

# Studies toward Soraphen A: an aldol metathesis avenue to the macrocyclic framework

**Guillaume Vincent,<sup>a</sup> Darren J. Mansfield,<sup>b</sup> Jean-Pierre Vors<sup>b</sup> and Marco A. Ciufolini<sup>\*a,c</sup>**

<sup>a</sup>*Laboratoire de Synthèse et méthodologie Organique (LSMO), CNRS UMR 5181, Université Claude Bernard-Lyon I and Ecole Supérieure de Chimie, Physique et Electronique de Lyon, 43, Bld du 11 Novembre 1918, 69622 Villeurbanne Cedex, France*

<sup>b</sup>*Bayer CropScience SA, 14-20 rue Pierre Baizet, 69009 Lyon, France*

<sup>c</sup>*Department of Chemistry, University of British Columbia, 2036 Main Mall, Vancouver, BC V6T 1Z1, Canada*

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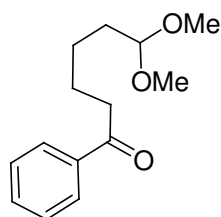
## Supporting Information

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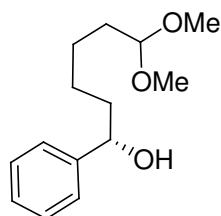
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**Experimental protocols :** Proton and  $^{13}\text{C}$  NMR spectra were obtained from  $\text{CDCl}_3$  as solvent. Chemical shifts are reported in parts per million (ppm) on the  $\delta$  scale and coupling constants,  $J$ , are in hertz (Hz). Proton NMR spectra were recorded at 300 or 500 MHz, as specified,  $^{13}\text{C}$  NMR spectra were recorded at 75 or 125 MHz, as specified. FT-IR spectra ( $\text{cm}^{-1}$ ) were recorded neat. Mass spectra ( $m/z$ ) were measured in the chemical ionization (CI, isobutene as the reagent gas), electrospray (ESI), electronic impact (EI) or liquid secondary mass spectroscopy (LSIMS) mode, as specified. All reactions were performed under dry Ar over dried flasks equipped with Teflon<sup>TM</sup> stirbars. All flasks were fitted with rubber septa for the introduction of substrates, reagents, and solvents via syringe. Commercial reagents were used without further purification, except THF (freshly distilled from Na/benzophenone under Ar) and  $\text{CH}_2\text{Cl}_2$  (freshly distilled from  $\text{CaH}_2$  under Ar).

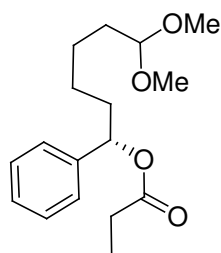
**\*Synthesis of fragment 2.**



**Compound 5:** Ozone was bubbled to a solution of 5.18 g of 1-phenylcyclohexene **4** (32.8 mmol) in 150 mL of dichloromethane and 150 mL of methanol at  $-78^\circ\text{C}$  until the apparition of a blue color (3 hours). Oxygen was then bubbled until the blue color disappeared (20 min), argon was bubbled 20 min and 12 mL of dimethyl sulfide (164 mmol) and 312 mg of *p*TsOH (1.6 mmol) were then added. The reaction was stirred 12 hrs at RT and concentrated under vacuum. The crude was then diluted with 200 mL of  $\text{CH}_2\text{Cl}_2$  and 200 mL of a saturated aqueous solution of  $\text{NaHCO}_3$ . The organic phase was separated and the aqueous phase was extracted with 200 mL of  $\text{CH}_2\text{Cl}_2$ . The combined extracts were dried with  $\text{Na}_2\text{SO}_4$  and concentrated. Silica gel chromatography of the residue (ethyl acetate/cyclohexane, 1:9) afforded the desired product **5** as a colorless oil (6.46 g, 83%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ): 7.97-7.93 (m, 2H), 7.58-7.43 (m, 3H), 4.38 (t,  $J = 5.6$  Hz, 1H), 3.32 (s, 6H), 2.98 (t,  $J = 7.3$  Hz, 2H), 1.85-1.62 (m, 4H), 1.48-1.41 (m, 2H).

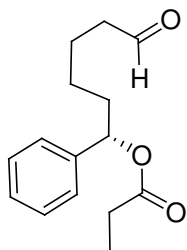


**Compound 6:** To a solution of 5.20 g of **5** (22.1 mmol) in 70 mL of THF at  $-30^\circ\text{C}$  were added 5 mL of a 1M solution of (R)-2-methyl-CBS-oxazaborolidine (5 mmol) in THF, then dropwise 22.1 mL of a 2M solution of  $\text{BH}_3\cdot\text{DMS}$  (44.1 mmol) in THF at  $-30^\circ\text{C}$ . The reaction mixture was then stirred 2 hrs at  $-10^\circ\text{C}$  and quenched with 10 mL of methanol. The reaction mixture was stirred 15 min at RT and a saturated aqueous solution of  $\text{NH}_4\text{Cl}$  (80 mL) was added. The organic phase was separated and the aqueous phase was extracted with 100 mL of EtOAc. The combined extracts were dried with  $\text{Na}_2\text{SO}_4$  and concentrated. Silica gel chromatography of the residue (ethyl acetate/cyclohexane, 2/8) afforded the desired product as a colorless oil (4.90 g, 93%) with a diastereomeric excess of 70% determined by the Mosher's method (see compounds **a** and **b**).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ): 7.35 -7.28 (m, 5H), 4.67 (m, 1H), 4.33 (t,  $J = 5.6$  Hz, 1H), 3.29 (s, 6H), 1.81-1.62 (m, 2H), 1.61-1.54 (m, 2H), 1.53-1.33 (m, 4H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ): 145.4, 128.7, 127.8, 126.3, 104.7, 74.7, 52.9, 39.4, 32.7, 26.0, 24.8. IR ( $\text{cm}^{-1}$ ): 3420, 2937, 1453, 1126, 1050, 701. HRMS (EI): calculated 237.1491, found 237.1493 ( $\text{M}^+ - \text{H}$ ).  $[\alpha]_D^{22}$  -22.6 (c 0.19,  $\text{CH}_2\text{Cl}_2$ ).

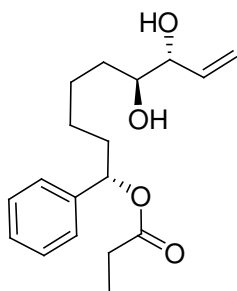


**Compound 7:** To a solution of 4.80 g of alcohol **6** (20.2 mmol) and 101 mg of DMAP (1.01 mmol) in 60 mL of  $\text{CH}_2\text{Cl}_2$  at  $0^\circ\text{C}$  were added 8.4 mL of  $\text{Et}_3\text{N}$  (61 mmol) and 3.6 mL of propionyl chloride (41 mmol). The reaction was stirred 12 hrs at RT and a saturated aqueous solution of  $\text{NaHCO}_3$  (40 mL) was added. The organic phase was separated and the

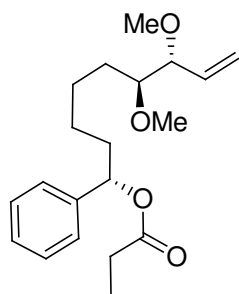
aqueous phase was extracted with 40 mL of  $\text{CH}_2\text{Cl}_2$ . The combined extracts were dried with  $\text{Na}_2\text{SO}_4$  and concentrated. Silica gel chromatography of the residue (ethyl acetate/ cyclohexane, 1:9) afforded the desired product as a colorless oil (5.32 g, 89%).  **$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):** 7.33-7.29 (m, 5H), 5.73 (dd,  $J = 7.5, 6.4$  Hz, 1H), 4.31 (t,  $J = 5.6$  Hz, 1H), 3.29 (s, 6H), 2.34 (dq,  $J = 7.5$  Hz, 3.0 Hz, 2H), 1.95-1.87 (m, 1H), 1.86-1.78 (m, 1H), 1.65-1.55 (m, 2H), 1.53-1.24 (m, 4H), 1.12 (t,  $J = 7.5$  Hz, 3H).  **$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):** 174.2, 141.4, 129.0, 128.3, 127.0, 104.8, 76.2, 53.1, 36.8, 32.8, 28.3, 25.9, 24.8, 9.5. **IR ( $\text{cm}^{-1}$ ):** 3418, 2938, 2858, 1737, 1454, 1385, 1189, 1127, 1051, 701. **MS (ESI):** 317.1 ( $\text{M}+\text{Na}^+$ ). **HRMS (EI):** calculated 293.1753, found 293.1751 ( $\text{M}^+-\text{H}$ ).  $[\alpha]_{\text{D}}^{22}$  -48.0 ( $c$  1.12,  $\text{CH}_2\text{Cl}_2$ ).



**Compound 8:** A solution of 2.10 g of acetal **7** (7.15 mmol) in 15 mL of  $\text{CHCl}_3$ , 4 mL of TFA and 4 mL of water was stirred 3 hrs at RT. The mixture was then diluted with 20 mL of water and 20 mL of  $\text{CH}_2\text{Cl}_2$ . The organic phase was separated and the aqueous phase was extracted with 30 mL of  $\text{CH}_2\text{Cl}_2$ . The organic phase was then washed with 30 mL of a saturated aqueous solution of  $\text{NaHCO}_3$ . The combined extracts were dried with  $\text{Na}_2\text{SO}_4$  and concentrated. The desired product was obtained as a colorless oil (1.65 g, 91%) and engaged immediately in the next step.  **$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):** 9.74 (s, 1H), 7.36-7.27 (m, 5H), 5.74 (dd,  $J = 7.5, 6.0$  Hz, 1H), 2.43-2.31 (m, 4H), 1.97-1.87 (m, 1H), 1.86-1.75 (m, 1H), 1.70-1.59 (m, 2H), 1.43-1.24 (m, 2H), 1.13 (t,  $J = 7.5$  Hz, 3H).  **$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):** 202.2, 173.6, 140.5, 128.3, 127.7, 126.3, 75.4, 43.5, 36.0, 27.7, 24.9, 21.6, 8.9. **IR ( $\text{cm}^{-1}$ ):** 2914, 2847, 1704, 1455, 1277, 1185, 1079.  $[\alpha]_{\text{D}}^{22}$  -54.6 ( $c$  1.2,  $\text{CH}_2\text{Cl}_2$ ).



**Compound 9:** To a solution of 3.80 g of allyl (cyclohexanol) dimethylsilane (19.2 mmol) in 50 mL of THF at  $-78^\circ\text{C}$  were added 19.2 mL of a 1M solution of potassium *tert*-butoxide (19.2 mmol) in THF and 7.8 mL of a 2.4 M solution of butyllithium (19.2 mmol) in hexane. The reaction was stirred 1 hr at  $-40^\circ\text{C}$  and cooled to  $-78^\circ\text{C}$ , 7.20 g of (+)-DIP chloride (22.4 mmol) were then added. The reaction was stirred 1 hr at  $-78^\circ\text{C}$  and 2.9 mL boron trifluoride, etherate (23 mmol) were added. After 5 min, 1.65 g of aldehyde **8** (6.60 mmol) in 5 mL of THF were added and the reaction was stirred 8 hrs at  $-78^\circ\text{C}$  and then let warmed overnight to RT. At this point 30 mL of methanol, 15 mL of 30% hydrogen peroxide in water, 12 g of  $\text{KHCO}_3$  and 6 g of potassium fluoride were added. The reaction was stirred 20 hrs at RT and 50 mL of a saturated aqueous solution of  $\text{Na}_2\text{S}_2\text{O}_3$  was added very carefully at  $0^\circ\text{C}$ . The mixture was diluted with 100 mL of AcOEt and 100 mL of a saturated aqueous solution of  $\text{NaHCO}_3$ . The organic phase was separated and the aqueous phase was extracted with 150 mL of AcOEt. The combined extracts were dried with  $\text{Na}_2\text{SO}_4$  and concentrated. Silica gel chromatography of the residue (ethyl acetate/ cyclohexane, 1:9 to 3:7) afforded the desired product as a colorless oil (1.02g, 51%) with a diastereomeric excess of 70% determined by the Mosher's method (see compounds **d** and **f**). Separation was effected at the next step.  **$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):** 7.36-7.26 (m, 5H), 5.87 (ddd,  $J = 17.1, 10.4, 6.4$  Hz, 1H), 5.73 (dd,  $J = 7.6, 6.1$  Hz, 1H), 5.20-5.32 (m, 2H), 4.04 (dd,  $J = 6.4, 3.6$  Hz, 1H), 3.65-3.59 (m, 1H), 2.34 (qd,  $J = 7.5, 2.8$  Hz, 2H), 1.97-1.82 (m, 1H), 1.81-1.70 (m, 1H), 1.56-1.46 (m, 1H), 1.42-1.22 (m, 5H), 1.12 (t,  $J = 7.5$  Hz, 3H).  **$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):** 174.4, 141.2, 136.5, 128.8, 128.2, 126.8, 117.9, 76.4, 76.1, 74.3, 36.7, 32.2, 28.2, 25.9, 25.8, 9.5. **IR ( $\text{cm}^{-1}$ ):** 3381, 2937, 2859, 1731, 1455, 1185, 1080, 997, 699. **MS (ESI):** 329.1 ( $\text{M}+\text{Na}^+$ ). **HRMS (CI):** calculated 307.1909, found 307.1908 ( $\text{M}+\text{H}^+$ ).  $[\alpha]_{\text{D}}^{22}$  -45.1 ( $c$  0.64,  $\text{CH}_2\text{Cl}_2$ ).

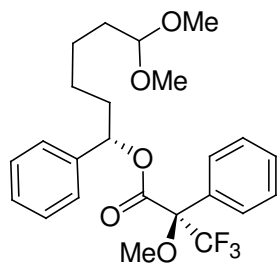


**Compound 2:** A solution of 200 mg of diol **9** (0.65 mmol), 979 mg of proton sponge® (4.57 mmol) and 677 mg of trimethyloxonium tetrafluoroborate (4.57 mmol) in 5 mL of  $\text{CH}_2\text{Cl}_2$  was stirred 12 hrs at RT; 10 mL of a 1N aqueous solution of hydrochloric acid and 5 mL of  $\text{CH}_2\text{Cl}_2$  were added. The organic phase was separated and the aqueous phase was extracted with 10 mL of  $\text{CH}_2\text{Cl}_2$ . The combined extracts were dried with  $\text{Na}_2\text{SO}_4$  concentrated. Silica gel chromatography of the residue (ethyl acetate/ cyclohexane, 1:9) afforded the dimethylated product **2** as a red oil (110 mg, 50%) with a diastereomeric excess of 90% and a mixture of the two monomethylated products as a red oil (65 mg, 31%).

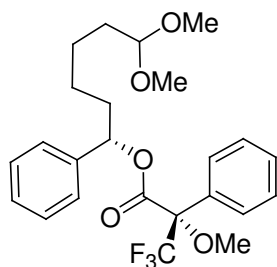
The monomethylated products could be methylated using the same procedure with 215 mg of proton sponge (1 mmol), 149 mg of trimethyloxonium tetrafluoroborate (1 mmol) in 3 mL of  $\text{CH}_2\text{Cl}_2$ . The pure dimethylated product **2** was obtained as a red oil (40 mg, 60%) with a diastereomeric excess of 90%. The overall yield of **2** is 70% (90% de).  **$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):** 7.35-7.23 (m, 5H), 5.80-5.68 (m, 2H), 5.32-5.21 (m, 2H), 3.55 (ddd,  $J = 7.6, 3.8, 0.8\text{ Hz}$ , 1H), 3.39 (s, 3H), 3.28 (s, 3H), 3.18-3.12 (m, 1H), 2.33 (qd,  $J = 7.6, 2.8\text{ Hz}$ , 2H), 1.99-1.85 (m, 1H), 1.82-1.70 (m, 1H), 1.46-1.25 (m, 6H), 1.12 (t,  $J = 7.6\text{ Hz}$ , 3H).  **$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):** 174.1, 141.3, 135.6, 128.8, 128.2, 127.0, 119.2, 84.7, 83.6, 76.2, 58.9, 57.1, 36.7, 30.5, 28.2, 26.0, 9.5. **IR ( $\text{cm}^{-1}$ ):** 2937, 2862, 1735, 1455, 1183, 1002, 997, 699, 637. **MS (ESI):** 357.1 ( $\text{M}+\text{Na}^+$ ). **HRMS (CI):** calculated 335.2222, found 335.2222 ( $\text{M}+\text{H}^+$ ).  **$[\alpha]_{\text{D}}^{22}$**  -56.2 ( $c$  0.60,  $\text{CH}_2\text{Cl}_2$ ).

\*Determination of the absolute configuration and enantioselectivity at C-17

According to the method of Mosher as in Dale, J. A.; Mosher, H. S. A. *J. Am. Chem. Soc.* **1973**, 95, 512.

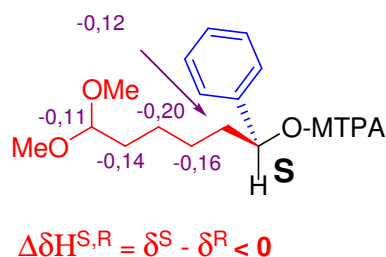


**Compound a:** A solution of 21 mg of alcohol **6** (0.088 mmol), 62 mg of (R)-(+)-alpha-methoxy-alpha-(trifluoromethyl)-phenylacetic acid (0.264 mmol), 55 mg of DCC (0.264 mmol) and 6 mg of DMAP (0.044 mmol) in 0.8 mL of  $\text{CH}_2\text{Cl}_2$  was stirred 24 hrs at RT. The crude was then diluted with 5 mL of  $\text{CH}_2\text{Cl}_2$  and 5 mL of a saturated aqueous solution of  $\text{NaHCO}_3$ . The organic phase was separated and the aqueous phase was extracted with 5 mL of  $\text{CH}_2\text{Cl}_2$ . The combined extracts were dried with  $\text{Na}_2\text{SO}_4$  concentrated. Silica gel chromatography of the residue (ethyl acetate/ cyclohexane, 1:9) afforded the desired product as a colorless oil (32 mg, 83%).  **$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):** 7.38-7.19 (m, 10H), 5.88 (dd,  $J = 7.9, 6.0\text{ Hz}$ , 1H), 4.31 (t,  $J = 5.6\text{ Hz}$ , 1H), 3.53 (s, 3H), 3.29 (s, 6H), 2.05-1.95 (m, 1H), 1.88-1.75 (m, 1H), 1.62-1.52 (m, 2H), 1.43-1.29 (m, 4H).  **$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):** 166.0, 139.3, 129.6, 128.6, 128.5, 128.4, 127.5, 126.9, 104.5, 79.0, 55.7, 52.9, 52.8, 36.1, 32.4, 25.5, 24.3.  **$^{19}\text{F}$  NMR (300 MHz,  $\text{CDCl}_3$ ):** -71.71 (s, 4F), -71.96 (s, 96F). **Diastereomeric excess:** 92%. **MS (ESI):** 477.0 ( $\text{M}+\text{Na}^+$ ).  **$[\alpha]_{\text{D}}^{22}$**  -5.5 ( $c$  1.30,  $\text{CH}_2\text{Cl}_2$ ).



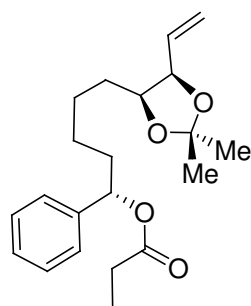
**Compound b:** This compound was prepared with the same procedure as compound **a** with 21 mg of alcohol **6** (0.088 mmol), 62 mg of (S)-(-)-alpha-methoxy-alpha-(trifluoromethyl)-phenylacetic acid (0.26 mmol), 54.5 mg of DCC (0.26 mmol) and 5 mg of DMAP (0.04 mmol) in 1 mL of  $\text{CH}_2\text{Cl}_2$ . The product was obtained as a colourless oil (28.5 mg, 71%).  **$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):** 7.45-7.28 (m, 10H), 5.95 (dd,

$J = 8.2, 5.7$ , Hz, 1H), 4.28 (t,  $J = 5.7$  Hz, 1H), 3.44 (s, 3H), 3.28 (s, 6H), 2.02–1.91 (m, 1H), 1.84–1.72 (m, 1H), 1.55–1.46 (m, 2H), 1.39–1.11 (m, 4H).  **$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )**: 166.0, 139.1, 132.4, 129.5, 128.6, 128.5, 128.4, 128.2, 127.3, 126.9, 104.3, 78.5, 55.4, 52.7, 52.5, 35.7, 32.2, 25.0, 24.0.  **$^{19}\text{F}$  NMR (300 MHz,  $\text{CDCl}_3$ )**: -71.67 (s, 4F), -71.71 (s, 96F). **Diastereomeric excess**: 92% **MS (ESI)**: 477.0 ( $\text{M}+\text{Na}^+$ ).  **$[\alpha]_{\text{D}}^{22}$**  -73.4 ( $c$  1.09,  $\text{CH}_2\text{Cl}_2$ ).

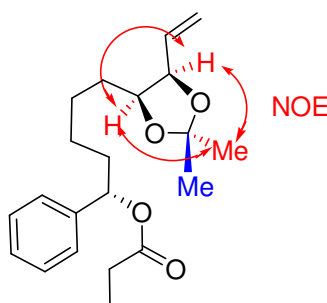


**The absolute configuration at C17 is (S) and the enantiomeric excess is 92%.**

\*Determination of the relative configuration between C11 and C12.



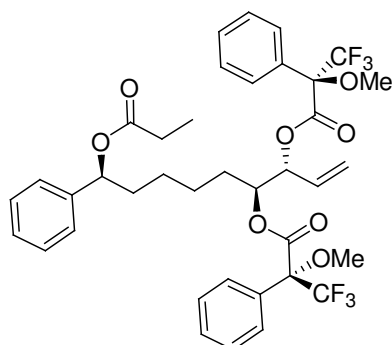
**Compound c**: A solution of 20 mg of diol **9** (0.065 mmol), 12  $\mu\text{L}$  of 2,2-dimethoxypropane (0.098 mmol) and pyridiniumparatoluensulfonate (0.006 mmol) in 1 mL of  $\text{CH}_2\text{Cl}_2$  was stirred 12 hrs at RT. The crude was then diluted with 5 mL of  $\text{CH}_2\text{Cl}_2$  and 5 mL of a saturated aqueous solution of  $\text{NaHCO}_3$ . The organic phase was separated and the aqueous phase was extracted with 5 mL of  $\text{CH}_2\text{Cl}_2$ . The combined extracts were dried with  $\text{Na}_2\text{SO}_4$  concentrated. Silica gel chromatography of the residue (ethyl acetate/ cyclohexane, 1:9) afforded the desired product as a colorless oil (22.5 mg, 95%).  **$^1\text{H}$ NMR (300 MHz,  $\text{CDCl}_3$ )**: 7.36–7.24 (m, 5H), 5.84–5.71 (m, 2H), 5.31–5.18 (m, 2H), 4.45 (t,  $J = 7.2$  Hz, 1H), 4.13–4.05 (m, 1H), 2.34 (qd,  $J = 7.5, 2.6$  Hz, 2H), 1.96–1.83 (m, 1H), 1.82–1.68 (m, 1H), 1.55–1.21 (m, 6H), 1.47 (s, 3H), 1.35 (s, 3H), 1.12 (t,  $J = 7.5$  Hz, 3H).  **$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )**: 174.2, 141.3, 134.9, 128.8, 128.2, 126.8, 118.6, 108.9, 80.9, 80.2, 76.1, 36.7, 30.7, 28.7, 28.2, 26.4, 26.0, 25.9, 9.5. **IR ( $\text{cm}^{-1}$ )**: 2915, 2848, 1736, , 1462, 1367, 1259, , 1081, 1016, 796, 638. **HRMS (EI)**: calculated 346.2144, found 346.2141 ( $\text{M}^+$ ).  **$[\alpha]_{\text{D}}^{22}$**  -47.1 ( $c$  0.37,  $\text{CH}_2\text{Cl}_2$ ).



**NOE demonstrates the anti relationship between substituents at C11 and C12.**

\*Determination of absolute configurations at C11 and C12 and stereoselectivity.

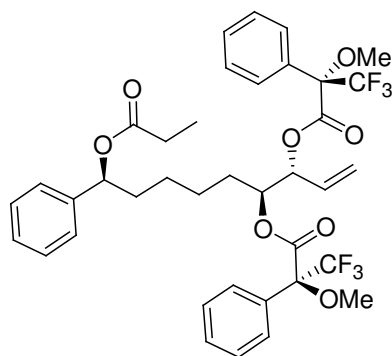
According to the method of Mosher for 1,2 anti diol as in Ichikawa, A.; Takahashi, H.; Ooi, T.; Kuzumi, T. *Biosci. Biotech. Biochem.* **1997**, *61*, 881. .



**Compound d:** This compound was prepared with the same procedure as compound **a** with 14 mg of diol **9** (0.045 mmol), 64.2 mg of (R)-(+)-alpha-methoxy-alpha-(trifluoromethyl)-phenylacetic acid (0.27 mmol), 55.7 mg of DCC (0.27 mmol) and 6 mg of DMAP (0.044 mmol) in 1 mL of CH<sub>2</sub>Cl<sub>2</sub>. The product was obtained as a colourless oil (25 mg, 75%).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** 7.48-7.27 (m, 15H), 5.80 (ddd, *J* = 17.0, 10.0, 6.4 Hz, 0.15H), 5.74-5.52 (m, 2.85H), 5.46 (d, *J* = 17.0 Hz, 0.15H), 5.40 (d, *J* = 10.0 Hz, 0.15H), 5.32-5.21 (m, 2.70H), 3.48 (s, 0.5H), 3.45 (s, 2.5H), 3.42-3.39 (br, 3H),

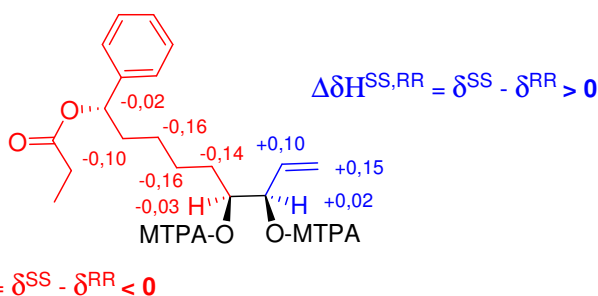
2.34 (qd, *J* = 7.5, 2.6 Hz, 2H), 1.91-1.78 (m, 1H), 1.77-1.66 (m, 1H), 1.45-1.15 (m, 6H), 1.13 (t, *J* = 7.5 Hz, 3H). **<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** 174.1, 166.5, 165.8, 146.5, 132.4, 132.2, 130.2, 130.0, 128.9, 128.8, 128.3, 127.8, 127.6, 126.8, 122.1, 85.2, 77.2, 76.6, 75.9, 55.8, 36.5, 29.8, 29.5, 28.2, 25.5, 9.5. **<sup>19</sup>F NMR (300 MHz, CDCl<sub>3</sub>):** -71.71 (s, 15F), -71.86 (s, 85F), -72.04 (s, 15F), -72.06 (s, 85F). **Diastereomeric excess:** 70% **MS (ESI):** 761.1 (M+Na<sup>+</sup>). **[α]<sub>D</sub><sup>22</sup>** = +10.4 (*c* = 0.64, CH<sub>2</sub>Cl<sub>2</sub>).



**Compound e:** This compound was prepared with the same procedure as compound **a** with 12.2 mg of diol **9** (0.04 mmol), 56 mg of (S)-(-)-alpha-methoxy-alpha-(trifluoromethyl)-phenylacetic acid (0.24 mmol), 49 mg of DCC (0.24 mmol) and 2.5 mg of DMAP (0.02 mmol) in 1 mL of CH<sub>2</sub>Cl<sub>2</sub>. The product was obtained as a colorless oil (22.4 mg, 76%).

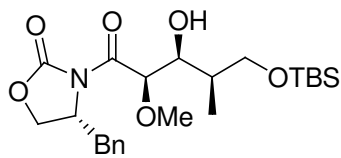
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** 7.55-7.25 (m, 15H), 5.80 (ddd, *J* = 17.7, 10.3, 7.5 Hz, 1H), 5.67 (dd, *J* = 7.2, 6.4 Hz, 1H), 5.61-5.57 (m, 1H), 5.45 (d, *J* = 17.7 Hz, 1H), 5.40 (d, *J* = 10.3 Hz, 1H), 5.35-5.22 (m, 1H), 3.48 (s, 2.55H), 3.46 (s, 0.45H),

3.41 (s, 3H), 2.35 (qd, *J* = 7.5, 3.0 Hz, 2H), 1.84-1.26 (m, 8H), 1.13 (t, *J* = 7.5 Hz, 3H). **<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** 173.8, 169.9, 165.6, 140.8, 138.8, 131.9, 131.8, 130.1, 129.6, 128.5, 128.4, 128.3, 127.8, 127.3, 127.2, 126.4, 122.6, 77.1, 75.8, 75.5, 55.4, 36.0, 29.4, 27.8, 25.0, 24.6, 9.1. **<sup>19</sup>F NMR (300 MHz, CDCl<sub>3</sub>):** -71.60 (85F), -71.77 (15F), -71.93 (85F), -71.96 (15F). **Diastereomeric excess:** 70% **MS (ESI):** 761.1 (M+Na<sup>+</sup>). **[α]<sub>D</sub><sup>22</sup>** = -59.3 (*c* = 0.91, CH<sub>2</sub>Cl<sub>2</sub>).

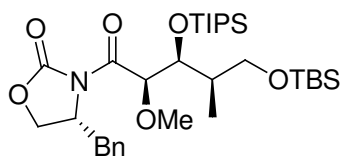


The absolute config. at C11 and C12 are (S) and (R) and the enantiomeric excess is 70%.

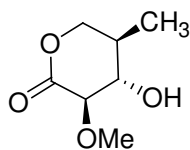
## \*Synthesis of fragment 3



**Compound 13:** To a solution of 7.39 g of imide **12** (29.7 mmol) in 80 mL of  $\text{CH}_2\text{Cl}_2$  at  $-78^\circ\text{C}$  were added 29 mL of a 1M solution of dibutylboron triflate (29.0 mmol) in  $\text{CH}_2\text{Cl}_2$  and 8.1 mL of  $\text{Et}_3\text{N}$  (58.0 mmol). The mixture was stirred 30 min at  $0^\circ\text{C}$  then cooled to  $-78^\circ\text{C}$ . A solution of 9.10 g of aldehyde **19** (44.5 mmol) in 10 mL of  $\text{CH}_2\text{Cl}_2$  was then added and the reaction was stirred 4 hrs at  $0^\circ\text{C}$ . The reaction mixture was then hydrolysed with 50 mL of a 2:1 mixture of methanol and phosphate buffer pH 7 and then 50 mL of a 2:1 mixture of methanol and 30% hydrogen peroxide at  $0^\circ\text{C}$ . After stirring 1 hr at  $0^\circ\text{C}$ , the mixture was concentrated. The crude was then diluted with 100 mL of  $\text{CH}_2\text{Cl}_2$  and 100 mL of a saturated aqueous solution of  $\text{NaHCO}_3$ . The organic phase was separated and the aqueous phase was extracted with 80 mL of  $\text{CH}_2\text{Cl}_2$ . The combined extracts were dried with  $\text{Na}_2\text{SO}_4$  and concentrated. Silica gel chromatography of the residue (ethyl acetate/cyclohexane, 3:7) afforded a 3 :1 mixture of the desired product **13** and imide **12** as a yellow oil (13.5 g). This mixture was used in the next step. A purification of 50 mg of this mixture on a preparative TLC (ethyl acetate/cyclohexane, 3:7) afforded pure **13**.  **$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):** 7.36-7.21 (m, 5H), 5.10 (d,  $J = 2.7$  Hz, 1H), 4.74-4.66 (m, 1H), 4.22-4.12 (m, 2H), 3.89-3.83 (m, 1H), 3.71 (dd,  $J = 9.8, 6.9$  Hz, 1H), 3.50 (dd,  $J = 9.8, 5.6$  Hz, 1H), 3.47 (s, 3H), 3.38 (dd,  $J = 13.3, 3.2$  Hz, 1H), 2.85 (dd,  $J = 13.3, 9.6$  Hz, 1H), 2.68 (d,  $J = 8.6$  Hz, 1H), 2.03-1.95 (m, 1H), 0.99 (d,  $J = 6.8$  Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H).  **$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):** 171.0, 153.2, 135.1, 129.4, 129.0, 127.4, 81.0, 73.6, 66.9, 66.3, 55.8, 39.4, 37.7, 25.9, 18.3, 12.2, -5.2. **IR ( $\text{cm}^{-1}$ ):** 2928, 2856, 1782, 1709, 1389, 1250, 1097, 836, 776, 701. **MS (ESI):** 474.2 ( $\text{M}+\text{Na}^+$ ), 925.0 ( $2\text{M}+\text{Na}^+$ ). **HRMS (CI):** calculated 452.2468, found 452.2470 ( $\text{M}+\text{H}^+$ ).  $[\alpha]_{\text{D}}^{22} -10.7$  (c 1.49,  $\text{CH}_2\text{Cl}_2$ ).



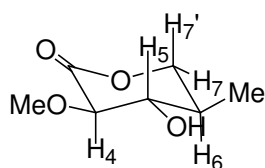
**Compound 14:** To 13.5 g of the 3:1 mixture of aldolised product **13** and imide **12** in 150 mL of  $\text{CH}_2\text{Cl}_2$  were added at  $0^\circ\text{C}$ : 9.5 mL of  $\text{Et}_3\text{N}$  (68 mmol) and 12 mL of TIPS triflate (45 mmol). The reaction was stirred 3 hrs at  $0^\circ\text{C}$  and a saturated aqueous solution of  $\text{NaHCO}_3$  (100 mL) was added. The organic phase was separated and the aqueous phase was extracted with 100 mL of  $\text{CH}_2\text{Cl}_2$ . The combined extracts were dried with  $\text{Na}_2\text{SO}_4$  and concentrated. Silica gel chromatography of the residue (ethyl acetate/ cyclohexane, 1:9) afforded the desired product **14** as a pale yellow oil (9.91 g, 53% on 2 steps).  **$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):** 7.35-7.21 (m, 5H), 5.18 (d,  $J = 6.8$  Hz, 1H), 4.63-4.56 (m, 1H), 4.31 (dd,  $J = 7.2, 2.6$  Hz, 1H), 4.22-4.12 (m, 2H), 3.66 (dd,  $J = 9.8, 6.8$  Hz, 1H), 3.45-3.38 (m, 2H), 3.40 (s, 3H), 2.76 (dd,  $J = 13.2, 9.8$  Hz, 1H), 1.58-1.50 (m, 1H), 1.10-1.04 (br, 21H), 0.91 (d,  $J = 7.1$  Hz, 3H), 0.87 (s, 9H), 0.00 (s, 6H).  **$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):** 172.7, 153.4, 135.5, 129.8, 129.4, 127.8, 74.1, 66.8, 65.9, 58.1, 56.6, 40.4, 38.2, 26.3, 18.7, 13.7, 11.5, -5.0. **IR ( $\text{cm}^{-1}$ ):** 2941, 2865, 1788, 1705, 1464, 1385, 1110, 835, 679. **MS (ESI):** 630.3 ( $\text{M}+\text{Na}^+$ ). **HRMS (CI):** calculated 608.3803, found 608.3800 ( $\text{M}+\text{H}^+$ ).  $[\alpha]_{\text{D}}^{22} -23.8$  (c 1.85,  $\text{CH}_2\text{Cl}_2$ ).



**Compound f:** To a solution of 20 mg of **14** (0.0344mmol) in 0.5 mL of THF were added 0.5 mL of  $\text{HF}\cdot\text{pyridine}$ . The reaction was stirred 2 hrs at RT and diluted with 3 mL of water and 3 mL of  $\text{AcOEt}$ . The organic phase was separated and the aqueous phase was extracted with 3 mL of  $\text{EtOAc}$ . The combined extracts were washed with 5 mL of a saturated aqueous solution of  $\text{NaHCO}_3$ , dried with  $\text{Na}_2\text{SO}_4$  and concentrated. Silica gel chromatography of the residue (ethyl acetate/ cyclohexane, 7:3) afforded as a colorless oil the lactone **f** (3.7 mg, 72%).  **$^1\text{H}$  NMR (300**



**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** 4.31 (dd, *J* = 11.6, 4.9 Hz, 1H), 3.86 (dd, *J* = 11.6, 9.0 Hz, 1H), 3.71 (s, 3H), 3.66 (d, *J* = 9.0 Hz, 1H), 3.57 (t, *J* = 9.0 Hz, 1H), 2.62-2.57 (br, 1H), 2.20-2.09 (m, 1H), 1.12 (d, *J* = 6.8 Hz, 3H). **<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** 171.0, 82.8, 74.5, 71.1, 61.0, 35.8, 14.5.



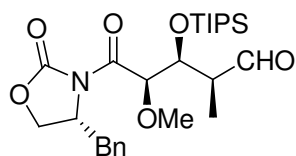
$$J_{H4-H5} = 9.0 \text{ Hz}$$

$$J_{H5-H6} = 9.0 \text{ Hz}$$

$$J_{H6-H7} = 4.9 \text{ Hz}$$

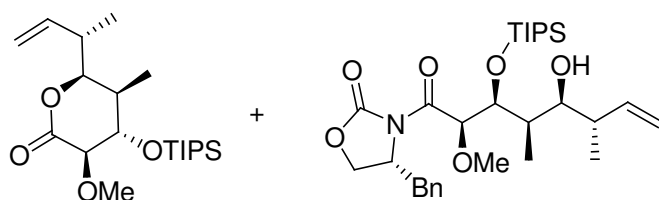
$$J_{H6-H7'} = 9.0 \text{ Hz}$$

**The coupling constants H4-H5 (9.0 Hz) and H5-H6 (9.0 Hz) demonstrate that H4, H5 and H6 are axial.**



**Compound 15:** A suspension of 5.03 g of **14** (8.3 mmol), 8.9 g of PCC (41 mmol), 5 g of MgSO<sub>4</sub> and 5 g of celite in 50 mL of CH<sub>2</sub>Cl<sub>2</sub> was stirred 3 days at RT. The suspension was then filtered on a pad of celite with AcOEt (150 mL). The filtrate was then concentrated.

Silica gel chromatography of the residue (ethyl acetate/ cyclohexane, 2:8) afforded the desired product **15** as a pale yellow oil (3.35 g, 82%). **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** 9.99 (s, 1H), 7.35-7.20 (m, 5H), 4.92 (d, *J* = 2.5 Hz, 1H), 4.66-4.63 (q, *J* = 2.5 Hz, 1H), 4.63-4.56 (m, 1H), 4.29-4.15 (m, 2H), 3.35-3.30 (m, 1H), 3.31 (s, 3H), 2.87 (dd, *J* = 13.3, 9.5 Hz, 1H), 2.59 (qd, *J* = 7.0, 1.8 Hz, 1H), 1.11 (d, *J* = 7.0 Hz, 3H), 1.10-1.05 (br, 21H). **<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** 202.1, 169.5, 153.3, 134.8, 129.4, 129.4, 127.6, 80.5, 75.1, 67.0, 58.5, 56.0, 50.6, 37.5, 18.1, 12.9, 9.8. **IR (cm<sup>-1</sup>):** 2946, 2867, 1780, 1719, 1455, 1389, 1196, 1110, 998, 882, 702, 676. **MS (CI) :** 492 (M+H<sup>+</sup>). **HRMS (CI):** calculated 492.2781, found 492.2789 (M+H<sup>+</sup>). [ $\alpha$ ]<sub>D</sub><sup>22</sup> + 47.7 (*c* 0.78, CH<sub>2</sub>Cl<sub>2</sub>).



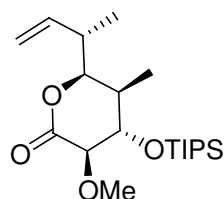
**Lactone 36 and alcohol 16:** To 25 mL of THF at -78°C were added: 10.2 mL of a 1M solution of potassium *tert*-butoxide (10.2 mmol) and 4.2 mL of a 2.4 M solution of butyllithium (10.2 mmol) and an excess of *trans*-2-butene. The mixture

was stirred 1 hr at -40°C, cooled to -78°C and 2.11 mL of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was added (10.3 mmol). The mixture was stirred 1 hr at -78°C and 1.3 mL of boron trifluoride-etherate (10.3 mmol) were added. After 10 min of stirring, 1192 mg of aldehyde **15** (2.4 mmol) in 3 mL of THF were added. The reaction was stirred 5 hrs at -78°C and then diluted with 30 mL of a saturated aqueous solution of NaHCO<sub>3</sub> and 20 mL of EtOAc. The organic phase was separated and the aqueous phase was extracted with 30 mL of EtOAc. The combined extracts were dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated. Silica gel chromatography of the residue (ethyl acetate/ cyclohexane, 1:9 to 3:7) afforded as a colorless oil a mixture of the lactone **36** and 2 diastereoisomers in a 9:1:1 ratio (174 mg, 20%) and a 9:1 mixture of alcohol **16** with a diastereoisomer and unknown impurities (670 mg). Mixture of lactone **36** and diastereoisomers and mixture of alcohol **16** with one diastereoisomer were used as it is in the next steps. Separations were effected at the next steps.

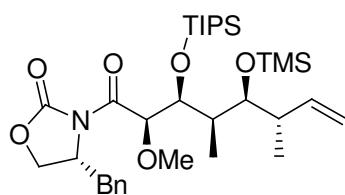
#### 9:1:1 mixture of lactone 36 and diastereoisomers:

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** 5.90 (ddd, *J* = 17.3, 10.4, 7.2 Hz, 0.9H), 5.80 (ddd, *J* = 17.0, 10.2, 8.8 Hz, 0.1H), 5.63 (ddd, *J* = 17.3, 10.2, 9.0 Hz, 0.1H), 5.15 (d, *J* = 17.3 Hz, 1H), 5.10 (d, *J* = 10.4 Hz, 1H), 4.23 (dd, *J* = 9.8, 1.5 Hz, 1H), 3.76 (d, *J* = 5.0 Hz, 1H), 3.73 (dd, *J* = 5.0,

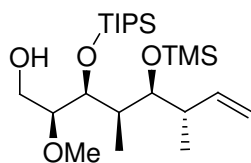
0.9 Hz, 1H), 3.56 (s, 3H) 2.51-2.42 (m, 1H), 2.12-2.07 (m, 1H), 1.14-1.02 (br, 21H), 0.99 (d,  $J = 6.9$  Hz, 3H), 0.91 (d,  $J = 7.5$  Hz, 3H). See full characterisation of pure **36** below:



**Compound 36:** To a solution of 9 mg of the 9:1 mixture of alcohol **16** with a diastereoisomer and unknown impurities at  $-78^{\circ}\text{C}$  in 0.5 mL of THF were added 18  $\mu\text{L}$  of a 2M solution of LDA in THF (0.036 mmol). The reaction was stirred 1 hr at  $-78^{\circ}\text{C}$ . The mixture was diluted with 3 mL of a saturated aqueous solution of  $\text{NaHCO}_3$  and 3 mL of EtOAc. The organic phase was separated and the aqueous phase was extracted with 3 mL of EtOAc. The combined extracts were dried with  $\text{Na}_2\text{SO}_4$  and concentrated. Silica gel chromatography of the residue (ethyl acetate/ cyclohexane, 1:9) afforded as a colorless oil the desired lactone **M1** (8 mg, 40% on 2 steps) without any diastereoisomers.  **$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):** 5.90 (ddd,  $J = 17.3, 10.4, 7.2$  Hz, 1H), 5.15 (d,  $J = 17.3$  Hz, 1H), 5.10 (d,  $J = 10.4$  Hz, 1H), 4.23 (dd,  $J = 9.8, 1.5$  Hz, 1H), 3.76 (d,  $J = 5.0$  Hz, 1H), 3.73 (dd,  $J = 5.0, 0.9$  Hz, 1H), 3.56 (s, 3H) 2.51-2.42 (m, 1H), 2.12-2.07 (m, 1H), 1.14-1.02 (br, 21H), 0.99 (d,  $J = 6.9$  Hz, 3H), 0.91 (d,  $J = 7.5$  Hz, 3H).  **$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):** 171.1, 139.8, 115.5, 83.6, 80.5, 77.5, 59.7, 40.3, 38.2, 17.9, 17.8, 17.7, 15.2, 12.1, 10.9. **IR ( $\text{cm}^{-1}$ ):** 2939, 2865, 1760, 1462, 1196, 1100, 993, 680. **MS (ESI):** 370.9 ( $\text{M}+\text{Na}^+$ ), 763.0 ( $2\text{M}+\text{Na}^+$ ). **HRMS (CI):** calculated 371.2618, found 371.2617 ( $\text{M}+\text{H}^+$ ).  $[\alpha]_{\text{D}}^{22} + 26.1$  (c 0.60,  $\text{CH}_2\text{Cl}_2$ ).

