Supporting Information

Concise Total Synthesis and Structure Revision of Metacridamides A and B

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Experimental Section

I. Basic procedure

a) All moisture-sensitive reactions were performed under an atmosphere of nitrogen using heat-dried flasks, syringes, etc., and the starting materials were azeotropically dried with toluene before use.

b) The reaction system was cooled in an ice-water bath (0 ºC), a dry ice-methanol bath (–78 ºC), and a thermostatic ethanol bath (–78 ~ 0 ºC). An oil bath was used to heat the reaction system.

c) The organic layer after extraction was dried by addition of Na_2SO_4 with vigorously stirring, and the solid was removed by filtration.

d) Concentration on a rotary evaporator was carried out under reduced pressure (10~100 mmHg) using a diaphragm pump. The residual solvent was removed using a vacuum pump (approx. 1 mmHg) fitted with a trap cooled by liquid nitrogen.

e) Celite® No. 535 purchased from Wako Pure Chemicals Co. was used for Celite filtration.

f) The ratio of mixed solvents is expressed as a volume ratio.

II. Chromatography

a) Analytical thin layer chromatography

E. Merck TLC plates, TLC Silica gel 60 F_{254}, were used; detection of compounds on the TLC plates was performed by UV lamp (254 nm) irradiation and the use of the following colorant. R_f values are listed as below.

R_f = numerical value (developing solvents)

(Colorant)

Phosphomolybdic acid solution

12 Molybdo(IV) phosphoric acid (50 g) was dissolved in ethanol (450 mL).

The TLC plate was immersed in this solution and then heated on a hot plate (300 ºC).

b) Column chromatography

Silica gel BW-820MH or PSQ 100B purchased from Fuji Silysia Chemical Ltd. was used as the filler. The packing materials and developing solvents used are listed below.

[filler, filler weight, developing solvents]

III. Instrumental analysis

a) Specific rotation ($[\alpha]_D^t$)

The instrument used was a digital optical rotation meter (DIP-1000) manufactured by JASCO Co. Chloroform through alumina [E. Merck Aluminium oxide 90 active neutral (activity stage I) for column chromatography], methanol for HPLC, or acetonitrile for HPLC was used as a measuring solvent. The measured values are listed as below, where t is the measurement temperature (ºC) and the unit of concentration of the solution is given as g / dL.

$[\alpha]_D^t$ specific rotation (*c* concentration, solvent)

b) Infrared absorption spectrum (IR)

The instrument used was a spectrophotometer (FT/IR-4100) manufactured by JASCO Co. Chloroform through alumina [E. Merck Aluminium oxide 90 active neutral (activity stage I) for column chromatography] was used as the measurement solvent. The chloroform solution of the sample was placed in a dedicated NaCl cell and the measured values are listed as below.

IR ($CHCl_3$) absorption wavelength (cm^{-1})

c) ^{1}H nuclear magnetic resonance spectrum (^{1}H NMR spectrum)

A Bruker DPX400 instrument (400 MHz) or an Avance600 instrument (600 MHz) was used for the measurements. Heavy chloroform ($CDCl_3$) and heavy methanol (methanol-d_4) were used as the measurement solvents. The measured values are listed as below.

^{1}H NMR (Measuring frequency, solvent) δ Chemical shift value (multiplicity, spin coupling value, a number of hydrogen)

Chemical shift values are listed as δ values (ppm), and residual protons of the measuring solvent [$CHCl_3$ (δ 7.26), CHD_2OD (δ 3.31)] were used as internal standards. Multiplicities were abbreviated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet, or overlap of multiple signals), and the broad signals were represented by the remark “br”. The spin coupling constant *J* is listed in Hz.

d) ^{13}C nuclear magnetic resonance spectrum (^{13}C NMR spectrum)

A Bruker DPX400 instrument (100 MHz) or an Avance600 instrument (150 MHz) was used for the measurements. Heavy chloroform ($CDCl_3$) and heavy methanol (methanol-d_4) were used as the measurement solvents. The measured values are listed as below.

^{13}C NMR (Measuring frequency, solvent) δ Chemical shift value

Chemical shift values are listed as δ values (ppm), and carbon signals of the measuring solvent [$CDCl_3$ (δ 77.00), methanol-d_4 (δ 49.00)] were used as internal standards.

f) High resolution mass spectrometry (HRMS)

The instrument used was JEOL AccuTOF CS (JMS-100CS), and measurements were performed by electron spray ionization (ESI). Methanol for HPLC was used as the measuring solvent and reserpine (*m/z* 609.2812) as the calibrant. The measured values are listed as below.

HRMS [ESI] calcd for molecular formula [ion] calculated value, found measured value.

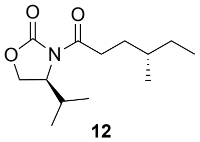
IV. Preparation of solvents

Dehydrated Solvents

Dry Et_2O, THF, DMF, EtOAc, MeCN, and MeOH were purchased from FUJIFILM Wako Pure Chemical Co. and used without further drying. Dry CH_2Cl_2 was purchased from FUJIFILM Wako Pure Chemical Co. and used after distillation: CH_2Cl_2 was dried by refluxing with powdered CaH_2 for at least 2 hours and then distilled.

Experimental procedure

Acylated oxazolidinone **12**

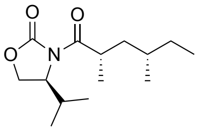


12

To a stirred solution of carboxylic acid **10**[1)] (8.37 g, 64.3 mmol) in dry THF (300 mL, 4.67 mL/mmol) were added NEt_3 (17.9 mL, 129 mmol, 2.00 equiv) and PivCl (9.40 mL, 77.2 mmol, 1.20 equiv) dropwise at −78 °C under N_2. After being stirred at room temperature for 1 h, (*S*)-4-isopropyl-2-oxazolidinone (**11**) (9.47 g, 77.2 mmol, 1.20 equiv) and anhydrous LiCl (8.18 g, 193 mmol, 3.00 equiv) were added to the reaction mixture. After being stirred at the same temperature for 24 h, the reaction mixture was quenched with H_2O. The organic layer was separated, and the aqueous layer was extracted with Et_2O (100 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the residual oil was purified by column chromatography on silica gel (PSQ 100B 160 g, hexane/EtOAc = 18/1) to afford acylated oxazolidinone **12** (16.0 g, 64.3 mmol, quant) as a colorless oil.

$R_f = 0.58$ (hexane/EtOAc = 3/1); $[\alpha]_D^{23}$ +71.3 (*c* 1.49, $CHCl_3$); IR ($CHCl_3$) 3028, 2965, 2932, 2876, 1780, 1700, 1487, 1464, 1388, 786 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.43–4.40 (m, 1H), 4.24 (t, *J* = 9.0 Hz, 1H), 4.18 (dd, *J* = 9.0, 3.1 Hz, 1H), 2.99 (ddd, *J* = 16.1, 10.6, 5.7 Hz, 1H), 2.82 (ddd, *J* = 16.1, 10.3, 6.1 Hz, 1H), 2.39–2.31 (m, 1H), 1.70–1.61 (m, 1H), 1.51–1.43 (m, 1H), 1.42–1.31 (m, 2H), 1.21–1.13 (m, 1H), 0.90–0.84 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 154.2, 63.4, 58.5, 34.2, 33.5, 31.2, 29.3, 28.5, 19.0, 18.1, 14.8, 11.4; HRMS [ESI] calcd for $C_{13}H_{23}NO_3Na$ $[M+Na]^+$ 264.1576, found 264.1600.

Alkylated product **13**



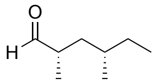
13

To a stirred solution of acylated oxazolidinone **12** (3.96 g, 18.1 mmol) in dry THF (180 mL, 10.0 mL/mmol) was added 1.2 M solution of NaHMDS in THF (20.3 mL, 24.4 mmol, 1.30 equiv) dropwise at −78 °C under N_2. After the reaction mixture was stirred at the same temperature for 1 h, MeI (2.93 mL, 47.1 mmol, 2.60 equiv) in dry THF (27.2 mL, 1.50 mL/mmol) was added dropwise to the reaction mixture. After being stirred at the same temperature for 1 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with Et_2O (100 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the residual oil was purified by column chromatography on silica gel (PSQ 100B 100 g, hexane/EtOAc = 22/1) to afford alkylated product **13** (3.55 g, 13.9 mmol, 77%) as a colorless oil.

$R_f = 0.75$ (hexane/EtOAc = 3/1); $[\alpha]_D^{23}$ +65.7 (*c* 1.17, $CHCl_3$); IR ($CHCl_3$) 3029, 2966, 2932, 2876, 1779, 1698, 1387, 1203, 1093 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.45–4.41 (m, 1H), 4.25 (t, *J* = 8.9 Hz, 1H), 4.18 (dd, *J* = 8.9, 3.0 Hz, 1H), 3.92–3.83 (m, 1H), 2.38–2.27 (m, 1H), 1.85–1.79 (m, 1H), 1.38–1.23 (m, 2H), 1.18 (d, *J* = 6.9

Hz, 3H), 1.13–1.05 (m, 2H), 0.89 (d, *J* = 7.0 Hz, 3H), 0.86–0.82 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 153.8, 63.4, 58.6, 40.3, 35.6, 32.5, 29.8, 28.6, 19.5, 19.1, 18.1, 14.9, 11.5; HRMS [ESI] calcd for $C_{14}H_{25}NO_3Na$ $[M+Na]^+$ 278.1732, found 278.1739.

Aldehyde **8**

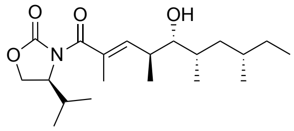


8

To a stirred solution of alkylated product **13** (500 mg, 1.96 mmol) in dry CH_2Cl_2 (16.2 mL, 8.30 mL/mmol) was added 1.02 M solution of DIBAL-H in CH_2Cl_2 (3.84 mL, 3.92 mmol, 2.00 equiv) dropwise at −78 °C under N_2. After being stirred at the same temperature for 15 min, the reaction mixture was quenched with saturated aqueous NH_4Cl, and then a saturated aqueous Rochelle salt was added. The organic layer was separated, and the aqueous layer was extracted with pentane (20 mL x 2). The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated, and the residual oil was purified by distillation under reduced pressure (1.9 kPa, 66 °C–70 °C) to afford aldehyde **8** (131 mg, 1.02 mmol, 52%) as a colorless oil.

R_f = 0.50 (hexane/EtOAc = 10/1); $[\alpha]_D^{23}$ +30.8 (*c* 0.367 $CHCl_3$); IR ($CHCl_3$) 2965, 2931, 2876, 1720, 1462, 1222 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.58 (d, *J* = 2.5 Hz, 1H), 2.48–2.38 (m, 1H), 1.75–1.68 (m, 1H), 1.46–1.31 (m, 2H), 1.19–1.10 (m, 2H), 1.08 (d, *J* = 6.9 Hz, 3H), 0.89 (d, *J* = 6.5 Hz, 3H), 0.87 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.8, 44.4, 38.1, 32.2, 29.4, 19.6, 14.4, 11.3; HRMS [ESI] calcd for $C_8H_{16}ONa$ $[M+Na]^+$ 151.1099, found 151.1123.

Alcohol **14**



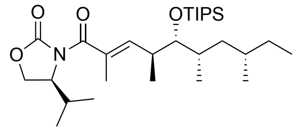
14

To a stirred solution of aldehyde **8** (1.08 g, 8.43 mmol, 3.00 equiv) in dry CH_2Cl_2 (32.0 mL, 11.4 mL/mmol) was added 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (4.22 mL, 4.22 mmol, 1.50 equiv) dropwise at −78 °C under N_2. After the reaction mixture was stirred at the same temperature for 30 min, a solution of *N*,*O*-ketene acetal **7** (952 mg, 2.81 mmol) in dry CH_2Cl_2 (64.6 mL, 23.0 mL/mmol) was added to the reaction mixture. After being stirred at −40 °C for 24 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$, and then saturated aqueous Rochelle salt was added. The organic layer was separated, and the aqueous layer was extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the residual oil was purified by column chromatography on silica gel (PSQ 100B 35.4 g, hexane/EtOAc = 15/1) to afford alcohol **14** (963 mg, 2.81 mmol, 97%) as a colorless oil.

R_f = 0.48 (hexane/EtOAc = 3/1); $[\alpha]_D^{23}$ +13.3 (*c* 1.01, $CHCl_3$); IR ($CHCl_3$) 3526, 3018, 2965, 2932, 2876, 1772, 1685, 1463, 1389, 1016 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (brd, *J* = 10.3 Hz, 1H), 4.57 (ddd, *J* = 9.0, 5.8, 4.6 Hz, 1H), 4.33 (t, *J* = 9.0 Hz, 1H), 4.18 (dd, *J* = 9.0, 5.8 Hz, 1H), 3.25 (d, *J* = 9.0 Hz, 1H), 3.07 (brs, 1H), 2.78–2.68 (m, 1H), 2.38–2.30 (m, 1H), 1.94 (d, *J* = 1.3 Hz, 3H), 1.82–1.77 (m, 1H), 1.54–1.39 (m, 2H), 1.37–1.33

(m, 1H), 1.14–1.03 (m, 2H), 0.94–0.83 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 154.7, 142.8, 131.3, 76.5, 63.6, 58.2, 41.8, 37.6, 31.5, 30.9, 29.7, 28.6, 19.5, 18.0, 15.7, 15.4, 14.1, 12.9, 11.4; HRMS [ESI] calcd for $C_{20}H_{35}NO_4Na$ [M+Na]$^+$ 376.2464, found 376.2436.

TIPS Ether **15**

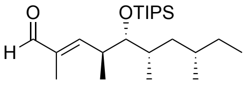


15

To a solution of alcohol **14** (247 mg, 0.699 mmol) in dry CH_2Cl_2 (1.94 mL, 2.78 mL/mmol) were added 2,6-lutidine (0.814 mL, 6.99 mmol, 10.0 equiv) and TIPSOTf (0.28 mL, 1.05 mmol, 1.50 equiv) at 0 °C under N_2. After being stirred at room temperature for 12 h, the reaction mixture was quenched with H_2O at 0 °C. The organic layer was separated, and the aqueous layer was extracted with EtOAc (10 mL x 3). The combined organic layers were washed with aqueous 1 M HCl, saturated aqueous $NaHCO_3$, and brine, successively; dried over Na_2SO_4; filtered; and then concentrated in vacuo. The residual oil was purified by column chromatography on silica gel (PSQ 100B 8.0 g, hexane/EtOAc = 21/1) to afford TIPS ether **15** (374 mg, 0.734 mmol, quant) as a colorless oil.

Rf = 0.70 (hexane/EtOAc = 3/1); $[\alpha]_D^{23}$ +2.38 (*c* 1.11, $CHCl_3$); IR ($CHCl_3$) 2965, 2868, 1784, 1682, 1464, 1387, 1015 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (brd, *J* = 9.7 Hz, 1H), 4.47–4.23 (m, 1H), 4.27 (t, *J* = 9.0 Hz, 1H), 4.18 (dd, *J* = 9.0, 5.1 Hz, 1H), 3.70 (t, *J* = 3.4 Hz, 1H), 2.77–2.69 (m, 1H), 2.41–2.36 (m, 1H), 1.90 (d, *J* = 1.3 Hz, 3H), 1.77–1.73 (m, 1H), 1.42–1.36 (m, 3H), 1.09–1.05 (m, 26H), 0.92–0.88 (m, 9H), 0.85–0.81 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 153.6, 141.6, 129.7, 80.3, 63.5, 58.6, 41.1, 37.3, 35.4, 32.1, 28.4, 20.3, 18.6, 18.0, 17.8, 17.5, 16.3, 15.1, 14.0, 13.6, 12.4, 11.5; HRMS [ESI] calcd for $C_{29}H_{55}NO_4SiNa$ [M+Na]$^+$ 532.3798, found 532.3784.

α,β-Unsaturated aldehyde **6**

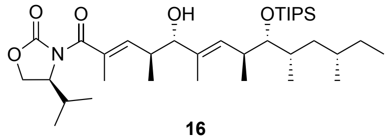


6

To a stirred solution of TIPS ether **15** (306 mg, 0.601 mmol) in dry CH_2Cl_2 (19.2 mL, 32.0 mL/mmol) was added 1.02 M solution of DIBAL-H in CH_2Cl_2 (1.18 mL, 1.20 mmol, 1.20 equiv) dropwise at −78 °C under N_2. After being stirred at the same temperature for 15 min, the reaction mixture was quenched with MeOH, and then a saturated aqueous Rochelle salt was added. The organic layer was separated, and the aqueous layer was extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the residual oil was purified by column chromatography on silica gel (PSQ 100B 6.00 g, hexane/EtOAc = 30/1) to afford unsaturated aldehyde **6** (181 mg, 0.473 mmol, 79%) as a colorless oil.

Rf = 0.60 (hexane/EtOAc = 5/1); $[\alpha]_D^{23}$ −12.5 (*c* 0.775 $CHCl_3$); IR ($CHCl_3$) 2963, 2928, 2869, 1679, 1463, 1377, 1097 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.39 (s, 1H), 6.76 (d, *J* = 9.7 Hz, 1H), 3.78 (t, *J* = 3.4 Hz, 1H), 2.93–2.86 (m, 1H), 1.76 (d, *J* = 0.9 Hz, 3H), 1.77–1.71 (m, 1H), 1.39–1.34 (m, 3H), 1.12–1.08 (m, 25H), 0.98–0.92 (m, 1H), 0.90 (d, *J* = 6.9 Hz, 3H), 0.84–0.81 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.8, 158.4, 137.6, 80.7, 40.4, 37.2, 36.3, 32.2, 28.4, 20.4, 18.60, 18.55, 18.4, 16.4, 13.7, 11.5, 9.5; HRMS [ESI] calcd for $C_{23}H_{46}O_2SiNa$ $[M+Na]^+$ 405.3165, found 405.3146.

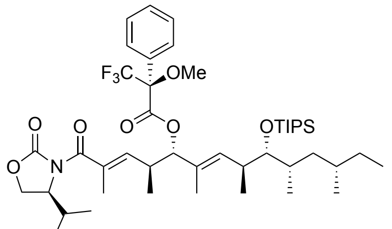
Alcohol **16**



16

To a stirred solution of unsaturated aldehyde **6** (98.0 mg, 0.256 mmol) in dry CH_2Cl_2 (1.33 mL, 5.10 mL/mmol) were added 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (0.130 mL, 0.130 mmol, 0.500 equiv) and a solution of *N*,*O*-ketene acetal **7** (132 mg, 0.394 mmol, 1.50 equiv) in dry CH_2Cl_2 (1.33 mL, 5.10 mL/mmol) dropwise at –78 °C under N_2. After being stirred at –40 °C for 24 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$, and then a saturated aqueous Rochelle salt was added. The organic layer was separated, and the aqueous layer was extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the residual oil was purified by column chromatography on silica gel (PSQ 100B 4.00 g, hexane/EtOAc = 12/1) to afford alcohol **16** (56.9 mg, 0.0936 mol, 36%) as a colorless oil
$R_f = 0.52$ (hexane/EtOAc = 3/1); $[\alpha]_D^{23}$ –7.61 (*c* 0.775, $CHCl_3$); IR ($CHCl_3$) 3516, 2964, 2946, 2929, 2869, 1774, 1685, 1389, 1015 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (brd, $J = 10.3$, 1H), 5.52 (d, $J = 9.2$ Hz, 1H), 4.59–4.55 (m, 1H), 4.34 (t, $J = 9.0$ Hz, 1H), 4.19 (dd, $J = 9.0$, 5.8 Hz, 1H), 3.66–3.64 (m, 2H), 3.15 (brs, 1H), 2.75–2.65 (m, 2H), 2.39–2.31 (m, 1H), 1.98 (d, $J = 1.2$ Hz, 3H), 1.77–1.70 (m, 1H), 1.67 (s, 3H), 1.41–1.34 (m, 3H), 1.12–1.04 (m, 23H), 1.00 (d, $J = 7.0$ Hz, 3H), 0.94–0.92 (m, 6H), 0.88 (d, $J = 6.8$ Hz, 3H), 0.83–0.80 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 154.6, 142.3, 133.0, 132.4, 131.9, 82.4, 80.1, 63.6, 58.3, 41.9, 38.3, 37.1, 34.9, 32.0, 28.6, 28.5, 20.2, 18.7, 18.6, 18.3, 18.0, 16.4, 16.3, 15.4, 14.1, 13.6, 11.4, 11.2; HRMS [ESI] calcd for $C_{35}H_{65}NO_5SiNa$ $[M+Na]^+$ 630.4530, found 630.4558.

(*S*)-MTPA Ester **S1**

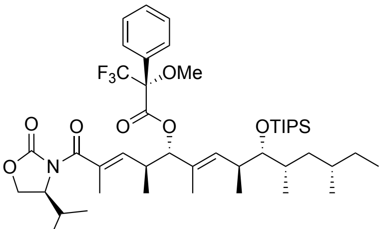


S1

To a stirred solution of alcohol **33** (3.00 mg, 4.93 mmol) in dry pyridine (0.0493 mL, 10.0 mL/mmol) was added (*R*)-(-)-α-methoxy-α-trifluoromethylphenylacetyl chloride (4.61 mL, 0.0247 mmol, 5.00 equiv) dropwise at 0 °C under N_2. After being stirred at room temperature for 12 h, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with EtOAc (10 mL x 3). The combined organic layers were washed with aqueous 1 M HCl, saturated aqueous $NaHCO_3$, and brine, successively; dried over Na_2SO_4; filtered; and then concentrated in vacuo. The residual oil was purified by column chromatography on silica gel (PSQ-100B 100 mg, hexane/EtOAc = 15/1) to afford (*S*)-MTPA ester **S1** (2.70 mg, 3.28 mmol, 67%) as a colorless oil.

R_f = 0.60 (hexane/EtOAc = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.48 (m, 2H), 7.34–7.32 (m, 3H), 5.81 (brd, *J* = 9.0 Hz, 1H), 5.75 (brd, *J* = 9.7 Hz, 1H), 5.29 (d, *J* = 9.0 Hz, 1H), 4.46–4.42 (m, 1H), 4.29 (t, *J* = 9.0 Hz, 1H), 4.18 (dd, *J* = 9.0, 4.6 Hz, 1H), 3.66 (t, *J* = 2.9 Hz, 1H), 3.53 (s, 3H), 2.92–2.82 (m, 1H), 2.68–2.64 (m, 1H), 2.44–2.36 (m, 1H) 1.78 (d, *J* = 1.2 Hz, 3H), 1.76–1.71 (m, 1H), 1.68 (d, *J* = 0.96 Hz, 3H), 1.38–1.32 (m, 3H), 1.14–1.07 (m, 21H), 1.02 (d, *J* = 7.0 Hz, 3H), 0.93–0.86 (m, 14H), 0.82–0.75 (m, 6H); HRMS [ESI] calcd for $C_{45}H_{72}F_3NO_7SiNa$ $[M+Na]^+$ 846.4928, found 846.4928.

(*R*)-MTPA Ester **S2**

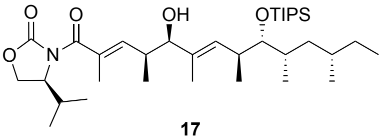


S2

Alcohol **33** (3.00 mg, 4.93 mmol) was acylated with (*S*)-(+)-*α*-methoxy-*α*-trifluoromethylphenylacetyl chloride according to the procedure reported above to give (*R*)-MTPA ester **33R (**2.61 mg, 3.16 mmol, 64%) as a colorless oil.

R_f = 0.61 (hexane/EtOAc = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.47 (m, 2H), 7.37–7.35 (m, 3H), 5.81–5.77 (m, 2H), 5.16 (d, *J* = 9.6 Hz, 1H), 4.48–4.44 (m, 1H), 4.31 (t, *J* = 9.0 Hz, 1H), 4.19 (dd, *J* = 9.0, 4.6 Hz, 1H), 3.66 (t, *J* = 2.6 Hz, 1H), 3.50 (s, 3H), 2.92–2.82 (m, 1H), 2.63–2.60 (m, 1H), 2.43–2.35 (m, 1H) 1.87 (d, *J* = 1.4 Hz, 3H), 1.74–1.71 (m, 1H), 1.46 (d, *J* = 0.9 Hz, 3H), 1.45–1.37 (m, 3H), 1.14–1.07 (m, 21H), 1.02–0.97 (m, 4H), 0.93–0.82 (m, 19H); HRMS [ESI] calcd for $C_{45}H_{72}F_3NO_7SiNa$ $[M+Na]^+$ 846.4928, found 846.4947.

syn-Alcohol **17**



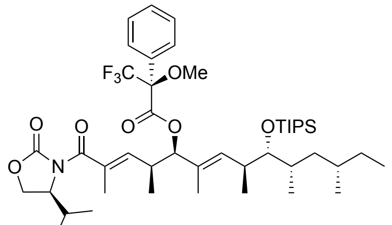
17

To a stirred solution of unsaturated aldehyde **6** (100 mg, 0.261 mmol) in dry CH_2Cl_2 (3.00 mL, 11.6 mL/mmol) were added 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (1.04 mL, 1.04 mmol, 4.00 equiv) and a solution of *N*,*O*-ketene acetal **7** (442 mg, 1.30 mmol, 5.00 equiv) in dry CH_2Cl_2 (1.51 mL, 5.80 mL/mmol) dropwise at −78 °C under N_2. After being stirred at −20 °C for 24 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$, and then a saturated aqueous Rochelle salt was added. The organic layer was separated, and the aqueous layer was extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the residual oil was purified by column chromatography on silica gel (PSQ 100B 2.00 g, hexane/EtOAc = 12/1) to afford *syn*-alcohol **17** (91.7 mg, 0.151 mol, 58%) as a colorless oil.

R_f = 0.52 (hexane/EtOAc = 3/1); $[\alpha]_D^{23}$ +47.7(*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3522, 3030, 2965, 2867, 1778, 1681, 1462, 1387, 883, 671 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.02 (brd, *J* = 9.7, 1H), 5.60 (d, *J* = 9.5 Hz, 1H), 4.56–4.52 (m, 1H), 4.32 (t, *J* = 9.0 Hz, 1H), 4.17 (dd, *J* = 9.0, 5.4 Hz, 1H), 4.13–4.11 (m, 1H), 3.64 (t, *J* = 3.5, 1H), 2.80–2.72 (m, 1H), 2.69–2.60 (m, 1H), 2.36–2.34 (brs, 1H), 2.39–2.26 (m, 1H) 1.95 (d, *J* = 1.4 Hz, 3H), 1.78–1.73 (m, 1H),

1.61 (d, J = 1.0 Hz, 3H), 1.41–1.35 (m, 3H), 1.10–1.06 (m, 22H), 1.02–0.97 (m, 4H), 0.96–0.88 (m, 12H), 0.84–0.81 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 154.1, 142.9, 133.3, 129.8, 129.7, 79.9, 78.3, 63.4, 58.2, 42.0, 37.22, 37.16, 34.4, 31.9, 28.6, 28.4, 20.0, 18.5, 18.4, 18.0, 17.8, 15.9, 15.1, 14.0, 13.6, 13.4, 13.1, 11.3; HRMS [ESI] calcd for $C_{35}H_{65}NO_5SiNa$ $[M+Na]^+$ 630.4530, found 630.4530.

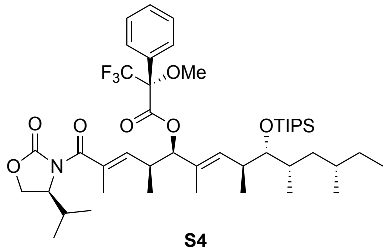
(*S*)-MTPA ester **S3**



S3

syn-Alcohol **34** (3.00 mg, 4.93 mmol) was acylated with (*R*)-(-)-*α*-methoxy-*α*-trifluoromethylphenyl acetyl chloride according to the above procedure for **S1** to give (*S*)-MTPA ester **S3** (2.50 mg, 62%) as a colorless oil. R_f = 0.60 (hexane/EtOAc = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.49 (m, 2H), 7.39–7.36 (m, 3H), 5.76 (d, J = 8.8 Hz, 1H), 5.63 (d, J = 10.0 Hz, 1H), 5.27 (d, J = 7.3 Hz, 1H), 4.42–4.38 (m, 1H), 4.26 (t, J = 9.0 Hz, 1H), 4.16 (dd, J = 9.0, 4.5 Hz, 1H), 3.63 (t, J = 3.5 Hz, 1H), 3.53 (s, 3H), 2.93–2.87 (m, 1H), 2.60–2.56 (m, 1H), 2.43–2.34 (m, 1H) 1.90 (d, J = 1.3 Hz, 3H), 1.71–1.61 (m, 1H), 1.46 (d, J = 0.9 Hz, 3H), 1.36–1.32 (m, 3H), 1.12–1.01 (m, 27H), 0.92–0.82 (m, 17H); HRMS [ESI] calcd for $C_{45}H_{72}F_3NO_7SiNa$ $[M+Na]^+$ 846.4928, found 846.4935.

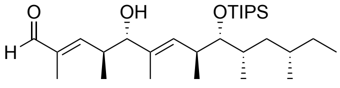
(*R*)-MTPA ester **S4**



S4

syn-Alcohol **34** (3.00 mg, 4.93 mmol) was acylated with (*S*)-(+)-*α*-Methoxy-*α*-trifluoromethylphenyl acetyl chloride according to the above procedure for **S1** to give (*R*)-MTPA ester **S4** (2.03 mg, 50%) as a colorless oil. R_f = 0.60 (hexane/EtOAc = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.49 (m, 2H), 7.39–7.35 (m, 3H), 5.81 (d, J = 9.2 Hz, 1H), 5.58 (brd, J = 10.0 Hz, 1H), 5.35 (d, J = 8.0 Hz, 1H), 4.41–4.37 (m, 1H), 4.26 (t, J = 9.0 Hz, 1H), 4.16 (dd, J = 9.0, 4.5 Hz, 1H), 3.64 (t, J = 3.0 Hz, 1H), 3.53 (s, 3H), 2.89–2.84 (m, 1H), 2.64–2.59 (m, 1H), 2.42–2.35 (m, 1H) 1.87 (d, J = 1.3 Hz, 3H), 1.68–1.65 (m, 1H), 1.61 (d, J = 1.0 Hz, 3H), 1.45–1.34 (m, 3H), 1.12–1.07 (m, 21H), 1.02 (d, J = 7.0 Hz, 3H), 0.96 (d, J = 6.7 Hz, 3H), 0.92–0.82 (m, 17H); HRMS [ESI] calcd for $C_{45}H_{72}F_3NO_7SiNa$ $[M+Na]^+$ 846.4928, found 846.4938.

