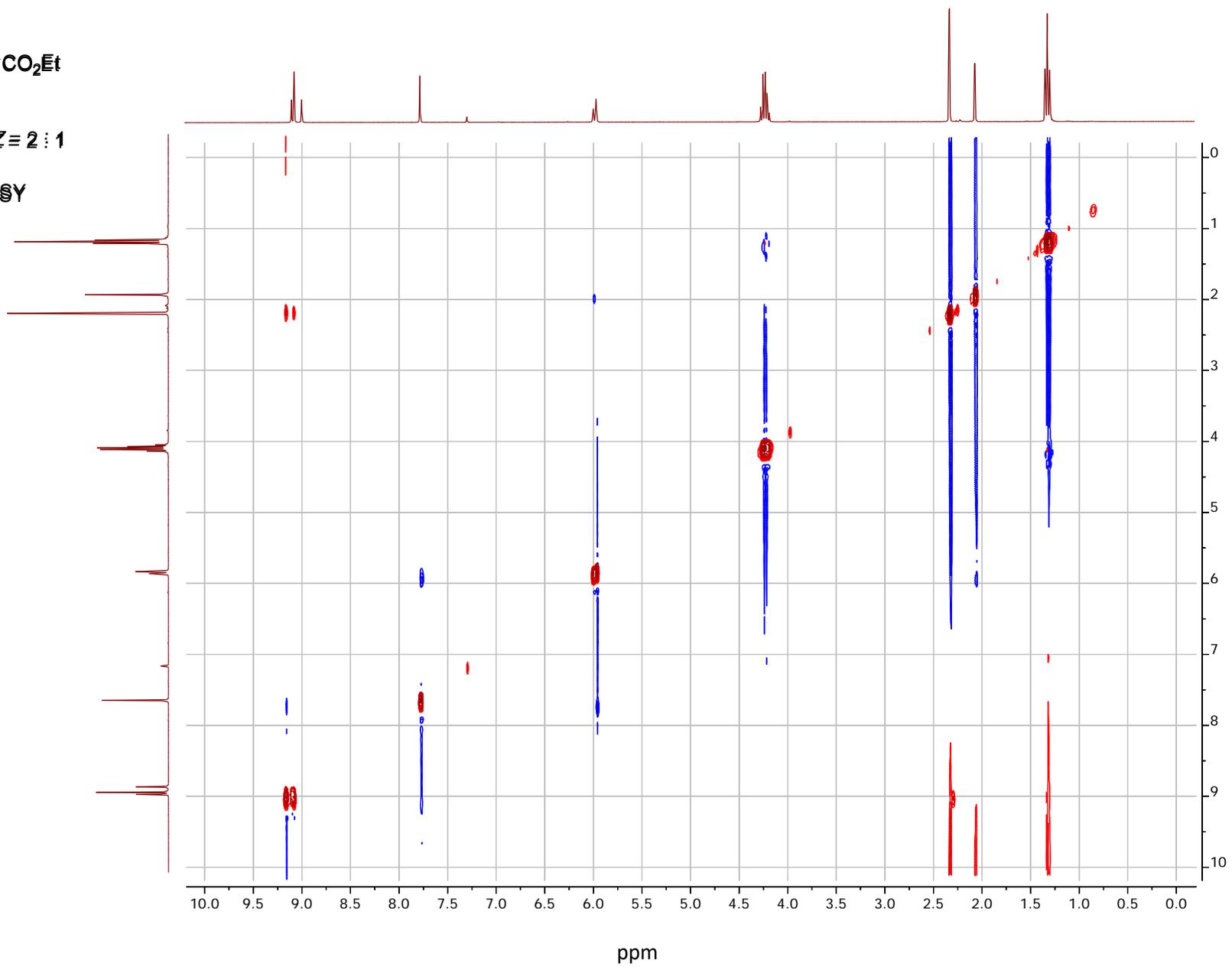
ppm

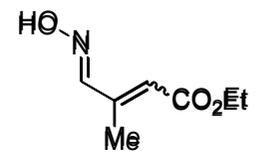
S36



1g±1g', *E/Z* = 2 : 1

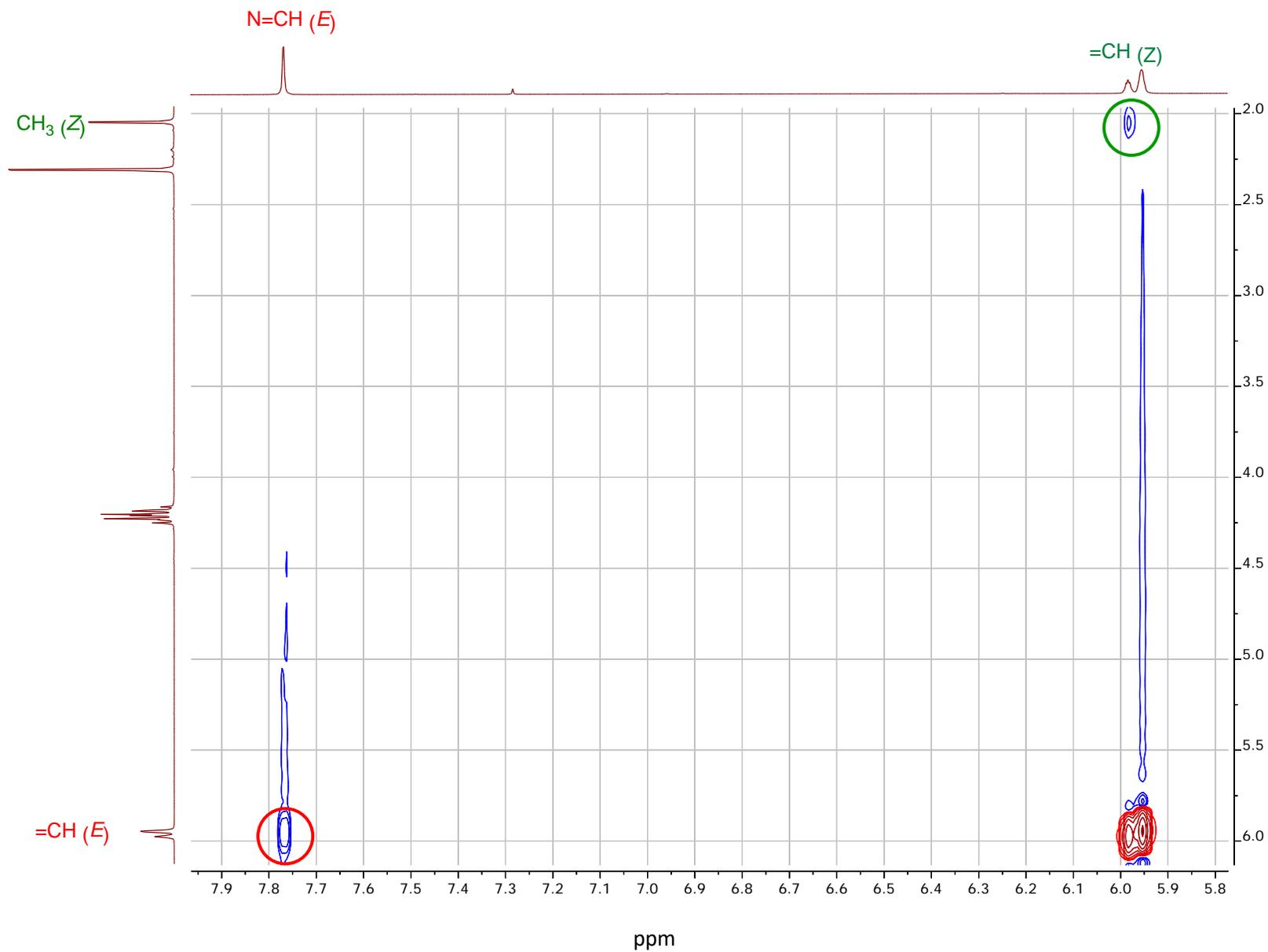
2D NOESY

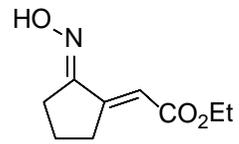




1g#1g', *E/Z* = 2 : 1

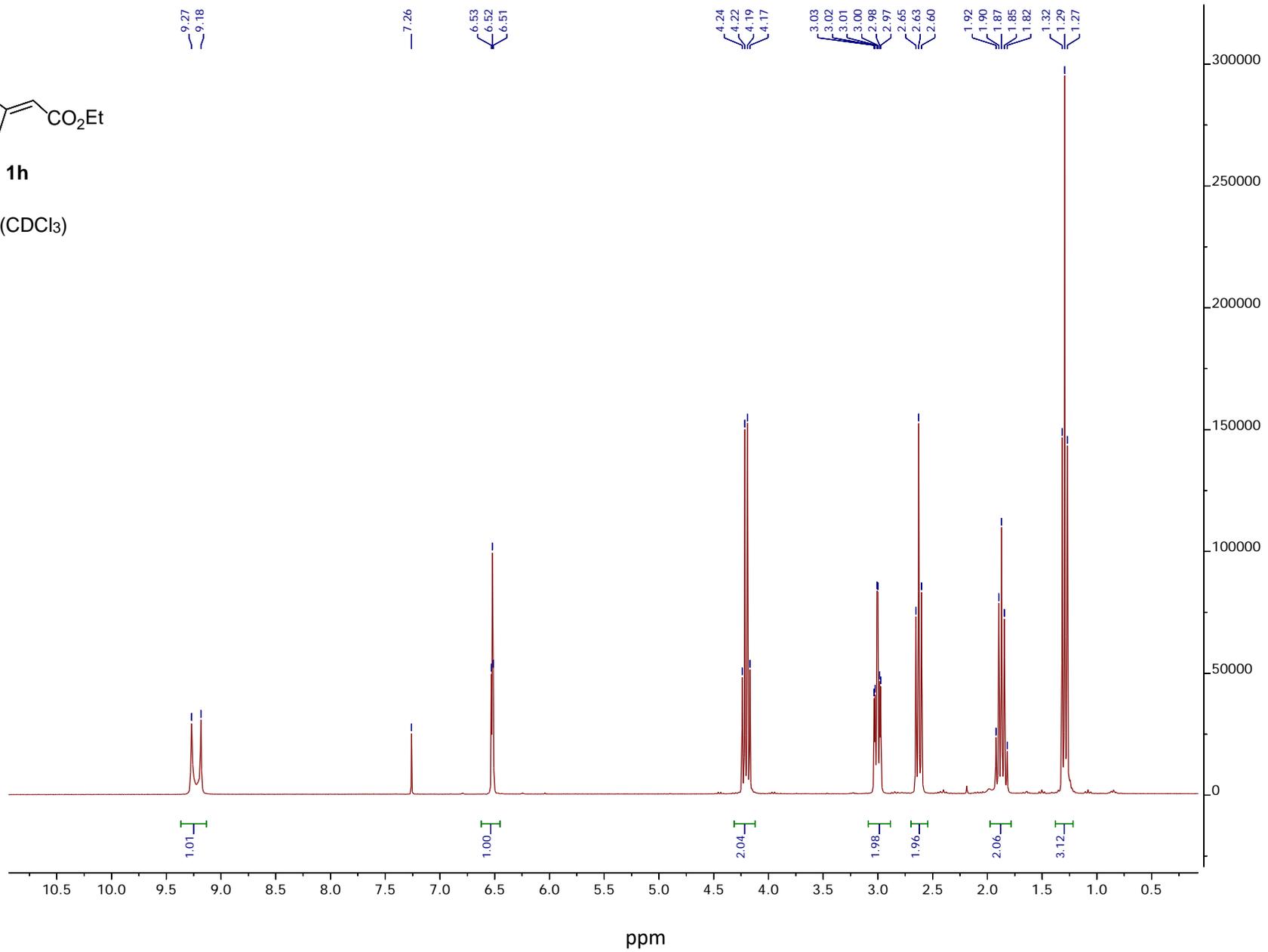
