SUPPORTING INFORMATION

Synthesis, Molecular Editing and Biological Assessment of the Potent Cytotoxin Leiodermatolide

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Biological Methods

Cell Treatments for Fluorescence Studies

U2OS cells were plated on a collagen-coated 96 well plate at approximately 2800 cells per well. After an overnight incubation, the cells were exposed to leiodermatolide continuously for 24 hours. Five replicate wells were treated with each concentration of leiodermatolide and three wells were treated with the negative and positive controls. DMSO was used as the solvent for leiodermatolide and thus 1% DMSO in culture media was the negative control, the positive controls were Mitomycin-C as a clastogenic control for micronucleus induction and Nocodazole as the positive control for induction of tubulin damage, centrosome amplification and micronuclei.

Cell Harvest and Staining

At the end of the 24-hour exposure, leiodermatolide was removed and cells were fixed directly in the 96 well plates with 100% ice cold methanol for 10 minutes. Cells were washed twice with Phosphate Buffered Saline (PBS) solution and then placed in blocking buffer containing 5% normal goat serum for 60 minutes at room temperature. A 1:1000 primary probe solution containing rabbit anti-pericentrin antibody and monoclonal anti-alpha tubulin antibody in mouse was prepared in antibody dilution solution. After removing the blocking buffer, cells were placed in primary probe solution overnight at 4°C. The next day, cells were washed twice with PBS and a secondary probe solution containing a 1:1000 goat anti-rabbit Alexa 488 (stain for centrosome), a 1:1000 goat anti-mouse Alexa 647 (stain for tubulin) and 1:1000 DAPI ((Biotium; stain for DNA) in PBS was applied for 30 minutes at room temperature. Following three washes with PBS, cells were covered with 200 microL PBS and the plate sealed in preparation for image analysis.

Cell Analysis

The cells were analyzed using the Cell Cycle Analysis version 4 bioapplication on the ArrayScan VTi HCS Reader (ThermoFisher) with 20X objective. The algorithm uses the DNA-binding dye DAPI to classify cells based on intensity and size parameters. Using the distribution of DNA content, gates are set to determine the percent of cells in each cell cycle phase (< 2N, 2N, 2–4N, 4N, and > 4N corresponds to SubG1, G0/G1, S, G2/M and polyploidy cells, respectively.). A minimum of 1000 nuclei per well were analyzed for cell cycle.

The average number of nuclei per field is calculated by the algorithm and this is compared to the negative control as the toxicity endpoint.

Centrosome spots are identified via a mask that is created around the nuclei, followed by the algorithm using intensity and size parameters to identify spots within the mask. A minimum of 1000 nuclei per well are analyzed for centrosome spots. Nuclei containing greater than 2 centrosome spots are considered to have amplification and the percent amplification for each dose is calculated. For this analysis the cells from replicate wells are pooled and bucketed into categories based on the number of centrosomes.

The cells were analyzed on a ThermoFisher ArrayScan VTi using the Micronucleus bioapplication and a 20X objective. The algorithm uses intensity and size parameters to identify the nuclear mask for each valid nucleus and micronucleus. Micronuclei are distinguished from nuclei based on size and proximity to a main nucleus. A minimum of 1000 nuclei per well are analyzed for micronuclei. The percent micronucleus induction is calculated by dividing the number of micronuclei by the total number of nuclei in the well. Statistics are performed using GraphPad Prism software. The treated cultures are compared to the negative control using a one way analysis of variance (ANOVA) with a Dunnett's multiple comparison follow up. The positive controls are evaluated with an unpaired t test and a two-tailed p value is reported.

The tubulin evaluation is qualitative. Images are chosen from doses representing the dose response.

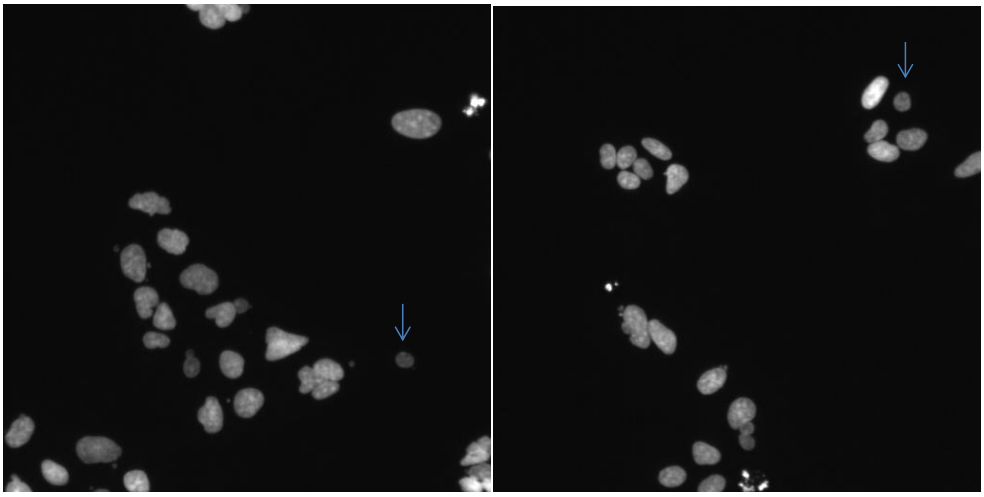


Figure S1: Representative image analysis field used to calculate cell cycle values. Arrow shows a cell being identified as Sub G1 (<2N DNA content).

■ Cytotoxicity Assay

N87 (gastric carcinoma), MDA-MB-361-DYT2 (breast carcinoma), HT29 (colon carcinoma), HL60 (leukemia), NB4 (leukemia), HEL (leukemia) and Raji (leukemia) cells were used to assess the anti-proliferative capacity of the compounds. Cells were seeded in 96-well plates at low density, then treated the following day with compound in 3-fold serial dilutions at 10 concentrations in duplicate. Cells were incubated for 4 days in a humidified 37^{o}C/5% CO_2 incubator. The plates were harvested by incubating with CellTiter® 96 AQueous One MTS Solution (Promega, Madison, WI) for 1.5 hour and absorbance measured on a Victor plate reader (Perkin-Elmer, Waltham, MA) at wavelength 490 nm. GI_{50} values were calculated using a four-parameter logistic model with XLfit (IDBS, Bridgewater, NJ).

Broad Panel Kinase Screen

Biochemical Kinase Screening Method (International Centre for Kinase Profiling, Dundee). At the International Centre for Kinase Profiling (ICKP) a radiometric filter binding assay is used to determine inhibitor specificity and potency at an approximate Km concentration of ATP. This method is sensitive, accurate and provides a direct measure of enzyme activity in the presence of inhibitors. The method utilized for lipid kinase screening is the Promega ADP Glo High Throughput Assay Kit. The principle of this assay is that it is a measurement of the ADP generated as a function of the enzyme reaction.

Biochemical Kinase Screening Method (Invitrogen, a Life Technology company). Invitrogen screening service uses a FRET-based kinase assays to assess inhibitor potency at a Km concentration of ATP. The experiments were conducted in Invitrogen Inc. (Carlsbad, CA) in their Madison, WI, facility. Most of the kinase panel assays were the FRET-based Z´-LYTE® assays that employ a fluorescence-based, coupled-enzyme format, taking advantage of the differential sensitivity of phosphorylated and non-phosphorylated peptides to proteolytic cleavage. Some kinases were tested using the TR-FRET-based Adapta® assay format that employs the Alexa Fluor® 647 labeled ADP tracer and Eu-labeled anti-ADP antibody. The assays of the above two formats were normally conducted with ATP concentrations near the KM,app. Another assay format used was the TR-FRET-based LanthaScreen® binding assays utilizing an Alexa Fluor®

tracer and Eu-labeled anti-tag antibody that binds to the respective affinity tag of the target kinase.

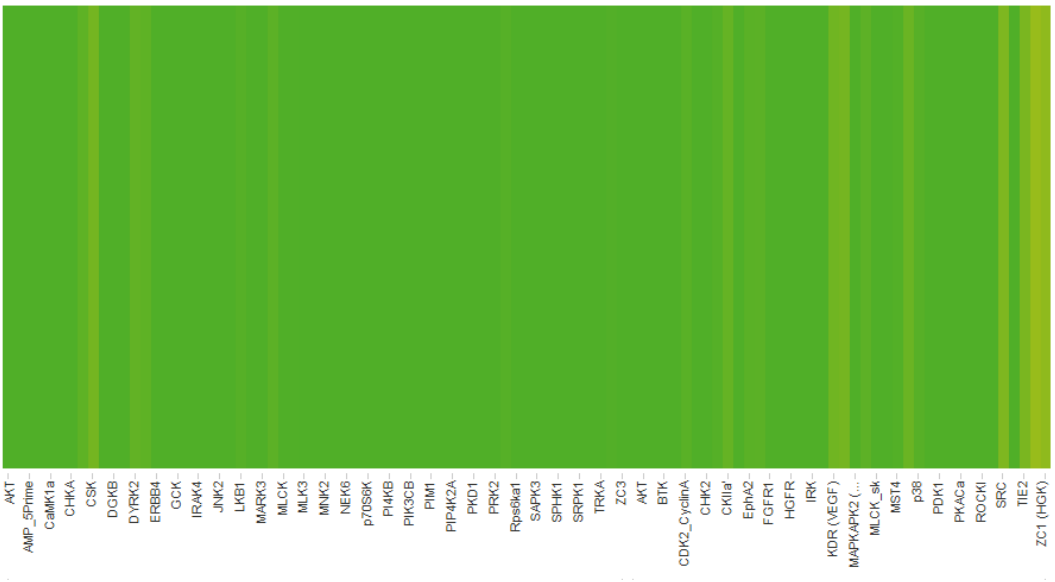


Figure S2: Kinase panel screen at 1 µM compound concentration. Color coding: green (0% inhibition, yellow: 50% inhibition)

Crystallographic Information

X-ray diffraction data for both compounds were collected using a Bruker AXS X8 Proteum diffractometer housed in front of a FR591 rotating anode equipped with graded multilayer focusing optics (Cu Kα, λ = 1.54184 Å) employing ϕ and ω scans to cover reciprocal space up to 67° 2θ with 99% completeness. The structures were solved by direct methods using SHELXS-97. Atomic positions and displacement parameters were refined using full-matrix least-squares methods based on Fsqd using SHELXL-97.[1]

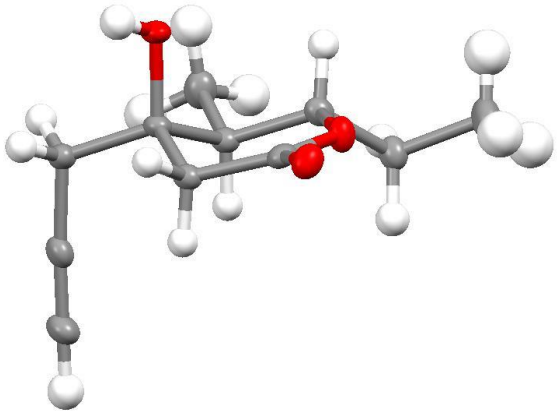


Figure S3. Structure of the homopropargylic alcohol ***epi*-31** in the solid state.

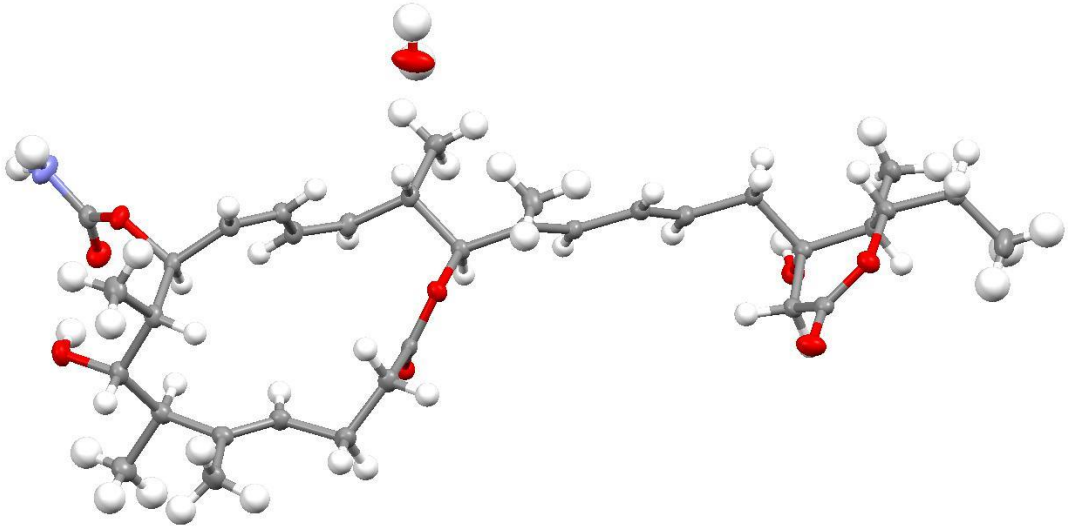
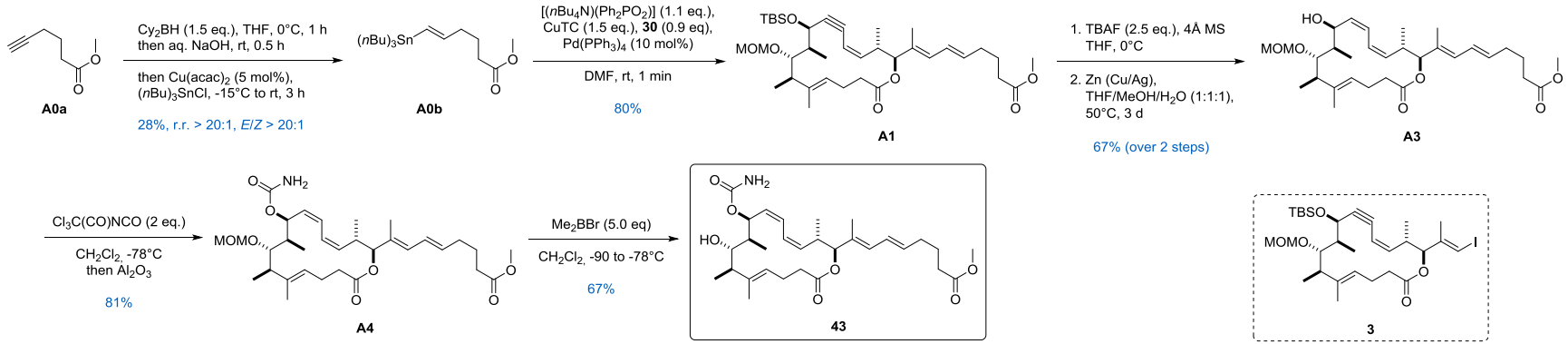
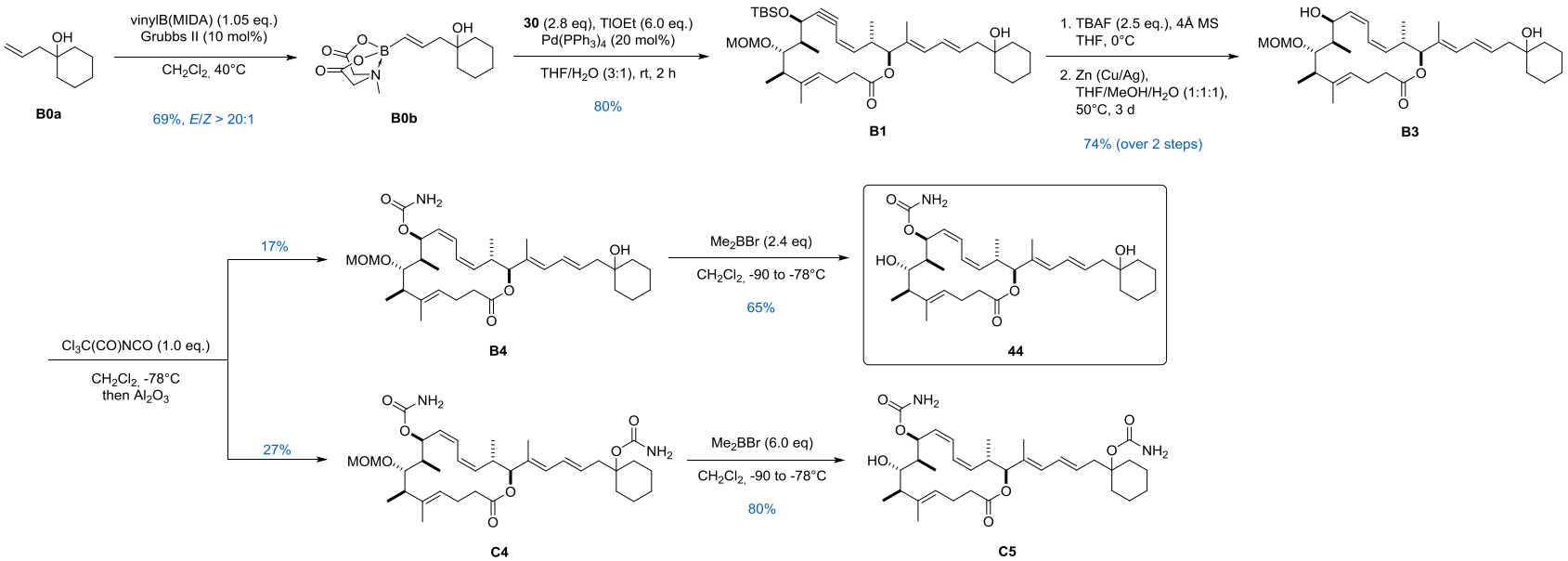


Figure S4. Structure of **leiodermatolide (1)·H_2O** in the solid state.

■ **Analogue 43**

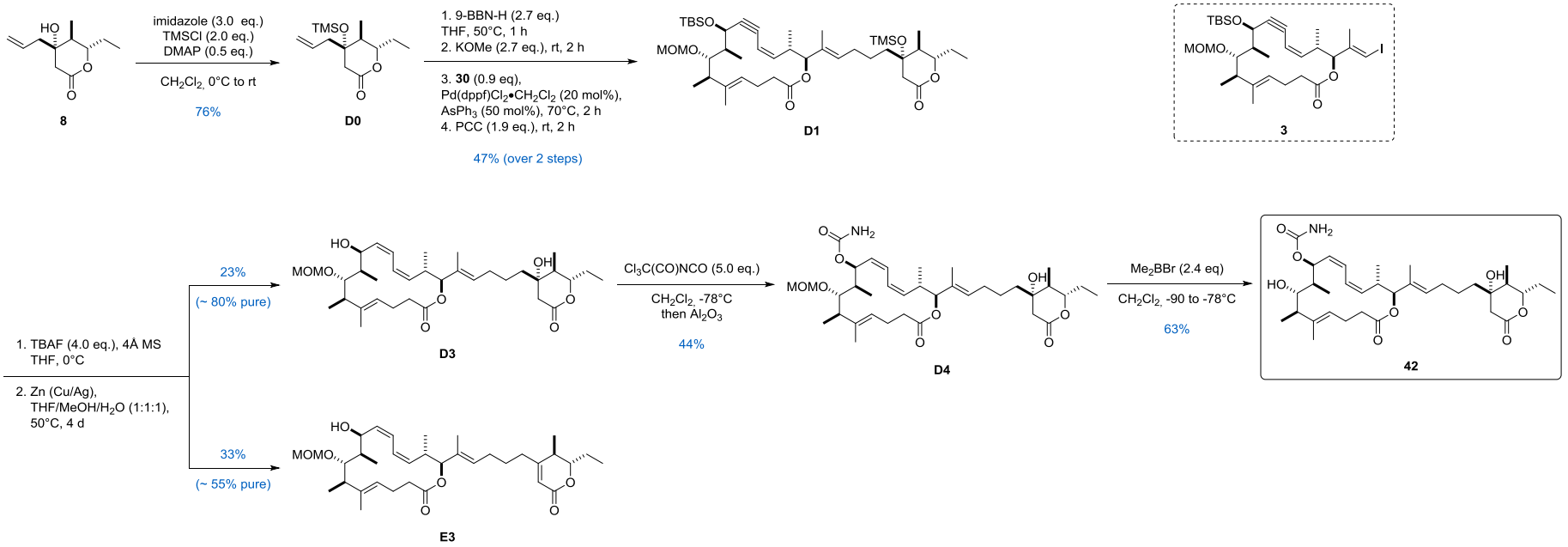


■ **Analogue 44**

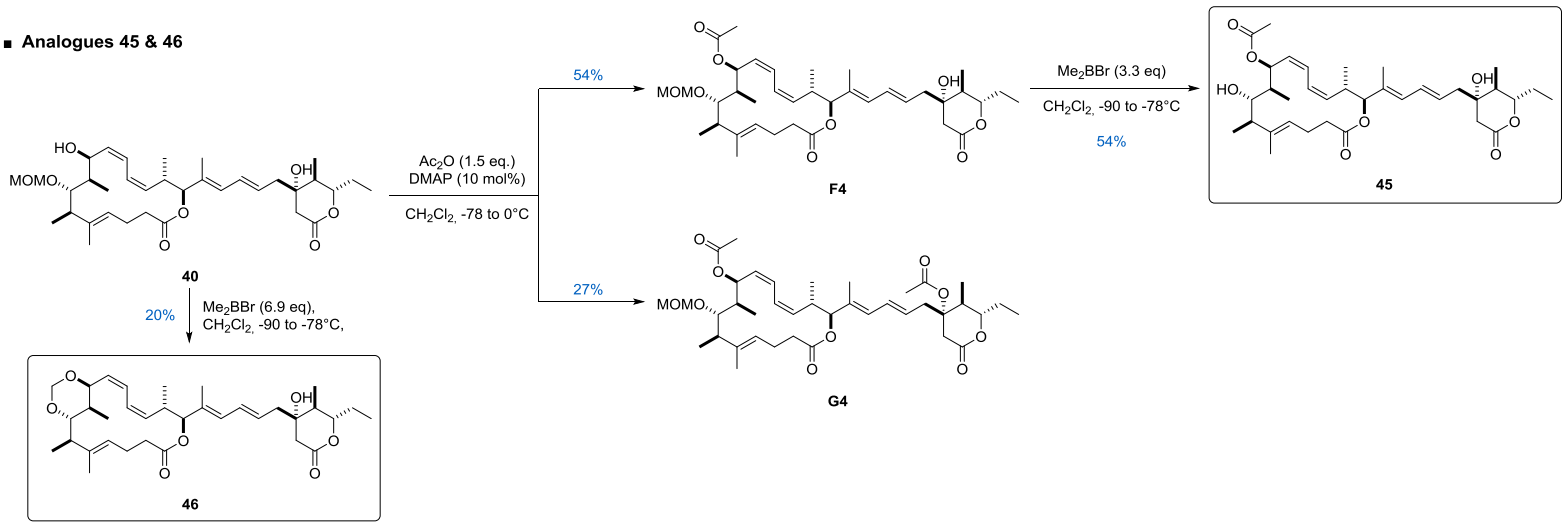


Scheme S1. Synthesis of analogues **43** and **44**.

■ **Analogue 42**



■ **Analogues 45 & 46**



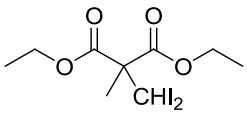
Scheme S2. Synthesis of analogues **42, 45** and **46**.

Total Synthesis of Leiodermatolide

General. All reactions were carried out under Ar in flame-dried glassware. The solvents were purified by distillation over the drying agents indicated and were transferred under Ar: THF, Et_2O (Mg/anthracene), CH_2Cl_2, MeCN (CaH_2), hexane, toluene (Na/K), MeOH (Mg), DMF (MS 4Å), DMSO (distilled over CaH_2, stored over MS 4Å). Microwave-assisted reactions: All reactions under microwave irradiation were performed at the specified temperature in a Biotage® Initiator 2.5 system equipped with a build-in pressure sensor and an IR temperature measurement sensor. Flash chromatography: Merck silica gel 60 (40–63 µm) or Florisil® (60-100 mesh). NMR: Spectra were recorded on Bruker DPX 300, AV 400, AV 500 or AVIII 600 spectrometers in the solvents indicated; chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. The solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: $\delta_C \equiv 77.16$ ppm; residual $CHCl_3$ in $CDCl_3$: $\delta_H \equiv 7.24$ ppm; CD_2Cl_2: $\delta_C \equiv 53.80$ ppm; residual $CDHCl_2$: $\delta_H \equiv 5.32$ ppm; C_6D_6: $\delta_C \equiv 128.06$ ppm; residual C_6D_5H: $\delta_H \equiv 7.16$ ppm, DMSO-d_6: $\delta_C \equiv 39.52$ ppm, residual $CD_2HS(O)CD_3$: $\delta_H \equiv 2.50$ ppm). IR: Spectrum One (Perkin-Elmer) spectrometer, wavenumbers ($\tilde{\nu}$) in cm^{-1}. MS (EI): Finnigan MAT 8200 (70 eV), ESI-MS: ESQ3000 (Bruker), accurate mass determinations: Bruker APEX III FT-MS (7 T magnet) or Mat 95 (Finnigan). Unless stated otherwise, all commercially available compounds (Fluka, Lancaster, Aldrich) were used as received.

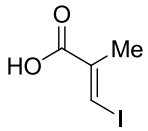
■ Synthesis of the Enyne Segment 6

Diethyl 2-(diiodomethyl)-2-methylmalonate (14). A solution of diethyl methylmalonate (**13**) (9.81 mL, 57.0 mmol) in Et_2O (20 mL) was added over 30 min to a suspension of NaH (1.65 g, 69.0 mmol) in Et_2O (100 mL), causing the mixture to reach reflux temperature while vigorous evolution of H_2 was noticed. Once the addition was complete, the mixture was stirred at reflux for 1.5 h before solid CHI_3 (22.6 g, 57.0 mmol) was added. Stirring was continued at reflux temperature for 12 h before the mixture was cooled to 0 °C and excess NaH was carefully quenched with aq. HCl (1 M, 100 mL). After stirring for 20 min, the layers were separated and the aqueous layer was extracted with Et_2O (3 x 65 mL). The combined organic layers were washed with brine (80 mL), dried over Na_2SO_4 and concentrated *in vacuo* to yield the title compound as a light brown viscous liquid (24.9 g, 99%), which

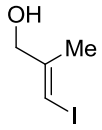


was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.73 (br s, 1H), 4.18 (dq, 4H, *J* = 7.1 Hz, 1.4 Hz), 1.75 (s, 3H), 1.25 (t, 6H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.2, 62.8, 62.3, 20.5, 14.1, –25.8; IR (film): $\tilde{\nu}$ = 1731, 1447, 1380, 1366, 1261, 1207, 1162, 1093, 1074, 1015, 859 cm^{-1}; MS (EI) *m*/*z* (%): 440 (12), 313 (9), 241 (22), 213 (27), 195 (17), 167 (12), 113 (7), 85 (12), 41 (16), 39 (23), 29 (100), 27 (15); HRMS (ESI): *m*/*z*: calcd. for $C_9H_{14}O_2I_2Na$ [M^++Na]: 462.88737, found 462.88705. The analytical and spectroscopic data are in agreement with those reported in the literature.[2] When applied to 20.5 mL (120 mmol) of compound **13,** this reaction yielded 52.2 g (>98%) of compound **4**.

(*E*)-3-Iodo-2-methylacrylic acid (15). KOH (15.9 g, 283 mmol) and H_2O (60 mL) were added to a solution of crude malonate **14** (24.8 g, 56.3 mmol) in EtOH (180 mL), and the resulting red solution was stirred at reflux temperature for 4 h. After cooling and evaporation of all volatile materials, the residue was dissolved in aq. K_2CO_3 (10% *w*/*w*, 150 mL), which was then carefully acidified with conc. HCl at 0 °C. Extraction with CH_2Cl_2 (8 x 50 mL) was followed by drying of the combined organic layers over Na_2SO_4 and concentration *in vacuo*. The residue was purified by flash chromatography (silica, hexanes/EtOAc, 9:1 + 0.5% HOAc) to yield the title compound as a light yellow solid (8.58 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.28 (br s, 1H), 8.00 (q, 1H, *J* = 1.2 Hz), 2.03 (d, 3H, *J* = 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.5, 139.2, 102.3, 20.0; IR (film): $\tilde{\nu}$ = 3079, 2966, 2596, 1682, 1593, 1409, 1379, 1296, 1235, 1108, 991, 915, 838, 727, 685 cm^{-1}; MS (EI) *m*/*z* (%): 212 (56), 167 (6), 127 (6), 85 (75), 57 (12), 45 (14), 43 (11), 41 (28), 40 (16), 39 (100), 38 (18), 37 (9), 29 (18); HRMS (EI): *m*/*z*: calcd. for $C_4H_5O_2I$ [*M*]: 211.93343, found 211.93359. The analytical and spectroscopic data are in agreement with those reported in the literature.[3] When applied to 123 g (280 mmol) of compound **14** this reaction yielded 54.0 g (91%) of compound **15**.



Alternative synthesis of (*E*)-3-iodo-2-methylprop-2-en-1-ol. BH_3•THF (1 M in THF, 60.0 mL, 60 mmol) was added over 2 h at –15 °C to a solution of acid **15** (10.6 g, 50.0 mmol) in THF (50 mL). The reaction mixture was allowed to reach room temperature and was stirred at this temperature for 2 h, when a second aliquot of BH_3•THF (1 M in THF, 15.0 mL, 15 mmol) was introduced. After additional 2 h, the mixture was carefully quenched by the slow addition of aq. K_2CO_3 (10% *w*/*w*, 50 mL) at 0 °C. After stirring for 10 min, the mixture was diluted with H_2O (50 mL) and MTBE (50 mL), and the aqueous layer was extracted with MTBE (2 x 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and

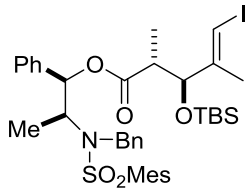


concentrated *in vacuo*. The residue was purified by flash chromatography (silica, pentane/Et_2O, 3:1) to yield the title compound as a light yellow liquid (7.40 g, >60% pure). An aliquot of this mixture was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.25 (m, 1H), 4.09 (d, 2H, *J* = 5.4 Hz), 1.85 – 1.81 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.4, 77.5, 67.3, 21.5; IR (film): $\tilde{\nu}$ = 3295, 2912, 2851, 1620, 1433, 1376, 1274, 1252, 1145, 1066, 1008, 942, 829, 771, 665 cm^{-1}; MS (EI) *m*/*z* (%): 198 (75), 183 (5), 127 (9), 71 (100), 53 (28), 43 (59), 31 (57), 39 (61), 38 (12), 31(34), 29(14), 27(26); HRMS (EI): *m*/*z*: calcd. for C_4H_7IO [*M*]: 197.95416, found 197.95410. The analytical and spectroscopic data are in agreement with those reported in the literature.[2]

Alternative synthesis of allylic aldehyde 16. [$Cu(MeCN)_4$] (236 mg, 750 μmol), 2,2'-bipyridine (117 mg, 750 μmol), TEMPO (117 mg, 750 μmol), and 1-methylimidazole (120 μL, 1.5 mmol) were successively added to a round-bottom flask purged with O_2 and containing a solution of **(***E*)-3-iodo-2-methylprop-2-en-1-ol (2.97 g, 15.0 mmol) in MeCN (40 mL), inducing a color change from light yellow to dark red/brown. The reaction mixture was vigorously stirred at room temperature for 1 h under O_2 atmosphere (balloon). Completion of the reaction occurred with a color change from dark red/brown to green/blue. The mixture was diluted with H_2O (300 mL) and pentanes (300 mL), the aqueous layer was extracted with pentanes (2 x 100 mL). The combined organic layers were dried over Na_2SO_4, carefully concentrated *in vacuo* (0 °C, 200 mbar) to yield the title compound as an orange liquid (2.14 g, 55% over two steps). Due to the unstable nature of this compound, it was dissolved in CH_2Cl_2 containing 4Å MS and was immediately used in the next step. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.52 (s, 1H), 7.8 (q, 1H, *J* = 1.2 Hz), 1.92 (d, 3H, *J* = 1.2 Hz) ^{13}C NMR (75 MHz, $CDCl_3$): δ = 189.5, 151.0, 109.6, 16.6; IR (film): $\tilde{\nu}$ = 2921, 2842, 1691, 1591, 1294, 1099, 1027, 1015, 798, 679 cm^{-1}; MS (EI) *m*/*z* (%): 196 (99), 167 (14), 127 (8), 69 (86), 41 (59), 30 (11), 39 (100), 38 (13), 29 (8); HRMS (EI): *m*/*z*: calcd. for C_4H_5IO [*M*]: 195.93852, found 195.93837.

(2*R*,3*S*,*E*)-((1*R*,2*S*)-2-(*N*-Benzyl-2,4,6-trimethylphenylsulfonamido)-1-phenylpropyl) 3-hydroxy-5-iodo-2,4-dimethylpent-4-enoate (17). NEt_3 (0.904 mL, 6.52 mmol) and (1*R*,2*S*)-2-(*N*-benzyl-2,4,6-trimethylphenylsulfonamido)-1-phenylpropyl propionate (**19**)[4] (2.61 g, 5.43 mmol) were dissolved in CH_2Cl_2 (45 mL) and the solution cooled to –78 °C. A solution of dicyclohexyboryl triflate (2.13 g, 6.52 mmol) in pentane (12 mL) was then added over 12 min to give a yellow

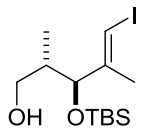
suspension, which was kept at this temperature for 5 h. A solution of freshly prepared aldehyde **6** (2.45 g, 12.5 mmol) in CH_2Cl_2 (10 mL) was then added and stirring continued for 1.5 h before the cooling bath was removed and the mixture allowed to reach room temperature. After 3 h, the reaction was quenched with aq. pH 7 buffer (30 mL) and treated with MeOH (100 mL) and aq. H_2O_2 (30% *w/w*, 15 mL) overnight. The mixture was concentrated *in vacuo*, the residue dissolved in CH_2Cl_2 (150 mL) and the organic layer washed with H_2O (60 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL), the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. ^{1}H NMR analysis of the crude product showed a diastereomeric ratio of 13:1. The residue was purified by flash chromatography to yield the title compound as a white solid (2.79 g, 76%, single isomer). $[\alpha]_{20}^{D}$ = +45.0 (c = 0.95, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 – 7.13 (m, 8H), 6.87 (s, 2H), 6.86- 6.82 (m, 2H), 6.28 (s, 1H), 5.83 (d, 1H, *J* = 4.0 Hz), 4.73 (d, 1H, *J* = 16.7 Hz), 4.54 (d, 1H, *J* = 16.7 Hz), 4.23 (dd, 1H, *J* = 8.9, 3.8 Hz), 4.09 (dq, 1H, *J* = 4.0, 7.0 Hz), 2.73 (d, 1H, *J* = 4.1 Hz, 1H), 2.64 – 2.52 (m, 1H), 2.48 (s, 6H), 2.26 (s, 3H), 1.80 (d, 3H, *J* = 1.1 Hz), 1.15 (d, 3H, *J* = 7.0 Hz), 0.94 (d, 3H, *J* = 7.23 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.1, 147.0, 142.7, 140.4, 138.7, 138.2, 133.5, 132.2, 128.6, 128.4, 128.1, 127.7, 127.3, 126.0, 81.3, 78.7, 78.6, 56.9, 48.4, 43.4, 23.1, 21.0, 18.9, 14.2, 13.5; IR (film): $\tilde{\nu}$ = 3496, 1741, 1604, 1496, 1455, 1379, 1317, 1151, 1117, 1031, 1011, 929, 858, 752, 730, 698, 659 cm^{-1}; MS (EI) *m*/*z* (%): 406 (1), 317 (20), 316 (100), 183 (5), 119 (17), 91 (60), 57 (3), 41 (3); HRMS (ESI): *m*/*z*: calcd. for $C_{32}H_{38}NO_5ISNa$ [M^++Na]: 698.14076, found 698.14108. The analytical and spectroscopic data are in agreement with those reported in the literature.[2]

(2*R*,3*S*,*E*)-((1*R*,2*S*)-2-(*N*-Benzyl-2,4,6-trimethylphenylsulfonamido)-1-phenylpropyl) 3-(*tert*-butyldimethylsilyloxy)-5-iodo-2,4-dimethylpent-4-enoate (17a). 

2,6-Lutidine (0.863 mL, 7.43 mmol) was added via syringe to a stirred solution of alcohol **17** (2.51 g, 3.71 mmol) in CH_2Cl_2 (20 mL). The mixture was cooled to 0 °C before TBSOTf (1.28 mL, 5.57 mmol) was slowly added. After stirring for 2 h at 0 °C, the reaction was quenched with sat. aq. NH_4Cl, the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL), the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to yield the title compound as a white solid, which was used in the next step without further purification (2.89 g, 95%). An analytically pure sample was obtained by flash chromatography (hexanes/EtOAc, 9:1). $[\alpha]_{20}^{D}$ = +36.3 (c = 0.85, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (d, 2H, *J* = 7.3 Hz), 7.30 – 7.22 (m, 3H), 7.19 – 7.13 (m, 1H), 7.07 (t, 2H, *J* = 7.5 Hz), 6.85 (s, 2H), 6.7 (d, 2H, *J* = 7.3 Hz), 6.18

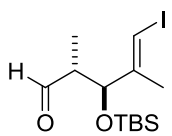
(s, 1H), 5.67 (d, 1H, J = 6.0 Hz), 4.85 (d, 1H, J = 16.1 Hz), 4.37 (d, 1H, J = 16.1 Hz), 4,29 (d, 1H, J = 9.3 Hz), 4.04 (dq, 1H, J = 6.6, 6.6 Hz), 2.61 (dq, 1H, J = 9.1, 7.3 Hz), 2.39 (s, 6H), 2.29 (s, 3H), 1.73 (d, 3H, J = 0.8 Hz), 1.16 (d, 3H, J = 6.9 Hz), 0.80 (s, 9H), 0.74 (d, 3H, J = 7.2 Hz), –0.03 (s, 3H), –0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0, 147.7, 142.5, 140.6, 138.6, 138.1, 133.1, 132.3, 128.6, 128.5, 128.4, 128.0, 127.5, 126.6, 80.8, 79.4, 77.9, 56.7, 48.3, 44.9, 25.9, 23.0, 21.0, 18.8, 18.3, 15.1, 14.0, –4.9, –5.0; IR (film): $\tilde{\nu}$ = 2956, 2935, 2857, 1743, 1605, 1455, 1379, 1325, 1254, 1154, 1072, 1030, 1011, 929, 857, 836, 777, 729, 698, 659 cm^{-1}; MS (EI) *m*/*z* (%): 406 (23), 317 (21), 316 (100), 183 (6), 132 (7), 119 (20), 91 (62), 73 (11); HRMS (ESI): *m*/*z*: calcd. for $C_{38}H_{52}NO_5ISSiNa$ [M^++Na]: 812.22724, found 812.22802.

(2*S*,3*S*,*E*)-3-(*tert*-Butyldimethylsilyloxy)-5-iodo-2,4-dimethylpent-4-en-1-ol (17b).



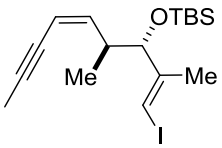
DIBAl-H (1 M in toluene, 9.38 mL, 9.38 mmol) was added over a period of 12 min to a solution of silyl ether **17a** (2.89 g, 95% pure, 3.48 mmol) in toluene (25 mL) at –78 °C. After stirring 2 h at this temperature, excess of DIBAl-H was carefully quenched with MeOH (2 mL). The mixture was diluted with MTBE (20 mL) and sat. aq. Rochelle salt (30 mL). The resulting mixture was stirred overnight at room temperature before the aqueous layer was extracted with MTBE (3 x 30 mL). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, hexanes/EtOAc, 9:1) to yield the title compound as a colorless viscous liquid (1.07 g, 83% over two steps). $[\alpha]_{20}^{D}$ = –32.3 (c = 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.18 (s, 1H), 4.00 (d, 1H, J = 8.0 Hz), 3.61 (dd, 1H, J = 4.5, 0.7 Hz), 3.60 (d, 1H, J = 4.8 Hz), 2.44 (t, 1H, J = 5.68 Hz), 1.88 – 1.78 (m, 1H), 1.76 (d, 3H, J = 1.0 Hz), 0.88 (s, 9H), 0.78 (d, 3H, J = 7.0 Hz), 0.06 (s, 3H), –0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.0, 83.0, 79.4, 66.3, 38.8, 25.9, 19.6, 18.2, 14.1, –4.6, –5.2; IR (film): $\tilde{\nu}$ = 339, 2956, 2928, 2884, 2857, 1615, 1471, 1462, 1376, 1361, 1252, 1140, 1064, 1037, 1004, 982, 938, 834, 774, 672 cm^{-1}; MS (EI) *m*/*z* (%): 313 (46), 311 (23), 271 (18), 185 (52), 171 (16), 115 (6), 111 (9), 75 (100), 73 (44), 53 (6), 45 (5), 43 (5), 41 (6); HRMS (ESI): *m*/*z*: calcd. for $C_{13}H_{27}O_2ISiNa$ [M^++Na]: 393.07172, found 393.07146.

(2*R*,3*S*,*E*)-3-(*tert*-Butyldimethylsilyloxy)-5-iodo-2,4-dimethylpent-4-enal (18). A

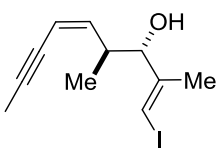


solution of alcohol **17b** (600 mg, 1.62 mmol) in CH_2Cl_2 (6 mL) was added to a suspension of Dess-Martin periodinane (756 mg, 1.78 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After stirring for 15 min, the mixture was allowed to warm to room temperature and stirring continued for 2 h. The

reaction was quenched with sat. aq. $Na_2S_2O_3/Na_2CO_3$ (1:1, 10 mL), the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was suspended in hexane/EtOAc (9:1) and the resulting suspension filtered through a short pad of SiO_2. The filtrate was then concentrated *in vacuo* to yield the rather unstable aldehyde **18**, which was immediately used in the next step (586 mg, 98%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.73 (d, 1H, *J* = 2.7 Hz), 6.28 (s, 1H), 4.27 (d, 1H, *J* = 8.4 Hz), 2.59 (dqd, 1H, *J* = 8.4, 7.1, 2.5 Hz), 1.79 (d, 3H, *J* = 1.0 Hz), 0.88 (d, 3H, *J* = 7.1 Hz), 0.85 (s, 9H), 0.03 (s, 3H), –0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 203.9, 147.8, 80.3, 79.2, 50.2, 25.7, 19.1, 18.2, 11.0, –4.7, –5.2.

***tert*-Butyl-((1*E*,3*S*,4*S*,5*Z*)-1-iodo-2,4-dimethylnona-1,5-dien-7-yn-3-yloxy)dimethylsilane (18a).** 

A precooled (–78 °C) solution of KHMDS (0.729 g, 3.66 mmol) in THF (6 mL) was added to a solution of sulfone **20** (1.00 g, 3.98 mmol) in THF (6 mL) at –55 °C, inducing a color change to dark-red. After stirring for 30 min at this temperature, a precooled (–78 °C) solution of aldehyde **9** (586 mg, 1.59 mmol) in THF (3 mL) was added dropwise via canula and the resulting mixture stirred at –55 °C for 13 h before being poured into brine (15 mL) and warmed to room temperature. Then, MTBE (20 mL) and H_2O (5 mL) were added, the aqueous layer was extracted with MTBE (2 x 20 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography to yield the title compound as a colorless viscous liquid (364 mg, 56%). $[\alpha]_{20}^{D}$ = +100.1 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.09 (m, 1H), 5.61 (dd, 1H, *J* = 10.3, 10.0 Hz), 5.39 (dq, 1H, *J* = 10.8, 2.3 Hz), 3.98 (d, 1H, *J* = 5.4 Hz), 2.92 (ddq, 1H, *J* = 9.3, 6.5, 6.4 Hz), 1.94 (d, 3H, *J* = 2.4 Hz), 1.76 (d, 3H, *J* = 0.9 Hz), 0.91 (d, 3H, *J* = 6.9 Hz), 0.86 (s, 9H), 0.01 (s, 3H), –0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.3, 143.9, 110.0, 89.5, 81.0, 78.1, 76.8, 39.6, 25.9, 20.8, 18.3, 17.2, 4.6, –4.7, –5.0; IR (film): $\tilde{\nu}$ = 2956, 2928, 2885, 2856, 2332, 2330, 2324, 1615, 1471, 1462, 1361, 1252, 1081, 1019, 1005, 938, 862, 833, 773, 749, 673 cm^{-1}; MS (EI) *m*/*z* (%): 347 (6), 312 (16), 311 (100), 146 (7), 127 (8), 115 (12), 91 (6), 75 (13), 73 (70), 59 (9), 53 (7); HRMS (ESI): *m*/*z*: calcd. for $C_{17}H_{29}OISiNa$ [M^++Na]: 427.09246, found 427.09258.

(1*E*,3*S*,4*S*,5*Z*)-1-Iodo-2,4-dimethylnona-1,5-dien-7-yn-3-ol (6). 

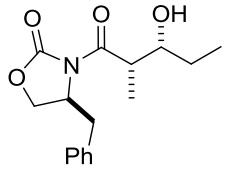
TBAF (1 M in THF, 1.42 mL, 1.42 mmol) was added to a solution of silyl ether **18a** (230 mg, 568 µmol) in THF (5 mL) at 0 °C and the mixture was stirred at this temperature for 3.5 h before it was quenched with H_2O

(5 mL), sat. aq. NH_4Cl (2 mL) and diluted with MTBE (10 mL). The aqueous layer was extracted with MTBE (3 x 10 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes/EtOAc, 9:1) to yield alcohol **6** as a colorless viscous liquid (163 mg, 99%). $[\alpha]_{20}^{D}$ = +24.0 (c = 0.50, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.24 (s, 1H), 5.64 (dd, 1H, *J* = 10.3 Hz, 10.1 Hz), 5.55 (dq, 1H, *J* = 10.7 Hz, 2.1 Hz), 3.91 (dd, 1H, *J* = 8.0 Hz, 3.1 Hz), 2.97 (dqd, 1H, *J* = 9.2, 7.2, 7.1 Hz), 1.97 (d, 3H, *J* = 2.2 Hz), 1.88 (d, 1H, *J* = 3.3 Hz), 1.83 (d, 3H, *J* = 0.8 Hz), 0.90 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.3, 143.0, 112.0, 91.0, 80.8, 79.8, 76.2, 38.9, 19.6, 17.0, 4.6; IR (film): $\tilde{\nu}$ = 3535, 3419, 2962, 2916, 2873, 2853, 1615, 1454, 1399, 1377, 1271, 1143, 1117, 1072, 1005, 933, 753, 671 cm^{-1}; MS (EI) *m/z* (%): 290 (1), 197 (59), 163 (10), 95 (9), 94, (100), 93 (16), 91(26)79 (89), 77 (40), 60 (5), 65 (9), 53 (10), 51 (7), 43 (12), 4 1 (6), 39 (25), 29 (5); HRMS (EI): *m/z*: calcd. for $C_{11}H_{15}OI$ [*M*]: 290.01676, found 290.01657.

When applied to 405 mg (1.00 mmol) of silyl ether **18a**, this reaction yielded 287 mg (99%) of **6**.

■ Synthesis of the Acid Segment 5

(*S*)-4-Benzyl-3-((2*S*,3*R*)-3-hydroxy-2-methylpentanoyl)oxazolidin-2-one (23a).

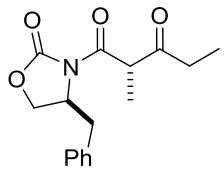


Bu_2BOTf (1 M in CH_2Cl_2, 49 mL, 49.0 mmol) was slowly added to a solution of oxazolidinone **23** (9.70 g, 41.6 mmol) in CH_2Cl_2 (92 mL) at 0 °C. Et_3N (7.6 mL, 55.0 mmol) was then added at such a rate as to keep the internal temperature below 2 °C. Once the addition was complete, the mixture was cooled to –78 °C before freshly distilled propionaldehyde (4.4 mL, 46.4 mmol) was introduced. The mixture was stirred for 30 min at –78 °C before the CO_2/acetone bath was replaced by an ice bath. Stirring was continued for 1 h and the reaction quenched with aq. phosphate buffer (46 mL, pH 7) and MeOH (138 mL) at such a rate as to keep the internal temperature below –6 °C. Then, a 1:2 mixture of MeOH and aq. H_2O_2 (30% *w/w*, 138 mL) was carefully added such that the internal temperature never rose above 10 °C. The mixture was stirred for 1 h once the addition was complete. After concentration on a rotary evaporator (bath-temperature ca. 30 °C), Et_2O (50 mL) was added to the slurry and the aqueous layer extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (12 mL) and brine (12 mL) before being dried over $MgSO_4$. Evaporation of the solvent and flash chromatography (silica, hexanes/EtOAc, 3:1) of the residue, followed by recrystallization

of the product from Et_2O/hexanes yielded the title compound as a white solid (11.71 g, 97%). $[\alpha]_{20}^{D}$ = +20.8 (*c* = 1.38, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36 – 7.25 (m, 3H), 7.22 – 7.16 (m, 2H), 4.68 (ddq, 1H, *J* = 13.7, 6.9, 3.4 Hz), 4.27 – 4.12 (m, 2H), 3.89 – 3.80 (m, 1H), 3.80 – 3.70 (m, 1H), 3.24 (dd, 1H, *J* = 13.4, 3.3 Hz), 2.76 (dd, 1H, *J* = 13.4, 9.5 Hz), 1.88 (br s, 1H), 1.66 – 1.32 (m, 2H), 1.23 (d, 3H, *J* = 7.0 Hz), 0.96 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.8, 153.2, 135.2, 129.6, 129.2, 127.6, 73.2, 66.4, 55.3, 41.9, 38.0, 26.9, 10.6, 10.4; IR (film): $\tilde{\nu}$ = 3466, 2969, 1778, 1696, 1455, 1385, 1210, 1113, 1030, 969, 762, 749, 702 cm^{-1}; MS (EI) *m*/*z* (%): 292 (7), 291 (30), 273 (9), 244 (46), 233 (30), 178 (42), 158 (100), 142 (12), 134 (63), 133 (20), 117 (38), 116 (23), 115 (49), 97 (26), 91 (56), 86 (80), 77 (7), 69 (34), 57 (45), 42 (15); HRMS (ESI): *m*/*z*: calcd. for $C_{16}H_{21}NO_4Na$ [M^++Na]: 314.13628, found 314.13637. The analytical and spectroscopic data are in agreement with those reported in the literature.[5]

When applied to 15.8 g (67.6 mmol) of **23** this reaction yielded 19.2 g (98%) of the aldol product **23a**.

(*S*)-1-((*S*)-4-Benzyl-2-oxo-oxazolidin-3-yl)-2-methylpentane-1,3-dione (24). The aldol product **23a** (5.70 g, 19.6 mmol) was dissolved in CH_2Cl_2 (92 mL) and DMSO (92 mL) and the solution cooled to –15 °C. Et_3N (8.20 ml, 58.8 mmol) was introduced followed by a dropwise addition of a solution of SO_3•pyridine (9.40 g, 58.8 mmol) in DMSO (92 mL) and the reaction mixture was stirred for 3 h. Then, Et_2O (400 mL) was added and the organic layer was washed with aq. $KHSO_4$ (1 M, 400 mL), sat. aq. $NaHCO_3$ (400 mL), brine (400 mL). Then, the organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, hexanes/EtOAc, 6:1 → 3:1) to yield product **24** as a white solid (4.96 g, 88%). Mp = 71-72 °C (hexanes); $[\alpha]_{20}^{D}$ = +137.4 (*c* = 0.91, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39 – 7.29 (m, 3H), 7.27 – 7.18 (m, 2H), 4.82 – 4.70 (m, 1H), 4.62 (q, 1H, *J* = 7.3 Hz), 4.31 – 4.09 (m, 2H), 3.33 (dd, 1H, *J* = 13.3, 3.3 Hz), 2.85 – 2.57 (m, 3H), 1.46 (d, 3H, *J* = 7.3 Hz), 1.09 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.4, 170.5, 154.0, 135.3, 129.6, 129.2, 127.5, 66.7, 55.5, 52.9, 38.2, 34.2, 13.1, 7.7; IR (film): $\tilde{\nu}$ = 2985, 1760, 1718, 1702, 1455, 1390, 1360, 1250, 1213, 1125, 1082, 1082, 1051, 1010, 974, 763, 748, 703 cm^{-1}; MS (EI) *m*/*z* (%): 289 (15) [M^+], 260 (15), 233 (15), 178 (10), 142 (25), 117 (40), 91 (25), 65 (5), 57 (100), 42 (5); HRMS (ESI): *m*/*z*: calcd. for $C_{16}H_{19}NO_4Na$ [M^+ + Na]: 312.12062, found 312.12043. The analytical and spectroscopic data are in agreement with those reported in the literature.[6]

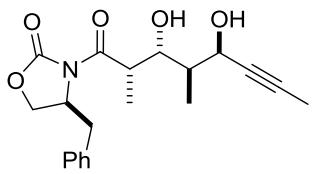


When applied to 9.50 g (32.6 mmol) of the aldol product **23a** obtained in the previous step this reaction yielded 7.22 g (75%) of compound **24**.

