Supporting Information

Total Synthesis of Aplyronine C

Ian Paterson*, Sarah J. Fink, Lydia Y. W. Lee, Stephen J. Atkinson, and Simon B. Blakey

University Chemical Laboratory, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, U. K.

ip100@cam.ac.uk

Contents

1. General Comments

^{1}H Nuclear magnetic resonance (NMR) spectra were recorded using an internal deuterium lock at ambient probe temperature on the following instruments: Bruker DRX500, Bruker Avance BB, or Bruker Avance TCI (500 MHz); and Bruker DPX400 (400 MHz). An internal reference of residual solvent protons was used as follows: δ_H = 7.26 ppm in $CDCl_3$, δ_H = 7.16 ppm in C_6D_6, and δ_H = 2.05 ppm in *d*6-acetone. All ^{1}H NMR data are represented as: chemical shift (in ppm on the δ scale relative to δ_{TMS} = 0 ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, br = broad, obs = obscured, app = apparent), and coupling constant (*J* in Hz). Coupling constants were taken directly from the spectra and are uncorrected. Assignments were determined either on the basis of unambiguous chemical shift or coupling pattern; ^{1}H–^{1}H COSY, HMBC, and HMQC experiments; or by analogy to fully interpreted data for related compounds.

Proton-decoupled ^{13}C NMR spectra were recorded using an internal deuterium lock at ambient probe temperature on the following instruments: Bruker DRX500, Bruker Avance BB, or Bruker Avance TCI (125 MHz); and Bruker DPX400 (100 MHz). An internal reference of δ_C = 77.00 ppm was used for carbons in $CDCl_3$, δ_C = 128.06 ppm in C_6D_6, and δ_C = 206.26 and 29.84 ppm in *d*6-acetone. All chemical shift values are reported in ppm on the δ scale relative to δ_{TMS} = 0 ppm.

Infrared spectra were recorded on a Perkin–Elmer Spectrum One FT-IR spectrometer. Absorbance frequencies (υ) are quoted in cm^{-1}. Optical rotations were measured on a Perkin–Elmer 241 polarimeter at the sodium D-line (589 nm) and are reported as follows: $[\alpha]_D^{20}$ at 20 °C (unless otherwise noted), concentration (*c* in g/dL), and solvent. High resolution mass spectra (HRMS) were recorded by either the Departmental Mass Spectrometry Service (University Chemical Laboratory, Cambridge, UK) or at the EPSRC Mass Spectrometry Service (Swansea, UK) using electron impact (EI) and electrospray ionization (ESI) techniques. The parent ion (M^+) is quoted with the indicated cation.

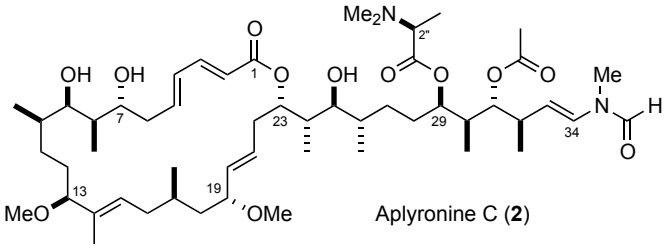
Analytical thin layer chromatography (TLC) was performed on Merck Kieselgel 60 F254 plates pre-coated with a 0.25 mm thickness of silica gel. Visualization was accomplished by ultraviolet light and/or phosphomolybdic acid/$Ce_2(SO4)_3$, potassium permanganate, anisaldehyde, or ninhydrin stains. Flash column chromatography was carried out on Merck Kieselgel 60 (230–400 mesh) silica gel, or Sigma–Aldrich Florisil (<200 mesh) where noted, under a positive pressure of regulated compressed air. Preparative TLC was carried out on Merck Kieselgel 60 F254 plates with 1.0 mm of film thickness.

Reagents and solvents were purified by standard means.[1] Dichloromethane (CH_2Cl_2), acetonitrile (MeCN), methanol (MeOH), benzene (PhH), and *tert*-butyl methyl ether (TBME) were distilled from calcium hydride (CaH_2) and stored under an argon atmosphere. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium or potassium wire/benzophenone, respectively, under an argon atmosphere. Triethylamine (Et_3N), dimethylethylamine (Me_2NEt), diisopropylethylamine (*i*-Pr_2NEt), 2,6-lutidine, and pyridine were distilled from and stored over calcium hydride. Acetaldehyde and propionaldehyde were distilled from $CaCl_2$ immediately prior to use. 2,3-Dichloro-5,6-dicyanobenzoquinone (DDQ) was recrystallized from chloroform. All other

[1] Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 4th ed.; Pergamon Press, 1996.

chemicals were used as received, except where noted otherwise. All experiments were performed under anhydrous conditions and under an inert atmosphere of argon, except where stated, using oven-dried apparatus and employing standard techniques for handling air-sensitive materials. Solvents used in workup, extraction, and column chromatography were distilled prior to use.

For the purpose of clarity, compounds relating to fragments of the aplyronines are numbered as proposed by Yamada and coworkers in the original aplyronine isolation and characterization publication:[2]



Aplyronine C (**2**)

[2] Yamada, K.; Ojika, M.; Ishigaki, T.; Yoshida, Y.; Ekimoto, H.; Arakawa, M. *J. Am. Chem. Soc.* **1993**, *115*, 11020.

2. Preparation of Reagents

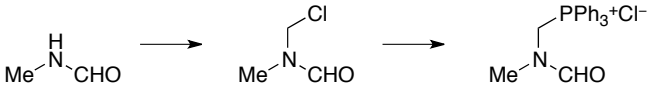
Tin(II) triflate ($Sn(OTf)_2$)

Tin granules (5.27 g, 44.4 mmol) were dried *in vacuo* for 24 h with vigorous stirring and occasional heating to melt. Under argon atmosphere, triflic acid (20.0 g, 133 mmol) was added and the mixture heated to 85 °C for 72 h. After cooling to room temperature, the light gray solid was washed with anhydrous Et_2O without exposure to air until the filtrate appeared colorless (6 × 50 mL), and then dried under high vacuum with vigorous stirring overnight. The resulting tin triflate (white-gray powder) was stored under argon atmosphere in the strict absence of moisture.

Samarium diiodide (SmI_2)[3]

A solution of samarium metal (55.0 mg, 0.366 mmol) and iodine (90.5 mg, 0.357 mmol) in anhydrous THF (3.57 mL) was refluxed under argon for 1 h, taking care to rigorously exclude oxygen. The resulting deep blue solution of SmI_2 (0.1 M in THF) was cooled to room temperature and used immediately.

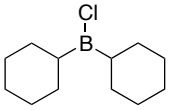
((*N*-Methylformamido)methyl)triphenylphosphonium chloride (12)[4]



12

A stirred suspension of paraformaldehyde (8.23 g, 274 mmol) in *N*-methylformamide (15.0 mL, 254 mmol) was heated to 130 °C over 1 h. The resulting homogeneous solution was cooled to 0 °C and thionyl chloride (32.6 g, 274 mmol) was added cautiously over 15 min. Hydrochloric acid and sulfur dioxide gases were trapped into an aqueous solution of sodium hydroxide. After 5 h, gas evolution ceased and the volatiles were removed *in vacuo* (30 mmHg, 30 °C). The resulting pale yellow liquid was purified by distillation under reduced pressure (0.2 mmHg, 38 °C) using a 30 cm Vigreux column to afford *N*-(chloromethyl)-*N*-methylformamide (15.0 g, 55%) as a colorless oil. This compound was immediately added dropwise to a stirred solution of triphenylphosphine (40.2 g, 153 mmol) in anhydrous Et_2O (300 mL). The reaction mixture was stirred at room temperature for 24 h, after which the resulting white slurry was filtered through a sintered funnel. The collected white solid was washed with anhydrous Et_2O (3 × 50 mL) and dried under high vacuum for 4 h to afford phosphonium salt **12** (32.0 g, 62%) as a free flowing, hygroscopic white solid.

Dicyclohexylboron chloride (*c*-Hex_2BCl)[5]



To a solution of freshly distilled cyclohexene (49 mL, 484 mmol) in Et_2O (200 mL) at –10 °C was added monochloroborane–dimethylsulfide complex (25.2 mL, 282 mmol) dropwise over 30 min. The reaction mixture

[3] Imamoto, T.; Ono, M. *Chem. Lett.* **1987**, *16*, 501.
[4] (a) Böhme, H.; Raude, E. *Chem. Ber.* **1981**, *114*, 3421. (b) Paterson, I.; Cowden, C. J.; Watson, C. *Synlett* **1996**, 209.
[5] Brown, H. C.; Ravindran, N.; Kulkarni, S. U. *J. Org. Chem.* **1979**, *44*, 2417.

was stirred at –10 °C for 1 h, then warmed to room temperature and stirred for a further 1 h during which the reaction mixture changed from a cloudy to clear solution. The solvent was removed by distillation under argon atmosphere at ambient pressure (35 °C). Subsequent distillation under reduced pressure (0.2 mmHg, 86 °C) afforded dicyclohexylboron chloride as a colorless liquid. The reagent was stored at –20 °C under an argon atmosphere in the strict absence of moisture.

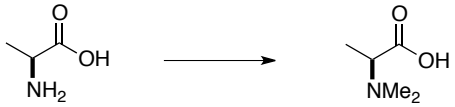
(Triphenylphosphine)copper hydride hexamer ($[CuH{\cdot}PPh_3]_6$)[6]

Copper(I) chloride (993 mg, 10.0 mmol), potassium *t*-butoxide (1.13 g, 10.0 mmol) and triphenylphosphine (5.24 g, 20.0 mmol) were weighed into a dry flask inside a glove box under argon atmosphere. The flask was charged with degassed benzene (50 mL, freshly distilled) and the contents were stirred for 30 min under argon to produce a dark brown solution. Dimethylphenylsilane (3.00 mL, 19.6 mmol) was added. After stirring for 2 h, the dark red mixture was transferred *via* cannula to a large Schlenk filter containing a small pad (1 cm) of celite. The reaction flask and celite pad were rinsed with anhydrous degassed benzene (4 × 10 mL). The red filtrate was concentrated *in vacuo* to a *ca.* 20 mL solution. Anhydrous degassed acetonitrile (40 mL) was slowly layered onto the top of the benzene solution *via* cannula to induce crystallization of the product. After standing overnight, the resulting red crystals were isolated by filtration, washed with anhydrous acetonitrile (3 × 10 mL), and dried under high vacuum to give Stryker's reagent (2.30 g, 70%) as bright red crystals.

Zinc borohydride ($Zn(BH_4)_2$)[7]

Zinc(II) chloride (3.07 g, 22.5 mmol) was dried by heating under vacuum for 1 h. The white solid was suspended in anhydrous Et_2O (125 mL) and heated to reflux for 2 h. The cooled supernatant was added *via* cannula to a suspension of $NaBH_4$ (1.70 g, 45.0 mmol) in anhydrous Et_2O (25 mL) and the mixture was stirred vigorously for 24 h. The resulting suspension was allowed to settle and the supernatant used as a 0.15 M solution of $Zn(BH_4)_2$ in Et_2O.

(*S*)-*N*,*N*-Dimethylalanine[8]



To a suspension of L-alanine (1.20 g, 13.5 mmol) in water (25 mL) was added aqueous formaldehyde (4.20 mL, 37% w/w, 51.7 mmol) and palladium on charcoal (500 mg, 10% Pd). The flask was purged with argon and then saturated with hydrogen under passive vacuum. After purging and back-filling with hydrogen three times, the reaction mixture was stirred under hydrogen at room temperature and atmospheric pressure for 36 h. Upon completion, the resulting aqueous slurry was heated to reflux for 30 min and then filtered while hot. The filtrate was concentrated *in vacuo* and azeotroped repeatedly with toluene to afford (*S*)-*N*,*N*-dimethylalanine (1.56 g, 99%) as a white solid.

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[6] Chiu, P.; Li, Z.; Fung, K. C. M. *Tetrahedron Lett.* **2003**, *44*, 455.
[7] Narasimhan, S.; Balakumar, R. *Aldrichimica Acta* **1998**, *31*, 19.
[8] Dzygiel, P.; Reeve, T. B.; Piarulli, U.; Krupicka, M.; Tvaroska, I.; Gennari, C. *Eur. J. Org. Chem.* **2008**, *7*, 1253.

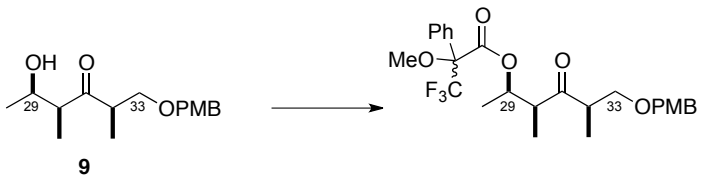
3. Experimental details: Total synthesis of aplyronine C

Aldol adduct 9[9]

To a solution of acid-free tin(II) triflate (5.00 g, 12.0 mmol) in CH_2Cl_2 (14 mL) at –78 °C was added Et_3N (1.80 mL, 12.9 mmol) followed by a pre-cooled (–78 °C) solution of ketone **8**[10] (2.18 g, 9.23 mmol) in CH_2Cl_2 (8 mL). The enolate solution was stirred at –78 °C for 2 h, after which a solution of freshly distilled acetaldehyde (1.55 mL, 27.7 mmol) in CH_2Cl_2 (8 mL) was added. The reaction mixture was stirred at –78 °C for a further 2 h and then quenched with pH 7 buffer (30 mL). After warming to room temperature, Na/K tartrate (70 mL, sat. aq.) was added and the biphasic mixture was stirred rapidly overnight. The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organics were subsequently dried over $MgSO_4$ and concentrated *in vacuo*. The crude was purified by flash chromatography (20 → 30% EtOAc/PE) to afford aldol adduct **9** (2.53 g, 97%, 15:1 *dr*) as a pale yellow oil. As the diastereomers were inseparable by flash chromatography, the product was carried forward as a mixture.

$\mathbf{R}_f$ 0.40 (50% EtOAc/PE); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.18 (2H, d, J = 8.7 Hz), 6.86 (2H, d, J = 8.7 Hz), 4.40 (1H, d, J = 11.6 Hz), 4.36 (1H, d, J = 11.5 Hz), 4.20–4.14 (1H, m), 3.79 (3H, s), 3.60 (1H, app t, J = 9.0 Hz), 3.42 (1H, dd, J = 8.8, 4.8 Hz), 3.14 (1H, dqd, J = 9.0, 7.0, 4.8 Hz), 2.94 (1H, d, J = 4.2 Hz), 2.72 (1H, qd, J = 7.1, 3.2 Hz), 1.11 (3H, d, J = 6.5 Hz), 1.08 (3H, d, J = 7.1 Hz), 1.00 (3H, d, J = 7.0 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 218.0, 159.3, 129.6, 129.3, 113.8, 73.1, 72.8, 67.0, 55.2, 51.9, 45.1, 19.6, 13.5, 9.3; $[\alpha]_D^{23}$ –12.6 (*c* 2.07, $CHCl_3$); **IR** (thin film) ν_{max} (cm^{-1}) 3444, 2972, 2935, 2872, 1705, 1612, 1513, 1456, 1374, 1302, 1246, 1173, 1093, 1033, 998, 910, 819; **HRMS** calc. for $C_{16}H_{24}O_4Na$ $[M+Na]^+$ 303.1572, found 303.1584.

MTPA esters of aldol adduct 9[11]



General Procedure: To a solution of (*R*)-hydroxy ketone **9** (10.0 mg, 0.0357 mmol) and (–)-(*R*)- or (+)-(*S*)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (42 mg, 0.179 mmol) in CH_2Cl_2 (0.4 mL) at room temperature was added DCC (0.18 mL, 1.0 M in CH_2Cl_2, 0.18 mmol) followed by DMAP (21.8 mg, 0.179 mmol). The reaction mixture was stirred at room temperature for 16 h. The resulting white suspension was purified directly by flash chromatography (5 → 10% EtOAc/PE) to afford the corresponding (*R*)-MTPA ester (**22**) or (*S*)-MTPA ester (**23**) as a colorless oil.

[9] Paterson, I.; Tillyer, R. D. *Tetrahedron Lett*. **1992**, *33*, 4233.
[10] Paterson, I.; Cowden, C. J.; Woodrow, M. D. *Tetrahedron Lett.* **1998**, *39*, 6037.
[11] Hoye, T. R.; Jeffrey, C. S.; Shao F. *Nat. Protoc.* **2007**, *2*, 2451.

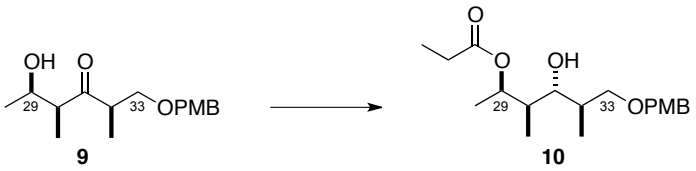
(*R*)-MTPA ester 22: 16.1 mg, 91% yield. $\mathbf{R}_f$ 0.16 (10% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.52 (2H, m), 7.40 (3H, m), 7.18 (2H, d, *J* = 8.6 Hz), 6.85 (2H, d, *J* = 8.8 Hz), 5.42 (1H, m), 4.39 (1H, d, *J* = 11.7 Hz), 4.33 (1H, d, *J* = 11.5 Hz), 3.80 (3H, s), 3.55 (1H, dd, *J* = 5.8, 4.7 Hz), 3.51 (3H, s), 3.40 (1H, dd, *J* = 8.9, 5.3 Hz), 3.02 (1H, dqd, *J* = 8.2, 7.0, 5.4 Hz), 2.89 (1H, qd, *J* = 7.1, 3.2 Hz), 1.22 (3H, d, *J* = 6.5 Hz), 1.12 (3H, d, *J* = 7.1 Hz), 1.02 (3H, d, *J* = 7.0 Hz).

(*S*)-MTPA ester 23: 15.7 mg, 89% yield. $\mathbf{R}_f$ 0.16 (10% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.53 (2H, m), 7.39 (3H, m), 7.19 (2H, d, *J* = 8.3 Hz), 6.86 (2H, d, *J* = 8.4 Hz), 5.39 (1H, m), 4.39 (1H, d, *J* = 11.6 Hz), 4.34 (1H, d, *J* = 11.7 Hz), 3.80 (3H, s), 3.55 (3H, s), 3.54 (1H, obs), 3.38 (1H, dd, *J* = 8.4, 5.5 Hz), 2.95 (1H, m), 2.89 (1H, m), 1.28 (3H, d, *J* = 6.2 Hz), 1.00 (3H, d, *J* = 7.1 Hz), 0.98 (3H, d, *J* = 7.3 Hz).

Table S1. Mosher ester analysis for Mosher esters **22** and **23**[12]

Proton	δ_H (*S*)-MTPA (**22**)	δ_H (*R*)-MTPA (**23**)	$\Delta\delta = \delta_S - \delta_R$
28	1.28	1.22	+0.06
30	2.89	2.89	0
30-Me	1.00	1.12	-0.12
32	2.95	3.02	-0.07
32-Me	0.98	1.02	-0.04
33a	3.54	3.55	-0.01
33b	3.38	3.40	-0.02

Alcohol 10[13]



To a solution of freshly distilled propionaldehyde (3.91 mL, 54.1 mmol) in anhydrous THF (12 mL) at –30 °C was added freshly prepared SmI_2 (18.1 mL, *ca.* 0.1 M in THF, 1.81 mmol) slowly; the blue coloring of SmI_2 disappeared to form a bright yellow solution. After stirring for 10 min, a solution of aldol adduct **9** (2.53 g, 9.02 mmol, 15:1 *dr*) in THF (12 mL) was added dropwise. The reaction mixture was stirred for 3 h and the temperature maintained between –20 °C and –10 °C. Upon completion, the reaction was quenched with $NaHCO_3$ (30 mL, sat. aq.) and warmed to room temperature. The mixture was extracted with Et_2O (2 × 30 mL) and CH_2Cl_2 (5 × 20 mL). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. The crude was purified by flash chromatography (30% EtOAc/PE) to afford alcohol **10** as a pale yellow oil (3.00 g, 98%, >95:5 *dr*). The product was carried forward as an inseparable mixture of diastereomers (15:1 *dr* from starting material).

$\mathbf{R}_f$ 0.47 (50% EtOAc/PE); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.23 (2H, d, *J* = 8.7 Hz), 6.87 (2H, d, *J* = 8.7 Hz), 5.40 (1H, qd, *J* = 6.5, 2.0 Hz), 4.43 (1H, d, *J* = 11.7 Hz), 4.39 (1H, d, *J* = 11.7 Hz), 3.80 (3H, s), 3.52 (1H, dd, *J* = 9.2, 4.9 Hz), 3.49 (1H, dd, *J* = 9.3, 5.1 Hz), 3.20–3.16 (2H, m), 2.30 (2H, q, *J* = 7.6 Hz), 2.01–1.95 (1H, m),

[12] Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.
[13] Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447.

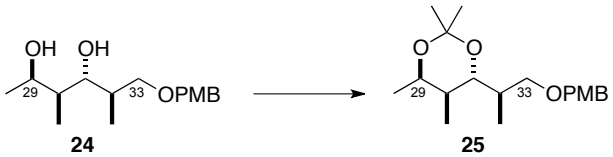
1.70–1.61 (1H, m), 1.22 (3H, d, J = 6.6 Hz), 1.12 (3H, t, J = 7.6 Hz), 1.08 (3H, d, J = 7.1 Hz), 0.89 (3H, d, J = 7.0 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 174.4, 159.2, 130.3, 129.1, 113.8, 76.6, 72.8, 71.9, 70.0, 55.2, 41.6, 34.8, 27.9, 17.9, 16.1, 10.2, 8.9; **$[\alpha]_D^{23}$** +2.3 (*c* 1.91, $CHCl_3$); **IR** (thin film) ν_{max} (cm^{-1}) 3511, 2976, 2937, 1730, 1613, 1514, 1462, 1372, 1247, 1204, 1082, 1035, 1010, 819; **HRMS** calc. for $C_{19}H_{31}O_5$ $[M+H]^+$ 339.2166, found 339.2168.

Diol 24

To a solution of crude alcohol **10** (89.0 mg, 0.263 mmol) in methanol (2.6 mL) at room temperature was added potassium carbonate (73.0 mg, 0.526 mmol). The reaction mixture was stirred for 3 h. Upon completion, the mixture was partitioned between Et_2O (10 mL) and brine (4 mL). The layers were separated and the aqueous phase extracted with Et_2O (4 × 10 mL). The combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by flash chromatography (25% Et_2O/CH_2Cl_2) to afford diol **24** (62.3 mg, 84% over 2 steps) as a colorless oil.

R*f* 0.38 (50% EtOAc/PE); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.23 (2H, d, J = 8.7 Hz), 6.88 (2H, d, J = 8.7 Hz), 4.45 (2H, s), 4.40 (1H, d, J = 2.6 Hz), 4.17 (1H, qt, J = 6.4, 2.0 Hz), 3.83 (1H, s), 3.80 (3H, s), 3.65 (1H, dd, J = 9.1, 3.9 Hz), 3.58–3.53 (1H, m), 3.44 (1H, dd, J = 9.0, 8.0 Hz), 2.17–2.06 (1H, m), 1.70–1.61 (1H, m), 1.14 (3H, d, J = 6.4 Hz), 1.01 (3H, d, J = 7.1 Hz), 0.84 (3H, d, J = 7.0 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 159.4, 129.5, 129.4, 113.9, 82.1, 75.5, 73.3, 67.3, 55.3, 39.3, 35.6, 20.2, 13.9, 11.1; **$[\alpha]_D^{23}$** –10.5 (*c* 1.95, $CHCl_3$); **IR** (thin film) ν_{max} (cm^{-1}) 3372, 2968, 2908, 1613, 1513, 1459, 1365, 1302, 1246, 1173, 1082, 1034, 995, 977, 912, 819, 754; **HRMS** calc. for $C_{16}H_{26}O_4Na$ $[M+Na]^+$ 305.1727, found 305.1723.

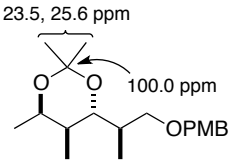
Acetonide 25



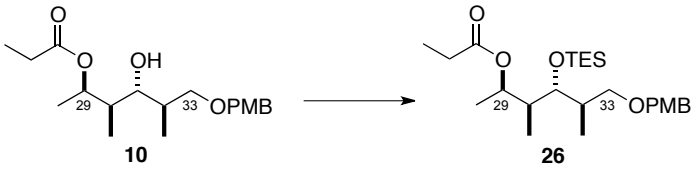
To a solution of diol **24** (87.0 mg, 0.308 mmol) in 2,2-dimethoxypropane (0.6 mL) was added camphor-10-sulfonic acid (CSA; spatula tip). The reaction mixture was stirred at room temperature for 90 min, after which the reaction was quenched with $NaHCO_3$ (2 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. The crude was purified by flash chromatography (8% EtOAc/PE) to afford acetonide **25** (92.7 mg, 93%) as a colorless oil.

$\mathbf{R}_f$ 0.67 (50% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.26 (2H, d, *J* = 8.4 Hz), 6.88 (2H, d, *J* = 8.7 Hz), 4.45 (1H, d, *J* = 11.6 Hz), 4.41 (1H, d, *J* = 11.6 Hz), 3.98 (1H, qd, *J* = 6.6, 4.6 Hz), 3.80 (3H, s), 3.57 (1H, dd, *J* = 9.2, 4.9 Hz), 3.32 (1H, dd, *J* = 9.2, 7.0 Hz), 3.24 (1H, dd, *J* = 7.4, 5.3 Hz), 1.99–1.90 (1H, m), 1.84–1.74 (1H, m), 1.31 (6H, s), 1.07 (3H, d, *J* = 6.6 Hz), 1.02 (3H, d, *J* = 6.9 Hz), 0.85 (3H, d, *J* = 6.8 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 159.0, 130.8, 129.1, 113.6, 100.0, 76.3, 72.7, 71.9, 65.0, 55.2, 37.6, 37.3, 25.6, 23.6, 16.6, 14.3, 12.2; $[\alpha]_D^{24}$ –5.3 (*c* 1.89, $CHCl_3$); **IR** (thin film) ν_{max} (cm^{-1}) 2981, 2935, 2904, 1613, 1513, 1457, 1377, 1302, 1245, 1223, 1183, 1172, 1149, 1089, 1035, 926, 907, 864, 820; **HRMS** calc. for $C_{19}H_{30}O_4Na$ $[M+Na]^+$ 345.2042, found 345.2054.

The C29,C31-*anti* diol stereochemistry was confirmed through ^{13}C NMR analysis of acetonide **25** according to the method of Rychnovsky and Evans.[14] The indicative chemical shifts of the acetonide carbons are shown on the right.



TES ether 26

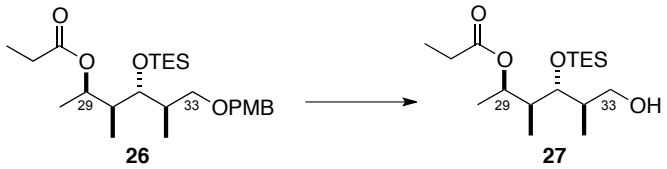


To a solution of alcohol **10** (6.00 g, 17.7 mmol) in CH_2Cl_2 (170 mL) at –78 °C was added 2,6-lutidine (6.23 mL, 53.2 mmol) and TESOTf (6.01 mL, 26.6 mmol). The reaction mixture was stirred at –78 °C for 90 min. Upon completion, the reaction was quenched with $NaHCO_3$ (100 mL, sat. aq) and warmed to room temperature. The aqueous phase was extracted with CH_2Cl_2 (3 × 75 mL), and the combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. The crude was purified by flash chromatography (PE → 5% EtOAc/PE) to afford TES ether **26** (7.95 g, 99%) as a colorless oil.

$\mathbf{R}_f$ 0.63 (20% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.25 (2H, d, *J* = 8.6 Hz), 6.87 (2H, d, *J* = 8.6 Hz), 5.06 (1H, qd, *J* = 6.3, 3.4 Hz), 4.41 (2H, s), 3.80 (3H, s), 3.58–3.51 (2H, m), 3.24 (1H, dd, *J* = 9.2, 8.0 Hz), 2.28 (2H, q, *J* = 7.6 Hz), 2.07–1.99 (1H, m), 1.67 (1H, app dqd, *J* = 7.1, 7.1, 3.4 Hz), 1.21 (3H, d, *J* = 6.4 Hz), 1.12 (3H, t, *J* = 7.6 Hz), 1.01 (3H, d, *J* = 6.9 Hz), 0.93 (9H, t, *J* = 7.9 Hz), 0.92 (3H, d, *J* = 7.7 Hz), 0.59 (6H, q, *J* = 8.0 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 173.8, 159.0, 130.8, 129.0, 113.6, 76.8, 72.6, 71.6, 70.6, 55.2, 42.7, 36.6, 27.9, 18.7, 15.9, 10.6, 9.1, 7.0, 5.3; $[\alpha]_D^{20}$ +3.0 (*c* 1.78, $CHCl_3$); **IR** (thin film) ν_{max} (cm^{-1}) 2956, 2877, 1733, 1613, 1513, 1461, 1373, 1302, 1246, 1194, 1093, 1034, 1009, 820, 738; **HRMS** calc. for $C_{25}H_{45}O_5Si$ $[M+H]^+$ 453.3031, found 453.3030.

[14] (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett*. **1990**, *31*, 945. (b) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem*. **1993**, *58*, 3511. (c) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett*. **1990**, *31*, 7099.

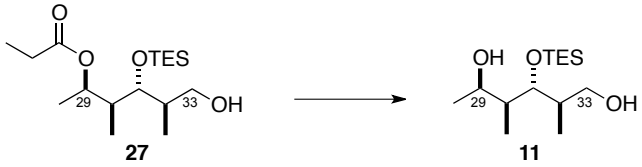
Alcohol 27



To a rapidly stirring biphasic mixture of PMB ether **26** (7.58 g, 17.3 mmol) in CH_2Cl_2 (175 mL) and pH 9 buffer (43 mL) at 0 °C was added DDQ (7.87 g, 34.7 mmol). The reaction mixture was stirred at 0 °C for 75 min and then quenched with $NaHCO_3$ (200 mL, sat. aq.). The aqueous phase was extracted with CH_2Cl_2 (8 × 50 mL). The combined organics were washed with brine (150 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The pale orange crude was purified by flash chromatography (5% EtOAc/toluene → 1:4:5 EtOAc/toluene/PE) and the product fractions concentrated *in vacuo* to a *ca.* 100 mL solution of alcohol **27** in toluene, removing the lower-boiling ethyl acetate. This solution was typically carried forward directly into the subsequent reaction.

R_f 0.25 (10% EtOAc/toluene); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.01 (1H, qd, *J* = 6.3, 4.1 Hz), 3.78 (1H, ddd, *J* = 11.1, 4.3, 4.3 Hz), 3.66 (1H, dd, *J* = 6.9, 3.4 Hz), 3.57 (1H, ddd, *J* = 11.0, 6.6, 4.8 Hz), 2.61 (1H, dd, *J* = 6.8, 4.5 Hz), 2.29 (2H, q, *J* = 7.6 Hz), 1.91–1.82 (1H, m), 1.78 (1H, app dqd, *J* = 7.0, 7.0, 4.1 Hz), 1.25 (2H, d, *J* = 6.3 Hz), 1.13 (3H, t, *J* = 6.3 Hz), 1.06 (3H, d, *J* = 7.1 Hz), 0.97 (9H, t, *J* = 7.9 Hz), 0.97 (3H, d, *J* = 7.0 Hz), 0.66 (6H, q, *J* = 7.8 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 174.1, 79.4, 70.9, 65.5, 44.2, 36.3, 28.2, 19.0, 16.5, 10.4, 9.3, 7.1, 5.4; $[\alpha]_D^{22}$ –3.2 (*c* 1.68, $CHCl_3$); **IR** (thin film) ν_{max} (cm^{-1}) 3523, 2956, 2878, 1735, 1461, 1413, 1377, 1345, 1234, 1195, 1157, 1085, 1010, 807, 739; **HRMS** calc. for $C_{17}H_{37}O_4Si$ $[M+H]^+$ 333.2461, found 333.2456.

Diol 11

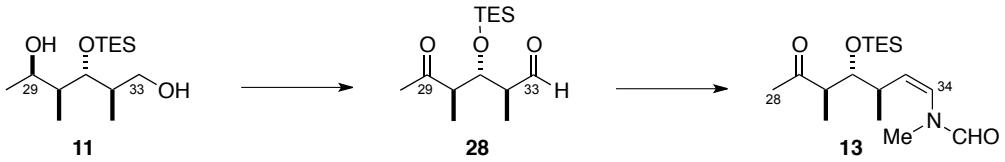


To the above solution of alcohol **27** in toluene (*ca.* 100 mL) at –78 °C was added DIBAL-H (52 mL, 1.0 M in CH_2Cl_2, 52 mmol). The reaction mixture was stirred at –78 °C for 90 min, then quenched with Na/K tartrate (100 mL, sat. aq.) and stirred rapidly at room temperature for 6 h. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (4 × 50 mL). The combined organics were subsequently dried over $MgSO_4$ and concentrated *in vacuo*. The crude was purified by flash chromatography (20% EtOAc/PE) to afford diol **11** (4.40 g, 92% over 2 steps) as a colorless oil.

R_f 0.24 (30% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.24 (1H, qdd, *J* = 6.4, 2.0, 2.0 Hz), 3.73 (1H, dd, *J* = 7.1, 3.6 Hz), 3.66 (2H, app t, *J* = 5.2 Hz), 2.87 (1H, d, *J* = 1.8 Hz), 2.01–1.93 (1H, m), 1.80 (1H, app t, *J* = 5.5 Hz), 1.61 (1H, qdd, *J* = 7.1, 3.6, 1.9 Hz), 1.15 (3H, d, *J* = 6.4 Hz), 1.01 (3H, d, *J* = 7.1 Hz), 0.99 (9H, t, *J* = 7.9 Hz), 0.98 (3H, d, *J* = 7.2 Hz), 0.70 (6H, q, *J* = 7.8 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 81.2, 66.6, 65.5, 40.3, 39.0, 21.1, 14.9, 11.1, 7.1, 5.4; $[\alpha]_D^{20}$ +6.0 (*c* 1.02, $CHCl_3$); **IR** (thin film) ν_{max} (cm^{-1}) 3408, 2960, 2911, 2879, 1461, 1415, 1381, 1241, 1100, 1073, 1028, 1004, 814, 738; **HRMS** calc. for $C_{14}H_{33}O_3Si$ $[M+H]^+$ 277.2193,

found 277.2196.

Enamide 13[15]



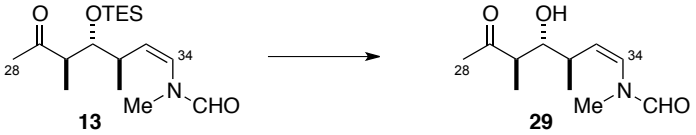
To a solution of oxalyl chloride (0.59 mL, 6.98 mmol) in CH_2Cl_2 (30 mL) at –78 °C was added DMSO (0.99 mL, 14.0 mmol) dropwise. The mixture was stirred for 15 min and then a solution of diol **11** (643 mg, 2.33 mmol) in CH_2Cl_2 (15 mL) was added. After an additional 15 min, Et_3N (3.87 mL, 27.9 mmol) was added. The reaction mixture was warmed incrementally, stirring at –78 °C for 40 min, then –45 °C for 15 min, then 0 °C for 15 min. Upon completion, the reaction was quenched by addition of NH_4Cl (30 mL, sat. aq.) and warmed to room temperature. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organics were washed sequentially with 0.5 M HCl (30 mL) and $NaHCO_3$ (30 mL, sat. aq.), dried over $MgSO_4$, and concentrated *in vacuo* to a colorless oil. As aldehyde **28** was observed to epimerize during purification, the crude material was used immediately in the subsequent reaction.

To a suspension of phosphonium salt **12** (1.29 g, 3.49 mmol) in THF (11.6 mL) at –78 °C was added freshly prepared LiHMDS (3.26 mL, 1.0 M in THF, 3.26 mmol). The ylide solution was warmed to 0 °C and stirred for 30 min, after which the yellow suspension was cooled back to –78 °C. A solution of aldehyde **28** (634 mg, 2.33 mmol, pre-dried in THF over CaH_2 for 1 h) in THF (4.7 mL) was added slowly. The reaction mixture was stirred at –78 °C for 2.5 h. Upon completion, the reaction was quenched with NH_4Cl (15 mL, sat. aq.) and warmed to room temperature. The mixture was extracted with Et_2O (15 mL) and EtOAc (3 × 10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude was purified by flash chromatography (5 → 15% EtOAc/CH_2Cl_2) to afford enamide **13** (574 mg, 75% over 2 steps, 8:1 *Z*/*E*) as a colorless oil.

R_f 0.41 (50% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.17 (1H, s), 5.95 (1H, d, *J* = 8.7 Hz), 5.35 (1H, dd, *J* = 10.7, 8.8 Hz), 3.85 (1H, dd, *J* = 8.0, 2.9 Hz), 3.01 (3H, s), 2.68–2.57 (2H, m), 2.16 (3H, s), 1.06 (3H, d, *J* = 6.9 Hz), 0.95 (9H, t, *J* = 7.9 Hz), 0.91 (3H, d, *J* = 7.1 Hz), 0.60 (6H, q, *J* = 7.9 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 211.3, 162.5, 127.4, 125.3, 77.4, 51.8, 34.0, 31.4, 30.7, 19.3, 13.0, 7.0, 5.2; $[\alpha]_D^{22}$ + 2.8 (*c* 2.8, $CHCl_3$); **IR** (thin film) ν_{max} (cm^{-1}) 2959, 1716, 1682, 1654; **HRMS** calc for $C_{17}H_{33}NNaO_3Si$ $[M+Na]^+$ 350.2127, found 350.2139.

[15] Paterson, I.; Cowden, C. J.; Watson, C. *Synlett* **1996**, 209.

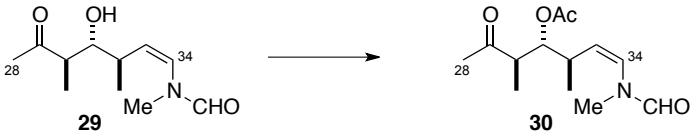
Alcohol 29



A mixture of TBAF (6.98 mL, 1.0 M in THF, 6.98 mmol) and glacial acetic acid (393 μL, 6.86 mmol) was stirred at 0 °C for 30 min. An aliquot of this solution (6.5 mL) was added to TES ether **13** (200 mg, 0.611 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 9 h. Upon completion, the reaction was quenched by addition of $NaHCO_3$ (20 mL, sat. aq.), then extracted with Et_2O (3 × 20 mL) and EtOAc (9 × 15 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude was purified by flash chromatography (50% EtOAc/PE → EtOAc) to afford alcohol **29** (128 mg, 98%, 10:1 *Z*/*E*) as a colorless oil.

R$_f$ 0.07 (50% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.15 (0.8H, s), [8.02] (0.2H, s), 5.99 (1H, d, *J* = 8.8 Hz), 5.31 (1H, dd, *J* = 10.8, 8.8 Hz), 3.60 (0.8H, dd, *J* = 7.9, 3.5 Hz), [3.52] (0.2H, m), [3.11] (0.6H, s), 3.01 (2.4H, s), 2.84 (1H, br s), 2.71–2.62 (1H, m), 2.59 (1H, dq, *J* = 7.6, 7.6 Hz), [2.19] (0.6H, s), 2.18 (2.4H, s), [1.15] (0.6H, obs), 1.13 (2.4H, d, *J* = 6.8 Hz), [1.06] (0.4H, d, *J* = 6.8 Hz), 1.04 (2.4H, d, *J* = 7.3 Hz); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 213.6, 162.6, 127.9, 124.8, 76.5, 50.2, 33.7, 31.5, 29.7, 18.9, 13.6; $[\alpha]_D^{22}$ + 45.1 (*c* 0.9, $CHCl_3$); **IR** (thin film) ν_{max} (cm^{-1}) 3446, 2967, 1712, 1673, 1649; **HRMS** calc for $C_{11}H_{19}NNaO_3$ $[M+Na]^+$ 236.1263, found 236.1252. Distinguishable resonances of the minor rotamer (4:1 ratio) are given in brackets.

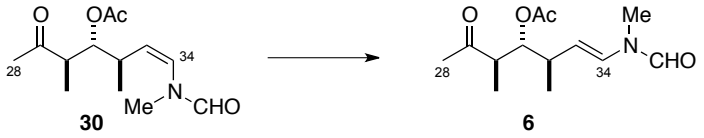
Enamide 30



To a solution of alcohol **29** (125 mg, 0.586 mmol, 10:1 *Z*/*E*) in CH_2Cl_2 (3.0 mL) at –10 °C was added triethylamine (0.45 mL, 3.22 mmol), acetic anhydride (0.28 mL, 2.93 mmol), and DMAP (3.5 mg, 0.029 mmol). The reaction mixture was stirred at –10 °C for 1 h and then quenched with $NaHCO_3$ (5 mL, sat. aq.). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organics were subsequently dried over $MgSO_4$ and concentrated *in vacuo*. The crude was filtered through a small column of Florisil (20% EtOAc/PE), concentrated *in vacuo*, and submitted directly to the subsequent isomerization reaction. For characterization purposes, the crude was purified by flash chromatography (50% EtOAc/PE) to afford enamide **30** (148 mg, 99%, 11:1 *Z*/*E*) as a pale yellow oil.

R$_f$ 0.39 (50% EtOAc/CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.15 (0.86H, s), [8.05] (0.14H, s), [6.25] (0.14H, d, *J* = 9.3 Hz), 6.00 (0.86H, d, *J* = 8.8 Hz), 5.14 (1H, dd, *J* = 10.9, 8.8 Hz), 5.09 (1H, dd, *J* = 8.3, 4.4 Hz), [3.16] (0.42H, s), 3.02 (2.58H, s), 2.90–2.79 (1H, m), 2.71 (1H, dq, *J* = 7.5, 7.1 Hz), 2.12 (3H, s), 2.02 (3H, s), 1.03 (3H, d, *J* = 7.2 Hz), 1.03 (3H, d, *J* = 6.8 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 209.2, 170.0, 162.4, 128.3, 123.3, 76.6, 49.6, 32.8, 31.4, 28.2, 20.7, 18.5, 13.0; $[\alpha]_D^{22}$ +15.6 (*c* 1.08, $CHCl_3$); **IR** (thin film) ν_{max} (cm^{-1}) 2971, 1741, 1682, 1654, 1358, 1233, 1021; **HRMS** calc. for $C_{13}H_{21}NO_4Na$ $[M+Na]^+$ 278.1368, found 278.1359. Distinguishable resonances of the minor rotamer (6:1 ratio) are given in brackets.

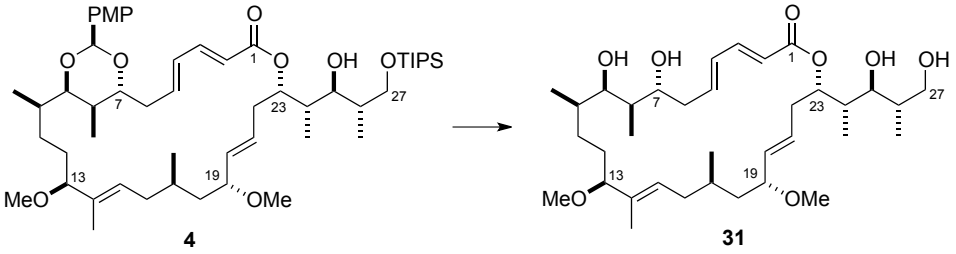
Enamide 6



To a solution of (*Z*)-enamide **30** (148 mg, 0.580 mmol, 11:1 *Z*/*E*) in CH_2Cl_2 (6.0 mL) in the dark was added iodine (220 mg, 0.867 mmol). The reaction mixture was stirred at room temperature in the dark for 24 h, then quenched with sodium thiosulfate (5 mL, sat. aq.) and stirred rapidly for 30 te. The bright orange organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (4 × 5 mL). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo* to a dark red oil. The crude was purified by flash chromatography (25 → 60% EtOAc/PE), eluting rapidly to minimize elimination on silica, to afford (*E*)-enamide **6** (139 mg, 94% over 2 steps) as a pale yellow oil.

R$_f$ 0.39 (50% EtOAc/CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 8.27 (0.67H, s), [8.07] (0.33H, s), [7.15] (0.33H, d, *J* = 14.6 Hz), 6.48 (0.67H, d, *J* = 14.1 Hz), 5.10 (1H, dd, *J* = 8.6, 4.0 Hz), [4.99] (0.33H, obs), 4.96 (0.67H, dd, *J* = 14.1, 9.5 Hz), [3.05] (1H, s), 3.01 (2H, s), 2.75 (0.67H, dq, *J* = 7.2, 6.5 Hz), [2.70] (0.33H, dq, *J* = 7.6, 7.6 Hz), 2.57–2.44 (1H, m), 2.14 (2H, s), [2.12] (1H, s), 2.02 (2H, s), [2.01] (1H, s), 1.09 (3H, d, *J* = 7.1 Hz), 1.04 (2H, d, *J* = 6.8 Hz), [1.04] (1H, d, *J* = 6.7 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C [209.8], 209.6, [170.2], 170.1, 162.1, [160.9], 129.5, [125.5], [112.1], 110.4, 77.1, [49.6], 49.3, [37.0], 36.9, [32.9], 28.4, [28.0], 27.5, 20.8, 18.8, [18.7], 13.2, [13.1]; $[\alpha]_D^{22}$ –69.6 (*c* 1.24, $CHCl_3$); **IR** (thin film) ν_{max} (cm^{-1}) 2973, 1740, 1696, 1656, 1374, 1234, 1092, 1071, 1021, 960, 725; **HRMS** calc. for $C_{13}H_{21}NO_4Na$ $[M+Na]^+$ 278.1368, found 278.1369. Distinguishable resonances of the minor rotamer (2:1 ratio) are given in brackets.

Tetraol 31



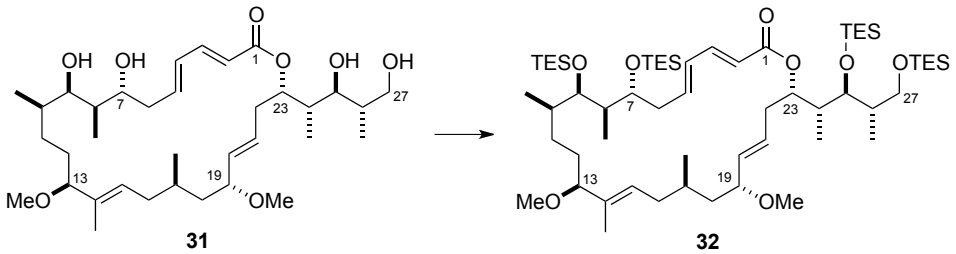
Macrolactone **4**[16] (115 mg, 0.130 mmol) was dissolved in MeCN (10 mL) and the solution was cooled to 0 °C. HF (10 mL, 40% aq. solution) was added dropwise. The resulting mixture was stirred for 50 min and then quenched by pipetting into a stirring solution of $NaHCO_3$ (200 mL, sat. aq.). The mixture was stirred vigorously for a further 10 min to ensure all HF was quenched, then extracted with EtOAc (5 × 20 mL). The combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (40 → 50% EtOAc/PE) afforded tetraol **31** as a white foam (76.8 mg, 97%).

R$_f$ 0.12 (80% EtOAc/PE); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.31 (1H, dd, *J* = 15.3, 10.2 Hz), 6.24 (1H, dd, *J* = 15.2, 10.3 Hz), 6.17 (1H, ddd, *J* = 15.2, 8.8, 5.1 Hz), 5.85 (1H, d, *J* = 15.3 Hz), 5.56 (1H, ddd, *J* = 15.2, 9.7, 4.1

[16] Paterson, I.; Woodrow, M. D.; Cowden, C. J. *Tetrahedron Lett.* **1998**, *39*, 6041.

Hz), 5.39 (1H, br d, *J* = 10.9 Hz), 5.18 (1H, dd, *J* = 15.2, 9.0 Hz), 5.12 (1H, t, *J* = 7.1 Hz), 3.95 (1H, d, *J* = 4.3 Hz), 3.89 (1H, ddd, *J* = 11.0, 2.9, 2.9 Hz), 3.77–3.71 (1H, m), 3.64 (1H, dd, *J* = 8.6, 4.2 Hz), 3.57 (1H, ddd, *J* = 11.7, 7.8, 4.5 Hz), 3.51 (1H, td, *J* = 9.5, 4.0 Hz), 3.43 (1H, t, *J* = 7.5 Hz), 3.21 (3H, s), 3.18 (3H, s), 3.17–3.11 (2H, m), 2.83 (1H, d, *J* = 6.0 Hz), 2.61 (1H, d, *J* = 4.6 Hz), 2.59–2.52 (1H, m), 2.51–2.44 (1H, m), 2.43–2.36 (1H, m), 2.32–2.27 (1H, m), 2.05–1.97 (1H, m), 1.91 (1H, dd, *J* = 8.0, 8.0 Hz), 1.87–1.82 (1H, m), 1.81–1.75 (1H, m), 1.72–1.65 (1H, m), 1.61 (2H, q, *J* = 7.1 Hz), 1.53–1.48 (1H, m), 1.48 (3H, s), 1.33–1.28 (2H, m), 1.26–1.20 (1H, m), 1.18–1.12 (1H, obs), 1.15 (3H, d, *J* = 7.0 Hz), 1.13–1.08 (1H, m), 1.06 (3H, d, *J* = 6.9 Hz), 0.91 (6H, d, *J* = 6.6 Hz), 0.78 (3H, d, *J* = 5.3 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 168.3, 145.5, 141.1, 134.8, 133.3, 130.8, 130.3, 128.8, 119.2, 87.2, 81.3, 77.6, 77.2, 75.4, 74.8, 72.9, 55.7, 55.7, 42.1, 40.9, 38.2, 38.1, 36.6, 36.2, 35.7, 35.1, 29.7, 29.6, 26.4, 19.5, 15.9, 15.5, 11.9, 10.2, 10.1; $[\alpha]_D^{22}$ + 40.8 (*c* 0.9, $CHCl_3$); **IR** (thin film) ν_{max} (cm^{-1}) 3425, 2924, 1690; **HRMS** calc. for $C_{35}H_{60}O_8Na$ $[M+Na]^+$ 631.4186, found 631.4192.