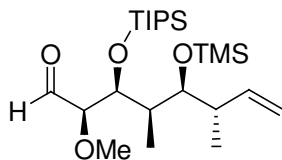


**Compound 17:** To a solution of the 670 mg of alcohol **16** with impurities in 15 mL of  $\text{CH}_2\text{Cl}_2$  were added at  $0^{\circ}\text{C}$ : 1.03  $\mu\text{L}$  of  $\text{Et}_3\text{N}$  (7.4 mmol) and 638  $\mu\text{L}$  of TMS triflate (3.3 mmol). The reaction was stirred 3 hrs at RT and then diluted with 10 mL of a saturated aqueous solution of  $\text{NaHCO}_3$  and 10 mL of  $\text{CH}_2\text{Cl}_2$ . The organic phase was separated and the aqueous phase was extracted with 10 mL of  $\text{CH}_2\text{Cl}_2$ . The combined extracts were dried with  $\text{Na}_2\text{SO}_4$  and concentrated. Silica gel chromatography of the residue (ethyl acetate/ cyclohexane, 1:9) afforded as a pale yellow oil a 9:1 mixture of the desired compound **17** and a diastereoisomer (635 mg, 42% on 2 steps). Separation was effected at the next step.  **$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):** 7.38-7.21 (m, 5H), 5.90 (ddd,  $J = 17.3, 10.2, 7.2$  Hz, 0.1H), 5.72 (ddd,  $J = 17.3, 10.2, 9.0$  Hz, 0.9H), 5.28 (d,  $J = 9.0$  Hz, 1H), 5.06 (dd,  $J = 17.3, 2.6$  Hz, 1H), 4.98 (dd,  $J = 10.2, 2.6$  Hz, 1H), 4.58-4.49 (m, 1H), 4.26 (d,  $J = 8.3$  Hz, 1H), 4.18-4.15 (m, 2H), 3.62 (d,  $J = 9.8$  Hz, 1H), 3.45 (dd,  $J = 13.2, 3.0$  Hz, 1H), 3.38 (s, 3H), 2.73 (dd,  $J = 13.2, 10.2$  Hz, 1H), 2.50-2.39 (m, 1H), 1.34-1.24 (m, 1H), 1.15-1.15 (br, 21H), 1.05 (d,  $J = 6.8$  Hz, 3H), 0.95 (d,  $J = 6.8$  Hz, 3H), 0.12 (m, 9H).  **$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):** 172.7, 153.1, 139.6, 135.3, 129.5, 129.2, 127.5, 115.6, 78.2, 74.4, 66.5, 57.2, 56.4, 40.8, 40.1, 37.9, 19.6, 18.7, 13.9, 11.6, 1.0. **IR ( $\text{cm}^{-1}$ ):** 2968, 2864, 1777, 1701, 1455, 1294, 1192, 1106, 878, 833. **MS (ESI):** 642.3 ( $\text{M}+\text{Na}^+$ ), 1261.3 ( $2\text{M}+\text{Na}^+$ ). **HRMS (LSIMS):** calculated 620.3803, found 620.3808 ( $\text{M}+\text{H}^+$ ).  $[\alpha]_{\text{D}}^{22} -29.4$  (c 1.55,  $\text{CH}_2\text{Cl}_2$ ).



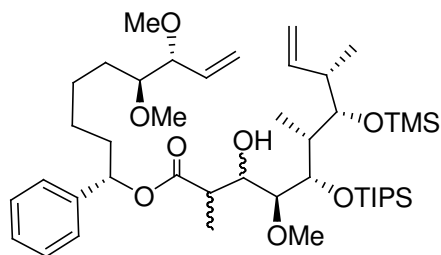
To a solution of 600 mg (0.97 mmol) of **17** in 6 mL of THF at  $0^{\circ}\text{C}$  were added 2.4 mL of a 2M solution of lithium borohydride in THF (4.85 mmol). The reaction was stirred 3 hrs at RT and then diluted with 10 mL of a saturated aqueous solution of  $\text{NaHCO}_3$  and 10 mL of  $\text{Et}_2\text{O}$ . The organic phase was separated and the aqueous phase was extracted with 10 mL of  $\text{Et}_2\text{O}$ . The combined extracts were dried with  $\text{Na}_2\text{SO}_4$  and concentrated. Silica gel chromatography of the residue (ethyl acetate/ cyclohexane, 1:9) afforded as a pale yellow oil the desired alcohol (270 mg, 62%).  **$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):** 5.85 (ddd,  $J = 16.8, 10.9,$

8.4 Hz, 1H), 5.06-4.99 (m, 2H), 4.08 (dd,  $J = 7.2, 2.0$  Hz, 1H), 3.85 (dd,  $J = 12.3, 3.4$  Hz, 1H), 3.66 (dd,  $J = 9.0, 2.0$  Hz, 1H), 3.54 (dd,  $J = 12.3, 3.8$  Hz, 1H), 3.38 (s, 3H), 2.24 (dt,  $J = 7.2, 3.4$  Hz, 1H), 2.52-2.42 (m, 1H), 1.80-1.63 (m, 2H), 1.11-1.08 (br, 21H), 1.04 (d,  $J = 7.2$  Hz, 3H), 0.90 (d,  $J = 6.8$  Hz, 3H), 0.13 (s, 9H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ): 140.4, 115.3, 84.7, 78.4, 72.2, 59.6, 57.2, 40.9, 39.3, 19.3, 18.7, 13.7, 11.2, 1.1. IR ( $\text{cm}^{-1}$ ): 3288, 2944, 2865, 1463, 1384, 1249, 1142, 1041, 800.  $[\alpha]_{\text{D}}^{22} +11.5$  (c 0.29,  $\text{CH}_2\text{Cl}_2$ ).

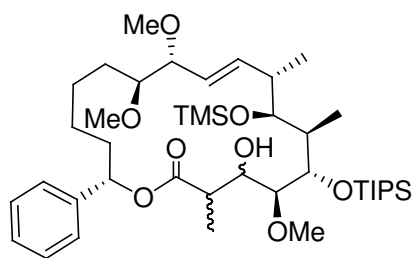


**Compound 18:** To a solution of 130 mg of the preceding alcohol (0.29 mmol) and 153  $\mu\text{L}$  of pyridine (1.9 mmol) in 2 mL of  $\text{CH}_2\text{Cl}_2$  were added 246 mg of Dess-Martin periodinane (0.58 mmol). The reaction was stirred 2 hrs and diluted with 2 mL of a saturated aqueous solution of  $\text{Na}_2\text{S}_2\text{O}_3$ , 2 mL of a saturated aqueous solution of  $\text{NaHCO}_3$  and 4 mL of  $\text{CH}_2\text{Cl}_2$ . The organic phase was separated and the aqueous phase was extracted with 4 mL of  $\text{CH}_2\text{Cl}_2$ . The combined extracts were dried with  $\text{Na}_2\text{SO}_4$  and concentrated. Silica gel chromatography of the residue (ethyl acetate/ cyclohexane, 1:9) afforded as a colorless oil the desired compound **18** (69 mg, 54%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ): 9.53 (d,  $J = 3.0$  Hz, 1H), 5.75 (ddd,  $J = 17.2, 10.3, 9.0$  Hz, 1H), 5.00-4.89 (m, 2H), 4.19 (dd,  $J = 7.2, 2.6$  Hz, 1H), 3.66 (dd,  $J = 8.3, 2.6$  Hz, 1H), 3.60 (dd,  $J = 7.2, 3.4$  Hz, 1H), 3.33 (s, 3H), 2.47-2.36 (m, 1H), 1.61-1.51 (m, 1H), 1.11-1.07 (br, 21 H), 1.00 (d,  $J = 7.2$  Hz, 3H), 0.95 (d,  $J = 6.8$  Hz, 3H), 0.11 (s, 9H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ): 201.3, 140.4, 115.3, 89.5, 77.3, 72.5, 57.9, 41.4, 40.0, 19.1, 18.6, 13.5, 10.8, 1.1. IR ( $\text{cm}^{-1}$ ): 2995, 2895, 1690, 1125, 1105, 884. MS (ESI): 445.0 ( $\text{M}+\text{H}^+$ ).  $[\alpha]_{\text{D}}^{22} +15.4$  (c 0.35,  $\text{CH}_2\text{Cl}_2$ ).

#### \*Assembly of the Soraphen A framework

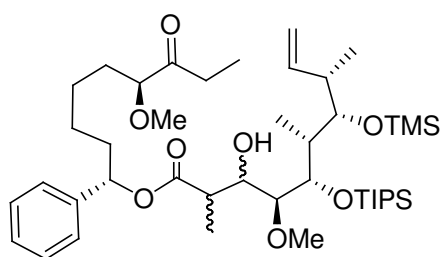


**Compound 21:** To a solution of 83 mg of ester **2** (0.25 mmol) in 0.5 mL of THF at  $-78^\circ\text{C}$  were added dropwise 150  $\mu\text{L}$  of a 2M solution of LDA (0.30 mmol) in THF. The reaction was stirred 35 min at  $-78^\circ\text{C}$  and 65 mg of aldehyde **18** (0.146 mmol) in 0.3 mL of THF was added dropwise and the reaction was stirred 4 hrs at  $-78^\circ\text{C}$ . The mixture was diluted with 3 mL of a saturated aqueous solution of  $\text{NaHCO}_3$  and 3 mL of EtOAc. The organic phase was separated and the aqueous phase was extracted with 3 mL of EtOAc. The combined extracts were dried with  $\text{Na}_2\text{SO}_4$  and concentrated. Silica gel chromatography of the residue (ethyl acetate/ cyclohexane, 1:9) afforded as a colorless oil a 3:1 mixture of 2 diastereoisomers of the desired compound **21** (76.1 mg, 67%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ): 7.35-7.26 (m, 5H), 5.88-5.67 (m, 3H), 5.29 (dd,  $J = 10.5, 1.3$  Hz, 1H), 5.23 (dd,  $J = 17.3, 1.3$  Hz, 1H), 5.08-5.01 (m, 2H), 4.14-4.07 (m, 1H), 3.71-3.49 (m, 3H), 3.46 (s, 1H), 3.40-3.37 (br, 5H), 3.28 (s, 3H), 3.17-3.12 (m, 1H), 3.08 (d,  $J = 7.9$  Hz, 0.75H), 2.98 (d,  $J = 9.3$  Hz, 0.25H), 2.71-2.58 (m, 2H), 2.49-2.41 (m, 0.75H), 2.28-2.23 (m, 0.25H), 2.00-1.85 (m, 1H), 1.84-1.70 (m, 1H), 1.70-1.57 (m, 1H), 1.47-1.24 (m, 3H), 1.21-1.15 (m, 3H), 1.13-1.08 (m, 21H), 1.07-1.01 (m, 3H), 0.95-0.89 (m, 5.25H), 0.77 (d,  $J = 6.8$  Hz, 0.75H), 0.14 (s, 9H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ): 174.3, 140.7, 140.4, 140.0, 139.8, 135.4, 128.6, 128.4, 126.6, 119.0, 115.8, 115.5, 84.8, 83.5, 82.9, 82.1, 78.7, 76.1, 72.2, 71.9, 71.7, 61.0, 60.9, 58.5, 56.8, 45.3, 44.8, 41.1, 39.9, 36.3, 30.4, 26.4, 25.7, 25.6, 19.8, 19.6, 18.7, 18.6, 14.6, 14.4, 14.1, 13.7, 12.4, 11.2, 11.0, 1.2. IR ( $\text{cm}^{-1}$ ): 2938, 2860, 1731, 1456, 1249, 1098, 882, 837.

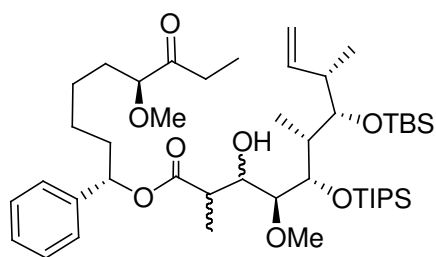


**Compound 22:** To a solution of 14 mg of the diene **21** (0.017 mmol) in 1 mL of degassed toluene were added 3.0 mg of Grubbs-Hoveyda II catalyst **24** (0.005mmol). The reaction was stirred 15 hrs at 80°C and the solvent was then evaporated. Silica gel chromatography of the residue (ethyl acetate/ cyclohexane, 2:8) afforded as a colorless oil the desired compound **22** as a mixture of diastereoisomers (4 mg, 30%) and the isomerised compound **23** (6 mg, 43%). **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** 7.36-7.28 (m, 5H), 5.89 (dd, *J* = 16.0, 7.5 Hz, 1H), 5.71 (dd, *J* = 10.5, 2.8 Hz, 1H), 5.28 (dd, *J* = 16.0, 5.3 Hz, 1H), 4.14-4.03 (m, 1H), 3.94-3.78 (m, 1H), 3.77-3.53 (m, 1H), 3.45-3.31 (m, 10H), 3.28-3.16 (m, 1H), 3.15-3.07 (m, 1H), 2.63-2.55 (m, 2H), 2.03-1.84 (m, 2H), 1.73-1.30 (m, 8H), 1.30-1.25 (m, 3H), 1.16-1.04 (br, 21H), 0.96 (d, *J* = 6.8 Hz, 3 H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.13 (s, 9H). **MS (ESI):** 773.4 (M+Na<sup>+</sup>). **HRMS (ESI):** calculated 773.4814, found 773.4807 (M+Na<sup>+</sup>).

\*Olefin isomerization during metathesis

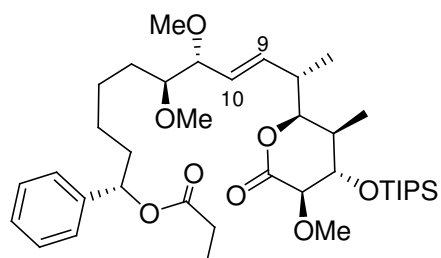


**Compound 23:** **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** 7.37-7.27 (m, 5H), 5.98-5.62 (m, 2H), 5.10-4.96 (m, 2H), 4.24-3.92 (m, 1H), 3.78-2.98 (m, 11 H), 2.78-2.55 (m, 2H), 2.54-2.42 (m, 2H), 2.00-1.86 (m, 1H), 1.85-1.70 (m, 1H), 1.70-0.86 (m, 40H), 0.16-0.13 (br, 9H). **MS (ESI):** 787.4 (M+Na<sup>+</sup>).



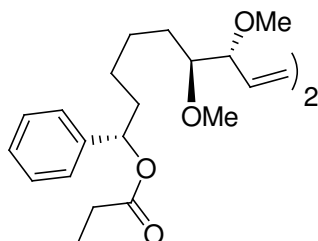
**Compound 33:** **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** 7.35-7.26 (m, 5H), 5.96-5.83 (m, 1H), 5.76-5.67 (m, 1H), 5.06-4.99 (m, 2H), 4.13-3.94 (m, 1H), 3.71-3.54 (m, 3H), 3.49-3.46 (m, 2H), 3.39-3.34 (m, 3H), 3.32-3.23 (m, 2H), 3.09-2.98 (m, 1H), 2.67-2.60 (m, 2H), 2.50-2.38 (m, 2H), 2.01-1.86 (m, 1H), 1.85-1.76 (m, 1H), 1.70-0.86 (m, 36H), 1.06 (d, *J* = 7.5 Hz, 3H), 0.93-0.88 (br, 12 H), 0.07 (s, 6H). **MS (ESI):** 829.4 (M+Na<sup>+</sup>).

\*Cross-metathesis avenue to *seco*-Soraphen A.



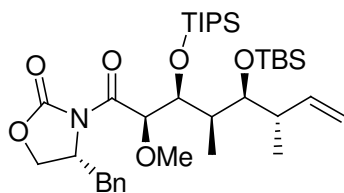
**Compound 37:** To a solution of 35 mg of **36** (0.094 mmol) and 63 mg of **F** (0.188 mmol) in 1 mL of degassed toluene were added 19 mg of Grubbs-Hoveyda II catalyst (0.062 mmol) in 3 portions. The reaction was stirred 30 hrs at 80°C and the solvent was then evaporated. Silica gel chromatography of the residue (ethyl acetate/ cyclohexane, 2:8) afforded as a colorless oil the desired compound **37** (17.3 mg, 26%) and the homocoupling compound **38** (20 mg, 33%). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** 7.32-7.26 (m, 5H), 5.75-5.71 (m, 2H), 5.48 (dd, *J* = 15.6, 8.1 Hz, 1H), 4.25-4.22 (d, *J* = 9.7 Hz, 1H), 3.78-3.69 (m, 2H), 3.57 (s, 3H), 3.54 (dd, *J* = 8.1, 4.1 Hz, 1H), 3.39 (s, 3H), 3.26 (s, 3H), 3.16-3.13 (m, 1H), 2.58-2.45 (m, 1H), 2.34 (dd, *J* = 7.5, 3.0 Hz, 2H), 2.15-2.03

(m, 1H), 1.98-1.84 (m, 1H), 1.83-1.72 (m, 1H), 1.45-1.19 (m, 6H), 1.12 (t,  $J = 7.5$  Hz, 3H), 1.08-1.03 (m, 21 H), 1.00 (d,  $J = 7.0$  Hz, 3H), 0.91 (d,  $J = 7.5$  Hz, 3H).  **$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )**: 174.1, 171.5, 141.4, 137.2, 128.8, 128.5, 128.1, 126.9, 84.7, 84.0, 80.8, 78.0, 76.2, 60.1, 59.1, 56.9, 40.7, 37.8, 36.8, 33.0, 31.1, 28.2, 26.1, 25.9, 18.3, 16.3, 12.6, 9.5. **IR ( $\text{cm}^{-1}$ )**: 2938, 2865, 1780, 1701, 1465, 1385, 1195, 1111, 1029, 918, 833. **MS (ES)**: 699.4 ( $\text{M}+\text{Na}^+$ ). **HRMS (ESI)**: calculated 699.4263, found 699.4258 ( $\text{M}+\text{Na}^+$ ).  **$[\alpha]_{\text{D}}^{22}$**  -28.6 ( $c$  0.35,  $\text{CH}_2\text{Cl}_2$ ).

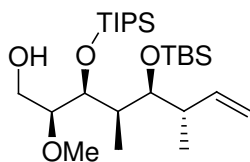


**Compound 38:**  **$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )**: 7.32-7.27 (m, 10H), 5.71 (dd,  $J = 7.7, 6.3$  Hz, 2H), 5.60-5.56 (m, 2H), 3.59-3.55 (m, 2H), 3.38 (s, 2H), 3.35 (s, 4H), 3.28 (s, 4H), 3.24 (s, 2H), 3.18-3.14 (m, 2H), 2.33 (dd,  $J = 7.7, 2.6$  Hz, 4H), 1.95-1.82 (m, 2H), 1.81-1.71 (m, 2H), 1.44-1.22 (m, 12 H), 1.12 (t,  $J = 7.7$  Hz, 6H).  **$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )**: 173.9, 141.0, 132.0, 128.5, 127.9, 126.6, 84.0, 83.4, 75.9, 58.7, 58.6, 56.8, 56.7, 36.5, 30.6, 28.0, 25.7, 25.6, 9.2. **MS (ESI)**: 663.3 ( $\text{M}+\text{Na}^+$ ).

**\*Synthesis of compounds 26, 27 and 28.**

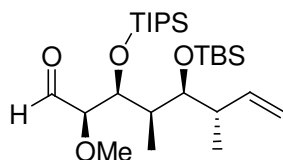


**Compound h:** The alcohol **16** was obtained from 1000 mg (2.0 mmol) of aldehyde **15** as described before. To a solution **16** in 5 mL of  $\text{CH}_2\text{Cl}_2$  were added at  $0^\circ\text{C}$ : 556  $\mu\text{L}$  of  $\text{Et}_3\text{N}$  (4.0 mmol) and 460  $\mu\text{L}$  of TBS triflate (2.0 mmol). The reaction was stirred 3 hrs at RT and then diluted with 10 mL of a saturated aqueous solution of  $\text{NaHCO}_3$  and 10 mL of  $\text{CH}_2\text{Cl}_2$ . The organic phase was separated and the aqueous phase was extracted with 10 mL of  $\text{CH}_2\text{Cl}_2$ . The combined extracts were dried with  $\text{Na}_2\text{SO}_4$  and concentrated. Silica gel chromatography of the residue (ethyl acetate/ cyclohexane, 1:9) afforded as a pale yellow oil the desired compound **i** (528 mg, 40% on 2 steps) without any diastereoisomers.  **$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )**: 7.37-7.23 (m, 5H), 5.81 (ddd,  $J = 17.3, 10.1, 7.9$  Hz, 1H), 5.24 (d,  $J = 7.9$  Hz, 1H), 5.05 (dd,  $J = 17.3, 2.6$  Hz, 1H), 4.93 (dd,  $J = 10.1, 2.6$  Hz, 1H), 4.57-4.51 (m, 1H), 4.21-4.13 (m, 3H), 3.62 (d,  $J = 9.4$  Hz, 1H), 3.45 (dd,  $J = 13.1, 3.0$  Hz, 1H), 3.38 (s, 3H), 2.76 (dd,  $J = 13.1, 10.1$  Hz, 1H), 2.44-2.34 (m, 1H), 1.38-1.28 (m, 1H), 1.14-1.10 (br, 21H), 1.04 (d,  $J = 6.8$  Hz, 3H), 0.94 (d,  $J = 7.1$  Hz, 3H), 0.90 (m, 9H), 0.06 (s, 6H).  **$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )**: 172.6, 153.0, 140.1, 135.2, 129.3, 129.0, 127.4, 115.2, 76.5, 66.4, 57.1, 56.4, 41.8, 40.2, 37.8, 26.3, 19.8, 18.5, 13.7, 11.3, -3.0, -3.8. **IR ( $\text{cm}^{-1}$ )**: 2930, 2862, 1766, 1707, 1456, 1380, 1180, 1111, 1032, 832, 698. **MS (ESI)**: 684.3 ( $\text{M}+\text{Na}^+$ ). **HRMS (LSIMS)**: calculated 662.4272, found 662.4277 ( $\text{M}+\text{H}^+$ ).  **$[\alpha]_{\text{D}}^{22}$**  -37.7 ( $c$  1.47,  $\text{CH}_2\text{Cl}_2$ ).

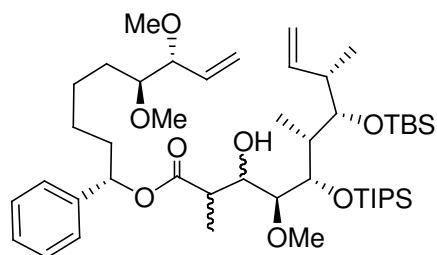


**Compound i:** To a solution of 267 mg (0.4 mmol) of **h** in 2 mL of THF at  $0^\circ\text{C}$  were added 1.6 mL of a 2M solution of lithium borohydride in THF (3.3 mmol) and 120  $\mu\text{L}$  (2.8 mmol) of methanol. The reaction was stirred 12 hrs at RT and then diluted with 10 mL of a saturated aqueous solution of  $\text{NaHCO}_3$  and 10 mL of  $\text{Et}_2\text{O}$ . The organic phase was separated and the aqueous phase was extracted with 10 mL of  $\text{Et}_2\text{O}$ . The combined extracts were dried with  $\text{Na}_2\text{SO}_4$  and concentrated. Silica gel chromatography of the residue (ethyl acetate/ cyclohexane, 1:9) afforded as a pale yellow oil the desired compound **i** (145 mg, 73%).  **$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )**: 5.91 (ddd,  $J = 18.1, 9.4, 8.7$  Hz, 1H), 5.04-4.99 (m, 2H), 4.04 (dd,  $J = 7.2, 1.9$  Hz, 1H), 3.88-3.82 (m, 1H), 3.70 (dd,  $J = 8.7, 1.5$  Hz, 1H), 3.59-3.52

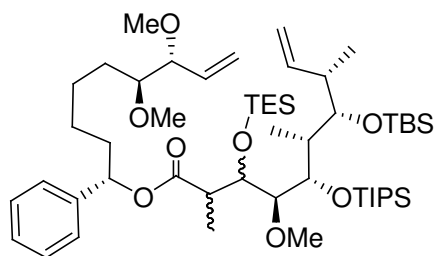
(m, 1H), 3.41 (s, 3H), 3.24 (p,  $J = 3.7$  Hz, 1H), 2.49-2.40 (m, 1H), 1.81-1.70 (m, 2H), 1.12-1.10 (br, 21H), 1.05 (d,  $J = 7.2$  Hz, 3H), 0.92-0.89 (br, 9H), 0.89 (d,  $J = 6.8$  Hz, 3H), 0.06 (s, 6H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ): 140.4, 115.1, 84.7, 76.8, 72.2, 59.6, 57.1, 41.8, 39.1, 26.3, 19.2, 18.5, 13.5, 11.1, -3.1, -3.7. IR ( $\text{cm}^{-1}$ ): 2927, 2863, 1463, 1253, 1034, 835, 773. MS (CI): 489 ( $\text{M}+\text{H}^+$ ). HRMS (CI): calculated 489.3795, found 489.3794 ( $\text{M}+\text{H}^+$ ).  $[\alpha]_{\text{D}}^{22} = +6.8$  ( $c = 0.995$ ,  $\text{CH}_2\text{Cl}_2$ ).



**Compound j:** To a solution of 113 mg of **i** (0.23 mmol) in 1 mL of  $\text{CH}_2\text{Cl}_2$  were added 0.95 mL of a 0.5 M solution of Dess-Martin periodinane (0.47 mmol). The reaction was stirred 2 hrs and diluted with 2 mL of a saturated aqueous solution of  $\text{Na}_2\text{S}_2\text{O}_3$ , 2 mL of a saturated aqueous solution of  $\text{NaHCO}_3$  and 4 mL of  $\text{CH}_2\text{Cl}_2$ . The organic phase was separated and the aqueous phase was extracted with 4 mL of  $\text{CH}_2\text{Cl}_2$ . The combined extracts were dried with  $\text{Na}_2\text{SO}_4$  and concentrated. Silica gel chromatography of the residue (ethyl acetate/ cyclohexane, 1:9) afforded as a colorless oil the desired compound **j** (73 mg, 65%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ): 9.56 (d,  $J = 3.4$  Hz, 1H), 5.83 (ddd,  $J = 18.6$ , 10.4, 8.8 Hz, 1H), 5.05-4.89 (m, 2H), 4.17 (dd,  $J = 7.4$ , 2.8 Hz, 1H), 3.69 (dd,  $J = 8.1$ , 2.6 Hz, 1H), 3.61 (dd,  $J = 7.2$ , 3.2 Hz, 1H), 3.34 (s, 3H), 2.46-2.34 (m, 1H), 1.65-1.57 (m, 1H), 1.13-1.07 (br, 21H), 1.02 (d,  $J = 7.0$  Hz, 3H), 0.94 (d,  $J = 6.8$  Hz, 3H), 0.90 (m, 9H), 0.05 (s, 6H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ): 201.4, 140.3, 115.0, 89.3, 75.9, 72.6, 57.9, 42.1, 39.9, 26.3, 18.9, 18.4, 13.4, 10.9, -3.1, -3.5. MS (CI): 487 ( $\text{M}+\text{H}^+$ ). HRMS (CI): calculated 487.3630, found 487.3636 ( $\text{M}+\text{H}^+$ ).  $[\alpha]_{\text{D}}^{22} +22.6$  ( $c = 0.87$ ,  $\text{CH}_2\text{Cl}_2$ ).

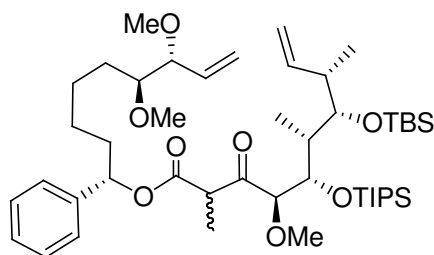


**Compound 26:** To a solution of 55 mg of ester **2** (0.164 mmol) in 0.5 mL of THF at  $-78^\circ\text{C}$  were added dropwise 102  $\mu\text{L}$  of a 2M solution of LDA (0.205 mmol) in THF. The reaction was stirred 35 min at  $-78^\circ\text{C}$  and 40 mg of aldehyde **j** (0.082 mmol) in 0.3 mL of THF were added dropwise and the reaction was stirred 4 hrs at  $-78^\circ\text{C}$ . The mixture was diluted with 3 mL of a saturated aqueous solution of  $\text{NaHCO}_3$  and 3 mL of EtOAc. The organic phase was separated and the aqueous phase was extracted with 3 mL of EtOAc. The combined extracts were dried with  $\text{Na}_2\text{SO}_4$  and concentrated. Silica gel chromatography of the residue (ethyl acetate/ cyclohexane, 1:9) afforded as a colorless oil a 3:1 mixture of 2 diastereoisomers of the desired compound **26** (47 mg, 70%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ): 7.33-7.26 (m, 5H), 5.98-5.83 (m, 1H), 5.79-5.67 (m, 2H), 5.30-5.20 (m, 2H), 5.06-4.99 (m, 2H), 4.12-4.02 (m, 1H), 3.70-3.52 (m, 3H), 3.46 (s, 1H), 3.40-3.37 (br, 5H), 3.28 (s, 3H), 3.16-3.13 (m, 1H), 3.07 (d,  $J = 8.1$  Hz, 0.75H), 2.98 (d,  $J = 8.6$  Hz, 0.25H), 2.71-2.59 (m, 2H), 2.47-2.41 (m, 0.75H), 2.24 (m, 0.25H), 1.96-1.89 (m, 1H), 1.82-1.77 (m, 1H), 1.74-1.65 (m, 1H), 1.45-1.17 (m, 6H), 1.14-1.09 (br, 21H), 1.05 (d,  $J = 7.2$  Hz, 3H), 0.94-0.90 (m, 14.25 H), 0.78 (d,  $J = 6.8$  Hz, 0.75H), 0.07 (s, 6H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ): 174.7, 174.3, 140.9, 140.5, 135.6, 128.9, 128.8, 128.3, 126.9, 119.3, 115.9, 115.7, 85.0, 83.8, 82.5, 77.7, 76.6, 76.4, 72.5, 72.4, 61.2, 58.8, 57.1, 45.5, 42.2, 40.3, 40.2, 36.6, 30.6, 26.8, 25.9, 20.1, 19.1, 18.9, 18.7, 15.0, 14.4, 14.3, 11.5, -2.5, -3.2. IR ( $\text{cm}^{-1}$ ): 2929, 2862, 1732, 1461, 1252, 1173, 1082, 1031, 638. MS (ESI): 843.5 ( $\text{M}+\text{Na}^+$ ). HRMS (LSIMS): calculated 843.5602, found 843.5609 ( $\text{M}+\text{Na}^+$ ).



**Compound 27:** To a solution of 30 mg of **26** (0.036 mmol) in 0.8 mL of  $\text{CH}_2\text{Cl}_2$  were added at  $0^\circ\text{C}$ , 20  $\mu\text{L}$  of  $\text{Et}_3\text{N}$  (0.14 mmol) and 16  $\mu\text{L}$  of TES triflate (0.073 mmol). The reaction was stirred 3 hrs at RT and diluted with 3 mL of a saturated aqueous solution of  $\text{NaHCO}_3$  and 4 mL of EtOAc. The organic phase was separated and the aqueous phase was extracted with 4 mL of EtOAc. The combined

extracts were dried with  $\text{Na}_2\text{SO}_4$  and concentrated. Silica gel chromatography of the residue (ethyl acetate/ cyclohexane, 1:9) afforded as a colorless oil a 3:1 mixture of 2 diastereoisomers of the desired compound **27** (25 mg, 73%).  **$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):** 7.31-7.25 (m, 5H), 6.19-5.96 (m, 1H), 5.79-5.60 (m, 2H), 5.29 (d,  $J = 10.6$  Hz, 1H), 5.23 (d,  $J = 17.3$  Hz, 1H), 5.12-4.98 (m, 2H), 4.23-3.93 (m, 2H), 3.71-3.66 (m, 1H), 3.54 (dt,  $J = 3.7, 7.5$  Hz, 1H), 3.79-3.71 (m, 3H), 3.31-3.31 (m, 6H), 3.15-3.11 (m, 1H), 2.93 (s, 1H), 2.91 (t,  $J = 7.3$  Hz, 0.75H), 2.77 (t,  $J = 7.3$  Hz, 0.25H), 2.62 (t,  $J = 7.2$  Hz, 0.25), 2.53 (t,  $J = 7.2$  Hz, 0.75H), 1.98-1.85 (m, 1H), 1.81-1.71 (m, 1H), 1.44-1.41 (m, 2H), 1.38-1.25 (m, 2H), 1.19 (d,  $J = 6.8$  Hz, 2H), 1.12-1.01 (m, 27H), 0.97-0.88 (m, 16H), 0.77 (t,  $J = 7.9$  Hz, 6H), 0.64-0.55 (m, 1.5H), 0.50-0.31 (m, 4.5H), 0.06 (s, 6H).  **$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):** 174.5, 141.0, 140.7, 140.5, 135.6, 128.7, 128.6, 128.2, 128.0, 127.3, 127.1, 119.3, 115.6, 85.0, 83.8, 78.4, 77.9, 76.5, 75.9, 58.8, 57.8, 57.1, 43.8, 41.1, 40.0, 37.1, 36.3, 30.7, 26.7, 25.9, 21.2, 20.8, 19.1, 19.0, 15.1, 14.5, 14.3, 12.6, 7.3, 5.3, 5.1, -2.5, -2.6, -3.0, -3.1. **IR ( $\text{cm}^{-1}$ ):** 2932, 2863, 1732, 1460, 1252, 1089, 1044, 834. **MS (ESI):** 957.5 ( $\text{M}+\text{Na}^+$ , 100%). **HRMS (CI):** calculated 957.6467, found 957.6465( $\text{M}+\text{Na}^+$ ).



**Compound 28:** To a solution of 38 mg of **26** (0.046 mmol) in 1 mL of  $\text{CH}_2\text{Cl}_2$  were added 0.3 mL of a 0.5M solution of Dess-Martin periodinane (0.15 mmol) in  $\text{CH}_2\text{Cl}_2$ . The reaction was stirred 2 hrs at RT and diluted with 2 mL of a saturated aqueous solution of  $\text{Na}_2\text{S}_2\text{O}_3$ , 2 mL of a saturated aqueous solution of  $\text{NaHCO}_3$  and 4 mL of  $\text{CH}_2\text{Cl}_2$ . The organic phase was separated and

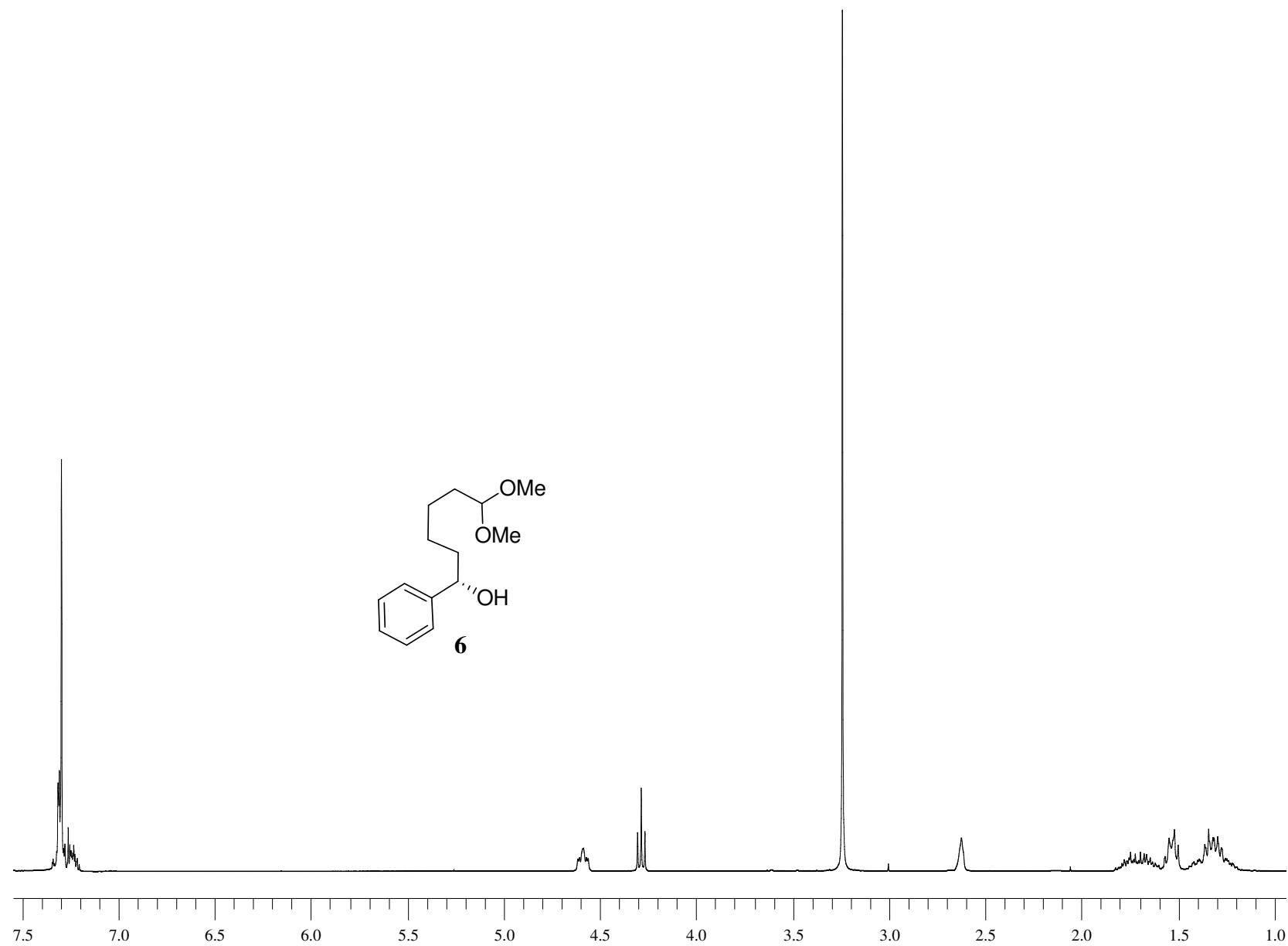
the aqueous phase was extracted with 4 mL of  $\text{CH}_2\text{Cl}_2$ . The combined extracts were dried with  $\text{Na}_2\text{SO}_4$  and concentrated. Silica gel chromatography of the residue (ethyl acetate/ cyclohexane, 1:9) afforded as a colorless oil a 3:2 mixture of 2 diastereoisomers of the desired compound **28** (27 mg, 72%).  **$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):** 7.35-7.26 (m, 5H), 5.93-5.70 (m, 3H), 5.31-5.22 (m, 2H), 5.05-4.72 (m, 2H), 4.17-4.15 (m, 0.6H), 4.05 (d,  $J = 5.6$  Hz, 0.4H), 3.97 (m, 0.6H), 3.86 (q,  $J = 7.2$  Hz, 0.4 H), 3.76 (dd,  $J = 6.6, 2.8$  Hz, 0.4H), 3.69-3.61 (m, 1.6H), 3.56-3.54 (m, 1H), 3.38 (s, 3H), 3.28 (s, 3H), 3.21 (s, 1H), 3.16-3.13 (m, 1H), 3.07 (s, 1H), 2.94 (s, 1H), 2.51-2.44 (m, 0.3H), 2.37-2.32 (m, 0.3H), 2.28-2.22 (m, 0.4H), 1.99-1.89 (m, 1H), 1.86-1.73 (m, 1H), 1.47-1.21 (m, 9H), 1.12-1.01 (m, 23.2H), 0.97 (t,  $J = 6.6$  Hz, 1.8H), 0.91-0.89 (m, 12H), 0.05-0.04 (m, 6H).  **$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):** 175.6, 169.5, 141.0, 140.4, 135.6, 128.9, 128.8, 127.2, 127.1, 126.8, 119.3, 115.4, 91.9, 90.0, 85.0, 83.8, 77.8, 77.6, 76.8, 75.6, 75.4, 58.9, 57.5, 57.1, 56.3, 51.9, 42.8, 41.8, 41.0, 30.6, 26.7, 25.9, 19.1, 19.0, 18.9, 18.8, 14.2, 14.0, 13.8, 11.6, 10.9, -2.6, -3.5. **IR ( $\text{cm}^{-1}$ ):** 2914, 2848, 1699, 1471, 1299, 1109, 1035, 882. **MS (ESI):** 841.4 ( $\text{M}+\text{Na}^+$ ). **HRMS (LSIMS):** calculated 841.5446, found 841.5444 ( $\text{M}+\text{Na}^+$ ).