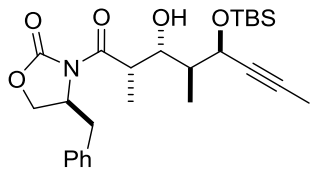
Alternative synthesis of but-2-ynal (25). TBACl (6.67 g, 24.0 mmol), TEMPO (3.75 g, 24.0 mmol) and NCS (51.3 g, 384 mmol, in three portions) were successively added to a solution of but-2-ynol (18.0 mL, 240 mmol) in CH_2Cl_2 (350 mL) and aq. pH 8.6 buffer (14.7 g of $NaHCO_3$ and 2.42 g of K_2CO_3 in 350 mL of H_2O), inducing a slight exothermic reaction. In order to quench the stoichiometric amount of HCl formed during the reaction, the flask was connected to a wash-flask filled with 1 M aq. NaOH solution. The resulting biphasic light orange mixture was then vigorously stirred at room temperature for 7 h. The aqueous layer was extracted with CH_2Cl_2 (100 mL), the combined organic layers were washed with brine, dried over Na_2SO_4 and directly distilled under reduced pressure at room temperature to yield but-2-ynal (**25**) as a light yellow liquid, which must be stored at low temperature (9.44 g, 45%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.13 (dd, J = 1.8, 0.9 Hz, 1H), 2.05 (d, J = 1.0 Hz, 3H). The analytical and spectroscopic data are in agreement with those reported in the literature.[7]

Propargylic alcohol (26). *$Sn(OTf)_2$ used in the second* syn*-aldol reaction was washed with Et_2O (3 x 6 mL) and dried overnight at 100 °C under reduced pressure prior to use.* Et_3N (324 µL, 2.32 mmol) was added dropwise via syringe to a solution of freshly purified $Sn(OTf)_2$ (969 mg, 2.32 mmol) in CH_2Cl_2 (10 mL). After cooling to –30 °C, a solution of ketone **13** (640 mg, 2.22 mmol) in CH_2Cl_2 (3.0 mL) was added via syringe over 5 min and the mixture stirred for 1 h at this temperature before it was cooled to –78 °C and a solution of but-2-ynal in CH_2Cl_2 (10 M, 1.11 mL, 11.1 mmol) was added dropwise via syringe. After additional 1 h, the mixture was diluted with CH_2Cl_2 (30 mL) and added to vigorously stirred aq. $NaHSO_4$ (1 M, 50 mL) at 0 °C. This slurry was stirred for 30 min before the aqueous layer was extracted with CH_2Cl_2 (2 x 40 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, hexanes/EtOAc, 4:1 $\rightarrow$ 2:1) to yield the the desired isomer as a white solid (1.32 g, 83%). ^{1}H NMR analysis of the crude product before flash chromatography indicated a diastereomeric ratio of 9.0:1 in favor of compound **26**. $[\alpha]_{20}^{D}$ = +101.1 (c = 0.55, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 – 7.25 (m, 3H), 7.23 – 7.14 (m, 2H), 4.90 (q, 1H, J = 7.3 Hz), 4.78 – 4.68 (m, 1H), 4.60 (s, 1H), 4.31 – 4.21 (m, 1H), 4.17 (dd, 1H, J = 9.1, 2.8 Hz), 3.28 (dd, 1H, J = 13.4,

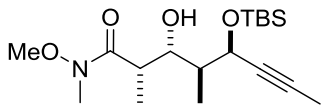
3.2 Hz), 3.02 – 2.88 (m, 1H), 2.76 (dd, 1H, *J* = 13.3, 9.6 Hz), 2.40 (s, 1H), 1.82 (d, 3H, *J* = 1.8 Hz), 1.47 (d, 3H, *J* = 7.2 Hz), 1.36 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.5, 170.7, 153.9, 135.2, 129.5, 129.2, 127.6, 82.7, 78.2, 66.6, 63.5, 55.4, 52.0, 50.5, 38.1, 12.9, 12.2, 3.6; IR (film): $\tilde{\nu}$ = 3511, 2940, 1775, 1716, 1690, 1454, 1357, 1212, 1117, 998, 913, 762, 735, 703 cm^{-1}; MS (EI) *m*/*z* (%): 357 (2), 339 (2), 311 (2), 289 (40), 260 (17), 233 (30), 204 (1), 178 (29), 159 (3), 156 (5), 142 (19), 134 (38), 125 (33), 117 (78), 112 (100), 107 (26), 101 (16), 97 (3), 91 (74), 86 (73), 83 (25), 79 (24), 77 (13), 69 (32), 65 (19), 57 (89), 42 (30), 39 (28), 29 (26); HRMS (ESI): *m*/*z*: calcd. for $C_{20}H_{23}NO_5Na$ [M^+ + Na]: 380.14685, found 380.14704.

(*S*)-4-Benzyl-3-((2*S*,3*R*,4*S*,5*R*)-3,5-dihydroxy-2,4-dimethyloct-6-ynoyl)oxazolidin-2-one (26a). 

$Me_4NBH(OAc)_3$ (3.72 g, 14.2 mmol) was dissolved in MeCN (260 mL) and HOAc (160 mL) and the resulting mixture cooled to –50 °C. A solution of compound **26** (1.01 g, 2.83 mmol) in MeCN (34 mL) was added and the mixture warmed to +10 °C overnight. The mixture was then poured into a pre-cooled (0 °C) mixture of sat. aq. Rochelle salt (140 mL) and MTBE (140 mL). Under vigorous stirring, sat. aq. $NaHCO_3$ and solid $NaHCO_3$ were added in small portions until no further gas evolution was observed. The phases were separated and the aqueous layer was extracted with MTBE (4 x 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to yield the desired diol (1.00 g, 98%) as a mixture of diastereomers (92:8 as determined by HPLC: 50 mm Ultra HAT Pro 18, 120 A, 2 μm, ∅ 3.0 mm, MeOH/H_2O = 60:40, 0.5 mL/min, 308 K, 27.4 MPa). $[\alpha]_{20}^{D}$ = + 36.0 (*c* =1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 – 7.25 (m, 3H), 7.21 – 7.15 (m, 2H), 4.75 – 4.66 (m, 1H), 4.45 (s, 1H), 4.27 – 4.15 (m, 3H), 4.14 – 4.01 (m, 1H), 3.89 – 3.76 (m, 2H), 3.22 (dd, 1H, *J* = 13.4, 3.4 Hz), 2.82 – 2.73 (m, 1H), 2.06 – 1.93 (m, 1H), 1.84 (t, 3H, *J* = 3.6 Hz), 1.24 (dd, 3H, *J* = 13.8, 7.0 Hz), 0.91 – 0.83 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.3, 152.9, 135.1, 129.6, 129.2, 127.7, 82.1, 78.5, 73.9, 67.5, 66.4, 55.1, 39.9, 39.3, 38.0, 13.1, 9.9, 3.8; IR (film): $\tilde{\nu}$ = 3417, 2974, 2921, 1778, 1698, 1455, 1388, 1287, 978, 762, 702 cm^{-1}; MS (EI) *m*/*z* (%): 359 (1), 341 (3), 308 (1), 273 (68), 262 (7), 244 (3), 233 (38), 183 (3), 178 (50), 165 (14), 159 (4), 149 (4), 142 (12), 136 (11), 134 (29), 126 (13), 117 (57), 109 (34), 103 (8), 96 (100), 91 (71), 86 (74), 80 (44), 77 (11), 69 (35), 67 (11), 65 (17), 57 (51), 41 (32), 39 (18), 29 (23), 27 (9); HRMS (ESI): *m*/*z*: calcd. for $C_{20}H_{25}NO_5Na$ [M^+ + Na]: 382.16250, found 382.16199.

(*S*)-4-Benzyl-3-((2*S*,3*R*,4*S*,5*R*)-5-(*tert*-butyldimethylsilyloxy)-3-hydroxy-2,4-dimethyloct-6-ynoyl)oxazolidin-2-one (26b). 

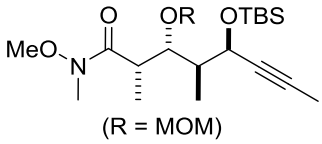
Et_3N (0.97 mL, 4.20 mmol) and TBSOTf (0.78 mL, 5.6 mmol) were successively added to a solution of diol **26a** (1.00 g, 2.78 mmol) in CH_2Cl_2 (15 mL) at –78 °C. After stirring for 3 h, the reaction was quenched with sat. aq. $NaHCO_3$ and the resulting mixture warmed to room temperature. The aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, hexanes/EtOAc, 9:1 → 7:1) to yield the title compound as a colorless viscous liquid (1.17 g, single isomer, 89%). $[\alpha]_{20}^{D}$ = +36.8 (*c* = 1.64, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 – 7.24 (m, 3H), 7.23 – 7.17 (m, 2H), 4.73 – 4.62 (m, 2H), 4.26 – 4.05 (m, 3H), 3.91 (d, 1H, *J* = 2.0 Hz), 3.85 (qd, 1H, *J* = 6.9, 2.4 Hz), 3.31 (dd, 1H, *J* = 13.3, 3.2 Hz), 2.74 (dt, 1H, *J* = 16.7, 8.4 Hz), 1.86 – 1.73 (m, 4H), 1.26 – 1.18 (m, 3H), 0.95 (d, 3H, *J* = 7.0 Hz), 0.87 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.7, 153.2, 135.5, 129.6, 129.1, 127.4, 82.2, 78.7, 72.7, 66.6, 66.3, 55.7, 42.0, 40.5, 37.9, 25.9, 18.3, 11.9, 9.3, 3.7, –4.4, –5.2; IR (film): $\tilde{\nu}$ = 3509, 2928, 1782, 1702, 1680, 1455, 1387, 1360, 1285, 1242, 1209, 1104, 1050, 1019, 984, 938, 836, 777, 702, 678 cm^{-1}; MS (EI) *m*/*z* (%): 473 (M+, 6), 416 (21), 398 (3), 348 (4), 341 (3), 337 (7), 336 (32), 324 (329, 318 (10), 306 (14), 290 (5), 273 (8), 262 (4), 252 (44), 239 (14), 233 (14), 183 (100), 178 (41), 165 (5), 159 (42), 147 (85), 143 (53), 136 (5), 133 (6), 127 (9), 119 (14), 117 (32), 115 (25), 109 (20), 97 (14), 91 (27), 81 (8), 77 (6), 75 (72), 73 (49), 57 (11), 29 (5); HRMS (ESI): *m*/*z*: calcd. for $C_{26}H_{39}NO_3SiNa$ [M^+ + Na]: 496.24897, found 496.24907.

(2*S*,3*R*,4*S*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-3-hydroxy-*N*-methoxy-*N*,2,4-trimethyl-oct-6-ynamide (26c). 

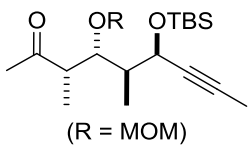
$AlMe_3$ (2 M in heptane, 4.2 mL, 8.31 mmol) was carefully added (exothermic reaction) to a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (0.811 g, 8.31 mmol) in THF (7 mL) at 0 °C and the resulting suspension was stirred for 15 min at this temperature and for 75 min at room temperature. The mixture was then cooled to –70 °C before a solution of compound **26b** (1.05 g, 2.15 mmol) in THF (10 mL) was slowly added. The mixture was warmed to –10 °C over 8 h before it was poured into chilled (0 °C) sat. aq. Rochelle salt (300 mL). The resulting suspension was stirred for 45 min and then repeatedly extracted with CH_2Cl_2 (2x40 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, hexanes/EtOAc, 6:1) to yield

the title compound as a colorless viscous liquid that solidified in the fridge (715 mg, 93%). $[\alpha]_{20}^{D}$ = +46.5 (*c* = 0.79, $CHCl_3$); mp ≈ 13 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.86 – 4.82 (m, 1H), 4.05 (s, 1H), 3.75 (dd, 1H, *J* = 9.2, 2.4 Hz), 3.69 (s, 3H), 3.18 (s, 3H), 3.06 – 2.92 (m, 1H), 1.80 (d, 3H, *J* = 2.2 Hz,), 1.73 – 1.63 (m, 1H), 1.11 (d, 3H, *J* = 7.1 Hz,), 0.95 (d, 3H, *J* = 6.9 Hz,), 0.86 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.5, 80.7, 80.4, 71.9, 63.3, 61.5, 42.4, 36.1, 32.2, 25.9, 18.3, 10.5, 9.7, 3.6, –4.4, –5.1; IR (film): $\tilde{\nu}$ = 3458, 2956, 2932, 2857, 1639, 1462, 1416, 1388, 1361, 1292, 1251, 1178, 1146, 1113, 1056, 1016, 998, 863, 833, 776, 684 cm^{-1}; MS (EI) *m*/*z* (%): 357 (1), 326 (2), 302 (3), 300 (47), 297 (13), 241 (9), 232 (3), 225 (6), 220 (34), 217 (24), 208 (27), 183 (100), 174 (7), 164 (16), 159 (8), 153 (16), 143 (24), 138 (7), 127 (7), 117 (30), 115 (42), 109 (17), 97 (19), 87 (9), 85 (11), 81 (12), 75 (90), 73 (64), 62 (8), 61 (12), 59 (12), 45 (7), 41 (8), 29 (14); HRMS (ESI): *m*/*z*: calcd. for $C_{18}H_{35}NO_4SiNa$ [M^+ + Na]: 380.22276, found 380.22281.

(2*S*,3*R*,4*S*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-*N*-methoxy-3-(methoxymethoxy)-*N*,2,4-trimethyloct-6-ynamide (26d). *i*Pr_2NEt (3.01 mL, 18.2 mmol) and MOMCl (0.691 mL, 9.10 mmol) were added to a solution of alcohol **26c** (650 mg, 1.82 mmol) in DMF (5 mL) and the resulting slightly fuming mixture stirred at 50 °C for 18 h. After cooling, MTBE (20 mL) and brine (30 mL) were introduced and the aqueous layer was extracted with MTBE (3 x 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, hexanes/EtOAc, 29:1 → 8:1) to yield product **26d** as a colorless viscous liquid (651 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.64 – 4.43 (m, 3H), 3.97 (dd, 1H, *J* = 8.8, 2.7 Hz), 3.65 (s, 3H), 3.31 (s, 3H), 3.15 (s, 3H), 2.96 (qd, 1H, *J* = 6.9, 2.7 Hz), 1.80 (d, 3H, *J* = 2.2 Hz), 1.78 – 1.68 (m, 1H), 1.09 (d, 3H, *J* = 7.0 Hz), 0.98 (d, 3H, *J* = 6.9 Hz), 0.86 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.4, 98.1, 81.0, 80.9, 79.7, 62.8, 61.0, 56.3, 44.3, 38.2, 25.9, 18.3, 11.0, 9.7, 3.6, –3.9, –4.9; IR (film): $\tilde{\nu}$ = 2931, 2890, 2857, 1672, 1463, 1408, 1377, 1250, 1168, 1143, 1031, 1002, 940, 920, 834, 776, 673 cm^{-1}; MS (EI) *m*/*z* (%): 370 (5), 357 (3), 356 (12), 344 (51), 341 (10), 312 (6), 300 (5), 282(11), 274 (16), 271 (34), 260 (8), 253 (7), 239 (10), 234 (14), 227 (15), 223 (18), 208 (32), 183 (62), 179 (25), 157 (19), 149 (12), 127 (12), 119 (15), 115 (28), 105 (16), 97 (28), 89 (73), 73 (84), 59 (179, 45 (100), 29 (6); HRMS (ESI): *m*/*z*: calcd. for $C_{20}H_{39}NO_5SiNa$ [M^+ + Na]: 424.24897, found 424.24886.

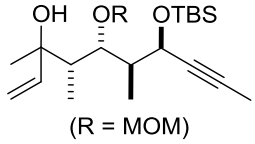


When applied to 690 mg (1.92 mmol) of compound **26c** this reaction yielded 760 mg (98%) of compound **26d**.

(3*S*,4*R*,5*S*,6*R*)-6-(*tert*-Butyldimethylsilyloxy)-4-(methoxymethoxy)-3,5-dimethylnon-7-yn-2-one (27). 

MeMgCl (2.76 M in THF, 1.76 mL, 4.86 mmol) was added dropwise via syringe to a solution of compound **26d** (650 mg, 1.62 mmol) in Et_2O (15.0 mL) at 0 °C and the resulting mixture was stirred for 2 h. The reaction was quenched with brine (15 mL), the aqueous layer was extracted with Et_2O (3 x 10 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to yield the title compound as a colorless viscous liquid which was used as such in the next step (562 mg, 97%, > 98% pure). An analytically pure sample was obtained by flash chromatography (hexanes/EtOAc, 29:1 → 8:1). $[\alpha]_{20}^{D}$ = +64.1 (*c* = 0.88, hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.65 – 4.43 (m, 3H), 4.03 (dd, 1H, *J* = 9.2, 1.9 Hz), 3.21 (s, 3H), 2.58 (qd, 1H, *J* = 6.9, 1.8 Hz), 2.19 (s, 3H), 1.81 (d, 3H, *J* = 2.2 Hz), 1.79 – 1.70 (m, 1H), 1.05 (d, 3H, *J* = 6.9 Hz,), 0.98 (d, 3H, *J* = 6.9 Hz), 0.88 (s, 9H), 0.14 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.4, 98.3, 81.8, 80.9, 80.3, 63.1, 56.3, 49.9, 44.5, 28.5, 26.3, 18.6, 11.4, 8.6, 3.9, –3.4, –4.5; IR (film): $\tilde{\nu}$ = 2931, 2857, 1716, 1462, 1360, 1251, 1188, 1142, 1090, 1058, 1032, 918, 834, 777, 677 cm^{-1}; MS (EI) *m*/*z* (%): 311 (1), 299 (1), 293 (3), 255 (4), 239 (12), 237 (99, 229 (59, 227 (9), 225 (4), 197 (27), 183 (86), 163 (46), 159 (27), 157 (15), 153 (15), 119 (19), 115 (18), 97 (21), 89 (57), 75 (55), 74 (6), 59 (17), 45 (100), 43 (46), 41 (8); HRMS (ESI): *m*/*z*: calcd. for $C_{19}H_{36}O_5SiNa$ [M^+ + Na]: 379.22751, found 379.22734.

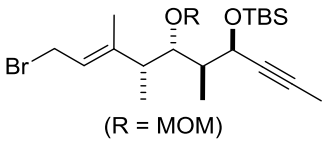
When applied to 760 mg (1.89 mmol) of compound **26d** this reaction yielded 665 mg (98%) of methyl ketone **27**.

(4*S*,5*R*,6*S*,7*R*)-7-(*tert*-Butyldimethylsilyloxy)-5-(methoxymethoxy)-3,4,6-trimethyl-dec-1-en-8-yn-3-ol (28). 

Vinylmagnesium bromide (1.0 M in THF, 3.15 mL, 3.15 mmol) was slowly added at –78 °C to a solution of ketone **27** (562 mg, 1.58 mmol) in THF (15 mL). The mixture was slowly warmed to room temperature (2 h) and stirred for additional 2 h. Sat. aq. NH_4Cl (25 mL) was then added and the aqueous layer extracted with Et_2O (3 x 12 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, hexanes/EtOAc, 10:1 → 8:1) to yield alcohol **28** as a mixture of isomers (2:1, ^{1}H NMR) (530 mg, 87%). $[\alpha]_{20}^{D}$ = +47.4 (*c* = 0.69, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, data given for the major isomer): δ = 5.92 – 5.68 (m, 1H), 5.39 – 5.16 (m, 1H), 5.12 – 4.95 (m, 1H), 4.79 – 4.59 (m, 2H),

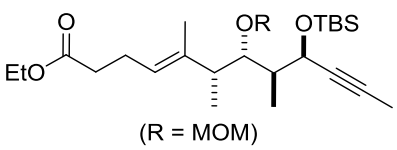
4.56 – 4.44 (m, 1H), 4.05 – 3.78 (m, 2H), 3.37 (s, 3H), 1.89 – 1.76 (m, 3H), 1.76 – 1.52 (m, 3H), 1.31 (s, 1H), 1.18 (d, 2H, J = 0.7 Hz), 1.03 – 1.01 (m, 2H), 0.95 – 0.90 (m, 3H), 0.89 – 0.83 (m, 9H), 0.16 – 0.05 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, data given for the major isomer): δ = 146.8, 111.7, 99.6, 82.8, 81.6, 80.6, 76.0, 63.2, 56.0, 44.6, 42.0, 27.4, 26.0, 18.3, 11.4, 7.2, 3.6, –3.5, –4.7; IR (film): $\tilde{\nu}$ = 3483, 2931, 2857, 1462, 1380, 1361, 1250, 1209, 1143, 1032, 920, 833, 814, 776, 678 cm^{-1}; MS (EI) *m*/*z* (%): 384, 339, 253 (1), 215 (4), 185 (11), 183 (100), 157 (9), 143 (10), 127 (7), 119 (7), 115 (9), 97 (11), 89 (22), 75 (24), 73 (37), 59 (6), 45 (34) ; HRMS (ESI): *m*/*z*: calcd. for $C_{21}H_{40}O_4SiNa$ [M^+ + Na]: 407.25881, found 407.25918.

When applied to 660 mg (1.89 mmol) of ketone **27** this reaction yielded 655 mg (92%) of compound **28**.

(5*S*,6*S*,7*R*)-5-((*R*,*E*)-5-Bromo-3-methylpent-3-en-2-yl)-6,9,9,10,10-pentamethyl-7-(prop-1-ynyl)-2,4,8-trioxa-9-silaundecane (29). 

Pyridine (0.32 mL, 3.92 mmol) was added at 0 °C to a solution of alcohol **28** (502 mg, 1.31 mmol) in Et_2O (6.1 mL), followed by dropwise addition of PBr_3 (1.0 M in toluene, 3.13 mL, 3.13 mmol). The resulting mixture was stirred for 3 h at 0 °C before it was diluted with Et_2O (20 mL). The reaction was carefully quenched with sat. aq. $NaHCO_3$ (100 mL) and the aqueous layer extracted with Et_2O (3 x 20 mL), the combined organic layers were dried over Na_2SO_4, filtered through a short pad of SiO_2 and concentrated *in vacuo*. The residual allyl bromide was very sensitive and therefore immediately used in the next step (556 mg, 95%). ^{1}H NMR (400 MHz, C_6D_6): δ = 5.49 – 5.42 (m, 1H), 4.95 (ddd, 1H, J = 4.8, 2.3, 2.3 Hz), 4.60 (d, 1H, J = 6.6 Hz), 4.47 (d, 1H, J = 6.6 Hz), 3.75 (dd, 1H, J = 8.4, 2.7 Hz), 3.66 (dd, 2H, J = 8.4, 2.1 Hz), 3.17 (s, 3H), 2.16 (dq, 1H, J = 6.8, 1.1 Hz), 2.04 – 1.96 (m, 1H), 1.55 (d, 3H, J = 1.0 Hz), 1.50 (d, 3H, J = 2.2 Hz), 1.13 (d, 3H, J = 6.8 Hz), 1.06 (s, 9H), 0.97 (d, 3H, J = 6.9 Hz), 0.36 (s, 3H), 0.28 (s, 3H); HRMS (ESI): *m*/*z*: calcd. for $C_{21}H_{39}BrO_3SiNa$ [M^++Na]: 469.17442, found 469.17489.

When applied to 655 mg (1.70 mmol) of compound **28** this reaction yielded 633 mg (83%) of compound **29**.

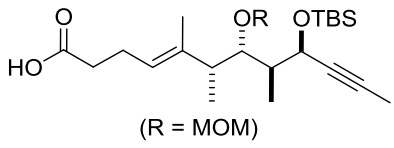
(6*R*,7*S*,8*S*,9*R*,*E*)-Ethyl 9-(*tert*-butyldimethylsilyloxy)-7-(methoxymethoxy)-5,6,8-trimethyldodec-4-en-10-ynoate (29a). 

*n*BuLi (1.6 M in hexanes, 14.6 mL, 23.4 mmol) was added to a solution of *i*Pr_2NH (3.47 mL, 24.7 mmol) in THF (20 mL) at 0 °C and the resulting mixture stirred for 1 h. In

parallel, CuI (8.90 g, 46.8 mmol) was suspended in THF (40 mL) and the suspension cooled to –110 °C (cooling bath: $Et_2O/CO_2/N_2$). EtOAc (2.43 mL, 24.7 mmol) was added via syringe followed by dropwise addition of the freshly prepared LDA-solution via canula. The mixture was warmed over 3 h to –30 °C, inducing a color change of the slurry from grey to yellow-brown. A solution of allyl bromide **29** (580 mg, 1.30 mmol) in THF (5 mL) was then slowly introduced and the mixture stirred for 2.5 h. The suspension was then cooled to –60 °C before being quenched with aq. NH_4Cl/NH_4OH (9:1; 63 g NH_4Cl, 17.5 mL 30% *w/w* aq. NH_4OH, filled up to 350 mL with H_2O). The aqueous layer was repeatedly extracted with MTBE, the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, hexanes/EtOAc, 100:0 → 19:1) to yield the title compound as a light yellow viscous liquid (369 mg, 62%). $[\alpha]_{20}^{D}$ = +16.0 (*c* = 0.24, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.17 (t, 1H, *J* = 6.3 Hz), 4.56 (ddd, 1H, *J* = 5.6, 2.1, 2.0 Hz), 4.52 (dd, 1H, *J* = 6.3 Hz), 4.43 (d, 1H, *J* = 6.3 Hz), 4.11 (q, 2H, *J* = 7.1 Hz), 3.61 (dd, 1H, *J* = 7.8, 3.6 Hz), 3.32 (s, 3H), 2.31 (m, 4H), 2.26 – 2.17 (m, 1H), 1.80 (d, 3H, *J* = 2.1 Hz), 1.78 – 1.71 (m, 1H), 1.64 (s, 3H), 1.24 (t, 3H, *J* = 7.1 Hz), 0.96 (dd, 6H, *J* = 6.9, 4.7 Hz), 0.88 (s, 9H), 0.13 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.4, 139.1, 123.3, 98.2, 81.3, 80.8, 80.7, 63.4, 60.4, 56.1, 44.5, 43.0, 34.4, 26.0, 23.8, 18.4, 16.0, 14.4, 12.6, 11.2, 3.6, –3.9, –4.9; IR (film): $\tilde{\nu}$ = 2956, 2929, 2857, 1727, 1462, 1374, 1249, 1143, 1116, 1093, 1033, 919, 835, 814, 777, 676 cm^{-1}; MS (EI) *m*/*z* (%): 439, 397 (1), 365 (1), 329 (4), 283 (13), 253 (3), 211 (6), 183 (100), 169 (11), 157 (17), 115 (9), 95 (17), 89 (17), 73 (29), 45 (31); HRMS (ESI): *m*/*z*: calcd. for $C_{25}H_{46}O_5SiNa$ [M^+ + Na]: 477.30067, found 477.30085.

When applied to 630 mg (1.70 mmol) of compound **29** this reaction yielded 462 mg (70%) of ester **29a**.

(6*R*,7*S*,8*S*,9*R*,*E*)-9-(*tert*-Butyldimethylsilyloxy)-7-(methoxymethoxy)-5,6,8-trimethyl-dodec-4-en-10-ynoic acid (5). TMSOK (593 mg, 4.62 mmol) was added to a solution of ethyl ester **29a** (420 mg, 924 µmol) in Et_2O (55 mL). The suspension was stirred for 48 h before being diluted with sat. aq. NH_4Cl (30 mL) and carefully acidified with HCl (1 M) to pH 4. The aqueous layer was extracted with EtOAc (3 x 30 mL) and the combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude acid **5**, obtained as a light yellow viscous liquid was judged pure and therefore used without further purification in the next step (390 mg, 98%). $[\alpha]_{20}^{D}$ = +44.7

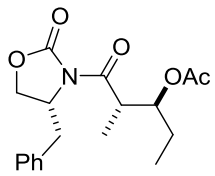


(c = 0.75, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.5 – 9.5 (br s, 1H), 5.16 (t, 1H, J = 6.1 Hz), 4.56 – 4.53 (m, 1H), 4.52 (d, 1H, J = 6.3 Hz), 4.43 (d, 1H, J = 6.3 Hz), 3.60 (dd, 1H, J = 7.8, 3.5 Hz), 3.32 (s, 3H), 2.42 – 2.29 (m, 4H), 2.28 – 2.20 (m, 1H), 1.80 (d, 3H, J = 2.7 Hz), 1.78 – 1.71 (m, 1H), 1.64 (s, 3H), 0.97 (t, 6H, J = 7.2 Hz), 0.89 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.8, 139.5, 122.9, 98.2, 81.3, 80.9, 80.8, 63.4, 56.1, 44.5, 43.0, 34.0, 26.0, 23.5, 18.4, 16.0, 12.6, 11.3, 3.6, –3.9, –4.9; IR (film): $\tilde{\nu}$ = 3095, 2929, 2857, 2333, 2171, 1712, 1463, 1377, 1250, 1143, 1033, 923, 834, 777, 676 cm^{-1}; MS (EI) m/z (%): 411, 337 (1), 307 (3), 283 (12), 227 (6), 183 (100), 173 (8), 157 (16), 154 (14), 115 (9), 97 (8), 89 (14), 75 (16), 73 (30), 45 (48); HRMS (ESI): m/z: calcd. for $C_{23}H_{42}O_5SiNa$ [M^+ + Na]: 449.26937, found 449.26952.

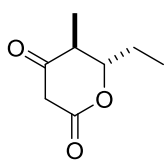
■ Synthesis of the δ-Lactone Segment 35

(*S*)-4-Benzyl-3-((2*R*,3*R*)-3-hydroxy-2-methylpentanoyl)oxazolidin-2-one.[8] *i*Pr_2NEt (3.44 mL, 19.7 mmol) was added to a cooled (0 °C) solution of *ent*-**23** (4.00 g, 17.1 mmol) and freshly distilled (*n*Bu)$_2$BOTf (7.38 mL, 34.3 mmol) in Et_2O (40 mL). After stirring for 45 min at 0 °C, the yellow suspension was cooled to –78 °C before a precooled (–78 °C) solution of freshly distilled propionaldehyde (1.62 mL, 22.2 mmol) in Et_2O (10 mL) was slowly introduced. After additional 30 min, the reaction was quenched by addition of solid tartaric acid (13 g) and the mixture stirred at room temperature for 2 h. The reaction was partitioned between ether and H_2O, and the combined organic layers were washed with sat. aq. $NaHCO_3$ (2 x 40 mL). A mixture of MeOH/30% H_2O_2 (3:1, 50 mL) was added under vigorous stirring at 0 °C and the resulting mixture stirred for 1 h at room temperature before it was extracted with Et_2O (2 x 30 mL). The combined organic layers were washed with $NaHCO_3$ and brine (30 mL each), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, hexanes/EtOAc, 3:1) to yield the title compound as an off-white solid (3.69 g, 74%, 11:1 dr.), along with additional 350 mg of mixed fractions. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 – 7.29 (m, 2H), 7.28 – 7.25 (m, 1H), 7.23 – 7.19 (m, 2H), 4.67 (ddd, 1H, J = 13.0, 6.8, 3.2 Hz), 4.21 – 4.12 (m, 2H), 3.90 (dq, 1H, J = 6.9, 6.9 Hz), 3.65 (dddd, 1H, J = 8.3, 8.3, 7.4, 3.5 Hz), 3.31 (dd, 1H, J = 13.5, 3.4 Hz), 2.76 (dd, 1H, J = 13.4, 9.6 Hz), 2.56 – 2.52 (m, 1H), 1.73 – 1.63 (m, 1H), 1.54 – 1.41 (m, 1H), 1.20 (d, 3H, J = 6.9 Hz), 1.00 (t, 3H, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.1, 153.7, 135.4, 129.6, 129.1, 127.5, 76.2, 66.2, 55.7, 43.0, 38.0, 28.0, 14.8, 9.9; IR (film): $\tilde{\nu}$ = 3516, 2967, 2936, 2879, 1775, 1695, 1455, 1385, 1351, 1291, 1209, 1111, 1051, 1015, 969, 762, 749, 702 cm^{-1};

MS (EI) *m*/*z* (%): 291 (10), 244 (28), 233 (18), 178 (32), 158 (15), 142 (13), 134 (24), 133 (16), 118 (14), 117 (51), 116 (25), 115 (42), 97 (27), 96 (11), 92 (39), 91 (100), 86 (87), 85 (25), 77 (11), 70 (13), 69 (37), 65 (29), 59 (57), 58 (19), 57 (89), 56 (24), 45 (27), 43 (22), 42 (33), 41 (38), 39 (18), 31 (42), 30 (15), 29 (73), 28 (22), 27 (33); HRMS (EI): *m*/*z*: calcd. for $C_{16}H_{21}NO_4Na$ [M^++Na]: 314.13628, found 314.13570.

(2*R*,3*R*)-1-((*S*)-4-Benzyl-2-oxooxazolidin-3-yl)-2-methyl-1-oxopentan-3-ylacetate (30). 

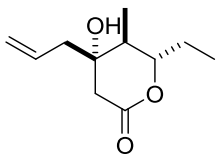
Et_3N (2.20 mL, 15.8 mmol) and freshly distilled acetic anhydride (1.40 mL, 14.6 mmol) were successively added to a solution of the above alcohol (3.55 g, 12.1 mmol) in CH_2Cl_2 (36 mL). The mixture was cooled to 0 °C and DMAP (296 mg, 2.40 mmol) was introduced. After 30 min, the ice bath was removed and stirring continued for 90 min before the reaction was quenched with sat. aq. NH_4Cl (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL), the combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, hexanes/EtOAc, 4:1 → 3:1) to yield the title compound as a single diastereomer in the form of a white solid (3.26 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 – 7.29 (m, 2H), 7.28 – 7.25 (m, 1H), 7.22 – 7.18 (m, 2H), 5.23 (ddd, 1H, *J* = 8.1, 8.0, 3.6 Hz), 4.70 – 4.63 (m, 1H), 4.20 – 4.10 (m, 3H), 3.25 (dd, 1H, *J* = 13.1, 3.3 Hz), 2.68 (dd, 1H, *J* = 13.3, 9.7 Hz), 2.00 (s, 3H), 1.88 – 1.78 (m, 1H), 1.63 – 1.52 (m, 1H), 1.17 (d, 3H, *J* = 7.1 Hz), 0.92 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.7, 170.2, 153.1, 135.3, 129.5, 129.1, 127.5, 75.8, 66.0, 55.4, 40.9, 37.9, 24.2, 21.1, 14.1, 8.9; IR (film): $\tilde{\nu}$ = 3029, 2978, 2944, 2883, 1782, 1737, 1699, 1491, 1455, 1378, 1349, 1291, 1208, 1111, 1098, 1049, 1016, 962, 884, 840, 762, 741, 726, 698 cm^{-1}; MS (EI) *m*/*z* (%): 273 (14), 244 (27), 178 (11), 157 (14), 117 (19), 97 (86), 96 (18), 91 (32), 69 (23), 57 (10), 43 (100), 41 (16), 29 (13); HRMS (EI): *m*/*z*: calcd. for $C_{18}H_{23}NO_5Na$ [M^++Na]: 356.14684, found 356.14686.

(5*R*,6*R*)-6-Ethyl-5-methyldihydro-2*H*-pyran-2,4(3*H*)-dione (9). 

A pre-cooled solution (–78 °C) of LiHMDS (4.5 g, 27.0 mmol) in THF (50 mL) was added via canula to a solution of acetate **30** (3.00 g, 9.01 mmol) in THF (50 mL) at –78 °C. After 1 h, the mixture was poured into sat. NH_4Cl/H_2O/MeOH (1:1:1, 250 mL) and diluted with EtOAc (150 mL). The organic layer containing the chiral auxiliary was separated, which could be recovered by flash chromatography (hexanes/EtOAc, 1:1). The aqueous layer was acidified with aq. HCl (1 M) to pH 2 and then extracted with CH_2Cl_2 (3 x 60 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash

chromatography (silica, hexanes/EtOAc, 3:1 → 1:1) to yield the desired ß-ketoester as a white solid (1.17 g, 83%). $[\alpha]_{20}^{D}$ = –14.4 (c = 0.55, Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.25 (ddd, 1H, *J* = 10.5, 7.6, 3.0 Hz), 3.53 (d, 1H, *J* = 19.1 Hz), 3.41 (d, 1H, *J* = 19.2 Hz), 2.40 (dq, 1H, *J* = 10.4, 7.1 Hz), 1.93 (tdd, 1H, *J* = 14.8, 7.3, 3.0 Hz), 1.69 (qdd, 1H, *J* = 14.7, 7.4, 7.3 Hz), 1.15 (d, 3H, *J* = 7.1 Hz), 1.08 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.9, 167.4, 81.4, 46.5, 45.9, 25.5, 10.8, 8.6; IR (neat): $\tilde{\nu}$ = 3205, 2969, 2928, 2763, 2346, 1652, 1587, 1450, 1395, 1376, 1323, 1275, 1260, 1220, 1152, 1127, 1084, 1055, 1039, 991, 964, 903, 872, 850, 823, 750, 697 cm^{-1}; MS (EI) *m*/*z* (%): 156 (12), 127 (20), 98 (70), 97 (14), 85 (58), 70 (29), 69 (16), 57 (35), 56 (100), 55 (34), 43 (12), 42 (41), 31 (18), 39 (13), 29 (35), 28 (25), 27 (20); HRMS (EI): *m*/*z*: calcd. for $C_8H_{12}O_3$ [*M*]: 156.07865, found 156.07866.

Alternative synthesis of homoallylic alcohol 8. A flame-dried microwave tubular vessel

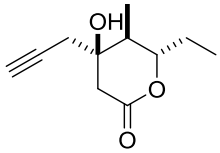


was charged with (*R*)-3,3'-dibromo-1,1'-bi-2-naphthol ((*R*)-**34**) (8.89 mg, 20.0 µmol) and toluene (0.67 mL) and *B*-allyl-1,3,2-dioxaborinane (**32**) (37.8 mg, 300 µmol) were then added. The mixture was stirred at room temperature for 5 min. Then β-ketoester **9** (31.3 mg, 200 µmol) was added and the reaction mixture submitted to microwave irradiation. The external reaction vessel temperature was measured via IR temperature probe and maintained at 130 °C for 3 h. After cooling to room temperature the solvent was concentrated *in vacuo* and the residue purified by flash chromatography (silica, hexanes/EtOAc, 4:1 → 2:1) to yield the desired isomer as a colorless liquid (33.6 mg, 85%). ^{1}H NMR analysis of the crude product before flash chromatography indicated a diastereomeric ratio of 6.1:1 in favor of compound **8**. $[\alpha]_{20}^{D}$ = +1.8 (c = 0.56, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6): δ = 5.70 (dddd, 1H, *J* = 17.1, 10.1, 7.5, 7.1 Hz), 5.02 (dddd, 1H, *J* = 10.1, 1.9, 0.9, 0.8 Hz), 4.95 (ddd, 1H, *J* = 17.1, 3.3, 1.4 Hz), 3.44 (ddd, 1H, *J* = 10.2, 7.4, 2.9 Hz), 2.57 (d, 1H, *J* = 16.4 Hz), 2.18 (dd, 1H, *J* = 16.5, 1.1 Hz), 1.98 (ddq, 1H, *J* = 13.9, 6.8, 1.1 Hz), 1.90 (br s, 1H), 1.78 – 1.71 (m, 1H), 1.55 (dq, 1H, *J* = 10.1, 6.9 Hz), 1.51 – 1.41 (m, 1H), 1.32 – 1.21 (m, 1H), 0.90 (t, 3H, *J* = 7.3 Hz), 0.57 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, C_6D_6): δ = 168.4, 132.2, 120.2, 82.5, 71.0, 43.1, 42.9, 38.9, 27.0, 10.7, 9.1; IR (neat): $\tilde{\nu}$ = 3434, 3078, 2974, 2939, 1721, 1640, 1463, 1377, 1247, 1163, 1085, 1042, 1006, 919, 838, 796 cm^{-1}; MS (EI) *m*/*z* (%): 157 (25), 127 (9), 111 (9), 99 (45), 98 (11), 95 (37), 71 (100), 67 (14), 57 (37), 55 (35), 53 (29), 43 (60), 42 (43), 41 (96), 40 (13), 39 (44), 29 (73), 27 (42); HRMS (EI): *m*/*z*: calcd. for $C_{11}H_{18}O_3Na$ [M^++Na]: 221.11481, found 221.11457. The analytical and spectroscopic data are in agreement with those reported in the literature.[13]

Alternative synthesis of homoallylic alcohol *epi*-8. Prepared analogously from β-ketoester **9**, *B*-allyl-1,3,2-dioxaborinane (**32**) and (*S*)-3,3'-dibromo-1,1'-bi-2-naphthol ((***S***)-**34**) and *tert*-butanol (38 μL, 400 μmol). The residue was purified by flash chromatography (silica, hexanes/EtOAc, 4:1 → 2:1) to yield the desired isomer as a white solid (26.7 mg, 68%). ^{1}H NMR analysis of the crude product before flash chromatography indicated a diastereomeric ratio of 9.0:1 in favor of compound *epi*-**8**. $[\alpha]_{20}^{D}$ = +4.4 (c = 0.88, MeCN); ^{1}H NMR (500 MHz, C_6D_6): δ = 5.45 (dddd, 1H, *J* = 17.1, 9.9, 7.3, 7.3 Hz), 4.94 (dddd, 1H, *J* = 10.1, 1.7, 0.7, 0.7 Hz), 4.88 (ddd, 1H, *J* = 17.0, 3.2, 1.3 Hz), 4.21 (ddd, 1H, *J* = 10.5, 7.7, 2.8 Hz), 2.48 (d, 1H, *J* = 17.3 Hz), 2.38 (br s, 1H), 2.21 (d, 1H, *J* = 17.3 Hz), 2.00 (dd, 1H, *J* = 13.7, 7.3 Hz), 1.90 (dd, 1H, *J* = 13.7, 7.6 Hz), 1.59 – 1.50 (m, 1H), 1.19 – 1.29 (m, 2H), 0.91 (t, 3H, *J* = 7.3 Hz), 0.63 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR (100 MHz, C_6D_6): δ = 169.1, 132.5, 120.1, 82.8, 71.1, 43.1, 43.1, 39.2, 27.0, 10.9, 9.2; IR (film): $\tilde{\nu}$ = 3429, 2978, 2935, 1710, 1460, 1442, 1385, 1326, 1261, 1107, 1008, 987, 919, 702 cm^{-1}; MS (EI) *m*/*z* (%): 157 (26), 127 (9), 111 (9), 99 (45), 98 (12), 95 (37), 71 (100), 67 (16), 57 (37), 55 (30), 53 (29), 43 (60), 42 (43), 41 (96), 40 (13), 39 (44), 29 (73), 27 (43); HRMS (EI): *m*/*z*: calcd. for $C_{11}H_{18}O_3Na$ [M^++Na]: 221.11481, found 221.11461.

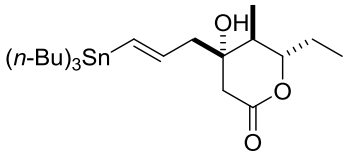
Homopropargylic alcohol 31. A flame-dried microwave tubular vessel was charged with (*R*)-3,3'-dibromo-1,1'-bi-2-naphthol ((*R*)-**34**) (44.5 mg, 100 μmol) and toluene (3.0 mL) and *B*-allenyl-1,3,2-dioxaborinane (**33**) (186 mg, 1.50 mmol) were then added. The mixture was stirred at room temperature for 5 min. Then β-ketoester **9** (157 mg, 1.0 mmol) was added and the reaction mixture submitted to microwave irradiation. The external reaction vessel temperature was measured via IR temperature probe and maintained at 130 °C for 3 h. After cooling to room temperature the solvent was concentrated *in vacuo* and the residue purified by flash chromatography (silica, hexanes/MTBE, 1:1) to yield the desired isomer as a colorless viscous liquid (171 mg, 87%). ^{1}H NMR analysis of the crude product before flash chromatography indicated a diastereomeric ratio of 7.6:1 in favor of compound **31**. $[\alpha]_{20}^{D}$ = –33.1 (c = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.91 (ddd, *J* = 10.3, 7.4, 3.2 Hz, 1H), 2.97 (d, *J* = 16.8 Hz, 1H), 2.57 – 2.52 (m, 1H), 2.52 – 2.49 (m, 1H), 2.49 (br s, 1H), 2.34 (dd, *J* = 16.7, 2.6 Hz, 1H), 2.15 (t, *J* = 2.6 Hz, 1H), 1.98 (dq, *J* = 10.1, 6.9 Hz, 1H), 1.84 (dqd, *J* = 14.9, 7.4, 3.2 Hz, 1H), 1.68 – 1.55 (m, 1H), 1.02 (d, *J* = 6.9 Hz, 3H), 1.00 (d, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 83.4, 78.6, 73.5, 71.0, 42.8, 41.8, 26.8, 26.7, 11.4, 9.0; IR (film): $\tilde{\nu}$ = 3423, 3286, 2973, 2939, 2883, 2122, 1713, 1462, 1427, 1378, 1326, 1247, 1209, 1161,

1133, 1059, 1009, 994, 951, 790, 645 cm^{-1}; HRMS (ESIpos): *m*/*z*: calcd. for $C_{11}H_{16}O_3Na$ [M^++Na]: 219.09916, found 219.09950.



Homopropargylic alcohol *epi*-31. Prepared analogously from β-ketoester **9** (31.3 mg, 200 μmol), *B*-allenyl-1,3,2-dioxaborinane (**33**) (37.2 mg, 300 μmol) and (*S*)-3,3'-dibromo-1,1'-bi-2-naphthol ((*S*)-**34**) (8.9 mg, 20 μmol) to yield the desired isomer (34.1 mg, 87%) as a white crystalline solid. ^{1}H NMR analysis of the crude product before flash chromatography indicated a diastereomeric ratio of 15:1 in favor of compound *epi*-***31***. A crystal suitable for X-ray analysis was obtained by slowly concentrating a solution of the title compound in hexanes/CH_2Cl_2 (2:3). $[\alpha]_{20}^{D}$ = –47.4 (c = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.29 (ddd, *J* = 10.4, 7.3, 2.9 Hz, 1H), 2.73 (s, 2H), 2.54 – 2.43 (br s, 1H), 2.49 (dd, *J* = 16.7, 2.7 Hz, 1H), 2.41 (dd, *J* = 16.7, 2.7 Hz, 1H), 2.10 (t, *J* = 2.7 Hz, 1H), 1.93 – 1.80 (m, 2H), 1.57 (dqd, *J* = 14.5, 7.3, 2.9 Hz, 1H), 1.01 (d, *J* = 7.3 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 82.6, 78.8, 72.5, 71.3, 42.7, 38.4, 30.4, 26.0, 9.7, 8.8; IR (film): $\tilde{\nu}$ = 3391, 3292, 3264, 2977, 2935, 2882, 1702, 1459, 1435, 1387, 1325, 1254, 1209, 1166, 1124, 1082, 1060, 1039, 1010, 989, 954, 895, 786, 688, 645, 596, 438 cm^{-1}; HRMS (ESIpos): *m*/*z*: calcd. for $C_{11}H_{16}O_3Na$ [M^++Na]: 219.09916, found 219.09960.

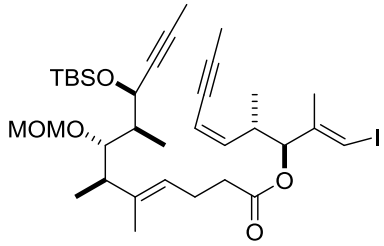
Vinyl stannane 35. *CH_2Cl_2 used for the hydrostannation was degassed by Ar bubbling for 30 min prior to use.* *i*Pr_2NEt (17 μL, 93.8 μmol) was added to a solution of $Pd_2(dba)_3$ (10.8 mg, 11.7 μmol) and Cy_3P•HBF_4 (17.3 mg, 46.9 μmol) in CH_2Cl_2 (6.0 mL) and the mixture was stirred at room temperature for 20 min, turning from dark red to light yellow. Subsequently, homopropargylic alcohol **31** (230 mg, 1.17 mmol) was added, followed by a solution of freshly distilled (*n*Bu)$_3$SnH (347 μL, 1.29 mmol) in CH_2Cl_2 (11.0 mL) added over 10 min. The reaction mixture was stirred at room temperature for 20 min and then concentrated *in vacuo*. The residue was purified by flash chromatography (silica, hexanes/MTBE, 5:1 → 1:1, toluene deposit) to yield the title compound as a colorless viscous liquid (411 mg, 72%). $[\alpha]_{20}^{D}$ = –7.3 (c = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.18 (d, *J* = 18.8 Hz, 1H), 5.97 (ddd, *J* = 18.8, 7.4, 6.3 Hz, 1H), 3.93 (ddd, *J* = 10.3, 7.3, 3.1 Hz, 1H), 2.78 (d, *J* = 16.8 Hz, 1H), 2.38 (d, *J* = 16.8 Hz, 1H), 2.34 (dd, *J* = 13.5, 7.4 Hz, 1H), 2.28 (dd, *J* = 13.5, 6.3 Hz, 1H), 1.98 (s, 1H), 1.96 – 1.89 (m, 1H), 1.85 (ddd, *J* = 14.5, 7.4, 3.1 Hz, 1H), 1.67 – 1.53 (m, 1H), 1.52 – 1.42 (m, 6H), 1.36 – 1.22 (m, 6H), 1.02 (d, *J* = 7.4 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.92 – 0.80 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7, 140.5, 137.1,



82.8, 70.0, 42.3, 42.1, 41.6, 28.4, 28.4, 28.4, 26.5, 26.5, 26.5, 26.0, 13.0, 13.0, 13.0, 10.4, 8.8, 8.8, 8.8, 8.1; IR (film): $\tilde{\nu}$ = 3434, 2955, 2923, 2872, 2851, 1719, 1597, 1462, 1376, 1243, 1212, 1070, 1043, 997, 959, 873, 776, 690, 662, 631, 595, 506 cm^{-1}; MS (ESIpos) *m*/*z* 511.2 [M^++Na]; HRMS (ESI): *m*/*z*: calcd. for $C_{23}H_{44}O_3SnNa$ [M^++Na]: 511.22039, found 511.22066.

■ Macrocyclization

Diyne 4. EDCI·HCl (83.1 mg, 433 µmol) was added to a solution of alcohol **6** (114 mg, 393 µmol) in CH_2Cl_2 (2.8 mL) and the resulting mixture cooled to 0 °C. Then, DMAP (52.9 mg, 433 µmol) was introduced in three portions and the mixture stirred for 10 min before a solution of acid **5** (185 mg, 433 µmol) in CH_2Cl_2 (2.5 mL) was slowly added. Stirring was continued for 30 min at 0 °C before the ice bath was removed. After 5 h at room temperature, the mixture was poured into brine (10 mL) and diluted with CH_2Cl_2 (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 8 mL), the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, hexanes/EtOAc, 29:1 → 19:1) to yield the title compound as a colorless viscous liquid (244 mg, 89%). $[\alpha]_{20}^{D}$ = +80.9 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.26 (s, 1H), 5.56 (dd, 1H, *J* = 10.1, 10.0 Hz), 5.43 (dq, 1H, *J* = 10.7, 2.2 Hz), 5.19 (1H, d, *J* = 7.4 Hz), 5.16 – 5.10 (br t, 1H), 4.56 – 4.52 (m, 1H), 4.51 (d, 1H, *J* = 6.3 Hz), 4.43 (d, 1H, *J* = 6.2 Hz), 3.60 (dd, 1H, *J* = 7.7, 3.6 Hz), 3.32 (s, 3H), 3.12 (ddq, 1H, *J* = 9.3, 7.1, 7.1 Hz), 2.37 – 2.27 (m, 4H), 2.27 – 2.19 (m, 1H), 1.96 (d, 3H, *J* = 2.2 Hz), 1.83 (d, 3H, *J* = 0.8 Hz), 1.80 (d, 3H, *J* = 2.1 Hz), 1.79 – 1.73 (m, 1H), 1.63 (s, 3H), 0.97 (d, 3H, *J* = 6.8 Hz), 0.96 (d, 3H, *J* = 6.9 Hz), 0.92 (d, 3H, *J* = 6.9 Hz), 0.87 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3, 144.8, 142.2, 139.2, 123.2, 111.2, 98.1, 90.5, 81.3, 80.9, 80.9, 80.6, 80.2, 76.2, 63.4, 56.1, 44.5, 43.0, 37.3, 34.5, 26.0, 23.8, 20.7, 18.4, 16.9, 16.0, 12.7, 11.2, 4.6, 3.6, –3.9, –4.9; IR (film): $\tilde{\nu}$ = 2955, 2928, 2856, 1738, 1618, 1461, 1376, 1248, 1142, 1117, 1091, 1075, 1061, 1031, 938, 920, 833, 775, 675 cm^{-1}; MS (EI) *m*/*z* (%): 458 (5), 283 (28), 185 (16), 184 (16), 183 (100), 174 (5), 169 (26), 163 (5), 159 (6), 157 (15), 153 (12), 146 (40), 145 (17), 137 (11), 131(29), 115 (7), 97 (6), 93 (8), 91 (8), 89 (16), 82 (8), 73 (29), 45 (39); HRMS (EI): *m*/*z*: calcd. for $C_{34}H_{55}IO_5SiNa$ [M^++Na]: 721.27557, found 721.27549.



