Supporting Information

Total Synthesis of (−)-Enigmazole A

Yanran Ai, Mariya V. Kozytska, Yike Zou, Anton S. Khartulyari and

Amos B. Smith, III*

Department of Chemistry, Monell Chemical Senses Center, and Laboratory for Research on the Structure of Matter, University of Pennsylvania, Philadelphia, PA 19104 U.S.A

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1. Materials and Methods

(1) Preparation of reagents and solvents

All chemicals were purchased from Sigma Aldrich, Acros, or TCI America, unless otherwise referenced. Anhydrous tetrahydrofuran (THF), diethyl ether (Et_2O), dichloromethane (CH_2Cl_2), and toluene were acquired from a Pure Solve PS-400 system. Triethylamine, diisopropylamine, diisopropylethylamine, and DMPU were freshly distilled from calcium hydride under an nitrogen atmosphere Commercial *n*-butyllithium (*n*-BuLi) and *tert*-butyllithium (*t*-BuLi) solutions were titrated by using diphenylacetic acid.

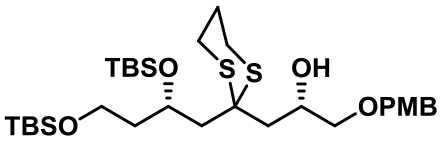
(2) Reaction equipment and conditions

All reactions that require anhydrous conditions were performed in oven- or flame-dried glassware under N_2 or Ar atmosphere. High vacuum (0.05 torr) was created by using an oil pump (Nandor Model 1400N). All reactions were stirred magnetically unless otherwise mentioned. Ice/water bath created 0 °C reaction temperature; dry ice/acetonitrile bath created −40 °C reaction temperature; dry ice/acetone bath created −78 °C reaction temperature. All yields refer to spectroscopically pure compounds. Microwave reactions were carried out in a Biotage Initiator microwave reactor employed vials and septa caps purchased from Biotage (Microwave Reaction Kits).

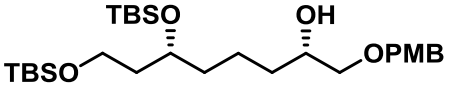
(3) Purifications and Analyses

Reactions were monitored by thin layer chromatography (TLC) with 250 mm pre-coated silica gel plates purchased from Silicycle Technology, and C18 Silica gel thin layer chromatography (C18 TLC) with 100 mm pre-coated C18 silica gel plates purchased from Sorbent Technologies. Flash chromatography was conducted by using ACS grade solvents and silica gel which was purchased from Silicycle Technology. Preparative thin layer chromatography (PTLC) with 500 mm or 1000 mm pre-coated silica gel plates purchased from Silicycle Technology. High-performance liquid chromatography (HPLC) was conducted by using Gilson 333/334 Pumps equipped with an UV-Vis dual wavelength detector and a C18 column (Vydac™ 5 μm C18, 250*10 mm). All melting points were obtained on a Thomas-Hoover apparatus and were uncorrected. All Infrared spectra were recorded on a Jasco Model FT/IR-480 Plus spectrometer. All optical rotations were measured on a Jasco P-2000 polarimeter. ^{1}H NMR, ^{13}C NMR and ^{31}P NMR spectra were recorded on Bruker Avance III 500 MHz spectrometer equipped with either an Oxford cryomagnet or a Spectrospin/Bruker cryomagnet (500MHz/52mm) with a 5 mm dual cryo probe by using either 5 mm or 3 mm NMR tubes. All chemical shifts (δ, in ppm) reported were referred to chloroform (δ 7.26) benzene (δ 7.16) or methanol (δ 3.30) for ^{1}H NMR and chloroform (δ 77.23), benzene (δ 128.39) or methanol (δ 49.00) for ^{13}C NMR. High-resolution mass spectra (HRMS) were acquired either on a Waters LC-TOF mass spectrometer (model LCT-XE Premier) or on a waters GCT Premier spectrometer at the University of Pennsylvania.

2. Experimental Procedures

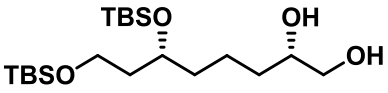


Dithiane (−)-**13**: A solution of *tert*-butyl(1,3-dithian-2-yl)dimethylsilane (4.12 g, 17.6 mmol, 1.2 equiv) in diethyl ether (30 mL) was treated dropwise with *n*-BuLi (7.70 mL, 19.3 mmol, 2.5 M in hexanes, 1.3 equiv) at 0 °C under a nitrogen atmosphere. The mixture was kept at 0 °C for 15 min, warmed to room temperature, and then stirred for 18 min before it was cooled to −78 °C. Epoxide (−)-**10** (4.00 g, 19.8 mmol, 1.35 equiv) in 40 mL of diethyl ether was added to the reaction mixture dropwise via a syringe followed by warming to −30 °C and stirring at that temperature for 2 hours. The reaction mixture was cooled back to −78 °C, and the epoxide (−)-**12** (2.85 g, 14.7 mmol, 1.0 equiv) in 25 mL of diethyl ether and 5 mL of DMPU was added dropwise via a syringe. The reaction mixture was kept at −78 °C for 30 min and then slowly warmed to room temperature overnight without removing the bath. The resulting mixture was quenched with the addition of saturated aqueous NH_4Cl (20 mL) and diluted with diethyl ether (30 mL). The organic layer was removed, and the aqueous layer extracted with diethyl ether (15 mL) twice. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO_2, ethyl acetate/hexanes 10:90, 15:85, 20:80) to furnish dithiane (−)-**13** (8.30 g, 13.2 mmol, 89.8%) as a light yellow oil. $[\alpha]_D^{20} = -3.8$ (*c* 4.0, $CHCl_3$); IR (film) 3466, 2954, 2928, 2856, 1613, 1514, 1471, 1250, 1097, 1038, 836, 775, 664 $cm^{-1;}$ ^1H NMR (500 MHz, $CDCl_3$) δ = 7.27 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 4.50 (s, 2H), 4.28 – 4.20 (m, 2H), 3.80 (s, 3H), 3.75–3.67 (m, 2H), 3.43 (dd, *J* = 4.5 Hz, 9.0 Hz, 1H), 3.39 (dd, *J* = 6.5 Hz, 9.0 Hz, 1H), 3.15 (s, 1H), 2.97–2.91 (m, 1H), 2.89–2.75 (m, 3H), 2.31 (m, 2H), 2.10 (m, 2H), 1.98 (m, 2H), 1.92 (m, 1H), 1.76 (m, 1H), 0.91 (s, 9H), 0.89 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 159.4, 130.4, 129.5, 112.9, 74.4, 73.0, 68.0, 67.6, 59.8, 55.4, 51.6, 47.1, 43.1, 42.2, 26.7, 26.3, 26.2, 26.1, 24.9, 18.3, 18.2, −3.6, −4.0, −5.1, −5.14; high resolution Mass-spectrum (ESI) m/z 653.3168 $[(M+Na)^+$ calcd for $C_{31}H_{58}O_5S_2Si_2Na]$.

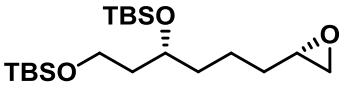


Alcohol (−)-**14**: Commercially available Raney nickel (19.0 g with water, Grade: Raney 2800 nickel from Aldrich) as a slurry in water was weighed into the 200 mL round-bottomed flask and washed with anhydrous ethanol (20 mL) three times under a nitrogen atmosphere. Dithane (−)-**13** (1.00 g, 1.59 mmol, 1.0 equiv) in 35 mL ethanol was added via syringe to the slurry mixture before hydrogen gas was bubbled through for 20 min. The mixture was heated to 80 °C and kept at that temperature for 2.5 hours with stirring under a hydrogen atmosphere before it was brought to room temperature. Then the liquid phase was carefully transferred using a pipet to separate the desired product from residual flammable Raney nickel and washed with ethanol (15 mL) four times. The combined liquid was concentrated and purified by column chromatography (SiO_2, ethyl ace-

tate/hexanes 10:90, 15:85, 20:80) to furnish alcohol (−)-**14** (0.79 g, 1.50 mmol, 94.5 %) as a colorless oil. $[\alpha]_D^{20}$= −4.1 (*c* 5.0, $CHCl_3$); IR: 3466, 2953, 2929, 2857, 1613, 1514, 1463, 1388, 1361, 1302, 1251, 1093, 1039, 836, 775, 664 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.25 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 4.48 (s, 2H), 3.80 (s, 3H), 3.80–3.75 (m, 2H), 3.64 (m, 2H), 3.47 (dd, *J* = 9.8 Hz, 2.8 Hz, 1H), 3.28 (t, *J* = 8.8 Hz, 1H), 2.31 (brs, 1H), 1.63 (q, *J* = 6.5 Hz, 2H) 1.55–1.30 (m, 6H), 0.88 (s, 9H), 0.87 (s, 9H), 0.04 (s, 9H), 0.03(s, 3H); IR (film) 3466, 2954, 2929, 2857, 1613, 1514, 1463, 1388, 1360, 1302, 1251, 1094, 1039, 836, 775, 664 cm^{-1}; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 159.4, 130.2, 129.4, 113.9, 74.4, 73.0, 70.3, 69.2, 60.0, 55.2, 40.1, 37.5, 33.4, 26.1, 26.0, 21.2, 18.3, 18.2, −4.3, −4.5, −5.2; high resolution mass-spectrum (ESI) m/z 549.3394 [$(M+Na)^+$ calcd for $C_{28}H_{54}O_5Si_2Na$].

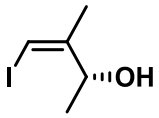


Diol (−)-**15**: Commercially available Raney nickel (9.0 g with water, Grade: Raney 2800 nickel from Aldrich) as a slurry in water was weighed out into the 100 mL round-bottomed flask and washed with anhydrous ethanol (10 mL) three times under a nitrogen atmosphere. Alcohol (−)-**14** (0.50 g, 0.95 mmol, 1.0 equiv) in 25 mL ethanol was added via syringe to the slurry mixture before hydrogen gas was bubbled through over 20 min. The mixture was heated to 80 °C and kept at that temperature for 15 hours with stirring under a hydrogen atmosphere before it was allowed to attain room temperature. The liquid phase was transferred carefully using a pipet to separate it from residual flammable Raney nickel and washed with ethanol (8 mL) 4 times. The combined liquid was concentrated and purified by column chromatography (SiO_2, ethyl acetate/hexanes, 20:80, 30:70, 40:60) to furnish diol (−)-**15** (337 mg, 0.83 mmol, 87.3 %) as a colorless oil. $[\alpha]_D^{20}$= −7.5 (*c* 5.0, $CHCl_3$); IR (film) 3379, 2953, 2929, 2857, 1472, 1361, 1255, 1094, 938, 836, 774, 664 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 3.81 (m, 1H), 3.71 (m, 1H), 3.70–3.63 (m, 3H), 3.43 (dd, *J* = 8.0 Hz, 11.0 Hz, 1H), 1.95–1.75 (brs, 2H), 1.65 (ddd, *J* = 2.3 Hz, 6.5 Hz, 11Hz, 2H), 1.58–1.42 (m, 5H), 1.42–1.35 (m, 1H), 0.89 (s, 9H), 0.88 (s, 9H), 0.04 (s, 6H), 0.04(s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 72.4, 69.3, 66.9, 60.2, 40.2, 37.5, 33.5, 26.2 (3C), 26.1 (3C), 21.3, 18.5, 18.3, −4.2, −4.4, −5.1; high resolution mass-spectrum (ESI) m/z 429.2844 [$(M+Na)^+$ calcd for $C_{20}H_{46}O_4Si_2Na$].

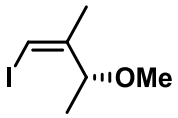


Epoxide (−)-7: To a solution of diol (−)-**15** (1.57 g, 3.87 mmol, 1.0 equiv) in 40 mL THF 223 mg of NaH (95 weight-%, 8.83 mmol, 2.28 equiv) was added at 0 °C in nitrogen atmosphere, followed by stirring at room temperature for 20 min. The reaction mixture was then cooled to 0 °C and solid TrisIm (1.54 g, 4.62 mmol, 1.2 equiv) was added in one portion. The resulting mixture was stirred for 1 hour before it was quenched with the addition of 10 mL saturated aqueous NH_4Cl and diluted with diethyl ether. The organic layer was removed, and the aqueous layer was extracted with diethyl ether (15 mL) twice. The combined organic layers were washed with the saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and concentrated. The resulting

oil was purified by column chromatography (SiO_2, ethyl acetate/hexanes 5:95, 10:90) to furnish epoxide (−)-7 (1.50 g, 3.86 mmol, quantitative) as a colorless oil. $[\alpha]_D^{20}$= −10.3 (*c* 4.4, $CHCl_3$); IR (film) 2954, 2929, 2857, 1472, 1388, 1361, 1255, 1095, 1006, 938, 836, 774, 664 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 3.83 (m, 1H), 3.71 (td, *J* = 6 Hz, 3.5 Hz, 2H), 2.90 (m, 1H), 2.75 (t, *J* = 4.5 Hz, 1H), 2.46 (dd, *J* = 5.2 Hz, 2.8 Hz, 1H), 1.65 (ddd, *J* = 11.0 Hz, 6.5 Hz, 2.3 Hz, 2H), 1.58 – 1.42 (m, 6H), 0.89 (s, 9H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 69.1, 59.9, 52.3, 47.0, 40.1, 37.3, 32.8, 26.1, 26.0, 21.7, 18.4, 18.2, −4.3, −4.4, −5.2; high resolution mass-spectrum (ESI) m/z 411.2729 [$(M+Na)^+$ calcd for $C_{20}H_{44}O_3Si_2Na$].

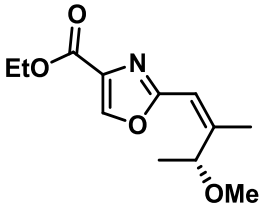


Iodide S1: To a stirred solution of (*R*)-3-butyn-2-ol (+)-**16** (12.4 g, 177 mmol, 1.0 equiv) in dry toluene (330 mL) at room temperature under a nitrogen atmosphere, CuI (17.4 g, 88.8 mmol, 0.5 equiv) was added portionwise. After complete addition, the temperature was decreased to −78 °C before the dropwise addition of MeMgBr solution (1.4 M in THF/Toluene, 1:3, 456 mL, 638 mmol, 3.6 equiv) over 2 hours. Then the reaction mixture was warmed gradually to room temperature and stirred overnight. The reaction was quenched with the dropwise addition of I_2 solution (162 g of I_2 in 250 mL THF, 638 mmol, 3.6 equiv) at −40 °C. The resulting mixture was washed with a saturated aqueous solution of $Na_2S_2O_3$ (250 mL). The organic layer was removed and the aqueous layer was extracted with diethyl ether (50 mL) twice. The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated carefully (volatile!), the resulting oil was purified using a column chromatography (pentane/Et_2O, 5:1) to afford iodide **S1** in a mixture with toluene (50 g). The mixture was moved to next step without further purification [see the procedure for iodide (+)-**17**].

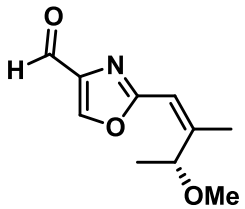


Iodide (+)-**17**: To a stirred suspension of NaH (24.0 g, 600 mmol, 60% in mineral oil, 3.4 equiv) in 250 mL of Et_2O at 0 °C under a nitrogen atmosphere, a solution of iodide **S1** [50 g, mixture with toluene made from 177 mmol of (+)-**16**, see the procedure for iodide **S1**] in 100 mL Et_2O was added slowly. After complete addition, the temperature was increased to room temperature and the reaction mixture was allowed to stir for 20 min before it was recooled to 0 °C. Methyl iodide (96.4 mL, 679 mmol, 3.8 equiv) was added dropwise, followed by very slow addition (over 40 min) of 15-crown-5 (30.5 g, 141 mmol, 0.8 equiv) at 0 °C. The resulted mixture was stirred overnight at room temperature and quenched at 0 °C by very careful addition of saturated aqueous NH_4Cl (100 mL over 1 hour). The organic layer was removed and the aqueous layer was extracted with diethyl ether (50 mL) twice. The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated carefully (volatile!), the resulting oil was purified by reduced pressure distillation (80 °C at 5 mm Hg) to give iodide (+)-**17** (30.7 g, 136 mmol, 76.8%, 2 steps) as a colorless liquid. $[\alpha]_D^{20}$= +9.5 (*c* 2.2, $CHCl_3$); IR (film) 2979, 2927, 2900, 2819, 1654, 1443, 1370, 1338, 1281, 1206, 1145, 1115, 1098, 1031, 968, 866, 774, 655 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.03 (d, *J* = 1.0 Hz, 1H), 4.27 (q, *J* = 6.5 Hz, 1H), 3.23 (s, 3H), 1.80 (d, *J* = 1.0 Hz, 3H),

1.20 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 147.5, 80.9, 75.7, 56.5, 18.6, 18.0; high resolution mass spectrum (CI) m/z 225.9852 [$(M)^+$ calcd for $C_6H_{11}IO$].

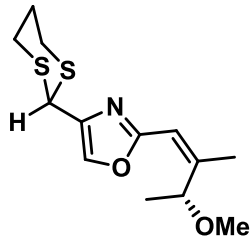


Ester (+)-**18**: To a solution of iodide (+)-**17** (19.0 g, 84.1 mmol, 1.0 equiv) in Et_2O (70 mL) under a nitrogen atmosphere at −78 °C, *t*-BuLi (99 mL, 1.7 M in pentane, 168.0 mmol, 2.0 equiv) was added dropwise over 30 min. The resulting heterogeneous mixture was stirred for one hour at the same temperature, then $ZnCl_2$ solution (100 mL, freshly prepared from solid flame-dried $ZnCl_2$, 1 M in THF, 100.0 mmol, 1.19 equiv) was added dropwise and the reaction mixture was allowed to warm to room temperature over a 30 min period. At this point pentane and diethyl ether were removed from the reaction under reduced pressure and nitrogen atmosphere. A solution of oxazolyl chloride 8 (14.9 g, 84.1 mmol, 1.0 equiv) and $Pd(PPh_3)_4$ (2.0 g, 1.73 mmol, 0.02 equiv) was separately prepared in THF (80 mL) and was added dropwise. The resulting mixture was vigorously stirred at reflux for two hours, then cooled to room temperature and quenched by the addition of a saturated aqueous NH_4Cl solution (50 mL). The mixture was diluted with diethyl ether. The organic layer was removed, and the aqueous layer was extracted with diethyl ether (30 mL) twice. The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated. The resulting oil was purified by column chromatography (SiO_2, ethyl acetate/hexanes 10:90, 15:85, 20:80) to furnish ester (+)-**18** (16.1 g, 67.3 mmol, 80.0%) as a colorless oil. $[\alpha]_D^{20}$= +43.9 (*c* 0.5, $CHCl_3$); IR (film) 2980, 1743, 1722, 1654, 1576, 1448, 1370, 1316, 1178, 1113, 1025, 839, 770 cm^{-1}; ^{1}H NMR (500 MHz, CDCl3) δ = 8.11 (s, 1H), 6.26 (s, 1H), 5.14 (q, J = 6.5 Hz), 4.39 (q, J = 7.1 Hz, 2H), 3.23 (s, 3H), 1.93 (d, J =1.0 Hz, 3H), 1.38 (t, J = 7.1 Hz, 3H), 1.32 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, CDCl3) δ = 161.4, 161.0, 153.2, 142.8, 134.2, 112.7, 74.8, 61.2, 56.5, 19.4, 17.9, 14.4; high resolution mass spectrum (ESI) m/z 262.1051 [$(M+Na)^+$ calcd for $C_{12}H_{17}NO_4Na$].

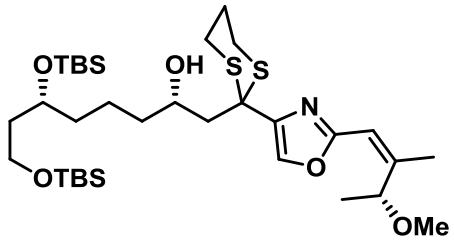


Aldehyde (+)-**S2**: A solution of ester (+)-**18** (9.00 g, 37.6 mmol, 1 equiv) in 200 mL CH_2Cl_2 was treated with DIBAL-H (1 M in hexanes, 75.2 mL, 75.2 mmol, 2.0 equiv) at −78 °C under nitrogen atmosphere, followed by stirring at that temperature for 30 min. The resulted mixture was quenched with MeOH (20 mL) at −78 °C before it was warmed to room temperature. Saturated aqueous Rochelle's salt (80 mL) was then added and the mixture was stirred vigorously for one hour. The resulting mixture was diluted with 100 mL diethyl ether. The organic layer was removed, and the aqueous layer was extracted with diethyl ether (50 mL) twice. The combined organic lay-

ers were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated, the resulting oil was purified by column chromatography (SiO_2, ethyl acetate/hexanes 10:90, 15:85, 20:80) to furnish aldehyde (+)-**S2** (6.35 g, 32.7 mmol, 87.0%) as a white solid. mp 55.0–57.0 °C; $[\alpha]_D^{20}$= +25.2 (*c* 1.0, $CHCl_3$); IR (film) 2978, 2924, 1699, 1651, 1562, 1114 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 9.95 (s, 1H), 8.18 (s, 1H), 6.23 (s, 1H), 5.24 (q, *J* = 6.5 Hz), 3.24 (s, 3H), 1.94 (d, *J* =1.5 Hz), 1.33 (d, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 184.8, 161.5, 154.8, 143.0, 141.7, 112.2, 75.0, 56.8, 19.4, 18.1; high resolution mass spectrum (ESI) m/z 196.0971 [$(M+H)^+$ calcd for $C_{10}H_{14}NO_3$].

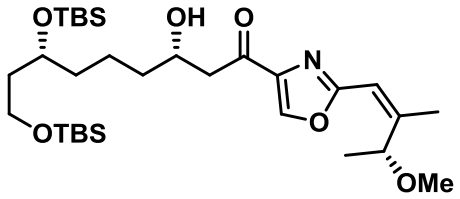


Dithiane (+)-**6**: A solution of aldehyde (+)-**S2** (2.30 g, 11.7 mmol, 1.0 equiv) in 60 mL CH_2Cl_2 was treated with 1,3-propanedithiol (1.75 mL 17.51 mmol, 1.5 equiv) and $BF_3.OEt_2$ (0.55 mL, 4.08 mmol, 0.35 equiv) respectively at 0 °C under a nitrogen atmosphere, followed by stirring at that temperature for 2 hours. The resulting mixture was quenched by the addition of a 2 M NaOH aqueous solution (20 mL), and diluted with 30 mL Et_2O. The organic layer was removed, and the aqueous layer was extracted with Et_2O (30 mL) twice. The combined organic layers were washed with the 2 M aqueous NaOH (15 mL) three times, saturated aqueous $NaHCO_3$ (20 mL), and brine (20 mL), dried over $MgSO_4$, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO_2, ethyl acetate/hexanes 10:90, 15:85, 20:80) to furnish dithiane (+)-**6** (3.21 g, 11.2 mmol, 96.1%) as an amorphous white solid. $[\alpha]_D^{20}$= +43.7 (*c* 4.75, $CHCl_3$); IR (film) 2977, 2931, 2900, 2819, 1654, 1542, 1446, 1422, 1368, 1273, 1204, 1149, 1112, 1095, 971.0, 875, 760 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.60 (s, 1H), 6.21 (t, *J* = 1.5 Hz, 1H), 5.16 (q, *J* = 6.5 Hz), 5.13 (s, 1H), 3.23 (s, 3H), 3.06–2.95 (m, 4H), 2.17 (m, 1H), 2.01 (m, 1H), 1.89 (d, *J* = 1.5 Hz, 3H) 1.31 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.2, 151.1, 140.6, 134.4, 113.2, 74.7, 56.4, 41.3, 30.3, 25.3, 19.2, 17.6; high resolution mass spectrum (ESI) m/z 286.0940 [$(M+H)^+$ calcd for $C_{13}H_{20}NO_2S_2$].

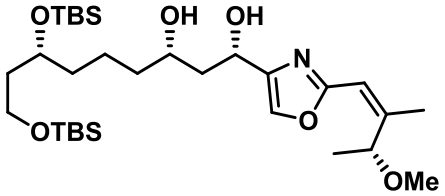


Dithiane (+)-**19**: To a solution of dithiane (+)-**6** (3.30 g, 11.6 mmol, 1.0 equiv) in 40 mL of Et_2O at −78 °C under a nitrogen atmosphere, a solution of *n*-BuLi (2.30 M in hexanes, 5.79 mL, 13.3 mmol, 1.15 equiv) was added over a 5 min period. After complete addition, the reaction mixture was stirred for 20 minutes at −78 °C. Epoxide (−)-7 (4.50 g, 11.57 mmol, 1.0 equiv) in 20 mL of Et_2O was added to reaction mixture dropwise at the same temperature over 5 minutes. The resulting mixture was gradually allowed to come to 0 °C over 2 hours before it was quenched by addition of

saturated aqueous NH_4Cl (20 mL). The organic layer was removed, and the aqueous layer was extracted with Et_2O (30 mL) twice. The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated, and the resulting oil was purified by column chromatography (SiO_2, ethyl acetate/hexanes 15:85, 20:80, 30:70) to furnish dithiane (+)-**19** (6.01 g, 8.92 mmol, 77.0%) as a colorless oil. $[\alpha]_D^{20}$= +16.0 (*c* 1.7, $CHCl_3$); IR (film) 2928, 2856, 1468, 1255, 1096, 836, 774 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.71 (s, 1H), 6.21 (s, 1H), 5.11 (q, *J* = 6.5 Hz, 1H), 3.89 (brs, 1H), 3.78 (m, 1H), 3.64, (dd, *J* = 10.5 Hz, 6.5 Hz, 2H), 3.49 (s, 1H), 3.23 (s, 3H), 2.78–2.92 (m, 4H), 2.22–2.35, (m, 2H), 2.01 (m, 2H), 1.90 (s, 3H), 1.45 (m, 2H), 1.47 – 1.52 (m, 6H), 1.31 (d, *J* = 6.5 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.03 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.9, 152.1, 143.9, 136.5, 113.3, 75.1, 69.4, 68.5, 60.2, 56.8, 49.5, 40.2, 37.9, 37.7, 27.8, 27.6, 26.2, 26.1, 25.0, 21.4, 19.4, 18.5, 18.3, 17.9, –4.2, –4.4, –5.09, –5.10; high resolution mass spectrum (ESI) m/z 674.3765 [(M+H)$^+$ calcd for $C_{33}H_{64}NO_5S_2Si_2$].

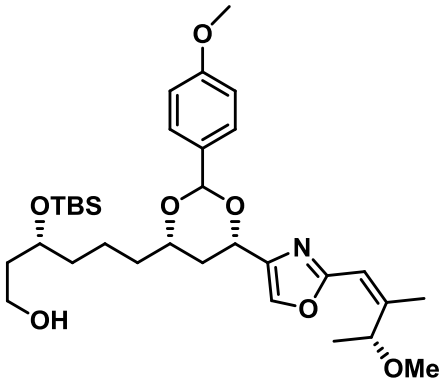


Ketone (+)-**S3**: To a solution of dithiane (+)-**19** (2.55 g, 3.77 mmol, 1.0 equiv) in ethyl acetate (40 mL) and water (40 mL), $Fe(acac)_3$ (271 mg, 0.757 mmol, 0.2 equiv), sodium iodide (848 mg, 5.66 mmol, 1.5 equiv) and 30% hydrogen peroxide (1.3 mL aqueous solution, 11.31 mmol, 3.0 equiv) were added sequentially at 0 °C under an air atmosphere. The reaction mixture was stirred for 30 minutes at the same temperature before it was quenched by the addition of saturated aqueous $Na_2S_2O_3$. The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (20 mL) three times. The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO_2, ethyl acetate: hexanes 15:85, 20:80, 30:70) to furnish ketone (+)-**S3** (1.65 g, 2.83 mmol, 75.0%) as a colorless oil. $[\alpha]_D^{20}$= +24.6 (*c* 1.4, $CHCl_3$); IR (film) 3465, 2928, 2856, 1686, 1562, 1463, 1386, 1255, 1096, 968, 836, 774, 664 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 8.15 (d, *J* = 1.5 Hz, 1H), 6.24 (s, 1H), 5.19 (q, *J* = 6.5 Hz, 1H), 4.19 (brs, 1H), 3.83 (brs, 1H), 3.67 (brs, 2H), 3.25 (s, 3H), 3.13 (d, *J* = 17.5 Hz, 2H), 3.01 (d, *J* = 17.5 Hz, 9.0 Hz, 1H), 1.95 (s, 3H), 1.66 (q, *J* = 6.0 Hz, 2H), 1.35–1.68 (m, 6H), 1.34 (dd, *J* = 6.5 Hz, 1.0 Hz, 3H), 0.891 (s, 9H), 0.887 (s, 9H), 0.05 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 196.1, 160.7, 154.2, 141.4, 141.2, 112.4, 75.1, 69.4, 67.9, 60.2, 56.8, 46.9, 40.2, 37.5, 37.2, 26.2, 26.1, 21.3, 19.4, 18.5, 18.3, 18.1, –4.2, –4.4, –5.1; high resolution mass spectrum (ESI) m/z 584.3802 [(M+H)$^+$ calcd for $C_{30}H_{58}NO_6Si_2$].



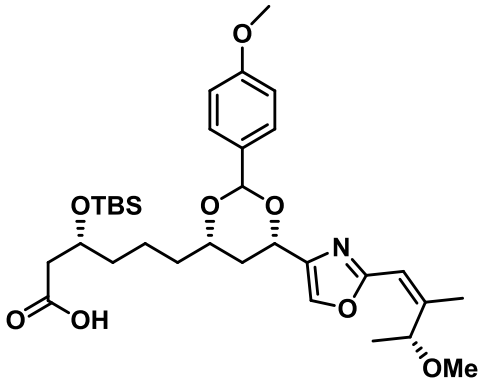
Diol (+)-**20**: To a solution of ketone (+)-**S3** (1.70 g, 2.91 mmol, 1.0 equiv) in 30 mL of THF/MeOH (4:1), a solution of Et_2BOMe (1M in THF, 6.11 mL, 6.11 mmol, 2.1 equiv) was added dropwise at –78 °C under a nitrogen atmosphere. After the reaction mixture was stirred for

15 minutes at the same temperature, $NaBH_4$ (250 mg, 6.58 mmol, 2.25 equiv) was added in one portion. The resulting mixture was stirred for 2 hours before it was diluted by MeOH (20 mL). The temperature was then allowed to increase to 0 °C followed by the addition of saturated aqueous Rochelle's salt solution (30 mL). The resulting miture was stirred at room temperature for 30 minutes before it was diluted by ethyl acetate (50 mL). The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (20 mL) three times. The combined organic layers were washed with 2 M aqueous NaOH (20 mL) for three times, saturated aqueous NH_4Cl (20 mL), and brine (20 mL), then dried over $MgSO_4$, filtered and concentrated. The resulting oil was purified by column chromatography (SiO_2, ethyl acetate/hexanes 20:80, 30:70, 50:50) to furnish diol (+)-**20** (1.62 g, 2.76 mmol, 95.0%) as a colorless oil. $[\alpha]_D^{20}$= +12.8 (*c* 1.0, $CHCl_3$); IR (film) 3388, 2929, 2857, 1655, 1472, 1363, 1255, 1095, 836, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.48 (s, 1H), 6.18 (s, 1H), 5.13 (q, *J* = 6.5 Hz, 1H), 4.93 (d, *J* = 7.0 Hz, 1H), 3.95 (brs, 1H), 3.81 (brs, 2H), 3.66 (brs, 2H), 3.21 (s, 3H), 3.13 (brs, 1H), 1.98 (d, *J* = 14.5 Hz, 1H), 1.88 (s, 3H), 1.86 (m, 1H), 1.64 (q, *J* = 6.0 Hz, 2H), 1.32–1.58 (m, 6H), 1.29 (dd, *J* = 6.5 Hz, 3H), 0.874 (s, 9H), 0.868 (s, 9H), 0.03 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.7, 151.1, 144.7, 133.1, 113.5, 75.0, 72.4, 69.4, 68.5, 60.2, 56.7, 43.0, 40.2, 38.5, 37.5, 26.2, 26.1, 21.0, 19.5, 18.5, 18.3, 17.9, −4.2, −4.4, −5.1; high resolution mass spectrum (ESI) m/z 586.3953 [$(M+H)^+$ calcd for $C_{30}H_{60}NO_6Si_2$].

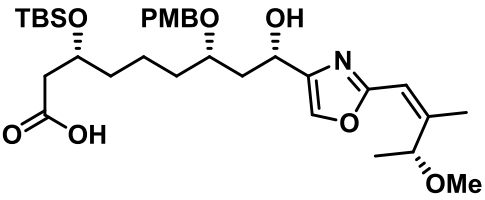


Alcohol (−)-**21**: To a solution of diol (+)-**20** (790 mg, 1.35 mmol, 1.0 equiv) in 20 mL of dichloromethane, CSA (30 mg, 0.13 mmol, 0.096 equiv) was added in one portion followed by addition of *p*-methoxybenzaldehyde dimethyl acetate (345 mg, 1.89 mmol, 1.4 equiv) at 0 °C under an air atmosphere. The resulting mixture was stirred for 10 minutes at the same temperature before addition of TBAF (1.0 M in THF, 10.80 mL, 10.80 mmol, 8.0 equiv) and acetic acid (473 mg, 6.75 mmol, 5.0 equiv). The resulting mixture was allowed to increase to room temperature and was allowed to stir for 16 hours before it was quenched with brine. The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (20 mL) twice. The combined organic layers were dried over $MgSO_4$, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO_2, ethyl acetate/hexanes 5:95, 10:90, 20:80) to furnish alcohol (−)-**21** (700 mg, 1.19 mmol, 88.0%) as a colorless oil. $[\alpha]_D^{20}$= −3.4 (*c* 1.6, $CHCl_3$); IR (film) 3435, 2929, 2856, 1615, 1518, 1463, 1368, 1336, 1250, 1171, 1112, 1035, 835, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.54 (s, 1H), 7.45 (d, *J* = 7.8 Hz, 2H), 6.88 (d, *J* = 7.8 Hz, 2H), 6.20 (s, 1H), 5.64 (s, 1H), 5.17 (q, *J* = 6.5 Hz, 1H), 4.92 (d, *J* = 11.0 Hz, 1H), 3.93 (brs, 2H), 3.81 (brs, 1H), 3.80 (s, 3H), 3.72 (brs, 1H), 3.22 (d, *J* = 1.0 Hz, 3H), 2.34 (brs, 1H), 2.00 (d, *J* = 12.8 Hz, 1H), 1.89 (s, 3H),

1.81 (m, 1H), 1.75 (m, 1H), 1.68 (m, 2H), 1.58 (m, 4H), 1.42 (m, 1H), 1.30 (d, J = 6.5 Hz, 3H), 0.89 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.5, 160.1, 150.6, 142.4, 133.9, 131.2, 127.6, 113.7, 113.6, 101.1, 76.8, 74.8, 72.9, 71.6, 60.3, 56.6, 55.4, 38.0, 36.9, 36.5, 36.1, 26.0, 21.0, 19.4, 18.1, 17.7, –4.3, –4.5; high resolution mass spectrum (ESI) m/z 590.3506 [$(M+H)^+$ calcd for $C_{32}H_{52}NO_7Si$].

