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Supporting Information

A Unified Approach for the Enantioselective Synthesis of the Brominated Chamigrene Sesquiterpenes

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Supporting Information

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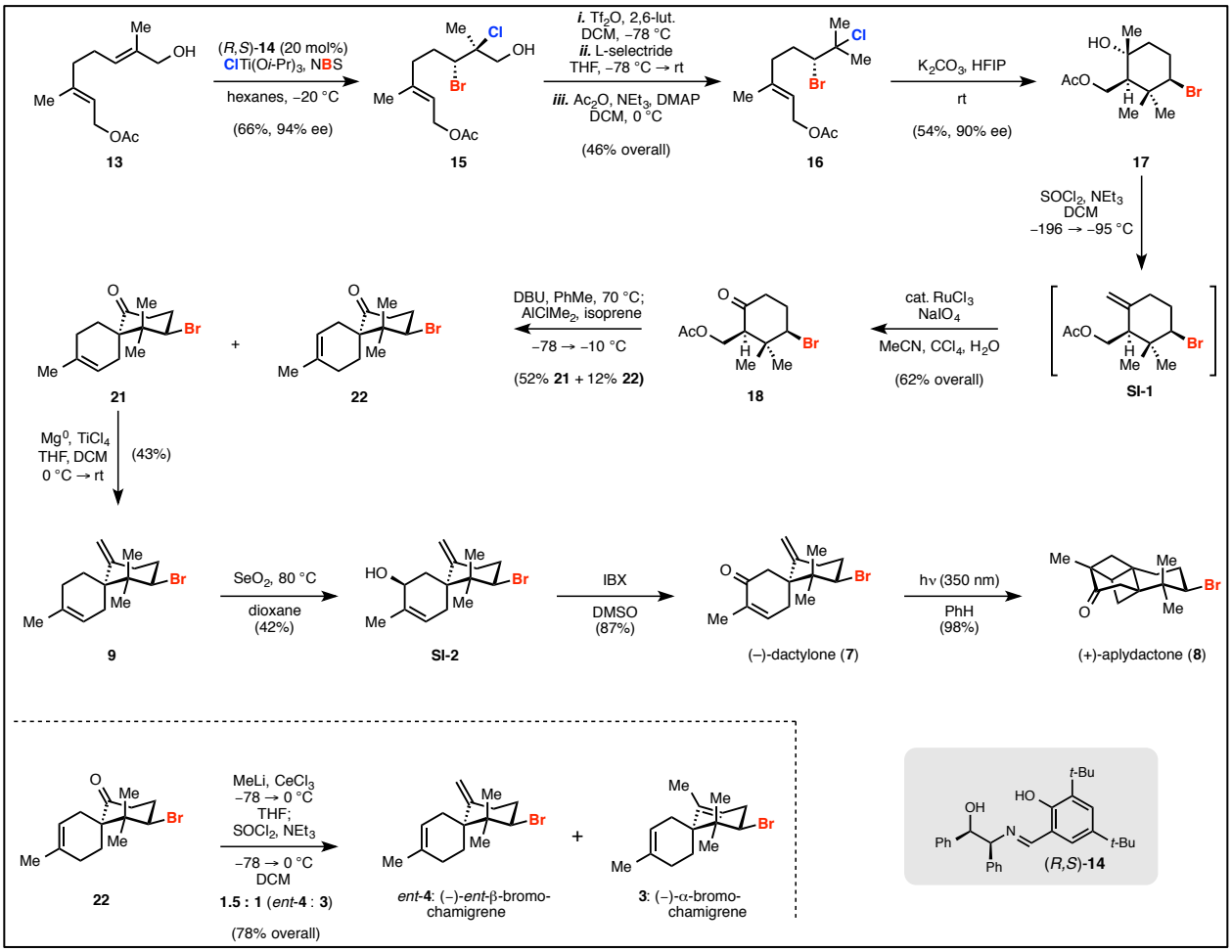
1. General Information

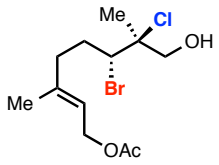
All reactions were conducted in oven- or flame-dried glassware under an atmosphere of nitrogen or argon unless otherwise noted. Commercial reagents and solvents were used as received unless otherwise noted with the exception of the following: hexanes (ACS grade, 4.2% various methylpentanes), toluene, tetrahydrofuran, acetonitrile, methanol, benzene, and dichloromethane were dried by passing through a bed of activated alumina in a JC Meyer Solvent System. HFIP (1,1,1,3,3,3-hexafluoro-2-propanol) was purchased from Oakwood Chemical and used as received. Flash column chromatography was performed using F60 silica gel (40-63 μm, 230-400 mesh, 60Å) purchased from Silicycle. Analytical thin-layer chromatography (TLC) was carried out on 250 μm 60-F_{254} silica gel plates purchased from EMD Millipore, and visualization was effected by observation of fluorescence-quenching with ultraviolet light and staining with either *p*-anisaldehyde or phosphomolybdic acid (PMA) with cerium sulfate as a developing agent. Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Varian Inova 600, Varian Inova 500, or Varian Mercury 400 spectrometers operating respectively at 600, 500, and 400 MHz for ^{1}H and at 150, 125, and 100 MHz for ^{13}C. Chemical shifts are reported in parts per million (ppm) with respect to residual protonated solvent for ^{1}H ($CHCl_3$ = δ 7.26, C_6D_6 = δ 7.16) and with respect to carbon resonances of the solvent for ^{13}C ($CDCl_3$ = δ 77.0, C_6D_6 = δ 128.5). NMR spectra were processed with the assistance of MestReNova Mnova NMR processing suite. Peak multiplicities were annotated as follows: app = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Infrared (IR) spectra were recorded on a Nicolet 6700 FT-IR spectrometer. LC-MS (ESI) data were collected on a Waters Micromass ZQ or a Waters Micromass LCT Premier mass spectrometer. Isotopic abundance patterns observed alongside each major ion reported matched calculated ratios. Optical rotations were measured using a JASCO P-2000 polarimeter. Chiral high-performance liquid chromatography (HPLC) analysis was performed using an Agilent 1260 with commercial ChiralPak 4.6 x 250 mm columns. HPLC trace integration was performed automatically by the Agilent OpenLab processing suite. Uncorrected melting point data were collected using a Thomas Hoover Uni-Melt apparatus.

2. Synthetic Schemes

Scheme SI-1. Synthesis of (–)-dactylone, (+)-aplydactone, (–)-α-, and (–)-*ent*-β-bromochamigrene.



3. Synthesis of (+)-Dactylone and (−)-Aplydactone



15

(+)-(6*R*,7*S*,*E*)-6-bromo-7-chloro-8-hydroxy-3,7-dimethyloct-2-en-1-yl acetate (15):

To a flame-dried 500 mL round bottom flask containing a stir bar was added neat hydroxyl-geranyl acetate[1] (1 equiv, 4.39 g, 21.0 mmol) and the contents were placed under an atmosphere of argon. To the flask was added hexanes (53 mL) resulting in the formation of a cloudy suspension. To this suspension was added freshly melted ClTi(O*i*-Pr)$_3$ (1.1 equiv, 23.0 mmol, 5.44 mL; prepared as a solution in 53 mL hexanes) slowly via cannula, resulting in a clear homogenous solution. To this mixture was added a solution of ligand (*R,S*)-**14**[2] (0.2 equiv, 4.1 mmol, 1.78 g; prepared as a solution in 105 mL hexanes) slowly via cannula. The rubber septum was replaced with a yellow cap and the solution was placed in an acetone bath over a stir plate at −15 °C in a refrigerator. To the cooled solution was added solid *N*-bromosuccinimide (1.05 equiv, 22.0 mmol, 3.87 g) all at once. The mixture was aggressively stirred at −15 °C for 3.5 hours, at which point it was quenched with 1M aq. Na_2SO_3 (200 mL), diluted with Et_2O (150 mL), and allowed to warm to room temperature. The biphasic mixture was transferred to an Erlenmeyer flask and a 10% aq. solution of L-tartaric acid (200 mL) was added. The biphasic mixture was stirred aggressively overnight and was then transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with Et_2O (2 x 200 mL). The organic layers were combined, washed with saturated aq. $NaHCO_3$ (200 mL) then brine (200 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (silica gel, 5 to 25% EtOAc/hexanes gradient) to provide the title compound in 66% yield (4.54g) in 94% ee as a >20:1 mixture of constitutional isomers. The absolute stereochemistry of the product and assignment of constitutional isomer was assigned by analogy to previously reported bromochlorides.[2]

For HPLC traces of the racemic and enantioenriched bromochloroalcohol see **S38**.

Physical properties: Clear, yellow viscous oil;

R_f = 0.40 (silica gel, 25% EtOAc in hexanes, visualized with anisaldehyde stain);

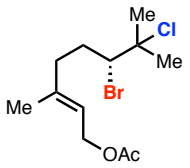
IR (film) ν_{max} 3440.4, 2933.3, 1732.3, 1716.1, 1444.4, 1383.0, 1231.6, 1052.8, 1024.3, 954.6, 582.7 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): 5.43 (td, *J* = 7.0, 1.4 Hz, 1H), 4.59 (d, *J* = 7.1 Hz, 2H), 4.22 (d, *J* = 10.6 Hz, 1H), 4.01 (dd, *J* = 12.3, 8.2 Hz, 1H), 3.78 (dd, *J* = 12.4, 6.0 Hz, 1H), 2.43 (m, 2H), 2.19 (m, 2H), 2.06 (s, 3H), 1.86 (m, 1H), 1.72 (s, 3H), 1.59 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$): 171.2, 140.1, 119.9, 77.02, 70.7, 61.2, 58.2, 37.4, 31.2, 21.0, 20.9, 16.3;

HR-LC/MS (ESI) calcd. for $C_{12}H_{20}{}^{35}Cl^{79}BrO_3$ $[M + Na]^+$ 349.0182, found 349.0168.

$[\alpha]_D^{23}$ = +46.8 (c = 1.0, $CHCl_3$) (at 94% ee).



16

(+)-(*R*,*E*)-6-bromo-7-chloro-3,7-dimethyloct-2-en-1-yl acetate (16):

The two-step triflation-deoxygenation sequence was done as previously reported.[3] To **15** (1 equiv, 13.7 mmol, 4.50 g,) in DCM (150 mL) under an argon atmosphere at −78 °C was added 3.20 mL of 2,6-lutidine (27.0 mmol, 2 equiv) followed by 2.80 mL of triflic anhydride (1.2 equiv, 16.4 mmol). The mixture was stirred for 1 hour and was then quenched via the addition of 100 mL of saturated aq. $NaHCO_3$. The mixture was warmed to room temperature and the layers were separated. The aqueous layer was extracted with DCM (2 x 100 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (silica gel, 5 to 15% EtOAc/hexanes gradient) to provide the triflate as a clear yellow oil in 85% yield (5.80 g).

To the trifluoromethanesulfonate of **15** (1 equiv, 10.9 mmol, 5.00 g) in an oven-dried two-neck round bottom flask, under an argon atmosphere, was added degassed THF (109 mL) and cooled to −78 °C (note: the cold bath should be at a sufficient height to cool the arm of the two-neck flask). To the cold solution was added a solution of L-Selectride (5.5 equiv, 60.0 mmol, 60 mL of a 1.0 M solution in THF) down the side arm of the two-neck flask over the span of one hour via syringe pump. The mixture was slowly warmed to room temperature and stirred overnight. The flask was equipped with an addition funnel, cooled to 0 °C and quenched via the sequential slow addition of water (30 mL), 3 M aq. NaOH (30 mL), and H_2O_2 (aq. 30%, 30 mL). The solution was then stirred for one hour at room temperature, transferred to a separatory funnel, and extracted with Et_2O (3 x 200 mL). The combined organic layers were washed with brine (1 x 300 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (silica gel, 5 to 25% EtOAc/hexanes gradient) to provide bromochlorogeraniol as a clear colorless oil in 58% yield (1.70 g).

To bromochlorogeraniol (1 equiv, 4.74 mmol, 1.28 g) in 50 mL DCM was added DMAP (0.05 equiv, 0.24 mmol, 29 mg) and triethylamine (1.22 equiv, 5.78 mmol, 804 µL). Acetic anhydride (1 equiv, 4.74 mmol, 448 µL) was added dropwise to the mixture at 0 °C. The mixture was stirred for 2 hours at 0 °C and the reaction was quenched via the addition of the solution to a separatory funnel containing 50 mL of water. The layers were separated and the aqueous layer was extracted with DCM (1 x 50 mL). The organic layers were combined and washed with 1 M aq. HCl (2 x 50 mL), saturated aq. $NaHCO_3$ (1 x 50 mL), and brine (1 x 50 mL). The organic layer was then dried over $MgSO_4$, filtered over a pad of silica gel, eluting with 33% EtOAc in hexanes (200 mL), and concentrated in vacuo to afford pure **16** in 94% yield (1.39 g).

Physical properties: Clear, colorless oil;

R_f = 0.32 (silica gel, 25% EtOAc in hexanes, visualized with anisaldehyde stain);

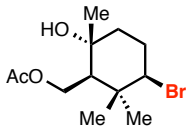
IR (film) ν_{max} 3322.2, 2981.7, 2932.9, 1455.1, 1386.8, 1371.0, 1226.3, 1103.1, 999.1, 639.9, 582.4 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) 5.43 (tt, *J* = 7.1, 1.3 Hz, 1H), 4.60 (d, 2H), 3.98 (dd, *J* = 11.0, 1.4 Hz, 1H), 2.42 (m, 2H), 2.18 (m, 1H), 2.06 (s, 3H), 1.85 (m, 1H), 1.78 (s, 3H), 1.72 (s, 3H), 1.66 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) 171.1, 140.2, 119.8, 71.9, 64.7, 61.2, 37.6, 33.2, 32.0, 26.9, 21.1, 16.3;

HR-LC/MS (ESI) calcd. for $C_{12}H_{20}{}^{35}Cl^{79}BrO_2$ $[M + Na]^+$ 333.0233, found 333.0237;

$[\alpha]_D^{23}$ = +52.2 (c = 1.2, $CHCl_3$) (at 82% ee).



17

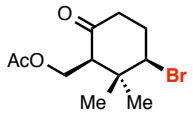
(−)-((1*S*,3*R*,6*R*)-3-bromo-6-hydroxy-2,2,6-trimethylcyclohexyl)methyl acetate (17):

To a 200 mL round bottom flask equipped with an egg-shaped magnetic stir bar was added neat bromochloride **16** (1 equiv, 4.43 mmol, 1.38 g, 94% ee) followed by solid K_2CO_3 (1.5 equiv, 6.64 mmol, 918 mg). Hexafluoroisopropanol (HFIP, 88.6 mL) was immediately charged to the flask and was tightly sealed with a yellow cap. The mixture was stirred for 2 days at room temperature. The mixture was then cooled to 0 °C and diluted with EtOAc (50 mL), transferred to a separatory funnel, and washed with brine (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered over a pad of silica gel, and concentrated under reduced pressure. The crude sample was purified by flash column chromatography (silica gel, 5 to 45% EtOAc in hexanes gradient) affording bromocycle 17 in 54% yield (705 mg) and 90% ee (96% es).

The data for **17** matched that previously reported.[4]

Enantiomeric excess was determined by chiral HPLC analysis of the benzoate derivative of **17** (for conditions and traces see **S36**).

Physical properties: white waxy solid;
$[\alpha]_D^{23}$ = –17.6 (c = 0.45, $CHCl_3$) (at 90% ee).



18

(–)-((1*S*,3*R*)-3-bromo-2,2-dimethyl-6-oxocyclohexyl)methyl acetate (18):

Protocol for dehydration of alcohol **17**:[5] To an oven-dried round bottom flask was added **17** (1 equiv, 2.39 mmol, 700 mg), placed under a nitrogen (nitrogen must be used instead of argon) atmosphere, and dissolved in 25 mL dry DCM. To the stirred solution was added freshly distilled NEt_3 (5 equiv, 12.0 mmol, 1.67 mL) and the mixture was cooled to -196 °C in a liquid nitrogen bath. Over the course of ten minutes a solution of $SOCl_2$ (1.5 equiv, 3.59 mmol, 0.261 mL) in dry DCM (5 mL) was added via syringe pump. The reaction was then removed from the liquid nitrogen bath and quickly immersed in a -95 °C (DCM/N_2) bath. The mixture was allowed to thaw and was stirred for a total of one hour before being quenched by the addition of methanol (0.5 mL). The mixture was transferred to a separatory funnel and washed with 1 M aq. HCl (40 mL). The aqueous layer was extracted with DCM (40 mL), the organic layers were combined and washed with saturated aq. $NaHCO_3$ (40 mL) and brine (40 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the exocyclic olefin, which was used immediately in the next step without further purification.

Protocol for oxidative cleavage of exocyclic olefin:[6] The crude olefin was dissolved in a biphasic mixture of MeCN (7 mL), CCl_4 (7 mL), and water (11 mL) to which was added solid $NaIO_4$ (1.46 equiv, 3.50 mmol, 750 mg) and $RuCl_3•7H_2O$ (0.02 equiv, 0.047 mmol, 10 mg). The mixture was stirred for 1 hour and was then quenched by the addition of 1M aq. Na_2SO_3 (20 mL) and diluted with DCM (20 mL). It should be noted that if the reaction stopped progressing (as monitored by TLC), portions of $NaIO_4$ and $RuCl_3$ could be added successively in small portions until all starting material was consumed. The layers were separated and the aqueous layer was extracted with DCM (2 x 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude keto-acetate was dissolved in 10 mL EtOAc and to the solution was added 100 mg $Pb(OAc)_4$ to remove residual amounts of ruthenium. The mixture was stirred overnight and was then filtered over a pad of celite/silica gel, washed with EtOAc, and the solution was concentrated under reduced pressure. The crude material was purified by flash column chromatography (silica gel, 10 to 40% EtOAc in hexanes gradient) to afford the title compound in 62% yield (398 mg) over two steps.

Physical properties: White amorphous solid;

R_f = 0.38 (silica gel, 25% EtOAc in hexanes, visualized with anisaldehyde stain);

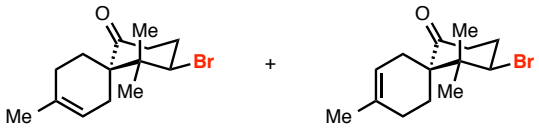
IR (film) ν_{max} 2973.1, 1735.9, 1720.6, 1455.1, 1366.9, 1236.7, 1038.6, 669.1 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) 4.49 (dd, *J* = 11.1, 8.2 Hz, 1H), 4.33 (dd, *J* = 12.5, 4.3 Hz, 1H), 4.22 (dd, *J* = 11.1, 3.3 Hz, 1H), 2.61 (dd, *J* = 8.2, 3.2 Hz, 1H), 2.58 – 2.51 (m, 1H), 2.50 – 2.41 (m, 2H), 2.35 – 2.22 (m, 1H), 2.01 (s, 3H), 1.30 (s, 3H), 0.87 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) 206.3, 170.9, 61.8, 60.0, 58.0, 43.5, 41.9, 33.6, 28.5, 21.0, 16.6;

LC/MS (ESI) calcd. for $C_{11}H_{17}{}^{79}BrO_3$ $[M + Na]^+$ 299.0, found 299.0;

$[\alpha]_D^{23}$ = –20.4 (c = 1.0, $CHCl_3$) (at 90% ee).



