Supporting Information

Total Synthesis of Biselide A

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1. General Information

All reactions described were performed under an atmosphere of dry nitrogen using oven dried glassware unless otherwise specified. Flash chromatography was carried out with 230-400 mesh silica gel (Silicycle, SiliaFlash® P60). Concentration and removal of trace solvents was done via a Büchi rotary evaporator using a dry ice/acetone condenser and vacuum applied from a Büchi V-500 pump.

All reagents and starting materials were purchased from Sigma Aldrich, Alfa Aesar, TCI America, or AK Scientific and were used without further purification. All solvents were purchased from Sigma Aldrich, EMD, Anachemia, Caledon, Fisher or ACP and used without further purification unless otherwise specified. Diisopropylamine and dichloromethane (CH_2Cl_2) were freshly distilled over calcium hydride. THF was freshly distilled over sodium metal/benzophenone. Cold temperatures were maintained by use of the following conditions: 5 °C, fridge (True Manufacturing, TS-49G); 0 °C, ice-water bath; −40 °C, acetonitrile-dry ice bath; −78 °C, acetone-dry ice bath; temperatures between −78 °C and 0 °C required for longer reaction times were maintained with a Neslab Cryocool Immersion Cooler (CC-100 II) in a ethanol/2-propanol bath.

Nuclear magnetic resonance (NMR) spectra were recorded using chloroform-*d* ($CDCl_3$), or methanol-d_4 (CD_3OD). Signal positions (δ) are given in parts per million from tetramethylsilane (δ 0) and were measured relative to the signal of the solvent (^{1}H NMR: $CDCl_3$: δ 7.26, CD_3OD: δ 3.31; ^{13}C NMR: $CDCl_3$: δ 77.16, CD_3OD: δ 49.0. Coupling constants (*J* values) are given in Hertz (Hz) and are reported to the nearest 0.1 Hz. ^{1}H NMR spectral data are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), coupling constants, number of protons. NMR spectra were recorded on a Bruker Avance 600 equipped with a QNP or TCI cryoprobe (600 MHz), Bruker 500 (500 MHz), or Bruker 400 (400 MHz). Assignments of ^{1}H and ^{13}C NMR spectra are based on analysis of ^{1}H-^{1}H COSY, HSQC, HMBC, and 1D NOESY spectra, where applicable.

Optical rotation was measured on a Perkin Elmer 341 Polarimeter at 589 nm.

Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum Two™ Fourier transform spectrometer with neat samples. Only selected, characteristic absorption data are provided for each compound.

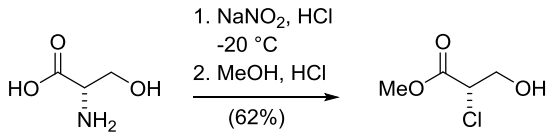
High resolution mass spectrometry was performed on an Agilent 6210 TOF LC/MS using ESI-MS or was carried out by the Notre Dame University Mass Spectrometry Department using EI technique.

High performance liquid chromatography (HPLC) was performed on an Agilent 1200 Series equipped with a variable wavelength UV-Vis detector (λ = 220 nm) using Phenomenex Kinetix XB-C_{18} column (4.6 × 250 mm, 5 µm).

Chiral GC analyses were performed on a 6890 Agilent Technologies gas chromatograph (Agilent Technologies Inc., Santa Clara, CA 95051, USA) employing an J & W Cyclodex-B chiral GC column (30 x 0.25 mm i.d.). Samples were analyzed isothermally. The injector and flame ionization detector of the GC were set to 250 ºC, and all samples were injected in split mode.

2. Experimental Procedures and Spectroscopic Data

Synthesis of α-chloroester 29

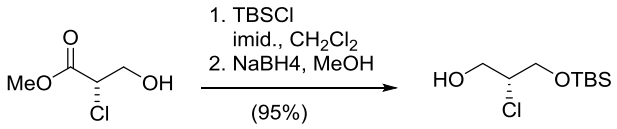


28 **29**

Following the reported procedure,[1] to a solution of aq. HCl (6N, 200 mL) and L-serine (**28**) (25.0 g, 238.0 mmol) at -15 ºC was added over 1 h (using graduated addition funnel) a solution of sodium nitrite (19.7 g, 285.5 mmol) in water (60 mL). This reaction mixture was not allowed to reach a temperature above -15 ºC and was stirred for an additional 12 h. After this time, NaCl (20 g) was added to the reaction mixture, which was then diluted with Et_2O (200 mL). The aqueous phase was extracted with Et_2O (3 x 150 mL) and the combined organic phases were washed with brine (150 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide the corresponding crude α-chloroacid (18.0 g) as a pale-yellow oil.

To a solution of the crude α-chloroacid (18.0 g, 144.5 mmol) in methanol (290 mL) was added concentrated HCl (5.0 mL). The solution was stirred for 12 h. After this time, the reaction mixture was concentrated *in vacuo,* diluted with water (75 mL), Et_2O (150 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 100 mL) and the combined organic phases were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide the α-chloroester **29** (21.5 g, 65% over two steps) as a clear oil: $[\alpha]^{25}_D$ +9.9 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.42 (t, 1H, *J* = 5.6 Hz), 4.03 (dd, 1H, *J* = 12.0, 5.6 Hz), 3.97 (dd, 1H, *J* = 12.0, 5.6 Hz), 3.83 (s, 3H); ^{13}C NMR (100 MHz, CDCl3) δ: 169.0, 64.3, 57.0, 53.4; HRMS (ESI): *m*/*z* calcd for $C_4H_8ClO_3$ $(M+H)^+$ 139.0162; found 139.0164

Synthesis of alcohol 30

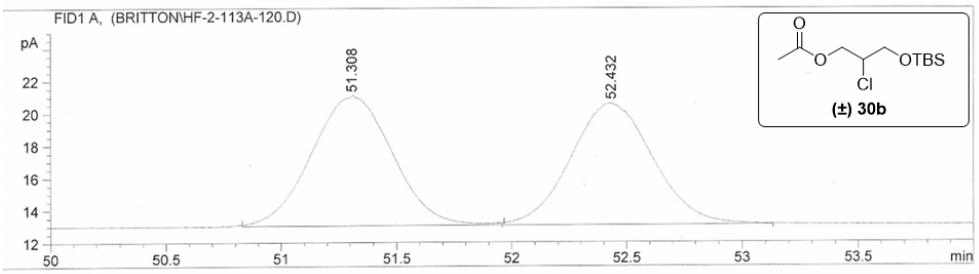


29 **30**

To a solution of the ester **29** (20.0 g, 144.3 mmol) in CH_2Cl_2 (250 mL) was added imidazole (19.0 g, 150.7 mmol), and the solution allowed to stir for 10 minutes. At this time, *tert*-butyldimethylsilane (24.0 g, 150.7 mmol) was added portion wise and the reaction mixture was allowed to stir for 18 h. After this time, water (100 mL) was added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 75 mL) and the combined organic phases were washed with brine (150 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude colorless syrup (36.0 g) was used without further purification.

To a solution of the TBS ether (36.0 g, 142.3 mmol) in methanol (240 mL) at 0 ºC was added $NaBH_4$ (13.5 g, 356.0 mmol) portion-wise. The temperature of the reaction mixture was gradually raised to room temperature over 1 h and the mixture was stirred at room temperature for 30 minutes. After this time, the reaction mixture was concentrated *in vacuo*, diluted with water (150 mL) and EtOAc (150 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic phases were washed with brine (150 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide the alcohol **30** (30.0 g, 95% over two steps) as a clear oil. The enantiomeric purity of alcohol **30** (98.2% *ee*) was determined in the following manner: To a solution of **30** (20.0 mg, 0.089 mmol) in CH_2Cl_2 (0.5 mL) was added pyridine (140 µL, 1.76 mmol), acetic anhydride (90 µL, 0.89 mmol) and the resulting mixture was stirred at room temperature for 16 h. After this time the reaction mixture was concentrated *in vacuo* and purified by column chromatography to afford the corresponding methyl ester **30a** (18 mg, 76%) as a colorless oil. The ester was analyzed by Chiral GC, using a 6890 Agilent Technologies gas chromatograph fitted with a J & W Cyclodex-B chiral GC column (30 x 0.25 mm). The sample was run at a constant temperature of 120 ºC (pressure = 10 psi). The retention time of the enantiomeric ester **30a** derived from alcohol **30** was 51.3 min and the retention time for the racemic ester **(±)30b** was 52.4 min (see chromatogram below). $[\alpha]^{20}_D$ +2.2 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) 4.02 (tt, 1H, *J* = 9.6, 5.0 Hz), 3.9 – 3.78 (m, 4H), 2.23 (s, 1H), 0.90 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 65.0, 64.9, 61.8, 25.9, 18.4, -5.3, -5.4; HRMS (ESI): *m*/*z* calcd for $C_9H_{22}ClO_2Si$ $(M+H)^+$ 225.1078; found 225.1070

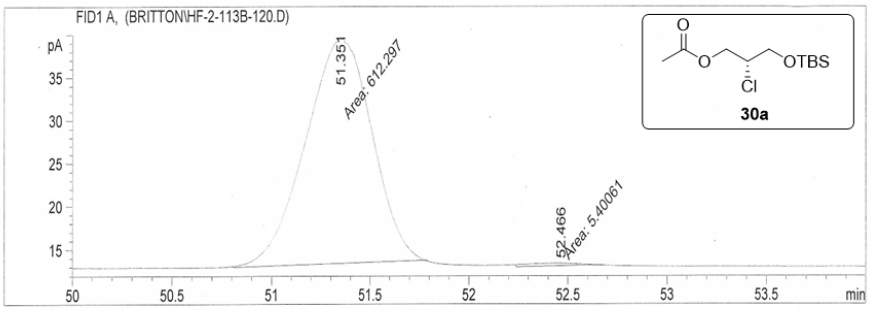
Figure S1: Chromatogram from chiral GC analysis of **(±) 30b**



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	51.308	BB	0.3815	195.83614	8.00323	51.04616
2	52.432	BB	0.3968	187.80904	7.48373	48.95384
Totals :				383.64517	15.48696	

Column J & W Cyclodex-B (30 x 0.25 mm)
Oven 120 ºC
Presure 10 psi

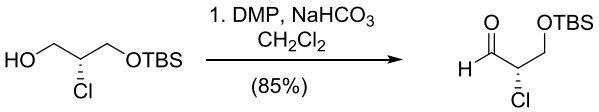
Figure S2: Chromatogram from chiral GC analysis of **30a**



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	51.351	MM	0.3903	612.29730	26.14701	99.12569
2	52.466	MM	0.3118	5.40061	2.88725e-1	0.87431
Totals :				617.69791	26.43574	

Column J & W Cyclodex-B (30 x 0.25 mm)
Oven 120 ºC
Presure 10 psi

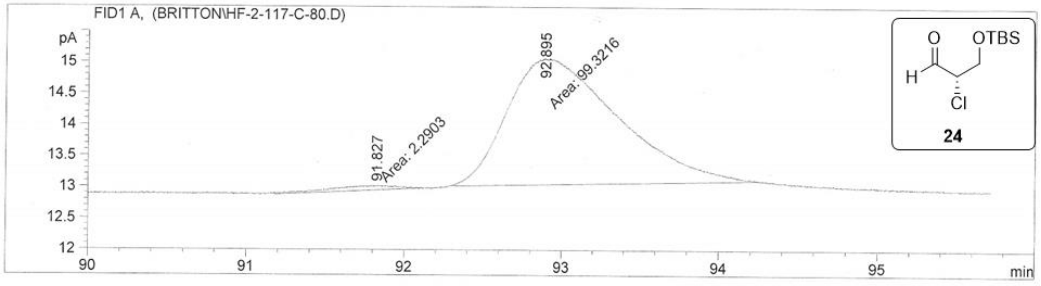
Synthesis of α-chloroaldehyde 24



30 **24**

To a stirred solution of alcohol **30** (10.0 g, 44.4 mmol) and $NaHCO_3$ (18.6 g, 222.0 mmol) in CH_2Cl_2 (100 mL) at 0 ºC was added Dess-Martin periodinane (22.5 g, 53.3 mmol) and the resulting mixture was stirred for 20 minutes. The temperature of the reaction mixture was raised to 22 ºC and the mixture was stirred at this temperature until TLC analysis indicated complete consumption of the substrate. Upon completion, the reaction mixture was cooled to 0 ºC and a mixture of water/saturated aqueous $NaHCO_3$/saturated aqueous $Na_2S_2O_3$ (150 mL; v/v 1:1:1) was added. The resulting mixture was allowed to warm to room temperature and was then stirred vigorously for 45 minutes. After this time, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 75 mL). The combined organic phases were then washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (EtOAc/hexanes: 0% → 30%) over silica gel to afford the aldehyde **24** (8.5 g, 85%) as a clear oil. The enantiomeric excess of aldehyde was determined to be 95.5% by chiral GC analysis, using a J & W Cyclodex-B chiral GC column. The sample was run at a constant temperature of 80 ºC (pressure = 10 psi). The retention time of the aldehyde **24** is 92.9 min (see chromatogram below). $[\alpha]^{25}_D$ +6.0 (*c* 1.5, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.52 (d, 1H, *J* = 2.5 Hz), 4.20 (ddd, 1H, *J* = 6.1, 49, 2.5 Hz), 4.08 (dd, *J* = 11.0, 4.9 Hz, 1 H), 4.02 (dd, *J* = 11.0, 6.1 Hz, 1 H), 0.88 (s, 9 H), 0.08 (s, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 195.2, 63.8, 63.0, 25.8, 18.4, -5.3, -5.4; IR (neat): 2955, 2930, 2857, 1710, 1632, 1471, 1256 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_9H_{20}ClO_2Si$ $(M+H)^+$ 223.0916; found 223.0910.

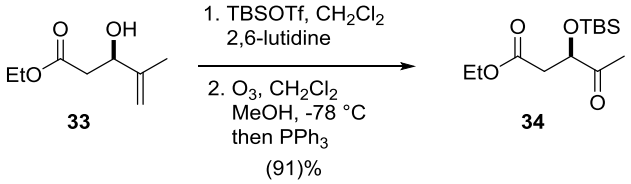
Figure S3: Chromatogram from chiral GC analysis **of 24**



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	91.827	MM	0.5281	2.29030	7.22849e-2	2.25397
2	92.895	MM	0.8168	99.32156	2.02655	97.74603
Totals :				101.61186	2.09884	

Column	J & W Cyclodex-B (30 x 0.25 mm)
Oven	80 ºC
Presure	10 psi

Synthesis of ketone 34

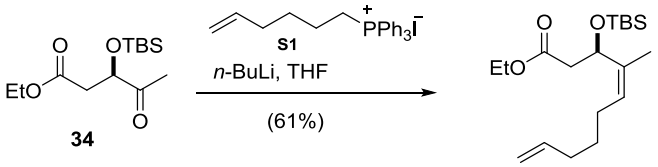


To a solution of known alcohol **33**[2] (0.23 g, 1.45 mmol) and 2,6-lutidine (0.34 mL, 2.90 mmol) in CH_2Cl_2 (5.0 mL) was added dropwise TBSOTf (0.5 mL, 2.17 mmol) at 0 °C. After stirring for 12 h at room temperature, saturated aqueous $NaHCO_3$ solution (10.0 mL) was added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were washed with brine (10.0 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo.* The crude brown syrup (0.4 g) was used without further purification.

The crude TBS ether (0.40 g, 1.47 mmol) was solubilized in a 2:1 solution of CH_2Cl_2/MeOH (14.0 mL:7.0 mL) and cooled to -78 ºC. The clear solution was bubbled with ozone at -78 ºC until it turned dark blue (~10 minutes), after which time it was bubbled with N_2 at -78 ºC until it turned back to clear (~5 minutes). PPh_3 (0.42g, 1.62 mmol) was then added to the stirring clear solution in one portion

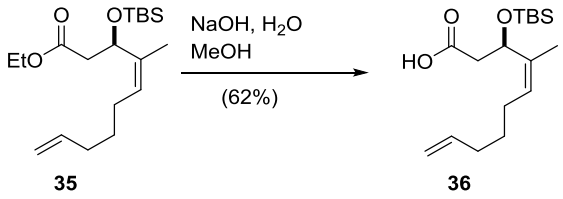
at -78 ºC, and the mixture was allowed to warm to room temperature and stirred at this temperature for 1 h. After this time, the reaction mixture was concentrated *in vacuo* to afford a crude white solid, which was extracted with hexanes (5 x 10.0 mL). The hexanes solution was cooled to -78 ºC to allow the byproduct to precipitate as a white solid, after which it was filtered off. This freeze-filter step was repeated two more times. Finally, the remaining hexanes solution was concentrated *in vacuo* to afford the ketone **34** as a colorless oil (0.37 g, 91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.35 (dd, *J* = 5.8, 5.3 Hz, 1H), 4.13 (m, 2H), 2.74 (dd, *J* = 15.3, 5.8 Hz, 1H), 2.64 (dd, *J* = 15.3, 5.3 Hz, 1H), 2.25 (s, 3H), 1.25 (t, 3H), 0.91 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 211.1, 170.4, 75.3, 60.9, 40.2, 26.2, 25.7, 18.1, 14.3, -4.8, -4.9 (2C); HRMS (ESI): *m*/*z* calcd for $C_{13}H_{26}NaO_4Si$ $(M+Na)^+$ 297.1493; found 297.1508.

Synthesis of Compound 35



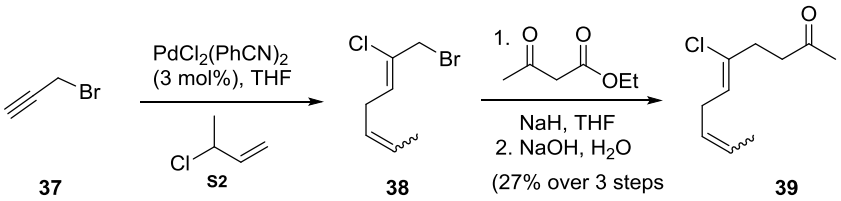
A suspension of hex-5-ene-triphenylphosphonium iodide[3] (**S1**) (0.47 g, 1.00 mmol) in THF (8 mL) was cooled to -78 ºC, and 2.52 M *n*-butyl lithium (0.40 mL, 1.00 mmol) was added drop-wise. The resulting bright orange mixture was cooled to -20 ºC and a solution of **34** (0.25 g, 0.911 mmol) in THF (1.0 mL) was added. The reaction mixture was then allowed to warm to room temperature and stirred at this temperature for 16 h. After this time, the resulting brown mixture was filtered, and the clear yellow filtrate was concentrated *in vacuo*. Purification of the crude mixture by flash chromatography (silica gel, 20:1 hexanes:ethyl aceteate) afforded diene **35** as a colourless oil (0.19 g, 61%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.81 (m, 1H), 5.14 (t, *J* = 7.1 Hz, 1H), 5.03 – 4.95 (m, 3H), 4.11 (q, *J* = 7.2 Hz, 2H), 2.62 (dd, *J* = 14.2, 9.2 Hz, 1H), 2.28 (dd, *J* = 14.2, 4.4 Hz, 1H), 2.13 – 2.01 (m, 4H), 1.67 (s, 3H), 1.44 (m, 2H), 1.26 (t, 3H, *J* = 7.2 Hz), 0.85 (s, 9H), 0.04 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.5, 138.8, 136.7, 126.5, 114.7, 67.7, 60.5, 42.2, 33.6, 29.3, 27.0, 25.8, 18.2, 17.7, 14.4, -4.8, -5.1; HRMS (ESI): *m*/*z* calcd for $C_{19}H_{37}O_3Si$ $(M+H)^+$ 341.2512; found 341.2506.

Synthesis of diene 36



To a stirred solution of **35** (185.0 mg, 0.54 mmol) in MeOH (5.0 mL) was added 2 M NaOH (2.0 mL) at room temperature. The resulting turbid white mixture was stirred at room temperature for 18 h, gradually turning clear. After this time, the reaction mixture was acidified to pH ~2 with 1 M HCl. The resulting mixture was partitioned between Et_2O (10.0 mL) and water (10.0 mL), and the combined organic phases were washed with brine (5.0 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the crude mixture by flash chromatography (silica gel, 10:1 hexanes: ethyl acetate) afforded carboxylic acid **36** as a viscous, colorless oil (113 mg, 66%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.80 (m, 1H), 5.18 (t, *J* = 7.2 Hz, 1H), 5.04 – 4.95 (m, 3H), 2.65 (dd, *J* = 14.7, 8.9 Hz, 1H), 2.37 (dd, *J* = 14.7, 4.4 Hz, 1H), 2.13 – 2.01 (m, 4H), 1.69 (s, 3H), 1.44 (m, 2H), 0.87 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 175.1, 138.7, 136.1, 127.2, 114.8, 67.5, 41.4, 33.5, 29.2, 27.0, 25.8, 18.2, 17.6, -4.8, -5.1; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{32}NaO_3Si$ $(M+Na)^+$ 335.2013; found 335.2041

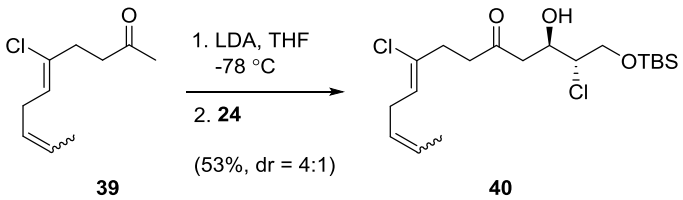
Synthesis of methyl ketone 39



Following Kaneda's procedure,[4] propargyl bromide (**37**) (1.85 mL, 15.0 mmol) and 3-chlorobutene (**S2**) (4.53 mL, 45.0 mmol) were reacted in the presence of $PdCl_2(PhCN)_2$ to form **38** which was not isolated, but filtered through a plug of Celite ™ and concentrated *in vacuo*. Meanwhile, to a stirred suspension of NaH (0.72 g, 18.0 mmol) in THF (30 mL) at -10 ºC was added ethyl acetoacetate (2.29 mL, 18.0 mmol) drop-wise over 15 minutes. The reaction mixture turned almost clear after completion of the addition and cessation of bubbling. At this point, the crude mixture of **38** was added in one portion at -10 ºC, and the resulting mixture was stirred for 16 h while gradually warming to room temperature. After this time, the cloudy brown reaction mixture was quenched with 1 M HCl (10 mL) and turned clear red. The phases were separated, and the aqueous phase was extracted with Et_2O (3 x 10.0 mL). The combined organic phases were washed with brine (10.0 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was subsequently solubilized in MeOH (15.0 mL), and 2 M NaOH (15.0 mL) was added. The resulting turbid mixture was

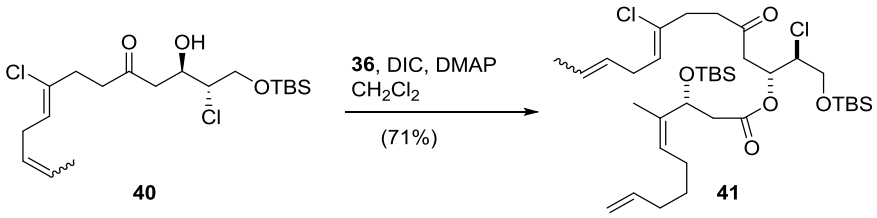
stirred at room temperature for 40 h, gradually turning clear. After this time, the reaction mixture was acidified to pH ~2 with 1 M HCl. The resulting mixture was partitioned between Et_2O (20.0 mL) and water (20.0 ml), and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 10.0 mL), and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude mixture by flash chromatography (silica gel, 15:1 hexanes: ethyl acetate) afforded ketone **39** as a light yellow oil (0.74 g, 1:1 *EIZ*, 27% over 4 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.70 (dt, *J* = 6.9 Hz, 0.5H), 5.53 – 5.32 (m, 2.5H), 2.92 – 2.80 (m, 2H), 2.72 – 2.58 (m, 4H), 2.16 (s, 3H), 1.65 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 207.4, 207.3, 128.3, 127.7, 127.3, 126.9, 126.6, 126.4, 125.6, 125.1, 124.9, 42.5, 41.7, 35.7, 34.7, 33.7, 31.9, 30.3, 29.7, 26.8, 18.0; HRMS (ESI): *m*/*z* calcd for $C_{10}H_{15}ClNaO$ $(M+Na)^+$ 209.0704; found 209.0703