2D NOESY

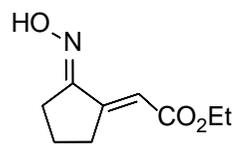




1h

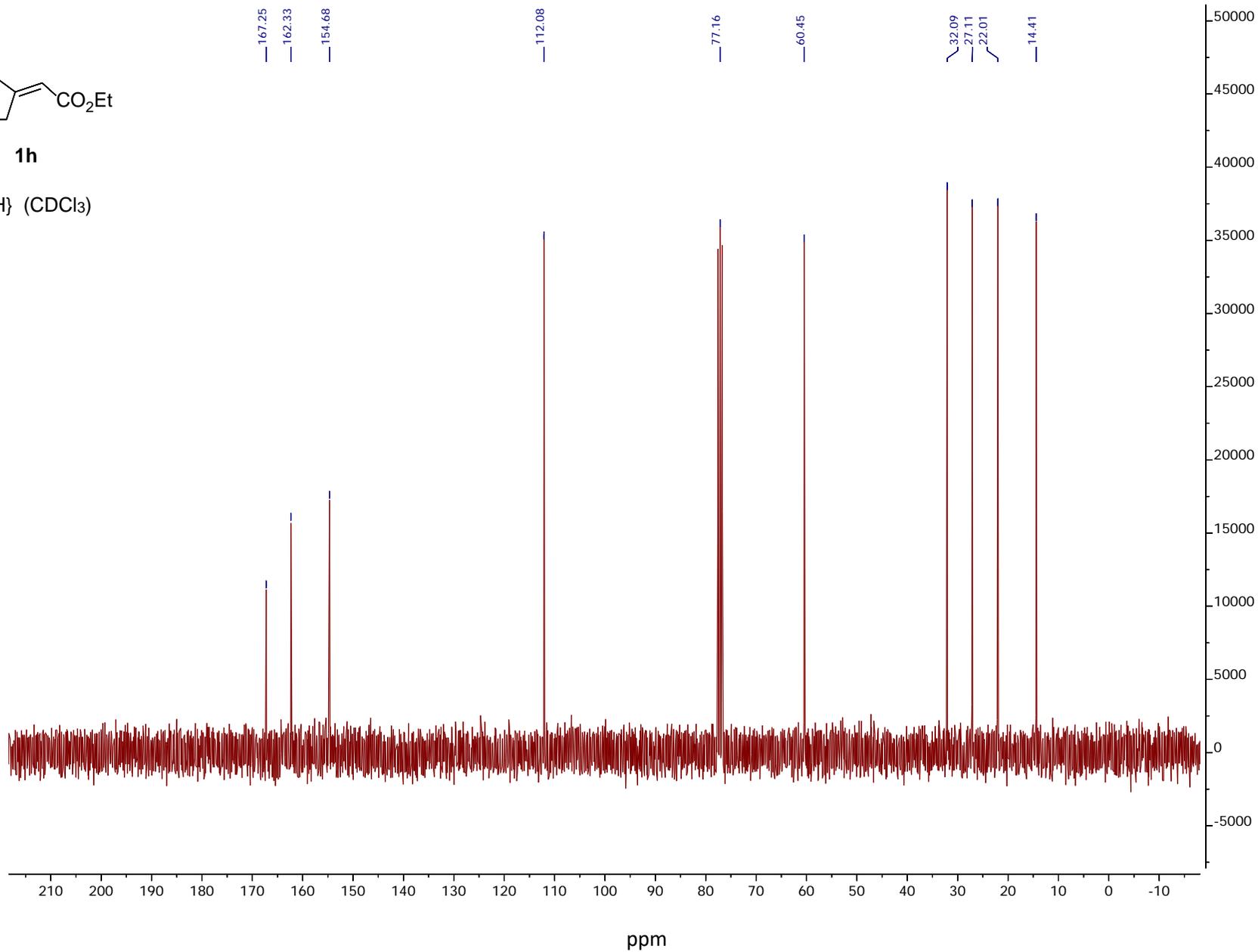
¹H (CDCl₃)

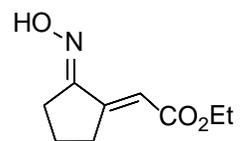




1h

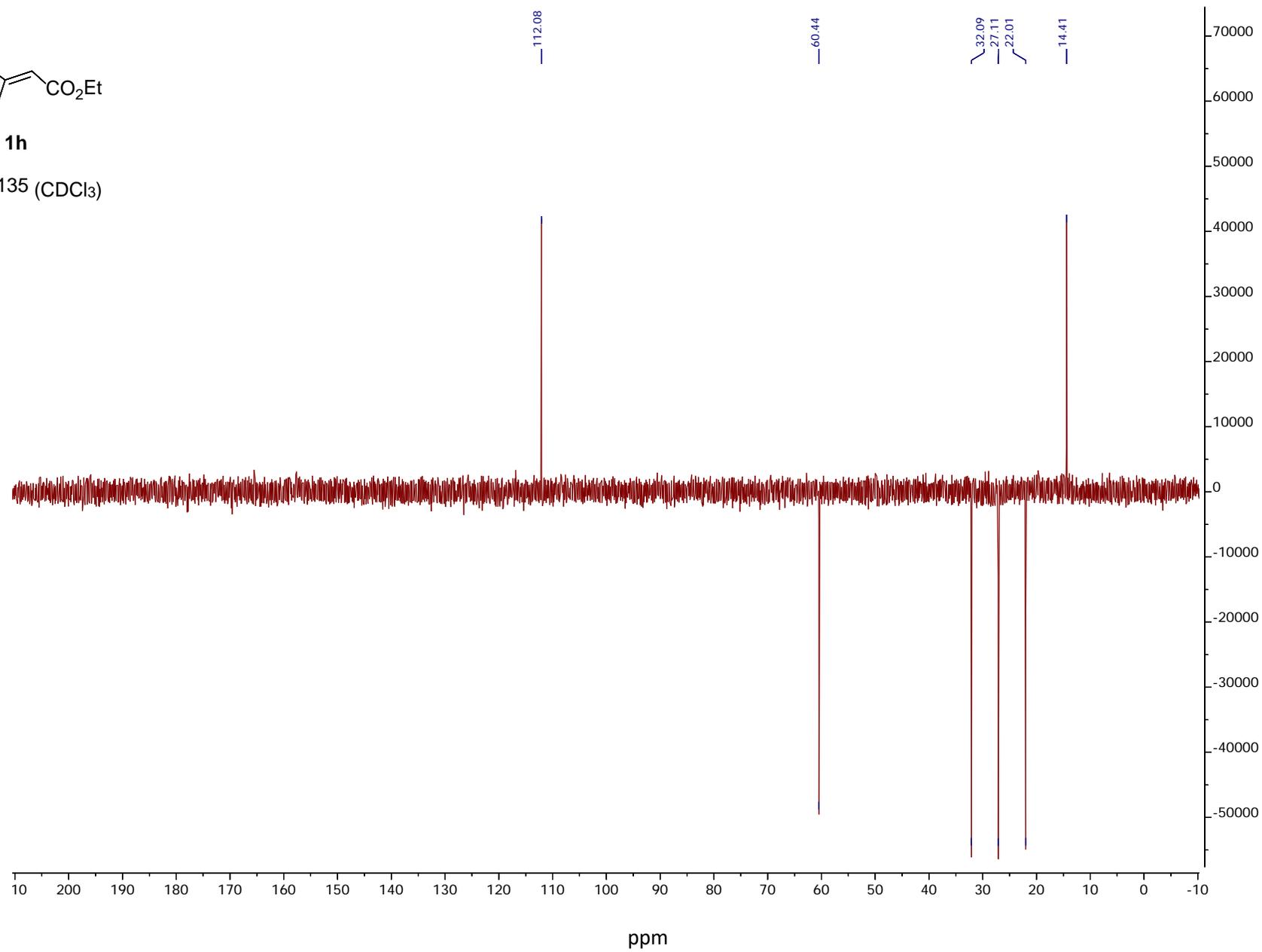
$^{13}\text{C}\{^1\text{H}\}$ (CDCl_3)



