Supporting Information

for

A Concise Total Synthesis of (±)- and (–)-Okilactomycin D

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I. Contents of Supporting Information

II. General Experimental Protocols

^{1}H and ^{13}C NMR spectra were recorded on Varian Inova 500 (500 MHz) and Varian Inova 300 (300 MHz) spectrometers. ^{1}H NMR chemical shifts in $CDCl_3$ are referenced to TMS (0.00 ppm) when TMS is present in the sample or to $CHCl_3$ (7.26 ppm) when not. The spectrum of the synthetic sample of okilactomycin D (**7**) in CD_3OD is referenced to CHD_2OD (3.31 ppm). Non-first order multiplets are identified as "nfom". ^{13}C NMR chemical shifts in $CDCl_3$ are referenced to chloroform (77.23 ppm) or methanol (49.15 ppm). The following format was used to report resonances: chemical shift in ppm (multiplicity, coupling constant(s) in Hz, integral value, and assignment). Coupling constant analysis was guided by methods we have described elsewhere.[1] Some complex structures are numbered in order to simplify identification of the proton assignment.

Infrared (IR) spectra were recorded on a Prospect MIDAC FT-IR spectrometer using a NaCl plate (thin film) or ZnSe plate (ATR). Absorptions are reported in cm^{-1}.

MPLC refers to medium pressure liquid chromatography (25-200 psi) using hand-packed columns of silica gel (18-32 μm, 60 Å pore size), a Waters HPLC pump, and a Waters R401 differential refractive index detector. Flash chromatography was performed using E. Merck silica gel (40-63 μm).

GCMS data were recorded on an Agilent 5975 MSD at 70 eV. The methods used are noted parenthetically: e.g., 5025015 refers to 2 min initial hold time at 50 °C, a ramp to 250 °C at a rate of 20 °C min^{-1}, and a final hold time of 3 min (for a total run time of 15 min). A 30 m × 0.32 mm × 0.25 μm film thickness HP-5 capillary column was used.

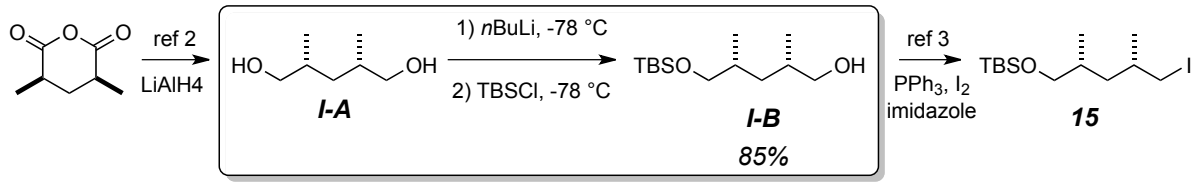
Optical rotations were recorded on a PerkinElmer 241 polarimeter at ambient temperature. The units for concentration (c) are g/100 mL.

The four single crystal structures were determined for racemic samples.

Reactions requiring anhydrous conditions were performed under an atmosphere of nitrogen or argon in flame or oven dried glassware. Anhydrous THF, diethyl ether, toluene, and methylene chloride were tapped immediately prior to use after being passed through a column of activated alumina. Triethylamine and pyridine were distilled from KOH. Diisopropylamine was distilled from CaH_2. DMF and DMSO were stored over 4Å molecular sieves.

III. Preparation Procedures and Characterization Data for All Key Compounds

(±)- *tert*-Butyl{[(*2R*,*4S*)-5-iodo-2,4-dimethylpentyl]oxy}dimethylsilane (15)

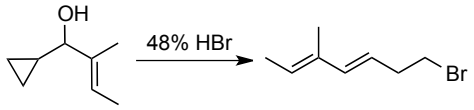


The synthesis of a racemic sample of **15** was accomplished via a known 3-step sequence (reduction,[2] TBS mono-protection, and iodination[3]) from cis-dimethyl glutaric anhydride as shown above. Our conditions for the reduction and iodination steps (1 and 3, respectively) were essentially identical to the reported procedures. Those for the conversion of **I-A** to **I-B** were modified somewhat, and the details are provided here.

Diol **I-A** (5.6 g, 42.4 mmol) was dissolved in THF (250 mL) in a 500 mL round bottom flask and cooled to -78 °C. To this solution was added *n*-BuLi (17.8 mL, 2.5 M in hexanes, 44.6 mmol) dropwise over 20 min. The resulting mixture was stirred at this temperature for 30 min. A solution of TBSCl (6.7 g, 44.6 mmol) in THF (25 mL) was added dropwise to the flask over 30 min. The resulting solution was stirred for an additional 1.5 h, at which time saturated NH_4Cl (50 mL) was added, and the resulting mixture was warmed to room temperature. Water (50 mL) was added to dissolve all inorganic salts. The aqueous layer was extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The crude mixture was subjected to flash chromatography (silica gel, hexanes:EtOAc = 12:1 then 4:1) to give (±)-**I-B** (8.8 g, 85%) as colorless oil.

A non-racemic sample of (+)-**15** was prepared by reported procedures.[4] These involved enantioselective, lipase-catalyzed (PPL) acetylation of diol **I-A** (the resulting mono-alcohol was measured to have an ca. 9:1 er by Mosher ester analysis), TBS protection, acetate methanolysis, and iodination. The sample of (+)-**15** had $[a]_D$ ($CHCl_3$, c = 2.0) = +3.1 [lit.[4] $[a]_D^{22}$ ($CHCl_3$, c = 2.09) = +3.50].

(2*E*,4*E*)-7-Bromo-3-methylhepta-2,4-diene (14)



17 ***14***

A neat sample of the crude alcohol **17** was cooled to 0 °C in an ice bath. Concentrated aqueous hydrobromic acid (48%, 22 mL) was added dropwise with vigorous stirring over 5 min. The mixture was stirred for an additional 8 min, at which time TLC showed full conversion. The resulting mixture was diluted with water and extracted with diethyl ether (50 mL x 3). The combined organic layers were washed sequentially with saturated $NaHCO_3$ (50 mL x 3) and brine (50 mL), dried over Na_2SO_4, and concentrated to give crude bromide **14**, which was vacuum distilled from CaH_2 to give **14** as a colorless liquid (18 g, 95 mmol, 71% overall). bp ca. 56 ^oC/2 mm Hg.

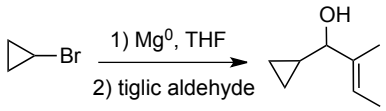
^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.15 (dq, *J* = 16.0 and 1.1 Hz, 1H, =CC*H*=CH), 5.52 (qq, *J* = 7.0 and 1.1 Hz, 1H, CH_3CH=), 5.48 (dt, *J* = 16.0 and 7.0 Hz, 1H, CH=C*H*-CH_2), 3.40 (t, *J* = 7.0 Hz, 2H, C*H*$_2$Br), 2.65 (dt, *J* = 7.0 and 7.0 Hz, 2H, C*H*$_2$$CH_2$Br), 1.74 (dd, *J* = 1.0 and 1.0 Hz, 3H, C*H*3C), and 1.72 (br d, *J* = 7.5 Hz, 3H, C*H*$_3$CH=).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 137.6, 134.0, 126.4, 122.8, 36.2, 32.8, 13.8, and 12.0 ppm.

IR (neat): 3032, 2962, 2918, 2858, 1650, 1445, 1379, 1260, 1206, 1034, 963, and 794 cm^{-1}.

GC-LRMS: t_R = 5.72 min. *m/z*: 190 (M^+), 188 (M^+), 109 (M^+ -Br), 95 (M^+ -CH_2Br), 81 (M^+ -CH_2CH_2Br), 67, and 55 ($C_4H_7^+$).

(±)-(*E*)-1-Cyclopropyl-2-methylbut-2-en-1-ol (17)



16 ***17***

A solution of **16** (18 g, 150 mmol) in THF (60 mL) was added dropwise to magnesium (3.6 g, 150 mmol) in THF (15 mL) under a nitrogen atmosphere at a rate to maintain a gentle reflux. The resulting mixture was stirred at room temperature for an additional 30 min and then cooled in an ice bath. Tiglic aldehyde (11.2 g, 133 mmol) in THF (25 mL) was then added over 15 min. The mixture was stirred at this temperature for 1 hour before saturated aqueous NH_4Cl was added. This mixture was extracted with diethyl ether (50 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give 18 g of crude alcohol. A portion of this crude alcohol was purified by flash chromatography (silica gel, hexanes:ether = 5:1) to give compound **17** as a colorless oil.

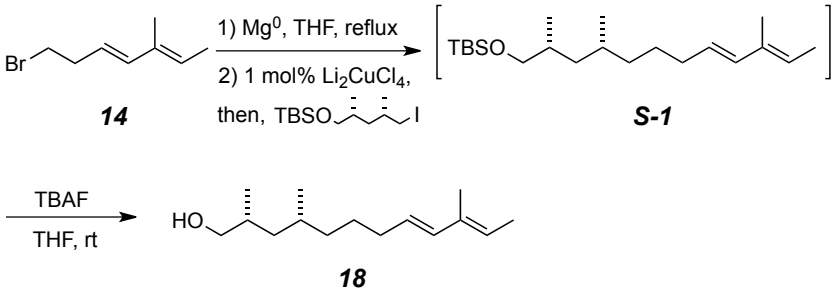
^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.47 (qq, *J* = 6.7 and 1.2 Hz, 1H, CH_3CH=), 3.21 (d, *J* = 8.6 Hz, 1H, CHOH), 1.71 (dq, *J* = 1.2 and 1.2 Hz, 3H, CH_3C=), 1.62 (qd, *J* = 6.7 and 1.2 Hz, 3H, CH_3CH=), 1.04 (ddddd, *J* = 8.6, 8.3, 8.3, 4.8 and 4.8 Hz, 1H, CHCHOH), 0.56 (dddd, *J* = 4.8, 4.8, 8.8, and 8.8 Hz, 1H), 0.50 (dddd, *J* = 4.8, 4.8, 8.8, and 8.8 Hz, 1H), 0.35 (dddd, *J* = 4.8, 4.8, 4.8, and 8.8 Hz, 1H), and 0.19 (dddd, *J* = 4.8, 4.8, 4.8, and 8.8 Hz, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 137.8, 120.6, 82.8, 16.4, 13.3, 11.9, 3.7, and 3.0 ppm.

IR (neat): 3400, 3080, 3005, 2919, 2862, 1671, 1433, 1380, 1022, and 1004 cm^{-1}.

GC-LRMS: t_R = 4.33 min; *m/z*: 126 (M+), 111 (M^+ -Me), 98 (M^+ -CH_2=CH_2), 91, 83, 69, and 55 ($C_4H_7^+$).

(±)-(2*R*,4*R*,8*E*,10*E*)-2,4,10-Trimethyldodeca-8,10-dien-1-ol (18)



A solution of bromodiene **14** (9.45 g, 50 mmol) in THF (27 mL) was added to crushed magnesium turnings (1.32 g, 55 mL) in THF (6 mL) under a nitrogen atmosphere at a rate to maintain a gentle reflux over 20 min. The Grignard reagent prepared was then transferred into a 100 mL round bottom flask cooled to 0 °C in an ice bath, to which a solution of Li_2CuCl_4 (5 mL, 0.1 M; made from a 2:1 mole ratio of anhydrous LiCl and $CuCl_2$) in THF was then added. The mixture was stirred at this temperature for 10 min, by which time the color of the solution had turned purple. Alkyl iodide **15** (4.5 g, 12.6 mmol) in THF (12 mL) was added. The resulting mixture was stirred at 0 °C for 2 h, at which time the solution had become grayish red. Aqueous saturated NH_4Cl (30 mL) was added. The aqueous layer was extracted with diethyl ether (50 mL x 2). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give crude diene silyl ether ***S-1*** (along with hydrocarbon by-products). Without further purification, this crude sample of ***S-1*** was dissolved in THF (75 mL) and cooled to 0 °C. TBAF (1.0 M in THF, 18 mL) was added dropwise over 10 min. The resulting solution was stirred overnight. The reaction mixture was quenched by addition of saturated NH_4Cl (30 mL). The aqueous layer was extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (silica gel, hexanes:EtOAc = 8:1) gave purified **18** (2.6 g, 12 mmol, 92% overall) as a colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.04 (d, *J* = 16.0 Hz, 1H, CH=$CHCH_2$), 5.53 (dt, *J* = 16.5 and 7.0 Hz, 1H, CH=CHCH_2), 5.43 (q, *J* = 7.0 Hz, 1H, CH_3CH=), 3.50 (dd, *J* = 5.0 and 10.0 Hz, 1H,

C*H*$_a$H$_b$OH), 3.36 (dd, *J* = 7.5 and 10.0 Hz, 1H, CH$_a$*H*$_b$OH), 2.08 (ddt, *J* = 14.0, 7.0 and 7.0 Hz, 1H, CH=CHC*H*$_a$H$_b$-), 2.03 (ddt, *J* = 14.0, 7.0, and 7.0 Hz, 1H, CH=CHCH$_a$*H*$_b$-), 1.71 (br s, 3H, C*H*$_3$C=CH), 1.69 (d, *J* = 7.5 Hz, 3H, C*H*$_3$CH=), 1.69 (m, 1H, HOCH$_2$C*H*-), 1.46-1.55 [m, 1H, HOCH$_2$CH(CH$_3$)CH$_2$C*H*(CH$_3$)-], 1.38-1.46 (m, 1H), 1.27-1.38 (m, 3H), 1.06 (m, 1H), 0.94 (m, 1H), 0.91 [d, *J* = 7.5 Hz, 3H, HOCH$_2$CH(C*H*$_3$)-], and 0.88 [d, *J* = 7.5 Hz, 3H, HOCH$_2$CH(CH$_3$)CH$_2$CH(C*H*$_3$)-].

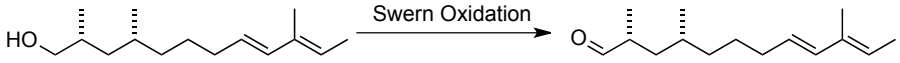
^{13}C NMR ($CDCl_3$, 125 MHz): 134.6, 134.4, 127.2, 124.4, 68.3, 41.0, 36.2, 33.2, 33.1, 29.9, 27.0, 20.3, 17.3, 13.7, and 12.1 ppm.

IR (neat): 3338, 2924, 2871, 2858, 1652, 1628, 1459, 1377, 1036, and 962 cm^{-1}.

GC-LRMS: t_R = 9.07 min. *m/z*: 224 (M^+), 209 (M^+-Me), 193 (M^+-CH_2OH), 151 (M^+-C_4H_8OH), 123, 109, 99, 95, 93, 81, 67, and 55 ($C_4H_7^+$).

The non-racemic sample of (+)-(2*R*,4*R*,8*E*,10*E*)-2,4,10-trimethyldodeca-8,10-dien-1-ol (**18**) had $[\alpha]_D$ = +12 (c = 3.5, $CHCl_3$).