Synthesis of ketochlorohydrin 40



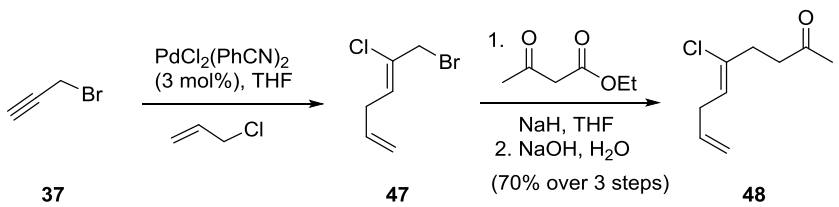
To a cold (-78 ºC) stirring solution of DIPA (0.25 mL, 1.80 mmol) in THF (15.0 mL) was slowly added *n*-BuLi (2.66 M in hexanes, 0.62 mL, 1.65 mmol). The resulting solution was stirred at -78 ºC for 30 minutes, then warmed to 0 ºC and stirred for an additional 15 minutes. After this time, the slightly yellow solution was cooled to -78 ºC and **39** (0.28 g, 1.50 mmol) was added in one portion. The reaction mixture was stirred for 30 minutes at -78 ºC. A solution of **24** (0.40 g, 1.80 mmol) in THF (2.0 mL) was then added dropwise over 5 minutes at -78 ºC, and the resulting mixture was stirred for an additional 30 minutes. Saturated aqueous NH_4Cl (10.0 mL) was added to quench the reaction, and the mixture was diluted with EtOAc (10.0 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (3 x 5.0 mL). The combined organic layers were washed with brine (15.0 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the crude mixture by flash chromatography (silica gel, 8:1 pentane:ethyl acetate) afforded chlorohydrin **40** as a yellow oil (0.35 g, 53%, 4:1 dr). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.71 (m, 0.5H), 5.54 – 5.32 (m, 2.5H), 4.34 (m, 1H), 3.98 – 3.79 (m, 3H), 3.45 (d, *J* = 3.8 Hz, 1H), 2.92 – 2.60 (m, 8H), 1.65 (m, 3H), 0.90 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 209.3, 133.2, 127.6, 126.4, 125.3, 69.6, 65.2, 63.2, 46.0, 41.7, 33.4, 31.9, 25.9, 18.0, 14.4, -5.3 (2C); HRMS (ESI): *m*/*z* calcd for $C_{19}H_{36}Cl_2NaO_3Si$ $(M+Na+2H)^+$ 433.1703; found 433.1696

Synthesis of ketoester 41



To a solution of **40** (90.0 mg, 0.22 mmol) in CH_2Cl_2 (1.5 mL) was added **36** (82 mg, 0.26 mmol), followed by DMAP (5.0 mg, 0.04 mmol). The reaction mixture was stirred at room temperature until dissolution of DMAP, and then treated with DIC (52 µl, 0.33 mmol). The clear solution gradually turned cloudy and was stirred at room temperature for 16 h. After this time, the reaction mixture was partitioned between CH_2Cl_2 (1.0 mL) and saturated aqueous $NaHCO_3$ (1.0 mL), and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 1.0 mL), and the combined organic phases were washed with brine (5.0 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the crude mixture by flash chromatography (silica gel, 15:1 hexanes:ethyl acetate) afforded ester **41** as a viscous colorless oil (110.0 mg, 71%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.81 (m, 1H), 5.69 (m, 0.5H), 5.60 – 5.36 (m, 3.5H), 5.13 (dt, *J* = 7.4, 7.0 Hz, 1H), 5.03 – 4.95 (m, 3H), 4.21 (m, 1H), 3.79 (m, 2H), 2.90 – 2.81 (m, 4H), 2.69 – 2.58 (m, 5H), 2.35 (dd, *J* = 15.0, 5.5 Hz, 0.5H), 2.29 (dd, *J* = 15.0, 5.5 Hz, 0.5H), 2.13 – 2.01 (m, 4H), 1.67 – 1.63 (m, 6H), 1.43 (m, 2H), 0.89 (s, 9H), 0.08 – 0.01 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 205.1, 170.2, 138.8, 136.4, 128.3, 126.9, 126.8, 125.5, 125.1, 114.7, 70.1, 67.1, 64.5, 62.4, 43.3, 41.7, 41.3, 35.5, 34.7, 33.6, 31.9, 29.3, 27.1, 25.9, 18.4, 18.2, 18.0, 17.7, -4.8 (2C), -5.3 (2C); HRMS (ESI): *m*/*z* calcd for $C_{36}H_{64}Cl_2NaO_5Si_2$ $(M+Na)^+$ 725.3562; found 725.3591

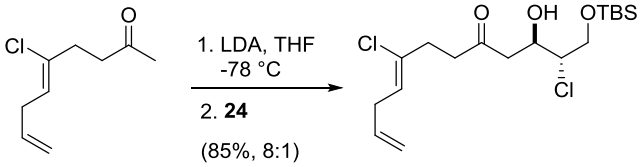
Synthesis of methyl ketone 48



To a stirred solution of THF (100 mL) at -10 ºC, sodium hydride (60% in oil, 2.6 g, 66.50 mmol) was added and stirred for 10 min. Ethyl acetoacetate (16.20 mL, 127.80 mmol) was added dropwise over 30 min. The reaction mixture turned almost clear after

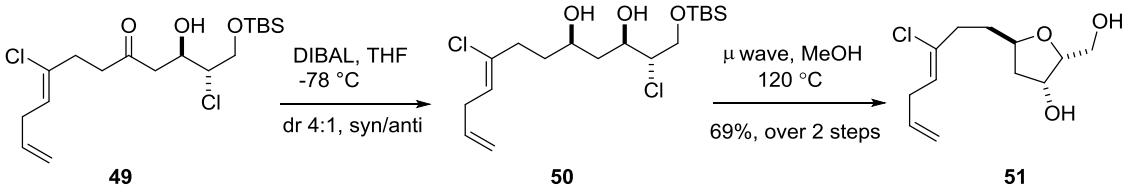
completion of the addition and cessation of bubbling. After this time, freshly prepared bromide **47**[4] (13.0 g, 66.50 mmol, dr 4:1) was added in one portion. The resulting mixture was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was quenched with aqueous 1N HCl (15.0 mL), and the phases were separated. The aqueous phase was extracted with EtOAc (2 x 25.0 mL) and the combined organic phases were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a pale-yellow oil. This oil was suspended in MeOH (100 mL) and aqueous 2N NaOH (100 mL) was added. The resulting turbid mixture was stirred at room temperature for 16 h, gradually turning clear. After this time, the reaction mixture was acidified to pH ~2 with concentrated HCl. The resulting mixture was partitioned between Et_2O (100 mL) and water (100 ml), and the phases were separated. The aqueous phase was extracted with Et_2O (2 x 100 mL). The combined organic extracts were washed with water (100 mL), brine (75 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo* and purified by flash column chromatography (EtOAc/hexanes: 10% → 25%) over silica gel to give the methyl ketone **48** (8.0 g, 70%, dr 4:1) as a colorless oil. To obtain an analytically pure sample, methyl ketone **48** was purified by flash column chromatography (EtOAc/hexanes: 10% → 25%) over silica gel impregnated with silver nitrate. IR (neat): 3080, 2978, 2920, 2227, 1718, 1432, 1362, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.77 (ddt, *J* = 16.4, 10.1, 6.3 Hz, 1H), 5.55 (tt, *J* = 7.1, 1.0 Hz, 1H), 5.08 – 4.99 (m, 2H), 2.90 (ddt, *J* = 6.5, 4.8, 1.3 Hz, 2H), 2.73 – 2.68 (m, 2H), 2.64 – 2.58 (m, 2H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.3, 135.2, 134.2, 123.9, 115.6, 41.6, 33.7, 32.9, 30.2; HRMS (ESI$^+$): *m*/*z* calculated for $C_9H_{13}ClNaO$ 195.0547 $(M+Na)^+$; found 195.0559

Synthesis of ketochlorohydrin 49



To a cold (-78 °C) stirred solution of *N,N*-diisopropylamine (2.0 mL, 14.90 mmol) in dry THF (200 mL) was added *n*-butyllithium (2.5 M in hexane, 6.0 mL, 14.90 mmol). The resulting solution was stirred at -78 ºC for 30 minutes, then warmed to 0 ºC and stirred for an additional 15 minutes. After this time, the reaction mixture was cooled to -78 °C and the methyl ketone **48** (2.0 g, 11.50 mmol) in THF (10.0 mL) was added dropwise over 15 min. The resulting mixture was stirred at -78 °C for 30 minutes. A solution of α-chloroaldehyde **24** (3.10 g, 13.90 mmol) in THF (5.0 mL) was added dropwise over 5 minutes at -78 °C and the resulting mixture was stirred for an additional 45 minutes. Saturated aqueous NH_4Cl (15 mL) was added to quench the reaction, and the mixture was diluted with EtOAc (20 mL). The phases were seperated and the aqueous phase was extracted with EtOAc (3 x 15.0 mL). The combined organic phases were washed with water (20.0 mL), brine (25.0 mL), dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (EtOAc/hexanes: 10% → 30%) afforded the *anti*-ketochlorohydrin **131** (3.8 g, 85%, dr 8:1, *anti/syn*) as a colourless oil. IR (neat): 3583, 3001, 2957, 2904, 2863, 2275, 1723, 1613, 1464, 1092 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.81 – 5.74 (m, 1H), 5.56 (td, *J* = 7.0, 1.0 Hz, 1H), 5.06 – 5.0 (m, 2H), 4.34 (ddd, *J* = 9.2, 6.5, 2.9 Hz, 1H), 3.97 – 3.86 (m, 3H), 2.92 – 2.62 (m, 8H), 0.90 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.2, 135.1, 134.0, 124.2, 115.7, 69.7, 65.2, 63.2, 46.0, 41.7, 33.4, 32.9, 25.9 (3C), 18.4, -5.3 (2C); HRMS (ESI$^+$): *m*/*z* calculated for $C_{18}H_{32}Cl_2NaO_3Si$ $(M+Na)^+$ 417.1390; found 417.1384

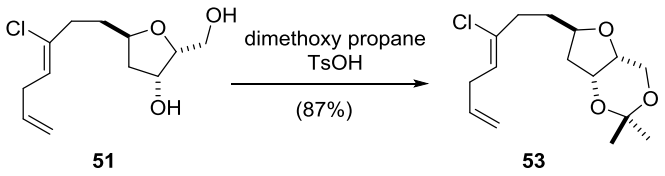
Synthesis of tetrahydrofuran diol 51



To a cold (–78 °C) solution of **49** (3.5 g, 8.85 mmol) in THF (30 mL) was added DIBAL-H (1.0 M in THF, 18.0 mL, 18.0 mmol) and the reaction mixture was stirred for 4 h. After this time, a solution of aqueous 1 M HCl (20.0 mL) was added, the mixture was diluted with Et_2O (30.0 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 15.0 mL), and the combined organic phases were washed with water (10.0 mL), brine (10.0 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide crude **50** as a colorless oil (dr 4:1, *syn/anti)*

The crude chlorodiol **50** in methanol (50.0 mL) was added to a microwave vial. The vial was sealed in a CEM Discover LabMate microwave reactor and the reaction mixture was heated to 120 °C (as monitored by a vertically focussed IR temperature sensor) and maintained at this temperature for 120 minutes. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography (MeOH/$CHCl_3$: 0% → 10%) over silica gel afforded the tetrahydrofuran diol **51** (1.52 g, 69% over two steps) as a colorless oil. $[\alpha]^{20}_D$ –2.5 (*c* 1.0, $CHCl_3$); IR (neat): 3453, 2952, 2857, 1658, 1639, 1430, 1255, 1087 cm^{-1};^1H NMR (600 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 16.6, 10.1, 6.3 Hz, 1H), 5.54 (t, *J* = 7.0 Hz, 1H), 5.09 – 4.99 (m, 2H), 4.53 (q, *J* = 3.9 Hz, 1H), 4.30 – 4.25 (m, 1H), 3.96 (m, 3H), 3.11 (d, *J* = 4.7 Hz, 1H), 2.93 (t, *J* = 6.7 Hz, 2H), 2.49 (ddd, *J* = 14.9, 8.9, 6.3 Hz, 1H), 2.44 – 2.38 (m, 1H), 2.25 (dd, *J* = 7.1, 4.5 Hz, 1H), 2.11 (ddd, *J* = 13.1, 5.7, 1.5 Hz, 1H), 1.85 – 1.73 (m, 3H); ^{13}C NMR (150 MHz, CDCl3) δ: 135.4, 135.2, 123.2, 115.6, 80.3, 77.5, 74.7, 62.1, 42.3, 36.4, 34.0, 32.9; HRMS (ESI$^+$): *m*/*z* calculated for $C_{12}H_{20}ClO_3$ $(M+H)^+$ 247.1095; found 247.1086

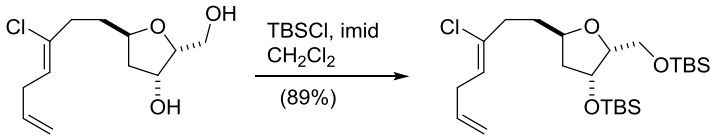
Synthesis of acetonide 53



51 **53**

To a stirred solution of tetrahydrofuran diol **51** (390 mg, 1.6 mmol) in 2,2-dimethoxypropane (8.0 mL) was added *p*-toluenesulfonic acid monohydrate (30 mg, 0.2 mmol). The reaction mixture was stirred for 18 h at room temperature. The reaction was then quenched with a saturated aqueous solution of $NaHCO_3$ (4.0 mL) and diluted with brine (4.0 mL) and water (4.0 mL). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2(3 x 10.0 mL). The combined organic phases were washed with brine (15.0 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the crude product by flash chromatography (pentane:ethyl acetate, 6:1) afforded compound **53** (395.0 mg, 1.4 mmol, 87%) as a clear colourless oil. $[\alpha]^{20}_D$ -6.5 (*c* 1.0, $CHCl_3$); IR: 3080, 2935, 1639, 1082 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 5.79 (m, 1H), 5.54 (t, *J* = 7.1 Hz, 1H), 5.03 (m, 2H), 4.42 (m, 1H), 4.32 (m, 1H), 3.99 (dd, *J* = 13.4, 4.5 Hz, 1H), 3.87 (m, 1H), 3.86 (m, 1H), 2.92 (t, *J* = 6.6 Hz, 2H), 2.51 (dt, *J* = 14.5, 7.5 Hz, 1H), 2.39 (dt, *J* = 14.5, 7.5 Hz, 1H), 2.11 (dd, *J* = 13.2, 5.4 Hz, 1H), 1.81 (m, 1H), 1.80 (m, 1H), 1.67 (ddd, *J* = 13.2, 10.0, 4.5 Hz, 1H), 1.43 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 135.4, 126.2, 123.0, 115.5, 97.8, 77.9, 74.0, 71.4, 61.0, 40.2, 36.5, 34.1, 32.9, 28.2, 20.2; HRMS (ESI^+): *m*/*z* calculated for $C_{15}H_{23}ClNaO_3$ $(M+Na)^+$ 309.1228; found 309.1265

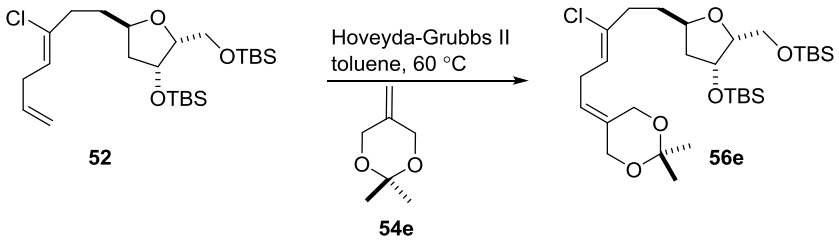
Synthesis of *bis*-silyl ether 52



51 **52**

To a stirred solution of compound **51** (350.0 mg, 1.4 mmol) in CH_2Cl_2 (3.0 mL) was added *tert*-butyldimethylsilyl chloride (450 mg, 2.1 mmol) and imidazole (290 mg, 4.3 mmol). The reaction mixture was stirred for 18 h at room temperature. The reaction was then quenched with water (2.0 mL). The mixture was extracted with CH_2Cl_2 (3 x 3.0 mL) and the combined organic phases were washed with brine (4.0 mL), dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (pentane:ethyl acetate, 97:3) afforded compound **52** (650.0 mg, 89%) as a colourless oil. $[\alpha]^{20}_D$ -20.1 (*c* 1.0, $CHCl_3$); IR: 2953, 2929, 2857, 1472, 1089 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.83 – 5.73 (m, 1H), 5.52 (t, *J* = 7.1 Hz, 1H), 5.02 (m, 2H), 4.37 (m, 1H), 4.16 (m, 1H), 3.87 (dt, *J* = 3.4, 6.1 Hz, 1H), 3.76 (dd, *J* = 6.3, 10.3 Hz, 1H), 3.69 (dd, *J* = 6.3, 10.3 Hz, 1H), 2.91 (m, 2H), 2.53 – 2.34 (m, 2H), 1.94 (ddd, *J* = 12.4, 5.4, 1.3 Hz, 1H), 1.84-1.71 (m, 2H), 1.63 (ddd, *J* = 12.7, 10, 4.4 Hz, 1H), 0.89 (s, 9H), 0.88 (s, 9H), 0.07-0.05 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 135.6, 135.4, 122.9, 115.4, 83.4, 76.7, 72.8, 62.0, 42.2, 36.5, 34.1, 32.9, 26.2, 25.9, 18.6, 18.2, -4.6, -5.0, -5.1 (2C); HRMS (ESI^+): *m*/*z* calculated for $C_{24}H_{47}ClNaO_3Si_2$ $(M+Na)^+$ 497.2644; found 497.2681

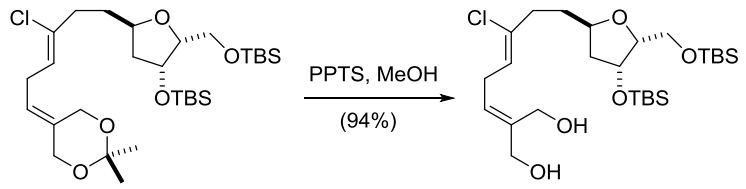
Synthesis of compound 56e



52 **54e** **56e**

To a stirred solution of 2,2-dimethyl-5-methylene-1,3-dioxane (**54e**) (335.0 mg, 2.61 mmol) in dry, nitrogen-sparged toluene (2.0 mL) was added Grubbs-Hoveyda II catalyst (4.2 mg, 0.0067 mmol in 0.6 mL toluene) followed by *bis*-silyl ether **52** (100.0 mg, 0.2 mmol). The reaction mixture was then heated to 60°C. After 1 hour a second portion of Grubbs-Hoveyda II catalyst was added (2.8 mg, 0.0045 mmol in 0.5 mL toluene) and the reaction mixture was stirred at 60 °C for another 4 hours. The heating was removed, and the reaction was allowed to cool to room temperature overnight while stirring. The solvent was removed *in vacuo* and the crude product was purified by flash chromatography (pentane:diethyl ether, 95:5) to afford compound **56e** (56.0 mg, 46%) as a colourless oil. $[\alpha]^{20}_D$ -11.8 (*c* 1.0, $CHCl_3$); IR: 2953, 2928, 2855, 1472, 1082 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.43 (t, *J* = 7.1 Hz, 1H), 5.20 (tt, *J* = 7.5, 1.5 Hz, 1H), 4.43 (s, 2H), 4.37 (m, 1H), 4.22 (s, 2H), 4.15 (m, 1H), 3.86 (dt, *J* = 6.1, 3.4 Hz, 1H), 3.77 (dd, *J* = 10.2, 6.3 Hz, 1H), 3.69 (dd, *J* = 10.2, 5.9 Hz, 1H), 2.83 (t, *J* = 7.1 Hz, 2H), 2.52 – 2.42 (m, 1H), 2.40 – 2.29 (m, 1H), 1.94 (ddd, *J* = 12.7, 5.5, 1.3 Hz, 1H), 1.80 – 1.70 (m, 2H), 1.67–1.57 (m, 1H), 1.43 (s, 6H), 0.89 (s, 9H), 0.88 (s, 9H), 0.06-0.05 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 135.5, 133.3, 122.8, 120.0, 99.3, 83.4, 76.8, 72.8, 64.5, 62.0, 60.0, 42.2, 36.5, 34.1, 26.5, 26.2, 25.9, 24.2, 18.6, 18.2, -4.6, -4.9, -5.0, -5.1; HRMS (ESI^+): *m*/*z* calculated for $C_{29}H_{55}ClNaO_5Si_2$ $(M+Na)^+$ 597.3169; found 597.3189

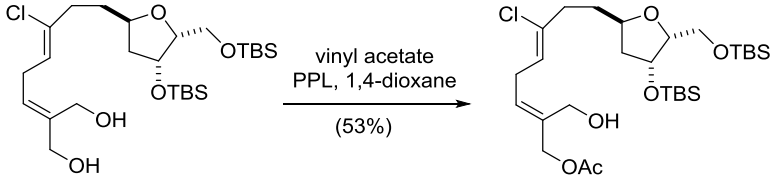
Synthesis of diol 57



56e **57**

To a stirred solution of acetonide **56e** (82.0 mg, 0.14 mmol) in methanol (7.0 mL) was added PPTS (7.0 mg, 0.03 mmol). The reaction mixture was stirred for 1 hour at room temperature. The reaction was then quenched with saturated aqueous $NaHCO_3$ (3.0 mL). The mixture was extracted with ethyl acetate (3 x 3.0 mL) and the combined organic phases were washed with water (4.0 mL), brine (4.0 mL), dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (hexanes:ethyl acetate, 1:1) afforded compound **57** (72.0 mg, 94%) as a colourless oil. $[\alpha]^{20}_D$ -7.8 (*c* 1.0, $CHCl_3$); IR: 3363, 2954, 2928, 1472, 1020 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.53 (t, *J* = 7.6 Hz, 1H), 5.47 (t, *J* = 7.1 Hz, 1H), 4.37 – 4.36 (m, 3H), 4.22 (d, *J* = 5.4 Hz, 2H), 4.15 (m, 1H), 3.86 (dt, *J* = 6.1, 3.5 Hz, 1H), 3.77 (dd, *J* = 10.3, 6.3 Hz, 1H), 3.69 (dd, *J* = 10.3, 6.0 Hz, 1H), 2.97 (t, *J* = 7.3 Hz, 2H), 2.47 (m, 1H), 2.36 (m, 1H), 1.92 (m, 3H), 1.75 (m, 2H), 1.63 (ddd, *J* = 14.0, 10.0, 4.2 Hz, 1H), 0.89 (m, 18H), 0.07– 0.05 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.3, 135.7, 127.2, 122.8, 83.4, 76.7, 72.8, 67.5, 62.0, 60.2, 42.2, 36.5, 34.1, 27.2, 26.2, 25.9, 18.6, 18.2, -4.6, -4.9, -5.0, -5.1; HRMS (ESI^+): *m/z* calculated for $C_{26}H_{52}ClO_5Si_2$ $(M+H)^+$ 535.3036; found 535.3006

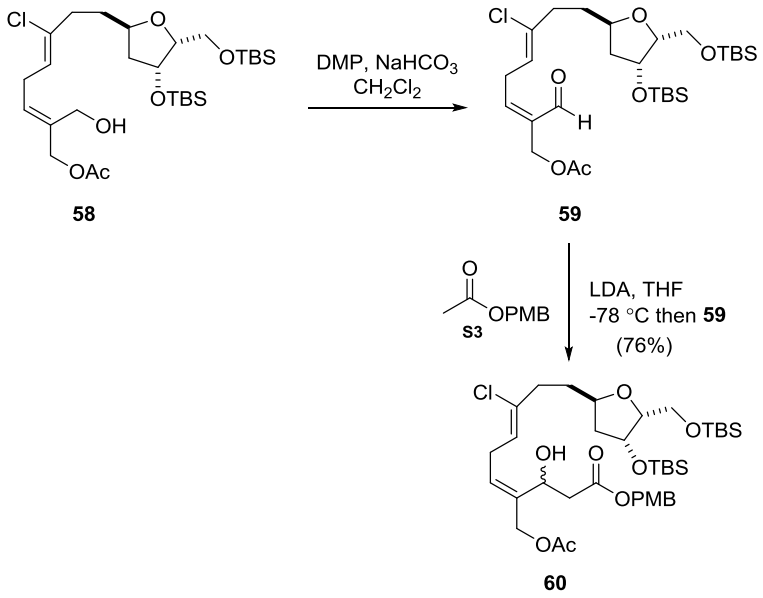
Synthesis of mono-acetate 58



57 **58**

To a stirred solution of diol **57** (42.0 mg, 0.078 mmol) in 1,4-dioxane (0.4 mL) was added vinyl acetate (74 µL, 0.80 mmol) and porcine pancreas lipase (42.0 mg). The reaction mixture was then stirred for 18 h at room temperature. The reaction mixture was then filtered and diluted with CH_2Cl_2(1.0 mL) and water (1.0 mL). The mixture was extracted with CH_2Cl_2 (3 x 1.0 mL) and the combined organic phases were washed with water (1.0 mL), brine (1.0 mL), dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (hexanes:ethyl acetate, 7:3) afforded compound **58** (24 mg, 53%) as a colourless oil. $[\alpha]^{20}_D$ -7.9 (*c* 1.0, $CHCl_3$); IR: 3457, 2954, 2929, 1472, 1022 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.61 (t, *J* = 7.5 Hz, 1H), 5.47 (t, *J* = 7.0 Hz, 1H), 4.64 (s, 2H), 4.36 (m, 1H), 4.22 (s, 2H), 4.15 (m, 1H), 3.86 (m, 1H), 3.76 (dd, *J* = 10.3, 6.3 Hz, 1H), 3.68 (dd, *J* = 10.3, 6.0 Hz, 1H), 3.00 (t, *J* = 7.2 Hz, 2H), 2.48 (dt, *J* = 15.2, 7.6 Hz, 1H), 2.35 (dt, *J* = 15.2, 7.6 Hz, 1H), 2.09 (s, 3H), 1.93 (ddd, *J* = 12.6, 5.5, 1.2 Hz, 1H), 1.79 – 1.72 (m, 3H), 1.63 (ddd, *J* = 12.6, 9.8, 4.5 Hz, 1H), 0.89 (s, 9H), 0.88 (s, 9H), 0.06 – 0.05 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.4, 136.0, 134.8, 130.4, 122.5, 83.4, 76.8, 72.8, 67.1, 62.0, 58.5, 42.2, 36.5, 34.1, 27.3, 26.2, 25.9, 21.2, 18.6, 18.2, -4.6, -4.9, -5.0, -5.1; HRMS (ESI^+): *m/z* calculated for $C_{28}H_{54}ClO_6Si_2$ $(M+H)^+$ 577.3142; found 577.3122

