SUPPORTING INFORMATION

Total Synthesis of Iejimalide A-D and Assessment of the Remarkable Actin-Depolymerizing Capacity of these Polyene Macrolides

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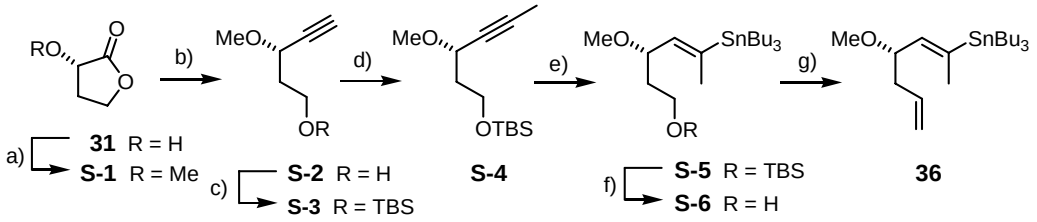
General Methods: All reactions were carried out in flame-dried glassware under Ar. The solvents were purified by distillation over the drying agents indicated and were transferred under Ar: THF, Et_2O, 1,4-dioxane (Mg-anthracene), CH_2Cl_2 (P_4O_{10}), MeCN, Et_3N, pyridine (CaH_2), MeOH (Mg), DMF (Desmodur®, dibutyltin dilaurate), hexane, toluene (Na/K). Flash chromatography: Merck silica gel 60 (230-400 mesh). NMR: Spectra were recorded on a Bruker DPX 300, AV 400, or DMX 600 spectrometer 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 ($CDCl_3$: $\delta_C \equiv 77.0$ ppm; residual $CHCl_3$ in $CDCl_3$: $\delta_H \equiv 7.24$ ppm; CD_2Cl_2: $\delta_C \equiv 53.8$ ppm; residual CH_2Cl_2 in CD_2Cl_2: $\delta_H \equiv 5.32$ ppm). IR: Nicolet FT-7199 spectrometer, wavenumbers ($\tilde{\nu}$) in cm^{-1}. MS (EI): Finnigan MAT 8200 (70 eV), ESI-MS: Finnigan MAT 95, accurate mass determinations: Bruker APEX III FT-MS (7 T magnet). Melting points: Büchi melting point apparatus B-540 (corrected). Elemental analyses: H. Kolbe, Mülheim/Ruhr. Unless stated otherwise, commercially available compounds (Fluka, Lancaster, Aldrich) were used as received.

‘First Generation’ Syntheses of the Building Blocks



Scheme S1. Reagents and conditions: a) MeI, Ag_2O, MeCN, 92%; b) (i) DIBAl-H, CH_2Cl_2, −78°C; (ii) $MeCOC(=N_2)P(O)(OMe)_2$, K_2CO_3, MeOH, 70% (over both steps); c) TBSCl, Et_3N, DMAP cat., CH_2Cl_2, 90%; d) *n*-BuLi, MeI, THF, 98%; e) Bu_3SnH, $(PPh_3)_2PdCl_2$ (5 mol%), THF, 65%; f) TBAF, THF, 93%; g) (i) Dess-Martin periodinane, CH_2Cl_2, 84%; (ii) $Ph_3P{=}CH_2$, *n*-BuLi, THF, −35°C → RT, 87%.

The original route to the northern hemisphere of **2** employed commercial lactone **31** (ee = 96%) as the starting material, which was O-methylated and reduced with DIBAl-H to the corresponding hemiacetal that allowed for the installation of an alkyne unit by reaction with the Ohira-Bestmann reagent (Scheme S1).[1] O-Silylation of **S-2** and end-capping of the alkyne in **S-3** with a methyl group set the stage for a palladium-catalyzed hydrostannation which converted **S-4** into product **S-5** in 65% yield.[2] The elaboration of this compound into the required building block **36** was readily achieved by cleavage of the silyl ether, oxidation of the resulting primary alcohol with Dess-Martin periodinane,[3] and Wittig olefination of the resulting aldehyde.

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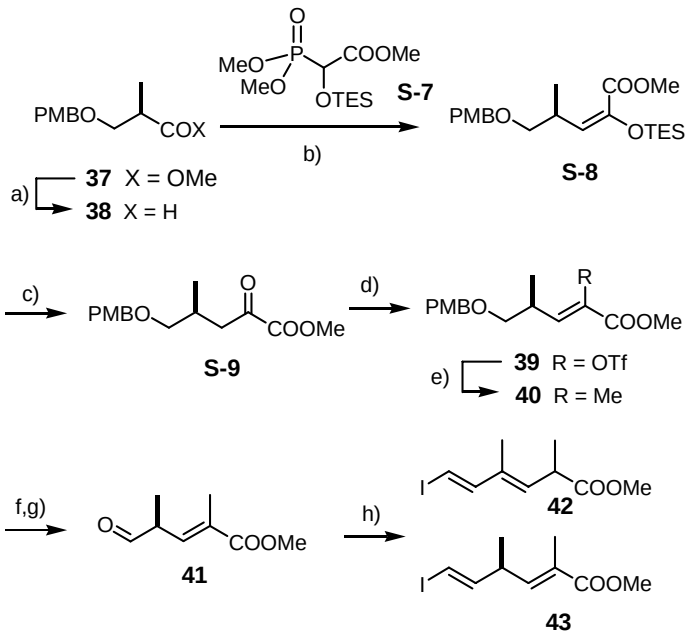
1 (a) Ohira, S. *Synth. Commun*. **1989**, *19*, 561. (b) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521.

2 Small amounts (10-15%) of the regioisomeric alkenyl-stannane could be separated by flash chromatography. Moreover, the corresponding pinacolborane has also been prepared; however, this compound failed to undergo productive cross coupling with alkenyl iodide **43**.

3 (a) Dess, D. B.; Martin, J. C. *J. Org. Chem*. **1983**, *48*, 4155. (b) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem*. **1994**, *59*, 7549. (c) Boeckman, R. K., Jr.; Shao, P.; Mullins, J. J. *Org. Synth*. **2000**, *77*, 141.



Scheme S2. Reagents and conditions: a) DIBAl-H, CH_2Cl_2, −78°C; b) compound **S-7**, LiHMDS, THF, −78°C → −40°C, 75% (over both steps); c) aq. HCl, THF, 91%; d) N-(5-chloro-2-pyridyl)-bis-(trifluoromethansulfonimide), KHMDS, THF, −78°C → −40°C, 60-65%; e) MeZnCl, $Pd(PPh_3)_4$ (5 mol%), THF, 50°C, 91%; f) DDQ, CH_2Cl_2/H_2O, 91%; g) Dess-Martin periodinane, CH_2Cl_2; h) CHI_3, $CrCl_2 \cdot 1.8$ THF, THF/1,4-dioxane (1:6), 62% (over two steps).

Access was gained by DIBAl-H reduction of the known Roche ester derivative **37**[4] and chain extension of the resulting aldehyde with the functionalized phosphonate **S-7**[5] furnishing enol silane **S-8** as a single isomer (Scheme S2). This compound was then converted into the corresponding enol triflate **39** of opposite double bond configuration by acid catalyzed hydrolysis followed by treatment of **S-9** with Comins reagent[6] in the presence of KHMDS as the optimal base. Triflate **39** could be cross coupled with MeZnCl in the presence of catalytic amounts of $Pd(PPh_3)_4$.[7] The elaboration of the resulting product **40** into the required building block **43** followed the route described in the Text of the paper.

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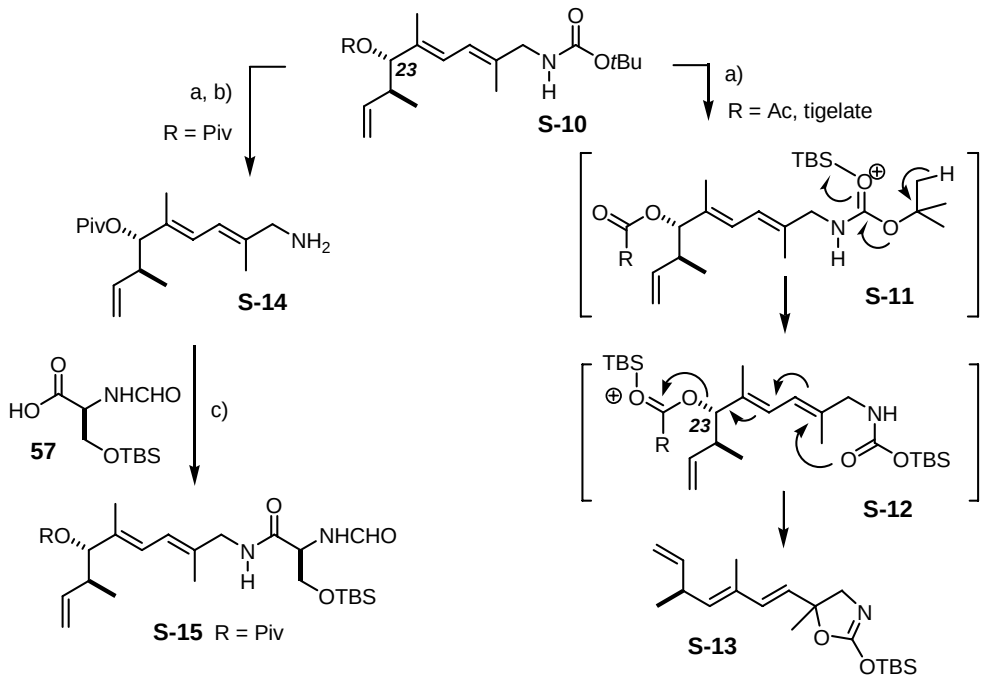
4 Heckrodt, T. J.; Mulzer, J. *Synthesis* **2002**, 1857.

5 (a) Ceccarelli, S. M.; Piarulli, U.; Telser, J.; Gennari, C. *Tetrahedron Lett.* **2001**, *42*, 7421. (b) Horne, D.; Gaudino, J.; Thompson, W. J. *Tetrahedron Lett*. **1984**, *25*, 3529.

6 Comins, D. L.; Dehghani, A. *Tetrahedron Lett*. **1992**, *33*, 6299.

7 Negishi, E.; Zheng, X.; Tan, Z.; Qian, M.; Hu, Q.; Huang, Z. In *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds., 2nd ed.; Wiley-VCH: Weinheim, 2004; Vol. 2; pp 815.



Scheme S3. Reagents and conditions: a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 40°C, 91% (R = Ac); 85% (R = –C(O)C(Me)=CHMe); b) HOAc, THF, 50°C; c) compound **57**, EDC, HOBt, N-methylmorpholine (NMM), CH_2Cl_2, 0°C → RT, 95% (over steps a)-c)).

Although the degradation pathway of **51** has not been rigorously investigated, model studies were undertaken that explain, at least in part, this unexpected behavior (Scheme S-3). Thus, treatment of the compound **S-10** (R = Ac, tiglinic acid) with TBSOTf/2,6-lutidine converted these compounds into a common product **S-13** which was obtained in high yield as a mixture of diastereomers. It is believed that the conjugated diene efficiently communicates activation of the Boc-moiety by the Lewis acid to the seemingly remote substituent residing at C.23 (iejimalide numbering). Rearrangement of the π-system with extrusion of the ester then engenders formation of the heterocyclic motif.

In striking contrast to the acetate case, however, the corresponding pivalate **S-10** (R = Piv) allowed for the clean removal of the Boc-substituent; the bulky ester most likely forces this substrate to adopt a conformation in which orbital overlap between the C-O σ-bond and the π-system of the diene is minimized, thus effectively blocking the decomposition pathway. The resulting amine **S-14** was coupled to the L-serine derivative **57**[8] under standard conditions to give product **S-15** in excellent overall yield. The striking difference in the behavior of acetate and pivalate clearly features our still limited capacity to properly assess the degree of the homology between recorded and projected cases.

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[8] Hill, D. R.; Hsiao, C.-N.; Kurukulasuriya, R.; Wittenberger, S. J. *Org. Lett.* **2002**, *4*, 111.

Caspase Assay. The activities of caspases 3 and 7 were quantified by the use of a commercial reagent kit (Caspase-Glo 3/7 by Promega) in a coupled enzymatic reaction, which has been used for assaying caspase activity and apoptosis in a large variety of applications.[9] In this assay the luciferin-coupled tetrapeptide DEVD is used as a luminogenic substrate for caspase 3/7. The substrate is added to the cells and following caspase cleavage, a new substrate for luciferase (amino-luciferin) is released, resulting in the luciferase reaction and the production of light. The luminescent signal, produced in the luciferase reaction is proportional to the caspase activity. The assay was performed according to the protocol provided by the supplier. Thus, 5 x 10^3 NIH3T3 cells were seeded in each well of a white-walled 96-well luminometer plate (Corning Life Sciences) and cultured in 100 µL Dulbecco's Modified Eagle Medium (Invitrogen) supplemented with 10 % fetal calf serum (DMEM/FCS) at 37°C and 5 % CO_2 in a humidified incubator. On the next day, cells were washed with PBS and fresh DMEM/FCS was added. The compounds were dissolved as 5 mM stock solution in DMSO. For each final concentration a 10x concentrated adding solution (AS) was prepared by diluting the stock solution in DMEM/FCS, e.g. for the final concentration 10 µM, 2 µL of the stock solution were added to 98 µL DMEM/FCS to prepare the 100 µM AS. Five percent DMSO in DMEM/FCS served as negative control AS. Ten microliters of each AS and of the negative control AS were added to the wells and the cells were incubated for another 24 h. Cells were washed with PBS and 100 µL of the lysis/test reagent was added to each well. The plate was covered with a plate sealer and incubated for 40 min at room temperature on a plate shaker. The luminescence was measured in a multi-well plate reader (CentroXS LB960, Berthold Technologies). The luminescence of the negative control was set as 100 % and all other values were referred to this value. All concentrations were tested in triplicates.

Actin Assay. Murine NIH/3T3 fibroblasts (CRL-1658 from ATCC) were cultured at 37°C and 5% CO_2 in Dulbecco's modified Eagle's medium supplemented with 4 mM L-glutamine, 4.5 g/L glucose and 10 % bovine calf serum. 2x10^4 cells were seeded on coverslips in one well of a 24-well plate. After adapting and attaching over night, the cells were incubated with 1 µM, 5 µM or 10 µM of the corresponding iejimalide derivative for 18 h. Before and after each fixation or staining step the cells were washed three times with TPBS (0.2% Tween20 in phosphate-buffered saline). Cells were fixed with 3.7% formalin in PBS. For blocking unspecific epitopes, fixed cells were incubated with 1% powdered milk in PBS. Actin filaments were stained for 1h with a solution of 77 nM TRITC labelled phalloidin (P1951, Sigma) in TPBS. Cell nuclei were stained with DAPI (2-(4-amidinophenyl)-6-indolecarbamidine dihydrochloride, D9542, Sigma). Cells were visualized and photographed with a Zeiss Axiophot fluorescence microscope.

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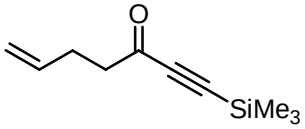
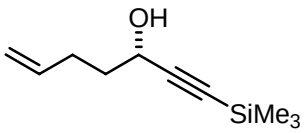
[9] (a) Feng, Y.; Ariza, M. E.; Goulet, A. C.; Shi, J.; Nelson, M. A. *Biochem. J.* **2005** *392*, 65. (b) Liu, D.; Li, C.; Chen, Y.; Burnett, C.; Liu, X.Y.; Downs, S.; Collins, R. D.; Hawiger, J. *J. Biol. Chem.* **2004**, *279*, 48434. (c) Notebaert, S.; Duchateau, L.; Meyer, E. *Vet. Res.* **2005**, *36*, 229. (d) Ren, Y. G.; Wagner, K. W.; Knee, D. A.; Aza-Blanc, P.; Nasoff, M.; Deveraux, Q. L. *Mol. Biol. Cell* **2004**, *15*, 5064.

Building Blocks: Preparation of Boronate 19

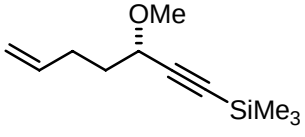
Compound 10. Bis(trimethylsilyl)acetylene (25.3 mL, 0.111 mol) was added to a solution of acid chloride **9** (12.3 mL, 0.111 mol) in anhydrous CH_2Cl_2 (140 mL). The mixture was cooled to 0°C before $AlCl_3$ (14.9 g, 0.111 mol) was added in small portions over 5 min. The reaction mixture was then stirred at 0°C for 10 min and at 20ºC for 1 h. For work-up, the mixture was poured onto aq. HCl (1 M) at 0°C, the aqueous phase was extracted with diethyl ether, the combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated (because of volatility of the product, the heating bath of the rotary evaporator was set to 20°C and the applied vacuum was kept at ≥ 30 mbar). The residue was purified by Kugelrohr distillation to yield **10** as a colorless oil (16.64 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.81 (tdd, J = 16.8, 10.2, 6.4 Hz, 1H), 5.04 (m, 2H), 2.66 (t, J = 7.4 Hz, 2H), 2.42 (m, 2H), 0.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.9, 136.3, 115.7, 101.9, 98.0, 44.3, 27.8, 0.8; IR (film): $\tilde{\upsilon}$ = 3081, 2963, 2902, 2152, 1680, 1643, 1439, 1409, 1356, 1253, 1227, 1115, 1094, 1031, 998, 968, 915, 865, 847, 762, 704, 626, 589 cm^{-1}; HRMS (EI/FE): *m*/*z*: calcd for $C_{10}H_{16}OSi$: 180.097041 [M^+]; found: 180.097232; elemental analysis calcd (%) for $C_{10}H_{16}OSi$: C 66.61, H 8.94; found: C 66.46, H 8.98.



Compound 12. A flame-dried Schlenk flask was charged with ketone **10** (8.37 g, 0.0446 mol) and degassed isopropanol (350 mL). The resulting solution was purged with Ar for 1.5 h before the ruthenium complex **11** was added as a solid (0.175 g, 0.0292 mol). The resulting mixture was again purged with Ar before it was stirred for 19 h at 20ºC. For work up, the mixture was transferred into a round-bottomed flask (with diethyl ether), the solvents were evaporated under reduced pressure (due to volatility of the product, the heating bath of the rotary evaporator was set to 20°C and the applied vacuum was kept at ≥ 30 mbar), and the crude product was purified by flash chromatography (hexanes/ethylacetate, 50:1→30:1) to give alcohol **12** as a colorless oil (8.31 g, 98 %). $[\alpha]_D^{20}$ = +6 (c = 0.43, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.84 (tdd, J = 6.7, 10.2, 16.9 Hz, 1H), 5.03 (m, 2H), 4.38 (t, J = 6.5 Hz, 1H), 2.23 (m, 2H), 1.77-1.83 (m, 2H), 0.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.7, 115.3, 106.5, 89.7, 62.4, 36.8, 29.4, -0.1; IR (film): $\tilde{\upsilon}$ = 3336, 3079, 2959, 2900, 2863, 2173, 1642, 1440, 1415, 1332, 1251, 1121, 1068, 1046, 1016, 955, 913, 895, 844, 761, 700, 648, 612, 555, 489 cm^{-1}; MS (EI): *m*/*z*: 167 (9), 149 (8), 140 (17), 127 (15), 125 (12), 99 (45), 92 (10), 91 (32), 75 (100), 73 (73), 61 (12), 45 (21), 43 (13), 41 (13); elemental analysis calcd (%) for $C_{10}H_{18}OSi$: C 65.87, H 9.95; found: C 65.72, H 9.84.

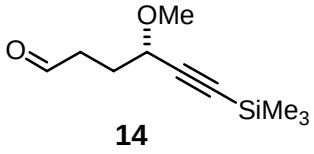


Compound 13. *n*-BuLi (10.6 mL, 1.6 M in hexanes) was added dropwise over a period of 10 min via a syringe pump to a solution of compound **12** (3.10 g, 0.017 mol) in THF (60 mL) at −78°C. Once the addition was complete, stirring was continued for 10 min at −78°C before MeI (8.5 mL, 0.137 mol) was added dropwise to the mixture. The temperature was then raised to



–25°C, at which point DMSO (2.5 mL) was slowly introduced, causing the formation of a white precipitate. After stirring for 1h at that temperature, the cooling bath was removed and stirring continued at 20ºC for 21 h. The reaction mixture was poured to a 1:1 mixture of ice and aq. sat. NH_4Cl, the organic phase was extracted with Et_2O, the organic layers were combined, washed with water and brine, dried over Na_2SO_4, and evaporated (due to high volatility of the product, the heating bath of the rotary evaporator bath was set to 20°C and pressure kept at ≥ 35 mbar) to give product **13** as pale yellow oil (3.30 g, 99%, ee = 98.8 %). The crude product is pure enough for immediate use in the next step. $[\alpha]_D^{20} = -37.9$ (c = 0.61, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.83 (tdd, J = 6.7, 10.2, 16.9 Hz, 1H), 5.00 (m, 2H), 3.93 (t, J = 6.6 Hz, 1H), 3.36 (s, 3H), 2.19 (m, 2H), 1.67-1.82 (m, 2H), 0.18 (s, 9H); ^{13}C NMR (MHz, $CDCl_3$): δ = 138.4, 115.1, 105.0, 90.9, 71.3, 56.4, 35.1, 29.8, 0.0; IR (film): $\tilde{\upsilon}$ = 3079, 2958, 2927, 2854, 2822, 2170, 1642, 1465, 1450, 1415, 1335, 1251, 1160, 1107, 1011, 994, 922, 844, 761, 700, 652, 612 cm^{-1}; HRMS (CI/FE *i*-butane): *m*/*z*: calcd for $C_{11}H_{20}OSi$+H: 197.135980 [M^++H]; found: 197.136170; elemental analysis calcd (%) for $C_{11}H_{20}OSi$: C 67.28, H 10.27; found: C 67.06, H 10.18.

Compound 14. To a solution of compound **13** (1.29 g, 0.0066 mol) in 1,4-dioxane/water (50/16 mL) at 20ºC were sequentially added 2,6-lutidine (1.5 mL, 0.0134 mol), OsO_4 (1.6 mL, 0.00013 mol, 2.5 % *w*/*w* in *t*-BuOH) and $NaIO_4$ (5.65 g, 0.0264 mol). The resulting heterogeneous mixture was stirred for 3 h before it was diluted with water, the aqueous phase was extracted with *tert*-butyl methyl ether and EtOAc, the combined organic layers were washed with HCl (1 M) and brine, dried over $MgSO_4$, and carefully evaporated (due to high volatility of the product, the heating bath of the rotary evaporator bath was set to 20°C and pressure kept at ≥ 35 mbar) The crude product was purified by flash chromatography (pentanes/Et_2O, 15:1) to give product **14** as a colorless oil (995 mg, 76%). $[\alpha]_D^{20} = -82.1$ (c = 0.51, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.79 (t, J = 1.5 Hz, 1H), 4.01 (t, J = 6.1 Hz, 1H), 3.38 (s, 3H), 2.61 (m, 2H), 2.04 (dt, J = 7.2, 6.2 Hz, 2H), 0.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.8, 103.5, 91.7, 70.5, 56.6, 39.7, 28.2, 0.1; IR (film): $\tilde{\upsilon}$ = 2960, 2941, 2900, 2824, 2724, 2170, 1727, 1466, 1440, 1412, 1390, 1334, 1251, 1201, 1178, 1114, 1091, 1017, 989, 958, 919, 844, 761, 700, 668, 612 cm^{-1}; HRMS (CI/FE *i*-butane): *m*/*z*: calcd for $C_{10}H_{18}O_2Si$+H: 199.115434 [M^++H]; found: 199.115280; elemental analysis calcd (%) for $C_{10}H_{18}O_2Si$: C 60.56, H 9.15; found: C 60.43, H 9.08.



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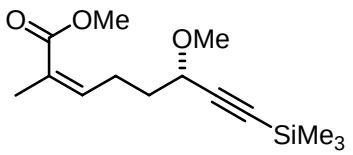
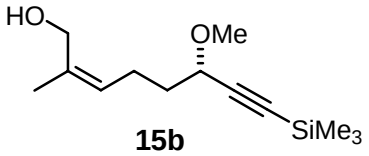
Compound 15. A Schlenk flask was charged with $(CF_3CH_2O)_2P(O)CH(Me)COOMe$ (1.63 g, 0.00489 mol), 18-crown-6 (0.860 g, 0.00325 mol) and toluene (27 mL). A solution of KHMDS (9.25 mL, 0.5 M in toluene) was added dropwise at 0°C and the resulting mixture was stirred at 0°C for 45 min before it was cooled to –20°C. A solution of aldehyde **14** (0.936 g, 0.00472 mol) in toluene (16 mL) was added over 15 min and stirring continued for 10 min at that temperature before the mixture was allowed to warm to 0°C. After stirring for another 1.5 h, the reaction was quenched at 0°C with aq. sat. NH_4Cl, the



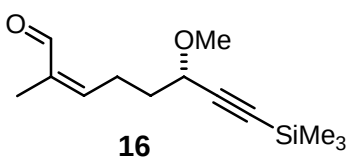
aqueous layer was extracted with *tert*-butyl methyl ether, the combined organic phases were dried over Na_2SO_4 and evaporated, and the crude product purified by flash chromatography (hexanes/ethyl acetate, 20:1) to give product **15** as a colorless oil (1.10 g, 87%, ee = 95.5%). $[\alpha]_D^{20} = -18.1$ (c = 0.44, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.95 (qt, J = 7.5, 1.5 Hz, 1H), 3.94 (t, J = 6.5 Hz, 1H), 3.74 (s, 3H), 3.39 (s, 3H), 2.59 (m, 2H), 1.90 (dd, J = 2.7, 1.3 Hz, 3H), 1.80 (m, 2H), 0.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 141.9, 127.7, 104.3, 90.7, 71.1, 56.4, 51.3, 35.2, 25.7, 20.7, 0.0; IR (film): $\tilde{\upsilon}$ = 2955, 2901, 2843, 2822, 2169, 1720, 1648, 1456, 1435, 1367, 1334, 1251, 1227, 1198, 1175, 1134, 1108, 1074, 1009, 950, 844, 761, 700, 672, 616 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{14}H_{24}O_3Si$+Na: 291.13916 [M^++Na]; found: 291.13924; elemental analysis calcd (%) for $C_{14}H_{24}O_3Si$: C 62.64, H 9.01; found: C 62.76, H 8.89.

Compound 16. A solution of DIBAl-H (7.0 mL, 1.0 M in hexanes) was slowly added to a solution of compound **15** (745 mg, 0.00277 mol) in CH_2Cl_2 (30 mL) at −78ºC and the resulting mixture was stirred at that temperature for 1 h. For work-up, the reaction was quenched with EtOAc (80 mL) and the solution was slowly warmed to 0ºC. A sat. aq. solution of Rochelle's salt was added (40 mL) and the mixture was stirred at 40ºC for 45 min to ensure a clean separation of the phases. The aqueous layer was extracted with EtOAc, and the combined organic phases were dried over $MgSO_4$ and evaporated, affording alcohol **15b** which is pure enough for immediate use in the next step (656 mg, 99%). $[\alpha]_D^{20} = -17.8$ (c = 1.7, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.25 (t, J = 7.6 Hz, 1H), 4.10 (s, 2H), 3.93 (t, J = 6.6 Hz, 1H), 3.37 (s, 3H), 2.20 (q, J = 7.2 Hz, 2H), 1.79 (d, J = 1.2 Hz, 3H), 1.80-1.67 (m, 2H), 0.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.8, 127.0, 104.3, 91.2, 70.6, 61.5, 56.1, 35.2, 23.4, 22.0, 0.0; IR (film): $\tilde{\upsilon}$ = 2360, 2358, 2550, 2341, 667 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{13}H_{24}O_2Si$+Na: 241.162142 [M^++ Na], found: 241.162386; elemental analysis calcd (%) for $C_{13}H_{24}O_2Si$: C 64.95, H 10.06; found: C 64.91, H 10.25.



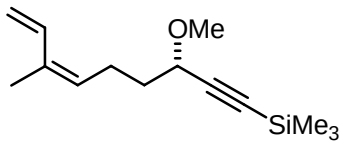
15b

MnO_2 (2.20 g, 0.0216 mol) was added in portions over 5 min to a solution of crude **15b** (260 mg, 0.00108 mol) in CH_2Cl_2 at 20ºC. The mixture was stirred for 13 h before it was filtered through a pad of Celite which was carefully rinsed with CH_2Cl_2. Evaporation of the combined filtrates gave aldehyde **16** as a colorless oil which was used in the next step without further purification (246 mg, 96%). $[\alpha]_D^{20} = -8.3$ (c = 1.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.98 (s, 1H), 6.51 (td, J = 8.3, 1.4 Hz, 1H), 3.95 (t, J = 6.3 Hz, 1H), 3.88 (s, 3H), 2.75 (m, 2H), 1.92-1.82 (m, 2H), 1.78 (d, J = 1.4 Hz, 3H), 0.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.2, 148.0, 136.7, 103.5, 91.6, 70.4, 56.5, 35.0, 22.4, 16.5, –0.1; IR (film): $\tilde{\upsilon}$ = 2960, 2901, 2824, 2170, 1723, 1682, 1450, 1381, 1334, 1251, 1108, 844, 761, 702 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{13}H_{22}O_2Si$+Na: 239.146505 [M^++Na]; found: 239.146734.

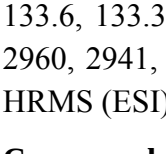


16

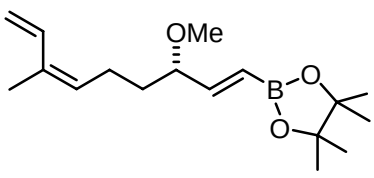
Compound 17. A solution of *n*-BuLi (0.7 mL, 1.58 M in hexanes) was added dropwise to a suspension of methyltriphenylphosphonium bromide (0.405 g, 0.00113 mol) in THF (3 mL) at −78ºC. The resulting mixture was allowed to reach ambient temperature. After stirring for 30 min, the orange solution was again cooled to −78ºC before a solution of aldehyde **16** (246 mg, 0.00103 mol) in THF (7 mL) was slowly added. The reaction was warmed to ambient temperature over the course of 1 h before being quenched with aq. sat. NH_4Cl. The aqueous phase was extracted with EtOAc, the combined organic extracts were dried over $MgSO_4$ and evaporated, and the crude product was adsorbed on Celite and purified by flash chromatography (hexanes/EtOAc, 100:1) to give product **17** as a colorless oil (243 mg, quant.). $[\alpha]_D^{20} = -1.2$ (c = 0.5, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.80 (ddd, J = 17.3, 10.8, 0.8 Hz, 1H), 5.37 (t, J = 7.7 Hz, 1H), 5.20 (dd, J = 17.3, 0.7 Hz, 1H), 5.08 (dt, J = 10.8, 1.6 Hz, 1H), 3.91 (t, J = 6.5 Hz, 1H), 3.38 (s, 3H), 2.33 (q, J = 7.5 Hz, 2H), 1.81 (d, J = 1.1 Hz, 3H), 1.80-1.60 (m, 2H), 0.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.6, 133.3, 129.8, 113.7, 104.5, 90.8, 70.9, 56.5, 35.5, 23.1, 19.8, 0.0; IR (film): $\tilde{\upsilon}$ = 3090, 2960, 2941, 2900, 2821, 2169, 1645, 1596, 1441, 1380, 1251, 1108, 1010, 902, 843, 760 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{14}H_{24}OSi$+Na: 236.159456 [M^++Na]; found: 236.159647.



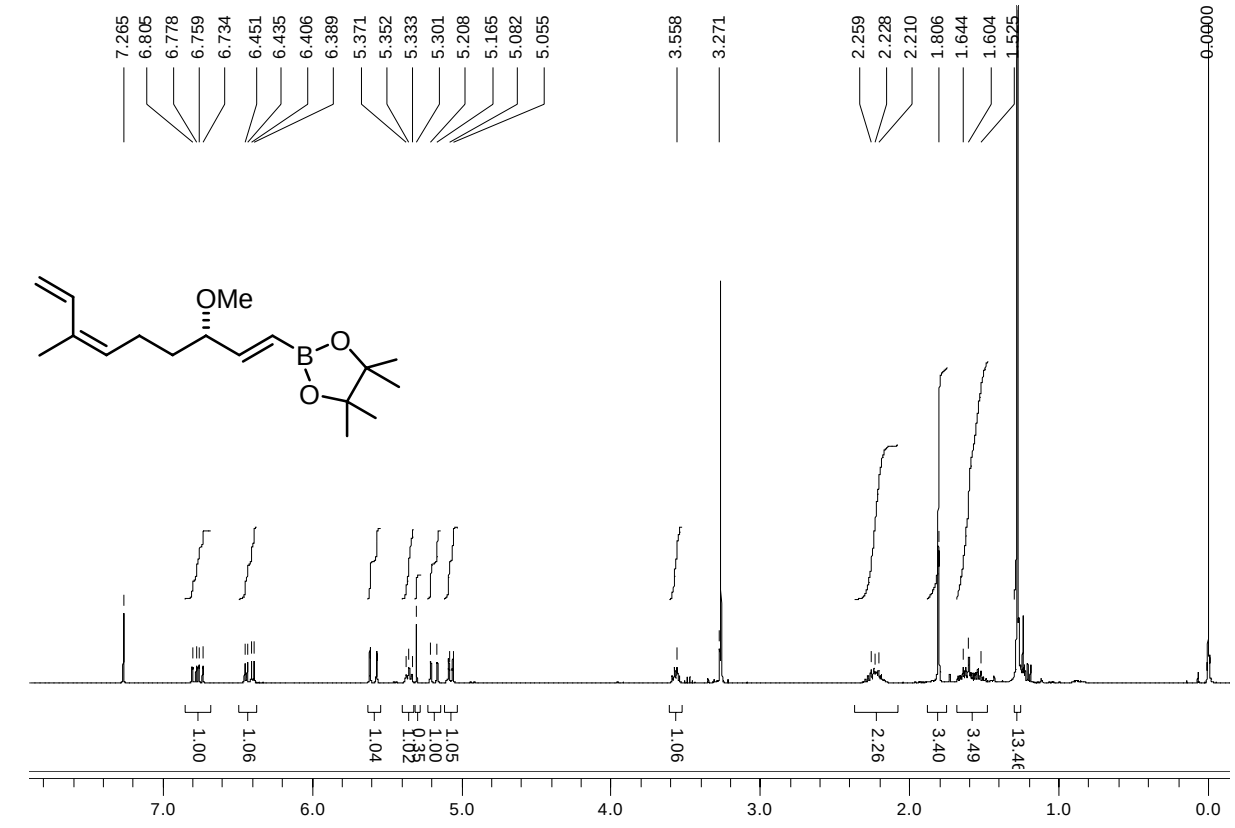
Compound 18. K_2CO_3 (426 mg, 0.00309 mol) was added in small portions over 5 min to a solution of compound **17** (243 mg, 0.00103 mol) in MeOH (20 mL). The resulting mixture was stirred for 3 h before it was filtered through a pad of Celite. The filtrate was evaporated and the crude product purified by flash chromatography (pentanes/Et_2O, 100:1) to give product **18** as a colorless oil (139 mg, 83%). Upon evaporation of the solvents, the heating bath of the rotary evaporator bath was set to 20°C and the pressure kept at ≥ 30 mbar. $[\alpha]_D^{20} = -17$ (c = 0.75, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.79 (ddd, J = 17.3, 10.8, 0.8 Hz, 1H), 5.37 (t, J = 7.6 Hz, 1H), 5.37 (t, J = 7.6 Hz, 1H), 5.20 (dd, J = 17.3, 0.7 Hz, 1H), 5.09 (dt, J = 10.8, 1.6 Hz, 1H), 3.91 (td, J = 6.6, 2.0 Hz, 1H), 3.40 (s, 3H), 2.45 (d, J = 2.0 Hz, 1H), 2.40-2.28 (m, 2H), 1.82 (d, J = 1.1 Hz, 3H), 1.87-1.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.5, 133.3, 129.5, 113.7, 82.6, 73.8, 70.2, 56.5, 35.5, 23.0, 19.8; IR (film): $\tilde{\upsilon}$ = 3297, 2939, 2856, 2824, 1644, 1597, 1462, 1441, 1382, 1355, 1260, 1107, 920, 905, 638 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{11}H_{16}O$+Na: 164.119954 [M^++Na]; found: 164.120114.



