SUPPORTING INFORMATION

Synthesis of C11-to-C14 Methyl-shifted all-*trans*-Retinal Analogues and Their Activities On Human Aldo-Keto Reductases

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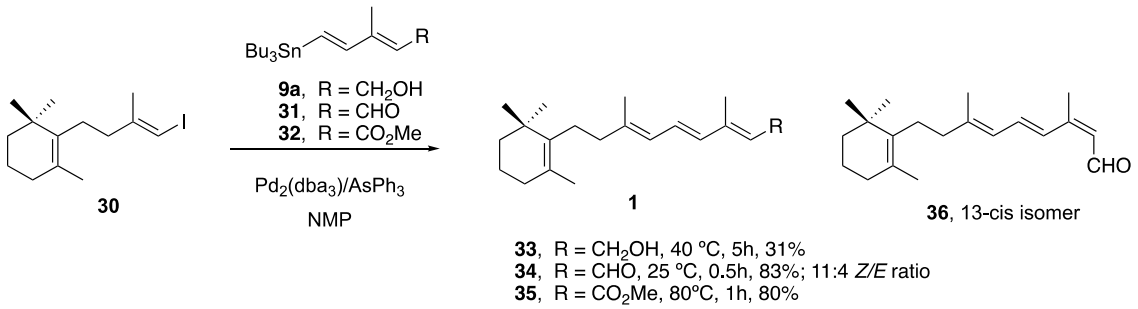
1. General information

Solvents were dried according to published methods and distilled before use. All other reagents were commercial compounds of the highest purity available. Unless otherwise indicated all reactions were carried out under argon atmosphere, and those not involving aqueous reagents were carried out in oven-dried glassware. Analytical thin layer chromatography (TLC) was performed on aluminum plates with Merck Kieselgel $60F_{254}$ and visualized by UV irradiation (254 nm) or by staining with an ethanolic solution of phosphomolybdic acid. Flash column chromatography was carried out using Merck Kieselgel 60 (230-400 mesh) C18-SiO_2 (Waters, 55–105 μm 125Å) and CN-SiO_2 (Silicycle 40-63 μm) under pressure. Electron impact (EI) mass spectra were obtained on a Hewlett-Packard HP59970 instrument operating at 70 eV. Alternatively an APEX III FT-ICR MS (Bruker Daltonics), equipped with a 7T actively shielded magnet was used and ions were generated using an Apollo API electrospray ionization (ESI) source, with a voltage between 1800 and 2200 V (to optimize ionization efficiency) applied to the needle, and a counter voltage of 450 V applied to the capillary. For ESI spectra samples were prepared by adding a spray solution of 70:29.9:0.1 (v/v/v) CH_3OH/water/formic acid to a solution of the sample at a v/v ratio of 1 to 5% to give the best signal-to-noise ratio. High Resolution Mass Spectra were taken on a VG Autospec instrument. ^1H NMR spectra were recorded in C_6D_6 and acetone-d_6 at ambient temperature on a Bruker AMX-400 spectrometer at 400 MHz with residual protic solvent as the internal reference.

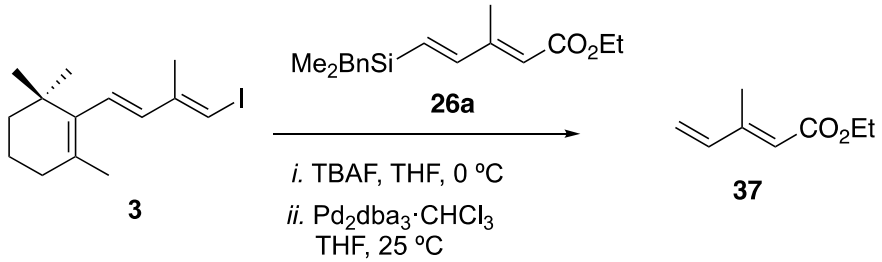
2. Experimental procedures

Additional observations related to the reactivity of dienylstannanes and dienylsilanes

In our experience with stannyldienals for the synthesis of retinoids, we have observed isomerizations in Stille-Kosugi-Migita cross-coupling reactions. As an example, the non-conjugated iododiene **30** was coupled to δ-stannyldienol, δ-stannyldienal and methyl δ-stannyldienoate (**9a**, **31** and **32**, respectively) to afford the corresponding all-trans-C7,C8-dihydroretinoids (**33-35**) in 31, 83 and 80% yields, respectively. Reaction conditions are also indicated, showing that the δ-stannyldienol **9a** underwent Stille-Kosugi-Migita cross-coupling at 40 ºC (5h), the δ-stannyldienoate **32** at 80 ºC (1h), and the δ-stannyldienal **31** at ambient temperature (25 ºC, 30 min). Moreover, despite the mild reaction conditions for the latter, a 11:4 isomer ratio favouring the 13-cis isomer (**36**) was found, thus indicating the incompatibility of the intact polyene structure with the Stille reaction conditions.



As an example of the unsuccessful Hiyama-Denmark cross-coupling of δ-silyldienyl esters, the reaction of **26a** with trienyliodide **3** afforded the recovery of the latter and extensive protodesilylation to give the corresponding terminal ethyl (*E*)-3-methylpentadienoate **37** as main product.[1]

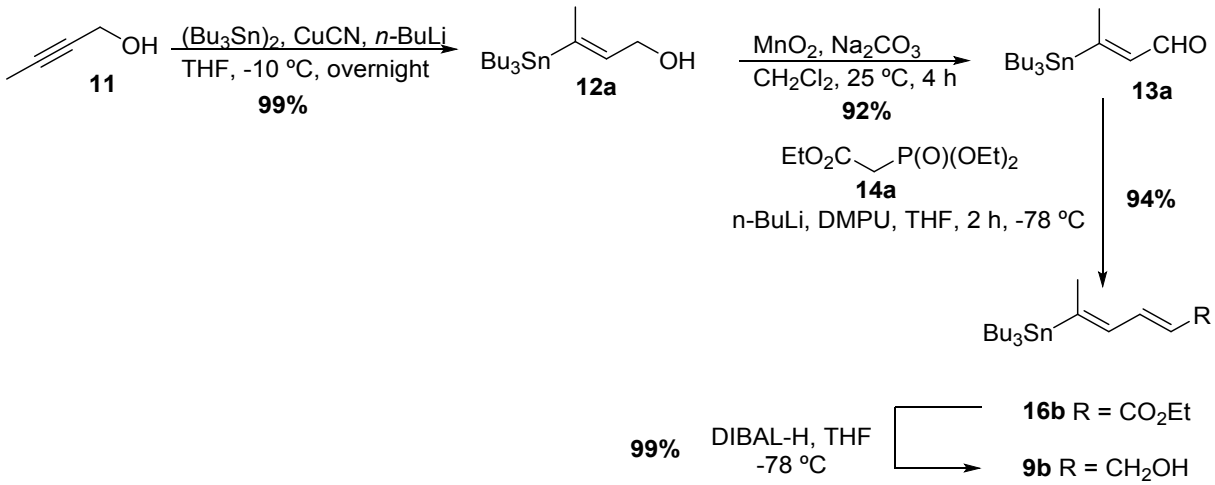


[1] Li, H. X., H.; Zhang, Z.; Xu, Y.; Lu, J.; Gao, L.; Song, Z. *Chem. Commun.* **2015**, *51*, 8484.

In contrast, δ-stannyldienyl esters afforded in high yields (50-80%) the corresponding methyl retinoates, as previously reported.[2]

Synthetic schemes and procedures for the preparation of known dienylstannanes and dienylsilanes

(2*E*,4*E*)-5-(Tributylstannyl)-hexa-2,4-dien-1-ol 9b.[3]



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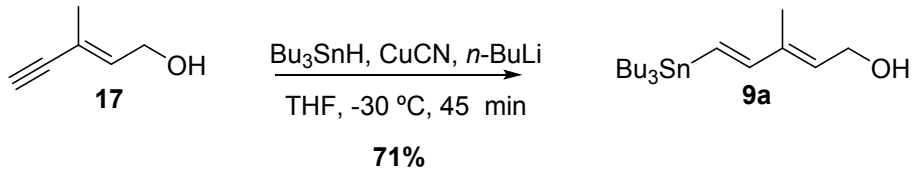
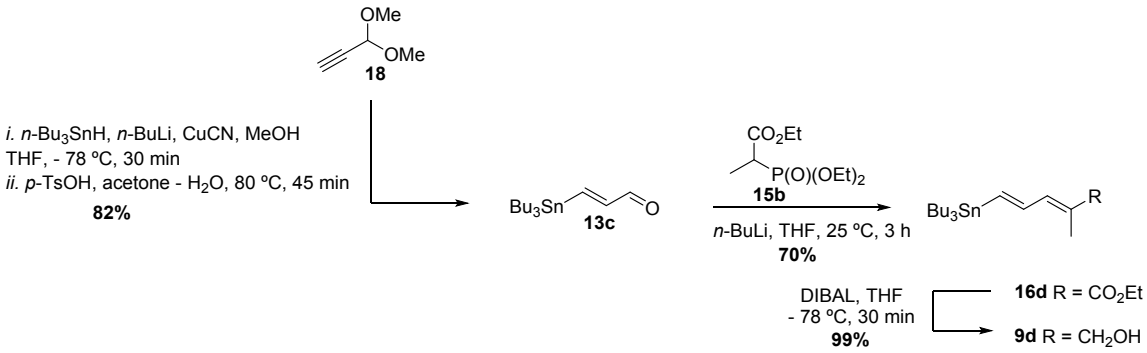
(2*E*,4*E*)-3-Methyl-5-(Tributylstanyl)-penta-2,4-dien-1-ol 9a.[4]

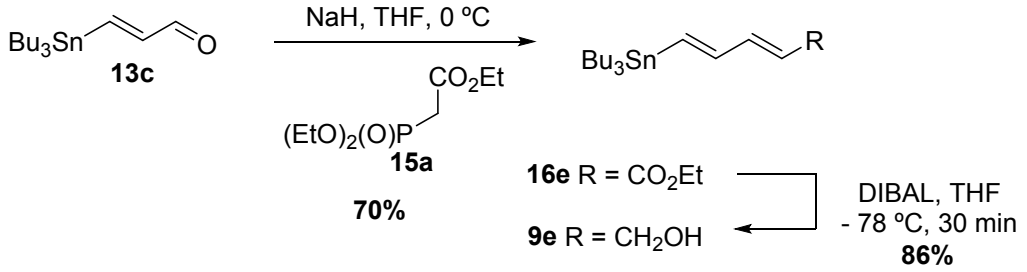


(2*E*,4*E*)-2-Methyl-5-(tributylstannyl)-penta-2,4-dien-1-ol 9d.[5,6]

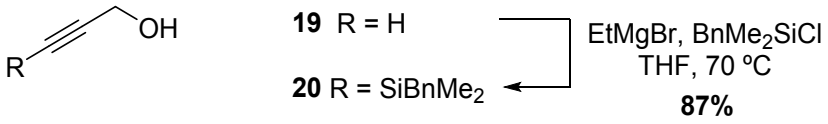
[2] Domínguez, B.; Iglesias, B.; de Lera, A. R. *Tetrahedron* **1999**, *55*, 15071.
[3] Otero, L.; Vaz, B.; Álvarez, R.; de Lera, A. R. *Chem. Commun,* **2013**, *49*, 5043.
[4] Betzer, J. F.; Delaloge, F.; Muller, B.; Pancrazi, A.; Prunet, J. *J. Org. Chem.* **1997**, *62*, 7768.
[5] Fontán, N.; Vaz, B.; Álvarez, R.; de Lera, A. R. *Chem. Commun.* **2013**, *49*, 2694.
[6] Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434.



(2*E*,4*E*)-5-(Tributylstannyl)-penta-2,4-dien-1-ol 9e.[7]



3-(Benzyldimethylsilyl)prop-2-yn-1-ol 20.

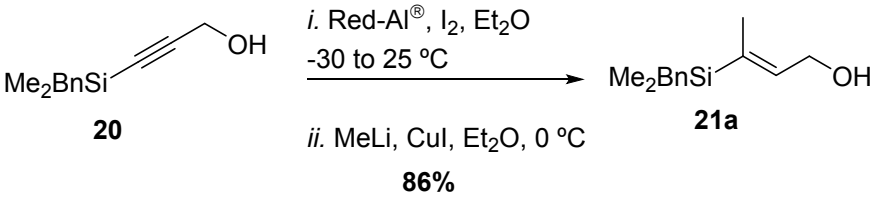


To a cooled (10 °C) solution of EtMgBr (29.9 mL, 1 M in THF, 29.94 mmol), a solution of prop-2-yn-1-ol **19** (0.62 g, 11.09 mmol) in THF (11.9 mL) was slowly added. After stirring overnight at 25 °C, the reaction was cooled down to 5 °C, $BnMe_2SiCl$ (5.9 mL, 29.94 mmol) was added and the solution was heated for 2 h at 70 °C. A 1.4 M aqueous solution of H_2SO_4 (38 mL) was added slowly without letting the temperature rise to higher than 40 °C. The mixture was extracted with Et_2O (3x) and the combined organic layers were washed with H_2O (2x) and dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by flash-column chromatography (silica gel, 70:30 hexane/EtOAc) to afford 1.98 g (87%) of a yellow oil, which was identified as 3-(benzyldimethylsilyl)prop-2-yn-1-ol **20**.[8] **^{1}H-NMR** (400.16 MHz, C_6D_6): δ 7.21-7.13 (m, 3H, ArH), 7.08 – 7.01 (m, 2H, ArH), 3.81 (d, J = 6.3 Hz, 2H, $2H_1$), 2.12 (s, 2H, $SiMe_2CH_2Ph$), 0.10 (s, 6H, $SiMe_2Bn$) ppm. **^{13}C-NMR** (100.63 MHz, C_6D_6): δ 139.1 (s), 128.7 (d, 2x), 128.6 (d, 2x), 124.9 (d), 106.4 (s), 88.6 (s), 51.2 (t), 26.3 (t), -2.1 (q, 2x) ppm. **IR** (NaCl): ν 3500 - 3100 (br, O-H), 2915 (m, C-H), 2854 (m, C-H), 2174 (w, C≡C), 1039 (s), 832 (s) cm^{-1}. **MS** (ESI$^+$-TOF): *m/z* (%) 205 ([M+H]$^+$, 74), 190

[7] Dias, L. C.; Jr. De Lucca, E. E. *J. Org. Chem.* **2017**, *82*, 3019.
[8] Gallenkamp, D.; Fürstner, A. *J. Am. Chem. Soc.* **2011**, *133*, 9232.

(17), 187 (74), 180 (14), 138 (100). **HRMS** (ESI^+): Calcd. for $C_{12}H_{17}OSi$ ($[M+H]^+$), 205.1043; found, 205.1045.

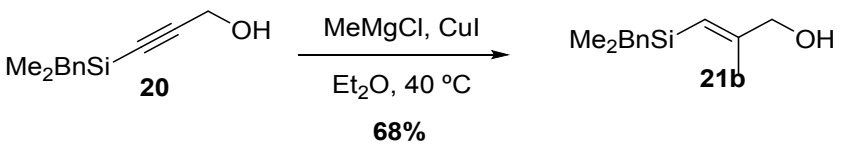
(*E*)-3-(Benzyldimethylsilyl)-3-methylprop-2-en-1-ol 21a.



To a solution of 3-(benzyldimethylsilyl)-prop-2-yn-1-ol **20** (0.2 g, 0.98 mmol) in Et_2O (0.52 mL), a solution of Red-Al® (0.35 mL, 1.25 mmol) in Et_2O (1.6 mL) was slowly added for 1h via addition funnel. Then, the mixture was cooled down to -30 °C and a solution of I_2 (0.5 g, 1.96 mmol) in THF (1 mL) was added. After stirring the resulting mixture for 30 min at 0 °C and for 2h at 25 °C, it was poured into a 10% aqueous solution of HCl and extracted with Et_2O (3x). The combined organic layers were washed with a saturated aqueous solution of $Na_2S_2O_3$ (3x), brine (3x) and dried (Na_2SO_4) and the solvent was removed to afford 0.294 g of a colorless oil which was used immediately without further purification.

To a cooled (-20 °C) suspension of CuI (0.841 g, 4.41 mmol) in Et_2O (1.18 mL), MeLi (5.52 mL, 1.6 M in Et_2O, 0.88 mmol) was added. After stirring for 1h at -20 °C, a solution of the residue obtained above (0.294 g, 0.88 mmol) in Et_2O (0.59 mL) was added and the mixture was stirred for 14 h at -20 °C and for 4.5 h at 0 °C. A saturated aqueous solution of NH_4Cl was added and the mixture was extracted with Et_2O (3x). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by flash-column chromatography (silica gel, 90:10 hexane/EtOAc) to afford 0.201 g (86%) of a colourless oil, which was identified as (*E*)-3-(benzyldimethylsilyl)-3-methylprop-2-en-1-ol **21a**.[9] **^{1}H-NMR** (400.16 MHz, C_6D_6): δ 7.30 – 7.22 (m, 2H, ArH), 7.18 – 7.08 (m, 1H, ArH), 7.08 – 7.02 (m, 2H, ArH), 5.95 (t, J = 5.5 Hz, 1H, H_2), 4.10 (d, J = 5.5 Hz, 2H, $2H_1$), 2.15 (s, 2H, $SiMe_2CH_2Ph$), 1.60 (s, 3H, C_3-CH_3), 0.12 (s, 6H, $SiMe_2Bn$) ppm. **^{13}C-NMR** (100.63 MHz, C_6D_6): δ 140.6 (d, 2x), 140.0 (s), 135.7 (s), 128.3 (d), 128.3 (d), 124.3 (d, 2x), 59.5 (t), 24.9 (t), 14.8 (q), -4.4 (q) ppm. **IR** (NaCl): ν 3500- 3100 (br, O-H), 2955 (m, C-H), 1599 (m), 1492 (m), 831 (s) cm^{-1}. **HRMS** (ESI^+): Calcd. for $C_{13}H_{21}OSi$ ($[M+H]^+$), 221.1356; found, 221.1364.

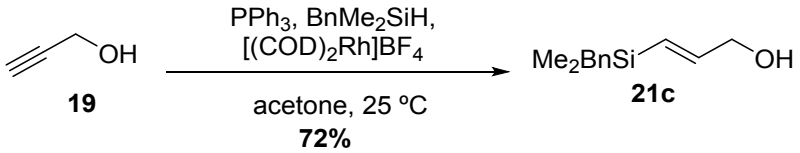
(*E*)-3-(Benzyldimethylsilyl)-2-methylprop-2-en-1-ol 21b.



[9] Anderl, F.; Grobl, S.; Wirtz, C.; Fürstner, A. *Angew. Chem. Int. Ed.* **2018**, *57*, 10712.

To a solution of 3-(benzyldimethylsilyl)-prop-2-yn-1-ol **20** (0.29 g, 1.46 mmol) in Et_2O (3.8 mL), CuI (0.03 g, 0.15 mmol) and MeMgCl (3.3 mL, 3 M in THF, 9.88 mmol) were sequentially added. After stirring at 40 °C for 21 h, the reaction was cooled down to 0 °C and an aqueous solution of NH_4Cl/NH_4OH (3.13 mL, 9:1 v/v) was slowly added. The mixture was extracted with Et_2O (3x) and dried (Na_2SO_4) and the solvent was evaporated to afford 0.22 g (68%) of a yellow oil, which was identified as (*E*)-3-(benzyldimethylsilyl)-2-methylprop-2-en-1-ol **21b**.[10] **^{1}H-NMR** (400.16 MHz, C_6D_6): δ 7.20 - 7.12 (m, 3H, ArH), 7.09 - 6.95 (m, 2H, ArH), 5.53 (s, 1H, H_3), 3.67 (s, 2H, $2H_1$), 2.12 (s, 2H, $SiMe_2CH_2Ph$), 1.47 (s, 3H, C_2-CH_3), 0.11 (s, 6H, $SiMe_2Bn$) ppm. **^{13}C-NMR** (100.63 MHz, C_6D_6): δ 155.1 (s), 140.4 (s), 128.6 (d, 2x), 128.5 (d, 2x), 124.5 (d), 118.9 (d), 68.7 (t), 26.9 (t), 18.6 (q), -1.7 (q, 2x) ppm. **UV** (MeOH): λ_{max} 218, 210 nm. **IR** (NaCl): ν 3500 - 3100 (br, O-H), 2957 (m, C-H), 2925 (m, C-H), 1460 (m), 961 (m) cm^{-1}. **MS** (ESI$^+$-TOF): *m/z* (%) 221 ([M+H]$^+$, 64), 204 (18), 203 (100), 190 (51). **HRMS** (ESI$^+$): Calcd. for $C_{13}H_{21}OSi$ ([M+H]$^+$), 221.1356; found, 221.1360.

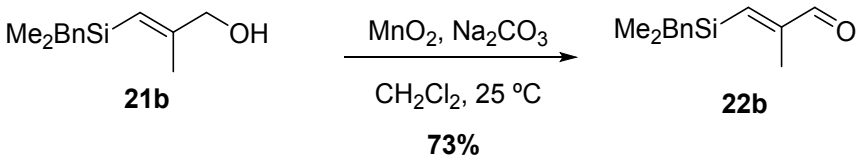
3-(Benzyldimethylsilyl)prop-2-en-1-ol 21c.



To a solution of bis(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate (11 mg, 0.03 mmol) and PPh_3 (14 mg, 0.05 mmol) in acetone (17.3 mL), propargylic alcohol **19** (0.3 g, 5.35 mmol) and benzyldimethylsilane (0.80 g, 5.35 mmol) were sequentially added and the reaction mixture was stirred for 15h at 25 °C. The solvent was evaporated and the residue was purified by flash-column chromatography (silica gel, 95:5 to 90:10 hexane/EtOAc) to afford 0.79 g (72%) of a yellow oil, which was identified as 3-(benzyldimethylsilyl)prop-2-en-1-ol **21c**.[11] **^{1}H-NMR** (400.13 MHz, C_6D_6): δ 7.16-7.13 (m, 2H, ArH), 7.05 – 6.99 (m, 1H, ArH), 6.99 – 6.95 (m, 2H, ArH), 5.96 (dt, *J* = 18.8, 3.9 Hz, 1H, H_2), 5.82 (dd, *J* = 18.9, 1.7 Hz, 1H, H_3), 3.81 (br s, 2H, $2H_1$), 2.04 (s, 2H, $SiMe_2CH_2Ph$), 0.02 (s, 6H, $SiMe_2Bn$) ppm. **^{13}C-NMR** (100.63 MHz, C_6D_6): δ 147.1 (d), 140.1 (s), 128.6 (d, 2x), 128.5 (d, 2x), 126.6 (d), 124.5 (d), 65.1 (t), 26.2 (t), -3.2 (q, 2x) ppm. **IR** (NaCl): ν 3500 - 3100 (br, O-H), 2955 (m, C-H), 1490 (m, C-H), 837 (m) cm^{-1}. **MS** (ESI$^+$-TOF): *m/z* (%) 208 (3), 207 ([M+H]$^+$), 10), 190 (13), 189 (100). **HRMS** (ESI$^+$): Calcd. for $C_{12}H_{19}OSi$ ([M+H]$^+$), 207.1198; found, 207.1199.

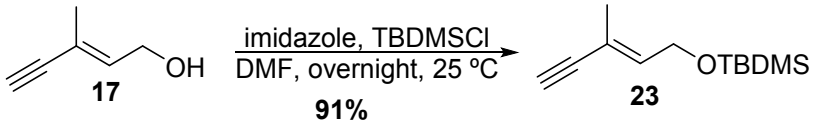
(*E*)-3-(Benzyldimethylsilyl)-2-methylacrylaldehyde 22b.

[10] Spino, C.; Grobdout, C. *J. Am. Chem. Soc.* **2003**, *125*, 12106.
[11] Takeuchi, R.; Nitta, S.; Watamabe, D. *J. Org. Chem.* **1995,** *60*, 3045.



General procedure for the oxidation of alcohols with MnO_2: To a cooled (0 °C) solution of (*E*)-3-(benzyldimethylsilyl)-2-methylprop-2-en-1-ol **21b** (0.22 g, 0.98 mmol) in CH_2Cl_2 (39 mL), MnO_2 (1.53 g, 17.54 mmol) and Na_2CO_3 (1.87 g, 17.64 mmol) were added and the reaction was stirred at 25 °C for 1.5 h. The mixture was filtered through Celite® and washed with CH_2Cl_2, and the solvent was evaporated to afford 0.16 g (73%) of a yellow oil, which was identified as (*E*)-3-(benzyldimethylsilyl)-2-methylacrylaldehyde **22b**.[12] **^{1}H-NMR** (400.16 MHz, C_6D_6): δ 9.25 (s, 1H, H_1), 7.12 (t, J = 7.6 Hz, 2H, ArH), 7.04 - 6.94 (m, 1H, ArH), 6.85 (d, J = 7.2 Hz, 2H, ArH), 6.15 (s, 1H, H_3), 1.94 (s, 2H, $SiMe_2CH_2Ph$), 1.68 (s, 3H, C_2-CH_3), -0.05 (s, 6H, $SiMe_2Bn$) ppm. **^{13}C-NMR** (100.63 MHz, C_6D_6): δ 194.6 (d), 153.6 (s), 149.3 (d), 139.1 (s), 128.7 (d, 2x), 128.4 (d, 2x), 124.9 (d), 25.6 (t), 12.8 (q), -2.8 (q, 2x) ppm. **UV** (MeOH): λ_{max} 220 nm. **IR** (NaCl): ν 3024 (w, C-H), 2956 (w, C-H), 2797 (w, C-H), 1693 (s, C=O), 845 (s) cm^{-1}. **HRMS** (ESI$^+$): Calcd. for $C_{13}H_{19}OSi$ ([M+H]$^+$), 219.1199; found, 219.1200.

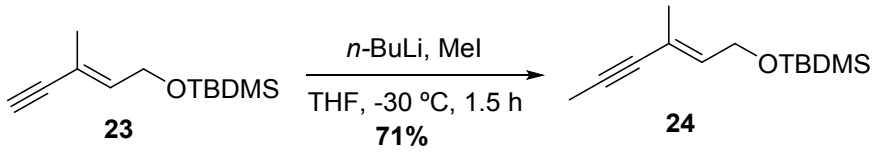
(*E*)-*tert*-Butyldimethyl-((3-methylpent-2-en-4-yn-1-yl)oxy)silane 23.



To a solution of imidazole (1.13 g, 16.645 mmol) in DMF (9 mL), a solution of (*E*)-3-methylpent-2-en-4-yn-1-ol **17** (1.00 g, 10.403 mmol) in DMF (9 mL) and then a solution of TBDMSCl (2.04 g, 13.53 mmol) in DMF (9 mL) were sequentially added. After stirring the resulting mixture overnight, water was slowly added and the reaction mixture was extracted with Et_2O (3x). The combined organic layers were dried and the solvent was removed. The residue was purified by flash-column chromatography (silica gel, 97:3 hexane/EtOAc) to afford 1.9 g (91%) of a yellow oil, which was identified as (*E*)-*tert*-butyldimethyl((3-methylpent-2-en-4-yn-1-yl)oxy)silane **23**.[13] **^{1}H-NMR** (400.16 MHz, $CDCl_3$): δ 6.01 (t, J = 6.0 Hz, 1H, H_2), 4.25 (d, J = 6.8 Hz, 2H, $2H_1$), 2.79 (s, 1H, H_5), 1.80 (s, 3H, C_3-CH_3), 0.90 (s, 9H, $Si(Me_2)^tBu$), 0.07 (s, 6H, $Si(Me_2)^tBu$) ppm. **^{13}C-NMR** (101.63 MHz, $CDCl_3$): δ 138.7 (d), 117.8 (s), 86.2 (s), 74.7 (d), 60.0 (t), 26.0 (q, 3x), 18.5 (s), 17.5 (q), -5.1 (q, 2x) ppm. **IR (NaCl):** ν 2933 (s, C-H), 2890 (s, C-H), 2859 (s, C-H), 1563 (m), 1219 (s), 772 (s) cm^{-1}. **MS** (ESI$^+$-TOF): *m/z* (%) 211 (2, [M+H]$^+$), 190 (3), 156 (100), 145 (60). **HRMS (ESI$^+$):** Calcd. for $C_{12}H_{23}OSi$ ([M+H]$^+$), 211.1513; found, 211.1526.

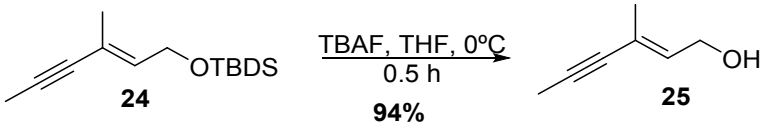
[12] Zhang, Y.; Panek, J. S. Z. *Org. Lett*. **2007**, *9*, 3142.
[13] Betzer, J. F.; Francette,F.; Muller, B.; Pancrazi, A.; Prunet, J. *J. Org. Chem.* **1997,** *62*, 7768.

(*E*)-*tert*-Butyldimethyl((3-methylhex-2-en-4-yn-1-yl)oxy)silane 24.



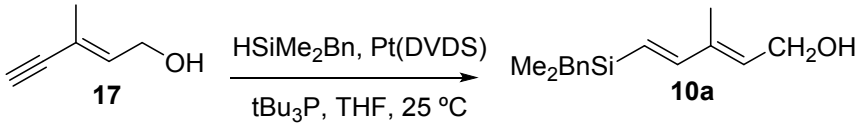
To a cooled (-30 °C) solution of (*E*)-*tert*-butyldimethyl((3-methylpent-2-en-4-yn-1-yl)oxyl)silane **23** (1.48 g, 7.04 mmol) in THF (70.3 mL), *n*-BuLi (3.12 mL, 2.48 M in hexanes, 7.74 mmol) was added and the mixture was stirred at this temperature for 30 min. MeI (2.19 mL, 35.17 mmol) was then added and the temperature was allowed to rise to 25 °C for 45 min. A saturated aqueous solution of NH_4Cl was added and the mixture was extracted with Et_2O (3x). The combined organic layers were dried and the solvent was removed. After purification by flash-column chromatography (silica gel, 95:5 hexane/EtOAc), 1.18 g (71%) of a yellow oil, which was identified as (*E*)-*tert*-butyldimethyl((3-methylhex-2-en-4-yn-1-yl)oxy)silane **24**, were obtained.[11] **^{1}H-NMR** (400.16 MHz, $CDCl_3$): δ 5.82 (t, J = 6.7 Hz, 1H, H_2), 4.22 (d, J = 6.4 Hz, 2H, $2H_1$), 1.93 (s, 3H, C_5-CH_3), 1.76 (s, 3H, C_3-CH_3), 0.89 (s, 9H, $Si(Me_2)^tBu$), 0.06 (s, 6H, $Si(Me_2)^tBu$) ppm. **^{13}C-NMR** (101.63 MHz, $CDCl_3$): δ 135.5 (d), 119.3 (s), 83.3 (s), 82.3 (s), 60.1 (t), 26.1 (q, 3x), 18.5 (s), 18.0 (q), 4.3 (q), -5.0 (q, 2x) ppm. **IR** (NaCl): ν 2955 (m, C-H), 2360 (w, C≡C), 1706 (s), 1271 (m), 1208 (m), 837 (s) cm^{-1}. **MS** (ESI$^+$-TOF): *m/z* (%) 225 ([M+H]$^+$, 5), 215 (3), 203 (3), 185 (7), 174 (3), 156 (100). **HRMS** (ESI$^+$): Calcd. for $C_{13}H_{24}OSi$ ([M+H]$^+$), 225.1669; found 225.1663.

(*E*)-Methylhex-2-en-4-yn-1-ol 25.



To a cooled (0 °C) solution of (*E*)-*tert*-butyldimethyl((3-methylhex-2-en-4-yn-1-yl)oxyl)silane **24** (1.1 g, 4.01 mmol) in THF (80.5 mL), TBAF (7.4 mL, 1 M in THF, 7.4 mmol) was added and the resulting mixture was stirred for 0.5 h at 25 °C. An aqueous solution of $NaHCO_3$ was added and the resulting mixture was extracted with Et_2O (3x). The combined organic layers were washed with brine (3x), dried (Na_2SO_4) and the solvent was evaporated. After purification by column chromatography (silica gel, 90:10 hexane/EtOAc), 0.505 g (94%) of a yellow oil, which was identified as (*E*)-methylhex-2-en-4-yn-1-ol **25**, were isolated.[11] **^{1}H-NMR** (400.16 MHz, $CDCl_3$): δ 5.90 (t, J = 7.5 Hz, 1H, H_2), 4.20 (m, 2H, $2H_1$), 1.94 (s, 3H, C_3-CH_3), 1.80 (s, C_5-CH_3) ppm. **^{13}C-NMR** (101.63 MHz, $CDCl_3$): δ 134.1 (d), 121.3 (s), 84.1 (s), 82.1 (s), 59.0 (t), 17.8 (q), 4.2 (q) ppm. **IR** (NaCl): ν 3362 (br, O-H), 2913 (m, C-H), 1633 (m, C≡H), 1435 (m), 1011 (m), 665 (m) cm^{-1}. **HRMS** (ESI$^+$): Calcd. for $C_7H_{10}NaO$ ([M+Na]$^+$), 133.0623; found, 133.0621.

(2*E*,4*E*)-5-(Benzyldimethylsilyl)-3-methylpenta-2,4-dien-1-ol 10a.