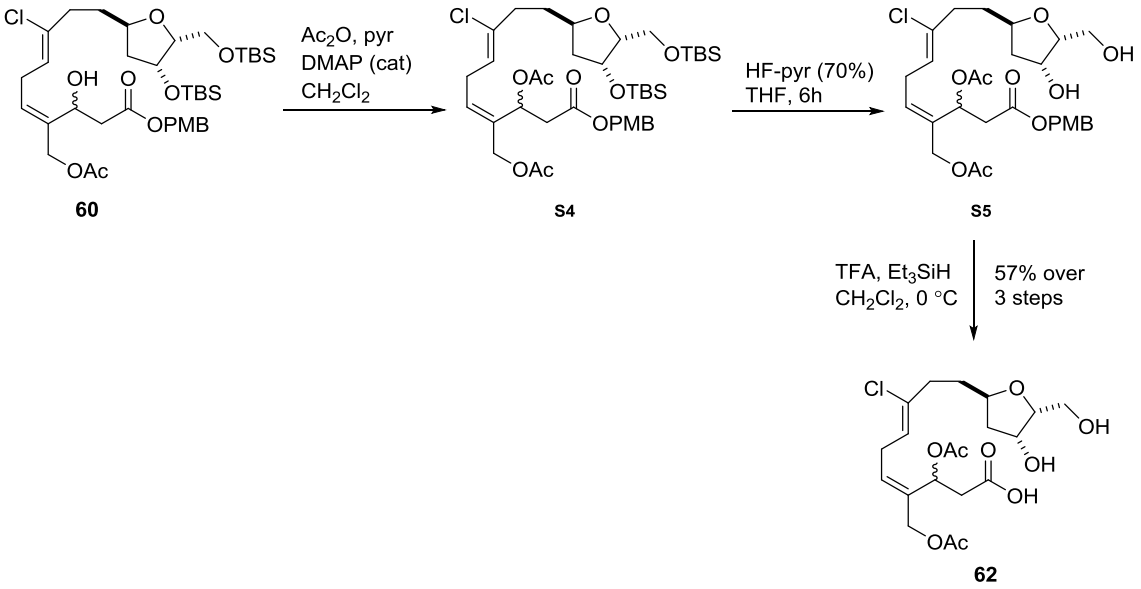
Synthesis of ester 60



To a stirred solution of compound **58** (24.0 mg, 0.042 mmol) in CH_2Cl_2 (1.5 mL) was added Dess-Martin periodinane (26.0 mg, 0.061 mmol) and $NaHCO_3$ (53.0 mg, 0.63 mmol). The reaction mixture was stirred for 45 minutes at room temperature. The reaction was then quenched with a solution of water/saturated aqueous $NaHCO_3$/saturated aqueous $Na_2S_2O_3$ (1.5 mL; v/v 1:1:1) at 0 ºC. The mixture was raised to room temperature and stirred vigorously for 20 minutes. After this time, phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 2.0 mL) and the combined organic phases were washed with brine (2.0 mL), dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo* to provide crude aldehyde **59** (21.0 mg), which was used immediately in the next reaction.

To a cold (0°C) stirred solution of *N,N*-diisopropyl amine (125 µL, 0.89 mmol) in dry THF(10.0 mL) was added n-butyllithium (2.2 M in hexane, 0.405 mL, 0.814 mmol). The reaction mixture was stirred for 15 minutes. After this time, the solution was cooled to -78 °C and 4-methoxybenzyl acetate (**S3**)[5] (170 µL, 0.74 mmol) was added. The reaction mixture was stirred at -78 °C for 30 minutes to prepare a 0.071 M stock solution of ester enolate. Separately, aldehyde **59** (21.0 mg, 0.0365 mmol) was stirred in dry THF (0.5 mL) and cooled to -78 °C. The enolate mixture (0.74 mL, 0.071 M, 0.055 mmol) was added to the solution of aldehyde and the reaction mixture was stirred at -78 °C for 30 minutes. The reaction was then quenched with a solution of saturated aqueous ammonium chloride (1.0 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 x 1.0 mL) and the combined organic phases were washed with water (1.0 mL), brine (1.0 mL), then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the crude product by flash chromatography (pentane:ethyl acetate, 75:25) afforded compound **60** (21 mg, 76%) as an inseparable mixture of diastereomers (1:1) at C3 as light yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.30 (d, *J* = 8.5 Hz, 2 H), 6.89 (d, *J* = 6.9 Hz, 2 H), 5.57 (t, *J* = 7.4 Hz, 1 H), 5.44 (t, *J* = 7.0 Hz, 1 H), 5.10 – 5.07 (m, 3H), 4.68 (d, *J* = 12.2 Hz, 1 H), 4.56 (d, *J* = 12.2 Hz, 1 H), 4.36 (t, *J* = 3.7 Hz, 1 H), 4.15 (m, 1 H), 3.86 (m, 1 H), 3.81 (s, 3H), 3.77 (dd, *J* = 10.8, 7.0 Hz, 1 H), 3.69 (dd, *J* = 10.2, 6.0 Hz, 1H), 2.97 (m, 2 H), 2.77 (dd, *J* = 16.5, 9.8 Hz, 1 H), 2.51 (m, 1 H), 2.49 (dd, *J* = 16.5, 3.2 Hz, 1 H), 2.34 (m, 1 H), 2.05, (s, 3 H), 1.93 (dd, *J* = 5.0, 12.1 Hz, 1 H), 1.74 (m, 2 H), 1.62 (m, 1 H), 0.89 (br s, 18 H), 0.06 (s, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 172.3, 170.8, 159.9, 136.1, 135.4, 130.4, 127.8, 122.3, 122.2, 114.2, 83.4, 77.4, 72.8, 66.7, 65.8, 65.0, 62.0, 55.4, 42.2, 40.8, 36.5, 34.2, 27.3, 26.2, 25.9, 21.3, 18.6, 18.2, -4.6, -4.9, -5.0, -5.1; HRMS (ESI$^+$): *m/z* calculated for $C_{38}H_{63}ClNaO_6Si_2$ $(M+Na)^+$ 777.3591; found 777.3590

Synthesis of seco acid 62

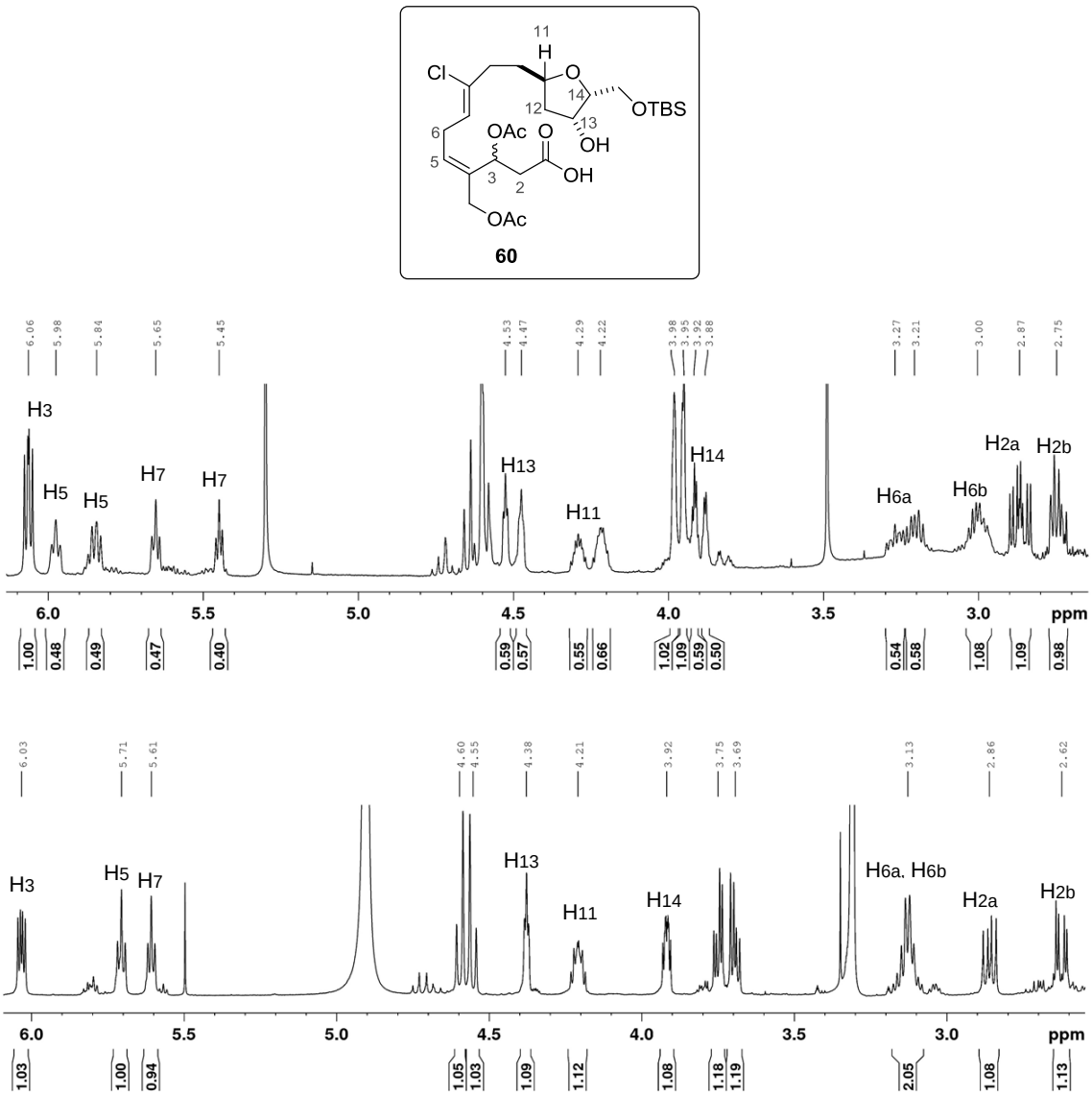


To a stirred solution of the PMB ester **60** (20.0 mg, 0.0264 mmol) in CH_2Cl_2 was added pyridine (0.1 mL) acetic anhydride (0.1 mL) and catalytic amount of DMAP successively. The reaction mixture was stirred for 1 h at room temperature and then the solvent was removed *in vacuo* to afford the crude acetate **S4** (20 mg, 95%) as a light yellow oil. To a stirred solution of the acetate **S4** (20.0 mg, 0.025 mmol) in THF (1.0 mL) was added 70 % HF.pyr (0.5 mL). The reaction mixture was stirred for 6 hours before EtOAc (3.0 mL) was added and quenched with saturated aqueous solution of $NaHCO_3$ (4.0 mL). The mixture was extracted with EtOAc (2 x 3.0 mL) and the combined organic extracts were washed with brine (3.0 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude yellow oil **S5** (13.0 mg, 91%) was used without further purification.

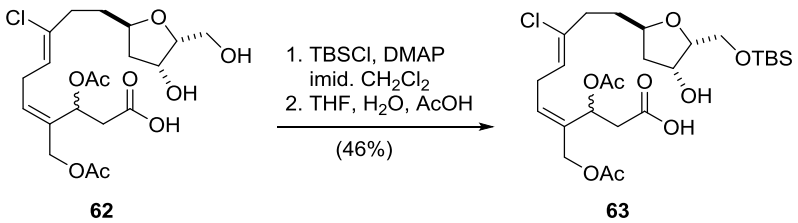
To a solution of the crude **S5** (13.0 mg, 0.022 mmol) and Et_3SiH (28 µL, 0.22 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C was slowly added TFA (0.05 mL).The reaction mixture was kept stirring at 0 °C until TLC indicated complete consumption of the substrate. Upon completion, the mixture was concentrated *in vacuo*. The resulting residue was purified by flash chromatography (CH_2Cl_2:MeOH, 92:8) afforded seco acid **62** (6.8 mg, 57% over 3 steps, dr 1:1) as a colorless oil. ^{1}H NMR (600 MHz, MeOD) δ: 6.03 (dd, *J* = 9.2, 5.3 Hz, 1H), 5.71 (t, *J* = 7.4 Hz, 1H), 5.61 (t, *J* = 7.0 Hz, 1 H), 4.60 (d, 12.4 Hz 1H), 4.55 (d, *J* = 12.4 Hz, 1H), 4.38 (t, *J* = 3.9 Hz, 1H), 4.21 (m, 1H), 3.92 (m, 1H), 3.75 (dd, *J* = 11.5, 5.1 Hz, 1H), 3.69 (dd, *J* = 11.4, 6.5 Hz, 1H), 3.13 (m, 2H), 2.86 (dd, *J* = 16.2, 9.5 Hz, 1H), 2.62 (dd, *J* = 16.2, 5.2 Hz, 1H), 2.45 (m, 2H), 2.05 (s, 3H), 2.04 (m, 1H), 2.02 (s, 3H), 1.82 – 1.71 (m, 3H); ^{13}C NMR (150 MHz, MeOD) δ: 173.4, 172.3, 171.6, 136.7, 133.8, 133.6, 123.8, 83.7, 77.9, 73.5, 69.5, 66.0, 62.1, 42.5, 39.2, 37.1, 35.0, 28.4, 21.0, 20.8; IR: 3364, 2923, 2852, 1737, 1674, 1515, 1435, 1375, 1231, 1029 cm^{-1}; HRMS (ESI$^+$): *m/z* calculated for $C_{20}H_{29}ClNaO_9$ $(M+Na)^+$ 471.1392; found 471.1384

The ^{1}H NMR analysis of the seco acid **62** (a 1:1 mixture of C3 epimers), the protons assigned to C1-C15 region of the molecule was distinct for each C3 epimer when the spectrum was recorded in $CDCl_3$ but not in CD_3OD (Figure-S4). These results suggest that the seco acid **62** adopts a distinct conformation dominated by hydrogen bonding between the carboxylic acid and the THF function. The role of hydrogen bonding in seco acid was further supported by molecular modelling (see modelling details below).

Figure S4: ^{1}H NMR (upper) of seco acid **62** in $CDCl_3$ and ^{1}H NMR (lower) of **62** in CD_3OD

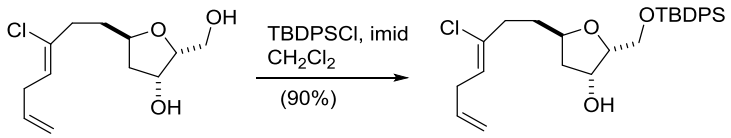


Synthesis of seco acid 63



To a solution of the *seco* acid **181** (7.0 mg, 0.016 mmol) in CH_2Cl_2 (0.3 mL) was added imidazole (4.2 mg, 0.062 mmol), a catalytic amount of DMAP and then TBSCl (5.9 mg, 0.039 mmol) and stirred for 2 hours while being monitored by TLC. The reaction was then diluted with CH_2Cl_2 (1.0 mL) and the reaction was quenched with a solution of 1M HCl (0.5 mL). The mixture was extracted with CH_2Cl_2 (3 x 1.0 mL) and the combined organic phases were washed with brine (1.0 mL), then dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. This crude mixture was then dissolved in a 2:1 mixture of THF and H_2O (0.5 mL) and cooled to 0 °C. To this mixture was added acetic acid (10.0 µL). After the mixture had been stirred for 1 h, the solvent was removed *in vacuo* and directly purified by flash chromatography (CH_2Cl_2:MeOH, 96:4) afforded compound **63** (4.0 mg, 46%, dr 1:1) as a colourless oil. ^{1}H NMR (600 MHz, MeOD) δ: 6.03 (dd, *J* = 9.4, 5.0 Hz, 1H), 5.70 (t, *J* = 7.6 Hz, 1H), 5.60 (t, *J* = 7.0 Hz, 1 H), 4.60 (d, 12.4 Hz 1H), 4.55 (d, *J* = 12.4 Hz, 1H), 4.35 (t, *J* = 4.2 Hz, 1H), 4.20 (m, 1H), 3.91– 3.86 (m, 2H), 3.77 (dd, *J* = 10.4, 6.0 Hz, 1H), 3.13 (m, 2H), 2.86 (dd, *J* = 16.2, 9.3 Hz, 1H), 2.61 (dd, *J* = 5.0, 16.3 Hz, 1H), 2.48 (m, 1H), 2.42 (m,1H), 2.05 (s, 3H), 2.04 (m, 1H), 2.02 (s, 3H), 1.79 – 1.73 (m, 3H), 0.92 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$); δ: 173.6, 172.3, 171.6, 136.7, 133.7 (2C), 123.8, 84.0, 77.8, 73.3, 69.6, 66.0, 63.6, 42.5, 39.3, 37.2, 35.0, 28.4, 26.4, 21.0, 20.8, 19.3, -5.1, -5.2; HRMS (ESI^+): *m/z* calculated for $C_{26}H_{47}ClNO_9Si$ $(M+NH_4)^+$ 580.2703; found 580.2673

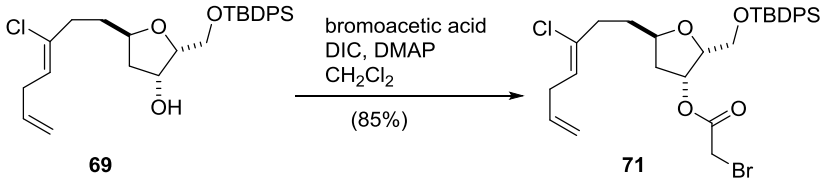
Synthesis of TBDPS ether 69



51 **69**

To a stirred solution of the diol **51** (1.0 g, 4.0 mmol) in CH_2Cl_2 (10.0 mL) was added *tert*-butyldiphenylsilyl chloride (1.23 g, 4.40 mmol) and imidazole (0.50 g, 8.0 mmol). The reaction mixture was stirred for 12 h at room temperature. The reaction mixture was then diluted with water (10.0 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 5.0 mL) and the combined organic phases were washed with brine (5.0 mL), dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. Purification of the crude product by flash column chromatography (EtOAc/hexanes: 5% → 30%) over silica gel afforded the compound **69** (1.77 g, 90%) as a colourless oil. $[\alpha]^{20}_D$ +2.3 (*c* 1.2, $CHCl_3$); IR (thin film): 3537, 2950, 2857, 1475, 1085 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.73 – 7.71 (m, 2H), 7.68 – 7.66 (m, 2H), 7.45 – 7.38 (m, 6H), 5.78 (ddt, *J* = 17.1, 10.2, 6.3 Hz, 1H), 5.52 (t, *J* = 7.0, 1.0 Hz, 1H), 5.07 – 4.98 (m, 2H), 4.60 – 4.57 (m, 1H), 4.26 (ddt, *J* = 10.1, 7.6, 5.1 Hz, 1H), 4.01 – 3.93 (m, 3H), 3.37 (d, *J* = 3.5 Hz, 1H), 2.93 – 2.89 (m, 2H), 2.54 – 2.47 (m, 1H), 2.43 – 2.34 (m, 1H), 2.13 (ddd, *J* = 13.0, 5.3, 1.3 Hz, 1H), 1.83 – 1.67 (m, 3H), 1.06 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.8 (2C), 135.6 (2C), 135.4 (2C), 130.1 (4C), 128.0 (4C), 123.0, 115.5, 80.5, 77.5, 74.3, 63.5, 41.8, 36.6, 34.0, 32.9, 26.9 (3C), 19.3; HRMS (ESI$^+$): *m/z* calculated for $C_{28}H_{41}ClNO_3Si$ $(M+NH_4)^+$ 502.2539; found 502.2533

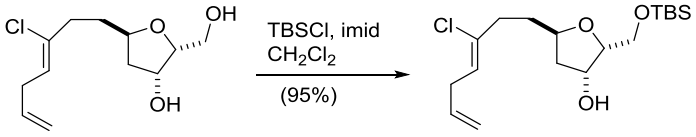
Synthesis of bromoacetate 71



69 **71**

To a stirred solution of the tetrahydrofuranol **69** (1.50 g, 3.0 mmol) in CH_2Cl_2 (15.0 mL) at 0 °C, was added DMAP (38.0 mg, 0.30 mmol), bromoacetic acid (0.52 g, 3.70 mmol), and DIC (0.70 mL, 4.60 mmol) successively, stirred for 15 min, and gradually allowed to warm to room temperature. The mixture was stirred at room temperature for 1 h. After this time, TLC analysis indicated the consumption of **69**. The reaction mixture was diluted with water (15.0 mL) and the phases were separated. The organic phase was extracted with CH_2Cl_2 (2 x 10.0 mL). The combined organic phases were washed with aqueous saturated. $NaHCO_3$ (5.0 mL), brine (5.0 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (EtOAc/hexanes: 0% → 10%) over silica gel to give the compound **71** (1.6 g, 85%) as a clear oil. $[\alpha]^{20}_D$ -3.3 (*c* 0.87, $CHCl_3$); IR (thin film): 2920, 1732, 1279, 1075, 830, 775 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.65 – 7.63 (m, 4H), 7.44 – 7.36 (m, 6H), 5.78 (ddt, *J* = 16.7, 10.2, 6.3 Hz, 1H), 5.54 – 5.49 (m, 2H), 5.07 – 4.98 (m, 2H), 4.18 (ddd, *J* = 7.5, 5.6, 3.7 Hz, 1H), 4.12 (dq, *J* = 9.7, 6.1 Hz, 1H), 3.88 – 3.78 (m, 2H), 3.65 – 3.63 (m, 2H), 2.91 (t, *J* = 6.8 Hz, 2H), 2.48 (dt, *J* = 14.7, 7.6 Hz, 1H), 2.38 (dt, *J* = 15.1, 7.8 Hz, 1H), 2.18 – 2.13 (m, 1H), 1.89 – 1.82 (m, 1H), 1.80 – 1.75 (m, 2H), 1.04 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.5, 135.8 (2C), 135.7(2C), 135.4, 135.1, 129.9 (4C), 127.9 (2C), 127.8 (2C), 123.3, 115.5, 80.6, 77.0, 76.5, 61.2, 39.1, 36.4, 33.9, 32.9, 26.9 (3C), 25.8, 19.3; HRMS (ESI$^+$): *m/z* calculated for $C_{30}H_{38}BrClNaO_4Si$ $(M+Na)^+$ 627.1303; found 627.1326