α,β-Unsaturated aldehyde **18**



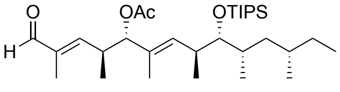
18

To a stirred solution of alcohol **16** (268 mg, 0.441 mmol) in dry CH_2Cl_2 (14.1 mL, 32.0 mL/mmol) was added 1.02 M solution of DIBAL-H in CH_2Cl_2 (1.29 mL, 1.32 mmol, 3.00 equiv) dropwise at −78 °C under N_2. After being stirred at the same temperature for 15 min, the reaction mixture was quenched with MeOH, and then a saturated aqueous Rochelle salt was added. The organic layer was separated, and the aqueous layer was extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the residual oil was purified by column chromatography on silica gel (PSQ 100B 3.00 g, hexane/EtOAc = 21/1) to afford unsaturated aldehyde **18** (158 mg, 0.329 mmol, 75%) as a colorless oil.

R_f = 0.71 (hexane/EtOAc = 3/1); $[\alpha]_D^{23}$ −25.1 (*c* 0.775 $CHCl_3$); IR ($CHCl_3$) 3604, 2963, 2946, 2930, 1683, 1642, 1462, 1378, 1282, 1098, 1004, 883 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.44 (s, 1H), 6.46 (brd, *J* = 9.6 Hz, 1H), 5.62 (d, *J* = 9.3 Hz, 1H), 3.87 (d, *J* = 8.7 Hz, 1H), 3.64 (t, *J* = 3.6 Hz, 1H), 2.94–2.85 (m, 1H), 2.69–2.61 (m, 1H), 1.80 (d, *J* = 1.2 Hz, 3H), 1.76–1.68 (m, 1H), 1.66 (d, *J* = 1.2 Hz, 3H), 1.41–1.36 (m, 3H), 1.13–1.07 (m, 22H), 1.01–0.93 (m, 1H), 1.00 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 7.2 Hz, 3H), 0.89 (d, *J* = 7.2 Hz, 3H), 0.85–0.82 (m, 6H), one proton (OH) was not observed.

^{13}C NMR (100 MHz, $CDCl_3$) δ 195.5, 157.5, 139.8, 133.6, 133.5, 82.8, 80.4, 41.6, 37.6, 36.8, 35.2, 32.1, 28.6, 20.3, 18.64, 18.62, 18.57, 16.6, 16.2, 13.7, 11.4, 11.3, 9.7; HRMS [ESI] calcd for $C_{29}H_{56}O_3SiNa$ $[M+Na]^+$ 503.3896, found 503.3866.

Acetate **5**



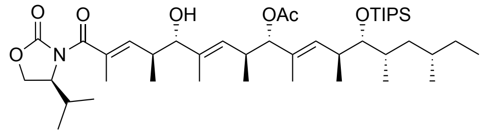
5

To a solution of unsaturated aldehyde **18** (150 mg, 0.312 mmol) in dry CH_2Cl_2 (2.10 mL, 6.80 mL/mmol) were added pyridine (0.30 mL, 3.72 mmol, 12.0 equiv), AcCl (0.133 mL, 1.87 mmol, 6.00 equiv), and DMAP (52.5 mg, 0.468 mmol, 1.5 equiv) at 0 °C under N_2. After being stirred at room temperature for 4 h, the reaction mixture was quenched with saturated aqueous NH_4Cl at 0 °C. The organic layer was separated, and the aqueous layer was extracted with Et_2O (10 mL x 3). The combined organic layers were washed with aqueous 2 M NaOH, saturated aqueous NH_4Cl, and brine, successively; dried over Na_2SO_4; filtered; and then concentrated in vacuo. The residual oil was purified by column chromatography on silica gel (PSQ-100B 3.00 g, hexane/EtOAc = 22/1) to afford acetate **5** (152 mg, 0.267 mmol, 91%) as a colorless oil.

R_f = 0.73 (hexane/EtOAc = 3/1); $[\alpha]_D^{23}$ −2.47 (*c* 1.41, $CHCl_3$); IR ($CHCl_3$) 2963, 2946, 2930, 2868, 1732, 1684, 1462, 1372, 1243, 1094, 1065, 1015 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.36 (s, 1H), 6.31 (brd, *J* = 10.0 Hz, 1H), 5.71 (d, *J* = 9.4 Hz, 1H), 5.12 (d, *J* = 9.1 Hz, 1H), 3.62 (t, *J* = 3.6 Hz, 1H), 3.08–2.99 (m, 1H), 2.66–2.59 (m, 1H), 1.91 (s, 3H), 1.77 (d, *J* = 1.2 Hz, 3H), 1.76–1.62 (m, 1H), 1.66 (d, *J* = 1.2 Hz, 3H), 1.38–1.31 (m, 3H), 1.11–1.04 (m, 23H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.84–0.80 (m, 6H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 195.3, 169.6, 156.0, 139.6, 134.7, 129.4, 82.0, 80.4, 41.0, 36.4, 36.3, 35.3, 32.0, 28.2, 20.9, 20.1, 18.6, 18.5, 18.4, 16.2, 16.0, 13.5, 12.2, 11.3, 9.3; HRMS [ESI] calcd for $C_{31}H_{58}O_4SiNa$ $[M+Na]^+$ 545.4002, found 545.3973.

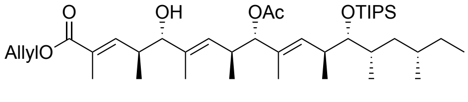
Alcohol **19**



19

To a stirred solution of aldehyde **5** (77.2 mg, 0.144 mmol) in dry CH_2Cl_2 (0.734 mL, 5.10 mL/mmol) were added 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (0.0720 mL, 0.0720 mmol, 0.50 equiv) and a solution of *N*,*O*-ketene acetal **7** (72.4 mg, 0.216 mmol, 1.50 equiv) in dry CH_2Cl_2 (0.734 mL, 5.10 mL/mmol) dropwise at −78 °C under N_2. After being stirred at −40 °C for 24 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$, and then a saturated aqueous Rochelle salt was added. The organic layer was separated, and the aqueous layer was extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the residual oil was purified by column chromatography on silica gel (PSQ 100B 2.00 g, hexane/EtOAc = 15/1) to afford alcohol **19** (44.5 mg, 0.0595 mmol, 42%) as a colorless oil. R_f = 0.48 (hexane/EtOAc = 3/1); $[\alpha]_D^{23}$ −5.87 (*c* 0.550, $CHCl_3$); IR ($CHCl_3$) 3517, 2965, 2929, 2869, 1774, 1727, 1686, 1371, 1249, 1018 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.74 (brd, *J* = 10.3 Hz, 1H), 5.63 (d, *J* = 9.1 Hz, 1H), 5.17 (d, *J* = 9.4 Hz, 1H), 5.01 (d, *J* = 9.1 Hz, 1H), 4.59–4.55 (m, 1H), 4.34 (t, *J* = 9.0 Hz, 1H), 4.19 (dd, *J* = 9.0, 5.7 Hz, 1H), 3.63–3.61 (m, 2H), 3.23 (brs, 1H), 2.80–2.66 (m, 2H), 2.66–2.59 (m, 1H), 2.39–2.31 (m, 1H), 1.97 (d, *J* = 1.2 Hz, 3H), 1.95 (s, 3H), 1.77–1.66 (m, 1H), 1.70 (s, 3H), 1.66 (s, 3H), 1.37–1.32 (m, 3H), 1.12–1.04 (m, 23H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.84–0.79 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 170.2, 154.6, 141.9, 135.3, 134.2, 132.0, 131.8, 130.7, 83.0, 82.1, 80.4, 63.6, 58.2, 41.4, 38.1, 36.7, 35.3, 35.1, 32.1, 28.6, 28.5, 21.2, 20.2, 18.7, 18.6, 18.5, 18.0, 17.2, 16.3, 16.1, 15.3, 14.1, 13.7, 12.3, 11.4, 11.1; HRMS [ESI] calcd for $C_{43}H_{77}NO_7SiNa$ $[M+Na]^+$ 770.5367, found 770.5380.

Allyl ester **20**

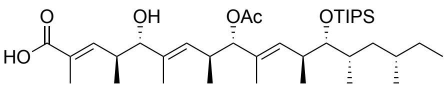


20

To a solution of allyl alcohol (0.0654 mL, 0.962 mmol, 12.0 equiv) in dry THF (1.47 mL, 18.3 mL/mmol) was added 1.0 M solution of EtMgBr in THF (0.241 mL, 0.241 mmol, 3.00 equiv) at 0 °C under N_2. After the mixture was stirred at the same temperature for 15 min, a solution of alcohol **19** (60.0 mg, 0.0802 mmol) in dry THF (0.201 mL, 2.50 mL/mmol) was added to the reaction mixture at the same temperature. After being stirred at room temperature for 3 h, the reaction mixture was quenched with saturated aqueous NH_4Cl at 0 °C. The organic layer was separated, and the aqueous layer was extracted with Et_2O (10 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo, and the residual oil was purified by column chromatography on silica gel (PSQ 100B 1.00 g, hexane/EtOAc = 18/1) to afford allyl ester **20** (48.0 mg, 0.0709 mmol, 89%) as a colorless oil.

R_f = 0.58 (hexane/EtOAc = 3/1); $[\alpha]_D^{23}$ −14.8 (*c* 0.733, $CHCl_3$); IR ($CHCl_3$) 3592, 2964, 2945, 2869, 1724, 1709, 1648, 1211, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (brd, J = 9.9 Hz, 1H), 6.01–5.91 (m, 1H), 5.63 (d, J = 9.2 Hz, 1H), 5.33 (brd, J = 17.2 Hz, 1H), 5.23–5.20 (m, 2H), 4.99 (d, J = 9.6 Hz, 1H), 4.64 (brd, J = 5.6 Hz, 2H), 3.75 (d, J = 9.0 Hz, 1H), 3.62 (t, J = 3.6 Hz, 1H), 2.78–2.64 (m, 2H), 2.64–2.59 (m, 1H), 1.94 (s, 3H), 1.91 (s, 3H), 1.67 (s, 3H), 1.72–1.66 (m, 1H), 1.65 (s, 3H), 1.37–1.32 (m, 3H), 1.12–1.05 (m, 23H), 0.96 (d, J = 7.0 Hz, 3H), 0.94–0.89 (m, 1H), 0.87 (d, J = 6.8 Hz, 3H), 0.83–0.81 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 167.8, 145.4, 136.0, 134.5, 132.7, 132.6, 130.0, 128.7, 118.0, 83.3, 82.5, 80.5, 65.4, 41.3, 37.2, 36.6, 35.2, 35.1, 32.1, 28.5, 21.3, 20.2, 18.64, 18.62, 18.5, 17.1, 16.5, 16.0, 13.7, 13.0, 12.2, 11.4, 11.2; HRMS [ESI] calcd for $C_{40}H_{72}O_6SiNa$ $[M+Na]^+$ 699.4996, found 699.5010.

Carboxylic acid **4**

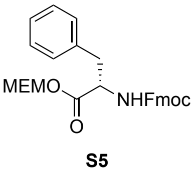


4

To a solution of allyl ester **20** (133 mg, 0.196 mmol) in dry THF (4.10 mL, 20.9 mL/mmol) were added $Pd(PPh_3)_4$ (22.6 mg , 0.0196 mmol, 0.10 equiv) and morpholine (0.169 mL, 1.96 mmol, 10.0 equiv) at 0 °C under N_2. After being stirred at room temperature for 12 h, the reaction mixture was quenched with brine at 0 °C. The organic layer was separated, and the aqueous layer was extracted with EtOAc (10 mL x 3). The combined organic layers were washed with aqueous 1 M HCl, saturated aqueous $NaHCO_3$, and brine, successively; dried over Na_2SO_4; filtered; and then concentrated in vacuo. The residual oil was purified by column chromatography on silica gel (PSQ-100B 2.0 g, $CHCl_3$/MeOH = 100/1) to afford carboxylic acid **4** (119 mg, 0.186 mmol, 95%) as a colorless oil.

R_f = 0.40 ($CHCl_3$/MeOH = 5/1); $[\alpha]_D^{23}$ −8.15 (*c* 0.733, $CHCl_3$); IR ($CHCl_3$) 3528, 2964, 2869, 1724, 1692, 1211, 785 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (d, J = 9.8 Hz, 1H), 5.63 (d, J = 9.2 Hz, 1H), 5.21 (d, J = 9.5 Hz, 1H), 5.00 (d, J = 9.6 Hz, 1H), 3.77 (d, J = 9.0 Hz, 1H), 3.62 (t, J = 3.6 Hz, 1H), 2.78–2.62 (m, 2H), 2.61–2.59 (m, 1H), 1.95 (s, 3H), 1.89 (s, 3H), 1.67 (s, 3H), 1.66 (s, 3H), 1.74–1.66 (m, 1H), 1.39–1.32 (m, 3H), 1.12–1.05 (m, 21H), 1.01–0.89 (m, 2H), 0.96 (d, J = 7.0 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H), 0.84–0.81 (m, 12H), two protons (COOH and OH) were not observed; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 170.5, 147.5, 136.0, 134.7, 132.5, 130.3, 128.1, 83.4, 82.4, 80.5, 41.3, 37.3, 36.6, 35.2, 35.1, 32.1, 28.5, 21.3, 20.2, 18.64, 18.62, 18.5, 17.1, 16.4, 16.0, 13.7, 12.6, 12.2, 11.4, 11.2; HRMS [ESI] calcd for $C_{37}H_{68}O_6SiNa$ $[M+Na]^+$ 659.4683, found 659.4659.

Fmoc-L-Phe-OMEM (**S5**)

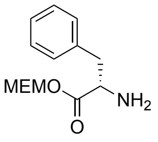


S5

To a solution of Fmoc-L-Phe-OH (2.00 g, 5.17 mmol) in dry CH_2Cl_2 (77.6 mL, 15.0 mL/mmol) were added DIEA (1.80 mL, 10.3 mmol, 2.0 equiv) and MEMCl (0.88 mL, 7.76 mmol, 1.50 equiv) at 0 °C under N_2. After being stirred at room temperature for 12 h, the reaction mixture was quenched with H_2O at 0 °C. The organic layer was separated, and the aqueous layer was extracted with EtOAc (100 mL x 3). The combined organic layers were washed with aqueous 1 M HCl, saturated aqueous $NaHCO_3$, and brine, successively; dried over Na_2SO_4; filtered; and then concentrated in vacuo. The residual oil was purified by column chromatography on silica gel (PSQ-100B 50.0 g, hexane/EtOAc = 7/1) to afford Fmoc-L-Phe-OMEM (**S5**) (2.45 g, 5.17 mmol, quant) as a colorless oil.

R_f = 0.35 (hexane/EtOAc = 2/1); $[\alpha]_D^{23}$ +11.7 (*c* 1.34, $CHCl_3$); IR ($CHCl_3$) 3432, 3028, 3013, 2931, 2896, 1720, 1509, 1450, 1247, 1110 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.5 Hz, 2H), 7.57 (brt, *J* = 6.0 Hz, 2H), 7.41 (brt, *J* = 7.5 Hz, 2H), 7.34–7.27 (m, 5H), 7.15 (d, *J* = 6.9 Hz, 2H), 5.40 (d, *J* = 6.0 Hz, 1H), 5.36 (d, *J* = 6.0 Hz, 1H), 5.33 (d, *J* = 8.0 Hz, 1H), 4.71 (dt, *J* = 8.0, 5.9 Hz, 1H), 4.45 (dd, *J* = 10.6, 7.0 Hz, 1H), 4.35 (dd, *J* = 10.6, 7.0 Hz, 1H), 4.21 (t, *J* = 7.0 Hz, 1H), 3.72 (t, *J* = 4.5 Hz, 2H), 3.52 (t, *J* = 4.5 Hz, 2H), 3.37 (s, 3H), 3.19 (dd, *J* = 13.9, 5.9 Hz, 1H), 3.13 (dd, *J* = 13.9, 5.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 155.8, 144.0, 143.9, 141.5, 135.8, 129.6, 128.8, 127.9, 127.4, 127.3, 125.3, 125.2, 120.2, 90.6, 71.6, 70.0, 67.2, 59.2, 55.0, 47.4, 38.2; HRMS [ESI] calcd for $C_{28}H_{29}NO_6Na$ $[M+Na]^+$ 498.1893, found 498.1909.

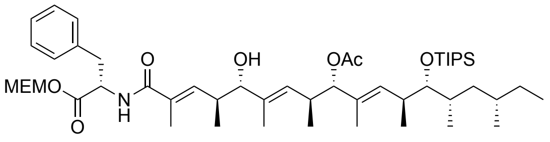
H-L-Phe-OMEM (**20**)



3

To a solution of Fmoc-L-Phe-OMEM (**S5**) (2.45 g, 5.17 mmol) in dry MeCN (51.7 mL, 10.0 mL/mmol) was added Et_2NH (5.37 mL, 51.7 mmol, 10.0 equiv) at room temperature under N_2. After being stirred at the same temperature for 1 h, the reaction mixture was diluted with toluene and then concentrated in vacuo. The resulting residue was used for the next reaction without further purification.

Amide **21**



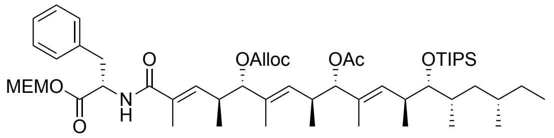
21

To a solution of carboxylic acid **4** (34.2 mg, 0.0536 mmol) in dry DMF (0.579 mL, 10.8 mL/mmol) were added HOAt (23.3 mg, 0.172 mmol, 3.20 equiv), DIEA (0.0338 mL, 0.194 mmol, 3.60 equiv), H-L-Phe-OMEM (**20**) (27.3 mg, 0.107 mmol, 2.00 equiv), and EDCI (25.1 mg, 0.161 mmol, 3.00 equiv) at 0 °C under N_2. After being stirred at room temperature for 12 h, the reaction mixture was quenched with brine at 0 °C. The organic layer was separated, and the aqueous layer was extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and then concentrated in vacuo. The residual oil was purified by column chromatography on silica gel (PSQ-100B 600 mg, hexane/EtOAc = 4/1) to afford amide **21** (46.7 mg, 0.0536 mmol, quant) as a colorless oil.

R_f = 0.45 (hexane/EtOAc = 1/1); $[\alpha]_D^{23}$ +1.03 (*c* 1.05, $CHCl_3$); IR ($CHCl_3$) 3441, 2964, 2930, 2869, 1728, 1669, 1632, 1506, 1248, 1105 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.22 (m, 3H), 7.17–7.15 (m, 2H), 6.31 (d, *J* =

7.5 Hz, 1H), 6.17 (d, *J* = 9.6 Hz, 1H), 5.63 (d, *J* = 7.9 Hz, 1H), 5.38 (d, *J* = 6.0 Hz, 1H), 5.34 (d, *J* = 6.0 Hz, 1H), 5.19 (d, *J* = 7.5 Hz, 1H), 5.00 (d, *J* = 9.6 Hz, 1H), 4.90 (dt, *J* = 7.5, 6.1 Hz, 1H), 3.72–3.67 (m, 3H), 3.62 (brt, *J* = 3.7 Hz, 1H), 3.53–3.51 (m, 2H), 3.37 (s, 3H), 3.21 (dd, *J* = 13.8, 6.1 Hz, 1H), 3.15 (dd, *J* = 13.8, 6.1 Hz, 1H), 2.77–2.70 (m, 1H), 2.70–2.56 (m, 2H), 1.93 (s, 3H), 1.85 (d, *J* = 1.0 Hz, 3H), 1.73–1.62 (m, 7H), 1.37–1.32 (m, 3H), 1.10–1.04 (m, 23H), 0.96 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.84–0.79 (m, 12H), one proton (OH?) was not observed; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 170.3, 168.9, 139.8, 136.1, 136.0, 134.7, 132.2, 131.5, 130.3, 129.5, 128.7, 127.3, 90.5, 83.4, 82.3, 80.4, 71.5, 69.9, 59.2, 53.5, 41.3, 37.8, 36.9, 36.6, 35.2, 35.1, 32.0, 28.5, 21.2, 20.2, 18.62,18.60, 18.5, 17.1, 16.8, 16.0, 13.7, 13.1, 12.1, 11.4, 11.3; HRMS [ESI] calcd for $C_{50}H_{85}NO_9SiNa$ $[M+Na]^+$ 894.5891, found 894.5890.

Alloc carbonate **22**

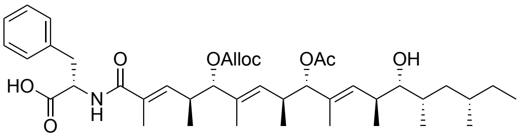


22

To a solution of amide **38** (52.7 mg, 0.0605 mmol) in dry THF (1.09 mL, 18.0 mL/mmol) were added pyridine (0.0487 mL, 0.605 mmol, 10.0 equiv) and AllocCl (0.0320 mL, 0.0303 mmol, 5.00 equiv) at 0 °C under N_2. After being stirred at room temperature for 5 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ at 0 °C. The organic layer was separated, and the aqueous layer was extracted with Et_2O (10 mL x 3). The combined organic layers were washed with aqueous 1 M HCl, saturated aqueous $NaHCO_3$, and brine, successively; dried over Na_2SO_4; filtered; and then concentrated in vacuo. The residual oil was purified by column chromatography on silica gel (PSQ-100B 1.0 g, hexane/EtOAc = 5/1) to afford **22** (51.9 mg, 0.0543 mmol, 89%) as a colorless oil.

R_f = 0.63 (hexane/EtOAc = 1/1); $[\alpha]_D^{23}$ −4.03 (*c* 0.525, $CHCl_3$); IR ($CHCl_3$) 3441, 3029, 2963, 2869, 1735, 1667, 1636, 1506, 1370, 1258 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.22 (m, 3H), 7.20–7.17 (m, 2H), 6.33 (d, *J* = 7.3 Hz, 1H), 5.92–5.83 (m, 1H), 5.90 (d, *J* = 10.3 Hz, 1H), 5.64 (d, *J* = 9.2 Hz, 1H), 5.39 (d, *J* = 6.1 Hz, 1H), 5.33 (d, *J* = 6.1 Hz, 1H), 5.31–5.27 (m, 2H), 5.21 (brd, *J* = 10.4 Hz, 1H), 5.00 (d, *J* = 9.7 Hz, 1H), 4.83 (dt, *J* = 7.3, 6.4 Hz, 1H), 4.73 (d, *J* = 9.1 Hz, 1H), 4.59–4.51 (m, 2H), 3.72–3.69 (m, 2H), 3.62 (t, *J* = 3.6 Hz, 1H), 3.53–3.51 (m, 2H), 3.37 (s, 3H), 3.22 (dd, *J* = 13.7, 6.4 Hz, 1H), 3.11 (dd, *J* = 13.7, 6.4 Hz, 1H), 2.84–2.70 (m, 2H), 2.63–2.58 (m, 1H), 1.89 (s, 3H), 1.81 (d, *J* = 1.0 Hz, 3H), 1.74–1.71 (m, 1H), 1.68 (d, *J* = 0.8 Hz, 3H), 1.63 (s, 3H), 1.37–1.32 (m, 3H), 1.10–1.05 (m, 21H), 0.96 (d, *J* = 7.0 Hz, 3H), 0.94–0.88 (m, 2H), 0.87–0.81 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 169.8, 169.6, 154.6, 137.4, 136.2, 134.8, 134.6, 132.2, 131.9, 131.8, 130.2, 129.5, 128.7, 127.2, 118.9, 90.4, 86.9, 82.8, 80.5, 71.5, 69.8, 68.5, 59.2, 53.6, 41.2, 37.8, 36.6, 35.6, 35.3, 35.2, 32.1, 28.4, 21.0, 20.2, 18.63, 18.60, 18.55, 17.0, 16.5, 16.0, 13.7, 13.1, 12.1, 12.0, 11.4; HRMS [ESI] calcd for $C_{54}H_{89}NO_{11}SiNa$ $[M+Na]^+$ 978.6103, found 978.6079.

Cyclization precursor **2**



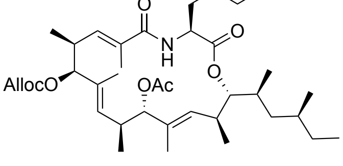
2

To a solution of **22** (80.0 mg, 0.0837 mmol) in dry dioxane (7.97 mL, 95.2 mL/mmol) was added 4.0 M solution of HCl in dioxane (7.97 mL, 95.2 mL/mmol) at 0 °C under N$_2$. After being stirred at room temperature for 15 min, the reaction mixture was diluted with toluene and then concentrated in vacuo. The resulting residue was used for the next reaction without further purification.

To a solution of the above residue in MeCN (14.0 mL, 167 mL/mmol) was added aqueous HF (5.98 mL, 71.4 mL/mmol, 47% w/w) at 0 °C under N$_2$. After being stirred at room temperature for 15 min, the reaction mixture was quenched with saturated aqueous NaHCO$_3$ at 0 °C and acidified with aqueous 2 M NaH$_2$PO$_4$. The organic layer was separated, and the aqueous layer was extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, filtered, and then concentrated. The residual oil was purified by column chromatography on silica gel (PSQ-100B 800 mg, CHCl$_3$/MeOH = 100/1) to afford cyclization precursor **2** (44.0 mg, 0.0618 mmol, 74% in 2 steps) as a colorless oil.

R_f = 0.40 (CHCl$_3$/MeOH = 5/1); $[\alpha]_D^{23}$ +3.67 (*c* 0.917, CHCl$_3$); IR (CHCl$_3$) 3666, 3517, 3438, 2964, 2929, 2873, 1731, 1665, 1632, 1509, 1372, 1261 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.36–7.33 (m, 2H), 7.28–7.25 (m, 3H), 6.30 (brd, *J* = 6.5 Hz, 1H), 5.94–5.84 (m, 2H), 5.37–5.24 (m, 4H), 4.84 (d, *J* = 9.0 Hz, 1H), 4.75–4.69 (m, 2H), 4.55 (brd, *J* = 5.6 Hz, 2H), 3.33 (dd, *J* = 14.3, 5.2 Hz, 1H), 3.23 (dd, *J* = 8.5, 2.8 Hz, 1H), 3.15 (dd, *J* = 14.3, 8.0 Hz, 1H), 2.84–2.73 (m, 2H), 2.62–2.55 (m, 1H), 1.93 (s, 3H), 1.80 (s, 3H), 1.78–1.72 (m, 1H), 1.69 (s, 3H), 1.62 (s, 3H), 1.46–1.35 (m, 3H), 1.12–1.02 (m, 3H), 0.90–0.84 (m, 17H), two protons (COOH and OH) were not observed; ^{13}C NMR (100 MHz, CDCl$_3$) δ 178.3, 171.0, 170.7, 154.7, 138.3, 136.3, 134.4, 133.6, 133.3, 132.0, 131.8, 130.1, 129.6, 128.9, 127.3, 119.0, 86.6, 84.0, 70.8, 68.5, 54.3, 41.6, 36.1, 35.6, 34.4, 31.5, 31.4, 29.9, 29.4, 21.2, 19.6, 17.0, 16.9, 16.5, 13.3, 13.0, 12.4, 12.0, 11.4; HRMS [ESI] calcd for $C_{41}H_{61}NO_9Na$ $[M+Na]^+$ 734.4244, found 734.4233.

Macrolactone **23**



23

To a solution of cyclization precursor **2** (8.5mg, 0.0123 mmol) in dry 1,2-dichloroethane (0.114 mL, 9.30 mL/mmol) was added *N*-methylynetoluenesulfonamide$^{xx)}$ (MYTsA) (2.8 mg, 0.0135 mmol, 1.10 equiv) at room temperature under N$_2$. After being stirred at the same temperature for 20 h, the reaction mixture was concentrated in vacuo. The resulting residue was used for the next reaction without further purification.

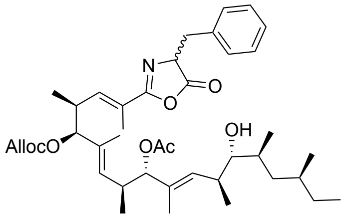
To a solution of the above residue in dry 1,2-dichloroethane (2.46 mL, 200 mL/mmol) was added TsOH•H$_2$O (0.4 mg, 0.00185 mmol, 15 mol%) at room temperature under N$_2$. After being stirred at the same temperature for

1.5 h, the reaction mixture was quenched with saturated aqueous NaHCO$_3$ at 0 °C. The organic layer was separated, and the aqueous layer was extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, filtered, and then concentrated in vacuo. The residual oil was purified by column chromatography on silica gel (PSQ-100B 100 mg, hexane/EtOAc = 5/1) to afford macrolactone **23** (5.40 mg, 0.00779 mmol, 65% in 2 steps) as a colorless oil.

R_f = 0.72 (hexane/EtOAc = 1/1); $[\alpha]_D^{23}$ +1.52 (*c* 0.592, CHCl$_3$); IR (CHCl$_3$) 3442, 3028, 2967, 2931, 1732, 1669, 1636, 1506, 1254, 967 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.29–7.27 (m, 2H), 7.20–7.18 (m, 3H), 5.97–5.88 (m, 3H), 5.34 (d, *J* = 17.2 Hz, 1H), 5.28 (d, *J* = 10.5 Hz, 1H), 5.11 (d, *J* = 5.1 Hz, 1H), 5.00–4.85 (m, 4H), 4.69–4.55 (m, 3H), 3.28 (dd, *J* = 14.0, 5.8 Hz, 1H), 3.20 (dd, *J* = 14.0, 6.0 Hz, 1H), 2.98–2.92 (m, 1H), 2.82–2.77 (m, 1H), 2.73–2.69 (m, 1H), 2.03 (s, 3H), 1.83 (s, 3H), 1.65 (s, 3H), 1.58 (s, 3H), 1.44–1.34 (m, 1H), 1.31–1.24 (m, 1H), 1.14 (d, *J* = 6.8 Hz, 3H), 1.11–1.08 (m, 1H), 0.92–0.80 (m, 3H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.82 (d, *J* = 6.6 Hz, 3H), 0.78–0.72 (m, 6H), 0.67 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.8, 169.8, 168.5, 154.8, 136.9, 133.7, 133.0, 132.0, 131.8, 131.1, 130.8, 129.8, 128.7, 127.0, 125.2, 118.5, 83.2, 82.9, 81.1, 68.3, 53.0, 40.1, 36.5, 36.4, 34.5, 33.7, 33.6, 31.3, 27.6, 21.3, 20.4, 18.9, 18.2, 16.0, 15.8, 14.9, 13.5, 13.1, 10.8; HRMS [ESI] calcd for $C_{41}H_{59}NO_8Na$ [M+Na]$^+$ 716.4138, found 716.4151.

Azlactone **24**

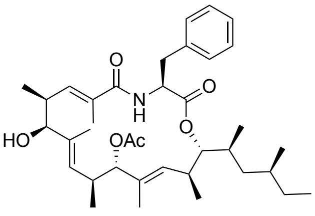
The azlactone **24** was provided as an undesired product in the macrolactonization promoted by MNBA/DMAPO or TCBC/Et$_3$N/DMAP.



