Catalytic Enantioselective Total Syntheses of Bakkenolides I, J and S: Application of a Carbene-Catalyzed Desymmetrization

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Supporting Information

GENERAL INFORMATION S2

EXPERIMENTAL PROCEDURES AND CHARACTERIZATION FOR THE SYNTHESIS OF BAKKENOLIDES I, J, AND S *S*2

SELECTED NMR SPECTRA *S*11

GC TRACES *S*27

COMPARATIVE ANALYSIS USING ^{1}H NMR SPECTRA *S*28

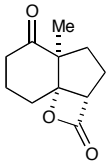
X-RAY CRYSTALLOGRAPHY OF **14** *S*30

X-RAY CRYSTALLOGRAPHY OF **A** *S*31

General Information

All reactions were carried out under a nitrogen atmosphere in flame-dried glassware with magnetic stirring. CH_3CN was purified by passage through a bed of activated alumina.[1] Reagents were purified prior to use unless otherwise stated following the guidelines of Perrin and Armarego.[2] Purification of reaction products was carried out by flash chromatography using EM Reagent silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and ceric ammonium nitrate stain or potassium permangenate stain followed by heating. Infrared spectra were recorded on a Perkin Elmer 1600 series FT-IR spectrometer. ^{1}H-NMR spectra were recorded on a Varian Inova 500 (500 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data are reported as (ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C-NMR spectra were recorded on a Varian Inova 500 (125 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm). Mass spectra data were obtained on a Varian 1200 Quadrupole Mass Spectrometer and Micromass Quadro II Spectrometer.

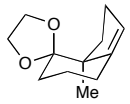
Experimental Procedures and Characterization for the Synthesis of Bakkenolides I, J, and S



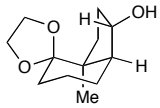
(2a*S*,4a*S*,8^1*S*)-4a-methylhexahydro-2*H*-indeno[1-*b*]oxete-2,5(6*H*)-dione (3): To a flame dried flask equipped with magnetic stirring bar was added aldehyde **2** (5.00 g, 25.7 mmol). The flask was sealed with a rubber septum and carried into a dry box under inert atmosphere. In the dry box, azolium salt **A** (622 mg, 1.3 mmol) was added. The material was diluted with degassed CH_2Cl_2 (128 mL, 0.2 M) and degassed i-Pr_2EtN (4.48 mL, 25.7 mmol). The flask was sealed with a rubber septum and removed from the dry box. The flask was then equipped with an N_2 inlet and heated to 30 °C for 48 hours. Upon consumption of starting material, the reaction was diluted with 200 mL of CH_2Cl_2 and was washed with 50 mL aqueous sat. NH_4Cl. The layers were separated and the organic layer was washed with 50 mL aqueous sat. NaCl. The layers were separated and the organic layer was dried over Na_2SO_4. The solution was filtered and concentrated. The material was purified by flash column chromatography with 20% EtOAc in hexanes to 30% EtOAc in hexanes as an eluent to yield **3** (3.44 g, 69%) as a white solid. Analytical data for **3**: IR (film) 3026, 2957, 2931, 1684, 1496, 1455, 1181 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.47 (dd, *J* = 7.6, 1.4 Hz, 1H), 2.74 (ddd, *J* = 1.9, 6.4, 6.4 Hz, 1H), 2.54 (ddd, *J*

1. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometal.* **1996**, *15*, 1518-1520.
2. Perrin, D. D. and Armarego, W. L. *Purification of Laboratory Chemicals;* 3rd Ed., Pergamon Press, Oxford. 1988.

= 5.9, 14.8, 14.8 Hz, 1H), 2.39-2.33 (m, 2H), 2.25 (dddd, *J* = 13.7, 3.1, 3.1, 1.4 Hz, 1H), 2.12-2.07 (m, 1H), 1.94 (dd, *J* = 12.8, 5.5 Hz, 1H), 1.63-1.49 (m, 2H), 1.41 (dddd, *J* = 28.5, 14.1, 3.7, 3.7 Hz, 1H), 1.28 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.4, 170.4, 89.4, 59.0, 58.7, 37.1, 31.8, 28.0, 24.5, 19.4, 18.3; LRMS (ES): Mass calcd for $C_{11}H_{14}O_3$ $[M]^+$, 194. Found $[M]^+$, 194; $[\alpha]_D$: +36.2 ($CHCl_3$, c = 0.4, er = 99:1). Enantiomeric ratio determined by GC (Beta Dex 225, 23.00 psi, 80 °C (hold for 20 min then increase temperature 5 °C/min) – 170°C, Rt_{major} = 26.95, Rt_{minor}, 27.15).

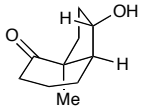


(*S*)-3a'-methyl-2',3',3a',5',6',7'-hexahydrospiro[[1,3]dioxolane-2,4'-indene] (4): To a tube equipped with a magnetic stirring bar was added **3** (2.25 g, 11.6 mmol) and 2.25 g SiO_2. The solution was diluted with benzene (5.3 mL, 2.2 M) the tube was sealed with a screw cap and rubber septum. The reaction vessel was heated to 70 °C for 48 hours. The material was filtered and the silica gel was washed with Et_2O. The solution was concentrated and used without further purification. To a flame dried flask equipped with magnetic stirring bar and N_2 inlet was added TMSOTf (116 μL, 0.12 mmol) and CH_2Cl_2 (2 mL, 5.8 M). The flask was cooled to –78 °C in a dry ice/acetone bath. $(TMSOCH_2)_2$ (2.39 g, 11.6 mmol) was added dropwise through a cannula. After 5 min., the ketone was transferred through a cannula to the reaction vessel in a dropwise fashion. Following the completion of the addition, to the flask previously containing the ketone was added 1 mL CH_2Cl_2. This solution was then transferred to the reaction through a cannula. After 3 hours of stirring at –78 °C, the reaction was warmed to –30 °C. After 12 hours the reaction was cooled to –78 °C and pyridine (234 μL, 2.9 mmol) was added. The reaction was poured into a separatory funnel containing aqueous sat. $NaHCO_3$ (5 mL). The material was extracted and the layers were separated. The aqueous layer was then extracted with diethyl ether (2 x 20 mL). The combined organics were washed with aqueous sat. NaCl, aqueous 10% $CuSO_4$, and aqueous sat. NaCl. The organic layer was dried over Na_2SO_4, filtered and concentrated. The material was purified by flash column chromatography with 5% ether in pentane as an eluent to afford ketal **4** (2.21 g, 98%) as a clear oil. Analytical data for **4**: IR (film) 2940, 2885, 1467, 1452, 1179, 1123, 1090 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.28 (m, 1H), 3.95 (s, 4H), 2.30-2.14 (m, 4H), 2.05-1.97 (m, 1H), 1.78-1.61 (m, 3H), 1.51-1.42 (m, 2H), 1.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.3, 121.6, 112.6, 65.1, 64.6, 54.7, 31.0, 30.2, 29.4, 24.6, 23.3, 21.9; LRMS (EI): Mass calcd for $C_{12}H_{18}O_2$ $[M]^+$, 194. Found $[M]^+$, 194; $[\alpha]_D$: +6.25 ($CHCl_3$, c = 0.1).

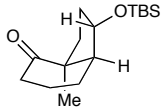


(1'*S*,3a'*S*,7a'*S*)-3a'-methyloctahydrospiro[[1,3]dioxolane-2,4'-inden]-1'-ol (5): To a flame-dried flask equipped with magnetic stirring bar and N_2 inlet was added ketal **4** (2.25 g, 11.6 mmol. The material was diluted with THF (12 mL, 0.97 M) and the flask was cooled to 0 °C with an ice/water bath. BH_3•SMe_2 (~10 M, 1.39 mL, 13.9 mmol) was added slowly through a syringe. The reaction stirred under N_2 atmosphere for 3 hours. To the reaction was added 3 N NaOH (11.6 mL, 34.8 mmol) and then H_2O_2 (30% solution in H_2O, 5.92 mL, 58 mmol). After 1 hour the reaction was diluted with diethyl ether (50 mL) and washed with aqueous sat. NaCl (10

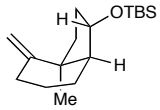
mL). The layers were separated and the organic layer was dried over Na_2SO_4, filtered and concentrated. The material was purified by flash column chromatography with 30% Et_2O in pentane to 40% Et_2O in pentane as an eluent to afford alcohol **5** (1.85 g, 75%) as a colorless oil. Analytical data for **5**: IR (film) 3376, 2937, 2870, 1457, 1343, 1121 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.28 (ddd, *J* = 8.3, 8.3, 5.4 Hz, 1H), 3.95-3.88 (m, 4H), 2.18-2.11 (m, 1H), 1.84-1.79 (m, 1H), 1.66-1.36 (m, 9H), 1.17, (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 112.8, 76.0, 75.3, 64.5, 56.0, 47.9, 33.4, 32.4, 30.6, 24.3, 22.3, 20.3; LRMS (ES): Mass calcd for $C_{12}H_{20}O_3$ $[M+1]^+$, 213. Found $[M+1]^+$, 213; $[\alpha]_D$: +2.69 ($CHCl_3$, c = 0.39).