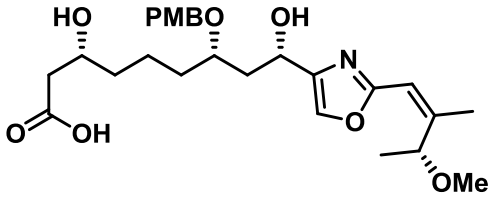


Carboxylic Acid (+)-**22**: To a solution of alcohol (–)-**21** (184 mg, 0.312 mmol, 1.0 equiv) in 2.5 mL of *t*-BuOH and 0.25 mL of pH 7 buffer solution, TEMPO solution (0.025 M in CH_3CN, 5 mL, 0.125 mmol, 0.4 equiv) was added at room temperature under an air atmosphere. The resulting mixture was stirred for 20 minutes at the same temperature before the subsequent addition of $NaClO_2$ (1 M in water, 0.624 mL, 0.624 mmol, 2.0 equiv) and NaClO (0.025 M in water, 12.5 mL, 0.312 mmol, 1.0 equiv) solution. The reaction was stirred at room temperature for 3 hours before it was quenched by saturated aqueous Na_2SO_3 (10 mL). After dilution with ethyl acetate (20 mL), the organic layer was separated, and the aqueous phase was extracted with ethyl acetate (20 mL) twice. The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO_2, ethyl acetate/hexanes 5:95, 10:90, 20:80, 30:70) to furnish carboxylic acid (+)-**22** (184 mg, 0.296 mmol, 95.0%) as a colorless oil. $[\alpha]_D^{20}$= +4.8 (*c* 1.0, $CHCl_3$); IR (film) 2930, 1711, 1518, 1250, 1114, 834, 776 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.55 (s, 1H), 7.45 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 6.23 (s, 1H), 5.64 (s, 1H), 5.15 (q, J = 6.5 Hz, 1H), 4.93 (d, J = 10.5 Hz, 1H), 4.14 (t, J = 5.4 Hz, 1H), 3.93 (brs, 1H), 3.80 (s, 3H), 3.23 (s, 3H), 2.50 (d, J = 6.1 Hz, 2H), 2.00 (d, J = 12.8 Hz, 1H), 1.89 (d, J = 1.5 Hz, 3H), 1.72 (m, 1H), 1.70 (m, 1H) , 1.59 (m, 4H), 1.45 (brs, 1H), 1.30 (d, J = 6.7 Hz, 3H), 0.87 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 176.4, 160.5, 160.0, 150.8, 142.3, 134.0, 131.2, 127.6, 113.7, 113.6, 101.1, 76.7, 75.0, 72.8, 69.4, 56.6, 55.4, 42.1, 37.4, 36.4, 36.0, 25.9, 20.8, 19.4, 18.1, 17.7, –4.4, –4.7; high resolution mass spectrum (ESI) m/z 626.3118 [$(M+Na)^+$ calcd for $C_{32}H_{49}NO_8SiNa$].

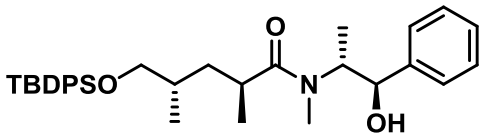


Carboxylic Acid (+)-**23**: To a solution of PMP acetal (+)-**22** (1.25 g, 2.07 mmol, 1.0 equiv) in 50 mL of dichloromethane, a DIBAL-H solution (1 M in hexanes, 9.93 mL, 9.93 mmol, 4.8 equiv) was

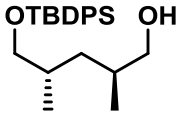
added dropwise at −78 °C under nitrogen atmosphere. The resulting mixture was stirred for 100 minutes at the same temperature before it was quenched with MeOH at −78 °C. The temperature was then allowed to increase to 0 °C followed by the addition of saturated aqueous Rochelle's salt (30 mL). The resulting mixture was stirred at room temperature for 30 minutes before it was diluted by ethyl acetate (50 mL). The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (30 mL) six times. The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated. The resulting oil was purified by column chromatography (SiO_2, ethyl acetate/hexanes 20:80, 30:70, 50:50, 80:20) to furnish carboxylic acid (+)-**23** (1.17 g, 1.93 mmol, 93.0%) as a colorless oil. $[\alpha]_D^{20}$= +32.4 (*c* 1.0, $CHCl_3$); IR (film) 2930, 1712, 1514, 1245, 1096, 836 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.43 (s, 1H), 7.26 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.19 (s, 1H), 5.11 (q, *J* = 6.5 Hz, 1H), 4.83 (dd, *J* =9.5 Hz, 2.9 Hz, 1H), 4.57 (d, *J* = 11.0 Hz, 1H), 4.39 (d, *J* = 11.0 Hz, 1H), 4.12 (m, 1H), 3.79 (s, 3H), 3.75 (m, 1H), 3.21 (s, 3H), 2.28 (d, *J* = 6.1 Hz, 2H), 2.05 (dt, *J* = 11.0 Hz, 3.5 Hz, 1H), 1.95 (m, 1H), 1.88 (s, 3H), 1.73 (m, 2H), 1.67 (m, 2H) , 1.42 (m, 2H), 1.29 (d, *J* = 6.5 Hz, 3H), 0.86 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 175.9, 160.7, 159.6, 150.8, 144.6, 133.5, 130.2, 129.8, 114.2, 113.6, 78.8, 75.0, 70.7, 69.4, 67.6, 56.6, 55.5, 42.2, 40.8, 37.7, 33.6, 26.0, 20.3, 19.5, 18.2, 17.8, −4.3, −4.6; high resolution mass spectrum (ESI) m/z 606.3466 [$(M+H)^+$ calcd for $C_{32}H_{52}NO_8Si$].



β-Hydroxyl Acid (+)-**5**: To a solution of carboxylic acid (+)-**23** (800 mg, 1.32 mmol, 1.0 equiv) in 30 mL of THF, TBAF (1.0 M in THF, 9.24 mL, 9.24 mmol, 7.0 equiv) was added dropwise followed by acetic acid (400 mg, 6.60 mmol, 5.0 equiv) at room temperature. The resulting mixture was stirred for 8 hours before it was quenched with brine. The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (20 mL) six times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO_2, ethyl acetate/hexanes 50:50, 80:20 then ethyl acetate: acetic acid 99:1) to furnish β-hydroxy acid (+)-**5** (569 mg, 1.16 mmol, 87.7%) as a colorless oil. $[\alpha]_D^{20}$= +56.2 (*c* 1.47, $CHCl_3$); IR (film) 3421, 2934, 1719, 1612, 1514, 1443, 1249, 1177, 1094, 1035, 822 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.46 (s, 1H), 7.26 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.21 (s, 1H), 5.03 (q, *J* = 6.5 Hz, 1H), 4.86 (dd, *J* = 9.3 Hz, 2.6 Hz, 1H), 4.58 (d, *J* = 11.0 Hz, 1H), 4.39 (d, *J* = 11.0 Hz, 1H), 4.04 (brs, 1H), 3.80 (s, 3H), 3.75 (brs, 1H), 3.21 (s, 3H), 2.50 (m, 2H), 2.13 (d, *J* = 14.3 Hz, 1H), 1.89 (m, 1H), 1.89 (s, 3H), 1.72 (m, 1H), 1.63 (m, 1H) , 1.38–1.58 (m, 4H), 1.29 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 176.1, 160.9, 159.5, 151.5, 144.2, 133.8, 130.2, 129.7, 114.1, 113.2, 79.1, 75.1, 70.5, 68.0, 67.4, 56.6, 55.4, 41.4, 40.7, 36.8, 33.3, 21.0, 19.5, 17.8; high resolution mass spectrum (ESI) m/z 490.2440 [$(M-H)^-$ calcd for $C_{26}H_{36}NO_8$].

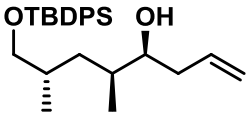


Amide S4: To a suspended solution of diisopropylamine (7.81 g, 77.2 mmol, 4.3 equiv) and flame dried LiCl (9.59 g, 226 mmol, 12.6 equiv) in 80 mL of THF, a *n*-BuLi solution (2.33 M in hexanes, 30.8 mL, 71.8 mmol, 4.0 equiv) was added dropwise over 15 minutes at 0 °C under a nitrogen atmosphere. The resulting mixture was stirred for 10 minutes at the same temperature before it was cooled to −78 °C. To the resulting mixture, amide (−)-**25** (8.35 g, 37.7 mmol, 2.1 equiv) in 80 mL of THF was then added dropwise at −78 °C over 30 minutes. The reaction mixture was then warmed to room temperature before the addition of iodide (−)-**24** (7.87g, 18.0 mmol, 1.0 equiv) in 30 mL of THF over 20 minutes. The resulting mixture was stirred overnight at room temperature before it was quenched by saturated aqueous NH_4Cl (30 mL) and diluted by EtOAc (200 mL). The organic layer was separated, and the aqueous phase was extracted with EtOAc (50 mL) twice. The combined organic layers were washed with saturated aqueous $NaHCO_3$ (30 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO_2, ethyl acetate/hexanes 90:10, 80:20, 60:40) to furnish amide **S4** with small amount of (−)-**25** derived impurity as an amorphous solid. The mixture was moved to next step without further purification [see the procedure for alcohol (−)-**26**].



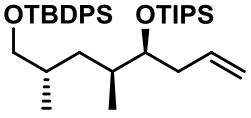
Alcohol (−)-26: To a solution of diisopropylamine (10.6 mL, 75.4 mmol, 4.2 equiv) in 60 mL of THF, a *n*-BuLi solution (2.33 M in hexanes, 30 mL, 70.0 mmol, 3.9 equiv) was added dropwise over 10 minutes at 0 °C under a nitrogen atmosphere. The resulting mixture was stirred for 15 minutes at the same temperature before the addition of ammonium-borane solid (2.22 g, 71.8 mmol, 4.0 equiv) in one portion at 0 °C. The temperature was increased to room temperature, and the reaction mixture was stirred for 30 minutes before it was recooled to 0 °C. A solution of amide **S4** (made from 18.0 mmol of iodide (−)-**24**, see the procedure for amide **S4**, 1.0 equiv) in 90 mL of THF was then added dropwise, and the temperature was allowed to increase to room temperature after the addition. The resulting mixture was stirred at the same temperature for 2 hours before it was slowly quenched with 100 mL of 3 N HCl aqueous solution over 20 minutes at 0 °C. The resulting mixture was stirred at 0°C for a further 30 minutes before the dilution with Et_2O (200 mL). The organic layer was separated, and the aqueous phase was extracted with Et_2O (50 mL) twice. The combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (30 mL), dried over $MgSO_4$, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO_2, ethyl acetate/hexanes 90:10, 80:20, 60:40) to furnish alcohol (−)-**26** (6.60 g, 17.81 mmol, 99.2% over 2 steps) as a colorless oil. $[\alpha]_D^{20} = -15.7$ (*c* 3.2, $CHCl_3$); IR (film) 3342, 2929, 2857, 1417, 1427, 1389, 1112, 1036, 824, 740, 701, 613.3 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ =7.72–7.65 (m, 4 H), 7.45–7.35 (m, 6H), 3.52–3.47 (m, 3H), 3.40 (m, 1H), 1.79 (m, 1H), 1.70 (m, 1H), 1.22 (ddd, *J* = 13.5 Hz, 9.0 Hz, 4. Hz), 1.14 (ddd, *J* = 13.5 Hz, 9.0 Hz, 4.5 Hz), 1.08 (s, 9H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 135.8, 134.3, 134.2, 129.7, 127.8, 68.8, 69.2, 37.0, 33.31, 33.26, 27.1, 19.5, 16.8, 16.6; high

resolution mass spectrum (ESI) m/z 371.2390 [(M+H)$^+$ calcd for $C_{23}H_{35}O_2Si$].



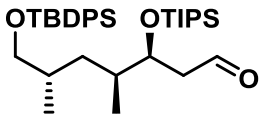
Olefin (−)-27: To a solution of alcohol (−)-**26** (6.50 g, 17.5 mmol, 1.0 equiv) in 70 mL dichloromethane, diisopropylethylamine (9.15 mL, 52.5 mmol, 3.0 equiv) and DMSO (6.21 mL, 87.5 mmol, 5.0 equiv) were added followed by portionwise addition of SO_3·pyridine (8.36 g, 52.5 mmol, 3.0 equiv) at 0 °C under an air atmosphere. The resulting mixture was stirred for 1 hour at the same temperature before it was quenched by 2 M $NaHSO_4$ aqueous solution (30 mL). The organic layer was separated, and the aqueous phase was extracted with Et_2O (50 mL) twice. The combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (30 mL), dried over $MgSO_4$, filtered and concentrated, and the resulting aldehyde was moved to the next step as a colorless oil without further purification.

To a solution of (−)-*B*-methoxydiisopinocampheylborane (9.41 g, 29.8 mmol, 1.7 equiv) in 50 mL Et_2O, allylmagnesium bromide solution (1.0 M in Et_2O, 21.87 mL, 21.87 mmol, 1.25 equiv) was added dropwise over 20 minutes at −78 °C under a nitrogen atmosphere. The resulting mixture was stirred for 1 hour at the same temperature. The temperature was allowed to increase to room temperature, and the reaction mixture was stirred for 1 hour before it was recooled to −78 °C. A solution of corresponding aldehyde of alcohol (−)-**26** (17.5 mmol, 1.0 equiv, crude) in 35 mL of Et_2O was then added dropwise to the reaction mixture at −78 °C over 20 minutes. The resulting mixture was stirred at the same temperature for 1 hour before the temperature was allowed to increase to 0 °C. A pH 7 buffer solution (30 mL) was then added followed by the careful addition of 30% aqueous H_2O_2 (7 mL) over 20 minutes at 0 °C. The resulting mixture was then stirred at room temperature overnight before it was diluted by Et_2O. The organic layer was separated, and the aqueous phase was extracted with Et_2O (60 mL) twice. The combined organic layers were washed with saturated aqueous NaS_2O_3 (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO_2, ethyl acetate/hexanes 10:90, 20:80, 30:70) to furnish olefin (−)-**27** (6.53 g, 15.93 mmol, 91.0% over 2 steps) as a colorless oil. $[\alpha]_D^{20}$= −13.4 (*c* 2.86, $CHCl_3$); IR (film) 3325, 3071, 2959, 2930, 2858, 1709, 1640, 1589, 1471, 1428, 1389, 1112, 914, 824, 702 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.68–7.62 (m, 4 H), 7.41–7.31 (m, 6H), 5.81 (dddd, *J* = 17.5 Hz, 9.7 Hz. 7.2 Hz, 6.5 Hz, 1H), 5.18–5.08 (m, 2H), 3.53–3.48 (m, 3H), 2.31–2.25 (m, 1H), 2.15 (m, 1H), 1.76 (brs, 1H), 1.62 (brs, 1H), 1.35–1.25 (m, 1H), 1.21–1.11 (m, 1H), 1.07 (s, 9H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.87 (d, *J* =6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 135.9, 135.7, 134.29, 134.27, 129.7, 127.8, 118.0, 74.7, 69.8, 39.2, 36.8, 35.3, 33.4, 27.1, 19.5, 16.7, 14.1; high resolution mass spectrum (ESI) m/z 411.2717 [(M+H)$^+$ calcd for $C_{26}H_{39}O_2Si$].



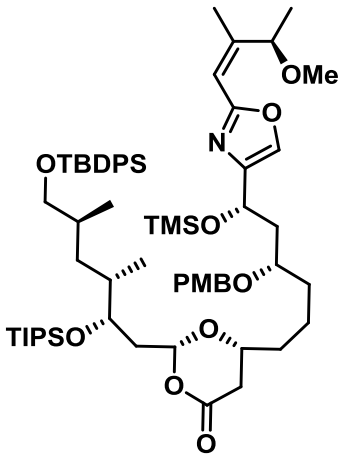
Olefin (−)-28: To a solution of olefin (−)-**27** (1.03 g, 2.51 mmol, 1.0 equiv) in 20 mL of dichloromethane at 0 °C under a nitrogen atmosphere, 2,6-lutidine (0.7 mL, 6.02 mmol, 2.4 equiv) was added, followed by the dropwise addition of TIPSOTf (0.80 g, 3.01 mmol, 1.2 equiv). The reac-

tion mixture was stirred for 2 hours at 0 °C before it was quenched by addition of saturated aqueous $NaHCO_3$ (10 mL). The organic layer was removed, and the aqueous layer was extracted with dichloromethane (10 mL) twice. The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated, the resulting oil was purified by column chromatography (SiO_2, ethyl acetate/hexanes 2:98, 5:95, 10:90) to furnish olefin (−)-**28** (1.29 g, 2.28 mmol, 90.7%) as a colorless oil. $[\alpha]_D^{20}$= −10.0 (c 2.22, $CHCl_3$); IR (film) 3072, 2942, 2865, 1463, 1428, 1388, 1112, 882, 824, 784, 701, 678, 613 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ =7.71–7.68 (m, 4 H), 7.43–7.36 (m, 6H), 5.78 (dddd, *J* = 17.2 Hz, 9.8 Hz. 7.2 Hz, 6.5 Hz, 1H), 5.04 (dd, *J* = 17.2 Hz, 1.8 Hz, 1H), 4.99 (dt, *J* = 9.8 Hz, 1.0 Hz, 1H), 3.79 (m,1H), 3.49 (m, 2H), 2.28 (m, 2H), 1.80–1.68 (m, 2H), 1.41 (td, *J* = 9.8 Hz, 4.0 Hz, 1H), 1.37 (td, *J* = 9.8 Hz, 4.0 Hz, 1H), 1.12–1.02 (m, 30 H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 136.1 135.87, 135.86, 134.39, 134.37, 129.7, 127.8, 116.6, 76.7, 70.0, 39.3, 36.4, 34.9, 33.5, 27.1, 19.5, 18.6, 18.5, 16.6, 13.9, 13.2; high resolution mass spectrum (ESI) m/z 589.3871 [$(M+Na)^+$ calcd for $C_{35}H_{58}O_2Si_2Na$.]



Aldehyde (−)-4: To a solution of olefin (−)-**28** (570 mg, 1.01 mmol, 1.0 equiv) in 35 mL of acetone/*tert*-butanol/water (3:3:1), NMO (357 mg, 3.0 mmol, 3.0 equiv) was added as one portion followed by potassium osmate(VI) dihydrate (30 mg, 0.08 mmol, 0.08 equiv) at 0 °C. The resulting mixture was stirred overnight at room temperature before it was quenched with 10 g of solid $Na_2S_2O_3$. The resulting heterogeneous mixture was stirred for a further 30 minutes before it was diluted by ethyl acetate (20 mL). The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (30 mL) three times. The combined organic layers were washed with saturated aqueous NH_4Cl (10 mL) and brine (5 mL), dried over $MgSO_4$, filtered and concentrated. The resulting diol was moved to the next step as a black oil without further purification.

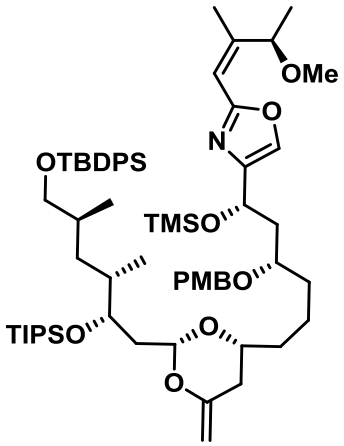
To a solution of the corresponding diol of (−)-**28** (1.01 mmol, crude) in 25 mL of acetone/water (4:1), $NaIO_4$ (750 mg, 3.50 mmol, 3.50 equiv) was added as one portion at room temperature under air atmosphere. The resulting mixture was stirred at the same temperature for three hours before it was diluted with ethyl acetate (30 mL). The organic layer was separated and the aqueous phase was extracted with ethyl acetate (20 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated, the resulting oil was purified by column chromatography (SiO_2, ethyl acetate/hexanes 2:98, 5:95, 10:90) to furnish aldehyde (−)-**4** (436 mg, 0.75 mmol, 75.0% over 2 steps) as a colorless oil. $[\alpha]_D^{20}$= −21.7 (*c* 1.75, $CHCl_3$); IR (film) 2943, 2865, 1727, 1463, 1427, 1389, 1112, 882, 824, 740, 702, 667 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 9.87 (t, *J* = 2.2 Hz, 1H), 7.71–7.68 (m, 4 H), 7.46–7.39 (m, 6H), 4.34 (m, 1H), 3.51 (d, *J* = 6.0 Hz, 2H), 2.54 (m, 2H), 1.82 (m, 1H), 1.73 (m, 1H), 1.39 (td, *J* = 13.0 Hz, 2.5 Hz, 1H), 1.27 (m, 1H), 1.09 (m, 30 H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 202.4, 135.8, 134.17, 134.15, 129.7, 127.3, 72.6, 70.0, 47.7, 36.8, 34.4, 33.3, 27.0, 19.4, 18.4, 18.3, 16.1, 15.2, 12.9; high resolution mass (ESI) m/z 591.3664 [$(M+Na)^+$ calcd for $C_{34}H_{56}O_3Si_2Na$].



Dioxanone (−)-**29**: To a solution of β–hydroxy acid (+)-**5** (58.0 mg, 0.118 mmol, 1.0 equiv) in 0.9 mL of THF, 0.6 mL of HMDS was added as one portion at room temperature under a nitrogen atmosphere. The resulting mixture was stirred for 22 hours at 40 to 45 °C before the HMDS/THF was removed under high vacuum (pressure < 5 Torr). The mixture was then azeotropically purified with toluene to remove the residual amount of HMDS, applying high vacuum with no access of air followed by stirring overnight at 40 to 45 °C under the same high vacuum conditions. The resulting tris-silylated ester was dissolved in 2 mL of dichloromethane before the addition of aldehyde (−)-**4** (80.0 mg, 0.138 mmol, 1.17 equiv) solution in 2 mL of dichloromethane at −78 °C under nitrogen atmosphere. TMSOTf (50.0 mg, 0.225 mmol, 1.90 equiv of a newly opened bottle purchased from Sigma-Aldrich®) was then added to the reaction mixture at −78 °C. The resulting mixture was stirred for 1 hour at −78 °C under a nitrogen atmosphere before allowing access to air via insertion of a needle (1.2 mm diameter) at −78 °C for 10 minutes to introduce small amount of moisture (H_2O). The reaction mixture was then stirred at −78 °C under a nitrogen atmosphere for 50 minutes before it was slowly diluted by 5 mL of dichloromethane at the same temperature. The resulting mixture was then quenched with 100 mg of 2,6-lutidine and attached to the high vacuum to partially remove solvent at 5 to 10 °C. The resulting solution (1 mL) was purified by column chromatography (SiO_2, ethyl acetate/hexanes, 10:90, 20:80) to furnish dioxanone (−)-**29** (125 mg, 0.112 mmol, 95.1%) as a colorless oil. $[\alpha]_D^{20}$ = −3.3 (*c* 1.15, $CHCl_3$); IR (film) 2930, 2864, 1752, 1513, 1463, 1428, 1388, 1250, 1112, 883, 824, 740, 702 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ = 7.81–7.79 (m, 4 H), 7.30 (d, *J* = 8.6 Hz, 2H), 7.27–7.24 (m, 7H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.16 (s, 1H), 5.58 (q, *J* = 6.5 Hz, 1H), 5.29 (q, *J* = 6.8 Hz, 1H), 5.08 (t, *J* = 6.4 Hz, 1H), 4.53 (d, *J* = 11.3 Hz, 1H), 4.42 (d, *J* = 11.3 Hz, 1H), 4.13 (m, 1H), 3.67 (m, 1H), 3.63–3.53 (m, 2H), 3.34 (s, 3H), 3.30–3.25 (m, 1H), 3.12 (s, 3H), 2.40–2.33 (m, 1H), 2.20–2.10 (m, 2H), 2.06–1.96 (m, 2H), 1.87–1.81 (m, 1H), 1.74 (d, *J* = 1.1 Hz, 3H), 1.48–1.25 (m, 6H), 1.39 (d, *J* = 6.5 Hz, 3H), 1.19 (s, 9H), 1.17–1.13 (m, 21 H), 1.12–1.05 (m, 3H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.92–0.89 (s, 1H), 0.83 (d, *J* = 6.7 Hz, 3H), 0.14 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ = 166.7, 161.3, 160.4, 152.3, 146.9, 136.7, 135.0, 134.3, 132.3, 130.6, 130.1, 129.2, 114.7, 113.9, 102.0, 76.0, 75.7, 75.1, 73.7, 71.4, 70.9, 66.9, 56.9, 55.4, 43.3, 40.1, 37.1, 36.9, 36.6, 35.22, 35.18, 34.3, 27.8, 21.4, 20.2, 20.0, 19.21, 19.15, 18.2, 16.9, 15.4, 13.0, 0.9; high resolution mass (ESI) m/z 1114.6652 [$(M+H)^+$ calcd for $C_{63}H_{100}NO_{10}Si_3$].

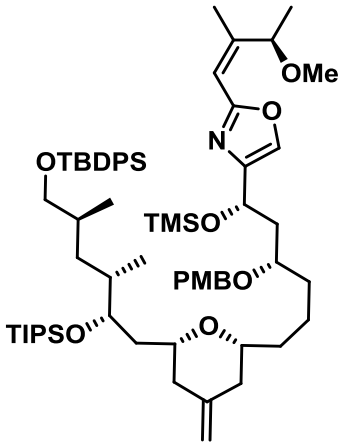
Note: Employing similar reaction conditions (HMDS, newly purchased/opened bottle of TMSOTf,

–78 °C), without introduction of air, gave the desired product in very low yield (<5%), with most of the starting materials, namely aldehyde (–)-**4** and a mixture of silylated (+)-**5** (mono-, bis-, or tris-) being recovered. Interestingly, the yield of the union reaction significantly increased (ca. 40–80%) through utilizing TMSOTf from frequently used bottles. This observation suggested that a trace amount of TfOH derived from TMSOTf facilitated the union. We therefore added a catalytic amount of either TfOH or H_2O to our reaction mixture at –78 °C. Unfortunately, the yield of desired product was unsatisfactory (5–25%); moreover no starting material could be recovered. The NMR analysis of multiple major by-products suggested that although the dioxanone moiety had been generated, an undesired loss of the TMS group or both the TMS and PMB groups had also occurred. The derived alcohol or diol then underwent further reactions with aldehyde (–)-**4** to form multiple complex by-products. This result confirmed that addition of TfOH was necessary but the substrates were sensitive under the acidic conditions utilizing measurable amount of TfOH or H_2O. Surprisingly however, slow introduction of moisture(H_2O) via simple exposure of the –78 °C reaction mixture to room temperature air via the insertion of a needle (1.2 mm diameter) for 5 to 10 minutes proved successful, and remarkably led to the desired product (–)-**29** in excellent yield (95%) as a single diastereomer, with no by-products observed! The possibilities of the involvement of other components of the introduced wet air, namely N_2 and O_2 gas, had been excluded through attempts of the union reaction in either dry N_2 or dry O_2 atmosphere (yield < 5%).



Enol Acetal (–)-**30**: To a solution of dioxanone (–)-**29** (200 mg, 0.180 mmol, 1.0 equiv) in 2.3 mL of THF in a glass microwave vial (2–5 mL), 0.08 mL of 2,6-lutidine was added followed by 2.4 mL of Petasis reagent (0.25 M in THF/toluene, freshly prepared, 0.60 mmol, 3.35 equiv) at room temperature under an air atmosphere. The resulting mixture was sealed and stirred for 3 hours at 100 °C in microwave at the "high" level of absorption setting before it was cooled down (three levels of absorption in Biotage microwave reactor: medium, high, very high). The resulting mixture was diluted by 20 mL of hexanes and stirred for 10 minutes before it was filtered and concentrated. The resulting oil was purified by column chromatography (SiO_2, ethyl acetate/hexanes, 5:95, 10:90) to furnish enol acetal (–)-**30** (174 mg, 0.157 mmol, 87.2%) as a colorless oil. $[\alpha]_D^{20} = -0.9$ (*c* 1.43, $CHCl_3$); IR (film) 2930, 2864, 1512, 1462, 1428, 1388, 1249, 1112, 883, 738, 702, 666 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ = 7.81–7.77 (m, 4 H), 7.31 (d, *J* = 8.6 Hz, 2H), 7.26–7.22 (m, 7H), 6.83 (d, *J* = 8.6 Hz, 2H), 6.15 (s, 1H), 5.59 (q, *J* = 6.5 Hz, 1H), 5.08 (q, *J* = 5.4 Hz, 1H), 4.93 (t, *J* = 5.9 Hz, 1H), 4.64 (s, 1H), 4.53–4.43 (m, 2H), 4.24 (brs, 1H), 4.10 (s, 1H), 3.72–3.67 (m, 1H), 3.61–3.53 (m, 2H), 3.48–3.44 (m, 1H), 3.31 (s, 3H), 3.12 (s, 3H), 2.40–2.33 (m, 1H), 2.17–2.06

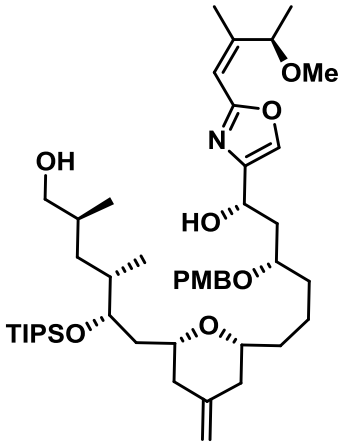
(m, 3H), 1.91–1.85 (m, 2H), 1.74 (s, 3H), 1.64–1.46 (m, 6H), 1.39 (d, J = 6.5 Hz, 3H) , 1.21–1.12 (m, 33H), 1.01 (d, J = 6.9 Hz, 3H), 0.98–0.94 (m, 1H), 0.89 (d, J = 6.7 Hz, 3H), 0.14 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ = 161.2, 160.3, 158.0, 152.1, 146.9, 136.7, 135.0, 134.2, 132.4, 130.5, 130.0, 129.1, 114.6, 113.9, 101.7, 93.6, 77.3, 76.2, 75.7, 74.0, 71.3, 70.8, 66.9, 56.8, 55.3, 43.3, 40.2, 37.1, 36.8, 35.87, 35.83, 35.3, 34.3, 27.8, 21.6, 20.2, 20.0, 19.24, 19.19, 18.2, 17.1, 15.2, 14.0, 0.9; high resolution mass (ESI) m/z 1112.6841 [(M+H)$^+$ calcd for $C_{64}H_{102}NO_9Si_3$].



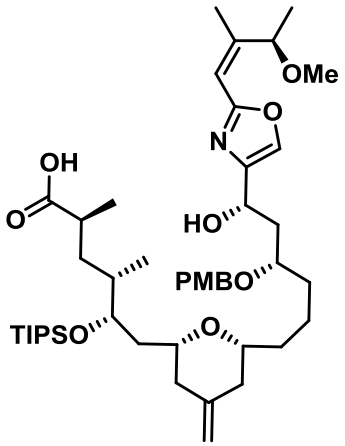
Methylene Tetrahydropyran (−)-31: To a solution of methyltriphenylphosphonium bromide (475 mg, 1.33 mmol) in 8 mL of THF, 2 mL of KO*t*-Bu solution (1.0 M solution in THF, 2.0 mmol) was added dropwise at 0 °C under a nitrogen atmosphere. The resulting mixture was stirred for 30 minutes at the same temperature to give the ylide solution (0.133 M in THF, 10 mL).

