Supporting Information for:

Towards the Total Synthesis of Marineosin A: Construction of the Macrocyclic Pyrrole and an Advanced, Functionalized Spiroaminal Model

Leslie N. Aldrich, Cynthia B. Berry, Brittney S. Bates, Leah C. Konkol, Mirando So, and Craig W. Lindsley*

Departments of Chemistry and Pharmacology
Vanderbilt University, Nashville, TN 37232

Table of Contents:

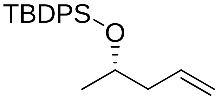
Methods and Materials:

All reagents and solvents were commercial grade and purified prior to use when necessary. Analytical thin layer chromatography (TLC) was performed on Sorbent Technologies HL 0.25 mm silica gel plates with UV indicator. Visualization was accomplished by irradiation under a 254 nm UV lamp and/or the use of an iodine chamber or potassium permanganate stain. Chromatography on silica gel was performed using Silica Gel 60 (230-400 mesh) from Sorbent Technologies.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 (400 and 100 MHz, respectively) NMR instrument. Chemical shifts are reported in ppm from the solvent resonance as an internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, bs = broad singlet), coupling constant (Hz), and number of protons.

Optical rotations were measured on a JASCO P-2000 digital polarimeter at room temperature. Concentration (c) in g/100 mL and solvent are given in parentheses.

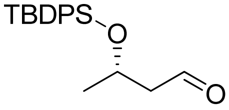
A Micromass Q-Tof API-US mass spectrometer was used to acquire high resolution mass spectrometry (HRMS) data. The value Δ is the error in the measurement (in ppm) given by the equation $\Delta = [(ME - MT)/ MT] \times 106$, where ME is the experimental mass and MT is the theoretical mass. The HRMS results were obtained with ES as the ion source and leucine enkephalin as the reference.



10

(*S*)-*tert*-butyl(pent-4-en-2-yloxy)diphenylsilane (10). Cuprous iodide (1.64 g, 8.61 mmol) was suspended in anhydrous tetrahydrofuran (17.5 mL) the resulting solution was cooled to -20 °C with vigorous stirring. Vinylmagnesium bromide (1.0 M in THF, 100 mL) was cannulated under a positive stream of argon into the stirring cuprous iodide over 20 min. The resulting black solution was stirred for 30 min before a solution of (*S*)-propylene oxide **9** (3.02 g, 43.04 mmol) in anhydrous tetrahydrofuran (5.5 mL) was added dropwise. The reaction mixture was stirred for 20 h at -20 °C. At this time, the reaction was quenched by slow addition of saturated aqueous ammonium chloride and warmed to room temperature. The mixture was extracted with diethyl ether, dried over sodium sulfate, and filtered through celite. The organic layer was carefully concentrated under reduced pressure to avoid evaporation of the volatile homoallylic alcohol. The remaining solvent was removed by gently blowing air across the surface of the crude reaction mixture. After 20 min, the remaining yellow oil was carried on to the next step without further purification. The crude homoallylic alcohol was suspended in dichloromethane (108 mL) and to this imidazole (5.86 g, 86.1 mmol) was added followed by *tert*-butyldiphenylchlorosilane (16.5 mL, 64.6 mmol) at room temperature. The reaction was stirred for 2 h at room temperature and quenched by the addition of water when complete. The mixture was extracted with dichloromethane, dried over sodium sulfate, and concentrated *in vacuo* to give a thick, yellow oil. The crude oil was purified by chromatography (0-10% ethyl acetate in hexanes) and condensed under reduced pressure to give silyl ether **10** as a clear yellow oil (11.3 g, 81% over 2 steps).

^{1}H NMR (CDCl$_3$, 400 MHz) δ (ppm): 1.14 (s, 9H), 1.145 (d, *J* = 3.0 Hz, 3H), 2.22-2.33 (m, 2H), 3.98 (sext, *J* = 6.0 Hz, 1H), 5.01-5.06 (m, 2H), 5.84 (dddd, *J* = 17.0, 11.2, 10.4, 7.6 Hz, 1H), 7.41-7.49 (m, 6H), 7.75-7.78 (m, 4H). **^{13}C NMR** (CDCl$_3$, 100 MHz) δ (ppm): 19.4, 23.0, 27.2, 44.1, 69.3, 116.9, 127.6, 127.6, 129.6, 129.6, 134.6, 134.9, 135.2, 136.0, 136.0. **HRMS**: $C_{21}H_{28}ONaSi$, Calculated $[M+Na]^+$: 347.1807, Found $[M+Na]^+$: 347.1804. $[\alpha]_D^{20}$ = -15.7 (c = 1.0, CHCl$_3$).

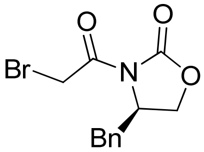


11

(S)-3-((*tert*-butyldiphenylsilyl)oxy)butanal (11). Olefin **10** (8.15 g, 25.1 mmol) was suspended in dichloromethane (251 mL) and cooled to -78 °C. Ozone was bubbled in until the solution turned blue (about 45 min). Triphenylphosphine (7.90 g, 30.1 mmol) was then added and the flask was purged with argon. This was stirred at room temperature under an atmosphere of argon for 1 h. The solution was then concentrated under vacuum and purified by column chromatography (0-5% ethyl acetate in hexanes) to give colorless oil **11** (6.90 g, 84%).

^{1}H NMR (CDCl$_3$, 400 MHz) δ (ppm): 1.12 (s, 9H), 1.24 (d, *J* = 6.4 Hz, 3H), 2.53-2.65 (m, 2H), 4.43 (sext, *J* = 6.0 Hz, 2H), 7.42-7.48 (m, 6H), 7.75 (dd, *J* = 8.0, 1.6 Hz, 4H), 9.79 (t, *J* = 6.4, 1H). **^{13}C NMR** (CDCl$_3$, 100 MHz) δ (ppm): 19.1, 23.8, 26.9, 52.7, 65.6, 127.6, 127.7, 129.7, 129.8, 133.5, 134.0, 135.8, 201.7. **HRMS**: $C_{20}H_{26}O_2NaSi$, Calculated $[M+Na]^+$: 349.1600, Found $[M+Na]^+$: 349.1601.

Spectral data matches that recorded in S. Barluenga, E. Moulin, P. Lopez, and N. Winssinger, *Chem. Eur. J.* **2005**, *11*, 4935-4952.

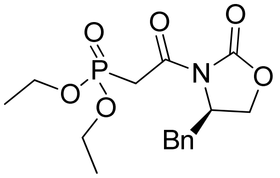


13

(R)-4-benzyl-3-(2-bromoacetyl)oxazolidin-2-one (13). (R)-4-benzyl-2-oxazolidinone **12** (12.5 g, 70.5 mmol) was dissolved in anhydrous tetrahydrofuran (282 mL) and cooled to -78 °C before adding *n*-butyl lithium (2.5 M in hexanes, 71.9 mmol) dropwise. This solution was stirred for 10 min at -78 °C. Bromoacetyl bromide (6.27 mL, 71.9 mmol) was added neat and this solution was stirred for 10 min at -78 °C then 1.5 h at room temperature. When the reaction was complete by TLC, it was quenched with saturated aqueous ammonium chloride, extracted with ethyl acetate, dried over sodium sulfate, and condensed *in vacuo*. The resulting oil was purified by column chromatography (0-50% ethyl acetate in hexanes) to give the product as a yellow oil (18.6 g, 88%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 2.81 (dd, *J* = 13.2, 9.6 Hz, 1H), 3.33 (dd, *J* = 13.6, 3.2 Hz, 1H), 4.21-4.30 (m, 2H), 4.54 (d, *J* = 3.2 Hz, 2H), 4.67-4.73 (m, 1H), 7.20-7.37 (m, 5H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 28.2, 37.4, 55.4, 66.6, 127.5, 129.0, 129.4, 134.7, 152.9, 165.9. **HRMS**: $C_{12}H_{13}NO_3Br$, Calculated $[M+H]^+$: 298.0079, Found $[M+H]^+$: 298.0081. $[\alpha]_D^{20}$ = -34.5 (c = 0.5, $CHCl_3$).

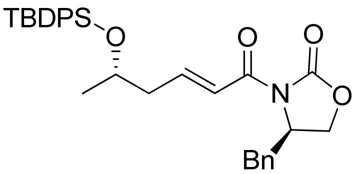
Spectral data matches that reported in D.A. Evans and A.E. Weber, *J. Am. Chem. Soc.* **1987**, *109*, 7151-7157.



7

(R)-diethyl (2-(4-benzyl-2-oxooxazolidin-3-yl)-2-oxoethyl)phosphonate (7). Acyloxazolidinone **13** (1.49 g, 5.00 mmol) was suspended neat in triethylphosphite (1.74 mL, 10.0 mmol). A reflux condenser was attached to the flask and the solution was heated at 100 °C for 2 h. This solution was loaded directly onto a column for chromatography (0-75% ethyl acetate in hexanes). This yielded the pure product as a yellow oil (1.45 g, 82%).

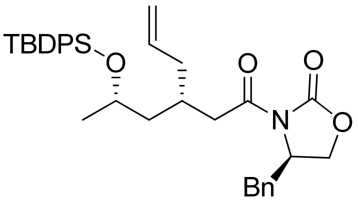
^{1}**H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 1.35 (t, *J* = 7.2, 6H), 2.75 (dd, *J* = 13.2, 10 Hz, 1H), 3.35 (dd, *J* = 13.2, 3.2 Hz, 1H), 3.80 (dq, *J* = 30.8, 19.7 Hz, 2H), 4.10-4.24 (m, 6H), 4.68-4.74 (m, 1H), 7.21-7.35 (m, 5H). ^{13}**C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 16.2, 16.3, 33.6, 34.9, 37.6, 55.4, 62.7, 65.9, 127.3, 128.9, 129.4, 135.0, 153.3, 165.0. **HRMS**: $C_{16}H_{23}NO_6P$, Calculated $[M+H]^+$: 356.1263, Found $[M+H]^+$: 356.1264. $[\alpha]_D^{20}$ = -35.3 (c = 1.0, $CHCl_3$).



14

(R)-4-benzyl-3-((S,E)-5-((tert-butyldiphenylsilyl)oxy)hex-2-enoyl)oxazolidin-2-one (14). Phosphonate **7** (10.8 g, 30.4 mmol) was suspended in anhydrous tetrahydrofuran (204 mL) and cooled to 0 °C. Sodium hydride (60% dispersion in mineral oil, 29.2 mmol) was added and the resulting solution was stirred for 15 min at 0 °C then 45 min at room temperature. This solution was cooled to -78 °C before adding aldehyde **11** (7.95 g, 24.3 mmol) in anhydrous tetrahydrofuran (98.0 mL). This was stirred at -78 °C for 10 min then allowed to warm to 0 °C. At 2 h, the reaction was complete by TLC and the solution was quenched with pH 7 phosphate buffer, extracted with ethyl acetate, dried over sodium sulfate, and concentrated *in vacuo*. The resulting oil was purified by column chromatography (0-25% ethyl acetate in hexanes; 100% ethyl acetate to recover excess phosphonate **7**) to give the pale yellow oil of acyloxazolidinone 1**4** (9.60 g, 75%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.07 (s, 9H), 1.13 (d, *J* = 6.2 Hz, 3H), 2.43 (q, *J* = 5.6 Hz, 2H), 2.78 (dd, *J* = 13.0, 9.6 Hz, 1H), 3.33 (dd, *J* = 13.5, 3.2 Hz, 1H), 4.03 (sext, *J* = 5.9 Hz, 1H), 4.19-4.23 (m, 2H), 4.73 (ddd, *J* = 13.2, 7.2, 3.4 Hz, 1H), 7.19-7.43 (m, 14 H), 7.68-7.70 (m, 4H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 19.4, 23.4, 26.5, 27.1, 38.0, 42.7, 55.4, 66.2, 68.7, 122.5, 127.4, 127.7, 127.8, 129.1, 129.6, 129.7, 129.8, 134.1, 134.5, 135.5, 136.0, 136.0, 148.2, 153.5, 164.8. **HRMS**: $C_{32}H_{37}NO_4NaSi$, Calculated $[M+Na]^+$: 550.2390, Found $[M+Na]^+$: 550.2393. $[\alpha]_D^{20}$ = -52.8 (c = 1.0, $CHCl_3$).

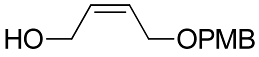


15

(*R*)-4-benzyl-3-((*S*)-3-((*S*)-2-((*tert*-butyldiphenylsilyl)oxy)propyl)hex-5-enoyl) oxazolidin-2-one (15). Recrystallized CuBr-S$(CH_3)_2$ complex (23.3 g, 113 mmol) (Procedure for recrystalization: 50 g CuBr-S$(CH_3)_2$ was dissolved in 250 mL dimethyl sulfide at 50 °C before dripping in 1 L hexanes and filtering off solvent) was suspended in dimethyl sulfide and tetrahydrofuran (1:2 v/v, 226 mL) and cooled to -78 ^{o}C. This solution was cannulated into a -78

^{o}C solution of allylmagnesium bromide (1.0 M in diethyl ether, 90.6 mmol). The resulting thick, black solution was vigorously stirred for 1 h at -78 ^{o}C and then acyloxazolidinone **14** (11.9 g, 22.6 mmol) in anhydrous tetrahydrofuran (75 mL) was slowly added over 20 min. The reaction mixture was stirred for an additional 1.5 h at -78 ^{o}C and then quenched with saturated aqueous ammonium chloride and warmed to room temperature. The black mixture was extracted with diethyl ether, dried over sodium sulfate, the solvent volume reduced to approximately 200 mL by rotary evaporation, and the resulting solid/oil mixture filtered through a celite plug with liberal diethyl ether washes. The solution was condensed *in vacuo* to give a turquoise oil that was purified by column chromatography (0-20% ethyl acetate in hexanes) to provide the desired conjugate addition adduct **15** as a clear, colorless oil (10.4 g, 81%) and a single diastereomer by ^{1}H NMR (>20:1).

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.05 (s, 9H), 1.12 (d, *J* = 6.1 Hz, 3H), 1.41 (quin, *J* = 7.0 Hz, 1H), 1.60 (quin, *J* = 7.0 Hz, 1H), 1.91-2.03 (m, 2H), 2.22 (quin, *J* = 6.1 Hz, 1H), 2.63 (dd, *J* = 17.9, 5.8 Hz, 1H), 2.68 (dd, *J* = 13.0, 10.0 Hz, 1H), 2.87 (dd, *J* = 17.9, 7.2 Hz, 1H), 3.28 (dd, *J* = 13.4, 3.3 Hz, 1H), 3.92 (sext, *J* = 6.2 Hz, 1H), 4.10-4.20 (m, 3H), 4.65 (ddd, *J* = 13.4, 6.9, 3.2 Hz, 1H), 4.92-4.91 (m, 2H), 5.62 (dddd, *J* = 16.7, 10.2, 9.0, 7.2 Hz, 1H), 7.20-7.43 (m, 11H), 7.66-7.70 (m, 4H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 19.3, 23.6, 26.5, 27.2, 30.4, 38.1, 38.4, 39.5, 43.8, 55.3, 66.2, 67.7, 77.4, 116.9, 127.5, 127.6, 127.7, 129.0, 129.1, 129.6, 129.6, 134.4, 134.9, 135.5, 136.1, 136.1, 136.3, 153.5, 172.5. **HRMS**: $C_{35}H_{43}NO_4NaSi$, Calculated $[M+Na]^+$: 592.2859, Found $[M+Na]^+$: 592.2854. $[\alpha]_D^{20}$ = -41.0 (c = 0.5, $CHCl_3$).

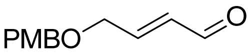


17

(*Z*)-4-((4-methoxybenzyl)oxy)but-2-en-1-ol (17). Sodium hydride (4.77 g, 119 mmol, 60% dispersion in mineral oil) was suspended in anhydrous tetrahydrofuran (227 mL). The solution was cooled to 0 °C and 1,4-*cis*-buten-1-ol **16** (10.0 g, 114 mmol) was added dropwise. The resulting mixture was stirred for 30 min at 0 °C at which time *p*-methoxybenzyl chloride (16.9 mL, 125 mmol) was added dropwise followed by addition of *tert*-butyl ammonium iodide (4.19 g, 11.4 mmol). The mixture was warmed to room temperature and stirred for 12 h. The reaction was quenched by dropwise addition of saturated aqueous ammonium chloride solution. The resulting mixture was extracted with ethyl acetate, dried over sodium sulfate, and concentrated under reduced pressure. The oil was purified by column chromatography (0-60% ethyl acetate in hexanes) to give PMB ether **17** (13.8 g, 68%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 3.80 (s, 3H), 4.05 (d, *J* = 6.0 Hz, 2H), 4.15 (d, *J* = 6.3 Hz, 2H), 4.45 (s, 2H), 5.76 (dm, *J* = 35.0 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 8.5, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 55.2, 58.6, 65.3, 72.0, 113.8, 128.2, 129.4, 129.9, 132.3, 159.2. **HRMS**: $C_{12}H_{16}O_3Na$, Calculated $[M+Na]^+$: 231.0997, Found $[M+Na]^+$: 231.0995.

Spectral data matches that reported in D. Könning, W. Hiller, and M. Christmann, *Org. Lett.* **2012**, *14*, 5258-5261.

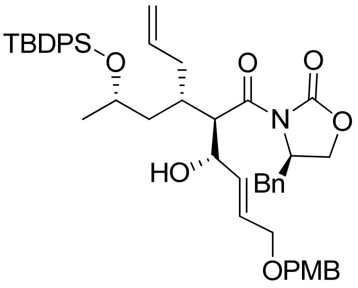


18

(*E*)-4-((4-methoxybenzyl)oxy)but-2-enal (18). PMB ether **17** (13.8 g, 76.7 mmol) was suspended in dichloromethane (153 mL). Manganese dioxide (80.0 g, 920 mmol) was added and the resulting heterogeneous mixture was vigorously stirred for 48 h at room temperature. The mixture was filtered through celite and condensed *in vacuo* to give a pale yellow oil. The oil was purified by column chromatography (0-40% ethyl acetate in hexanes) to provide aldehyde **18** as a clear, colorless oil (5.00 g, 36%).

^{1}H NMR (CDCl$_3$, 400 MHz) δ (ppm): 3.83 (s, 3H), 4.28 (dd, *J* = 4.1, 1.9 Hz, 2H), 4.54 (s, 2H), 6.41 (ddt, *J* = 15.9, 8.0, 1.9 Hz, 1H), 6.86 (dt, *J* = 15.9, 4.1 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 9.60 (d, *J* = 7.7 Hz, 1H). **^{13}C NMR** (CDCl$_3$, 100 MHz) δ (ppm): 55.4, 68.4, 72.8, 114.1, 129.5, 129.6, 131.9, 153.4, 159.6, 193.5. **HRMS**: $C_{12}H_{14}O_3Na$, Calculated [M+Na]$^+$: 229.0841, Found [M+Na]$^+$: 229.0841.

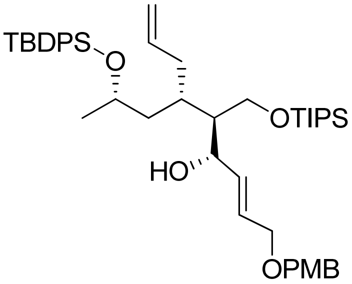
Spectral data matches that reported in D. Könning, W. Hiller, and M. Christmann, *Org. Lett.* **2012**, *14*, 5258-5261.



19

(*R*)-4-benzyl-3-((2*R*,3*S*,*E*)-2-((4*S*,6*S*)-6-((*tert*-butyldiphenylsilyl)oxy)hept-1-en-4-yl)-3-hydroxy-6-((4-methoxybenzyl)oxy)hex-4-enoyl)oxazolidin-2-one (19). Acyloxazolidinone **15** (8.81 g, 15.5 mmol) was suspended in anhydrous dichloromethane (154 mL) and cooled to 0 °C. Titanium tetrachloride (1.78 mL, 16.2 mmol) was added dropwise and the resulting yellow solution was stirred for 15 min. At 0 °C, diisopropylethylamine (2.96 mL, 17.0 mmol) was slowly added and the dark red mixture was stirred for 40 min while maintaining the temperature at 0 °C. N-methylpyrrolidinone (1.49 mL, 15.5 mmol) was added dropwise and the solution stirred for 10 min. Aldehyde **18** (3.35 g, 16.2 mmol) in anhydrous dichloromethane (65.0 mL) was added dropwise at 0 °C. After addition was complete, the solution was stirred for 1.5 h at 0 °C, quenched with saturated aqueous ammonium chloride, and warmed to room temperature. The dark orange solution was extracted with dichloromethane and filtered through a celite plug. The solvent was removed under reduced pressure at room temperature, and the resulting orange oil was purified by column chromatography (0-45% ethyl acetate in hexanes) to provide the *syn* aldol adduct **7** (5.24 g, 65% brsm, 10:1 dr).

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.05 (s, 9H), 1.07 (d, *J* = 6.0 Hz, 3H), 1.49-1.56 (m, 1H), 1.61-1.67 (m, 1H), 1.80-1.86 (m, 2H), 2.01-2.09 (m, 1H), 2.11-2.18 (m, 1H), 2.48 (dd, *J* = 13.0, 10.7 Hz, 1H), 3.30 (dd, *J* = 13.2, 3.2 Hz 1H), 3.79 (s, 3H), 3.97-4.04 (m, 5H), 4.27 (t, *J* = 7.5 Hz, 1H), 4.43 (s, 3H), 4.46-4.50 (m, 1H), 4.60-4.66 (m, 1H), 4.83 (d, *J* = 17.1 Hz, 1H), 4.90 (d, *J* = 10.0 Hz, 1H), 5.55 (dddd, *J* = 16.8, 9.9, 7.2, 5.0 Hz, 1H), 5.81-5.83 (m, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 7.17-7.43 (m, 14H), 7.66-7.71 (m, 4H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 19.3, 23.1, 27.1, 34.7, 35.2, 38.4, 40.9, 50.6, 55.4, 55.7, 66.0, 67.6, 69.8, 72.0, 113.9, 117.1, 127.4, 127.6, 127.7, 129.1, 129.4, 129.5, 129.6, 129.7, 130.2, 130.4, 131.9, 134.5, 134.8, 135.5, 136.05, 153.8, 159.3, 173.4. **HRMS**: $C_{47}H_{58}NO_7Si$ Calculated $[M+H]^+$: 776.3983, Found $[M+H]^+$: 776.3982. $[\alpha]_D^{20}$ = -22.1 (c = 1.2, $CHCl_3$).

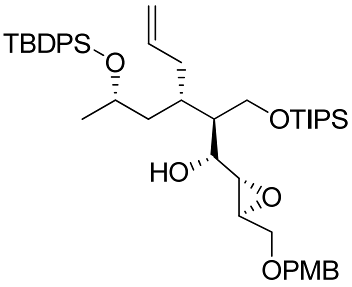


20

(4*S*,5*S*,6*S*,*E*)-6-((*S*)-2-((*tert*-butyldiphenylsilyl)oxy)propyl)-1-((4-methoxybenzyl)oxy-

5(((triisopropylsilyl)oxy)methyl)nona-2,8-dien-4-ol (20). Aldol adduct **19** (6.11 g, 7.87 mmol) was suspended in anhydrous tetrahydrofuran (78.7 mL) and cooled to 0 °C. Anhydrous methanol (1.28 mL, 31.4 mmol) was added followed by lithium borohydride slowly (15.7 mL, 2.0 M in tetrahydrofuran), and the reaction was stirred for 6 h until complete by TLC. Water was added dropwise to quench and the solution was extracted with ethyl acetate, dried over sodium sulfate, condensed *in vacuo*, and purified by column chromatography (0-50% ethyl acetate in hexanes) to give diol product as a clear, colorless oil (2.09 g, 44%). This diol (3.34 g, 5.54 mmol) was suspended in anhydrous dichloromethane (55.0 mL) and imidazole (1.88 g, 27.7 mmol) was added followed by dropwise addition of chlorodiisopropylsilane (2.37 mL, 11.1 mmol) at room temperature. After 1 h, an additional 27.7 mmol of imidazole and 11.1 mmol of chlorodiisopropylsilane were added. After 1 h, 1.15 mL of chlorodiisopropylsilane was added and the solution was stirred for an additional 1 h and quenched by addition of water after the reaction was determined to be complete by TLC. The mixture was extracted with dichloromethane, dried over sodium sulfate, condensed *in vacuo*, and purified by column chromatography (0-30% ethyl acetate in hexanes) to give triisopropylsilyl ether **20** as clear, colorless oil (3.47 g, 82%).

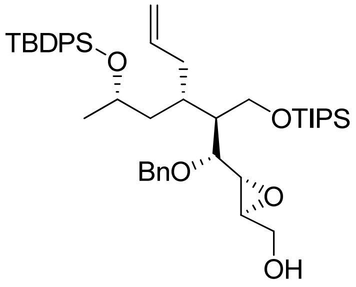
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.04 (s, 33H), 1.44-1.49 (m, 1H), 1.55-1.63 (m, 1H), 1.71 (quin, *J* = 7.2 Hz, 1H), 1.87-1.93 (m, 1H), 2.03-2.09 (m, 1H), 3.45 (d, *J* = 7.2 Hz, 1H), 3.76 (d, *J* = 6.8 Hz, 2H), 3.80 (s, 3H), 3.90 (sext, *J* = 6.2 Hz, 1H), 4.00 (d, *J* = 3.0 Hz, 2H), 4.25-4.29 (m, 1H), 4.45 (s, 2H), 4.84-4.91 (m, 2H), 5.49 (dddd, *J* = 16.9, 9.8, 7.2, 7.0 Hz, 1H), 5.84-5.85 (m, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 7.26 (d, *J* = 8.6 Hz, 2H), 7.34-7.43 (m, 6H), 7.66-7.69 (m, 4H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 11.9, 18.1, 19.3, 23.4, 27.2, 33.3, 35.1, 41.9, 47.5, 55.4, 63.4, 68.2, 70.1, 71.8, 73.9, 113.9, 116.4, 127.6, 127.7, 128.5, 129.4, 129.6, 129.7, 130.6, 133.35, 134.5, 134.9, 136.0, 136.7, 159.3. **HRMS**: $C_{46}H_{71}O_5Si_2$, Calculated $[M+H]^+$: 759.4840, Found $[M+H]^+$: 759.4836. $[\alpha]_D^{20}$ = -16.2 (c = 1.0, $CHCl_3$).



21

(1*R*,2*S*,3*S*)-3-((*S*)-2-((*tert*-butyldiphenylsilyl)oxy)propyl)-1-((2*S*,3*S*)-3-(((4-methoxybenzyl)oxy)methyl) oxiran-2-yl)-2-(((triisopropylsilyl)oxy)methyl)hex-5-en-1-ol (21). Triisopropylsilyl ether **20** (1.89 g, 2.45 mmol) was suspended in anhydrous dichloromethane (10.0 mL) and the solution was cooled to 0 °C. Vanadyl acetylacetonate (31.0 mg, 0.123 mmol) was added followed by dropwise addition of *tert*-butyl hydrogen peroxide (1.34 mL, ~5.5 M in decane). The resulting dark red solution was stirred at 0 °C for 4 h and an additional 5 mol% vanadyl acetylacetonate was added. Once the reaction had proceeded to completion the crude reaction mixture was transferred directly to a silica column that had been equilibrated with 1% triethylamine in hexanes and was purified using 0-25% ethyl acetate in hexanes to give oxirane **21** as a clear, colorless oil and a single diastereomer by ^{1}H NMR (1.79 g, 94%).

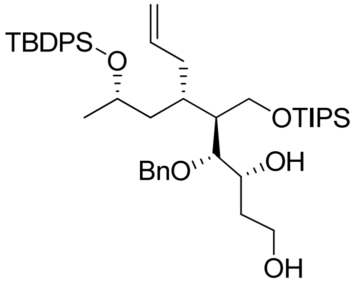
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.03 (s, 33H), 1.46 (quin, *J* = 6.4 Hz, 1H), 1.64 (quin, 7.2 Hz, 1H), 1.72 (quin, *J* = 7.2 Hz, 1H), 1.86-1.89 (m, 2H), 2.13-2.18 (m, 1H), 2.85 (d, *J* = 4.7 Hz, 1H), 3.08 (dd, *J* = 4.4, 2.3 Hz, 1H), 3.20 (dt, *J* = 6.1, 2.2 Hz, 1H), 3.38 (dd, *J* = 11.6, 6.2 Hz, 1H), 3.76-3.86 (m, 4H), 3.80 (s, 3H), 3.92 (sext, *J* = 6.4 Hz, 1H), 4.50 (dd, *J* = 25.6, 11.6 Hz, 2H), 4.86-4.90 (m, 2H), 5.53 (dddd, *J* = 19.6, 9.8, 9.2, 7.4 Hz, 1H), 6.88 (d, *J* = 8.6 Hz, 2H), 7.27 (d, *J* = 8.6 Hz, 2H), 7.33-7.43 (m, 6H), 7.67-7.69 (m, 4H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 11.9, 18.1, 19.3, 23.3, 27.2, 32.9, 35.4, 42.1, 47.0, 54.5, 55.4, 56.5, 62.7, 68.3, 69.9, 70.6, 73.0, 113.9, 116.2, 127.5, 127.6, 129.5, 129.6, 130.1, 134.5, 134.9, 136.0, 137.3, 159.4. **HRMS**: $C_{46}H_{71}O_6Si_2$, Calculated $[M+H]^+$: 775.4789, Found $[M+H]^+$: 775.4785. $[\alpha]_D^{20}$ = -8.9 (c = 1.0, $CHCl_3$).



22

((2*S*,3*S*)-3-((1*R*,2*S*,3*S*)-1-(benzyloxy)-3-((*S*)-2-((*tert*-butyldiphenylsilyl)oxy)propyl)-2-(((triisopropylsilyl) oxy)methyl)hex-5-en-1-yl)oxiran-2-yl)methanol (22). Sodium hydride (60% dispersion in mineral oil, 361 mg, 9.03 mmol) was suspended in anhydrous tetrahydrofuran (45.0 mL) and the solution was cooled to 0 °C. A solution of oxirane **21** (3.50 g, 4.52 mmol) in tetrahydrafuran (15.0 mL) was slowly added to the sodium hydride solution, followed by immediate addition of benzyl bromide (2.14 mL, 18.1 mmol) and *tert*-butylammonium iodide (333 mg, 0.903 mmol). The solution was warmed to room temperature and stirred for 2 h. An additional 361 mg sodium hydride and 2.14 mL benzyl bromide were added at room temperature. The reaction was stirred 2 h until confirmed to be finished by LCMS. The reaction was quenched by the addition of saturated aqueous ammonium chloride, extracted with ethyl acetate, dried over sodium sulfate, and condensed *in vacuo* to give a yellow oil that was purified by column chromatography (0-15% ethyl acetate in hexanes) to provide the benzyl ether as a clear, colorless oil (3.10 g, 79%). This benzyl ether (1.90 g, 2.20 mmol) was suspended in a mixture of dichloromethane and pH 7 phosphate buffer (7:1 v/v, 44 mL). The solution was cooled to 0 °C and 2,3-dichloro-5,6-dicyanobenzoquinone (598 mg, 2.64 mmol) was added. The resulting biphasic solution was vigorously stirred for 12 h at 0 °C. The reaction was quenched by addition of saturated aqueous sodium bicarbonate, extracted with dichloromethane, dried over sodium sulfate, and condensed *in vacuo* to provide a yellow residue that was purified by column chromatography (0-20% ethyl acetate in hexanes) to provide alcohol **22** as a clear, colorless oil (1.19 g, 73%).

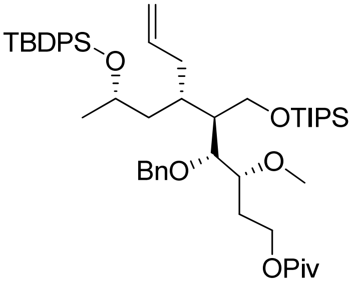
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.02-1.05 (m, 33H), 1.44-1.53 (m, 2H), 1.62-1.67 (m, 1H), 1.68-1.75 (m, 1H), 1.84-1.91 (m, 1H), 1.94-2.01 (m, 1H), 2.21-2.27 (m, 1H), 3.05 (dd, *J* = 4.88, 2.2 Hz, 1H), 3.11 (quin, *J* = 2.3 Hz, 1H), 3.44 (ddd, *J* = 12.7, 7.4, 5.0 Hz, 1H), 3.63 (t, *J* = 5.1 Hz, 1H), 3.68-3.82 (m, 3H), 3.95 (sext, *J* = 6.2 Hz, 1H), 4.52 (dd, *J* = 55.6, 11.8 Hz, 2H), 4.83-4.87 (m, 2H), 5.54 (dddd, *J* = 15.3, 10.2, 7.2, 6.2 Hz, 1H), 7.25-7.42 (m, 11H), 7.68 (d, *J* = 7.2 Hz, 4H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 12.1, 18.2, 19.3, 23.5, 27.1, 32.9, 35.9, 42.8, 47.5, 56.7, 56.8, 60.7, 61.8, 68.6, 73.8, 77.4, 115.7, 127.5, 127.6, 127.6, 128.4, 129.6, 129.6, 134.8, 135.0, 136.0, 138.3, 139.1. **HRMS**: $C_{45}H_{69}O_5Si_2$, Calculated $[M+H]^+$: 745.4684, Found $[M+H]^+$: 745.4681. $[\alpha]_D^{20}$ = -6.5 (c = 0.5, $CHCl_3$).



23

(3*R*,4*R*,5*S*,6*S*)-4-(benzyloxy)-6-((*S*)-2-((*tert*-butyldiphenylsilyl)oxy)propyl)-5-(((triisopropylsilyl)oxy) methyl)non-8-ene-1,3-diol (23). Alcohol **22** (1.74 g, 2.34 mmol) was suspended in anhydrous tetrahydrofuran (156 mL) and cooled to 0 °C. Sodium bis(2-methoxyethoxy)aluminum hydride (65 wt% in toluene, 4.35 mL, 14.0 mmol) was added dropwise and the resulting solution was warmed to room temperature and stirred for 5 h, until the reaction neared completion and the undesired free primary alcohol resulting from TIPS deprotection began to form. At this time, saturated sodium potassium tartrate solution was added dropwise and the resulting cloudy emulsion was diluted with 50 mL of ethyl acetate and stirred for 30 min until the organic layer became clear. The product was extracted with ethyl acetate, dried over sodium sulfate, and condensed *in vacuo* to give a thick, clear oil. This oil was purified by column chromatography (0-30% ethyl acetate in hexanes) to provide the desired 1,3-diol **23** (1.10 g, 79% based on recovered starting material) as the only product (^{1}H NMR >20:1 1,3 diol:1,2 diol).

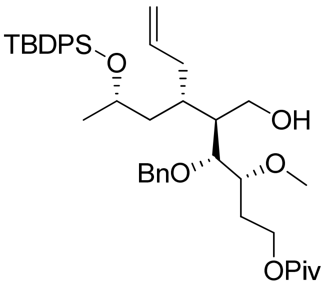
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.04-1.09 (m, 33H), 1.49-1.56 (m, 1H), 1.60-1.67 (m, 1H), 1.74-1.82 (m, 3H), 1.89-1.95 (m, 1H), 2.04-2.12 (m, 1H), 2.16-2.21 (m, 1H), 2.94 (bs, 1H), 3.51 (t, *J* = 6.0 Hz, 1H), 3.74-3.89 (m, 5H), 3.95-4.02 (m, 2H), 4.52 (s, 2H), 4.83-4.87 (m, 2H), 5.37-5.47 (m, 1H), 7.26-7.44 (m, 11H), 7.68-7.71 (m, 4H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 12.0, 18.1, 18.2, 19.3, 23.2, 27.1, 32.0, 34.8, 34.9, 42.3, 46.2, 60.9, 62.6, 68.7, 73.4, 74.6, 82.3, 116.5, 127.6, 127.6, 127.7, 127.8, 128.5, 129.6, 129.6, 134.7, 135.0, 136.0, 136.8, 138.5. **HRMS**: $C_{45}H_{71}O_5Si_2$, Calculated $[M+H]^+$: 747.4840, Found $[M+H]^+$: 747.4843. $[\alpha]_D^{20}$ = -20.0 (c = 1.0, $CHCl_3$).