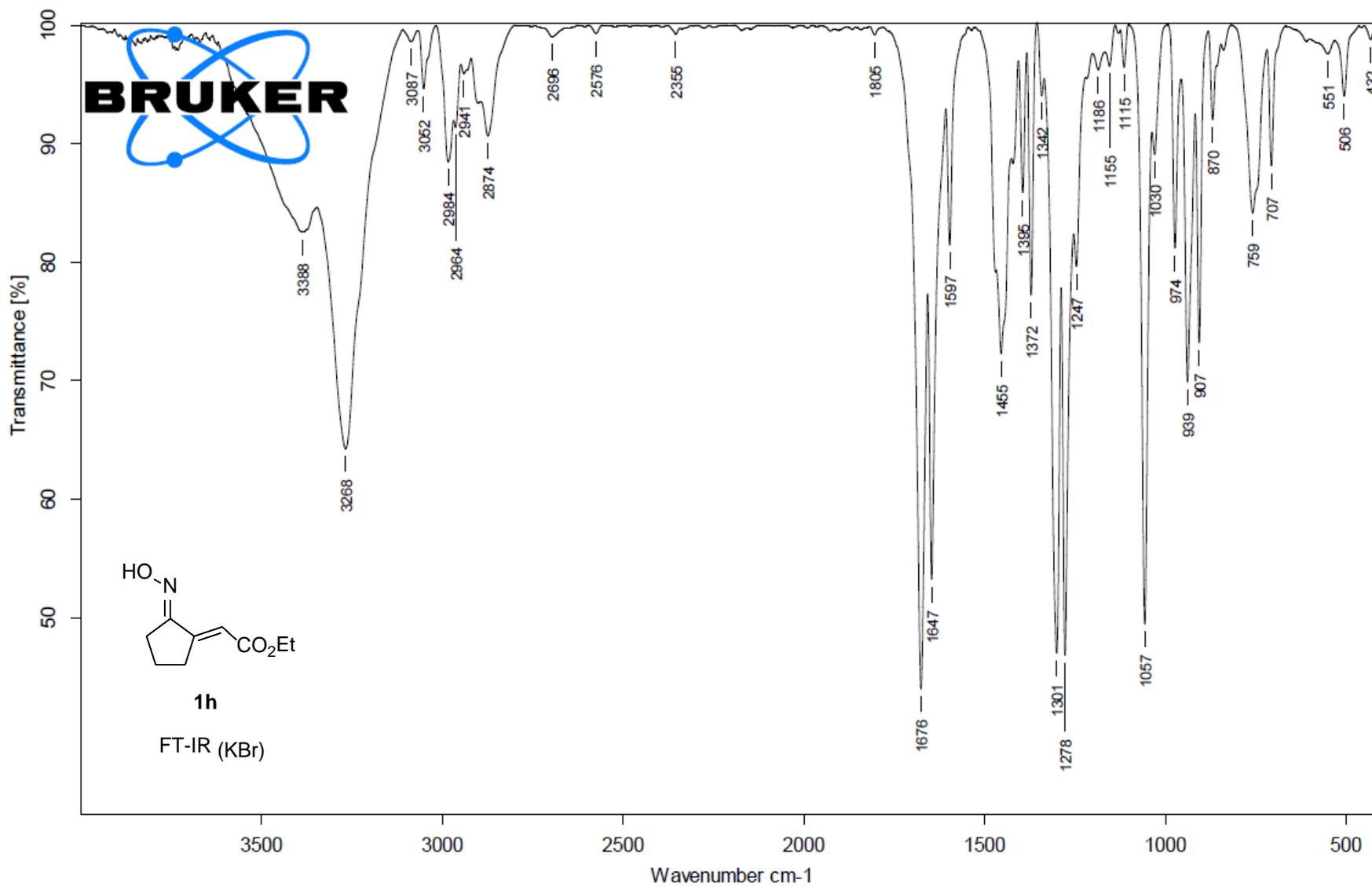


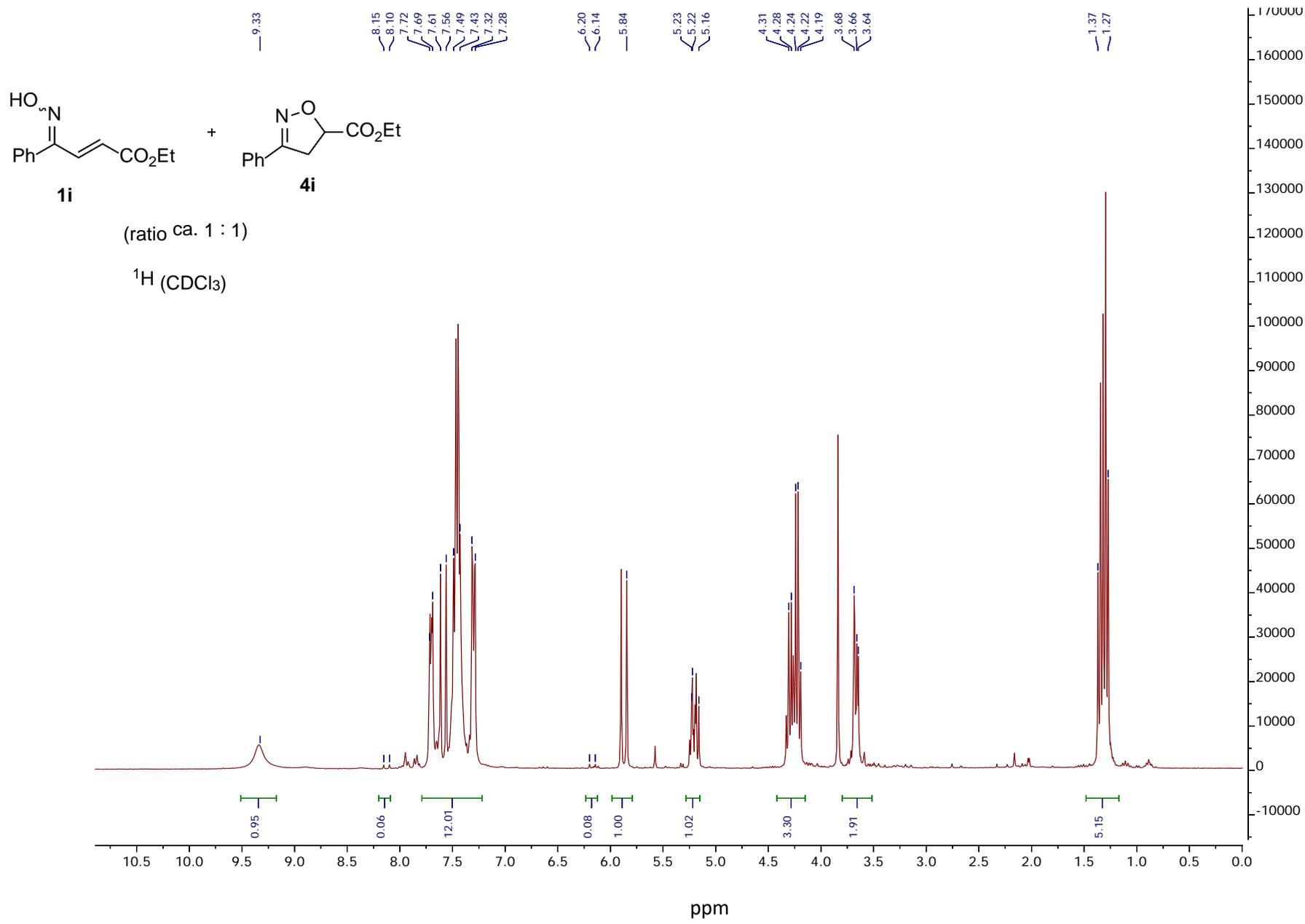
1h

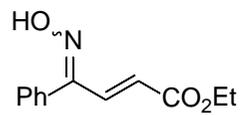
DEPT135 (CDCl₃)



FT-IR

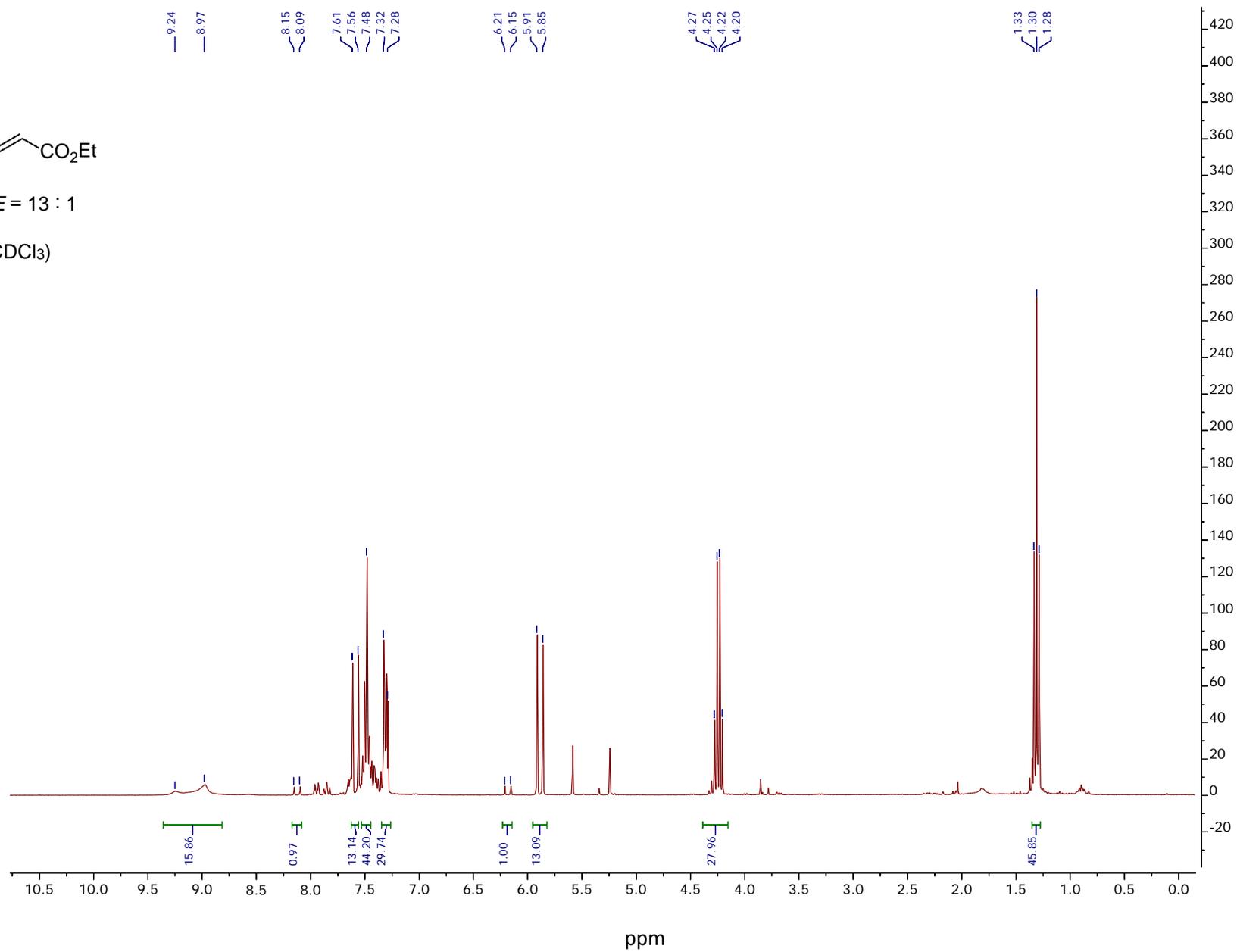


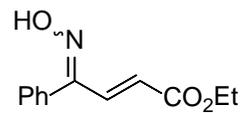




1i, *Z/E* = 13 : 1

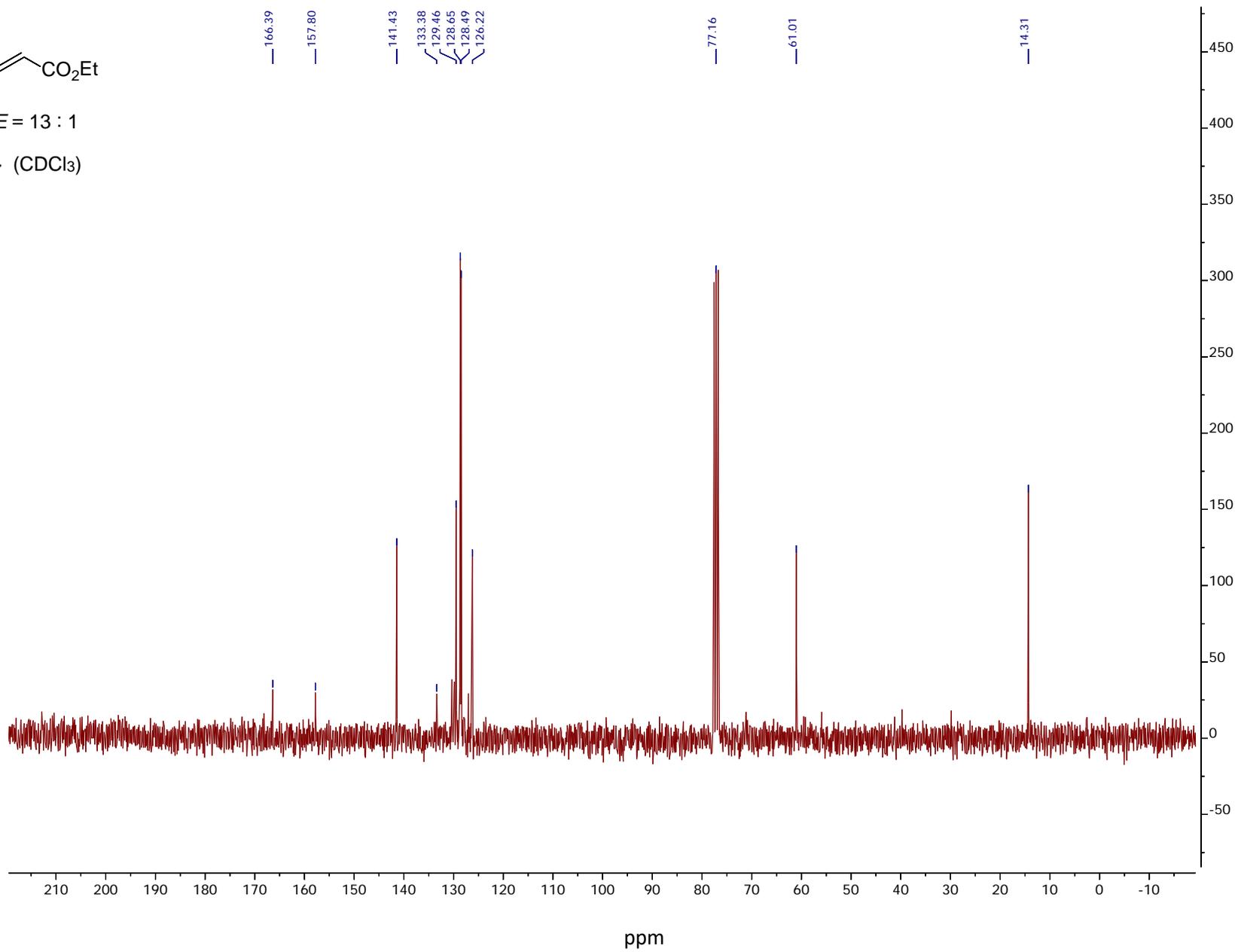
^1H (CDCl_3)