21 **22**

(+)-(4*R*,6*S*)-4-bromo-5,5,9-trimethylspiro[5.5]undec-8-en-1-one (21) and **(–)-(4*R*,6*R*)-4-bromo-5,5,9-trimethylspiro[5.5]undec-8-en-1-one (22):**

Ketoacetate **18** (1 equiv, 1.32 mmol, 365 mg) was charged to an oven dried round bottom flask, placed under an argon atomosphere, and dissolved in dry toluene (13.2 mL).[7] DBU (1.1 equiv, 1.45 mmol, 0.217 mL) was added and the mixture was heated to 70 °C for 15 minutes (consumption of **18** was determined by TLC analysis) and then subsequently cooled to room temperature. Isoprene (20 equiv, 26.4 mmol, 2.64 mL) was added and the reaction mixture was cooled to −78 °C. A solution of $AlClMe_2$ (3.5 equiv, 4.62 mmol, 4.62 mL of a 1M solution in hexanes) was added dropwise via syringe pump over ten minutes. The reaction mixture was then warmed to −10 °C and stirred for 15 minutes. The mixture was quenched via the dropwise addition of water at −10 °C (1.5 mL) and was then diluted with Et_2O (20 mL) and 1M aq. HCl (20 mL). The layers were separated and the aqueous layer was extracted with Et_2O (20 mL). The combined organic layers were washed with saturated aq. $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by *careful* flash column chromatography (silica gel, 0 to 10% Et_2O in hexanes gradient) to afford spiroketone **21** in 52% yield (196 mg) and spiroketone **22** in 12% yield (45 mg).

Physical properties for 21 (major): White crystalline solid;

m.p. = 59–61 °C;

R_f = 0.50 (silica gel, 10% EtOAc in hexanes, visualized with anisaldehyde stain);

IR (film) ν_{max} 2972.8, 2939.9, 1708.0, 1444.4, 1393.4, 1374.2, 1154.4, 962.4, 859.6, 779.2 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) 5.26 (dp, *J* = 5.3, 1.8 Hz, 1H), 4.66 (m, 1H), 2.75 (m, 1H), 2.46 (m, 2H), 2.38 – 2.15 (m, 5H), 1.89 (m, 1H), 1.57 (s, 3H), 1.51 (ddd, *J* = 13.1, 10.7, 7.0 Hz, 1H), 1.10 (s, 3H), 0.97 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) 212.1, 135.6, 116.5, 61.1, 55.1, 45.5, 37.4, 34.0, 29.1, 28.4, 24.6, 24.2, 23.0, 18.5;

LC/MS (ESI) calcd. for $C_{14}H_{21}{}^{79}BrO$ $[M + H]^+$ 285.1, found 285.1;

$[\alpha]_D^{23}$ = +12.5 (c = 1.5, $CHCl_3$) (at 90% ee).

Physical properties for 22 (minor): White crystalline solid;

m.p. = 90–94 °C;

R_f = 0.41 (silica gel, 10% EtOAc in hexanes, visualized with anisaldehyde stain);

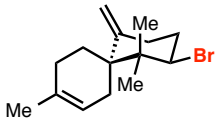
IR (film) ν_{max} 2974.2, 2961.0, 2945.8, 2908.7, 2876.1, 1700.8, 1454.7, 1214.7, 751.1, 668.1 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) 5.38 (s, 1H), 4.80 (dd, *J* = 12.6, 4.7 Hz, 1H), 2.92 – 2.72 (m, 1H), 2.59 – 2.44 (m, 1H), 2.43 – 2.10 (m, 5H), 2.00 – 1.74 (m, 3H), 1.58 (s, 3H), 1.15 (s, 3H), 0.90 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) 210.9, 131.2, 120.5, 61.1, 56.0, 45.0, 37.7, 33.8, 27.4, 27.2, 26.9, 24.3, 23.1, 17.6;

LC/MS (ESI) calcd. for $C_{14}H_{21}{}^{79}BrO$ $[M + H]^+$ 285.1, found 285.1;

$[\alpha]_D^{23}$ = −59.0 (c = 1.0, $CHCl_3$) (at 90% ee).



9

(+)-(6*R*,8*R*)-8-bromo-3,7,7-trimethyl-11-methylenespiro[5.5]undec-2-ene (9):

To an oven-dried microwave vial and stir bar, was added freshly activated Mg powder (40-80 mesh, 8 equiv, 1.403 mmol, 34.1 mg), then sealed and placed under an atmosphere of argon.[8] DCM (2 mL) was added and the vial was cooled to 0 °C. To the mixture was added $TiCl_4$ (2 equiv, 0.351 mmol, 0.351 mL of a 1 M solution in DCM) dropwise followed by the dropwise addition of a solution of spiroketone **21** (1 equiv, 0.175 mmol, 50 mg, prepared as a solution in 1 mL DCM + 1 mL THF). The mixture was allowed to stir for 30 minutes at 0 °C, during which the color changed from light green to dark green/black, and was then warmed to room temperature and stirred for an additional 1.5 hours. The mixture was then diluted with Et_2O (3 mL) and washed with 1M aq. HCl (20 mL). The layers were separated and the aqueous layer was washed with pentane (2 x 20 mL). The organic layers were combined, washed with saturated aq. $NaHCO_3$ (40 mL) followed by brine (40 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (silica gel, 100% pentane) to afford spirodiene **9** as a clear colorless oil in 43% yield (21.4 mg).

Physical properties: Clear, colorless oil;

R_f = 0.85 (silica gel, 10% EtOAc in hexanes, visualized with anisaldehyde stain);

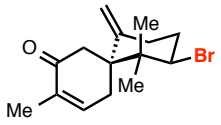
IR (film) ν_{max} 2945.4, 2908.8, 1637.9, 1449.6, 1389.7, 1368.2, 1213.1, 895.7, 876.2, 866.7, 775.8 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) 5.27 (m, 1H), 4.97 (dd, *J* = 1.7, 0.9 Hz, 1H), 4.76 (d, *J* = 1.7 Hz, 1H), 4.47 (dd, *J* = 8.5, 4.1 Hz, 1H), 2.47 – 2.20 (m, 4H), 2.19 – 2.05 (m, 3H), 1.89 (td, *J* = 21.5, 17.6, 10.0 Hz, 2H), 1.68 (ddd, *J* = 13.5, 11.5, 6.4 Hz, 1H), 1.58 (s, 3H), 1.07 (s, 3H), 1.04 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 147.5, 133.2, 118.7, 111.1, 66.2, 46.0, 43.1, 35.4, 31.4, 29.1, 28.2, 26.1, 24.4, 23.1, 21.0;

HR-LC/MS (ESI) calcd. for $C_{15}H_{23}{}^{79}Br$ $[M + H]^+$ 283.1061, found 283.1050;

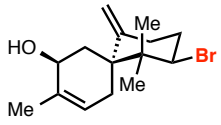
$[\alpha]_D^{23}$ = +8.9 (c = 1.2, $CHCl_3$) (at 90% ee).



7

(–)-dactylone (7):

Spirodiene **9** (1 equiv, 33.7 mg, 0.119 mmol) was charged to a 25 mL round bottom flask equipped with a stir bar and dissolved in 4.0 mL 1,4-dioxane. To the solution was added SeO_2 (1.5 equiv, 0.178 mmol, 19.8 mg) and the vessel was tightly sealed with a yellow cap and heated to 80 °C for 2 hours. The reaction mixture was cooled to room temperature, diluted with Et_2O (10 mL) and subsequently washed with saturated aq. Na_2SO_3 (10 mL), 10% aq. NaOH (w/w) (3 x 10 mL), and brine (10 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (silica gel, 0 to 10% EtOAc in hexanes gradient) to afford allylic alcohol **SI-2** in 42% yield (15.0 mg) as a single diastereomer (confirmed by nOe analysis).



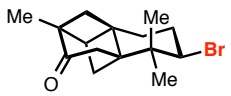
SI-2

Allylic alcohol **SI-2** (1 equiv, 0.021 mmol, 6.3 mg) was charged to a flame-dried 10 mL round bottom flask equipped with a stir bar, placed under an atmosphere of argon, and dissolved in 1 mL dry DMSO. To the solution was added solid IBX (2 equiv, 0.042 mmol, 11.8 mg) all at once. The mixture was stirred for 1 hour, diluted with Et_2O (10 mL) and sequentially washed with saturated aq. Na_2SO_3 (10 mL), saturated aq. $NaHCO_3$ (3 x 10 mL), and brine (10 mL). The organic layer was dried over Na_2SO_4, decanted, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (silica gel, 2% EtOAc (distilled) in hexanes (HPLC grade)) to afford (–)-dactylone (**7**) in 87% yield (5.4 mg).
For HPLC traces of the racemic and enantioenriched dactylone see **S38**.

Physical properties for 7: White solid;
R_f = 0.26 (silica gel, 10% EtOAc in hexanes, visualized with anisaldehyde stain);
IR (film) ν_{max} 2975.3, 2950.6, 1661.0, 1449.7, 1430.4, 1371.7, 1261.2, 1115.1, 900.9, 866.5 cm^{-1};
^{1}H NMR (500 MHz, $CDCl_3$) 6.50 (ddq, *J* = 4.6, 3.0, 1.5 Hz, 1H), 4.97 (d, *J* = 1.7 Hz, 1H), 4.60 (s, 1H), 4.52 (dd, *J* = 12.7, 4.5 Hz, 1H), 2.74 (dt, *J* = 16.3, 1.2 Hz, 1H), 2.65 (dt, *J* = 4.9, 1.6 Hz, 2H), 2.56 (d, *J* = 16.4 Hz, 1H), 2.35 (tdt, *J* = 13.7, 5.2, 1.6 Hz, 1H), 2.25 (dtd, *J* = 12.3, 4.8, 2.1 Hz, 1H), 2.16 (ddd, *J* = 13.9, 5.3, 2.1 Hz, 1H), 2.09 (dtd, *J* = 13.6, 12.7, 5.3 Hz, 1H), 1.73 (q, *J* = 1.8 Hz, 3H), 1.19 (s, 3H), 0.99 (s, 3H);
^{13}C NMR (125 MHz, $CDCl_3$) 199.5, 145.9, 141.4, 135.3, 114.2, 63.1, 51.2, 44.0, 43.1, 35.2, 33.5, 29.7, 25.0, 17.5, 15.3;
LC/MS (ESI) calcd. for $C_{15}H_{21}{}^{79}BrO$ $[M + H]^+$ 297.1, found 297.1;

$[\alpha]_D^{25}$ = –145.8 (c = 0.04, MeOH) (at 90% ee); lit[9] $[\alpha]_D^{20}$ = –145 (c = 0.1, MeOH).[a]

[a] We have provided an HPLC trace of racemic and synthetic 90% ee (–)-dactylone (**S40**).



8

(+)-aplydactone 8

To a 16x100 mm test tube was added (−)-dactylone (0.018 mmol, 5.4 mg) as a solution in benzene (5.4 mL). The test tube was sealed with a rubber septum and the mixture was degassed with argon for 10 minutes. The septum was wrapped with aluminum foil and the vessel was placed in a Luzchem photoreactor and irradiated with 350 nm light for 36 hours. The mixture was concentrated under reduced pressure and purified by flash column chromatography (silica gel, 2% EtOAc in hexanes) to afford (+)-aplydactone in 98% yield (5.3 mg). Recrystallization via slow evaporation from hexanes afforded X-ray quality single crystals.

Physical properties: White crystalline solid;

m.p. = 141–145 ˚C (recrystallized from hexanes); lit.[10] = 195–196 ˚C;

R_f = 0.26 (silica gel, 10% EtOAc in hexanes, visualized with anisaldehyde stain);

IR (film) ν_{max} 2956.9, 2920.5, 2845.1, 1712,2, 1456.6, 1367.1, 668.5, 650.4 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) 4.33 (m, 1H), 2.91 (dd, *J* = 16.6, 2.8 Hz, 1H), 2.37 (m, 1H), 2.35 (d, *J* = 16.6 Hz, 1H), 2.34 (d, *J* = 11.0 Hz, 1H), 2.14 (d, *J* = 5.6 Hz, 1H), 1.90 – 2.05 (m, 4H), 1.84 (d, *J* = 11.0 Hz, 1H), 1.42 (d, *J* = 11.4 Hz, 1H), 1.11 (s, 3H), 1.01 (s, 3H), 0.93 (s, 3H);

^{1}H NMR (600 MHz, C_6D_6) 3.89 (dd, *J* = 11.5, 4.3 Hz, 1H), 2.51 (dd, *J* = 16.4, 2.8 Hz, 1H), 2.13 (d, *J* = 16.4 Hz, 1H), 1.80 (d, *J* = 10.8 Hz, 1H), 1.64 – 1.75 (m, 3H), 1.58 (d, *J* = 5.6 Hz, 1H), 1.32 (m, 2H), 1.29 (d, *J* = 10.6 Hz, 1H), 1.10 (s, 3H), 1.05 (d, *J* = 11.3 Hz, 1H), 0.75 (s, 3H), 0.70 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) 213.5, 65.5, 49.2, 47.1, 45.5, 42.9, 40.7, 40.4, 38.2, 34.0, 31.9, 30.7, 22.9, 18.4, 18.3;

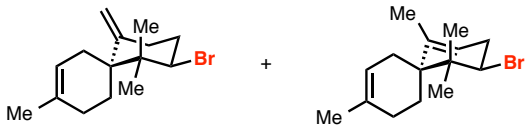
^{13}C NMR (125 MHz, C_6D_6) 211.0, 66.3, 49.3, 47.5, 45.9, 43.4, 41.0, 40.6, 38.7, 34.3, 32.1, 31.4, 23.3, 19.1, 18.7;

LC/MS (ESI) calcd. for $C_{15}H_{21}{}^{79}BrO$ $[M + H]^+$ 297.1, found 297.1;

$[\alpha]_D^{23}$ = +13.3 (c = 0.2, EtOH) (at 90% ee); lit[10] **$[\alpha]_D^{20}$** = +33 (c = 0.2, EtOH). [b]

[b] At present the observed discrepancy in optical rotation between our synthetic material and data from the natural isolate cannot be rectified. A natural sample could not be obtained for comparison. We have obtained an X-ray crystal structure of synthetic (+)-**8** (see S44).

4. Synthesis of (–)-α- and (–)-*ent*-β-bromochamigrene



4 **3**

(–)-α-bromochamigrene (3) and **(–)-*ent*-β-bromochamigrene (4):**

To a flame-dried conical microwave vial equipped with a magnetic stir bar was added a solution of anhydrous $CeCl_3$ (5.4 equiv, 0.263 mmol, 263 µL of a 1 M solution in THF) under an argon atmosphere and was further diluted with an additional 600 µL of dry THF.[11] The mixture was cooled to −78 °C and MeLi (4.8 equiv, 0.237 mmol, 210 µL of a 1.15 M solution in Et_2O) was added dropwise. The mixture was stirred for 1 hour at this temperature resulting in a milky light-yellow suspension. Spiroketone **22** (1 equiv, 0.049 mmol, 14 mg) was added dropwise via syringe as a solution in 600 µL THF. The syringe was rinsed with THF (2 x 100 µL) and the mixture was stirred for 15 minutes at −78 °C and then warmed to 0 °C and stirred for an additional 30 minutes. The mixture was diluted with ether and quenched with saturated aq. NH_4Cl (2 mL). The layers were separated and the aqueous phase was extracted with Et_2O (5 mL). The organic phases were combined, washed sequentially with saturated aq. $NaHCO_3$ (10 mL) and brine (10 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The crude mixture was used immediately in the next step without further purification.

The crude mixture was placed under an argon atmosphere and dissolved in dry DCM (600 µL). To the solution was added freshly distilled triethylamine (5.4 equiv, 0.263 mmol, 40 µL) and then cooled to –78 °C. Thionyl chloride (2.1 equiv, 0.105 mmol, 7.7 µL prepared as a stock solution in 150 µL DCM) was added dropwise and the mixture was allowed to stir for 1 hour at –78 °C. The mixture was then warmed to 0 °C and stirred for an additional 15 minutes before being quenched with 100 µL methanol. The mixture was diluted with DCM (5 mL) and sequentially washed with 1M aq. HCl (5 mL), saturated aq. $NaHCO_3$ (5 mL), and brine (5 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (silica gel, 100% pentane) to afford a 1.0 : 1.5 mixture of α : β in 78% yield (10.8 mg). Analytical samples of **3** and **4** were obtained by careful preparative thin-layer chromatography (100% hexanes).

Physical properties for (–)-α-bromochamigrene (3): Clear colorless oil;

R_f = 0.52 (silica gel, 100% pentane, visualized with anisaldehyde stain);

IR (film) ν_{max} 2972.8, 2924.0, 2846.2, 1447.0, 1434.5, 1369.2, 1072.2, 1048.5, 1019.0, 843.7, 790.2, 668.6 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) 5.43 (dq, *J* = 4.9, 1.5 Hz, 1H), 5.19 (ddd, *J* = 4.4, 3.0, 1.5 Hz, 1H), 4.75 (dd, *J* = 10.9, 6.8 Hz, 1H), 2.65 (dddd, *J* = 18.1, 6.6, 4.2, 2.0 Hz, 1H), 2.51 – 2.60 (m, 1H), 2.25 (dt, *J* = 18.1, 2.7

Hz, 1H), 1.86 – 1.96 (m, 3H), 1.79 (ddd, *J* = 12.4, 10.9, 6.9 Hz, 1H), 1.64 (ddt, *J* = 2.9, 2.2, 1.0 Hz, 6H), 1.58 – 1.64 (m, 1H), 1.10 (s, 3H), 0.93 (s, 3H);

^{1}H NMR (600 MHz, C_6D_6) 5.30 (s, 1H), 4.94 (m, 1H), 4.58 (dd, *J* = 10.4, 7.3 Hz, 1H), 2.54 (m, 2H), 2.04 (dt, *J* = 18.4, 2.8 Hz, 1H), 1.62 – 1.83 (m, 3H), 1.57 (m, 6H), 1.50 (td, *J* = 12.3, 5.7 Hz, 1H), 1.22 (ddd, *J* = 10.5, 4.9, 2.4 Hz, 1H), 1.05 (s, 3H), 0.94 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) 140.7, 134.0, 122.1, 121.4, 63.3, 43.8, 41.7, 36.5, 30.9, 29.7, 28.6, 24.9, 23.4 (2C), 16.9;

^{13}C NMR (125 MHz, C_6D_6) 140.9, 134.2, 123.1, 122.3, 63.5, 44.4, 42.2, 37.3, 31.5, 30.5, 29.3, 25.5, 24.01, 23.98, 17.6;

HR-LC/MS (ESI) calcd. for $C_{15}H_{23}{}^{79}Br$ $[M + H]^+$ 283.1061, found 283.1058;

$[\alpha]_D^{25}$ = –114.9 (c = 0.16, $CHCl_3$) (at 90% ee); lit[12] **$[\alpha]_D$** = –71.1 (c = 0.18, $CHCl_3$).[c]

Physical properties for (–)-β-bromochamigrene (4): Clear colorless oil;

R_f = 0.42 (silica gel, 100% pentane, visualized with anisaldehyde stain);

IR (film) ν_{max} 2942.3 (br), 2876.4, 2854.7, 1638.1, 1453.0, 1389.2, 1369.2, 1019.9, 894.8, 1019.9, 894.8, 870.4, 777.0 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) 5.28 (m, 1H), 4.93 (t, *J* = 1.8 Hz, 1H), 4.65 (dd, *J* = 12.9, 4.5 Hz, 1H), 4.61 (t, *J* = 1.4 Hz, 1H), 2.36 (tdt, *J* = 13.8, 4.9, 1.3 Hz, 1H), 2.23 (m, 2H), 2.14 (ddd, *J* = 13.7, 4.9, 2.3 Hz, 1H), 2.05 (dtd, *J* = 13.9, 12.8, 4.9 Hz, 1H), 2.04 (d, *J* = 15.1 Hz, 1H), 1.87 (m, 1H), 1.75 (m, 1H), 1.60(m, 2H), 1.57 (dd, *J* = 2.6, 1.4 Hz, 3H), 1.10 (s, 3H), 0.93 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) 145.6, 132.7, 119.7, 112.6, 66.2, 47.0, 42.7, 35.7, 33.0, 30.3, 27.5, 25.6, 23.8, 23.2, 17.5;

HR-LC/MS (ESI) calcd. for $C_{15}H_{23}{}^{79}Br$ $[M + H]^+$ 283.1061, found 283.1049;

$[\alpha]_D^{23}$ = –65.2 (c = 0.1, $CHCl_3$) (at 90% ee); lit[13] for *ent*-**4** **$[\alpha]_D^{22}$** = +70.5 (c = 1.15, $CHCl_3$).