24

R_f = 0.74 (hexane/EtOAc = 1/1); IR (CHCl$_3$) 3533, 2963, 2930, 2874, 1813, 1737, 1656, 1621, 1455, 1370, 1260, 982, 909 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$, mixture of diastereomers) δ 7.28–7.20 (m, 5H), 6.29 (d, *J* = 9.3 Hz, 0.5H), 6.26 (d, *J* = 9.3 Hz, 0.5H), 5.94–5.82 (m, 1H), 5.37–5.19 (m, 4H), 4.85 (d, *J* = 7.1 Hz, 0.5H), 4.82 (d, *J* = 7.0 Hz, 0.5H), 4.76 (d, *J* = 8.6 Hz, 1H), 4.56–4.52 (m, 3H), 3.29–3.24 (m, 1H), 3.20–3.18 (m, 1H), 3.14–3.09 (m, 1H), 2.95–2.88 (m, 1H), 2.79–2.71 (m, 1H), 2.61–2.56 (m, 1H), 1.96–1.94 (m, 3H), 1.94 (s, 1.5H), 1.92 (s, 1.5H), 1.79–1.65 (m, 1H), 1.67 (d, *J* = 1.1 Hz, 1.5H), 1.64 (d, *J* = 1.1 Hz, 1.5H), 1.62 (d, *J* = 1.0 Hz, 1.5H), 1.61 (d, *J* = 1.1 Hz, 1.5H), 1.49–1.40 (m, 3H), 1.11–1.03 (m, 3H), 0.92–0.81 (m, 17H); ^{13}C NMR (100 MHz, CDCl$_3$, mixture of diastereomers) δ 177.5, 170.4, 165.5, 162.9, 154.03, 153.97, 142.5, 142.4, 135.4, 134.19, 134.15 134.0, 133.9, 133.4, 131.8, 131.7, 129.6, 129.5, 128.3, 127.1, 124.1, 118.71, 118.67, 86.34, 86.30, 83.7, 83.6, 68.3, 66.59, 66.56, 51.5, 41.6, 37.3, 36.1, 34.2, 31.4, 31.2, 29.7, 29.4, 21.0, 19.5, 16.80, 16.78, 16.68, 16.66, 16.3, 16.2, 13.1, 12.2, 12.1, 12.0, 11.90, 11.87, 11.2; HRMS [ESI] calcd for $C_{41}H_{59}NO_8Na$ [M+Na]$^+$ 716.4138, found 716.4138.

Metacridamide A (Revised structure) (**1a’**)

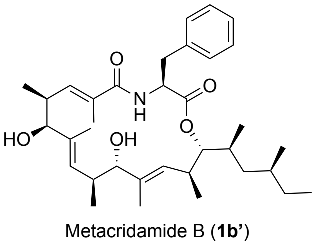


Metacridamide A (**1a’**)
(Revised structure)

To a solution of macrolactone **23** (1.71 mg, 2.47 mmol) in dry THF (0.0419 mL, 17.0 mL/mmol) were added $Pd(PPh_3)_4$ (0.285 mg , 0.247 mmol, 0.100 equiv) and *N*-methylaniline (2.67mL, 24.7 mmol, 10.0 equiv) at 0 °C under N_2. After being stirred at room temperature for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl at 0 °C. The organic layer was separated, and the aqueous layer was extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and then concentrated in vacuo. The residual oil was purified by column chromatography on silica gel (PSQ-100B 100 mg, hexane/EtOAc = 5/1) to afford metacridamide A (**1a’**) (1.50 mg, 2.46 mmol, quant) as a colorless oil.

R_f = 0.50 (hexane/EtOAc = 2/1); $[\alpha]_D^{23}$ −8.71 (*c* 0.283, $CHCl_3$); IR ($CHCl_3$) 3470, 3019, 2965, 2929, 1728, 1668, 1635, 1558, 1249, 1218, 1211, 1014 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27–7.19 (m, 5H), 6.03 (dd, *J* = 9.5, 1.4 Hz, 1H), 5.92 (d, *J* = 8.6 Hz, 1H), 5.11 (d, *J* = 9.7 Hz, 1H), 5.02 (brd, *J* = 6.8 Hz, 1H), 4.95–4.92 (m, 1H), 4.92 (d, *J* = 3.7 Hz, 1H), 4.61 (dd, *J* = 8.8, 2.3 Hz, 1H), 3.96 (brs, 1H), 3.27 (dd, *J* = 14.0, 6.1 Hz, 1H), 3.20 (dd, *J* = 14.0, 5.8 Hz, 1H), 2.85–2.81 (m, 2H), 2.73–2.70 (m, 1H), 2.04 (s, 3H), 1.82 (d, *J* = 1.4 Hz, 3H), 1.63 (d, *J* = 1.2 Hz, 3H), 1.61 (s, 3H), 1.63−1.60 (m, 1H), 1.42–1.38 (m, 1H), 1.30–1.25 (m, 1H), 1.20 (d, *J* = 7.0 Hz, 3H), 1.14–1.08 (m, 1H), 0.92 (d, *J* = 7.0 Hz, 3H), 0.88–0.83 (m, 2H), 0.81 (d, *J* = 6.6 Hz, 3H), 0.75 (d, *J* = 6.6 Hz, 3H), 0.74 (t, *J* = 7.4 Hz, 3H), 0.66 (d, *J* = 6.9 Hz, 3H), one proton (OH) was not observed; ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.9, 169.8, 168.7, 137.1, 137.0, 133.7, 132.7, 131.0, 130.9, 129.8, 128.7, 127.0, 124.2, 82.7, 81.4, 78.3, 53.0, 40.1, 36.6, 36.4, 35.4, 33.7, 33.5, 31.3, 27.6, 21.4, 20.5, 19.4, 18.2, 16.1, 16.0, 15.0, 13.5, 13.1, 10.8; HRMS [ESI] calcd for $C_{37}H_{55}NO_6Na$ $[M+Na]^+$632.3927, found 632.3908.

Metacridamide B (Revised structure) (**1b’**)



Metacridamide B (**1b’**)
(Revised structure)

To a solution of metacridamide A (**1a’**) (3.00 mg, 4.92 mmol) in dry THF (1.51 mL, 306 mL/mmol) was added 4.0 M aqueous solution of $LiOH\cdot H_2O$ (1.51 mL, 306 mL/mmol) at room temperature under N_2. After being stirred at 60 °C for 24 h, the reaction mixture was quenched with saturated aqueous NH_4Cl at 0 °C. The organic layer was separated, and the aqueous layer was extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and then concentrated in vacuo. The residual oil was purified by column chromatography on silica gel (PSQ-100B 100 mg, hexane/EtOAc = 4/1) to afford metacridamide B (**1b’**) (2.0 mg, 3.5 mmol, 72%) as a colorless oil.

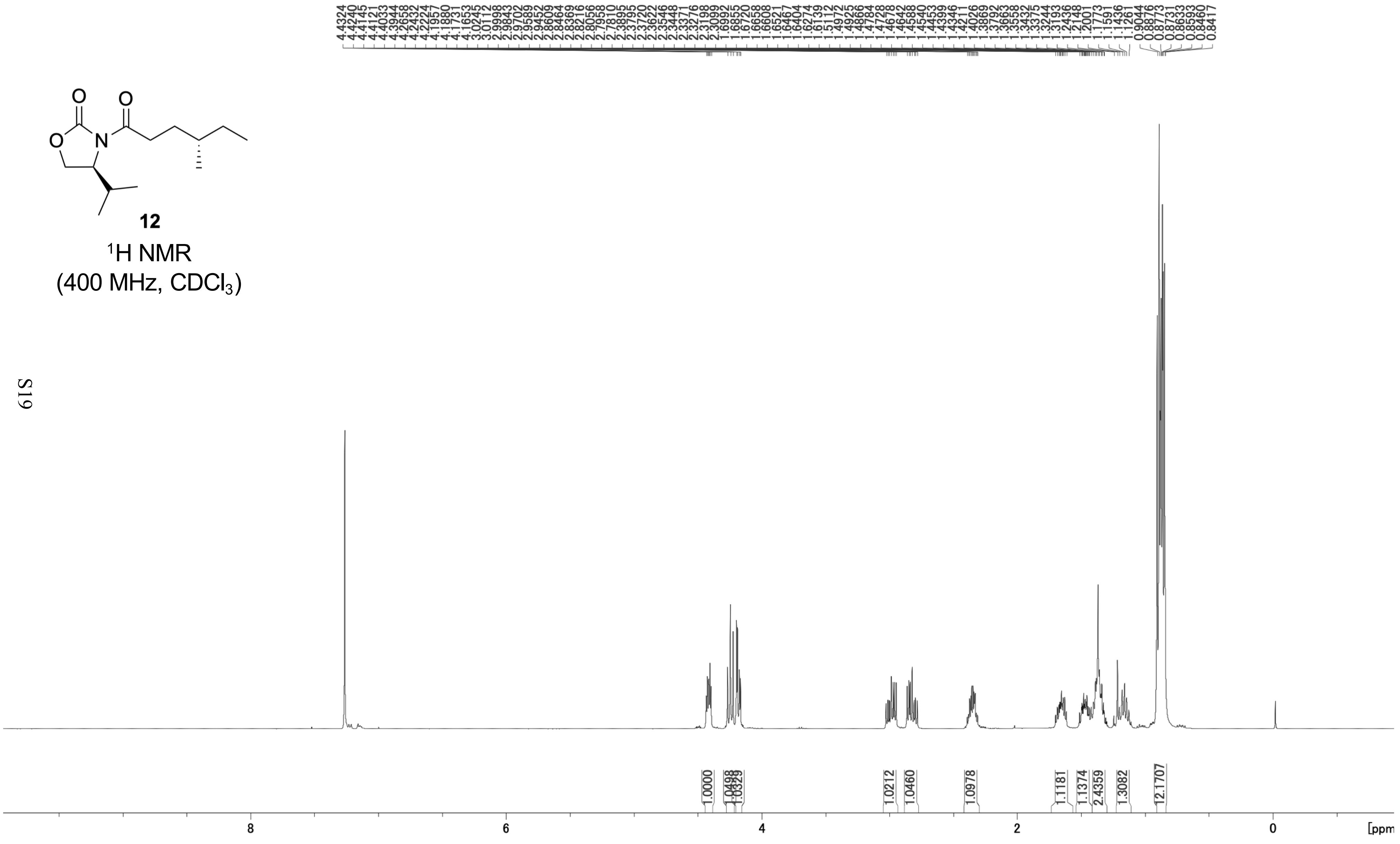
R$_f$ = 0.38 (hexane/EtOAc = 2/1); $[\alpha]_D^{23}$ +24.3 (*c* 0.150, $CHCl_3$); IR ($CHCl_3$) 3420, 3023, 2961, 2928, 2360, 1725, 1667, 1559, 1507, 1456, 1011 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD) δ 7.25–7.22 (m, 4H), 7.18–7.15 (m, 1H), 6.14 (d, *J* = 9.6 Hz, 1H), 5.25 (d, *J* = 10.4 Hz, 1H), 5.11 (d, *J* = 10.0 Hz, 1H), 4.85 (brs, 1H), 4.69 (dd, *J* = 8.0, 1.8 Hz, 1H), 3.93 (s, 1H), 3.83 (d, *J* = 3.6 Hz, 1H), 3.33 (m, 1H), 2.94 (dd, *J* = 14.2, 10.1 Hz, 1H), 2.82–2.78 (m, 2H), 2.73–2.70 (m, 1H), 1.70–1.67 (m, 1H), 1.66 (d, *J* = 1.2 Hz, 3H), 1.64 (d, *J* = 1.4 Hz, 3H), 1.59 (s, 3H), 1.42–1.34 (m, 2H), 1.31–1.26 (m, 1H), 1.17 (d, *J* = 7.0 Hz, 3H), 1.00 (d, *J* = 7.0 Hz, 3H), 0.98–0.94 (m, 1H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.91–0.88 (m, 1H), 0.86 (d, *J* = 6.6 Hz, 3H), 0.83 (t, *J* = 7.4 Hz, 3H), 0.76 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 172.9, 172.4, 139.4, 136.8, 136.2, 135.9, 132.4, 130.22, 130.19, 129.3, 127.5, 127.3, 83.5, 80.8, 79.2, 54.2, 42.1, 40.5, 37.1, 36.6, 35.4, 35.1, 32.8, 29.3, 20.6, 19.6, 19.2, 16.1, 15.9, 15.0, 13.6, 13.4, 11.6; HRMS [ESI] calcd for $C_{35}H_{53}NO_5Na$ $[M+Na]^+$ 590.3821, found 590.3811.

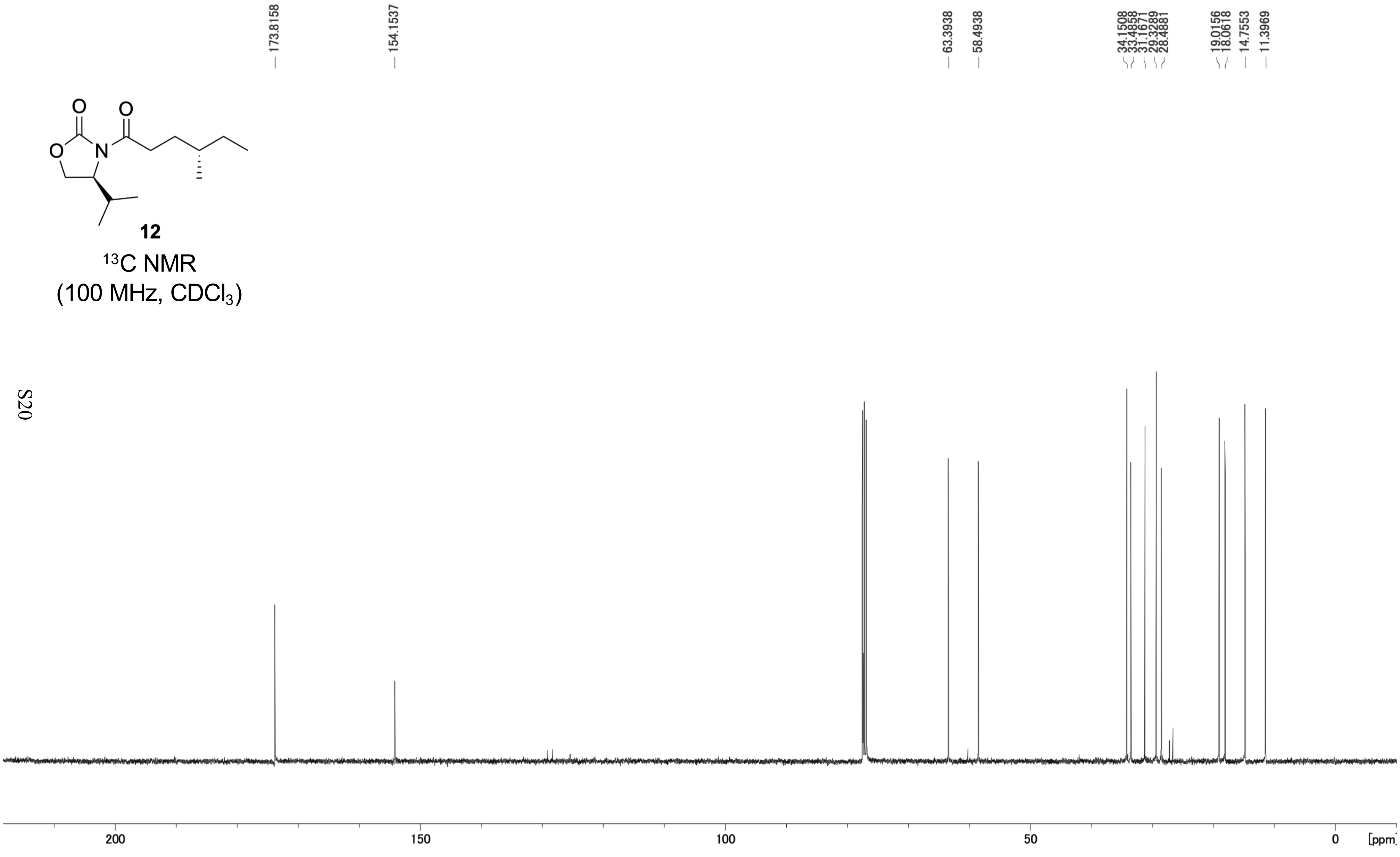
Evaluation of cytotoxicity

Stock cultures of cancer cells (MCF-7 : ATCC HTB-22, HCT-116 : ATCC CCL-247) were maintained in Dulbecco's Modified Eagle Medium (nacalai tesque) containing 10% fetal bovine serum (gibco), 1% antibiotic (penicillin-streptomycin mixed solution, nacalai tesque) at 37 °C under 5% CO_2. For the purpose of the experiment, 2 x 10^3 cells suspended in 100 μL of medium per well were plated in 96-well plate and incubated at 37 °C under 5% CO_2. After incubation for 24 h, a solution of compound in DMSO (1 μL, concentration: 0.001, 0.01, 0.1, 1, 10 μM, respectively) was added to the above-mentioned well, resulting in various concentrations of the compound (0.01, 0.1, 1, 10, 100 μM) or solvent control (1% DMSO). After incubation for 72 h under the same conditions, 1.4 mg/mL MTT solution in phosphate buffer saline (100 μL) was added to the cell culture. After 4 h, the culture medium was removed, and the precipitated formazan product was dissolved in DMSO (150 μL). Optical density at 570 nm was measured with a TECAN microplate reader (Infinite 200 Pro). All assays were performed in triplicate to confirm reproducibility.

12

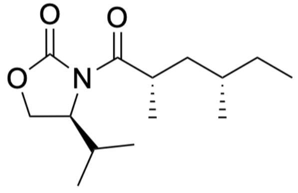
^{1}H NMR
(400 MHz, $CDCl_3$)





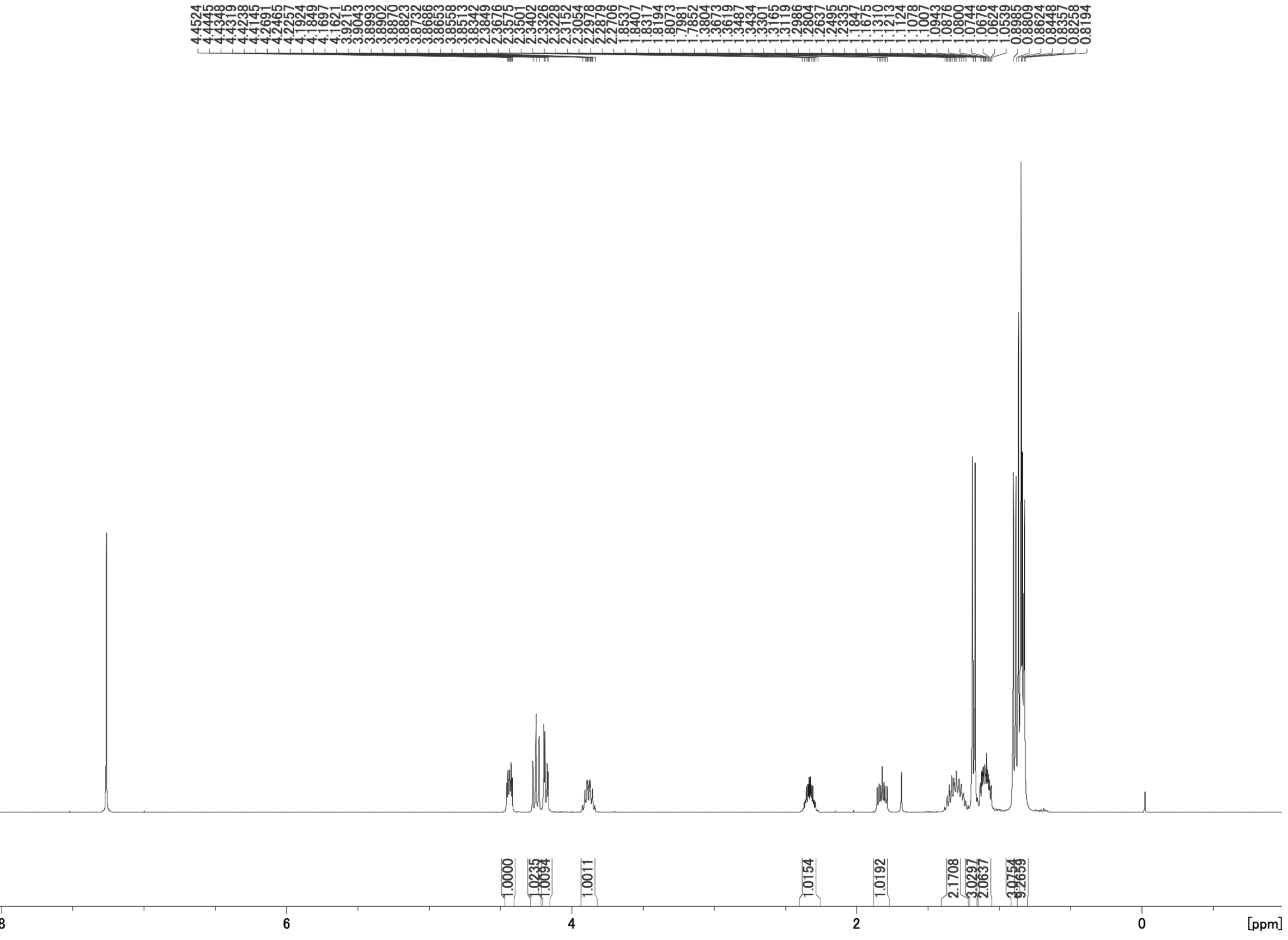
12

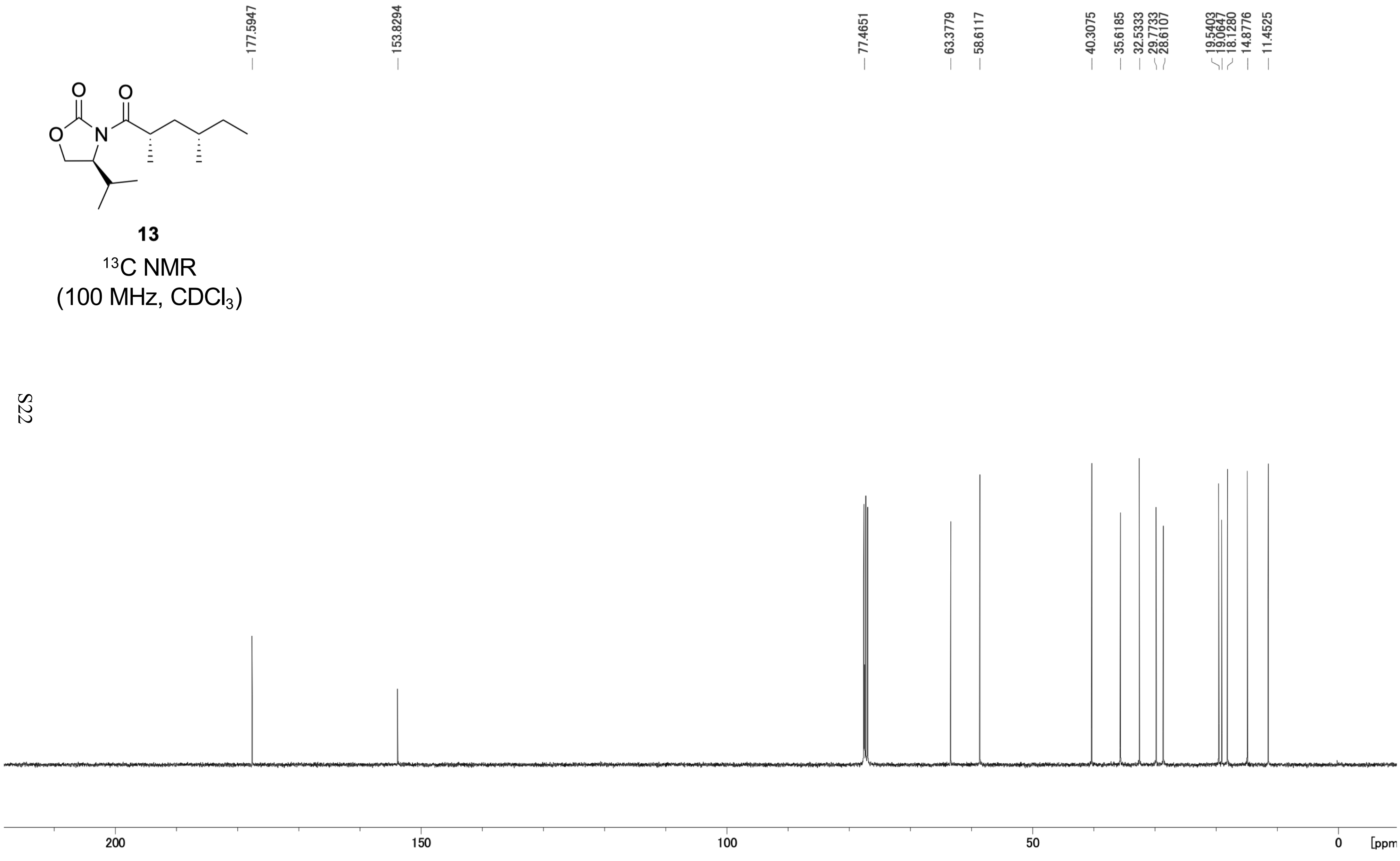
^{13}C NMR
(100 MHz, $CDCl_3$)



13

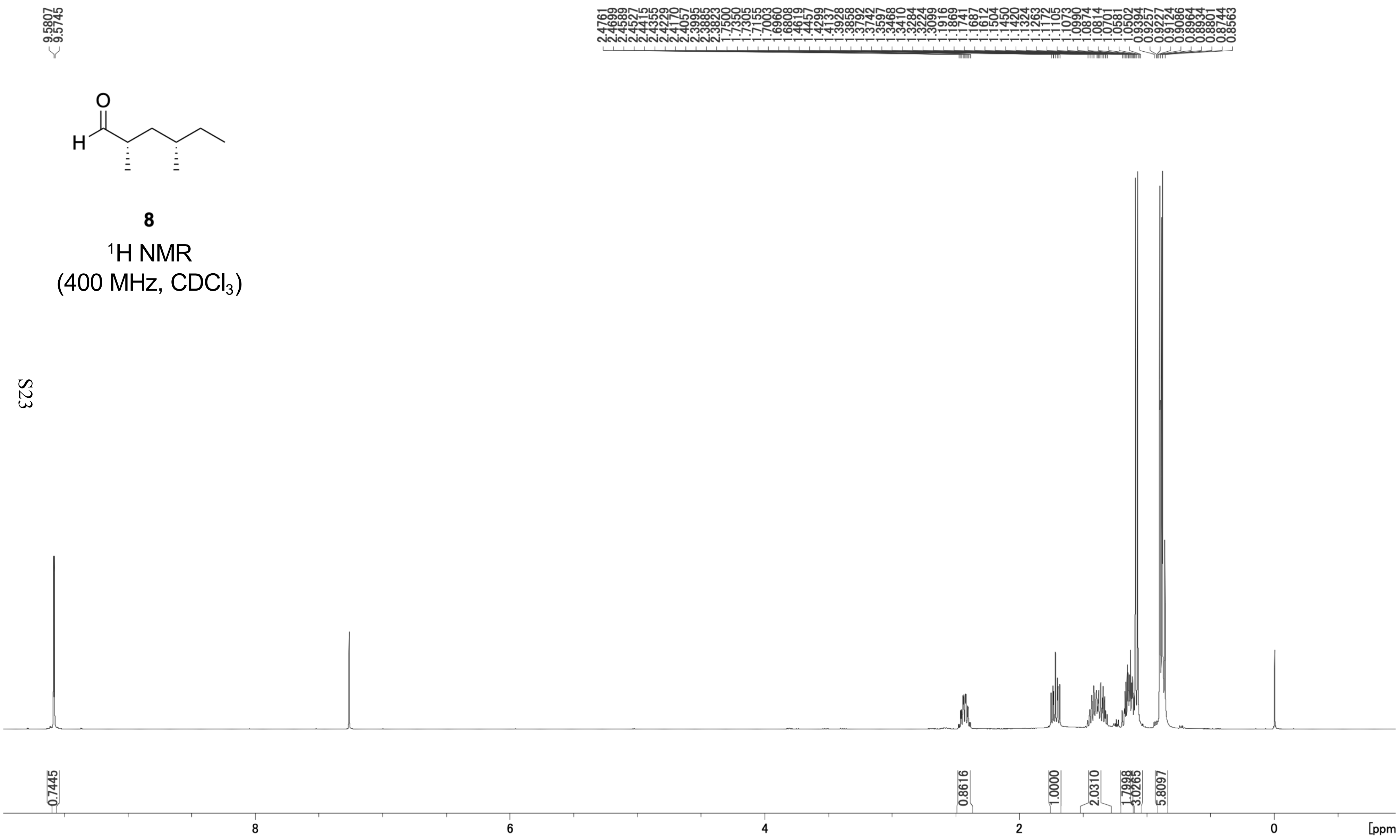
^{1}H NMR
(400 MHz, $CDCl_3$)





13

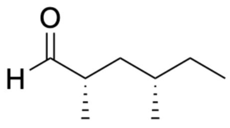
^{13}C NMR
(100 MHz, $CDCl_3$)