Compound 19. Pinacol borane (159 µL, 1.02 mmol) and 9-BBN (10.4 mg, 0.085 mmol) were added to a solution of compound **18** (139 mg, 0.85 mmol) in THF (1.7 mL) and the resulting mixture was stirred for 60 h at 45ºC. For work up, the reaction was quenched with aq. sat. NH_4Cl, the aqueous phase was extracted with EtOAc, the combined organic layers were dried over $MgSO_4$ and evaporated, and the crude product purified by flash chromatography (hexanes/EtOAc, 100:1→20:1) to give product **19** as a pale yellow oil (138 mg, 56%, 64% based on recovered **18**). $[\alpha]_D^{20} = +23$ (c = 0.3, CH_2Cl_2); ^{1}H



NMR (400 MHz, $CDCl_3$): δ = 6.77 (ddd, J = 17.4, 10.9, 0.8 Hz, 1H), 6.42 (dd, J = 18.1, 6.7 Hz, 1H), 5.69 (dd, J = 18.1, 1.1 Hz, 1H), 5.35 (t, J = 7.5 Hz, 1H), 5.18 (dd, J = 17.4, 0.9 Hz, 1H), 5.07 (dt, J = 10.9, 1.6 Hz, 1H), 3.59-3.54 (m, 1H), 3.27 (s, 3H), 2.32-2.16 (m, 2H), 1.81 (d, J = 1.1 Hz, 3H), 1.66-1.49 (m, 2H), 1.28 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.0, 133.7, 132.8, 130.4, 113.4, 83.3, 82.8, 56.8, 35.0, 24.8 (2C), 23.2, 19.8; the C-atom directly bonded to boron could not be detected because of line broadening caused by C,B-coupling; IR (film): $\tilde{\upsilon}$ = 3089, 2978, 2930, 1641, 1596, 1366, 1335, 1146, 990, 970, 849 cm^{-1}; HRMS (ESI): *m/z*: calcd for $BC_{17}H_{29}O_3$+Na: 315.210315 [M^++Na]; found: 315.210193.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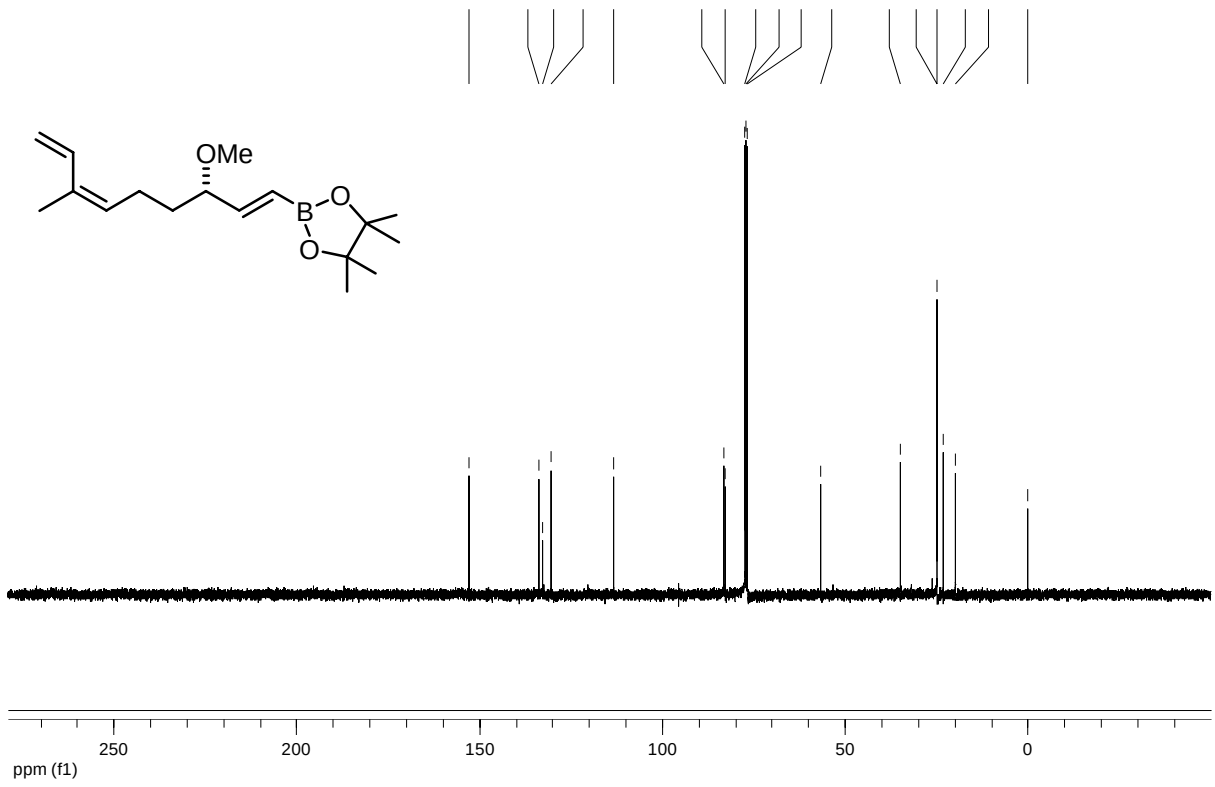
OMe
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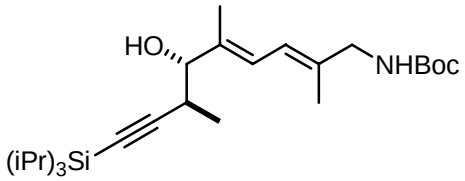
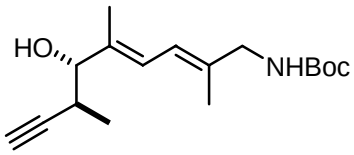
Building Blocks: Preparation of Vinyl Iodide 30

Compound 26. $Pd(OAc)_2$ (11 mg, 0.0489 mmol) and PPh_3 (13 mg, 0.0495 mmol) were added to a solution of mesylate **25a** (570 mg, 1.87 mmol)[10] in THF (15 mL) at −78°C. After stirring for 5 min, a solution of aldehyde **24** (231 mg, 0.965 mmol)[11] in THF (15 mL) was introduced, followed by the dropwise addition of a solution of $ZnEt_2$ (3.0 mL, 1 M in hexane). After stirring for 30 min, the mixture was warmed to –20°C over a period of 30 min and stirred overnight at that temperature. The reaction was quenched with aq. sat. NH_4Cl, the aqueous phase was extracted with *tert*-butyl methyl ether, the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated, and the crude product (d.r. = 7.5:1, NMR) was purified by flash chromatography (hexanes/EtOAc, 10:1→4:1) to give product **26** as a colorless oil (311 mg, 72%). $[\alpha]_D^{20}$ = +56.3 (*c* = 1.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.24 (d, *J* = 11.1 Hz, 1H), 6.12 (d, *J* = 11.1 Hz, 1H), 4.58 (bs, 1H), 3.85 (d, *J* = 7.2 Hz, 1H), 3.74 (d, *J* = 4.9 Hz, 2H), 2.74 (m, 1H), 2.38 (bs, 1H), 1.75 (s, 3H), 1.73 (s, 3H), 1.45 (s, 9H), 1.13 (d, *J* = 7.0 Hz, 3H), 1.05 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.1, 136.1, 135.6, 123.3, 120.9, 109.7, 83.8, 81.0, 79.5, 48.4, 33.1, 28.5, 18.7, 18.0, 15.0, 12.1, 11.3; IR (film): $\tilde{\upsilon}$ = 3358, 2941, 2865, 2164, 1696, 1506, 1462, 1388, 1247, 1168, 1075, 1017, 996, 882, 850, 675 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{26}H_{47}NO_3Si$+Na: 472.321738 [M^++Na]; found: 472.322127; elemental analysis calcd (%) for $C_{26}H_{47}NO_3Si$: C 69.43, H 10.53; found: C 69.54, H 10.46.



Compound 27. A solution of TBAF (0.09 mL, 1 M in THF) was added to a solution of compound **26** (226 mg, 0.502 mmol) in THF (8 mL) at 0°C. After stirring for 60 min, the reaction was quenched with H_2O, the aqueous phase was extracted with *tert*-butyl methyl ether, and the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. Purification of the residue by flash chromatography (hexanes/EtOAc, 2:1) gave product **27** as a colorless oil (139 mg, 94%). $[\alpha]_D^{20}$ = +48.3 (*c* = 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.23 (d, *J* = 11.1 Hz, 1H), 6.11 (d, *J* = 11.1 Hz, 1H), 4.62 (bs, 1H), 3.90 (dd, *J* = 7.6, 3.4 Hz, 1H), 3.73 (d, *J* = 5.4 Hz, 2H), 2.80-2.60 (m, 1H), 2.24 (d, *J* = 3.4 Hz, 1H), 2.16 (d, *J* = 2.4 Hz, 1H), 1.75 (s, 3H), 1.72 (s, 3H), 1.44 (s, 9H), 1.10 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.6, 135.5, 123.1, 120.1, 85.4, 80.5, 70.5, 47.8, 30.9, 28.0, 17.2, 14.5, 11.4; IR (film): $\tilde{\upsilon}$ = 3309, 2977, 2934, 1691, 1507, 1366, 1247, 1162, 1008, 752 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{17}H_{27}NO_3$+Na: 316.188315 [M^++Na]; found: 316.188513.



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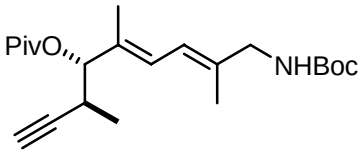
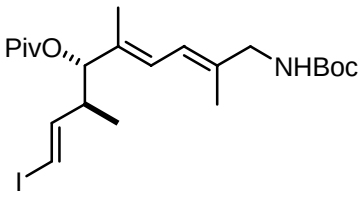
10 Marshall, J. A.; Eidam, P.; Eidam, H. S. *J. Org. Chem.* **2006**, *71*, 4840.

11 Cottard, M.; Kann, N.; Rein, T.; Akermark, B.; Helquist, P. *Tetrahedron Lett.* **1995**, *36*, 3115.

Compound 28. Pivaloyl chloride (0.29 mL, 0.00235 mol) was added dropwise to a solution of compound **27** (460 mg, 0.00157 mol) in pyridine (4 mL) at 0ºC. The mixture was stirred for 48 h at ambient temperature before the reaction was diluted with EtOAc and quenched with aq. HCl (1 M; saturated with NaCl). The aqueous phase was extracted with EtOAc, the combined organic layers were washed with brine, dried over $MgSO_4$ and adsorbed on silica. Purification by flash chromatography (hexanes/EtOAc, 25:1) gave product **28** as a yellow oil (416 mg, 76%). $[\alpha]_D^{20}$ = +17.7 (*c* = 1.19, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.27 (d, *J* = 11.3 Hz, 1H), 6.08 (d, *J* = 11.3 Hz, 1H), 5.07 (d, *J* = 7.8 Hz, 1H), 4.63 (bs, 1H), 3.72 (d, *J* = 5.3 Hz, 2H), 2.79 (m, 1H), 2.01 (d, *J* = 2.4 Hz, 1H), 1.73 (s, 3H), 1.71 (s, 3H), 1.43 (s, 9H), 1.21 (s, 9H), 1.10 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.3, 156.1, 136.5, 132.8, 124.6, 85.3, 80.8, 79.5, 69.7, 48.3, 39.1, 29.5, 28.5, 27.3, 17.6, 15.1, 12.6; IR (film): $\tilde{\upsilon}$ = 3314, 2976, 2933, 1712 (br), 1513, 1480, 1455, 1392, 1366, 1278, 1248, 1153, 1060, 1010, 969, 936, 874 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{22}H_{35}NO_4$+Na: 400.245951 [M^++Na]; found: 400.245829; elemental analysis calcd (%) for $C_{22}H_{35}NO_4$: C 69.99, H 9.34; found: C 69.95, H 9.60.

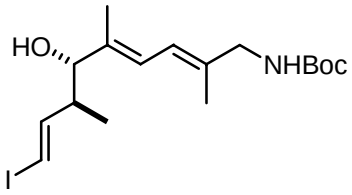


Compound 29. A solution of compound **28** (75.0 mg, 0.20 mmol) in THF (1.7 mL) was added dropwise to a suspension of Schwartz reagent (61 mg, 0.24 mmol) in THF (1 mL). After stirring for 1 h *in the dark*, the mixture was cooled to 0ºC before a solution of I_2 (76 mg, 0.30 mmol) in THF (1.5 mL) was added dropwise until a pale yellow color persisted. After stirring for 5 min, the reaction was quenched with aq. sat. $Na_2S_2O_3$ and diluted with *tert*-butyl methyl ether, and stirring was continued for another 10 min. The aqueous phase was then extracted with *tert*-butyl methyl ether, the combined organic layers were dried over $MgSO_4$ and evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc, 20:1) to give product **29** as a yellow oil (85 mg, 85%). $[\alpha]_D^{20}$ = +3 (*c* = 0.28, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.38 (dd, *J* = 14.4, 8.8 Hz, 1H), 6.20 (d, *J* = 11.0 Hz, 1H), 6.08 (d, *J* = 11.0 Hz, 1H), 6.06 (dd, *J* = 14.4, 0.7 Hz, 1H), 4.95 (d, *J* = 8.4 Hz, 1H), 4.59 (brs, 1H), 3.73 (d, *J* = 5.4 Hz, 2H), 2.59-2.50 (m, 1H), 1.75 (s, 3H), 1.70 (s, 3H), 1.50 (s, 9H), 1.09 (s, 9H), 0.93 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.1, 155.9, 147.5, 136.2, 132.8, 124.4, 120.2, 81.1, 75.9, 48.2, 43.3, 38.9, 28.4, 27.2, 16.3, 15.0, 12.4; one carbon signal is missing due to overlapping; IR (film): $\tilde{\upsilon}$ = 3380, 2975, 1717 (br), 1509, 1479, 1366, 1279, 1161, 963 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{22}H_{36}INO_4$+Na: 528.157591 [M^++Na]; found: 528.158125; elemental analysis calcd (%) for $C_{22}H_{36}INO_4$: C 52.37, H 6.87; found: C 52.28, H 7.18.



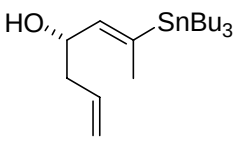
Compound 30. A solution of DIBAl-H (0.62 mL, 1 M in hexanes) was added dropwise to a solution of compound **29** (121 mg, 0.24 mmol) in CH_2Cl_2 (2.1 mL) at −78ºC. After stirring for 1 h, the reaction was quenched with EtOAc and warmed to ambient temperature before a saturated aqueous solution of Rochelle´s salt was introduced and stirring continued at 45ºC for 30 min. The

two phases were separated, the aqueous layer was extracted with EtOAc, the combined organic extracts dried over $MgSO_4$ and evaporated, and the crude product purified by flash chromatography (hexanes/EtOAc, 10:1→4:1) to give product **30** as a colorless oil (94 mg, 87%). $[\alpha]_D^{20}$ = +59 (*c* = 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 6.53 (dd, *J* = 14.4, 8.4 Hz, 1H), 6.20-6.10 (m, 3H), 4.61-4.57 (brs, 1H), 3.80 (d, *J* = 7.9 Hz, 2H), 3.75-3.73 (m, 2H), 2.46-2.36 (m, 1H), 1.76 (s, 3H), 1.73 (s, 3H), 1.46 (s, 9H), 0.91 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 156.2, 149.2, 137.4, 136.3, 123.4, 120.5, 81.4, 75.9, 48.4, 44.9, 28.5, 16.4, 15.0, 11.9; one carbon signal is missing due to overlapping; IR (film): $\tilde{\upsilon}$ = 3367, 2976, 1694 (br), 1512, 1366, 1249, 1168, 1008 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{17}H_{28}INO_3$+Na: 444.1010 [M^++ Na]; found: 444.1006.



Optimized Synthesis of Stannane 36

Compound 35. MnO_2 (4.9 g, 56 mmol) was added to a solution of compound **33** (774 mg, 2.14 mmol)[12] in CH_2Cl_2 (30 mL) and the resulting mixture stirred for 20 h. After filtration through a pad of Celite and evaporation of the filtrate, aldehyde **34** was obtained in sufficient quality for immediate use in the subsequent allylation (730 mg, 95% crude yield). The recorded spectroscopic data were identical to those reported in literature.[13]



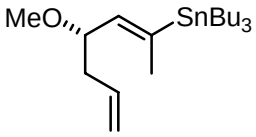
A solution of allylmagnesium bromide (2.85 mL, 1 M in Et_2O) was added dropwise over 30 min to a solution of (–)-Ipc_2BOMe (930 mg, 2.94 mmol) in Et_2O (2 mL) at 0°C. The resulting mixture was stirred for 30 min at 0°C before it was allowed to reach ambient temperature over the course of 1 h. The precipitated salts were filtered off under Ar through a pad of dried Celite and the filtrate was cooled to −78°C. A solution of crude aldehyde **34** (730 mg, 2.03 mmol) in Et_2O (2 mL) was added dropwise over 30 min and the resulting mixture stirred at that temperature for 2 h. The mixture was then allowed to reach ambient temperature over the course of 1 h before it was quenched with a mixture of H_2O_2 (1.5 mL, 30% *w/w*) and aq. NaOH (3.6 mL, 3 M). The mixture was refluxed for 1 h and then stirred at ambient temperature for 15 h before being diluted with EtOAc and extracted with brine. The organic layers were dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc, 20:1) to give product **35** as a colorless oil (614 mg, 75%, ee = 93%). $[\alpha]_D^{20}$ = –12 (*c* = 0.23, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.80 (m, 1H), 5.54 (m, 1H), 5.10 (m, 2H), 4.59 (m, 1H), 2.28 (m, 2H), 1.89 (s, 3H), 1.47 (m, 6H), 1.31 (m, 6H), 0.89 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.5, 141.6, 134.4, 117.8, 66.5, 41.9, 29.1, 27.3, 19.6, 13.6, 9.1; IR (film): $\tilde{\upsilon}$ = 3321, 2956, 2923, 2871, 2853,

[12] Betzer, J.-F.; Delaloge, F.; Muller, B.; Pancrazi, A.; Prunet, J. *J. Org. Chem.* **1997**, *62*, 7768.

[13] Dominguez, B.; Pazos, Y.; De Lera, A. R. *J. Org. Chem.* **2000**, *65*, 5917.

1641, 1463, 1376, 1339, 1292, 1070, 1018, 998, 911, 864, 663 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{19}H_{38}OSn$+Na: 425.183615 [M^++Na]; found: 425.183295; elemental analysis calcd (%) for $C_{19}H_{38}OSn$: C 56.88, H 9.55; found: C 56.68, H 9.56.

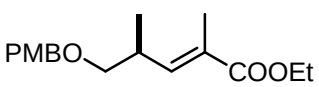
Compound 36. A solution of compound **35** (530 mg, 1.32 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 15 min to a mixture of Meerwein salt (260 mg, 1.75 mmol) and proton sponge (434 mg, 2.02 mmol) in CH_2Cl_2 (10 mL) at 0°C. After warming to ambient temperature within 1 h, the suspension was stirred for 14 h. For work up, the mixture was filtered through a pad of Celite, the filtrate was diluted with EtOAc and extracted with brine, the organic phases were dried over Na_2SO_4 and evaporated, and the residue purified by flash chromatography (hexanes/EtOAc, 20:1) to give product **36** as a colorless oil (481 mg, 88%). $[\alpha]_D^{20} = -23.6$ (*c* = 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.80 (m, 1H), 5.37 (dd, *J* = 8.6, 1.8 Hz, 1H), 5.05 (m, 2H), 4.14 (m, 1H), 3.27 (s, 3H), 2.35 (m, 1H), 2.22 (m, 1H), 1.88 (d, *J* = 1.8 Hz, 3H), 1.49 (m, 6H), 1.30 (m, 6H), 0.88 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.5, 140.5, 134.4, 116.3, 75.1, 55.5, 28.8, 26.9, 19.4, 13.3, 13.3, 7.2; IR (film): $\tilde{\upsilon}$ = 2956, 2924, 1641, 1463, 1098 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{20}H_{40}OSn$+Na: 439.199261 [M^++Na]; found: 439.199124.



Building Blocks: 'Second Generation' Synthesis of Compound 43

Compound 40. A solution of DIBAl-H (5.5 mL, 1 M in CH_2Cl_2) was added dropwise at −78ºC to a solution of compound **37** (1.2 g, 5 mmol) in CH_2Cl_2 (25 mL) and the resulting mixture was stirred for 30 min at that temperature before the reaction was quenched with EtOAc (6 mL).

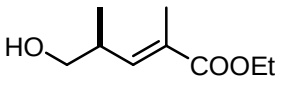
In a separated flask, phosphonate **44** (1.32 mL, 6.0 mmol) was added dropwise to a solution of LiHMDS (1.1 g, 6.5 mmol) in THF (25 mL) at −78°C and the mixture was stirred for 20 min before the solution containing the crude aldehyde **38** was slowly introduced. The resulting mixture was warmed to −40ºC and stirred for 17 h. For work up, the reaction was quenched with aq. sat. NH_4Cl, the mixture was stirred at 40ºC, an aq. solution of Rochelle´s salt (1 M) was added and stirring continued for 1 h until a clean separation of the phases was reached. The aqueous layer was extracted with EtOAc, the combined organic extracts were washed with brine, dried over $MgSO_4$ and evaporated to give the crude product as a 2.8:1 (*Z*/*E* mixture) which was used in the next step without further purification.



AIBN (164 mg, 1 mmol) and diphenyldisulfide (546 mg, 2.5 mmol) were successively added to a solution of the crude enoate **45** (5 mmol) in THF (17 mL) and the resulting mixture was stirred at reflux for 96 h until GC showed complete isomerization to the desired *E*-configurated isomer **40**. For work up, the mixture was evaporated and the residue purified by flash chromatography to give product **40** as a colorless oil (1.12 g, 77% over 3 steps). $[\alpha]_D^{20} = +8$ (*c* = 2.8, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.24 (ddd, *J* = 8.7, 2.8, 2.1 Hz, 2H), 6.87 (ddd, *J* = 8.7, 2.8, 2.1

Hz, 2H), 6.56 (dq, *J* = 9.7, 1.4 Hz, 1H), 4.41 (s, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 3.35 (d, *J* = 6.7 Hz, 2H), 2.88-2.77 (m, 1H), 1.84 (d, *J* = 1.4 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.01 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 168.7, 160.0, 145.0, 131.4, 129.9, 128.8, 114.4, 74.9, 73.4, 61.1, 55.9, 34.6, 17.1, 14.8, 13.1; IR (film): $\tilde{\upsilon}$ = 2961, 2932, 2856, 1708, 1650, 1613, 1586, 1513, 1463, 1366, 1301, 1246, 1172, 1146, 1085, 1035, 820, 749 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{17}H_{24}O_4$+Na: 315.1566 [M^++Na]; found: 315.1567.

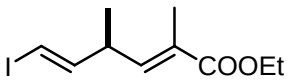
Compound 40b. DDQ (85 mg, 0.37 mmol) was added in one portion to a solution of compound **40** (100 mg, 0.34 mmol) in CH_2Cl_2 (2 mL) and H_2O (0.45 mL). After stirring for 1 h, the mixture was diluted with CH_2Cl_2 and successively washed with aq. sat. $NaHCO_3$ (2 x) and brine, the organic layer was dried over $MgSO_4$ and evaporated, and the residue purified by flash chromatography (hexanes/EtOAc, 8:1→4:1) to give product **40b** as a colorless oil (49 mg, 83%).



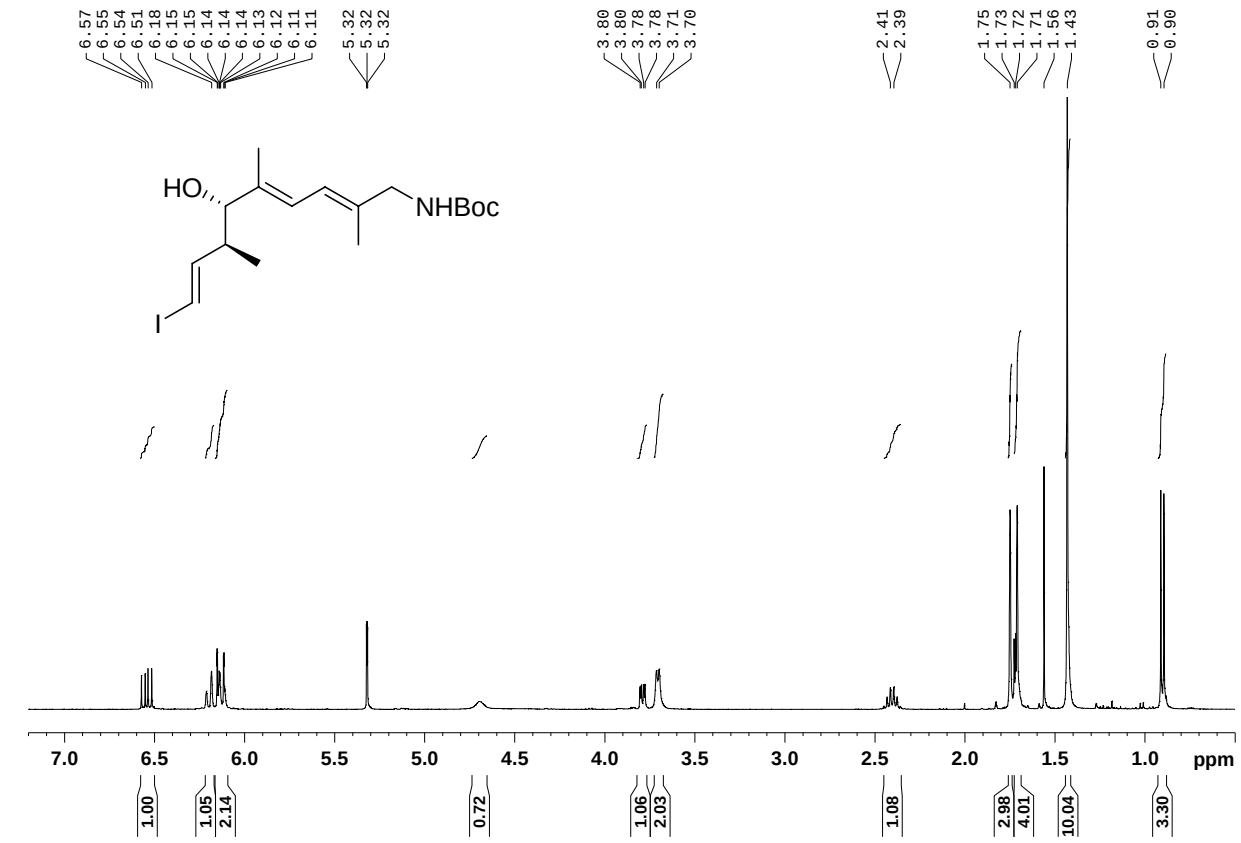
40b

$[\alpha]_D^{20}$ = –25.0 (*c* = 0.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.55 (dd, *J* = 9.9, 1.4 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.60-3.45 (m, 2H), 2.82-2.70 (m, 1H), 1.89 (d, *J* = 1.4 Hz, 3H), 1.40 (br, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.03 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.7, 143.3, 128.9, 66.8, 60.2, 35.9, 15.7, 13.9, 12.4; IR (film): $\tilde{\upsilon}$ = 3440, 2962, 2932, 2874, 1707, 1649, 1448, 1368, 1259, 1128, 1032, 748 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_9H_{16}O_3$+H: 173.1178 [M^++H]; found: 173.1176.

Compound 43. Dess-Martin periodinane (125 mg, 0.29 mmol) was added in one portion to a solution of compound **40b** (46 mg, 0.27 mmol) in CH_2Cl_2 (1.8 mL). After stirring for 30 min, the reaction was quenched with aq. sat. $NaHCO_3$ and the mixture diluted with hexanes before it was filtered through a pad of Celite. The aqueous phase was extracted with hexanes, and the combined organic phases were washed with brine, dried over $MgSO_4$ and evaporated. The residue was triturated with hexanes, insoluble residues were filtered off through a pad of Celite, and the filtrate was evaporated to give crude **41** which was immediately used in the next operation.



A solution of crude **41** thus formed and CHI_3 (173 mg, 0.440 mmol) in 1,4-dioxane (3.6 mL) was added dropwise to a suspension of $CrCl_2$·1.8 THF (278 mg, 1.1 mmol) in THF (0.7 mL). After stirring for 1 h, H_2O was introduced, the mixture was concentrated under vacuum, the aqueous phase was repeatedly extracted with *tert*-butyl methyl ether, the combined organic extracts were washed with brine, dried over $MgSO_4$ and evaporated, and the residue purified by flash chromatography (hexanes/Et_2O, 1:0→25:1) to give product **43** as a colorless oil (33 mg, 51%, containing < 15% **42**). $[\alpha]_D^{20}$ = +30 (*c* = 0.05, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2): δ (major product **43**) = 6.52-6.48 (m, 1H), 6.49 (dd, *J* = 14.5, 6.8 Hz, 1H), 6.10 (dd, *J* = 14.5, 1.3 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.30-3.20 (m, 1H), 1.84 (d, *J* = 1.5 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.14 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ (major product) = 168.1, 148.3, 142.4, 128.5, 75.5, 61.0, 40.1, 19.5, 14.4, 12.7; IR (film): $\tilde{\upsilon}$ = 2973, 1711, 1447, 1367, 1248, 1179, 1117, 947, 748, 720, 682 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{10}H_{15}O_2I$+Na: 317.00109 [M^++Na], found: 317.00090.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3.78
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3.70
2.41
2.39
1.75
1.73
1.72
1.71
1.56
1.43
0.91
0.90
HO
NHBoc
I
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6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
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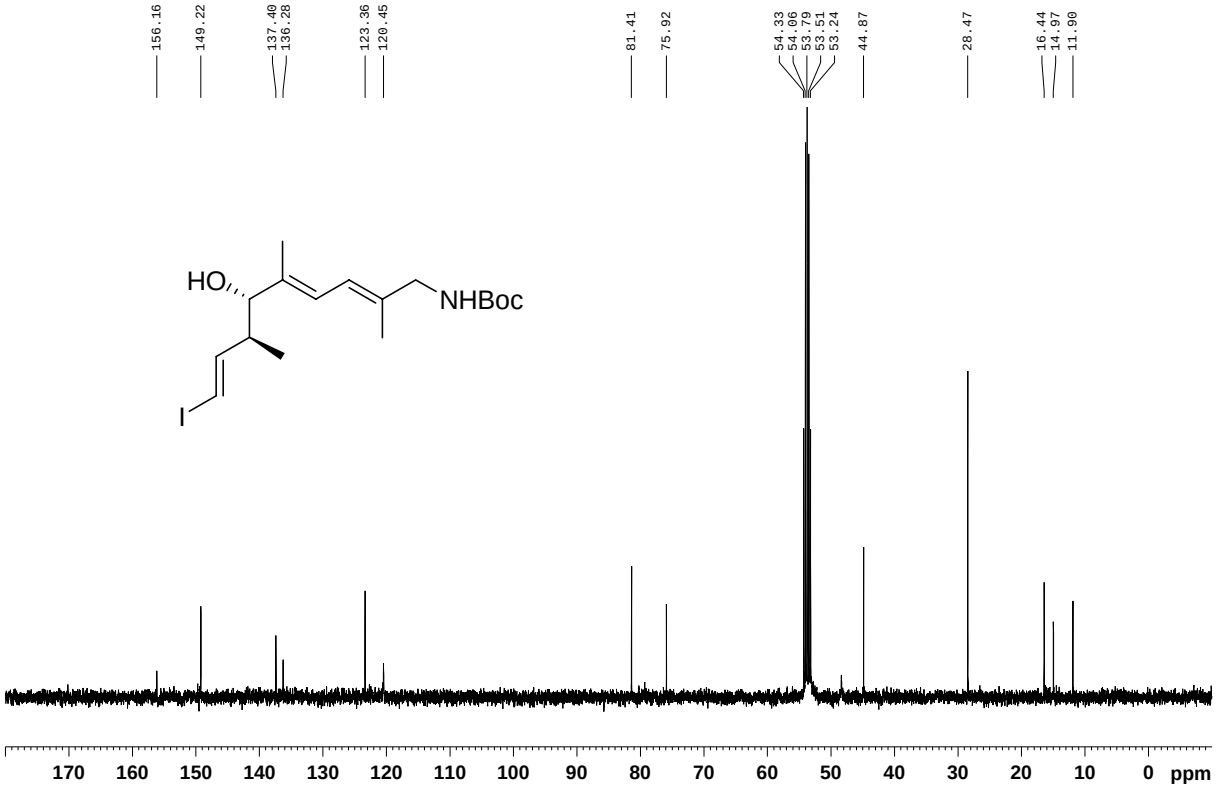
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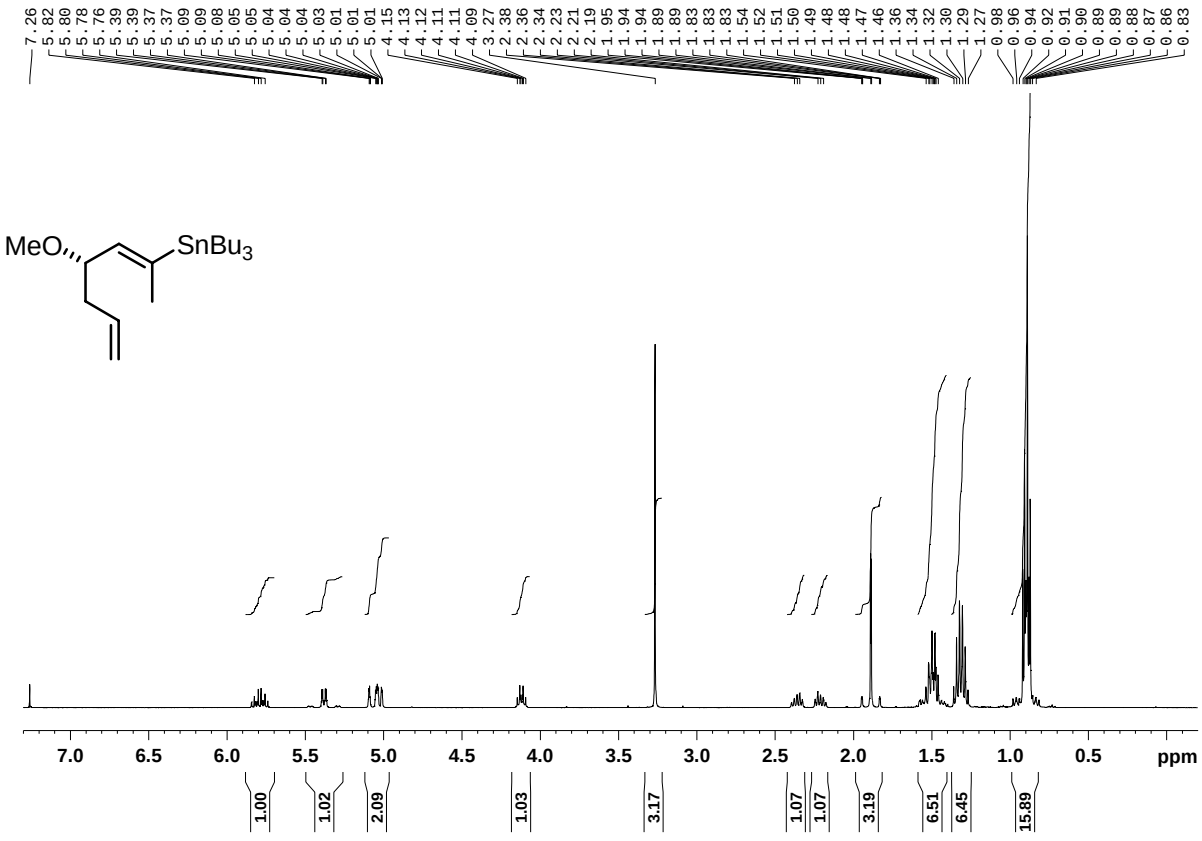
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3.19
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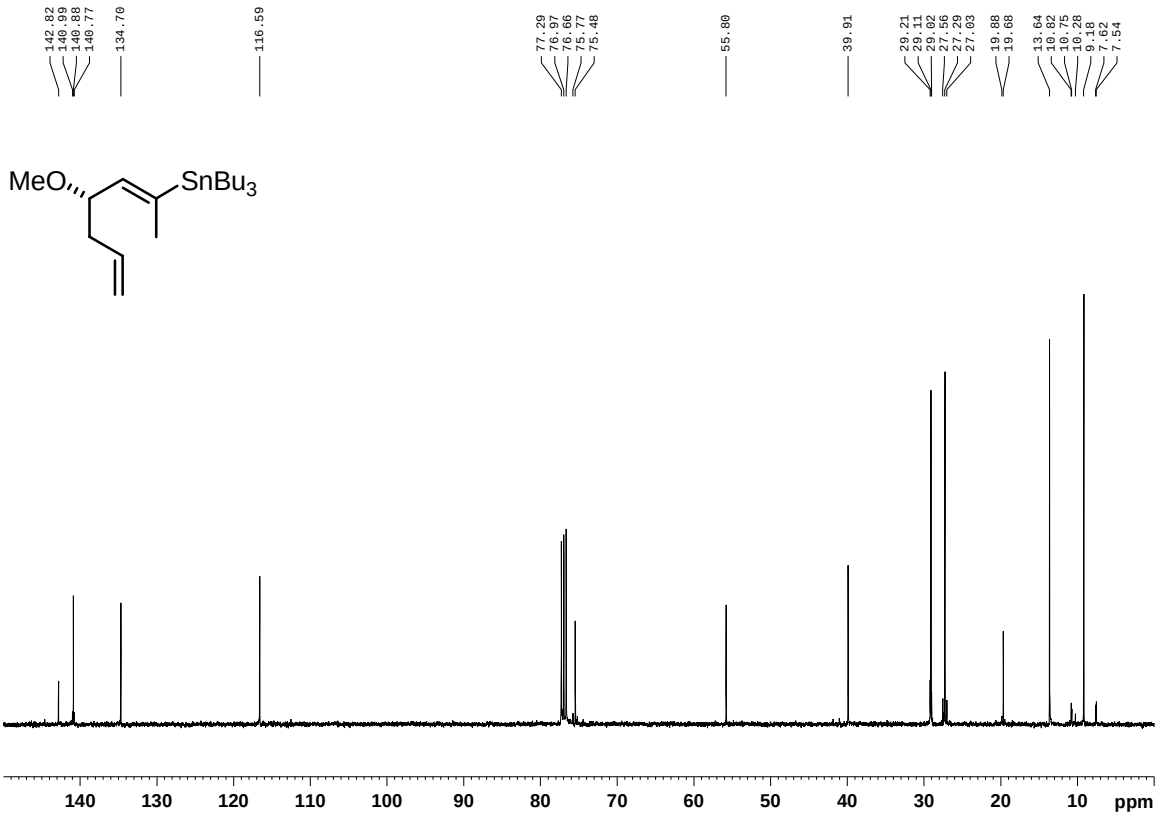
15.89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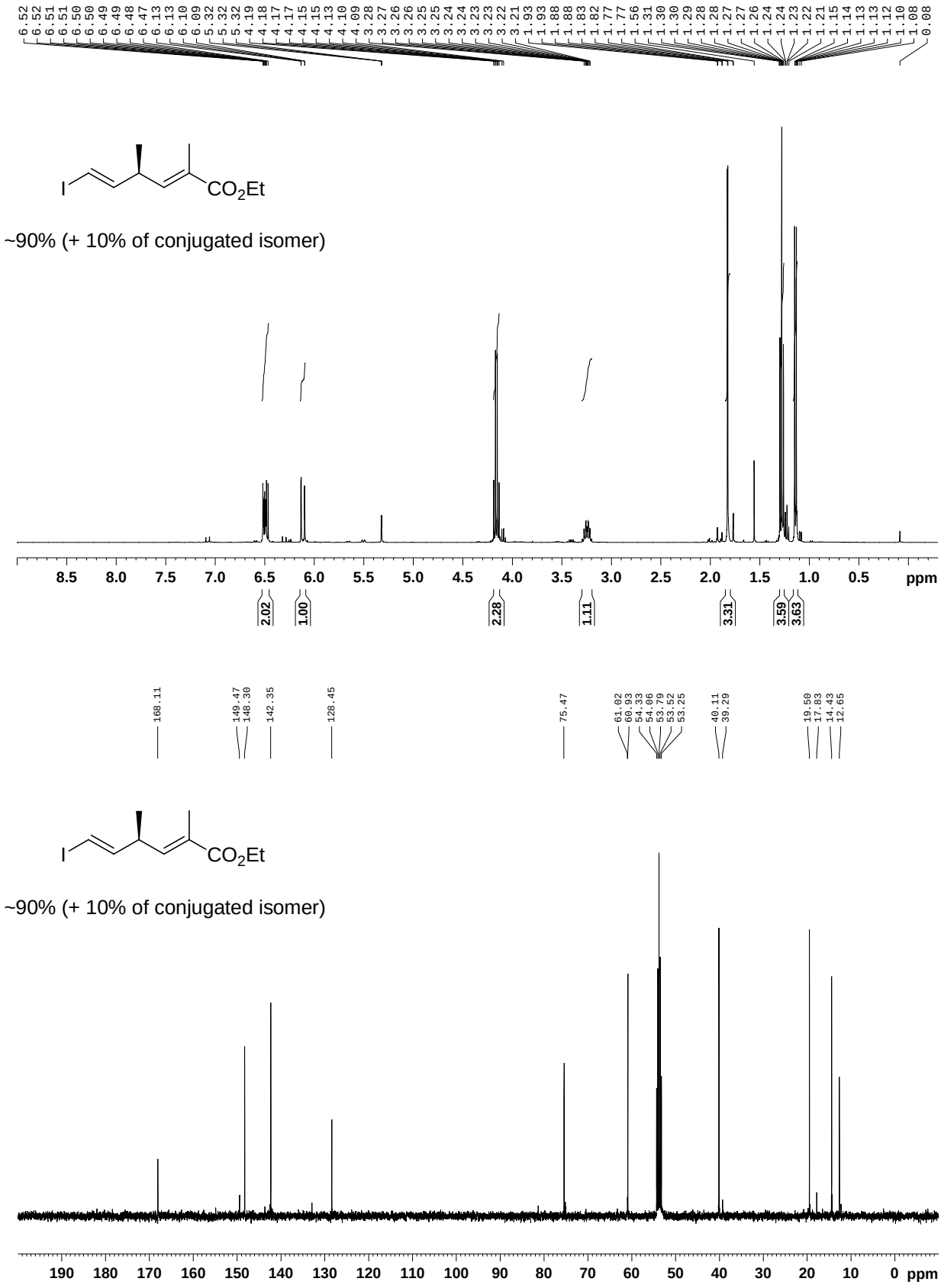
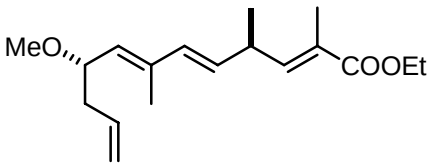
ppm

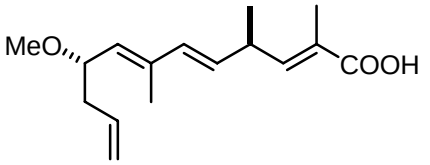


Fragment Coupling Reactions and Formation of Macrocycle 51

Compound 46. Compound **36** (358 mg, 0.86 mmol), compound **43** (containing ~10% of **42**, 221 mg, 0.75 mmol), CuTC (179 mg, 0.94 mmol) and $Pd(PPh_3)_4$ (38 mg, 0.033 mmol) were successively added to a solution of thoroughly dried $Ph_2PO_2NBu_4$ (432 mg, 0.94 mmol) in degassed DMF (8.4 mL). The resulting brown mixture was stirred for 1 h before it was diluted with H_2O/EtOAc, and filtered through a pad of Celite. The organic phase was washed with brine before it was dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexanes/EtOAc, 20:1) to give product **46** as a colorless oil (175 mg, 80%, containing about 10% of other isomers which cannot be separated at this stage). $[\alpha]_D^{20} = -25.8$ (c = 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.60 (d, J = 9.7 Hz, 1H), 6.08 (d, J = 15.7 Hz, 1H), 5.77 (m, 1H), 5.57 (dd, J = 15.7, 6.8 Hz, 1H), 5.28 (d, J = 9.0 Hz, 1H), 5.05 (m, 2H), 4.19 (q, J = 7.1 Hz, 2H), 4.04 (m, 1H), 3.28 (m, 1H), 3.24 (s, 3H), 2.37 (m, 1H), 2.23 (m, 1H), 1.87 (s, 3H), 1.77 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H), 1.16 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.4, 144.8, 136.5, 134.6, 133.5, 131.5 (2x), 126.8, 117.0, 76.9, 60.6, 56.1, 40.1, 36.4, 20.4, 14.4, 13.1, 12.6; IR (film): $\tilde{\upsilon}$ = 2977, 2929, 2873, 1711, 1643, 1448, 1367, 1263, 1240, 1098, 966, 750 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{18}H_{28}O_3$+Na: 315.193066 [M^++Na]; found: 315.192829.