(±)-(2*R*,4*R*,8*E*,10*E*)-2,4,10-Trimethyldodeca-8,10-dienal (19)



18 ***19***

To a stirred solution of oxalyl chloride (2.02 mL, 23.2 mmol) in CH_2Cl_2 (55 mL) cooled at -78 °C was added dropwise a solution of DMSO (3.08 mL, 46.4 mmol) in CH_2Cl_2 (8 mL). The resulting mixture was stirred at this temperature for 3 min, when a solution of diene alcohol **18** (2.6 g, 12 mmol) in CH_2Cl_2 (35 mL) was added. The resulting solution was stirred at this temperature for an additional 20 min, and triethylamine (9.7 mL, 69.6 mmol) was added. The resulting mixture was allowed to warm to 0 °C over 1 h with stirring. The mixture was quenched by addition of water (40 mL). The aqueous layer was extracted with CH_2Cl_2 (50 mL x 2). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The resulting crude aldehyde was subjected to flash chromatography (silica gel, hexanes:EtOAc = 15:1) to give purified aldehyde **19** (2.2 g, 85%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.58 (d, *J* = 2.5 Hz, 1H, -C*H*O), 6.05 (d, *J* = 15.5 Hz, 1H, CH$_3$CH=C(CH$_3$)C*H*=), 5.53 (dt, *J* = 15.0 and 7.0 Hz, 1H, CH$_3$CH=C(CH$_3$)CH=C*H*-), 5.43 (q, *J* = 6.5 Hz, 1H, CH$_3$C*H*=), 2.43 (dqd, *J* = 14.0, 7.0 and 2.6 Hz, 1H, -C*H*CHO), 2.07 (ddt, *J* = 14.0, 6.5, and 6.5 Hz, 1H, -CH=CH-C*Ha*Hb-), 2.05 (ddt, *J* = 14.0, 6.5, and 6.5 Hz, 1H, -CH=CH-CHa*Hb*-), 1.73 (m, 1H, CHOCH(CH$_3$)C*Ha*Hb-), 1.72 (br s, 3H, CH$_3$CH=C(C*H*$_3$)-), 1.70 (d, *J* = 7.5 Hz, 3H, C*H*$_3$CH=), 1.50 [m, 1H, CHOCH(CH$_3$)CH$_2$C*H*(CH$_3$)-], 1.28-1.49 [m, 4H, CHOCH(CH$_3$)CH$_2$CH(CH$_3$)C*H*$_2$C*H*$_2$-], 1.10-1.16 [m, 1H, CHOCH(CH$_3$)CHa*Hb*-], 1.08 [d, *J* = 7.0 Hz, 3H, CHOCH(C*H*$_3$)-], and 0.90 [d, *J* = 7.5 Hz, 3H, CHOCH(CH$_3$)CH$_2$CH(C*H*$_3$)-].

^{13}C NMR ($CDCl_3$, 125 MHz): δ 205.5, 134.9, 134.4, 127.0, 124.5, 44.2, 38.2, 36.3, 33.0, 30.3,

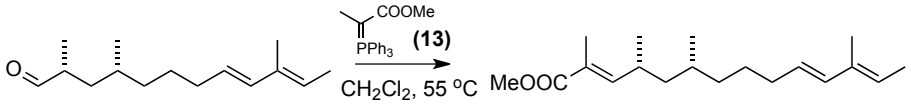
26.9, 19.8, 14.2, 13.7, and 12.1 ppm.

IR (neat): 2961, 2928, 2837, 2857, 2706, 1727, 1458, 1378, 1239, and 963 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{15}H_{26}NaO)^+$: 245.1876. Found: 245.1876.

The non-racemic sample of (-)-(2*R*,4*R*,8*E*,10*E*)-2,4,10-trimethyldodeca-8,10-dienal (**19**) had $[\alpha]_D$ = -5.1 (c = 2.0, $CHCl_3$).

(±)-(2*E*,4*R*,6*R*,10*E*,12*E*)-Methyl 2,4,6,12-Tetramethyltetradeca-2,10,12-trienoate (S-2)



19 ***S-2***

To a solution of aldehyde **19** (2.2 g, 9.9 mmol) in CH_2Cl_2 (82.5 mL) was added carbomethoxyethylidene triphenylphosphorane (**13**, 13.7 g, 39.6 mmol). The resulting solution was heated at 55 °C for 48 h in two capped culture tubes, at which time GC analysis showed full consumption of starting material. The resulting solution was concentrated in vacuo. The resulting yellow solid was triturated with hexanes and filtered. The solid cake was washed with additional hexanes (100 mL x 2). The combined filtrates were then concentrated and purified by flash chromatography (silica gel, hexanes:EtOAc = 15:1) to give triene ester **S-2** (2.9 g, 99%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.50 (dq, *J* = 10.0 and 1.5 Hz, 1H, $MeO_2CC(CH_3)$=C*H*-), 6.04 (d, *J* = 15.5 Hz, 1H, CH_3CH=CH(CH_3)C*H*=), 5.53 (dt, *J* = 15.0 and 7.0 Hz, 1H, CH_3CH=CH(CH_3)CH=C*H*-), 5.43 (q, *J* = 6.5 Hz, 1H, CH_3CH=), 3.73 (s, 3H, -COOCH_3), 2.60 (m, 1H, $MeO_2CC(CH_3)$=CHC*H*(CH_3)CH_2-), 2.04 (dt, *J* = 7.0 and 7.0 Hz, 2H, -CH=CH-CH_2-), 1.84 (d, *J* = 1.5 Hz, 3H, $MeO_2CC(CH_3)$=CHCH(CH_3)CH_2-), 1.72 (br s, 3H, CH_3CH=C(CH_3)CH=), 1.70 (d, *J* = 7.0 Hz, 3H, CH_3CH=), 1.22-1.45 (m, 5H), 1.05-1.18 (m, 2H), 0.97 (d, *J* = 6.5 Hz, 3H, $MeO_2CC(CH_3)$=CHCH(CH_3)CH_2-), and 0.82 [d, *J* = 6.0 Hz, 3H, $MeO_2CC(CH_3)$=CHCH(CH_3)CH_2CH(CH_3)-].

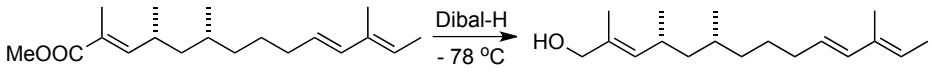
^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.9, 148.5, 134.7, 134.4, 127.2, 125.9, 124.4, 51.7, 44.5, 37.2, 33.1, 30.9, 30.7, 27.0, 20.6, 19.5, 13.7, 12.5, and 12.1 ppm.

IR (neat): 2954, 2926, 2869, 1717, 1649, 1454, 1435, 1377, 1312, 1274, 1225, 1191, 1155, 1098, 963, and 760 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{19}H_{32}NaO_2)^+$ 315.2295. Found: 315.2292.

The non-racemic sample of (-)-(2*E*,4*R*,6*R*,10*E*,12*E*)-methyl 2,4,6,12-yetramethyltetradeca-2,10,12-trienoate (**S-2**) had $[\alpha]_D$ = -14.0 (c = 3.1, $CHCl_3$).

(±)-(2*E*,4*R*,6*R*,10*E*,12*E*)-2,4,6,12-Tetramethyltetradeca-2,10,12-trien-1-ol (S-3)



S-2 ***S-3***

To a solution of triene ester **S-2** (2.9 g, 9.9 mmol) in toluene (100 mL) cooled at -78 °C was added dropwise a Dibal-H solution (20 mL, 1.5 M in toluene, 3.1 equiv). The reaction mixture was stirred at this temperature for 2 h, at which time TLC showed full consumption of starting material. The mixture was quenched at -78 °C by slow addition of a solution containing AcOH (2.5 g, 41.7 mmol), NaOAc (2.4 g, 29.1 mmol), THF (9.5 mL), and water (40 mL). The mixture was allowed to warm to room temperature, Celite was added, and stirring was continued for 30 min. The mixture was filtered through a Celite bed. The aqueous layer was extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The resulting crude mixture was purified with flash chromatography (silica gel, hexanes:EtOAc = 10:1) to give triene alcohol **S-3** (2.46 g, 9.4 mmol, 94%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.04 [d, *J* = 15.5 Hz, 1H, CH_3CH=$CH(CH_3)CH$=], 5.53 (dt, *J* = 15.0 and 7.0 Hz, 1H, =$CH$$CH_2$), 5.44 (q, *J* = 6.5 Hz, 1H, CH_3CH=), 5.10 [dtq, *J* = 10.0, 1.5, and 1.5 Hz, 1H, -CH=$C(CH_3)CH_2OH$], 3.98 (br s, 2H, -CH_2OH), 2.48 [m, 1H, -$CH(CH_3)CH$=], 2.04 (dt, *J* = 7.5 Hz, 7.5 Hz, 2H, =CH-CH_2-), 1.72 [dt, *J* = 1.5 and 1.5 Hz, 3H, -CH=$C(CH_3)CH_2OH$], 1.70 (d, *J* = 7.0 Hz, 3H, CH_3CH=), 1.67 [d, *J* = 1.5 Hz, 3H, CH_3CH=$C(CH_3)$=], 1.30-1.42 (m, 3H), 1.21-1.30 (m, 2H), 1.02-1.15 (m, 2H), 0.91 [d, *J* = 6.5 Hz, 3H, =CHCH(CH_3)-], and 0.82 [d, *J* = 6.5 Hz, 3H, =CHCH(CH_3)$CH_2CH(CH_3)$-].

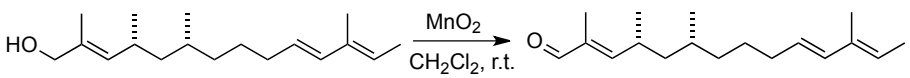
^{13}C NMR ($CDCl_3$, 125 MHz): δ 134.6, 134.4, 133.1, 133.0, 127.3, 124.4, 69.1, 45.1, 37.2, 33.2, 30.4, 29.6, 27.1, 21.6, 19.6, 13.8, 13.7, and 12.1 ppm.

IR (neat): 3200-3600, 2953, 2924, 2866, 1651, 1628, 1455, 1377, 1069, 1009, 962, 848, and 798 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{18}H_{32}NaO)^+$ 287.2346. Found: 287.2345.

The non-racemic sample of (-)-(2*E*,4*R*,6*R*,10*E*,12*E*)-2,4,6,12-tetramethyltetradeca-2,10,12-trien-1-ol (**S-3**) had $[\alpha]_D$ = -2.9 (c = 6.0, $CHCl_3$).

(±)-(2*E*,4*R*,6*R*,10*E*,12*E*)-2,4,6,12-Tetramethyltetradeca-2,10,12-trienal (20)



S-3 ***20***

To a solution of triene alcohol **S-3** (2.46 g, 9.4 mmol) in CH_2Cl_2 (250 mL) was added activated MnO_2 (16.3 g, 188 mmol, <5 μm) in three batches at 1 hour intervals at room temperature. The

resulting mixture was stirred at room temperature overnight. The mixture was filtered through a pad of silica gel and Celite, and the filter pad was thoroughly washed with additional CH_2Cl_2 (100 mL x 2). The combined filtrate was concentrated in vacuo. The crude aldehyde was purified by flash chromatography (silica gel, hexanes:EtOAc = 20:1) to give aldehyde **20** (2.34 g, 9.0 mmol, 96%) as a clear colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.38 (s, 1H, -C*H*O), 6.21 [dq, *J* = 10.0 and 1.5 Hz, 1H, OHCC(CH_3)=C*H*-], 6.03 [d, *J* = 15.5 Hz, 1H, CH=CH(CH_3)C*H*=], 5.51 [dt, *J* = 15.0, and 7.0 Hz, 1H, CH_3CH=CH(CH_3)CH=C*H*-], 5.43 (q, *J* = 6.5 Hz, 1H, CH_3C*H*=), 2.80 [m, 1H, OHCC(CH_3)=CHC*H*(CH_3)CH_2-], 2.04 (dt, *J* = 7.5 and 7.5 Hz, 2H, -CH=CH-CH_2-), 1.75 [d, *J* = 1.0 Hz, 3H, OHCC(CH_3)=CH-], 1.71 [dd, *J* = 1.5 and 1.5 Hz, 3H, CH_3CH=C(CH_3)CH=], 1.69 (d, *J* = 7.5 Hz, 3H, CH_3CH=), 1.33-1.44 (m, 2H), 1.17-1.32 (m, 4H), 1.10-1.17 (m, 1H), 1.03 [d, *J* = 6.5 Hz, 3H, OHCC(CH_3)=CHCH(CH_3)CH_2-], 0.83 [d, *J* = 6.0 Hz, 3H, CH_2CH(CH_3)CH_2].

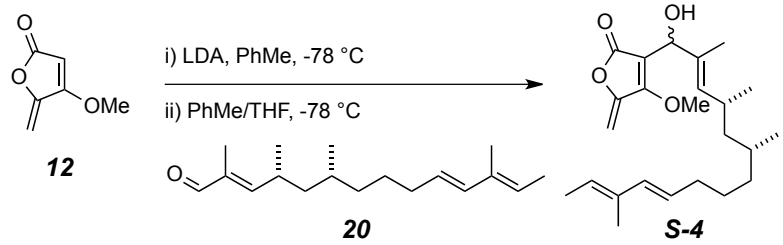
^{13}C NMR ($CDCl_3$, 125 MHz): δ 195.6, 160.8, 137.9, 134.8, 134.4, 127.0, 124.5, 44.4, 37.1, 33.1, 31.2, 30.8, 27.0, 20.4, 19.5, 13.7, 12.1, and 9.4.

IR (neat): 2960, 2926, 2870, 2857, 2706, 1690, 1644, 1456, 1378, 1312, 1013, and 963 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{18}H_{30}NaO)^+$ 285.2189. Found: 285.2194.

The non-racemic sample of (+)-(2*E*,4*R*,6*R*,10*E*,12*E*)-2,4,6,12-tetramethyltetradeca-2,10,12-trienal (**20**) had $[\alpha]_D$ = +8.7 (c = 5.1, $CHCl_3$).