[c] At the present time the observed discrepancies in data (optical rotation) between our synthetic material and data from the natural isolate cannot be rectified. A natural sample could not be obtained for comparison.

5. NMR Comparisons of Synthetic and Isolated Natural Products

Table SI-1. ^{1}H NMR comparison for (−)-dactylone.[9]

Synthetic (−)-dactylone ($CDCl_3$, 500 MHz)	**Natural (−)-dactylone ($CDCl_3$)[d]**
0.99 (s, 3H)	0.99 (s, 3H)
1.19 (s, 3H)	1.19 (s, 3H)
1.73 (q, *J* = 1.8 Hz, 3H)	1.73 (d, *J* = 1.8 Hz, 3H)
2.09 (dtd, *J* = 13.6, 12.7, 5.3 Hz, 1H)	2.11 (m, 1H)
2.16 (ddd, *J* = 13.9, 5.3, 2.1 Hz, 1H)	2.17 (m, 1H)
2.25 (dtd, *J* = 12.3, 4.8, 2.1 Hz, 1H)	2.26 (m, 1H)
2.35 (tdt, *J* = 13.7, 5.2, 1.6 Hz, 1H)	2.37 (m, 1H)
2.56 (d, *J* = 16.4 Hz, 1H)	2.57 (d, *J* = 16.5 Hz, 1H)
2.65 (dt, *J* = 4.9, 1.6 Hz, 2H)	2.65 (m, 2H)
2.74 (dt, *J* = 16.3, 1.2 Hz, 1H)	2.74 (br. d, *J* = 16.5 Hz, 1H)
4.52 (dd, *J* = 12.7, 4.5 Hz, 1H)	4.52 (dd, *J* = 12.5, 4.5 Hz, 1H)
4.60 (s, 1H)	4.61 (s, 1H)
4.97 (d, *J* = 1.7 Hz, 1H)	4.98 (br. d, *J* = 1.5 Hz, 1H)
6.50 (ddq, *J* = 4.6, 3.0, 1.5 Hz, 1H)	6.50 (m, 1H)

Table SI-2. ^{13}C NMR comparison for (−)-dactylone.[9]

Synthetic (−)-dactylone ($CDCl_3$, 125 MHz)	**Natural (−)-dactylone ($CDCl_3$)[d]**
15.3	15.3
17.5	17.7
25.0	25.1
29.7	30.0
33.5	33.7
35.2	35.5
43.1	43.2
44.0	44.2
51.2	51.4
63.1	63.0
114.2	114.0
135.3	135.5
141.4	140.7
145.9	146.1
199.5	198.8

[d] The reported spectra were taken at 250 or 300 MHz but were not specified.[9]

Table SI-3. ^{1}H NMR comparison for (+)-aplydactone in $CDCl_3$.[10]

Synthetic (+)-aplydactone ($CDCl_3$, 500 MHz)	**Natural (+)-aplydactone ($CDCl_3$, 300 MHz)**
0.93 (s, 3H)	0.93 (s, 3H)
1.01 (s, 3H)	1.02 (s, 3H)
1.11 (s, 3H)	1.12 (s, 3H)
1.42 (d, *J* = 11.4 Hz, 1H)	1.43 (d, *J* = 11.3 Hz, 1H)
1.84 (d, *J* = 11.0 Hz, 1H)	1.83 (d, *J* = 11.0 Hz, 1H)
1.90 – 2.05 (m, 4H)	1.89 – 2.08 (m, 4H)
2.14 (d, *J* = 5.6 Hz, 1H)	2.14 (d, *J* = 5.5 Hz, 1H)
2.34 (d, *J* = 11.0 Hz, 1H)	2.34 (d, *J* = 11 Hz, 1H)
2.35 (d, *J* = 16.6 Hz, 1H)	2.36 (d, *J* = 17.1 Hz, 1H)
2.37 (m (obsc), 1H)	2.37 (ddd, *J* = 11.3, 5.5, 3.0 Hz, 1H)
2.91 (dd, *J* = 16.6, 2.8 Hz, 1H)	2.90 (dd, *J* = 17.1, 3.0 Hz, 1H)
4.33 (m, 1H)	4.35 (m, 1H)

Table SI-4. ^{13}C NMR comparison for (+)-aplydactone.[10]

Synthetic (+)-aplydactone ($CDCl_3$, 125 MHz)	**Natural (+)-aplydactone ($CDCl_3$, 75 MHz)**
18.3	18.4
18.4	18.5
22.9	23.0
30.7	30.9
31.9	32.0
34.0	34.1
38.2	38.3
40.4	40.6
40.7	40.9
42.9	43.1
45.5	45.7
47.1	47.2
49.2	49.3
65.5	65.5
213.5	213.4

Table SI-5. ^{1}H NMR comparison for (+)-aplydactone in C_6D_6.[10]

Synthetic (+)-aplydactone (C_6D_6, 500 MHz)	**Natural (+)-aplydactone (C_6D_6, 300 MHz)**
0.70 (s, 3H)	0.70 (s, 3H)
0.75 (s, 3H)	0.75 (s, 3H)
1.05 (d, *J* = 11.3 Hz, 1H)	1.05 (d, *J* = 11.3 Hz, 1H)
1.10 (s, 3H)	1.09 (s, 3H)
1.29 (d, *J* = 10.6 Hz, 1H)	1.29 (d, *J* = 11.0 Hz, 1H)
1.32 (m, 2H)	1.30 (m, 2H)
1.58 (d, *J* = 5.6 Hz, 1H)	1.58 (d, *J* = 5.6 Hz, 1H)
1.64 – 1.75 (m, 3H)	1.69 (m, 2H)
	1.72 (ddd, *J* = 11.3, 5.6, 2.7, 1H)
1.80 (d, *J* = 10.8 Hz, 1H)	1.81 (d, *J* = 11.0 Hz, 1H)
2.13 (d, *J* = 16.4 Hz, 1H)	2.12 (d, *J* = 16.5 Hz, 1H)
2.51 (dd, *J* = 16.4, 2.8 Hz, 1H)	2.51 (dd, *J* = 16.5, 2.7 Hz, 1H)
3.89 (dd, *J* = 11.5, 4.3 Hz, 1H)	3.90 (m, 1H)

Table SI-6. ^{13}C NMR comparison for (+)-aplydactone.[10]

Synthetic (+)-aplydactone (C_6D_6 *ref = 128.5 ppm*, **125 MHz)**	**Synthetic (+)-aplydactone (C_6D_6,** *ref =128.206*, **125 MHz)**	**Natural (+)-aplydactone (C_6D_6,** *ref =128.206*, **75 MHz)**
18.7	18.4	18.3
19.1	18.8	18.6
23.3	23.0	22.9
31.4	31.1	31.0
32.1	31.8	31.7
34.3	34.0	33.8
38.7	38.4	38.2
40.6	40.3	40.2
41.0	40.7	40.6
43.4	43.1	42.9
45.9	45.6	45.5
47.5	47.2	47.1
49.3	49.0	48.9
66.3	66.0	65.7
211.0	210.7	210.4

Note: synthetic (+)-aplydactone C_6D_6 was referenced to the central benzene peak 128.5 ppm in the ^{13}C spectra. The original isolation C_6D_6 spectra was reported relative to the central benzene peak at 128.2 ppm.

Table SI-7. ^{1}H NMR comparison for (–)-α-bromochamigrene **3** in C_6D_6.[14]

Synthetic (–)-α-bromochamigrene (C_6D_6, 500 MHz)	**Natural (–)-α-bromochamigrene (C_6D_6, 300 MHz)**
0.94 (s, 3H)	0.94 (s, 3H)
1.05 (s, 3H)	1.05 (s, 3H)
1.22 (ddd, *J* = 10.5, 4.9, 2.4 Hz, 1H)	1.23 (tdd, *J* = 12.7, 5.0, 2.3 Hz, 1H)
1.50 (td, *J* = 12.3, 5.7 Hz, 1H)	1.50 (ddd, *J* = 12.7, 11.5, 5.9 Hz, 1H)
1.57 (m, 6H)	1.57 (br. s, 6H)
1.62 – 1.83 (m, 3H)	1.68 (br. dd, *J* = 18.1, 3.7 Hz, 1H)
	1.71 (m, 2H)
2.04 (dt, *J* = 18.4, 2.8 Hz, 1H)	2.04 (br. dd, *J* = 18.1, 5.0 Hz, 1H)
2.54 (m, 2H)	2.51 (qddd, *J* = 7.8, 3.8, 1.5 Hz, 1H)
	2.57 (qddd, *J* = 17.8, 9.7, 3.5, 1.5 Hz, 1H)
4.58 (dd, *J* = 10.4, 7.3 Hz, 1H)	4.58 (dd, *J* = 9.7, 7.8 Hz, 1H)
4.94 (m, 1H)	4.94 (qt, *J* = 3.5, 1.5 Hz, 1H)
5.30 (m, 1H)	5.33 (m, 1H)

Table SI-8. ^{13}C NMR comparison for (–)-α-bromochamigrene **3** in C_6D_6.[14]

Synthetic (–)-α-bromochamigrene (C_6D_6, 125 MHz)	**Natural (–)-α-bromochamigrene (C_6D_6, 75 MHz)**
17.6	17.8
23.98	24.2
24.01	24.2
25.5	25.6
29.3	29.5
30.5	30.7
31.5	31.7
37.3	37.5
42.2	42.5
44.4	44.6
63.5	63.7
122.3	122.5
123.1	123.3
134.2	134.4
140.9	134.4[e]

Note: synthetic (–)-α-bromochamigrene C_6D_6 was referenced to the central benzene peak 128.5 ppm in the ^{13}C spectra. The original isolation C_6D_6 spectra was reported relative to residual TMS at 0 ppm.

[e] The authors report a peak at 134.41 ppm twice in the ^{13}C NMR spectra which we believe to have been done in error. We observe a peak at 140.9 ppm and have unambiguously determined its assignment through HMBC analysis (see S36-37).

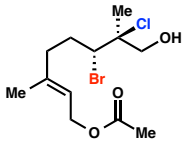
Table SI-9. ^{1}H NMR comparison for (−)-β-bromochamigrene **4** in $CDCl_3$.[13]

Synthetic (−)-β-bromochamigrene ($CDCl_3$, 500 MHz)	**Natural (−)-β-bromochamigrene ($CDCl_3$, 300 MHz)**
0.93 (s, 3H)	0.94 (s, 3H)
1.10 (s, 3H)	1.10 (s, 3H)
1.57 (dd, *J* = 2.6, 1.4 Hz, 3H)	1.54 (br. s, 3H)
1.60 (m, 2H)	1.58 (m, 1H)
	1.62 (m, 1H)
1.75 (m, 1H)	1.76 (m, 1H)
1.87 (m, 1H)	1.88 (dm, *J* = 10.8 Hz, 1H)
2.04 (d, *J* = 15.1 Hz, 1H)	2.04 (br. d, *J* = 15.3 Hz, 1H)
2.05 (dtd, *J* = 13.9, 12.8, 4.9 Hz, 1H)	2.06 (dddd, *J* = 13.8, 12.8, 12.7, 4.8 Hz, 1H)
2.14 (ddd, *J* = 13.7, 4.9, 2.3 Hz, 1H)	2.14 (ddd, *J* = 13.8, 4.8, 2.2 Hz, 1H)
2.23 (m, 2H)	2.23 (dddd, *J* = 12.8, 5.2, 4.4, 2.2 Hz, 2H)
2.36 (tdt, *J* = 13.8, 4.9, 1.3 Hz, 1H)	2.37 (ddd, *J* = 13.8, 13.8, 5.2 Hz, 1H)
4.61 (t, *J* = 1.4 Hz, 1H)	4.61 (br. s, 1H)
4.65 (dd, *J* = 12.9, 4.5 Hz, 1H)	4.65 (dd, *J* = 12.7, 4.4 Hz, 1H)
4.93 (t, *J* = 1.8 Hz, 1H)	4.93 (t, *J* = 1.8 Hz, 1H)
5.28 (m, 1H)	5.28 (br. s, 1H)

Table SI-10. ^{13}C NMR comparison for (−)-β-bromochamigrene **4** in $CDCl_3$.[13]

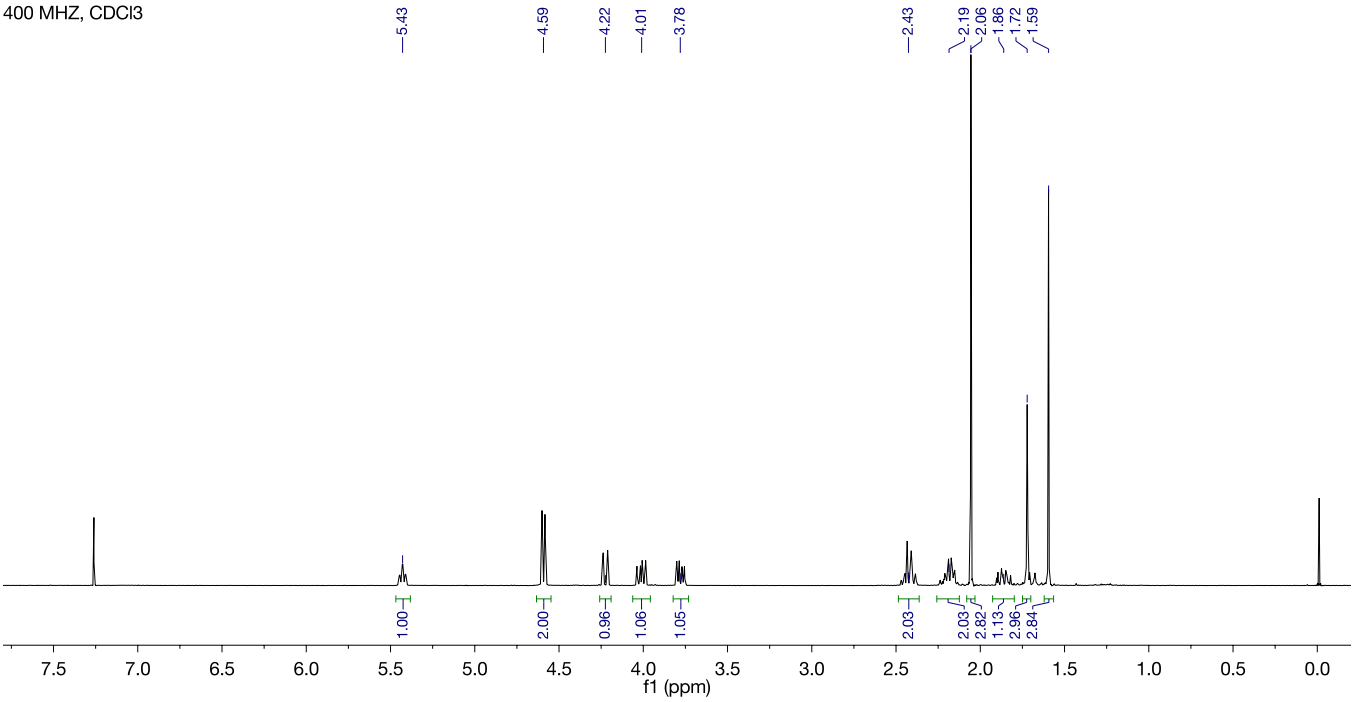
Synthetic (−)-β-bromochamigrene ($CDCl_3$, 125 MHz)	**Natural (−)-β-bromochamigrene ($CDCl_3$, 75.5 MHz)**
17.5	17.5
23.2	23.1
23.8	23.9
25.6	25.6
27.5	27.5
30.3	30.3
33.0	33.9
35.7	35.7
42.7	42.7
47.0	47.0
66.2	66.1
112.6	112.6
119.7	119.7
132.7	132.7
145.6	145.6

6. ^{1}H and ^{13}C NMR Spectra

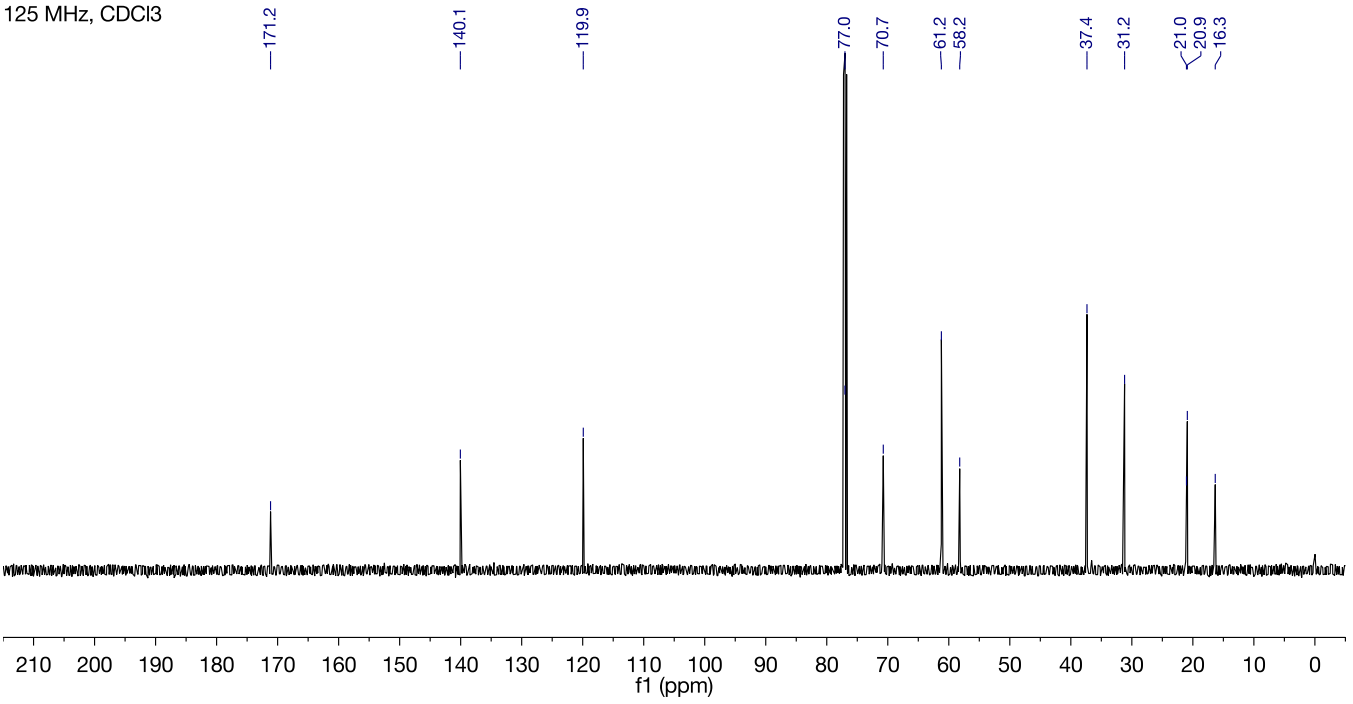


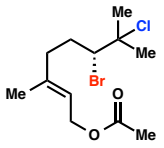
15

400 MHZ, CDCl3



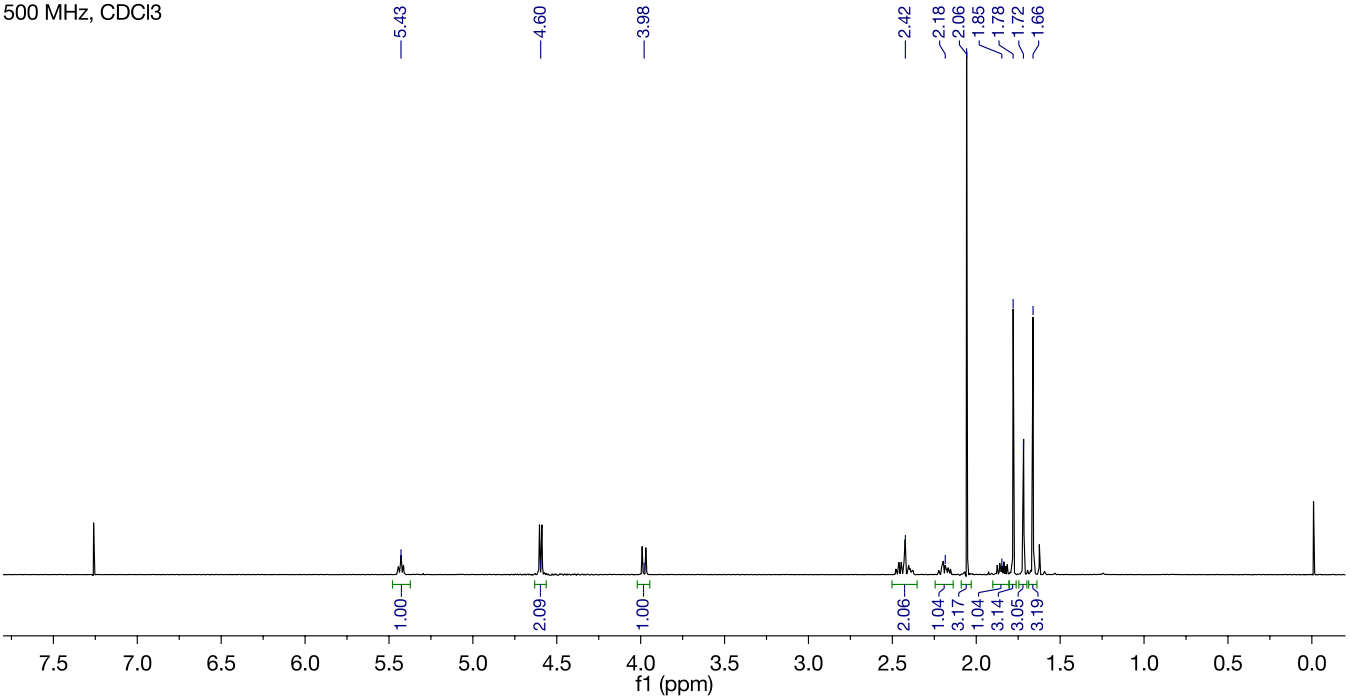
125 MHz, CDCl3



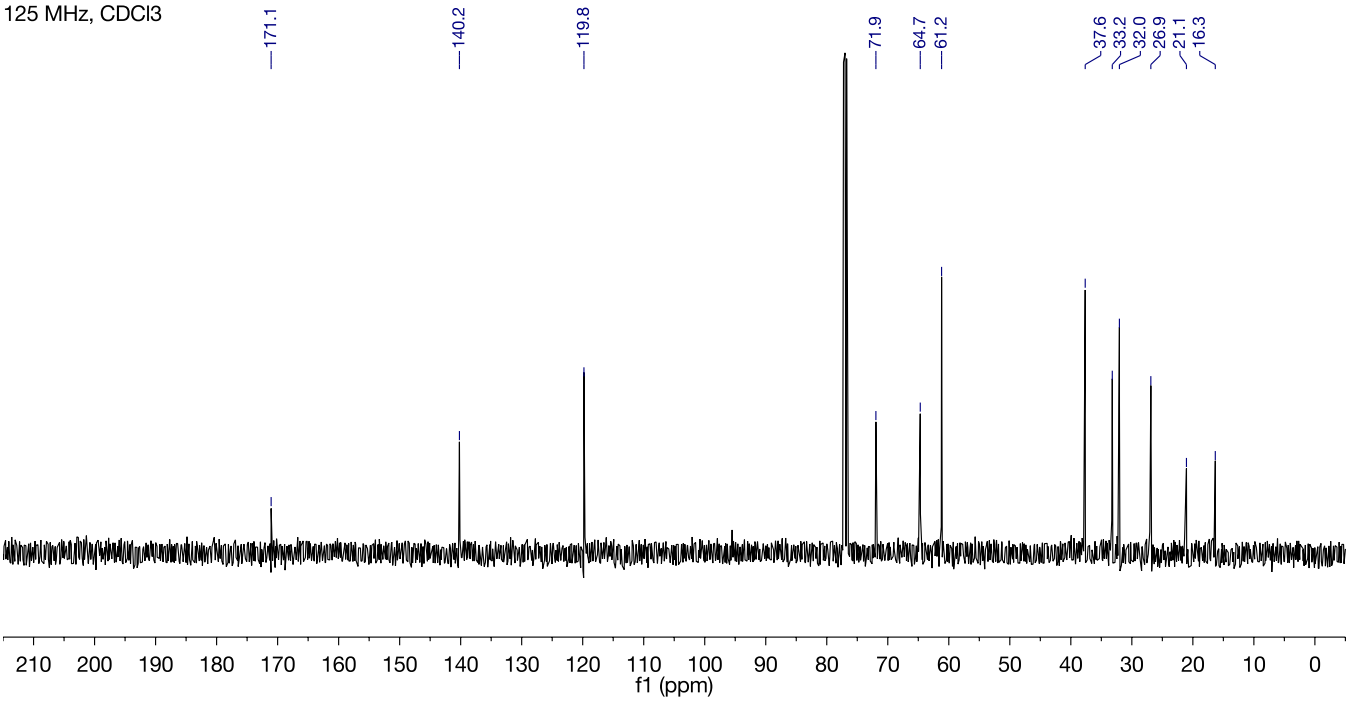


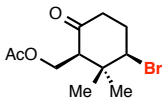
16

500 MHz, CDCl3



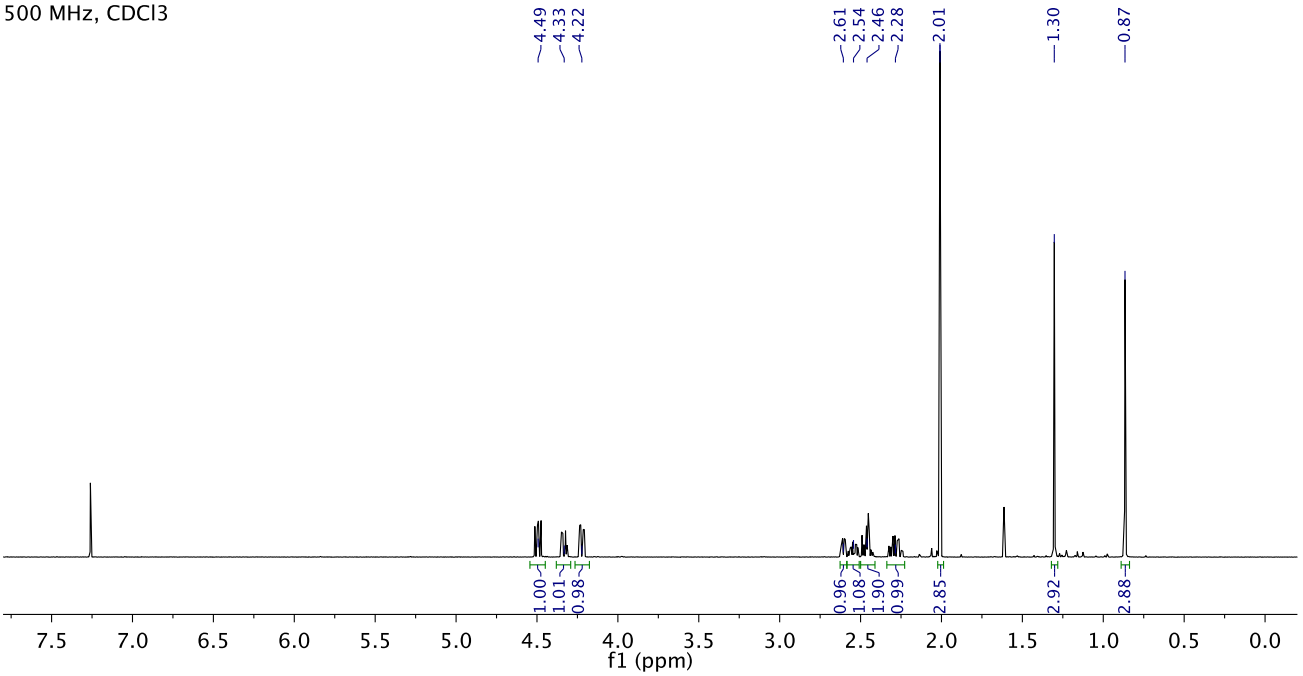
125 MHz, CDCl3



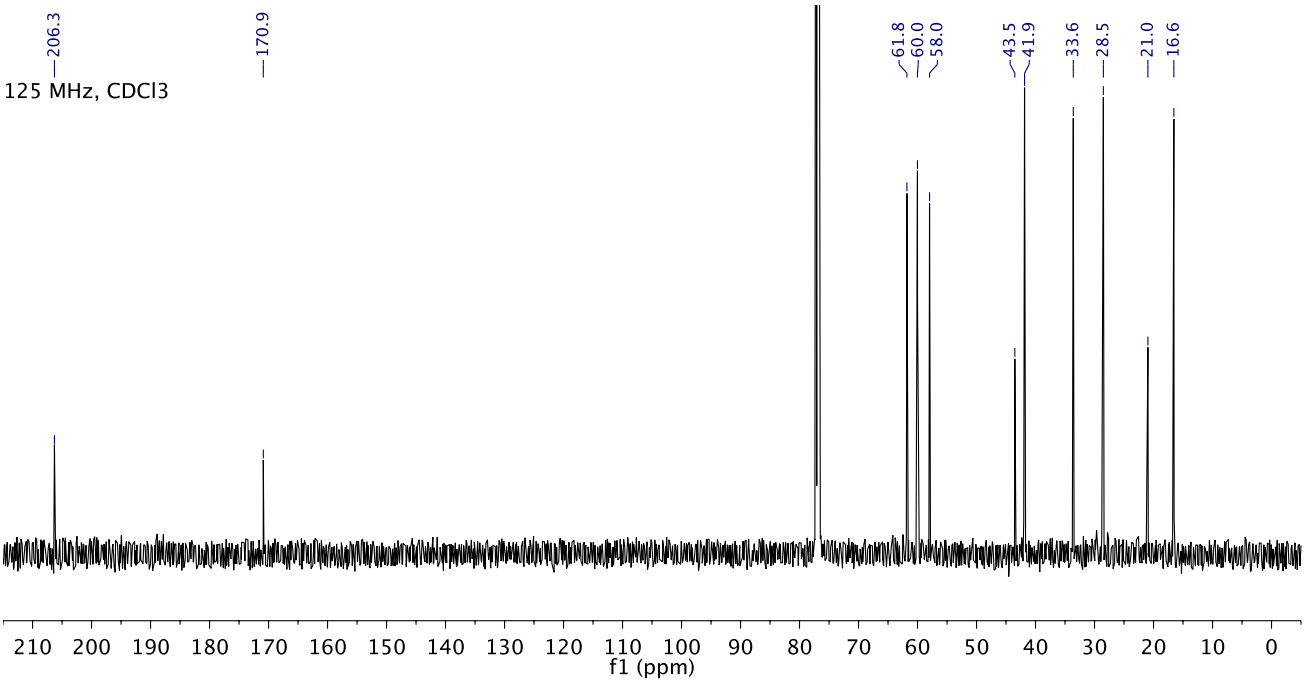


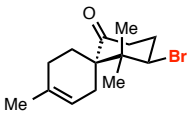
18

500 MHz, CDCl3

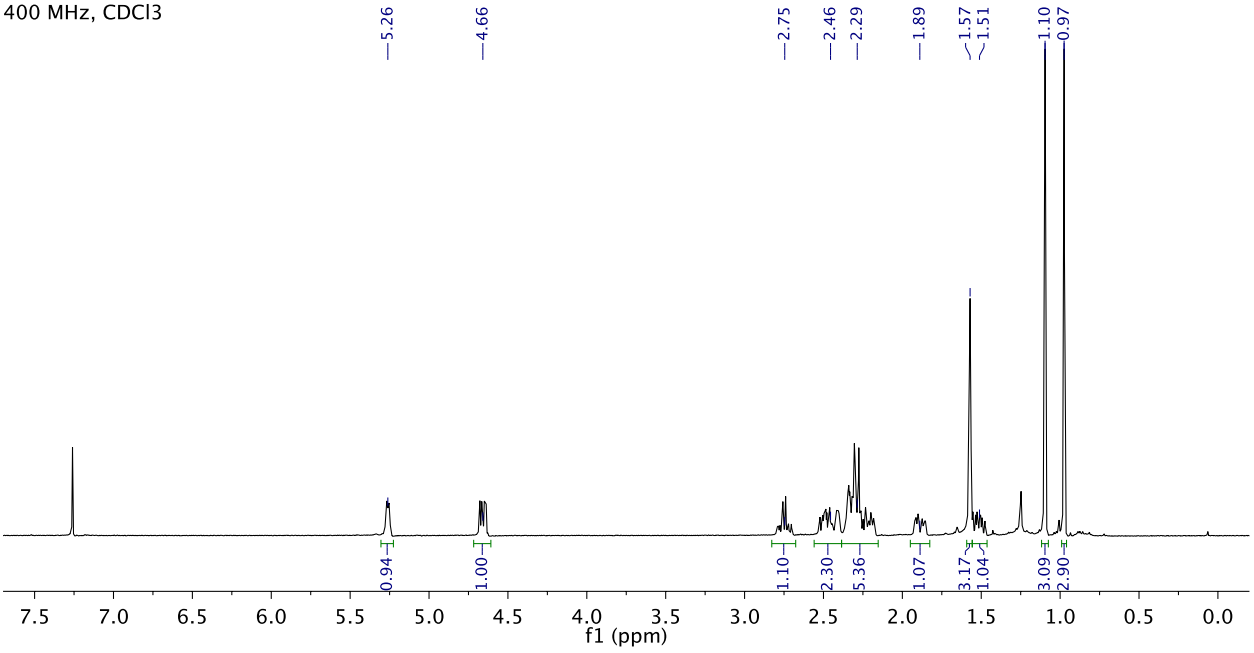


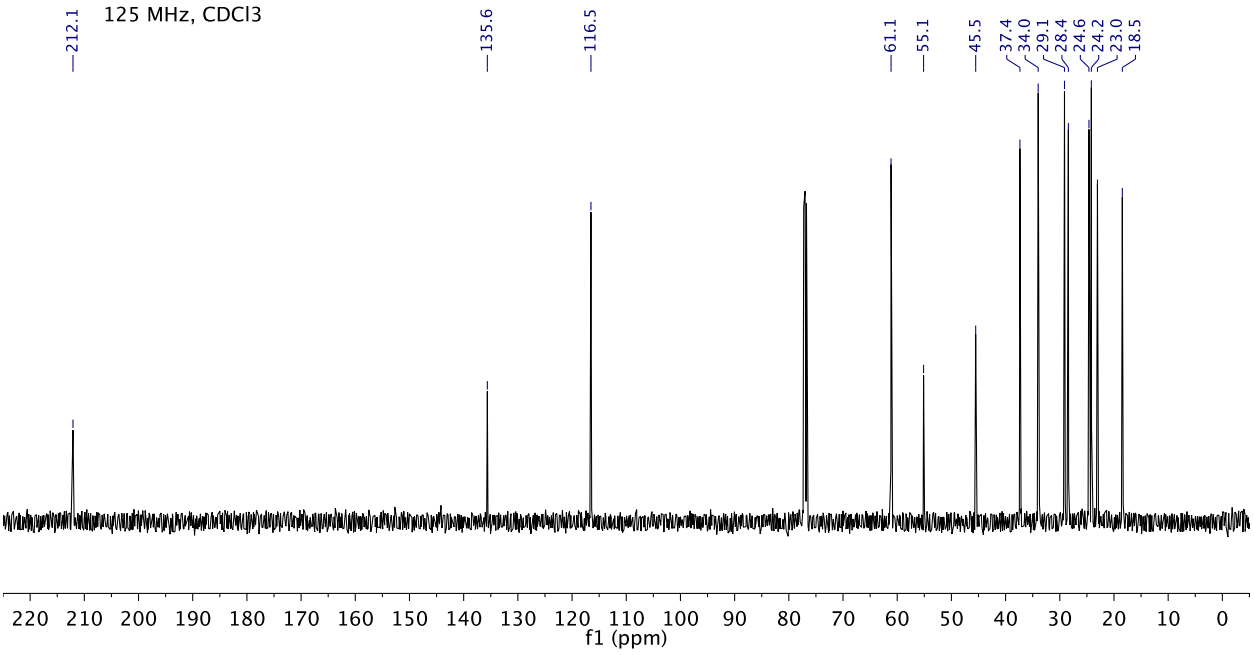
125 MHz, CDCl3

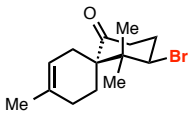



O
Me
Br
Me
Me

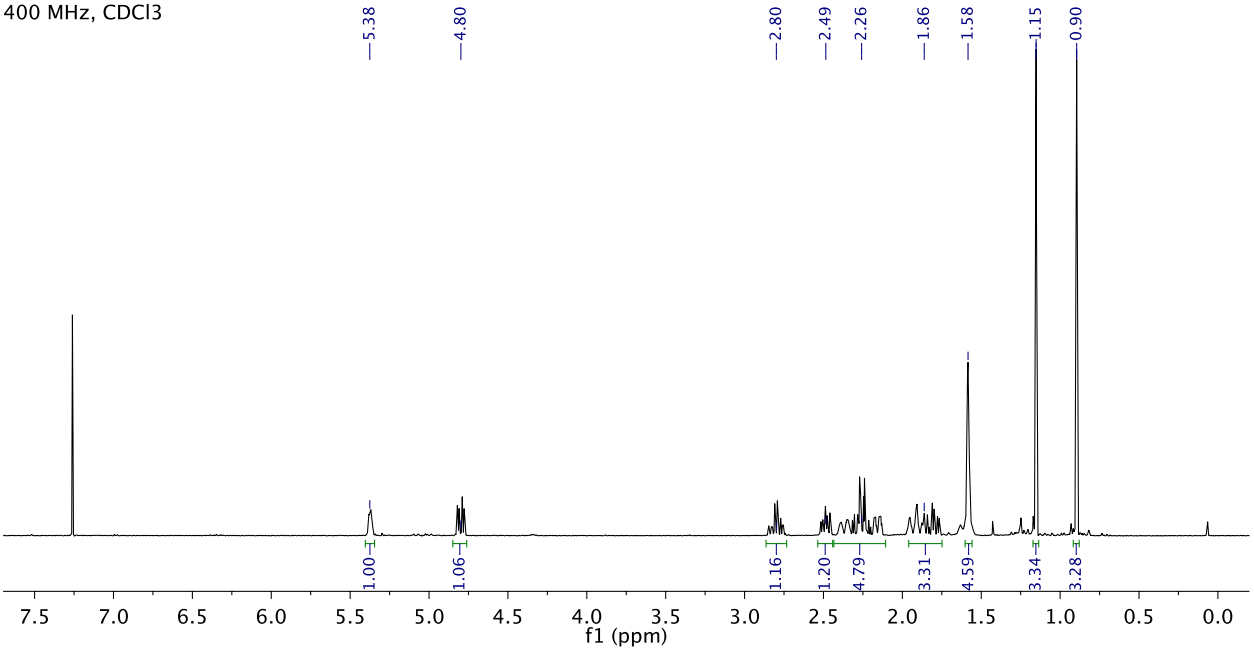
21

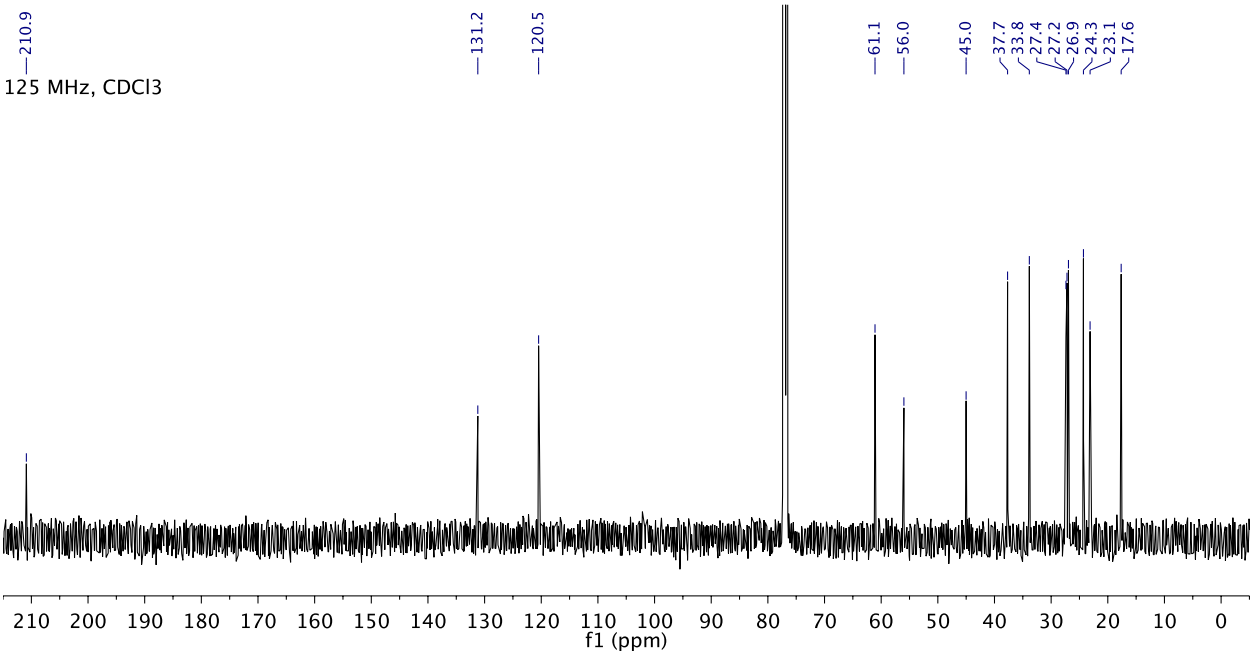

400 MHz, CDCl3
5.26
4.66
2.75
2.46
2.29
1.89
1.57
1.51
1.10
0.97
0.94
1.00
1.10
2.30
5.36
1.07
3.17
1.04
3.09
2.90
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

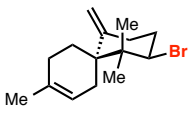

125 MHz, CDCl3
212.1
135.6
116.5
61.1
55.1
45.5
37.4
34.0
29.1
28.4
24.6
24.2
23.0
18.5
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
Me
Br
Me
Me

22

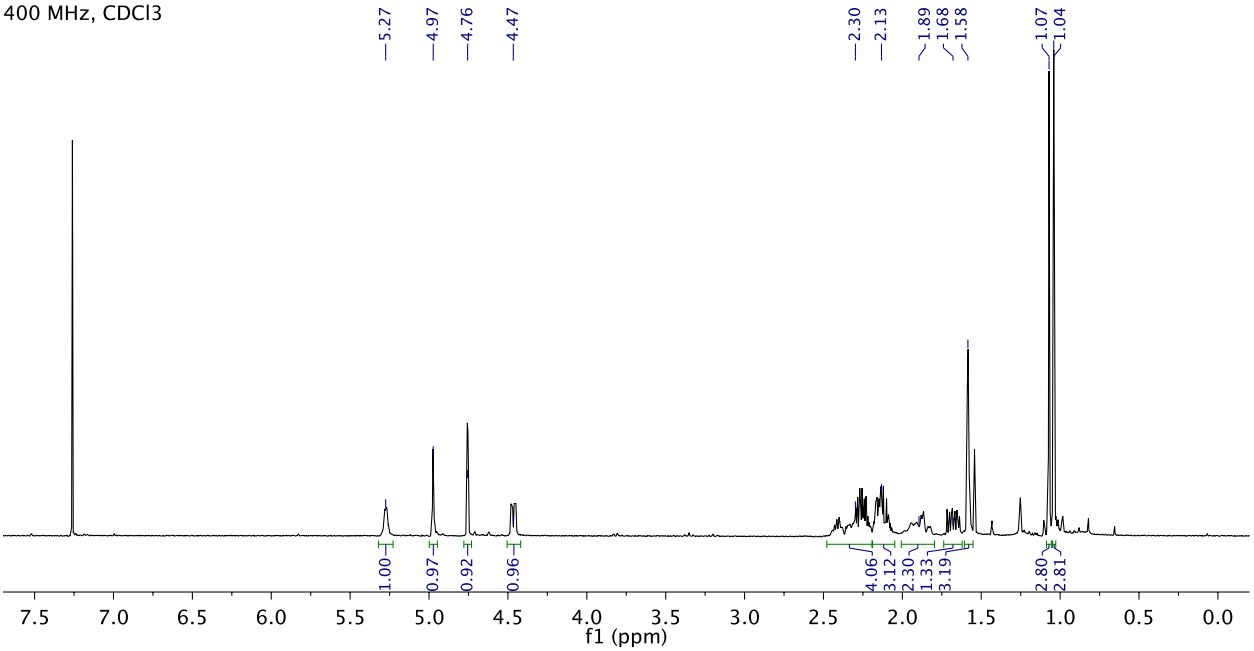

400 MHz, CDCl3
5.38
4.80
2.80
2.49
2.26
1.86
1.58
1.15
0.90
1.00
1.06
1.16
1.20
4.79
3.31
4.59
3.34
3.28
f1 (ppm)


125 MHz, CDCl3
210.9
131.2
120.5
61.1
56.0
45.0
37.7
33.8
27.4
27.2
26.9
24.3
23.1
17.6
f1 (ppm)

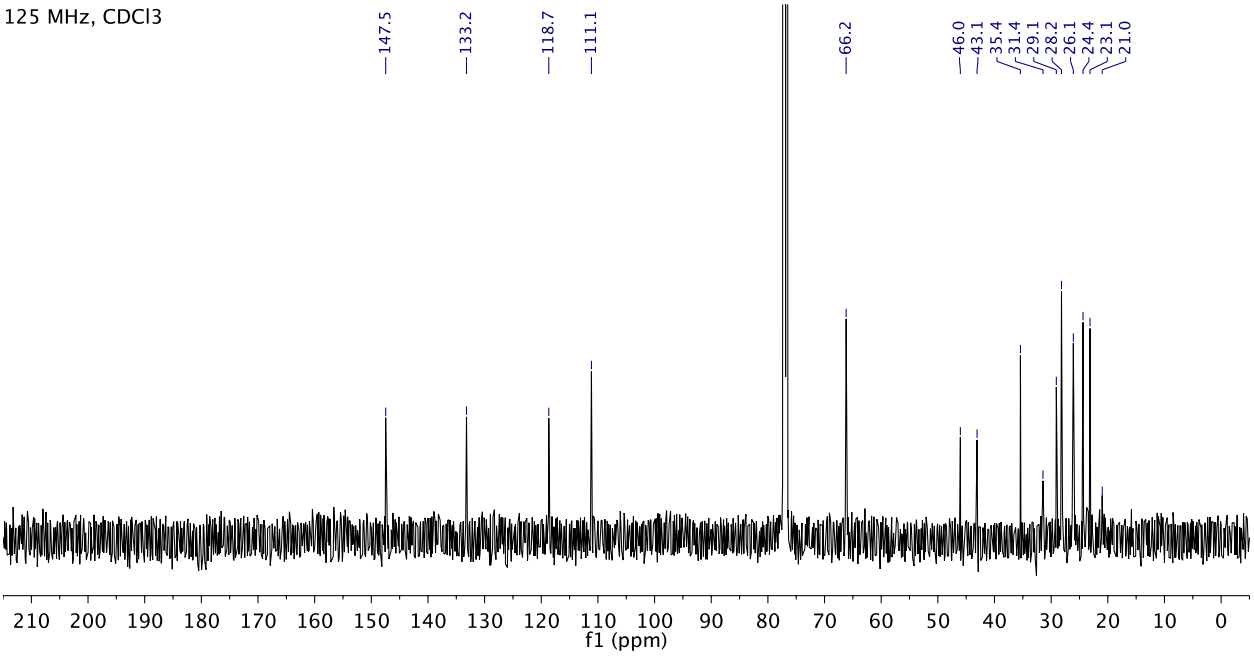


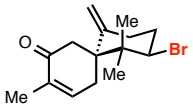
9

400 MHz, CDCl3

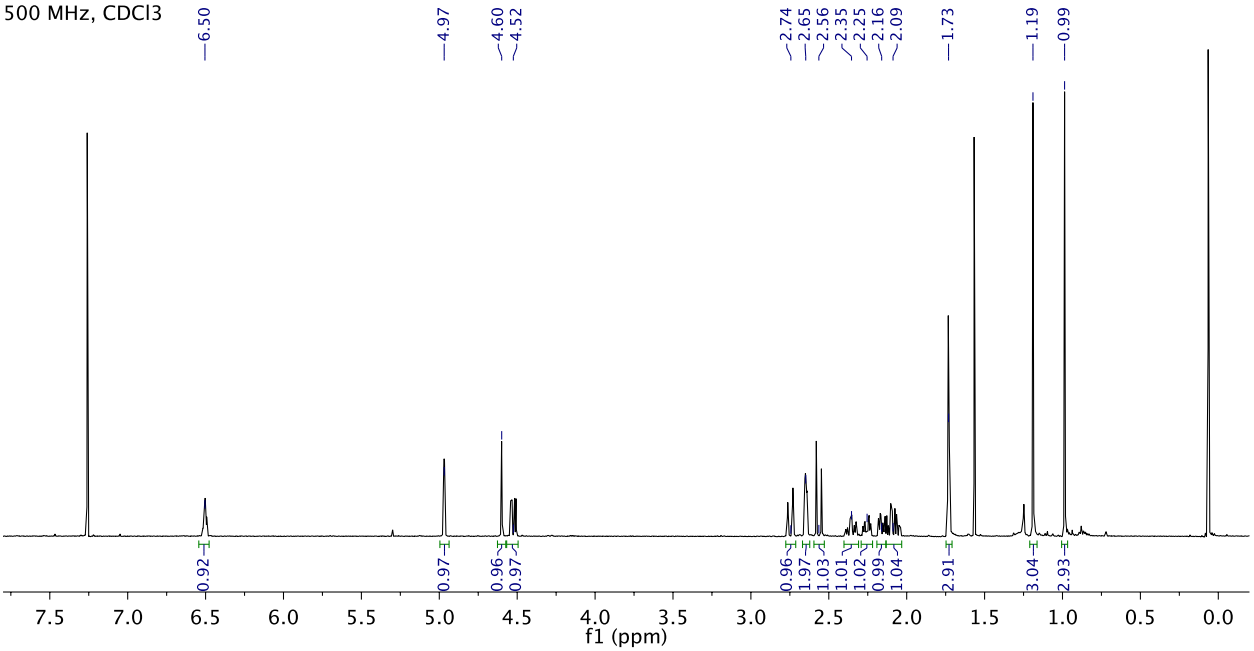


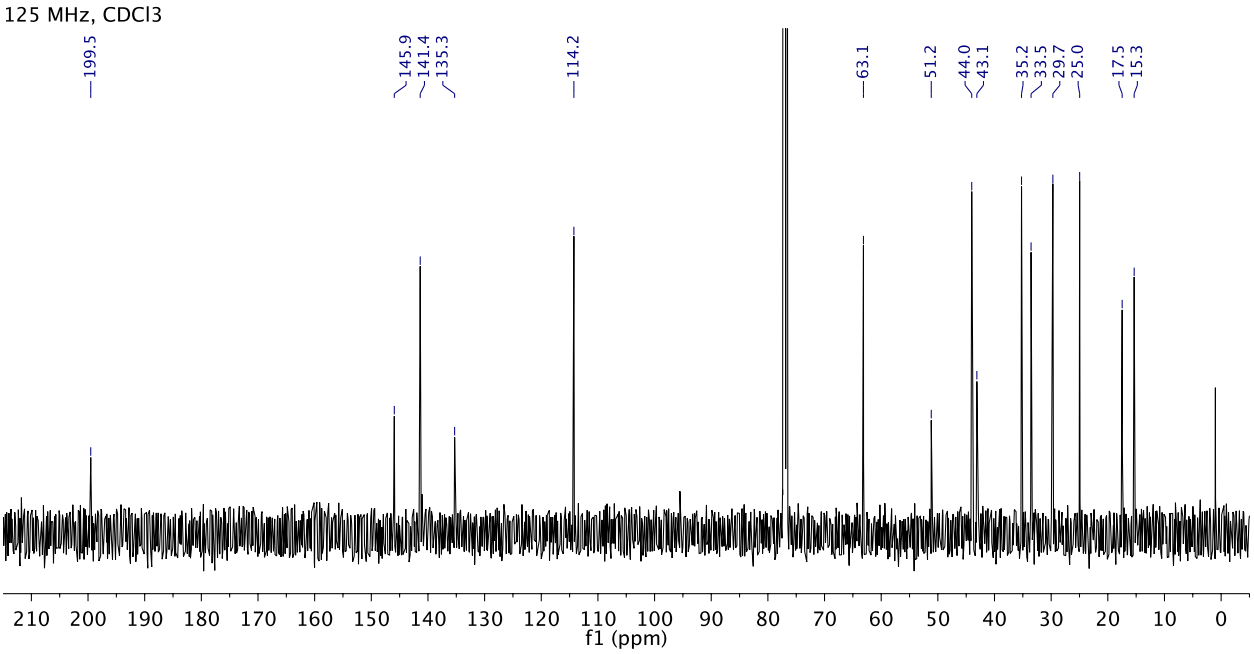
125 MHz, CDCl3

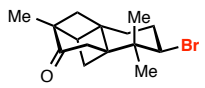



O
Me
Me
Me
Br

7

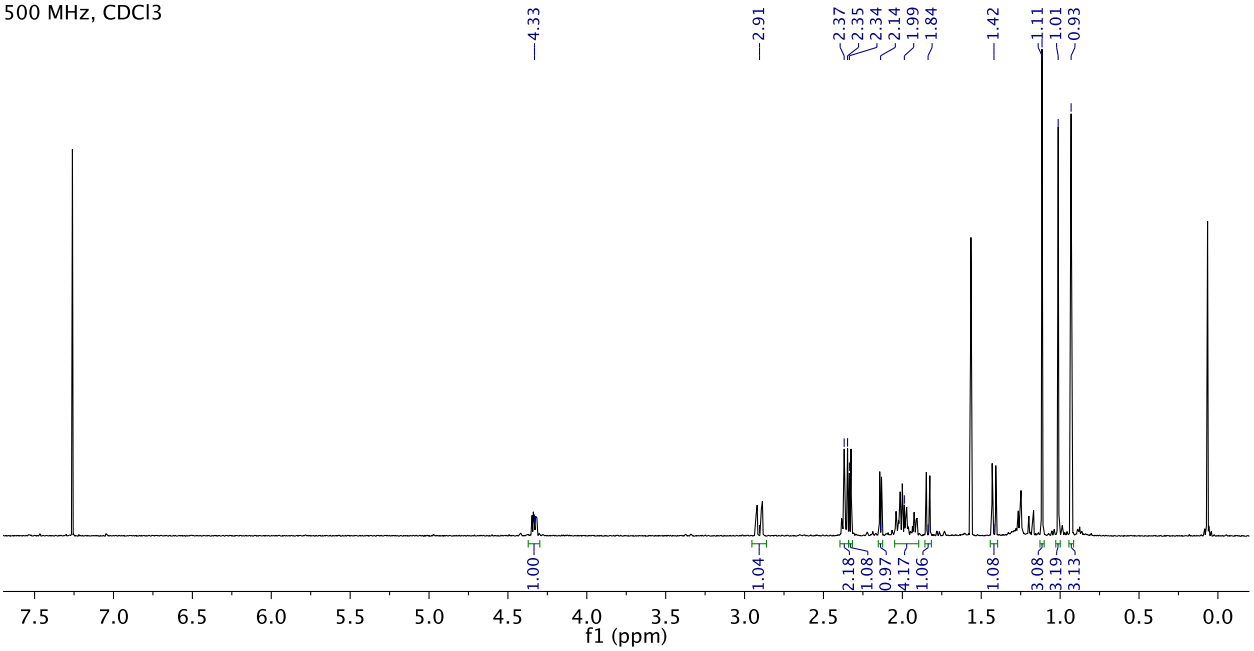

500 MHz, CDCl3
6.50
4.97
4.60
4.52
2.74
2.65
2.56
2.35
2.25
2.16
2.09
1.73
1.19
0.99
0.92
0.97
0.96
0.97
0.96
1.97
1.03
1.01
1.02
0.99
1.04
2.91
3.04
2.93
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


125 MHz, CDCl3
199.5
145.9
141.4
135.3
114.2
63.1
51.2
44.0
43.1
35.2
33.5
29.7
25.0
17.5
15.3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

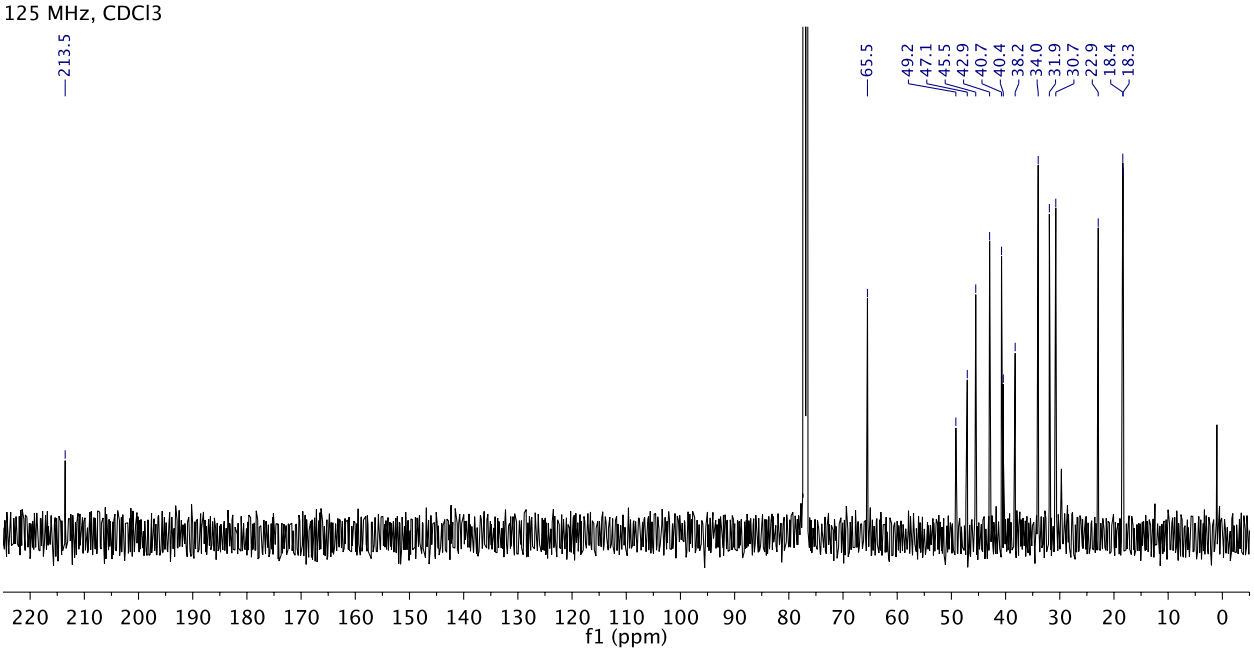


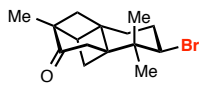
8

500 MHz, CDCl3



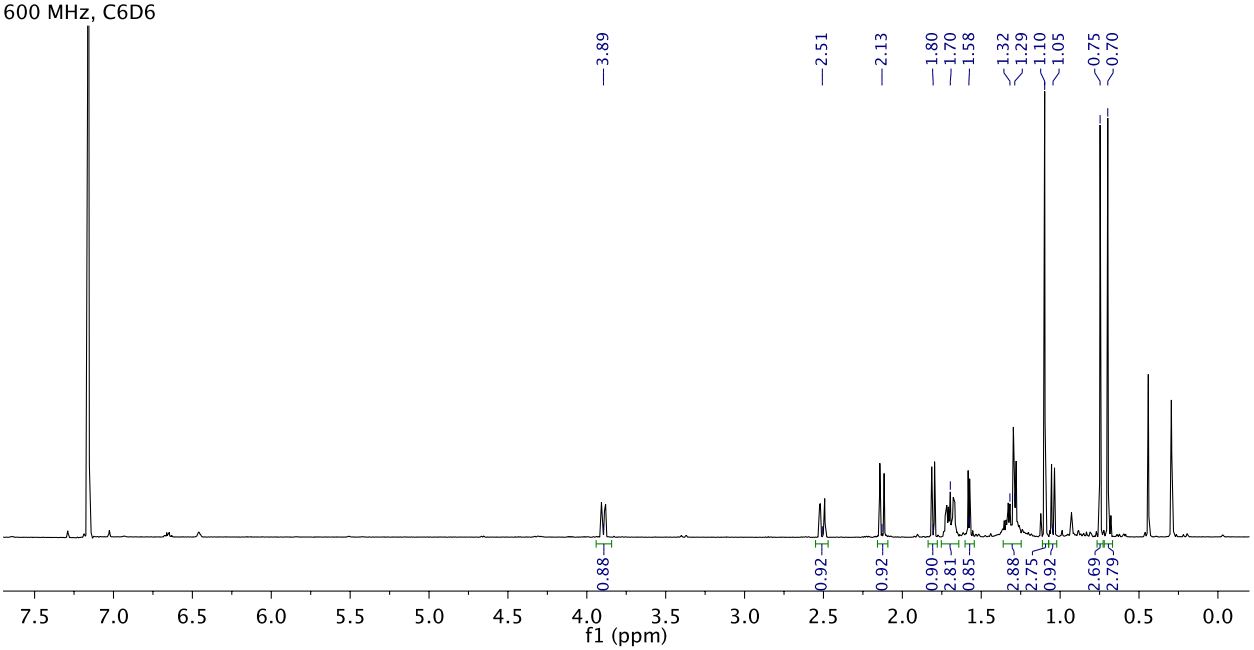
125 MHz, CDCl3



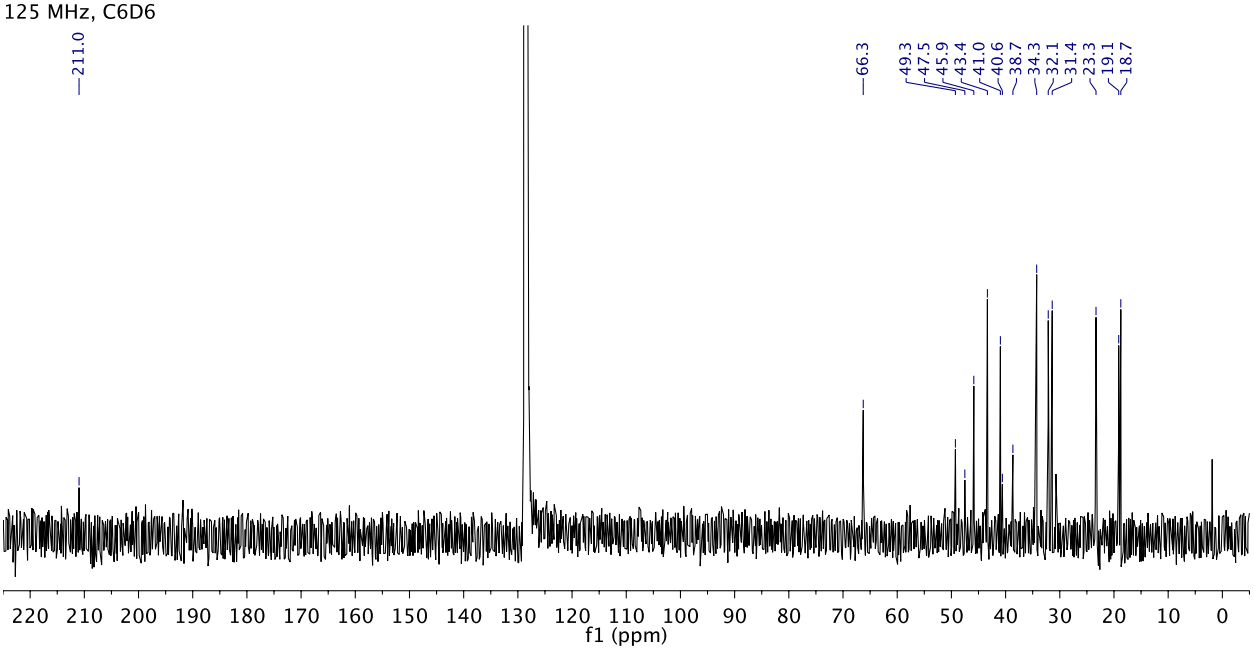


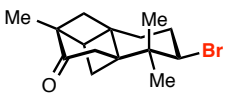
8

600 MHz, C6D6



125 MHz, C6D6

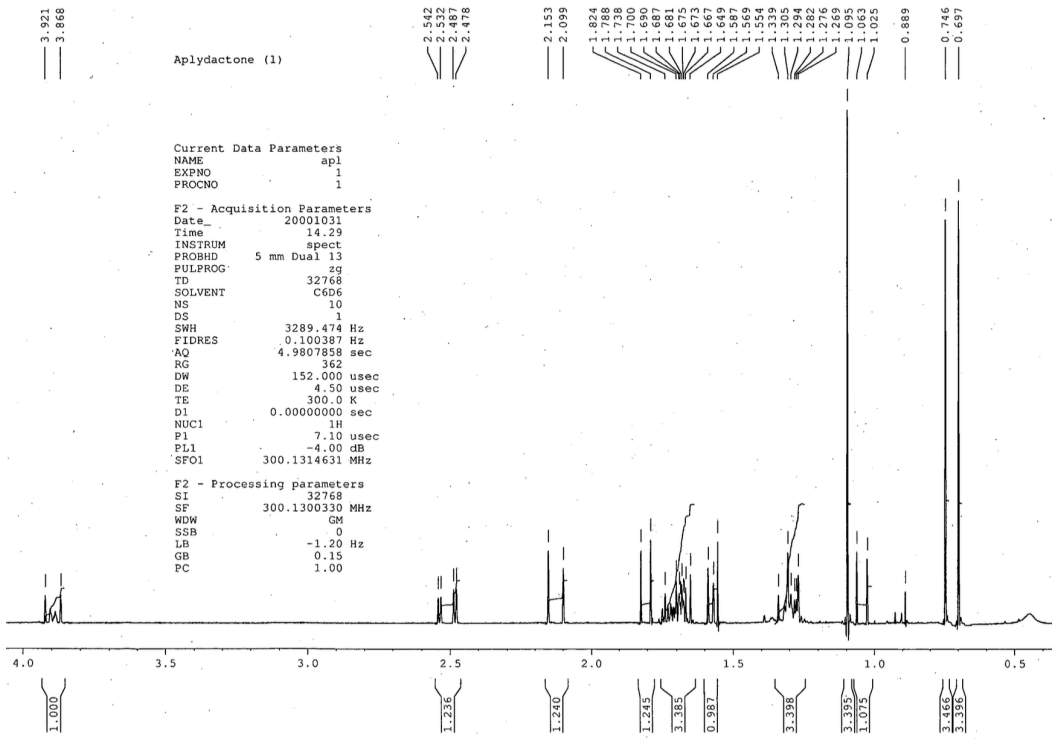


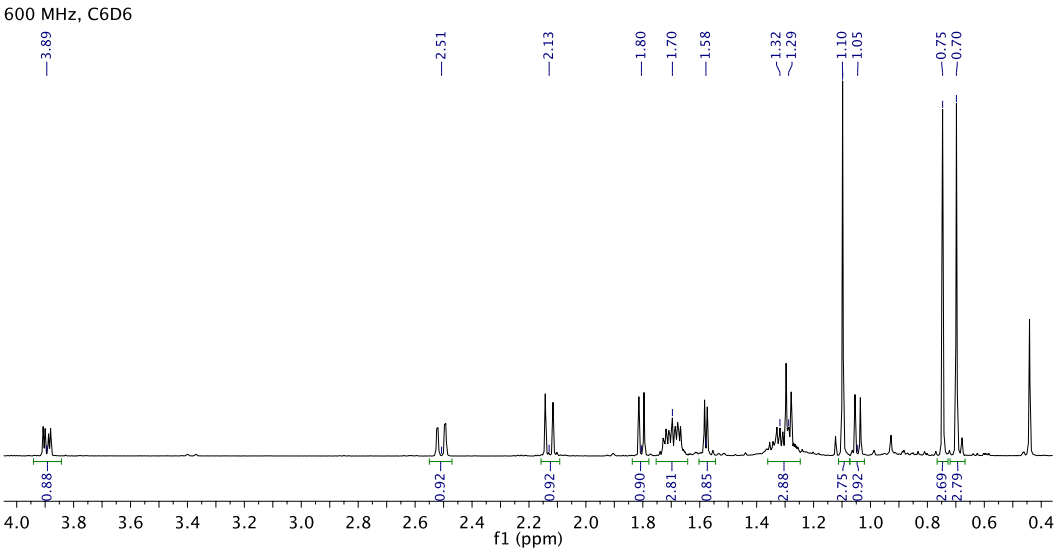


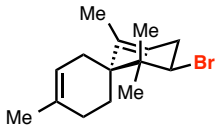
8

^{1}H NMR Comparison of (+)-aplydactone (8)

The only published ^{1}H NMR spectra for (+)-aplydactone by Stonik and co-workers (top, C_6D_6, 300 MHz) compared to synthetic (+)-aplydactone from this work (bottom, C_6D_6, 600 MHz):

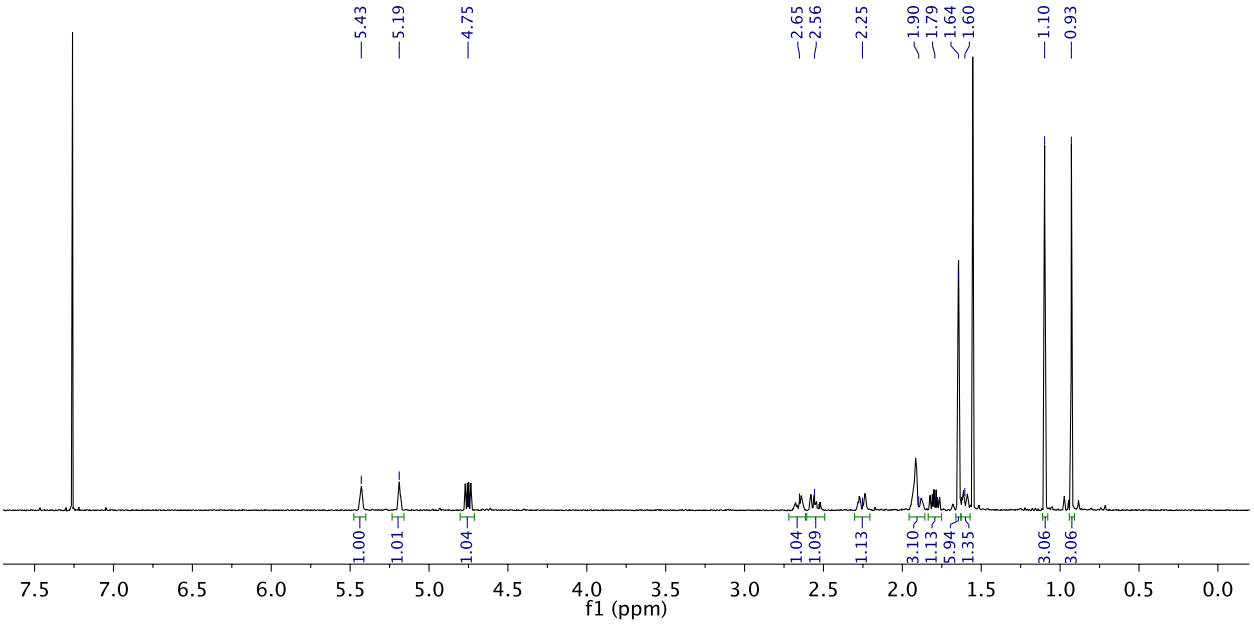




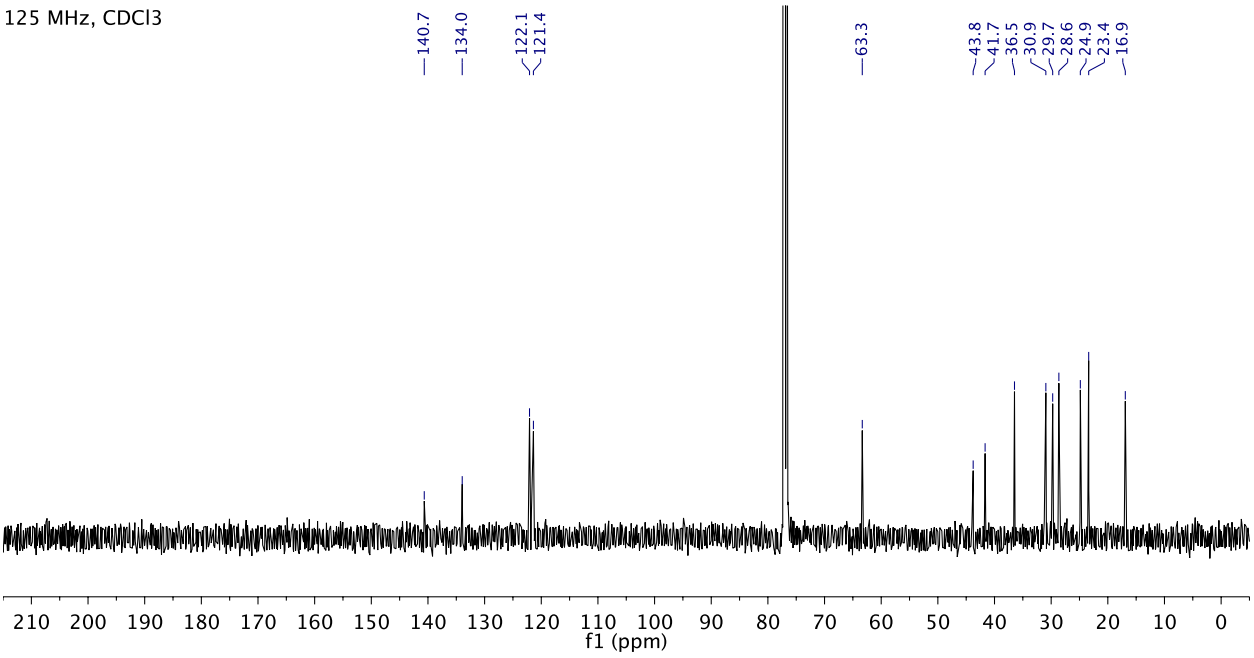


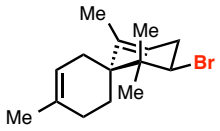
3

500 MHz, CDCl3



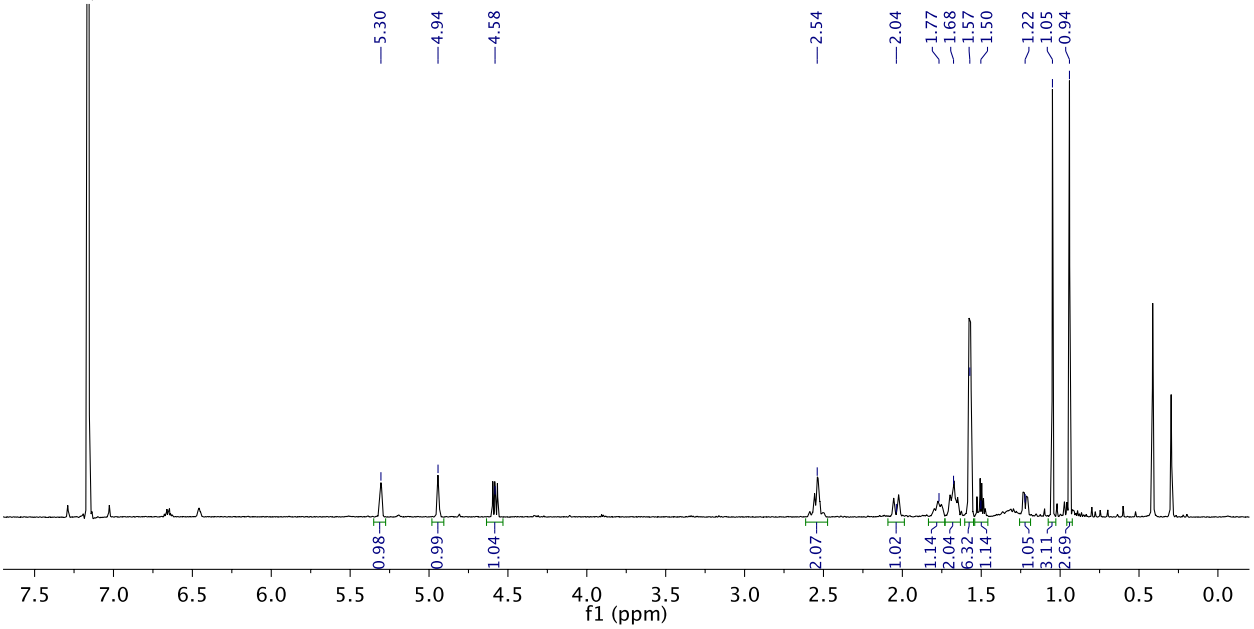
125 MHz, CDCl3



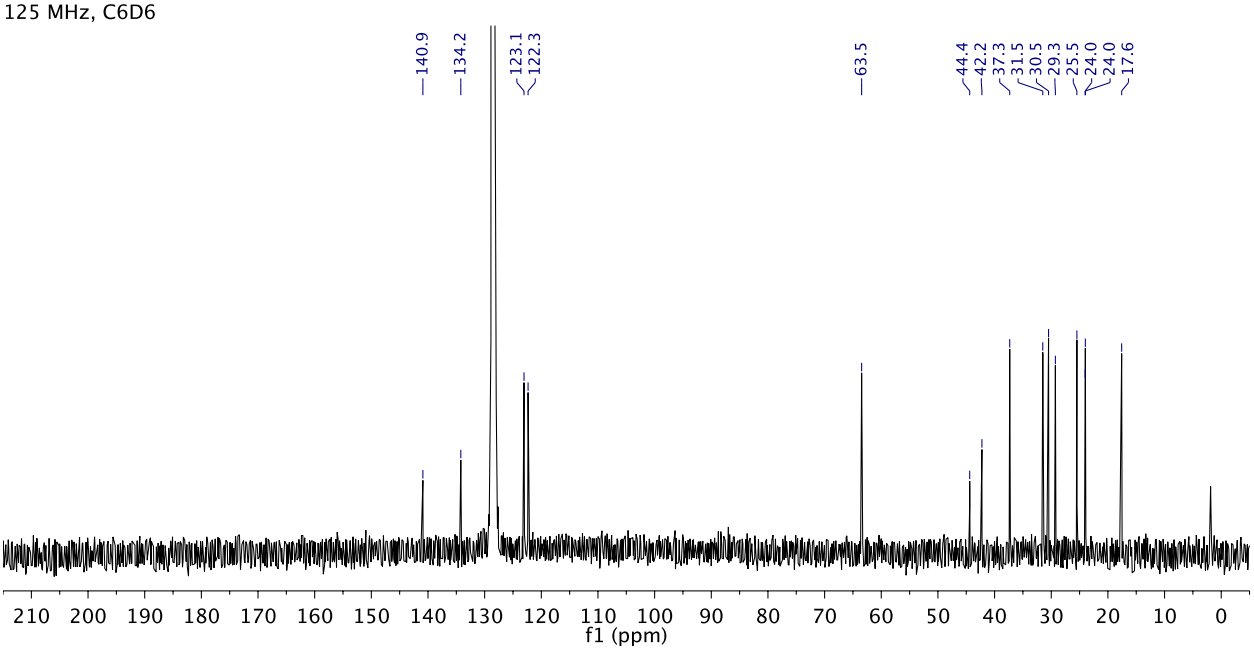


3

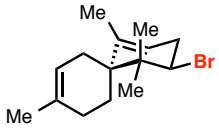
600 MHz, C6D6



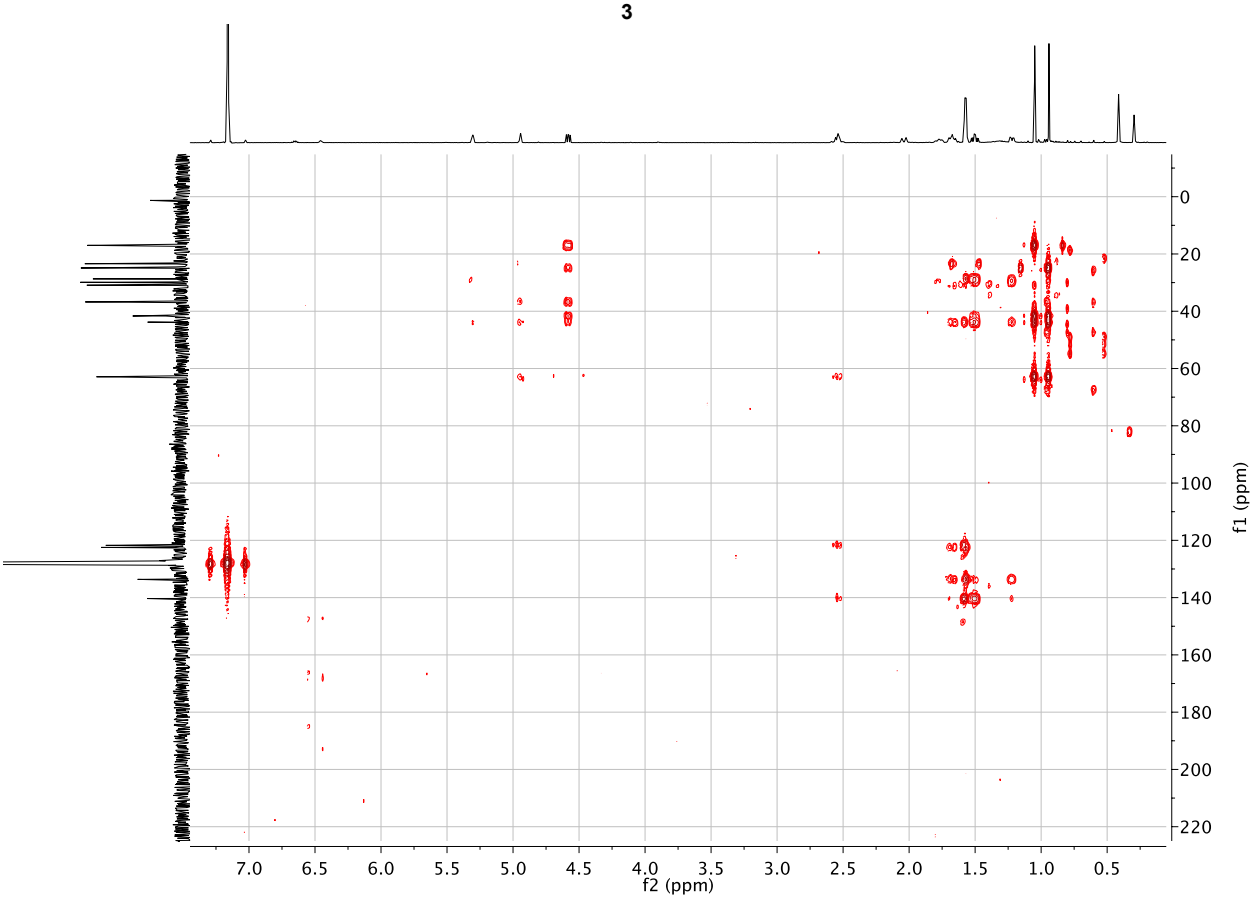
125 MHz, C6D6



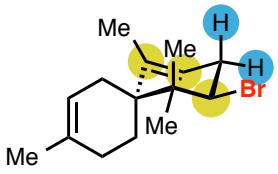
HMBC Spectra of **3**

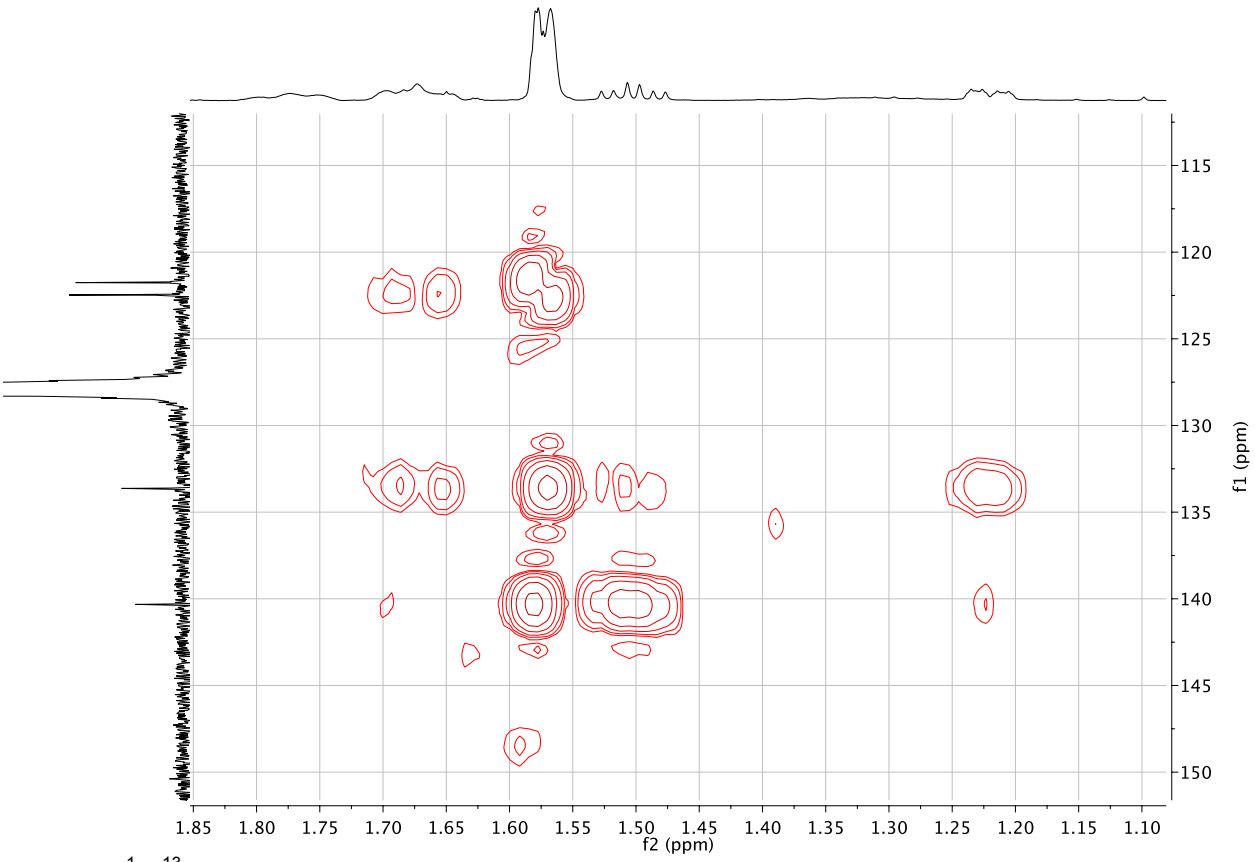


3

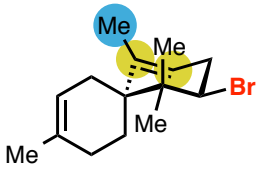


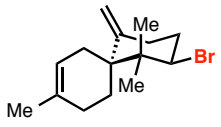
The listed $^{1}H/^{13}C$ HMBC correlations were used to assign the olefinic carbon at 140.9 ppm to the bromide containing spiro-cyclohexane: 2.54 ppm (^{1}H)/63.5 ppm (^{13}C), 2.54 ppm (^{1}H)/122.3 ppm (^{13}C), 2.54 ppm (^{1}H)/140.9 ppm (^{13}C).



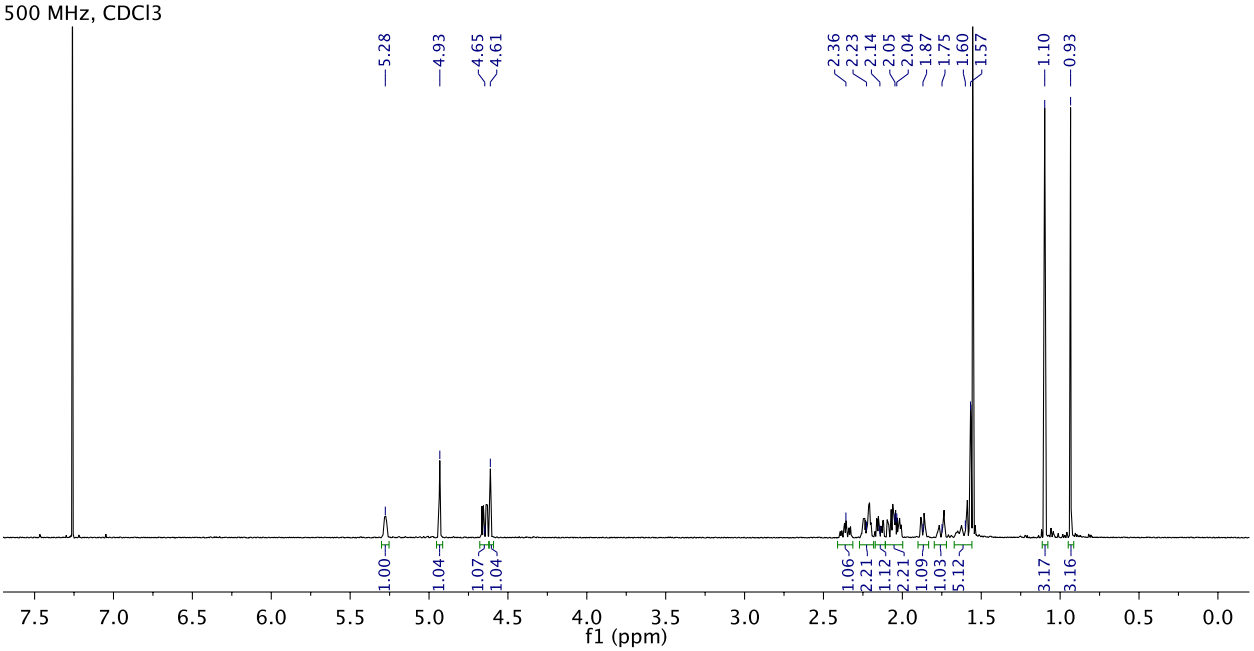


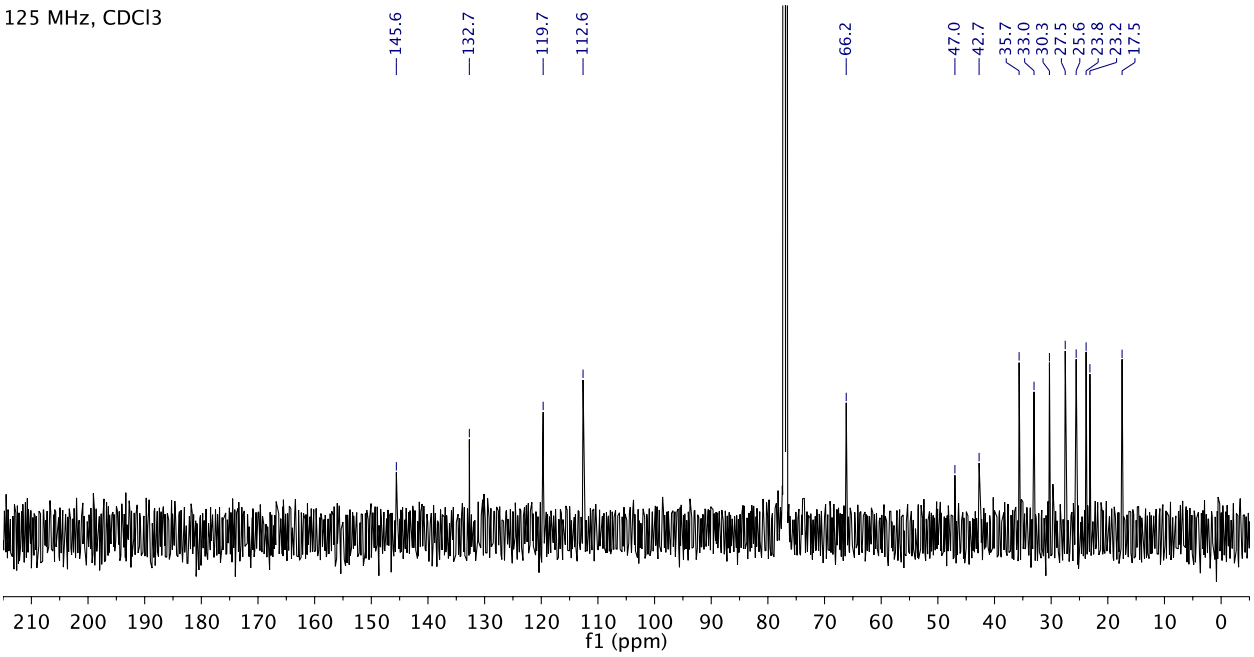
The listed $^{1}H/^{13}C$ HMBC correlations were used to assign through-bond coupling between olefinic carbon at 140.9 ppm and the methyl group : 1.580 ppm (^{1}H)/122.3 ppm (^{13}C), 1.580 ppm (^{1}H)/140.9 ppm (^{13}C).



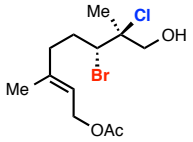

Me
Br
Me
Me

4


500 MHz, CDCl3
5.28
4.93
4.65
4.61
2.36
2.23
2.14
2.05
2.04
1.87
1.75
1.60
1.57
1.10
0.93
1.00
1.04
1.07
1.04
1.06
2.21
1.12
2.21
1.09
1.03
5.12
3.17
3.16
f1 (ppm)

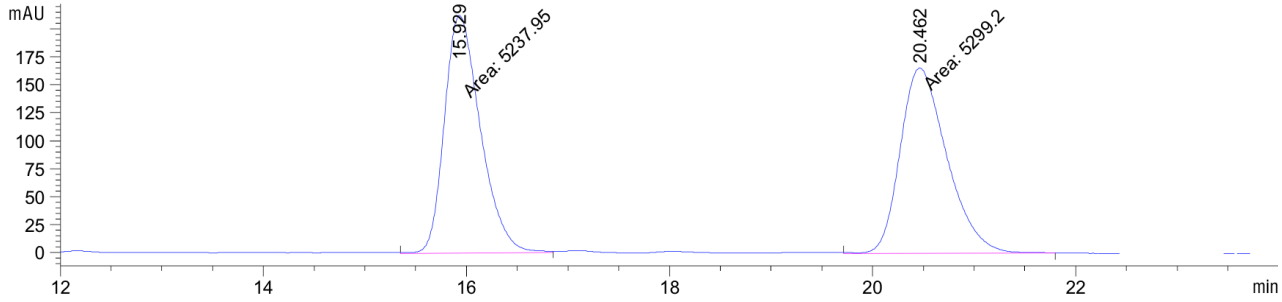

125 MHz, CDCl3
145.6
132.7
119.7
112.6
66.2
47.0
42.7
35.7
33.0
30.3
27.5
25.6
23.8
23.2
17.5
f1 (ppm)

7. Chiral HPLC Traces



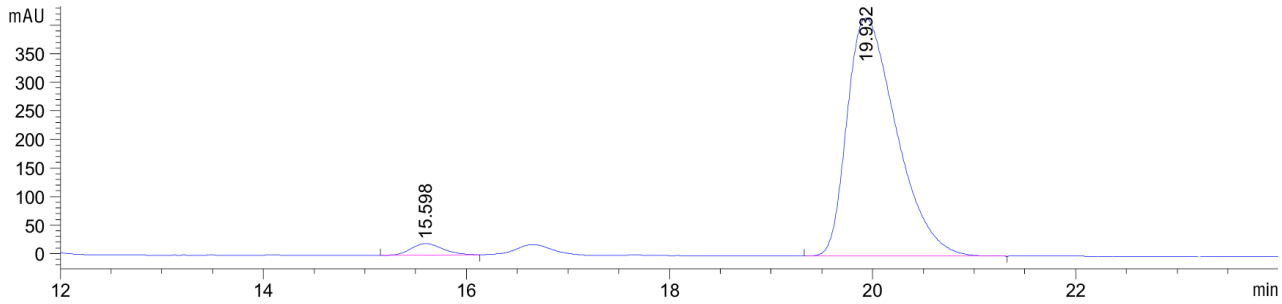
15

Racemic Sample: Chiralpak AD-H column, 10% EtOH in hexanes, 1 mL/min, 210 nm:



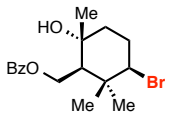
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.929	MM	0.4104	5237.94629	212.73911	49.7094
2	20.462	MM	0.5325	5299.19775	165.85707	50.2906
Totals :				1.05371e4	378.59618	

Scalemic Sample: Chiralpak AD-H column, 10% EtOH in hexanes, 1 mL/min, 210 nm:



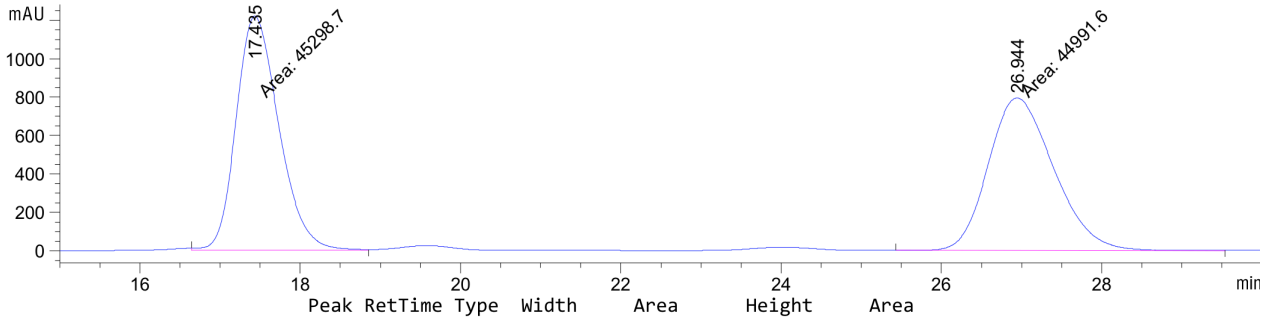
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.598	BB	0.3235	431.15173	19.99991	2.9690
2	19.932	BB	0.5178	1.40908e4	417.44406	97.0310
Totals :				1.45219e4	437.44397	

Benzoate derivative of **17**:



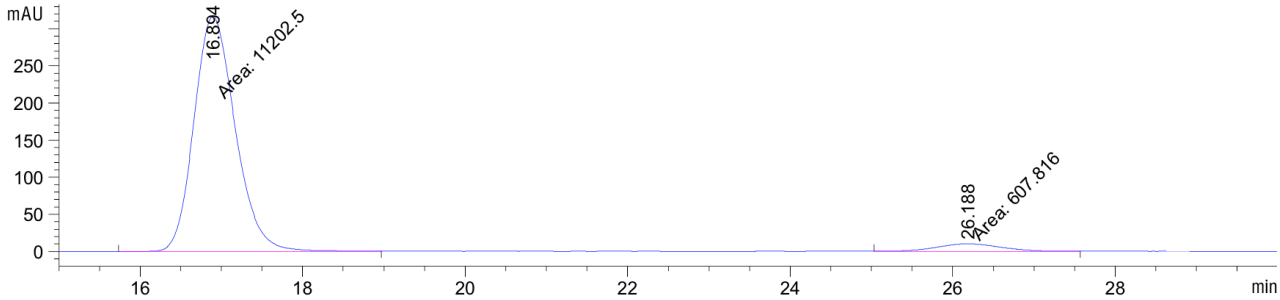
SI-3

Racemic Sample: Chiralpak AS-H column, 3% *i*-PrOH in hexanes, 1 mL/min, 230 nm:



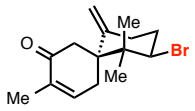
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.435	MF	0.6186	4.52987e4	1220.37012	50.1701
2	26.944	MM	0.9454	4.49916e4	793.20428	49.8299
Totals :				9.02903e4	2013.57440	

Scalemic Sample: Chiralpak AS-H column, 3% *i*-PrOH in hexanes, 1 mL/min, 230 nm:



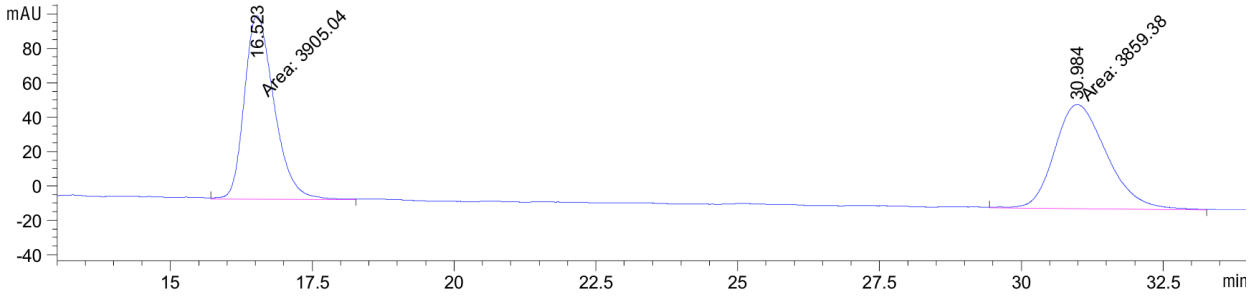
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.894	FM	0.5884	1.12025e4	317.30896	94.8535
2	26.188	MF	0.9727	607.81622	10.41420	5.1465
Totals :				1.18103e4	327.72316	

Racemic and Enantioenriched Dactylone



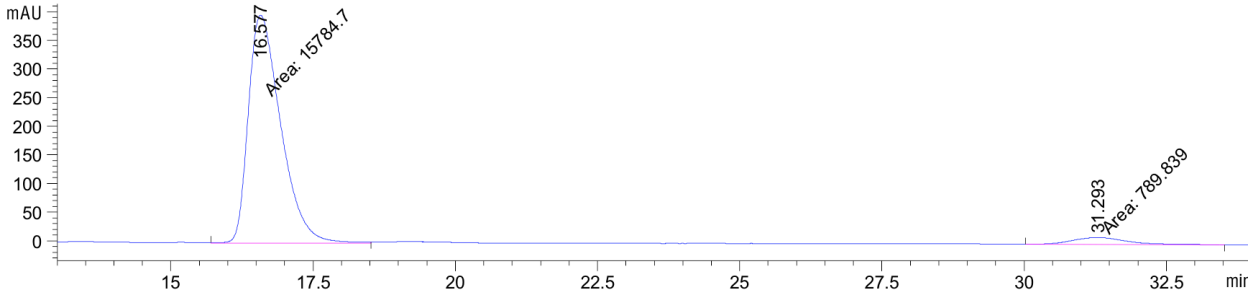
7

Racemic Sample: Chiralpak AS-H column, 2% *i*-PrOH in hexanes, 1 mL/min, 230 nm:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.523	MM	0.6099	3905.03662	106.71702	50.2940
2	30.984	MM	1.0638	3859.37720	60.46611	49.7060
Totals :				7764.41382	167.18312	

Racemic Sample: Chiralpak AS-H column, 2% *i*-PrOH in hexanes, 1 mL/min, 230 nm:



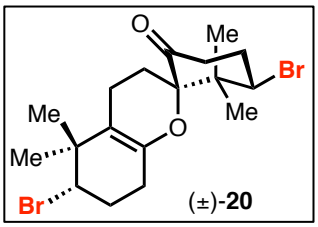
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.577	MF	0.6612	1.57847e4	397.85446	95.2346
2	31.293	MM	1.0967	789.83905	12.00329	4.7654
Totals :				1.65746e4	409.85775	

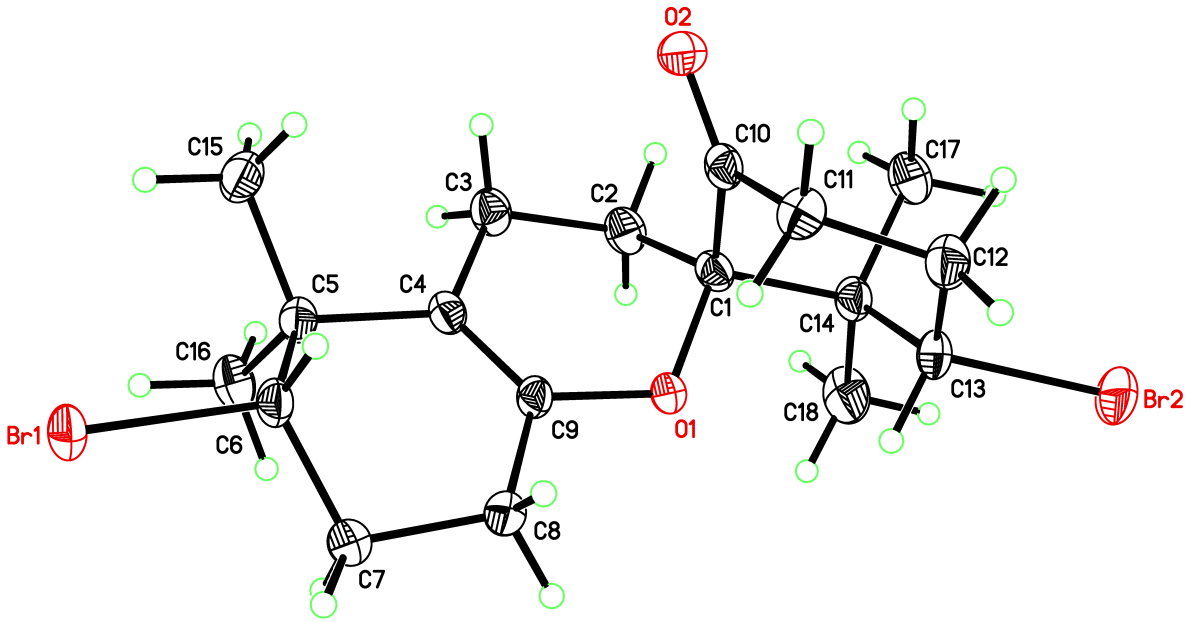
8. Irradiation of (–)-Dactylone in Ambient Sunlight

Protocol: (–)-dactylone (**7**) (ca. 1 mg) was dissolved in $CDCl_3$ (700 μL), and the solution was added to an NMR tube and sealed with a plastic cap. The tube was secured with a clamp at a distance of ca. 1 in. from a glass window as depicted in the image below. The reaction mixture was analyzed by ^1H NMR after 8 days of sunlight irradiation (see Table 1, entry 4 in the main text).

9. X-Ray Crystallographic Information

Figure SI-1. X-ray crystallographic structure of (±)-**20** (su1604).





DISCUSSION

The compound crystallizes as colorless tablet-like crystals from a hexanes solution. There are two molecules of the compound in the unit cell of the primitive, centrosymmetric, triclinic space group P-1.

The structure corresponds to the proposed, spiro-configuration, rather than another proposed three 6-8-6 fused-ring system.

Bond distances and angles within the molecule are as expected.

CRYSTAL SUMMARY

Crystal data for $C_{18}H_{26}Br_2O_2$; M_r = 434.21; Triclinic; space group P-1; *a* = 8.4426(7) Å; *b* = 9.5333(7) Å; *c* = 11.9143(9) Å; α = 79.7210(10)°; β = 86.3530(10)°; γ = 71.2830(10)°; V = 893.62(12) $Å^3$; Z = 2; T = 120(2) K; λ(Mo-Kα) = 0.71073 Å; μ(Mo-Kα) = 4.541 mm^{-1}; d_{calc} = 1.614g.cm^{-3}; 20427 reflections collected; 4443 unique (R_{int} = 0.0305); giving R_1 = 0.0287, wR_2 = 0.0703 for 3666 data with [I>2σ(I)] and R_1 = 0.0372, wR_2 = 0.0734 for all 4443 data. Residual electron density ($e^-.Å^{-3}$) max/min: 1.063/-0.343.

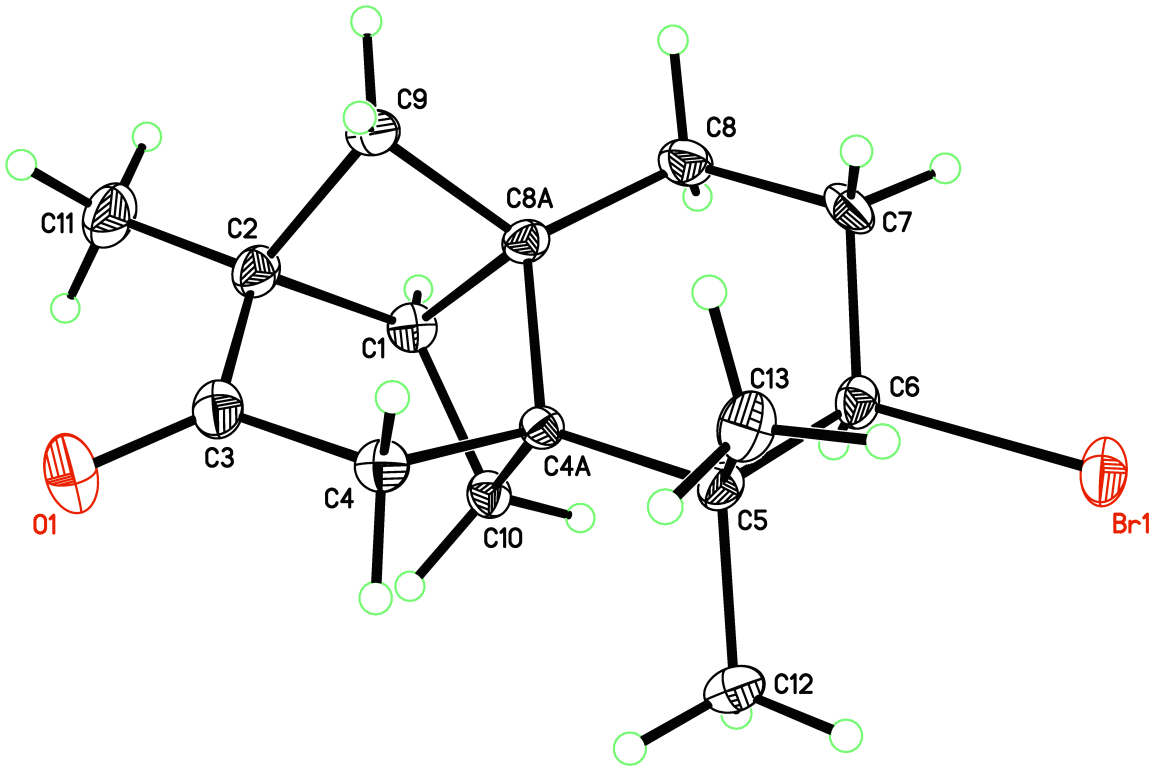
An arbitrary sphere of data were collected on a colorless tablet-like crystal, having approximate dimensions of 0.210 × 0.165 × 0.098 mm, on a Bruker APEX-II diffractometer using a combination of ω- and φ-scans of 0.5° [1]. Data were corrected for absorption and polarization effects and analyzed for

space group determination. The structure was solved by intrinsic phasing methods and expanded routinely [2]. The model was refined by full-matrix least-squares analysis of F^2 against all reflections [3]. All non-hydrogen atoms were refined with anisotropic atomic displacement parameters. Unless otherwise noted, hydrogen atoms were included in calculated positions. Atomic displacement parameters for the hydrogens were tied to the equivalent isotropic displacement parameter of the atom to which they are bonded (U_{iso}(H) = 1.5U_{eq}(C) for methyl, 1.2U_{eq}(C) for all others).

Crystal data and structure refinement for su1604

Identification code	su1604
Empirical formula	$C_{18}H_{26}Br_2O_2$
Formula weight	434.21
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	*a* = 8.4426(7) Å α = 79.7210(10)°
	b = 9.5333(7) Å β = 86.3530(10)°
	c = 11.9143(9) Å γ = 71.2830(10)°
Volume	893.62(12) Å^3
Z	2
Density (calculated)	1.614 g.cm^{-3}
Absorption coefficient (μ)	4.541 mm^{-1}
F(000)	440
Crystal color, habit	colorless, tablet
Crystal size	0.210 × 0.165 × 0.098 mm^3
θ range for data collection	1.737 to 28.363°
Index ranges	-11 ≤ h ≤ 11, -12 ≤ k ≤ 12, -15 ≤ l ≤ 15
Reflections collected	20427
Independent reflections	4443 [R_{int} = 0.0305]
Completeness to θ = 25.242°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7452 and 0.5868
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4443 / 0 / 203
Goodness-of-fit on F^2	1.083
Final R indices [I>2σ(I)]	R_1 = 0.0287, wR_2 = 0.0703
R indices (all data)	R_1 = 0.0372, wR_2 = 0.0734
Extinction coefficient	n/a
Largest diff. peak and hole	1.063 and -0.343 e$^-$.Å^{-3}

Figure SI-2. X-ray crystallographic structure of synthetic **(+)-Aplydactone 8** (su1610).



DISCUSSION

The compound crystallizes as colorless block-like crystals from a hexanes solution. There are two molecules of the compound in the unit cell of the primitive, acentric, monoclinic space group $P2_1$. The correct enantiomorph of the space group and hence stereochemistry of the molecule was determined by comparison of Friedel pairs of reflections. Two techniques were employed yielding a Flack *x* parameter = 0.019(3) [4] and a Hooft *y* parameter = 0.020(6) [5]. Values close to zero indicate the correct absolute configuration.

The structure of the fused polycycle is as expected (see Figures). Bond distances and angles within the molecule reflect the strained geometry imposed by the fused four-membered ring systems (see Tables of Bond Distances and Angles).

CRYSTAL SUMMARY

Crystal data for $C_{15}H_{21}BrO$; M_r = 297.23; Monoclinic; space group $P2_1$; *a* = 7.1207(3) Å; *b* = 12.3187(6) Å; *c* = 7.5441(4) Å; α = 90°; β = 92.4050(10)°; γ = 90°; V = 661.17(6) $Å^3$; Z = 2; T = 120(2) K; λ(Mo-Kα) = 0.71073 Å; μ(Mo-Kα) = 3.091 mm^{-1}; d_{calc} = 1.493g.cm^{-3}; 22199 reflections collected; 3317 unique (R_{int} = 0.0328); giving R_1 = 0.0196, wR_2 = 0.0429 for 3118 data with [I>2σ(I)] and R_1 = 0.0221, wR_2 = 0.0437 for all 3317 data. Residual electron density (e^-.$Å^{-3}$) max/min: 0.309/-0.199.

An arbitrary sphere of data were collected on a colorless block-like crystal, having approximate dimensions of 0.189 × 0.118 × 0.086 mm, on a Bruker APEX-II diffractometer using a combination of ω- and φ-scans of 0.5° [1]. Data were corrected for absorption and polarization effects and analyzed for space group determination. The structure was solved by intrinsic phasing methods and expanded

routinely [2]. The model was refined by full-matrix least-squares analysis of F^2 against all reflections [3]. All non-hydrogen atoms were refined with anisotropic atomic displacement parameters. Unless otherwise noted, hydrogen atoms were included in calculated positions. Atomic displacement parameters for the hydrogens were tied to the equivalent isotropic displacement parameter of the atom to which they are bonded (U_{iso}(H) = 1.5U_{eq}(C) for methyl, 1.2U_{eq}(C) for all others).

Crystal data and structure refinement for su1610

Identification code	su1610
Empirical formula	$C_{15}H_{21}BrO$
Formula weight	297.23
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	*a* = 7.1207(3) Å α = 90°
	b = 12.3187(6) Å β = 92.4050(10)°
	c = 7.5441(4) Å γ = 90°
Volume	661.17(6) $Å^3$
Z	2
Density (calculated)	1.493 $g.cm^{-3}$
Absorption coefficient (μ)	3.091 mm^{-1}
F(000)	308
Crystal color, habit	colorless, block
Crystal size	0.189 × 0.118 × 0.086 mm^3
θ range for data collection	2.702 to 28.412°
Index ranges	-9 ≤ h ≤ 9, -16 ≤ k ≤ 16, -10 ≤ l ≤ 10
Reflections collected	22199
Independent reflections	3317 [R_{int} = 0.0328]
Completeness to θ = 25.242°	100.0 %
Absorption correction	Numerical
Max. and min. transmission	0.8120 and 0.6628
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3317 / 1 / 157
Goodness-of-fit on F^2	1.018
Final R indices [I>2σ(I)]	R_1 = 0.0196, wR_2 = 0.0429
R indices (all data)	R_1 = 0.0221, wR_2 = 0.0437
Absolute structure parameter	0.019(3)
Extinction coefficient	n/a
Largest diff. peak and hole	0.309 and -0.199 $e^-.Å^{-3}$

REFERENCES

[1] Bruker AXS. (2016). *APEX-2*. Bruker-Nonius AXS, Madison, Wisconsin, USA.

[2] G. M. Sheldrick, *Acta Cryst.*, **2015**, *A71*, 3.

[3] G. M. Sheldrick, *Acta Cryst.*, **2015**, *C71*, 3.

[4] S. Parsons, H. D. Flack & T. Wagner, *Acta Cryst.*, **2013**, *B69*, 249.

[5] R. W. W. Hooft, L. H. Straver & A. L. Spek, *J. Appl. Cryst.*, **2008**, *41*, 96.

10. References

(1) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526-5528.

(2) Hu, D. X.; Seidl, F. J.; Bucher, C. B.; Burns, N. Z. *J. Am. Chem. Soc.* **2015**, *137*, 3795-3798.

(3) Bucher, C. B.; Deans, R. M.; Burns, N. Z. *J. Am. Chem. Soc.* **2015**, *137*, 12784-12787.

(4) Snyder, S. A.; Treitler, D. S. *Angew. Chem. Int. Ed.* **2009**, *48*, 7899-7903.

(5) Snyder, S. A.; Treitler, D. S.; Brucks, A. P. *J. Am. Chem. Soc.* **2010**, *132*, 14303-14314.

(6) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936-3938.

(7) Antonsen, S.; Skattebøl, L.; Stenstrøm, Y. *Molecules* **2014**, *19*, 29664-20670.

(8) Yan, T.; Tsai, C.; Chien, C.; Cho, C.; Huang, P. *Org. Lett.* **2004**, *6*, 4961-4963.

(9) Lyakhova, E. G.; Federov, S. N.; Shubina, L. K.; Radchenko, O. S.; Kalinovsky, A. I.; Dvitrenok, P. S.; Stonki, V. A. *Russ. Chem. Bull. Int. Ed.* **2003**, *52*, 970-974.

(10) Federov, S. N.; Radchenko, O. S.; Shubina, L. K.; Kalinovsky, A. I.; Gerasimenko, A. V.; Popov, D. Y.; Stonik, V. A. *J. Am. Chem. Soc.* **2001**, *123*, 504-505.

(11) White, D. E.; Stewart, I. C.; Grubbs, R. H.; Stoltz, B. M.; *J. Am. Chem. Soc.* **2008**, *130*, 810-811.

(12) Howard, B. M.; Fenical, W. *Tet. Lett.* **1976**, *29*, 2519-2520.

(13) König, G. M.; Wright, A. D. *Phytochem. Anal.* **1997**, *8*, 167-172.

(14) Guella, G.; Öztunç, A.; Mancini, I.; Pietra, F. *Tet. Lett.* **1997**, *38*, 8261-8264.