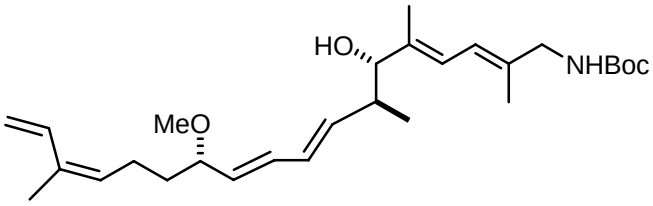


Compound 47. A solution of LiOH (1.5 mL, 1 M in H_2O) was added to a solution of compound **46** (66 mg, 0.226 mmol, about 90% of the main isomer) in MeOH (1 mL) and THF (1 mL) and the resulting mixture was stirred for 24 h. For work up, the mixture was acidified to a pH ≈ 3 with aq. HCl (0.5 M) and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and evaporated, and the residue purified by flash chromatography (hexanes/EtOAc, 4:1) to give isomerically and analytically pure product **47** as a colorless oil (50 mg, 85%). $[\alpha]_D^{20} = -42.7$ (c = 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 6.75 (dd, J = 9.8, 1.2 Hz, 1H), 6.11 (d, J = 15.7 Hz, 1H), 5.82-5.70 (m, 1H), 5.61 (dd, J = 15.7, 6.9 Hz, 1H), 5.27 (d, J = 9.0 Hz, 1H), 5.08-4.99 (m, 2H), 4.10-4.00 (m, 1H), 3.38-3.23 (m, 1H), 3.31 (s, 3H), 2.40-2.30 (m, 1H), 2.27-2.18 (m, 1H), 1.87 (d, J = 1.2 Hz, 3H), 1.78 (d, J = 1.2 Hz, 3H), 1.17 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 174.3, 148.3, 137.2, 135.5, 134.4, 132.5, 131.8, 126.6, 117.2, 77.5, 56.4, 40.7, 37.3, 20.7, 13.6, 12.7; IR (film): $\tilde{\upsilon}$ = 2964, 2927, 1683, 1640, 1418, 1274, 1094, 963 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{16}H_{24}O_3$-H: 263.165268 [M^--H]; found: 263.165497.

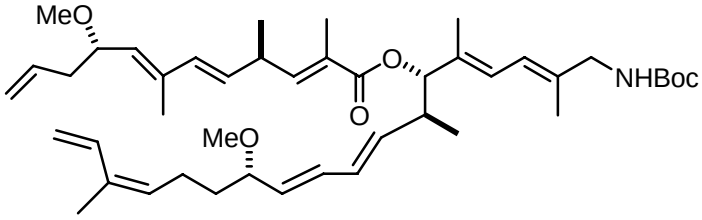


Compound 48. $Pd(dppf)Cl_2$ (3 mg, 0.0039 mmol) and $Ba(OH)_2 \cdot 8H_2O$ (12 mg, 0.039 mmol) were added to a solution of compounds **19** (9 mg, 0.031 mmol) and **30** (11 mg, 0.026 mmol) in DMF (0.6 mL). The mixture was vigorously stirred at 40ºC for 3 h, before it was diluted with EtOAc and quenched with ice water. The aqueous phase was repeatedly extracted with EtOAc, the combined organic extracts were washed with brine, dried over $MgSO_4$ and evaporated, and the residue purified by flash chromatography (hexanes/EtOAc, 4:1) to give product **48** as a colorless

oil (8.0 mg, 66%). $[\alpha]_D^{20}$ = +13 (*c* = 0.14, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 6.69 (dd, *J* = 17.4, 10.9 Hz, 1H), 6.08 (m, 4H), 5.30 (m, 1H), 5.23 (m, 2H), 5.10 (d, *J* = 17.4 Hz, 1H), 4.99 (d, *J* = 10.8 Hz, 1H), 4.60 (brs, 1H), 3.62 (m, 3H), 3.43 (m, 1H), 3.12 (s, 3H), 2.14 (m, 2H), 2.10 (m, 2H), 1.72 (s, 3H), 1.66 (s, 3H), 1.64 (s, 3H), 1.45 (m, 2H), 1.35 (s, 9H), 0.79 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 135.8, 132.9, 132.0, 131.6, 130.2, 129.8 (2x), 122.1, 119.5, 112.3, 80.9, 80.4, 55.1, 47.3, 40.4, 34.8, 27.3, 22.4, 18.7, 16.1, 13.8, 10.7; IR (film): $\tilde{\upsilon}$ = 3415, 3348,3088, 2974, 2929, 2871, 2822, 1700, 1659, 1595, 1512, 1453, 1390, 1366, 1250, 1170, 1099, 991, 935, 868, 802 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{28}H_{45}NO_4$+Na: 482.324190 [M^++ Na]; found: 482.324076.

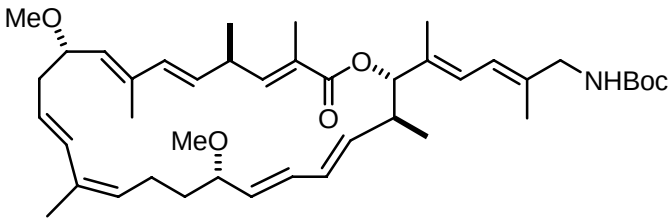


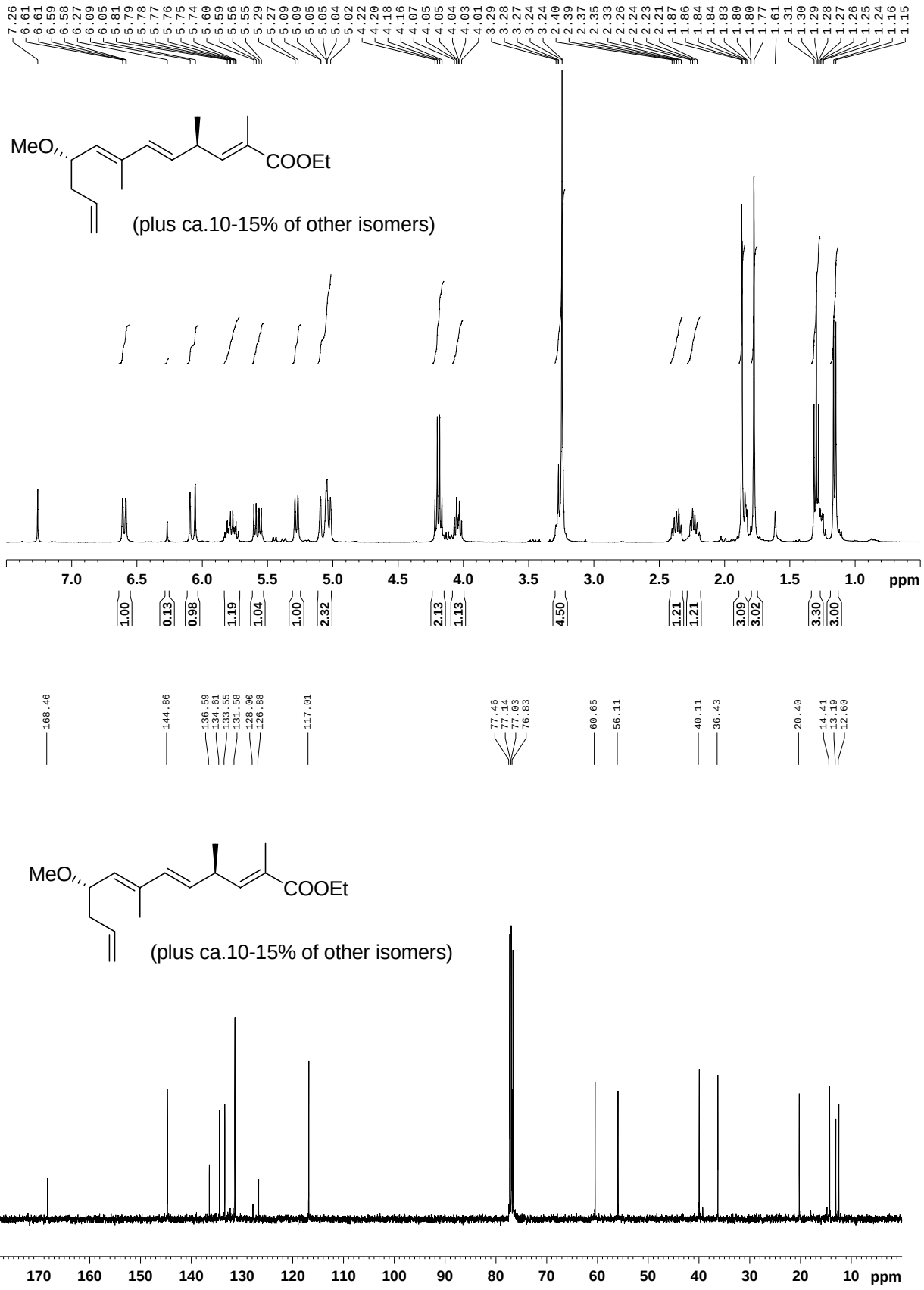
Compound 49. 2,4,6-Trichlorobenzoylchloride (14 µL, 0.088 mmol), Et_3N (10 µL, 0.066 mmol), and DMAP (3 mg, 0.022 mmol) were added to a solution of compounds **47** (13 mg, 0.044 mmol) and **48** (13 mg, 0.029 mmol) in toluene (1 mL) and the resulting mixture was stirred at ambient temperature for 4 days. The crude mixture was adsorbed on silica and the product purified by flash chromatography (hexanes/EtOAc, 4:1) to give compound **49** as a yellow oil (15 mg, 73 %). ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 6.77 (dd, *J* = 17.3, 11.2 Hz, 1H), 6.57 (dd, *J* = 9.7, 1.4 Hz, 1H), 6.25 (d, *J* = 10.4 Hz, 1H), 6.17-6.02 (m, 4H), 5.76 (m, 1H), 5.59 (m, 2H), 5.43-5.28 (m, 2H), 5.26-5.13 (m, 2H), 5.10-4.97 (m, 4H), 4.70 (bs, 1H), 4.04 (m, 1H), 3.69 (d, *J* = 5.8 Hz, 2H), 3.49 (q, *J* = 6.8 Hz, 1H), 3.25-3.19 (m, 1H), 3.20 (s, 3H), 3.17 (s, 3H), 2.62 (m, 1H), 2.34 (m, 1H), 2.26-2.13 (m, 3H), 1.83 (d, *J* = 1.5 Hz, 3H), 1.80 (d, *J* = 0.9 Hz, 3H), 1.76 (d, *J* = 1.1 Hz, 3H), 1.74 (s, 6H), 1.66-1.55 (m, 2H), 1.43 (s, 9H), 1.13 (d, *J* = 6.7 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 167.4, 156.1, 145.1, 136.8, 136.7, 136.3, 135.2, 134.3, 134.1, 133.7, 133.1, 132.9, 132.7, 131.9, 131.8, 131.0, 130.6, 127.1, 124.4, 120.3, 116.8, 113.4, 83.0, 81.6, 77.1 (2x), 56.1, 56.0, 48.4, 40.4, 39.9, 36.6, 36.0, 28.5, 23.6, 20.5, 19.9, 17.0, 15.0, 13.2, 12.7, 12.6; IR (film): $\tilde{\upsilon}$ = 3355, 3073, 2974, 2929, 2874, 2817, 1713, 1644, 1585, 1508, 1450, 1389, 1366, 1262, 1168, 1099, 990, 968 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{44}H_{67}NO_6$+Na: 728.486059 [M^++Na]; found: 728.485578.



Compound 51. Complex **50** (0.6 mg, 0.00071 mmol) was added to a solution of compound **49** (5 mg, 0.007 mmol) in CH_2Cl_2 (10 mL) and the resulting solution was stirred at ambient temperature for 24 h. At that point, a second batch of **50** (0.6 mg, 0.00071 mmol) was introduced and stirring continued for additional 24 h. The reaction was then quenched with ethyl vinyl ether, all volatile materials were evaporated, and the residue purified by flash chromatography (hexanes/EtOAc, 4:1) to give product **51** as a yellow oil (4.8 mg, 96%). $[\alpha]_D^{20}$ = +14.0 (*c* = 0.05,

CH_2Cl_2); ^{1}H NMR (600 MHz, CD_2Cl_2): δ = 6.57 (dq, J = 10.3, 1.5 Hz, 1H), 6.47 (d, J = 15.4 Hz, 1H), 6.30 (dq, J = 11.2, 1.3 Hz, 1H), 6.13 (dq, J = 11.2, 1.4 Hz, 1H), 6.04 (dd, J = 14.8, 10.5 Hz, 1H), 5.97 (dd, J = 15.2, 10.5 Hz, 1H), 5.89 (d, J = 15.5 Hz, 1H), 5.52 (ddd, J = 15.5, 10.1, 4.5 Hz, 1H), 5.48 (dd, J = 15.4, 8.9 Hz, 1H), 5.38 (dd, J = 15.2, 8.0 Hz, 1H), 5.37 (dd, J = 14.8, 9.2 Hz, 1H), 5.18 (dd, J = 9.2, 6.0 Hz, 1H), 5.10 (d, J = 10.1 Hz, 1H), 5.08 (d, J = 9.8 Hz, 1H), 4.68 (brs, 1H), 4.11 (ddd, J = 10.0, 9.5, 2.8 Hz, 1H), 3.70 (m, 2H), 3.26 (ddd, J = 10.4, 8.0, 3.2 Hz, 1H), 3.21 (s, 3H), 3.14 (m, 1H), 2.94 (s, 3H), 2.63 (d, J = 13.6 Hz, 1H), 2.54 (tq, J = 9.6, 6.9 Hz, 1H), 2.53-2.51 (m, 1H), 2.30 (ddd, J = 13.7, 10.0, 10.0 Hz, 1H), 1.90 (dq, J = 13.6, 6.0 Hz, 1H), 1.78 (s, 3H), 1.77 (s, 3H), 1.77 (d, J = 1.3 Hz, 3H), 1.75 (s, 3H), 1.74 (d, J = 1.2 Hz, 3H), 1.58 (ddt, J = 13.9, 9.7, 4.8 Hz, 1H), 1.43 (s, 9H), 1.29 (dddd, J = 14.0, 11.2, 5.3, 3.3 Hz, 1H), 1.04 (d, J = 6.7 Hz, 3H), 0.92 (d, J = 6.8 Hz, 1H); ^{13}C NMR (150 MHz, CD_2Cl_2): δ = 167.6, 156.2, 145.6, 137.2, 137.1, 136.3, 133.8, 133.7, 133.3, 133.1, 132.4, 132.3, 132.1, 131.2, 129.8, 128.8, 126.0, 125.7, 125.4, 120.3, 83.3, 79.8, 77.9, 77.0, 56.5, 55.9, 48.4, 41.0, 41.0, 38.3, 35.3, 28.5, 23.2, 21.5, 20.8, 16.8, 15.1, 13.2, 12.1, 12.1; HRMS (ESI): m/z: calcd for $C_{42}H_{63}NO_6$+Na: 700.4552 [M^++Na]; found: 700.4546.

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MeO
COOEt
(plus ca.10-15% of other isomers)
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 ppm
1.00 0.13 0.98 1.19 1.04 1.00 2.32 2.13 1.13 4.50 1.21 1.21 3.09 3.02 3.30 3.00
168.46 144.86 136.59 134.61 133.55 131.58 128.00 126.88 117.01 77.46 77.14 77.03 76.83 60.65 56.11 40.11 36.43 20.40 14.41 13.19 12.60
MeO
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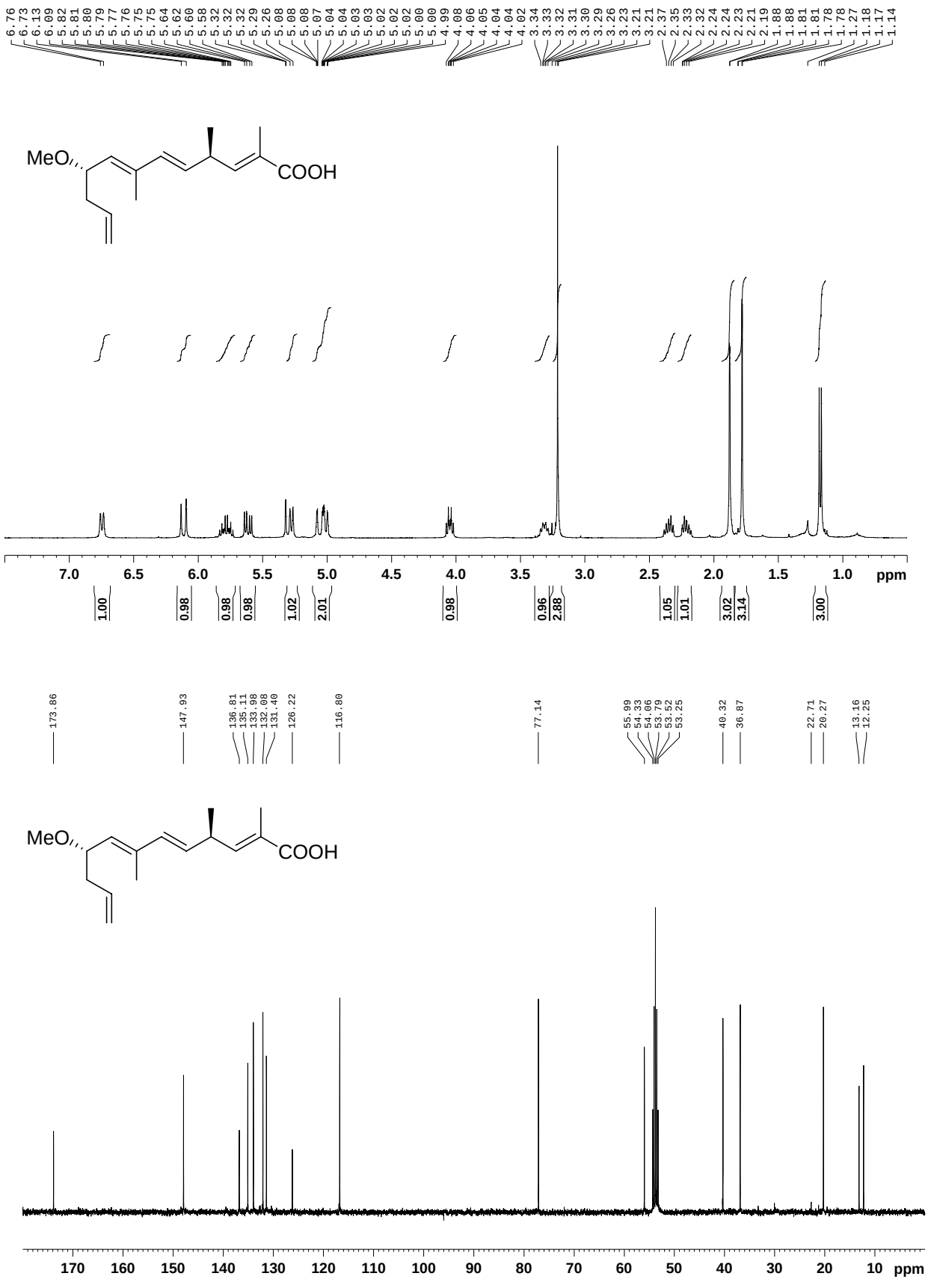
(plus ca.10-15% of other isomers)
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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MeO
COOH
7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00 0.98 0.98 0.98 1.02 2.01 0.98 0.96 2.88 1.05 1.01 3.02 3.14 3.00
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COOH
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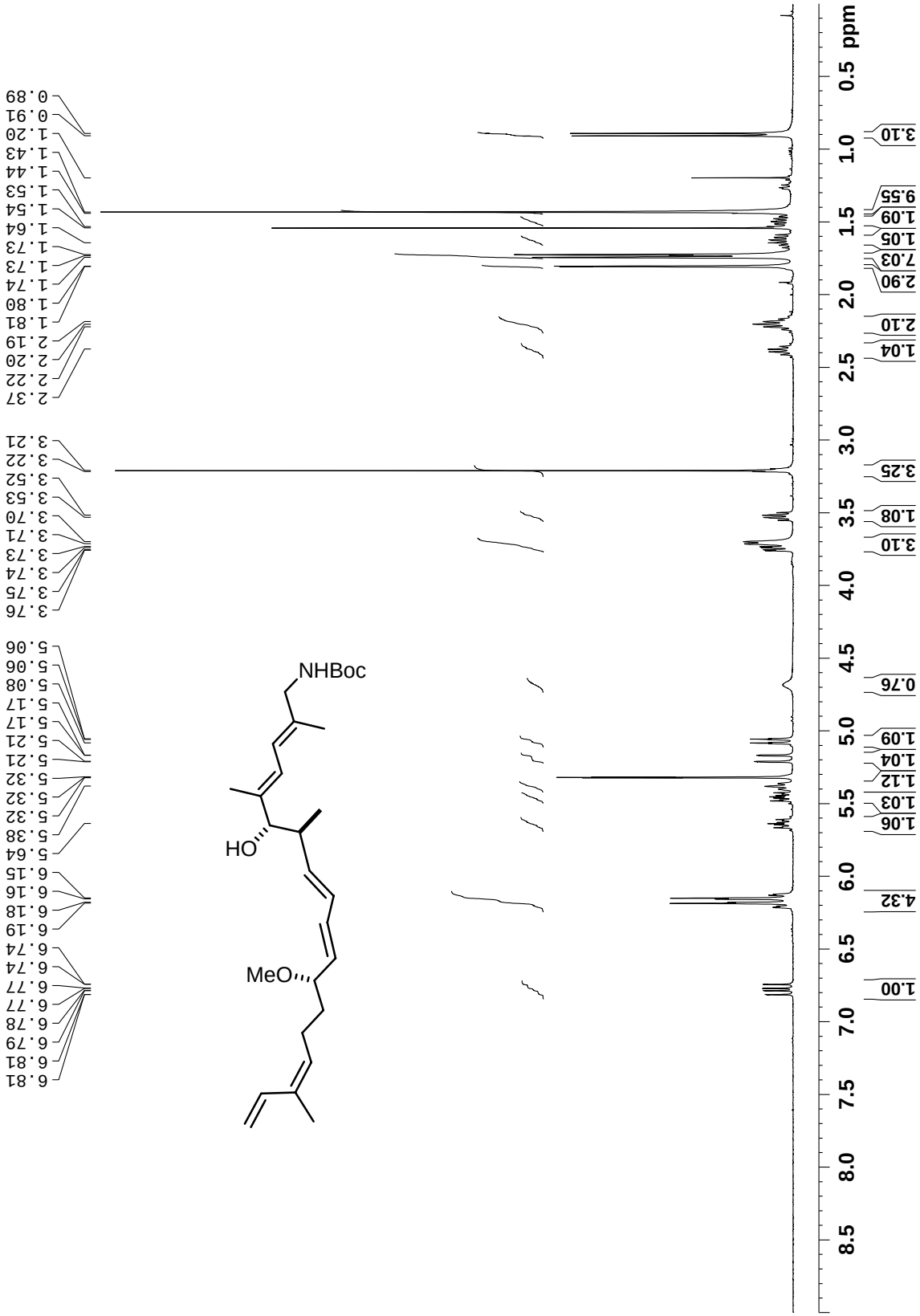
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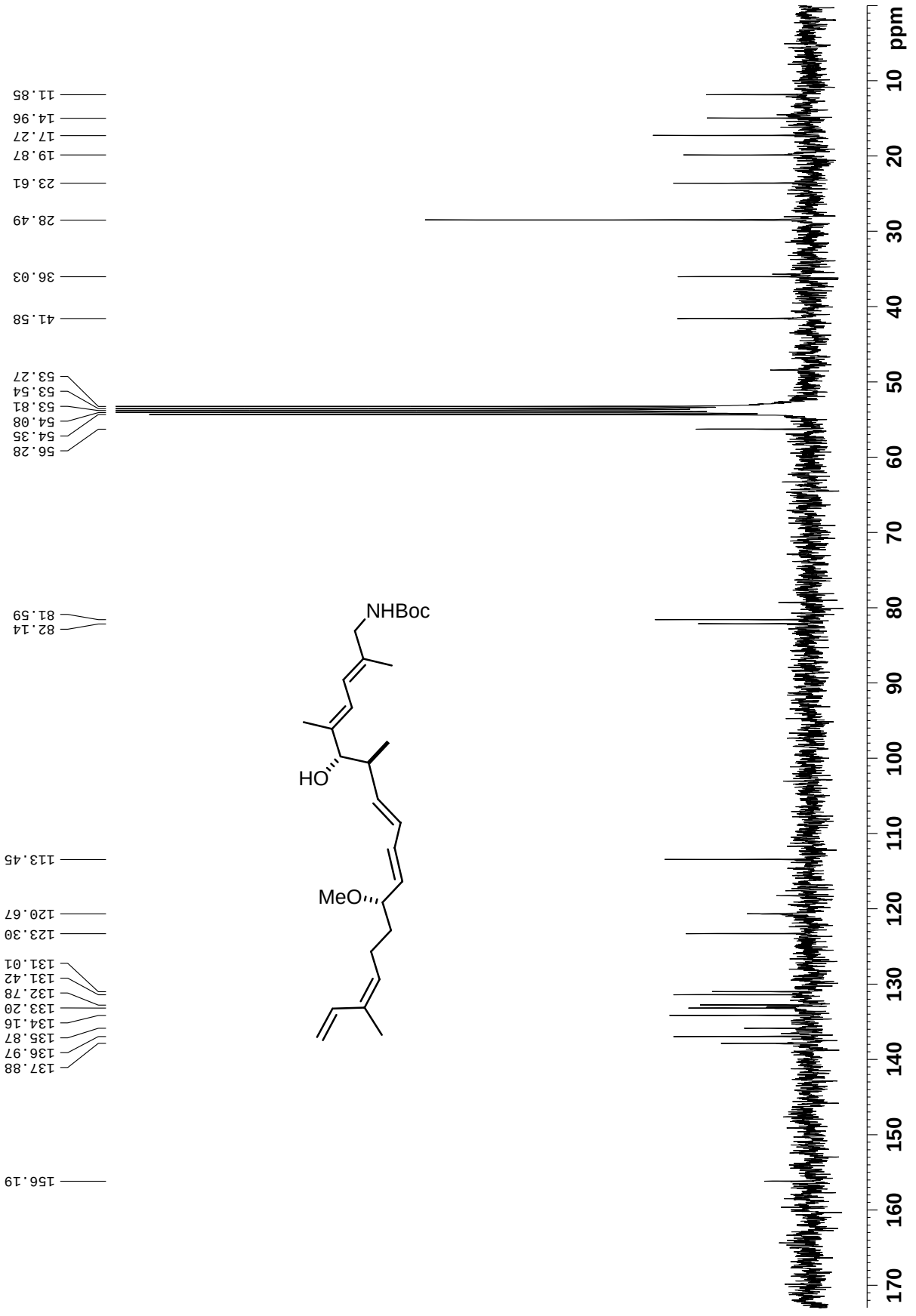
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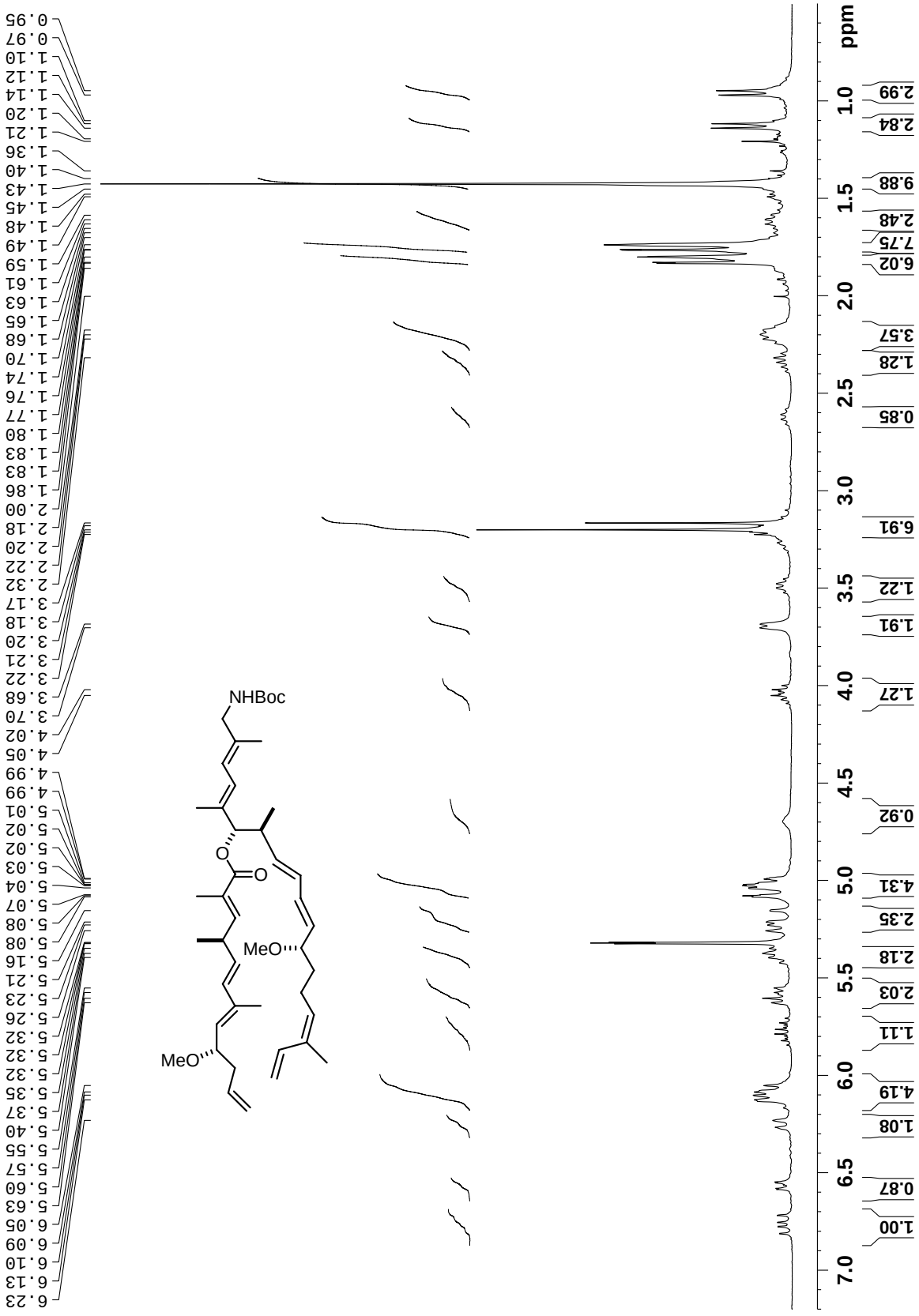
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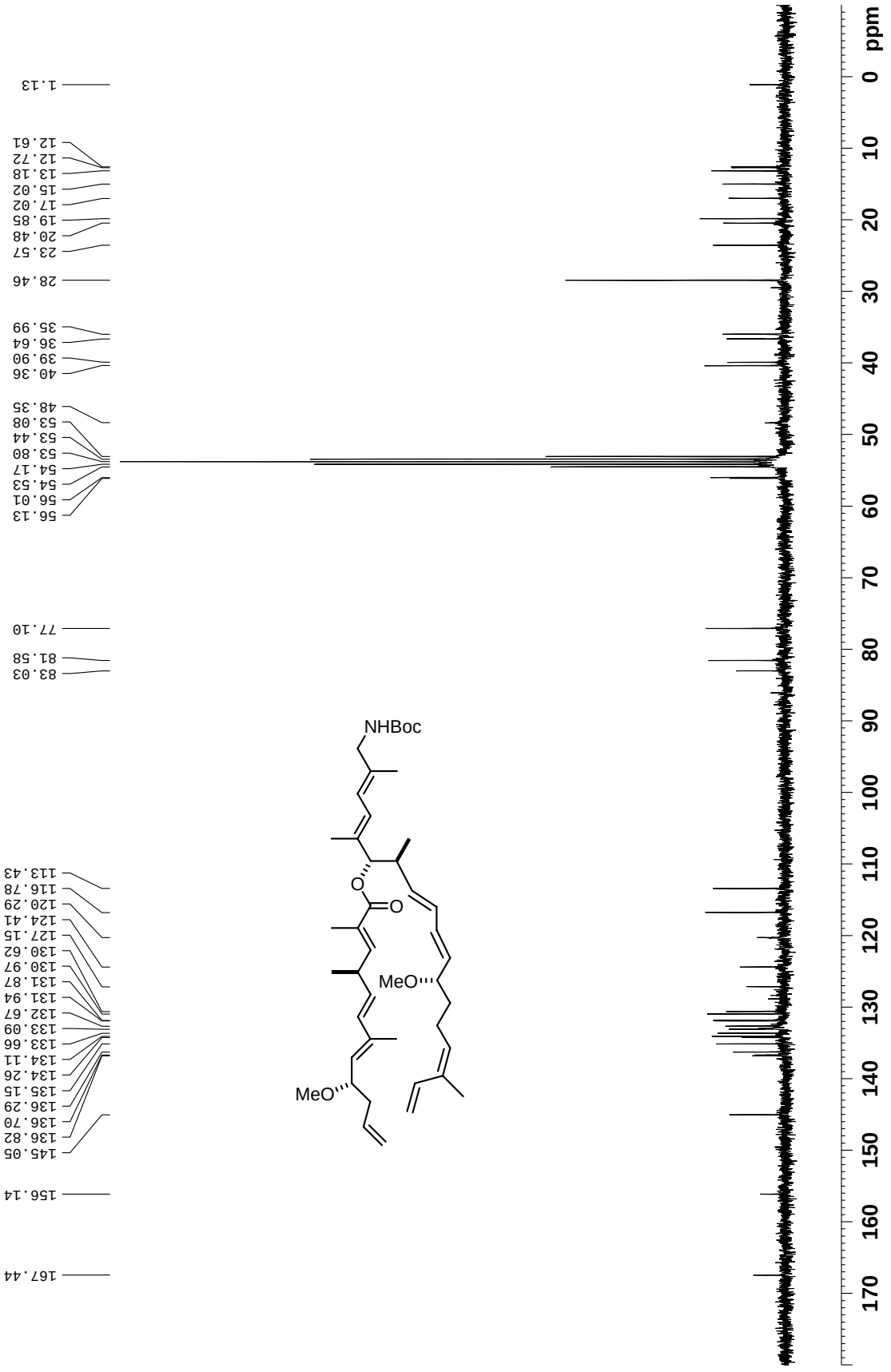
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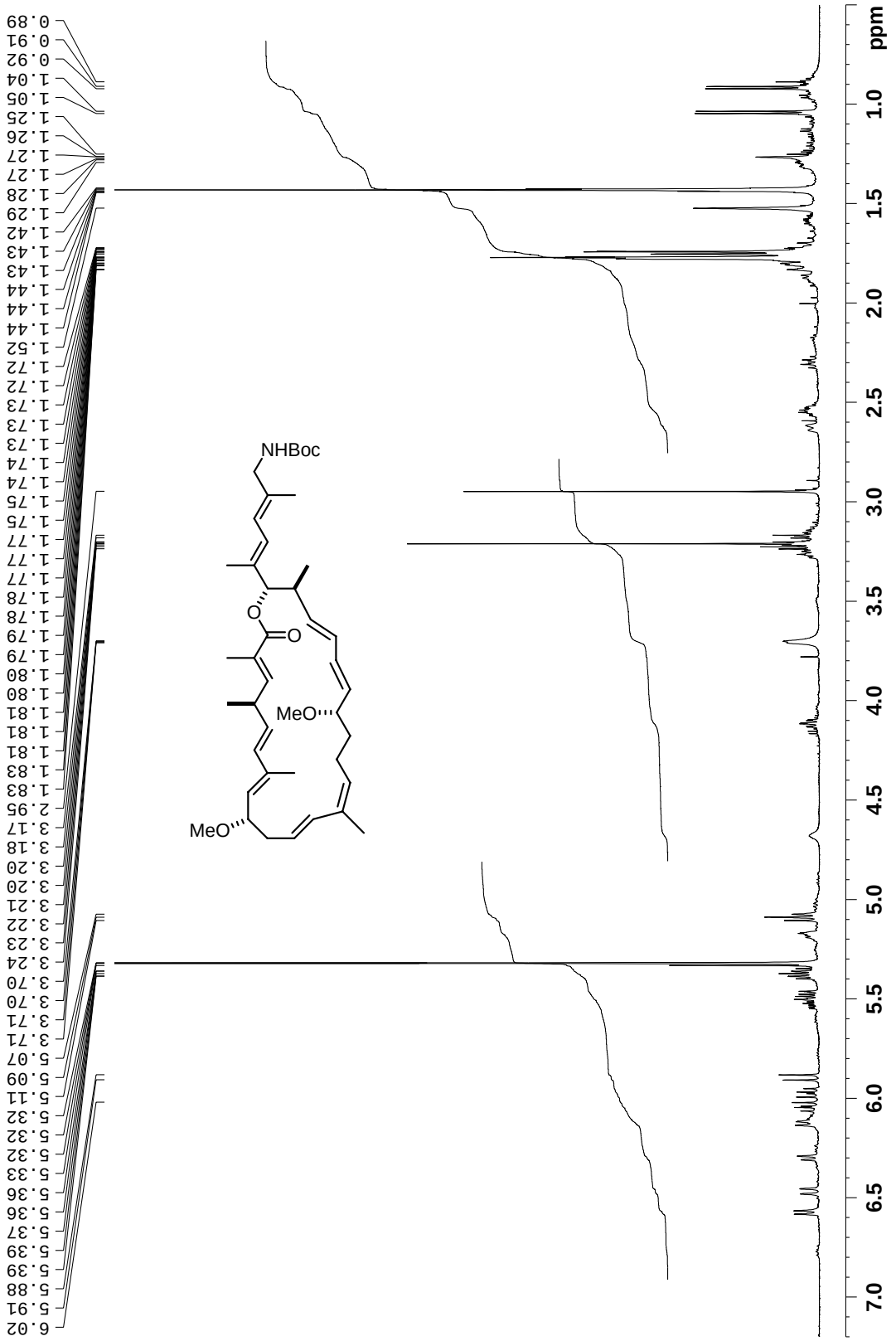
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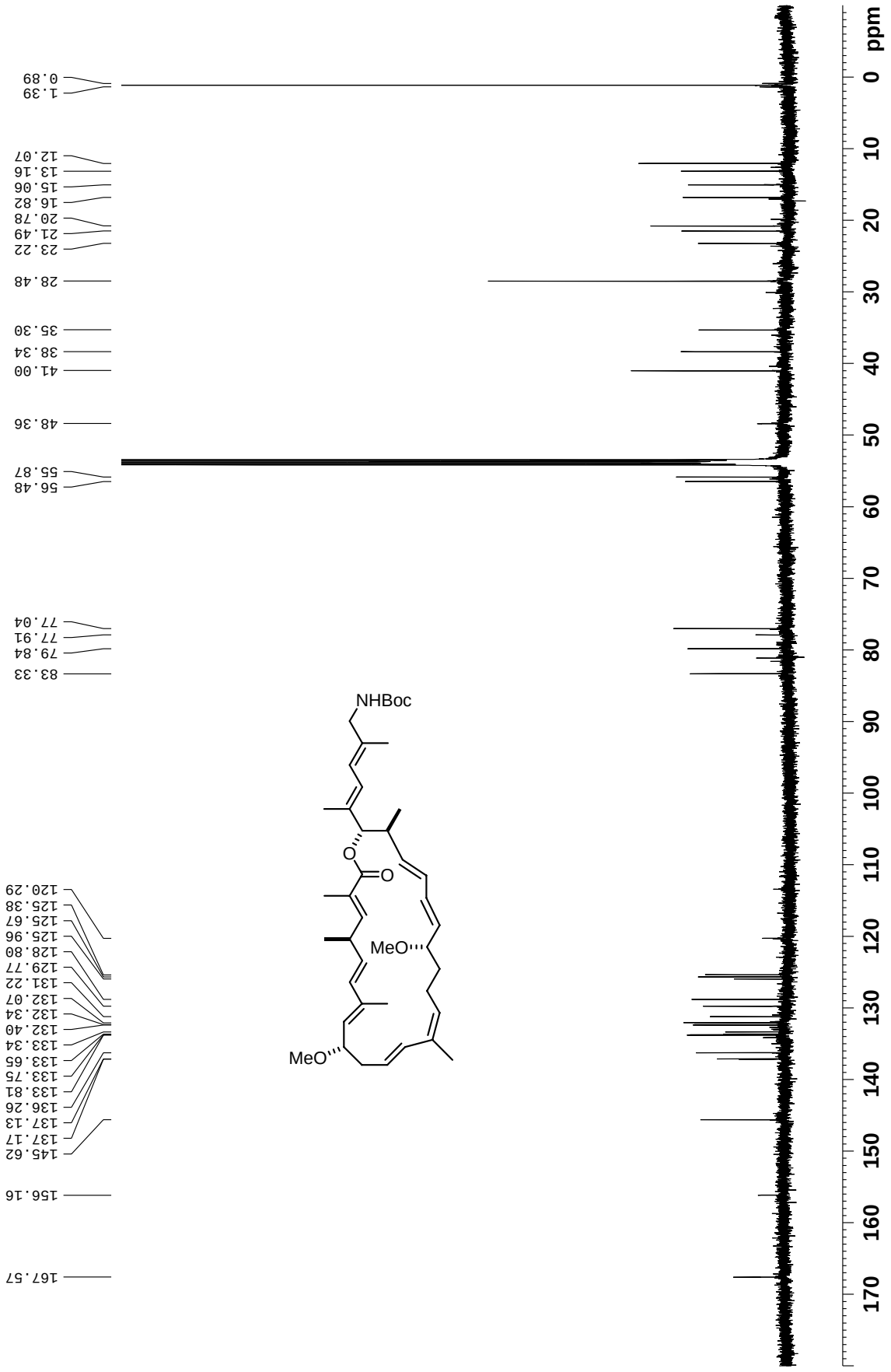
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40
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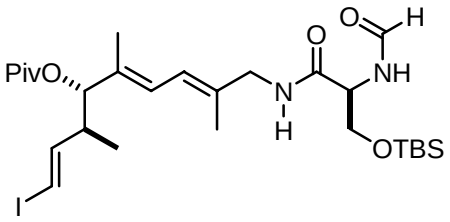
60
70
80
90
100
110
120
130
140
150
160
170

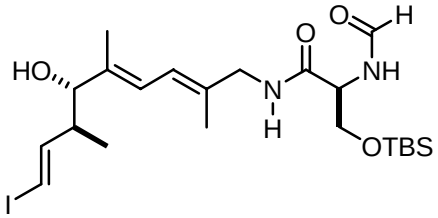
‘First Generation’ Total Synthesis of Iejimalide B

Compound 52. TMSOTf (50 μL, 0.279 mmol) was added dropwise to a solution of 2,6-lutidine (38 μL, 0.325 mmol) in CH_2Cl_2 (0.5 mL) at 0°C. After stirring for 5 min, the resulting solution was transferred via syringe to a solution of compound **29** (47 mg, 0.093 mmol) in CH_2Cl_2 (1 mL) at 0°C. The resulting mixture was stirred for 3 h before the reaction was quenched with aq. sat. $NaHCO_3$, the aqueous phase was extracted with CH_2Cl_2, the combined organic phases were washed with aq. CsF (0.5 M), and the fluoride solution was extracted with CH_2Cl_2. The combined organic extracts were washed with brine before being dried over Na_2SO_4 and evaporated.