(±)-3-((1*R*,2*E*,4*R*,6*R*,10*E*,12*E*)- and (±)-3-((1*S*,2*E*,4*R*,6*R*,10*E*,12*E*)-1-Hydroxy-2,4,6,12-tetramethyltetradeca-2,10,12-trien-1-yl)-4-methoxy-5-methylenefuran-2(5*H*)-one (S-4)



Diisopropylamine (2.78 mL, 19.8 mmol) was dissolved in toluene (120 mL) in a 500 mL round bottom flask cooled at -78 °C. To this solution was added *n*BuLi (7.8 mL, 2.5 M in hexanes, 19.5 mmol) dropwise over 10 min. The resulting mixture was stirred at this temperature for 1 h. A solution of the methyl tetronate **12**[5] (2.26 g, 18 mmol) in a mixture of toluene (21 mL) and THF (18 mL) was added dropwise to the LDA solution over 10 min. The reaction mixture was stirred for an additional 5 min, during which the color of the reaction turned to dark brown. Aldehyde **20** (2.34 g, 9.0 mmol) was dissolved in toluene (35 mL) and added dropwise to the flask over 15 min, and the resulting solution was stirred for 1.5 h. When TLC showed full conversion of starting material, the saturated NH_4Cl (50 mL) was added, and the resulting mixture was warmed

to room temperature. Water (50 mL) was added to dissolve all inorganic salts. The aqueous layer was extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The crude mixture was subjected to flash chromatography (silica gel, hexanes:EtOAc = 12:1 then 4:1) to give, in order of elution, an epimeric mixture of the alcohols **S-4** (3.15 g, 8.12 mmol, 91%, ca. 1:1 dr as determined by ^{1}H NMR) as a pale yellow oil and unreacted **12** (1.05 g) as white solid.

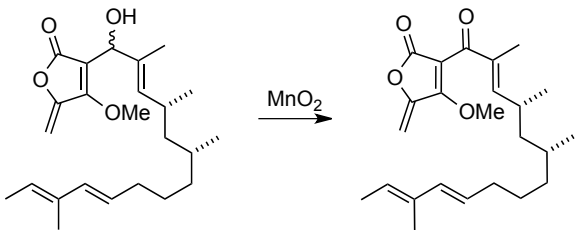
^{1}H NMR ($CDCl_3$, 500 MHz, for the mixture of diastereomers): δ 6.03^+ (d, *J* = 15.5 Hz, 0.5H, CH_3CH=$CH(CH_3)C$*H*=), $6.03^–$ (d, *J* = 15.5 Hz, 0.5H, CH_3CH=$CH(CH_3)C$*H*=), 5.52 (dt, *J* = 15.5 and 7.0 Hz, 0.5H, CH_3CH=$CH(CH_3)CH$=C*H*-), 5.51 (dt, *J* = 15.5 and 7.0 Hz, 0.5H, CH_3CH=$CH(CH_3)CH$=C*H*-), 5.43 (q, *J* = 6.5 Hz, 1H, CH_3C*H*=), 5.20 (d, *J* = 8.5 Hz, 2H, -O*H*), 5.13 (br d, *J* = 9.5 Hz, 2H, -C*H*=$C(CH_3)$CHOH-), 5.06 (m, 2H, CH_2=), 4.11 (s, 1.5H, MeO-), 4.10 (s, 1.5H, MeO-), 3.63 (d, *J* = 8.5 Hz, 0.5H, HOC*H*=), 3.61 (d, *J* = 8.5 Hz, 0.5H, HOC*H*=), 2.50 (m, 1H, -C*H*(CH_3)CH=$C(CH_3)$CHOH-), 2.02 (m, 2H, CH_3CH=$C(CH_3)CH$=CH-CH_2-), 1.70 (m, 3H, -CH=C(CH_3)CH_2OH), 1.69 (m, 6H, CH_3CH=CCH_3), 1.17-1.42 (m, 5H), 1.00-1.15 (m, 2H), 0.90 (d, *J* = 6.5 Hz, 1.5H, -HOCHC(CH_3)=CHCH(CH_3)-), 0.88 (d, *J* = 7.0 Hz, 1.5H, -HOCHC(CH_3)=CHCH(CH_3)-), 0.81 (d, *J* = 6.5 Hz, 1.5H, -HOCHC(CH_3)=CHCH$(CH_3)CH_2$CH(CH_3)-), and 0.80 (d, *J* = 6.5 Hz, 1.5H, -HOCHC(CH_3)=CHCH$(CH_3)CH_2$CH(CH_3)-).

^{13}C NMR ($CDCl_3$, 500 MHz, for the mixture of diastereomers): δ 169.95, 169.90, 162.27, 162.20, 149.41, 149.36, 134.69, 134.66, 134.45, 134.42, 134.08, 134.03, 133.14^+, $133.14^–$, 127.27, 127.21, 124.36, 124.32, 105.17, 105.05, 99.22, 99.21, 69.91, 69.88, 60.71, 60.56, 45.00, 44.97, 37.17, 37.13, 33.12, 33.10, 30.54, 30.49, 29.79, 29.77, 27.14, 27.12, 21.35, 21.28, 19.66, 19.63, 13.71, 13.68^+, $13.68^–$, 13.58, 12.09^+, and $12.09^–$ ppm.

IR (neat): 3150-3650, 2955, 2925, 2866, 1748, 1667, 1621, 1615, 1462, 1455, 1354, 1277, 1142, 1084, 1031, 978, 866, and 781 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{24}H_{36}NaO_4)^+$ 411.2506. Found: 411.2511.

(±)-4-Methoxy-5-methylene-3-((2*E*,4*R*,6*R*,10*E*,12*E*)-2,4,6,12-tetramethyltetradeca-2,10,12-trienoyl)furan-2(5*H*)-one (11)



S-4 ***11***

To a solution of alcohol **S-4** (3.15 g, 8.12 mmol) dissolved in CH_2Cl_2 (400 mL) was added activated MnO_2 (13.9 g, 160 mmol, <5 μm) in three batches at 1 hour intervals at room

temperature. The resulting mixture was stirred at room temperature overnight. The mixture was then filtered through a pad of silica gel and Celite, and the pad was thoroughly washed with additional CH_2Cl_2 (100 mL x 3). The combined filtrates were concentrated in vacuo. The crude mixture was purified by flash chromatography (silica gel, hexanes:EtOAc = 12:1) to give, in order of elution, ketone **11** (1.88 g, 4.88 mmol, 60%; 66% borsm) as a clear colorless oil and unreacted **S-4** (0.29 g, 0.7 mmol).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.31 [dq, *J* = 10.5 and 0.5 Hz, 1H, -COC(CH_3)C*H*-], 6.04 [d, *J* = 15.5 Hz, 1H, =C(CH_3)C*H*=CH-], 5.52 [dt, *J* = 14.5 and 6.5 Hz, 1H, =C(CH_3)CH=C*H*CH_2], 5.44 (q, *J* = 6.5 Hz, 1H, CH_3C*H*=), 5.17 (d, *J* = 2.5 Hz, 1H, C$H_a$$H_b$=C), 5.15 (d, *J* = 2.5 Hz, 1H, $CH_a$$H_b$=C), 3.91 (s, 3H, C$H_3$O-), 2.77 [m, 1H, =CHC*H*(CH_3)-], 2.05 (dt, *J* = 7.0 and 7.0 Hz, 2H, =CH-CH_2), 1.90 [d, *J* = 0.5 Hz, 3H, -COC(CH_3)=], 1.72 [br s, 3H, CH_3CH=C(CH_3)-], 1.70 (d, *J* = ca. 7 Hz, 3H, CH_3CH=), 1.24-1.41 (m, 5H), 1.08-1.24 (m, 2H), 1.02 [d, *J* = 7.0 Hz, 3H, =CHCH(CH_3)-], and 0.85 [d, *J* = 6.0 Hz, 3H, -CH_2CH(CH_3)CH_2].

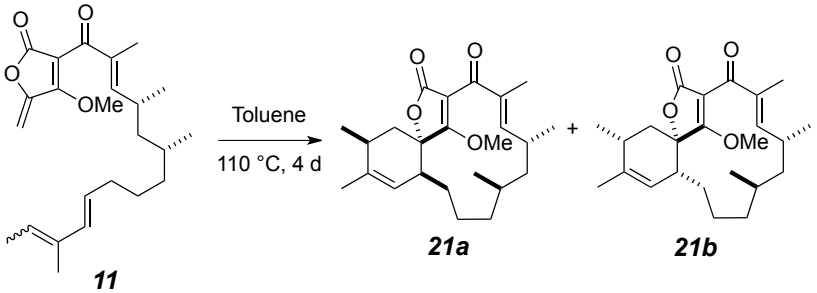
^{13}C NMR ($CDCl_3$, 125 MHz): δ 191.4, 166.0, 165.3, 157.1, 148.9, 136.6, 134.8, 134.4, 127.1, 124.4, 104.8, 94.1, 60.9, 44.2, 37.0, 33.0, 31.8, 30.7, 27.0, 20.1, 19.7, 13.7, 12.1, and 11.3 ppm.

IR (neat): 3029, 2959, 2928, 2870, 1939, 1780, 1660, 1461, 1388, 1289, 1257, 1206, 1150, 992, and 876 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{24}H_{34}NaO_4)^+$ 409.2350. Found: 409.2349.

The non-racemic sample of (-)-4-methoxy-5-methylene-3-((2*E*,4*R*,6*R*,10*E*,12*E*)-2,4,6,12-tetramethyltetradeca-2,10,12-trienoyl)furan-2(5*H*)-one (**11**) had $[\alpha]_D$ = -44 (c = 1.2, $CHCl_3$).

(±)-4-Methoxy-5-methylene-3-((2*E*,4*R*,6*R*,10*E*,12*Z*)-2,4,6,12-tetramethyltetradeca-2,10,12-trienoyl)furan-2(5*H*)-one (11-*Z*);
(±)-(5*E*,7*R*,9*R*,12a*S*,15*S*,16a*S*)-8,9,10,11,12,12a,15,16-Octahydro-17-methoxy-5,7,9,14,15-pentamethyl-16a,3-metheno-2H-1-benzoxacyclotetradecin-2,4(7H)-dione [(±)-*O*-Methyl Okilactomycin D (21a)];
(±)-(5*E*,7*R*,9*R*,12a*R*,15*R*,16a*S*)-8,9,10,11,12,12a,15,16-Octahydro-17-methoxy-5,7,9,14,15-pentamethyl-16a,3-metheno-2H-1-benzoxacyclotetradecin-2,4(7H)-dione [(±)-*O*-Methyl 12a,15-bisepi-Okilactomycin D (21b)]



11
E:Z = 13:1
11-Z unreactive

21a ***21b***

Ketone **11** (1.75 g, 4.53 mmol), which contained ca. 8% of the C12-*Z* isomer (**11-*Z***), and hydroquinone (50 mg, 0.453 mmol) were dissolved in toluene (450 mL), and the resulting solution was heated in an oil bath at 110 ^{o}C in a pressure vessel sealed with a threaded cap for 4 d, at which time ^{1}H NMR analysis showed full consumption of **11-*E***. The solution was concentrated in vacuo, and the resulting mixture was subjected to flash chromatography (silica gel, hexanes:EtOAc = 12:1 then 5:1). The fractions containing mixtures were further purified using MPLC to yield, in order of elution, unreacted **11-*Z*** as pale yellow oil (110 mg), co-eluting **21b** and two other Diels-Alder adducts as foamy solid (123 mg, 7% as a mixture), and **21a (**0.99 g, 62%**)** as a white solid. Recrystallization (EtOAc) gave a sample of **30a** suitable for single crystal x-ray analysis. Compound **21b** could be selectively crystallized from the co-eluting mixture using a vial-in-a-vial vapor diffusion crystallization. The mixture was dissolved in EtOAc in an open inner vial and cyclohexane was placed in the outer vial, which was then capped. After standing overnight at room temperature, **21b** was obtained as colorless crystals, suitable for single crystal x-ray analysis.

Compound 11-Z

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.44 [d, *J* = 15.5 Hz, 1H, =C(CH_3)C*H*=CH], 6.31 [dq, *J* = 10.0 Hz, 1.5 Hz, 1H, -COC(CH_3)C*H*-], 5.65 [dt, *J* = 15.5 Hz, 7.5 Hz, 1H, =C(CH_3)CH=C*H*CH_2], 5.32 (q, *J* = 6.5 Hz, 1H, CH_3C*H*=), 5.17 (d, *J* = 2.5 Hz, 1H, C$H_a$$H_b$=C), 5.15 (d, *J* = 2.5 Hz, 1H, C$H_a$$H_b$=C), 3.91 (s, 3H, C$H_3$O-), 2.79 [m, 1H, =CHC*H*(CH_3)-], 2.11 (dt, *J* = 7.0 and 7.0 Hz, 2H, =CH-CH_2), 1.92 (d, *J* = 1.0 Hz, 3H, -COC(CH_3)=), 1.78 [br s, 3H, CH_3CH=C(CH_3)-], 1.71 (app d, *J* = 6.0 Hz, 3H, CH_3CH=), 1.24-1.45 (m, 5H), 1.08-1.24 (m, 2H), 1.03 [d, *J* = 6.5 Hz, 3H, =CHCH(CH_3)-], and 0.86 [d, *J* = 6.5 Hz, 3H, -CH_2CH(CH_3)CH_2].

^{13}C NMR ($CDCl_3$, 125 MHz, DEPT): 157.1 (CH), 130.3 (CH), 126.9 (CH), 122.6 (CH), 94.1

(CH_2), 60.9 (CH_3), 44.2 (CH_2), 37.0 (CH_2), 33.5 (CH_2), 31.8 (CH), 30.7 (CH), 27.0 (CH_2), 20.6 (CH_3), 20.1 (CH_3), 19.7 (CH_3), 13.0 (CH_3), and 11.2 (CH_3) ppm.

IR (neat): 2957, 2926, 2870, 1773, 1636, 1454, 1388, 1287, 1257, 990, 973, and 874 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{24}H_{34}NaO_4)^+$ 409.2350. Found: 409.2354.

Compound 21a

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.44 [dq, *J* = 7.7 and 1.4 Hz, 1H, -COC(CH_3)=C*H*], 5.45 (ddq, *J* = 4.5, 1.6, and 1.6 Hz, 1H, CH_3C=C*H*-), 3.82 (s, 3H, C*H*$_3$O), 2.61 [ddqd, *J* = 10.9, 7.2, 7.2, and 3.8 Hz, 1H, -COC(CH_3)=CHC*H*], 2.43 [ddqddq, *J* = 10.5, 6.5, 6.5, 1.5, 1.5, and 1.5 Hz, 1H, CH_3C*H*(CH_2-)C=], 2.11 [dddq, *J* = 10, 4.5, 3.2, and 1.6 Hz, 1H, CH_3C(CH-)=CHC*H*-], 1.87 [d, *J* = 1.3 Hz, 3H, O=CC(C*H*$_3$)=], 1.88-1.82 [m, 2H, CH_3C(CHC*H*$_a$H$_b$)=CH and CH_3C(CH-)=CHCHC*H*$_a$H$_b$], 1.70 [ddd, *J* = 1.4, 1.4, and 1.4 Hz, 3H, C*H*$_3$C(CH-)=CH], 1.67-1.58 (m, 1H), 1.64 [dd, *J* = 13.5, and 10.5 Hz, 1H, CH_3C(CHCH$_a$*H*$_b$)=CH], 1.44 (ddddd, *J* = 14.5, 7.4, 7.4, 7.4, and 4.8 Hz, 1H, CH_2C*H*$_a$H$_b$$CH_2$),1.42-1.35 (m, 1H), 1.35-1.19 (m, 4H), 1.14 [dddd, *J* = 14.0, 10.0, 6.5, and 6.5 Hz, 1H, C*H*$_3$C(CH-)=CHCHCH$_a$*H*$_b$], 1.07 [d, *J* = 7.0 Hz, 3H, C*H*$_3$CH(CH_3)CH_2C], 1.02 (d, *J* = 7.0 Hz, 3H, C*H*$_3$CHCH=C), and 0.89 (d, *J* = 6.0 Hz, 3H, CH_2C*H*$_3$CHCH_2).