6

(3*R*,4*R*,5*S*,6*S*)-4-(benzyloxy)-6-((*S*)-2-((*tert*-butyldiphenylsilyl)oxy)propyl)-3-methoxy-5-(((triisopropylsilyl)oxy)methyl)non-8-en-1-yl pivalate (6). Diol **23** (978 mg, 1.31 mmol) was suspended in anhydrous dichloromethane (65.4 mL). Pyridine was added (1.05 mL, 13.1 mmol) followed by addition of pivaloyl chloride (0.970 mL, 7.85 mmol) at room temperature, and the resulting solution was stirred for 2 h. The reaction was quenched by addition of saturated aqueous sodium bicarbonate, extracted with dichloromethane, dried over sodium sulfate, and condensed *in vacuo* to give a cloudy, white residue. This residue was purified by column chromatography (0-20% ethyl acetate in hexanes) to give the pivalate ester as a clear, colorless oil (850 mg, 78%). This pivalate ester (1.10 g, 1.41 mmol) was suspended in anhydrous dichloromethane (132 mL). To this 1,8-Bis(dimethylamino) naphthalene (1.70 g, 7.94 mmol) was added followed by addition of trimethyloxonium tetrafluoroborate (0.979 g, 6.62 mmol) at room temperature. The resulting solution was stirred at room temperature for 1.5 h until TLC indicated that the reaction was complete. The reaction was quenched by addition of saturated aqueous sodium bicarbonate, extracted with dichloromethane, dried over sodium sulfate, and condensed *in vacuo* to give a pale yellow residue. This residue was purified by flash chromatography (0-15% ethyl acetate in hexanes) to provide the desired methyl ether **6** as a clear, colorless oil (812 mg, 73%).

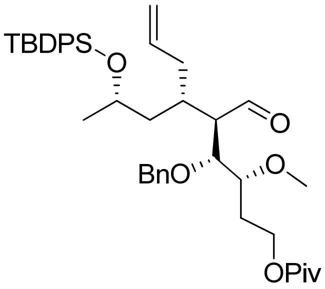
^{1}H NMR (CDCl$_3$, 400 MHz) δ (ppm): 1.00-1.07 (m, 33H), 1.19 (s, 9H), 1.45 (quin, *J* = 6.8 Hz, 1H), 1.61-1.74 (m, 3H), 1.82-1.94 (m, 1H), 1.95-2.05 (m, 1H), 2.07-2.13 (m, 1H), 2.14-2.21(m, 1H), 3.36 (s, 3H), 3.55 (d, *J* = 9.2 Hz, 1H), 3.60-3.68 (m, 2H), 3.80 (dd, *J* = 8.4, 1.7 Hz, 1H), 3.92 (sext, *J* = 6.1 Hz, 1H), 4.11-4.17 (m, 1H), 4.21-4.27 (m, 1H), 4.70 (dd, *J* = 143.5, 11.4 Hz, 2H), 4.78-4.82 (m, 2H), 5.42-5.52 (m, 1H) 7.22-7.41 (m, 11H), 7.65-7.67 (m, 4H). **^{13}C NMR** (CDCl$_3$, 100 MHz) δ (ppm): 12.1, 18.3, 19.3, 23.4, 27.1, 27.4, 28.9, 33.0, 35.8, 38.8, 43.1, 46.2, 57.5, 61.9, 62.5, 68.7, 74.0, 77.4, 78.4, 81.4, 115.4, 127.3, 127.5, 127.6, 127.8, 128.3, 129.5, 129.5, 134.7, 135.2, 136.0, 138.8, 139.2, 178.7. **HRMS**: $C_{51}H_{80}O_6NaSi_2$, Calculated [M+Na]$^+$: 867.5391, Found [M+Na]$^+$: 867.5389. $[\alpha]_D^{20}$ = -7.5 (c = 1.0, CHCl$_3$).



24

(3*R*,4*R*,5*S*,6*S*)-4-(benzyloxy)-6-((*S*)-2-((*tert*-butyldiphenylsilyl)oxy)propyl)-5-(hydroxymethyl)-3-methoxynon-8-en-1-yl pivalate (24). Methyl ether **6** (808 mg, 0.956 mmol) was suspended in anhydrous dichloromethane (95.6 mL). Boron trifluoride diethyl etherate (46.5%, 0.507 mL, 1.91 mmol) was added dropwise at room temperature and the resulting mixture was stirred for 30 min until TLC showed that the reaction had reached completion. The reaction was quenched by addition of saturated aqueous sodium bicarbonate, extracted with dichloromethane, dried over sodium sulfate, and condensed *in vacuo* to give a clear oil. This oil was purified by flash chromatography (0-30% ethyl acetate in hexanes) to give the free primary alcohol **24** as a clear, colorless oil (565 mg, 86%).

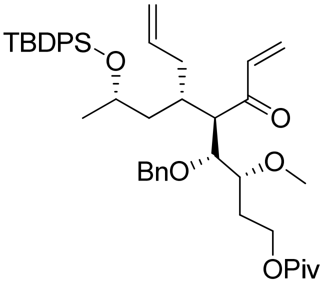
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.02 (s, 9H), 1.03 (d, J = 6.2 Hz, 3H), 1.20 (s, 9H), 1.46 (quin, J = 6.6 Hz, 1H), 1.61-1.71 (m, 2H), 1.77-1.83 (m, 1H), 1.85 (t, J = 5.3 Hz, 1H), 1.88-1.97 (m, 1H), 1.99-2.05 (m, 1H), 2.06-2.12 (m, 1H), 3.39 (s, 3H), 3.51-3.65 (m, 3H), 3.74 (dd, J = 8.3, 2.2 Hz, 1H), 3.93 (sext, J = 6.1 Hz, 1H), 4.20 (dd, J = 7.7, 5.5 Hz, 1H), 4.63 (dd, J = 115.4, 11.6 Hz, 2H), 4.84-4.87 (m, 2H), 5.40-5.50 (m, 1H), 7.25-7.42 (m, 11H), 7.65-7.68 (m, 4H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 19.3, 23.2, 27.2, 27.4, 29.6, 33.1, 35.5, 38.9, 42.3, 46.0, 58.0, 60.8, 62.0, 68.8, 73.7, 77.4, 79.0, 80.6, 116.1, 127.5, 127.6, 127.6, 128.0, 128.4, 129.6, 129.6, 134.6, 134.9, 136.0, 137.9, 138.7, 178.7. **HRMS**: $C_{42}H_{60}O_6NaSi$, Calculated $[M+Na]^+$: 711.4057, Found $[M+Na]^+$: 711.4055. $[\alpha]_D^{20}$ = -9.7 (c = 0.2, $CHCl_3$).



25

(3R,4R,5R,6S)-4-(benzyloxy)-6-((S)-2-((tert-butyldiphenylsilyl)oxy)propyl)-5-formyl-3-methoxynon-8-en-1-yl pivalate (25). Alcohol **24** (324 mg, 0.470 mmol) was suspended in dichloromethane/dimethylsulfoxide (4:1 v/v, 23.5 mL) and cooled to 0 °C. Triethylamine (0.660 mL, 4.70 mmol) was added followed by addition of sulfur trioxide pyridine complex (300 mg, 1.88 mmol). The resulting solution was allowed to warm to room temperature and stirred for 6 h. Additional portions of triethylamine (0.660 mL, 4.70 mmol) and sulfur trioxide pyridine complex (300 mg, 1.88 mmol) were added. The reaction was stirred for 10 h and then quenched by addition of water, extracted with dichloromethane, dried over sodium sulfate, and condensed *in vacuo* to give a pale yellow oil. This oil was purified by flash chromatography (0-15% ethyl acetate in hexanes) to provide aldehyde **25** as a clear, colorless oil (220 mg, 68%).

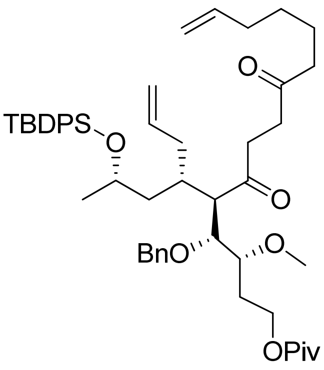
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.99 (s, 9H), 1.01 (d, *J* = 6.4 Hz, 3H), 1.18 (s, 9H), 1.50 (ddd, *J* = 14.4, 7.6, 5.6 Hz, 1H), 1.68-1.78 (m, 2H), 1.80-1.85 (m, 1H), 2.26 (dm, *J* = 14.0 Hz, 1H), 2.34-2.41 (m, 1H), 2.71 (dt, *J* = 9.8, 2.8 Hz, 1H), 3.19-3.23 (m, 1H), 3.36 (s, 3H), 3.99 (sext, *J* = 6.0 Hz, 1H), 4.11-4.20 (m, 3H), 4.66 (dd, *J* = 123.6, 11.6 Hz, 2H), 4.90-4.97 (m, 2H), 5.53 (ddt, *J* = 23.0, 9.8, 7.2 Hz, 1H), 7.27-7.41 (m, 6H), 7.64-7.67 (m, 4H), 9.62 (d, *J* = 2.4 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 19.3, 23.4, 27.2, 27.4, 29.4, 32.9, 35.6, 38.9, 41.4, 56.0, 58.0, 61.5, 68.1, 74.0, 75.5, 81.3, 117.1, 127.6, 127.7, 128.0, 128.5, 129.6, 129.8, 134.3, 134.9, 136.1, 136.1, 137.0, 138.4, 178.6, 202.9. **HRMS**: $C_{42}H_{58}O_6NaSi$, Calculated $[M+Na]^+$: 709.3900, Found $[M+Na]^+$: 709.3896. $[\alpha]_D^{20}$ = +3.7 (c = 0.4, $CHCl_3$).



26

(3*R*,4*R*,5*R*,6*S*)-5-acryloyl-4-(benzyloxy)-6-((*S*)-2-((*tert*-butyldiphenylsilyl)oxy)propyl)-3-methoxynon-8-en-1-yl pivalate (26). Aldehyde **25** (200 mg, 0.291 mmol) was suspended in anhydrous tetrahydrofuran (29.0 mL). The solution was cooled to -78 °C and vinylmagnesium bromide (1.0 M in tetrahydrofuran, 0.582 mmol, 0.580 mL) was added dropwise. The resulting mixture was stirred at -78 °C for 1 h until TLC indicated the reaction had reached completion. Saturated aqueous ammonium chloride was added, and the mixture was extracted with ethyl acetate, dried over sodium sulfate, condensed *in vacuo*, and purified by flash chromatography (0-25% ethyl acetate in hexanes) to provide the allylic alcohol as a clear, colorless oil. The resultant alcohol (230 mg, 0.322 mmol) was suspended in anhydrous dichloromethane (32.0 mL). Dess Martin Periodinane (205 mg, 0.483 mmol) was added and the cloudy white reaction was stirred for 45 minutes at room temperature. It was then quenched with saturated aqueous sodium bicarbonate, extracted with dichloromethane, dried over sodium sulfate, and concentrated *in vacuo*. The oil was purified by flash chromatography (0-20% ethyl acetate in hexanes) to provide enone **26** as a clear, colorless oil (208 mg, 68% over 2 steps).

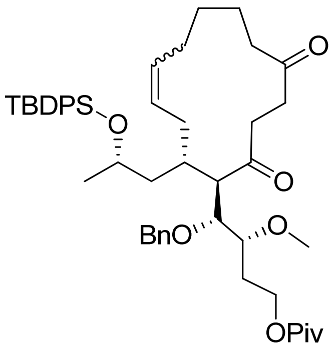
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.95 (d, J = 6.2 Hz, 3H), 0.98 (s, 9H), 1.15 (s, 9H), 1.17-1.21 (m, 1H), 1.43 (dt, J = 13.7, 6.5 Hz, 1H), 1.62 (quin, J = 7.0 Hz, 2H), 1.69-1.78 (m, 1H), 1.80-1.89 (m, 1H), 2.01-2.05 (m, 1H), 2.29 (quin, J = 6.9 Hz, 1H), 3.04 (d, J = 10.0 Hz, 1H), 3.09 (dd, J = 10.6, 2.8 Hz, 1H), 3.35 (s, 3H), 3.85 (sext, J = 6.2 Hz, 1H), 4.10-4.18 (m, 2H), 4.23 (d, J = 10.5 Hz, 1H), 4.64 (dd, J = 169.3, 11.4 Hz, 2H), 4.88-4.97 (m, 2H), 5.56 (dddd, J = 17.2, 10.2, 7.2, 7.2 Hz, 1H), 5.67 (dd, J = 10.3, 1.1 Hz, 1H), 6.08 (dd, J = 17.6, 1.0 Hz, 1H), 6.22 (dd, J = 17.6, 10.3 Hz, 1H), 7.24-7.41 (m, 11H), 7.61-7.67 (m, 4H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 19.3, 23.4, 27.2, 27.4, 29.3, 34.7, 36.1, 38.9, 41.3, 51.4, 57.9, 61.5, 68.0, 73.9, 81.0, 117.0, 127.6, 127.7, 127.9, 128.4, 128.7, 129.6, 129.7, 134.4, 134.8, 136.1, 137.4, 137.8, 138.7, 178.6, 201.4. **HRMS**: $C_{44}H_{60}O_6NaSi$, Calculated $[M+Na]^+$: 735.4057, Found $[M+Na]^+$: 735.4046. $[\alpha]_D^{20}$ = +17.5 (c = 1.0, $CHCl_3$).



27

(3*R*,4*R*,5*R*)-4-(benzyloxy)-5-((4*S*,6*S*)-6-((*tert*-butyldiphenylsilyl)oxy)hept-1-en-4-yl)-3-methoxy-6,9-dioxopentadec-14-en-1-yl pivalate (27). Enone **26** (50.0 mg, 0.070 mmol) was suspended in 1,4-dioxane (1.4 mL) in a microwave vial. 3-Benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (18.9 mg, 0.070 mmol) was added followed by triethylamine (14.7 mg, 0.105 mmol) at room temperature. 6-hepten-1-al (31.5 mg, 0.281 mmol) in 1,4 dioxane (0.2 mL) was added and the vial was capped and heated to 70 °C for 12 h. The reaction was quenched by addition of water and extracted with dichloromethane. The extract was dried over sodium sulfate, condensed *in vacuo*, and purified by flash chromatography (0-15% ethyl acetate in hexanes) to give 1,4-dione **27** (37.0 mg, 64 %).

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.99 (s, 12H), 1.18 (s, 9H), 1.33-1.42 (m, 2H), 1.52-1.68 (m, 8H), 1.73-1.89 (m, 2H), 2.02-2.09 (m, 2H), 2.17-2.24 (m, 1H), 2.44 (t, *J* = 7.3 Hz, 2H), 2.49-2.57 (m, 2H), 2.59-2.70 (m, 1H), 2.89 (dd, *J* = 10.4, 3.0 Hz, 1H), 3.09 (d, *J* = 8.9 Hz, 1H), 3.32 (s, 3H), 3.92 (sext, *J* = 6.2 Hz, 1H), 4.05-4.09 (m, 1H), 4.18 (dd, *J* = 7.8, 5.5 Hz, 2H), 4.60 (dd, *J* = 158.0, 11.4 Hz, 2H), 4.87-5.03 (m, 4H), 5.52 (dddd, *J* = 17.0, 10.1, 7.0, 6.9 Hz, 1H), 5.78 (dddd, *J* = 17.4, 10.4, 7.0 6.6 Hz, 1H), 7.23-7.40 (m, 11H), 7.62-7.67 (m, 4H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 19.3, 23.3, 23.5, 27.2, 27.4, 28.6, 29.5, 33.7, 34.2, 35.6, 36.0, 38.9, 39.1, 41.3, 42.8, 54.2, 57.8, 62.0, 68.1, 73.7, 81.0, 114.8, 116.9, 127.6, 127.6, 127.7, 127.9, 128.4, 129.6, 129.7, 129.7, 134.6, 134.8, 136.1, 137.6, 138.7, 138.7, 178.6, 208.8, 210.3. **HRMS**: $C_{51}H_{72}O_7NaSi$, Calculated $[M+Na]^+$: 847.4945, Found $[M+Na]^+$: 847.4926. $[\alpha]_D^{20}$ = +3.2 (c = 1.0, $CHCl_3$).

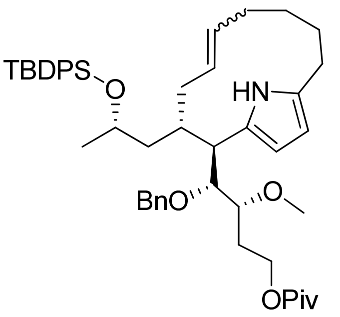


28

(3*R*,4*R*)-4-(benzyloxy)-4-((1*R*,2*S*)-2-((*S*)-2-((*tert*-butyldiphenylsilyl)oxy)propyl)-10,13-dioxocyclotridec-4-en-1-yl)-3-methoxybutyl pivalate (28). 1,4-dione **27** (85.0 mg, 0.103 mmol) was suspended in anhydrous dichloromethane (206 mL) with a reflux condenser attached. Grubb's first generation catalyst (25.4 mg, 0.031 mmol) was added and the resulting solution was stirred at 40 °C for 9 h. The reaction was cooled to room temperature and the dichloromethane was removed *in vacuo*. The dark brown residue was purified by flash chromatography (0-15% ethyl acetate in hexanes) to give a 1:1 mixture of the *cis*:*trans* macrocyclic alkene that could be combined for the next reaction (69 mg, 84%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.02 (s, 4.5 H), 1.03 (s, 4.5H), 1.04 (d, *J* = 6.2 Hz, 1.5 H), 1.06 (d, *J* = 6.2 Hz, 1.5H), 1.18 (s, 4.5H), 1.19 (s, 4.5H), 1.42-1.53 (m, 4H), 1.62- 1.83 (m, 6H), 1.84-1.93 (m, 2H), 1.97-2.04 (m, 2H), 2.10-2.14 (m, 1H), 2.15-2.23 (m, 1H), 2.27-2.32 (m, 0.5H), 2.40-2.56 (m, 2H), 2.60-2.70 (m, 1H), 2.71-2.79 (m, 1H), 2.81-2.86 (m, 1H), 2.99 (ddd, *J* = 15.4, 10.0, 3.1 Hz, 0.5H), 3.13 (d, *J* = 10.0 Hz, 0.5H), 3.16-3.19 (m, 0.5H), 3.31 (s, 1.5H), 3.39

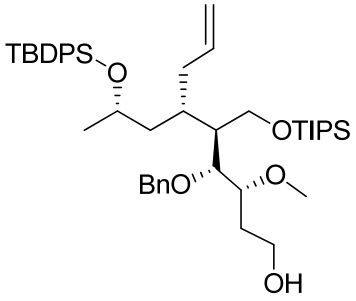
(s, 1.5H), 3.78-3.83 (m, 1H), 3.89-3.92 (m, 1H), 4.10-4.13 (m, 1.5H), 4.16-4.22 (m, 1H), 4.57 (dd, *J* = 276.2, 11.3 Hz, 1H), 4.59 (dd, *J* = 50.6, 11.9 Hz, 1H), 4.92-4.96 (m, 0.5H), 5.14-5.19 (m, 0.5H), 5.23-5.31 (m, 1H), 7.26-7.42 (m, 11H), 7.61-7.69 (m, 4H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 19.3, 19.3, 22.5, 22.6, 22.8, 22.9, 25.1, 26.9, 27.1, 27.2, 27.3, 27.4, 27.9, 29.7, 29.9, 30.0, 30.3, 33.0, 34.6, 35.6, 35.8, 36.3, 38.7, 38.9, 40.3, 40.6, 41.2, 41.4, 51.8, 55.8, 58.0, 58.1, 61.5, 61.9, 68.2, 68.4, 73.4, 78.1, 78.3, 79.8, 80.7, 126.4, 127.6, 127.7, 127.7, 127.7, 127.7, 128.0, 128.0, 128.2, 128.4, 128.6, 128.7, 129.6, 129.7, 129.7, 131.9, 133.1, 134.6, 134.7, 136.0, 136.0, 136.0, 138.0, 138.6, 178.6, 210.1, 210.1, 211.5, 211.8. **HRMS**: $C_{49}H_{68}O_7NaSi$, Calculated $[M+Na]^+$: 819.4632, Found $[M+Na]^+$: 819.4630.



4

(3*R*,4*R*)-4-(benzyloxy)-4-((2*S*,3*S*)-3-((*S*)-2-((*tert*-butyldiphenylsilyl)oxy)propyl)-14-azabicyclo[9.2.1]tetradeca-1(13),5,11-trien-2-yl)-3-methoxybutyl pivalate (4). Macrocyclic 1,4-dione **28** (45.0 mg, 0.057 mmol) was suspended in anhydrous methanol (5.60 mL) in a microwave vial. Ammonium acetate (131 mg, 1.69 mmol) was added and the vial was capped and heated in the microwave at 120 °C for 20 min. The solution was cooled to room temperature, quenched with water, diluted with dichloromethane, and then extracted with dichloromethane. The extract was dried over sodium sulfate, condensed *in vacuo*, and purified by flash chromatography (0-15% ethyl acetate in hexanes) to give the pyrrolophane **5** (40.0 mg, 91 %).

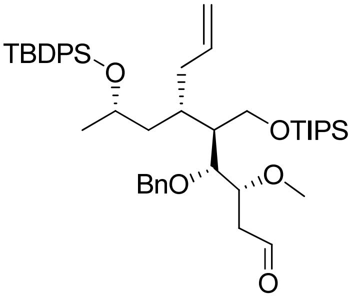
^{1}**H NMR** (CDCl$_3$, 400 MHz) δ (ppm): 0.88-0.90 (m, 1H), 0.97 (d, *J* = 6.6 Hz, 1H), 1.03 (s, 9H), 1.04-1.07 (m, 4H), 1.09 (s, 9H), 1.20-1.33 (m, 4H), 1.50-1.65 (m, 5H), 1.71-1.89 (m, 2H), 2.47-2.58 (m, 2H), 2.72 (bs, 1H), 3.16-3.24 (m, 1H), 3.27 (s, 3H), 3.78-3.87 (m, 1H), 3.90 (dd, *J* = 1.6, 9.8 Hz, 1H), 4.05-4.12 (m, 2H), 4.61 (d, *J* = 11.5 Hz, 1H), 4.90 (d, *J* = 11.5 Hz, 1H), 5.08 (bs, 1H), 5.18 (m, 1H), 5.63-5.80 (m, 2H), 7.27-7.41 (m, 11H), 7.65 (d, *J* = 6.5 Hz, 4H). ^{1}**H NMR** (CDCl$_3$, 400 MHz) δ (ppm): 0.82-0.91 (m, 1H), 1.00 (s, 9H), 1.04 (d, *J* = 6.0 Hz, 3H), 1.06-1.10 (m, 1H), 1.13 (s, 9H), 1.17 (d, *J* = 9.3 Hz, 1H), 1.25 (s, 2H), 1.26-1.37 (m, 2H), 1.40-1.49 (m, 1H), 1.54 (s, 9H), 1.55-1.61 (m, 1H), 1.62-1.72 (m, 2H), 1.75-1.92 (m, 4H), 2.05 (dd, *J* = 5.6, 9.4 Hz, 1H), 2.28-2.37 (m, 1H), 2.42 (dt, *J* = 3.0, 13.6 Hz, 1H), 2.53 (m, 1H), 2.58 (dd, *J* = 4.7, 9.8 Hz, 1H), 3.19-3.24 (m, 1H), 3.28 (s, 3H), 3.87 (sext, *J* = 6.9 Hz, 1H), 3.94 (dd, *J* = , 9.7 Hz, 1H), 4.07-4.18 (m, 2H), 4.56 (d, *J* = 11.5 Hz, 1H), 4.69-4.79 (m, 1H), 4.93 (d, *J* = 11.5 Hz, 1H), 5.14-5.26 (m, 1H), 5.53-5.66 (m, 2H), 7.27-7.42 (m, 11H), 7.65 (d, J = 7.3 Hz, 4H), 7.71 (bs, 1H). ^{13}**C NMR** (CDCl$_3$, 150 MHz) δ (ppm): 13.7, 14.1, 17.3, 17.3, 17.4, 19.1, 19.1, 20.4, 21.0, 21.2, 22.7, 27.0, 27.2, 27.7, 29.3, 29.7, 30.6, 31.9, 56.0, 60.4, 64.4, 71.8, 96.1, 97.6, 99.8, 127.5, 128.8, 130.9, 132.4, 135.9, 167.9, 170.9, 171.3. **HRMS**: C$_{49}$H$_{68}$NO$_5$Si, Calculated [M+H]$^+$: 778.4867, Found [M+H]$^+$: 778.4865. $[\alpha]_D^{20}$ = -5.4 (c = 0.3, CHCl$_3$).



29

(3*R*,4*R*,5*S*,6*S*)-4-(benzyloxy)-6-((*S*)-2-((*tert*-butyldiphenylsilyl)oxy)propyl)-3-methoxy-5-(((triisopropylsilyl)oxy)methyl)non-8-en-1-ol (29). Pivalate ester **6** (240 mg, 0.284 mmol) was suspended in anhydrous dichloromethane (28.0 mL) and cooled to -78 °C. Diisobutylaluminum hydride (1.0 M in dichloromethane, 0.850 mL, 0.852 mmol) was added dropwise, and the resulting solution was stirred for 1 h until TLC indicated the reaction was complete. The reaction was quenched by addition of saturated aqueous sodium potassium tartrate, warmed to room temperature, and stirred until the organic layer became clear. The mixture was extracted with dichloromethane, dried over sodium sulfate, and condensed *in vacuo* to give a clear oil. This oil was purified by flash chromatography (0-35% ethyl acetate in hexanes) to provide the desired free primary alcohol **29** as a clear, colorless oil (200 mg, 93%).

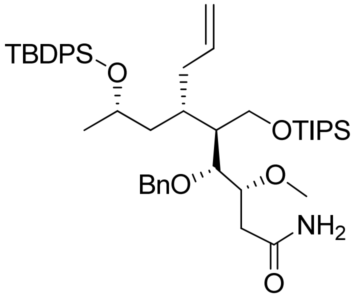
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.00 (s, 9H), 1.02 (d, *J* = 6.1 Hz, 3H), 1.05 (s, 21H), 1.43 (quin, *J* = 6.8 Hz, 1H), 1.57-1.63 (m, 1H), 1.65-1.74 (m, 2H), 1.75-1.81 (m, 1H), 1.98-2.07 (m, 1H), 2.10-2.16 (m, 2H), 2.87 (d, *J* = 6.3 Hz, 1H), 3.41 (s, 3H), 3.58 (dd, *J* = 10.5, 6.2 Hz, 1H), 3.66 (dd, *J* = 10.7, 3.6 Hz, 1H), 3.71-3.82 (m, 4H), 3.91 (sext, *J* = 6.1 Hz, 1H), 4.69 (dd, *J* = 156.8, 11.4 Hz, 2H), 4.81-4.85 (m, 2H), 5.42-5.52 (m, 1H) 7.23-7.41 (m, 11H), 7.65-7.68 (m, 4H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 12.1, 18.2, 19.3, 23.5, 27.1, 31.3, 33.0, 35.6, 42.9, 46.5, 57.0, 61.4, 62.1, 68.6, 74.2, 78.2, 85.0, 115.6, 127.5, 127.5, 127.6, 128.0, 128.3, 129.5, 129.6, 134.6, 135.1, 136.0, 138.6, 138.9. **HRMS**: $C_{46}H_{73}O_5Si_2$, Calculated $[M+H]^+$: 761.4997, Found $[M+]^+$: 761.4995. $[\alpha]_D^{20}$ = -8.2 (c = 1.0, $CHCl_3$).



30

(3R,4R,5S,6S)-4-(benzyloxy)-6-((S)-2-((tert-butyldiphenylsilyl)oxy)propyl)-3-methoxy-5-(((triisopropylsilyl)oxy)methyl)non-8-enal (30). Alcohol **29** (200 mg, 0.263 mmol) was suspended in dichloromethane/dimethylsulfoxide (4:1 v/v, 13.0 mL) and cooled to 0 °C. Triethylamine (0.370 mL, 2.63 mmol) was added followed by addition of sulfur trioxide pyridine complex (167 mg, 1.05 mmol). The resulting solution was stirred for 4 h at 0 °C, quenched by addition of water, extracted with dichloromethane, dried over sodium sulfate, and condensed *in vacuo* to give a pale yellow oil. This oil was purified by flash chromatography (0-20% ethyl acetate in hexanes) to provide aldehyde **30** as a clear, colorless oil (185 mg, 93%).

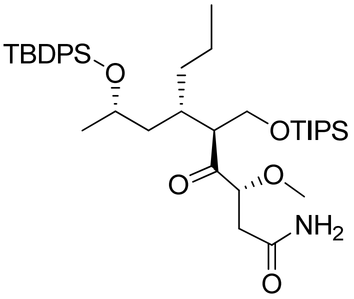
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.99 (s, 9H), 1.02 (d, *J* = 6.1 Hz, 3H), 1.04-1.06 (m, 21H), 1.41 (quin, *J* = 6.7 Hz, 1H), 1.57-1.71 (m, 3H), 2.04-2.11 (m, 2H), 2.54 (dd, *J* = 16.7, 1.5 Hz, 1H), 2.74 (dd, *J* = 16.7, 3.0 Hz, 1H), 3.39 (s, 3H), 3.57 (dd, *J* = 10.9, 6.8 Hz, 1H), 3.66 (dd, *J* = 10.8, 3.3 Hz, 1H), 3.82 (dd, *J* = 9.0, 1.8 Hz, 1H), 3.90 (sext, *J* = 6.2 Hz, 1H), 4.12 (ddd, *J* = 8.2, 3.7, 2.1 Hz, 1H), 4.67 (dd, *J* = 134.0, 11.4 Hz, 2H), 4.80- 4.84 (m, 2H), 5.38-5.48 (m, 1H) 7.22-7.41 (m, 11H), 7.63-7.67 (m, 4H), 9.78 (dd, *J* = 2.8, 1.5 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 12.0, 18.2, 19.3, 23.4, 27.1, 32.8, 35.3, 42.8, 43.9, 46.8, 57.2, 61.8, 68.5, 74.3, 78.9, 80.1, 115.8, 127.5, 127.6, 127.9, 128.3, 129.5, 129.6, 134.5, 135.0, 136.0, 138.4, 138.7, 202.1.



31

(3*R*,4*R*,5*S*,6*S*)-4-(benzyloxy)-6-((*S*)-2-((*tert*-butyldiphenylsilyl)oxy)propyl)-3-methoxy-5-(((triisopropylsilyl)oxy)methyl)non-8-enamide (31). To a stirring solution of aldehyde **30** (182 mg, 0.240 mmol) in *tert*-butanol (9.00 mL) was added 2-methyl-2-butene (0.260 mL, 2.40 mmol). In a separate vial, monobasic sodium phosphate (252 mg, 1.82 mmol) was dissolved in water (9.00 mL) and sodium chlorite (163 mg, 1.80 mmol) was added. The *tert*-butanol solution was cooled to 0 °C and the chlorite/phosphate solution in water was added dropwise. The resulting yellow solution was stirred at 0 °C for 30 min and was then quenched with saturated aqueous sodium thiosulfate and acidified to pH 3. The aqueous solution was then extracted with ethyl acetate, dried over sodium sulfate, and concentrated *in vacuo* to give a clear oil. This oil was purified by flash chromatography (0-50% ethyl acetate in hexanes) yielding the carboxylic acid as a clear, colorless oil (180 mg, 97%). This acid (225 mg, 0.290 mmol) was suspended in dimethylformamide (1.50 mL). 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (83.4 mg, 0.440 mmol) and 1-hydroxybenzotriazole (58.8 mg, 0.440 mmol) were added subsequently at room temperature, followed by addition of diisopropylethylamine (0.200 mL, 1.16 mmol) and ammonium chloride (31.0 mg, 0.580 mmol). The resulting solution was stirred for 6 h at room temperature until TLC indicated complete conversion. The reaction was quenched by addition of water, extracted with dichloromethane, dried over sodium sulfate, and condensed *in vacuo* to give a pale yellow residue. This residue was purified by flash chromatography (0-50% ethyl acetate in hexanes then 75% ethyl acetate in hexanes) to give amide **31** as a clear colorless oil (180 mg, 80%).

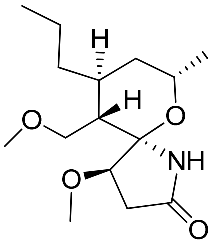
^{1}H NMR (CDCl$_3$, 400 MHz) δ (ppm): 1.00 (s, 9H), 1.02 (d, *J* = 6.1 Hz, 3H), 1.04-1.07 (m, 21H), 1.44 (quin, *J* = 6.8 Hz, 1H), 1.63-1.73 (m, 3H), 2.01-2.08 (m, 1H), 2.16-2.22 (m, 1H), 2.43 (dd, *J* = 15.8, 3.0 Hz, 1H), 2.53 (dd, *J* = 15.8, 8.4 Hz, 1H), 3.41 (s, 3H), 3.62-3.71 (m, 2H), 3.86-3.95 (m, 3H), 4.67 (dd, *J* = 124.8, 11.5 Hz, 2H), 4.79-4.84 (m, 2H), 5.16 (bs, 1H), 5.42-5.52 (m, 1H), 5.98 (bs, 1H), 7.23-7.41 (m, 11H), 7.64-7.66 (d, *J* = 7.6 Hz, 4H). **^{13}C NMR** (CDCl$_3$, 100 MHz) δ (ppm): 12.0, 18.9, 19.3, 23.5, 27.1, 33.1, 35.8, 36.4, 43.1, 46.1, 57.2, 61.7, 68.6, 74.3, 78.2, 81.0, 115.6, 127.5, 127.5, 127.6, 127.8, 128.4, 129.5, 129.6, 134.7, 135.0, 136.0, 138.6, 138.9, 174.1. **HRMS**: $C_{46}H_{72}NO_5Si_2$, Calculated [M+H]$^+$: 774.4949, Found [M+H]$^+$: 774.4951. $[\alpha]_D^{20}$ = -15.4 (c = 1.2, CHCl$_3$).



32

(3*R*,5*S*,6*S*,8*S*)-8-((*tert*-butyldiphenylsilyl)oxy)-3-methoxy-4-oxo-6-propyl-5-(((triisopropylsilyl)oxy)methyl)nonanamide (32). Amide **31** (180 mg, 0.232 mmol) was suspended in anhydrous ethyl acetate (23.0 mL). 10% palladium on activated carbon (62.0 mg, 0.058 mmol) was added and the flask was sealed and evacuated then back-filled with argon (3 x). The flask was then evacuated and refilled with hydrogen (3 x) from a balloon. The reaction was stirred for 8 h at room temperature until the reaction was complete by TLC. The mixture was filtered through celite and washed liberally with ethyl acetate. The filtrate was condensed *in vacuo* to give the secondary alcohol as a clear, colorless oil that was carried on to the next step without further purification (158 mg, 99%). The resultant alcohol (152 mg, 0.222 mmol) was suspended in anhydrous dichloromethane (22.0 mL) with 4 Å molecular sieves (100 mg). The reaction was cooled to 0 °C and 4-methylmorpholine N-oxide (52.0 mg, 0.443 mmol) was added followed by tetrapropylammonium perruthenate (15.6 mg, 0.044 mmol). The reaction was warmed to room temperature and stirred for 2 h. Upon complete conversion as indicated by TLC, the mixture was filtered through celite and washed liberally with dichloromethane. The filtrate was condensed *in vacuo* to give a dark green residue that was purified by flash chromatography (0-75% ethyl acetate in hexanes) to give hydroxyketoamide **32** as a clear, colorless oil (129 mg, 85 %).