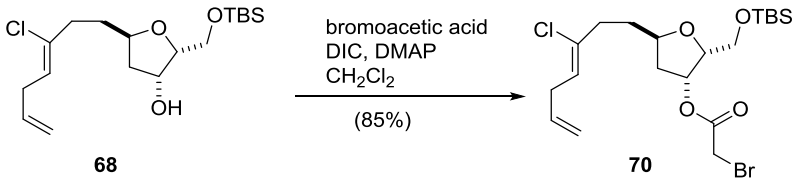
Synthesis of silyl ether 68



51 **68**

To a stirred solution of the diol **51** (2.50 g, 10.0 mmol) in CH_2Cl_2 (15 mL) was added *tert*-butyldimethylsilyl chloride (1.70 g, 11.10 mmol) and imidazole (2.80 g, 20.0 mmol). The reaction mixture was stirred for 12 h at room temperature. After this time, the reaction mixture was diluted with water (10.0 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic phases were washed with brine (10 mL), dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. Purification of the crude product by flash column chromatography (EtOAc/hexanes: 5% → 25%) over silica gel afforded the compound **68** (3.48 g, 95%) as a colourless oil. $[\alpha]^{20}_D$ –12.5. (*c* 1.0, $CHCl_3$); IR (thin film): 3530, 2953, 2857, 1472, 1089 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 16.6, 10.1, 6.3 Hz, 1H), 5.52 (dd, *J* = 7.6, 6.5 Hz, 1H), 5.08 – 4.98 (m, 2H), 4.52 (td, *J* = 4.0, 2.6 Hz, 1H), 4.22 (dq, *J* = 9.8, 6.0 Hz, 1H), 3.97 – 3.89 (m, 3H), 3.56 (d, *J* = 3.9 Hz, 1H), 2.94 – 2.90 (m, 2H), 2.51 – 2.45 (m, 1H), 2.41 – 2.35 (m, 1H), 2.08 (ddd, *J* = 13.0, 5.4, 1.4 Hz, 1H), 1.80 – 1.75 (m, 2H), 1.71 – 1.66 (m, 1H), 0.90 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.4 (2C), 123.0, 115.5, 80.4, 77.5, 74.4, 63.0, 41.9, 36.5, 33.9, 32.9, 25.9 (3C), 18.3, -5.3, -5.4; HRMS (ESI$^+$): *m/z* calculated for $C_{18}H_{33}ClNaO_3Si$ $(M+Na)^+$; 383.1780; found 383.1775

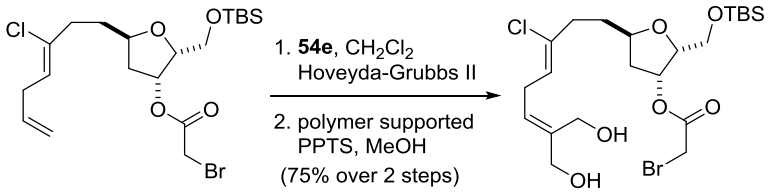
Synthesis of bromoacetate 70



68 **70**

To a stirred solution of the mono-TBS tetrahydrofuranol **68** (3.0 g, 8.30 mmol) in CH_2Cl_2 (30.0 mL) at 0 °C, DMAP (0.10 g, 0.80 mmol), bromoacetic acid (1.38 g, 9.90 mmol), and DIC (1.90 mL, 12.40 mmol) were added successively and stirred for 15 min at 0 °C. After this time, TLC analysis indicated the consumption of compound **68**. The reaction mixture was diluted with water (15.0 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 10.0 mL). The combined organic phases were washed with brine (15.0 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo.* The resulting residue was purified by flash column chromatography (EtOAc/hexanes: 0% → 15%) to give the compound **70** (3.40 g, 85%) as a clear oil. $[\alpha]^{20}_D$ –20.0 (*c* 0.10, $CHCl_3$); IR (thin film): 2928, 1738, 1275, 1089, 836, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.79 (ddt, *J* = 16.3, 10.1, 6.2 Hz, 1 H), 5.53 (t, *J* = 7.0 Hz, 1 H), 5.49 (ddd, *J* = 5.2, 3.6, 1.1 Hz, 1 H), 5.09 – 4.99 (m, 2 H), 4.17 (dq, *J* = 9.2, 6.0 Hz, 1 H), 4.09 (ddd, *J* = 7.1, 5.9, 3.8 Hz, 1 H), 3.82 (s, 2 H), 3.76 (dd, *J* = 5.9, 2.9 Hz, 1 H), 2.92 (t, *J* = 6.6 Hz, 2 H), 2.53 – 2.36 (m, 2 H), 2.15 (ddd, *J* = 14.0, 6.0, 1.4 Hz, 1 H), 1.87 (m, 1 H), 1.79 (dt, *J* = 7.9, 6.6 Hz, 2 H), 0.87 (s, 9 H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 166.5, 135.4, 135.1, 123.4, 115.5, 80.8, 77.0, 76.5, 61.1, 39.0, 36.4, 33.9, 32.9, 26.0 (3C), 25.9, -5.2, -5.3; HRMS (ESI^+): *m*/*z* calculated for $C_{20}H_{34}BrClNaO_4Si$ $(M+Na)^+$ 503.0990; found 503.0993

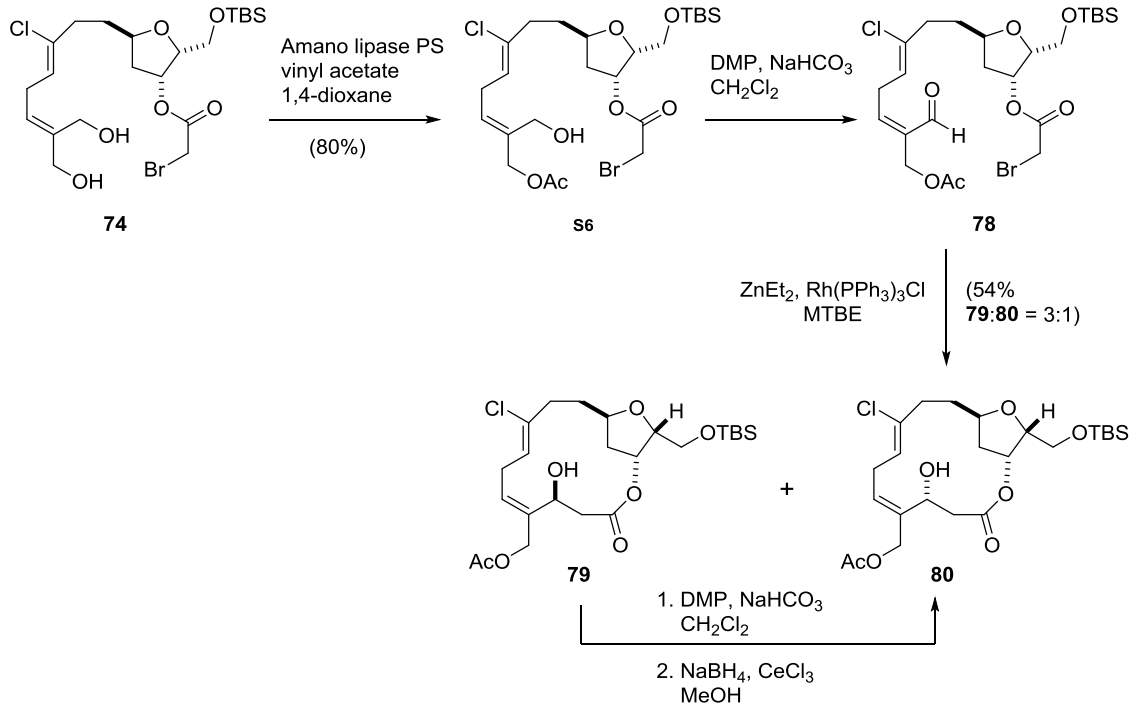
Synthesis of diol 74



70 **74**

To a 10 mL 3-neck round bottom flask fitted with a reflux condensor and septa was charged the Hoveyda-Grubbs II catalyst (50 mg, 0.08 mmol). 2,2-dimethyl-5-methylene-1,3-dioxane (**54e**) (0.40 g, 3.0 mmol) in degassed CH_2Cl_2 (1.0 mL) and the diene **70** (0.50 g, 1.0 mmol) in degassed CH_2Cl_2 (1.0 mL) were added simultaneously via a syringe to the round bottom flask through the septa. The reaction mixture was stirred for 12 h at 40-45 ºC. After this time, the reaction mixture was cooled to room temperature and the solvent was removed by rotaory evaporation to give a dark brown syrupy residue. This residue was passed through a Sephadex LH-20 column (Methanol: 100%) and the solvent was removed *in vacuo* to give a colorless oil. To this oil was added methanol (3.0 mL), polymer supported PPTS (7.50 mg, 0.03 mmol) at 0 °C and stirred for 30 min. After this time, TLC analysis indicated the consumption of substarte. Upon completion of the reaction, the reaction mixture was filtered through a pad of Celite ™ with an additional quantity of EtOAc (5.0 mL) and the filtrate was concentrated *in vacuo*. The resulting residue was purified by flash column chromatography ($MeOH/CHCl_3$: 0% → 10%) over silica gel to afforde the diol **74** (0.42 g, 75% over two steps) as a pale brown oil. $[\alpha]^{20}_D$ –22.7 (*c* 0.30, $CHCl_3$); IR (thin film): 3366, 2928, 2856, 1739, 1462, 1277, 1256, 1092, 1007, 838, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.55 – 5.46 (m, 3 H), 4.36 (br s, 2 H), 4.23 (br s, 2 H), 4.18 – 4.13 (m, 1H), 4.11 – 4.06 (m, 1H), 3.83 (s, 2 H), 3.76 (dd, *J* = 6.3, 2.4 Hz, 2 H), 2.97 (t, *J* = 7.4 Hz, 2 H), 2.51 – 2.43 (m, 1 H), 2.41 – 2.33 (m, 1 H), 2.15 (ddd, *J* = 14.0, 5.8, 1.1 Hz, 1H), 1.89 – 1.82 (m, 1 H), 1.81 – 1.75 (m, 2 H), 0.87 (s, 9 H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 165.6, 137.5, 134.2, 125.9, 122.3, 79.8, 76.1, 75.6, 66.4, 60.1, 59.1, 38.0, 35.3, 32.8, 26.3, 24.9 (3C), 17.4, -6.2, -6.3; HRMS (ESI^+): *m*/*z* calculated for $C_{22}H_{38}BrClNaO_6Si$ $(M+Na)^+$ 563.1202; found 563.1196

Synthesis of macrocycle 80



To a stirred solution of the diol **74** (200 mg, 0.37 mmol) in dry 1,4-dioxane (4.0 mL), was added 4 Å molecular sieves and stirred at room temperature for 20 minutes. To the resultant suspension, vinyl acetate (95.0 µL, 1.10 mmol)) and Amano PS-D Lipase (20.0 mg) were added. The reaction mixture was stirred for 6 h at room temperature. After this time, TLC analysis indicated the consumption of the substrate **74**. To this mixture was then added EtOAc (5.0 mL), anhydrous magnesium sulfate (100 mg) and the mixture was filtered through a pad of Celite ™ with an additional quantity of EtOAc (3.0 mL). The solvent was removed *in vacuo* and the resulting residue was purified by flash column chromatography (EtOAc/hexanes: 0% → 40%) over silica gel gave the monoacetylated compound **S6** (170 mg, 80%) as a colorless oil. $[\alpha]^{20}_{D}$ –5.3 (*c* 0.30, $CHCl_3$); IR (thin film): 3442, 2933, 2857, 1739, 1279, 1257, 1096, 1022, 837 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.62 (t, *J* = 7.6 Hz, 1H), 5.50 – 5.47 (m, 2H), 4.65 (br s, 2H), 4.23 (d, *J* = 6.2 Hz, 2H), 4.19 – 4.14 (m, 1H), 4.10 – 4.07 (m, 1H), 3.83 (s, 2H), 3.75 (dd, *J* = 6.5, 4.4 Hz, 2H), 3.01 (t, *J* = 7.2 Hz, 2H), 2.51 – 2.45 (m, 1H), 2.40 – 2.34 (m, 1H), 2.15 (ddd, *J* = 13.9, 5.9, 1.3 Hz, 1H), 2.09 (s, 3H), 1.88 – 1.84 (m, 1H), 1.80 – 1.76 (m, 2H), 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 171.4, 166.6, 135.4, 134.9, 130.2, 122.9, 80.8, 77.0, 76.5, 67.1, 61.1, 58.5, 39.0, 36.3, 33.9, 27.3, 26.0 (3C), 21.2, 18.4, -5.2, -5.3; HRMS (ESI^+): *m*/*z* calculated for $C_{24}H_{40}BrClNaO_6Si$ $(M+Na)^+$ 605.1307; found 605.1297

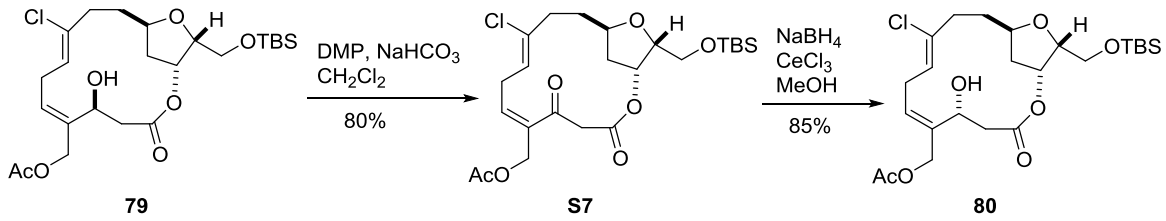
To a stirred solution of monoacetate **S6** (30.0 mg, 51.3 µmol) and $NaHCO_3$ (10 mg, 126.0 µmol) in CH_2Cl_2 (0.5 mL) was added Dess-Martin periodinane (21 mg, 61.6 µmol) and stirred for 45 minutes. The reaction mixture was then diluted with CH_2Cl_2 (1.5 mL), a mixture of saturated solutions of $Na_2S_2O_3$/ $NaHCO_3$/water (1.5 mL; v/v 1:1:1) at 0 ºC. The temperature of the reaction mixture was brought to room temperature and stirred vigorously for 20 minutes. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 0.5 mL). The combined organic phases were then washed with brine (1.0 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the crude aldehyde **78** (30 mg).which was used immediately in the next reaction without any further purification.

To a suspension of $Rh(PPh_3)_3Cl$ (6.5 mg, 7.0 µmol) in *tert*-butyl methylether (13.0 mL) was added $ZnEt_2$ (15% in toluene , 0.7 mL, 1.03 mmol) and stirred vigorously at room temperature. A solution of aldehyde **78** (30.0 mg, 51.5 µmol) in *tert*-butyl methylether (3.0 mL) was added dropwise into the stirred solution over a period of 1 h. After addition, the reaction mixture was stirred for 1 h at room temperature. The reaction was then quenched with an aqueous solution of saturated ammonium chloride (5.0 mL) and filtered through a pad of Celite ™ with an additional quantity of EtOAc (5.0 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (3 x 3.0 mL). The combined organic phases were washed with brine (5.0 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo.* The resulting residue was purified by flash chromatography (EtOAc/hexanes: 0% → 30%) over silica gel to afford the undesired major diastereomer **79** (10.8 mg, 42%) as a colourless oil, and the desired minor diastereomer **80** (3.0 mg, 12%) as a colourless oil.

Data for the desired diastereomer **80**:

$[\alpha]^{20}_{D}$ –11.7 (*c* 0.70, $CHCl_3$); IR (thin film): 3460, 2955, 2930, 2857, 1737, 1464, 1377, 1250, 1081, 837, 778 cm^{-1} ^1H NMR (600 MHz, $CDCl_3$) δ 6.0 (dd, *J* = 10.8, 7.2 Hz, 1H), 5.23 (t, *J* = 3.5 Hz, 1H), 5.17 (ddd, *J* = 8.3, 2.6, 1.4 Hz, 1H), 5.02 (d, *J* = 12.9 Hz, 1H), 4.70 (m, 1H), 4.67 (d, *J* = 13.0 Hz, 1H), 4.13 (td, *J* = 7.0, 3.8 Hz, 1H), 3.86 (tt, *J* = 11.7, 3.9 Hz, 1H), 3.76 (d, J = 7.0 Hz, 2H), 3.35 (m, 1H), 2.86 (dd, *J* = 11.7, 4.1 Hz, 1H), 2.71 – 2.65 (m, 2H), 2.52 (m, 1H), 2.42 (d, *J* = 6.2 Hz, 1H), 2.37 (dt, *J* = 12.7, 5.1 Hz, 1H), 2.17 (ddd, *J* = 13.9, 12.6, 5.5 Hz, 1H), 2.10 (s, 3H), 2.0 (dd, *J* = 12.7, 3.4 Hz, 1H), 1.48 – 1.40 (m, 2H), 0.86 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.0, 169.0, 136.3, 132.9 (2C), 124.2, 80.6, 76.3, 75.3, 65.8, 65.3, 61.0, 40.8, 37.8, 35.0, 28.1, 26.5, 26.0 (3C), 21.3, 18.4, -5.2, -5.3; HRMS (ESI^+): *m*/*z* calculated for $C_{24}H_{39}ClNaO_7Si$ $(M+Na)^+$ 525.2046; found 525.2047

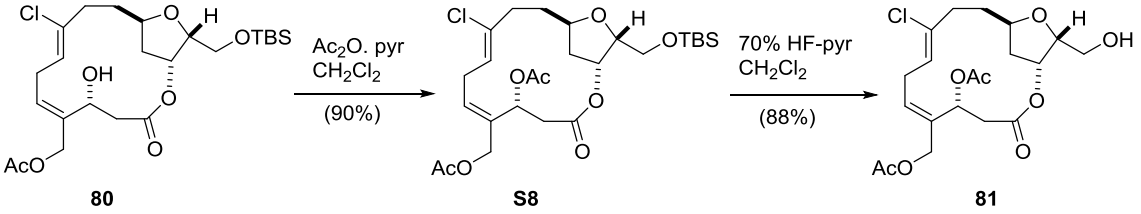
Inversion of (3*S*)-epimer 79 to (3*R*)-epimer 80



To a stirred solution of compound **79** (11.0 mg, 21.8 µmol) and $NaHCO_3$ (5.5 mg, 65.5 µmol) in CH_2Cl_2 (0.5 mL) was added Dess-Martin periodinane (11.2 mg, 26.2 µmol) and stirred for 1 h. The reaction mixture was then diluted with CH_2Cl_2 (1.0 mL) and quenched with a mixture of saturated solutions of $Na_2S_2O_3$/ $NaHCO_3$/water (1.0 mL; v/v 1:1:1) at 0 ºC . The biphasic mixture was then stirred vigorously for 20 minutes at room temperature. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 0.5 mL). The combined organic phases were then washed with brine (1.0 mL), dried over Na_2SO_4, and concentrated *in vacuo* . The resulting residue was purified by flash chromatography (EtOAc/hexanes: 0% → 25%) over silica gel to afford the ketone **S7** (8.8 mg, 80%) as colorless oil. $[\alpha]^{20}_D$ –12.5 (*c* 0.8, $CHCl_3$); IR (thin film): 2958, 1738, 1430, 1052, 845, 775 cm^{-1}; ^1H NMR (600 MHz, CDC_3) δ 6.63 (dd, *J* = 9.4, 7.4 Hz, 1H), 5.46 (t, *J* = 6.4 Hz, 1H), 5.41 (m, 1H), 4.99 (d, *J* = 12.8 Hz, 1H), 4.89 (d, *J* = 12.9 Hz, 1H), 4.15 (ddd, *J* = 7.6, 6.0, 3.7 Hz, 1H), 3.77 – 3.70 (m, 4H), 3.52 (m, 1H), 3.48 (dd, *J* = 15.7, 8.3 Hz, 1H), 3.17 (dd, *J* = 15.1, 7.1 Hz, 1H), 2.45 (br d, *J* = 13.9 Hz, 1H), 2.30 – 2.24 (m, 1H), 2.16 (td, *J* = 13.1, 4.3 Hz, 1H), 1.94 (dd, *J* = 12.9, 3.6 Hz, 1H), 1.50 – 1.41 (m, 2H), 0.87 (br s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 192.6, 170.5, 165.4, 147.0, 134.5, 133.9, 122.6, 80.5, 76.2, 76.1, 66.9, 61.1, 49.0, 38.3, 35.6, 29.9, 28.9, 27.4, 26.0, 21.1, 18.4, -5.2, -5.3; HRMS (ESI^+): *m*/*z* calculated $C_{24}H_{37}ClNaO_7Si$ $(M+Na)^+$ 523.1889; found 523.1874

To a stirred solution of ketone **S7** (7.5 mg, 14.9 µmol) and $CeCl_3$. $7H_2O$ (5.5 mg, 14.9µmol) in ethanol (0.3 mL) at -30 ºC was added sodium borohydride (1.5 mg, 37.4µmol) and stirred at same temperature for 30 minutes. The temperature of the reaction mixture was raised to 0 ºC and stirred for 15 minutes. After this time, TLC indicated complete consumption of **S7**. The reaction was quenched with aqueous saturated ammonium chloride (0.5 mL) and diluted with EtOAc (2.0 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (2 x 0.5 mL). The combine organic phases were washed with brine (1.0 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (EtOAc/hexanes: 0% → 30%) over silica gel to afford the desired single diastereomer **80** (6.5 mg, 85%) as a colourless oil.

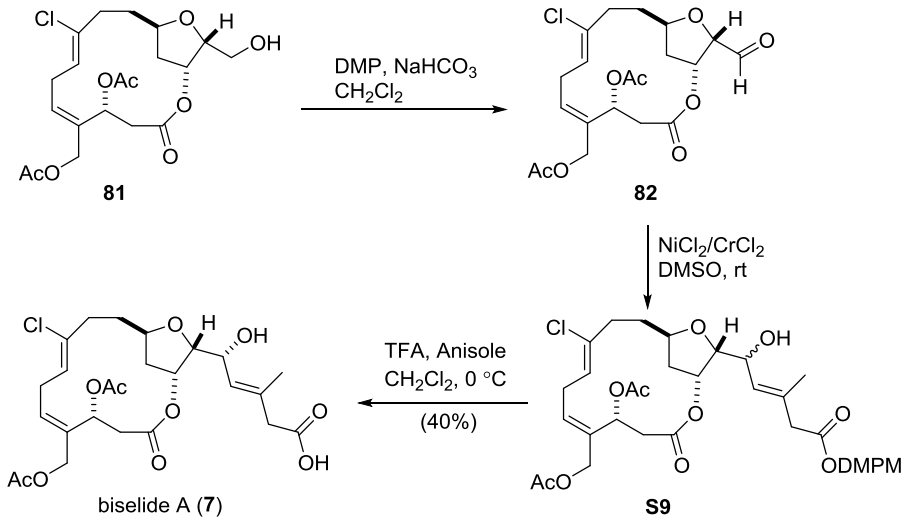
Synthesis of alcohol 81



To a stirred solution of macrocycle **80** (8.3 mg, 16.4 µmol) in CH_2Cl_2 (0.5 mL) at room temperature was added a catalytic amount of DMAP (1.0 mg), acetic anhydride (2.5 µL, 24.7 µmol) and pyridine (4.0 µL, 49.4 µmol). The reaction mixture was stirred for 5 h and then the solvent was removed *in vacuo*. Purification of the crude product by flash column chromatography (EtOAc/hexanes: 0% → 25%) over silica gel afforded compound **S8** (8.0 mg, 90%) as a pale-yellow oil. $[\alpha]^{20}_D$ –14.1 (*c* 0.31, $CHCl_3$); IR (thin film): 2959, 2929, 1739, 1433, 1373, 1229, 1079, 838, 780 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.05 (dd, *J* = 11.0, 7.0 Hz, 1H), 5.82 (dd, *J* = 11.9, 4.6 Hz, 1H), 5.26 (t, *J* = 3.5 Hz, 1H), 5.20 (br d, *J* = 7.3 Hz, 1H), 4.96 (d, *J* = 13.3 Hz, 1H), 4.73 (d, *J* = 13.4 Hz, 1H), 4.13 (ddd, *J* = 7.6, 7.1, 3.7 Hz, 1H), 3.90 (ttt, *J* = 11.8, 3.5 Hz, 1H), 3.77 (d, *J* = 7.2 Hz 2H), 3.62 (m, 1H), 2.84 (t, *J* = 11.8 Hz, 1H), 2.74 (dd, *J* = 11.9, 4.6 Hz, 1H), 2.66 (m, 1H), 2.52 (m, 1H), 2.39 (dtd, *J* = 13.9, 10.7, 8.8, 4.3 Hz, 1H), 2.18 (td, *J* = 13.3, 5.4 Hz, 1H), 2.10 (s, 3H), 2.07 (m, 1H), 2.04 (s, 3H), 1.49 – 1.40 (m, 2H), 0.86 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.7, 169.4, 168.0, 134.3, 133.0, 132.1, 124.3, 80.7, 76.3, 75.7, 66.5, 64.2, 60.9, 38.0, 37.8, 35.0, 29.9, 28.0, 26.9, 26.0 (3C), 21.3, 21.2, 18.4, -5.2, -5.3; HRMS (ESI^+): *m*/*z* calculated $C_{26}H_{41}ClNaO_8Si$ $(M+Na)^+$ 567.2151; found 567.2161

To a stirred solution of macrocycle **S8** (8 mg, 14.6 µmol) in THF (0.5 mL) was added HF·py (60 µL). The reaction mixture was stirred at room temperature for 1 h and quenched with aqueous saturated $NaHCO_3$ (2.0 mL). The mixture was extracted with EtOAc (3 × 3.0 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (EtOAc/hexanes: 0% → 60%) over silica gel afforded the compound **81** (5.5 mg, 88%) as clear oil. $[\alpha]^{20}_D$ +6.8 (*c* 0.22, $CHCl_3$); IR (thin film): 3454, 2956, 2855, 1736, 1232, 1047, 930, 838, 777 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.06 (dd, *J* = 11.0, 7.0 Hz, 1H), 5.81 (dd, *J* = 11.8, 4.5 Hz, 1H), 5.26 (t, *J* = 3.7 Hz, 1H), 5.21 (m,1H), 4.90 (d, *J* = 13.2 Hz, 1H), 4.71 (d, *J* = 13.2 Hz, 1H), 4.22 (ddd, *J* = 7.6, 4.4, 3.6 Hz, 1H), 3.92 (tt, *J* = 11.7, 3.7 Hz, 1H), 3.87 (ddd, *J* = 11.6, 7.1, 4.2 Hz, 1H), 3.67 (ddd, *J* = 11.7, 7.4, 4.6 Hz, 1H), 3.57 (m, 1H), 2.83 (t, *J* = 12.0 Hz, 1H), 2.74 (dd, *J* = 12.1, 4.5 Hz, 1H), 2.67 (m, 1H), 2.54 (m, 1H), 2.41 (m, 1H), 2.19 (ddd, *J* = 13.9, 12.5, 5.5 Hz, 1H), 2.10 (m,1H), 2.09 (s, 3H), 2.04 (s, 3H), 1.84 (dd, *J* = 4.4, 4.1 Hz, 1H), 1.52 – 1.43 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.8, 169.5, 168.1, 134.8, 133.1, 131.9, 124.3, 80.7, 76.2, 76.1, 66.4, 64.3, 61.7, 38.0 (2C), 35.0, 27.8, 26.9, 21.3, 21.2; HRMS (ESI^+): *m*/*z* calculated $C_{20}H_{27}ClNaO_8$ $(M+Na)^+$ 453.1287; found 453.1283.