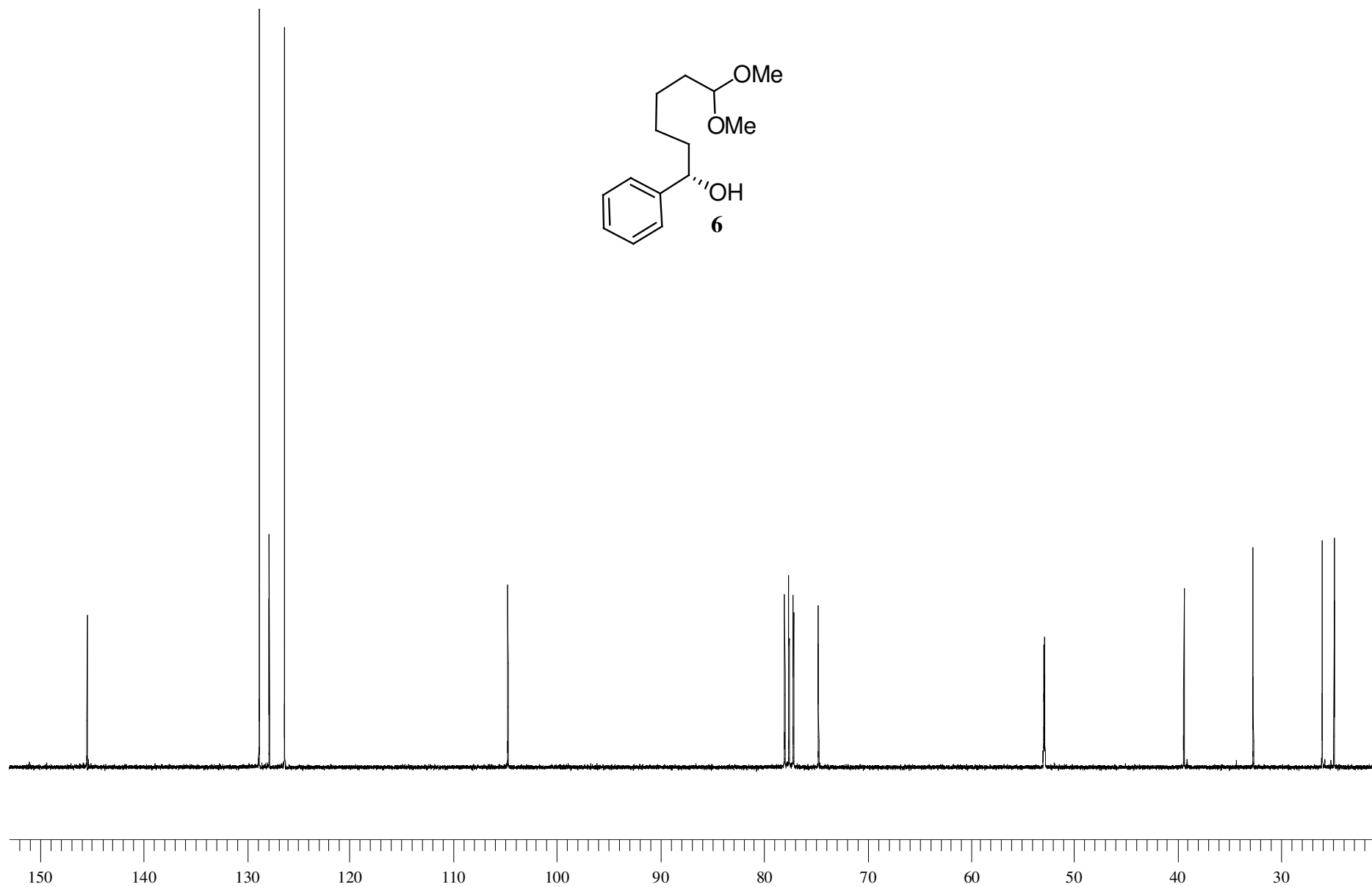
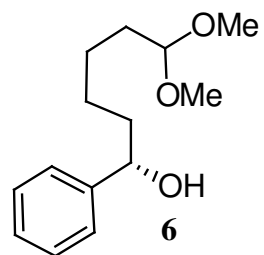
# HARDCOPY $^1\text{H}$ and $^{13}\text{C}$ NMR SPECTRA

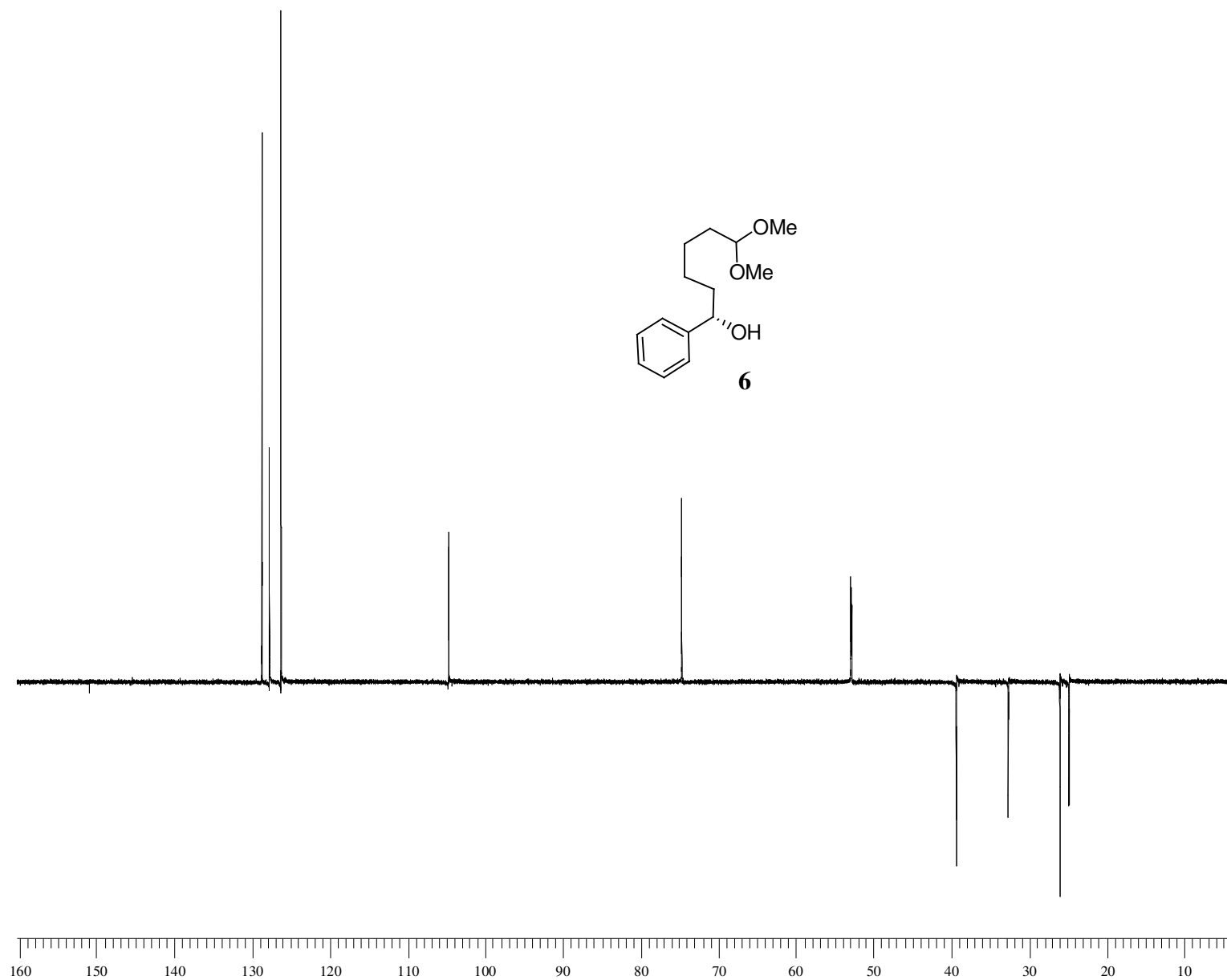
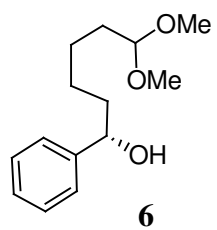
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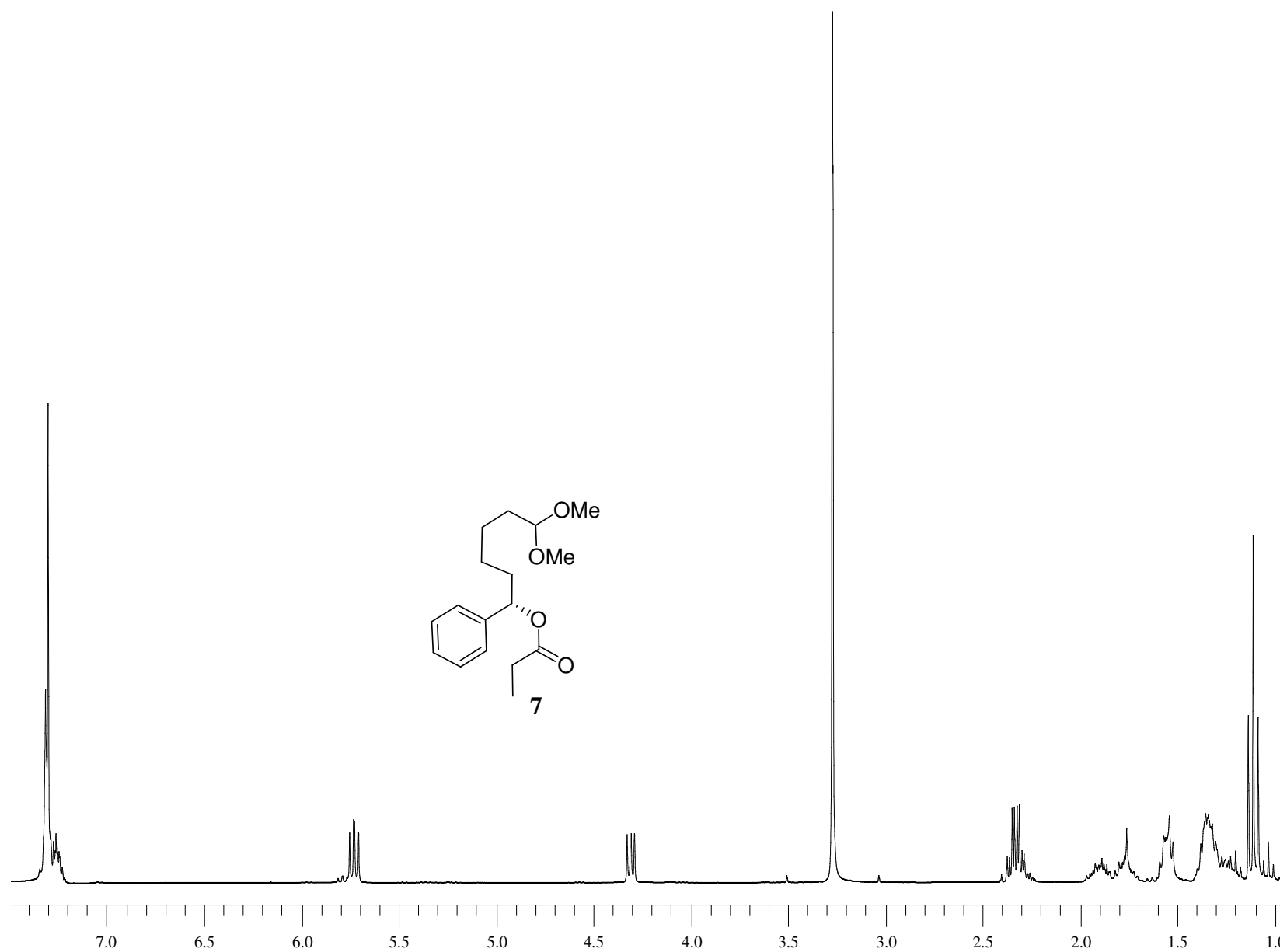
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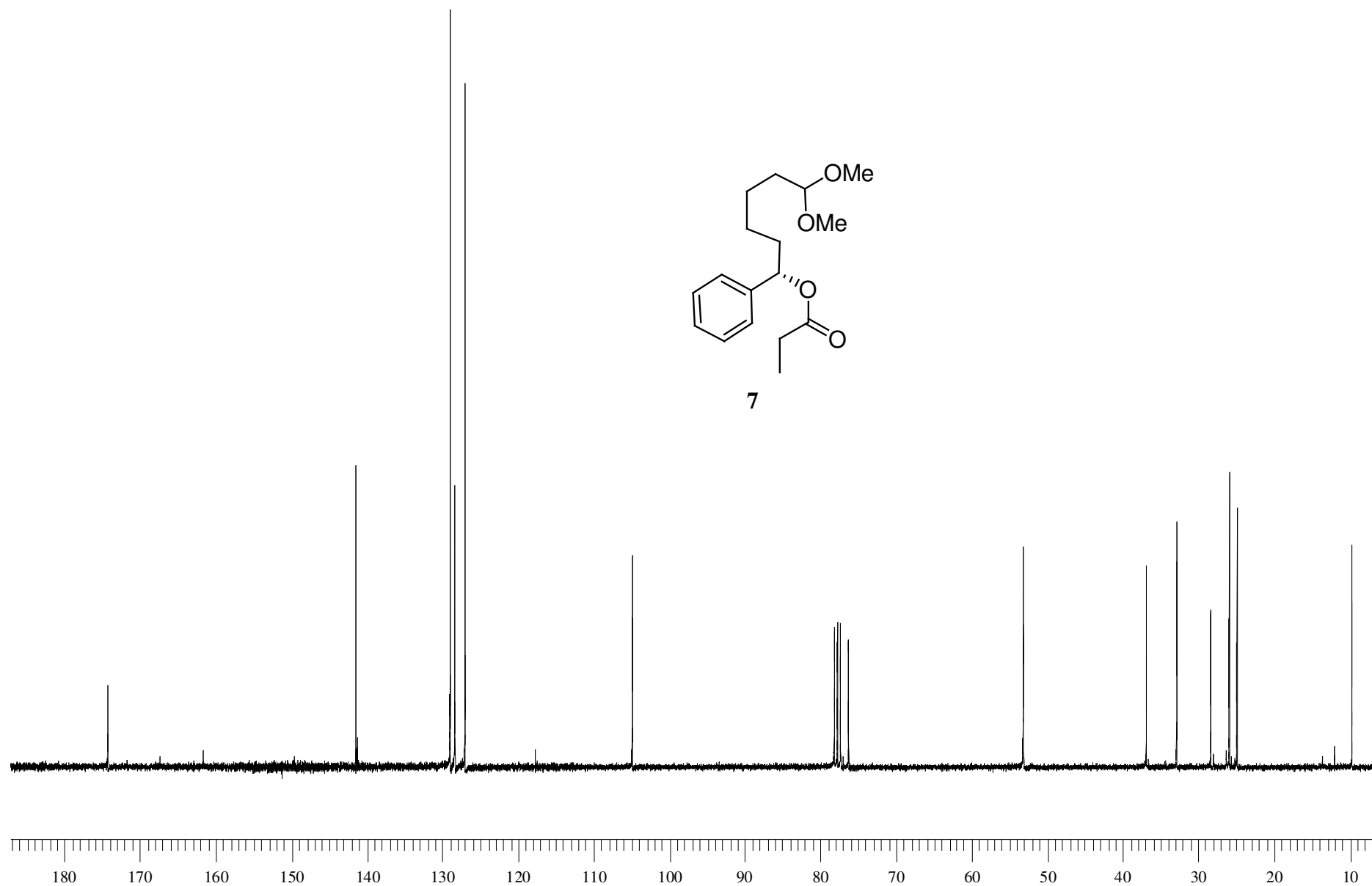
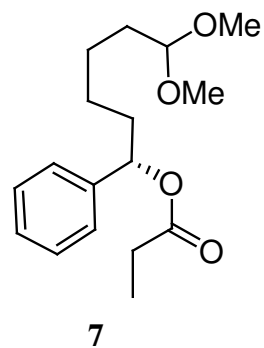


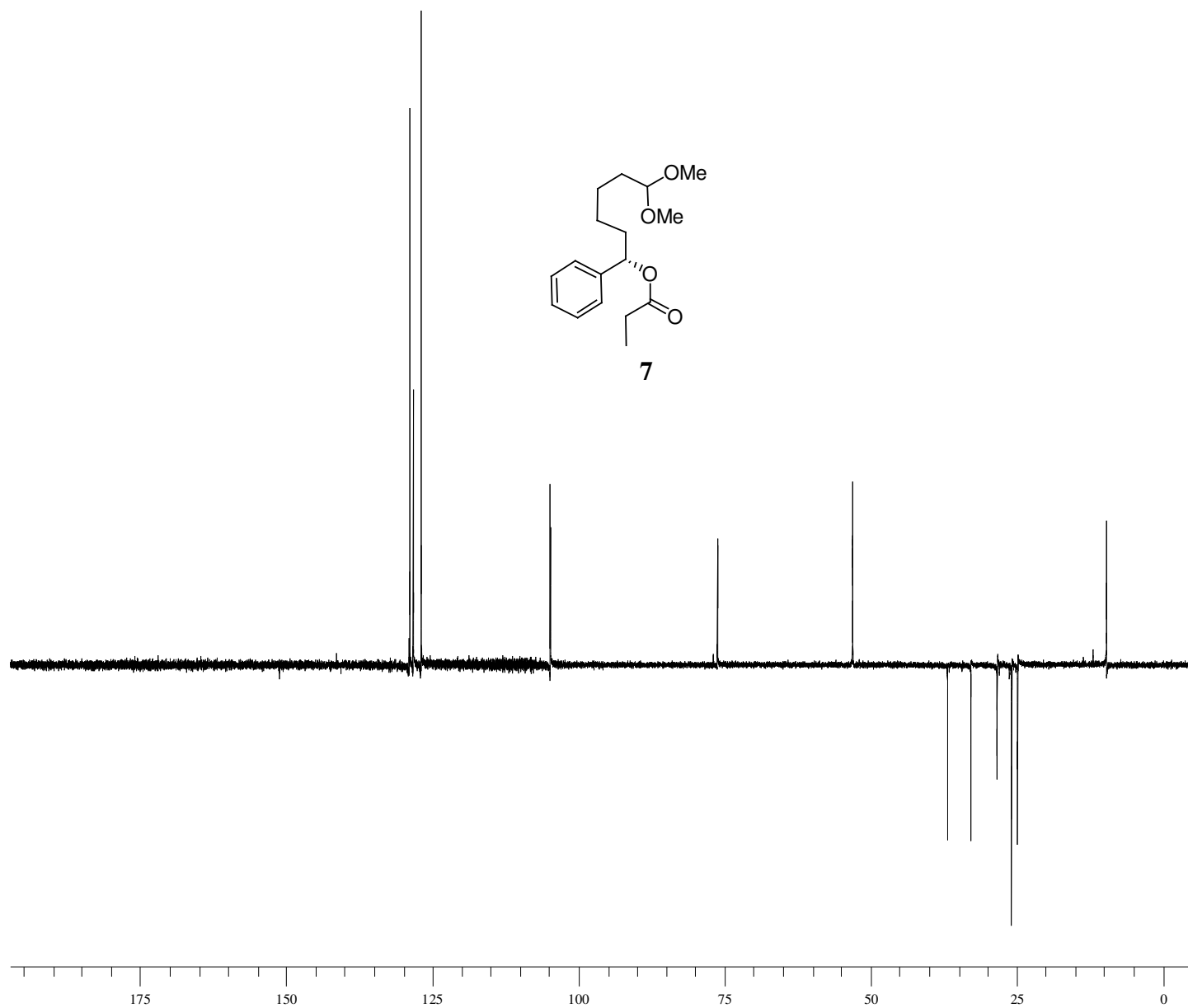
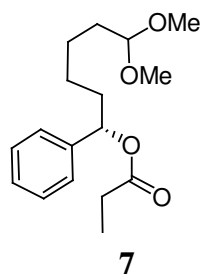


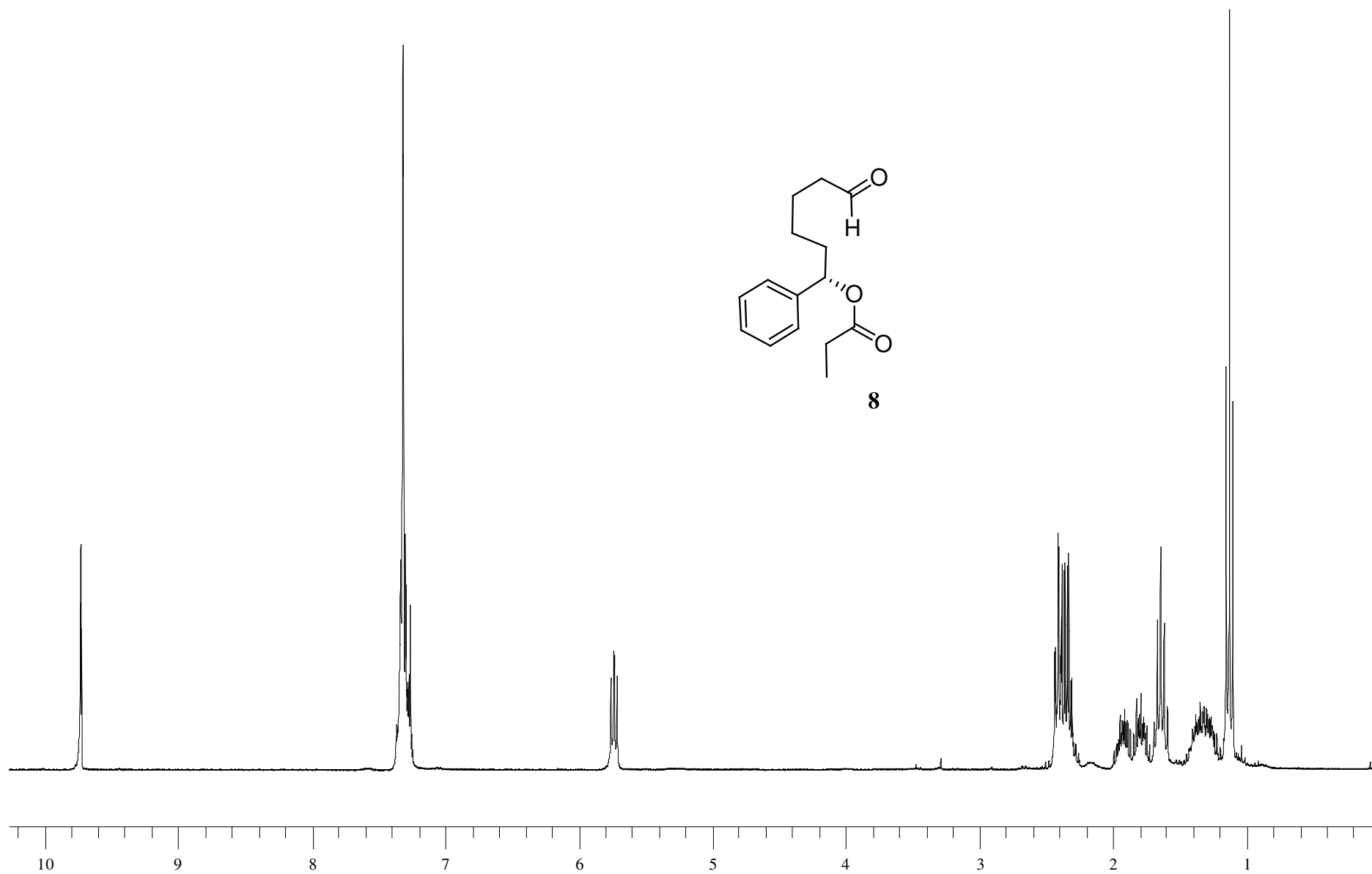
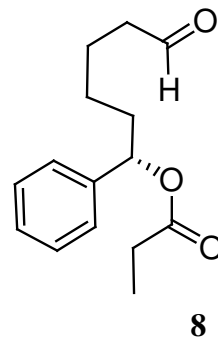


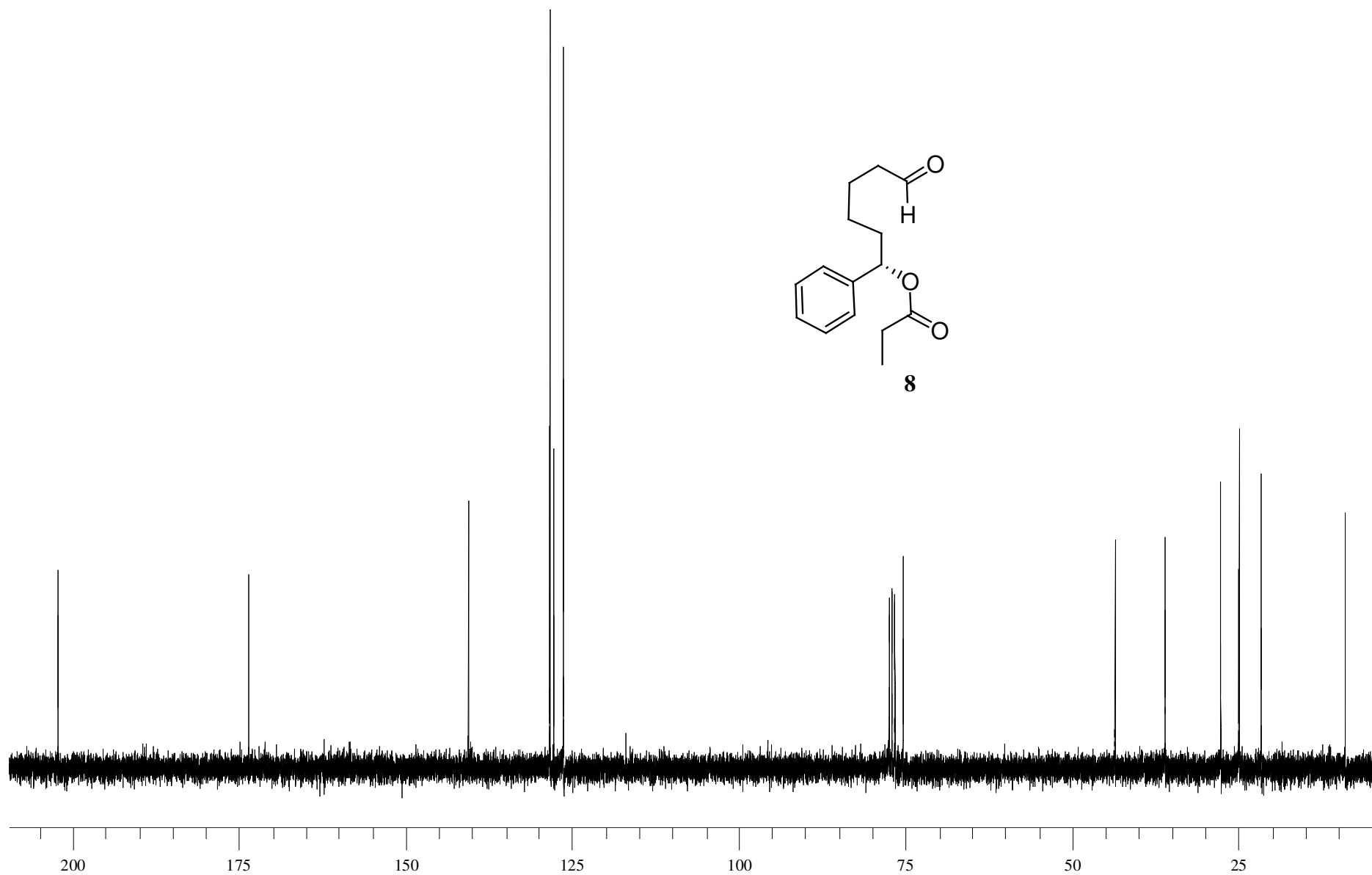
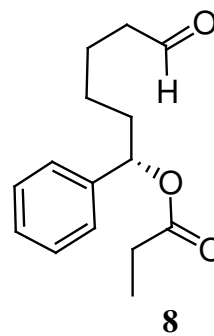




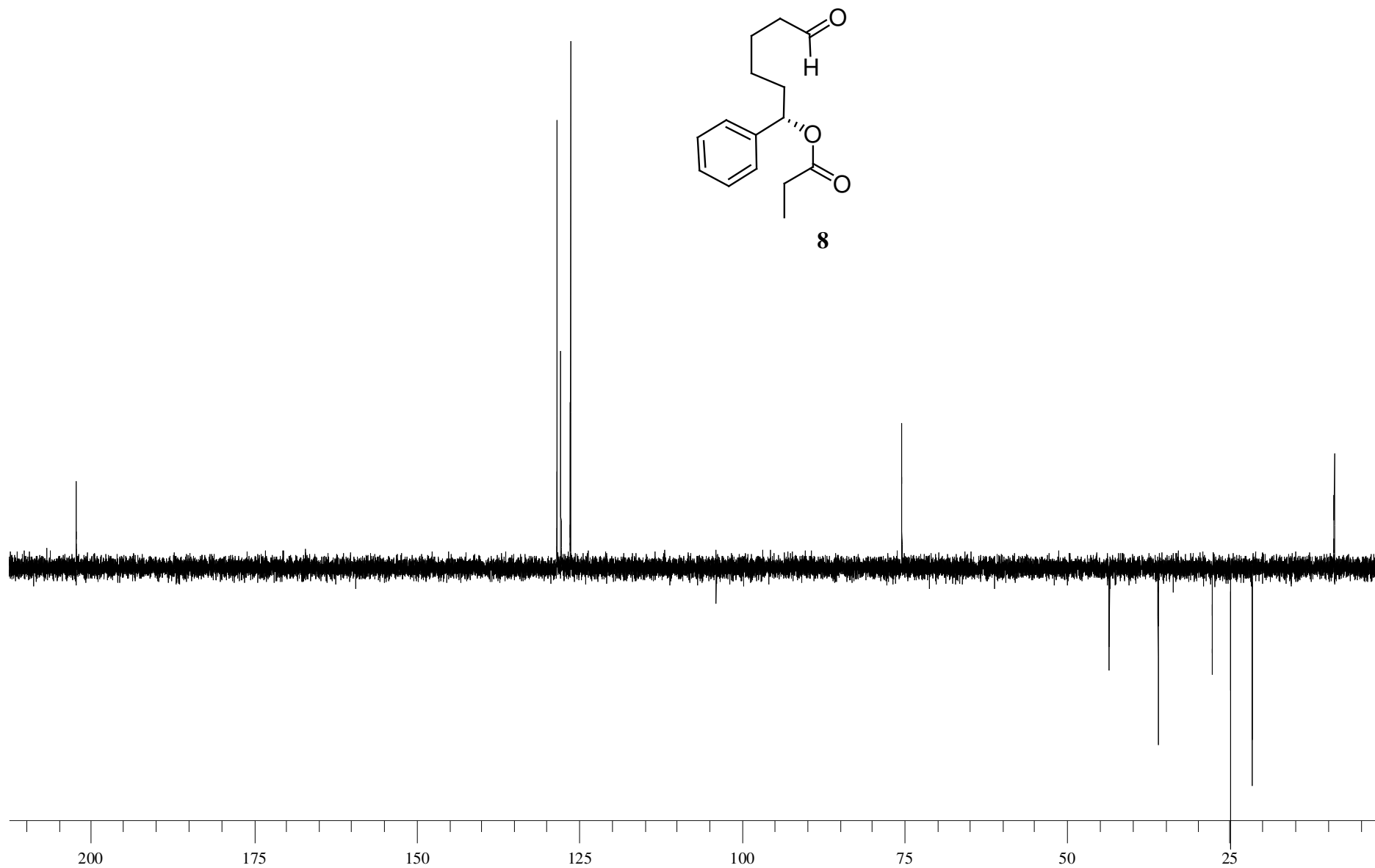
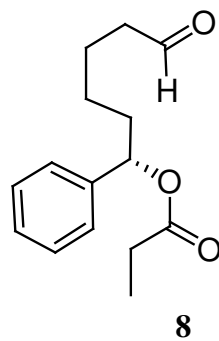


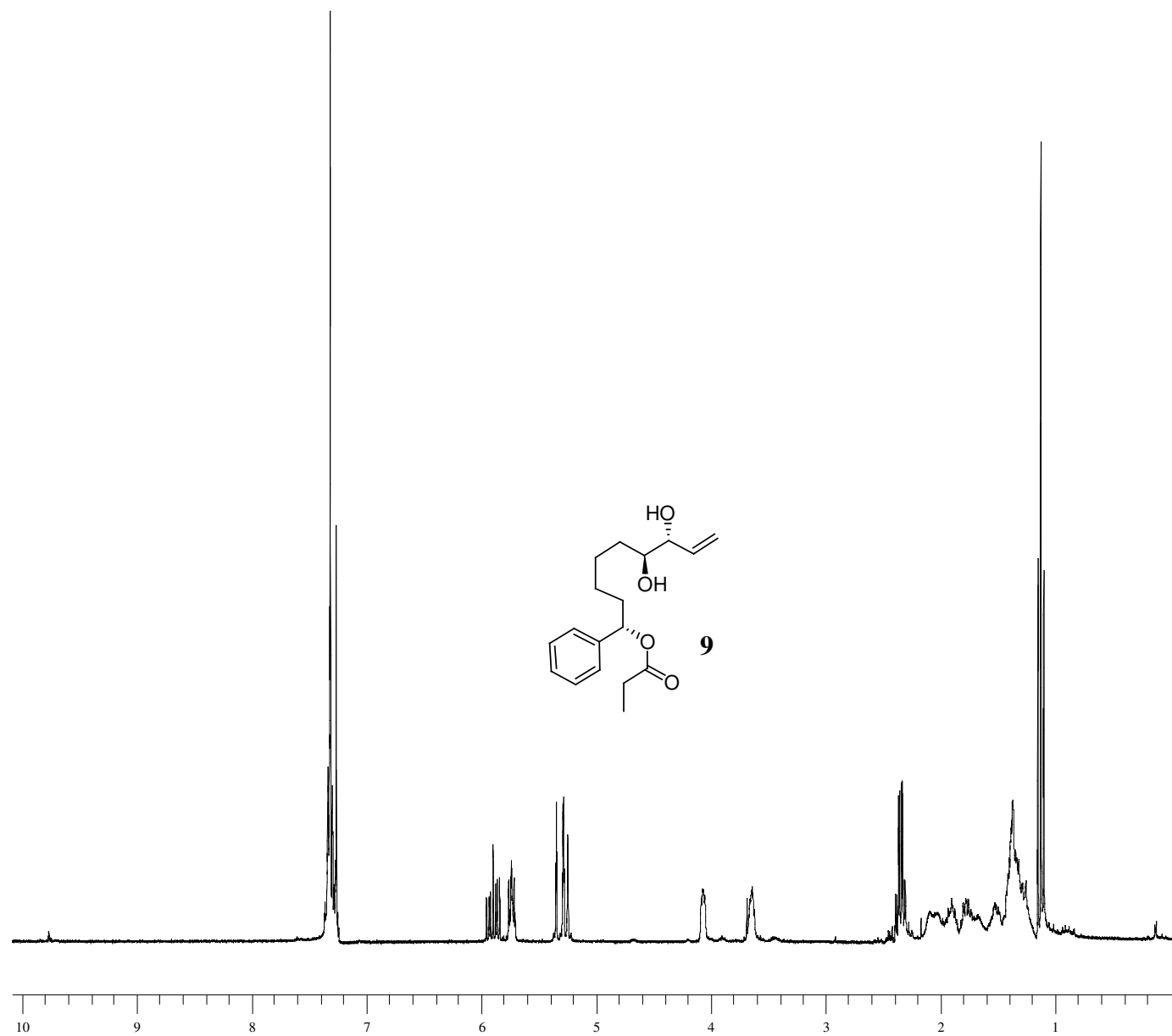


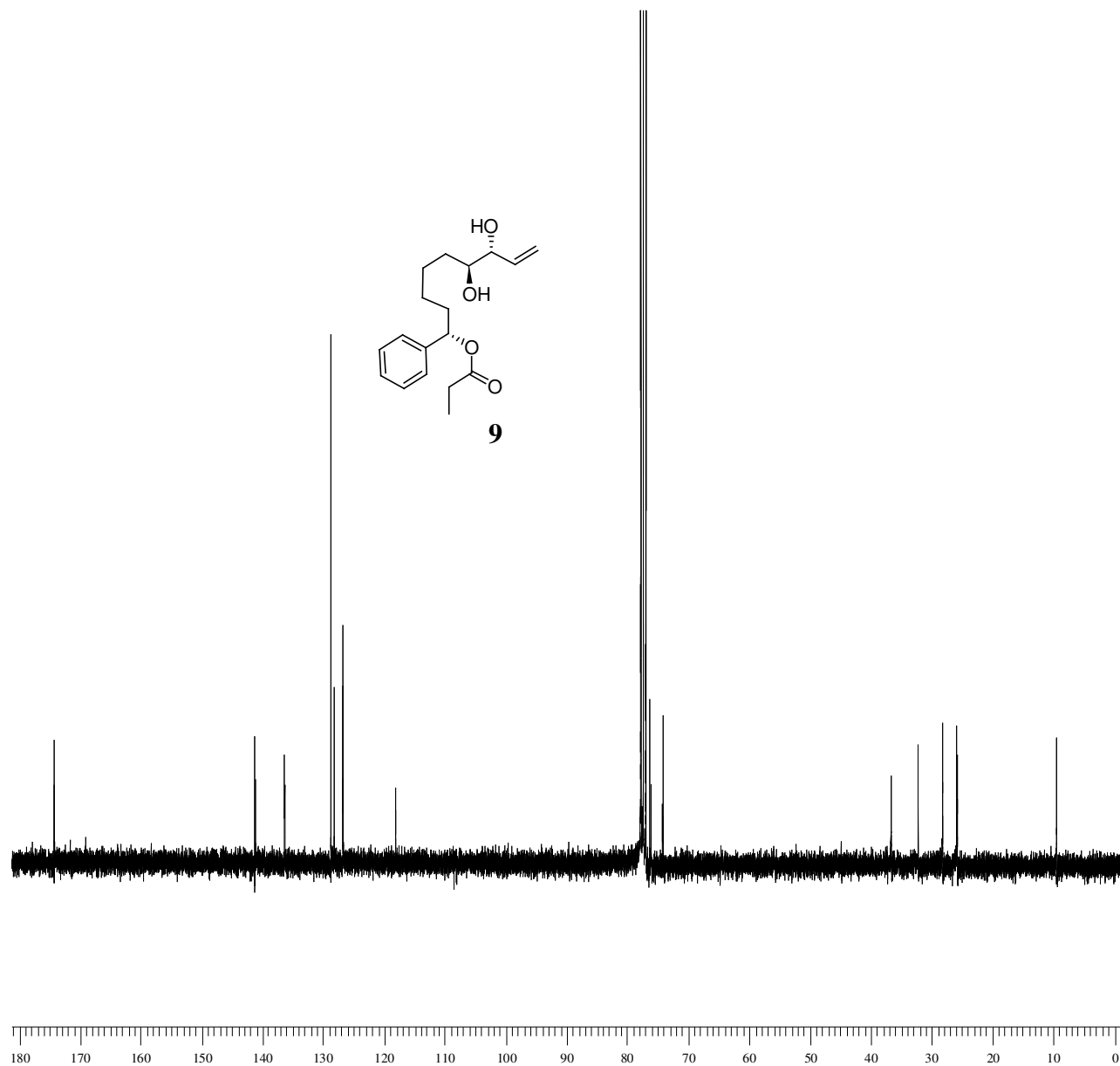
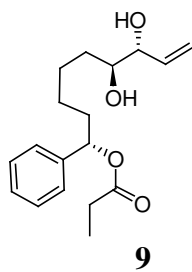


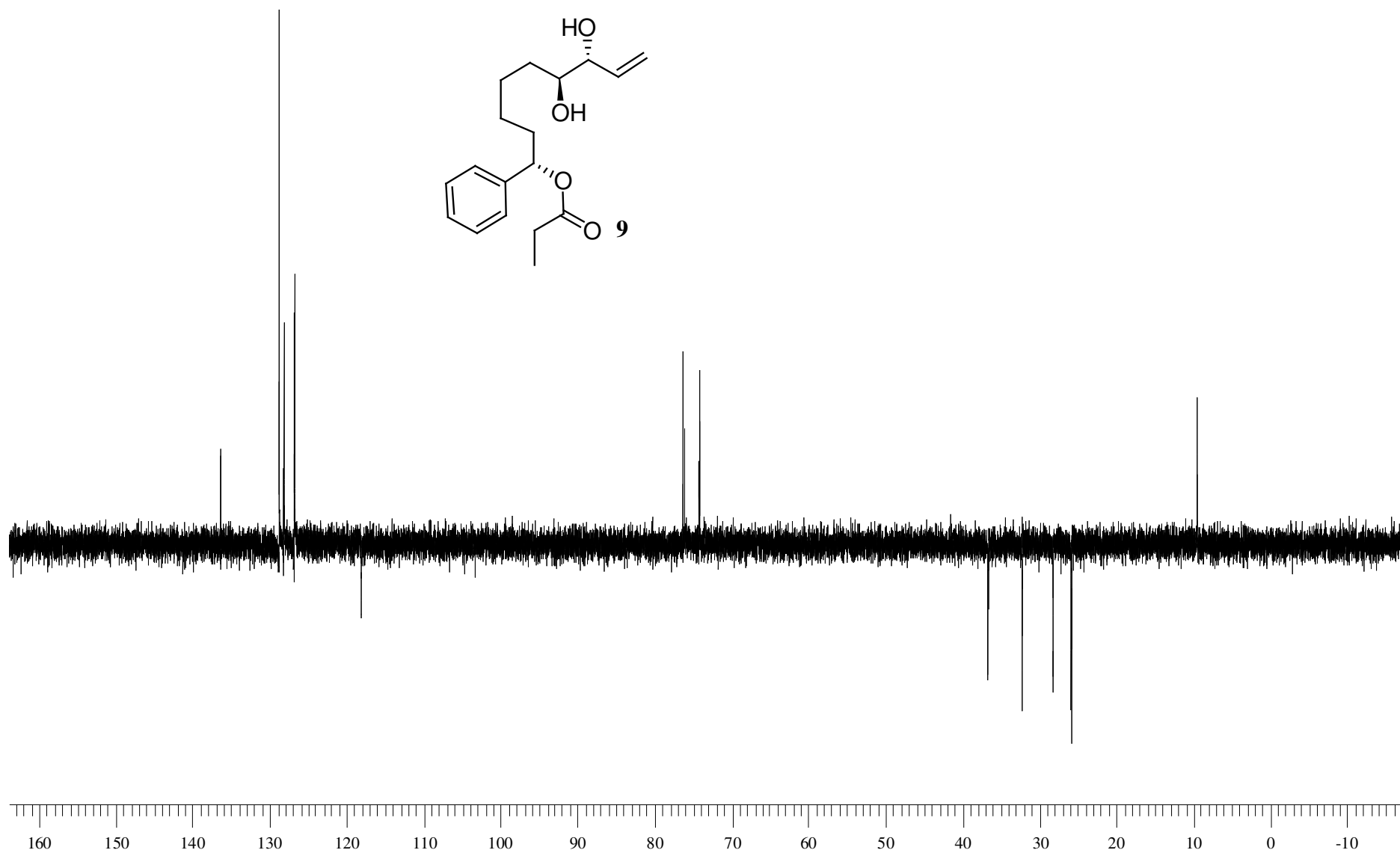
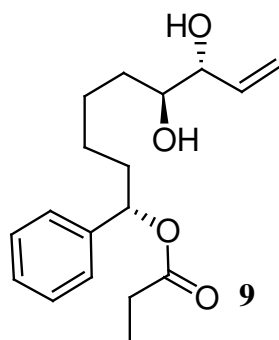