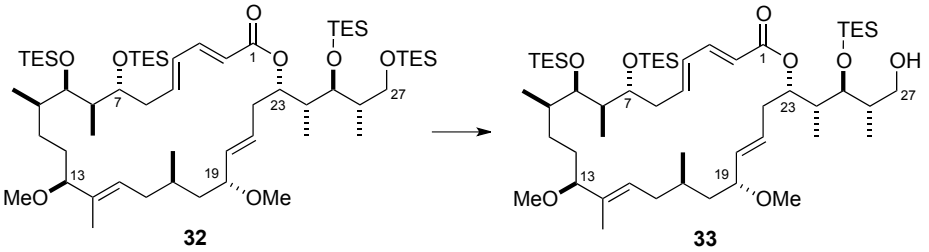
Tetra-TES ether 32



To a solution of tetraol **31** (38 mg, 0.063 mmol) in CH_2Cl_2 (4 mL) at −78 °C was added 2,6-lutidine (58 μL, 0.50 mmol) and TESOTf (84 μL, 0.375 mmol). The solution was stirred at −78 °C for 2 h and then quenched with $NaHCO_3$ (5 mL, sat. aq.). The mixture was warmed to room temperature and extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (1 → 4% EtOAc/PE) gave tetra-TES ether **32** as a colorless oil (64 mg, 96%).

$\mathbf{R}_f$ 0.60 (20% EtOAc/PE); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.20 (1H, dd, *J* = 15.3, 10.3 Hz), 6.22 (1H, ddd, *J* = 15.1, 9.5, 4.4 Hz), 6.13 (1H, dd, *J* = 15.3, 10.3 Hz), 5.82 (1H, d, *J* = 15.3 Hz), 5.56 (1H, ddd, *J* = 15.0, 10.3, 4.3 Hz), 5.29 (1H, ddd, *J* = 10.6, 4.1, 1.9 Hz), 5.07 (2H, m), 3.69 (1H, dd, *J* = 9.8, 4.8 Hz), 3.61 (1H, dd, *J* = 8.6, 3.7 Hz), 3.57 (1H, dd, *J* = 5.2, 5.2 Hz), 3.50 (1H, td, *J* = 9.1, 4.2 Hz), 3.43 (1H, dd, *J* = 9.8, 7.1 Hz), 3.39 (1H, obs), 3.37 (1H, dd, *J* = 10.8, 4.3 Hz), 3.19 (3H, s), 3.16 (3H, s), 2.42–2.36 (1H, m), 2.36–2.28 (1H, m), 2.29–2.22 (1H, m), 2.02–1.88 (3H, m), 1.85–1.77 (1H, m), 1.76–1.40 (5H, m), 1.42 (3H, s), 1.30–1.13 (3H, m), 1.14–1.02 (2H, m), 1.00 (3H, d, *J* = 7.0 Hz), 0.98–0.92 (42H, m), 0.90 (3H, d, *J* = 6.7 Hz), 0.79 (3H, d, *J* = 5.9 Hz), 0.66–0.53 (24H, m); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 166.1, 144.1, 141.8, 134.0, 132.7, 131.6, 129.7, 129.6, 120.6, 87.5, 81.6, 77.2, 76.9, 72.6, 71.9, 64.6, 55.6, 55.6, 42.6, 41.8, 40.4, 39.6, 38.4, 36.8, 36.2, 30.9, 29.6, 26.9, 20.0, 14.9, 14.5, 12.6, 11.5, 9.6, 7.1, 7.0, 7.0, 6.8, 6.7, 5.4, 5.3, 5.2, 4.4; $[\alpha]_D^{22}$ + 68.6 (*c* 0.9, $CHCl_3$); **IR** (thin film) ν_{max} (cm^{-1}) 2954, 1719, 1643, 1461; **HRMS** calc. for $C_{59}H_{116}O_8NaSi_4$ $[M+Na]^+$ 1087.7639, found 1087.7554.

Alcohol 33

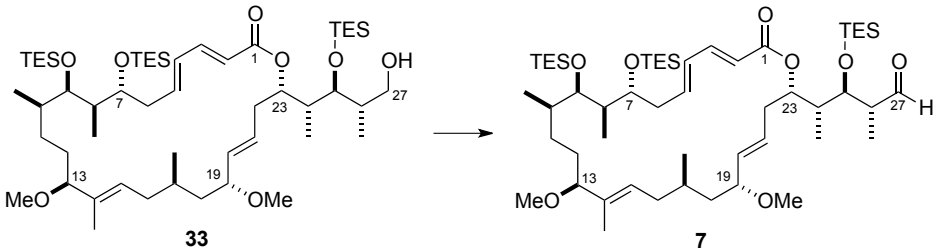


32 **33**

To a solution of tetra-TES ether **32** (40.0 mg, 0.0375 mmol) in THF (7.5 mL) at 0 °C was added water (1.85 mL) and glacial acetic acid (1.85 mL). The reaction mixture was warmed to room temperature and stirred for 2 h, after which the reaction was cooled to 0 °C and quenched by slow addition of $NaHCO_3$ (*ca.* 30 mL, sat. aq.) until all bubbling stopped. The aqueous phase was extracted with Et_2O (4 × 25 mL). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo* to a pale yellow oil. The crude was purified by flash chromatography (20% EtOAc/PE) to afford alcohol **33** (29.3 mg, 82%) as a colorless oil.

R_f 0.23 (20% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.22 (1H, dd, *J* = 15.3, 10.6 Hz), 6.24 (1H, ddd, *J* = 15.0, 9.9, 4.2 Hz), 6.14 (1H, dd, *J* = 15.1, 10.8 Hz), 5.83 (1H, d, *J* = 15.3 Hz), 5.55 (1H, ddd, *J* = 15.0, 10.3, 4.2 Hz), 5.23 (1H, ddd, *J* = 10.8, 4.7, 1.6 Hz), 5.04 (1H, dd, *J* = 15.4, 9.1 Hz), 5.04–4.97 (1H, m), 3.70 (1H, app br d, *J* = 10.8 Hz), 3.65 (1H, dd, *J* = 4.8, 4.8 Hz), 3.63–3.55 (2H, m), 3.50 (1H, dt, *J* = 9.0, 3.8 Hz), 3.41–3.33 (2H, m), 3.19 (3H, s), 3.16 (3H, s), 2.57 (1H, br s), 2.43–2.37 (1H, m), 2.33 (1H, app t, *J* = 10.7 Hz), 2.33–2.21 (1H, m), 2.00–1.88 (3H, m), 1.89–1.82 (1H, m), 1.75–1.43 (6H, m), 1.42 (3H, s), 1.27–1.14 (2H, m), 1.12–1.04 (2H, obs), 1.02 (3H, d, *J* = 5.0 Hz), 1.00 (3H, d, *J* = 5.0 Hz), 0.98–0.91 (30H, m), 0.89 (3H, d, *J* = 6.6 Hz), 0.79 (3H, d, *J* = 5.5 Hz), 0.67 (6H, q, *J* = 7.5 Hz), 0.63–0.51 (12H, m); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 166.2, 144.7, 142.3, 134.1, 133.2, 131.0, 129.6, 129.5, 120.1, 87.5, 81.6, 79.5, 77.2, 72.6, 71.9, 65.8, 55.6, 55.6, 43.5, 42.5, 40.4, 38.3, 37.2, 36.8, 36.3, 30.9, 29.7, 29.6, 19.9, 16.2, 14.4, 11.5, 9.6, 7.0, 7.0, 7.0, 5.4, 5.2, 5.2, 2C obscured; $[\alpha]_D^{22}$ + 89.7 (*c* 1.0, $CHCl_3$); **IR** (thin film) ν_{max} (cm^{-1}) 3477, 2955, 1716; **HRMS** calc. for $C_{53}H_{102}O_8NaSi_3$ $[M+Na]^+$ 973.6780, found 973.6769.

Aldehyde 7



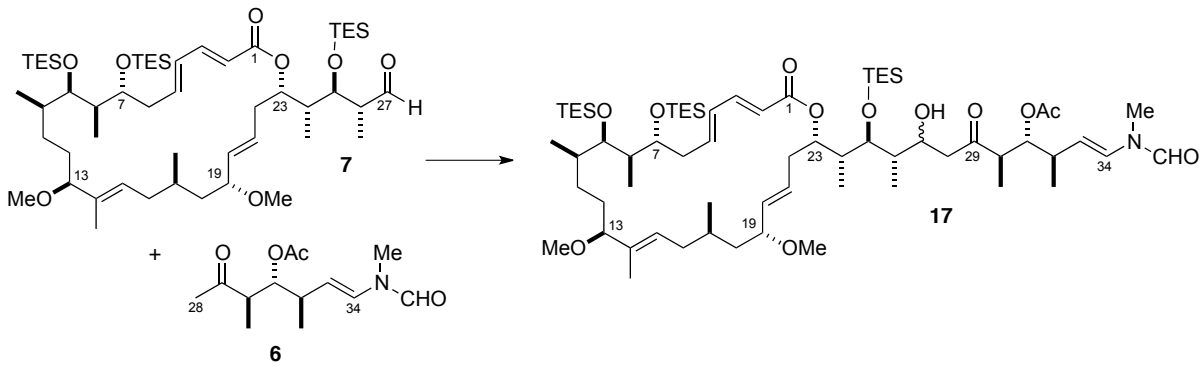
33 **7**

To a solution of oxalyl chloride (14 μL, 0.17 mmol) in CH_2Cl_2 (0.40 mL) at –78 °C was added DMSO (24 μL, 0.33 mmol) dropwise. After stirring for 20 min, a solution of alcohol **33** (53.0 mg, 0.0557 mol) in CH_2Cl_2 (0.70 mL) was added. The mixture was stirred for 30 min and then Et_3N (93 μL, 0.67 mmol) was added. The reaction mixture was stirred at –78 °C for 30 min, then warmed to –40 °C for 10 min before being quenched with NH_4Cl (2 mL, sat. aq.) and warmed to room temperature. The aqueous phase was extracted with CH_2Cl_2 (4 × 8 mL). The combined organics were subsequently dried over $MgSO_4$ and concentrated *in vacuo*. The crude was purified

by flash chromatography (2 → 5% EtOAc/PE, Florisil) to afford aldehyde **7** as a colorless oil. The aldehyde was submitted immediately to the subsequent aldol reaction.

R_f 0.41 (20% EtOAc/PE); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 9.77 (1H, d, *J* = 2.0 Hz), 7.22 (1H, dd, *J* = 15.3, 10.8 Hz), 6.24 (1H, ddd, *J* = 14.3, 9.5, 4.2 Hz), 6.15 (1H, dd, *J* = 15.3, 10.8 Hz), 5.83 (1H, d, *J* = 15.3 Hz), 5.56 (1H, ddd, *J* = 14.8, 9.2, 5.3 Hz), 5.28 (1H, dt, *J* = 9.3, 3.9 Hz), 5.05 (1H, dd, *J* = 15.2, 9.1 Hz), 5.01 (1H, br d, *J* = 11.9 Hz), 3.92 (1H, t, *J* = 4.9 Hz), 3.62 (1H, dd, *J* = 9.2, 4.6 Hz), 3.51 (1H, td, *J* = 9.0, 3.9 Hz), 3.41 (1H, m), 3.37 (1H, dd, *J* = 10.8, 4.2 Hz), 3.20 (3H, s), 3.17 (3H, s), 2.63 (1H, m), 2.35 (2H, m), 2.27 (1H, m), 2.02–1.92 (2H, m), 1.85 (1H, m), 1.78–1.61 (3H, m), 1.60 (1H, obs), 1.43 (1H, m), 1.42 (3H, s), 1.23 (3H, m), 1.12 (3H, d, *J* = 7.0 Hz), 1.08 (2H, m), 0.93 (33H, m), 0.90 (3H, d, *J* = 6.7 Hz), 0.79 (3H, d, *J* = 5.6 Hz), 0.65–0.54 (18H, m); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 204.3, 166.2, 144.8, 142.4, 134.2, 133.2, 131.0, 129.6 (2C), 119.9, 87.5, 81.5, 77.2, 76.3, 72.6, 71.6, 55.6, 55.6 (2C), 50.0, 43.2, 42.5, 40.4, 38.0, 36.8 (2C), 36.3, 31.0, 29.7, 29.6, 19.9, 14.5, 11.5, 11.0, 9.6, 7.0, 7.0, 6.9, 5.4, 5.2, 5.1; $[\alpha]_D^{22}$ + 60.8 (*c* 0.8, $CHCl_3$); **IR** (thin film) ν_{max} (cm^{-1}) 2954, 1722; **HRMS** calc. for $C_{53}H_{100}O_8NaSi_3$ $[M+Na]^+$ 971.6624, found 971.6626.

Aldol adduct 17[17]



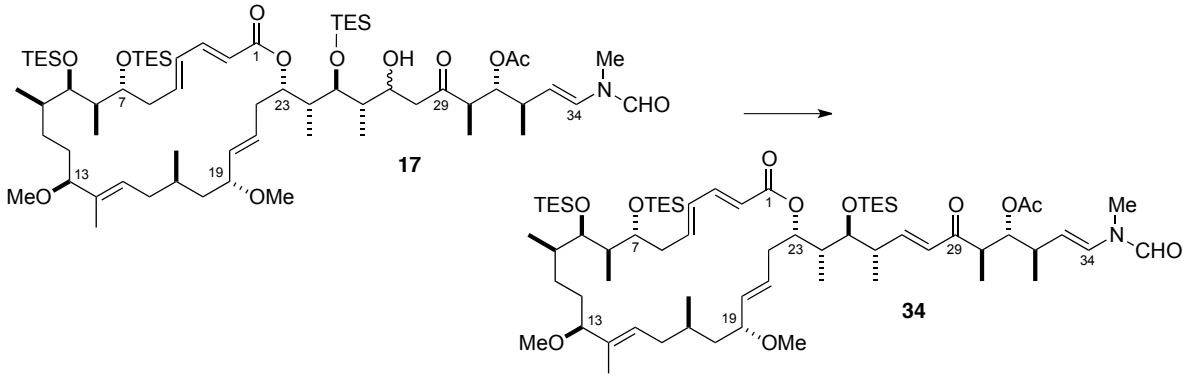
A stock solution of enolate (0.10 M in Et_2O) was prepared: To a solution of dicyclohexylboron chloride (131 μL, 0.599 mmol) in anhydrous Et_2O (2.00 mL) at –78 °C was added Et_3N (166 μL, 1.20 mmol) dropwise, followed by a solution of ketone **6** (170 mg, 0.666 mmol, pre-dried by azeotroping with benzene). The enolate solution instantly formed a cloudy white slurry. The mixture was warmed to –20 °C and stirred for 1 h, after which the pale yellow slurry was cooled back to –78 °C.

To a solution of aldehyde **7** (52.9 mg, 0.0557 mmol, dried over CaH_2) in Et_2O (3 mL) at –78 °C was added an aliquot of the above enolate stock solution (1.20 mL, 0.120 mmol). The resulting mixture was stirred at –78 °C for 2.5 h, at which time an additional aliquot of enolate (0.60 mL, 0.060 mmol) was added. After stirring for an additional 2.5 h, the reaction mixture was warmed to 0 °C and quenched by addition of methanol (3.5 mL) and pH 7 buffer (3 mL). The biphasic mixture was stirred rapidly for 30 min. The mixture was extracted with Et_2O (5 mL) and EtOAc (6 × 5 mL). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. The crude was purified by flash chromatography (1 → 5% MeOH/CH_2Cl_2, Florisil) to afford aldol adduct **17** (41.2 mg, 61% over 2 steps) as a colorless oil.

[17] (a) Paterson, I.; Ashton, K.; Britton, R.; Cecere, G.; Chouraqui, G.; Florence, G. J.; Knust, H.; Stafford, J. *Chem. Asian. J.* **2008**, *3*, 367. (b) Dalby, S. M.; Goodwin-Tindall, J.; Paterson, I. *Angew. Chem. Int. Ed.* **2013**, in press.

R_f 0.05 (10% EtOAc/CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 8.28 (0.67H, s), [8.08] (0.33H, s), 7.21 (1H, dd, *J* = 15.3, 10.6 Hz), [7.17] (0.33H, d, *J* = 14.7 Hz), 6.50 (0.67H, d, *J* = 14.1 Hz), 6.23 (1H, ddd, *J* = 14.7, 9.3, 4.6 Hz), 6.14 (1H, dd, *J* = 15.3, 10.7 Hz), 5.83 (1H, d, *J* = 15.2 Hz), 5.55 (1H, ddd, *J* = 15.1, 10.5, 4.1 Hz), 5.26 (1H, ddd, *J* = 10.6, 4.1, 2.1 Hz), [5.17] (0.33H, obs), 5.16 (0.67H, dd, *J* = 8.9, 3.9 Hz), 5.07–4.98 (2H, m), [4.99] (0.33H, obs), 4.97 (0.67H, dd, *J* = 14.0, 9.4 Hz), 4.14–4.07 (1H, m), 3.69 (1H, dd, *J* = 4.9, 4.9 Hz), 3.61 (1H, dd, *J* = 8.1, 3.8 Hz), 3.46 (1H, ddd, *J* = 9.8, 9.8, 3.9 Hz), 3.40 (1H, obs), 3.37 (1H, dd, *J* = 10.9, 4.3 Hz), 3.19 (3H, s), 3.16 (3H, s), 3.16 (0.67H, d, *J* = 2.8 Hz), [3.14] (0.33H, d, *J* = 2.8 Hz), [3.07] (1H, s), 3.03 (2H, s), 2.82 (0.67H, dq, *J* = 8.8, 7.1 Hz), [2.78] (0.33H, dq, *J* = 9.1, 7.1 Hz), 2.63 (1H, m), 2.60–2.46 (2H, m), 2.38 (1H, m), 2.35–2.22 (2H, m), 2.02 (2H, s), [2.02] (1H, s), 2.00–1.91 (2H, m), 1.91–1.85 (1H, m), 1.84–1.77 (1H, m), 1.75–1.44 (6H, m), 1.42 (3H, s), 1.27–1.15 (2H, m), 1.10 (2H, obs), 1.09 (2H, d, *J* = 7.1 Hz), [1.08] (1H, d, *J* = 7.2 Hz), 1.05 (2H, d, *J* = 6.9 Hz), [1.04] (1H, d, *J* = 7.1 Hz), 0.98 (3H, d, *J* = 7.0 Hz), 0.98–0.92 (30H, m), 0.93 (3H, obs), 0.89 (3H, d, *J* = 6.9 Hz), 0.80 (3H, d, *J* = 5.8 Hz), 0.69–0.63 (6H, m), 0.63–0.53 (12H, m); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C [212.6], 212.4, [170.2], 170.1, 166.1, 162.1, [160.9], 144.5, 142.2, 134.1, 133.0, 131.2, 129.6, 129.5 (2C), [125.5], 120.2, [111.9], 110.3, 87.5, 81.5, 77.8, 77.6, 77.2, 77.2, 72.6, 71.7, 68.5, [68.4], 55.6 (2C), [49.4], 49.2, 46.0, [45.6], 42.9, [42.8], [41.7], 41.7, 40.4, 38.6, [37.0], 36.8, 36.8, 36.3, [33.0], 30.8, 29.6 (2C), 27.5, 23.8, 20.9, 20.0, 18.8, 14.4, 13.7, [13.5], 13.1, [12.1], 12.1, 11.5, 9.6, 7.1, 7.0, 7.0, 5.4, 5.2, 5.2; $[\alpha]_D^{23}$ +20.7 (*c* 1.62, $CHCl_3$); **IR** (thin film) ν_{max} (cm^{-1}) 3676, 2954, 2876, 1742, 1699, 1657, 1456, 1376, 1084, 1007, 966, 737, 721; **HRMS** calc. for $C_{66}H_{125}O_{12}N_2Si_3$ $[M+NH_4]^+$ 1221.8532, found 1221.8535. Distinguishable resonances of the minor rotamer (2:1 ratio) are given in brackets.

Enone 34[17]

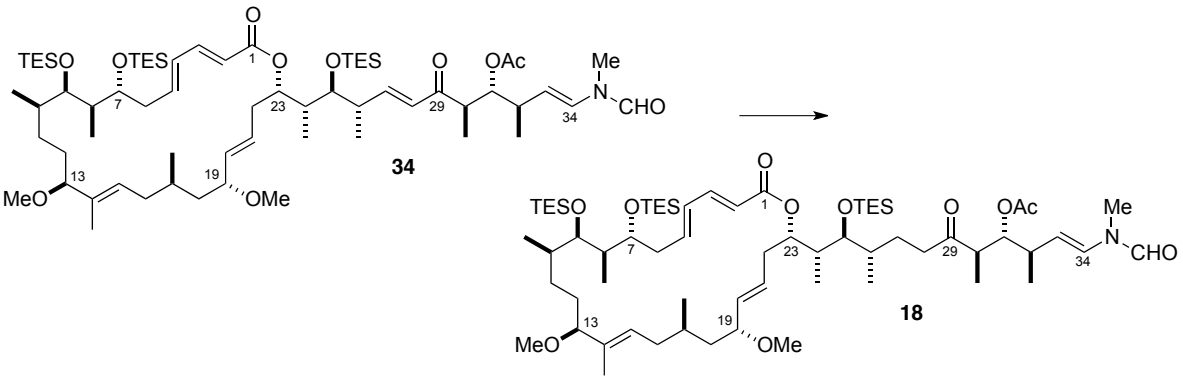


To a solution of aldol adduct **17** (6.3 mg, 5.2 μmol) in THF (500 μL) was added Burgess reagent (6.3 mg, 26 μmol). The reaction mixture was stirred at room temperature for 25 h and then quenched with NH_4Cl (2 mL, sat. aq.). The mixture was diluted with CH_2Cl_2 (3 mL) and the aqueous phase extracted with CH_2Cl_2 (2 × 3 mL) and EtOAc (4 × 3 mL). The combined organics were subsequently dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (10 → 15% acetone/PE) provided enone **34** (5.8 mg, 93%) as a colorless oil.

R_f 0.26 (20% EtOAc/CH_2Cl_2); **^{1}H NMR** (500 MHz, CDCl3) δ_H 8.32 (0.67H, s), [8.10] (0.33H, s), 7.21 (1H, dd, *J* = 15.3, 10.6 Hz), [7.17] (0.33H, d, *J* = 15.5 Hz), 6.99 (1H, dd, *J* = 15.8, 8.1 Hz), 6.50 (0.67H, d, *J* = 14.1 Hz), 6.24 (1H, ddd, *J* = 14.7, 9.0, 4.4 Hz), 6.20–6.12 (2H, m), 5.82 (1H, d, *J* = 15.3 Hz), 5.56 (1H, ddd, *J* = 15.4, 9.0,

4.9 Hz), 5.29–5.23 (1H, m), 5.18 (1H, dd, *J* = 8.7, 4.0 Hz), 5.08–4.98 (2H, m), 4.99 (1H, dd, *J* = 14.2, 9.3 Hz), 3.64–3.58 (2H, m), 3.50 (1H, ddd, *J* = 13.2, 10.1, 4.3 Hz), 3.40 (1H, obs), 3.37 (1H, dd, *J* = 10.4, 4.2 Hz), 3.19 (3H, s), 3.16 (3H, s), [3.07] (1H, s), 3.03 (2H, s), 2.98 (0.67H, dq, *J* = 8.6, 7.1 Hz), [2.94] (0.33H, dq, *J* = 8.8, 6.8 Hz), 2.65–2.47 (2H, m), 2.38–2.22 (3H, m), 1.98 (2H, s), [1.97] (1H, s), 1.97–1.91 (2H, m), 1.78–1.43 (7H, m), 1.42 (3H, s), 1.24–1.17 (2H, m), 1.11–1.02 (11H, m), 0.97–0.91 (30H, m), 0.92 (3H, d, *J* = 6.9 Hz), 0.89 (3H, d, *J* = 6.8 Hz), 0.79 (3H, d, *J* = 5.6 Hz), 0.66–0.53 (18H, m); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C [200.4], 200.4, 170.0, 166.2, 162.1, [160.9], 150.6, [150.4], 144.6, 142.4, 134.2, 133.2, [132.2], 131.0, 129.6, 129.5, 129.4, [128.5], 128.0, [125.4], [120.2], 120.1, [112.4], 110.7, 87.5, 81.6, 78.0, 77.2, 77.2, 72.5, 71.5, 55.6 (2C), 49.4, [46.7], 46.4, 43.2, [43.1], 42.7, 40.4 (2C), 38.3, 37.0, 36.9, [36.8], 36.3, [33.0], 30.9, 29.7, 29.6, [28.4], 27.6 (2C), 20.8, 20.0, 18.8, [18.7], 18.0, [17.8], 14.4, 13.4, [13.2], 11.4, 9.6, 7.1 (2C), 7.0, 5.4, 5.3, 5.3; $[\alpha]_D^{22}$ +15.4 (*c* 0.76, $CHCl_3$); **IR** (thin film) ν_{max} (cm^{-1}) 2957, 2906, 1742, 1719, 1694, 1659, 1456, 1373, 1302, 1259, 1091, 1054, 1014, 1005, 966, 742, 728; **HRMS** calc. for $C_{66}H_{123}O_{11}N_2Si_3$ $[M+NH_4]^+$ 1203.8428, found 1203.8429. Distinguishable resonances of the minor rotamer (2:1 ratio) are given in brackets.

Ketone 18[17]

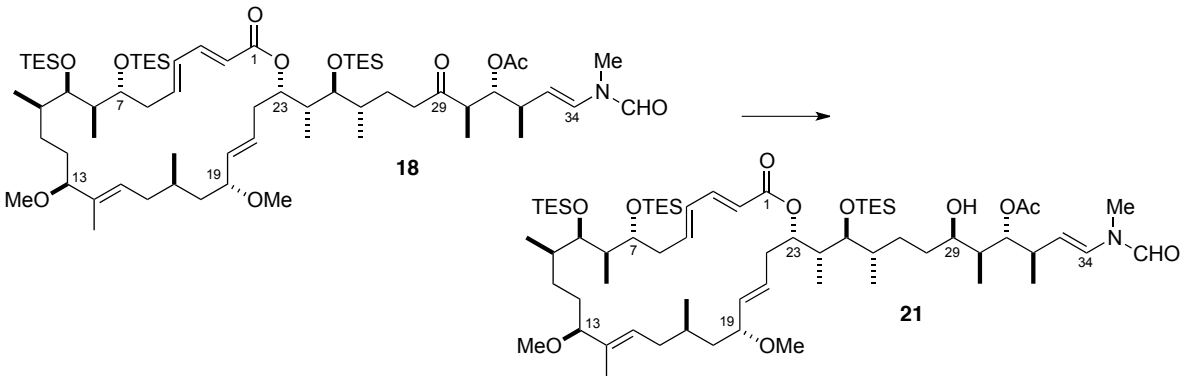


A solution of $[CuH{\cdot}PPh_3]_6$ (4.0 mg, 33 μmol) in degassed wet toluene (400 μL, 99:1 PhMe/H_2O; degassed by 6 freeze/pump/thaw cycles) was added to a flask containing enone **34** (4.0 mg, 33 μmol) *via* cannula, taking care to rigorously exclude oxygen. The bright red reaction mixture was stirred at room temperature for 3 h, after which $NaHCO_3$ (2 mL, sat. aq.) was added and the mixture stirred open to air for 30 min. The mixture was diluted with Et_2O (3 mL). The aqueous phase was subsequently extracted with EtOAc (6 × 3 mL), and the combined organics dried over $MgSO_4$ and concentrated *in vacuo*. The crude was purified by flash chromatography (10 → 15% acetone/PE, Florisil) to provide the product with triphenylphosphine oxide as a contaminant. Further purification by preparative TLC (30% EtOAc/CH_2Cl_2) provided ketone **18** (3.9 mg, 98%) as a colorless oil.

$\mathbf{R}_f$ 0.26 (20% EtOAc/CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 8.29 (0.67H, s), [8.08] (0.33H, s), 7.20 (1H, dd, *J* = 15.3, 10.4 Hz), [7.16] (0.33H, d, *J* = 14.4 Hz), 6.49 (0.67H, d, *J* = 14.0 Hz), 6.22 (1H, ddd, *J* = 14.7, 9.4, 4.1 Hz), 6.14 (1H, dd, *J* = 15.2, 10.6 Hz), 5.82 (1H, d, *J* = 15.3 Hz), 5.56 (1H, ddd, *J* = 14.9, 6.9, 6.9 Hz), 5.32–5.27 (1H, m), [5.14] (0.33H, dd, *J* = 9.1, 3.3 Hz), 5.13 (0.67H, dd, *J* = 8.7, 3.8 Hz), 5.06–4.99 (2H, m), 4.98 (1H, dd, *J* = 14.0, 9.4 Hz), 3.61 (1H, dd, *J* = 7.9, 3.8 Hz), 3.50 (1H, ddd, *J* = 13.4, 10.2, 4.3 Hz), 3.42 (3H, m), 3.19 (3H, s), 3.16 (3H, s), [3.07] (1H, s), 3.03 (2H, s), 2.78 (0.67H, dq, *J* = 8.8, 7.2 Hz), [2.75] (0.33H, dq, *J* = 9.0, 7.1 Hz),

2.58–2.36 (3H, m), 2.34 (2H, m), 2.30–2.22 (1H, m), 2.01 (2H, s), [2.00] (1H, s), 2.00–1.91 (2H, m), 1.80–1.45 (9H, m), 1.42 (3H, s), 1.33–1.18 (3H, m), 1.10 (2H, obs), 1.06 (3H, d, J = 7.0 Hz), 1.05 (2H, d, J = 6.9 Hz), [1.04] (1H, d, J = 6.9 Hz), 0.95 (30H, m), 0.93 (3H, obs), 0.90 (3H, d, J = 6.9 Hz), 0.89 (3H, d, J = 6.6 Hz), 0.80 (3H, d, J = 5.8 Hz), 0.67–0.54 (18H, m); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C [211.7], 211.6, [170.0], 170.0, 166.1, 162.1, [160.9], 144.2, 142.0, 134.1, 132.8, 131.4, 129.7, 129.6, 129.5, [125.5], 120.5, [112.2], 110.5, 87.5, 81.6, 79.3, 77.2, 77.2, 72.6, 71.7, [71.7], 55.6, 55.6, [48.8], 48.5, 42.6, 42.2, 40.8, 40.5, 40.1, [39.8], 38.7, [37.0], 36.9, 36.2, 36.1, [33.0], 30.8, 29.6 (2C), 27.6, 25.0, [24.9], 23.8, 20.8, [20.8], 20.0, [18.8], 17.5, [17.3], 17.0, 14.6, 13.3, [13.3], 12.0, 11.5, 9.6, 7.1, 7.1, 7.0, 5.4, 5.4, 5.2; $[\alpha]_D^{22}$ +37.5 (*c* 0.93, $CHCl_3$); **IR** (thin film) ν_{max} (cm^{-1}) 2958, 2937, 2911, 2870, 1737, 1707, 1701, 1659, 1456, 1378, 1233, 1092, 1070, 1049, 1004, 968, 736; **HRMS** calc. for $C_{66}H_{125}O_{11}N_2Si_3$ $[M+NH_4]^+$ 1205.8586, found 1205.8582. Distinguishable resonances of the minor rotamer (2:1 ratio) are given in brackets.

Alcohol 21

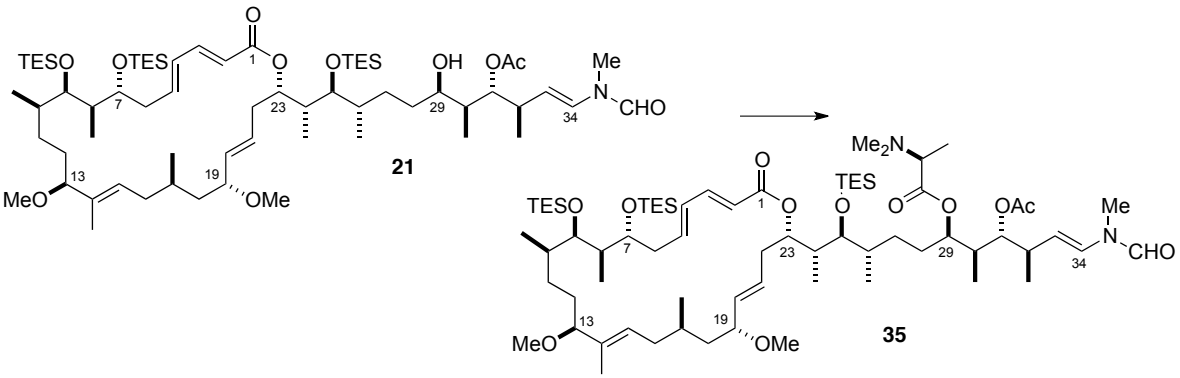


To a solution of ketone **18** (1.9 mg, 16 μmol) in Et_2O (100 μL) at 0 °C was added zinc borohydride (100 μL, 0.15 M in Et_2O, 0.15 mmol). The reaction mixture was stirred at 0 °C for 7 h and then quenched with Na/K tartrate (4 mL, sat. aq.). The biphasic mixture was stirred rapidly for 1 h. The mixture was diluted with Et_2O (4 mL) and the phases separated. The aqueous phase was extracted with EtOAc (4 × 3 mL). The combined organics were subsequently dried over $MgSO_4$ and concentrated *in vacuo*. The crude was purified by flash chromatography (30% EtOAc/CH_2Cl_2) to provide alcohol **21** (1.7 mg, 90%, 10:1 *dr*) as a colorless oil.

$\mathbf{R}_f$ 0.29 (30% EtOAc/PE); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 8.29 (0.67H, s), [8.08] (0.33H, s), 7.21 (1H, dd, J = 15.6, 10.5 Hz), [7.17] (0.33H, d, J = 15.0 Hz), 6.51 (0.67H, d, J = 14.1 Hz), 6.22 (1H, ddd, J = 15.0, 9.4, 4.2 Hz), 6.14 (1H, dd, J = 14.7, 10.7 Hz), 5.82 (1H, d, J = 15.3 Hz), 5.57 (1H, ddd, J = 14.9, 4.8, 4.8 Hz), 5.32–5.28 (1H, m), 5.06–4.98 (3H, m), 4.83 (0.67H, dd, J = 9.7, 3.1 Hz), [4.81] (0.33H, dd, J = 9.0, 3.8 Hz), 3.61 (1H, br dd, J = 8.4, 3.9 Hz), 3.50 (1H, ddd, J = 10.0, 10.0, 4.3 Hz), 3.46–3.35 (4H, m), 3.20 (3H, s), 3.16 (3H, s), [3.06] (1H, s), 3.02 (2H, s), [2.64–2.59] (0.33H, m), 2.59–2.54 (0.67H, m), 2.53 (0.67H, d, J = 4.3 Hz), [2.52] (0.33H, d, J = 3.6 Hz), 2.39–2.30 (2H, m), 2.30–2.23 (1H, m), 2.16 (2H, s), [2.15] (1H, s), 2.02–1.90 (2H, m), 1.81–1.74 (1H, m), 1.74–1.47 (9H, m), 1.47–1.35 (3H, m), 1.42 (3H, s), 1.29–1.15 (2H, m), 1.11 (2H, obs), 1.06 (2H, d, J = 6.9 Hz), [1.05] (1H, d, J = 6.7 Hz), 0.95 (30H, m), 0.92 (3H, d, J = 7.0 Hz), 0.90 (3H, d, J = 7.0 Hz), 0.89 (3H, obs), 0.89 (3H, d, J = 6.6 Hz), 0.80 (3H, d, J = 5.9 Hz), 0.67–0.54 (18H, m); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 172.4, [172.4], 166.1, 162.1, [160.9], 144.2, 142.0, 134.0, 132.7, 131.6, 129.7, 129.6, 129.4, [125.5], 120.5, [112.0],

110.2, 87.4, 81.6, 79.5, 79.5, 79.3, 72.6, [71.8], 71.8, [70.2], 70.1, 55.6, 55.6, 42.6, 42.0, 40.4, [39.6], 39.6, 38.7, [37.1], 37.1, 36.8, [36.4], 36.3, 33.0, 32.3, 30.8, [29.7], 29.6 (2C), 28.3, 27.5, 23.8, 20.9, 20.9, [20.8], 20.0, 19.4, [19.3], 17.0, [17.0], 14.5, [12.4], 12.4, 9.6, [8.4], 8.4, 7.2, 7.1, 7.0, 5.4, 5.4, 5.2; $[\alpha]_D^{22}$ +25.4 (*c* 0.20, $CHCl_3$); **IR** (thin film) ν_{max} (cm^{-1}) 3438, 2953, 2876, 1718, 1699, 1658, 1458, 1414, 1378, 1301, 1239, 1173, 1134, 1078, 1005, 970, 808, 740; **HRMS** calc. for $C_{66}H_{127}O_{11}N_2Si_3$ $[M+NH_4]^+$ 1207.8737, found 1207.8742. Distinguishable resonances of the minor rotamer (2:1 ratio) are given in brackets.

(*S*)-*N*,*N*-Dimethylalanine ester 35[18]



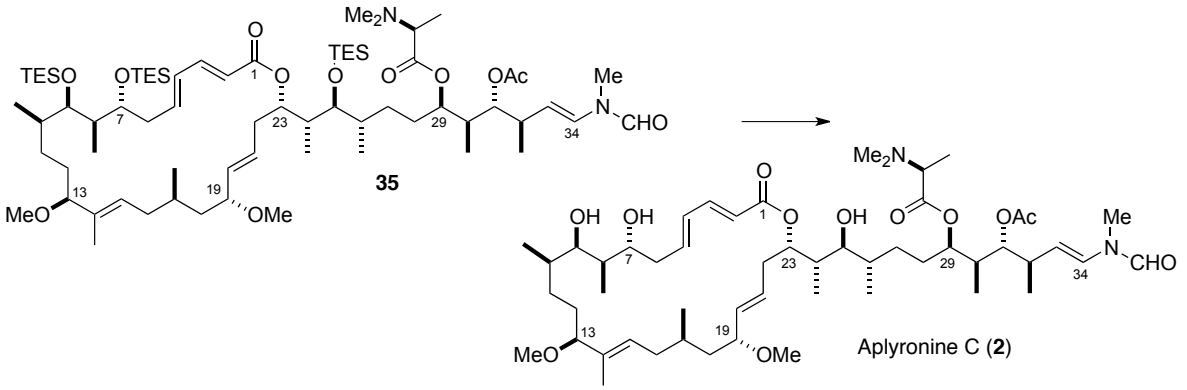
To a mixture of alcohol **21** (1.0 mg, 0.84 μmol), (*S*)-dimethylalanine (2.2 mg, 19 μmol), DMAP (5.6 mg, 50 μmol), and CSA (4.5 mg, 19 μmol) was added a solution of DCC (0.20 M CH_2Cl_2, in 100 μL, 20 μmol). The reaction mixture was stirred at room temperature for 11 h, during which the clear, colorless solution became a cloudy off-white suspension. Upon completion, the reaction was quenched with $NaHCO_3$ (2 mL, sat. aq.). The mixture was diluted with EtOAc (2 mL), and then the aqueous phase was extracted with EtOAc (5 × 2 mL). The combined organics were subsequently dried over $MgSO_4$ and concentrated *in vacuo* to a white solid. The crude was taken up in Et_2O (1 mL) and filtered through a small plug of cotton, washing the residue with Et_2O (4 mL). The filtrate and washings were concentrated *in vacuo*, then purified by flash chromatography (10% EtOAc/CH_2Cl_2, then 5% MeOH/CH_2Cl_2) to afford dimethylalanine ester **35** (0.8 mg, 74%) as a colorless amorphous solid.

R_f 0.16 (5% MeOH/CH_2Cl_2); **^{1}H NMR** (500 MHz, *d*6-acetone) δ_H 8.37 (0.67H, s), [8.11] (0.33H, s), 7.23 (1H, dd, *J* = 15.2 10.6 Hz), [7.16] (0.33H, d, *J* = 14.5 Hz), 6.86 (0.67H, d, *J* = 14.2 Hz), 6.39 (1H, dd, *J* = 15.3, 10.9 Hz), 6.31 (1H, ddd, *J* = 15.2, 9.5, 4.3 Hz), 5.95 (1H, d, *J* = 15.3 Hz), 5.59 (1H, ddd, *J* = 14.9, 9.2, 5.6 Hz), 5.37–5.33 (1H, m), 5.16 (1H, br dd, *J* = 10.4, 3.8 Hz), [5.09] (0.33H, dd, *J* = 14.5, 9.4 Hz), 5.04 (0.67H, dd, *J* = 14.1, 9.5 Hz), 5.04–4.96 (2H, m), [4.81] (0.33H, dd, *J* = 10.0, 2.3 Hz), 4.81 (0.67H, dd, *J* = 10.1, 2.6 Hz), 3.76–3.71 (1H, m), 3.61–3.55 (1H, m), 3.50 (1H, ddd, *J* = 10.0, 5.3, 2.7 Hz), 3.49–3.43 (2H, m), [3.20] (0.33H, q, *J* = 7.2 Hz), 3.19 (0.67H, q, *J* = 7.2 Hz), 3.12 (3H, s), 3.12 (3H, s), [3.09] (1H, s), 2.97 (2H, s), [2.71–2.67] (0.33H, m), 2.68–2.62 (0.67H, m), 2.41–2.35 (2H, m), [2.34] (2H, s), 2.33 (4H, s), 2.30–2.24 (1H, m), 2.20–2.14 (1H, m), 2.06 (3H, obs), 2.03–1.90 (2H, m), 1.84–1.58 (6H, m), 1.58–1.44 (4H, m), 1.45 (3H, s), 1.36–1.26 (4H, m), [1.26] (1H, d, *J* = 7.2 Hz), 1.26 (2H, d, *J* = 7.1 Hz), 1.24–1.15 (1H, m), 1.12–1.04 (1H, m), 1.01 (2H, d, *J* = 7.2 Hz), [1.00] (1H, obs), 1.00 (3H, d, *J* = 6.5 Hz), 1.00–0.96 (36H, m), 0.96 (3H, d, *J* = 6.8 Hz), 0.82 (3H, d, *J* =

[18] Kigoshi, H.; Ojika, M.; Ishigaki, T.; Suenaga, K.; Mutou, T.; Sakakura, A.; Ogawa, T.; Yamada, K. *J. Am. Chem. Soc.* **1994**, *116*, 7443.

6.4 Hz), 0.74–0.61 (18H, m); **^{13}C NMR** (125 MHz, *d*6-acetone) δ_C 172.8, [172.8], 170.8, [170.8], 166.7, 163.0, [161.8], 145.1, 142.4, 135.0, 133.9, 132.3, 131.2 (2C), 130.6, [126.4], 121.9, [112.0], 109.9, 88.1, 82.3, 80.4, 80.3, 77.4 (2C), [77.3], 72.8, 72.4, 63.6, [62.9], 55.6, 55.6, 43.2, 41.4, 39.3, 37.9, [37.9], 37.8, 37.7, 37.2, [37.2], 37.0, 36.9, [33.1], [30.9], 30.7, 30.5, 29.3, 27.9, [27.9], 27.4, 21.1, 20.6, 20.1, [20.0], 17.5, 16.0, 12.5, 12.2, 10.0, [9.9], 9.9, 7.6, 7.5, 7.5, 6.2, 6.1, 6.0, 4C obscured; $[\alpha]_D^{22}$ +29.8 (*c* 0.35, $CHCl_3$); **IR** (thin film) ν_{max} (cm^{-1}) 2951, 2886, 1714, 1700, 1660, 1459, 1378, 1234, 1080, 736; **HRMS** calc. for $C_{71}H_{133}O_{12}N_2Si_3$ $[M+H]^+$ 1289.9161, found 1289.9149. Distinguishable resonances of the minor rotamer (2:1 ratio) are given in brackets.

Aplyronine C (2)[18]

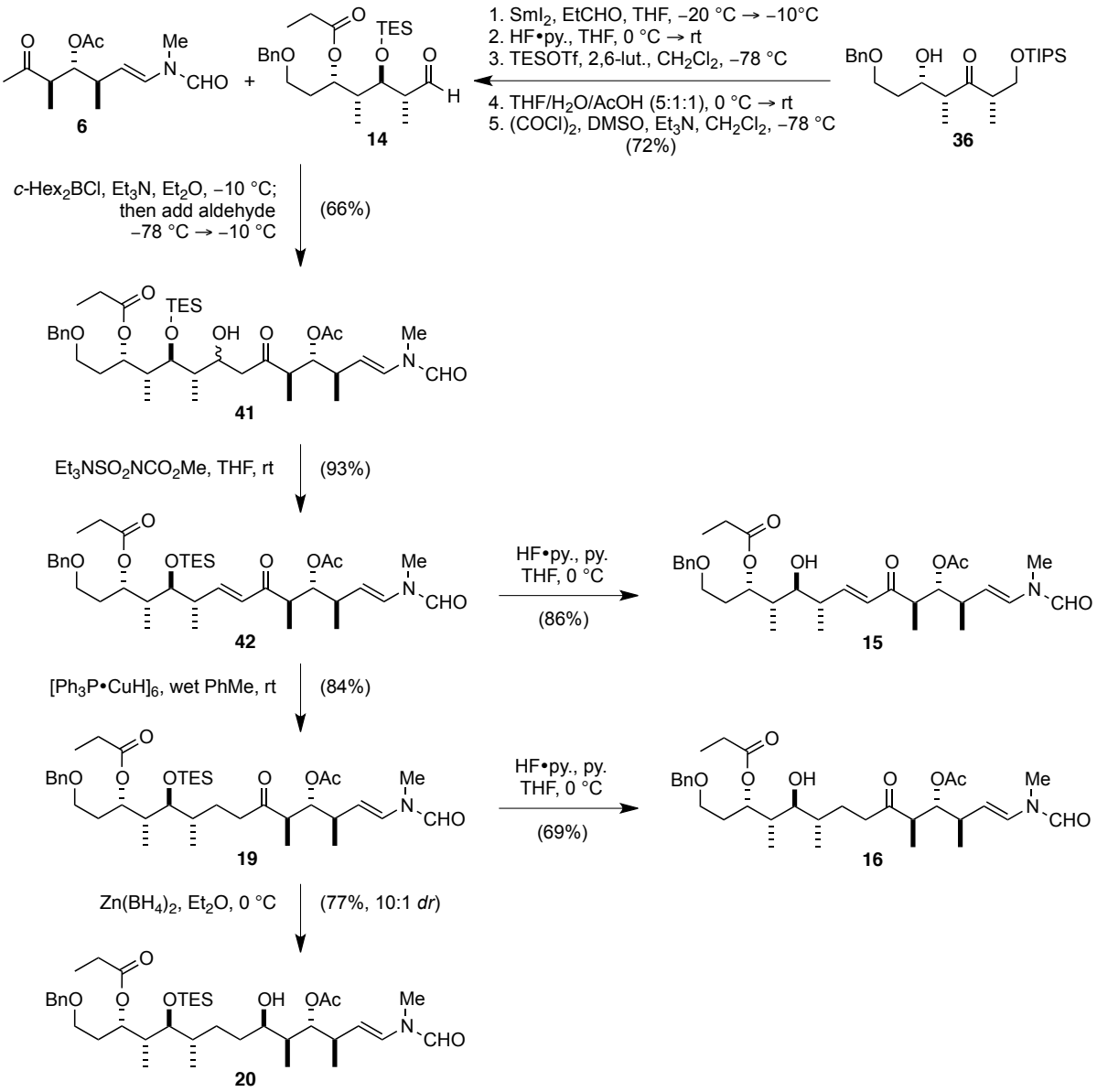


HF·pyridine (100 μL, 70% HF) was added to pyridine (0.30 mL) in a Teflon vessel at 0 °C. The solution was stirred for 30 min and then added to a solution of *tris*-TES ether **35** (3.7 mg, 2.87 μmol) in THF (100 μL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 6 h. Upon completion, the reaction was diluted with EtOAc (2 mL) and quenched by pipetting carefully onto rapidly stirring $NaHCO_3$ (15 mL, sat. aq.) at 0 °C. The aqueous phase was extracted with EtOAc (4 × 5 mL). The combined organics were subsequently dried over $MgSO_4$ and concentrated *in vacuo*. The crude was purified by flash chromatography (1 → 10% MeOH/CH_2Cl_2) and then by preparative TLC (15% MeOH/CH_2Cl_2) to afford aplyronine C (**2**; 2.4 mg, 89%) as a colorless amorphous solid.

