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One Pot Vinylogous Aldol Addition of β,γ-Unsaturated Esters Under Mild Conditions

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General Methods

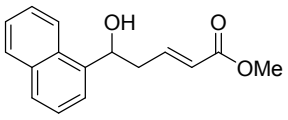
Reagents were commercial grade and were used as supplied. Tetrahydrofuran (THF) was dried by MBraun-SPS-Solvent Purification System. Reactions were monitored by TLC using Merck TLC plates (Silicagel 60 F 254). Chromatographic separations and isolations were performed using Fluka 70–230 mesh silica gel. Solvents, required for SiO_2 column chromatography, were commercial grade and were used as supplied. ^1H NMR and ^{13}C NMR data were recorded on a Varian 400-NMR (400 MHz) spectrometer. Chemical shifts for ^1H NMR and ^{13}C NMR are reported in δ (ppm). $CDCl_3$ peaks were used as reference in ^1H NMR (7.26 ppm) and ^{13}C NMR (77.16 ppm), respectively. MestReNova NMR Processing Software was used for processing NMR spectra.

Example Procedure

To a two-necked round bottom flask 34 mg of Ag_2CO_3 (0.125 mmol, 0.5 eq.) and 4 mL of anhydrous DMF were added. The mixture was stirred about 20 minutes at room temperature and cooled down to 0 ºC in ice bath. Then 28 µL of methyl 3-butenoate (0.25 mmol, 1 eq.) and 33 µL of TMSCl (0.25 mmol, 1 eq.) were added sequentially. After solution was stirred 1 h at 0 ºC, 72 µL 1-naphthaldehyde (0.5 mmol, 2 eq.) and 0.25 mL TBAF (1.0 in M THF) (0.25 mmol, 1 eq.) were added to the reaction mixture. The final mixture was allowed to warm to room temperature and stirred for 24 h. The mixture was poured into 30 mL of water and extracted with Et_2O (3x40 mL). Combined organic phase was dried over $MgSO_4$ and excess solvent was removed under reduced pressure. Purification of crude product on SiO_2 column (1:6 →1:4; EtOAc:Hexane) furnished 48 mg of (*E*)-methyl 5-hydroxy-5-(naphthalen-5-yl)pent-2-enoate (**8**) as yellow oil in 75% yield.

Analytical Data of Obtained Compounds

Methyl (*E*)-5-hydroxy-5-(naphthalen-1-yl)pent-2-enoate (8)



$C_{16}H_{16}O_3$

8

Light yellow oil

Yield: 75%

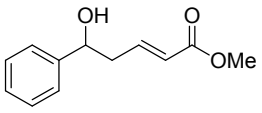
R_f: 0.46 (1:2, EtOAc:Hexane)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 9.2 Hz, 1H), 7.88 (d, J = 7.5 Hz, 1H), 7.79 (d, J = 8.2 Hz, 1H), 7.65 (d, J = 7.1 Hz, 1H), 7.56 – 7.44 (m, 3H), 7.10 (dt, J = 15.6, and 7.2 Hz, 1H), 5.94 (dt, J = 15.7, and 1.5, 1H), 5.58 (dd, J = 8.2, and 4.1 Hz, 1H), 3.71 (s, 3H), 2.88 – 2.79 (m, 1H), 2.79 – 2.69 (m, 1H), 2.44 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.91, 145.58, 139.09, 133.91, 130.14, 129.15, 128.41, 126.37, 125.77, 125.56, 123.51, 122.97, 122.82, 69.89, 51.63, 40.98.

HRMS: $[M+Na]^+$: $C_{16}H_{16}O_3$ found as: 279.0986 (Calculated for $[M+Na]^+$: 279.0997)

Methyl (*E*)-5-hydroxy-5-phenylpent-2-enoate (15)



$C_{12}H_{14}O_3$

15

Light yellow oil

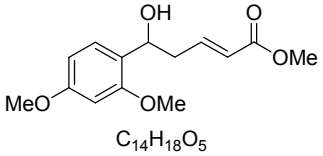
Yield: 41%

R_f: 0.56 (1:2, EtOAc:Hexane)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 5H), 7.00 – 6.91 (m, 1H), 5.93 – 5.85 (m, 1H), 4.81 (s, 1H), 3.70 (s, 3H), 2.69 – 2.59 (m, 2H), 2.18 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.85, 145.11, 143.53, 128.76, 128.07, 125.85,123.72, 73.22, 51.64, 41.96.

Methyl (*E*)-5-(2,4-dimethoxyphenyl)-5-hydroxypent-2-enoate (16)



$C_{14}H_{18}O_5$

16

Light yellow oil

Yield: 12%

R_f: 0.3 (1:2, EtOAc:Hexane)

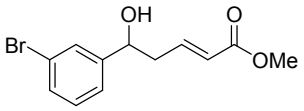
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 8.1 Hz, 1H), 7.05 – 6.94 (m, 1H), 6.50 – 6.44 (m, 2H), 5.89 (dd, J = 15.7, and 0.9 Hz, 1H), 4.96 (s, 1H), 3.82 (s, 3H),

3.80 (s, 3H), 3.71 (s, 3H), 2.67 (t, J = 7.2 Hz, 2H), 2.53 (s, 1H).

^{13}C NMR (101 MHz $CDCl_3$) δ 166.99, 160.47, 157.60, 146.15, 127.53, 123.83, 123.06, 104.30, 98.86, 69.43, 55.53, 55.45, 51.57, 40.28.

HRMS: $[M+Na]^+$: $C_{14}H_{18}NaO_5$ found as: 289.1010 (Calculated for $[M+Na]^+$: 289.1052)

Methyl (*E*)-5-(3-bromophenyl)-5-hydroxypent-2-enoate (17)



$C_{12}H_{13}BrO_3$

17

Light yellow oil

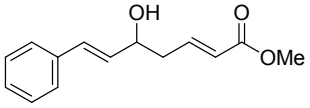
Yield: 67%

R_f: 0.4 (1:2, EtOAc:Hexane)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (t, J = 1.5 Hz, 1H), 7.41 (dt, J = 7.5, and 1.6 Hz, 1H), 7.28 – 7.18 (m, 2H), 6.99 – 6.89 (m, 1H), 5.89 (dt, J = 15.7, and 1.3 Hz, 1H), 4.81 –4.75 (m, 1H), 3.71 (s, 3H), 2.63 – 2.57 (m, 2H), 2.44 (s, 1H).

13C NMR (100 MHz, CDCl3) δ 166.83, 145.89, 144.63, 131.02, 130.28, 128.95, 124.48, 123.96, 122.83, 72.40, 51.71, 41.92.

Methyl (*2E*,*6E*)-5-hydroxy-7-phenylhepta-2,6-dienoate (19)



$C_{14}H_{16}O_3$

19

Light yellow oil

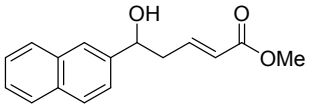
Yield: 28%

R_f: 0.53 (1:2, EtOAc:Hexane)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 7.3 Hz, 2H), 7.32 (t, J = 7.6 Hz, 2H), 7.28 – 7.26 (m, 1H), 7.01 (dt, J = 14.9, and 7.3 Hz, 1H), 6.62 (d, J = 15.9 Hz, 1H), 6.23 (dd, J = 15.9, and 6.6 Hz, 1H), 5.95 (d, J = 15.7 Hz, 1H), 4.45 (q, J = 6.4 Hz, 1H), 3.73 (s, 3H), 2.55 (t, J = 6.9 Hz, 2H), 1.93 (s, 1H).

(NMR data matches with the literature study. Gazaille, J. A.; Sammakia, T., The Vinylogous Aldol Reaction of Unsaturated Esters and Enolizable Aldehydes Using the Novel Lewis Acid Aluminum Tris(2,6-di-2-naphthylphenoxide). Organic Letters 2012, 14 (11), 2678-2681.)