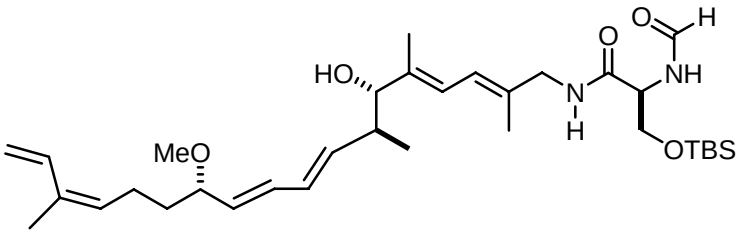
Compound **57** (30 mg, 0.12 mmol), *N*-methylmorpholine (30 μL, 0.28 mmol) and HOBt (15 mg, 0.11 mmol) were successively added to a solution of the crude amine thus formed in CH_2Cl_2 (2 mL). The resulting solution was cooled to 0°C before EDC (25 mg, 0.13 mmol) was introduced and stirring continued overnight at ambient temperature. The mixture was evaporated and the residue partitioned between H_2O and EtOAc. The combined organic layers were washed with aq. HCl (0.1 M) and brine, before they were dried over Na_2SO_4 and evaporated. Flash chromatography of the residue (hexanes/EtOAc, 55:45) afforded product **52** as a colorless oil (50 mg, 85%). $[\alpha]_D^{20}$ = +11.8 (*c* = 1.35, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 8.23 (s, 1H), 6.60-6.50 (bs, 2H), 6.40 (dd, *J* = 14.4, 8.8 Hz, 1H), 6.22-6.08 (m, 3H), 4.93 (d, *J* = 8.3 Hz, 1H), 4.43-4.38 (m, 1H), 4.10-4.00 (m, 1H), 3.97-3.80 (m, 2H), 3.62 (dd, *J* = 9.8, 7.7 Hz, 1H), 2.62-2.53 (m, 1H), 1.75 (s, 3H), 1.71 (s, 3H), 1.18 (s, 9H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 9H), 0.09 (d, *J* = 9.8 Hz, 6H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 177.7, 170.2, 161.6, 148.5, 136.0, 134.5, 124.8, 122.0, 81.8, 76.6, 63.5, 47.8, 44.0, 39.6, 27.7, 26.3, 18.8, 16.9, 15.6, 13.0, –5.1; IR (film): $\tilde{\upsilon}$ = 3303, 2957, 2929, 2857, 1727, 1650, 1534, 1383, 1245, 1150, 836 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{27}H_{47}N_2O_5NaSiI$: 657.219121 [M^++Na]; found: 657.219663.

Compound 53. A solution of $LiBEt_3H$ (236 μL, 1.0 M in THF) was added dropwise to a solution of compound **52** (50 mg, 0.0788 mmol) in THF (2 mL) at 0°C and the resulting mixture was stirred for 1 h before additional $LiBEt_3H$ (39 μL, 1.0 M in THF) was introduced. After 30 min, a third portion of $LiBEt_3H$ (39 μL, 1.0 M in THF) was added and stirring continued for another 30 min. At this point the solution was neutralized with aq. sat. NH_4Cl, the aqueous phase was extracted with *tert*-butyl methyl ether, the combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc, 1:1) to give product **53** as a colorless oil (30 mg, 70%). $[\alpha]_D^{20}$ = +29.3 (*c* = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 8.22 (s, 1H), 6.63-6.48 (m, 3H), 6.20-6.10 (m, 3H), 4.47-4.40 (m, 1H), 4.04 (dd, *J* =

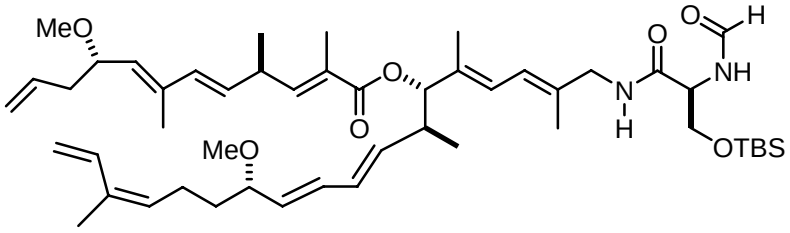


9.8, 4.0 Hz, 1H), 3.98-3.81 (m, 2H), 3.78 (d, J = 7.9 Hz, 1H), 3.62 (dt, J = 8.8, 1.9 Hz, 1H), 2.44-2.35 (m, 1H), 1.74 (s, 3H), 1.71 (s, 3H), 0.90-0.85 (m, 12H), 0.10 (s, 3H). 0.08 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 170.2, 161.6, 149.6, 138.5, 135.3, 123.5, 122.3, 81.7, 76.4, 63.5, 53.4, 47.8, 45.2, 26.3, 18.8, 16.8, 15.5, 12.4, –5.0; IR (film): $\tilde{\upsilon}$ = 3302, 2928, 2857, 1650, 1530, 1385, 1255, 1107, 953, 834, 710 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{22}H_{39}N_2O_4ISi$+Na: 573.161605 [M^++Na]; found: 573.161674.

Compound 54. $Pd(dppf)Cl_2$ (4.0 mg, 0.0054 mmol) and $Ba(OH)_2 \cdot 8H_2O$ (17 mg, 0.054 mmol) were added to a solution of compounds **19** (12 mg, 0.040 mmol) and **53** (20 mg, 0.036 mmol) in DMF (0.8 mL). The mixture was vigorously stirred at 20ºC for 3 h before it was diluted with *tert*-butyl methyl ether and quenched with ice water. The aqueous phase was extracted with *tert*-butyl methyl ether, and the combined organic extracts were repeatedly washed with brine before they were dried over $MgSO_4$ and evaporated. Purification of the residue by flash chromatography (hexanes/EtOAc, 5:1→1:1) furnished product **54** as a colorless oil (15 mg, 70%). $[\alpha]_D^{20}$ = +6.3 (c = 0.5, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 8.26 (s, 1H), 6.76 (ddd, J = 17.3, 10.8, 0.6 Hz, 1H), 6.61-6.59 (brm, 2H), 6.20-6.13 (m, 4H), 5.63 (dd, J = 12.1, 3.9 Hz, 1H), 5.46 (dd, J = 14.4, 8.1 Hz, 1H), 5.36 (t, J = 7.2 Hz, 1H), 5.18 (d, J = 17.3 Hz, 1H), 5.07 (d, J = 10.8 Hz, 1H), 4.49-4.44 (m, 1H), 4.09 (dd, J = 9.6, 4.0 Hz, 1H), 3.96-3.86 (m, 2H), 3.75 (d, J = 8.5 Hz, 1H), 3.58 (dd, J = 9.6, 8.4 Hz, 1H), 3.56-3.50 (m, 1H), 3.24 (s, 3H), 2.38 (m, 1H), 2.21-2.18 (m, 2H), 1.81 (s, 3H), 1.75 (s, 3H), 1.74 (s, 9H), 1.68-1.50 (m, 2H), 0.90 (d, J = 8.1 Hz, 3H), 0.88 (s, 9H), 0.115 (s, 6H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 169.2, 160.6, 137.5, 135.9, 133.5, 133.4, 132.6, 132.4, 132.0, 131.0, 130.1, 122.8, 121.8, 113.0, 81.5, 80.9, 75.9, 62.2, 55.9, 52.5, 47.0, 40.9, 35.2, 25.5, 22.9, 19.5, 17.7, 16.7, 14.6, 11.4, –5.8, –5.9; IR (film): $\tilde{\upsilon}$ = 3286, 2929, 2859, 1652, 1548, 1462, 1386, 1257, 1106, 990, 837, 778 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{33}H_{56}N_2O_5Si$+Na: 611.385351 [M^++ Na]; found: 611.385069.



Compound 55. DCC (5.3 mg, 0.0255 mmol) and 4-pyrrolidinyl-pyridine (1.2 mg, 0.0076 mmol) were added in portions to a solution of acid **47** (7.5 mg, 0.0255 mmol) in CH_2Cl_2 (0.1 mL) at 0ºC. After stirring for 10 min, the mixture was cooled to 0ºC and a solution of compound **54** (15 mg, 0.0255 mmol) in THF (0.1 mL) was added dropwise. The mixture was allowed to reach ambient temperature and was stirred for 17 h before being filtered through a pad of Celite. Evaporation of the filtrate followed by purification of the residue by flash chromatography (hexanes/EtOAc, 20:1→1:1) provided



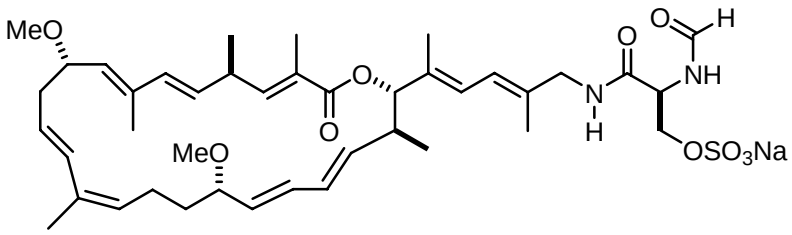
product **55** as a pale yellow oil (18 mg, 85%). $[\alpha]_D^{20}$ = +10 (*c* = 1.1, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 8.22 (s, 1H), 6.76 (ddd, *J* = 16.2, 11.1, 0.6 Hz, 1H), 6.56 (dd, *J* = 9.6, 1.2 Hz, 1H), 6.51-6.48 (brm, 2H), 6.23 (d, *J* = 10.2 Hz, 1H), 6.15-6.06 (m, 4H), 5.77 (ddt, *J* = 17.4, 10.2, 7.2 Hz, 1H), 5.61-5.57 (m, 2H), 5.41-5.33 (m, 2H), 5.24 (d, *J* = 9.0 Hz, 1H), 5.19 (d, *J* = 17.4 Hz, 1H), 5.07-5.05 (m, 4H), 4.42 (td, *J* = 6.6, 4.2 Hz, 1H), 4.07-4.00 (m, 2H), 3.62 (dd, *J* = 9.6, 7.8 Hz, 1H), 3.50 (dd, *J* = 12.6, 7.8 Hz, 1H), 3.29-3.20 (m, 1H), 3.21 (s, 3H), 3.18 (s, 3H), 2.55 (m, 1H), 2.25-2.18 (m, 2H), 1.85 (d, *J* = 1.2 Hz, 3H), 1.82 (d, *J* = 1.2 Hz, 3H), 1.79 (d, *J* = 1.2 Hz, 3H), 1.76 (bs, 6H), 1.65-1.60 (m, 1H), 1.52-1.46 (m, 1H), 1.15 (d, *J* = 6.6 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.90 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 169.8 167.4, 161.1, 145.1, 136.8, 136.2, 135.3, 135.2, 134.9, 134.1, 133.7, 133.1, 132.9, 132.7, 131.9, 131.9, 131.0, 130.7, 127.1, 124.3, 121.8, 116.8, 113.4, 83.0, 81.6, 77.1, 63.1, 56.1, 56.0, 53.5, 47.4, 40.4, 39.9, 36.7, 36.0, 25.9, 23.6, 20.5, 19.8, 18.4, 17.0, 15.2, 13.2, 12.8, 12.6, –5.4, –5.5; IR (film): $\tilde{\upsilon}$ = 3294, 2926, 2855, 1733, 1653 (br), 1547, 1462, 1378, 1259 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{49}H_{78}N_2O_7Si$+Na: 857.547735 [M^++Na]; found: 857.547048.

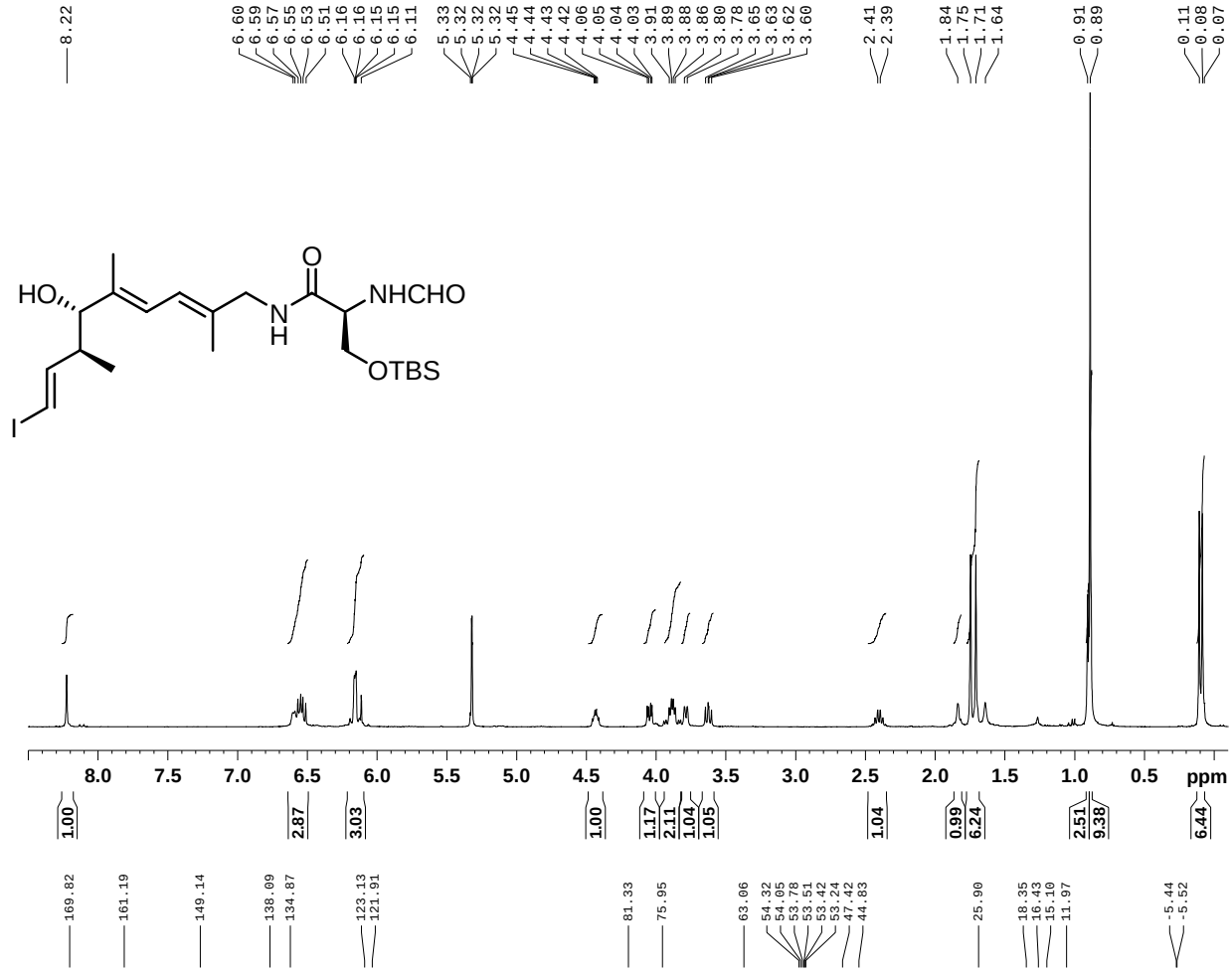
Compound 56. Complex **50** (2.7 mg, 0.00324 mmol) was added to a solution of compound **55** (18 mg, 0.0216 mmol) in CH_2Cl_2 (22 mL) and the resulting mixture was stirred at ambient temperature for 48 h. The reaction was quenched with ethyl vinyl ether (20 μL). After stirring for 10 min, all volatile materials were evaporated while keeping the temperature of the bath at 20ºC. The residue was adsorbed on Celite and purified by flash chromatography (hexanes/EtOAc, 3:1→1.5:1) to give product **56** as a yellow oil (10 mg, 69%). $[\alpha]_D^{20}$ = +4 (*c* = 0.54, CH_2Cl_2); ^{1}H NMR (600 MHz, CD_2Cl_2): δ = 8.22 (s, 1H), 6.57 (dd, *J* = 10.3, 1.3 Hz, 1H), 6.56-6.48 (m, 2H), 6.46 (d, *J* = 15.5 Hz, 1H), 6.28 (d, *J* = 11.6 Hz, 1H), 6.15 (d, *J* = 11.6 Hz, 1H), 6.04 (dd, *J* = 14.6, 10.2 Hz, 1H), 5.97 (dd, *J* = 15.2, 10.2 Hz, 1H), 5.89 (d, *J* = 15.4 Hz, 1H), 5.52 (ddd, *J* = 15.5, 10.2, 4.8 Hz, 1H), 5.48 (dd, *J* = 15.4, 8.9 Hz, 1H), 5.40-5.35 (m, 2H), 5.19-5.17 (m, 1H), 5.09 (d, *J* = 10.1 Hz, 1H), 5.08 (d, *J* = 8.8 Hz, 1H), 4.44-4.41 (m, 1H), 4.12 (ddd, *J* = 9.8, 9.6, 2.8 Hz, 1H), 4.06 (dd, *J* = 9.7, 3.9 Hz, 1H), 3.95-3.83 (m, 2H), 3.62 (dd, *J* = 9.7, 7.7 Hz, 1H), 3.29-3.24 (m, 1H), 3.22 (s, 3H), 3.19-3.14 (m, 1H), 2.96 (s, 3H), 2.64 (brd, *J* = 12.8 Hz, 1H), 2.58-2.52 (m, 2H), 2.31 (dt, *J* = 12.8, 9.8 Hz, 1H), 1.91-1.86 (m, 1H), 1.79 (s, 3H), 1.78 (brs, 6H), 1.77 (s, 3H), 1.76 (s 3H), 1.63-1.59 (m, 1H), 1.30-1.28 (m, 1H), 1.06 (d, *J* = 6.7 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H) 0.90 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (150 MHz, CD_2Cl_2): δ = 169.8, 167.5, 161.1, 145.6, 137.1, 136.2, 135.8, 134.3, 133.8, 133.8, 133.3, 132.4, 132.3, 132.0, 131.2, 129.8, 128.8, 125.9, 125.5, 125.4, 121.8, 83.2, 79.8, 77.0, 63.0, 56.5, 55.9, 53.8, 47.4, 41.0, 40.9, 38.3, 35.3, 25.9, 23.2, 21.5, 20.8, 18.4, 16.8, 15.2, 13.2, 12.1, 12.1, –5.4, –5.5; IR (film): $\tilde{\upsilon}$ = 3300, 2926, 2856, 1651 (br), 1533, 1462, 1385, 1257, 1216, 1105, 989, 964, 837, 778, 744 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{47}H_{74}N_2O_7Si$+Na: 829.515918 [M^++Na]; found: 829.515750.

Iejimalide B (2). A solution of TBAF (6.5 μL, 1 M in THF) was added dropwise to a solution of compound **56** (5 mg, 0.0062 mmol) in THF (62 μL) at 0ºC. After stirring at that temperature for 15 min, hexane (100 μL) was added and the mixture was adsorbed on silica. Purification by flash chromatography (hexanes/EtOAc, 2:1→0:1) furnished product **2** as a colorless oil (4 mg, 80%). The spectroscopic data are in full agreement to those published for natural **2**.[14] $[\alpha]_D^{20} = -16$ (c = 0.2, CH_2Cl_2) (Lit[14a]: –17.6, $CHCl_3$); ^{1}H NMR (600 MHz, CD_2Cl_2): δ = 8.26 (s, 1H), 6.70 (d, J = 6.5 Hz, 1H), 6.63 (t, J = 5.8 Hz, 1H), 6.58 (dq, J = 10.4, 1.4 Hz, 1H), 6.45 (d, J = 16.1 Hz, 1H), 6.28 (dd, J = 11.2, 1.5 Hz, 1H), 6.14 (dq, J = 11.2, 1.4 Hz, 1H), 6.05 (dd, J = 14.5, 10.5 Hz, 1H), 5.99 (dd, J = 15.2, 10.5 Hz, 1H), 5.89 (d, J = 15.5 Hz, 1H), 5.52 (ddd, J = 15.1, 10.1, 4.8 Hz, 1H), 5.49 (dd, J = 15.5, 8.9 Hz, 1H), 5.39 (dd, J = 14.0, 9.1 Hz, 1H), 5.38 (dd, J = 14.5, 8.4 Hz, 1H), 5.20-5.17 (m, 1H), 5.09 (d, J = 9.8 Hz, 1H), 5.07 (d, J = 9.7 Hz, 1H), 4.48-4.46 (m, 1H), 4.15-4.09 (m, 2H), 3.92-3.85 (m, 2H), 3.64 (ddd, J = 11.3, 8.6, 4.9 Hz, 1H), 3.30-3.25 (m, 1H), 3.21 (s, 3H), 3.19-3.14 (m, 1H), 3.01 (dd, J = 8.6, 3.9 Hz, 1H), 2.96 (s, 3H), 2.65-2.61 (m, 1H), 2.58-2.47 (m, 2H), 2.29 (dt, J = 13.8, 10.2 Hz, 1H), 1.91-1.86 (m, 1H), 1.78 (d, J = 0.9 Hz, 3H), 1.77 (s, 6H), 1.75 (d, J = 0.7 Hz, 3H), 1.73 (d, J = 1.2 Hz, 3H), 1.61-1.58 (m, 1H), 1.33-1.30 (m, 1H), 1.05 (d, J = 6.7 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, CD_2Cl_2): δ = 170. 7, 167.5, 161.8, 145.6, 137.2, 136.1, 135.5, 134.4, 133.7, 133.7, 133.3, 132.4, 132.3, 132.1, 131.2, 129.8, 128.8, 126.0, 125.3, 125.1, 121.2, 83.1, 80.0, 77.1, 62.8, 56.5, 55.9, 52.9, 47.1, 41.0, 40.8, 38.2, 35.3, 23.3, 21.5, 20.8, 16.8, 15.2, 13.2, 12.3, 12.1; IR (film): $\tilde{\upsilon}$ = 3329, 2925, 2856, 1654 (br), 1541, 1453, 1383, 1260, 1096, 965, 800, 698 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{41}H_{60}N_2O_7$+Na: 715.429344 [M^++Na]; found: 715.429268.

[14] (a) Kobayashi, J.; Cheng, J.; Ohta, T.; Nakamura, H.; Nozoe, S.; Hirata, Y.; Ohizumi, Y.; Sasaki, T. *J. Org. Chem.* **1988**, *53*, 6147. (b) Kikuchi, Y.; Ishibashi, M.; Sasaki, T.; Kobayashi, J. *Tetrahedron Lett.* **1991**, *32*, 797. (c) Nozawa, K.; Tsuda, M.; Ishiyama, H.; Sasaki, T.; Tsuruo, T.; Kobayashi, J. *Bioorg. Med. Chem.* **2006**, *14,* 1063. (d) Tsuda, M.; Nozawa, K.; Shimbo, K.; Ishiyama, H.; Fukushi, E.; Kawabata, J.; Kobayashi, J. *Tetrahedron Lett.* **2003**, *44*, 1395.

Iejimalide D (4). SO_3·Py (17 mg, 0.108 mmol) and DMF (50 μL) were successively added to a solution of **2** (1.5 mg, 0.0022 mmol) in pyridine (100 μL) and the resulting mixture was stirred for 1h. All volatiles were evaporated under a flow of argon, and the residue was dissolved in EtOAc. Filtration through Celite, evaporation of the solvent, and purification of the residue by HPLC (CH_3CN + 0.1% trifluoro-acetic acid) gave, after lyophilization of the product-containing fractions, compound **4** as a white solid (0.7 mg, 42%). ^{1}H NMR (600 MHz, CD_2Cl_2): δ = 8.16 (s, 1H), 6.60 (dd, *J* = 10.4, 1.4 Hz, 1H), 6.46 (d, *J* = 16.1 Hz, 1H), 6.30 (d, *J* = 11.1 Hz, 1H), 6.19 (d, *J* = 11.1 Hz, 1H), 6.06 (dd, *J* = 15.0, 10.5 Hz, 1H), 5.96-5.92 (m, 2H), 5.60-5.50 (m, 1H), 5.39-5.33 (m, 2H), 5.20-5.17 (m, 1H), 5.10 (d, *J* = 10.1 Hz, 1H), 5.08 (d, *J* = 9.7 Hz, 1H), 4.68 (t, *J* = 5.0 Hz, 1H), 4.29 (dd, *J* = 10.7, 5.6 Hz, 1H), 4.23-4.20 (m, 2H), 3.83-3.79 (m, 2H), 3.26 (m, 1H), 3.23 (s, 3H), 3.22 (m, 1H), 2.96 (s, 3H), 2.66-2.63 (m, 1H), 2.59-2.51 (m, 2H), 2.30-2.24 (m, 1H), 1.88-1.86 (m, 1H), 1.81 (s, 3H), 1.78 (s, 6H), 1.76 (s, 3H), 1.75 (d, *J* = 0.6 Hz, 3H), 1.61-1.55 (m, 1H), 1.05 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H); HRMS (ESI): *m/z*: calcd for $C_{41}H_{59}N_2O_{10}S$: 771.389596 [M^--Na]; found: 771.389627.