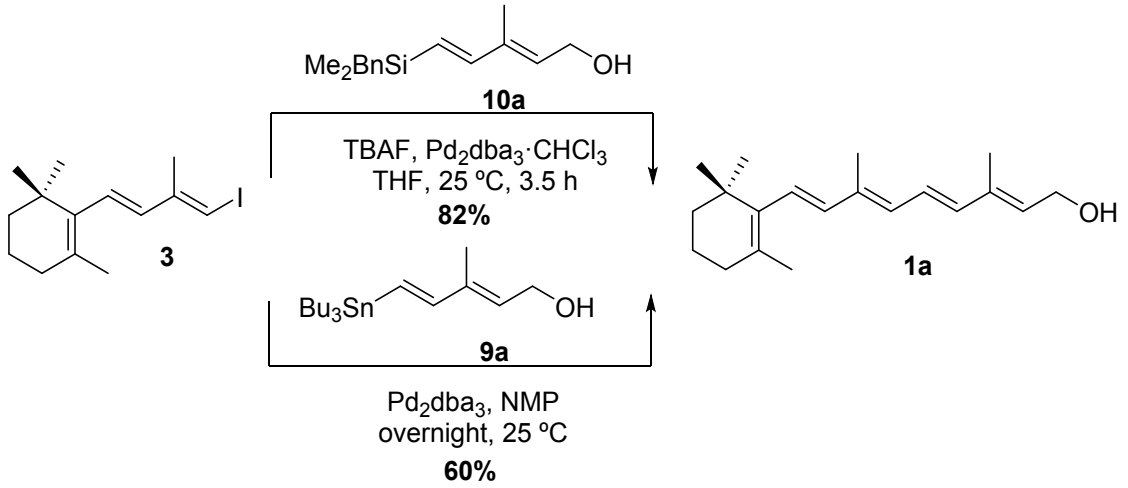


69%

To a degassed solution of Pt(DVDS) (0.92 mL, 2% in xylene, 0.04 mmol) and $^{t}Bu_3P$ (0.04 mL, 1M in toluene, 0.04 mmol) in THF (25 mL), $HSiMe_2Bn$ (3.3 mL, 20.6 mmol) was added. After stirring for 30 min at 25 °C, a solution of (*E*)-3-methylpent-2-en-4-yn-1-ol **17** (0.79 g, 8.26 mmol) in THF (25 mL) was added and the reaction mixture was stirred at 25 °C for 1.5 h. The solvent was evaporated and the residue was purified by flash-column chromatography (silica gel, 80:20 hexane/EtOAc) to afford 1.40 g (69%) of a yellow oil, which was identified as (2*E*,4*E*)-5-(benzyldimethylsilyl)-3-methylpenta-2,4-dien-1-ol **10a**.[14] **^{1}H-NMR** (400.16 MHz, C_6D_6): δ 7.20 - 7.14 (m, 2H, ArH), 7.08 - 6.94 (m, 3H, ArH), 6.60 (d, *J* = 19.0 Hz, 1H, H_4), 5.82 (d, *J* = 19.0 Hz, 1H, H_5), 5.58 (t, *J* = 6.5 Hz, 1H, H_2), 3.97 (d, *J* = 6.5 Hz, 2H, $2H_1$), 2.09 (s, 2H, $SiMe_2CH_2Ph$), 1.57 (s, 3H, C_3-CH_3), 0.08 (s, 6H, $SiMe_2Bn$) ppm. **^{13}C-NMR** (100.63 MHz, C_6D_6): δ 149.5 (d), 140.1 (s), 136.5 (s), 133.3 (d), 128.6 (d, 2x), 128.5 (d, 2x), 125.7 (d), 124.5 (d), 59.3 (t), 26.4 (t), 12.1 (q), -3.1 (q, 2x) ppm. **UV** (MeOH): λ_{max} 243 nm. **IR** (NaCl): ν 3500- 3100 (br, O-H), 3023 (m, C-H), 2954 (m, C-H), 1578 (m), 1492 (m), 1246 (m), 1152 (m) cm^{-1}. **HRMS** (ESI^+): Calcd. for $C_{15}H_{23}OSi$ ($[M+H]^+$), 247.1513; found, 247.1512.

[14] Bergueiro, J.; Montenegro, J.; F.; Saá, C.; López, S. *Chem. Eur. J.* **2012**, *18*, 14100.

All-*trans*-retinol 1a.



Spectroscopic data for all-*trans*-retinol **1a**.[13] **^{1}H-NMR** (400.16 MHz, $(CD_3)_2CO$): δ 6.66 (dd, *J* = 15.2, 11.3 Hz, 1H, H_{11}), 6.34 (d, *J* = 15.3 Hz, 1H, H_{12}), 6.27 – 6.08 (m, 3H, $H_7 + H_8 + H_{10}$), 5.70 (t, *J* = 6.5 Hz, 1H, H_{14}), 4.25 (d, *J* = 6.5 Hz, 2H, $2H_{15}$), 2.04 (t, *J* = 6.6 Hz, 2H, $2H_4$), 1.98 (s, 3H, C_{13}-CH_3), 1.84 (s, 3H, C_9-CH_3), 1.72 (s, 3H, C_5-CH_3), 1.68 – 1.59 (m, 2H, $2H_3$), 1.53 – 1.44 (m, 2H, $2H_2$), 1.05 (s, 6H, C_1-$(CH_3)_2$) ppm. **^{13}C-NMR** (101.63 MHz, $(CD_3)_2CO$): δ 139.0 (d), 138.8 (s), 138.2 (d), 136.1 (s), 135.7 (s), 133.8 (d), 131.7 (d), 129.6 (s), 127.0 (d), 125.2 (d), 59.5 (t), 40.5 (t), 35.0 (s), 33.7 (t), 29.4 (q, 2x), 22.1 (q), 20.1 (t), 12.8 (q) ppm. **UV** (MeOH): λ_{max} (ε) 378 (14 800) nm. **IR** (NaCl): ν 3500 - 3100 (br, O-H), 2925 (m, C-H), 2863 (m, C-H), 1454 (m), 967 (m) cm^{-1}. **HRMS** (ESI$^+$): Calcd. for $C_{20}H_{30}O$ ($[M+H]^+$), 286.2304; found, 286.2305.

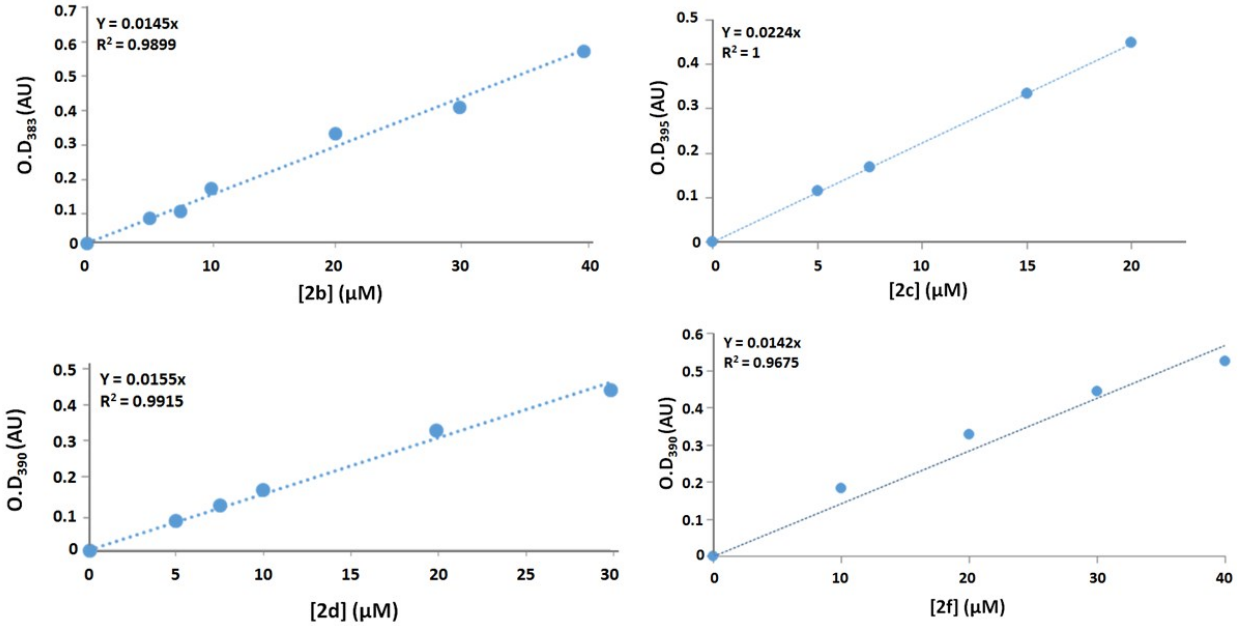
3. Expression and purification of AKR1B enzymes

AKR1B1 and AKR1B10 enzymes were expressed and purified from pET-15b expression vector. The pET-15b constructs allow the expression of proteins with an N-terminal fused histidine tag under the control of phage T7 RNA polymerase promoter and lac operon. For protein expression, transformed E. coli BL21(DE3) pLysS strains were grown in 1L of 2xYT medium in the presence of 33 μg/mL ampicillin and 50 μg/mL chloramphenicol, and cells were incubated at 37ºC until O.D.595 = 0.6 was reached. Protein expression was then induced by the addition of 1 mM IPTG and cells were grown overnight at 22ºC. AKR1B enzymes were purified as described previously for AKR1B10. [15]

4. HPLC enzymatic activity assay

[15] Gallego, O.; Belyaeva, Olga V.; Porté, S.; Ruiz, F. X.; Stetsenko, Anton V.; Shabrova, Elena V.; Kostereva, Natalia V.; Farrés, J.; Parés, X.; Kedishvili, Natalia Y. *Biochem. J.* **2006**, *399*, 101.

Activity assays with the C11 to C14-methyl shifted retinal analogues were carried out using an HPLC-based methodology.[17] Briefly, the stock solutions of substrates prepared in ethanol were solubilized using glass tubes by a 10-min sonication at molar ratio 1:1 with fatty acid-free bovine serum albumin in 100 mM potassium chloride, pH 7.4.[17] The actual concentration of solubilized compound was determined based on the corresponding molar absorption coefficient determined in Figure 1: ε_{383} = 14 500 $M^{-1}\cdot cm^{-1}$ for **2b**, ε_{395} = 22 400 $M^{-1}\cdot cm^{-1}$ for **2c**, ε_{390} = 15 500 $M^{-1}\cdot cm^{-1}$ for **2d** and ε_{390} = 14 200 $M^{-1}\cdot cm^{-1}$ for **2f**. The enzymatic reaction was carried out for 15 min at 37 °C in a final volume of 0.5 mL. To measure the steady-state enzymatic activity, the concentration of enzyme was kept from 25- to 100-fold lower than that of the substrate for all the enzymatic assays. The reactions were stopped by the addition of 1 mL of cold methanol and, after two rounds of extraction with hexane and the subsequent evaporation of the organic phase under a N_2 stream, C11 to C14-methyl shifted vitamin A analogues were analysed by HPLC. Briefly, these compounds were dissolved in 200 µL of hexane and injected on a Nova Pak Silica column (4 µm, 3.9 x 150 mm, Waters) as previously described.[16] Quantification of C11 to C14-methyl shifted vitamin A analogues (aldehyde substrates **2b, 2c, 2d** and **2f,** and alcohol products **1b, 1c, 1d** and **1f**) was performed by interpolation of HPLC peak areas into a calibration curve of known compound concentrations. The specific activity of AKR1B1 and AKR1B10 enzymes was obtained from the product appearance while the substrate conversion was controlled to assure the optimal enzymatic conditions regarding to initial linear rate (V_0). The kinetic constants were calculated using the non-linear regression program GraFit 5.0 (Erithacus software) and expressed as the mean ± standard error from three independent determinations.

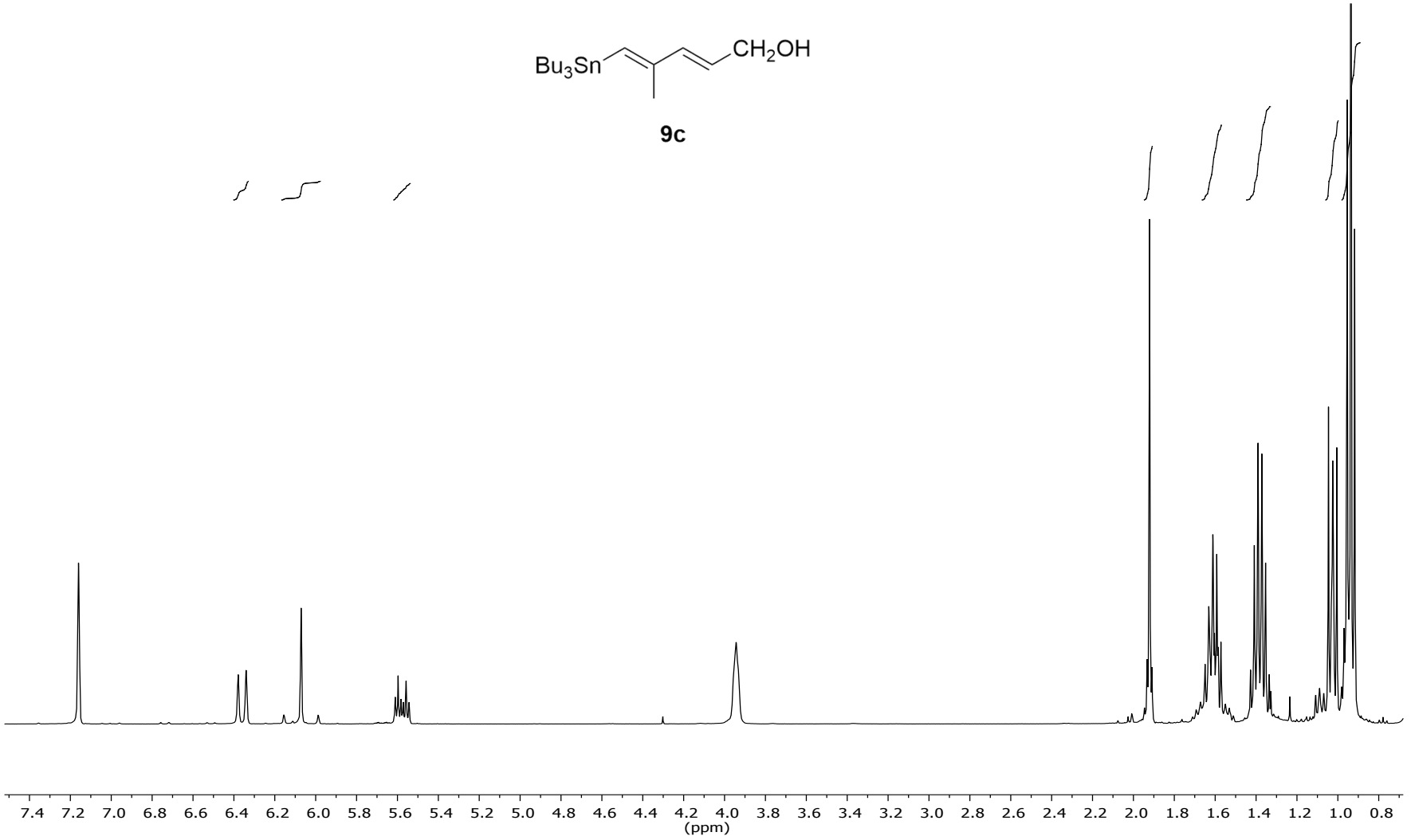


[16] Domínguez, M.; Pequerul, R.; Alvarez, R.; Giménez-Dejoz, J.; Birta, E.; Porté, S.; Rühl, R.; Parés, X.; Farrés, J.; de Lera, A. R. *Tetrahedron* **2018**, *74*, 2567.

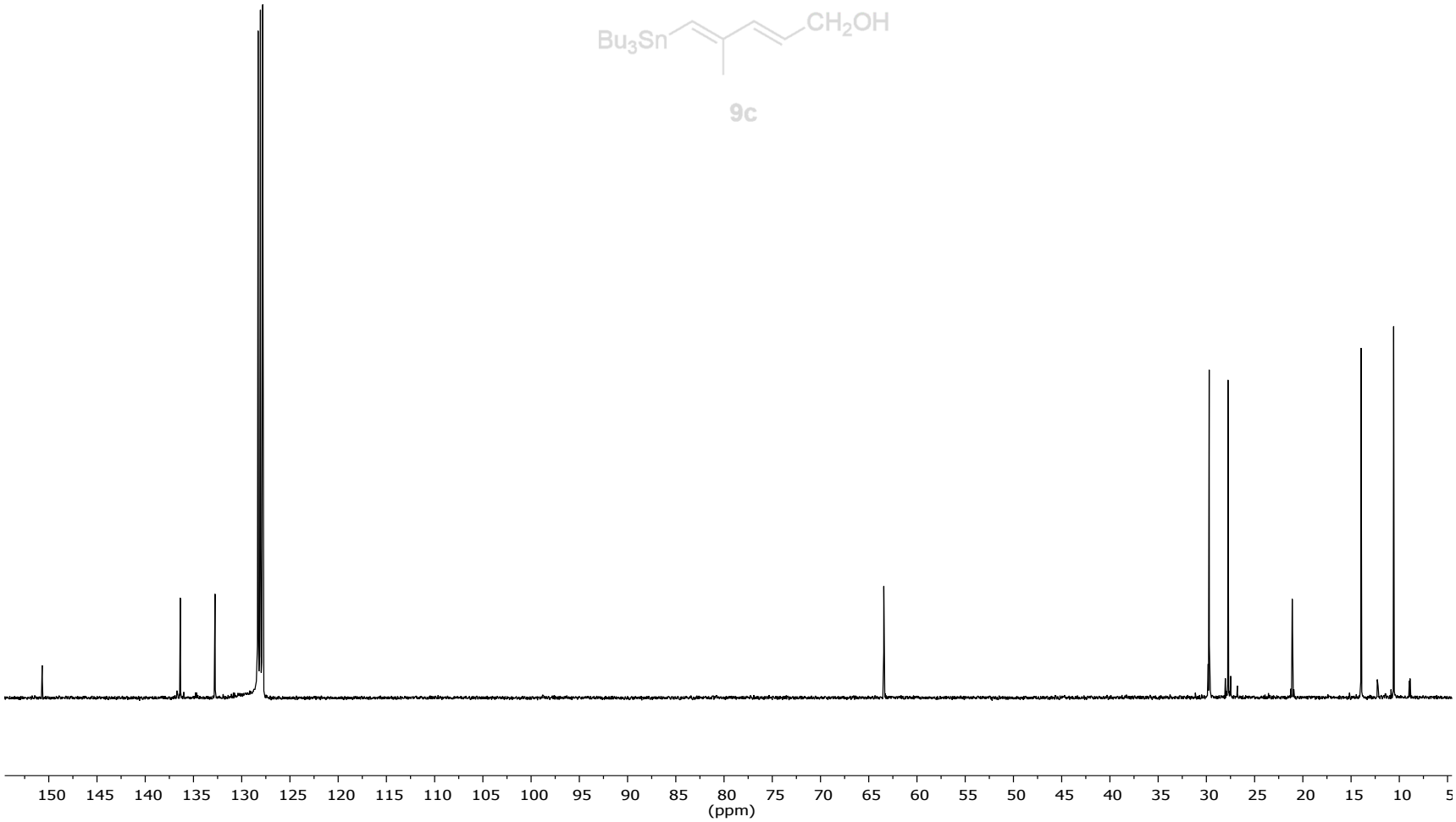
Figure 1. Linear regression plots to determine the molar extinction coefficients for compounds **2b**, **2c**, **2d** and **2f**. The compound concentrations tested ranged 5 – 40 μM.