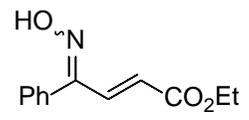




1i, *Z/E* = 13 : 1

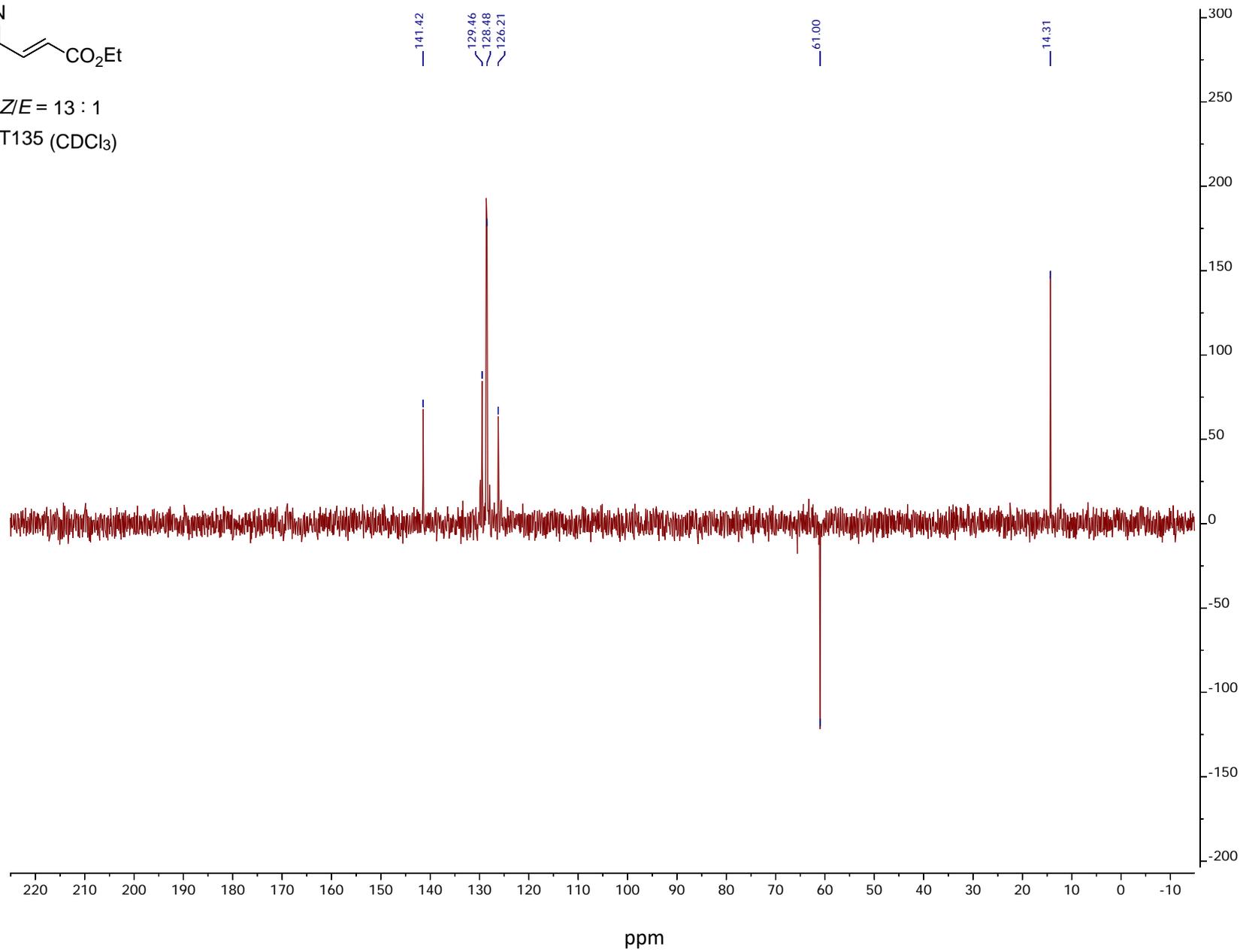
$^{13}\text{C}\{^1\text{H}\}$ (CDCl_3)

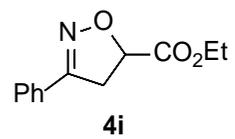




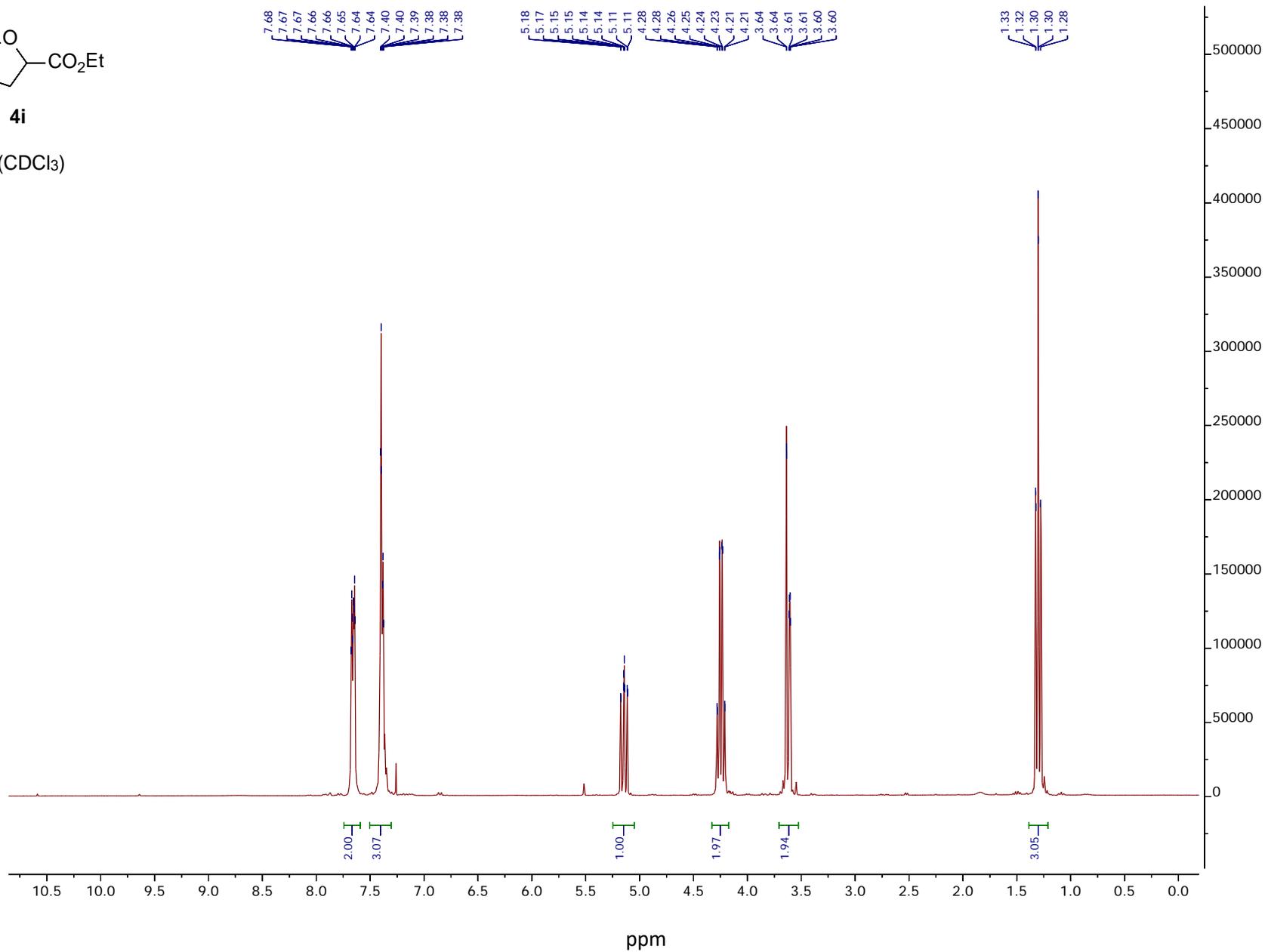
1i, Z/E = 13 : 1

DEPT135 (CDCl₃)

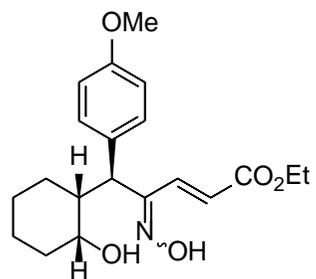




^1H (CDCl₃)

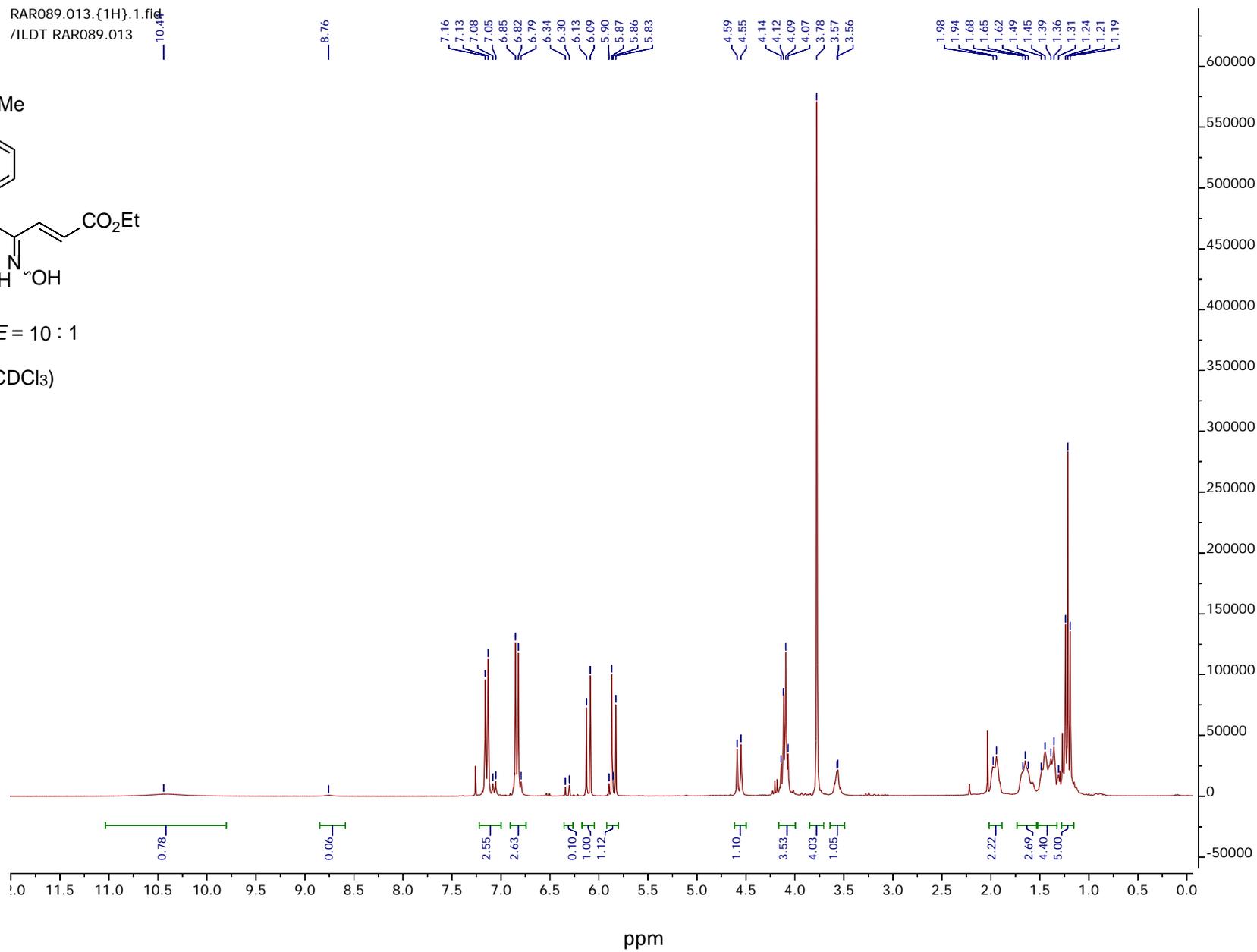


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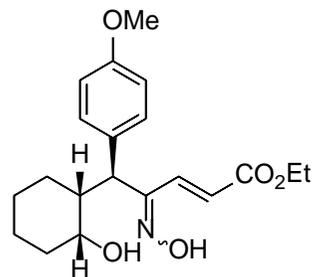


1j, Z/E = 10 : 1

¹H (CDCl₃)