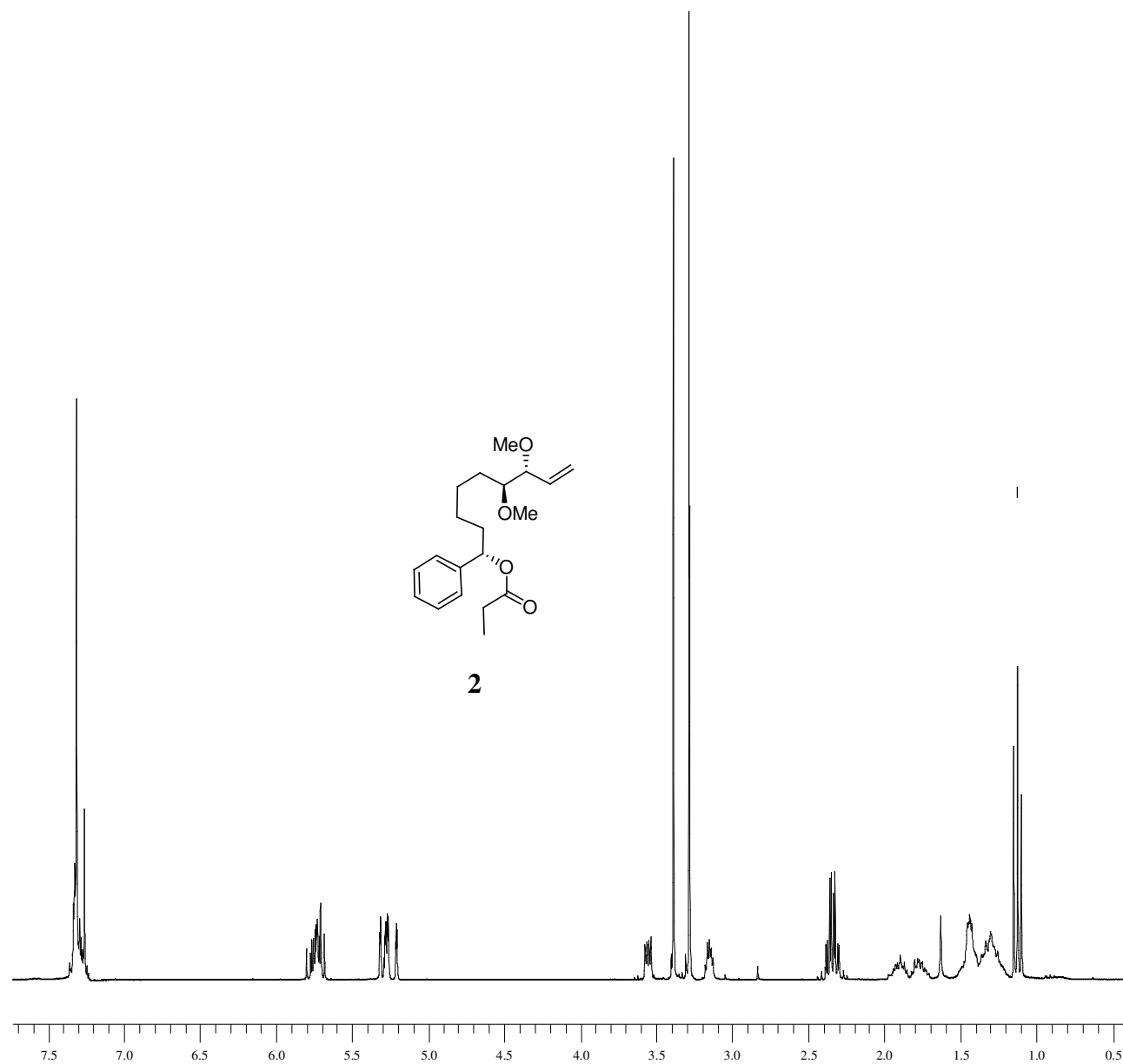


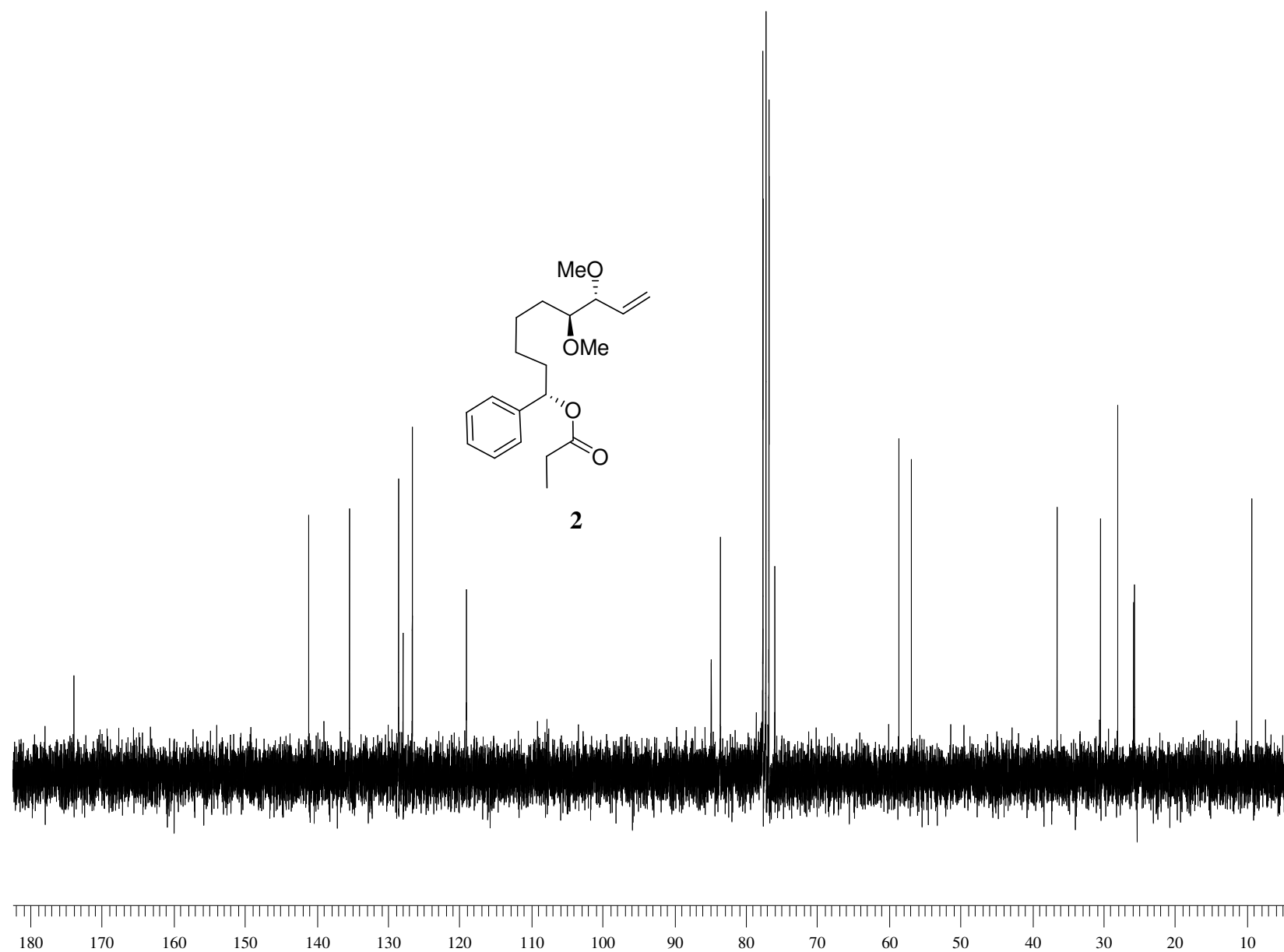


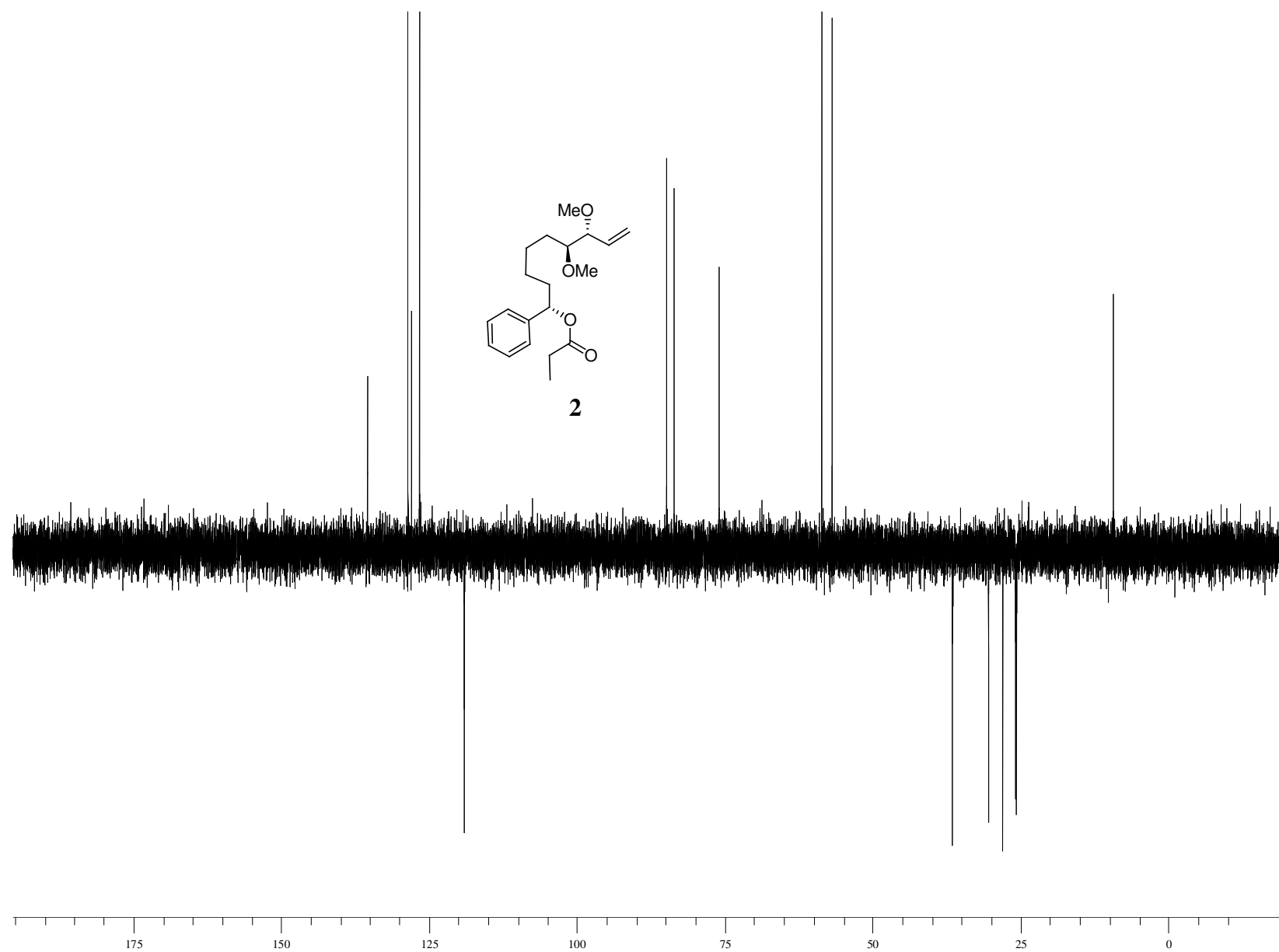


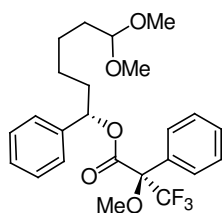
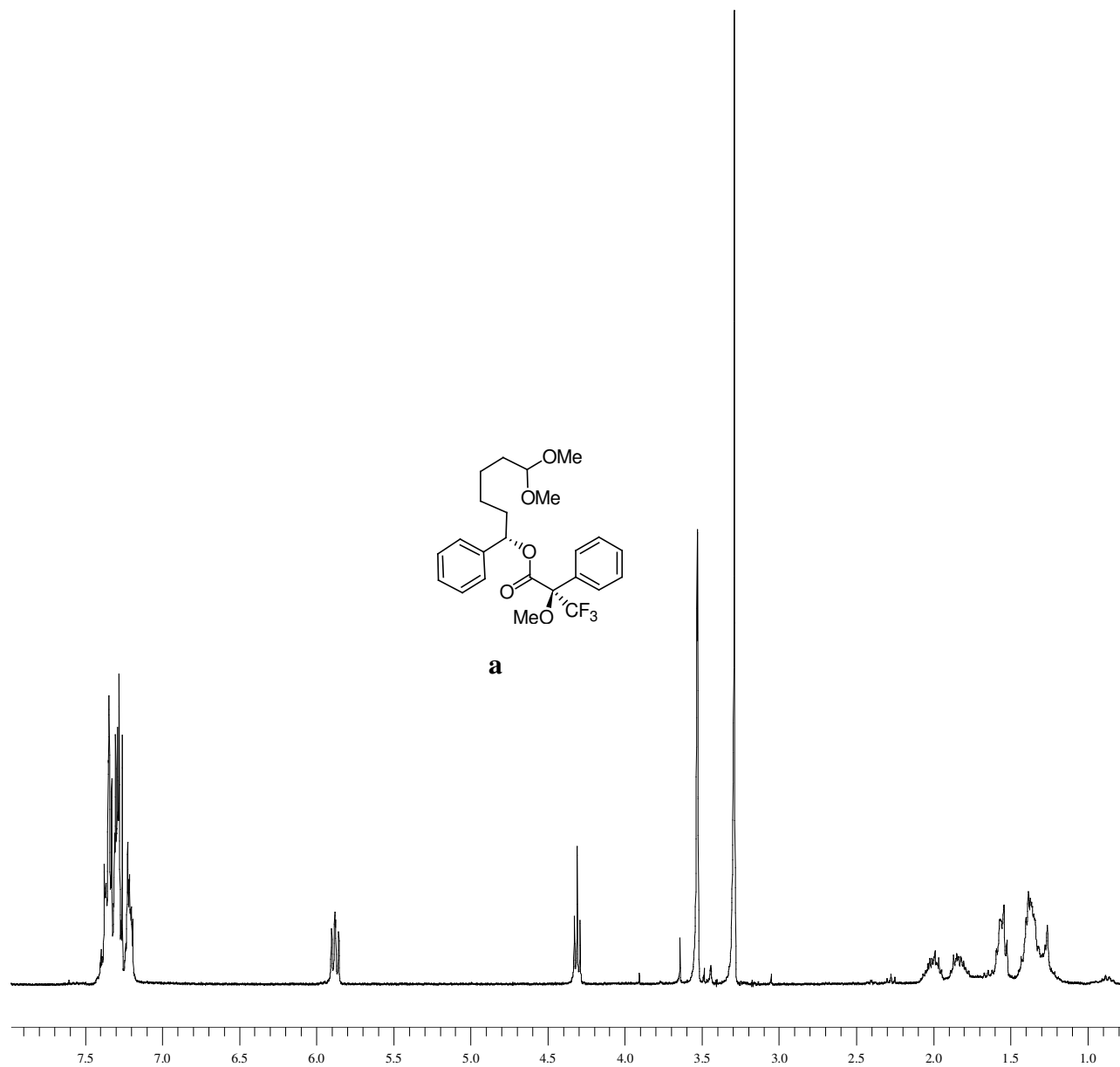




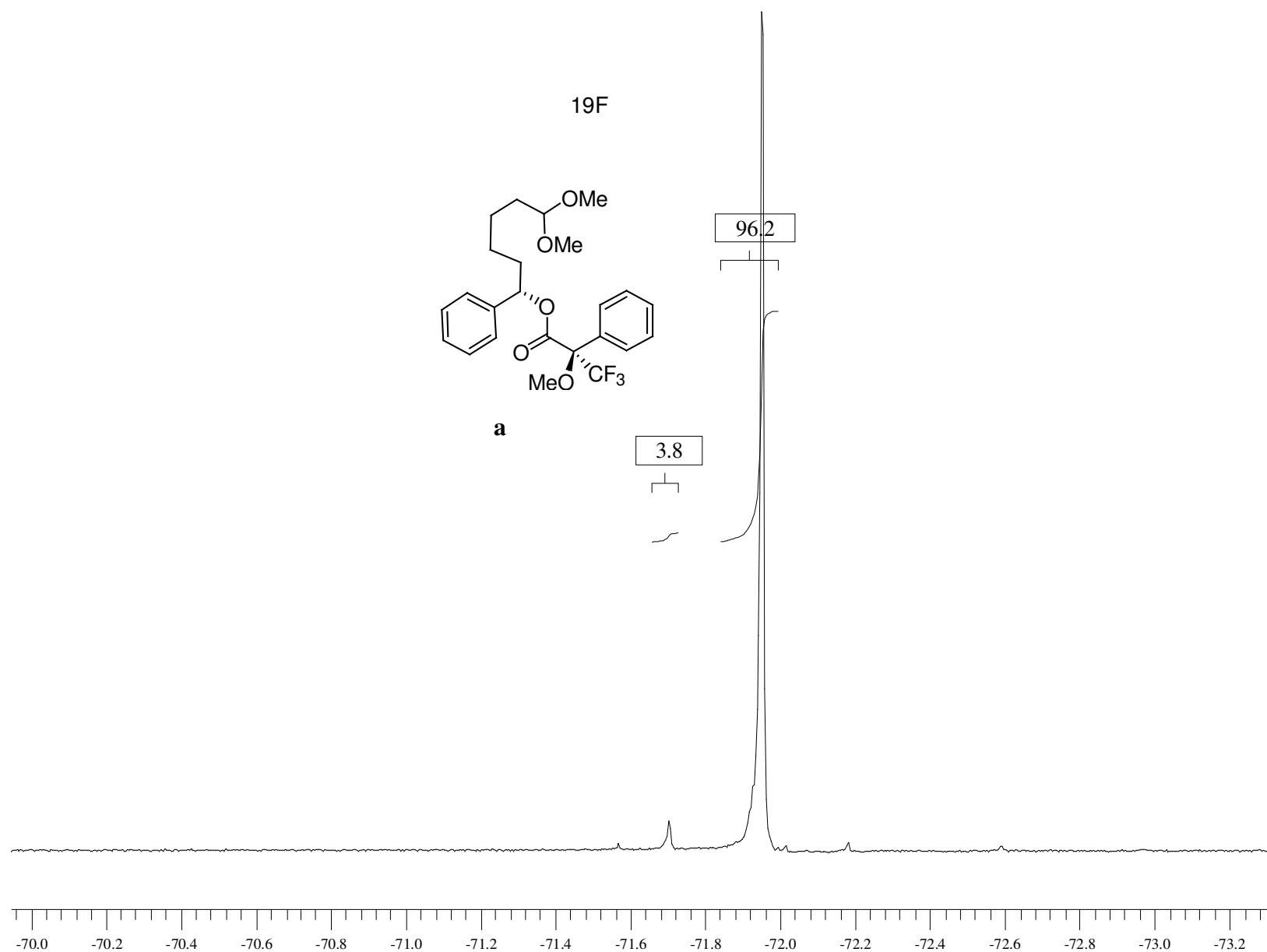


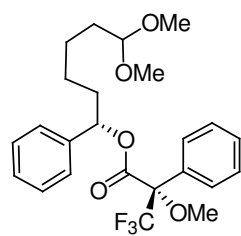
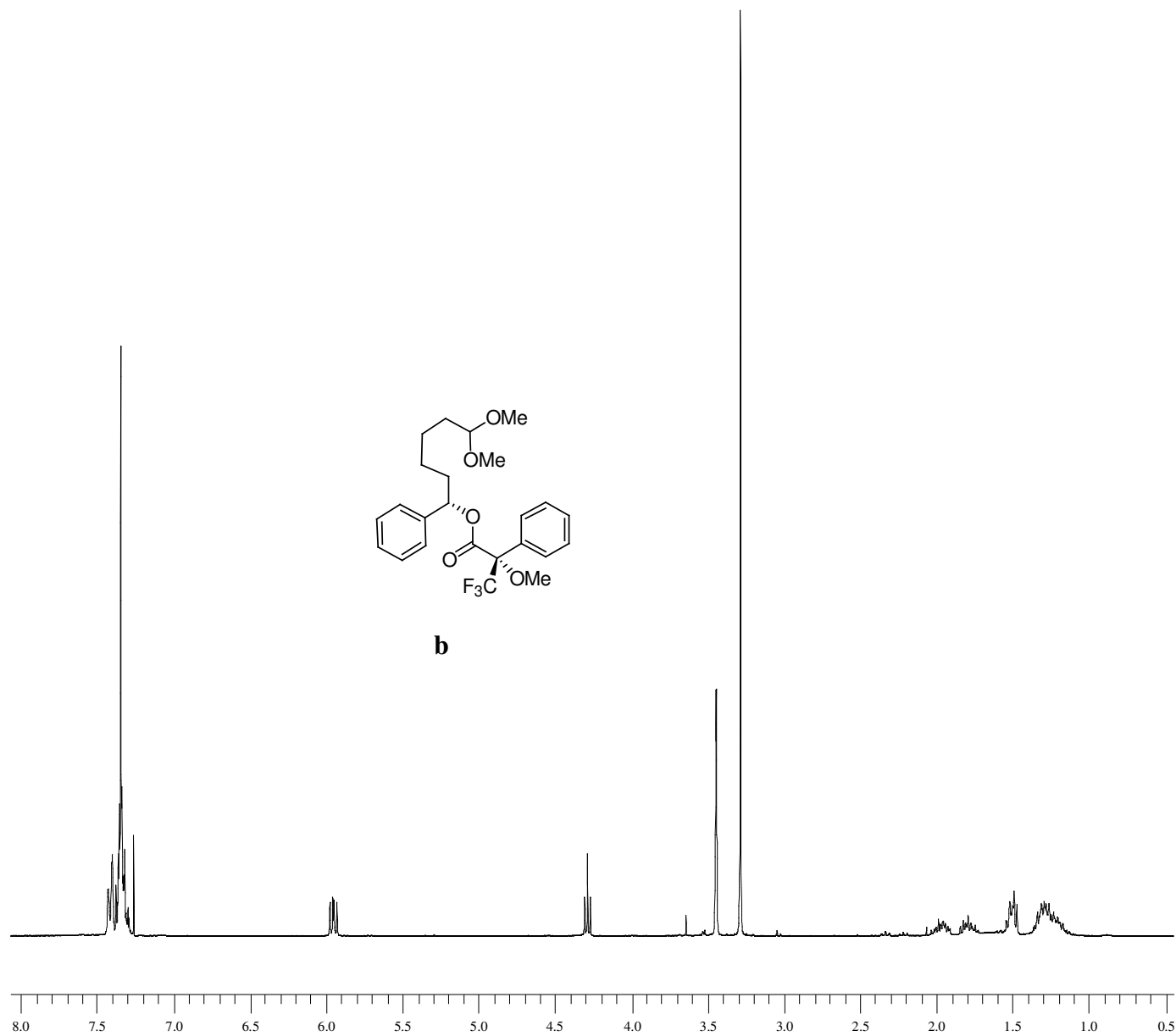


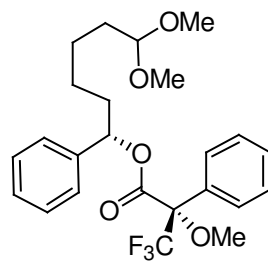
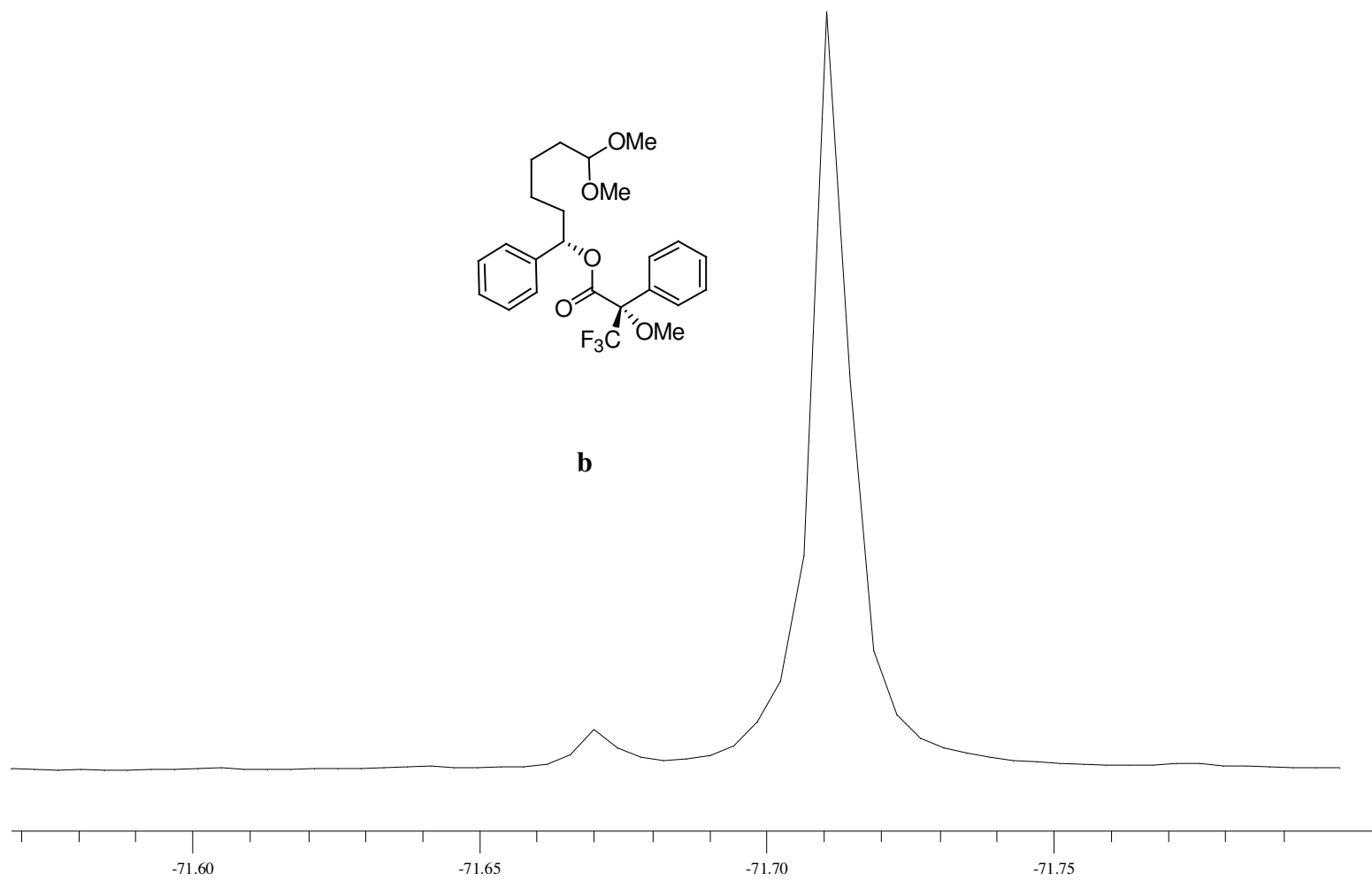


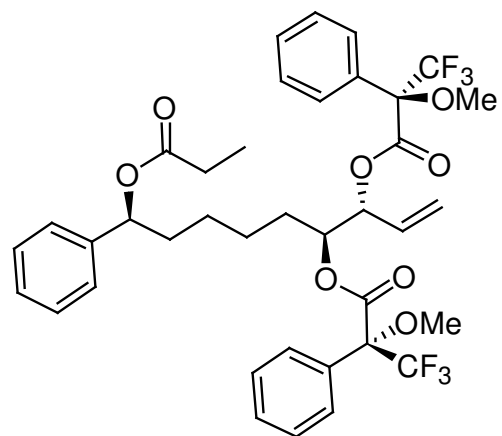
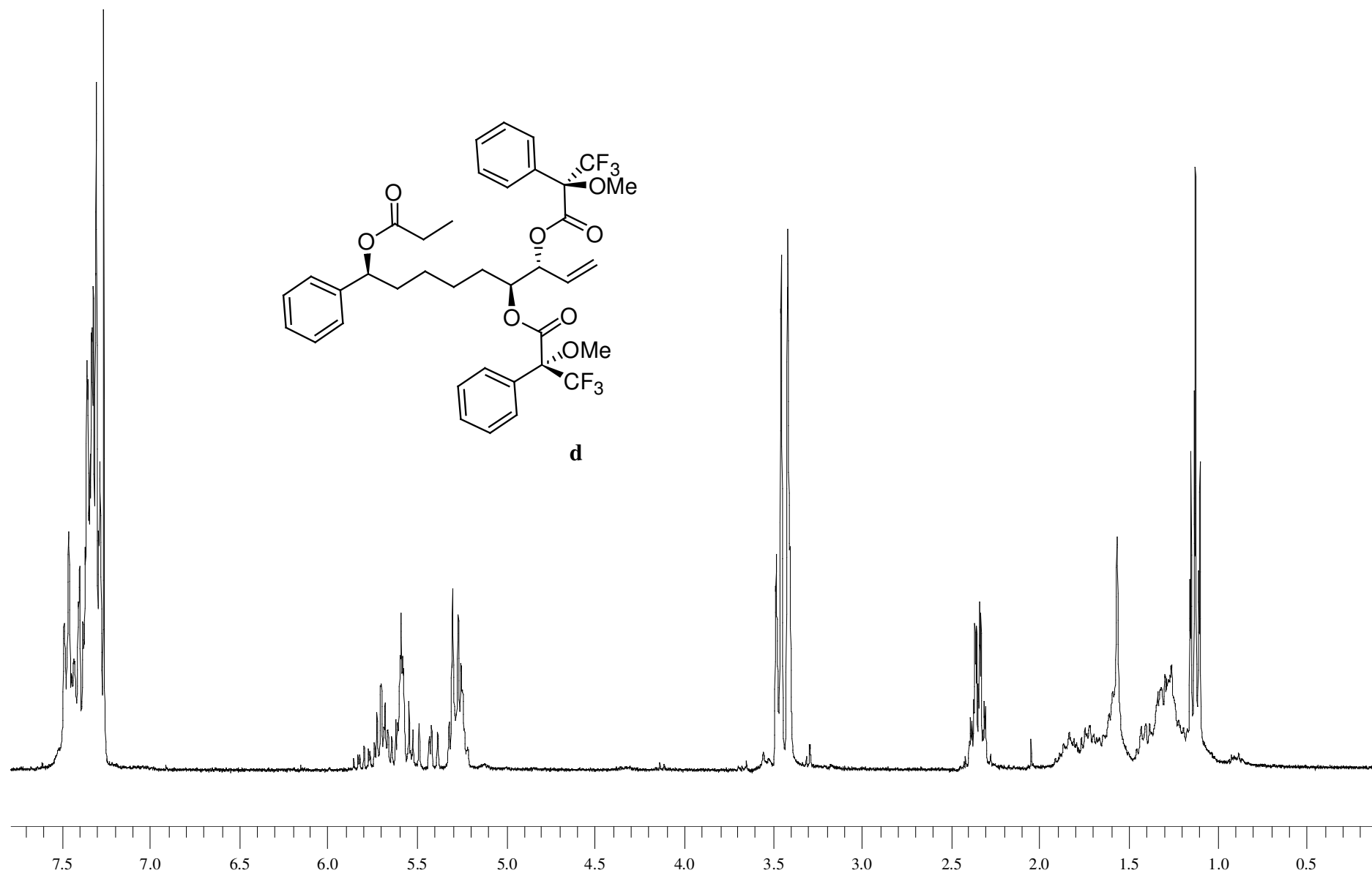
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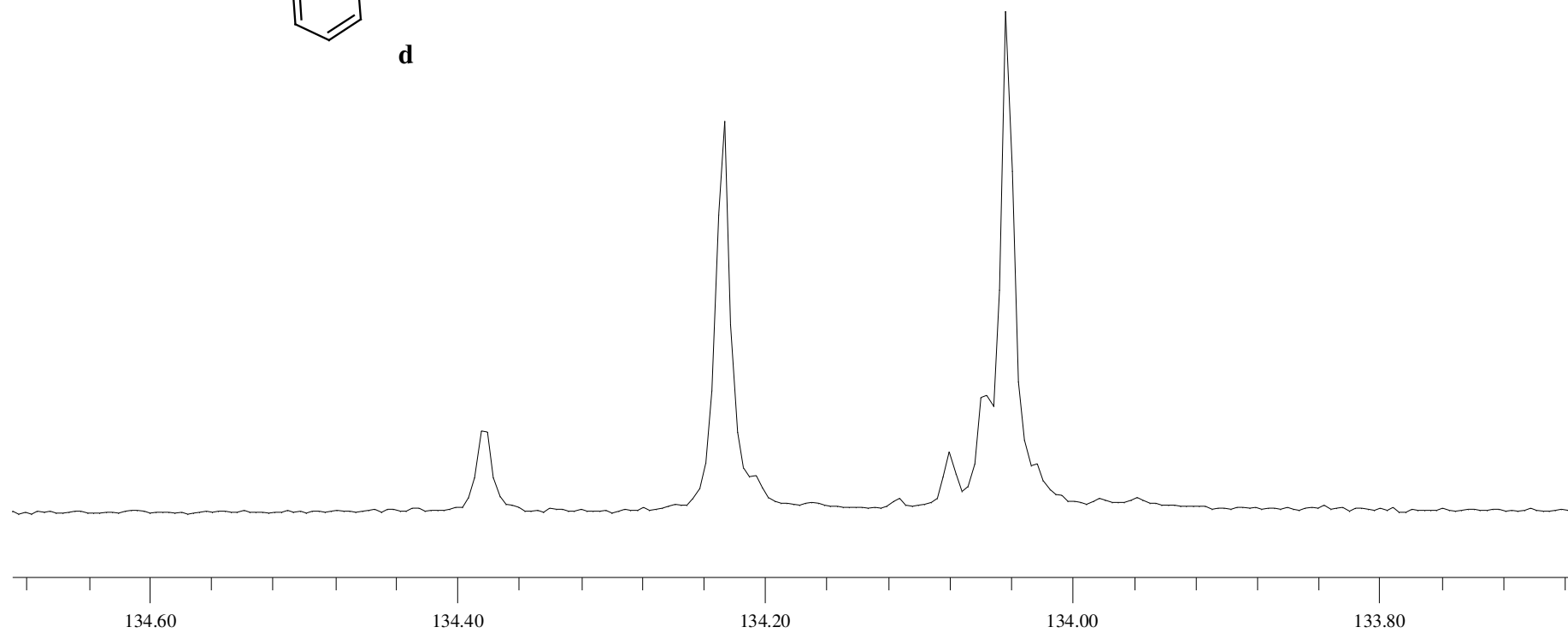
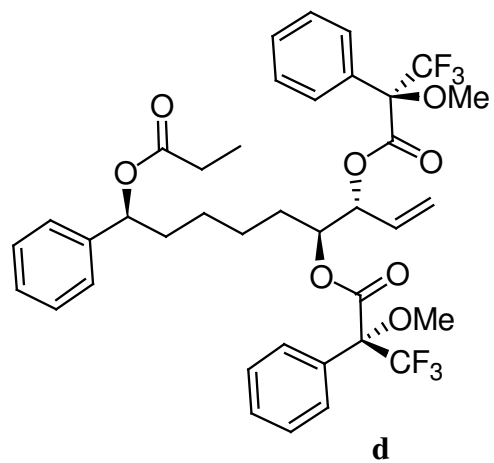


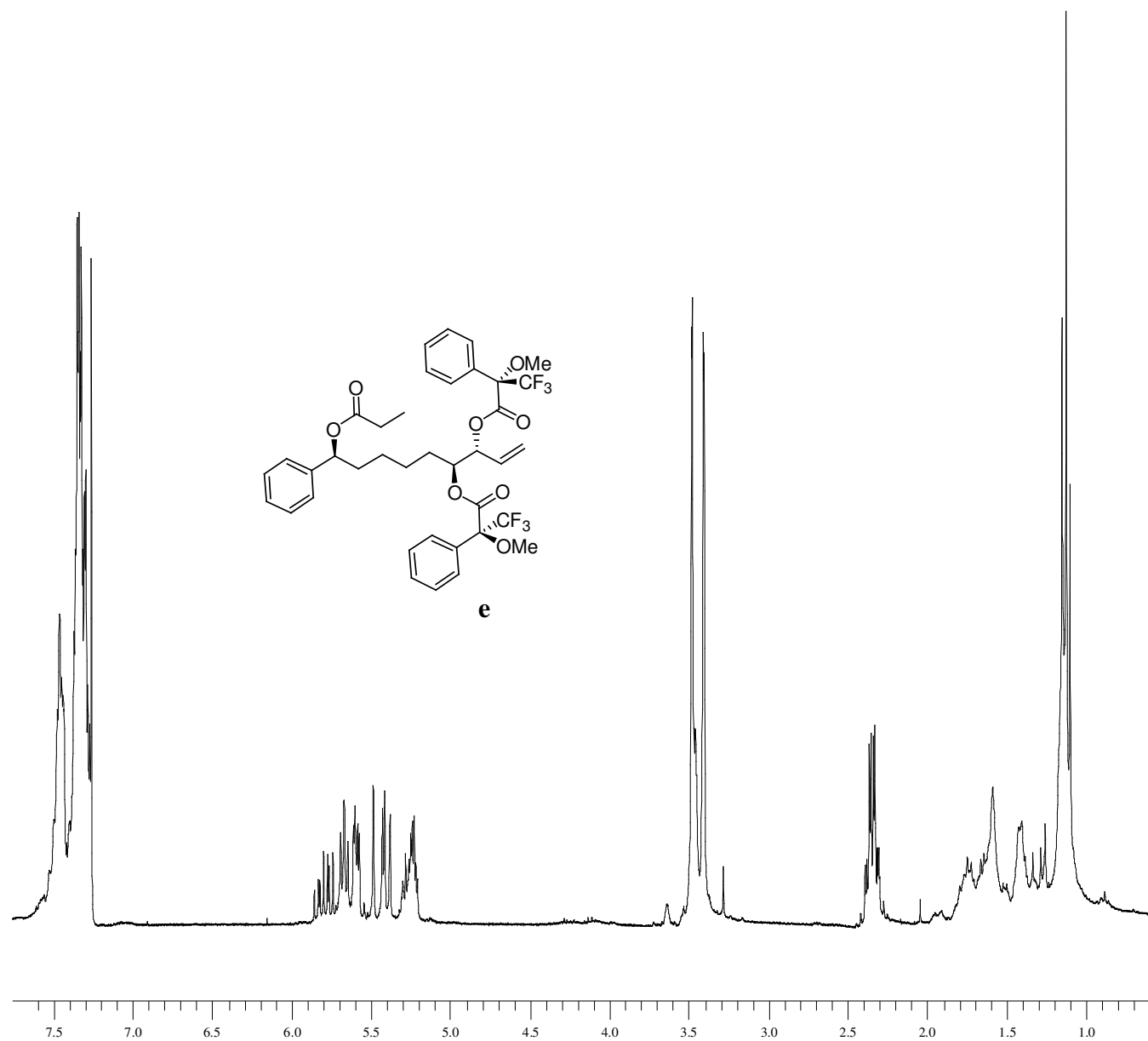


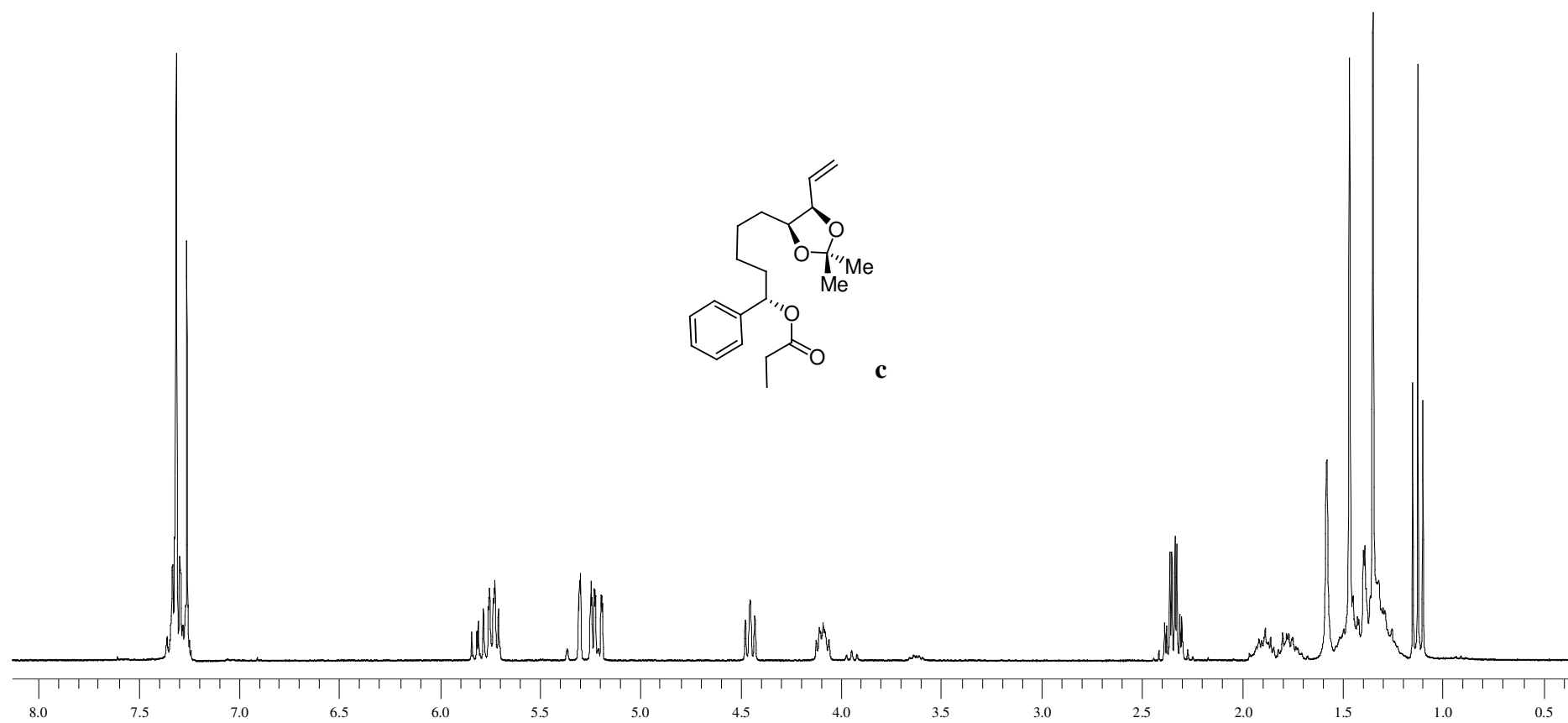
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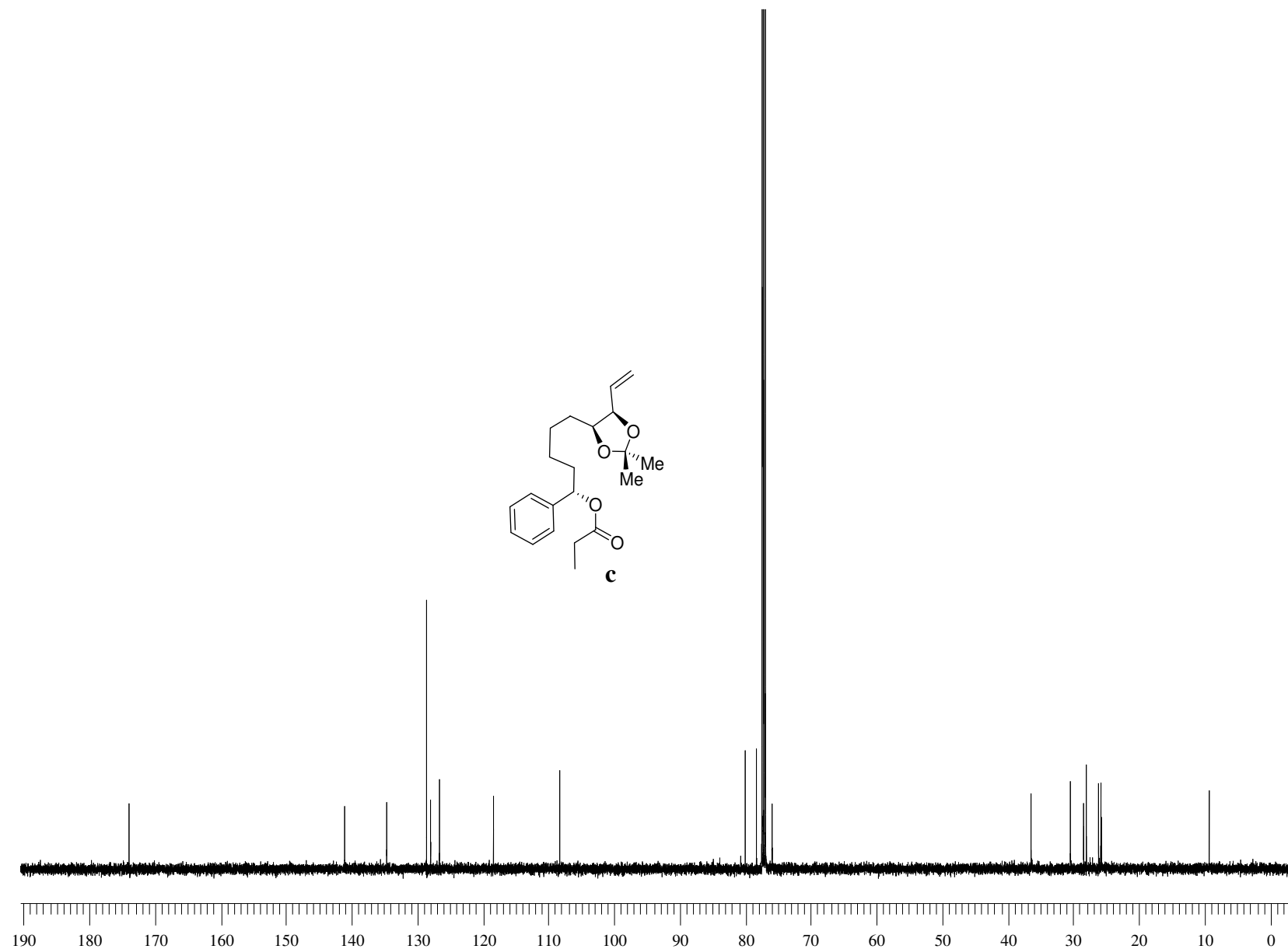
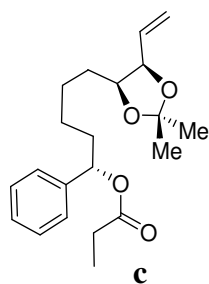
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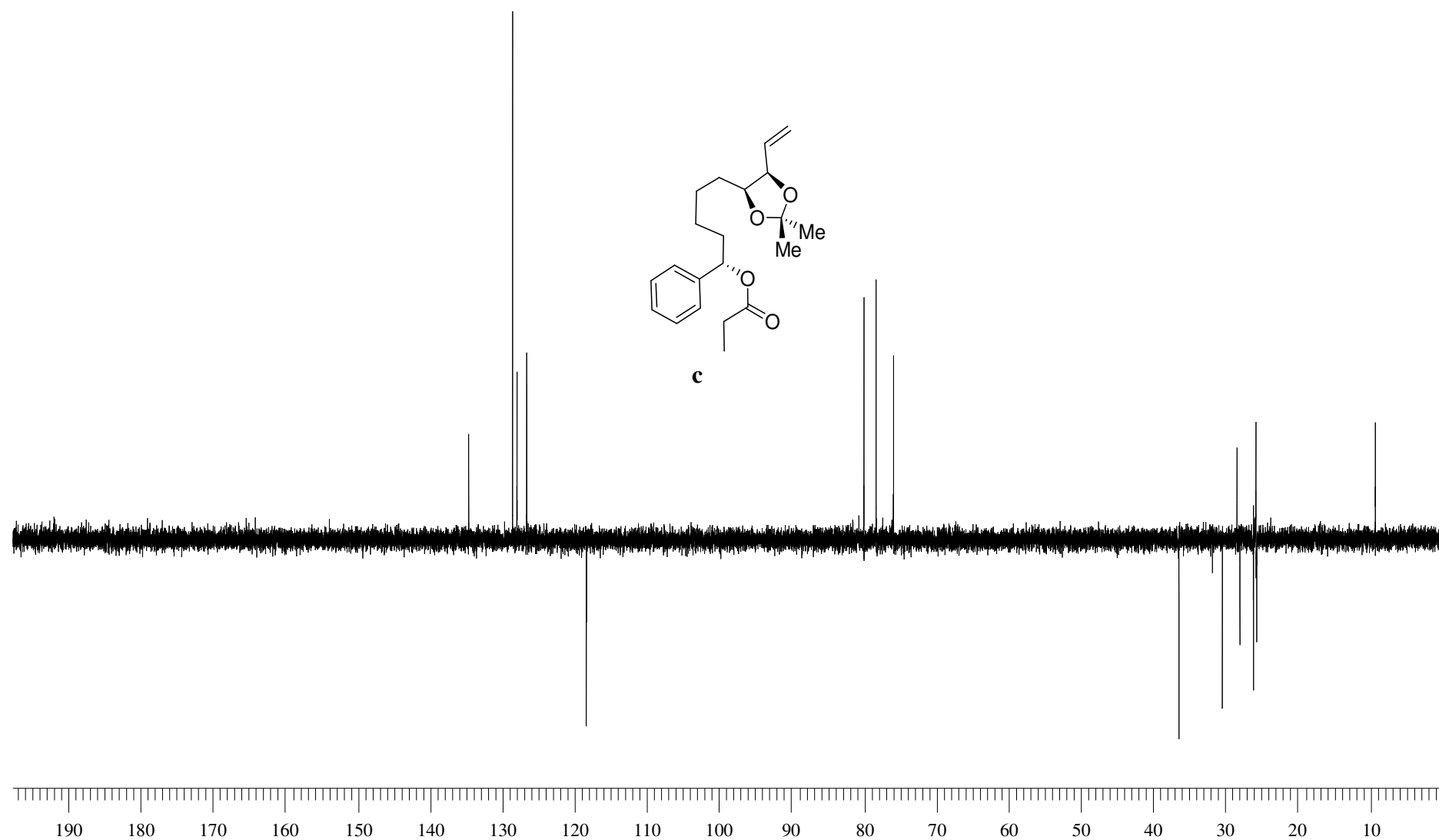
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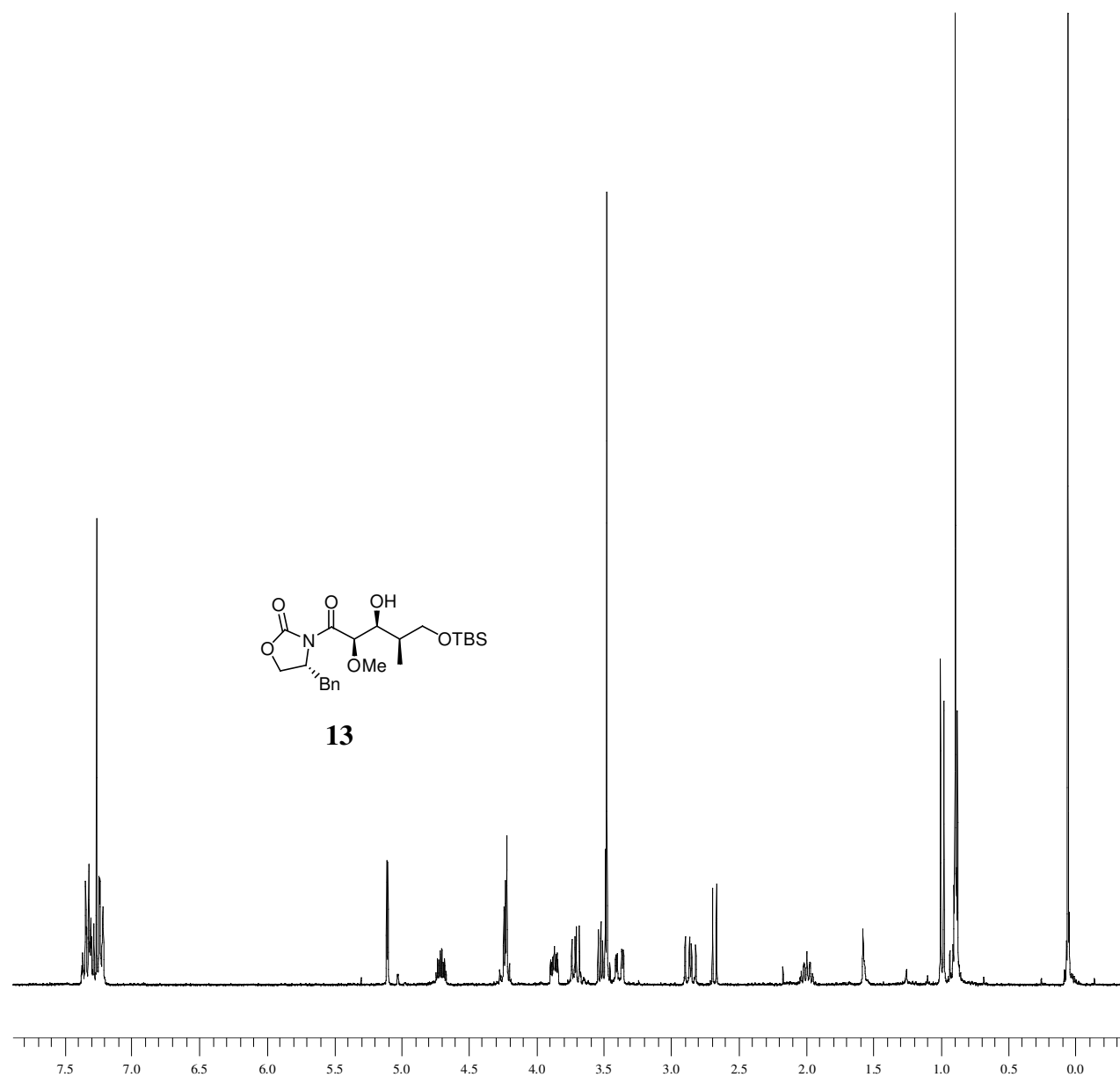