Methyl (*E*)-5-hydroxy-5-(naphthalen-2-yl)pent-2-enoate (20)



$C_{16}H_{16}O_3$

20

Light yellow oil

Yield: 69%

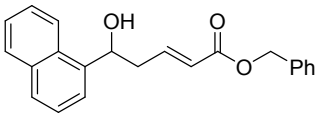
R_f: 0.43 (1:2, EtOAc:Hexane)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.79 (m, 3H), 7.76 (s, 1H), 7.48 (dt, J =4.8, and 3.3 Hz, 2H), 7.44 (dd, J = 8.6, and 1.6 Hz, 1H), 7.03 – 6.93 (m, 1H), 5.89 (d, J = 15.7 Hz, 1H), 4.95 – 4.88 (m, 1H), 3.68 (s, 3H), 2.79 – 2.59 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.89, 145.20, 140.94, 133.30, 133.12, 128.51, 128.06, 127.77, 126.33, 126.08, 124.63, 123.84, 123.56, 73.15, 51.58, 41.79.

HRMS: $[M+Na]^+$: $C_{16}H_{16}NaO_3$ found as: 279.0971 (Calculated for $[M+Na]^+$:279.0997)

Benzyl (*E*)-5-hydroxy-5-(naphthalen-1-yl)pent-2-enoate (27)



$C_{22}H_{20}O_3$

27

Light yellow oil

Yield: 51%

R_f: 0.4 (1:2, EtOAc-Hexane)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 7.5 Hz, 1H), 7.89 (d, J = 7.2 Hz, 1H), 7.80 (d, J = 8.2 Hz, 1H), 7.66 (d, J = 7.0 Hz, 1H), 7.56 – 7.45 (m, 3H), 7.40 – 7.31 (m, 5H), 7.20 – 7.11 (m, 1H), 6.00 (dd, J = 15.7, and 0.7 Hz, 1H), 5.58 (dd, J = 8.0, and 3.8 Hz, 1H), 5.17 (s, 2H), 2.87 – 2.69 (m, 2H), 2.45 (s, 1H).

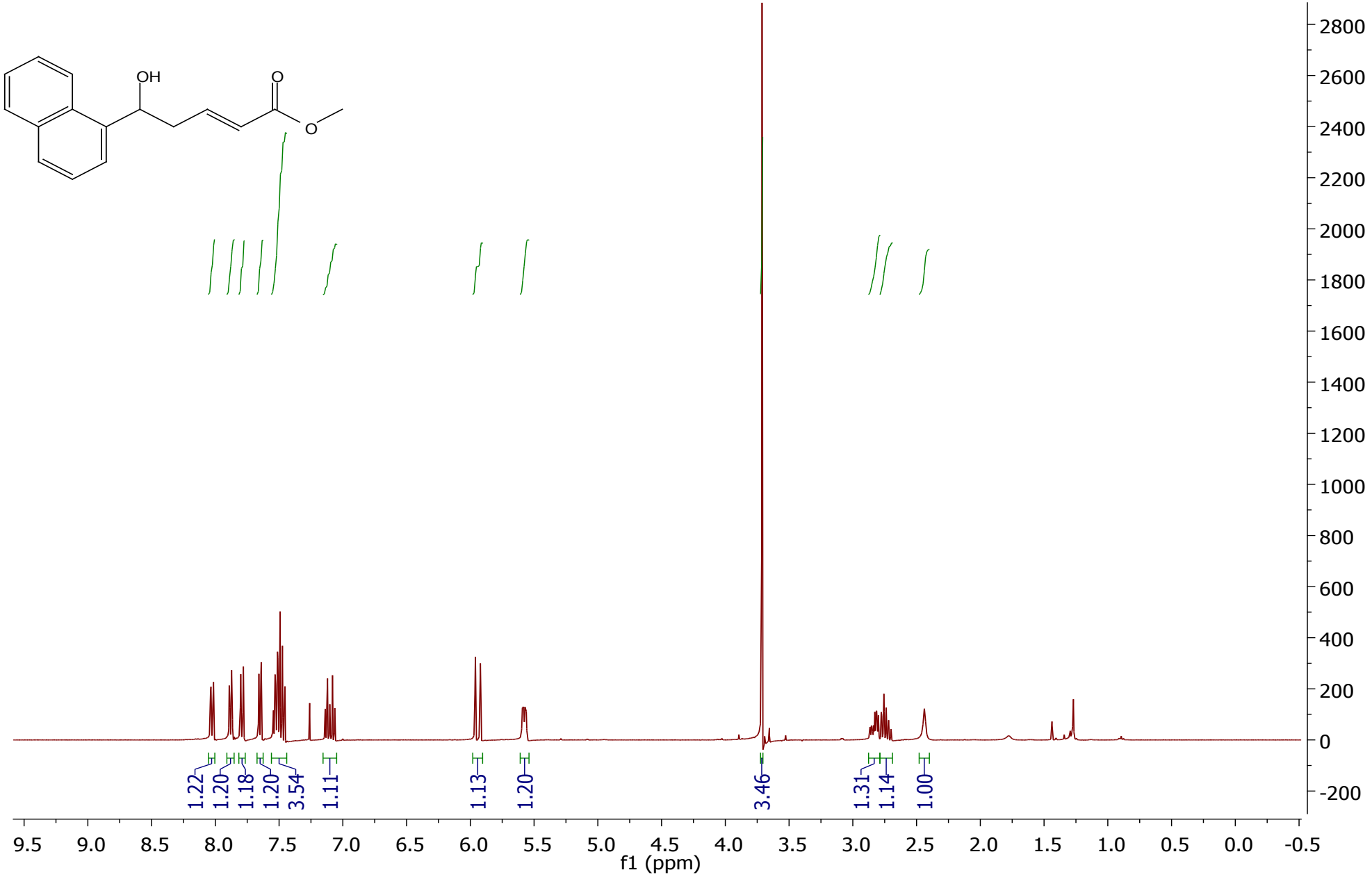
^{13}C NMR (100 MHz, $CDCl_3$) δ 164.76, 150.97, 150.70, 138.31, 137.89, 133.34, 133.14, 128.54, 128.17, 127.81, 126.42, 126.23, 125.12, 124.97, 124.22, 124.07, 120.94, 120.46, 110.13, 76.24, 35.50, 31.24.