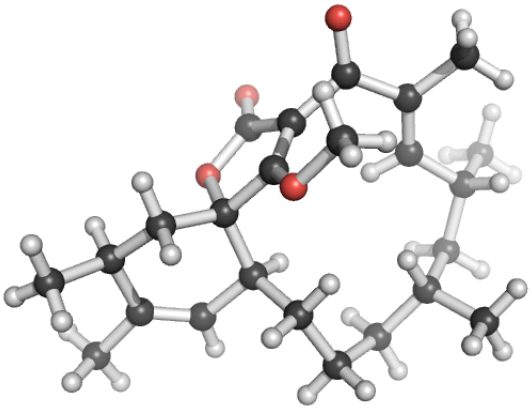
^{13}C NMR ($CDCl_3$, 75 MHz): 192.2, 179.8, 168.4, 157.2, 140.7, 136.4, 122.3, 103.2, 86.0, 59.7, 46.2, 45.0, 35.2, 34.0, 32.0, 30.6, 28.6, 28.4, 23.1, 20.9, 19.8, 19.5, 18.7, and 10.9 ppm.

IR (neat): 2963, 2922, 2860, 1745, 1644, 1635, 1455, 1371, 1355, 1260, 1002, and 945 cm^{-1}.

HRMS (ESI-TOF): Calcd for $(C_{24}H_{34}NaO_4)^+$ 409.2350. Found: 409.2358.

mp: 215-216 °C [**(±)-21a**]; 232-233 °C [(-)-**21a**]

Three-dimensional rendering of **21a** from the single crystal X-ray structure coordinates:



The non-racemic sample of (-)-(5*E*,7*R*,9*R*,12a*S*,15*S*,16a*S*)-8,9,10,11,12,12a,15,16-octahydro-17-methoxy-5,7,9,14,15-pentamethyl-16a,3-metheno-2H-1-benzoxacyclotetradecin-2,4(7H)-dione (**21a**) had $[\alpha]_D$ = -57 (c = 0.3, MeOH).

Compound 21b

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.65 (dq, *J* = 8.0 and 1.1 Hz, 1H, -COC(CH_3)=C*H*), 5.24 [br q, *J* = 1.7 Hz, 1H, HC(CH_3)C=C*H*-], 3.79 (s, 3H, C*H*$_3$O), 2.61 [ddqd, *J* = 12, 8, 7, and 2.5 Hz, 1H, -COC(CH_3)=CHC*H*], 2.44 (ddddd, *J* = 8.6, 2.2, 2.2, 2.2, and 2.2 Hz, 1H, CH_2C*H*CH=C), 2.27 (dqdq, *J* = 7, 7, 1.5 and 1.5 Hz), 2.20 (dd, *J* = 13.9 and 7.1 Hz, 1H, CH_3CH(C=)C*H*$_a$H$_b$), 1.86 (d, *J* = 1.2 Hz, 3H, O=CC(C*H*$_3$)=), 1.74 [dd, *J* = 1.8 and 1.8 Hz, 3H, C*H*$_3$C(CH-)=CH], 1.69 (d, *J* = 13.8 Hz, 1H, CH_3CH(C=)CH$_a$*H*$_b$), 1.63-1.70 (m, 1H), 1.50-1.38 (m, 4H), 1.26-1.34 (nfom, 1H), 1.20 (d, *J* = 7.2 Hz, 3H, C*H*$_3$CHCH$_2$CO), 1.12-1.19 (m, 3H), 1.05 [d, *J* = 6.9 Hz, 3H, C*H*$_3$CHCH=C(CH_3)C=O], and 0.88 [br d, *J* = 5.9 Hz, 3H, C*H*$_3$CHCH$_2$CH(CH_3)C=].

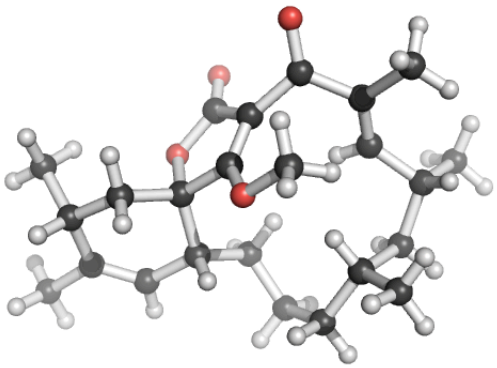
^{13}C NMR ($CDCl_3$, 75 MHz): 194.1, 178.8, 169.7, 158.9, 139.7, 137.1, 120.7, 106.0, 84.9, 60.3, 43.6, 38.0, 37.1, 34.6, 32.3, 32.1, 29.9, 26.8, 23.1, 22.1, 21.6, 20.2, 19.5, and 11.3 ppm.

IR (neat): 2957, 2923, 2868, 1754, 1638, 1448, 1350, 1260, 1230, 1096, 998, and 958 cm^{-1}.

HRMS: Calcd for $(C_{24}H_{34}NaO_4)^+$ 409.2350. Found: 409.2352.

mp: 171-172 °C.

Three-dimensional rendering of **21b** from the single crystal X-ray structure coordinates:



(±)-(5*E*,7*R*,9*R*,12a*S*,15*S*,16a*S*)-8,9,10,11,12,12a,15,16-Octahydro-17-hydroxy-5,7,9,14,15-pentamethyl-16a,3-metheno-2H-1-benzoxacyclotetradecin-2,4(7H)-dione [(±)-Okilactomycin D (7)] and its Sodium Salt S-5

21a

R = Na, ***S-5***
R = H, ***7***

For R = Na: Compound **21a** (300 mg, 0.78 mmol) and LiCl (495 mg, 11.6 mmol) were dissolved in DMSO (30 mL). The solution was heated at 55 °C for 48 h. The reaction solution was partitioned between EtOAc and half-saturated aqueous NaCl solution. The organic layer was washed with half-saturated NaCl three more times, dried over Na_2SO_4, and concentrated to give **S-5** as a white amorphous solid (292 mg, 0.77 mmol, 95%). The NMR spectrum of this sample shows no evidence of anything other than **S-5**.

For R = H: Compound **21a** (500 mg, 1.30 mmol) and LiCl (780 mg, 18.4 mmol) were dissolved in DMSO (75 mL).The reaction solution was cooled to room temperature and partitioned between EtOAc and 10% aqueous HCl solution. The organic layer was dried (Na_2SO_4) and carefully concentrated to provide okilactomcyin D (**7**) (465 mg and 96%) as a white amorphous solid. The NMR spectrum of this sample indicates a purity level of ca. 95%. The material was passed through a bed of SiO_2 using 90:9.9:0.1 (DCM:EtOAc:TFA) as the eluant. This resulted in ca. 120% mass recovery of a slightly yellow solid, presumably due to retention of a portion of TFA. The purity level (^{1}H NMR) was virtually the same as prior to this treatment.

Compound S-5

^{1}H NMR (CD_3OD, 500 MHz): δ 5.86 [br d, *J* = 7.9 Hz, 1H, -COC(CH_3)=C*H*], 5.51 (ddq, *J* = 5.2, 1.8, and 1.8 Hz, 1H, CH_3C=C*H*-), 2.54-2.45 (m, 1H, O=CC=CHC*H*), 2.39-2.28 (m, 2H, $CH_3CHCH_aH_bC$-O), 1.83 [br s, 3H, O=CC(C*H*$_3$)=], 1.83 (m, 1H, CH_3C=CHC*H*), 1.68 (ddd, *J* = 1.2, 1.2, and 1.2 Hz, 3H, C*H*$_3$C=CHCH), 1.71-1.56 (m, 4H), 1.30-1.14 (m, 3H), 1.10 (ddd, *J* = 13.5, 8.0, and 2.8 Hz, 1H, $CH_3CHCH_aH_bCHCH_3$), 1.04 (d, *J* = 7.1 Hz, 3H, C*H*$_3$CHCH2C-O), 1.05-0.97 (m, 2H), 0.92 (d, *J* = 6.8 Hz, 3H, C*H*$_3$CHCH=CC=O), and 0.86 [d, *J* = 6.6 Hz, 3H, C*H*$_3$CHCH$_2$CH(CH_3)C=].

^{13}C NMR (CD_3OD, 75 MHz): 200.2, 199.5, 177.1, 145.4, 139.7, 136.1, 126.4, 97.1, 86.8, 47.7, 46.8, 37.6, 36.0, 32.8, 32.2, 30.6, 30.2, 27.3, 22.2, 21.4, 21.1, 19.7, and 12.8 ppm.

HRMS: Calcd for $(C_{23}H_{31}O_4)^-$ 371.2227. Found: 371.2221.

The non-racemic sample of (-)-(**S-5**) had $[\alpha]_D$ = -25 (c = 1.0, MeOH).

(±)-*Okilactomycin D* (7)

^{1}H NMR (CD_3OD, 500 MHz): See Table S-1.

^{13}C NMR (CD_3OD, 75 MHz): See Table S-1.

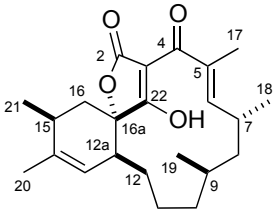
IR (neat): 2954, 2920, 2870, 1698, 1621, 1558, 1455, 1360, 1307, 1259, 1082, 968, 886, and 846 cm^{-1}.

mp: 132-134 °C.

^{1}H NMR ($CDCl_3$, 500 MHz): δ ca. 10.3-9.3 (br s, OH), 5.94 [br d, *J* = 7.7 Hz, 1H, -COC(CH_3)=C*H*], 5.41 (ddq, *J* = 5.5, 1.5, and 1.5 Hz, 1H, CH_3C=C*H*-), 2.49 (dddq, *J* = 7.0, 7.0, 7.0 and 7.0 Hz, 1H, O=C(CH_3)C=CHC*H*), 2.43-2.32 (br ddq, *J* = 7.5, 7.5, and 7.5 Hz, 1H, CH_3C*H*CH_2C-O), 1.99 [br s, 3H, O=CC(C*H*$_3$)=], 1.91-1.87 (br s, 1H), ca. 1.84-1.75 (m, 1H), 1.75 (br d, *J* = 8.6 Hz, 2H, $CH_3CHCH_aH_b$C-O), 1.69 (ddd, *J* = 1.4, 1.4, and 1.4 Hz, 3H, C*H*$_3$C=CHCH), 1.67-1.57 (m, 1H), 1.37-1.12 (m, 7H), 1.04 (d, *J* = 7.1 Hz, 3H, C*H*$_3$CHCH_2C-O), 0.92 (d, *J* = 6.8 Hz, 3H, C*H*$_3$CHCH=CC=O), and 0.86 [d, *J* = 6.6 Hz, 3H, C*H*$_3$CHCH_2CH(CH_3)C=].

The non-racemic sample of (-)-(5*E*,7*R*,9*R*,12a*S*,15*S*,16a*S*)-8,9,10,11,12,12a,15,16-octahydro-17-hydroxy-5,7,9,14,15-pentamethyl-16a,3-metheno-2H-1-benzoxacyclotetradecin-2,4(7H)-dione (**7**) had $[\alpha]_D$ = -32 (c = 0.3, MeOH).

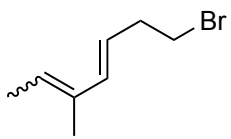
Table S-1: Comparison of the ^{1}H and ^{13}C NMR spectral data of natural (CD_3OD, 500 and 125 MHz)[6] and synthetic (CD_3OD, 500 and 75 MHz, this work) okilactomycin D (**7**). Atom numbering scheme (following CAS nomenclature) shown in the structure to the right.



Position	Natural 7 δ (multiplicity; *J* in Hz)	Synthetic 7 δ (multiplicity; *J* in Hz)	Δδ	Natural 7 (δ)	Synthetic 7 (δ)	Δδ
2	–	–	–	172.1	171.8	-0.3
3	–	–	–	101.2	102.9	1.7
4	–	–	–	194.3	194.0	-0.3
5	–	–	–	140.1	140.3	0.2
6	6.38 (dd; 7.5, 1.2)	6.42 (dq; 7.5, 1.4)	0.04	154.3	155.0	0.7
7	2.64 (m)	2.65 (ddqd; 10.2, 7.1, 7.1, 3.3)	0.01	33.1	33.3	0.2
8	1.22 (m) 1.38 (m)	1.22 (ddd; 13.6, 8.5, 3.3)	0.00	46.4	46.5	0.1
9	1.45 (m)	1.68-1.76 (m; 1H) 1.33-1.48 (m; 4H) 1.08-1.23 (m; 2H)	N/A	29.8	29.9	0.1
10	1.18 (m) 1.36 (m)			36.8	37.0	0.2
11	1.37 (m) 1.73 (m)			25.6	25.7	0.1
12	1.12 (m) 2.21 (m)	2.20 (dddd; 14.0, 8.6, 6.0, 2.8)	-0.01	30.0	30.1	0.1
12a	2.02 (m)	2.02-2.06 (m)	0.02	47.3	47.8	0.5
13	5.57 (dt; 5.0, 1.5)	5.58 (ddq; 5.0, 1.8, 1.8)	0.01	125.0	124.9	-0.1
14	–	–	–	136.9	137.1	0.2
15	2.38 (dq; 10.7, 6.7)	2.38 (br dqd; 10.8, 7.1, 5.9)	0.00	32.1	32.3	0.2
16	1.73 (dd; 14.2, 10.4) 1.80 (ddd; 13.8, 5.9, 1.6)	1.73 (dd; 13.9, 10.9) 1.82 (ddd; 13.8, 5.9, 1.6)	0.00 0.02	35.3	35.4	0.1
16a	–	–	–	87.3	87.4	0.1
17	1.86 (d; 1.1)	1.86 (d; 1.1)	0.00	11.8	11.8	0.0
18	1.01 (d; 7.0)	1.01 (d; 7.0)	0.00	20.2	20.3	0.1
19	0.89 (d; 6.8)	0.89 (d; 6.5)	0.00	20.9	21.0	0.1
20	1.72 (d; 1.2)	1.72 (ddd; 1.4, 1.4, 1.4)	0.00	21.2	21.4	0.2
21	1.10 (d; 7.0)	1.10 (d; 7.0)	0.00	19.4	19.5	0.1
22	–	–	–	187.3	186.3	-1.0