When applied to 285 mg (982 µmol) of compound **6** this reaction yielded 653 mg (96%) of compound **4**.

Macrocyle 3. *All glassware used for the ring closing alkyne metathesis reaction was flame-dried under vacuum and backfilled with Ar after cooling to room-temperature (3 cycles). All solvents used were freshly distilled (toluene from Na/K, CH_2Cl_2 from CaH_2), stored over 4Å MS and degassed by 4 freeze-pump-thaw cycles prior to use.* A stock solution of activated catalyst was prepared as follows: CH_2Cl_2 (205 µL, 3.26 mmol) was added to a solution of complex **11** (80.0 mg, 128 µmol)[9,10] in toluene (6.4 mL). The resulting brown solution was stirred for 30 min to give a 0.0194 M stock solution of the active catalyst. Diyne **4** (150 mg, 215 µmol) was azeotropically dried with toluene (3 x 2 mL). It was then transferred as a toluene solution to a two-necked round-bottom flask equipped with a reflux condenser and septum. Additional toluene was added to reach a total volume of 150 mL. The solution was heated to 100 °C and an aliquot of the activated catalyst solution (3.30 mL, 65.0 µmol, 0.30 eq.) was introduced via syringe. The reaction was stirred at 100 °C for 7 h before a second aliquot of the catalyst solution (0.11 mL, 22.0 µmol, 0.10 eq.) was added. Stirring was continued at 100 °C for further 12 h. After reaching room temperature, the mixture was diluted with Et_2O (200 mL) to slowly form a brown precipitate which was filtered off through a short pad of SiO_2, eluting with Et_2O (250 mL). The light brown filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (silica, hexanes/EtOAc, 39:1 → 19:1) to yield a mixture of *N*-*tert*-butyl-3,5-dimethylaniline and the desired product. The amine was removed at 60 °C under high vacuum overnight to leave the title compound as a light yellow viscous liquid (99.2 mg, 72%). $[\alpha]_{20}^{D}$ = +83.0 (c = 0.57, *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.34 (d, 1H, *J* = 1.0 Hz), 5.63 (dd, 1H, *J* = 10.6, 9.6 Hz), 5.54 (dd, 1H, *J* = 10.6, 1.6 Hz), 5.36 – 5.30 (m, 1H), 5.24 (d, 1H, *J* = 9.6 Hz); 4.73 (d, 1H, *J* = 6.8 Hz), 4.62 (d, 1H, *J* = 6.8 Hz), 4.37 (dd, 1H, *J* = 9.1, 1.1 Hz), 3.43 (d, 1H, *J* = 9.2 Hz), 3.39 (s, 3H), 3.17 (dddd, 1H, *J* = 16.5, 9.7, 6.9, 6.8 Hz), 2.98 – 2.88 (m, 1H), 2.45 – 2.36 (m, 1H), 2.35 – 2.19 (m, 3H), 2.07 (dddd, 1H, *J* = 15.5, 7.2, 7.2, 0.6 Hz), 1.83 (d, 3H, *J* = 1.0 Hz), 1.48 (s, 3H), 1.07 (d, 3H, *J* = 7.1 Hz), 1.00 (d, 3H, *J* = 7.0 Hz), 0.89 (s, 9H), 0.82 (d, 3H, *J* = 6.9 Hz), 0.11 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 144.7, 144.5, 137.6, 126.6, 110.5, 99.1, 97.1, 87.2, 82.6, 82.1, 80.7, 64.1, 56.2, 46.2, 42.2, 37.9, 34.7, 25.9, 22.7, 19.7, 18.3, 17.6, 16.5, 12.3, –4.3, –4.9; IR (film): $\tilde{\nu}$ = 2957, 2929, 2856, 1732, 1617, 1462, 1377, 1361, 1257, 1143, 1058, 1031, 990, 932, 858, 835, 801, 775, 753, 672 cm^{-1};

MS (pos. ESI) *m*/*z* (%): 683 (M+K, 30), 667 (M+Na, 100); HRMS (EI): *m*/*z*: calcd. for $C_{30}H_{49}IO_5SiNa$ [M^++Na]: 667.22862, found 667.22903.

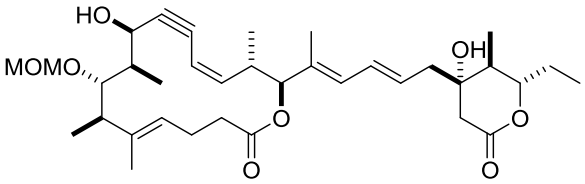
When applied to 295 mg (422 µmol) of compound **4** this reaction yielded 195 mg (72%) of compound **3**.

Completion of the Total Synthesis (Route A)

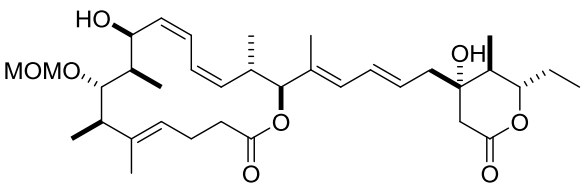
Alternative synthesis of silyl ether 39a. *DMF used for the Stille-Migita cross coupling was degassed by Ar bubbling for 30 min prior to use. Tetra*-n-*butylammonium diphenylphosphinate was melted and allowed to return to room temperature under high vacuum (10^{-2} mbar) twice prior to use.* A solution of vinyl iodide **3** (100 mg, 155 µmol) and vinyl stannane **35** (106 mg, 217 µmol) in DMF (3.2 mL) was added to a Schlenk tube containing flame-dried [(nBu$_4$N)(Ph$_2$PO$_2$)] (107 mg, 233 µmol). Copper-thiophene carboxylate complex (CuTC, 47.3 mg, 248 µmol) was then introduced followed by Pd(PPh$_3$)$_4$ (9.0 mg, 7.75 µmol) inducing color changes of the reaction mixture from yellow to orange and dark green respectively. The reaction mixture was then stirred at room temperature for 1 min before being quenched with H_2O (10 mL). The aqueous layer was extracted with Et_2O (5 x 20 mL), the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, hexanes/EtOAc, 5:1 → 3:1) to yield the title compound as a yellow solid (103 mg, 93%). $[\alpha]_{20}^{D}$ = +117.3 (c = 0.88, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.31 (dd, 1H, *J* = 15.0, 10.9 Hz), 6.01 (d, 1H, *J* = 11.0 Hz), 5.70 (ddd, 1H, *J* = 15.0, 7.5, 7.5 Hz), 5.65 (dd, 1H, *J* = 10.3, 10.2 Hz), 5.52 (dd, 1H, *J* = 10.8, 0.9 Hz), 5.37 – 5.32 (m, 1H), 5.07 (d, 1H, *J* = 9.8 Hz), 4.71 (d, 1H, *J* = 6.8 Hz), 4.61 (d, 1H, *J* = 6.8 Hz), 4.35 (d, 1H, *J* = 8.8 Hz), 3.92 (ddd, 1H, *J* = 10.0, 7.3, 2.9 Hz), 3.41 (br d, 1H, *J* = 7.6 Hz), 3.38 (s, 3H), 3.24 – 3.13 (m, 1H), 3.00 – 2.80 (br s, 1H), 2.77 (d, 1H, *J* = 16.7 Hz), 2.45 – 2.37 (m, 2H), 2.35 (d, 1H, *J* = 16.7 Hz), 2.33 – 2.24 (m, 2H), 2.23 – 2.12 (m, 2H), 2.08 (ddd, 1H, *J* = 15.4, 7.6, 7.5 Hz), 1.90 (ddd, 1H, *J* = 16.8, 6.9, 6.9 Hz), 1.83 (ddq, 1H, *J* = 14.7, 7.3, 2.8 Hz), 1.73 (s, 3H), 1.60 (ddq, 1H, *J* = 14.7 Hz, 7.3, 7.3 Hz), 1.45 (s, 3H), 1.06 (d, 3H, *J* = 7.1 Hz), 1.02 – 0.97 (m, 9H), 0.87 (s, 9H), 0.80 (d, 3H, *J* = 6.9 Hz), 0.09 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.4, 170.4, 145.3, 137.2, 134.2, 131.6, 129.0, 127.6, 126.9, 110.0, 99.1, 96.7, 87.3, 83.8, 82.7, 82.3, 71.7, 64.1, 56.1, 46.2, 42.8, 42.7, 42.0, 38.0, 37.7, 34.8, 26.9,

25.9, 22.6, 18.3, 17.5, 17.0, 16.7, 12.3, 12.1, 11.3, 9.1, –4.3, –5.0; IR (film): $\tilde{\nu}$ = 3448, 2961, 2930, 2857, 1724, 1462, 1377, 1248, 1144, 1058, 1032, 1004, 983, 919, 858, 835, 750, 667 cm^{-1}; MS (EI) *m*/*z* (%): 714 (5), 696 (4), 657 (4), 425 (5), 381 (13), 357 (8), 325 (7), 299 (9), 267 (12), 249 (27), 222 (72), 173 (11), 171 (14), 169 (68), 159 (11), 157 (16), 145 (13), 143 (11), 137 (18), 133 (18), 119 (17), 107 (16), 95 (25), 89 (36), 81 (20), 75 (41), 73 (100), 72 (24); HRMS (EI): *m*/*z*: calcd. for $C_{41}H_{66}O_8SiNa$ [M^++Na]: 737.44119, found 737.44102.

Propargylic alcohol 39a. TBAF (1 M in THF, 92.6 µL, 93.0 µmol) was slowly added to a suspension of silyl ether **39** (26.5 mg, 37.0 µmol) and activated 4Å molecular sieves (powder) in THF (0.5 mL) at 0 °C. After 40 min, the reaction was quenched with H_2O/brine (2:1, 4 mL) and diluted with EtOAc (3 mL). The aqueous layer was extracted with EtOAc (3 x 4 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was quickly purified by flash chromatography (Florisil®, hexanes/EtOAc, 2:1 → 1:2), keeping the contact time with the stationary phase as short as possible. The white solid (19.2 mg, 85%) thus obtained was immediately used in the next step as it decomposes upon storage in a freezer. ^{1}H NMR (400 MHz, C_6D_6): δ = 6.36 (dd, 1H, *J* = 14.9, 10.8 Hz), 6.15 (d, 1H, *J* = 10.8 Hz), 5.73 (dt, 1H, *J* = 15.0, 7.5 Hz), 5.53 – 5.46 (m, 3H), 5.41 – 5.35 (m, 1H), 5.08 (br t, 1H, *J* = 2.7 Hz), 4.41 (s, 2H), 3.52 (ddd, 1H, *J* = 10.0, 7.4, 2.8 Hz), 3.42 (dd, 1H, *J* = 8.6, 2.5 Hz), 3.36 – 3.26 (m, 1H), 3.12 (s, 3H), 3.12 – 3.10 (m, 1H), 2.65 (d, 1H, *J* = 16.4 Hz), 2.56 (dq, 1H, *J* = 7.4, 7.3 Hz), 2.30 – 2.15 (m, 6H), 2.14 – 2.02 (m, 2H), 1.93 (dd, 1H, *J* = 14.3, 7.7 Hz), 1.74 (s, 3H), 1.61 (dd, 1H, *J* = 15.9, 9.1, 6.9, 2.2 Hz), 1.50 (ddq, 1H, *J* = 14.6, 7.2, 3.1 Hz), 1.41 (s, 3H), 1.33 – 1.23 (m, 1H), 1.32 (d, 3H, *J* = 7.1 Hz), 1.01 (d, 3H, *J* = 7.0 Hz), 0.93 (d, 3H, *J* = 6.9 Hz), 0.91 (t, 3H, *J* = 7.3 Hz), 0.67 (d, 3H, *J* = 6.8 Hz); IR (film): $\tilde{\nu}$ = 3454, 2972, 2932, 1727, 1462, 1379, 1246, 1193, 1151, 1090, 1029, 1022, 986, 844, 759 cm^{-1}; HRMS (ESIpos): *m*/*z*: calcd. for $C_{35}H_{52}O_8Na$ [M^++Na]: 623.35544, found 623.35513.



When applied to 80.1 mg (112 µmol) of compound **39** this reaction yielded 54.5 mg (81%) of compound **39a**.

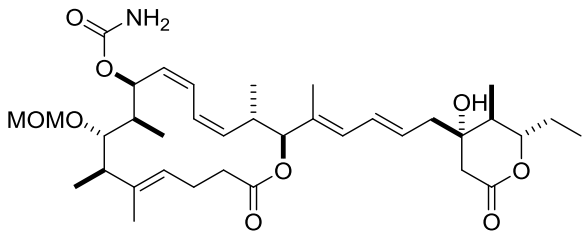


Allylic alcohol 40. A solution of propargyl alcohol **39a** (14.0 mg, 241 µmol) in THF (0.3 mL) was added to a suspension of freshly prepared

Zn(Cu/Ag)[11] (1.3 g) in degassed MeOH/H_2O (1:1, 1.1 mL) and the resulting mixture was stirred at 50 °C for 18 h. After cooling to room-temperature, the mixture was diluted with EtOAc (5 mL) and filtered through a short pad of Celite®, which was carefully rinsed with EtOAc (140 mL) and EtOH (15 mL). The combined filtrates were concentrated *in vacuo* to ca. 1/10 of the original volume and then washed with brine/H_2O (1:1, 15 mL). The aqueous layer was extracted with EtOAc (2 x 15 mL), the combined organic layers were dried over Na_2SO_4 and concentrated *in* vacuo. The residue was purified by flash chromatography (Florisil®, hexanes/EtOAc, 2:1 → 1:1) to yield the title compound as a white solid (12.9 mg, 89%). $[\alpha]_{20}^{D}$ = –72.0 (c = 0.66, CH_2Cl_2); ^{1}H NMR (600 MHz, CD_2Cl_2): see Table S-1; ^{13}C NMR (150 MHz, CD_2Cl_2): see Table S-1; IR (film): $\tilde{\nu}$ = 3447, 2966, 2932, 1729, 1456, 1415, 1368, 1243, 1206, 1147, 1089, 1020, 985, 918, 863, 783, 748, 736, 700 cm^{-1}; HRMS (ESIpos): *m*/*z*: calcd. for $C_{35}H_{54}O_8Na$ [M^++Na]: 625.37109, found 625.37092.

When applied to 54.5 mg (90.7 µmol) of compound **39a** this reaction yielded 50.2 mg (92%) of compound **40**.

Allylic carbamate 41. A solution of trichloroacetyl isocyanate (1.0 M in CH_2Cl_2, 16.4 µL, 16.4 µmol) was added to a precooled solution (–78 °C) of the allylic alcohol **40** (9.0 mg, 15.0 µmol) in CH_2Cl_2 (500 µL). The mixture was stirred at –78 °C for 2 h, before being quenched with MeOH (100 µL) at this temperature. After warming and concentration *in vacuo*, the residue was dissolved in CH_2Cl_2 (1 mL) and the solution soaked on basic alumina. After 1.5 h, the alumina was loaded onto a short pad of Celite®, which was eluted with EtOAc/EtOH (9:1, 12 mL) and the solvent was concentrated *in vacuo*. The residue was purified by flash chromatography (Florisil®, hexanes/EtOAc, 1:1 → 1:2) to yield the title compound as a white foam (8.1 mg, 84%). $[\alpha]_{20}^{D}$ = –66.4 (c = 0.94, CD_2Cl_2); ^{1}H NMR (600 MHz, CD_2Cl_2): see Table S-2; ^{13}C NMR (150 MHz, CD_2Cl_2): see Table S-2; IR (film): $\tilde{\nu}$ = 3452, 3365, 2965, 2931, 1723, 1602, 1455, 1376, 1312, 1259, 1209, 1146, 1092, 1058, 1033, 954, 916, 863, 801, 748, 710, 679 cm^{-1}; HRMS (ESIpos): *m*/*z*: calcd. for $C_{36}H_{55}NO_9Na$ [M^++Na]: 668.37800, found 668.37740.



When applied to 50.2 mg (83.3 µmol) of compound **40** this reaction yielded 40.5 mg (75%) of compound **41**.

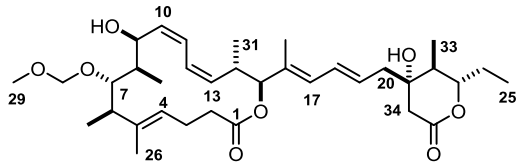


Table S-1: ^{1}H and ^{13}C data of the semi-reduced product **40**; numbering scheme as shown in the insert.

	^{1}H NMR (CD_2Cl_2, 600 MHz)					^{13}C NMR (CD_2Cl_2, 150 MHz)	
Nr	**δ (ppm)**	**Integral**	**Splitting**	**COSY**	***J* (Hz)**	**δ (ppm)**	**HMBC**
1	-	-	-	-	-	172.4	2, 15
2a	2.31 - 2.36	1H	m	2b, 3a	-	33.7	1, 3, 5, 26
2b	1.91 - 1.96	1H	m	2a, 3b	-		
3	2.15 - 2.23	2H	m	2a, 2b, 4	-	22.2	1, 2, 4, 26
4	5.09 - 5.14	1H	m	3a, 3b, 26	-	126.3	2, 3, 6, 26
5	-	-	-	-	-	137.0	3, 6, 7, 26, 27
6	2.54 - 2.63	1H	m	7, 27	-	47.9	4, 5, 7, 26, 27
7	3.35	1H	d	6	10.6	89.3	6, 9, 27, 28, 30
8	1.62 - 1.69	1H	m	30	-	38.9	7, 9, 10, 30
9	5.04	1H	d	10	9.8	65.0	7, 8, 11, OH1, 30
10	5.57	1H	dd	9, 11	9.9, 10.8	132.2	8, 9, 12, OH1
11	6.29	1H	dd	10, 12	10.9, 11.4	124.3	9, 12, 13, 14
12	6.45	1H	dd	11, 13	10.7, 11.4	124.4	10, 13, 14, 31
13	5.28	1H	dd	12, 14	10.4, 10.7	136.3	11, 14, 15, 31
14	2.98 - 3.03	1H	m	13, 15, 31	-	35.1	12, 13, 15, 31
15	5.09	1H	d	14	10.4	82.9	13, 14, 16, 17, 31, 32
16	-	-	-	-	-	133.8	14, 15, 17, 18
17	6.09	1H	d	18	10.9	129.7	15, 16, 18, 19, 32
18	6.38	1H	dd	17, 19	11.0, 15.0	131.4	17, 20, 32
19	5.77	1H	ddd	20a, 20b	7.5, 7.5, 15.0	128.5	17, 18, 20, 21
20a	2.41	1H	dd	19, 20b	14.0, 7.2	38.5	18, 19, 21, 22, 34
20b	2.16 - 2.22	1H	m	19, 20a	-		
21	-	-	-	-	-	72.0	19, 20a, 20b, 22, 34
22	1.88	1H	dq	23, 33	10.0, 6.9	43.2	20, 33, 34,
23	3.91	1H	ddd	22, 24a, 24b	10.0, 7.4, 2.8	83.8	22, 24, 25
24a	1.83	1H	ddq	23, 24b, 25	7.3, 7.4, 3.0	27.1	23, 25
24b	1.60	1H	ddq	23, 24b, 25	7.3, 7.3, 7.4		
25	1.00	3H	t	24a, 24b	7.3	9.2	24
26	1.43	3H	s	4	-	11.3	4, 5, 6
27	1.09	3H	d	6	6.8	16.4	5, 7, 30
28a	4.72	1H	d	28b	6.5	99.8	7, 29
28b	4.63	1H	d	28a	6.5		
29	3.40	3H	s	-	-	56.6	28
30	1.06	3H	d	8	7.3	12.0	5, 9
31	0.86	3H	d	14	6.7	16.6	13, 14, 15
32	1.79	3H	s	17	-	12.0	15, 17
33	1.01	3H	d	22	6.9	11.5	21, 22
34a	2.72	1H	d	34b	16.5	42.8	21, 35
34b	2.34	1H	d	34a	16.6		
35	-	-	-	-	-	170.3	34a, 34b
OH1	2.91	1H	br s				
OH2	2.17 - 2.26	1H	br s				

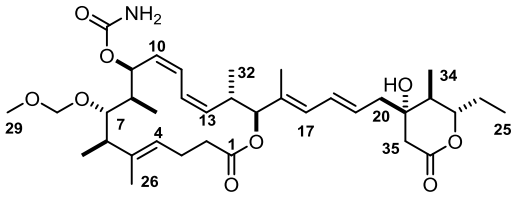


Table S-2: ^{1}H and ^{13}C data of the allylic carbamate **41**; numbering scheme as shown in the insert.

	^{1}H (CD_2Cl_2, 600 MHz)					^{13}C (CD_2Cl_2, 150 MHz)	
Nr	**δ (ppm)**	**Integral**	**Splitting**	**COSY**	***J* (Hz)**	**δ (ppm)**	**HMBC**
1	-	-	-	-	-	172.3	2, 15
2a	2.27 - 2.33	1H	m	2b, 3a	-	33.8	1, 4, 5, 26
2b	1.93 - 2.02	1H	m	2a, 3b	-		
3	2.18 - 2.23	2H	m	2a, 2b, 4	-	22.3	1
4	5.05 - 5.11	1H	m	3a, 3b, 26	-	126.1	6
5	-	-	-	-	-	137.3	3, 26, 27
6	2.45 - 2.55	1H	m	7, 27	-	48.2	6, 26, 27
7	3.30	1H	d	6	9.9	85.9	9, 27, 29
8	1.72 - 1.79	1H	br m	30	-	38.6	30
9	5.92	1H	br d	10	9.3	67.3	7, 11, 12, 30
10	5.50	1H	br dd	9, 11	9.3, 10.0	129.2	12
11	6.32	1H	br dd	10, 12	10.1, 11.1	125.1	9, 13, 15
12	6.68	1H	br dd	11, 13	10.7, 11.0	124.9	10, 14
13	5.29 - 5.36	1H	m	12, 14	-	136.8	11, 14, 15, 32
14	2.95 - 3.03	1H	m	13, 15, 32	-	34.9	12, 13, 15, 32
15	5.08	1H	d	14	10.3	82.7	13, 14, 16, 17, 32, 33
16	-	-	-	-	-	133.9	14, 15, 17, 18, 19, 33
17	6.10	1H	d	18	10.9	129.8	15, 16, 17, 18, 19, 33
18	6.39	1H	dd	17, 19	10.9, 15.1	131.5	17, 20, 33
19	5.77	1H	ddd	18, 20a, 20b	7.6, 7.6, 15.1	128.3	17, 20, 21, 33
20a	2.41	1H	dd	19, 20b	14.0, 7.3	38.6	18, 19, 21, 22, 35
20b	2.19 - 2.22	1H	m	19, 20a	-		
21	-	-	-	-	-	72.1	19, 20, 22, 34, 35
22	1.89	1H	dq	23, 34	9.9, 6.8	43.1	20, 34, 35
23	3.91	1H	ddd	22, 24a, 24b	10.1, 7.4, 2.9	83.8	22, 24, 25, 34
24a	1.84	1H	ddq	23, 24b, 25	7.4, 7.3, 2.8	27.1	23, 25
24b	1.62	1H	ddq	23, 24b, 25	7.3, 7.3, 7.4		
25	1.00	3H	t	24a, 24b	7.4	9.2	24
26	1.43	3H	br s	-	-	11.3	2, 6, 7
27	1.08	3H	d	6	6.6	16.7	5, 6, 7
28a	4.70	1H	d	28b	6.7	98.8	29
28b	4.58	1H	d	28a	6.7	-	-
29	3.38	3H	s	-	-	56.2	28
30	1.13	3H	d	8	7.1	13.7	8, 27
31	-	-	-	-	-	156.3	-
32	0.86	3H	d	14	6.6	16.6	13, 14, 15
33	1.79	3H	d	17	0.7	12.0	15, 16, 17, 19
34	1.01	3H	d	22	7.1	11.6	21, 22
35a	2.73	1H	d	34b	16.5	42.8	21, 36
35b	2.35	1H	dd	34a	16.6, 0.3		
36	-	-	-	-	-	170.3	34a, 34b
NH2	4.51 - 4.66	2H	br s	-	-	-	-
OH1	1.66 - 1.69	1H	br s	-	-	-	-

Leiodermatolide (1). A solution of compound **41** (9.0 mg, 13.9 µmol) in CH_2Cl_2 (1.6 mL) was cooled to –90 °C ($Et_2O/CO_2/N_2$ cooling bath) before a solution of freshly prepared Me_2BBr (0.5 M in CH_2Cl_2, 30.6 µL, 15.3 µmol)[12] was carefully added via the cold wall of the flask. The reaction mixture was allowed to reach –78 °C and was stirred at this temperature for 1.5 h, when a second aliquot of Me_2BBr (0.5 M, 30.6 µL, 15.3 µmol) was introduced. After additional 1.5 h, the mixture was transferred via canula into a vigorously stirred mixture of sat. $NaHCO_3/H_2O$/THF (1:1:1, 10 mL) and the flask was rinsed with THF (2 x 0.7 mL). After stirring for 10 min, the mixture was diluted with EtOAc (10 mL), the aqueous layer was extracted with EtOAc (3 x 10 mL), the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography (TLC Silica gel 60 F254 (20 x 20 cm), hexanes/EtOAc, 2:5) to yield the title compound as a white solid (5.1 mg, 61%). $[\alpha]_{24}^{D}$ = –74.3 (c = 0.41, MeOH); ^{1}H NMR (600 MHz, CD_2Cl_2, 4.8 mg in 0.3 mL CD_2Cl_2): δ = 6.53 (dd, 1H, *J* = 11.7, 11.3 Hz), 6.39 (dd, 1H, *J* = 15.3, 10.7 Hz), 6.37 (dd, 1H, *J* = 11.3, 11.2), 6.10 (d, 1H, *J* = 10.9 Hz), 5.89 (d, 1H, *J* = 10.1 Hz), 5.77 (ddd, 1H, *J* = 15.1, 7.6, 7.6 Hz), 5.53 (dd, 1H, *J* = 10.4, 10.4 Hz), 5.35 (dd, 1H, *J* = 10.5, 10.4°Hz), 5.09 (m, 1H), 5.07 (d, 1H, *J* = 10.3 Hz), 4.84 – 4.63 (br s, 2H), 3.91 (ddd, 1H, *J* = 10.1, 7.4, 2.9 Hz), 3.26 (br t, 1H), 2.97 (ddq, 1H, *J* = 10.1, 10.1, 6.7 Hz), 2.73 (d, 1H, *J* = 16.5 Hz), 2.46 (dq, 1H, *J* = 11.2, 5.8 Hz), 2.42 (dd, 1H, *J* = 14.0, 7.3 Hz), 2.35 (dd, 1H, *J* = 16.6, 0.9 Hz), 2.31 (ddd, 1H, *J* = 16.7, 5.8, 3.0 Hz), 2.21 (dd, 1H, *J* = 13.9, 8.0 Hz), 2.27 – 2.17 (m, 3H), 2.13 – 2.06 (br s, 1H), 1.99 (ddd, 1H, *J* = 16.7, 10.6, 3.6 Hz), 1.89 (dq, 1H, *J* = 10.3, 7.0 Hz), 1.83 (ddq, 1H, *J* = 7.4, 7.3, 3.1 Hz), 1.79 (d, 3H, *J* = 0.9 Hz), 1.74 (q, 1H, *J* = 7.2 Hz), 1.62 (ddq, 1H, *J* = 14.7, 7.4, 7.3 Hz), 1.42 (s, 3H), 1.12 (d, 3H, *J* = 6.7 Hz), 1.08 (d, 3H, *J* = 7.3 Hz), 1.02 (d, 3H, *J* = .6.8 Hz), 1.01 (t, 3H, *J* = 7.3 Hz), 0.86 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR (150 MHz, CD_2Cl_2, 4.8 mg in 0.3 mL): δ = 172.2, 170.3, 157.4, 137.6, 137.2, 133.8, 131.5, 129.8, 128.5, 128.4, 126.2, 125.6, 124.1, 83.8, 82.5, 78.2, 72.1, 67.6, 48.5, 43.1, 42.8, 39.3, 38.6, 35.0, 33.7, 27.1, 22.2, 16.6, 16.5, 12.5, 12.0, 11.6, 11.3, 9.2; IR (film): $\tilde{\nu}$ = 3360, 2963, 2924, 1708, 1605, 1455, 1375, 1312, 1246, 1207, 1148, 1082, 1056, 1040, 986, 949, 915, 778, 745 cm^{-1}; MS (ESI) *m*/*z* (%): 624.4 (100); HRMS (ESIpos): *m*/*z*: calcd. for $C_{34}H_{51}NO_8Na$ [M^++Na]: 624.35069, found 624.35132.

When applied to 40.5 mg (62.7 µmol) of compound **41** this reaction yielded 32.3 mg (86%) of leiodermatolide (**1**).

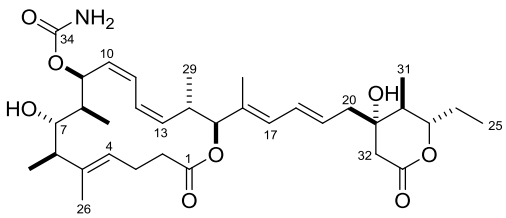
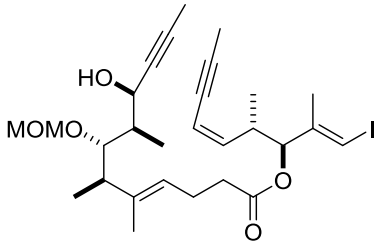


Table S-3: ^{1}H and ^{13}C data of leiodermatolide (**1**); numbering scheme as shown in the insert, data was obtained with 0.8 mg in 0.3 mL CD_2Cl_2.

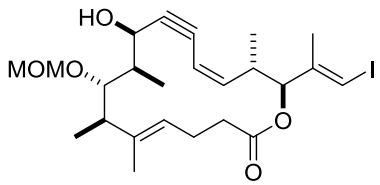
	^{1}H (CD_2Cl_2, 600 MHz)					^{13}C NMR (CD_2Cl_2, 150 MHz)	
Nr	**δ (ppm)**	**Integral**	**Splitting**	**COSY**	***J* (Hz)**	**δ (ppm)**	**HMBC**
1	--	--	--	--	--	172.2	2, 3, 15
2a	2.31	1H	ddd	2b, 3	16.7, n.d.	33.7	3, 4, 26
2b	1.99	1H	ddd	2a, 3	16.7, n.d.		
3	2.20	2H	m	2, 4, 26	--	22.2	2, 4, 5, 26
4	5.09	1H	ddq	3, 26	9.9, 5.5, 1.6	125.6	2, 3, 5, 6, 26
5	--	--	--	--	--	137.2	3, 4, 6, 26, 27
6	2.46	1H	dq	7, 27	10.5, 6.7	48.5	4, 7, 25, 26, 27
7	3.26	1H	br t	OH, 6, 8	9.9	78.2	6, 8, 9, 28
8	1.74	1H	qt	7, 27, 28	7.4, n.d.	39.3	7, 10, 28
9	5.89	1H	d	10	10.0	67.6	7, 28, 11
10	5.53	1H	ddt	9, 11	10.7, 10.0, 1.4	128.5	9, 11, 12, 13
11	6.38	1H	ddt	10, 12	12.0, 10.9	126.2	9, 10, 12, 13
12	6.53	1H	ddt	11, 13	11.8, 11.0, 1.0	124.4	10, 11, 13, 14
13	5.35	1H	ddt	12, 14	10.8, 10.2, 1.4	137.6	11, 12, 14, 15, 29
14	2.98	1H	tq	13, 15, 29	10.2, 6.7	35.0	12, 13, 15, 29, 30
15	5.07	1H	d	14	10.3	82.5	12, 13, 14, 17, 29, 30
16	--	--	--	--	--	133.8	14, 15, 17, 18, 30
17	6.10	1H	dq	18, 30	10.9, 1.4	129.7	15, 16, 18, 19, 30
18	6.40	1H	ddt	17,19, 20	15.1, 10.9, 1.3	131.5	16, 17, 20, 30
19	5.76	1H	dt	18, 20	15.0, 7.6	128.4	17, 20, 30
20a	2.41	1H	dd	19, 20b	14.0, 7.5	38.6	18, 19, 32
20b	2.22	1H	dd	19, 20a	13.8, 7.9		
21						72.1	18, 19, 20, 22, 31, 32
22	1.89	1H	dq	23, 31	10.5, 6.7	43.1	20, 21, 23, 24, 31, 32
23	3.91	1H	ddd	22, 24	10.0, 7.6, 3.1	83.8	22, 24, 25, 31
24a	1.85	1H	ddq	23, 24b, 25	14.5, 7.4, 3.1	27.1	22, 23, 25
24b	1.62	1H	dq	23, 24a, 25	14.6, 7.4		
25	1.01	3H	t	24	7.3	9.2	23, 24
26	1.42.	3H	s	3, 4	-	11.3	3, 4, 5, 6
27	1.12	3H	d	6	6.7	16.5	5, 6
28	1.08	3H	d	8	7.3	12.5	7, 8, 9
29	0.87	3H	d	14	6.7	16.6	13, 14, 15
30	1.79	3H	d	17	1.0	12.0	14, 15, 16, 17, 18, 19
31	1.02	3H	d	22	6.8	11.6	21, 22, 23, 32
32a	2.72	1H	d	32b	16.4	42.8	21, 22, 31, 33
32b	2.35	1H	dd	32a	16.5, 1.0		
33	--	--	--	--	--	170.3	32
34	--	--	--	--	--	157.4	9
NH2	4.66	2H	br s	--	--	--	--
C7-OH	2.16	1H	d	7	7.9	--	--
C21-OH	1.91	1H	s	--	--	--	--

■ Completion of the Total Synthesis (Route B)

Diyne 37. A solution of silyl ether **4** (60.0 mg, 85.9 µmol) in THF (0.6 mL) was cooled to 0 °C and a solution of TBAF (1.0 M in THF, 258 µL, 258 µmol) was added dropwise via syringe. The reaction mixture was allowed to warm to room temperature and was stirred for 3 h before being quenched with brine (5 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica, hexanes/EtOAc, 6:1 → 5:1) to yield the title compound as a colorless viscous liquid (44.2 mg, 88% yield). $[\alpha]_{20}^{D}$ = +97.0 (c = 1.15, CH_2Cl_2). ^{1}H NMR (500 MHz, C_6D_6): δ = 6.22 (s, 1H), 5.54 – 4.46 (m, 2H), 5.29 (d, *J* = 7.6 Hz, 1H), 5.09 (dd, *J* = 7.1 Hz, 6.7 Hz, 1H), 5.05 (br s, 1H), 4.36 (s, 2H), 3.54 (dd, *J* = 7.6, 4.0 Hz, 1H), 3.33 (br s, 1H), 3.28 – 3.19 (m, 1H), 3.05 (s, 3H), 2.25 – 2.18 (m, 3H), 2.15 (dd, *J* = 7.8, 6.7 Hz, 1H), 2.12 – 2.05 (m, 1H), 2.02 – 1.95 (m, 1H), 1.80 (s, 3H), 1.60 (d, *J* = 1.3 Hz, 3H), 1.55 (*d*, *J* = 2.2 Hz, 3H), 1.23 (d, *J* = 6.9 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ = 171.6, 145.1, 142.6, 138.7, 124.0, 111.5, 99.4, 90.8, 84.1, 81.5, 81.2, 80.3, 80.1, 76.7, 63.2, 56.2, 44.0, 42.3, 37.6, 34.3, 23.8, 20.6, 16.8, 15.5, 13.1, 12.1, 4.2, 3.4; IR (film): $\tilde{\nu}$ = 3480, 2967, 2918, 2864, 1736, 1454, 1376, 1243, 1213, 1142, 1088, 1023, 980, 927, 757, 674 cm^{-1}; MS (ESI) *m*/*z* (%): 607.2 (100); HRMS (ESIpos): *m*/*z*: calcd. for $C_{28}H_{41}O_5I_1Na$ [M^++Na]: 607.18909, found 607.18933.



Macrocycle 38. *Care should be taken to exclude moisture during the ring closing alkyne metathesis step.* A flame-dried Schlenck tube was charged with 5Å MS (1.2 g) and flame-dried until a stable vacuum was obtained. Toluene (45 mL) and a solution of diyne **37** (45.0 mg, 77.0 µmol) in toluene (1.0 mL + 0.5 mL rinse) was added via syringe and the resulting suspension stirred for 30 min at room temperature. A solution of catalyst **10** (12.0 mg, 11.5 µmol) in toluene (1.2 mL) was added and the reaction mixture stirred for 13 h at room temperature. After complete conversion of starting material (HPLC: 50 mm Zorbax Eclipse Plus C18, 1.8 µm, 3mm Ø, MeOH/H_2O = 90:10, 0.5 mL/min 224 bar: R_t (product) = 1.09 min; R_t (starting material) = 1.49 min; R_t (dimer) = 3.57 min), the reaction mixture was filtered through a pad of Celite®, rinsed with Et_2O (150 mL) and the filtrate concentrated *in vacuo*. The residue was purified by flash column chromatography (silica,



hexanes/EtOAc, 6:1 → 4:1) to yield the title compound as a light yellow viscous liquid (24.8 mg, 61% yield). $[\alpha]_{20}^{D}$ = +86.7 (c = 0.83, CH_2Cl_2). ^{1}H NMR (400 MHz,): δ = 6.16 (dq, *J* = 1.2, 1.0 Hz, 1H), 5.64 (dd, *J* = 10.5, 8.5 Hz, 1H), 5.58 (dd, *J* = 10.7, 0.9 Hz), 5.34 (td, *J* = 6.7, 1.0 Hz, 1H), 5.27 (d, *J* = 5.1 Hz, 1H), 4.97 (s, 1H), 4.71 (d, *J* = 6.7 Hz, 1H), 4.66 (d, *J* = 6.7 Hz, 1H), 3.46 (dd, *J* = 9.4, 2.4 Hz, 1H), 3.42 (s, 3H), 3.27 (d, *J* = 2.1 Hz, 1H), 2.56 (dq, *J* = 9.2, 6.9 Hz, 1H), 2.44 – 2.37 (m, 2H), 2.37 – 2.30 (m, 1H), 2.28 – 2.22 (m, 1H), 1.91 (qt, *J* = 7.2, 2.5 Hz, 1H), 1.78 (d, *J* = 1.0 Hz, 3H), 1.54 (d, *J* = 0.8 Hz, 3H), 1.19 (d, *J* = 7.2 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.7, 144.1, 138.2, 125.5, 111.3, 99.2, 96.1, 87.7, 80.8, 79.8, 79.6, 63.2, 56.7, 46.7, 40.6, 38.7, 34.3, 22.7, 22.2, 17.0, 14.8, 13.3, 12.9; IR (film): $\tilde{\nu}$ = 3481, 2962, 2928, 2869, 1737, 1456, 1378, 1261, 1185, 1146, 1091, 1025, 929, 754 cm^{-1}; MS (ESI) *m*/*z* (%): 553.1 (100); HRMS (ESIpos): *m*/*z*: calcd. for $C_{24}H_{35}O_5I_1Na$ [M^++Na]: 553.14214, found 553.14202.

Alternative synthesis of propargylic alcohol 39a. *DMF used for the Stille-Migita cross coupling was degassed by Ar bubbling for 30 min prior to use. Tetra*-n-*butylammonium diphenylphosphinate was melted and allowed to return to room temperature under high vacuum (10^{-2} mbar) twice prior to use.* A solution of vinyl iodide **38** (22.0 mg, 41.5 µmol) and vinyl stannane **35** (28.3 mg, 58.1 µmol) in DMF (1.2 mL) was added to a Schlenk tube containing flame-dried [(*n*Bu_4N)(Ph_2PO_2)] (28.6 mg, 62.3 µmol). Copper-thiophene carboxylate complex (CuTC, 12.7 mg, 66.4 µmol) was then introduced followed by $Pd(PPh_3)_4$ (2.4 mg, 2.1 µmol) inducing color changes of the reaction mixture from yellow to orange and dark brown respectively. The reaction mixture was then stirred at room temperature for 1 min before being quenched with H_2O (1.5 mL). The aqueous layer was extracted with Et_2O (5 x 4 mL), the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography (Florisil®, hexanes:EtOAc, 3:1 → 3:2) to yield the title compound as a yellow solid (22.4 mg, 90%). The analytical data matched those of the compound obtained by Route A.

Synthesis of Leiodermatolide Analogues

For the synthesis and spectra of compound 2 bearing the enantiomeric δ-lactone side chain, see the Supporting Information of our previous communication.[13]

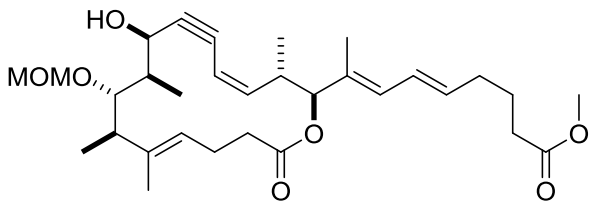
■ Analogue A (Compound 44)

Vinyl stannane A0b. A solution of methyl 5-hexynoate **A0a** (63.1 mg, 500 µmol) in dry THF (1.0 mL) was added slowly to a suspension of freshly prepared dicyclohexylborane (128 mg, 750 µmol) in dry THF (1.0 mL) at 0 °C.[14] The reaction mixture was stirred for 1 h at 0 °C and then carefully treated with aq. NaOH (2 M, 375 µL, 750 µmol) at 0 °C, allowed to warm to room temperature and stirred for 30 min. The reaction mixture was cooled to –15 °C and $Cu(acac)_2$ (6.6 mg, 25 µmol) and $(n\text{Bu})_3\text{SnCl}$ (179 mg, 550 µmol) were succesively added. The reaction mixture was warmed to room temperature over 5 h, poured into H_2O (10 mL) and extracted with hexanes (4 × 10 mL). The combined organic layer were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, hexanes:EtOAc, 9:1 → 1:1) to yield the title compound as a colorless liquid (58.0 mg, 28%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.02 – 5.73 (m, 2H), 3.64 (s, 3H), 2.33 – 2.25 (m, 2H), 2.19 – 2.08 (m, 2H), 1.75 – 1.67 (m, 2H), 1.53 – 1.38 (m, 6H), 1.32 – 1.23 (m, 6H), 0.93 – 0.73 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.4, 148.1, 128.8, 51.6, 37.2, 33.5, 29.2, 29.2, 29.2, 27.4, 27.4, 27.4, 24.2, 13.9, 13.9, 13.9, 9.5, 9.5, 9.5; IR (film): $\tilde{\nu}$ = 2954, 2924, 2871, 2852, 1742, 1599, 1456, 1436, 1247, 1196, 1170, 1071, 988, 873, 689, 663, 631, 594, 505 cm^{-1}; MS (ESI) *m*/*z* 376.2 [M^++Na]; HRMS (ESI): *m*/*z*: calcd. for $C_{19}H_{38}O_2SnNa$ [M^++Na]: 441.17853, found 441.17871.

Silyl ether A1. *DMF used for the Stille-Migita cross coupling was degassed by Ar bubbling for 30 min prior to use. Tetra-*n*-butylammonium diphenylphosphinate was melted and allowed to return to room temperature under high vacuum (10^{-2} mbar) twice prior to use.* A solution of vinyl iodide **3** (25.0 mg, 38.8 µmol) and vinyl stannane **A0b** (17.9 mg, 42.7 µmol) in DMF (400 µL) was added to a Schlenk tube containing flame-dried $[(n\text{Bu}_4\text{N})(Ph_2PO_2)]$ (19.7 mg, 42.7 µmol). Copper-thiophene carboxylate complex (CuTC, 11.1 mg, 58.2 µmol) was then introduced followed by $Pd(PPh_3)_4$ (4.5 mg, 3.9 µmol) inducing color changes of the reaction mixture from yellow to orange and dark

green respectively. The reaction mixture was then stirred at room temperature for 1 min before being quenched with H_2O (1.0 mL). The aqueous layer was extracted with Et_2O (5 x 2 mL), the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, hexanes:EtOAc, 9:1 → 17:3) to yield the title compound as a yellow viscous liquid (19.9 mg, 80%). $[\alpha]_{20}^{D}$ = +100.8 (c = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.21 (dd, *J* = 15.2, 10.9 Hz, 1H), 5.99 (dd, *J* = 11.0, 1.7 Hz, 1H), 5.66 (ddd, *J* = 15.0, 7.6, 7.6 Hz, 1H), 5.72 – 5.60 (m, 1H), 5.52 (dd, *J* = 10.7, 1.7 Hz, 1H), 5.42 – 5.30 (m, 1H), 5.08 (d, *J* = 9.8 Hz, 1H), 4.73 (d, *J* = 6.8 Hz, 1H), 4.62 (d, *J* = 6.8 Hz, 1H), 4.36 (dd, *J* = 9.2, 1.8 Hz, 1H), 3.64 (s, 3H), 3.43 (br d, *J* = 9.2 Hz, 1H), 3.39 (s, 3H), 3.19 (ddq, *J* = 9.8, 9.8, 6.6 Hz, 1H), 2.95 (br s, 1H), 2.47 – 2.33 (m, 1H), 2.34 – 2.25 (m, 4H), 2.24 – 2.03 (m, 4H), 1.74 (s, 3H), 1.81 – 1.66 (m, 2H), 1.46 (s, 3H), 1.08 (d, *J* = 7.1 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.81 (d, *J* = 6.8 Hz, 3H), 0.11 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.1, 172.3, 145.6, 137.2, 134.9, 132.1, 130.0, 127.0, 126.6, 109.8, 99.1, 96.6, 87.3, 83.0, 82.5, 64.1, 56.2, 51.6, 46.2, 42.1, 37.9, 34.9, 33.6, 32.4, 25.9, 24.6, 22.7, 18.3, 17.6, 16.8, 16.8, 12.1, 12.1, –4.3, –5.0; IR (film): $\tilde{\nu}$ = 2953, 2930, 2857, 1737, 1436, 1362, 1339, 1250, 1218, 1144, 1059, 1034, 986, 920, 859, 836, 776, 754 cm^{-1}; HRMS (ESIpos): *m*/*z*: calcd. for $C_{37}H_{60}NaO_7Si$ [M^++Na]: 667.40005, found 667.39994.

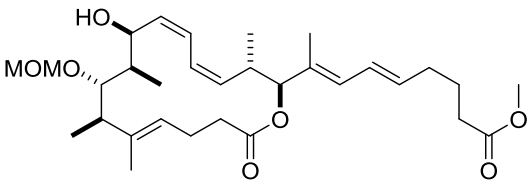
Propargylic alcohol A2. TBAF (1 M in THF, 21.3 µL, 21.3 µmol) was slowly added to a suspension of silyl ether **A1** (5.5 mg, 8.5 µmol) and activated 4Å molecular sieves (13.0 mg, powder) in THF (100 µL) at 0 °C. After 20 min, the reaction was quenched with H_2O/brine (2:1, 1 mL) and diluted with EtOAc (1 mL). The aqueous layer was extracted with EtOAc (3 x 1 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was quickly purified by flash chromatography (Florisil®, hexanes/EtOAc, 4:1 → 2:3), keeping the contact time with the Florisil® as short as possible. The yellow viscous liquid (3.4 mg, 76%) thus obtained was immediately used in the next step as it decomposes upon storage in a freezer. ^{1}H NMR (400 MHz, C_6D_6): δ = 6.24 (ddt, *J* = 13.7, 10.8, 1.5 Hz, 1H), 6.13 – 6.03 (m, 1H), 5.58 – 5.42 (m, 4H), 5.41 – 5.31 (m, 1H), 5.07 (br t, *J* = 3.3 Hz, 1H), 4.37 (s, 2H), 3.39 (dd, *J* = 8.6, 3.0 Hz, 1H), 3.33 (s, 3H), 3.35 – 3.27 (m, 1H), 3.08 (s, 3H), 2.86 (d, *J* = 3.1 Hz, 1H), 2.61 – 2.48 (m, 1H), 2.27 – 2.14 (m, 3H), 2.14 – 2.00 (m, 4H), 2.02 – 1.89 (m, 2H), 1.67 (d, *J* = 1.3 Hz, 3H), 1.66 – 1.52 (m, 2H), 1.38 (d, *J* = 1.3 Hz, 3H), 1.31 (d, *J* = 7.1 Hz,



3H), 0.98 (d, J = 6.9 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H); IR (film): $\tilde{\nu}$ = 3483, 2931, 2299, 1736, 1438, 1365, 1148, 1023, 758 cm^{-1}; HRMS (ESIpos): *m*/*z*: calcd. for $C_{31}H_{46}NaO_7$ [M^++Na]: 553.31357, found 553.31357.

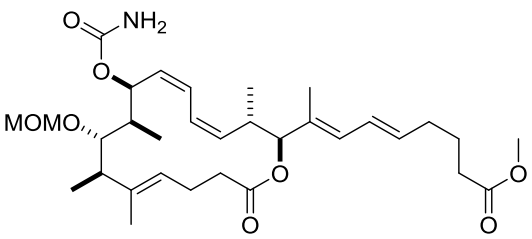
When applied to 22.9 mg (35.5 µmol) of silyl ether **A1** this reaction yielded 12.9 mg (69%) of propargylic alcohol **A2**.

Allylic alcohol A3. A solution of propargyl alcohol **A2** (17.3 mg, 31.8 µmol) in THF



(200 µL) was added to a suspension of freshly prepared Zn(Cu/Ag) (590 mg) in degassed MeOH/H_2O (1:1, 400 µL) and the resulting mixture was stirred at 50 °C for 72 h. After cooling to room temperature, the mixture was diluted with EtOAc (2 mL) and filtered through a short pad of Celite®, which was carefully rinsed with EtOAc (50 mL) and EtOH (5 mL). The combined filtrates were concentrated *in vacuo*. The residue was purified by flash chromatography (Florisil®, hexanes/EtOAc, 4:1 → 1:1) to yield the title compound as a colorless viscous liquid (15.2 mg, 88%). $[\alpha]_{20}^{D}$ = –7.8 (c = 1.00, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.41 (dd, J = 14.0, 8.6 Hz, 1H), 6.30 – 6.22 (m, 1H), 6.22 – 6.10 (m, 1H), 6.00 (d, J = 10.7 Hz, 1H), 5.64 (dt, J = 14.6, 7.0 Hz, 1H), 5.60 – 5.48 (m, 1H), 5.33 – 5.19 (m, 1H), 5.17 – 5.09 (m, 1H), 5.09 – 4.98 (m, 1H), 5.06 (d, J = 10.1 Hz, 1H), 4.70 (d, J = 6.5 Hz, 1H), 4.62 (d, J = 6.5 Hz, 1H), 3.63 (s, 3H), 3.40 (s, 3H), 3.32 (d, J = 10.7 Hz, 1H), 2.98 – 2.86 (m, 2H), 2.61 – 2.46 (m, 1H), 2.33 – 2.21 (m, 4H), 2.19 – 2.05 (m, 3H), 1.98 – 1.85 (m, 1H), 1.73 (s, 3H), 1.72 – 1.58 (m, 3H), 1.39 (s, 3H), 1.07 (d, J = 7.2 Hz, 3H), 1.06 (d, J = 6.9 Hz, 3H), 0.83 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.0, 172.3, 136.5, 136.3, 135.0, 131.7, 131.6, 130.3, 126.5, 126.4, 124.4, 124.2, 99.6, 89.2, 83.0, 64.9, 56.6, 51.6, 47.7, 38.8, 35.0, 33.6, 33.5, 32.3, 24.5, 22.0, 16.7, 16.4, 12.1, 11.9, 11.3; IR (film): $\tilde{\nu}$ = 3531, 2961, 2928, 1734, 1452, 1437, 1366, 1243, 1205, 1148, 1091, 1021, 985, 968, 949, 917, 748 cm^{-1}; HRMS (ESIpos): *m*/*z*: calcd. for $C_{31}H_{48}NaO_7$ [M^++Na]: 555.32922, found 555.32968.