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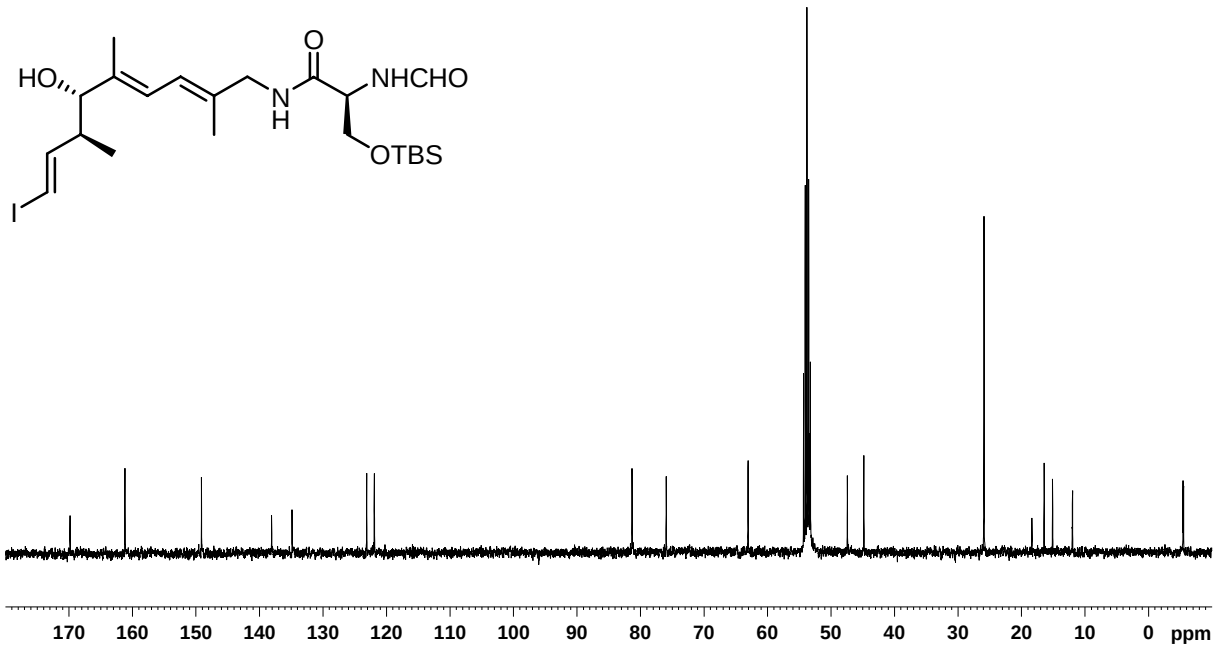
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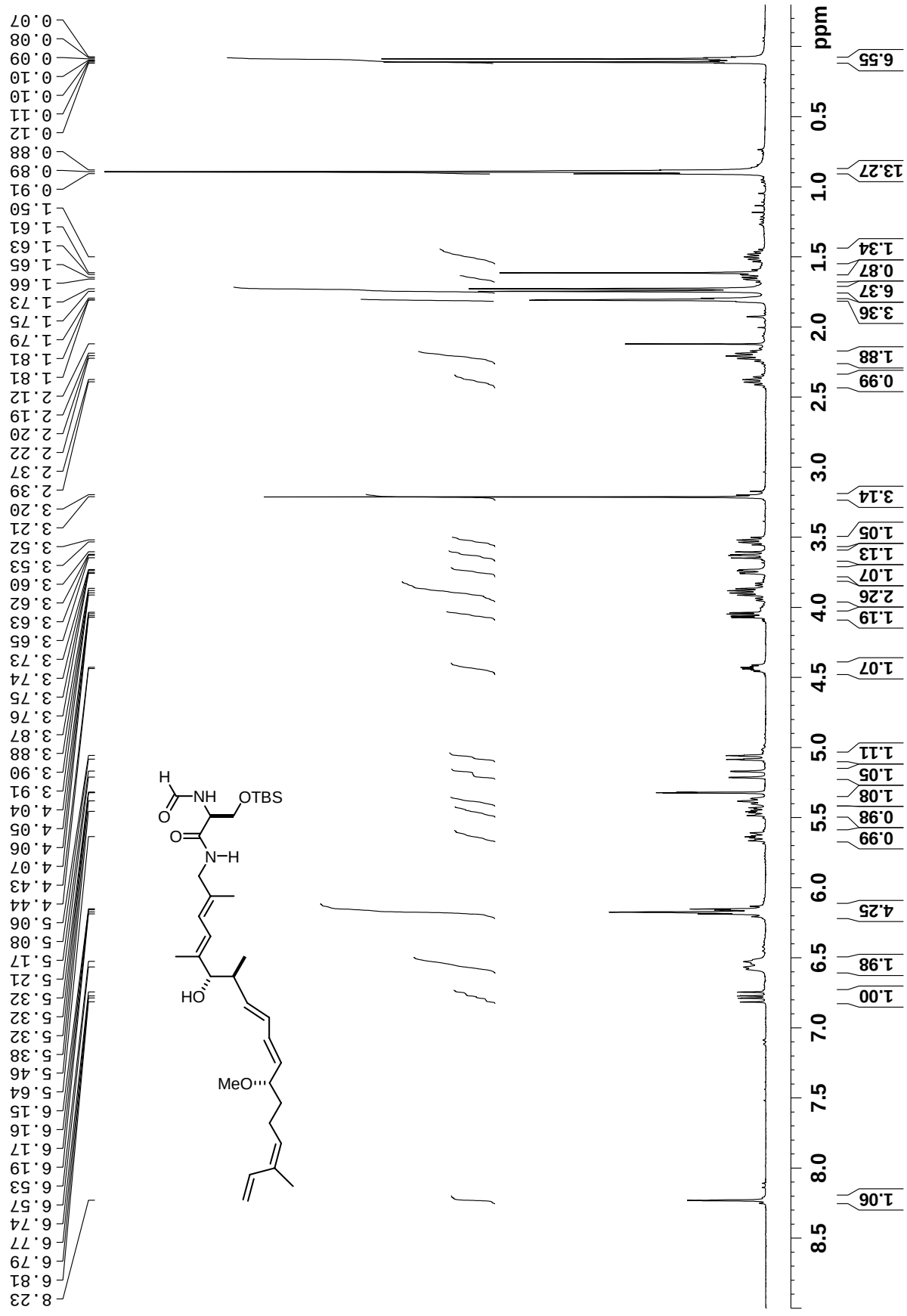
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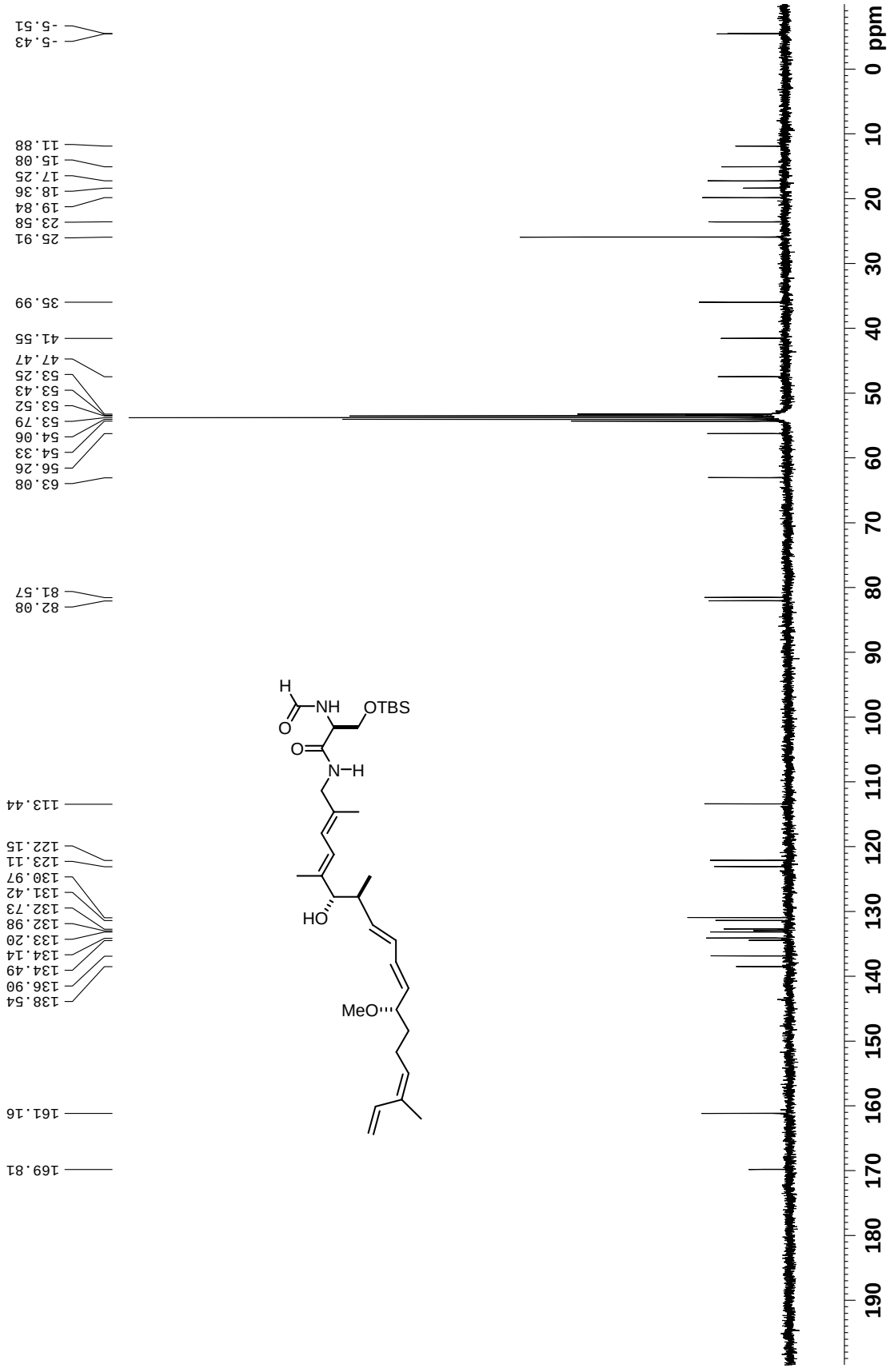
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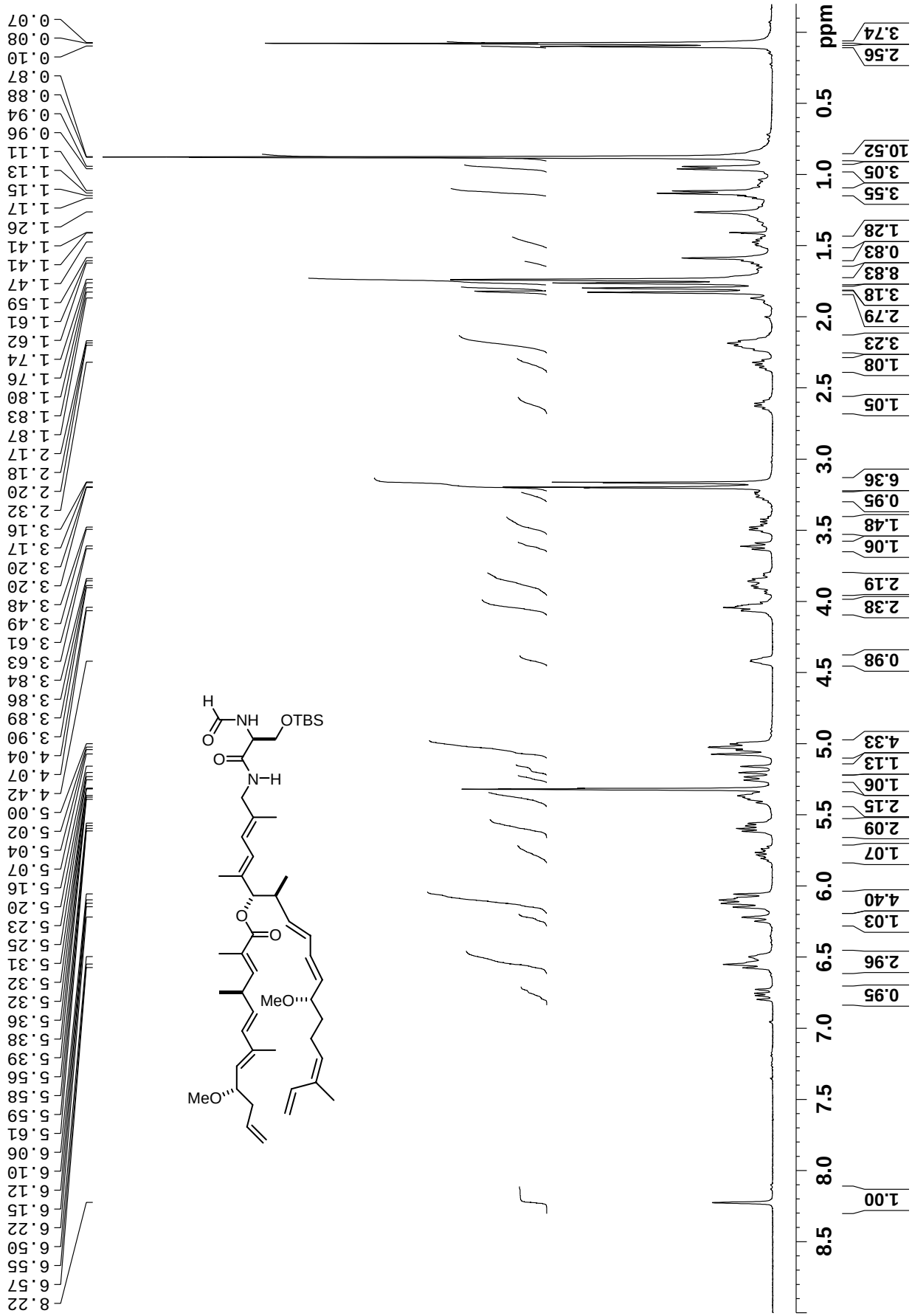
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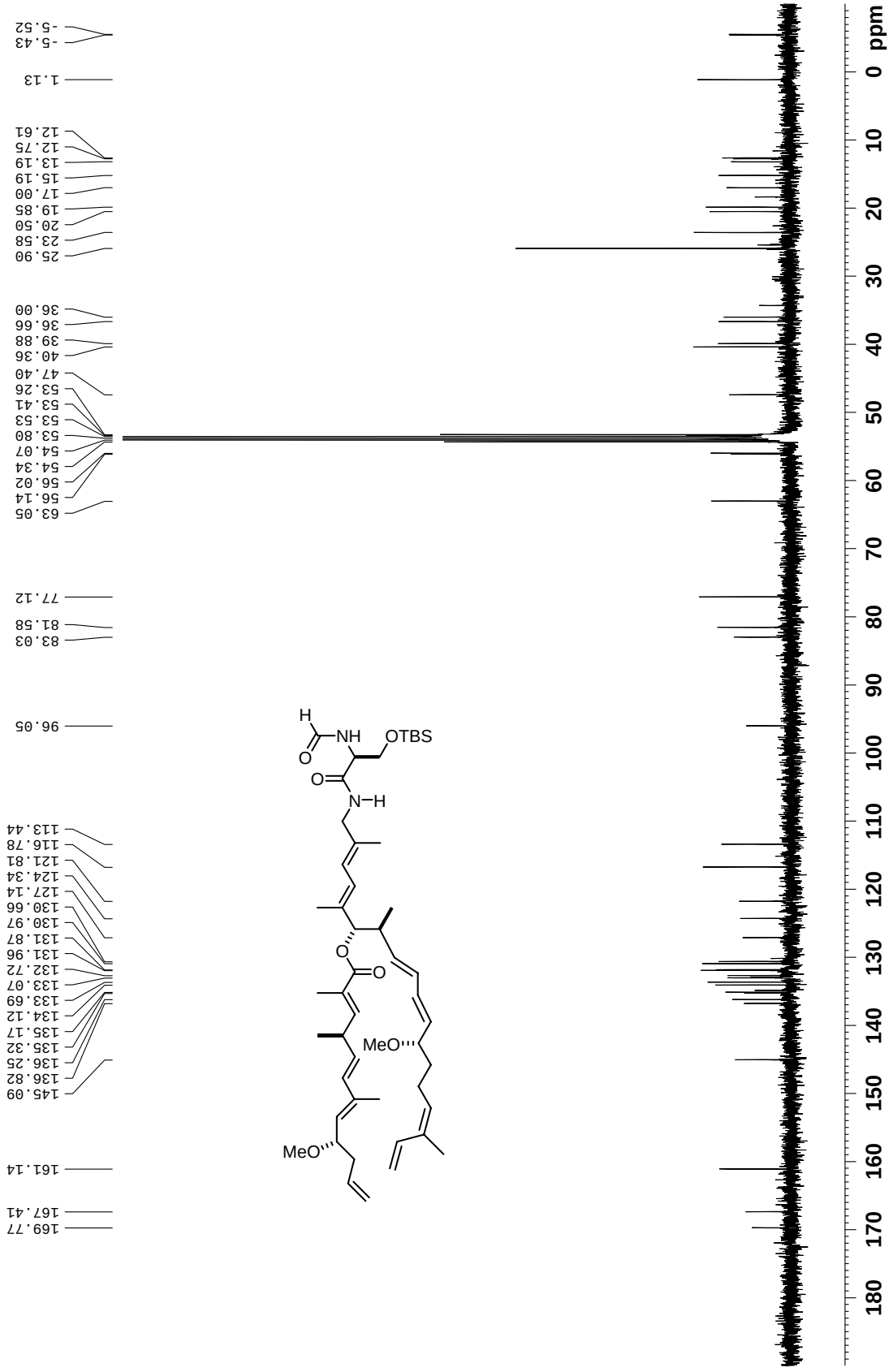
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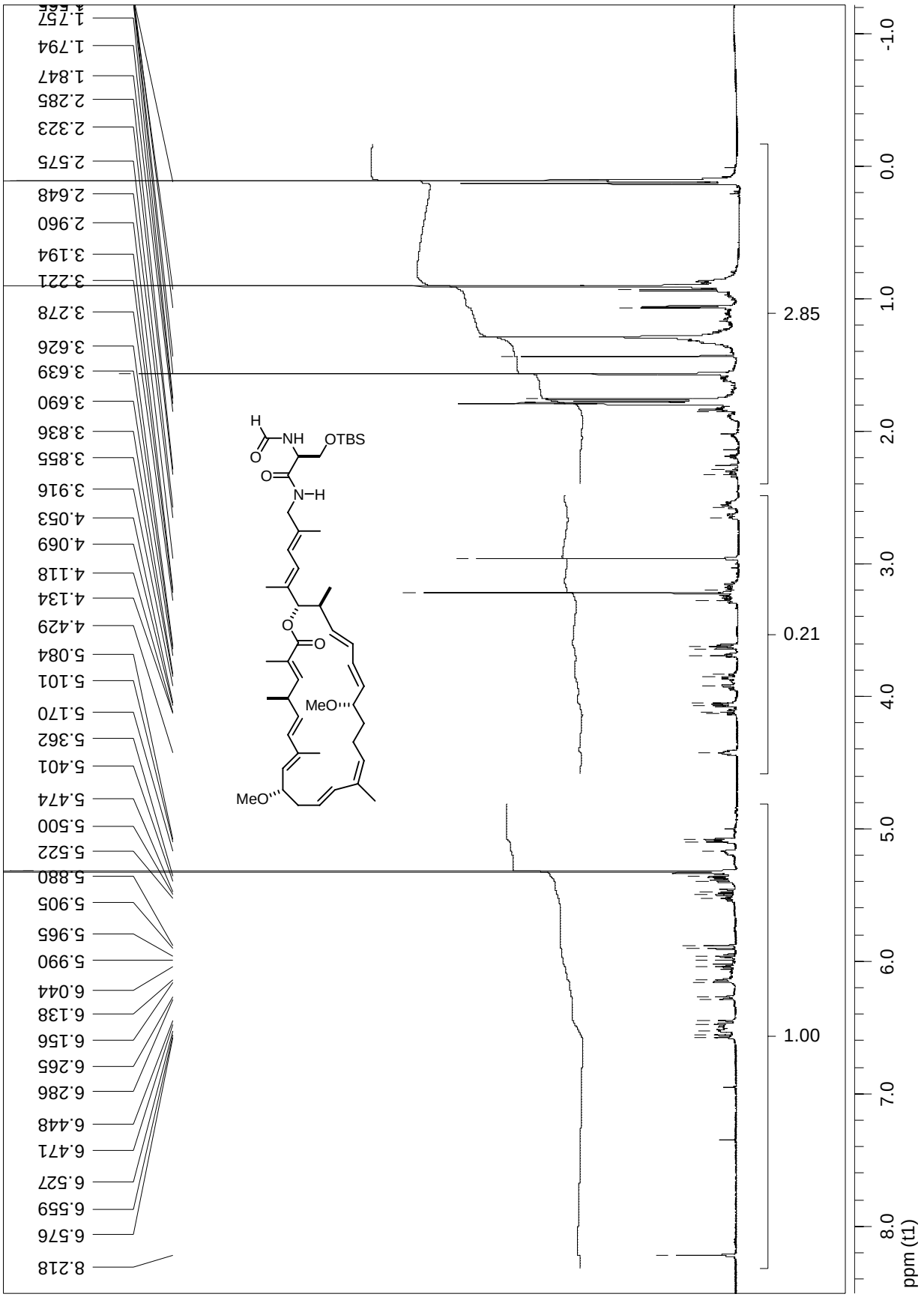
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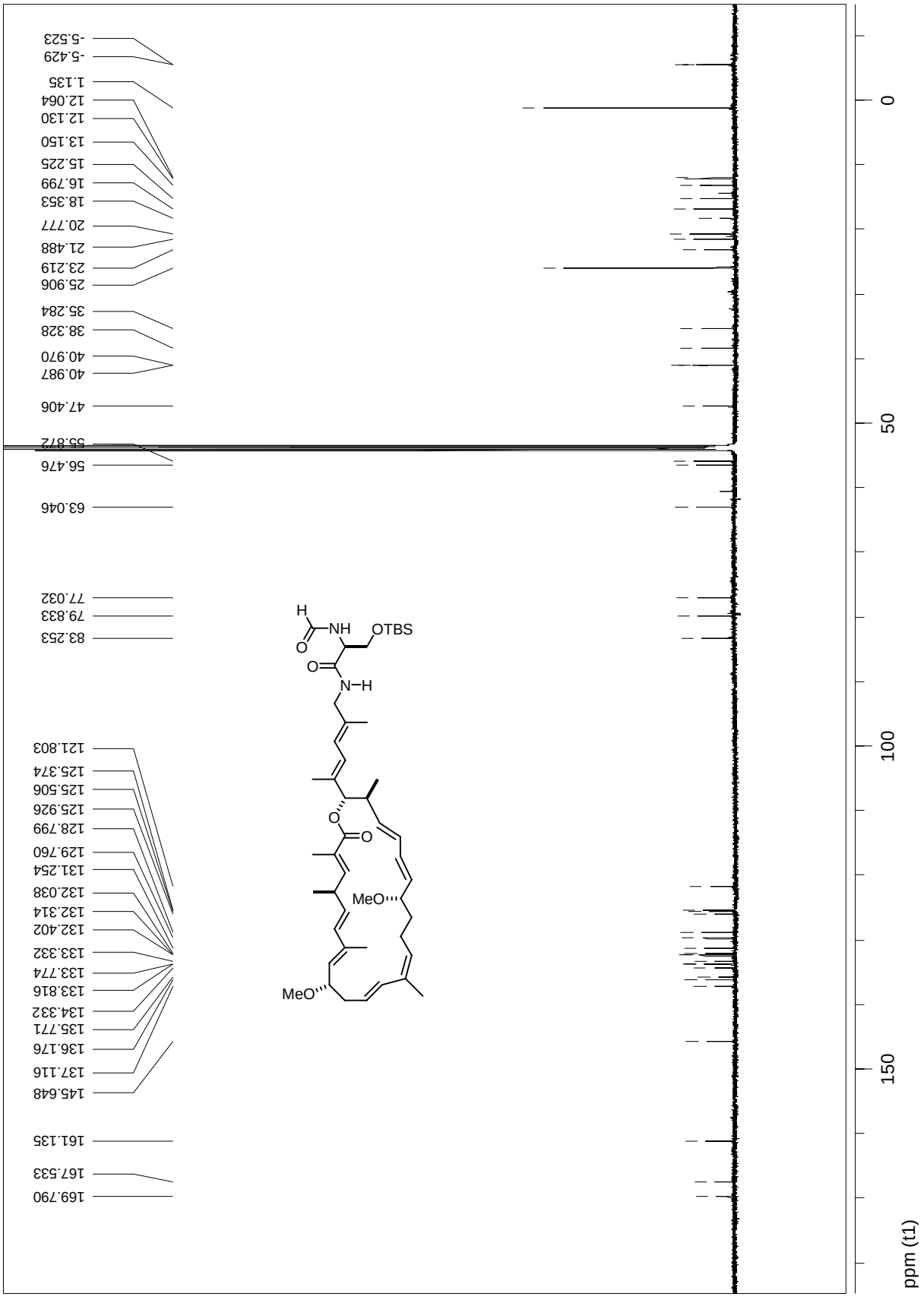
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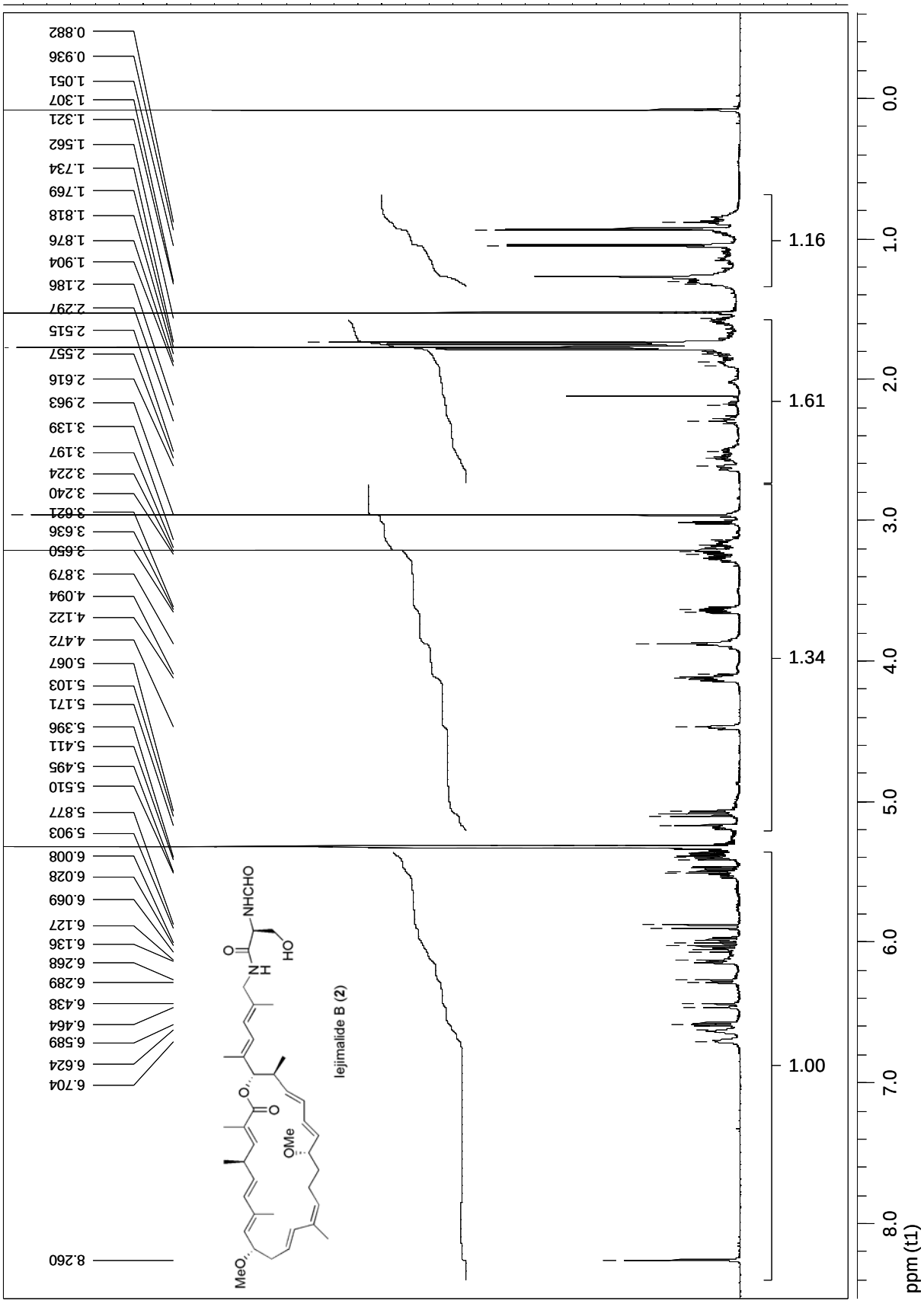
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H
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MeO
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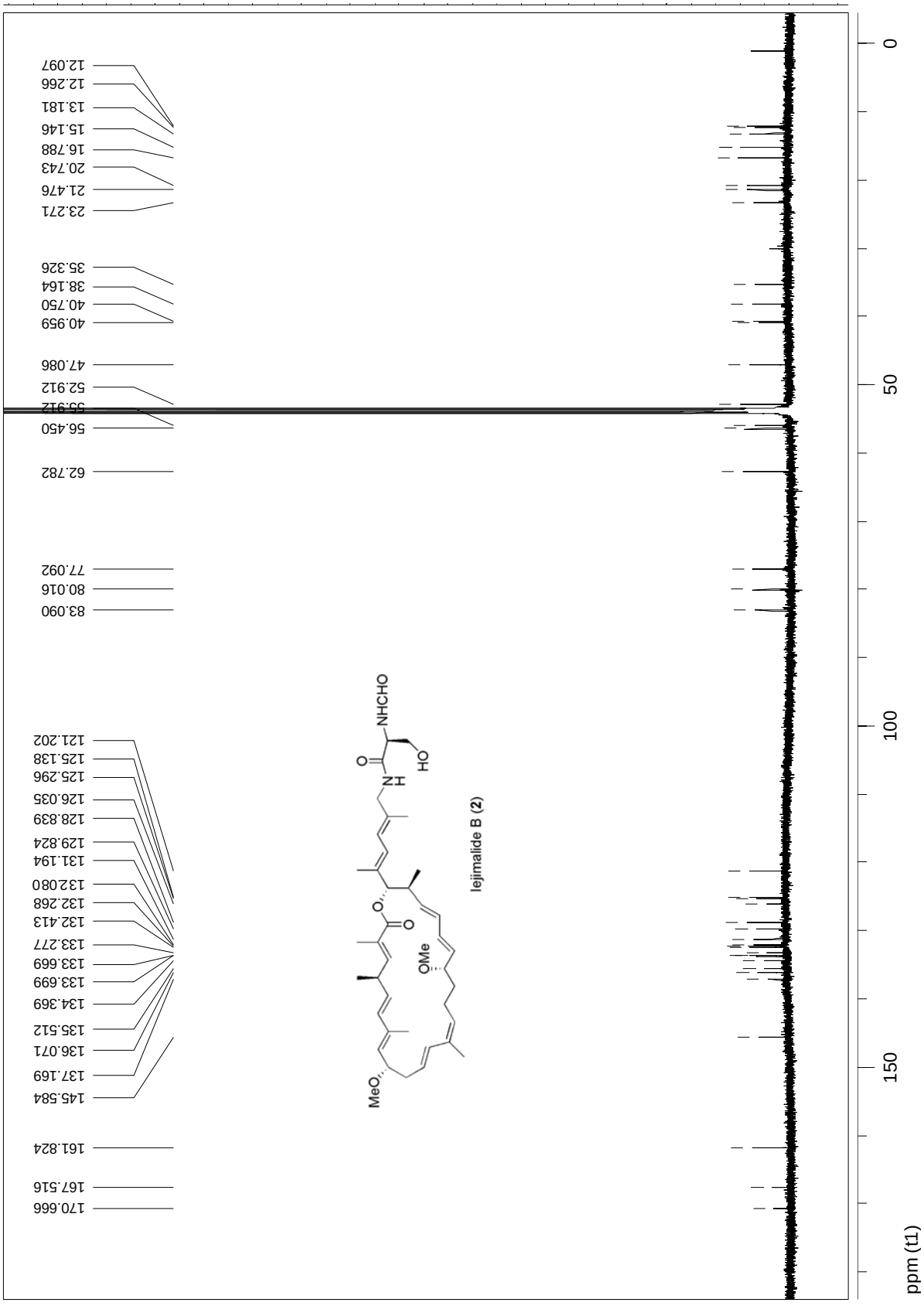
7.0
8.0
ppm (t1)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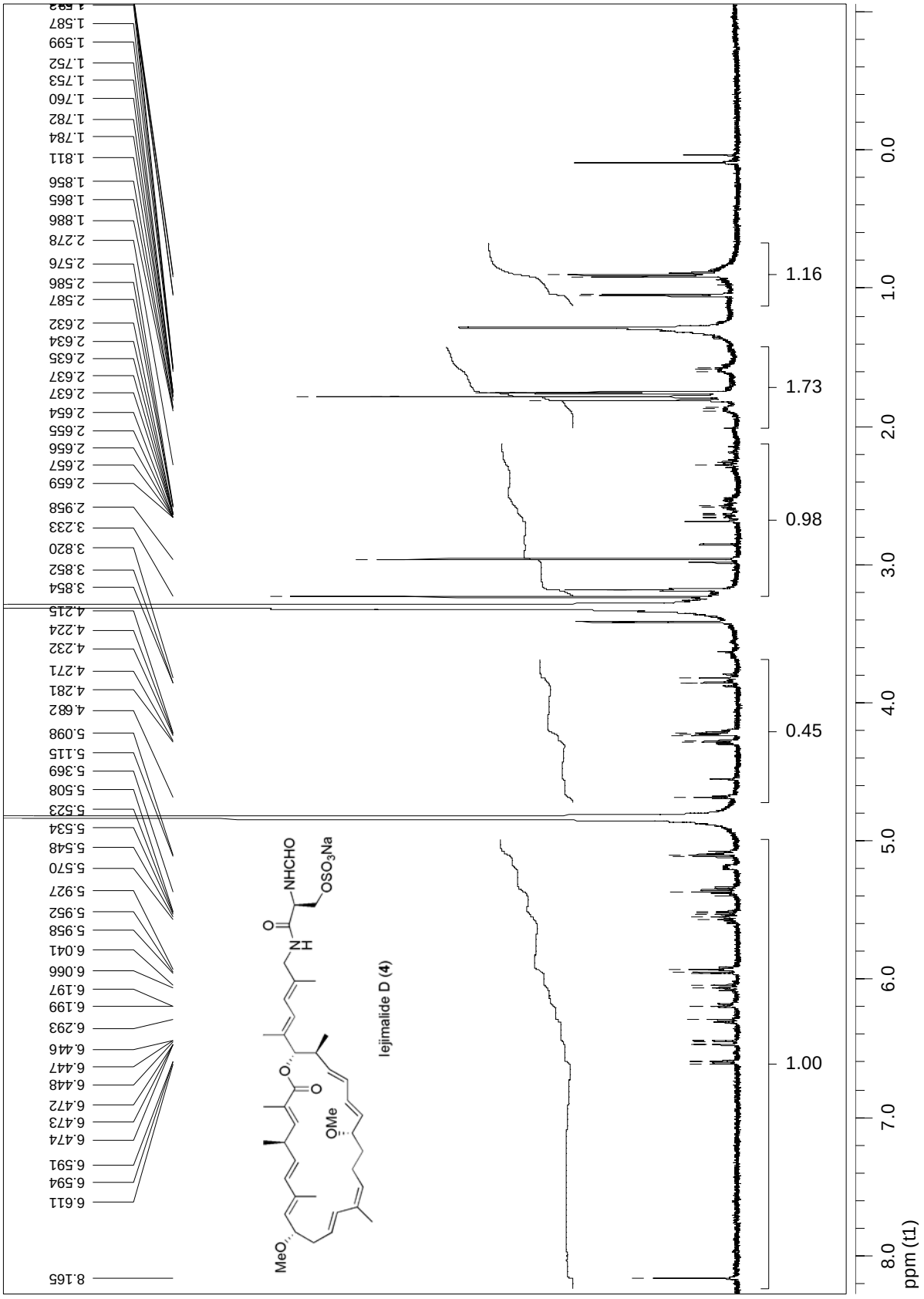
ppm (t1)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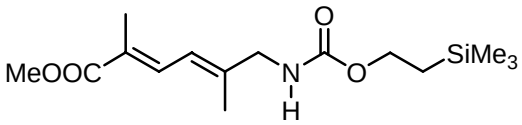
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)
Iejimalide D (4)
NHCHO
OSO3Na
MeO
OMe

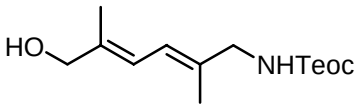
Total Synthesis of Iejimalide B – 'Teoc-Strategy'

Compound 58. TFA (10 mL, 130 mmol)) was added dropwise to a solution of compound **23** (799 mg, 2.97 mmol) in CH_2Cl_2 (35 mL) at 0°C. The mixture was stirred at ambient temperature for 1 h before it was evaporated and the crude amine thus formed was dried under high vacuum for 1 h.



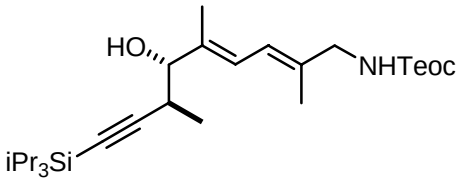
Et_3N (2.8 mL, 20 mmol) and 4-nitrophenyl-2-trimethylsilylethyl-carbonate (1.7 g, 6 mmol) were added to a solution of the crude amine in CH_2Cl_2 (35 mL). The resulting yellow solution was stirred for 24 h before it was extracted with aq. sat. Na_2CO_3 to remove the released nitrophenol. The mixture was washed with brine, the organic layer was dried over Na_2SO_4 and evaporated, and the crude product purified by flash chromatography (hexanes/EtOAc, 4:1) to give product **58** as a pale yellow oil (887 mg, 96%). ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.43 (d, J = 11.8 Hz, 1H), 6.24 (d, J = 11.8 Hz, 1H), 4.98 (bs, 1H), 4.16 (t, J = 8.3 Hz, 2H), 3.82 (d, J = 6.0 Hz, 2H), 3.72 (s, 3H), 1.92 (s, 3H), 1.86 (s, 3H), 0.98 (t, J = 8.3 Hz, 2H), 0.05 (s, 9H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 169.2, 157.1, 144.0, 133.6, 126.8, 120.3, 63.5, 52.0, 48.5, 18.0, 15.6, 13.0, –1.5; IR (film): $\tilde{\upsilon}$ = 3348, 2952, 1695, 1523, 1434, 1244, 1110, 1059, 941, 834, 751 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{15}H_{27}NO_4Si$+Na: 336.160159 [M^++Na]; found: 336.160418; elemental analysis calcd (%) for $C_{15}H_{27}NO_4Si$: C 57.47, H 8.68; found: C 57.40, H 8.72.

Compound 59. DIBAl-H (6.5 mL, 1 M in hexane) was added dropwise to a solution of compound **58** (770 mg, 2.46 mmol) in CH_2Cl_2 (17 mL) at –78°C. After stirring for 1 h at that temperature, the reaction was quenched with EtOAc (2 mL) and the mixture was allowed to reach ambient temperature at which point sat. aq. Rochelle salt solution (10 mL) was introduced. After stirring at 40°C for 1 h, the mixture was diluted with EtOAc and extracted with brine, the combined organic layers were dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc, 2:1) to give product **59** as a white solid (671 mg, 95%). ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 6.25 (d, J = 11.2 Hz, 1H), 6.15 (d, J = 11.2 Hz, 1H), 4.80 (bs, 1H), 4.14 (t, J = 8.4 Hz, 2H), 4.04 (s, 2H), 3.76 (d, J = 6.1 Hz, 2H), 1.76 (s, 3H), 1.75 (s, 3H), 1.63 (s, 1H), 0.98 (t, J = 8.4 Hz, 2H), 0.04 (s, 9H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 157.0, 137.7, 135.2, 121.1, 120.3, 68.8, 63.3, 48.8, 18.0, 14.9, 14.2, –1.5; IR (film): $\tilde{\upsilon}$ = 3331, 2954, 2914, 1689, 1531, 1346, 1246, 1130, 1063, 1001, 832, 690, 664 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{14}H_{27}NO_3Si$+Na: 308.165245 [M^++Na]; found: 308.165153; elemental analysis calcd (%) for $C_{14}H_{27}NO_3Si$: C 58.91, H 9.53; found: C 58.84, H 9.57.



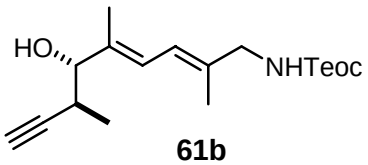
Compound 61. MnO_2 (8.5 g, 97 mmol) was added to a solution of compound **59** (827 mg, 2.9 mmol) in CH_2Cl_2 (30 mL) and the resulting mixture was stirred for 1 h. After filtration through a pad of Celite and evaporation of the filtrate, aldehyde **60** was obtained in quantitative yield and used directly in the next step. Characteristic data: ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 9.45 (s, 1 H),

7.13 (d, J = 11.6 Hz, 1H), 6.44 (d, J = 11.6 Hz, 1H), 4.98 (bs, 1H), 4.16 (t, J = 8.6 Hz, 2H), 3.87 (d, J = 5.9 Hz, 2H), 1.97 (s, 3H), 1.82 (s, 3H), 0.99 (t, J = 8.6 Hz, 2H), 0.1 (s, 9H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 196.7, 158.4, 148.4, 145.4, 139.1, 121.4, 65.0, 50.0, 19.5, 17.3, 10.9, 0.0; HRMS (ESI): m/z: calcd for $C_{14}H_{25}NO_3Si$+H: 284.168201 [M^++H]; found: 284.168231.



$Pd(OAc)_2$ (33 mg, 0.147 mmol) and PPh_3 (40 mg, 0.152 mmol) were added to a solution of compound **25** (1.32 g, 4.3 mmol) in THF (30 mL) at –78°C. After stirring for 5 min, a solution of the crude aldehyde **60** in THF (10 mL) was introduced followed by the dropwise addition of a solution of $ZnEt_2$ (8.7 mL, 1.0 M in hexanes). The resulting mixture was stirred at that temperature for 30 min before it was warmed to –20°C over a period of 1 h and stirring was continued overnight. The reaction was quenched with aq. sat. NH_4Cl, the aqueous phase was extracted with EtOAc, the combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated, and the crude material (d.r. = 7.5:1, NMR) was purified by flash chromatography (hexanes/EtOAc, 10:1→4:1) to give product **61** (dr > 15:1) as a colorless oil (1.02 g, 71%, ee = 96.8%). $[\alpha]_D^{20}$ = +47.5 (c = 0.9, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 6.26 (d, J = 11.2 Hz, 1H), 6.16 (d, J = 11.2 Hz, 1H), 4.78 (bs, 1H), 4.15 (t, J = 8.4 Hz, 2H), 3.85 (dd, J = 7.0, 4.3 Hz, 1H), 3.76 (d, J = 6.1 Hz, 2H), 2.75 (m, 1H), 2.29 (d, J = 4.3 Hz, 1H), 1.75 (s, 3H), 1.72 (s, 3H), 1.13 (d, J = 6.9 Hz, 3H), 1.05 (m, 21H), 0.98 (t, J = 8.4 Hz, 2H), 0.04 (s, 9H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 157.0, 136.9, 135.8, 123.1, 121.0, 110.3, 83.7, 81.0, 63.3, 48.8, 33.2, 18.8, 18.2, 18.1, 15.0, 12.2, 11.5, –1.4; IR (film): $\tilde{\upsilon}$ = 3344, 2943, 2865, 2160, 1701, 1515, 1462, 1382, 1249, 1124, 1060, 1016, 858, 835, 675 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{27}H_{51}NO_3Si_2$+Na: 516.329970 [M^++Na]; found: 516.330321; elemental analysis calcd (%) for $C_{27}H_{51}NO_3Si_2$: C 65.66, H 10.41; found: C 65.76, H 10.34.

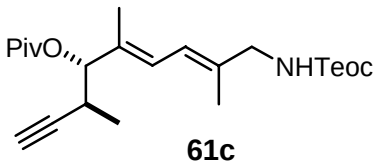
Compound 61b. A solution of TBAF (1.2 mL, 1 M in THF) was added in 4 portions over 2 h to a solution of compound **61** (501 mg, 1.01 mmol) in THF (20 mL) at 0°C and the resulting mixture was stirred at that temperature for 30 min. The reaction was then quenched with H_2O, the aqueous phase extracted with EtOAc, the combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc, 4:1) to give product **61b** as a colorless oil (304 mg, 89%). $[\alpha]_D^{20}$ = +49.3 (c = 1.55, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 6.25 (d, J = 11.3 Hz, 1H), 6.15 (d, J = 11.3 Hz, 1H), 4.78 (bs, 1H), 4.15 (t, J = 8.7 Hz, 2H), 3.89 (d, J = 7.1 Hz, 1H), 3.76 (d, J = 5.8 Hz, 2H), 2.69 (m, 1H), 2.18 (d, J = 2.3 Hz, 1H), 1.76 (s, 3H), 1.72 (s, 3H), 1.10 (d, J = 7.2 Hz, 3H), 0.98 (t, J = 8.7 Hz, 2H), 0.04 (s, 9H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 158.4, 138.2, 137.6, 124.9, 122.2, 87.7, 82.5, 72.3, 64.7, 50.2, 33.1, 19.5, 19.3, 16.5, 13.5, 0.0; IR (film): $\tilde{\upsilon}$ = 3310, 2970, 2953, 1737, 1721, 1520, 1372, 1248, 1230, 1217, 1058, 858, 836, 694 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{18}H_{31}NO_3Si$+Na: 360.196542 [M^++Na]; found:



61b

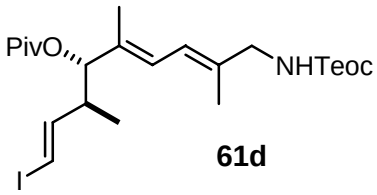
360.196099; elemental analysis calcd (%) for $C_{18}H_{31}NO_3Si$: C 64.05, H 9.26; found: C 64.11, H 9.30.

Compound 61c. DMAP (10 mg, 0.08 mmol) and pivaloyl chloride (0.9 mL, 7.3 mmol) were successively added to a solution of compound **61b** (546 mg, 1.61 mmol) in pyridine (5 mL) at 0°C. The mixture was stirred at ambient temperature for 20 h before it was diluted with EtOAc and extracted with brine. The combined organic layers were dried over Na_2SO_4 and evaporated, and the residue purified by flash chromatography (hexanes/EtOAc, 10:1) to give product **61c** as a colorless oil (643 mg, 94%). $[\alpha]_D^{20}$ = +21.4 (*c* = 0.82, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 6.29 (d, *J* = 11.3 Hz, 1H), 6.13 (d, *J* = 11.3 Hz, 1H), 5.06 (d, *J* = 7.7 Hz, 1H), 4.78 (bs, 1H), 4.14 (t, *J* = 8.3 Hz, 2H), 3.76 (d, *J* = 5.9 Hz, 2H), 2.82 (m, 1H), 2.08 (d, *J* = 2.3 Hz, 1H), 1.76 (s, 3H), 1.74 (s, 3H), 1.21 (s, 9H), 1.11 (d, *J* = 7.0 Hz, 3H), 0.98 (t, *J* = 8.3 Hz, 2H), 0.04 (s, 9H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 176.7, 156.4, 136.3, 133.8, 123.9, 119.8, 85.1, 80.4, 69.2, 62.7, 48.1, 38.6, 29.1, 26.7, 17.4, 17.1, 14.5, 12.1, –2.0; IR (film): $\tilde{\upsilon}$ = 3314, 2970, 2955, 1725, 1520, 1366, 1248, 1231, 1217, 1149, 1061, 966, 942, 858, 835, 693 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{23}H_{39}NO_4Si$+Na: 444.254058 [M^++Na]; found: 444.254501; elemental analysis calcd (%) for $C_{23}H_{39}NO_4Si$: C 65.52, H 9.32; found: C 65.40, H 9.28.