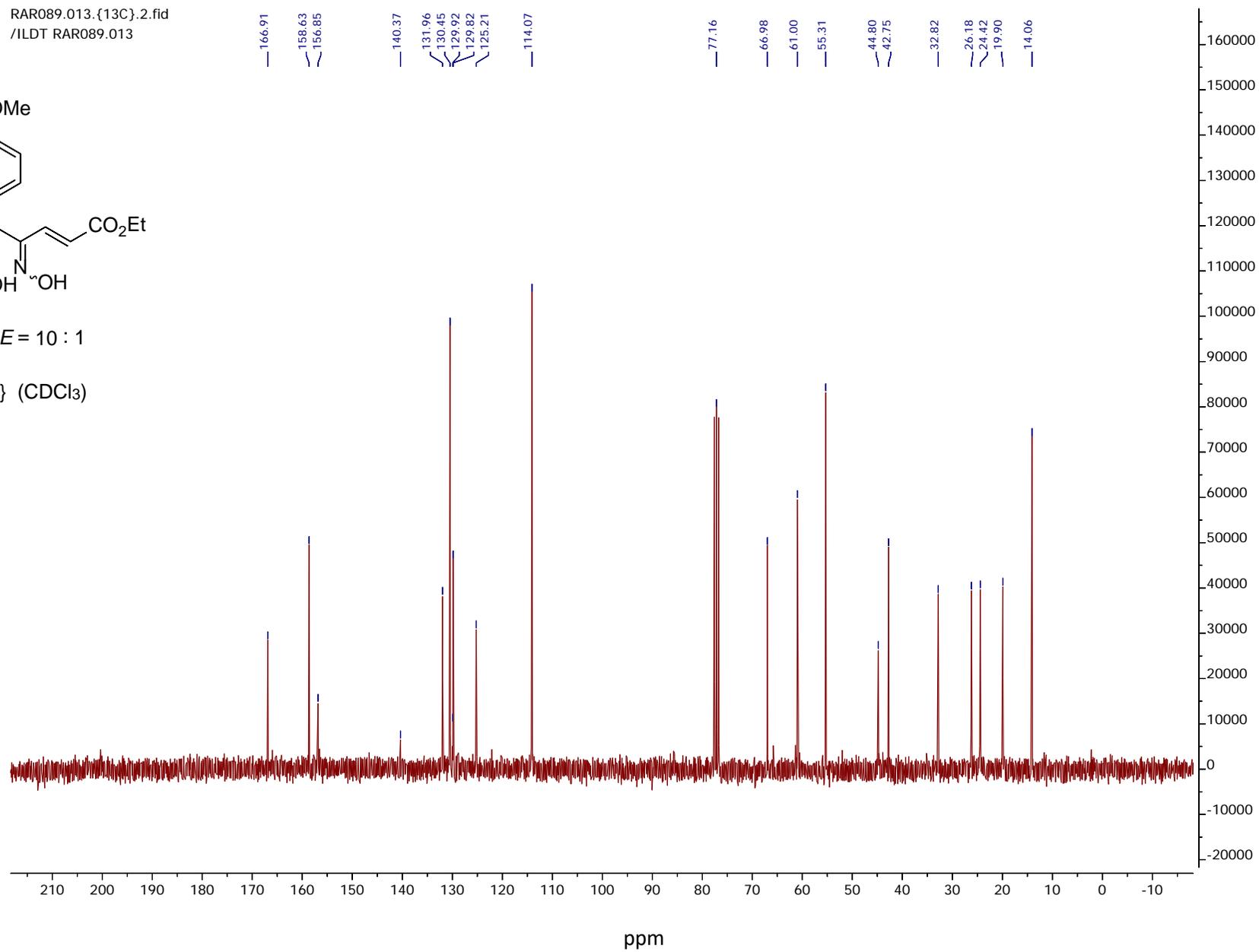


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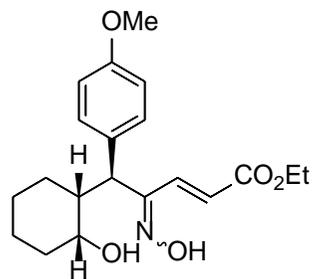


1j, Z/E = 10 : 1

¹³C{¹H} (CDCl₃)

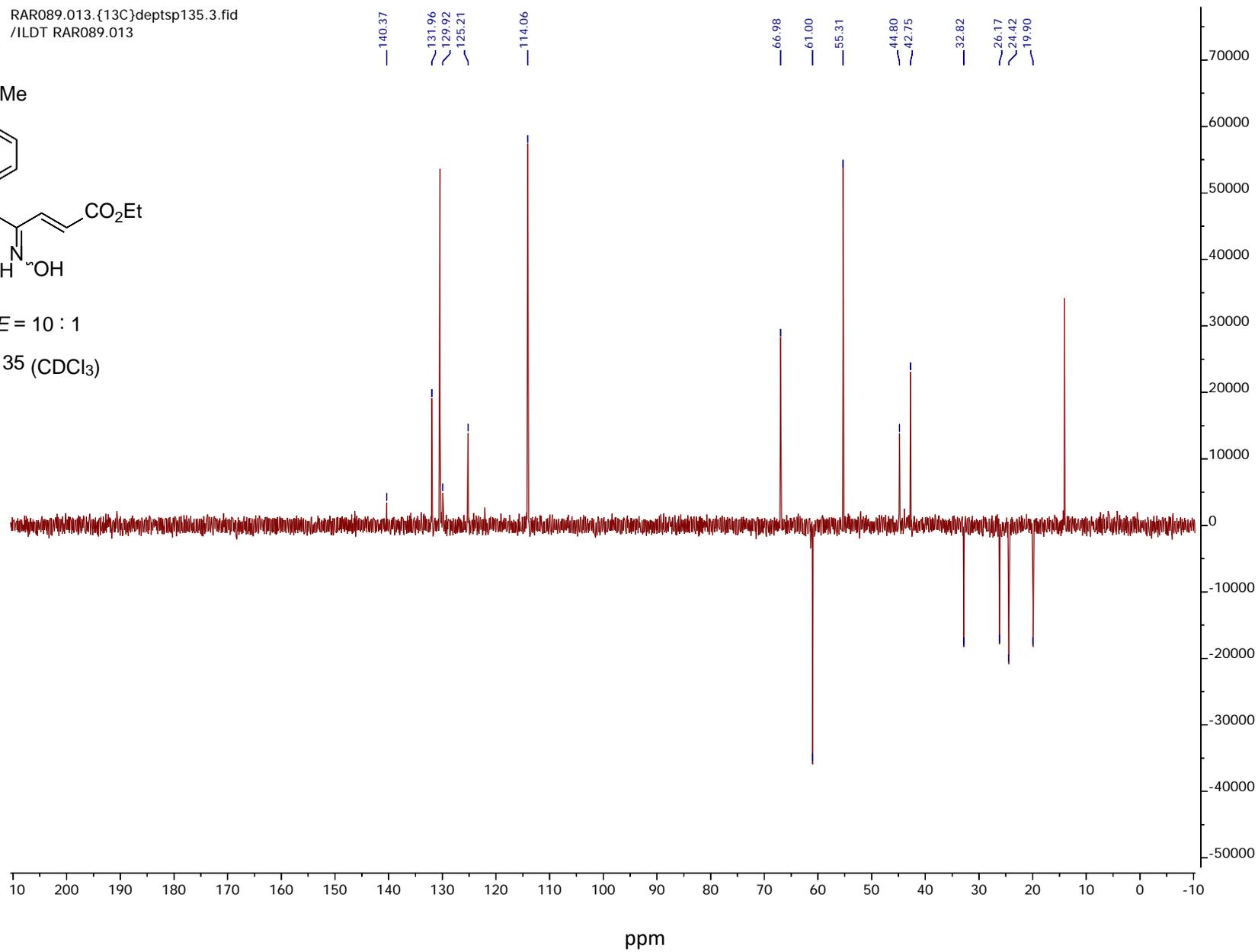


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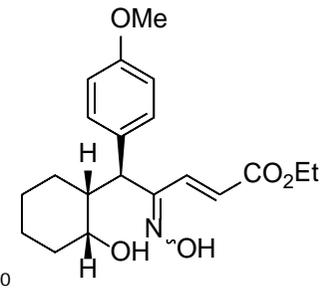
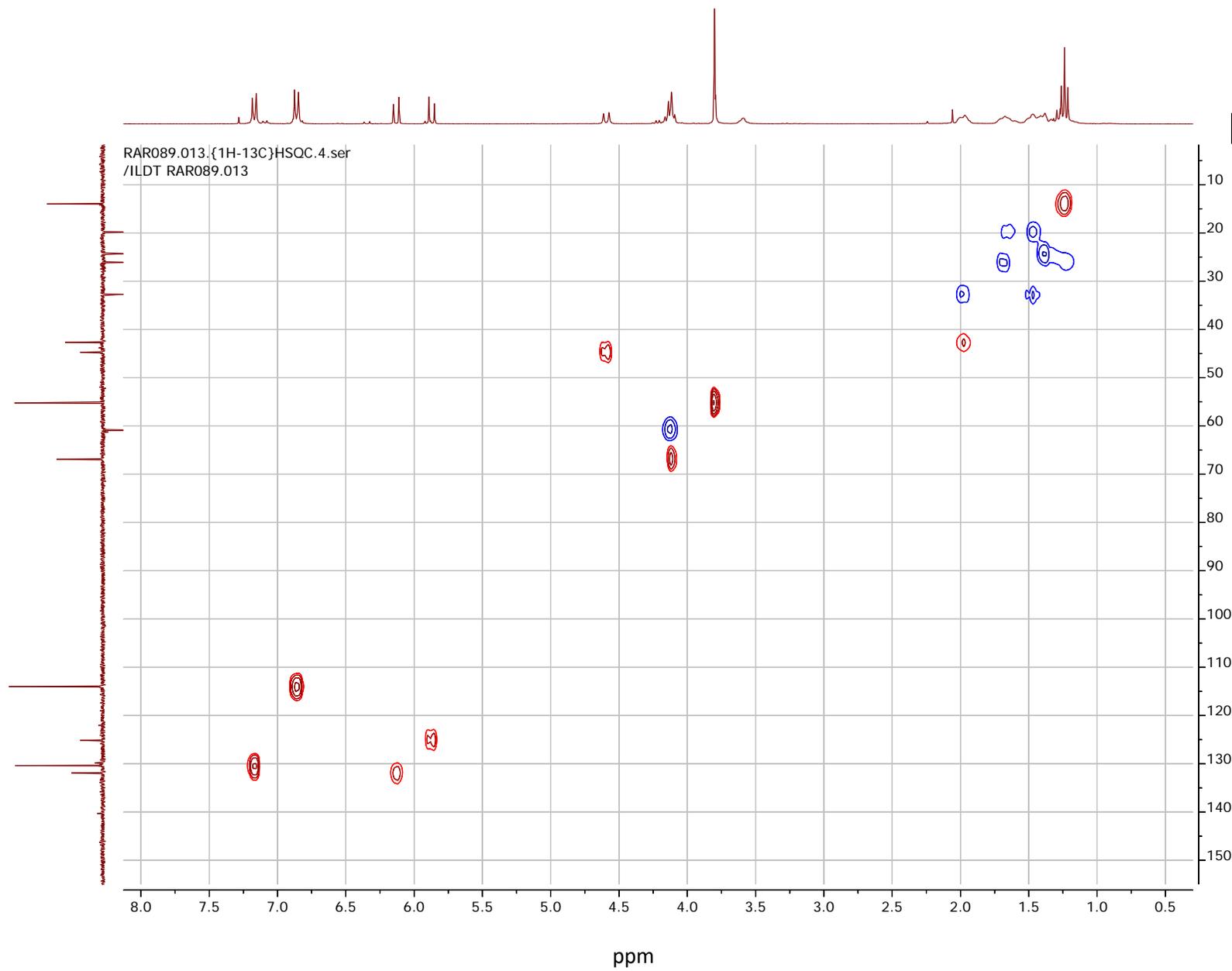


1j, Z/E = 10 : 1

DEPT135 (CDCl₃)



S50

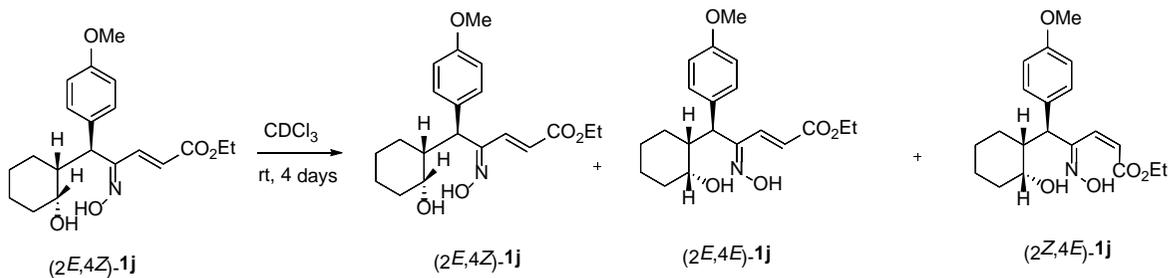


1j, *Z/E* = 10 : 1
HSQC (CDCl₃)