^{1}H and ^{13}C NMR Spectra

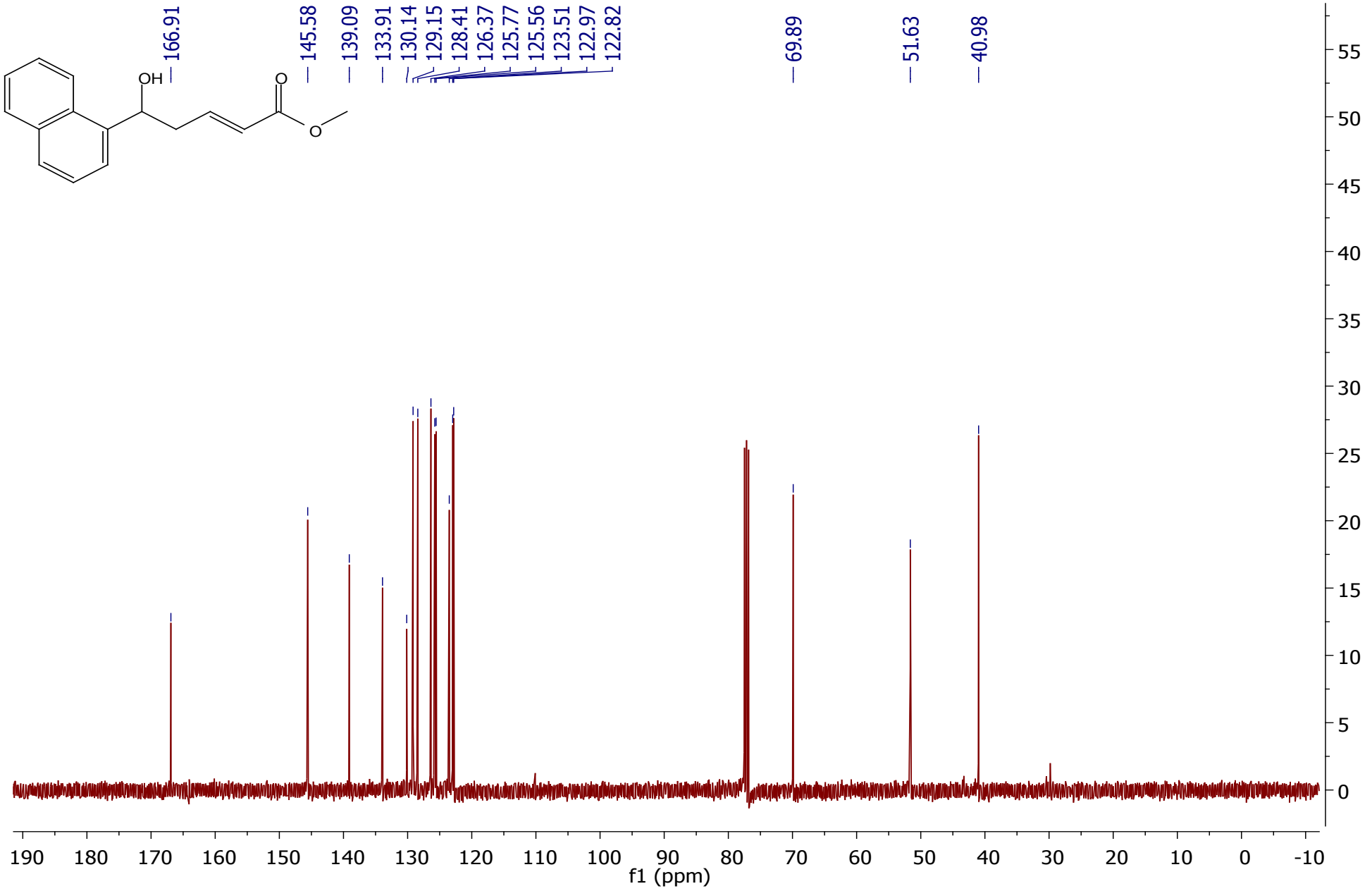
of

Obtained Compounds

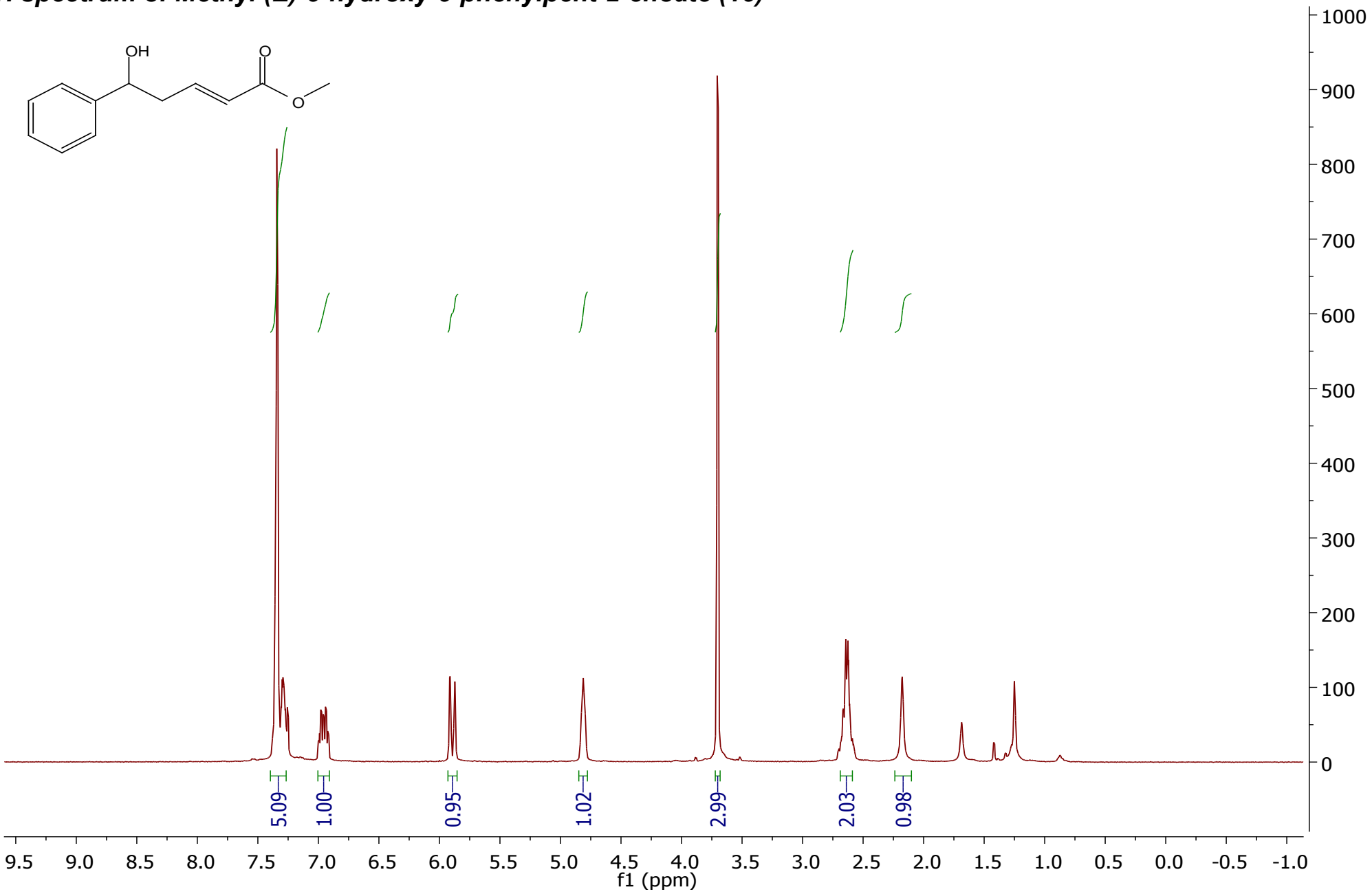
^{1}H spectrum of Methyl (E)-5-hydroxy-5-(naphthalen-1-yl)pent-2-enoate (8)



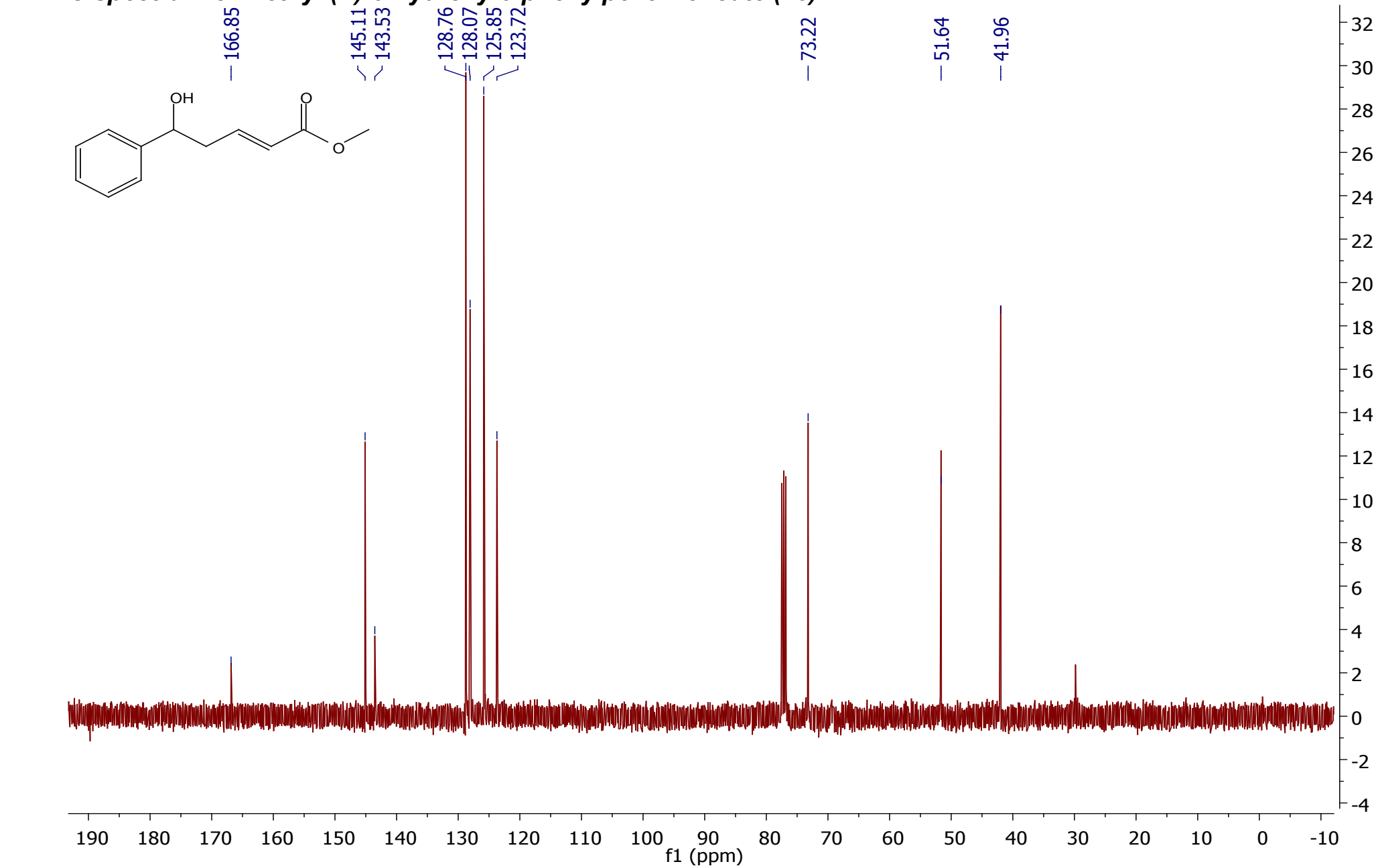
^{13}C spectrum of Methyl (E)-5-hydroxy-5-(naphthalen-1-yl)pent-2-enoate (8)