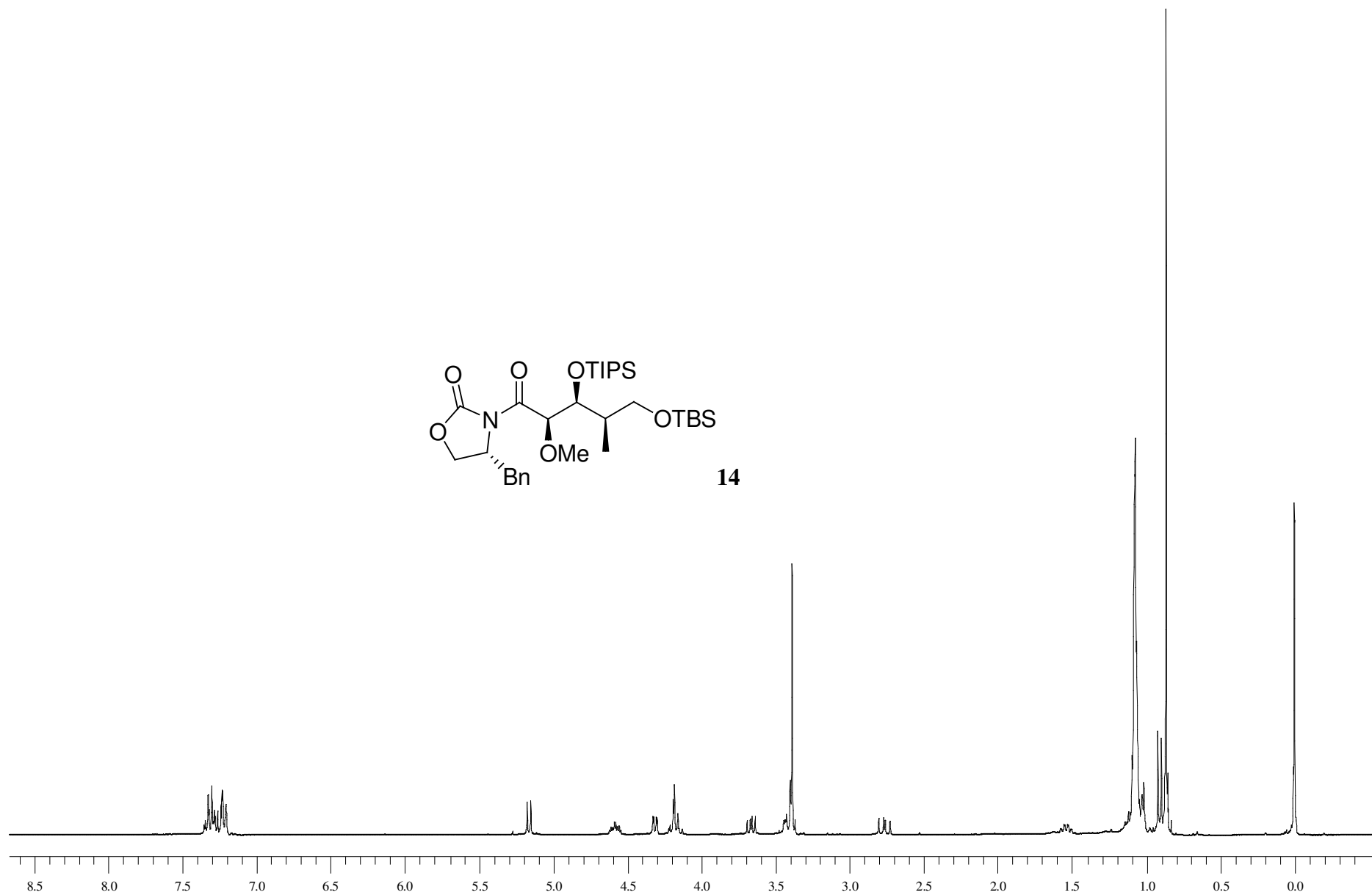
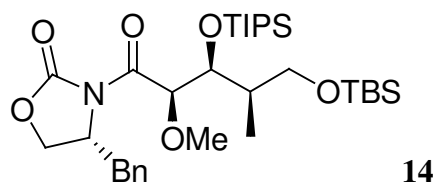


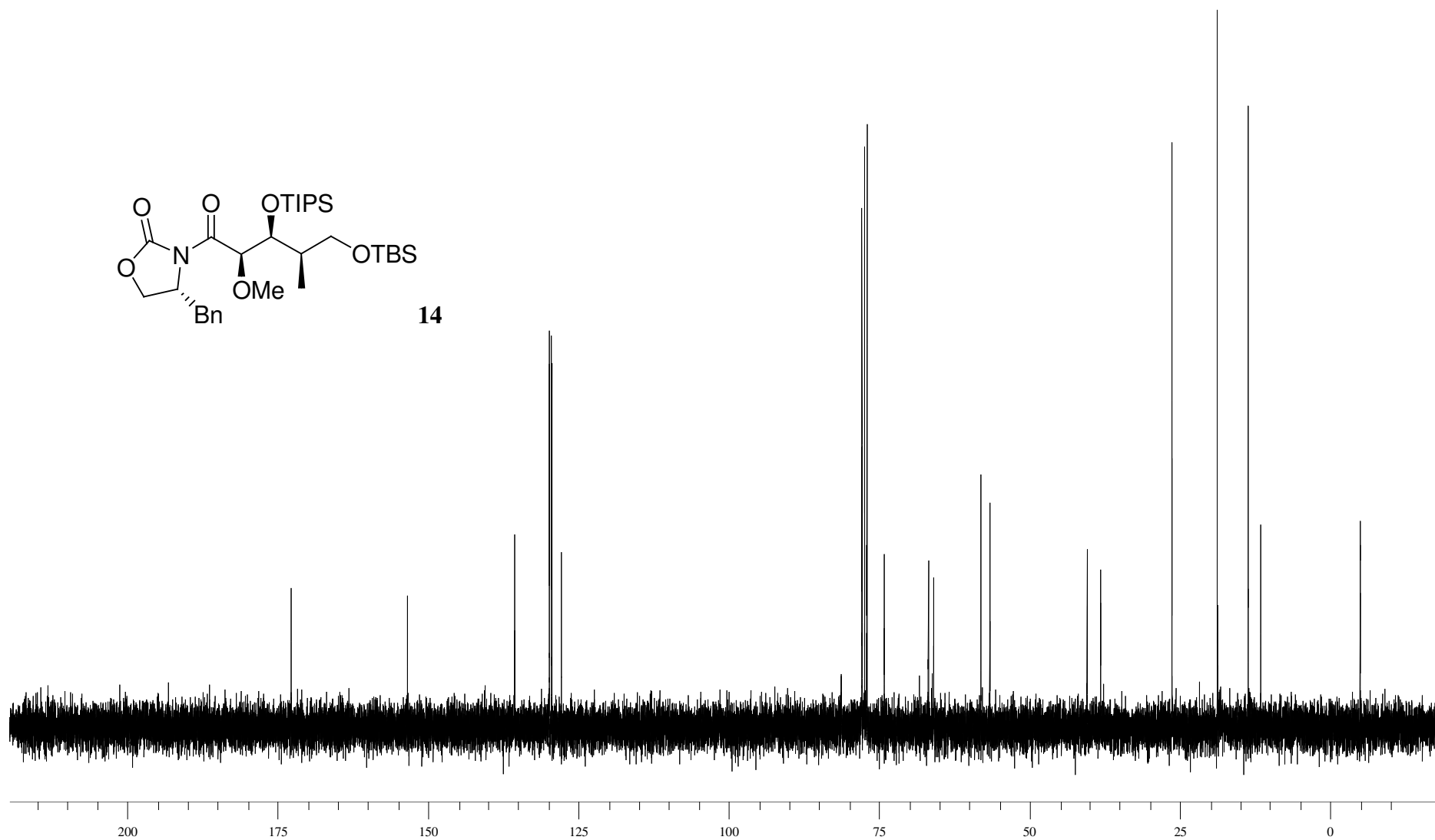
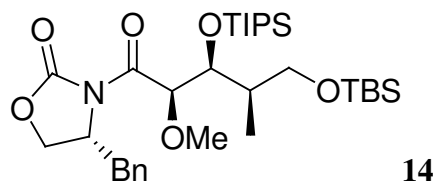


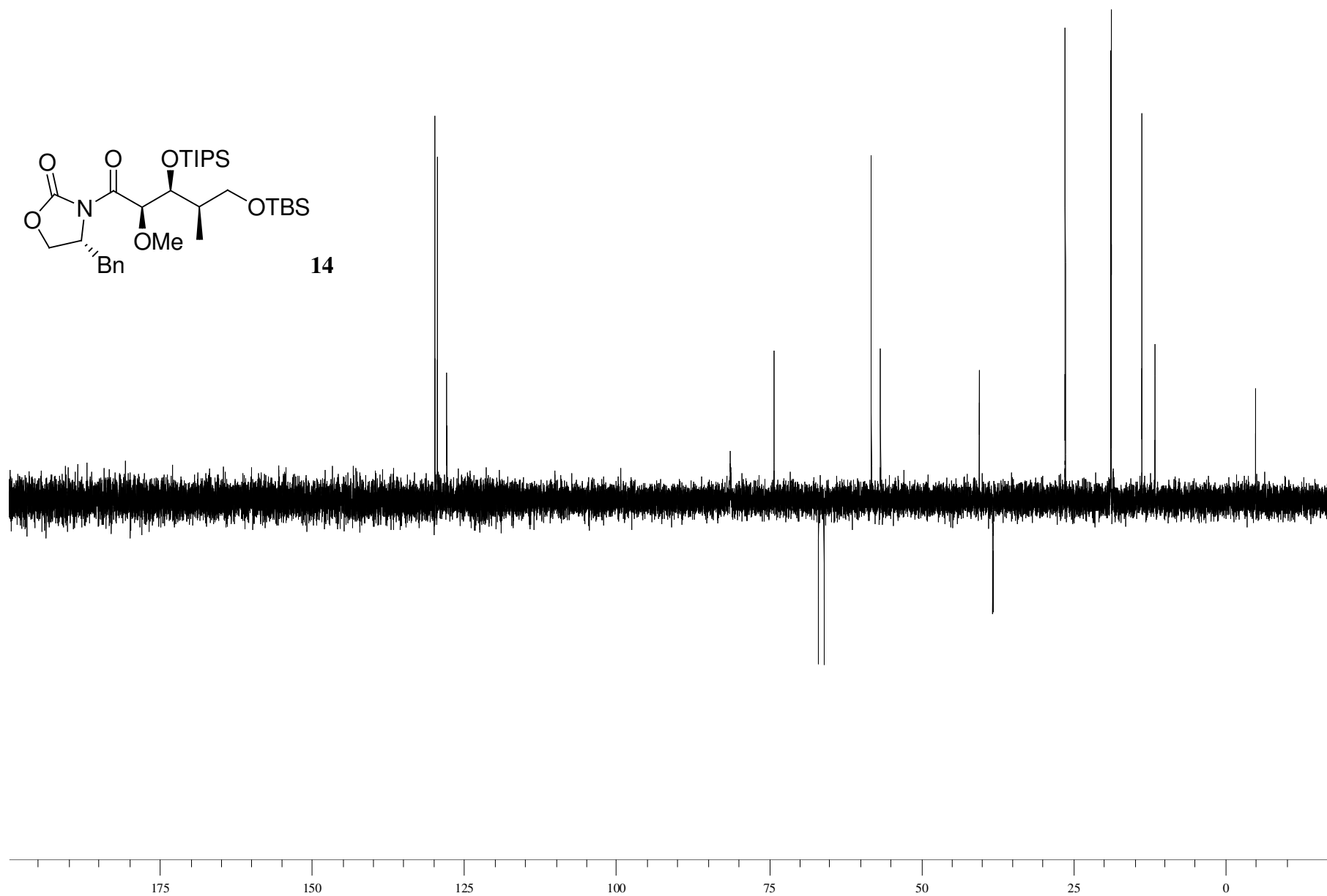
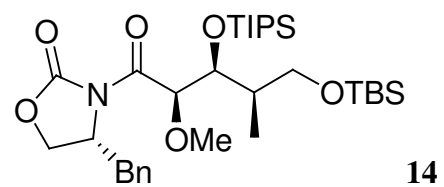


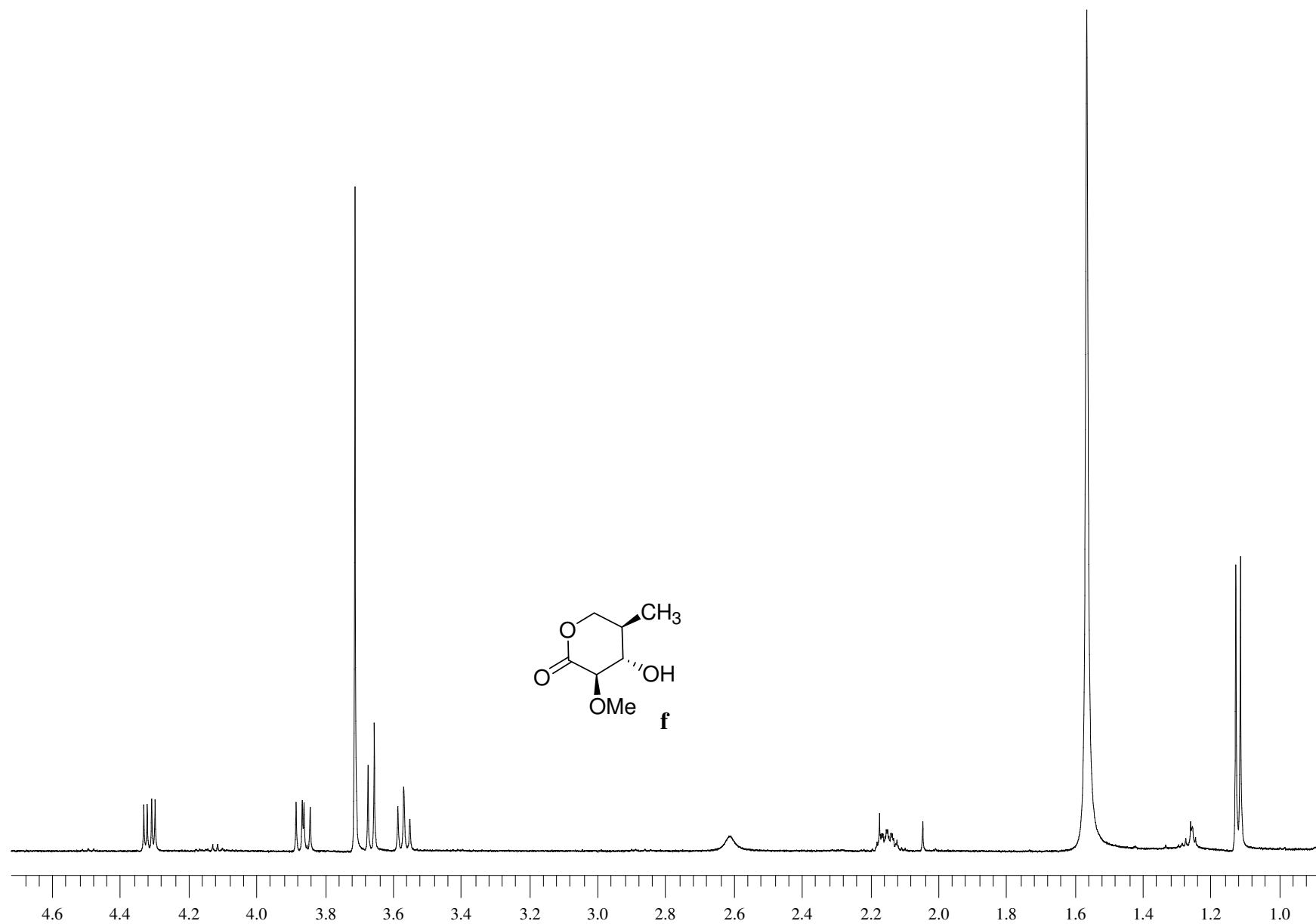


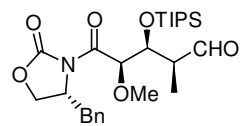
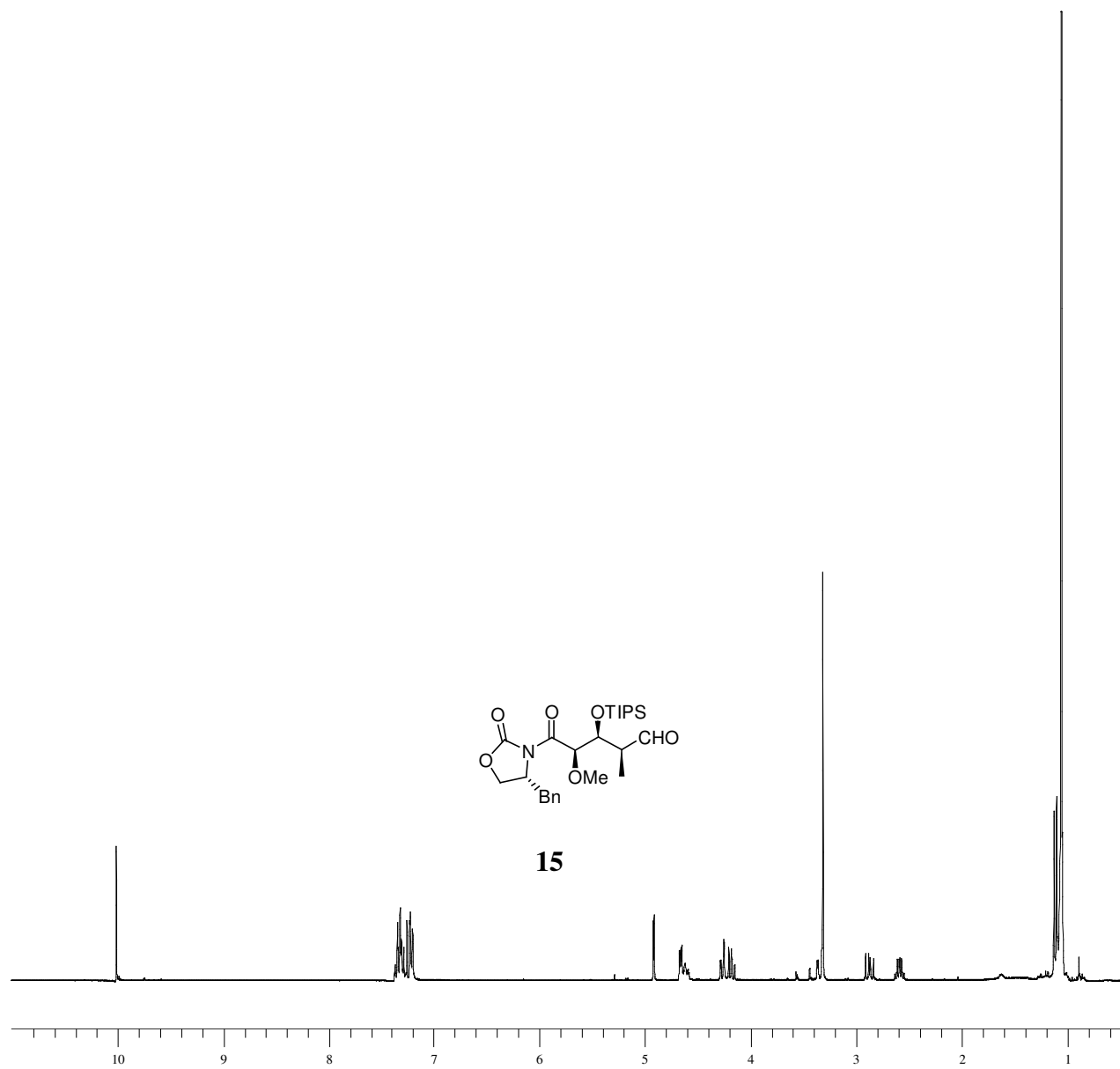


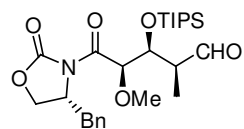
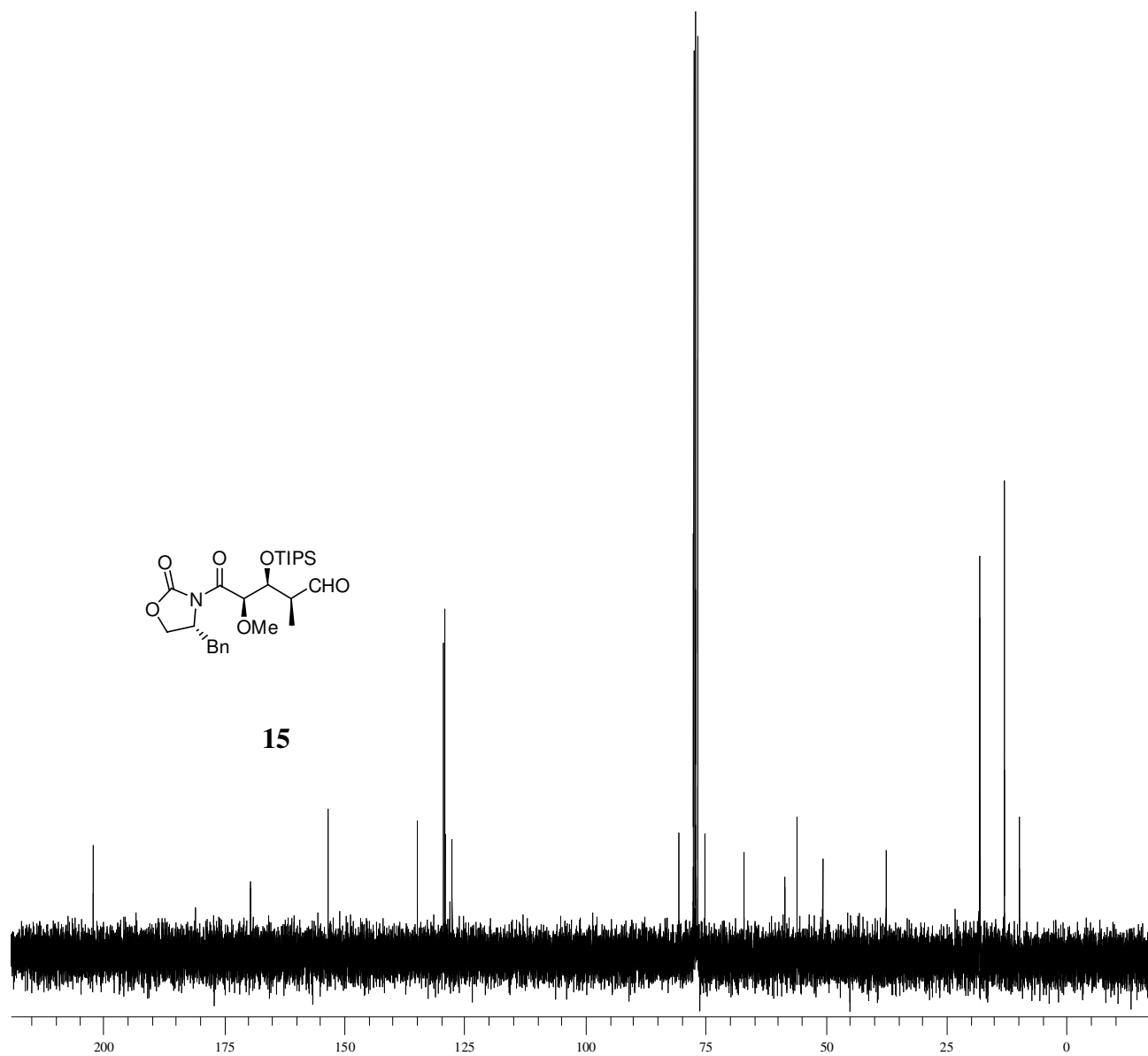




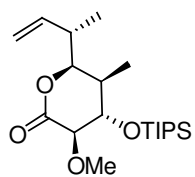
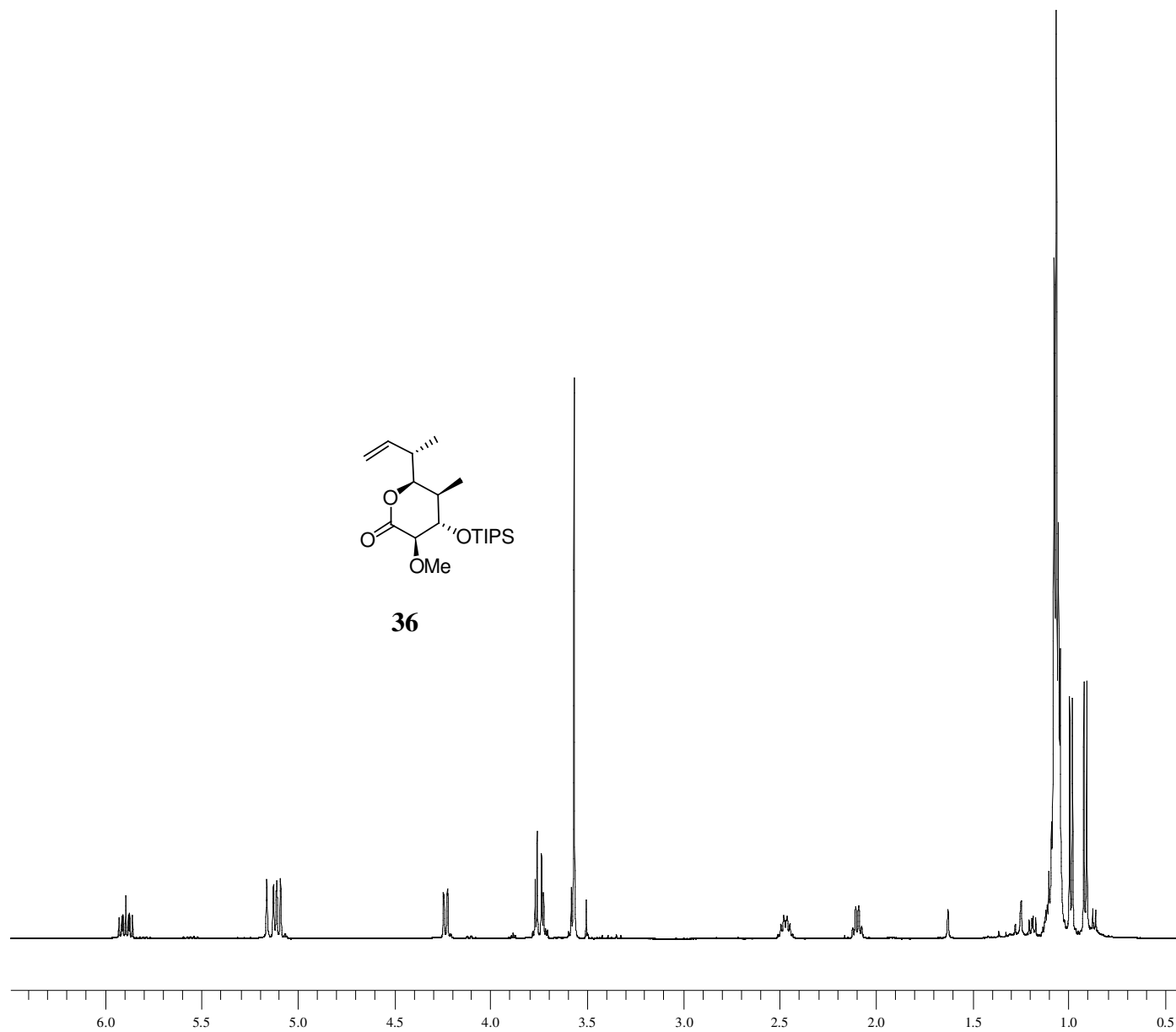


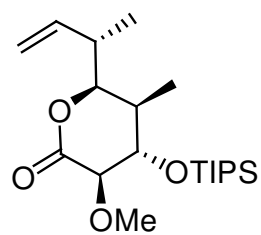
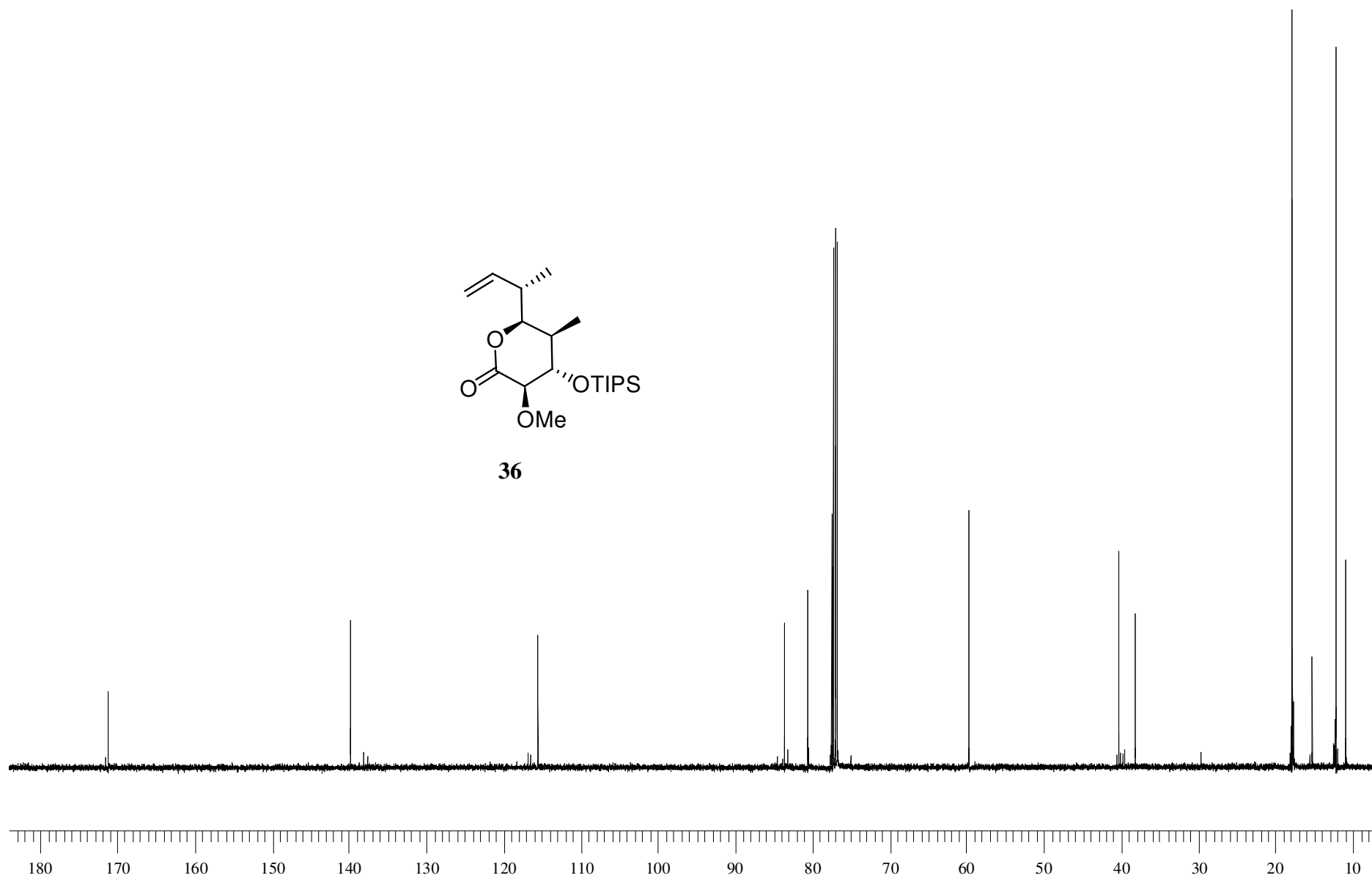


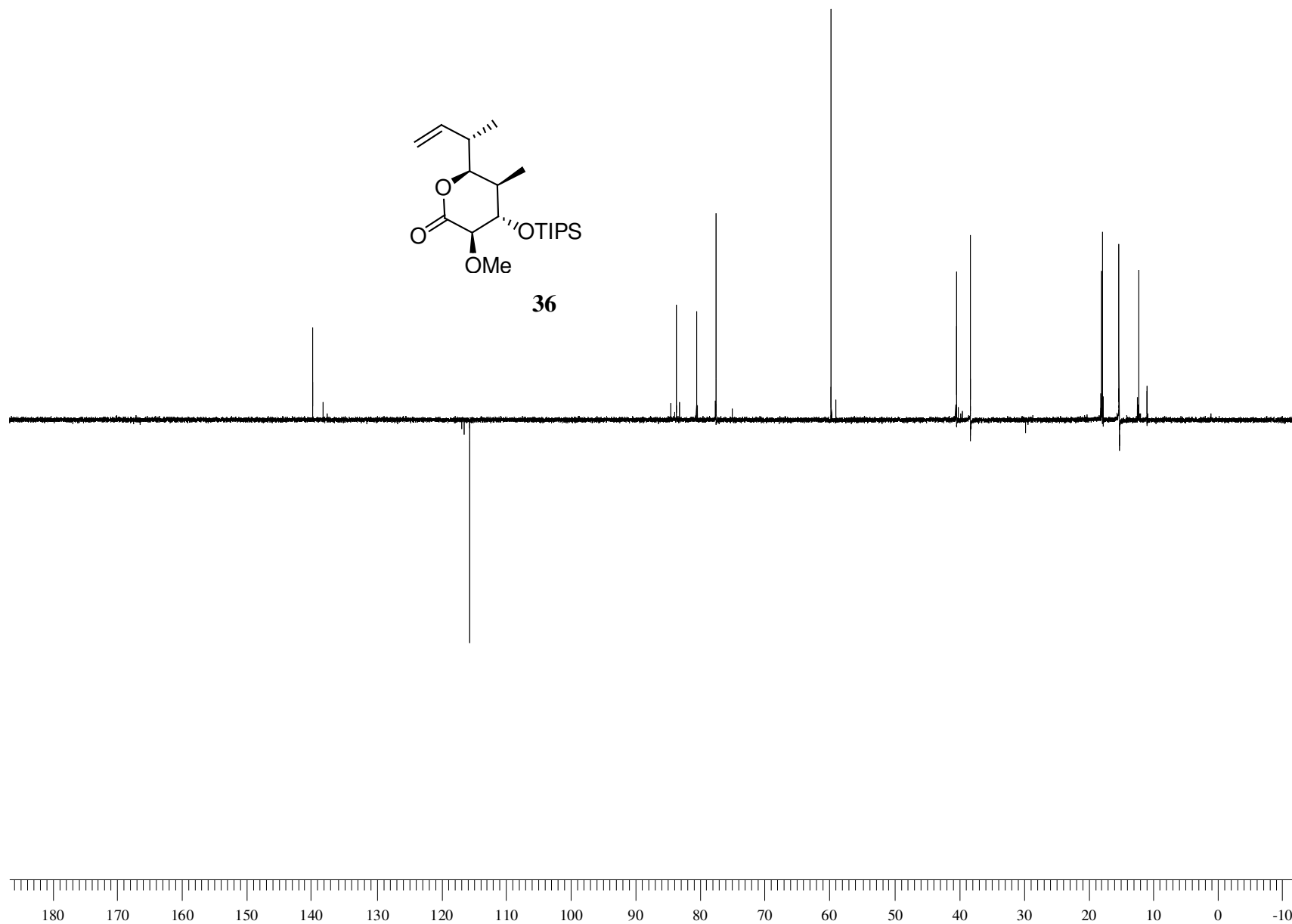
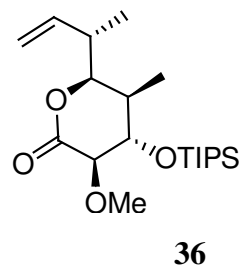
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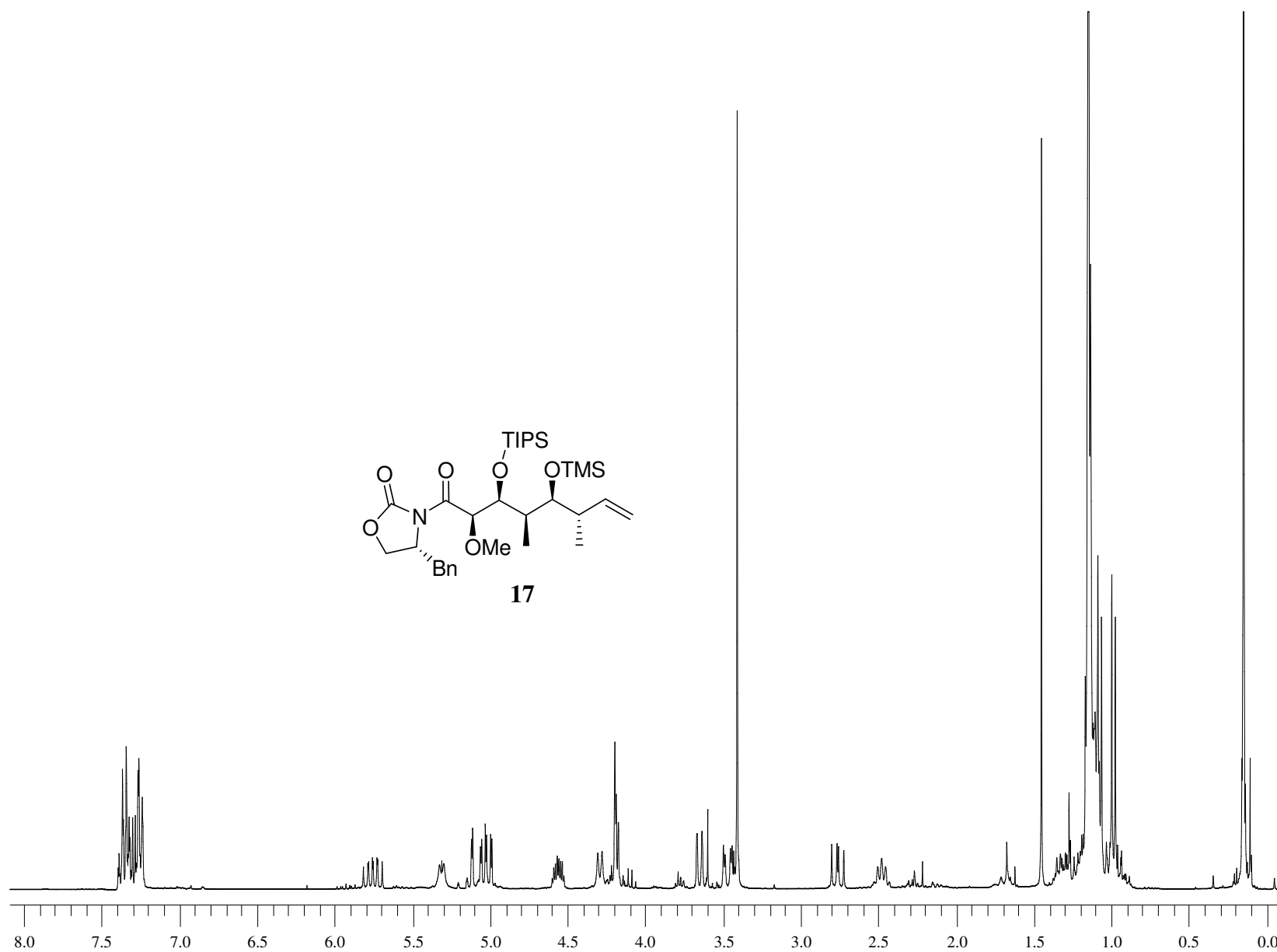
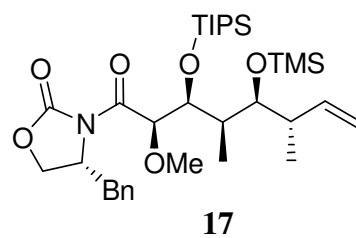
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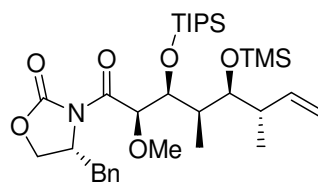
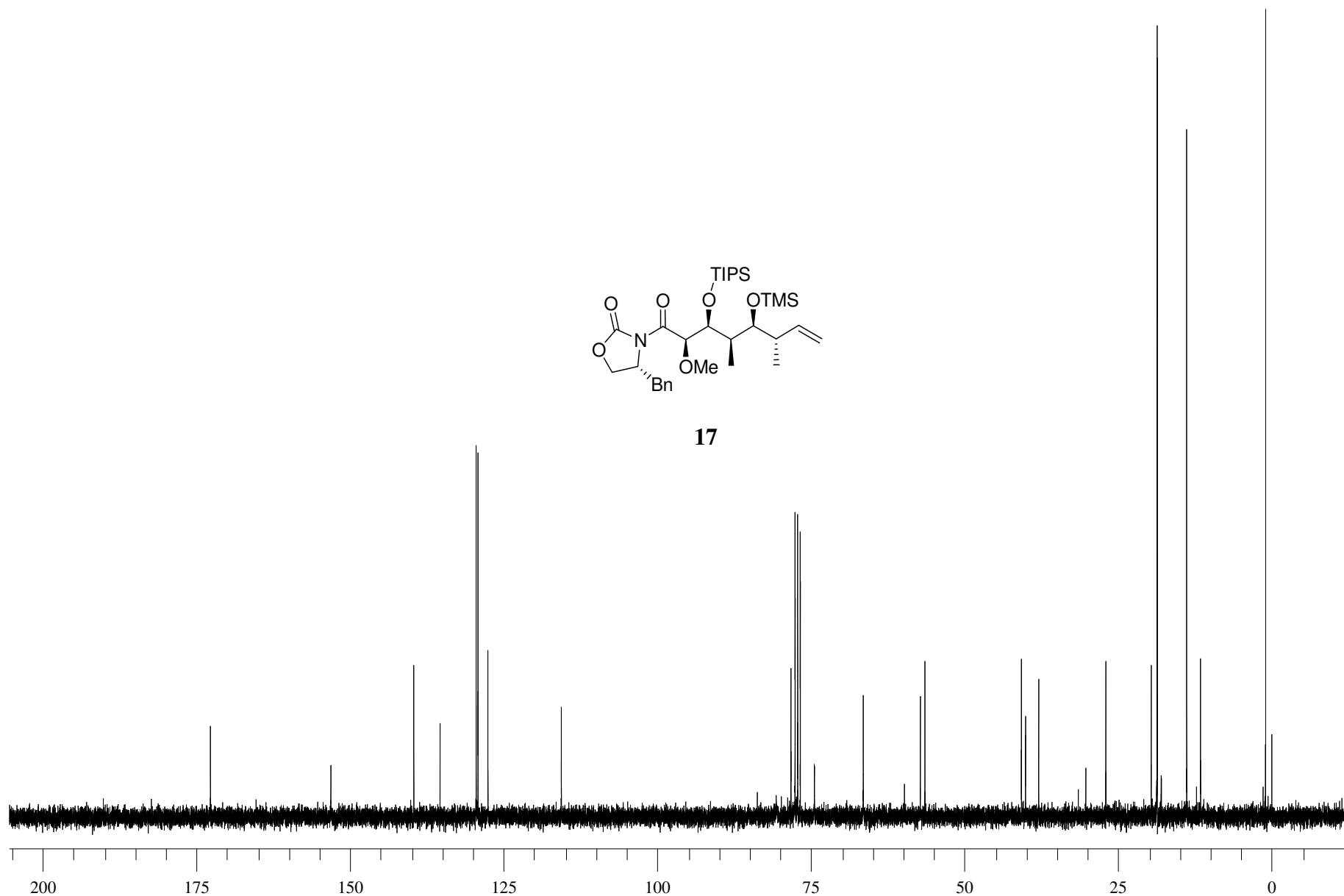