Allylic carbamate A4. A solution of trichloroacetyl isocyanate (0.5 M in CH_2Cl_2,

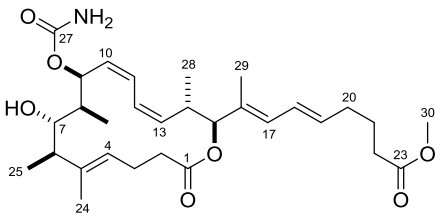


45.0 µL, 22.5 µmol) was carefully added at –78 °C along the cold wall of a precooled solution of the allylic alcohol **A3** (6.0 mg, 11.2 µmol) in CH_2Cl_2 (400 µL). The mixture was stirred at –78 °C for 0.5 h, before being quenched with MeOH (50 µL) at this

temperature. After warming and concentration *in vacuo*, the residue was dissolved in CH_2Cl_2 (1 mL) and the solution soaked on basic alumina. After 1.5 h, the alumina was loaded onto a short pad of Celite®, which was eluted with EtOAc/EtOH (9:1, 25 mL) and the solvent was concentrated *in vacuo*. The residue was purified by flash chromatography (Florisil®, hexanes/EtOAc, 3:2 → 1:2) to yield the title compound as a colorless viscous liquid (5.2 mg, 81%). $[\alpha]_{20}^{D}$ = –57.4 (c = 1.00, CH_2Cl_2); ^{1}H NMR (600 MHz, CD_2Cl_2): δ = 6.67 (dd, *J* = 11.5 Hz, 11.4 Hz, 1H), 6.35 – 6.29 (m, 1H), 6.26 (ddt, *J* = 15.1, 10.9, 1.3 Hz, 1H), 6.03 (dd, *J* = 10.9, 1.6 Hz, 1H), 5.91 (d, *J* = 10.4 Hz, 1H), 5.70 (dt, *J* = 15.1, 7.1 Hz, 1H), 5.49 (t, *J* = 11.0 Hz, 1H), 5.36 – 5.28 (m, 1H), 5.10 – 5.01 (m, 1H), 5.05 (d, *J* = 10.4 Hz, 1H), 4.70 (d, *J* = 6.8 Hz, 1H), 4.57 (d, *J* = 6.8 Hz, 1H), 4.51 (br s, 2H), 3.62 (s, 3H), 3.37 (s, 3H), 3.29 (d, *J* = 10.7 Hz, 1H), 3.05 – 2.91 (m, 1H), 2.54 – 2.44 (m, 1H), 2.34 – 2.27 (m, 3H), 2.24 – 2.16 (m, 2H), 2.16 – 2.10 (m, 2H), 2.02 – 1.91 (m, 1H), 1.79 – 1.73 (m, 1H), 1.76 (s, 3H), 1.73 – 1.65 (m, 2H), 1.42 (s, 3H), 1.12 (d, *J* = 7.4 Hz, 3H), 1.08 (d, *J* = 6.7 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, CD_2Cl_2): δ = 174.0, 172.2, 156.2, 137.1, 136.9, 135.4, 131.8, 130.4, 128.9, 126.5, 126.0, 125.0, 124.6, 98.7, 85.8, 82.8, 67.1, 56.1, 51.6, 48.1, 38.4, 34.7, 33.6, 33.5, 32.4, 24.6, 22.2, 16.6, 16.5, 13.6, 11.7, 11.3; IR (film): $\tilde{\nu}$ = 3374, 2956, 2924, 2854, 1729, 1676, 1602, 1455, 1437, 1367, 1312, 1260, 1204, 1146, 1092, 1057, 1027, 915, 801, 745, 701 cm^{-1}; HRMS (ESIpos): *m*/*z*: calcd. for $C_{32}H_{49}NNaO_8$ [M^++Na]: 598.335037, found 598.33537.

When applied to 9.2 mg (17.3 µmol) of allylic alcohol **A3** this reaction yielded 7.6 mg (77%) of allylic carbamate **A4**.

Analogue 43. A solution of allylic carbamate **A4** (1.5 mg, 2.60 µmol) in CH_2Cl_2 (260 µL) was cooled to –90 °C ($Et_2O/CO_2/N_2$ cooling bath) before a solution of freshly prepared Me_2BBr (0.5 M in CH_2Cl_2, 6.4 µL, 3.20 µmol) was carefully added via the cold wall of the flask. The reaction mixture was allowed to reach –78 °C and was stirred at this temperature for 1 h, when a second aliquot of Me_2BBr (0.5 M in CH_2Cl_2, 6.4 µL, 3.20 µmol) was introduced. After additional 0.5 h, the mixture was transferred via canula into a vigorously stirred mixture of sat. $NaHCO_3/H_2O$/THF (1:1:1, 3 mL) and the flask was rinsed with THF (2 x 200 µL). After stirring for 0.5 h, the mixture was diluted with EtOAc (3 mL), the aqueous layer was extracted with EtOAc (3 x 3 mL), the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography (TLC Silica gel 60 F254 (20 x 20 cm), $MeOH/CH_2Cl_2$, 7:93) to yield the title compound as a colorless viscous liquid (1.0 mg,



67%, ~90% purity). ^{1}H NMR (600 MHz, CD_2Cl_2): see Table S-4; ^{13}C NMR (150 MHz, CD_2Cl_2): see Table S-4; IR (film): $\tilde{\nu}$ = 3356, 2952, 2923, 2854, 1731, 1666, 1607, 1456, 1435, 1375, 1316, 1259, 1203, 1149, 1082, 1056, 1026, 988, 965, 892, 797, 745, 699 cm^{-1}; HRMS (ESIpos): *m*/*z*: calcd. for $C_{30}H_{45}NNaO_7$ [M^++Na]: 554.30882, found 554.30886. When applied to 3.1 mg (5.38 µmol) of allylic carbamate **A4** this reaction yielded 1.23 mg (43%, ~90% purity) of analogue **44**.

Table S-4: ^{1}H and ^{13}C data of leiodermatolide analogue **44**; numbering scheme as shown in the insert.

	^{1}H (CD_2Cl_2, 600 MHz)					^{13}C NMR (CD_2Cl_2, 150 MHz)	
Nr	**δ (ppm)**	**Integral**	**Splitting**	**COSY**	***J* (Hz)**	**δ (ppm)**	**HMBC**
1	–	–	–	–	–	172.2	2, 3, 15
2a	2.29	1H	m	2b, 3	–	33.8	3
2b	1.99	1H	m	2a, 3	–		
3	2.20	2H	m	2, 4, 26	–	22.3	2, 4
4	5.10	1H	m	3, 26	–	125.7	2, 3, 6
5	–	–	–	–	–	137.3	3, 24, 25
6	2.46	1H	dq	7, 25	10.4, 6.7	48.6	4, 24, 25
7	3.26	1H	br t	OH, 6, 8	9	78.2	6, 8, 9, 25, 26
8	1.74	1H	m	7, 28	–	39.4	26
9	5.90	1H	d	10	10.1	67.8	11, 26
10	5.52	1H	t	9, 11	10.4	128.5	8, 9, 11, 12
11	6.37	1H	t	10, 12	11.3	126.3	9, 12, 13
12	6.52	1H	t	11, 13	11.4	124.4	10, 11, 14
13	5.35	1H	m	12, 14	–	137.9	11, 14, 15, 28
14	2.97	1H	tq	13, 15, 28	10.3, 6.7	35.1	12, 13, 15, 28
15	5.05	1H	d	14	10.3	82.8	12, 13, 14, 16, 17, 28
16	–	–	–	–	–	131.9	14, 15, 18, 29
17	6.04	1H	d	18, 29	10.9, n.d.	130.6	15, 18, 19, 29
18	6.27	1H	ddt	17,19, 20	15.1, 10.8, 1.4	126.7	17, 20, 29
19	5.71	1H	dt	18, 20	15.1, 7.1	135.5	17, 20, 21, 29
20	2.15	2H	q	18, 19, 21	7.4	32.6	18, 19, 21, 22
21	1.71	2H	qi	20, 22	7.6	24.8	19, 20, 22
22	2.30	2H	t	21	7.5	33.7	20, 21
23	–	–	–	–	–	174.3	21, 22, 24
24	1.42	3H	s	3, 4	–	11.3	4, 6
25	1.12	3H	d	6	6.7	16.3	25
26	1.08.	3H	d	8	7.3	12.5	8, 9
27	–	–	–	–	–	157.3	9
28	0.86	3H	d	14	6.7	16.6	13, 14, 15
29	1.77	3H	d	17	1.0	11.9	15, 17
30	3.62	3H	s	–	–	51.6	–
NH_2	4.65	2H	br s	–	–	–	–
C7-OH	2.14	1H	d	7	n.d.	–	–

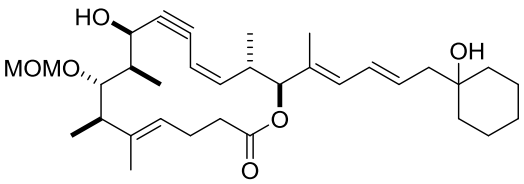
■ Analogue B

Vinyl boronate B0b. A flame-dried Schlenk flask was charged with the Grubbs-II catalyst (42.5 mg, 50 µmol) and vinylB(MIDA) (96.1 mg, 525 µmol), evacuated and backfilled with Ar (3 cycles). A solution of the homoallylic alcohol **B0a** (70.2 mg, 500 µmol) in CH_2Cl_2 (5.0 mL) was then introduced and the flask fitted with a reflux condenser and an Ar bubbler, allowing the generated ethylene to evaporate. The reaction mixture was heated to 40 °C for 22 h. After cooling to room temperature, DMSO (300 µL) was added and the mixture stirred for 8 h. The reaction mixture was then concentrated *in vacuo* and the residue was purified by flash chromatography (silica, MeCN/MTBE, 1:9 → 1:1) to yield the title compound as a white solid (102 mg, 69%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.05 (dt, *J* = 17.6, 7.0 Hz, 1H), 5.37 (d, *J* = 17.6 Hz, 1H), 4.17 (d, *J* = 17.1 Hz, 2H), 3.95 (br s, 1H), 3.95 (d, *J* = 17.1 Hz, 2H), 2.74 (s, 3H), 2.17 (dd, *J* = 7.0, 1.4 Hz, 2H), 1.63 – 1.49 (m, 2H), 1.45 – 1.14 (m, 8H); ^{13}C NMR (100 MHz, , DMSO-d_6): δ = 169.1, 169.1, 140.7, 128.7, 69.6, 61.2, 61.2, 48.8, 46.7, 37.0, 37.0, 25.5, 21.7, 21.7; IR (film): $\tilde{\nu}$ = 3499, 3008, 2931, 2857, 1760, 1642, 1453, 1339, 1292, 1259, 1195, 1151, 1123, 1090, 1022, 999, 961, 892, 863, 753 cm^{-1}; HRMS (ESI): *m*/*z*: calcd. for $C_{14}H_{22}BNO_5Na$ [M^++Na]: 318.14832, found 318.14834.

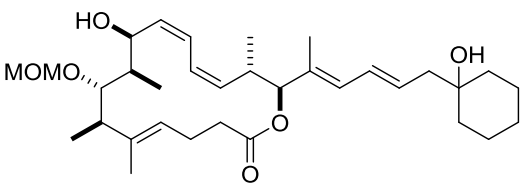
Silyl ether B1. *THF/H_2O used for the Suzuki-Miyaura cross coupling was degassed by 3 freeze-pump-thaw cycles prior to use.* A solution of vinyl iodide **3** (21.0 mg, 32.5 µmol) in THF/H_2O (3:1, 325 µL) was added to a degassed solution of MIDA ester **B0b** (11.6 mg, 11.6 µmol) and $Pd(PPh_3)_4$ (7.6 mg, 6.5 µmol). Thallium ethoxide (13.9 µL, 196 µmol) was added via syringe to the resulting yellow mixture, which was stirred at room temperature for 1.5 h before being diluted with MTBE (3 mL) and transferred to a round-bottom flask fitted with a stirbar. Aqueous HCl (0.5 M, 3 mL) was introduced (pH ~ 2) and the mixture stirred for 1 h. H_2O (12 mL) was added and the aqueous layer was extracted with *tert*-butyl methyl ether (5 x 12 mL). The combined organic layers were washed with brine (12 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, hexanes/EtOAc, 1:0 → 3:2) to yield the title compound as a yellow viscous liquid (13.2 mg, 62%). $[\alpha]_{20}^{D}$ = +119.3 (c = 0.40, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.27 (ddt, *J* = 15.1, 10.9, 1.2 Hz, 1H), 6.03 (dd, *J* = 10.8, 1.6 Hz, 1H), 5.76 (dt, *J* = 15.2, 7.7 Hz, 1H), 5.67 (t, *J* = 10.4 Hz, 1H), 5.53 (dd, *J* = 10.7, 1.7 Hz, 1H), 5.42 – 5.34 (m, 1H),

5.09 (d, *J* = 9.8 Hz, 1H), 4.73 (d, *J* = 6.8 Hz, 1H), 4.63 (d, *J* = 6.9 Hz, 1H), 4.36 (dd, *J* = 9.2, 1.7 Hz, 1H), 3.43 (br s, 1H), 3.39 (s, 3H), 3.20 (ddq, *J* = 9.9, 9.8, 6.8 Hz, 1H), 2.96 (br s, 1H), 2.41 (dd, *J* = 13.9, 7.5 Hz, 1H), 2.33 – 2.26 (m, 2H), 2.26 – 2.22 (m, 2H), 2.21 – 2.16 (m, 1H), 2.10 (ddq, *J* = 8.4, 7.0, 1.4 Hz, 1H), 1.75 (d, *J* = 1.3 Hz, 3H), 1.64 – 1.44 (m, 8H), 1.46 (s, 3H), 1.44 – 1.37 (m, 2H), 1.35 (br s, 1H), 1.08 (d, *J* = 7.1 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.82 (d, *J* = 6.9 Hz, 3H), 0.11 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.4, 145.5, 137.2, 132.6, 130.7, 129.8, 129.5, 127.0, 109.9, 99.1, 96.6, 87.4, 83.0, 82.5, 71.6, 64.1, 56.2, 46.2, 46.1, 42.1, 37.9, 37.6, 37.6, 34.9, 25.9, 25.9, 25.9, 25.9, 22.7, 22.3, 22.3, 18.4, 17.6, 17.0, 16.8, 12.2, 12.1, –4.3, –5.0; IR (film): $\tilde{\nu}$ = 2927, 2857, 1730, 1454, 1251, 1145, 1062, 1034, 969, 860, 836, 775 cm^{-1}; HRMS (ESIpos): *m*/*z*: calcd. for $C_{39}H_{64}O_6SiNa$ [M^++Na]: 679.43644, found 679.43659.

Propargylic alcohol B2. TBAF (1 M in THF, 80.0 µL, 80.0 µmol) was slowly added to a suspension of silyl ether **B1** (21.0 mg, 32.0 µmol) and activated 4Å molecular sieves (60.0 mg, powder) in THF (100 µL) at 0 °C. After 20 min, the reaction was quenched with H_2O/brine (2:1, 5 mL) and diluted with EtOAc (5 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was quickly purified by flash chromatography (Florisil®, hexanes/EtOAc, 4:1 → 2:3), keeping the contact time with the Florisil® as short as possible. The yellow viscous liquid (15.0 mg) thus obtained was immediately used in the next step as it decomposes upon storage in a freezer. ^{1}H NMR (400 MHz, C_6D_6): δ = 6.33 (ddt, *J* = 15.0, 10.9, 1.3 Hz, 1H), 6.18 (d, *J* = 10.9, 1H), 5.75 (dt, *J* = 15.0, 7.6 Hz, 1H), 5.58 – 5.41 (m, 3H), 5.41 – 5.33 (m, 1H), 5.07 (br t, *J* = 3.1 Hz, 1H), 4.38 (s, 2H), 3.39 (dd, *J* = 8.6, 3.0 Hz, 1H), 3.35 – 3.24 (m, 1H), 3.09 (s, 3H), 2.88 (d, *J* = 3.1 Hz, 1H), 2.62 – 2.46 (m, 1H), 2.29 – 2.16 (m, 3H), 2.16 – 2.04 (m, 3H), 2.04 – 1.96 (m, 1H), 1.71 (s, 3H), 1.63 – 1.51 (m, 2H), 1.50 – 1.25 (m, 5H), 1.39 (s, 3H), 1.31 (d, *J* = 7.1 Hz, 3H), 1.25 – 1.14 (m, 3H), 1.13 – 1.02 (m, 1H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H); IR (film): $\tilde{\nu}$ = 2929, 2849, 1727, 1448, 1379, 1266, 1145, 1029, 971 cm^{-1}; HRMS (ESIpos): *m*/*z*: calcd. for $C_{33}H_{50}O_6Na$ [M^++Na]: 565.34996, found 565.34942.

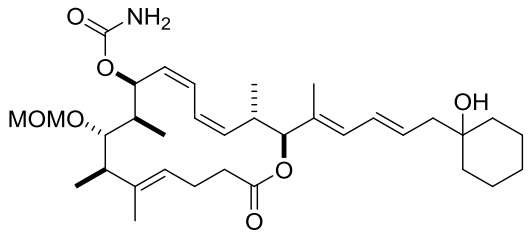


Allylic alcohol B3. A solution of propargyl alcohol **B2** (15.0 mg, 27.6 µmol) in THF (200 µL) was added to a suspension of freshly prepared Zn(Cu/Ag) (610 mg) in degassed



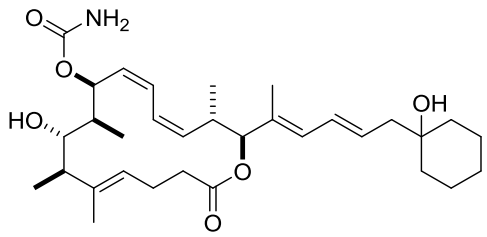
MeOH/H_2O (1:1, 400 µL) and the resulting mixture was stirred at 50 °C for 72 h. After cooling to room temperature, the mixture was diluted with EtOAc (2 mL) and filtered through a short pad of Celite®, which was carefully rinsed with EtOAc (100 mL) and EtOH (5 mL). The combined filtrates were concentrated *in vacuo*. The residue was purified by flash chromatography (Florisil®, hexanes/EtOAc, 4:1 → 1:1) to yield the title compound as a colorless viscous liquid (12.7 mg, 74% over two steps). $[\alpha]_{20}^{D}$ = –6.6 (c = 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.43 (dd, *J* = 11.3, 11.2 Hz, 1H), 6.35 – 6.19 (m, 2H), 6.05 (dd, *J* = 10.8, 1.7 Hz, 1H), 5.77 (dt, *J* = 15.2, 7.7 Hz, 1H), 5.58 (dd, *J* = 10.4, 10.3 Hz, 1H), 5.28 (dd, *J* = 11.5, 9.7 Hz, 1H), 5.20 – 5.10 (m, 1H), 5.10 – 5.00 (m, 2H), 4.71 (d, *J* = 6.6 Hz, 1H), 4.63 (d, *J* = 6.6 Hz, 1H), 3.41 (s, 3H), 3.33 (d, *J* = 10.6 Hz, 1H), 3.07 – 2.83 (m, 2H), 2.65 – 2.49 (m, 1H), 2.38 – 2.10 (m, 5H), 1.99 – 1.84 (m, 1H), 1.76 (s, 3H), 1.66 – 1.55 (m, 3H), 1.54 – 1.43 (m, 6H), 1.43 – 1.34 (m, 3H), 1.41 (s, 3H), 1.08 (d, *J* = 7.3 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.4, 136.5, 136.2, 132.1, 131.7, 130.9, 130.3, 129.4, 126.4, 124.5, 124.2, 99.6, 89.3, 83.0, 71.5, 64.9, 56.6, 47.7, 46.1, 38.8, 37.6, 37.6, 35.0, 33.6, 25.9, 22.3, 22.3, 22.1, 16.7, 16.4, 12.2, 12.0, 11.4; IR (film): $\tilde{\nu}$ = 3509, 2930, 2861, 1732, 1452, 1413, 1367, 1246, 1207, 1148, 1090, 1068, 1022, 970, 947, 913, 748 cm^{-1}; HRMS (ESIpos): *m*/*z*: calcd. for $C_{33}H_{52}O_6Na$ [M^++Na]: 567.36561, found 567.36600.

Allylic carbamate B4. **A** solution of trichloroacetyl isocyanate (0.1 M in CH_2Cl_2, 92.7 µL, 9.27 µmol) was carefully added at –78 °C along the cold wall of a precooled solution of the allylic alcohol **B3** (10.1 mg, 18.5 µmol) in CH_2Cl_2 (1.0 mL). The reaction mixture was allowed to reach –78 °C and was stirred at this temperature for 20 min, when a second aliquot of trichloroacetyl isocyanate (0.1 M in CH_2Cl_2, 46.4 µL, 4.6 µmol) was introduced. After additional 20 min, a third aliquot of trichloroacetyl isocyanate (0.1 M in CH_2Cl_2, 46.4 µL, 4.6 µmol) was introduced the mixture was stirred at –78 °C for 20 min, before being quenched with MeOH (100 µL) at this temperature. After warming and concentration *in vacuo*, the residue was dissolved in CH_2Cl_2 (1 mL) and the solution soaked on basic alumina. After 1 h, the alumina was loaded onto a short pad of Celite®, which was eluted with EtOAc/EtOH (9:1, 50 mL) and the solvent was concentrated *in vacuo*. The residue was purified by flash chromatography (Florisil®, hexanes/EtOAc, 1:1 → 1:2) to yield the desired mono-carbamate **B4** as a colorless viscous liquid (1.8 mg, 17%) along with bis-carbamate **C4** compound as colorless viscous liquid (3.0 mg, 27%).



^{1}H NMR (600 MHz, CD_2Cl_2): δ = 6.67 (dd, *J* = 11.5, 11.4 Hz, 1H), 6.36 – 6.26 (m, 2H), 6.07 (dd, *J* = 10.9, 1.1 Hz, 1H), 5.91 (d, *J* = 10.4 Hz, 1H), 5.80 (dt, *J* = 15.2, 7.7 Hz, 1H), 5.49 (t, *J* = 10.5 Hz, 1H), 5.34 – 5.30 (m, 1H), 5.10 – 5.04 (m, 1H), 5.06 (d, *J* = 10.3 Hz, 1H), 4.70 (d, *J* = 6.8 Hz, 1H), 4.57 (d, *J* = 6.8 Hz, 1H), 4.50 (br s, 2H), 3.37 (s, 3H), 3.29 (d, *J* = 10.6 Hz, 1H), 3.04 – 2.92 (m, 1H), 2.53 – 2.44 (m, 1H), 2.36 – 2.26 (m, 1H), 2.26 – 2.22 (m, 2H), 2.21 – 2.13 (m, 3H), 2.04 – 1.89 (m, 2H), 1.77 (d, *J* = 1.0 Hz, 3H), 1.78 – 1.72 (m, 1H), 1.63 – 1.54 (m, 2H), 1.53 – 1.43 (m, 3H), 1.42 (s, 3H), 1.40 – 1.35 (m, 2H), 1.32 – 1.25 (m, 2H), 1.12 (d, *J* = 6.5 Hz, 3H), 1.08 (d, *J* = 6.7 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, CD_2Cl_2): δ = 172.2, 156.1, 137.2, 136.8, 132.2, 131.2, 130.3, 129.3, 129.0, 126.0, 125.0, 124.6, 98.7, 85.8, 82.8, 71.4, 67.1, 56.1, 48.1, 38.4, 38.4, 37.6, 37.6, 34.7, 33.6, 26.0, 22.4, 22.4, 22.2, 16.6, 16.6, 13.6, 11.8, 11.3; HRMS (ESIpos): *m*/*z*: calcd. for $C_{34}H_{53}NO_7Na$ [M^++Na]: 610.37142, found 610.37192.

Analogue 44. A solution of allylic carbamate **B4** (1.4 mg, 2.38 µmol) in CH_2Cl_2 (250 µL) was cooled to –90 °C ($Et_2O/CO_2/N_2$ cooling bath) before a solution of freshly prepared Me_2BBr (0.1 M in CH_2Cl_2, 28.6 µL, 2.86 µmol) was carefully added via the cold wall of the flask. The reaction mixture was allowed to reach –78 °C and was stirred at this temperature for 0.5 h, when a second aliquot of Me_2BBr (0.1 M in CH_2Cl_2, 28.6 µL, 2.86 µmol) was introduced. After additional 0.5 h, the mixture was transferred via canula into a vigorously stirred mixture of sat. $NaHCO_3/H_2O$/THF (1:1:1, 3 mL) and the flask was rinsed with THF (2 x 200 µL). After stirring for 0.5 h, the mixture was diluted with EtOAc (3 mL), the aqueous layer was extracted with EtOAc (3 x 3 mL), the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography (TLC Silica gel 60 F254 (20 x 20 cm), MeOH/CH_2Cl_2, 7:93) to yield the title compound as a colorless viscous liquid (0.84 mg, 65%). ^{1}H NMR (600 MHz, CD_2Cl_2): δ = 6.53 (dd, *J* = 11.5, 11.4 Hz, 1H), 6.38 (dd, *J* = 11.6, 11.0 Hz, 1H), 6.31 (ddt, *J* = 15.0, 10.9, 1.2 Hz, 1H), 6.08 (dd, *J* = 10.9, 1.1 Hz, 1H), 5.90 (d, *J* = 10.1 Hz, 1H), 5.81 (dt, *J* = 15.3, 7.7 Hz, 1H), 5.53 (t, *J* = 10.4 Hz, 1H), 5.39 – 5.33 (m, 1H), 5.12 – 5.08 (m, 1H), 5.06 (d, *J* = 10.3 Hz, 1H), 4.64 (br s, 2H), 3.26 (br t, *J* = 9.5 Hz, 1H), 3.03 – 2.93 (m, 1H), 2.46 (dq, *J* = 13.2, 6.6 Hz, 1H), 2.32 – 2.27 (m, 1H), 2.27 – 2.24 (m, 2H), 2.24 – 2.10 (m, 3H), 2.04 – 1.96 (m, 2H), 1.78 (d, *J* = 1.1 Hz, 3H), 1.74 (dd, *J* = 14.6, 7.3 Hz, 1H), 1.62 – 1.54 (m, 3H), 1.51 – 1.44 (m, 3H), 1.42 (s, 3H), 1.41 – 1.38 (m, 2H), 1.36 – 1.30 (m, 2H), 1.13 (d, *J* = 6.7 Hz, 3H), 1.09 (d, *J* =



7.3 Hz, 3H), 0.87 (d, *J* = 6.7 Hz, 3H); HRMS (ESIpos): *m*/*z*: calcd. for $C_{32}H_{49}NO_6Na$ [M^++Na]: 566.34521, found 566.34571.

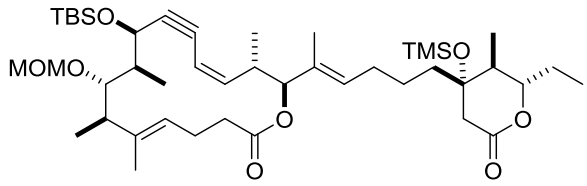
Analogue C5. A solution of bis-carbamate **C4** (1.7 mg, 2.69 µmol) in CH_2Cl_2 (300 µL) was cooled to –90 °C ($Et_2O/CO_2/N_2$ cooling bath) before a solution of freshly prepared Me_2BBr (0.5 M in CH_2Cl_2, 10.8 µL, 5.39 µmol) was carefully added via the cold wall of the flask. The reaction mixture was allowed to reach –78 °C and was stirred at this temperature for 1 h, when a second aliquot of Me_2BBr (0.5 M in CH_2Cl_2, 21.6 µL, 10.8 µmol) was introduced. After additional 1 h, the mixture was transferred via canula into a vigorously stirred mixture of sat. $NaHCO_3/H_2O$/THF (1:1:1, 3 mL) and the flask was rinsed with THF (2 x 200 µL). After stirring for 1 h, the mixture was diluted with EtOAc (3 mL), the aqueous layer was extracted with EtOAc (3 x 3 mL), the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography (TLC Silica gel 60 F254 (20 x 20 cm), MeOH/CH_2Cl_2, 7:93) to yield the title compound as a colorless viscous liquid (1.26 mg, 80%). ^{1}H NMR (600 MHz, CD_2Cl_2): δ = 6.53 (dd, *J* = 11.4, 11.3 Hz, 1H), 6.38 (dd, *J* = 11.3, 11.2 Hz, 1H), 6.30 (ddt, *J* = 15.0, 10.9, 1.4 Hz, 1H), 6.06 (dd, *J* = 10.8, 1.2 Hz, 1H), 5.90 (d, *J* = 10.1 Hz, 1H), 5.73 (dt, *J* = 15.1, 7.6 Hz, 1H), 5.56 – 5.50 (m, 1H), 5.38 – 5.34 (m, 1H), 5.12 – 5.07 (m, 1H), 5.06 (d, *J* = 10.3 Hz, 1H), 4.65 (br s, 2H), 4.47 (br s, 2H), 3.26 (br t, *J* = 9.4 Hz, 1H), 2.98 (dq, *J* = 10.2, 6.5 Hz, 1H), 2.76 – 2.65 (m, 2H), 2.50 – 2.42 (m, 1H), 2.33 – 2.26 (m, 1H), 2.23 – 2.18 (m, 2H), 2.17 – 2.10 (m, 3H), 2.04 – 1.96 (m, 1H), 1.77 (s, 3H), 1.74 (q, *J* = 7.2 Hz, 1H), 1.62 – 1.54 (m, 2H), 1.52 – 1.48 (m, 2H), 1.42 (s, 3H), 1.40 – 1.33 (m, 2H), 1.33 – 1.23 (m, 2H), 1.13 (d, *J* = 6.7 Hz, 3H), 1.08 (d, *J* = 7.3 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H); HRMS (ESIpos): *m*/*z*: calcd. for $C_{33}H_{50}N_2O_7Na$ [M^++Na]: 609.35102, found 609.35105.

■ Analogue D

TMS-ether D0. Imidazole (57.7 mg, 847 µmol) and DMAP (17.3 mg, 142 µmol) were successively added to a solution of homoallylic alcohol **8** (56.0 mg, 283 µmol) in CH_2Cl_2 (15 mL) at 0 °C. After stirring for 10 min at this temperature, TMSCl (72 µL, 566 µmol) was added to the reaction mixture. After stirring for 0.5 h at this temperature, the reaction

mixture was warmed to room temperature and stirred for additional 14 h. Then, the reaction was quenched with sat. aq. $NaHCO_3$ (5 mL) and H_2O (5 mL), the aqueous layer was extracted with Et_2O (4 x 10 mL), the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, hexanes/EtOAc, 19:1 → 17:3) to yield the title compound as a colorless viscous liquid (57.6 mg, 76%). $[\alpha]_{20}^{D}$ = +35.2 (c = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.79 (dddd, *J* = 17.8, 10.3, 8.1, 5.8 Hz, 1H), 5.11 (d, *J* = 10.2 Hz, 1H), 5.05 (d, *J* = 17.1 Hz, 1H), 3.90 (ddd, *J* = 10.3, 7.2, 3.0 Hz, 1H), 2.84 (d, *J* = 16.4 Hz, 1H), 2.39 (d, *J* = 16.6 Hz, 1H), 2.38 – 2.28 (m, 1H), 1.99 (dd, *J* = 13.9, 8.3 Hz, 1H), 1.91 – 1.73 (m, 2H), 1.62 – 1.46 (m, 1H), 1.06 – 0.92 (m, 6H), 0.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 133.0, 119.2, 83.8, 74.8, 43.9, 43.4, 39.9, 27.0, 11.1, 9.0, 2.5; IR (film): $\tilde{\nu}$ = 2962, 1741, 1639, 1462, 1435, 1376, 1325, 1308, 1250, 1216, 1139, 1100, 1079, 1008, 996, 941, 879, 840, 755, 667 cm^{-1}; HRMS (EI): *m*/*z*: calcd. for $C_{14}H_{26}O_3SiNa$ [M^++Na]: 293.15435, found 293.15411.

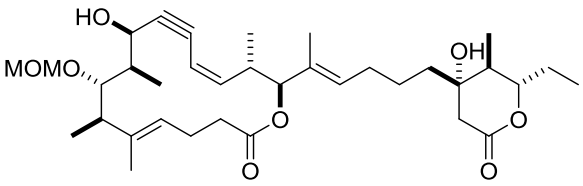
Disilyl ether D1. *THF used for the B-alkyl Suzuki-Miyaura cross coupling was degassed by Ar bubbling for 30 min prior to use.* A solution of 9-BBN dimer (3.7 mg, 15.0 μmol) in THF (0.5 mL) was added dropwise via syringe to a solution of allylic δ-lactone **D0** (3.0 mg, 11.0 μmol) in THF (0.5 mL) and the reaction mixture was stirred at 50 °C for 1 h. The solution of the resulting alkylborane was cooled to 0 °C, KOMe (2.1 mg, 30.0 μmol) was added in one portion and the reaction mixture was stirred at room temperature for 2 h. The resulting borate-solution was transferred dropwise via syringe to a solution of vinyl iodide **3** (6.5 mg, 10.0 μmol), $Pd(dppf)Cl_2$•CH_2Cl_2 (1.7 mg, 2.0 μmol) and $AsPh_3$ (1.6 mg, 5.0 μmol) in THF (0.5 mL).[15] THF (0.5 mL) was used to rinse the vessel and the reaction mixture was stirred at 70 °C for 2 h. The reaction was quenched with sat. aq. NH_4Cl (5 mL) and diluted with EtOAc (3 mL). The aqueous layer was then extracted with EtOAc (3 x 5 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica, hexanes/MTBE, 1:0 → 7:3) to yield a mixture of the title compound and the corresponding rather unstable γ-lactol as a yellow viscous liquid (4.1 mg). Then, PCC (4.5 mg, 20.8 μmol) was added to a solution of this mixture in CH_2Cl_2 (5.0 mL) and the reaction mixture was stirred at room temperature for 2 h. The resulting dark brown suspension was then filtered through a short pad of SiO_2, washed with MTBE (25 mL)



and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, hexanes/EtOAc, 9:1 → 4:1) to yield the title compound as a colorless viscous liquid (2.0 mg, 47% over two steps). $[\alpha]_{20}^{D}$ = +68.3 (c = 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.67 (dd, *J* = 10.4, 10.3 Hz, 1H), 5.52 (dd, *J* = 10.7, 1.7 Hz, 1H), 5.41 (td, *J* = 7.1, 1.6 Hz, 1H), 5.39 – 5.34 (m, 1H), 5.06 (d, *J* = 9.8 Hz, 1H), 4.73 (d, *J* = 6.8 Hz, 1H), 3.02 – 2.89 (m, 1H), 4.62 (d, *J* = 6.8 Hz, 1H), 4.36 (dd, *J* = 9.6, 1.3 Hz, 1H), 3.87 (ddd, *J* = 10.3, 7.4, 3.1 Hz, 1H), 3.44 (br s, 1H), 3.39 (s, 3H), 3.16 (ddq, *J* = 9.9, 9.7, 6.9 Hz, 1H), 2.96 (br s, 1H), 2.82 (d, *J* = 16.2 Hz, 1H), 2.47 – 2.35 (m, 2H), 2.35 – 2.24 (m, 2H), 2.20 (dt, *J* = 12.8, 7.7 Hz, 1H), 2.10 (ddq, *J* = 8.5, 7.1, 1.4 Hz, 1H), 2.05 – 1.94 (m, 2H), 1.88 – 1.76 (m, 2H), 1.61 (d, *J* = 1.3 Hz, 3H), 1.66 – 1.33 (m, 4H), 1.46 (s, 3H), 1.27 – 1.17 (m, 1H), 1.08 (d, *J* = 7.1 Hz, 3H), 0.99 (t, *J* = 7.0 Hz, 3H), 1.02 – 0.95 (m, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.80 (d, *J* = 6.8 Hz, 3H), 0.11 (s, 12H), 0.07 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.3, 170.4, 145.7, 137.1, 132.4, 130.9, 127.1, 109.7, 99.1, 96.5, 87.5, 84.2, 83.3, 82.5, 75.0, 64.1, 56.2, 46.2, 44.0, 43.3, 42.1, 37.6, 34.9, 34.3, 27.9, 27.2, 25.9, 25.9, 25.9, 22.8, 22.7, 18.4, 17.6, 16.9, 16.9, 12.1, 11.5, 11.3, 9.2, 2.6, 2.6, 2.6, –4.3, –5.0; IR (film): $\tilde{\nu}$ = 2956, 2929, 2861, 1729, 1462, 1375, 1375, 1361, 1324, 1250, 1144, 1056, 1056, 1033, 1004, 985, 915, 836, 775, 752 cm^{-1}; HRMS (ESIpos): *m*/*z*: calcd. for $C_{44}H_{76}O_8Si_2Na$ [M^++Na]: 811.49710, found 811.49652.

When applied to 43.5 mg (67.5 µmol) of vinyl iodide **3** this reaction yielded 10.0 mg (19%) of disilyl ether **D1**.

Propargylic alcohol D2. TBAF (1 M in THF, 25.4 µL, 25.4 µmol) was slowly added to a suspension of disilyl ether **D1** (10.0 mg, 12.7 µmol) and activated 4Å molecular sieves (20.0 mg, powder) in THF (200 µL) at 0 °C. After 1.5 h, a second aliquot of TBAF (1 M in THF, 25.4 µL, 25.4 µmol) was introduced. After additional 1.5 h, the reaction was quenched with H_2O/brine (2:1, 5 mL) and diluted with EtOAc (5 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was quickly purified by flash chromatography (Florisil®, hexanes/EtOAc, 7:3 → 3:7), keeping the contact time with the stationary phase as short as possible. The yellow viscous liquid thus obtained presented a mixture (~1:1) of the title compound and the dehydrated lactone **E2**. It was immediately used in the next step as it decomposes upon storage in the freezer. HRMS (ESIpos): *m*/*z*: calcd. for $C_{35}H_{54}O_8Na$ [M^++Na]: 625.37109, found 625.37132.

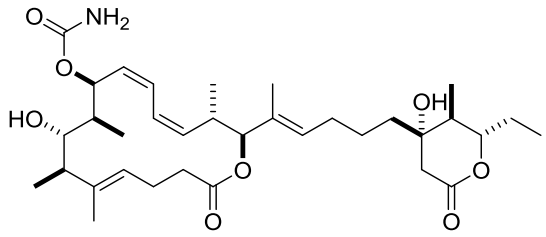


Allylic alcohol D3. A solution of a mixture (~1:1) of propargyl alcohol **D2** and dehydrated lactone **E2** (5.0 mg, 8.3 μmol) in THF (300 μL) was added to a suspension of freshly prepared Zn(Cu/Ag) (570 mg) in degassed MeOH/H_2O (1:1, 600 μL) and the resulting mixture was stirred at 50 °C for 89 h. After cooling to room temperature, the mixture was diluted with EtOAc (2 mL) and filtered through a short pad of Celite®, which was carefully rinsed with EtOAc (50 mL) and EtOH (5 mL). The combined filtrates were concentrated *in vacuo*. The residue was purified by flash chromatography (Florisil®, hexanes/EtOAc, 4:1 → 1:1) to yield the title compound as a colorless viscous liquid (1.9 mg, 23% yield over two steps, ~80% purity) along with the dehydrated lactone **E3** as colorless viscous liquid (3.9 mg, 33% yield over two steps, ~55% purity). ^{1}H NMR (600 MHz, CD_2Cl_2): δ = 6.44 (dd, *J* = 11.5, 11.4 Hz, 1H), 6.28 (dd, *J* = 11.3, 11.2 Hz, 1H), 5.56 (dd, *J* = 11.4, 10.6 Hz, 1H), 5.51 – 5.43 (m, 1H), 5.28 (dd, *J* = 11.2, 10.8 Hz, 1H), 5.15 – 5.10 (m, 1H), 5.05 (d, *J* = 10.3 Hz, 1H), 5.08 – 5.01 (m, 1H), 4.73 (d, *J* = 6.4 Hz, 1H), 4.64 (d, *J* = 6.4 Hz, 1H), 3.89 – 3.86 (m, 1H), 3.41 (s, 3H), 3.35 (d, *J* = 10.7 Hz, 1H), 2.99 – 2.92 (m, 1H), 2.86 (br s, 1H), 2.74 (d, *J* = 16.4 Hz, 1H), 2.62 – 2.54 (m, 1H), 2.36 – 2.30 (m, 2H), 2.28 – 2.19 (m, 2H), 2.09 – 2.05 (m, 2H), 2.05 – 1.97 (m, 1H), 1.96 – 1.89 (m, 1H), 1.88 – 1.77 (m, 2H), 1.65 (s, 3H), 1.62 – 1.58 (m, 2H), 1.50 – 1.46 (m, 2H), 1.44 (s, 3H), 1.41 – 1.34 (m, 2H), 1.10 (d, *J* = 6.8 Hz, 3H), 1.07 (d, *J* = 7.3 Hz, 3H), 1.01 (t, *J* = 7.4 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.86 (d, *J* = 6.7 Hz, 3H); HRMS (ESIpos): *m*/*z*: calcd. for $C_{35}H_{56}O_8Na$ [M^++Na]: 627.38674, found 627.38634.

Allylic carbamate D4. A solution of trichloroacetyl isocyanate (0.1 M in CH_2Cl_2, 20.0 μL, 2.00 μmol) was carefully added along the cold wall of a solution of the allylic alcohol **D3** (1.5 mg, 2.48 μmol) in CH_2Cl_2 (100 μL) precooled at –78 °C. The reaction mixture was allowed to reach –78 °C and was stirred at this temperature for 30 min, when a second aliquot of trichloroacetyl isocyanate (0.1 M in CH_2Cl_2, 5.0 μL, 5.00 μmol) was introduced. After additional 15 min, a third aliquot of trichloroacetyl isocyanate (0.1 M in CH_2Cl_2, 3.0 μL, 3.00 μmol) was introduced and the mixture was stirred at –78 °C for 15 min, before being quenched with MeOH (50 μL) at this temperature. After warming and concentration *in vacuo*, the residue was dissolved in

CH_2Cl_2 (1 mL) and the solution soaked on basic alumina. After 1 h, the alumina was loaded onto a short pad of Celite®, which was eluted with EtOAc/EtOH (9:1, 50 mL) and the solvent was concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography (TLC Silica gel 60 F254 (20 x 20 cm), hexanes/EtOAc, 7:3) to yield the title compound as a colorless viscous liquid (1.1 mg, 44%, ~80% purity). ^{1}H NMR (500 MHz, CD_2Cl_2): δ = 6.73 – 6.60 (m, 1H), 6.42 – 6.23 (m, 1H), 6.01 – 5.81 (m, 1H), 5.56 – 5.42 (m, 2H), 5.37 – 5.33 (m, 1H), 5.12 – 5.06 (m, 1H), 5.04 (d, *J* = 10.3 Hz, 1H), 4.70 (d, *J* = 6.7 Hz, 1H), 4.59 (d, *J* = 6.7 Hz, 1H), 4.49 (br s, 2H), 3.87 (ddd, *J* = 9.9, 7.6, 3.1 Hz, 1H), 3.38 (s, 3H), 3.35 – 3.27 (m, 1H), 3.00 – 2.91 (m, 1H), 2.73 (d, *J* = 16.5 Hz, 1H), 2.53 – 2.45 (m, 1H), 2.34 (d, *J* = 16.5 Hz, 1H), 2.30 – 2.25 (m, 1H), 2.24 – 2.11 (m, 3H), 2.08 (q, *J* = 7.2 Hz, 2H), 2.02 (d, *J* = 6.4 Hz, 1H), 1.88 – 1.75 (m, 2H), 1.67 – 1.64 (m, 3H), 1.63 – 1.58 (m, 2H), 1.50 – 1.45 (m, 2H), 1.41 – 1.35 (m, 2H), 1.26 (s, 3H), 1.13 (d, *J* = 7.3 Hz, 3H), 1.09 (d, *J* = 6.7 Hz, 3H), 1.01 (t, *J* = 7.4 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H); HRMS (ESIpos): *m*/*z*: calcd. for $C_{36}H_{57}NO_9Na$ [M^++Na]: 670.39255, found 670.39212.

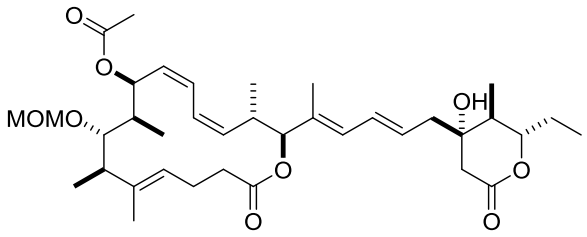
Analogue 42. A solution of allylic carbamate **B4** (0.8 mg, 1.23 µmol) in CH_2Cl_2 (120 µL) was cooled to –90 °C ($Et_2O/CO_2/N_2$ cooling bath) before a solution of freshly prepared Me_2BBr (0.1 M in CH_2Cl_2, 14.9 µL, 1.49 µmol) was carefully added via the cold wall of the flask. The reaction mixture was allowed to reach –78 °C and was stirred at this temperature for 1 h, when a second aliquot of Me_2BBr (0.1 M in CH_2Cl_2, 14.9 µL, 1.49 µmol) was introduced. After additional 0.5 h, the mixture was transferred via canula into a vigorously stirred mixture of sat. $NaHCO_3/H_2O$/THF (1:1:1, 3 mL) and the flask was rinsed with THF (2 x 200 µL). After stirring for 0.5 h, the mixture was diluted with EtOAc (3 mL), the aqueous layer was extracted with EtOAc (3 x 3 mL), the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography (TLC Silica gel 60 F254 (20 x 20 cm), MeOH/CH_2Cl_2, 7:93) to yield the title compound as a colorless viscous liquid (0.56 mg, 63%, ~90% purity). ^{1}H NMR (500 MHz, CD_2Cl_2): δ = 6.52 (dd, *J* = 11.5 , 11.4 Hz, 1H), 6.37 (dd, *J* = 11.3, 11.2 Hz, 1H), 5.90 (d, *J* = 10.1 Hz, 1H), 5.57 – 5.45 (m, 3H), 5.13 – 5.06 (m, 1H), 5.03 (d, *J* = 10.3 Hz, 1H), 4.64 (br s, 2H), 3.87 (ddd, *J* = 10.3, 7.6, 3.2 Hz, 1H), 3.26 (br t, *J* = 9.7 Hz, 1H), 3.00 – 2.90 (m, 1H), 2.74 (d, *J* = 16.5 Hz, 1H), 2.45 (dq, *J* = 10.5, 6.6 Hz, 1H), 2.34 (d, *J* = 16.5 Hz, 1H), 2.32 – 2.26 (m, 1H), 2.24 – 2.16 (m,



2H), 2.17 – 2.11 (m, 1H), 2.11 – 2.03 (m, 2H), 2.03 – 1.95 (m, 1H), 1.88 – 1.78 (m, 2H), 1.77 – 1.70 (m, 1H), 1.65 (d, *J* = 1.3 Hz, 3H), 1.64 – 1.55 (m, 2H), 1.49 – 1.43 (m, 2H), 1.42 (d, *J* = 1.4 Hz, 3H), 1.40 – 1.33 (m, 2H), 1.13 (d, *J* = 6.7 Hz, 3H), 1.08 (d, *J* = 7.3 Hz, 3H), 1.01 (t, *J* = 7.4 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H); HRMS (ESIpos): *m*/*z*: calcd. for $C_{34}H_{53}NO_8Na$ [M^++Na]: 626.36634, found 626.36684.

■ Analogue F

Allylic acetate F4. Acetic anhydride (2.3 µL, 25 µmol), triethylamine (4.6 µL, 33 µmol) and DMAP (0.2 mg, 1.7 µmol) were added subsequently to a –78°C solution of alcohol **40** (10.0 mg, 16.6 µmol) in CH_2Cl_2 and stirred for 1 h. The reaction mixture was then allowed to warm to 0 °C and stirred for further 18 h before being quenched with a mixture of brine and H_2O (1:1, 4 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 4 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica, hexanes/EtOAc, 3:1 → 2:1) to yield the desired mono-acetylated **F4** product as a white solid (5.8 mg, 54% yield, ~95% purity) along with the bis-acetylated compound as an off-white foam (3.1 mg, 27% yield). $[\alpha]_{20}^{D}$ = –65.7 (c = 0.48, CH_2Cl_2). ^{1}H NMR (600 MHz, CD_2Cl_2): δ = 6.65 (br t, *J* = 12.2 Hz, 1H), 6.38 (ddt, *J* = 15.0, 10.7, 1.2 Hz, 1H), 6.31 (br t, *J* = 10.3 Hz, 1H), 6.09 (dd, *J* = 10.8, 1.7 Hz, 1H), 6.03 (d, *J* = 10.8 Hz, 1H), 5.75 (dt, *J* = 15.2, 7.6 Hz, 1H), 5.47 (br t, *J* = 10.0 Hz, 1H), 5.36 – 5.30 (m, 1H), 5.09 – 5.04 (m, 2H), 4.66 (d, *J* = 6.7 Hz, 1H), 4.55 (d, *J* = 6.7 Hz, 1H), 3.90 (ddd, *J* = 10.3, 7.5, 3.2 Hz, 1H), 3.36 (s, 3H), 3.27 (br s, 1H), 2.97 (ddq, *J* = 10.3, 6.7, 6.6 Hz, 1H), 2.72 (d, *J* = 16.5 Hz, 1H), 2.52 – 2.44 (m, 1H), 2.41 (dd, *J* = 14.0, 7.4 Hz, 1H), 2.34 (d, *J* = 16.5, 0.9 Hz, 1H), 2.32 – 2.27 (m, 1H), 2.24 – 2.17 (m, 4H), 2.00 – 1.95 (m, 2H), 1.94 (s, 3H), 1.88 (dq, *J* = 9.8, 7.1 Hz, 1H), 1.84 (ddd, *J* = 14.7, 7.3, 3.2 Hz, 1H), 1.78 (d, *J* = 1.0 Hz, 3H), 1.77 – 1.74 (m, 1H), 1.68 – 1.54 (m, 3H), 1.15 (d, *J* = 7.4 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H), 1.02 – 0.99 (m, 6H), 0.86 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (150 MHz, CD_2Cl_2): δ = 172.5, 170.4, 170.3, 137.6, 137.2, 135.6, 134.3, 131.9, 129.9, 129.2, 128.5, 126.4, 125.0, 99.1, 86.1, 84.1, 83.0, 72.4, 66.8, 56.5, 48.4, 43.4, 43.1, 42.3, 34.0, 27.4, 22.6, 21.6, 16.9, 16.7, 13.8, 12.3, 11.8, 11.6, 9.4; IR (film): $\tilde{\nu}$ = 3480, 2967, 2930, 1732, 1457, 1369, 1243, 1208, 1148, 1091, 1036, 949, 748 cm^{-1}; MS (ESI)



m/*z* (%): 667.5 (100); HRMS (ESIpos): *m*/*z*: calcd. for $C_{37}H_{56}O_9Na$ [M^++Na]: 667.38165, found 667.38167.

Analogue 45. A solution of allylic acetate **F4** (4.8 mg, 7.4 µmol) in CH_2Cl_2 (0.8 mL) was cooled to –90 °C ($Et_2O/CO_2/N_2$ cooling bath) before a solution of freshly prepared Me_2BBr (0.5 M in CH_2Cl_2, 16.4 µL, 8.2 µmol) was carefully added via the cold wall of the flask. The mixture was allowed to reach –78 °C and was stirred at this temperature for 1.5 h, when a second aliquot of Me_2BBr (0.5 M, 16.4 µL, 8.2 µmol) was introduced. The reaction mixture was stirred for 1.5 h, when a third aliquot of Me_2BBr (0.5 M, 16.4 µL, 8.2 µmol) was introduced. After additional 1.5 h, the mixture was transferred via canula into a vigorously stirred mixture of sat. $NaHCO_3/H_2O$/THF (1:1:1, 7 mL) and the flask was rinsed with THF (2 x 0.5 mL). After stirring for 10 min, the mixture was diluted with EtOAc (10 mL), the aqueous layer was extracted with EtOAc (3 x 10 mL), the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography (TLC Silica gel 60 F254 (20 x 20 cm), hexanes/EtOAc, 1:1) to yield the title compound as an off-white solid (2.4 mg, 54% yield). ^{1}H NMR (600 MHz, CD_2Cl_2): see Table S-5; ^{13}C NMR (150 MHz, CD_2Cl_2): see Table S-5; IR (film): $\tilde{\nu}$ = 3472, 2956, 2924, 2854, 1733, 1459, 1371, 1259, 1246, 1207, 1149, 1100, 1015, 979 cm^{-1}MS (ESI) *m*/*z* (%): 593.4 (100); HRMS (ESIpos): *m*/*z*: calcd. for $C_{34}H_{50}O_7Na$ [M^++Na]: 593.34487, found 593.34547.

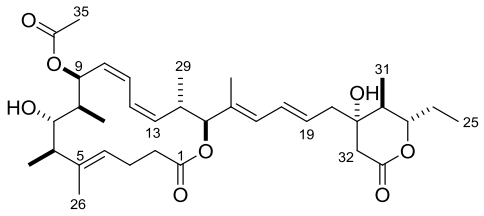


Table S-5: ^{1}H and ^{13}C data of leiodermatolide analogue **45**; numbering scheme as shown in the insert.