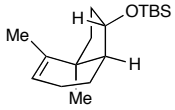
(1*S*,3a*S*,7a*S*)-1-hydroxy-3a-methylhexahydro-1*H*-inden-4(2*H*)-one (18): To a round bottom flask equipped with a magnetic stirring bar was added ketal **5** (1.52 g, 7.2 mmol). Acetone (20 mL, 0.24 M) and H_2O (7.2 mL, 1 M). The reaction was cooled to 0 °C and *p*-TsOH (685 mg, 3.6 mmol) was added in one portion and the flask was covered with a rubber septum. The reaction was allowed to warm to 20 °C gradually. After 5 hours the reaction was diluted with brine and the solution was extracted with CH_2Cl_2 (3 x 60 ml). The combined organics were washed with brine twice more. The solution was dried over Na_2SO_4, filtered and concentrated to afford pure **18** (1.20 g, 99%) as a colorless oil. Analytical data for **18**: IR (film) 3373, 2935, 2872, 1479, 1489 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.92 (dd, *J* = 13.8, 7.5 Hz, 1H), 2.50 (ddd, *J* = 15.1, 11.5, 6.3 Hz, 1H), 2.40 (ddd, 12.9, 8.7, 5.8 Hz, 1H), 2.26 (dddd, *J* = 15.1, 4.5, 4.5, 1.4 Hz, 1H), 1.98-1.75 (m, 6H), 1.54-1.40 (m, 2H), 1.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.8, 75.4, 57.4, 54.1, 38.6, 32.6, 31.8, 25.9, 23.2, 23.0; LRMS (EI): Mass calcd for $C_{10}H_{16}O_2$ $[M]^+$, 166. Found $[M]^+$, 166. $[\alpha]_D$: –27.71 ($CHCl_3$, c = 1).



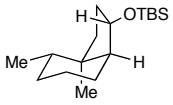
(1*S*,3a*S*,7a*S*)-1-(*tert*-butyldimethylsilyloxy)-3a-methylhexahydro-1*H*-inden-4(2*H*)-one (6): To a flame dried flask equipped with magnetic stirring bar and rubber septum was added ketone **18** (1.20 g, 7.2 mmol) and CH_2Cl_2 (24 mL, 0.3 M). The reaction vessel was cooled to 0 °C in an ice/water bath. Imidazole (1.5 g, 21.6 mmol) was added in one portion. After 5 minutes TBSCl (3.26 g, 21.6 mmol) was added in one portion. The flask was then removed from the ice bath and allowed to warm to 20 °C. After 6 hours the reaction was diluted with 30 mL CH_2Cl_2 and washed with 10 mL H_2O. The layers were separated and the organic layer was washed with aqueous sat. NaCl (10 mL) and dried over Na_2SO_4, filtered and concentrated. The material was purified by flash column chromatography with 5% EtOAc in hexanes to 10% EtOAc in hexanes as an eluent to afford silyl ether **6** (2.00 g, 98%) as a colorless oil. Analytical data for **6**: IR (film) 2930, 2883, 2857, 1708, 1462, 1109 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.78 (dd, *J* = 14.6, 7.8 Hz, 1H), 2.50 (ddd, *J* = 14.9, 11.4, 6.2 Hz, 1H), 2.37 (ddd, *J* = 12.9, 8.9, 6.5 Hz, 1H), 2.25 (dddd, *J* = 14.8, 4.2, 4.2, 1.4 Hz, 1H), 1.95-1.77 (m, 5H), 1.71-1.67 (m, 1H), 1.50-1.36 (m, 2H), 1.27 (s, 3H), 0.87 (s, 9H), 0.020 (s, 3H), 0.016 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.3, 75.2, 57.2, 53.3, 38.6, 32.4, 31.3, 26.0, 23.092, 23.086, 22.8, 18.3, -4.1, -4.5; LRMS (ES): Mass calcd for $C_{16}H_{30}O_2Si$ $[M+1]^+$, 283. Found $[M+1]^+$, 283; $[\alpha]_D$: –10.7 ($CHCl_3$, c = 1.0).



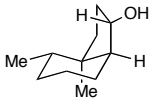
***tert*-butyldimethyl((1*S*,3a*S*,7a*S*)-3a-methyl-4-methyleneoctahydro-1*H*-inden-1-yloxy)silane (7)**: To a round bottom flask equipped with magnetic stirring bar, rubber septum, and N_2 inlet was added methyl-triphenylphosphonium bromide (azeotroped with benzene 3x, 9.9 g, 27.7 mmol) and toluene (68.3 mL, 0.1 M). To the flask was added dropwise freshly prepared KHMDS solution (30 mL, 0.82 M in toluene). After one hour of stirring at 20 °C, the reaction was cooled to 0 °C and a solution of ketone **6** (1.93 g, 6.83 mmol) in toluene (68.3 mL, 0.1 M) was added dropwise to the phosphonium ylide through a cannula. After the ketone was completely added the reaction was allowed to warm to 20 °C and stir for three hours. Upon consumption of starting material the reaction was quenched with H_2O (30 mL) and extracted with Et_2O (2 x 30 mL). The combined organic layers were washed with aqueous sat. NaCl (20 mL), dried over Na_2SO_4, filtered and concentrated. The solid was then diluted with hexanes and filtered. The solid material was washed with hexanes (5 x 20 mL). The combined filtrate was concentrated. The yellow oil was purified by flash column chromatography with 1% EtOAc in hexanes as an eluent affording alkene **7** (1.55 g, 81%) as a colorless oil. Analytical data for **7**: IR (film) 3080, 2929, 2893, 2856, 1741, 1636, 1383, 1254, 1097 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.69 (dd, *J* = 1.5, 1.5 Hz, 1H), (4.67 (*J* = 1.5, 1.5 Hz, 1H), 4.01-3.96 (m, 1H), 2.21 (m, 1H), 2.14-2.10 (m, 1H), 2.07-1.97 (m, 2H), 1.70-1.42 (m, 7H), 1.18 (s, 3H), 0.87 (s, 9H), 0.021 (s, 3H), 0.019 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.1, 106.5, 75.2, 56.1, 45.8, 35.1, 33.3, 31.2, 27.1, 26.3, 24.3, 23.0, 18.4, -4.2, -4.4; LRMS (ES): Mass calcd for $C_{17}H_{32}OSi$ $[M-1]^+$, 279. Found $[M-1]^+$, 279. $[\alpha]_D$: +1.1 ($CHCl_3$, c = 0.63).



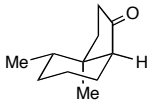
***tert*-butyl((1*S*,3a*S*,7a*S*)-3a,4-dimethyl-2,3,3a,6,7,7a-hexahydro-1*H*-inden-1-yloxy)dimethylsilane (8)**: To a flame dried Schlenk flask was added alkene **7** (1.43 g, 5.1 mmol) and CH_2Cl_2 (50 mL, 0.1 M). The solution was then degassed. After degassing, the flask was purged with H_2 using a balloon. H_2 was also bubbled through the solution. The flask was cooled to 0 °C and Crabtree's catalyst (41 mg, 0.051 mmol) was added in one portion. H_2 was bubbled through the solution until the liquid became colorless. The reaction was then allowed to stir under H_2 atmosphere at 20 °C. After 12 hours the solution was concentrated, diluted with diethyl ether, and filtered through silica gel. The solution was concentrated and purified by flash column chromatography with 1% EtOAc in hexanes as an eluent to afford **8** (1.42 g, 99%) as a colorless oil. Analytical data for **8**: IR (film) 2953, 2929, 2857, 1471, 1381, 1260, 835 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.28 (m, 1H), 3.92 (dd, *J* = 13.0, 6.6 Hz, 1H), 1.94-1.91 (m, 2H), 1.80-1.73 (m, 1H), 1.66-1.45 (m, 6H), 1.12 (s, 3H), 0.89 (s, 9H), 0.89 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.2, 121.6, 75.6, 54.4, 43.1, 35.1, 33.6, 27.4, 26.2, 22.3, 20.3, 19.3, 18.5, -4.1, -4.3; LRMS (EI): Mass calcd for $C_{17}H_{32}OSi$ $[M]^+$, 280. Found $[M]^+$, 280; $[\alpha]_D$: +40.1 ($CHCl_3$, c = 1)



***tert*-butyl((1*S*,3a*R*,4*S*,7a*S*)-3a,4-dimethyloctahydro-1*H*-inden-1-yloxy)dimethylsilane (10)**: To a conical flask was added silyl ether x (1.40 g, 5.0 mmol) and 95% EtOH (100 mL, 0.05 M). The solution was then transferred to an H-CUBE (30 °C, H_2 (40 bar)). The solution was concenctrated to yield a 6:1 mixture of diastereomers favoring **10**. The material was purified by flash column chromatography with 100% hexanes to 1% EtOAc in hexanes as an eluent to afford **10** (982 mg, 69%) as a colorless oil. Analytical data for **10**: IR (film) 2956, 2928, 2877, 1463, 1382, 1111, 1088, 835 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.23-4.21 (m, 1H), 2.02-1.96 (m, 1H), 1.67-1.62 (m, 2H), 1.49-1.36 (m, 10H), 1.25-1.21 (m, 1H), 1.12-1.09 (m, 1H), 0.884 (s, 9H), 0.876 (s, 3H), 0.75 (d, *J* = 6.64 Hz, 3H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 74.4, 55.0, 41.9, 35.6, 35.0, 32.1, 30.7, 21.8, 21.7, 20.0, 18.2; LRMS (ES): Mass calcd for $C_{17}H_{34}OSi$ $[M+1]^+$, 283. Found $[M+1]^+$, 283; $[\alpha]_D$: +40.5 ($CHCl_3$, c = 1)