R_f 0.26 (10% MeOH/CH_2Cl_2); **^{1}H NMR** (500 MHz, *d*6-acetone) δ_H 8.37 (0.67H, s), [8.10] (0.33H, s), 7.26 (1H, dd, *J* = 15.3 10.3 Hz), [7.15] (0.33H, d, *J* = 14.5 Hz), 6.85 (0.67H, d, *J* = 14.0 Hz), 6.42 (1H, ddd, *J* = 15.2, 9.0, 4.9 Hz), 6.37 (1H, dd, *J* = 15.4, 9.7 Hz), 5.93 (1H, d, *J* = 15.4 Hz), 5.62 (1H, ddd, *J* = 15.2, 10.3, 3.9 Hz), 5.47 (1H, br d, *J* = 10.9 Hz), 5.21 (1H, br dd, *J* = 10.9, 4.7 Hz), [5.10] (0.33H, dd, *J* = 14.8, 9.5 Hz), 5.05 (0.67H, dd, *J* = 14.1, 9.5 Hz), 5.03–5.01 (1H, m), 4.99 (1H, dd, *J* = 15.3, 9.2 Hz), [4.81] (0.33H, dd, *J* = 10.0, 3.2 Hz), 4.80 (0.67H, dd, *J* = 10.1, 2.7 Hz), 3.81 (1H, br s), 3.69–3.64 (1H, m), 3.64–3.58 (1H, m), 3.55–3.45 (2H, m), 3.42–3.39 (1H, m), 3.39 (1H, br s), [3.21] (0.33H, q, *J* = 7.1 Hz), 3.20 (0.67H, q, *J* = 7.1 Hz), 3.12 (3H, s), 3.11 (3H, s), [3.09] (1H, s), 3.07–3.03 (1H, m), 2.97 (2H, s), [2.72–2.67] (0.33H, m), 2.69–2.61 (0.67H, m), 2.49–2.40 (1H, m), 2.34 (6H, s), 2.31–2.26 (1H, m), 2.26–2.21 (1H, m), 2.19–2.16 (1H, m), 2.09 (2H, s), [2.09] (1H, s), 2.00–1.94 (1H, m), 1.93–1.91 (1H, m), 1.82–1.78 (1H, m), 1.76–1.68 (3H, m), 1.68–1.62 (2H, m), 1.62–1.55 (3H, m), 1.55–1.50 (1H, m), 1.43 (3H, s), 1.39–1.33 (1H, m), [1.26] (1H, d, *J* = 7.3 Hz), 1.26 (2H, d, *J* = 7.1 Hz), 1.23–1.13 (5H, m), 1.00 (3H, d, *J* = 6.5 Hz), 1.00 (6H, d, *J* = 6.9 Hz), 0.98 (3H, d, *J* = 7.4 Hz), 0.97 (3H, d, *J* = 6.9 Hz), 0.89 (3H, d, *J* = 7.0 Hz), 0.78 (3H, d, *J* = 6.4 Hz); **^{13}C NMR** (125 MHz, *d*6-acetone) δ_C 172.8, 170.9,

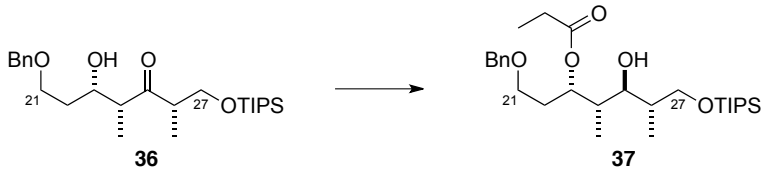
[170.8], 167.9, 163.1, [161.9], 145.9, 143.7, 134.9, 133.4, 133.0, 131.2, 130.9, 130.8, [126.4], 120.7, [112.1], 110.0, 87.1, 82.3, 77.5, [77.4], 77.3, 77.0, 73.4, 72.9, 72.8, 63.6, [62.9], 55.7, 55.5, 42.0, 41.9, 41.7, 41.4, 38.2 (2C), [37.9], 37.7, 37.5, 36.7, 34.8, 34.2, [33.1], [30.9], 30.7, 30.5, 29.3, 27.4, 25.3, 24.4, 21.1, 20.3, 20.0, [20.0], 18.0, 16.5, 16.0, [15.3], 11.9, 10.7, 10.2, 10.1, [10.0]; $[\alpha]_D^{21}$ +16.8 (*c* 0.08, MeOH), lit. $[\alpha]_D^{27}$ +18 (*c* 0.017, MeOH); **IR** (thin film) ν_{max} (cm^{-1}) 3478, 2952, 2925, 2856, 1740, 1724, 1694, 1656, 1458, 1376, 1300, 1239, 1171, 1092, 1081, 1017, 974, 818, 729; **HRMS** calc. for $C_{53}H_{91}O_{12}N_2$ $[M+H]^+$ 947.6567, found 947.6560. Distinguishable resonances of the minor rotamer (2:1 ratio) are given in brackets.

4. Experimental details: Model system and side chain analogs



Scheme S1. Model system and synthesis of side chain analogs **15** and **16**

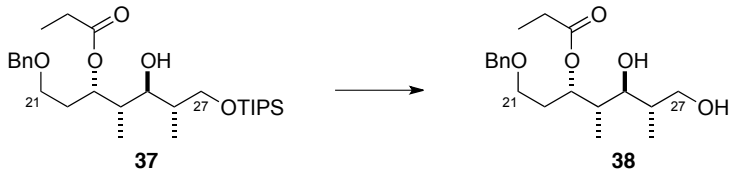
Alcohol 37



To a solution of freshly distilled propionaldehyde (6.15 mL, 85.2 mmol) in anhydrous THF (50 mL) at –20 °C was added freshly prepared SmI_2 (18.9 mL, *ca.* 0.15 M in THF, 2.84 mmol) slowly; the blue coloring of SmI_2 disappeared to form a bright yellow solution. After stirring for 10 min, a solution of aldol adduct **36**[19] (6.20 g, 14.2 mmol, 6:1 *dr*) in THF (50 mL) was added dropwise. The reaction mixture was warmed to –10 °C over 1 h. Upon completion, the reaction was quenched with $NaHCO_3$ (50 mL, sat. aq.) and warmed to room temperature. The mixture was extracted with Et_2O (2 × 50 mL) and CH_2Cl_2 (4 × 30 mL). The combined organics were subsequently dried over $MgSO_4$ and concentrated *in vacuo*. The crude was purified by flash chromatography (2 → 5% EtOAc/PE) to afford alcohol **37** as a yellow oil (6.38 g, 91%, 6:1 *dr* from starting material). The product was carried forward as an inseparable mixture of diastereomers.

R_f 0.44 (20% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.28–7.24 (4H, m), 7.24–7.17 (1H, m), 5.45 (1H, ddd, *J* = 9.0, 4.3, 1.8 Hz), 4.41 (2H, s), 3.73–3.71 (2H, m), 3.52 (1H, d, *J* = 5.8Hz), 3.43 (2H, dd, *J* = 7.1, 6.3 Hz), 3.13 (1H, ddd, *J* = 8.5, 5.8, 4.0 Hz), 2.25 (1H, dq, *J* = 16.0, 7.6 Hz), 2.20 (1H, dq, *J* = 16.0, 7.5 Hz), 2.04–1.93 (1H, m), 1.92–1.85 (1H, m), 1.86–1.78 (1H, m), 1.79–1.70 (1H, m), 1.05 (3H, t, *J* = 7.6 Hz), 1.02–0.98 (21H, m), 0.98 (3H, obs), 0.89 (3H, d, *J* = 7.0 Hz); **^{13}C NMR** (100 MHz, C_6D_6) δ_C 174.9, 139.2, 128.2, 128.0, 127.7, 77.0, 71.3, 67.3, 66.0, 41.1, 37.5, 33.8, 27.9, 18.3, 18.3, 16.2, 12.3, 10.9, 9.4; $[\alpha]_D^{20}$ –5.6 (*c* 2.00, $CHCl_3$); **IR** (thin film) ν_{max} (cm^{-1}) 3499, 2942, 2866, 1715, 1462, 1383, 1364, 1277, 1200, 1084, 995, 920, 882, 800, 735, 682, 659; **HRMS** calc. for $C_{28}H_{51}O_5Si$ $[M+H]^+$ 495.3500, found 495.3497.

Diol 38



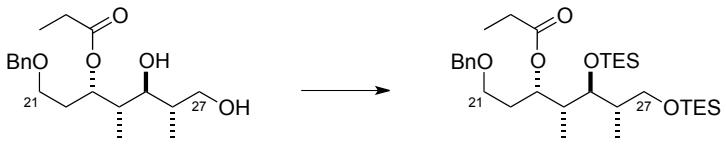
To a solution of TIPS ether **37** (770 mg, 1.61 mmol) in THF (28 mL) at 0 °C was added HF·pyridine (2.00 mL, 70% HF). The reaction mixture was warmed to room temperature and stirred for 6 h. Upon completion, the reaction mixture was diluted with EtOAc (20 mL) and pipetted slowly onto a stirred solution of $NaHCO_3$ (100 mL, sat. aq.) at 0 °C. The aqueous phase was extracted with Et_2O (2 × 50 mL) and EtOAc (4 × 30 mL). The combined organics were subsequently dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (30 → 50% EtOAc/PE) afforded diol **38** (488 mg, 94%) as a colorless oil.

R_f 0.22 (50% EtOAc/PE); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.37–7.24 (5H, m), 5.45 (1H, ddd, *J* = 9.5, 3.6, 1.6 Hz), 4.50 (1H, d, *J* = 11.8 Hz), 4.45 (1H, d, *J* = 11.9 Hz), 3.95 (1H, d, *J* = 4.6 Hz), 3.87 (1H, app dt, *J* = 11.1,

[19] Paterson, I.; Cowden, C. J.; Woodrow, M. D. *Tetrahedron Lett.* **1998**, *39*, 6037.

2.8 Hz), 3.55 (1H, ddd, *J* = 11.9, 7.6, 4.7 Hz), 3.50–3.41 (2H, m), 3.13 (1H, ddd, *J* = 9.4, 4.7, 3.2 Hz), 2.94 (1H, br d, *J* = 7.6 Hz), 2.32 (1H, dq, *J* = 14.6, 7.6 Hz), 2.27 (1H, dq, *J* = 14.6, 7.5 Hz), 2.07–1.97 (1H, m), 1.88–1.75 (3H, m), 1.13 (3H, d, *J* = 6.9 Hz), 1.11 (3H, t, *J* = 7.6 Hz), 0.86 (3H, d, *J* = 7.0 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 175.9, 138.1, 128.3, 127.7, 127.6, 77.6, 73.1, 71.2, 66.8, 64.4, 41.1, 35.2, 33.0, 27.7, 15.8, 10.0, 9.2; $[\alpha]_D^{20}$ –15.8 (*c* 1.00, $CHCl_3$); **IR** (thin film) ν_{max} (cm^{-1}) 3443, 2974, 2876, 1713, 1455, 1363, 1278, 1203, 1079, 1028, 978, 738, 699; **HRMS** calc. for $C_{19}H_{30}O_5Na$ $[M+Na]^+$ 361.1985, found 361.1992.

***Bis*-TES ether 39**

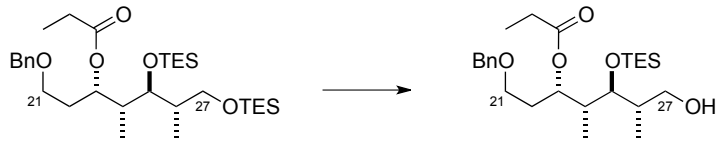


38 **39**

To a solution of diol **38** (590 mg, 1.83 mmol) in CH_2Cl_2 (9.0 mL) at –78 °C was added 2,6-lutidine (1.07 mL, 9.15 mmol) and TESOTf (1.03 mL, 4.57 mmol). The reaction mixture was stirred at –78 °C for 60 min. Upon completion, the reaction was quenched with $NaHCO_3$ (7 mL, sat. aq.) and warmed to room temperature. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organics were subsequently dried over $MgSO_4$ and concentrated *in vacuo*. The crude was purified by flash chromatography (PE → 8% EtOAc/PE) to afford *bis*-TES ether **39** (987 mg, 93%) as a colorless oil.

R_f 0.17 (5% EtOAc/PE); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.34–7.31 (4H, m), 7.29–7.25 (1H, m), 5.21 (1H, ddd, *J* = 7.5, 5.3, 3.3 Hz), 4.49 (1H, d, *J* = 11.6 Hz), 4.45 (1H, d, *J* = 11.8 Hz), 3.69 (1H, dd, *J* = 9.9, 5.3 Hz), 3.54 (1H, dd, *J* = 6.6, 4.1 Hz), 3.51–3.45 (2H, m), 3.39 (1H, dd, *J* = 9.8, 7.6 Hz), 2.27 (2H, q, *J* = 7.7 Hz), 1.99–1.89 (2H, m), 1.89–1.79 (2H, m), 1.10 (3H, t, *J* = 7.6 Hz), 0.98–0.91 (24H, m), 0.61 (6H, q, *J* = 8.2 Hz), 0.58 (6H, q, *J* = 8.2 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 173.9, 138.4, 128.3, 127.6, 127.4, 76.6, 73.0, 71.8, 67.5, 64.2, 41.1, 39.2, 33.6, 27.9, 15.1, 11.2, 9.2, 7.1, 6.8, 5.4, 4.4; $[\alpha]_D^{20}$ –12.7 (*c* 1.00, $CHCl_3$); **IR** (thin film) ν_{max} (cm^{-1}) 2955, 2876, 1735, 1458, 1362, 1190, 1087, 1005, 808, 732, 697; **HRMS** calc. for $C_{31}H_{62}O_5Si_2Na$ $[M+NH_4]^+$ 584.4161, found 584.4159.

Alcohol 40



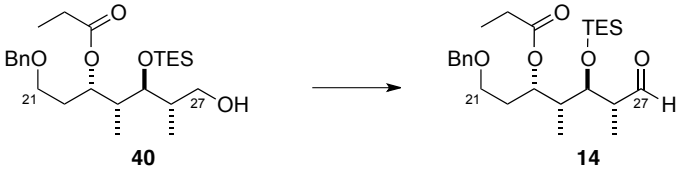
39 **40**

To a solution of *bis*-TES ether **39** (1.00 g, 1.82 mmol) in THF (300 mL) at 0 °C was added water (60 mL) followed by glacial acetic acid (60 mL). The reaction mixture was warmed to room temperature and stirred for 3 h, then cooled back to 0 °C and quenched carefully with $NaHCO_3$ until the pH neutralized and bubbling ceased. The mixture was extracted with Et_2O (4 × 100 mL) and CH_2Cl_2 (4 × 75 mL). The combined organics were

subsequently washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude was purified by flash chromatography (8 → 15% EtOAc/PE) to afford alcohol **40** (714 mg, 92%) as a colorless oil.

R_f 0.23 (20% EtOAc/PE); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.35–7.30 (4H, m), 7.30–7.23 (1H, m), 5.14 (1H, ddd, *J* = 7.3, 5.4, 4.1 Hz), 4.49 (1H, d, *J* = 11.8 Hz), 4.45 (1H, d, *J* = 11.8 Hz), 3.75 (1H, ddd, *J* = 11.1, 4.3, 4.3 Hz), 3.65 (1H, dd, *J* = 6.4, 3.7 Hz), 3.57 (1H, ddd, *J* = 11.4, 6.4, 5.3 Hz), 3.53–3.42 (2H, m), 2.54 (1H, dd, *J* = 6.6, 4.8 Hz), 2.28 (2H, q, *J* = 7.6 Hz), 1.99–1.83 (4H, m), 1.11 (3H, t, *J* = 7.6 Hz), 1.04 (3H, t, *J* = 7.1 Hz), 0.96 (9H, t, *J* = 7.7 Hz), 0.96 (3H, obs), 0.65 (6H, q, *J* = 8.0 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 174.0, 138.3, 128.3, 127.7, 127.5, 79.1, 73.1, 71.9, 65.4, 61.5, 42.4, 36.4, 33.4, 27.9, 16.3, 10.4, 9.2, 6.9, 5.2; $[\alpha]_D^{22}$ –14.7 (*c* 1.50, $CHCl_3$); **IR** (thin film) ν_{max} (cm^{-1}) 3466, 2953, 1725; **HRMS** calc. for $C_{25}H_{45}O_5Si$ $[M+H]^+$ 453.3036, found 453.3030.

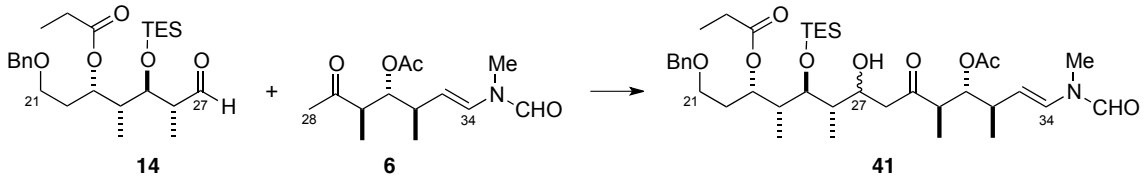
Aldehyde 14



To a solution of oxalyl chloride (81 μL, 0.95 mmol) in CH_2Cl_2 (4 mL) at –78 °C was added DMSO (136 μL, 1.91 mmol) dropwise. After stirring for 15 min, a solution of alcohol **40** (144 mg, 0.318 mol) in CH_2Cl_2 (3 mL) was added. The mixture was stirred for 30 min and then Et_3N (0.53 mL, 3.82 mmol) was added. The reaction mixture was stirred at –78 °C for 45 min before being quenched with NH_4Cl (10 mL, sat. aq.) and warmed to room temperature. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (4 × 8 mL). The combined organics were subsequently dried over $MgSO_4$ and concentrated *in vacuo*. The crude was filtered through a plug of Florisil, eluting with 2% EtOAc/PE, to afford aldehyde **14** (140 mg, 98%) as a colorless oil.

R_f 0.48 (20% EtOAc/PE); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 9.77 (1H, d, *J* = 1.9 Hz), 7.36–7.30 (4H, m), 7.30–7.24 (1H, m), 5.23 (1H, ddd, *J* = 8.4, 5.6, 3.1 Hz), 4.49 (1H, d, *J* = 11.9 Hz), 4.45 (1H, d, *J* = 12.0 Hz), 3.93 (1H, dd, *J* = 6.8, 2.7 Hz), 3.53–3.43 (2H, m), 2.60–2.53 (1H, m), 2.29 (2H, q, *J* = 7.6 Hz), 1.99–1.79 (3H, m), 1.12 (3H, t, *J* = 7.4 Hz), 1.12 (3H, d, *J* = 6.9 Hz), 0.94 (9H, t, *J* = 7.9 Hz), 0.88 (3H, d, *J* = 6.9 Hz), 0.61 (6H, q, *J* = 7.9 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 204.2, 174.0, 138.2, 128.3, 127.7, 127.5, 75.6, 73.1, 71.6, 67.2, 50.3, 41.9, 33.2, 27.9, 11.0, 10.1, 9.2, 6.9, 5.1; $[\alpha]_D^{22}$ –25.7 (*c* 1.40, $CHCl_3$); **IR** (thin film) ν_{max} (cm^{-1}) 2954, 1731; **HRMS** calc. for $C_{25}H_{46}NO_5Si$ $[M+NH_4]^+$ 468.3415, found 468.3417.

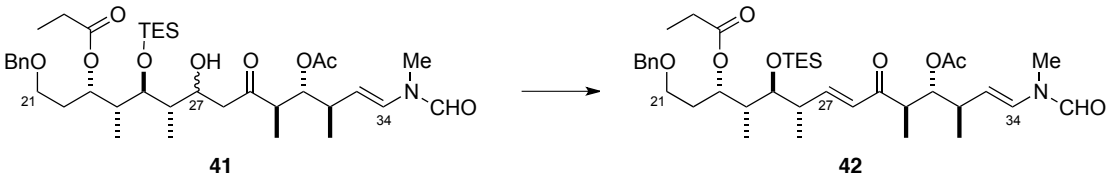
Aldol adduct 41



To a solution of dicyclohexylboron chloride (106 μL, 0.486 mmol) in anhydrous Et_2O (1.0 mL) at –78 °C was added Et_3N (134 μL, 0.974 mmol) followed by a solution of ketone **6** (138 mg, 0.540 mmol; pre-dried by azeotroping with benzene) in Et_2O (0.20 mL). The mixture was warmed to –10 °C and stirred for 90 min, during which the solution turned cloudy white. The enolate solution was cooled back to –78 °C and a solution of aldehyde **14** (98 mg, 0.216 mmol; dried by stirring over CaH_2) in Et_2O (0.30 mL) was added. The resulting mixture was slowly warmed to –10 °C over 4 h. Upon completion, the reaction mixture was poured onto stirring pH 7 buffer (10 mL) at 0 °C. Methanol (3 mL) was added and the mixture stirred for 30 min. The methanol was removed *in vacuo*, and the aqueous phase was subsequently extracted with EtOAc (7 × 5 mL). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. The crude was purified by flash chromatography (5 → 25% EtOAc/DCM, Florisil) to afford clean aldol adduct **41** (60 mg, 10:1 *dr*) plus a mixture of aldol adduct **41** and ketone **6** (71 mg, *ca.* 1:2.1 molar ratio by ^{1}H NMR analysis). The combined yield of aldol adduct **41** was 66%. Ketone **6** was carried through and separated after the subsequent step.

R_f 0.21 (20% EtOAc/CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 8.28 (0.67H, s), [8.08] (0.33H, s), 7.35–7.28 (4H, m), 7.28–7.23 (1H, m), [7.16] (0.33H, d, *J* = 14.6 Hz), 6.49 (0.67H, d, *J* = 13.9 Hz), 5.19–5.11 (2H, m), [4.98] (0.33H, dd, *J* = 14.7, 9.0 Hz), 4.96 (0.67H, dd, *J* = 14.1, 9.3 Hz), 4.48 (1H, d, *J* = 11.8 Hz), 4.46 (1H, d, *J* = 11.8 Hz), 4.14–4.07 (1H, m), 3.68 (1H, dd, *J* = 6.9, 3.5 Hz), 3.52–3.41 (2H, m), 3.14 (0.67H, d, *J* = 2.9 Hz), [3.11] (0.33H, d, *J* = 3.1 Hz), [3.06] (1H, s), 3.02 (2H, s), 2.84–2.72 (1H, m), 2.68 (1H, dd, *J* = 17.4, 2.3 Hz), 2.60–2.45 (2H, m), 2.28 (2H, q, *J* = 7.6 Hz), 2.00 (2H, s), [2.00] (1H, s), 1.98–1.79 (4H, m), 1.11 (3H, t, *J* = 7.7 Hz), 1.08 (2H, d, *J* = 7.2 Hz), [1.07] (1H, d, *J* = 7.2 Hz), 1.05 (2H, d, *J* = 6.9 Hz), [1.04] (1H, d, *J* = 6.9 Hz), 0.96 (3H, d, *J* = 7.0 Hz), 0.94 (9H, t, *J* = 7.9 Hz), 0.89 (3H, d, *J* = 7.1 Hz), 0.63 (6H, q, *J* = 7.7 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C [212.9], 212.7, 174.0, [170.2], 170.1, 162.1, [160.9], 138.3, 129.5, 128.3, 127.7, 127.5, [125.5], [111.9], 110.3, 77.2, 77.1, 73.1, 71.7, 68.3, [68.2], 67.3, [49.4], 49.1, 46.3, [45.9], 42.1, [42.0], [41.2], 41.1, 36.9, [36.9], 33.6, [33.0], [29.7], 27.9, 27.5, 20.9, 18.8, 13.7, [13.6], 13.1, 10.6, 9.2, 7.0, 5.2; $[\alpha]_D^{20}$ –49.0 (*c* 1.21, $CHCl_3$); **IR** (thin film) ν_{max} (cm^{-1}) 3470, 2958, 2876, 1732, 1695, 1655, 1456, 1374, 1319, 1231, 1192, 1073, 1008, 960, 821, 735, 699; **HRMS** calc. for $C_{38}H_{63}NO_9SiNa$ $[M+Na]^+$ 728.4170, found 728.4164. Distinguishable resonances of the minor rotamer (2:1 ratio) are given in brackets.

Enone 42

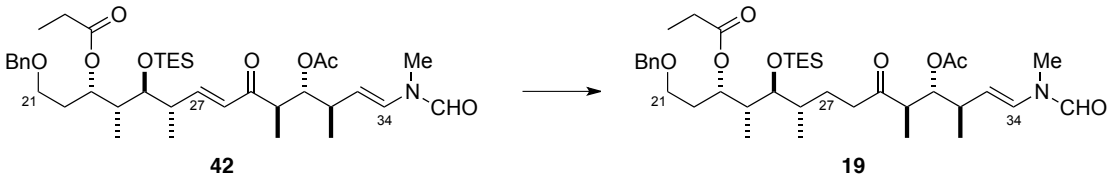


41 **42**

To a solution of aldol adduct **41** (*ca.* 55.0 mg, 0.0779 mmol) and ketone **6** (*ca.* 4.9 mg, 0.0195 mmol) in THF (0.50 mL) was added Burgess reagent (30 mg, 0.114 mmol). The reaction mixture was stirred at room temperature for 18 h and then quenched with NH_4Cl (3 mL, sat. aq.). The mixture was extracted with Et_2O (3 mL × 2) and EtOAc (6 × 3 mL). The combined organics were subsequently dried over $MgSO_4$ and concentrated *in vacuo*. Purification by preparative TLC (10% EtOAc/CH_2Cl_2) provided enone **42** (49.5 mg, 93%) and recovered ketone **6** as colorless oils.

R_f 0.24 (10% EtOAc/CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 8.28 (0.67H, s), [8.07] (0.33H, s), 7.34–7.29 (4H, m), 7.28–7.24 (1H, m), [7.16] (0.33H, d, *J* = 14.6 Hz), 7.00 (1H, dd, *J* = 15.8, 8.1 Hz), 6.49 (0.67H, d, *J* = 14.1 Hz), 6.17 (0.67H, d, *J* = 15.8 Hz), [6.16] (0.33H, d, *J* = 15.9 Hz), 5.20–5.15 (2H, m), [5.00] (0.33H, dd, *J* = 13.6, 9.5 Hz), 4.98 (0.67H, dd, *J* = 13.9, 9.4 Hz), 4.47 (1H, d, *J* = 11.8 Hz), 4.44 (1H, d, *J* = 11.8 Hz), 3.61–3.57 (1H, m), 3.50–3.40 (2H, m), [3.05] (1H, s), 3.02 (2H, s), 3.01–2.90 (1H, m), 2.61–2.52 (1H, m), [2.61–2.52] (0.33H, m), 2.52–2.46 (0.67H, m), 2.26 (2H, q, *J* = 7.6 Hz), 1.97 (2H, s), [1.96] (1H, s), 1.95–1.86 (1H, m), 1.84–1.76 (1H, m), 1.72 (1H, qd, *J* = 7.1, 3.5 Hz), 1.10 (3H, t, *J* = 7.6 Hz), 1.08 (3H, d, *J* = 6.8 Hz), 1.06 (2H, obs), [1.05] (1H, obs), 1.03 (2H, d, *J* = 6.9 Hz), [1.03] (1H, d, *J* = 7.0 Hz), 0.93 (9H, t, *J* = 7.9 Hz), 0.85 (3H, d, *J* = 7.0 Hz), 0.60 (6H, q, *J* = 7.8 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C [200.4], 200.3, 173.9, 170.1, [170.0], 162.1, [160.9], 150.3, [150.1], 138.2, 129.4, 128.3, 127.8, 127.7, 127.5, [125.4], [112.3], 110.7, 77.2, 77.1, 73.2, 71.6, [67.3], 67.2, [46.7], 46.5, 42.2, [42.1], [40.4], 40.3, [37.0], 36.9, 33.4, [33.0], 27.8, 27.5, 20.8, [19.7], 18.8, 17.7, [17.4], 13.4, 10.6, 9.2, 7.0, 5.3; **$[\alpha]_D^{20}$** –43.3 (*c* 0.40, $CHCl_3$); **IR** (thin film) ν_{max} (cm^{-1}) 2965, 1735, 1695, 1658, 1457, 1374, 1234, 1191, 1073, 1017, 739; **HRMS** calc. for $C_{38}H_{62}NO_8Si$ $[M+H]^+$ 688.4245, found 688.4240. Distinguishable resonances of the minor rotamer (2:1 ratio) are given in brackets.

Ketone 19



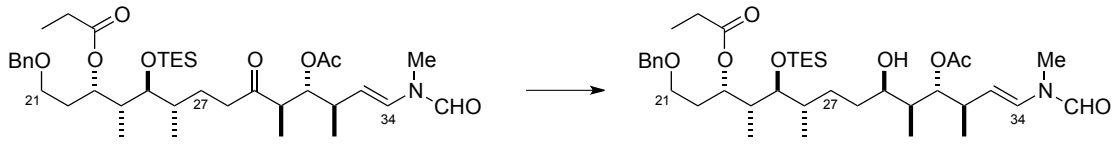
42 **19**

A solution of $[CuH{\cdot}PPh_3]_6$ (50.0 mg, 0.0255 mmol) in degassed wet toluene (9.0 mL, 99:1 PhMe/H_2O; degassed by bubbling argon for 1 h) was added to a flask containing enone **42** (67.5 mg, 0.0981 mmol) *via* cannula, taking care to rigorously exclude oxygen. The bright red reaction mixture was stirred at room temperature for 18 h, after which petroleum ether (10 mL) was added and the mixture stirred open to air for 30 min. The solution was filtered through celite and concentrated *in vacuo*. The crude residue was purified by flash chromatography

(5 → 20% EtOAc/CH_2Cl_2, Florisil) and fractions contaminated with triphenylphosphine oxide were further purified by preparative TLC (15% EtOAc/CH_2Cl_2) to provide ketone **19** (56.7 mg, 84%) as a colorless oil.

R*f* 0.25 (10% EtOAc/CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 8.28 (0.67H, s), [8.07] (0.33H, s), 7.37–7.29 (4H, m), 7.28–7.23 (1H, m), [7.16] (0.33H, d, *J* = 15.3 Hz), 6.48 (0.67H, d, *J* = 14.0 Hz), 5.18 (1H, app td, *J* = 5.7, 2.5 Hz), [5.14] (0.33H, obs), 5.13 (0.67H, dd, *J* = 8.8, 3.7 Hz), [4.99] (0.33H, dd, *J* = 14.5, 9.6 Hz), 4.97 (0.67H, dd, *J* = 14.0, 9.4 Hz), 4.48 (1H, d, *J* = 11.7 Hz), 4.44 (1H, d, *J* = 11.8 Hz), 3.52–3.42 (2H, m), 3.40 (1H, dd, *J* = 7.3, 2.7 Hz), [3.06] (1H, s), 3.02 (2H, s), 2.78 (0.67H, dq, *J* = 8.7, 7.1 Hz), [2.78] (0.33H, dq, *J* = 9.1, 6.9 Hz), 2.57–2.34 (3H, m), 2.26 (2H, q, *J* = 7.6 Hz), 1.99 (2H, s), [1.99] (1H, s), 1.98–1.91 (1H, m), 1.86–1.80 (1H, m), 1.80–1.74 (1H, m), 1.73– 1.65 (1H, m), 1.62–1.55 (1H, m), 1.35–1.25 (1H, m), 1.10 (3H, t, *J* = 7.6 Hz), 1.06 (3H, d, *J* = 7.3 Hz), 1.04 (2H, d, *J* = 7.0 Hz), [1.04] (1H, d, *J* = 6.9 Hz), 0.93 (9H, t, *J* = 7.9 Hz), 0.90 (6H, d, *J* = 7.1 Hz), 0.60 (6H, q, *J* = 7.7 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C [211.7], 211.6, 173.9, [170.0], 169.9, 162.1, [160.9], 138.4, 129.4, 128.3, 127.7, 127.4, [125.4], [112.1], 110.5, 78.6, 77.2, 73.0, 71.8, 67.5, [48.8], 48.5, 41.0, [41.0], 40.0, [39.7], [36.9], 36.8, 35.4, 33.5, [32.9], 27.9, 27.5, 24.0, [24.0], 20.8, 18.8, 17.2, [17.1], 13.3, 10.7, [10.7], 9.2, 7.1, 5.4; $[\alpha]_D^{21}$ –44.0 (*c* 2.01, $CHCl_3$); **IR** (thin film) ν_{max} (cm^{-1}) 2956, 2877, 1733, 1698, 1658, 1457, 1373, 1233, 1192, 1072, 1016, 978, 819, 739; **HRMS** calc. for $C_{38}H_{64}NO_8Si$ $[M+H]^+$ 690.4415, found 690.4401. Distinguishable resonances of the minor rotamer (2:1 ratio) are given in brackets.

Alcohol 20

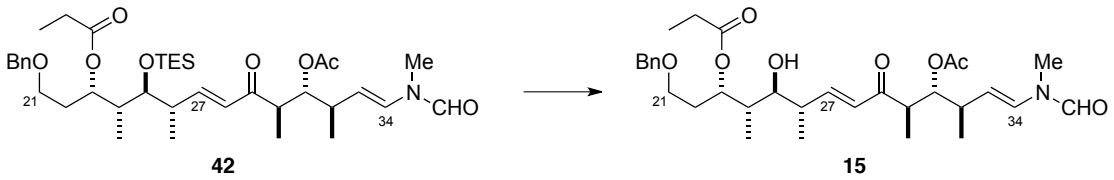


To a solution of ketone **19** (13.0 mg, 0.0188 mmol) in Et_2O (0.10 mL) at 0 °C was added zinc borohydride (1.25 mL, 0.15 M in Et_2O, 0.188 mmol). The reaction mixture was stirred at 0 °C for 8 h and then quenched with Na/K tartrate (4 mL, sat. aq.). The biphasic mixture was stirred rapidly for 1 h. The aqueous phase was then extracted with Et_2O (5 mL) and EtOAc (4 × 5 mL). The combined organics were subsequently dried over $MgSO_4$ and concentrated *in vacuo*. The crude was purified by flash chromatography (20% EtOAc/CH_2Cl_2) to provide alcohol **20** (10 mg, 77%, 10:1 *dr*) as a colorless oil.

R$_f$ 0.25 (20%EtOAc/CH_2Cl_2); **^{1}H NMR** (500MHz, $CDCl_3$) δ_H 8.29 (0.67H, s), [8.06] (0.33H, s), 7.35–7.31 (4H, m), 7.29–7.25 (1H, m), [7.18] (0.33H, d, *J* = 14.5 Hz), 6.50 (0.67H, d, *J* = 14.0 Hz), 5.19 (1H, ddd, *J* = 5.6, 5.6, 2.4 Hz), [5.03] (0.33H, dd, *J* = 14.6, 9.8 Hz), 5.01 (0.67H, dd, *J* = 14.2, 9.3 Hz), [4.85] (0.33H, dd, *J* = 8.5, 3.9 Hz), 4.82 (0.67H, dd, *J* = 10.0, 3.3 Hz), 4.49 (1H, d, *J* = 11.9 Hz), 4.45 (1H, d, *J* = 11.8 Hz), 3.52–3.45 (2H, m), 3.45–3.40 (1H, m), 3.39 (1H, dd, *J* = 7.5, 2.6 Hz), [3.04] (1H, s), 3.02 (2H, s), [2.64–2.58] (0.33H, m), 2.60–2.53 (0.67H, m), 2.53 (1H, br s), 2.26 (2H, q, *J* = 7.6 Hz), 2.15 (2H, s), [2.14] (1H, s), 2.00–1.91 (1H, m), 1.87–1.79 (1H, m), 1.80–1.73 (1H, m), 1.64–1.52 (4H, m), 1.44–1.35 (2H, m), 1.10 (3H, t, *J* = 7.6 Hz), 1.05 (2H, d, *J* = 6.9 Hz), [1.05] (1H, d, *J* = 6.6 Hz), 0.92 (9H, t, *J* = 7.9 Hz), 0.92 (3H, obs), 0.88 (3H, d, *J* = 7.1 Hz), 0.85 (3H, d, *J* = 6.9 Hz), 0.61 (6H, q, *J* = 8.0 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 174.0, 172.4, 162.1, [160.8], 138.4,

129.4, 128.3, 127.7, 127.4, [125.5], [111.9], 110.2, [79.4], 79.3, 78.7, 77.2, 73.0, 72.0, [71.9], 70.1, 67.5, [41.1], 41.0, 39.6, 36.5, [36.4], 36.3, 33.6, [33.0], 32.5, 27.9, 27.5, [27.4], 20.9, 19.4, [19.3], 17.3, [17.3], 11.0, 9.2, 8.4, 7.1, 5.5; $[\alpha]_D^{21}$ –25.8 (*c* 0.77, $CHCl_3$); **IR** (thin film) ν_{max} (cm^{-1}) 3463, 2932, 2876, 1732, 1692, 1657, 1459, 1368, 1244, 1194, 1079, 1017, 740; **HRMS** calc. for $C_{38}H_{66}NO_8Si$ $[M+H]^+$ 692.4558, found 692.4551. Distinguishable resonances of the minor rotamer (2:1 ratio) are given in brackets.

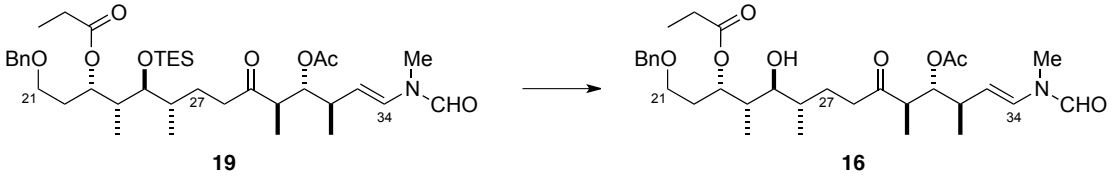
Analog 15



A stock solution of HF·pyridine in pyridine was prepared by adding HF·pyridine (200 μL, 70% HF) to pyridine (600 μL) in a Teflon vessel at 0 °C. The solution was stirred for 1 h, and then 200 μL was added to a solution of TES ether **42** (10.8 mg, 0.0157 mmol) in THF (0.40 mL). The reaction mixture was stirred at room temperature for 2 h. Upon completion, the reaction was diluted with EtOAc (2 mL) and quenched by pipetting onto rapidly stirring $NaHCO_3$ (20 mL, sat. aq.) at 0 °C. The aqueous phase was extracted with EtOAc (4 × 10 mL). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. The crude was purified by flash chromatography (CH_2Cl_2 → 40% EtOAc/CH_2Cl_2, Florisil) to afford analog **15** (7.7 mg, 86%) as a colorless oil.

$\mathbf{R}_f$ 0.24 (10% EtOAc/CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 8.29 (0.67H, s), [8.05] (0.33H, s), 7.35–7.31 (2H, m), 7.31–7.27 (3H, m), [7.16] (0.33H, d, *J* = 14.6 Hz), 6.94 (0.67H, dd, *J* = 15.9, 8.9 Hz), [6.92] (0.33H, dd, *J* = 16.3, 9.1 Hz), 6.50 (0.67H, d, *J* = 14.1 Hz), 6.18 (0.67H, d, *J* = 16.0 Hz), [6.16] (0.33H, d, *J* = 15.9 Hz), 5.43 (1H, app t, *J* = 4.9 Hz), 5.16 (1H, dd, *J* = 8.6, 3.9 Hz), [5.02] (0.33H, dd, *J* = 14.7, 9.6 Hz), 5.00 (0.67H, dd, *J* = 14.4, 9.2 Hz), 4.48 (1H, d, *J* = 11.9 Hz), 4.43 (1H, d, *J* = 11.9 Hz), [3.60] (0.33H, d, *J* = 4.6 Hz), 3.58 (0.67H, d, *J* = 4.6 Hz), 3.50–3.43 (1H, m), 3.43–3.38 (1H, m), 3.09–2.99 (2H, m), [3.04] (1H, s), 3.03 (2H, s), 2.59–2.47 (2H, m), 2.33–2.24 (2H, m), 2.04–1.98 (1H, m), 1.97 (2H, s), [1.96] (1H, s), 1.74–1.66 (2H, m), 1.18 (3H, d, *J* = 6.8 Hz), [1.11] (1H, t, *J* = 7.6 Hz), 1.10 (2H, t, *J* = 7.7 Hz), 1.08 (2H, d, *J* = 7.1 Hz), [1.07] (1H, d, *J* = 6.8 Hz), 1.04 (2H, d, *J* = 6.9 Hz), [1.03] (1H, d, *J* = 6.7 Hz), 0.84 (3H, d, *J* = 6.9 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C [200.7], 200.5, [176.0], 175.9, 170.0, [170.0], 162.1, [161.0], 148.6, [148.4], 138.1, 129.5, [129.3], 128.3, 127.8, 127.7, 127.6, [125.5], [112.3], 110.6, 77.2, 75.3, [75.3], 73.2, 71.2, [71.1], 66.7, [46.1], 46.0, 41.9, [41.8], 39.0, [37.0], 36.9, [33.0], 32.9, 27.7, 27.6, 20.8, 18.9, 18.2, [18.1], [13.4], 13.4, 9.6, [9.5], 9.3; $[\alpha]_D^{22}$ –62.0 (*c* 0.68, $CHCl_3$); **IR** (thin film) ν_{max} (cm^{-1}) 3476, 2966, 2941, 1741, 1692, 1656, 1454, 1374, 1234, 1196, 1075, 1019, 984, 741; **HRMS** calc. for $C_{32}H_{48}NO_8$ $[M+H]^+$ 574.3374, found 574.3374. Distinguishable resonances of the minor rotamer (2:1 ratio) are given in brackets.

Analog 16



A stock solution of HF·pyridine in pyridine was prepared by adding HF·pyridine (200 μL, 70% HF) to pyridine (600 μL) in a Teflon vessel at 0 °C. The solution was stirred for 1 h, and then 200 μL was added to a solution of TES ether **19** (4.5 mg, 6.5 μmol) in THF (200 μL). The reaction mixture was stirred at room temperature for 4 h. Upon completion, the reaction was diluted with EtOAc (2 mL) and quenched by pipetting onto rapidly stirring $NaHCO_3$ (15 mL, sat. aq.) at 0 °C. The aqueous phase was extracted with EtOAc (4 × 7 mL). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. The crude was purified by flash chromatography (CH_2Cl_2 → 40% EtOAc/CH_2Cl_2, Florisil) to afford alcohol **16** (2.6 mg, 69%) as a colorless oil.

R_f 0.24 (10% EtOAc/CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 8.29 (0.67H, s), [8.08] (0.33H, s), 7.35–7.28 (4H, m), 7.28–7.24 (1H, m), [7.16] (0.33H, d, *J* = 14.6 Hz), 6.49 (0.67H, d, *J* = 13.6 Hz), 5.44 (1H, ddd, *J* = 9.8, 1.8, 1.8 Hz), 5.13 (1H, dd, *J* = 8.9, 3.8 Hz), [5.00] (0.33H, dd, *J* = 14.6, 9.5 Hz), 4.98 (0.67H, dd, *J* = 14.2, 9.4 Hz), 4.49 (1H, d, *J* = 11.9 Hz), 4.45 (1H, d, *J* = 12.0 Hz), 3.51–3.41 (2H, m), 3.27 (0.67H, d, *J* = 4.7 Hz), [3.26] (0.33H, obs), [3.07] (1H, s), 3.03 (2H, s), 2.99–2.95 (1H, m) 2.78 (0.67 H, dq, *J* = 9.0, 7.1 Hz), [2.74] (0.33 H, dq, *J* = 9.2, 7.1 Hz), 2.56–2.38 (3H, m), 2.29 (2H, app septet, *J* = 7.5 Hz), 2.05–2.00 (1H, m), 2.00 (2H, s), [1.99] (1H, s), 1.82–1.73 (2H, m), 1.73–1.66 (1H, m), 1.66–1.59 (1H, m), 1.41–1.31 (1H, m), 1.10 (3H, t, *J* = 7.7 Hz), 1.06 (3H, d, *J* = 7.1 Hz), 1.04 (3H, d, *J* = 6.9 Hz), 0.97 (3H, d, *J* = 6.8 Hz), 0.85 (3H, d, *J* = 6.9 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C [211.9], 211.8, 175.8, 170.0, 162.1, [160.9], 138.2, 129.5, 128.4, 127.7, 127.6, [125.4], [112.1], 110.5, 77.2, 76.3, 73.1, 71.5, 66.9, [48.8], 48.6, 40.5, 39.3, [39.1], [37.0], 36.8, 33.2, [33.1], [33.0], 33.0, 27.7, 27.6, 22.1, [22.1], 20.9, 18.8, 17.5, 13.3, [9.8], 9.8, 9.3; $[\alpha]_D^{22}$ –80.3 (*c* 0.33, $CHCl_3$); **IR** (thin film) ν_{max} (cm^{-1}) 3484, 2967, 2942, 2349, 1734, 1700, 1657, 1451, 1371, 1236, 1204, 1077, 1019, 979, 736; **HRMS** calc. for $C_{32}H_{50}NO_8$ $[M+H]^+$ 576.3531, found 576.3519. Distinguishable resonances of the minor rotamer (2:1 ratio) are given in brackets.

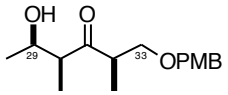
5. NMR comparison between natural and synthetic aplyronine C

Table S2. ^{1}H and ^{13}C NMR comparison for aplyronine C in *d*6-acetone

Proton	Natural aplyronine C[20]			Synthetic aplyronine C		
	δ_H	Mult (*J* in Hz)	δ_C	δ_H	Mult (*J* in Hz)	δ_C
1			167.8			167.9
2	5.93	d (15.0)	120.7	5.93	d (15.4)	120.7
3	7.26	dd (15.0, 9.6)	145.8	7.26	dd (15.3, 10.3)	145.9
4	6.37	dd (15.0, 9.6)	130.7	6.37	dd (15.4, 9.7)	130.9
5	6.42	ddd (15.0, 9.2, 5.0)	143.5	6.42	ddd (15.2, 9.0, 4.9)	143.7
6	2.15, 2.26	m	36.8	2.17, 2.24	m	36.7
7	3.68	m	73.4	3.67	m	73.4
7-OH	3.80	br s		3.81	br s	
8	1.72	m	41.7	1.72	m	41.9
8-Me	1.00	d (7.0)	11.9	1.00	d (6.9)	11.9
9	3.43	m	77.2	3.41	m	77.3
9-OH	3.35	br s		3.39	br s	
10	1.67	m	34.3[b]	1.70	m	34.2[b]
10-Me	0.98	d (6.5)	16.4	0.97	d (6.9)	16.5
11	1.20	m	24.5[b]	1.18	m	24.4[b]
12	1.59	m	29.5	1.59	m	29.3
13	3.50	m	87.1	3.50	m	87.1
13-OMe	3.13	s	55.6	3.12	s	55.7
14			134.8			134.9
14-Me	1.45	s	10.1	1.43	s	10.1
15	5.22	br dd (10.4, 4.6)	130.7	5.21	br dd (10.9, 4.7)	130.8
16	1.81, 1.96	m	37.4	1.80, 1.92	m	37.5
17	1.26	m	30.5	1.23	m	30.5
17-Me	0.79	d (6.5)	20.3	0.78	d (6.4)	20.3
18	1.17, 1.55	m	41.3	1.17, 1.55	m	41.4
19	3.50	m	82.2	3.50	m	82.3
19-OMe	3.12	s	55.4	3.11	s	55.5
20	5.01	dd (15.0, 9.2)	133.4	4.99	dd (15.3, 9.2)	133.4
21	5.63	ddd (15.0, 10.4, 4.0)	132.8	5.62	ddd (15.2, 10.3, 3.9)	133.0
22	2.29, 2.45	m	38.1	2.29, 2.45	m	38.2
23	5.48	br d (10.8)	72.8	5.47	br d (10.9)	72.9
24	1.74	m	42.0	1.74	m	42.0
24-Me	0.90	d (7.0)	10.7	0.89	d (7.0)	10.7
25	3.06	m	76.9	3.05	m	77.0
25-OH	3.58	br d (5.6)		3.61	m	
26	1.65	m	34.8	1.65	m	34.8
26-Me	0.99	m	17.9	0.98	d (7.4)	18.0
27	1.16, 1.38	m	25.2[b]	1.16, 1.36	m	25.3[b]
28	1.53, 1.65	m	30.7 (30.9)[a]	1.53, 1.65	m	30.7 (30.9)[a]
29	5.03	m	72.7	5.02	m	72.8
30	1.98	m	38.1	1.97	m	38.2
30-Me	1.00	d (7.0)	10.1 (10.0)[a]	1.00	d (6.9)	10.2 (10.0)[a]
31	4.80 (4.81)[a]	dd (10.0, 2.8)	77.4	4.80 (4.81)[a]	dd (10.1, 2.7)	77.5 (77.4)[a]
32	2.65 (2.67)[a]	m	37.6 (37.8)[a]	2.65 (2.69)[a]	m	37.7 (37.9)[a]
32-Me	1.01	m	19.9	1.00	d (6.5)	20.0 (20.0)[a]
33	5.05 (5.11)[a]	dd (14.4, 9.2)	110.0 (112.1)[a]	5.05 (5.10)[a]	dd (14.1, 9.5)	110.0 (112.1)[a]
34	6.84 (7.16)[a]	d (14.4)	131.1 (126.3)[a]	6.85 (7.15)[a]	d (14.0)	131.2 (126.4)[a]
34-NMe	2.97 (3.10)[a]	s	27.3 (33.0)[a]	2.97 (3.09)[a]	s	27.4 (33.1)[a]
CHO	8.37 (8.11)[a]	s	163.0 (161.7)[a]	8.37 (8.10)[a]	s	163.1 (161.9)[a]
1”			172.8			172.8
2”	3.19 (3.22)[a]	m	63.5 (62.9)[a]	3.20 (3.21)[a]	q (7.1)	63.6 (62.9)[a]
2”-NMe_2	2.34 (2.32)[a]	s	41.6	2.34	s	41.7
3”	1.27 (1.22)[a]	d (7.0)	15.9 (15.2)[a]	1.26 (1.26)[a]	d (7.1)	16.0 (15.3)[a]
31-OAc	2.04 (2.03)[a]	s	21.0, 170.7	2.09 (2.09)[a]	s	21.1, 170.9

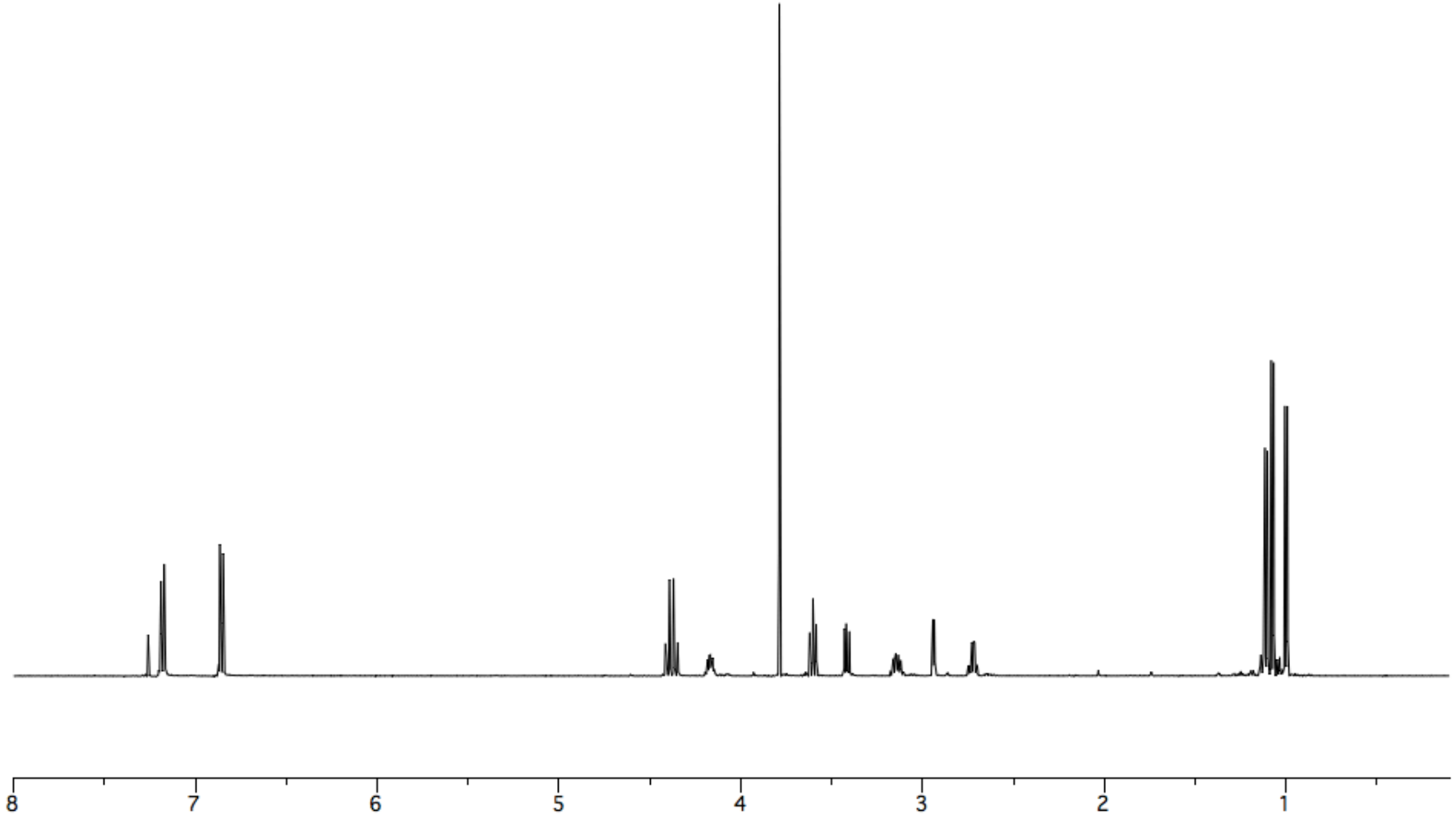
[a] The minor counterparts of doubled signals in the ratio of 2:1 are given in parentheses
[b] Broad signals

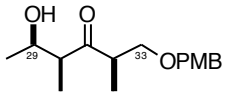
[20] ^{1}H NMR (600 MHz); ^{13}C NMR (150 MHz). Ojika, M.; Kigoshi, H.; Yoshida, Y.; Ishigaki, T.; Nisiwaki, M.; Tsukada, I.; Arakawa, M.; Ekimoto, H.; Yamada, K. *Tetrahedron* **2007**, *63*, 3138.



9

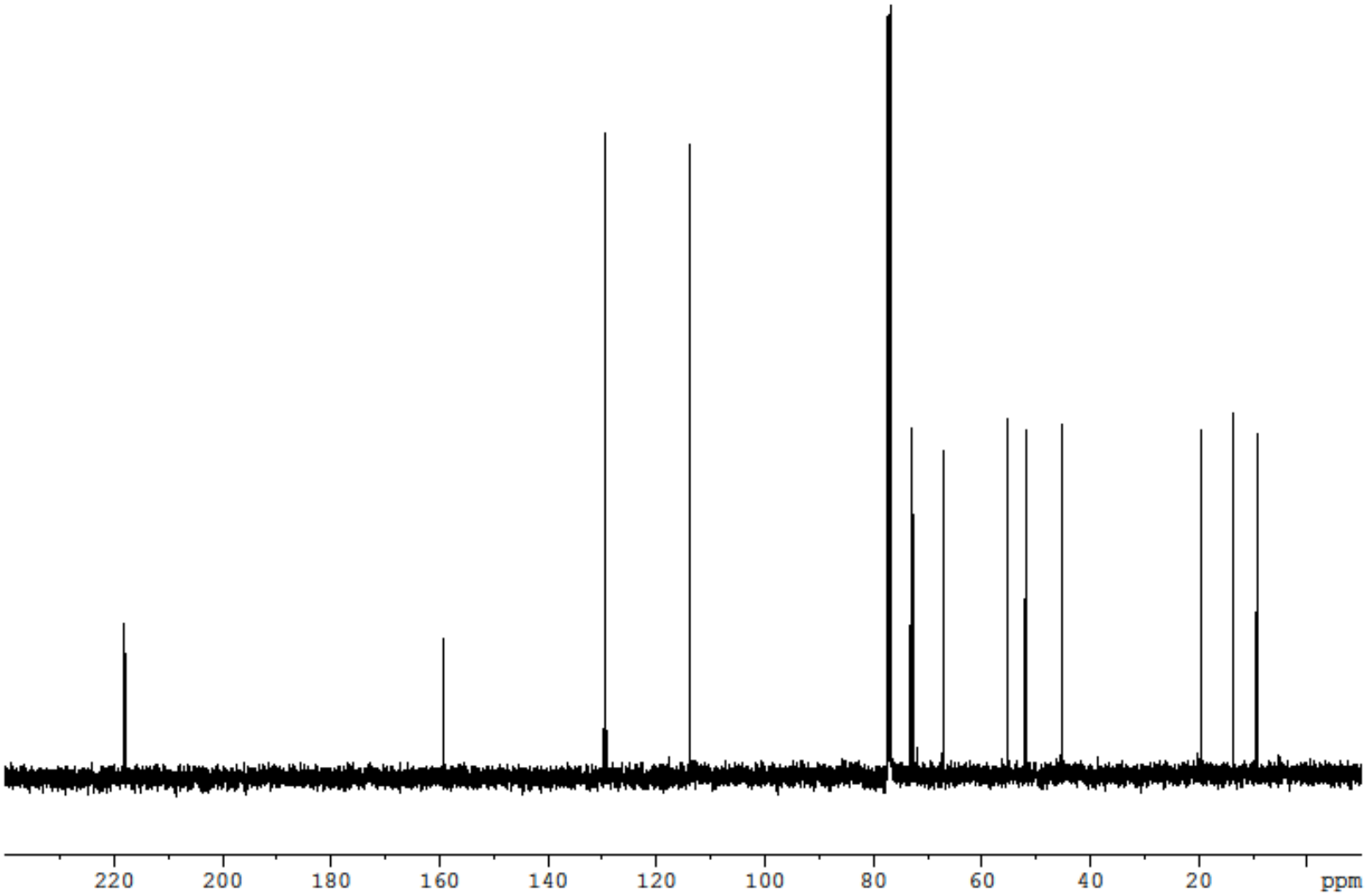
^{1}H NMR (500 MHz, $CDCl_3$)

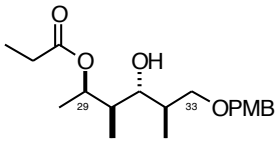




9

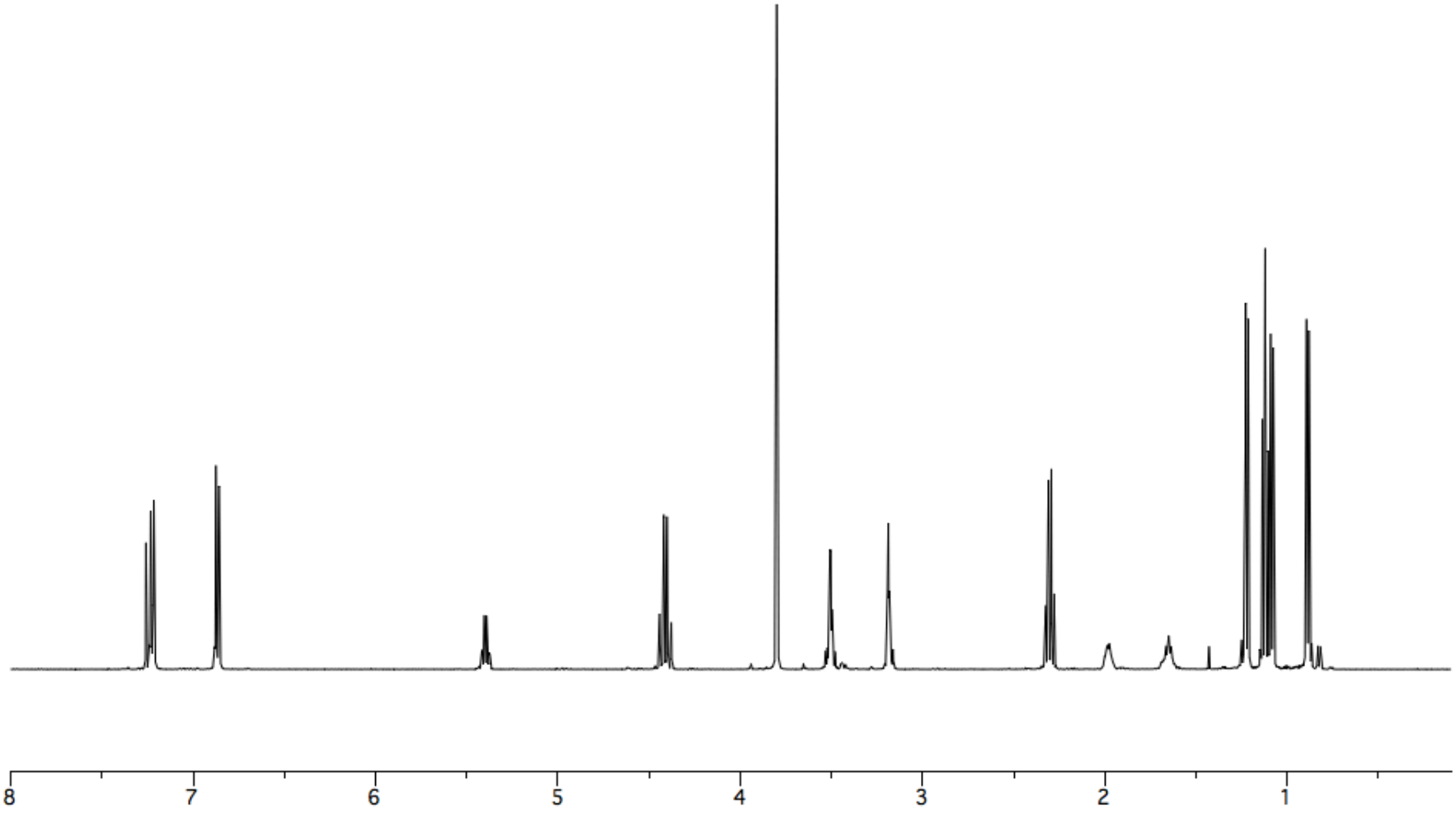
^{13}C NMR (125 MHz, $CDCl_3$)

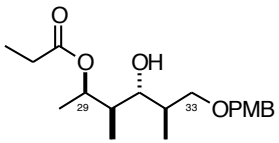




10

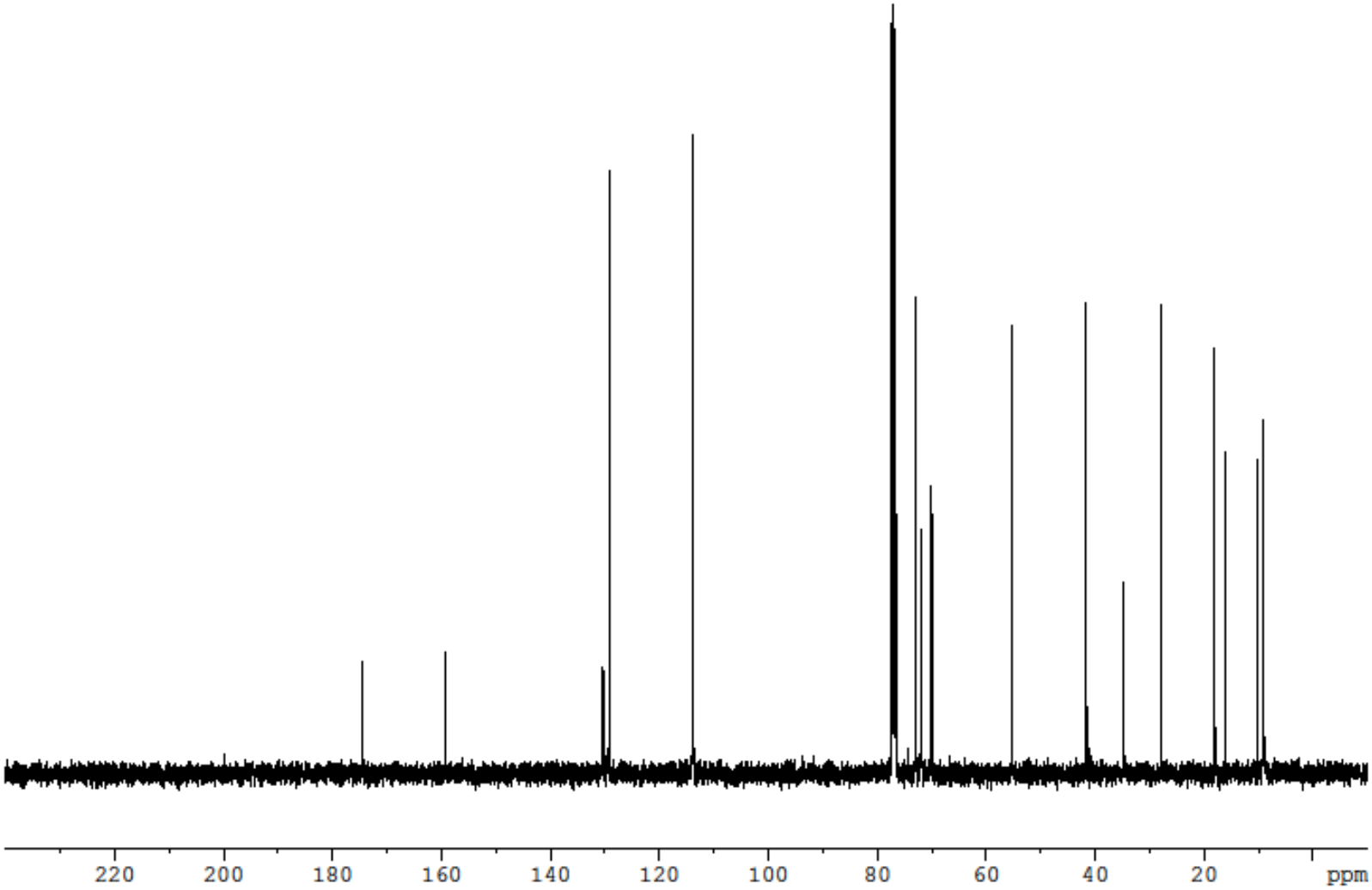
^{1}H NMR (500 MHz, $CDCl_3$)

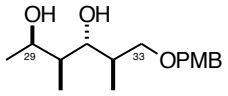




10

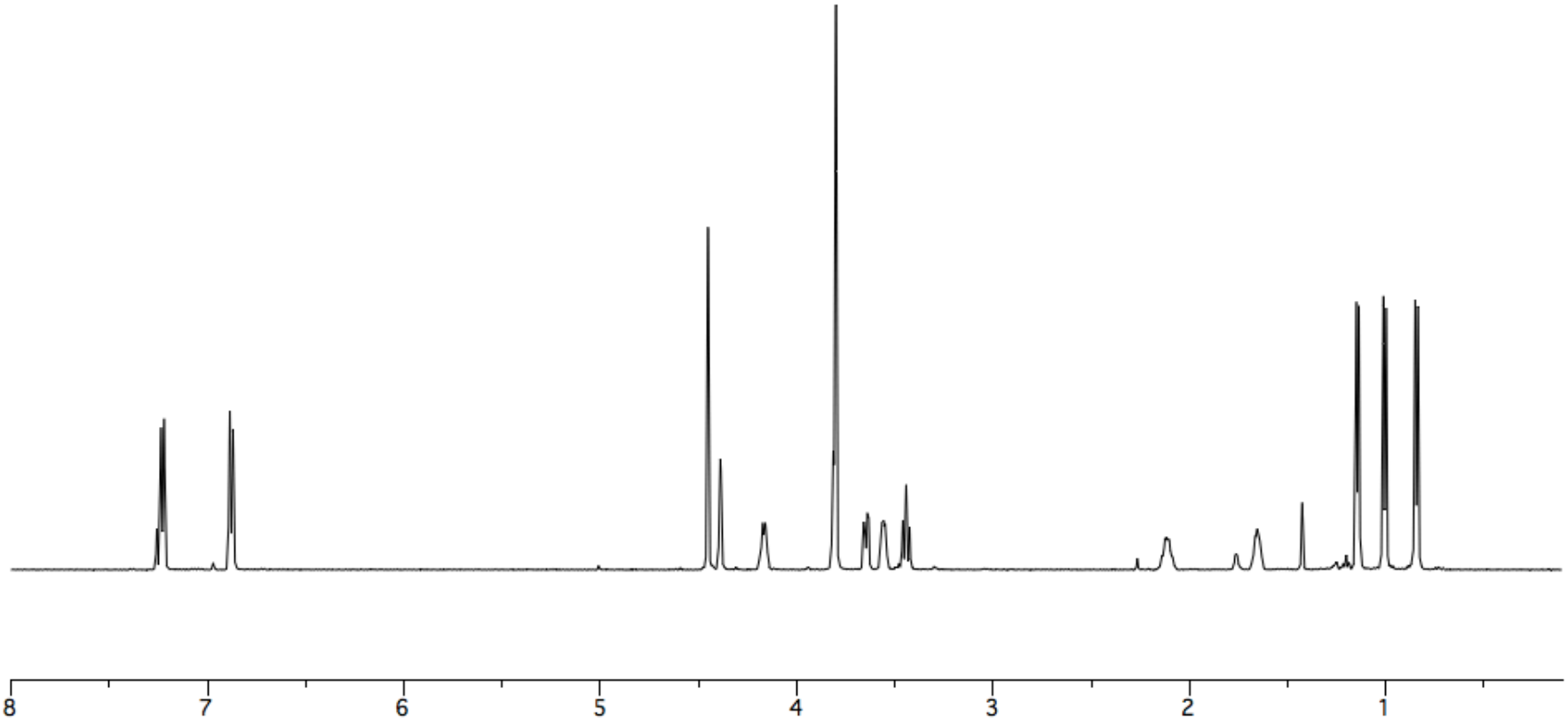
^{13}C NMR (125 MHz, $CDCl_3$)

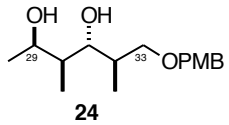




24

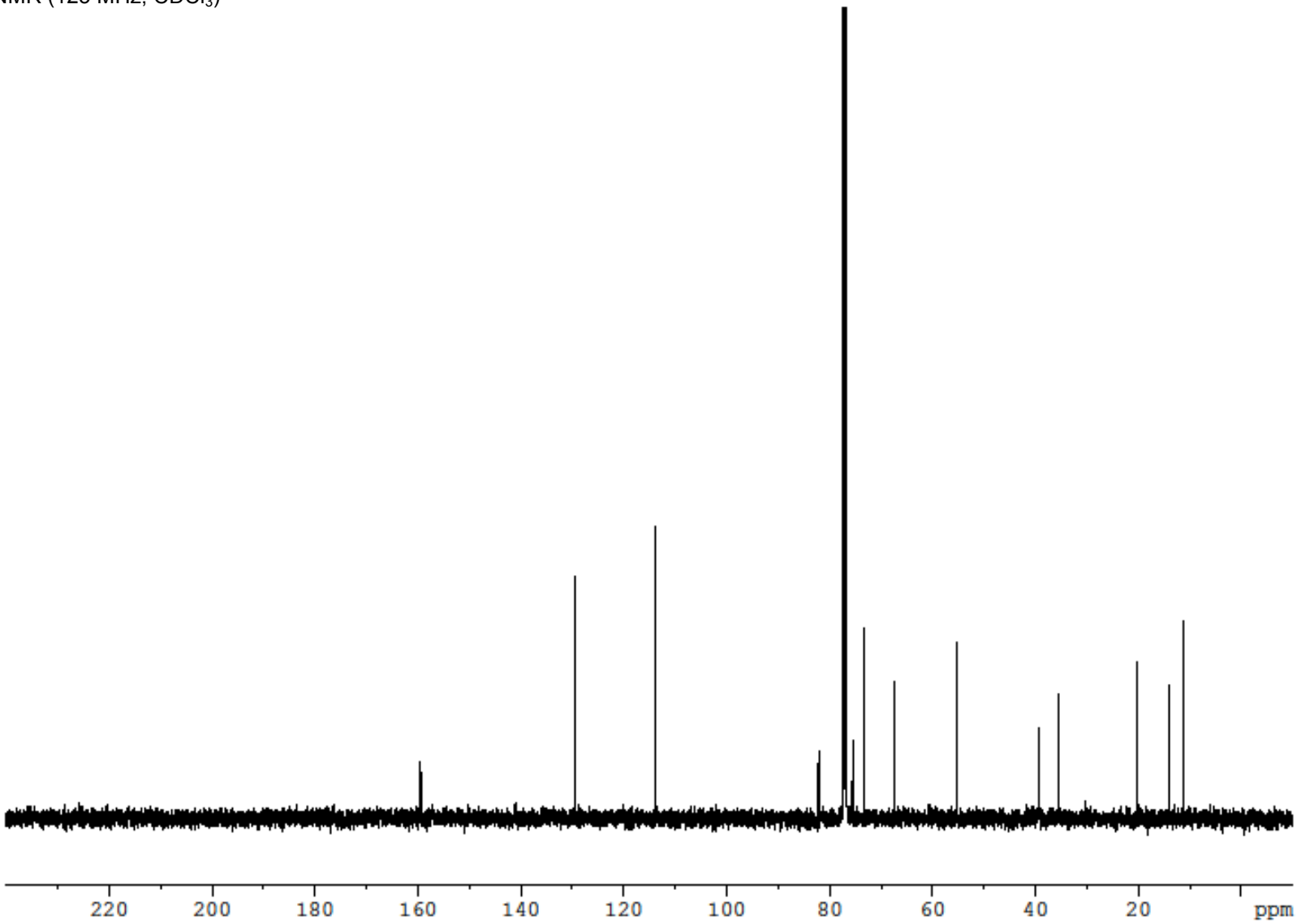
^{1}H NMR (500 MHz, $CDCl_3$)

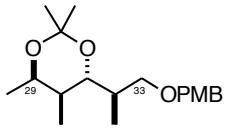




24

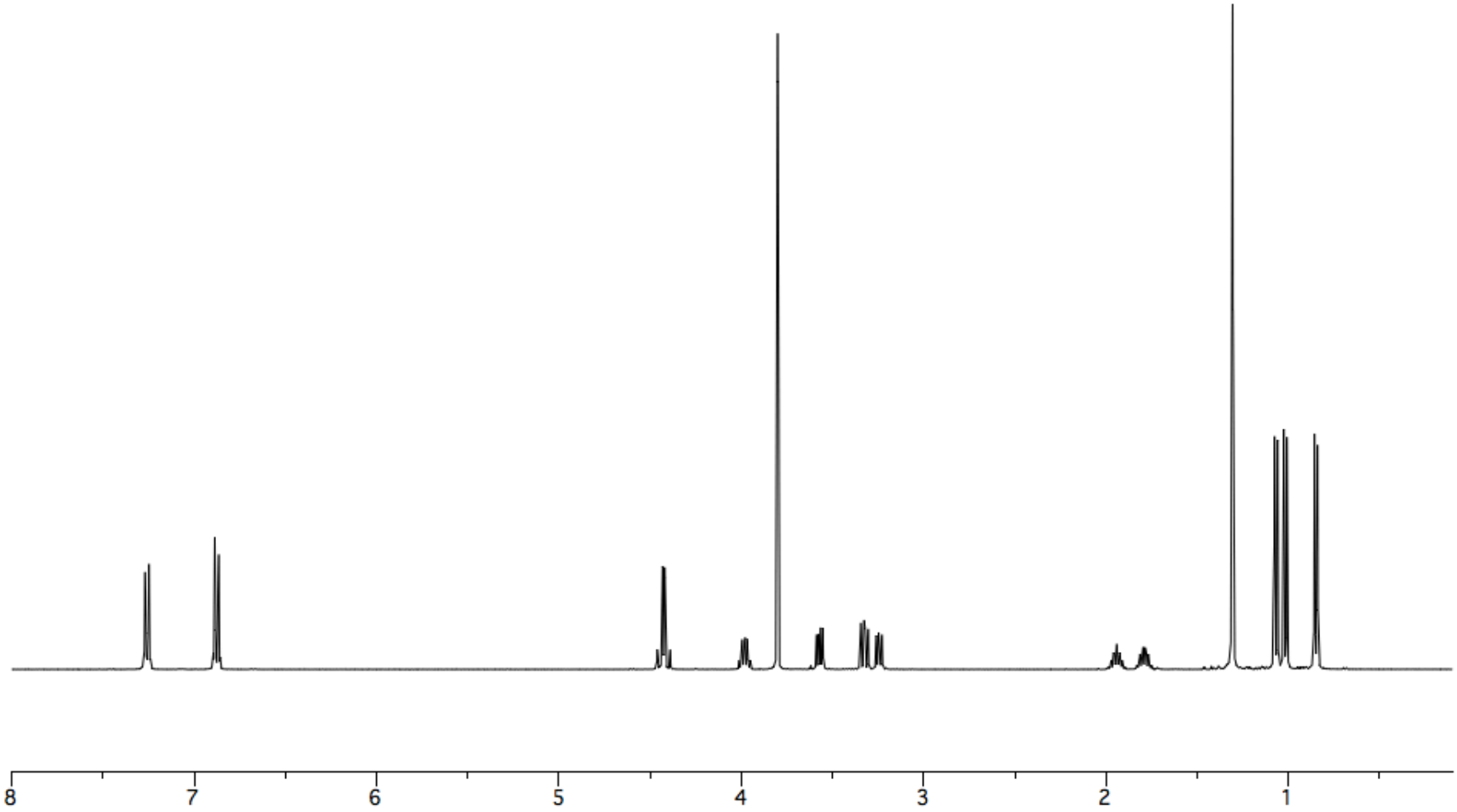
^{13}C NMR (125 MHz, $CDCl_3$)

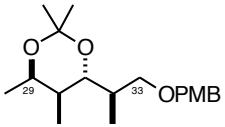




25

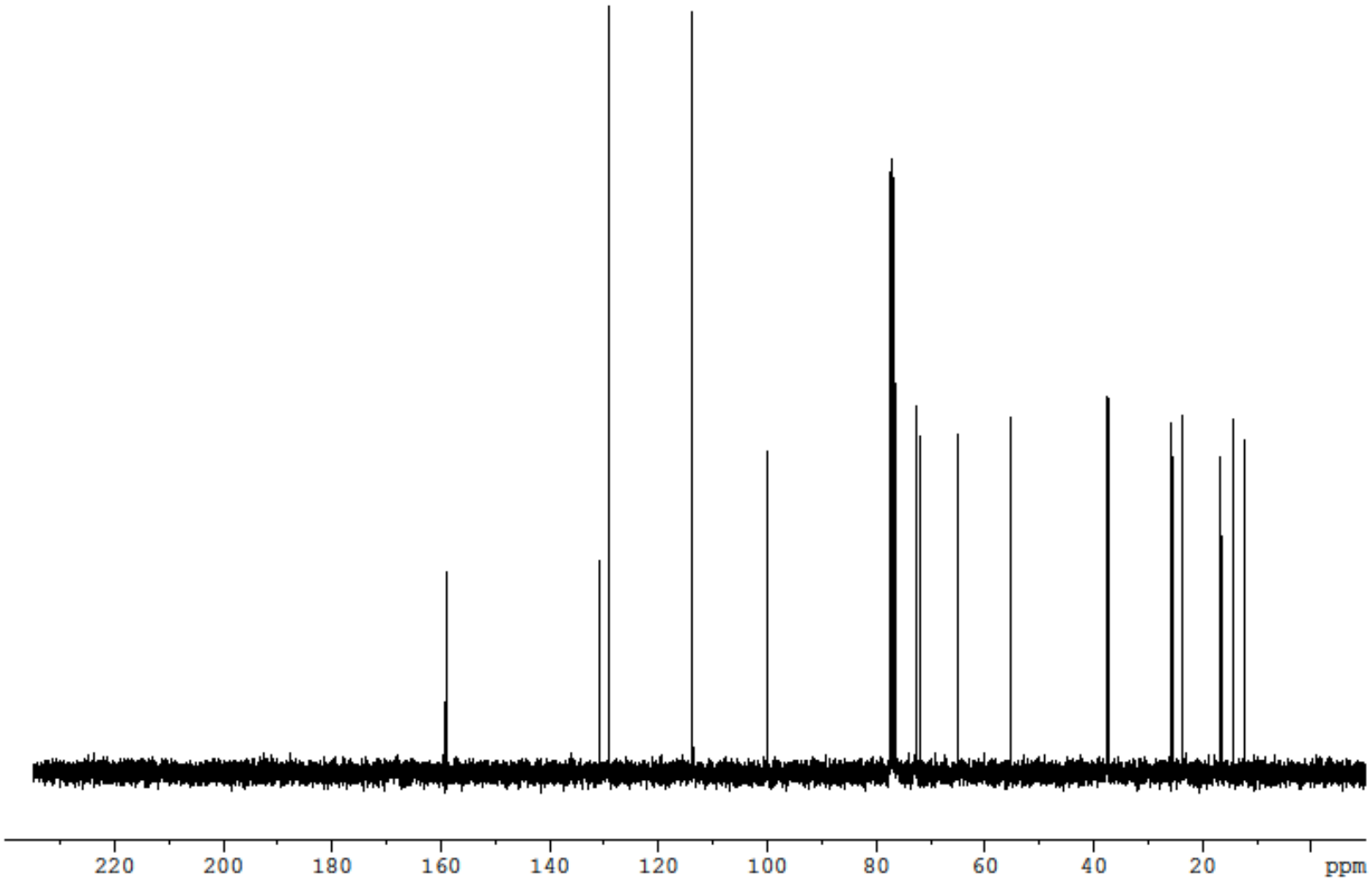
^{1}H NMR (400 MHz, $CDCl_3$)

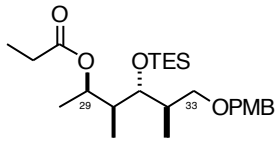




25

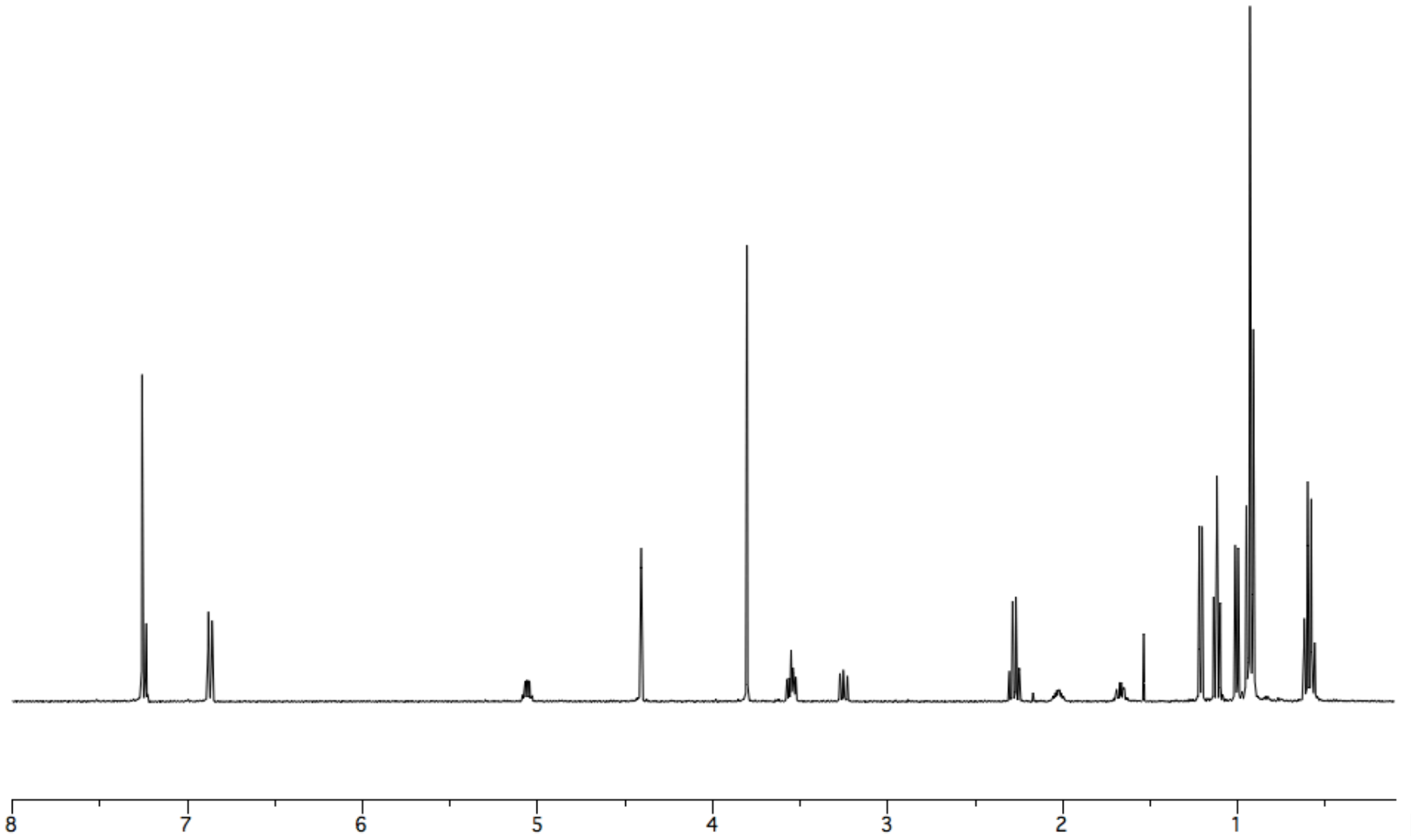
^{13}C NMR (100 MHz, $CDCl_3$)

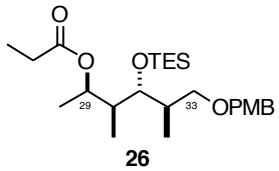




26

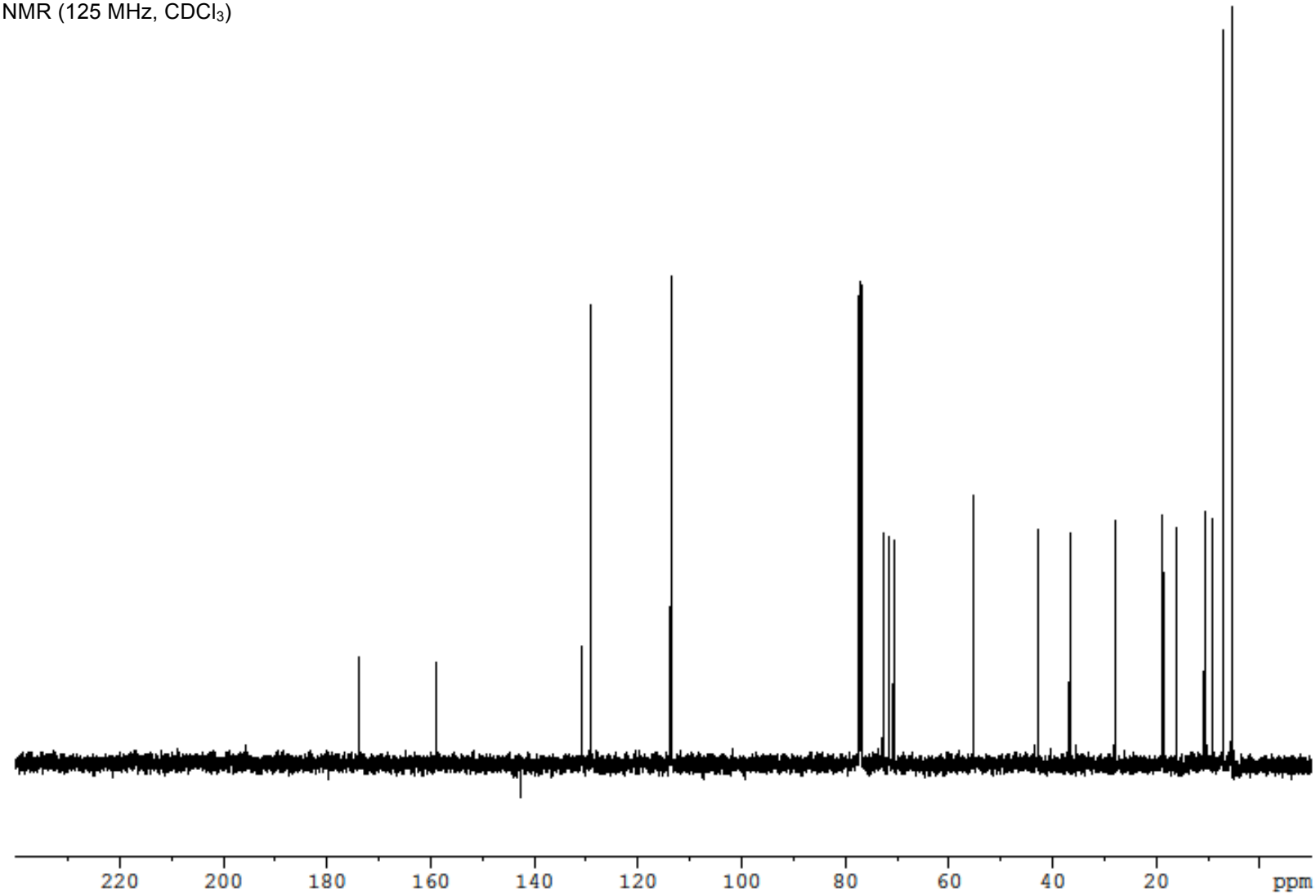
^{1}H NMR (400 MHz, $CDCl_3$)

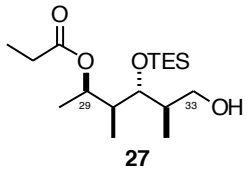




26

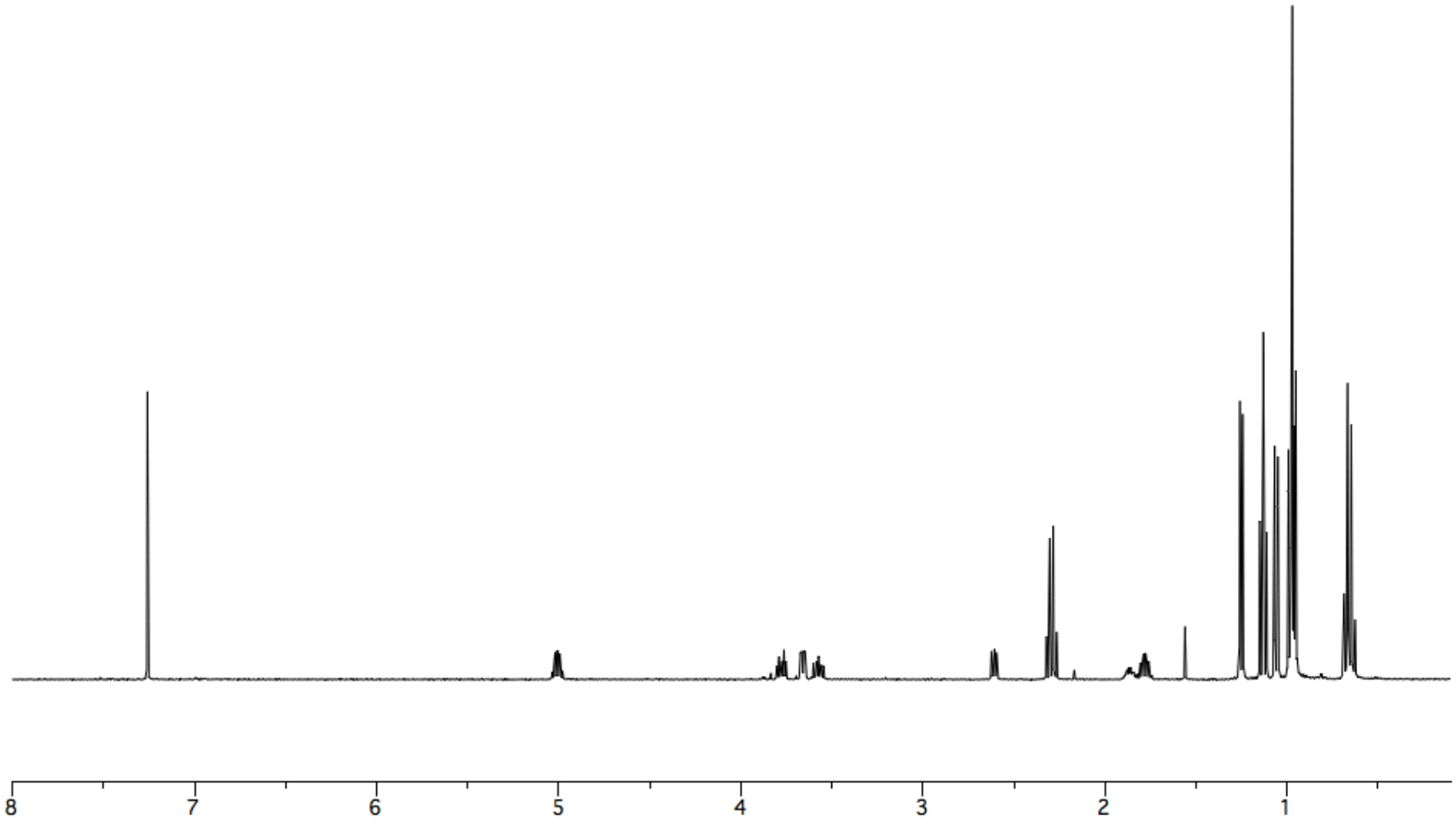
^{13}C NMR (125 MHz, $CDCl_3$)

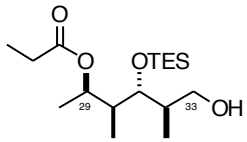




27

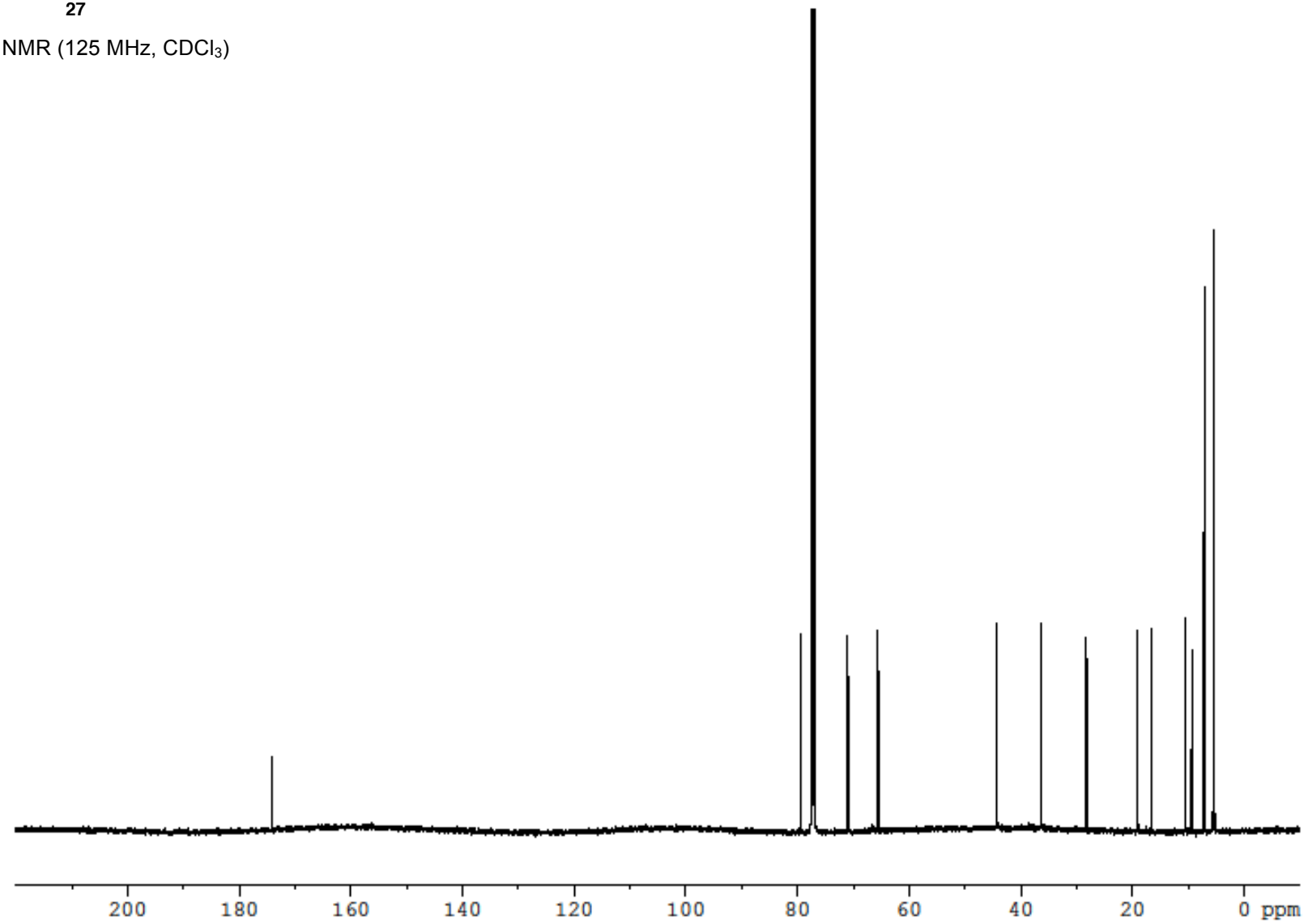
^{1}H NMR (400 MHz, $CDCl_3$)

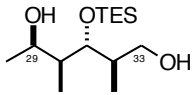




27

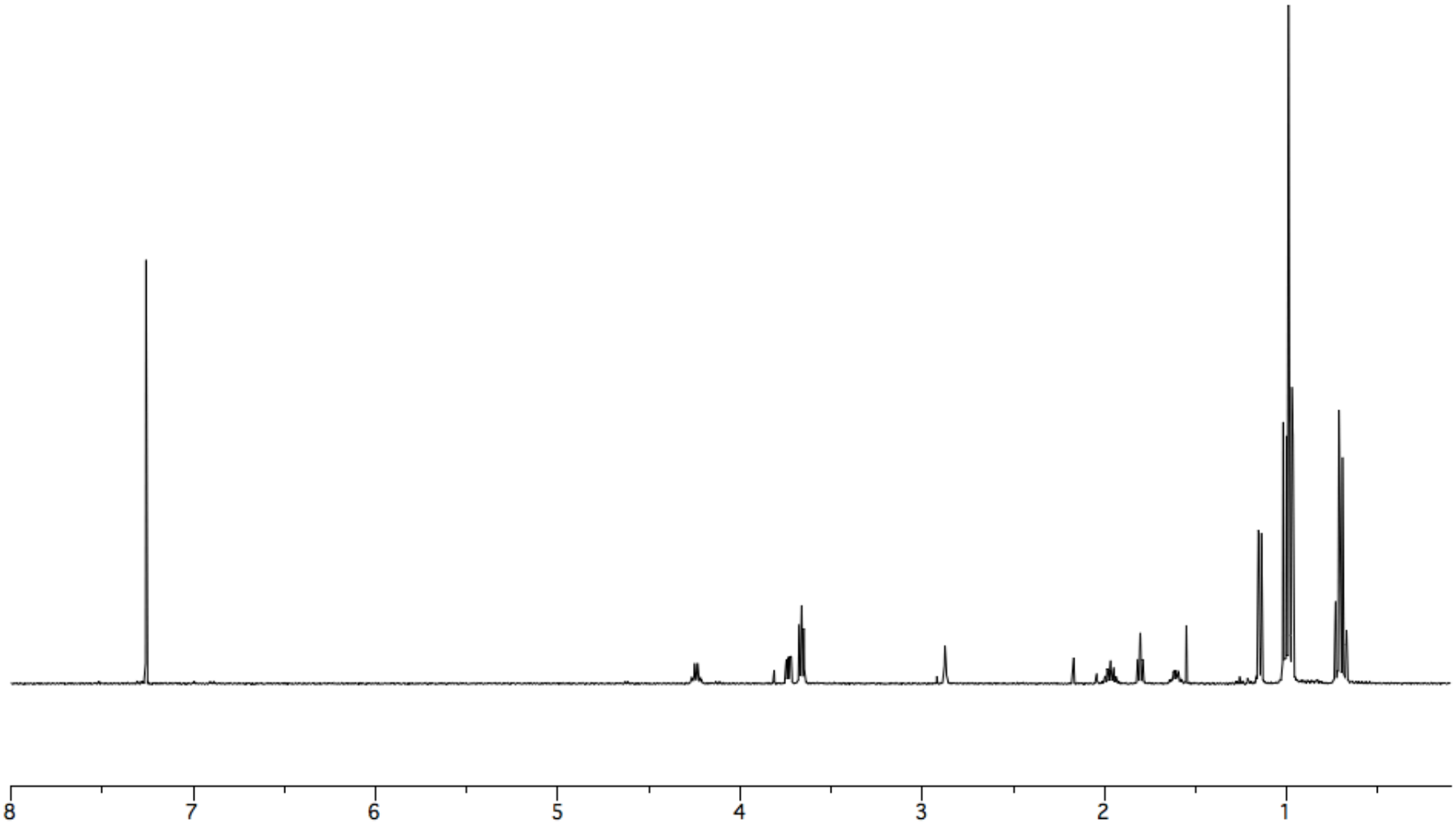
^{13}C NMR (125 MHz, $CDCl_3$)

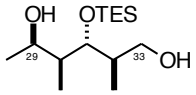




11

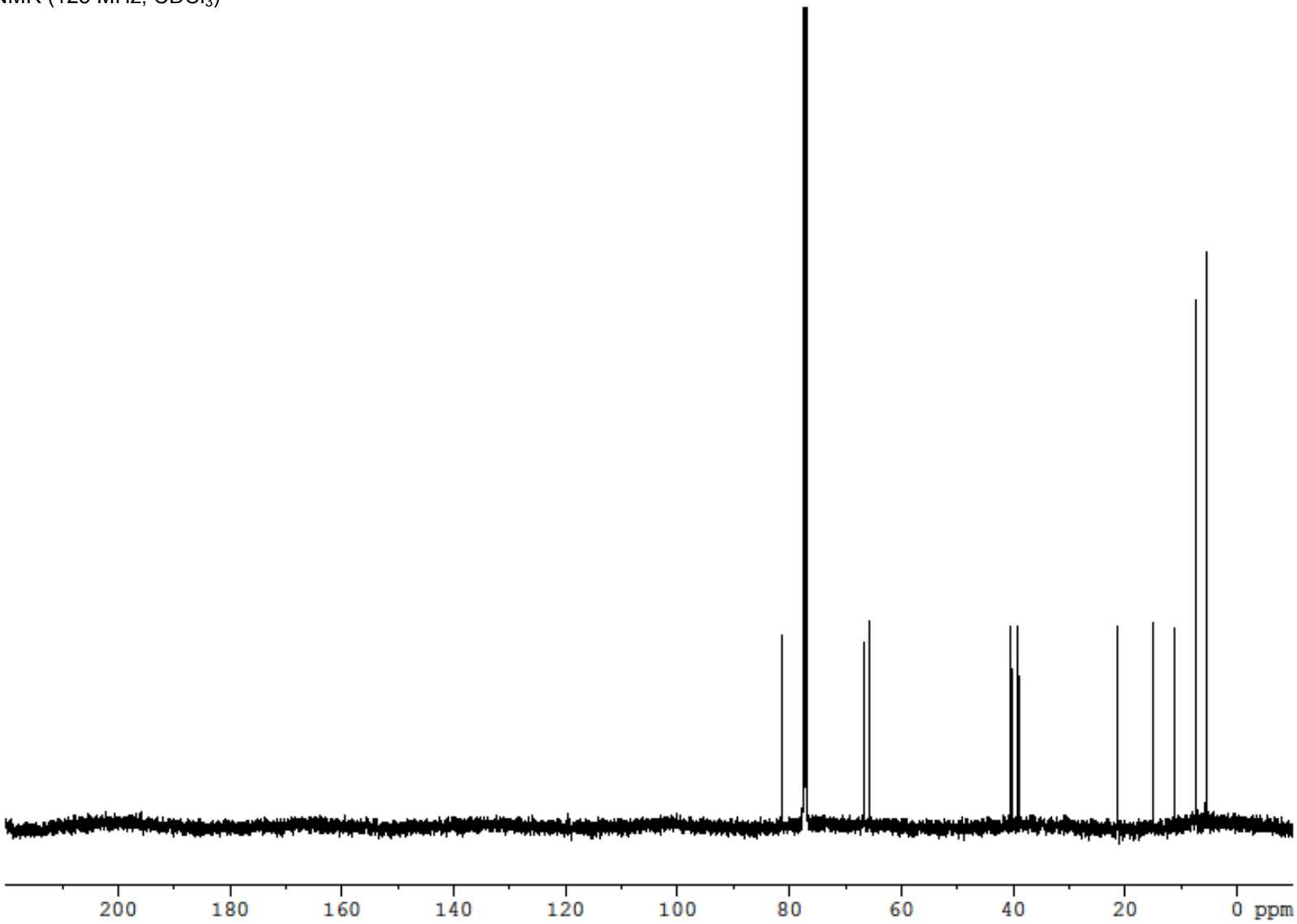
^{1}H NMR (400 MHz, $CDCl_3$)

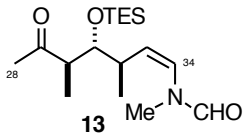




11

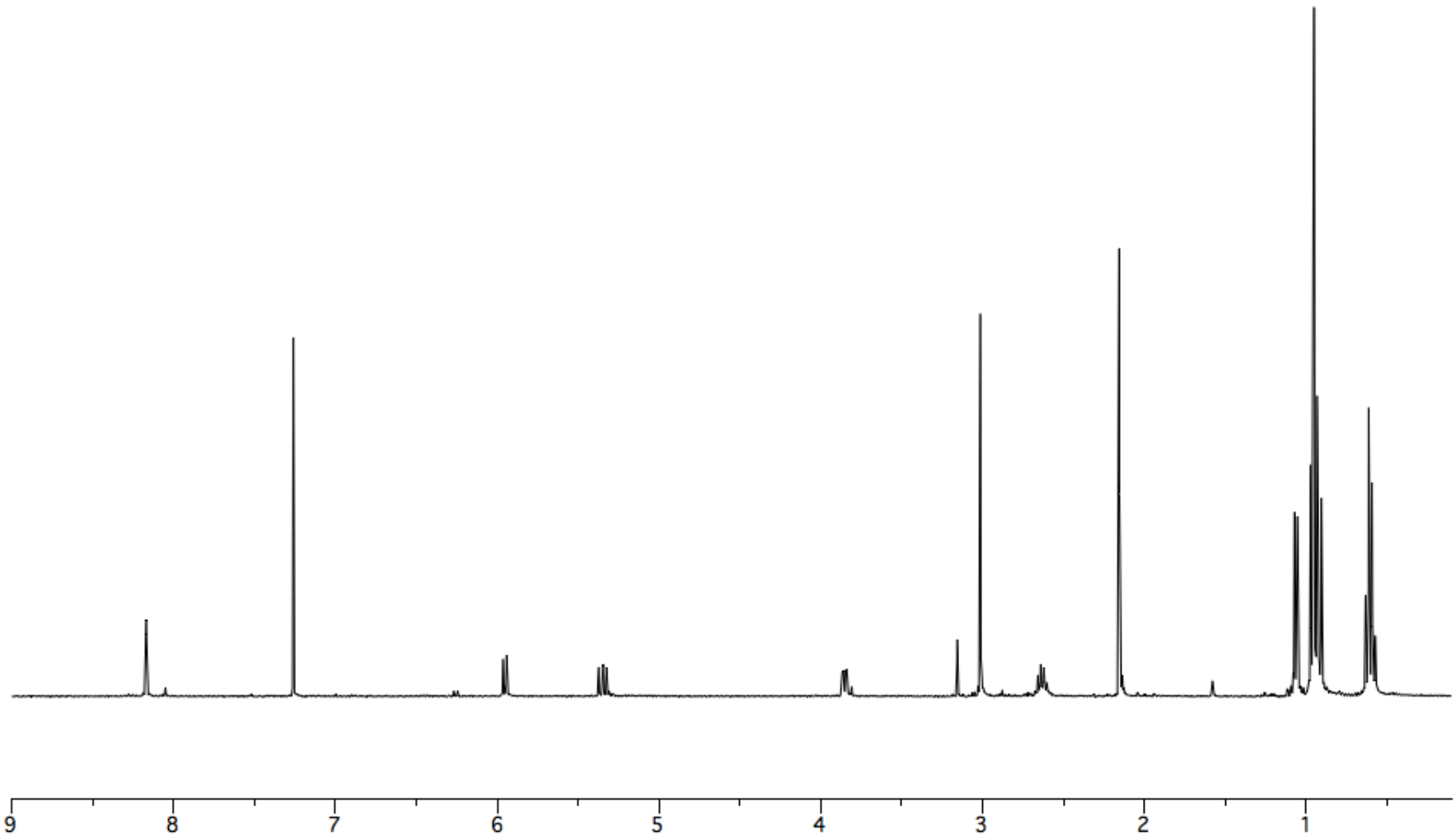
^{13}C NMR (125 MHz, $CDCl_3$)

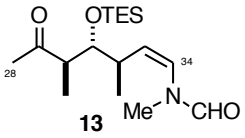




13

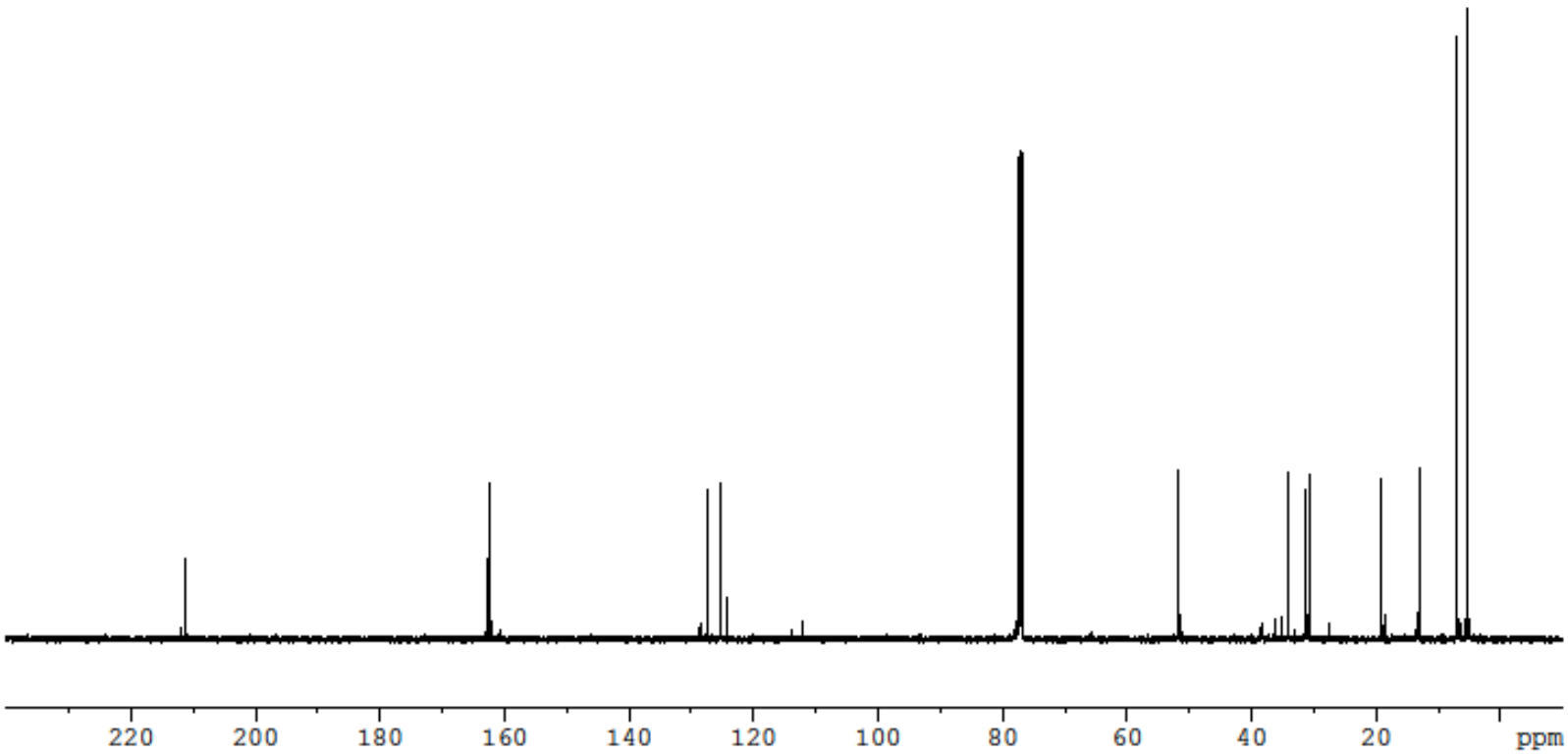
^{1}H NMR (400 MHz, $CDCl_3$)

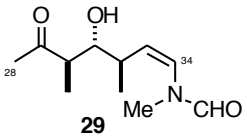




13

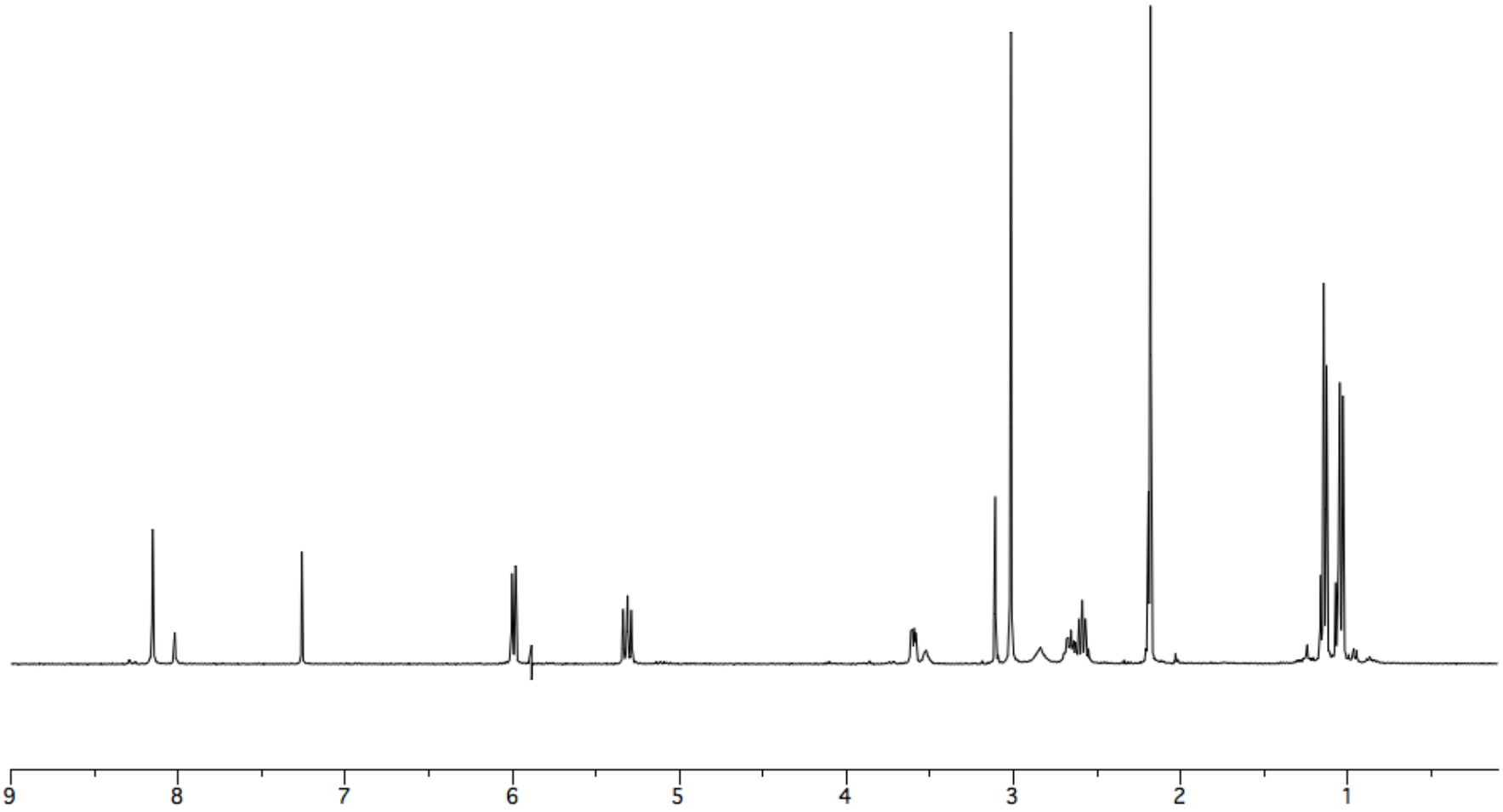
^{13}C NMR (125 MHz, $CDCl_3$)

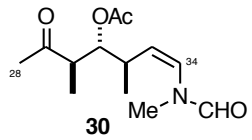




29

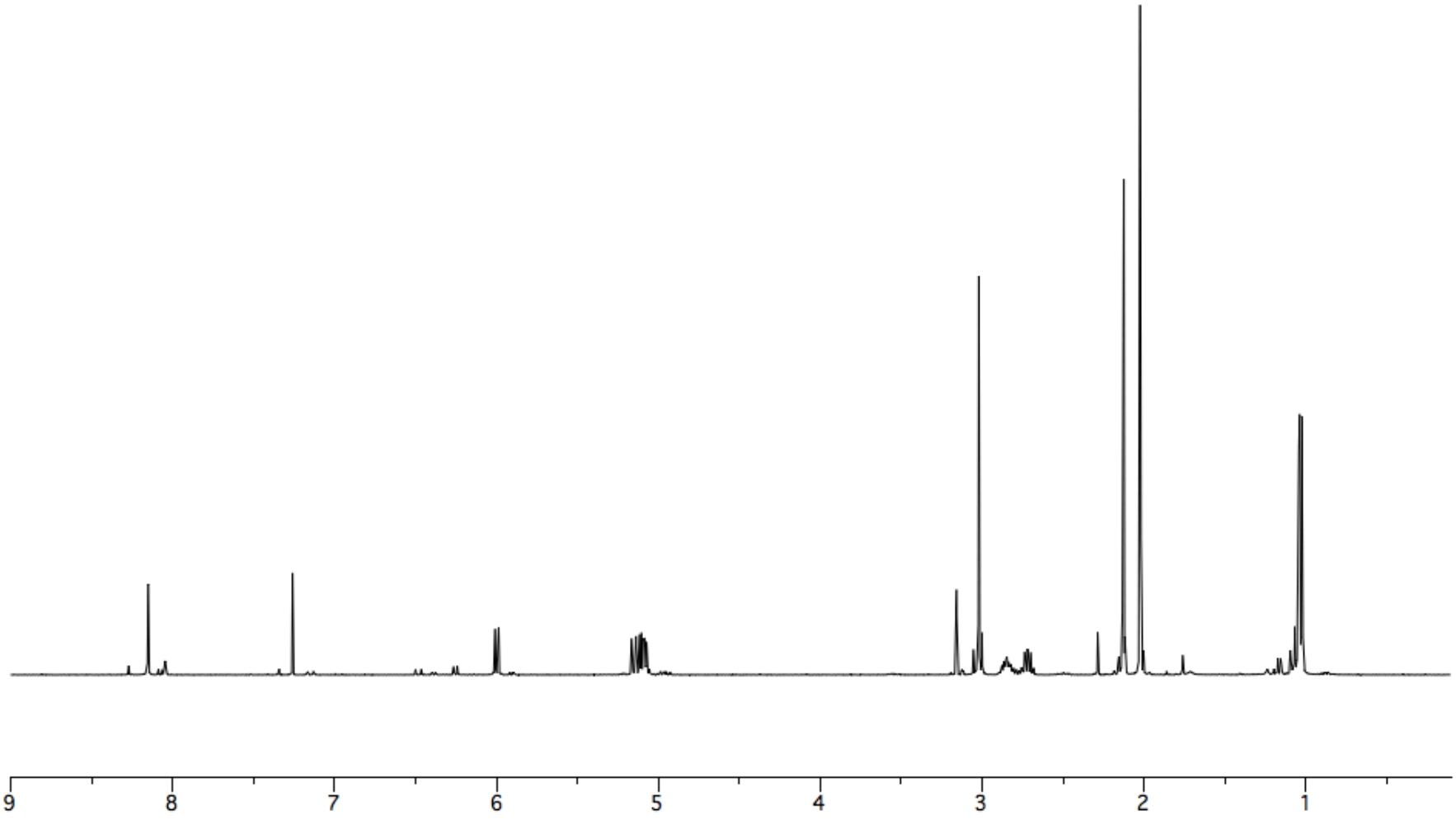
^{1}H NMR (400 MHz, $CDCl_3$)

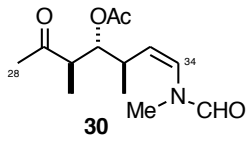




30

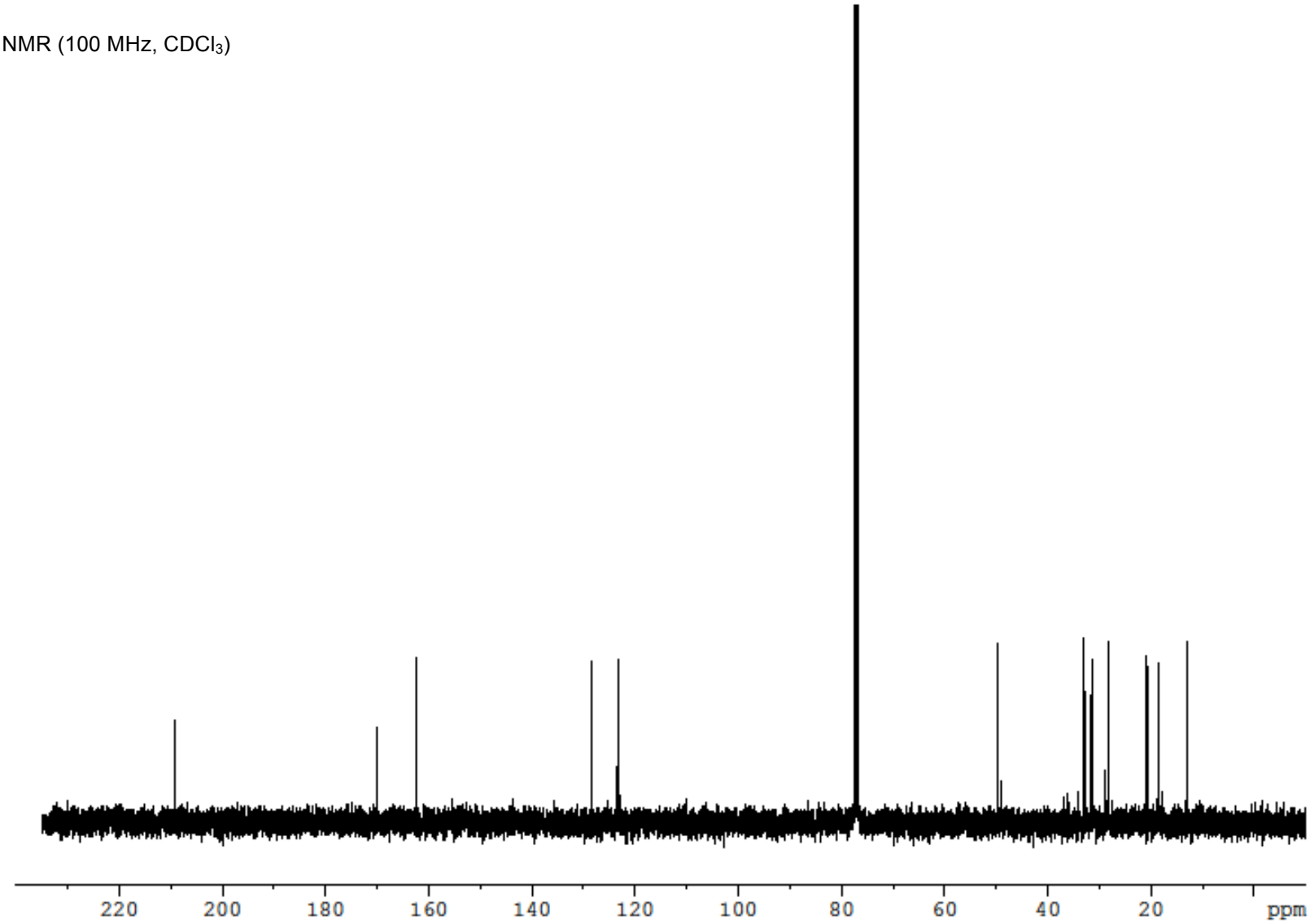
^{1}H NMR (400 MHz, $CDCl_3$)

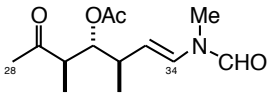




30

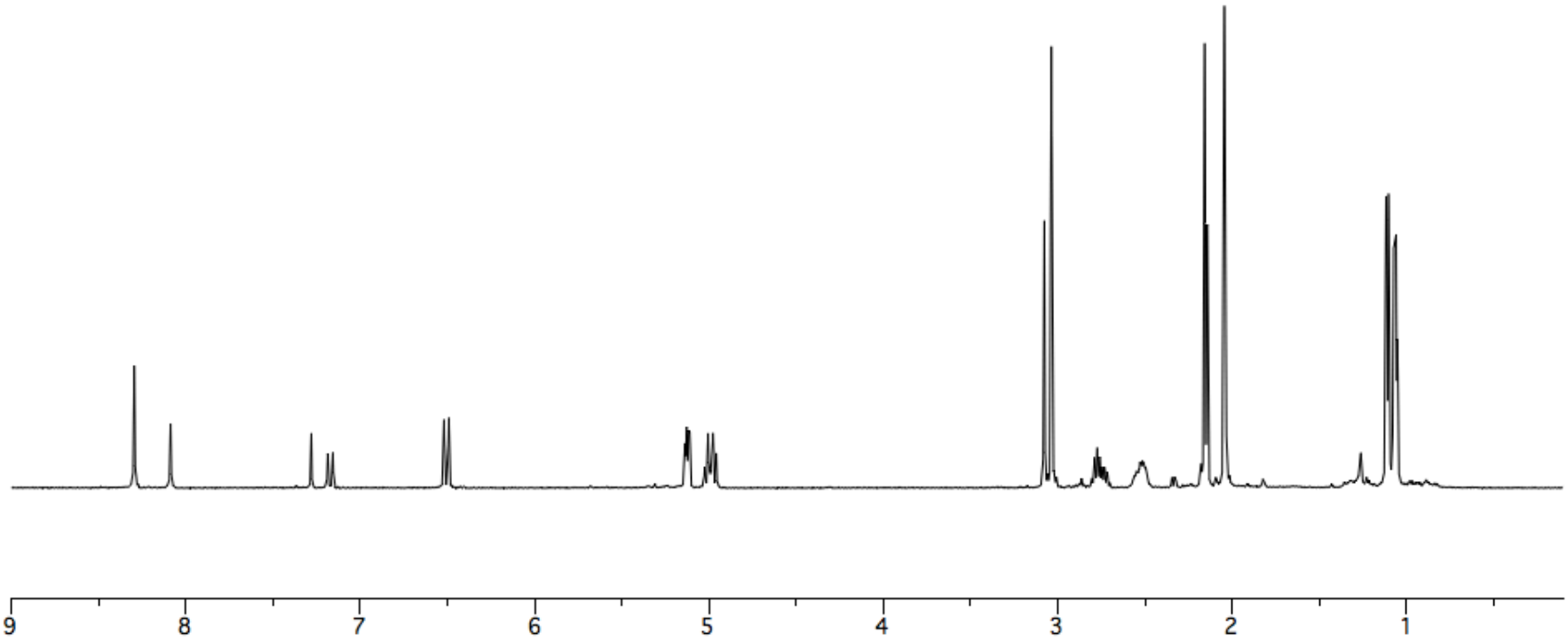
^{13}C NMR (100 MHz, $CDCl_3$)

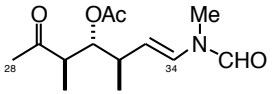




6

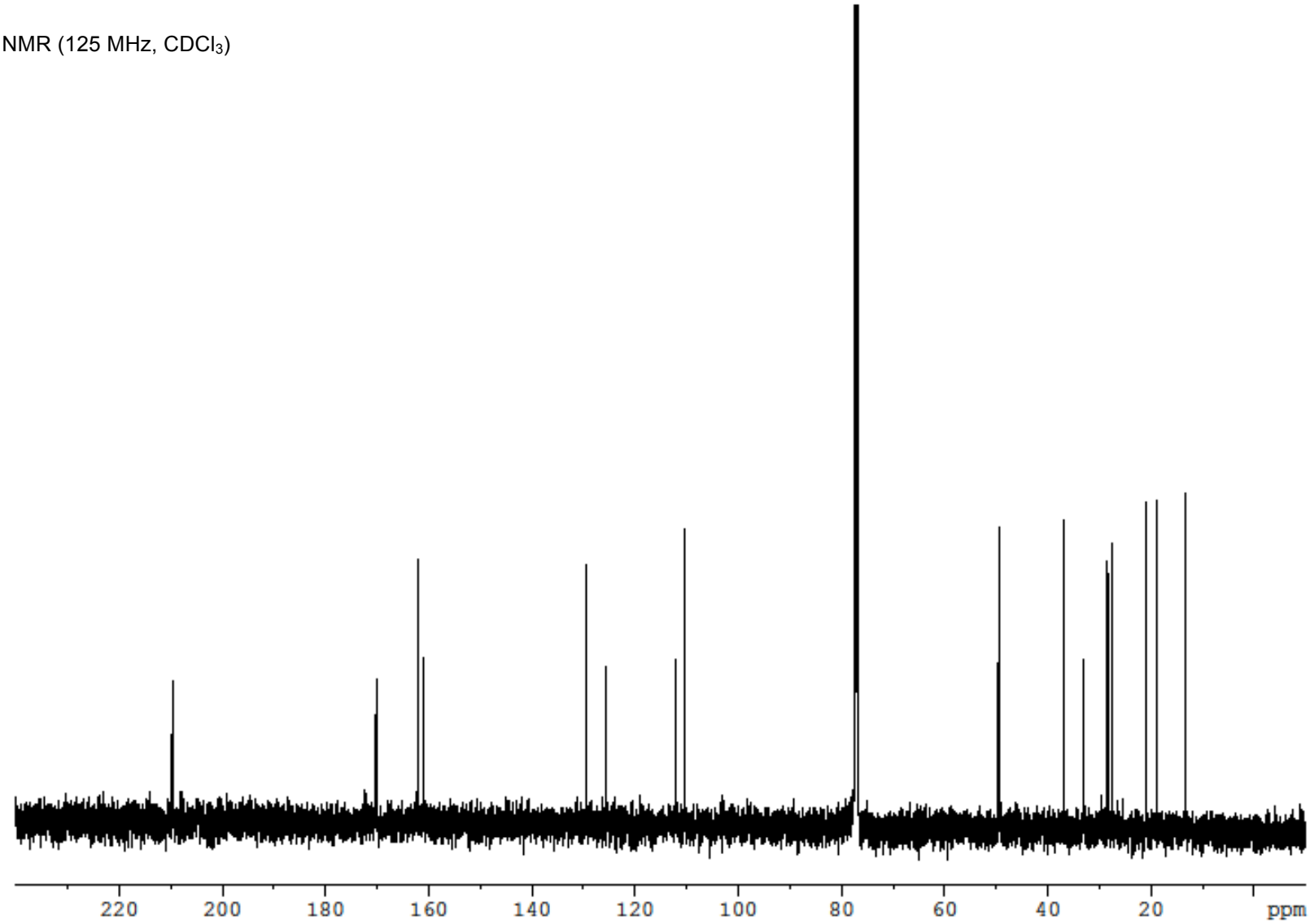
^{1}H NMR (500 MHz, $CDCl_3$)

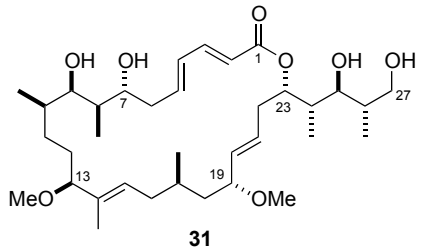




6

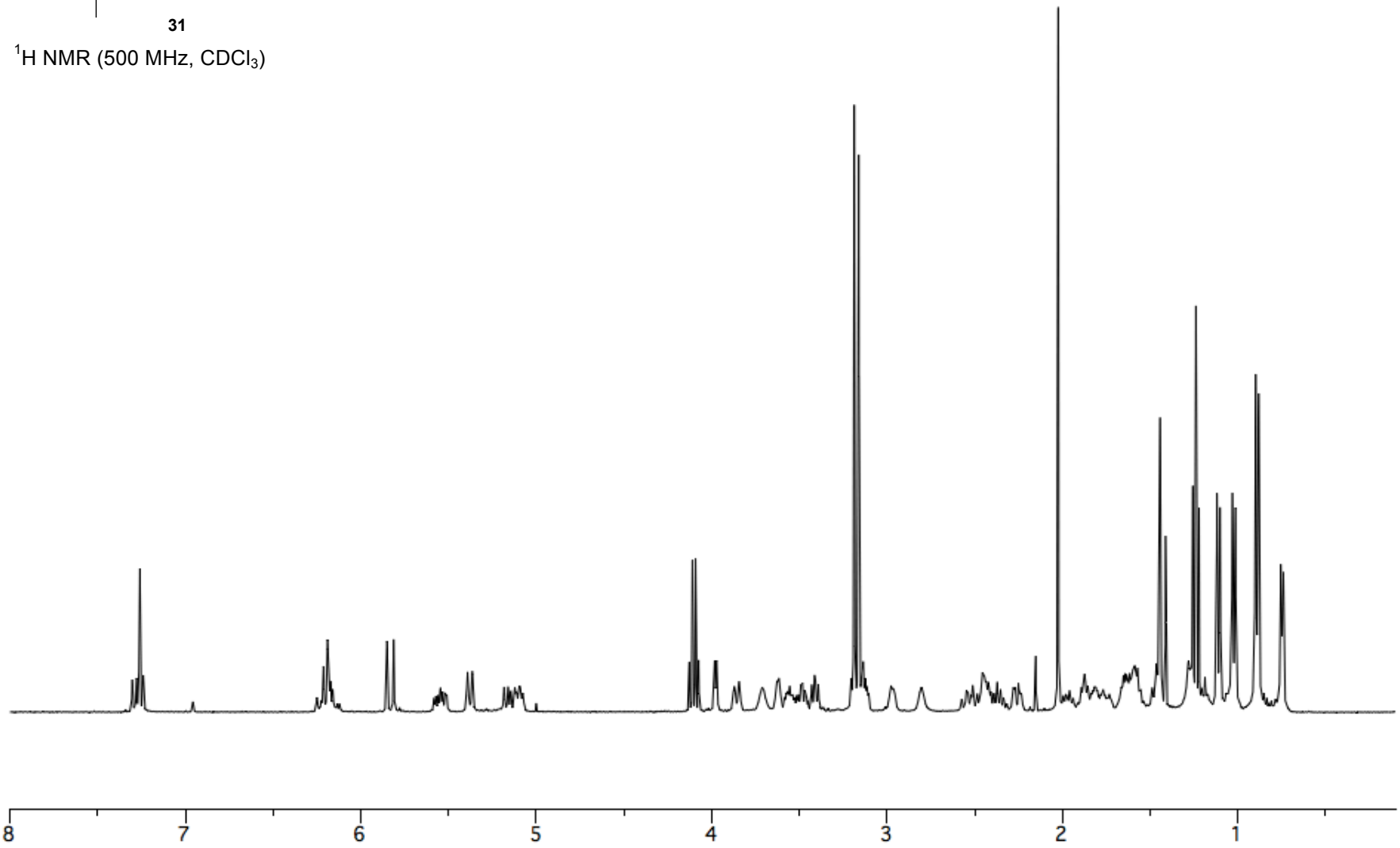
^{13}C NMR (125 MHz, $CDCl_3$)

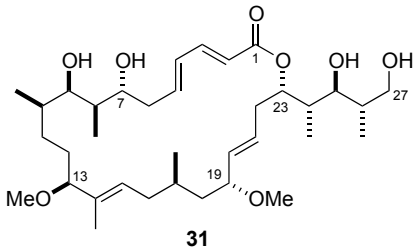




31

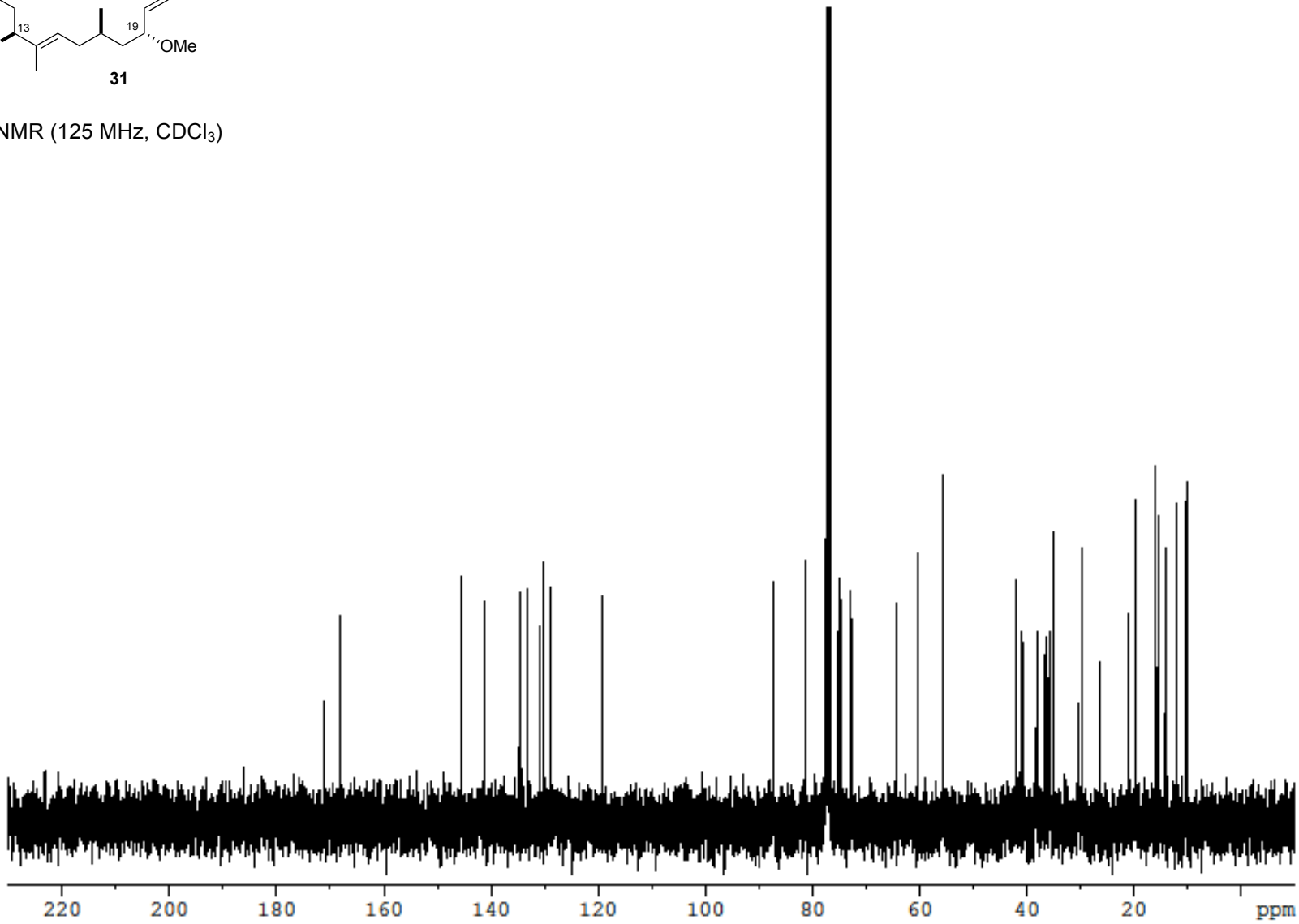
^{1}H NMR (500 MHz, $CDCl_3$)

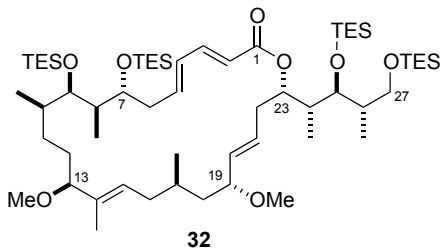




31

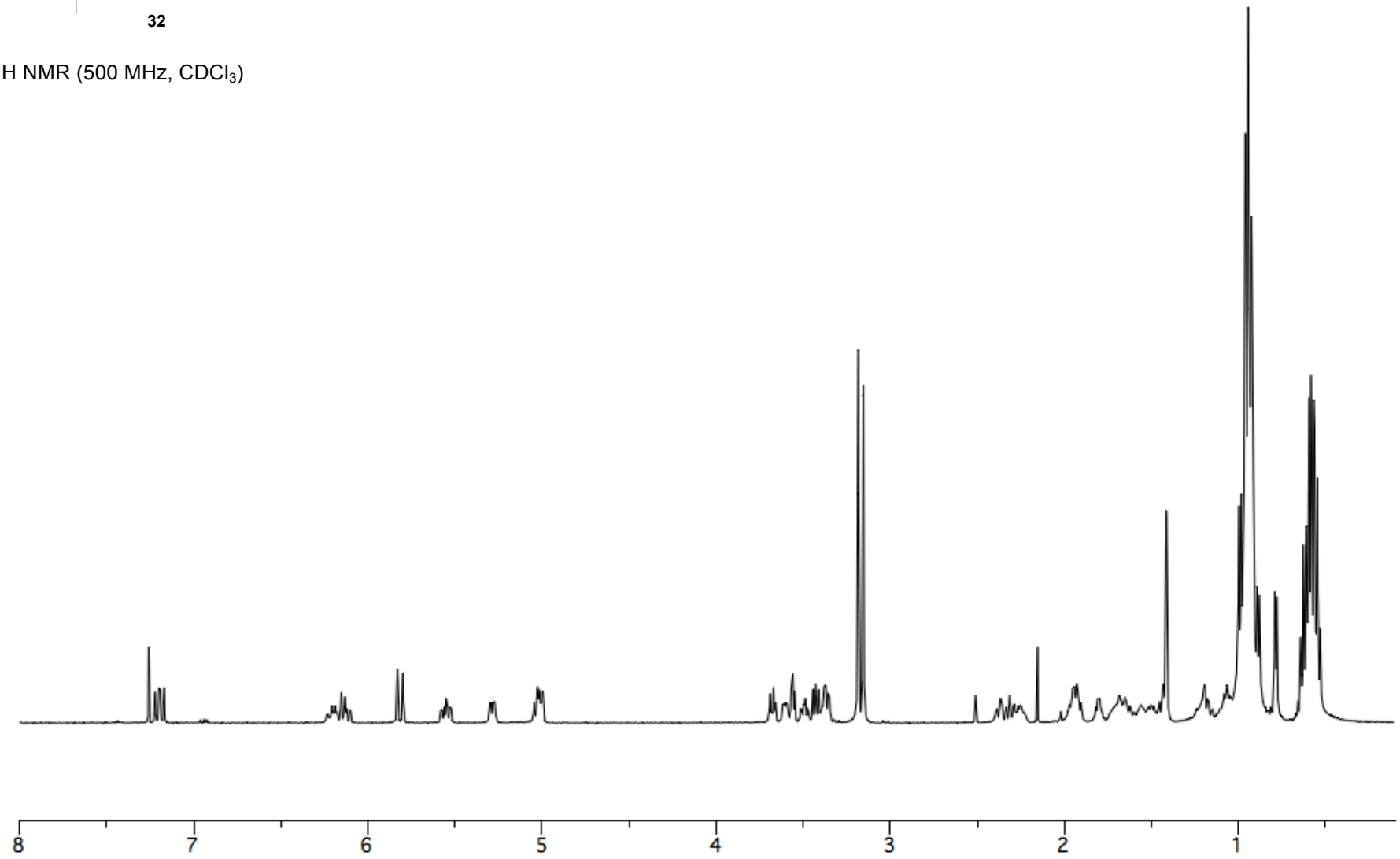
^{13}C NMR (125 MHz, $CDCl_3$)

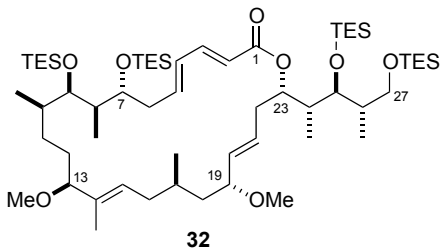




32

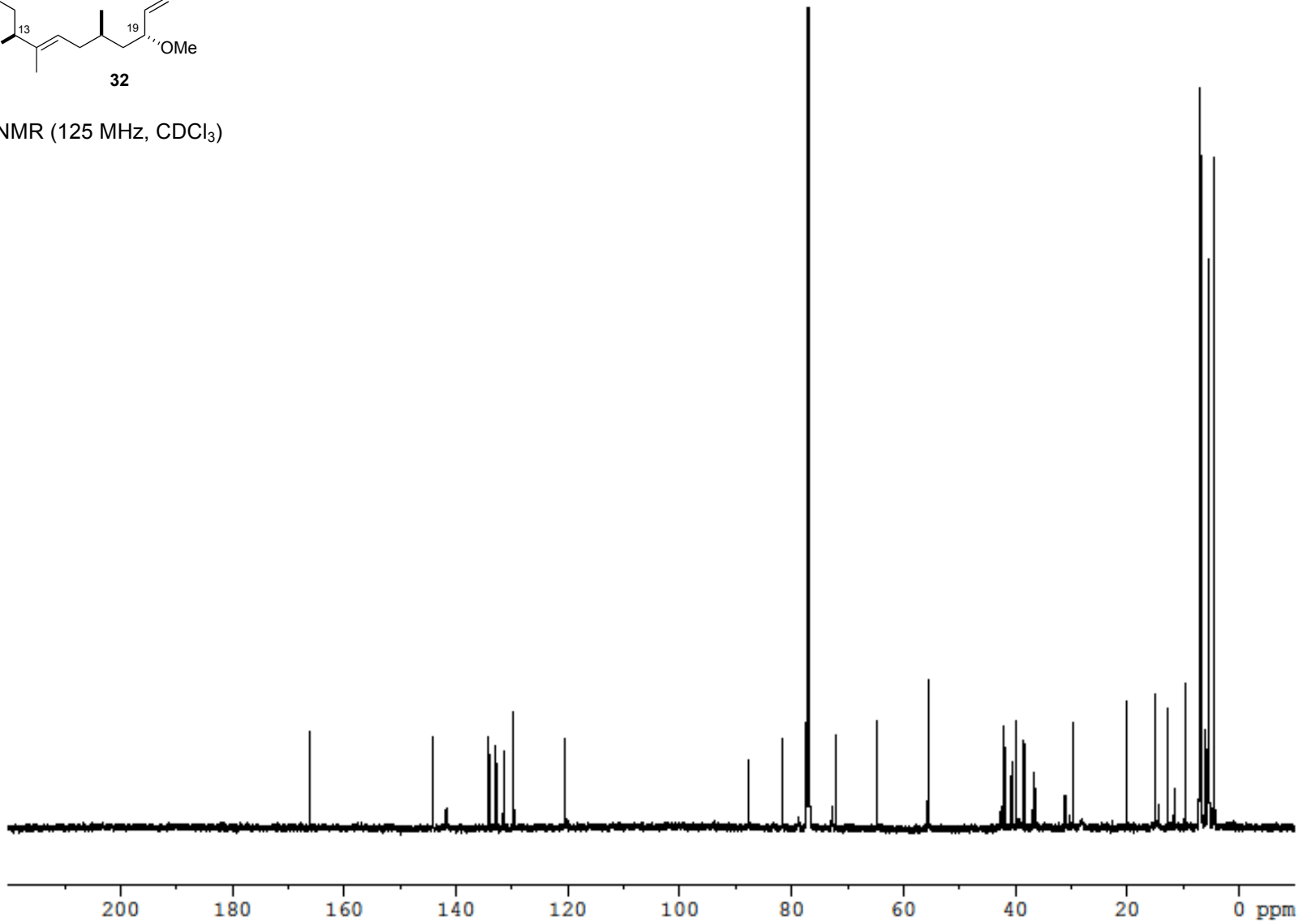
^{1}H NMR (500 MHz, $CDCl_3$)

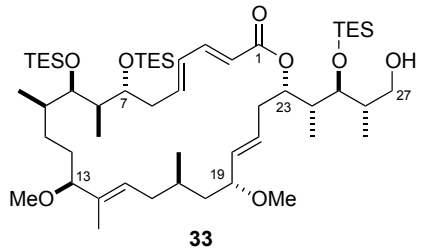




32

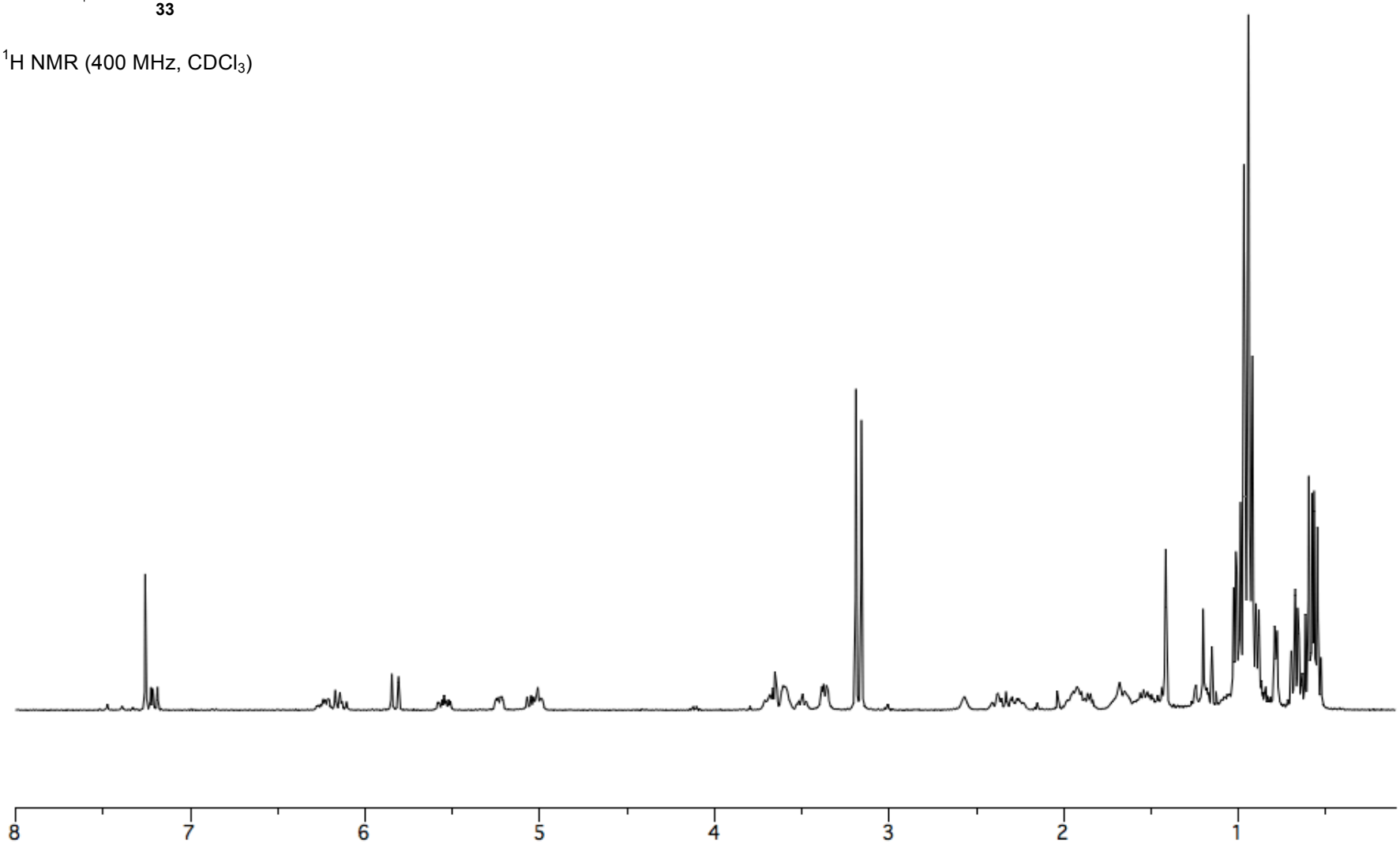
^{13}C NMR (125 MHz, $CDCl_3$)

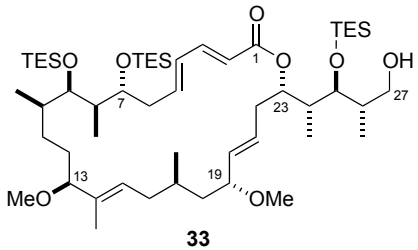




33

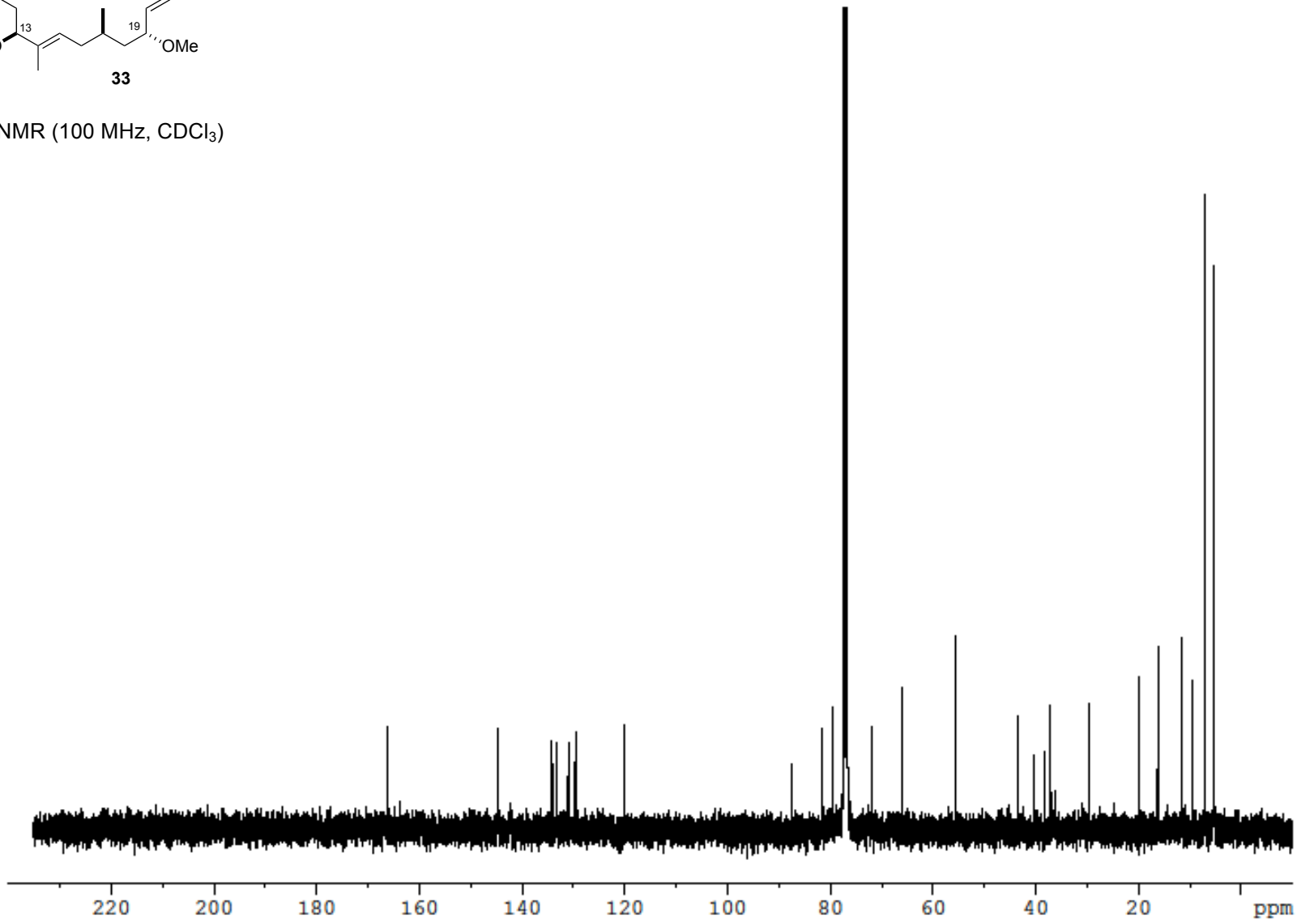
^{1}H NMR (400 MHz, $CDCl_3$)

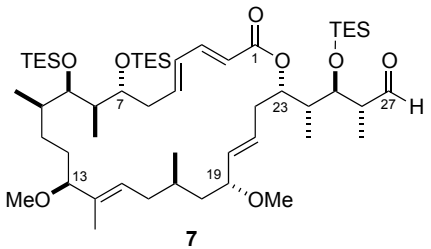




33

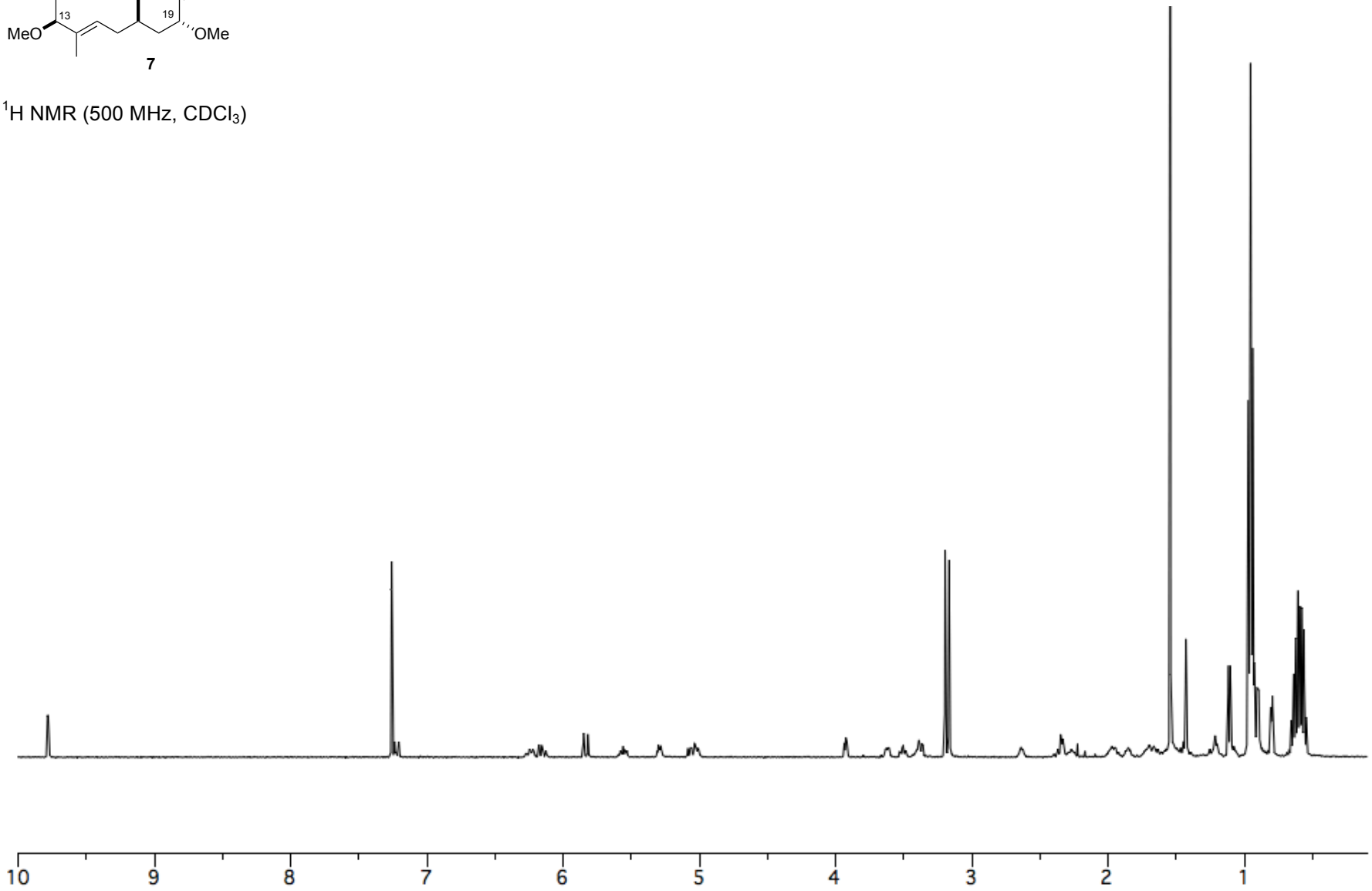
^{13}C NMR (100 MHz, $CDCl_3$)

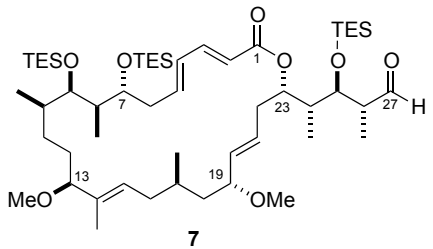




7

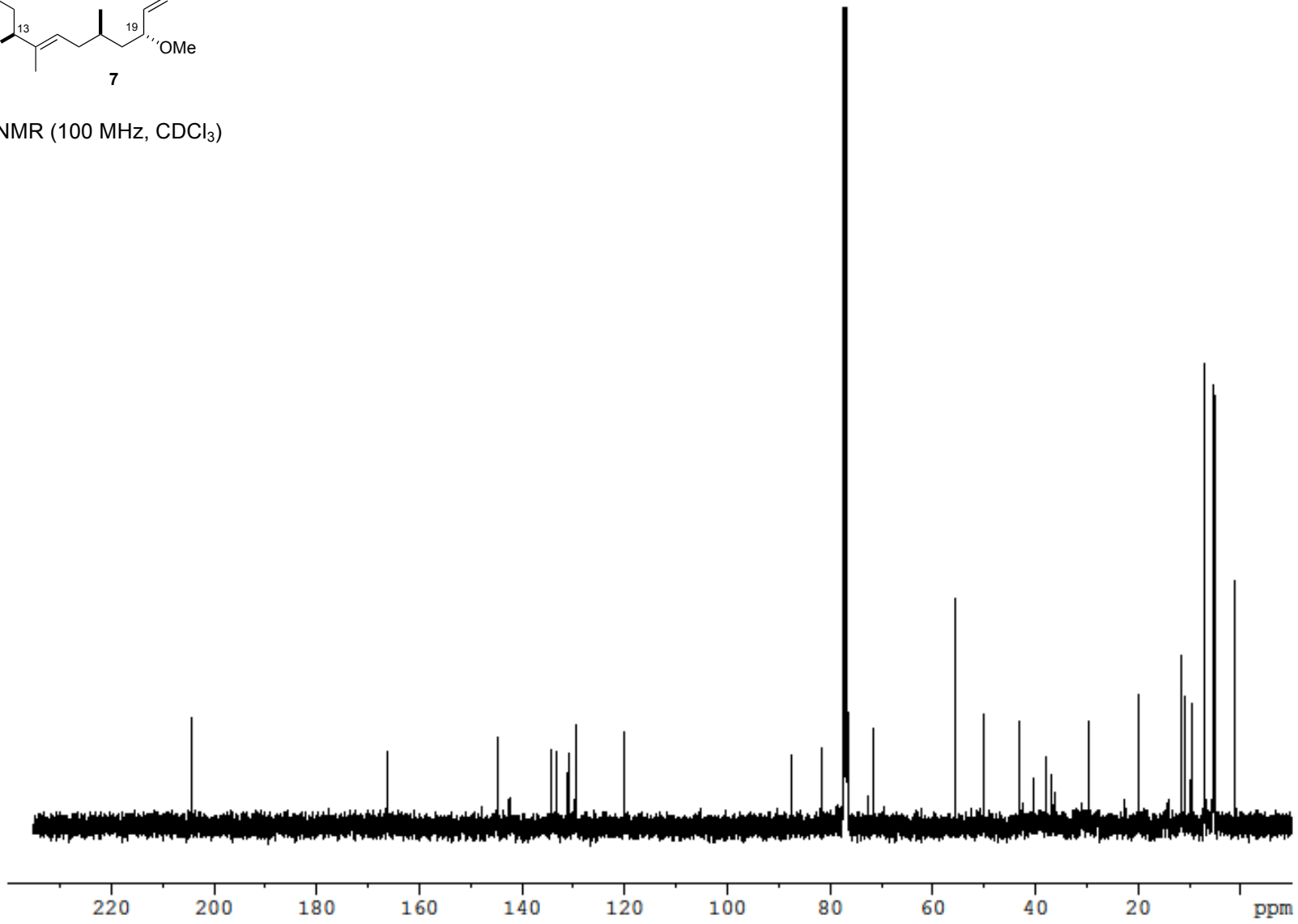
^{1}H NMR (500 MHz, $CDCl_3$)

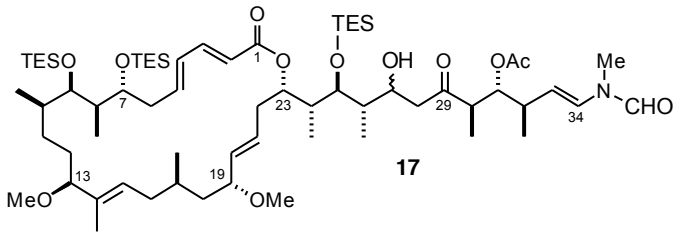




7

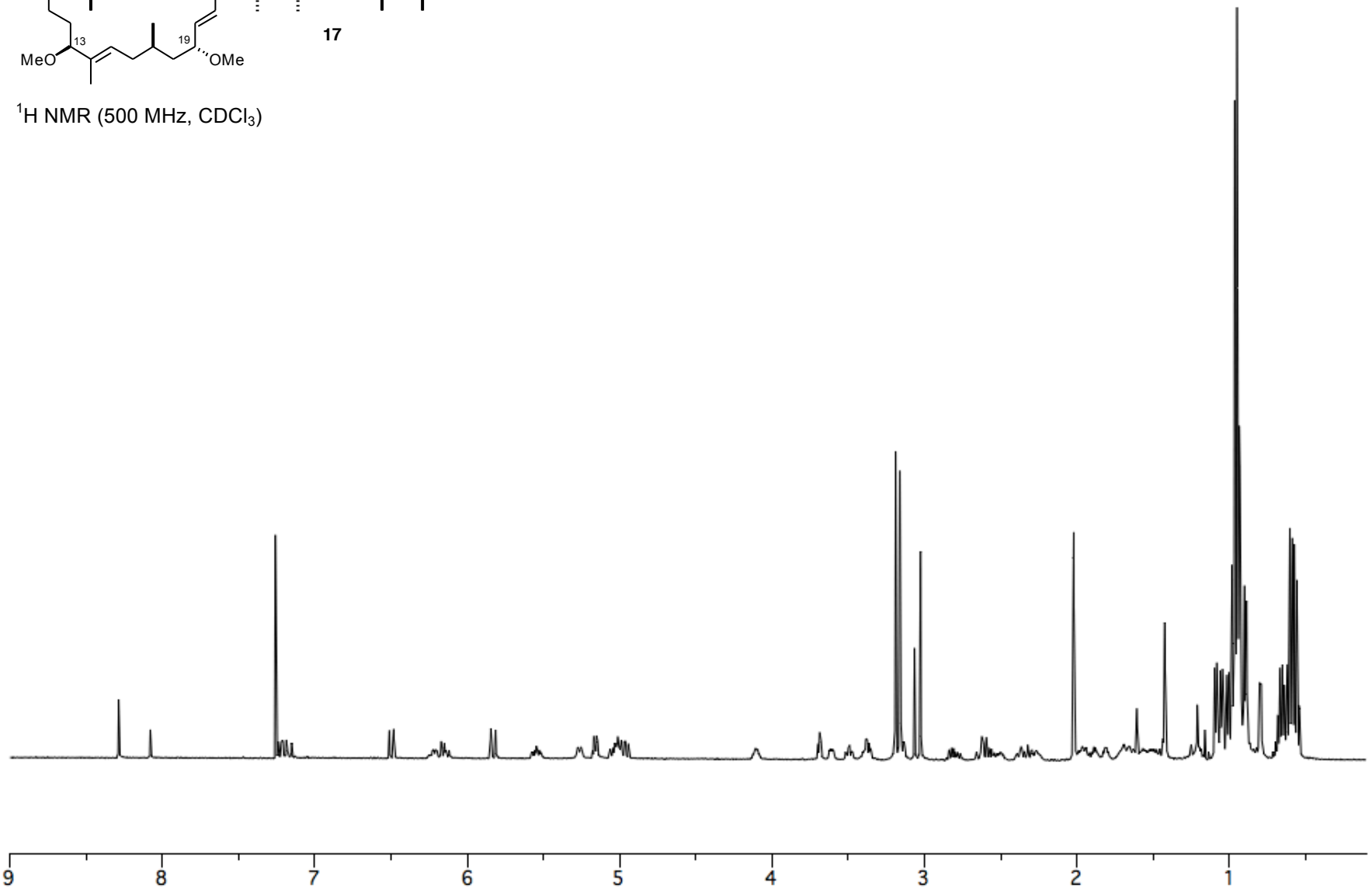
^{13}C NMR (100 MHz, $CDCl_3$)

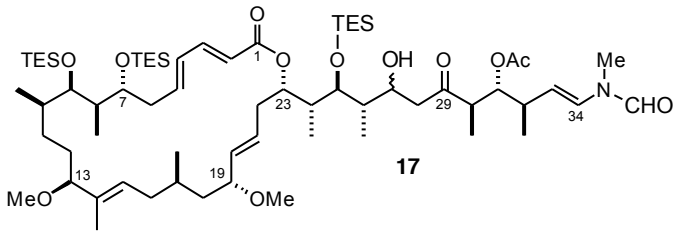




17

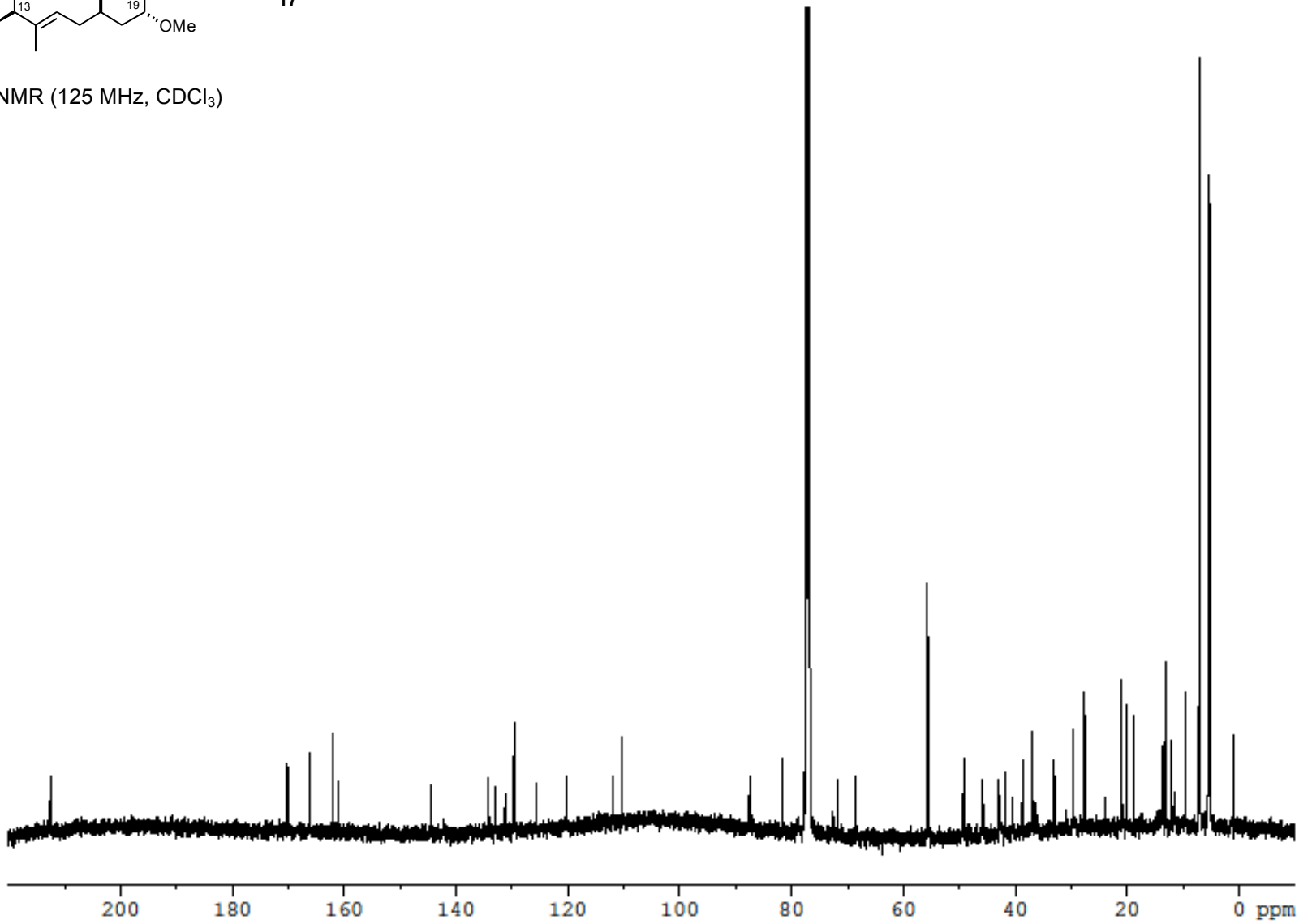
^{1}H NMR (500 MHz, $CDCl_3$)

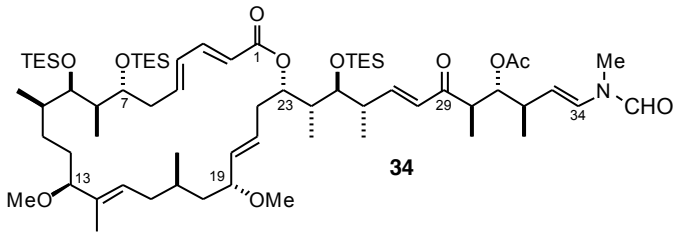




17

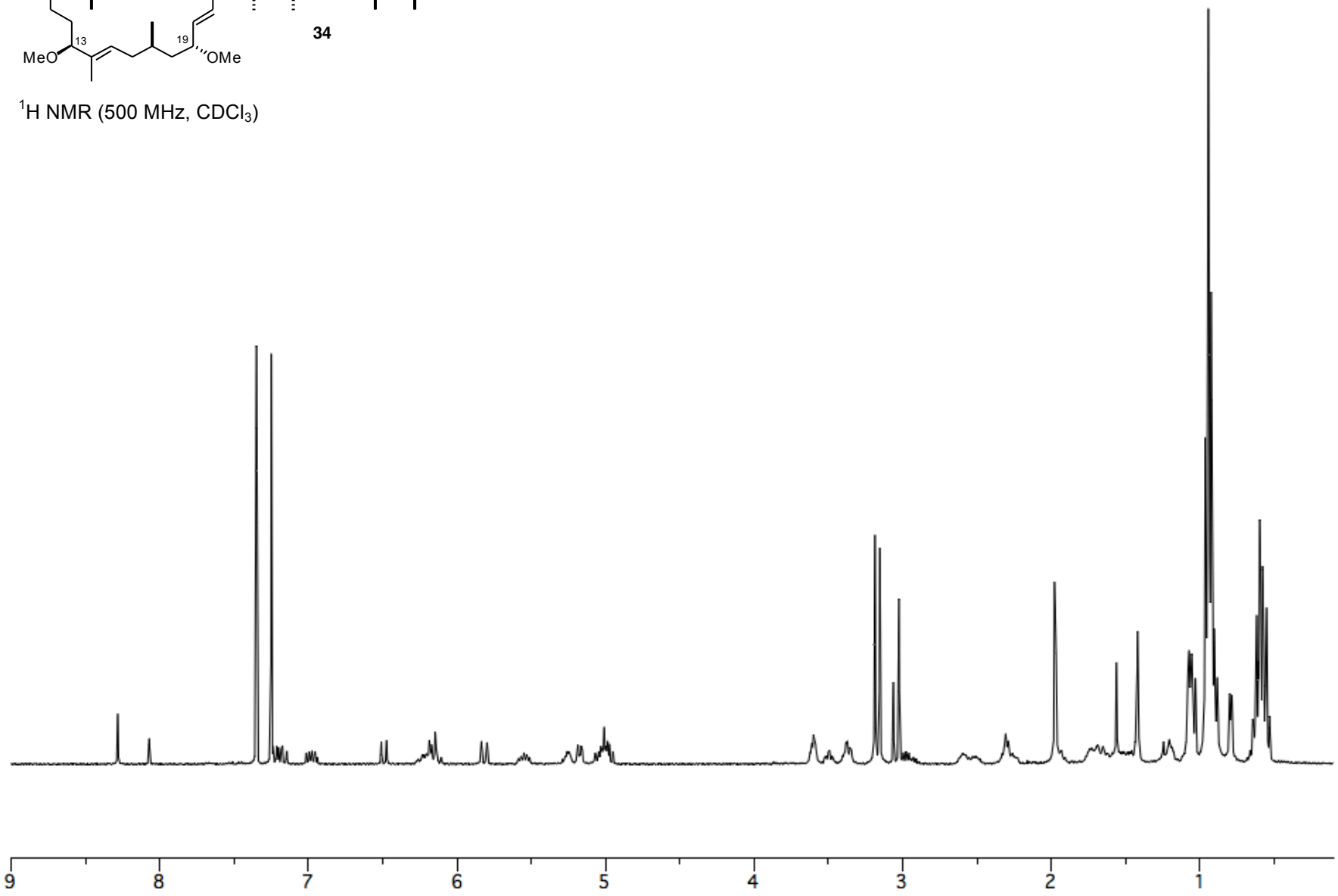
^{13}C NMR (125 MHz, $CDCl_3$)

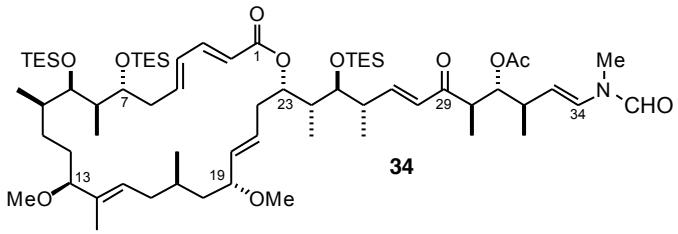




34

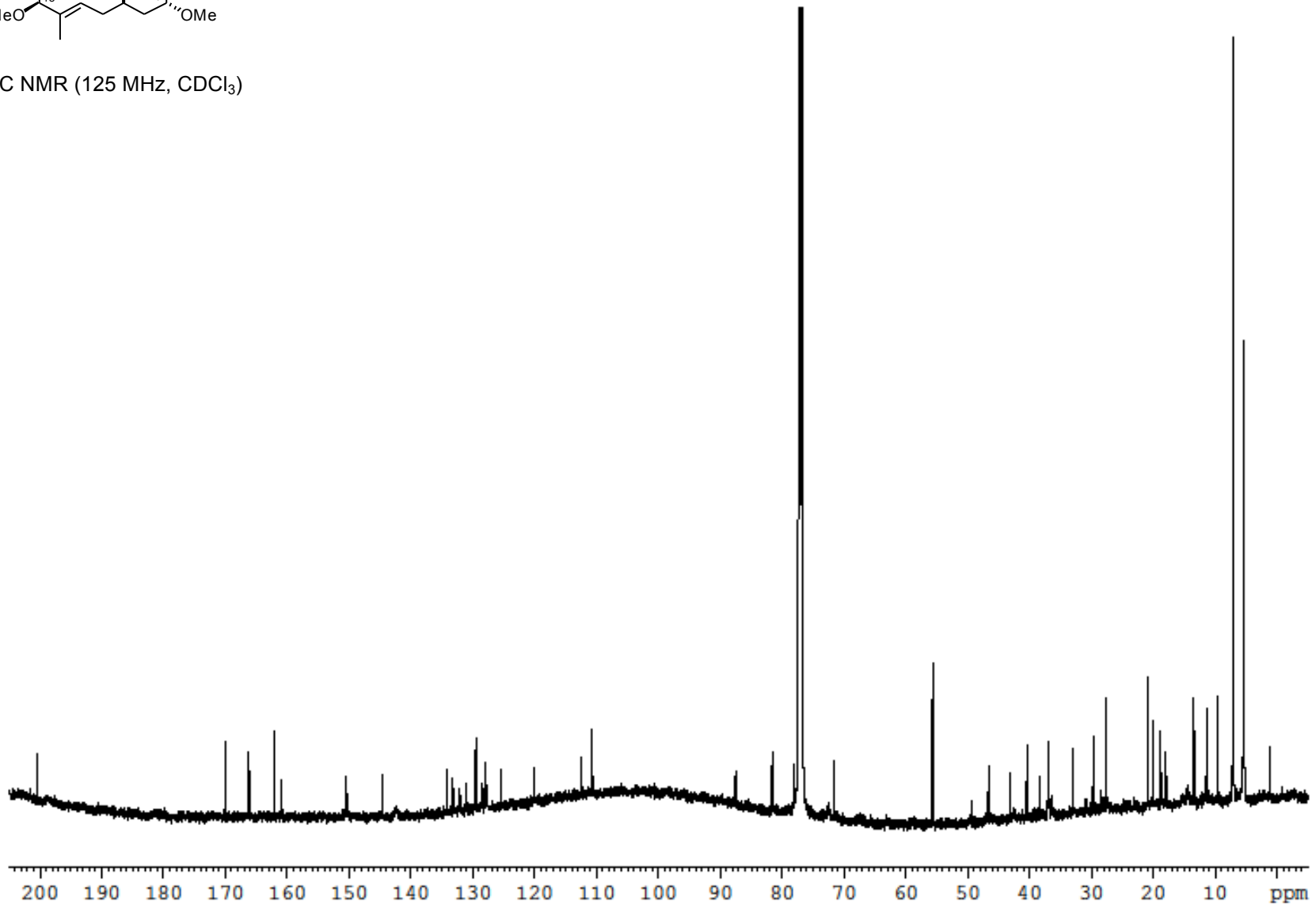
^{1}H NMR (500 MHz, $CDCl_3$)

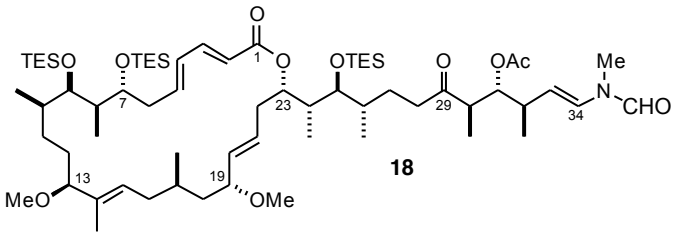




34

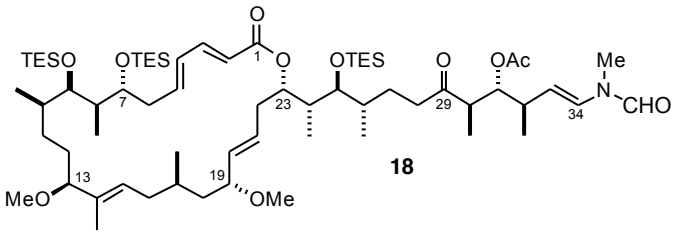
^{13}C NMR (125 MHz, $CDCl_3$)





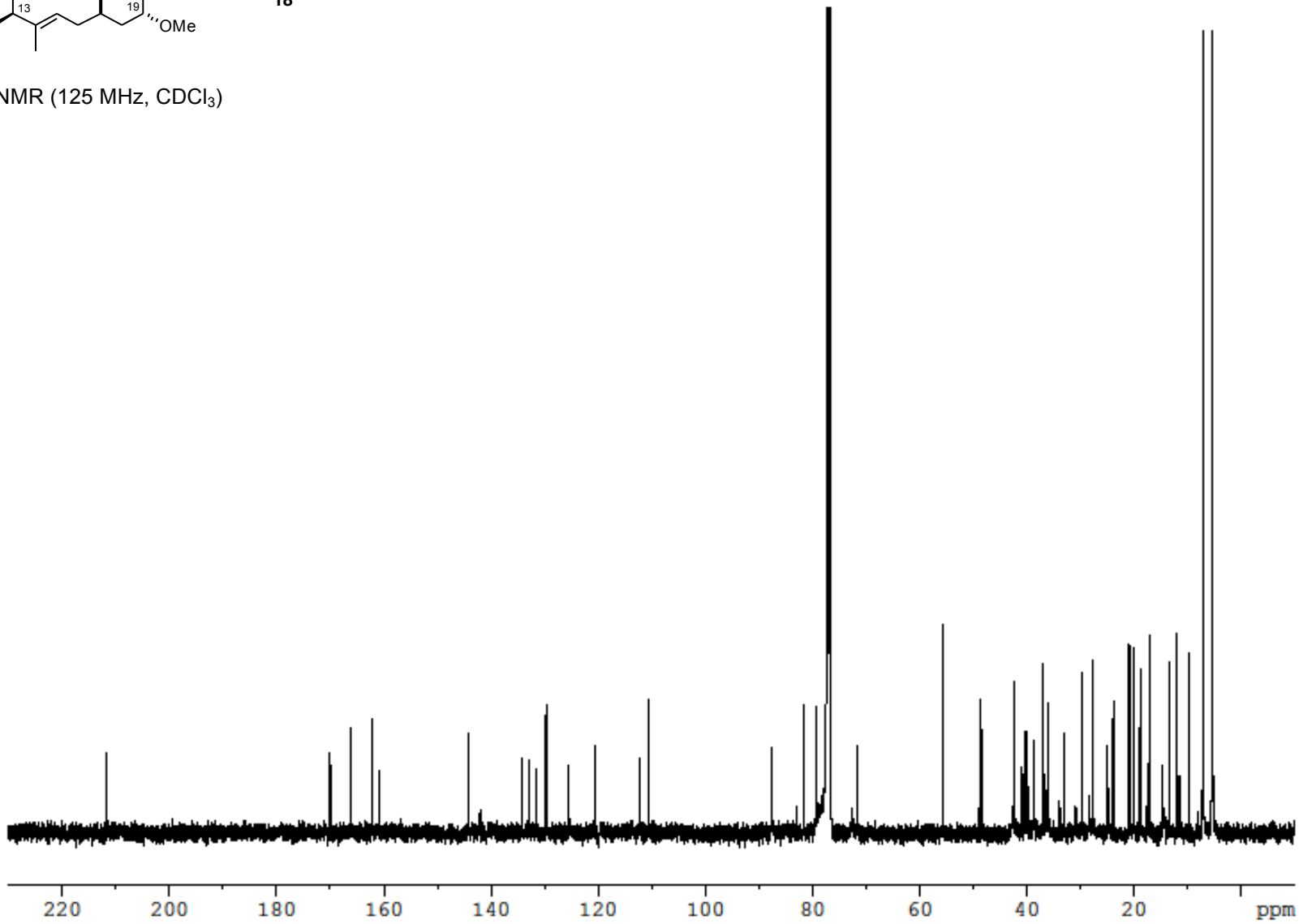
18

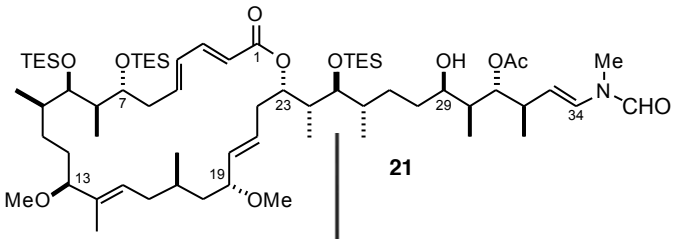
^{1}H NMR (500 MHz, $CDCl_3$)



18

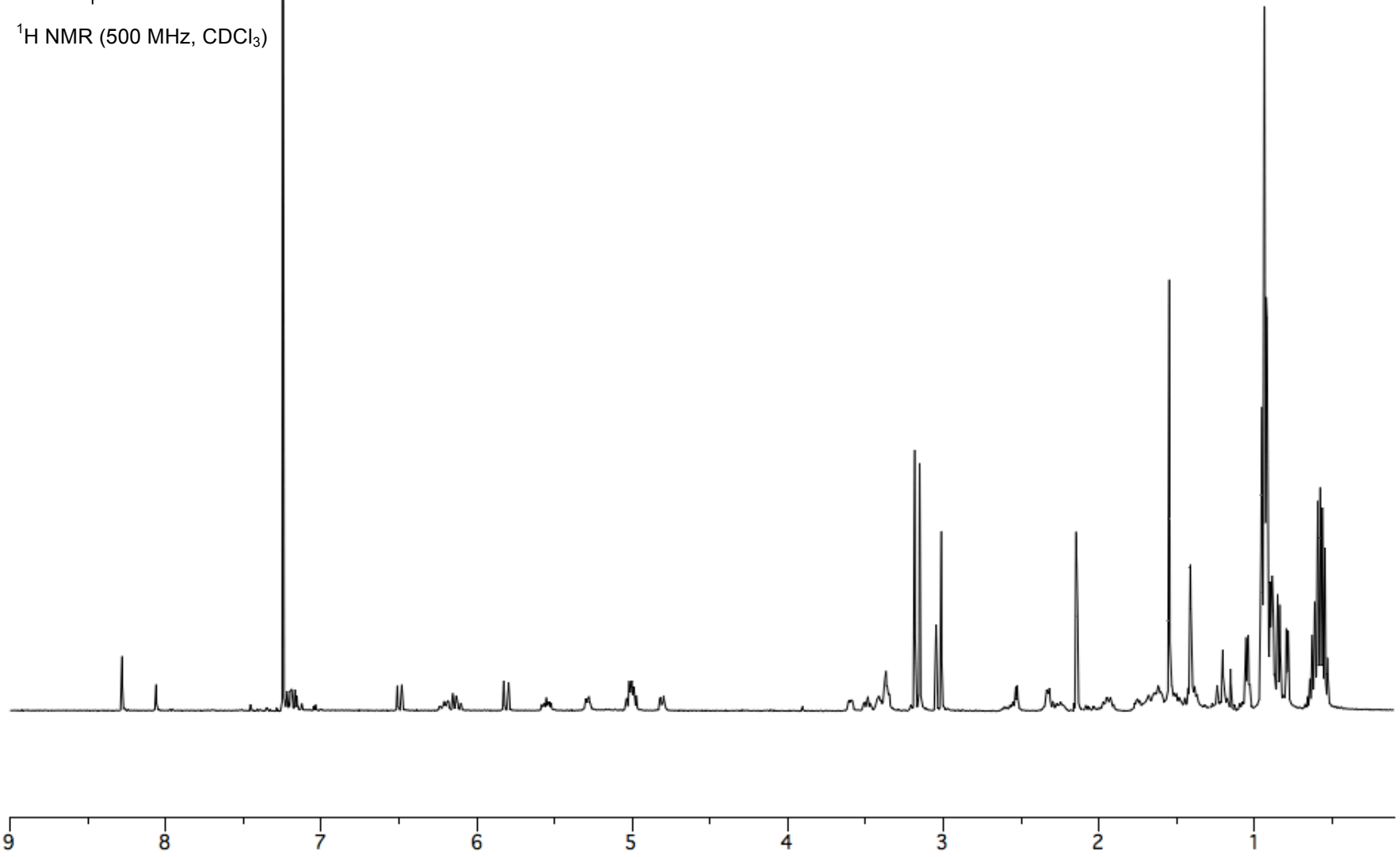
^{13}C NMR (125 MHz, $CDCl_3$)

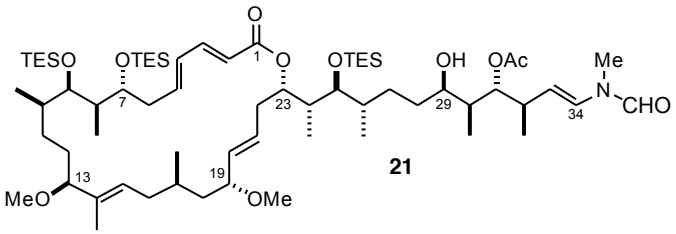




21

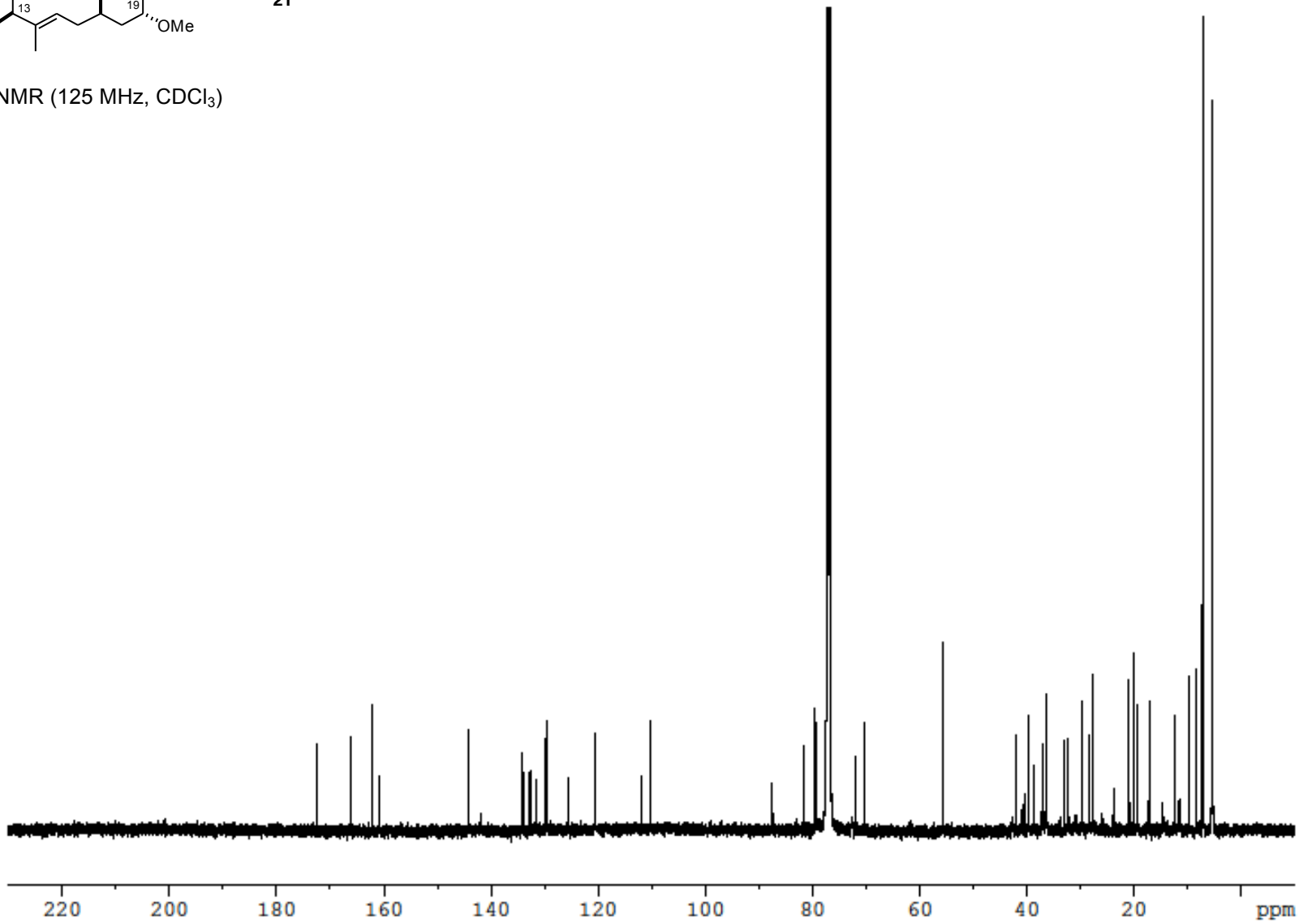
^{1}H NMR (500 MHz, $CDCl_3$)

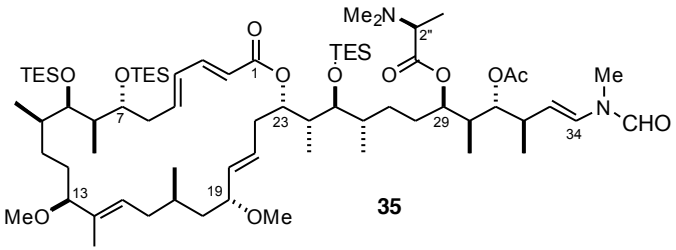




21

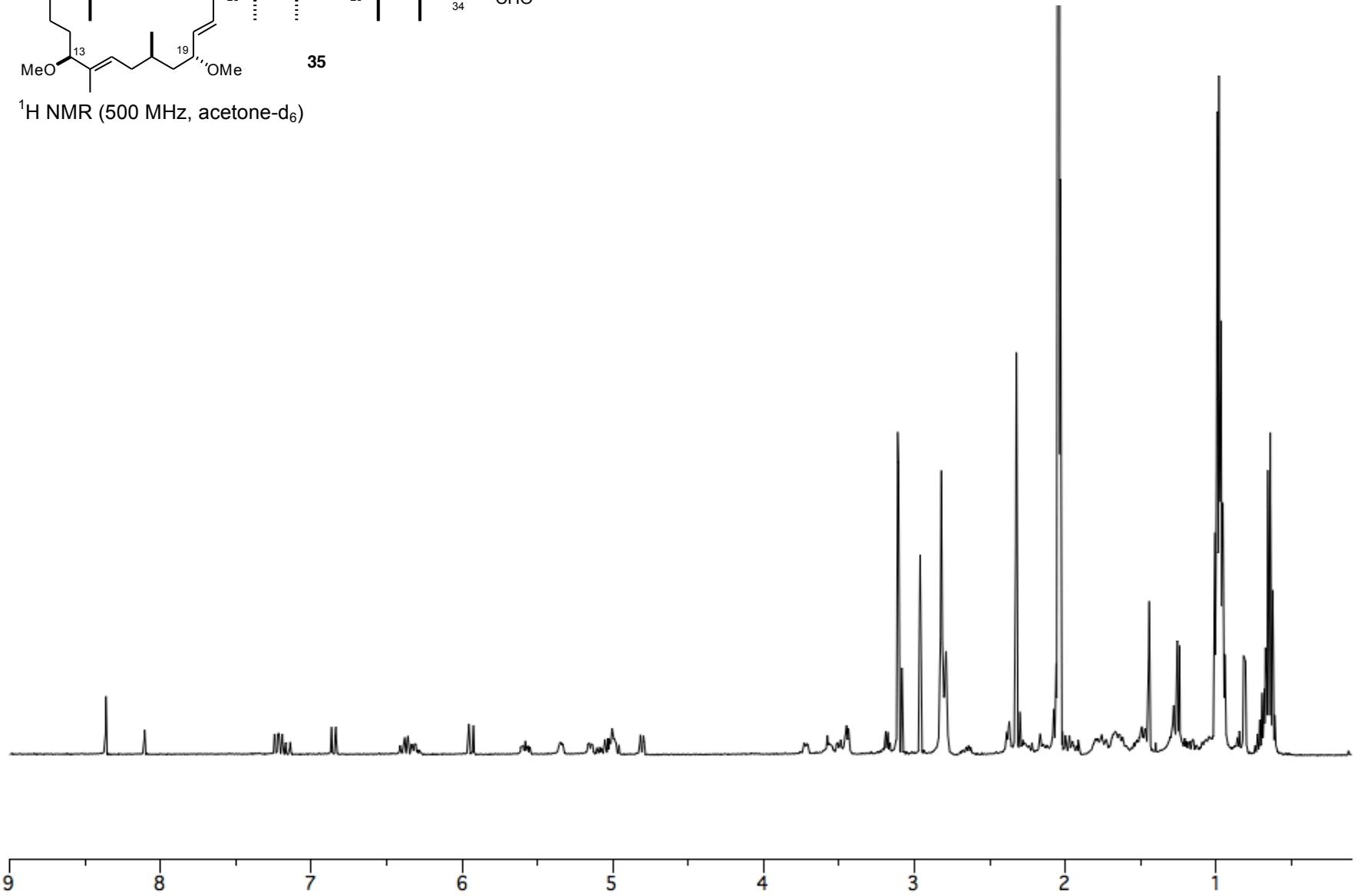
^{13}C NMR (125 MHz, $CDCl_3$)

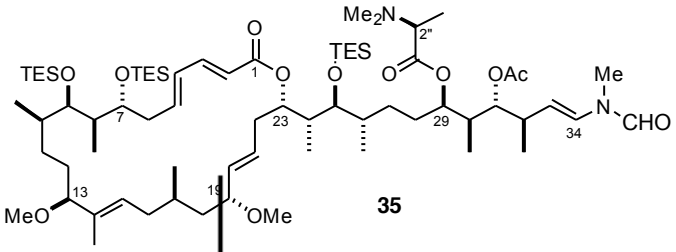




35

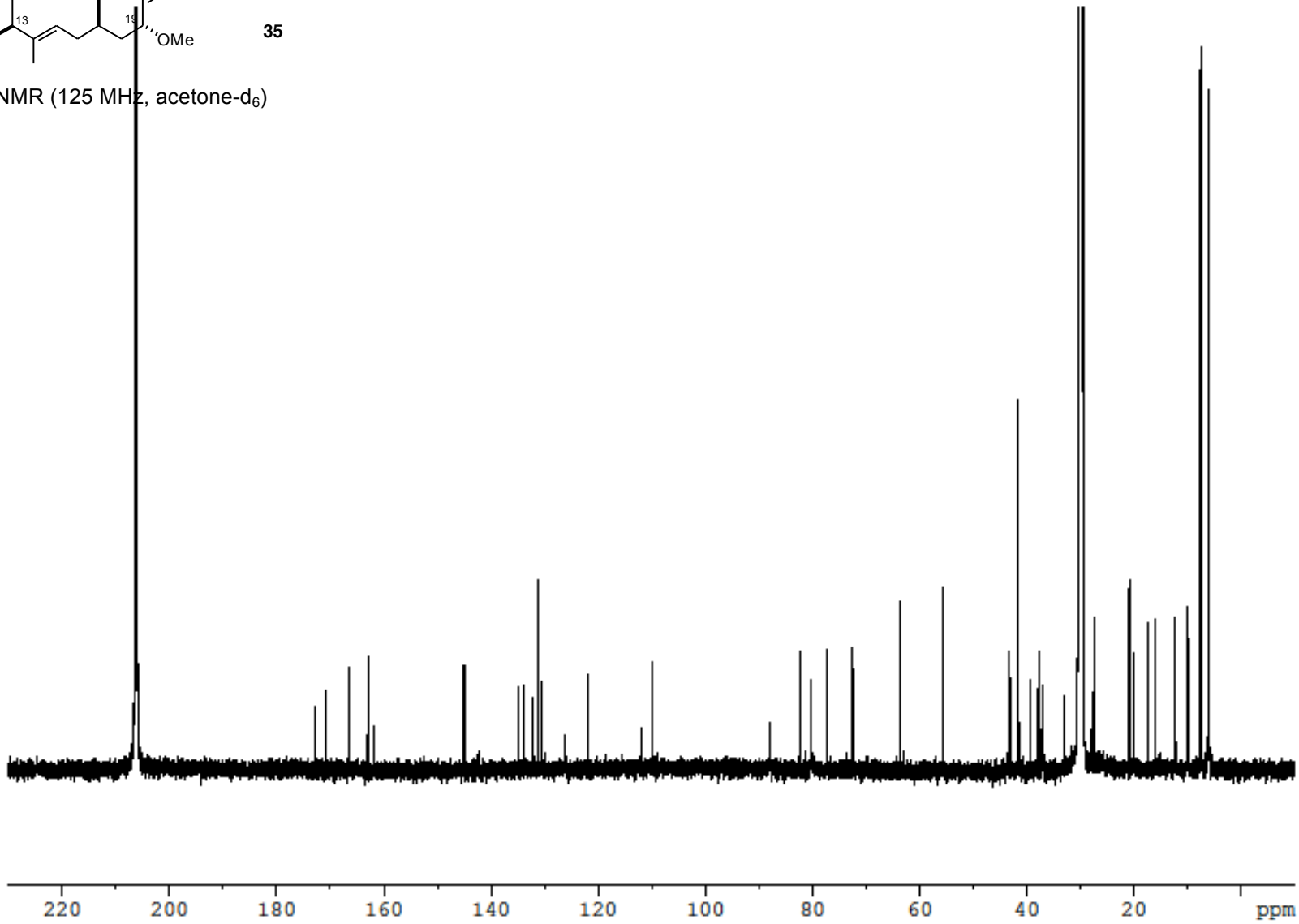
^{1}H NMR (500 MHz, acetone-d_6)

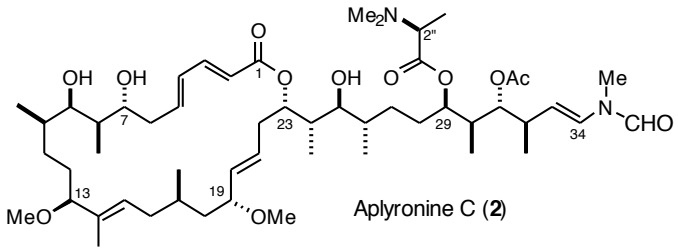




35

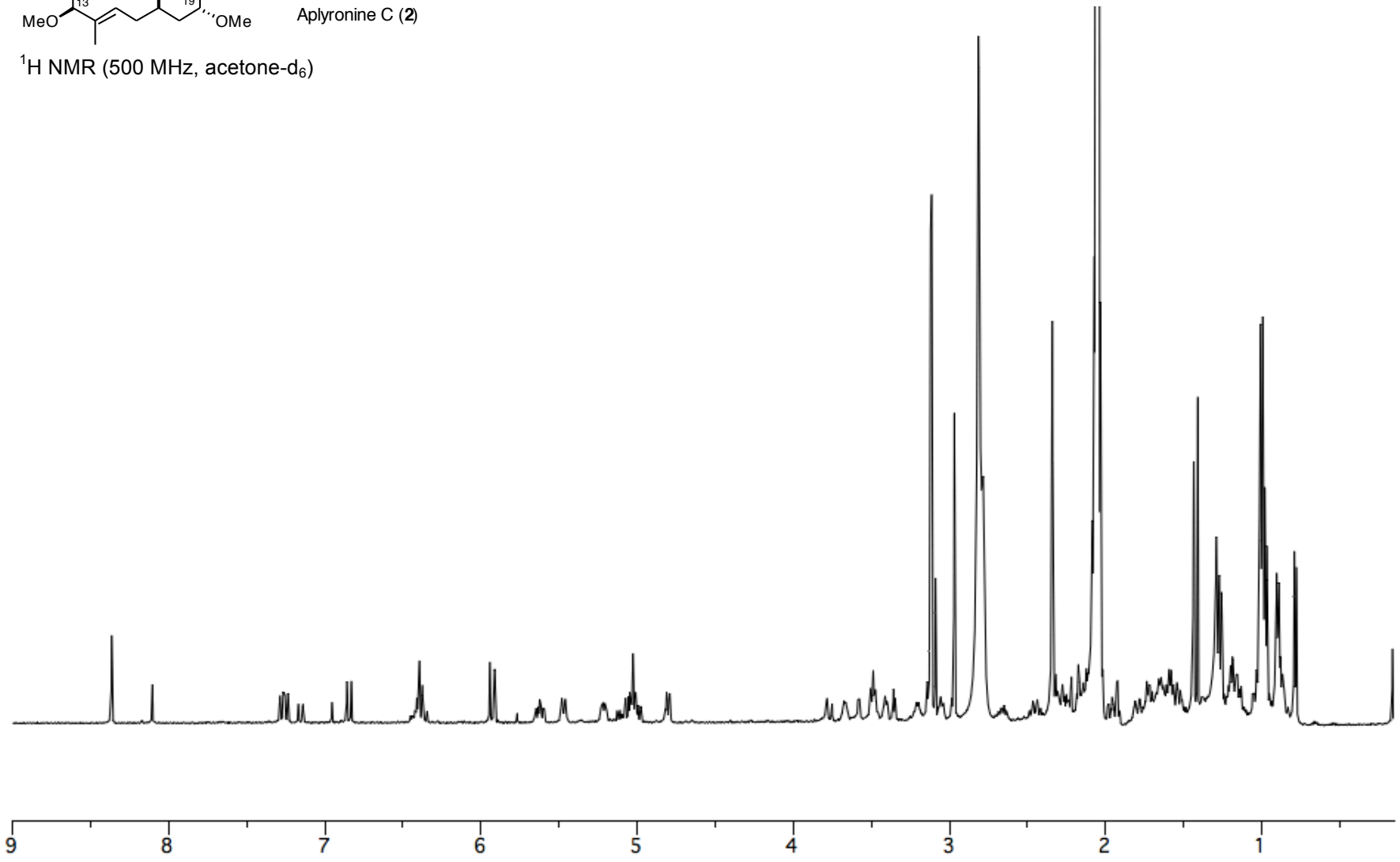
^{13}C NMR (125 MHz, acetone-d_6)

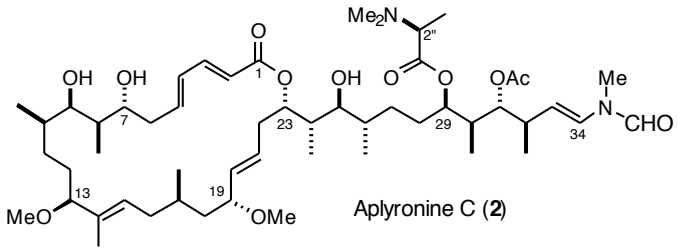




Aplyronine C (**2**)

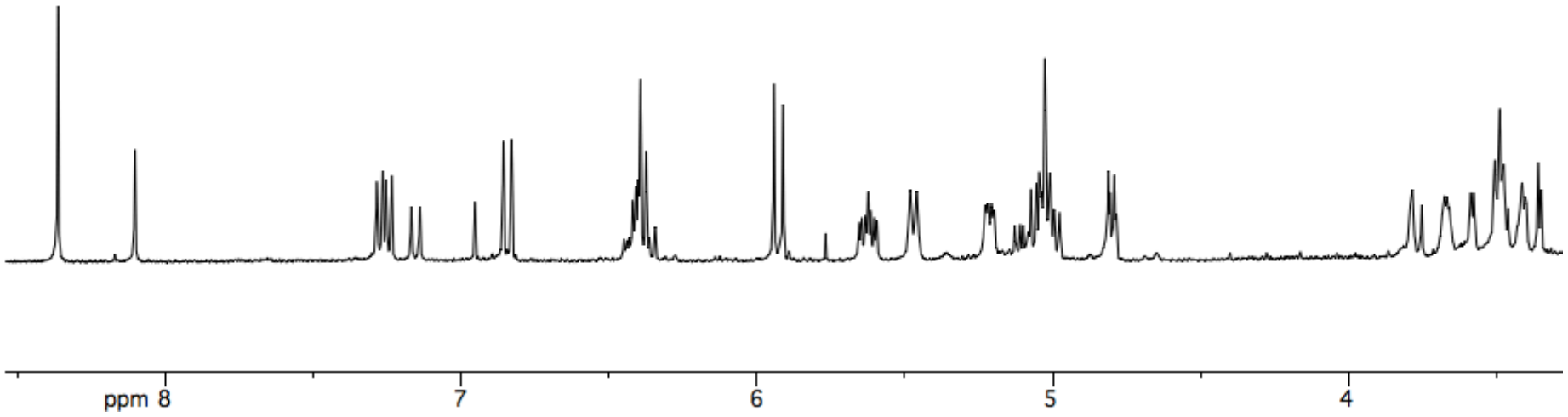
^{1}H NMR (500 MHz, acetone-d_6)

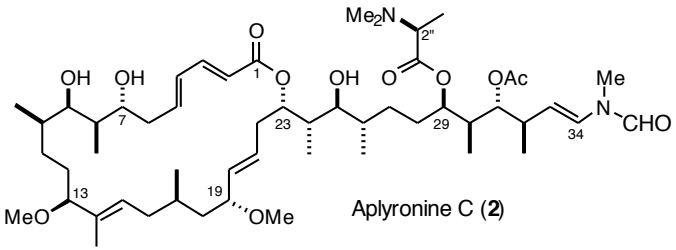




Aplyronine C (**2**)

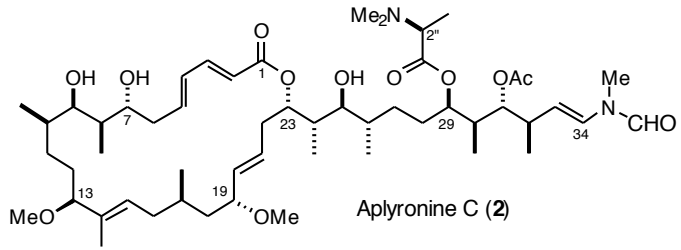
^{1}H NMR (500 MHz, acetone-d_6)





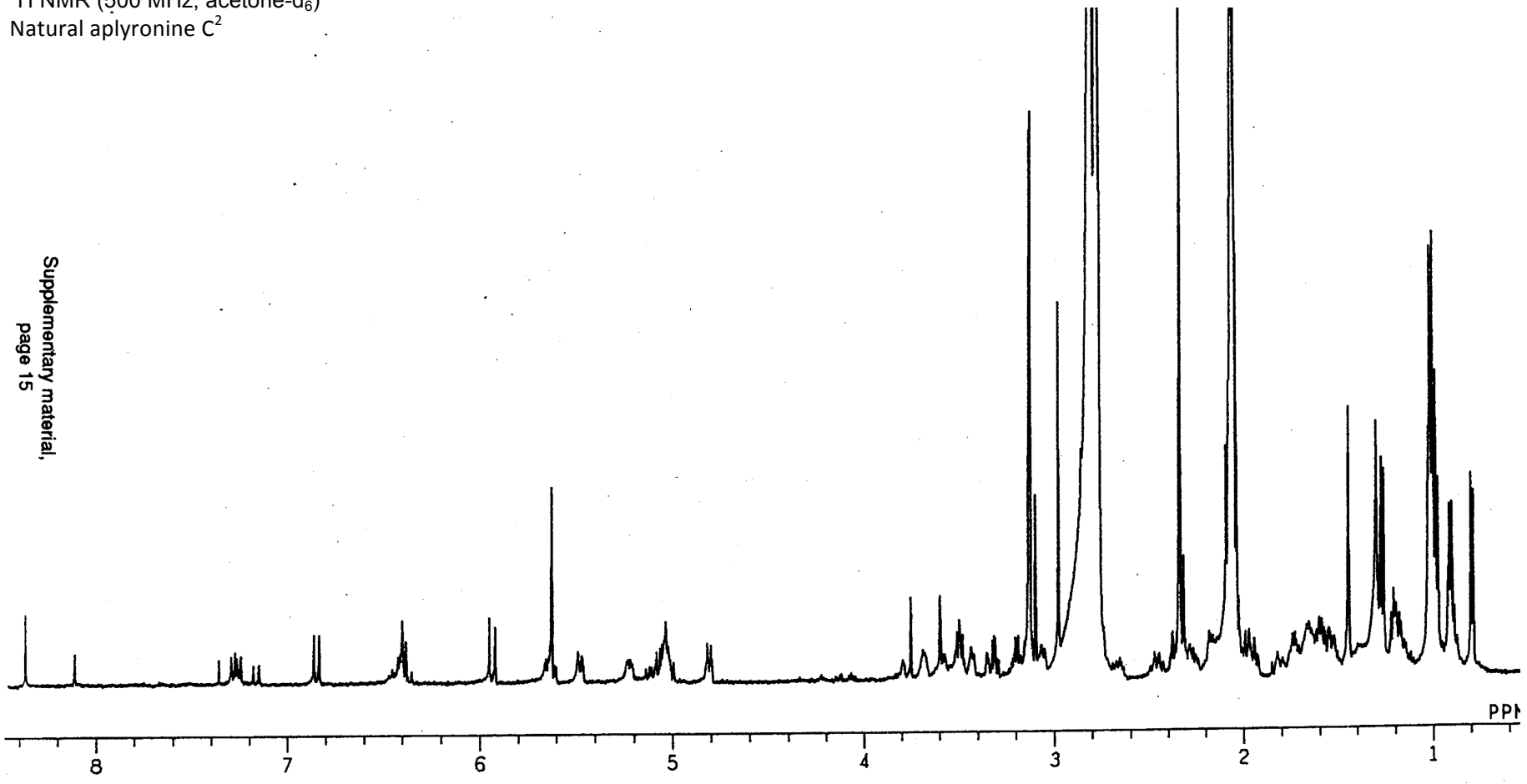
Aplyronine C (**2**)

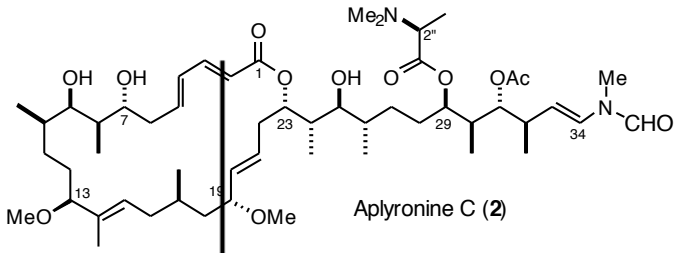
^{1}H NMR (500 MHz, acetone-d_6)



Aplyronine C (**2**)

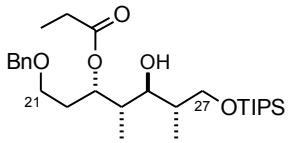
^{1}H NMR (500 MHz, acetone-d_6)
Natural aplyronine C[2]





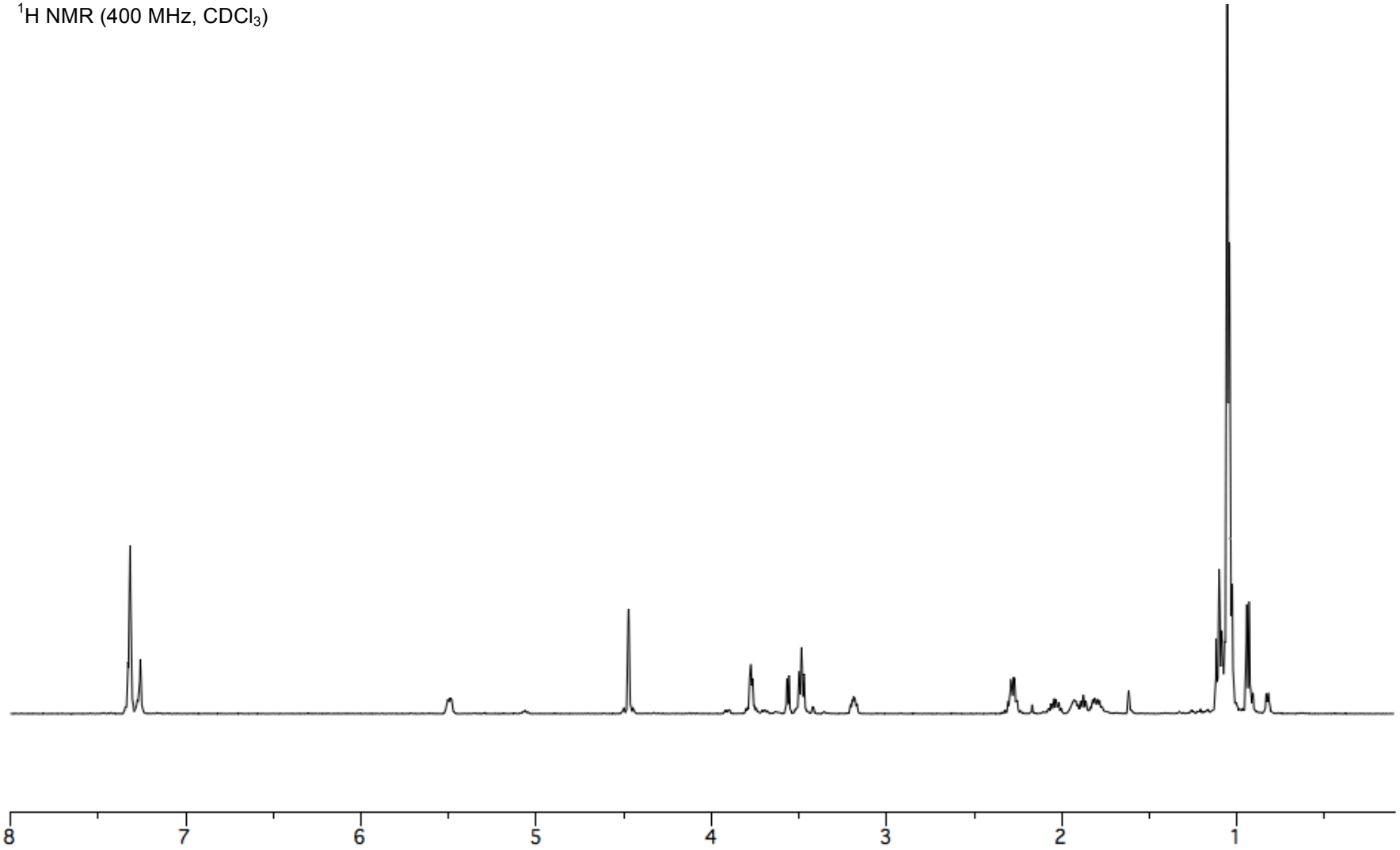
Aplyronine C (**2**)

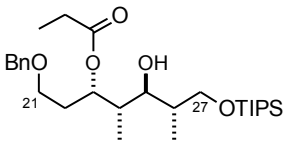
^{13}C NMR (125 MHz, acetone-d_6)



37

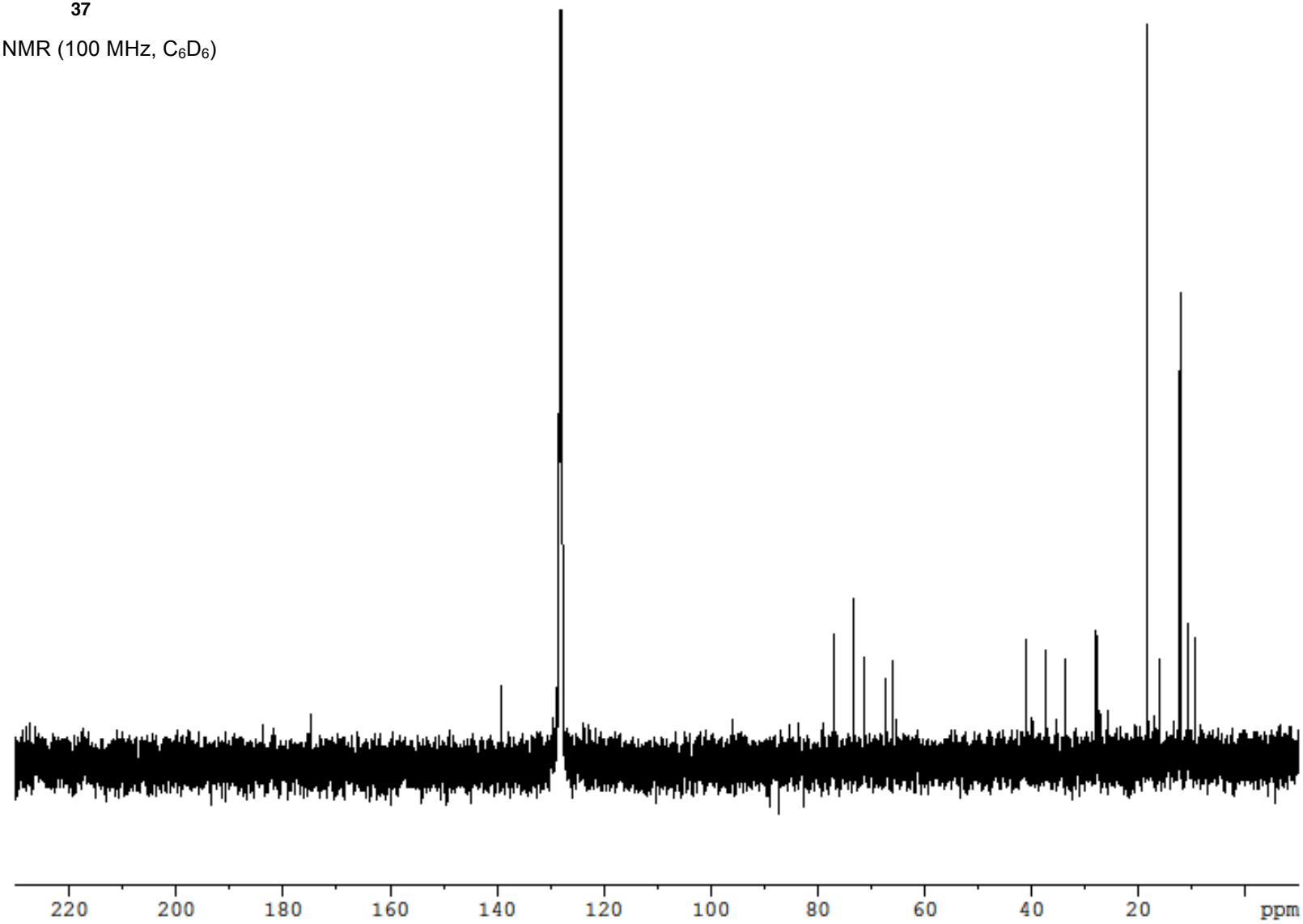
^{1}H NMR (400 MHz, $CDCl_3$)

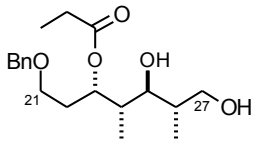




37

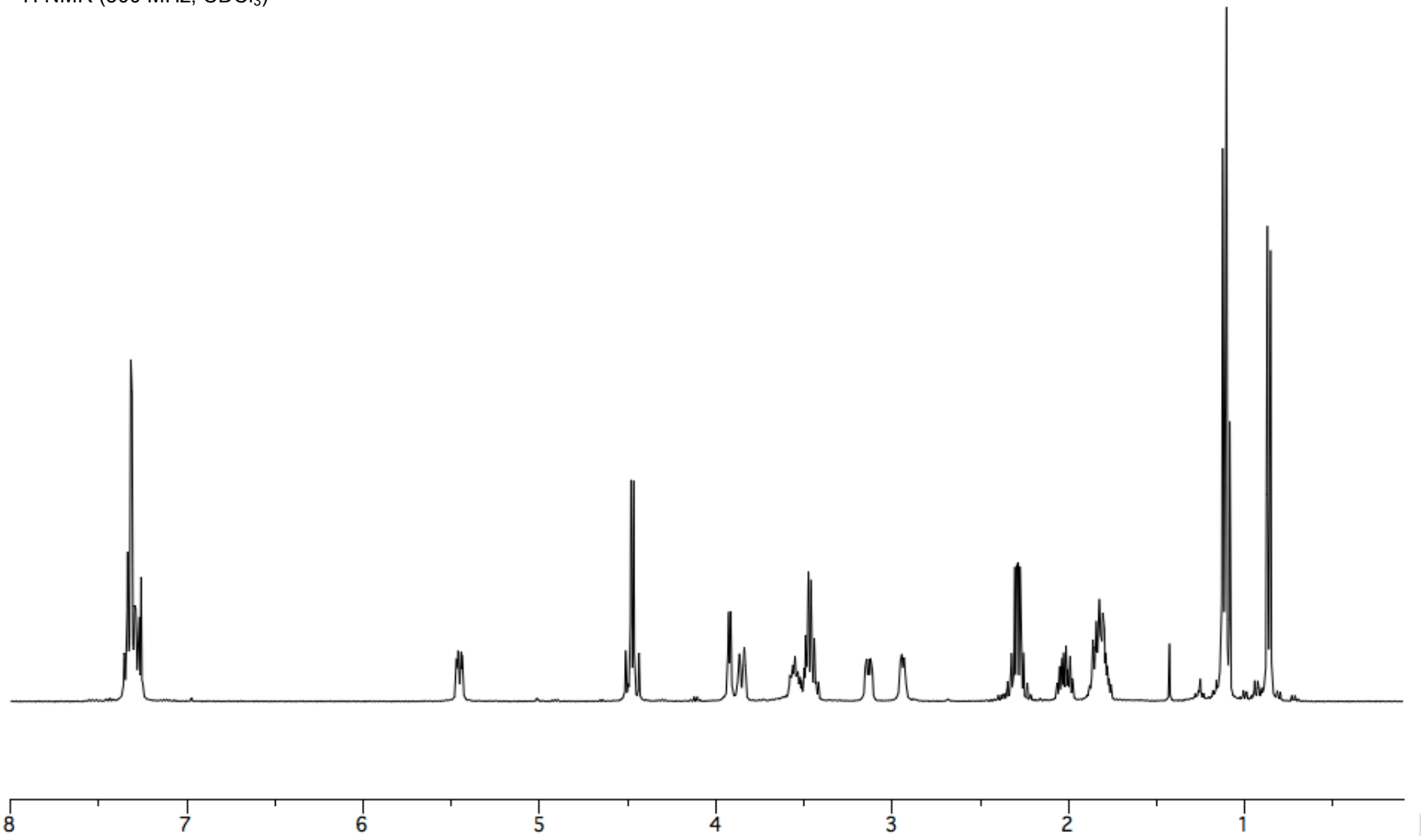
^{13}C NMR (100 MHz, C_6D_6)

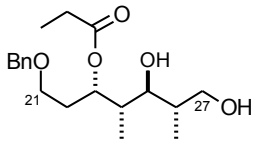




38

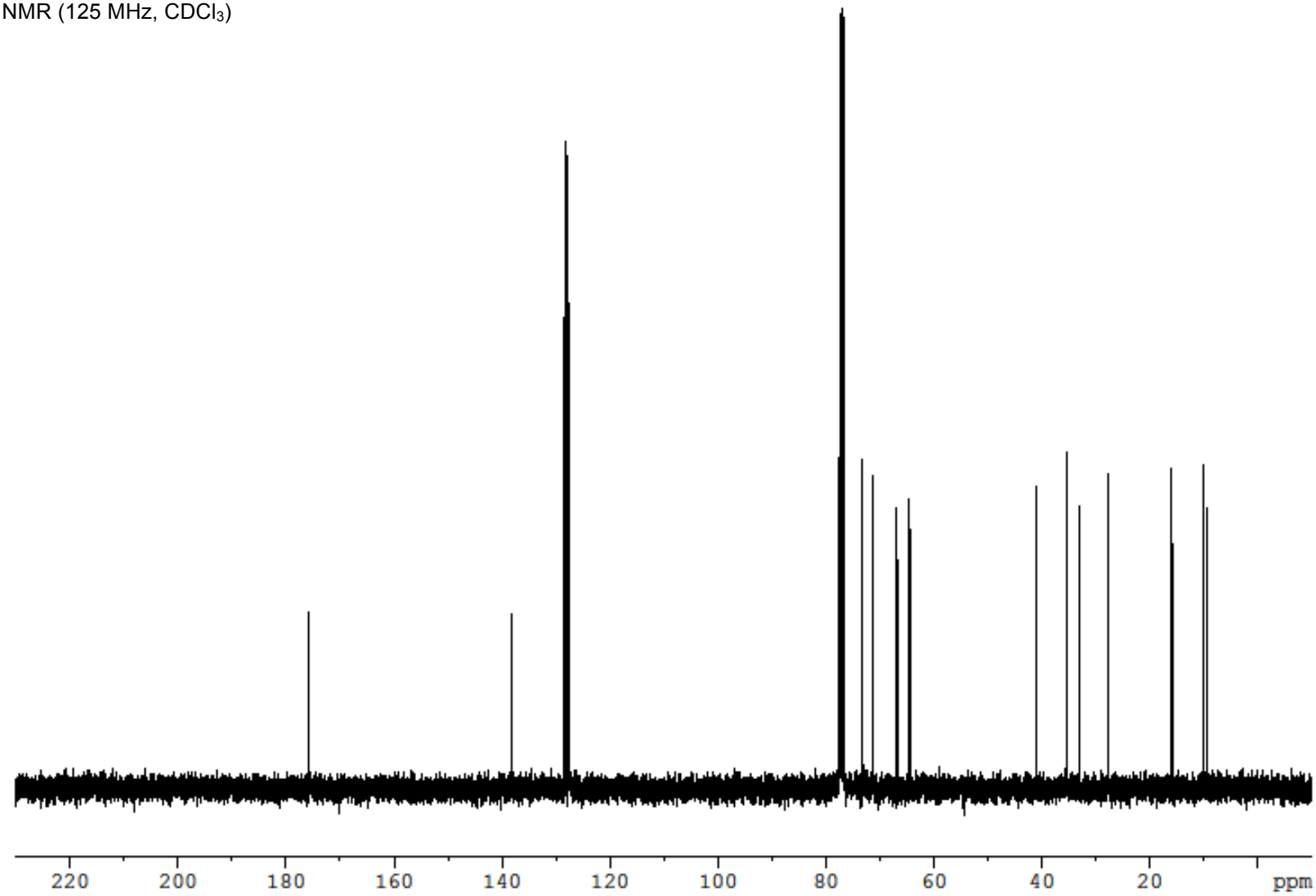
^{1}H NMR (500 MHz, $CDCl_3$)

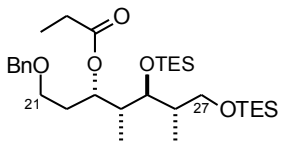




38

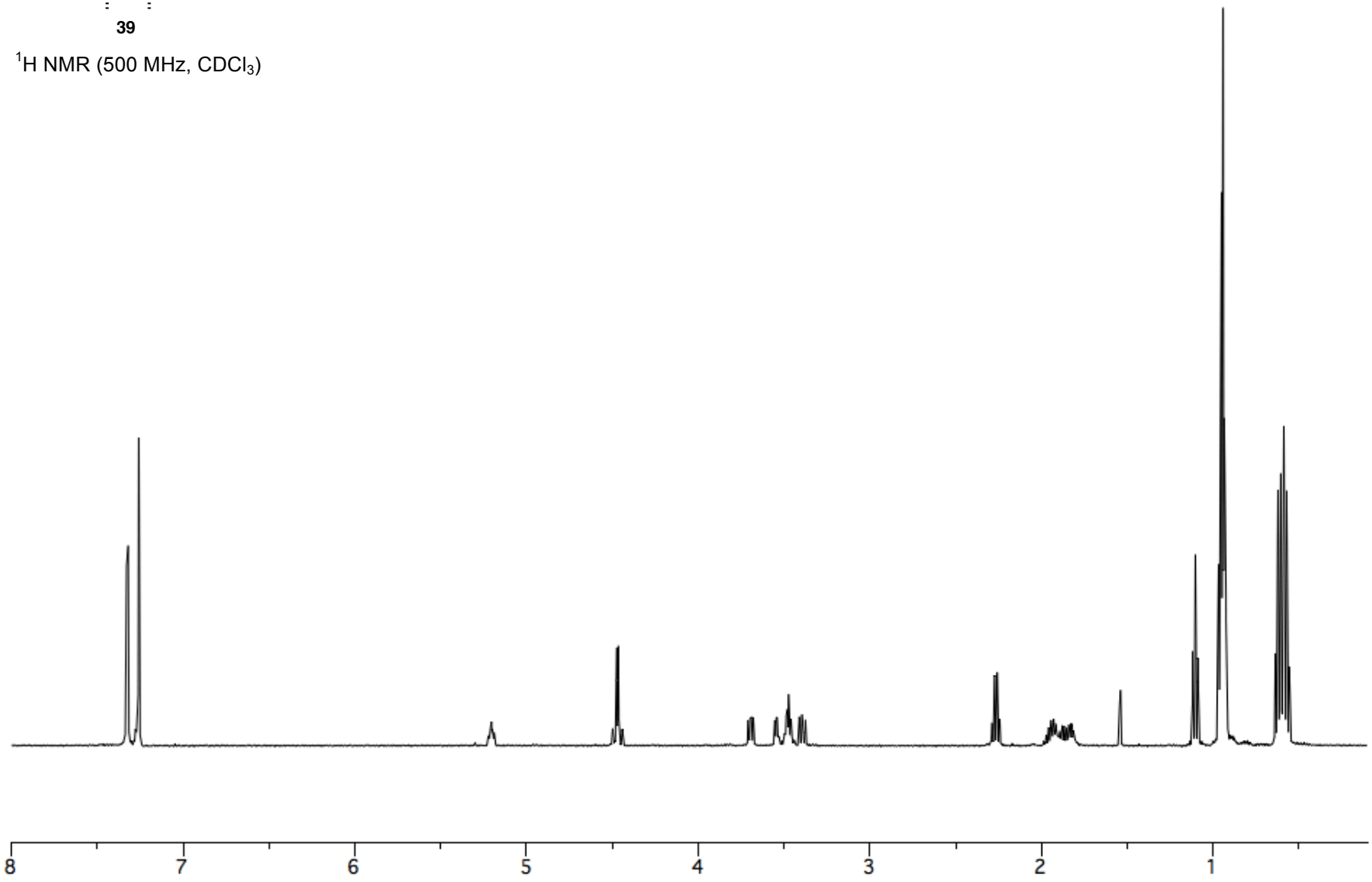
^{13}C NMR (125 MHz, $CDCl_3$)

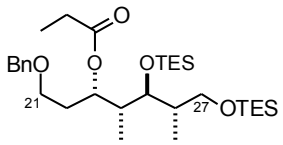




39

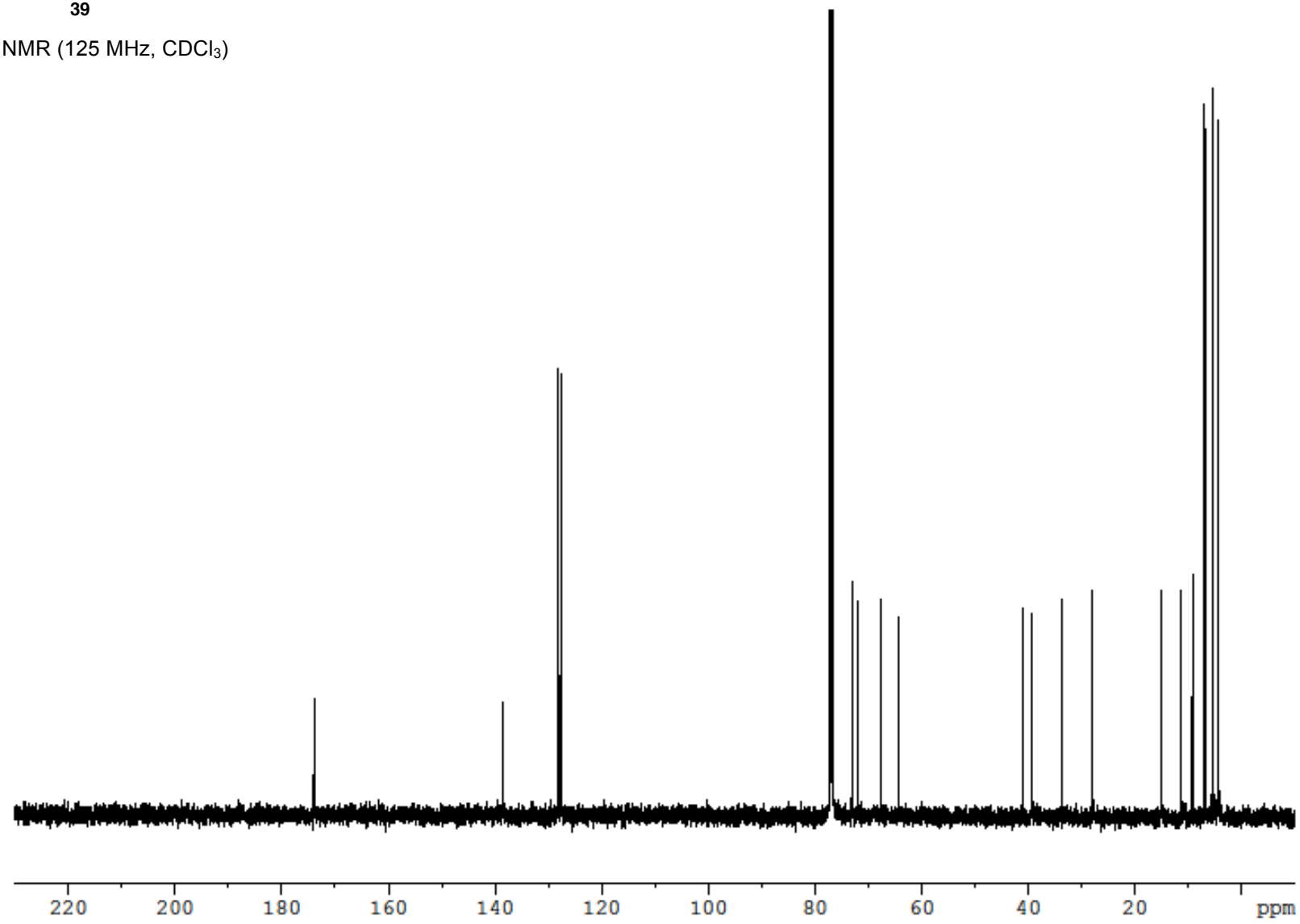
^{1}H NMR (500 MHz, $CDCl_3$)

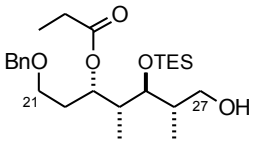




39

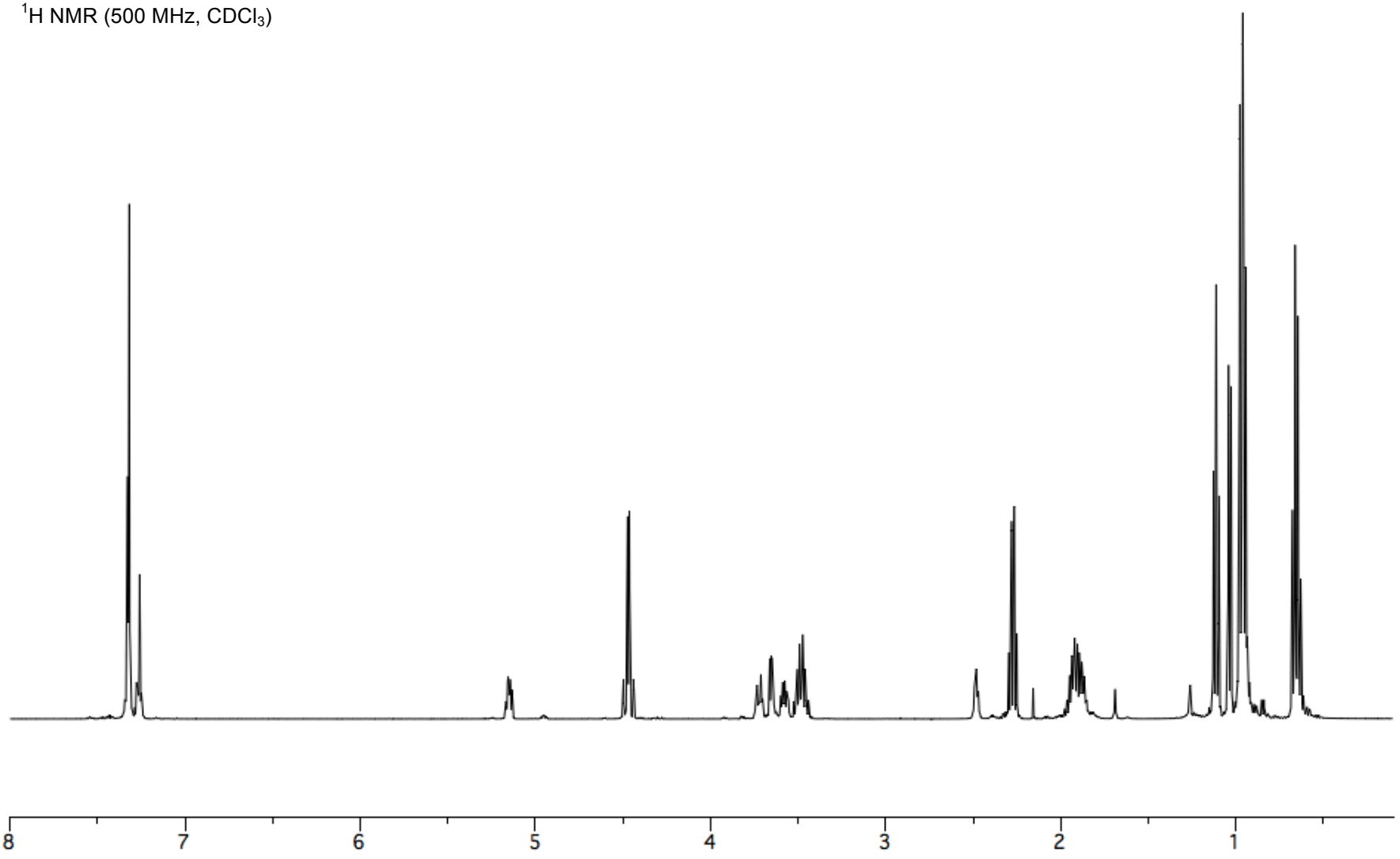
^{13}C NMR (125 MHz, $CDCl_3$)

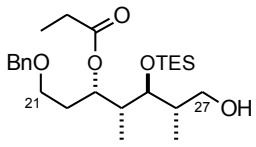




40

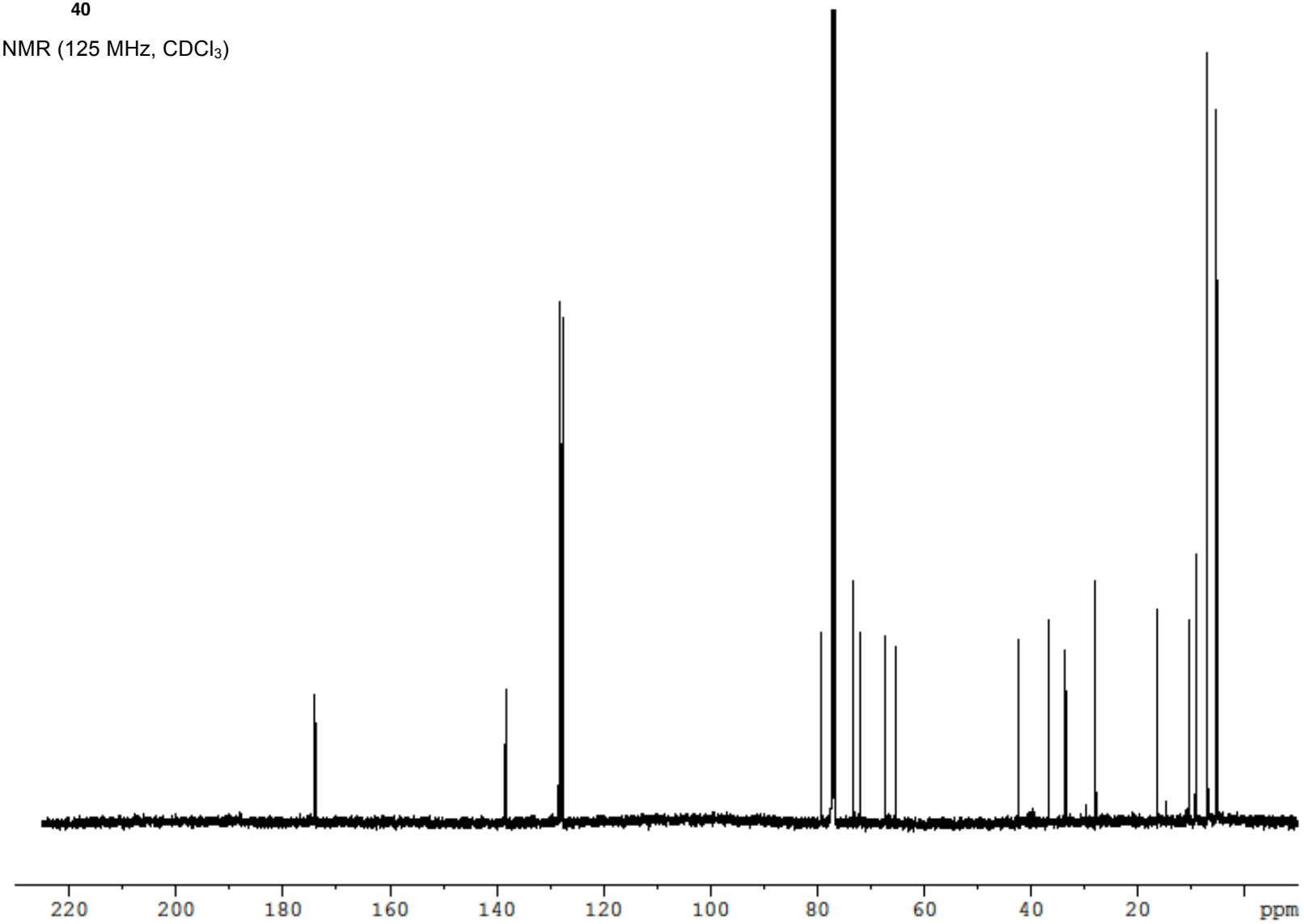
^{1}H NMR (500 MHz, $CDCl_3$)

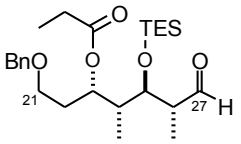




40

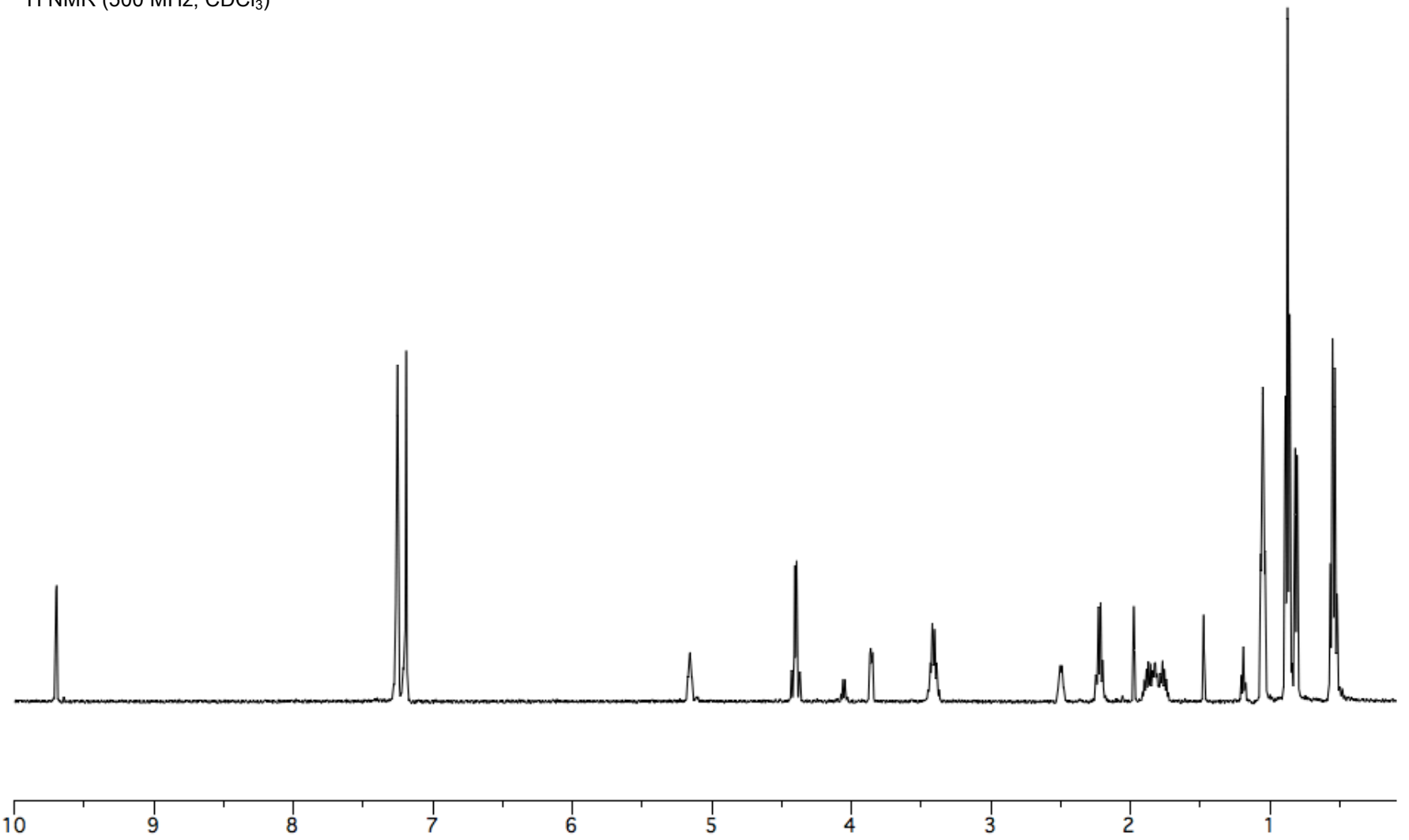
^{13}C NMR (125 MHz, $CDCl_3$)

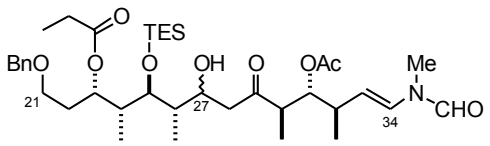




14

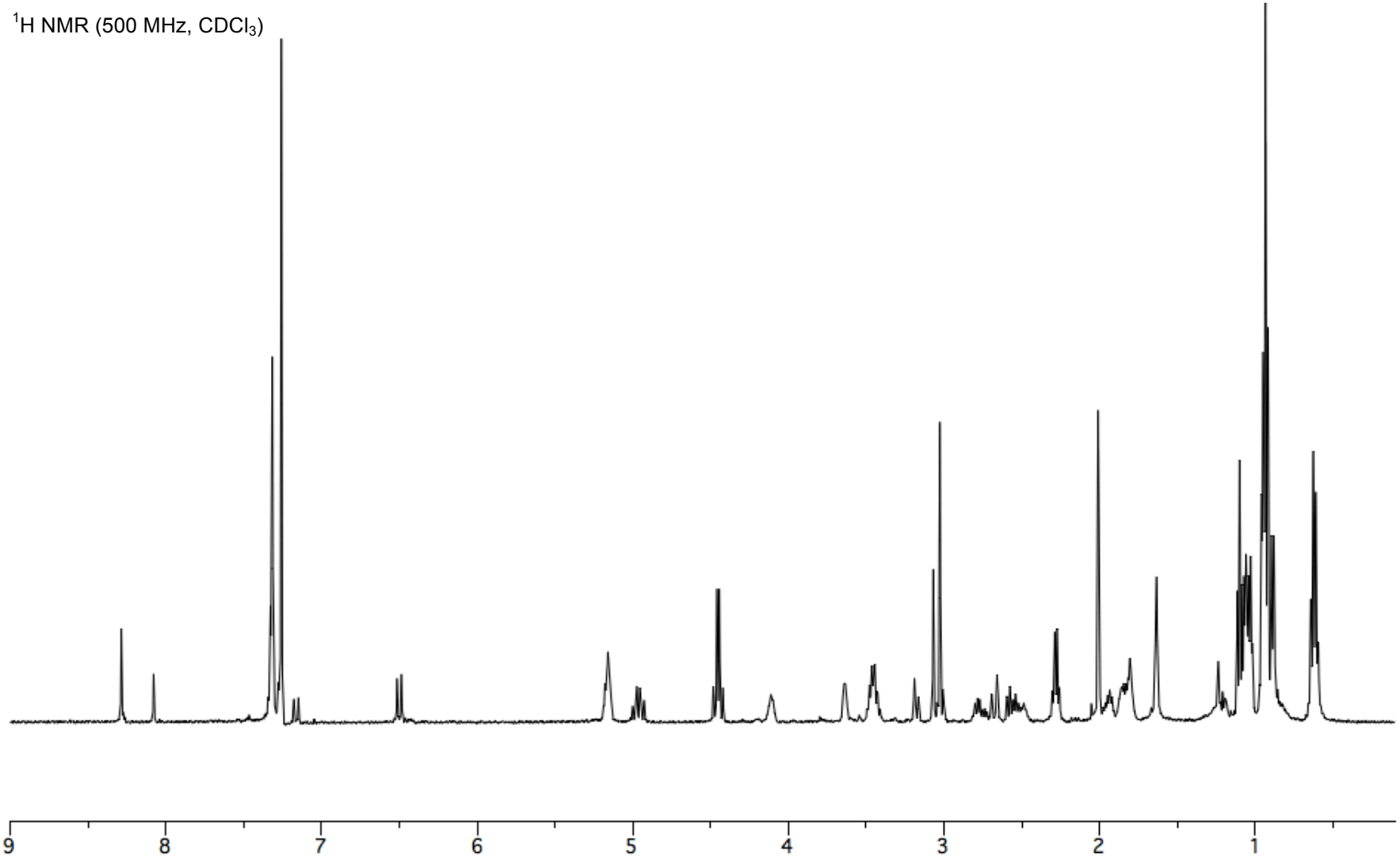
^{1}H NMR (500 MHz, $CDCl_3$)

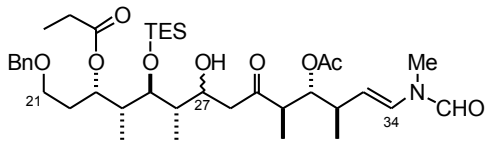




41

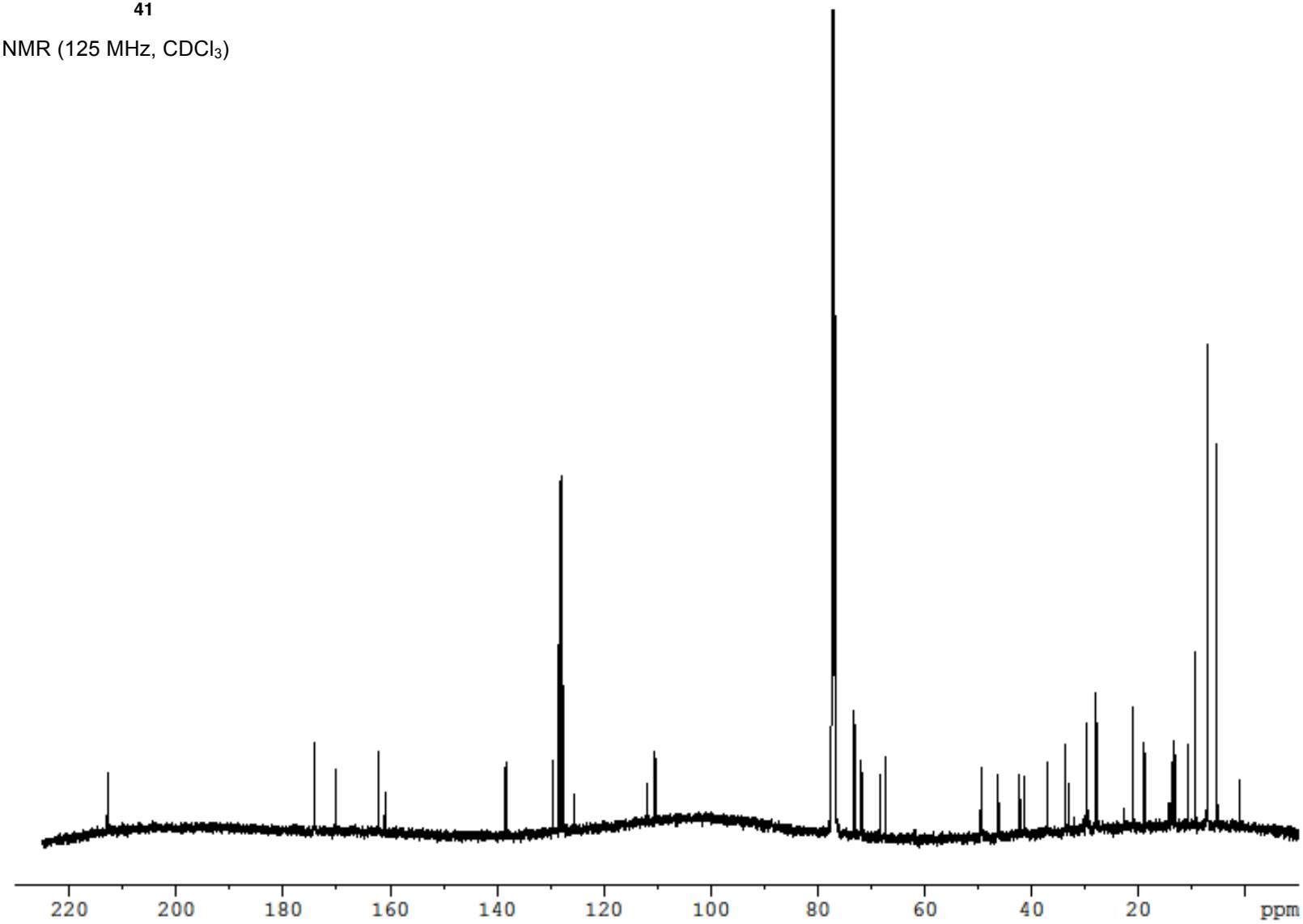
^{1}H NMR (500 MHz, $CDCl_3$)

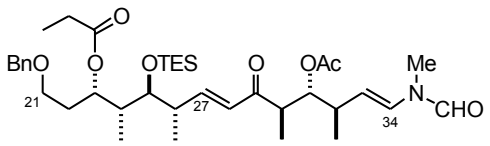




41

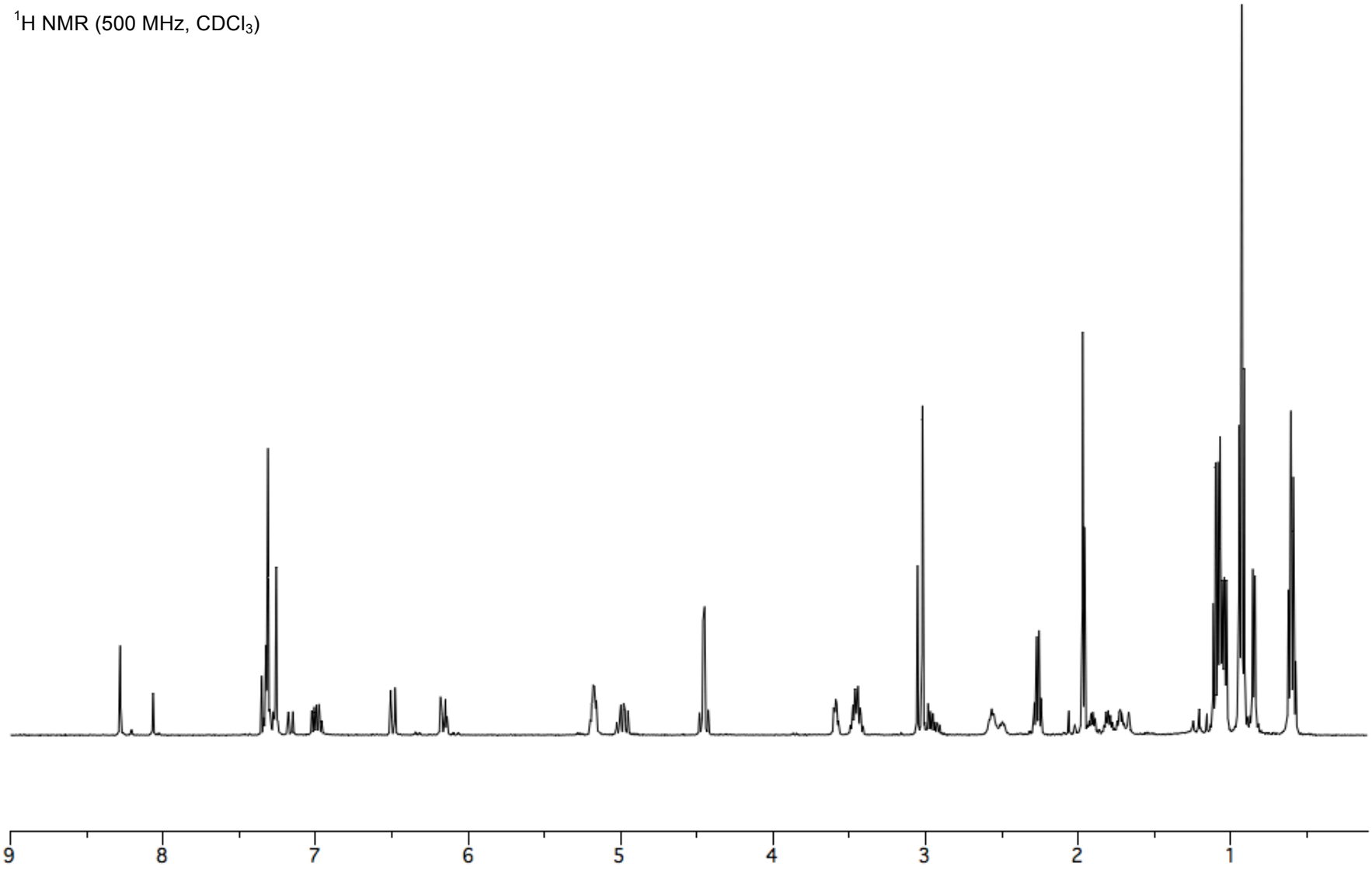
^{13}C NMR (125 MHz, $CDCl_3$)

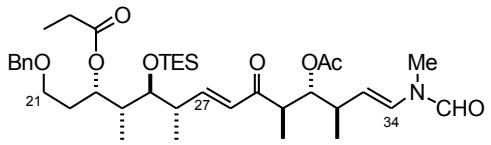




42

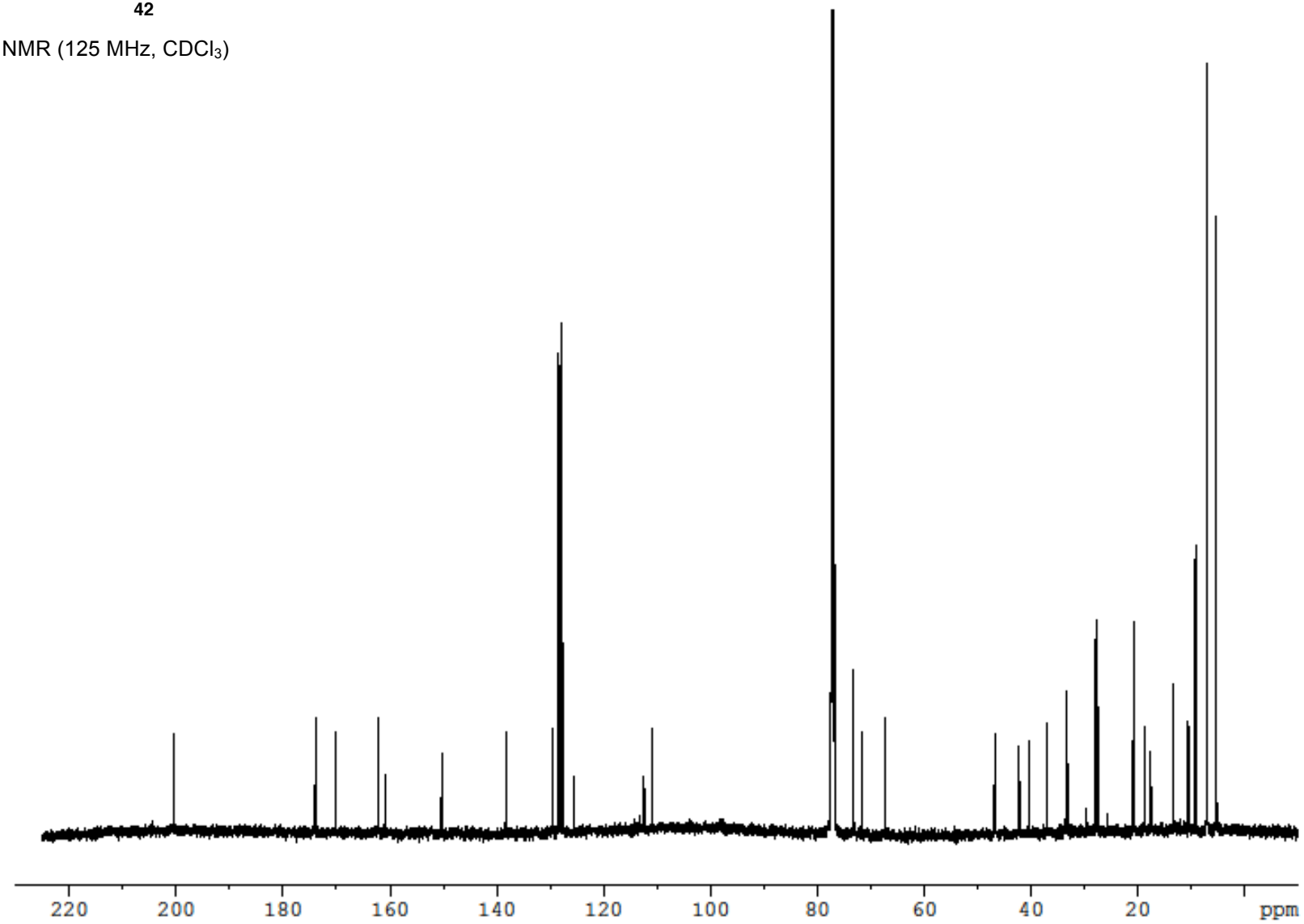
^{1}H NMR (500 MHz, $CDCl_3$)

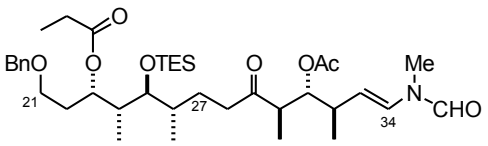




42

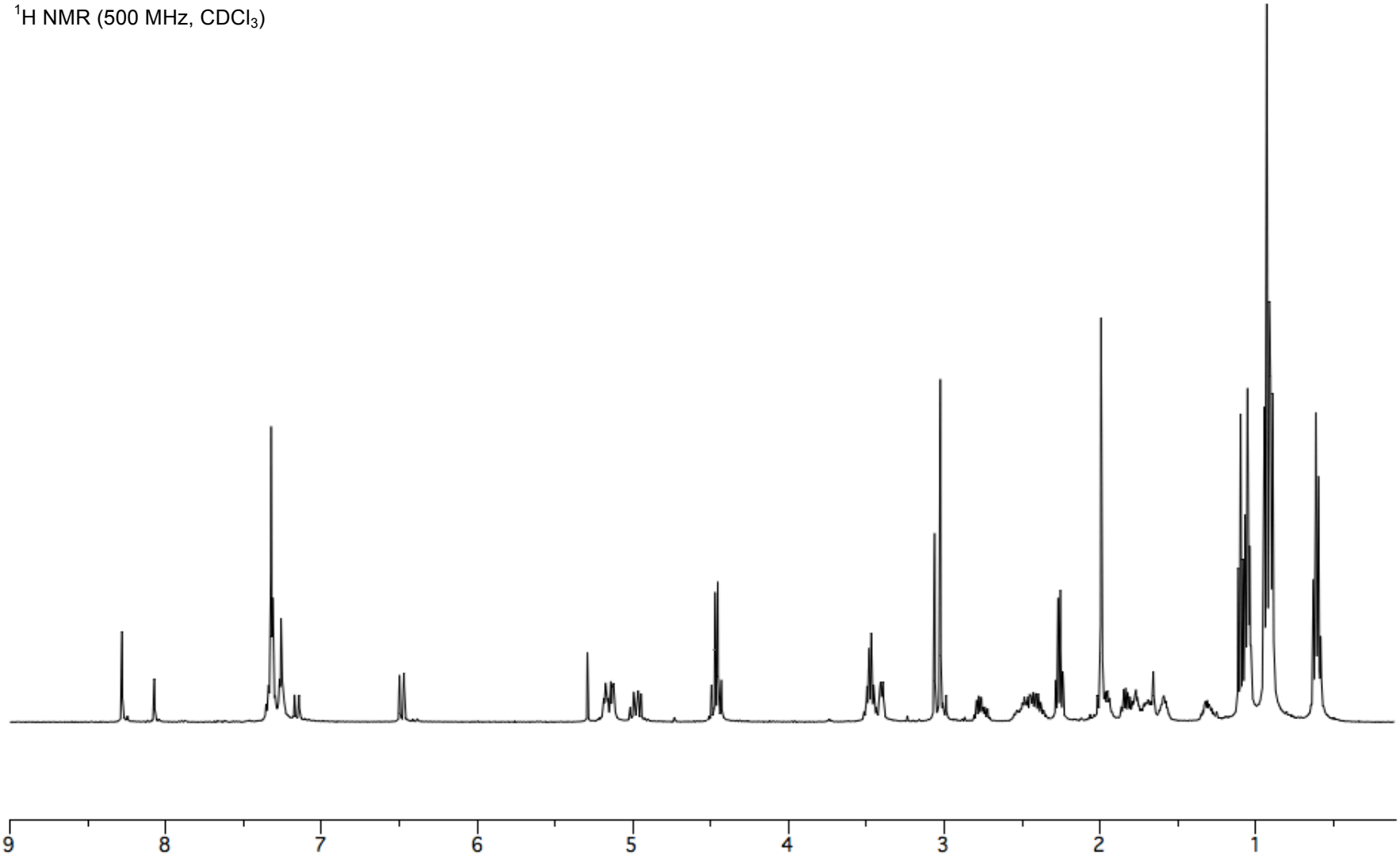
^{13}C NMR (125 MHz, $CDCl_3$)

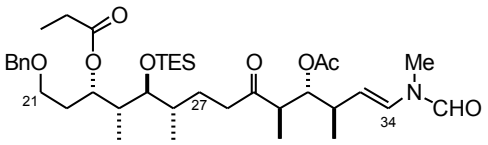




19

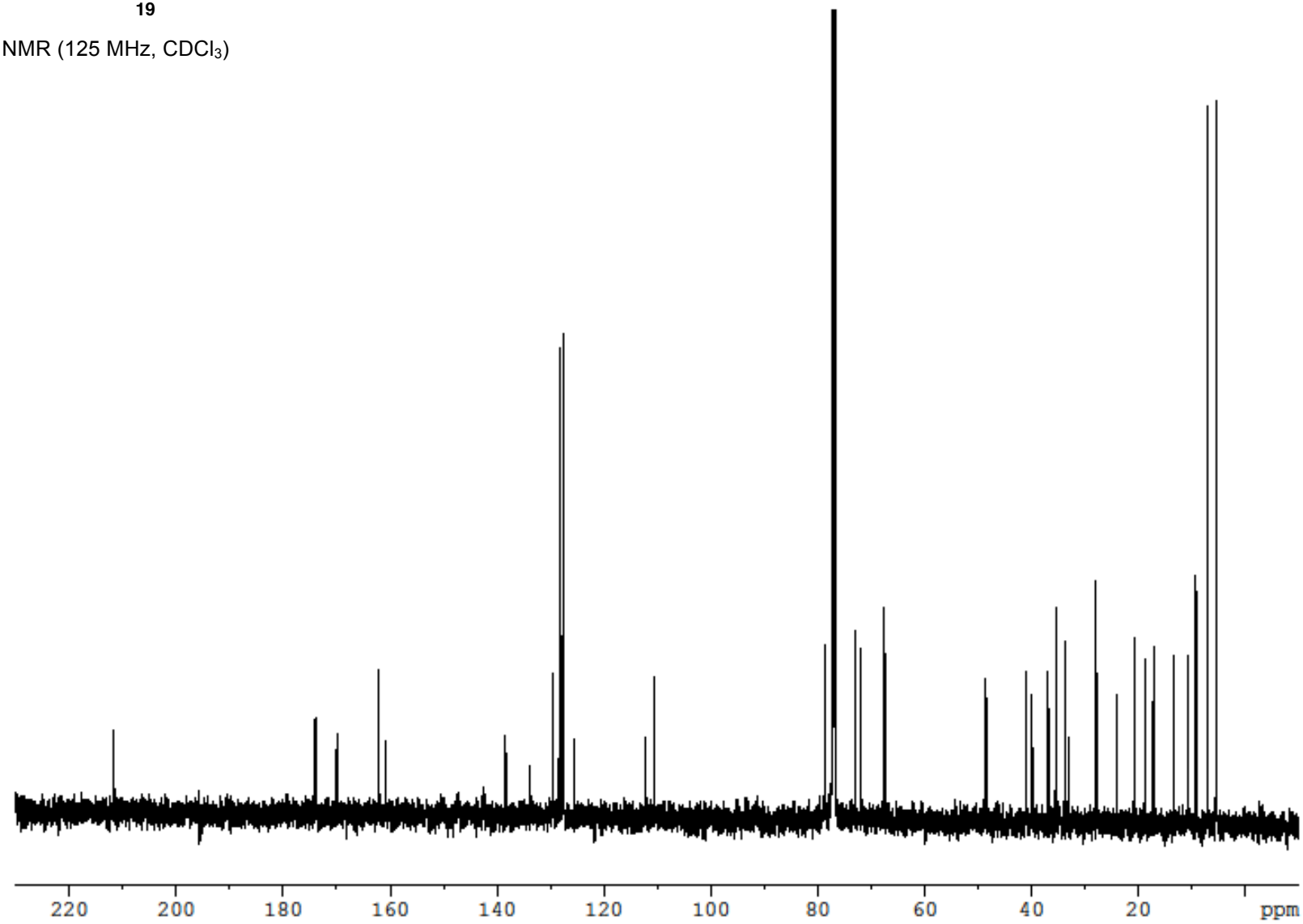
^{1}H NMR (500 MHz, $CDCl_3$)

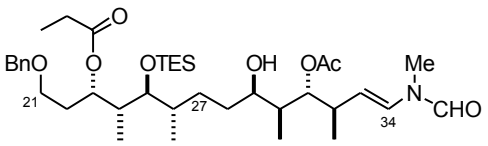




19

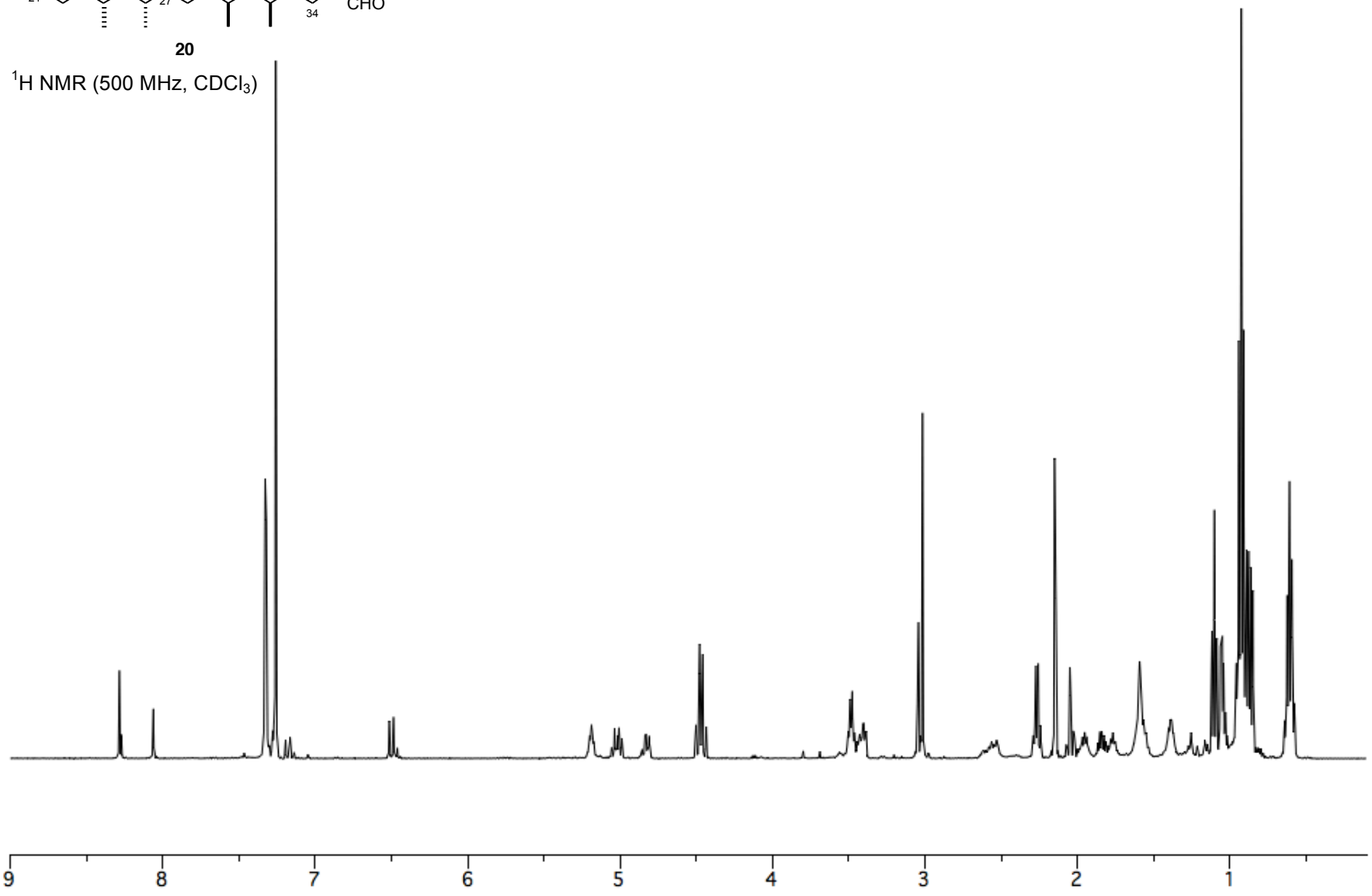
^{13}C NMR (125 MHz, $CDCl_3$)

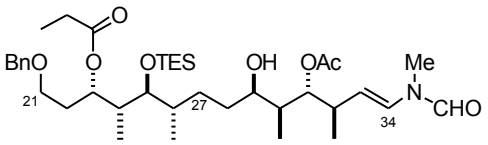




20

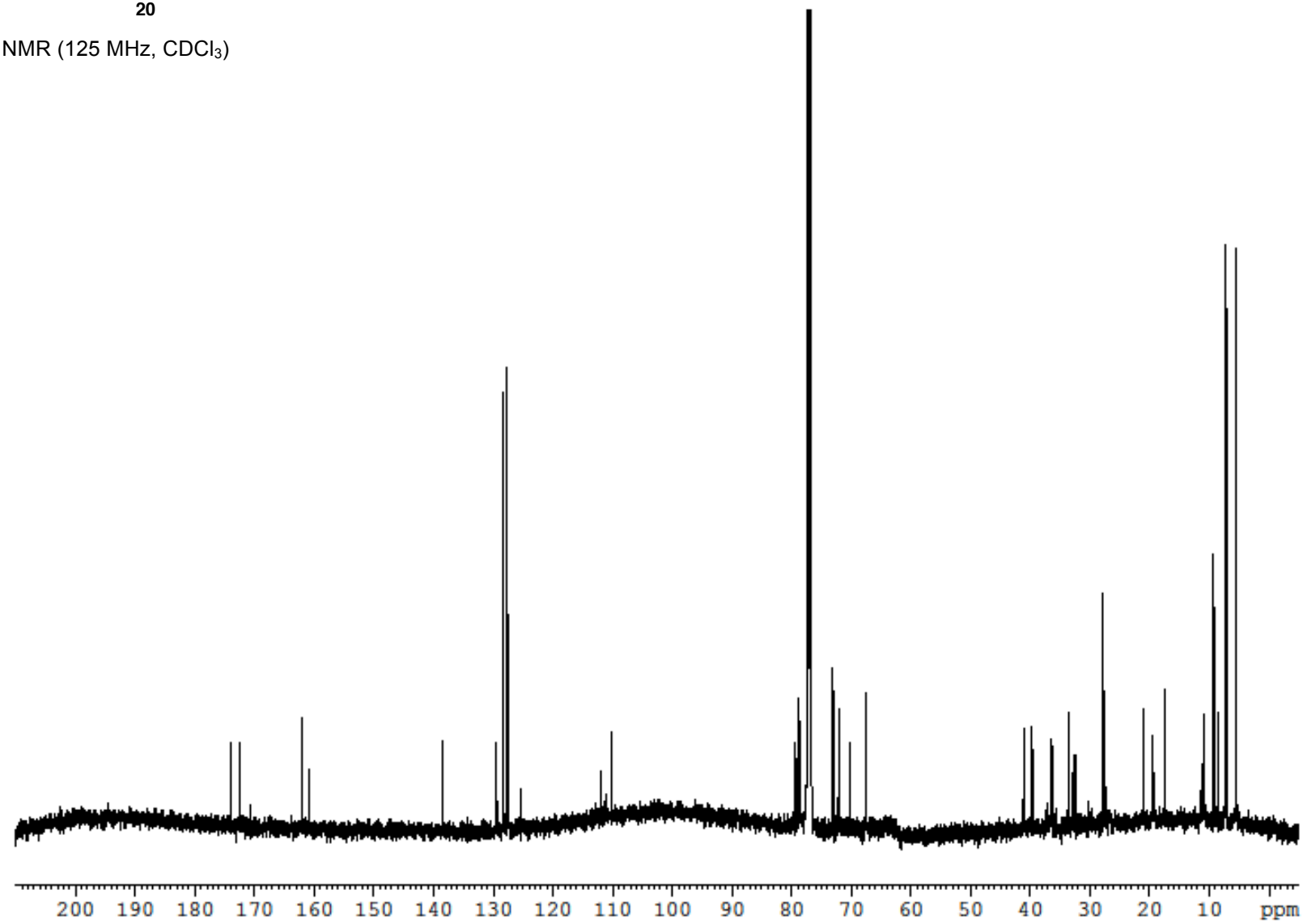
^{1}H NMR (500 MHz, $CDCl_3$)

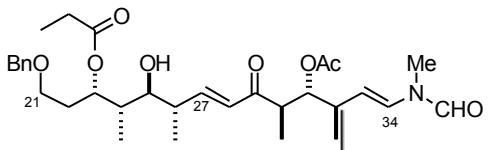




20

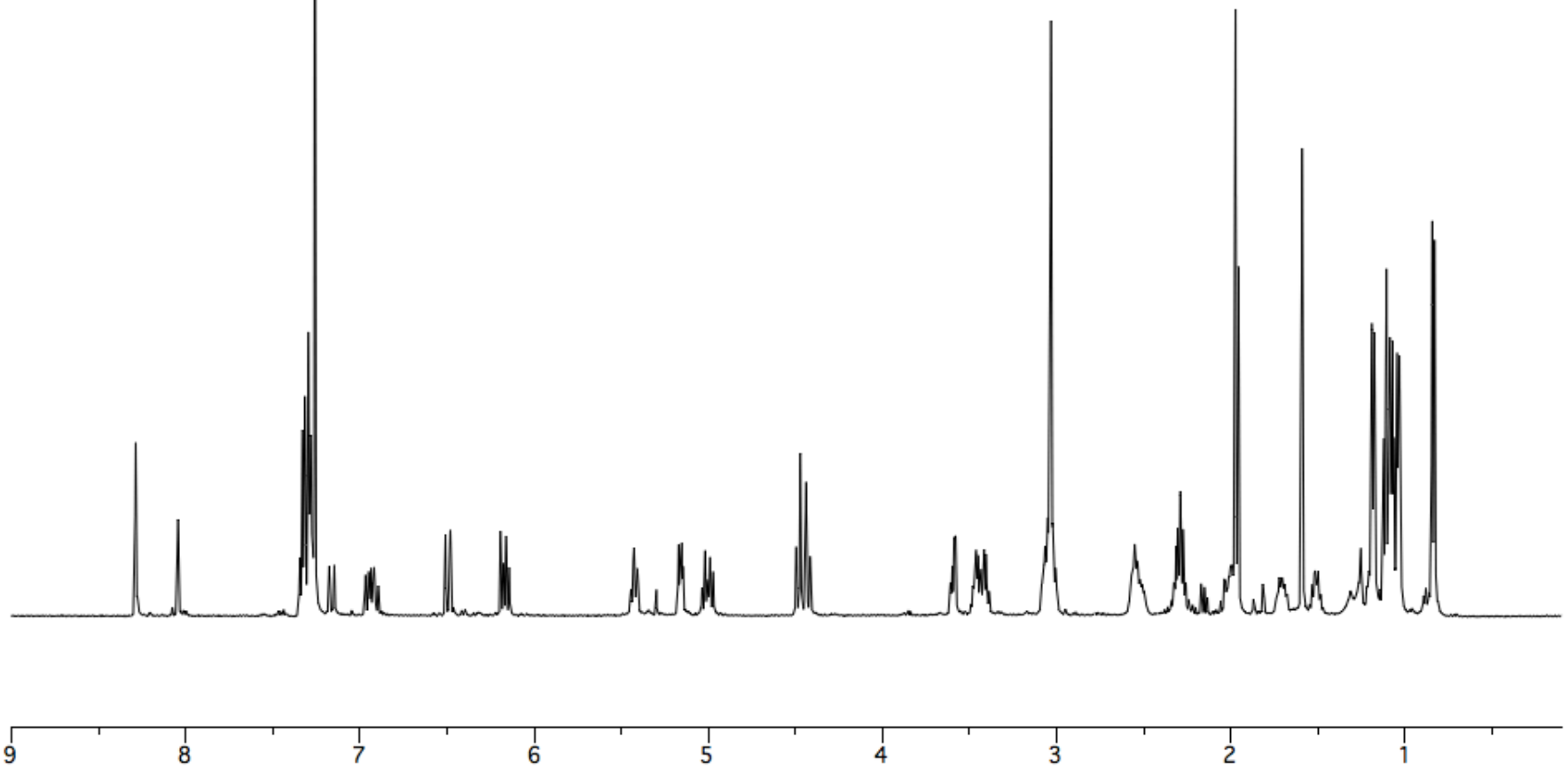
^{13}C NMR (125 MHz, $CDCl_3$)

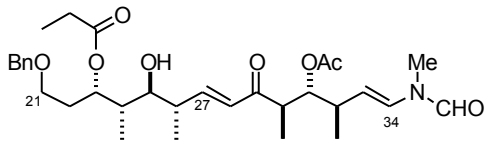




15

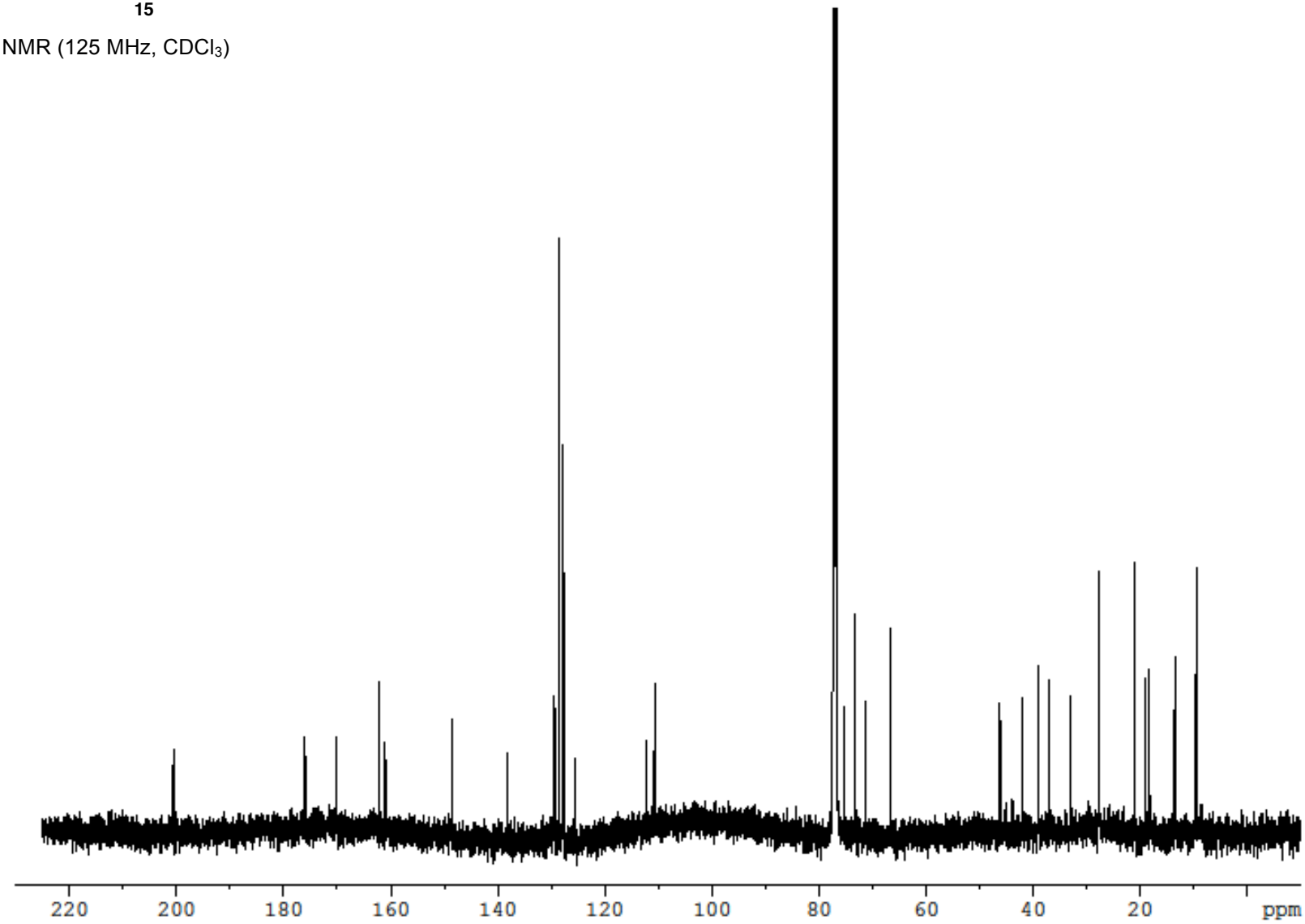
^{1}H NMR (500 MHz, $CDCl_3$)

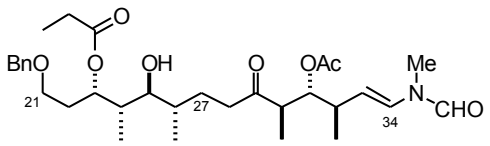




15

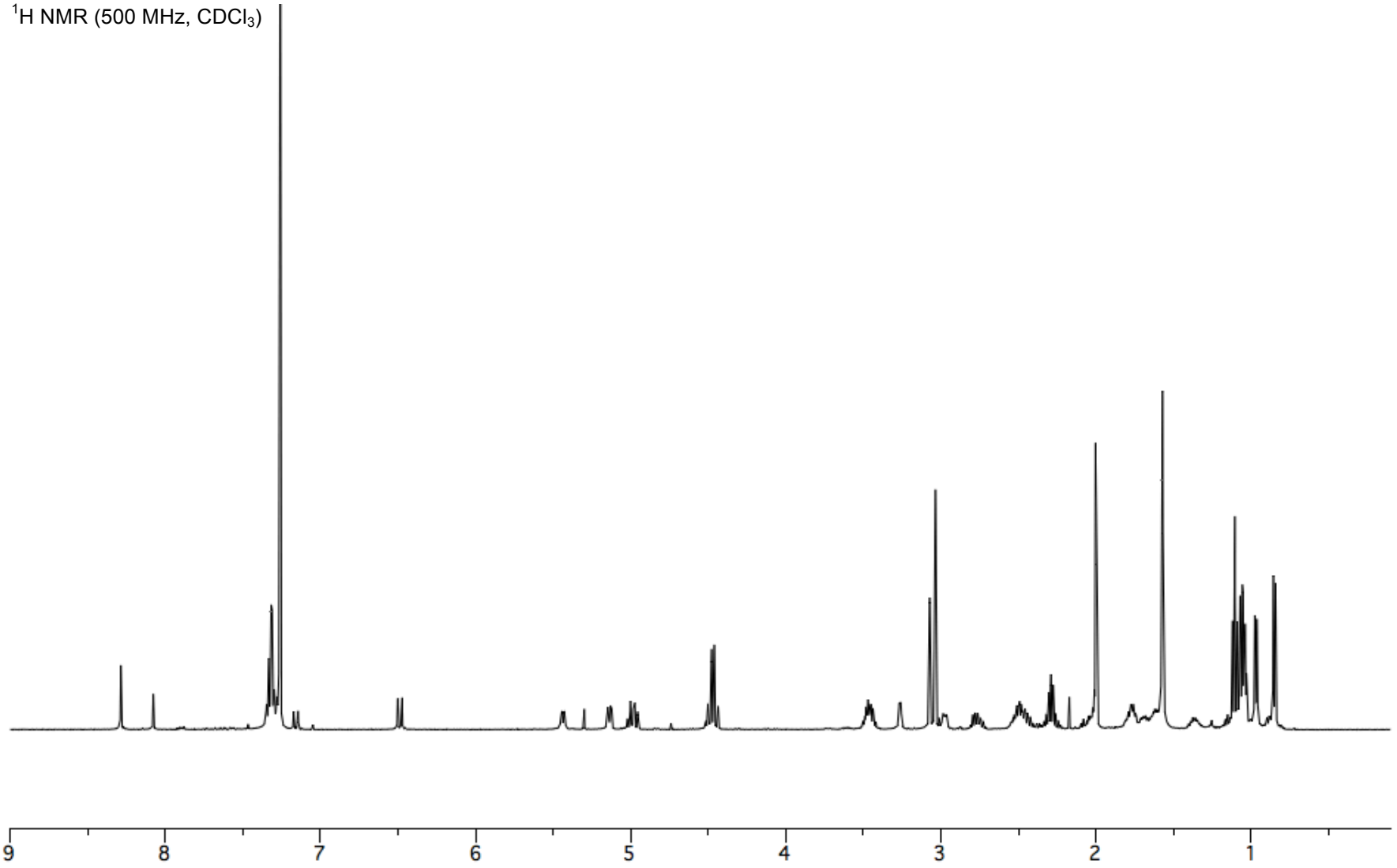
^{13}C NMR (125 MHz, $CDCl_3$)

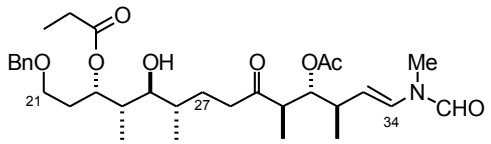




16

^{1}H NMR (500 MHz, $CDCl_3$)





16

^{13}C NMR (125 MHz, $CDCl_3$)