To a solution of enol acetal (−)-**30** (70 mg, 0.0629 mmol, 1.0 equiv) in 7 mL of THF, 0.31 mL of dimethylaluminum chloride solution (1.0 M in hexanes, newly opened, 0.31 mmol, 4.9 equiv) was added over 3 seconds at −78 °C under a nitrogen atmosphere. The resulting mixture was stirred for 30 seconds at −78 °C before the addition of freshly prepared ylide solution (0.133 M in THF, 4.2 mL, 0.559 mmol, 8.9 equiv) at the same temperature. The resulting mixture was stirred for a further 10 minutes at −78 °C before it was quenched by 10 mL of saturated aqueous NH_4Cl solution. The resulting mixture was diluted by 20 mL of ethyl acetate. The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (10 mL) twice. The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO_2, ethyl acetate/hexanes 2:98, 5:95, 10:90) to furnish methylene tetrahydropyran (−)-**31** (59 mg, 0.0531 mmol, 84.4%) as a colorless oil. $[\alpha]_D^{20}$= −4.1 (*c* 0.83, $CHCl_3$); IR (film) 2930, 2864, 1589, 1513, 1462, 1428, 1388, 1249, 1112, 883, 740, 702 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ = 7.83–7.80 (m, 4 H), 7.35 (d, J = 8.5 Hz, 2H), 7.28–7.23 (m, 7H), 6.86 (d, J = 8.5 Hz, 2H), 6.16 (s, 1H), 5.63 (q, J = 6.5 Hz, 1H), 5.14 (t, J = 6.2 Hz, 1H), 4.76 (d, J = 4.3 Hz, 2H), 4.53 (d, J = 5.9 Hz, 2H), 4.28–4.25 (m, 1H), 3.80–3.73 (m, 1H), 3.66–3.56 (m, 3H), 3.32 (s, 3H), 3.32–3.29 (m, 1H), 3.13 (s, 3H), 2.44–2.37 (m, 1H), 2.25–2.19 (m, 1H), 2.14 (d, J = 13.1Hz, 2H) 2.01 (d, J = 11.7 Hz, 1H), 1.92 (t, J = 11.7 Hz, 2H), 1.82–1.70 (m, 3H), 1.75 (d, J = 1.2 Hz, 3H), 1.72–1.62 (m, 2H), 1.60–1.53 (m, 2H), 1.44 (d, J = 6.3 Hz, 3H) , 1.25–1.12 (m, 33H), 1.03 (d, J = 6.6 Hz, 3H), 0.95–0.91 (m, 1H), 0.91 (d, J = 7.3 Hz, 3H), 0.17 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ = 160.6, 159.7, 151.5, 146.5, 145.6, 136.1, 134.6, 133.7, 132.0, 130.0, 129.5, 128.6, 114.0, 113.4, 108.4, 78.6, 75.8, 75.5, 75.2, 74.5, 70.8, 70.6, 66.4, 56.3, 54.8, 42.9, 42.2, 41.3, 40.4, 37.3 36.8, 35.0, 34.1, 33.8, 27.2, 21.8, 19.6, 19.5, 18.8, 18.7,

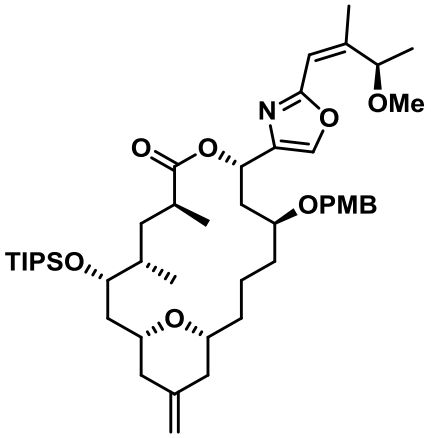
17.7, 16.3, 15.5, 13.6, 0.4; high resolution mass (ESI) m/z 1110.7103 [(M+H)$^+$ calcd for $C_{65}H_{105}NO_8Si_3$].



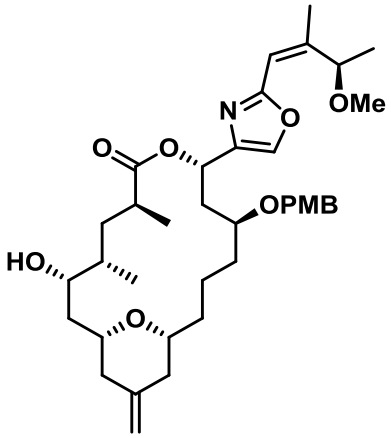
Diol (+)-**S5**: To a solution of methylene tetrahydropyran (−)-**31** (47.0 mg, 0.0424 mmol, 1.0 equiv) in 16.5 mL of THF/H_2O (45:1), 18-crown-6 (550 mg, 2.08 mmol, 49.0 equiv) was added followed by KOH (420 mg, 7.49 mmol, 177 equiv) at room temperature. The resulting mixture was stirred for 3 hours at the same temperature before it was quenched by the addition of saturated aqueous NH_4Cl solution (10 mL). The resulting mixture was diluted by 20 mL of ethyl acetate. The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (10 mL) twice. The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO_2, ethyl acetate/hexanes 30:70, 40:60, 50:50) to furnish diol (+)-**S5** (28.4 mg, 0.0355 mmol, 83.7%) as a colorless oil. $[\alpha]_D^{20}$= +3.1 (*c* 1.5, $CHCl_3$); IR (film) 2932, 2864, 1727, 1514, 1463, 1249, 1092 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.44 (s, 1H), 7.26 (d, *J* = 8.1 Hz, 2H), 6.87 (d, *J* = 8.1 Hz, 2H), 6.18 (s, 1H), 5.12 (q, *J* = 6.5 Hz, 1H), 4.83 (d, *J* = 8.7 Hz, 1H), 4.68 (s, 2H), 4.60 (d, *J* = 10.9 Hz, 1H), 4.39 (d, *J* = 10.9 Hz, 1H), 3.98 (brs, 1H), 3.79 (s, 3H), 3.79–3.77 (brs, 1H), 3.52–3.47 (m, 1H), 3.42–3.39 (m, 1H), 3.34 (t, *J* = 10.1 Hz, 1H), 3.20 (s, 3H), 3.20–3.17 (m, 1H), 2.18 (d, *J* = 12.6 Hz, 1H), 2.15–2.03 (m, 2H), 1.99–1.87 (m, 3H), 1.87 (s, 3H), 1.80–1.73 (brs, 1H), 1.70–1.59 (m, 4H), 1.59–1.50 (m, 2H), 1.49–1.40 (m, 3H), 1.32–1.25 (m, 1H), 1.29 (d, *J* = 6.4 Hz, 3H), 1.20 (m, 1H), 1.11–0.99 (m, 21H), 0.87 (d, *J* = 6.5 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.6, 159.6, 150.4, 145.2, 144.8, 133.4, 130.2, 129.8, 114.2, 113.8, 108.4, 79.3, 78.3, 75.6, 75.0, 74.1, 70.5, 69.4, 68.3, 56.6, 55.5, 41.9, 41.0, 40.3, 36.9, 36.2, 34.3, 33.7, 33.4, 20.9, 19.5, 18.6, 18.51, 18.48, 17.8, 16.2, 15.0, 13.3; high resolution mass (ESI) m/z 800.5486 [(M+H)$^+$ calcd for $C_{46}H_{78}NO_8Si$].



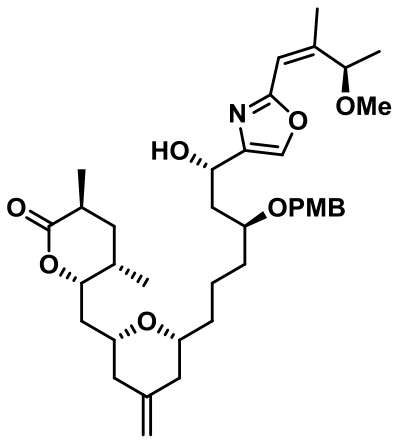
Carboxylic Acid (+)-**32:** To a solution of diol (+)-**S5** (15.8 mg, 0.0199 mmol, 1.0 equiv) in 0.5 mL of *t*-BuOH and 0.2 mL of pH 7 buffer solution, TEMPO solution (0.025 M in CH_3CN, 0.88 mL, 0.022 mmol, 1.1 equiv) was added at room temperature under an air atmosphere. The resulting mixture was stirred for 20 minutes at the same temperature before the subsequent addition of $NaClO_2$ (1 M in water, 0.068 mL, 0.0677 mmol, 3.4 equiv) and NaClO (0.025 M in water, 1.44 mL, 0.036 mmol, 1.8 equiv) solution. The reaction was stirred at room temperature for 3 hours before it was quenched by saturated aqueous $Na_2S_2O_3$ solution (3 mL), after dilution with ethyl acetate (5 mL), the organic layer was separated, and the aqueous phase was extracted with ethyl acetate (5 mL) twice. The combined organic layers were washed with brine (2 mL), dried over $MgSO_4$, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO_2, ethyl acetate/hexanes 20:80, 30:70, 50:50, 80:20) to furnish acid (+)-**32** (12.1 mg, 0.0149 mmol, 74.7%) as a colorless oil. $[\alpha]_D^{20}$= +3.1 (*c* 0.3, $CHCl_3$); IR (film) 2926, 2865, 1735, 1707, 1514, 1463, 1381, 1248, 883, 821, 666 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.46 (s, 1H), 7.27 (d, *J* = 8.1 Hz, 2H), 6.87 (d, *J* = 8.1 Hz, 2H), 6.22 (s, 1H), 5.03 (q, *J* = 6.5 Hz, 1H), 4.89 (d, *J* = 8.8 Hz, 1H), 4.68 (d, *J* = 6.0 Hz, 2H), 4.61 (d, *J* = 11.2 Hz, 1H), 4.40 (d, *J* = 11.2 Hz, 1H), 3.98 (t, *J* = 6.5 Hz, 1H), 3.80 (s, 3H), 3.80–3.77 (brs, 1H), 3.27–3.20 (m, 1H), 3.21 (s, 3H), 3.20–3.13 (m, 1H), 2.48 (m, 1H), 2.21–2.10 (m, 3H), 2.01–1.97 (m, 1H), 1.89 (s, 3H), 1.89–1.87 (m, 1H). 1.78–1.65 (m, 5H), 1.61–1.50 (m, 5H), 1.48–1.35 (m, 2H), 1.29 (d, *J* = 6.5 Hz, 3H), 1.30–1.25 (m, 1H), 1.20–1.14 (m, 4H) 1.11–1.03 (m, 19H), 1.02–0.93 (m, 1H), 0.87 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 180.4, 160.9, 159.5, 151.1, 145.0, 144.5, 133.7, 130.1, 129.7, 114.1, 113.4, 108.4, 79.7, 78.6, 75.9, 75.0, 73.3, 70.5, 68.0, 56.6, 55.4, 42.0, 41.2, 41.0, 40.8, 37.9, 36.8, 36.6, 36.3, 33.7, 21.6, 19.5, 18.5, 18.4, 18.0, 17.8, 14.6, 13.3; high resolution mass (ESI) m/z 814.5298 [$(M+H)^+$ calcd for $C_{46}H_{76}NO_9Si$].



Macrolide (+)-33: To a solution of carboxylic acid (+)-32 (24 mg, 0.030 mmol, 1.0 equiv) in 0.75 mL of THF, Hunig's base (0.06 mL) was added followed by 2,4,6-trichlorobenzoyl chloride (54 mg, 0.22 mmol, 7.5 equiv) at room temperature under a nitrogen atmosphere. The resulting mixture was stirred for 3 hours at the same temperature before it was diluted by toluene (3 mL). This resulting activated macrolide precursor solution was stored at room temperature for further use. To a solution of DMAP (120 mg, 0.98 mmol, 33 equiv) in 30 mL of toluene, the activated macrolide precursor solution was slowly added using a syringe pump over 5 hours at reflux temperature under a nitrogen atmosphere. The resulting mixture was stirred for a further 12 hours at the same temperature before it was cooled to room temperature. The resulting mixture was filtered and concentrated, the resulting mixture was purified by column chromatography (SiO_2, ethyl acetate: hexanes 5:95, 10:90, 20:80) to give the crude macrolide, which was then purified by PTLC (SiO_2, ethyl acetate/hexanes 10:90) to furnish macrolide (+)-33 (20.8 mg, 0.0261 mmol, 88.5%) as a colorless oil. $[\alpha]_D^{20}$= +10.3 (*c* 0.33, $CHCl_3$); IR (film) 2927, 2856, 1750, 1653, 1613. 1577, 1548, 1513, 1464, 1378, 1248, 1160, 1097, 883, 820, 666 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.44 (s, 1H), 7.30 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.20 (s, 1H), 5.96 (dd, *J* = 12.6 Hz, 2.6 Hz, 1H), 5.20 (q, *J* = 6.5 Hz, 1H), 4.70 (s, 2H), 4.64 (d, *J* = 10.9 Hz, 1H), 4.43 (d, *J* = 10.9 Hz, 1H), 4.12 (dd, *J* = 11.1 Hz, 4.1 Hz, 1H), 3.81 (s, 3H), 3.42 (t, *J* = 10.0 Hz, 1H), 3.30 (t, *J* = 11.1 Hz, 1H), 3.21 (s, 3H), 3.10 (t, *J* = 9.2 Hz, 1H), 2.73 (td, *J* = 13.3 Hz, 3.5 Hz, 1H), 2.69–2.63 (m, 1H), 2.13–2.03 (m, 3H), 1.99–1.93 (m, 1H), 1.91 (d, *J* = 1.3 Hz, 3H), 1.89–1.85 (m, 1H). 1.83–1.70 (m, 4H), 1.66–1.58 (m, 4H), 1.50–1.55 (m, 1H), 1.48–1.35 (m, 2H), 1.31 (d, *J* = 6.6 Hz, 3H), 1.30–1.25 (m, 2H), 1.14 (d, *J* = 6.8 Hz, 3H) 1.12–1.05 (m, 19H), 0.95–0.90 (m, 1H), 0.85 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 175.0, 160.7, 159.5, 151.4, 145.0, 141.3, 134.0, 130.9, 129.7, 114.1, 113.4, 108.7, 76.1, 75.9, 75.0, 74.5, 71.8, 71.3, 65.0, 56.7, 55.5, 42.5, 41.8, 41.5, 39.2, 38.6, 37.6, 35.2, 34.5, 31.6, 20.8, 19.4, 18.6, 18.5, 18.1, 17.9, 14.3, 13.4; high resolution mass (ESI) m/z 796.5194 [$(M+H)^+$ calcd for $C_{46}H_{74}NO_9Si$].

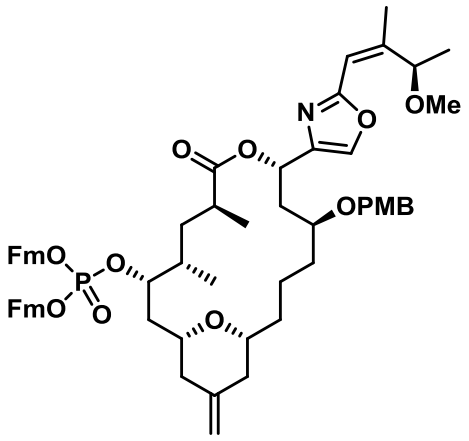


Alcohol (+)-**34**: To a solution of TIPS ether (+)-**33** (9.0 mg, 0.0113 mmol, 1.0 equiv) in 3.5 mL of THF in a plastic container, pyridine (3.9 mL) was added followed by HF/pyridine complex (1.0 mL) at room temperature in an air atmosphere. The resulting mixture was stirred for 48 hours at 45 °C before it was quenched slowly with saturated aqueous $NaHCO_3$ (12.0 mL) at room temperature. The resulting mixture was diluted with ethyl acetate (20 mL). The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (8 mL) twice. The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated, the resulting mixture was purified by column chromatography (SiO_2, ethyl acetate/hexanes, 30:70. 40:60, 50:50) to furnish alcohol (+)-**34** (5.1 mg, 0.0080 mmol, 70.5%) as a colorless oil. $[\alpha]_D^{20}$= +4.9 (*c* 0.42, $CHCl_3$); IR (film) 2917.8, 2849.3, 1708.1, 1552.4, 1513.4, 1463.2, 1378.4, 1149.9, 1096.8, 807.1, 720.3 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.49 (s, 1H), 7.27 (d, *J* = 8.1 Hz, 2H), 6.87 (d, *J* = 8.1 Hz, 2H), 6.20 (s, 1H), 5.84 (dd, *J* = 12.6 Hz, 2.6 Hz, 1H), 5.16 (q, *J* = 6.5 Hz, 1H), 4.68 (s, 2H), 4.60 (d, *J* = 10.9 Hz, 1H), 4.41 (d, *J* = 10.9 Hz, 1H), 3.80 (s, 4H), 3.47 (t, *J* = 10.4 Hz, 1H), 3.30 (q, *J* = 10.4 Hz, 2H), 3.23 (s, 3H), 2.75 (td, *J* = 12.6 Hz, 3.2 Hz, 1H), 2.70–2.64 (m, 1H), 2.13 (d, *J* = 13.5 Hz, 2H), 2.04–1.95 (m, 2H), 1.90 (s, 3H), 1.86–1.76 (m, 3H), 1.76–1.60 (m, 5H), 1.48–1.33 (m, 4H), 1.30 (d, *J* = 6.4 Hz, 3H), 1.18 (d, *J* = 6.5 Hz, 3H), 0.85 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 175.9, 160.6, 159.4, 151.2, 145.0, 140.6, 134.7, 130.7, 129.7, 114.0, 113.4, 108.5, 76.1, 75.7, 75.03, 74.95, 71.0, 68.9, 65.8, 56.7, 55.4, 41.9, 41.7, 41.5, 38.0, 37.0, 36.5, 35.4, 33.8, 31.6, 21.1, 19.4, 17.8, 16.7, 13.1; high resolution mass (ESI) m/z 640.3849 [$(M+H)^+$ calcd for $C_{37}H_{54}NO_8$].

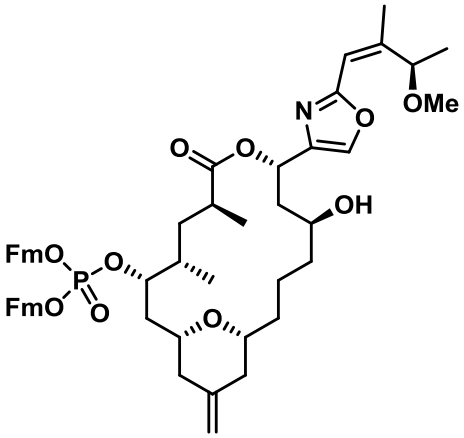


δ-Lactone (−)-**S6**: δ-lactone (−)-**S6** was isolated as a by-product of TIPS removal reaction of macro-

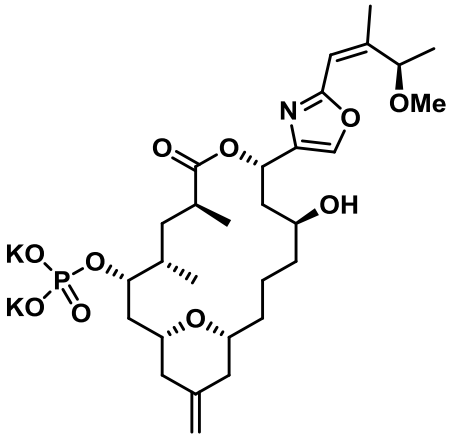
lide (+)-33. $[\alpha]_D^{20}$= −3.5 (*c* 0.7, $CHCl_3$); IR (film) 2923, 2852, 1738, 1553, 1514, 1463, 1379, 1249, 1174, 1099, 1036, 804 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.45 (s, 1H), 7.27 (d, *J* = 8.3 Hz, 2H), 6.88 (d, *J* = 8.3 Hz, 2H), 6.18 (s, 1H), 5.13 (q, *J* = 6.5 Hz, 1H), 4.83 (d, *J* = 9.0 Hz, 1H), 4.71 (s, 2H), 4.62 (d, *J* = 5.5 Hz, 1H), 4.60 (d, *J* = 10.9 Hz, 1H), 4.41 (d, *J* = 10.9 Hz, 1H), 3.98 (s, 1H), 3.80 (s, 4H), 3.57 (t, *J* = 10.4 Hz, 1H), 3.30–3.24 (m, 1H), 3.21 (s, 3H), 2,63–2.57 (m, 1H), 2.22–2.18 (m, 2H), 2.07 (d, *J* = 14.3 Hz, 1H), 2.06–1.98 (m, 1H), 1.98–1.82 (m, 3H), 1.90 (s, 3H), 1.75–1.52 (m, 5H), 1.51–1.42 (m, 4H), 1.32 (d, *J* = 6.4 Hz, 3H), 1.26 (d, *J* = 6.5 Hz, 3H), 1.01 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 174.8, 160.6, 159.6, 150.5, 144.9, 144.3, 133.4, 130.2, 129.8, 114.2, 113.8, 109.1, 80.3, 79.2, 78.2, 75.0, 74.2, 70.5, 68.2, 56.7, 55.5, 41.5, 41.02, 40.98, 40.0, 36.7, 36.0, 33.5, 31.5, 30.6, 20.7, 19.5, 18.1, 17.8, 11.9; high resolution mass (ESI) m/z 640.3859 [$(M+H)^+$ calcd for $C_{37}H_{54}NO_8$].



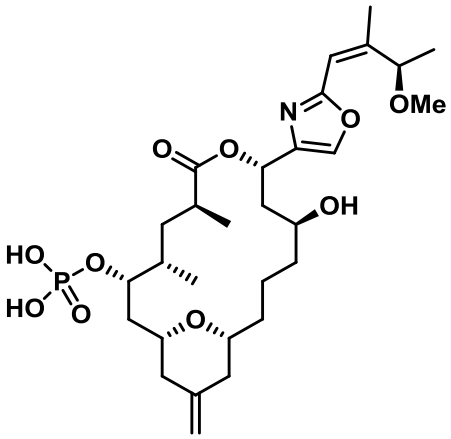
Phosphoric Ester S7: To a solution of alcohol (+)-**34** (3.5 mg, 0.0055 mmol, 1.0 equiv) in 0.2 mL of acetonitrile, 1*H*-tetrazole solution (0.45 M in acetonitrile, 0.195 mL, 0.088 mmol, 16.0 equiv) was added followed by *i*-$Pr_2NP(OFm)_2$ solution (57.5 mg in 0.2 mL dichloromethane, 0.110 mmol, 20.0 equiv) at room temperature in an argon atmosphere. The resulting mixture was stirred for 50 minutes at the same temperature before it was cooled to 0 °C. 0.2 mL of H_2O_2 solution (50% in water) was added to the reaction mixture at 0 °C, allowing the resulting mixture to be stirred at the same temperature for 30 minutes. The resulting mixture was quenched by saturated aqueous $NaHCO_3$ (3.0 mL) at room temperature. The resulting mixture was diluted by ethyl acetate (5 mL). The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (3 mL) twice. The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated, and the resulting mixture was purified by column chromatography (SiO_2, ethyl acetate/hexanes, 40:60, 50:50, 60:40) to furnish phosphorus ester S7 together with inseparable phosphate impurity as a colorless oil. The mixture was moved to next step without further purification [see the procedure for alcohol (−)-**35**].



Alcohol (−)-35: To a solution of phosphoric ester **S7** [made from 0.0055 mmol of alcohol (+)-**24**, see the procedure for phosphoric ester **S7**, 1.0 equiv] in CH_2Cl_2/pH 7 aqueous buffer solution (4.4 mL, 10:1), DDQ (8.0 mg) was added in one portion at room temperature. The resulting mixture was stirred for 30 minutes at the same temperature before it was diluted by diethyl ether (10 mL). The organic layer was separated, and the aqueous phase was extracted with diethyl ether (2 mL) twice. The combined organic layers were washed with brine (1 mL), dried over $MgSO_4$, filtered and concentrated, and the resulting mixture was purified by column chromatography (SiO_2, ethyl acetate/hexanes, 50:50, 60:40, 80:20) to furnish alcohol (−)-**35** (3.2 mg, 0.00334 mmol, 61.0% over two steps) as a colorless oil. $[\alpha]_D^{20} = -4.00$ (*c* 0.6, $CHCl_3$); IR (film) 2925, 2853, 1729, 1555, 1451, 1381, 1252, 1076, 1012, 741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.76–7.68 (m, 4H), 7.56–7.49 (m, 3H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.41–7.31 (m, 4H), 7.39 (s, 1H), 7.30–7.20 (m, 4H), 6.16 (s, 1H), 5.98 (dd, *J* = 11.8 , 3.1 Hz, 1H), 5.18 (q, *J* = 6.5 Hz, 1H), 4.72 (d, *J* = 3.1 Hz, 2H), 4.60 (m, 1H), 4.30–4.23 (m, 2H), 4.23–4.15 (m, 2H), 4.15–4.10 (m, 2H), 3.63 (brt, *J* = 9.2 Hz, 1H), 3.30 (t, *J* = 10.7 Hz, 1H), 3.22 (s, 1H), 3.07 (t, *J* = 9.1 Hz, 1H), 2.71 (m, 1H), 2.49 (m, 1H), 2.10 (d, *J* = 13.5 Hz, 1H), 2.03 (d, *J* = 13.5 Hz, 1H), 1.94–1.82 (m, 2H), 1.89 (s, 3H), 1.75 (dd, *J* = 13.5, 4.4 Hz, 2H), 1.72–1.60 (m, 4H), 1.86–1,76 (m, 3H), 1.47–1.39 (m, 2H), 1.39–1.30 (m, 2H), 1.28 (d, *J* = 6.4 Hz, 3H), 1.09 (m, 1H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 174.4, 160.7, 151.6, 144.6, 143.38, 143.35, 143.32, 143.29, 141.5, 141.2, 133.9, 128.13, 128.11, 128.09, 127.38, 127.36, 127.31, 125.4, 125.3, 125.24, 125.22, 120.32, 120.27, 120.25, 113.2, 108.9, 78.81, 78.75, 75.1, 75.0, 74.6, 69.55, 69.48, 69.43, 69.21, 69.17, 64.9, 56.7, 48.23, 48.21, 48.18, 48.14, 42.0, 41.5, 41.4, 39.0, 38.4, 38.2, 35.2, 33.8, 33.7, 33.1, 20.9, 19.4, 17.9, 17.8, 14.3; ^{31}P NMR (202 MHz, $CDCl_3$) δ = −1.53; high resolution mass (ESI) m/z 956.4521 [$(M+H)^+$ calcd for $C_{57}H_{67}NO_{10}P$].

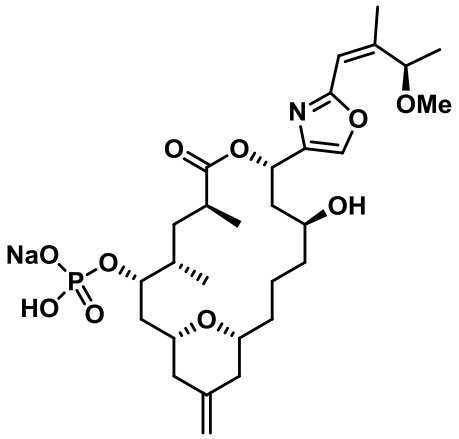


Enigmazole A (Dipotassium Phosphate Form) (−)-36: To a solution of phosphoric ester (−)-**35** (1 mg, 0.001 mmol, 1.0 equiv) in 0.33 ml of MeOH/H_2O (10:1), 2.9 mg of K_2CO_3 was added at room temperature. The resulting mixture was stirred for 6 hours at the same temperature, at which time C18 TLC indicated the completion of the reaction. The mixture was diluted with H_2O (0.7 mL) before it was extracted with pentane (0.5 mL) for three times. The resulting mixture was purified by a C18 silica column chromatography (0.4 g of 40–75 μm, 70 Å, C18 silica gel, purchased from Sorbent Technology, was packed into a Fisherbrand 9-inch Pasteur pipet, 100% H_2O then 2:3 H_2O/MeOH) to give 0.3 mg of enigmazole A (−)-**36** (dipotassium phosphate form). $[\alpha]_D^{20}$= −0.8 (*c* 0.03, MeOH) Dipotassium phosphate (−)-**36** displayed the same ^{1}H NMR spectrum as the disodium phosphate (−)-**37** [see the NMR data for(−)-**37**].

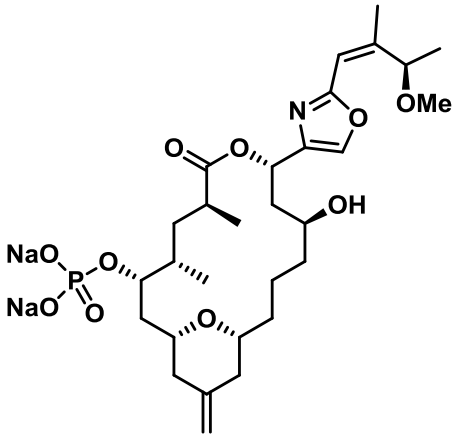


Enigmazole A (Free Acid Form) (−)-1: To a solution of phosphorus ester (−)-**35** (2.0 mg, 0.0021 mmol, 1.0 equiv) in 0.4 ml of MeOH/H_2O (2:1), 6 mg of Na_2CO_3 was added at room temperature. The resulting mixture was stirred for 24 hours at the same temperature before the addition of CD_3COOD (15 mg). The resulting mixture then stirred at the same temperature for 10 minutes before it was extracted with pentane (0.5 mL) for three times. The solvent and CD_3COOD was removed under high vaccum from the mixture to furnish enigmazole A (−)-**1** together with CD_3COONa. The further purification was achieved by RP HPLC (Vydac™ 5 μm C18, 250*10 mm, 5% MeCN/95% H_2O with 0.1% TFA to 40% MeCN/60% H_2O with 0.1% TFA linear gradient over 15 min, then 40% MeCN/60% H_2O with 0.1% TFA for 15 min, 10 mL/min, λ = 261 nm) to give enigmazole A free acid form (1.4 mg, 0.0020 mmol, 95.0%) as a colorless oil. $[\alpha]_D^{20}$= −1.7 (*c* 0.2, MeOH); UV (MeCN/H_2O, 0.5% TFA) λ_{max} 261 nm; ^{1}H NMR (500 MHz, CD_3OD) δ = 7.70 (s, 1H), 6.21 (s, 1H), 5.97 (dd, *J* = 12.8, 2.2 Hz, 1H), 5.24 (q, *J* = 6.5 Hz, 1H), 4.72 (s, 2H),

4.58 (m, 1H), 3.58 (td, *J* = 10.1 Hz, 3.0 Hz, 1H), 3.20 (s, 3H), 3.14 (m, 1H), 2.87 (m, 1H), 2.51 (td, J = 13.7 Hz, 3.8 Hz, 1H), 2.20–2.13 (m, 2H), 2.01–1.94 (m, 3H), 1.89 (d, *J* = 1.2 Hz, 3H), 1.86–1.83 (m, 1H), 1.78–1.70 (m, 4H), 1.69–1.60 (m, 2H), 1.48 (q, *J* = 12.4 Hz, 1H), 1.44–1.37 (m, 1H), 1.37–1.30 (m, 1H), 1.26 (d, *J* = 6.6 Hz, 3H), 1.11 (d, *J* = 6.7 Hz, 3H), 1.05–1.01 (m, 1H), 0.98 (d, *J* = 5.9 Hz, 1H) ^{13}C NMR (125 MHz, CD_3OD) δ = 176.2, 161.9, 152.8, 146.2, 142.2, 136.0, 114.0, 109.0, 77.8 (d, *J* = 5.8 Hz), 76.9, 76.2, 75.9, 69.8, 65.9, 56.8, 43.0, 42.6, 42.4, 40.1, 39.6, 39.2, 36,1, 34.6 (d, *J* = 5.2 Hz), 33.6, 21.9, 19.5, 18.1, 17.7, 15.6.



Enigmazole A (**Monophosphate Form**) (**–**)-**38**: To the neat phosphoric acid (–)-**1** (1.4 mg) in a 3 mm glass NMR tube, 0.2 mL of saturated $NaHCO_3/CD_3OD$ solution was added to furnish monophosphate (–)-38 in CD_3OD solution. $[\alpha]_D^{20}$= –2.1 (*c* 0.2, MeOH); IR (film) 3411 (br) 2934, 2851, 1681, 1538, 1438, 1382, 1208, 1139, 1080, 967, 909, 726, 653 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ = 7.68 (s, 1H), 6.21 (s, 1H), 5.95 (dd, *J* = 12.8, 2.5 Hz, 1H), 5.24 (q, *J* = 6.5 Hz, 1H), 4.70 (d, *J* = 1.5 Hz, 1H), 4.69 (d, *J* = 1.5 Hz, 1H), 4.42 (m, 1H), 3.62 (td, *J* = 10.1 Hz, 2.9 Hz, 1H), 3.20 (s, 3H), 3.12 (dd, *J* = 10.2 Hz, 8.9 Hz, 1H), 2.98 (m, 1H), 2.50 (td, *J* = 13.4 Hz, 3.9 Hz, 1H), 2.21 (d, *J* =12.8 Hz, 1H), 2.13 (d, *J* = 12.8 Hz, 1H). 2.10 (m, 1H), 1.97 (t, *J* = 12.2, 1H), 1.89 (s, 3H), 1.88–1.83 (m, 3H), 1.80–1.72 (m, 3H), 1.66–1.60 (m, 2H), 1.54 (q, *J* = 12.4 Hz, 1H), 1.39 (t, *J* = 11.3 Hz, 1H), 1.37 (t, *J* = 11.1 Hz, 1H), 1.26 (d, *J* = 6.4 Hz, 3H), 1.10 (d, *J* = 6.6 Hz, 3H), 1.02 (td, *J* = 12.0 Hz, 2.6 Hz, 1H), 0.97 (d, *J* = 6.6 Hz, 1H) ^{13}C NMR (125MHz, CD_3OD) δ = 176.5, 161.9, 152.7, 146.6, 142.4, 136.0, 113.9, 108.6, 77.6, 76.2, 75.7, 75.2 (d, *J* = 6.4 Hz), 69.8, 65.7, 56.8, 43.0, 42.6, 42.5, 40.1, 39.6, 39.3, 36,2, 34.7 (d, *J* = 6.6 Hz), 33.6, 21.8, 19.4, 18.3, 17.7, 15.0; ^{31}P (202 MHz, CD_3OD) δ = 1.45; high resolution mass (ESI) m/z 598.2759 [$(M-H)^-$ calcd for $C_{29}H_{45}NO_{10}P$].