Synthesis of biselide A (7)



To a stirred solution of the macrocycle **119** (5.5 mg, 11.6 µmol) and $NaHCO_3$ (3.0 mg, 35.0 µmol) in CH_2Cl_2 (0.5 mL) was added Dess-Martin periodinane (4.0 mg, 9.7 µmol) and the reaction mixture was stirred for 45 minutes. The reaction mixture was then diluted with CH_2Cl_2 (1.0 mL), a mixture of saturated solutions of $Na_2S_2O_3$/ $NaHCO_3$/water (1.0 mL; v/v 1:1:1) was added at 0 ºC. The biphasic mixture was then stirred vigorously for 20 minutes at room temperature. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 0.5 mL). The combined organic phases were then washed with brine (1.0 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the crude aldehyde **82** (5.0 mg), which was used immediately in the next step without any further purification.

Following the reported procedure,[6] to a stirred solution of the above crude aldehyde **82** (5 mg, 11.6 µmol), and vinyl iodide **120** (13.0 mg, 35 µmol) in degassed DMSO (0.4 mL) was added $CrCl_2$ doped with $NiCl_2$ (1.0 % wt/wt, 14.2 mg, 116 µmol). The reaction was stirred for 12 h at room temperature. After this time, the reaction mixture was cooled to 0 °C, diluted with water (2.0 mL), and extracted with Et_2O (8 x 5.0 mL). The combined organic extracts were dried over Na_2SO_4, concentrated and purified by flash column chromatography (EtOAc/hexanes: 30% → 80%) to afford the compound **S9** (4.5 mg, 57%) as a diastereomeric mixture (3:1) at C15. The spectroscopic data of the material is in complete agreement with that reported.[6]

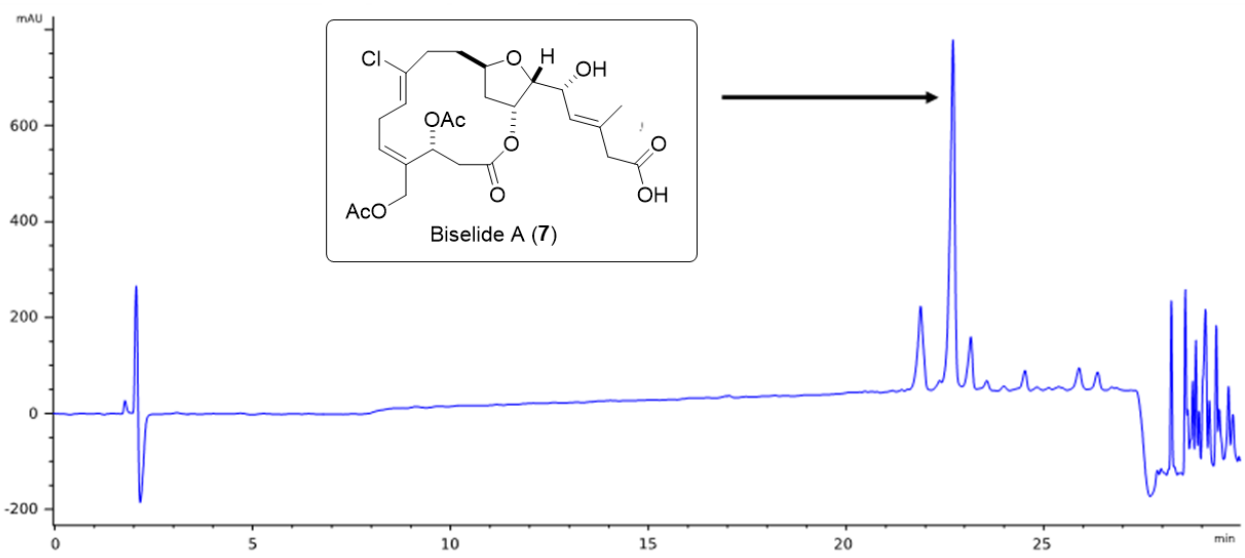
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.23 (d, *J* = 9.0 Hz, 1H), 6.46 (m, 2H), 6.06 (dd, *J* = 10.9, 7.2 Hz, 1H), 5.83 (dd, *J* = 11.5, 4.7 Hz, 1H), 5.42 (d, *J* = 7.9, Hz, 1H), 5.31 (m, 1H), 5.21 (m, 1H), 5.09 (s, 2H), 4.93 (d, *J* = 13.0 Hz, 1H), 4.73 (d, *J* = 13.2 Hz, 1H), 4.58 (t, *J* = 8.0 Hz, 1H), 3.94 (dd, *J* = 7.8, 3.7 Hz, 2H), 3.81 (s, 6H), 3.60 (m, 1H), 3.08 (s, 2H), 2.87 – 2.79 (m, 2H), 2.66 (m, 1H), 2.51 (m, 1H), 2.39 (m, 1H), 2.17 (m, 1H), 2.10 (m, 1H), 2.10 (s, 3H), 2.04 (s, 3H), 1.84 (s, 3H), 1.50 – 1.39m (m, 2H).

HRMS (ESI$^+$) calculated for $C_{34}H_{47}ClNO_{12}$: 696.2781 $(M+NH_4)^+$; found 696.2775

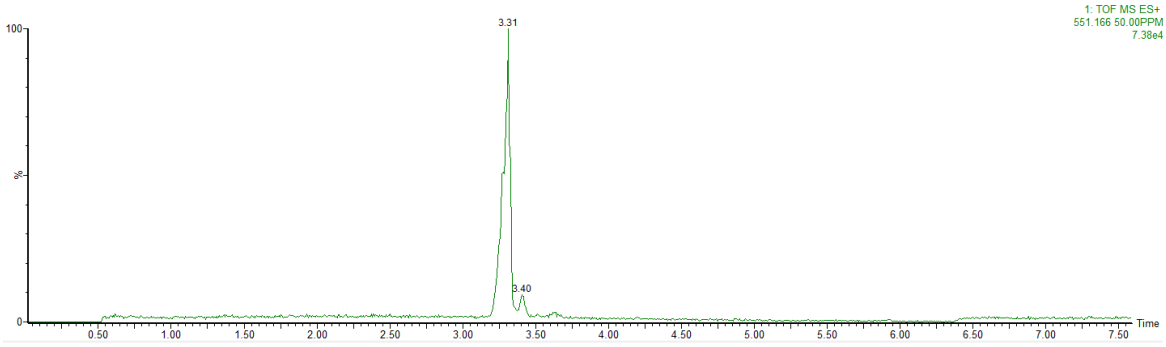
To a stirred solution of the ester **S9** (3.2 mg, 47.1 µmol) in dichloromethane (0.2 mL) at 0 °C, anisole (1M solution in CH_2Cl_2, 50 µL), and TFA (1M solution in CH_2Cl_2, 50 µL) were added. The reaction mixture was stirred for 4 h at 0 °C . After this time, the solvent was removed by rotary evaporation. The crude compound was purified by HPLC to afford biselide A (**7**) (1.1 mg, 40%) as a colorless oil. IR (thin film): 3454, 2956, 2855, 1736, 1232, 1047, 930, 838, 777 cm^{-1}; ^{1}H NMR (600 MHz, MeOD) δ 6.10 (dd, *J* = 10.9, 7.1 Hz, 1H), 5.85 (dd, *J* = 11.2, 4.9 Hz, 1H), 5.39 (dq, *J* = 8.5, 1.3 Hz, 1H), 5.34 – 5.32 (m, 2H), 4.97 (d, *J* = 13.0 Hz, 1H), 4.71 (d, *J* = 13.0 Hz, 1H), 4.54 (t, *J* = 8.6 Hz, 1H), 3.96 (m, 1H), 3.92 (dd, *J* = 8.6, 3.7 Hz, 1H), 3.56 (m, 1H), 3.06 (br s, 2H), 2.89 (dd, *J* = 12.0, 5.1 Hz, 1H), 2.86 (dd, *J* = 12.0, 11.1 Hz, 1H), 2.62 (m, 1H), 2.47 (m, 1H), 2.34 – 2.27 (m, 2H), 2.10 (m, 1H), 2.08 (s, 3H), 2.03 (s, 3H), 1.84 (d, *J* = 1.3 Hz, 3H), 1.54 (m, 1H), 1.41 (m, 1H); ^{13}C NMR (150 MHz, MeOD) δ 175.4, 172.5, 171.1, 169.4, 135.9, 135.0, 133.9, 133.6, 130.7, 125.8, 84.5, 78.1, 76.7, 67.7, 66.5, 65.5, 45.7, 38.8, 38.7, 35.5, 29.0, 27.7, 21.0 (2C), 17.3; HRMS (ESI$^+$): *m/z* calculated for $C_{25}H_{33}ClNaO_{10}$ $(M+Na)^+$ 551.1660; found 551.1654.

HPLC Purification of Synthetic Biselide A (7): The final reaction product was purified by RP-HPLC (Phenomenex Kinetix XB-C_{18} 4.6 x 250 mm, 5 µm) using a gradient of MeCN: H_2O with 0.1% TFA (0-5 min. 15% MeCN, 5-25 min. 15-50% MeCN, 25.1-30 min. 100% MeCN, 30-38 min. 15% MeCN) at a flow rate of 1.25 mL min^{-1}, monitoring UV wavelength 210 nm to give 1.1 mg of the final compound biselide A (t_R = 22.5)

Figure S5: RP-HPLC trace of synthetic biselide A (7). Absorbance displayed at 210 nm with reference set at 360 nm, Bw 100 nm.



HR-MS of Synthetic Biselide A (7): Measurement of biselide A (**7**) was performed with an Acquity UPLC H-Class (Waters) using an HSS C18, 100 mm x 2.1 mm, 1.7 μm column (Waters). Separation of 5 μL sample was achieved by a gradient of (A) H_2O + 0.1% FA to (B) MeCN + 0.1% FA at a flow rate of 500 μL/min and 45°C for 7.5 min (0-0.3 min 5% MeCN, 0.3-4.7 min 5-90% MeCN, 4.7-5.5 min 90-98% MeCN, 5.5-5.8 min 98% MeCN, 5.81-7.5 min 5% MeCN). The LC flow was split to 5 μL/min into a Synapt G2-Si operated in positive ion mode. Analysis was conducted using the MS^E mode which was set to alternate between collision energies of 0eV and 30eV every 0.3 sec. The instrument was operated in electrospray mode with 20 μg/mL leucine enkephalin lockspray infusion enabled every 10 sec. Mass spectra were acquired from 50-1500 m/z at 2Hz scan rate in centroid mode with automatic lockmass correction

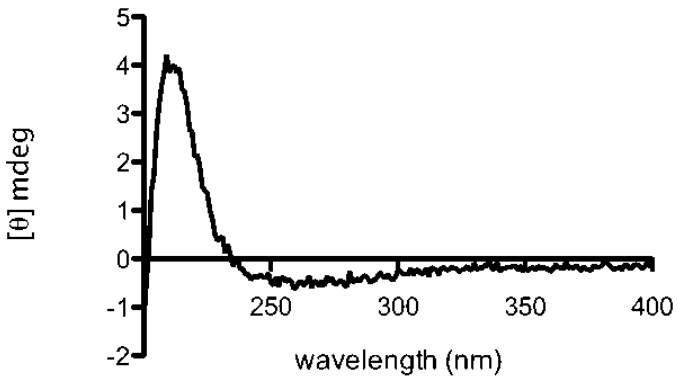


EIC for *m/z* 551.166 $[M+Na]^+$ with 50 ppm window of value for $C_{25}H_{33}ClO_{10}Na$ $[M+Na]^+$.

Expansion of MS spectrum at 3.31 minutes. Shown are values corresponding to biselide A (**7**): *m/z* 551.1654 $[M+Na]^+$, calcd 551.1654 $C_{25}H_{33}ClO_{10}Na$; *m/z* 546.2106 $[M+NH_4]^+$, calcd 546.2101 for $C_{25}H_{33}ClO_{10}NH_4$; *m/z* 511.1738 $[M+H-H_2O]^+$, calcd 511.1729 for $C_{25}H_{32}ClO_9$ $[M+H-H_2O]^+$.

Circular dichroism: Synthetic biselide A (**7**) was diluted in MeOH to a concentration of 1 mg/mL. From the prepared sample, 600 µL was transferred to quartz cuvettes (path length 2.0 mm) for circular dichroism (CD) analysis. The spectrum was acquired on a Chirascan qCD from 400 nm to 200 nm at a 1 nm resolution at a scan rate of 0.5 scans/sec. The methanol blank scans were automatically subtracted and the average of three scans is reported below with a maximum of +4.22 millidegrees at 209 nm.

Figure S6: CD spectrum (MeOH) of biselide A **(7)**



3. Comparison of the NMR Data of Natural and Synthetic Biselide A (7)

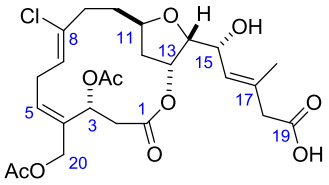


Table S1: Comparison of ^{1}H and ^{13}C NMR data between synthetic and natural biselide A (7) in CD_3OD

Position	^{13}C (natural product)	^{13}C (synthetic)	Difference Δ δnat- syn	^{1}H (natural product)	^{1}H (synthetic)	Difference Δ δnat- syn
1	169.4	169.4	0			
2a	38.7	38.7	0	2.83 dd (12.0, 11.1)	2.86 dd (12.0, 11.1)	-0.03
2b				2.88 dd (12.0, 5.2)	2.89 dd (12.0, 5.1)	-0.01
3	67.8	67.7	0.1	5.84 dd (11.1, 5.2)	5.85 dd (11.2, 4.9)	-0.01
4	135.0	135.0	0			
5	133.9	133.9	0	6.08 dd (11.1, 7.1)	6.10 dd (10.9, 7.1)	-0.02
6a	27.7	27.7	0	2.61 m	2.62 m	-0.01
6b				3.55 m	3.56 m	-0.01
7	125.8	125.8	0	5.32 m	5.34 m	-0.01
8	133.6	133.6	0			
9a	35.5	35.5	0	2.31 m	2.33 m	-0.02
9b				2.45 m	2.47 m	-0.02
10a	29.0	29.0	0	1.39 m	1.41 m	-0.02
10b				2.28 m	2.30 m	-0.02
11	78.1	78.1	0	3.94 m	3.96 m	-0.02
12a	38.8	38.8	0	1.53 m	1.54 m	-0.01
12b				2.09 m	2.10 m	-0.01
13	76.7	76.7	0	5.30 m	5.32 m	-0.02
14	84.5	84.5	0	3.91 dd (8.6, 3.7)	3.92 dd (8.6, 3.7)	-0.01
15	66.5	66.5	0	4.53 t (8.6)	4.54 t (8.6)	-0.01
16	130.7	130.7	0	5.38 d (8.6)	5.39 dq (8.5, 1.3)	-0.01
17	135.9	135.9	0			
18	45.7	45.7	0	3.04 br s 2H	3.06 br s 2H	-0.02
19	175.4	175.4	0			
20a	65.5	65.5	0	4.70 d (12.9)	4.71 d (13.0)	-0.01
20b				4.96 d (12.9)	4.97 d (13.0)	-0.01

Position	^{13}C (natural product)	^{13}C (synthetic)	Difference Δ δnat- syn	^{1}H (natural product)	^{1}H (synthetic)	Difference Δ δnat- syn
21	17.3	17.3	0	1.82 br s 3H	1.84 d 3H (1.3)	-0.02
22	171.1	171.1	0			
23	21.0	21.0	0	2.02 s 3H	2.03 s 3H	-0.01
24	172.5	172.5	0			
25	20.9	21.0	-0.1	2.07 s 3H	2.08 s 3H	-0.01

4. Computational methods

To interrogate possible modes of hydrogen bonding in seco acids ***(R)*-62** *and* ***(S)*-62** a representative set of low energy conformations were generated, visually inspected for hydrogen bonding, and their percent population at room temperature in chloroform was estimated via a Boltzmann population analysis as follows

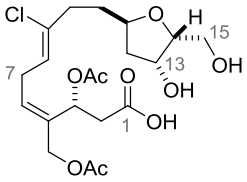
Molecular Dynamics (MD) Conformational Search for Representative Set of Low Energy Conformations of Seco-Acids ***(R)*-62** *and* ***(S)*-62**

A conformational search of ***(R)*-62** and ***(S)*-62** was carried out using the Tinker molecular modelling package.[7] Initial geometries for ***(R)*-62** and ***(S)*-62** were generated using the distance geometry algorithm as implemented in RDKit 2017.09.[8] Subsequently, ***(R)*-62** and ***(S)*-62** were parametrized for use with the MMFF94 force field[9] using the sdf2tinkerxyz program.[10] Each of the initial geometries were rapidly heated to 1000 K over the course of a 1 ps NVT MD simulation with temperature coupling controlled via the Berendsen thermostat[11] ($\tau = 0.1\ ps$), and a time step of 1 fs. The molecular geometry in the last frame of the MD simulation was then subjected to energy minimization with a Newton-Raphson minimization algorithm, as implemented in Tinker, until an atom root mean square gradient of 0.01 kcal/mol/Å was achieved. The above heating-minimization process was iteratively repeated 10,000 times, with the starting molecular geometry for subsequent MD simulations taken from the energy minimized geometry of the preceding iteration. Solvation effects of chloroform modelled in both the MD and energy minimization steps by setting the distance dependent dielectic constant ($\epsilon = 4.81$). Additionally, throughout the course of the MD simulations and energy minimizations, stereochemistry was enforced and a soft harmonic restraint (k = 0.01 kcal/Å^2) was applied to the torsion angles of all alkenes when they rotated beyond 45° from their ideal geometries (*ie: E* or *Z)*. This ensured that the correct stereochemistry was maintained throughout the simulations and prevented double bonds from isomerizing while ensuring maximum conformational flexibility during the heating and energy minimization processes. After the completion of 10,000 iterations of the above process, the 10,000 resultant conformations were sorted from lowest to highest energy. To eliminate redundant conformations, all pairwise combinations of conformations were overlaid in RDKit and their atom root mean square deviations (RMSD) were calculated. If the atom RMSD was less than 0.25 Å between any pair of conformations, the higher energy conformation was discarded.

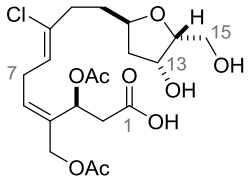
Quantum Mechanics Refinement of Low Energy Conformers
The resultant set of MMFF94 conformations within 4.0 kcal/mol from their respective minima were subjected to further geometry optimization in Gaussian 09 revision e.01[12] using the relatively low cost semi-empirical PM6 method.[13] The moderate size (238 electrons) and numerous conformations of ***(R)*-62** and ***(S)*-62** (>200) precluded geometry optimization with an *ab initio* method. Solvation effects for chloroform were included via the polarizable continuum model using the integral equation formalism variant.[14] All optimized geometries were verified to be true minima by vibrational frequency analysis.

Population analysis of Conformers of ***(R)*-62** and ***(S)*-62**
Using the PM6 sum of electronic and thermal free energies, the relative and fractional populations of each conformation of ***(R)*-62** and ***(S)*-62** within 2.0 kcal/mol of their respective minima were estimated at 298.15 K by means of a Boltzmann distribution. Critically, these estimates assume both that *i)* the lowest energy conformation identified by the MD/QM conformational search is the true global minimum and *ii)* conformations greater than 2.0 kcal/mol above the global minimum have negligible contributions to the population of conformations. **Figure S7** summarizes the population analysis and shows whether each conformation has visually evident hydrogen bonding, and where present, the key interacting functional groups and hydrogen bond length. Images of each of the low energy conformations listed in **Figure S7** and their key hydrogen bonding interactions were rendered with CYLView[15], and are shown below for visual clarity.

Figure S7: Conformer Population Analysis and H-bonding modes for **(*R*)-62** and **(*S*)-62**



***(R)*-62**

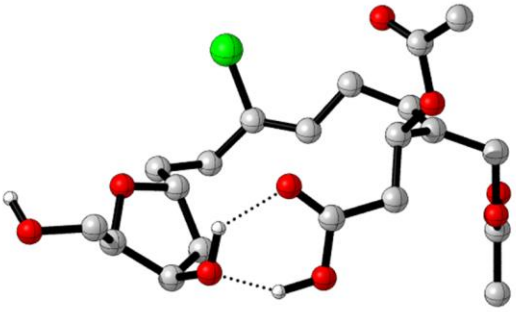


***(S)*-62**

***(R)*-62**						
ID	$\epsilon_0 + G_{corr}$[a]	**ΔG kcal/mol**	**P_i/P_0[b]**	**% population[b]**	**H-bonding Interaction[c]**	**H-bond Length (Å)**
1	-0.349635	0.00	1.000	80.0	(C1)OH···OH(C13) (C1)=O···HO(C13)	1.63 1.84
2	-0.347623	1.26	0.119	9.5	(C15)OH···AcO(C3) (C13)OH···OH(C15)	1.91 1.86
3	-0.347258	1.49	0.081	6.5	(C1)OH···O(C11/14) (C1)=O···HO(C13)	1.65 1.94
4	-0.346826	1.76	0.051	4.1	(C4')OAc···HO(C13)	1.91
***(S)*-62**						
ID	$\epsilon_0 + G_{corr}$	**ΔG kcal/mol**	**P_i/P_0**	**% population**	**Interaction**	**H-bond Length (Å)**
1	-0.347604	0.00	1.000	36.2	(C1)OH···OH(C13)	1.72
2	-0.347324	0.18	0.743	26.9	(C1)OH···OH(C15) (C15)OH···O(C11/14) (C1)=O···HO(C13)	1.55 1.83 2.03
3	-0.347041	0.35	0.551	19.9	(C1)OH···OH(C15) (C15)OH···O(C11/14) (C3)OAc···HO(C13)	1.59 1.91 1.90
4	-0.346182	0.89	0.222	8.0	(C1)OH···OH(C15) (C15)OH···O(C11/14) (C3)OAc···HO(C13)	1.62 2.00 1.93
5	-0.345823	1.12	0.152	5.5	(C13)OH···AcO(C3)	1.92
6	-0.345378	1.40	0.095	3.4	None	N/A

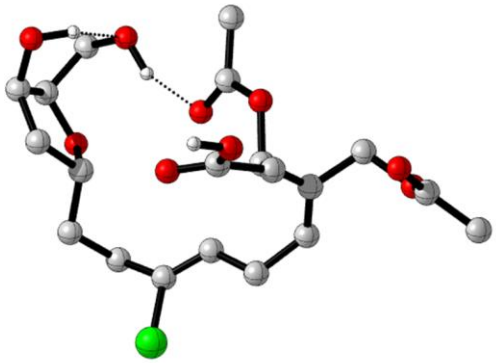
[a] Refers to the PM6 sum of electronic and thermal free energies. [b] Relative and percent populations are estimates from a Boltzmann distribution at room temperature (298.15K). [c] Dotted lines indicate which atoms are participating in hydrogen bonding.