5. NMR Spectra

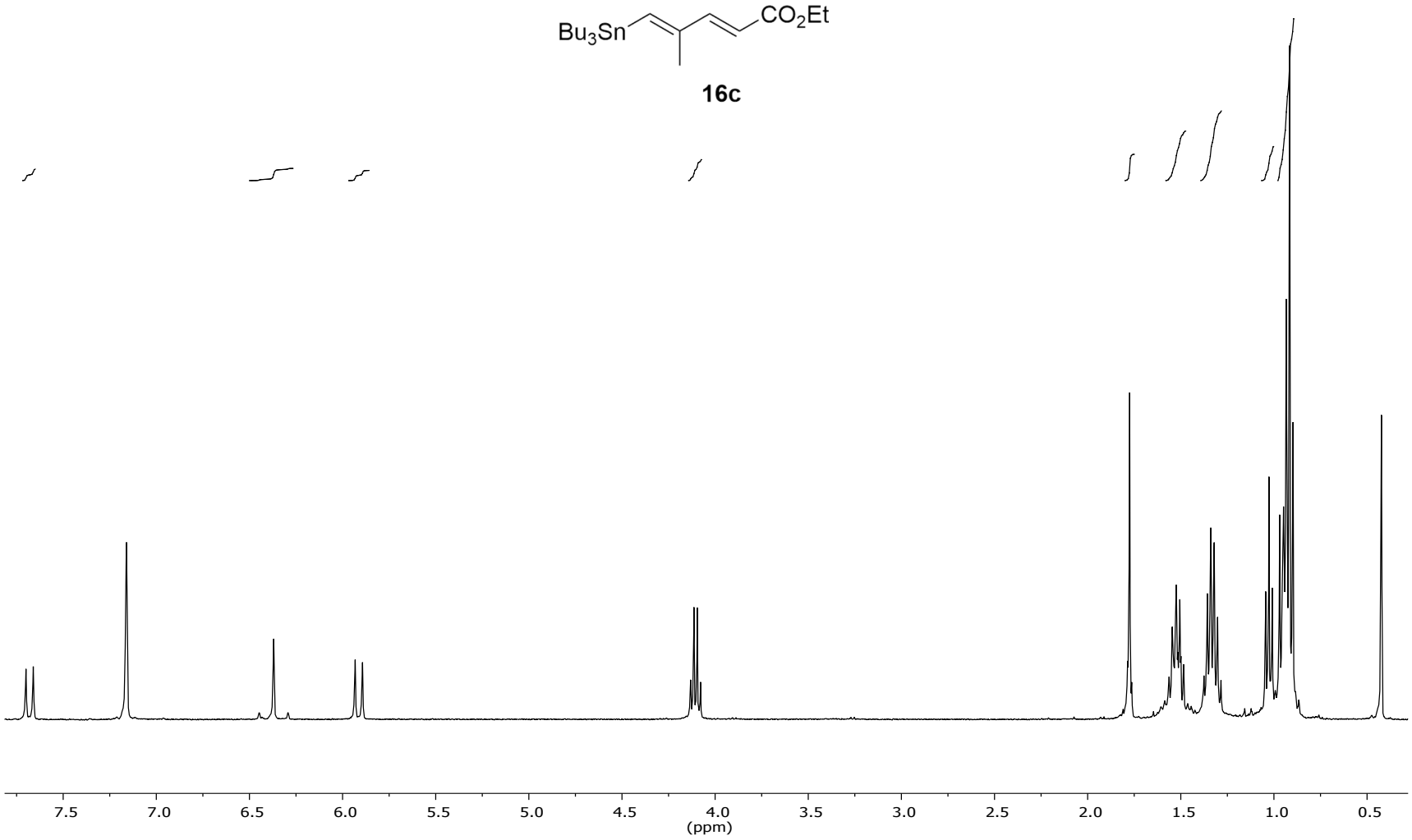
^{1}H-NMR (400.16 MHz, C_6D_6) of 9c



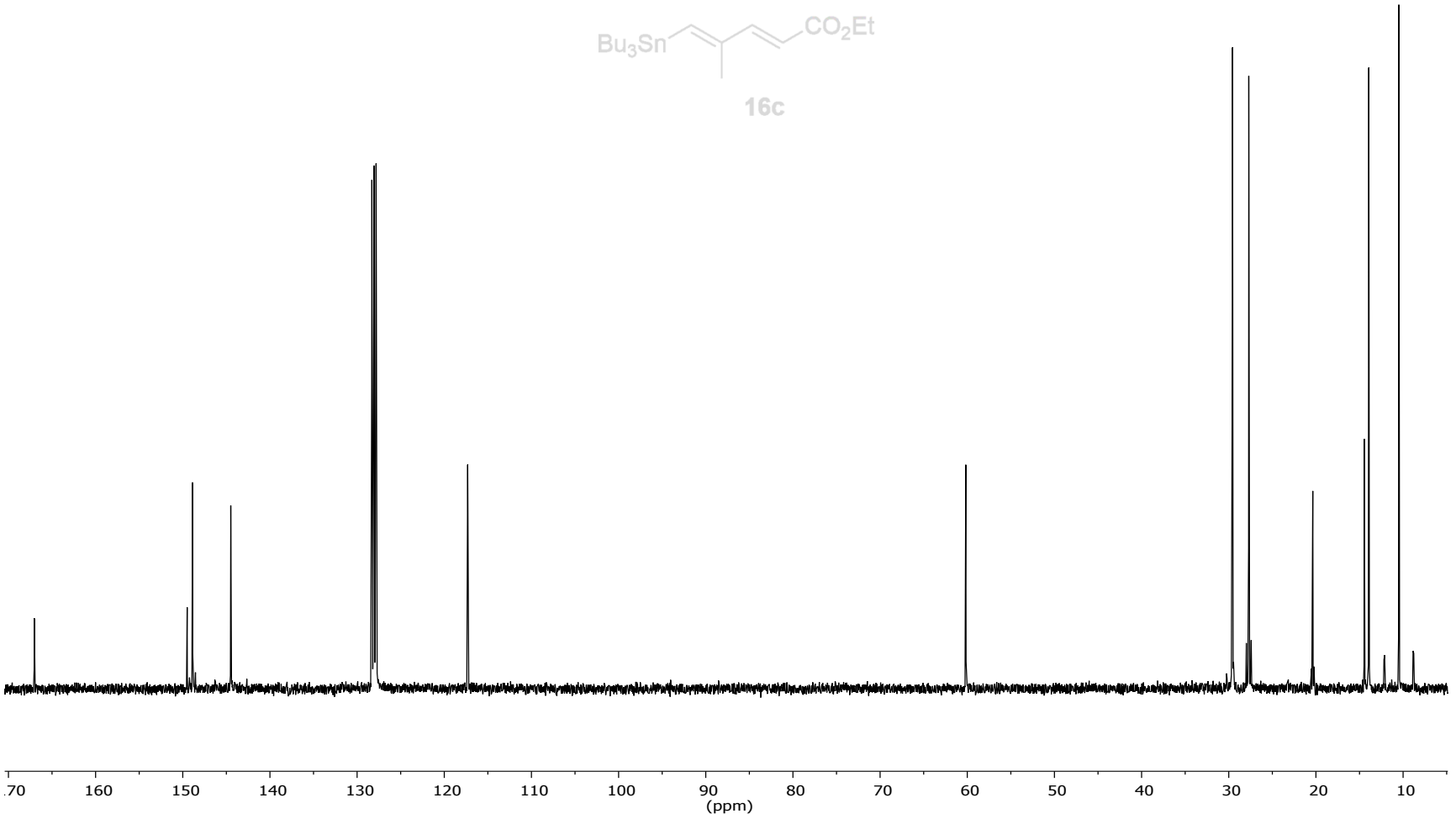
^{13}C-NMR (100.63 MHz, C_6D_6) of 9c



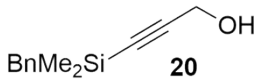
^{1}H-NMR (400.16 MHz, C_6D_6) of 16c



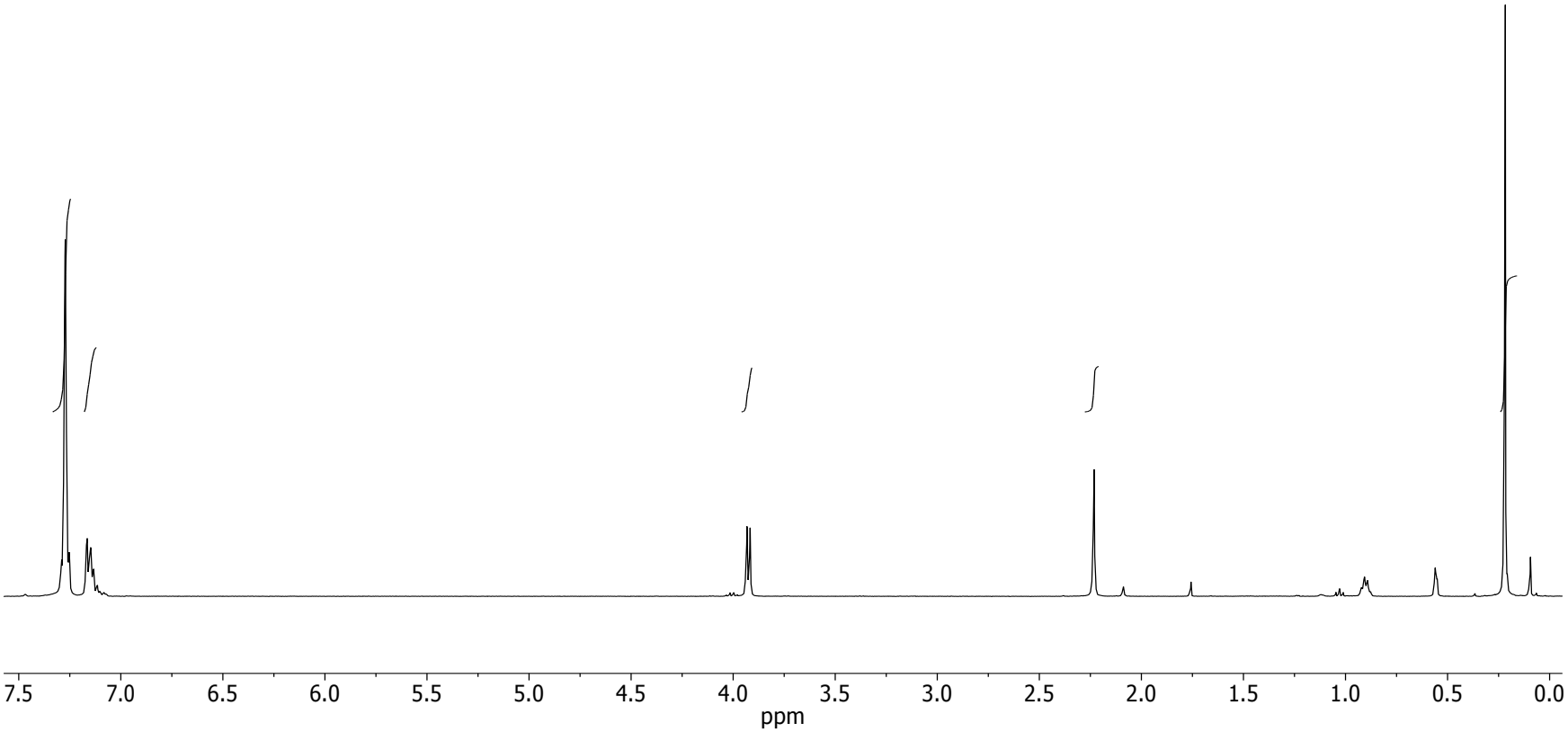
^{13}C-NMR (100.63 MHz, C_6D_6) of 16c



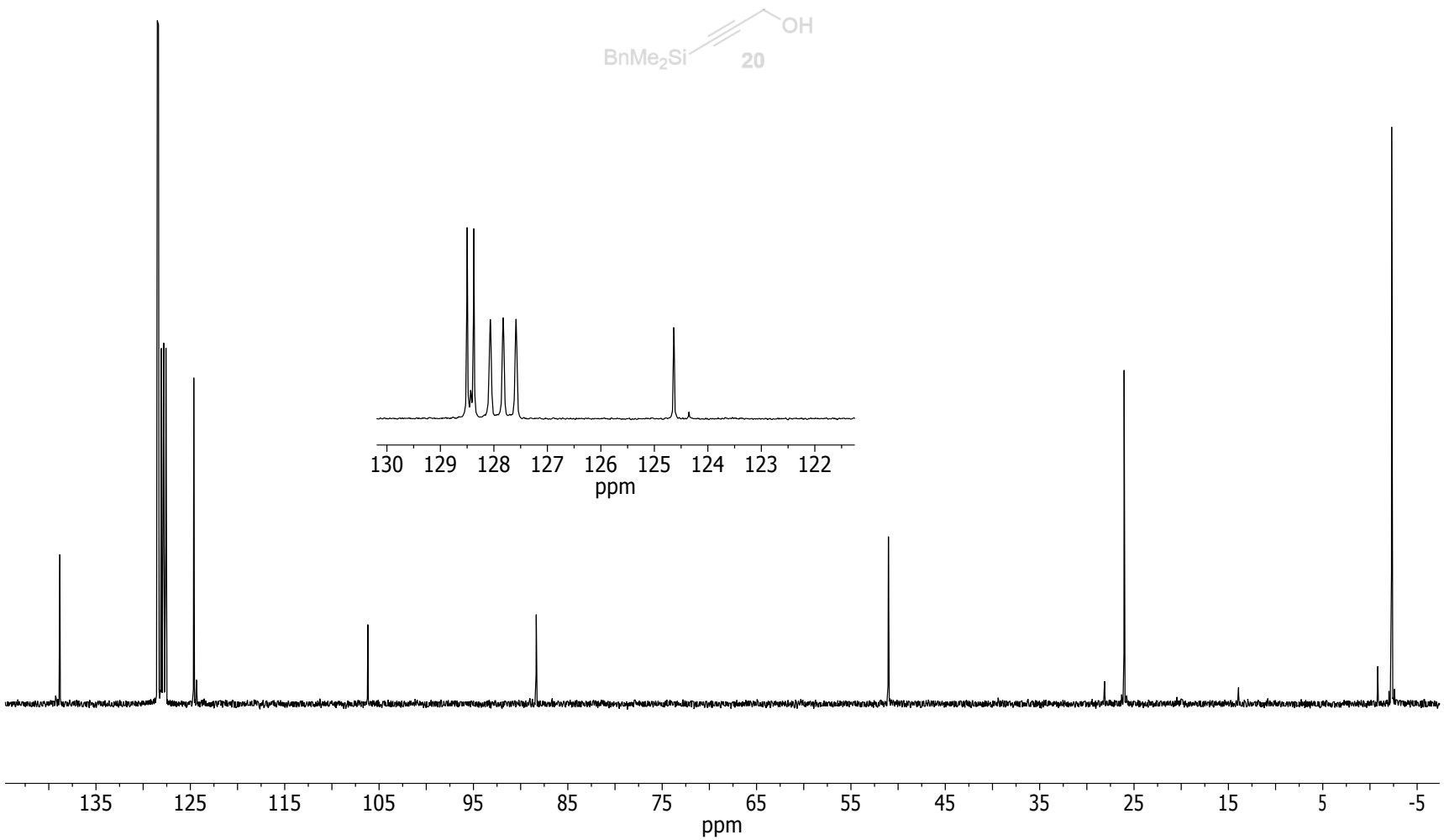
^{1}H-NMR (400.16 MHz, C_6D_6) of 20



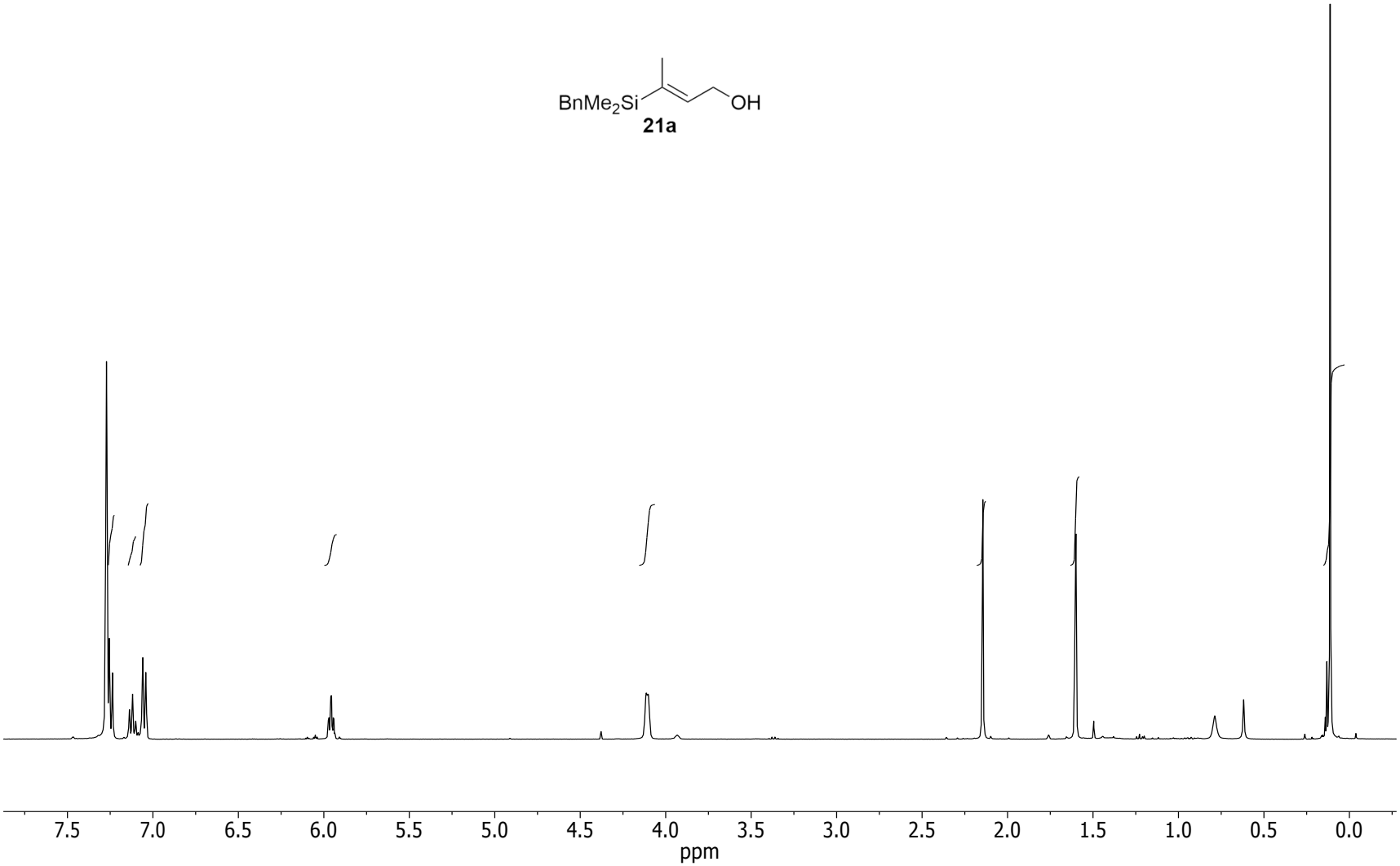
20



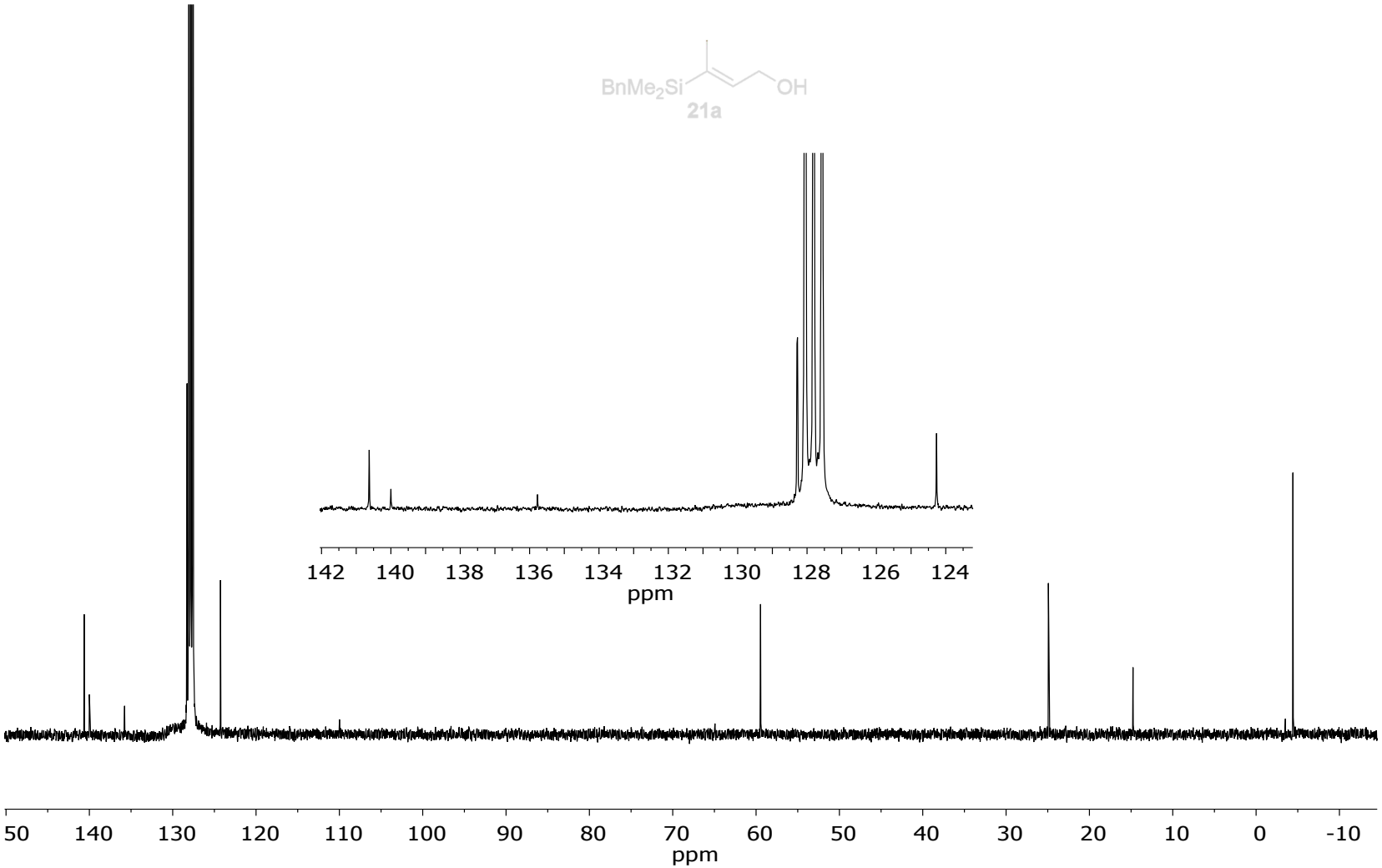
^{13}C-NMR (100.63 MHz, C_6D_6) of 20



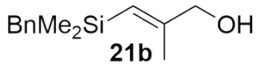
^{1}H-NMR (400.16 MHz, C_6D_6) of 21a



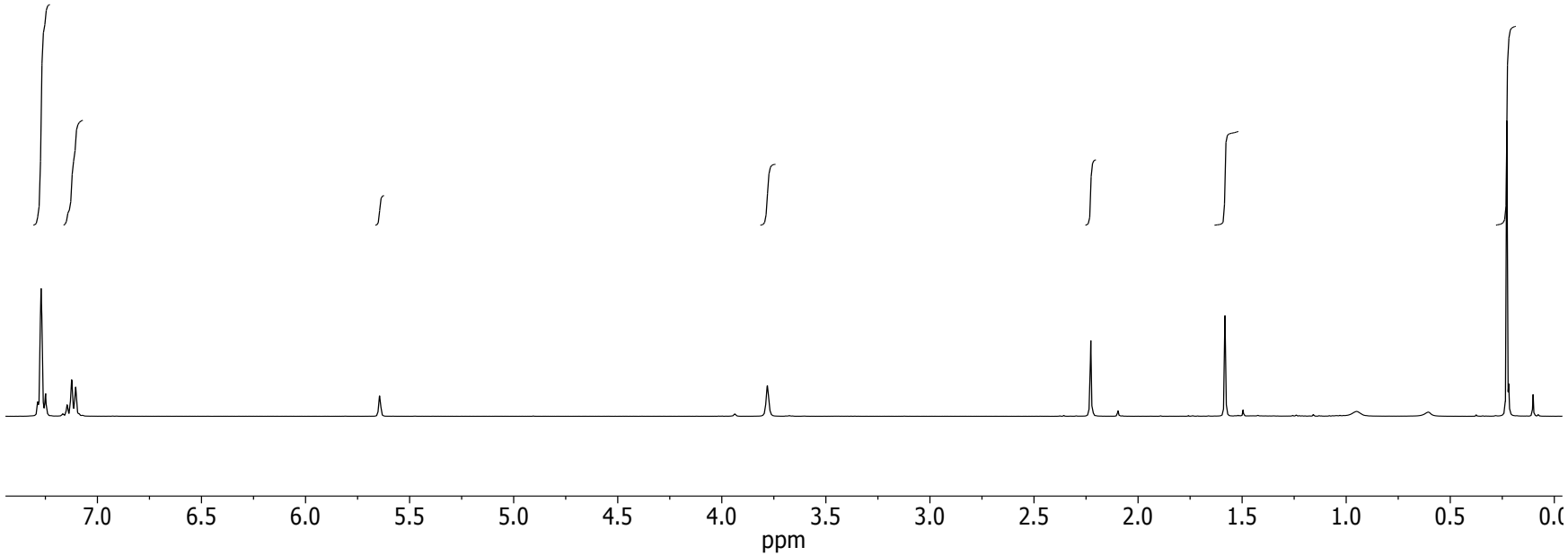
^{13}C-NMR (100.63 MHz, C_6D_6) of 21a



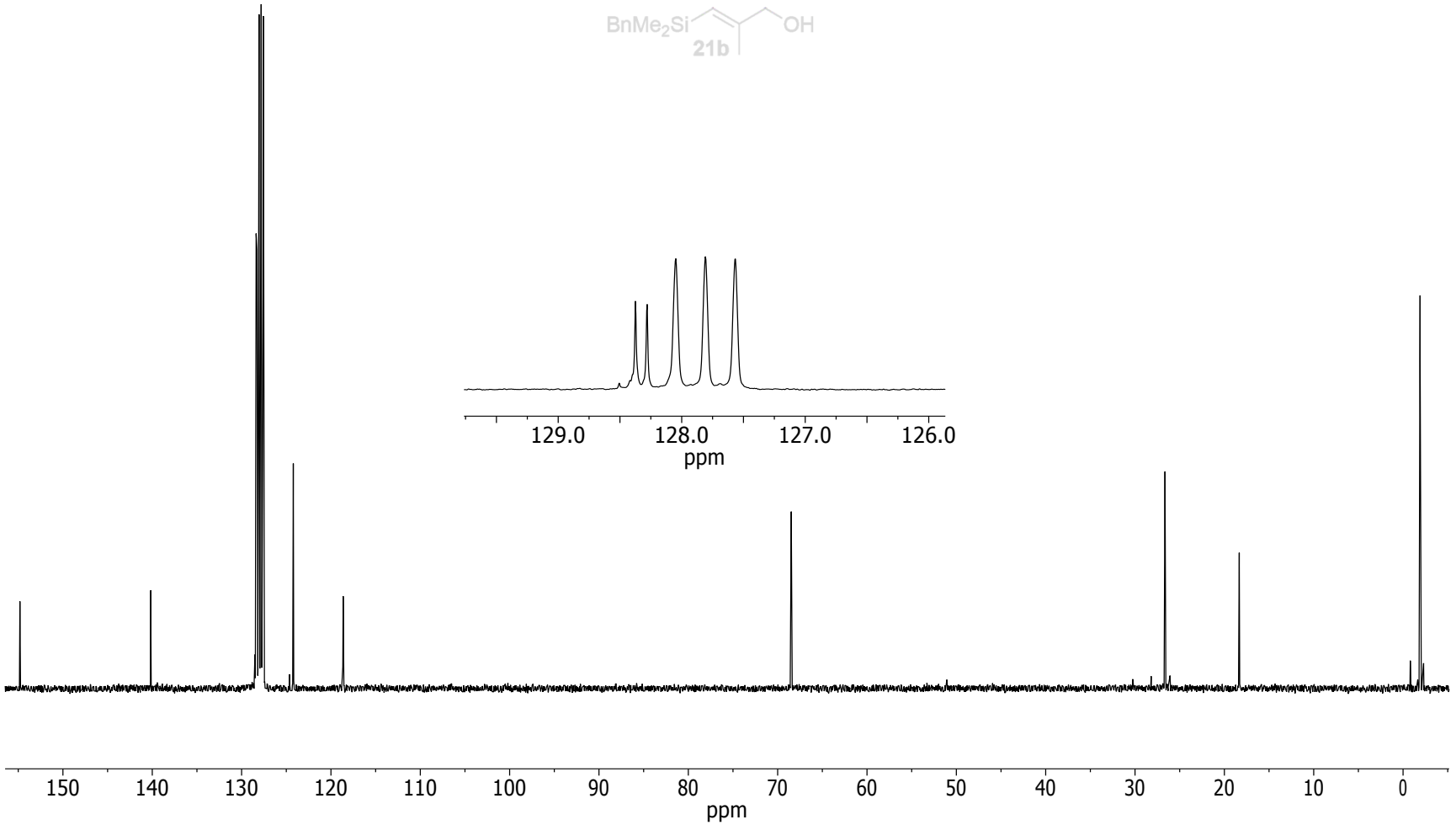
^{1}H-NMR (400.16 MHz, C_6D_6) of 21b



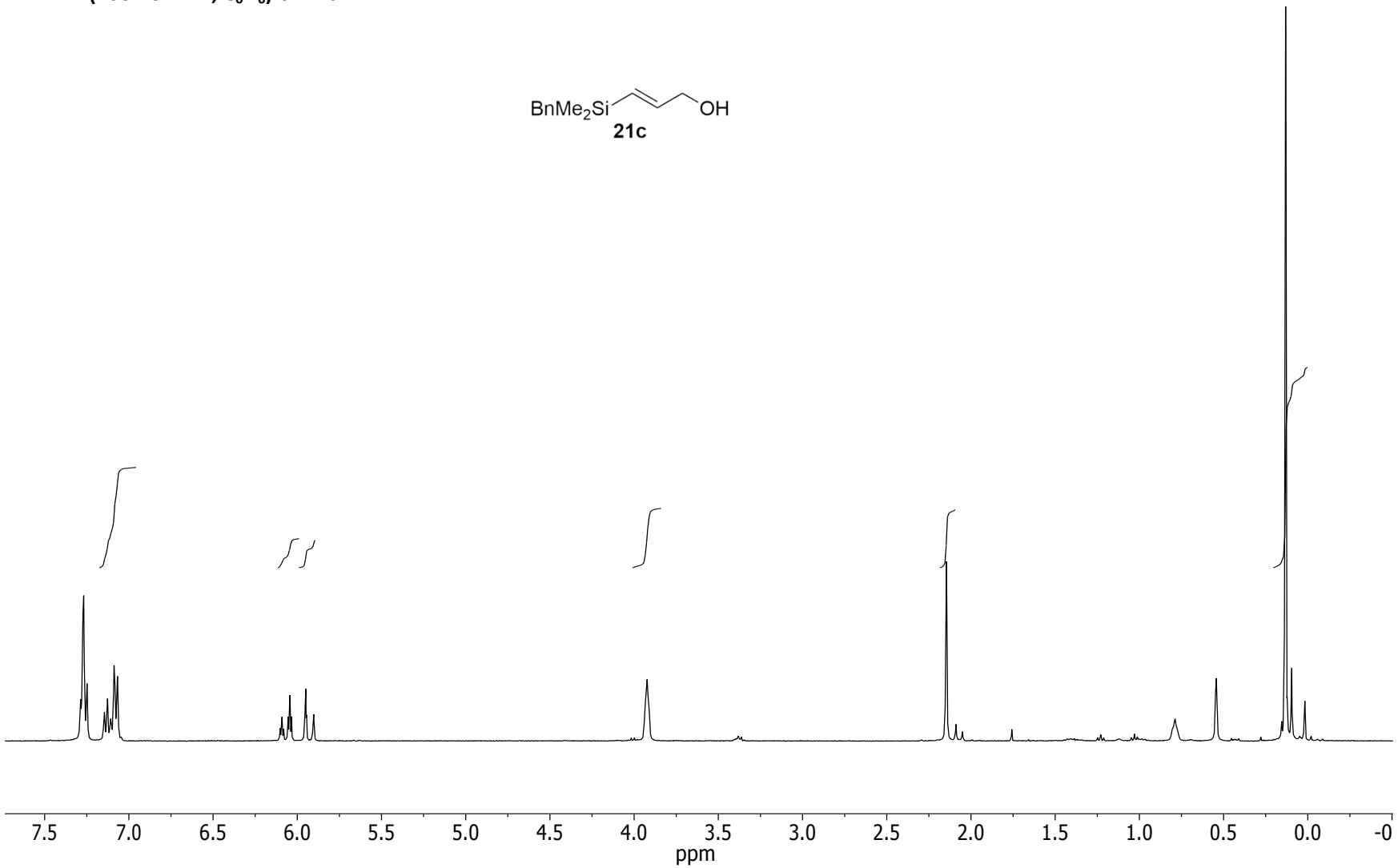
21b



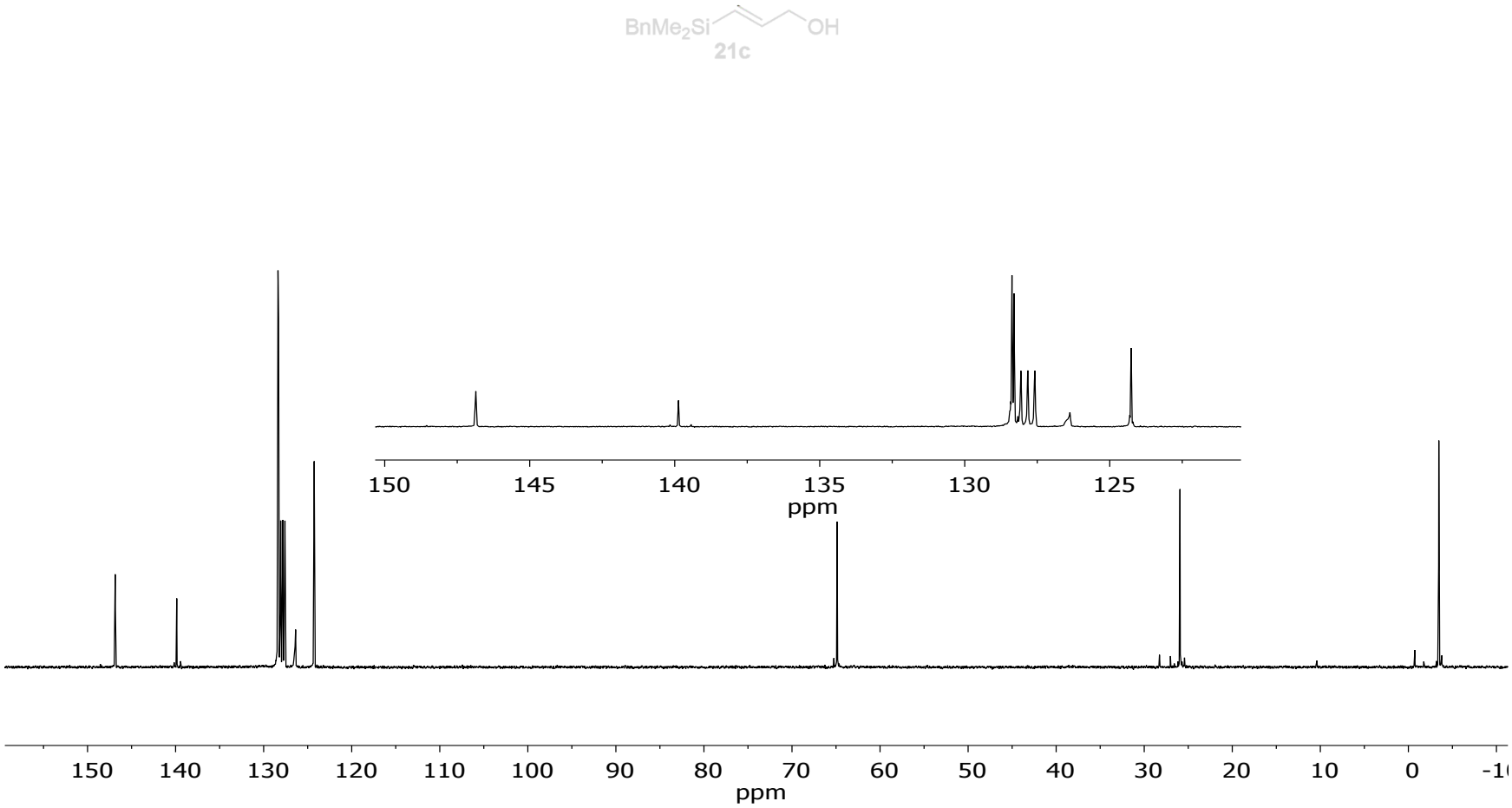
^{13}C-NMR (100.63 MHz, C_6D_6) of 21b