Enigmazole A (**Disodium phosphate form**) (−)-37: To a solution of enigmazole A (monophosphate form) (−)-38 (1.4 mg) in 0.2 mL of saturated $NaHCO_3$ CD_3OD solution in 3 mm glass NMR tube, 0.02 mL of 1 M NaOH CD_3OD solution was added to furnish enigmazole A (disodium phosphate form) (−)-37 in CD_3OD solution. $[\alpha]_D^{20}$ = −1.8 (*c* 0.2, MeOH) ; ^{1}H NMR (500 MHz, CD_3OD) δ = 7.68 (s, 1H), 6.21 (s, 1H), 5.93 (dd, *J* = 13.1, 2.9 Hz, 1H), 5.23 (q, *J* = 6.5 Hz, 1H), 4.67 (s, 2H), 4.31 (m, 1H), 3.64 (td, *J* = 10.8 Hz, 2.8 Hz, 1H), 3.20 (s, 3H), 3.14 (m, 1H), 3.09 (m, 1H), 2.50 (td, J = 12.3 Hz, 3.1 Hz, 1H), 2.29–2.20 (m, 2H), 2.14–2.09 (m, 1H), 2.06–1.95 (m, 2H), 1.88 (d, *J* = 1.2 Hz, 3H), 1.87–1.78 (m, 2H), 1.78–1.70 (m, 2H), 1.78–1.67 (m, 2H), 1.63–1.51 (m, 3H), 1.48 (q, *J* = 12.4 Hz, 1H), 1.40–1.47 (m, 3H), 1.26 (d, *J* = 6.6 Hz, 3H), 1.12 (d, *J* = 6.5 Hz, 3H), 1.06–0.99 (m, 1H), 0.97 (d, *J* = 6.7 Hz, 1H); ^{13}C NMR (125MHz, CD_3OD) δ = 177.4, 161.9, 152.6, 147.0, 142.5, 135.9, 114.0, 108.3, 78.0, 76.3, 75.7, 73.6, 69.8, 65.7, 56.8, 43.2, 42.7, 42.6, 40.3, 39.8, 39.5, 36,3, 34.9 (d, *J* = 6.8 Hz), 33.7, 21.8, 19.5, 18.6, 17.7, 15.4 (Na_2CO_3 peak is shown in 161.5).

3. Tables

^{1}H NMR Shifts of (−)-Enigmazole A in CD_3OD (Natural vs. Synthetic Monosodium Phosphate)

Atom No.	Natural	Synthetic	Δ δ (ppm)
1			
2	2.98	2.98 m	0.0
3a	1.38 (t, 10.8)	1.39 (t, 11.3)	+0.01
3b	1.88, m	1.88, m	0.0
4	1.62	1.62 m	0.0
5	4.42, m	4.42, m	0.0
6a	1.87, m	1.87, m	0.0
6b	2.10, m	2.10, m	0.0
7	3.12 (dd, 10.3, 9.8)	3.12 (dd, 10.2, 8.9)	0.0
8a	1.97 (dd, 12.8, 12.3)	1.97 (t, 12.2)	0.0
8b	2.21 (d, 12.8)	2.21 (d, 12.8)	0.0
9			
10a	1.84	1.84, m	0.0
10b	2.13 (d, 12.8)	2.13 (d, 12.8)	0.0
11	3.29	Covered by CD_3OD	
12a	1.37 (t, 11.3)	1.37 (t, 11.1)	0.0
12b	1.64	1.64 m	0.0
13a	1.54 (q, 12.4)	1.54 (q, 12.4)	0.0
13b	1.72	1.72 m	0.0
14a	1.02 (td, 12.0, 3.4)	1.02 (td, 12.0, 2.6)	0.0
14b	1.76	1.76 m	0.0
15	3.62 (td, 11.1, 4.3)	3.62 (td, 12.4, 3.9)	0.0
16a	1.77	1.77, m	0.0
16b	2.50 (td, 13.2 3.4)	2.50 (td 13.4 3.9)	0.0
17	5.95 (dd, 12.8, 2.5)	5.95 (dd, 12.8, 2.5)	0.0
18			
19	7.68, s	7.68, s	0.0
20			
21	6.21, s	6.21, s	0.0
22			
23	5.24 (q, 6.5)	5.24 (q, 6.5)	0.0
24	1.26 (d, 6.4) (3H)	1.26 (d, 6.4) (3H)	0.0
25	1.89, s (3H)	1.89, s (3H)	0.0
26	1.10 (d, 6.4) (3H)	1.10 (d, 6.4) (3H)	0.0
27	0.97 (d, 6.4) (3H)	0.97 (d, 6.4) (3H)	0.0
28a	4.69 (d, 1.5)	4.69 (d, 1.5)	0.0
28b	4.70 (d, 1.5)	4.70 (d, 1.5)	0.0
23-OMe	3.20, s (3H)	3.20, s (3H)	0.0

^{1}H NMR in MeOD, 500 MHz, ppm, *J*(Hz)

The natural enigmazole A data is from the isolation paper.[1]

^{13}C NMR Shifts of (−)-Enigmazole A in CD_3OD (Literature vs. Synthetic Monosodium phosphate)

Atom No.	Literature	Synthetic	Δ δ (ppm)
1	176.5	176.5	0.0
2	39.6	39.6	0.0
3	39.3	39.3	0.0
4	34.7 (d, 6.1)	34.7 (d, 6.6)	0.0
5	75.2 (d, 6.1)	75.2 (d, 6.4)	0.0
6	40.1	40.1	0.0
7	77.6	77.6	0.0
8	43.0	43.0	0.0
9	146.6	146.6	0.0
10	42.5	42.5	0.0
11	75.7	75.7	0.0
12	36.2	36.2	0.0
13	21.8	21.8	0.0
14	33.6	33.6	0.0
15	69.8	69.8	0.0
16	42.6	42.6	0.0
17	65.6	65.7	+0.1
18	142.3	142.4	+0.1
19	136.0	136.0	0.0
20	161.9	161.9	0.0
21	113.9	113.9	0.0
22	152.7	152.7	0.0
23	76.2	76.2	0.0
24	19.4	19.4	0.0
25	17.7	17.7	0.0
26	18.3	18.3	0.0
27	15.0	15.0	0.0
28	108.6	108.6	0.0
23-OMe	56.8	56.8	0.0

^{13}C NMR in CD_3OD, 125 MHz, ppm, J(Hz)

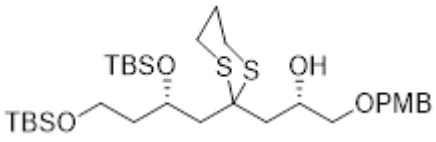
The literature enigmazole A data is from Molinski's synthesis paper, in which ^{13}C NMR spectra of both synthetic and natural enigmazole A were disclosed for the first time, and were proved identical.[2]

4. Abbreviations

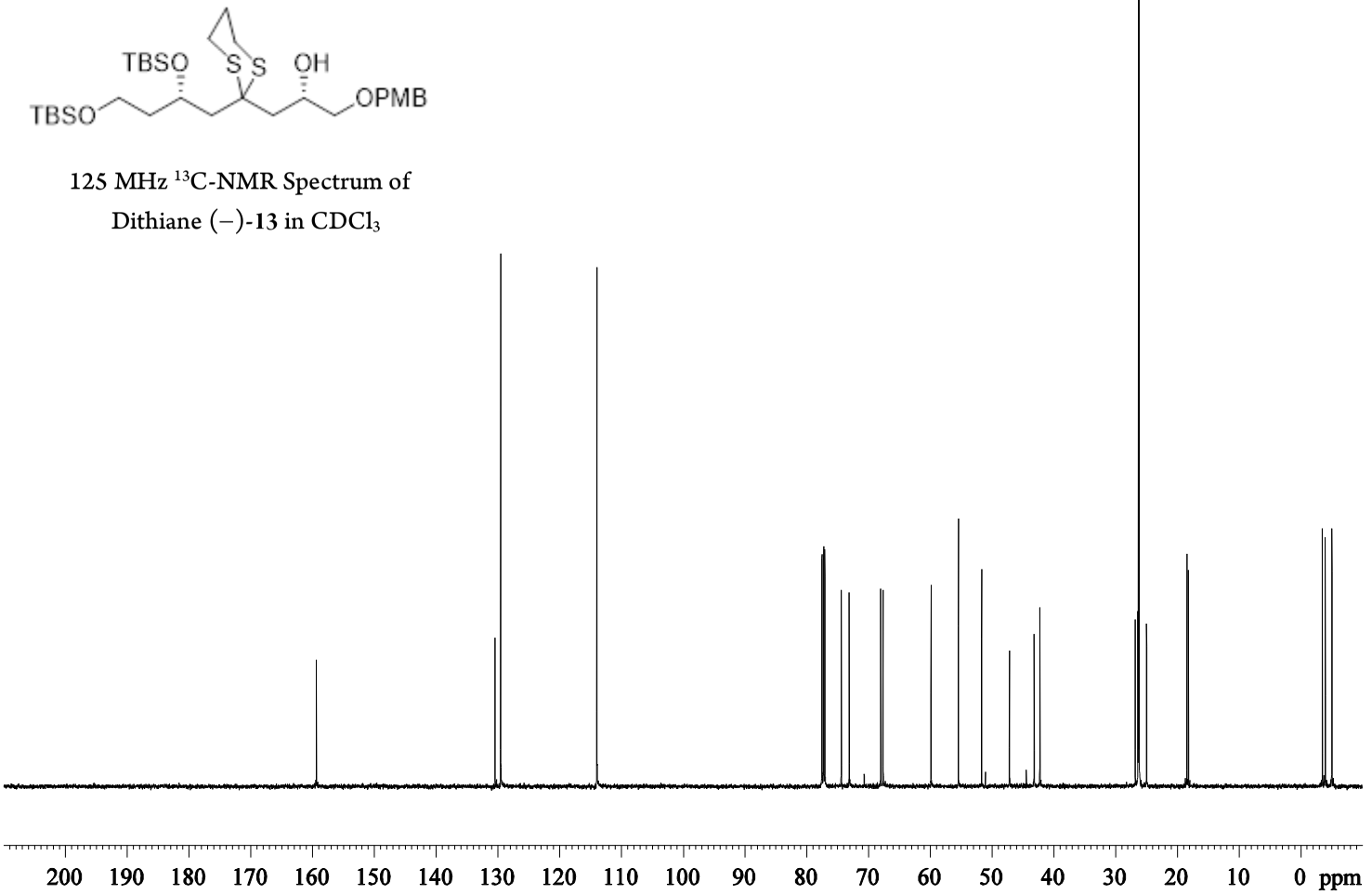
Ac……Acetyl
ACN……Acetonitrile
AcOH……Acetic Acid
ARC……Anion Relay Chemistry
ASG…… Anion Stabilizing Group
BAIB……[Bis(acetoxy)iodo]benzene
Bn.……Benzyl
Boc……*tert*-Butyl Carbamates
BPS……*tert*-Butyldiphenylsilyl Chloride
BuLi…… Butyllithium
Cp……Cyclopentadienyl
CSA……10-Camphorsulfonic Acid
DCC……..*N,N'*-Dicyclohexylcarbodiimide
DCM……Dichloromethane
DDQ……2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H……..Disobutylaluminum Hydride
DIPEA……..Diisopropylethylamine
DMAP……..4-(*N,N*-Dimethylamino)pyridine
DMF……Dimethylformamide
DMSO……..Dimethyl Sulfoxide
DMPU……1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
d.r.……Diastereomeric Ratio
DtBMP……2,6-Di-*tert*-butyl-4-methylpyridine
EDC.HCl……1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide Hydrochloride
EtOAc……..Ethyl Acetate
EtOH……Ethanol
Fm……9-Fluorenylmethyl
GI_{50}……Growth Inhibition of 50%
HMDS……Hexamethyldisilazane
HMPA……Hexamethylphosphoramide
HPLC……High Pressure Liquid Chromatography
IC_{50}……Half Maximal Inhibitory Concentration
Ipc……Isopinocampheyl
LA……Lewis Acid
LG……Leaving Group
LDA……Lithium Diisopropylamide
IR……Infrared
*m*CPBA…… *meta*-Chloroperoxybenzoic acid
MeOH……Methanol
MHz……Megahertz
MS……Mass Spectrometry

Ms……Methanesulfonyl
MOM……Methoxymethyl
Nap……2-Naphthylmethyl
NMO……*N*-Methylmorpholine *N*-Oxide
NMR……Nuclear Magnetic Resonance
PG……Protecting Group
Ph……Phenyl
Ph_3P……Triphenylphosphine
PMB……4-Methoxybenzyl
PMP……4-Methoxyphenyl
PTLC……Preparative Thin Layer Chromatography
Py……Pyridine
r.t.……Room Temperature
TASF……Tris(dimethylamino)sulfonium Difluorotrimethylsilicate
TBAF……Tetrabutylammonium Fluoride
TBAI……Tetrabutylammonium Iodide
TBAT…… Tetrabutylammonium Difluorotriphenylsilicate
TBDPS……*tert*-Butyldiphenylsilyl
TBS……*tert*-Butyldimethylsilyl
TEMPO……2,2,6,6-Tetramethyl-1-piperidinyloxyl, Free Radical
TIPS……Triisopropylsilyl
Tf……Trifluoromethyl
TFA……Trifluoromethylacetic Acid
TfOH……Trifluoromethanesulfonic Acid
THF……Tetrahydrofuran
TLC……Thin Layer Chromatography
TMS……Trimethylsilyl
Tris-imid……2,4,6-Triisopropylbenzylsulfonylimidazole
UV……Ultraviolet

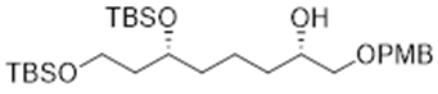
5. Spectroscopic Data



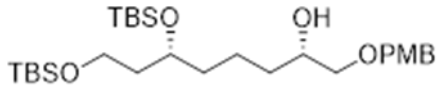
500 MHz ^{1}H-NMR Spectrum of
Dithiane (−)-**13** in $CDCl_3$



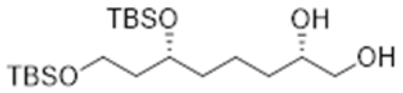
125 MHz ^{13}C-NMR Spectrum of
Dithiane (−)-13 in $CDCl_3$



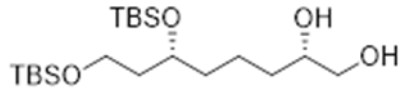
500 MHz ^{1}H-NMR Spectrum of
Alochol (−)-**14** in $CDCl_3$



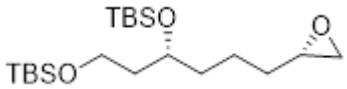
125 MHz ^{13}C-NMR Spectrum of
Alcohol (−)-**14** in $CDCl_3$



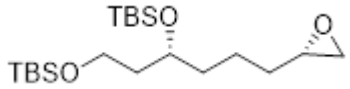
500 MHz ^{1}H-NMR Spectrum of
Diol (−)-**15** in $CDCl_3$



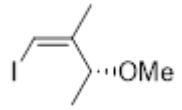
125 MHz ^{13}C-NMR Spectrum of
Diol (−)-**15** in $CDCl_3$



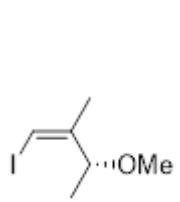
500 MHz ^{1}H-NMR Spectrum of
Epoxide (−)-7 in $CDCl_3$



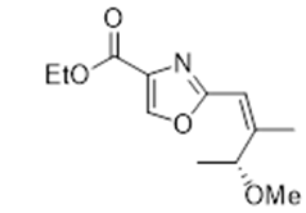
125 MHz ^{13}C-NMR Spectrum of
Epoxide (−)-7 in $CDCl_3$



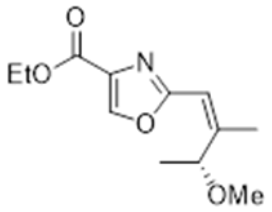
500 MHz ^{1}H-NMR Spectrum of
Iodide (+)-**17** in $CDCl_3$



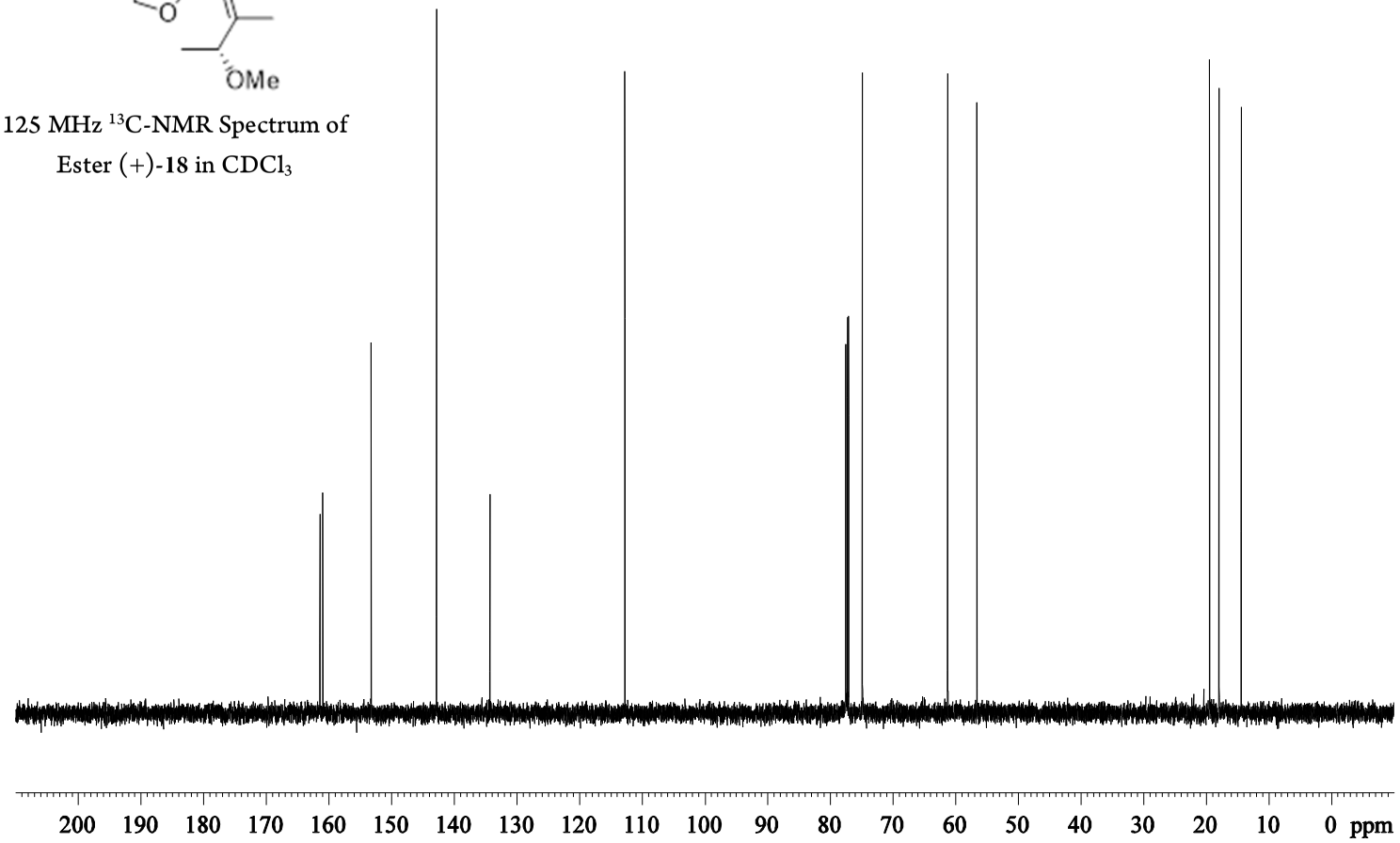
125 MHz ^{13}C-NMR Spectrum of
Iodide (+)-**17** in $CDCl_3$



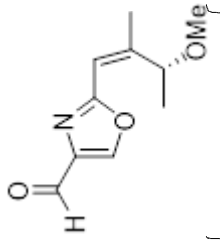
500 MHz ^{1}H-NMR Spectrum of
Ester (+)-**18** in $CDCl_3$

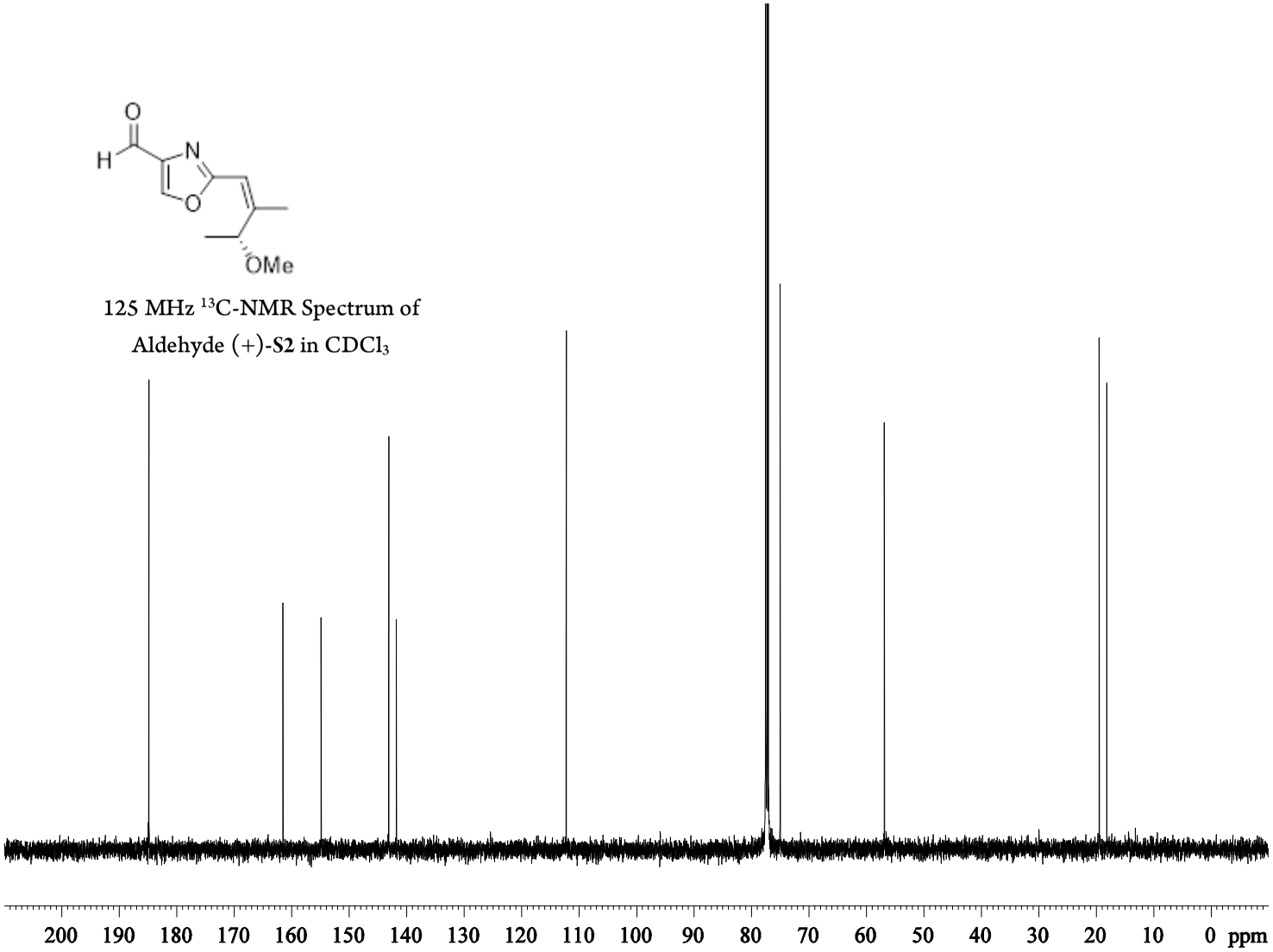


125 MHz ^{13}C-NMR Spectrum of
Ester (+)-18 in $CDCl_3$

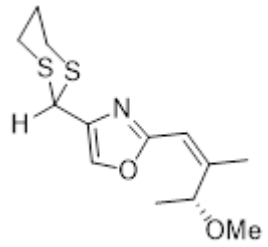


500 MHz ^{1}H-NMR Spectrum of
Aldehyde (+)-**S2** in $CDCl_3$

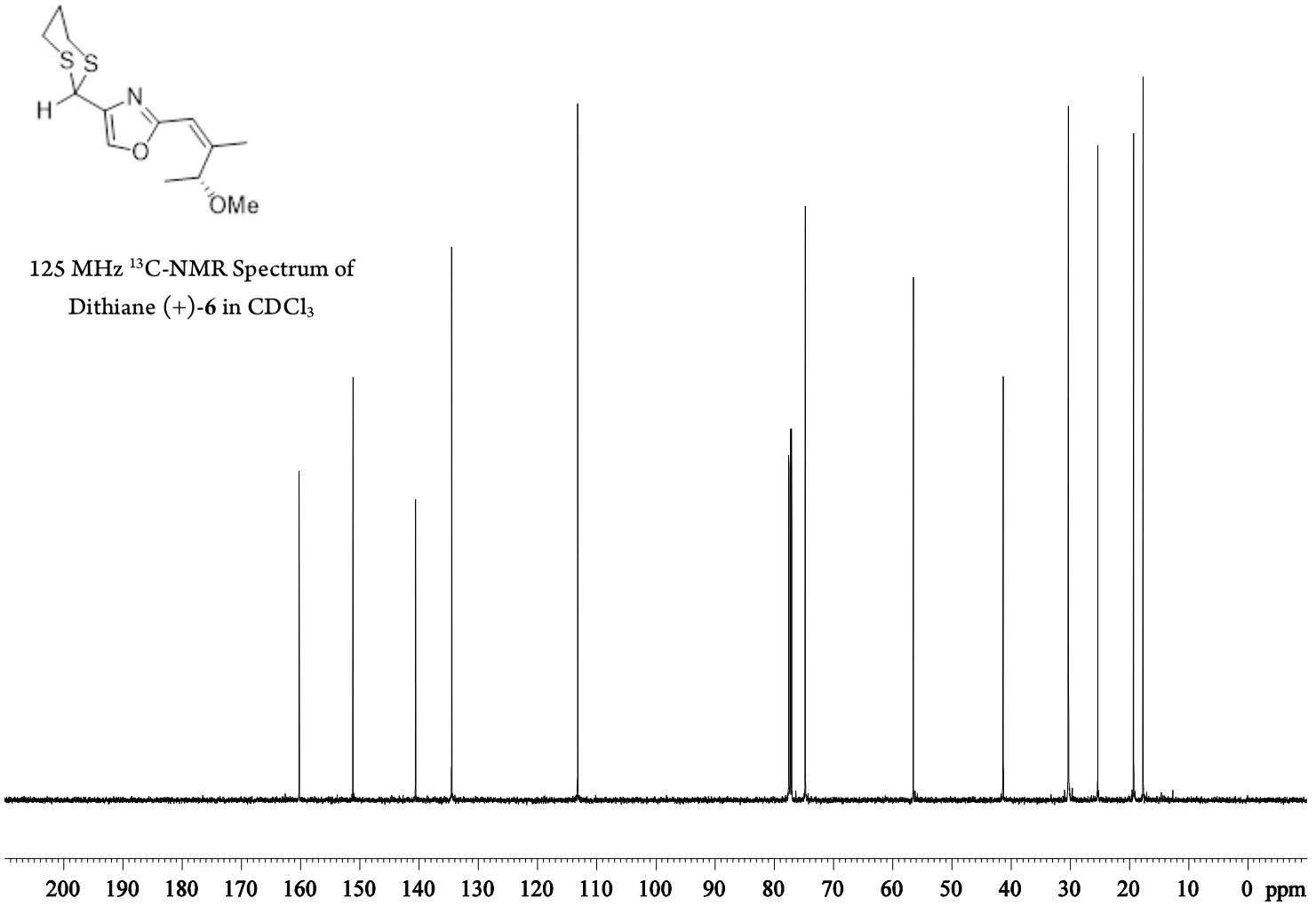




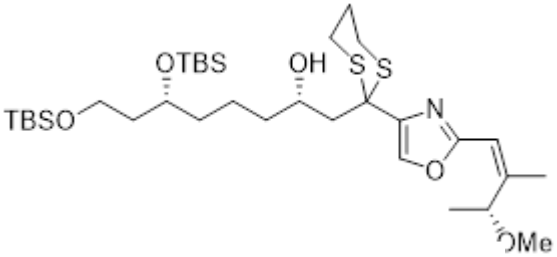
125 MHz ^{13}C-NMR Spectrum of
Aldehyde (+)-**S2** in $CDCl_3$



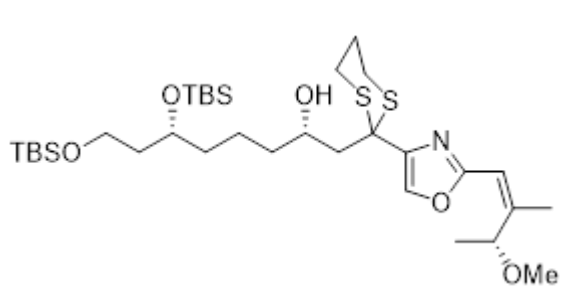
500 MHz ^{1}H-NMR Spectrum of
Dithiane (+)-**6** in $CDCl_3$



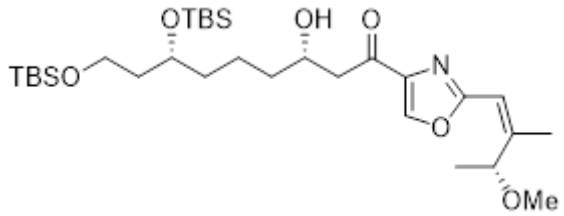
125 MHz ^{13}C-NMR Spectrum of
Dithiane (+)-**6** in $CDCl_3$



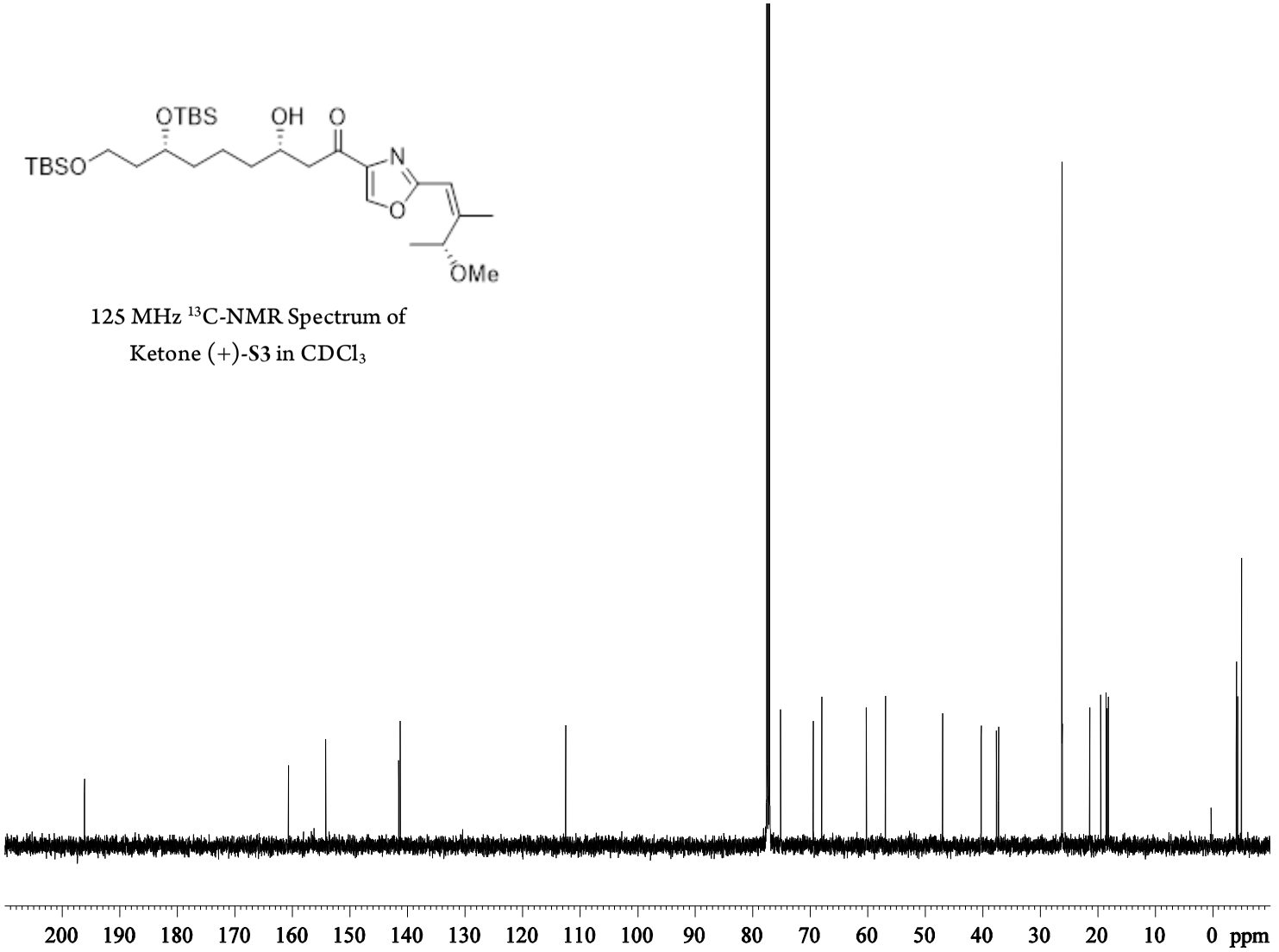
500 MHz ^{1}H-NMR Spectrum of
Dithiane (+)-**19** in $CDCl_3$



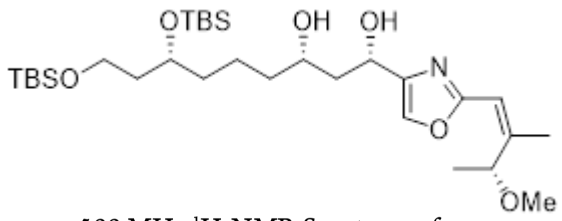
125 MHz ^{13}C-NMR Spectrum of
Dithiane (+)-**19** in $CDCl_3$