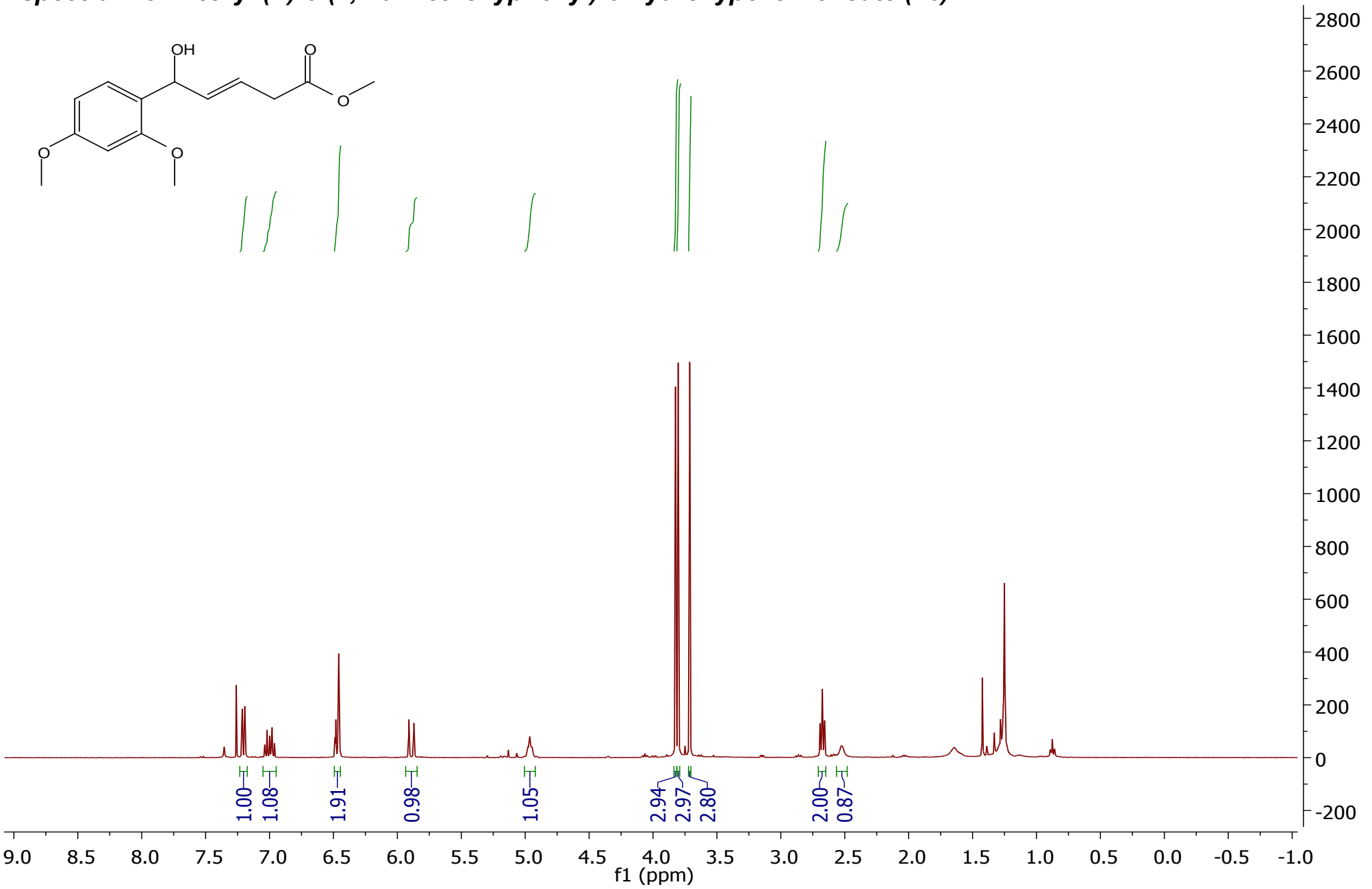
^{1}H spectrum of Methyl (E)-5-hydroxy-5-phenylpent-2-enoate (15)



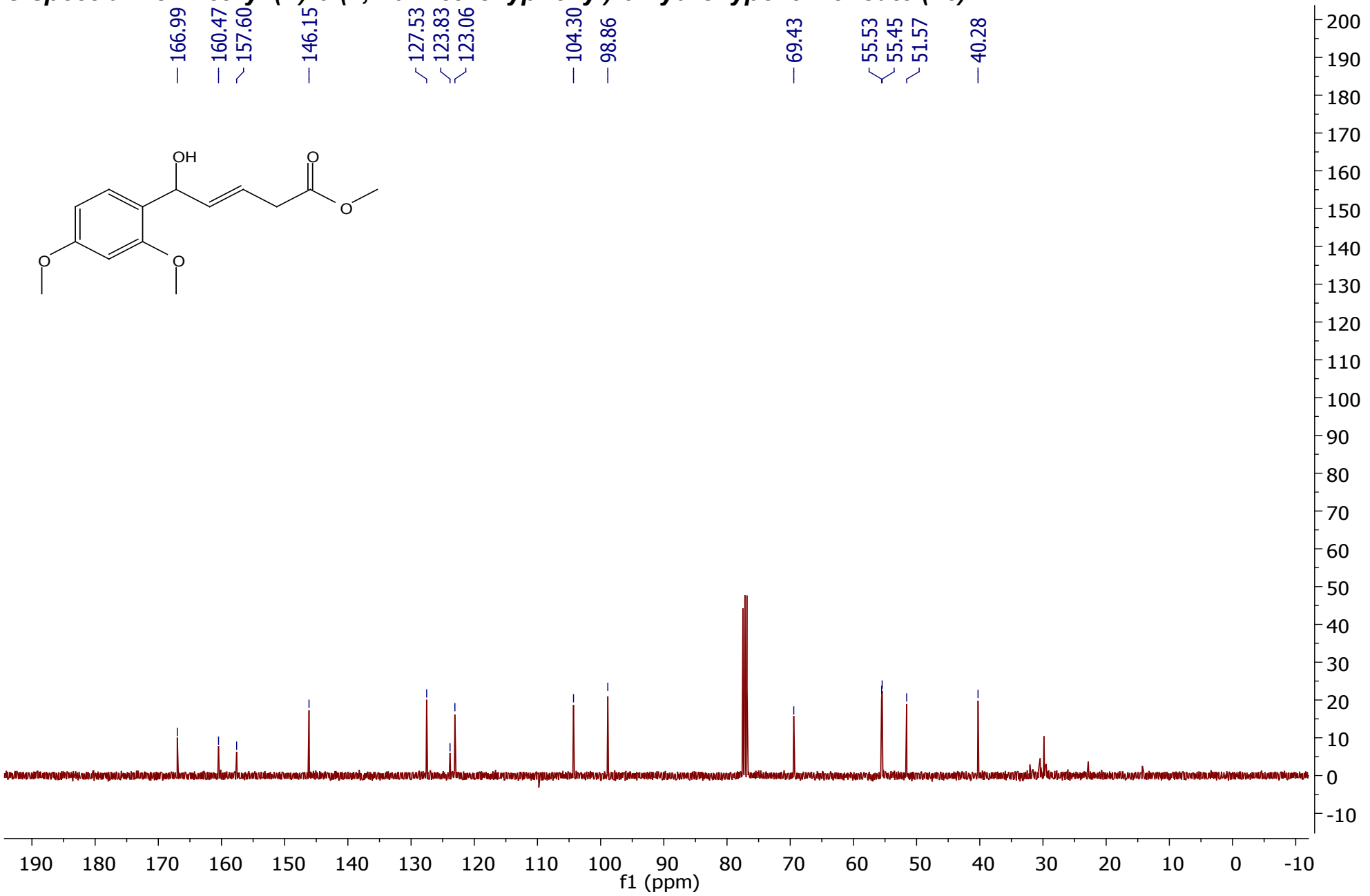
^{13}C spectrum of Methyl (E)-5-hydroxy-5-phenylpent-2-enoate (15)