61c

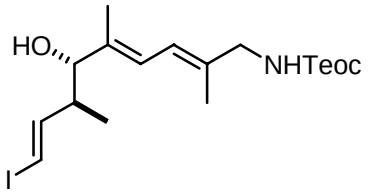
Compound 61d. A solution of compound **61c** (260 mg, 0.616 mmol) in THF (7 mL) was added to a solution of Schwartz reagent (275 mg, 1.06 mmol) in THF (7 mL). The mixture was stirred in the dark for 45 min before it was cooled to 0°C and a solution of iodine (270 mg, 1.06 mmol) in THF (5 mL) was introduced. After stirring for 5 min, the reaction was quenched with aq. sat. $Na_2S_2O_3$, the mixture was stirred for 10 min, diluted with EtOAc and extracted with brine. The combined organic layers were dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc, 10:1) to give product **61d** as a colorless syrup (273 mg, 81%). $[\alpha]_D^{20}$ = +15.6 (*c* = 0.9, CH_2Cl_2); ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 6.40 (dd, *J* = 14.4, 8.3 Hz, 1H), 6.22 (d, *J* = 11.1 Hz, 1H), 6.10 (m, 2H), 4.93 (d, *J* = 8.2 Hz, 1H), 4.83 (bs, 1H), 4.14 (t, *J* = 8.6 Hz, 2H), 3.75 (d, *J* = 6.1 Hz, 2H), 2.57 (m, 1H), 1.75 (s, 3H), 1.71 (s, 3H), 1.18 (s, 9H), 0.98 (t, *J* = 8.6 Hz, 2H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.04 (s, 9H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 177.3, 157.0, 148.2, 136.7, 133.7, 124.5, 120.5, 81.5, 76.1, 63.3, 48.7, 43.7, 39.2, 27.4, 18.0, 16.5, 15.1, 12.6, –1.4; IR (film): $\tilde{\upsilon}$ = 3352, 2970, 2954, 1725, 1517, 1455, 1365, 1247, 1229, 1217, 1149, 1061, 946, 858, 835, 766, 694 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{23}H_{40}NO_4SiI$+Na: 572.166357 [M^++Na]; found: 572.166845; elemental analysis calcd (%) for $C_{23}H_{40}NO_4SiI$: C 50.27, H 7.34; found: C 50.20, H 7.39.



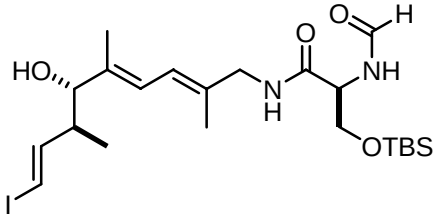
61d

Compound 62. A solution of $LiBEt_3H$ (1.2 mL, 1 M in THF) was added dropwise to a solution of compound **61d** (195 mg, 0.355 mmol) in THF (20 mL) at 0°C. After stirring for 2 h at that temperature, the reaction was quenched with aq. sat. NH_4Cl, diluted with EtOAc and extracted

with brine. The combined organic layers were dried over Na_2SO_4 and evaporated, and the crude product was purified by flash chromatography (hexanes/EtOAc, 4:1) to give compound **62** as a colorless oil (135 mg, 82%). $[\alpha]_D^{20}$ = +28.1 (*c* = 1.05, CH_2Cl_2); ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 6.55 (dd, *J* = 14.5, 8.3 Hz, 1H), 6.15 (m, 3H), 4.76 (bs, 1H), 4.15 (t, *J* = 8.4 Hz, 2H), 3.78 (m, 3H), 2.40 (m, 1H), 1.94 (bs, 1H), 1.76 (s, 3H), 1.71 (s, 3H), 0.98 (t, *J* = 8.4 Hz, 2H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.05 (s, 9H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 157.0, 149.2, 137.7, 135.9, 123.6, 120.7, 81.3, 75.9, 63.3, 48.7, 44.8, 18.0, 16.5, 15.0, 12.0, –1.4; IR (film): $\tilde{\upsilon}$ = 3337, 2966, 2887, 1694, 1519, 1466, 1394, 1248, 1171, 1060, 945, 856, 835, 776, 693 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{18}H_{32}NO_3SiI$+Na: 488.108836 [M^++Na]; found: 488.108256; elemental analysis calcd (%) for $C_{18}H_{32}NO_3SiI$: C 46.45, H 6.93; found: C 46.53, H 7.06.

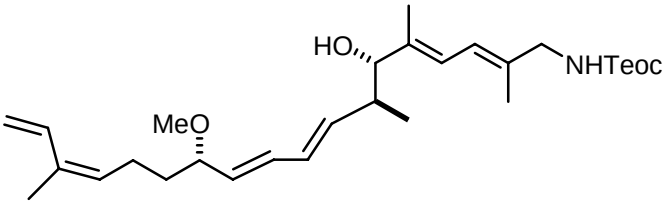


Compound 53. A solution of TBAF (0.5 mL, 1 M in THF) was added dropwise to a solution of compound **62** (128 mg, 0.275 mmol) in THF (6 mL) at 0°C. The mixture was stirred overnight at ambient temperature before a second batch of TBAF (0.5 mL, 1 M in THF) was introduced. After additional 8 h, the mixture was diluted with EtOAc and extracted with aq. sat. Na_2CO_3, and the organic layers were washed with brine, dried over Na_2SO_4, and evaporated.



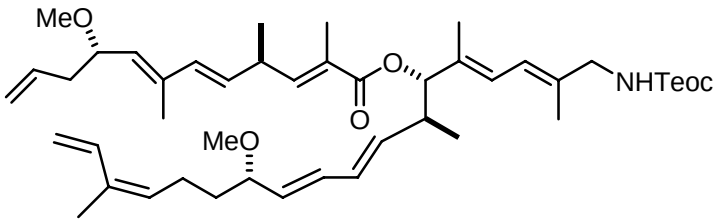
The resulting free amine **63** was dissolved in CH_2Cl_2 (5 mL). **57** (75 mg, 0.3 mmol), HOBt (40 mg, 0.3 mmol), and N-methylmorpholine (NMM, 0.088 mL, 0.8 mmol) were successively added and the mixture was cooled to 0°C. EDC·HCl (68 mg, 0.35 mmol) was then introduced and the mixture stirred at ambient temperature for 20 h. After dilution with EtOAc and extraction with brine, the combined organic layers were dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc 1:1) to give product **53** as a white solid (121 mg, 80%). $[\alpha]_D^{20}$ = +29.3 (*c* = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 8.22 (s, 1H), 6.63-6.48 (m, 3H), 6.20-6.10 (m, 3H), 4.47-4.40 (m, 1H), 4.04 (dd, *J* = 9.8, 4.0 Hz, 1H), 3.98-3.81 (m, 2H), 3.78 (d, *J* = 7.9 Hz, 1H), 3.62 (dt, *J* = 8.8, 1.9 Hz, 1H), 2.44-2.35 (m, 1H), 1.74 (s, 3H), 1.71 (s, 3H), 0.90-0.85 (m, 12H), 0.10 (s, 3H). 0.08 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 170.2, 161.6, 149.6, 138.5, 135.3, 123.5, 122.3, 81.7, 76.4, 63.5, 53.4, 47.8, 45.2, 26.3, 18.8, 16.8, 15.5, 12.4, –5.0; IR (film): $\tilde{\upsilon}$ = 3302, 2928, 2857, 1650, 1530, 1385, 1255, 1107, 953, 834, 710) cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{22}H_{39}N_2O_4ISi$+Na: 573.161605 [M^++Na]; found: 573.161674.

Compound 64. $Ba(OH)_2 \cdot 8H_2O$ (50 mg, 0.158 mmol) and (dppf)$PdCl_2$ (12 mg, 0.016 mmol) were added to a degassed solution containing compounds **62** (50 mg, 0.107 mmol) and **19** (37 mg, 0.127 mmol) in DMF (2.5 mL). The mixture was stirred for 2 h at ambient temperature before it was diluted with

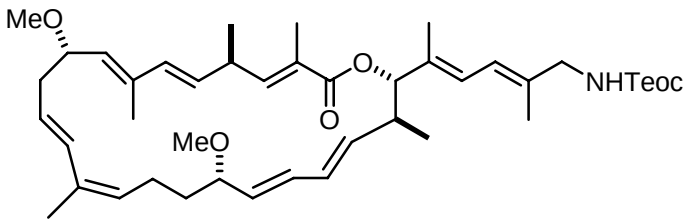


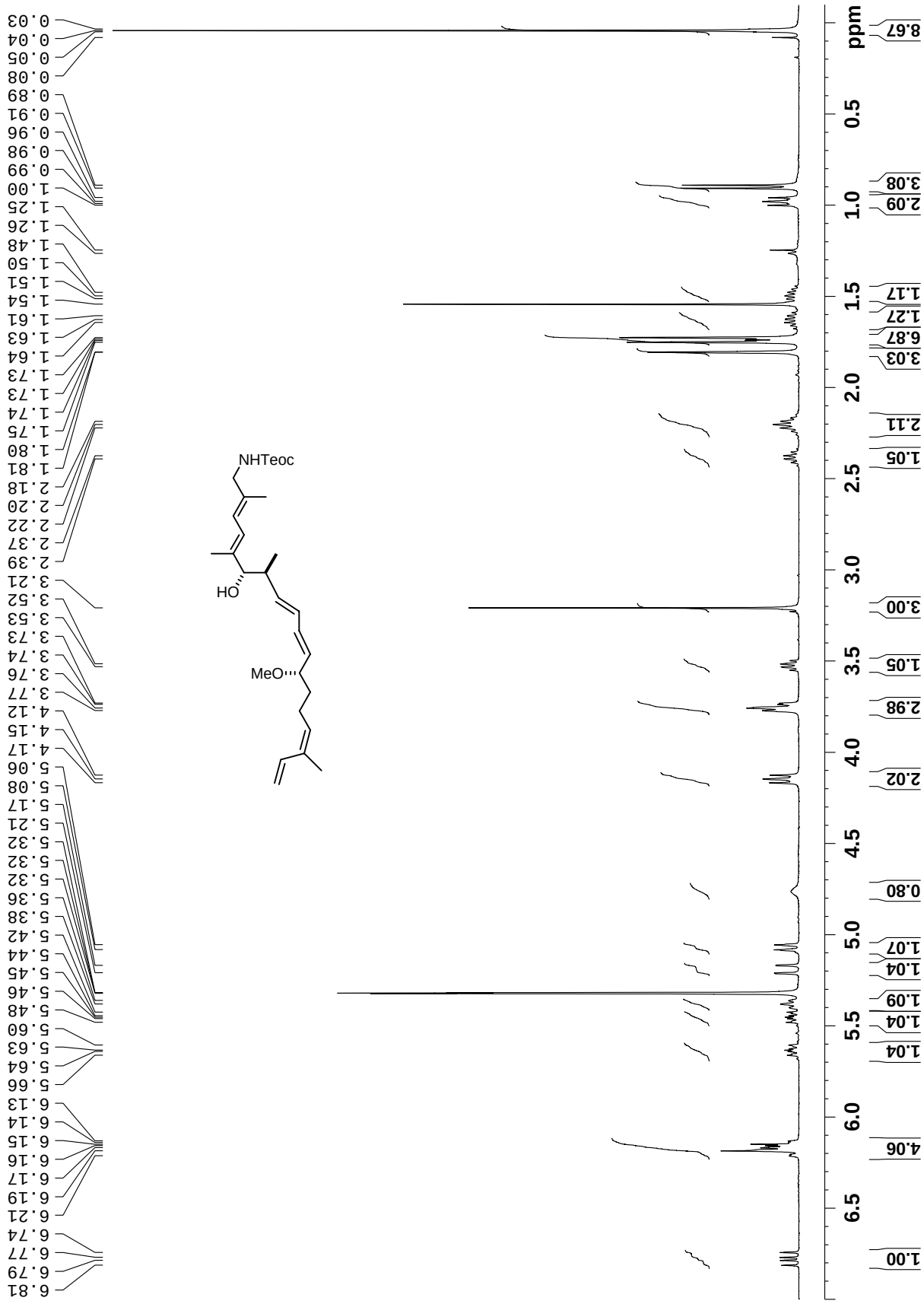
EtOAc and extracted with brine. The combined organic layers were dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc, 4:1) to give product **64** as a colorless syrup (39 mg, 70%). $[\alpha]_D^{20}$ = +26.6 (*c* = 0.78, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 6.78 (ddd, *J* = 17.3, 10.8, 0.8 Hz, 1H), 6.18 (m, 4H), 5.64 (m, 1H), 5.45 (m, 1H), 5.38 (m, 1H), 5.19 (dd, *J* = 17.3, 0.8 Hz, 1H), 5.07 (m, 1H), 4.79 (bs, 1H), 4.15 (t, *J* = 8.4 Hz, 2H), 3.75 (m, 3H), 3.52 (m, 1H), 3.21 (s, 3H), 2.38 (m, 1H), 2.20 (m, 2H), 1.81 (s, 3H), 1.75 (s, 3H), 1.73 (s, 3H), 1.63 (m, 1H), 1.49 (m, 1H), 0.98 (t, *J* = 8.4 Hz, 2H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.04 (s, 9H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 157.0, 138.1, 136.9, 135.6, 134.1, 133.2, 133.0, 132.8, 131.4, 131.0, 123.2, 121.0, 113.4, 82.1, 81.6, 63.3, 56.3, 48.8, 41.6, 36.0, 23.6, 19.9, 18.1, 17.3, 15.0, 11.9, –1.4; IR (film): $\tilde{\upsilon}$ = 3457, 2925, 2855, 1737, 1516, 1448, 1366, 1229, 1216, 1099, 1060, 989, 858, 836, 776, 694 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{29}H_{49}NO_4Si$+Na: 526.332305 [M^++Na]; found: 526.332366; elemental analysis calcd (%) for $C_{29}H_{49}NO_4Si$: C 69.14, H 9.80; found: C 68.96, H 9.72.

Compound 65. EDC·HCl (14.5 mg, 0.0756 mmol) and 4-pyrrolidino-pyridine (14.5 mg, 0.0983 mmol) were added to a solution of compounds **47** (20 mg, 0.0756 mmol) and **64** (19 mg, 0.0377 mmol) in CH_2Cl_2 (1.0 mL) at 0ºC. The mixture was warmed to ambient temperature and stirred for 48 h. It was then cooled again to 0°C before additional EDC·HCl (2.2 mg, 0.0115 mmol) and 4-pyrrolidino-pyridine (1.7 mg, 0.0115 mmol) were introduced. After another 48 h at ambient temperature, the mixture was diluted with EtOAc, filtered through a pad of Celite, the filtrate was adsorbed on silica and submitted to flash chromatography (hexanes/EtOAc, 20:1→2:1) to furnish product **65** as a colorless oil (22 mg, 78%). $[\alpha]_D^{20}$ = +17.0 (*c* = 0.20, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 6.73 (dd, *J* = 17.3, 10.8 Hz, 1H), 6.53 (dd, *J* = 9.7, 1.3 Hz, 1H), 6.21 (d, *J* = 11.2 Hz, 1H), 6.11-6.02 (m, 4H), 5.74 (ddt, *J* = 17.3, 10.2, 7.0 Hz, 1H), 5.58-5.52 (m, 2H), 5.38-5.33 (m, 2H), 5.21(d, *J* = 9.1 Hz, 1H), 5.15 (d, *J* = 17.4 Hz, 1H), 5.09-4.91 (m, 4H), 4.74 (brs, 1H), 4.11 (dd, *J* = 8.3, 8.3 Hz, 2H), 4.00 (dt, *J* = 9.0, 6.4 Hz, 1H), 3.72 (d, *J* = 5.9 Hz, 2H), 3.45 (q, *J* = 7.3 Hz, 1H), 3.25-3.17 (m, 1H), 3.17 (s, 3H), 3.13 (s, 3H), 2.64-2.54 (m, 1H), 2.29 (m, 1H), 2.20-2.12 (m, 3H), 1.80 (d, *J* = 1.4 Hz, 3H), 1.76 (d, *J* = 1.3 Hz, 3H), 1.73 (d, *J* = 1.0 Hz, 3H), 1.71 (s, 6H), 1.62-1.55 (m, 1H), 1.47-1.39 (m, 1H), 1.10 (d, *J* = 6.7 Hz, 3H), 0.99-0.96 (m, 2H), 0.93 (d, *J* = 6.8 Hz, 3H), -0.02 (s, 9H); ^{13}C NMR (150 MHz, CD_2Cl_2): δ = 168.9, 158.4, 146.5, 138.3, 137.7, 136.6, 135.9, 135.6, 135.1, 134.4, 134.1, 133.4, 133.3, 132.4, 132.1, 128.6, 125.8, 122.1, 118.2, 114.9, 84.5, 83.0, 78.6, 64.7, 57.6, 57.5, 50.2, 41.8, 41.3, 38.1, 37.4, 25.0, 21.9, 21.3, 19.5, 18.5, 16.5, 14.6, 14.2, 14.1, 0.0; IR (film): $\tilde{\upsilon}$ = 3336, 2924, 1712, 1519, 1448, 1249, 1098, 991, 966, 859, 834 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{45}H_{71}NO_6Si$+Na: 772.4944 [M^++Na]; found: 772.4942.



Compound 66. Complex **50** (1 mg, 0.0012 mmol) was added to a solution of compound **65** (9.0 mg, 0.0116 mmol) in CH_2Cl_2 (20 mL) and the mixture was stirred at ambient temperature. After 24 h, a second portion of complex **50** (0.5 mg, 0.0006 mmol) was introduced and stirring continued for 48 h before the reaction was quenched with ethyl vinyl ether (50 μL). After stirring for 1 h, all volatile materials were evaporated and the residue purified by flash chromatography (hexanes/EtOAc, 12:1→8:1) to give product **66** as a pale brown solid (6.5 mg, 78%). $[\alpha]_D^{20}$ = +5.0 (*c* = 0.10, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 6.57 (dd, *J* = 10.3, 1.4 Hz, 1H), 6.46 (d, *J* = 15.7 Hz, 1H), 6.29 (d, *J* = 11.2 Hz, 1H), 6.12 (dq, *J* = 11.2, 1.2 Hz, 1H), 6.04 (dd, *J* = 14.3, 10.5 Hz, 1H), 5.97 (dd, *J* = 14.5, 10.5 Hz, 1H), 5.89 (d, *J* = 15.5 Hz, 1H), 5.52 (ddd, *J* = 15.5, 9.7, 4.6 Hz, 1H), 5.48 (dd, *J* = 15.5, 9.0 Hz, 1H), 5.38 (dd, *J* = 14.1, 7.9 Hz, 1H), 5.36 (dd, *J* = 14.5, 9.7 Hz, 1H), 5.18 (dd, *J* = 10.5, 5.8 Hz, 1H), 5.09 (d, *J* = 10.1 Hz, 1H), 5.08 (d, *J* = 9.5 Hz, 1H), 4.76 (brs, 1H), 4.14 (dd, *J* = 8.5, 8.3 Hz, 2H), 4.16-4.09 (m, 1H), 3.76 (d, *J* = 6.0 Hz, 2H), 3.29-3.23 (m, 1H), 3.21 (s, 3H), 3.18-3.12 (m, 1H), 2.95 (s, 3H), 2.65-2.61 (m, 1H), 2.58-2.48 (m, 2H), 2.29 (dt, *J* = 13.5, 10.1 Hz, 1H), 1.90-1.86 (m, 1H), 1.78 (s, 3H), 1.77 (s, 3H), 1.77 (s, 3H), 1.76 (s, 3H), 1.74 (d, *J* = 1.0 Hz, 3H), 1.63-1.56 (m, 1H), 1.33-1.25 (m, 1H), 1.03 (d, *J* = 6.7 Hz, 3H), 0.98 (dd, *J* = 8.5, 8.4 Hz, 2H), 0.91 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (150 MHz, CD_2Cl_2): δ = 167.6, 157.0, 145.6, 137.1, 136.9, 136.2, 133.9, 133.8, 133.7, 133.3, 132.4, 132.3, 132.1, 131.2, 129.8, 128.8, 126.0, 125.6, 125.4, 120.6, 83.3, 79.9, 77.0, 63.3, 56.5, 55.9, 48.8, 41.0, 38.3, 35.3, 23.2, 21.5, 20.8, 18.1, 16.8, 15.1, 13.2, 12.1, 12.1, –1.4; IR (film): $\tilde{\upsilon}$ = 2927, 1712, 1514, 1455, 1251, 1100, 989, 965, 836 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{43}H_{67}NO_6$+Na: 744.4627 [M^++Na]; found: 744.4629.

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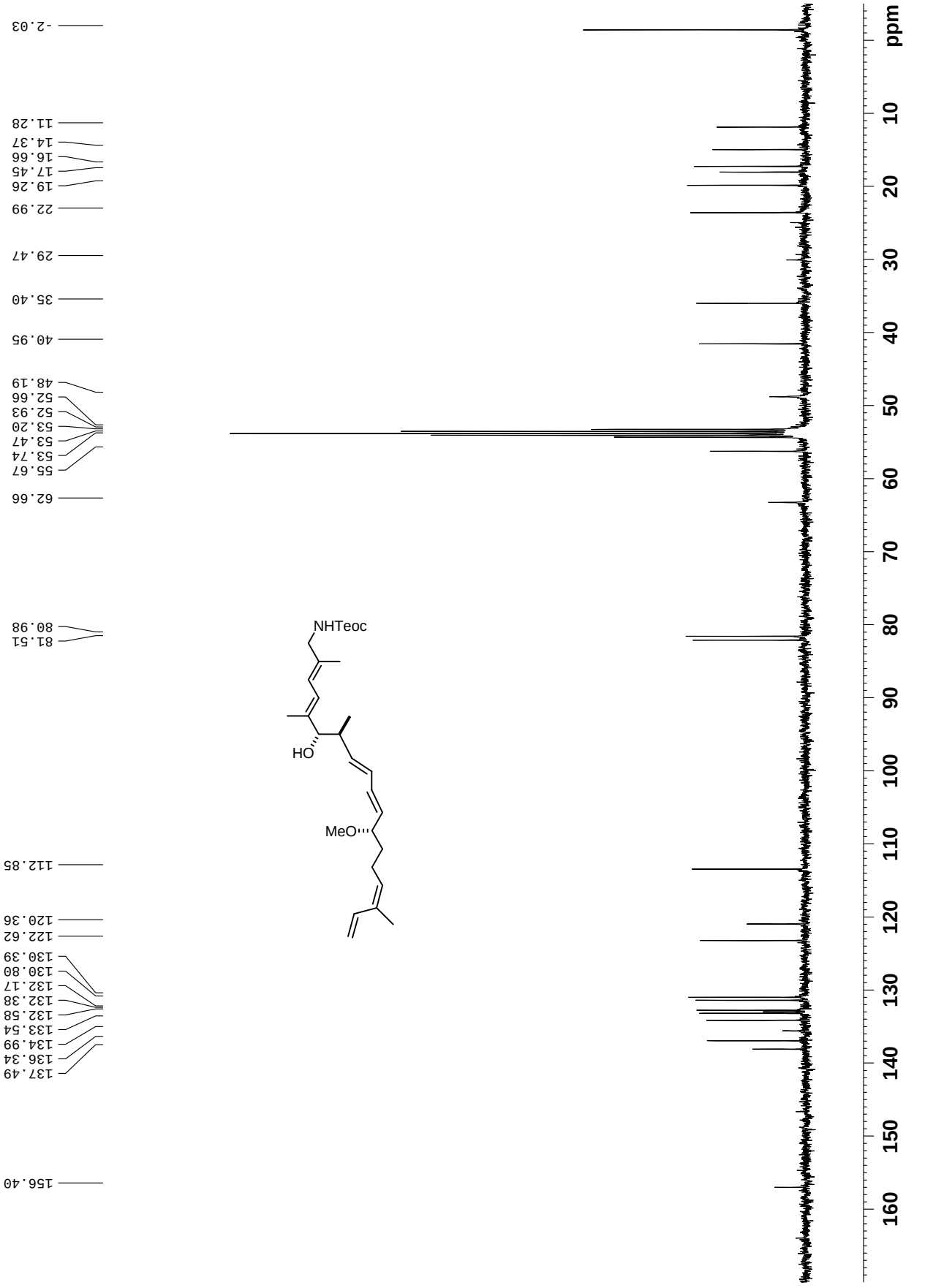
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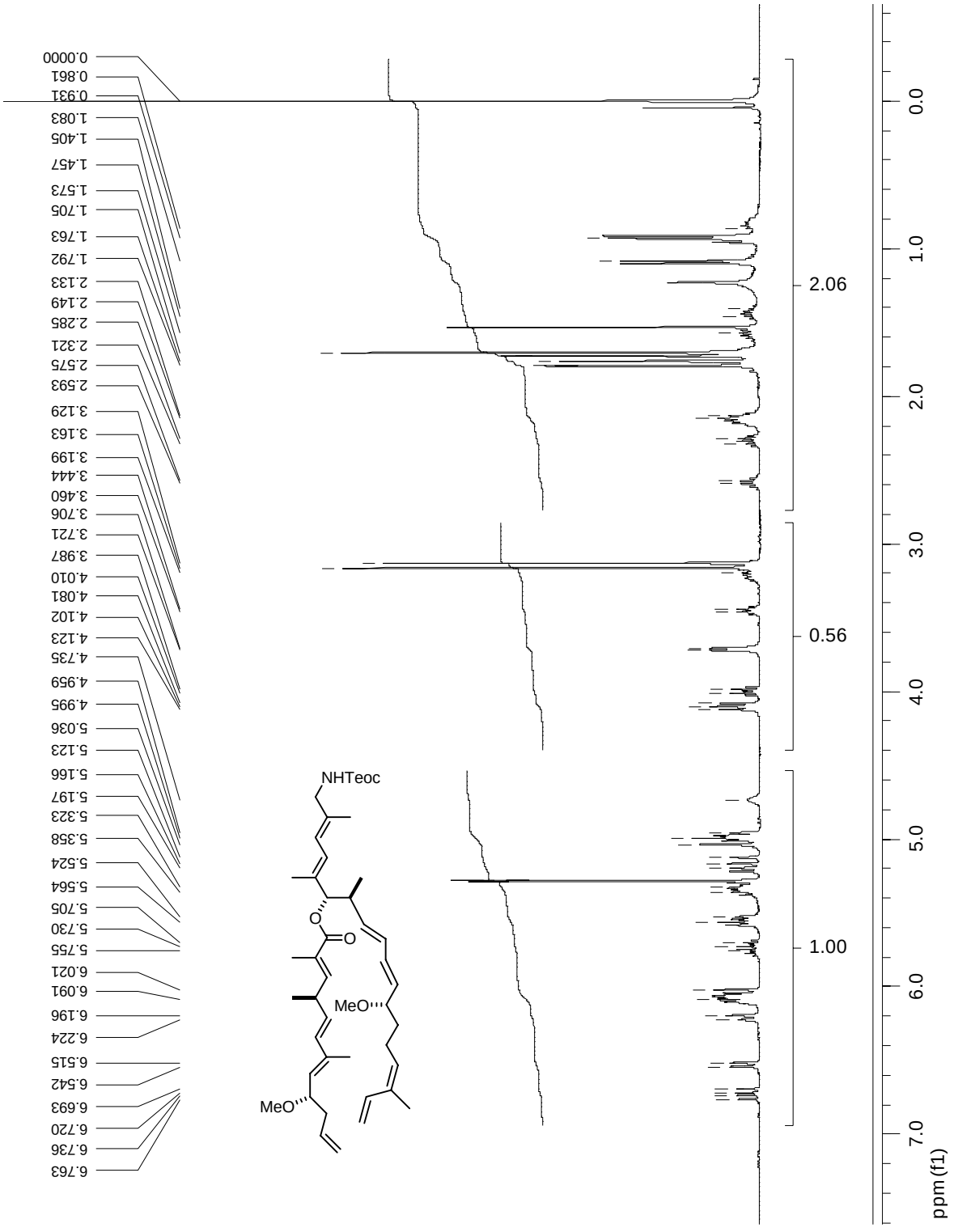
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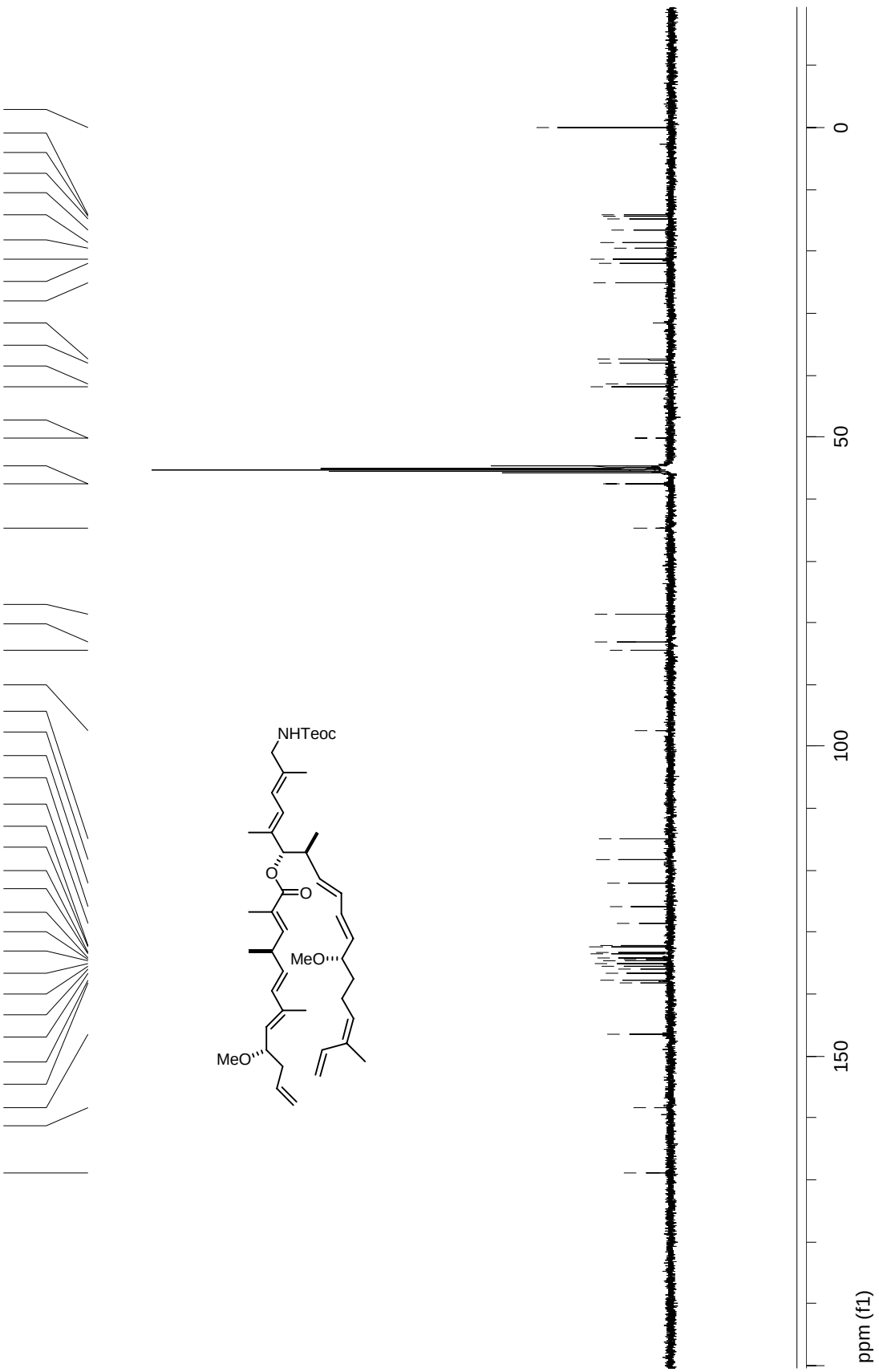
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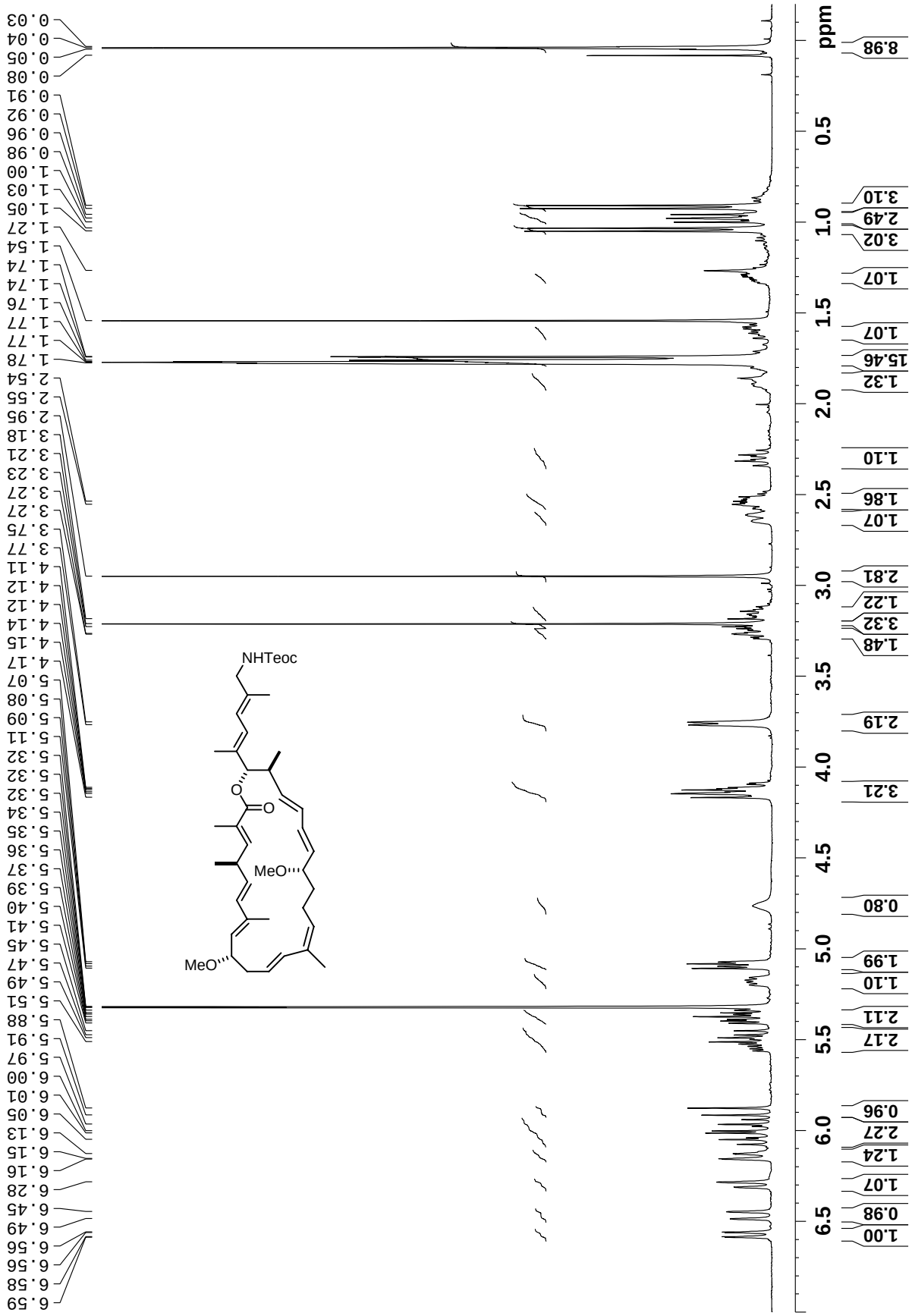
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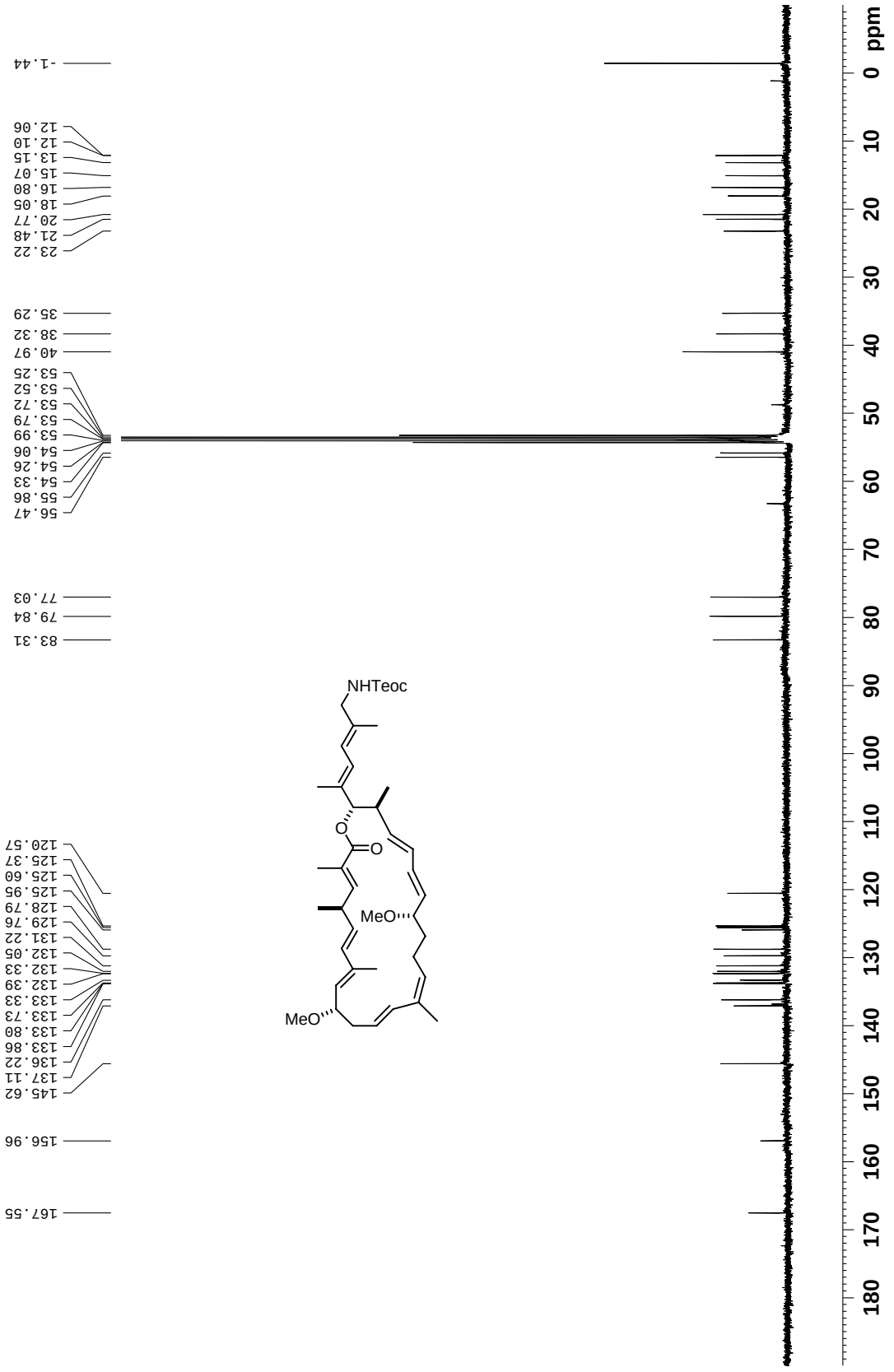
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100
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120
130
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150
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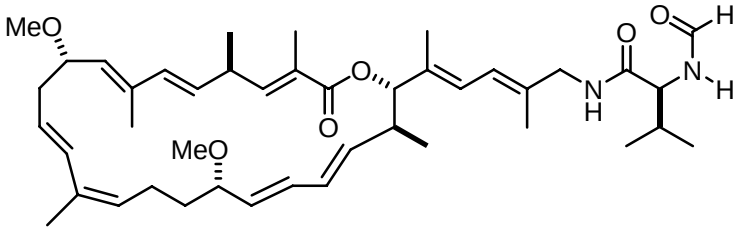
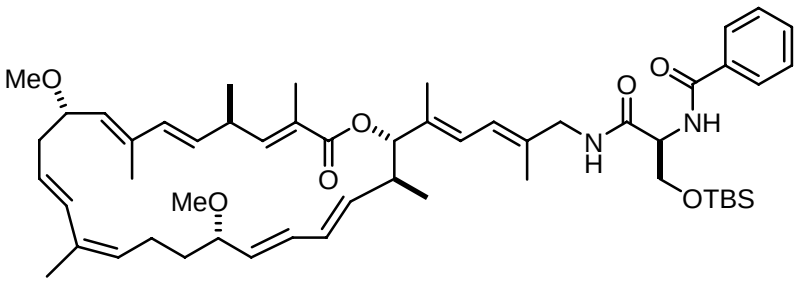
170
180
ppm

Iejimalide Analogues

Compound 68. A solution of TBAF (17 μL, 1 M in THF) was added dropwise to a solution of compound **66** (3.0 mg, 0.0042 mmol) in THF (0.1 mL) at 0°C. The mixture was allowed to reach ambient temperature and was stirred for 36 h before it was diluted with EtOAc and extracted with aq. sat. NH_4Cl. The combined organic phases were dried over $MgSO_4$ and evaporated to give amine **67** which was immediately used in the next step without further purification.