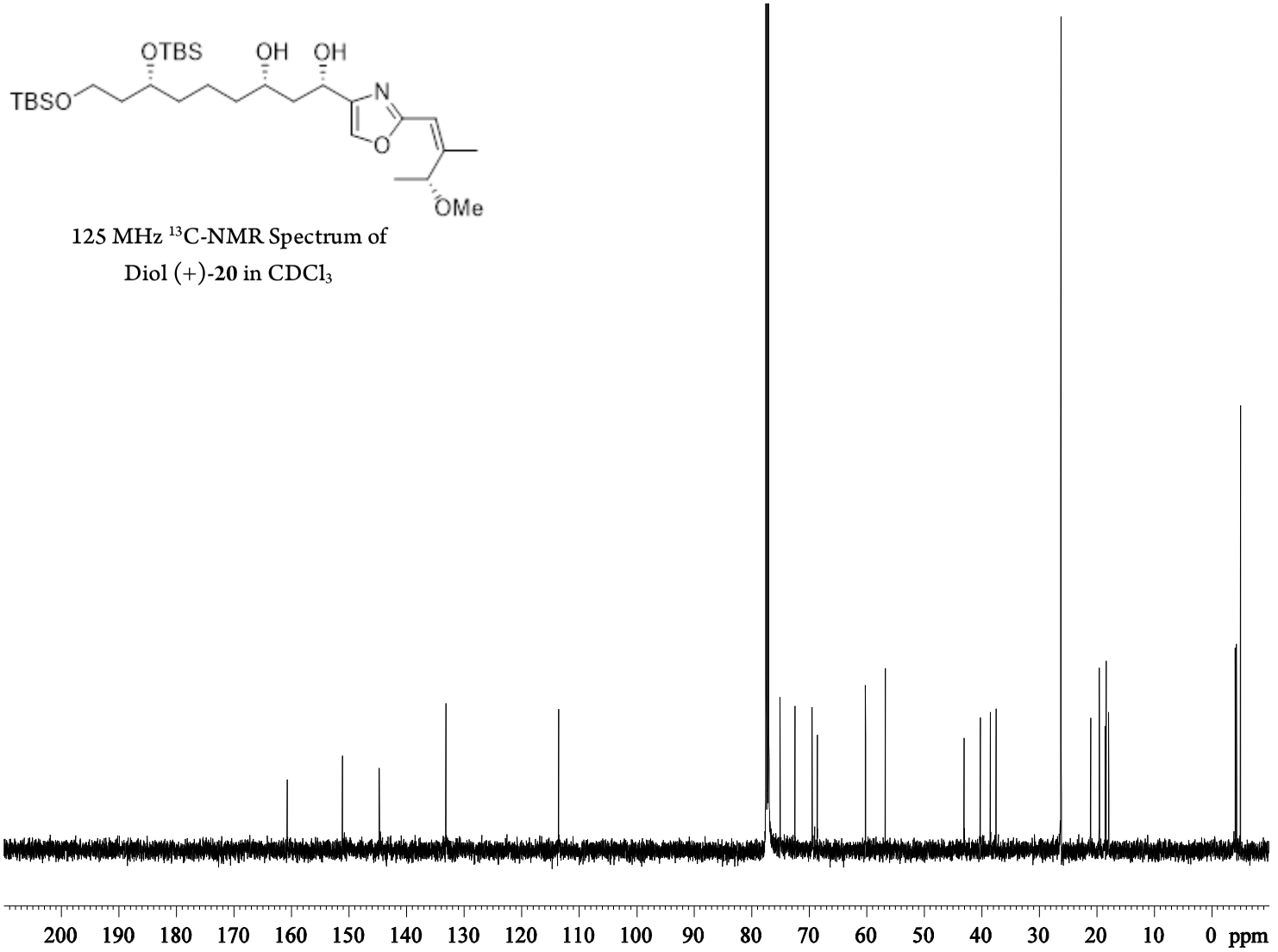
500 MHz ^{1}H-NMR Spectrum of
Ketone (+)-S3 in $CDCl_3$



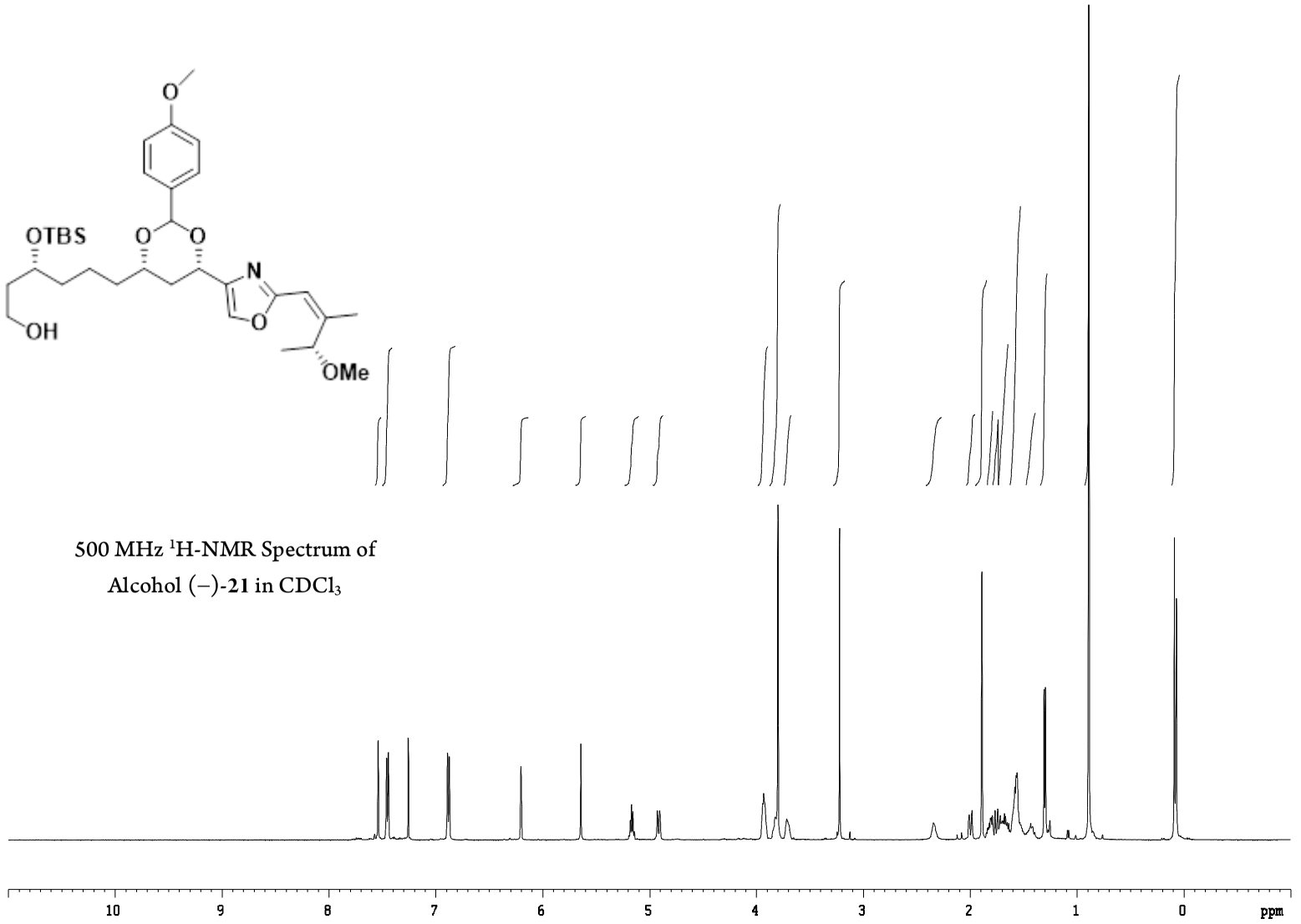
125 MHz ^{13}C-NMR Spectrum of
Ketone (+)-S3 in $CDCl_3$



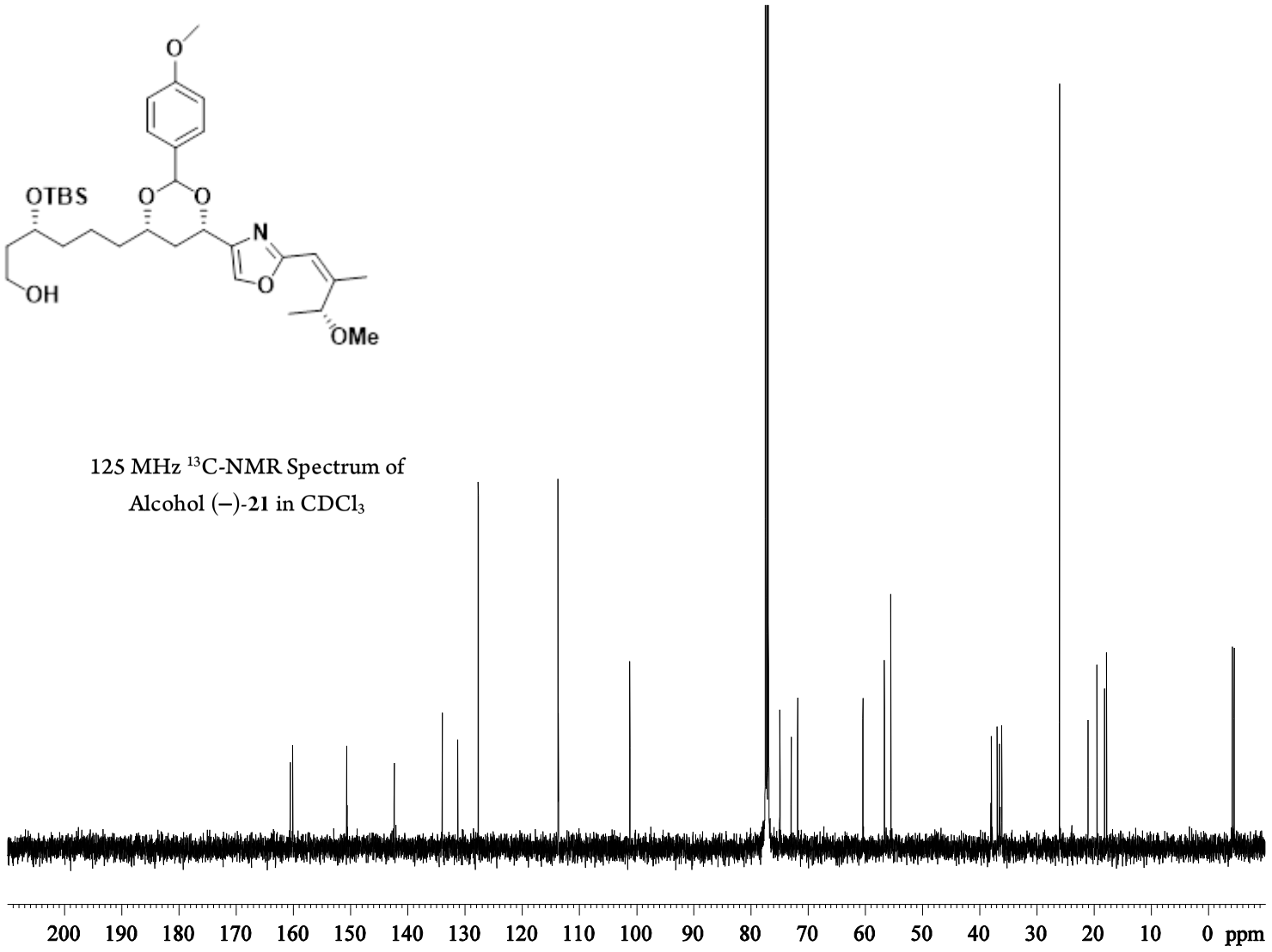
500 MHz ^{1}H-NMR Spectrum of
Diol (+)-**20** in $CDCl_3$



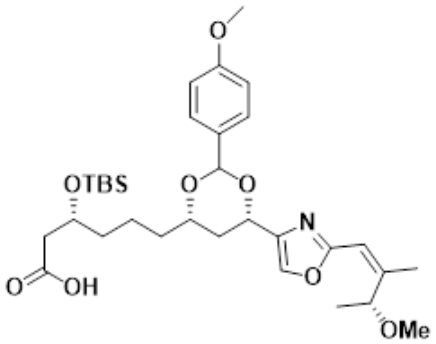
125 MHz ^{13}C-NMR Spectrum of
Diol (+)-**20** in $CDCl_3$



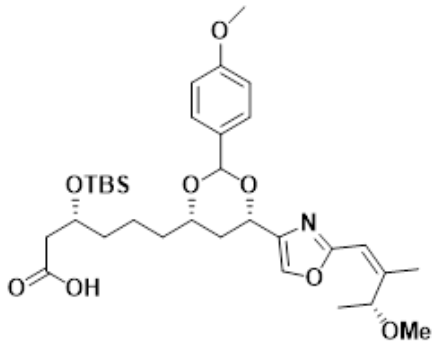
500 MHz ^{1}H-NMR Spectrum of
Alcohol (−)-**21** in $CDCl_3$



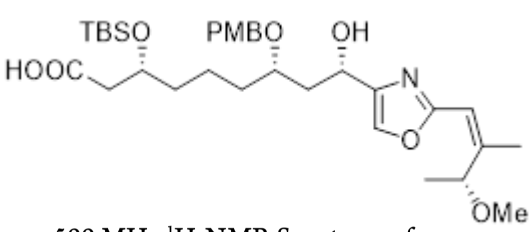
125 MHz ^{13}C-NMR Spectrum of
Alcohol (–)-**21** in $CDCl_3$



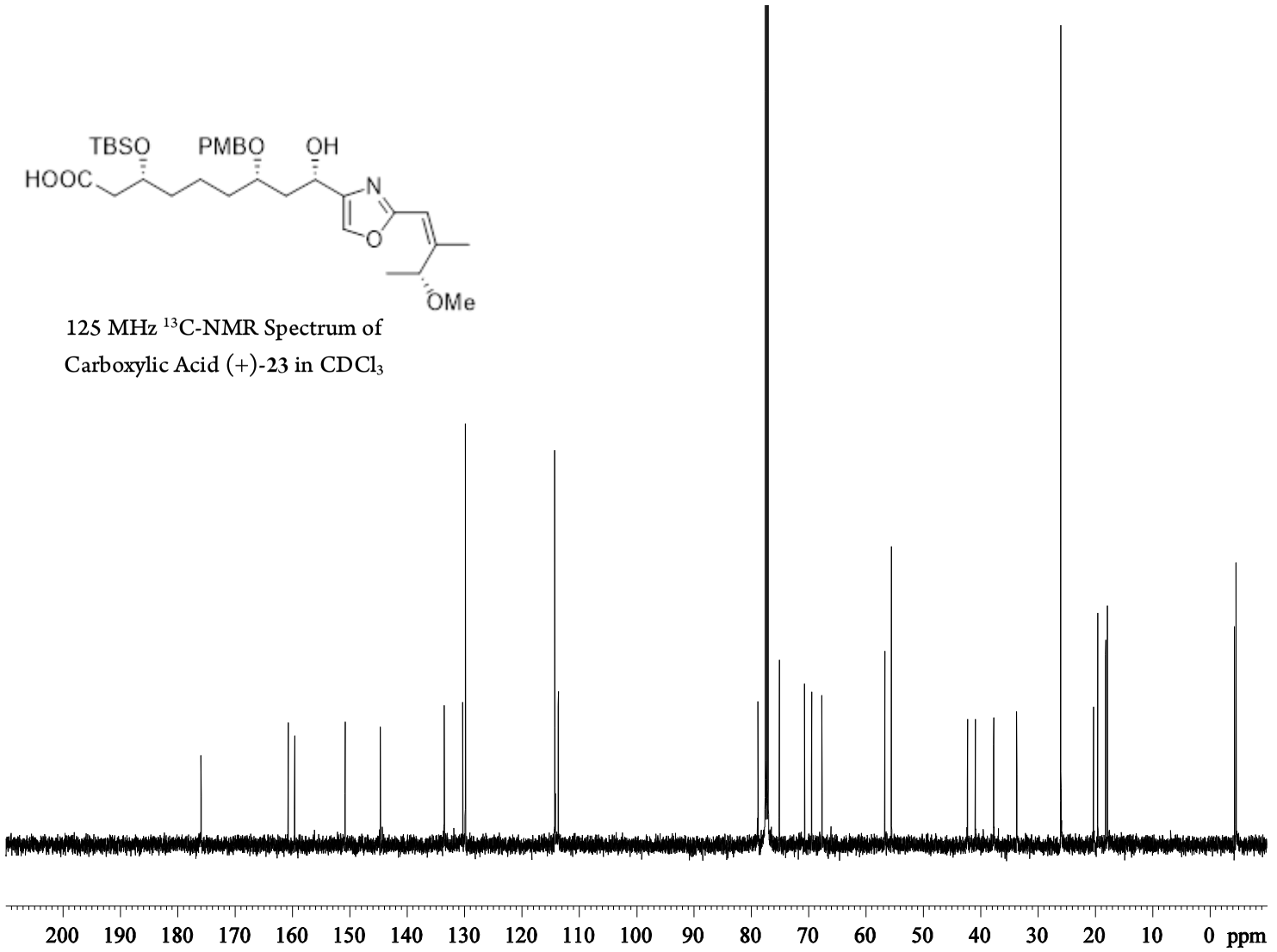
500 MHz ^{1}H-NMR Spectrum of
Carboxylic Acid (+)-**22** in $CDCl_3$



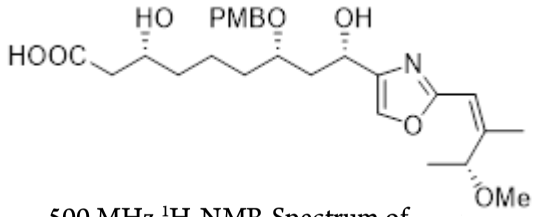
125 MHz ^{13}C-NMR Spectrum of
Carboxylic Acid (+)-**22** in $CDCl_3$



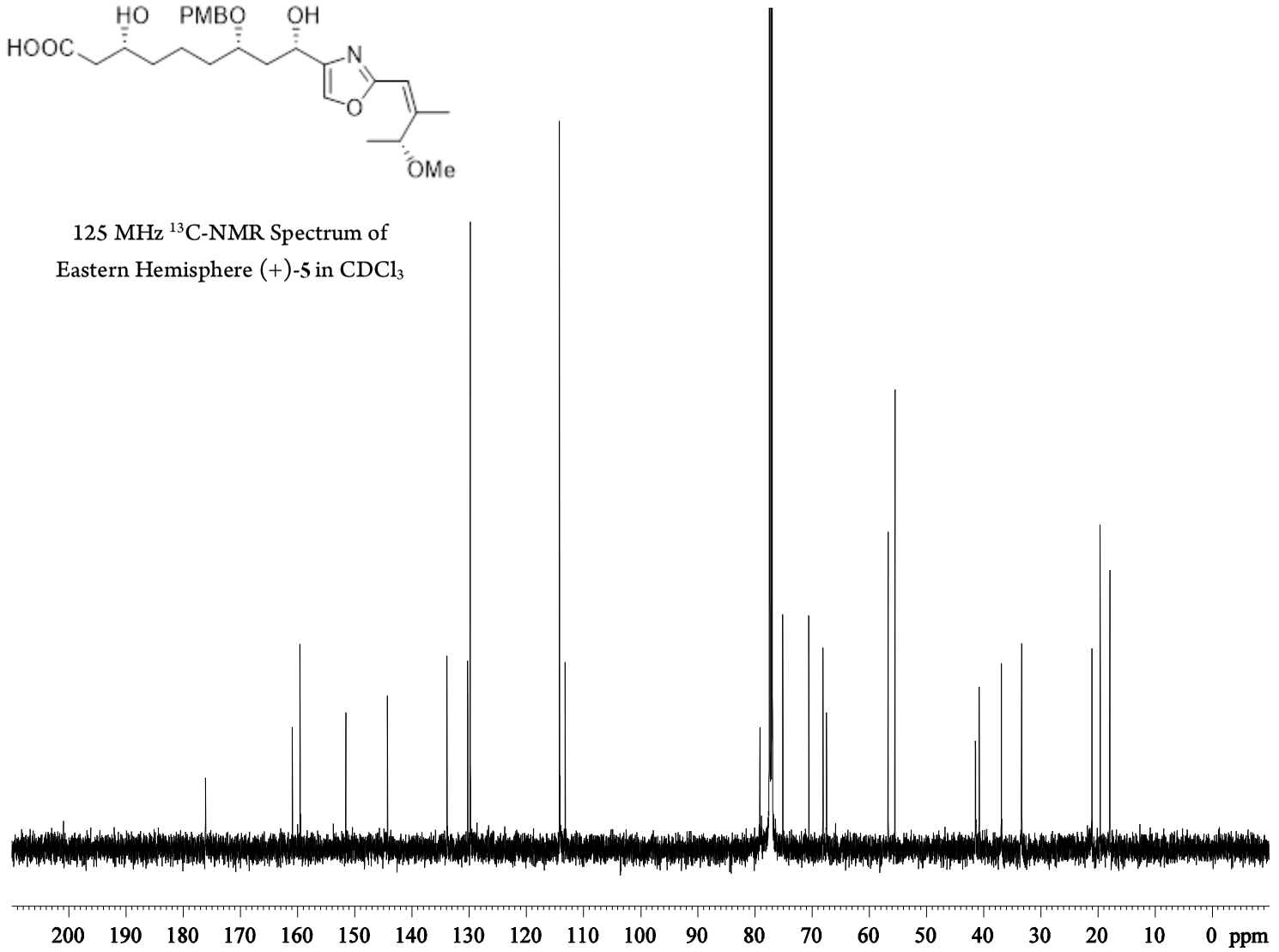
500 MHz ^{1}H-NMR Spectrum of
Carboxylic Acid (+)-**23** in $CDCl_3$



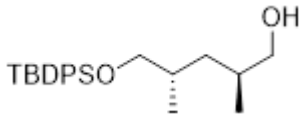
125 MHz ^{13}C-NMR Spectrum of
Carboxylic Acid (+)-**23** in $CDCl_3$



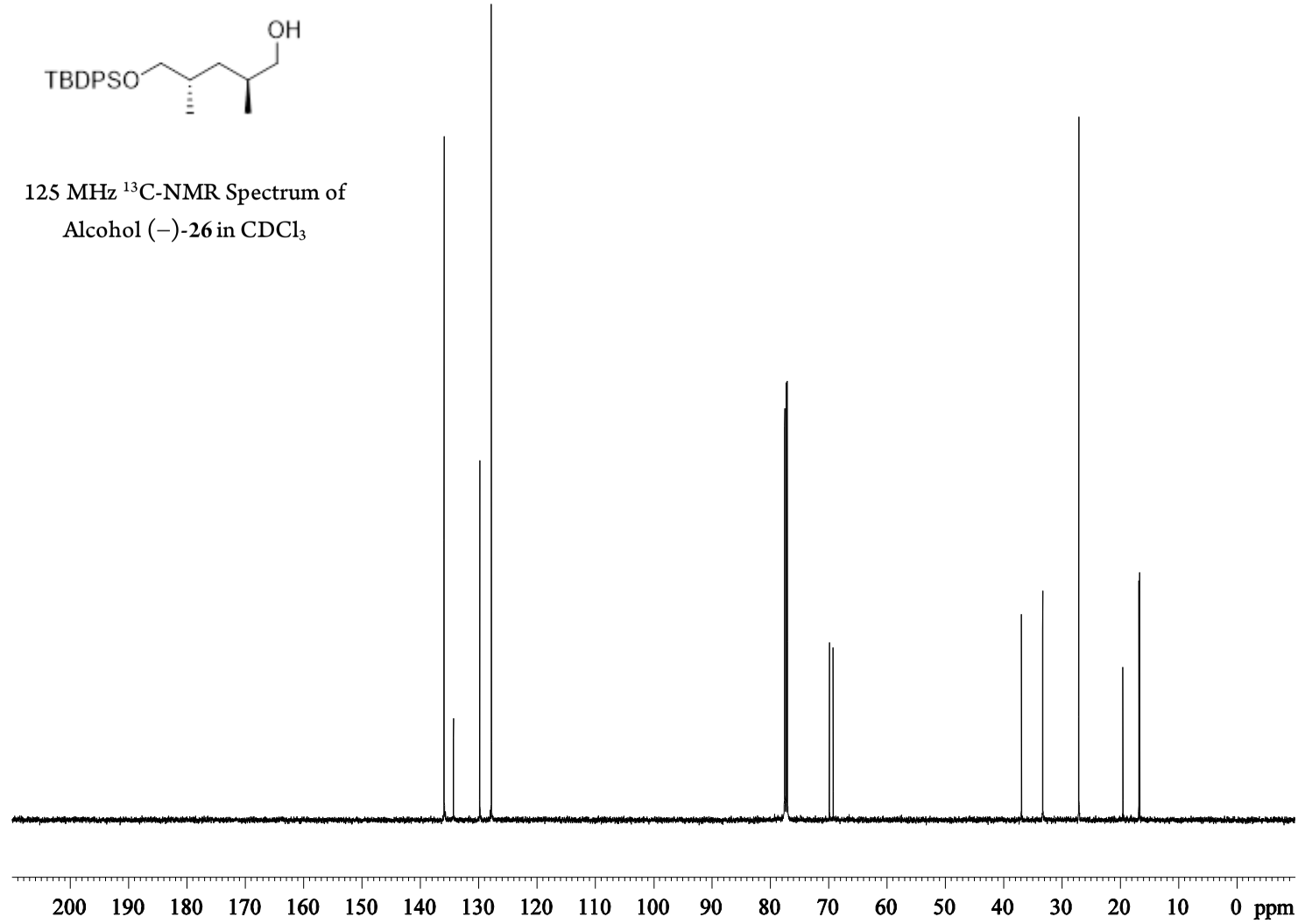
500 MHz ^{1}H-NMR Spectrum of
Eastern Hemisphere (+)-**5** in $CDCl_3$



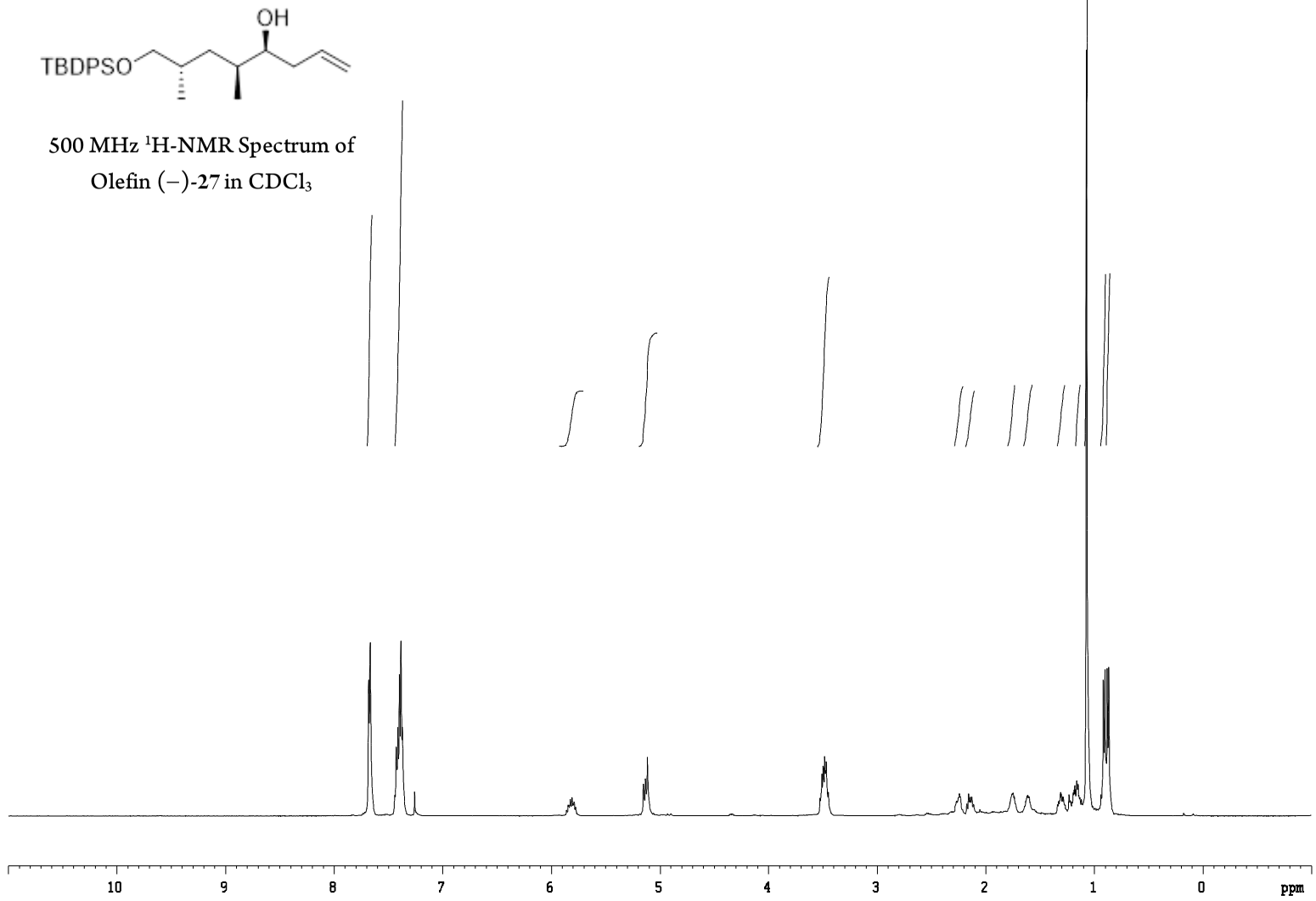
125 MHz ^{13}C-NMR Spectrum of
Eastern Hemisphere (+)-**5** in $CDCl_3$



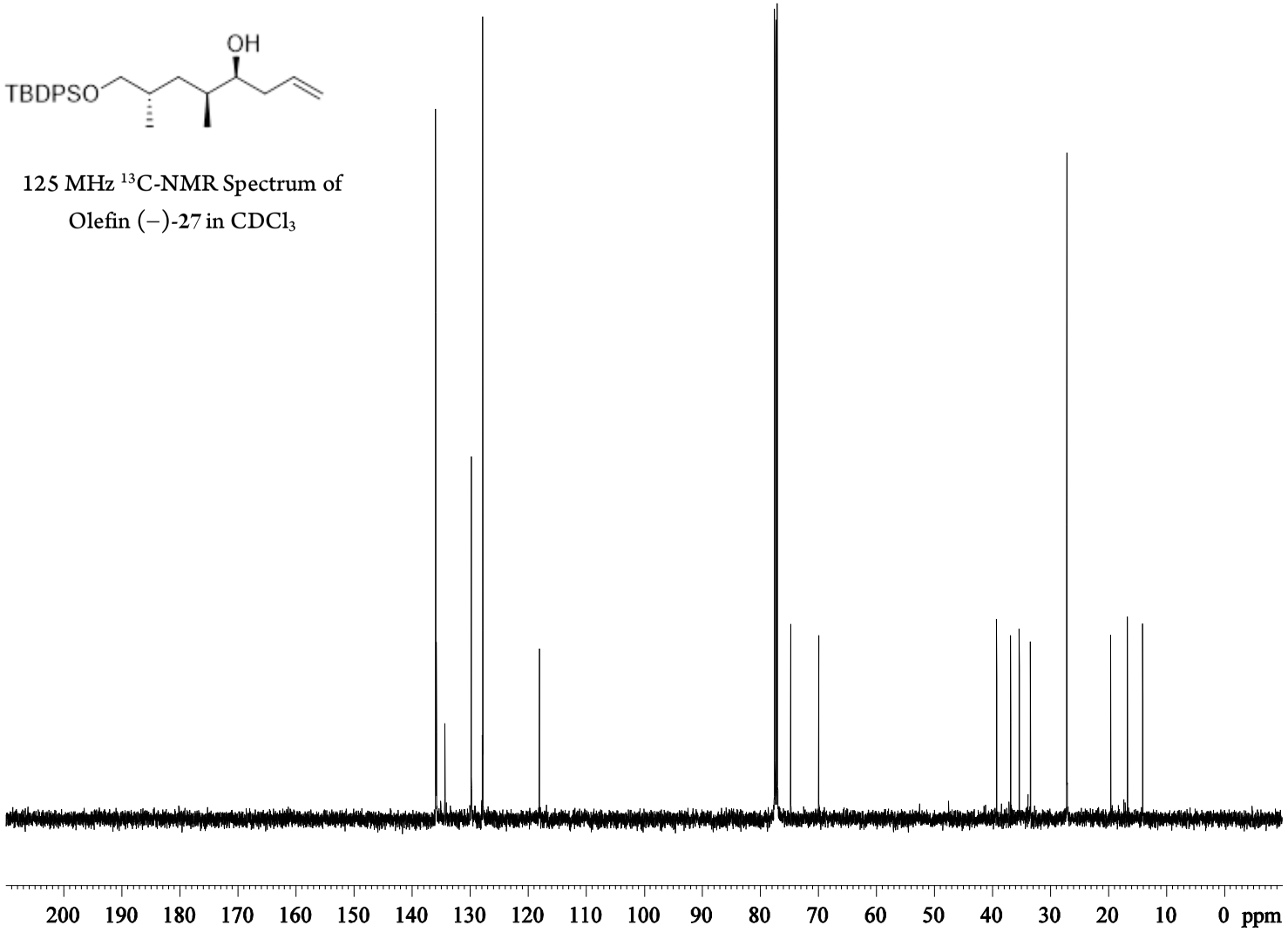
500 MHz ^{1}H-NMR Spectrum of
Alcohol (−)-**26** in $CDCl_3$



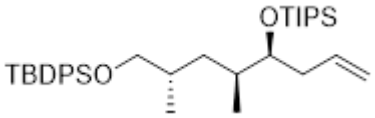
125 MHz ^{13}C-NMR Spectrum of
Alcohol (–)-**26** in $CDCl_3$