IV. Copies of ^{1}H and ^{13}C NMR spectra of each isolated compound (pp S20-S48)

CDCl3 500 MHz



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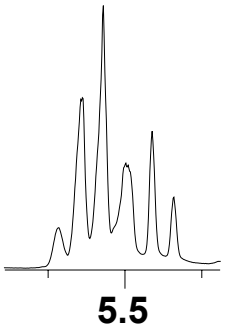
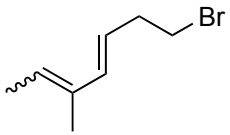


CDCl3 125 MHz



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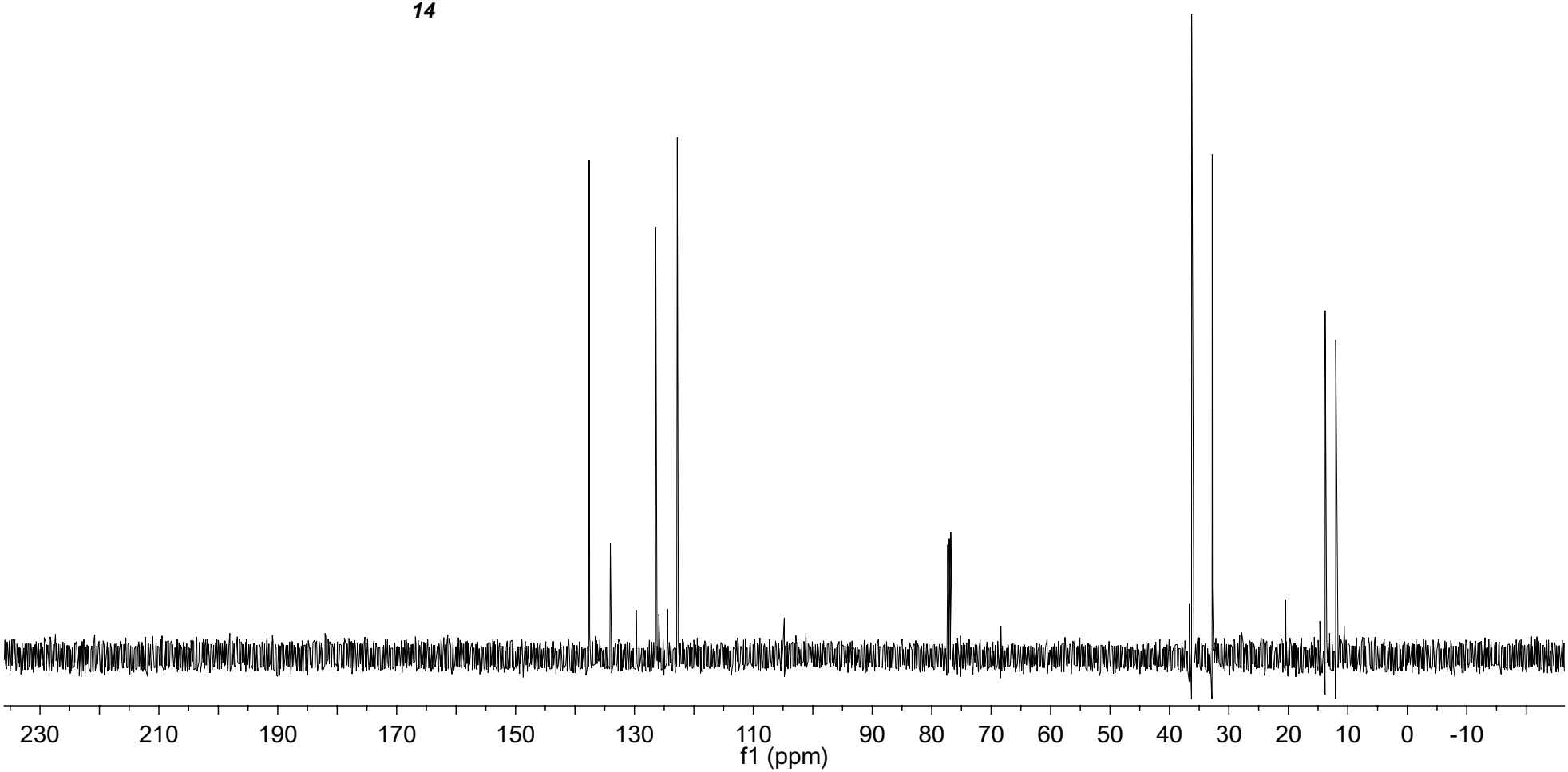
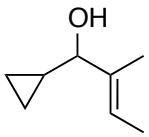
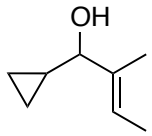


CDCl3 500 MHz



17

CDCl3 125 MHz



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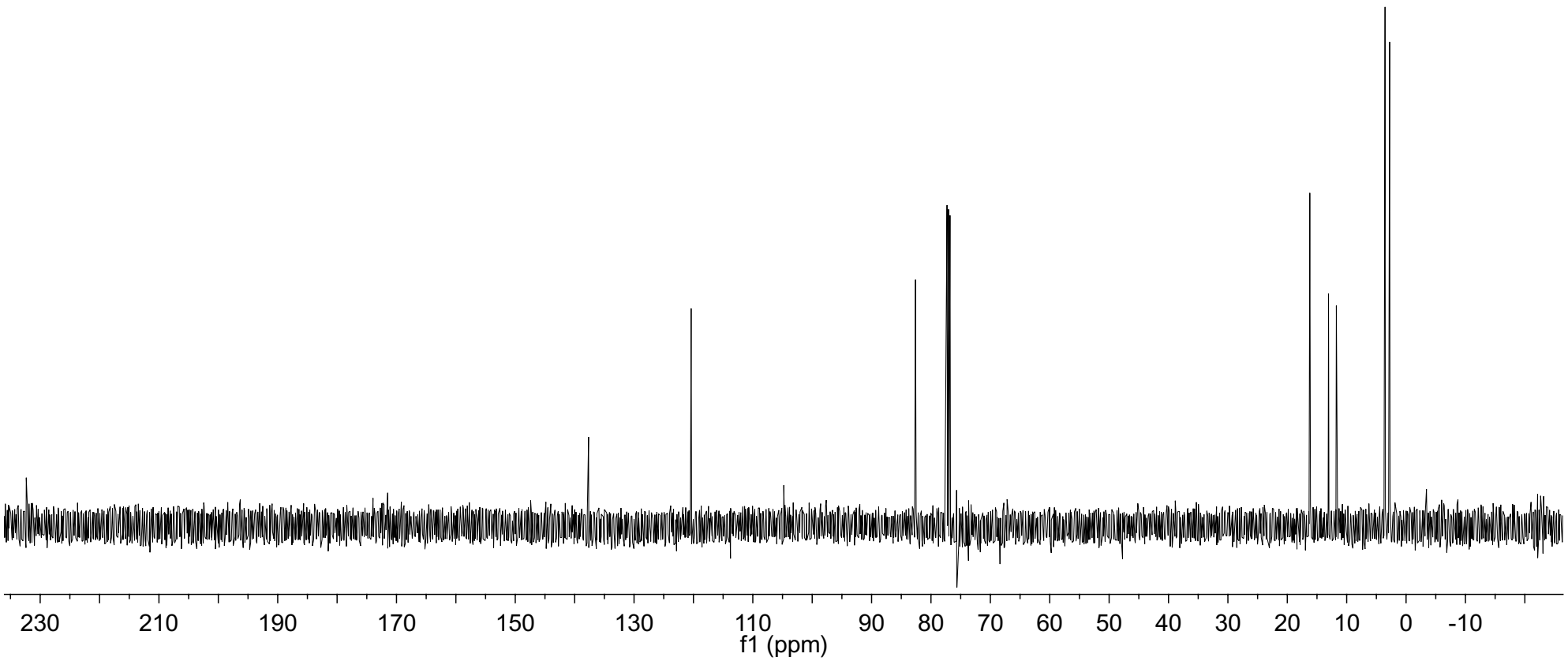
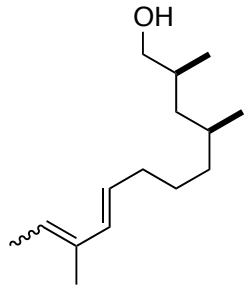
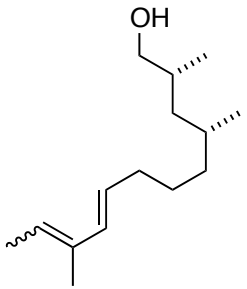


CDCl3 500 MHz



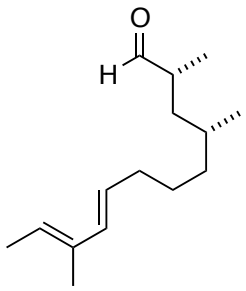
18

CDCl3 125 MHz



18

CDCl3 500 MHz



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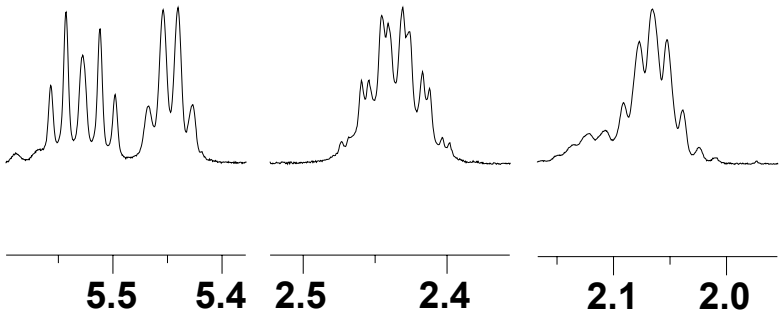
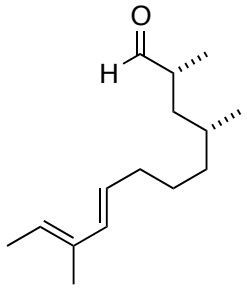


CDCl3 125 MHz



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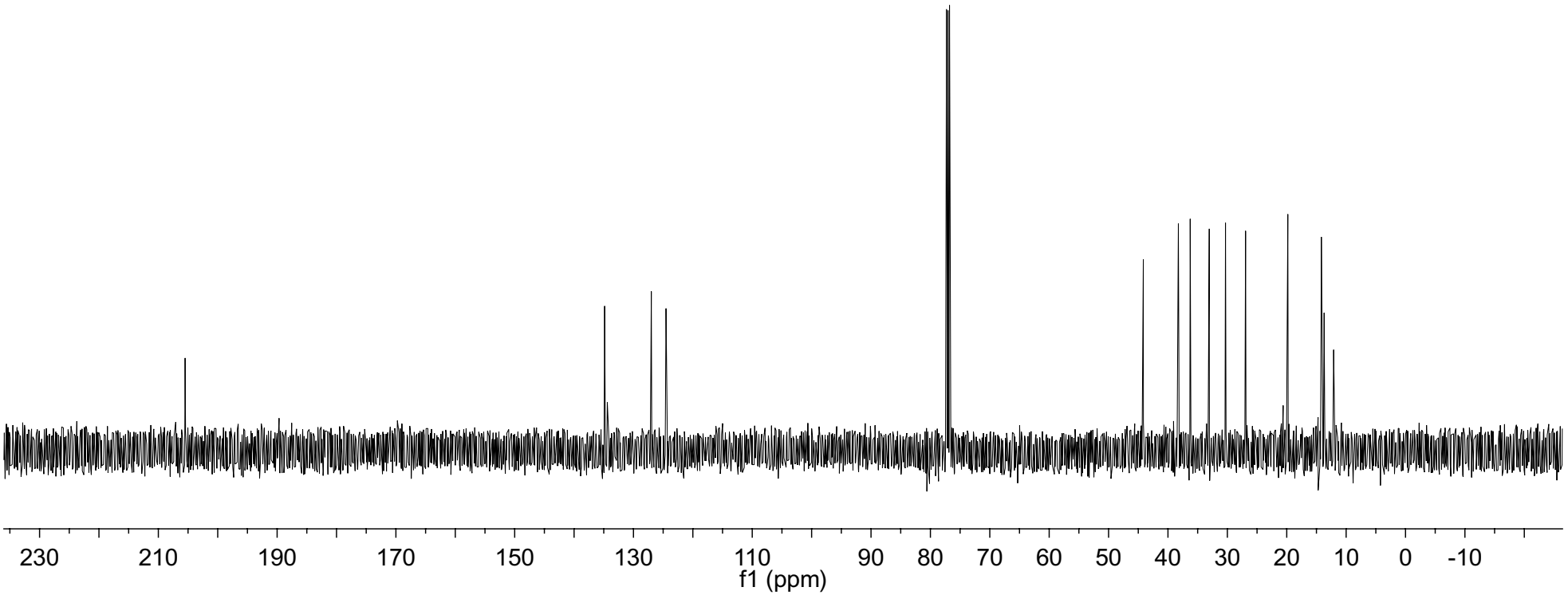
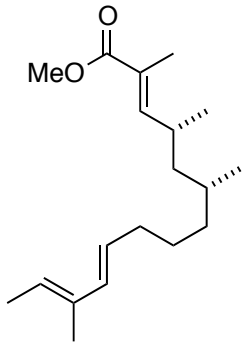
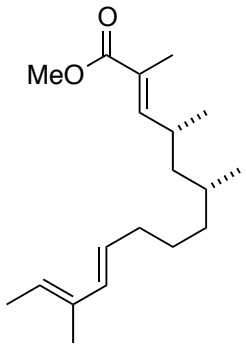