8

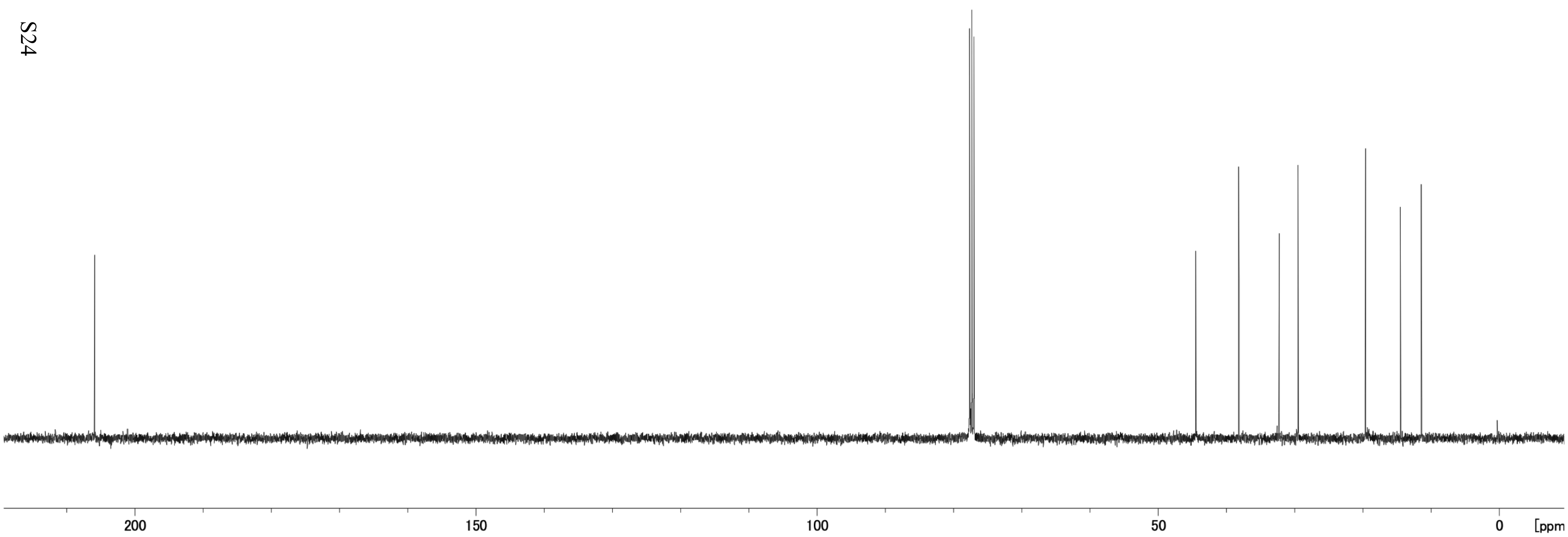
^{1}H NMR

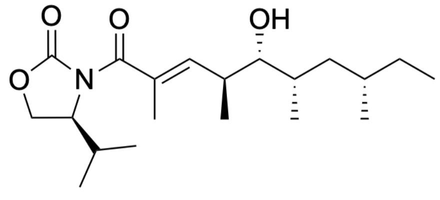
(400 MHz, $CDCl_3$)



8

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

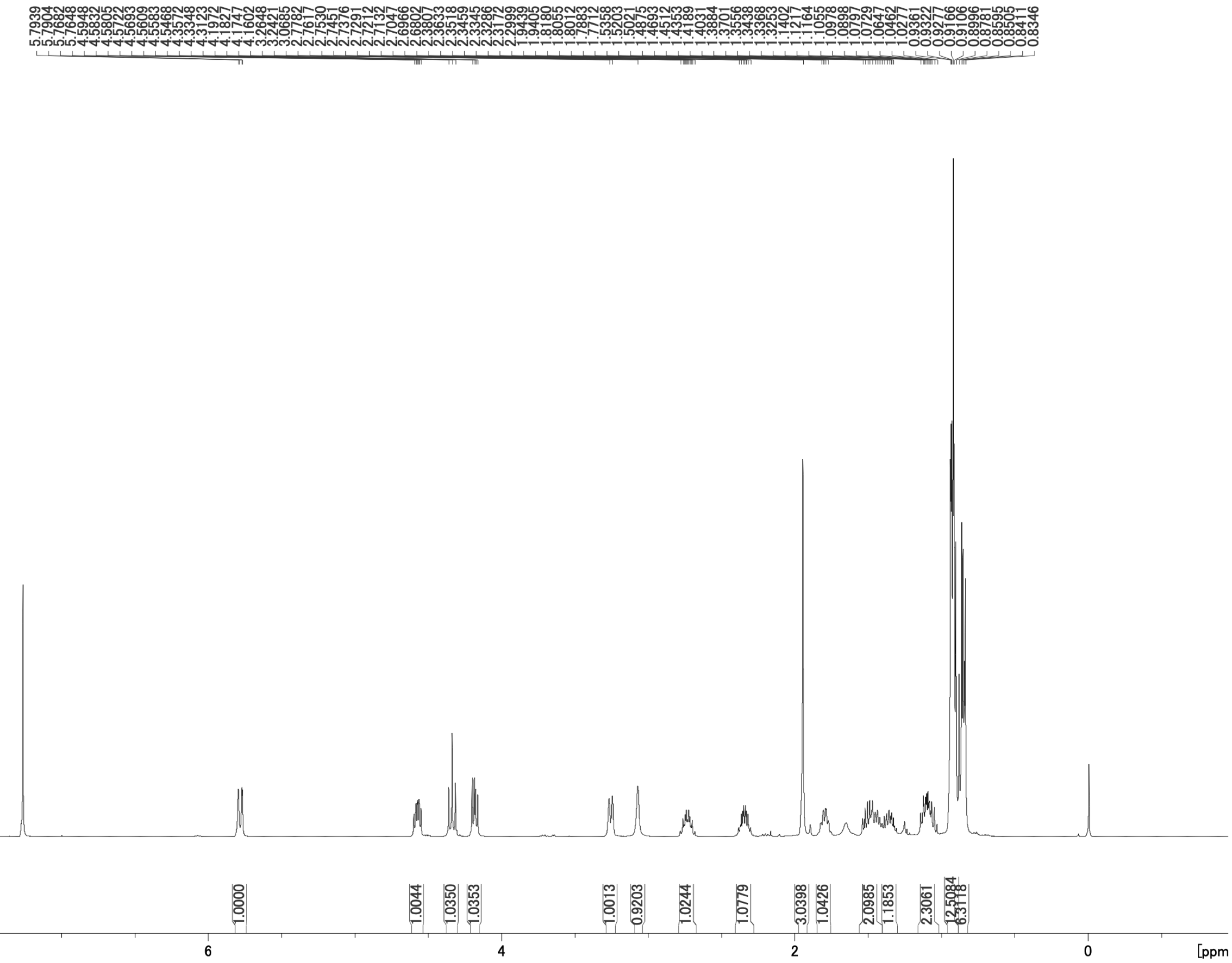


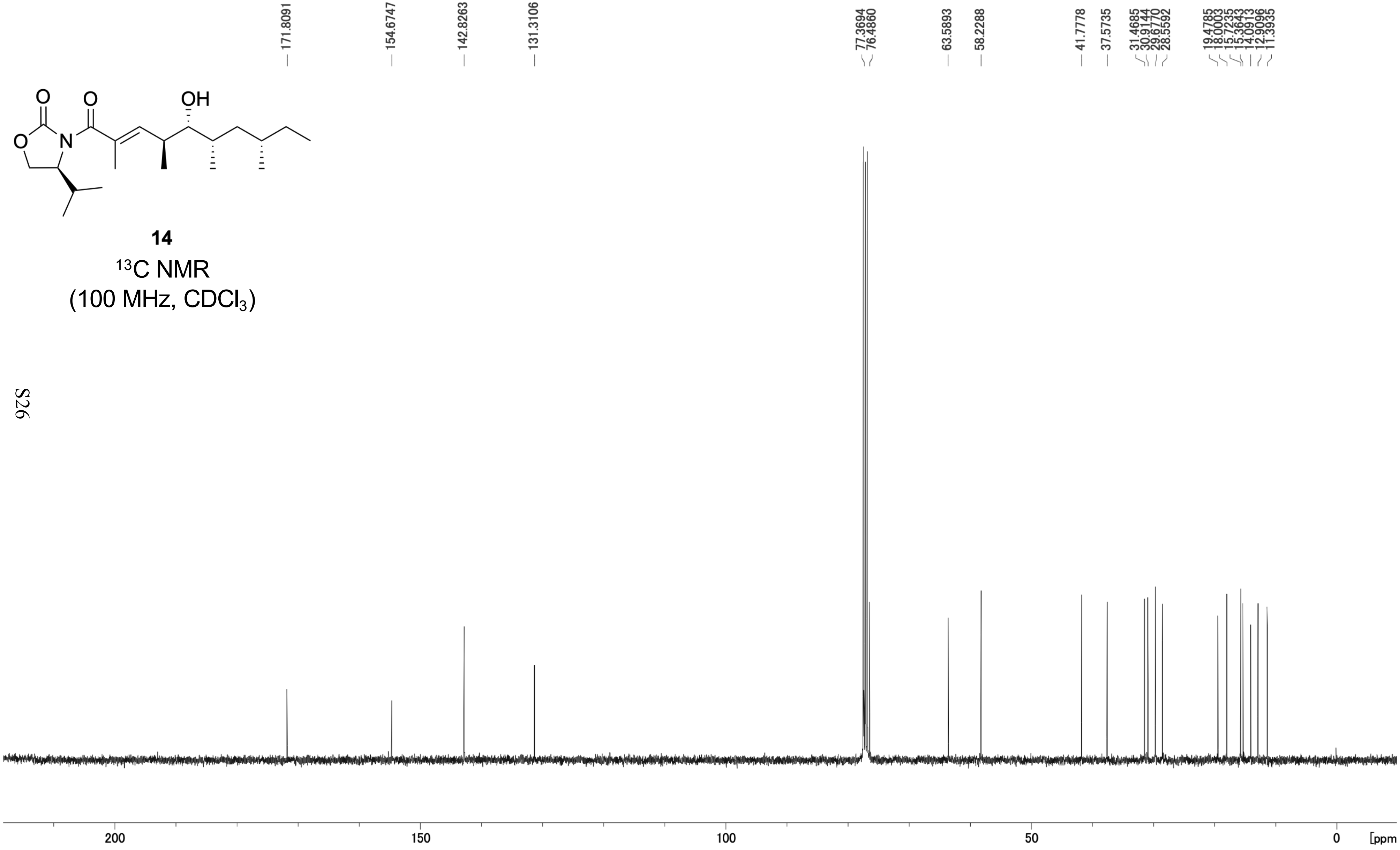


14

^{1}H NMR

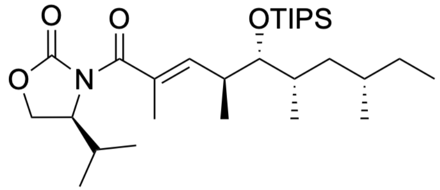
(400 MHz, $CDCl_3$)





14

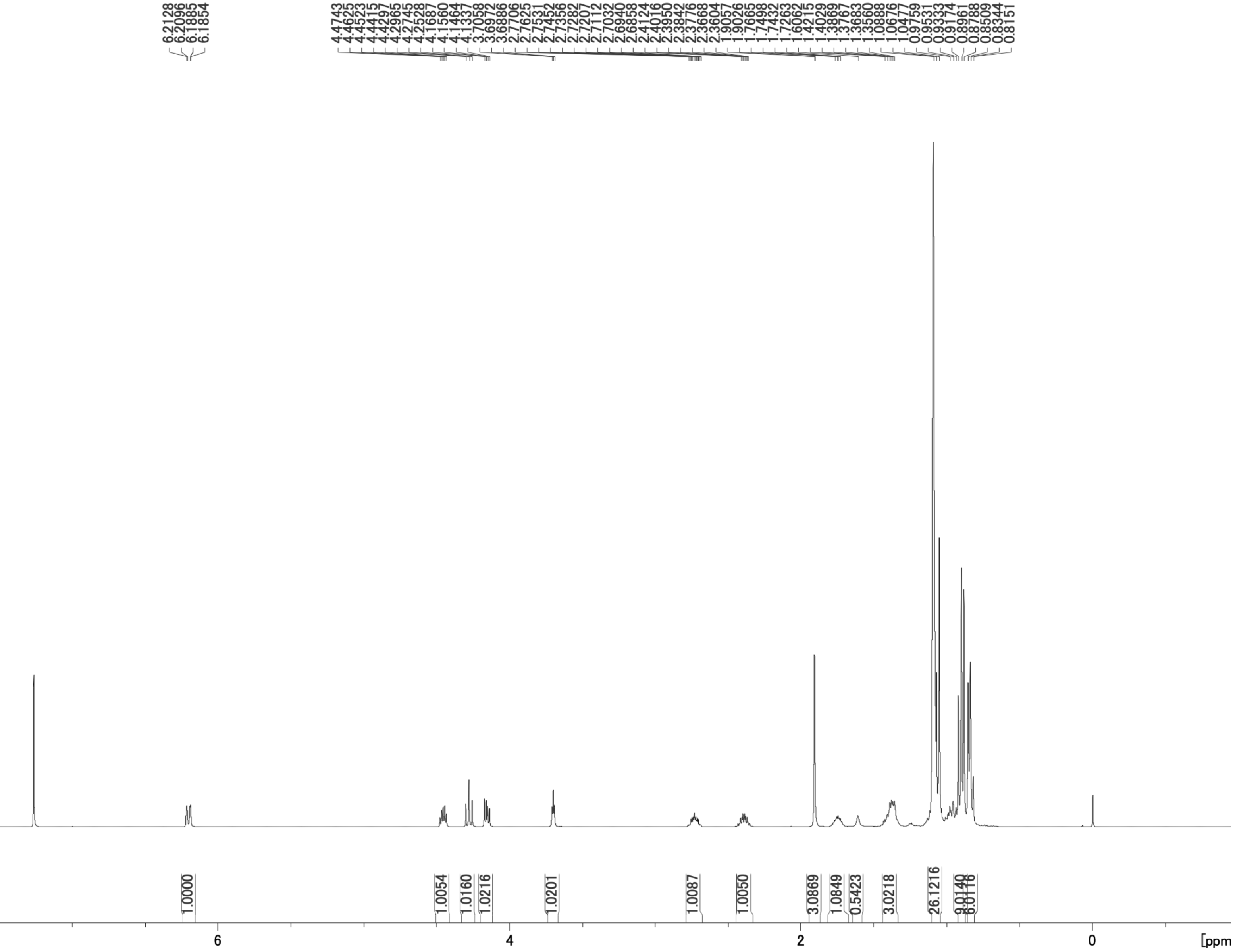
^{13}C NMR
(100 MHz, $CDCl_3$)

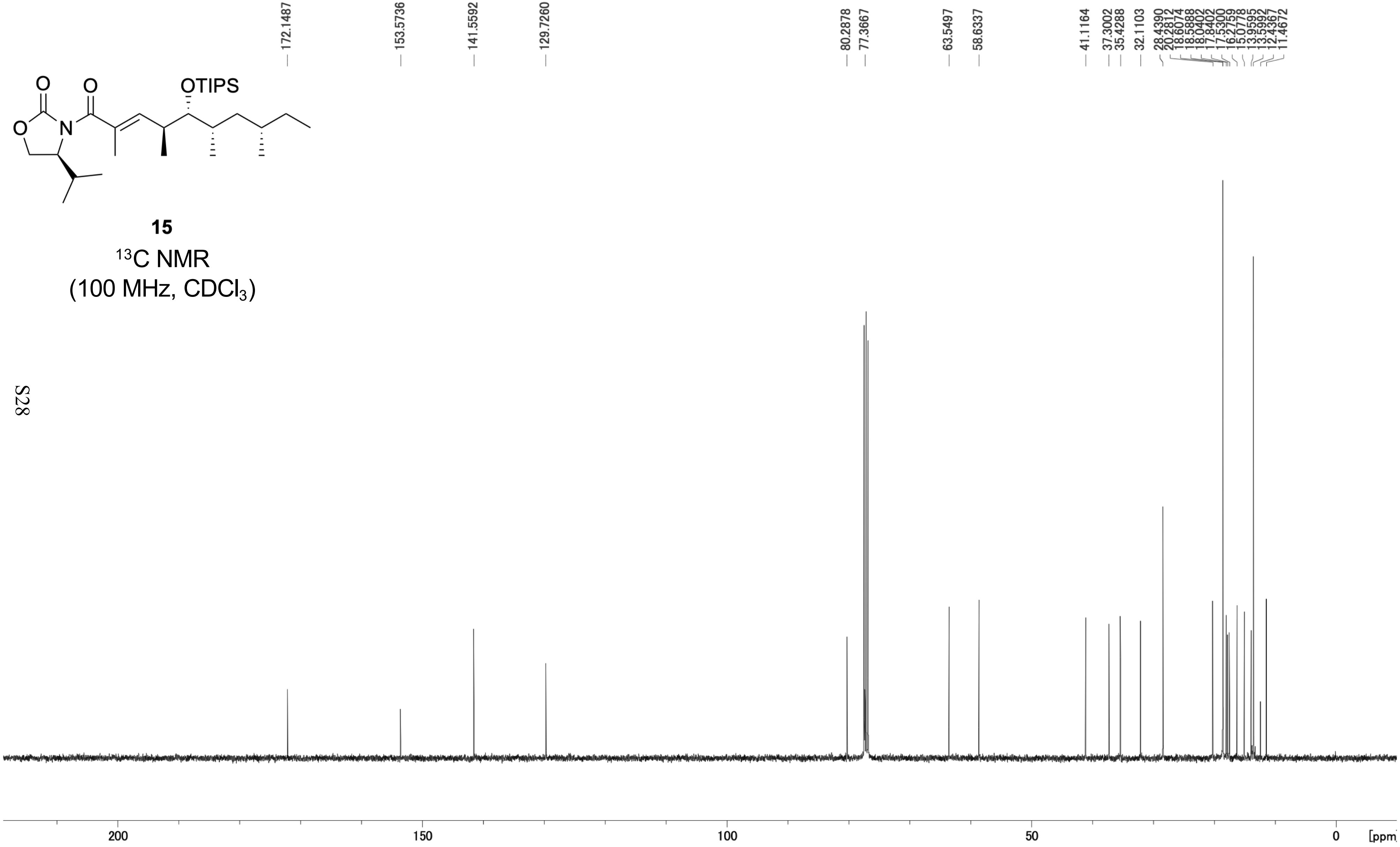


15

^{1}H NMR

(400 MHz, $CDCl_3$)

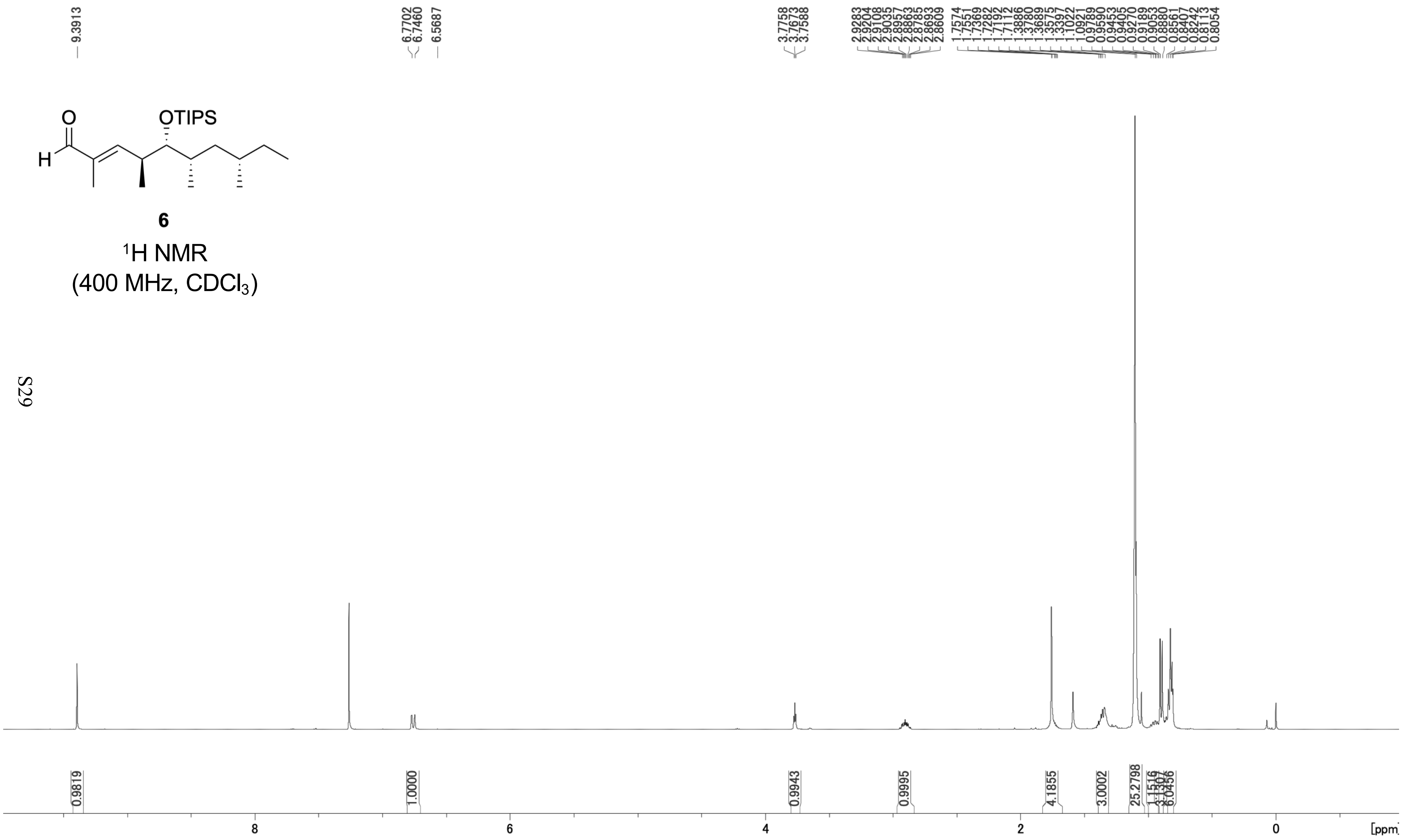




15

^{13}C NMR

(100 MHz, $CDCl_3$)