	^{1}H (CD_2Cl_2, 600 MHz)					^{13}C NMR (CD_2Cl_2, 150 MHz)	
Nr	**δ (ppm)**	**Integral**	**Splitting**	**COSY**	***J* (Hz)**	**δ (ppm)**	**HMBC**
1	–	–	–	–	–	172.4	2ab, 3, 15
2a	2.31	1	ddd	2b, 3	16.7, 6.2, 2.8	34.0	3, 4, (26)
2b	1.99	1	ddd	2a, 3	16.7, 11.0, 3.2		
3	2.25 – 2.18	2	m	2ab, 4	–	22.5	2a(b), 4
4	5.11	1	ddd	3ab, 26	9.4, 5.1, 1.2	126.1	2ab, 3, 6, 26
5	–	–	–	–	–	137.4	3, 6, 26, 27
6	2.44	1	dq	7, 27	9.0, 6.6	48.5	4, (8), 26, 27
7	3.31	1	br d	6, OH	8.7	78.6	6, (8), 9, 27, 28
8	1.77	1	q	28	7.3	39.4	(9), (10), 28
9	6.02	1	d	10	10.3	67.0	(8), 11, 28, 35
10	5.52	1	ddt	9, 11, 13	10.6, 10.3, 1.2	128.6	(8), 9, 12
11	6.36	1	dd	10, 13	11.6, 10.8	126.3	9, 12, 13
12	6.56	1	dd	11, 13	11.5, 11.3	124.8	10, 11, 14
13	5.35	1	ddt	10, 12, 14	11.2, 10.1, 1.2,	137.8	11, (13), 14, 15, 29
14	2.98	1	ddq	13, 15, 29	10.1, 7.9, 6.6	35.3	12, 13, 15, 29
15	5.08	1	d	14	10.3	82.8	(12), 14, 17, 29, 30
16	–	–	–	–	–	134.2	14, 15, (17), 18, 30
17	6.10	1	dq	18, 30	10.8, 1.1	129.9	15, 18, 19, 30
18	6.40	1	ddt	17, 19, 20	14.9, 10.6, 0.8	131.9	17, 20ab, 30
19	5.76	1	ddd	18, 20ab	15.0, 7.6, 7.5	128.4	17, 20ab, (30)
20a	2.24 – 2.19	1	m	19, 20b	–	38.9	18, 19, 22, 32ab
20b	2.41	1	dd	19, 20a	13.6, 7.4		
21	–	–	–	–	–	72.4	19, 20ab, 22, 32ab, 31
22	1.89	1	dq	23, 31	10.0, 6.8	43.4	(23), 24ab, 31, 32ab
23	3.91	1	ddd	22, 24a, 24b	10.1, 7.3, 3.0	84.1	22, 24ab, 25, 31
24a	1.85	1	dqd	23, 24b, 25	14.7, 7.3, 3.2	27.4	22, (23), 25, 31
24b	1.63	1	dqd	23, 24a, 25	14.6, 7.4, 7.3		
25	1.02	3	t	24ab	7.4	9.42	23, 24ab, (31)
26	1.43	3	s	4	–	11.6	4, 6
27	1.11	3	d	6	6.7	16.6	6
28	1.10	3	d	8	7.3	12.9	8, 9
29	0.87	3	d	14	6.7	16.9	13, 14, 15
30	1.80	3	d	17	1.2	12.3	15, 17
31	1.02	3	d	22	6.5	11.9	22, (23)
32a	2.73	1	d	32b	16.4	43.1	20ab, 22
32b	2.35	1	dd	32a	16.4, 1.0		
33	–	–	–	–	–	170.3	32ab
34	–	–	–	–	–	171.5	9, 35
35	1.98	3	s	–	–	21.7	–
C7-OH	1.66 – 1.63	1	–	7		–	–
C21-OH	1.92 – 1.88	1	–			–	–

Analogue 46. A solution of alcohol **40** (4.0 mg, 6.66 µmol) in CH_2Cl_2 (0.71 mL) was cooled to -90 °C ($Et_2O/CO_2/N_2$ cooling bath) before a solution of freshly prepared Me_2BBr (0.5 M in CH_2Cl_2, 30.6 µL, 15.3 µmol) was carefully added via the cold wall of the flask. The mixture was allowed to reach -78 °C and was stirred at this temperature for 1.5 h, when a second aliquot of Me_2BBr (0.5 M, 14.6 µL, 15.3 µmol) was introduced. This was repeated after another 1.5 h. After additional 1.5 h, the mixture was transferred via canula into a vigorously stirred mixture of sat. $NaHCO_3/H_2O$/THF (1:1:1, 7 mL) and the flask was rinsed with THF (2 x 0.5 mL). After stirring for 10 min, the mixture was diluted with EtOAc (10 mL), the aqueous layer was extracted with EtOAc (3 x 10 mL), the combined extracts were dried over Na_2SO_4 and concentrated. The residue was purified by preparative thin layer chromatography (TLC Silica gel 60 F254 (20 x 20 cm), hexanes/EtOAc, 3:2) to give the title compound as an off-white solid (1.1 mg, ~75% purity, 20% yield). ^{1}H NMR (600 MHz, CD_2Cl_2): δ = see Table S-6; ^{13}C NMR (150 MHz, CD_2Cl_2): δ = see Table S-6; IR (film): $\tilde{\nu}$ = 3469, 2963, 2924, 2855, 1732, 1458, 1376, 1249, 1206, 1146, 1080, 1042, 1006, 898, 800, 739 cm^{-1}. MS (ESI) *m*/*z* (%): 593.4 (100); HRMS (ESIpos): *m*/*z*: calcd. for $C_{34}H_{50}O_7Na$ [M^++Na]: 593.34487, found 593.34547.

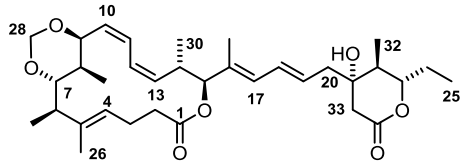


Table S-6: ^{1}H and ^{13}C data of dioxane **46**; numbering scheme as shown in the Insert.

	^{1}H NMR (CD_2Cl_2, 600 MHz)					^{13}C NMR (CD_2Cl_2, 150 MHz)	
Nr	**δ (ppm)**	**Integral**	**Splitting**	**COSY**	***J* (Hz)**	**δ (ppm)**	**HMBC**
1	-	-	-	-	-	172.4	2, 15
2a	2.31 - 2.38	1H	m	2b, 3a, 3b	-	33.8	1, 3, 5, 26
2b	1.88 - 1.96	1H	m	2a, 3a, 3b	-		
3	2.18 - 2.30	2H	m	2a, 2b, 4	-	22.1	1, 2, 4, 26
4	5.12	1H	dd	3a, 3b, (26)	10.2, 4.5	126.1	2, 3, 6, 26
5	-	-	-	-	-	137.0	3, 6, 7, 26, 27
6	2.49	1H	dq	7, 27	10.9, 6.6	48.3	4, 5, 7, 26, 27
7	3.44	1H	d	6	11.0	80.4	6, 9, 27, 28, 29
8	1.60-1.66	1H	m	7, 9, 29	-	38.4	7, 9, 10, 29
9	5.07	1H	d	10	10.1	65.2	7, 8, 11, OH1, 29
10	5.56 – 5.60	1H	m	9, 11	--	131.7	8, 9, 12, OH1
11	6.31 – 6.38	1H	m	10, 12	--	123.7	9, 12, 13, 14
12	6.46	1H	dd	11, 13	10.3, 11.4	126.7	10, 13, 14, 30
13	5.28	1H	dd	12, 14	10.3, 10.2, 0.7	137.7	11, 14, 15, 30
14	2.96 - 3.02	1H	m	13, 15, 31	-	35.3	12, 13, 15, 30
15	5.09	1H	d	14	10.3	83.1	13, 14, 16, 17, 30, 31
16	-	-	-	-	-	134.0	14, 15, 17, 18
17	6.05	1H	d	18	10.8	129.7	15, 16, 18, 19, 31
18	6.38 – 6.42	1H	m	17, 19	-	131.7	17, 20, 31
19	5.77	1H	ddd	20a, 20b	7.5, 7.5, 15.1	128.3	17, 18, 20, 21
20a	2.41	1H	dd	19, 20b	14.3, 7.9	38.7	18, 19, 21, 22, 33
20b	2.22	1H	dd	19, 20a	14.2, 7.6		
21	-	-	-	-	-	72.1	19, 20a, 20b, 22, 33
22	1.89	1H	dq	23, 32	10.1, 7.1	43.2	20, 32, 33
23	3.91	1H	ddd	22, 24a, 24b	10.1, 7.4, 2.9	83.9	22, 24, 25
24a	1.86 – 1.90	1H	m	23, 24b, 25	-	27.2	23, 25
24b	1.63	1H	ddq	23, 24b, 25	7.3, 7.3, 7.4		
25	1.02	3H	t	24a, 24b	7.2	9.2	24
26	1.44	3H	s	4	-	11.3	4, 5, 6
27	1.11	3H	d	6	6.9	16.1	5, 7
28a	5.00	1H	d	28b	6.2	88.7	7,9
28b	4.80	1H	d	28a	6.3		
29	1.07	3H	d	8	7.2	12.1	6, 9, (28)
30	0.87	3H	d	14	6.8	16.6	13, 14, 15
31	1.79	3H	d	17	0.6	12.2	15, 17
32	0.98	3H	d	22	6.9	11.7	21, 22
33a	2.73	1H	d	33b	16.5	42.9	21, 34
33b	2.35	1H	d	33a	16.6		
34	-	-	-	-	-	170.1	33a, 33b
OH	2.17 - 2.26	1H	br s			-	-

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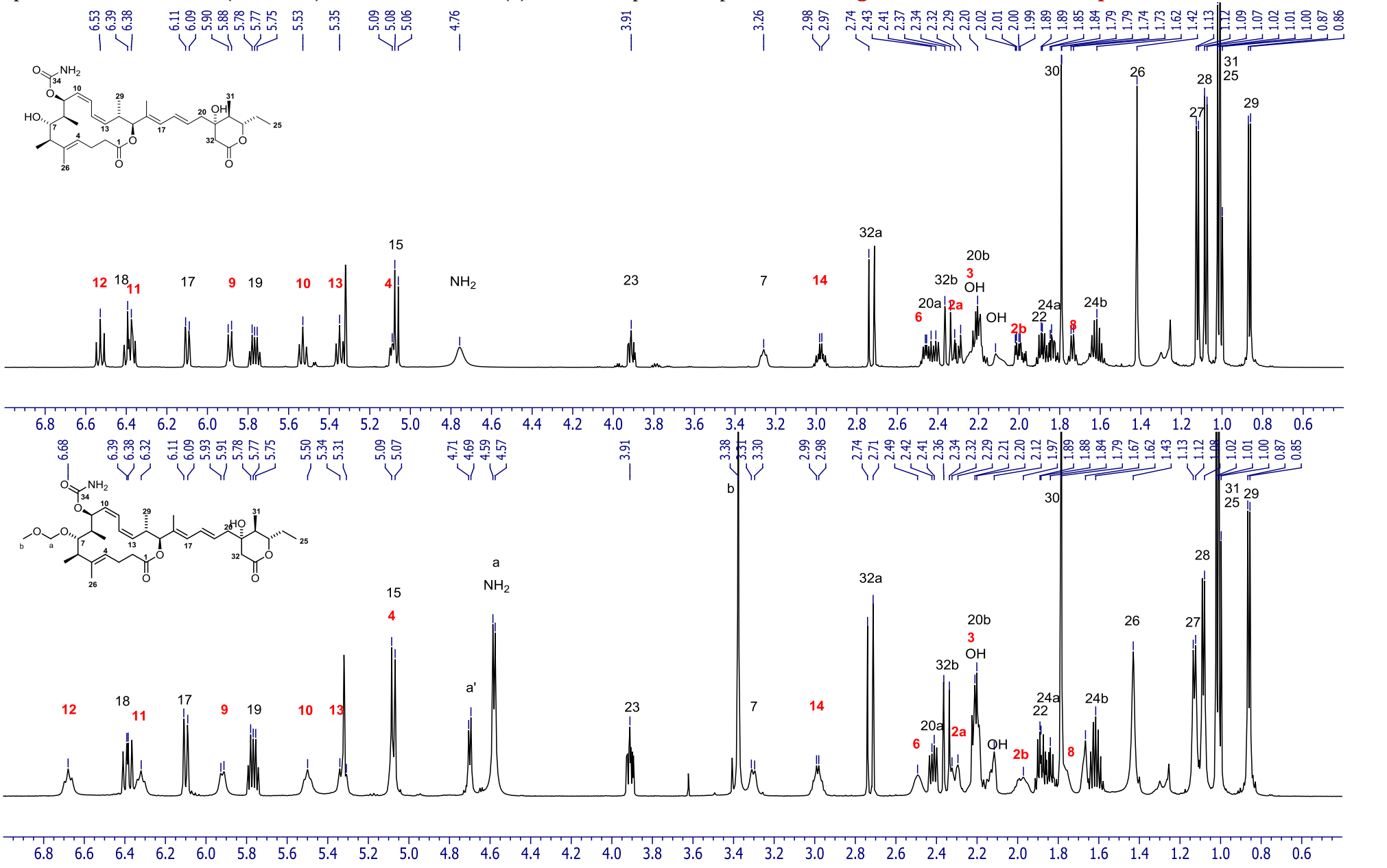
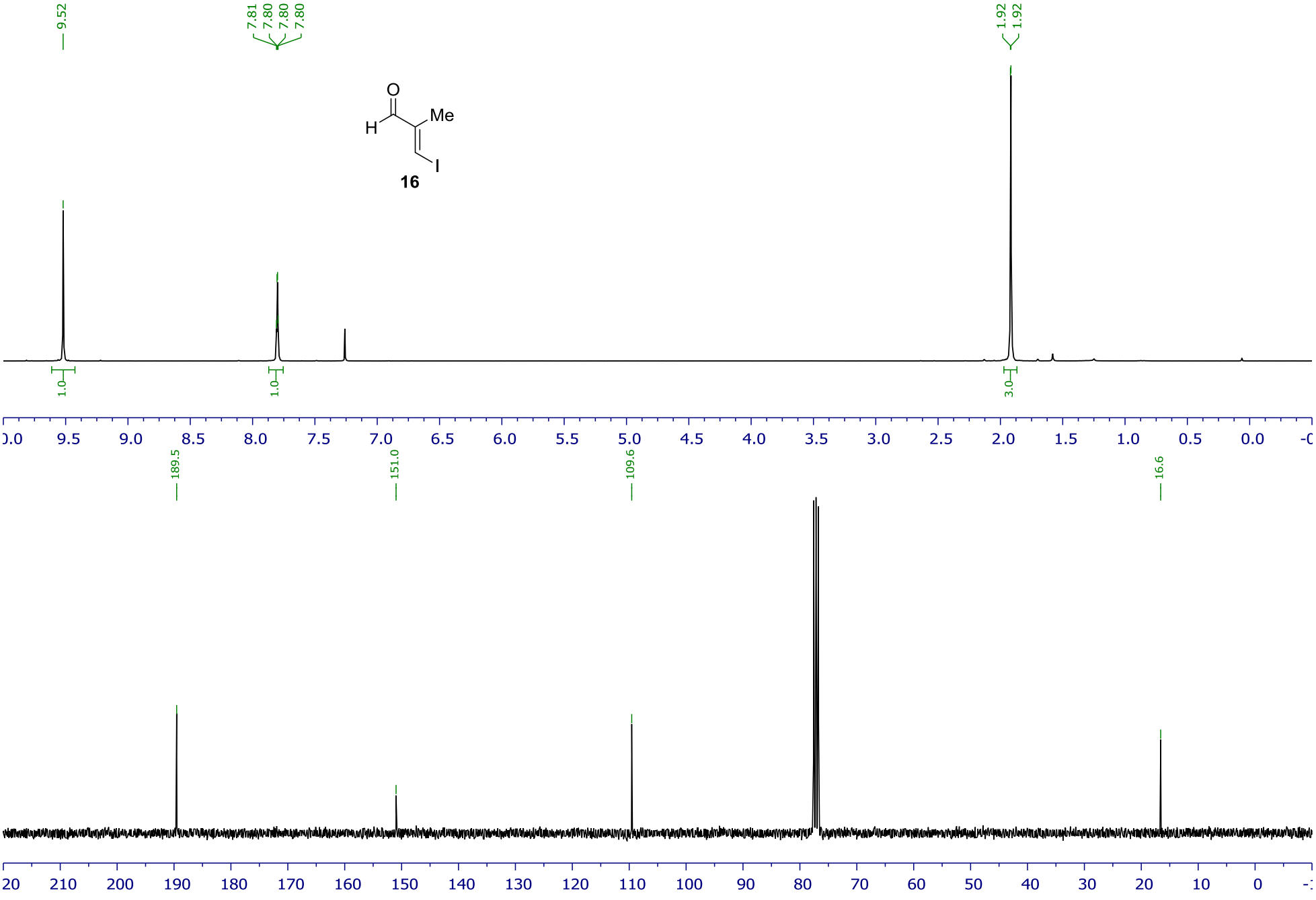
Comparison of the ^{1}H NMR (600 MHz) of Leiodermatolide (**1**) and MOM-protected precursor **41**; **signals that resolve after deprotection are marked in red**.

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Me
I
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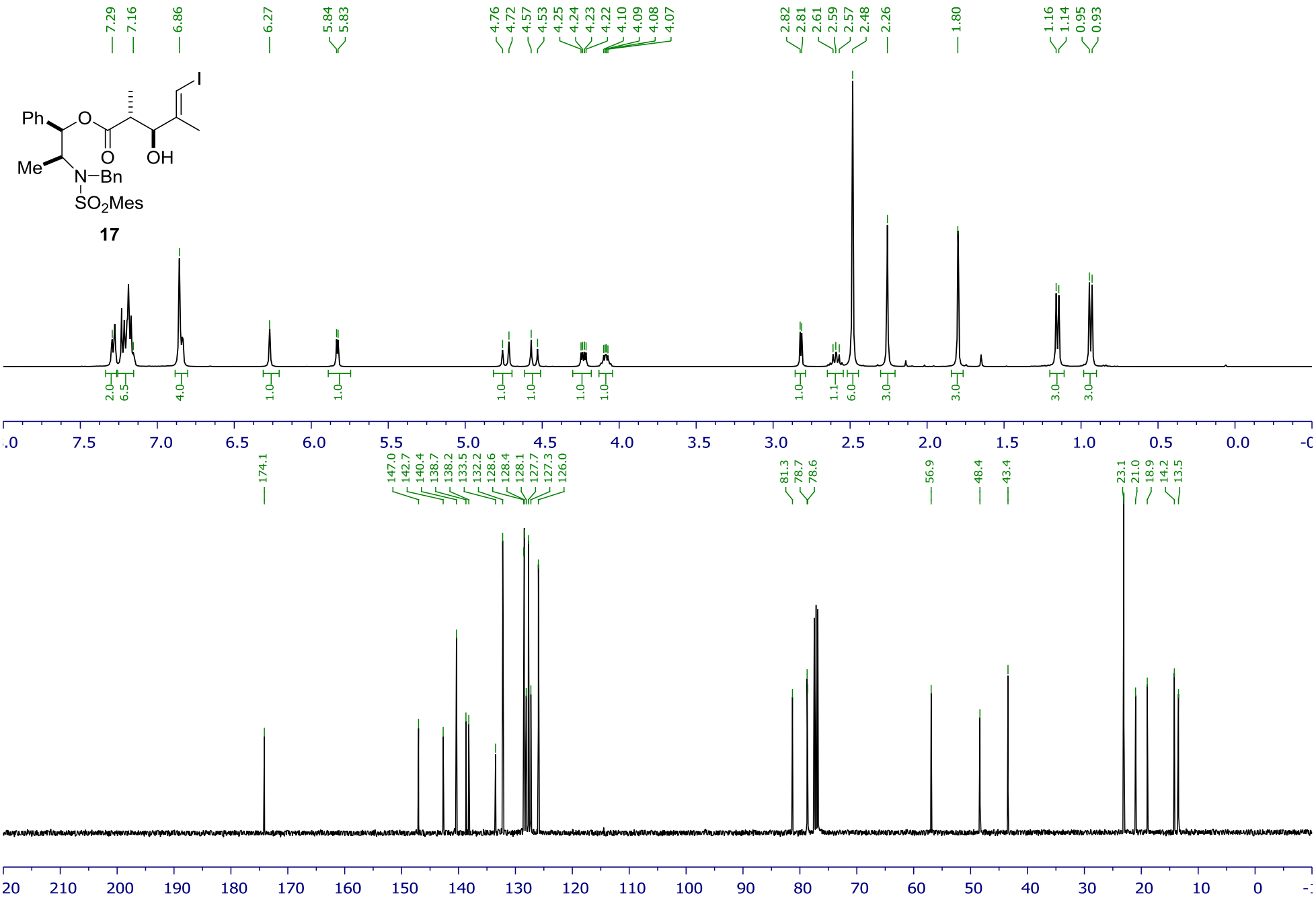
3.0
189.5
151.0
109.6
16.6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4.22
4.10
4.09
4.08
4.07
2.82
2.81
2.61
2.59
2.57
2.48
2.26
1.80
1.16
1.14
0.95
0.93
Ph
O
O
OH
Me
N–Bn
SO2Mes
I
17
174.1
147.0
142.7
140.4
138.7
138.2
133.5
132.2
128.6
128.4
128.1
127.7
127.3
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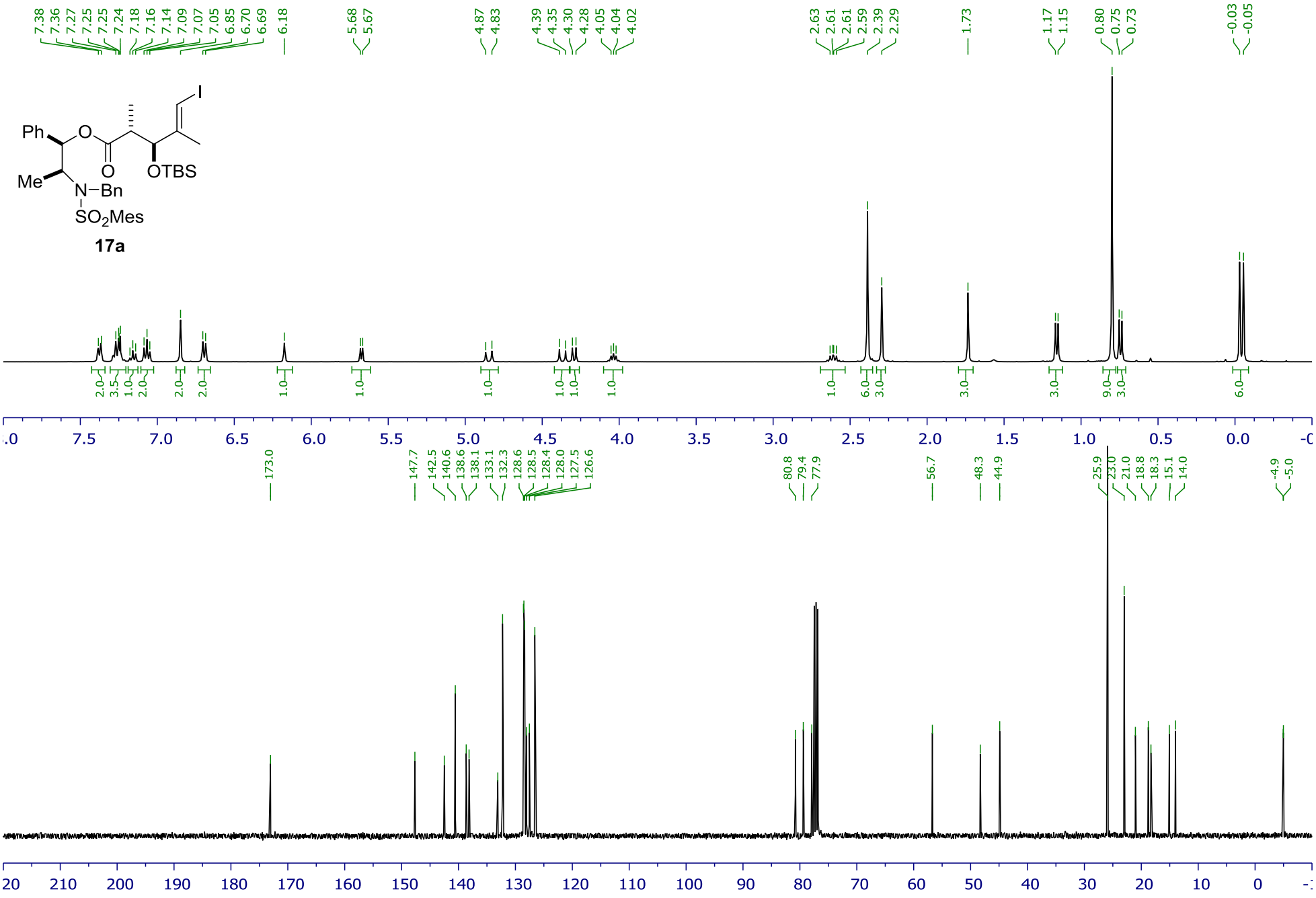
43.4
23.1
21.0
18.9
14.2
13.5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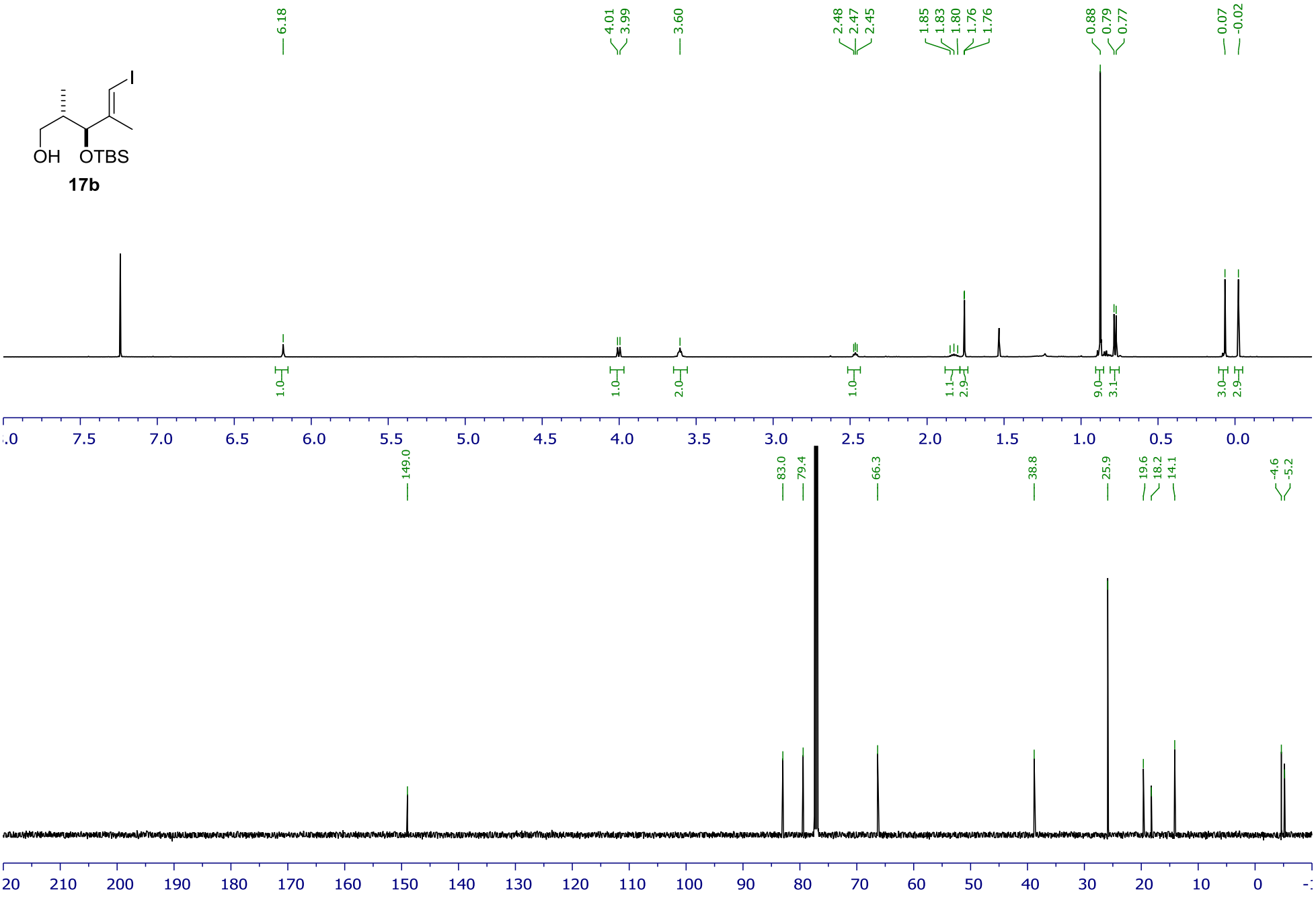
O
OTBS
Me
N–Bn
SO2Mes
I
17a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1.80
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1.76
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0.79
0.77
0.07
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1.0
2.0
1.0
1.1
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9.0
3.1
3.0
2.9
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
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79.4
66.3
38.8
25.9
19.6
18.2
14.1
-4.6
-5.2
210
200
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120
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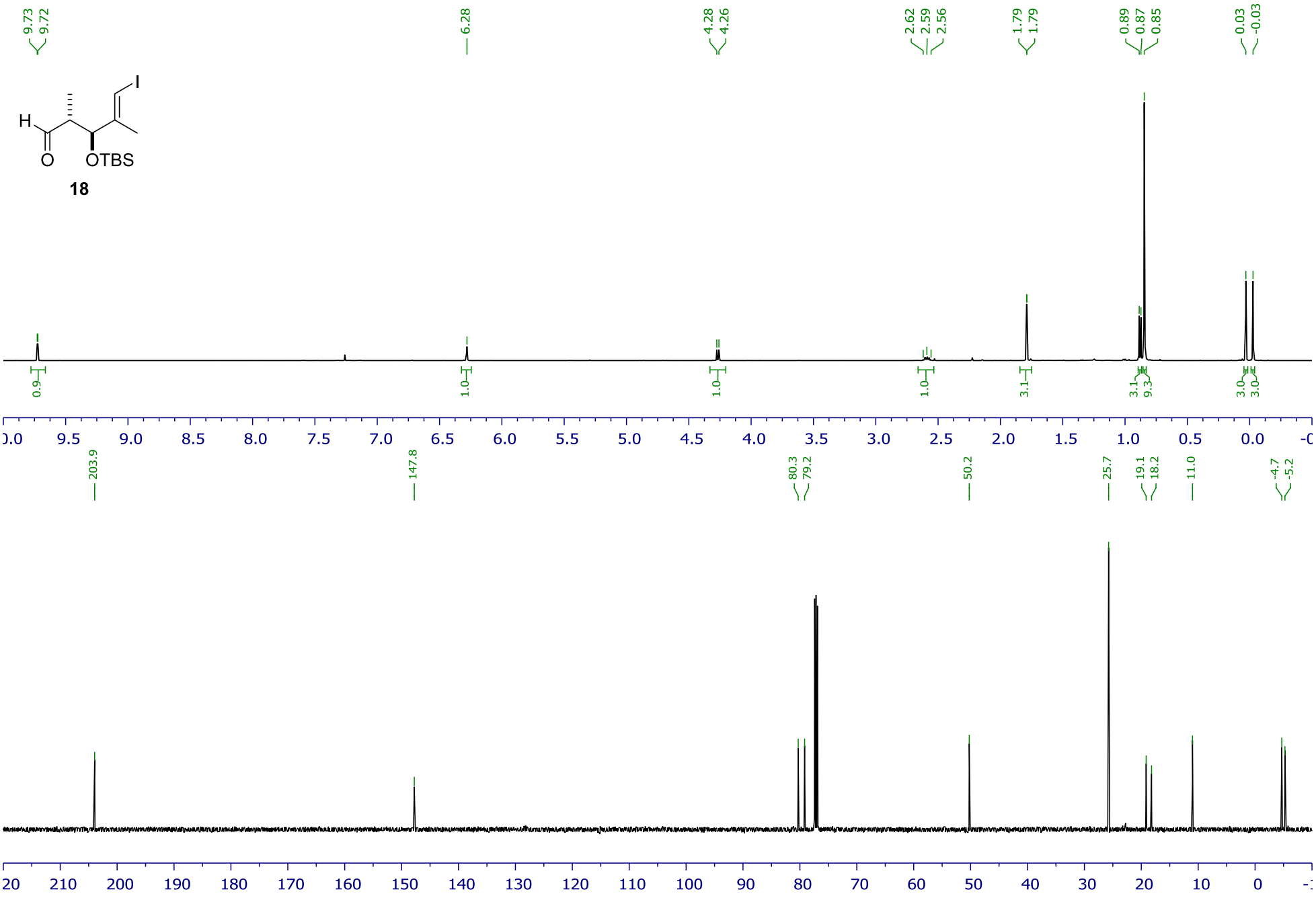
20
10
0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0.85
0.03
-0.03
H
O
OTBS
I
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1.0
1.0
3.1
3.1
9.3
3.0
3.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
203.9
147.8
80.3
79.2
50.2
25.7
19.1
18.2
11.0
-4.7
-5.2
210
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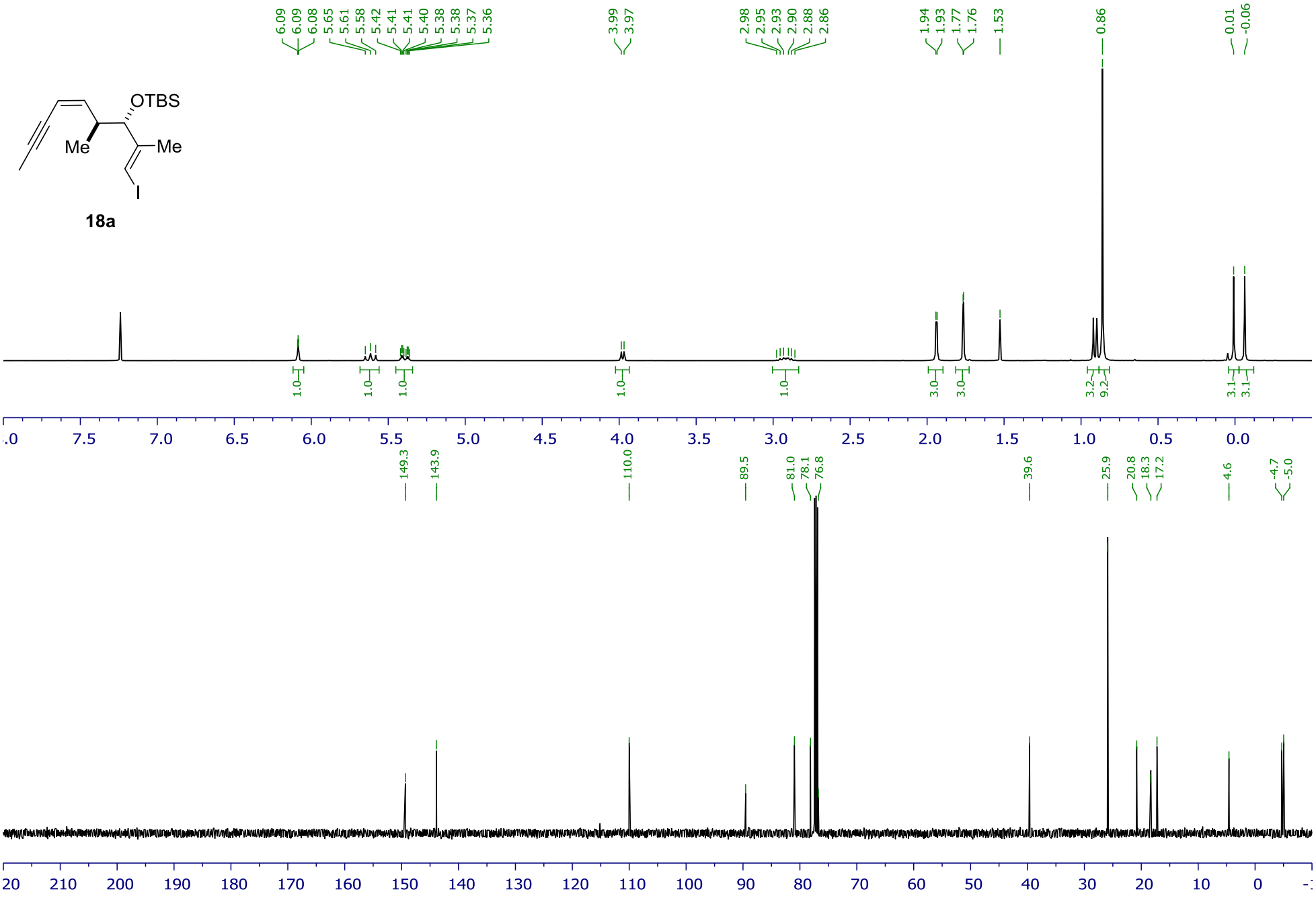
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5.41
5.40
5.38
5.38
5.37
5.36
3.99
3.97
2.98
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2.90
2.88
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1.76
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76.8
39.6
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20.8
18.3
17.2
4.6
-4.7
-5.0
210
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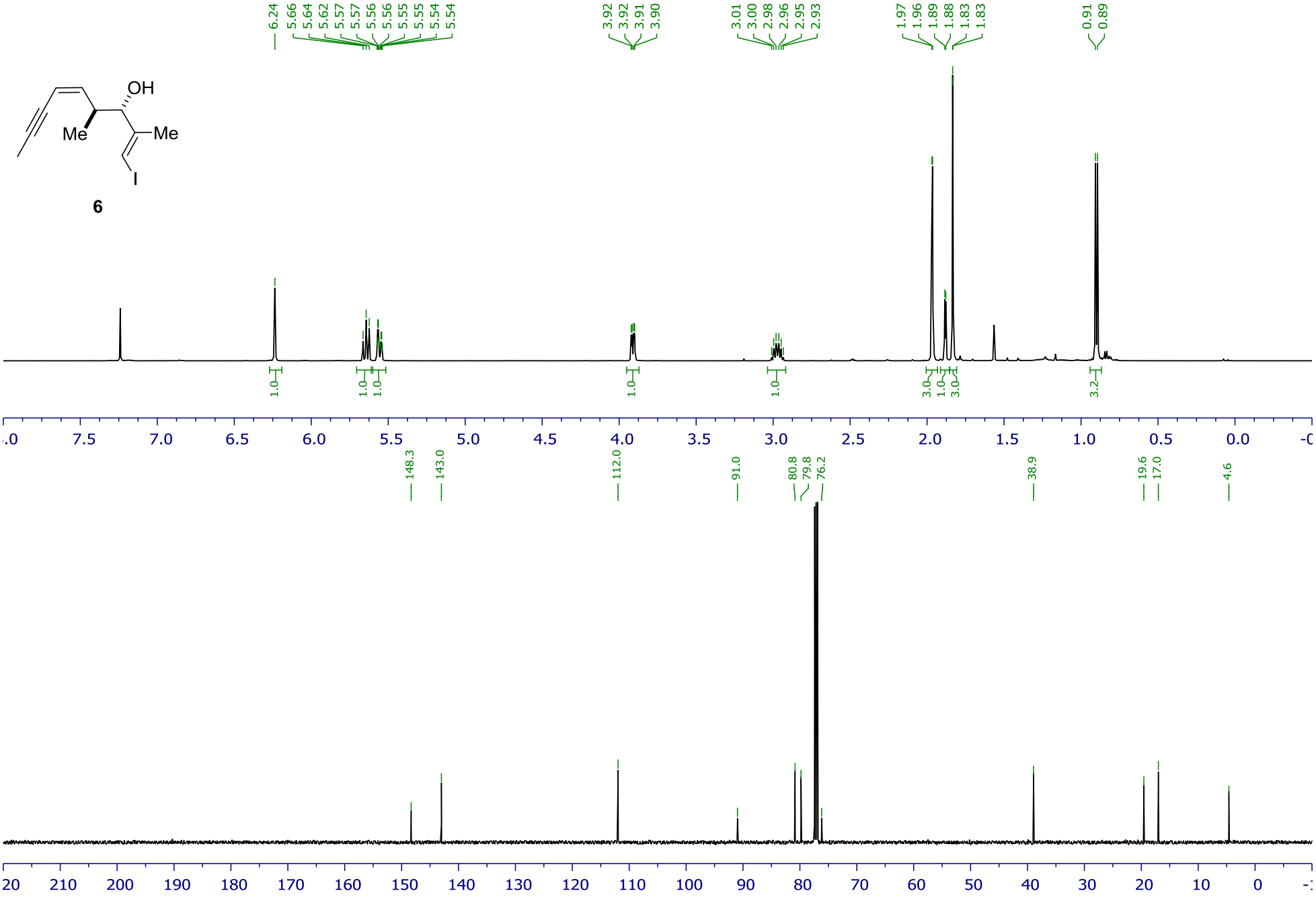
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3.00
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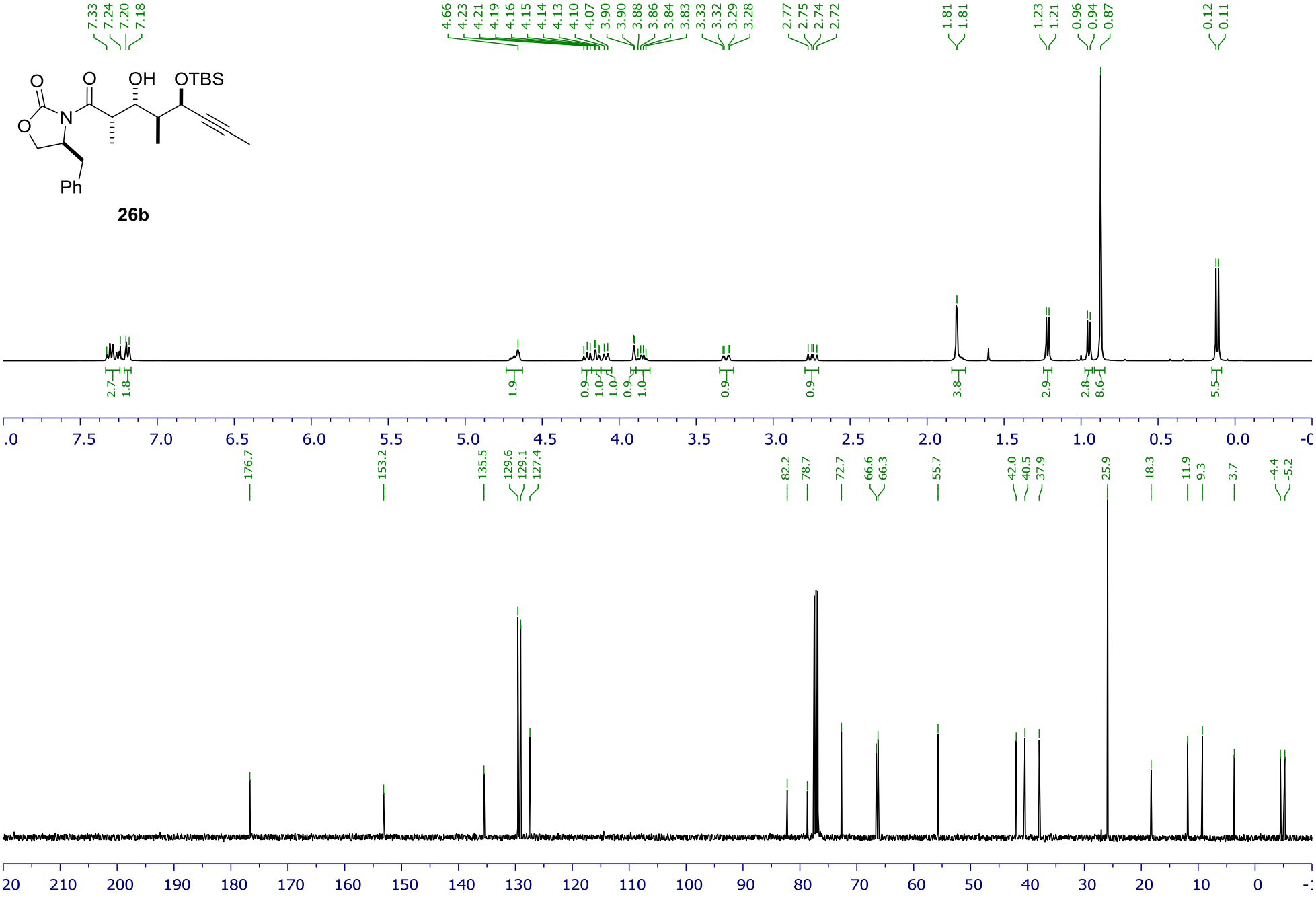
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4.07
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3.33
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1.21
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0.94
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0.12
0.11
O
O
OH
OTBS
N
O
Ph
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1.9
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1.0
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127.4
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66.3
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11.9
9.3
3.7
-4.4
-5.2
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200
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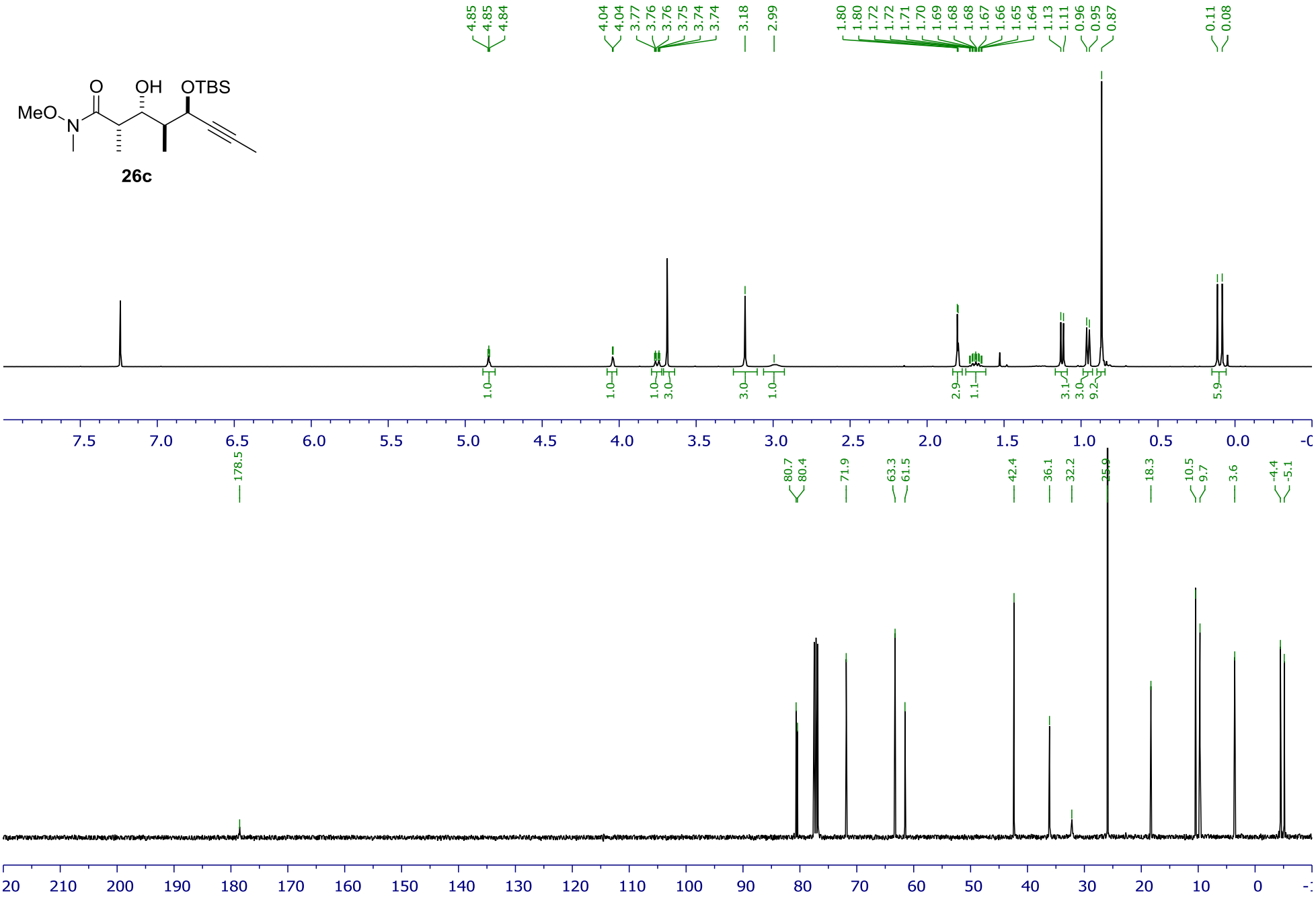
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OH
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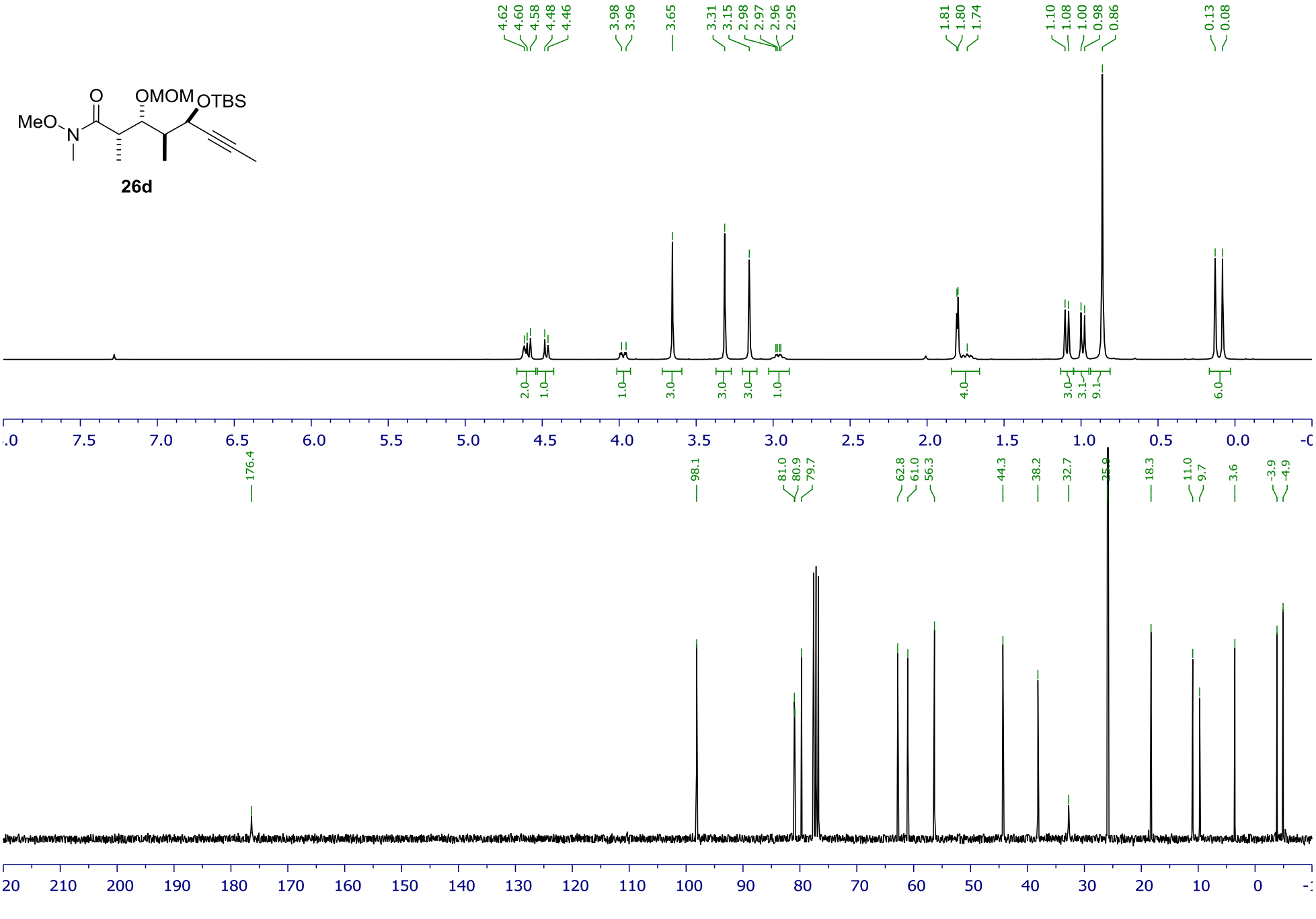
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2.97
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56.3
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38.2
32.7
25.9
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10
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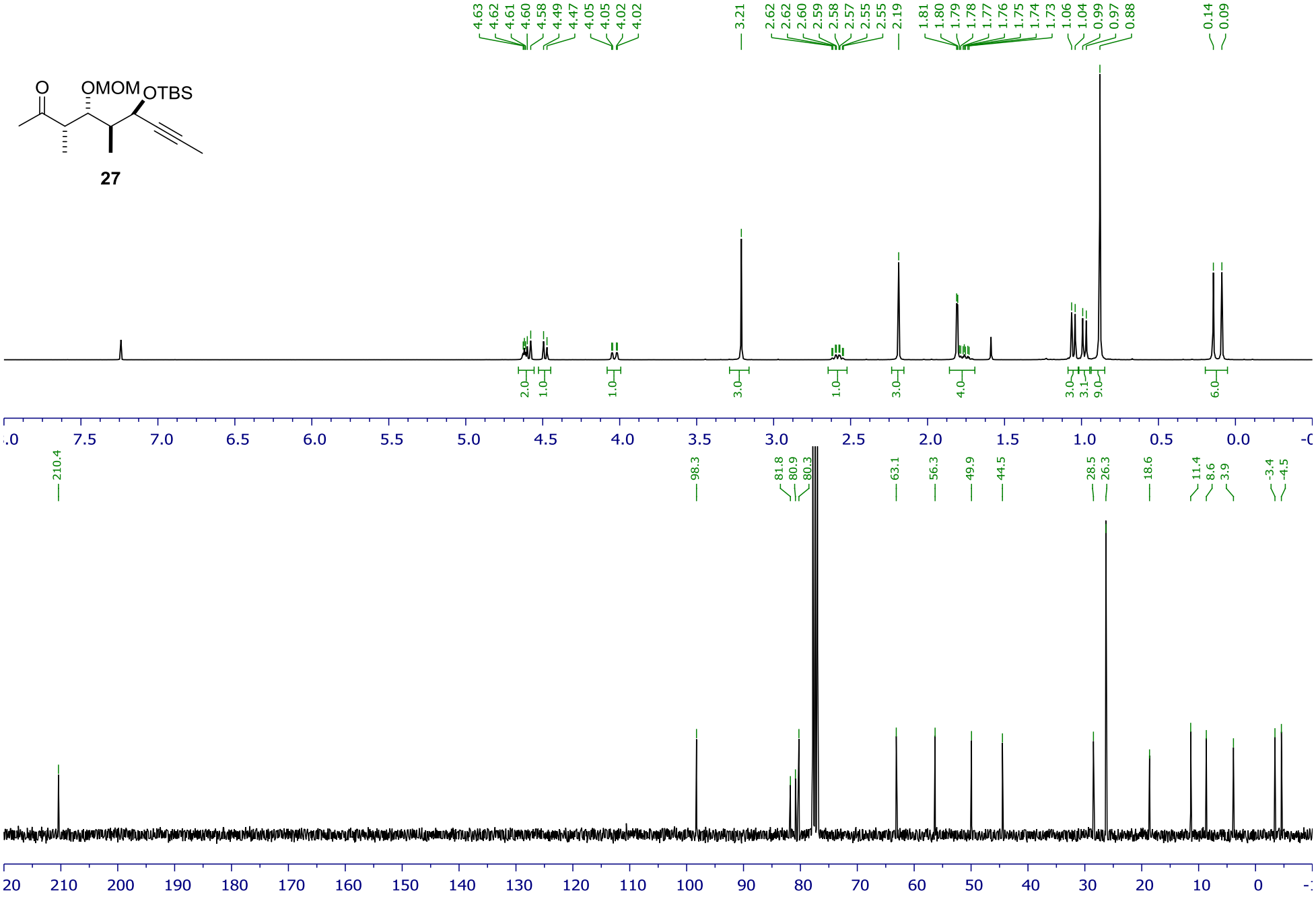
O
OMOM
OTBS
27
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3.21
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1.81 1.80 1.79 1.78 1.77 1.76 1.75 1.74 1.73 1.06 1.04 0.99 0.97 0.88
0.14 0.09
2.0 1.0 1.0 3.0 1.0 3.0 4.0 3.0 3.1 9.0 6.0
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
210.4
98.3
81.8 80.9 80.3
63.1
56.3
49.9
44.5
28.5 26.3
18.6
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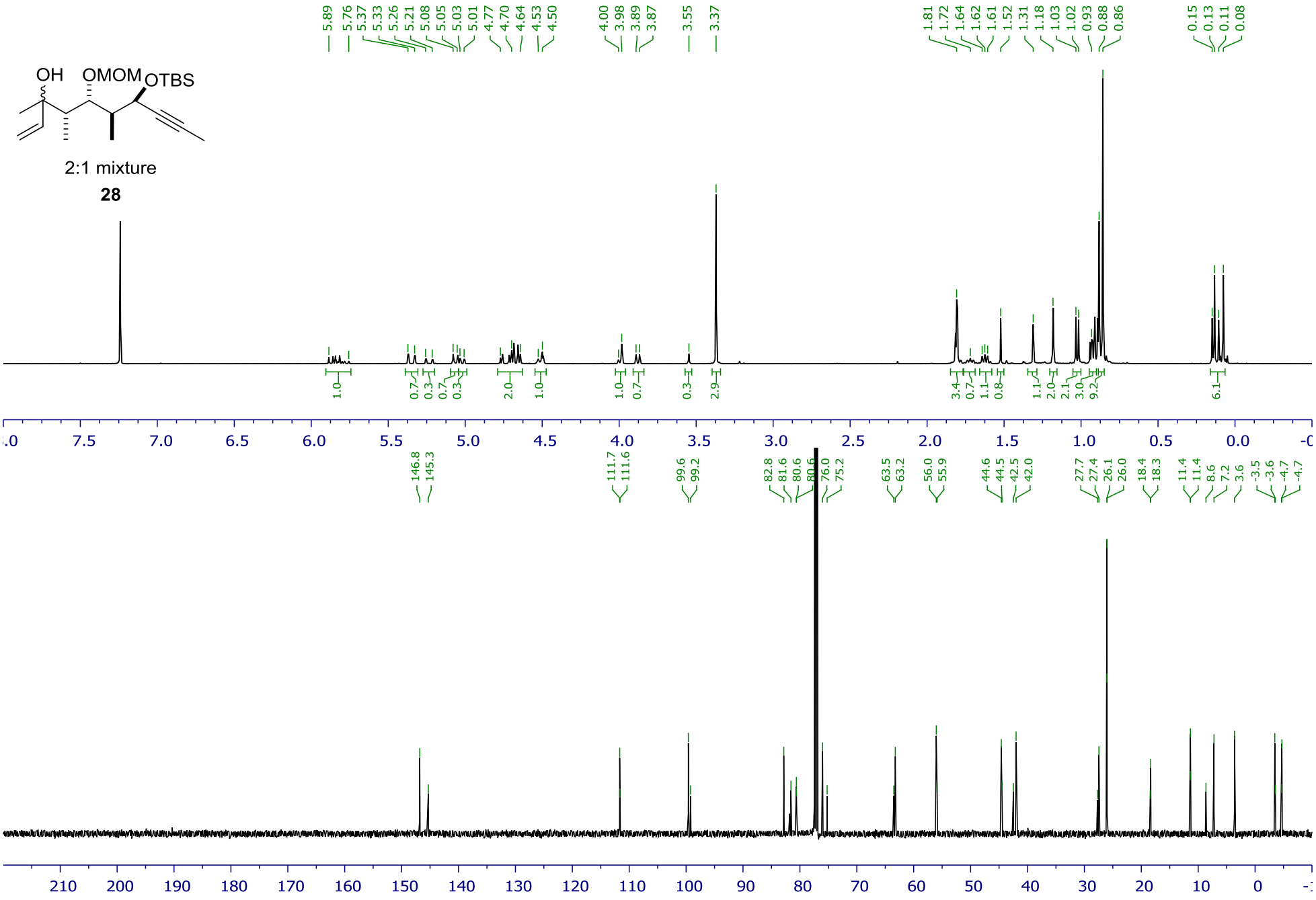
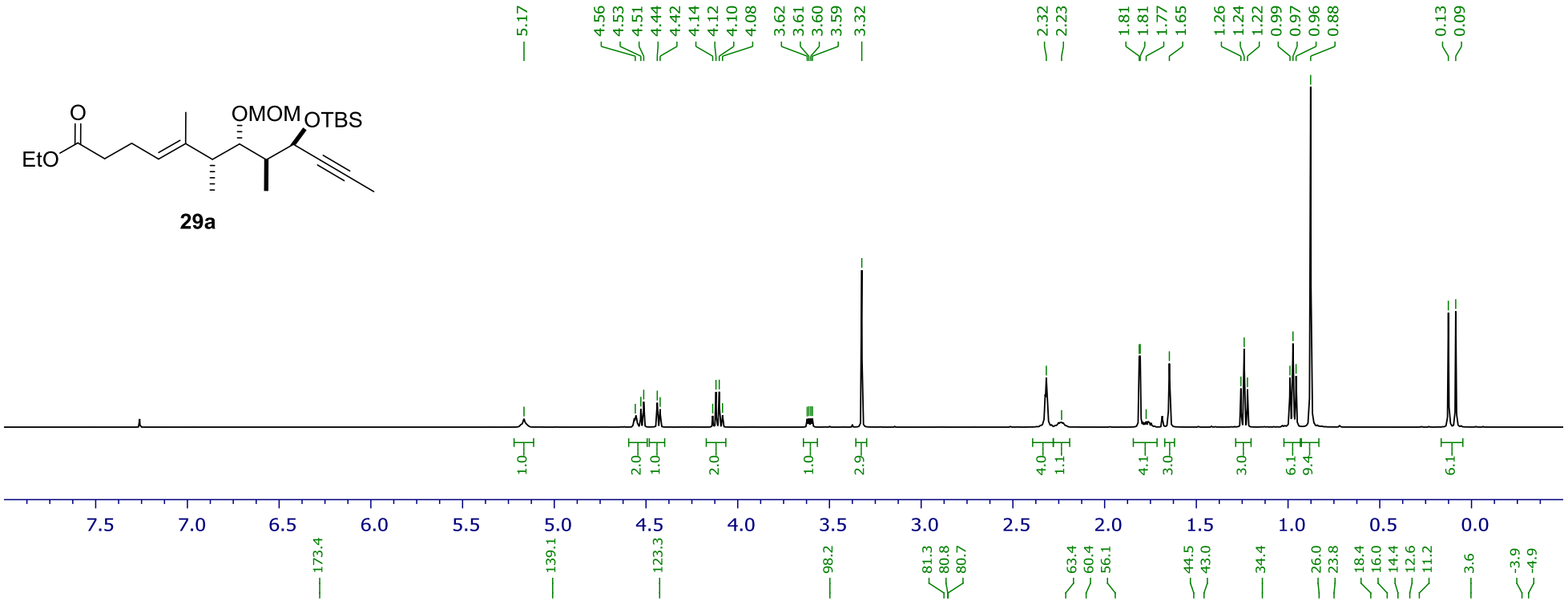