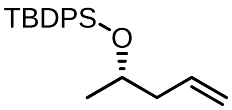
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.67 (t, *J* = 6.8 Hz, 3H), 0.79-0.93 (m, 3H), 1.02 (s, 30H), 1.09 (d, *J* = 6.1 Hz, 3H), 1.25 (ddd, *J* = 13.7, 8.1, 4.1 Hz, 2H), 1.41 (ddd, *J* = 13.7, 8.9, 4.6 Hz, 1H), 1.65-1.73 (m, 1H), 2.37 (dd, *J* = 14.8, 8.1 Hz, 1H), 2.59 (dd, *J* = 15.3, 4.1 Hz, 1H), 3.00 (ddd, *J* = 8.7, 6.8, 4.8 Hz, 1H), 3.38 (s, 3H), 3.70 (dd, *J* = 9.5, 4.7 Hz, 1H), 3.78-3.83 (m, 2H), 4.17 (dd, *J* = 8.1, 4.0 Hz, 1H), 5.27 (bs, 1H), 5.86 (bs, 1H), 7.34-7.43 (m, 6H), 7.65-7.68 (m, 4H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 12.0, 14.5, 18.1, 18.8, 19.3, 22.8, 27.1, 32.3, 34.0, 37.0, 42.3, 53.1, 58.3, 63.6, 68.2, 83.9, 127.7, 127.7, 129.7, 134.7, 136.0, 136.0, 172.0, 212.4. **HRMS**: $C_{39}H_{66}NO_5Si_2$, Calculated $[M+H]^+$: 684.4480, Found $[M+H]^+$: 684.4485. $[\alpha]_D^{20}$ = -17.4 (c = 0.5, $CHCl_3$).



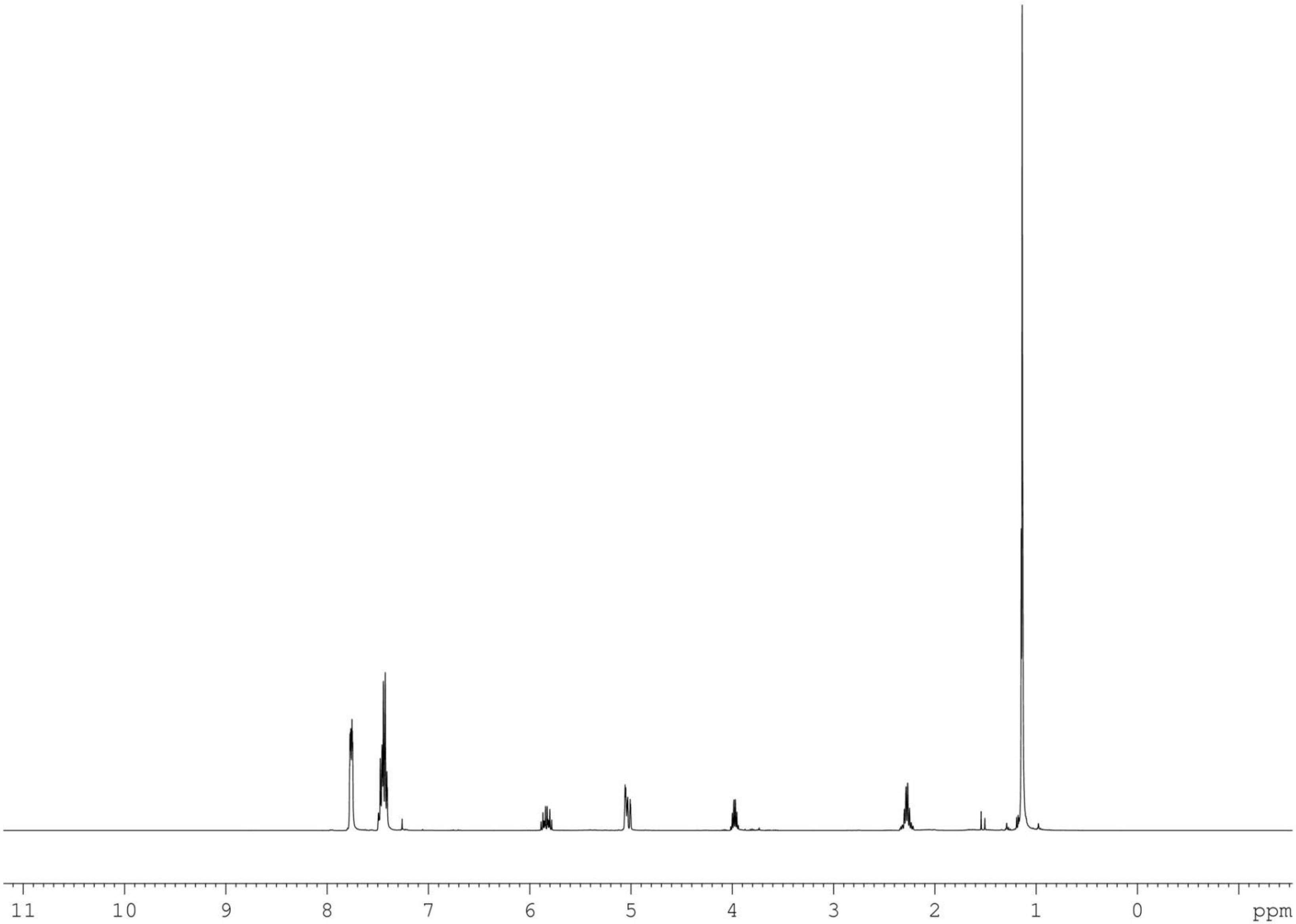
8

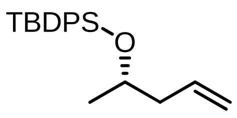
(4R,5R,7S,9S,10S)-4-methoxy-10-(methoxymethyl)-7-methyl-9-propyl-6-oxa-1-azaspiro[4.5]decan-2-one (8). Hydroxyketoamide **32** (68.0 mg, 0.099 mmol) was suspended in anhydrous methanol (30.0 mL). Concentrated hydrochloric acid (0.026 mL, 0.300 mmol) was added at room temperature and the reaction was allowed to stir for 10 h. After this time the reaction was quenched by dropwise addition of saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The organic layers were combined, dried over sodium sulfate, and condensed *in vacuo* to give a clear, colorless residue. The crude residue was purified by flash chromatograpy (0-85% ethyl acetate in hexanes) to yield the desired marineosin A model stereoisomer **8** as a clear, colorless oil (22.0 mg, 82%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.89-0.94 (m, 5H), 1.14-1.16 (m, 3H), 1.20 (d, *J* = 6.6 Hz, 3H), 1.93-1.96 (m, 1H), 2.34-2.37 (m, 1H) 2.52 (m, 2H) 3.22 (dd, *J* = 10.4, 4.4 Hz, 1H), 3.28-3.31 (m, 1H), 3.31 (s, 3H), 3.44 (s, 3H), 3.74-3.79 (m, 1H), 4.15 (dd, *J* = 9.6, 8.0 Hz, 1H), 6.23 (bs, 1H). **^{13}C NMR** ($CDCl_3$, 150 MHz) δ (ppm): 14.0, 22.2, 26.0, 30.6, 35.2, 40.6, 55.9, 58.2, 62.0, 65.4, 70.4, 72.7, 79.2, 90.3, 175.3. **HRMS**: $C_{15}H_{28}NO_4$, Calculated $[M+H]^+$: 286.3871, Found $[M+H]^+$: 286.3877.