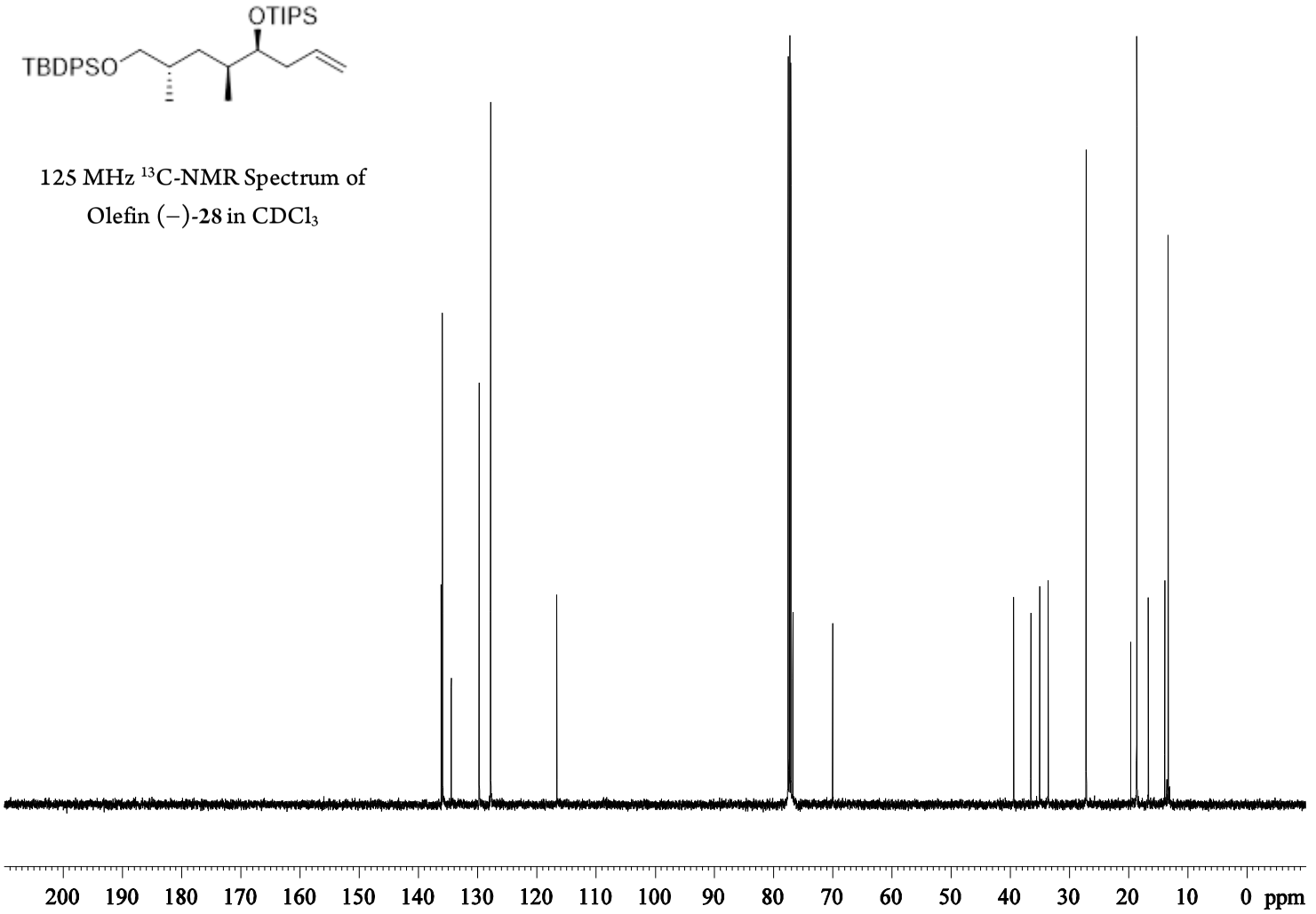
500 MHz ^{1}H-NMR Spectrum of
Olefin (−)-**27** in $CDCl_3$



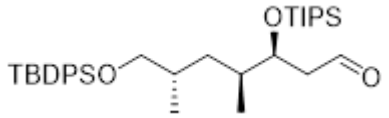
125 MHz ^{13}C-NMR Spectrum of
Olefin (−)-**27** in $CDCl_3$



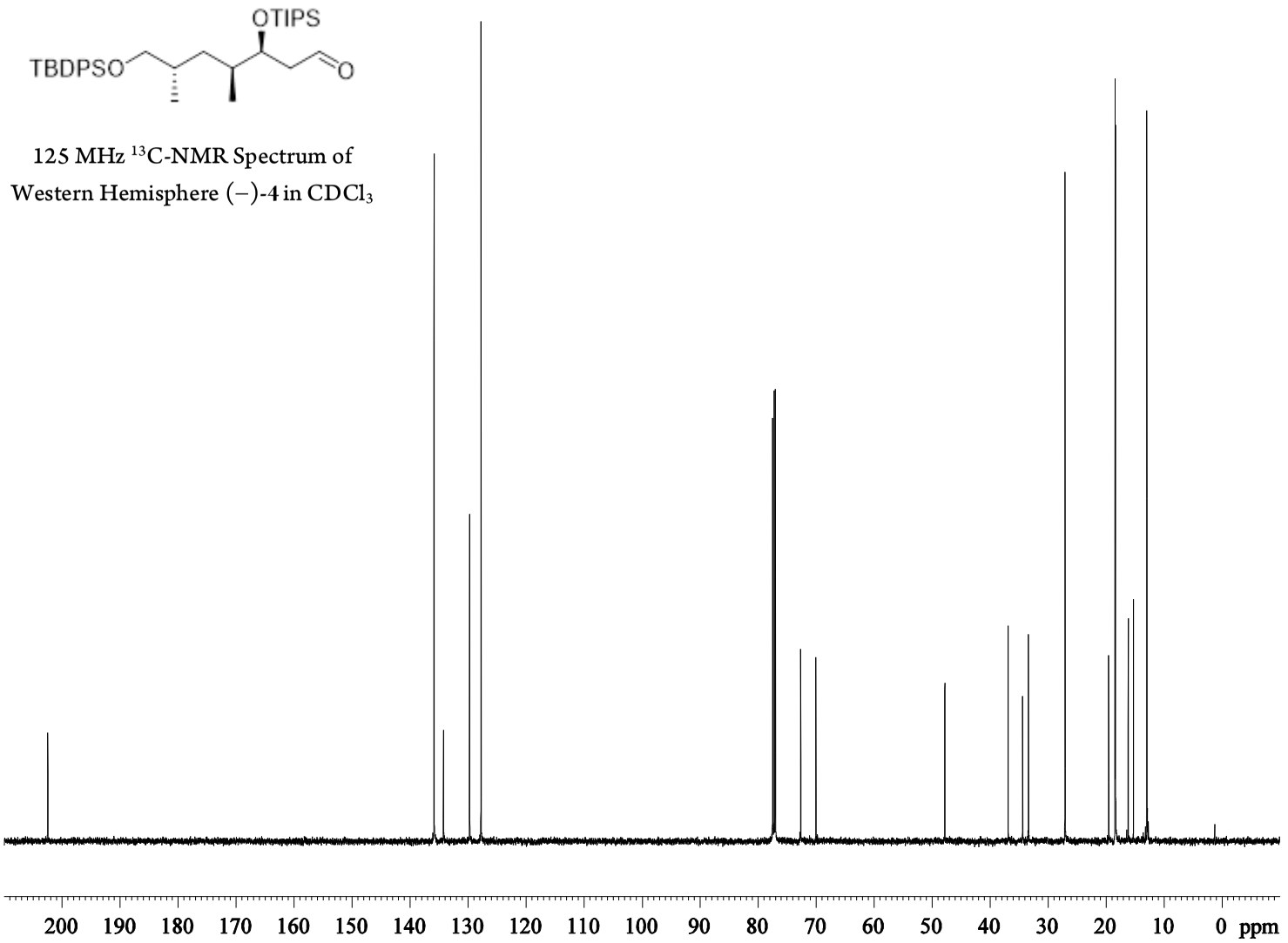
500 MHz ^{1}H-NMR Spectrum of
Olefin (−)-**28** in $CDCl_3$



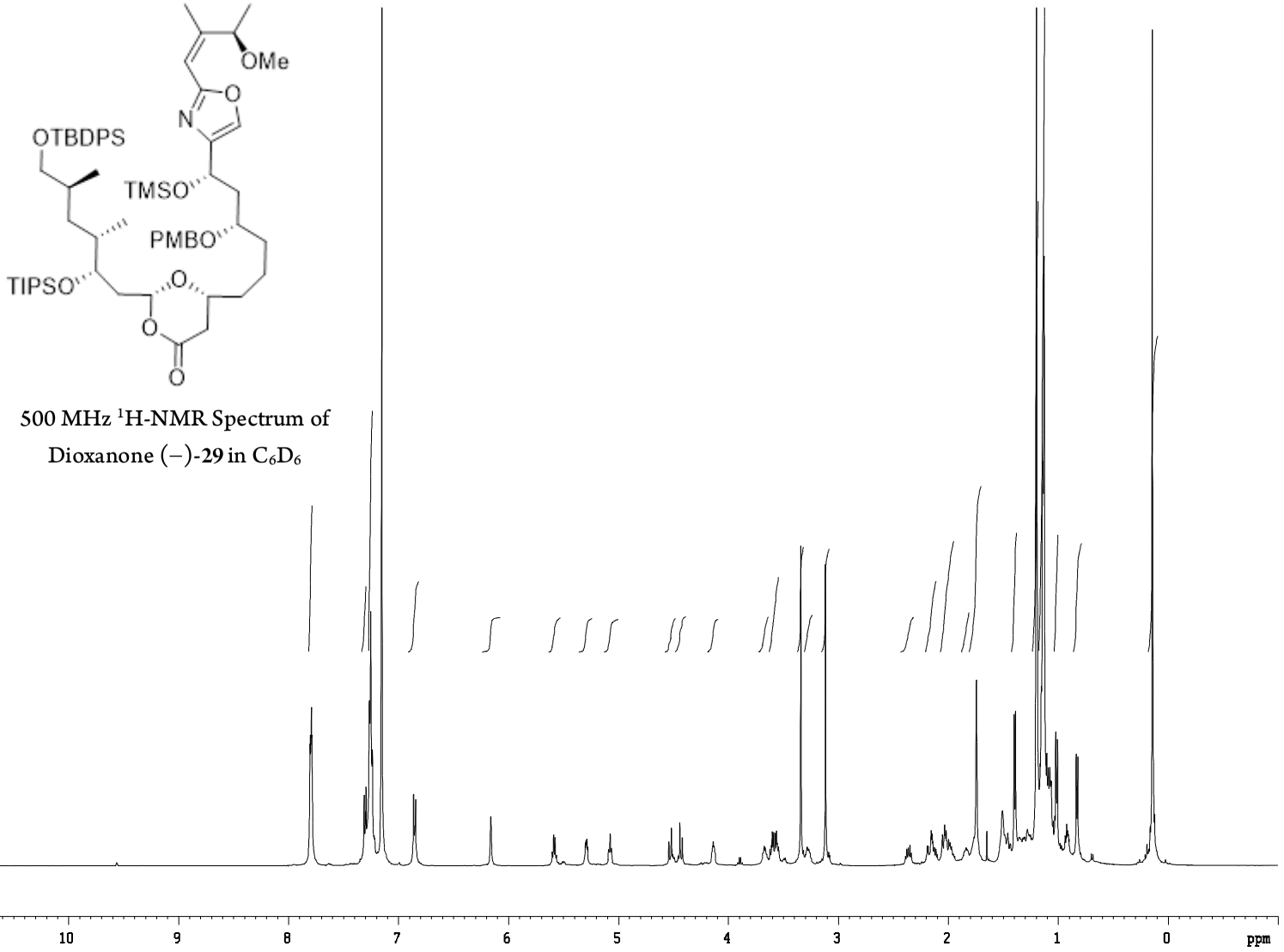
125 MHz ^{13}C-NMR Spectrum of
Olefin (−)-**28** in $CDCl_3$



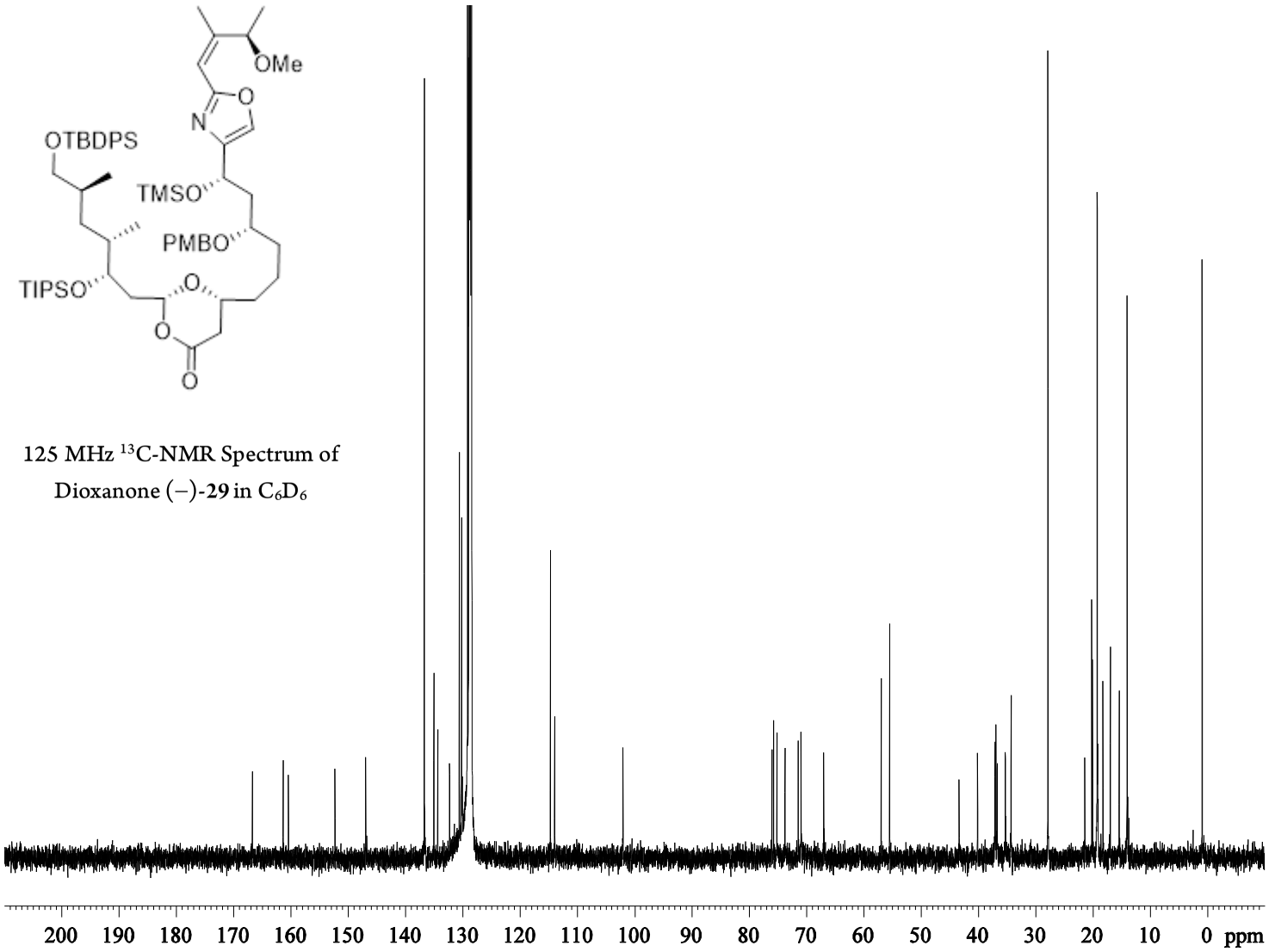
500 MHz ^{1}H-NMR Spectrum of
Western Hemisphere (−)-**4** in $CDCl_3$



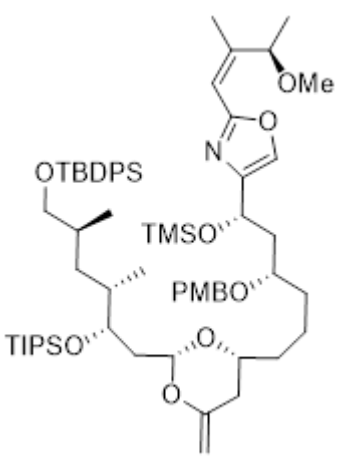
125 MHz ^{13}C-NMR Spectrum of
Western Hemisphere (−)-4 in $CDCl_3$



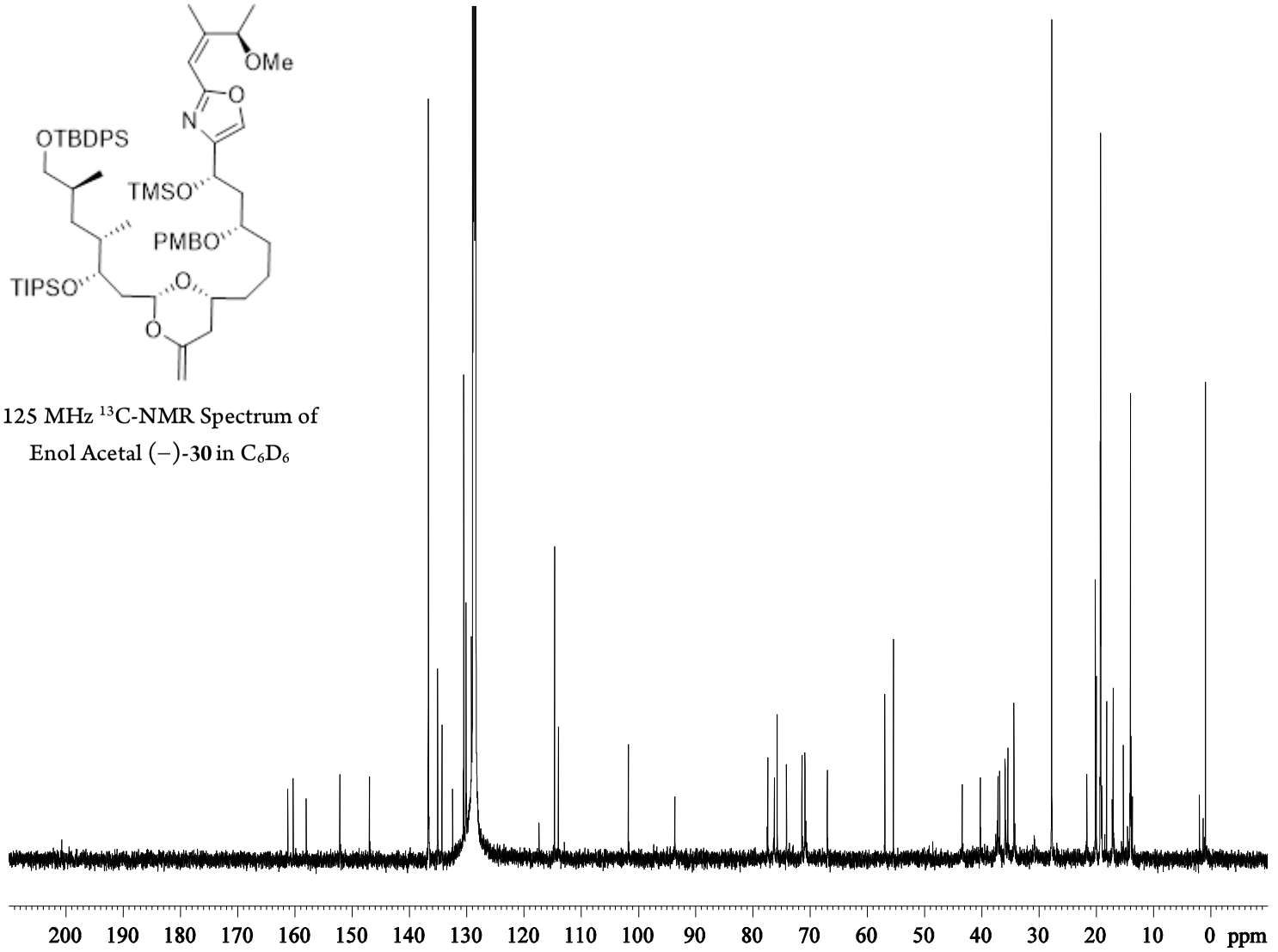
500 MHz ^{1}H-NMR Spectrum of
Dioxanone (−)-**29** in C_6D_6



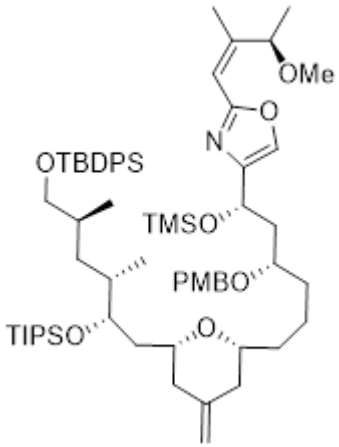
125 MHz ^{13}C-NMR Spectrum of
Dioxanone (−)-**29** in C_6D_6



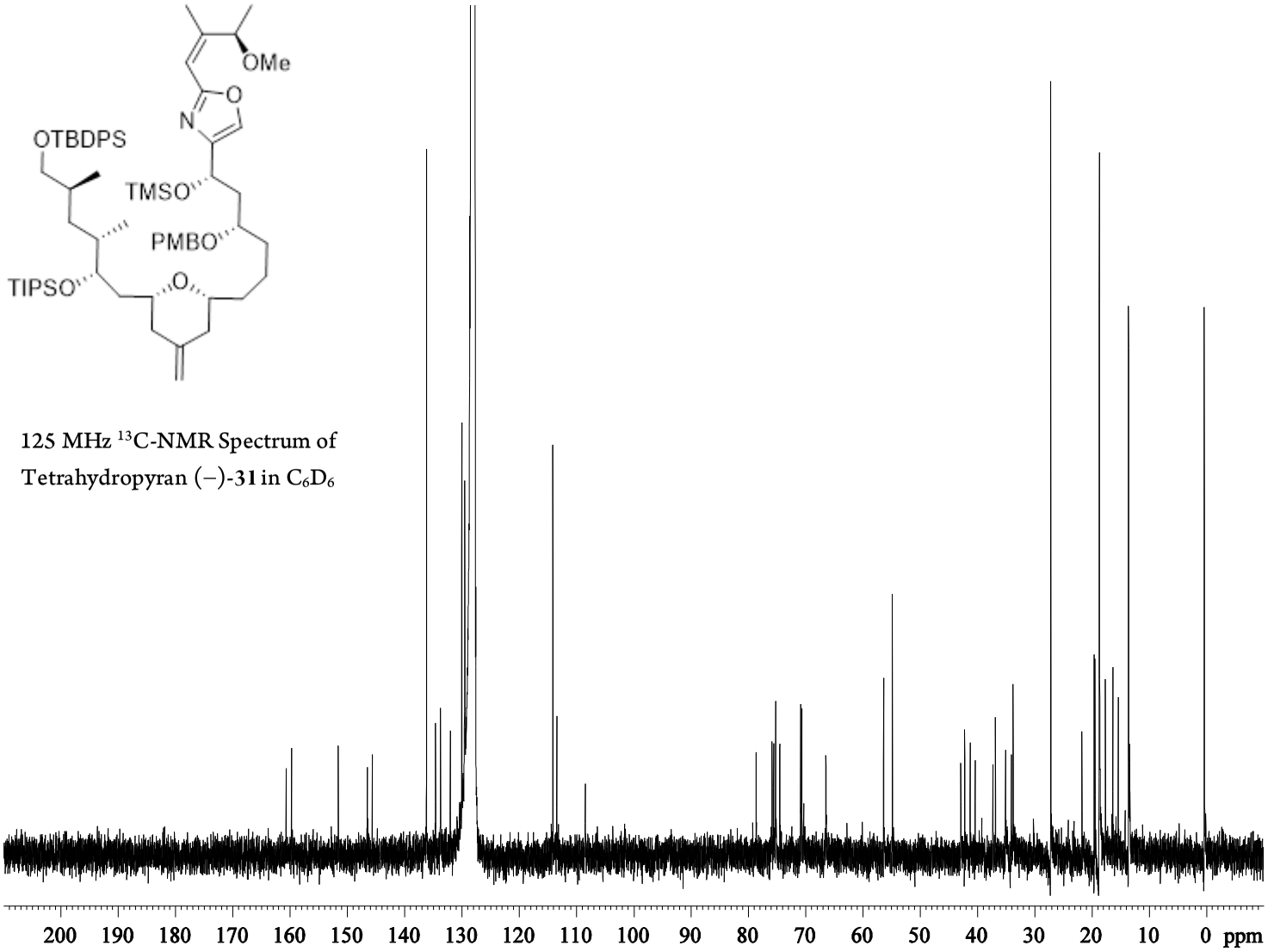
500 MHz ^{1}H-NMR Spectrum of
Enol Acetal (−)-**30** in C_6D_6



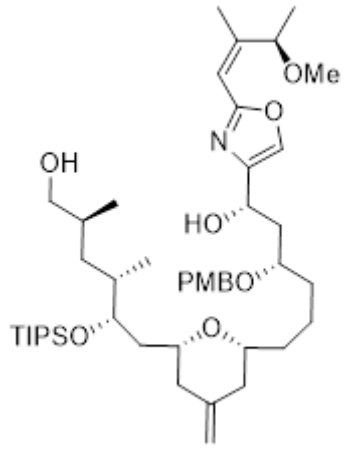
125 MHz ^{13}C-NMR Spectrum of
Enol Acetal (−)-**30** in C_6D_6



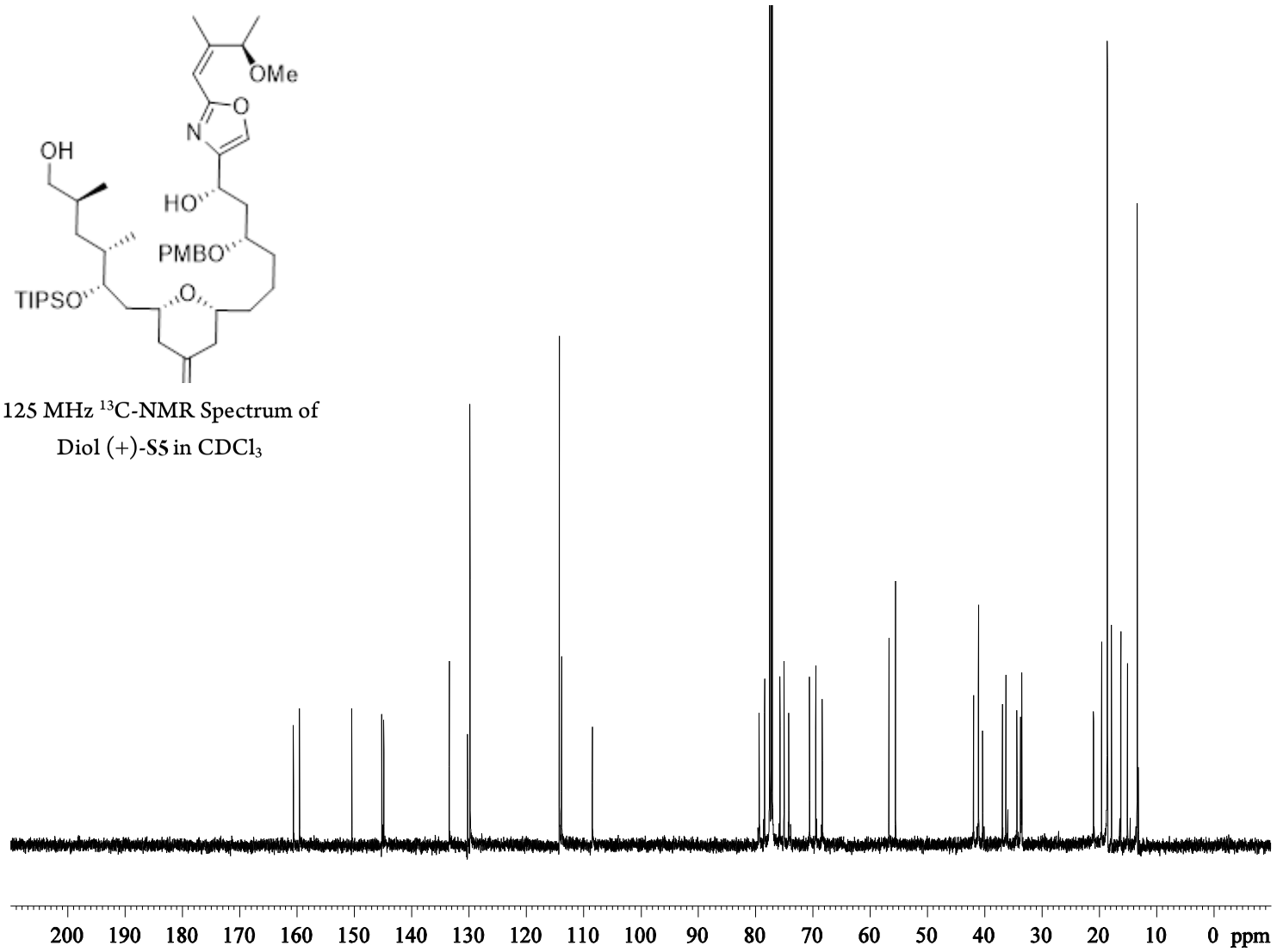
500 MHz ^{1}H-NMR Spectrum of
Tetrahydropyran (−)-**31** in C_6D_6



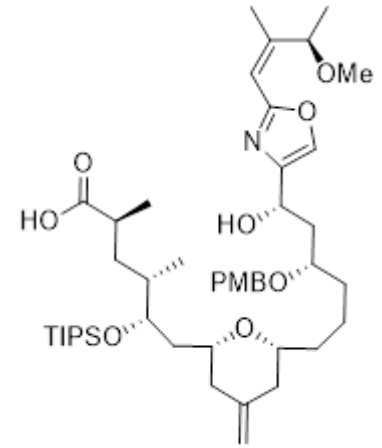
125 MHz ^{13}C-NMR Spectrum of
Tetrahydropyran (−)-**31** in C_6D_6



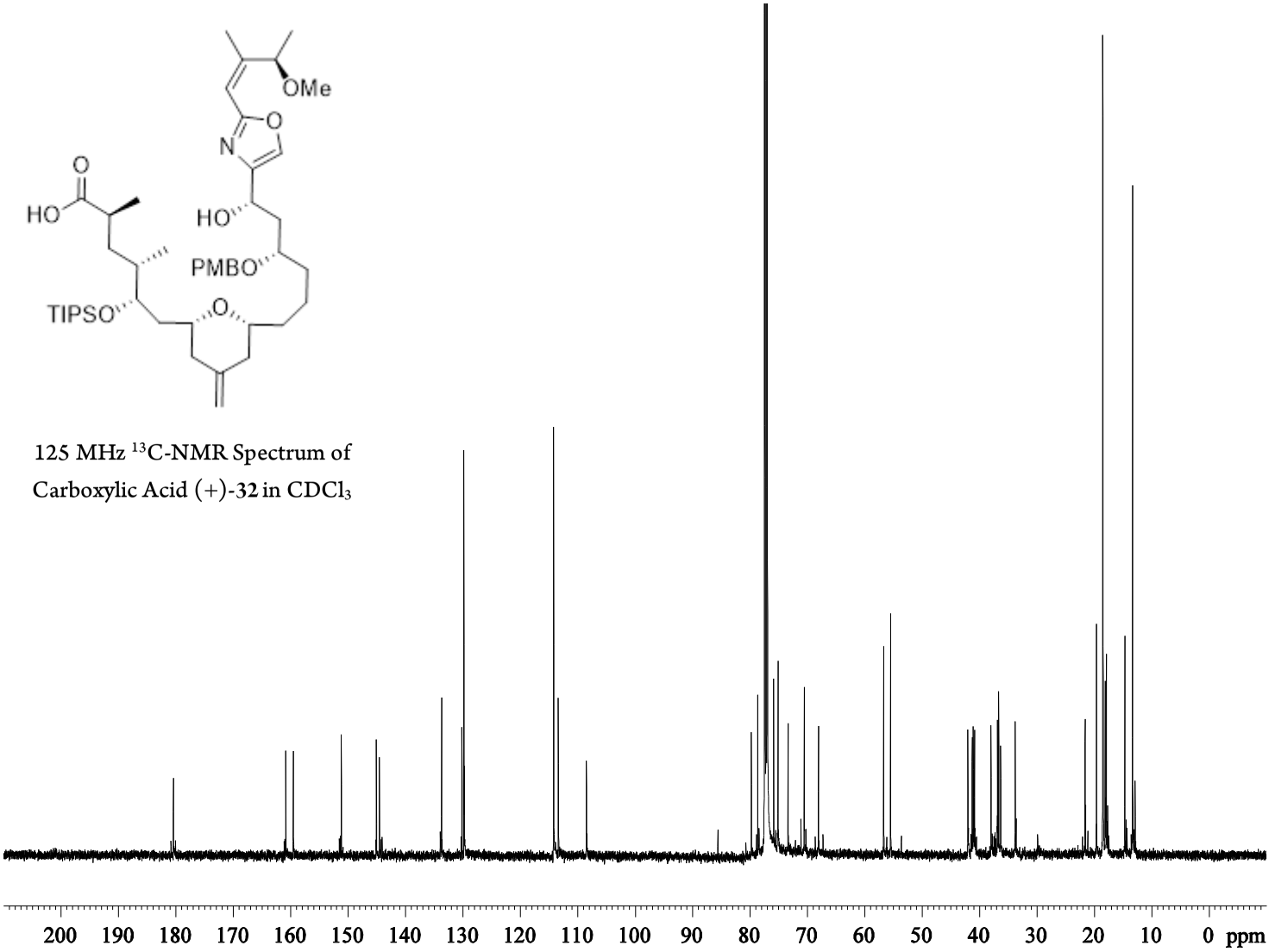
500 MHz ^{1}H-NMR Spectrum of
Diol (+)-S5 in $CDCl_3$