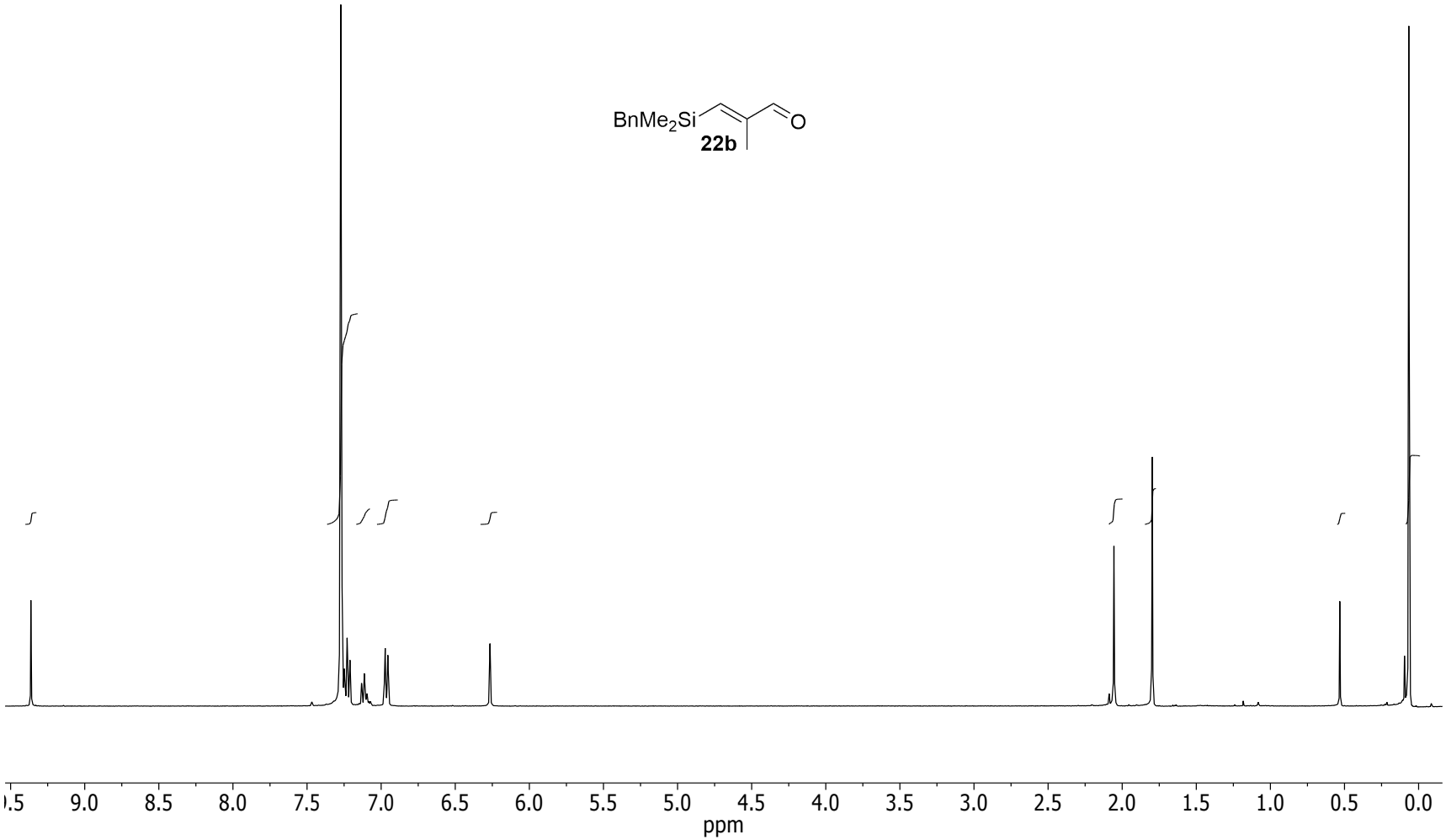
^{1}H-NMR (400.16 MHz, C_6D_6) of 21c



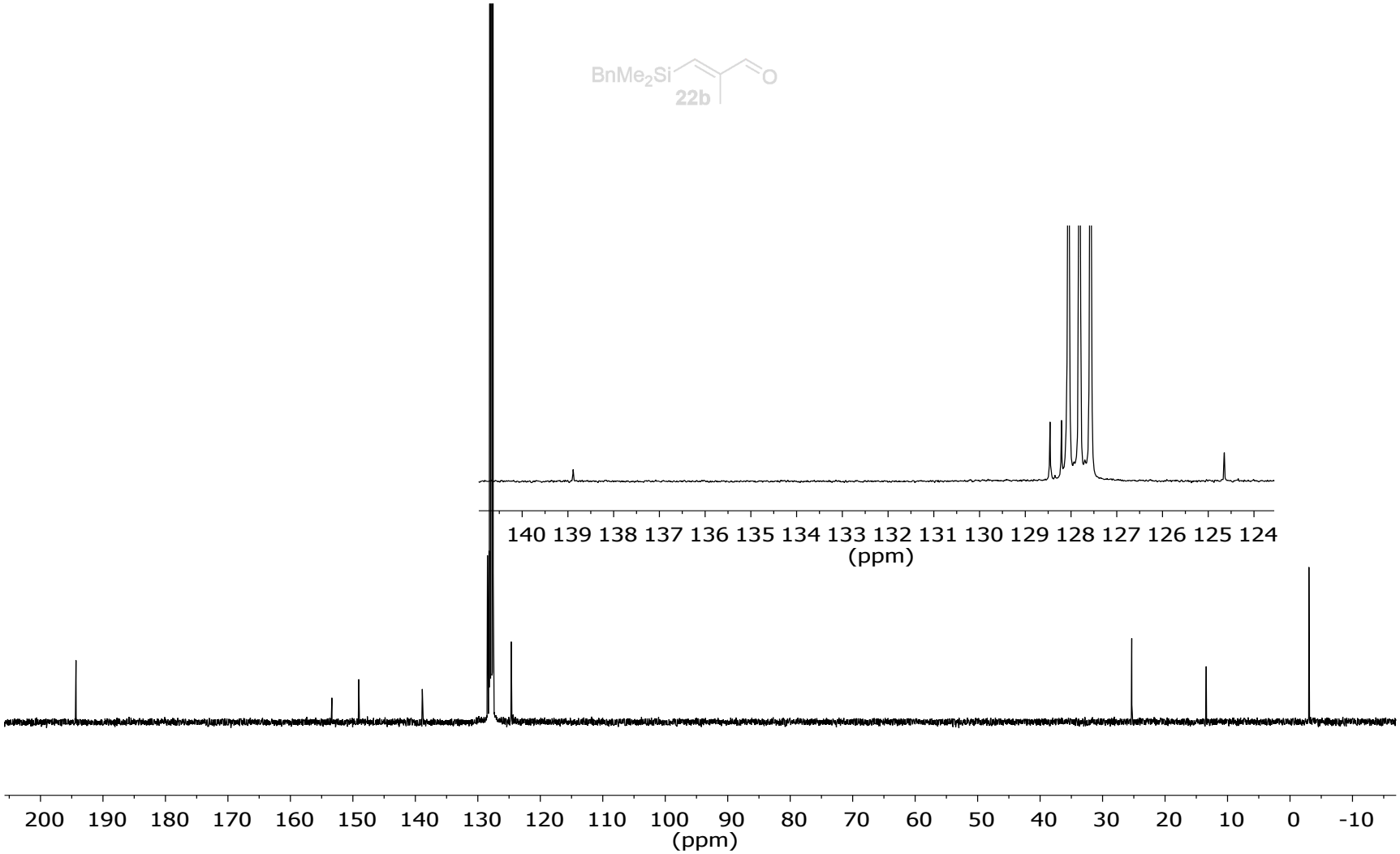
^{13}C-NMR (100.63 MHz, C_6D_6) of 21c



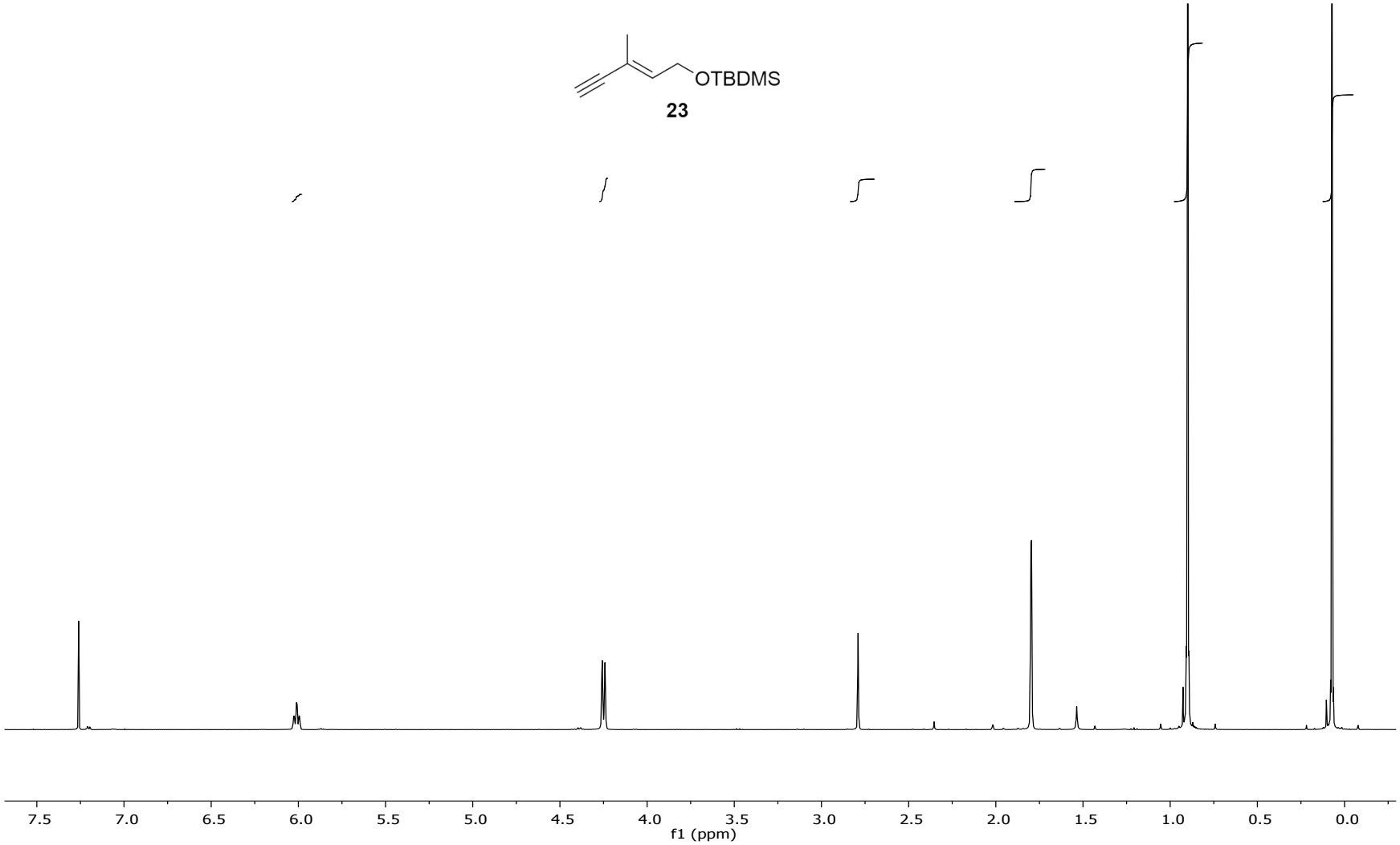
^{1}H-NMR (400.16 MHz, C_6D_6) of 22b



^{13}C-NMR (100.63 MHz, C_6D_6) of 21b

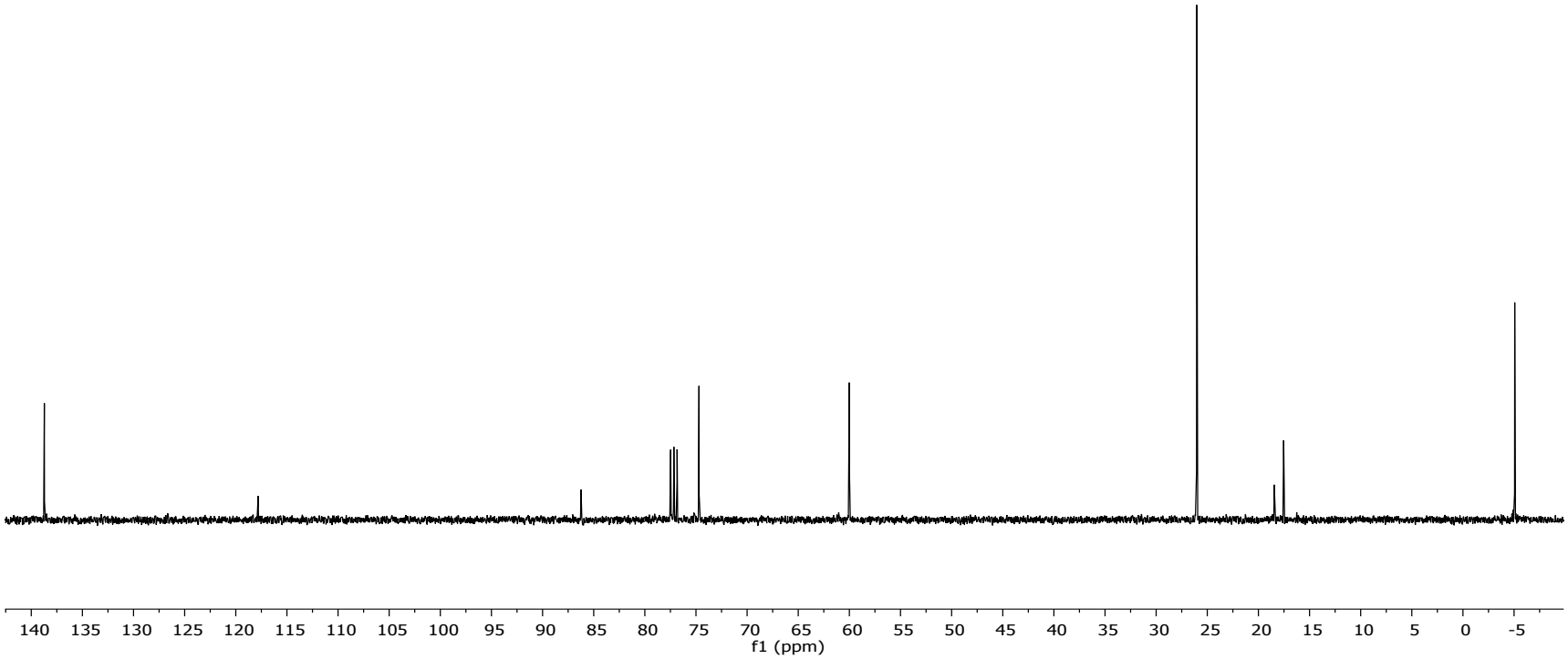


^{1}H-NMR (400.16 MHz, $CDCl_3$) of 23

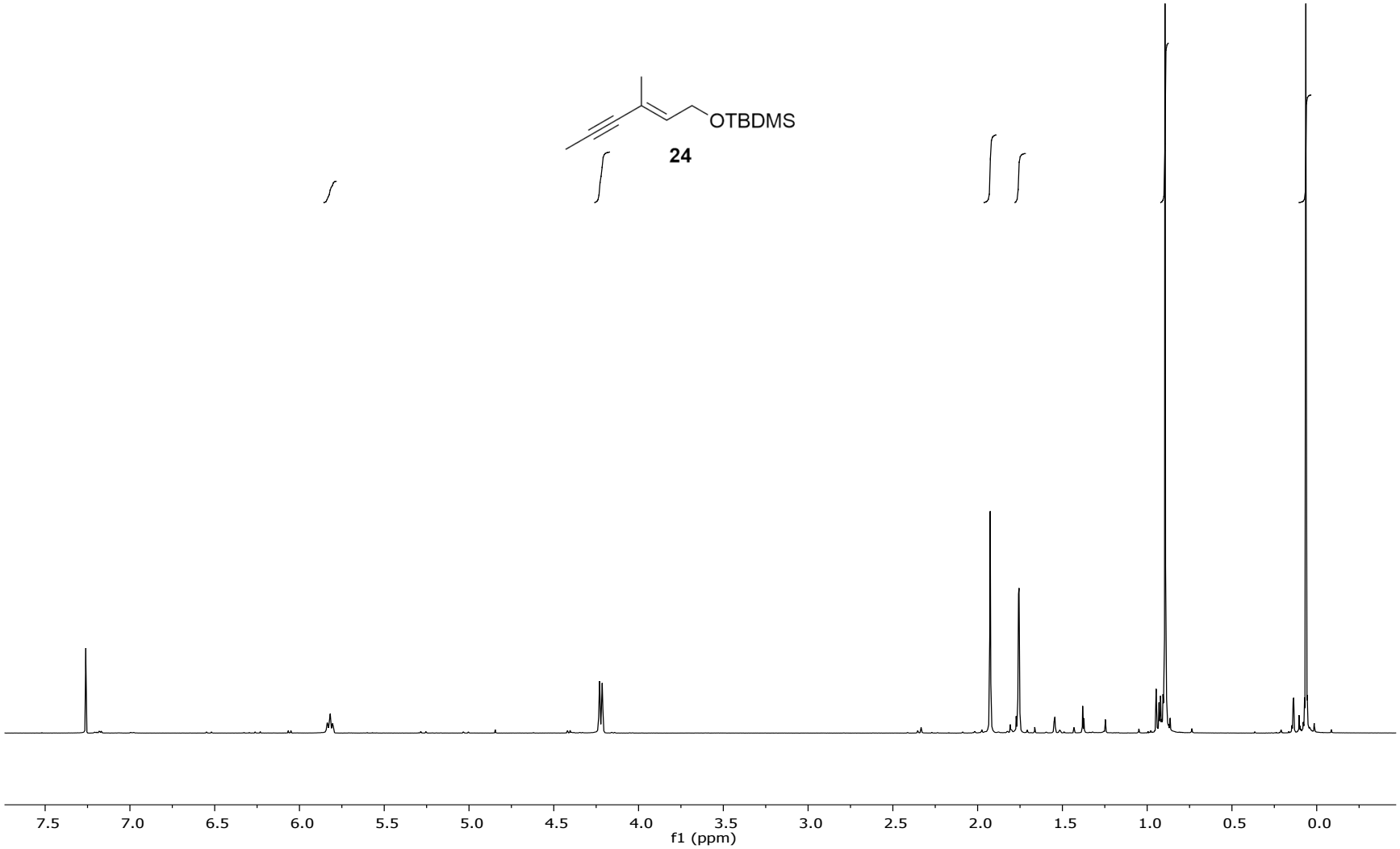


^{13}C-NMR (100.63 MHz, $CDCl_3$) of 23

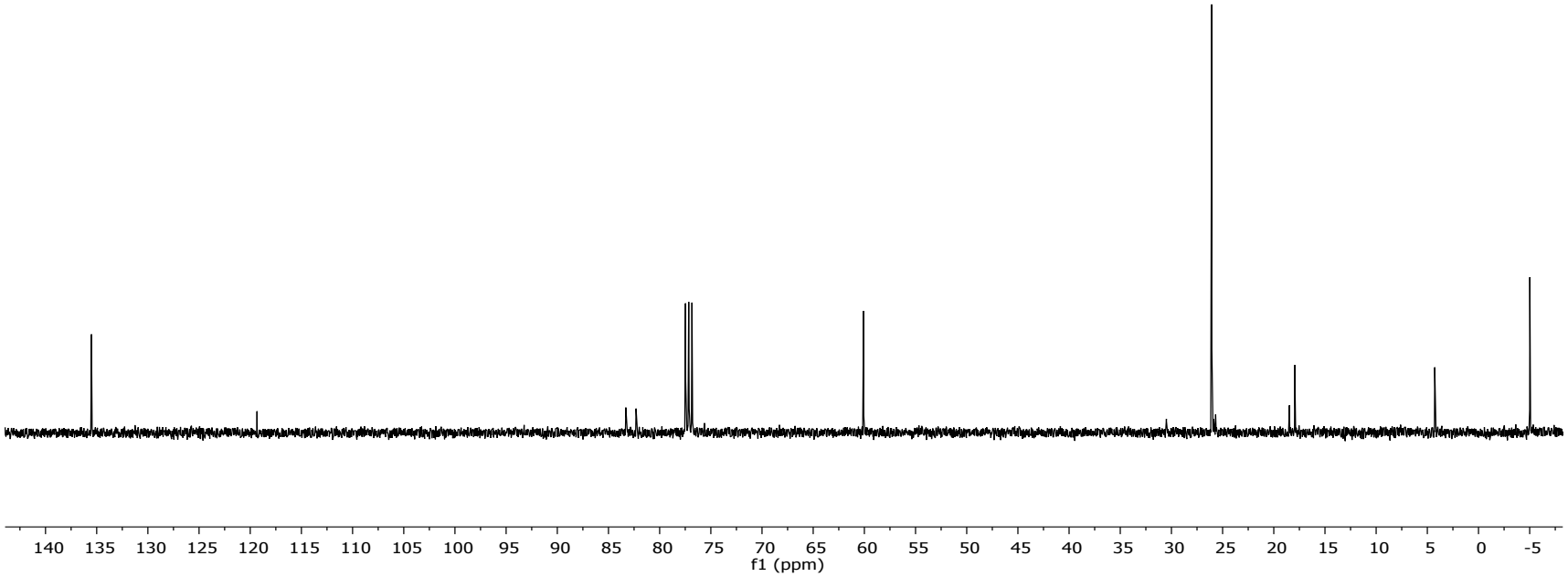
23



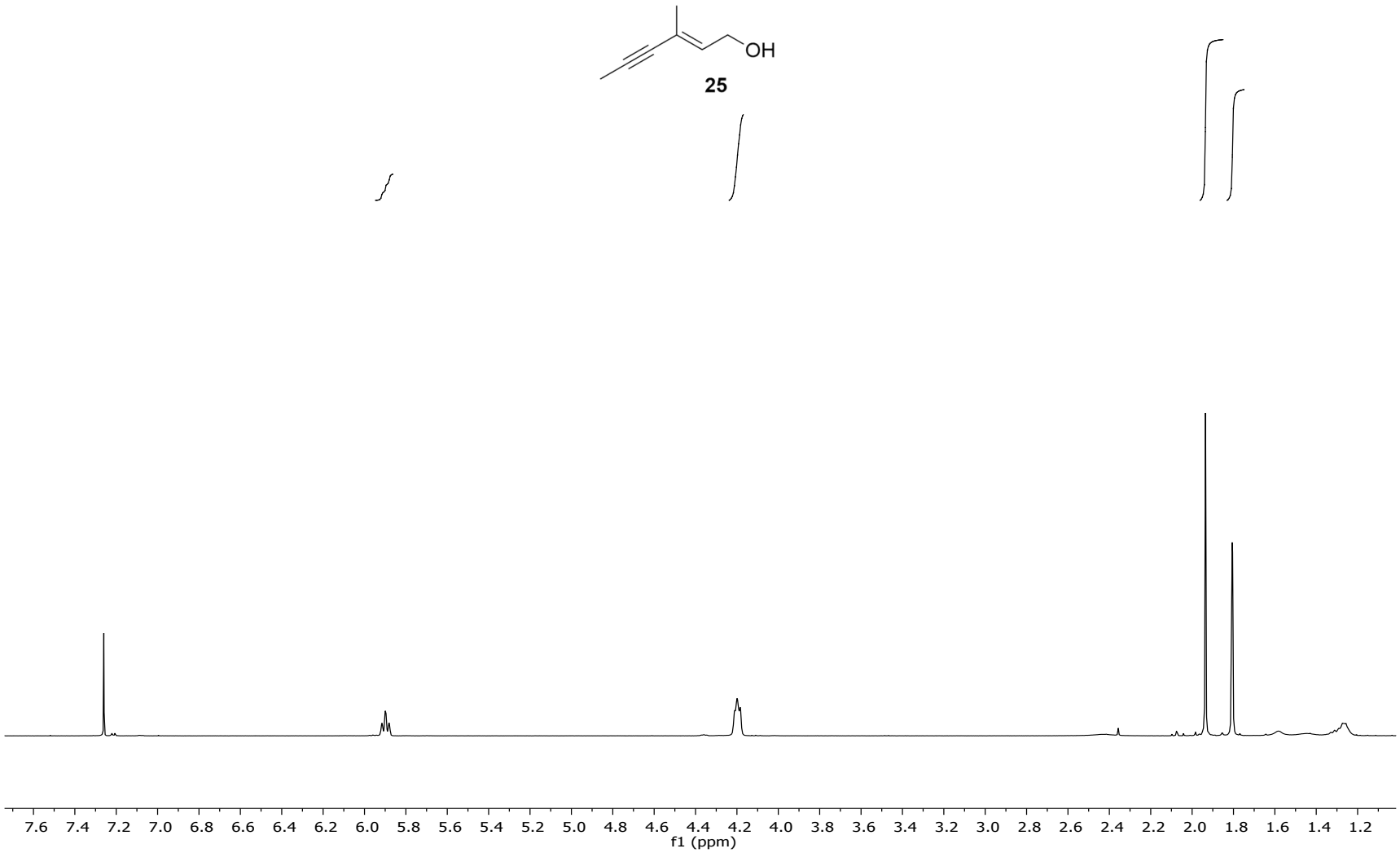
^{1}H-NMR (400.16 MHz, $CDCl_3$) of 24



^{13}C-NMR (100.63 MHz, $CDCl_3$) of 24

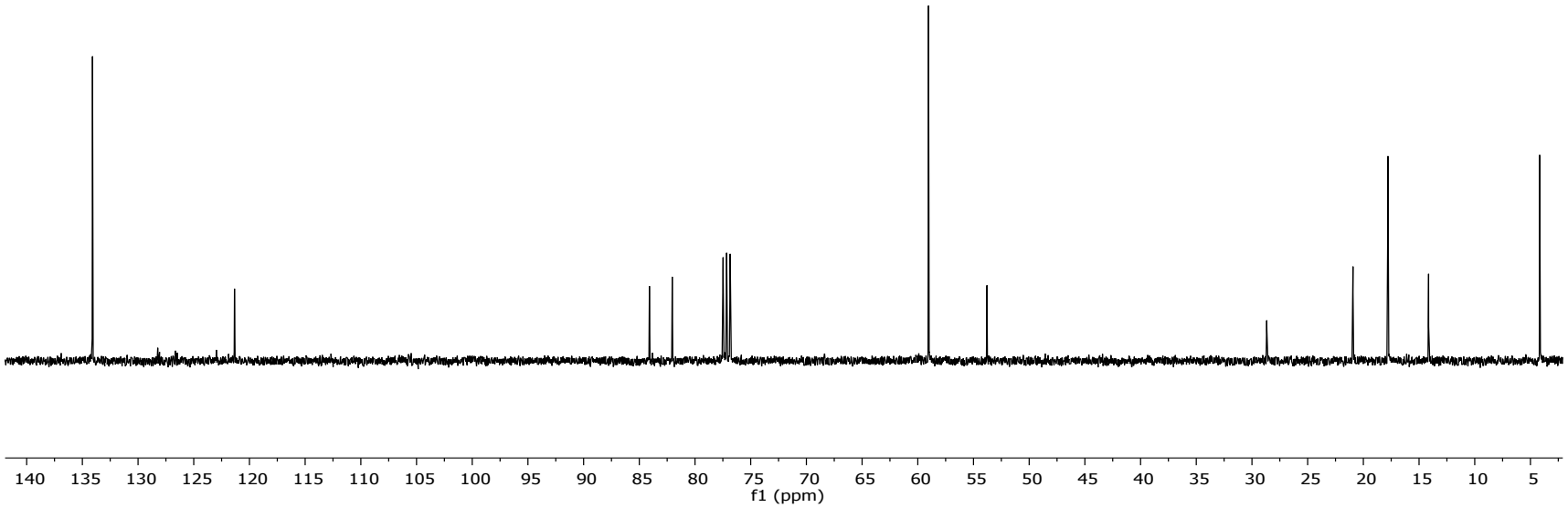


^{1}H-NMR (400.16 MHz, $CDCl_3$) of 25

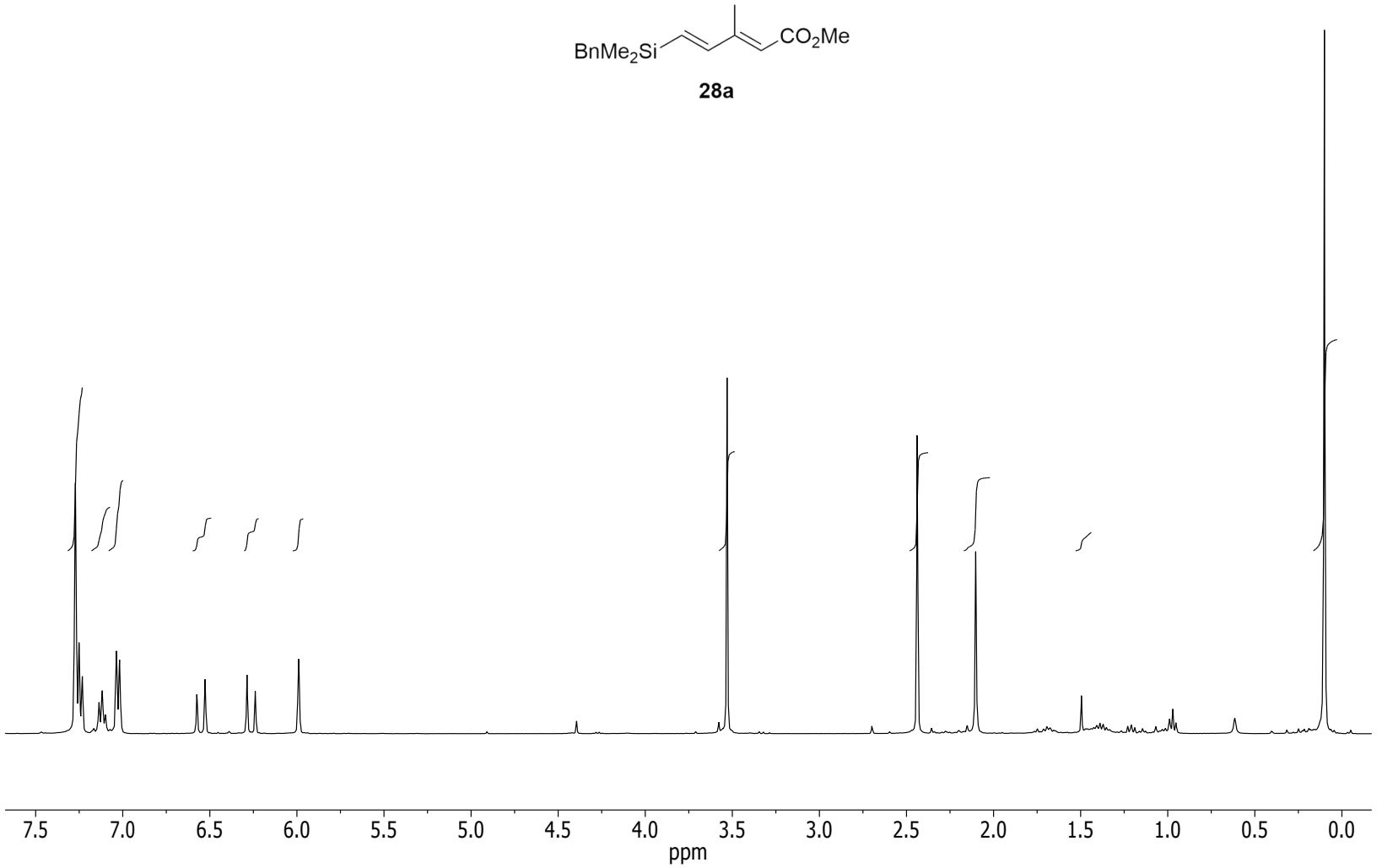


^{13}C-NMR (100.63 MHz, $CDCl_3$) of 25

25



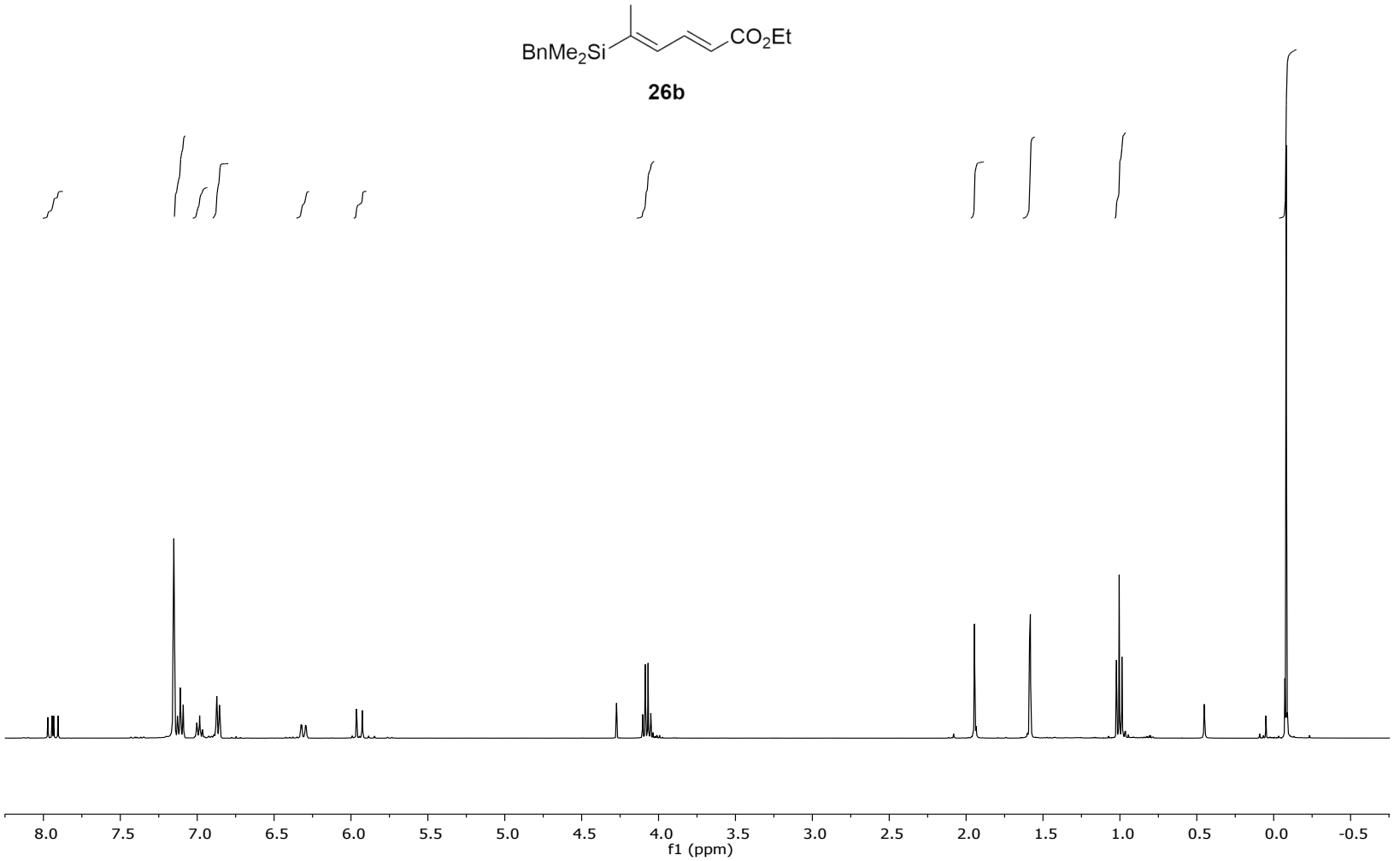
^{1}H-NMR (400.16 MHz, C_6D_6), spectrum of 28a.