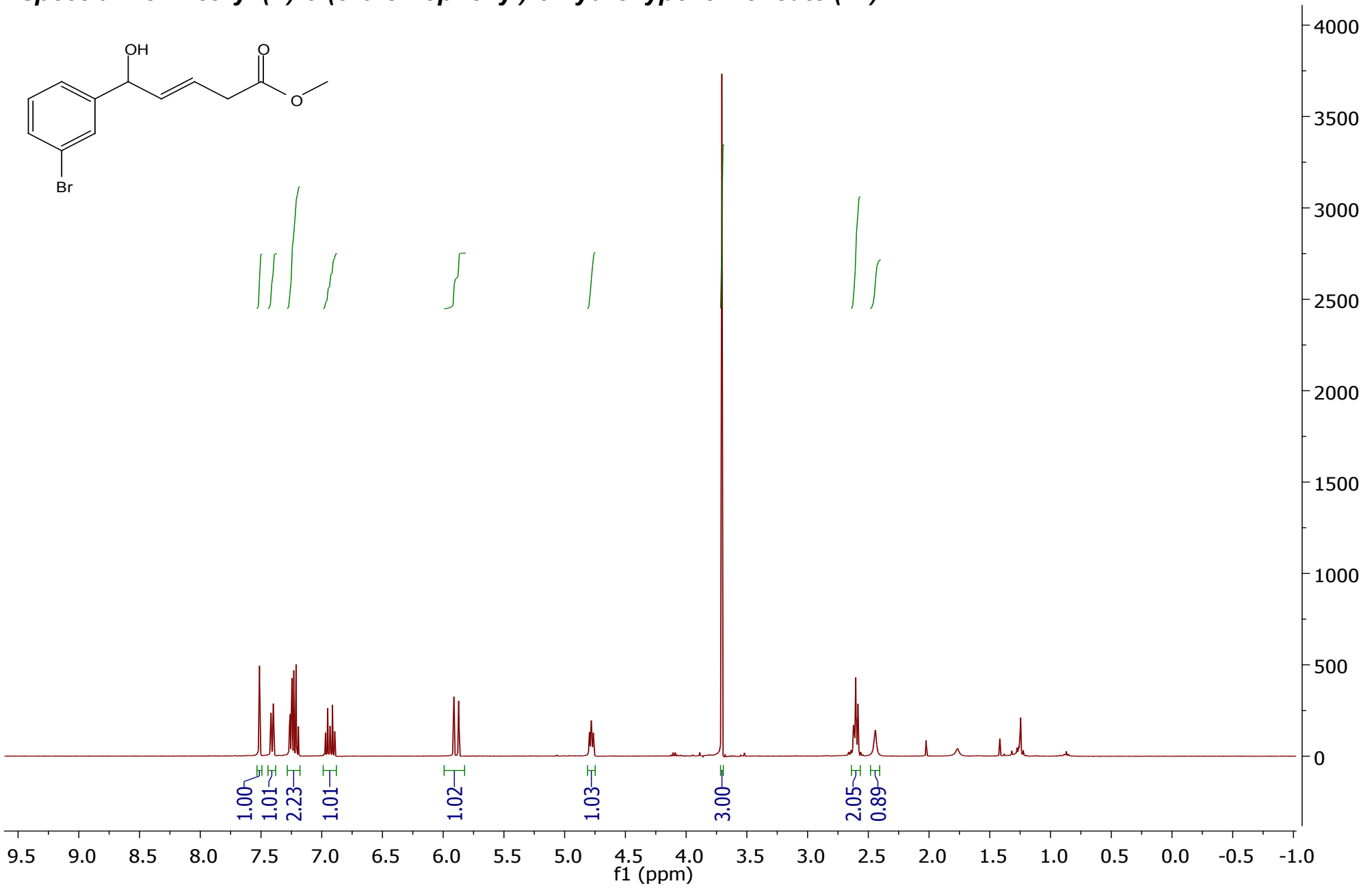
^{1}H spectrum of Methyl (E)-5-(2,4-dimethoxyphenyl)-5-hydroxypent-2-enoate (16)



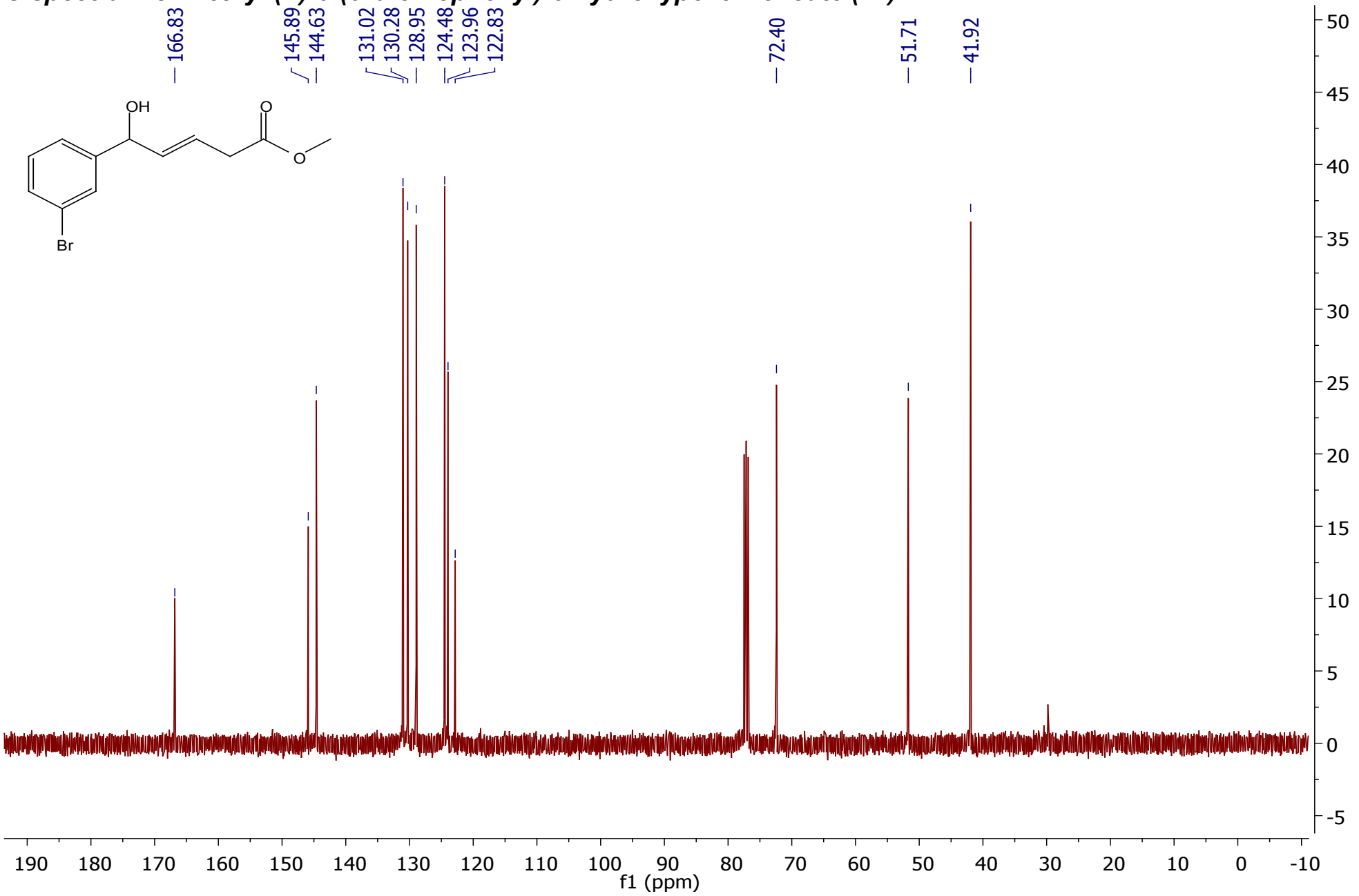
^{13}C spectrum of Methyl (E)-5-(2,4-dimethoxyphenyl)-5-hydroxypent-2-enoate (16)