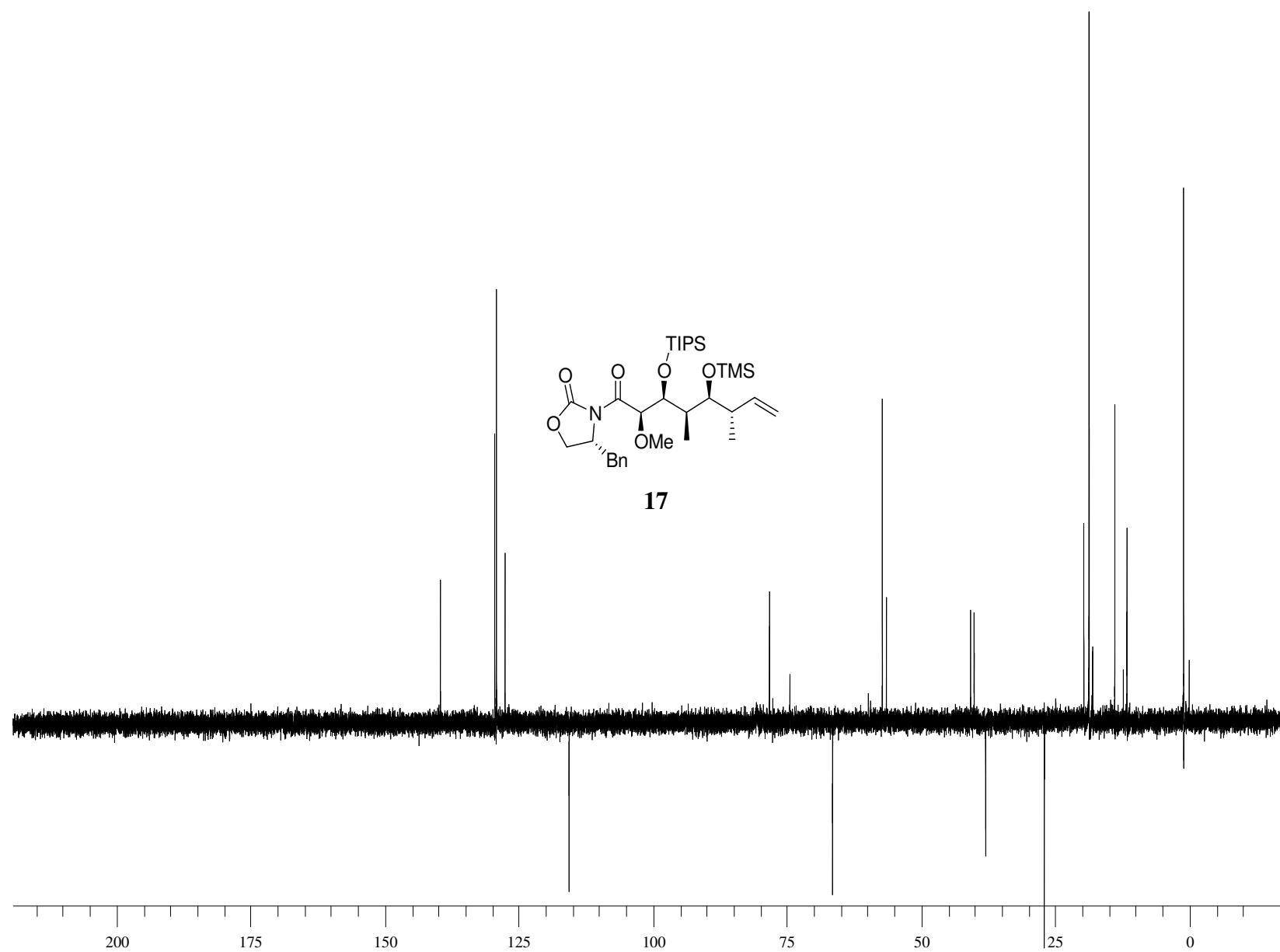
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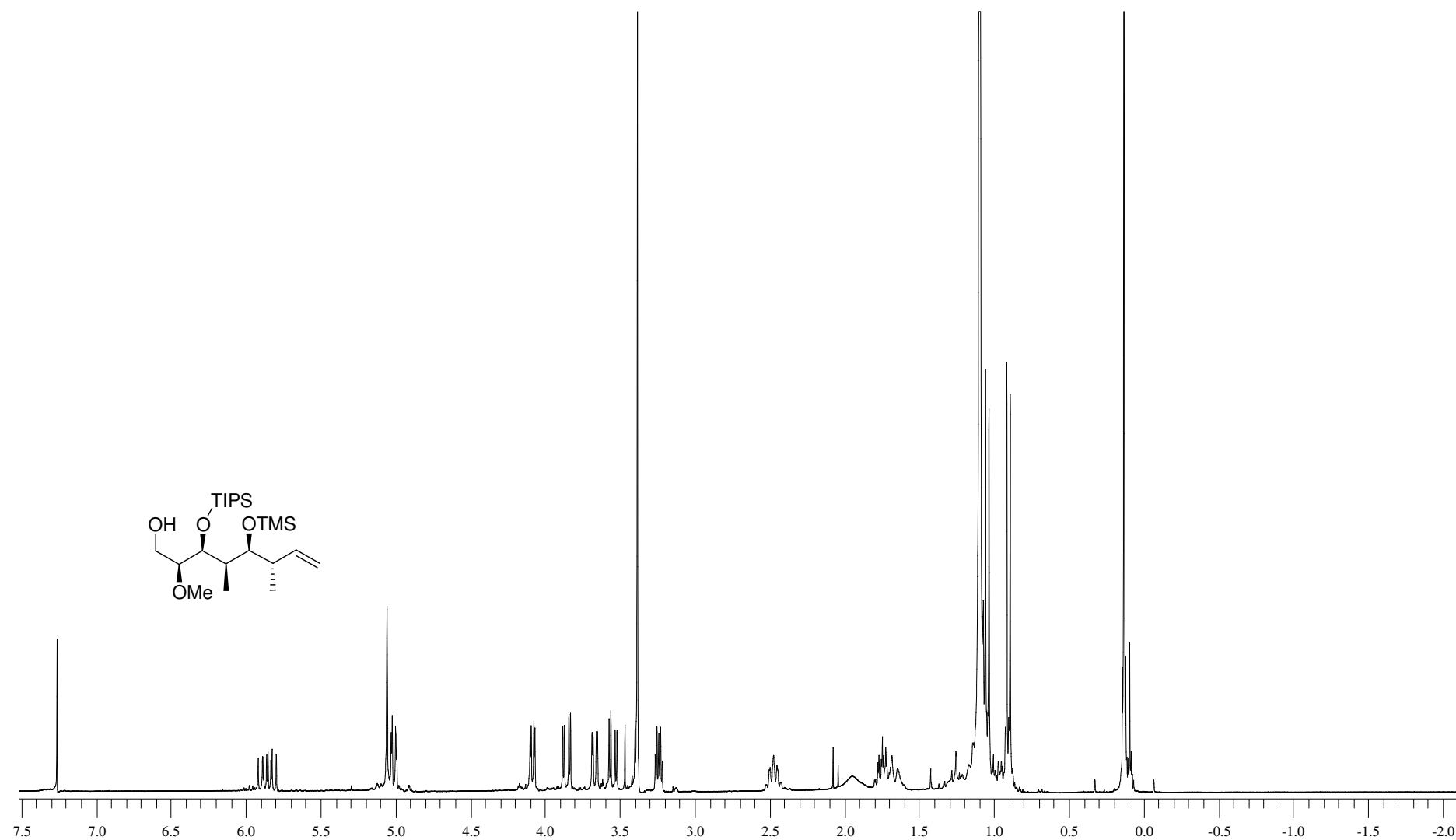
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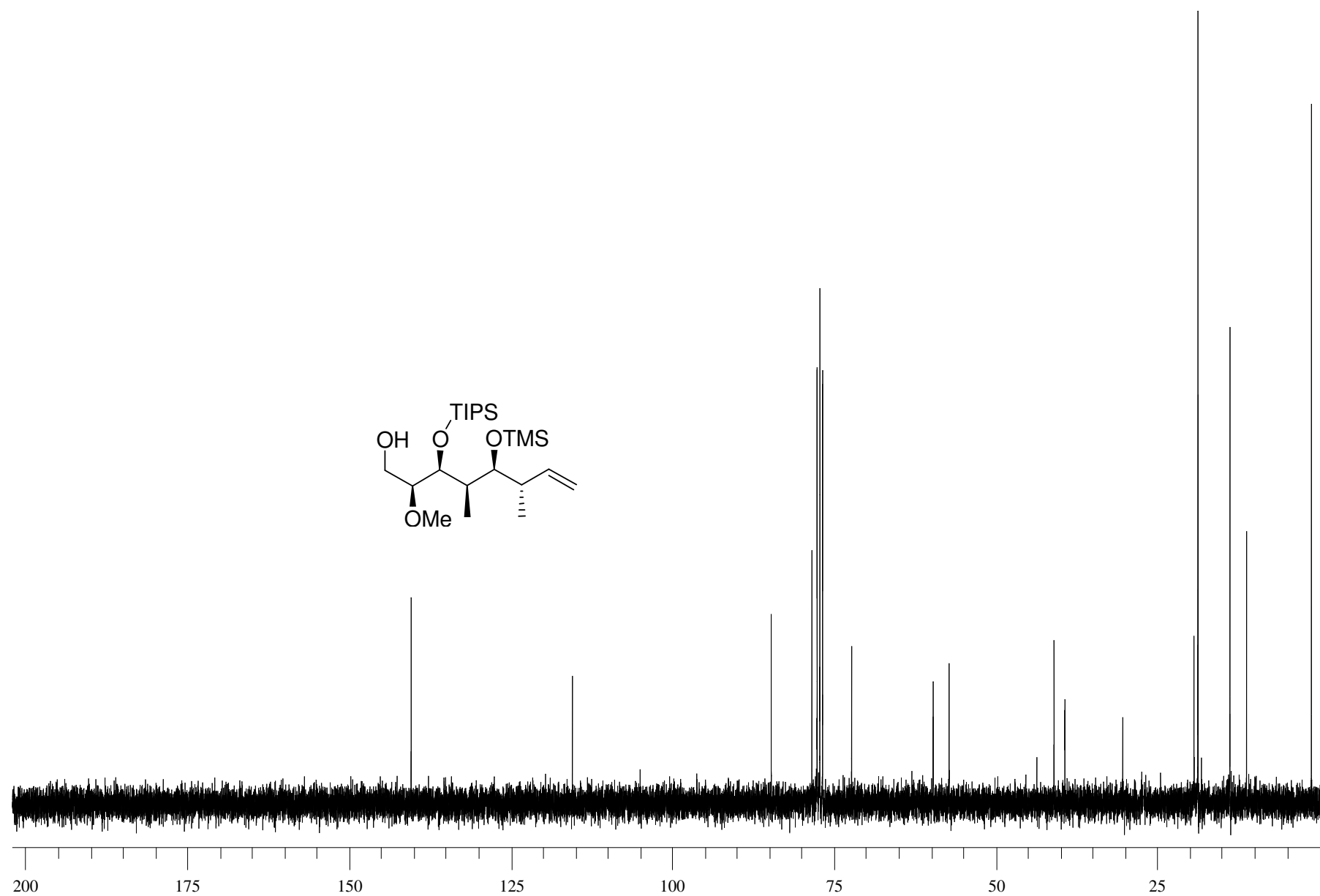




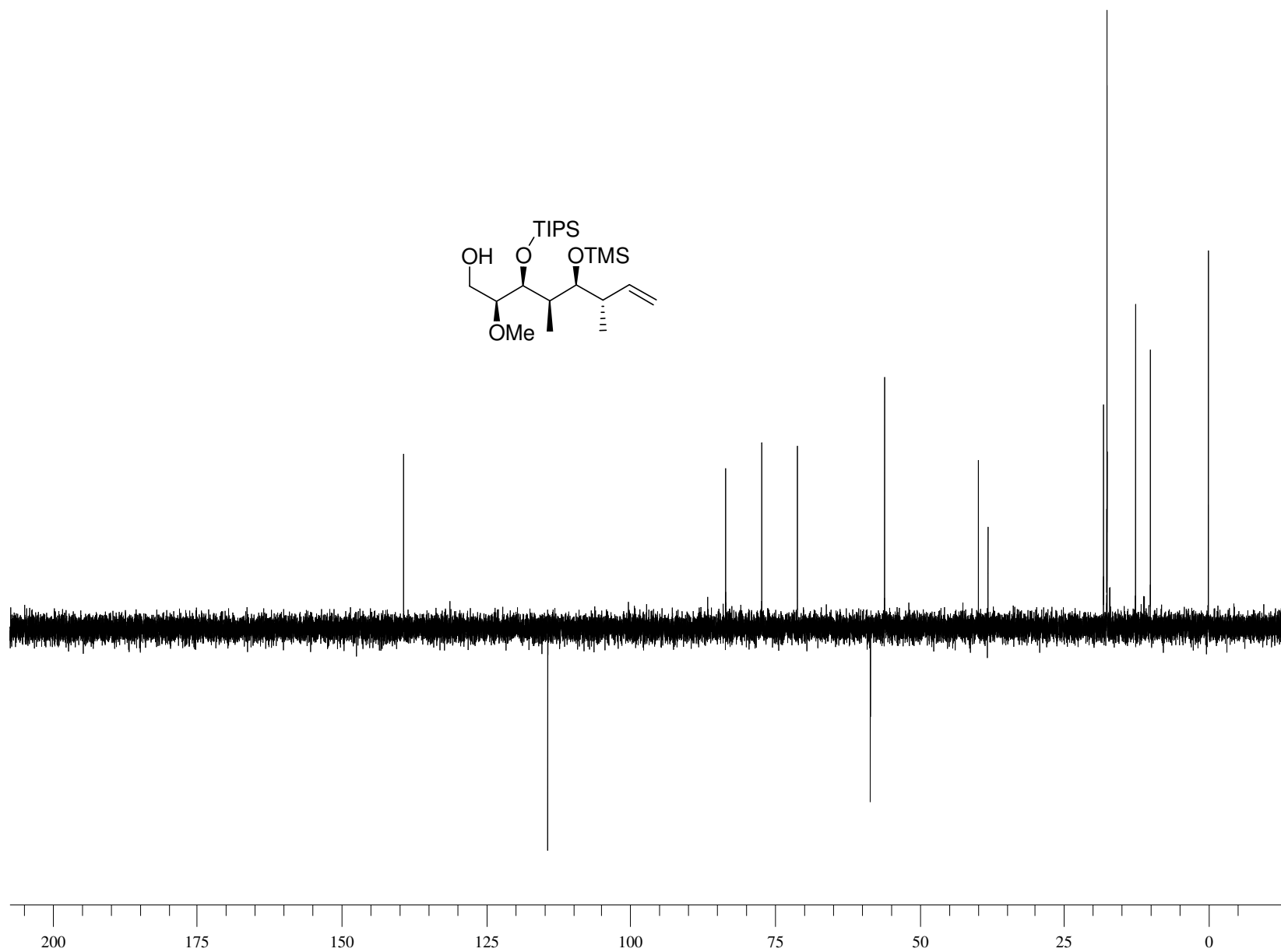
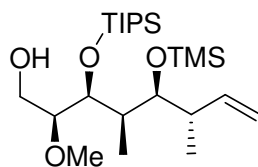
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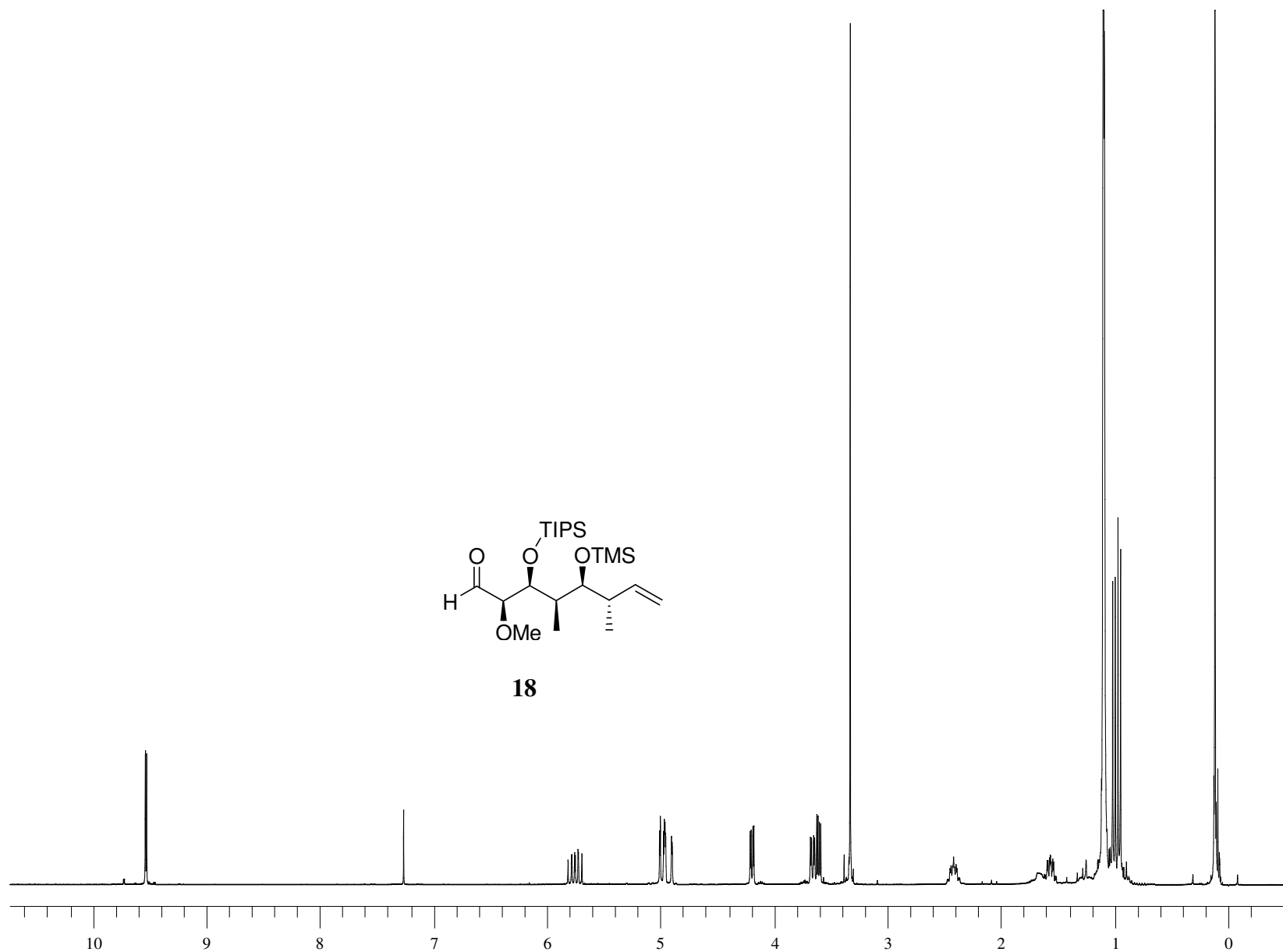
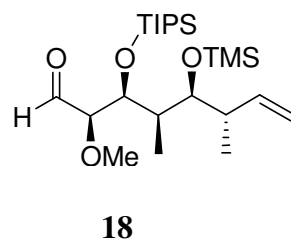


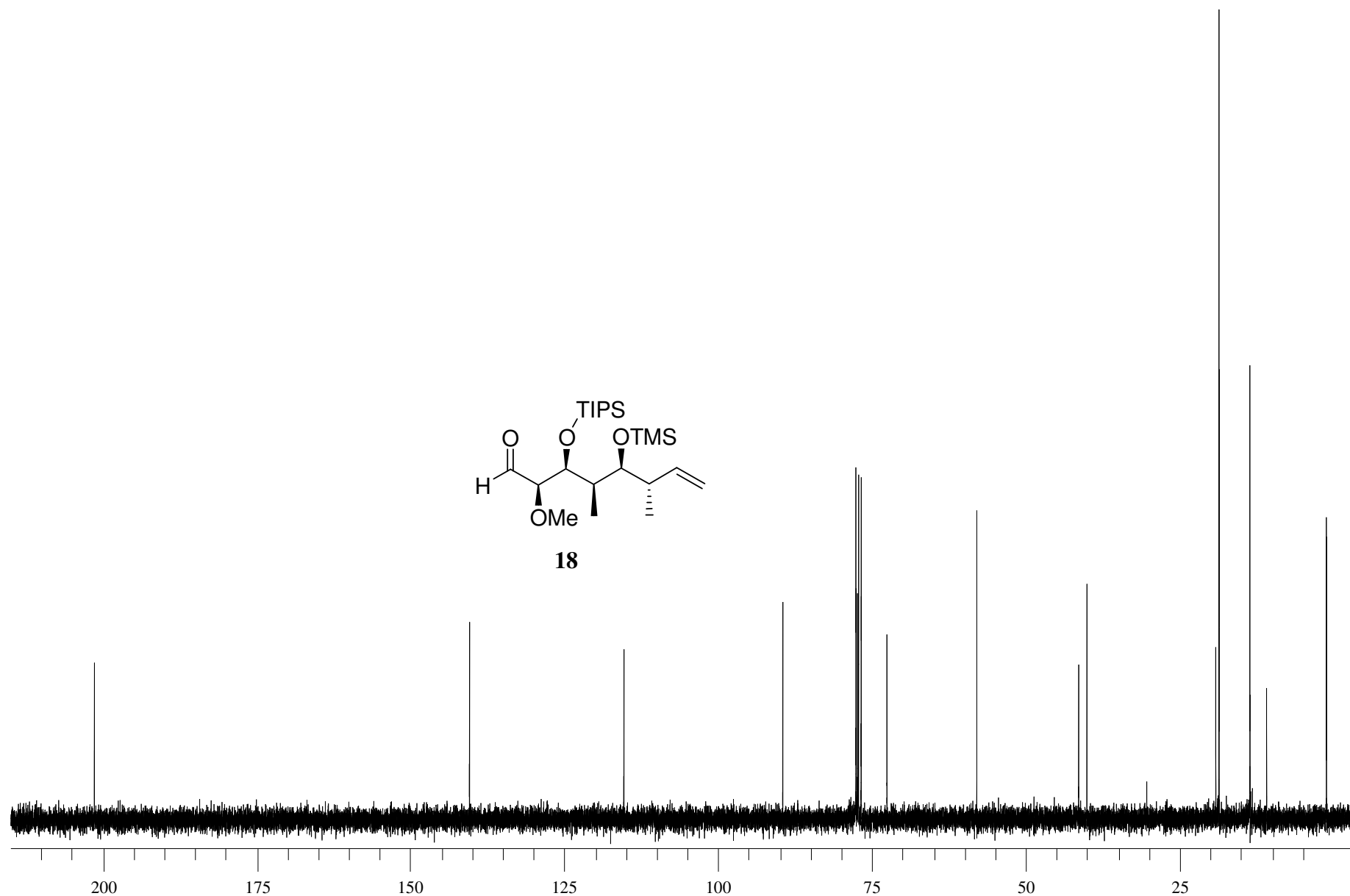
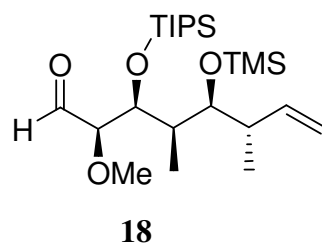


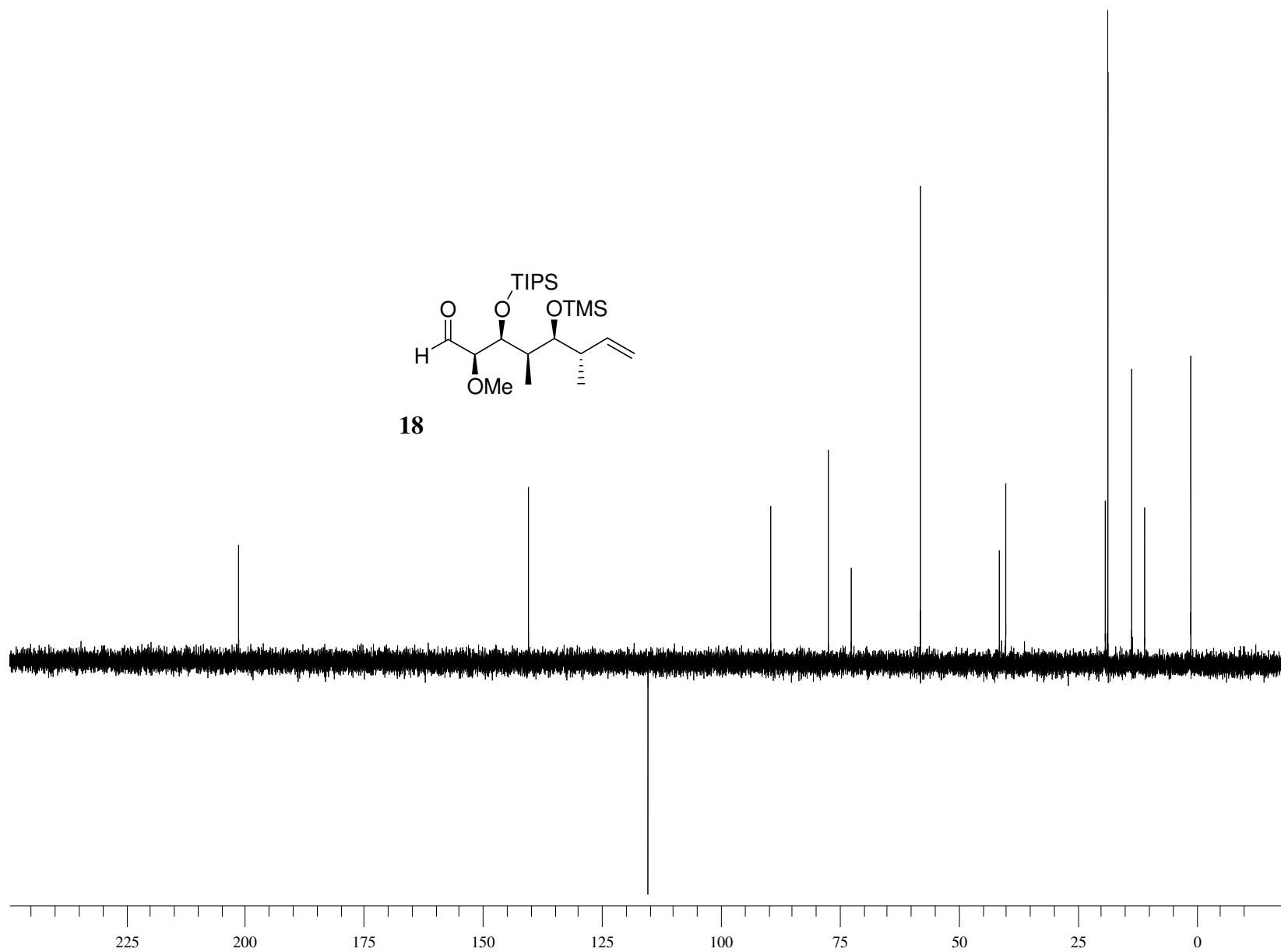
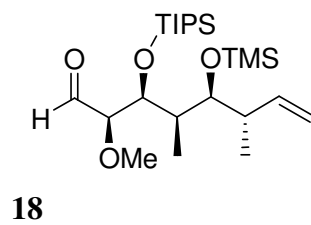


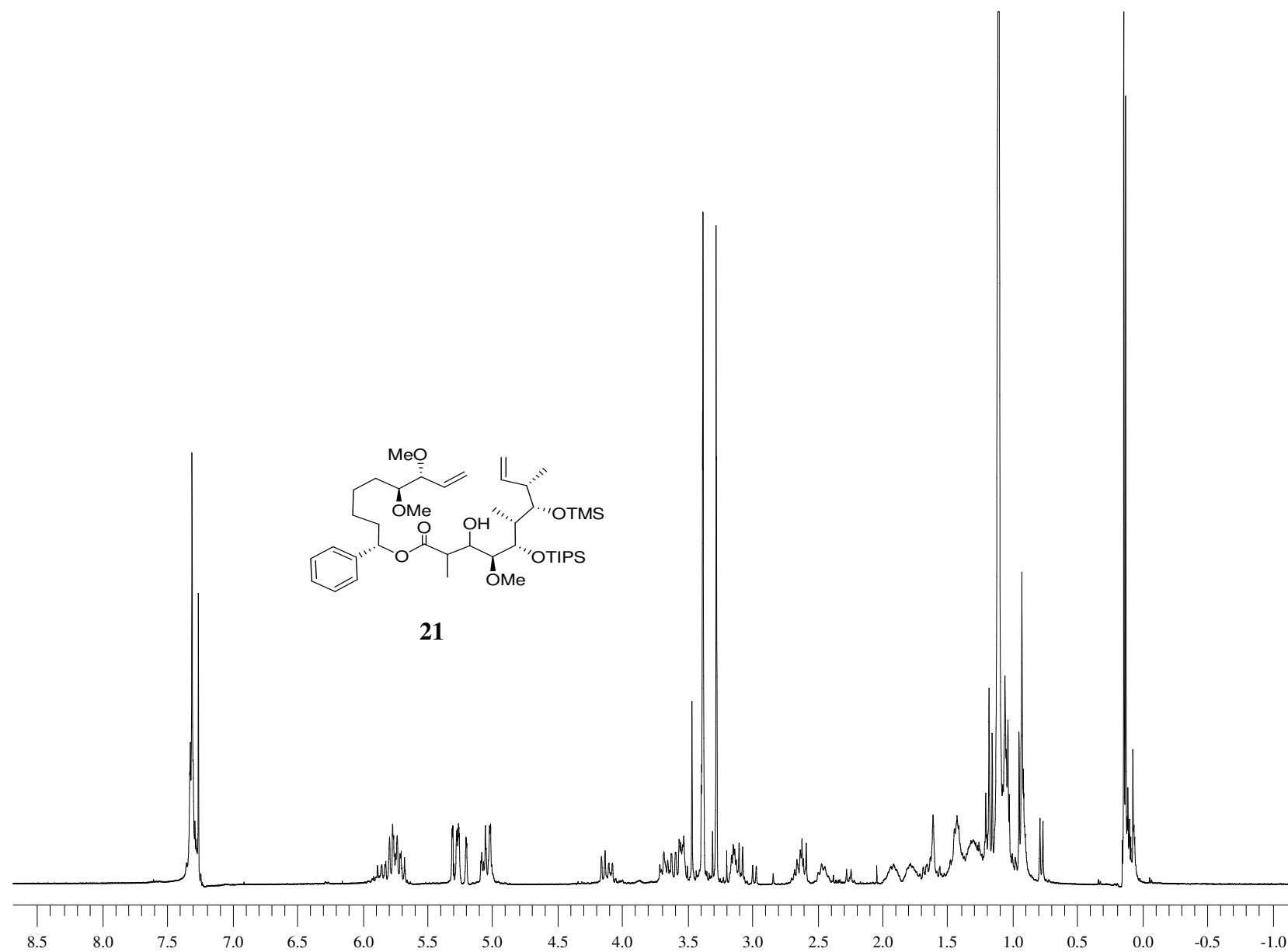


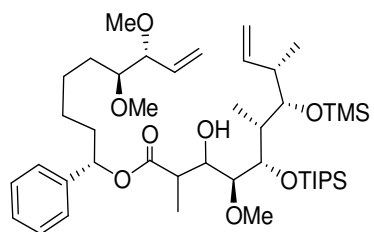
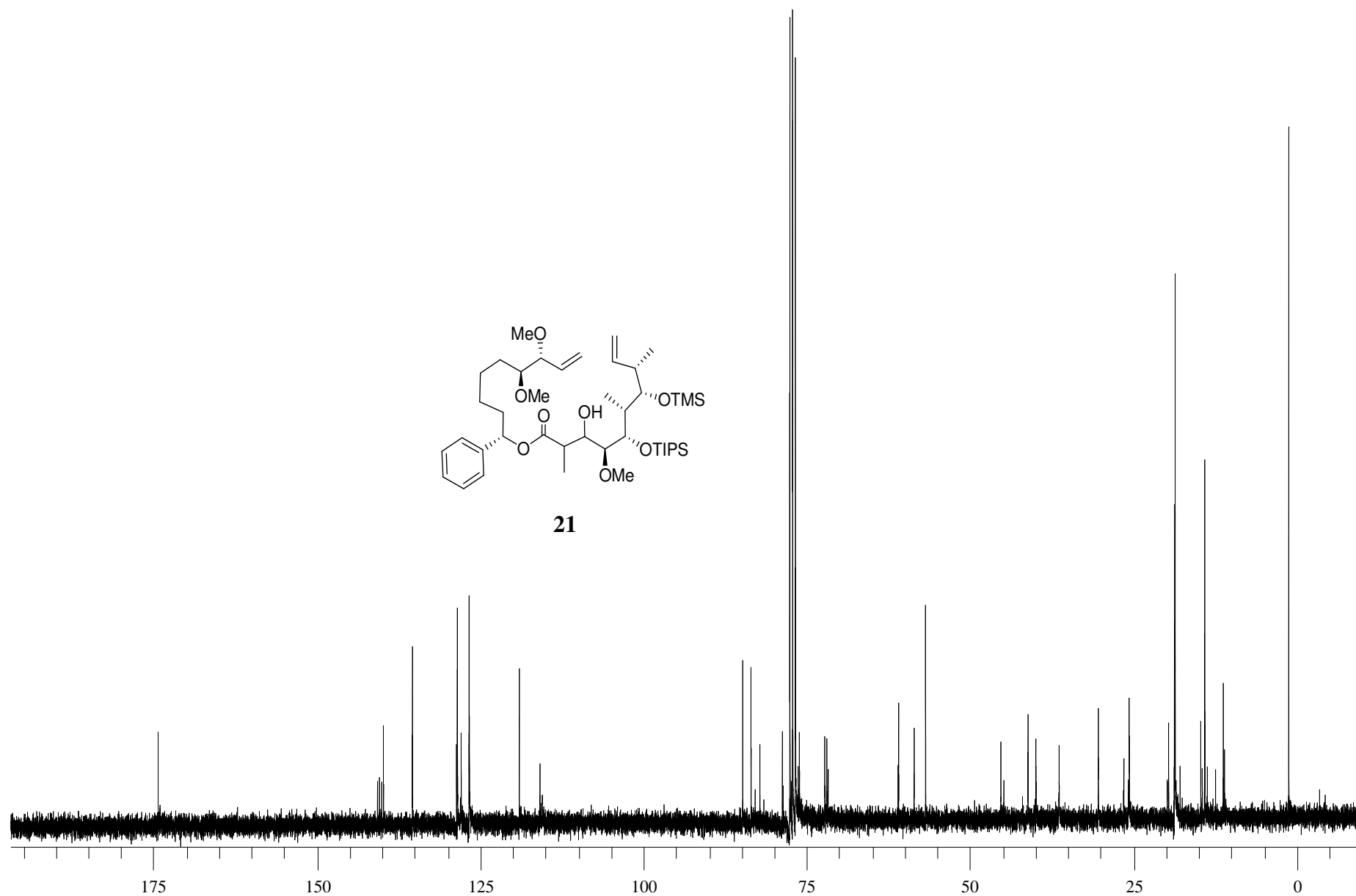