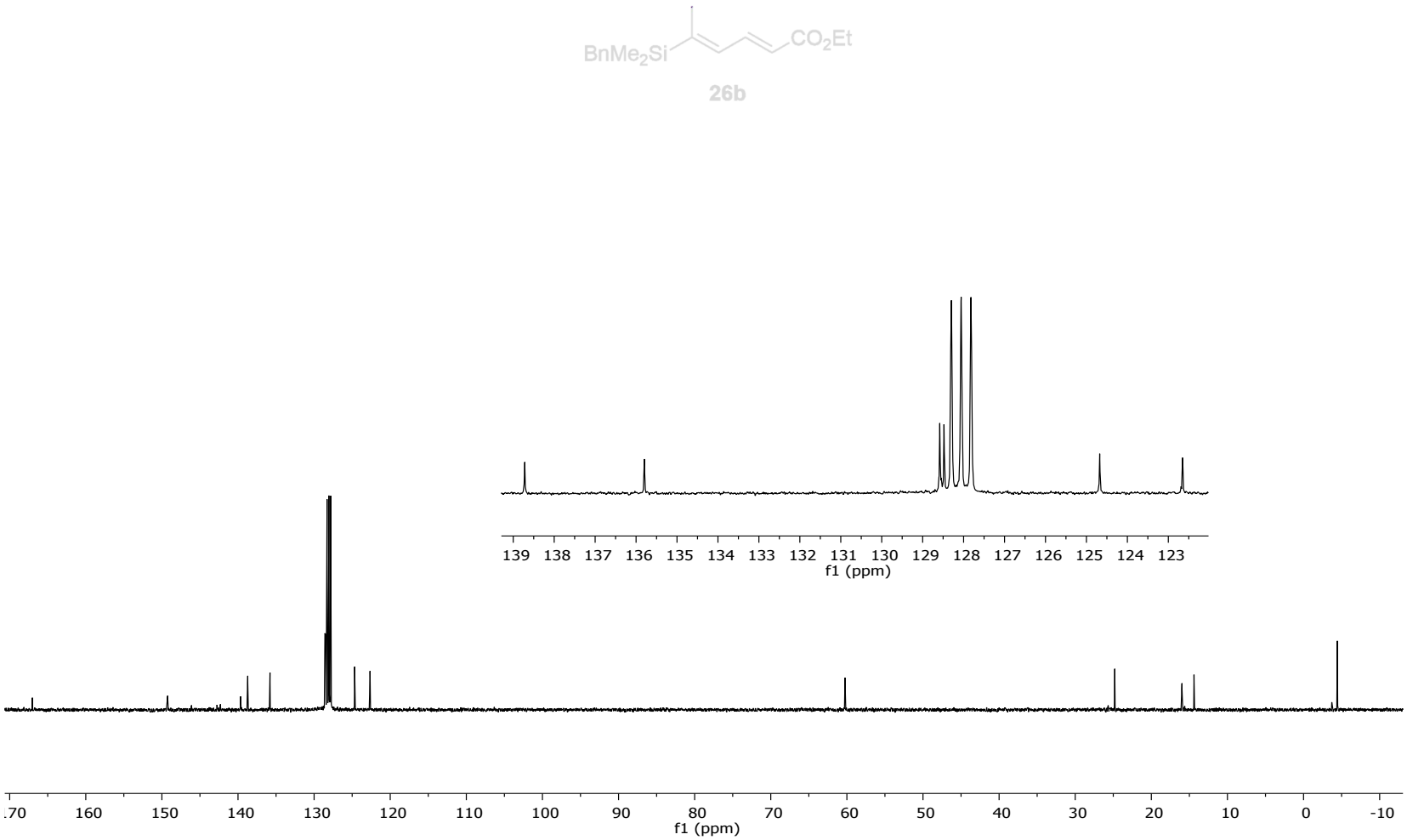
^{13}C-NMR (100.63 MHz, C_6D_6) of 28a

28a

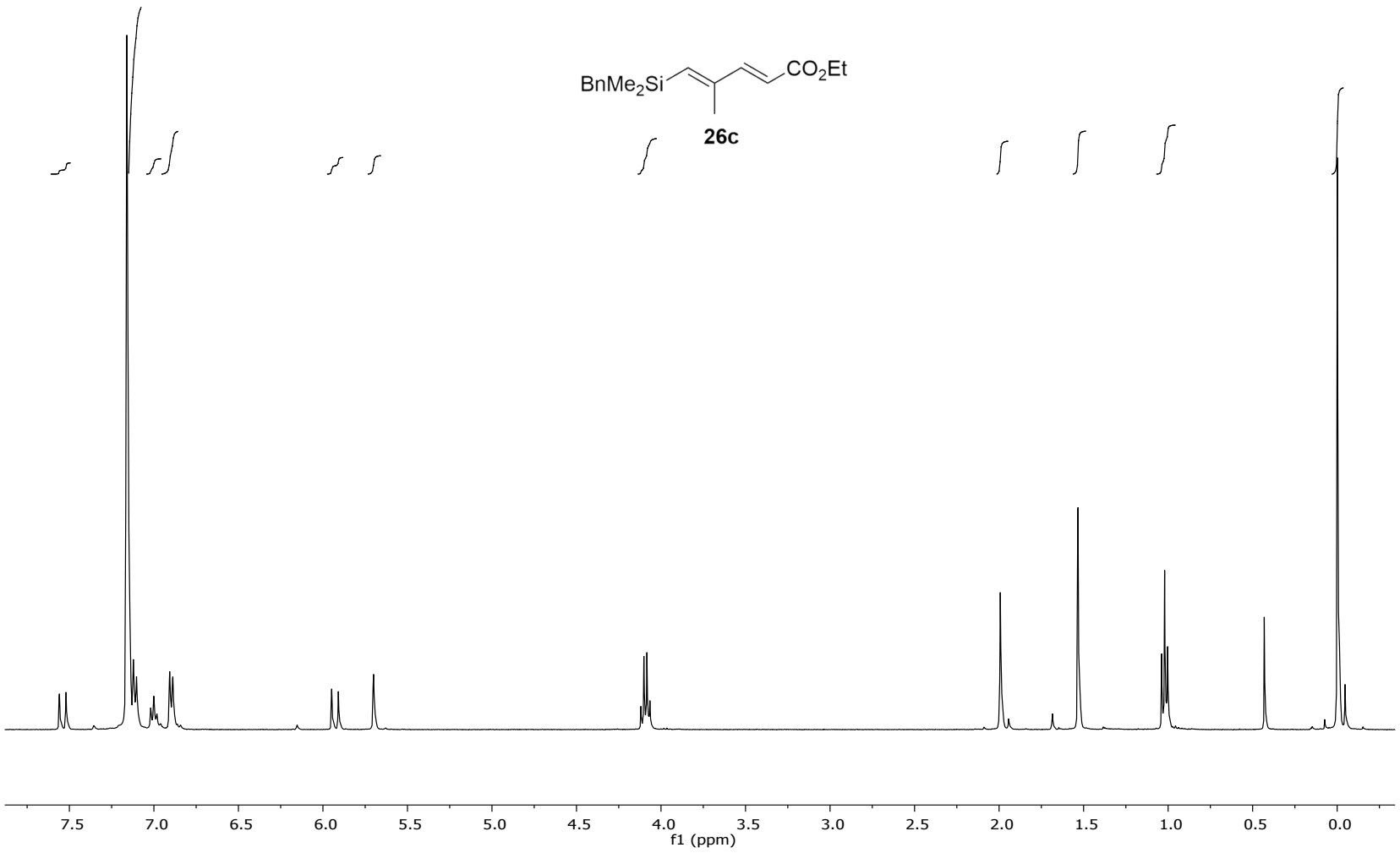
^{1}H-NMR (400.16 MHz, C_6D_6) of 26b



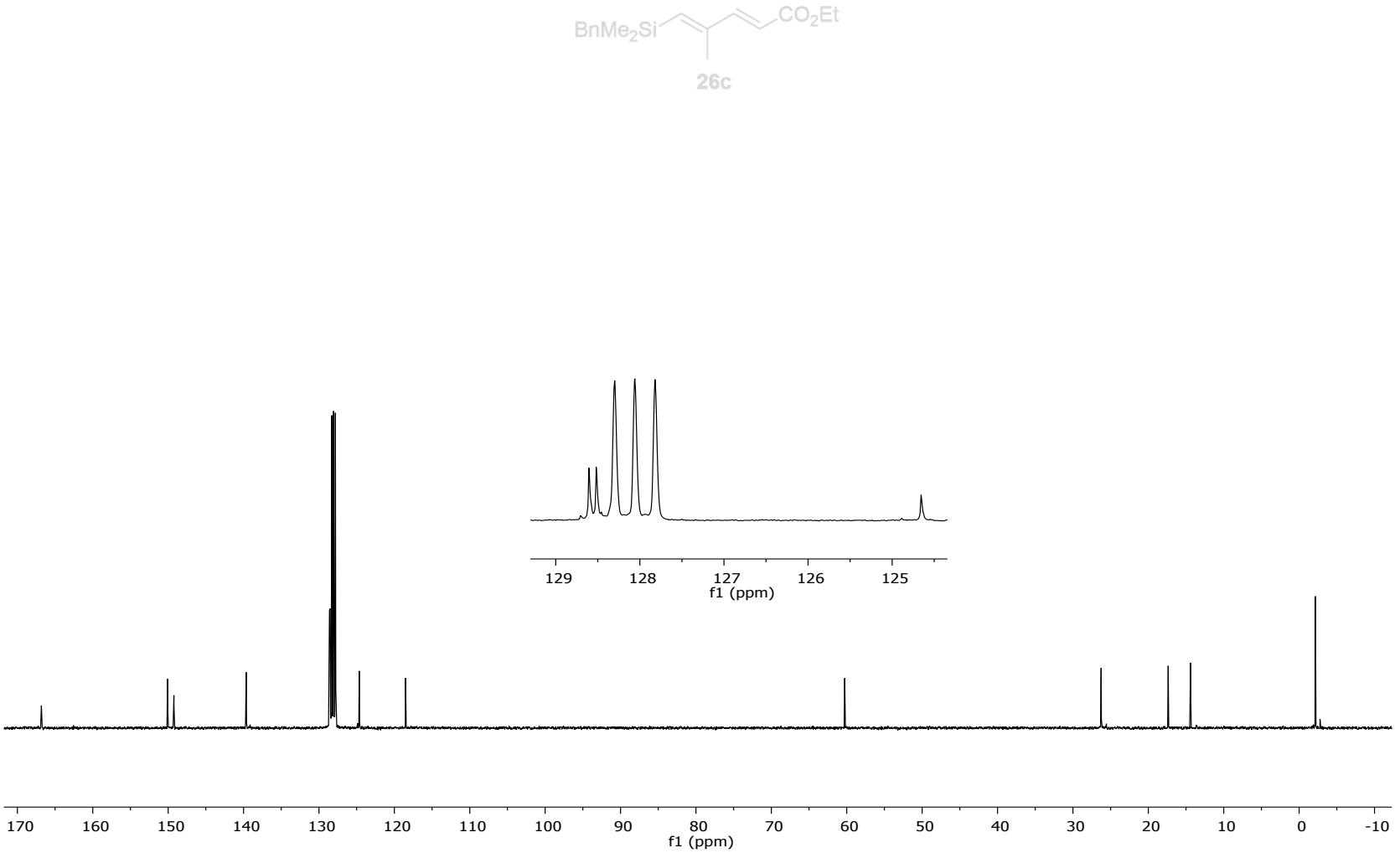
^{13}C-NMR (100.63 MHz, C_6D_6) of 26b



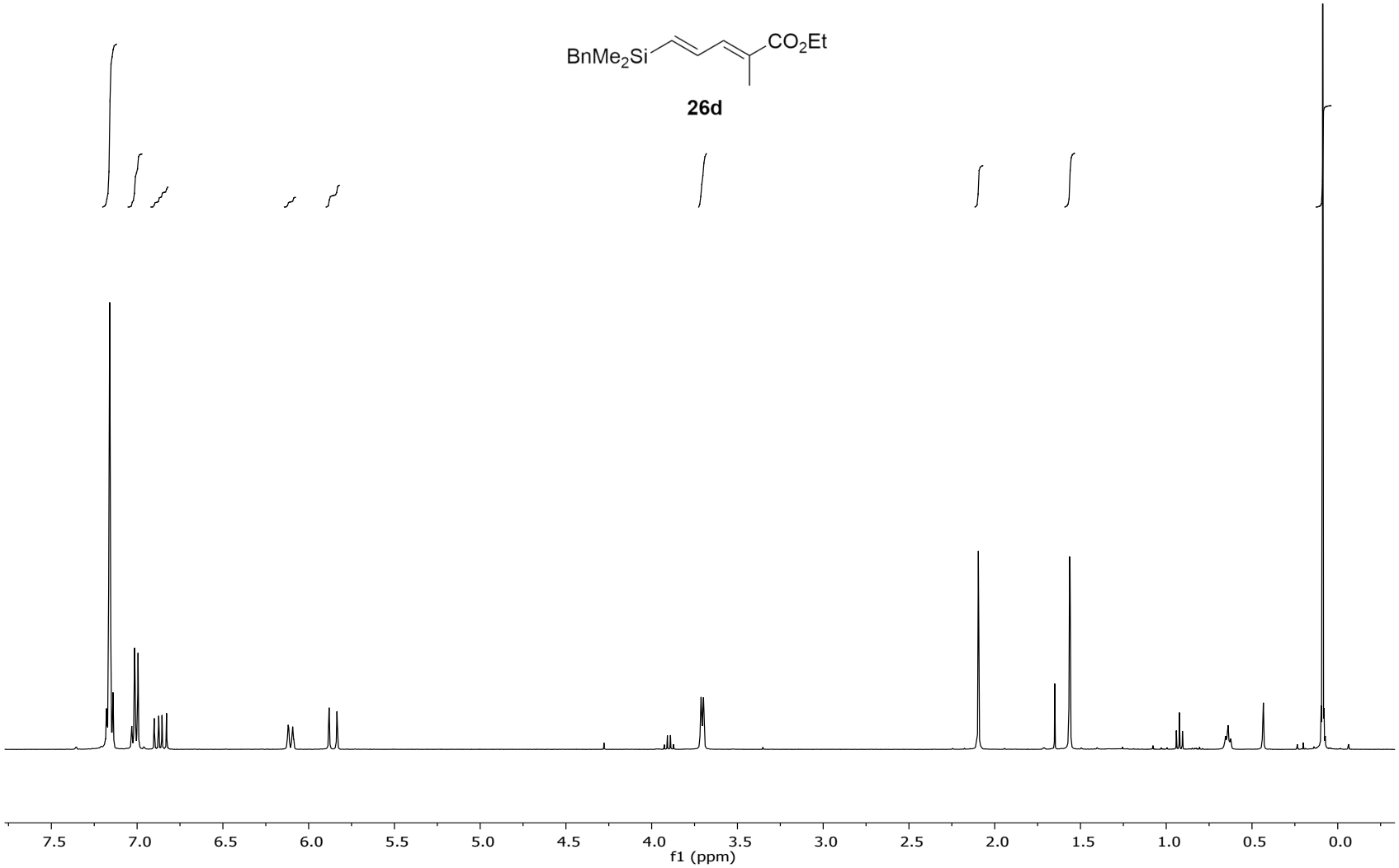
^{1}H-NMR (400.16 MHz, C_6D_6) of 26c



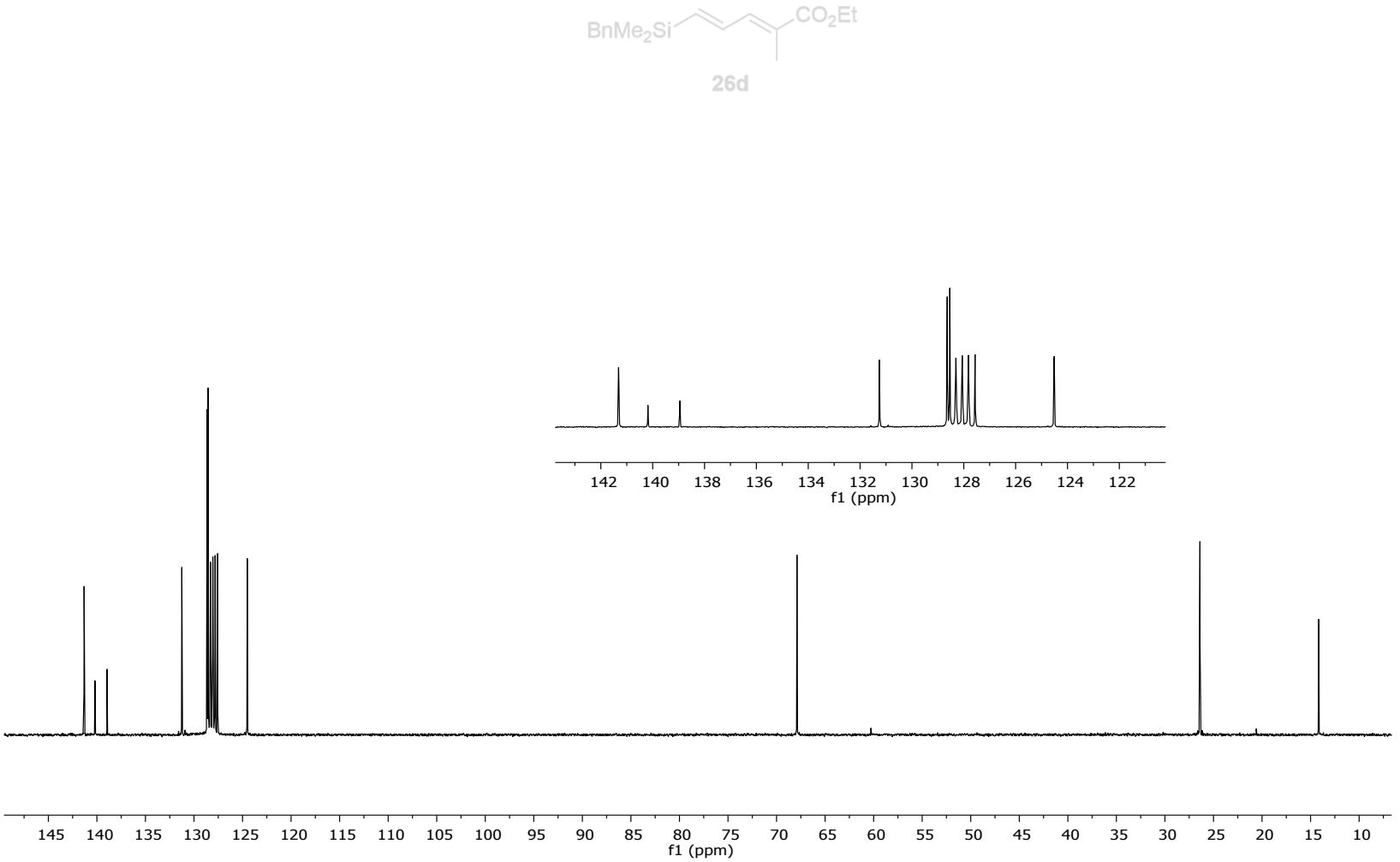
^{13}C-NMR (100.63 MHz, C_6D_6) of 26c



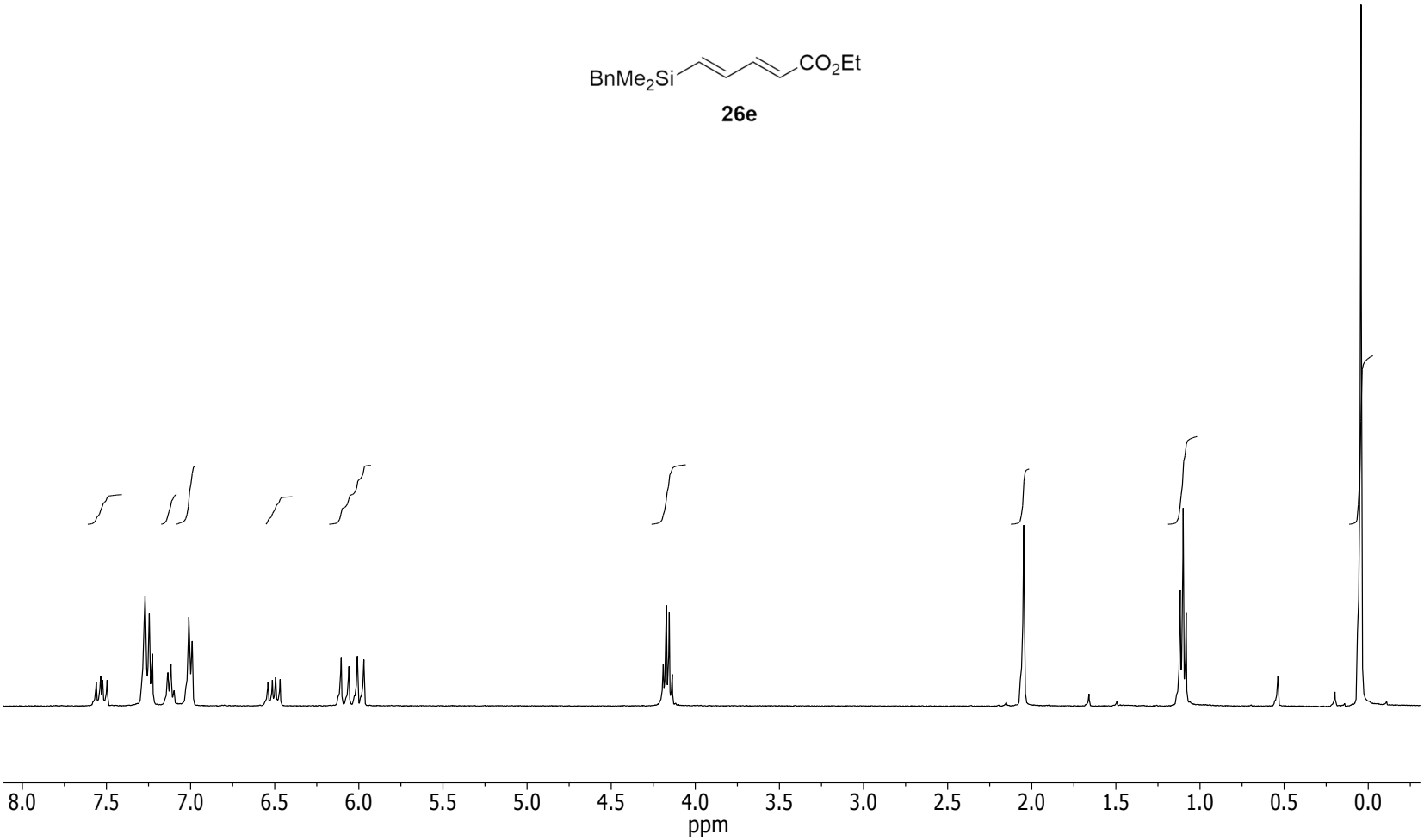
^{1}H-NMR (400.16 MHz, C_6D_6) of 26d



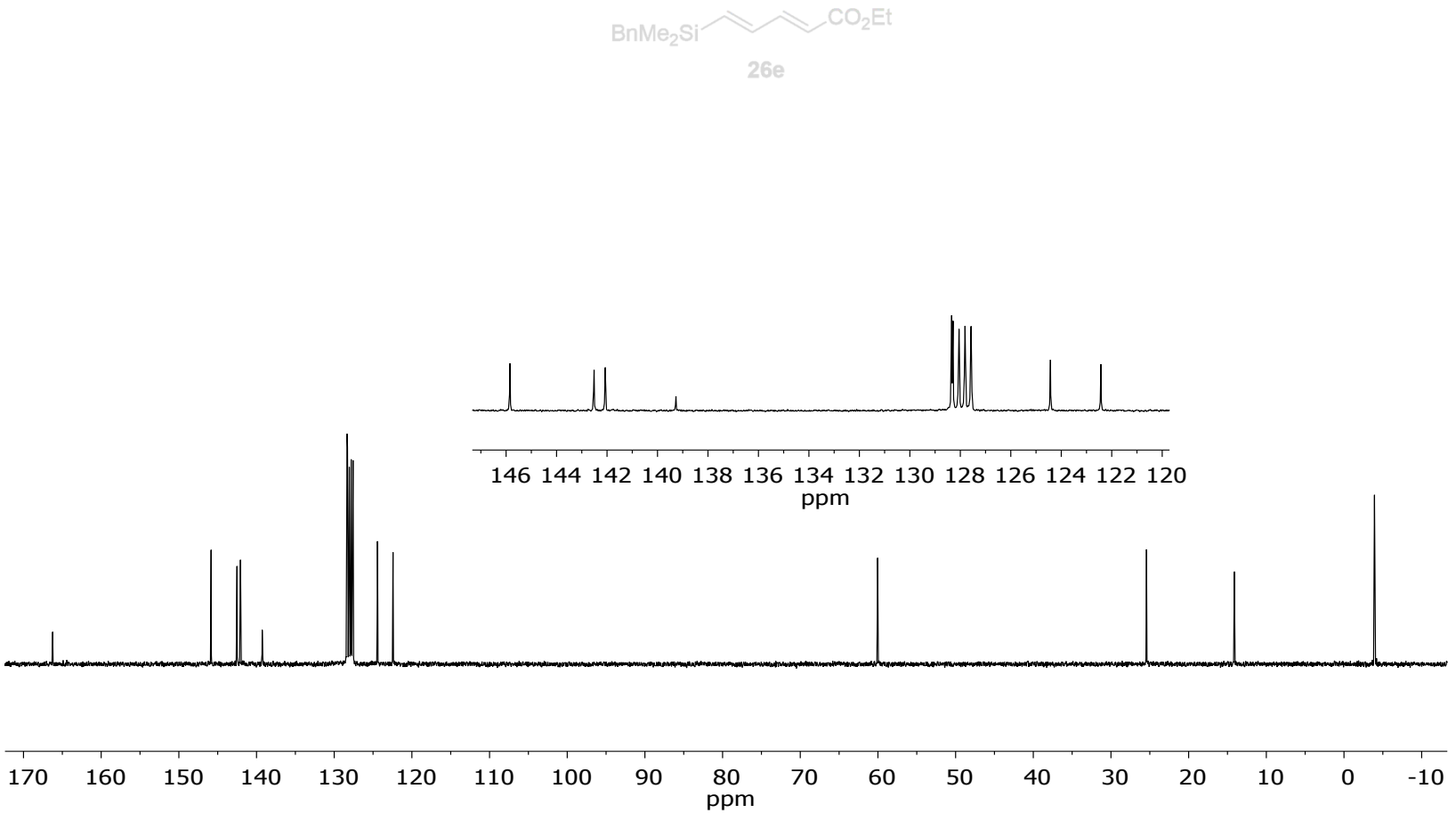
^{13}C-NMR (100.63 MHz, C_6D_6) of 26d



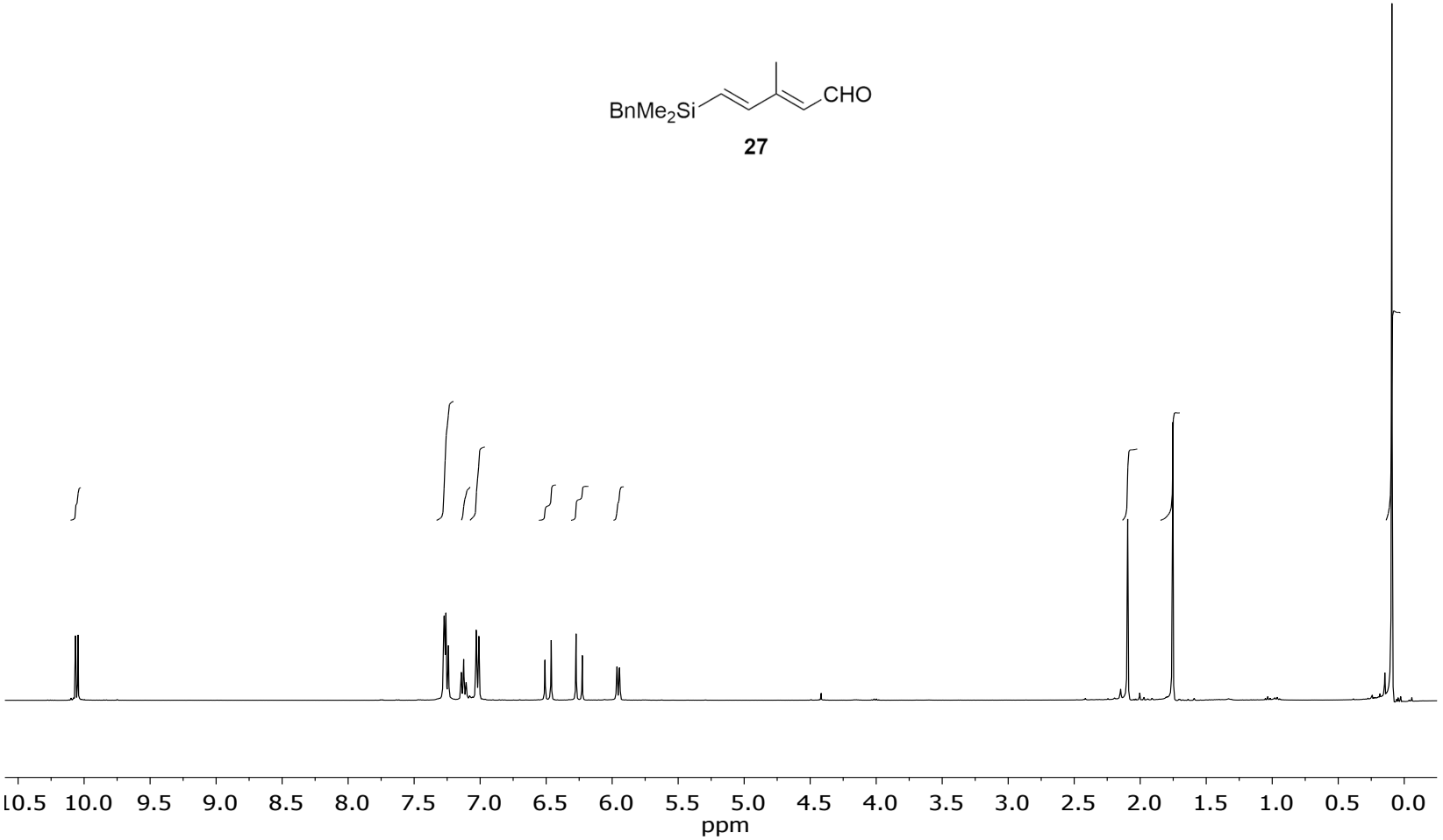
^{1}H-NMR (400.16 MHz, C_6D_6) of 26e



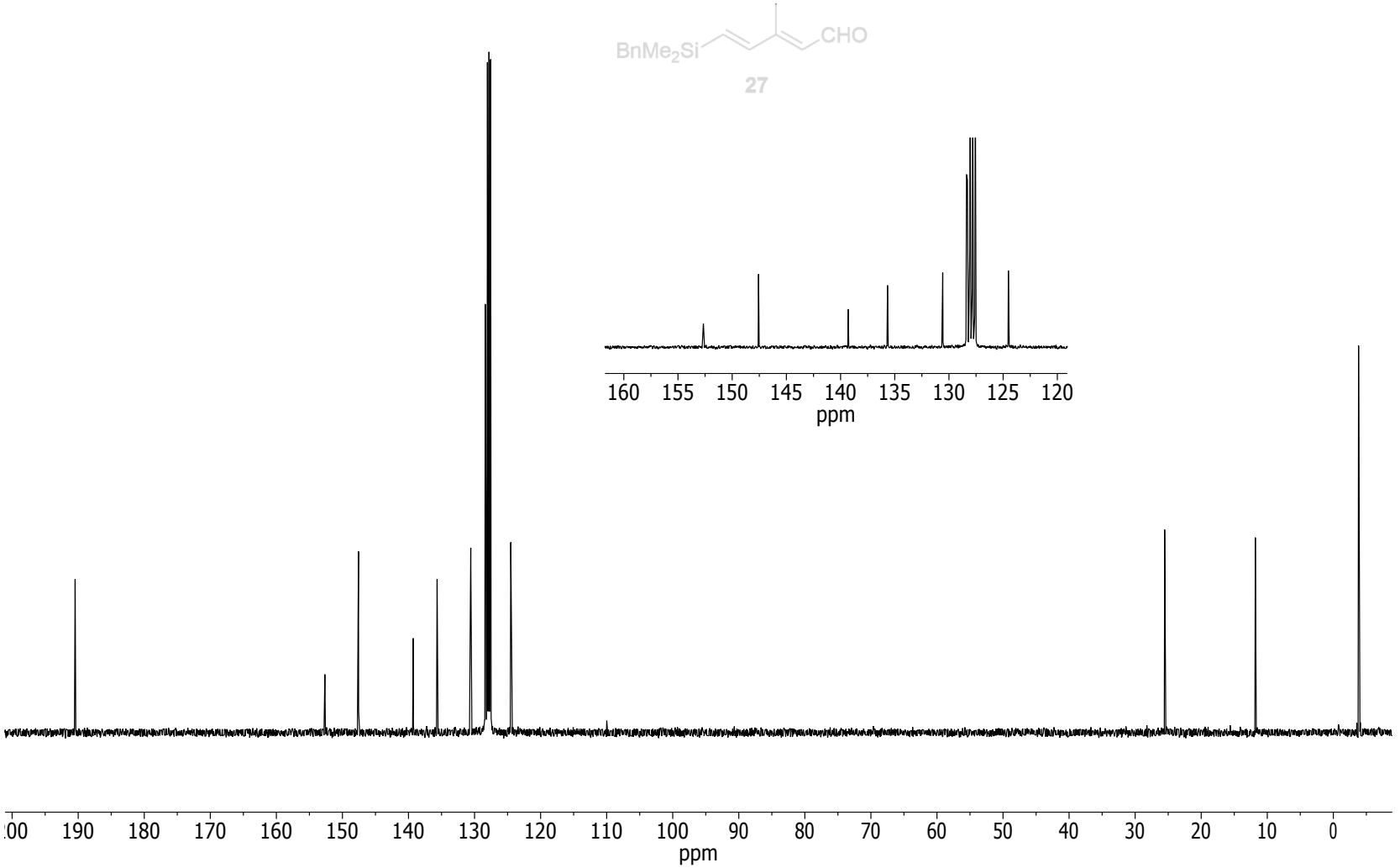