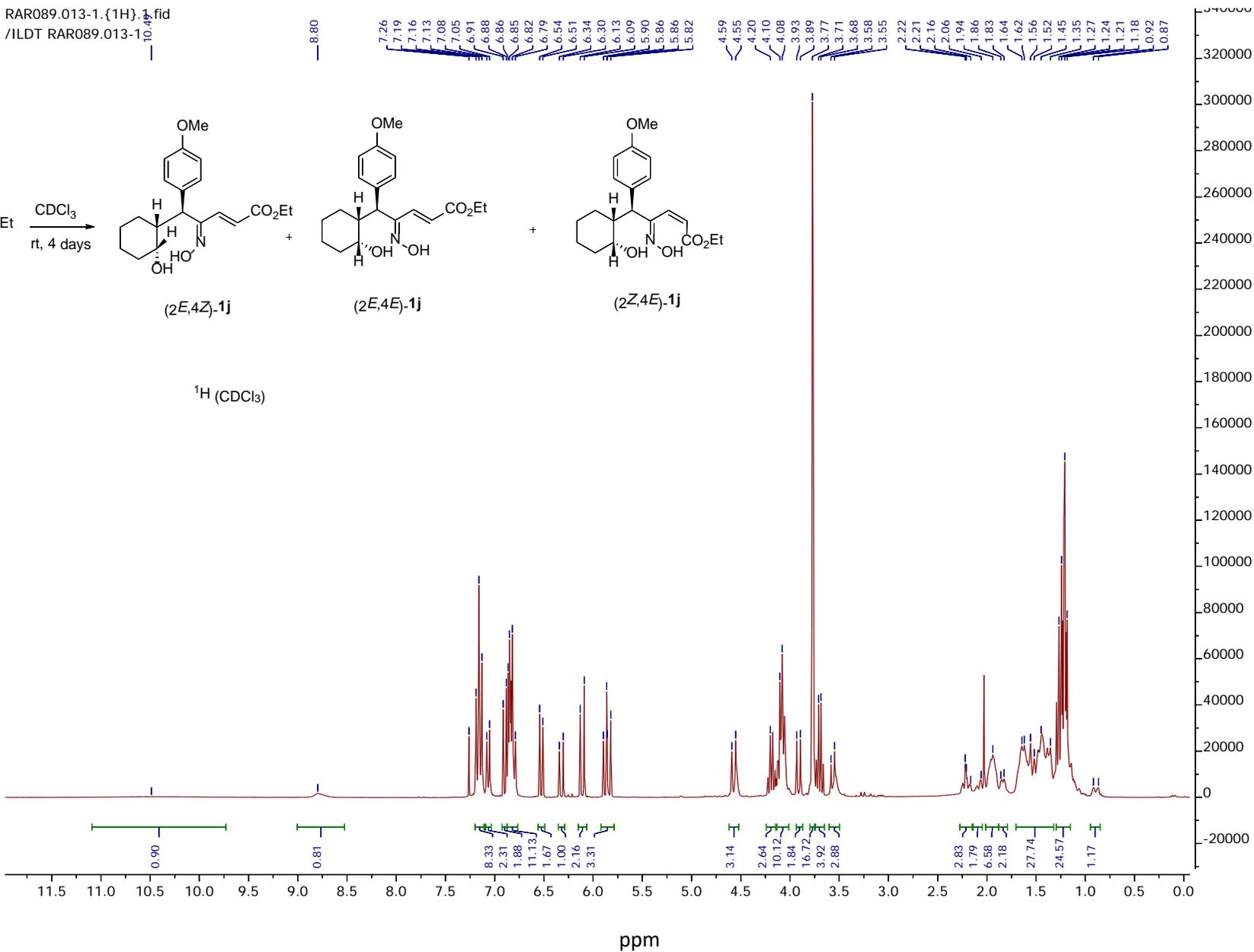
ppm

S51

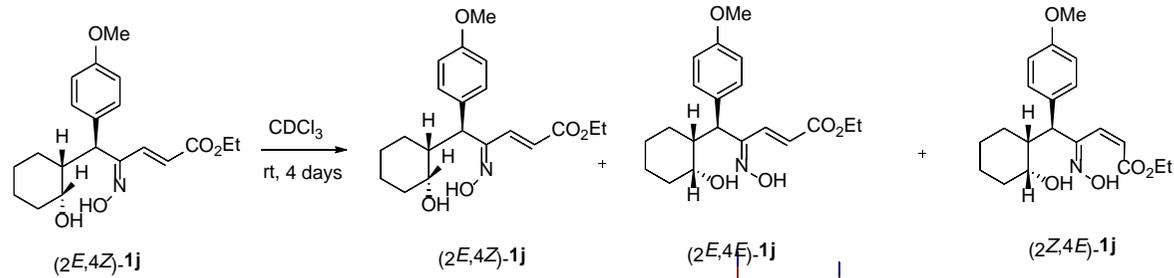
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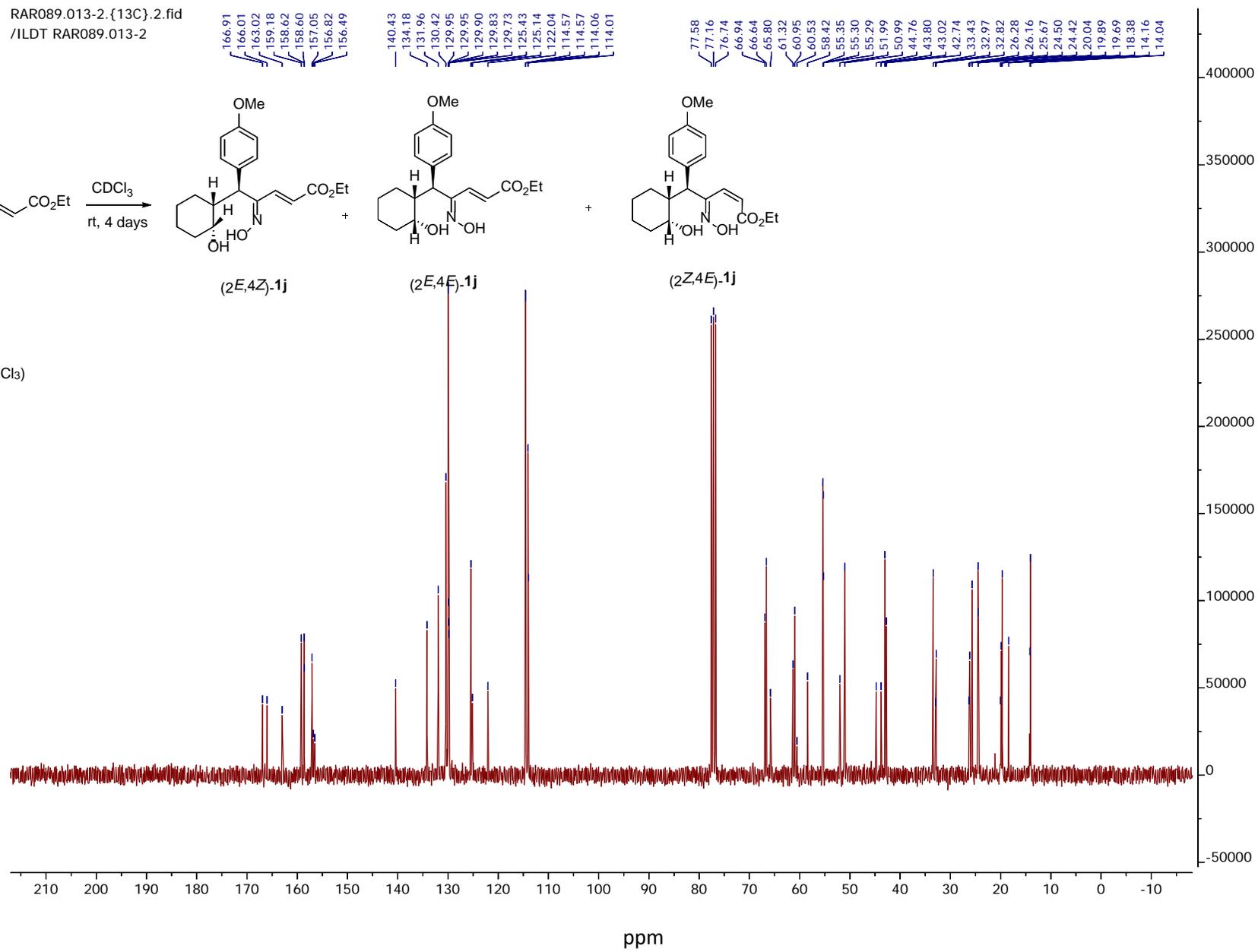
¹H (CDCl₃)



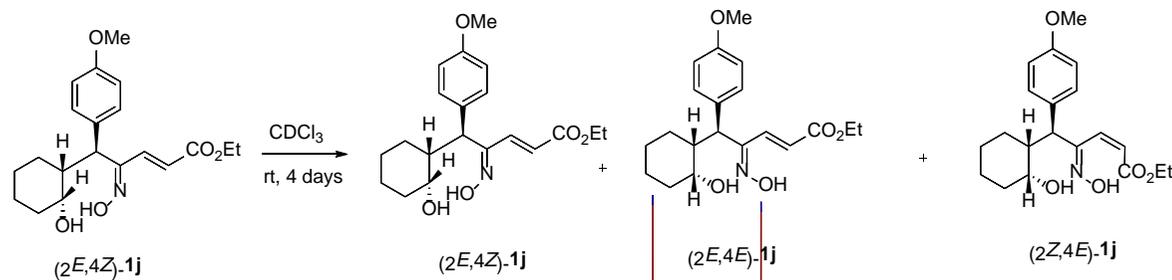
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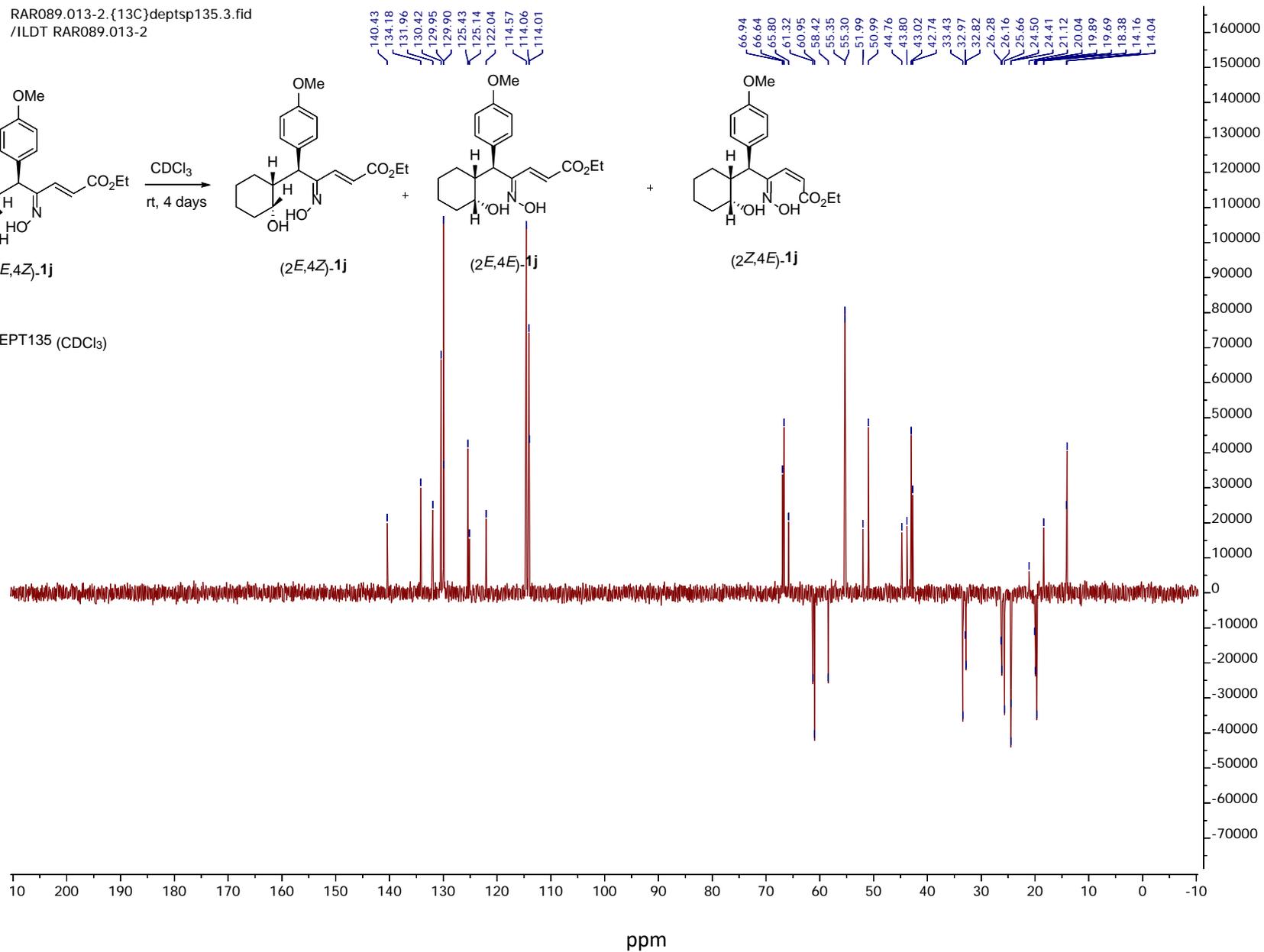
$^{13}\text{C}\{^1\text{H}\}$ (CDCl₃)