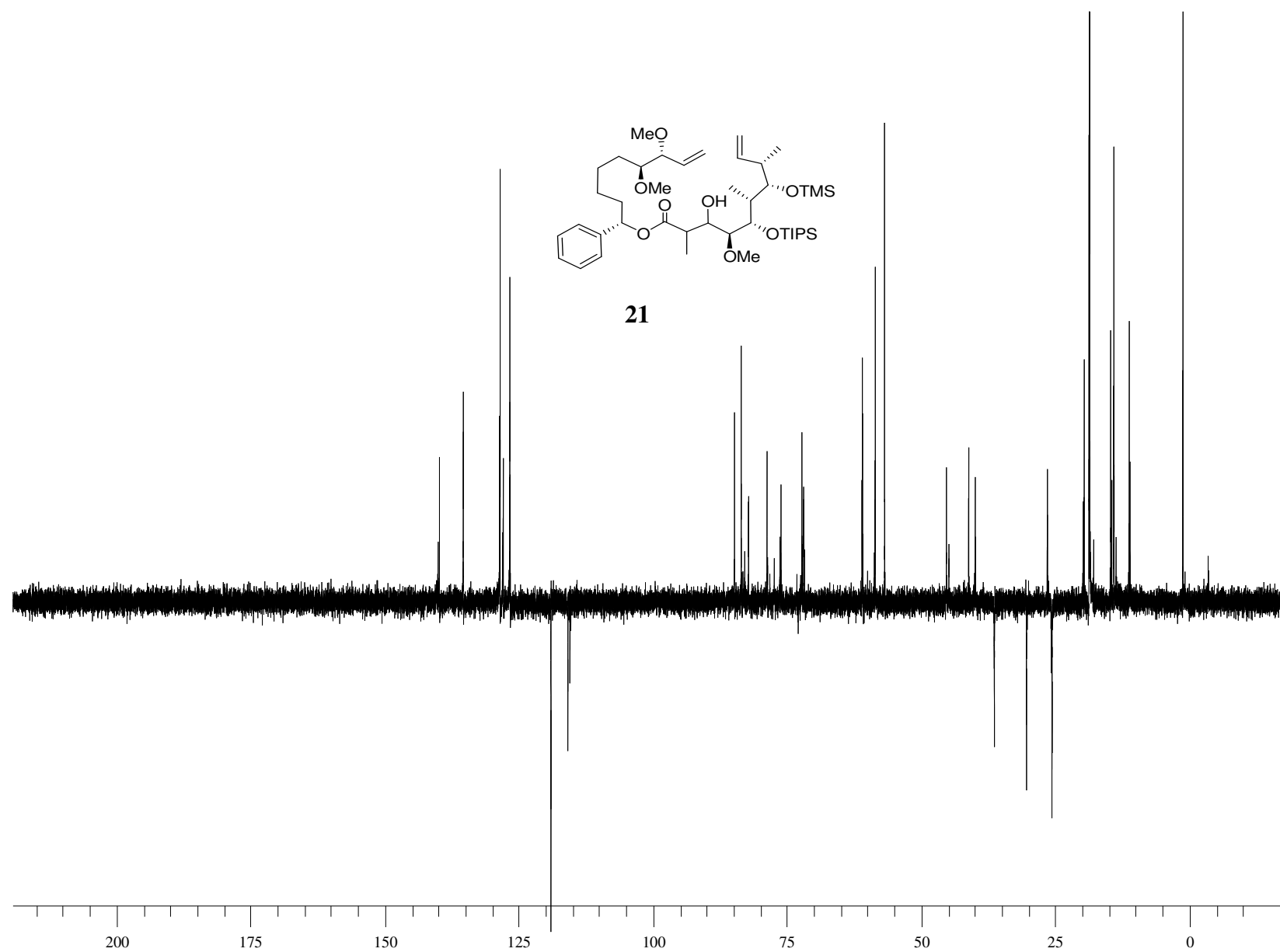


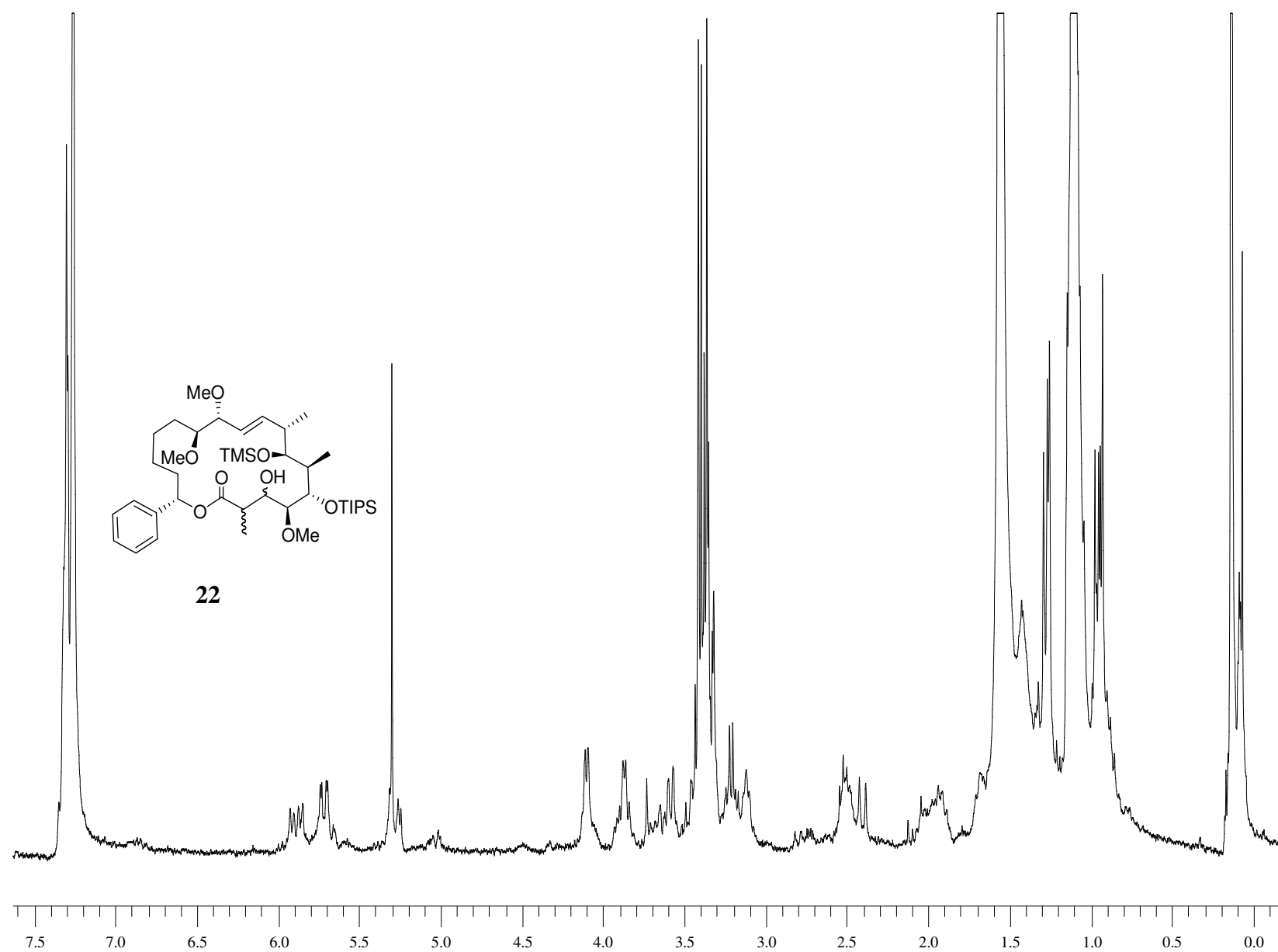




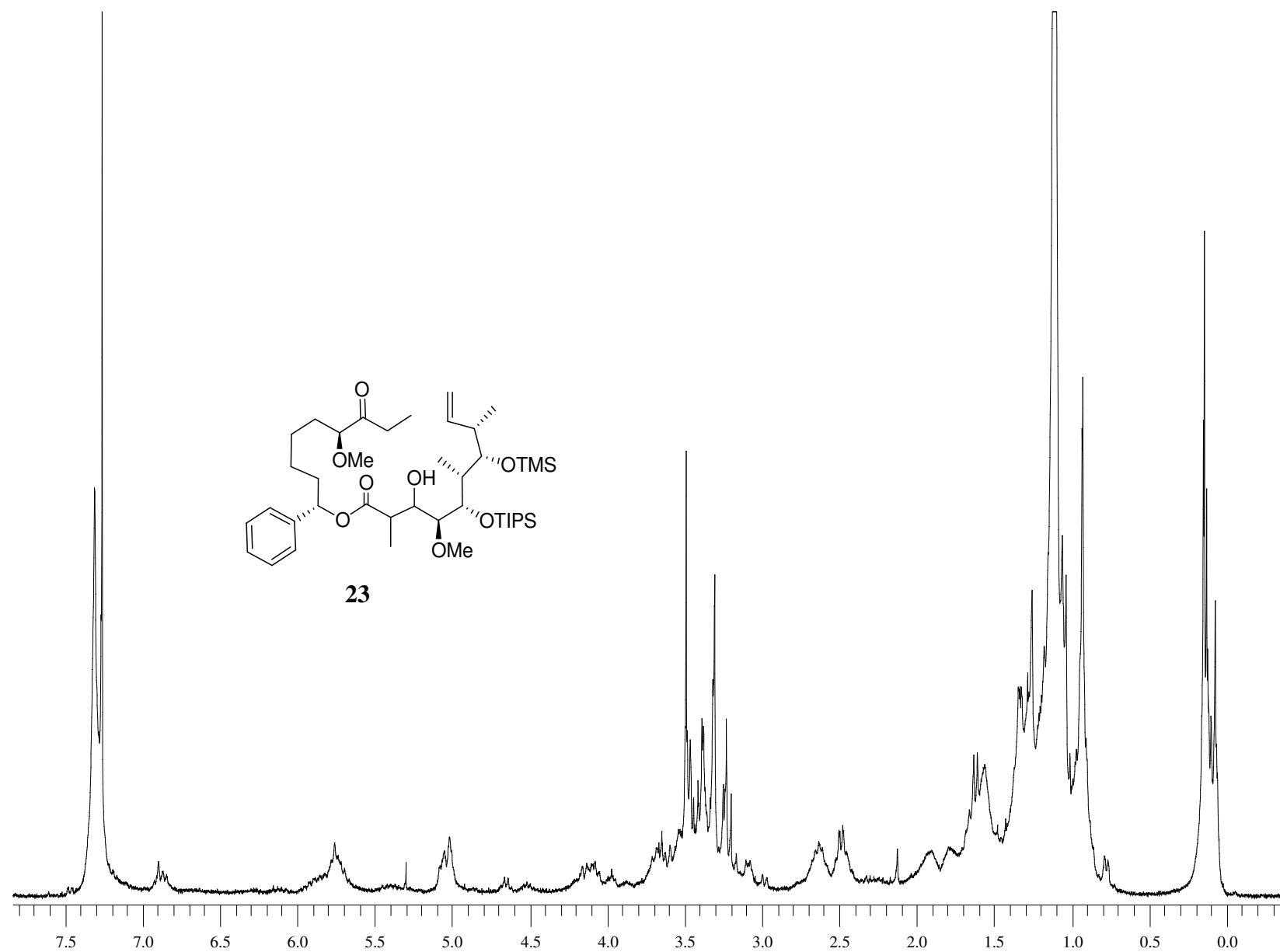


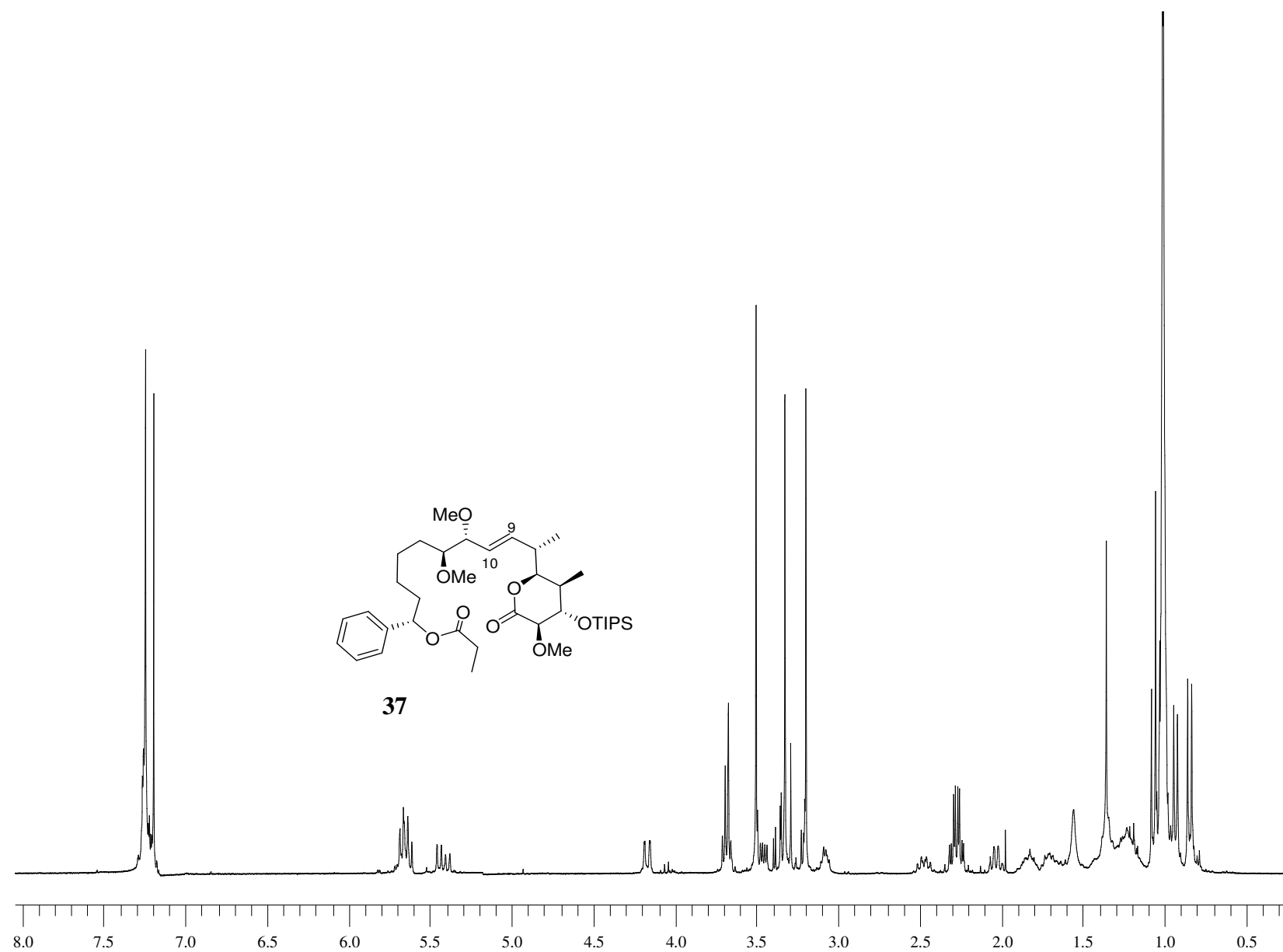
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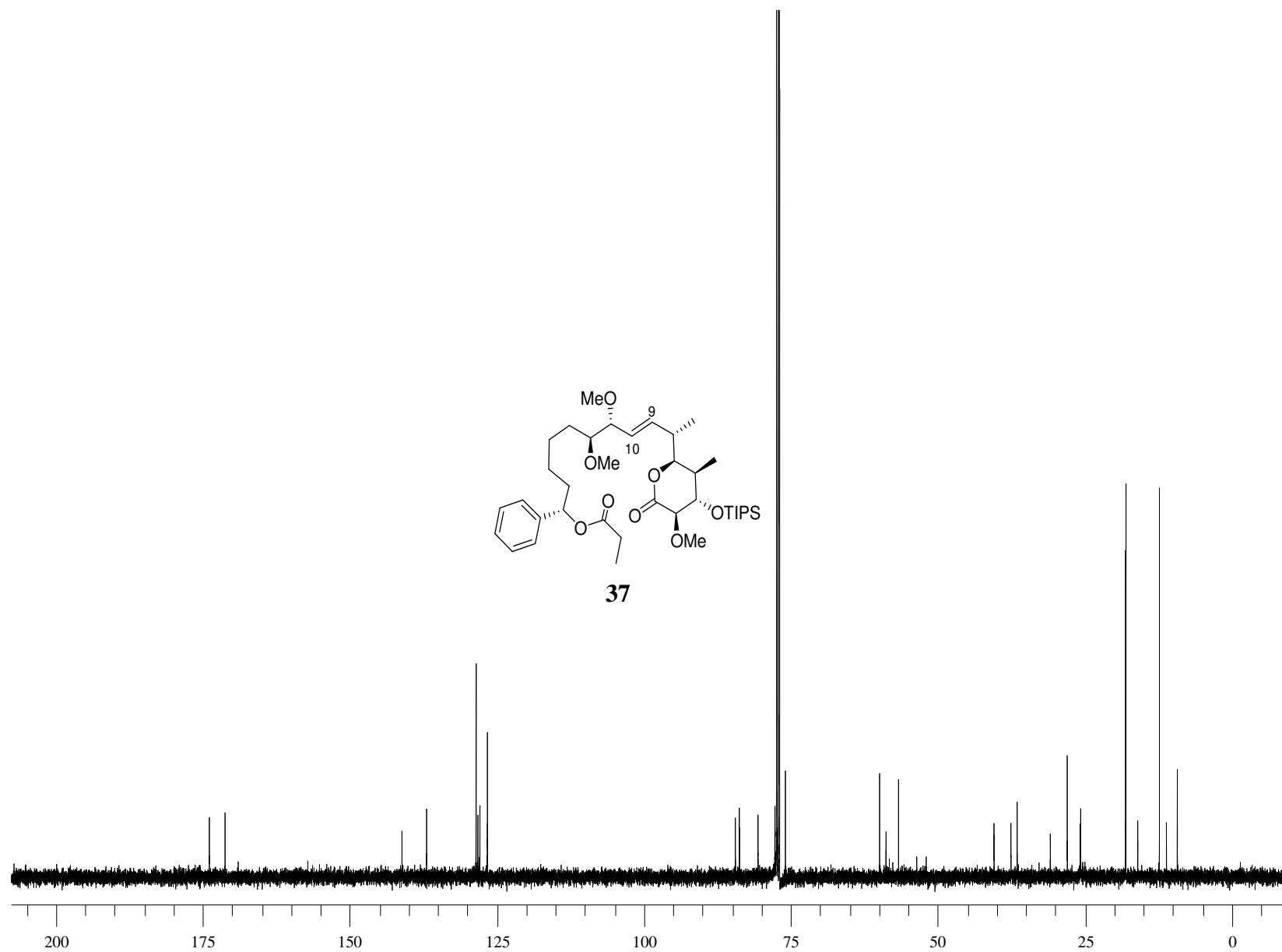


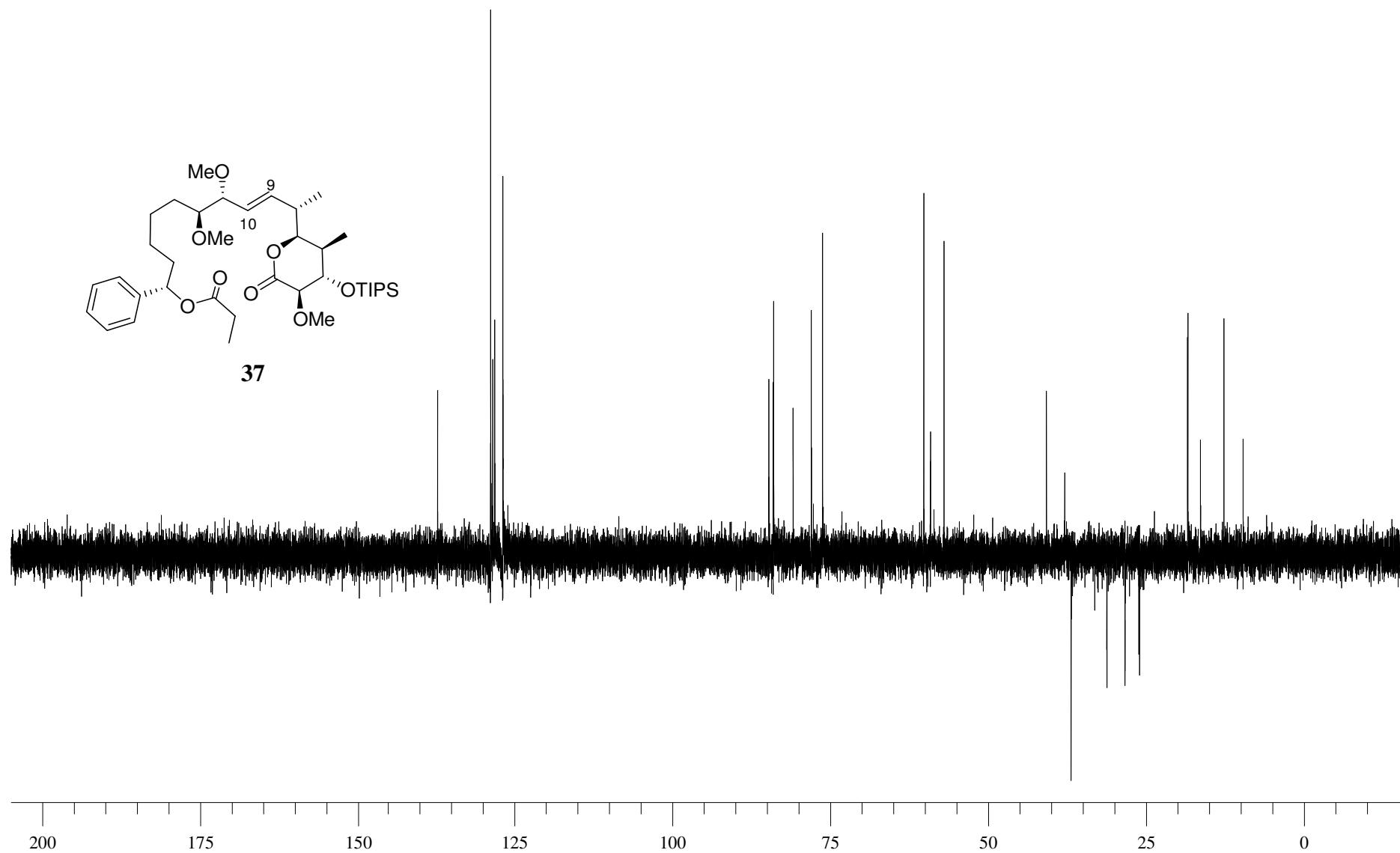
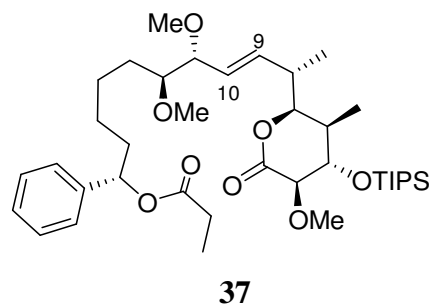


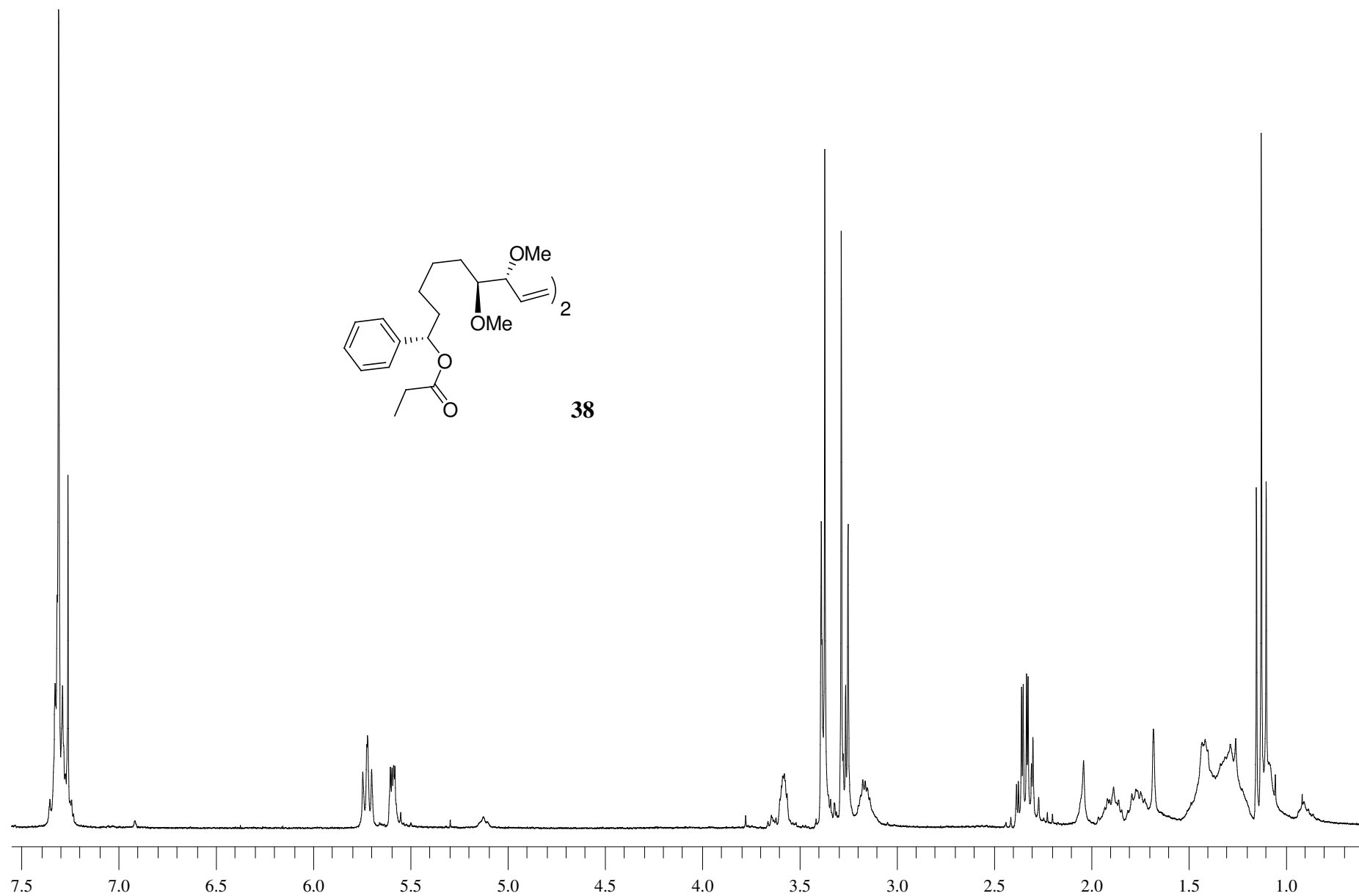
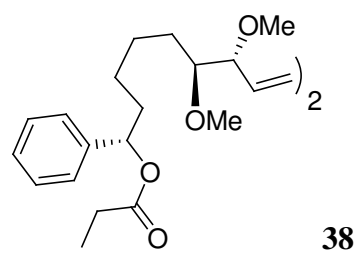


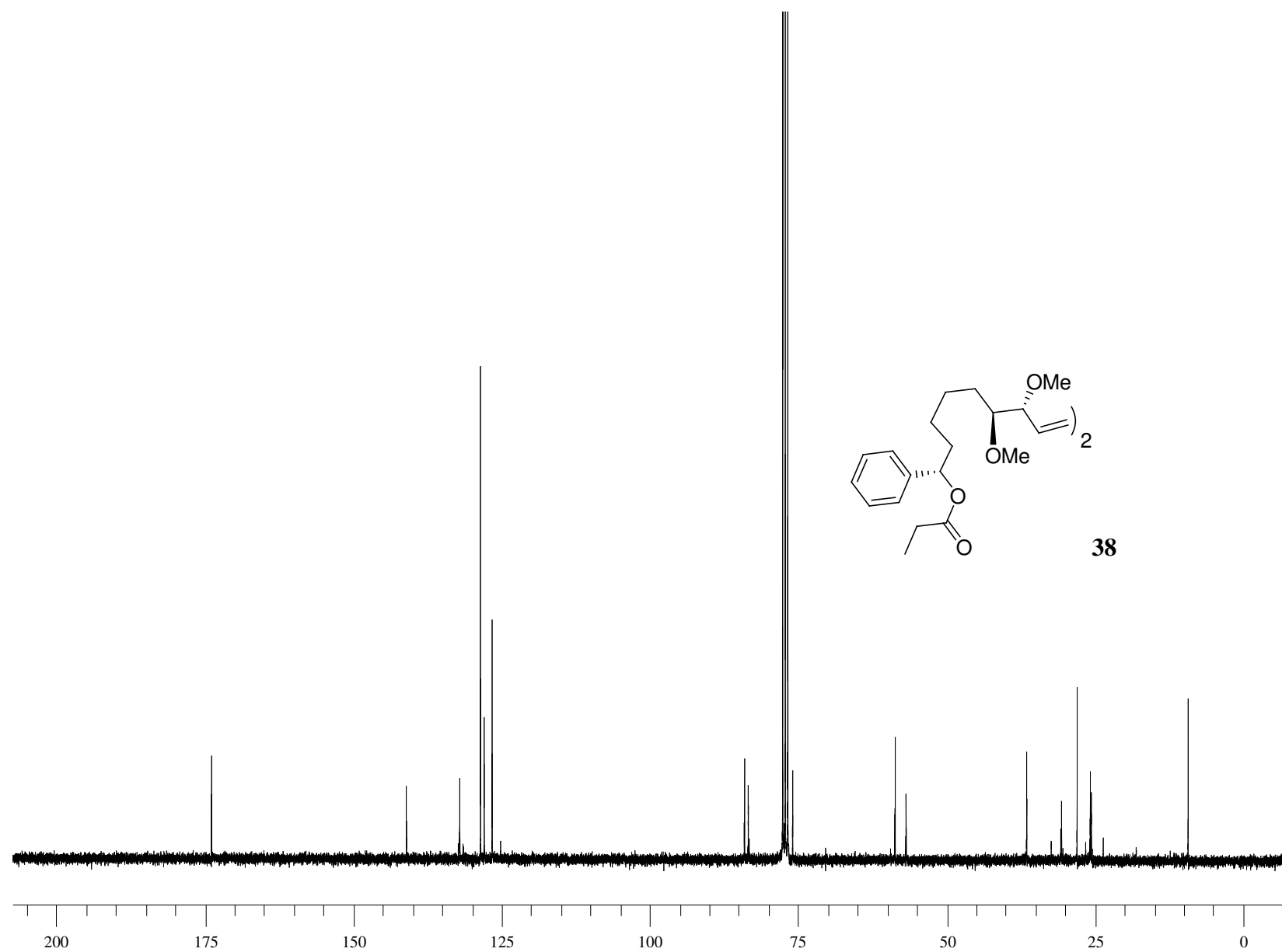


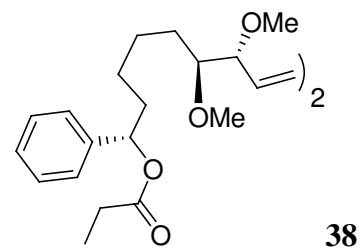
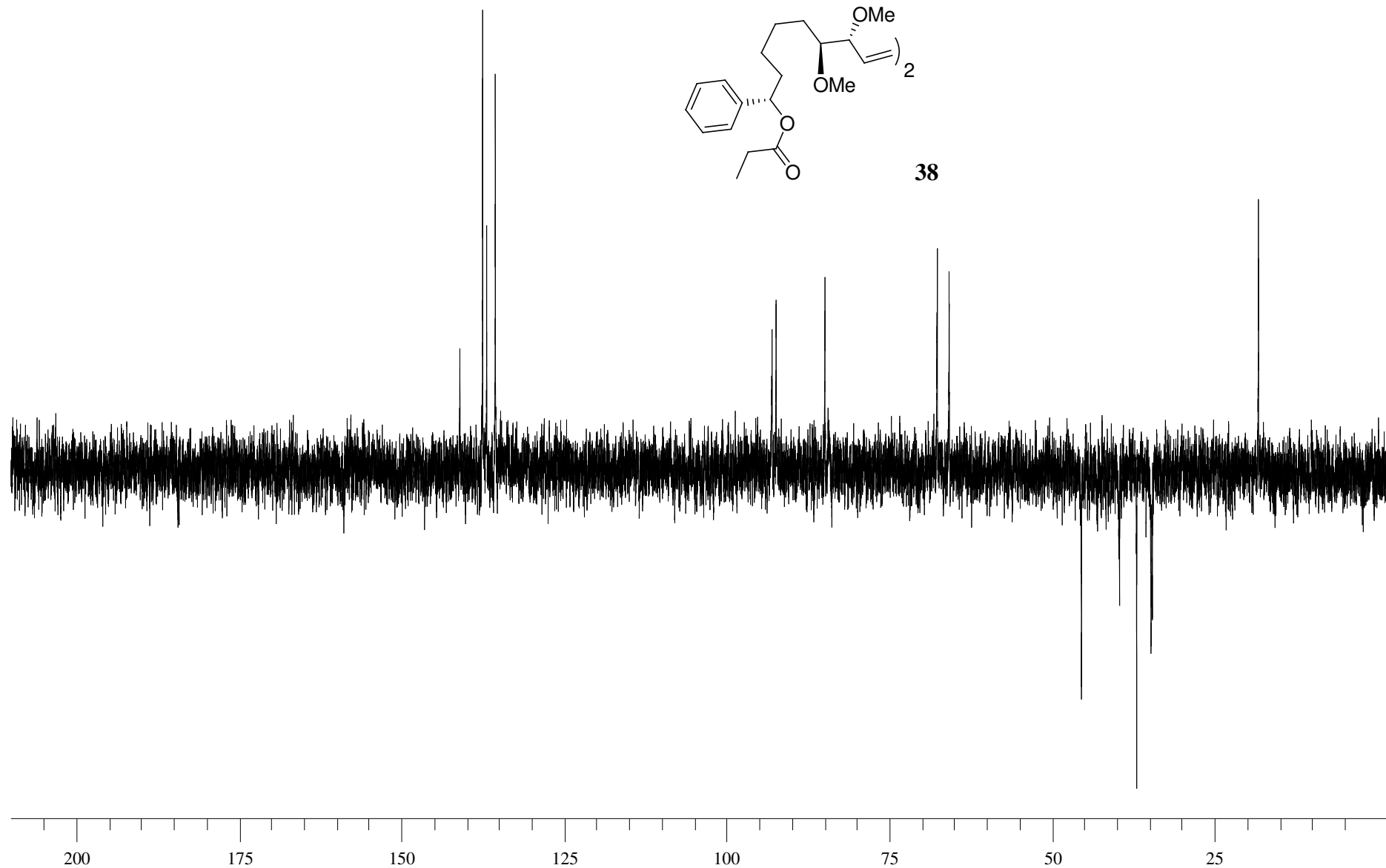


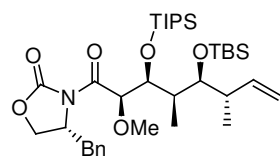
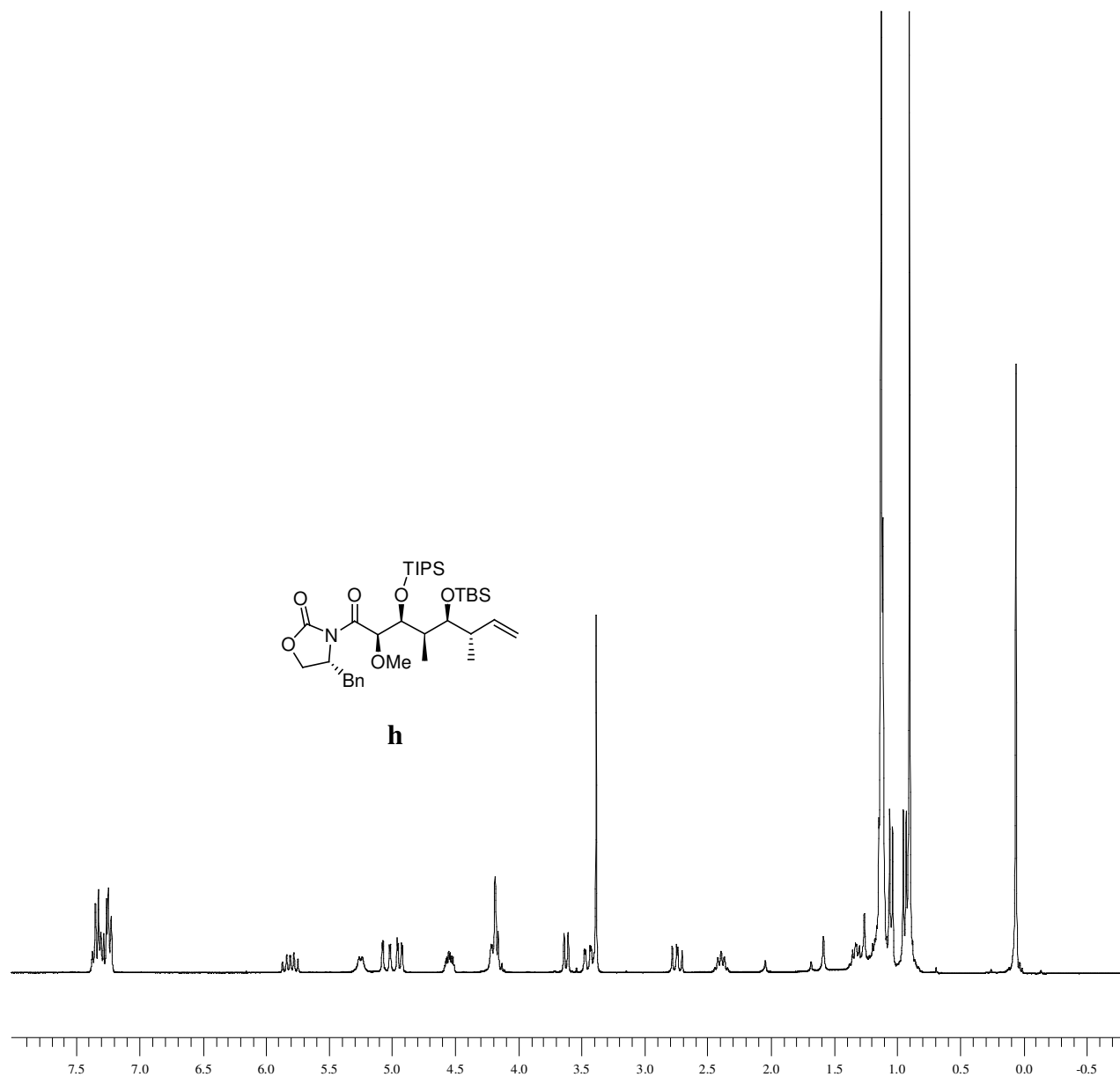




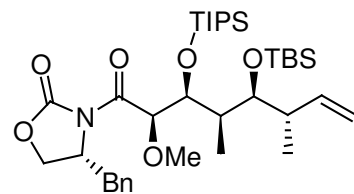
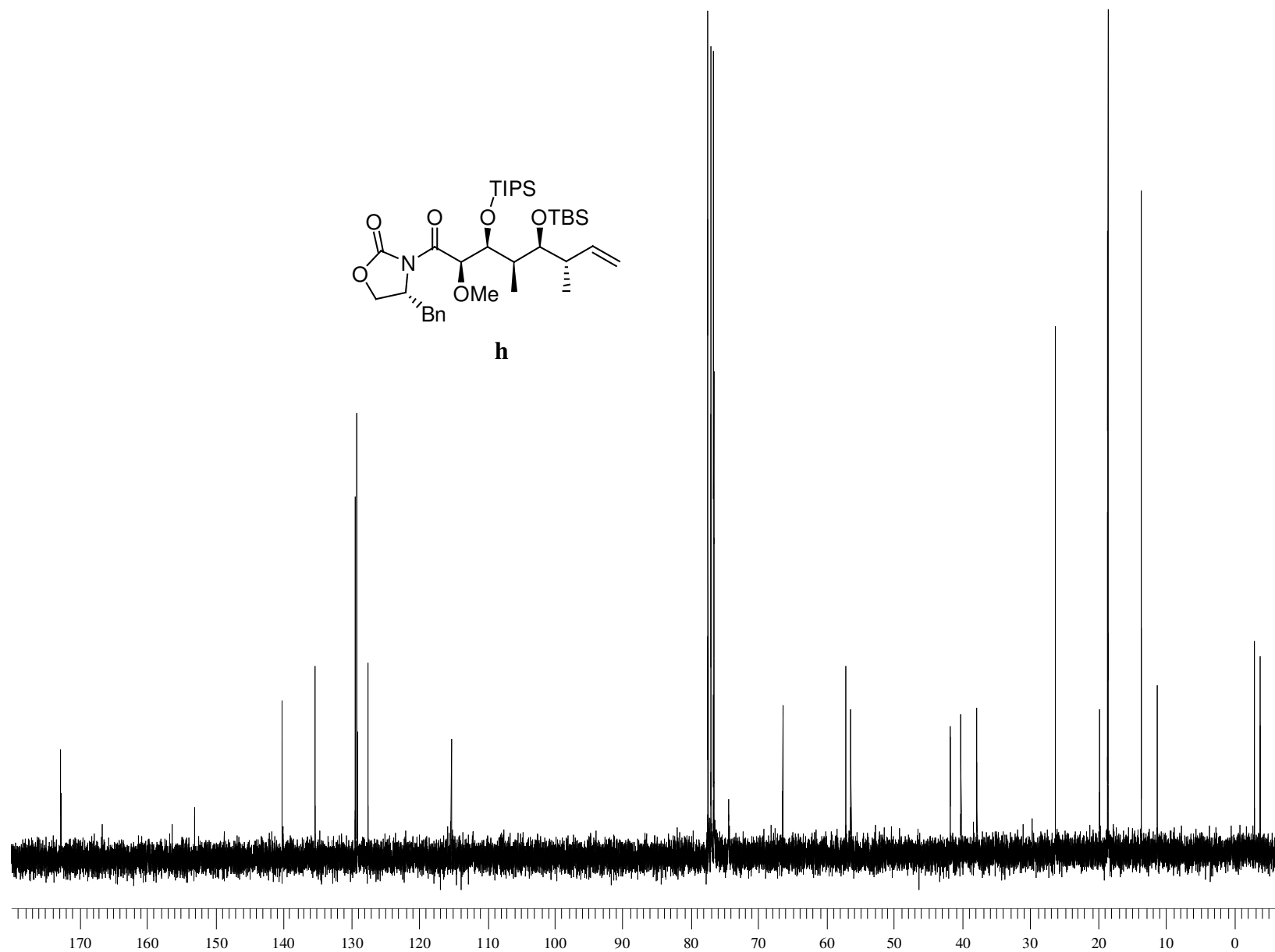


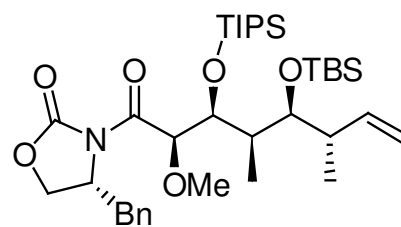
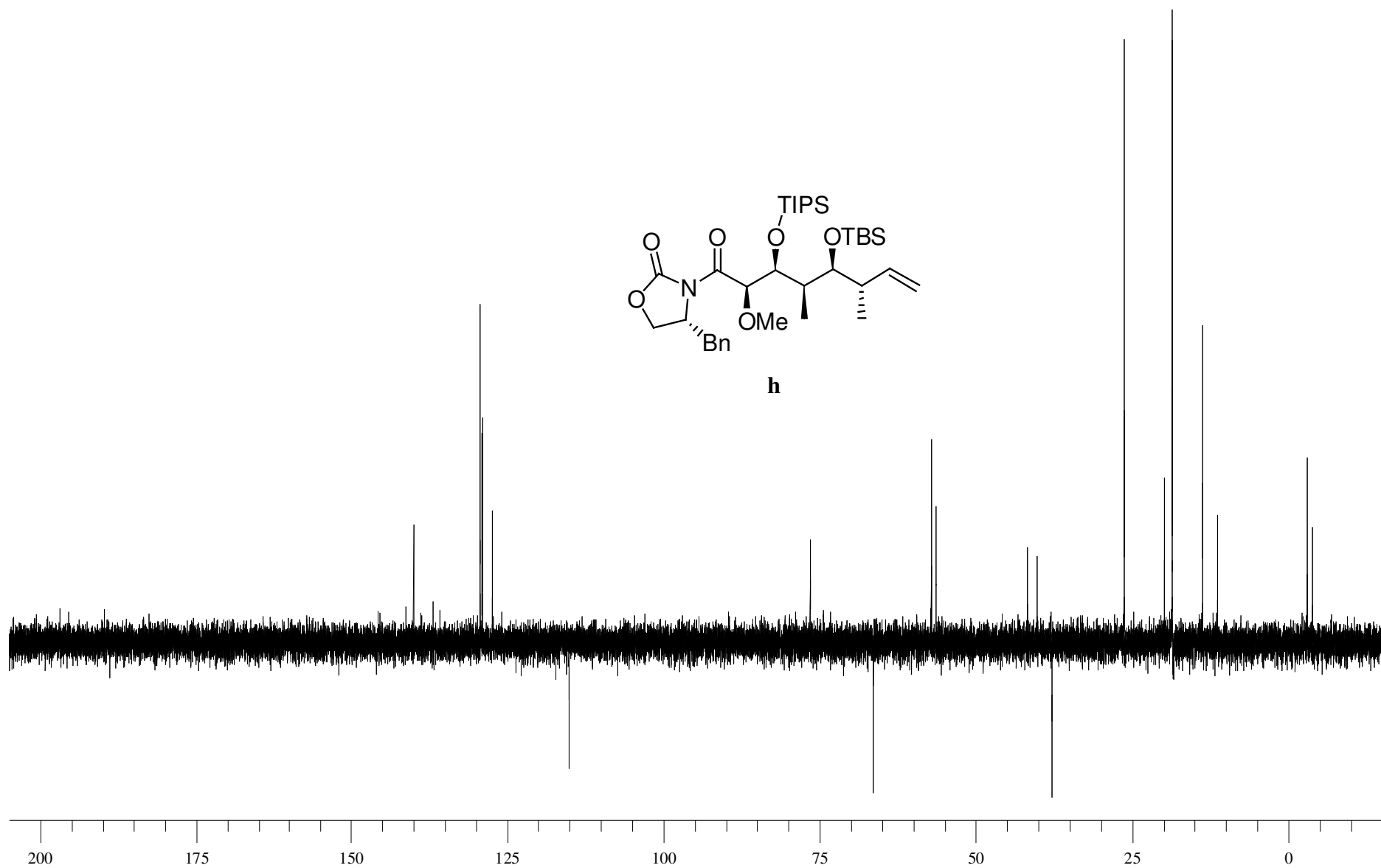


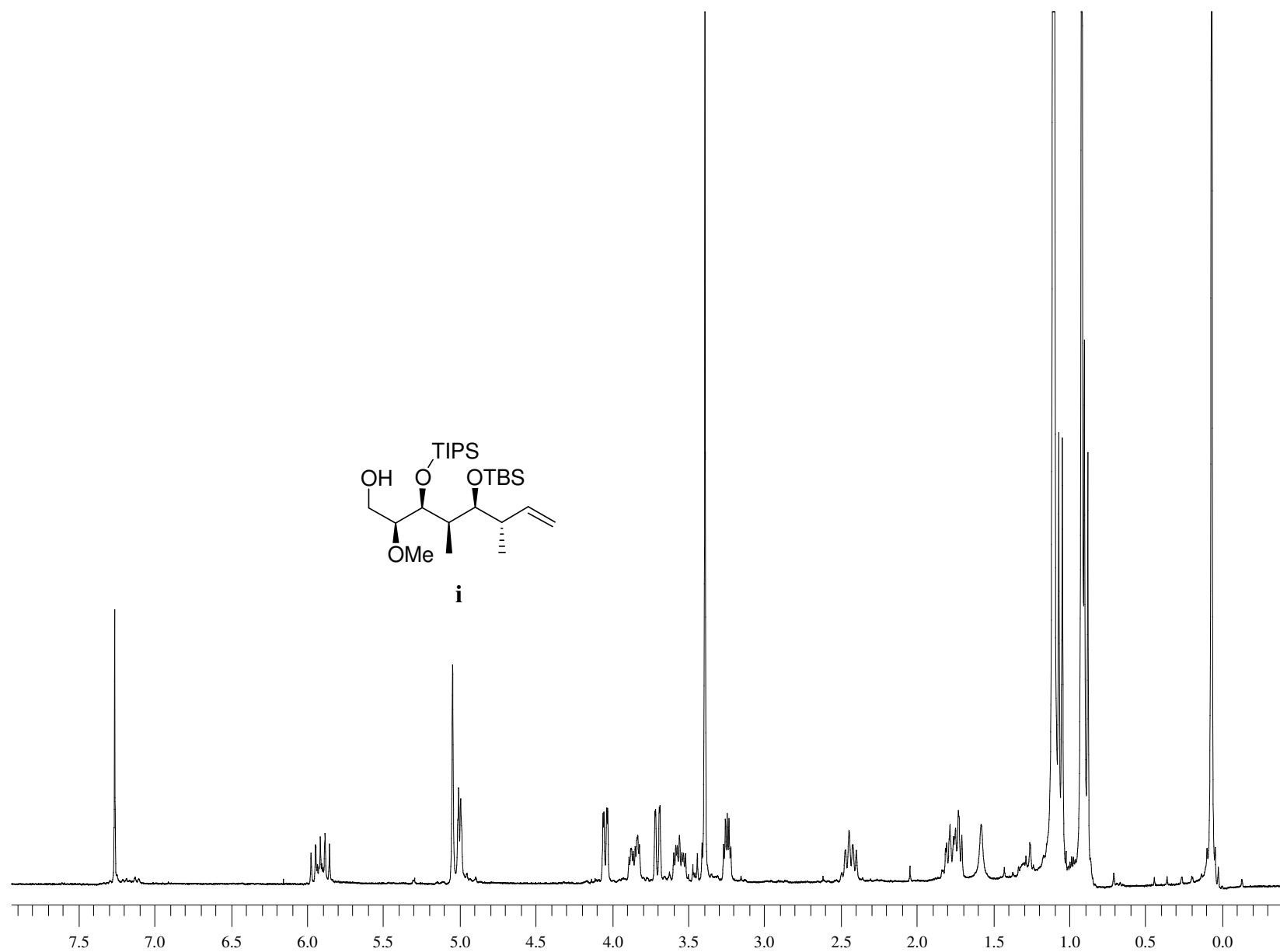
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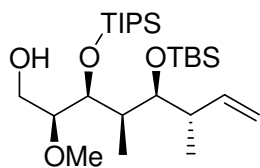
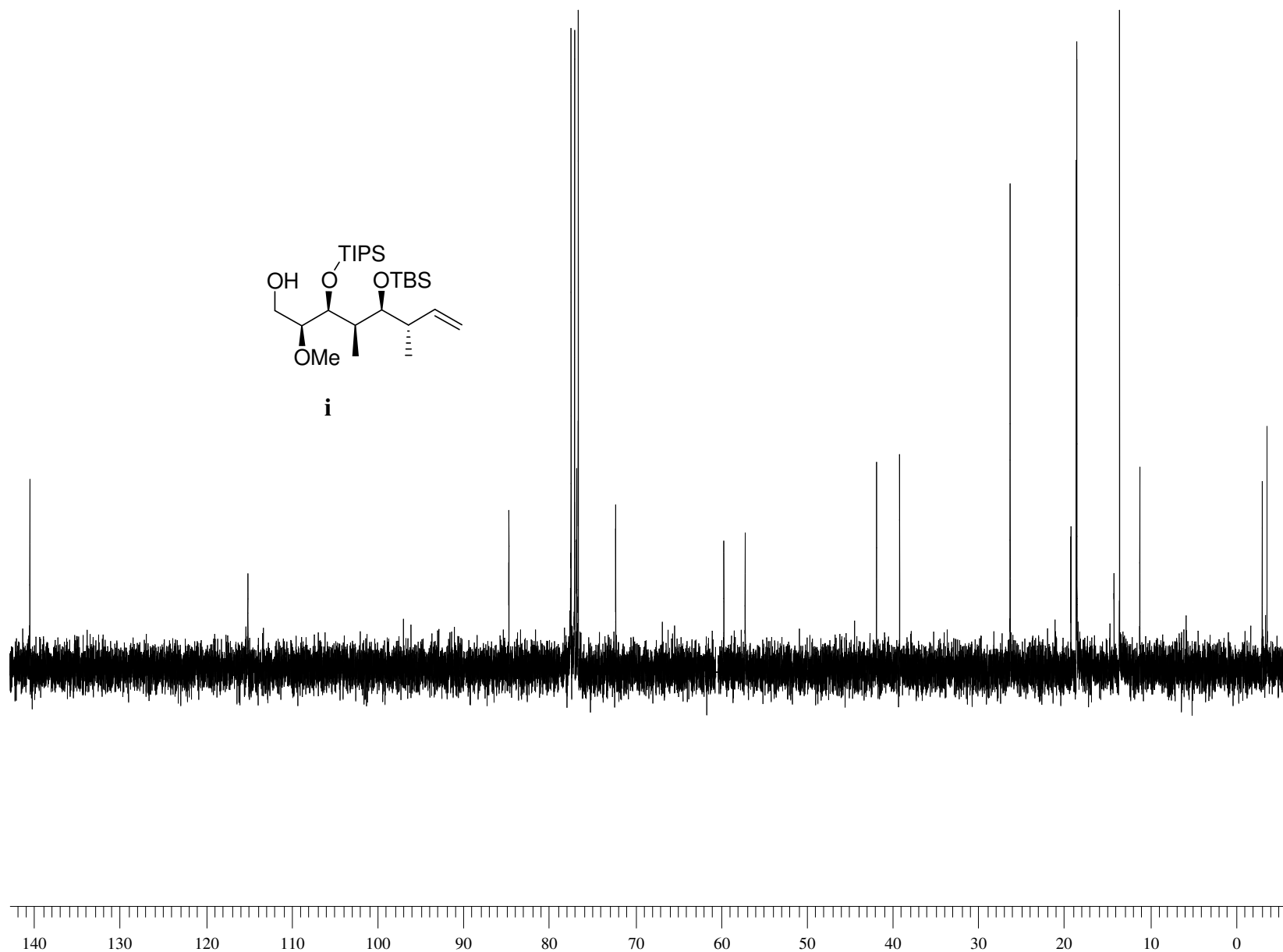
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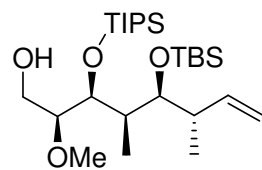
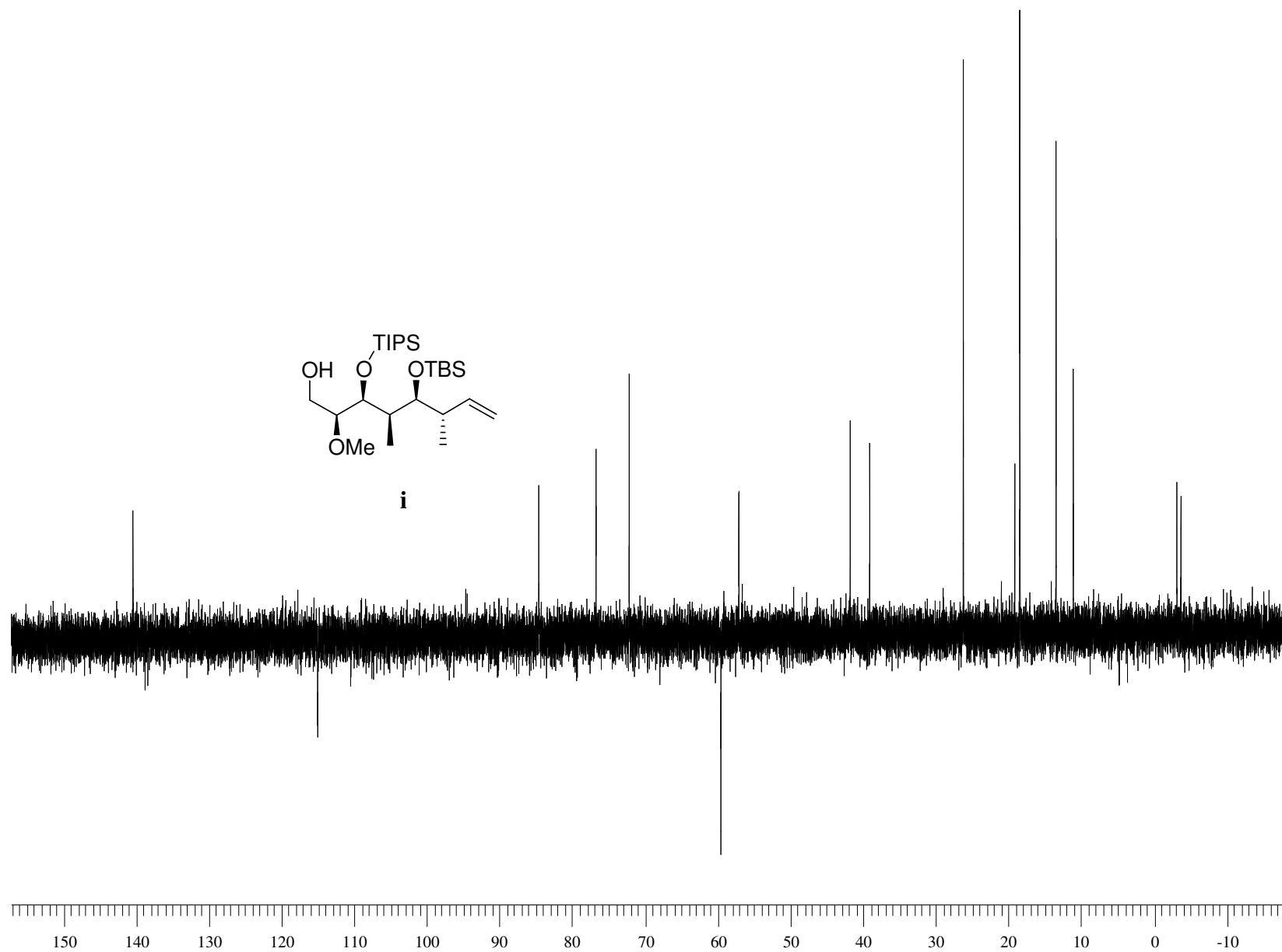