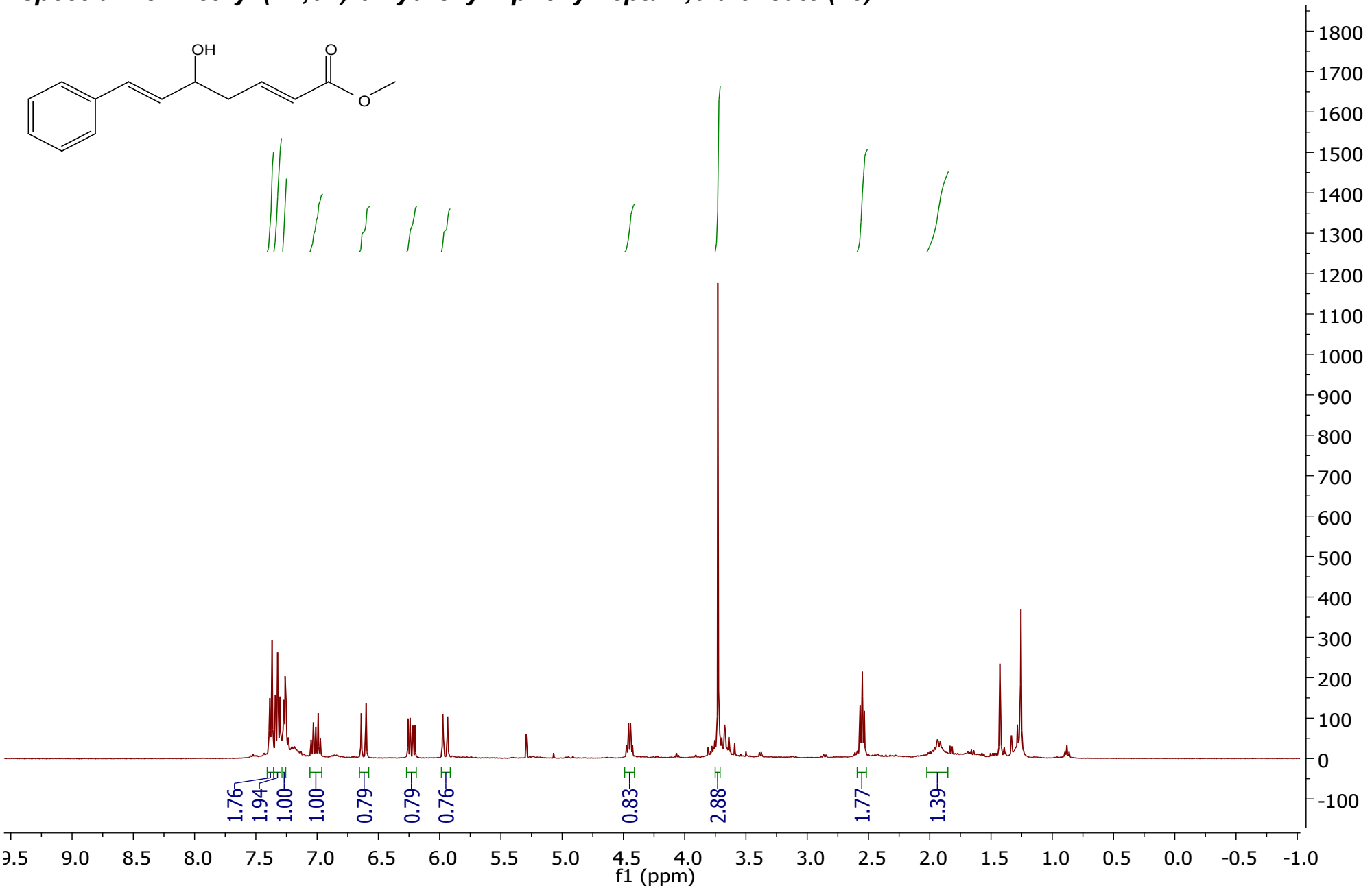
[1]H spectrum of Methyl (E)-5-(3-bromophenyl)-5-hydroxypent-2-enoate (17)



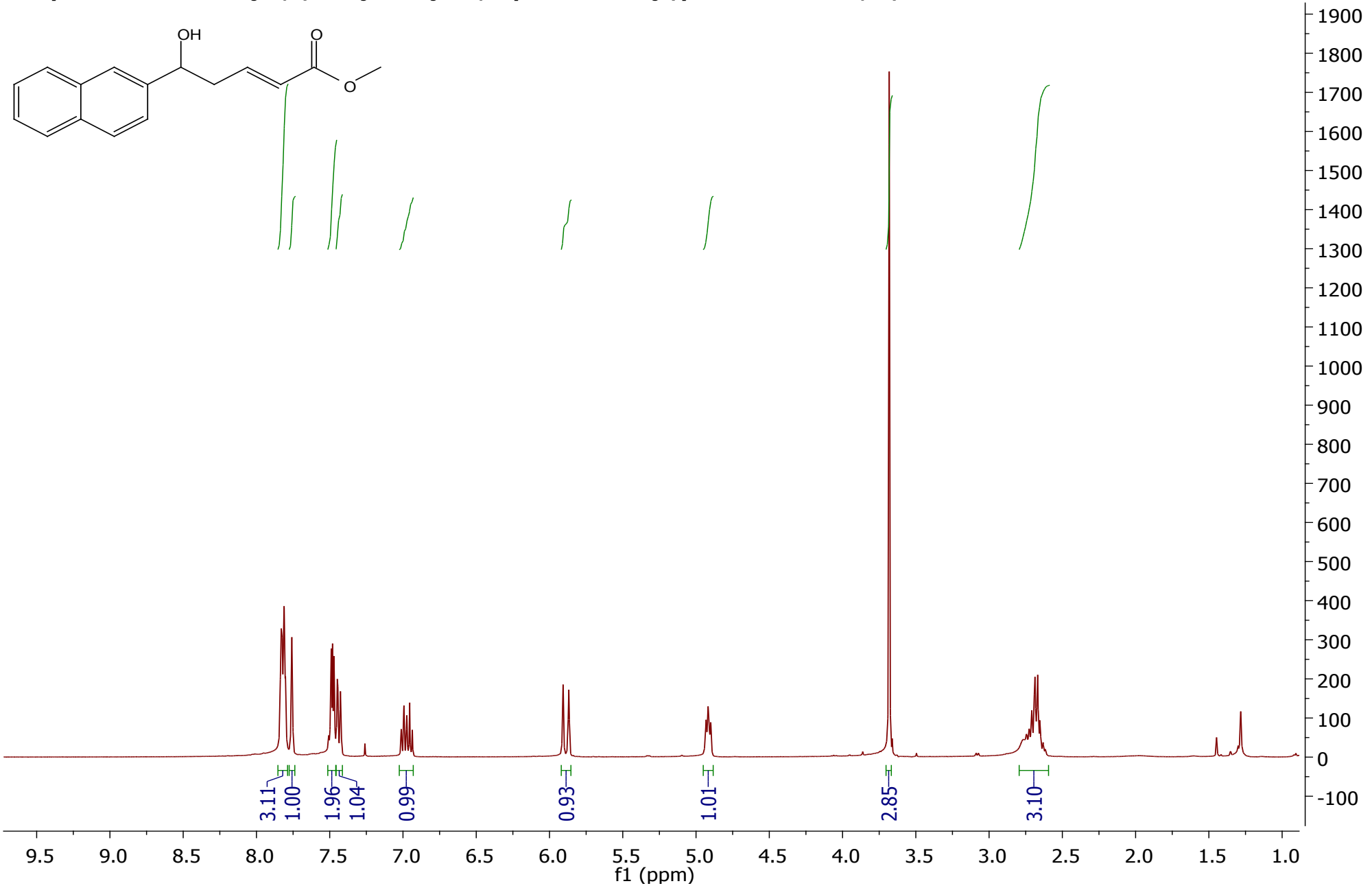
^{13}C spectrum of Methyl (E)-5-(3-bromophenyl)-5-hydroxypent-2-enoate (17)