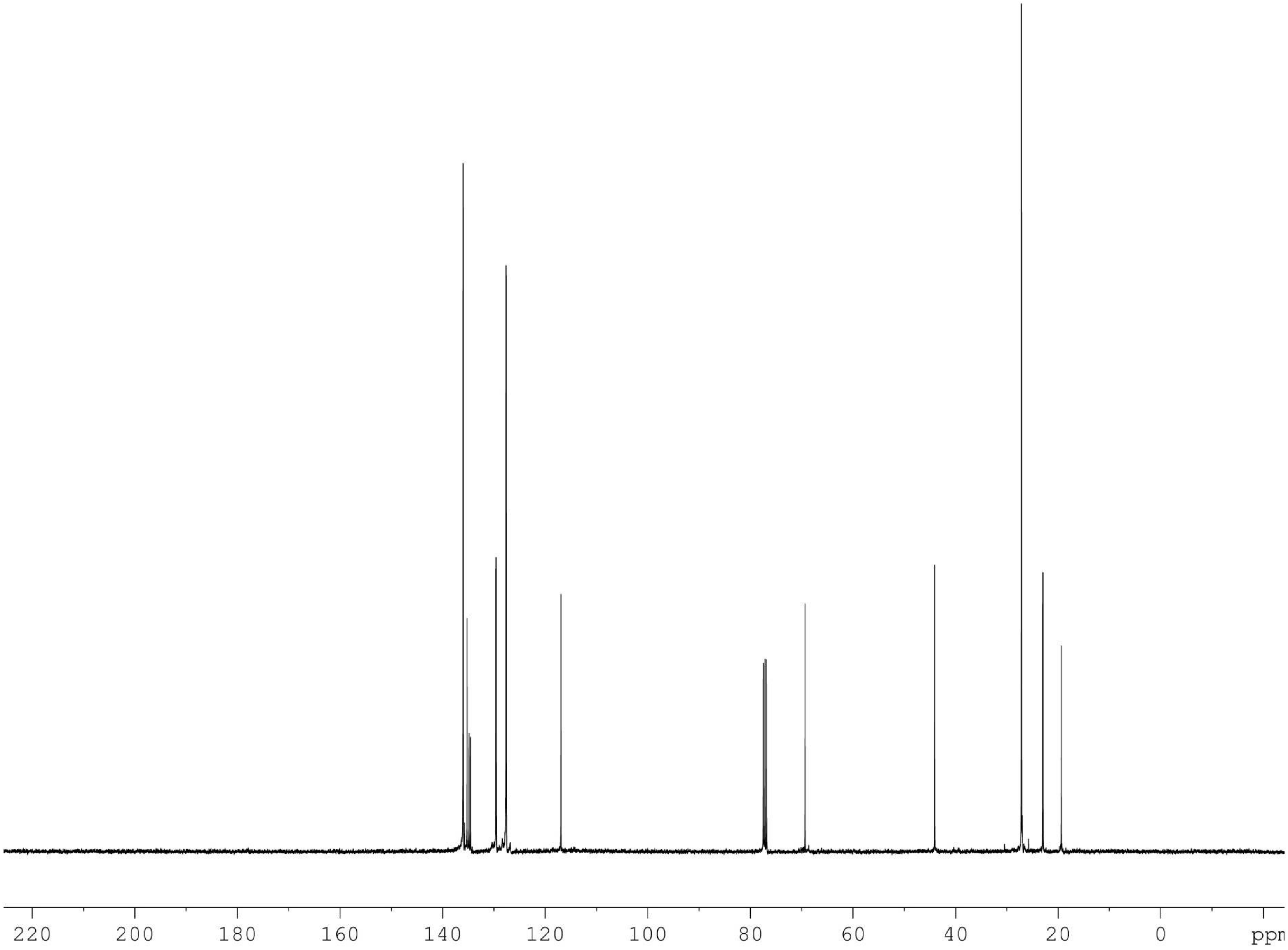


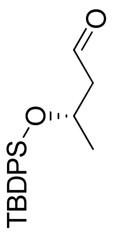
10



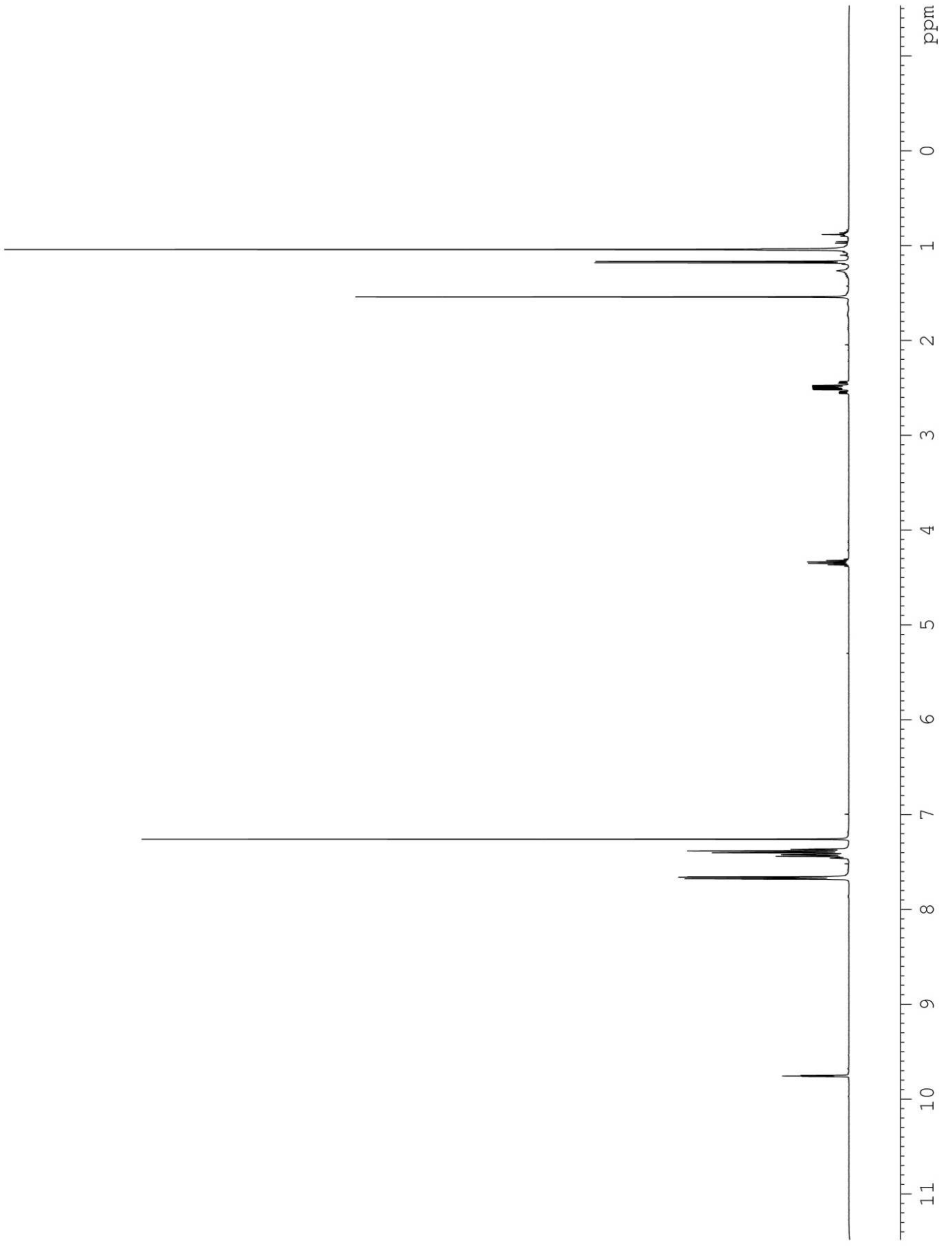


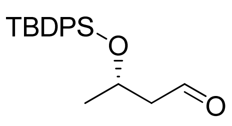
10



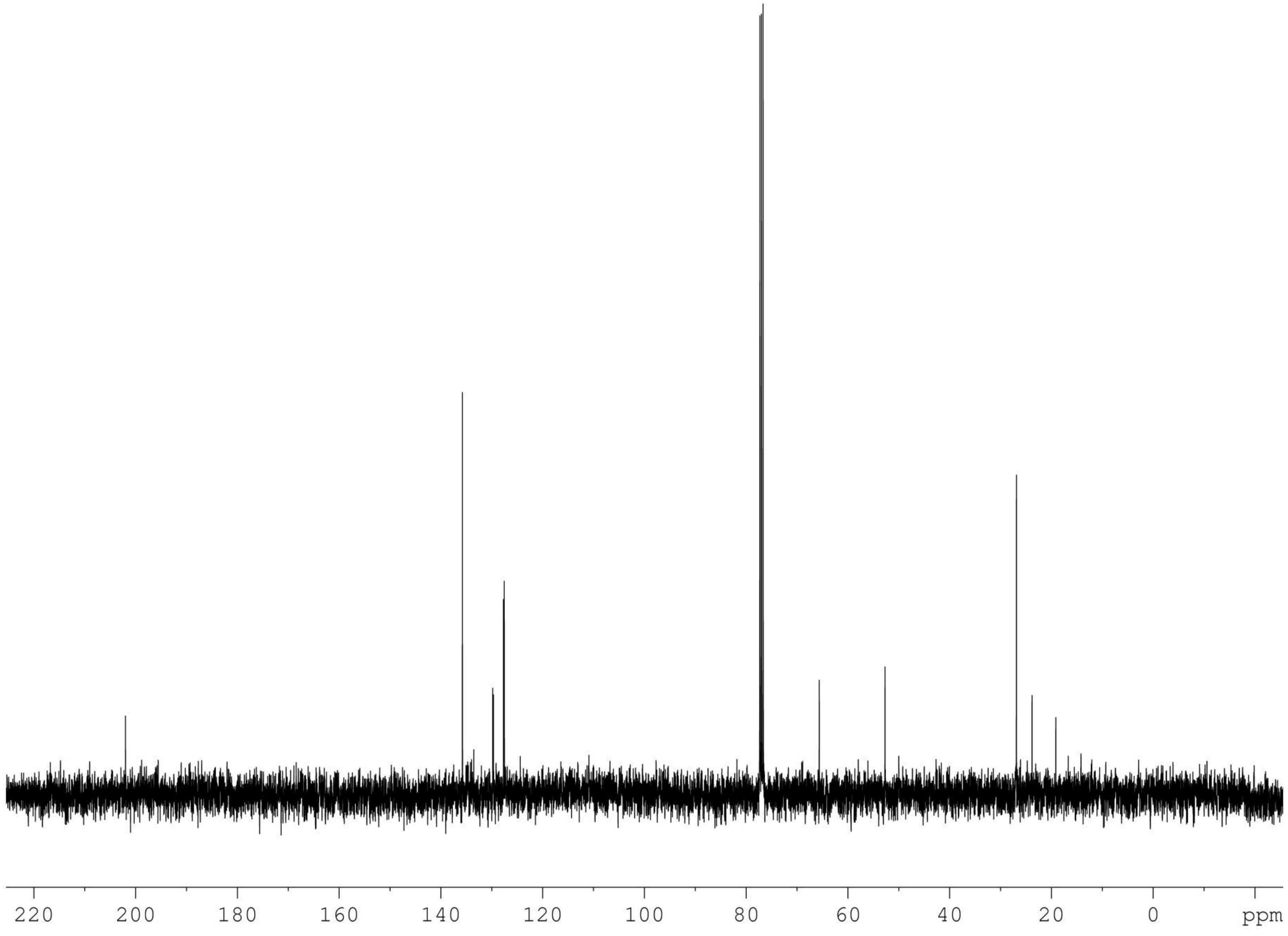


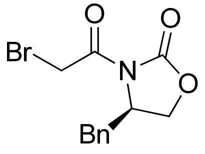
11



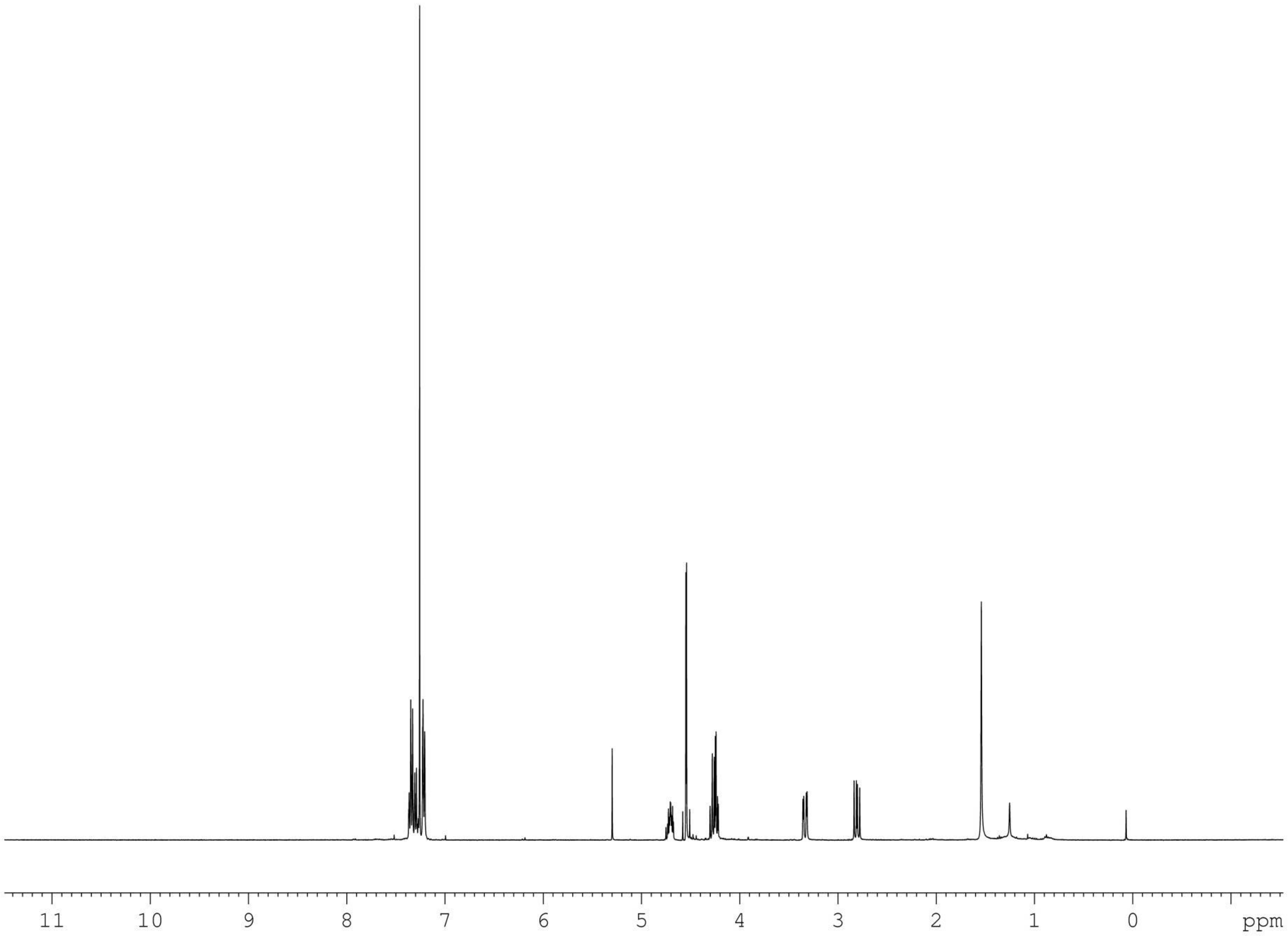


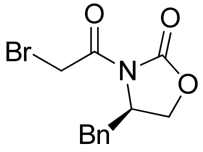
11



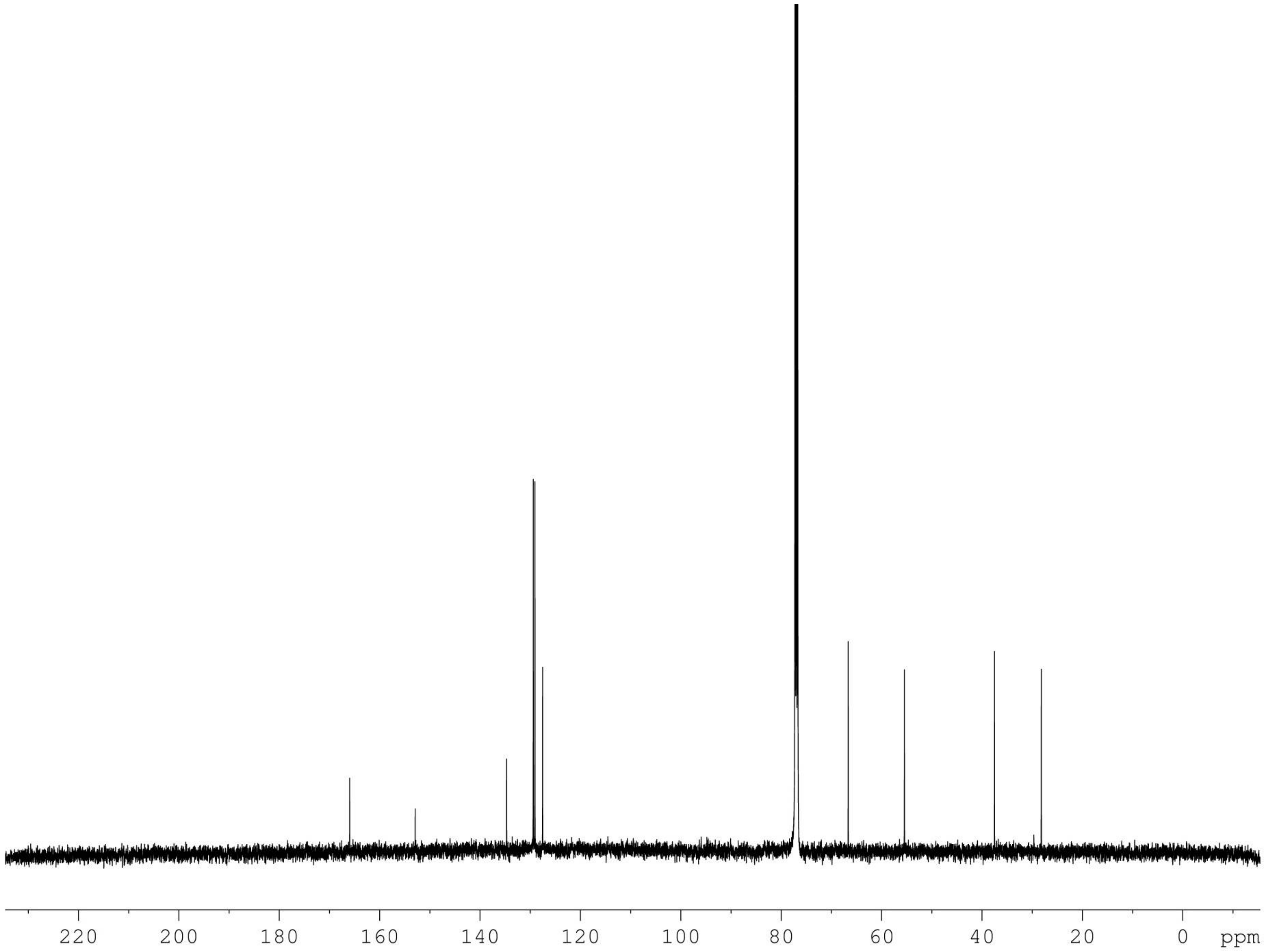


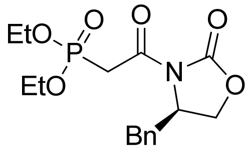
13



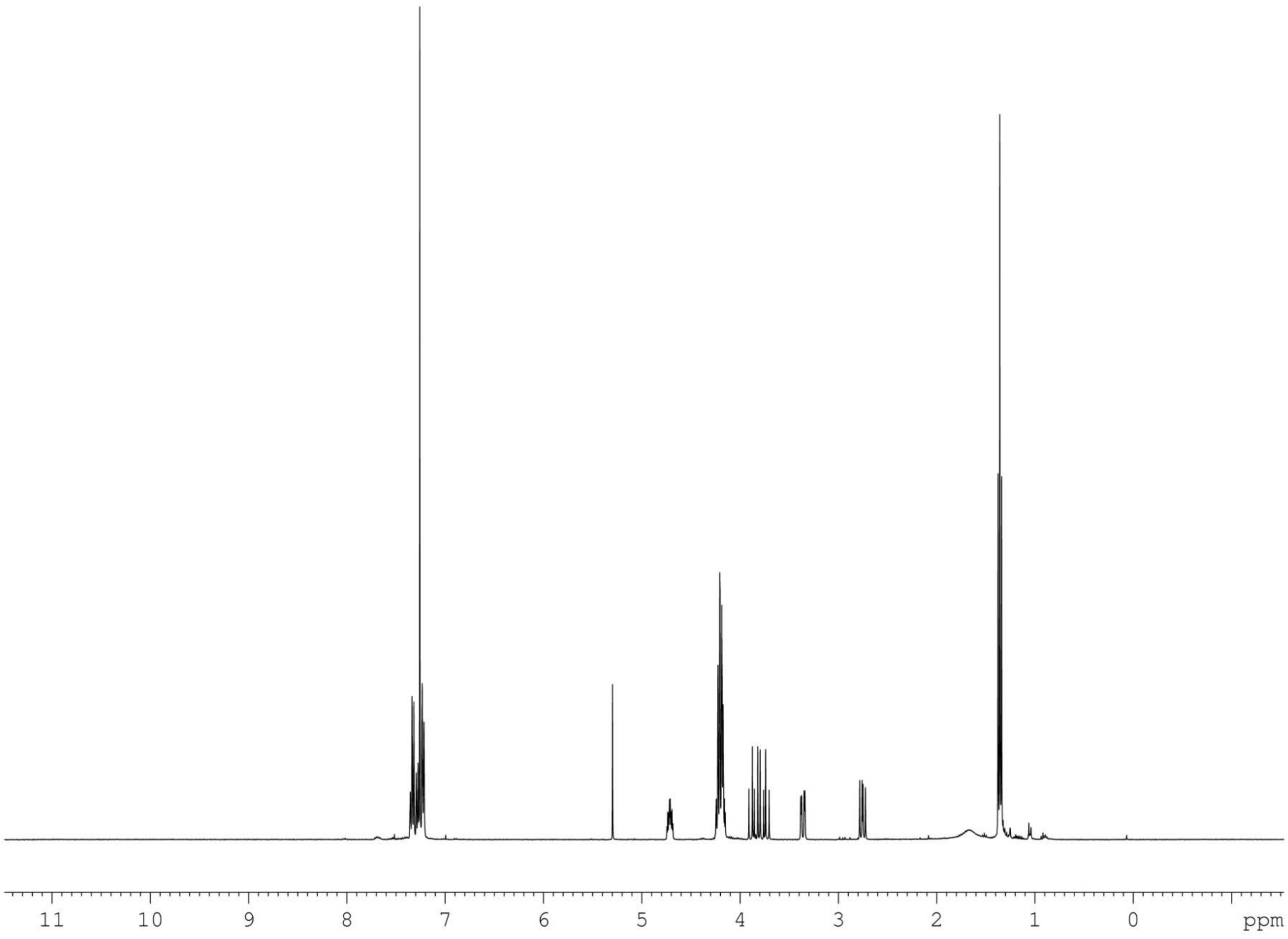


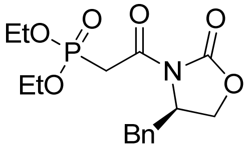
13



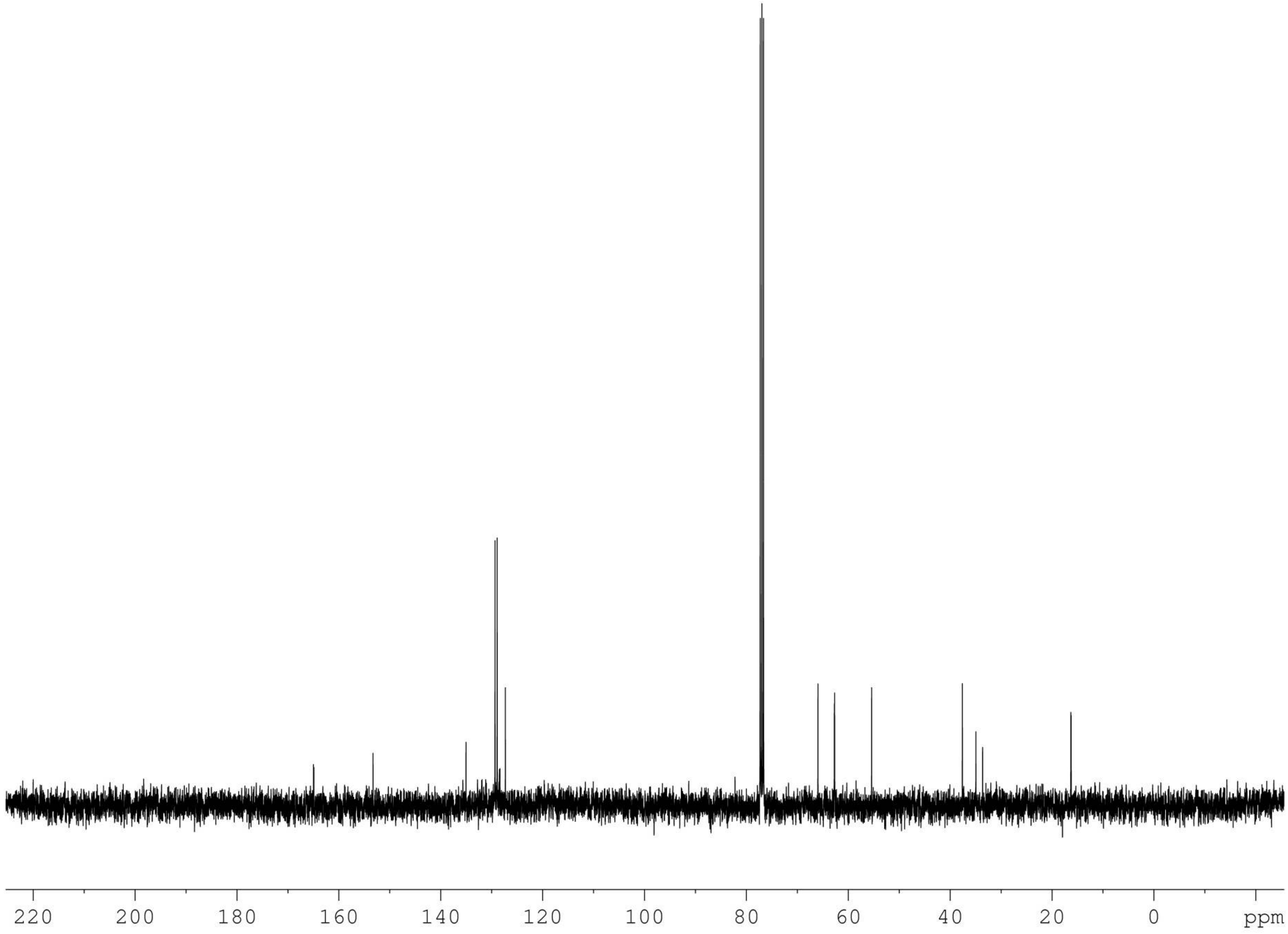


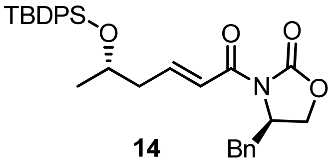
7



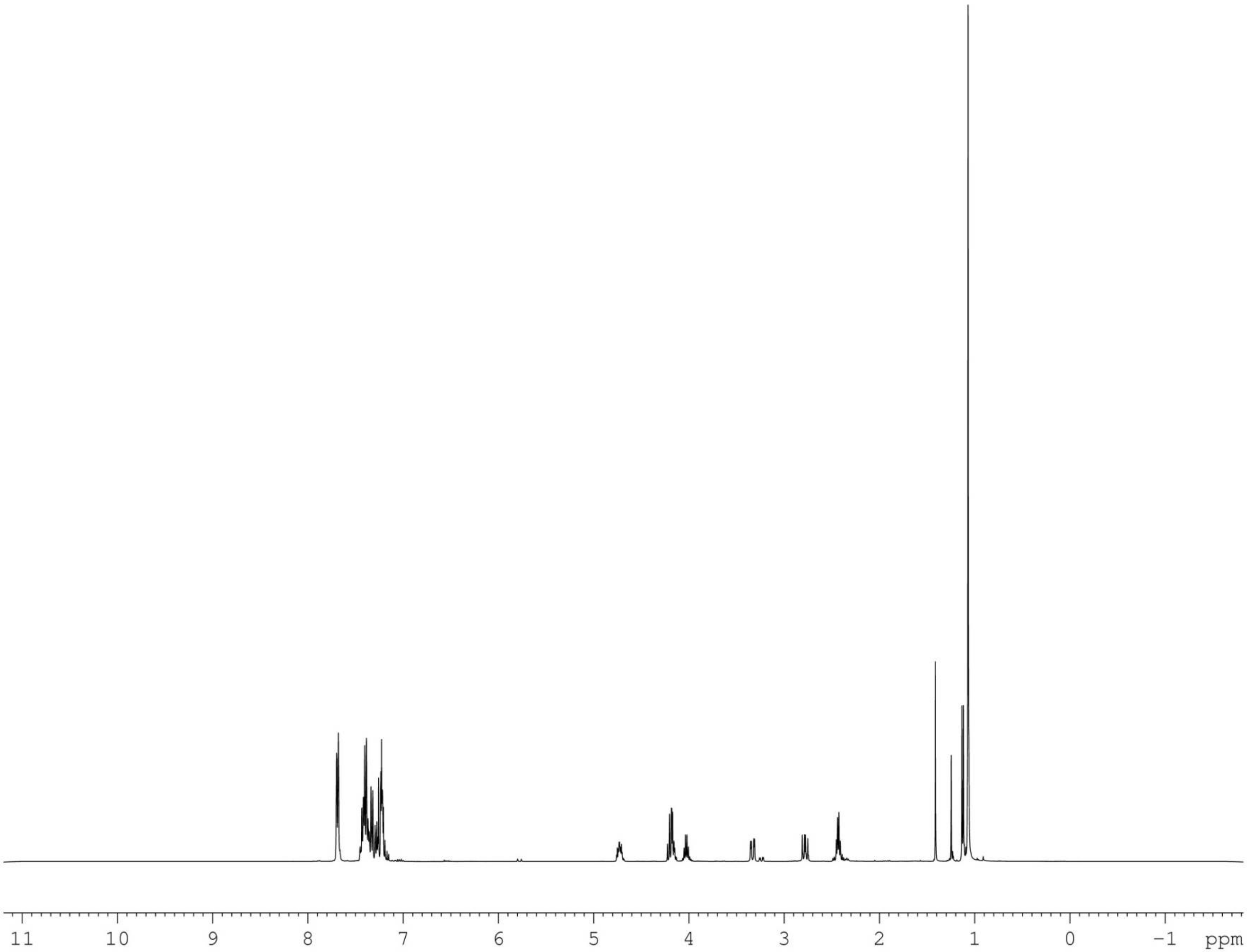


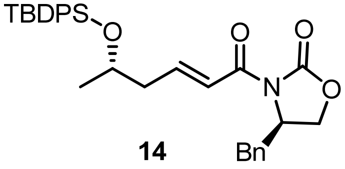
7



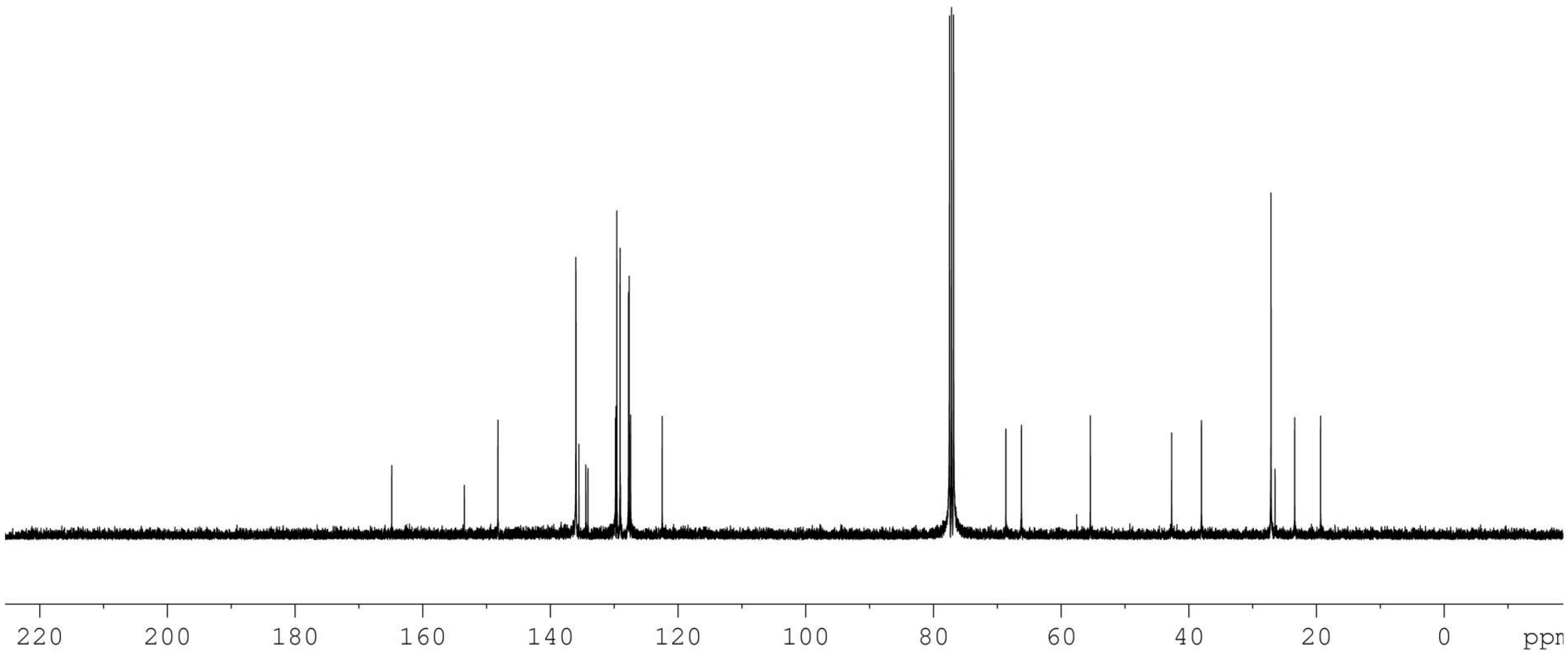


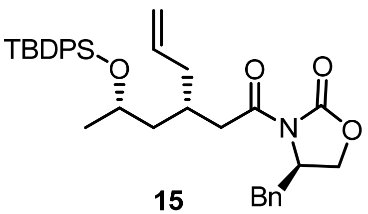
14



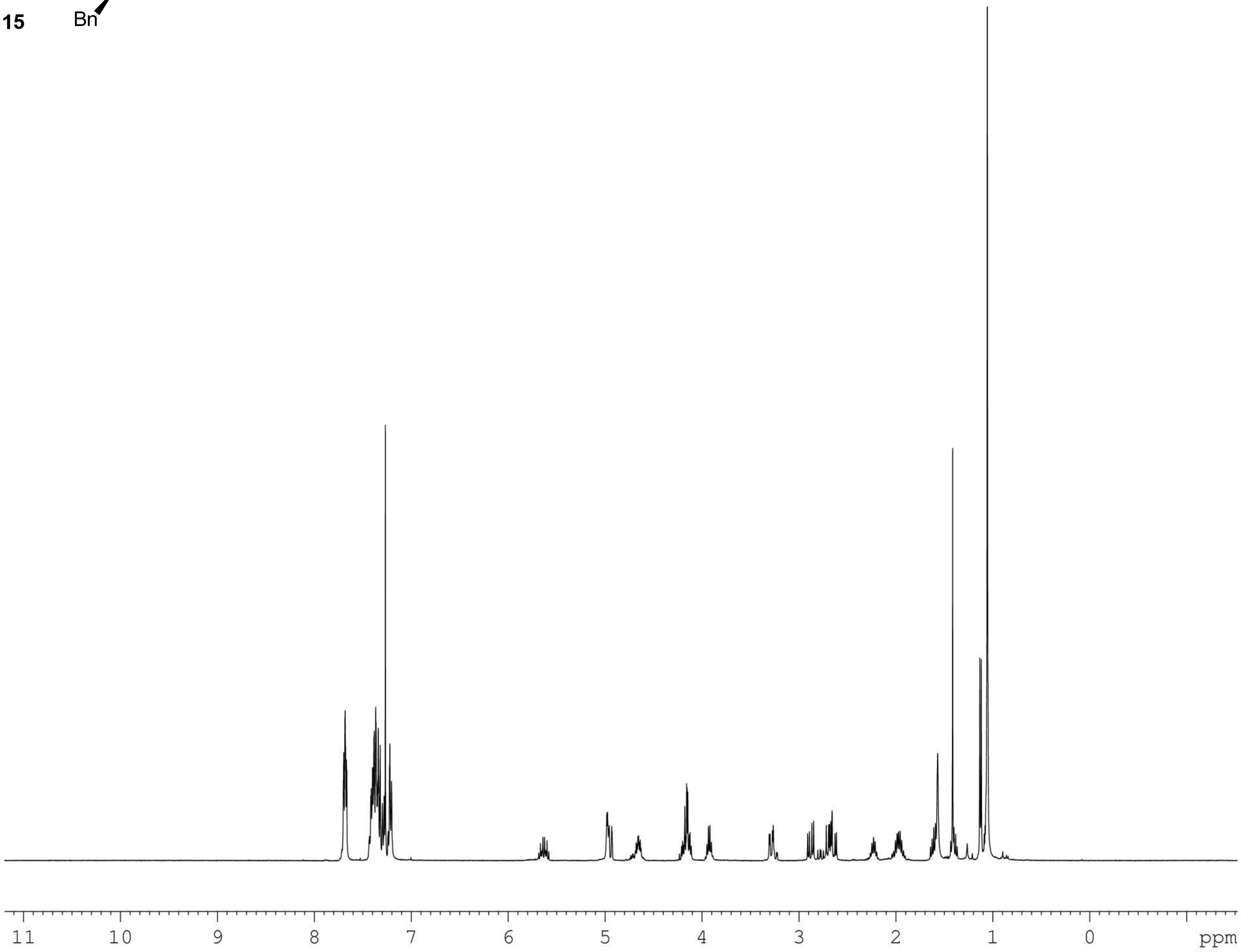


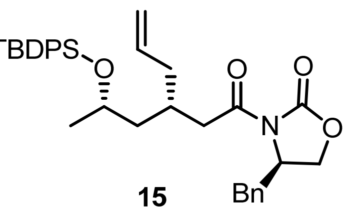
14



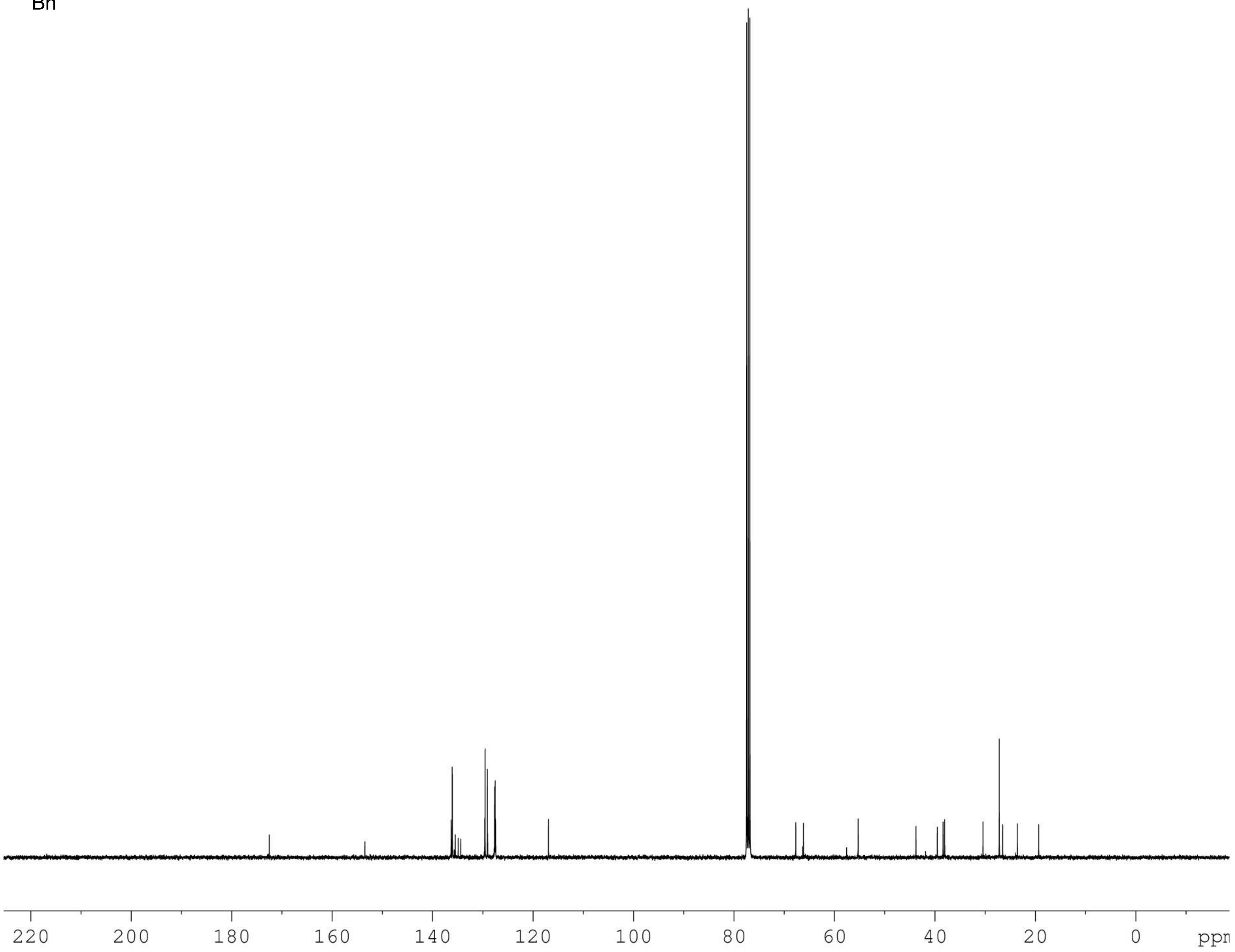


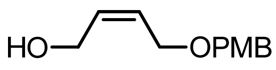
15



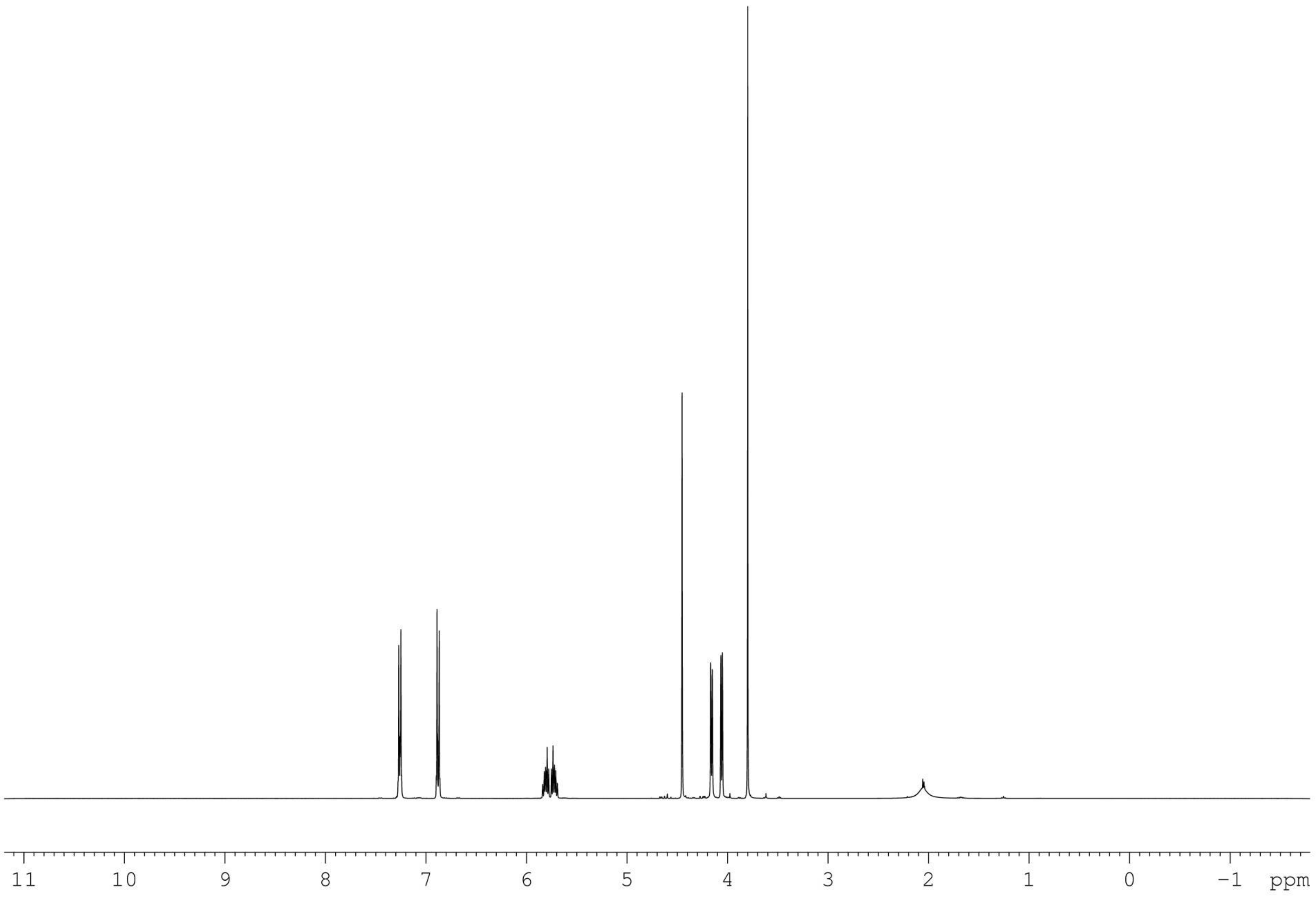


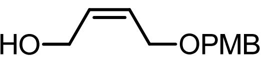
15