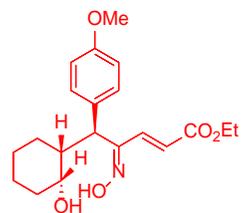
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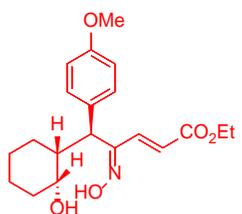
DEPT135 (CDCl₃)



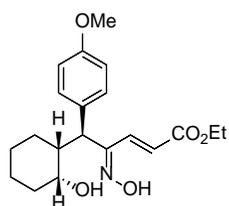
COSY (CDCl₃)



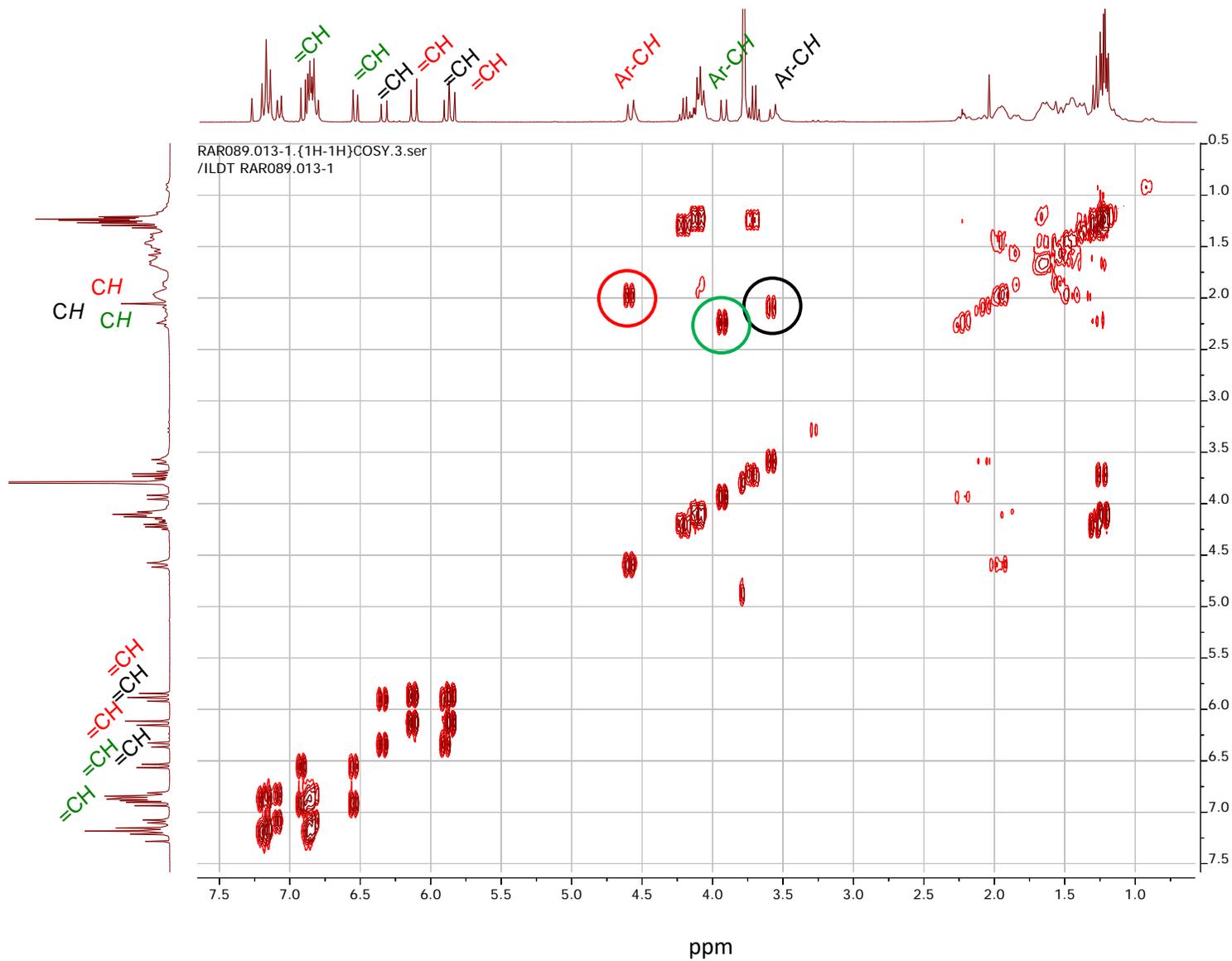
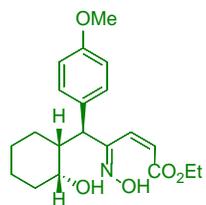
rt, 4 days | CDCl₃



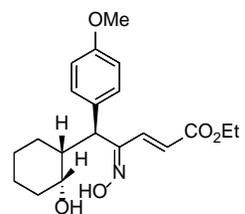
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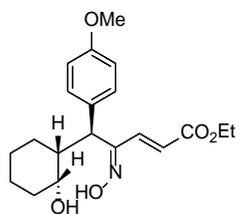


HSQC (CDCl₃)



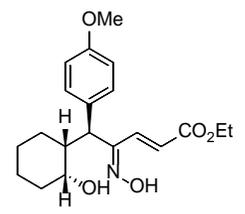
(2*E*,4*Z*)-1j

rt, 4 days
↓
CDCl₃



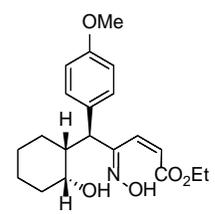
(2*E*,4*Z*)-1j

+

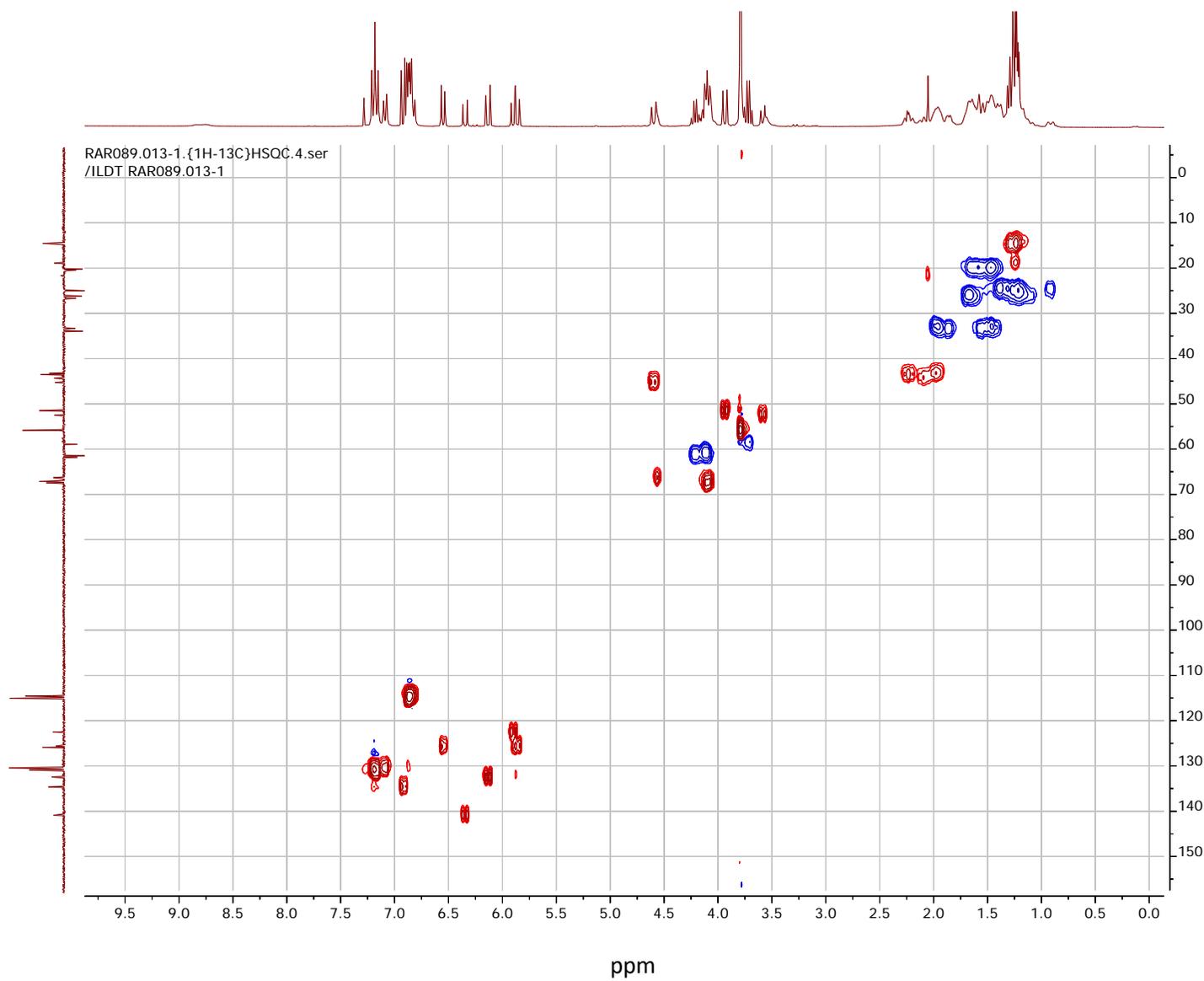


(2*E*,4*E*)-1j

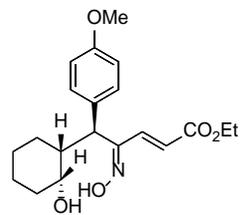
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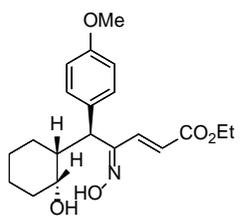
(2*Z*,4*E*)-1j



HMBC (CDCl₃)