N-Formyl-L-valine (0.8 mg, 0.0054 mmol), HOAt (0.70 mg, 0.0050 mmol), and collidine (1.7 μL, 0.013 mmol) were added to a solution of crude **67** in CH_2Cl_2 (0.1 mL) and the solution was cooled to 0°C before EDC·HCl (1.2 mg, 0.0063 mmol) was introduced. The mixture was stirred at ambient temperature for 20 h. A standard extractive work up followed by flash chromatography of the crude material (hexanes/EtOAc, 5:1→1:2) afforded product **68** (3 mg, 100%) contaminated with ca. 10% isomeric impurities. An analytically pure sample was obtained by preparative HPLC as a colorless oil (2.6 mg, 75%). $[\alpha]_D^{20} = -5.0$ (c = 0.12, CH_2Cl_2); ^{1}H NMR (600 MHz, C_6D_6): δ = 7.68 (s, 1H), 7.01 (d, J = 11.4 Hz, 1H), 6.81 (d, J = 15.6 Hz, 1H), 6.48 (d, J = 11.2 Hz, 1H), 6.11 (d, J = 11.2 Hz, 1H), 6.01 (dd, J = 15.0, 10.5 Hz, 1H), 5.79 (d, J = 15.7 Hz, 1H), 5.75 (dd, J = 15.2, 10.5 Hz, 1H), 5.60-5.57 (m, 1H), 5.54 (d, J = 10.2 Hz, 1H), 5.48-5.43 (m, 2H), 5.35 (dd, J = 15.2, 9.5 Hz, 1H), 5.27-5.23 (m, 2H), 5.20-5.15 (m, 2H), 4.16 (dd, J = 7.9, 7.9 Hz, 1H), 3.98 (td, J = 9.5, 1.6 Hz, 1H), 3.74 (dd, J = 15.5, 6.3 Hz, 1H), 3.54 (dd, J = 15.5, 5.6 Hz, 1H), 3.39-3.36 (m, 1H), 3.14 (s, 3H), 3.13 (s, 3H), 2.99-2.88 (m, 2H), 2.86-2.80 (m, 1H), 2.56-2.48 (m, 2H), 1.94 (s, 3H), 1.90-1.86 (m, 2H), 1.84 (s, 3H), 1.82 (s, 3H), 1.79-1.71 (m, 1H), 1.49 (s, 6H), 1.36-1.17 (m, 1H), 0.88-0.85 (m, 9H), 0.78 (d, J = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, C_6D_6): δ = 170.4, 167.1, 160.4, 145.9, 136.9, 136.0, 135.9, 133.9, 133.7, 133.3, 133.1, 132.5, 131.8, 131.7, 130.0, 129.2, 126.0, 125.9, 125.5, 121.1, 83.1, 79.5, 76.9, 57.2, 56.4, 55.5, 46.7, 41.6, 41.4, 38.5, 35.3, 31.3, 23.3, 21.3, 21.2, 19.5, 18.1, 16.9, 14.9, 13.0, 12.2, 12.1; IR (film): $\tilde{\upsilon}$ = 3287, 2959, 2924, 2854, 1651 (br), 1547, 1461, 1377, 1259, 1217, 1102, 965, 801, 744 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{43}H_{64}N_2O_6$+Na: 727.4663 [M^++Na]; found: 727.4657.



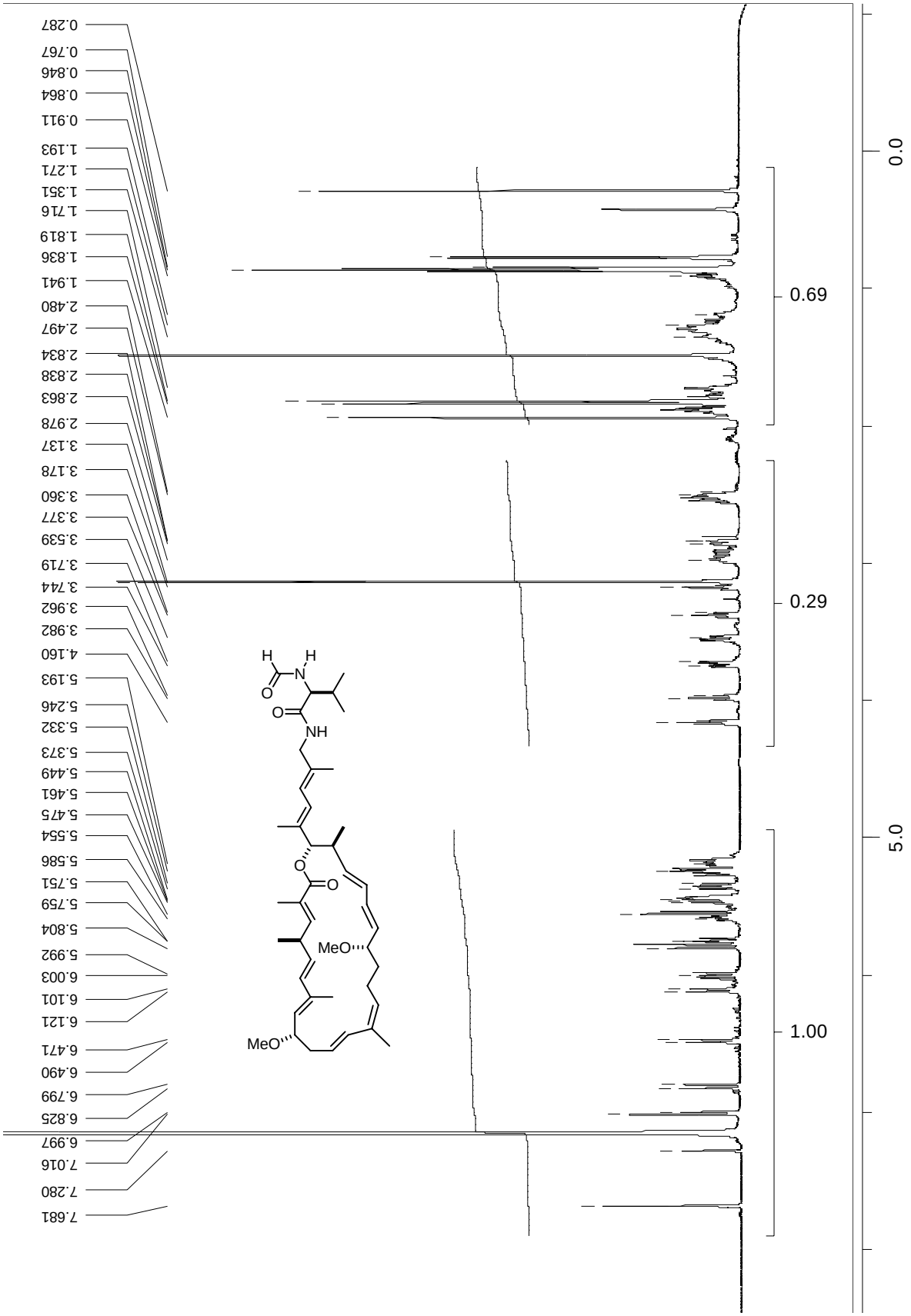
Compound 69b. Amine **67** was prepared as described above from compound **66** (8 mg, 0.0113 mmol) and TBAF (45 μL, 1M in THF). N-Benzoyl-O-TBS-L-serine (7.5 mg, 0.023 mmol), HOBt (2.8 mg, 0.01 mmol), and

NMM (4 μL, 0.036 mmol) were added to a solution of crude amine **67** in CH_2Cl_2 (1.5 ml) and the mixture was cooled to 0°C before EDC·HCl (4 mg, 0.02 mmol) was introduced. After stirring for 20 h at ambient temperature, the mixture was adsorbed on silica and the product purified by flash chromatography (hexanes/EtOAc, 2:1), furnishing product **69b** (3 mg, 31%) that contained ca. 5-10% of isomeric impurities. $[\alpha]_D^{20} = -7$ (c = 0.15, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.81 (m, 2H), 7.54 (m, 1H), 7.46 (m, 2H), 7.14 (d, J = 5.7 Hz, 1H), 6.63 (m, 1H), 6.57 (d, J = 10.2 Hz, 1H), 6.46 (d, J = 15.5 Hz, 1H), 6.28 (d, J = 11.4 Hz, 1H), 6.16 (d, J = 11.4 Hz, 1H), 6.09-5.85 (m, 3H), 5.56-5.43 (m, 2H), 5.42-5.34 (m, 2H), 5.18 (m, 1H), 5.08 (m, 2H), 4.54 (m, 1H), 4.20-4.05 (m, 2H), 4.00-3.82 (m, 2H), 3.71 (m, 1H), 3.29-3.21 (m, 1H), 3.20 (s, 3H), 3.18-3.10 (m, 1H), 2.95 (s, 3H), 2.67-2.47 (m, 3H), 2.30 (m, 1H), 1.87 (m, 1H), 1.77 (bs, 12H), 1.75 (s, 3H), 1.67-1.51 (m, 1H), 1.33-1.24 (m, 1H), 1.03 (d, J = 6.7 Hz, 3H), 0.90 (m, 12H), 0.14 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 170.4, 167.5, 167.2, 145.6, 137.1, 135.9, 134.3, 134.2, 134.1, 133.8, 133.7, 133.3, 132.4, 132.3, 132.1 (2x), 132.0, 131.2, 129.8, 128.9, 128.8, 127.3, 125.5, 125.4, 121.6, 83.3, 79.8, 77.0, 63.2, 56.5, 55.9, 55.0, 47.4, 41.0 (2x), 38.3, 35.3, 25.9, 23.2, 21.5, 20.8, 18.4, 16.8, 15.2, 13.1, 12.1, 12.0, –5.4, –5.5; IR (film): $\tilde{\upsilon}$ = 3298, 2925, 2856, 1711, 1640, 1535, 1463, 1258, 1215, 1100, 988, 963, 836, 778, 692 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{53}H_{78}N_2O_7Si$+Na: 905.547050 [M^++Na]; found: 905.547729.

Compound 69. A solution of TBAF (4 μL, 1 M in THF) was added to a solution of compound **69b** (3 mg, 0.0034 mmol) in THF (0.2 mL) at 0°C and stirring was continued at that temperature for 20 min. The mixture was adsorbed on silica and the product purified by flash chromatography (hexanes/ EtOAc, 1:1) to give compound **69** (1.5 mg, 57%) which contained ~10% of isomeric impurities. An analytically pure sample was obtained by preparative HPLC. $[\alpha]_D^{20} = +4$ (c = 0.16, CH_2Cl_2); ^{1}H NMR (600 MHz, CD_2Cl_2): δ = 7.82 (m, 2H), 7.55 (m, 1H), 7.47 (m, 2H), 7.27 (d, J = 6.6 Hz, 1H), 6.92 (t, J = 5.6 Hz, 1H), 6.57 (m, 1H), 6.45 (d, J = 15.2 Hz, 1H), 6.27 (d, J = 10.9 Hz, 1H), 6.13 (m, 1H), 6.06-5.94 (m, 2H), 5.89 (d, J = 15.2 Hz, 1H), 5.55-5.45 (m, 2H), 5.40-5.34 (m, 2H), 5.18 (m, 1H), 5.08 (m, 2H), 4.60 (m, 1H), 4.23 (m, 1H), 4.11 (dt, J = 9.9, 2.2 Hz, 1H), 3.95-3.83 (m, 2H), 3.74 (m, 1H), 3.27 (m, 1H), 3.21 (s, 3H), 3.20 (m, 1H), 3.15 (m, 1H), 2.95 (s, 3H), 2.63 (m, 1H), 2.55-2.47 (m, 2H), 2.29 (m, 1H), 1.88 (m, 1H), 1.77 (s, 3H), 1.76 (s, 3H), 1.75 (s, 3H), 1.74 (s, 3H), 1.70 (s, 3H), 1.61-1.54 (m, 1H), 1.33-1.25 (m, 1H), 1.04 (d, J = 6.8 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2): δ = 171.3, 168.2, 167.5, 145.6, 137.1, 136.1, 135.6, 134.2, 133.8, 133.7, 133.7, 133.3, 132.4 (2x), 132.3, 132.1, 131.2, 129.8, 129.0, 128.8, 127.5, 126.0, 125.4, 125.3, 121.0, 83.1, 80.0, 77.1, 63.1, 56.5, 55.9, 55.4, 47.0, 41.0, 40.8, 38.2, 35.3, 23.2, 21.5, 20.8, 16.8, 15.2, 13.2, 12.1, 12.0; IR (film): $\tilde{\upsilon}$ = 3333, 2925, 1710, 1643, 1529, 1448, 1257, 1216, 1104,

989, 964, 744, 712 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{47}H_{64}N_2O_7$+Na: 791.460572 [M^++Na]; found: 791.460821.

Compound 70. Et_3N (0.4 μL, 0.0031 mmol) and dansyl chloride (0.8 mg, 0.0029 mmol) were sequentially added to a solution of crude amine **67** [prepared from **66** (2 mg) as described above] in CH_2Cl_2 (0.03 mL) at 0ºC. After stirring for 6 h, the mixture was adsorbed on silica and the product purified by flash chromatography (hexanes/EtOAc, 20:1→5:1) to give product **70** as a white solid (1 mg, 45% over 2 steps). $[\alpha]_D^{20}$ = +4 (*c* = 0.1, CH_2Cl_2); ^{1}H NMR (600 MHz, CD_2Cl_2): δ = 8.54 (d, *J* = 8.6 Hz, 1H), 8.26 (d, *J* = 8.6 Hz, 1H), 8.20 (dd, *J* = 7.4, 1.0 Hz, 1H), 7.58 (dd, *J* = 8.4, 7.8 Hz, 1H), 7.52 (dd, *J* = 8.4, 7.4 Hz, 1H), 7.21 (d, *J* = 7.4 Hz, 1H), 6.56 (dd, *J* = 10.2, 1.3 Hz, 1H), 6.46 (d, *J* = 15.8 Hz, 1H), 6.10 (d, *J* = 10.5 Hz, 1H), 6.04-5.93 (m, 3H), 5.89 (d, *J* = 15.4 Hz, 1H), 5.54-5.45 (m, 2H), 5.39-5.37 (m, 2H), 5.08 (d, *J* = 9.4 Hz, 1H), 5.01 (d, *J* = 10.2 Hz, 1H), 4.77 (t, *J* = 6.2 Hz, 1H), 4.10 (td, *J* = 10.0, 2.9 Hz, 1H), 3.51 (d, *J* = 6.1 Hz, 2H), 3.27-3.23 (m,1H), 3.21 (s, 3H), 3.18-3.15 (m, 1H), 2.94 (s, 3H), 2.88 (s, 6H), 2.64-2.61 (m, 1H), 2.56-2.47 (m, 2H), 2.29 (dt, *J* = 10.4, 9.5 Hz, 1H), 1.89-1.83 (m, 1H), 1.77 (s, 6H), 1.75 (d, *J* = 1.3 Hz, 3H), 1.63 (s, 3H), 1.61-1.52 (m, 1H), 1.34-1.28 (m, 1H), 1.04 (d, *J* = 6.7 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H); IR (film): $\tilde{\upsilon}$ = 3346, 2926, 1712, 1652, 1614, 1553, 1446, 1389, 1262, 1212, 1147, 1098, 990, 967 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{49}H_{66}N_2O_8S$+Na: 833.4539 [M^++Na]; found: 833.4534.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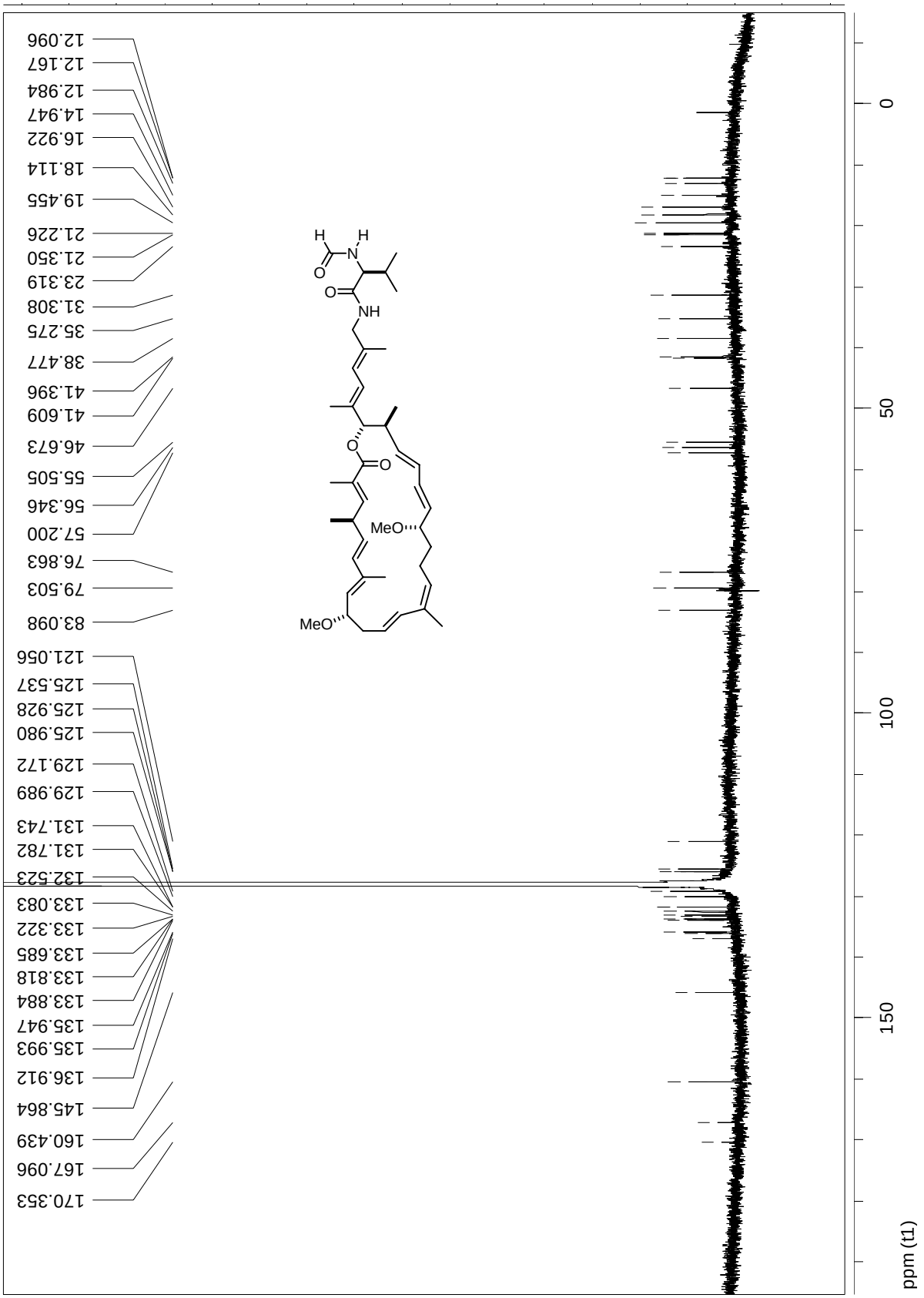
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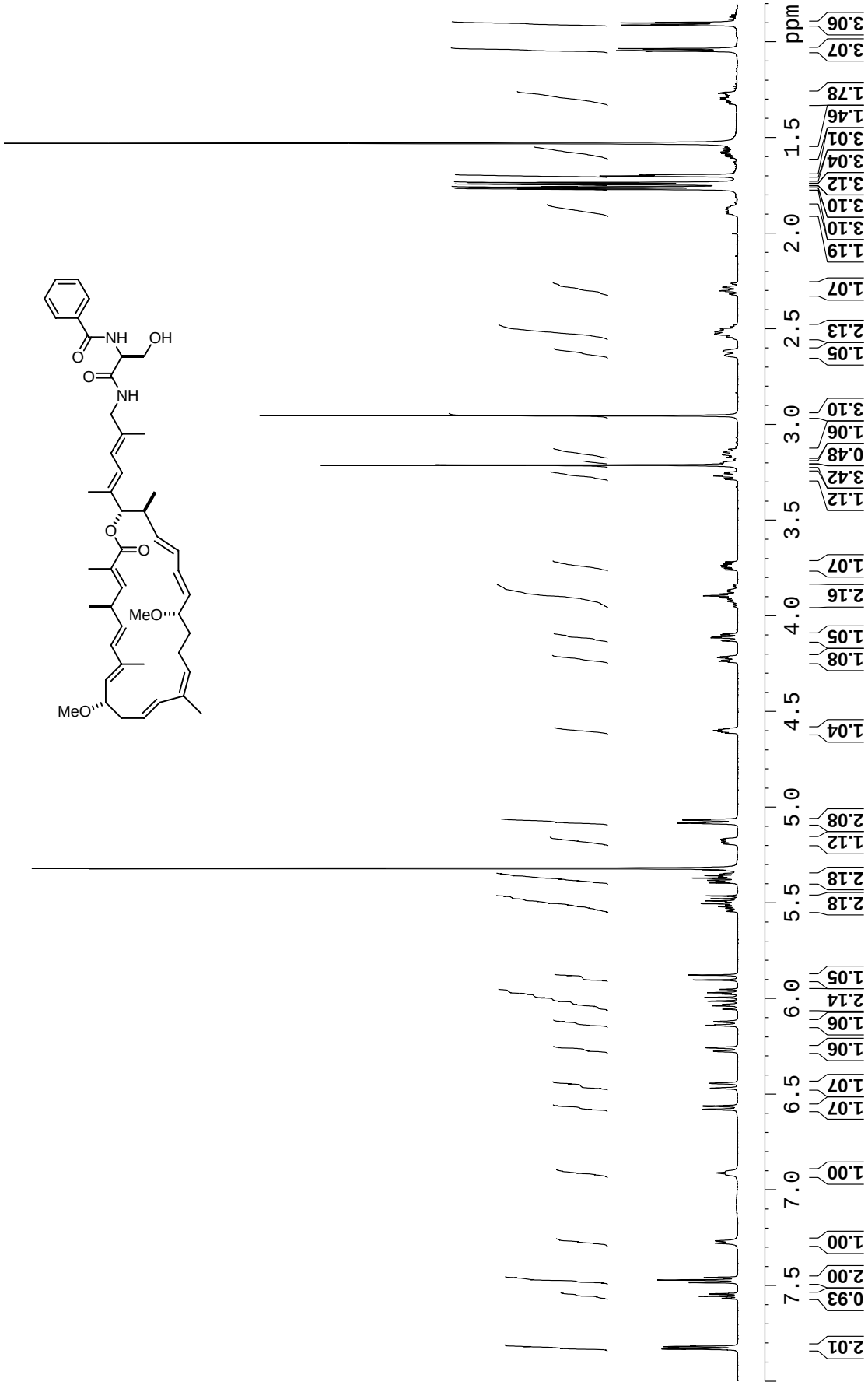
ppm (t1)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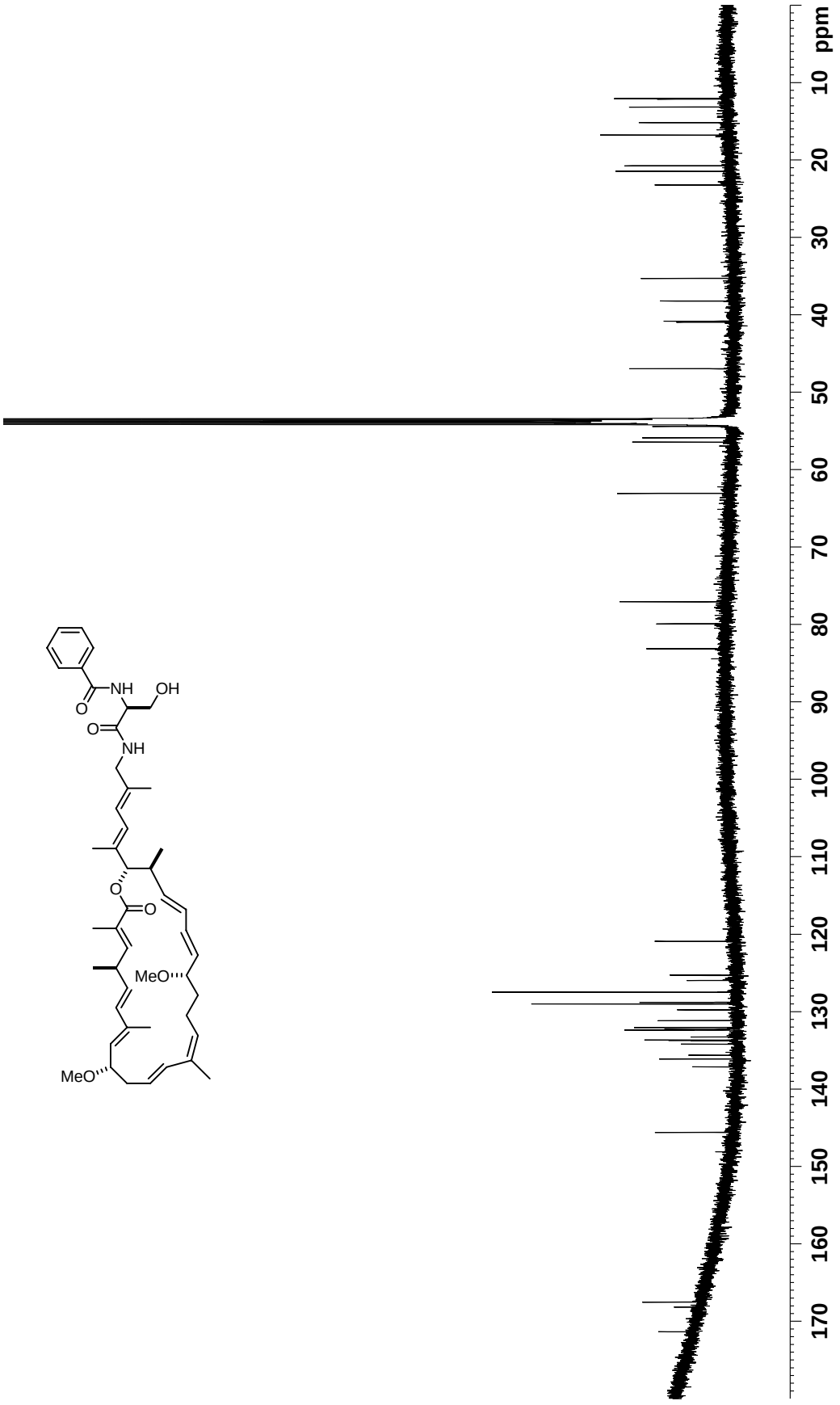
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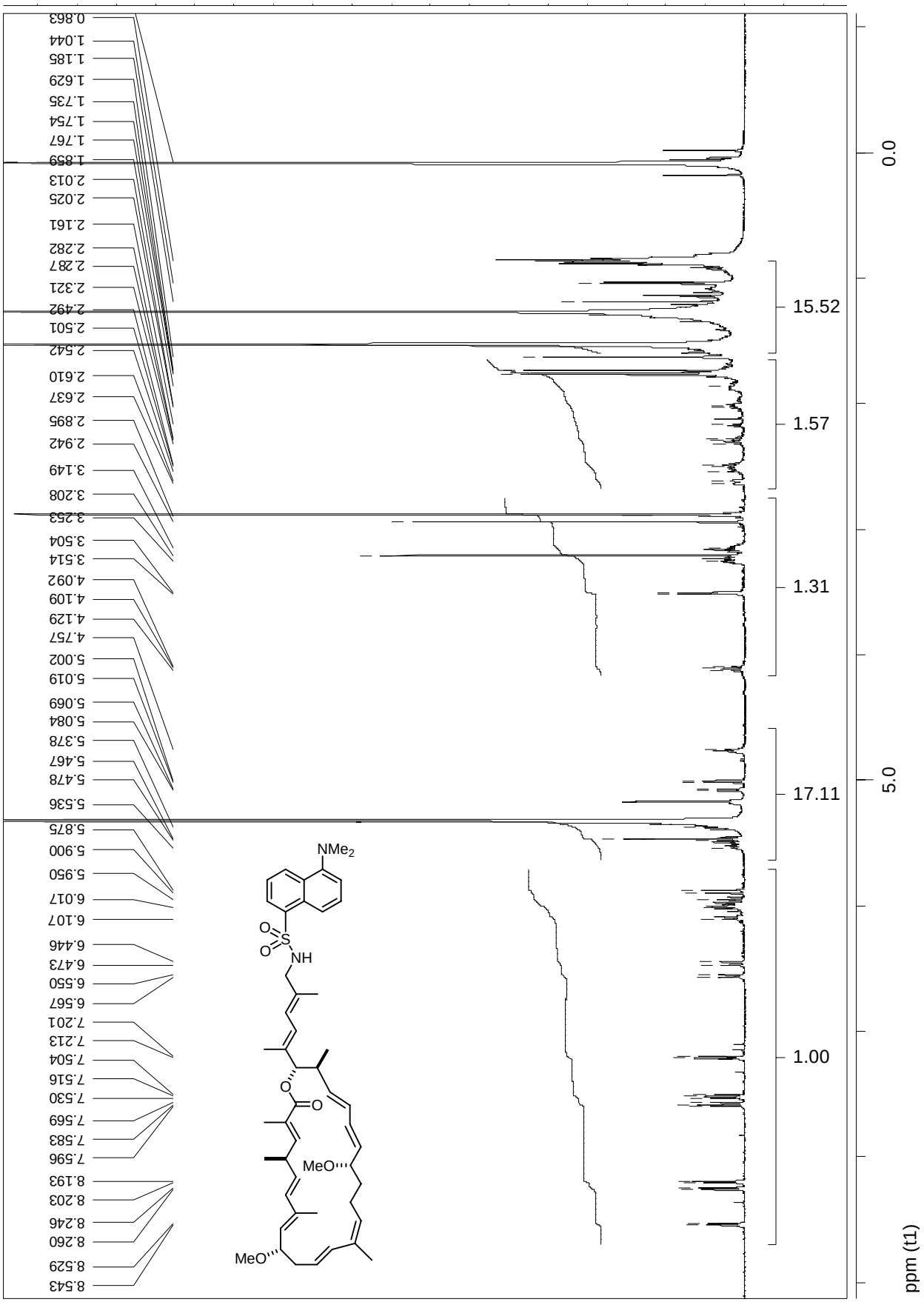
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MeO
MeO
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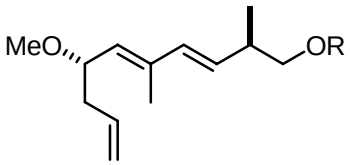
ppm (t1)

Total Synthesis of Iejimalide A

Compound 76. Compounds **36** (335 mg, 0.807 mmol) and **75**[15] (332 mg, 0.74 mmol), CuTC (200 mg, 1.05 mmol) and $Pd(PPh_3)_4$ (51 mg, 0.0044 mmol) were successively added to thoroughly dried $Ph_2PO_2NBu_4$ (475 mg, 1.034 mmol) in degassed DMF (12 mL). The resulting brown mixture was stirred for 1 h before it was diluted with H_2O and EtOAc. The mixture was filtered through a pad of Celite, the filtrate was diluted with EtOAc and washed with brine, the organic layer was dried over Na_2SO_4 and evaporated, and the residue purified by flash chromatography (hexanes/EtOAc, 20:1) to give the silyl ether **76b** (R = TBDPS) as a colorless oil (271 mg, 82%). $[\alpha]_D^{20} = -18.5$ (*c* = 1.05, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.67 (m, 4H), 7.40 (m, 6H), 6.13 (d, *J* = 15.7 Hz, 1H), 5.78 (m, 1H), 5.65 (dd, *J* = 15.7, 7.5 Hz, 1H), 5.23 (d, *J* = 8.8 Hz, 1H), 5.08-4.98 (m, 2H), 4.05 (m, 1H), 3.56 (m, 2H), 3.21 (s, 3H), 2.48 (m, 1H), 2.35 (m, 1H), 2.21 (m, 1H), 1.77 (d, *J* = 1.2 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 137.2, 136.0, 135.3, 134.4, 134.3, 132.6, 131.2, 129.9, 128.0, 116.7, 77.2, 69.1, 56.0, 40.5, 39.9, 27.0, 19.5, 16.9, 13.2; IR (film): $\tilde{\upsilon}$ = 2958, 2931, 2858, 1472, 1428, 1389, 1188, 1103, 965, 965, 914, 823, 739, 701 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{29}H_{40}O_2Si$+Na: 471.268976 [M^++Na]; found: 471.269022; elemental analysis calcd (%) for $C_{29}H_{40}O_2Si$: C 77.62, H 8.99; found: C 77.68, H 9.06.



A solution of TBAF (0.4 mL, 1 M in THF) was added to a solution of compound **76b** (114 mg, 0.254 mmol) in THF (6 mL) at 0°C and the mixture was stirred at ambient temperature for 16 h. A standard extractive work up followed by flash chromatography of the crude product (hexanes/EtOAc, 4:1) gave compound **76** (R = H) as a colorless oil (50 mg, 94%). $[\alpha]_D^{20} = -9.6$ (*c* = 0.65, CH_2Cl_2); ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 6.18 (d, *J* = 15.8 Hz, 1H), 5.79 (m, 1H), 5.56 (dd, *J* = 15.8, 7.8 Hz, 1H), 5.27 (d, *J* = 9.0 Hz, 1H), 5.03 (m, 2H), 4.05 (m, 1H), 3.45 (m, 2H), 3.20 (s, 3H), 2.30 (m, 2H), 2.22 (m, 1H), 1.79 (s, 3H), 1.65 (bs, 1H), 1.03 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 136.9, 135.2, 135.1, 132.1, 131.7, 116.8, 77.1, 67.7, 56.2, 40.4 (2x), 16.8, 13.2; IR (film): $\tilde{\upsilon}$ = 3403, 2974, 2926, 1641, 1450, 1383, 1241, 1189, 1079, 1037, 964, 914, 816 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{13}H_{22}O_2$+Na: 233.151197 [M^++Na]; found: 233.151456; elemental analysis calcd (%) for $C_{13}H_{22}O_2$: C 74.24, H 10.54; found: C 74.20, H 10.42.

Compound 84. 4-Pyrrolidinylpyridine (1.4 mg, 0.0095 mmol) and DCC (13.3 mg, 0.0646 mmol) were added to a solution of $(EtO)_2P(O)CH_2COOH$ (10.4 μL, 0.0646 mmol) in CH_2Cl_2 (0.15 mL) at 0°C. After stirring for 10 min at ambient temperature, the resulting suspension was cooled to 0°C before a solution of compound **54** (38 mg, 0.0646 mmol) in CH_2Cl_2 (0.2 mL) was

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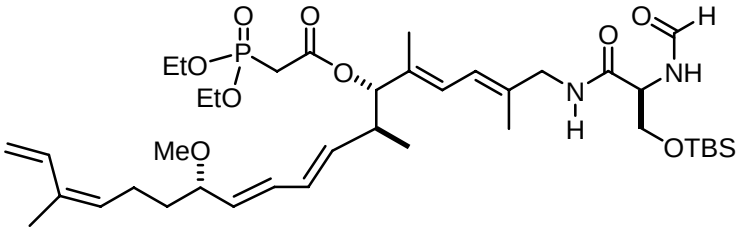
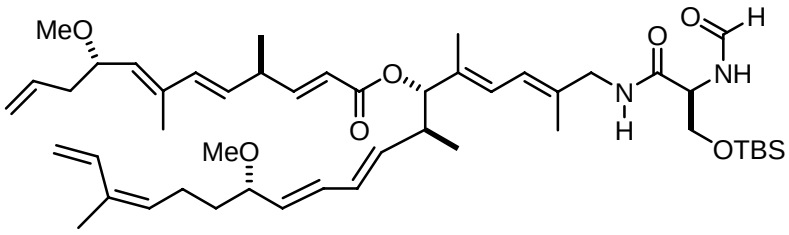
[15] Prepared as described for the other enantiomer in: Paquette, L. A.; Guevel, R.; Sakamoto, S.; Kim, I. H.; Crawford, J. *J. Org. Chem.* **2003**, *68,* 6096.

introduced. The mixture was warmed to ambient temperature within 1 h and stirred for 48 h. After this time, the mixture was again cooled to 0°C before more $(EtO)_2P(O)CH_2COOH$ (10.4 μL, 0.0646 mmol), 4-pyrrolidinyl-pyridine (1.4 mg, 0.0095 mmol), and DCC (13.3 mg, 0.0646 mmol) were introduced. After stirring for another 48 h, a standard extractive work up followed by purification of the crude material by flash chromatography (hexanes/EtOAc, 4:1) gave product **84** as a colorless oil (41 mg, 82%). $[\alpha]_D^{20} = +23.6$ (c = 0.42, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 8.23 (s, 1H), 6.76 (dd, J = 17.3, 10.8 Hz, 1H), 6.53 (m, 2H), 6.23 (d, J = 11.2 Hz, 1H), 6.11 (m, 3H), 5.65 (dd, J = 14.5, 7.8 Hz, 1H), 5.43 (m, 1H), 5.37 (m, 1H), 5.19 (d, J = 17.3 Hz, 1H), 5.07 (d, J = 10.8 Hz, 1H), 5.01 (d, J = 8.3 Hz, 1H), 4.43 (m, 1H), 4.07 (m, 5H), 3.88 (m, 2H), 3.62 (m, 1H), 3.50 (m, 1H), 3.19 (s, 3H), 2.89 (m, 2H), 2.59 (m, 1H), 2.19 (m, 2H), 1.80 (s, 3H), 1.75 (s, 6H), 1.62 (m, 1H), 1.48 (m, 1H), 1.29 (t, J = 6.9 Hz, 6H), 0.95 (d, J = 6.9 Hz, 3H), 0.89 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 169.8, 165.3, 161.2, 135.9, 135.8, 134.2, 134.1, 133.0 (2x), 132.9, 131.0, 130.7, 124.8, 121.7, 113.5, 84.5, 81.6, 63.1, 62.8, 56.2, 53.5, 47.4, 39.4, 36.0, 34.0, 25.9, 23.6, 19.8, 18.4, 16.9, 16.6, 16.5, 15.2, 12.6, –5.4, –5.5; IR (film): $\tilde{\upsilon}$ = 3291, 2928, 2857, 1733, 1656, 1532, 1463, 1388, 1255, 1100, 1050, 1022, 972, 835, 777 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{39}H_{67}N_2O_9PSi$+Na: 789.424569 [M^++Na]; found: 789.423875; elemental analysis calcd (%) for $C_{39}H_{67}N_2O_9PSi$: C 61.07, H 8.80; found: C 61.18, H 8.73.