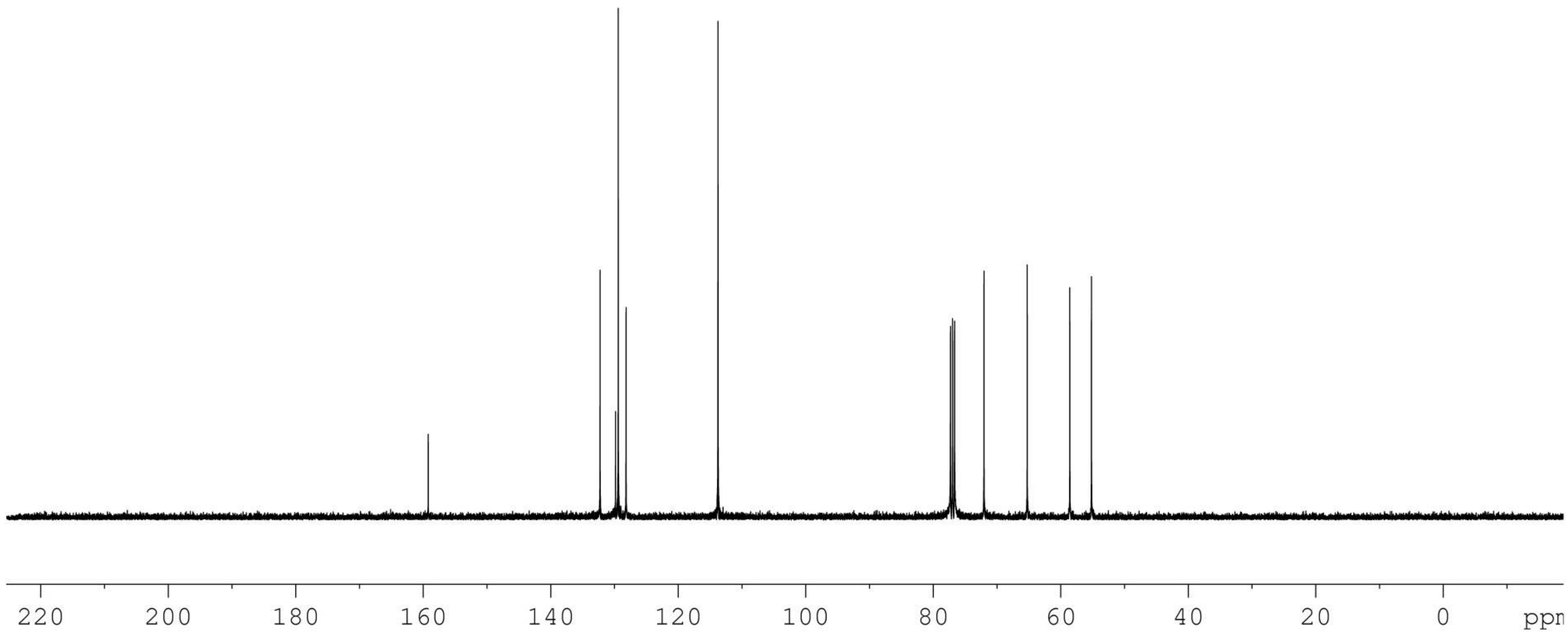


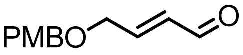
17



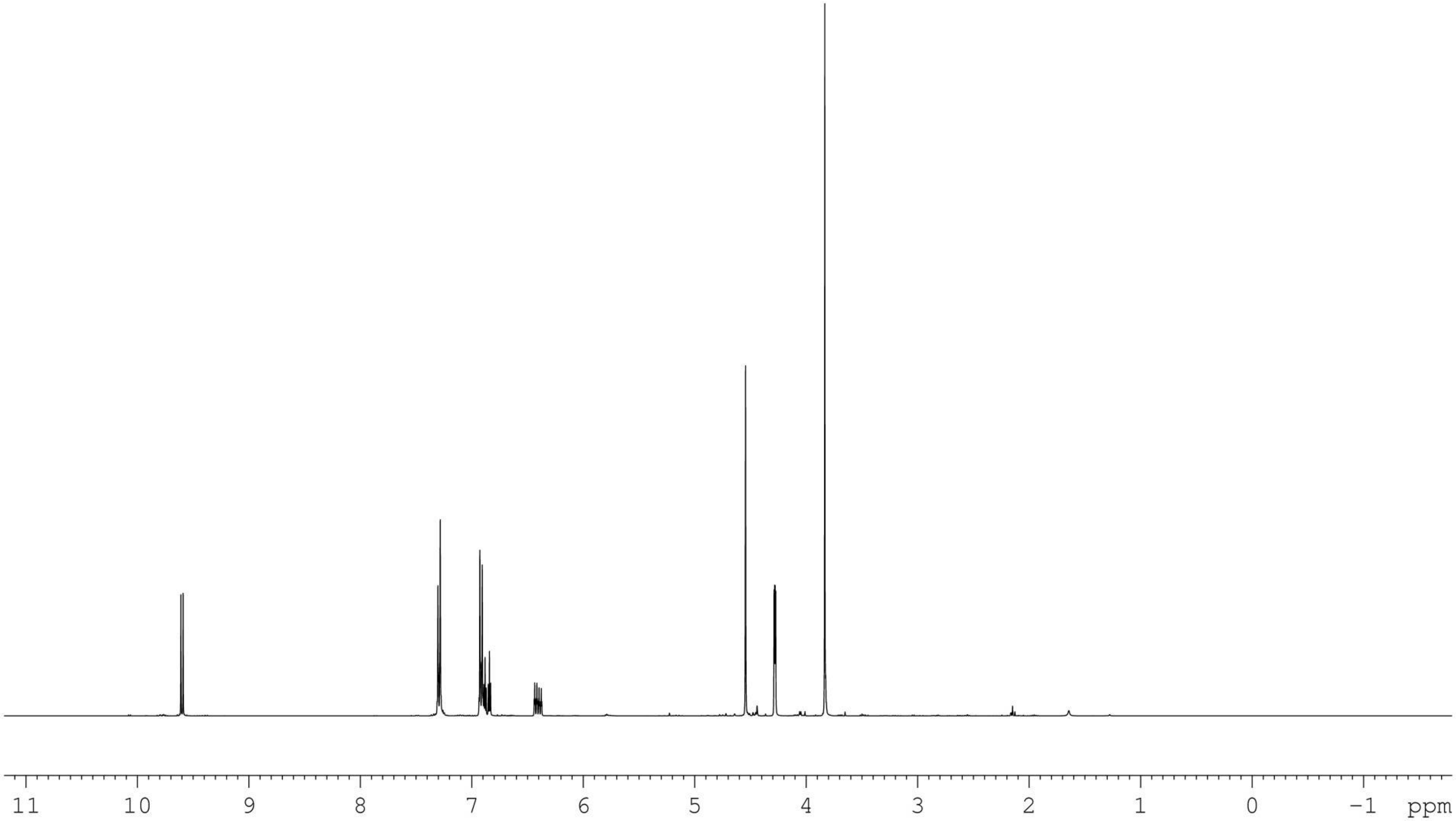


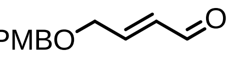
17



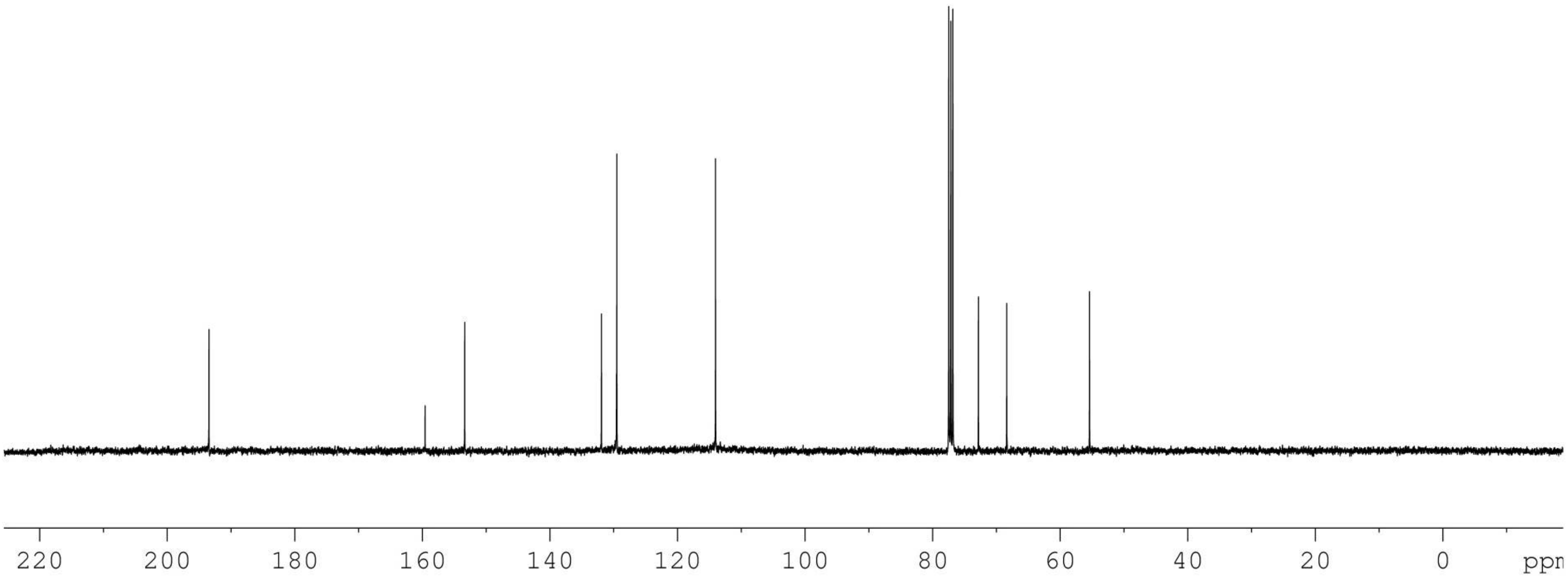


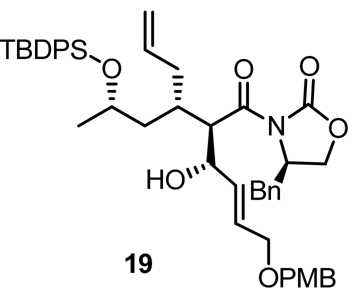
18



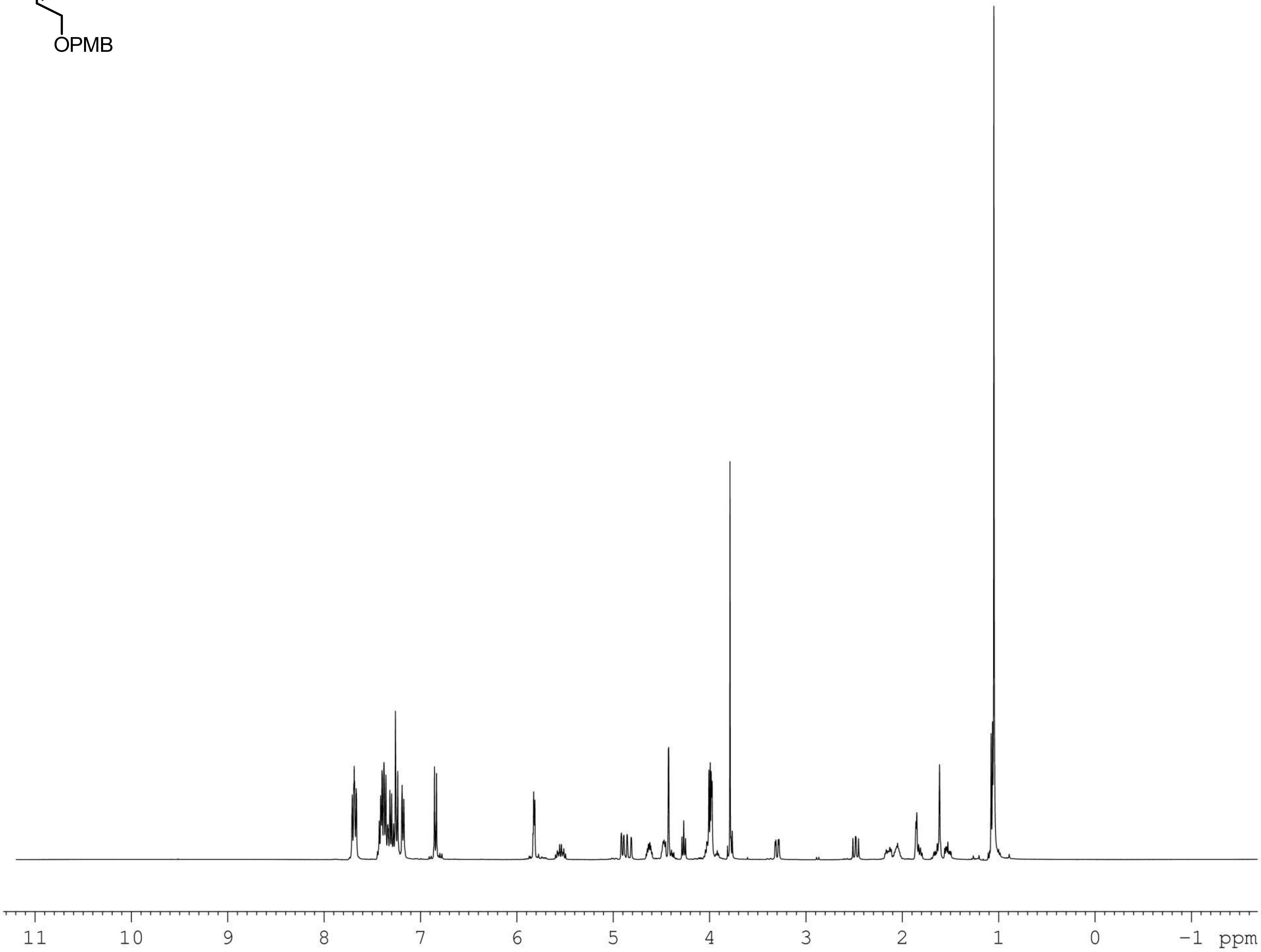


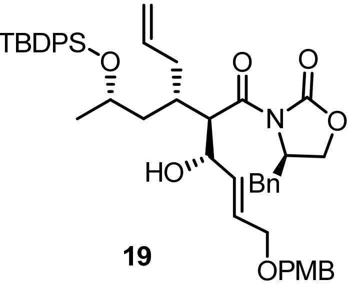
18



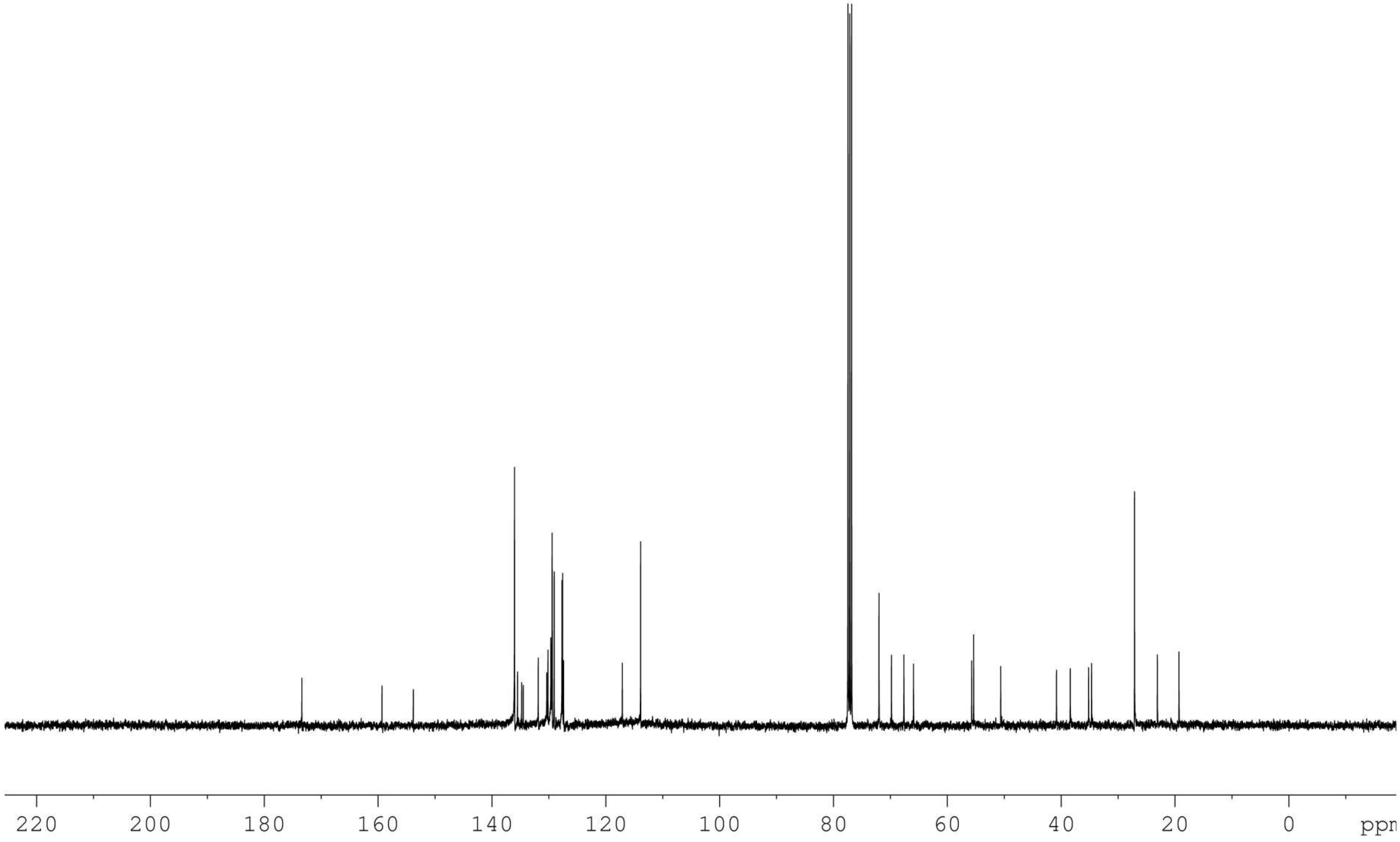


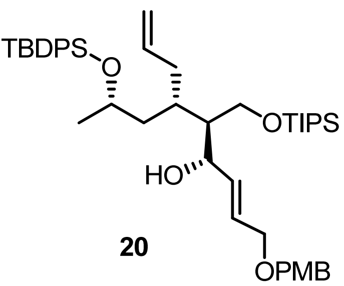
19



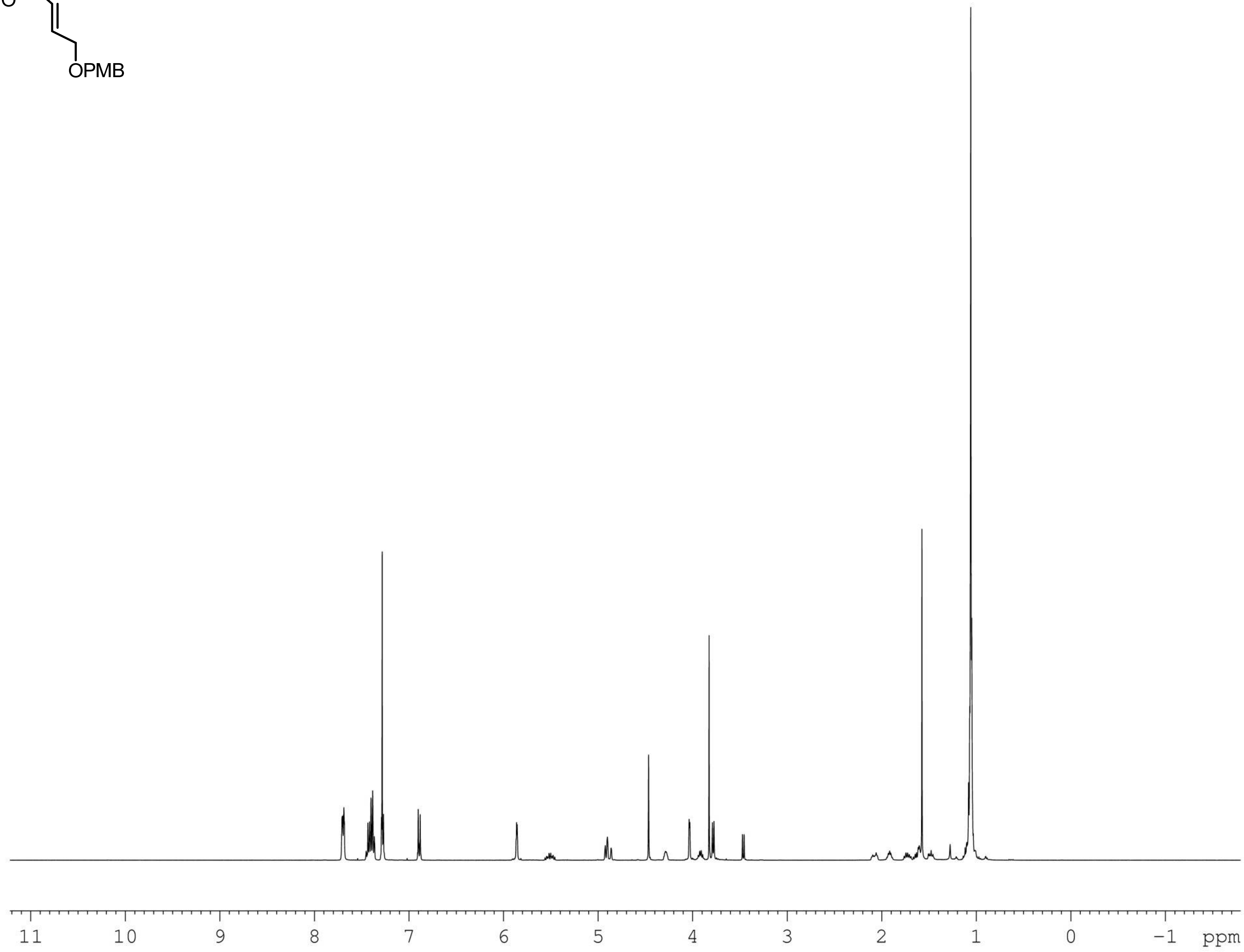

TBDPS
O
O
O
N
O
HO
Bn
OPMB

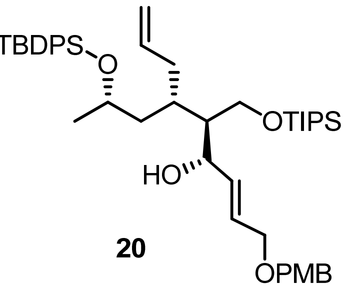
19


220
200
180
160
140
120
100
80
60
40
20
0
ppn

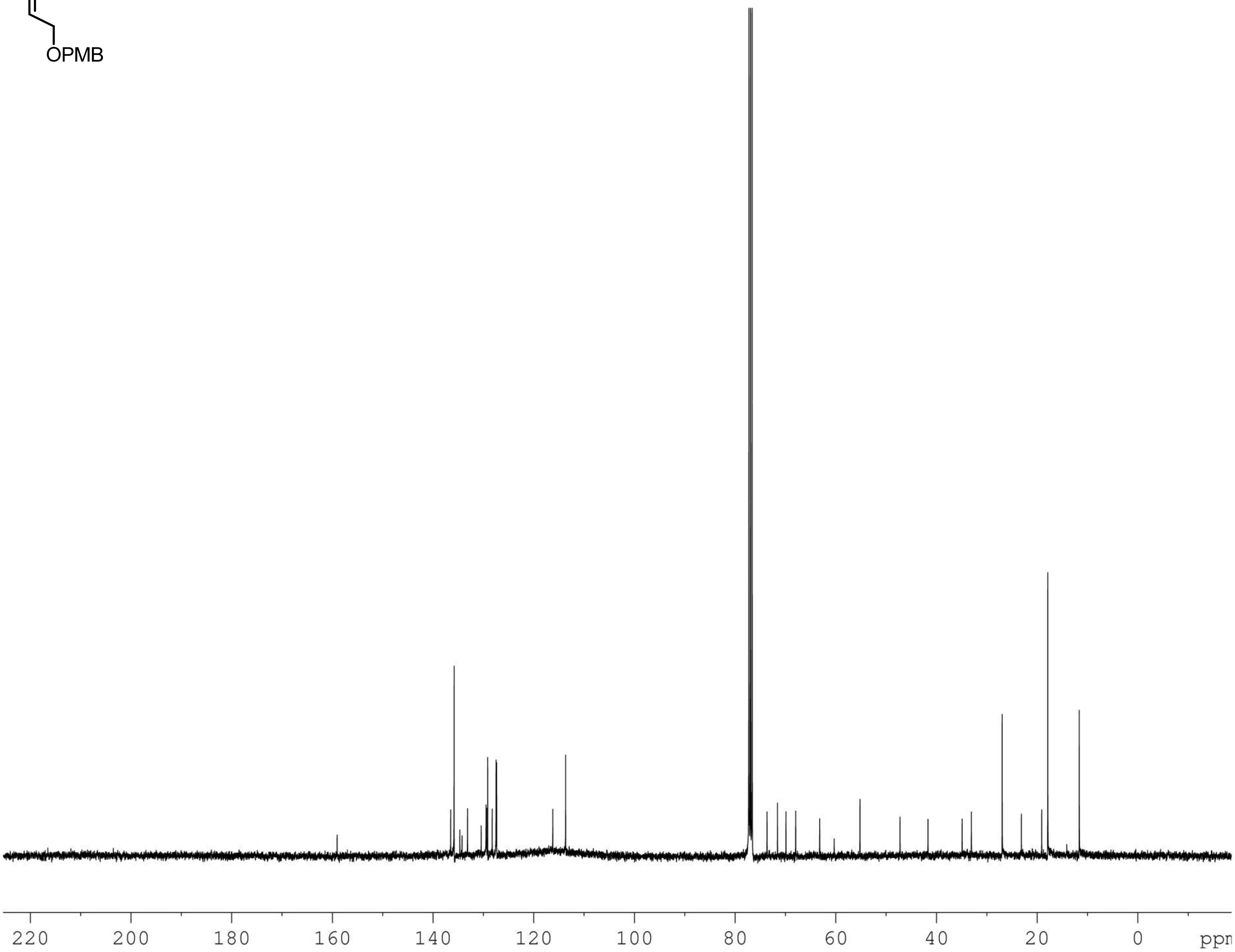


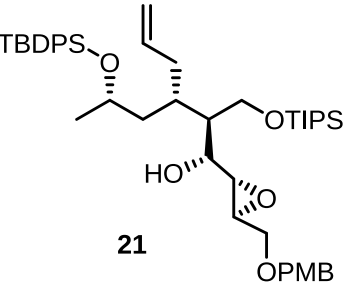
20



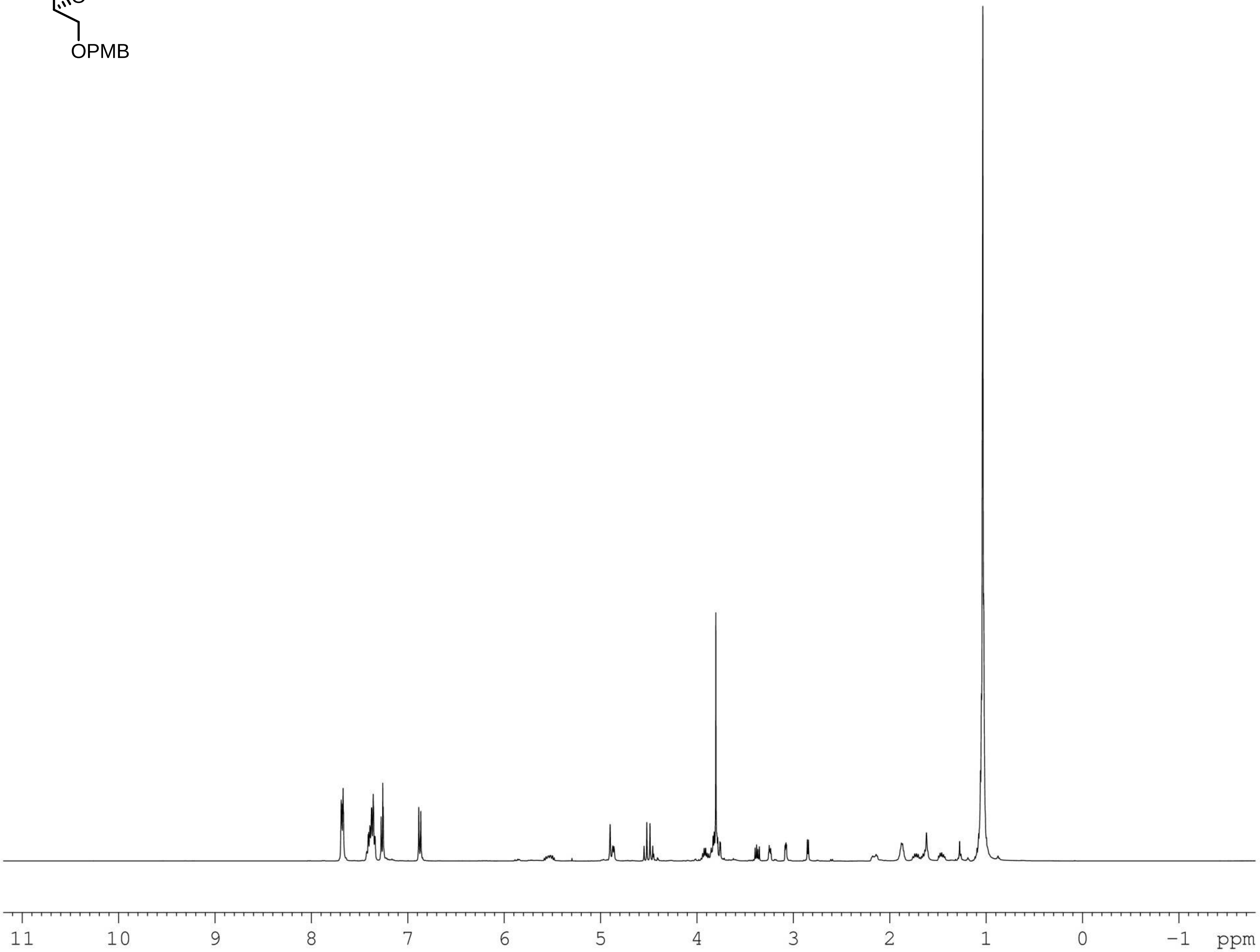

TBDPS
O
OTIPS
HO
OPMB

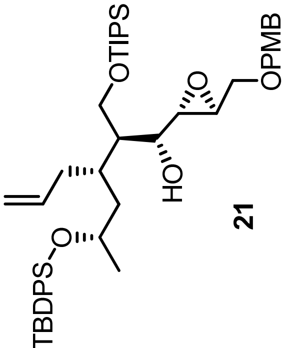
20


220
200
180
160
140
120
100
80
60
40
20
0
ppm

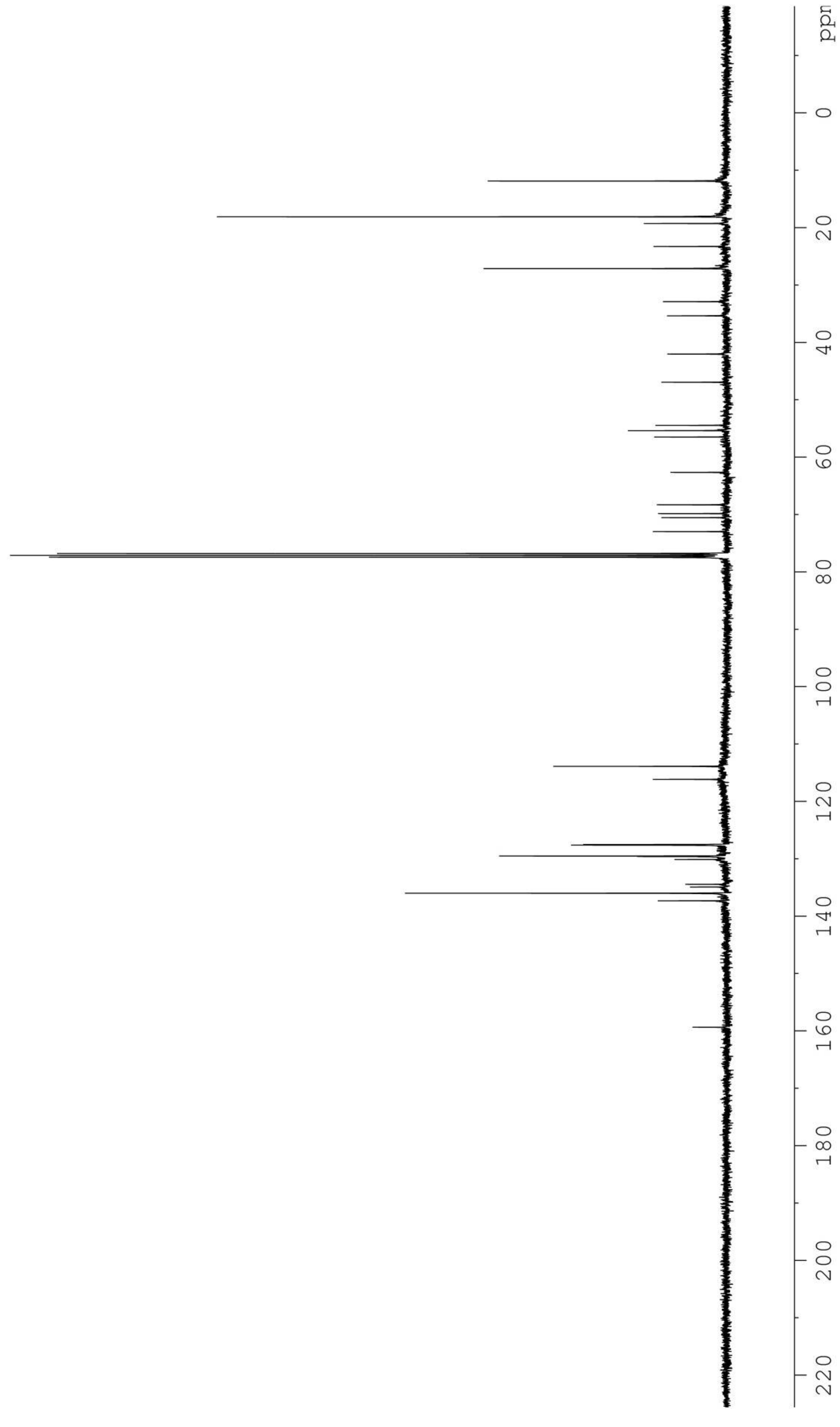


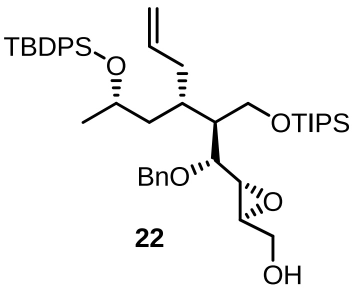
21



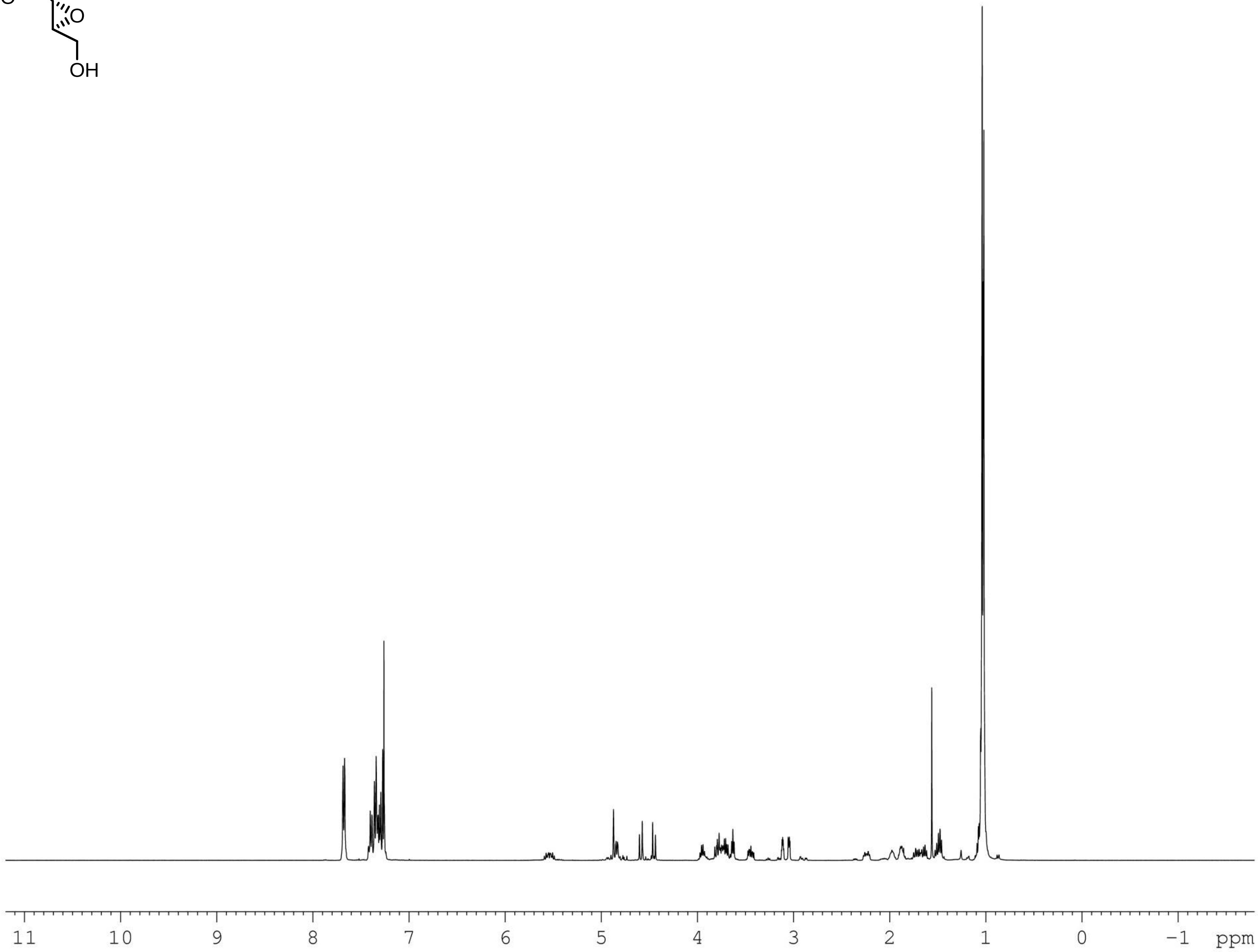

TBDPS
O
OTIPS
HO
O
OPMB

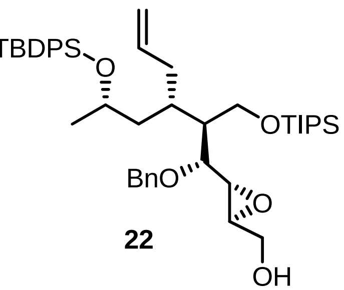
21


ppm
0
20