(*R*)-62-1



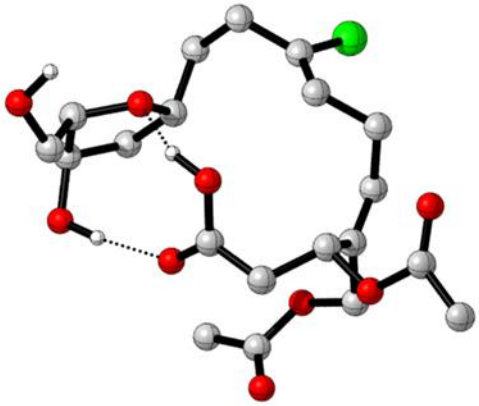
ΔG = 0.0 kcal/mol (relative)

(*R*)-62-2



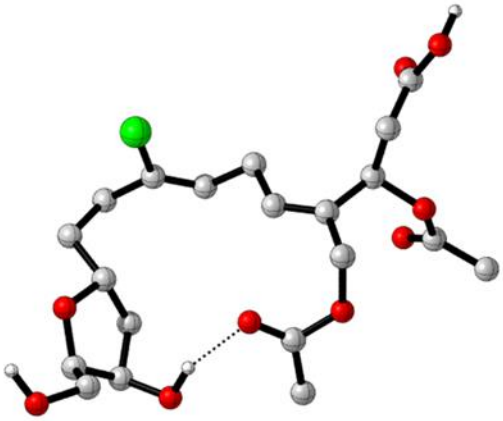
ΔG = 1.26 kcal/mol (relative)

(*R*)-62-3



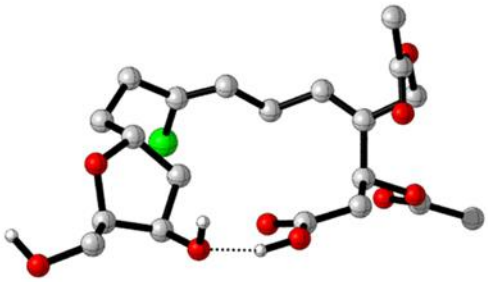
ΔG = 1.49 kcal/mol (relative)

(*R*)-62-4



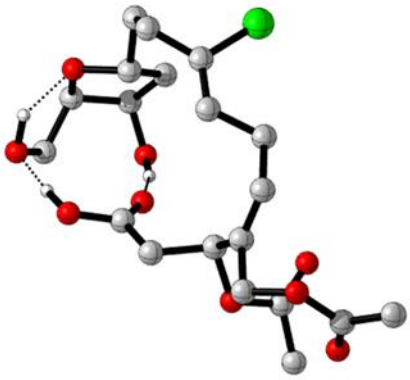
ΔG = 1.76 kcal/mol (relative)

(*S*)-62-1



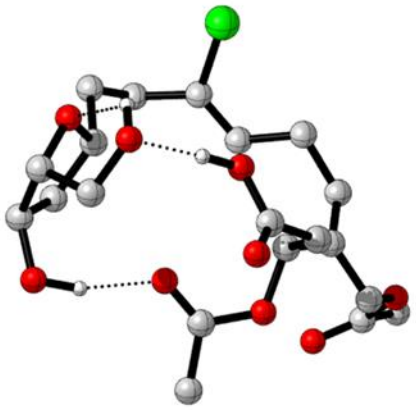
ΔG = 0.0 kcal/mol (relative)

(*S*)-62-2



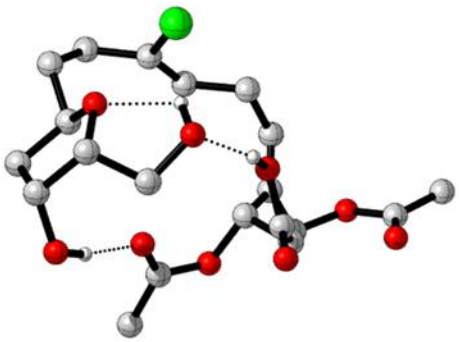
ΔG = 0.18 kcal/mol (relative)

(*S*)-62-3



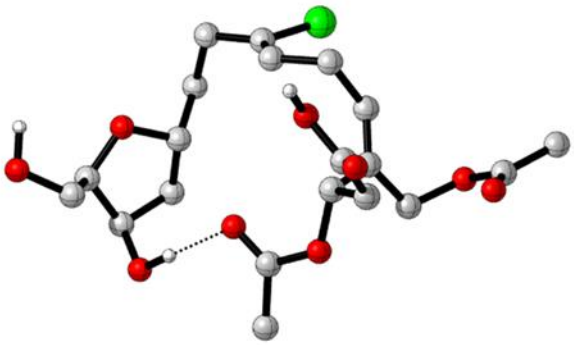
ΔG = 0.35 kcal/mol (relative)

(*S*)-62-4



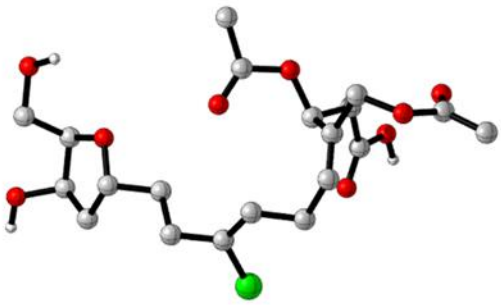
ΔG = 0.89 kcal/mol (relative)

(*S*)-62-5



ΔG = 1.12 kcal/mol (relative)

(*S*)-62-6



ΔG = 1.40 kcal/mol (relative)

5. References

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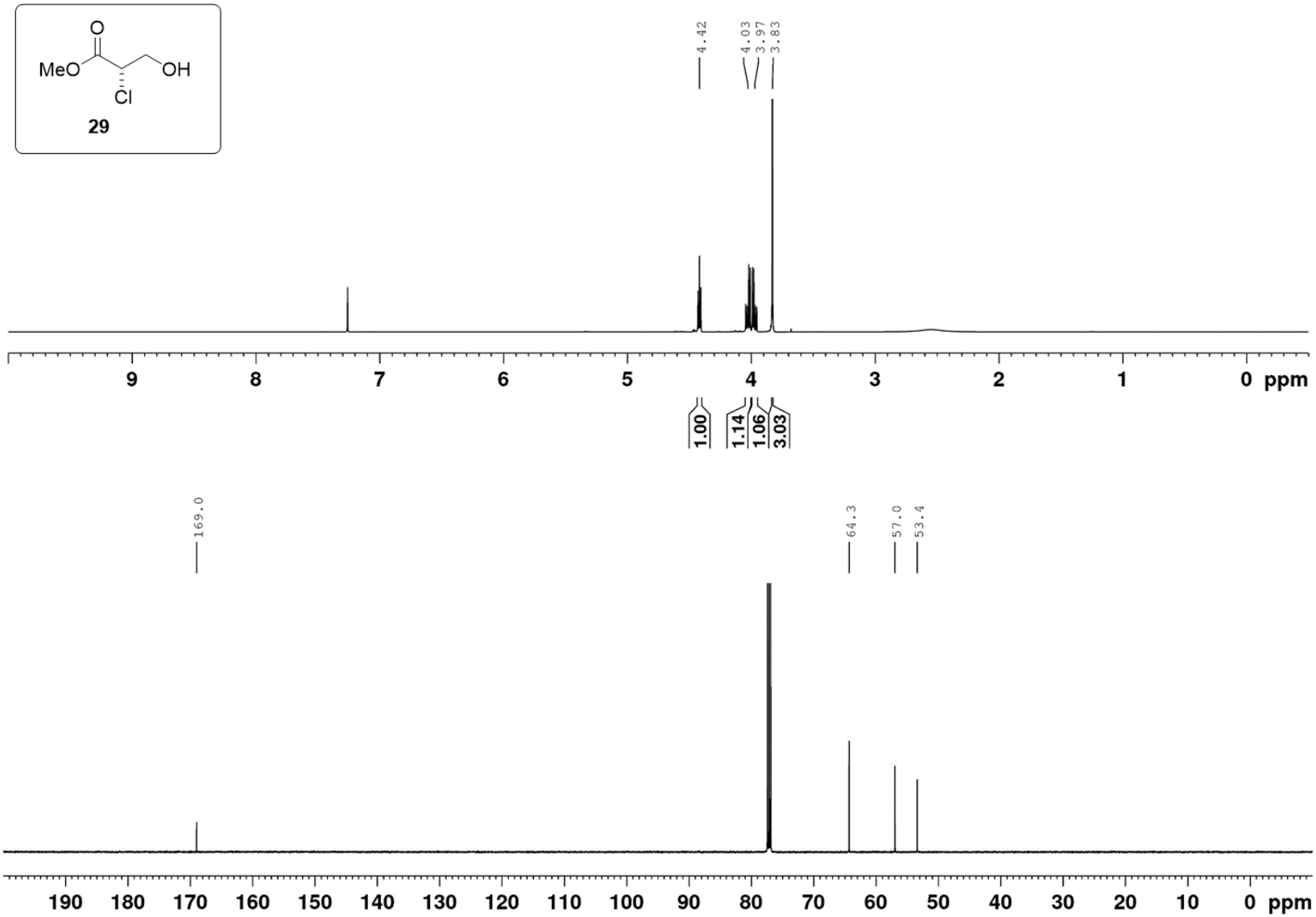
6. NMR Spectra:

^{1}H and ^{13}C NMR spectra for intermediates involved in the synthesis of biselide A (7) [compounds: 7, 24, 29, 30, 48, 49, 51, 68, 70, 74, 80, 81, S6, S7, S8]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O
OH
Cl
29
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4.03
3.97
3.83
1.00
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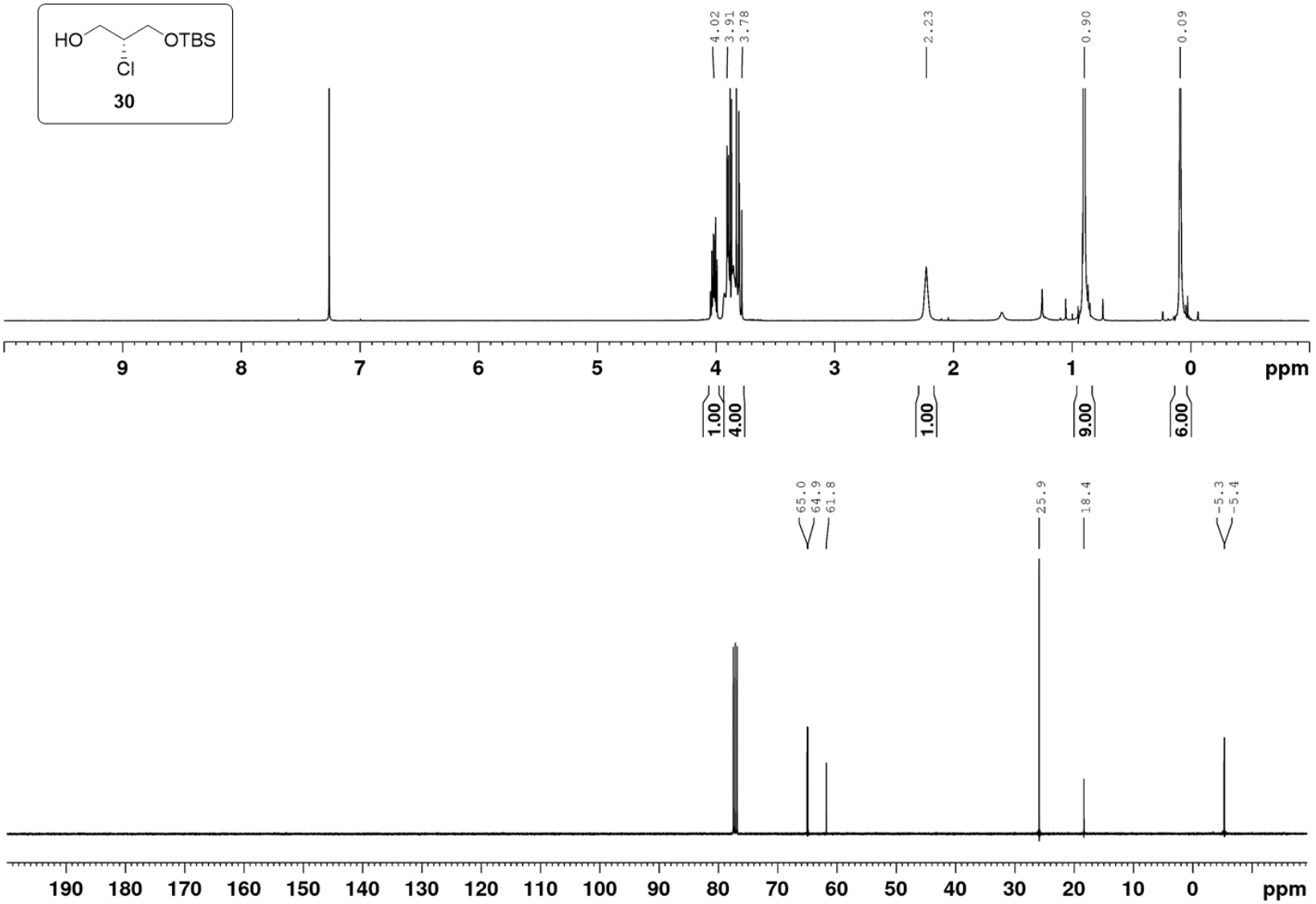
1.06
3.03
9
8
7
6
5
4
3
2
1
0 ppm
169.0
64.3
57.0
53.4
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm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OTBS
Cl
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8
7
6
5
4
3
2
1
0
ppm
1.00
4.00
1.00
9.00
6.00
65.0
64.9
61.8
25.9
18.4
-5.3
-5.4
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130
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60
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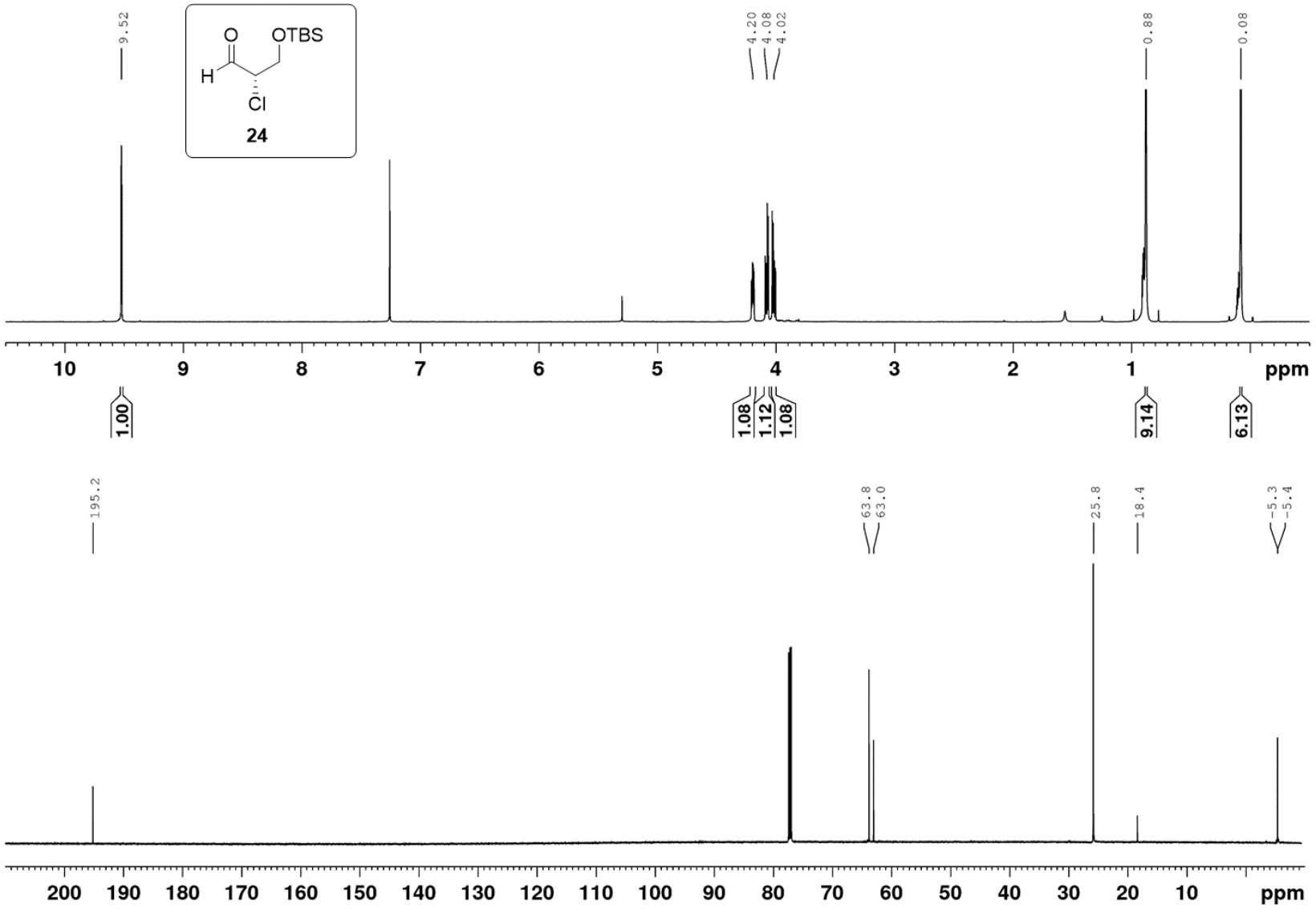
30
20
10
0
ppm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4.08
4.02
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H
Cl
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9
8
7
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5
4
3
2
1
ppm
1.00
1.08
1.12
1.08
9.14
6.13
195.2
63.8
63.0
25.8
18.4
-5.3
-5.4
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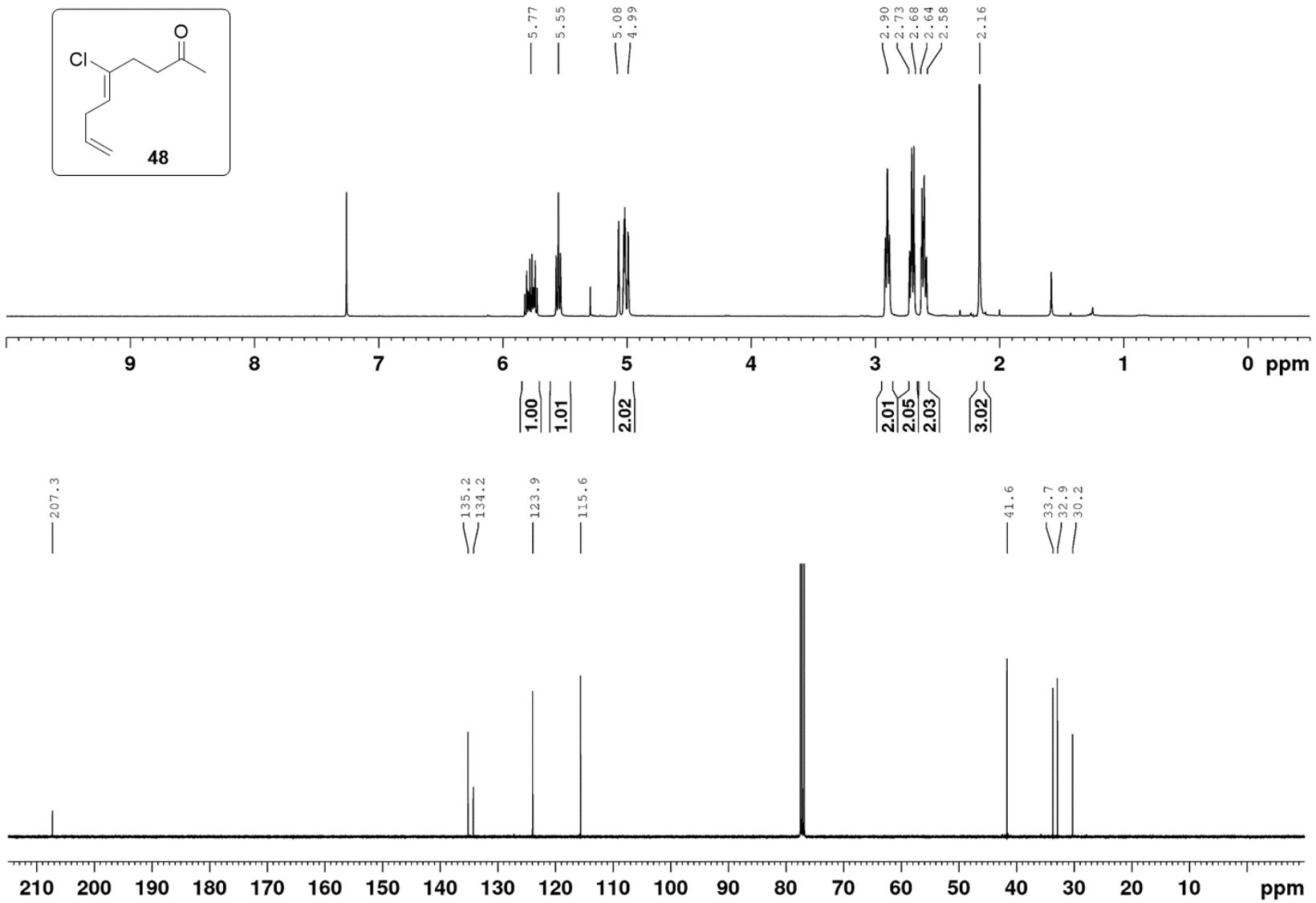
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O
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5.08
4.99
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2.64
2.58
2.16
9
8
7
6
5
4
3
2
1
0 ppm
1.00
1.01
2.02
2.01
2.05
2.03
3.02
207.3
135.2
134.2
123.9
115.6
41.6
33.7
32.9
30.2
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70
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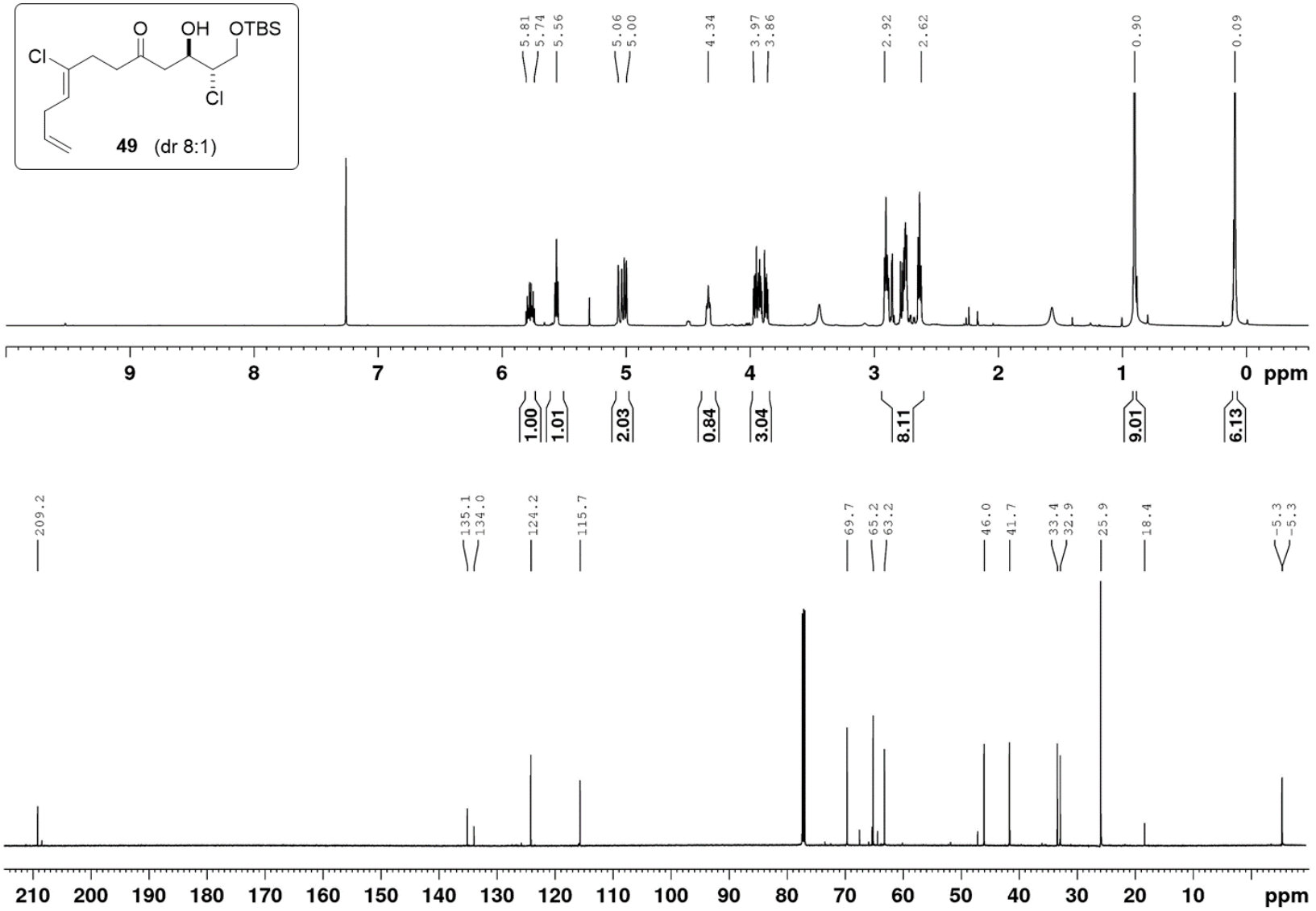
50
40
30
20
10
ppm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OH
OTBS
Cl
Cl
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5.56
5.06
5.00
4.34
3.97
3.86
2.92
2.62
0.90
0.09
9
8
7
6
5
4
3
2
1
0 ppm
1.00
1.01
2.03
0.84
3.04
8.11
9.01
6.13
209.2
135.1
134.0
124.2
115.7
69.7
65.2
63.2
46.0
41.7
33.4
32.9
25.9
18.4
-5.3
-5.3
210
200
190
180
170
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150
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110
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90
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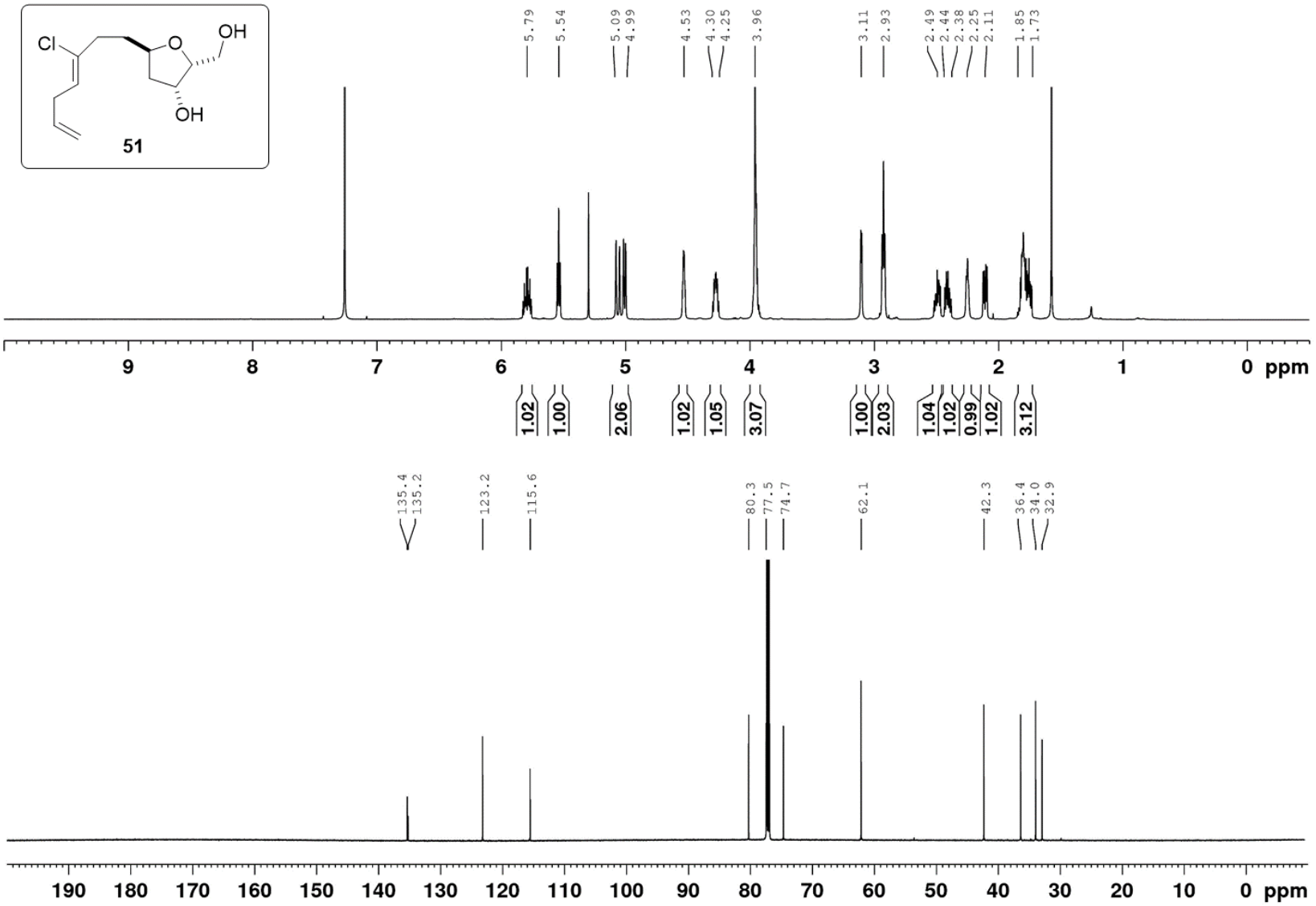
70
60
50
40
30
20
10
ppm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OH
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4.25
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2.93
2.49
2.44
2.38
2.25
2.11
1.85
1.73
9
8
7
6
5
4
3
2
1
0 ppm
1.02
1.00
2.06
1.02
1.05
3.07
1.00
2.03
1.04
1.02
0.99
1.02
3.12
135.4
135.2
123.2
115.6
80.3
77.5
74.7
62.1
42.3
36.4
34.0
32.9
190
180
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150
140
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110
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70
60
50
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30
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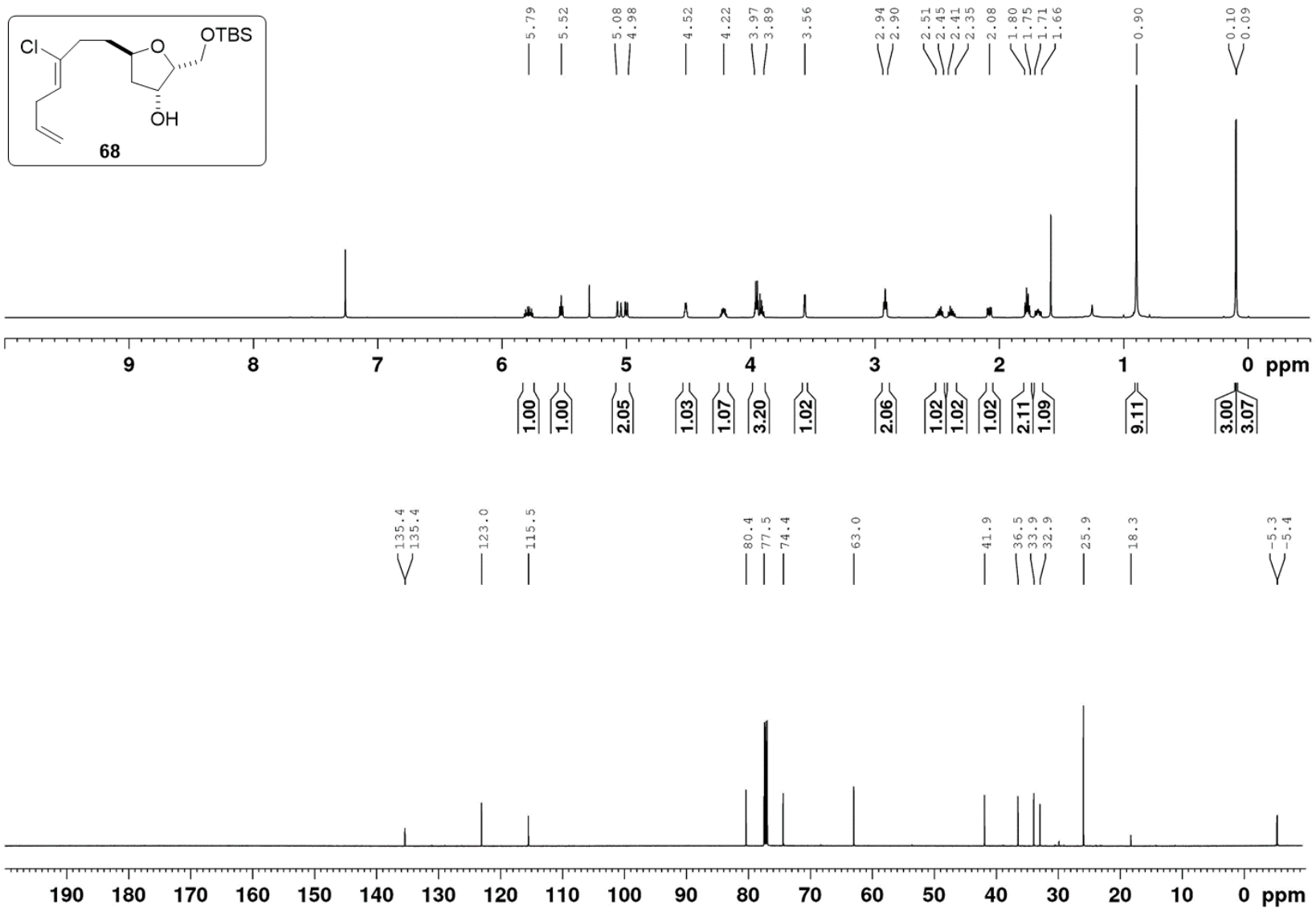
Cl
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OH
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5.79
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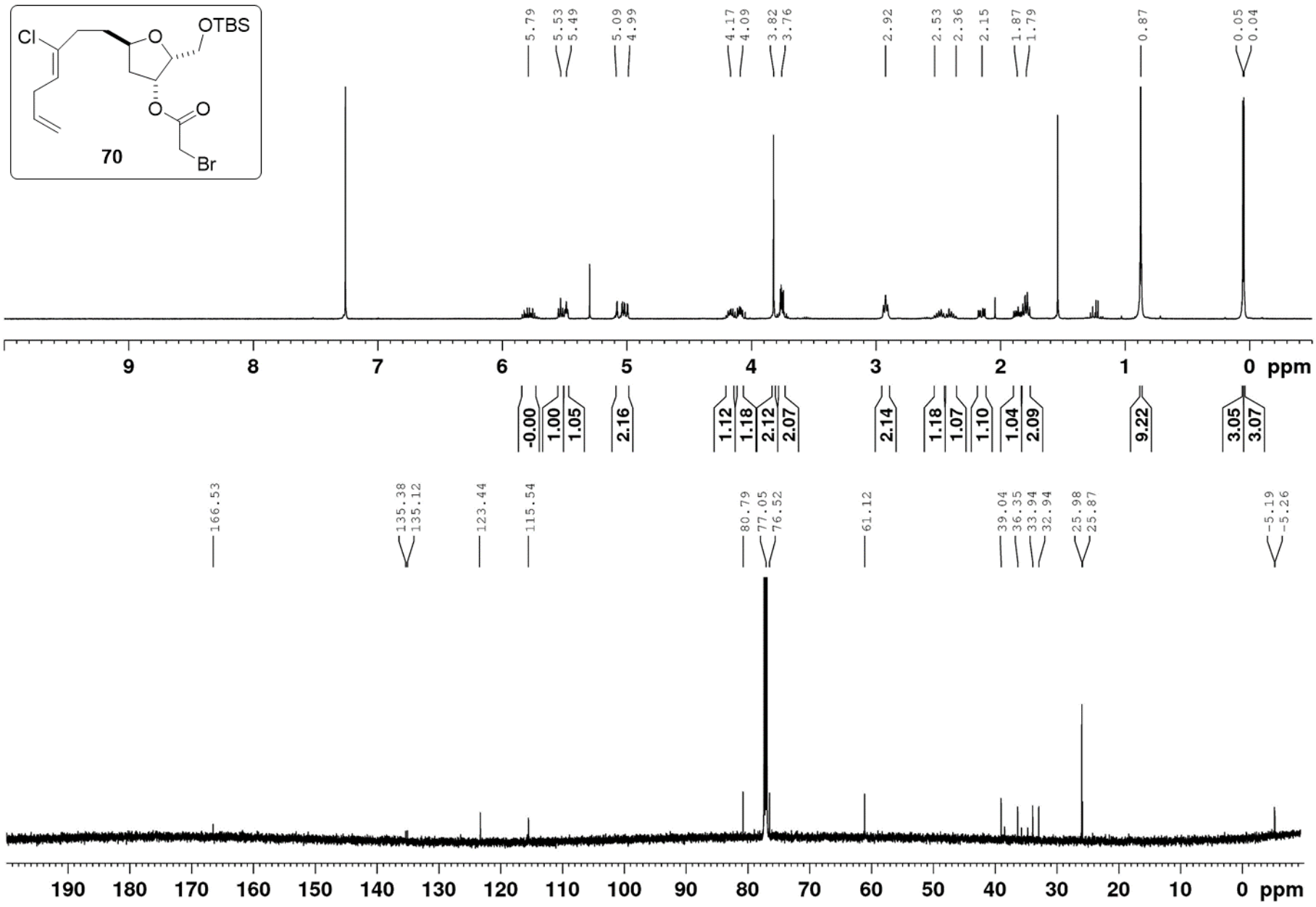
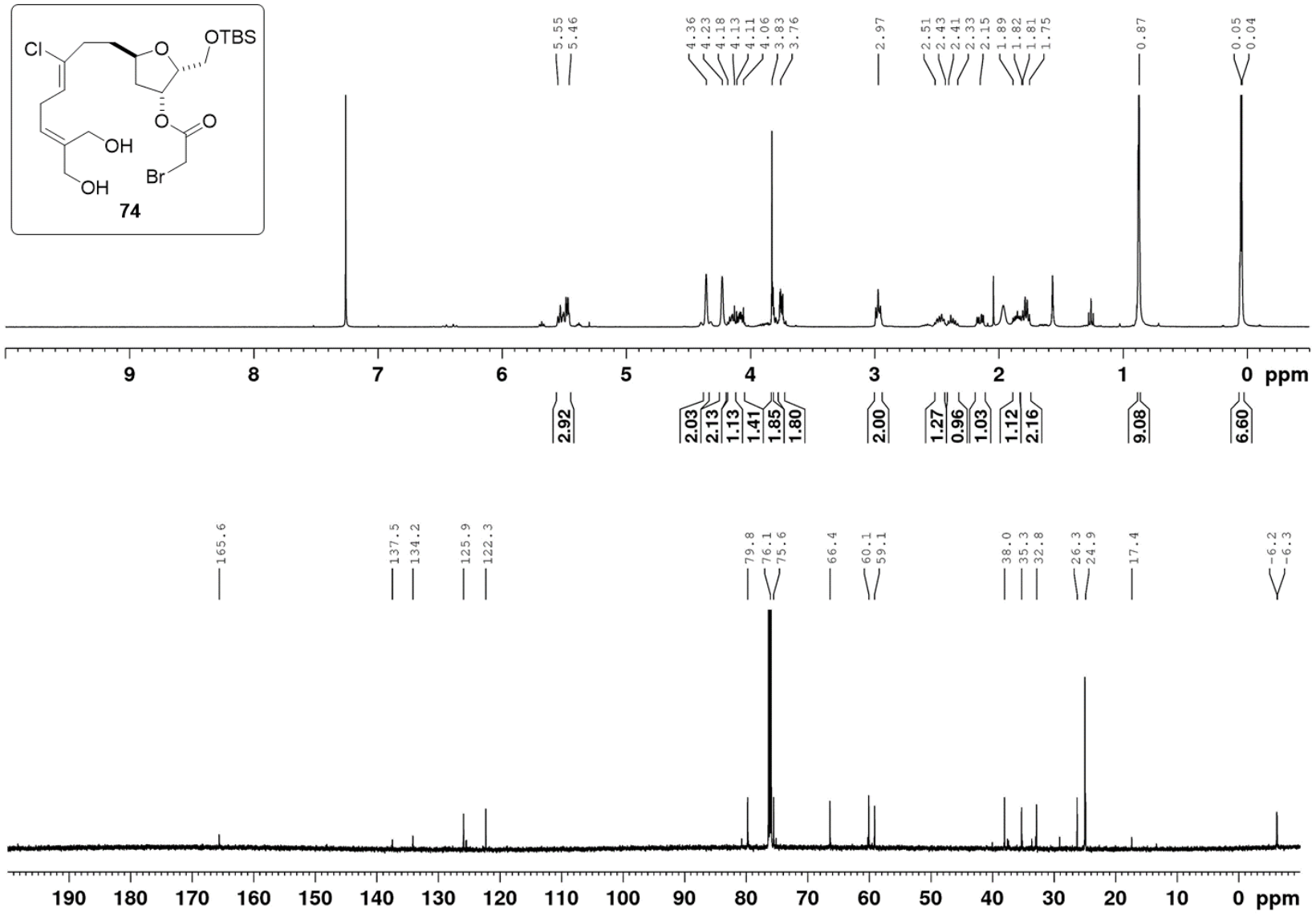
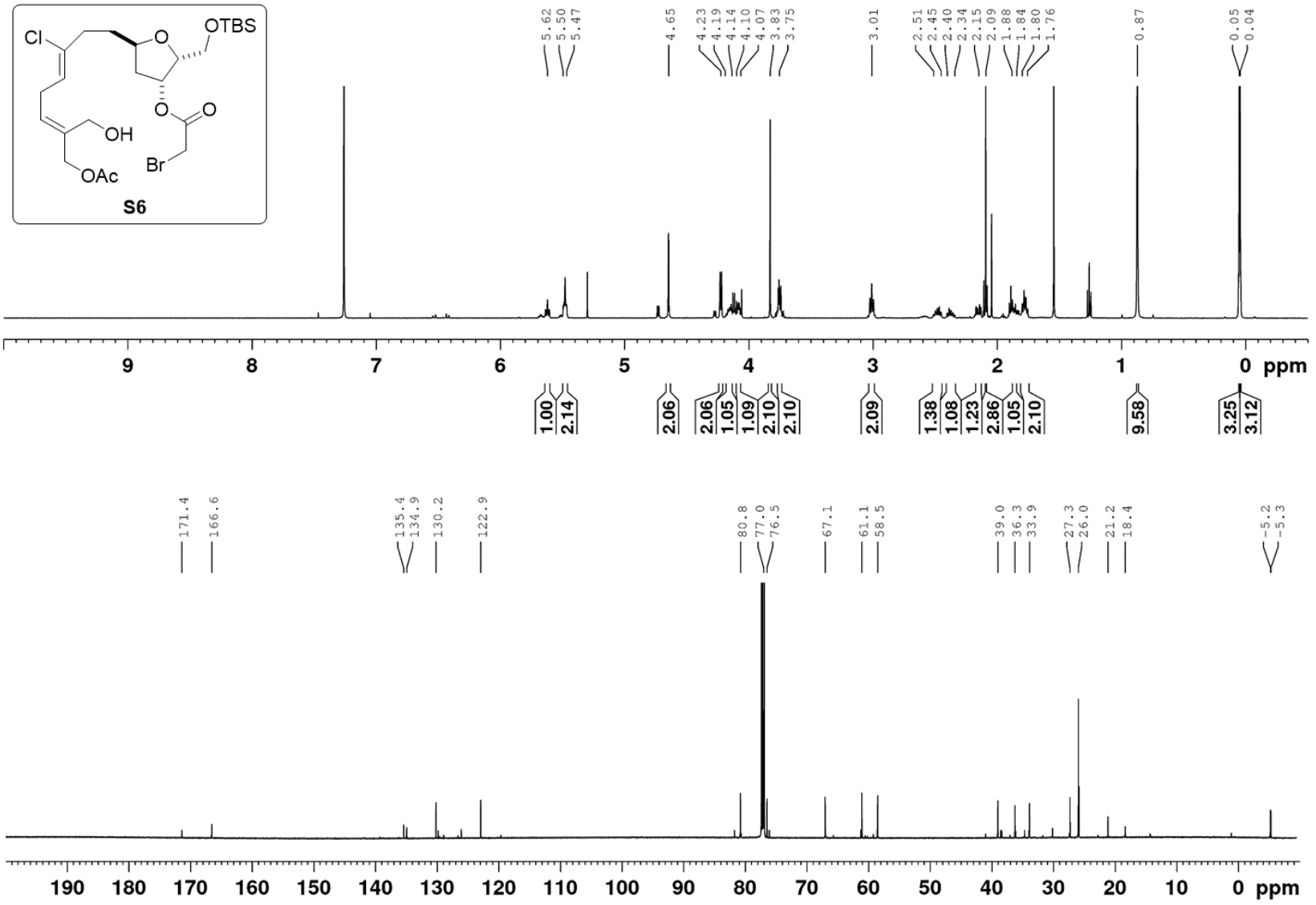
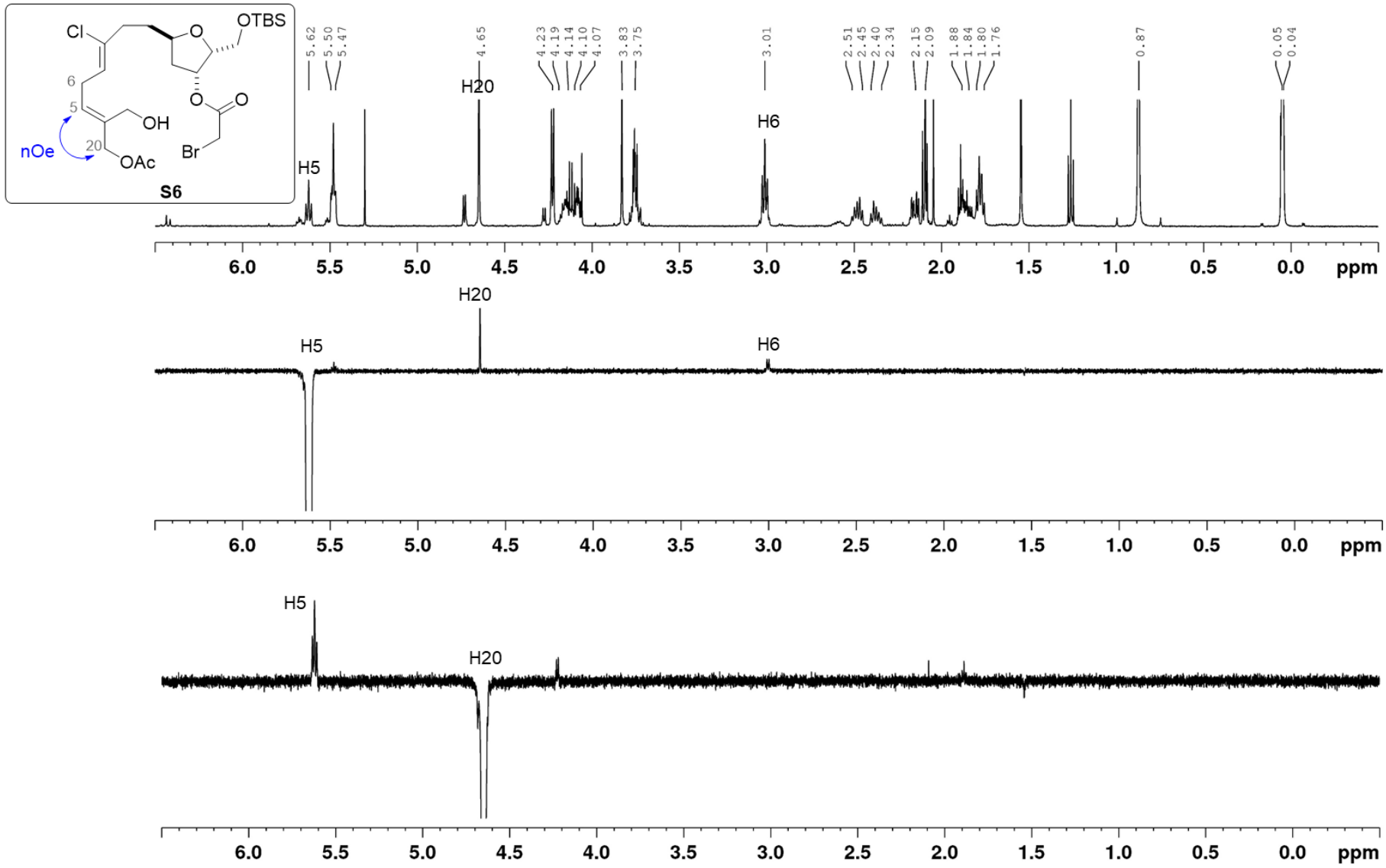
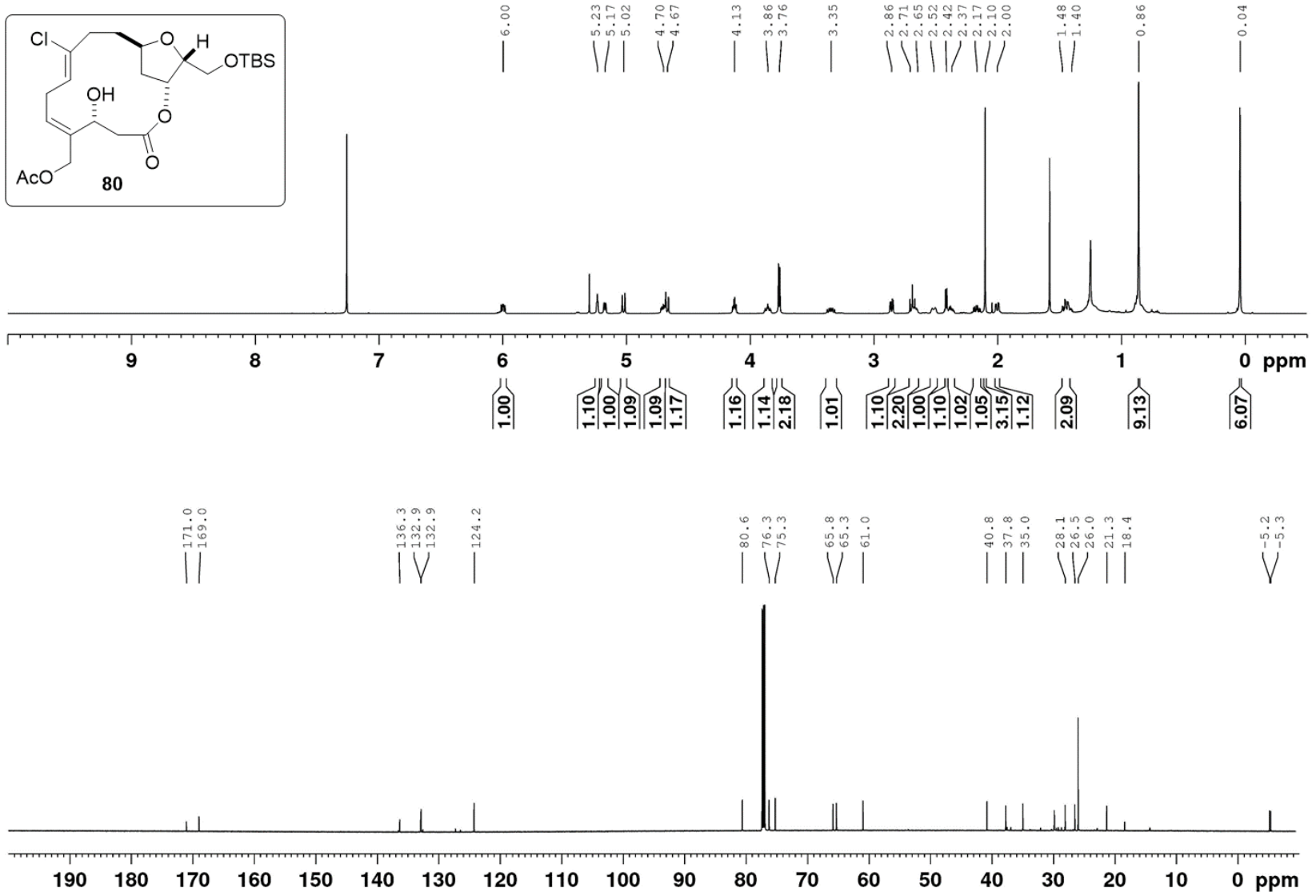
2.90
2.51
2.45
2.41
2.35
2.08
1.80
1.75
1.71
1.66
0.90
0.10
0.09
9 8 7 6 5 4 3 2 1 0 ppm
1.00 1.00 2.05 1.03 1.07 3.20 1.02 2.06 1.02 1.02 1.02 2.11 1.09 9.11 3.00 3.07
135.4
135.4
123.0
115.5
80.4
77.5
74.4
63.0
41.9
36.5
33.9
32.9
25.9
18.3
-5.3
-5.4
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