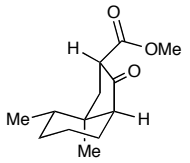


(1*S*,3a*R*,4*S*,7a*S*)-3a,4-dimethyloctahydro-1*H*-inden-1-ol (19): To a round bottom flask equipped with magnetic stirring bar and rubber septum was added silyl ether **10** (800 mg, 2.8 mmol). The material was diluted with THF (28 mL, 0.1 M) and the flask was cooled to 0 °C in an ice/water bath. TBAF (2.8 mL, 1M in THF) was added slowly. Once TBAF had been fully added the flask was removed from the ice/water bath and allowed to warm to 20 °C. After 6 hours the reaction was diluted with CH_2Cl_2 and washed with aqueous sat. NH4Cl. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organics were washed with aqueous sat. NaCl, dried over Na_2SO_4, filtered and concentrated. The material was purified by flash column chromatography with 20% EtOAc in hexanes as an eluent to afford **19** (471 mg, 99%) as a colorless oil. Analytical data for **19**: IR (film) 3325, 2956, 2924, 2867, 1461, 1068 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.29 (dddd, *J* = 4.7, 4.7, 8.6, 8.6 Hz, 1H), 2.14-2.12 (m, 1H), 1.69 (m, 2H), 1.55-1.37 (m, 5H), 1.25-1.22 (m, 3H), 1.12 (ddd, *J* = 3.6, 12.8, 12.8 Hz, 1H), 0.90 (s, 3H), 0.76 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 74.4, 55.7, 42.8, 35.6, 34.6, 31.8, 30.5, 22.0, 21.8, 19.4, 16.7; LRMS (ES): Mass calcd for $C_{11}H_{20}O$ $[M+1]^+$, 169. Found $[M+1]^+$, 169; $[\alpha]_D$: +7.7 ($CHCl_3$, c = 0.13)

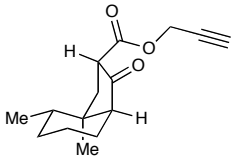


(3a*R*,4*S*,7a*S*)-3a,4-dimethyloctahydro-1*H*-inden-1-one (11): To a flame dried round bottom flask equipped with magnetic stirring bar and rubber septum was added alcohol **19** (400 mg, 2.4 mmol). The material was dissolved in CH_2Cl_2 (12 mL, 0.2 M) while under N_2 atmosphere. Dess-Martin periodinane (1.12 g, 2.6 mmol) was then added in one portion. After 3 hours the reaction was diluted with 20 mL CH_2Cl_2 and washed with aqueous 10% $Na_2S_2O_3$. The layers were separated and the organic layer was washed a second time with aqueous 10% $Na_2S_2O_3$. The organic layer was washed with aqueous sat. NaCl, dried over Na_2SO_4, filtered, and concentrated. The material was purified by flash column chromatography with 5% Et_2O in pentane as an eluent to afford ketone **11** (391 mg, 98%) as a colorless oil. Analytical data for **11**: IR (film) 2956,

2927, 2861, 1738, 1462 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.24 (ddd, *J* = 10.0, 2.40, 1.35 Hz, 1H), 2.23 (dd, *J* = 10.87, 8.22 Hz, 1H), 2.07-2.02 (m, 2H), 1.91-1.89 (m, 1H), 1.50-1.35 (m, 4H), 1.18-1.09 (m, 3H), 1.06 (s, 3H), 0.85 (d, *J* = 6.46 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 220.2, 58.1, 41.8, 34.9, 33.9, 31.4, 29.9, 23.0, 20.5, 20.1, 16.6; LRMS (EI): Mass calcd for $C_{11}H_{18}O$ $[M]^+$, 166. Found $[M]^+$, 166; $[\alpha]_D$: +16.59 ($CHCl_3$, c = 1).

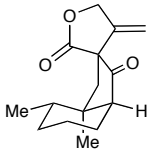


(2*S*,3a*R*,4*S*,7a*S*)-methyl 3a,4-dimethyl-1-oxooctahydro-1*H*-indene-2-carboxylate (20): To a flame dried round bottom flask equipped with magnetic stirring bar and rubber septum at 0 °C was added LDA (1.51 mL, 1.09 M in THF/hexanes) from a stock solution. The flask was cooled to –78 °C and a solution of ketone **11** (300 mg, 1.8 mmol) in THF (9 mL, 0.2 M) in a flame-dried conical vial was added dropwise through a cannula. After the addition of **11** had completed the reaction was allowed to stir for 60 minutes at –78 °C. A solution of Mander's reagent (198 μL, 2.5 mmol) in THF (2 mL, 1.25 M) in a flame-dried conical flask was added dropwise to the enolate. The reaction was allowed to stir for three hours at –78 °C under N_2 atmosphere. Upon consumption of starting material, to the reaction was added aqueous sat. NH_4Cl (5 mL). The solution was poured into a separatory funnel containing CH_2Cl_2 (30 mL). The flask was rinsed with CH_2Cl_2 (2 x 5 mL) and the material was extracted. The layers were separated and the organic layer was washed with aqueous sat. NaCl, dried over Na_2SO_4, filtered, and concentrated. The material was purified by flash column chromatograph with 5% Et_2O in pentane as an eluent to afford **20** and its enol tautomer (295 mg, 73%) as a colorless oil. Analytical data for **20**: IR (film) 3388, 2958, 2929, 2855, 1755, 1728 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.73 (s, 3H), 3.28 (dd, *J* = 11.07, 8.75 Hz, 1H), 2.35 (dd, *J* = 13.32, 8.74 Hz, 1H), 2.13-2.12 (m, 1H), 2.09-2.06 (m, 1H), 1.87 (dd, *J* = 13.3, 11.1 Hz, 1H), 1.52-1.37 (m, 4H), 1.14-1.05 (m, 2H), 1.11 (s, 3H), 0.87 (d, *J* = 6.39 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.8, 170.5, 58.0, 52.5, 52.1, 39.9, 35.9, 35.0, 29.6, 22.9, 20.5, 19.6, 16.4; LRMS (ES): Mass calcd for $C_{13}H_{20}O_3$ $[M+1]^+$, 225. Found $[M+1]^+$, 225; $[\alpha]_D$: +33.6 ($CHCl_3$, c = 0.64).

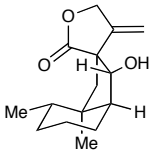


(2*S*,3a*R*,4*S*,7a*S*)-prop-2-ynyl 3a,4-dimethyl-1-oxooctahydro-1*H*-indene-2-carboxylate (12): To a round bottom flask equipped with magnetic stirring bar was added 4Å ms. The flask was flame dried and equipped with a rubber septum. To the flask was added toluene (3 mL) through a syringe. The septum was removed briefly and DMAP (9 mg, 0.07 mmol) was added. Propargyl alcohol (322 μL, 5.5 mmol), which was distilled over CaH2, was added through a syringe. A solution of **18** (246 mg, 1.1 mmol) in toluene (2 mL, 0.55 M) was added through a cannula to the reaction vessel. The septum was removed and quickly replaced with a reflux condenser. The reaction was heated to 100 °C under N_2 atmosphere. After 30 hours the reaction was cooled to 20 °C and aqueous sat. NH_4Cl (3 mL) was added. The solution was extracted CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with aqueous sat. NaCl, dried

over Na_2SO_4, filtered, and concentrated. The material was purified by flash column chromatography with 10% Et_2O in pentane to 30% Et_2O in pentane to afford **12** as a 9:1 mixture of diastereomers and its enol tautomer (200 mg, 82%) as a light yellow oil. Analytical data for **12**: IR (film) 3275, 2961, 2931, 2851, 1756, 1733, 1463, 1141 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.74 (d, *J* = 2.48 Hz, 1H), 4.71 (d, *J* = 2.51 Hz, 1H), 3.32 (dd, *J* = 11.2, 8.7 Hz, 1H), 2.49 (dd, *J* = 2.5, 2.5 Hz, 1H), 2.39 (dd, *J* = 13.3, 8.7 Hz, 1H), 2.14-2.13 (m, 1H), 2.10-2.06 (m, 1H), 1.88 (dd, *J* = 13.3, 11.7 Hz, 1H), 1.53-1.37 (m, 4H), 1.12-1.08 (m, 2H), 1.11 (s, 3H), 0.87 (d, *J* = 6.41, Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.1, 169.3, 77.2, 75.2, 58.1, 52.8, 52.0, 40.0, 36.0, 35.0, 29.6, 22.9, 20.5, 19.6, 16.4; LRMS (ES): Mass calcd for $C_{15}H_{20}O_3$ $[M+1]^+$, 249. Found $[M+1]^+$, 249. $[\alpha]_D$: +29.5 ($CHCl_3$, c = 1.0).

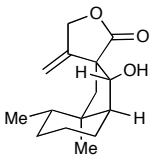


(2'*S*,3a'*R*,4'*S*,7a'*S*)-3a',4'-dimethyl-4-methyleneoctahydro-2*H*-spiro[furan-3,2'-indene]-1',2(3'*H*)-dione (13): To flame dried flask equipped with magnetic stirring bar was added $Mn(OAc)_3•H_2O$ (627 mg, 2.7 mmol) and degassed (freeze-pump-thaw) absolute ethanol (4 mL). A solution of ester **12** (200 mg, 0.9 mmol) in degassed absolute ethanol (6 mL, 0.15 M) was transferred dropwise to the reaction vessel through a cannula. After 20 hours the reaction was filtered through a mixture of SiO_2 and celite with Et_2O as the eluent. The material was concentrated and purified by flash column chromatography with 10% EtOAc in hexanes to 20% EtOAc in hexanes as an eluent to afford **13** (140 mg, 70%) as a colorless oil. Analytical data for **13**: IR (film) 2961, 2931, 2850, 1779, 1734, 1461, 1266, 1139 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.15-5.14 (m, 1H), 5.08-5.07 (m, 1H), 5.02 (ddd, *J* = 12.8, 2.5, 2.5 Hz, 1H), 4.82 (ddd, *J* = 12.8, 1.6, 1.6 Hz, 1H), 2.64 (d, *J* = 14.4 Hz, 1H), 2.41-2.40 (m, 1H), 1.98-1.94 (m, 1H), 1.69 (d, *J* = 14.4 Hz, 1H), 1.61-1.41 (m, 3H), 1.26-1.24 (m, 1H), 1.22 (dddd, *J* = 13.9, 3.9, 3.9, 0.2 Hz, 1H), 1.16 (s, 3H), 1.12 (dd, *J* = 12.2, 2.9 Hz, 1H), 0.94 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.1, 175.1, 145.8, 106.9, 70.7, 61.3, 54.9, 40.7, 38.9, 35.4, 29.7, 22.1, 20.0, 19.8, 16.3; LRMS (EI): Mass calcd for $C_{15}H_{20}O_3$ $[M]^+$, 248. Found $[M]^+$, 248; $[\alpha]_D$: +24.6 ($CHCl_3$, c = 0.1).

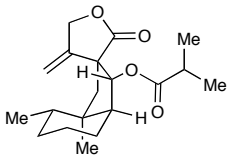


(1'*R*,2'*S*,3a'*R*,4'*S*,7a'*S*)-1'-hydroxy-3a',4'-dimethyl-4-methylenedecahydro-2*H*-spiro[furan-3,2'-inden]-2-one (14): To flame-dried flask was added samarium (692 mg, 4.6 mmol) and THF (4.6 mL, distilled over benzophenone/sodium). 1,2-diiodoethane (1.18 g, 4.2 mmol) was added in one portion. After 3 hours the reaction became a deep blue color and H_2O (327 μL, 18.2 mmol) was added. Upon the addition of water the blue solution became purple. Immediately, a solution of ketone **13** (130 mg, 0.52 mmol) in THF (10.4 mL, 0.05 M) was added dropwise to SmI_2 through a cannula. After 2 hours the reaction was diluted with diethyl ether (30 mL) and washed with H_2O (5 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (2 x 20 mL). The combined organic layers were washed with aqueous sat.

$NaHCO_3$, and then aqueous sat. NaCl. The material was dried over Na_2SO_4, filtered, and concentrated. The material was purified by flash column chromatography with 40% EtOAc in hexanes as an eluent to afford **14** (116 mg, 89%) as a white solid. Analytical data for **14**: mp = 107-109 °C; IR (film) 3433, 2957, 2929, 2857, 1755, 1460, 1354 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.30 (bs, 1H), 5.13 (bs, 1H), 4.88 (dddd, *J* = 12.8, 2.6, 2.6, 0.8 Hz, 1H), 4.74 (dddd, *J* = 12.8, 1.7, 1.7, 1.7 Hz, 1H), 4.50 (dd, *J* = 10.9, 10.9, 1H), 2.40 (dd, *J* = 14.6, 1.2 Hz, 1H), 1.80-1.42 (m, 8H), 1.15-1.07 (m, 1H), 0.98 (s, 3H), 0.84 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.4, 148.2, 109.0, 80.7, 71.8, 55.8, 52.7, 47.3, 38.9, 35.9, 30.7, 21.3, 21.0, 20.2, 16.6; LRMS (ES): Mass calcd for $C_{15}H_{22}O_3$ $[M+1]^+$, 251. Found $[M+1]^+$, 251. $[\alpha]_D$: +52.1 ($CHCl_3$, c = 1.3).

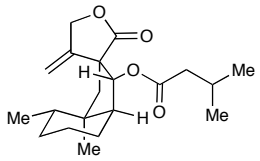


(1'*R*,2'*R*,3a'*R*,4'*S*,7a'*S*)-1'-hydroxy-3a',4'-dimethyl-4-methylenedecahydro-2*H*-spiro[furan-3,2'-inden]-2-one (bakkenolide S) (15): To round bottom flask equipped with magnetic stirring bar was added alcohol **14** (20 mg, 0.08 mmol). The flask was sealed with a rubber septum and equipped with a N_2 inlet. The material was diluted with THF (2 mL) and cooled to 0 °C in an ice/water bath. TBAF (100 μL, 1M in THF) was added dropwise. After 40 minutes of stirring at 0 °C under N_2 atmosphere, to the reaction was added H_2O (2 mL). The solution was diluted with EtOAc (10 mL) and extracted. The layers were separated and the aqueous layer was extracted a second time with EtOAc (10 mL). The combined organic layers were washed with aqueous 10% $NaHCO_3$, followed by aqueous sat. NaCl. The solution was dried over Na_2SO_4, filtered, and concentrated. The material was purified by flash column chromatography with 30% EtOAc in hexanes to 40% EtOAc in hexanes as a gradient to afford **15** (14.4 mg, 72%) as 5:1 mixture of **15** to **14**. Analytical data for **15**: mp = 130-133 °C; IR (film) 3436, 2958, 2931, 2872, 1758, 1446, 1163 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.13-5.11 (m, 2H), 4.90 (ddd, J = 12.8, 2.4, 2.4 Hz, 1H), 4.80 (ddd, J = 12.8, 1.8, 1.8 Hz, 1H), 4.21 (dd, J = 10.0, 7.5 Hz, 1H), 2.09 (d, J = 14.4 Hz, 1H), 2.09-2.05 (m, 1H), 1.90 (d, J = 14.3 Hz, 1H), 1.72-1.68 (m, 1H), 1.60-1.40 (m, 4H), 1.25-1.20 (m, 2H), 1.01 (s, 3H), 0.85 (d, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.1, 149.8, 106.3, 82.4, 70.9, 56.6, 52.8, 46.4, 40.3, 36.4, 30.8, 21.1, 20.9, 19.7, 16.4; LRMS (ES): Mass calcd for $C_{15}H_{22}O_3$ $[M+1]^+$, 251. Found $[M+1]^+$, 251; $[\alpha]_D$: –29.2 (MeOH, c = 0.23)



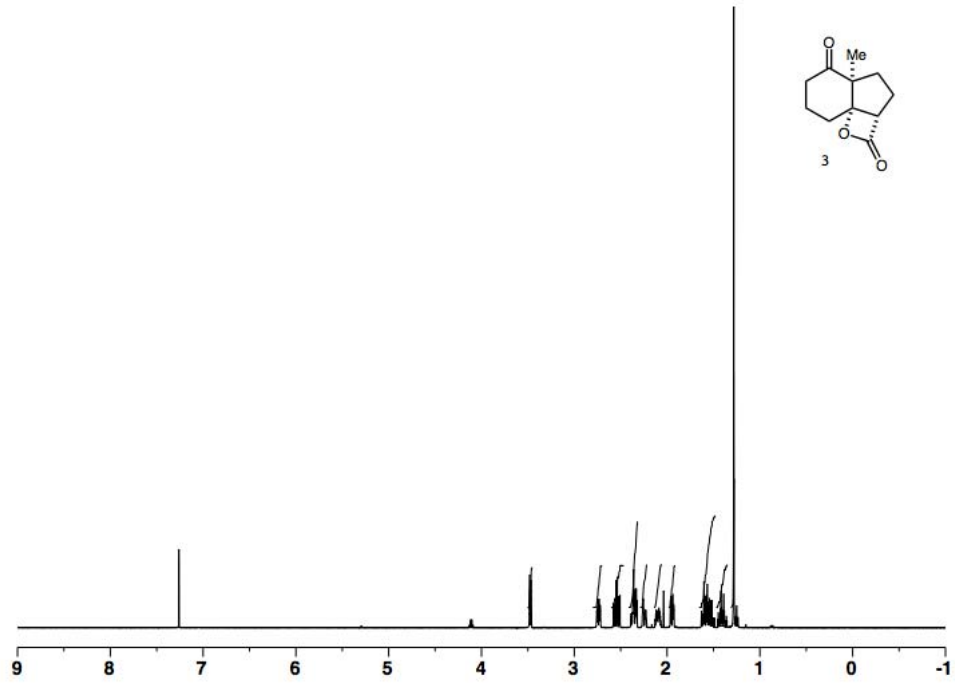
(1'*R*,2'*R*,3a'*R*,4'*S*,7a'*S*)-3a',4'-dimethyl-4-methylene-2-oxodecahydro-2*H*-spiro[furan-3,2'-indene]-1'-yl isobutyrate (bakkenolide I) (16): To round bottom flask equipped with magnetic stirring bar was added alcohol **14** (10 mg, 0.04 mmol). The flask was sealed with a rubber septum and equipped with a N_2 inlet. The material was diluted with THF (1 mL, 0.04 M) and cooled to 0 °C in an ice/water bath. TBAF (50 μL, 1M in THF) was added dropwise. After 40 minutes, to the reaction was added Et_3N (53 mL, 0.38 mmol) through a syringe. *iso*-Butyryl

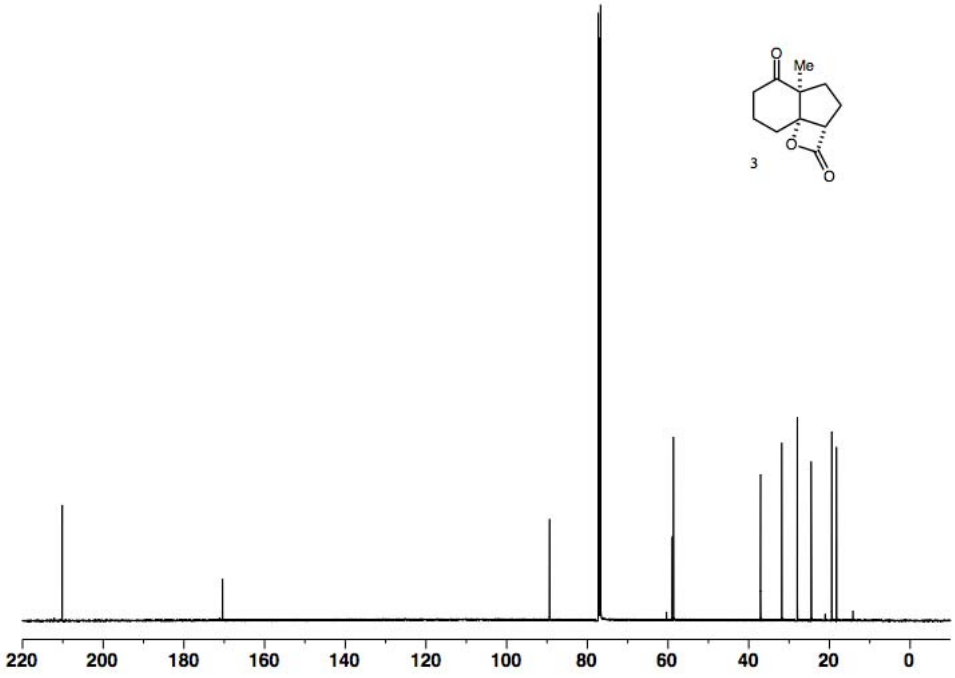
chloride (32 μL, 0.3 mmol) was added through a syringe followed by DMAP (5 mg, 0.04 mmol). The reaction was allowed to warm to 20 °C. After 40 hours the reaction was diluted with Et_2O (10 mL) and washed with aqueous sat. NaCl (3 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The combined organic layers were washed with aqueous sat. NaCl, dried over $MgSO_4$, filtered, and concentrated. The material was purified by flash column chromatography with 5% EtOAc in hexanes to 10% EtOAc in hexanes to afford **16** (8.8 mg, 69%). Analytical data for **16**: IR (film) 2962, 2928, 2856, 1780, 1738, 1466, 1159 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.44 (d, *J* = 11.7 Hz, 1H), 5.20 (dd, *J* = 2.7, 2.7 Hz, 1H), 5.14 (dd, *J* = 3.2, 3.2 Hz, 1H), 4.69 (ddd, *J* = 13.0, 1.8, 1.8 Hz, 1H), 4.66 (ddd, *J* = 13.0, 2.4, 2.4, 1H), 2.58-2.52 (m, 1H), 2.36-2.33 (m, 1H), 2.19 (d, *J* = 14.3 Hz, 1H), 1.96 (d, *J* = 14.3 Hz, 1H), 1.53-1.50 (m, 5H), 1.38-1.34 (m, 1H), 1.22-1.18 (m, 1H), 1.16 (d, *J* = 7.0 Hz, 3H), 1.15 (d, *J* = 6.9 Hz, 3H), 1.04 (s, 3H), 0.88 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4, 172.7, 148.3, 107.8, 82.8, 70.6, 54.2, 49.7, 47.2, 43.4, 40.1, 36.2, 30.7, 25.5, 22.3, 22.3, 21.2, 20.9, 19.5, 16.3; LRMS (ES): Mass calcd for $C_{19}H_{28}O_4$ $[M+H_2O]^+$, 338. Found $[M+H_2O]^+$, 338. $[\alpha]_D$: –5.3 (MeOH, c = 0.53).

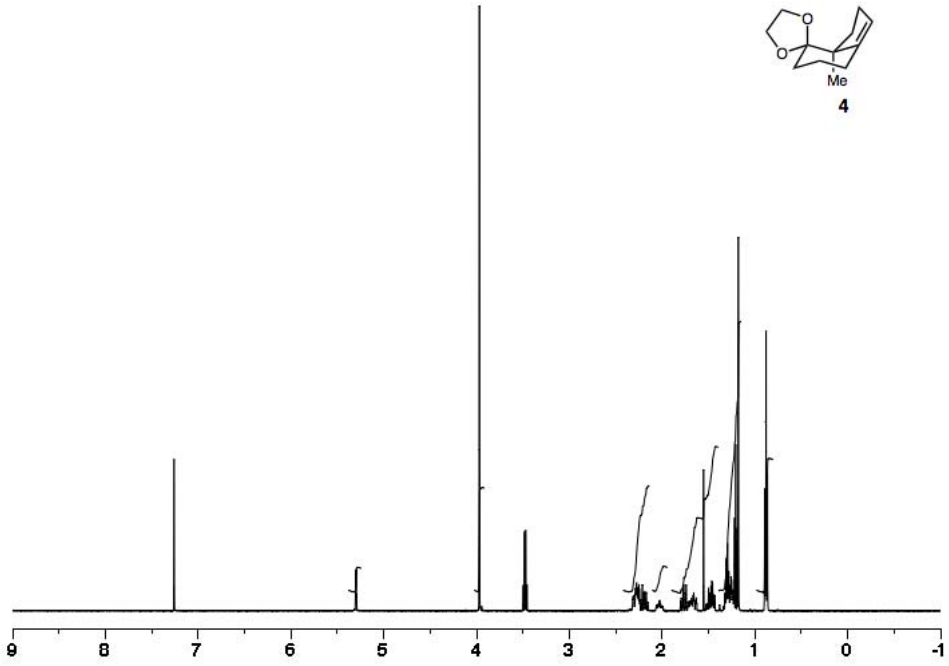


(1'*R*,2'*R*,3a'*R*,4'*S*,7a'*S*)-3a',4'-dimethyl-4-methylene-2-oxodecahydro-2*H*-spiro[furan-3,2'-indene]-1'-yl 3-methylbutanoate (bakkenolide J) (17): To round bottom flask equipped with magnetic stirring bar was added alcohol **14** (20 mg, 0.08 mmol). The flask was sealed with a rubber septum and equipped with a N_2 inlet. The material was diluted with THF (2 mL, 0.04 M) and cooled to 0 °C in an ice/water bath. TBAF (100 μL, 1M in THF) was added dropwise. After 40 minutes, to the reaction was added Et_3N (106 mL, 0.72 mmol) through a syringe. *iso*-Valeryl chloride (74 μL, 0.6 mmol) was added through a syringe followed by DMAP (10 mg, 0.08 mmol). The reaction was allowed to warm to 20 °C. After 40 hours the reaction was diluted with Et_2O (20 mL) and washed with aqueous sat. NaCl (6 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The combined organic layers were washed with aqueous sat. NaCl, dried over $MgSO_4$, filtered, and concentrated. The material was purified by flash column chromatography with 5% acetone in hexanes to afford **17** (17 mg, 64%). Analytical data for **17**: IR (film) 2961, 2930, 2872, 1780, 1738, 1464, 1163 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.46 (d, *J* = 11.6 Hz, 1H), 5.21 (bs, 1H), 5.14 (bs, 1H), 4.73-4.65 (m, 2H), 2.36 (ddd, *J* = 3.8, 11.5, 3.8 Hz, 1H), 2.20 (d, *J* = 7.39 Hz, 2H), 2.19 (d, *J* = 14.4 Hz, 1H), 2.12-2.01 (m, 1H), 1.96 (d, *J* = 14.3 Hz, 1H), 1.54-1.48 (m, 4H), 1.40-1.38 (m, 1H), 1.25-1.14 (m, 2H), 1.04 (s, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4, 172.7, 148.3, 107.8, 82.8, 70.6, 54.2, 49.7, 47.2, 43.4, 40.1, 36.2, 30.7, 25.5, 22.3, 22.3, 21.2, 20.9, 19.5, 16.3; LRMS (ES): Mass calcd for $C_{20}H_{30}O_4$ $[M+1]^+$, 335. Found $[M+1]^+$, 335. $[\alpha]_D$: –26.9 (MeOH, c = 0.26).

Selected NMR Spectra



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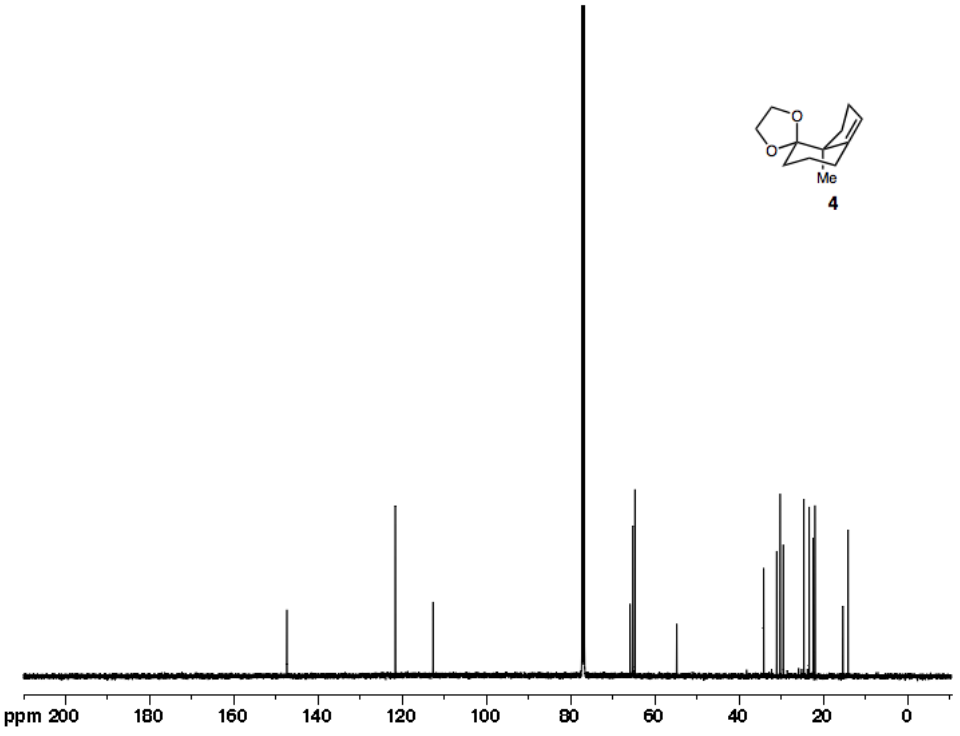
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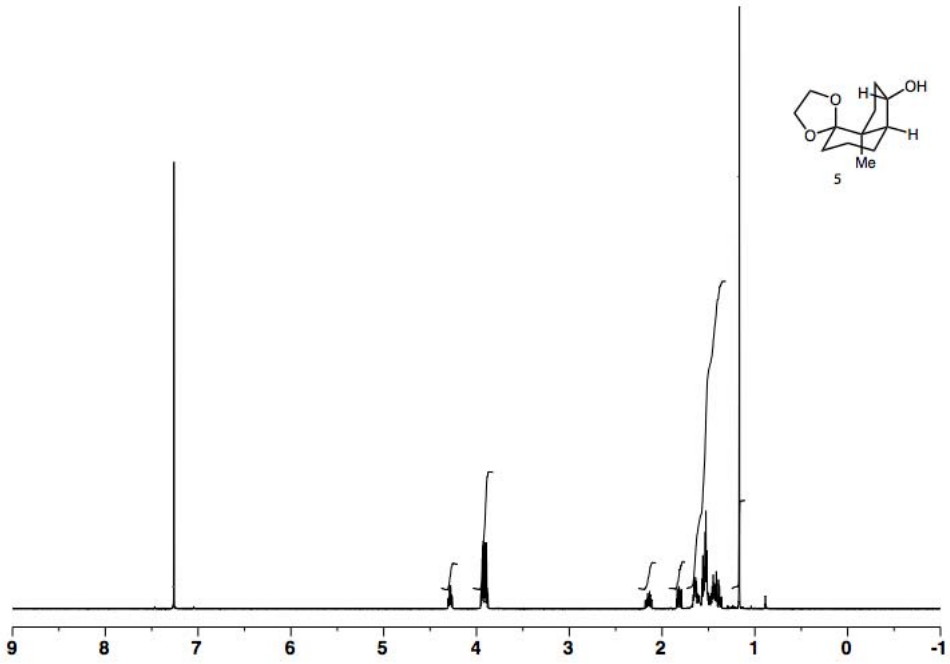
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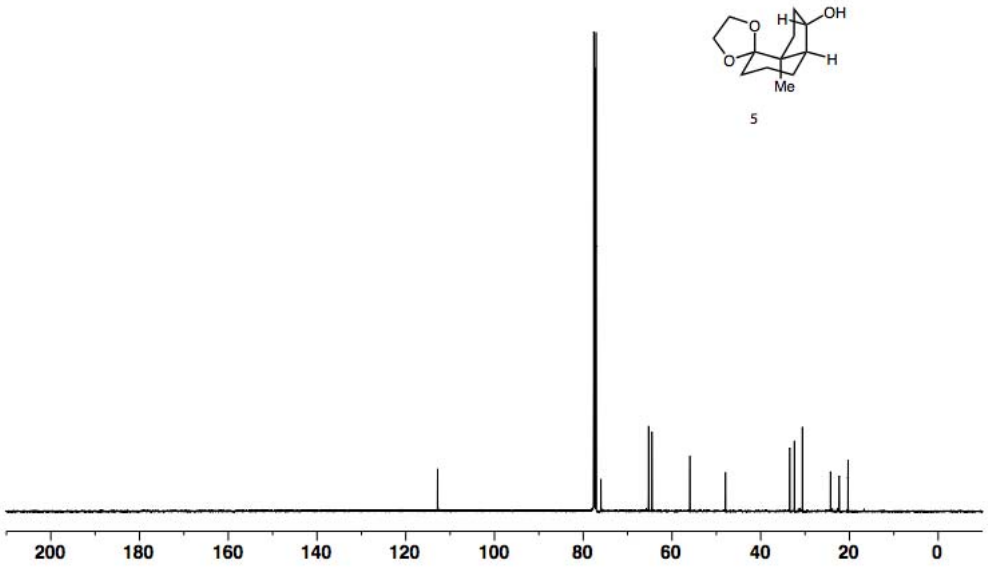
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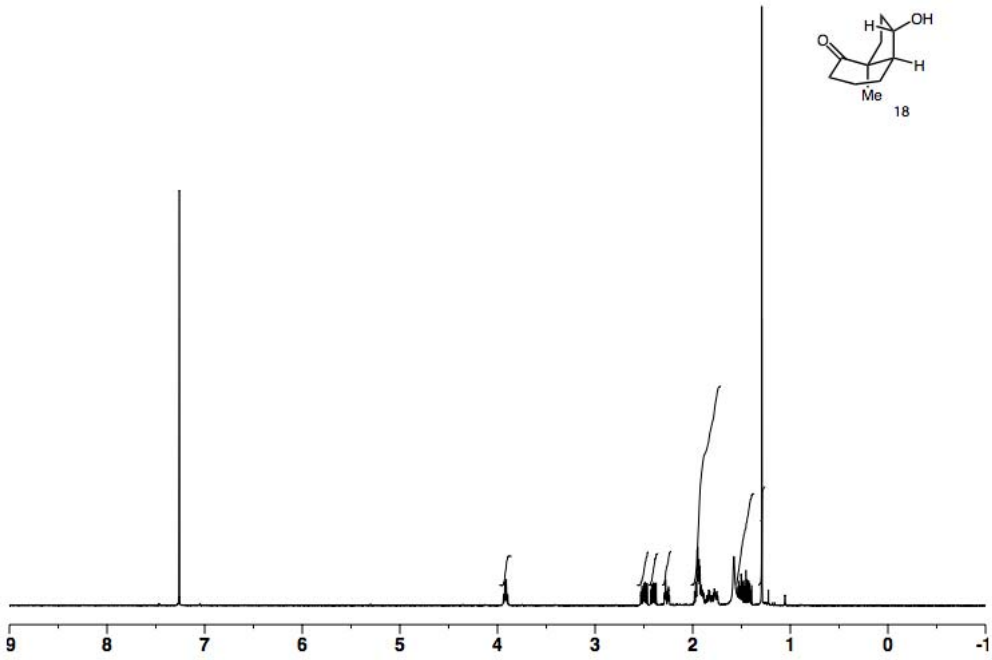
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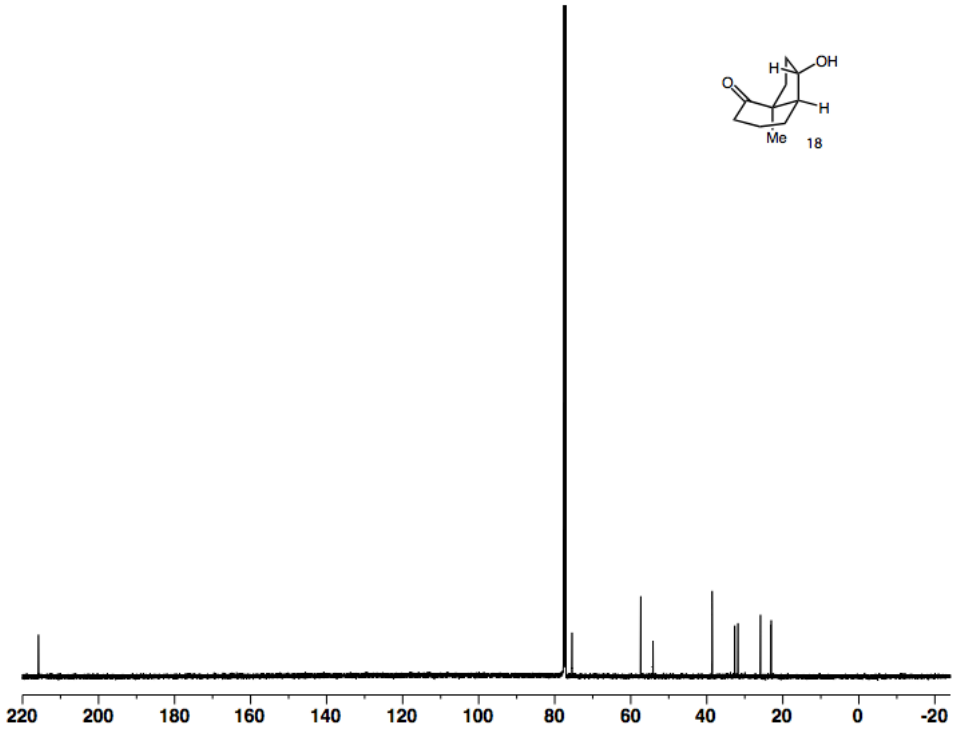
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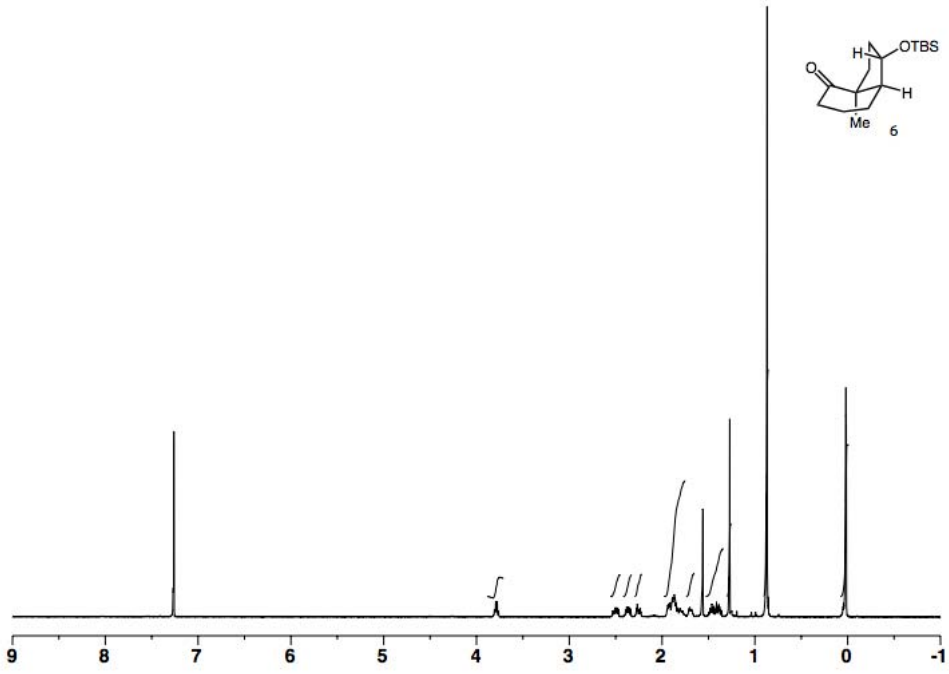
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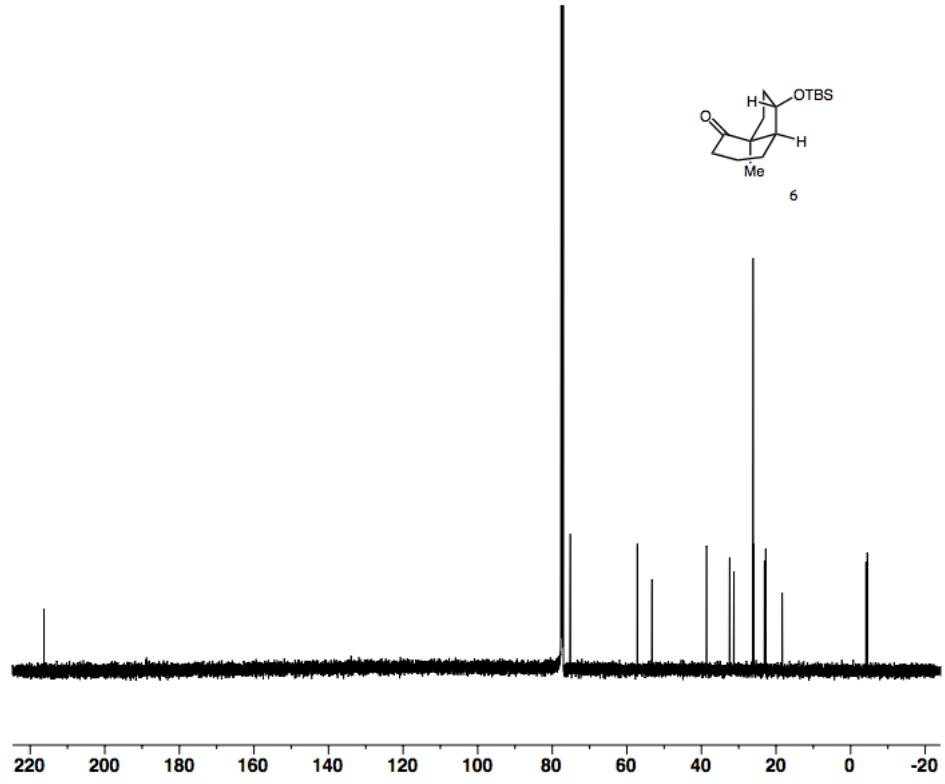
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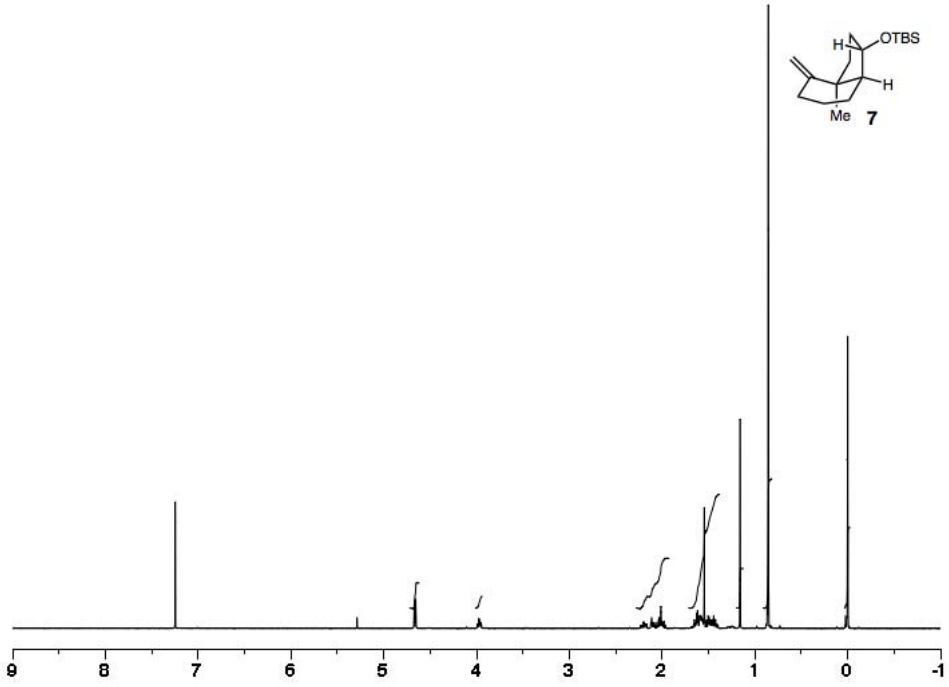
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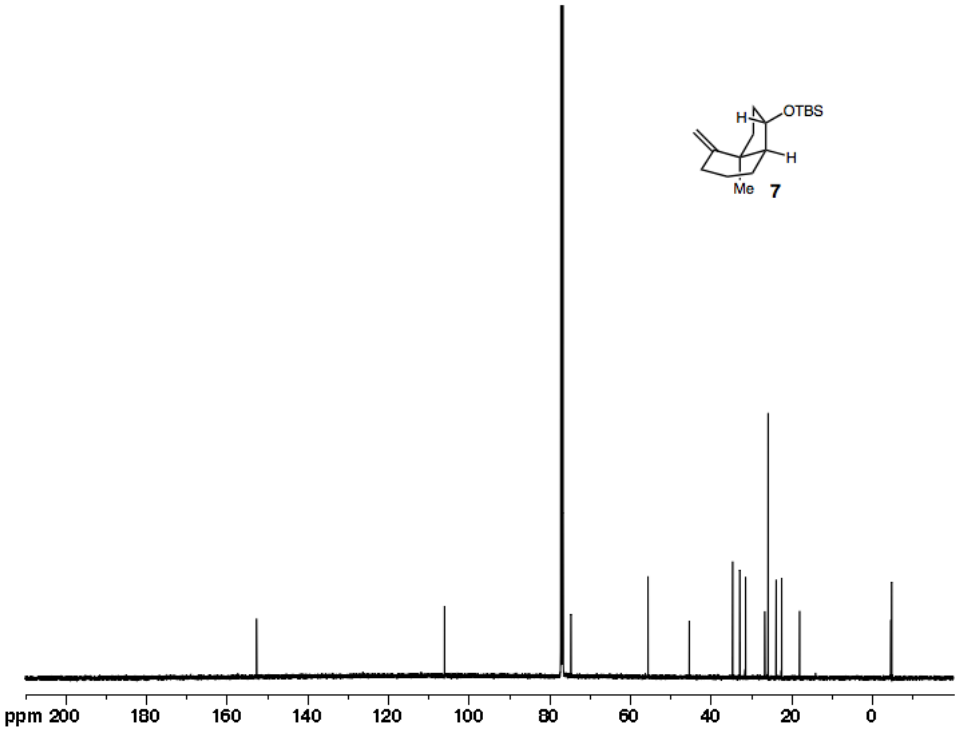