Compound 85. *Method A:* Hünig base (3.8 μL, 0.021 mmol) was added to a mixture of compound **84** (15 mg, 0.0195 mmol) and LiCl (1.7 mg, 0.04 mmol) in MeCN (0.7 mL) at 0°C. After stirring at ambient temperature for 15 min, the mixture was again cooled to 0°C before a solution of crude aldehyde **77** [*freshly* prepared in situ upon oxidation of **76** (8 mg, 0.038 mmol)][16] in MeCN (0.4 mL) was added dropwise. After stirring at ambient temperature for 16 h, the mixture was diluted with EtOAc and extracted with brine, the organic phase was dried over Na_2SO_4 and evaporated,

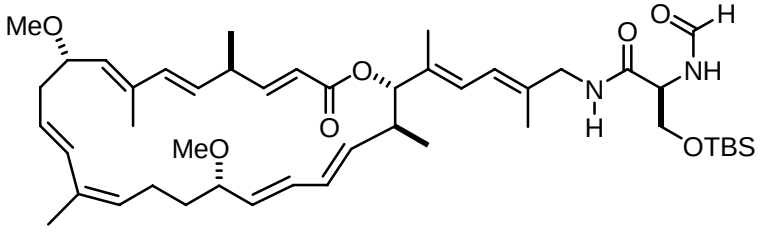


[16] Dess-Martin periodinane (20 mg, 0.047 mmol) was added to a solution of compound **76** (8 mg, 0.038 mmol) in CH_2Cl_2 (2 mL) and the mixture stirred at ambient temperature for 30 min. After dilution with hexane and aq. sat. $NaHCO_3$, the suspension was filtered through a pad of Celite and extracted with aq. sat. $NaHCO_3$, aq. sat. $Na_2S_2O_3$ and brine. Drying of the organic phase over $MgSO_4$ and evaporation of the solvent gave crude **77** which was *immediately used* in the next step because it is very unstable even upon storage at low temperature.

and the residue purified by flash chromatography (hexanes/EtOAc, 1:1) to give product **85** (5 mg, 31%, ≥ 85% pure) and recovered **84** (8 mg, 47% conversion).

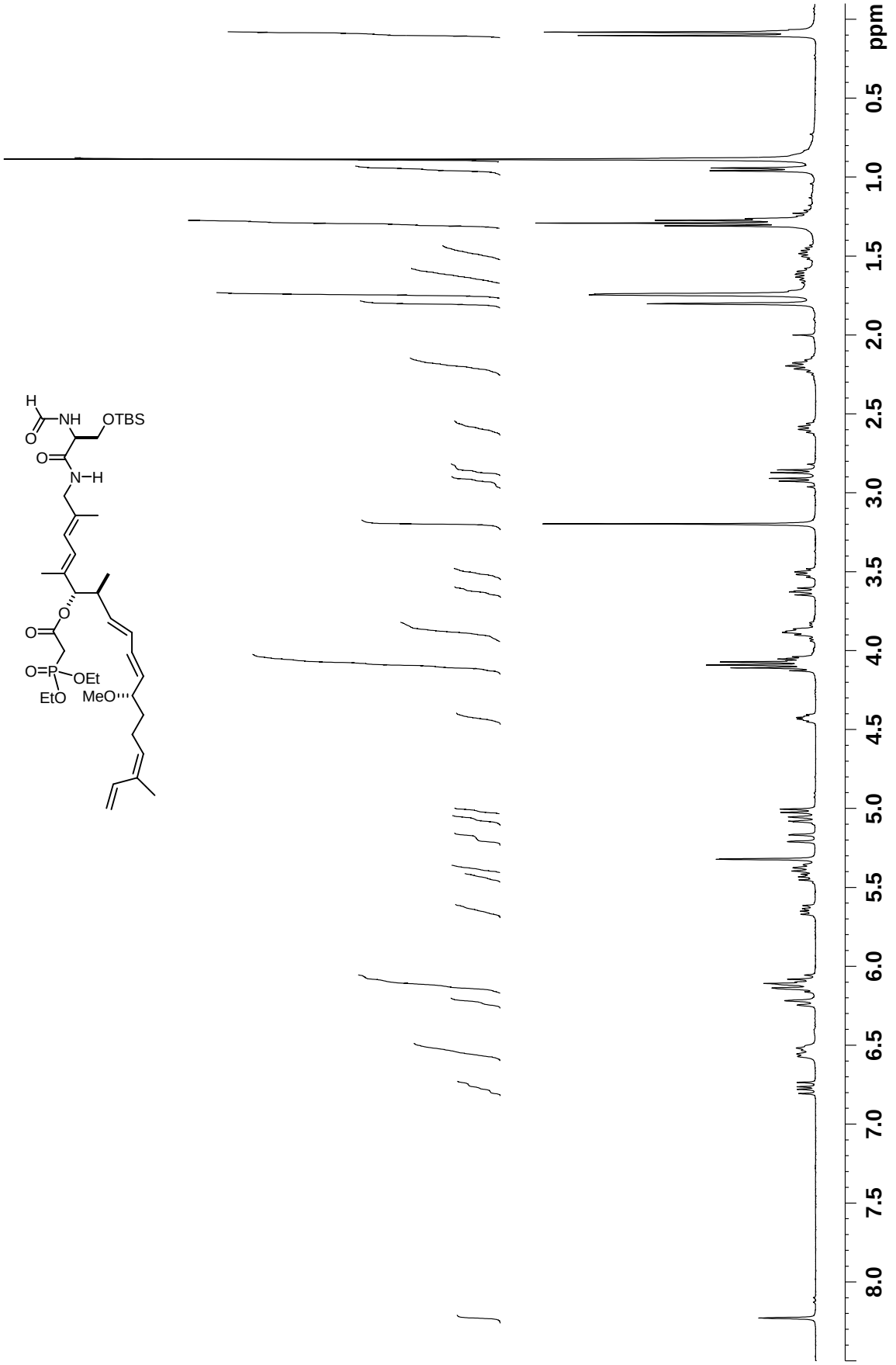
Method B: Hünig base (2.2 μL, 0.012 mmol) was added to a mixture of compound **84** (9 mg, 0.0117 mmol) and LiCl (1 mg, 0.023 mmol) in MeCN (0.3 mL) at 0°C. After stirring at ambient temperature for 15 min, the mixture was again cooled to 0°C before a solution of crude **77** [*freshly* prepared upon oxidation of **76** (3.5 mg, 0.0167 mmol)] in MeCN (0.1 mL) was slowly introduced. After stirring at ambient temperature for 20 h, the mixture was again cooled to 0°C and another batch of **77** [*freshly* prepared from 2 mg of **76** (0.0095 mmol)] was added. Stirring was continued for another 16 h before a standard extractive work up and flash chromatography of the crude material (hexanes/EtOAc, 1:1) gave product **85** (3.5 mg, 36%, ≥ 85% pure) and recovered **84** (4 mg, 55% conversion). $[\alpha]_D^{20}$ = +16.4 (*c* = 0.35, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 8.23 (s, 1H), 6.89 (dd, *J* = 15.7, 6.8 Hz, 1H), 6.77 (dd, *J* = 17.3, 10.8 Hz, 1H), 6.51 (m, 2H), 6.22 (d, *J* = 11.3 Hz, 1H), 6.17-6.05 (m, 4H), 5.79 (m, 2H), 5.60 (m, 2H), 5.38 (m, 2H), 5.27 (d, *J* = 8.8 Hz, 1H), 5.19 (d, *J* = 17.3 Hz, 1H), 5.11-4.98 (m, 4H), 4.42 (m, 1H), 4.05 (m, 2H), 3.87 (m, 2H), 3.62 (m, 1H), 3.50 (m, 1H), 3.21 (s, 3H), 3.18 (s, 3H), 3.08 (m, 1H), 2.60 (m, 1H), 2.35 (m, 1H), 2.27-2.13 (m, 3H), 1.80 (s, 3H), 1.78 (s, 3H), 1.74 (s, 6H), 1.63 (m, 1H), 1.47 (m, 1H), 1.18 (d, *J* = 6.7 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 169.8, 166.0, 161.1, 152.5, 136.7, 136.3, 135.4, 135.2, 134.8, 134.7, 134.2, 133.1, 133.0, 132.8, 132.3, 131.2, 131.0, 130.6, 124.4, 121.8, 120.3, 116.8, 113.5, 82.9, 81.6, 77.2, 63.1, 56.2, 56.1, 53.4, 47.5, 40.4, 39.8, 39.7, 36.0, 25.9, 23.6, 19.8, 17.0, 15.2, 16.5, 15.2, 13.2, 12.8, –5.4, –5.5; IR (film): $\tilde{\upsilon}$ = 3295, 2926, 2856, 1717, 1651, 1539, 1463, 1380, 1257, 1171, 1098, 988, 836, 778 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{48}H_{76}N_2O_7Si$+Na: 843.531401 [M^++Na]; found: 843.530737.

Compound 86. Complex **50** (1 mg, 0.0012 mmol) was added to a solution of compound **85** (9.5 mg, 0.0115 mmol, ca. 85% pure) in CH_2Cl_2 (18 mL) and the resulting mixture was stirred at ambient temperature for 24 h before a second portion of catalyst **50** (0.5 mg, 0.0006 mmol) was introduced and stirring was continued for another 48 h. The reaction was quenched with ethyl vinyl ether (50 μL) and stirred for 15 min. Evaporation of the solvent followed by flash chromatography (hexanes/EtOAc, 1:1) gave product **86** as a mixture of isomers (5 mg, 55%, ≥ 80% pure). Purification by preparative HPLC gave **86** in ≥ 90% purity. $[\alpha]_D^{20}$ = –18 (*c* = 0.13, CH_2Cl_2); ^{1}H NMR (600 MHz, MeOD): δ = 8.14 (s, 1H), 6.85 (dd, *J* = 15.4, 9.3 Hz, 1H), 6.47 (d, *J* = 15.4 Hz, 1H), 6.32 (d, *J* = 10.8 Hz, 1H), 6.22 (d, *J* = 10.8 Hz, 1H), 6.10 (dd, *J* = 15.0, 10.3 Hz, 1H), 6.01 (m, 2H), 5.77 (d, *J* = 15.4 Hz, 1H), 5.61-5.52 (m, 2H), 5.48 (dd, *J* = 14.8, 8.9 Hz, 1H), 5.40 (dd, *J* = 15.0, 8.3 Hz, 1H), 5.24 (m, 1H), 5.13 (m, 2H), 4.53 (m, 1H), 4.26 (m, 1H), 3.96 (m, 1H), 3.86 (m, 3H), 3.38 (m, 1H), 3.27 (s, 3H), 3.07 (s,



3H), 3.05 (m, 1H), 2.67-2.54 (m, 2H), 2.44 (m, 1H), 2.32 (m, 1H), 1.97 (m, 1H), 1.81 (s, 6H), 1.79 (s, 6H), 1.60 (m, 1H), 1.38 (m, 1H), 1.13 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H), 0.91 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (150 MHz, MeOD): δ = 171.8, 167.8, 163.8, 154.1, 138.3, 136.9, 136.7, 135.2, 134.4, 134.1, 133.6, 133.5, 132.9, 132.5, 131.9, 130.7, 129.3, 126.6, 126.0, 121.9, 120.2, 84.5, 81.5, 78.1, 64.4, 56.9, 56.1, 55.4, 47.8, 42.9, 41.3, 41.1, 36.1, 26.3, 23.9, 22.1, 20.9, 19.1, 17.2, 15.3, 13.4, 12.3, –5.4; IR (film): $\tilde{\upsilon}$ = 2926, 2857, 1717, 1648, 1455, 1377, 1347, 1259, 1221, 1106, 987, 836, 779 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{46}H_{72}N_2O_7Si$+Na: 815.500098 [M^++Na]; found: 815.499381.

Iejimalide A (1). A solution of TBAF (4.4 μL, 1 M in THF) was added to a solution of compound **86** (3.5 mg, 0.0044 mmol) in THF (0.2 mL) at 0°C. After stirring for 10 min at this temperature, the mixture was adsorbed on silica and the product purified by flash chromatography (hexanes/EtOAc, 1:1) to give iejimalide A (2 mg, 67%, ≥ 80% pure). An analytically pure sample of **1** was obtained by preparative HPLC. The spectroscopic data are in full agreement with those of the natural product reported in the literature. $[\alpha]_D^{20}$ = –32 (c = 0.06, CH_2Cl_2) (–36.4, $CHCl_3$);[14a] ^{1}H NMR (600 MHz, MeOD): δ = 8.17 (s, 1H), 6.83 (dd, J = 15.5, 9.4 Hz, 1H), 6.45 (d, J = 15.6 Hz, 1H), 6.32 (d, J = 11.1 Hz, 1H), 6.21 (dd, J = 11.1, 1.3 Hz, 1H), 6.07 (dd, J = 14.9, 10.3 Hz, 1H), 5.97 (m, 2H), 5.74 (d, J = 15.5, 0.5 Hz, 1H), 5.60 (m, 1H), 5.56 (dd, J = 15.5, 8.9 Hz, 1H), 5.45 (dd, J = 15.1, 8.9 Hz, 1H), 5.38 (dd, J = 15.1, 7.9 Hz, 1H), 5.22 (m, 1H), 5.12 (d, J = 9.5 Hz, 1H), 5.09 (d, J = 9.9 Hz, 1H), 4.50 (t, J = 4.7 Hz, 1H), 4.23 (td, J = 9.5, 3.1 Hz, 1H), 3.89-3.77 (m, 4H), 3.38-3.34 (m, 1H), 3.25 (s, 3H), 3.05 (s, 3H), 3.03-3.00 (m, 1H), 2.64-2.61 (m, 1H), 2.60-2.54 (m, 1H), 2.44-2.40 (m, 1H), 2.34-2.28 (m, 1H), 1.96-1.93 (m, 1H), 1.79 (s, 3H), 1.78 (s, 3H), 1.77 (s, 3H), 1.76 (s, 3H), 1.61-1.55 (m, 1H), 1.40-1.32 (m, 1H), 1.11 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, MeOD): δ = 172.1, 167.8, 163.9, 154.0, 138.3, 137.0, 136.7, 135.2, 134.2, 134.1, 133.6, 133.5, 132.9, 132.6, 131.9, 130.7, 129.3, 126.6, 126.0, 121.2, 120.2, 84.6, 81.5, 78.1, 63.0, 56.9, 56.1, 55.5, 47.5, 42.9, 41.3, 41.1, 36.1, 23.9, 22.0, 20.9, 17.2, 15.1, 13.4, 12.2; IR (film): $\tilde{\upsilon}$ = 3367, 2924, 2853, 1716, 1658, 1468, 1260, 1108, 989, 838 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{40}H_{58}N_2O_7$+Na: 701.413622 [M^++Na]; found: 701.413317.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OTBS
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N–H
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O
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EtO
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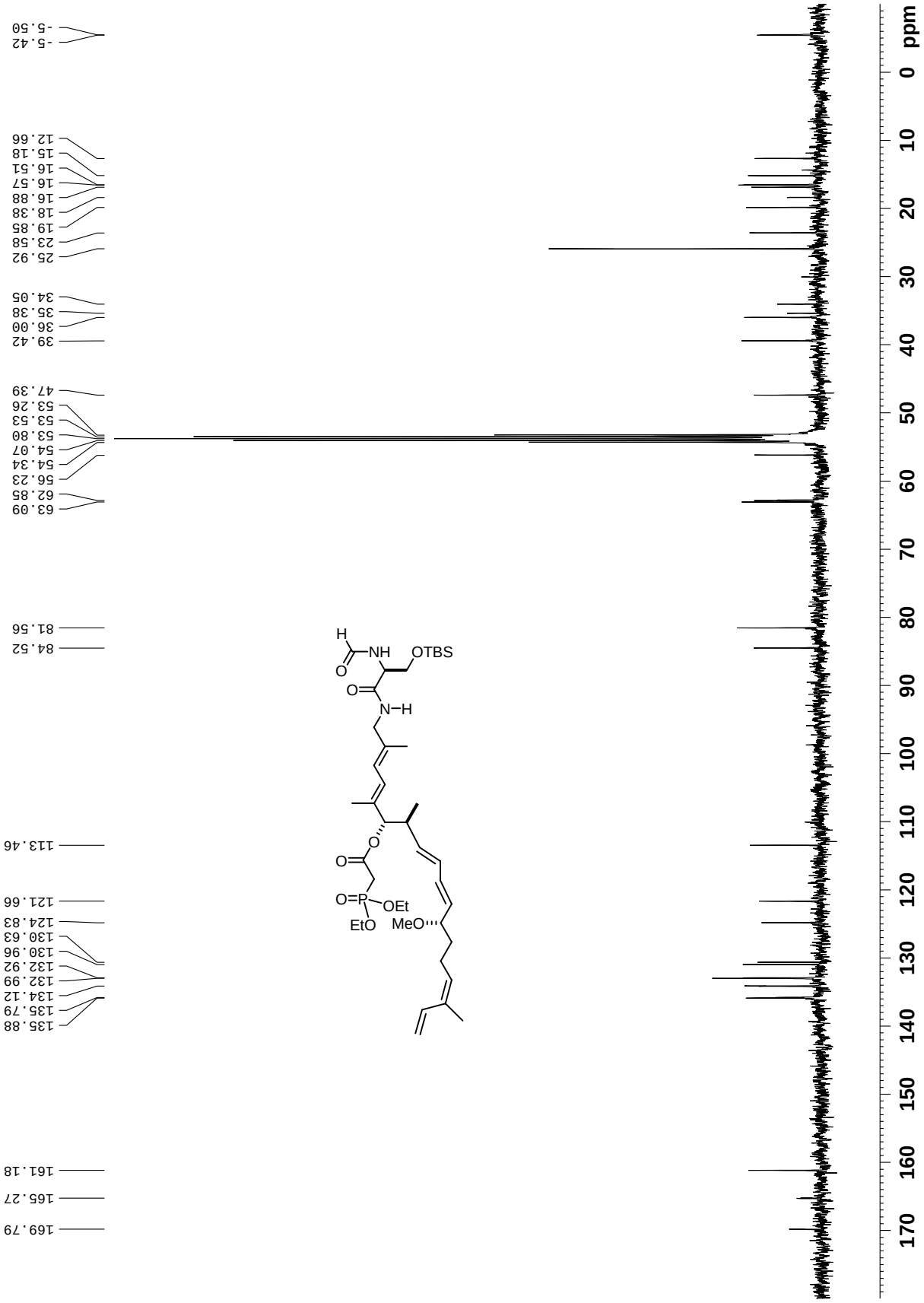
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36.00
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53.26
53.53
53.80
54.07
54.34
56.23
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63.09
81.56
84.52
113.46
121.66
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130.63
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132.92
132.99
134.12
135.79
135.88
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169.79
H
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OTBS
O
O
N–H
O
O
O=P
OEt
EtO
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110
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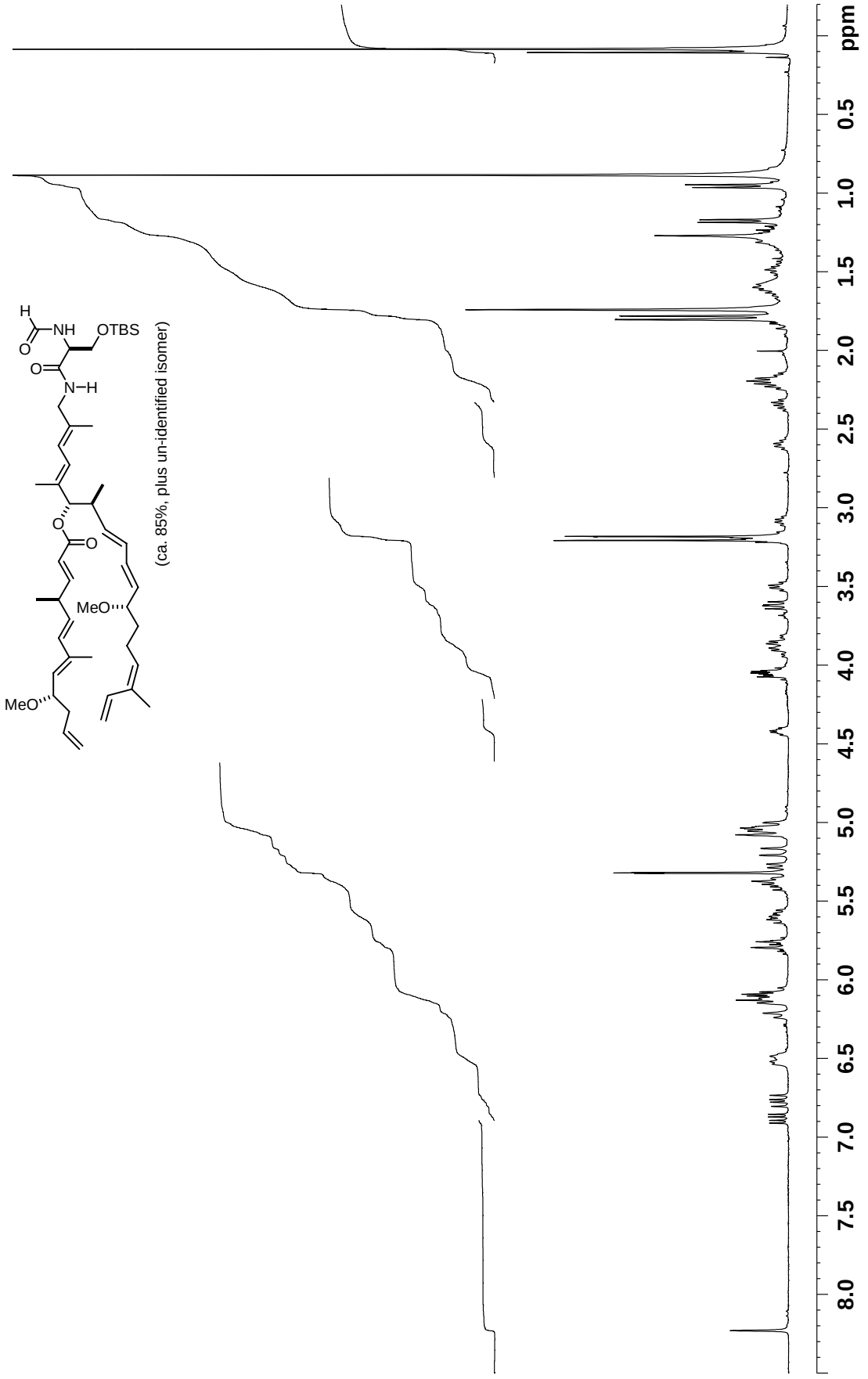
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N–H
O
O
MeO
MeO
(ca. 85%, plus un-identified isomer)
ppm
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7.0
6.5
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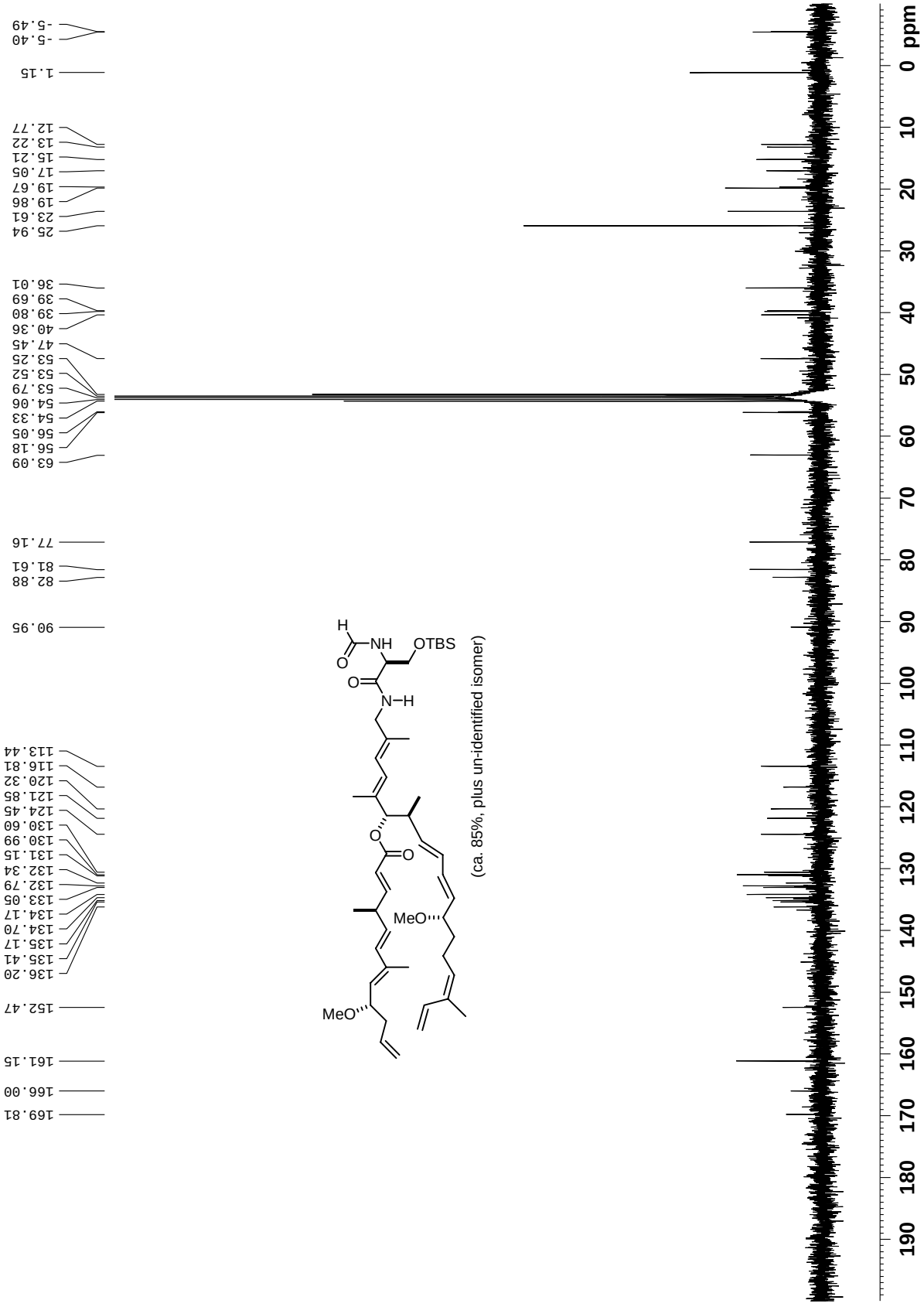
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O
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MeO
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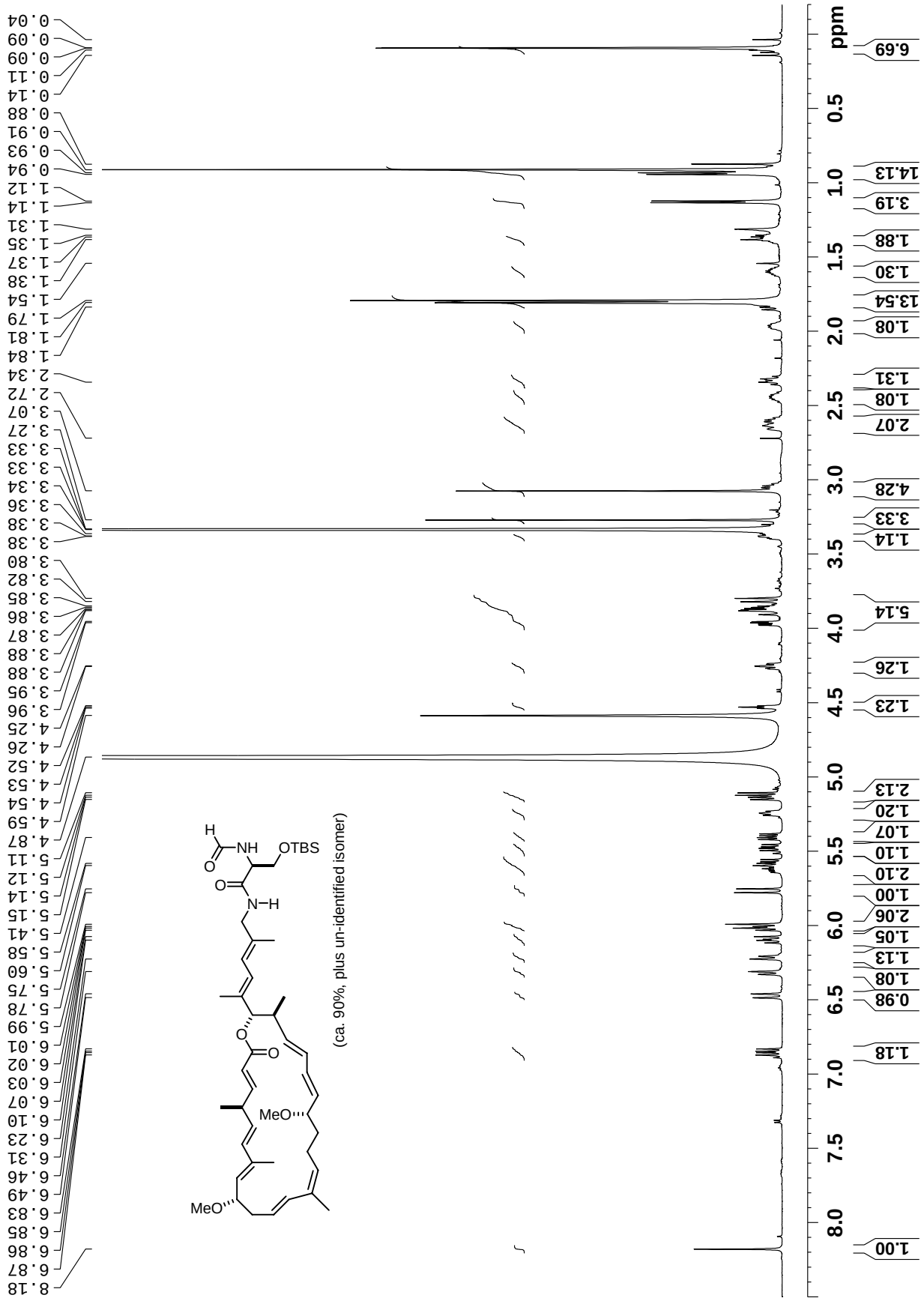
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1.79
1.81
1.84
2.34
2.72
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3.87
3.88
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3.95
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6.46
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6.85
6.86
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O
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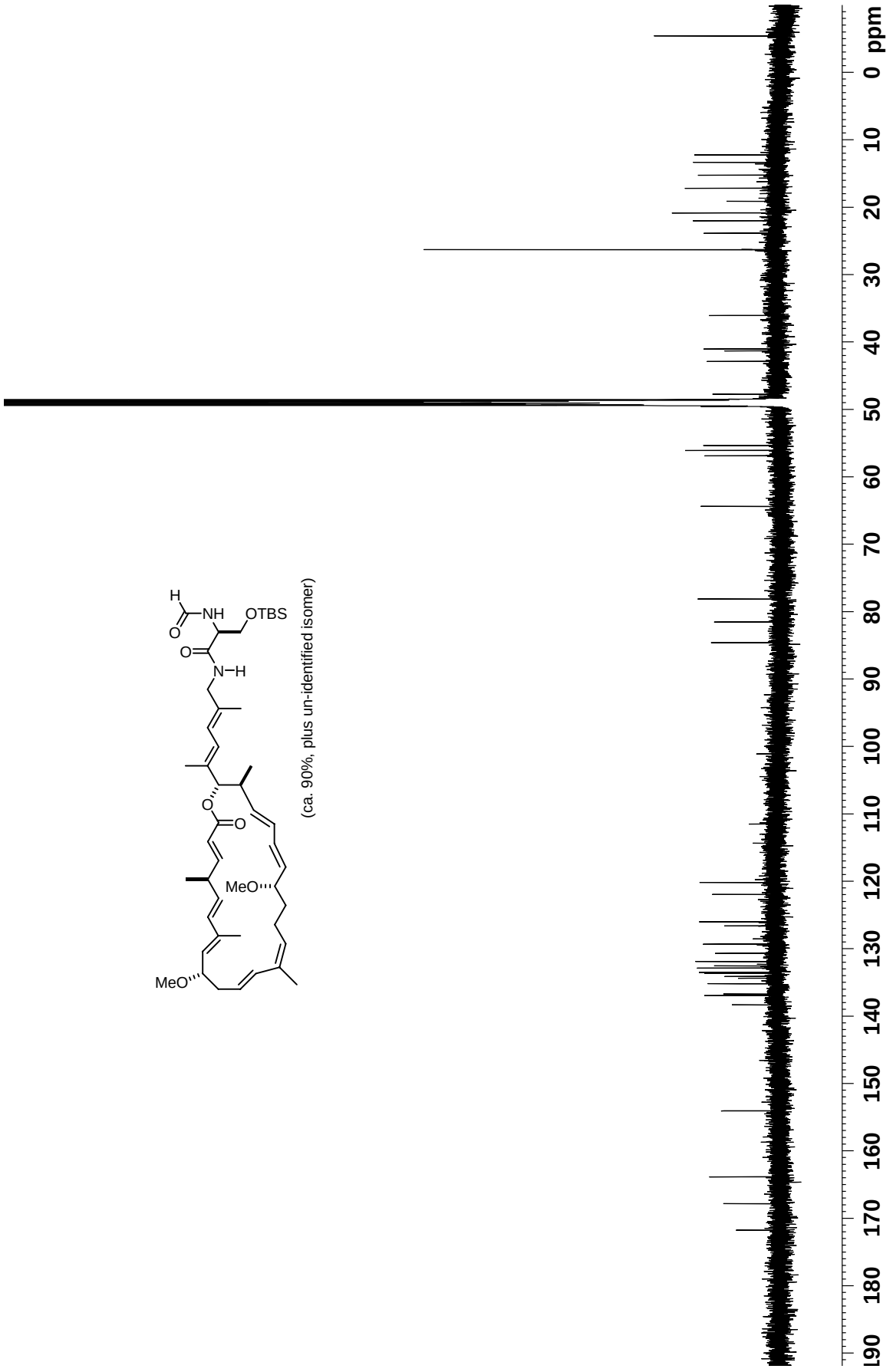
MeO
(ca. 90%, plus un-identified isomer)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OTBS
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N–H
O
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MeO
MeO
(ca. 90%, plus un-identified isomer)
ppm
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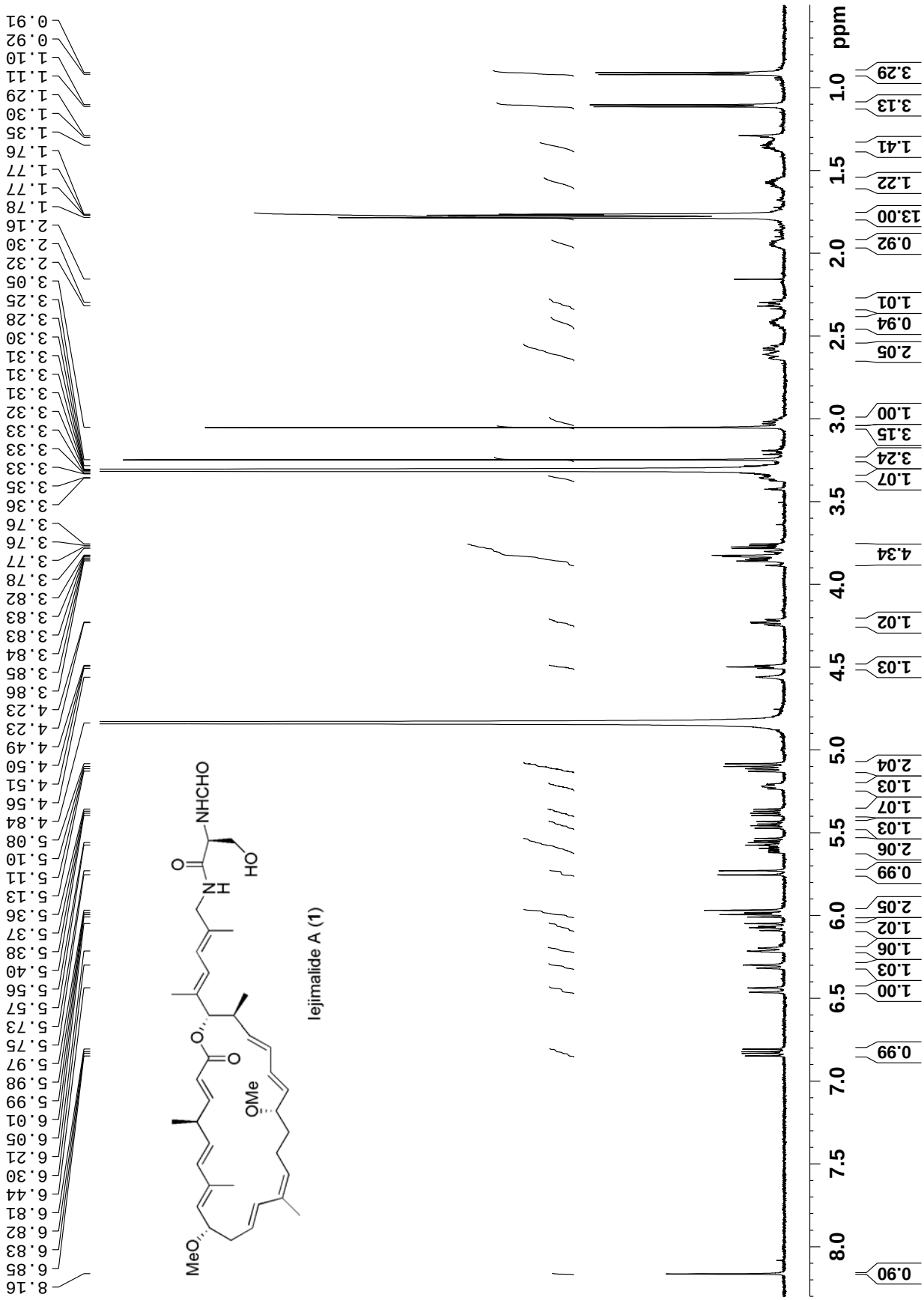
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1.5
1.0
0.90
0.99
1.00
1.03
1.06
1.02
2.05
0.99
2.06
1.03
1.07
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1.41
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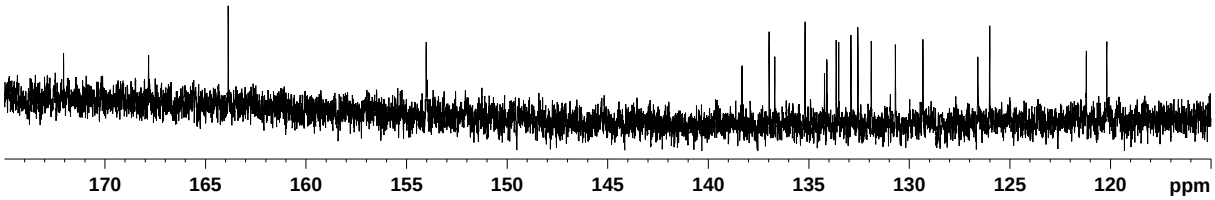
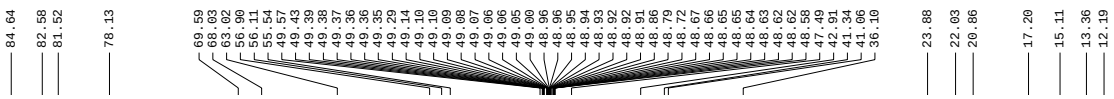
3.29

Iejimalide A (**1**)





Iejimalide A (**1**)