OH
OMOM
OTBS
2:1 mixture
28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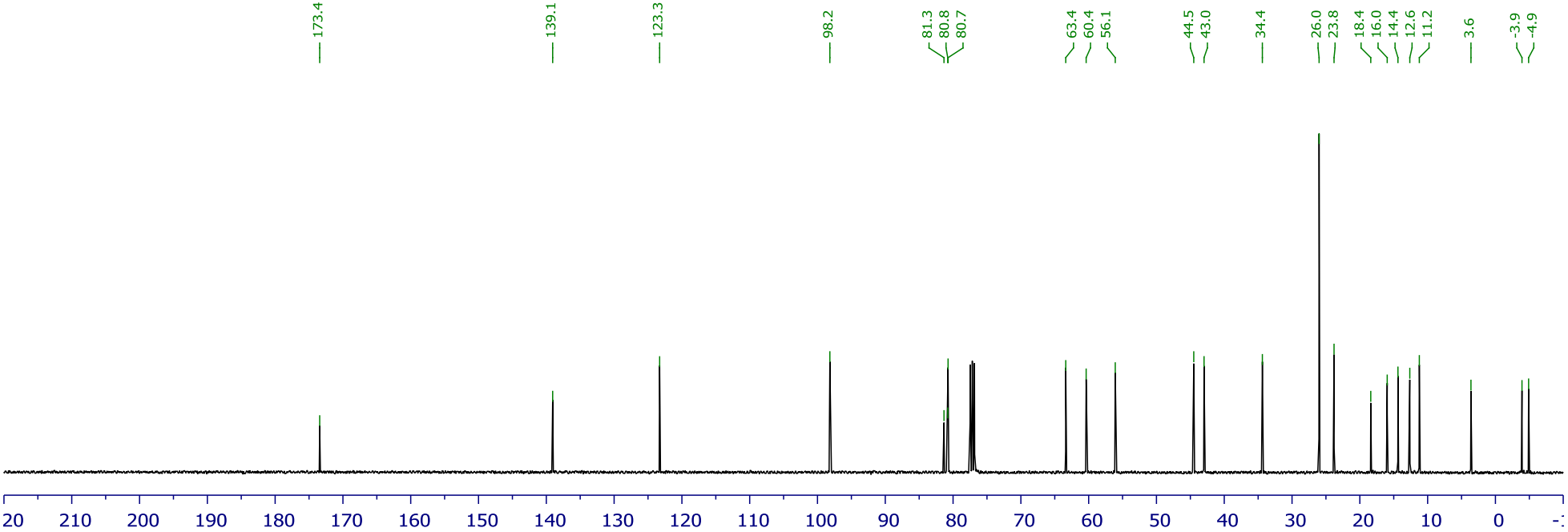
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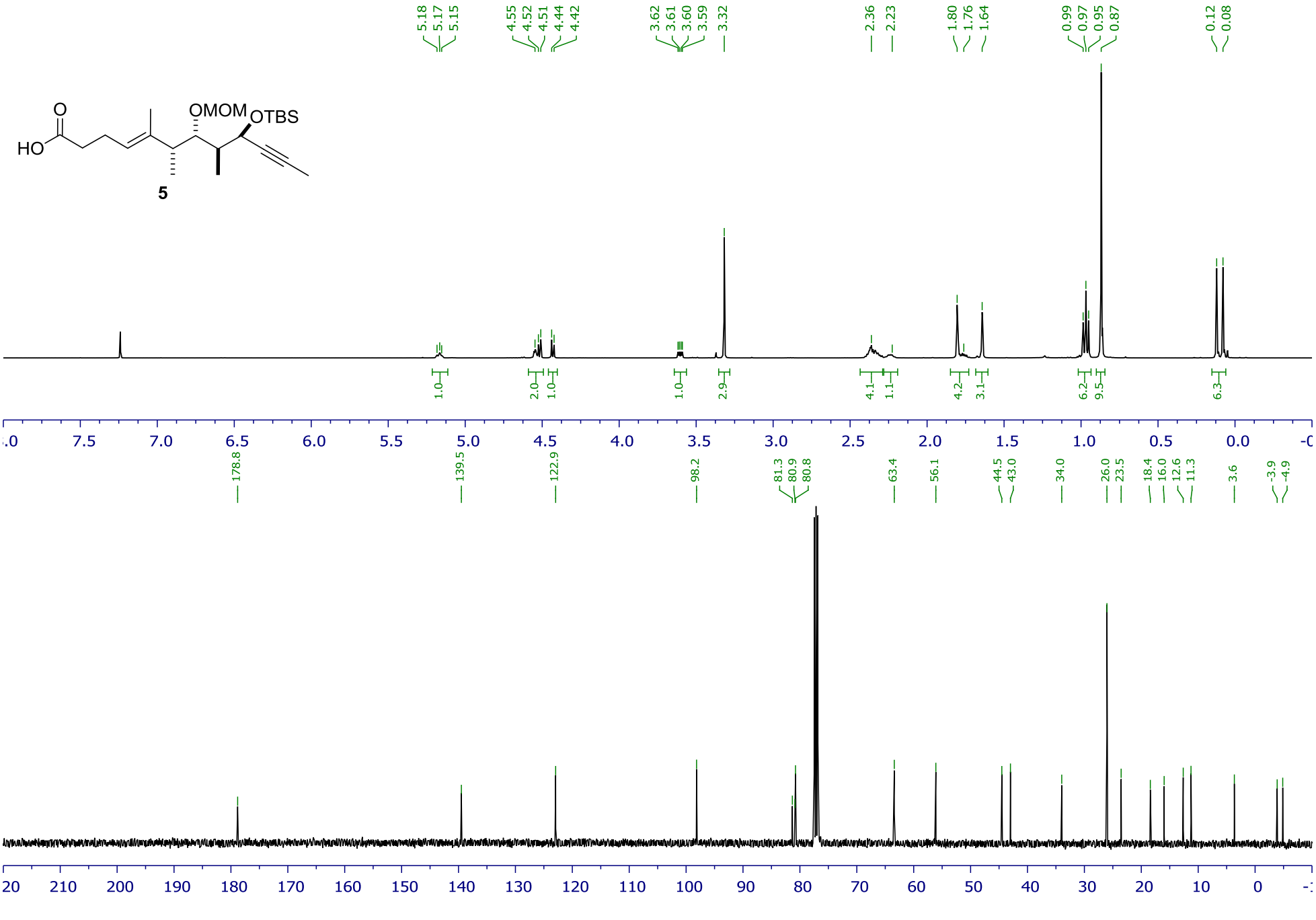
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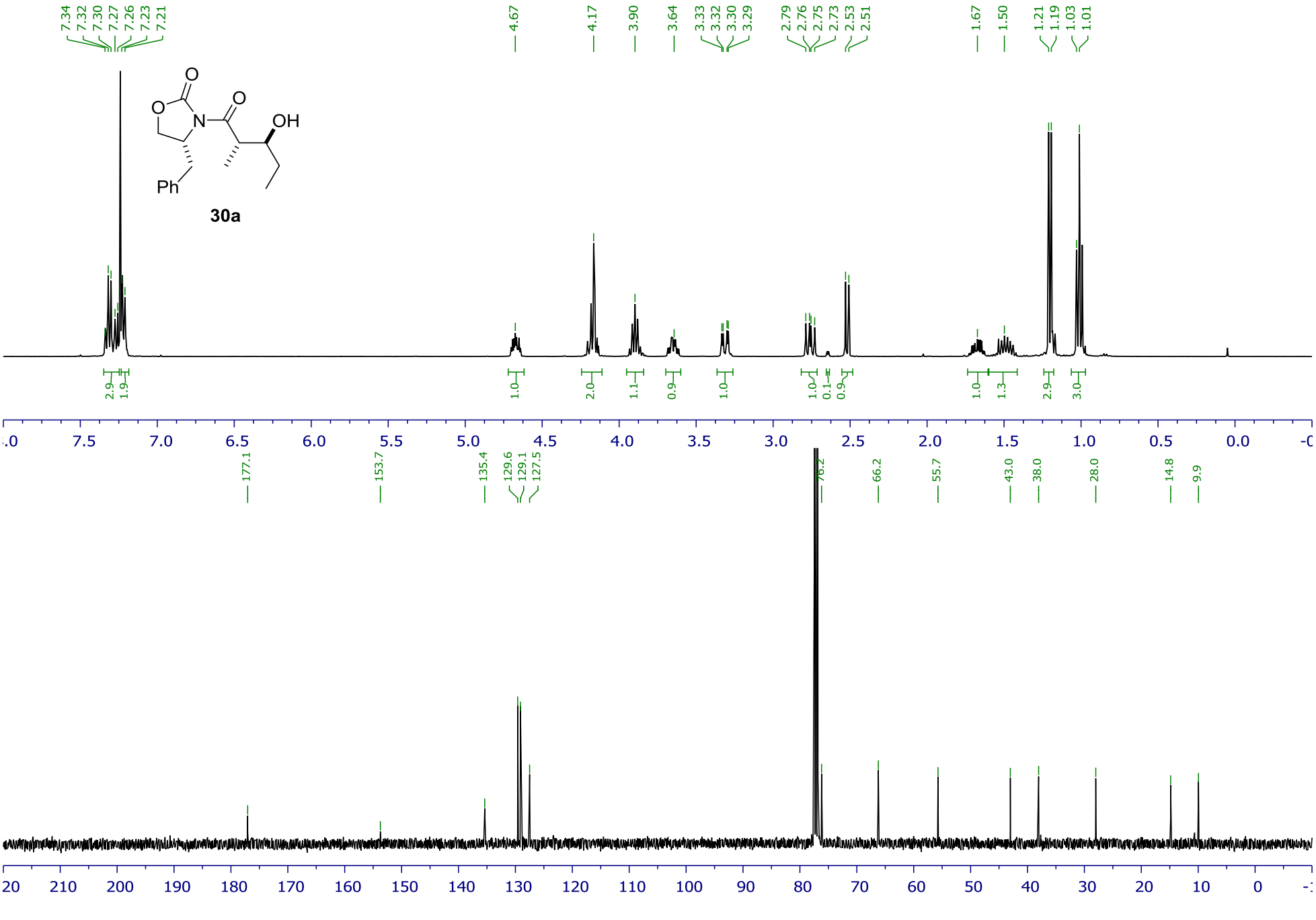
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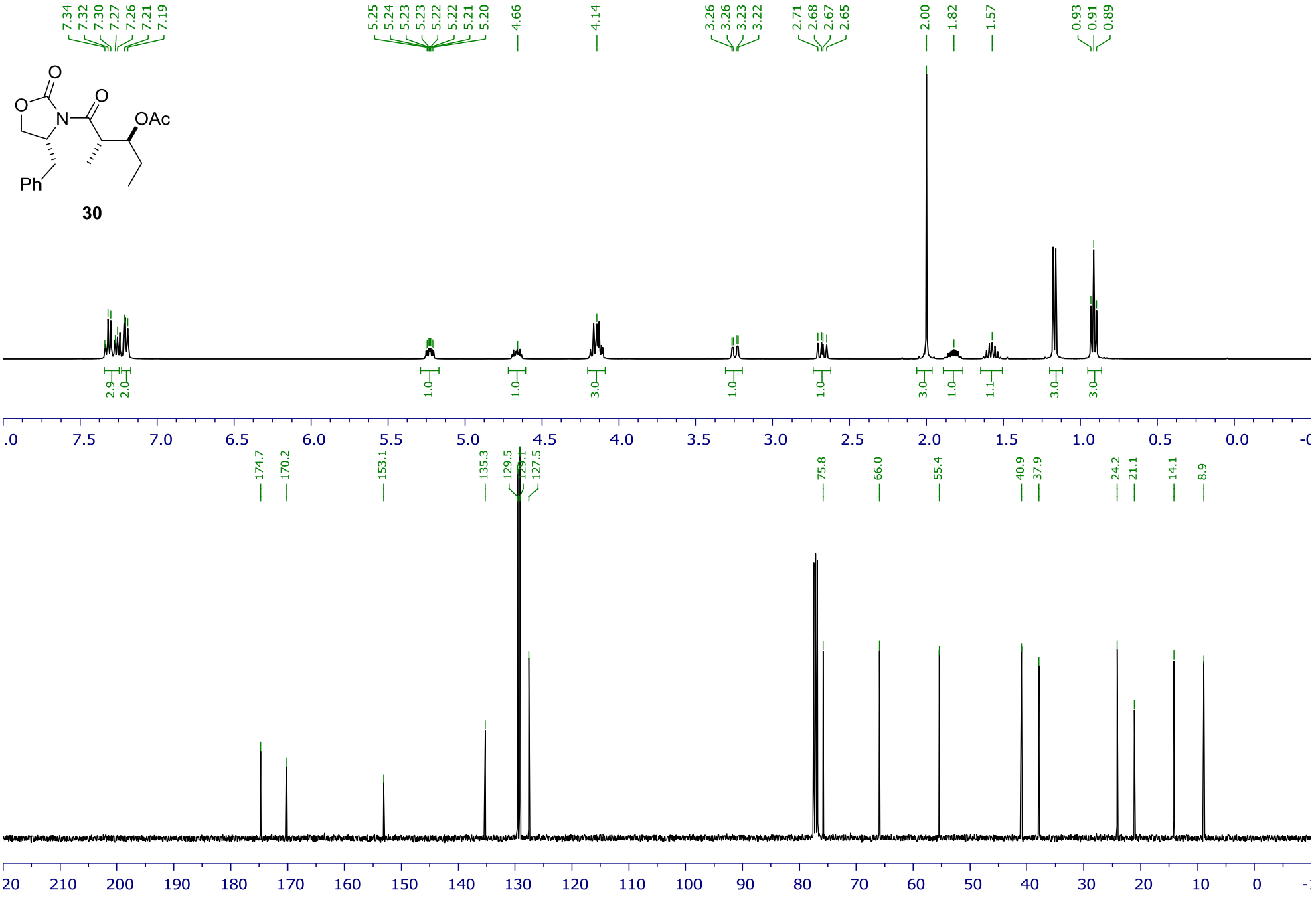
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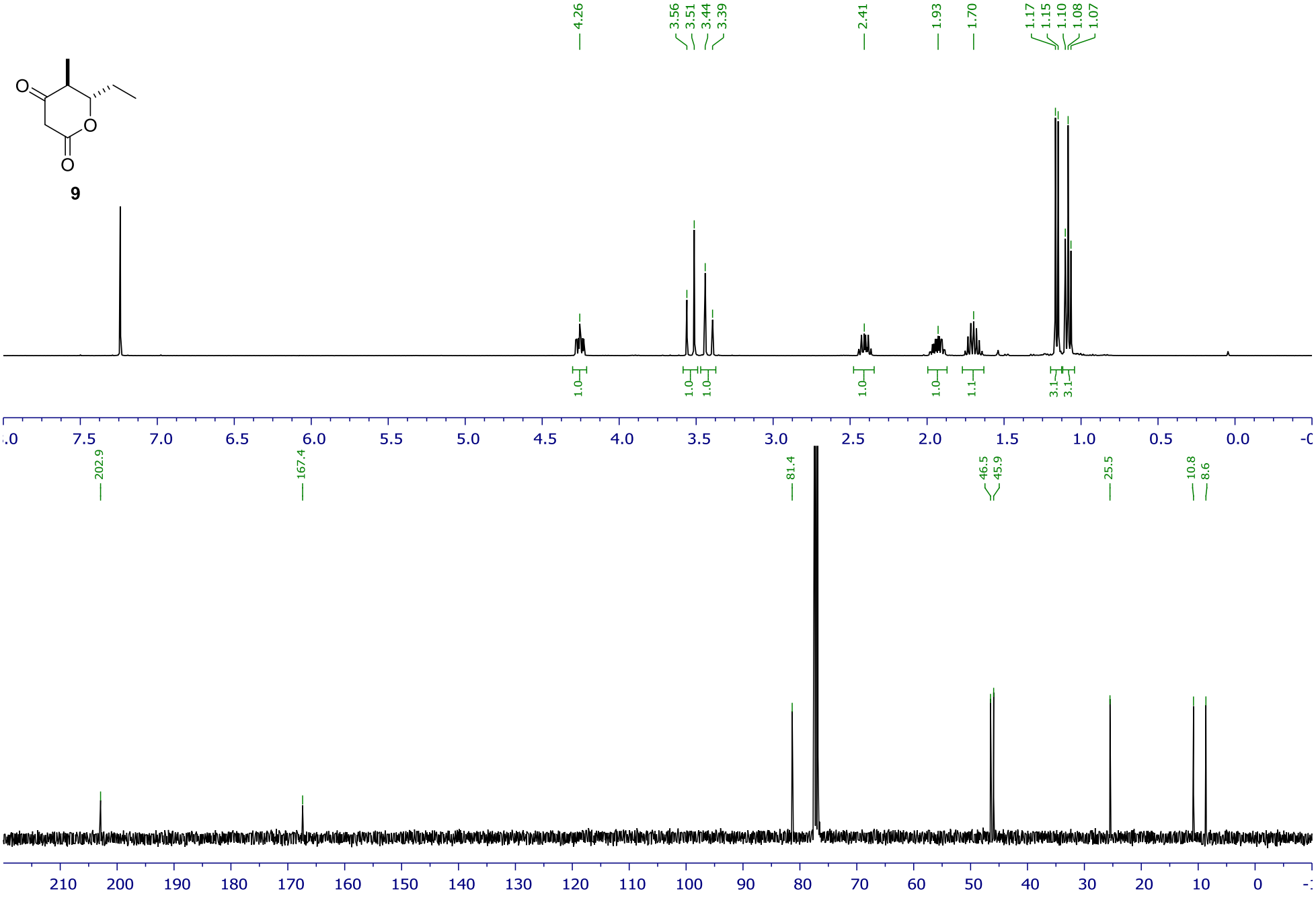
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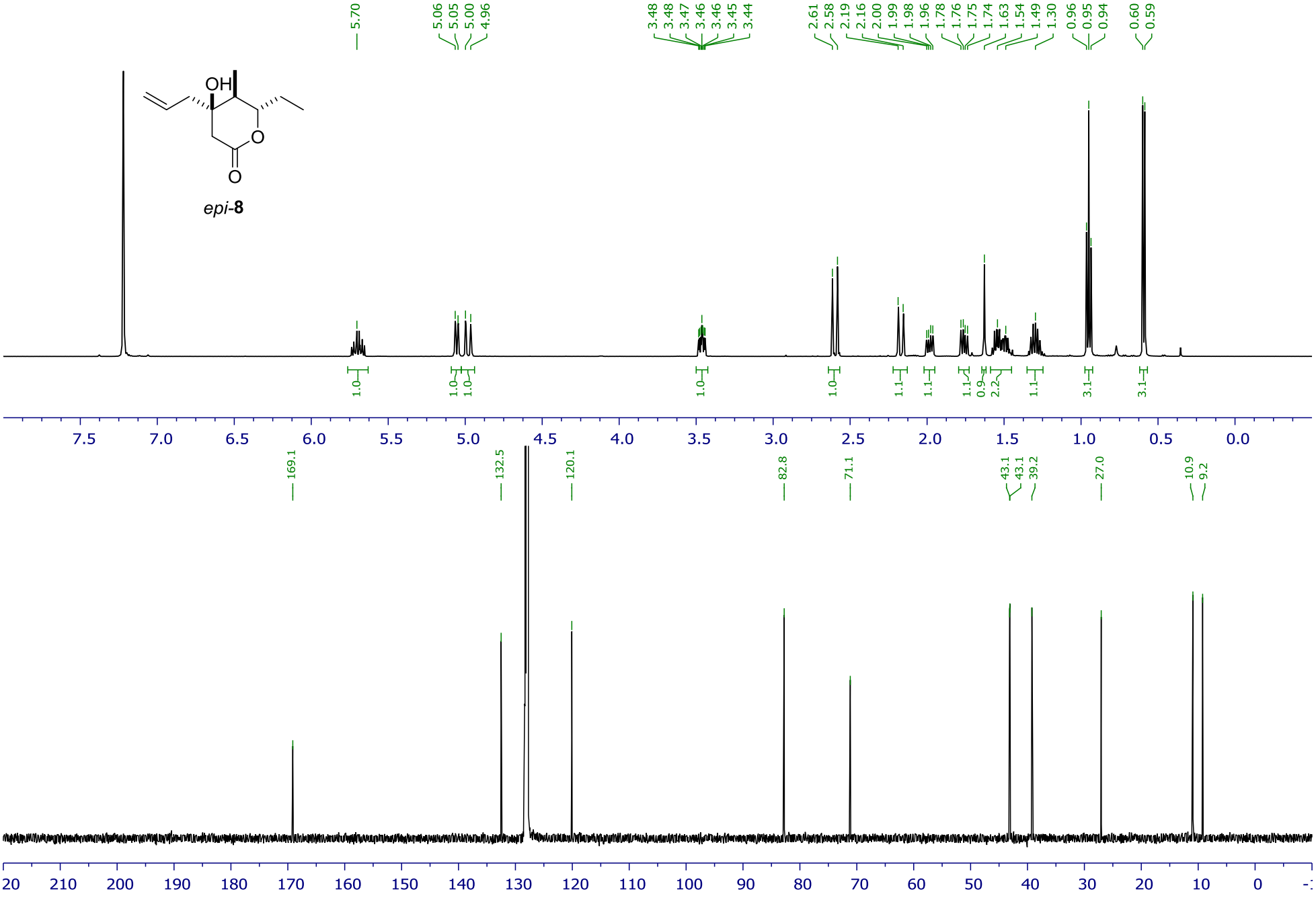
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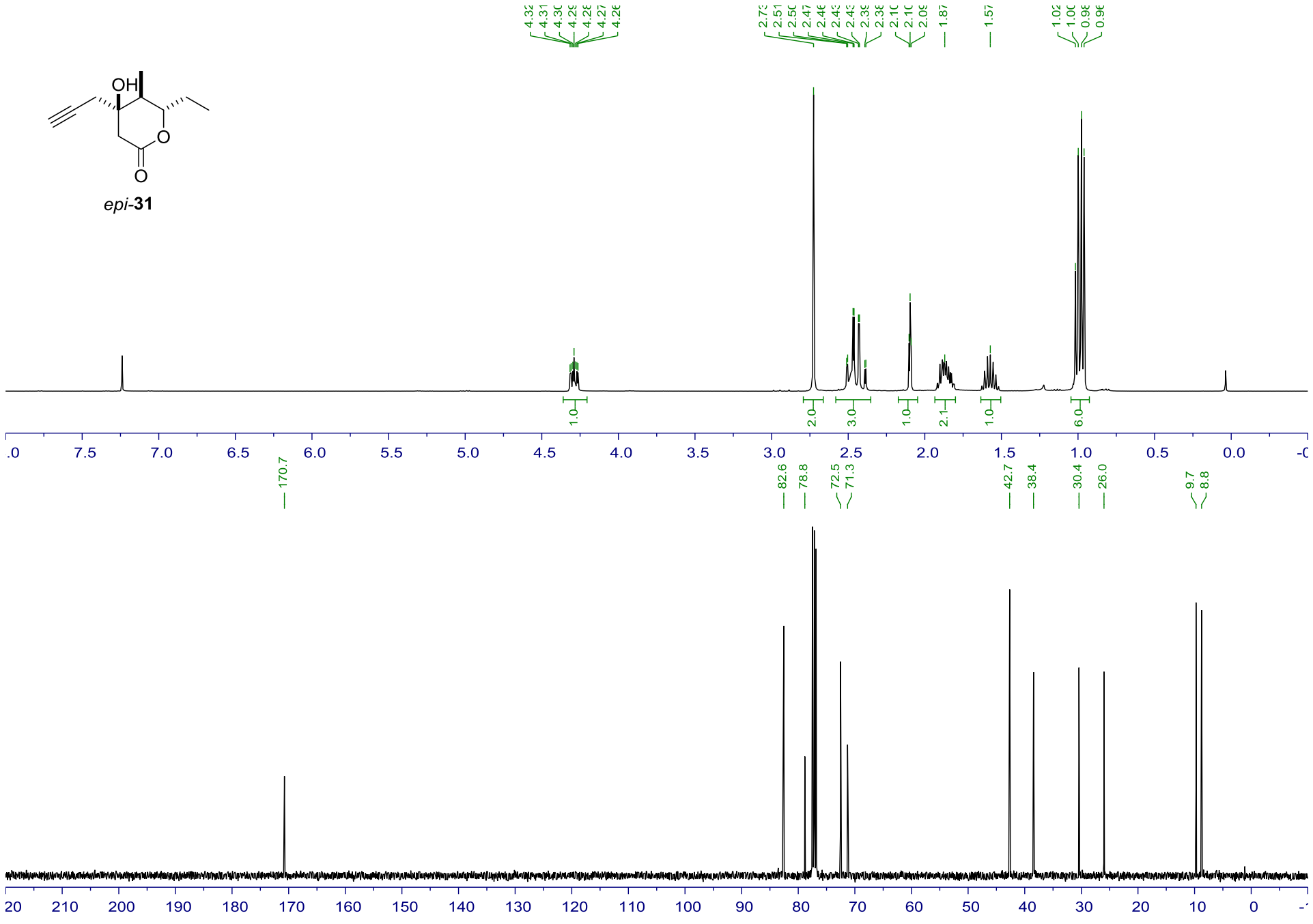
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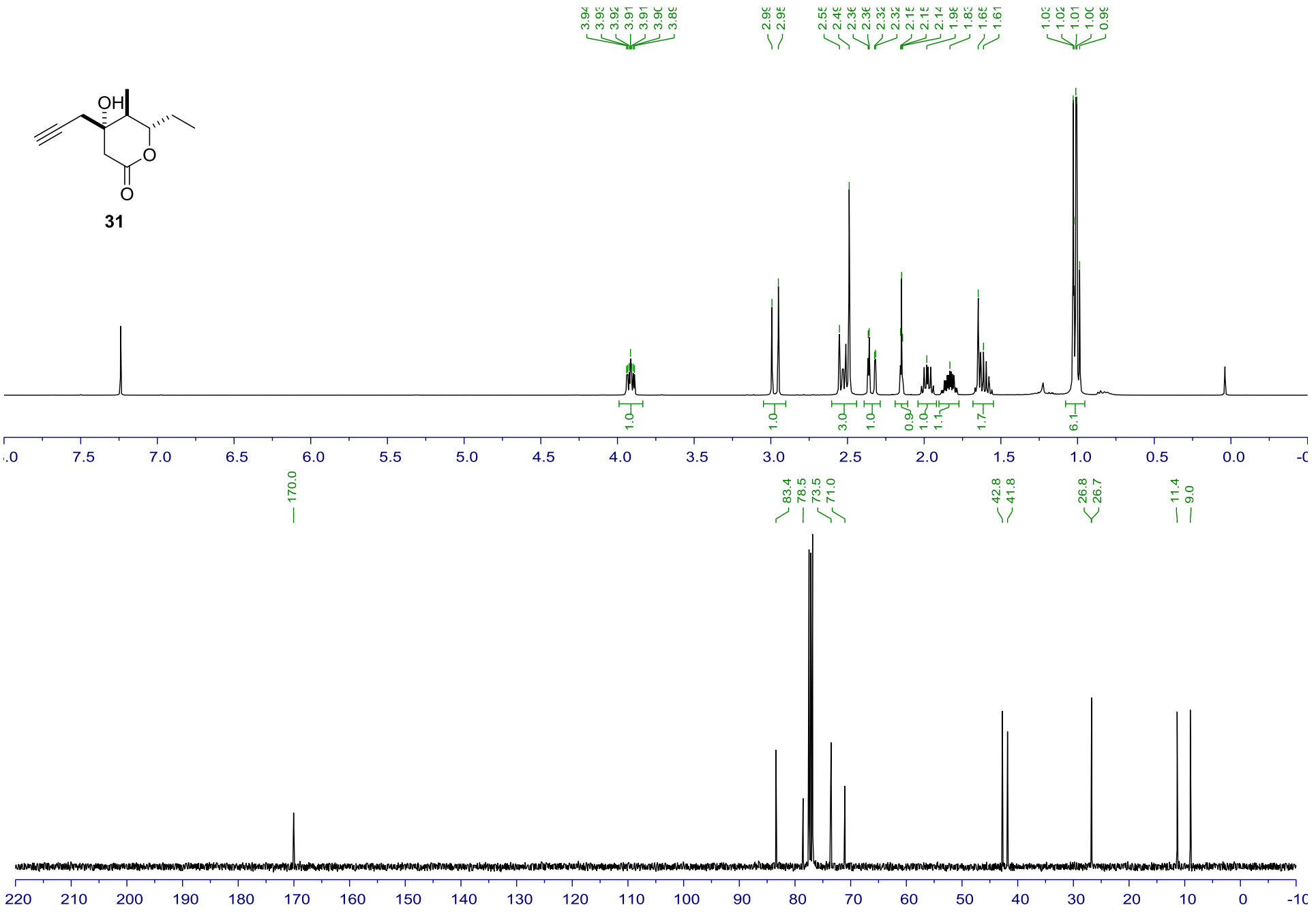
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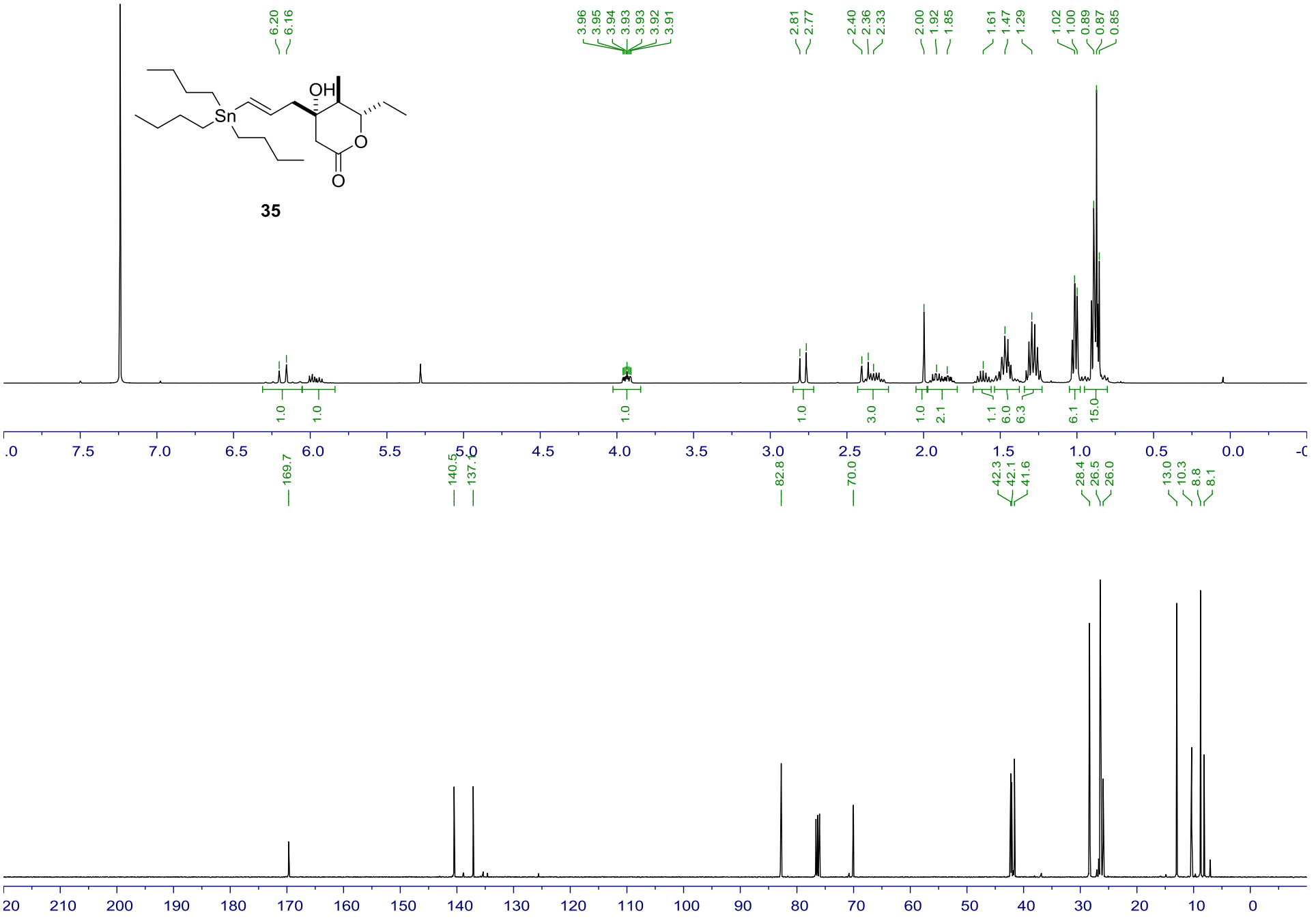
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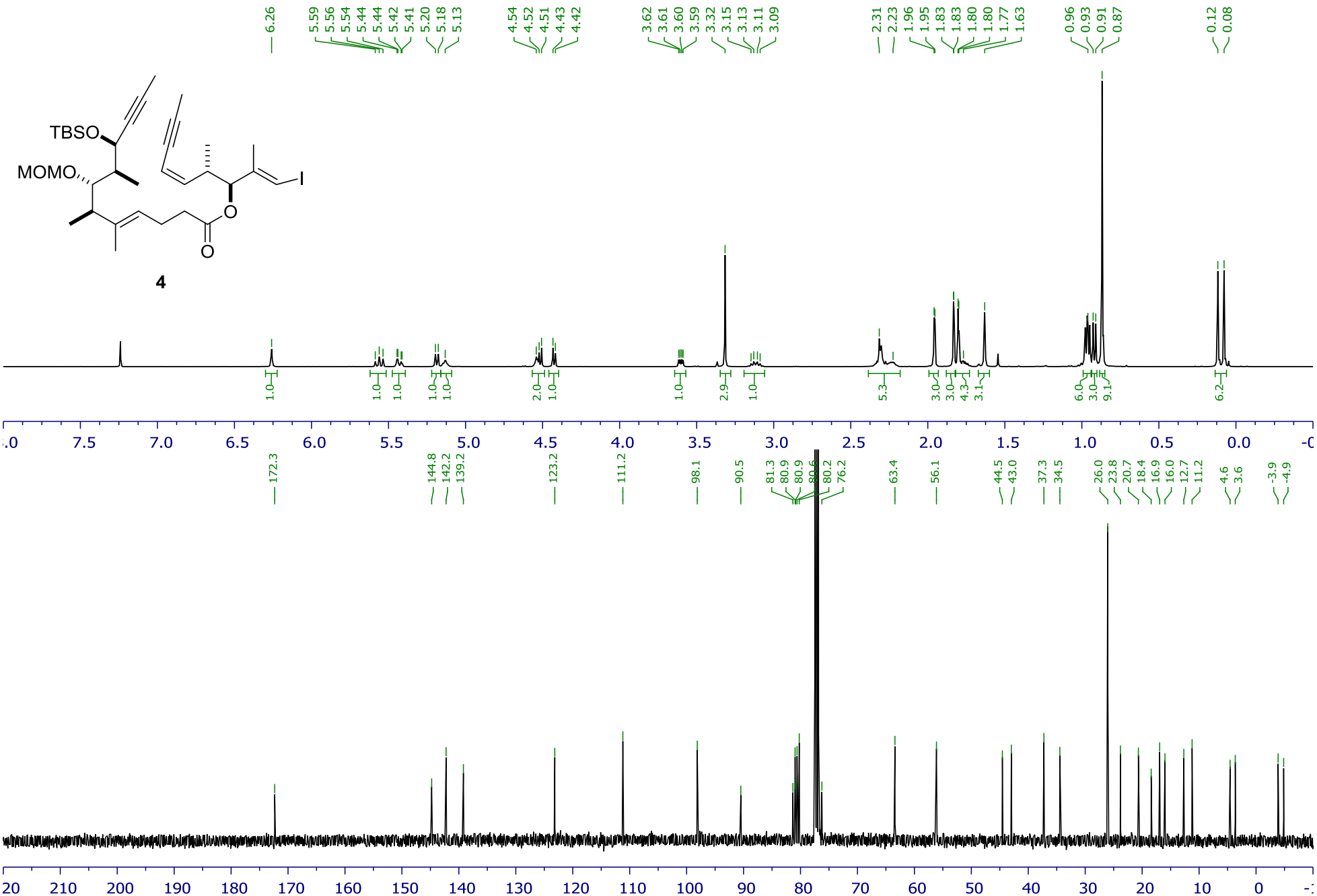
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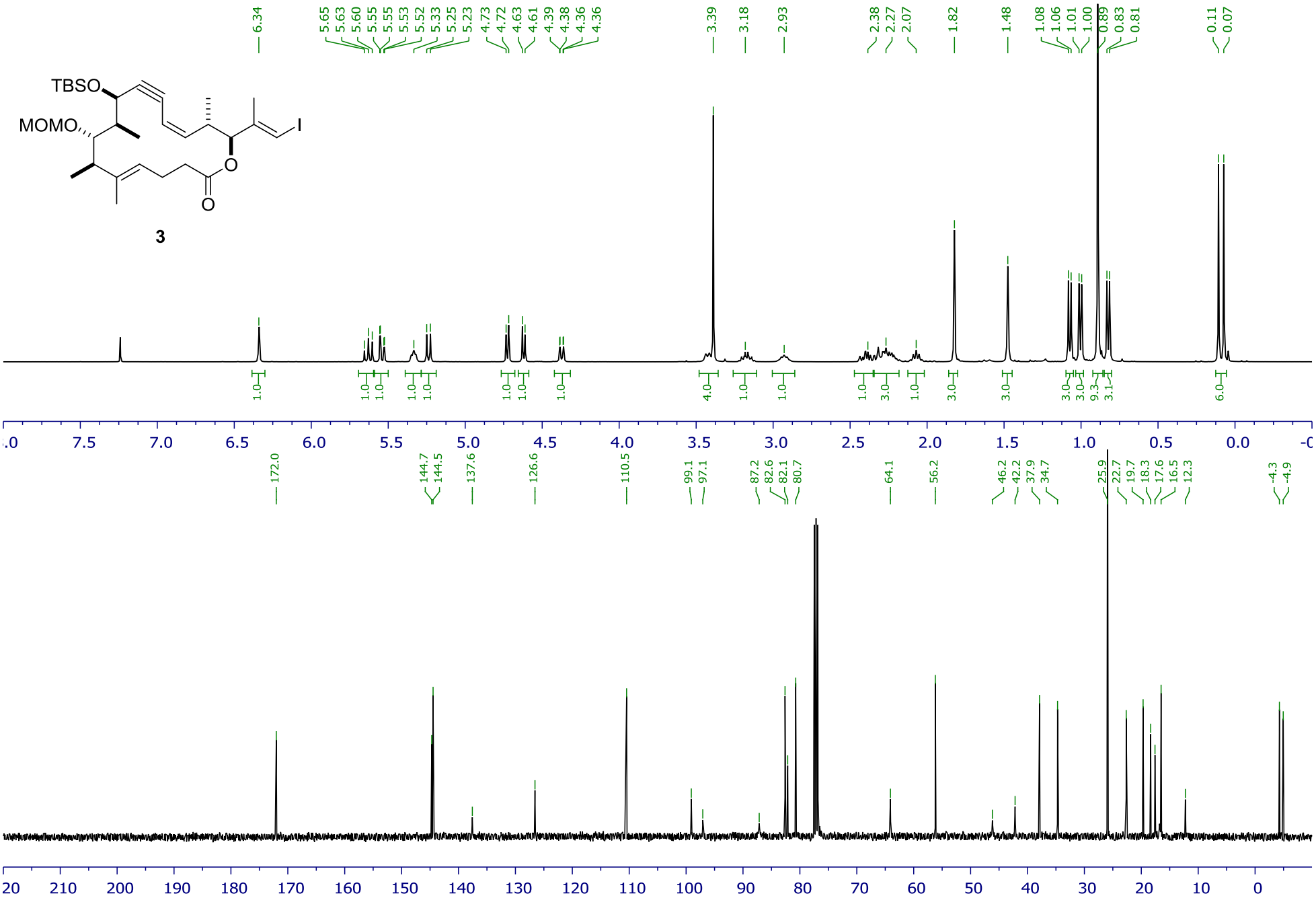
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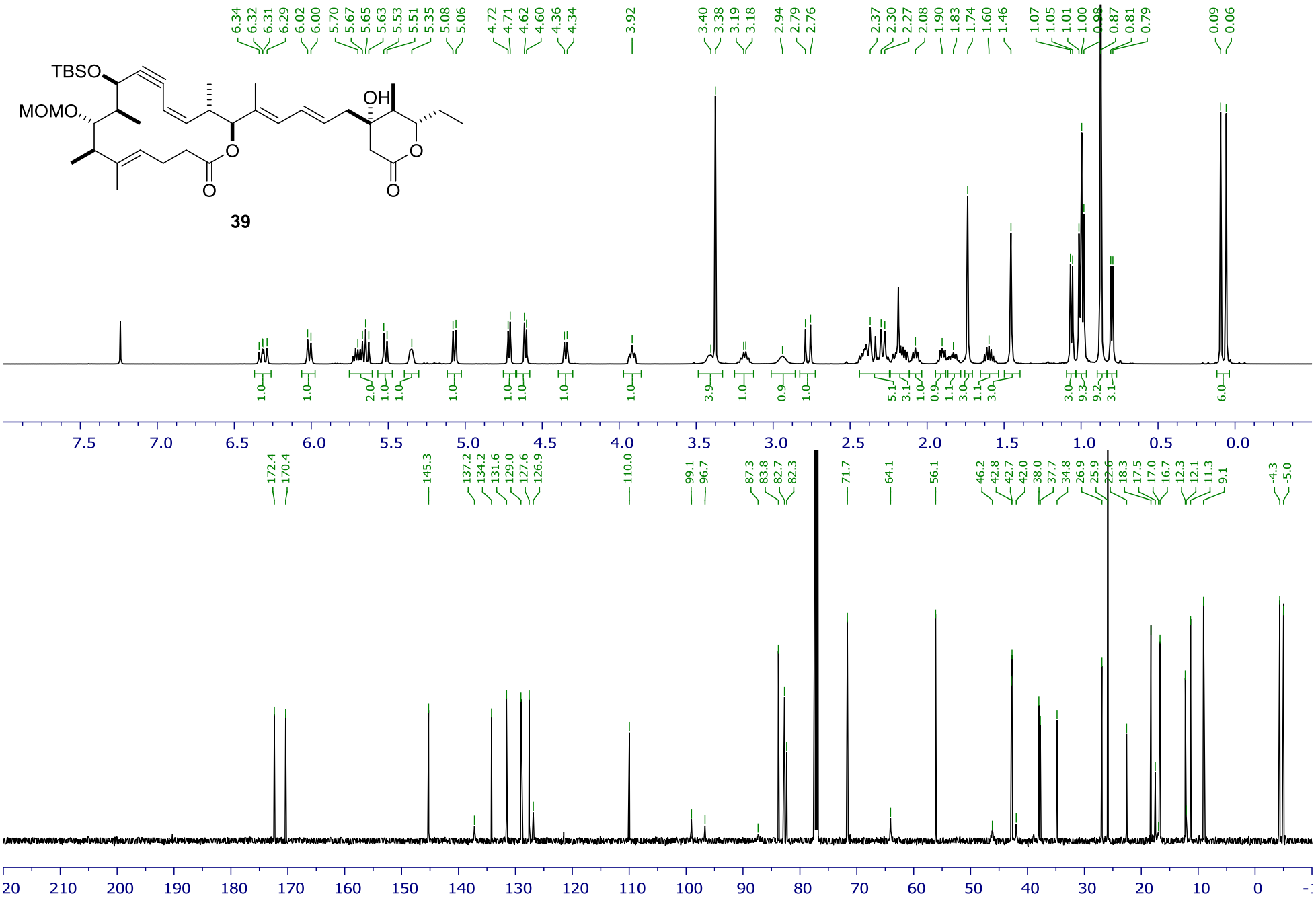
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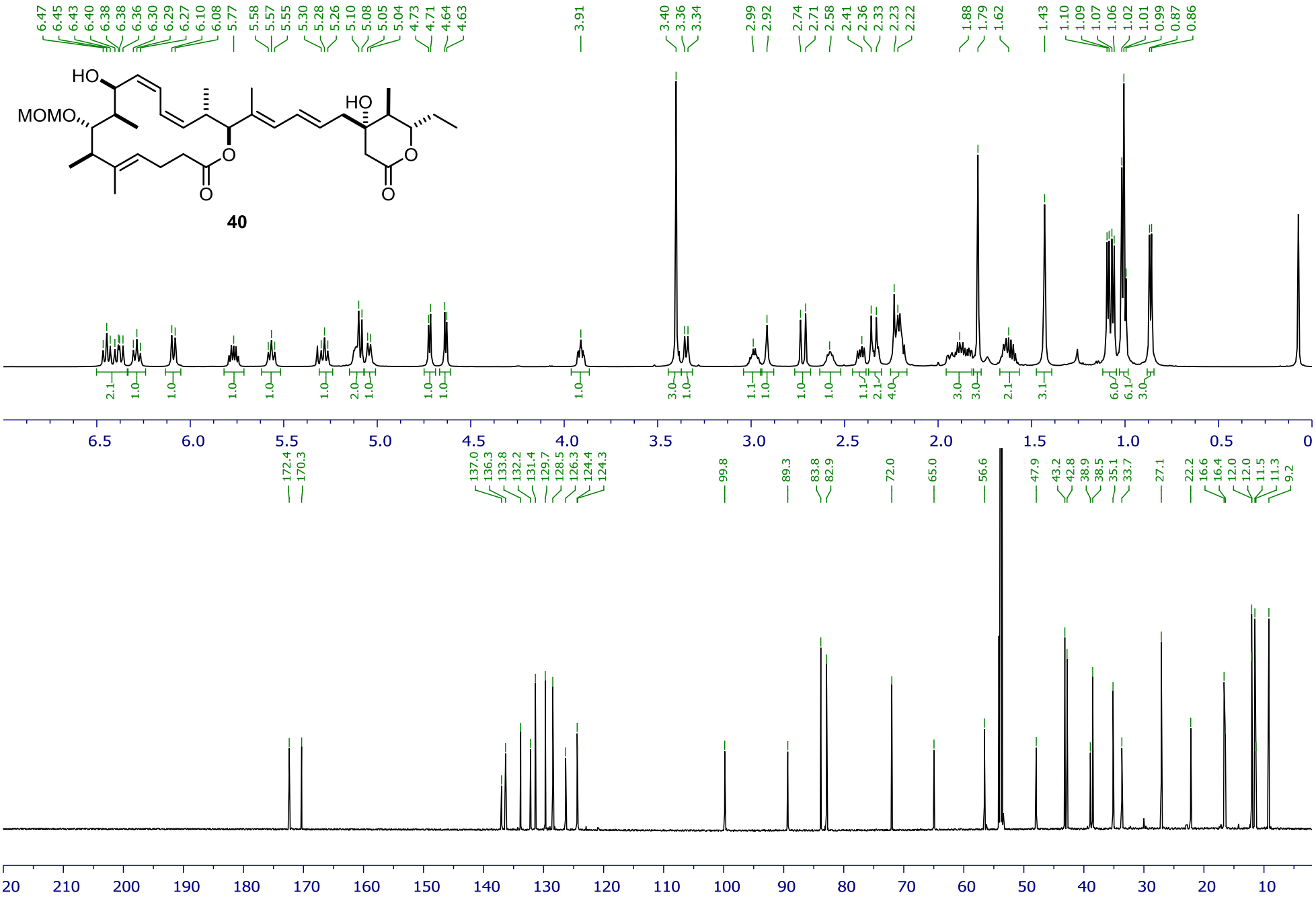