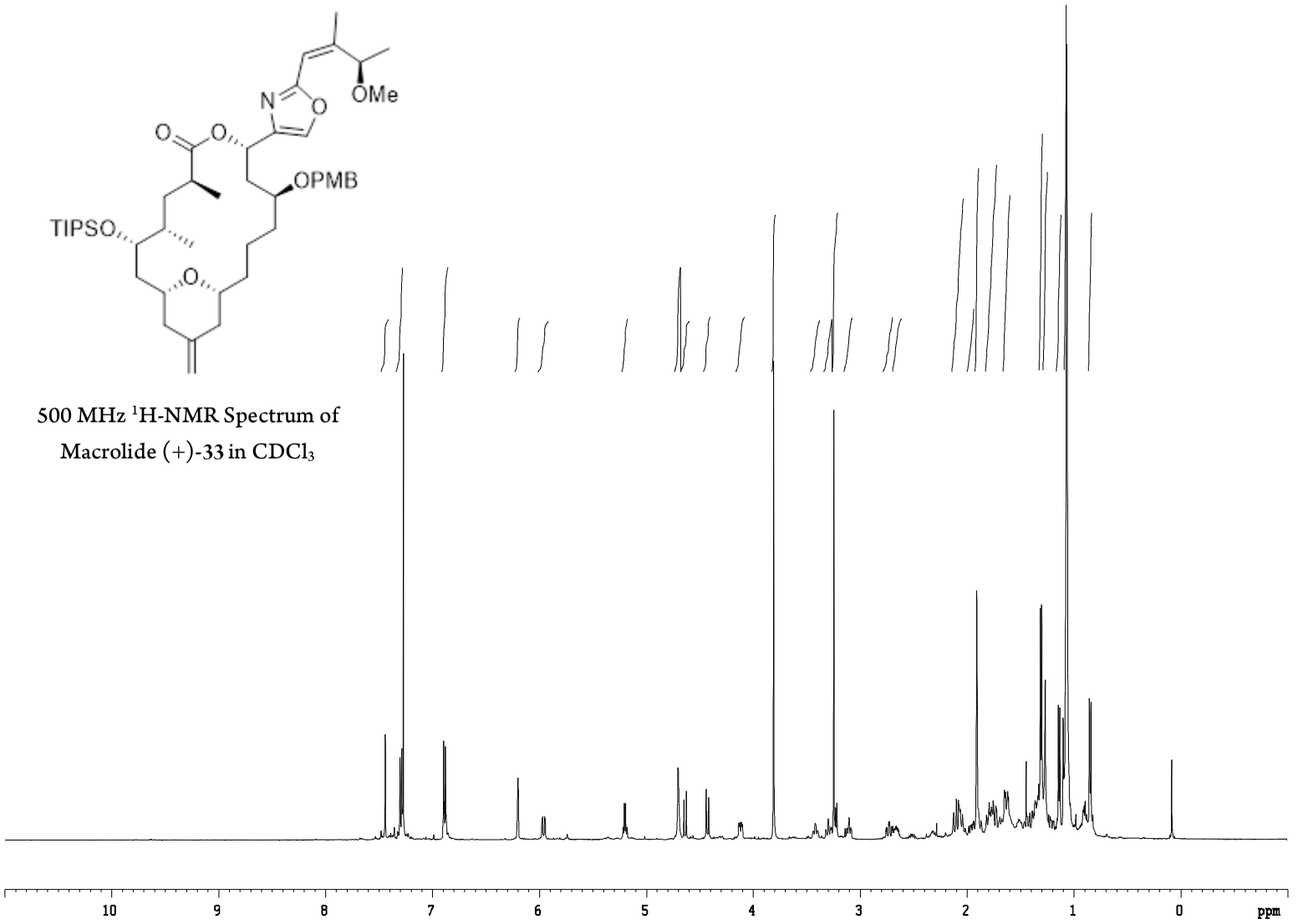
125 MHz ^{13}C-NMR Spectrum of
Diol (+)-S5 in $CDCl_3$



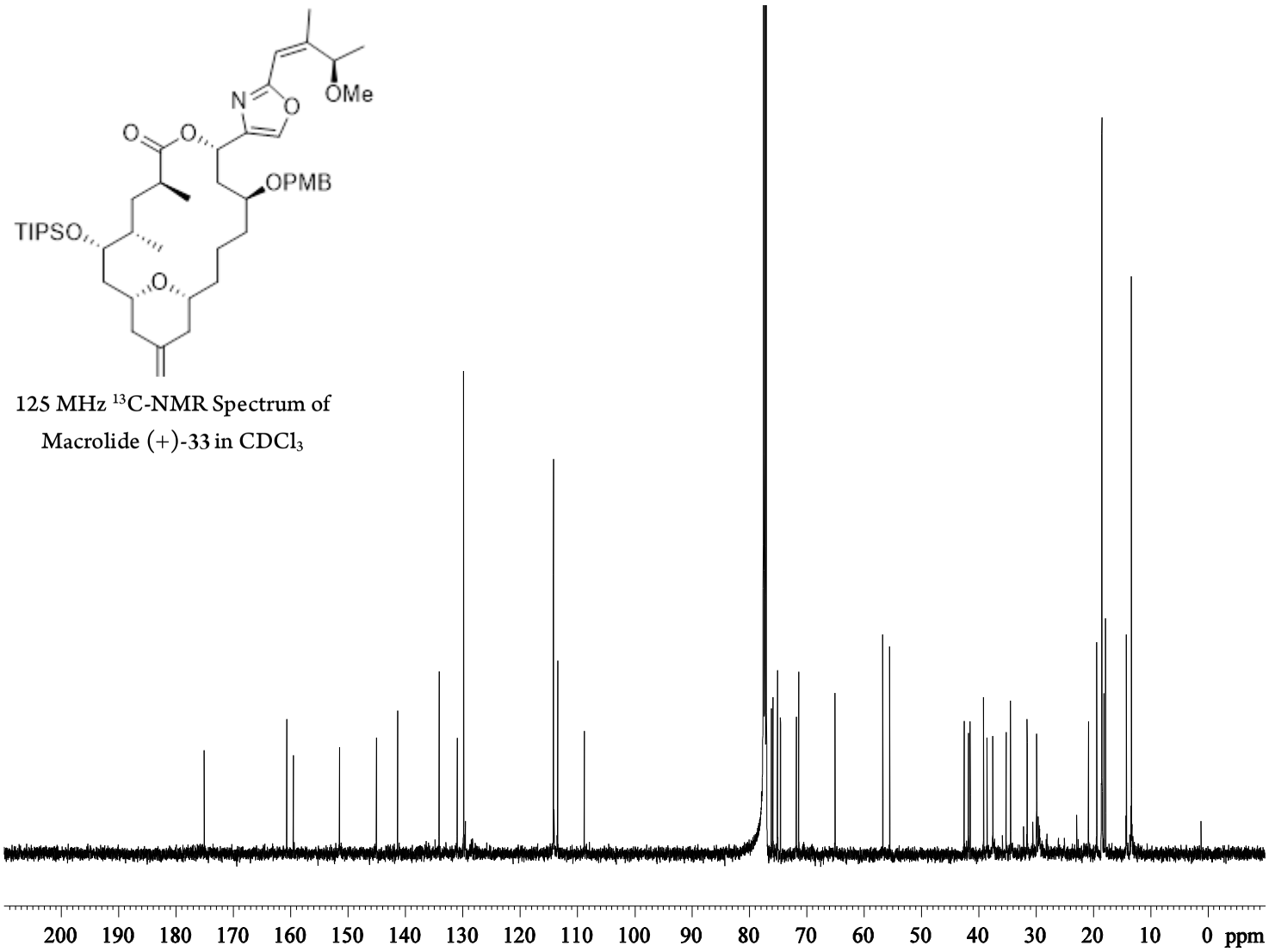
500 MHz ^{1}H-NMR Spectrum of
Carboxylic Acid (+)-**32** in $CDCl_3$



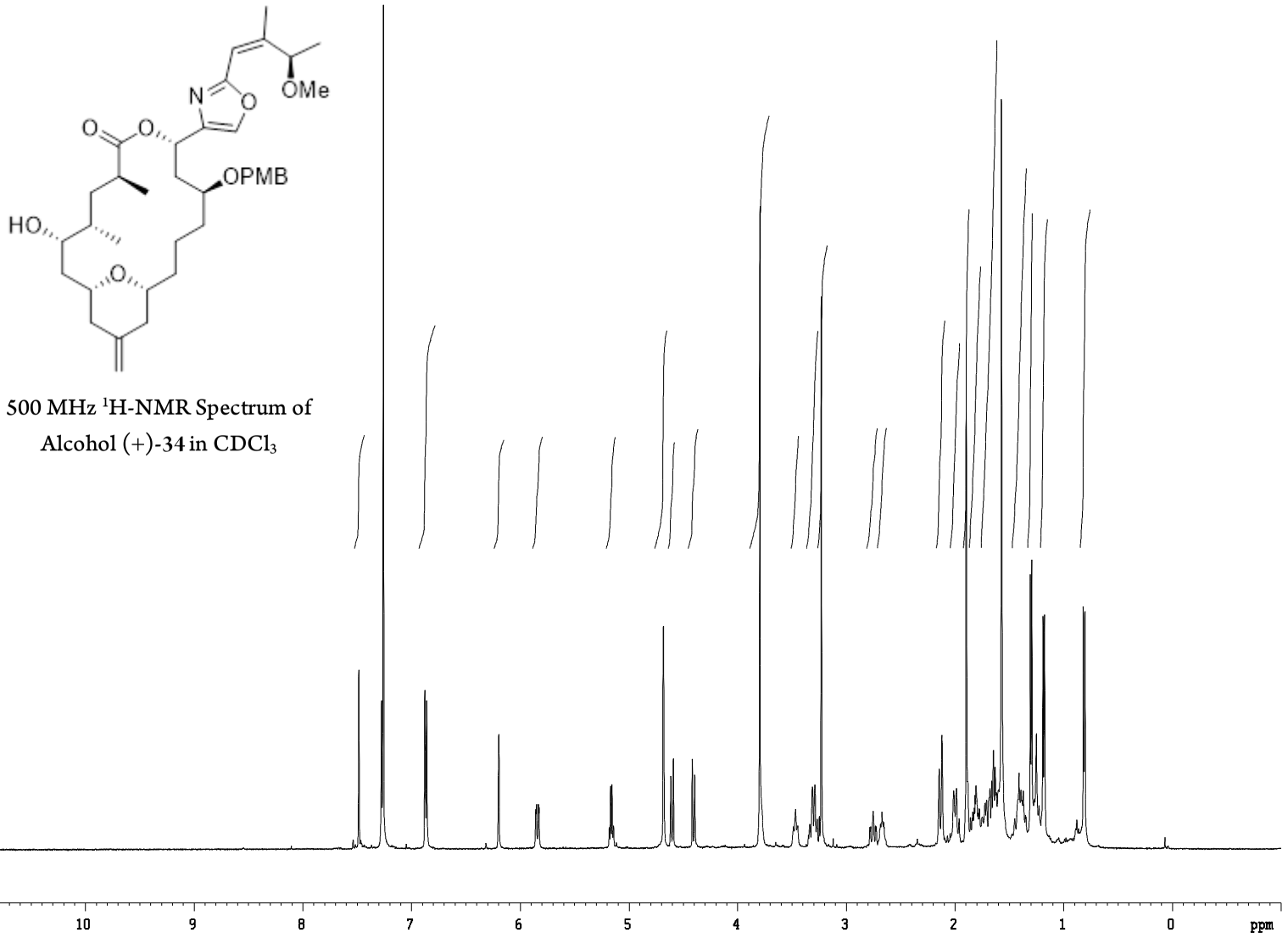
125 MHz ^{13}C-NMR Spectrum of
Carboxylic Acid (+)-**32** in $CDCl_3$



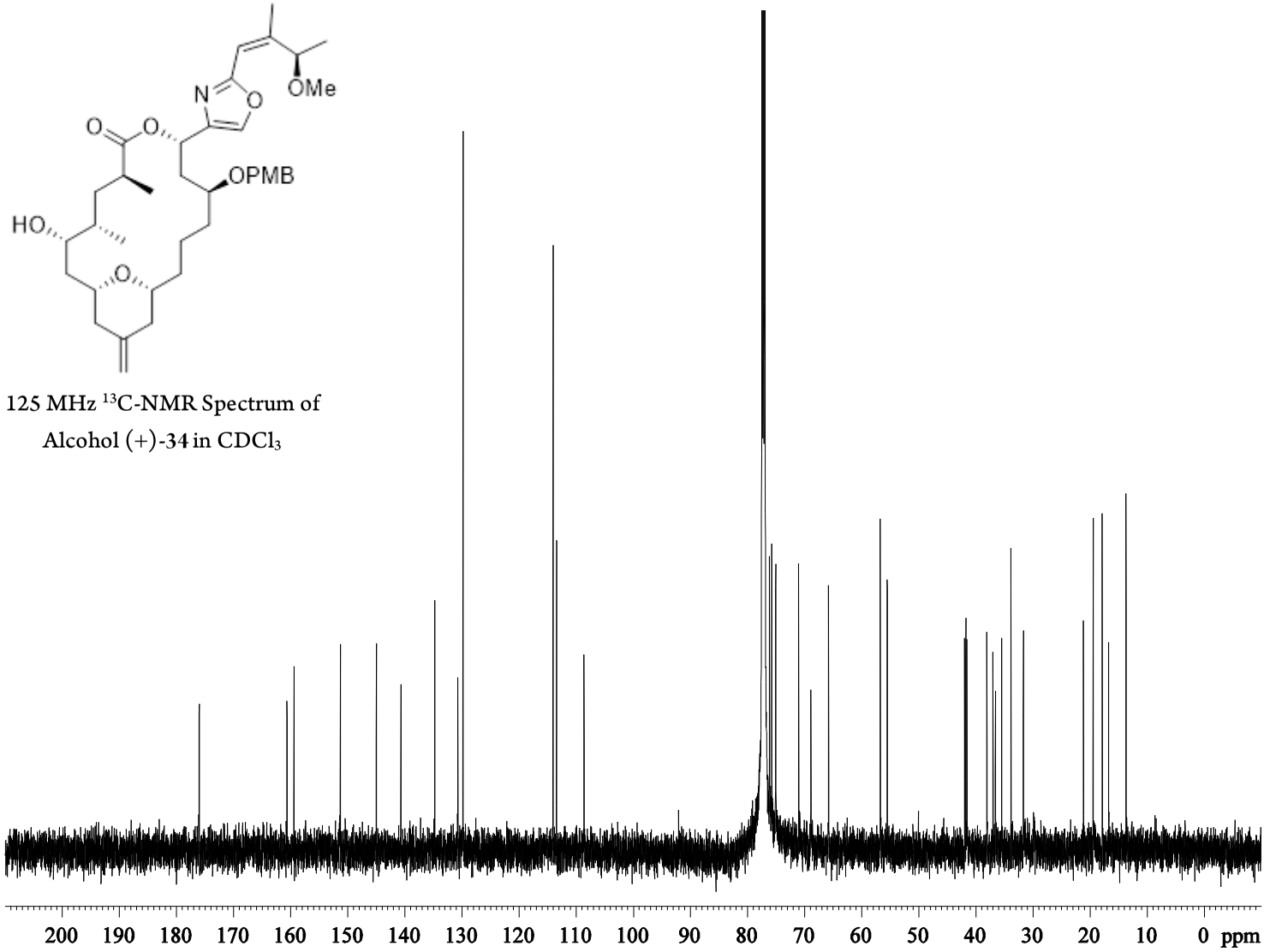
500 MHz ^{1}H-NMR Spectrum of Macrolide (+)-33 in $CDCl_3$



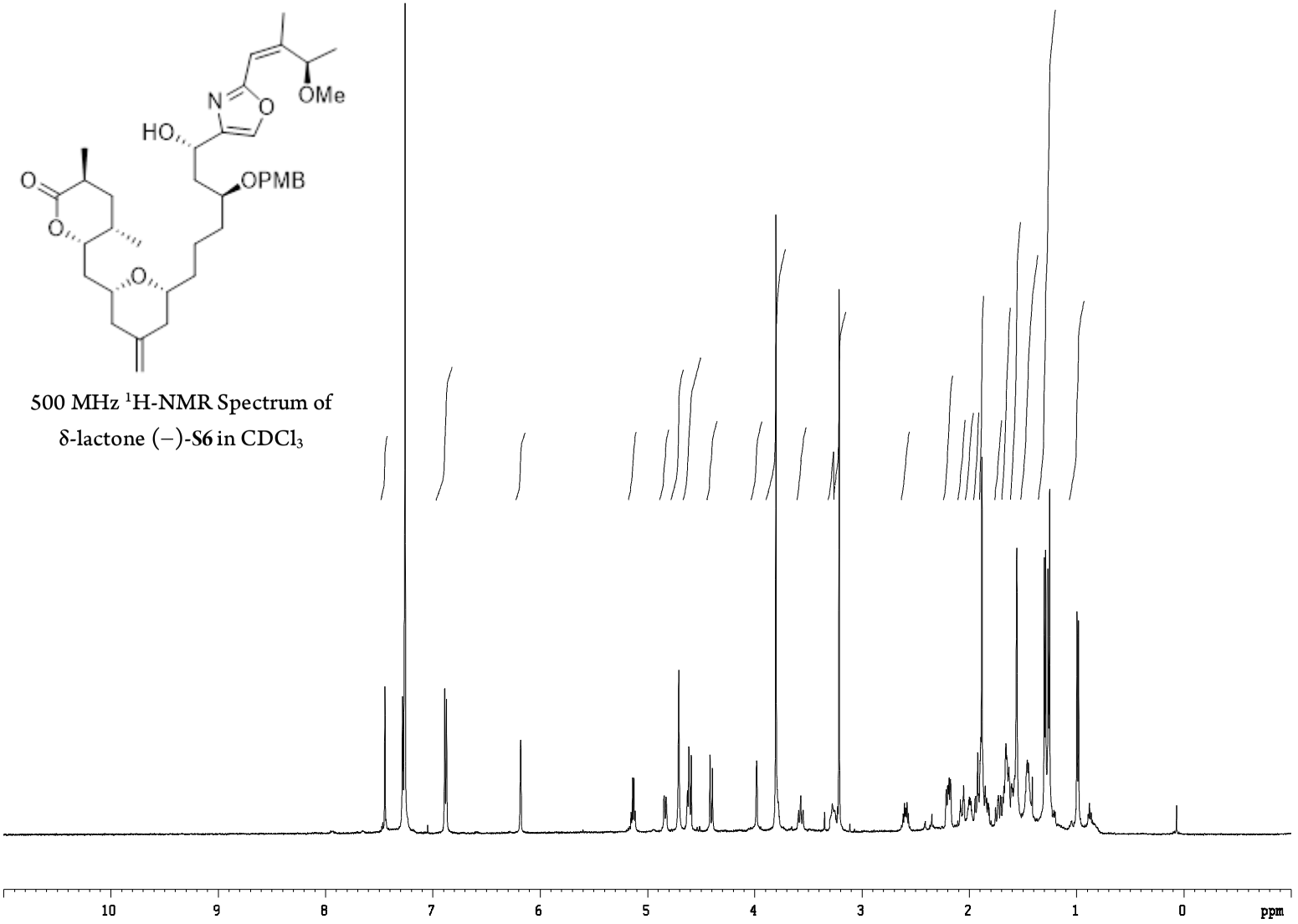
125 MHz ^{13}C-NMR Spectrum of
Macrolide (+)-33 in $CDCl_3$



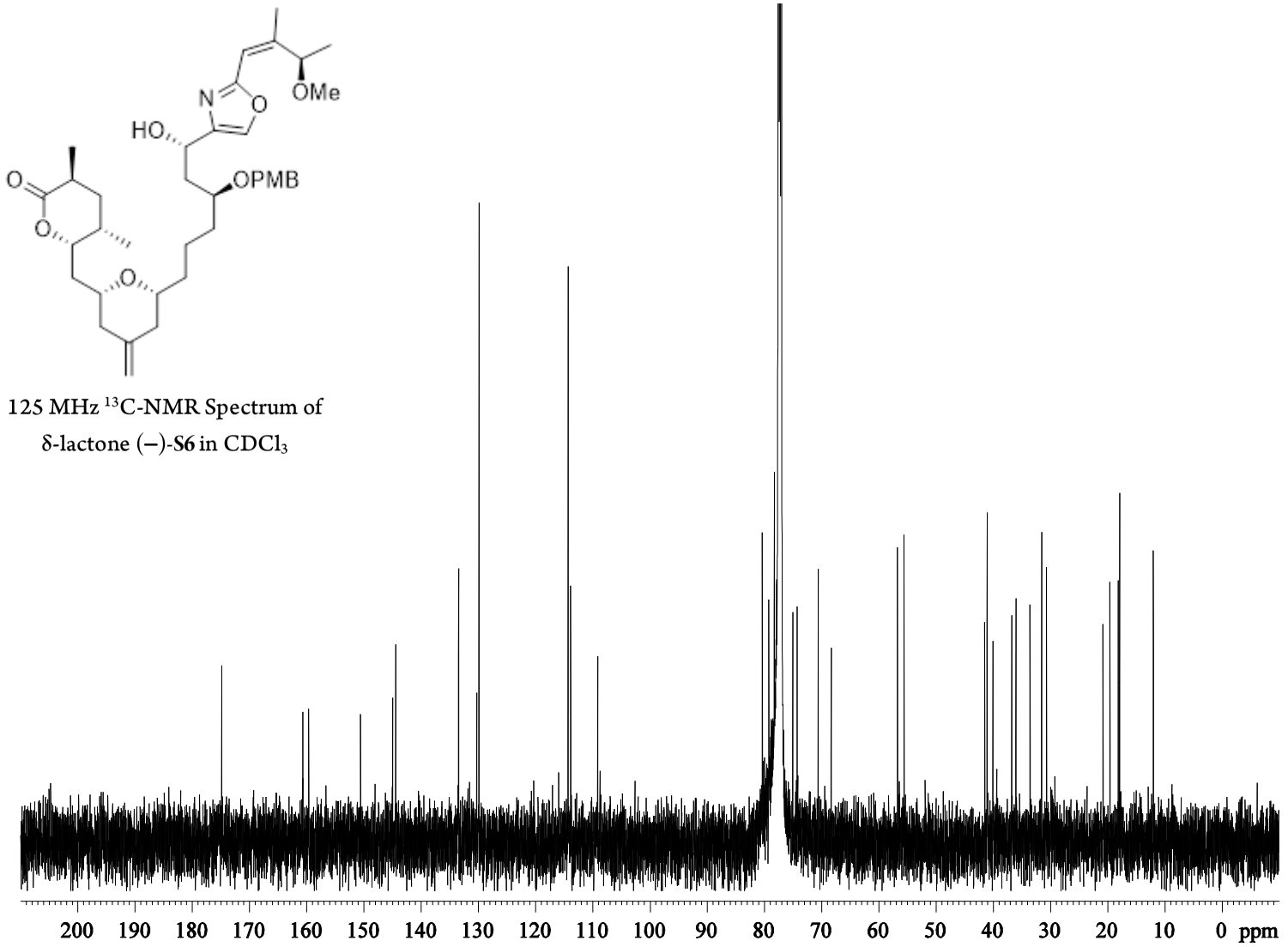
500 MHz ^{1}H-NMR Spectrum of
Alcohol (+)-**34** in $CDCl_3$



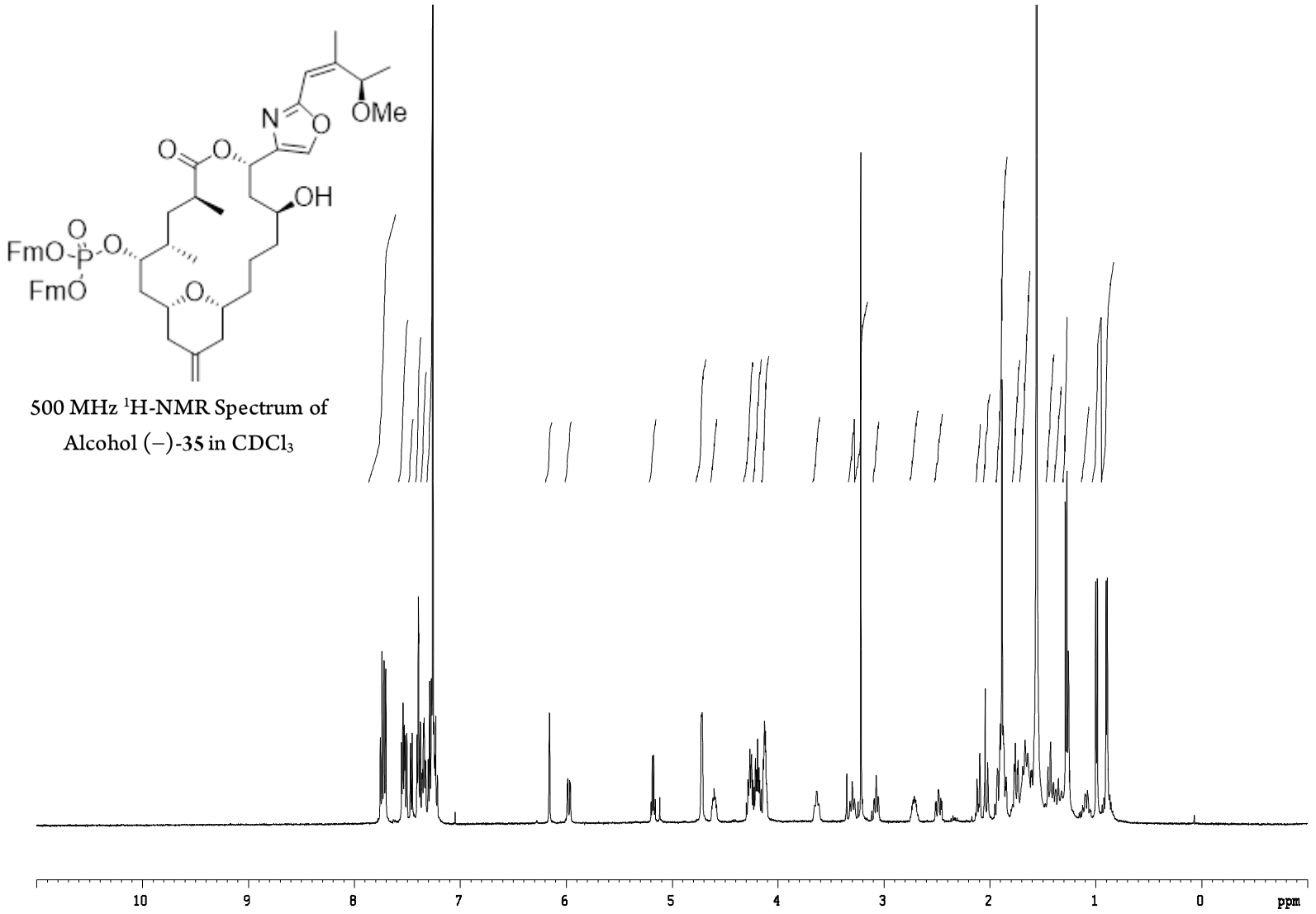
125 MHz ^{13}C-NMR Spectrum of
Alcohol (+)-34 in $CDCl_3$



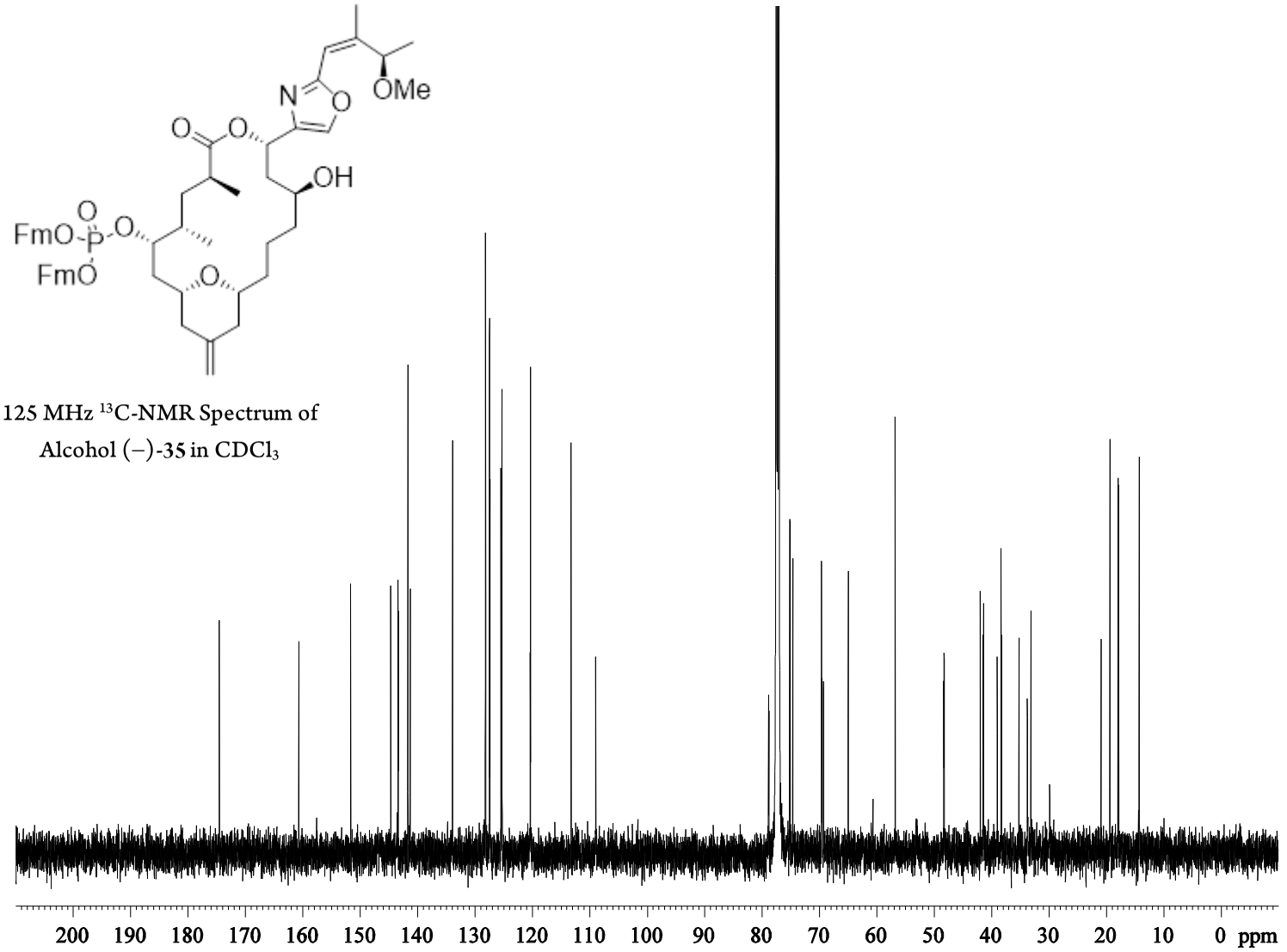
500 MHz ^{1}H-NMR Spectrum of
δ-lactone (−)-**S6** in $CDCl_3$



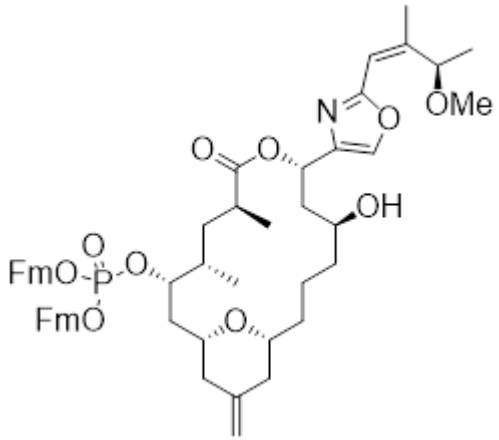
125 MHz ^{13}C-NMR Spectrum of
δ-lactone (−)-**S6** in $CDCl_3$



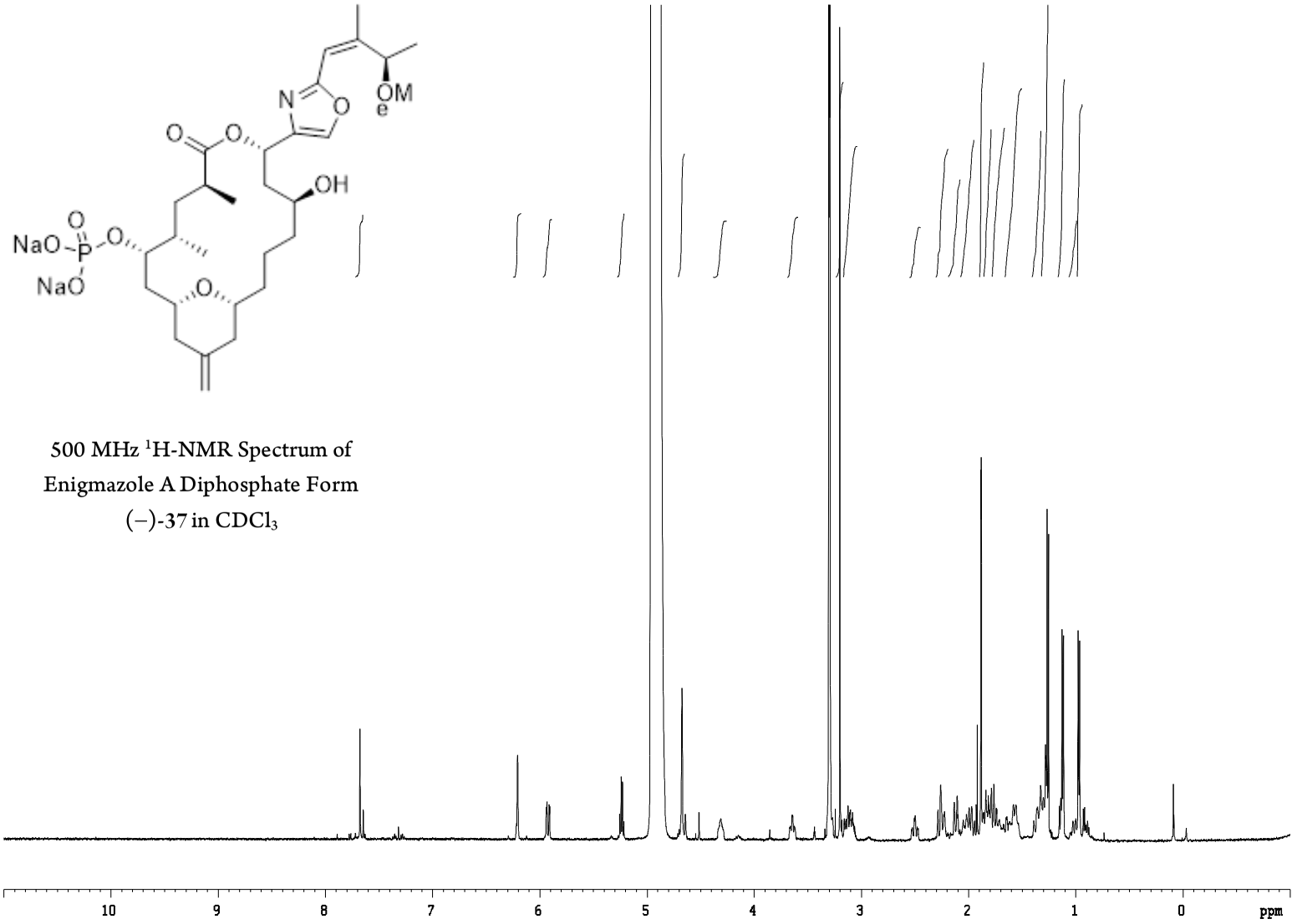
500 MHz ^{1}H-NMR Spectrum of
Alcohol (−)-35 in $CDCl_3$