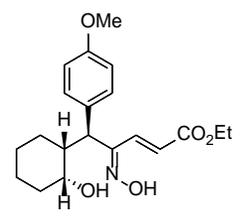


rt, 4 days
CDCl₃



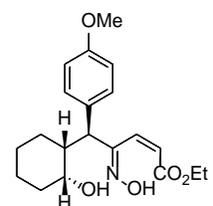
(2*E*,4*Z*)-1j

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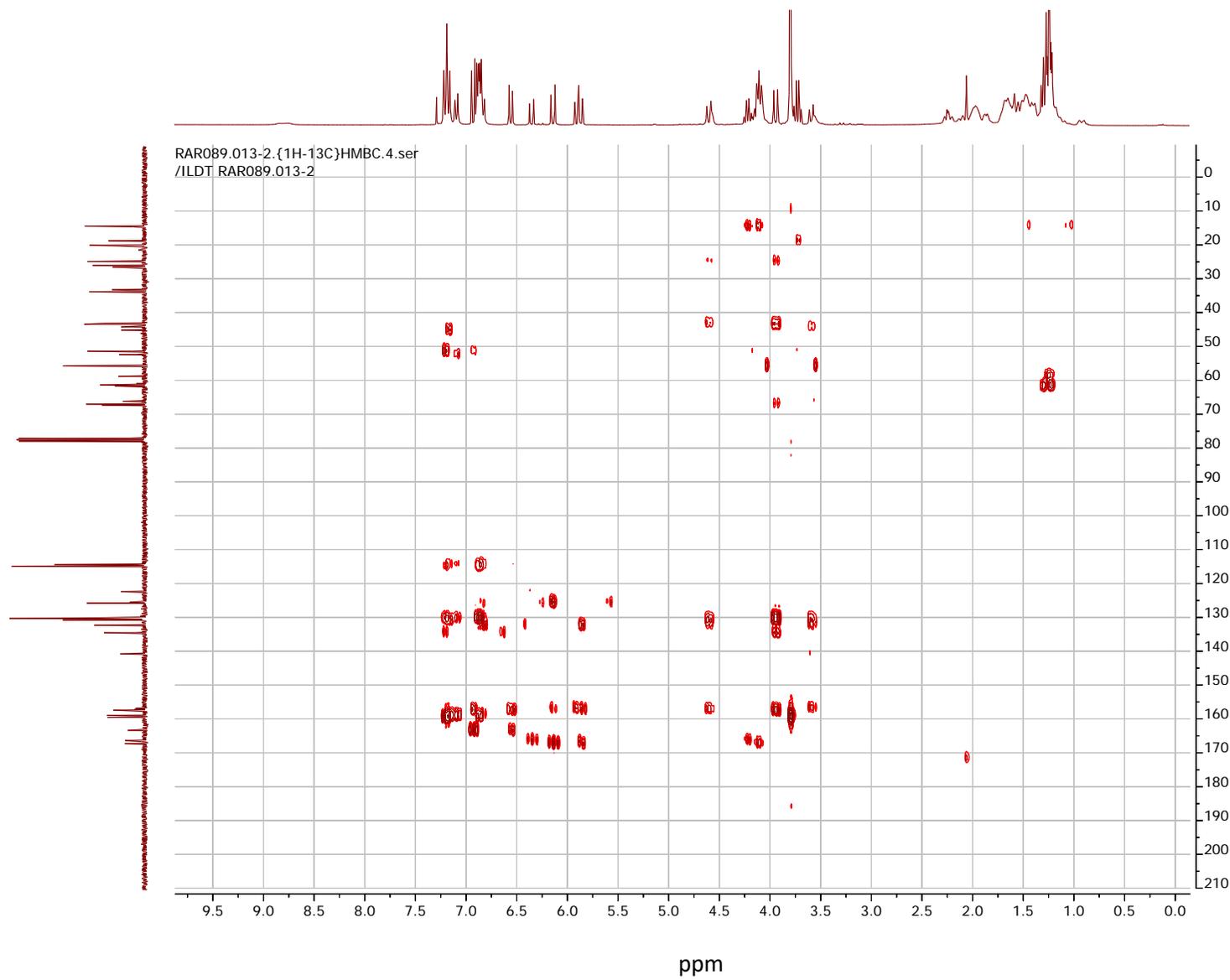


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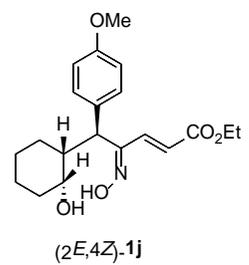
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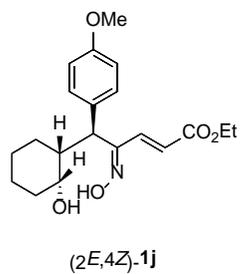
(2*Z*,4*E*)-1j



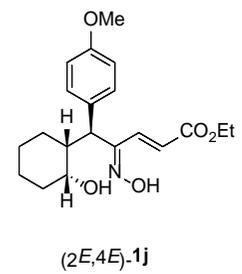
HMBC (CDCl₃)



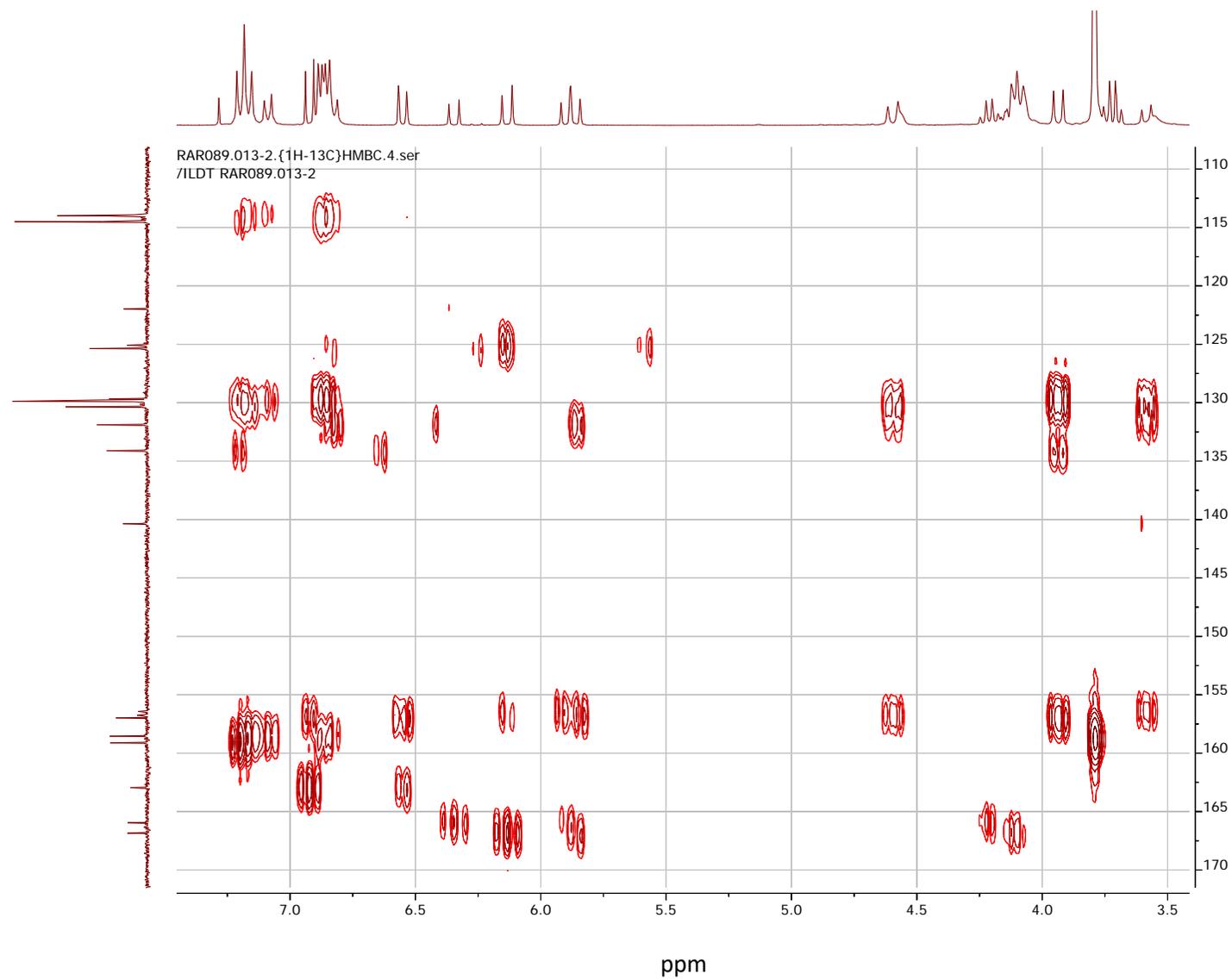
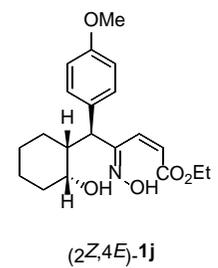
rt, 4 days
↓
CDCl₃



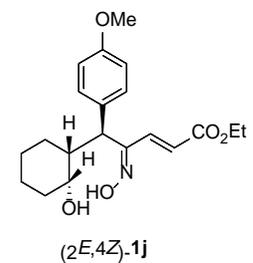
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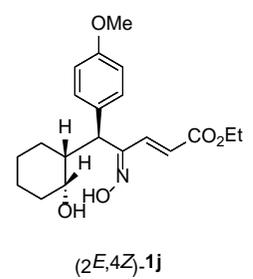
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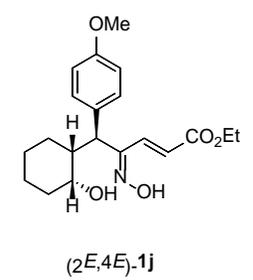
NOESY (CDCl₃)



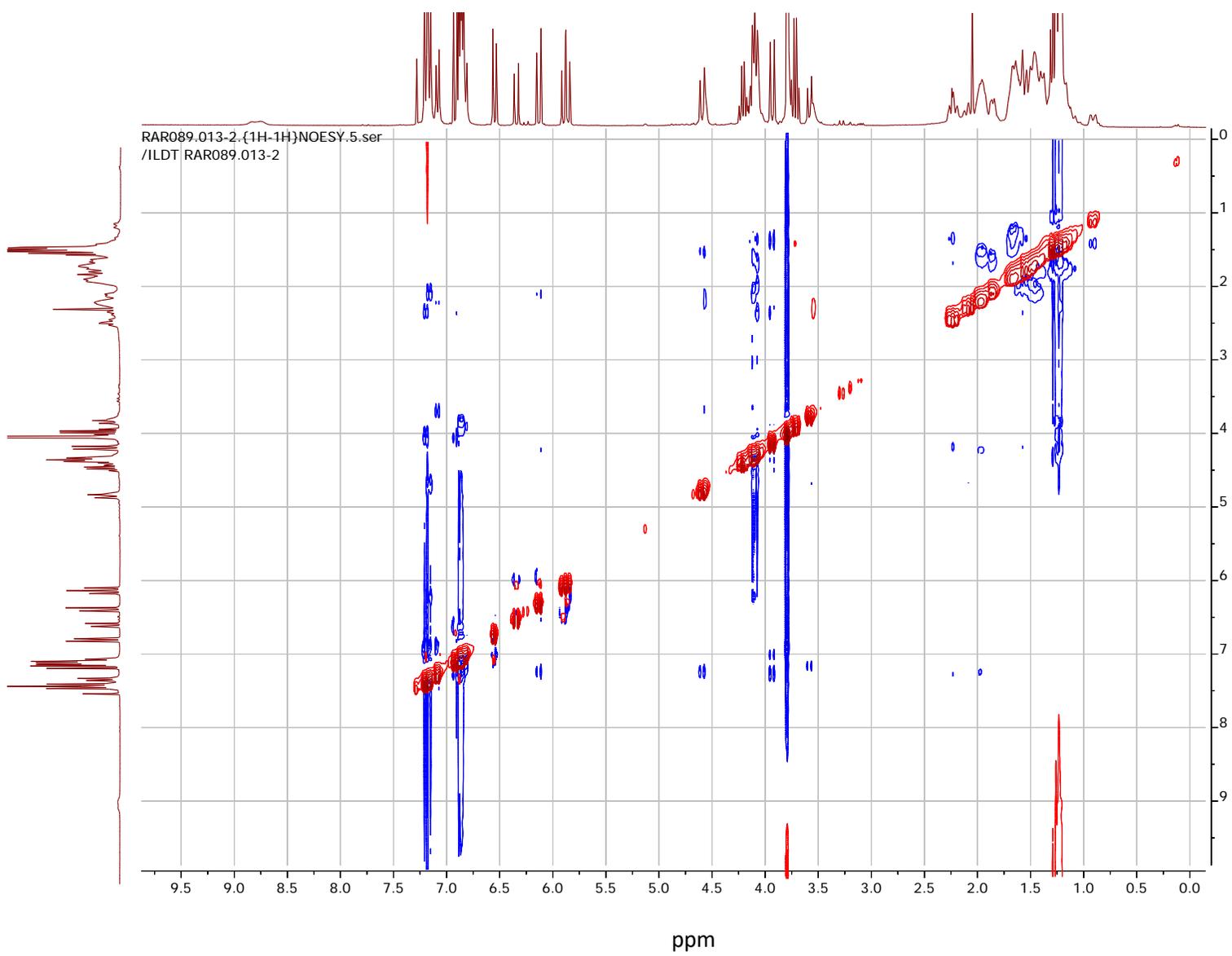
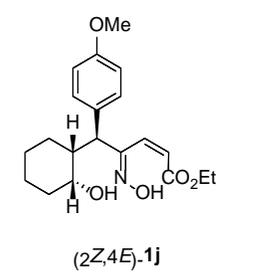
rt, 4 days ↓ CDCl₃



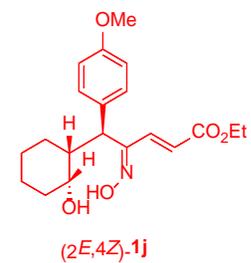
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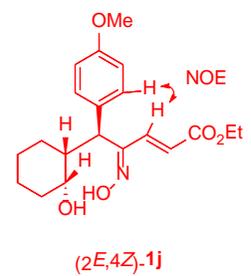
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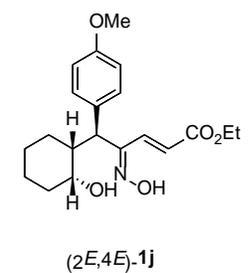
NOESY (CDCl₃)



rt, 4 days | CDCl₃



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