^{13}C-NMR (100.63 MHz, C_6D_6) of 26e



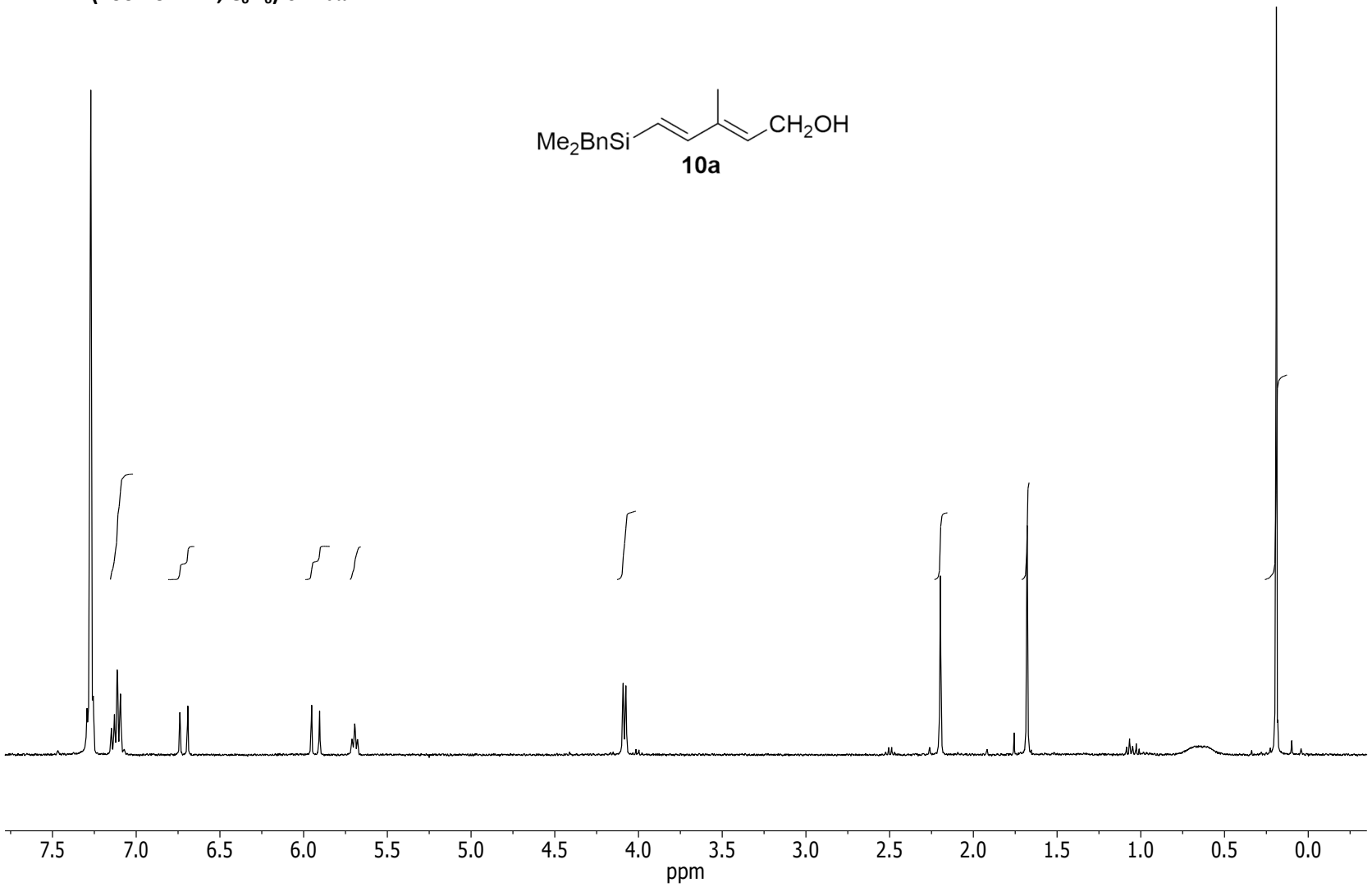
^{1}H-NMR (400.16 MHz, C_6D_6) of 27



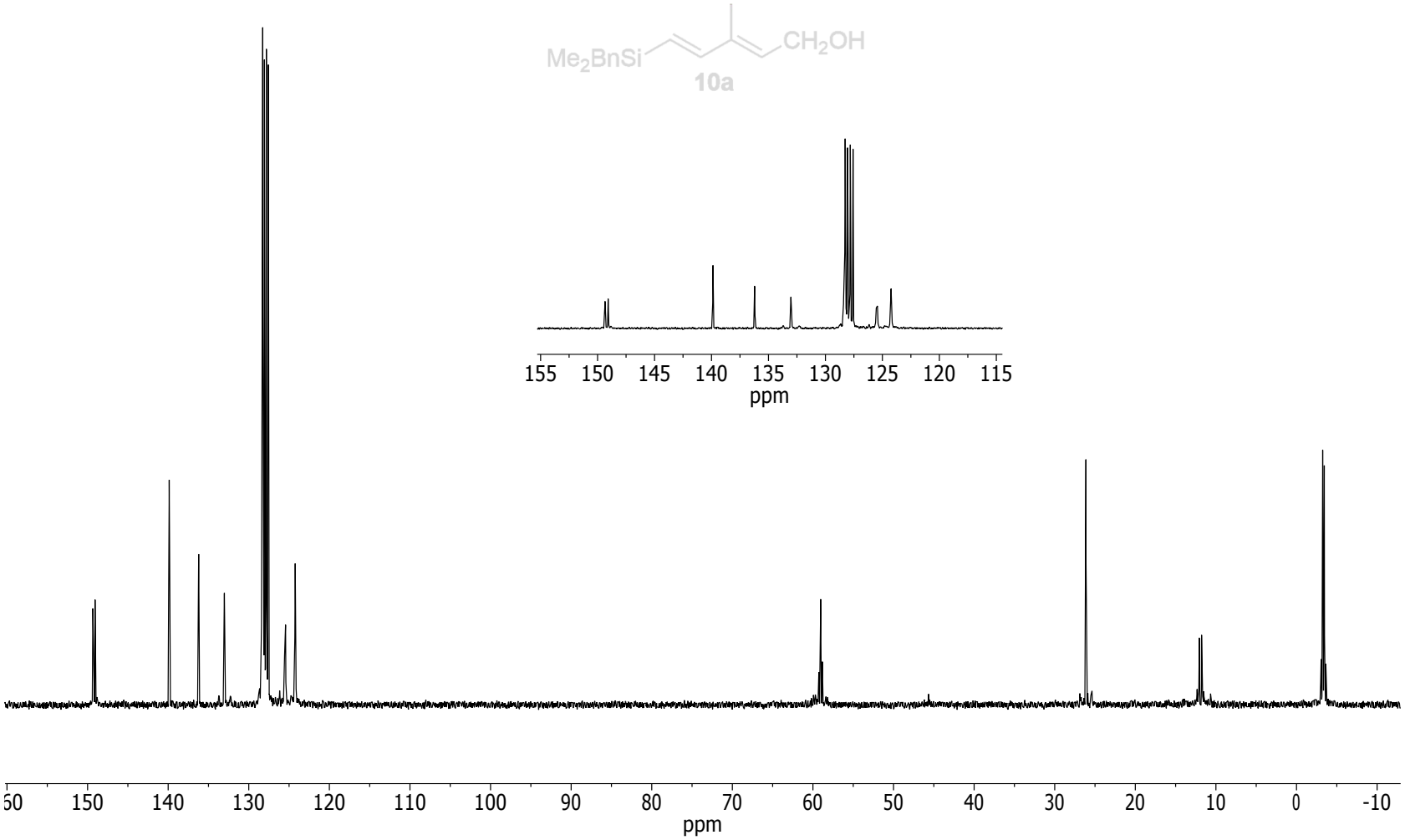
^{13}C-NMR (100.63 MHz, C_6D_6) of 27



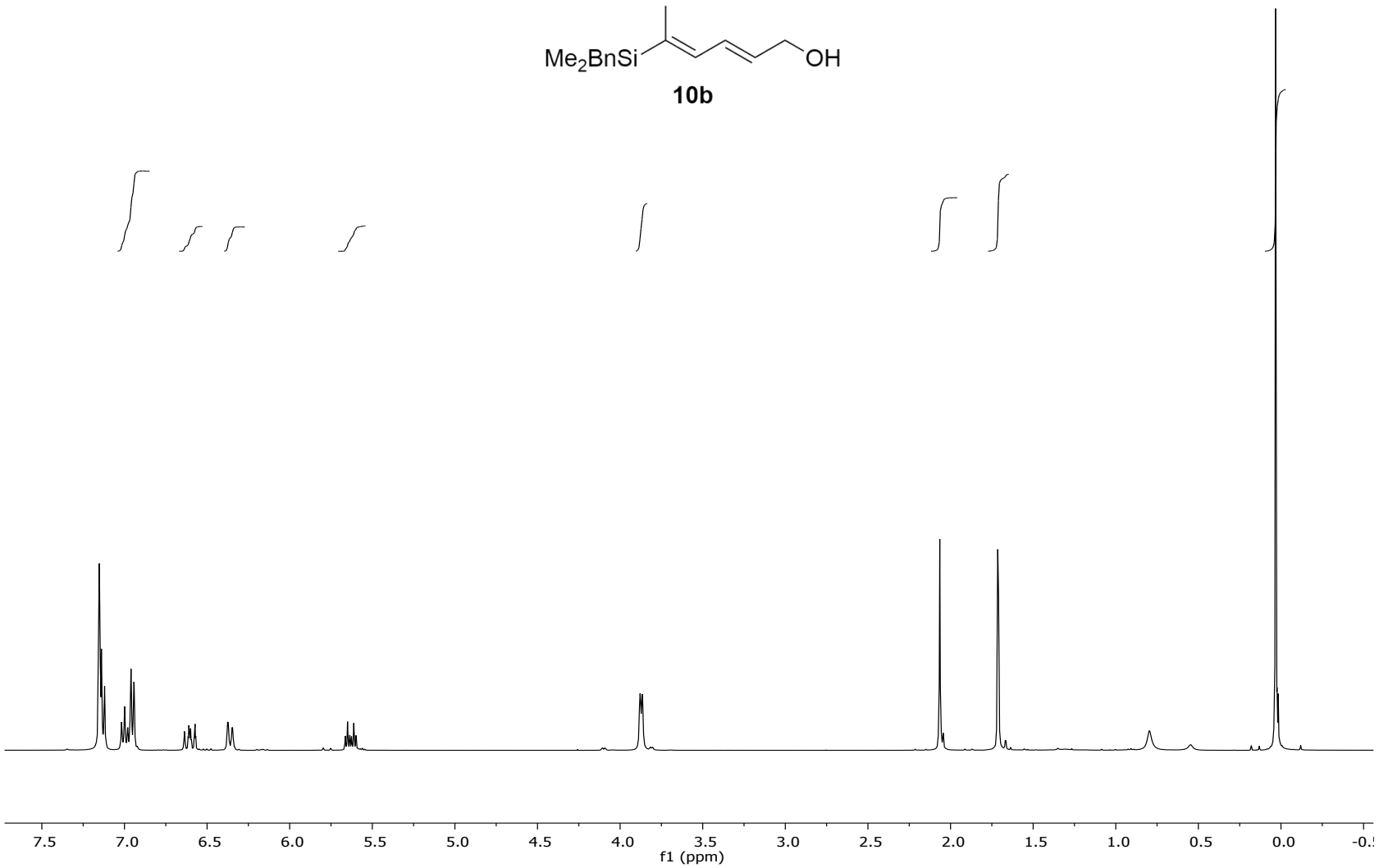
^{1}H-NMR (400.16 MHz, C_6D_6) of 10a



^{13}C-NMR (100.63 MHz, C_6D_6) of 10a

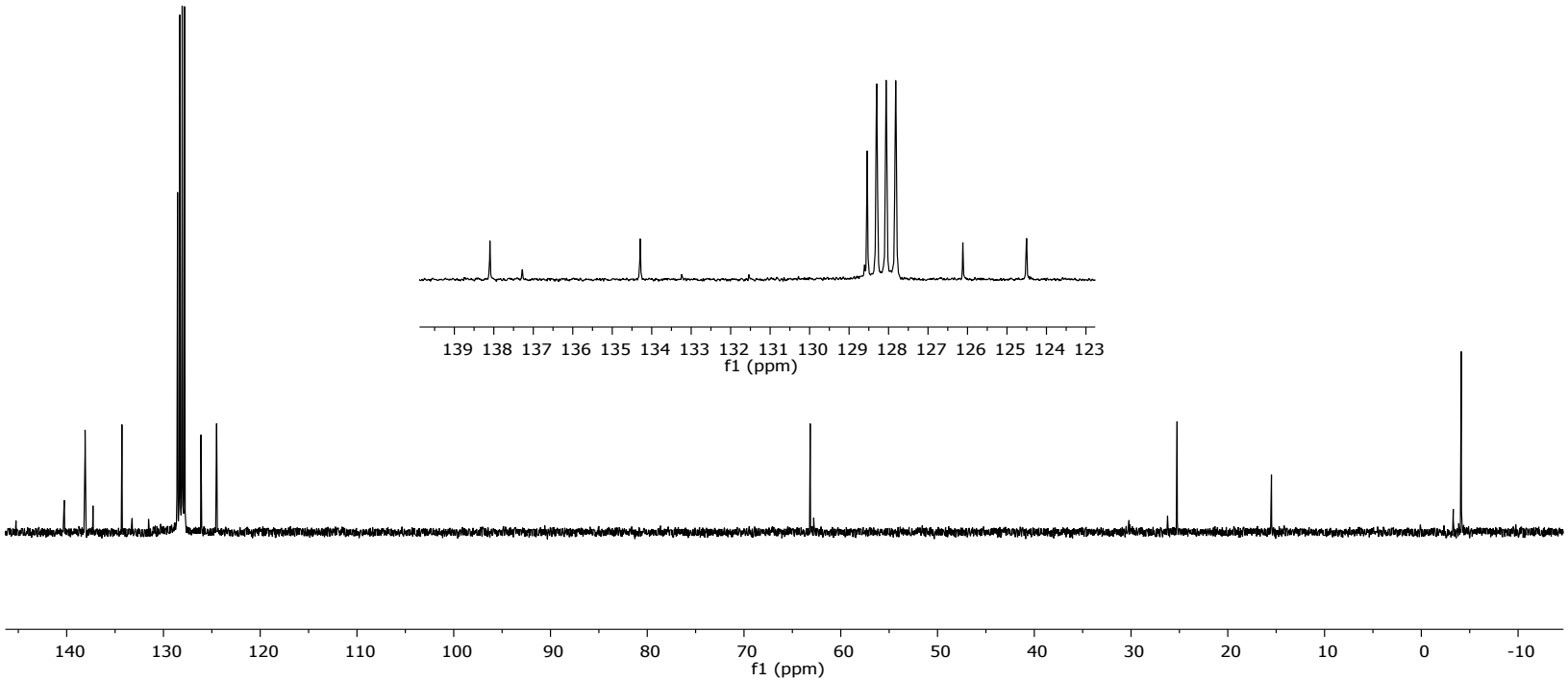


^{1}H-NMR (400.16 MHz, C_6D_6) of 10b

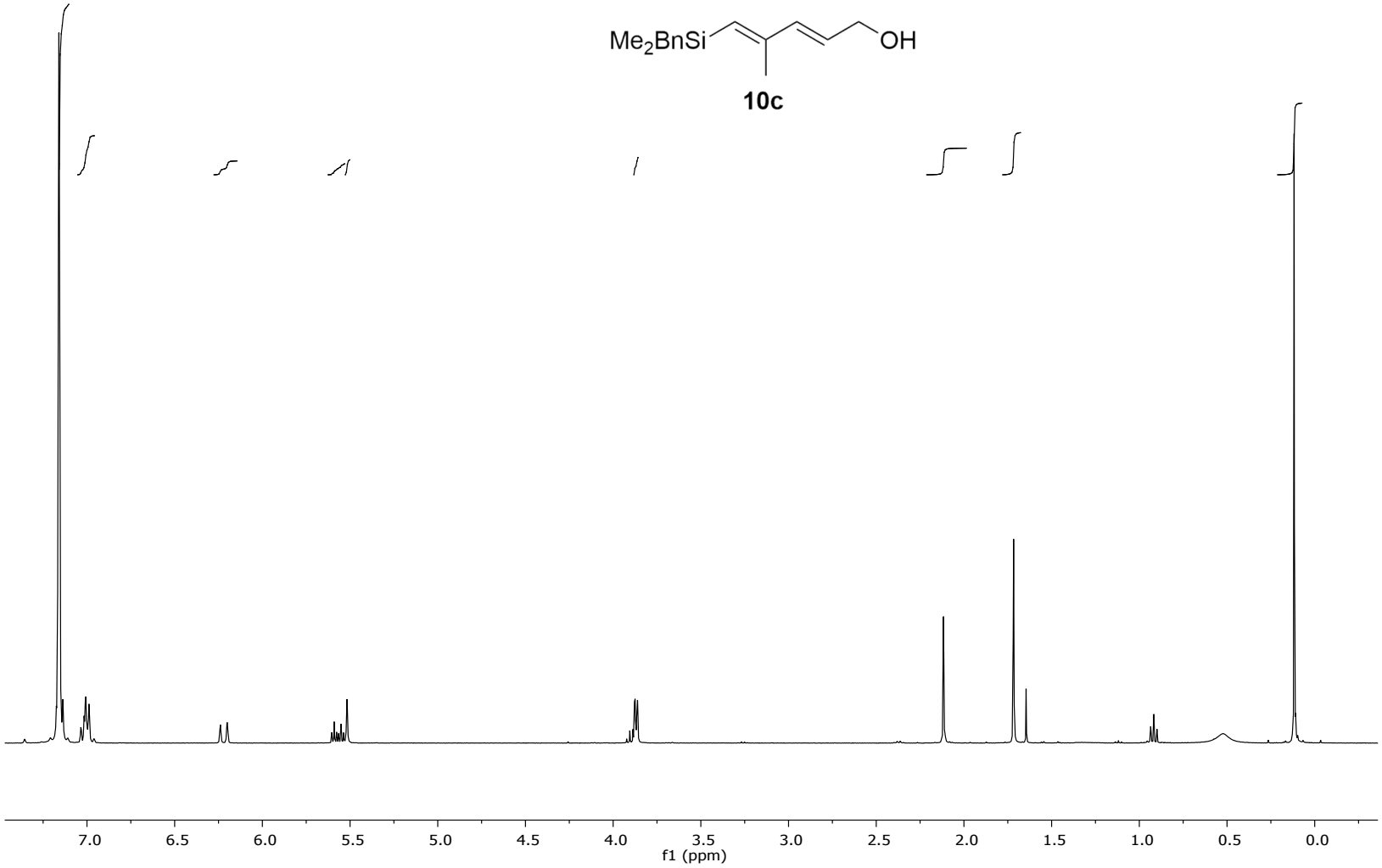


^{13}C-NMR (100.63 MHz, C_6D_6) of 10b

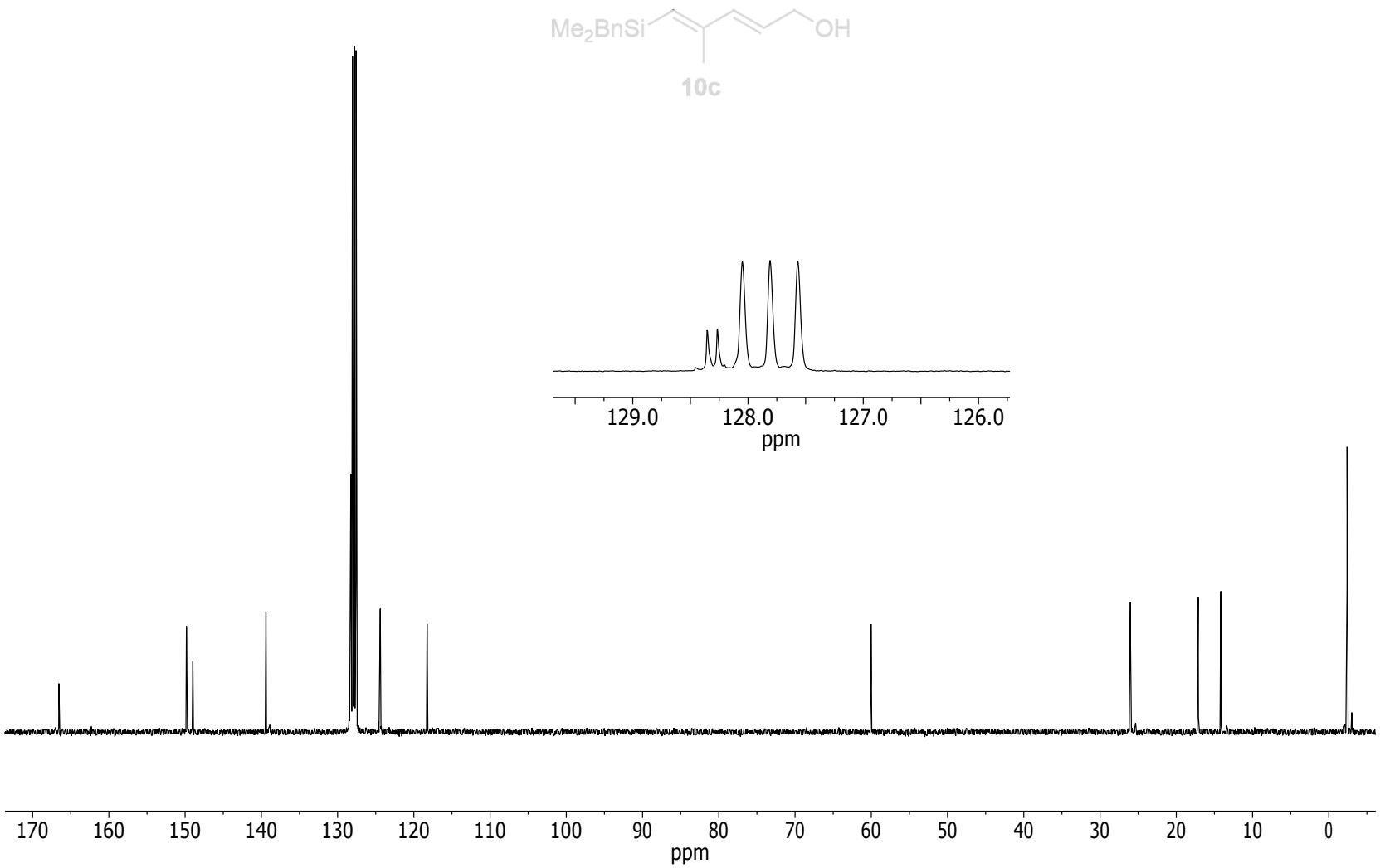
10b



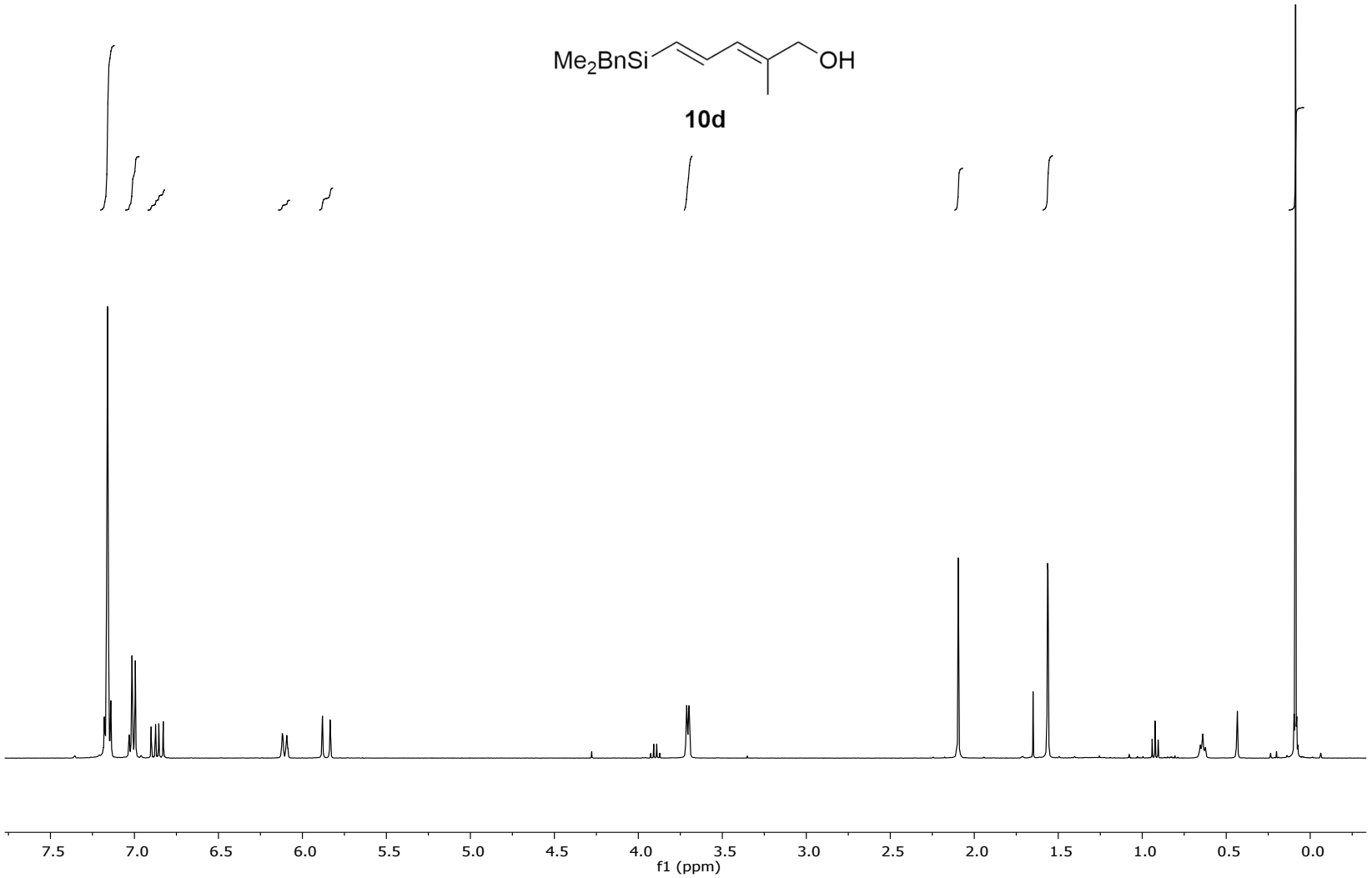
^{1}H-NMR (400.16 MHz, C_6D_6) of 10c



^{13}C-NMR (100.63 MHz, C_6D_6), spectrum of 10c.