CDCl3 500 MHz



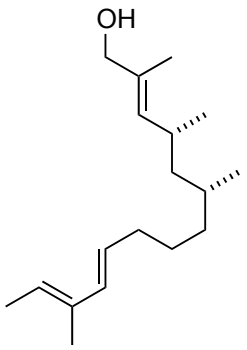
S-2

CDCl3 125 MHz



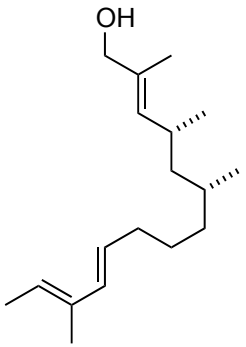
S-2

CDCl3 500 MHz

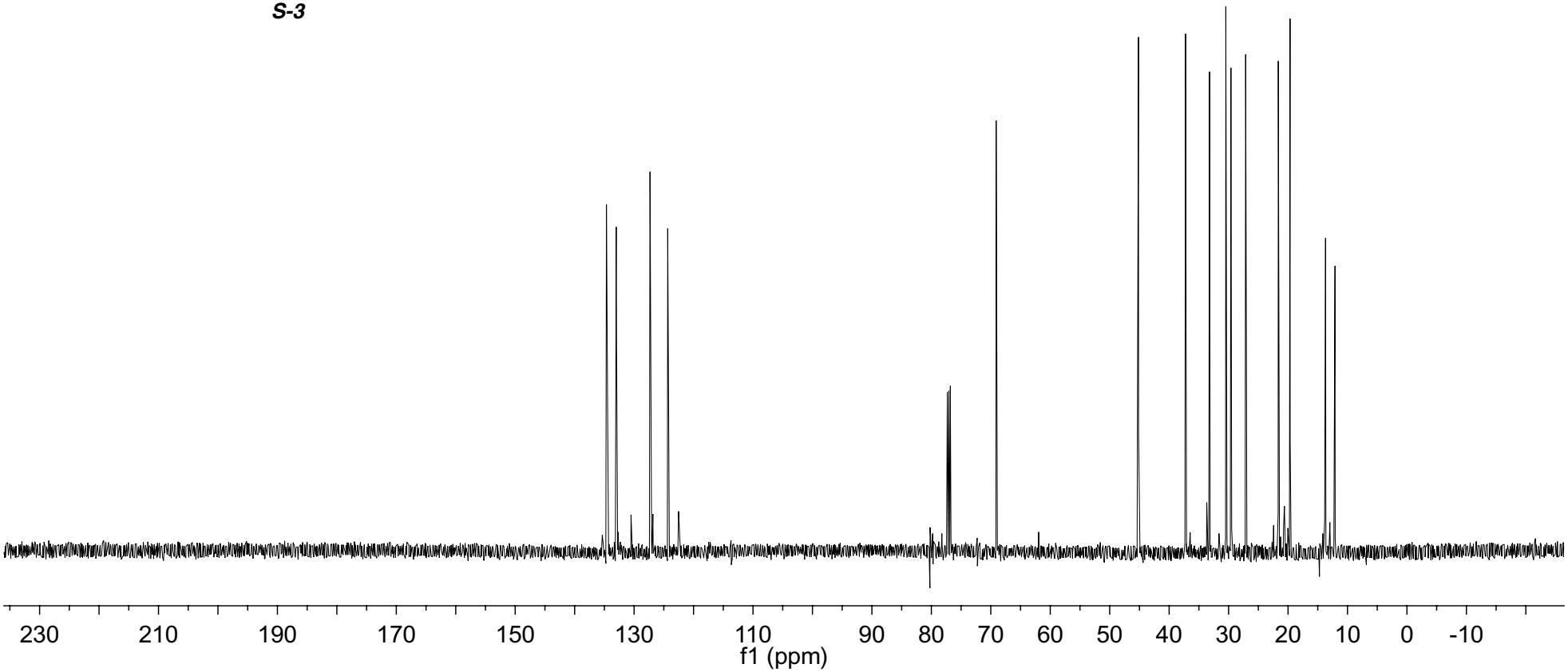


S-3

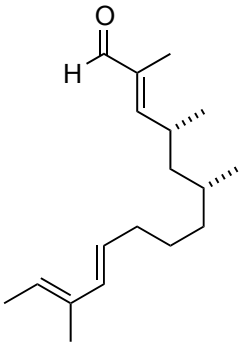
CDCl3 125 MHz



S-3



CDCl3 500 MHz



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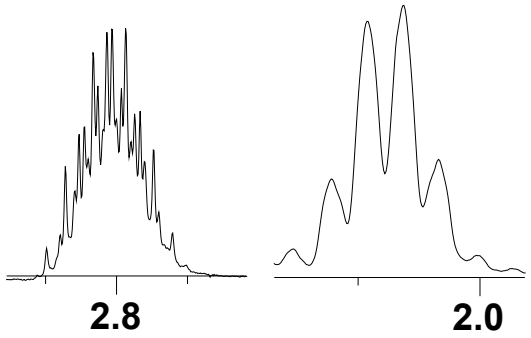
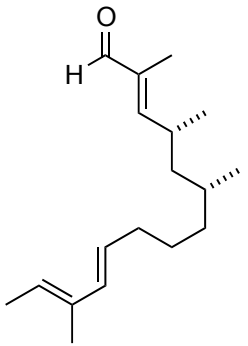


CDCl3 125 MHz



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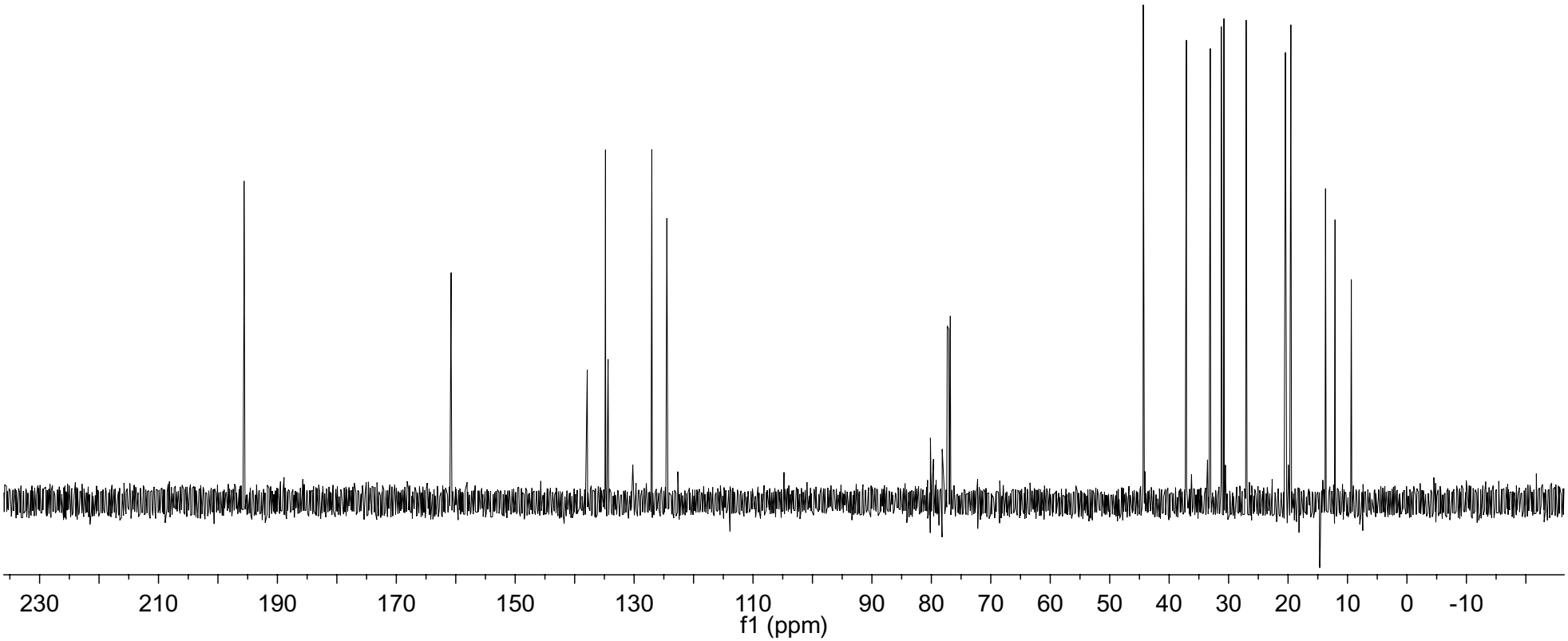
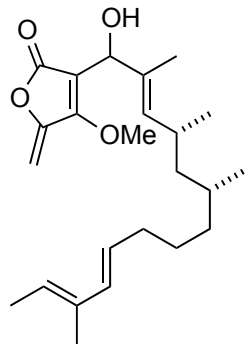
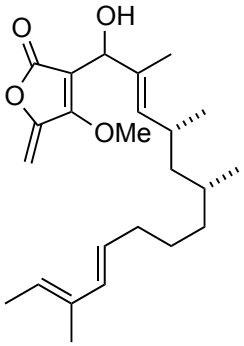