40
60
80
100
120
140
160
180
200
220

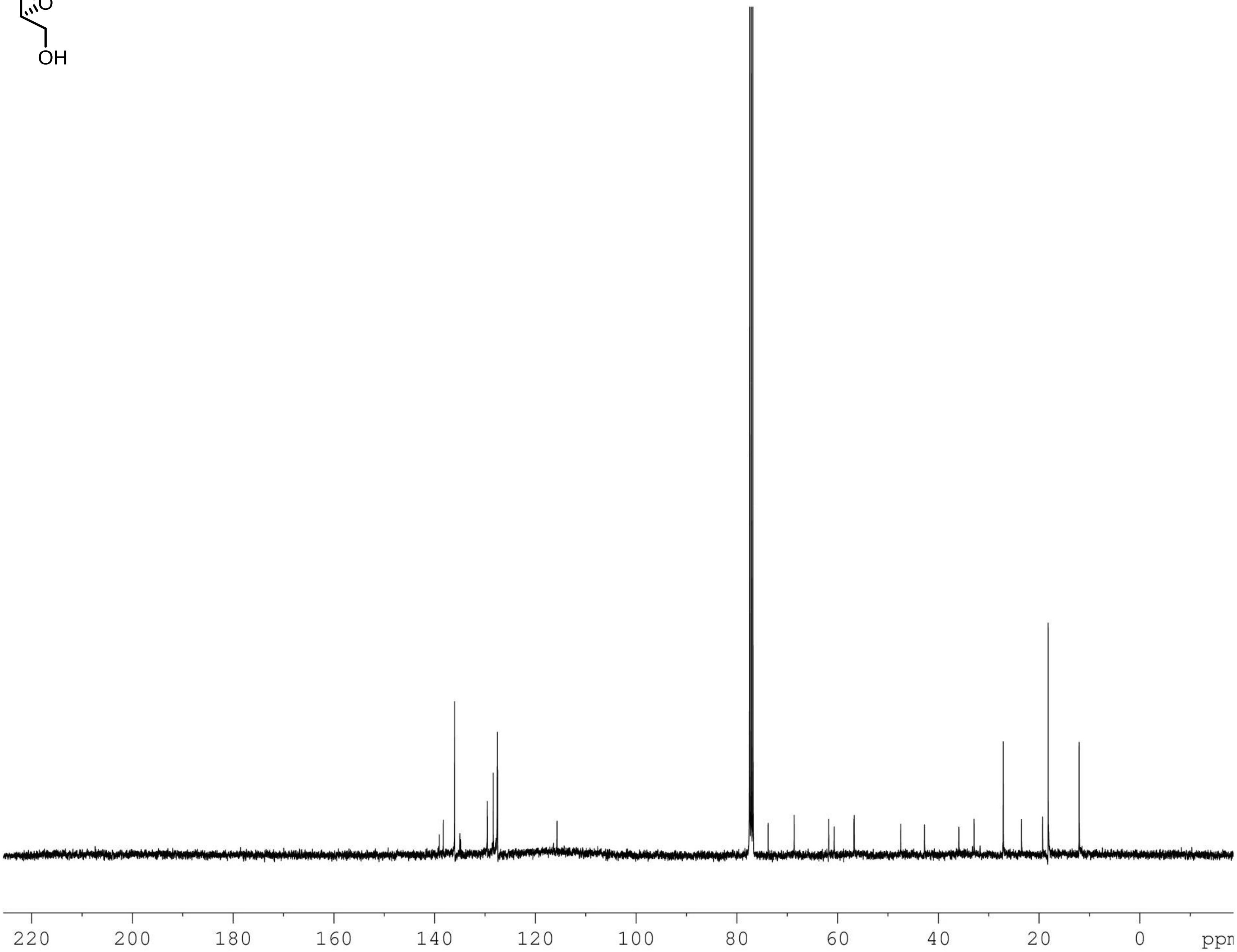


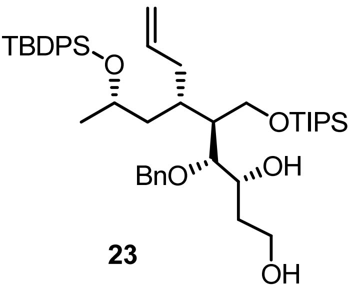
22



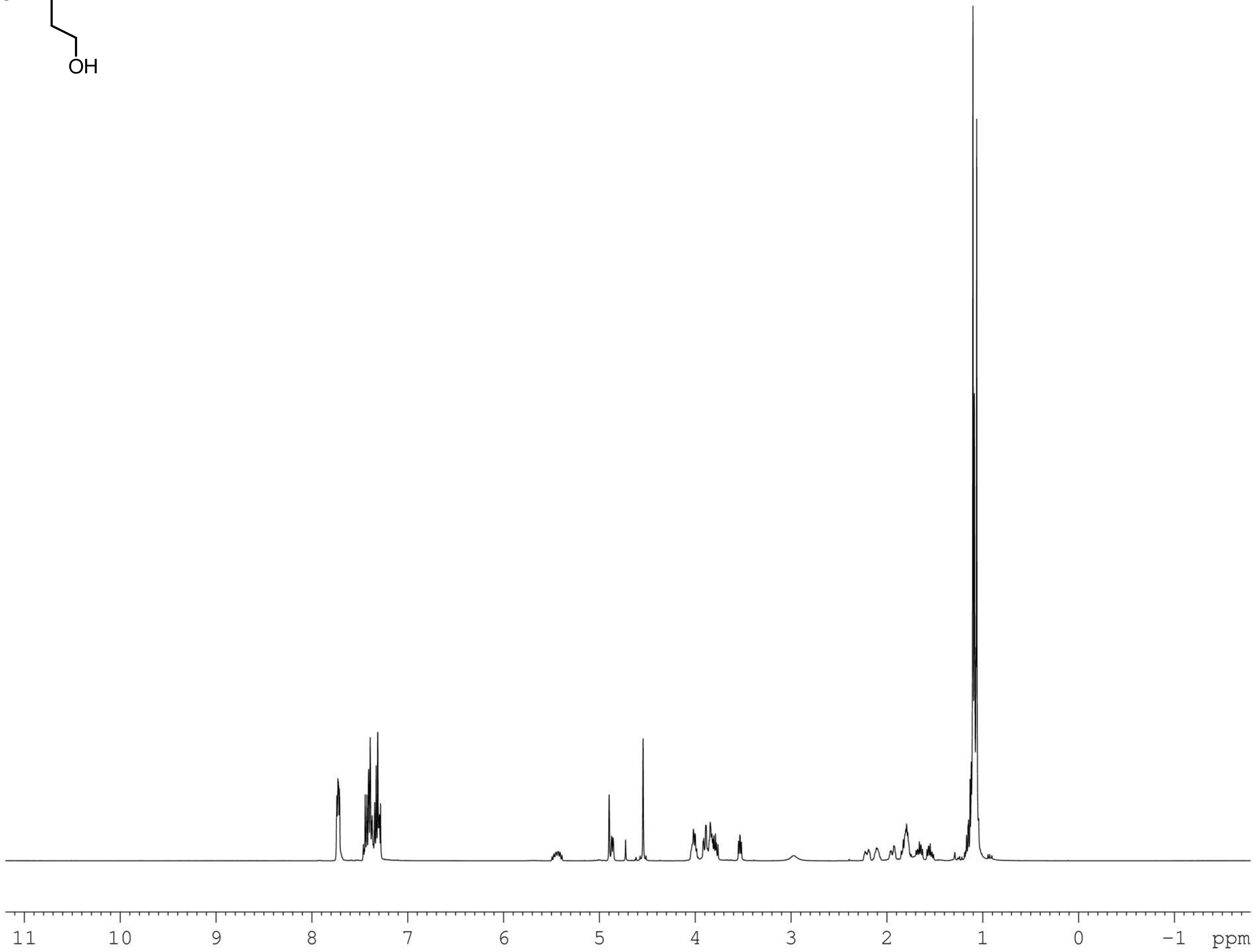

TBDPS
O
OTIPS
BnO
O
OH

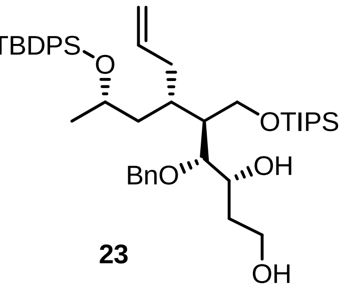
22


220
200
180
160
140
120
100
80
60
40
20
0
ppm

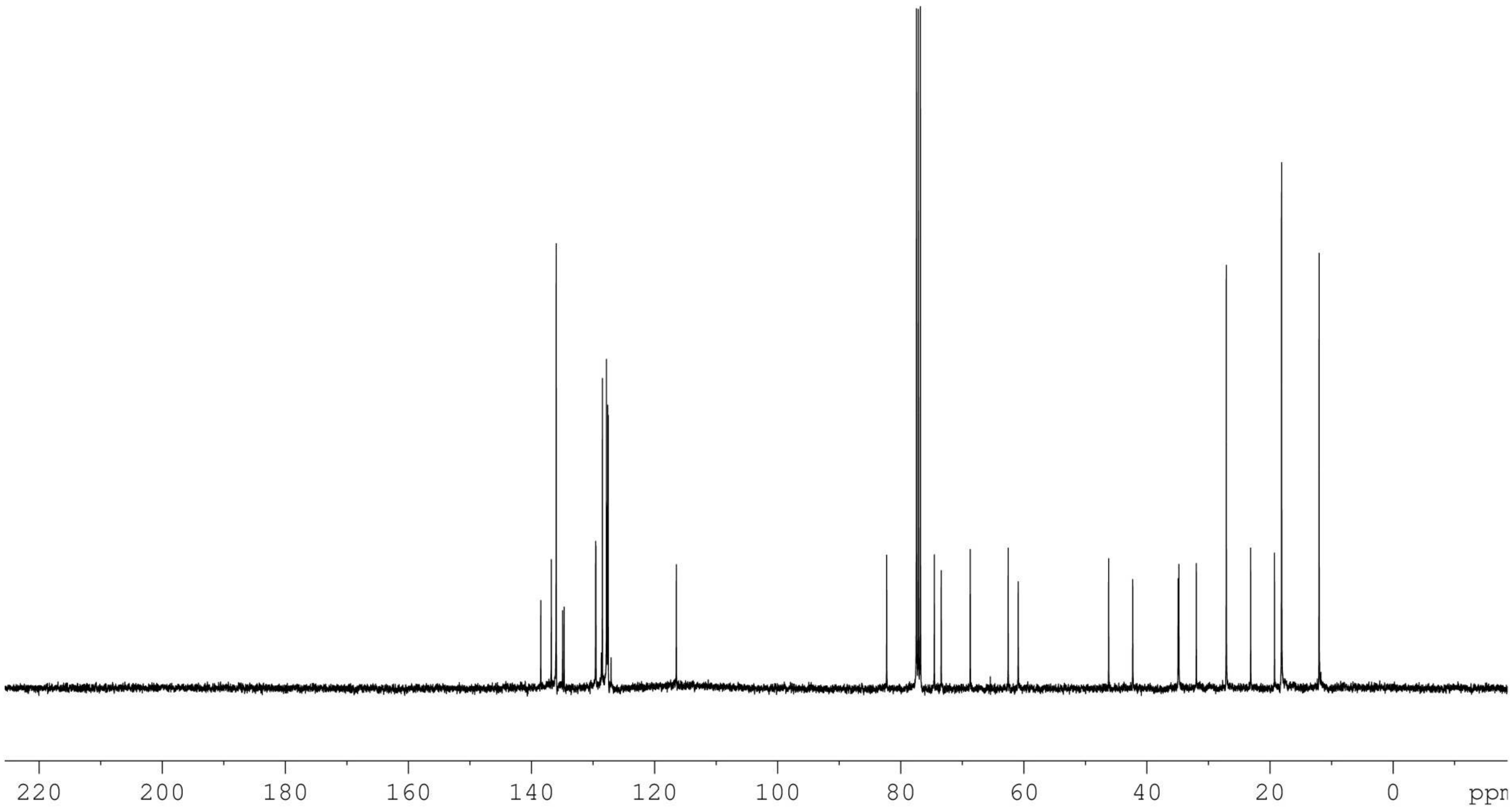


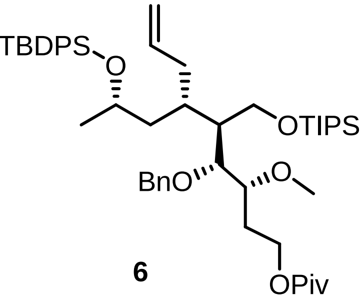
23



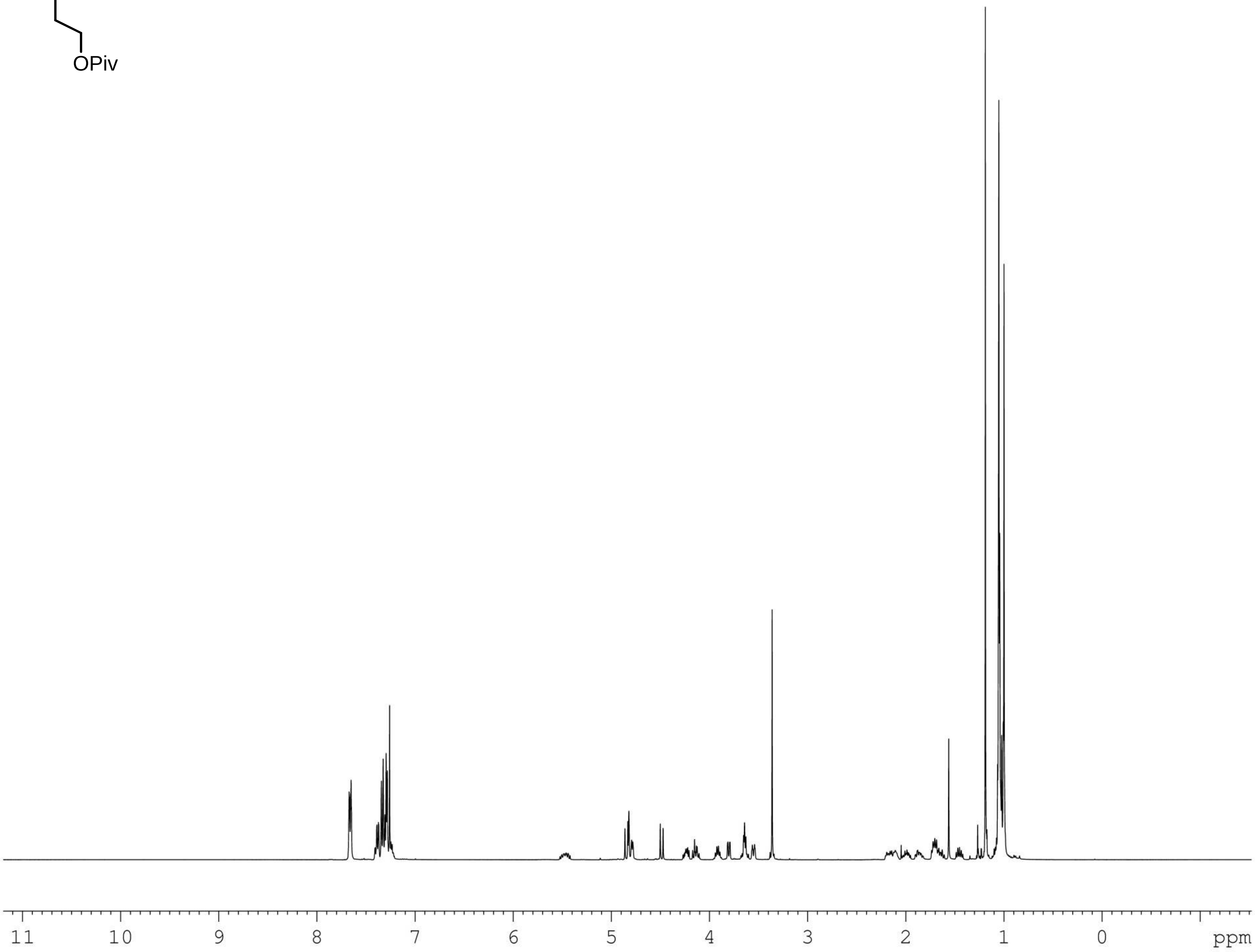

TBDPS
O
OTIPS
BnO
OH
OH

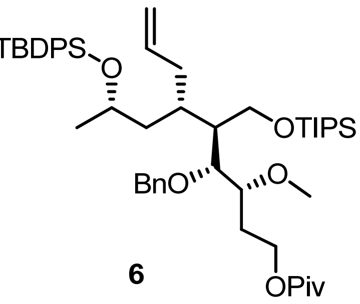
23


220
200
180
160
140
120
100
80
60
40
20
0
ppm

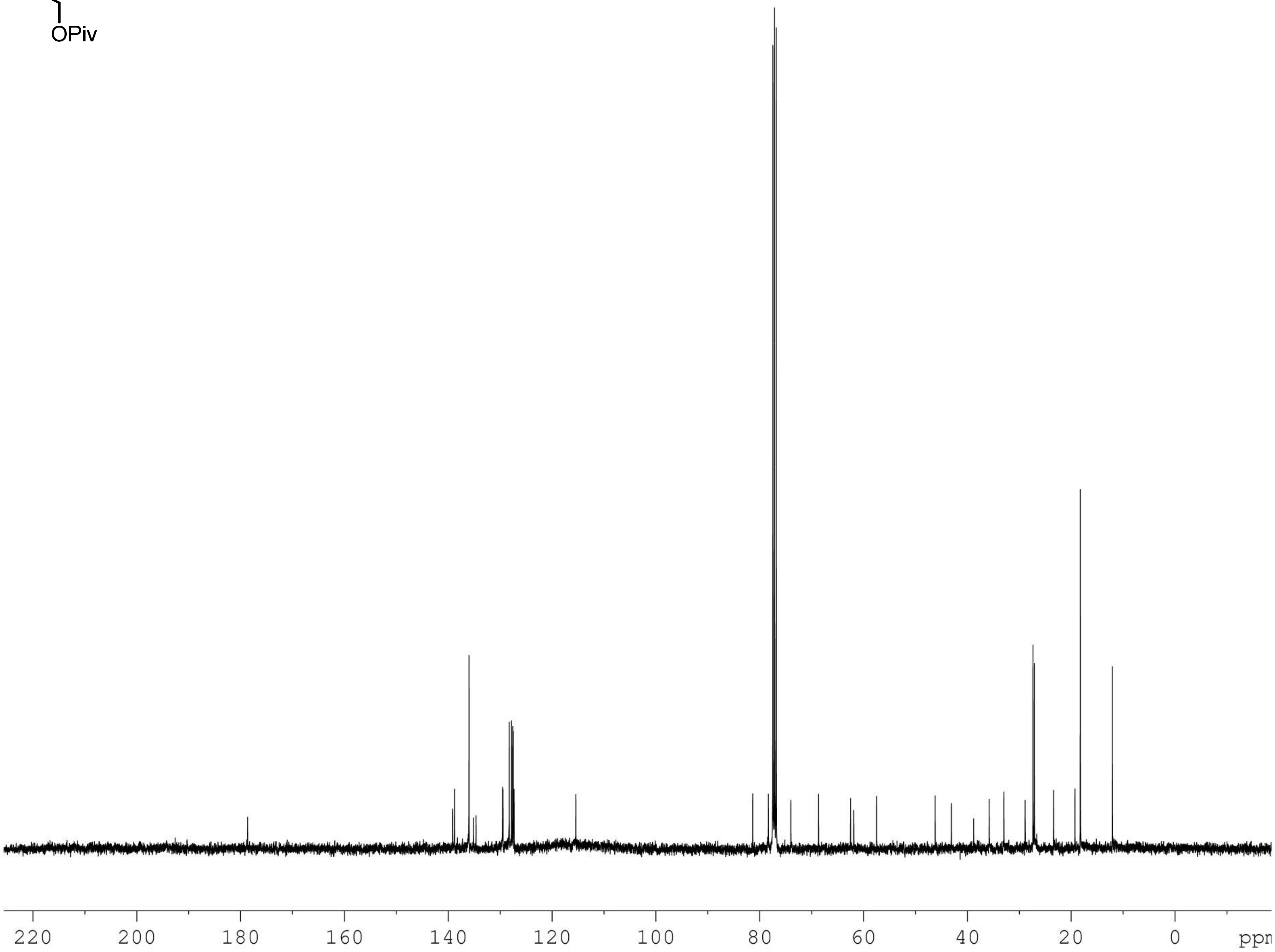


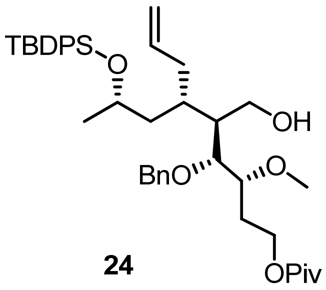
6



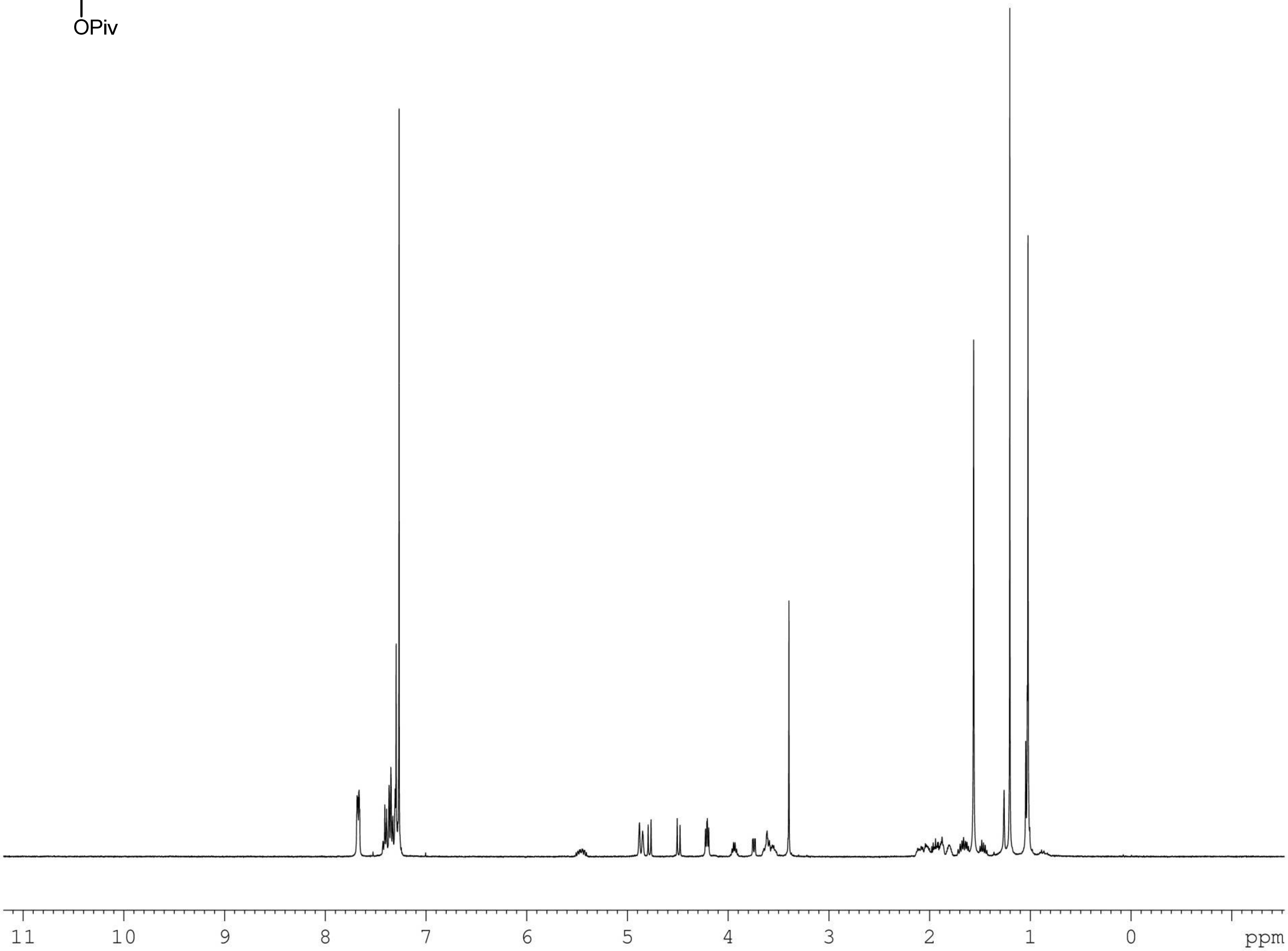

TBDPS
O
OTIPS
BnO
O
OPiv

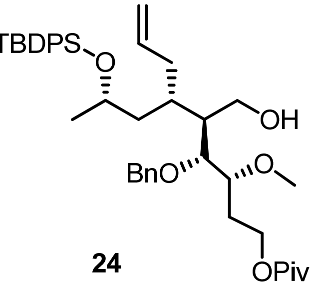
6


220
200
180
160
140
120
100
80
60
40
20
0
ppm

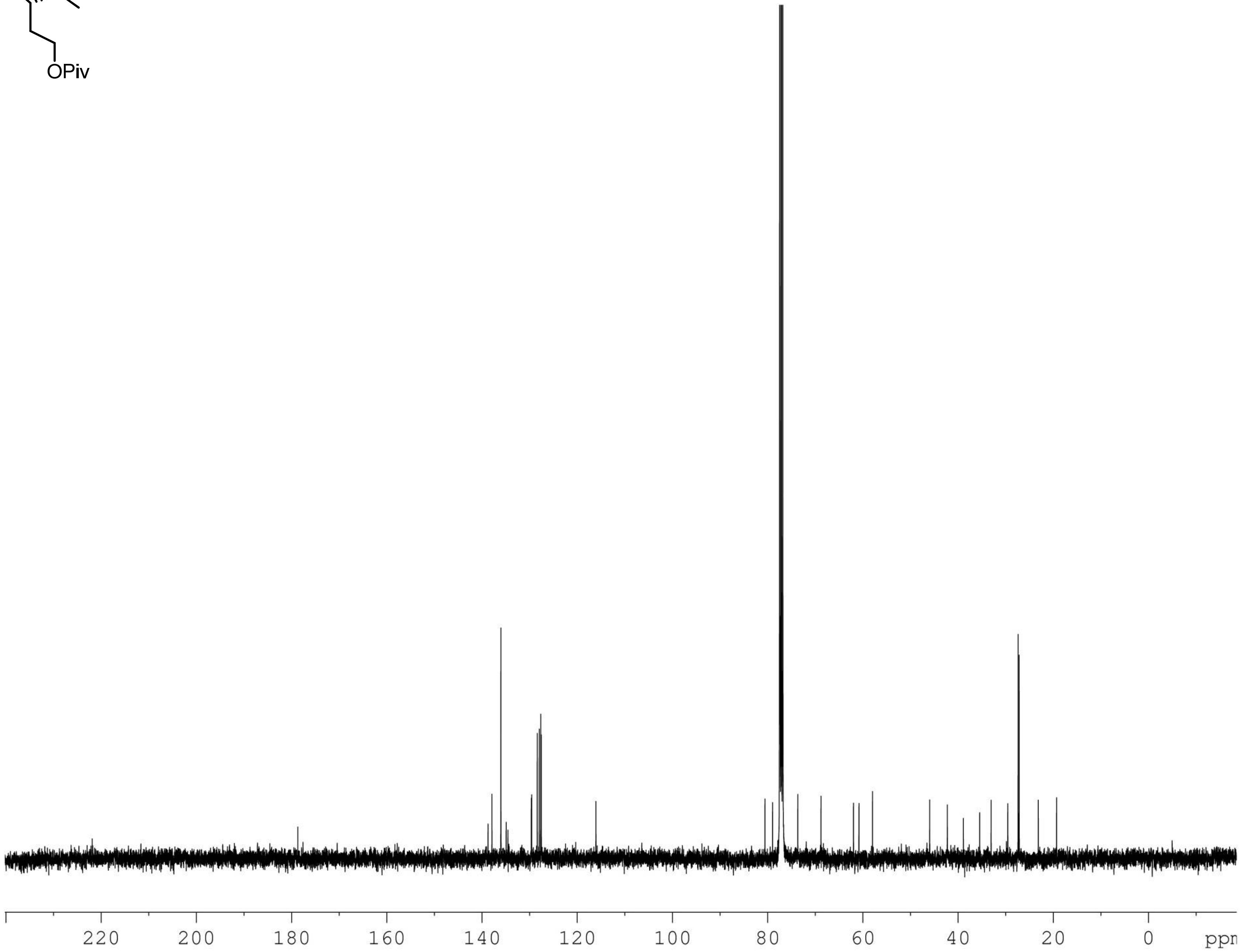


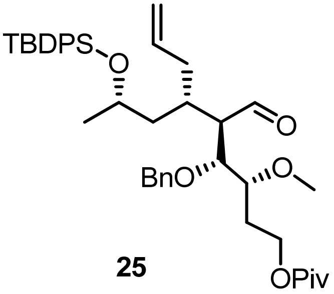
24



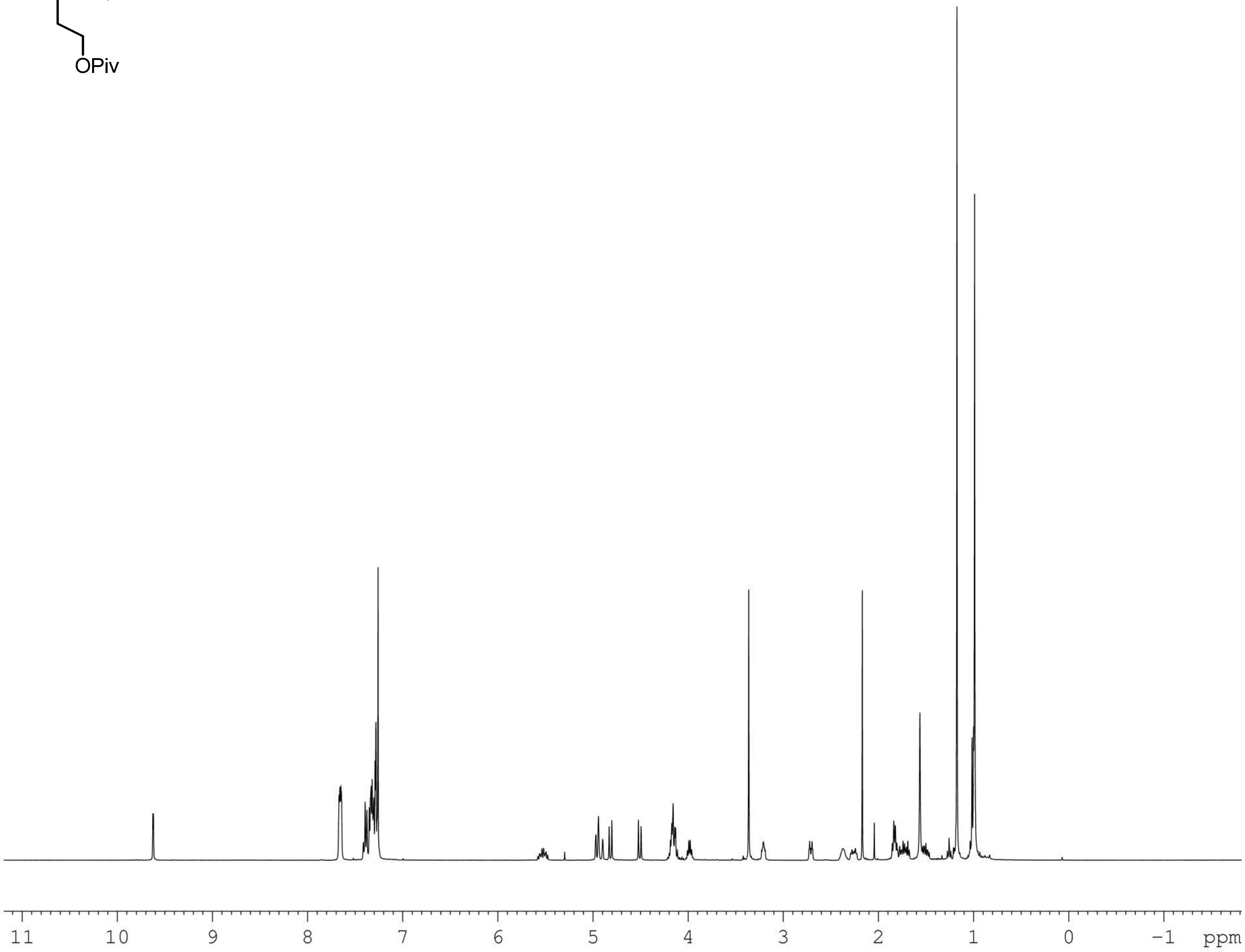


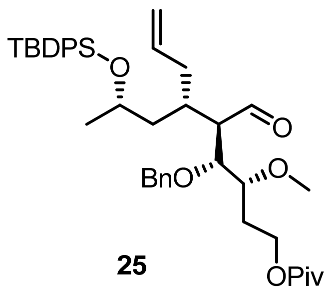
24



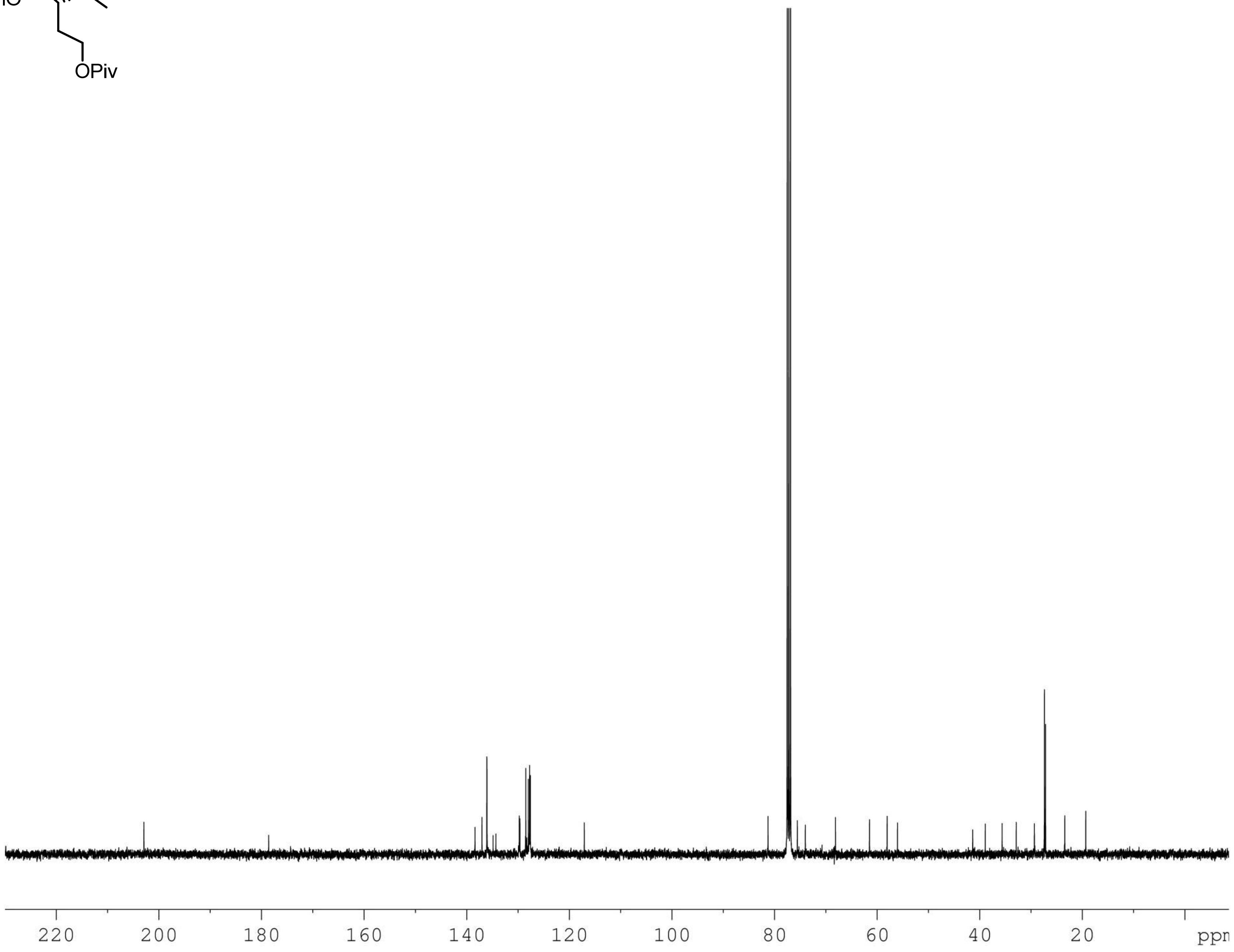


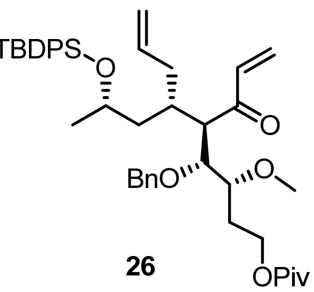
25