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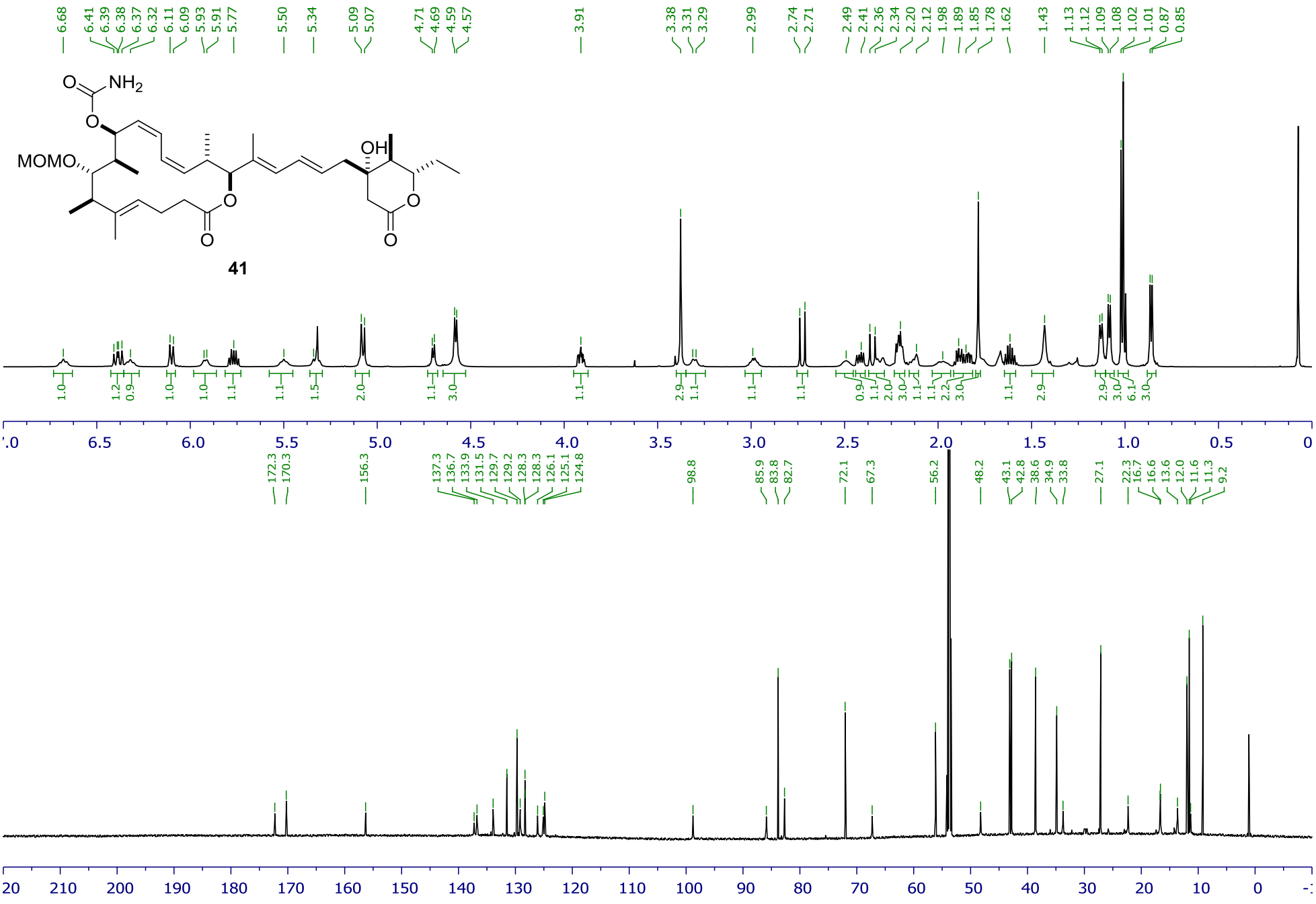
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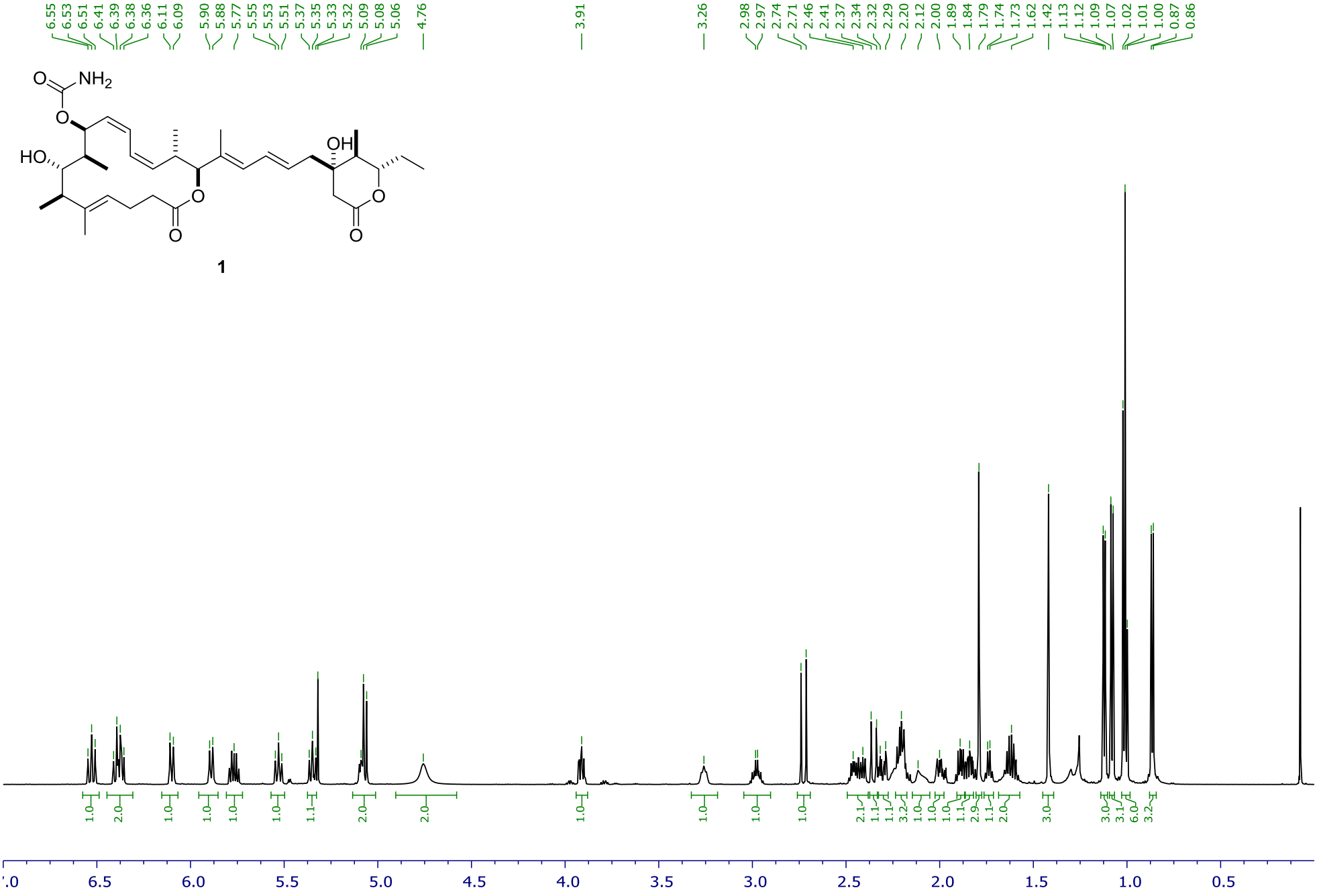
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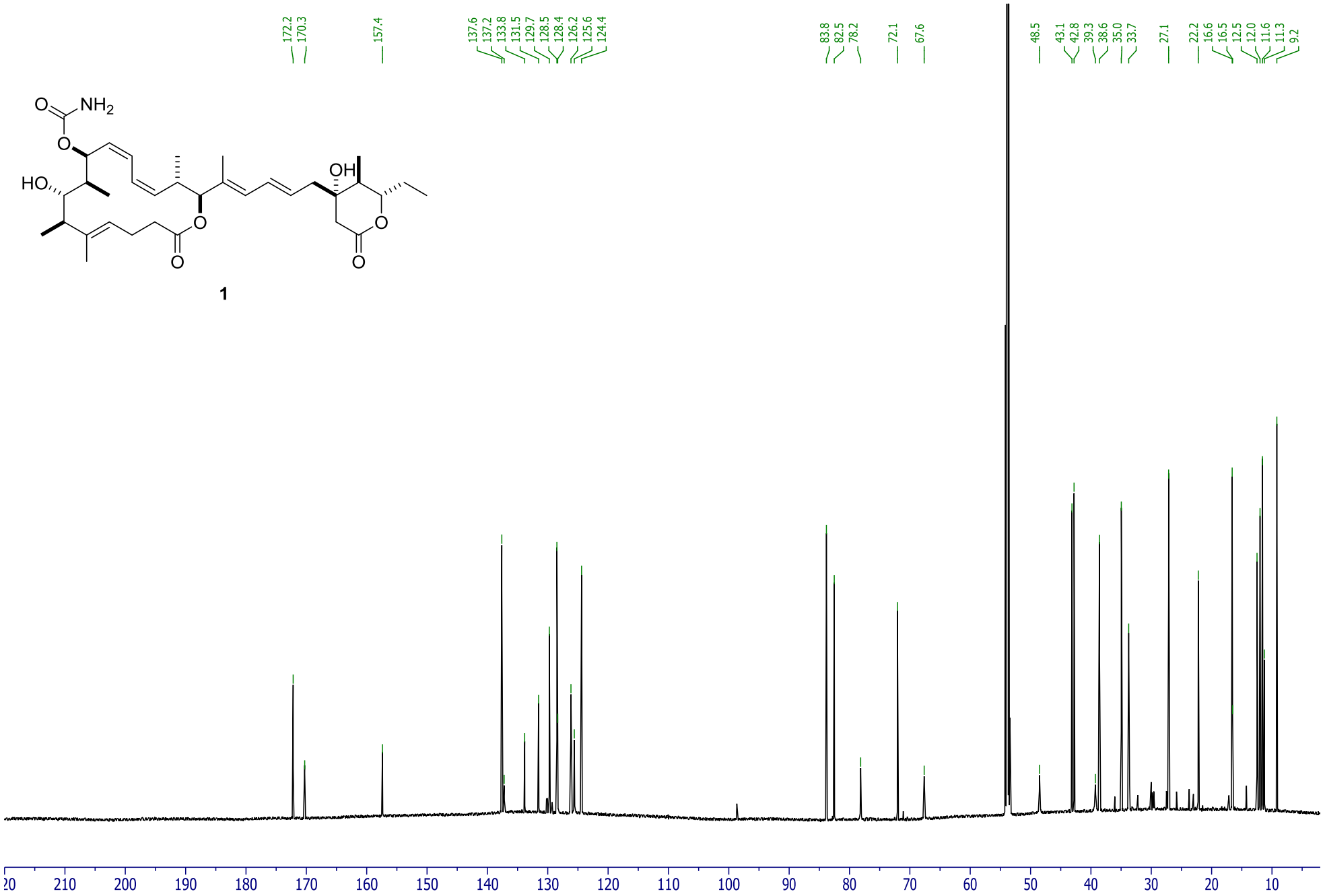
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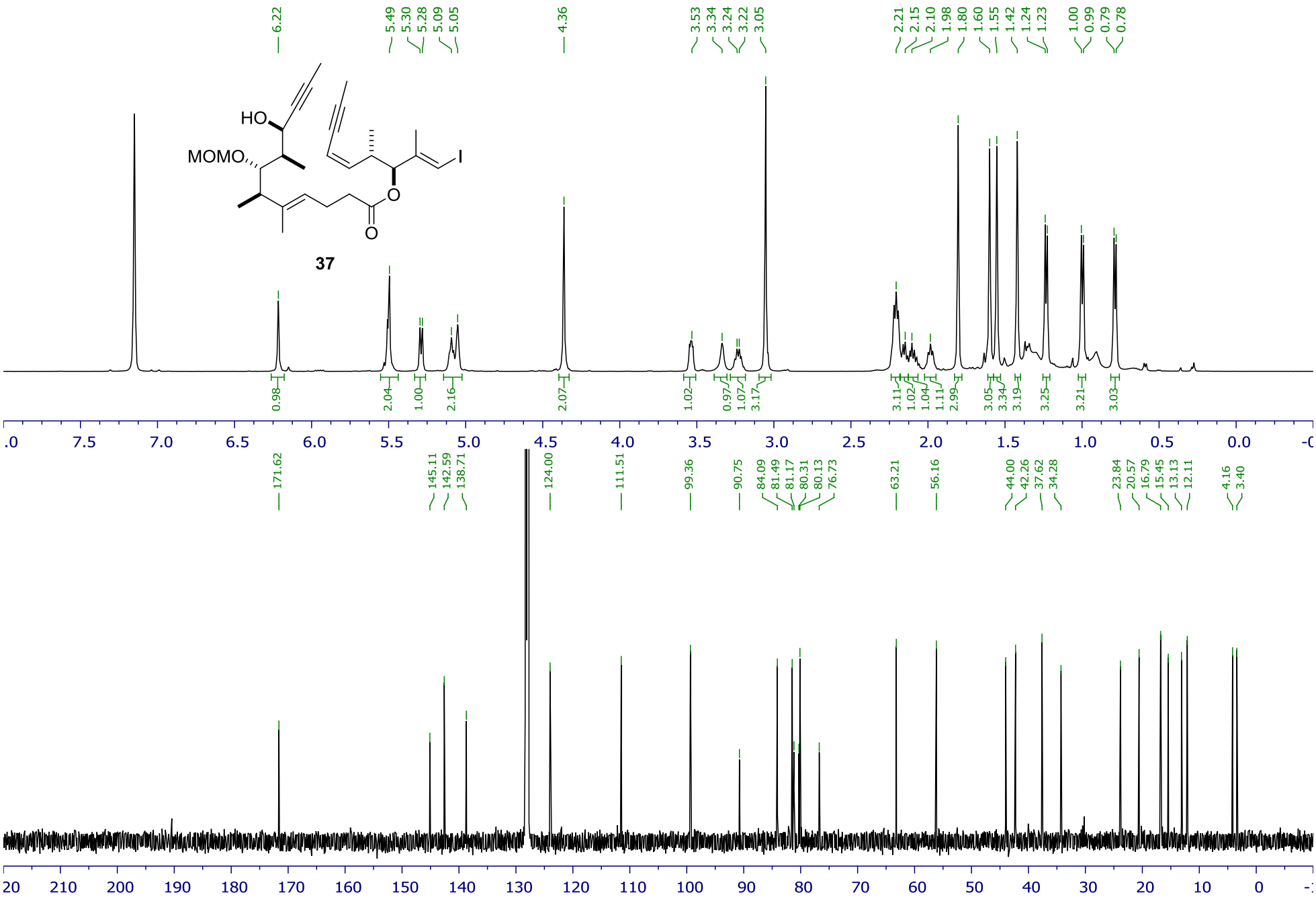
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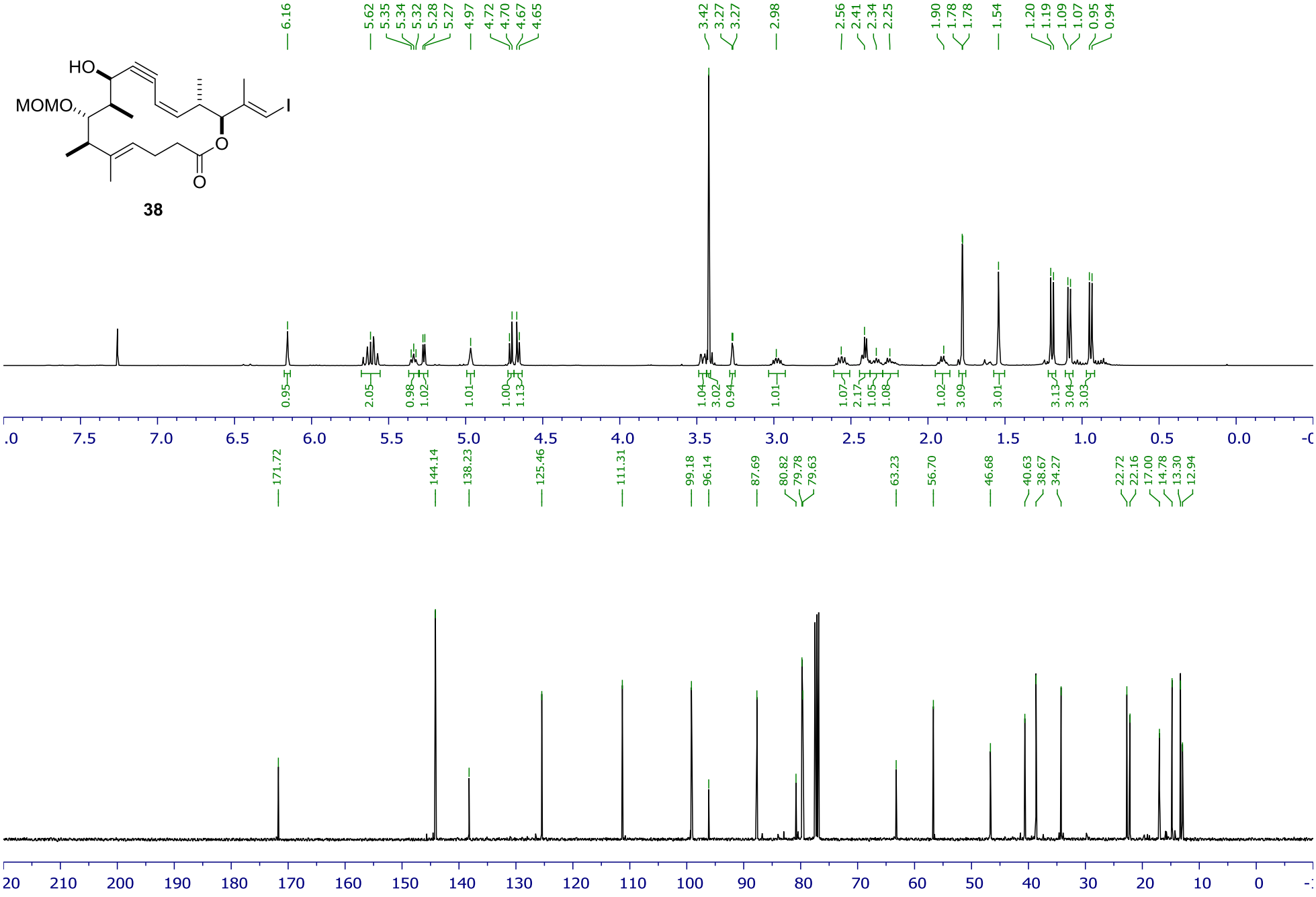
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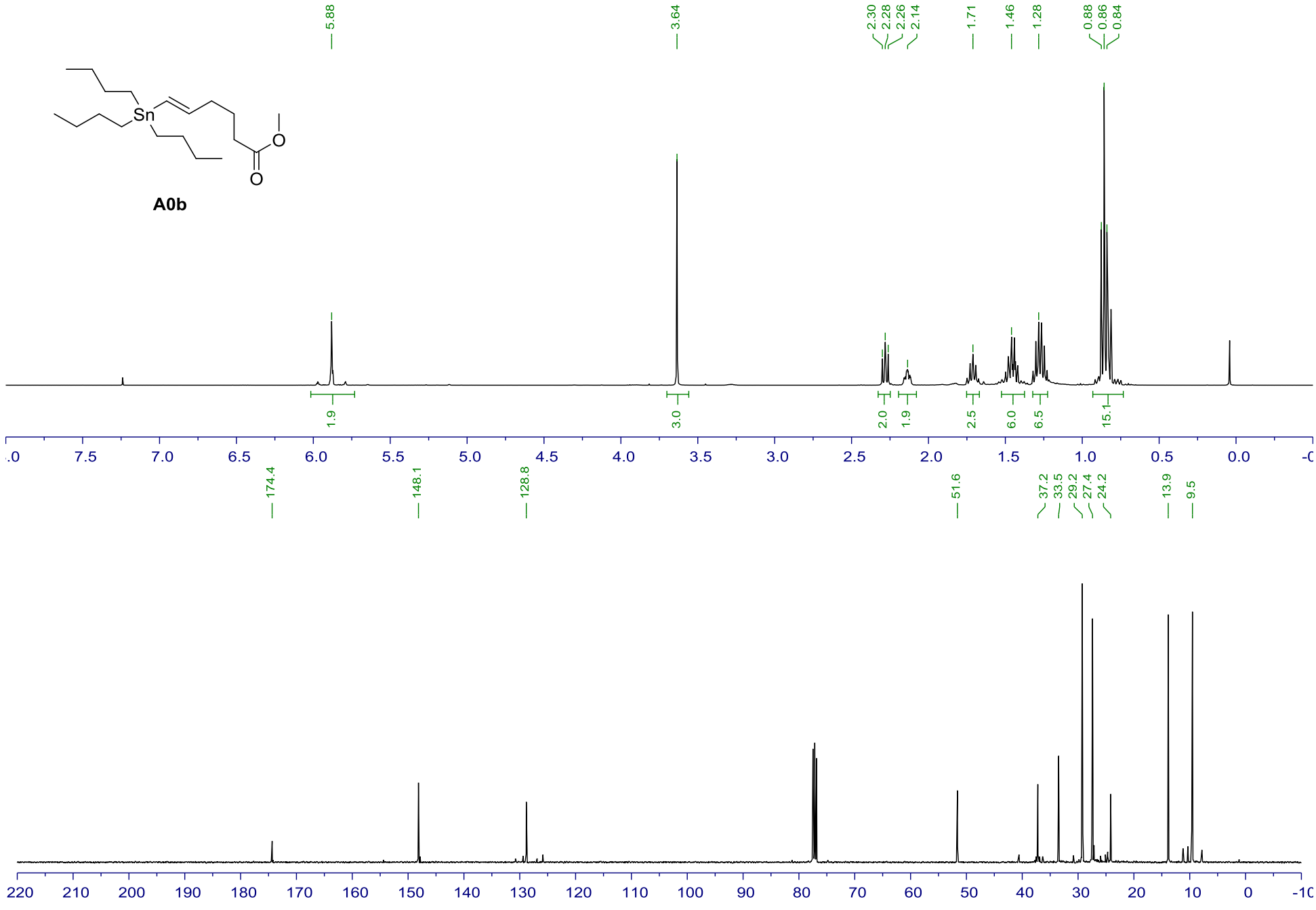
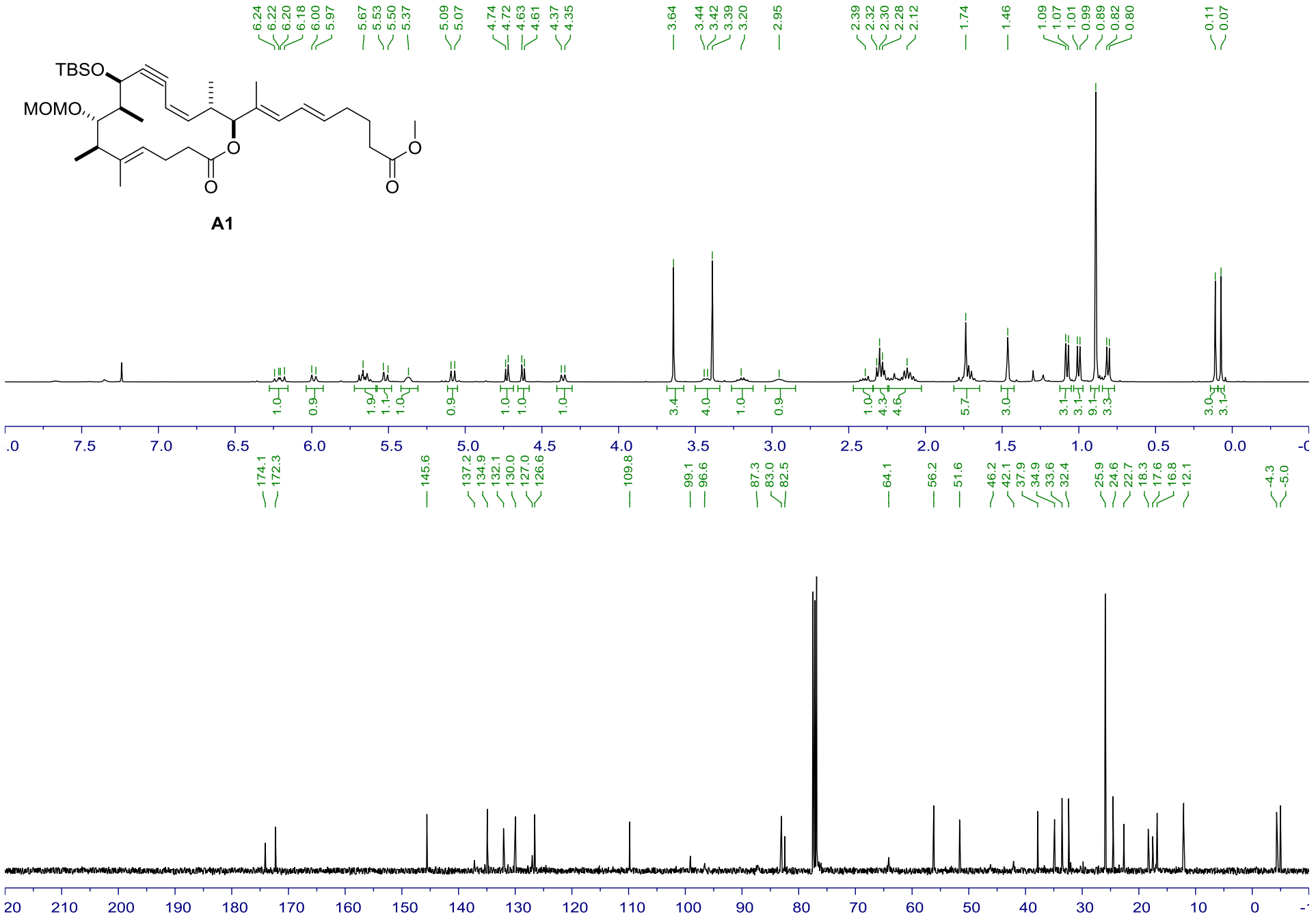
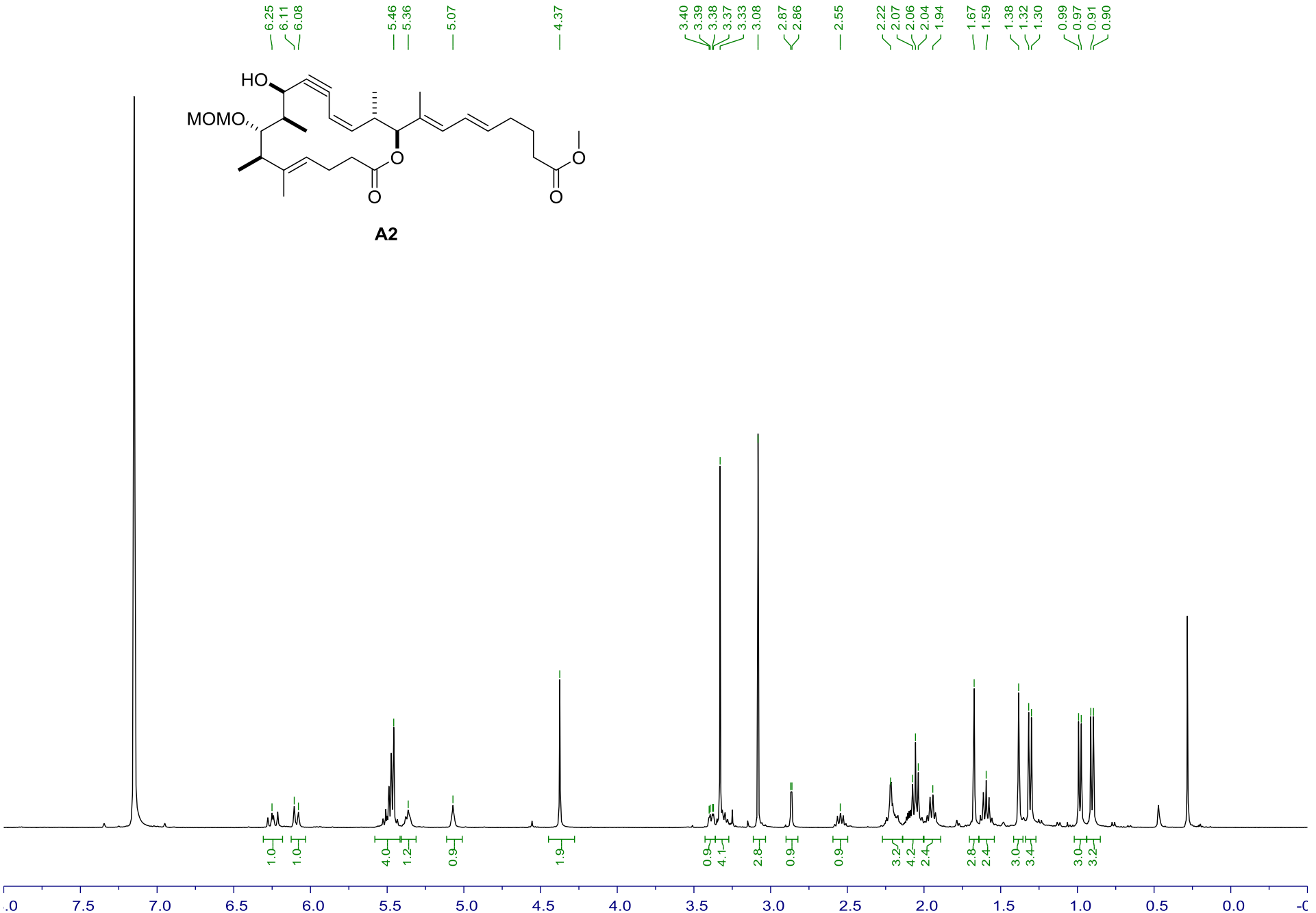
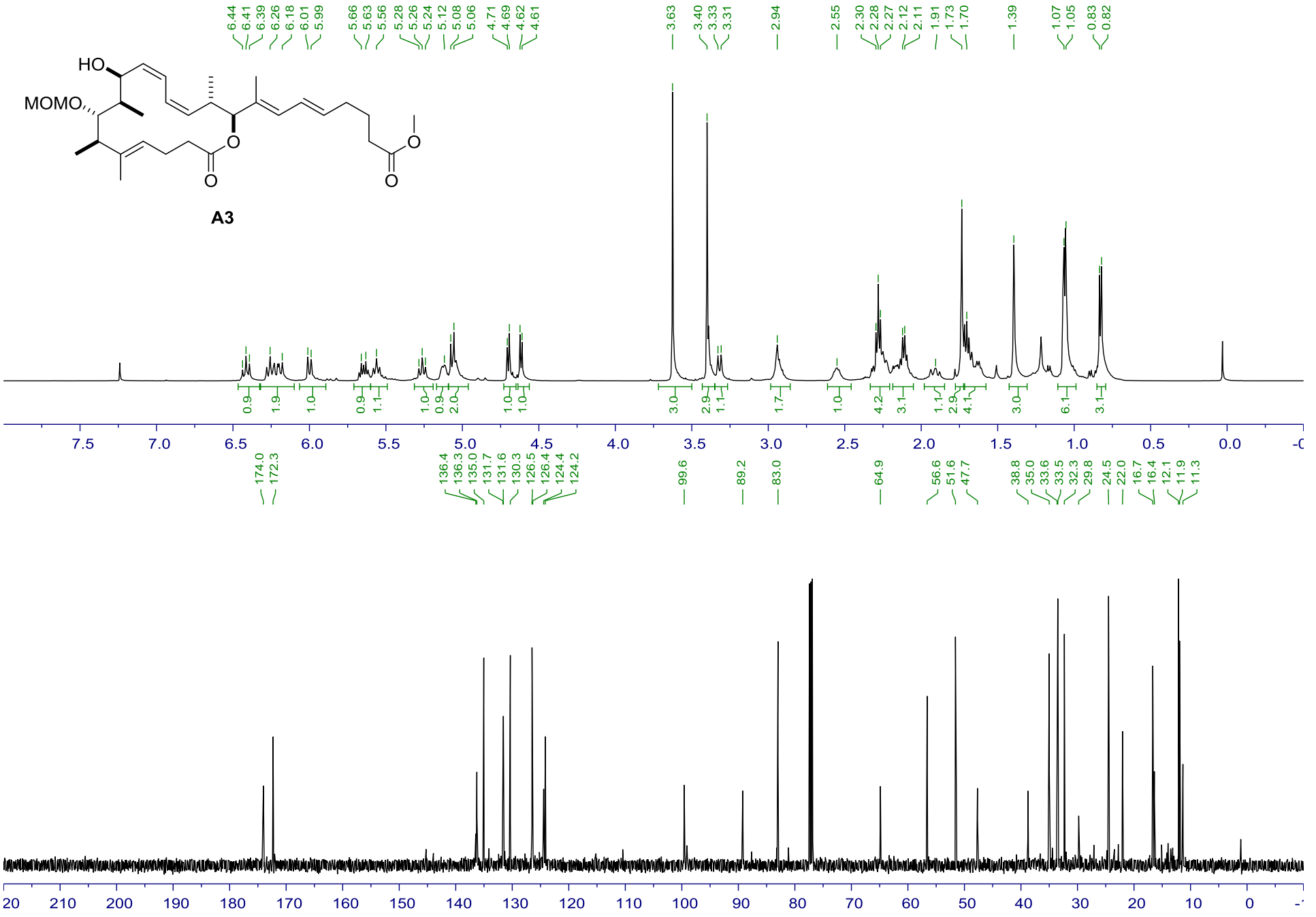
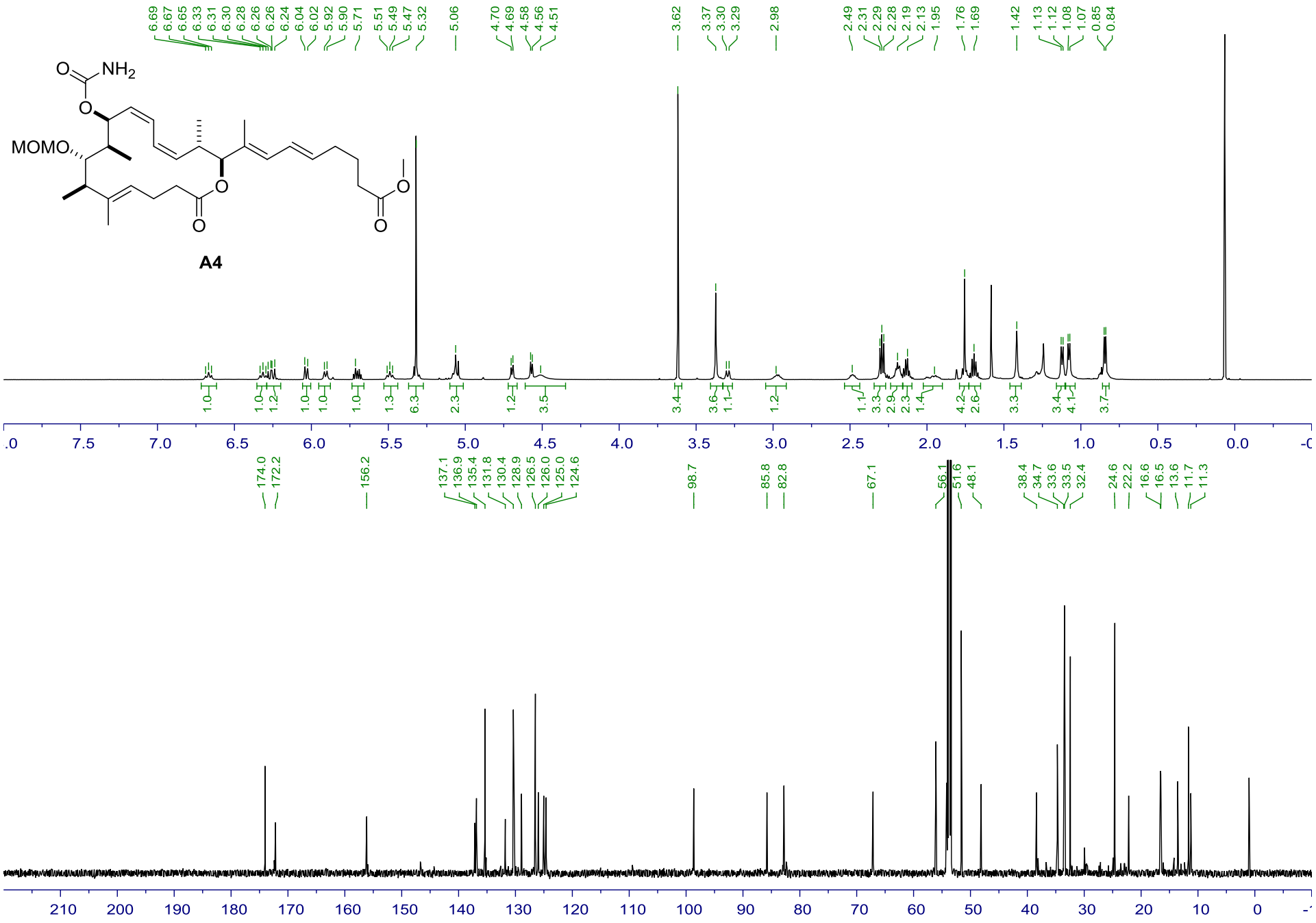
13.30
12.94

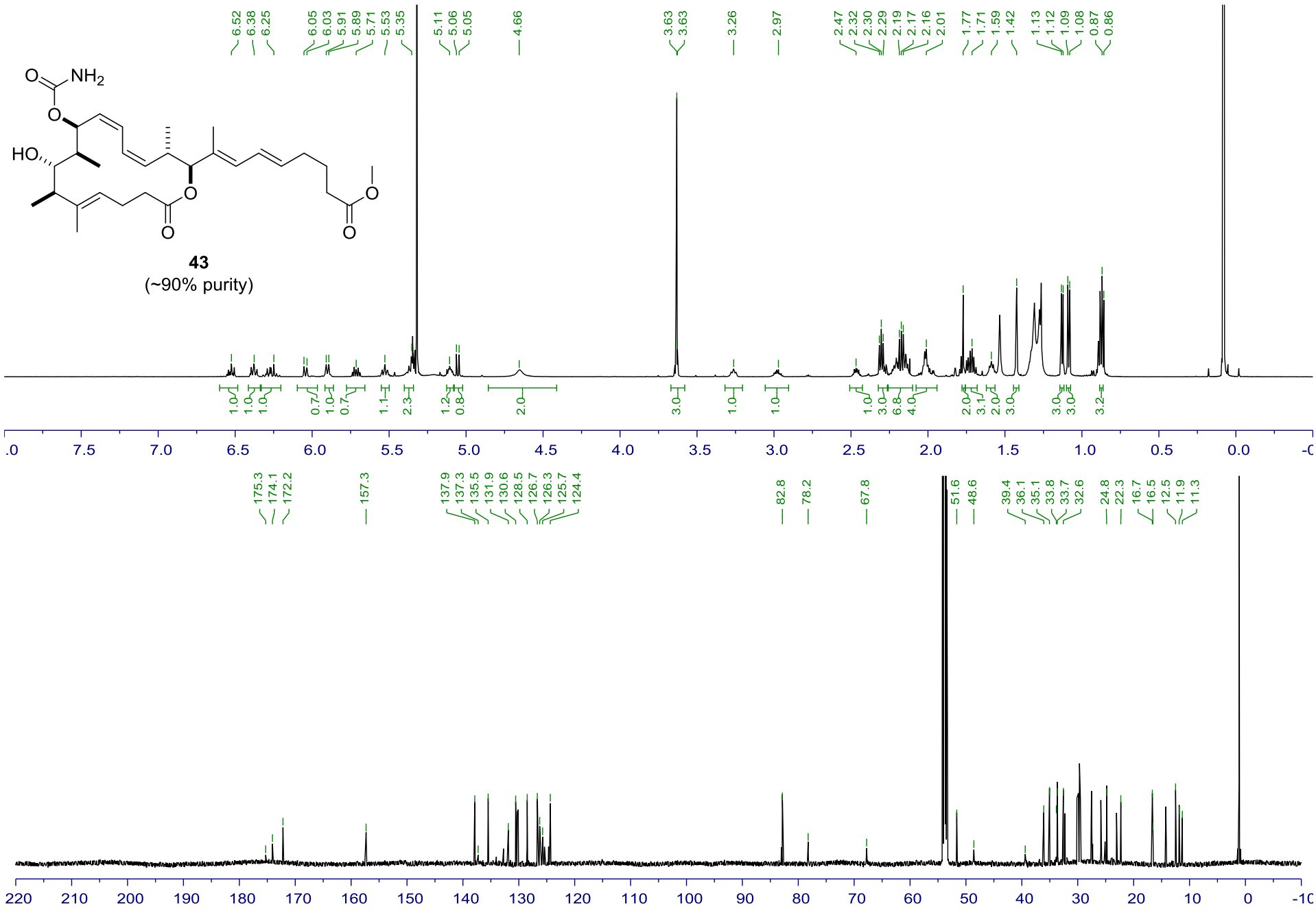

Sn
O
O
A0b
5.88
3.64
2.30
2.28
2.26
2.14
1.71
1.46
1.28
0.88
0.86
0.84
1.9
3.0
2.0
1.9
2.5
6.0
6.5
15.1
174.4
148.1
128.8
51.6
37.2
33.5
29.2
27.4
24.2
13.9
9.5

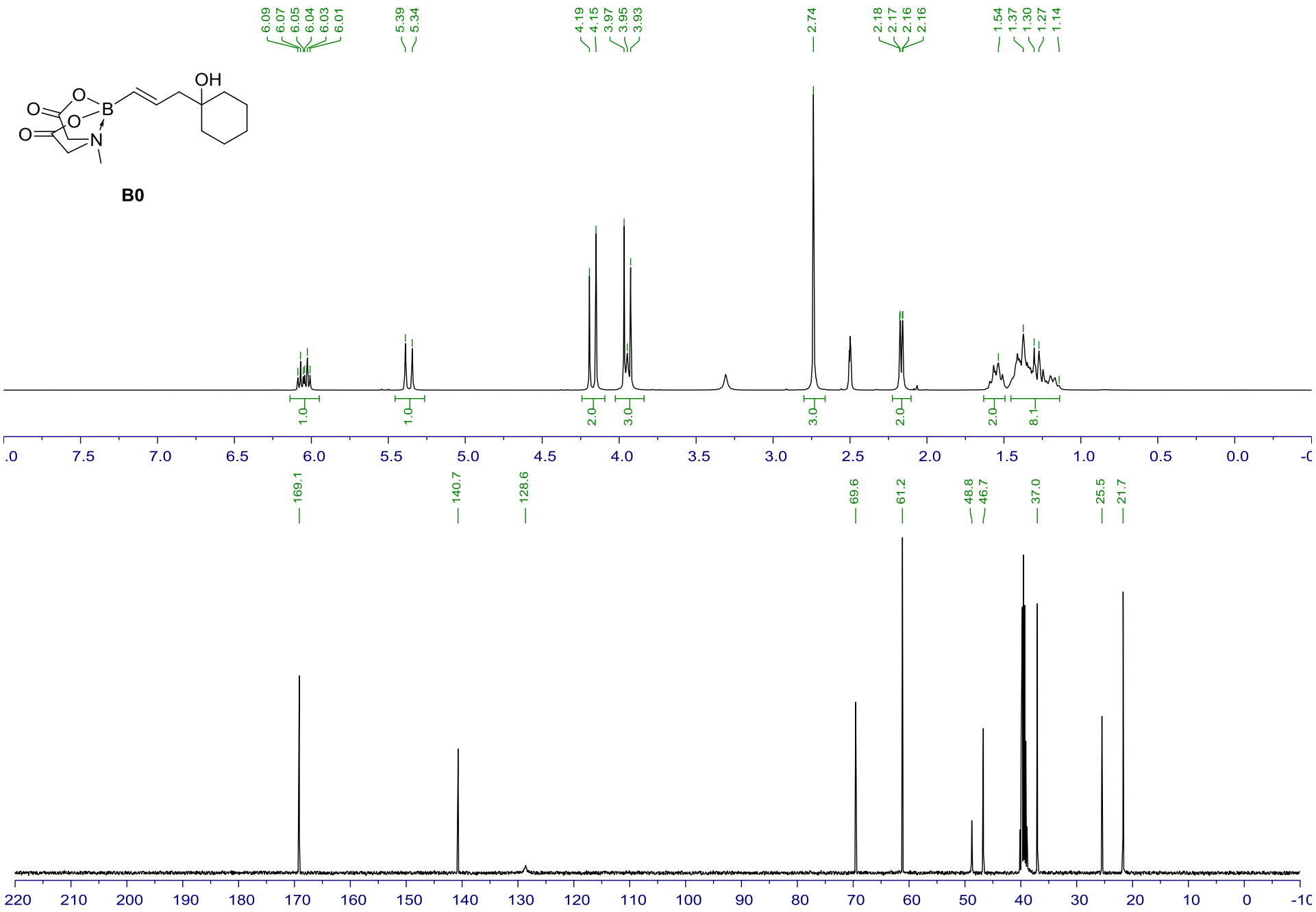

TBSO
MOMO
O
O
O
O
A1
6.24
6.22
6.20
6.18
6.00
5.97
5.67
5.53
5.50
5.37
5.09
5.07
4.74
4.72
4.63
4.61
4.37
4.35
3.64
3.44
3.42
3.39
3.20
2.95
2.39
2.32
2.30
2.28
2.12
1.74
1.46
1.09
1.07
1.01
0.99
0.89
0.82
0.80
0.11
0.07
1.0
0.9
1.9
1.1
1.0
0.9
1.0
1.0
1.0
3.4
4.0
1.0
0.9
1.0
4.3
4.6
5.7
3.0
3.1
3.1
9.1
3.3
3.0
3.1
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
174.1
172.3
145.6
137.2
134.9
132.1
130.0
127.0
126.6
109.8
99.1
96.6
87.3
83.0
82.5
64.1
56.2
51.6
46.2
42.1
37.9
34.9
33.6
32.4
25.9
24.6
22.7
18.3
17.6
16.8
12.1
-4.3
-5.0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