CDCl3 500 MHz



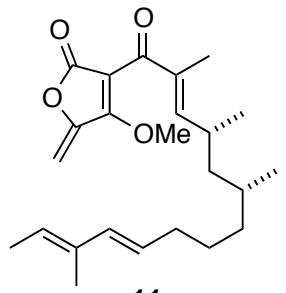
S-4
dr 1:1

CDCl3 125 MHz



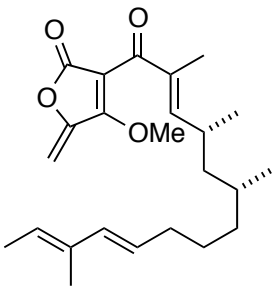
S-4
dr 1:1

CDCl3 500 MHz

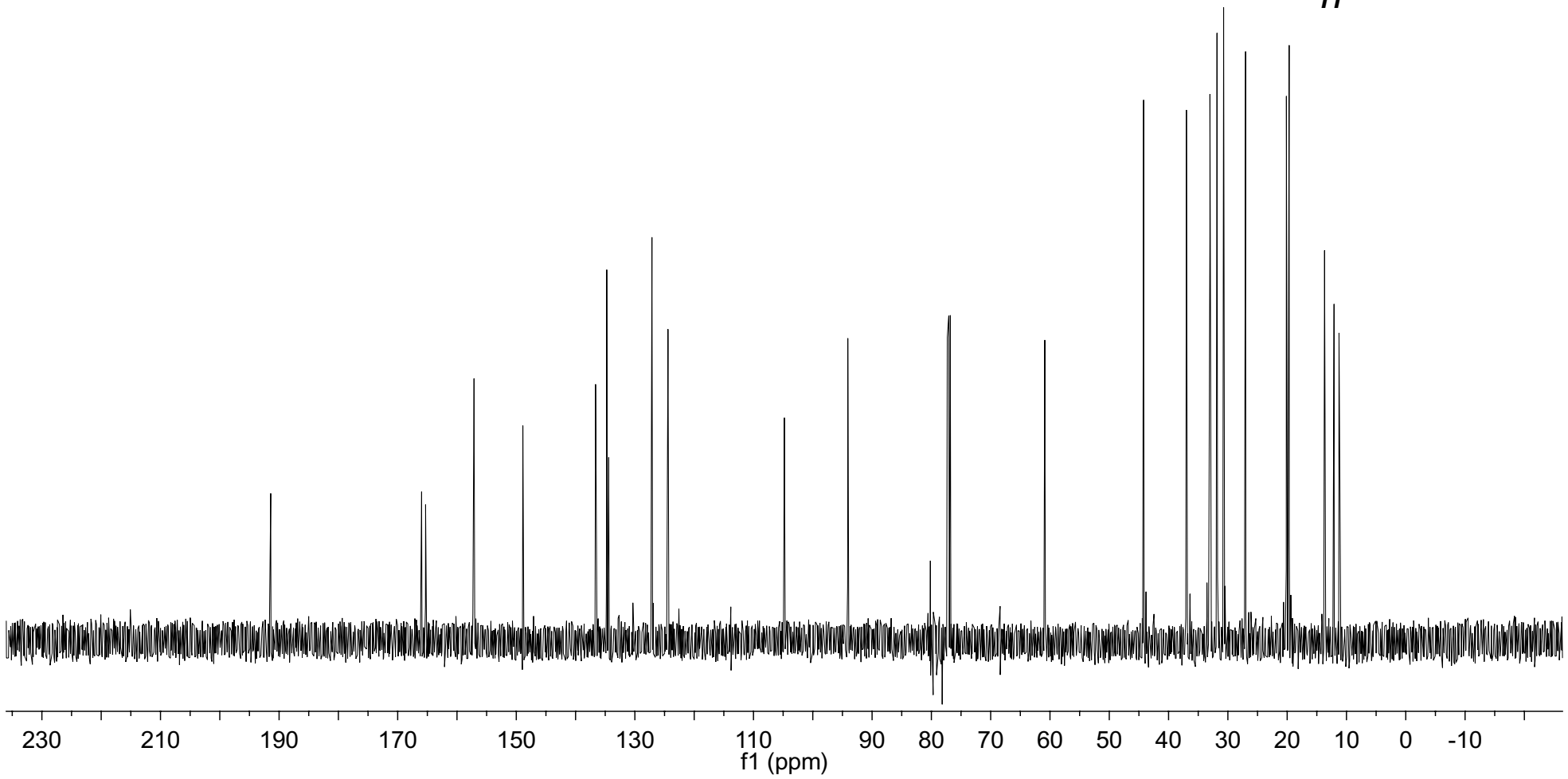


11

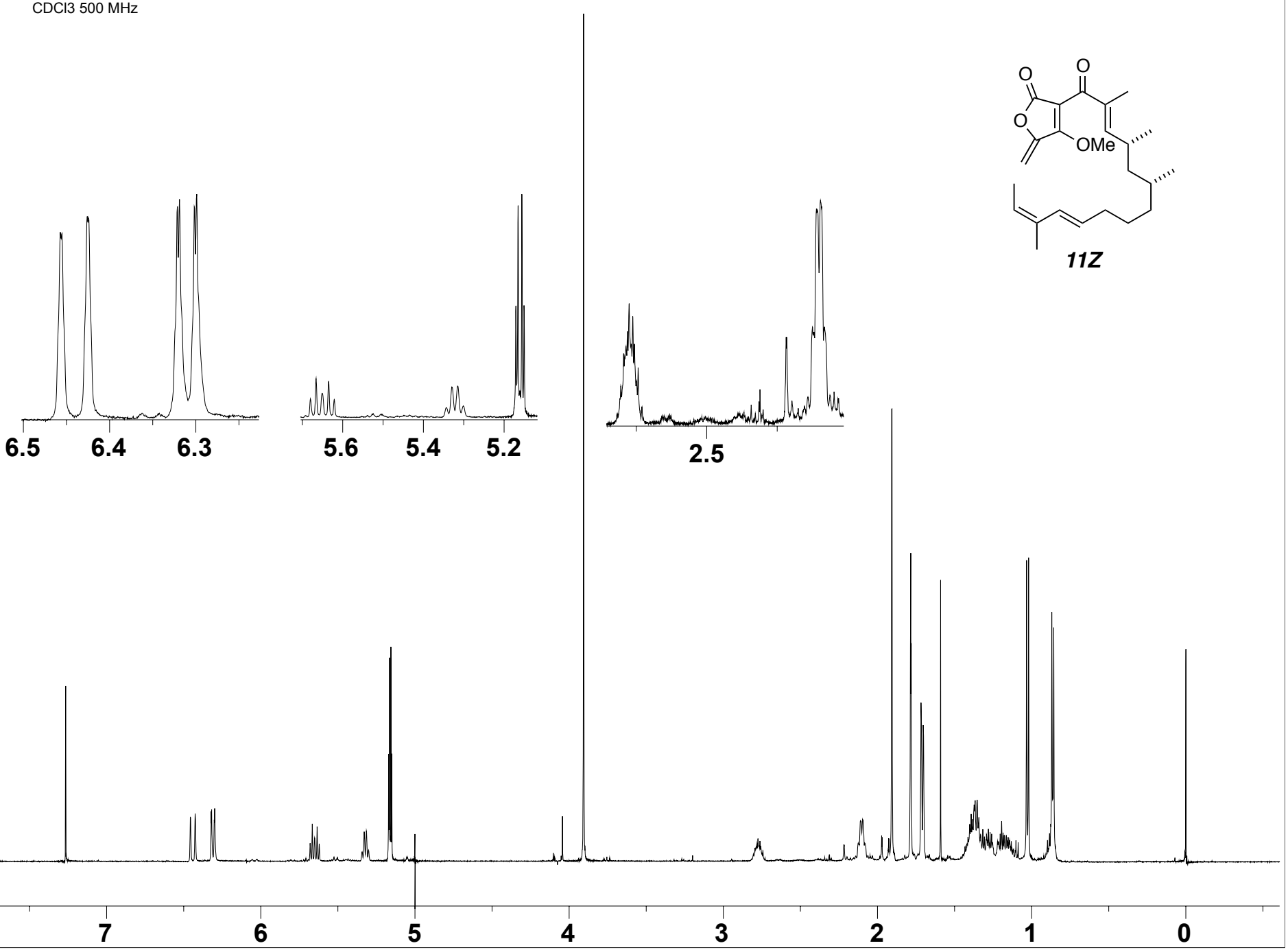
CDCl3 125 MHz

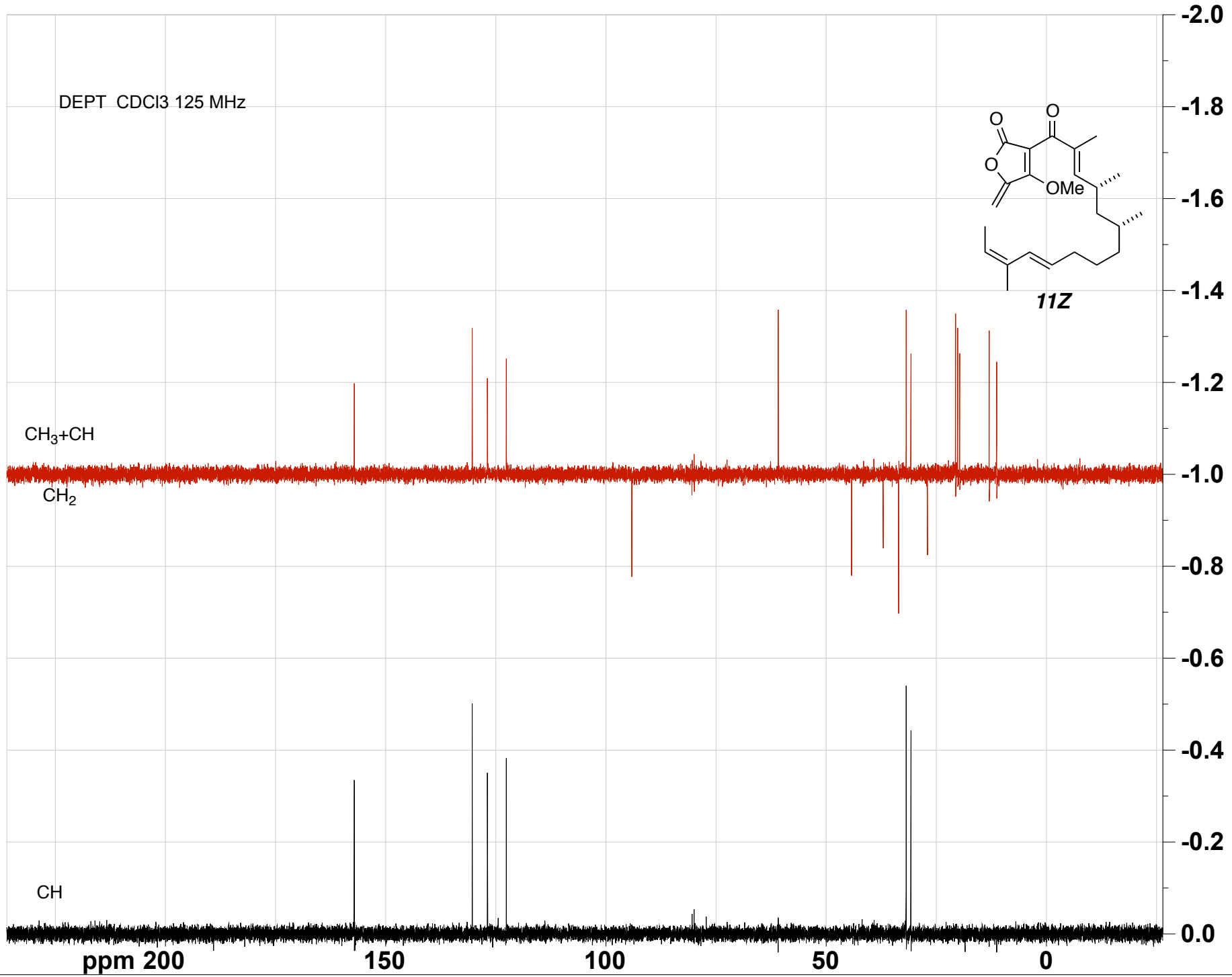


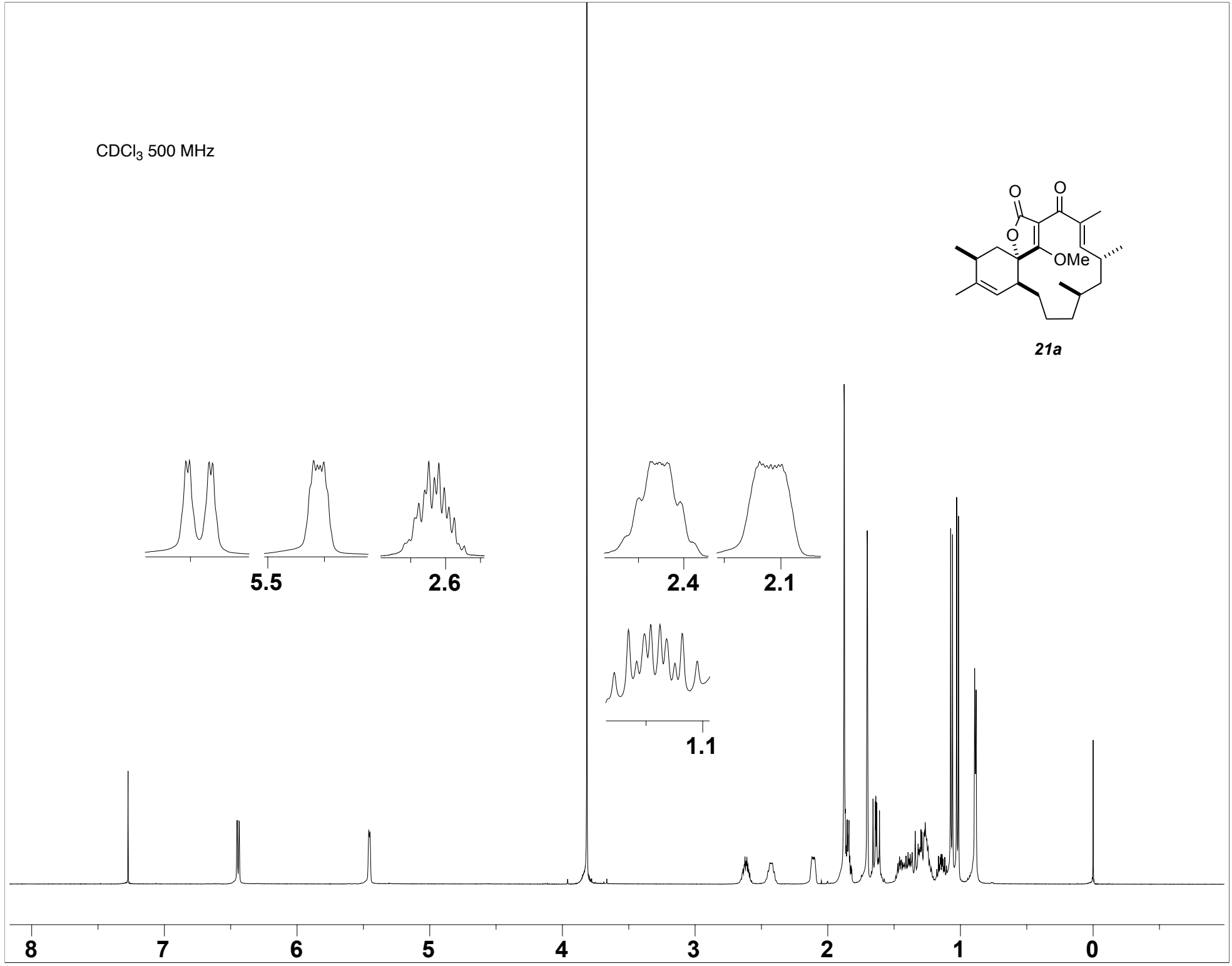
11



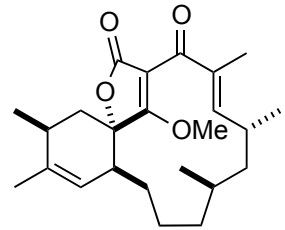
CDCl3 500 MHz



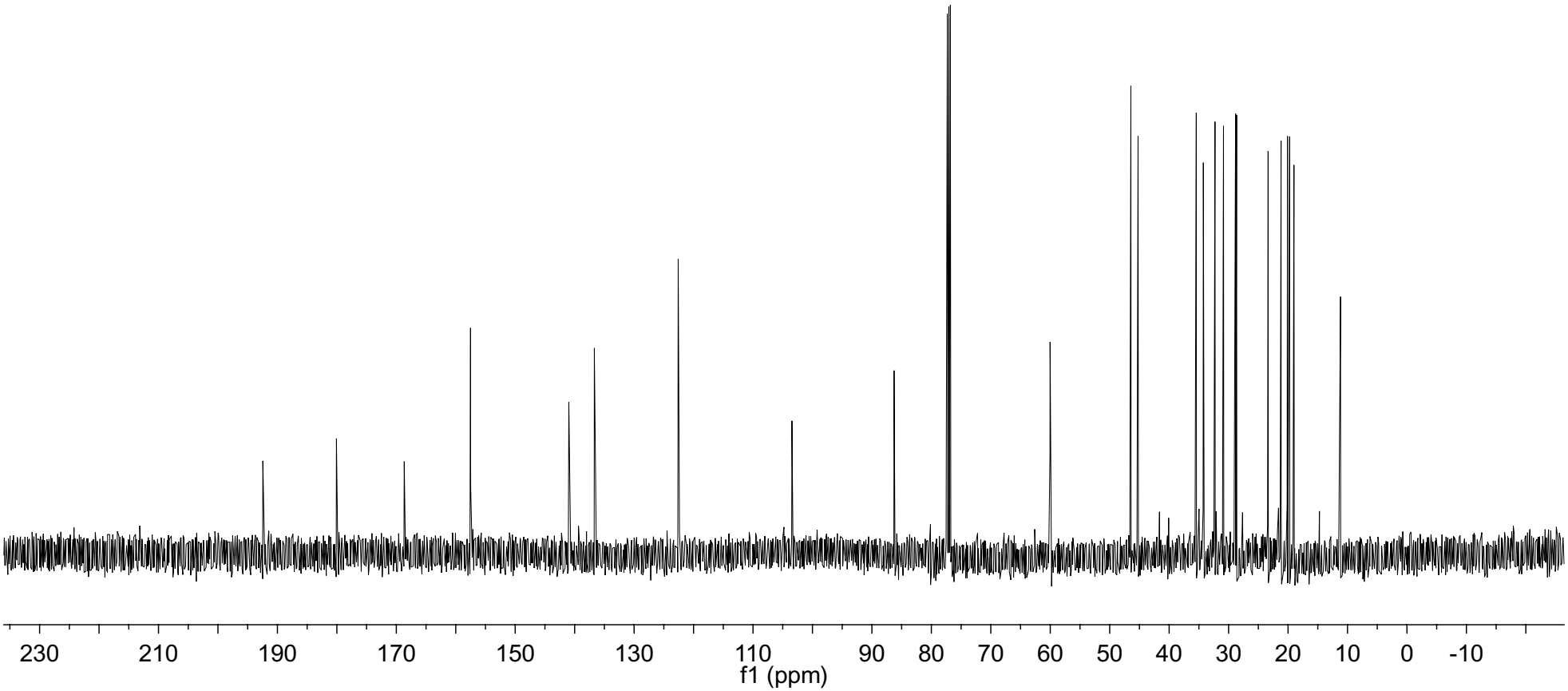

DEPT CDCl3 125 MHz
O
O
O
OMe
11Z
CH3+CH
CH2
CH
-2.0
-1.8
-1.6
-1.4
-1.2
-1.0
-0.8
-0.6
-0.4
-0.2
0.0
ppm 200
150
100
50
0