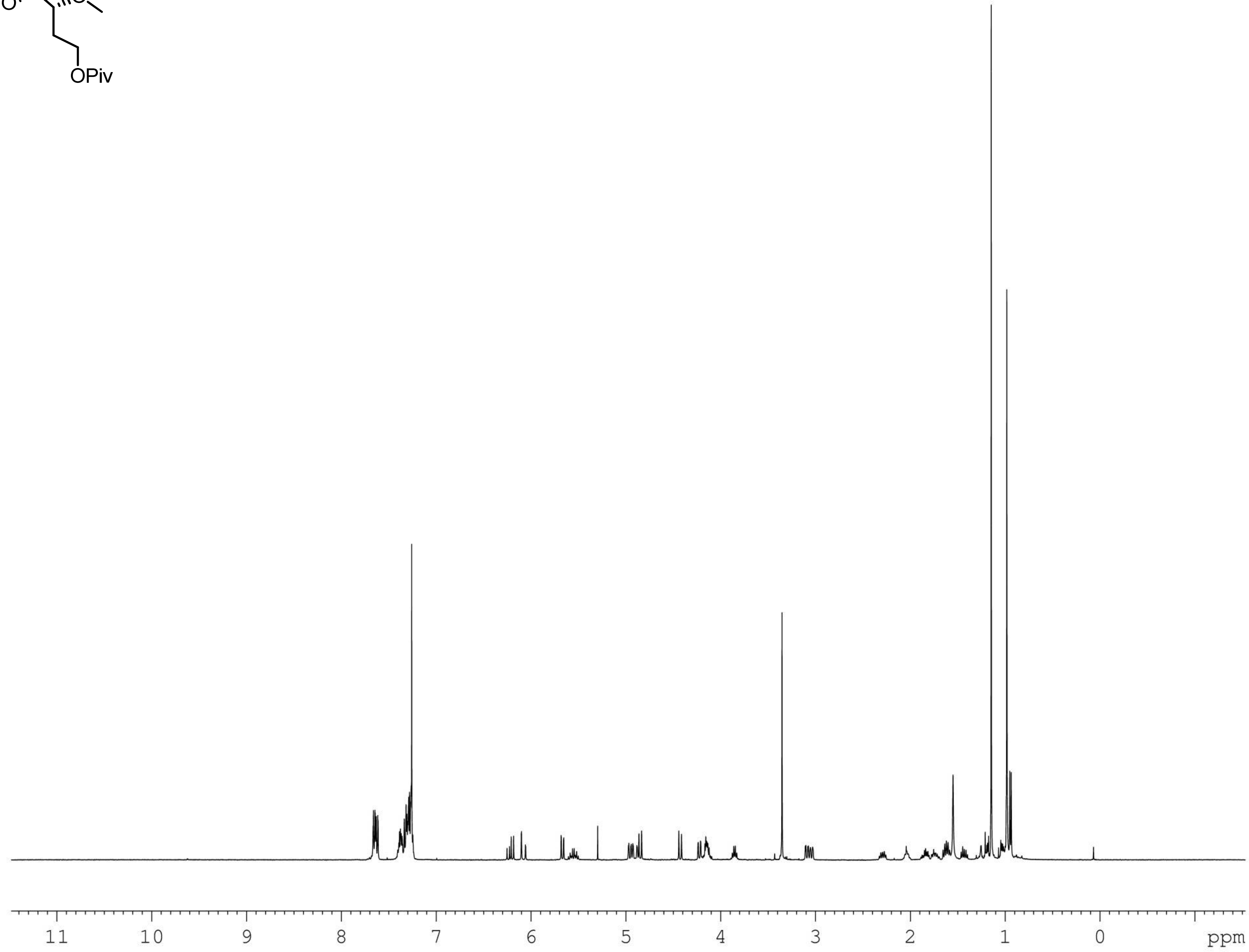


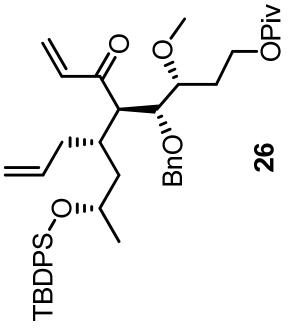
25



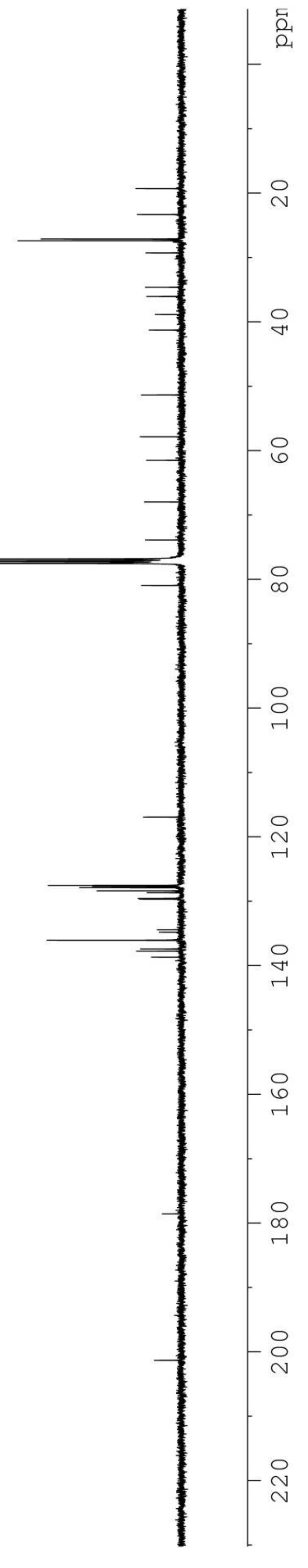


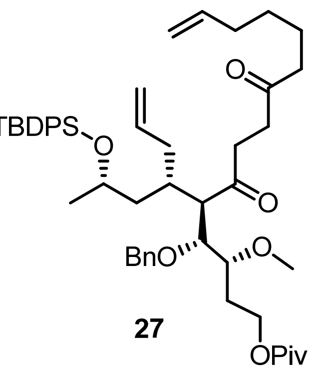
26



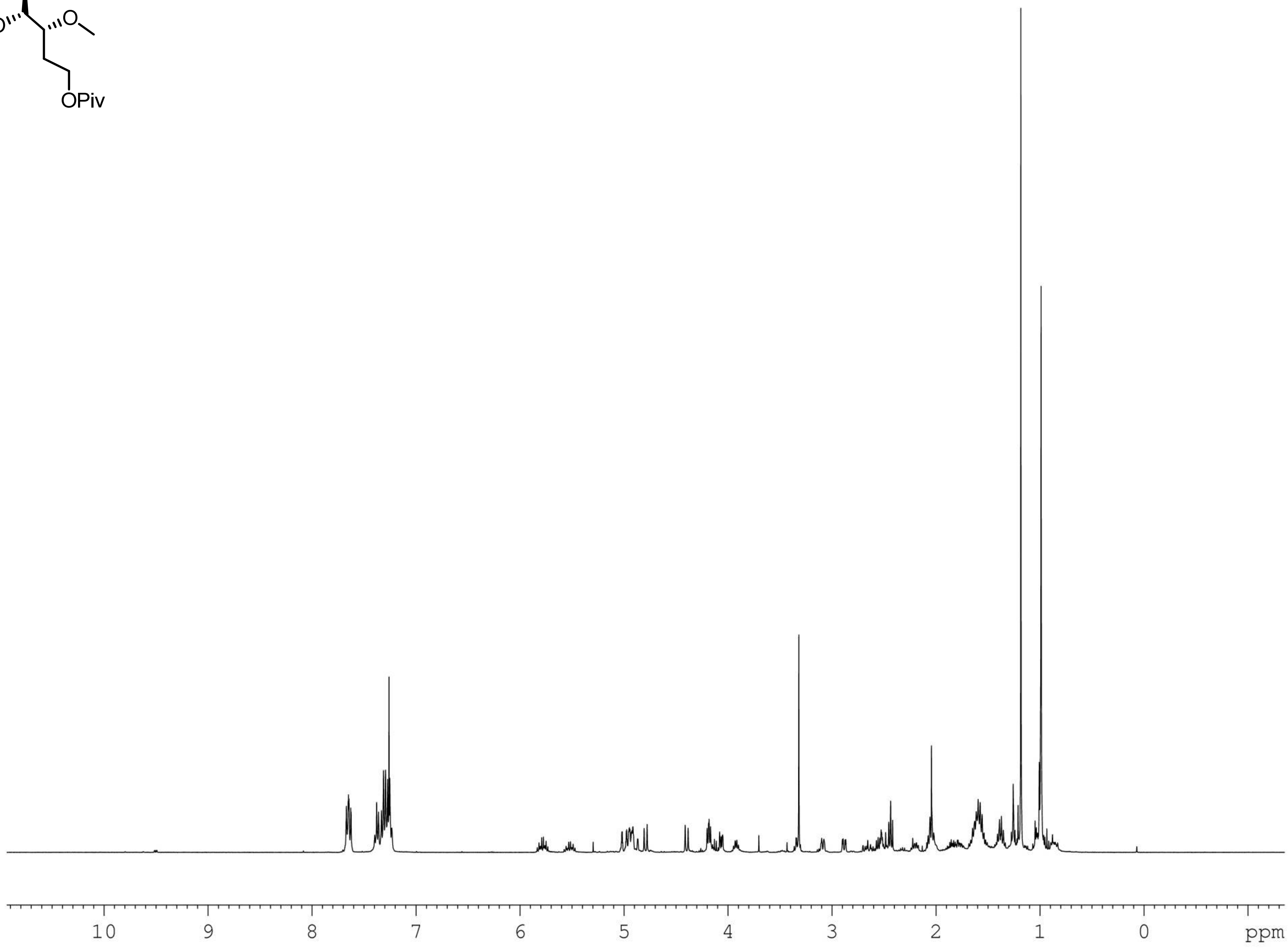


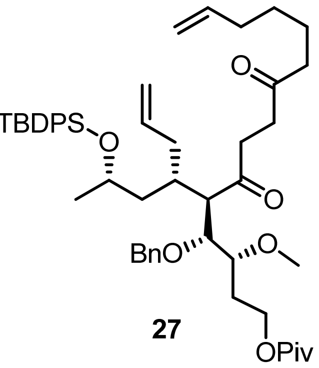
26



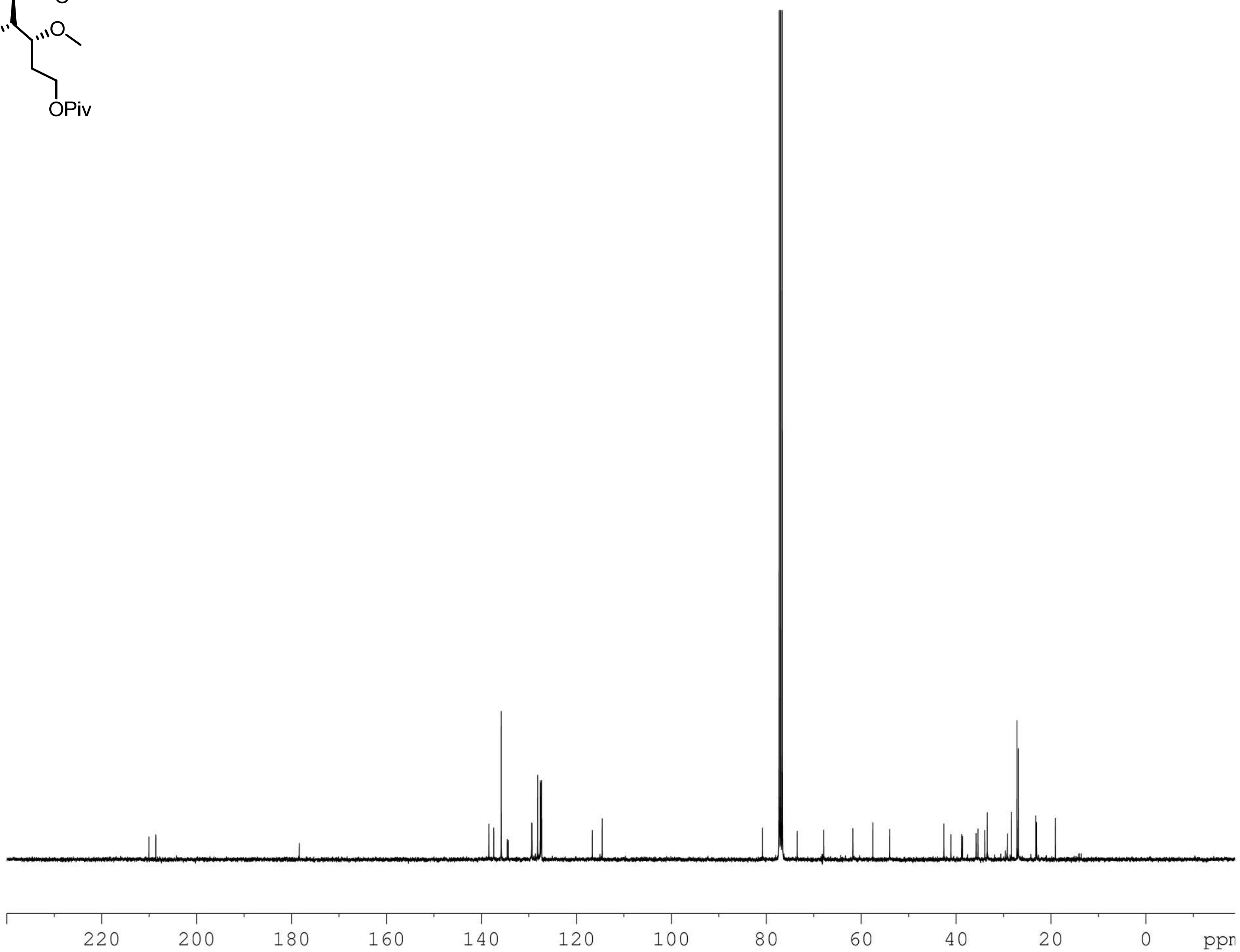


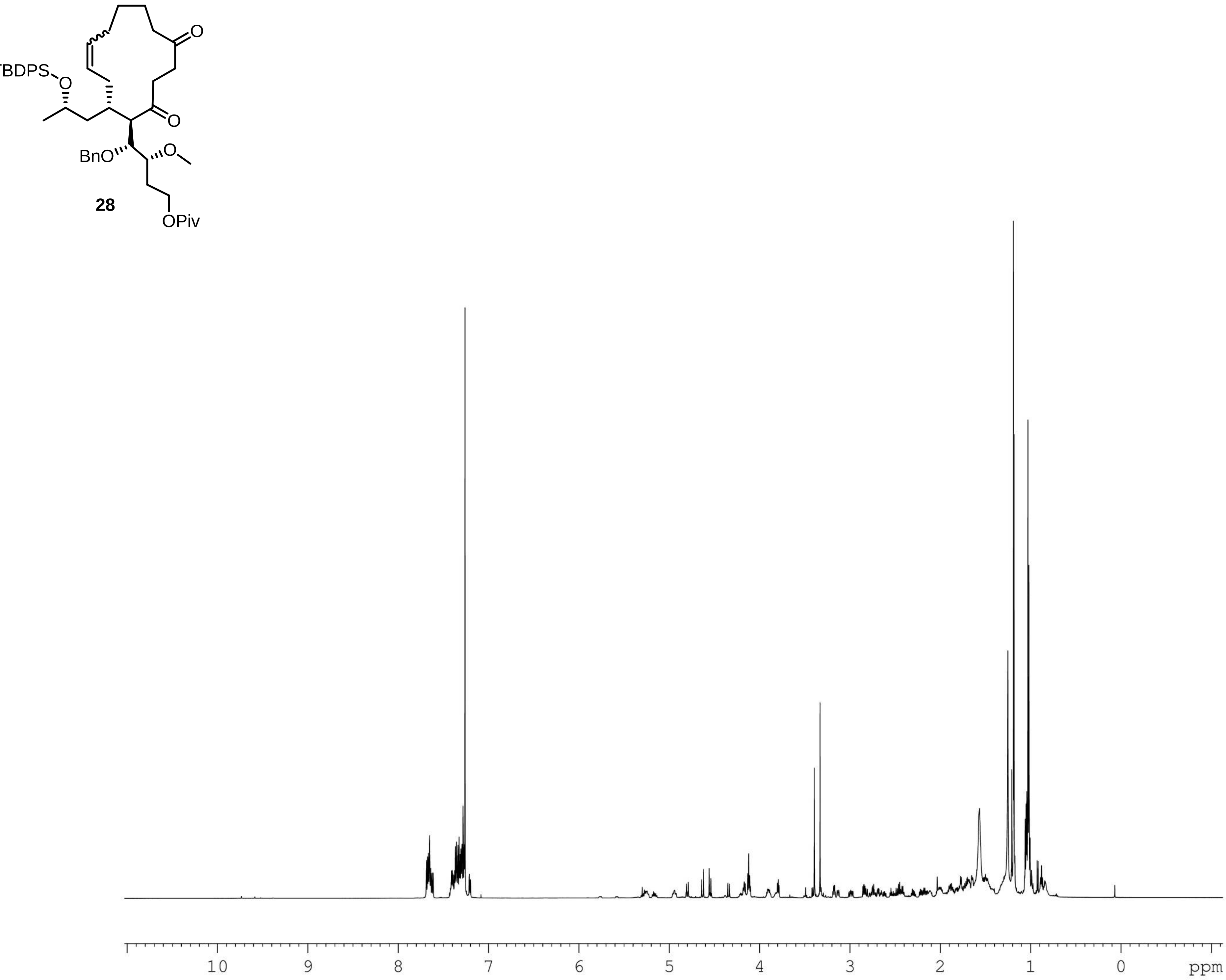
27

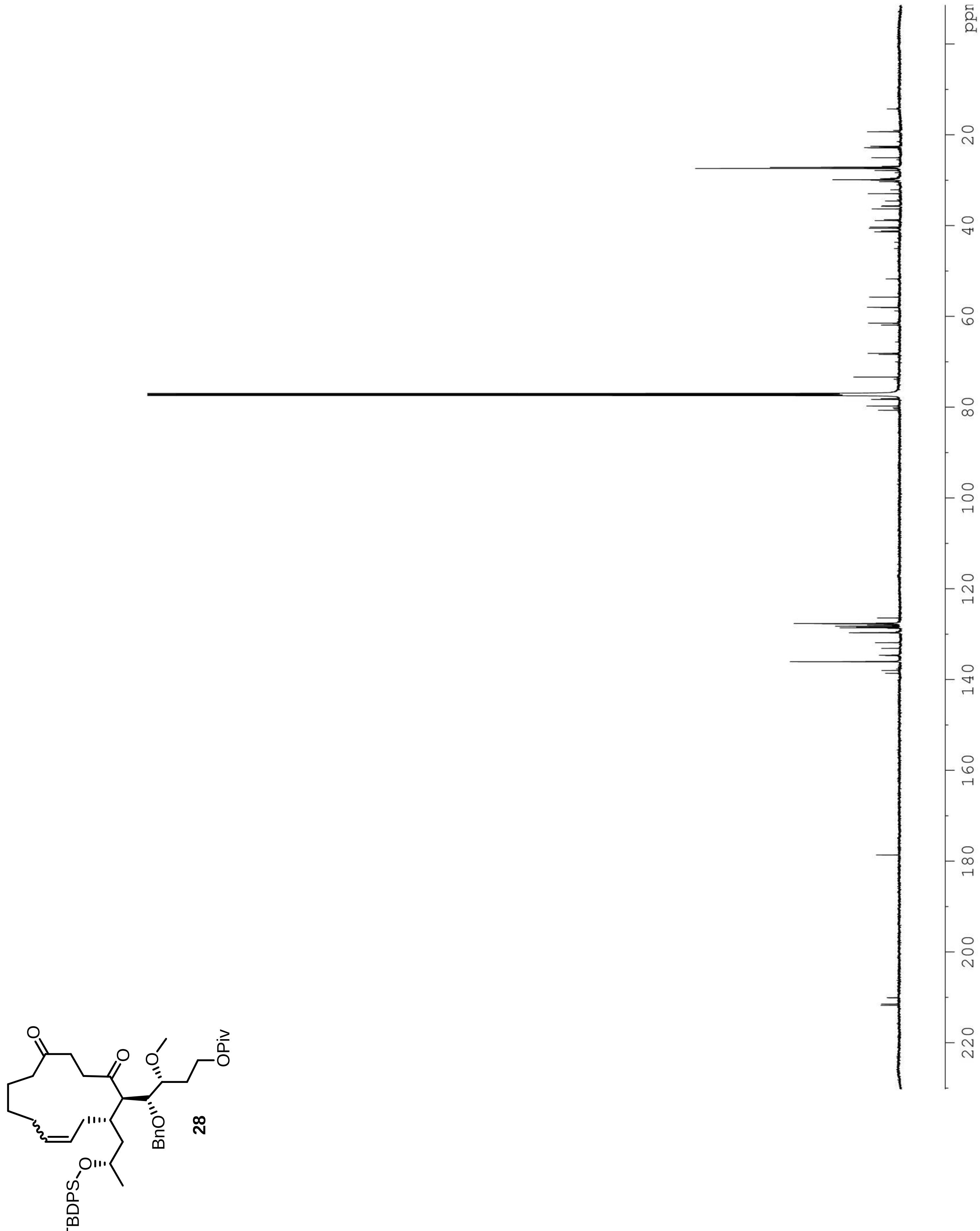




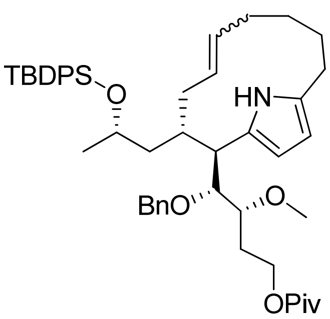
27



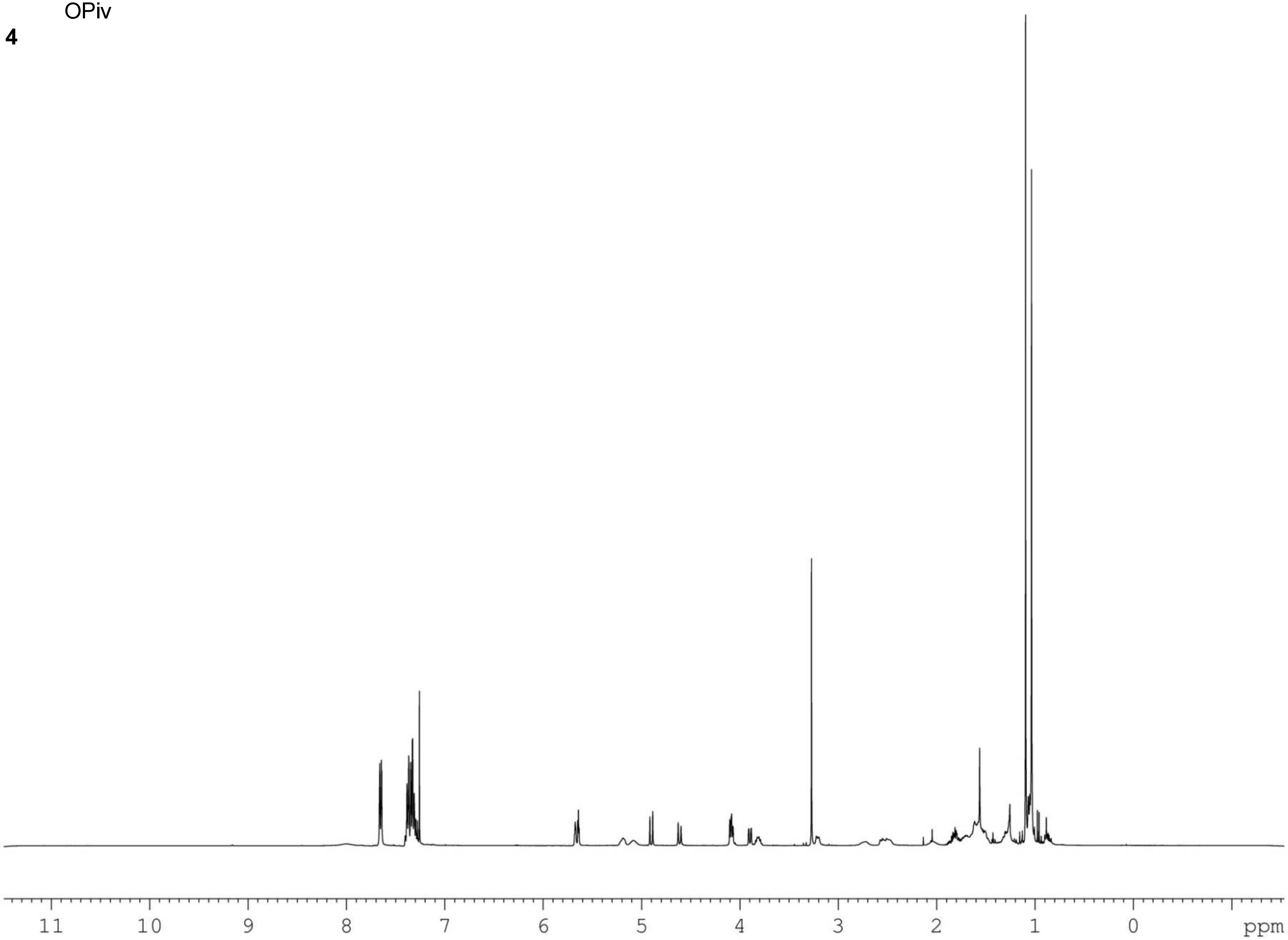

28

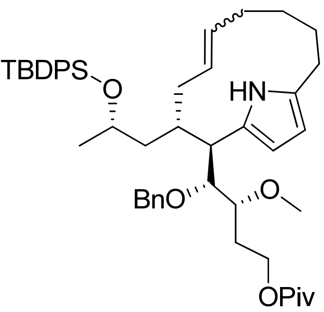


28

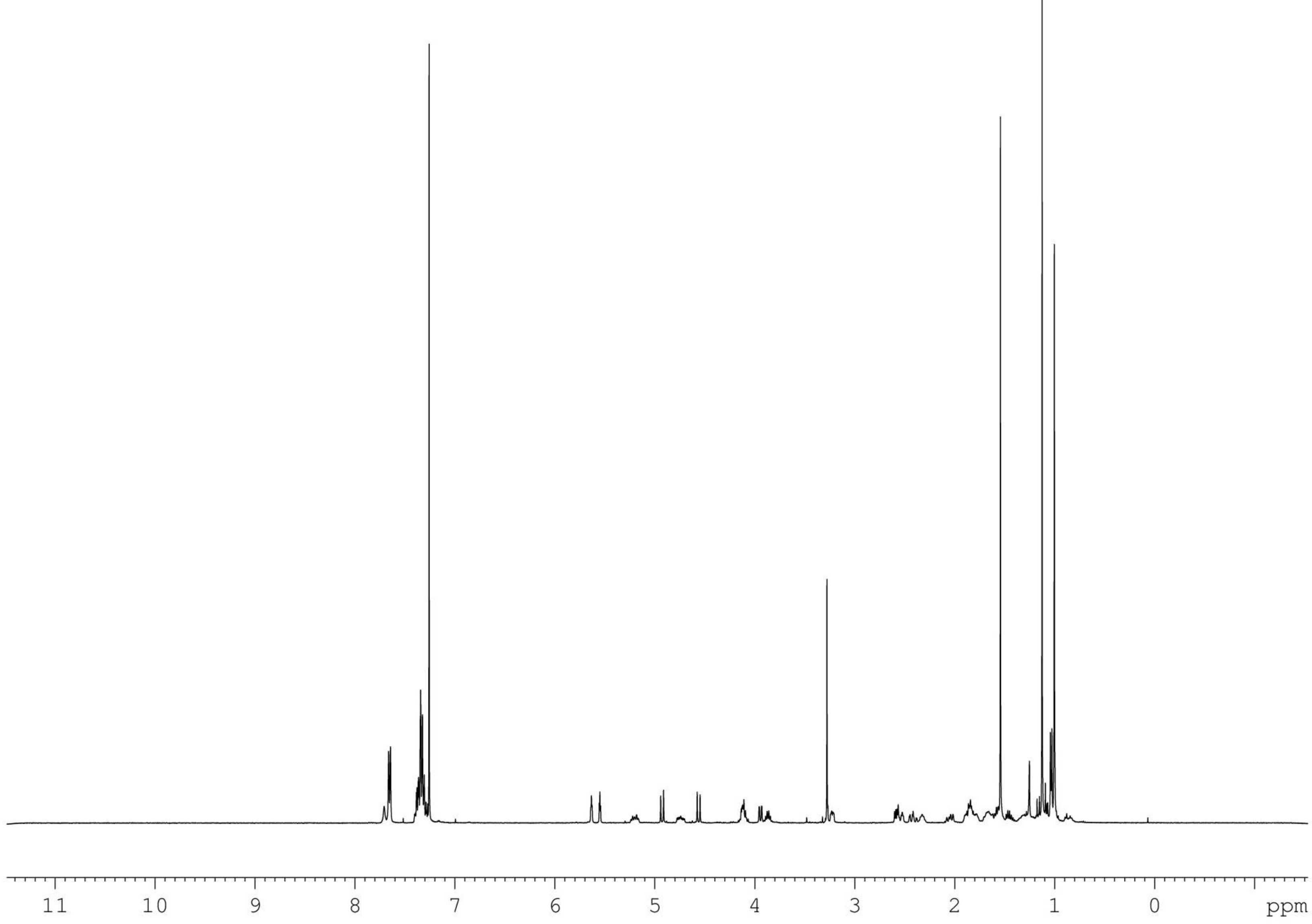


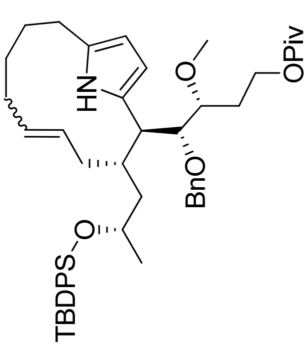
4



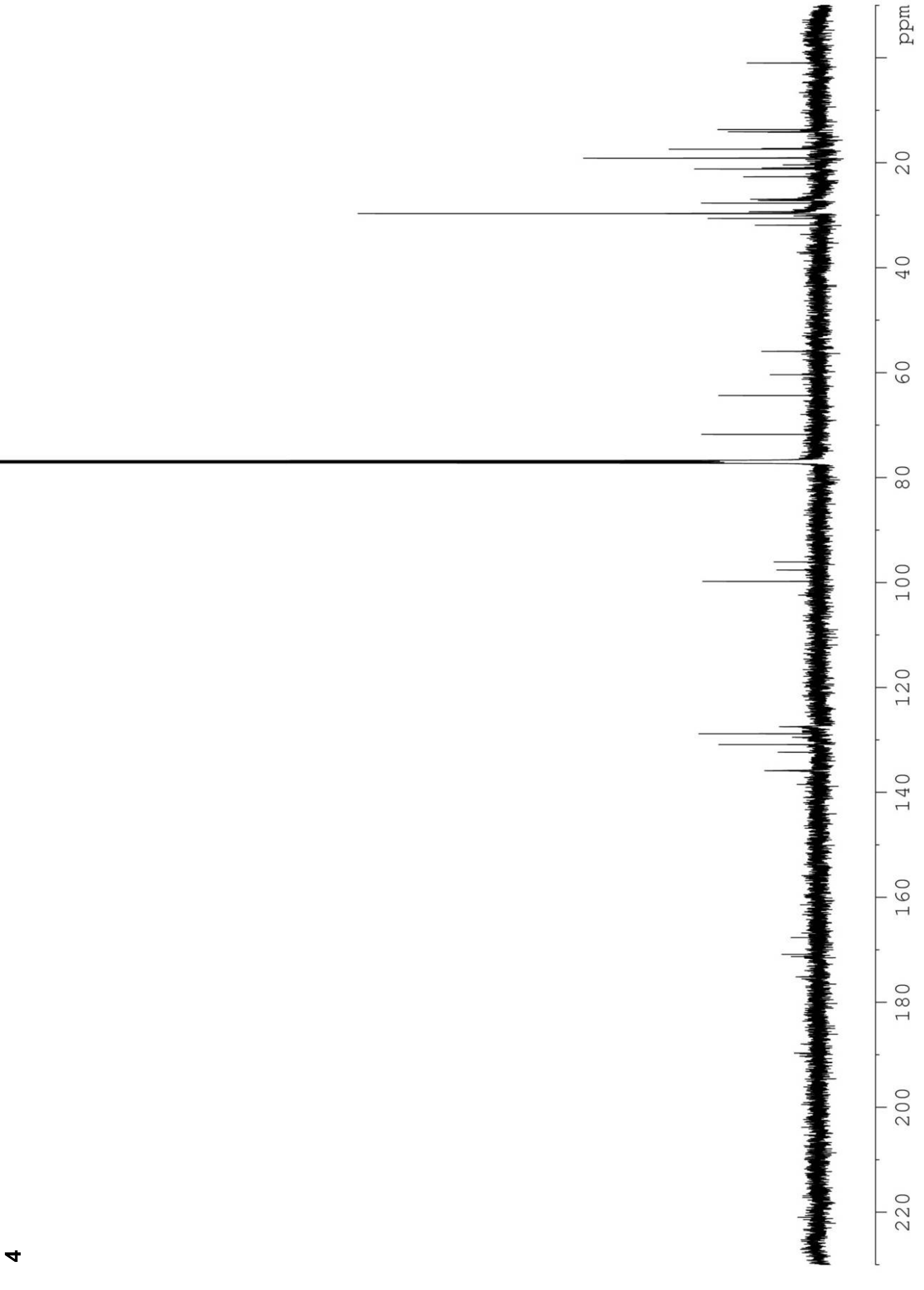


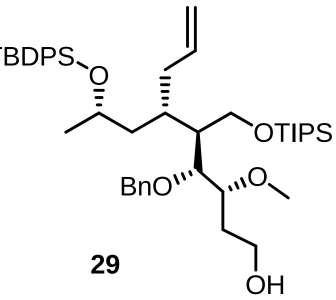
4



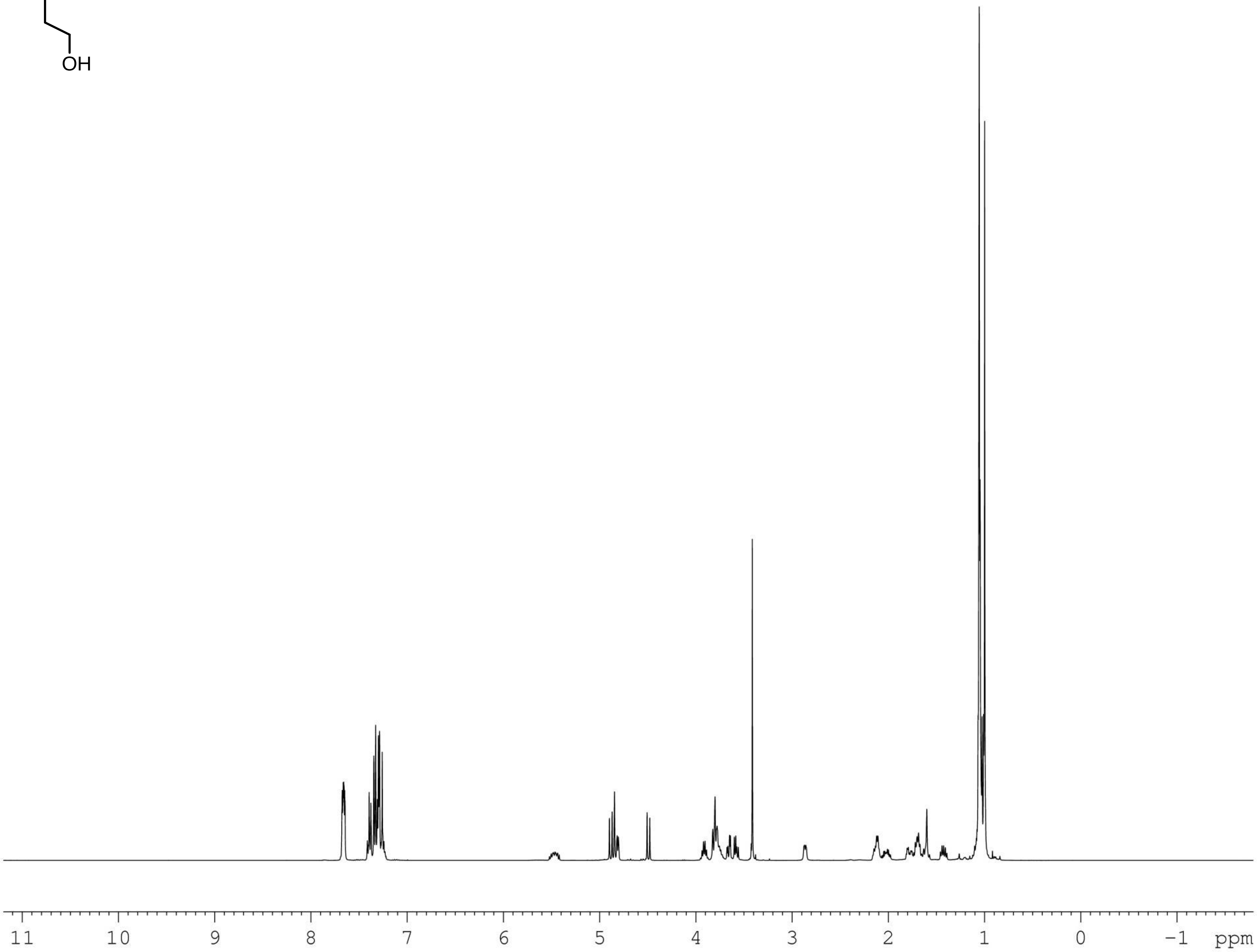


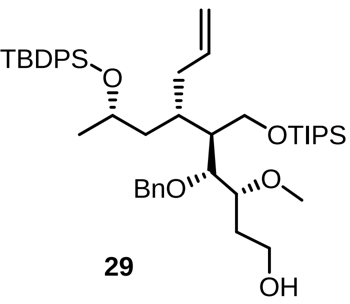
4



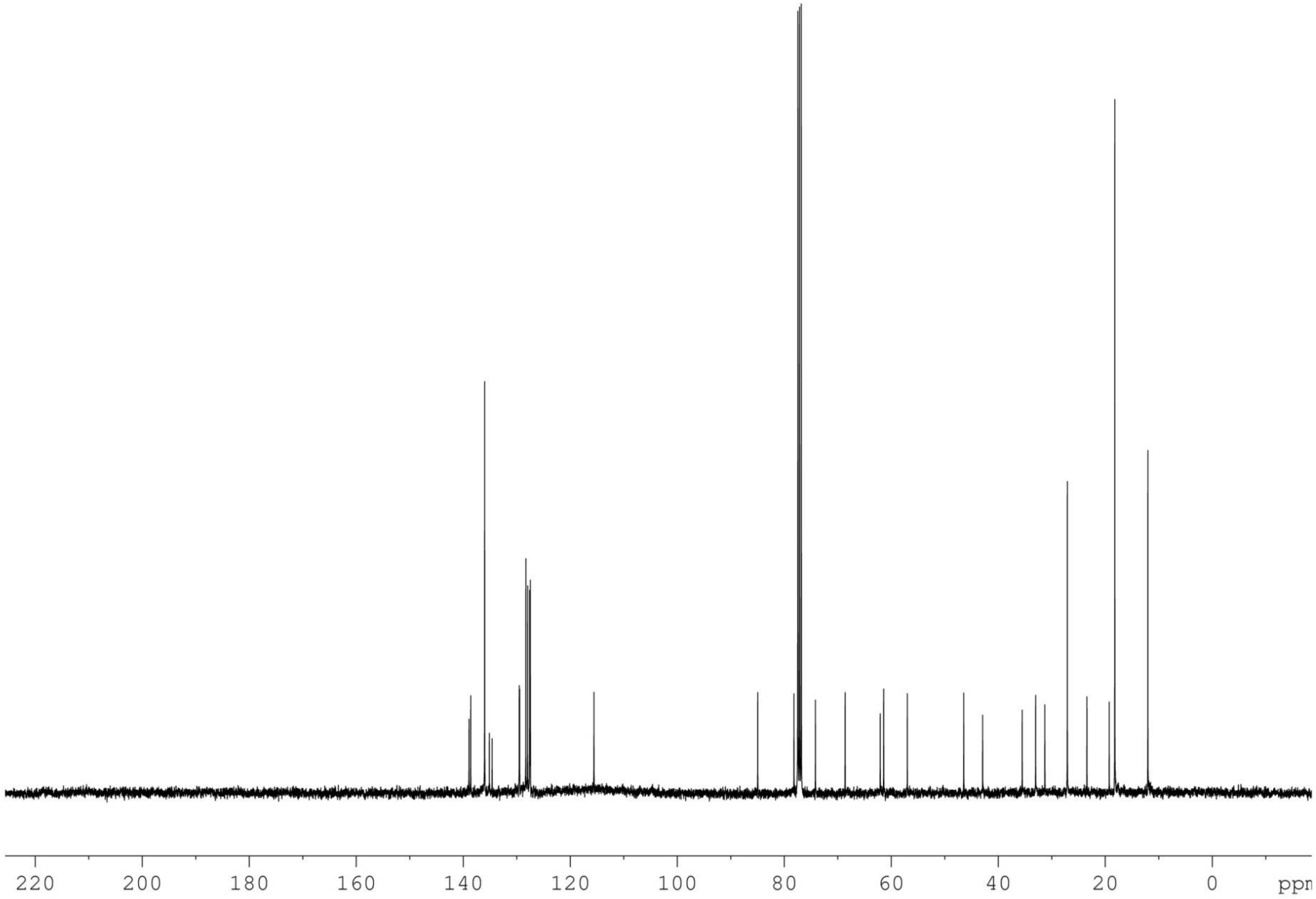


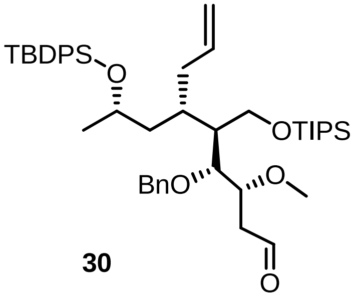
29



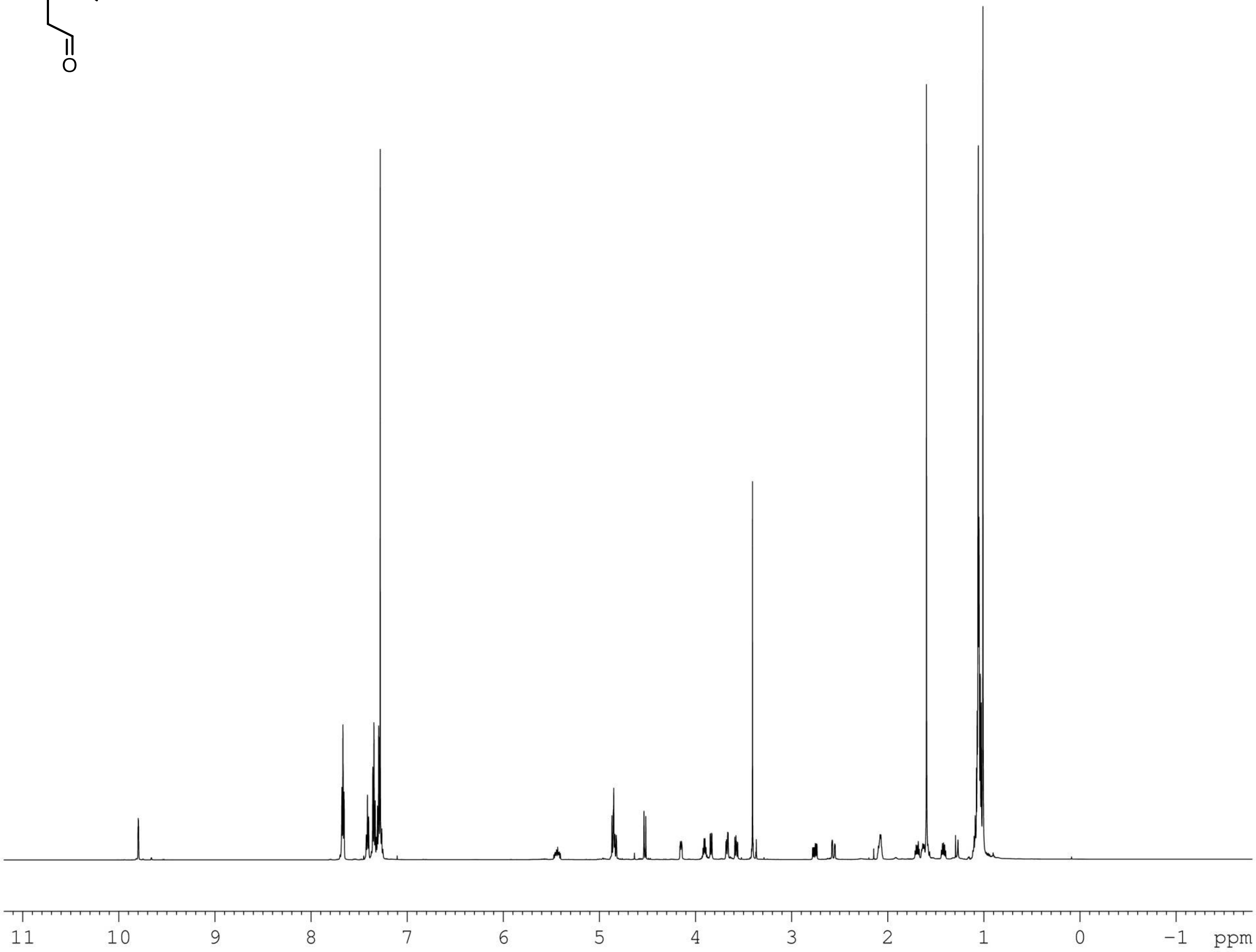

TBDPS
O
OTIPS
BnO
O
OH

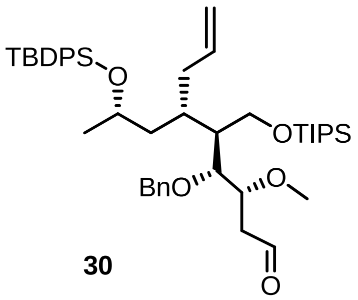
29


220
200
180
160
140
120
100
80
60
40
20
0
ppm

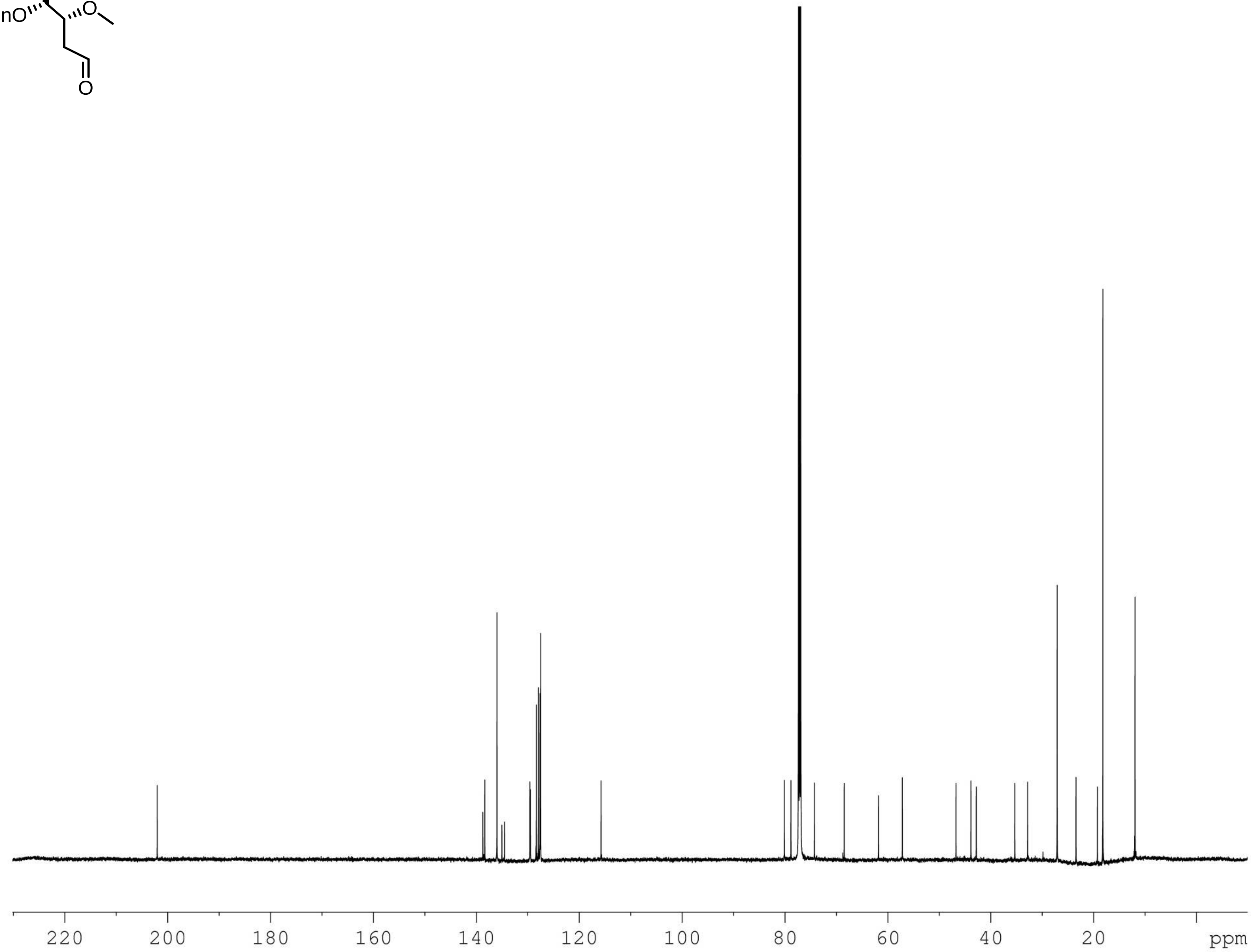


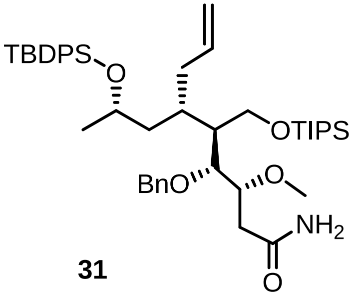
30



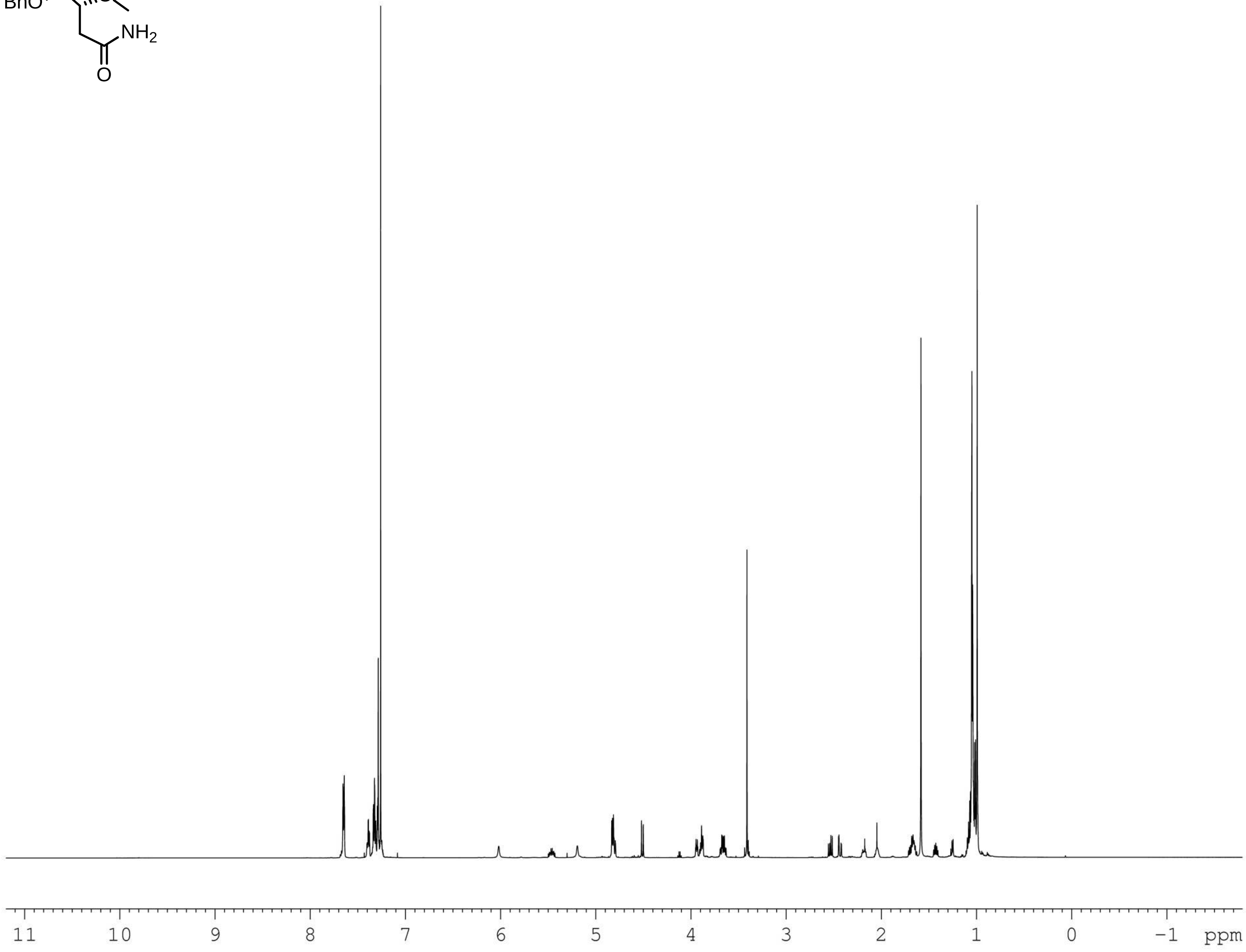


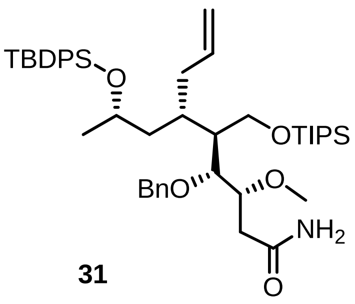
30



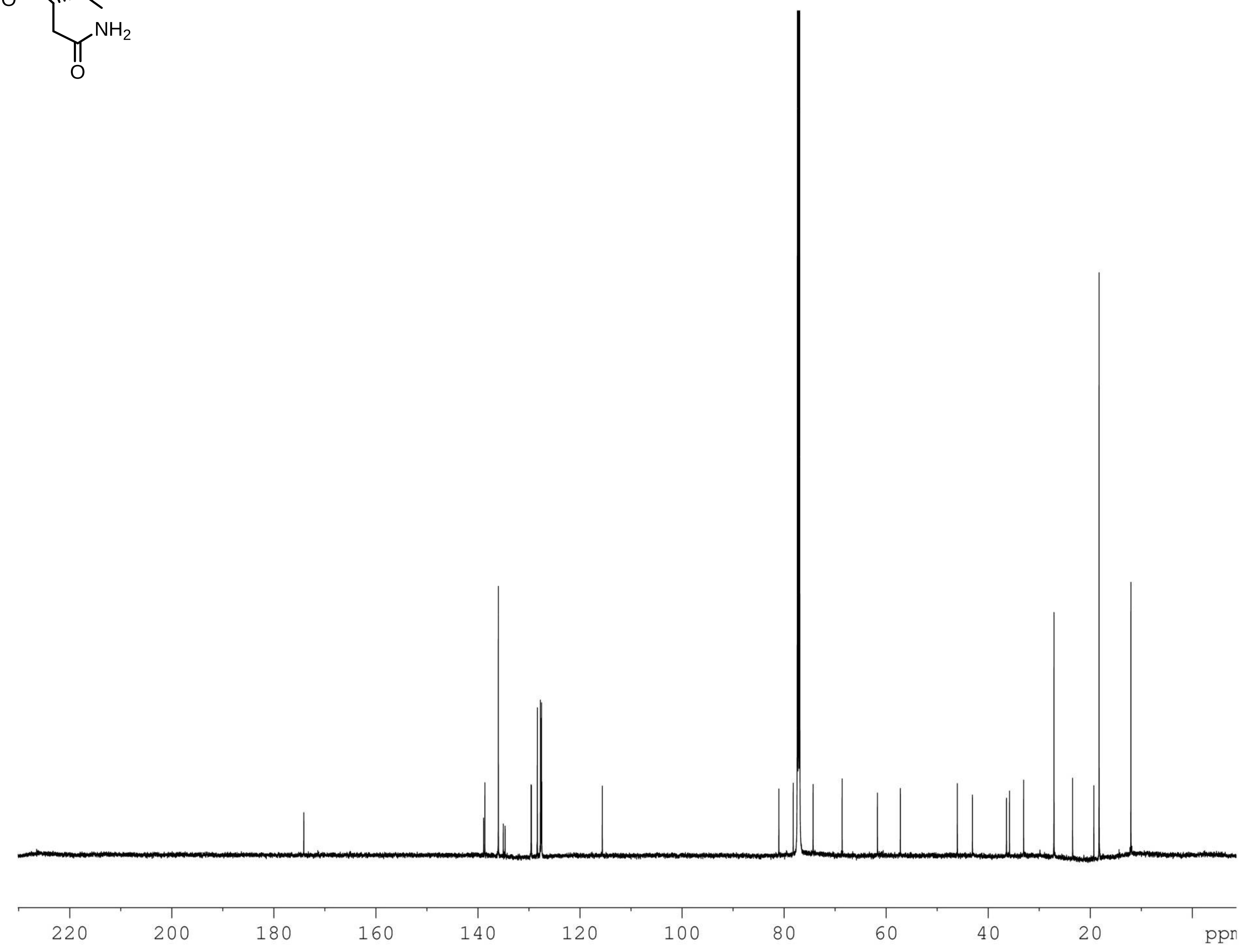


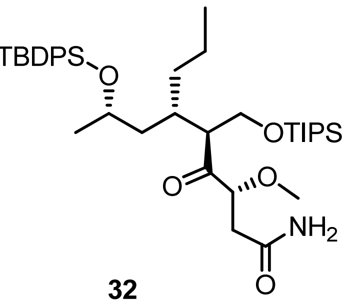
31



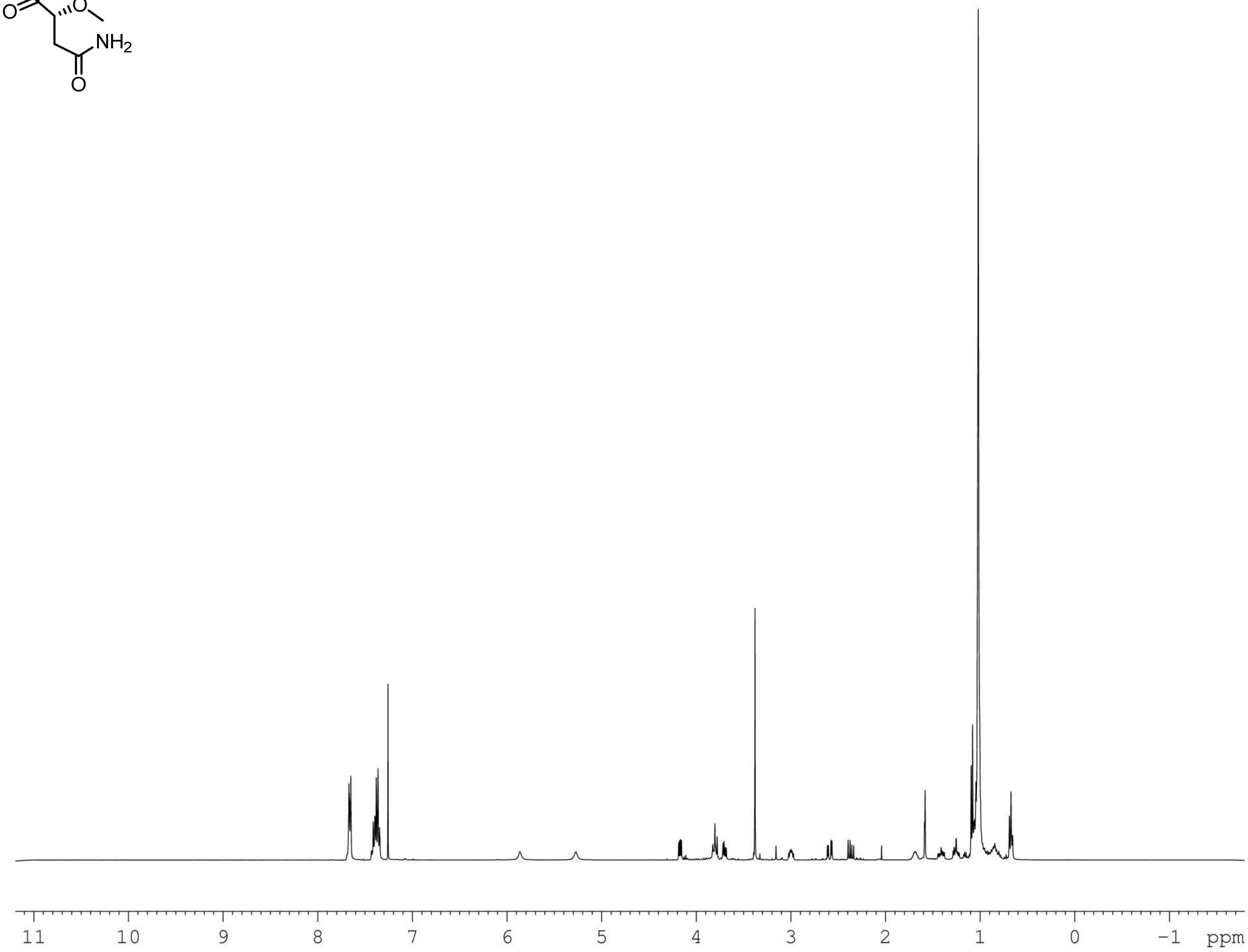

TBDPS
O
OTIPS
BnO
O
NH2
O

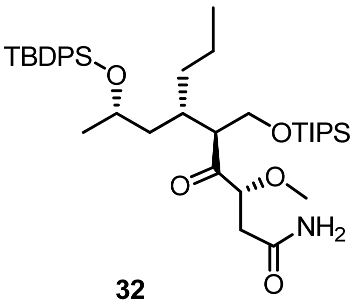
31


220
200
180
160
140
120
100
80
60
40
20
ppm

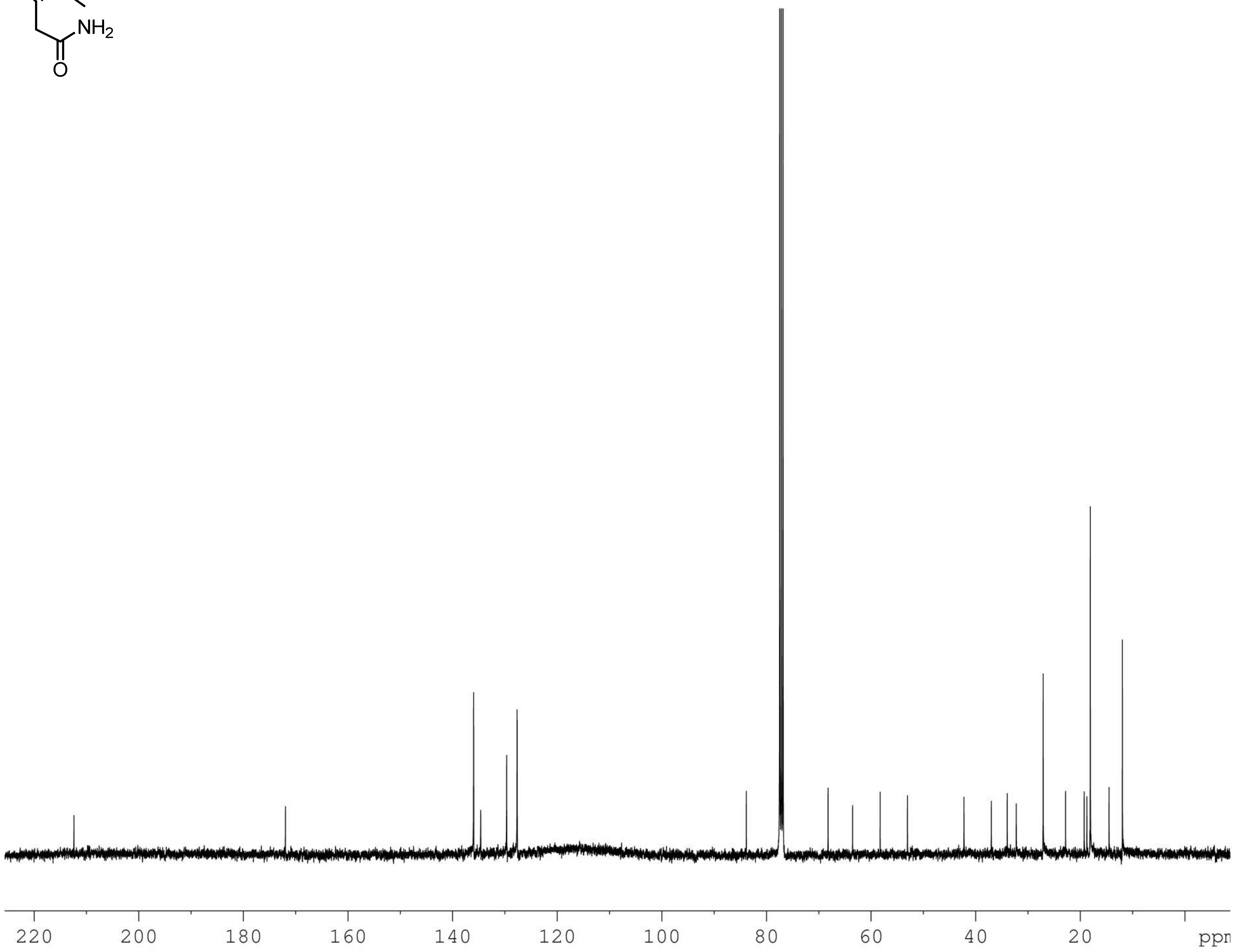


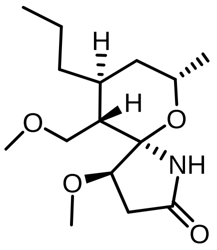
32



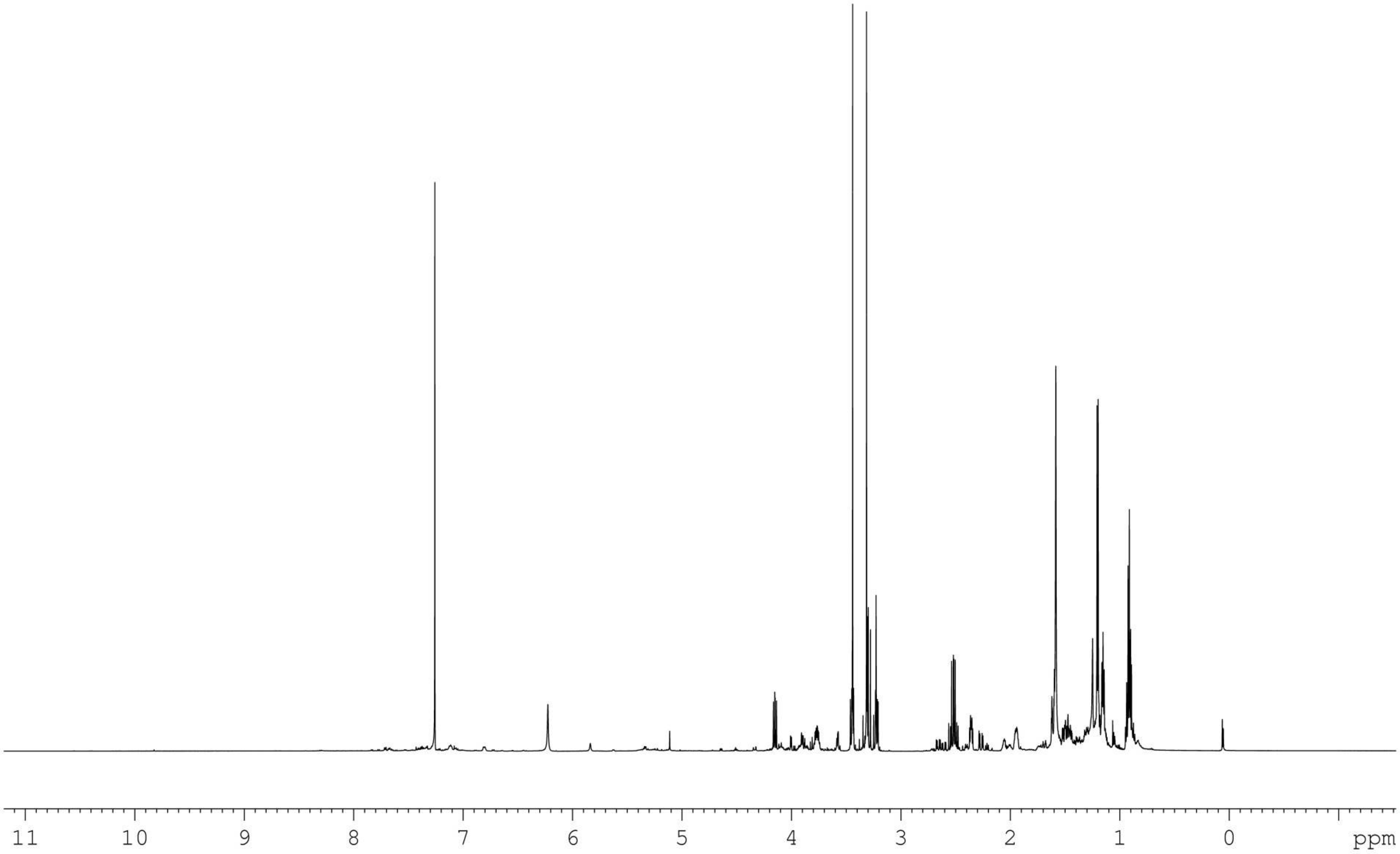


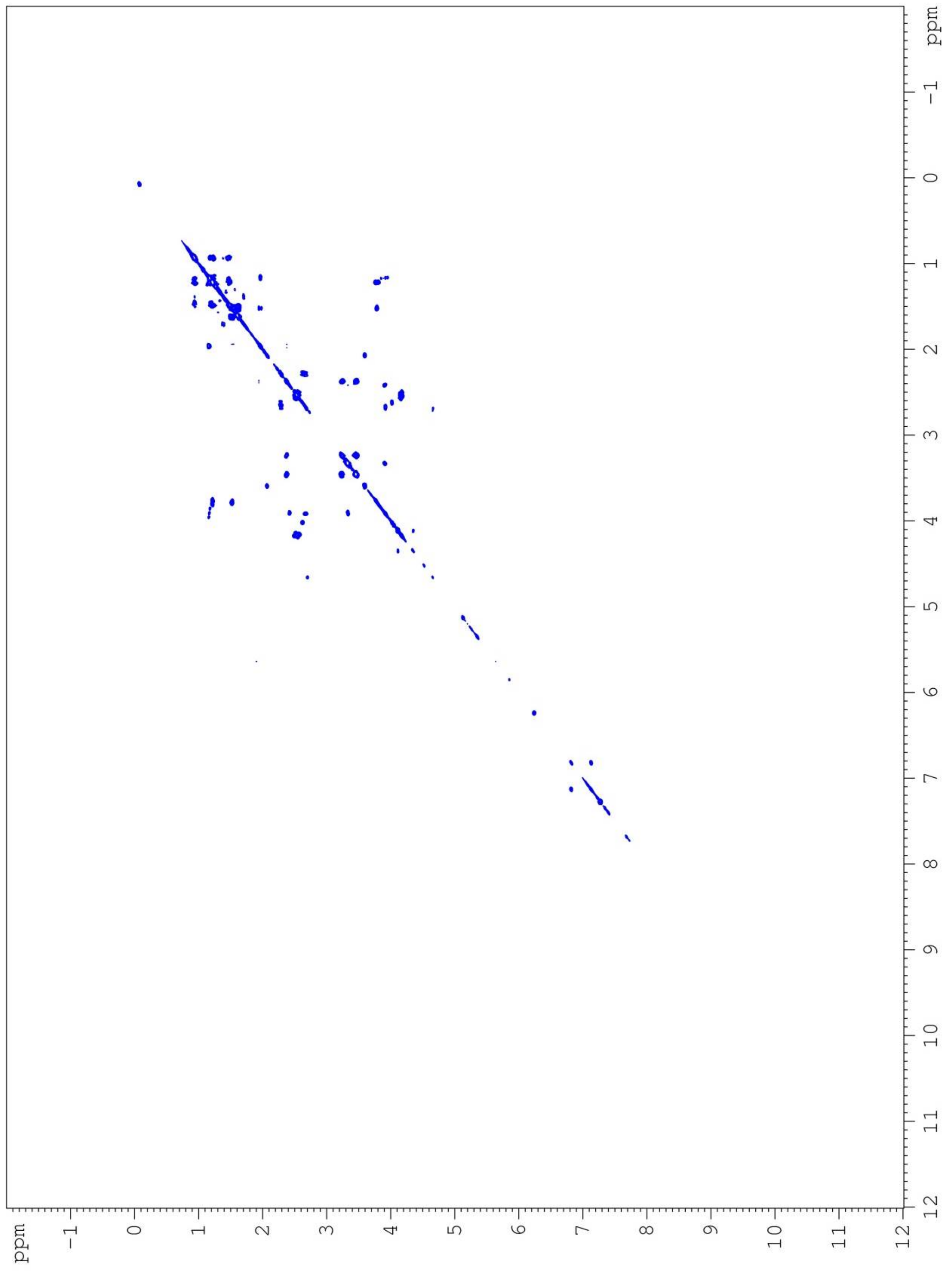
32

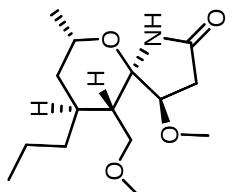




8

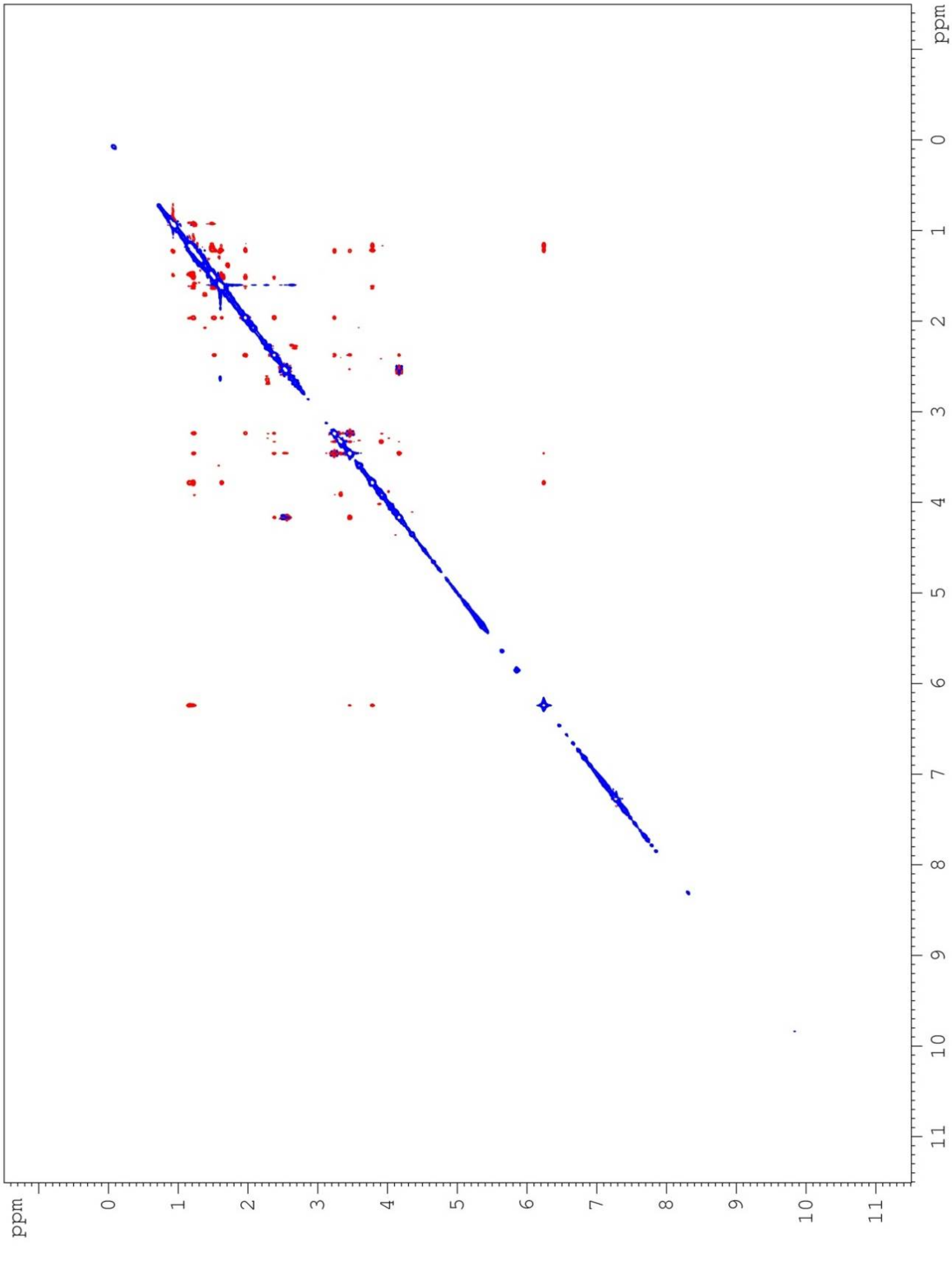


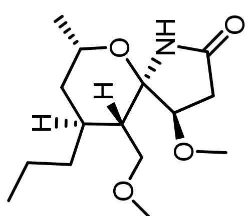




8

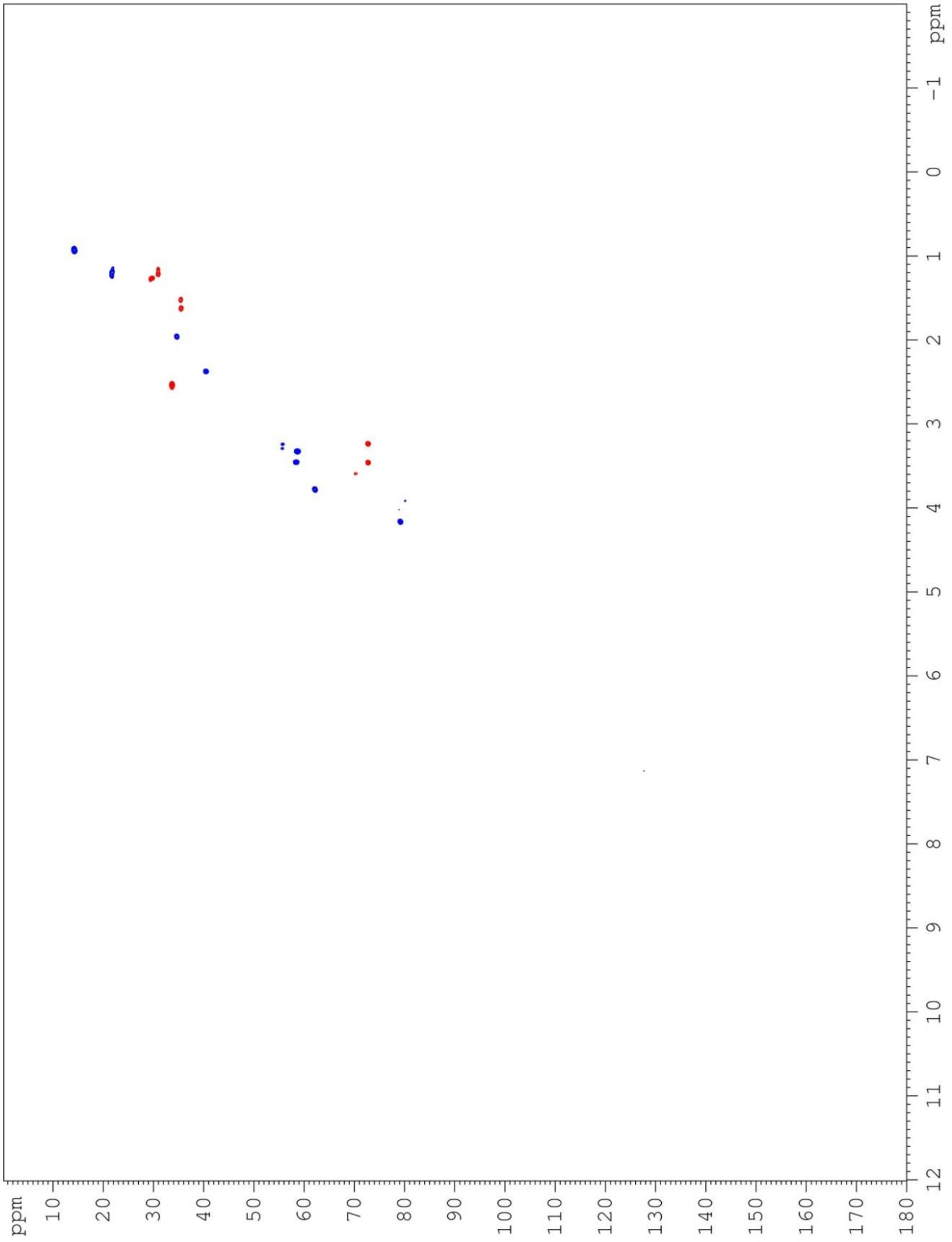
CO
SY

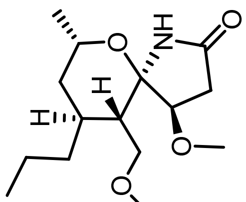




8

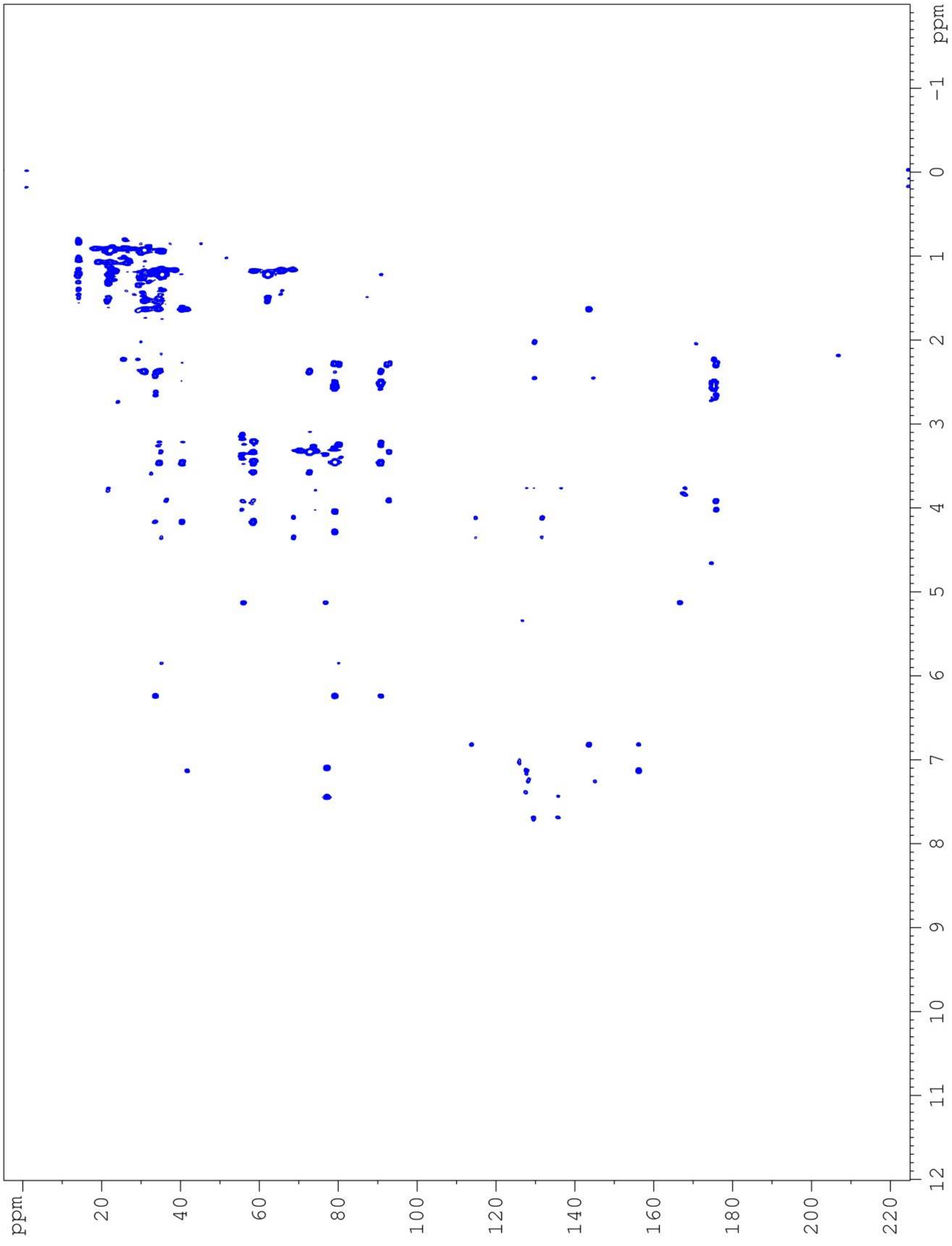
NOESY


ppm
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180

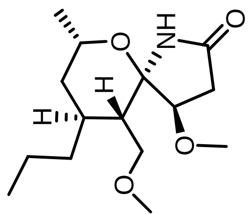


8

HSQC


ppm
12
11
10
9
8
7
6
5
4
3
2
1
0
−1
ppm
20
40
60
80
100
120
140
160
180
200
220

HMBC


NH
O
O
H
H
O
O

8