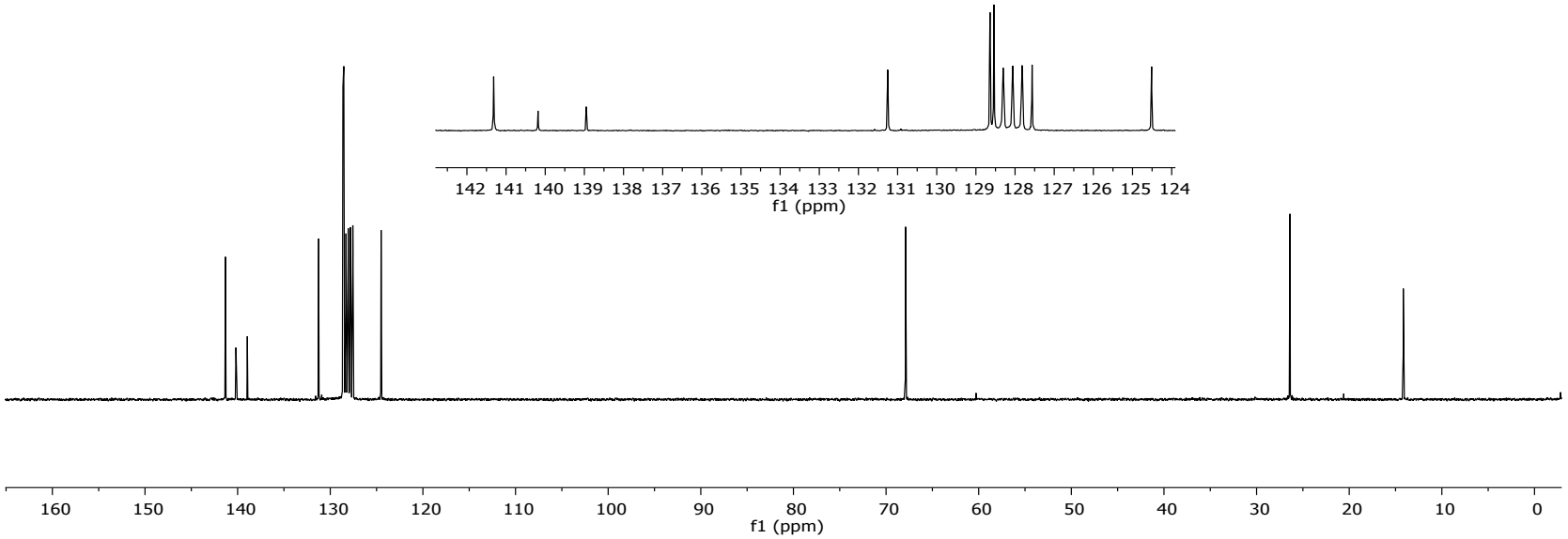


^{1}H-NMR (400.16 MHz, C_6D_6) of 10d

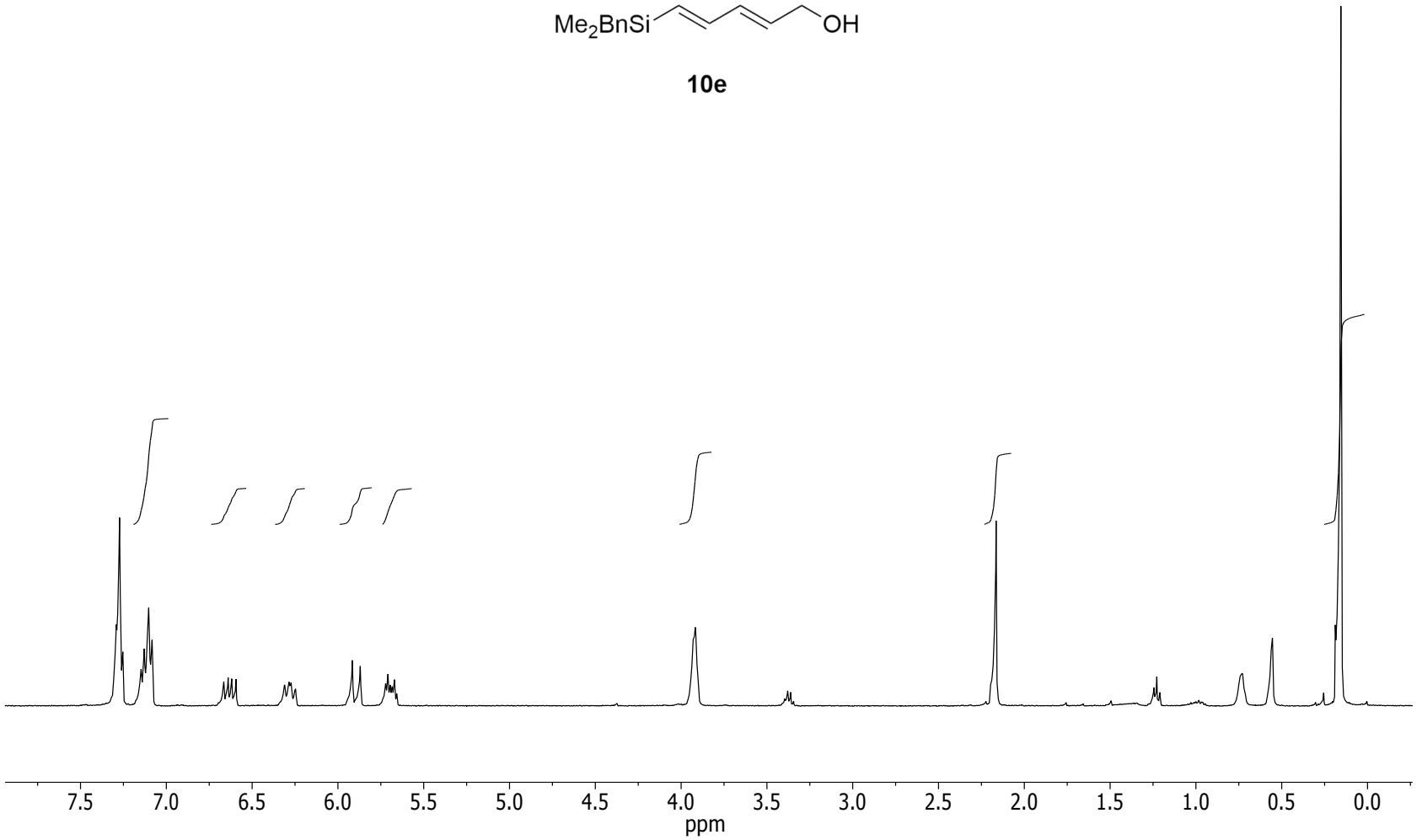


^{13}C-NMR (100.63 MHz, C_6D_6) of 10d

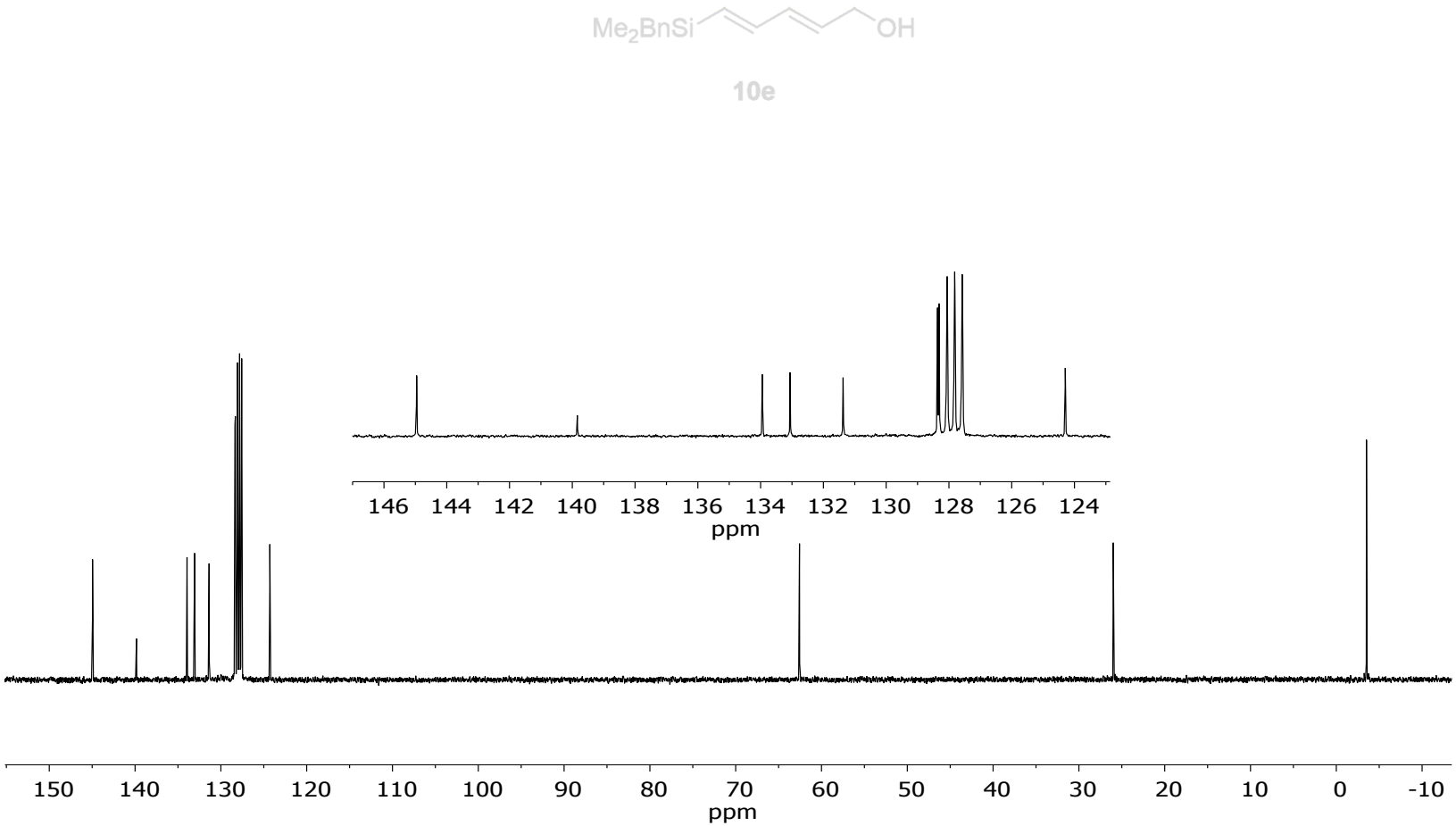
10d



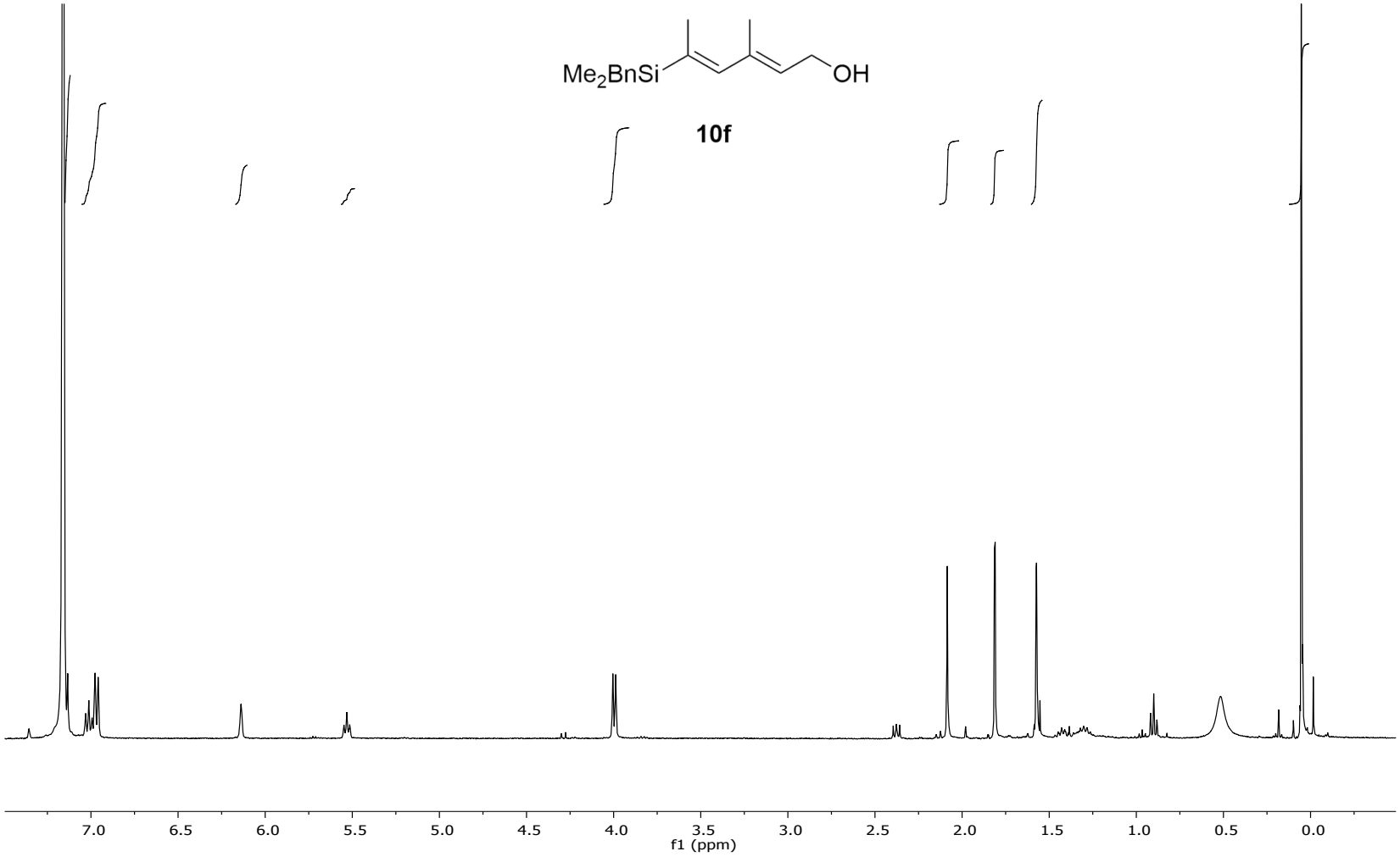
^{1}H-NMR (400.16 MHz, C_6D_6) of 10e



^{13}C-NMR (100.63 MHz, C_6D_6) of 10e

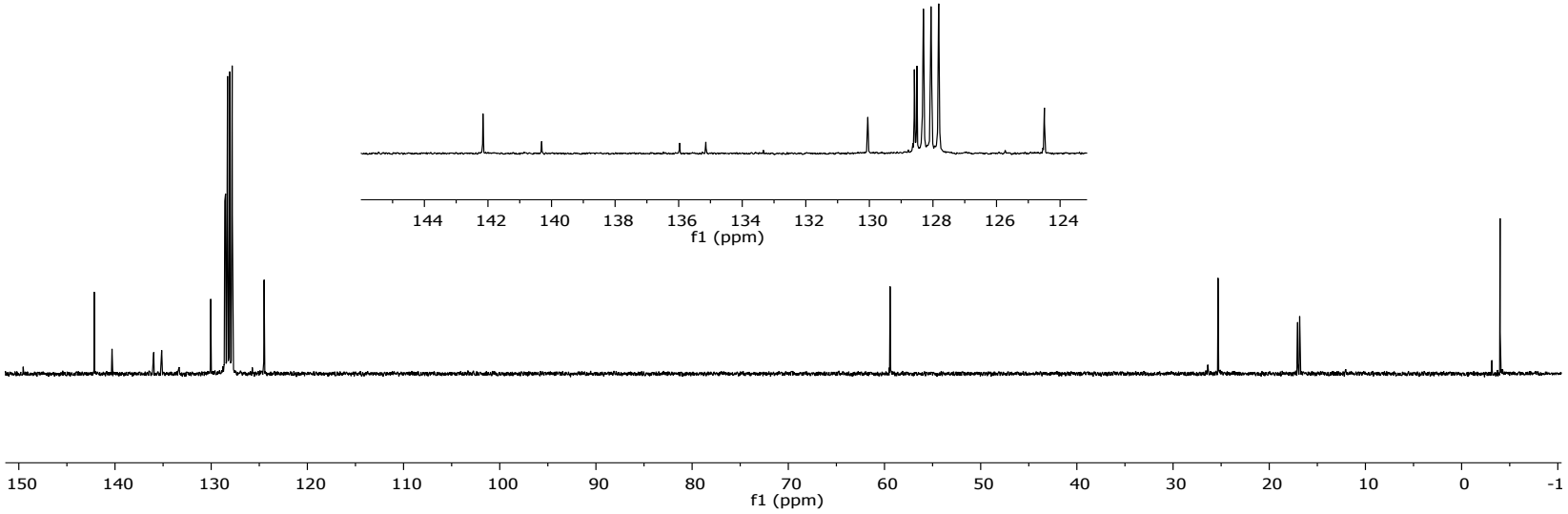


^{1}H-NMR (400.16 MHz, C_6D_6) of 10f

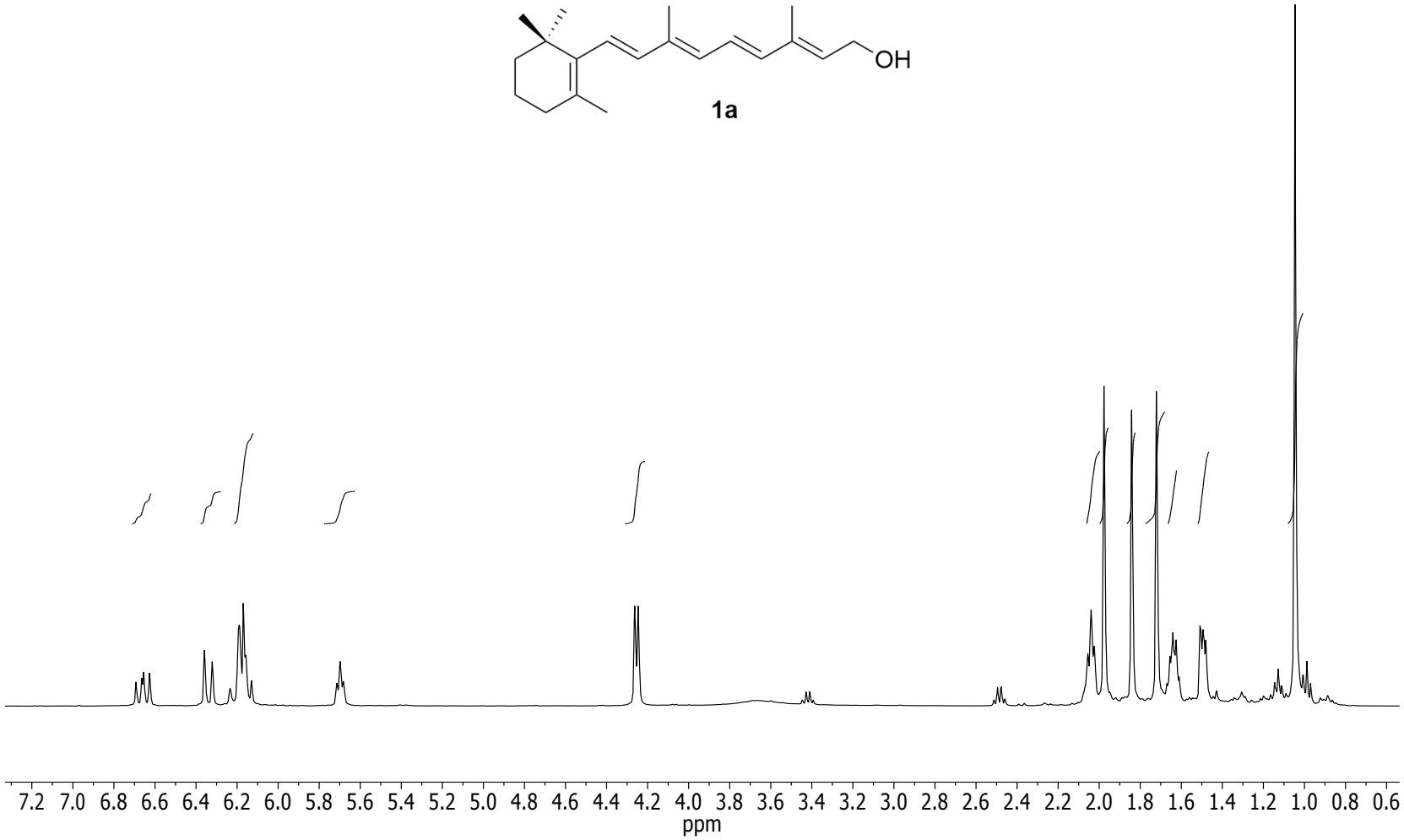


^{13}C-NMR (100.63 MHz, C_6D_6) of 10f

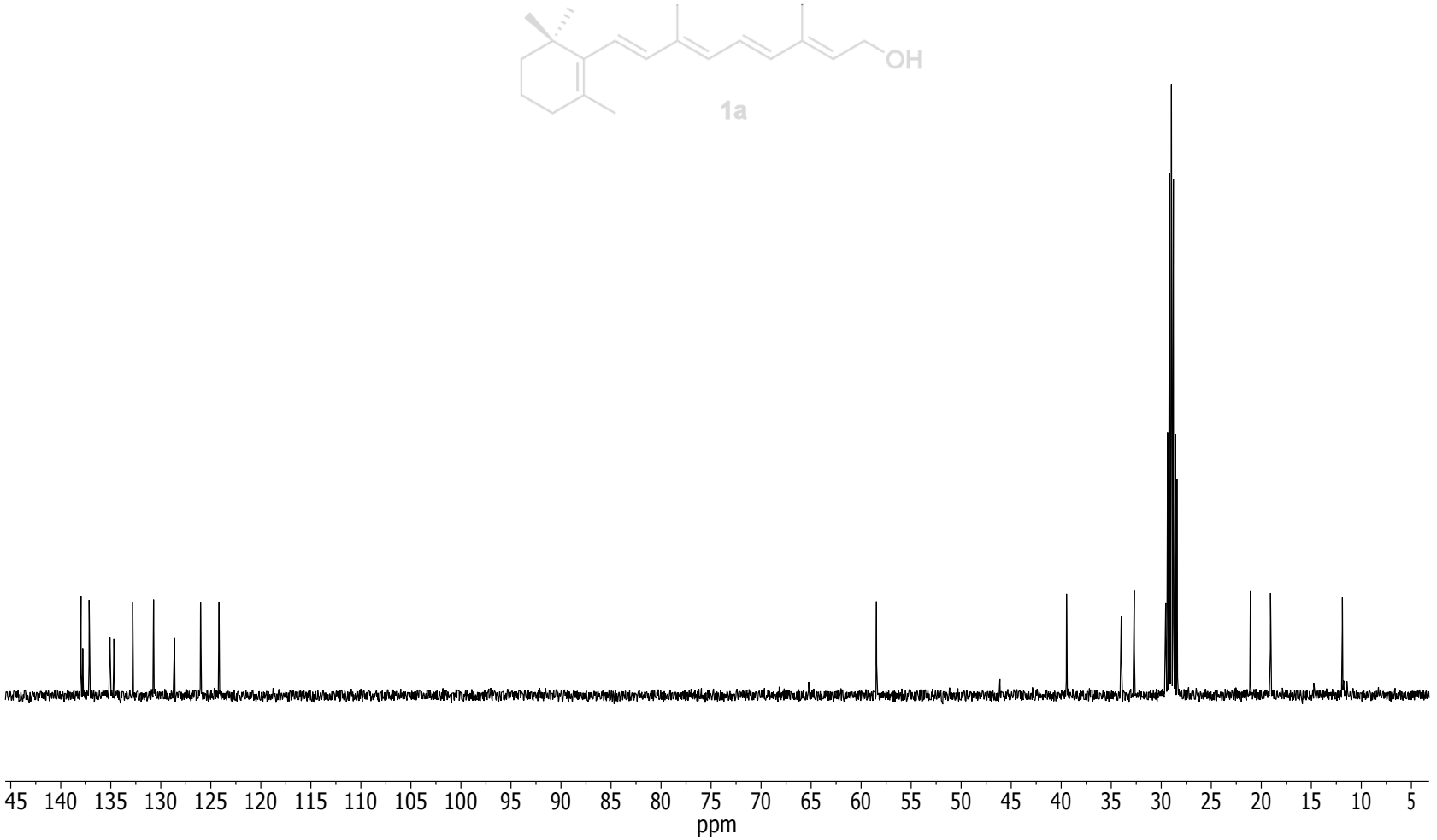
10f



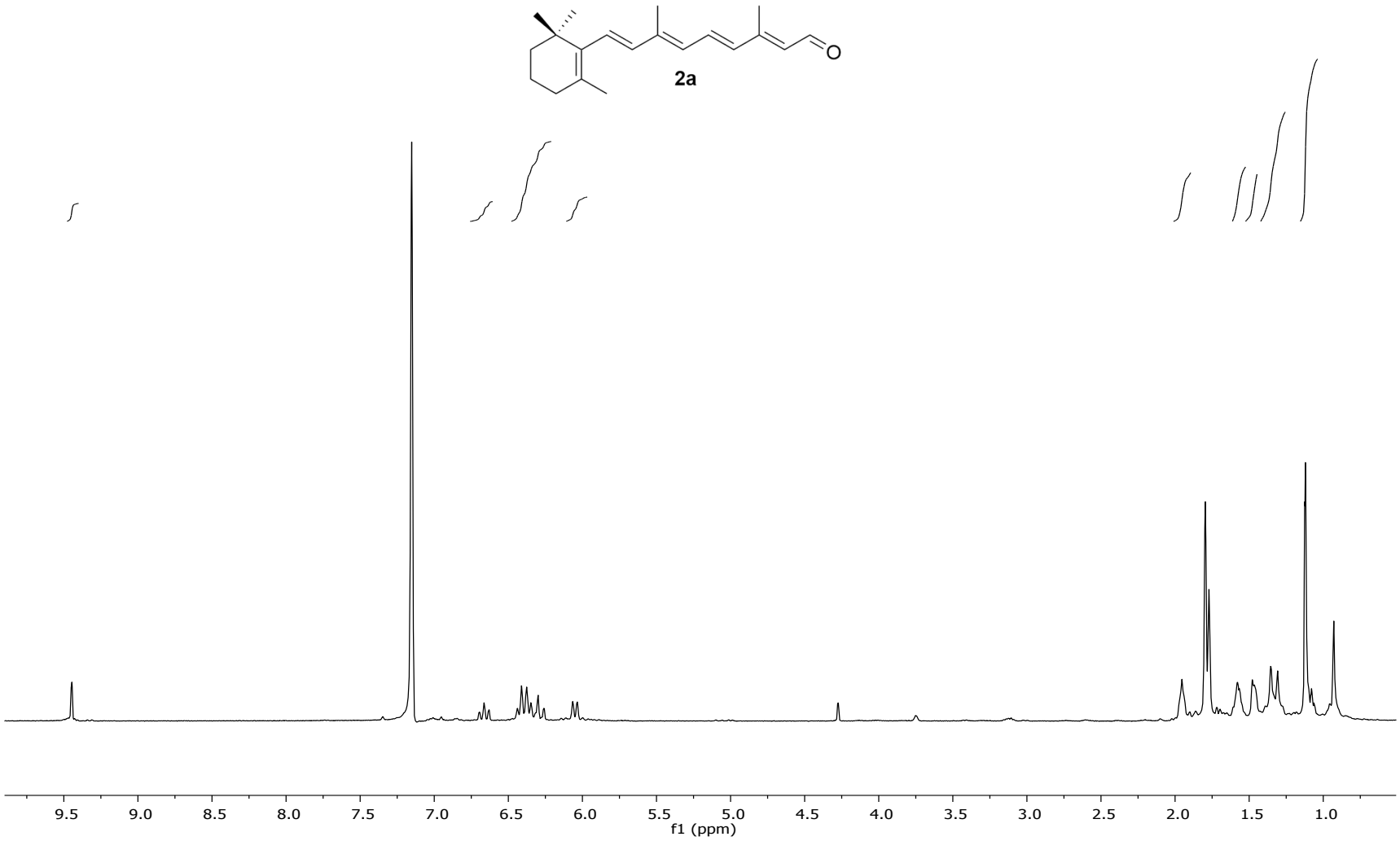
^{1}H-NMR (400.16 MHz, $(CD_3)_2CO$) of 1a



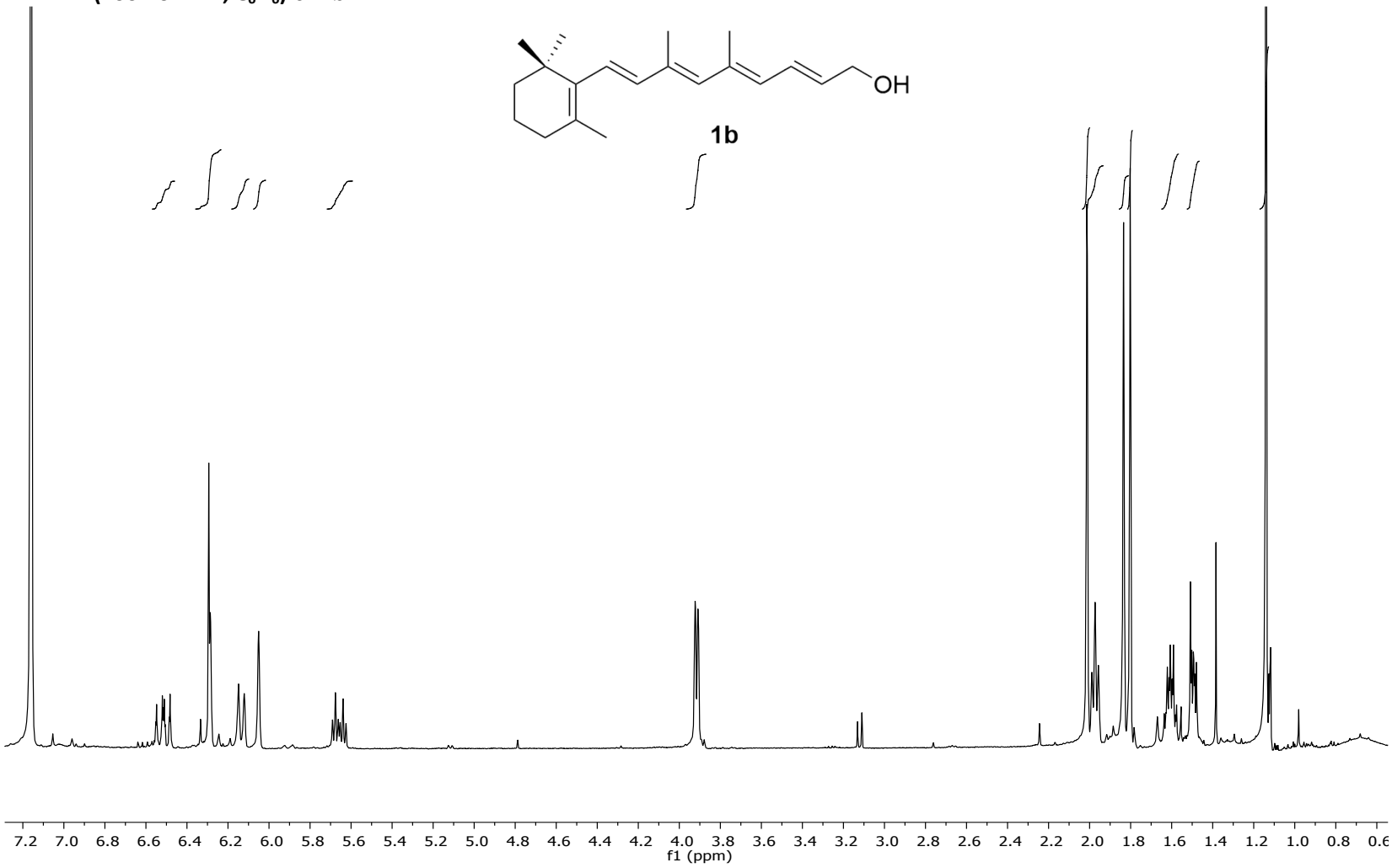
^{13}C-NMR (100.63 MHz, $(CD_3)_2CO$) of 1a