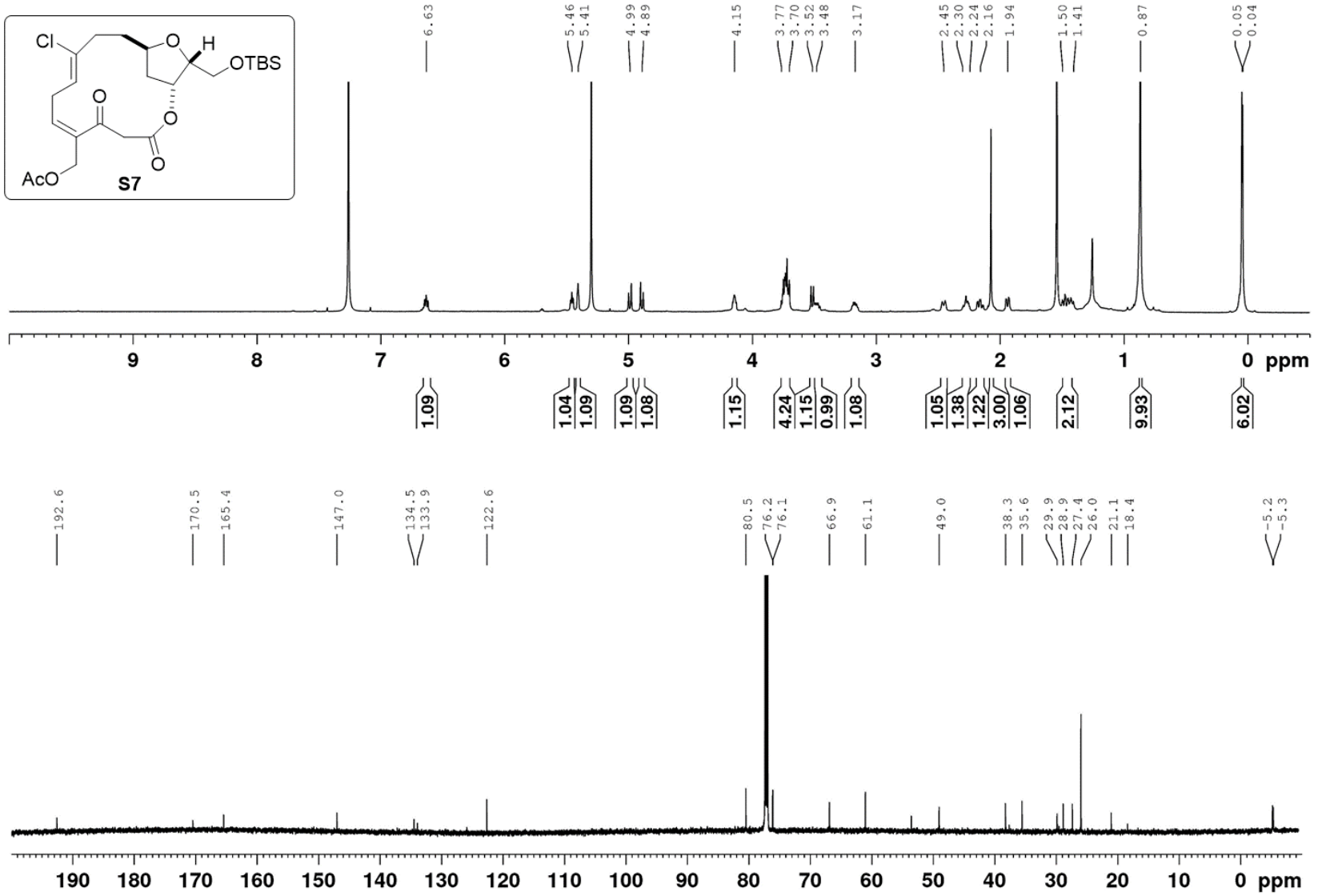

Cl
OTBS
O
O
O
Br
70
5.79
5.53
5.49
5.09
4.99
4.17
4.09
3.82
3.76
2.92
2.53
2.36
2.15
1.87
1.79
0.87
0.05
0.04
9
8
7
6
5
4
3
2
1
0 ppm
-0.00
1.00
1.05
2.16
1.12
1.18
2.12
2.07
2.14
1.18
1.07
1.10
1.04
2.09
9.22
3.05
3.07
166.53
135.38
135.12
123.44
115.54
80.79
77.05
76.52
61.12
39.04
36.35
33.94
32.94
25.98
25.87
-5.19
-5.26
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm

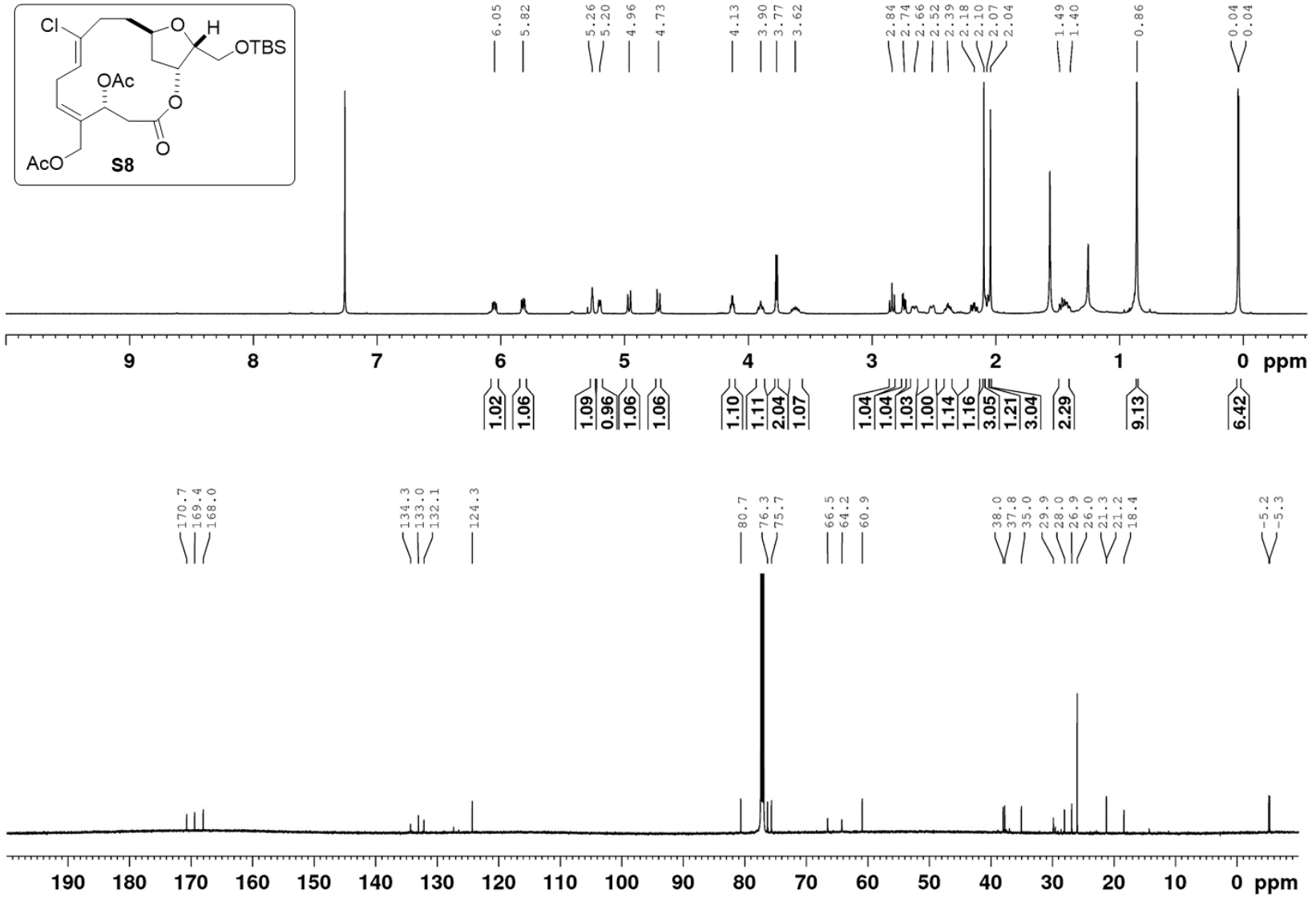

Cl
OTBS
O
O
O
OH
OH
Br
74
5.55
5.46
4.36
4.23
4.18
4.13
4.11
4.06
3.83
3.76
2.97
2.51
2.43
2.41
2.33
2.15
1.89
1.82
1.81
1.75
0.87
0.05
0.04
9 8 7 6 5 4 3 2 1 0 ppm
2.92
2.03
2.13
1.13
1.41
1.85
1.80
2.00
1.27
0.96
1.03
1.12
2.16
9.08
6.60
165.6
137.5
134.2
125.9
122.3
79.8
76.1
75.6
66.4
60.1
59.1
38.0
35.3
32.8
26.3
24.9
17.4
-6.2
-6.3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

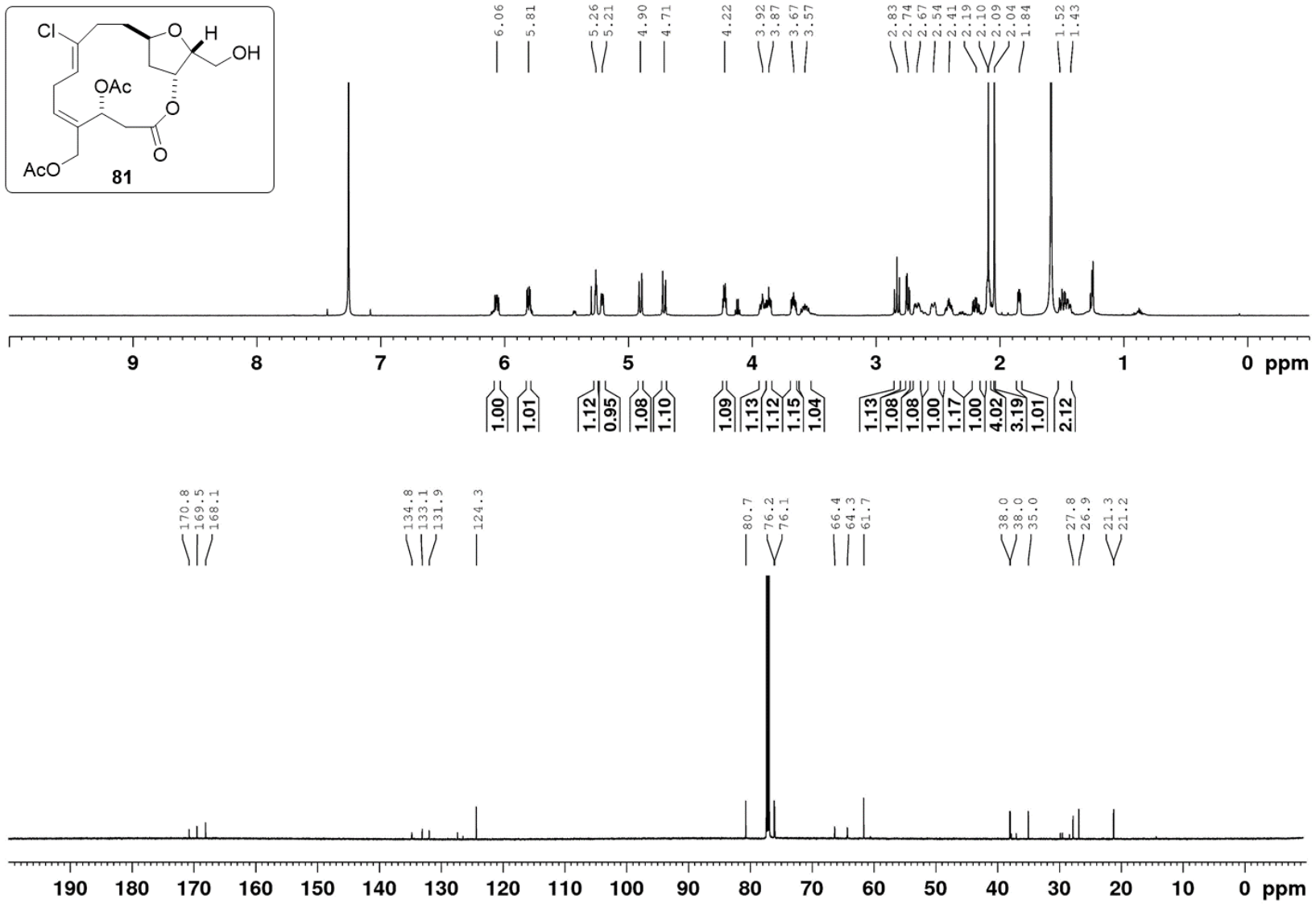

Cl
OTBS
O
O
O
OH
OAc
Br
S6
5.62
5.50
5.47
4.65
4.23
4.19
4.14
4.10
4.07
3.83
3.75
3.01
2.51
2.45
2.40
2.34
2.15
2.09
1.88
1.84
1.80
1.76
0.87
0.05
0.04
9
8
7
6
5
4
3
2
1
0 ppm
1.00
2.14
2.06
2.06
1.05
1.09
2.10
2.10
2.09
1.38
1.08
1.23
2.86
1.05
2.10
9.58
3.25
3.12
171.4
166.6
135.4
134.9
130.2
122.9
80.8
77.0
76.5
67.1
61.1
58.5
39.0
36.3
33.9
27.3
26.0
21.2
18.4
-5.2
-5.3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm

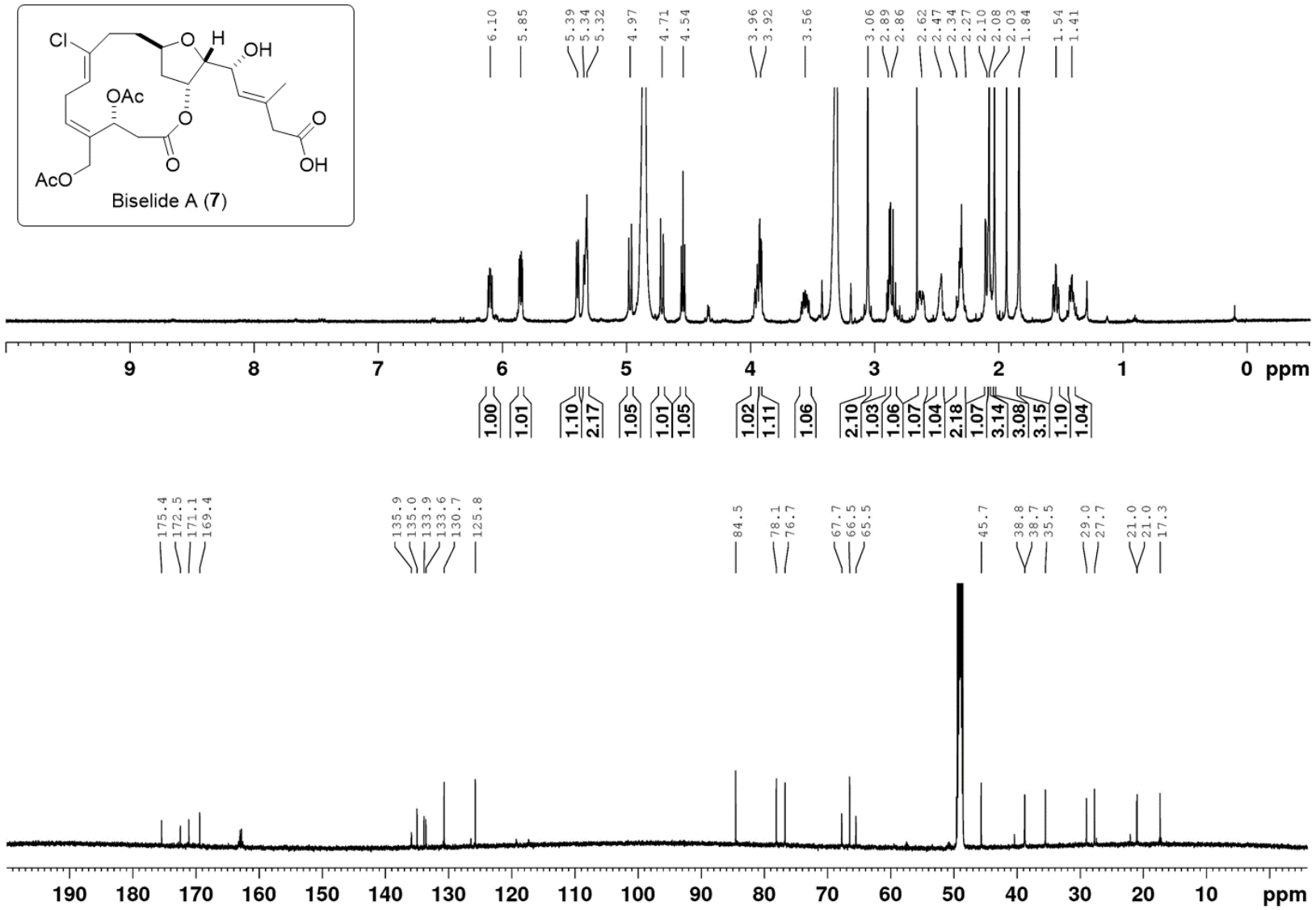

Cl
OTBS
O
6
5
OH
O
O
nOe
20
OAc
Br
S6
5.62
5.50
5.47
4.65
4.23
4.19
4.14
4.10
4.07
3.83
3.75
3.01
2.51
2.45
2.40
2.34
2.15
2.09
1.88
1.84
1.80
1.76
0.87
0.05
0.04
H5
H20
H6
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm


Cl
O
H
OTBS
OH
O
O
AcO
O
80
6.00
5.23
5.17
5.02
4.70
4.67
4.13
3.86
3.76
3.35
2.86
2.71
2.65
2.52
2.42
2.37
2.17
2.10
2.00
1.48
1.40
0.86
0.04
9 8 7 6 5 4 3 2 1 0 ppm
1.00
1.10
1.00
1.09
1.09
1.17
1.16
1.14
2.18
1.01
1.10
2.20
1.00
1.10
1.02
1.05
3.15
1.12
2.09
9.13
6.07
171.0
169.0
136.3
132.9
132.9
124.2
80.6
76.3
75.3
65.8
65.3
61.0
40.8
37.8
35.0
28.1
26.5
26.0
21.3
18.4
-5.2
-5.3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


Cl
O
H
OTBS
O
O
O
AcO
S7
6.63
5.46
5.41
4.99
4.89
4.15
3.77
3.70
3.52
3.48
3.17
2.45
2.30
2.24
2.16
1.94
1.50
1.41
0.87
0.05
0.04
1.09
1.04
1.09
1.09
1.08
1.15
4.24
1.15
0.99
1.08
1.05
1.38
1.22
3.00
1.06
2.12
9.93
6.02
9 8 7 6 5 4 3 2 1 0 ppm
192.6
170.5
165.4
147.0
134.5
133.9
122.6
80.5
76.2
76.1
66.9
61.1
49.0
38.3
35.6
29.9
28.9
27.4
26.0
21.1
18.4
-5.2
-5.3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


Cl
O
H
OTBS
OAc
O
O
AcO
S8
6.05
5.82
5.26
5.20
4.96
4.73
4.13
3.90
3.77
3.62
2.84
2.74
2.66
2.52
2.39
2.18
2.10
2.07
2.04
1.49
1.40
0.86
0.04
0.04
9 8 7 6 5 4 3 2 1 0 ppm
1.02 1.06 1.09 0.96 1.06 1.06 1.10 1.11 2.04 1.07 1.04 1.04 1.03 1.00 1.14 1.16 3.05 1.21 3.04 2.29 9.13 6.42
170.7
169.4
168.0
134.3
133.0
132.1
124.3
80.7
76.3
75.7
66.5
64.2
60.9
38.0
37.8
35.0
29.9
28.0
26.9
26.0
21.3
21.2
18.4
-5.2
-5.3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


Cl
O
H
OH
OAc
O
O
AcO
81
6.06
5.81
5.26
5.21
4.90
4.71
4.22
3.92
3.87
3.67
3.57
2.83
2.74
2.67
2.54
2.41
2.19
2.10
2.09
2.04
1.84
1.52
1.43
9
8
7
6
5
4
3
2
1
0 ppm
1.00
1.01
1.12
0.95
1.08
1.10
1.09
1.13
1.12
1.15
1.04
1.13
1.08
1.08
1.00
1.17
1.00
4.02
3.19
1.01
2.12
170.8
169.5
168.1
134.8
133.1
131.9
124.3
80.7
76.2
76.1
66.4
64.3
61.7
38.0
38.0
35.0
27.8
26.9
21.3
21.2
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm


Cl
O
H
OH
OAc
O
O
O
AcO
O
OH
Biselide A (7)
6.10
5.85
5.39
5.34
5.32
4.97
4.71
4.54
3.96
3.92
3.56
3.06
2.89
2.86
2.62
2.47
2.34
2.27
2.10
2.08
2.03
1.84
1.54
1.41
9
8
7
6
5
4
3
2
1
0 ppm
1.00
1.01
1.10
2.17
1.05
1.01
1.05
1.02
1.11
1.06
2.10
1.03
1.06
1.07
1.04
2.18
1.07
3.14
3.08
3.15
1.10
1.04
175.4
172.5
171.1
169.4
135.9
135.0
133.9
133.6
130.7
125.8
84.5
78.1
76.7
67.7
66.5
65.5
45.7
38.8
38.7
35.5
29.0
27.7
21.0
21.0
17.3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm