The enantioselective total synthesis of (-)-dactylolide

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Experimental Procedures and Spectroscopic Data:

1. Optical rotations α were measured using an Optical Activity PolAAr 2001 Automatic polarimeter with the sodium D line (589 nm) at ambient temperature. Optical rotations were recorded in the indicated solvent and run in a 0.25 dm cell. Specific rotations $[\alpha]_D$ are expressed in units of 10^{-1}deg.cm^{2}g^{-1} and concentrations (*c*) are reported as *c* g solute/100 cm^3 solution.

2. Analytical thin layer chromatography was performed using aluminium backed precoated silica gel plates (Merck Kieselgel 60 F254). Compounds were visualized by ultra-violet fluorescence or by staining with acidified ethanolic solution of anisaldehyde, alkaline potassium permanganate solution or phosphomolybdic acid and ceric sulfate in sulfuric acid.

3. ^{1}H Nuclear magnetic resonance (NMR) spectra were recorded using a Bruker AC200 (200.1 MHz), Bruker AVANCE DPX200 (200 MHz), Bruker AVANCE DPX300 (300.1 MHz), or Bruker DPX400 (400.1 MHz) spectrometer at 300 K. Spectra were recorded in deuteriochloroform unless otherwise stated. Data is expressed as parts per million (ppm) downfield shift from tetramethylsilane with either tetramethylsilane or chloroform as an internal standard and is reported as chemical shift (δ), relative integral, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet with descriptors br = broad), coupling constant (*J* Hz) and assignment. All multiplicities and coupling constants are apparent.

4. ^{13}C Nuclear magnetic resonance (NMR) spectra were recorded using a Bruker AC200 (50.3 MHz), Bruker AVANCE DPX200 (50 MHz), Bruker AVANCE DPX300 (75.5 MHz), or Bruker DPX400 (100.4 MHz) spectrometer at 300 K. Spectra were recorded in deuteriochloroform unless otherwise stated. The chemical shifts are reported relative to chloroform (δ 77.3) and are expressed as chemical shift (δ), while numbers in brackets following the chemical shift refer to the number of carbon environments contributing to the

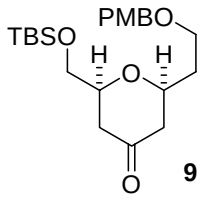
signal. FID's were manipulated prior to Fourier transformation applying an exponential line broadening function to improve the signal to noise ratio.

5. Infrared absorption spectra were obtained using a Perkin Elmer 1600 Fourier Transform Infrared spectrometer as a thin film between 0.5 cm sodium chloride plates. Absorption maxima are expressed in wavenumbers (cm^{-1}).

6. Low resolution electron impact mass spectra were recorded on either an AEI model Kratos MS902 double focusing mass spectrometer with an accelerating voltage of 8000 V and using electron impact (EI) ionisation mode at 70eV, or a Finnegan PolarisQ ion trap mass spectrometer using electron impact ionisation mode at 40 or 70 eV. High resolution electron impact mass spectra were recorded on a VC Autospec mass spectrometer operating at 70 eV (Australian National University, Canberra). Low resolution electrospray mass spectra were recorded on a Finnegan LCQ mass spectrometer. High resolution electrospray mass spectra were recorded on a Bruker ApexII Fourier Transform Ion CyclotronResonance mass spectrometer with a 7.0 T magnet, fitted with an off-axis Analytica electrospray source (University of New South Wales, Sydney). Major fragments are quoted as x (% relative to base peak), where x is the mass to charge ratio. High resolution mass spectra were recorded at a nominal resolution of 8000 to 9000 a.u.

7. All compounds were named using the CS ChemDraw® Ultra version 9.0 software. Carbon numbers used in assignment of spectra and in the discussion correspond to the numbers on the dactylolide macrocycle.

(2*S*,6*S*)-2-((*tert*-Butyldimethylsilyloxy)methyl)-6-(2-(4-methoxybenzyloxy)ethyl)dihydro-2*H*-pyran-4(3*H*)-one **9**[i]



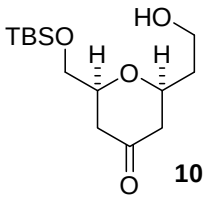
9

Diene **6** (3.26 g, 9.35 mmol) was added *via cannula* to a stirred pre-cooled (0 °C) mixture of aldehyde **7**[ii] (2.3 mL, 12.2 mmol), (*1S*,2*R*) chromium catalyst **8** (0.32 g, 0.65 mmol) and 4 Å molecular sieves (1.2 g, 0.1g/mmol of aldehyde) under argon. The mixture was allowed to warm to room temperature and stirred for 12 h. The reaction mixture was then cooled to 0 °C and dissolved in tetrahydrofuran (45 mL). Acetic acid (0.65 mL, 11.2 mmol) and tetra

butylammonium fluoride (9.4 mL, 9.35 mmol, 1.0 M in tetrahydrofuran) were then added and the reaction stirred for 15 mins. The solution was then concentrated *in vacuo*. Flash chromatography (30% ethyl acetate/hexane) afforded the pyranone **9** as a single diastereomer (3.13 g, 82%).

The product was isolated in 99% ee (Chiralcel AD-H, 5% isopropyl alcohol/hexane: ret. time 10.8 (major – **9**), 11.6 (minor – *ent*-**9**) min)) $[\alpha]_D^{20}$ -14 (*c* 2.8, $CHCl_3$) (lit.[i] $[\alpha]_D^{20}$ -16.4 (*c* 2.5, $CHCl_3$)); R_f 0.45 (30% ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (2H, d, *J* 8.6 Hz, 2 x Ar**H**), 6.87 (2H, d, *J* 8.6 Hz, 2 x Ar**H**), 4.42 (2H, s, ArC**H$_2$**), 3.80 (3H, s, OC**H$_3$**), 3.51-3.78 (6H, m, 2 x OC**H$_2$**, **H**COC**H**), 2.20-2.40 (4H, m, 2 x C=OC**H$_2$**), 1.72-1.98 (2H, m, OCH_2C**H$_2$**), 0.89 (9H, s, SiC(C**H$_3$**)$_3$), 0.06 (6H, s, Si(C**H$_3$**)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.7, 159.4, 130.6, 129.4, 114.0, 77.5, 77.4, 74.2, 72.9, 66.0, 55.4, 48.0, 44.3, 36.6, 26.0, 18.5, -5.1 (2C); IR (thin film): 1734 (s, C=O) cm^{-1}; *m/z* (ES+) 463 ([M+Na+MeOH]$^+$, 100%); HRMS (ES+) calc. for $[C_{22}H_{36}O_5SiNa]^+$ 431.2226, found 431.2238.

(2*S*,6*S*)-2-((*tert*-Butyldimethylsilyloxy)methyl)-6-(2-hydroxyethyl)dihydro-2*H*-pyran-4(3*H*)-one **10**

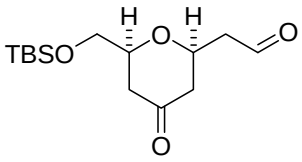


10

To a 0 °C stirred solution of pyranone **9** (3.0 g, 7.34 mmol) in dichloromethane (130 mL) and pH 7 buffer (13 mL) was added anhydrous sodium carbonate (0.93 g, 8.8 mmol), and DDQ (2.5 g, 11.0 mmol) and the resultant dark red solution stirred at room temperature for 2 h. The reaction mixture was then decanted, filtered through a plug of celite and concentrated *in vacuo*. Flash chromatography (50% ethyl acetate/hexane) afforded the alcohol **10** as a light red oil (1.74 g, 82%).

$[\alpha]_D^{20}$ -8.0 (*c* 1.5, $CHCl_3$); R_f 0.21 (50% ethyl acetate/hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.67 - 3.92 (4H, m, **H**COC**H**, TBSOC**H$_2$**), 3.77 (2H, t, *J* 4.9 Hz, C**H$_2$**OH), 2.36-2.42 (4H, m, (C=O)C**H$_2$**), 2.18 (1H, brs, O**H**), 1.87 (2H, m, C**H$_2$**CH_2OH), 0.90 (9H, s, SiC(C**H$_3$**)$_3$), 0.07 (6H, s, Si(C**H$_3$**)$_2$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 206.9, 78.0, 77.2, 66.1, 61.6, 48.1, 44.2, 38.4, 26.2, 18.6, -5.0 (2C); IR (thin film): 1734 (s, C=O) cm^{-1}; *m/z* (ES+) 599 ([2M+Na]$^+$, 100%); HRMS (ES+) calc. for $[C_{14}H_{28}O_4SiNa]^+$ 311.1650, found 311.1643.

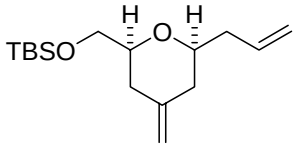
(2*S*,6*S*)-2-(6-((*tert*-Butyldimethylsilyloxy)methyl)-4-oxotetrahydro-2*H*-pyran-2-yl)acetaldehyde



Triethylamine (13.7 mL, 98.3 mmol) was added to a stirred solution of alcohol **10** (5.67 g, 19.7 mmol) in dichloromethane (35 mL) and cooled to 0 °C. In a separate flask, sulfur trioxide pyridine complex (9.4 g, 59.0 mmol) was dissolved in dimethylsulfoxide (35 mL) and added *via cannula* to the cold solution of the alcohol and triethylamine in dichloromethane. The mixture was allowed to warm up to room temperature and stirred for 3 h. The reaction was diluted with dichloromethane (50 mL) and quenched with water (100 mL). The layers were separated and the aqueous phase was extracted with dichloromethane (3 x 50 mL). The combined organic extracts were washed with brine (150 mL), dried over sodium sulfate and concentrated *in vacuo*. Flash chromatography (30% ethyl acetate/hexane) of the crude residue afforded the titled aldehyde as a light yellow oil (4.43 g, 79%).

$[\alpha]_D^{20}$ = -8.4 (*c* 1.1, $CHCl_3$); R_f = 0.22 (30% ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.80 (1H, dd, *J* = 1.5, 2.4 Hz, C**H**O), 4.16 (1H, m, **H**COCH), 3.65 – 3.78 (3H, m, TBSOC$\mathbf{H_2}$, HCOC**H**), 2.78 (1H, ddd, *J* = 2.4, 7.9, 16.7 Hz, C$\mathbf{H_a}$H$_b$CHO), 2.59 (1H, ddd, *J* = 1.5, 4.6, 16.6 Hz, CH$_a$**H$_b$**CHO), 2.18-2.48 (4H, m, 2 x C$\mathbf{H_2}$C=O), 0.90 (9H, s, SiC(C$\mathbf{H_3}$)$_3$), 0.05 (6H, s, Si(C$\mathbf{H_3}$)$_2$). ^{13}C NMR (50 MHz, $CDCl_3$) δ 206.3, 199.7, 77.9, 72.3, 65.9, 49.7, 47.4, 44.1, 26.2, 18.6, -5.0 (2C); IR (thin film): 1718 (s, C=O), 1732 (s, CHO) cm^{-1}; *m/z* (ES+) 373 ([M+Na+2MeOH]$^+$, 100%); HRMS (ES+) calc. for $[C_{14}H_{26}O_4SiNa]^+$ 309.1494, found 309.1491.

(2*S*,6*S*)-((6-Allyl-4-methylidenetetrahydro-2*H*-pyran-2-yl)methoxy)(*tert*-butyl)dimethylsilane

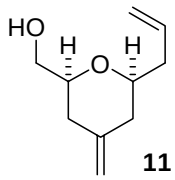


To a 0 °C stirred solution of methyltriphenylphosphonium bromide (8.2 g, 22.9 mmol) in tetrahydrofuran (30 mL) under argon was added *n*-butyllithium (1.61 M in hexanes, 13.5 mL, 21.8 mmol). The resultant yellow solution was stirred at 0 °C for 20 min after which (2*S*,6*S*)-2-(6-((*tert*-Butyldimethylsilyloxy)methyl)-4-oxotetrahydro-2*H*-pyran-2-yl)acetaldehyde (1.56 g, 5.45 mmol) in tetrahydrofuran (24 mL) was added *via cannula* and the resultant orange mixture allowed to warm up to room temperature. The reaction was then heated at reflux for

24 h. On completion the reaction was diluted with diethyl ether (100 mL) and quenched with saturated ammonium chloride (70 mL). The layers were separated and the aqueous phase was extracted with ether (3 x 70 mL). The combined organic extracts were washed with brine (150 mL), dried over sodium sulfate and concentrated *in vacuo*. Flash chromatography (5% ethyl acetate/hexane) of the crude residue afforded the titled diene as a clear oil (1.25 g, 81%).

$[\alpha]_D^{20}$ = -18 (*c* 2.1, $CHCl_3$); R_f = 0.31 (5% ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86 (1H, m, C**H**=CH_2), 5.00-5.10 (2H, m, CH=C**H$_2$**), 4.73 (2H, m, C=C**H$_2$**), 3.71 (1H, dd, *J* = 5.3, 10.4 Hz, C**H$_a$**H$_b$OTBS), 3.56 (1H, dd, *J* = 5.5, 10.4 Hz, CH$_a$**H$_b$**OTBS), 3.28-3.40 (2H, m, **H**COC**H**), 2.12-2.43 (4H, m, 2 x C**H$_2$**C=CH_2), 1.92 (2H, m, C**H$_2$**CH=CH_2), 0.90 (9H, s, SiC(C**H$_3$**)$_3$), 0.06 (6H, s, Si(C**H$_3$**)$_2$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.9, 135.1, 117.1, 109.0, 79.3, 78.2, 67.0, 41.0, 40.7, 37.7, 26.3, 18.7, -4.8 (2C); IR (thin film): 1651 (s, C=C) cm^{-1}; *m/z* (ES+) 305 ([M+Na]$^+$, 100%); HRMS (ES+) calc. for $[C_{16}H_{30}O_2SiNa]^+$ 305.1909, found 305.1902.

(2*S*,6*S*)-(6-Allyl-4-methylidenetetrahydro-2*H*-pyran-2-yl)methanol **11**



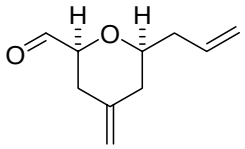
11

To a 0 °C stirred solution of (2*S*,6*S*)-((6-Allyl-4-methylidenetetrahydro-2*H*-pyran-2-yl)methoxy)(*tert*-butyl)dimethylsilane (1.25 g, 4.42 mmol) in tetrahydrofuran (45 mL) was added tetra-*n*-butylammonium fluoride (1.0 M in tetrahydrofuran, 5.7 mL, 5.75 mmol) and the mixture stirred at 0 °C for 1 h. On completion, the reaction was diluted with diethyl ether (50 mL) and concentrated *in vacuo*. Flash chromatography (25% ethyl acetate/hexane) of the crude residue afforded the alcohol **11** as a clear oil (0.67 g, 90%).

$[\alpha]_D^{20}$ -10.8 (*c* 5.2, $CHCl_3$); R_f 0.23 (25% ethyl acetate/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78-5.89 (1H, m, C**H**=CH_2), 5.05-5.12 (2H, m, CH=C**H$_2$**), 4.75 (2H, t, *J* 1.7 Hz, C=C**H$_2$**), 3.65 (1H, dd, *J* 3.2, 11.4 Hz, C**H$_a$**H$_b$OH), 3.55 (1H, dd, *J* 6.9, 11.3 Hz, CH$_a$**H$_b$**OH), 3.47-3.35 (2H, m, **H**COC**H**), 2.37 (1H, m, C**H$_a$**H$_b$CH=CH_2), 2.25 (2H, m, C**H$_2$**C=CH_2), 2.12 (1H, dt, *J* 2.3, 13.2 Hz, CH$_a$**H$_b$**CH=CH_2), 1.98 (2H, m, C**H$_2$**C=CH_2), 1.82 (1H, brs, O**H**). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1, 134.7, 117.4, 109.6, 78.9, 78.1, 66.3, 40.9, 40.6, 36.6; IR (thin film): 1653 (s,

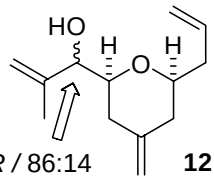
C=C) 3420 (brs, OH) cm^{-1}; *m/z* (ES+) 186 ($[M+NH_4]^+$, 100%); HRMS (ES+) calc. for $[C_{10}H_{16}NaO_2]^+$ 191.1043, found 191.1042.

(2*S*,6*S*)-6-Allyl-4-methylidenetetrahydro-2*H*-pyran-2-carbaldehyde



Triethylamine (2.8 mL, 20.1 mmol) was added to a stirred solution of alcohol **11** (668 mg, 3.97 mmol) and 4 Å molecular sieves (100 mg/mmol of alcohol) in dichloromethane (7.5 mL) and cooled to 0 °C. In a separate flask, sulfur trioxide pyridine complex (1.9 g, 11.9 mmol) was dissolved in dimethylsulfoxide (7.5 mL) and added *via cannula* to the cold solution of the alcohol and triethylamine in dichloromethane. The mixture was warmed up to room temperature and stirred for 3 h. Once t.l.c showed total consumption of starting material, the reaction was diluted with dichloromethane (50 mL) and concentrated *in vacuo*. Flash chromatography (30% diethyl ether/hexane) of the crude residue afforded the titled aldehyde as a light yellow oil (574 mg, 87%) which was carried on immediately in the following reaction. R_f = 0.20 (30% diethyl ether/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 (1H, d, *J* = 0.6 Hz, C**H**O), 5.87 (1H, m, C**H**=CH_2), 5.10 (2H, m, CH=C**H$_2$**), 4.83 (2H, m, C=C**H$_2$**) 3.76 (1H, ddd, *J* = 0.5, 2.9, 12.1 Hz, **H**COCH) 3.41 (1H, m, HCOC**H**), 2.44 (2H, m, C**H$_2$**C=CH_2), 2.29 (2H, m, C**H$_2$**C=CH_2), 2.02 (2H, m, C**H$_2$**CH=CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 201.7, 142.3, 134.4, 117.8, 110.9, 82.4, 78.6, 40.8, 40.3, 35.3.

(*S*)-1-((2*S*,6*S*)-6-Allyl-4-methylidenetetrahydro-2*H*-pyran-2-yl)-2-methylprop-2-en-1-ol and (*R*)-1-((2*S*,6*S*)-6-Allyl-4-methylidenetetrahydro-2*H*-pyran-2-yl)-2-methylprop-2-en-1-ol **12**



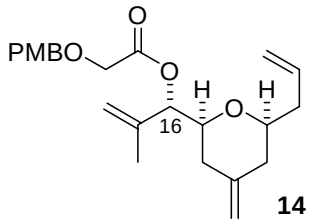
S:*R* / 86:14 **12**

A flask containing freshly distilled 2-bromopropene (3.4 mL, 38.3 mmol) in diethyl ether (40 mL), maintained at -78 °C under a nitrogen atmosphere, was charged with *tert*-butyllithium (45.6 mL of a 1.7 M solution in pentane, 77.5 mmol) and the resulting mixture stirred at -78 °C for 15 min after which $MgBr_2$•Et_2O (10.1 mL, 10.1 mmol, 1.0 M in ether/benzene) was added

and the mixture stirred at -78 °C for a further 15 min. (2*S*,6*S*)-6-Allyl-4-methylidenetetrahydro-2*H*-pyran-2-carbaldehyde (1.29 g, 7.75 mmol) in diethyl ether (40 mL) was then added *via cannula* and the reaction mixture stirred for 15 min at -78 °C before being warmed up to room temperature, then quenched with water (70 mL) and extracted with diethyl ether (3 x 70 mL). The combined organic extracts were washed with brine (50 mL), dried over sodium sulfate and concentrated *in vacuo*. Flash chromatography (10% ethyl acetate/hexane) of the crude residue afforded an inseparable diastereomeric mixture of alcohols **12** (1.015 g, 63%).

The product was isolated in a 86:14 / *S*:*R* diasteromeric ratio as determined by ^{1}H NMR. $[\alpha]_D^{20}$ +29 (*c* 2.2, $CHCl_3$); R_f 0.23 (10% ethyl acetate/hexane); IR (thin film): 1655 (C=C), 3470 (brs, OH) cm^{-1}; Major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (1H, m $CH_2C\mathbf{H}=CH_2$), 4.95 – 5.12 (4H, m, $CH_3C=C\mathbf{H_2}$, $CH_2CH=C\mathbf{H_2}$), 4.73 (2H, s, $C=C\mathbf{H_2}$), 3.92 (1H, d, *J* 7.5 Hz, C**H**OH), 3.24–3.46 (2H, m, C**H**-O-C**H**), 2.75 (1H, brs, O**H**), 2.20-2.40 (4H, m, $C\mathbf{H_2}CH=CH_2$, $C\mathbf{H_2}C(CH_2)CH_2$), 2.10 (1H, m, $CH_2C(CH_2)C\mathbf{H_a}H_b$), 1.92 (1H, m, $CH_2C(CH_2)CH_a\mathbf{H_b}$), 1.74 (3H, d, *J* 1.2 Hz, $C\mathbf{H_3}C=CH_2$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.9, 143.6, 134.6, 117.4, 112.3, 109.8, 79.8, 79.4, 78.1, 40.8, 40.4, 36.9, 17.9; Minor diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (1H, m $CH_2C\mathbf{H}=CH_2$), 4.95 – 5.12 (4H, m, $CH_3C=C\mathbf{H_2}$, $CH_2CH=C\mathbf{H_2}$), 4.73 (2H, s, $C=C\mathbf{H_2}$), 4.19 (1H, d, *J* 3.7 Hz, C**H**OH), 3.24–3.46 (2H, m, C**H**-O-C**H**), 2.75 (1H, brs, O**H**), 2.20-2.40 (4H, m, $C\mathbf{H_2}CH=CH_2$, $C\mathbf{H_2}C(CH_2)CH_2$), 2.10 (1H, m, $CH_2C(CH_2)C\mathbf{H_a}H_b$), 1.92 (1H, m, $CH_2C(CH_2)CH_a\mathbf{H_b}$), 1.74 (3H, d, *J* 1.2 Hz, $C\mathbf{H_3}C=CH_2$).

(*S*)-1-((2*S*,6*S*)-6-Allyl-4-methylidenetetrahydro-2*H*-pyran-2-yl)-2-methylallyl 2-(4-methoxybenzyloxy)acetate **14**.



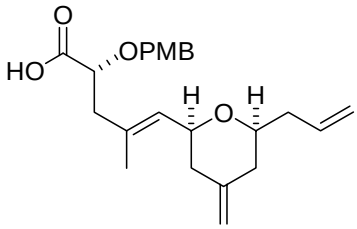
14

To a 0 °C stirred solution of a mixture of diastereomeric alcohol **12** (370 mg, 1.78 mmol), acid **13**[iii] (870 mg, 4.44 mmol) and 4-dimethylaminopyridine (477 mg, 3.91 mmol) in dichloromethane (18 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (920 mg, 4.80 mmol) and the mixture warmed to room temperature and stirred for 30 min after which it was left to stir overnight at 45 °C. The reaction was then diluted with

dichloromethane (50 mL) and quenched with water (50 mL). The layers were separated and the aqueous phase was extracted with dichloromethane (3 x 50mL). The organic extracts were combined, dried over sodium sulfate and concentrated *in vacuo*. Flash chromatography (10% ethyl acetate/hexane) of the crude residue followed by preparative HPLC (Zorbax Sil 10% ethyl acetate/hexane: ret. time 17.4 (major – **14**) 20.1 (minor – C16-*epi*-**14**) min)) afforded diasteromerically pure ester **14** (520 mg, 76%).

$[\alpha]_D^{20}$ -16 (*c* 2.9, $CHCl_3$); R_f 0.13 (10% ethyl acetate/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (2H, d, *J* 8.5 Hz, 2 x Ar**H**), 6.88 (2H, d, *J* 8.5 Hz, 2 x Ar**H**), 5.79 (1H, m, $CH_2C\mathbf{H}=CH_2$), 5.33 (1H, d, *J* 6.9 Hz, $CH_2COOC\mathbf{H}$), 4.99 – 5.07 (4H, m, $CH_3C=C\mathbf{H_2}$, $CH_2CH=C\mathbf{H_2}$), 4.74 (2H, m, $CH_2C(C\mathbf{H_2})CH_2$), 4.58 (2H, m, $ArC\mathbf{H_2}O$), 4.12 (2H, m, $PMBOC\mathbf{H_2}$), 3.80 (3H, s, $OC\mathbf{H_3}$), 3.46 (1H, qd, *J* 2.1, 7.0 Hz, $\mathbf{H_a}COCH_b$), 3.29 (1H, m, $H_aCOC\mathbf{H_b}$), 2.30 (1H, m, $C\mathbf{H_a}H_bCH=CH_2$), 2.19–2.22 (2H, m, $CH_a\mathbf{H_b}CH=CH_2$, $C\mathbf{H_a}H_bC(CH_2)CH_2$), 2.08 (1H, m, $CH_a\mathbf{H_b}C(CH_2)CH_2$), 1.94 (2H, m, $CH_aH_bC(CH_2)C\mathbf{H_2}$), 1.76 (3H, s $C\mathbf{H_3}C=CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 159.4, 143.6, 140.2, 134.6, 129.7, 129.4, 116.8, 115.6, 113.8, 109.5, 79.4, 78.1, 77.9, 72.8, 66.9, 55.3, 40.4, 40.0, 36.4, 18.9; IR (thin film): 1655 (s, C=C), 1751 (s, COOMe) cm^{-1}; *m/z* (ES+) 409 ($[M+Na]^+$, 100%); HRMS (ES+) calc. for $[C_{23}H_{30}NaO_5]^+$ 409.1986, found 409.1989.

(*R*,*E*)-5-((2*S*,6*S*)-6-Allyl-4-methylidenetetrahydro-2*H*-pyran-2-yl)-2-(4-methoxybenzyloxy)-4-methylpent-4-enoic acid **15**



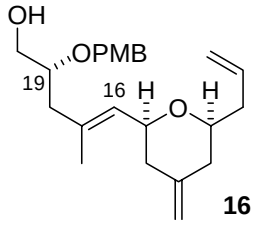
15

Ester **14** (0.544 g, 1.41 mmol) was dissolved in tetrahydrofuran (24 mL) cooled to -78 °C and treated dropwise with lithium hexamethyldisilazide (1.0 M in tetrahydrofuran, 4.20 mL, 4.22 mmol). The mixture was stirred for 45 min after which freshly distilled trimethylsilyl chloride (0.90 mL, 7.16 mmol) was added and the mixture left to warm up gradually over 12 h. The reaction was then diluted with dichloromethane (50 mL) and HCl (1.0 M, 30 mL) was added. The layers were separated and the aqueous phase extracted with dichloromethane (3 x 30 mL). The organic extracts were combined, dried over sodium sulfate and concentrated *in*

vacuo. Flash chromatography (10% MeOH/DCM) of the crude residue afforded the acid **15** as a single diastereomer (determined by ^{1}H NMR) (0.544 g, 100%). This was immediately taken on to the next step.

R_f = 0.27 (10% methanol/dichloromethane). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.28 (2H, d, *J* = 8.4 Hz, 2 x Ar**H**), 6.87 (2H, d, *J* = 8.7 Hz, 2 x Ar**H**), 6.80 (1H, brs, COO**H**), 5.82 (1H, m, CH_2C**H**=CH_2), 5.31 (1H, d, *J* = 6.9 Hz, CH_3C=C**H**), 5.07 (2H, m, CH_2CH=C**H$_2$**), 4.74 (2H, s, C=C**H$_2$**), 4.63 (1H, dd, *J* = 2.8, 11.3 Hz, ArC**H$_a$**H_bO), 4.44 (1H, dd, *J* = 5.4, 11.3 Hz, ArCH_a**H$_b$**O), 3.95–4.11 (2H, m, PMBOC**H**C, **H$_a$**$COCH_b$), 3.81 (3H, s, OC**H$_3$**), 3.27 (1H, m, H_aCOC**H$_b$**), 1.87–2.51 (8H, m, 4 x **H$_2$**CC=C), 1.68 (3H, s, **H$_3$**CC=C).

(*R*,*E*)-5-((2*S*,6*S*)-6-Allyl-4-methylidenetetrahydro-2*H*-pyran-2-yl)-2-(4-methoxybenzyloxy)-4-methylpent-4-en-1-ol **16**.



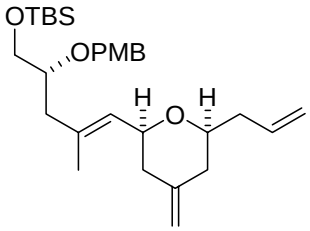
16

Acid **15** (72 mg, 0.186 mmol) was dissolved in anhydrous diethyl ether (2 mL) and cooled to 0 °C. Lithium aluminium hydride (15.5 mg, 0.41 mmol) was then added and grey mixture stirred for 3 h. The reaction was then quenched with HCl (1.0 M, 10 mL) and extracted into diethyl ether (3 x 20 mL). The combined organic extracts were washed with brine (50 mL), dried over sodium sulfate and concentrated *in vacuo*. Flash chromatography (50% ethyl acetate/hexane) of the crude residue afforded the alcohol **16** as a pale yellow oil (55 mg, 79%).

$[\alpha]_D^{20}$ -28.3 (*c* 2.3, $CHCl_3$); R_f 0.46 (50% ethyl acetate/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (2H, d, *J* 8.6 Hz, 2 x Ar**H**), 6.88 (2H, d, *J* 8.6 Hz, 2 x Ar**H**), 5.84 (1H, m, CH_2C**H**=CH_2), 5.33 (1H, d, *J* 7.8 Hz, CH_3C=C**H**), 5.06 (2H, m, CH_2CH=C**H$_2$**), 4.73 (2H, s, C=C**H$_2$**), 4.51 (2H, m, ArC**H$_2$**O), 3.99 (1H, m, **H$_a$**$COCH_b$), 3.80 (3H, s, OC**H$_3$**), 3.65 (2H, m, C**H$_2$**OH), 3.51 (1H, m, PMBOC**H**C), 3.36 (1H, m, H_aCOC**H$_b$**), 2.39 (2H, m, C**H$_2$**CH=CH_2), 2.24 (2H, m, C**H$_2$**$C(CH_3)$=CH), 2.16 (2H, m, C**H$_2$**$C(CH_2)CH_2$), 2.04 (1H, t, *J* 12.2 Hz, $CH_2C(CH_2)C$**H$_a$**H_b), 1.93 (1H, t, *J* 12.2 Hz, $CH_2C(CH_2)CH_a$**H$_b$**), 1.88 (1H, brs, O**H**), 1.71 (3H, s, $CH_2C(C$**H$_3$**)=CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 144.5, 135.6, 134.6, 130.4, 129.5, 128.6, 116.9, 113.9,

108.7, 77.8, 77.3, 76.7, 75.5, 71.4, 64.5, 55.3, 41.4, 40.7, 39.9, 17.4; IR (thin film): 1651 (s, C=C), 3458 (brs, OH) cm^{-1}. *m/z* (ES+) 395 ($[M+Na]^+$, 100%); HRMS (ES+) calc. for $[C_{23}H_{32}O_4Na]^+$ 395.2193, found 395.2190.

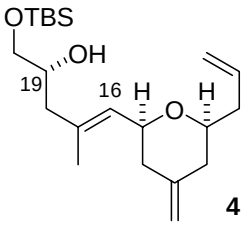
((*R*,*E*)-5-((2*S*,6*S*)-6-Allyl-4-methylidenetetrahydro-2*H*-pyran-2-yl)-2-(4-methoxybenzyloxy)-4-methylpent-4-enyloxy)(*tert*-butyl)dimethylsilane



To a 0 °C stirred solution of alcohol **16** (326 mg, 0.876 mmol) in dichloromethane (1.0 mL) was added triethylamine (0.2 mL, 1.49 mmol) and *tert*-butyldimethylsilyl chloride (170 mg, 1.13 mmol). The mixture was warmed up to room temperature and stirred for 12 h. The reaction was then diluted with dichloromethane (3 mL) and concentrated *in vacuo*. Flash chromatography (25% ethyl acetate/hexane) of the crude residue afforded the titled compound as a clear oil (379 mg, 89%).

$[\alpha]_D^{20}$ = -5.4 (*c* 2.2, $CHCl_3$); R_f = 0.63 (25% ethyl acetate/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (2H, d, *J* = 8.4 Hz, 2 x Ar**H**), 6.87 (2H, d, *J* = 8.5 Hz, 2 x Ar**H**), 5.87 (1H, m, $CH_2C\mathbf{H}=CH_2$), 5.35 (1H, d, *J* = 7.7 Hz, $CH_3C=C\mathbf{H}$), 5.09 (2H, m, $CH_2CH=C\mathbf{H_2}$), 4.76 (2H, s, $C=C\mathbf{H_2}$), 4.63 (1H, d, *J* = 11.3 Hz, $ArC\mathbf{H_a}H_b$), 4.52 (1H, d, *J* = 11.3 Hz, $ArCH_a\mathbf{H_b}$), 4.02 (1H, m, $\mathbf{H_a}COCH_b$), 3.82 (3H, s, $OC\mathbf{H_3}$), 3.70 (1H, m, $OC\mathbf{H_a}H_b$), 3.57–3.65 (2H, m, PMBOC**H**C, $OCH_a\mathbf{H_b}$), 3.39 (1H, m, $H_aCOC\mathbf{H_b}$), 2.43 (1H, m, $C\mathbf{H_a}H_bCH=CH_2$), 2.16–2.29 (5H, m, $C\mathbf{H_2}C(CH_2)CH_2$, $C\mathbf{H_2}C(CH_3)=CH$, $CH_a\mathbf{H_b}CH=CH_2$), 2.07 (1H, t, *J* = 11.7 Hz, $CH_2C(CH_2)C\mathbf{H_a}H_b$), 1.96 (1H, t, *J* = 12.2 Hz, $CH_2C(CH_2)CH_a\mathbf{H_b}$), 1.68 (3H, s, $CH_2C(C\mathbf{H_3})C=CH$), 0.93 (9H, s, $SiC(C\mathbf{H_3})_3$), 0.08 (6H, s, $Si(C\mathbf{H_3})_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 145.3, 136.8, 135.3, 131.7, 129.8, 128.8, 117.4, 114.2, 109.1, 78.9, 78.3, 76.2, 72.5, 66.1, 55.8, 42.7, 42.4, 41.4, 40.6, 30.3, 26.5, 18.1, -4.7 (2C); IR (thin film): 1612, 1651 (s, C=C) cm^{-1}; *m/z* (ES+) 509 ($[M+Na]^+$, 100%); HRMS (ES+) calc. for $[C_{29}H_{46}O_4SiNa]^+$ 509.3059, found 509.3046.

(*R*,*E*)-5-((2*S*,6*S*)-6-Allyl-4-methylidenetetrahydro-2*H*-pyran-2-yl)-1-(*tert*-butyldimethylsilyloxy)-4-methylpent-4-en-2-ol **4**.

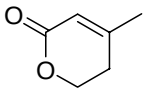


4

To a 0 °C stirred solution of ((*R*,*E*)-5-((2*S*,6*S*)-6-Allyl-4-methylidenetetrahydro-2*H*-pyran-2-yl)-2-(4-methoxybenzyloxy)-4-methylpent-4-enyloxy)(*tert*-butyl)dimethylsilane (307 mg, 0.63 mmol) in dichloromethane (7.6 mL) and pH 7 buffer (0.4 mL) was added DDQ (186 mg, 0.82 mmol) and the resultant dark red solution stirred at room temperature for 2 h. The reaction mixture was then decanted, filtered through a plug of celite and concentrated *in vacuo*. Flash chromatography (10% ethyl acetate/hexane) afforded the alcohol **4** as a pale yellow oil (191 mg, 83%).

$[\alpha]_D^{20}$ -16 (*c* 0.57, $CHCl_3$); R_f 0.23 (10% ethyl acetate/hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.84 (1H, m, $CH_2C\mathbf{H}=CH_2$), 5.31 (1H, dd, *J* 1.1, 7.8 Hz, $C(CH_3)=C\mathbf{H}$), 5.07 (2H, m, $CH_2CH=C\mathbf{H_2}$), 4.76 (2H, s, $C=C\mathbf{H_2}$), 4.01 (1H, m, $\mathbf{H_a}COCH_b$), 3.80 (1H, m, C**H**OH), 3.61 (1H, dd, *J* 3.8, 9.9 Hz $OC\mathbf{H_a}H_b$), 3.46 (1H, dd, *J* 6.8, 10.0 Hz, $OCH_a\mathbf{H_b}$), 3.35 (1H, m, $H_aCOC\mathbf{H_b}$), 2.27–2.46 (1H, m, $C(OH)HC\mathbf{H_a}CH_b$), 2.10-2.25 (6H, m, O**H**, $C(OH)HCH_aC\mathbf{H_b}$, 2 x $C\mathbf{H_2}C=C$), 1.82-2.04 (2H, m, $HCOCHC\mathbf{H_2}$) 1.73 (3H, d, *J* 1.2 Hz, $CH_2C(C\mathbf{H_3})=CH$), 0.90 (9H, s, $SiC(C\mathbf{H_3})_3$), 0.07 (6H, s, $Si(C\mathbf{H_3})_2$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.9, 136.2, 135.1, 128.9, 117.2, 109.0, 78.1, 75.9, 70.0, 67.3, 43.6, 41.2, 41.1, 40.4, 26.3, 18.7, 17.3, -4.9 (2C); IR (thin film): 1654 (s, C=C), 3458 (brs, OH) cm^{-1}. *m/z* (ES+) 389 ($[M+Na]^+$, 100%); HRMS (ES+) calc. for $[C_{21}H_{38}O_3SiNa]^+$ 389.2484, found 389.2499.

4-Methyl-5,6-dihydro-2*H*-pyran-2-one **19**[iv]



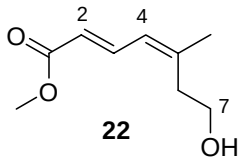
19

3-Methylbut-3-enyl acrylate **18**[v] (0.739 g, 5.28 mmol) was dissolved in 1,2-dichloroethane (40 mL). The solution was degassed and heated to 100 ºC. A degassed solution of Grubbs' second generation catalyst **20** (0.224 g, 0.26 mmol) in 1,2-dichloroethane (10.2 mL) was added *via* syringe pump (0.5 mL/h). After 21 h, TLC (1:2, ethyl acetate / hexane) showed complete conversion to a lower R_f product. Upon cooling to room temperature, the reaction

mixture was applied directly to a flash chromatography column (1:3 then 3:1, diethyl ether / pentane), which gave lactone **19** (0.564 g, 95%).

R_f 0.15 (33% ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.77 (1H, m, C2-**H**), 4.34 (2H, t, *J* 6.3 Hz, C5-**H**), 2.35 (2H, br t, *J* 6.3 Hz, C4-**H**), 1.97 (3H, s, C**H$_3$**C=C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 157.8, 116.6, 65.8, 29.1, 22.9; IR (thin film): 1720 (C=O), 1400, 1223, 1151, 1065 cm^{-1}.

(2*E*,4*Z*)-Methyl 7-hydroxy-5-methylhepta-2,4-dienoate **22**

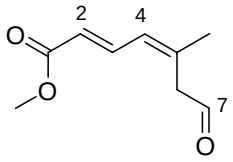


22

DibalH (1.0 M in PhMe, 3.24 mL, 3.24 mmol) was added dropwise to lactone **19** (0.302 g, 2.70 mmol) in dichloromethane (30 mL) at -78 ºC. After 90 mins at -78 ºC, TLC (1:2, ethyl acetate / hexane) showed complete conversion to a higher R_f product. Sodium potassium tartrate (1.0 M,10 mL) was added and the reaction mixture warmed to room temperature. Additional sodium potassium tartrate (1.0 M, 25 mL) was added, and the resultant mixture was extracted with dichloromethane (4 x 30 mL). The combined dichloromethane extracts were dried (Na_2SO_4) and concentrated to give 4-methyl-5,6-dihydro-2*H*-pyran-2-ol as a solution in toluene (~3 mL). Additional toluene (45 mL) was added, followed by methyl triphenylphosphoranylidene acetate (1.172 g, 3.51 mmol) and the reaction mixture was stirred for 16 h at 100 ºC. TLC (1:2, ethyl acetate / hexane) suggested a new product at the same R_f. The reaction mixture was cooled to room temperature and applied directly to a flash chromatography column (1:3 then 2:1, diethyl ether / pentane), which enabled separation of the minor (2Z,4Z)- contaminant and afforded (2*E*,4*Z*)-methyl 7-hydroxy-5-methylhepta-2,4-dienoate **22** (0.397 g, 86%).

R_f 0.2 (33% ethyl acetate/hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.57 (1H, dd, *J* 11.7, 15.2 Hz, C3-**H**), 6.12 (1H, br d, *J* 11.7 Hz, C4-**H**), 5.80 (1H, d, *J* 15.2 Hz, C2-**H**), 3.73 (3H, s, OC**H$_3$**), 3.80-3.70 (2H, m, C7-**H**), 2.57 (2H, t, *J* 6.6 Hz, C6-**H**), 1.92 (3H, s, C**H$_3$**C=C), 1.62 (1H, br s, O**H**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 146.1, 140.4, 126.2, 119.3, 60.9, 51.4, 36.0, 24.5; IR (thin film): 3700-3100 (OH), 1713 (C=O), 1635, 1281, 1155 cm^{-1}; *m/z* (ES+) 171 ([M+H]$^+$, 100%); HRMS (ES+) calc. for $[C_9H_{14}O_3Na]^+$ 193.0835, found 193.0835.

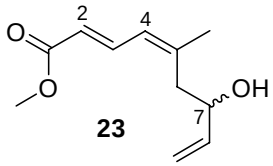
(2*E*,4*Z*)-Methyl 5-methyl-7-oxohepta-2,4-dienoate



(2*E*,4*Z*)-Methyl 7-hydroxy-5-methylhepta-2,4-dienoate **22** (0.342 g, 2.01 mmol) was dissolved in dichloromethane (20 mL) and Dess-Martin periodinane (1.109 g, 2.6 mmol) was added in a single portion. After 90 mins, TLC (1:2, ethyl acetate / hexane) suggested complete conversion to a higher R_f product. A 1:1 mixture of saturated $NaHCO_3$ solution (20 mL) and saturated $Na_2S_2O_3$ solution (20 mL) was added and the mixture stirred for 15 mins until homogeneous, before extraction with dichloromethane (3 x 20 mL). The combined extracts were washed with saturated NaCl solution (20 mL), dried (Na_2SO_4) and concentrated. The resultant residue was adsorbed onto silica from dichloromethane and subjected to flash chromatography (60% diethyl ether / hexane) which gave (2*E*,4*Z*)-methyl 5-methyl-7-oxohepta-2,4-dienoate (0.295 g, 87%).

R_f 0.5 (1:2, ethyl acetate / hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.62 (1H, t, *J* 1.8 Hz, C7-**H**), 7.42 (1H, dd, *J* 11.7, 15.1 Hz, C3-**H**), 6.25 (1H, d, *J* 11.7 Hz, C4-**H**), 5.87 (1H, d, *J* 15.1 Hz, C2-**H**) 3.74 (3H, s, OC**H$_3$**), 3.42 (2H, d, *J* 1.5 Hz, C6-**H**), 1.92 (3H, s, C**H$_3$**C=C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.3, 167.5, 139.3, 138.9, 127.6, 120.9, 51.6, 47.8, 25.2; IR (thin film): 1713 (C=O), 1639, 1435, 1277, 1155 cm^{-1}. *m/z* (EI+) 169 ([M+H]$^+$, 15%), 151 (30), 125 (55), 107 (25), 81 (40), 79 (100), 77 (45), 39 (50); HRMS (EI+) calc. for $[C_9H_{12}O_3]^+$ 168.0786, found 168.0783.

(2*E*,4*Z*)-Methyl 7-hydroxy-5-methylnona-2,4,8-trienoate **23**



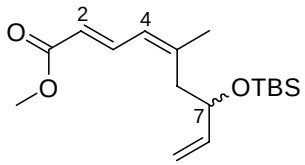
23

To dry[vi] cerium(III) chloride (0.220 g, 0.893 mmol) in THF (3 mL), at -78 ºC, was added vinylmagnesium bromide (0.84 M, 1.06 mL, 0.893 mmol). After 45 mins at -78 ºC, a solution of (2*E*,4*Z*)-methyl 5-methyl-7-oxohepta-2,4-dienoate (0.100 g, 0.595 mmol) in THF (3 mL) was added *via* cannula. The reaction mixture was maintained at -78 ºC for 2 h, when TLC (1:1, ethyl acetate / hexane) suggested very little starting aldehyde (R_f 0.7) and the formation of a new product (R_f 0.65). Saturated NH_4Cl solution (3 mL) was added and the reaction

mixture warmed to room temperature. The reaction mixture was partitioned between diethyl ether (50 mL) and saturated NH_4Cl solution (30 mL). The aqueous mixture was further extracted with diethyl ether (3 x 40 mL). The combined organic extracts were washed with saturated NaCl solution (30 mL), dried (Na_2SO_4) and concentrated. The residue obtained was dissolved in dichloromethane and adsorbed onto silica, giving a dry powder which was subjected to flash chromatography (30% ethyl acetate / hexane), to afford (2*E*,4*Z*)-methyl 7-hydroxy-5-methylnona-2,4,8-trienoate **23** (0.065 g, 56%).

R_f 0.3 (30% ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (1H, dd, *J* 11.7, 15.1 Hz, C3-**H**), 6.12 (1H, d, *J* 11.7 Hz, C4-**H**), 5.89 (1H, ddd, *J* 17.2, 10.4, 6.0 Hz, C8-**H**), 5.79 (1H, d, *J* 15.1 Hz, C2-**H**), 5.26 (1H, td, *J* 1.2, 17.2 Hz, C9-**H**$_a$), 5.13 (1H, td, *J* 1.2, 10.4 Hz, C9-**H**$_b$), 4.34-4.24 (1H, m, C7-**H**), 3.72 (3H, s, OC**H**$_3$), 2.63 (1H, dd, *J* 8.2, 13.5 Hz, C6-**H**$_a$), 2.41 (1H, dd, *J* 5.3, 13.5 Hz, C6-**H**$_b$), 1.92 (3H, s, C**H**$_3$C=C), 1.90 (1H, br s, O**H**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 145.7, 140.5, 140.1, 126.5, 119.4, 115.9, 71.4, 51.4, 40.5, 25.0; IR (thin film): 3600-3200 (OH), 1713 (C=O), 1632, 1435, 1281, 1157 cm^{-1}; *m/z* (EI+) 197 ($[M+H]^+$, 55%), 179 (100), 147 (25), 125 (35) 119 (20), 107 (23); HRMS (EI+) calc. for $[C_{11}H_{17}O_3]^+$ 197.1172, found 197.1181.

(2*E*,4*Z*)-Methyl 7-(*tert*-butyldimethylsilyloxy)-5-methylnona-2,4,8-trienoate

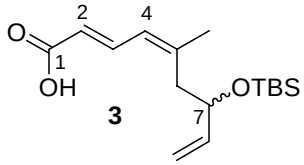


To a -78 °C solution of alcohol **23** (102 mg, 0.52 mmol) in dichloromethane (5 ml) was added 2,6-lutidine (80 μL, 0.68 mmol) followed by *tert*-butyldimethylsilyltrifluoromethanesulfonate (120 μL, 0.52 mmol). The reaction mixture was stirred for 30 mins at -78 °C, warmed to room temperature and quenched with water (10 mL). The layers were separated and the aqueous phase extracted with dichloromethane (3 x 20 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (5% ethyl acetate / hexane) afforded the title trienoate (145 mg, 90%), as a pale yellow oil.

R_f 0.7 (1:3, ethyl acetate / hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (1H, dd, *J* 11.7, 15.1 Hz, C3-**H**), 6.06 (1H, d, *J* 11.7 Hz, C4-**H**), 5.81 (1H, ddd, *J* 6.0, 10.3, 17.1 Hz, C8-**H**), 5.76 (1H, d, *J* 15.1 Hz, C2-**H**), 5.17 (1H, td, *J* 1.2, 17.1 Hz, C9-**H**$_a$), 5.04 (1H, td, *J* 1.2, 10.3 Hz, C9-

H$_b$), 4.29–4.21 (1H, m, C7-**H**), 3.73 (3H, s, OC**H$_3$**), 2.58 (1H, dd, *J* 7.6, 13.2 Hz, C6-**H**$_a$), 2.35 (1H, dd, *J* 5.4, 13.2 Hz, C6-**H**$_b$), 1.90 (3H, s, C**H$_3$**C=C), 0.86 (9H, s, SiC(C**H$_3$**)$_3$), 0.01 (3H, s, Si(C**H$_3$**)$_2$), 0.00 (3H, s, Si(C**H$_3$**)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 146.3, 141.3, 141.0, 126.1, 118.7, 114.2, 72.8, 51.3, 41.7, 25.8, 25.6, 18.1, -4.6, -4.9; IR (thin film): 1720 (C=O), 1637, 1435, 1259, 1153 cm^{-1}; *m/z* (ES+) 333 ([M+Na]$^+$, 30%), 311 ([M+H]$^+$, 53); HRMS (ES+) calc. for $[C_{17}H_{30}O_3SiNa]^+$ 333.1856, found 333.1858.

(2*E*,4*Z*)-7-(*tert*-Butyldimethylsilyloxy)-5-methylnona-2,4,8-trienoic acid **3**[vii]

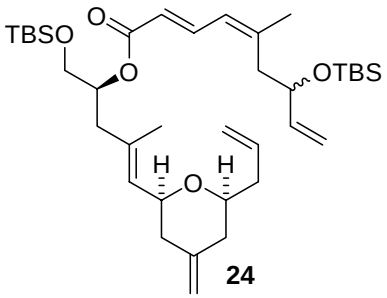


3

(2*E*,4*Z*)-Methyl 7-(*tert*-butyldimethylsilyloxy)-5-methylnona-2,4,8-trienoate (0.098 g, 0.32 mmol) was dissolved in MeOH (1.6 mL) and cooled to 0 ºC. NaOH solution (1.0 M, 0.79 mL, 0.79 mmol) was added dropwise. After 5 mins, the reaction mixture was warmed to room temperature and THF (0.5 mL) was added to aid dissolution. The reaction mixture was stirred at 24 ºC for 16 h. Additional NaOH solution (1.0 M, 0.1 mL) was added and stirring continued for 2 h. TLC (1:3, ethyl acetate/hexane) then suggested complete conversion to a lower R_f product. Upon addition of HCl solution (1.0 M, 0.9 mL), a precipitate was observed. The reaction mixture was diluted with H_2O (20 mL) and extracted into ethyl acetate (3 x 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Addition of toluene effected azeotropic removal of H_2O, giving (2*E*,4*Z*)-7-(*tert*-butyldimethylsilyloxy)-5-methylnona-2,4,8-trienoic acid **3** (0.087 g, 93%).

R_f 0.3 (25% ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (1H, dd, *J* 11.7, 15.1 Hz, C3-**H**), 6.10 (1H, d, *J* 11.7 Hz, C4-**H**), 5.81 (1H, ddd, *J* 6.1, 10.4, 16.9 Hz, C8-**H**), 5.76 (1H, d, *J* 15.1 Hz, C2-**H**), 5.18 (1H, td, *J* 1.4, 17.1 Hz, C9-**H**$_a$), 5.06 (1H, td, *J* 1.4, 10.4 Hz, C9-**H**$_b$), 4.32-4.22 (1H, m, C7-**H**), 2.60 (1H, dd, *J* 7.7, 13.2 Hz, C6-**H**$_a$), 2.36 (1H, dd, *J* 5.2, 13.2 Hz, C6-**H**$_b$), 1.93 (3H, s, C**H$_3$**C=C), 0.86 (9H, s, SiC(C**H$_3$**)$_3$), 0.01 (3H, s, Si(C**H$_3$**)$_2$), 0.00 (3H, s, Si(C**H$_3$**)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 147.8, 143.5, 140.9, 126.0, 118.1, 114.3, 72.9, 41.9, 25.8, 25.7, 18.1, -4.5, -4.9; IR (thin film): 3400-2400 (COOH), 1688 (C=O), 1632, 1283, 1256 cm^{-1}; *m/z* (ES-) 295 ([M-H]$^-$, 100%); HRMS (ES-) calc. for $[C_{16}H_{27}O_3Si]^-$ 295.1735, found 295.1736.

(2*E*,4*Z*)-((*S*,*E*)-5-((2*S*,6*S*)-6-Allyl-4-methylenetetrahydro-2*H*-pyran-2-yl)-1-(*tert*-butyldimethylsilyloxy)-4-methylpent-4-en-2-yl) 7-(*tert*-butyldimethylsilyloxy)-5-methylnona-2,4,8-trienoate **24**[vii]

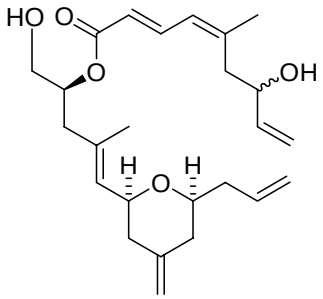


24

Alcohol **4** (30 mg, 81.8 μmol) and acid **3** (50 mg, 0.17 mmol) were dissolved in degassed toluene (700 μl) and added *via cannula* to a solution of DEAD (40 μl, 0.25 mmol) and triphenylphosphine (66 mg, 0.25 mmol) in degassed toluene (1 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min and then at room temperature for 2 h. The reaction was then quenched with saturated sodium bicarbonate and extracted with ether (3 x 10 mL). The organic extracts were combined, dried over sodium sulfate and concentrated *in vacuo*. Flash chromatography (5% Ethyl acetate/hexane) afforded the ester **24** as a pale yellow oil (33 mg, 63%).

The product was isolated as a 1:1 mixture of diastereomers; $[\alpha]_D^{20}$ -47 (*c*. 0.11, CH_2Cl_2) (*ent*-**24** lit.[vii] $[\alpha]_D^{20}$ +28 (*c* 0.05, CH_2Cl_2)); R_f 0.13 (5% ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (1H, dd, *J* 11.7, 15.1 Hz, C3-**H**), 6.06 (1H, d, *J* 11.6 Hz, C4-**H**), 5.74 – 5.90 (2H, m, C8-**H**, C9-**H**), 5.76 (1H, d, *J* 15.1 Hz, C2-**H**), 5.31 (1H, d, *J* 7.7 Hz, C16-**H**), 5.02 – 5.17 (5H, m, C8=C**H$_2$**, C9=C**H$_2$,** C19-**H**), 4.72 (2H, s, C13=C**H$_2$**), 4.25 (1H, m, C7-**H**), 4.00 (1H, m, C15-**H**), 3.65 – 3.69 (2H, m, C20-**H**), 3.34 (1H, m, C11-**H**), 2.50-2.44 (10H, m, 5 x C**H$_2$**C=C), 1.91 (3H, s, C5-C**H$_3$**), 1.73 (3H, s, C17-C**H$_3$**), 0.88 (9H, s, SiC(C**H$_3$**)$_3$), 0.86 (9H, s, SiC(C**H$_3$**)$_3$), 0.07 (3H, s, Si(C**H$_3$**)$_2$), 0.04 (3H, s, Si(C**H$_3$**)$_2$), 0.01 (6H, s, Si(C**H$_3$**)$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0 (2C), 146.2, 146.1, 144.5 (2C), 141.1 (2C), 141.0, 140.97, 135.0, 134.0, 134.6 (2C), 128.8, 128.7, 126.2, 126.1, 119.4, 119.37, 116.8 (2C), 114.2 (2C), 108.6 (2C), 77.7 (2C), 75.5 (2C), 72.9 (2C), 72.8, 72.78, 63.78, 63.76, 42.4 (2C), 40.8 (2C), 40.7 (2C), 40.5 (2C), 39.9 (2C), 25.8 (6C), 25.6, 25.5, 18.3, 18.1, 17.3, 17.2, -4.5, -4.9, -5.3 (2C); *m/z* (ESI) 667 ([M+Na]$^+$, 100%); HRMS (ESI) calc. for $[C_{37}H_{64}O_5Si_2Na]^+$ 667.41900, found 667.4172.

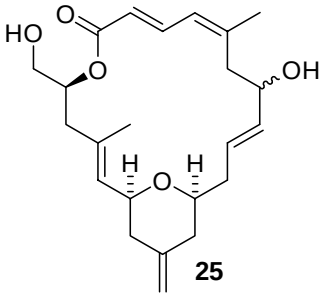
(2*E*,4*Z*)-((*S*,*E*)-5-((2*S*,6*S*)-6-Allyl-4-methylenetetrahydro-2*H*-pyran-2-yl)-1-hydroxy-4-methylpent-4-en-2-yl) 7-hydroxy-5-methylnona-2,4,8-trienoate[vii]



Ester **24** (30 mg, 46.5 μmol) was dissolved in methanol (1.0 mL) and dichloromethane (250 μl) and cooled to 0 °C. Aqueous HCl (1.0 M, mL) was added and the solution warmed up to room temperature and stirred for 6 h. The reaction was diluted with dichloromethane (5mL) and concentrated *in vacuo*. Flash chromatography (50% ethyl acetate/hexane) afforded the titled compound as a pale yellow solid (11.6 mg, 60%).

$[\alpha]_D^{20}$ = -14 (*c*. 1.2, CH_2Cl_2) (lit.[v] $[\alpha]_D^{20}$ = +11 (*c* 0.07, CH_2Cl_2)); R_f = 0.33 (50% Ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (1H, m, C3-**H**), 6.13 (1H, d, *J* = 11.7 Hz, C4-**H**), 5.74 – 5.95 (3H, m, C2-**H**, C8-**H**, C9-**H**,), 5.32 (1H, d, *J* = 8.1 Hz, C16-**H**), 5.01 – 5.30 (5H, m, C8=C**H$_2$**, C9=C**H$_2$**, C19-**H**), 4.72 (2H, s, C13=C**H$_2$**), 4.28 (1H, m, C7-**H**), 3.98 (1H, m, C15-**H**), 3.75 (1H, m, C20-**H$_a$**), 3.64 (1H, m, C20-**H$_b$**), 3.35 (1H, m, C11-**H**), 2.65 (1H, m, C**H$_a$**C=C), 1.96 - 2.45 (11H, m, C**H$_b$**C=C, 4 x C**H$_2$**C=C, 2 x O**H**), 1.94 (3H, s, C5-C**H$_3$**), 1.73 (3H, s, C17-C**H$_3$**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8 (2C), 146.3 (2C), 144.5 (2C), 141.4, 141.3, 140.4, 140.3, 134.7 (2C), 134.54, 134.46, 129.4 (2C), 126.6 (2C), 119.52, 119.47, 117.0 (2C), 115.4, 115.3, 108.8 (2C), 77.9 (2C), 75.7, 75.6 73.8, 73.7, 71.63, 71.57, 64.5, 64.4, 40.8 (4C), 40.7 (4C), 40.0 (2C), 25.3 (2C), 17.3 (2C).

(1*S*,2*E*,5*S*,8*E*,10*Z*,14*E*,17*S*)-13-Hydroxy-5-(hydroxymethyl)-3,11-dimethyl-19-methylene-6,21-dioxabicyclo[15.3.1]henicosa-2,8,10,14-tetraen-7-one **25**[vii]

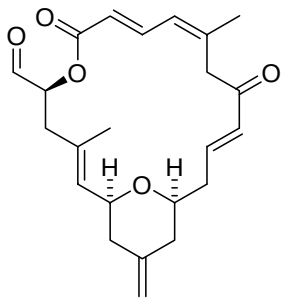


25

(2*E*,4*Z*)-((*S*,*E*)-5-((2*S*,6*S*)-6-Allyl-4-methylenetetrahydro-2*H*-pyran-2-yl)-1-hydroxy-4-methylpent-4-en-2-yl) 7-hydroxy-5-methylnona-2,4,8-trienoate (11.6 mg, 27.8 μmol) was dissolved in degassed dichloromethane (28 mL) under an argon atmosphere. Grubbs' second generation catalyst **20** (2.3 mg, 2.80 μmol) was then added and the light purple solution stirred at room temperature for 70 mins. The mixture was then concentrated *in vacuo*. Flash chromatography (60% ethyl acetate/hexane) afforded **25** as a white solid (8.8 mg, 82%).

$[\alpha]_D^{20}$ +2.7 (*c*, 0.88, CH_2Cl_2); R_f 0.33 (60% Ethyl acetate/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (1H, dd, *J* 11.6, 15.1 Hz, C3-**H**)/7.45 (1H, dd, *J* 11.6, 15.2 Hz, C3-**H**)*****, 6.06 (2H, d, *J* 11.7 Hz, 2 x C4-**H**), 5.81 (1H, d, *J* 15.2 Hz, C2-**H**)/5.76 (1H, d, *J* 15.2 Hz, C2-**H**)***,** 5.56 – 5.76 (4H, m, 2 x C8-**H**, 2 x C9-**H**,), 5.29 (1H, d, *J* 7.6 Hz, C19-**H**)/5.24 (1H, d, *J* 7.7 Hz, C19-**H**)*****, 5.13 – 5.21 (2H, m, 2 x C16-**H**), 4.71 - 4.73 (4H, m, 2 x C13-C**H$_2$**), 4.30 – 4.40 (1H, m, C7-**H**)/4.19 – 4.28***** (1H, m, C7-**H**), 3.91 – 3.98 (2H, m, 2 x C15-**H**), 3.66 – 3.80 (4H, m, 2 x C20-**H**), 3.29 – 3.35 (2H, m, 2 x C11-**H**), 2.59 – 2.86 (24H, m, 10 x C**H$_2$**C=C, 4 x O**H**), 1.99 (3H, s, C5-C**H$_3$**)/ 1.88 (3H, s, C5-C**H$_3$**),***** 1.72 (3H, s, C17-C**H$_3$**)/ 1.69 (3H, s, C17-C**H$_3$**)***** (***** due to diastreromers); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 167.3, 147.6, 146.0, 144.4 (2C), 140.8, 140.6, 133.5 (2C), 131.9 (2C), 129.6 (2C), 129.1, 128.5, 125.7, 125.6, 119.5, 119.3, 108.7, 108.6, 77.7, 77.3, 75.9, 75.6, 72.6, 72.3, 72.1, 69.6, 65.3, 65.2, 41.7, 41.2, 41.1, 40.7, 40.6, 40.5, 40.2 (2C), 39.2, 38.6, 25.5, 23.9, 16.7, 16.5.

(-)-Dactylolide **1**[vii,viii]



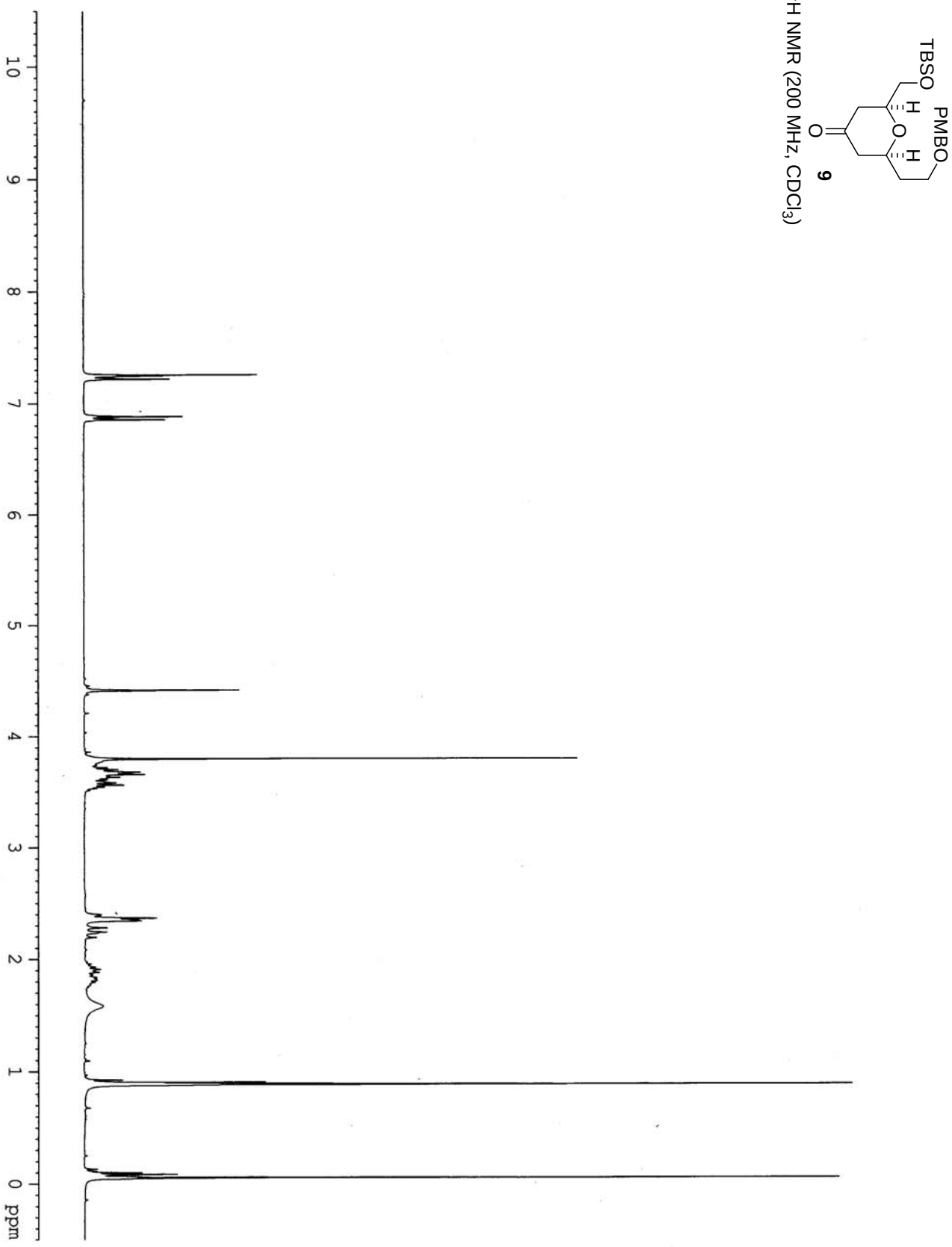
(-)-dactylolide **1**

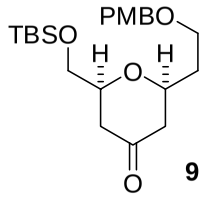
A solution of **25** (8.8 mg, 22.6 μmol) in dichloromethane (2.8 mL) was treated with anhydrous sodium bicarbonate (26.5 mg) followed by Dess-Martin periodinane (57.5 mg, 0.14 mmol). The white suspension was stirred for 1 h at room temperature and then quenched with

saturated $NaHCO_3/Na_2S_2O_3$ (1:1, 8 mL). After stirring for 30 min, the biphasic mixture was extracted with dichloromethane (4 x 5 mL). The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo*. Flash chromatography (50% ethyl acetate/hexane) afforded (-)-dactylolide **1** as a white solid (6.2 mg, 71%).

$[\alpha]_D^{20}$ -169 (*c*, 0.42 MeOH); R_f 0.27 (50% ethyl acetate/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (1H, s, C20-**H**), 7.63 (1H, dd, *J* 11.6, 15.0 Hz, C3-**H**), 6.85 (1H, ddd, *J* 6.3, 8.4, 15.0, C9-**H**), 6.16 (1H, d, *J* 11.5 Hz, C4-**H**), 5.86 – 6.02 (2H, m, C2-**H**, C8-**H**,), 5.31 (1H, d, *J* 11.7 Hz, C19-**H**), 5.24 (1H, d, *J* 8.0 Hz, C16-**H**), 4.74 (2H, s, C13-C**H$_2$**), 3.95 (1H, d, *J* 14.5 Hz, C6-**H$_a$**H$_b$), 3.94 (1H, m, C15-**H**), 3.30 – 3.35 (1H, m, C11-**H**), 3.23 (1H, d, *J* 14.3 Hz, C6-H$_a$**H$_b$**), 2.55 (1H, d, *J* 13.7 Hz, C=CC-**H$_a$**H$_b$), 2.24 – 2.43 (3H, m, C=CC-H$_a$**H$_b$**, C=CC**H$_2$**), 2.17 (1H, d, *J* 13.0 Hz, C=CC-**H$_a$**H$_b$), 2.11 (1H, d, *J* 12.9 Hz, C=CC-H$_a$**H$_b$**), 1.97 (1H, d, *J* 12.7 Hz, C=CC-**H$_a$**H$_b$), 1.91 (1H, d, *J* 14.8 Hz, C=CC-H$_a$**H$_b$**), 1.86 (3H, s, C5-C**H$_3$**), 1.72 (3H, s, C17-C**H$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ. 199.1, 197.4, 166.3, 146.0, 144.0, 143.5140.4, 131.4, 130.9, 130.5, 125.6, 119.8, 109.3, 76.7, 75.7, 75.5, 44.9, 41.0, 40.8, 39.9, 39.7, 24.1, 16.0; *m/z* (ESI) 439 ($[M+Na+MeOH]^+$, 100%).

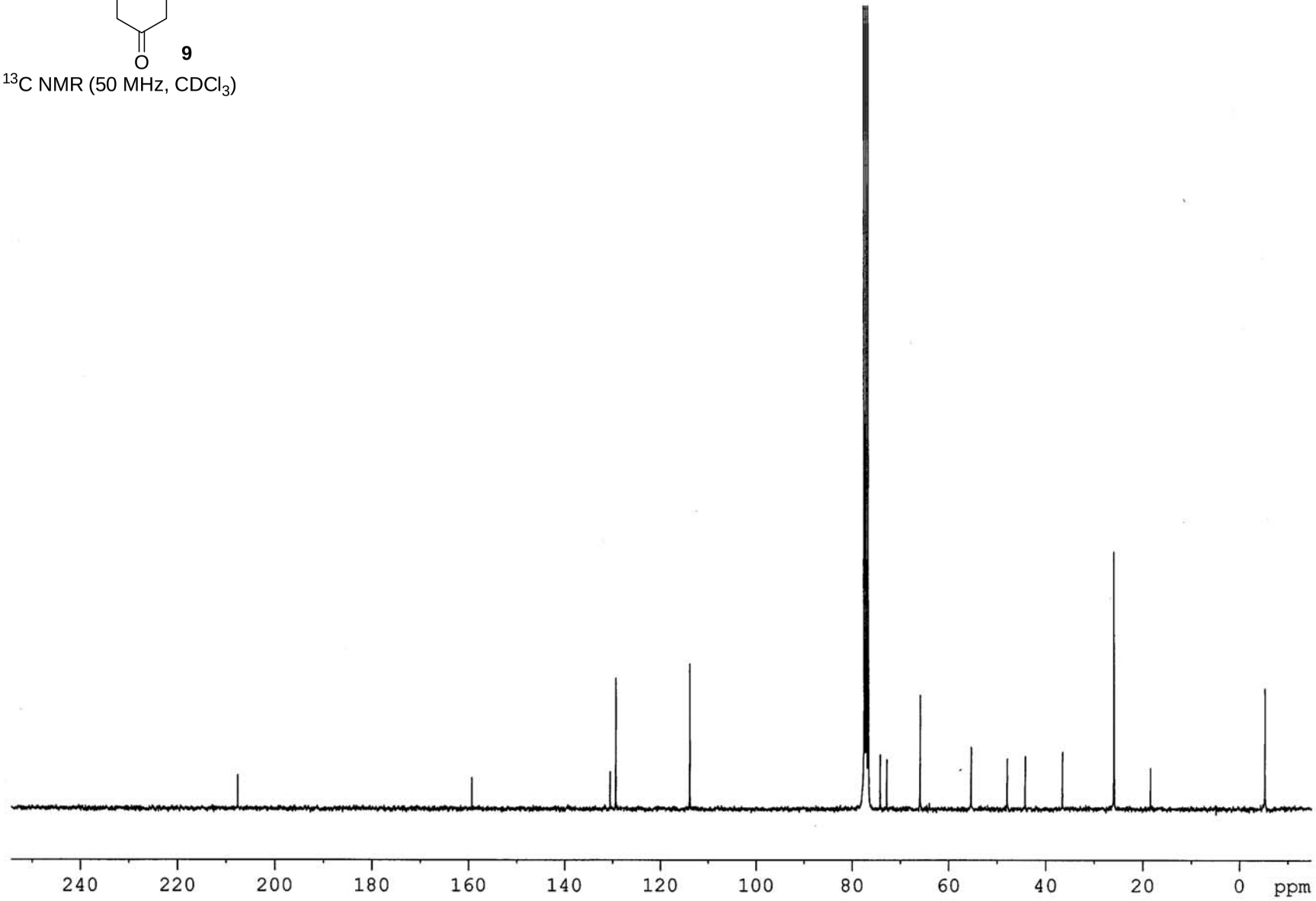
^{1}H and ^{13}C Spectra

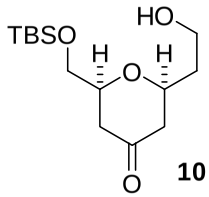




9

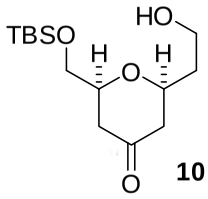
^{13}C NMR (50 MHz, $CDCl_3$)





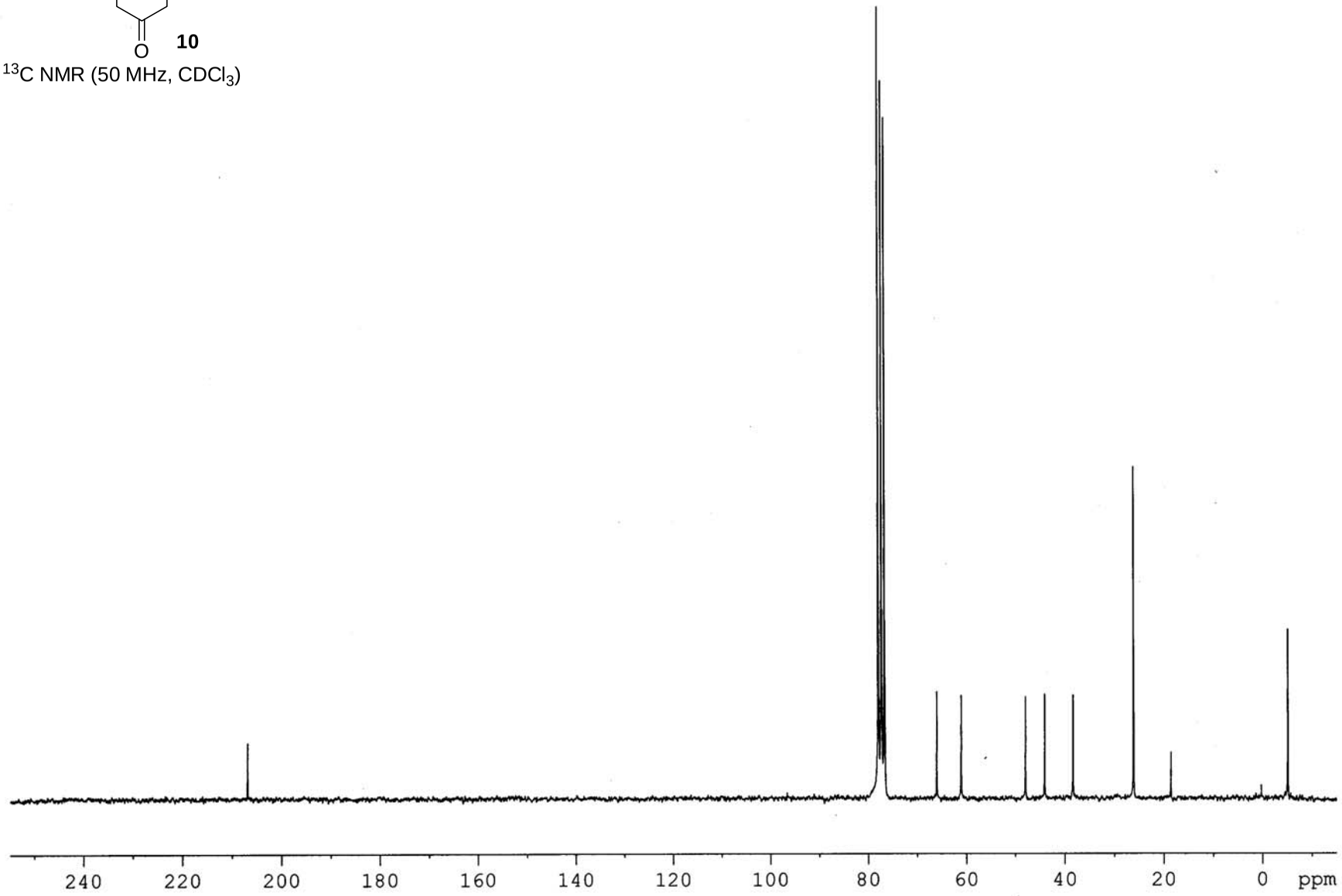
10

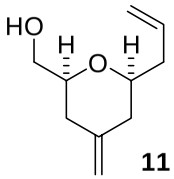
^{1}H NMR (200 MHz, $CDCl_3$)



10

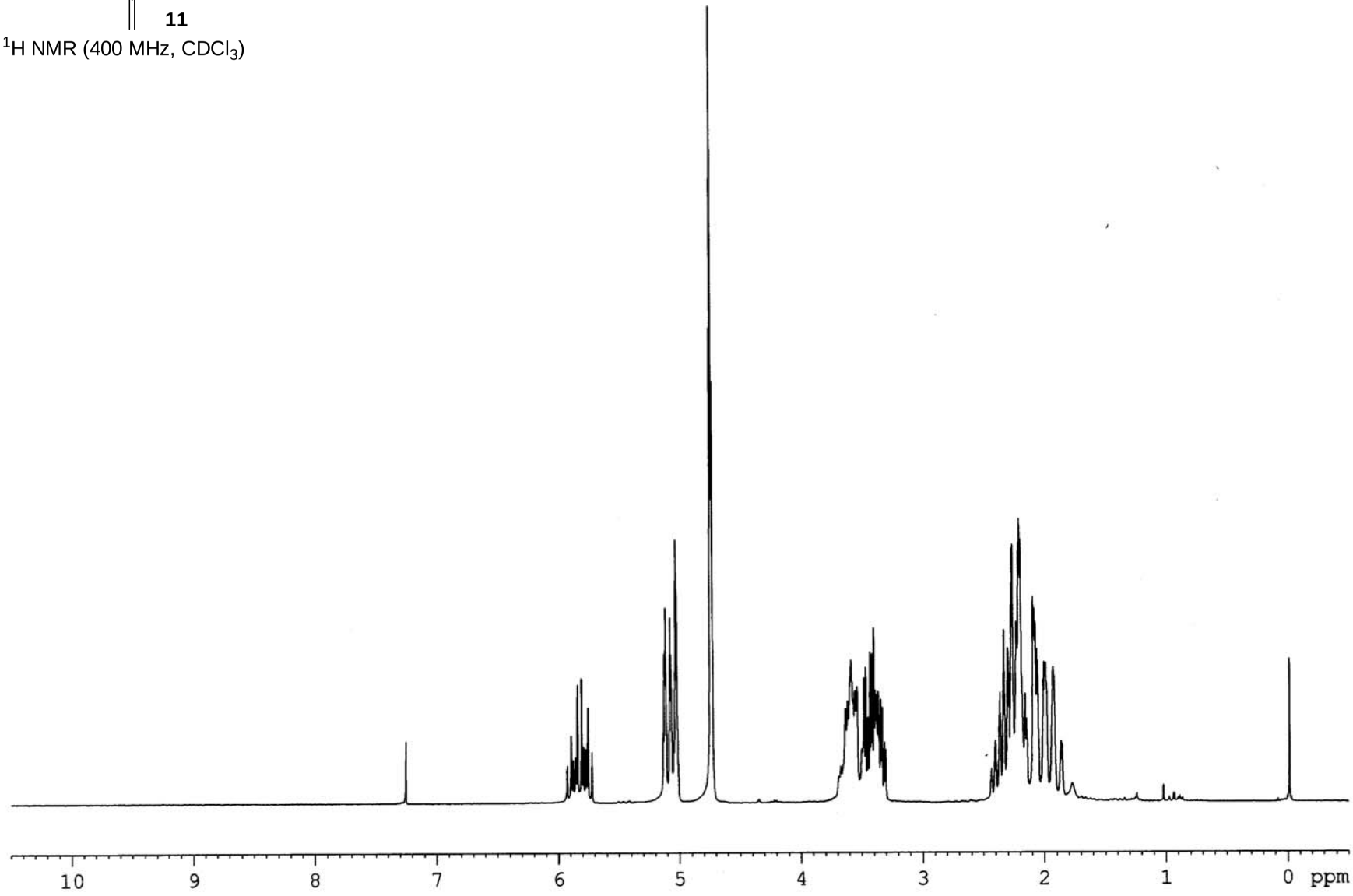
^{13}C NMR (50 MHz, $CDCl_3$)

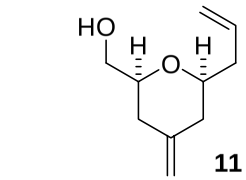




11

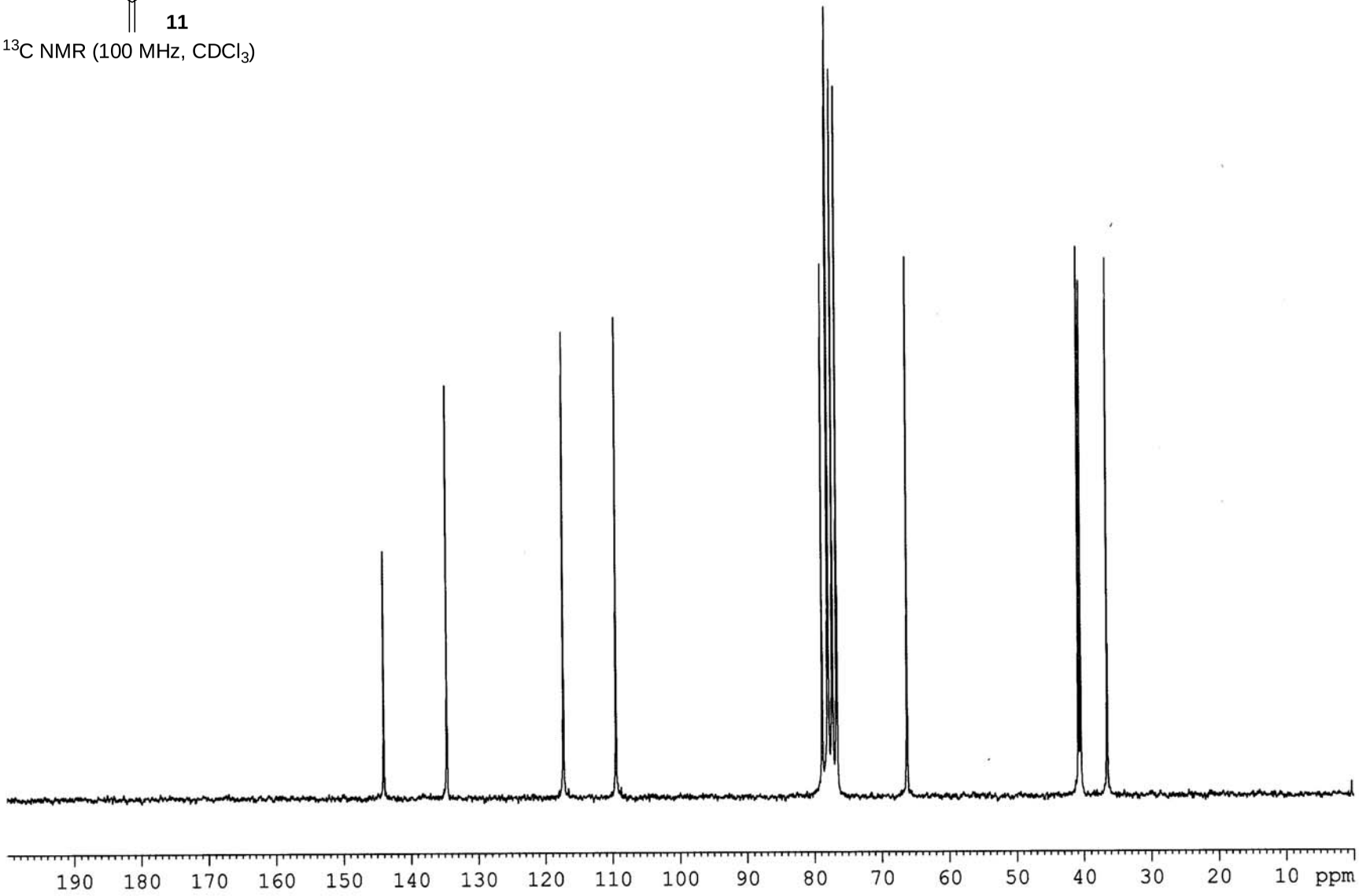
^{1}H NMR (400 MHz, $CDCl_3$)

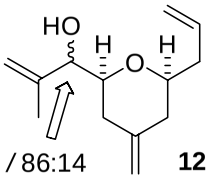




11

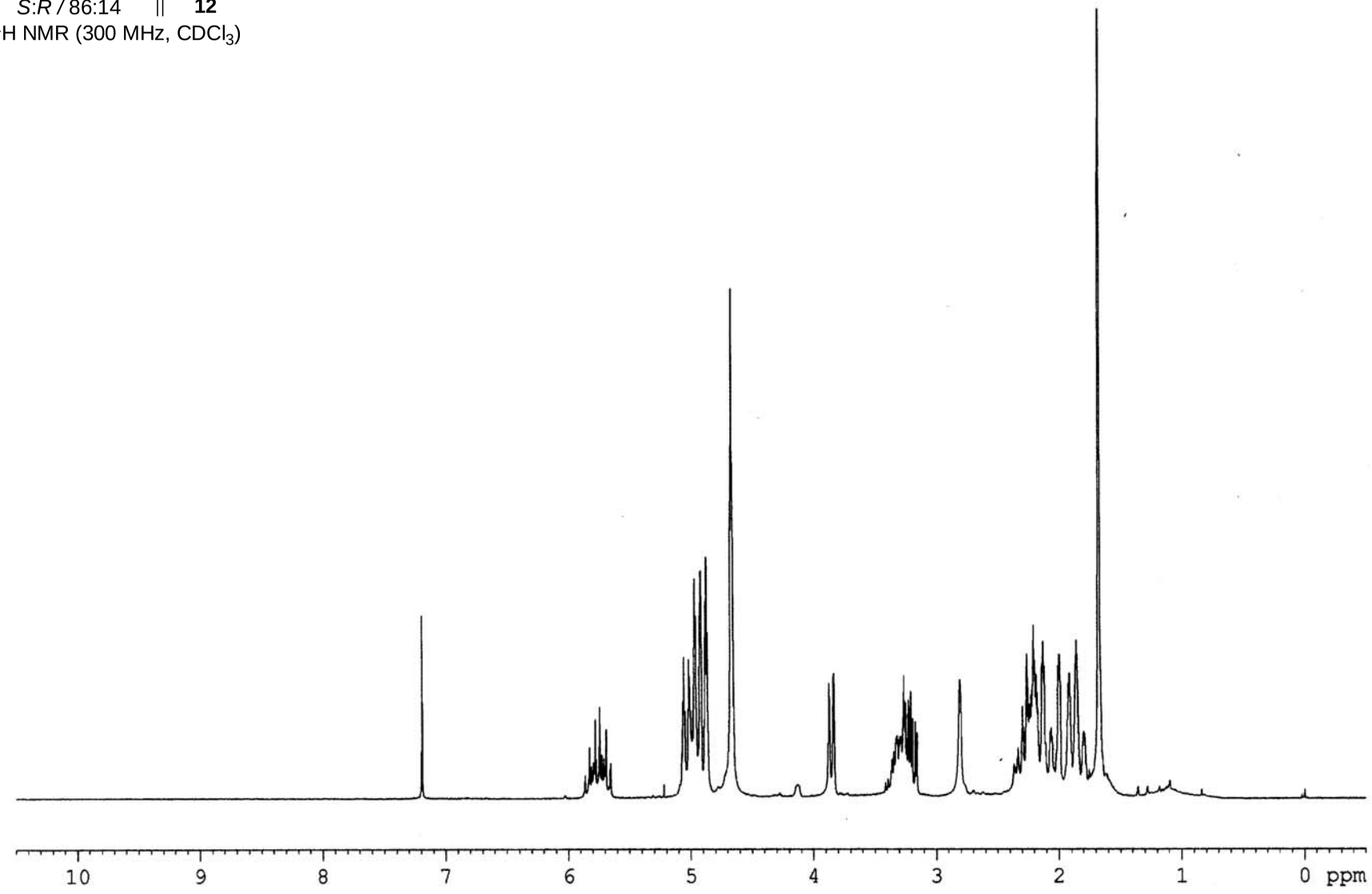
^{13}C NMR (100 MHz, $CDCl_3$)

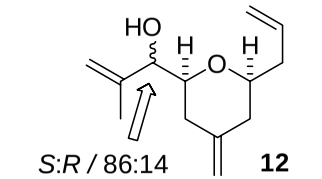




S:*R* / 86:14 **12**

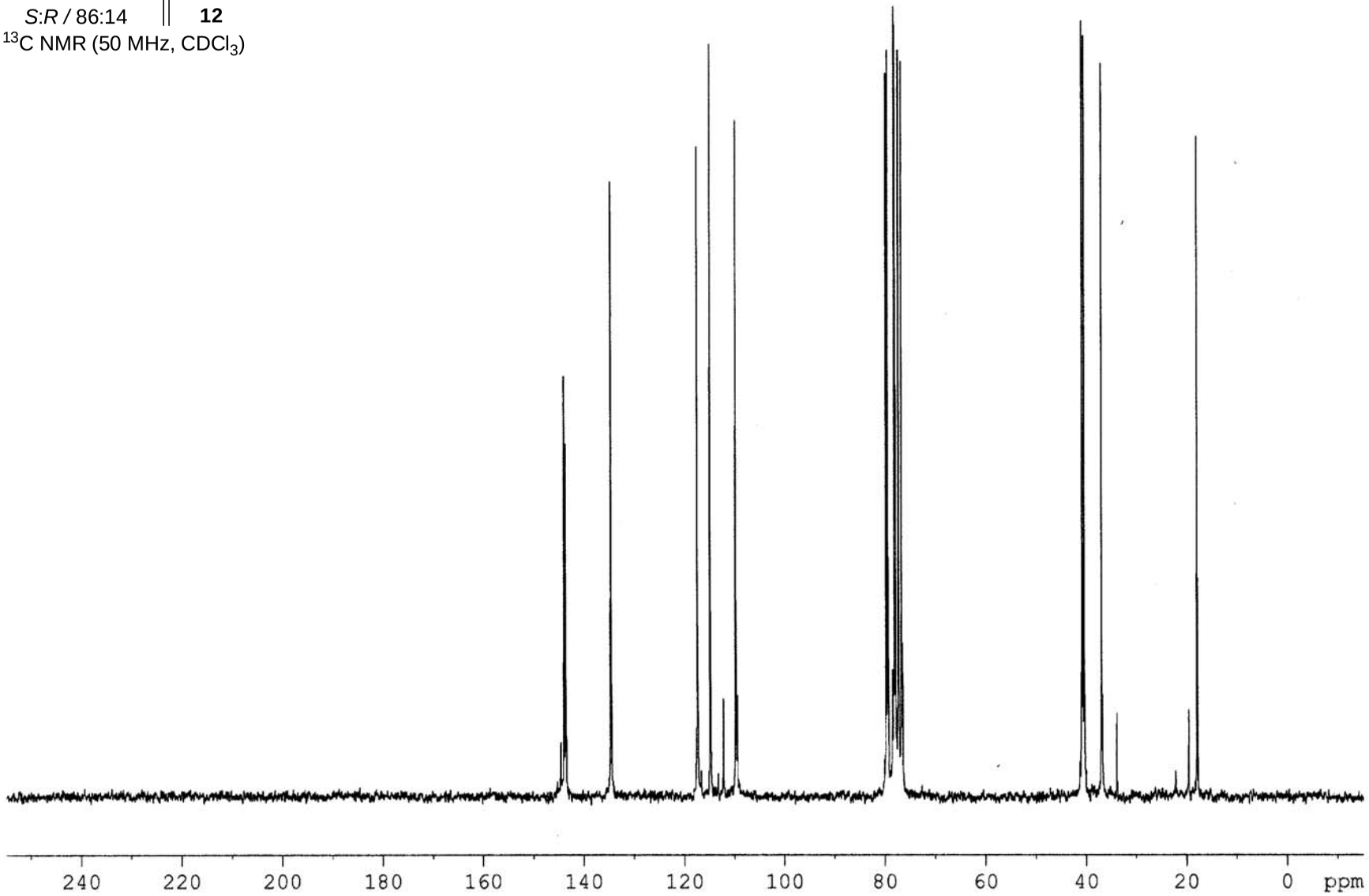
^{1}H NMR (300 MHz, $CDCl_3$)

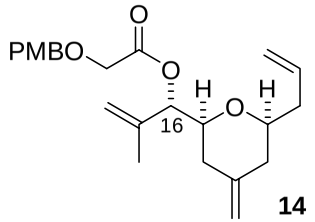




S:R / 86:14 **12**

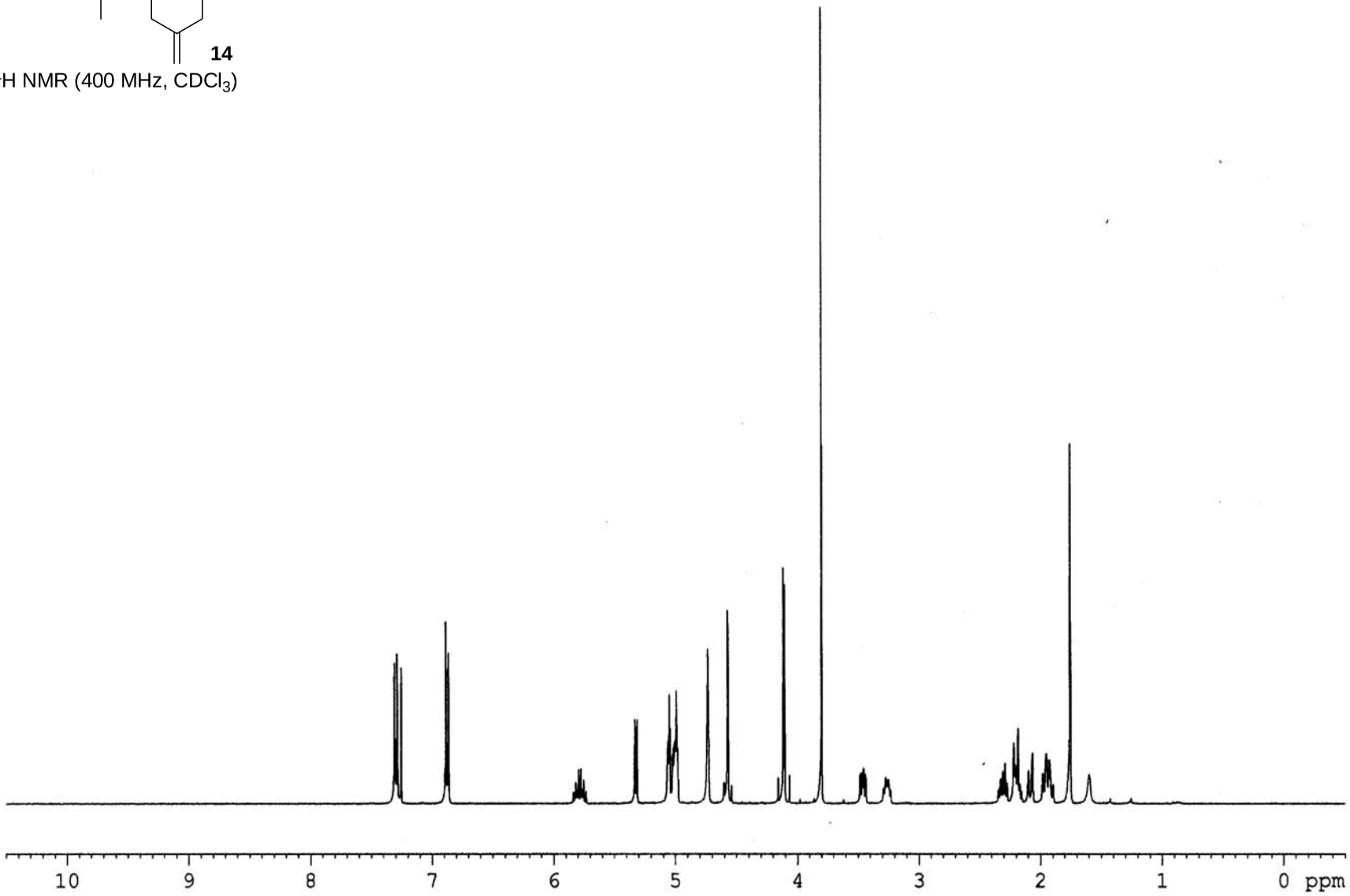
^{13}C NMR (50 MHz, $CDCl_3$)

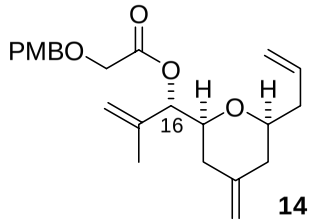




14

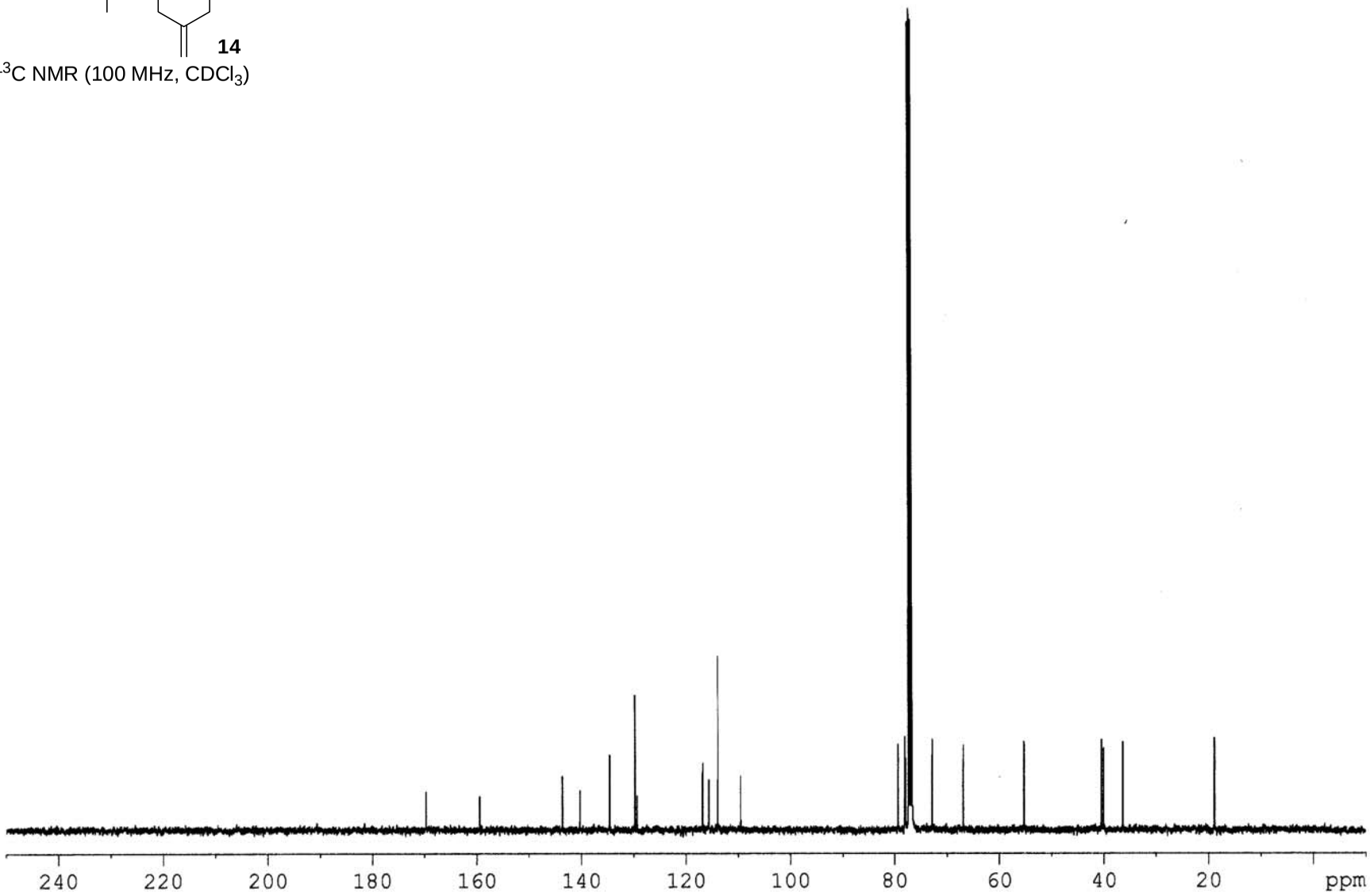
^{1}H NMR (400 MHz, $CDCl_3$)

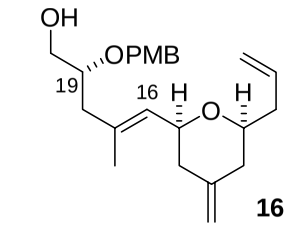




14

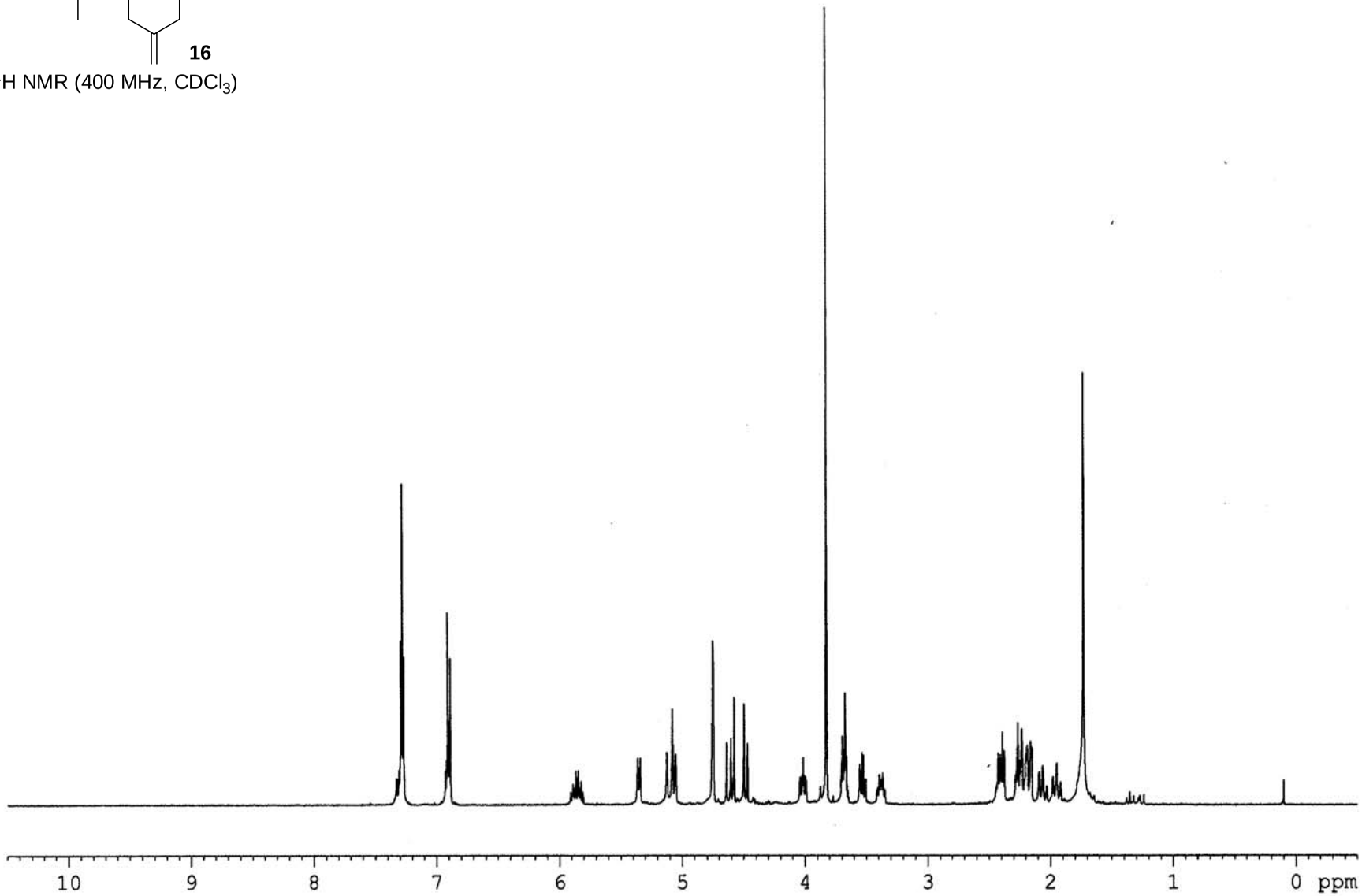
^{13}C NMR (100 MHz, $CDCl_3$)

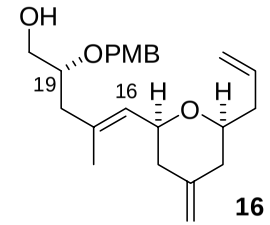




16

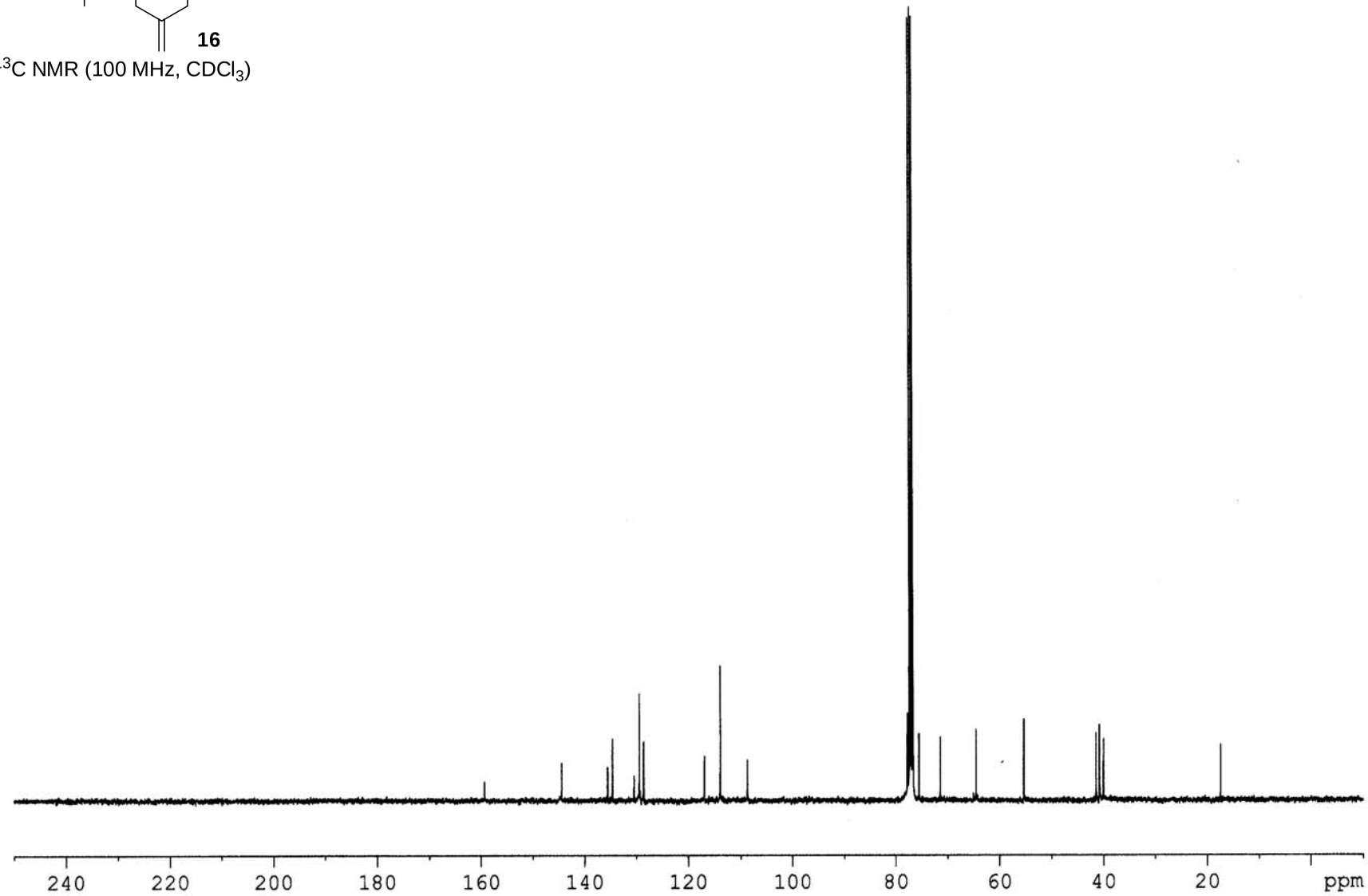
^{1}H NMR (400 MHz, $CDCl_3$)

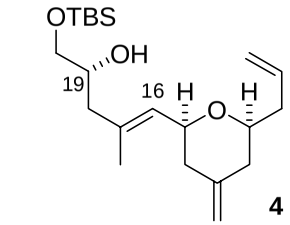




16

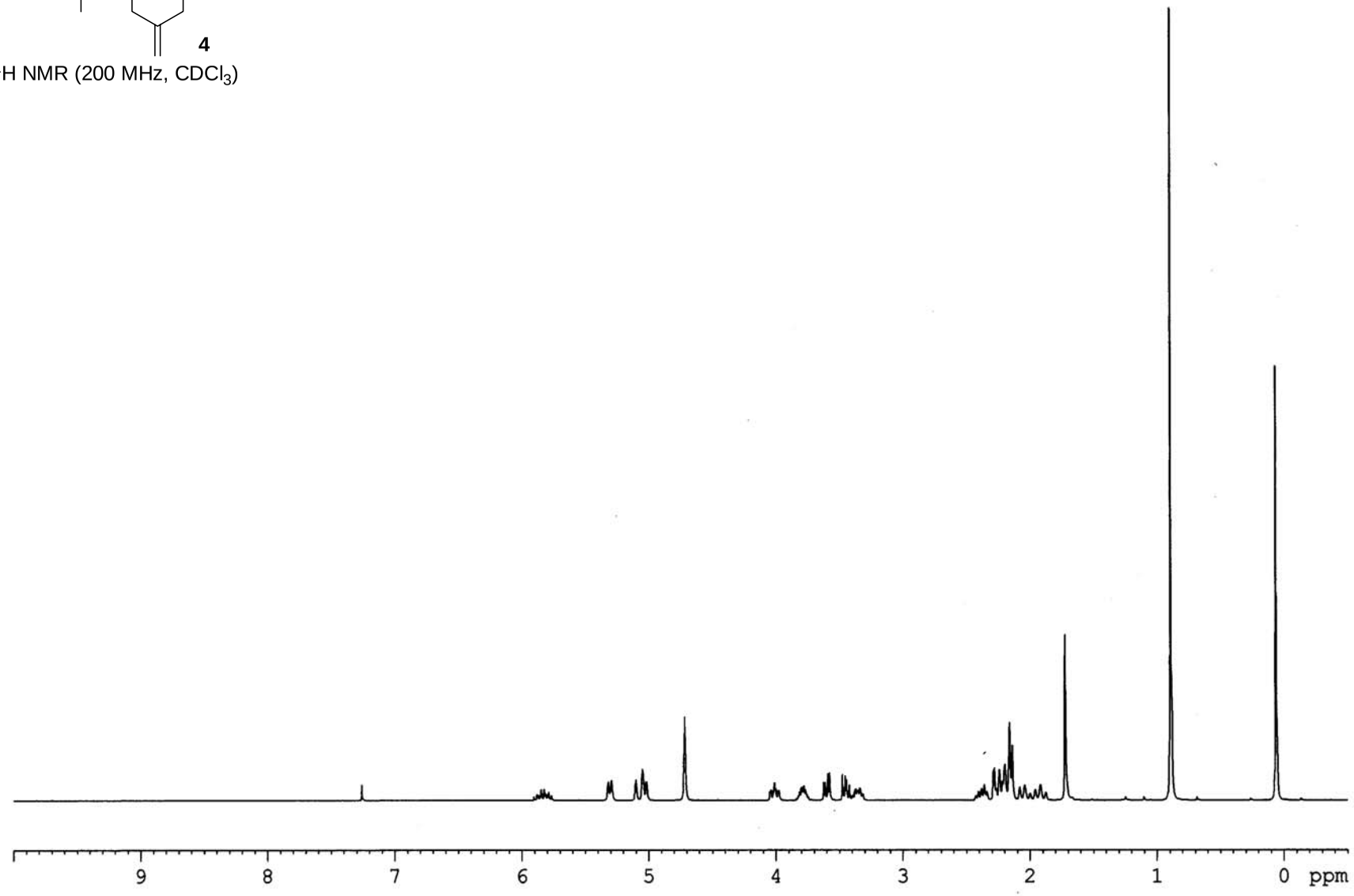
^{13}C NMR (100 MHz, $CDCl_3$)

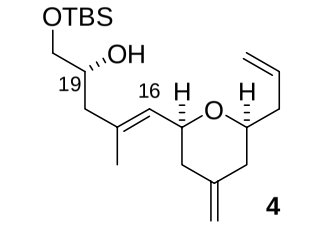




4

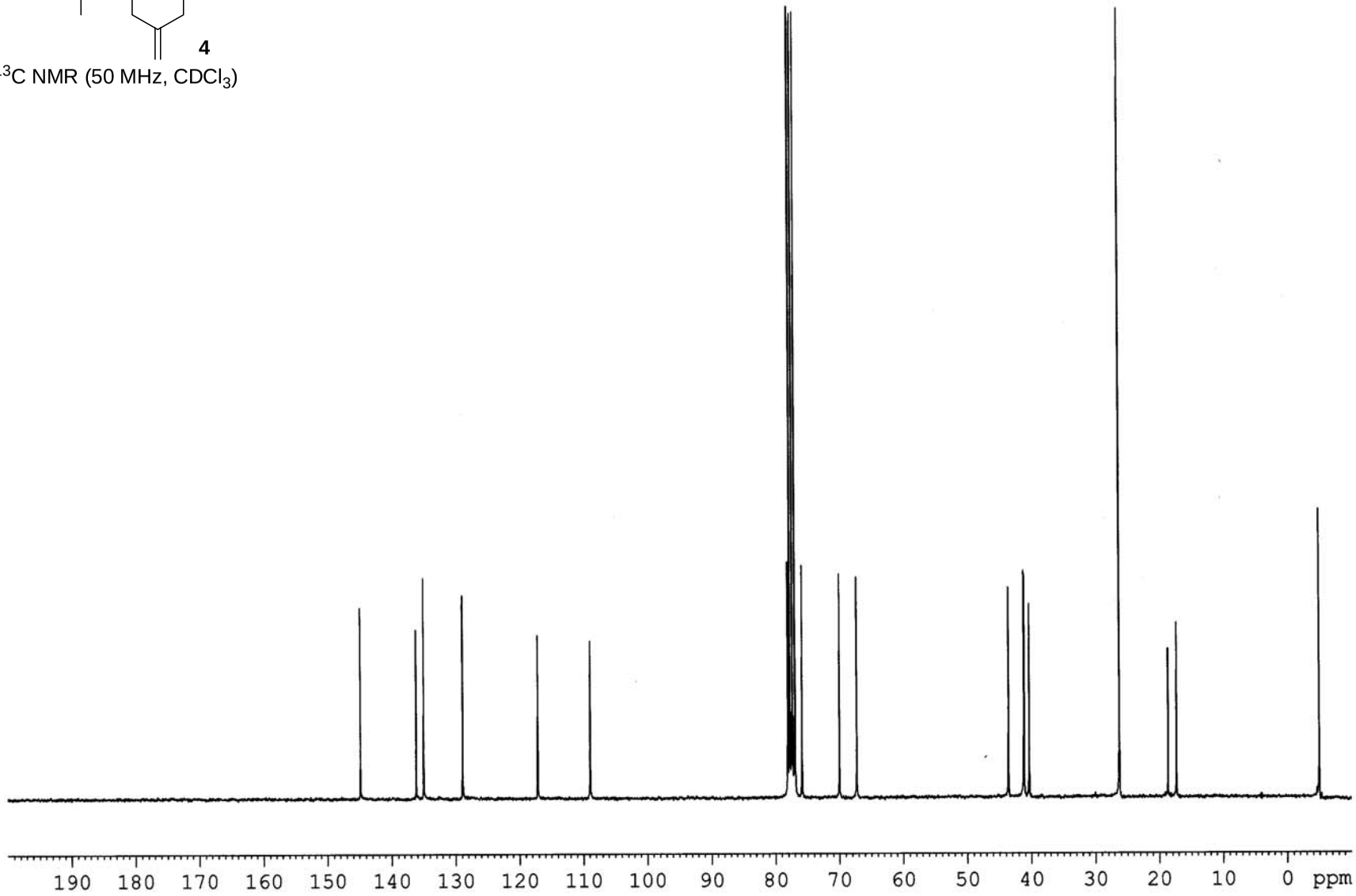
^{1}H NMR (200 MHz, $CDCl_3$)

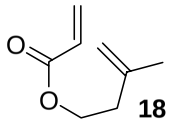




4

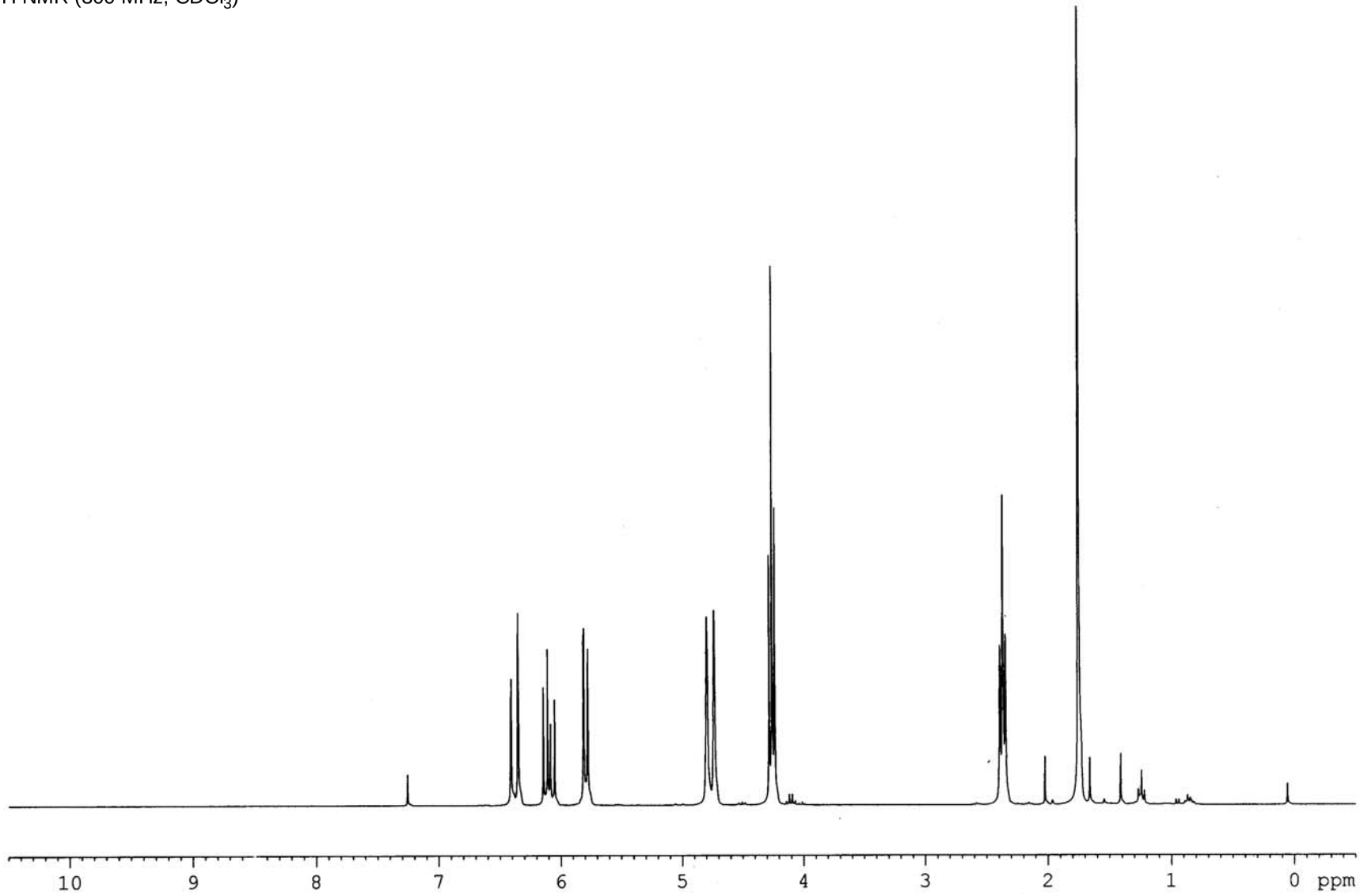
^{13}C NMR (50 MHz, $CDCl_3$)

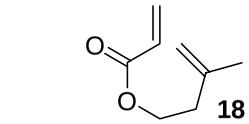




18

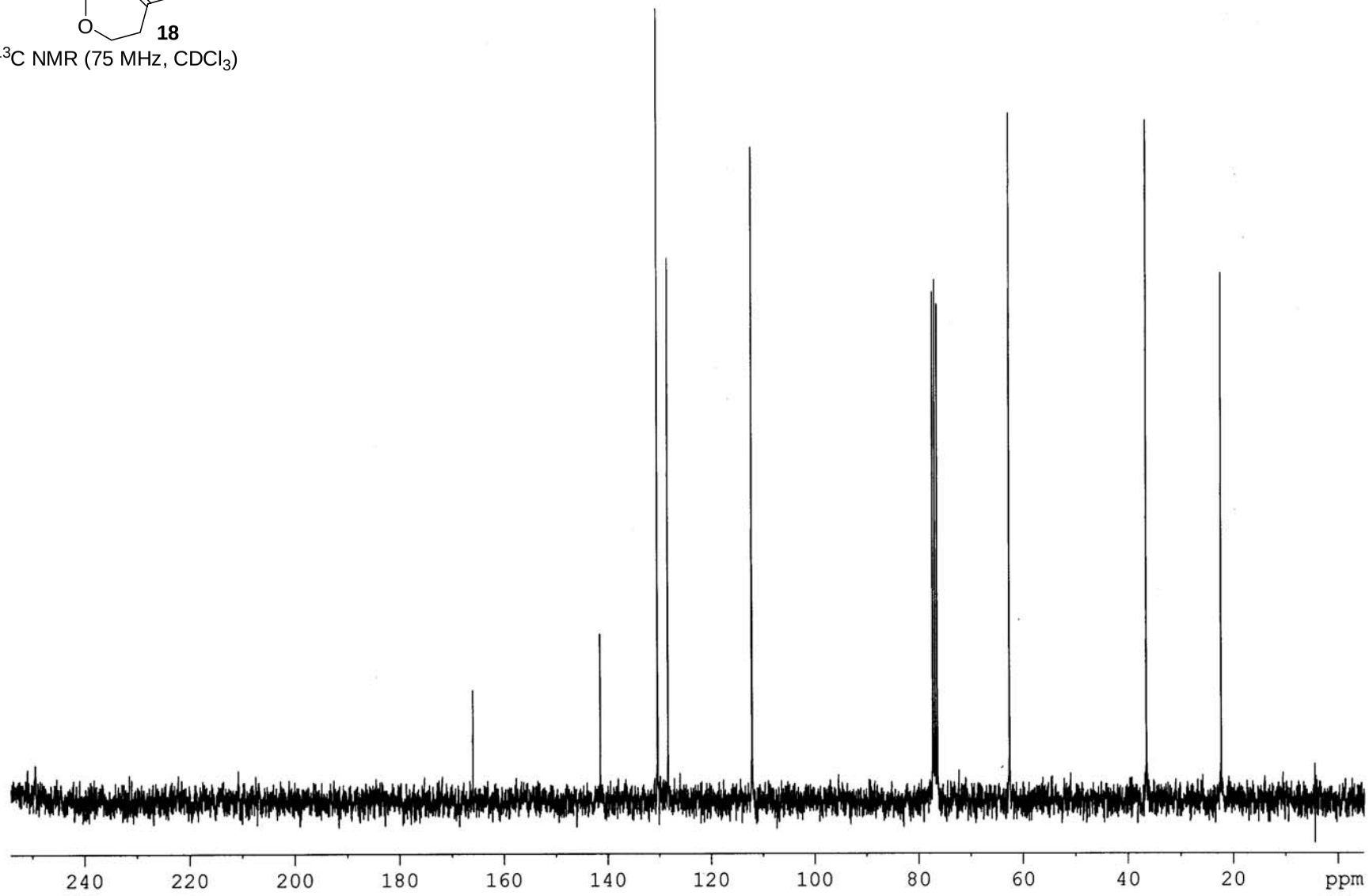
^{1}H NMR (300 MHz, $CDCl_3$)

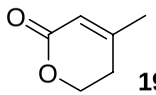




18

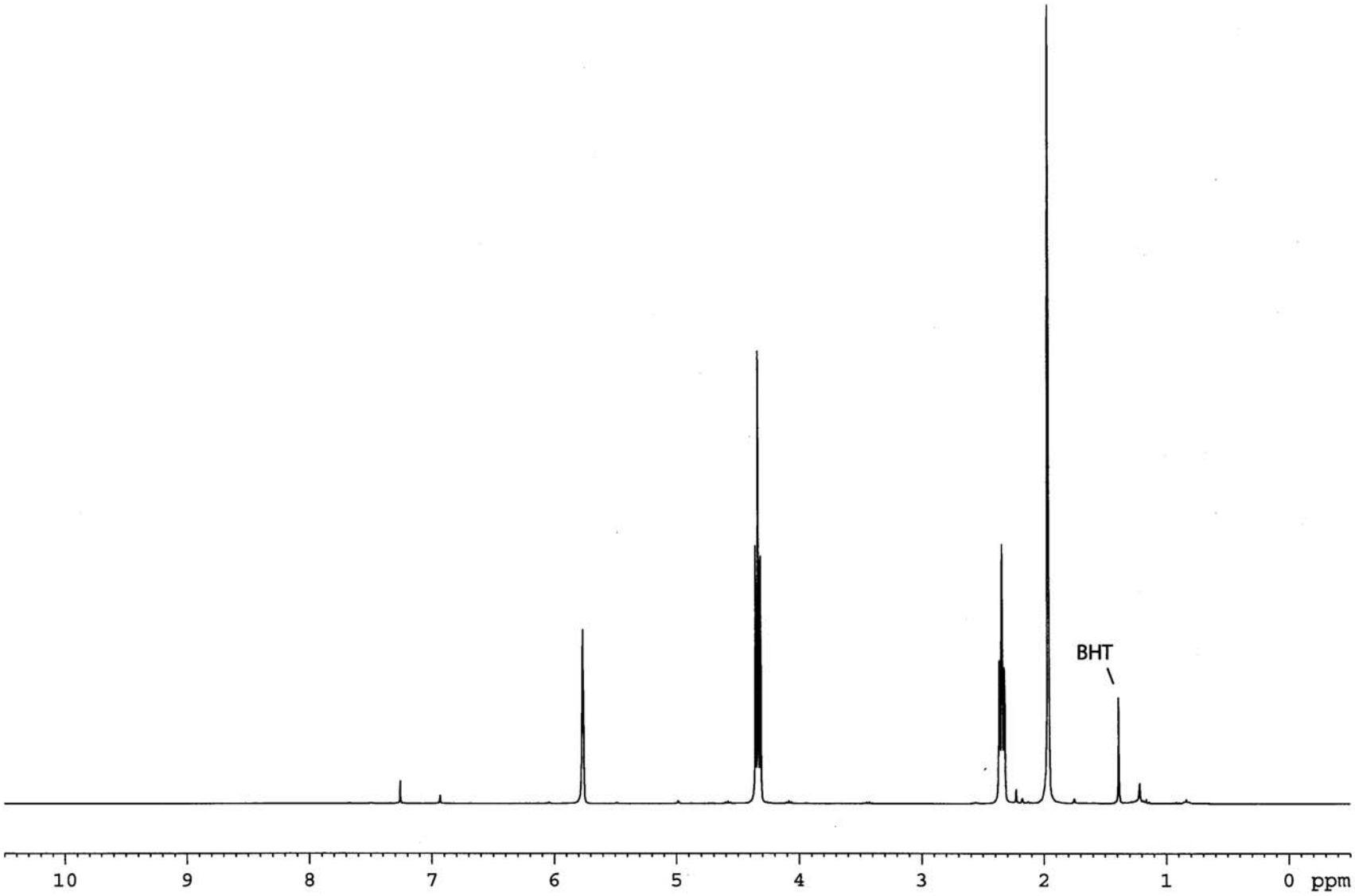
^{13}C NMR (75 MHz, $CDCl_3$)

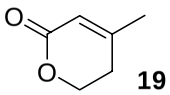




19

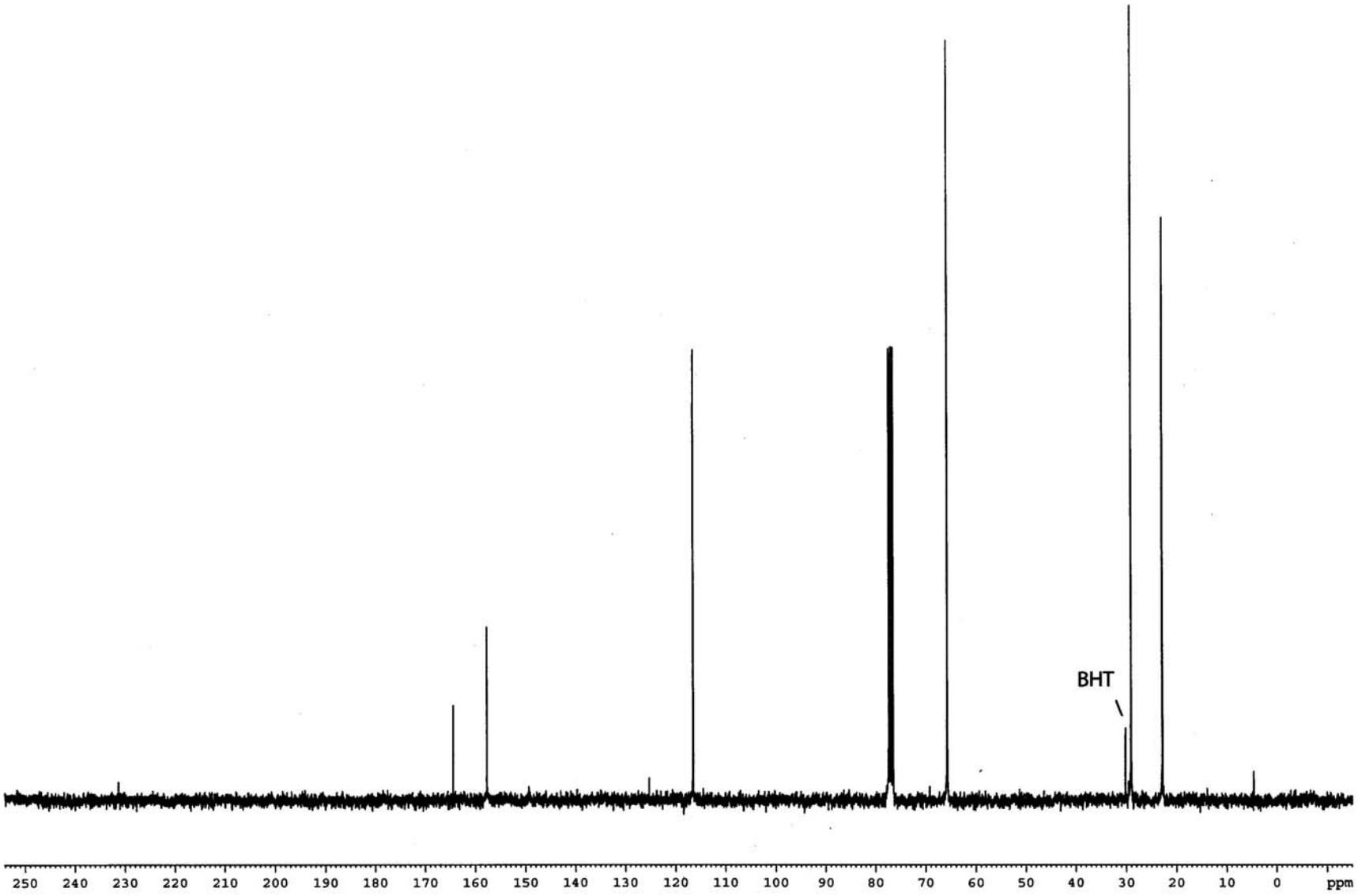
^{1}H NMR (300 MHz, $CDCl_3$)

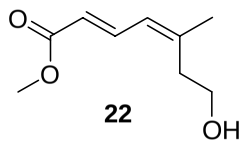




19

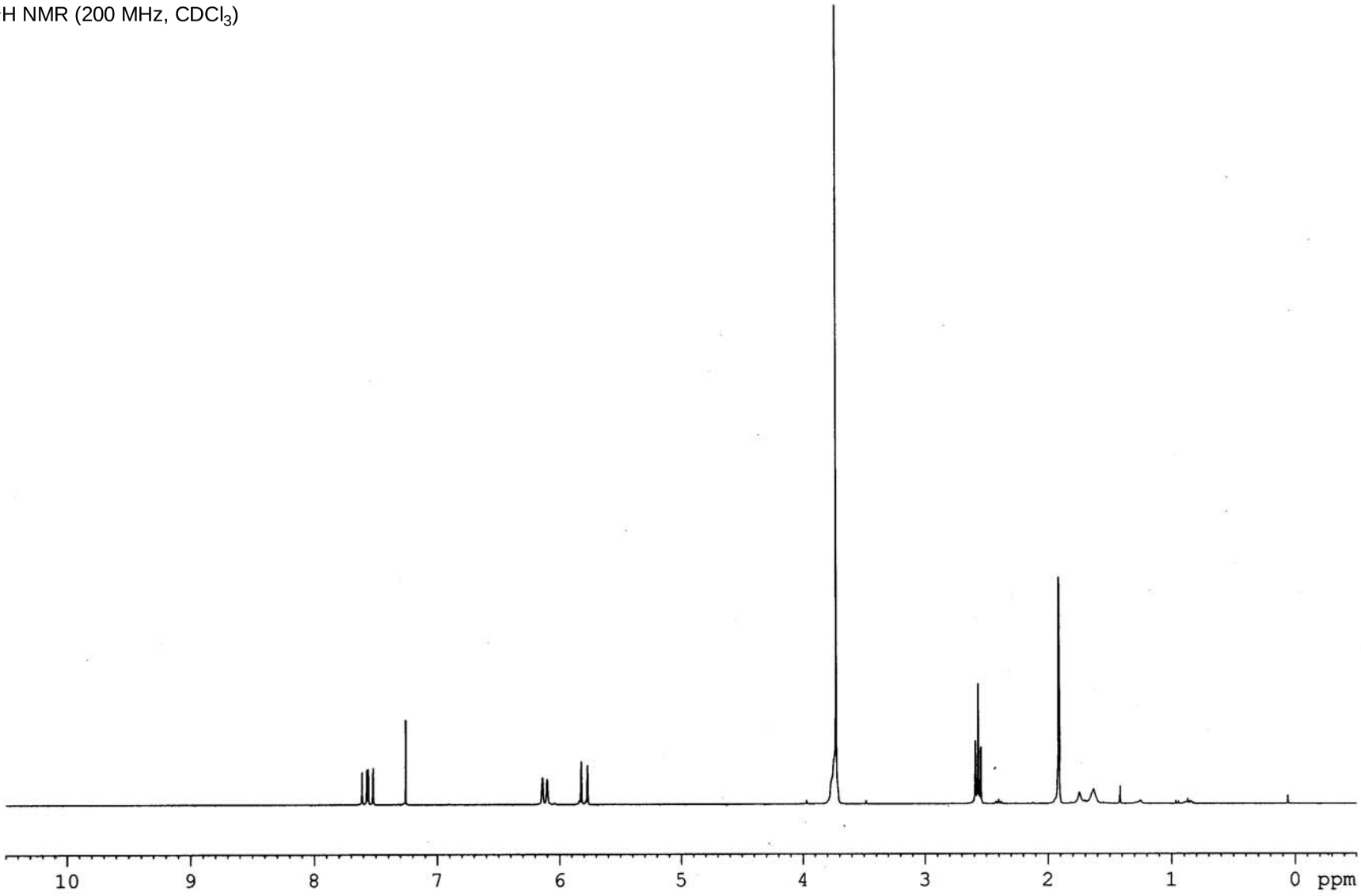
^{13}C NMR (75 MHz, $CDCl_3$)

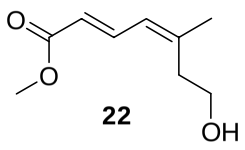




22

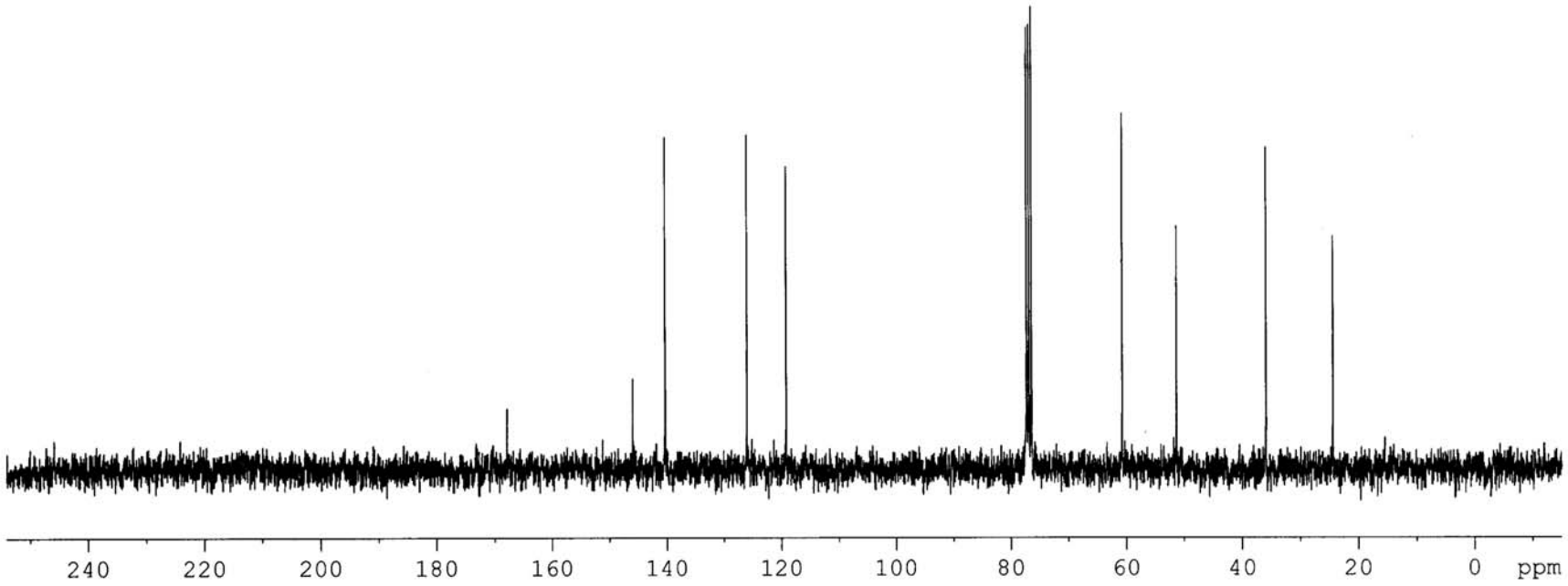
^{1}H NMR (200 MHz, $CDCl_3$)

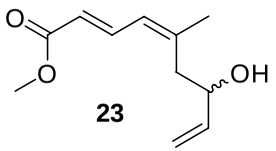




22

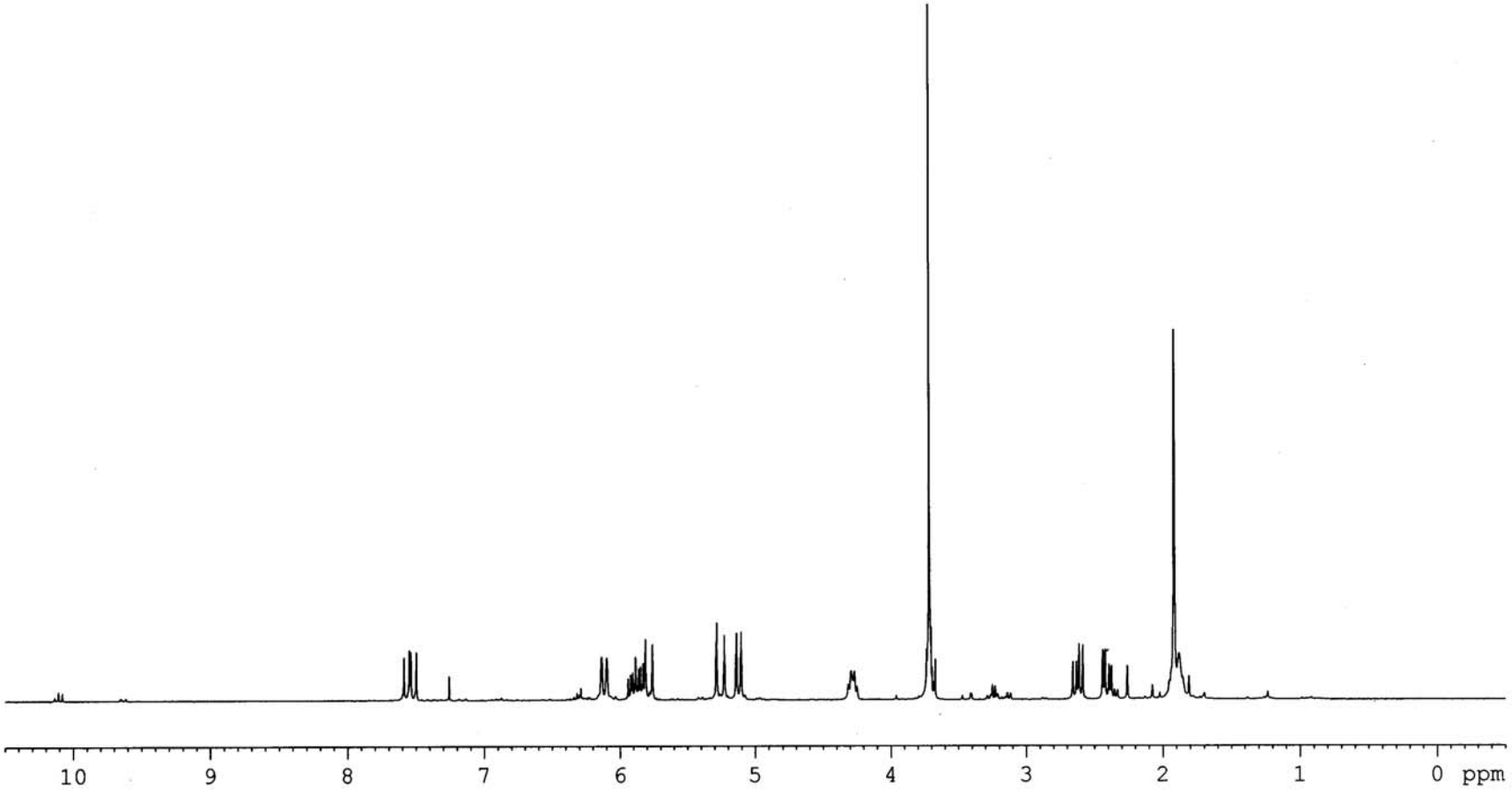
^{13}C NMR (75 MHz, $CDCl_3$)

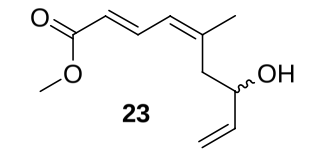




23

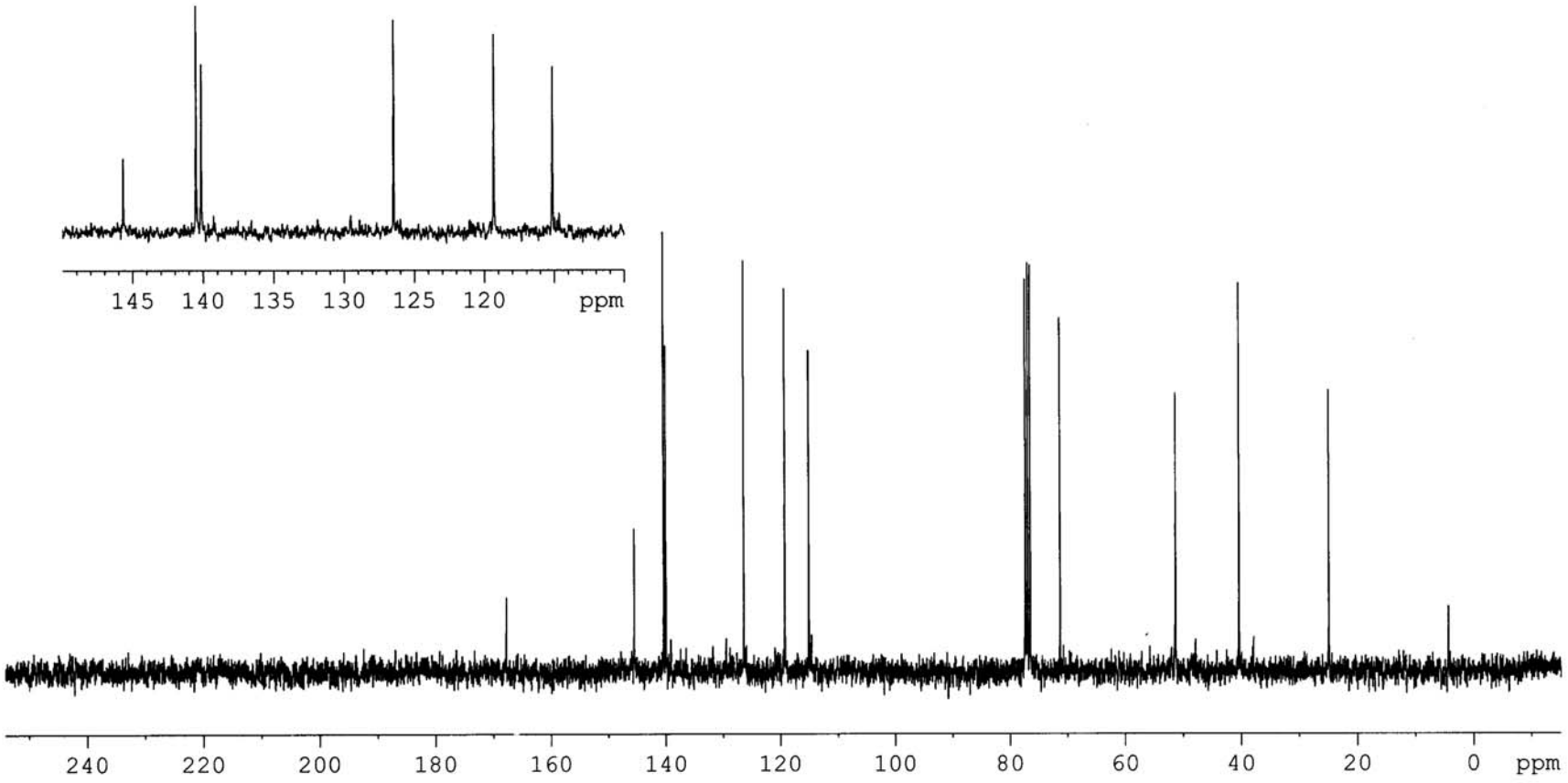
^{1}H NMR (300 MHz, $CDCl_3$)

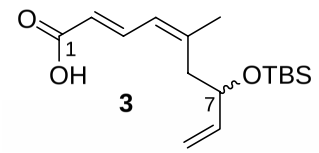




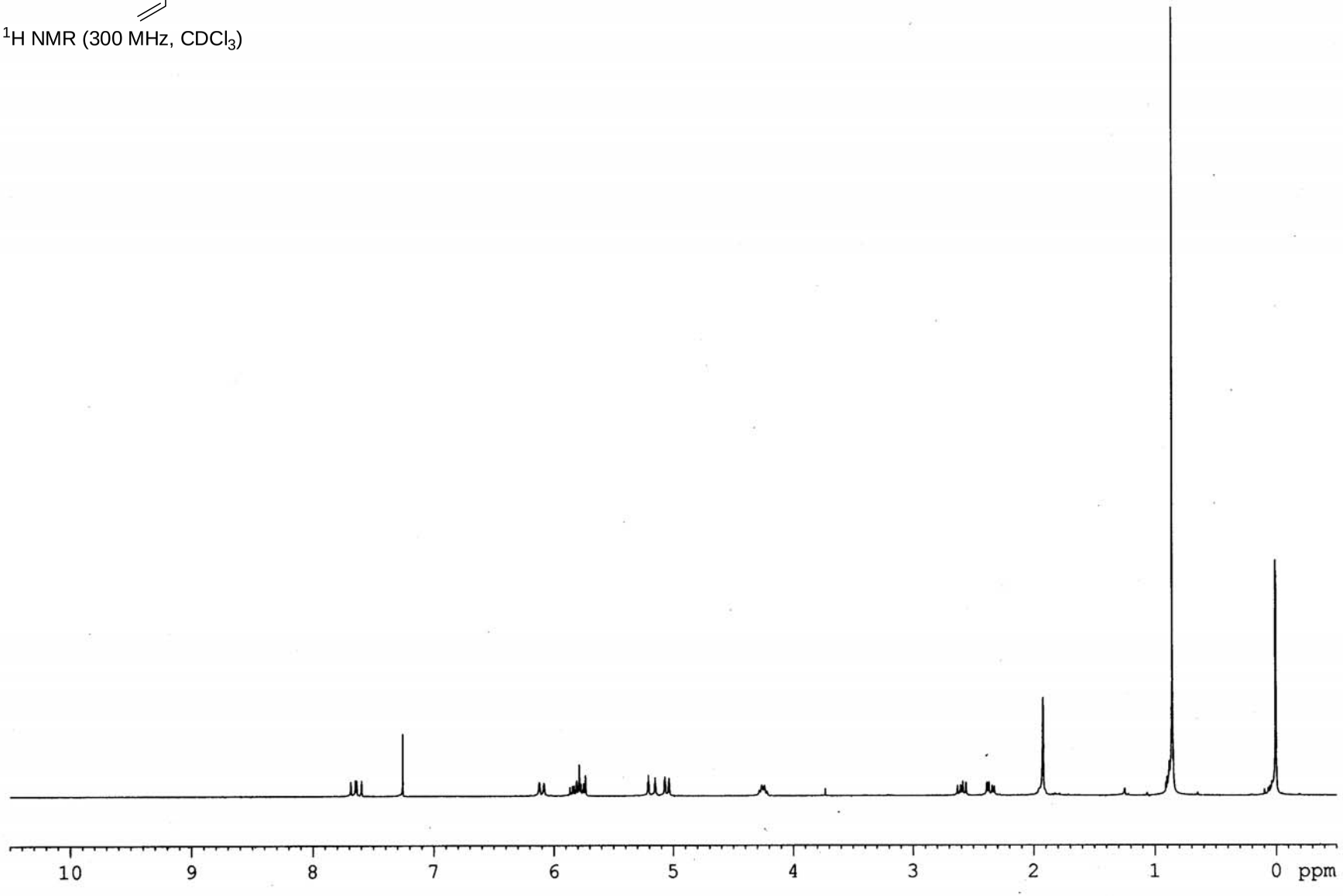
23

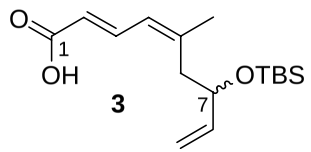
^{13}C NMR (75 MHz, $CDCl_3$)



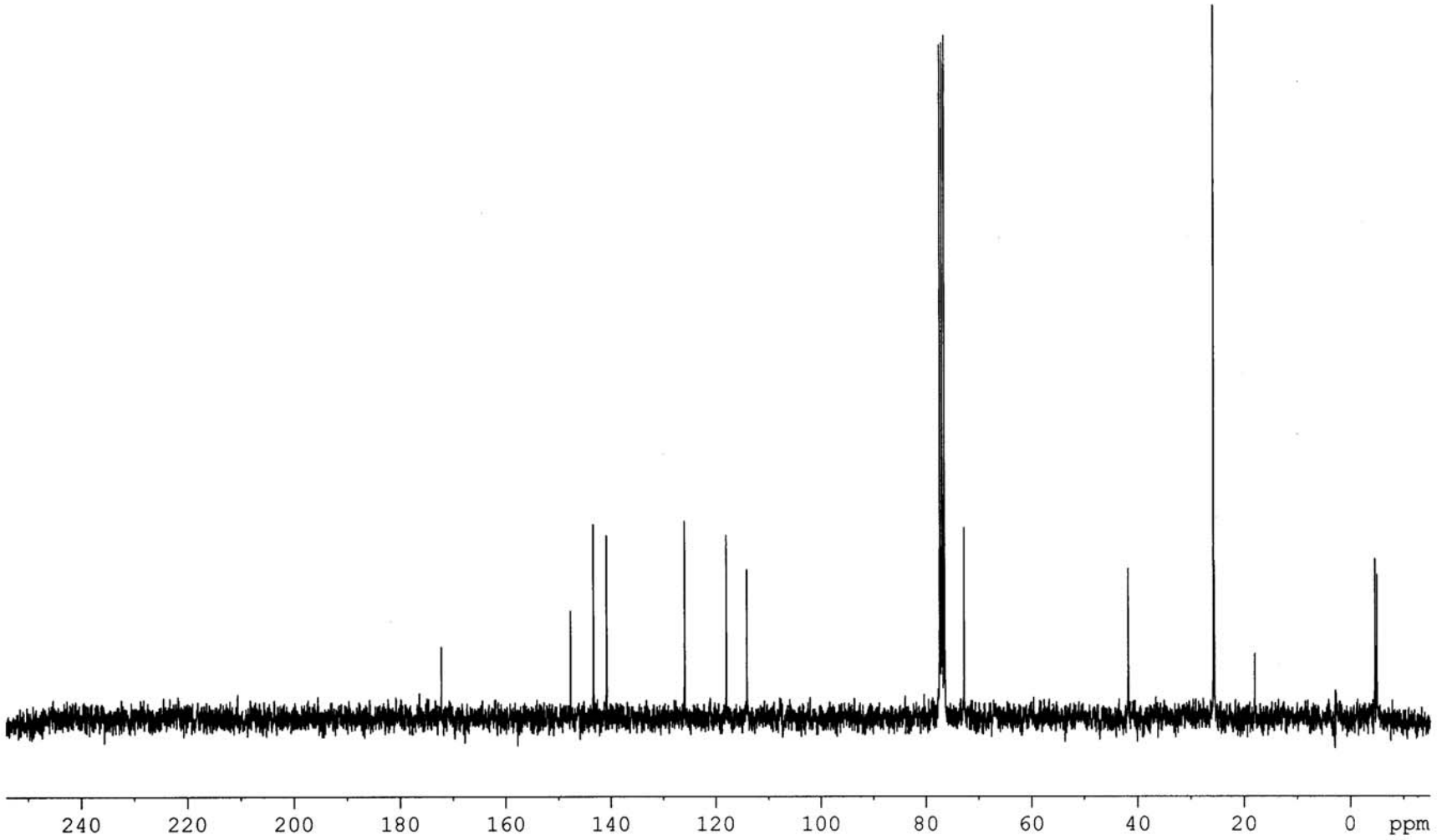


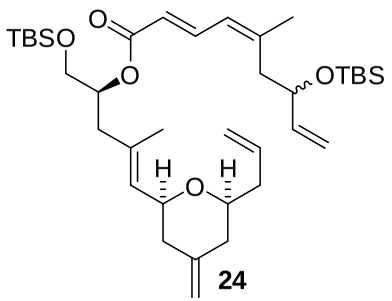
^{1}H NMR (300 MHz, $CDCl_3$)





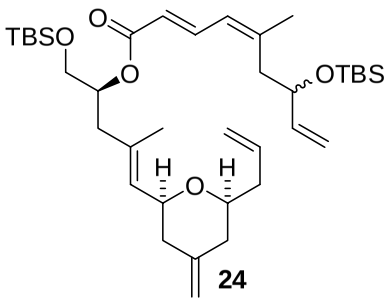
^{13}C NMR (75 MHz, $CDCl_3$)





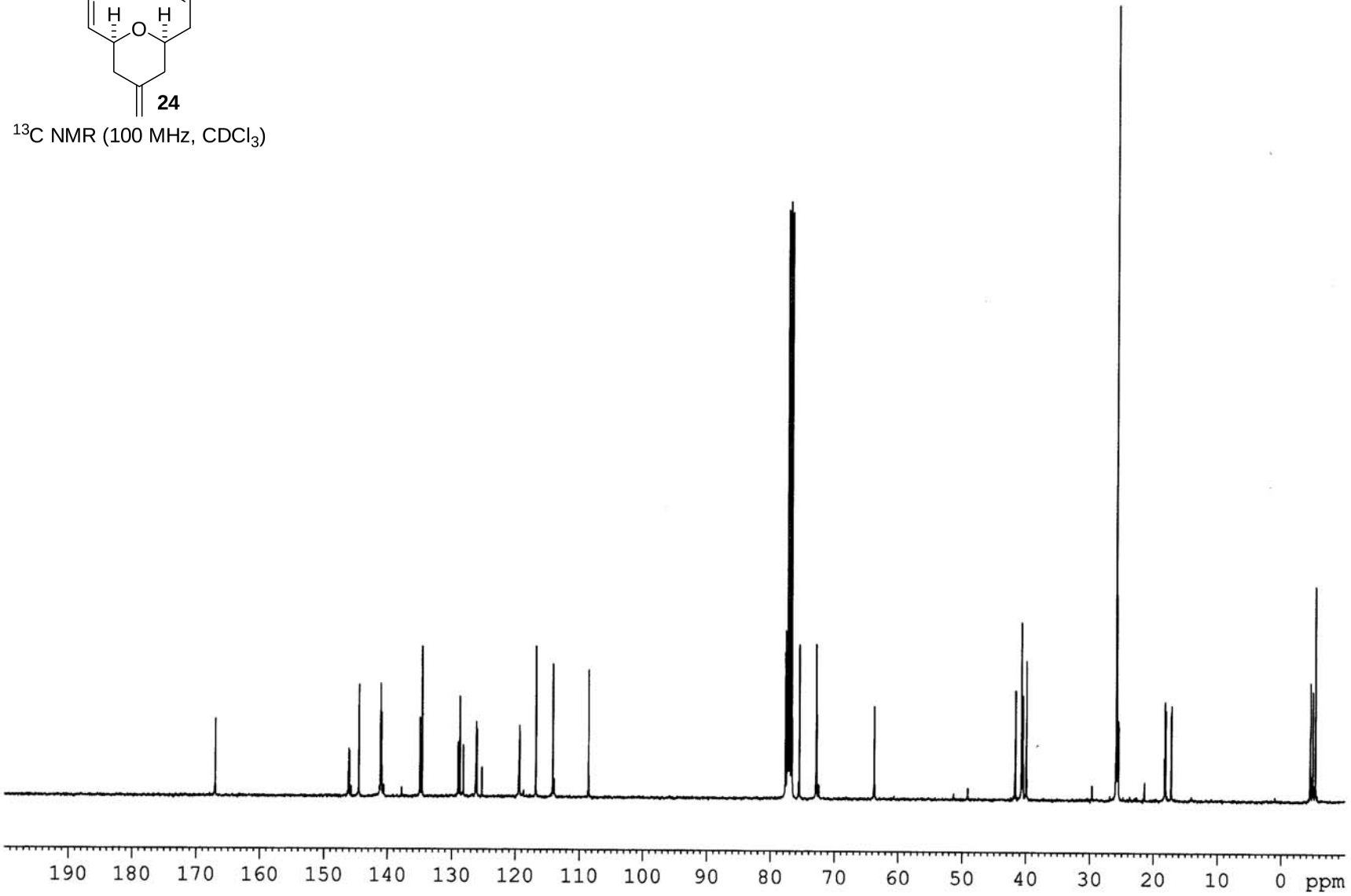
24

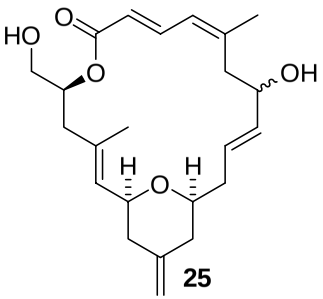
^{1}H NMR (300 MHz, $CDCl_3$)



24

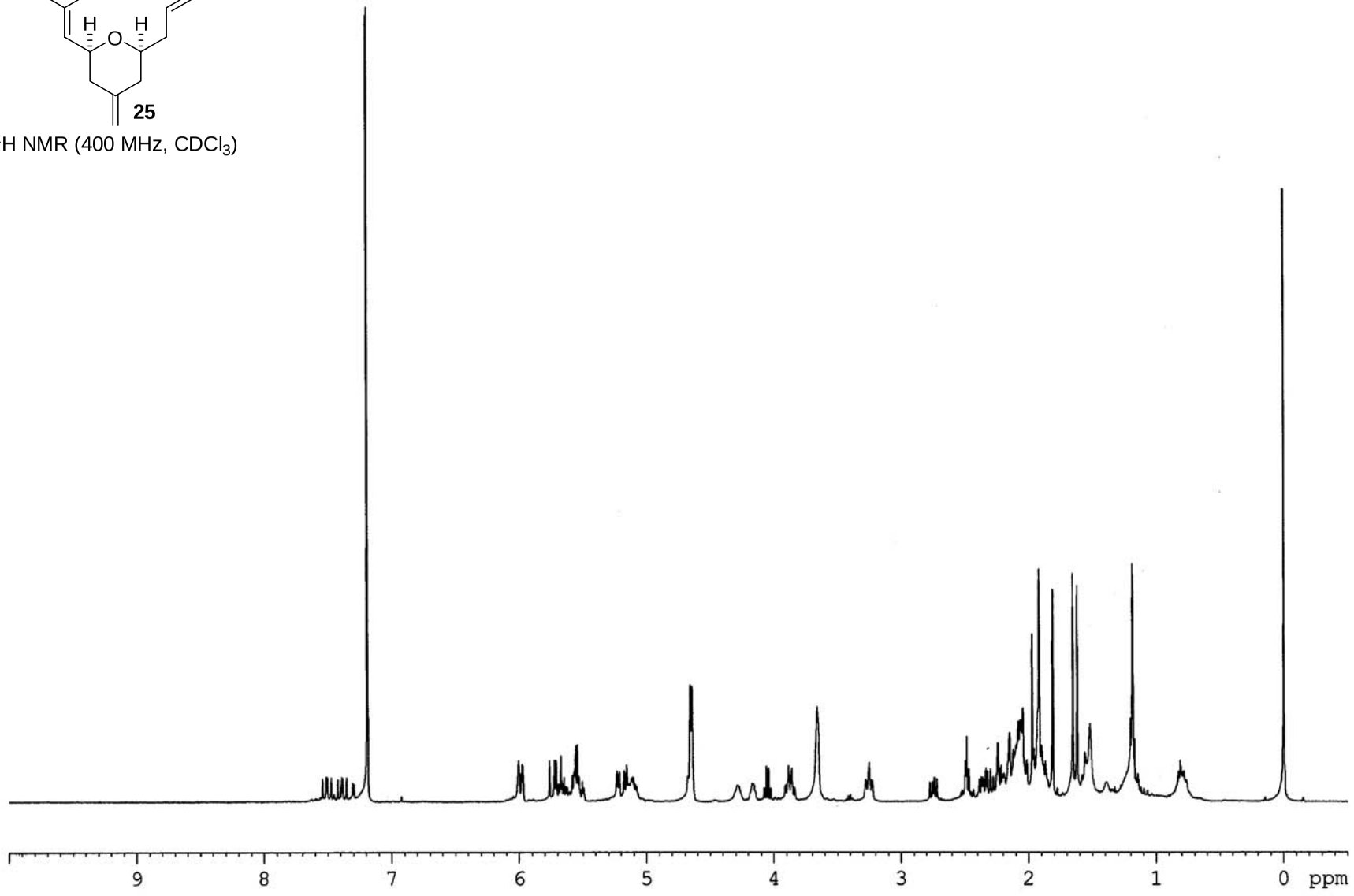
^{13}C NMR (100 MHz, $CDCl_3$)

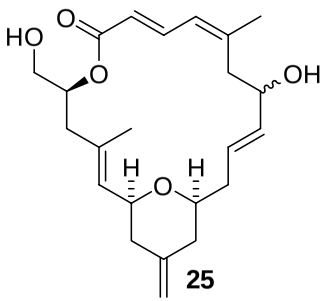




25

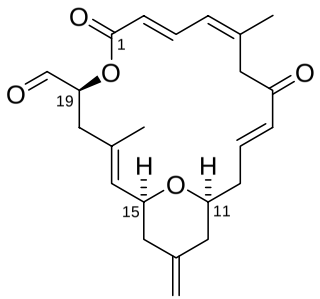
^{1}H NMR (400 MHz, $CDCl_3$)





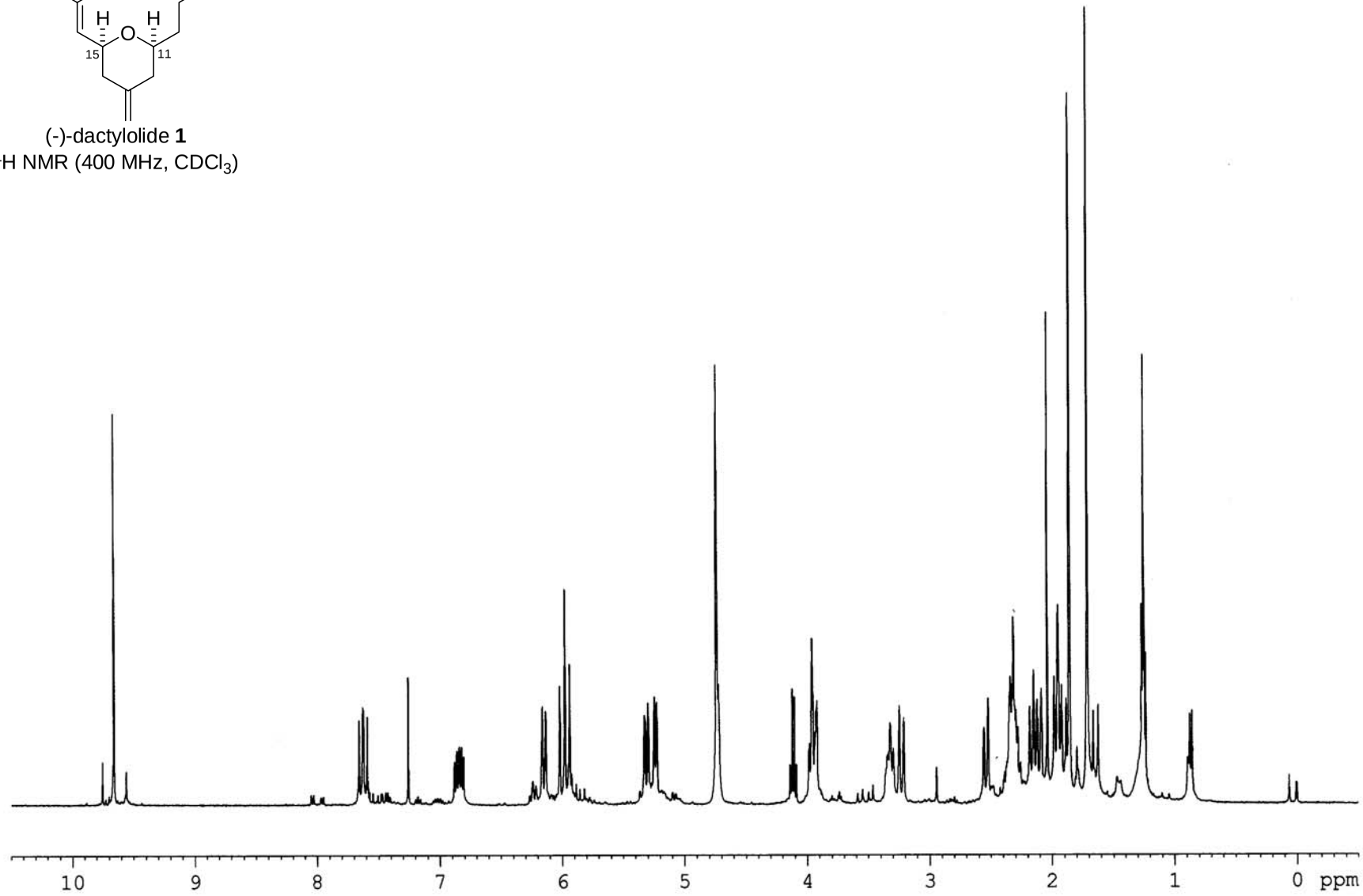
25

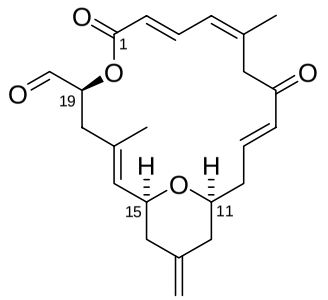
^{13}C NMR (100 MHz, $CDCl_3$)



(-)-dactylolide **1**

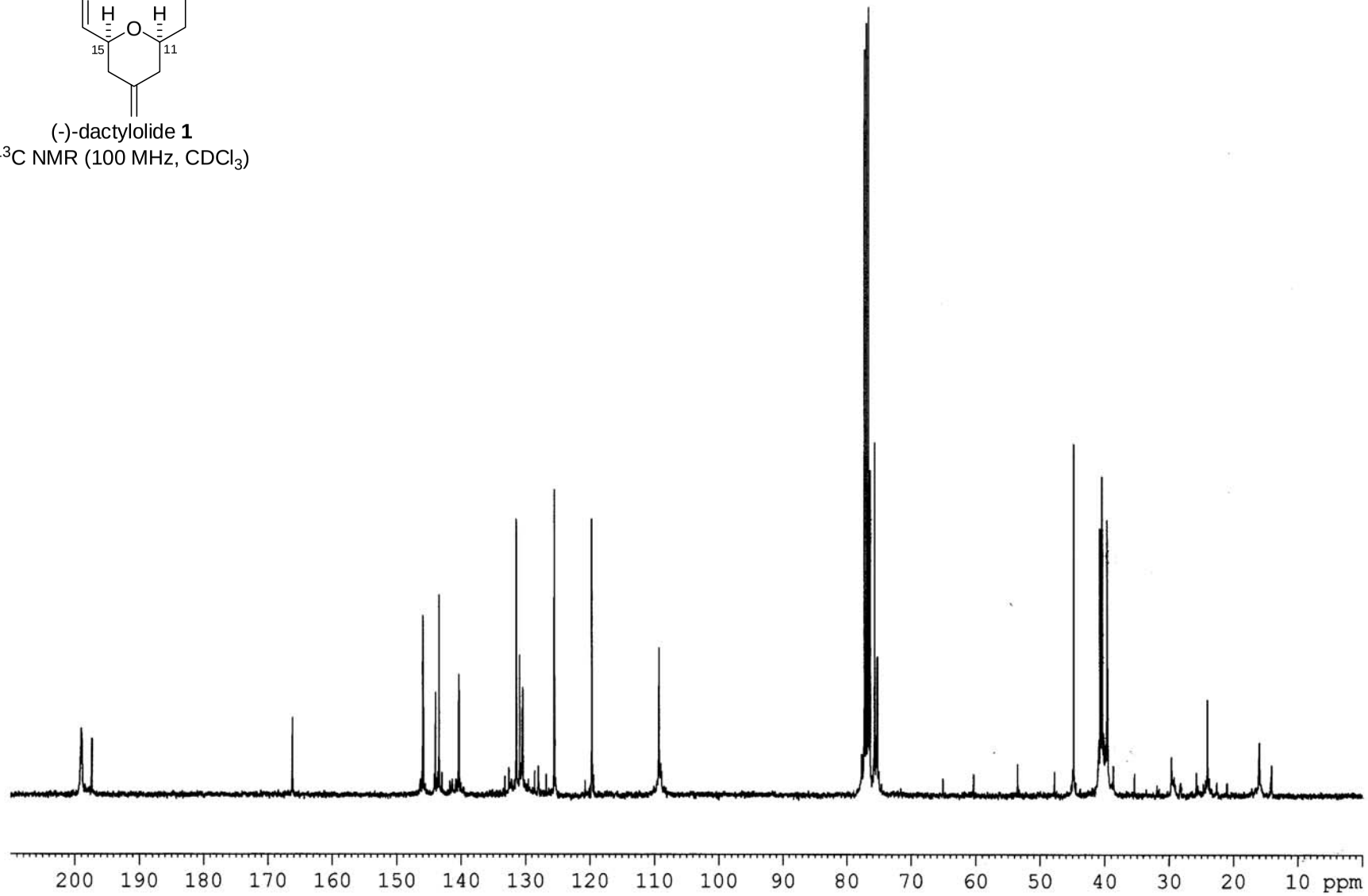
^{1}H NMR (400 MHz, $CDCl_3$)





(-)-dactylolide **1**

^{13}C NMR (100 MHz, $CDCl_3$)



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