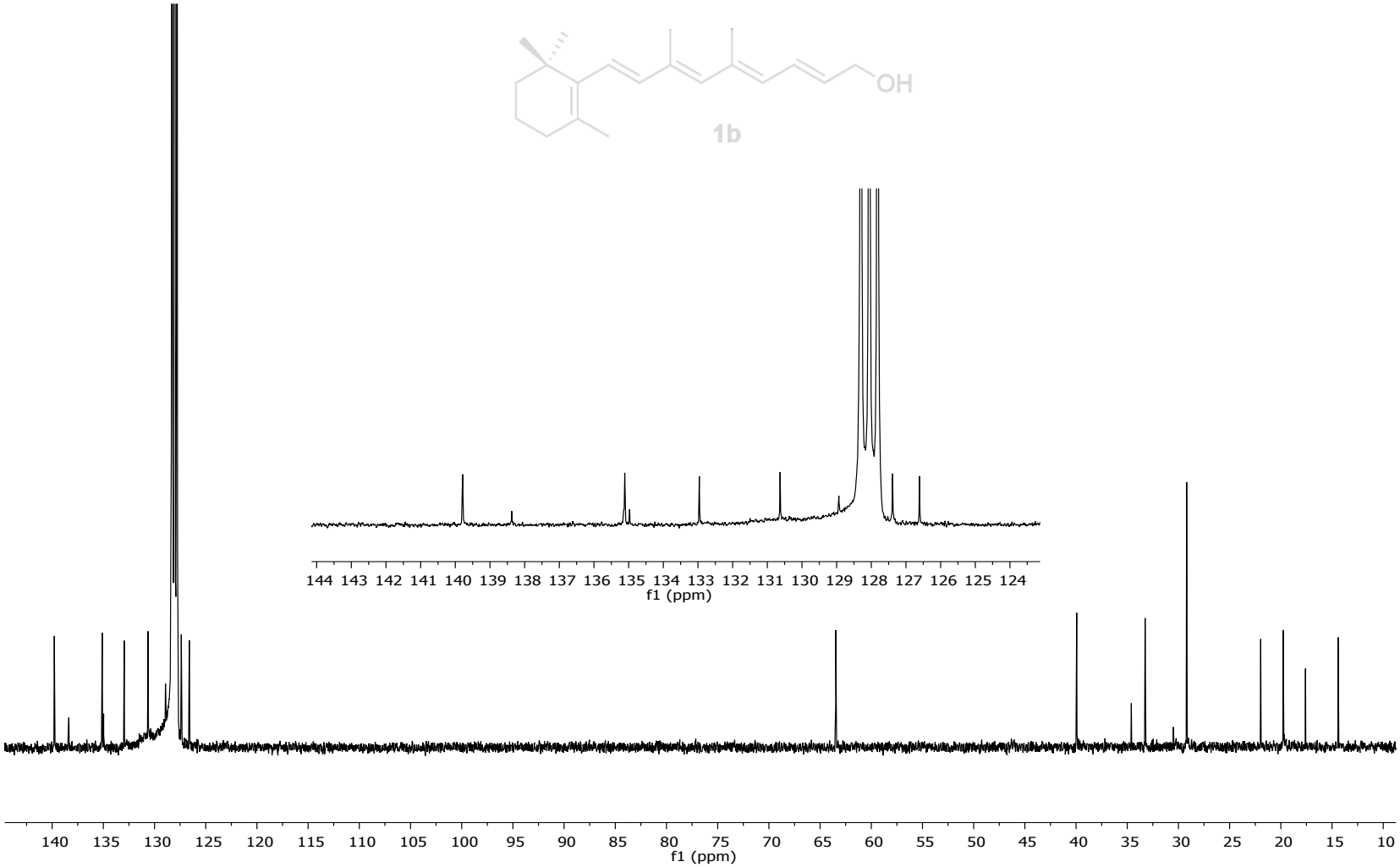
^{1}H-NMR (400.16 MHz, C_6D_6) of 2a



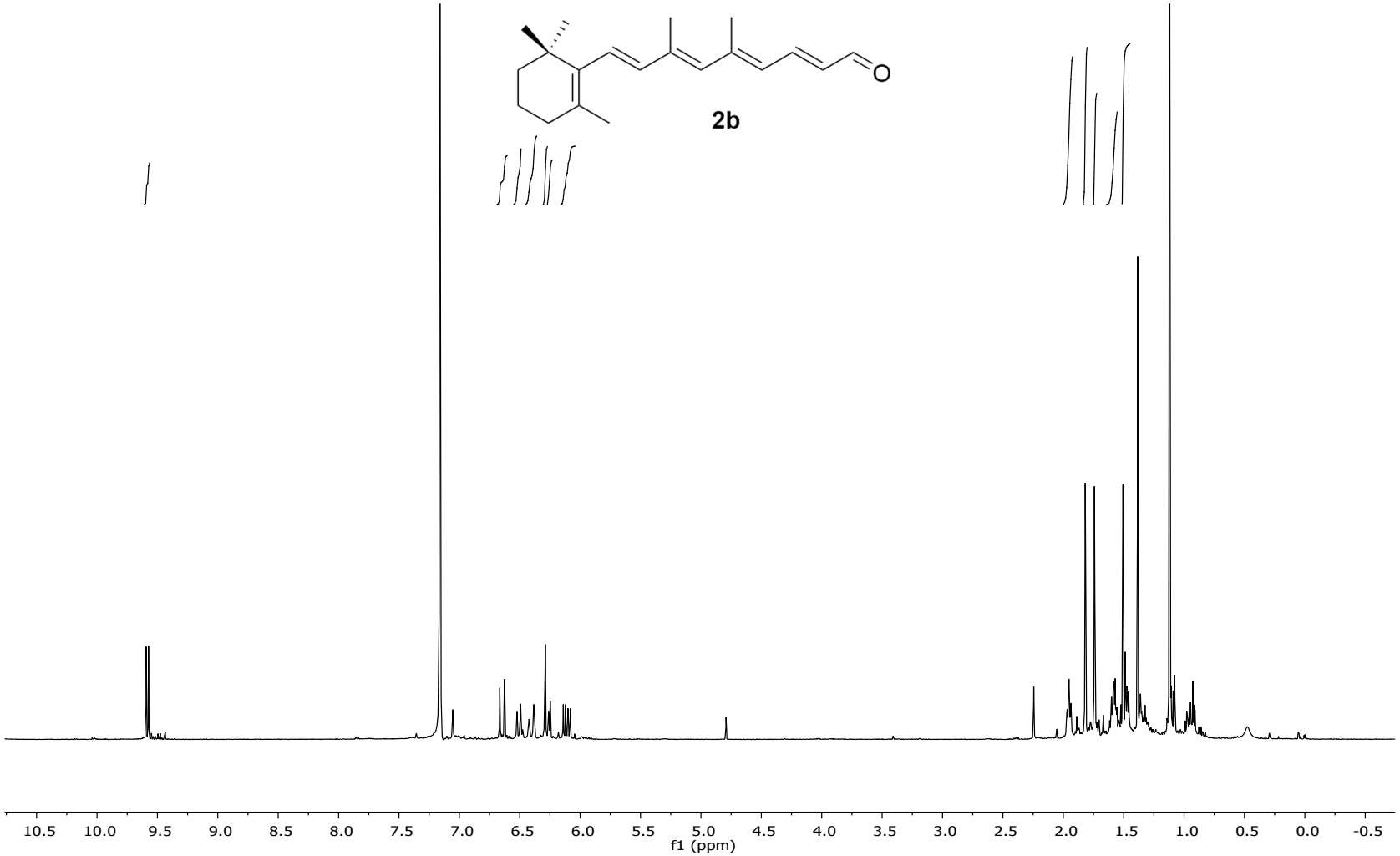
^{1}H-NMR (400.16 MHz, C_6D_6) of 1b



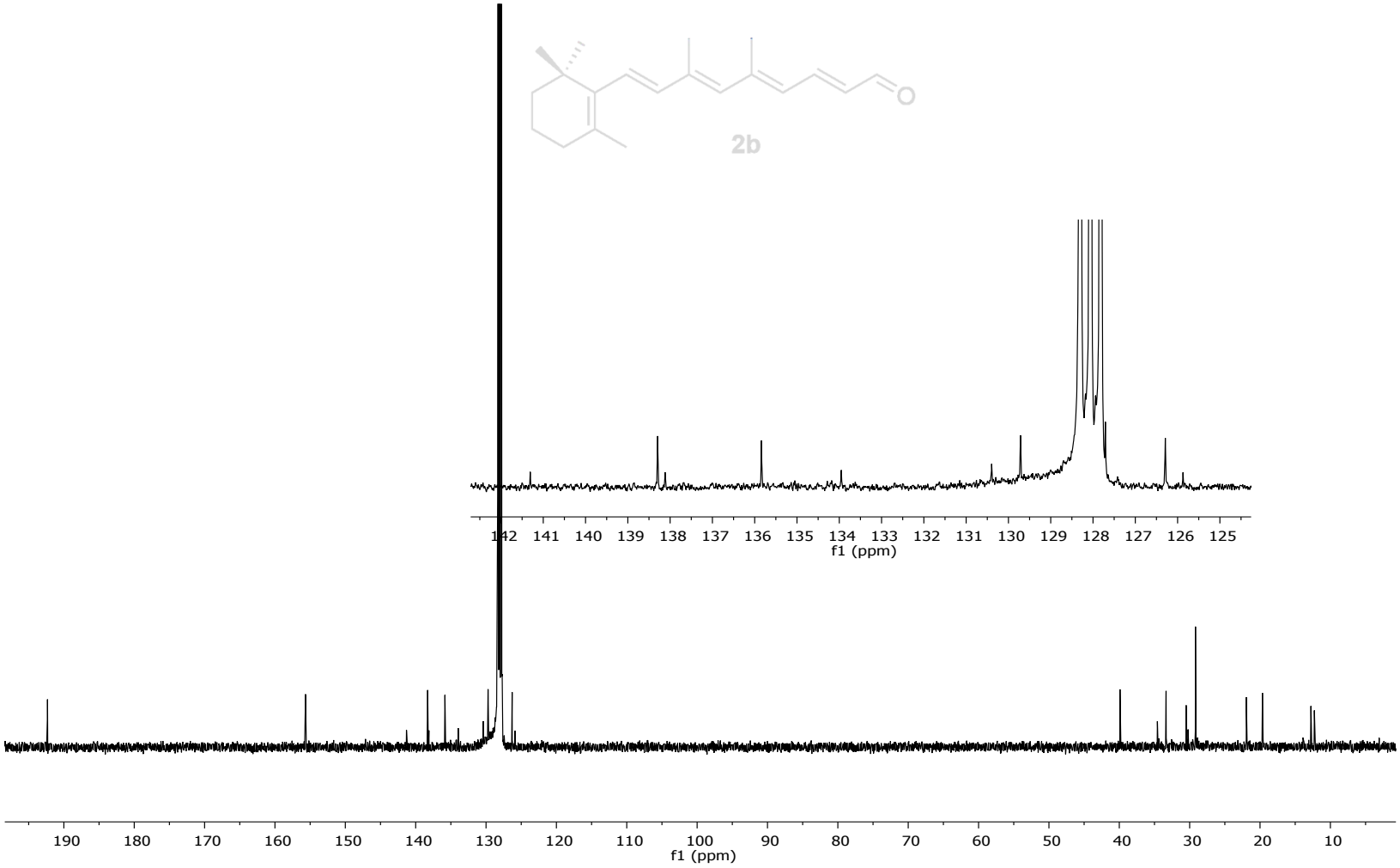
^{13}C-NMR (100.63 MHz, C_6D_6) of 1b



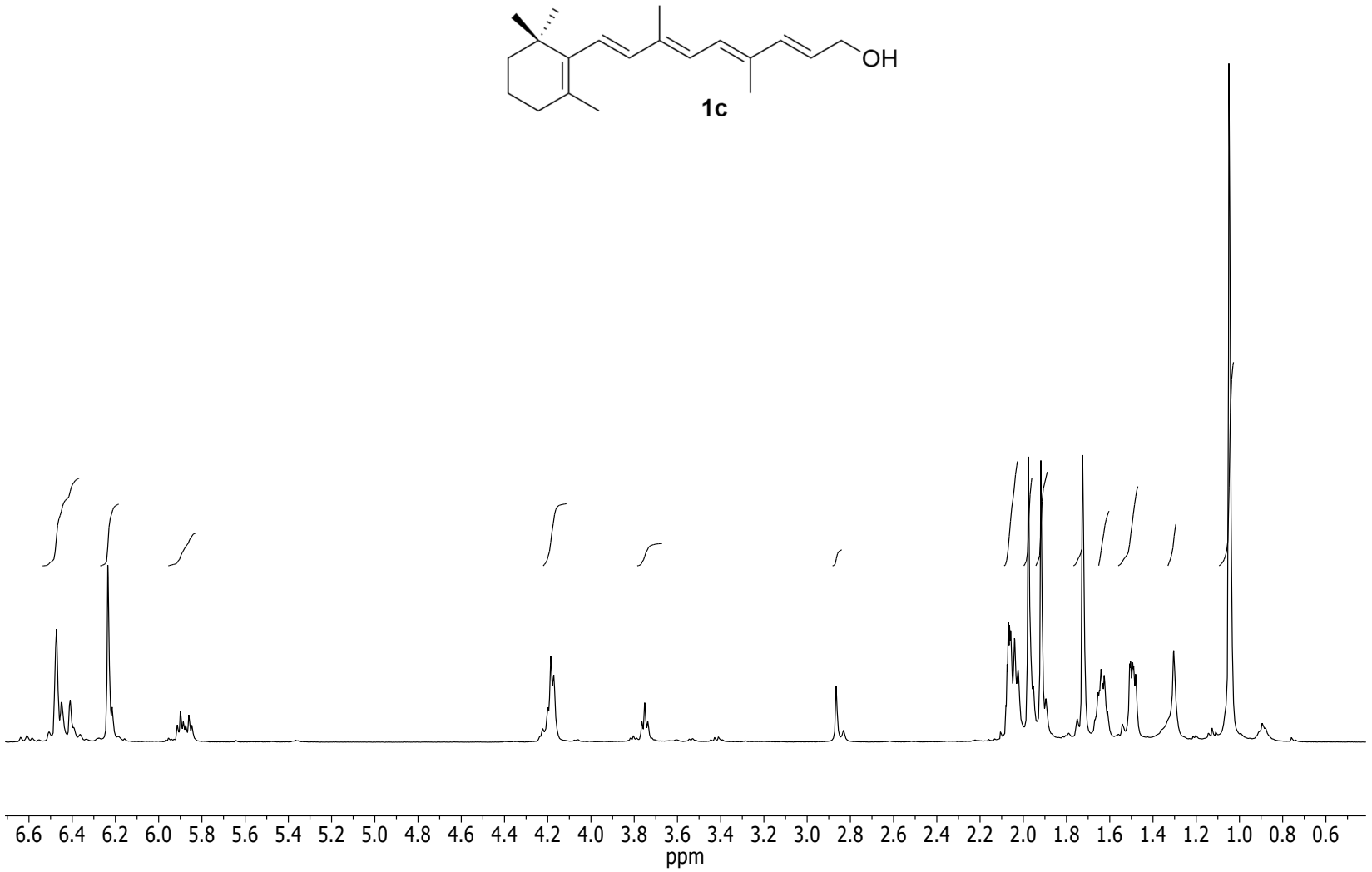
^{1}H-NMR (400.16 MHz, C_6D_6) of 2b



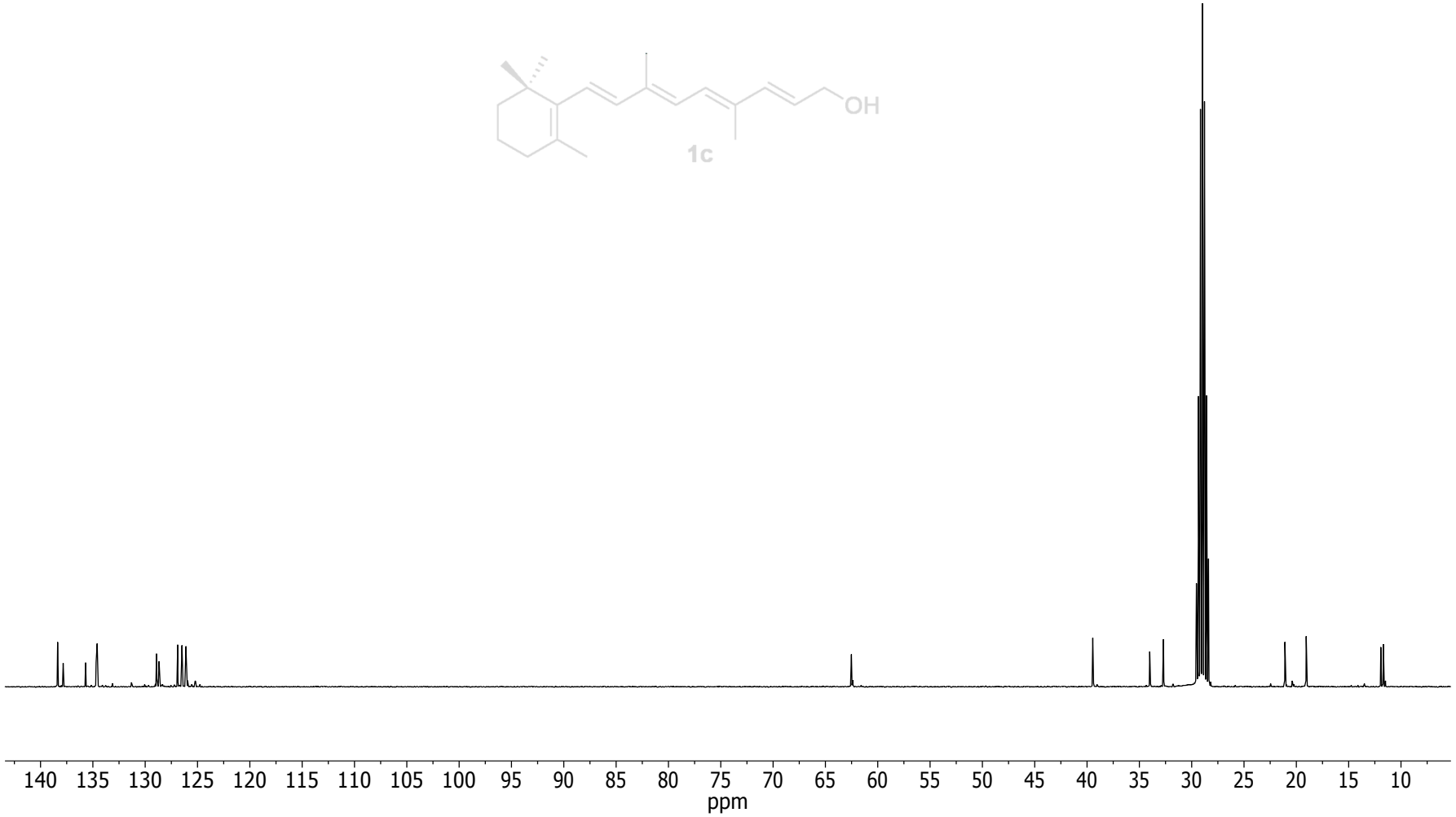
^{13}C-NMR (100.63 MHz, C_6D_6) of 2b



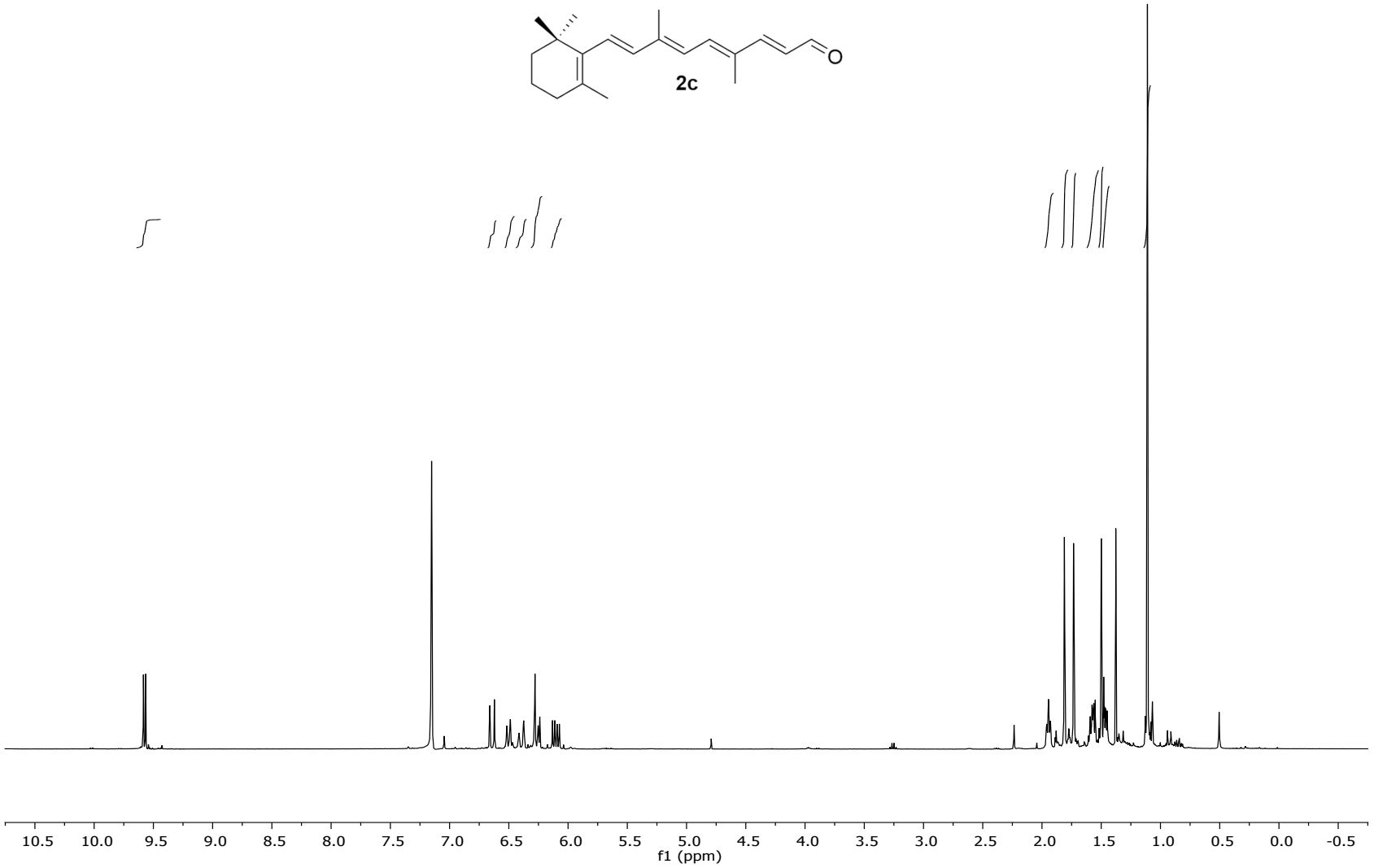
^{1}H-NMR (400.16 MHz, C_6D_6) of 1c



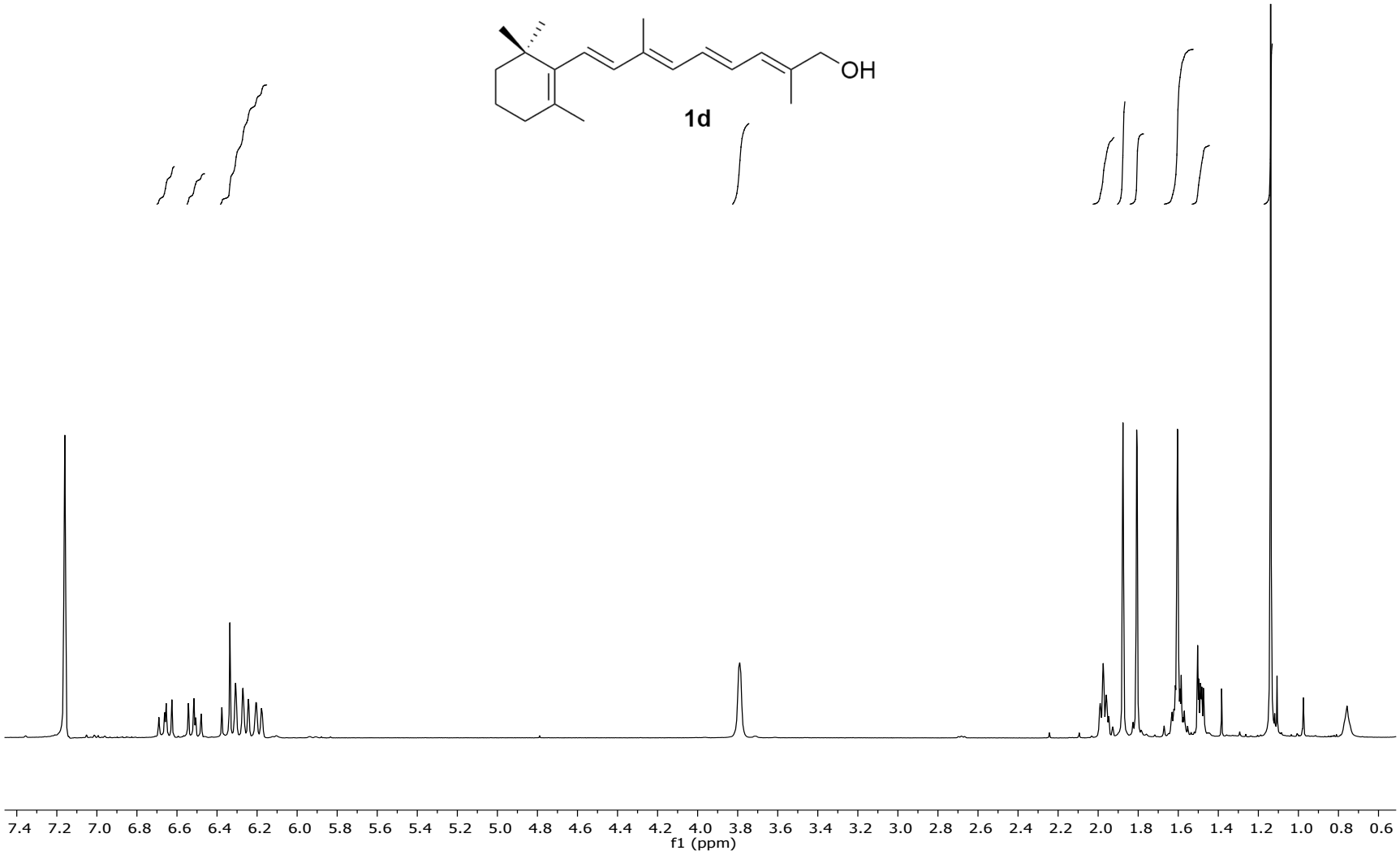
^{13}C-NMR (100.63 MHz, C_6D_6) of 1c



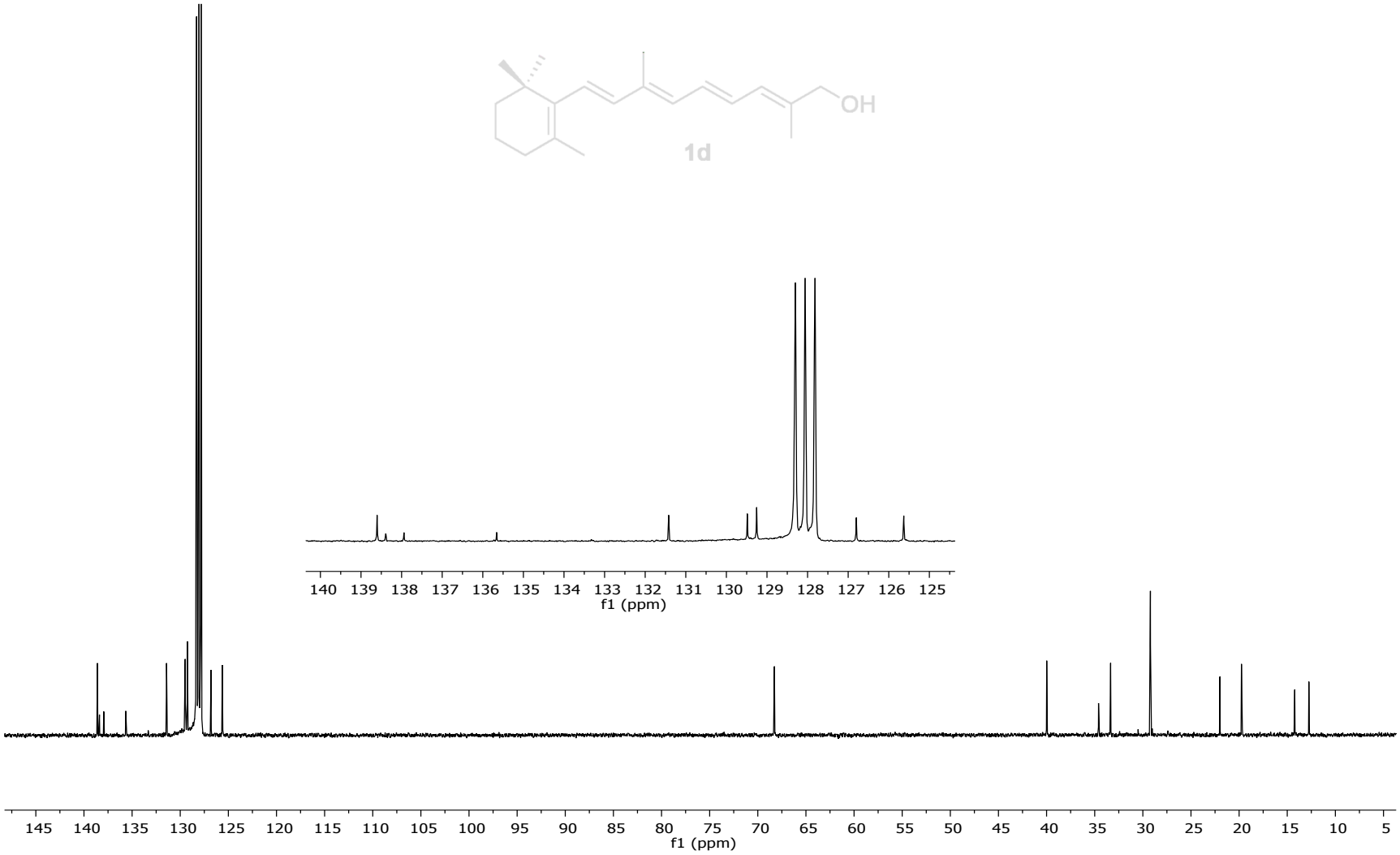
^{1}H-NMR (400.16 MHz, C_6D_6) of 2c



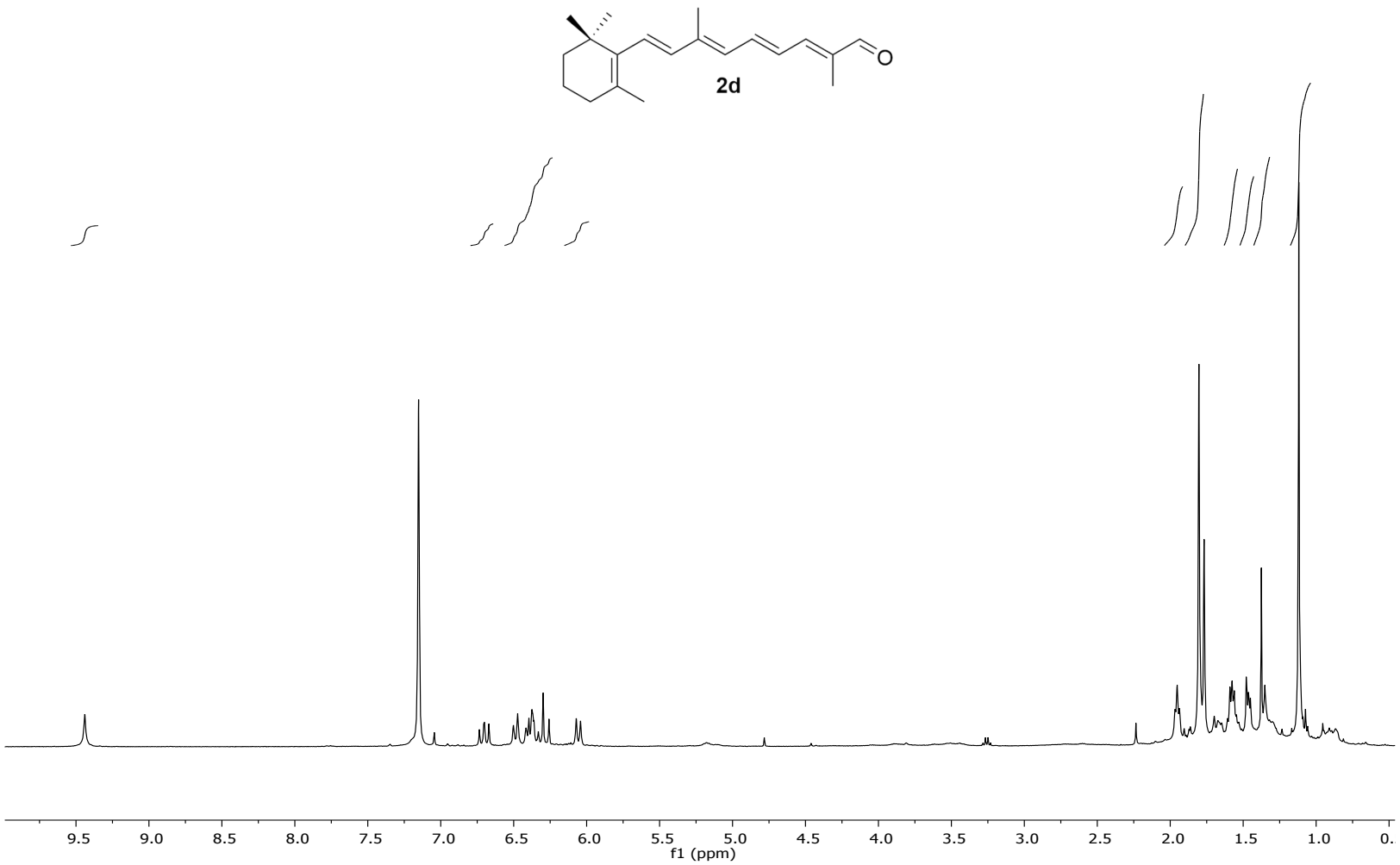
^{1}H-NMR (400.16 MHz, C_6D_6) of 1d



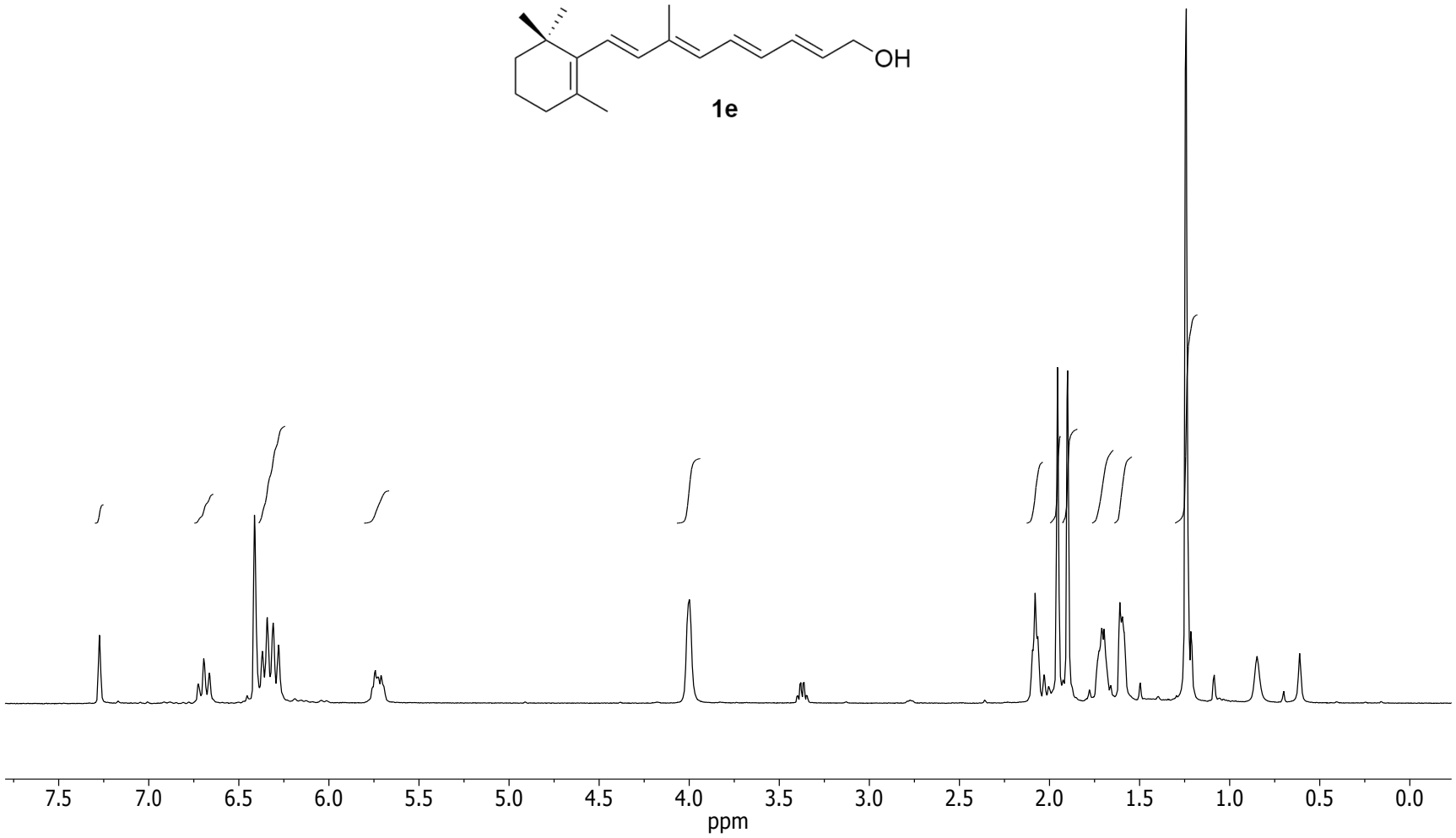
^{13}C-NMR (100.63 MHz, C_6D_6) of 1d



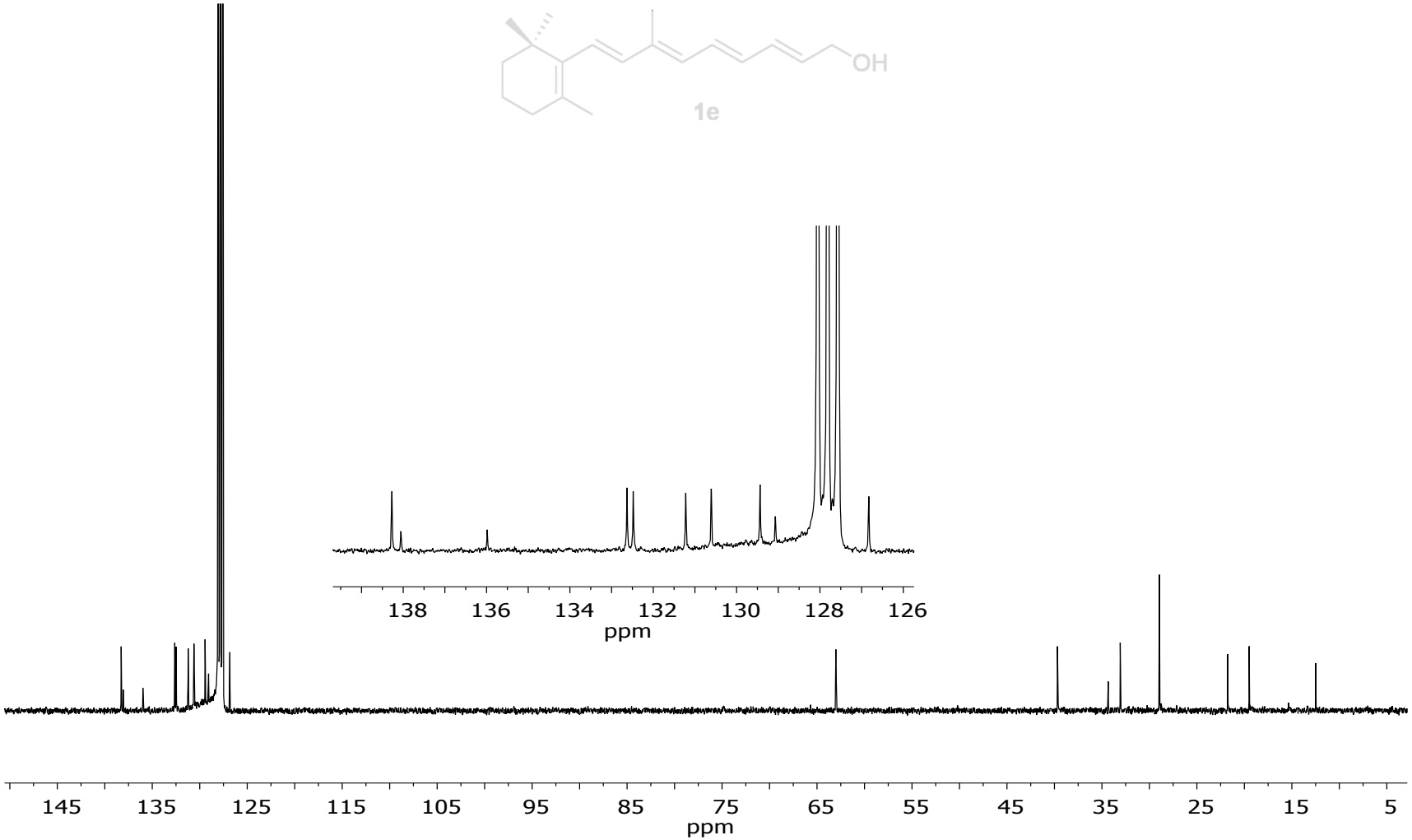
^{1}H-NMR (400.16 MHz, C_6D_6) of 2d


O
2d
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.
f1 (ppm)

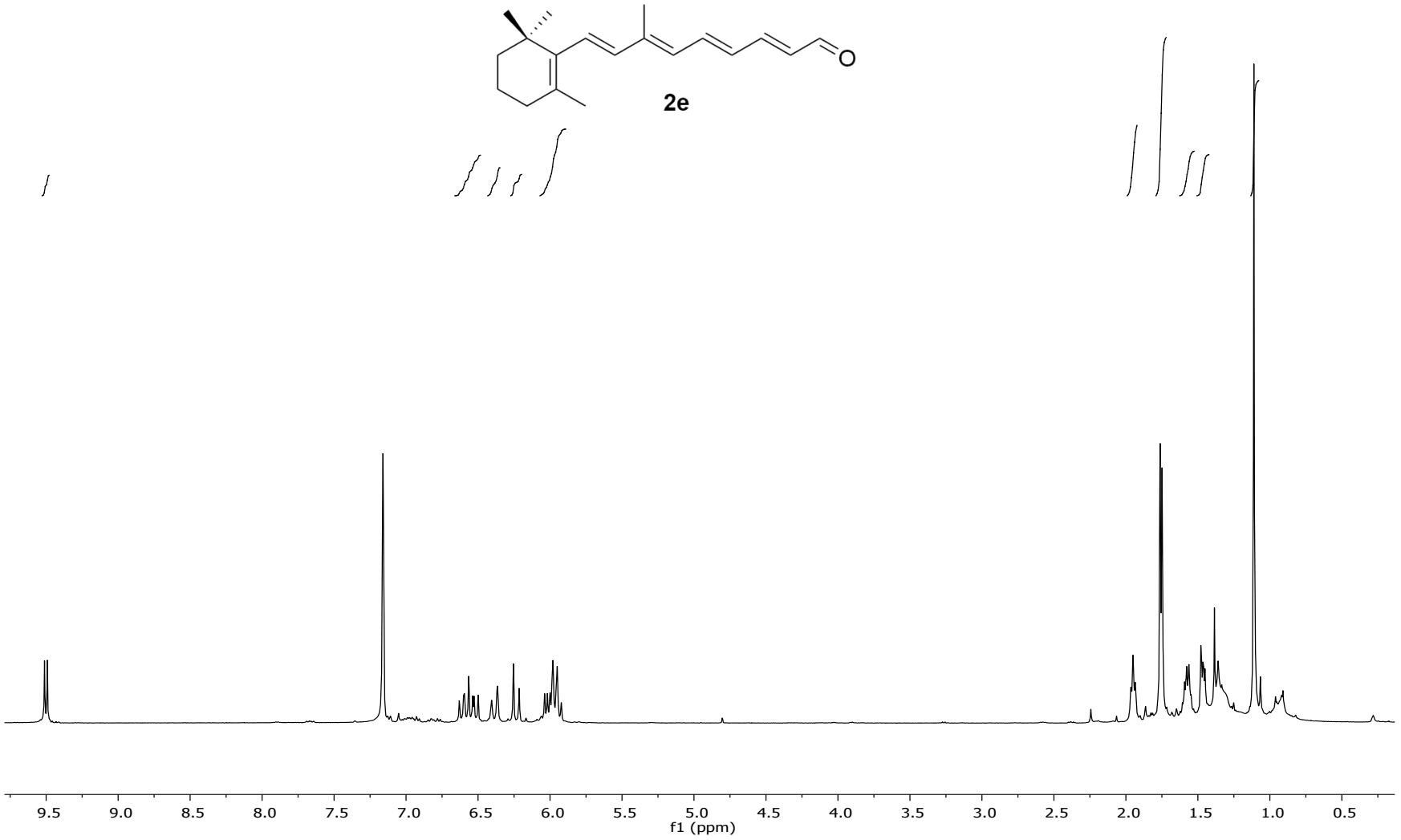
^{1}H-NMR (400.16 MHz, C_6D_6) of 1e



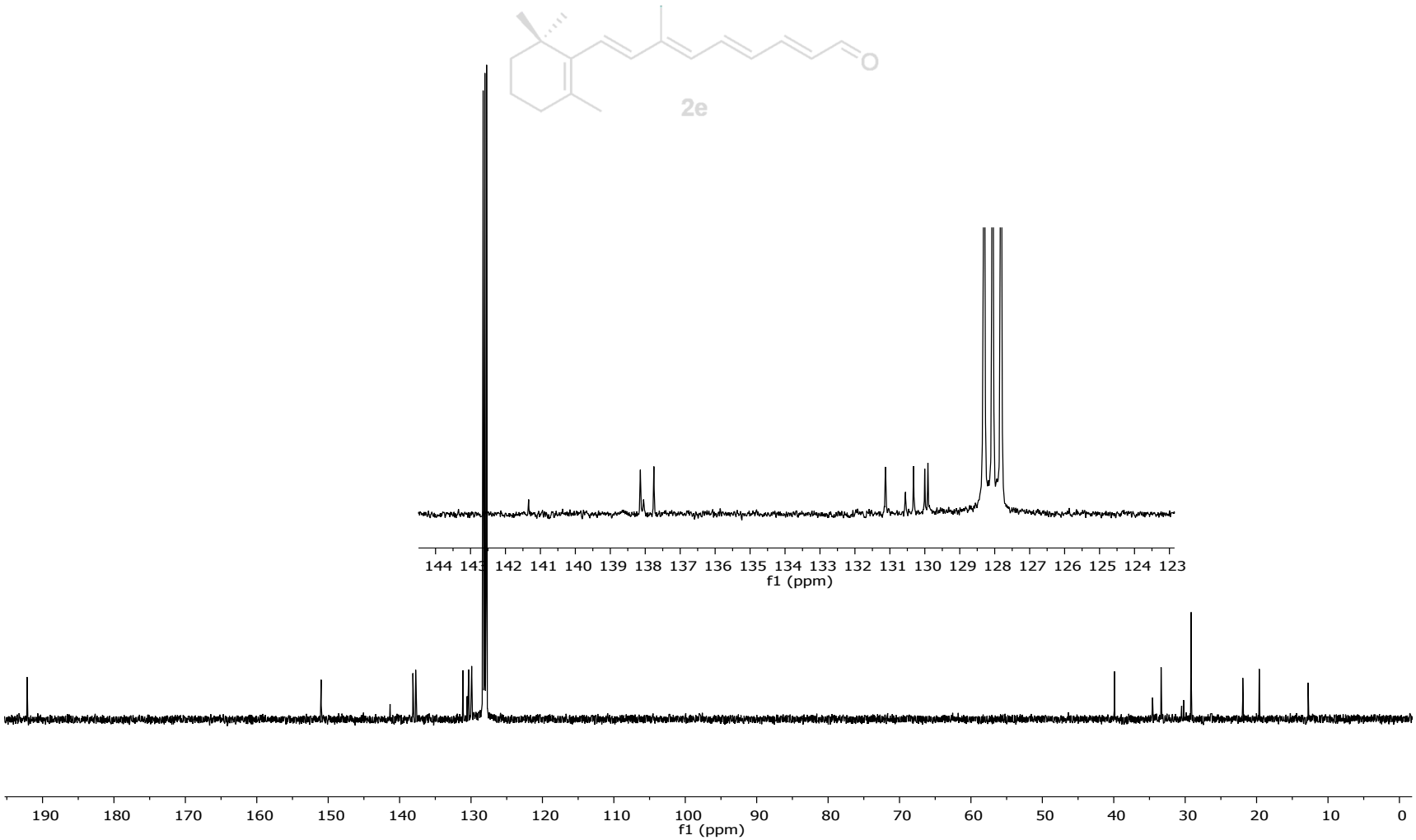
^{13}C-NMR (100.63 MHz, C_6D_6) of 1e



^{1}H-NMR (400.16 MHz, C_6D_6) of 2e

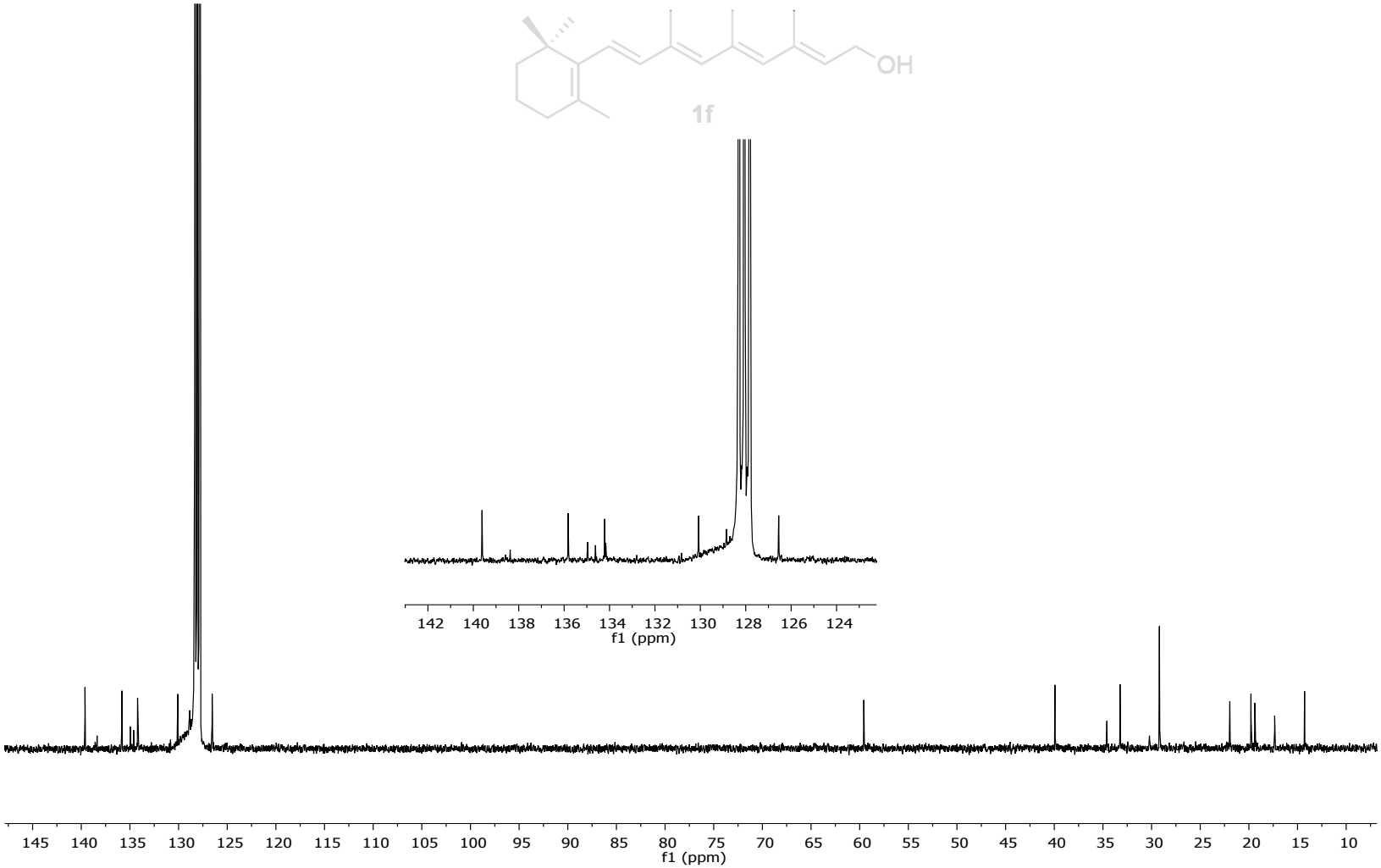


^{13}C-NMR (100.63 MHz, C_6D_6) of 2e

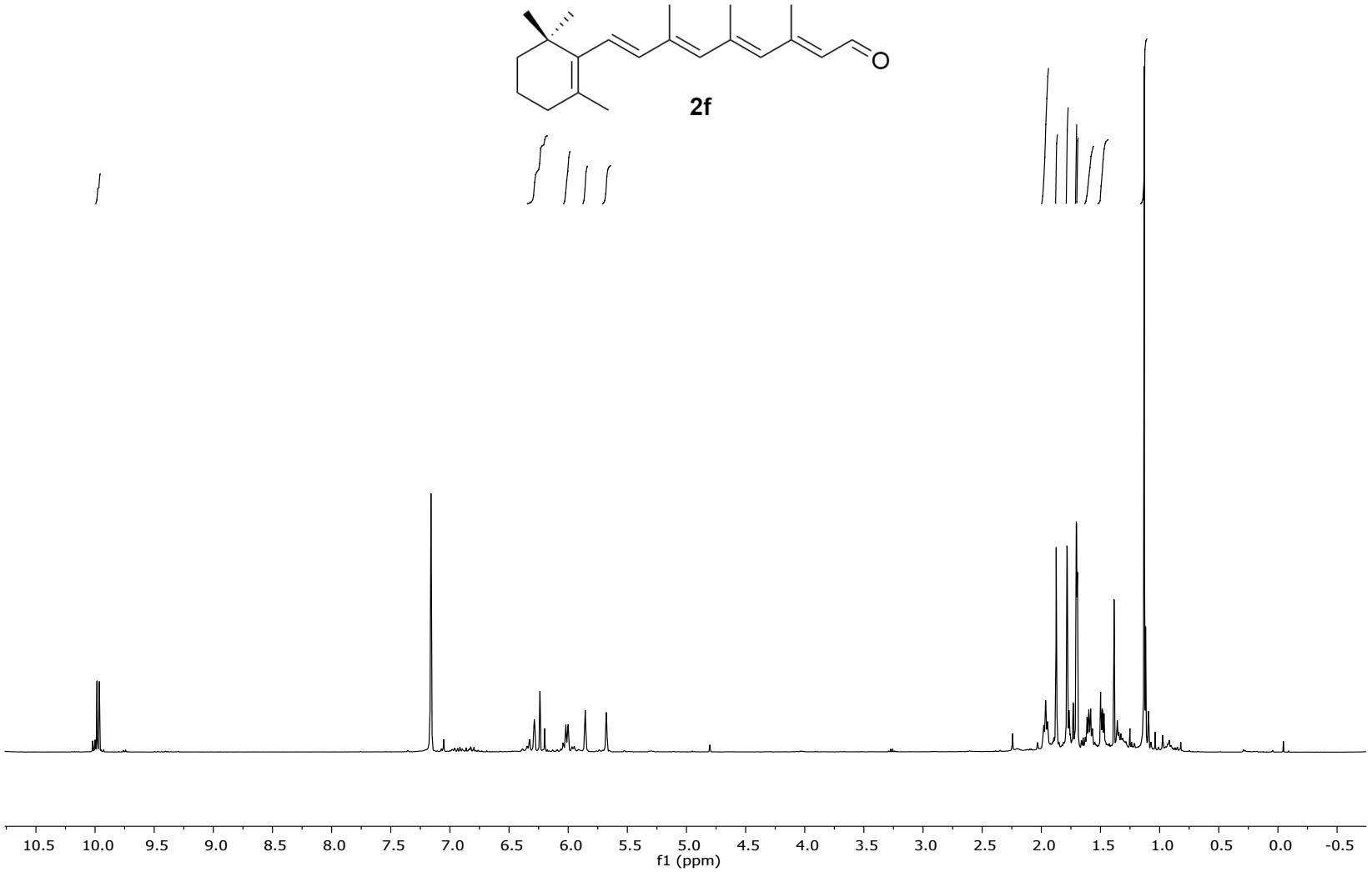


^{1}H-NMR (400.16 MHz, C_6D_6) of 1f

^{13}C-NMR (100.63 MHz, C_6D_6) of 1f



^{1}H-NMR (400.16 MHz, C_6D_6) of 2f



^{13}C-NMR (100.63 MHz, C_6D_6) of 2f