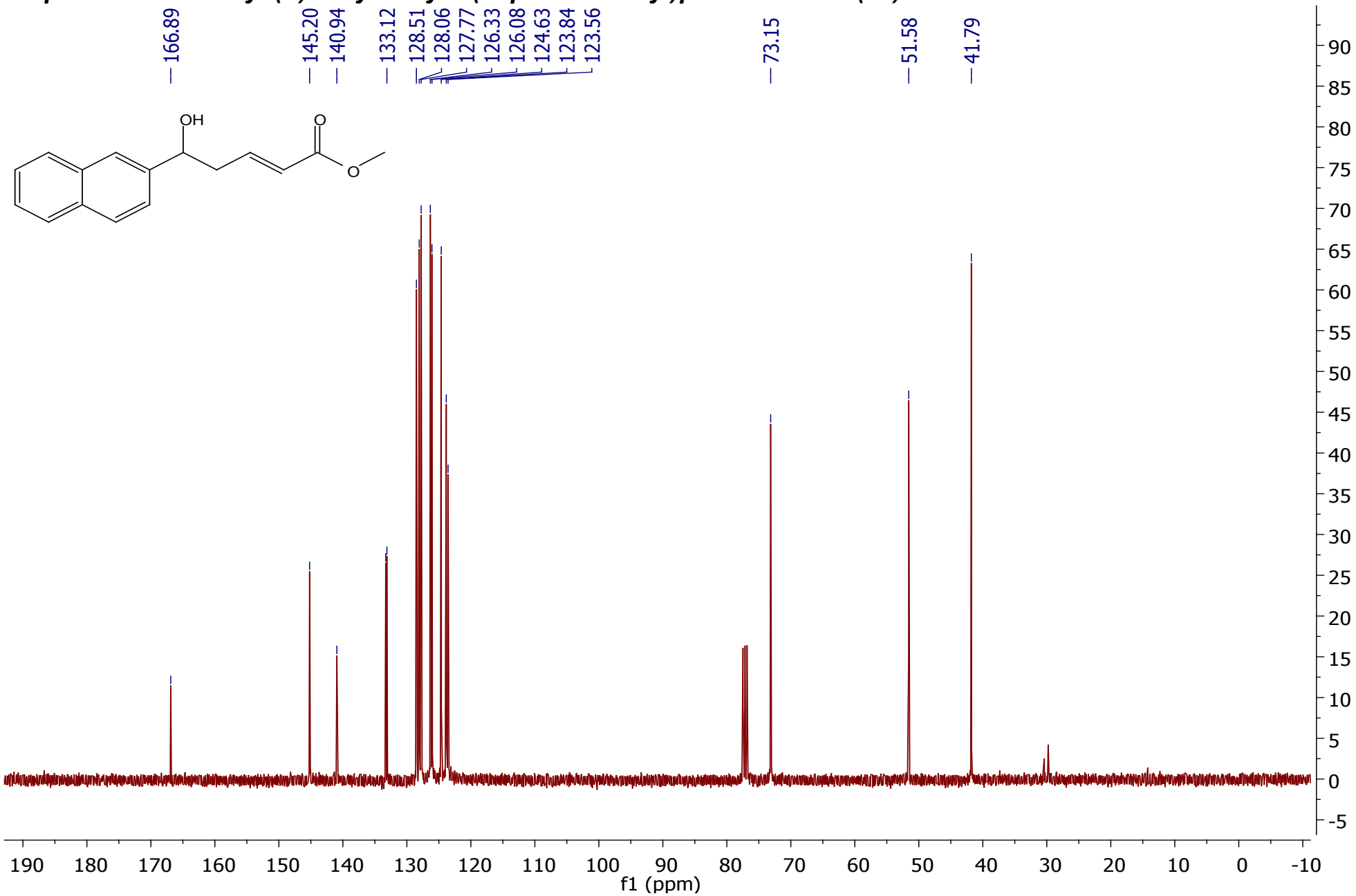
^{1}H spectrum of Methyl (2E,6E)-5-hydroxy-7-phenylhepta-2,6-dienoate (19)



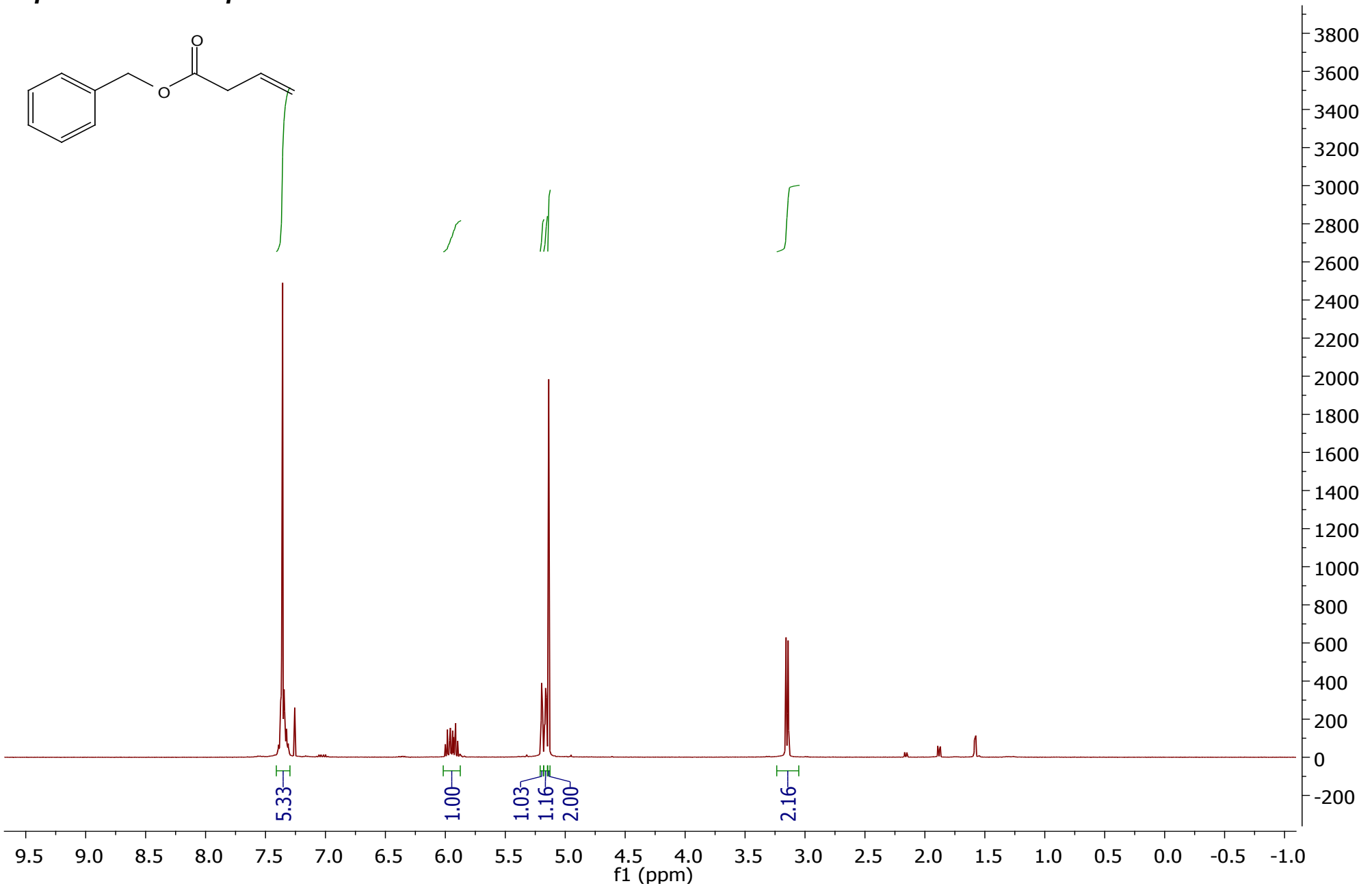
^{1}H spectrum of Methyl (E)-5-hydroxy-5-(naphthalen-2-yl)pent-2-enoate (20)