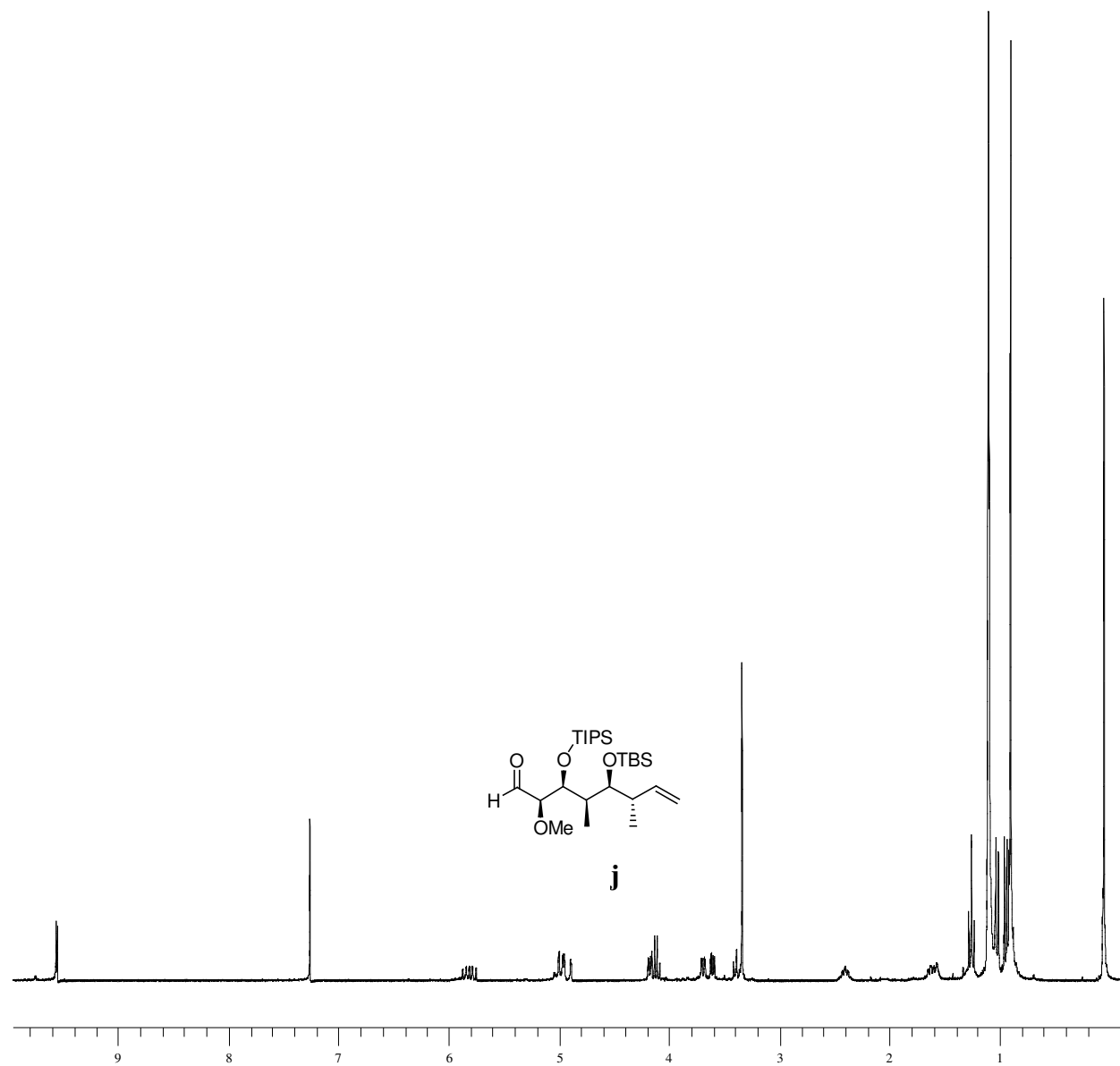
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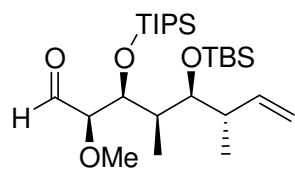
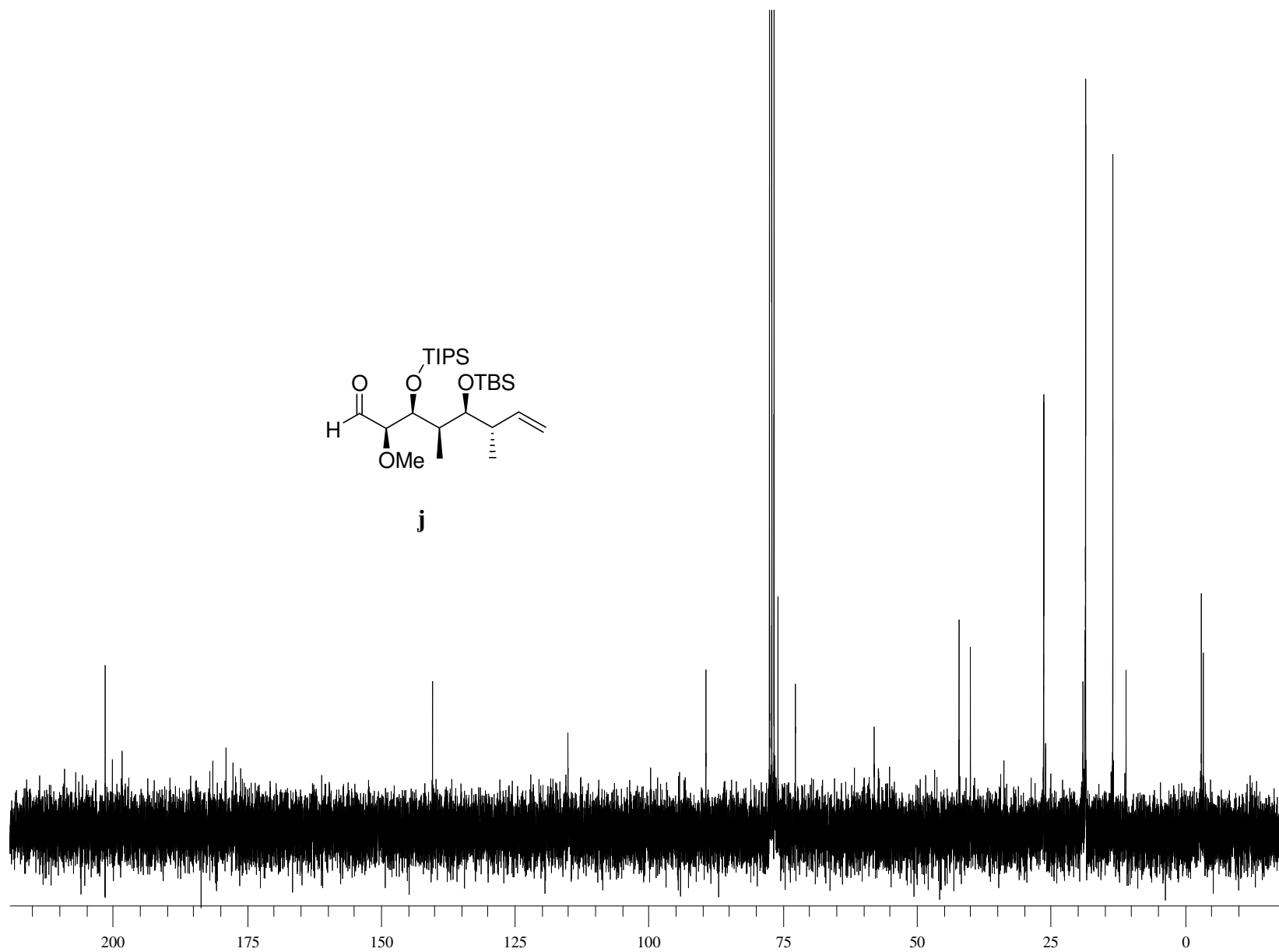
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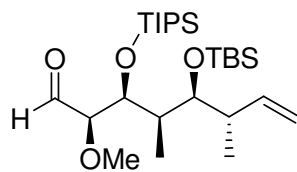
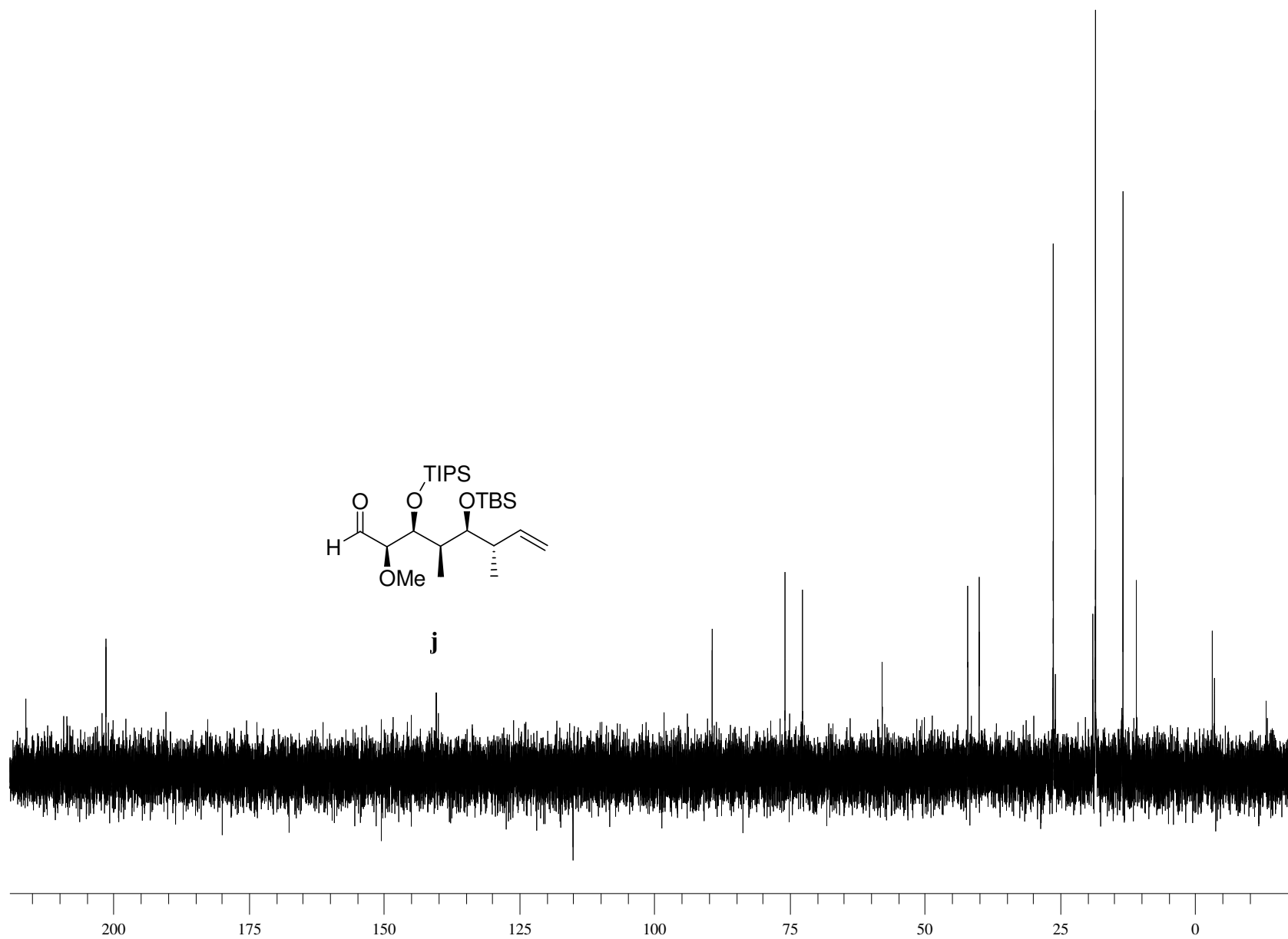


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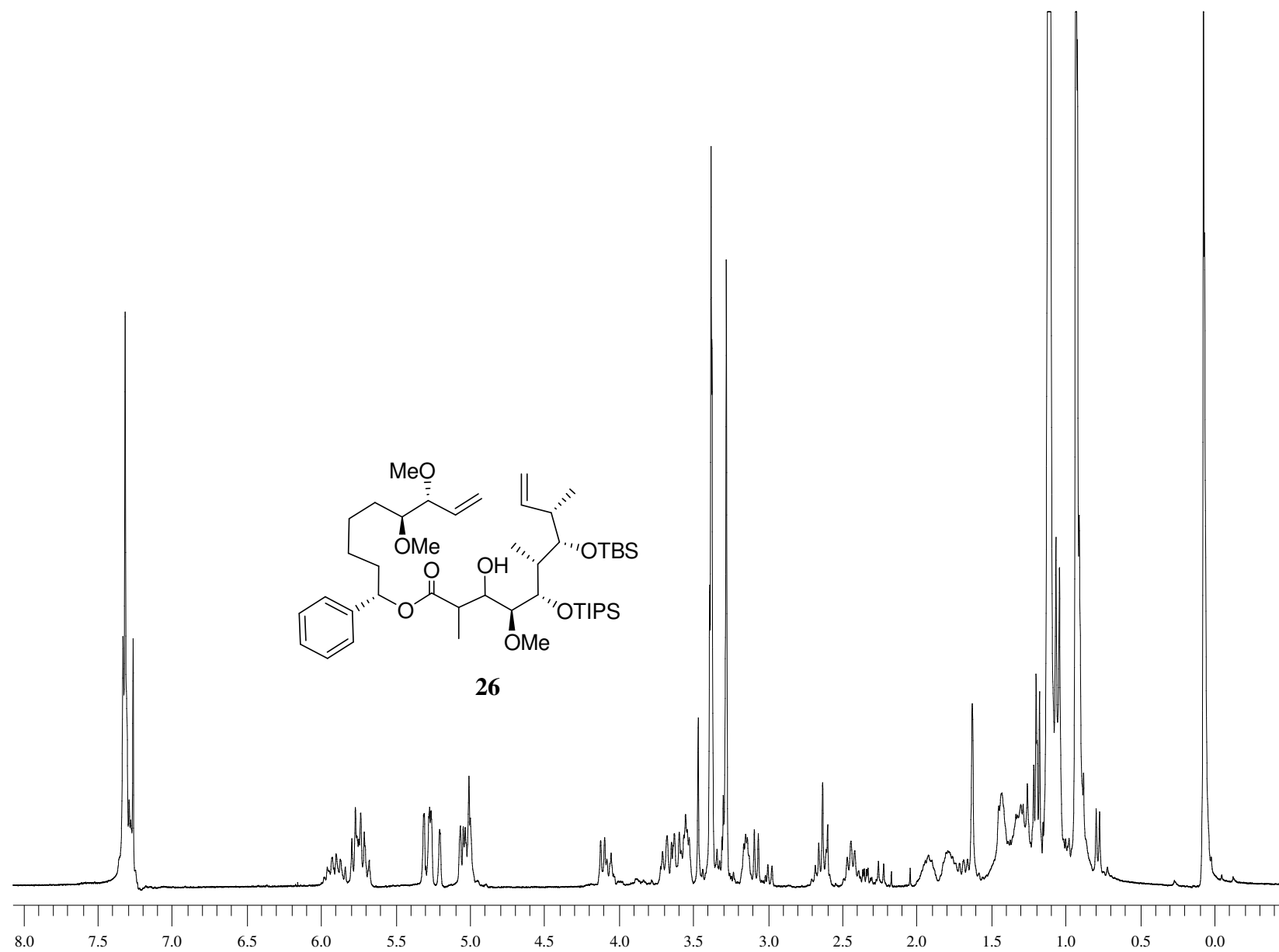
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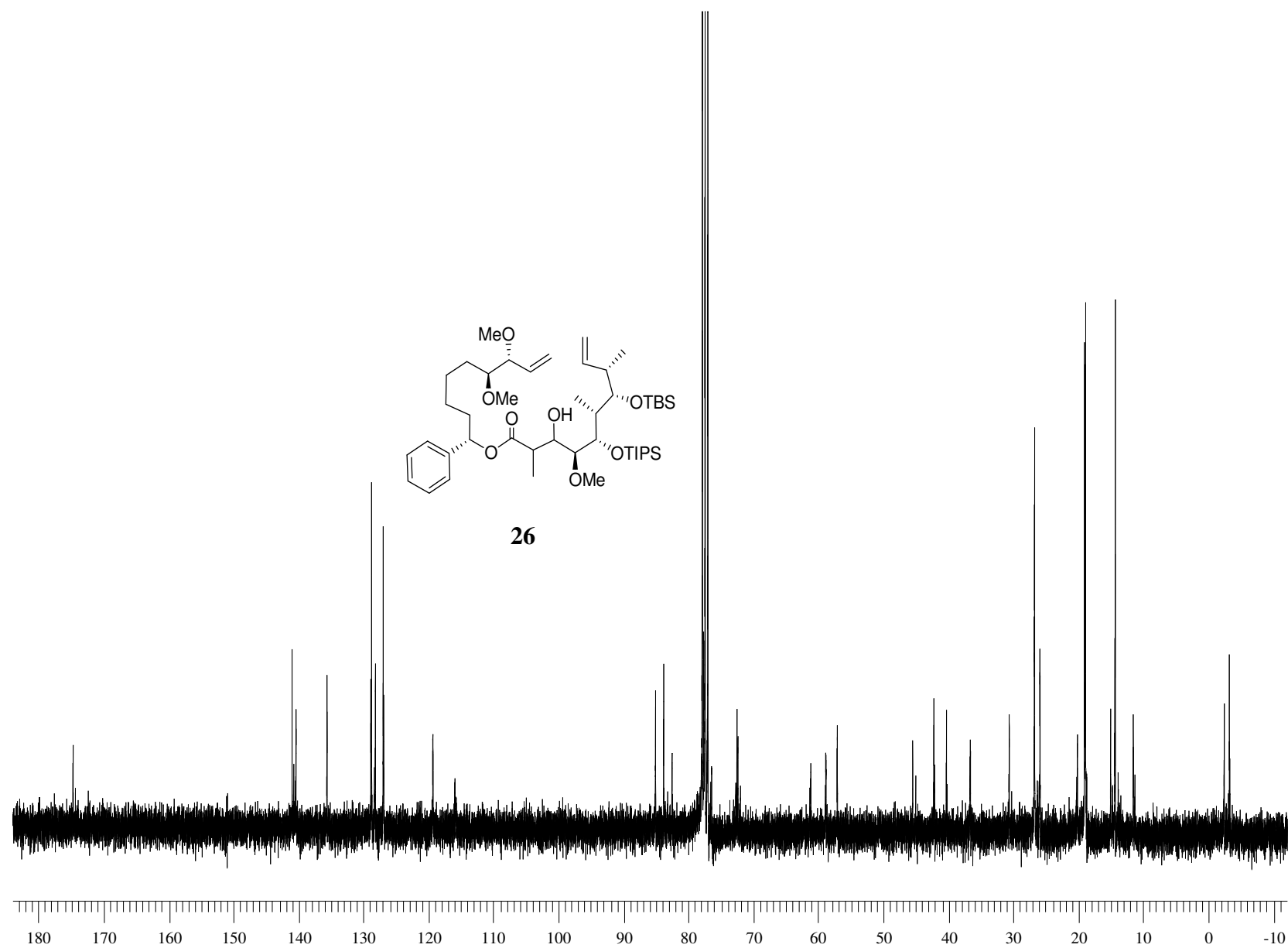


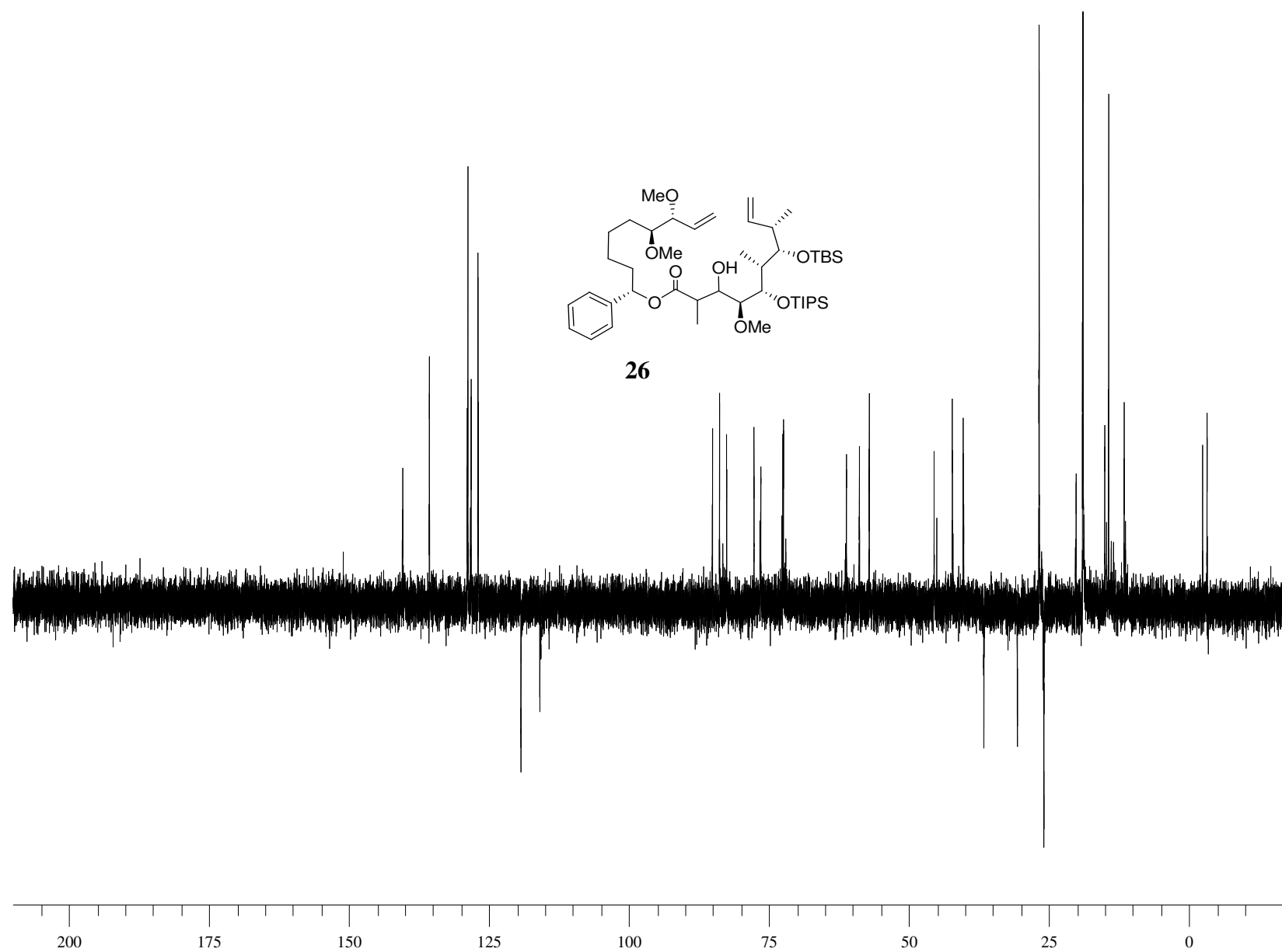
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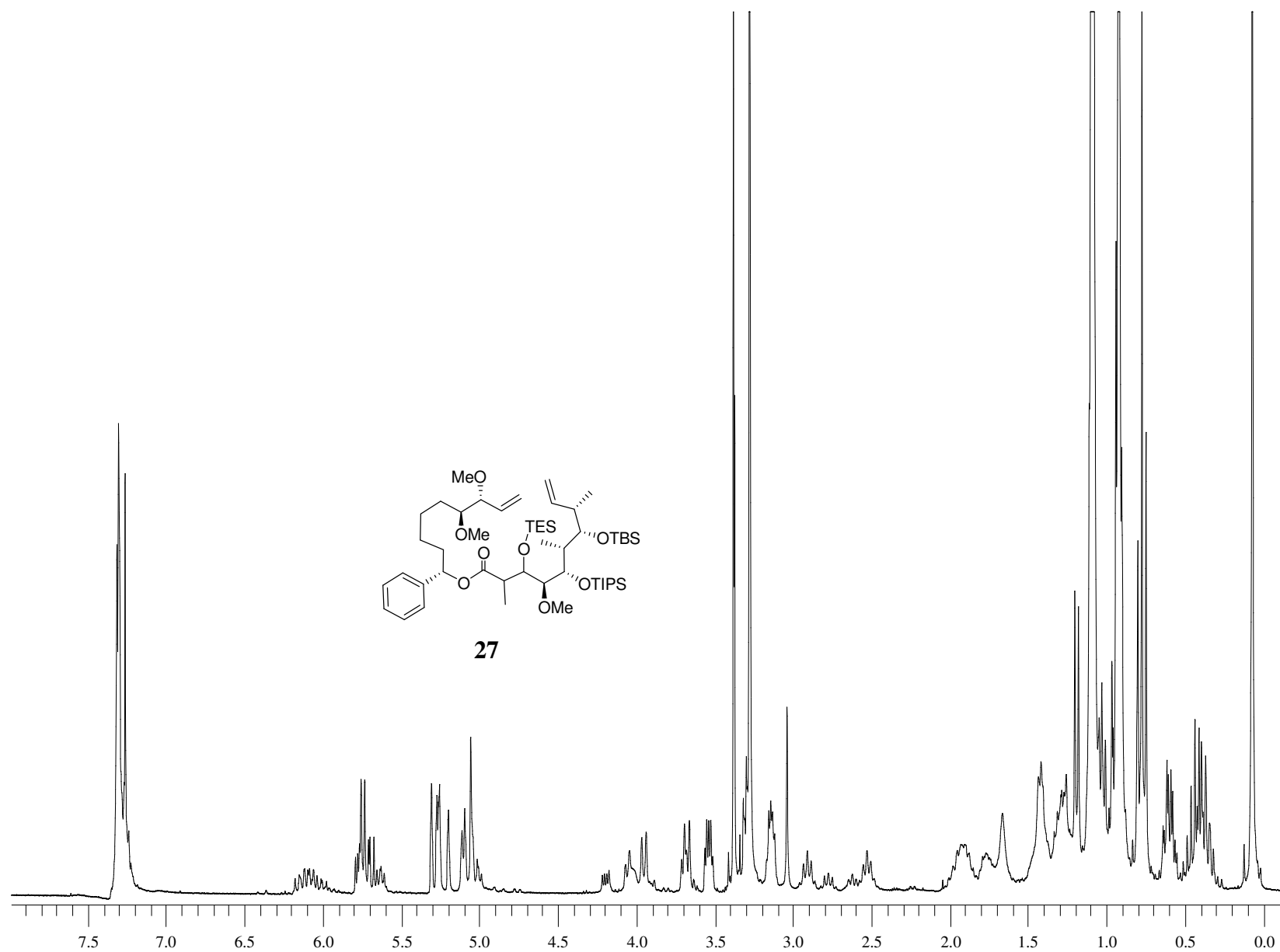
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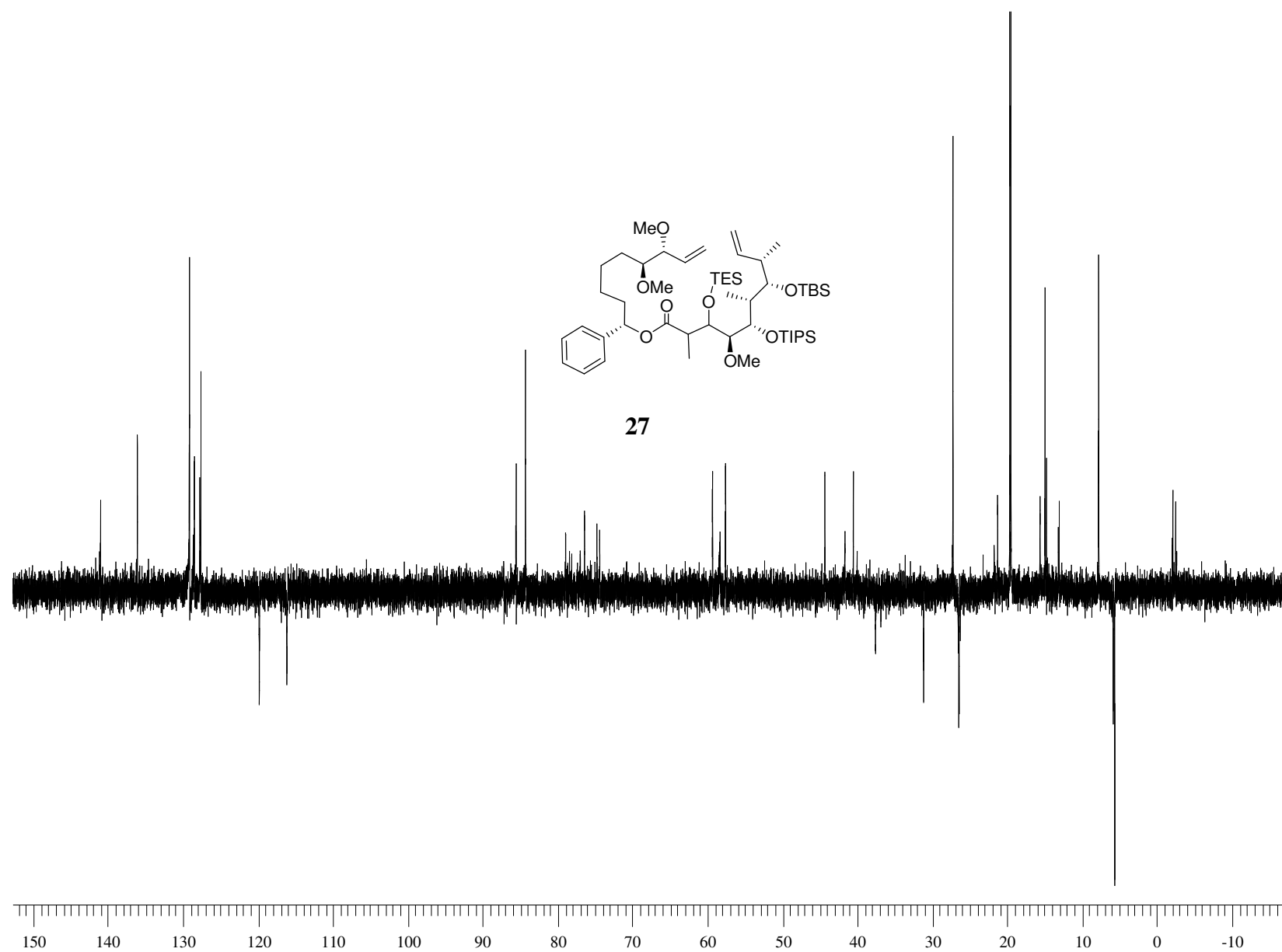


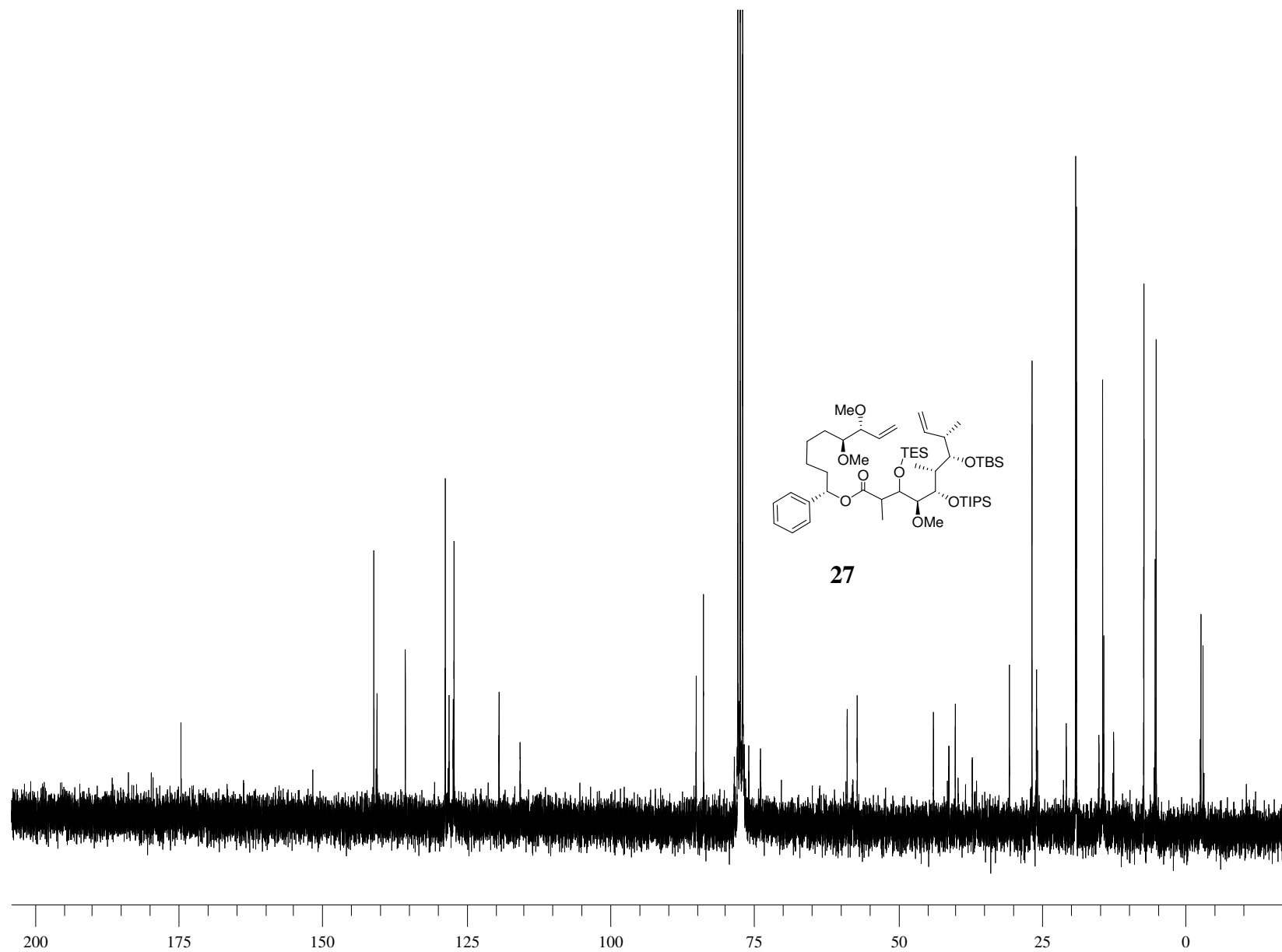


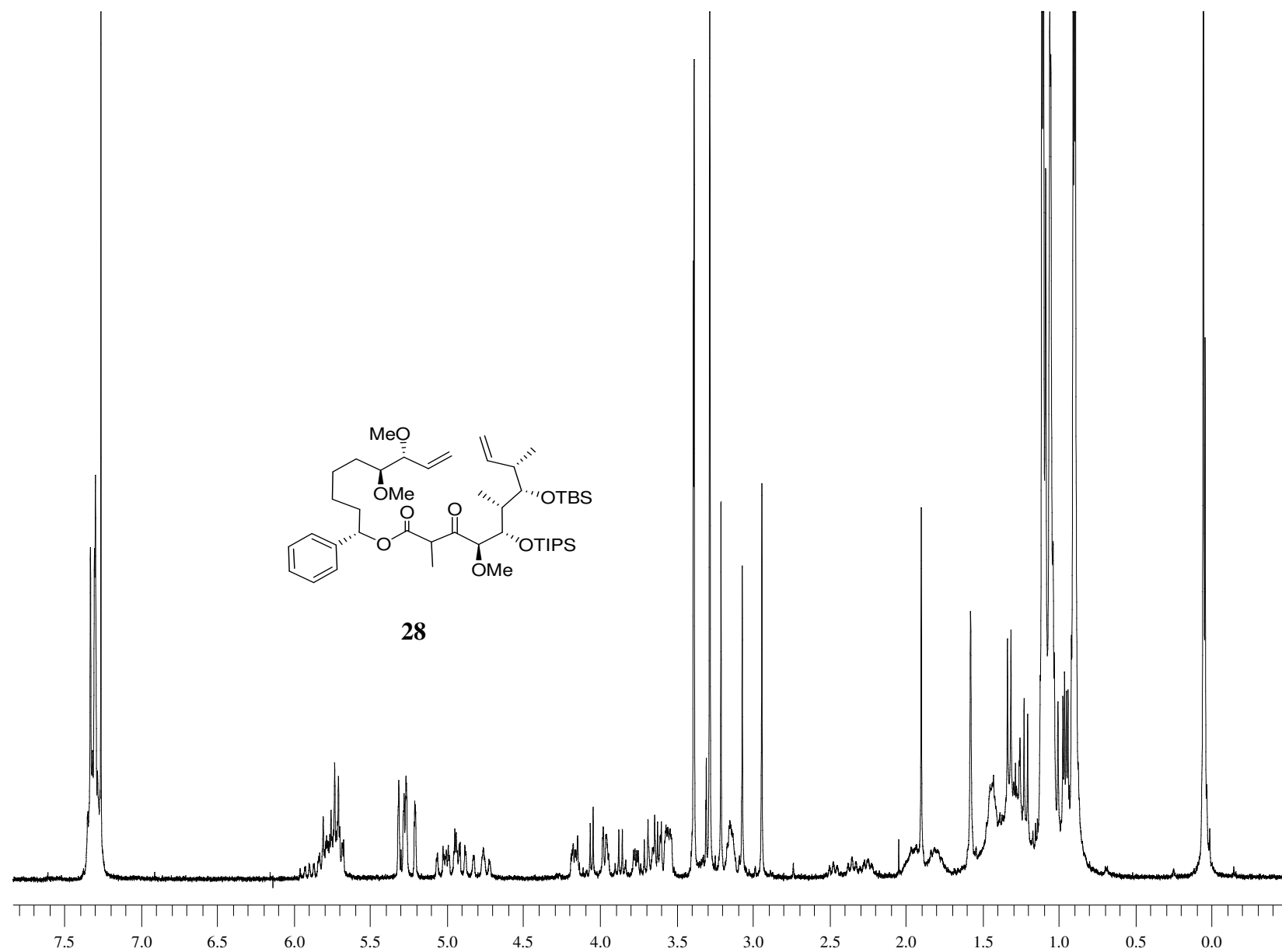


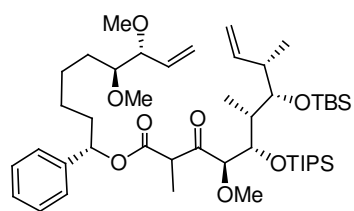
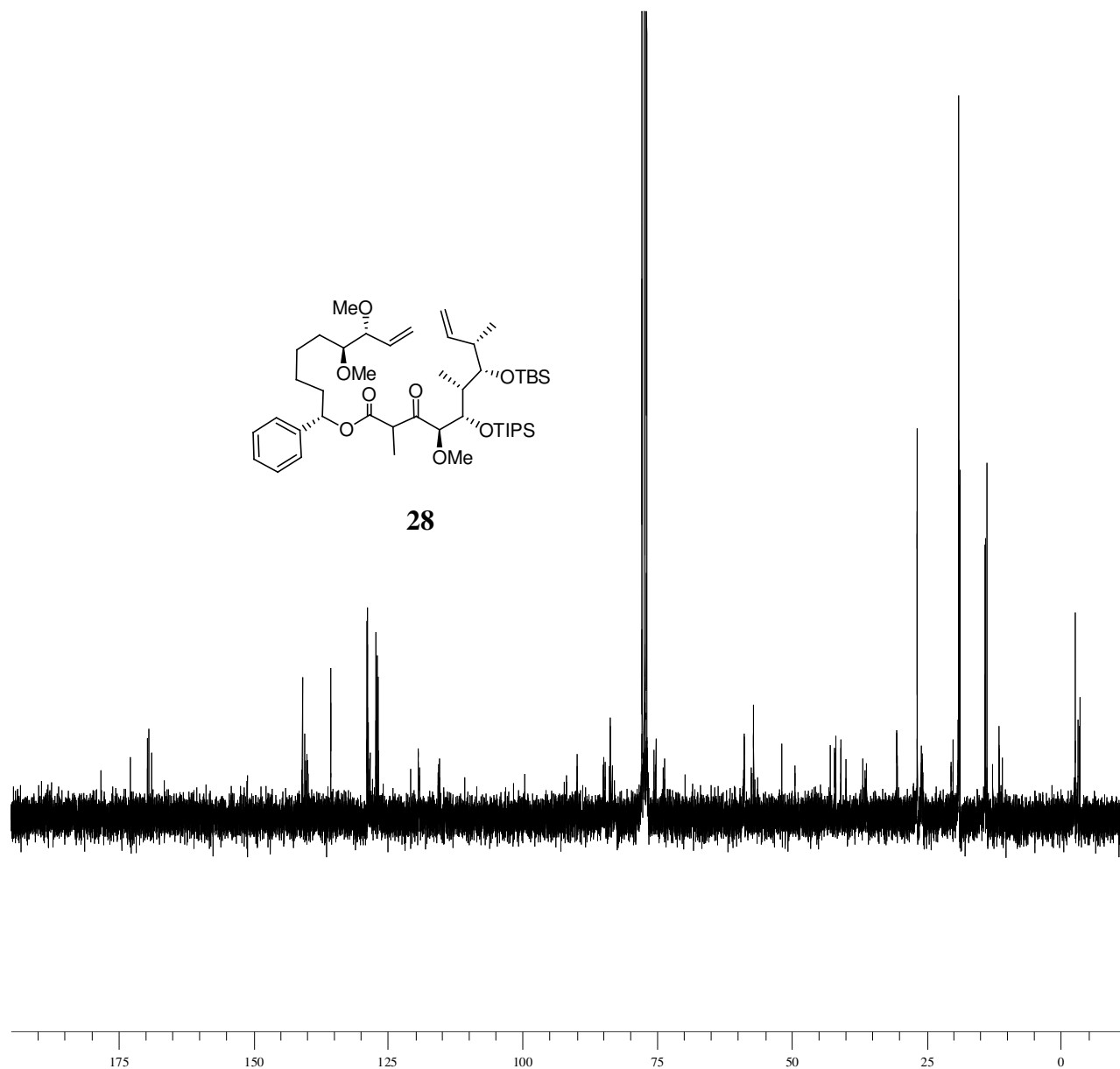




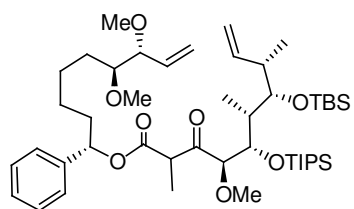






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