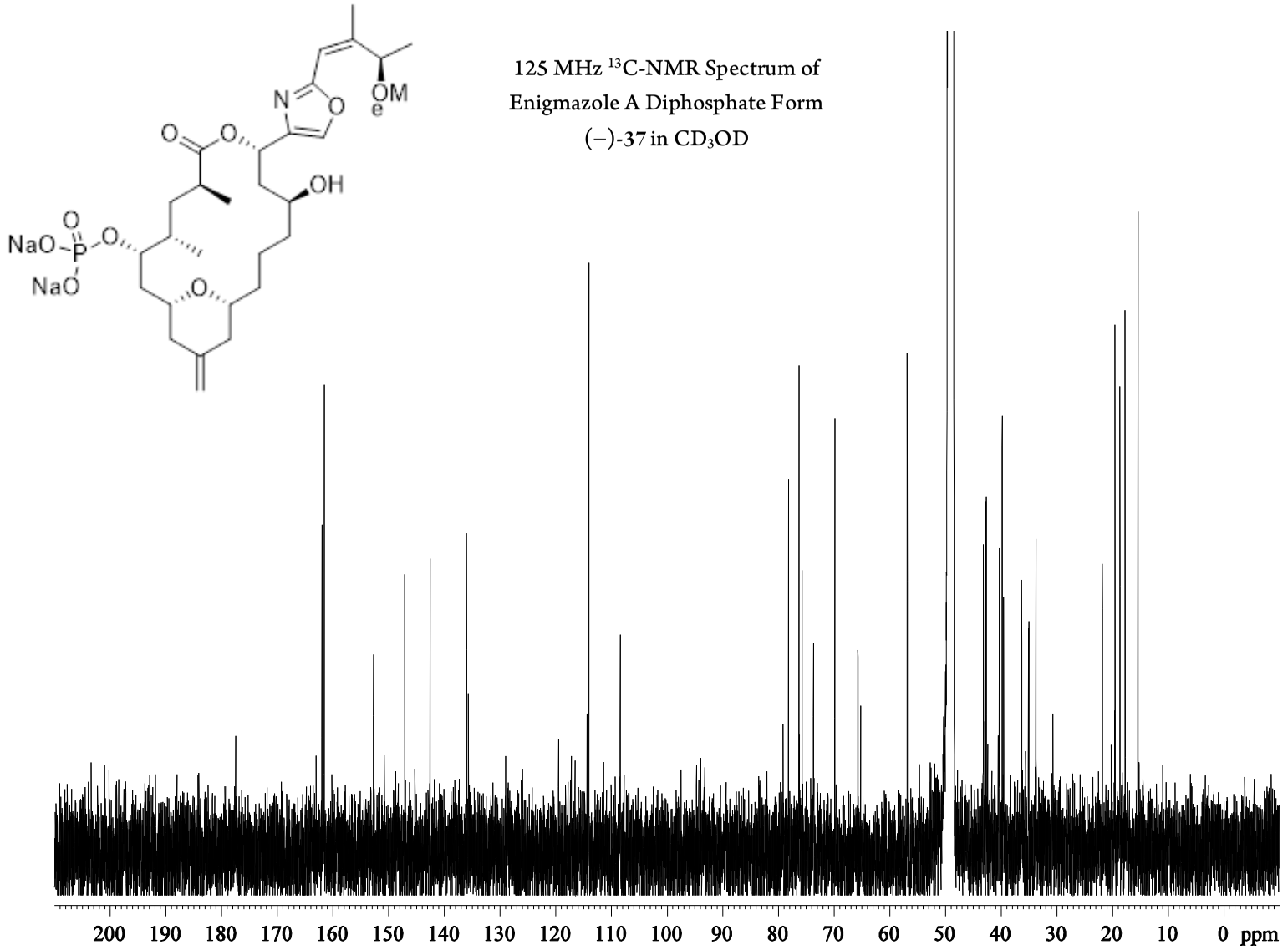
125 MHz ^{13}C-NMR Spectrum of
Alcohol (−)-35 in $CDCl_3$

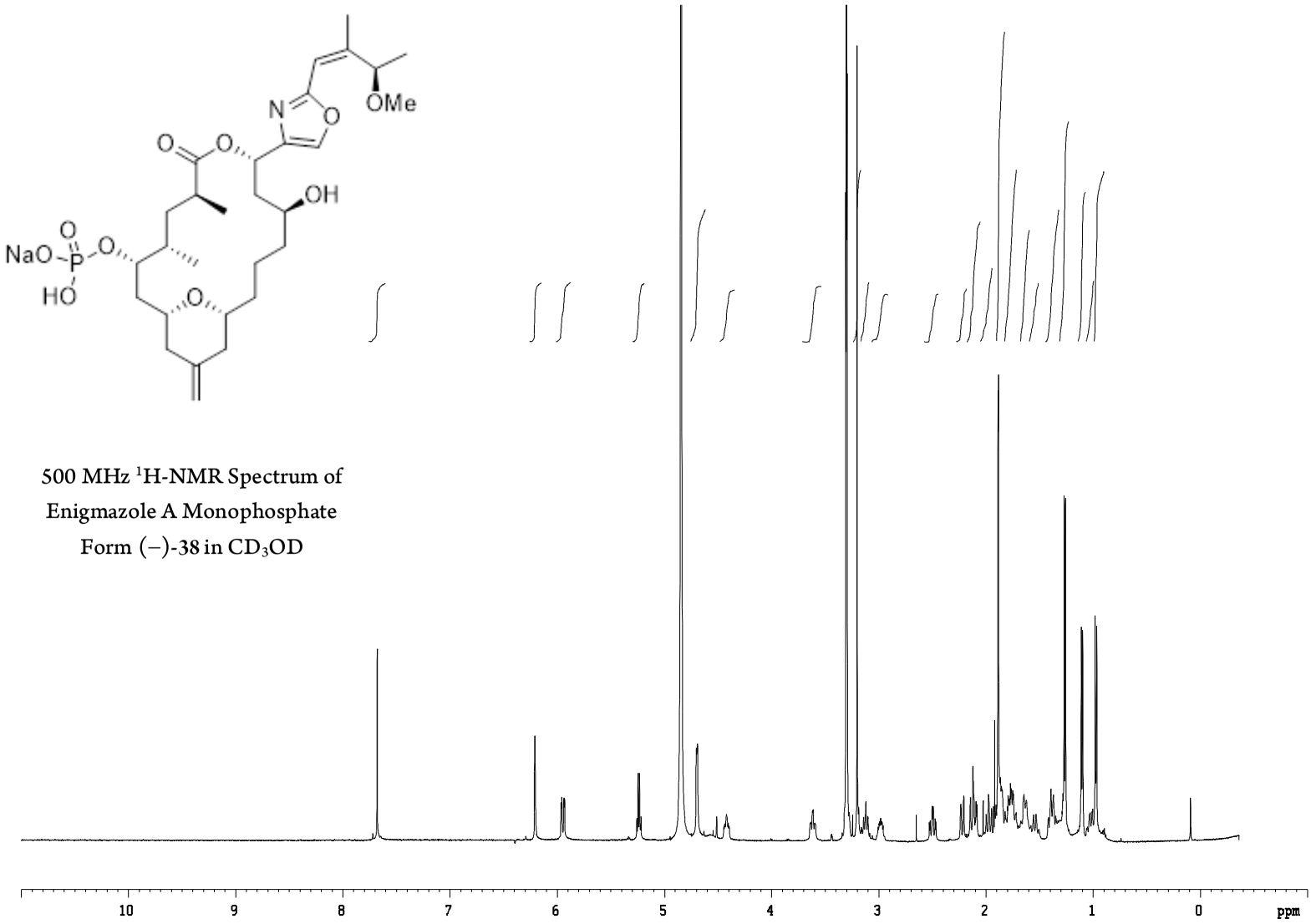


202 MHz ^{31}P-NMR Spectrum of
Alcohol (−)-**35** in $CDCl_3$

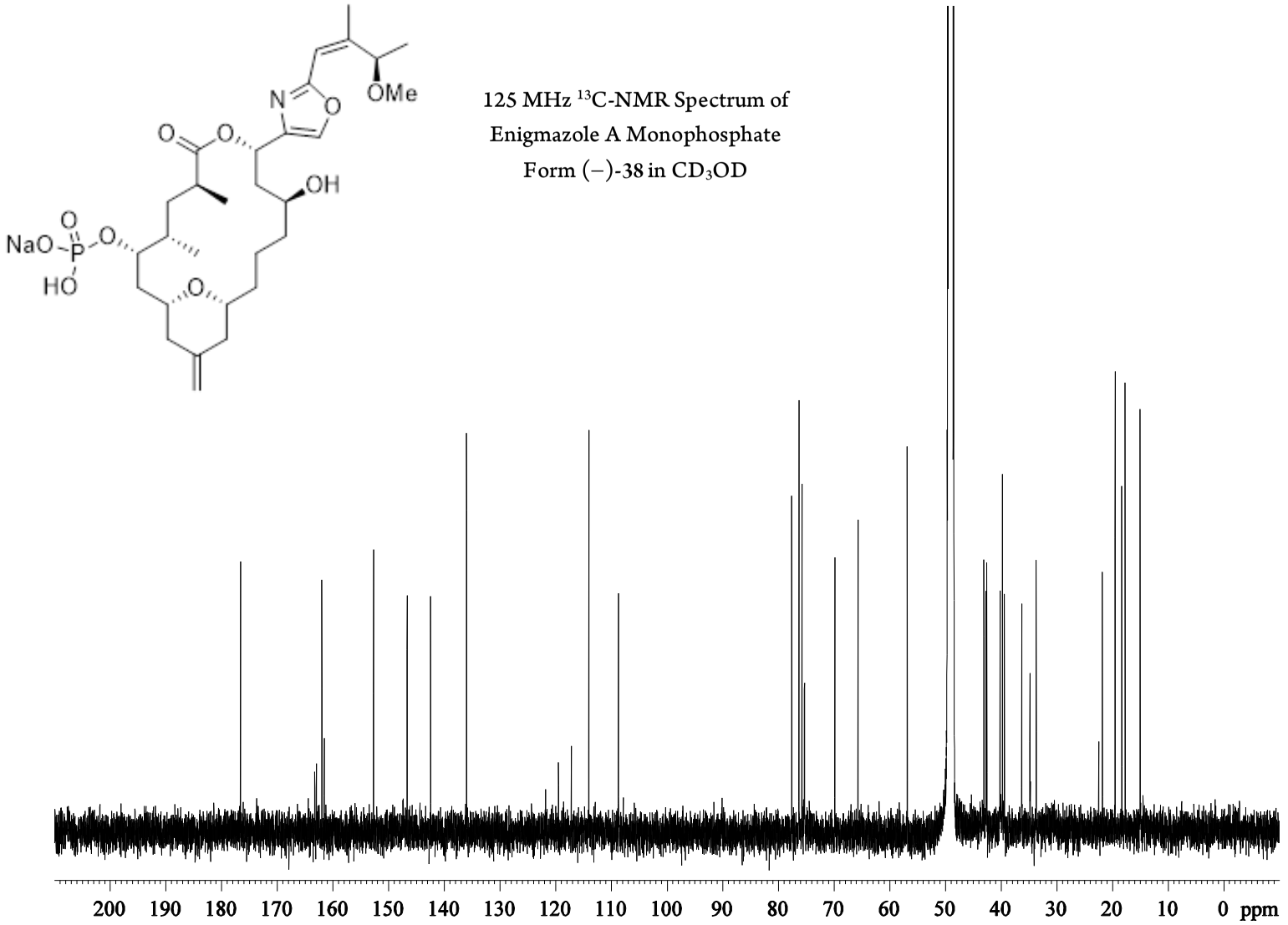


500 MHz ^{1}H-NMR Spectrum of
Enigmazole A Diphosphate Form
(−)-37 in $CDCl_3$

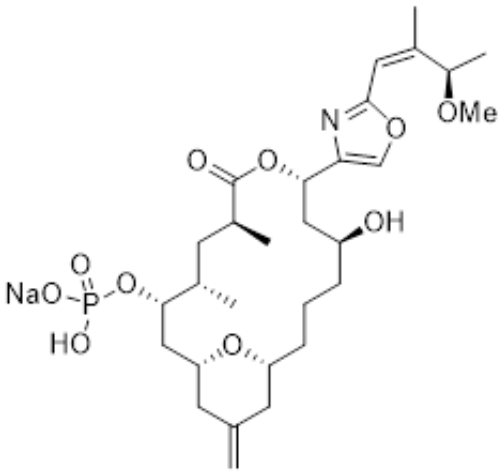

125 MHz ^{13}C-NMR Spectrum of
Enigmazole A Diphosphate Form
(−)-37 in CD_3OD
NaO
NaO
OH
OMe
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



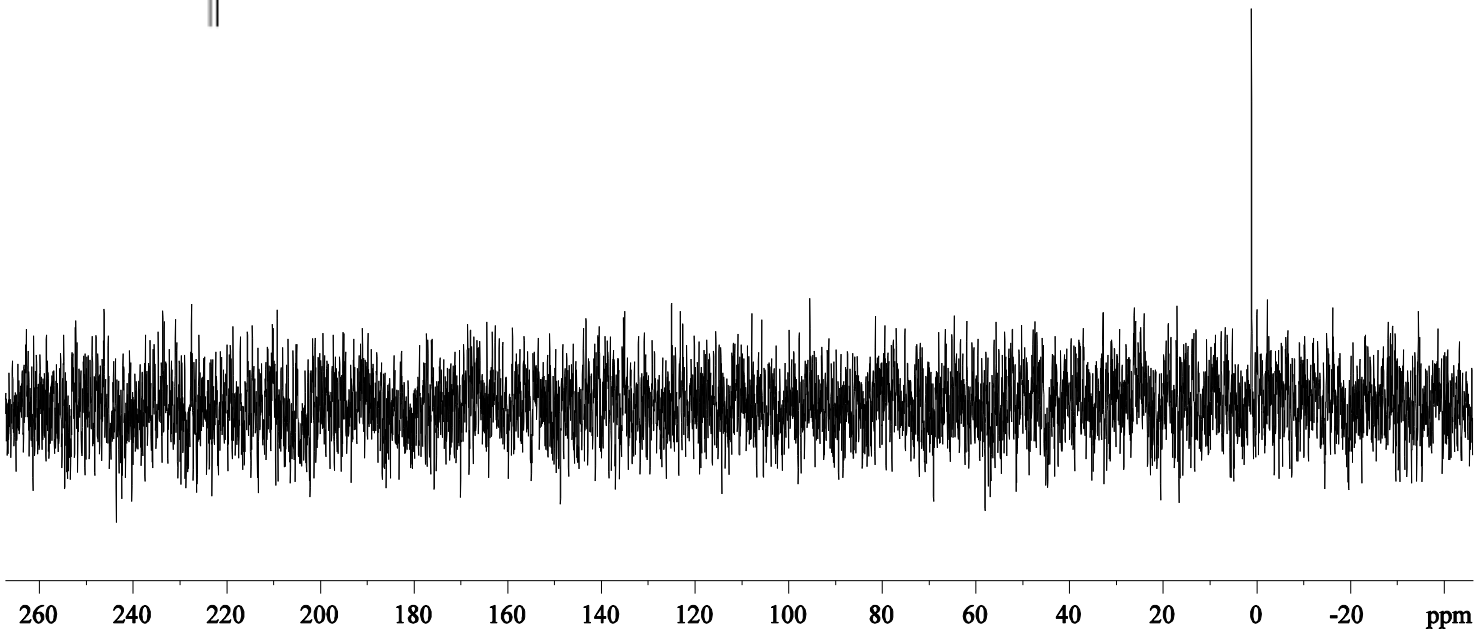
500 MHz ^{1}H-NMR Spectrum of
Enigmazole A Monophosphate
Form (−)-38 in CD_3OD

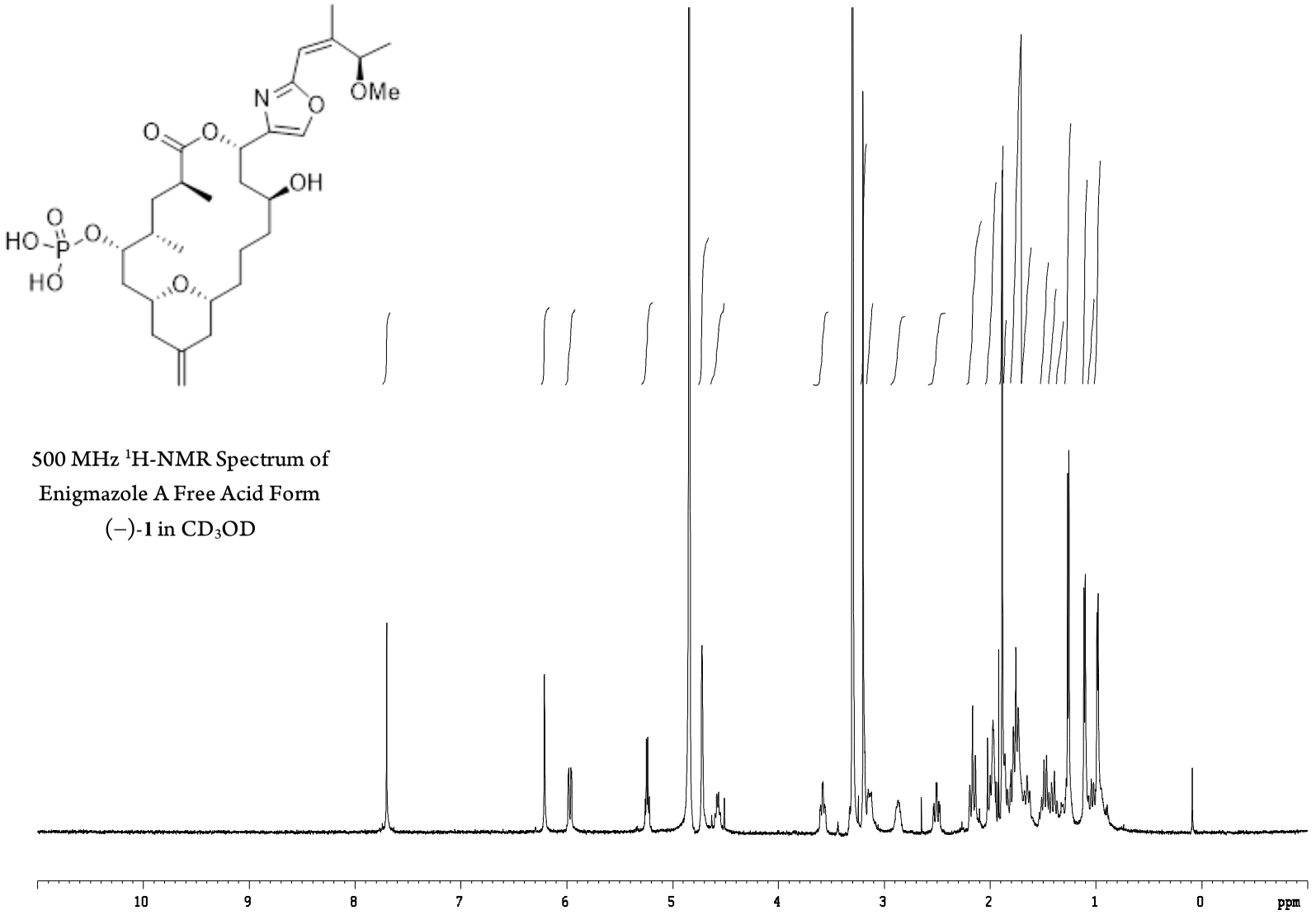


125 MHz ^{13}C-NMR Spectrum of
Enigmazole A Monophosphate
Form (−)-38 in CD_3OD

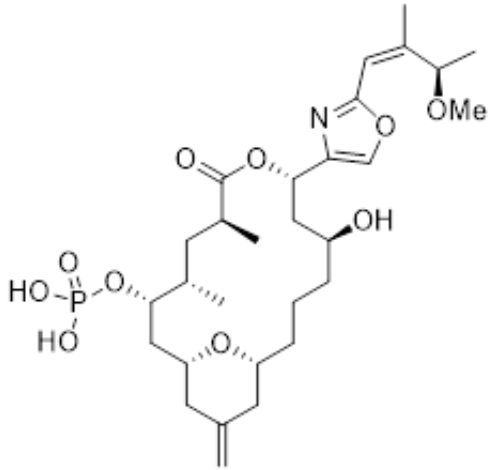


202 MHz ^{31}P-NMR Spectrum of
Enigmazole A Monophosphate
Form (−)-**38** in CD_3OD

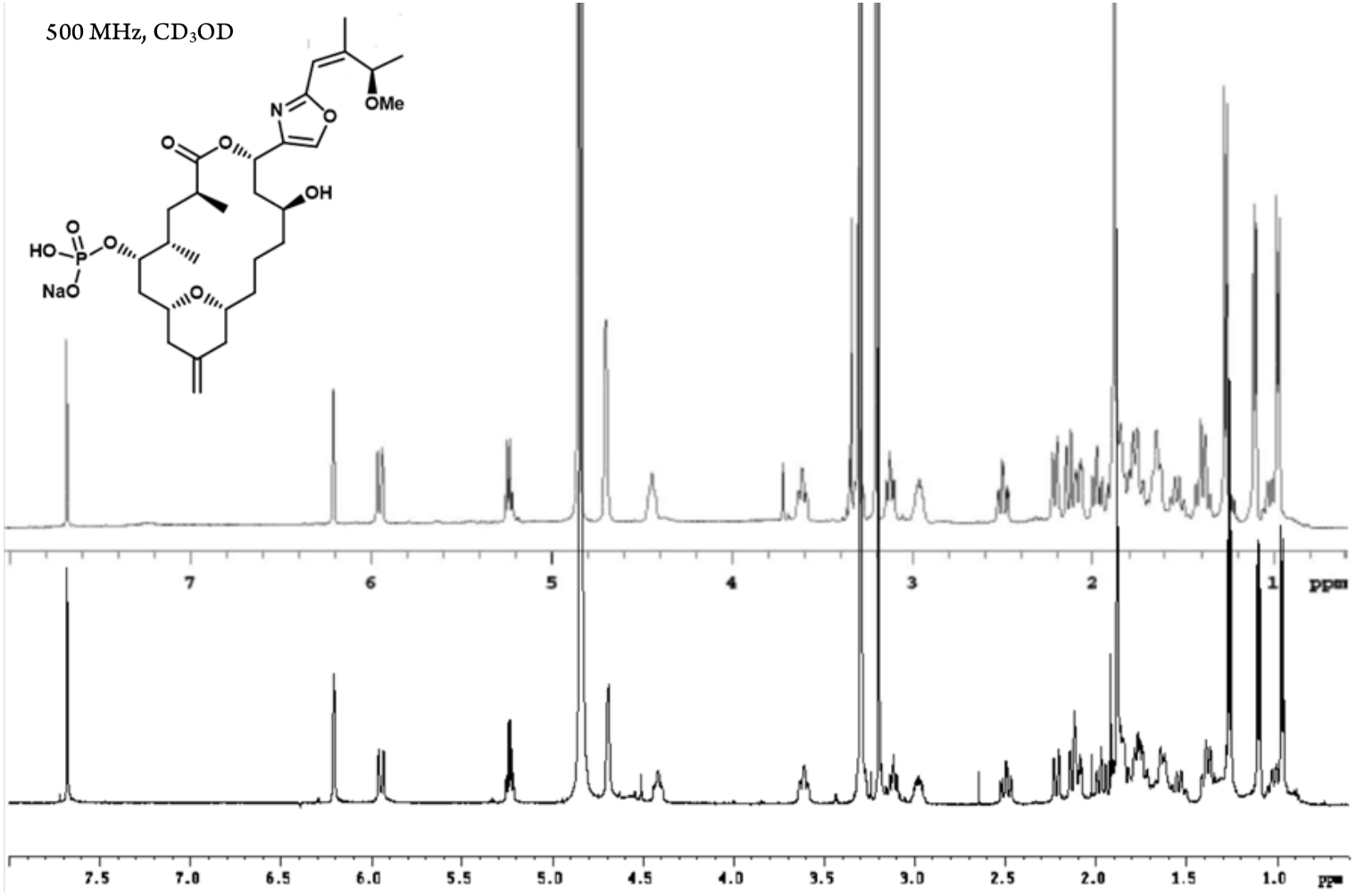




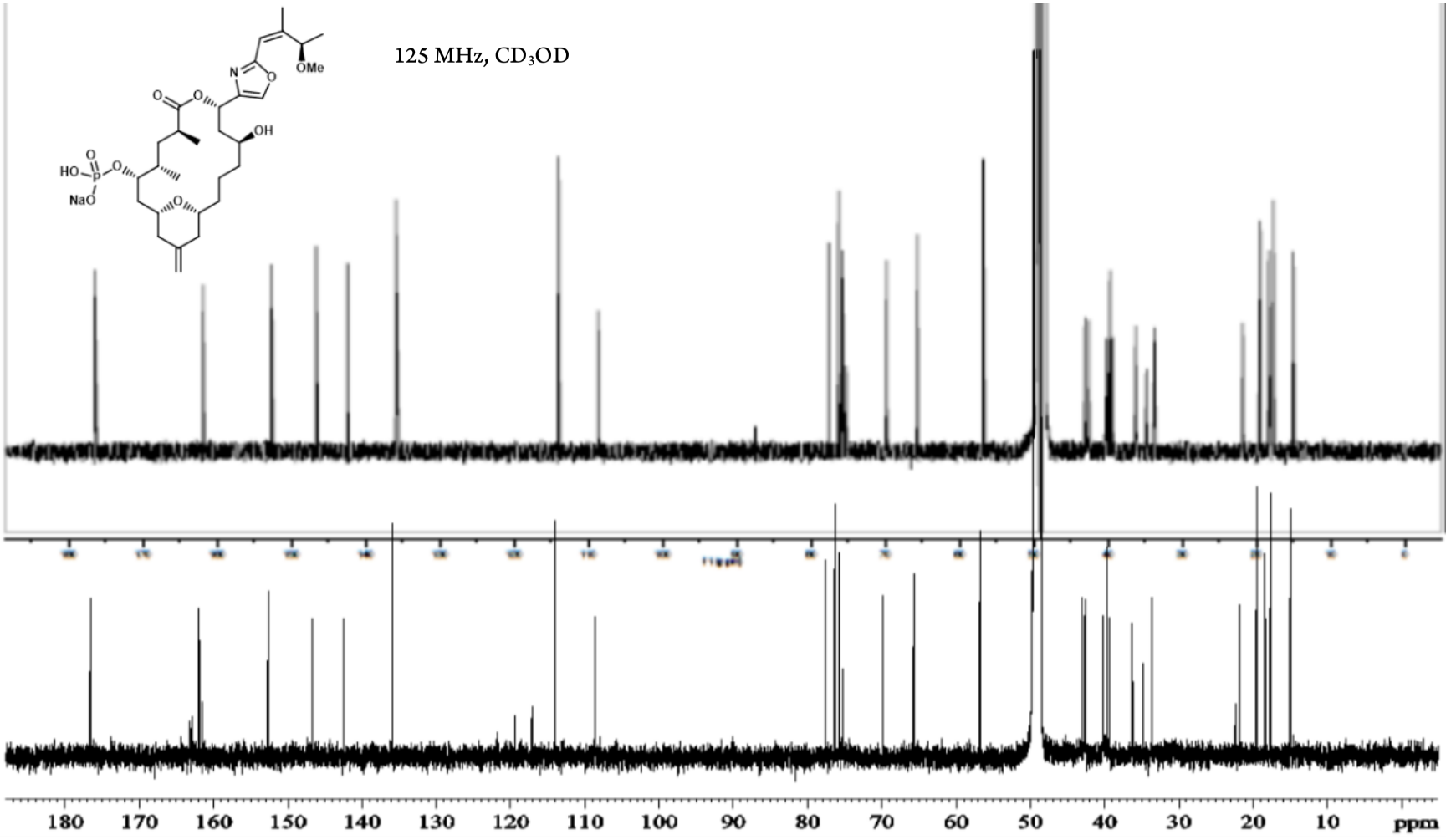
500 MHz ^{1}H-NMR Spectrum of
Enigmazole A Free Acid Form
(−)-**1** in CD_3OD



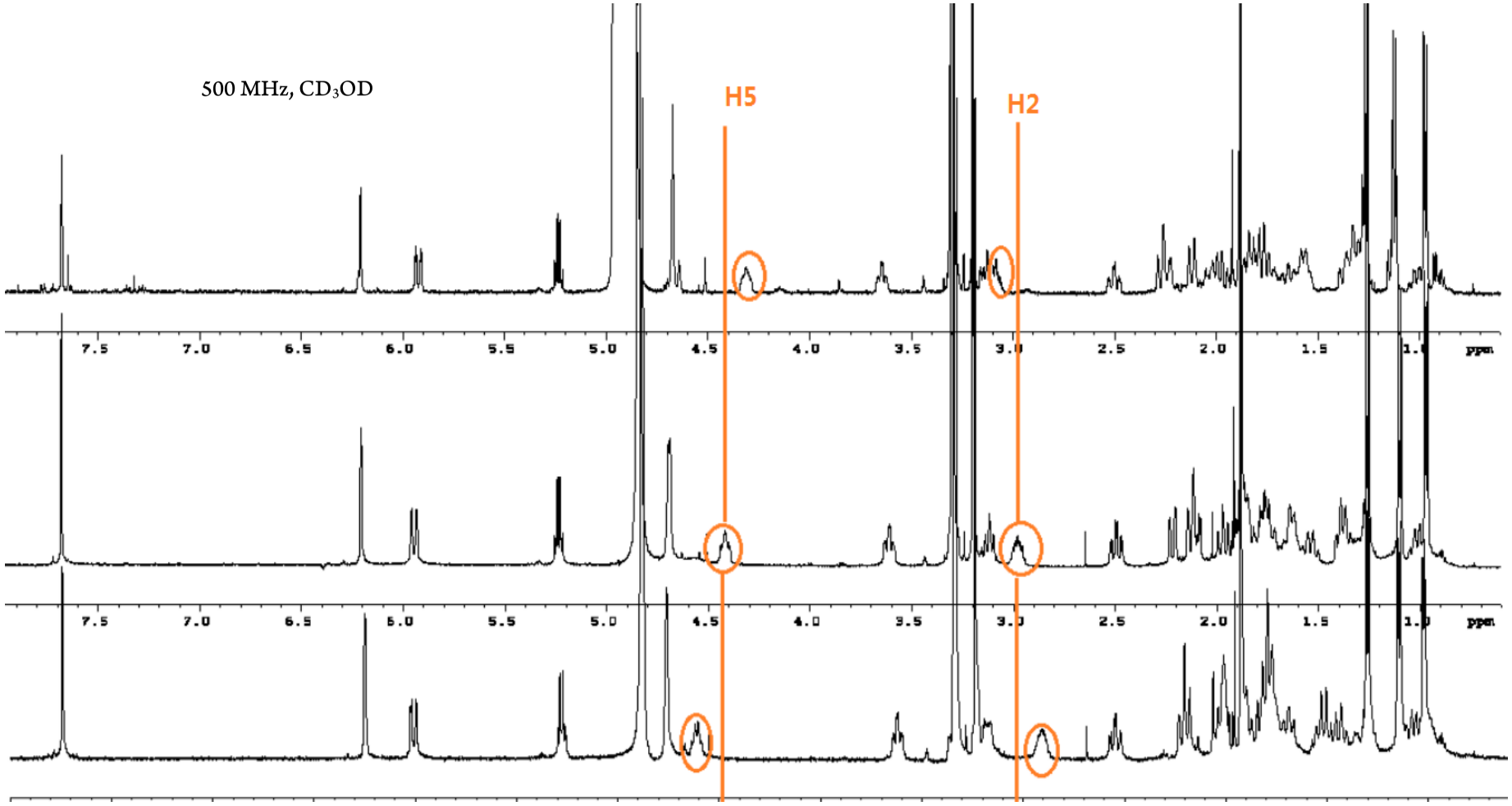
125 MHz ^{13}C-NMR Spectrum of
Enigmazole A Free Acid Form
(–)-**1** in CD_3OD



Comparisons of 1H NMR Spectra of Synthetic Monophosphate (−)-38 (lower) with Natural Enigmazole A (upper)



Comparisons of 1H NMR Spectra of Synthetic Monophosphate (−)-38 (lower) with Literature Enigmazole A (upper)



Comparisons of ^{1}H NMR Spectra of Three Phosphate Forms of Enigmazole A [Upper: Diphosphate (−)-**37**, Middle: Monophosphate (−)-**38**, Lower: Free Acid (−)-**1**, H2, H5 and low field protons have considerable differences]

6. References

1) Oku, N.; Takada, K.; Fuller, R. W.; Wilson, J. A.; Peach, M. L.; Pannell, L. K.; McMahon, J. B.; Gustafson, K. R. *J. Am. Chem. Soc.* **2010**, *132*, 10278
2) Skepper, C. K.; Quach, T.; Molinski, T. F. *J. Am. Chem. Soc.* **2010**, *132*, 10286.