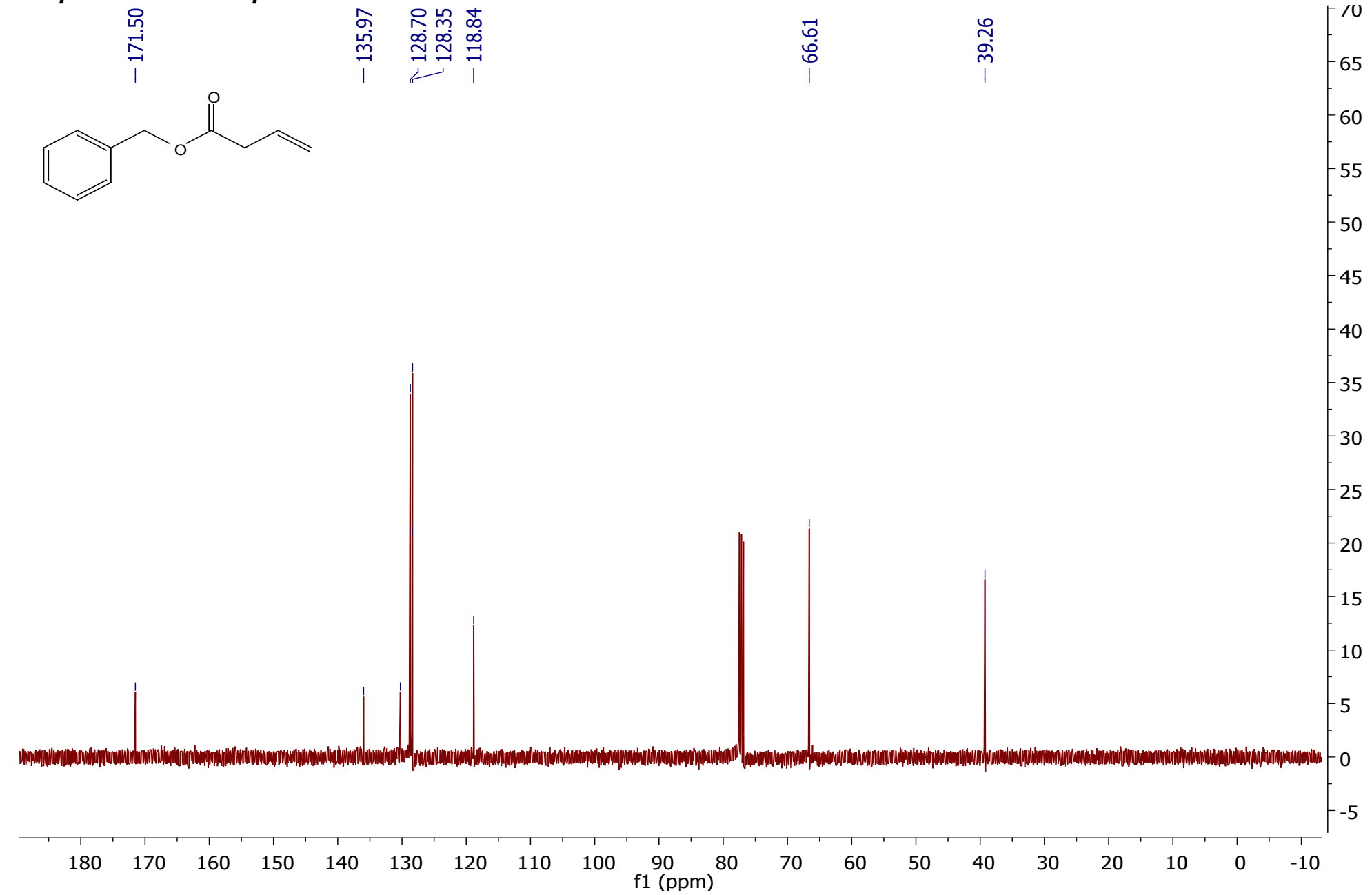
^{13}C spectrum of Methyl (E)-5-hydroxy-5-(naphthalen-2-yl)pent-2-enoate (20)



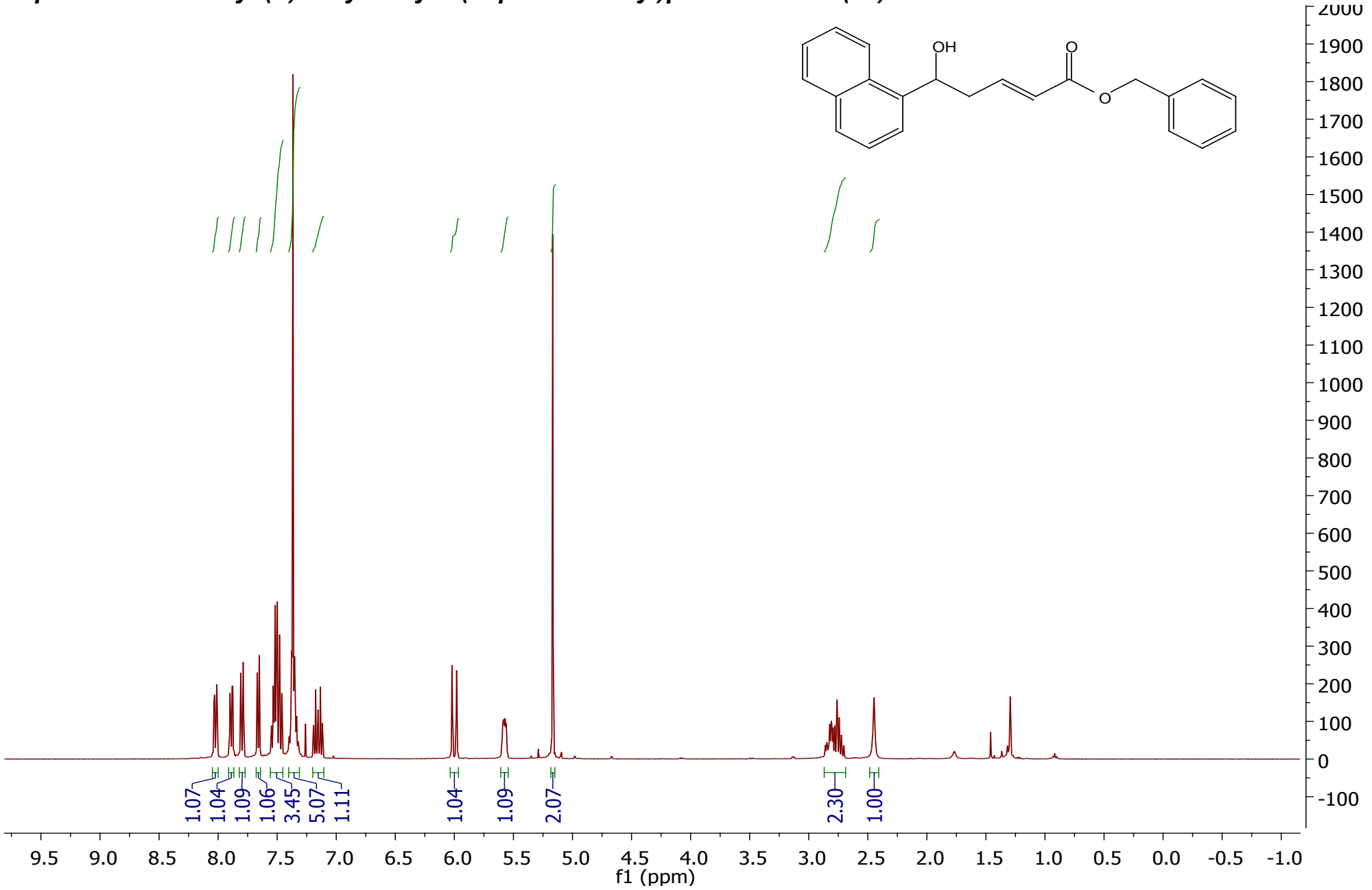
^{1}H spectrum of compound 25



^{13}C spectrum of compound 25



^{1}H spectrum of Benzyl (E)-5-hydroxy-5-(naphthalen-1-yl)pent-2-enoate (27)



^{13}C spectrum of Benzyl (E)-5-hydroxy-5-(naphthalen-1-yl)pent-2-enoate (27)