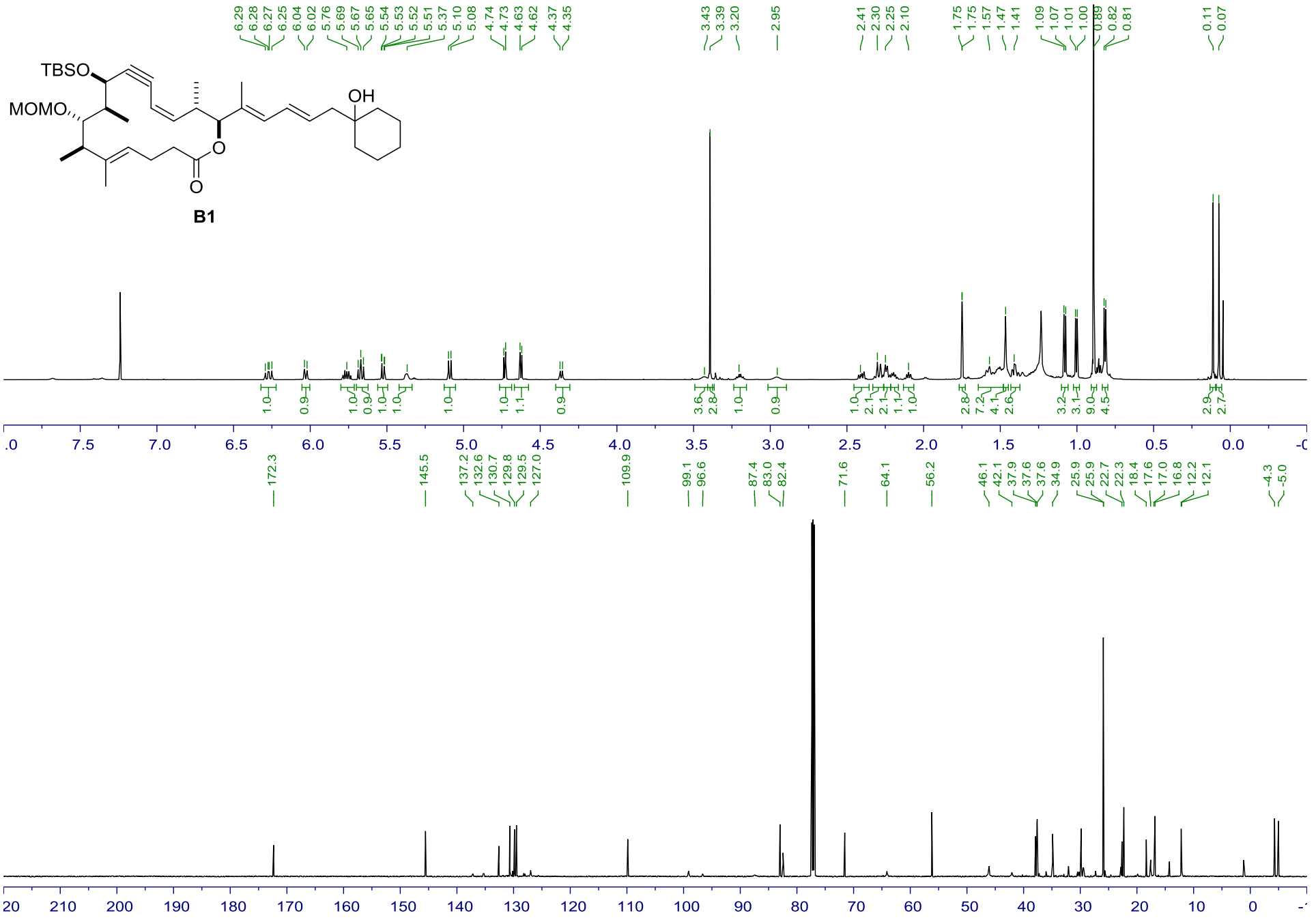

6.25
6.11
6.08
5.46
5.36
5.07
4.37
3.40
3.39
3.38
3.37
3.33
3.08
2.87
2.86
2.55
2.22
2.07
2.06
2.04
1.94
1.67
1.59
1.38
1.32
1.30
0.99
0.97
0.91
0.90
HO
MOMO
O
O
O
O
A2
1.0
1.0
4.0
1.2
0.9
1.9
0.9
4.1
2.8
0.9
0.9
3.2
4.2
2.4
2.8
2.4
3.0
3.4
3.0
3.2
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

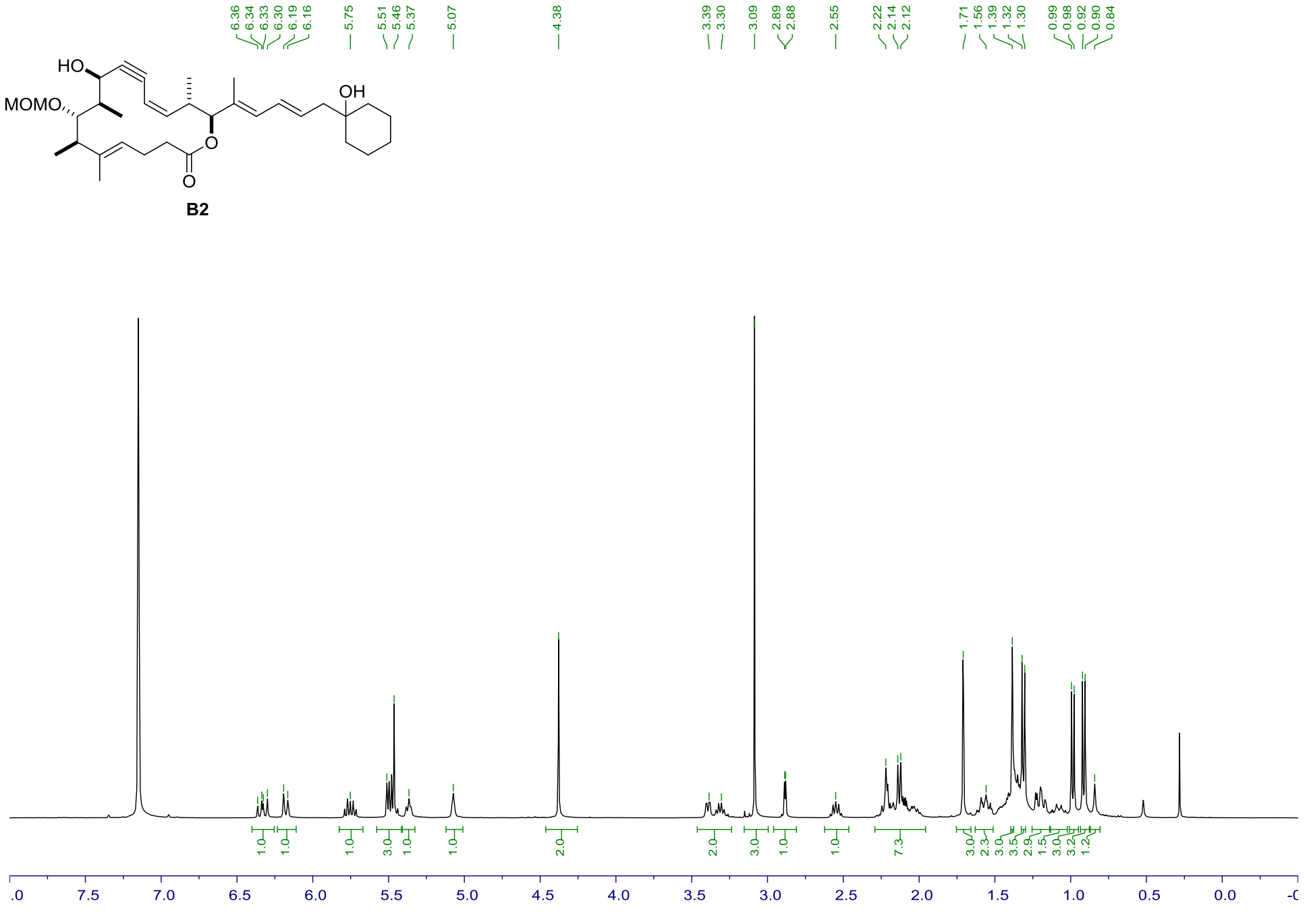

HO
MOMO
O
O
O
O
A3
6.44 6.41 6.39 6.26 6.18 6.01 5.99 5.66 5.63 5.56 5.28 5.26 5.24 5.12 5.08 5.06 4.71 4.69 4.62 4.61
3.63 3.40 3.33 3.31 2.94 2.55 2.30 2.28 2.27 2.12 2.11 1.91 1.73 1.70 1.39 1.07 1.05 0.83 0.82
0.9 1.9 1.0 0.9 1.1 1.0 0.9 2.0 1.0 1.0 3.0 2.9 1.1 1.7 1.0 4.2 3.1 1.1 2.9 4.1 3.0 6.1 3.1
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
174.0 172.3 136.4 136.3 135.0 131.7 131.6 130.3 126.5 126.4 124.4 124.2 99.6 89.2 83.0 64.9 56.6 51.6 47.7 38.8 35.0 33.6 33.5 32.3 29.8 24.5 22.0 16.7 16.4 12.1 11.9 11.3
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


6.69
6.67
6.65
6.33
6.31
6.30
6.28
6.26
6.26
6.24
6.04
6.02
5.92
5.90
5.71
5.51
5.49
5.47
5.32
5.06
4.70
4.69
4.58
4.56
4.51
3.62
3.37
3.30
3.29
2.98
2.49
2.31
2.29
2.28
2.19
2.13
1.95
1.76
1.69
1.42
1.13
1.12
1.08
1.07
0.85
0.84
O
NH2
O
MOMO
O
O
O
O
A4
1.0
1.0
1.2
1.0
1.0
1.0
1.3
6.3
2.3
1.2
3.5
3.4
3.6
1.1
1.2
1.1
3.3
2.9
2.3
1.4
4.2
2.6
3.3
3.4
4.1
3.7
.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
174.0
172.2
156.2
137.1
136.9
135.4
131.8
130.4
128.9
126.5
126.0
125.0
124.6
98.7
85.8
82.8
67.1
56.1
51.6
48.1
38.4
34.7
33.6
33.5
32.4
24.6
22.2
16.6
16.5
13.6
11.7
11.3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

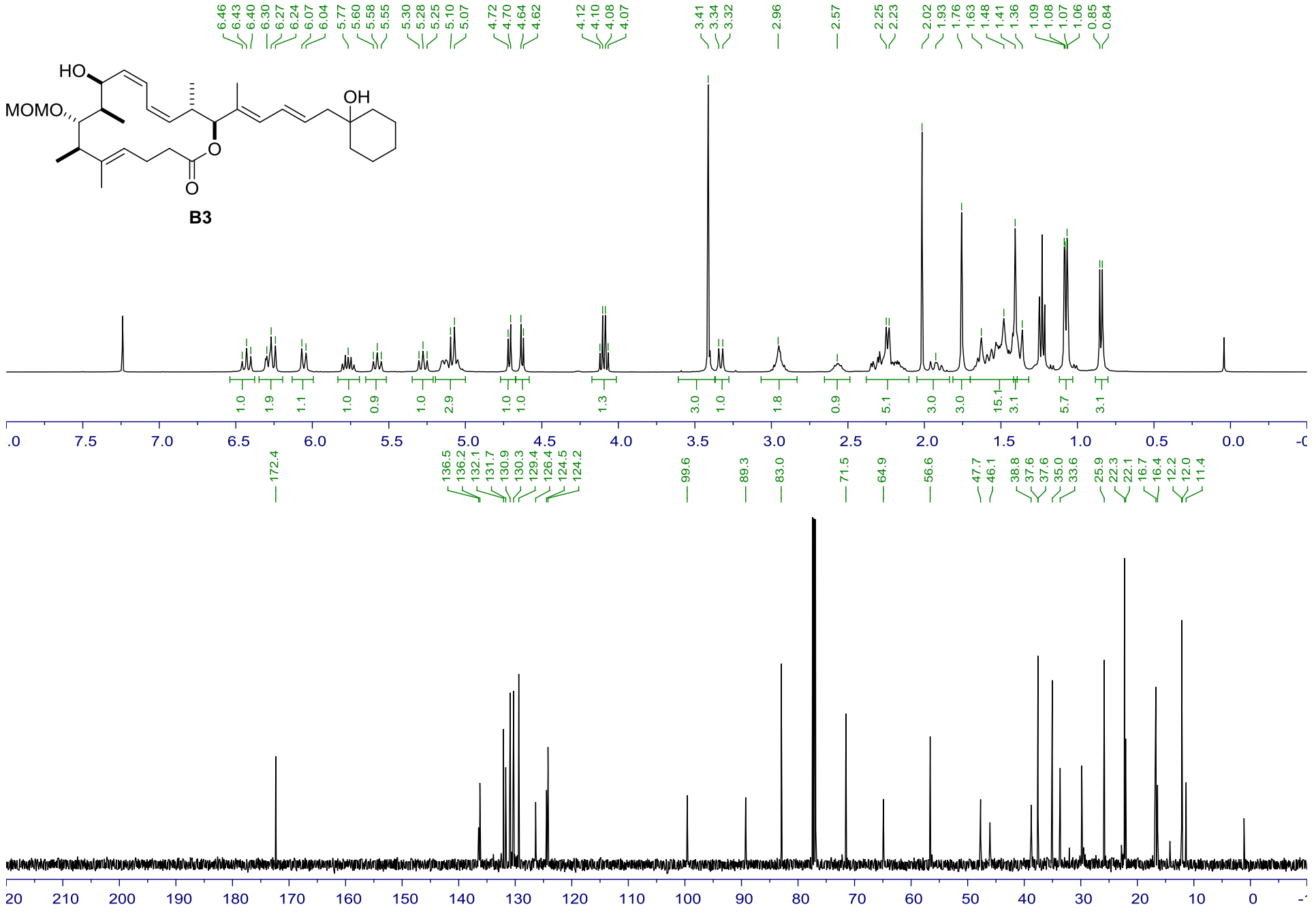

43
(~90% purity)

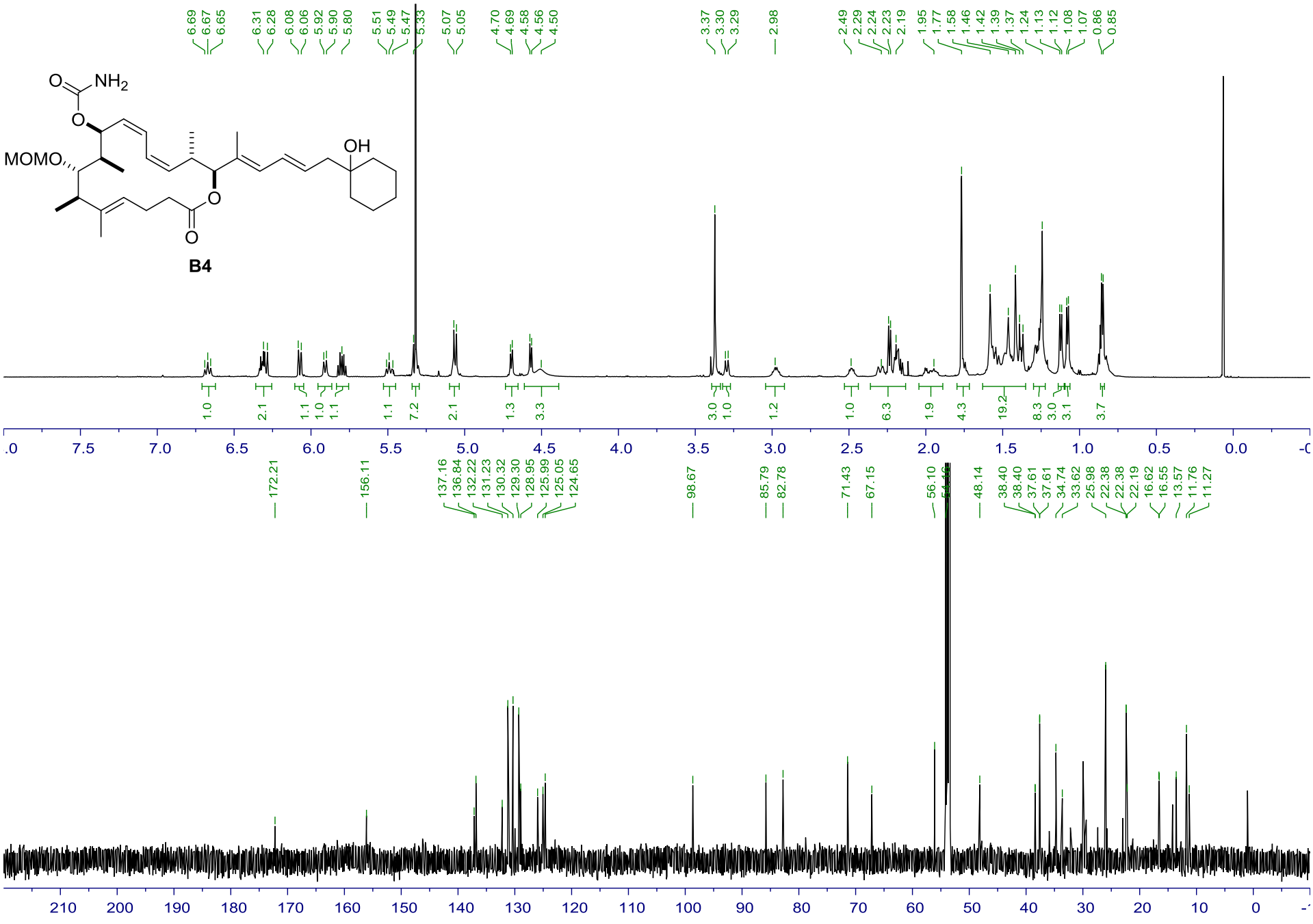

6.09
6.07
6.05
6.04
6.03
6.01
5.39
5.34
4.19
4.15
3.97
3.95
3.93
2.74
2.18
2.17
2.16
2.16
1.54
1.37
1.30
1.27
1.14
OH
O
O
B
O
O
N
B0
1.0
1.0
2.0
3.0
3.0
2.0
2.0
8.1
169.1
140.7
128.6
69.6
61.2
48.8
46.7
37.0
25.5
21.7

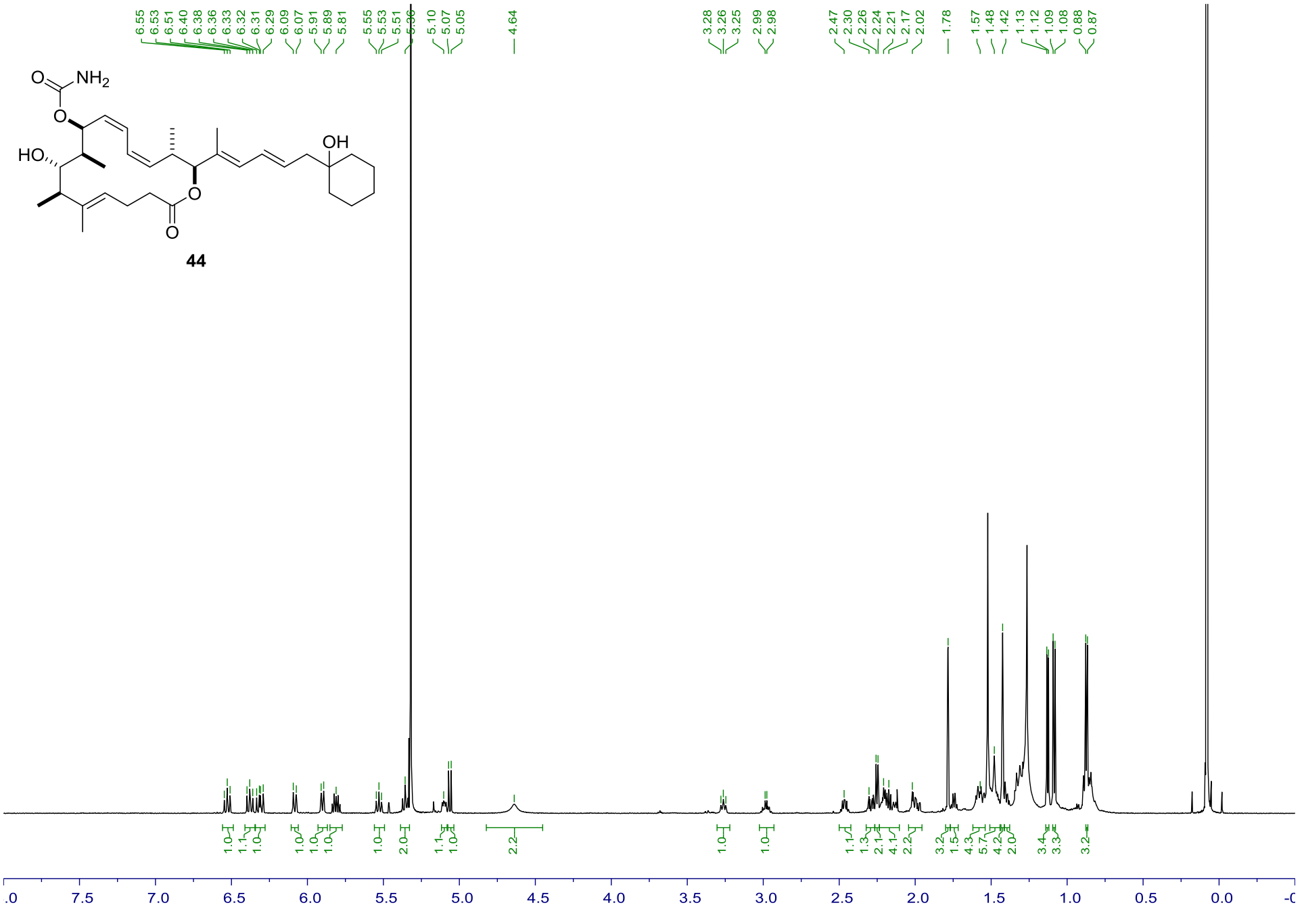

TBSO
MOMO
OH
O
O
B1

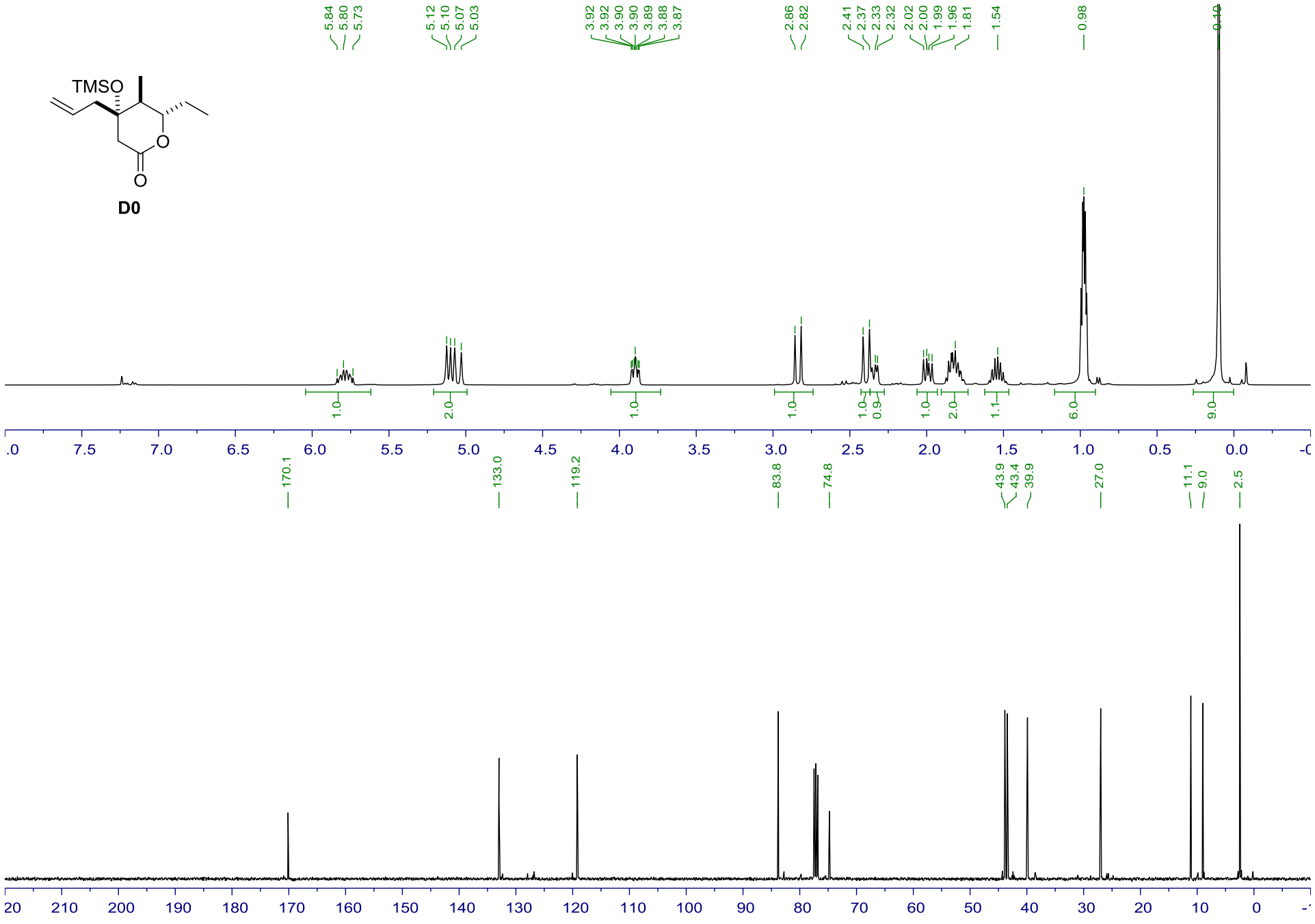

6.36
6.34
6.33
6.30
6.19
6.16
5.75
5.51
5.46
5.37
5.07
4.38
3.39
3.30
3.09
2.89
2.88
2.55
2.22
2.14
2.12
1.71
1.56
1.39
1.32
1.30
0.99
0.98
0.92
0.90
0.84
HO
MOMO
OH
O
O
1.0
1.0
1.0
3.0
1.0
1.0
2.0
2.0
3.0
1.0
1.0
7.3
3.0
2.3
3.0
3.5
2.9
1.5
3.0
3.2
1.2
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

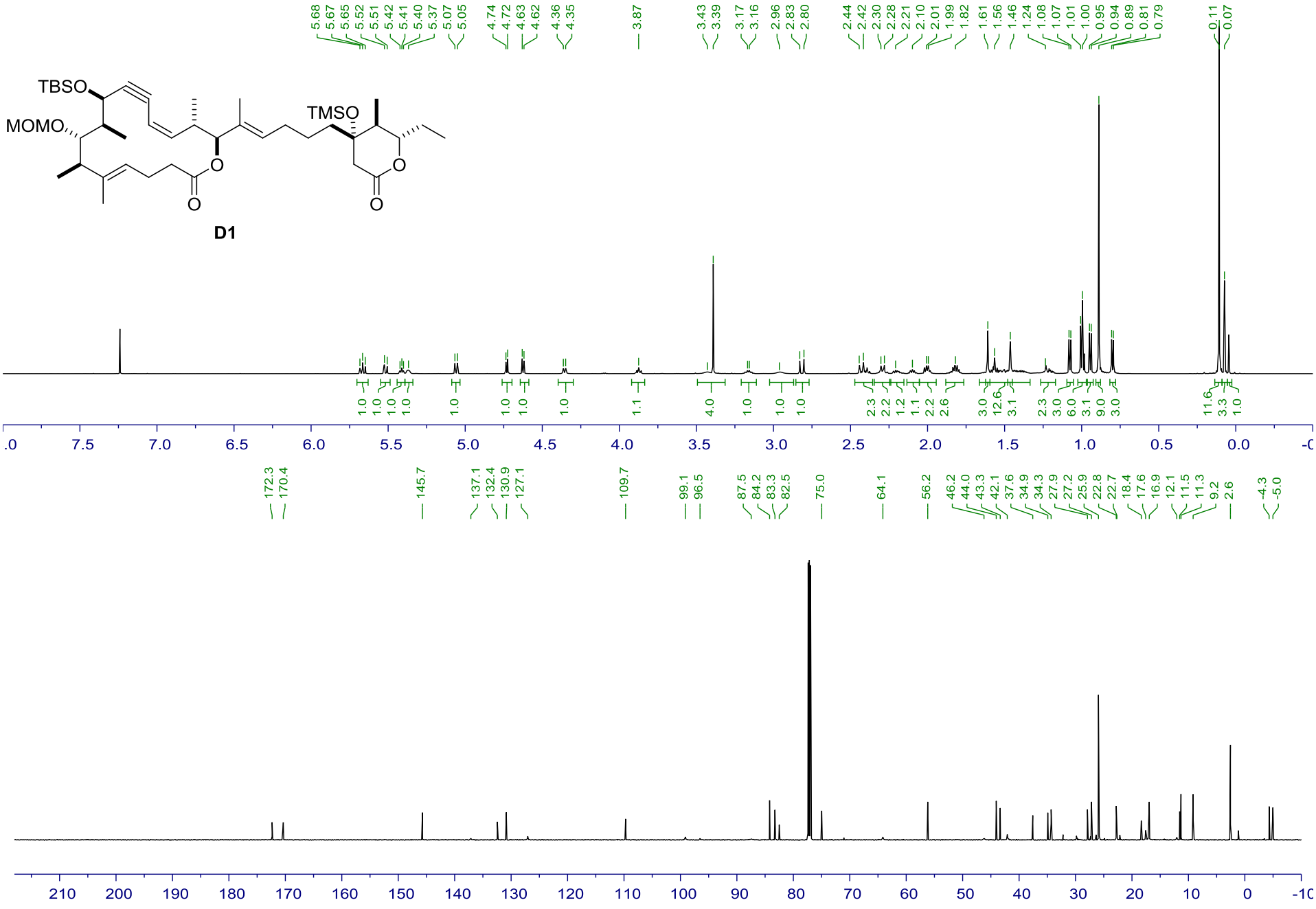
B2

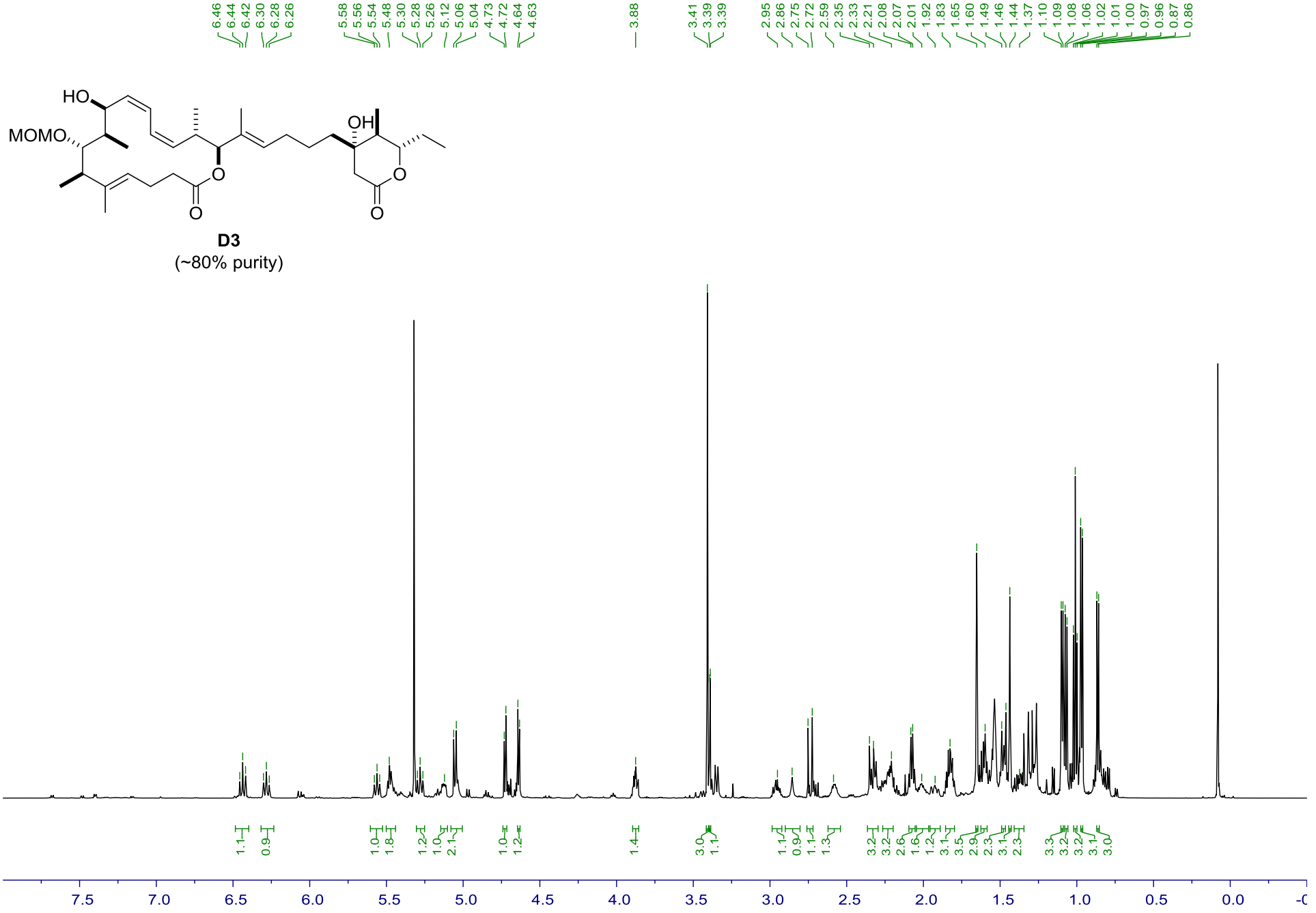

HO
MOMO
OH
O
O
B3

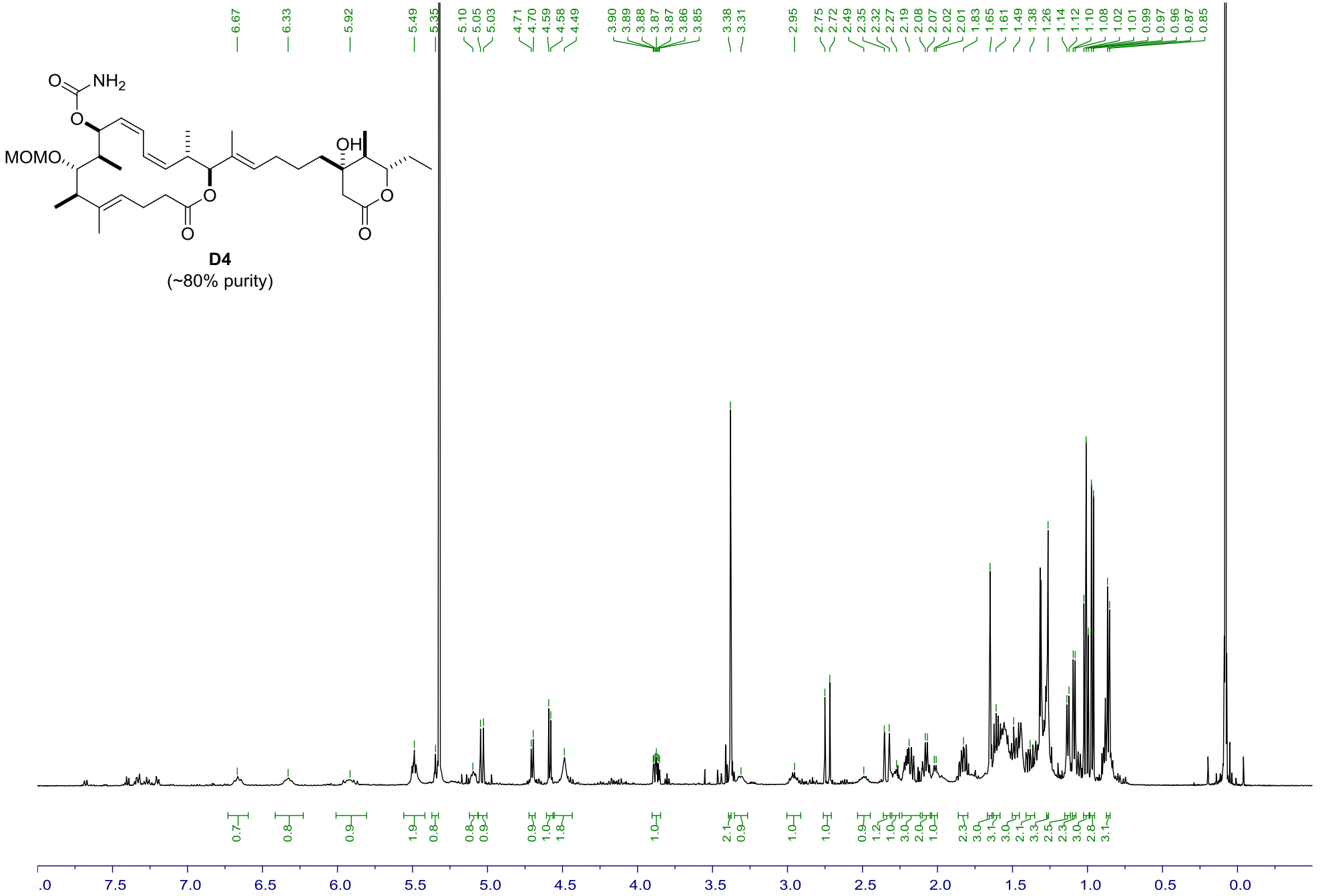

O
NH2
O
MOMO
OH
O
O
B4
6.69
6.67
6.65
6.31
6.28
6.08
6.06
5.92
5.90
5.80
5.51
5.49
5.47
5.33
5.07
5.05
4.70
4.69
4.58
4.56
4.50
3.37
3.30
3.29
2.98
2.49
2.29
2.24
2.23
2.19
1.95
1.77
1.58
1.46
1.42
1.39
1.37
1.24
1.13
1.12
1.08
1.07
0.86
0.85
1.0
2.1
1.1
1.0
1.1
1.1
7.2
2.1
1.3
3.3
3.0
1.0
1.2
1.0
6.3
1.9
4.3
19.2
8.3
3.0
3.1
3.7
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
172.21
156.11
137.16
136.84
132.22
131.23
130.32
129.30
128.95
125.99
125.05
124.65
98.67
85.79
82.78
71.43
67.15
56.10
48.14
38.40
38.40
37.61
37.61
34.74
33.62
25.98
22.38
22.19
16.62
16.55
13.57
11.76
11.27
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

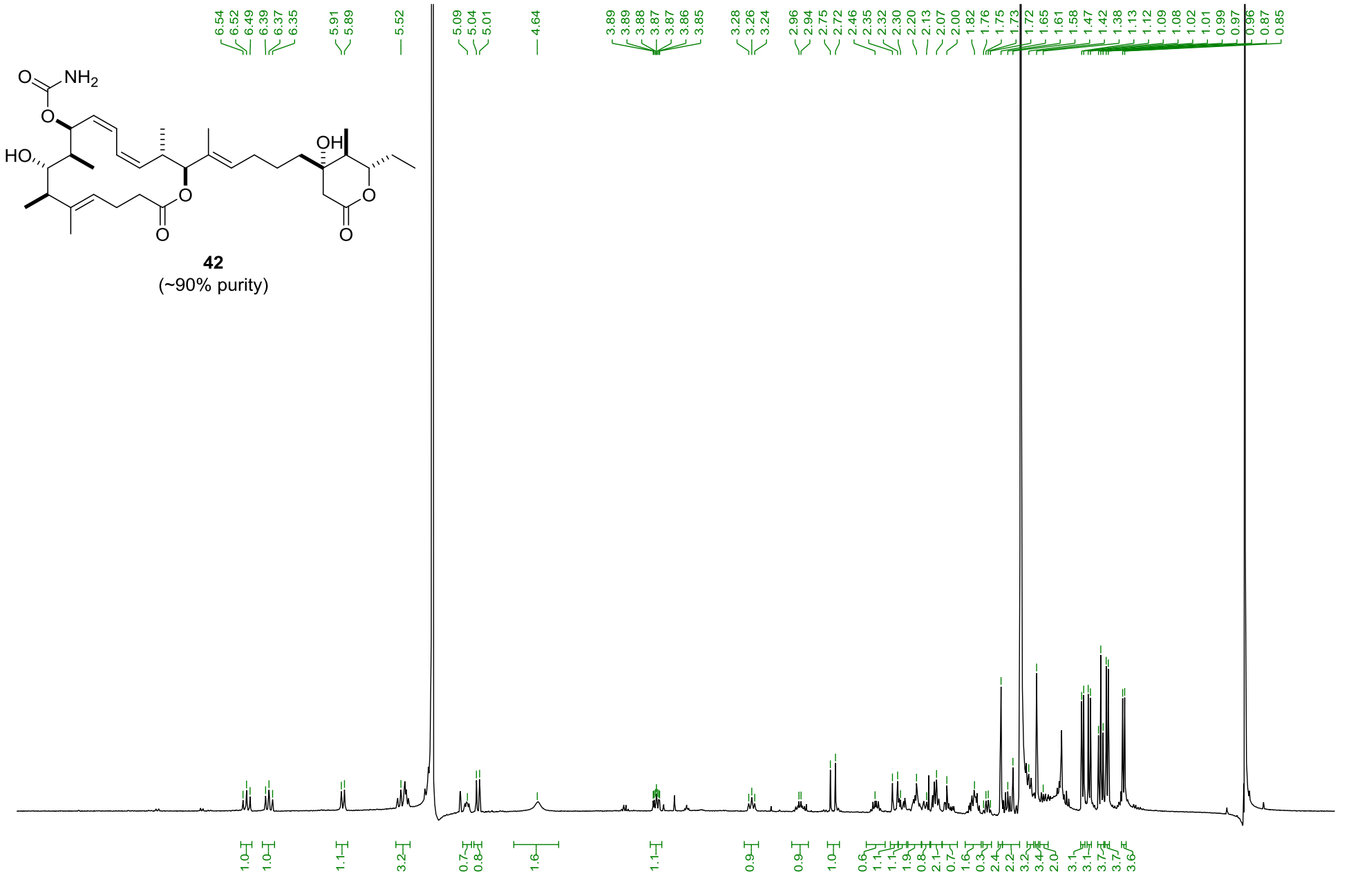

6.55
6.53
6.51
6.40
6.38
6.36
6.33
6.32
6.31
6.29
6.09
6.07
5.91
5.89
5.81
5.55
5.53
5.51
5.36
5.10
5.07
5.05
4.64
3.28
3.26
3.25
2.99
2.98
2.47
2.30
2.26
2.24
2.21
2.17
2.02
1.78
1.57
1.48
1.42
1.13
1.12
1.09
1.08
0.88
0.87
O
NH2
O
HO
OH
O
O
44

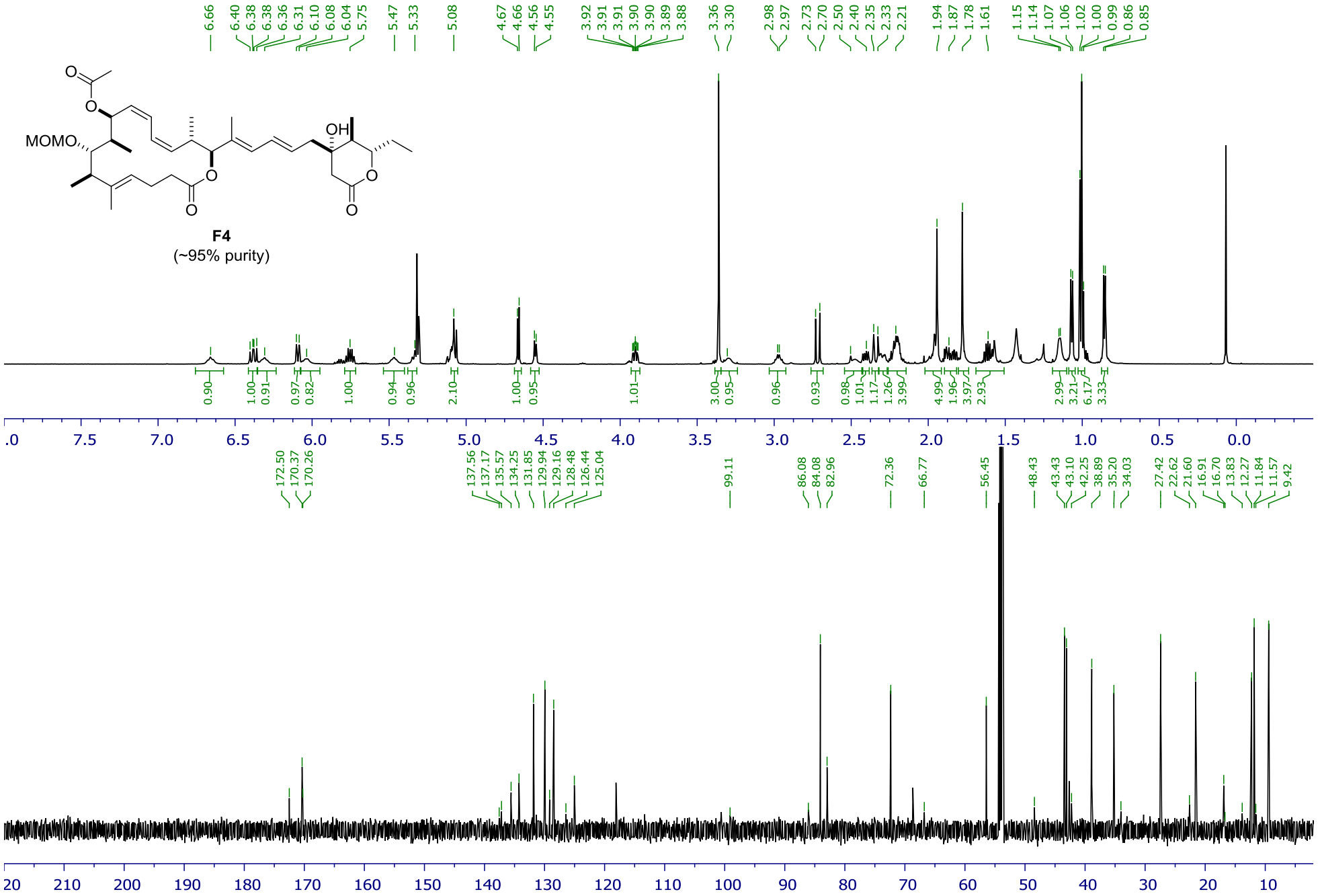

TMSO
O
O
D0
5.84
5.80
5.73
5.12
5.10
5.07
5.03
3.92
3.92
3.90
3.90
3.89
3.88
3.87
2.86
2.82
2.41
2.37
2.33
2.32
2.02
2.00
1.99
1.96
1.81
1.54
0.98
0.10
1.0
2.0
1.0
1.0
1.0
0.9
1.0
2.0
1.1
6.0
9.0
170.1
133.0
119.2
83.8
74.8
43.9
43.4
39.9
27.0
11.1
9.0
2.5

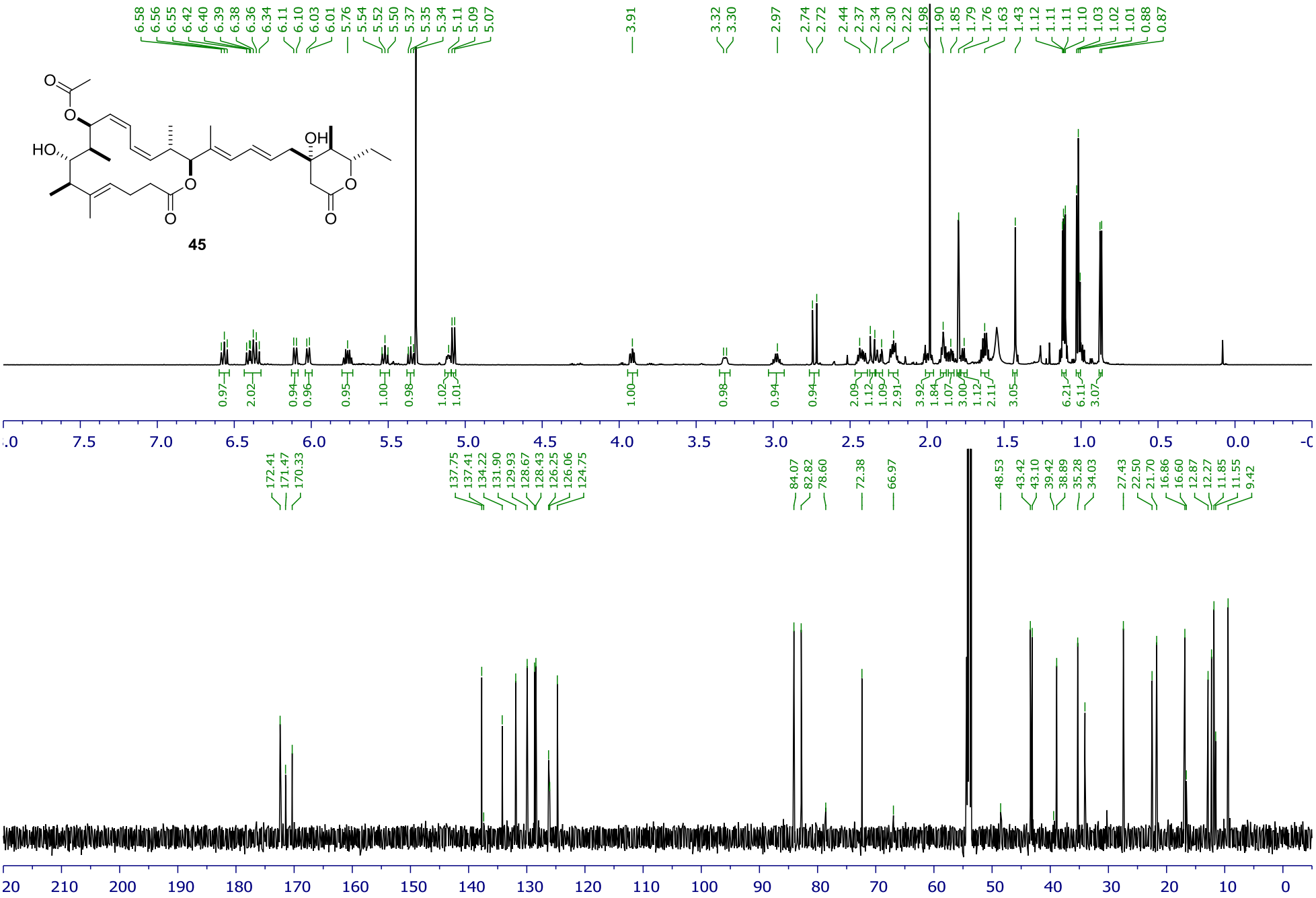

TBSO
MOMO
TMSO
O
O
O
O
D1


6.46
6.44
6.42
6.30
6.28
6.26
5.58
5.56
5.54
5.48
5.30
5.28
5.26
5.12
5.06
5.04
4.73
4.72
4.64
4.63
3.88
3.41
3.39
3.39
2.95
2.86
2.75
2.72
2.59
2.35
2.33
2.21
2.08
2.07
2.01
1.92
1.83
1.65
1.60
1.49
1.46
1.44
1.37
1.10
1.09
1.08
1.06
1.02
1.01
1.00
0.97
0.96
0.87
0.86
HO
MOMO
OH
O
O
O
O
D3
(~80% purity)
1.1
0.9
1.0
1.8
1.2
1.0
2.1
1.0
1.2
1.4
3.0
1.1
1.1
0.9
1.1
1.3
3.2
3.2
2.6
1.6
1.2
3.1
3.5
2.9
2.3
3.1
2.3
3.3
3.2
3.2
3.1
3.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


6.67
6.33
5.92
5.49
5.35
5.10
5.05
5.03
4.71
4.70
4.59
4.58
4.49
3.90
3.89
3.88
3.87
3.87
3.86
3.85
3.38
3.31
2.95
2.75
2.72
2.49
2.35
2.32
2.27
2.19
2.08
2.07
2.02
2.01
1.83
1.65
1.61
1.49
1.38
1.26
1.14
1.12
1.10
1.08
1.02
1.01
0.99
0.97
0.96
0.87
0.85
O
NH2
O
MOMO
OH
O
O
O
O
D4
(~80% purity)
0.7
0.8
0.9
1.9
0.8
0.8
0.9
0.9
1.0
1.8
1.0
2.1
0.9
1.0
1.0
0.9
1.2
1.0
3.0
2.0
1.0
2.3
3.0
3.1
3.0
2.1
3.3
2.5
2.3
3.0
2.8
3.1
.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


6.54
6.52
6.49
6.39
6.37
6.35
5.91
5.89
5.52
5.09
5.04
5.01
4.64
3.89
3.89
3.88
3.87
3.87
3.86
3.85
3.28
3.26
3.24
2.96
2.94
2.75
2.72
2.46
2.35
2.32
2.30
2.20
2.13
2.07
2.00
1.82
1.76
1.75
1.73
1.72
1.65
1.61
1.58
1.47
1.42
1.38
1.13
1.12
1.09
1.08
1.02
1.01
0.99
0.97
0.96
0.87
0.85
O
NH2
O
HO
OH
O
O
O
O
42
(~90% purity)
1.0
1.0
1.1
3.2
0.7
0.8
1.6
1.1
0.9
0.9
1.0
0.6
1.1
1.1
1.9
0.8
2.1
0.7
1.6
0.3
2.4
2.2
3.2
3.4
2.0
3.1
3.1
3.7
3.7
3.6
.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


MOMO
OH
O
O
O
O
O
O
F4
(~95% purity)


6.58 6.56 6.55 6.42 6.40 6.39 6.38 6.36 6.34 6.11 6.10 6.03 6.01 5.76 5.54 5.52 5.50 5.37 5.35 5.34 5.11 5.09 5.07
3.91
3.32 3.30
2.97
2.74 2.72
2.44 2.37 2.34 2.30 2.22
1.98 1.90 1.85 1.79 1.76 1.63 1.43 1.12 1.11 1.11 1.10 1.03 1.02 1.01 0.88 0.87
O
O
HO
O
O
OH
O
O
45
0.97 2.02 0.94 0.96 0.95 1.00 0.98 1.02 1.01 1.00 0.98 0.94 0.94 2.09 1.12 1.09 2.91 3.92 1.84 1.07 3.00 1.12 2.11 3.05 6.21 6.11 3.07
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
172.41 171.47 170.33
137.75 137.41 134.22 131.90 129.93 128.67 128.43 126.25 126.06 124.75
84.07 82.82 78.60 72.38 66.97
48.53 43.42 43.10 39.42 38.89 35.28 34.03 27.43 22.50 21.70 16.86 16.60 12.87 12.27 11.85 11.55 9.42
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0