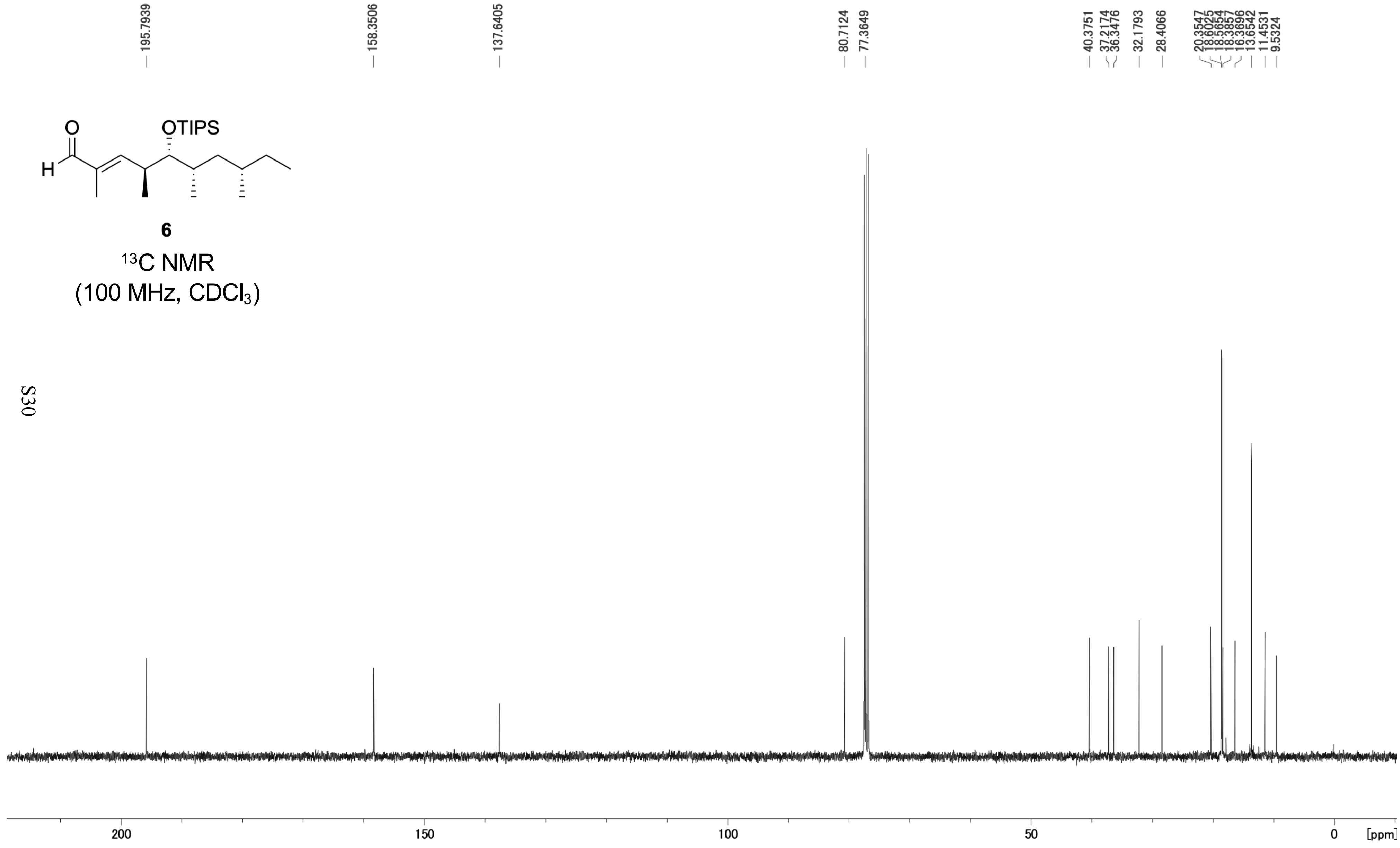


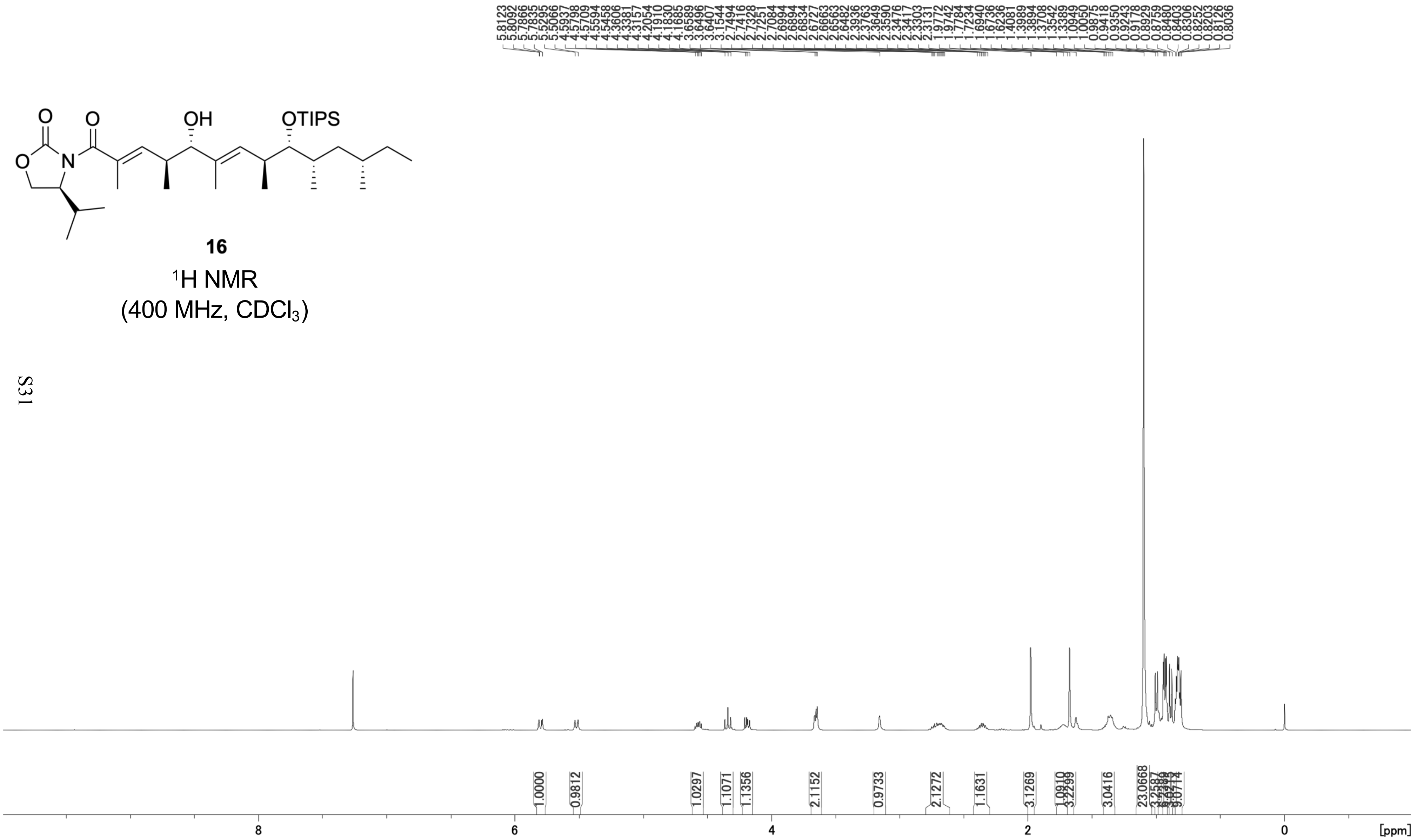
6

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

6

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



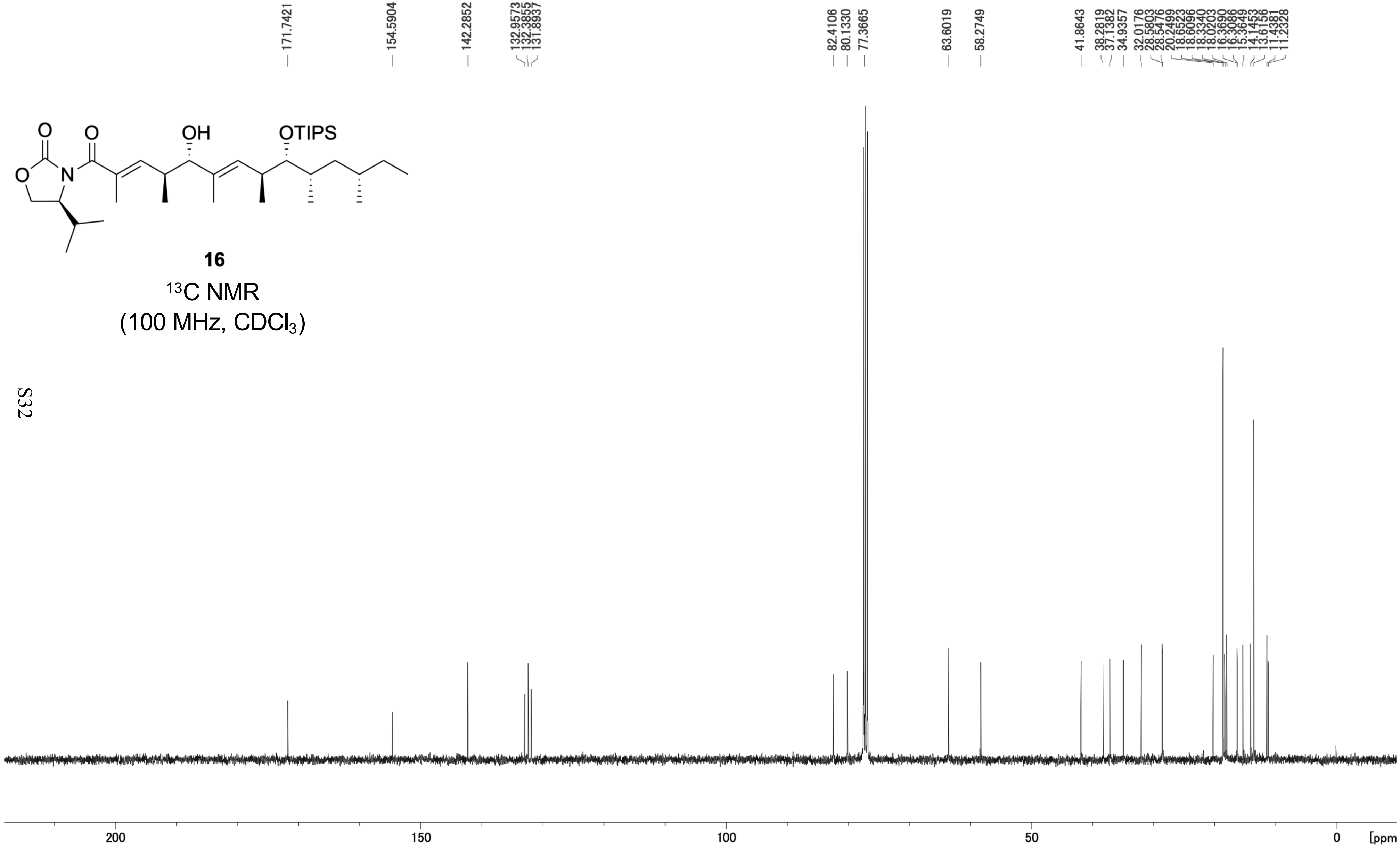


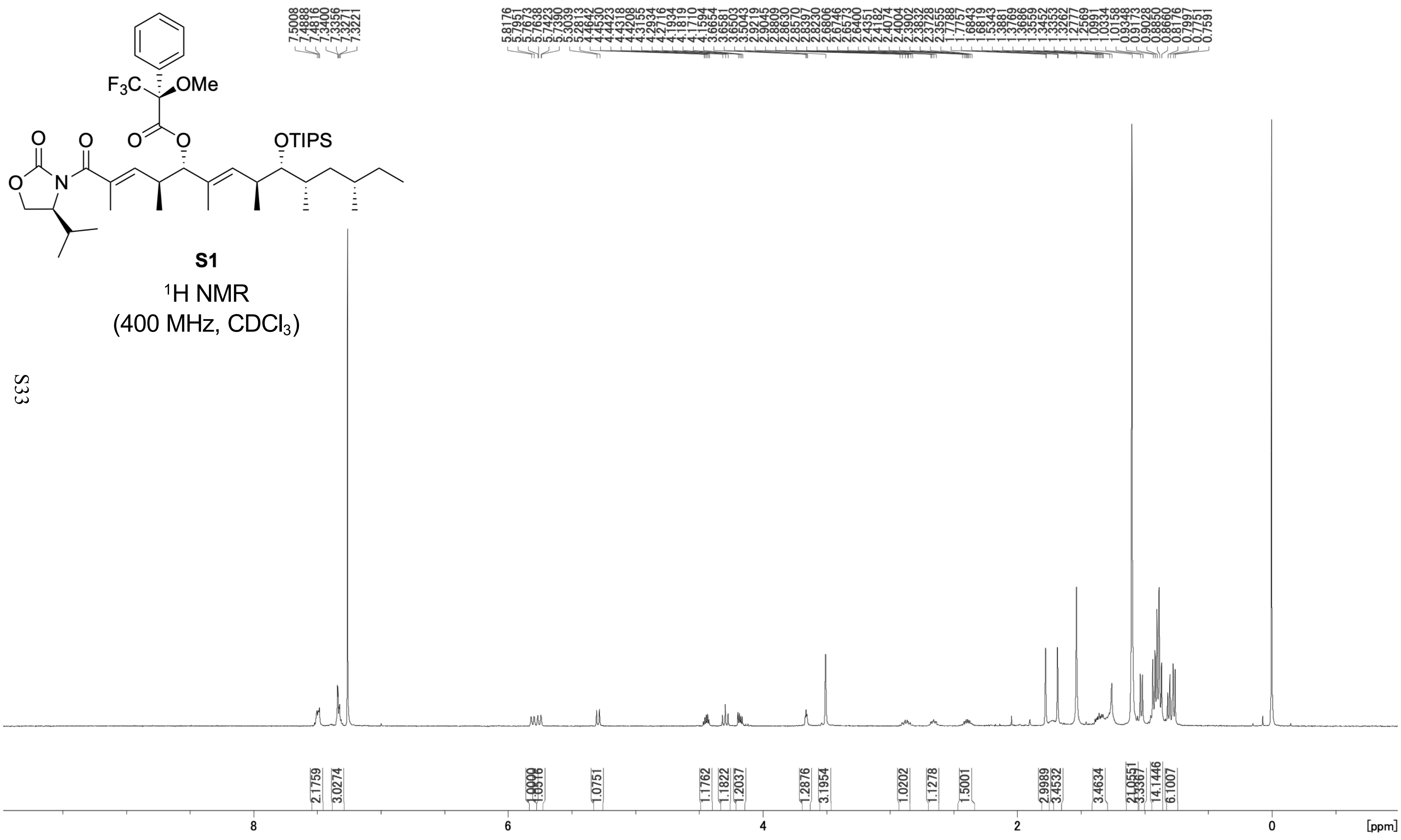
16

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

16

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

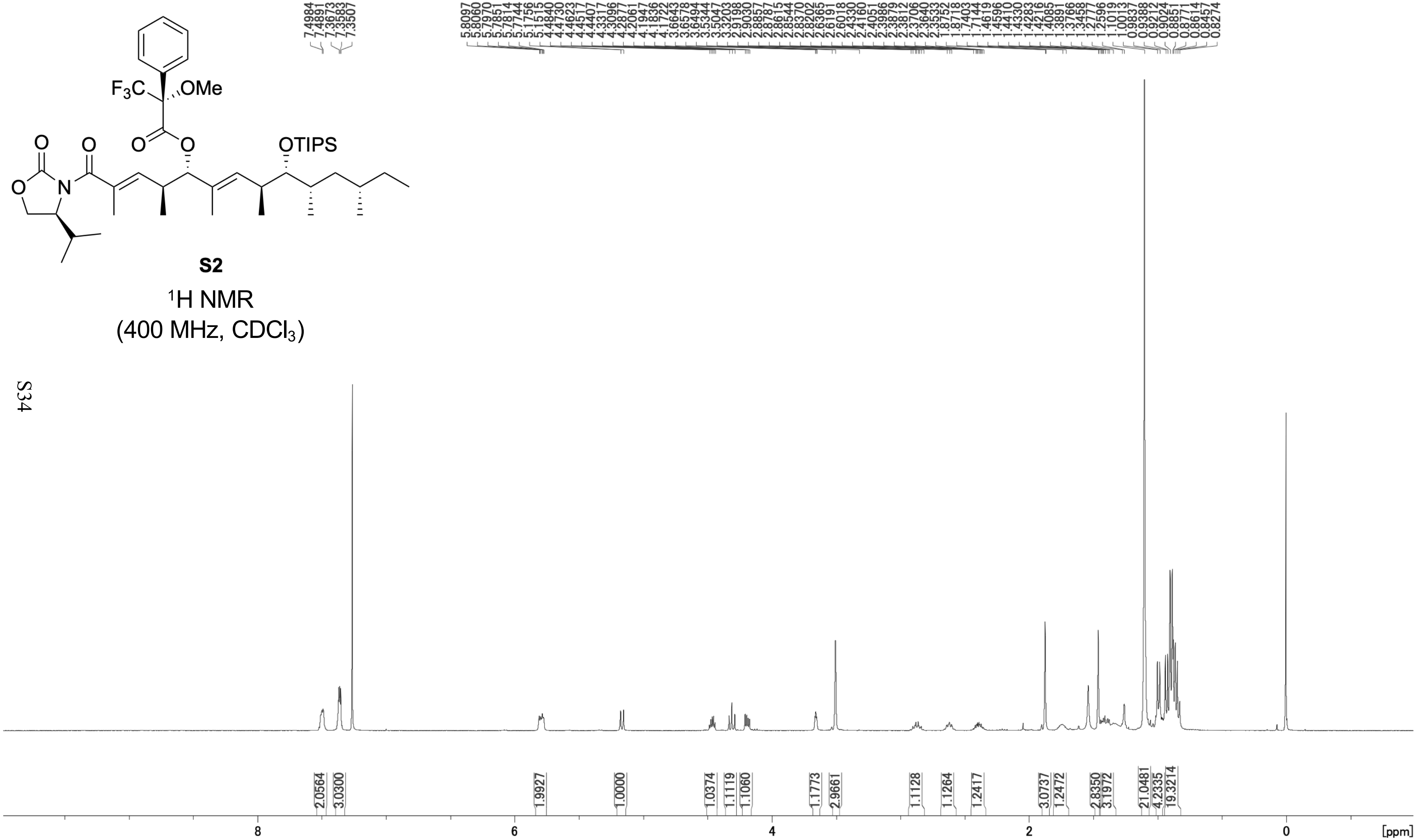




S1

^{1}H NMR

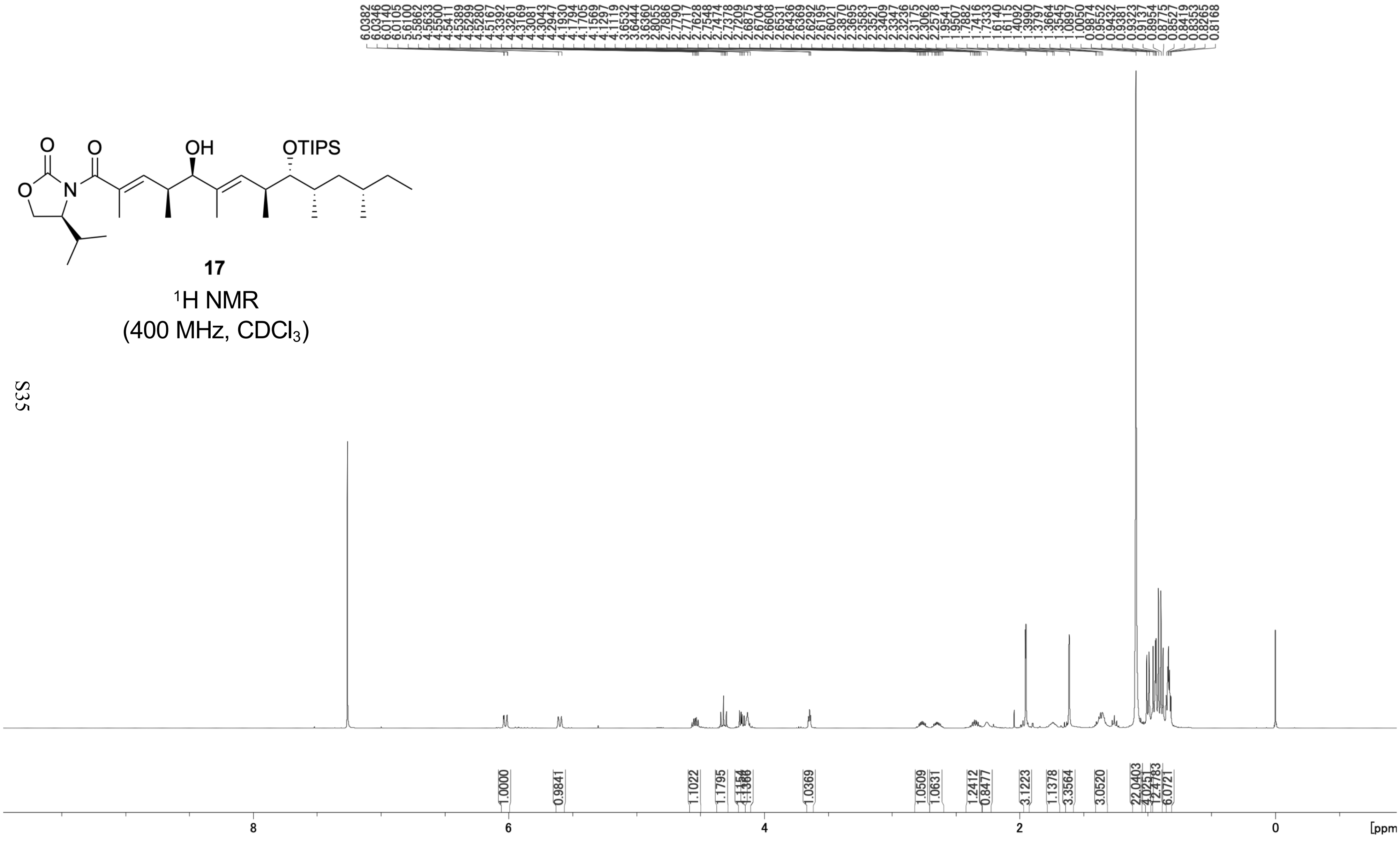
(400 MHz, $CDCl_3$)



S2

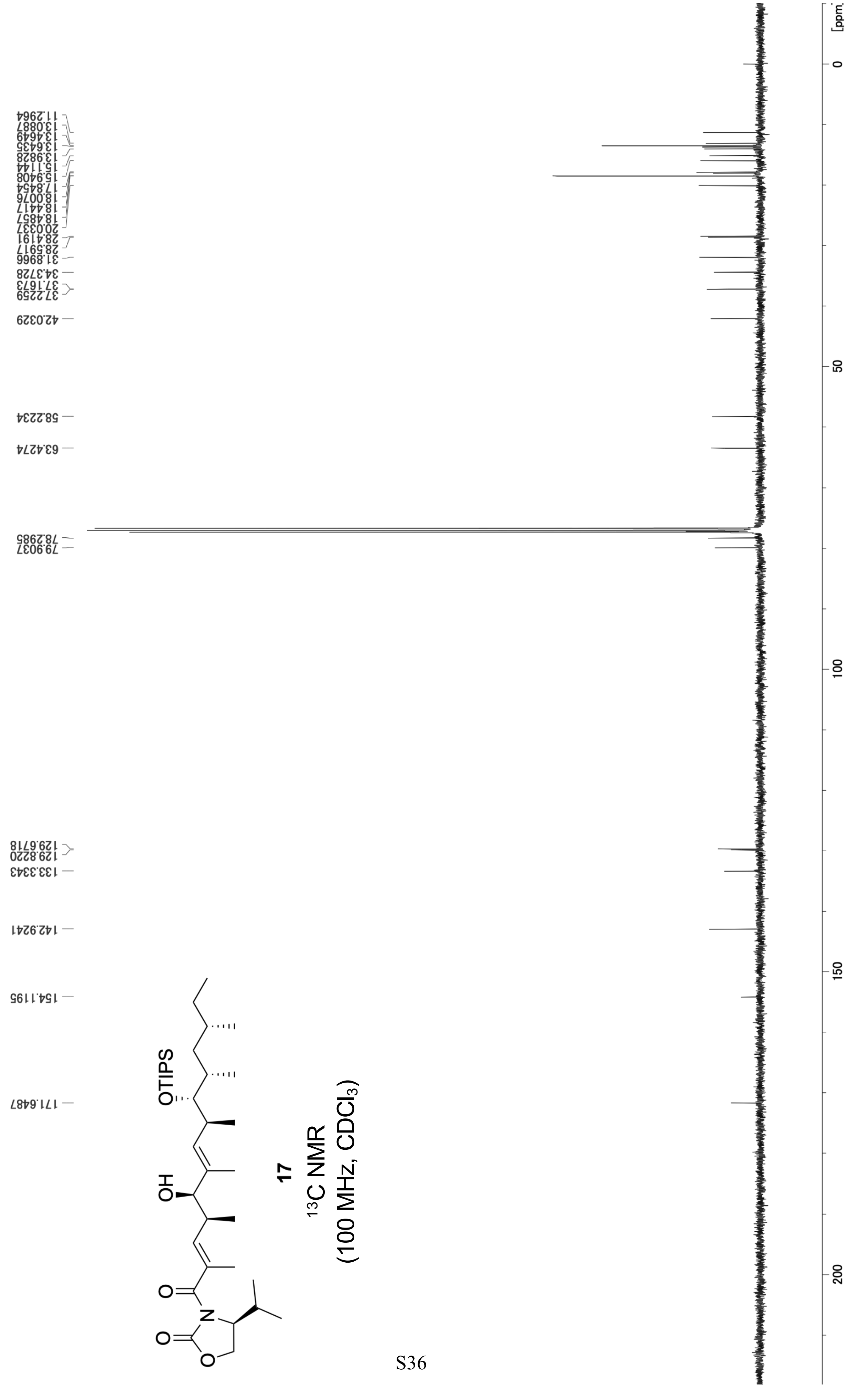
^{1}H NMR

(400 MHz, $CDCl_3$)



17

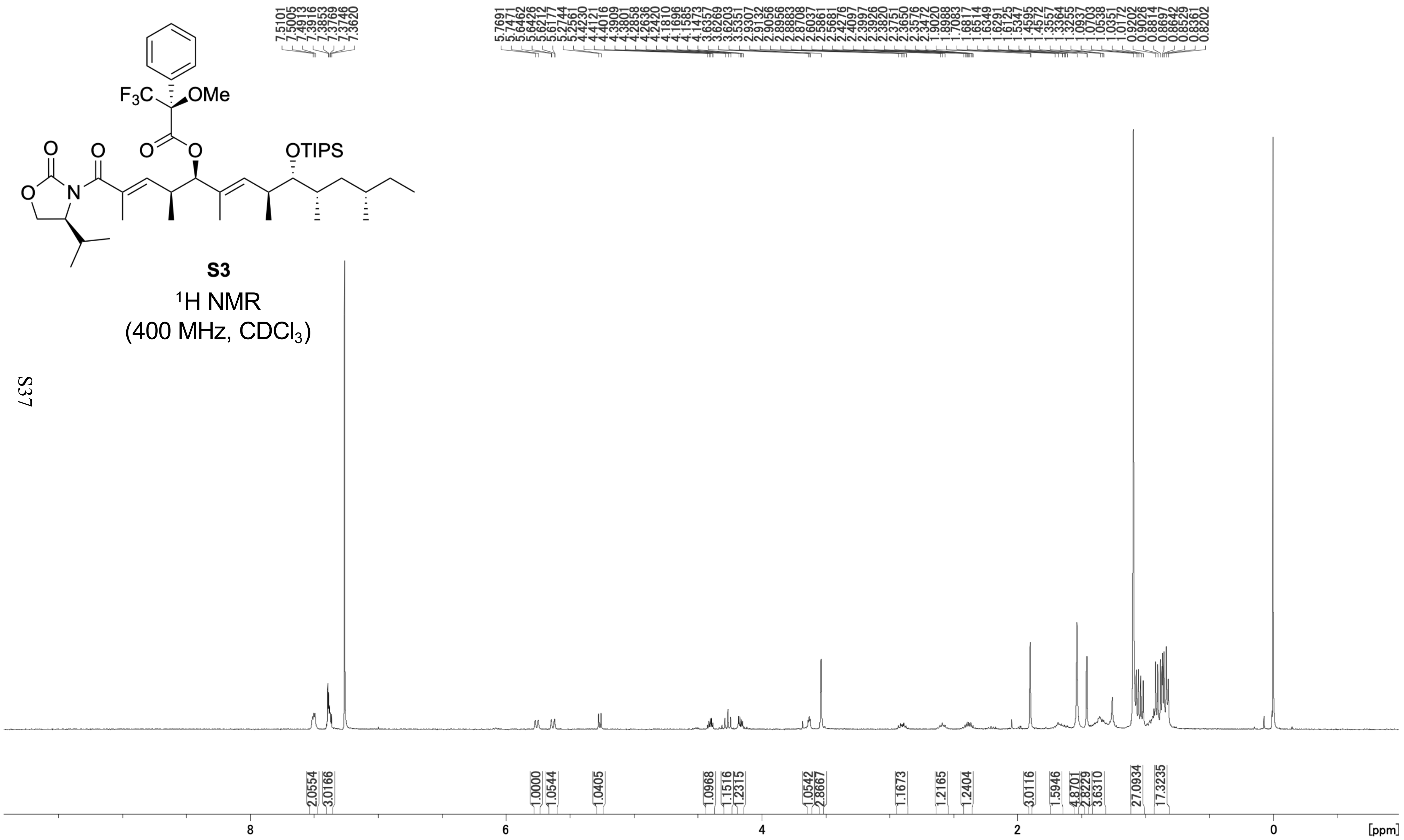
^{1}H NMR
(400 MHz, $CDCl_3$)



17

^{13}C NMR

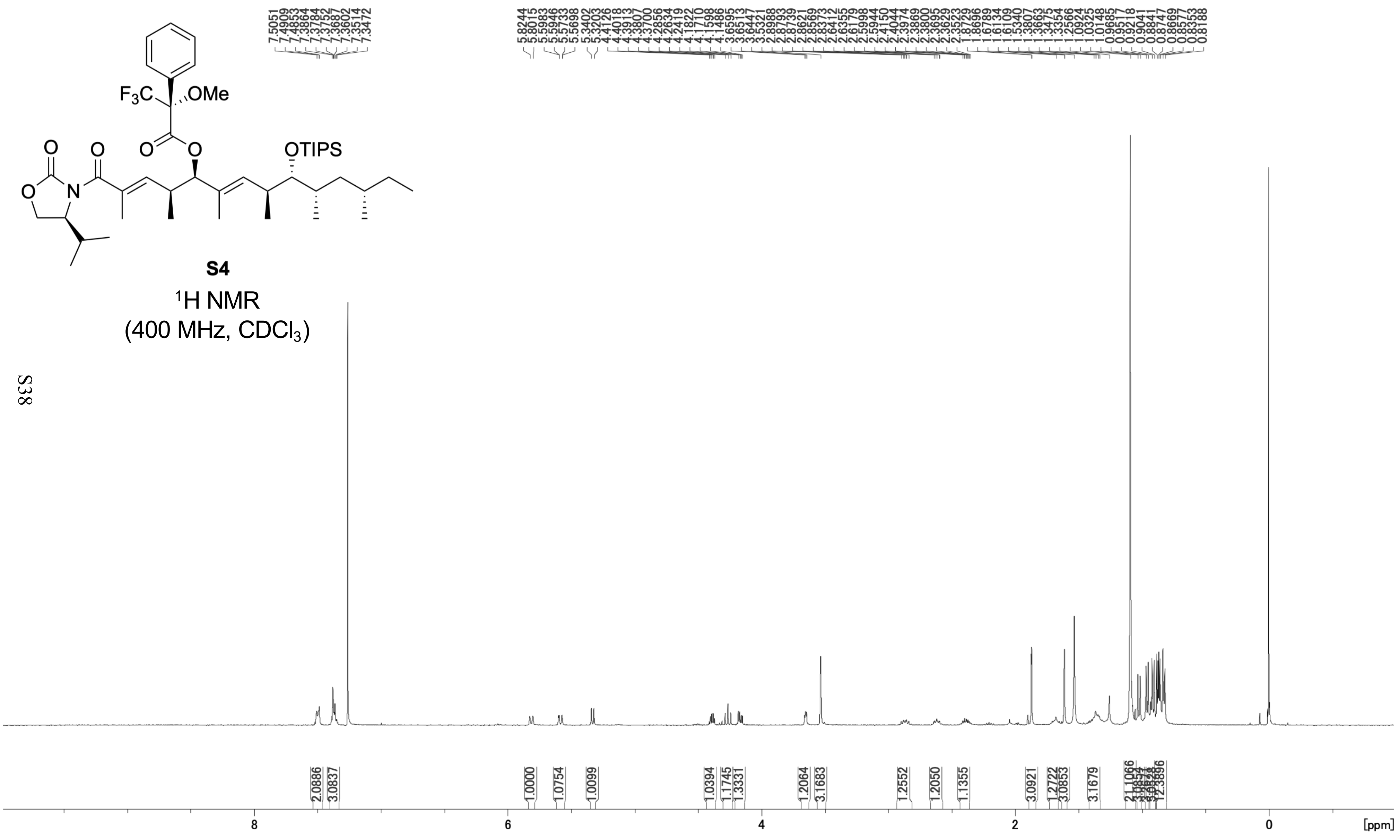
(100 MHz, $CDCl_3$)



S3

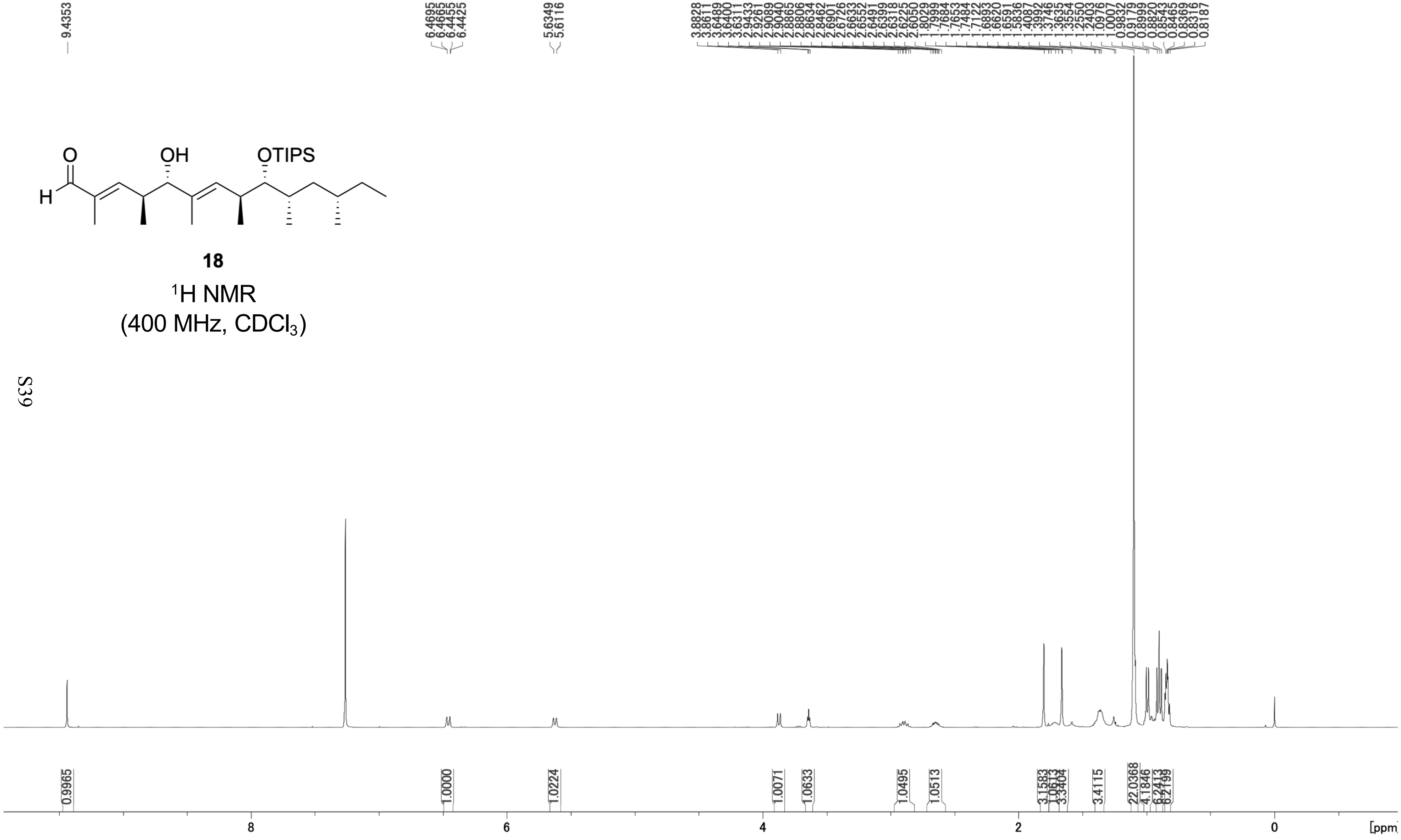
^{1}H NMR

(400 MHz, $CDCl_3$)



S4

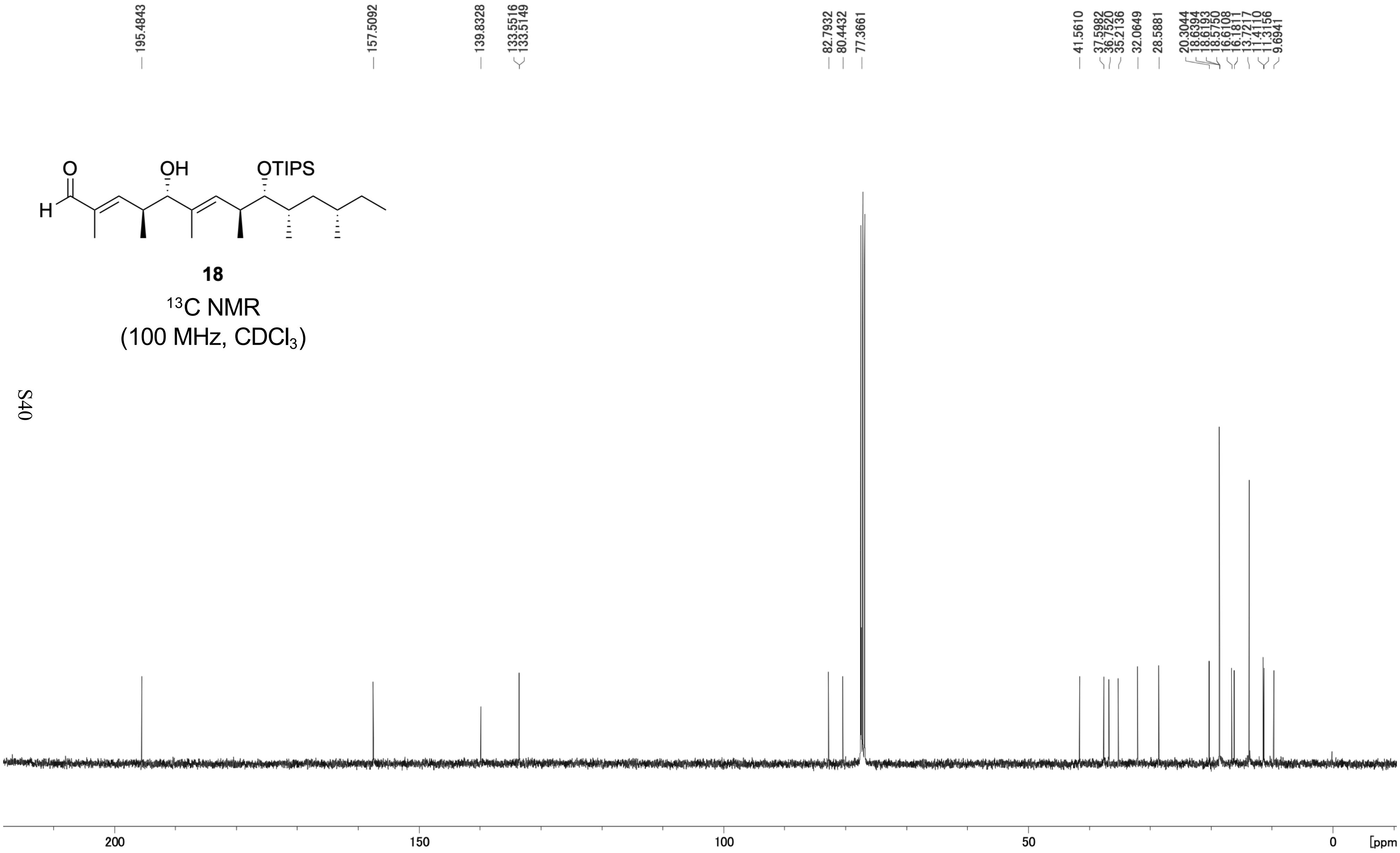
^{1}H NMR
(400 MHz, CDCl$_3$)



18

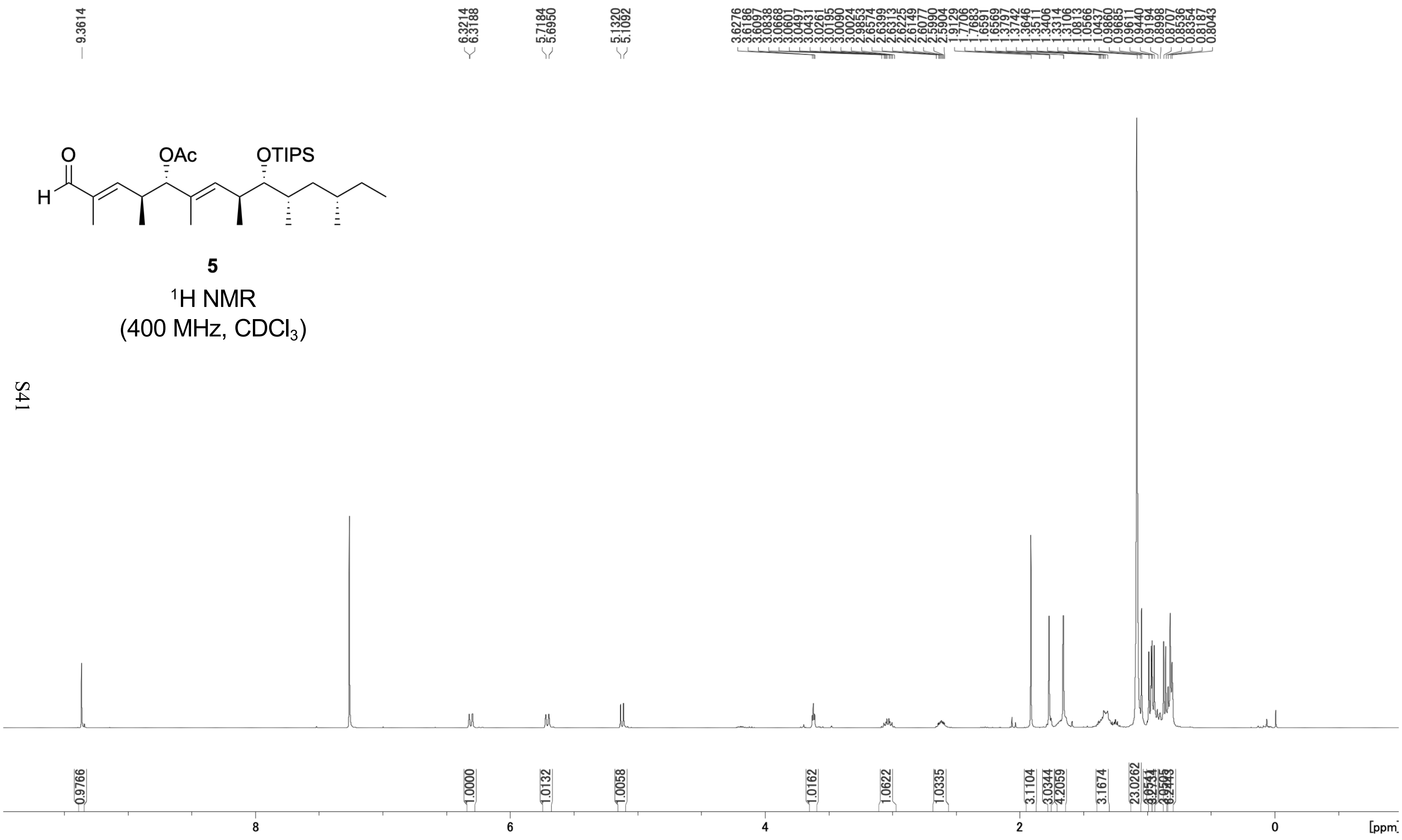
^{1}H NMR

(400 MHz, $CDCl_3$)



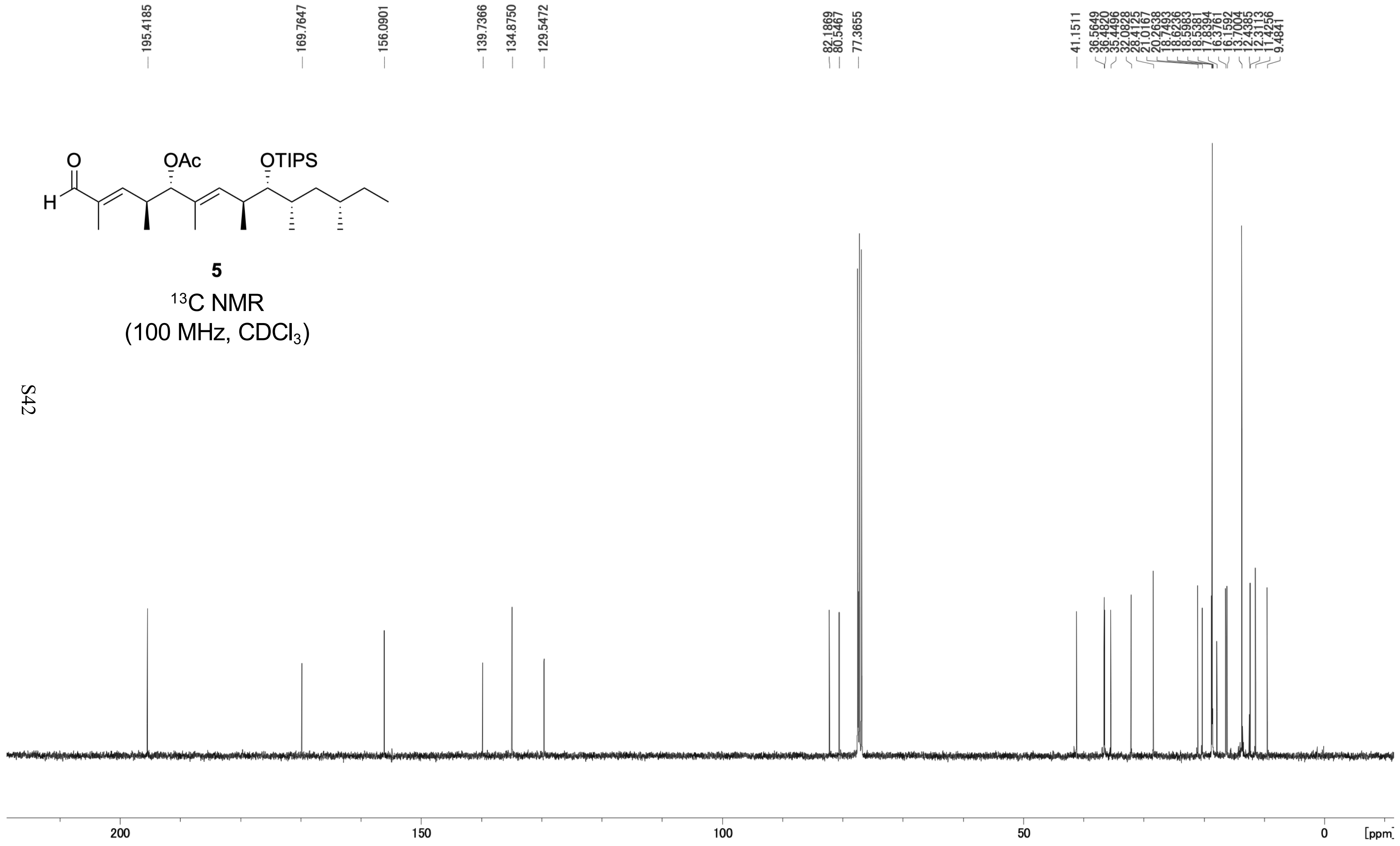
18

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



5

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



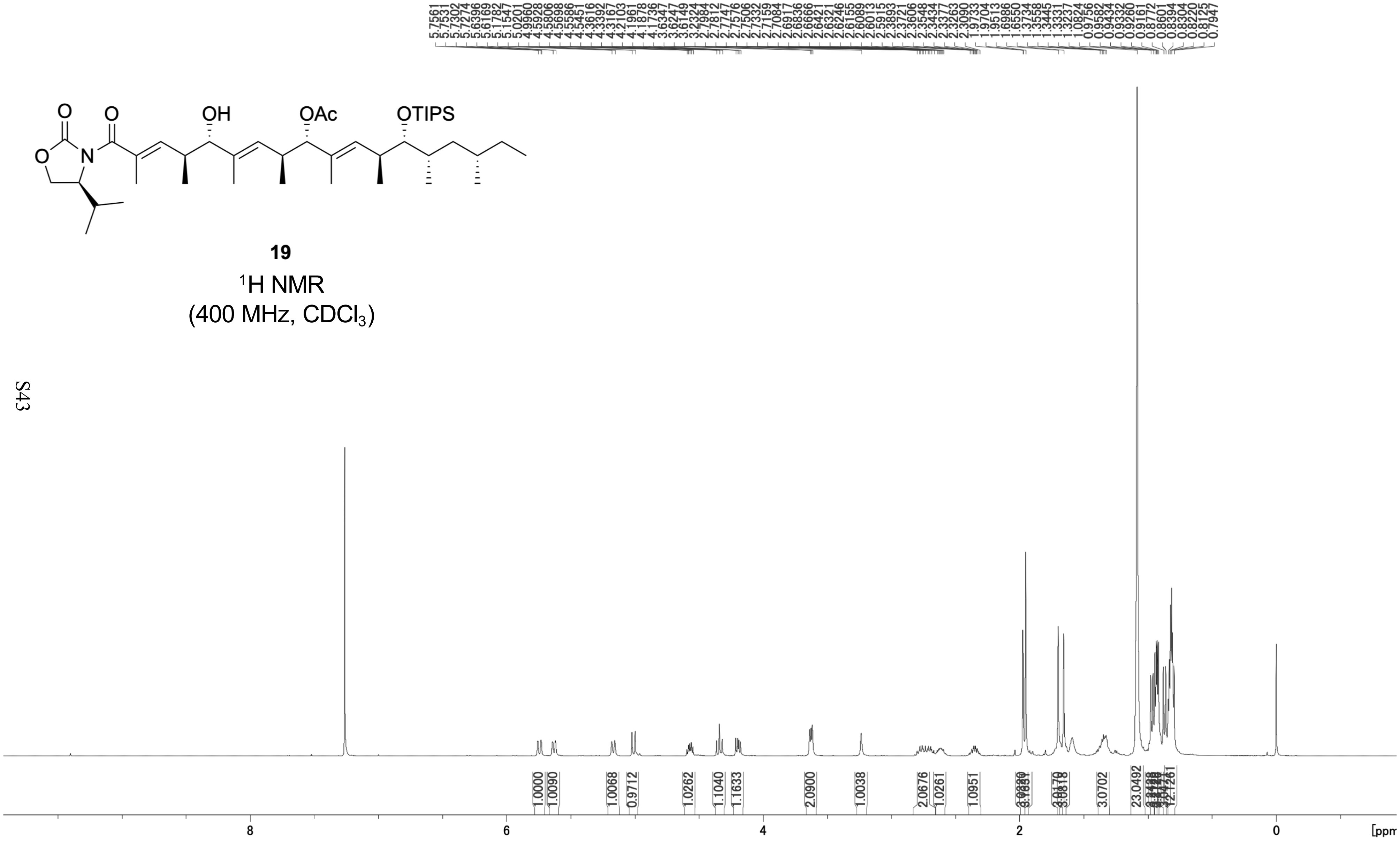
5

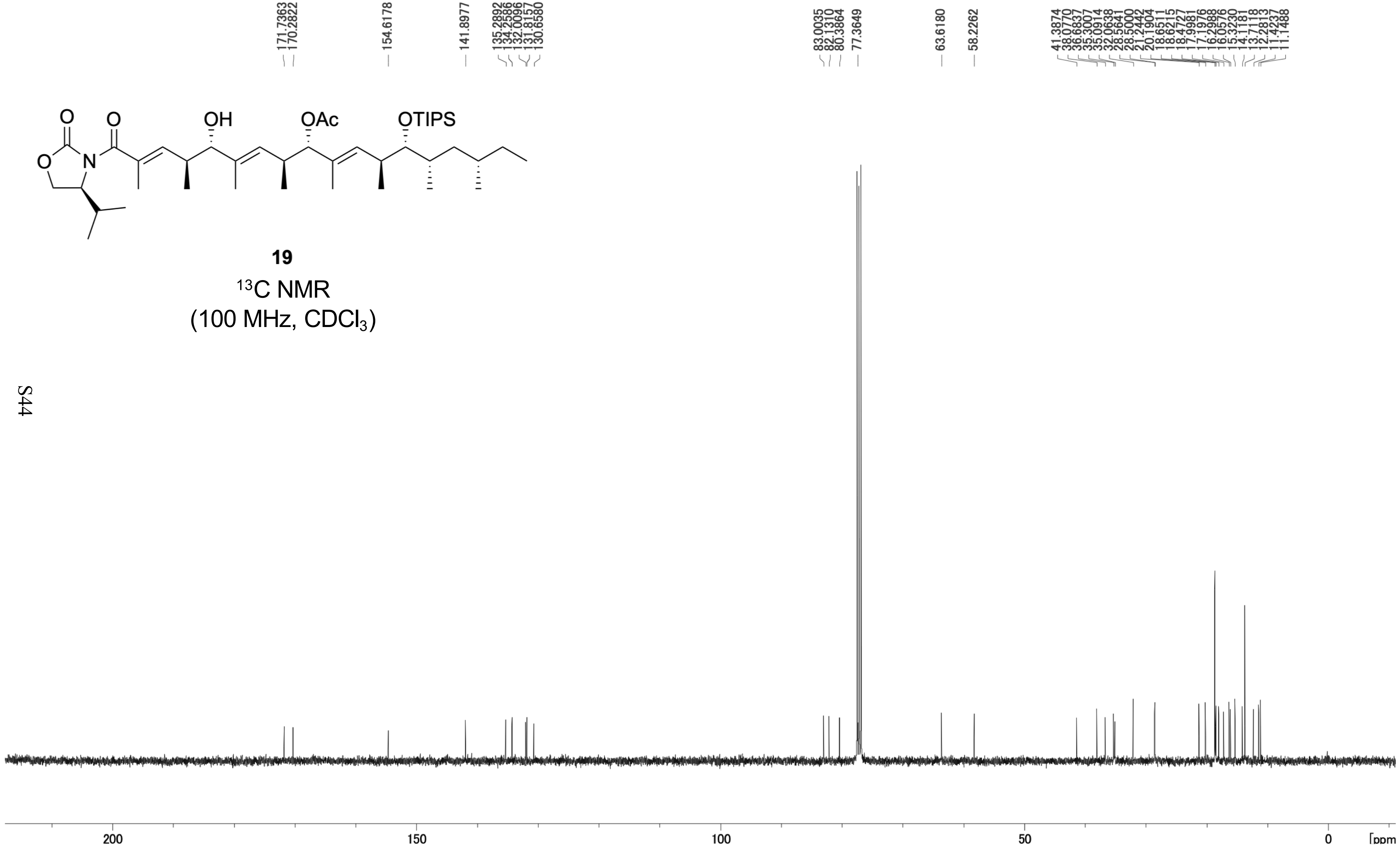
^{13}C NMR
(100 MHz, $CDCl_3$)

19

^{1}H NMR

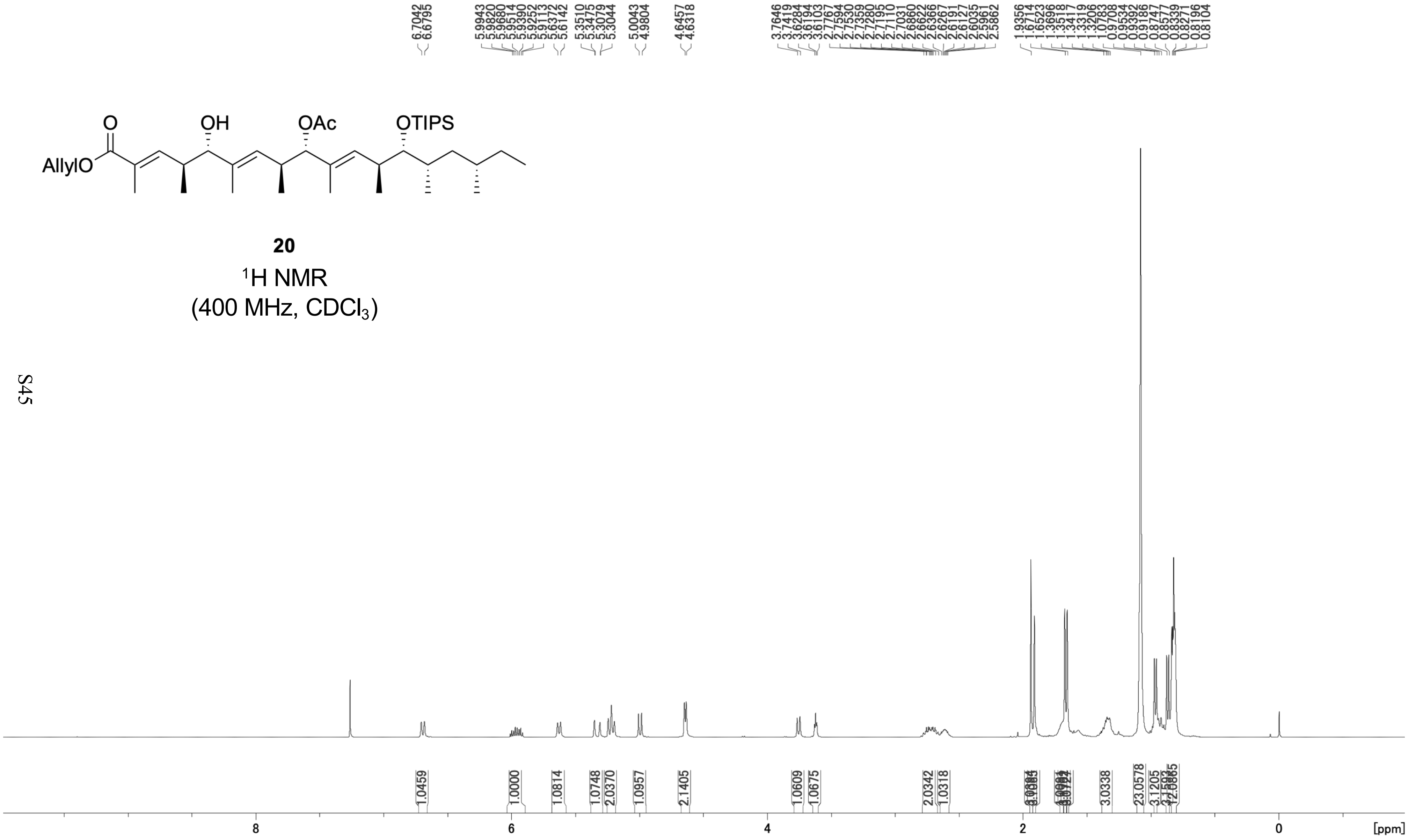
(400 MHz, $CDCl_3$)





19

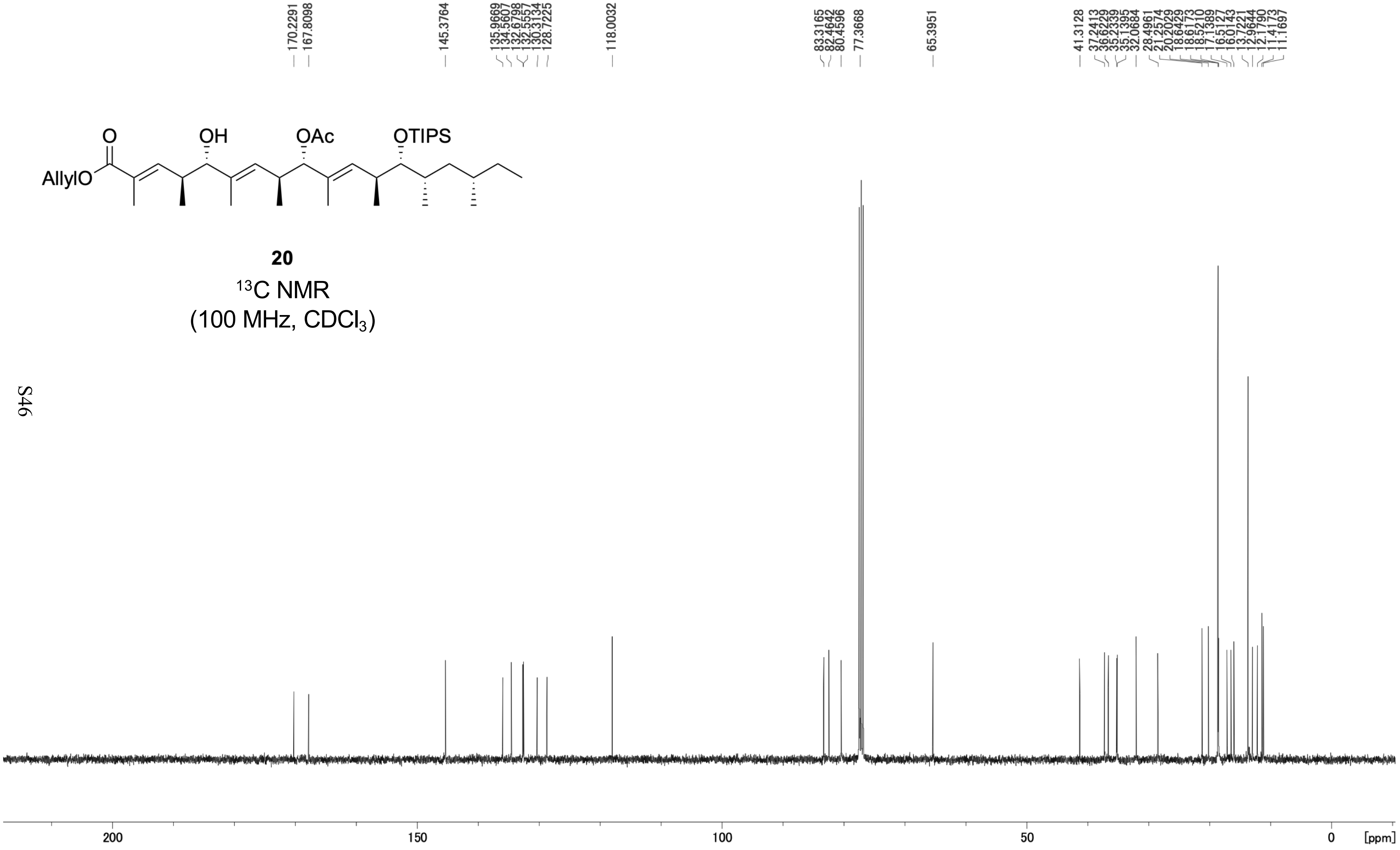
^{13}C NMR
(100 MHz, $CDCl_3$)



20

^{1}H NMR

(400 MHz, $CDCl_3$)



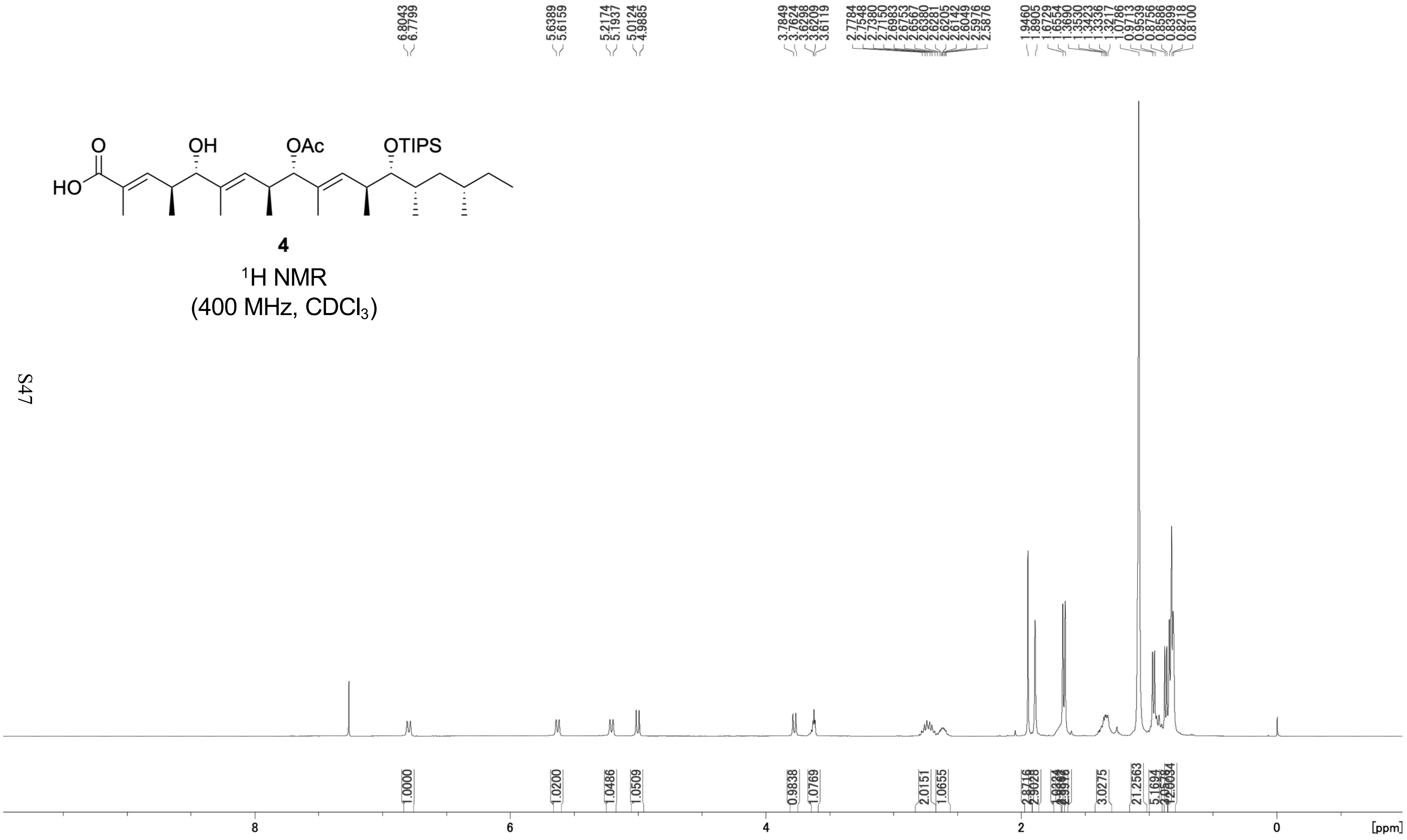
20

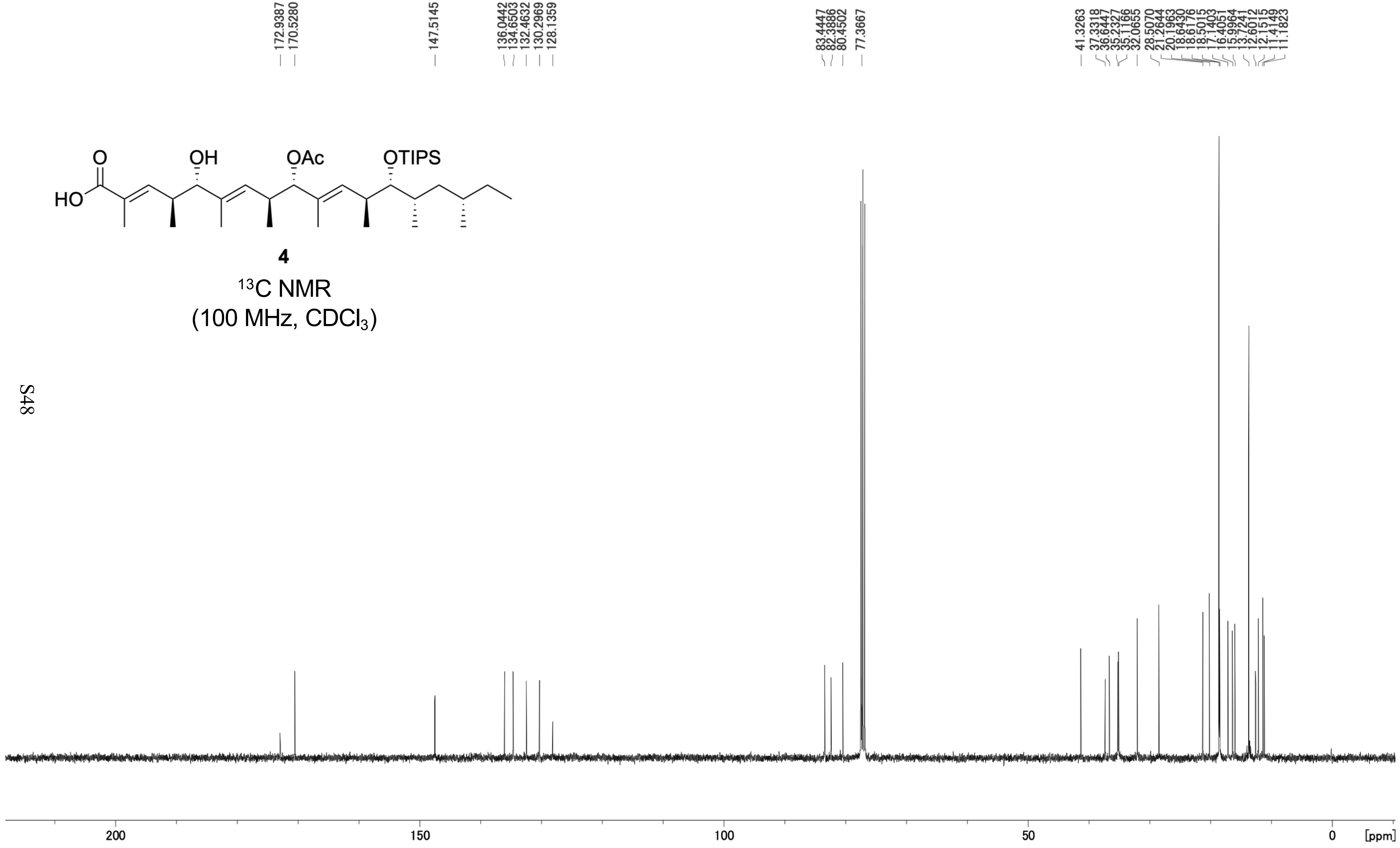
^{13}C NMR

(100 MHz, $CDCl_3$)

4

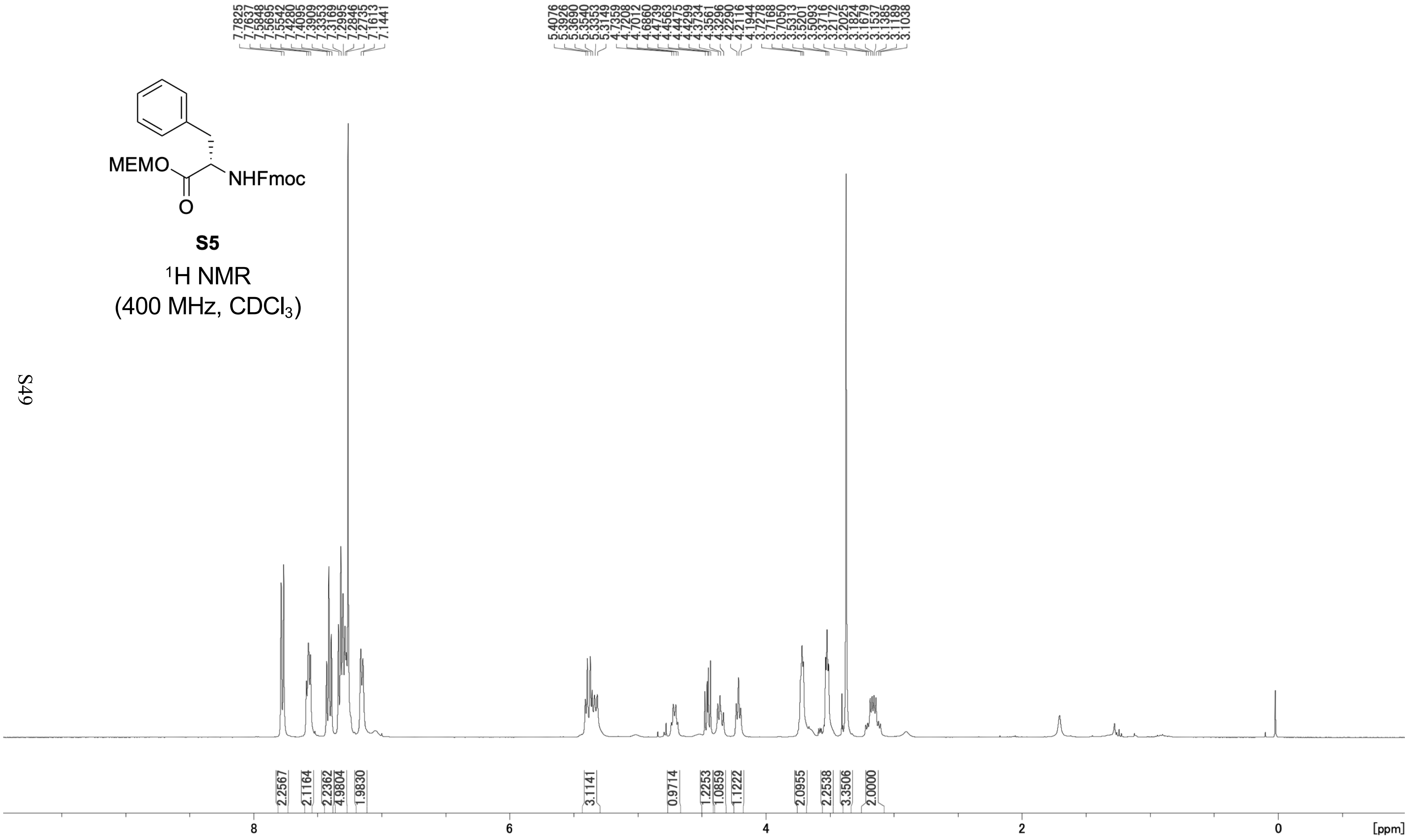
^{1}H NMR
(400 MHz, $CDCl_3$)





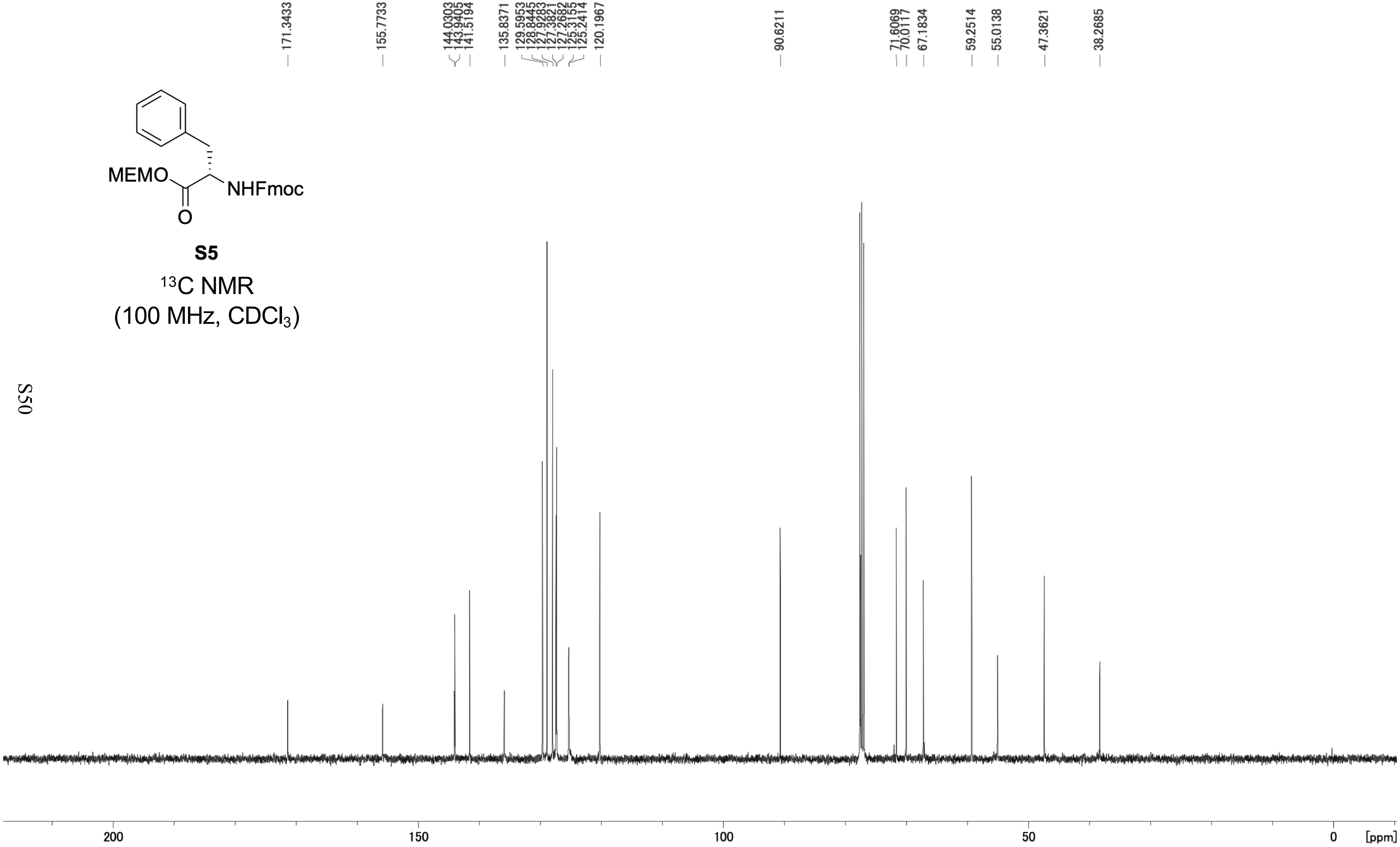
4

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



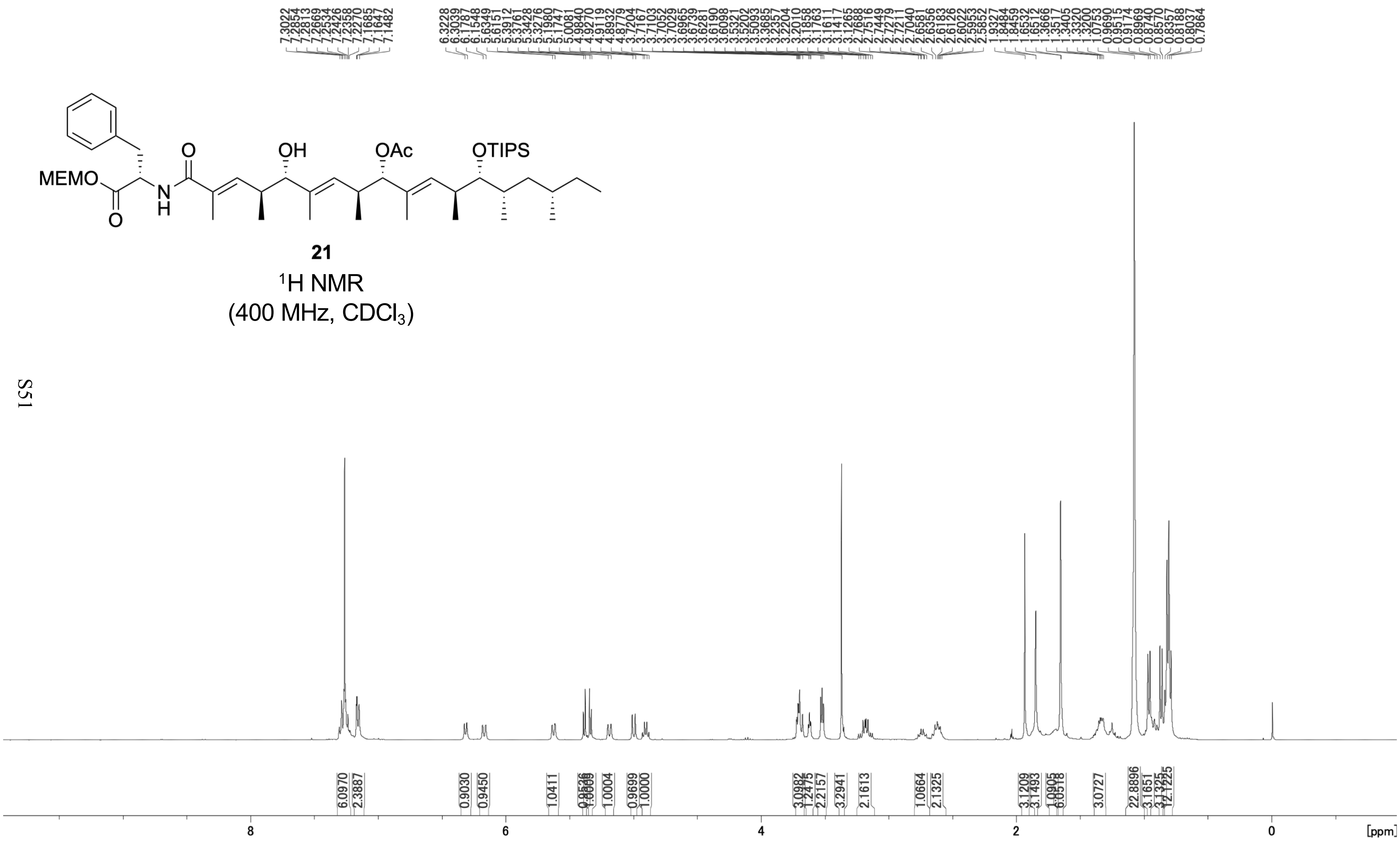
S5

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



S5

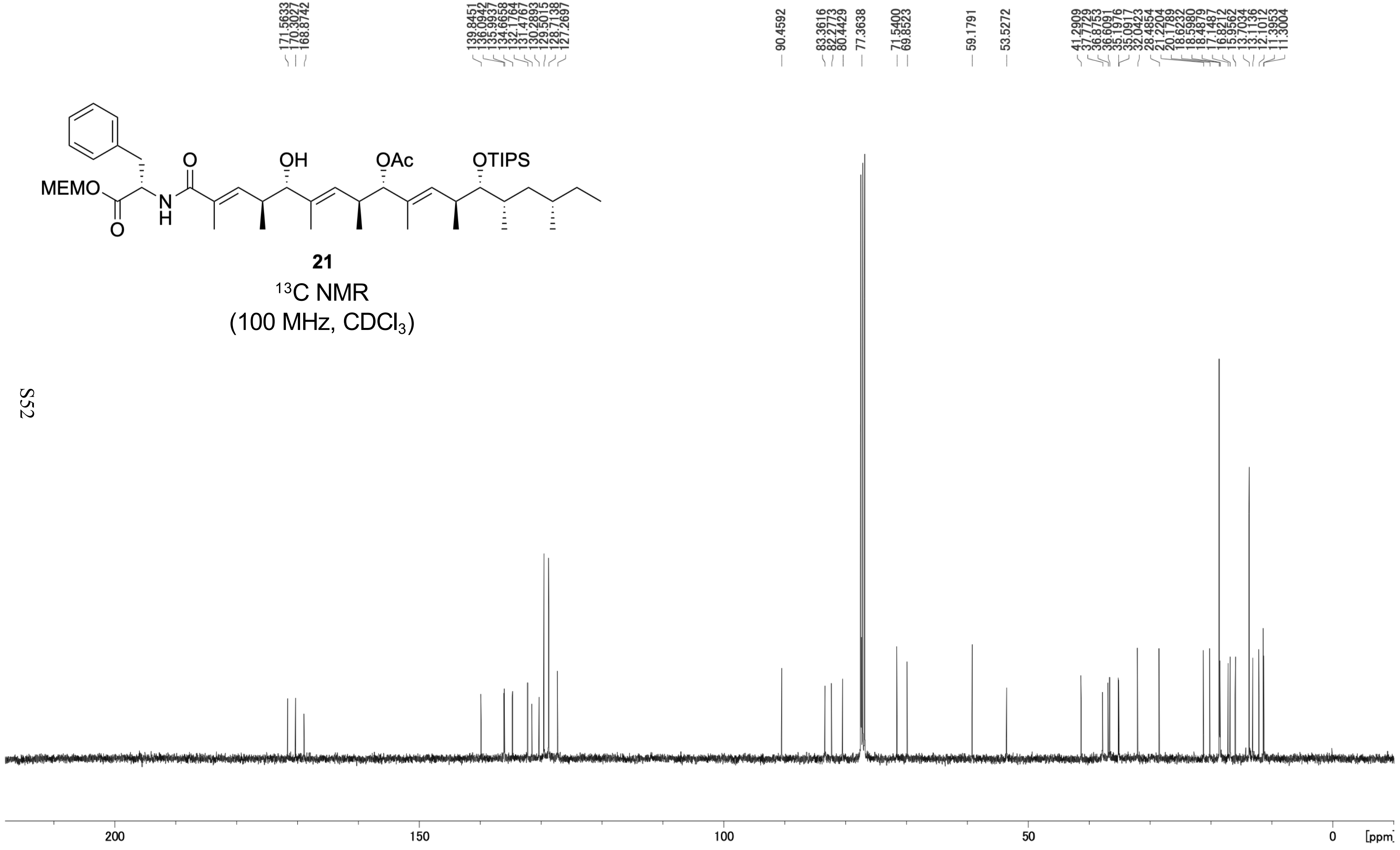
^{13}C NMR
(100 MHz, $CDCl_3$)



21

^{1}H NMR

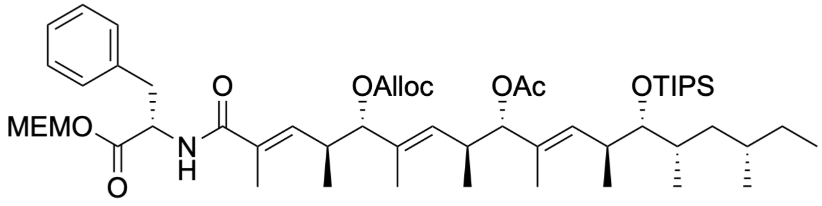
(400 MHz, $CDCl_3$)



21

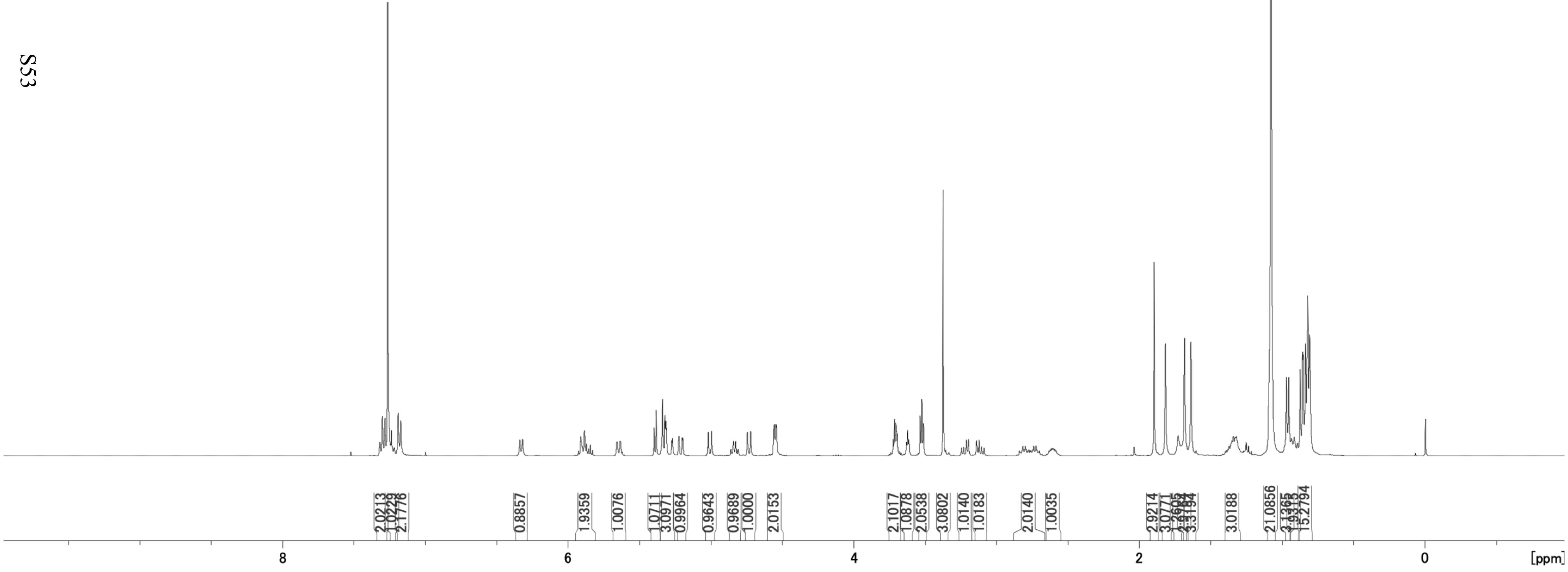
^{13}C NMR

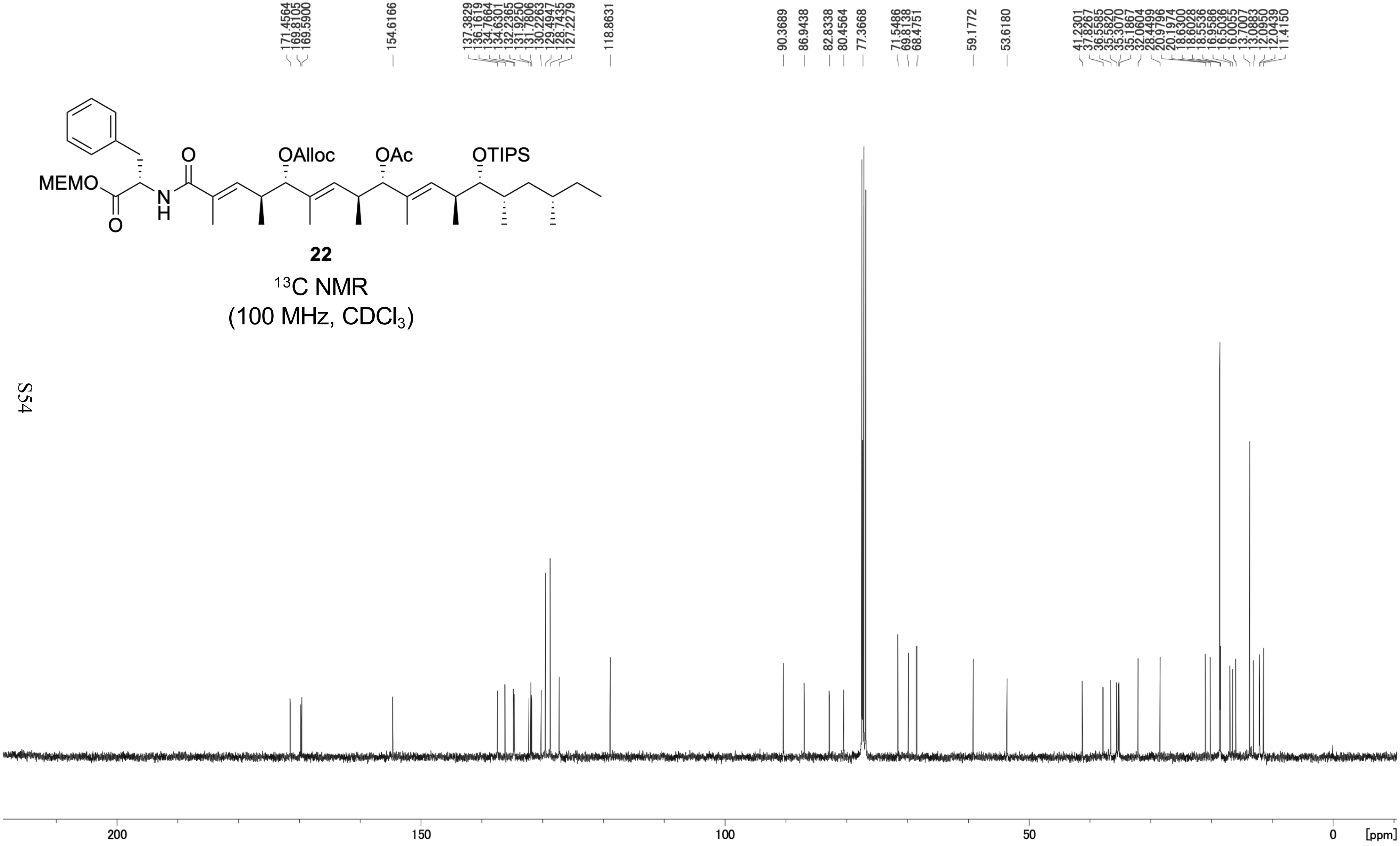
(100 MHz, $CDCl_3$)



22

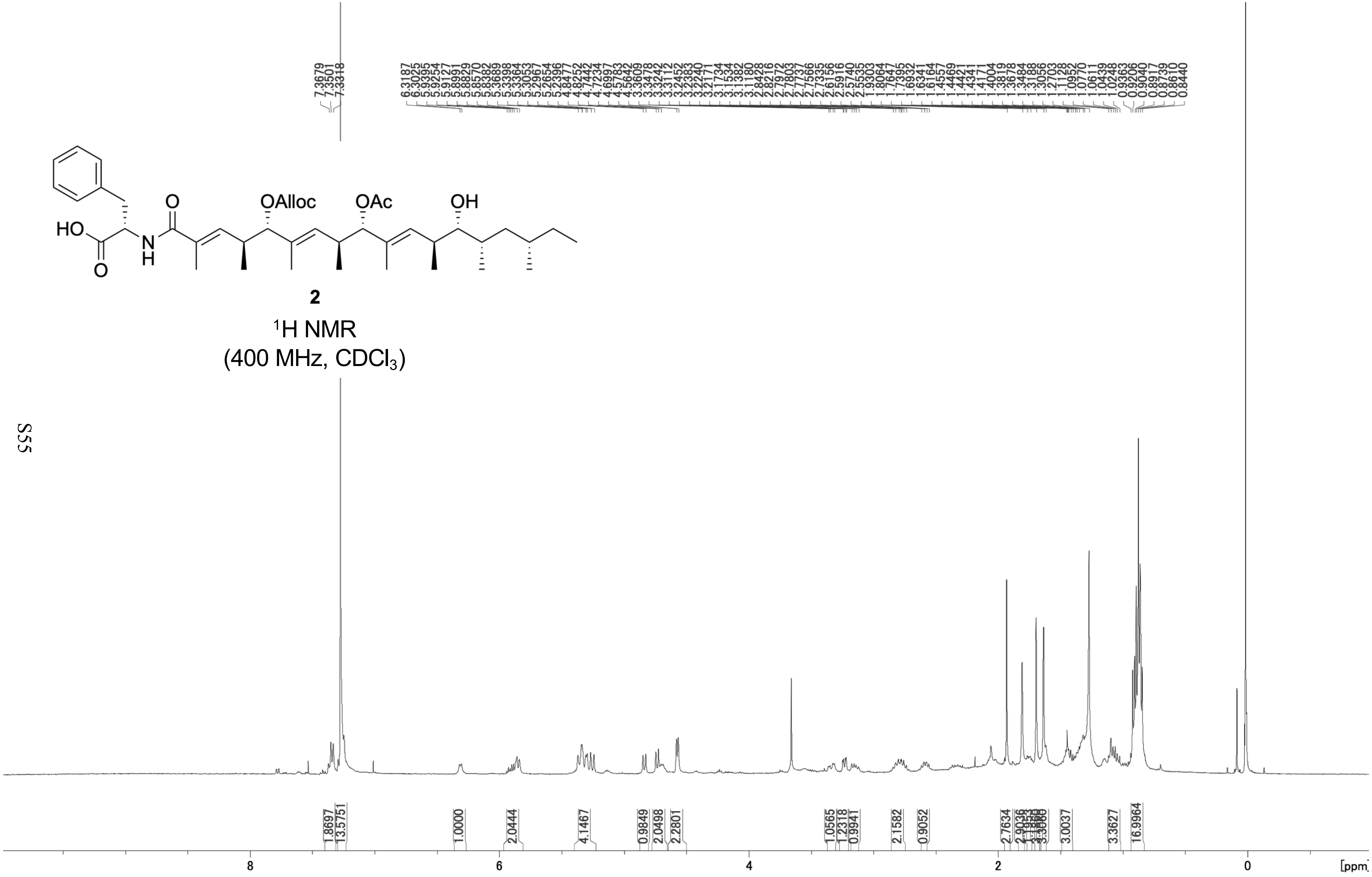
^{1}H NMR
(400 MHz, $CDCl_3$)





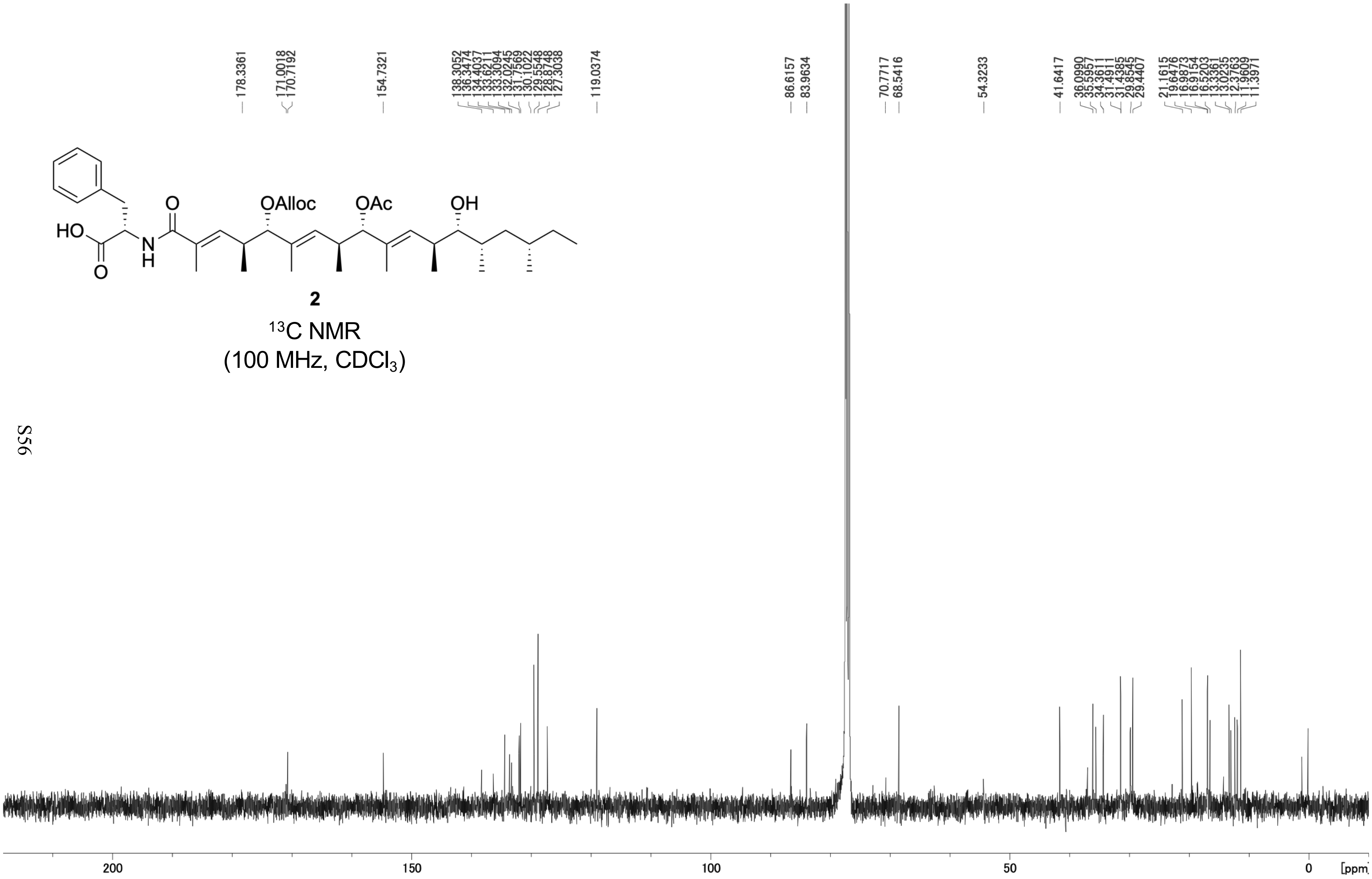
22

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



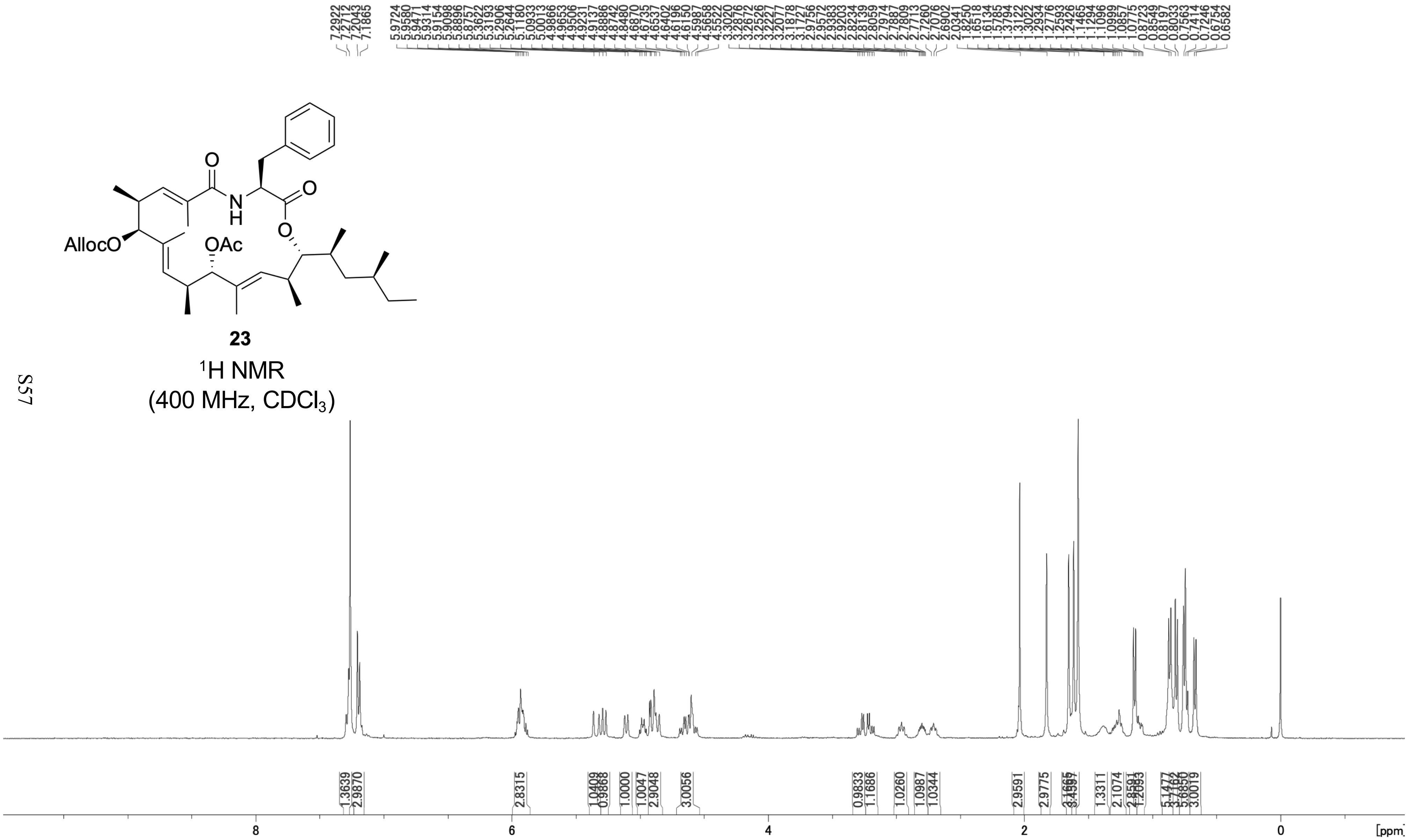
2

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



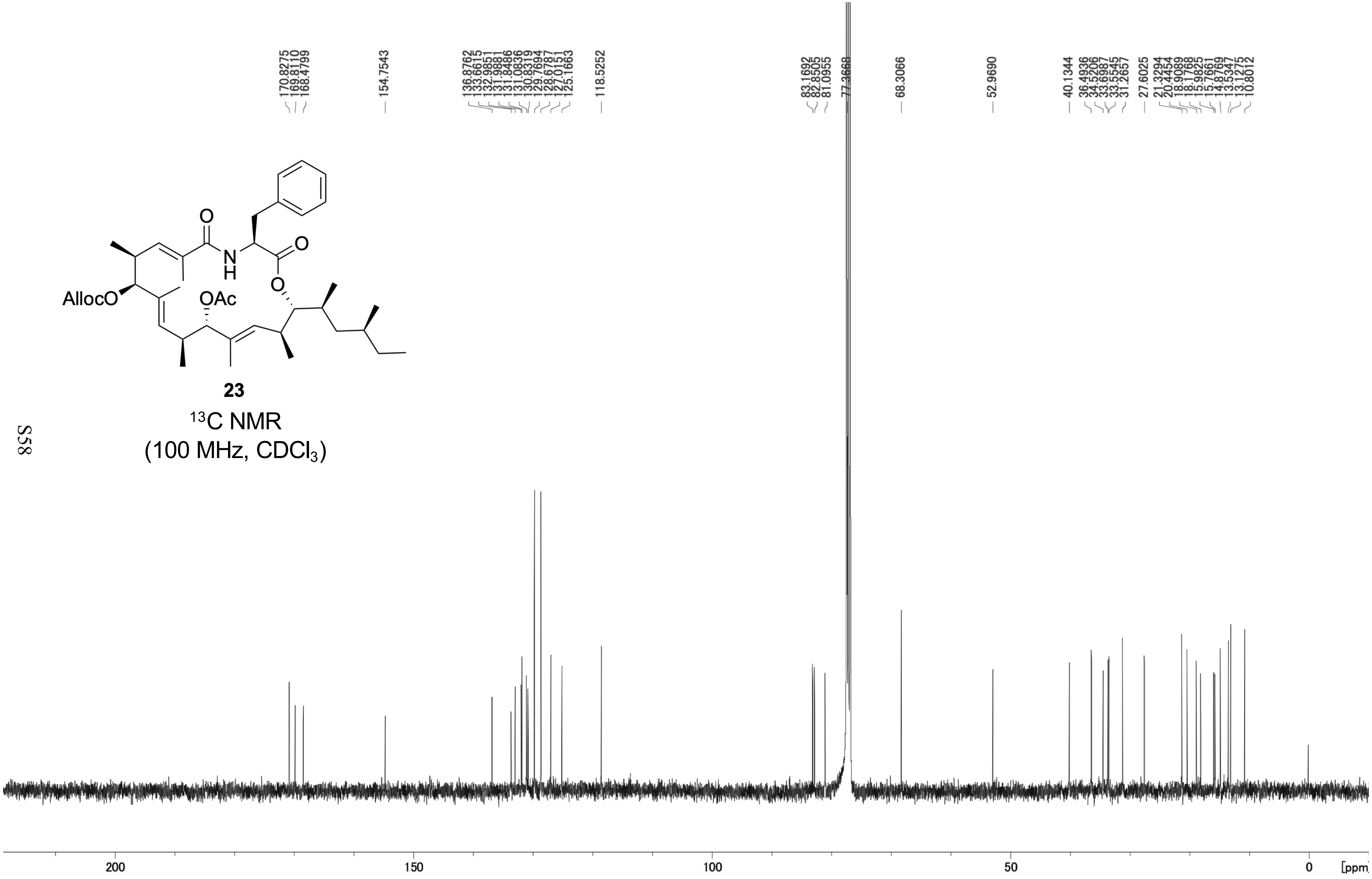
2

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



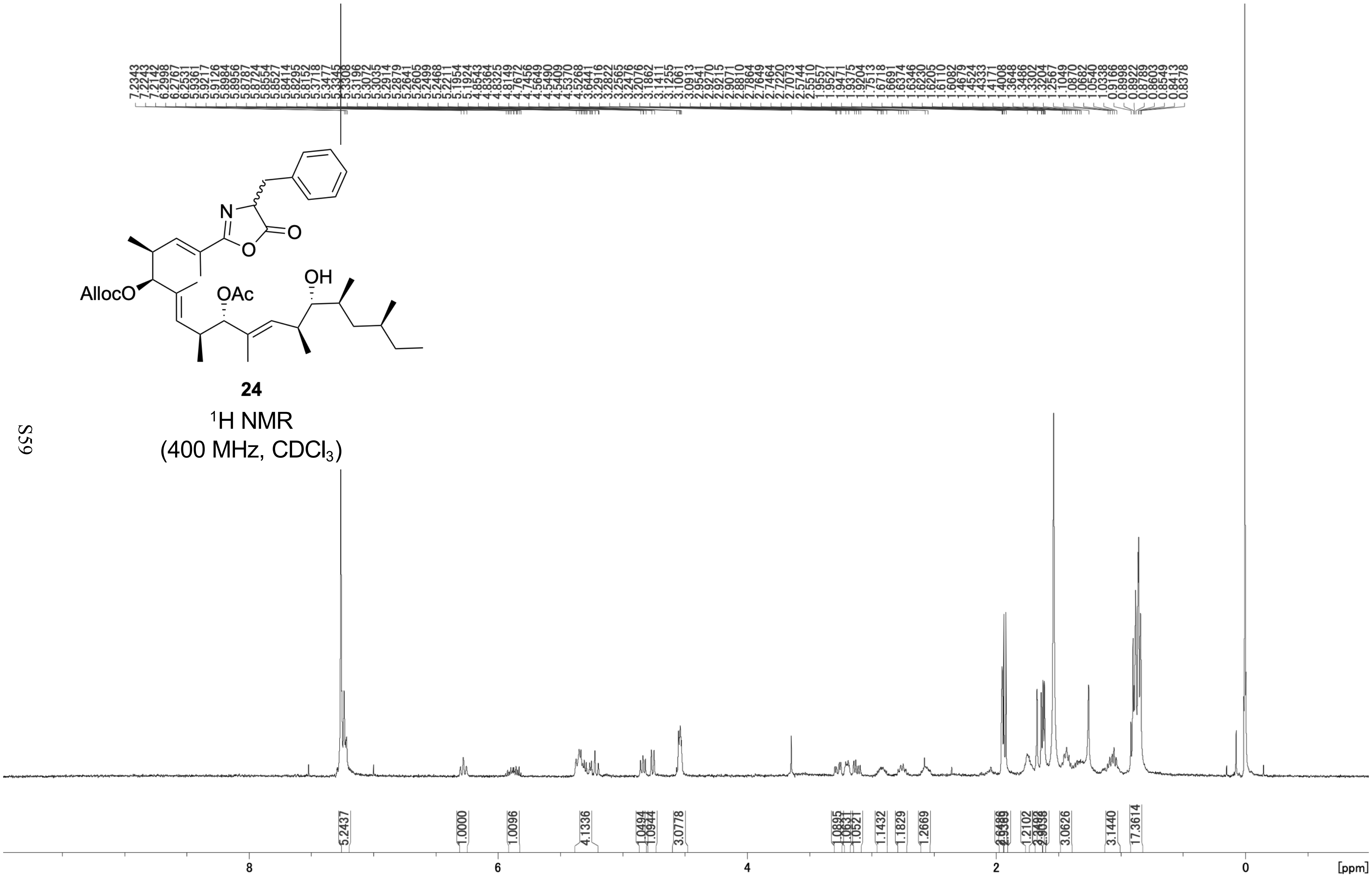
23

^{1}H NMR
(400 MHz, CDCl$_3$)



23

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

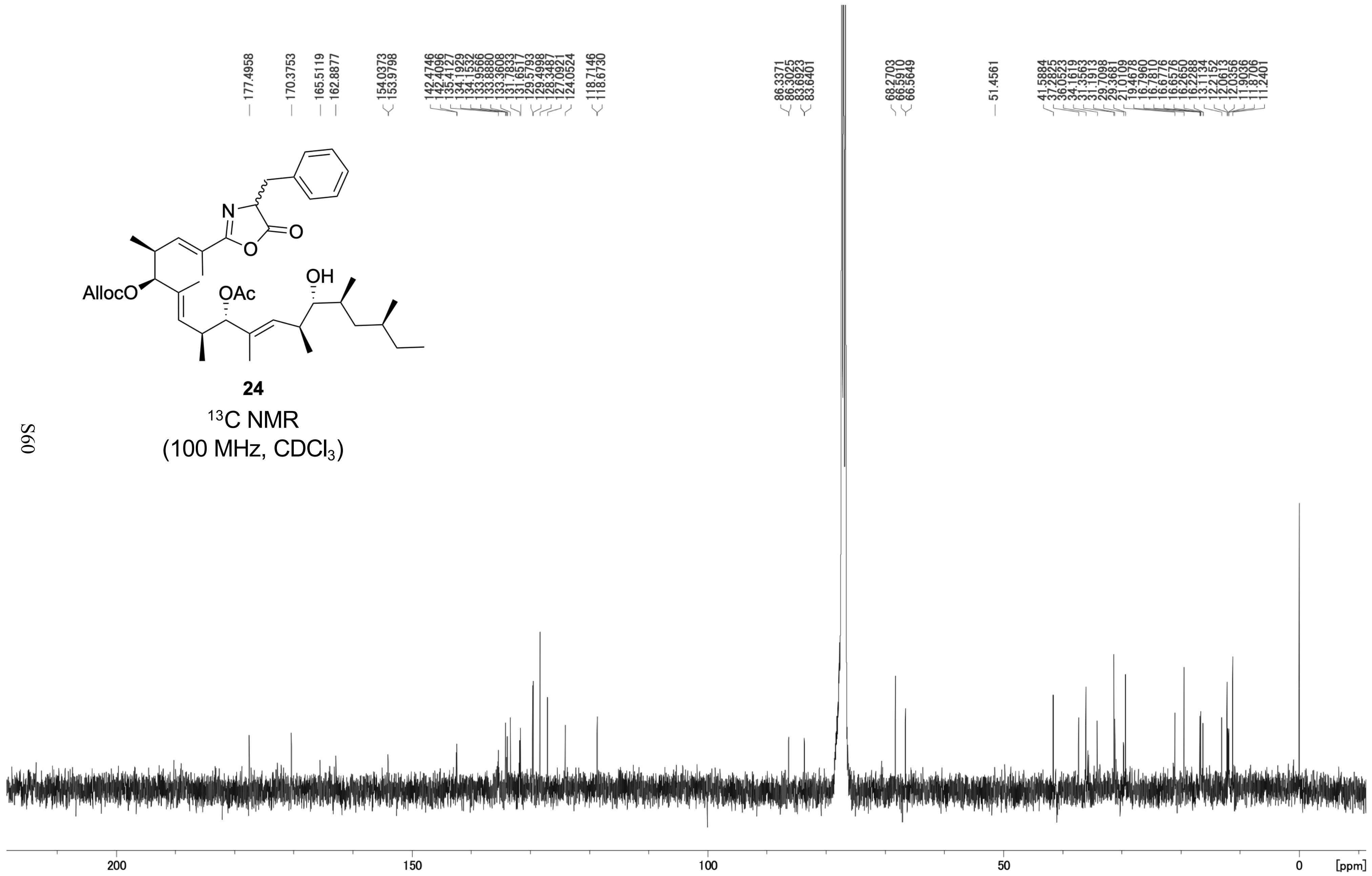


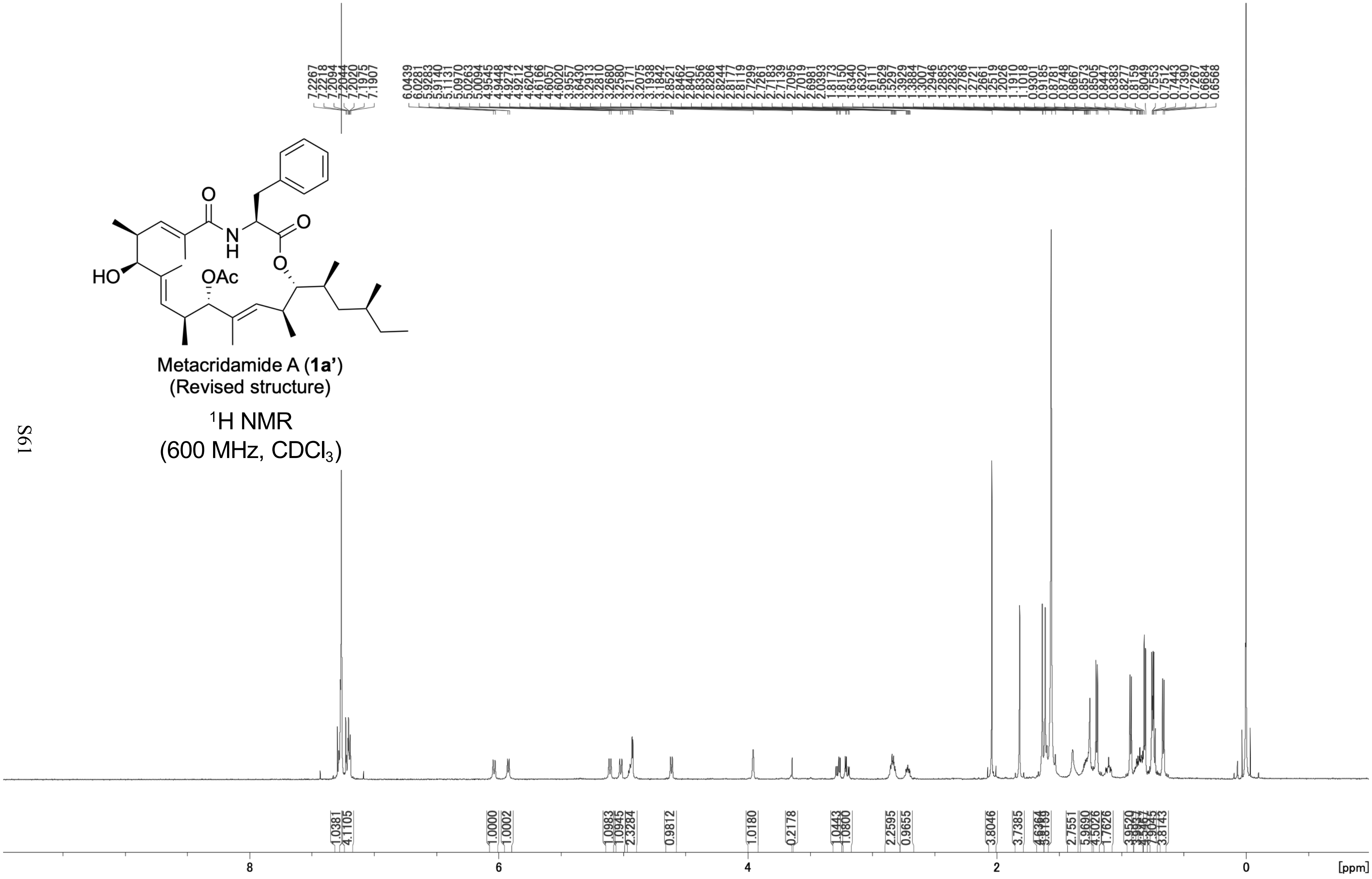
24

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

24

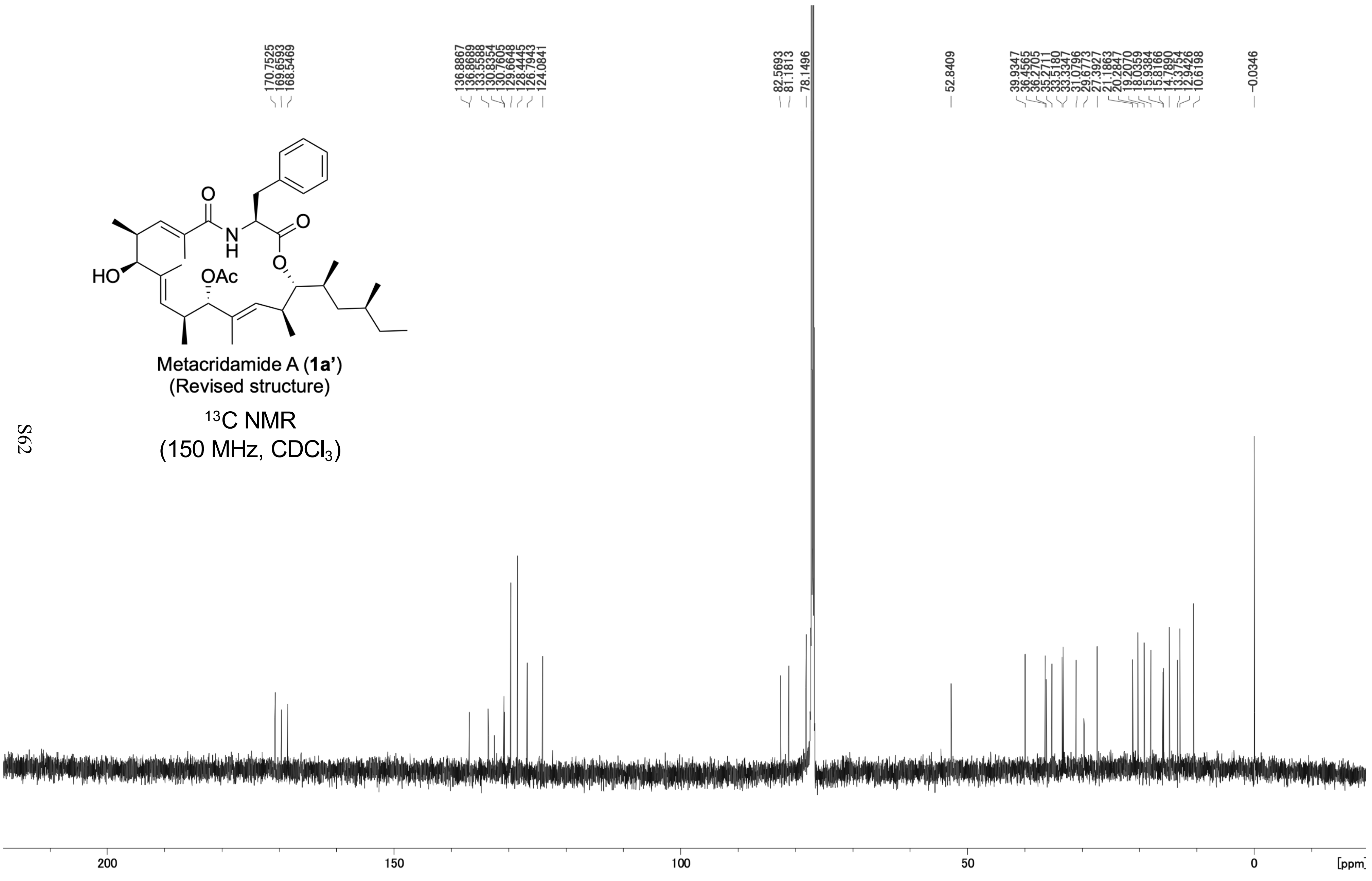
^{13}C NMR
(100 MHz, $CDCl_3$)





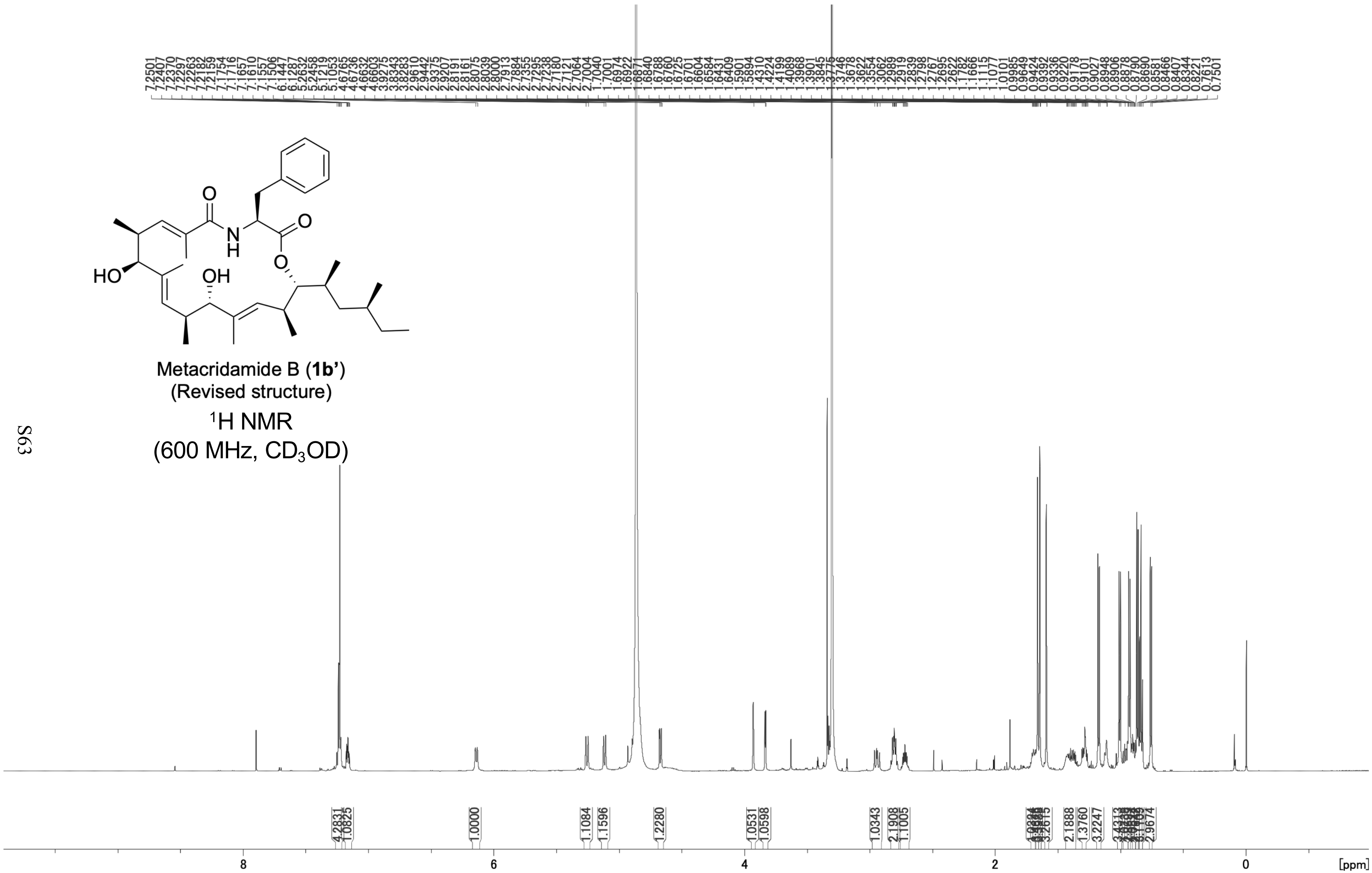
Metacridamide A (**1a’**)
(Revised structure)

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



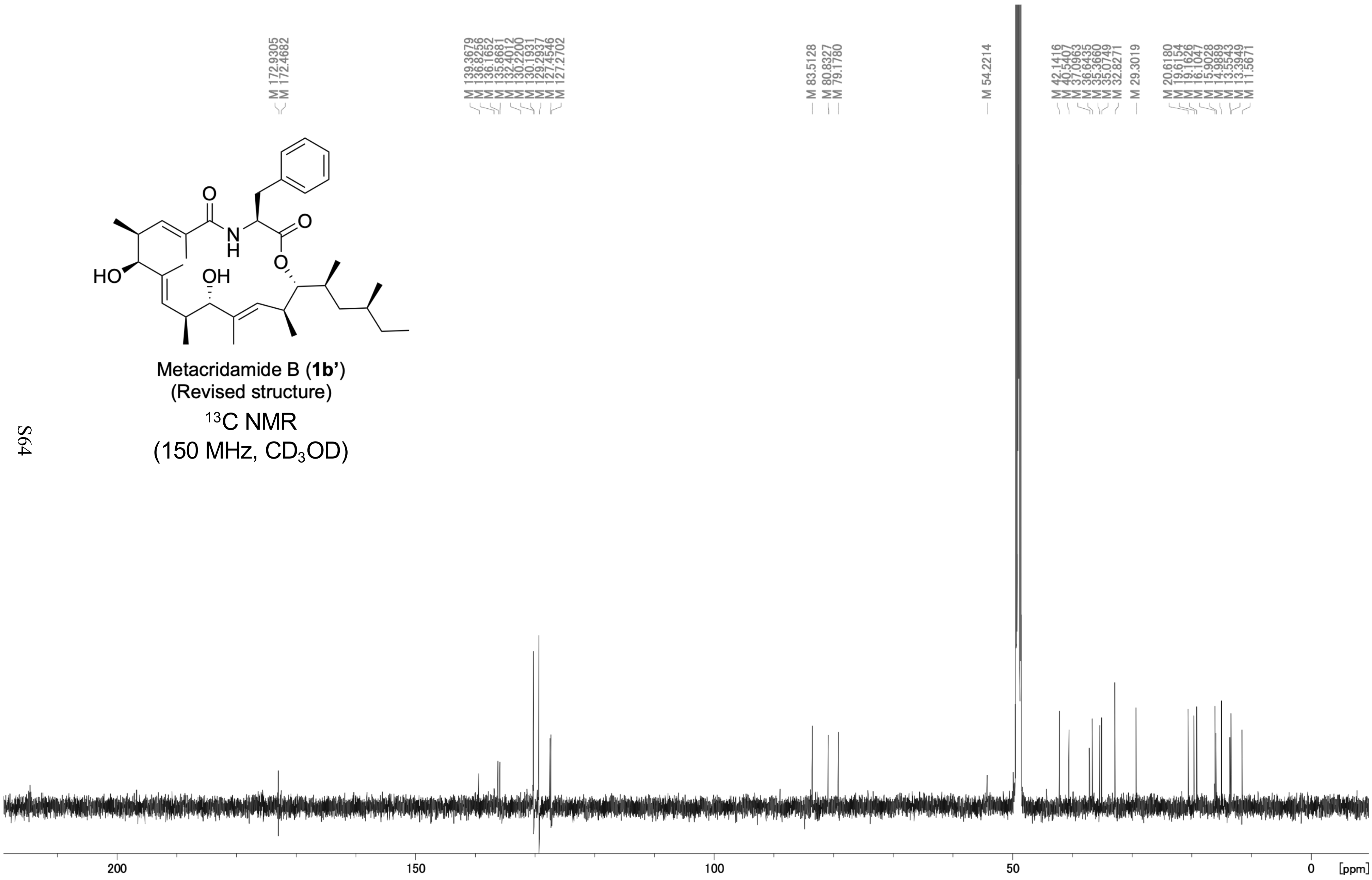
Metacridamide A (**1a’**)
(Revised structure)

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



Metacridamide B (**1b’**)
(Revised structure)

^{1}H NMR
(600 MHz, CD_3OD)



Metacridamide B (**1b'**)
(Revised structure)
^{13}C NMR
(150 MHz, CD_3OD)