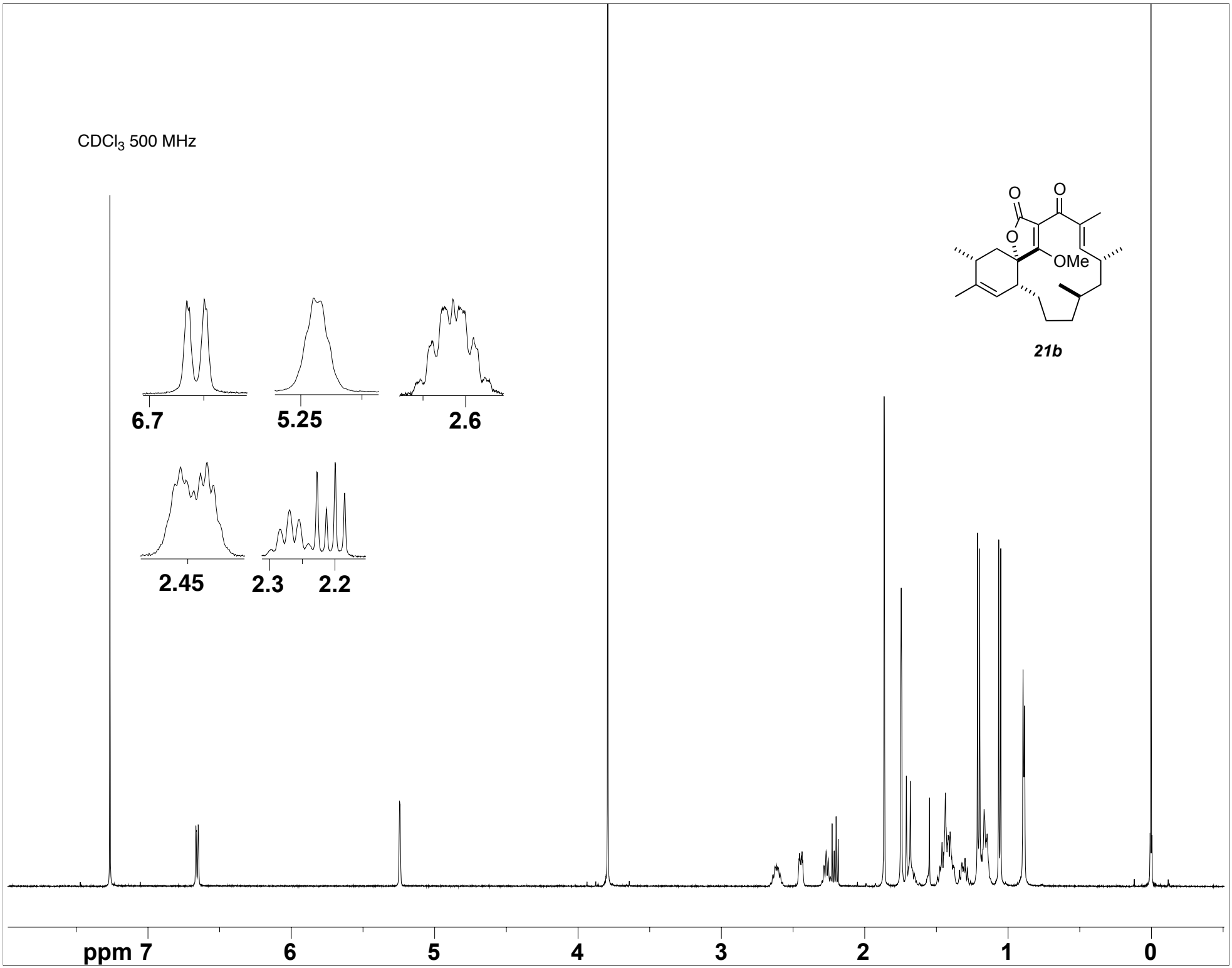

CDCl3 500 MHz
O
O
O
OMe
21a
5.5
2.6
2.4
2.1
1.1
8
7
6
5
4
3
2
1
0

$CDCl_3$ 125 MHz

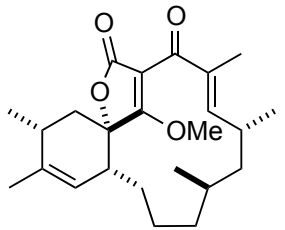


21a

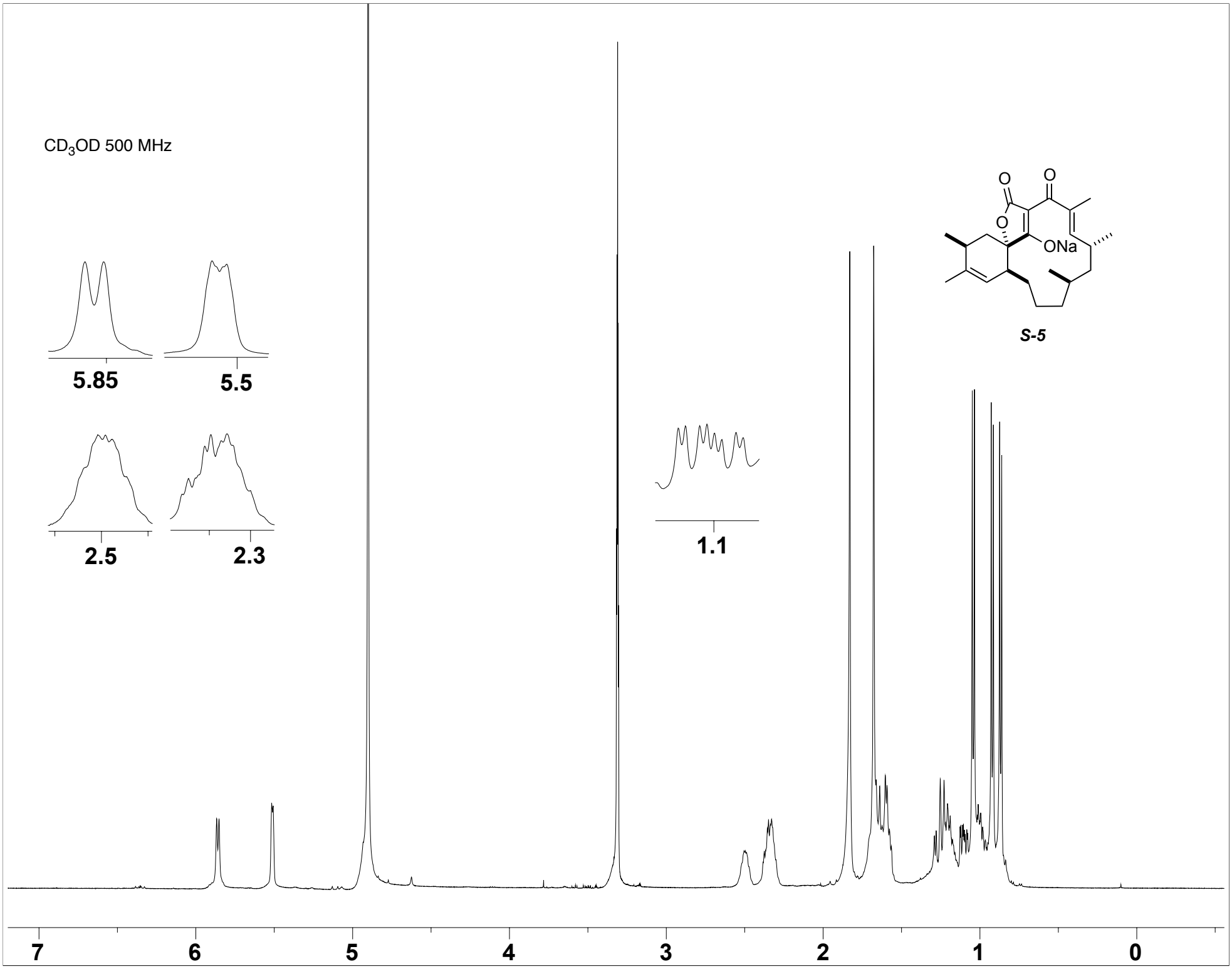



CDCl3 500 MHz
6.7
5.25
2.6
2.45
2.3
2.2
O
O
O
OMe
21b
ppm 7
6
5
4
3
2
1
0

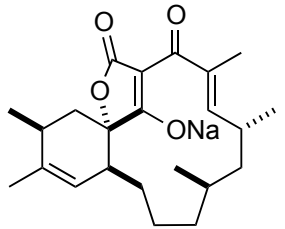
$CDCl_3$ 75 MHz



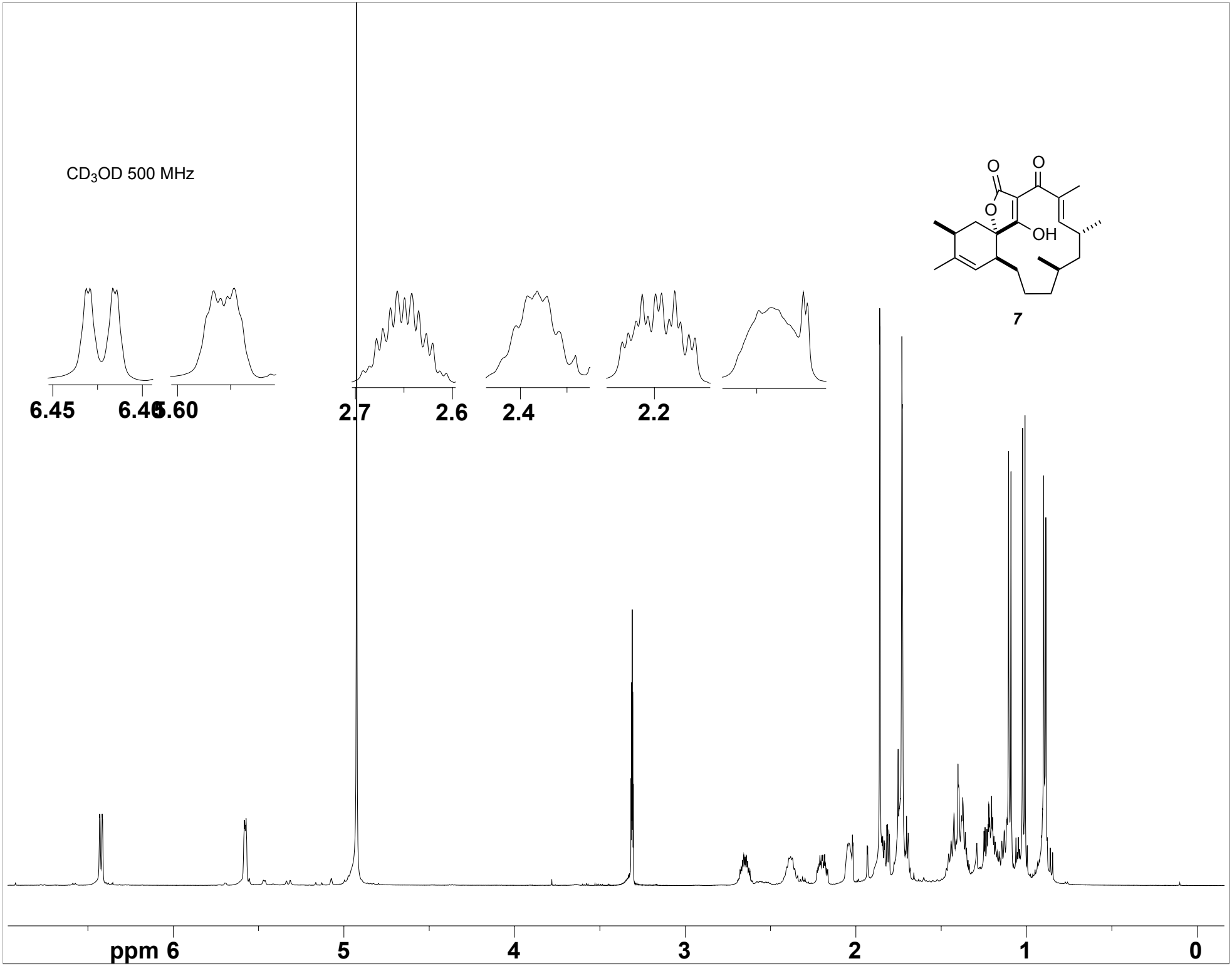
21b

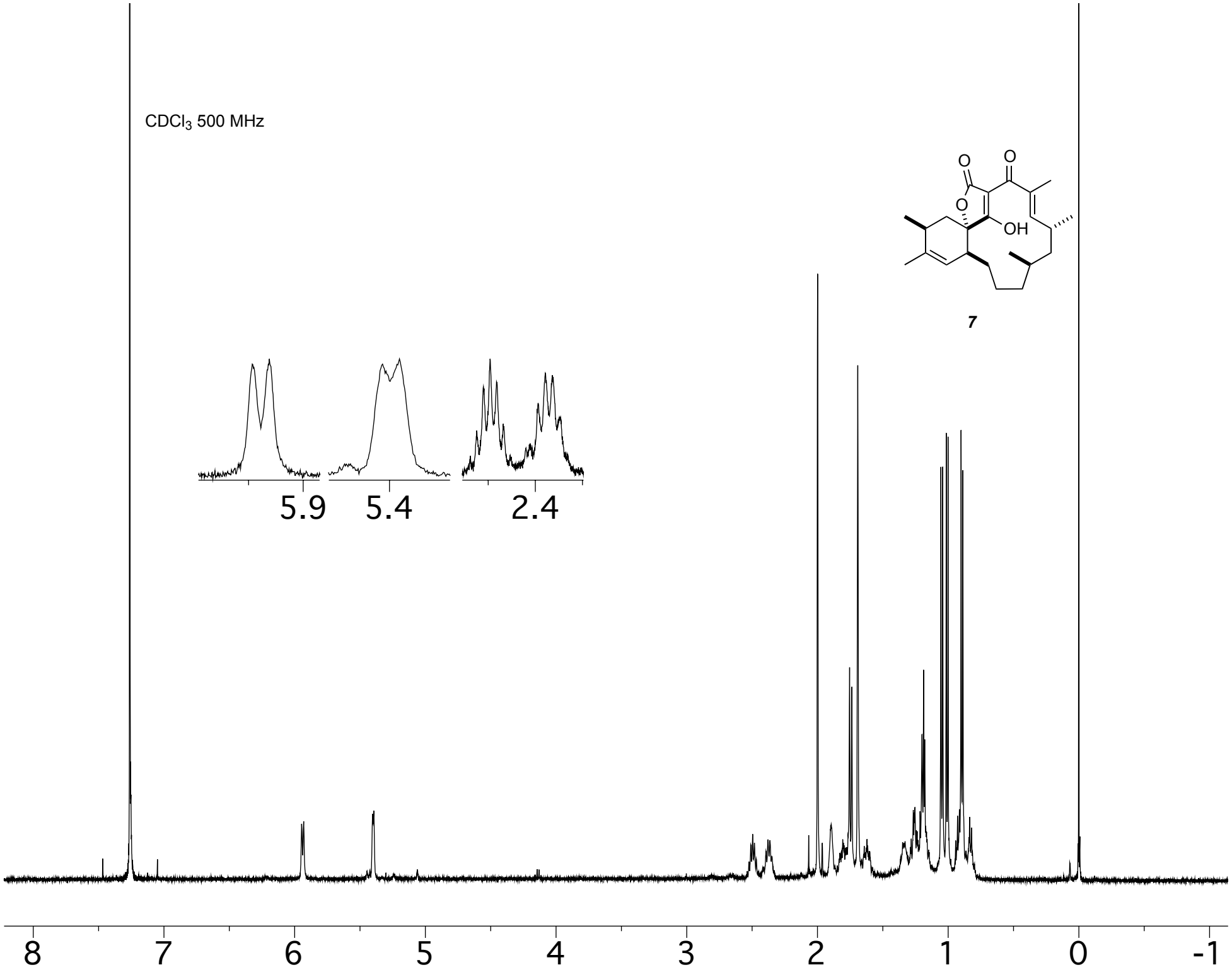

CD3OD 500 MHz
O
O
O
ONa
S-5
5.85
5.5
2.5
2.3
1.1
7
6
5
4
3
2
1
0

CD_3OD 75 MHz

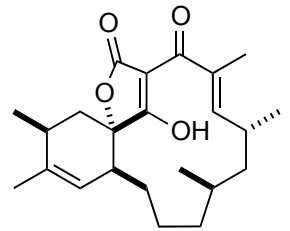


S-5


CD3OD 500 MHz
O
O
O
OH
7
6.45
6.46
6.60
2.7
2.6
2.4
2.2
ppm 6
5
4
3
2
1
0


CDCl3 500 MHz
O
O
O
OH
7
5.9
5.4
2.4
8
7
6
5
4
3
2
1
0
-1

CD_3OD 75 MHz



7

V. Supporting Information References

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