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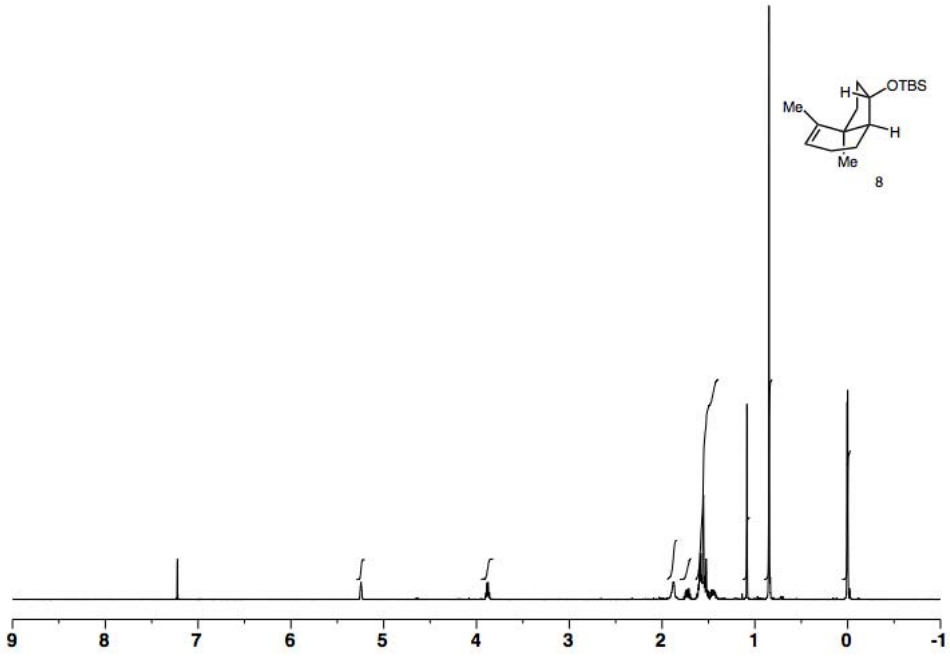
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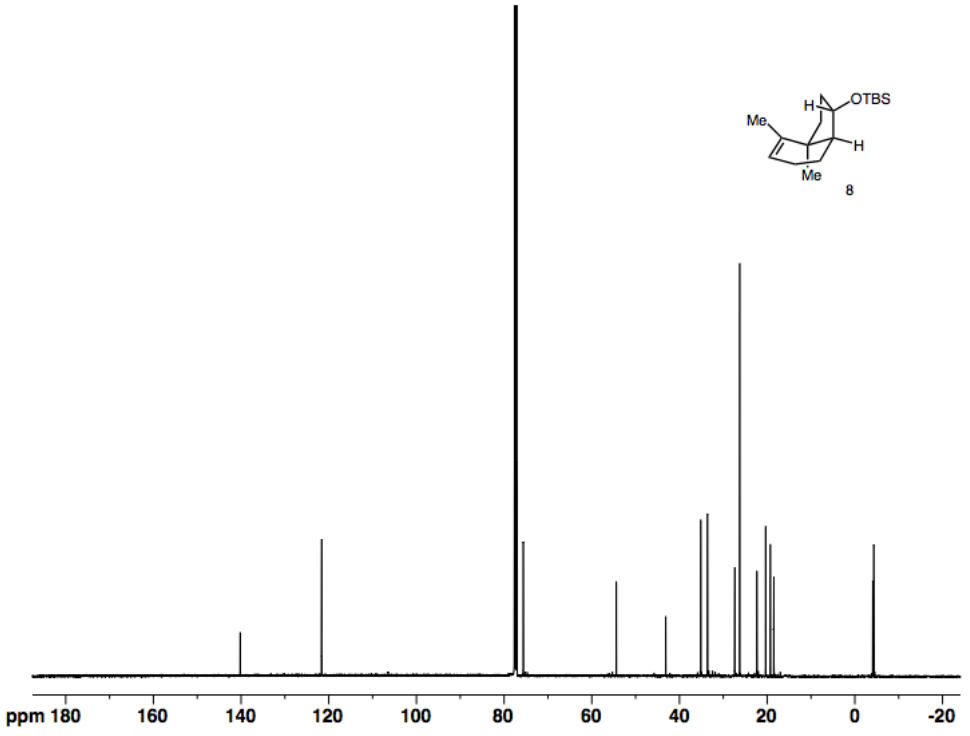
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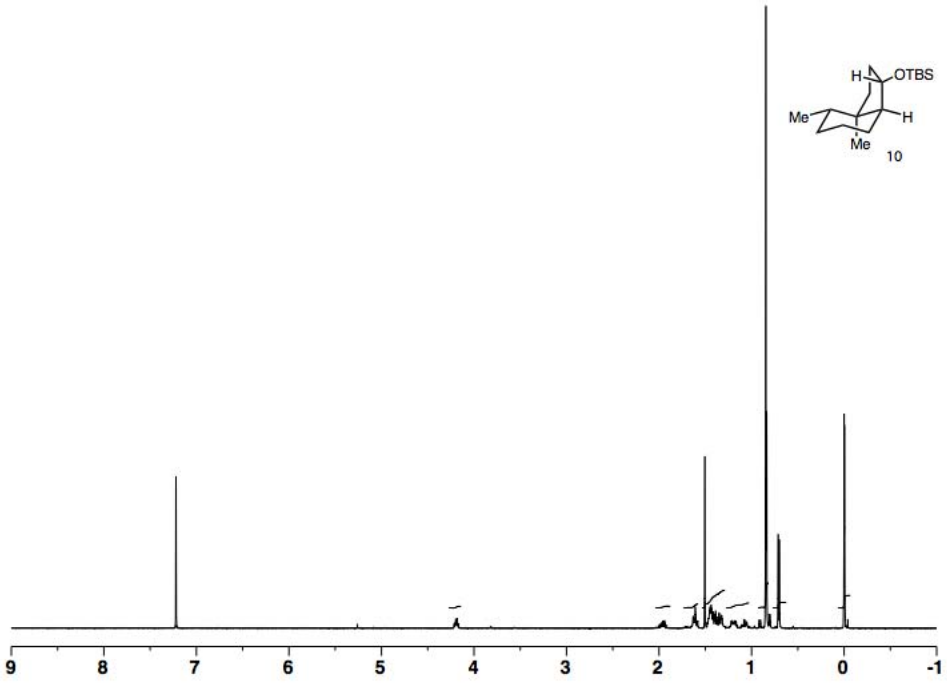
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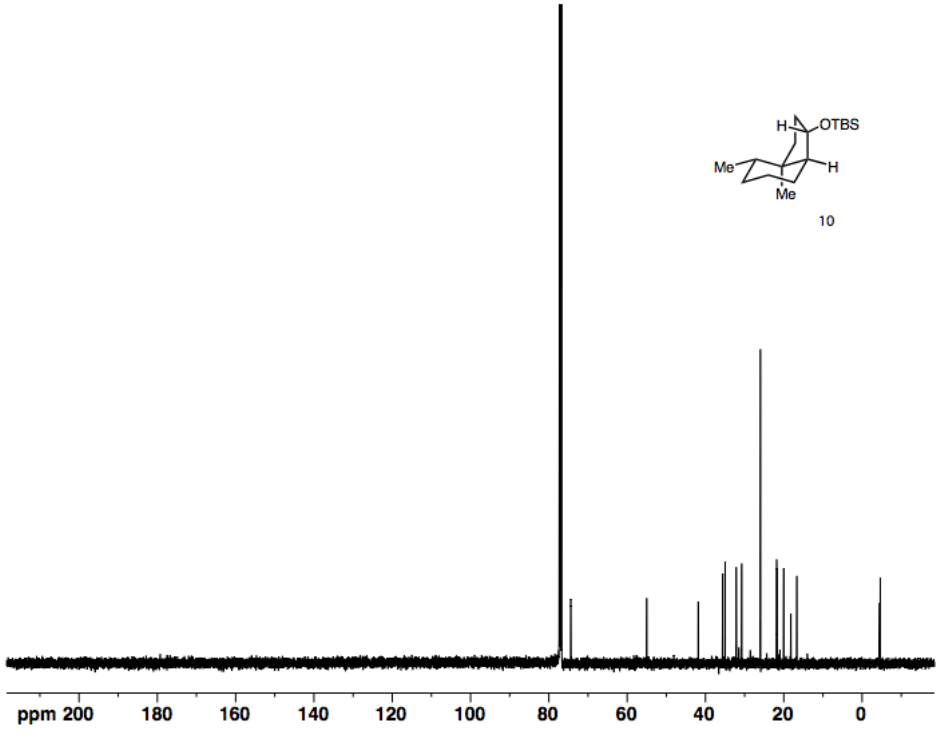
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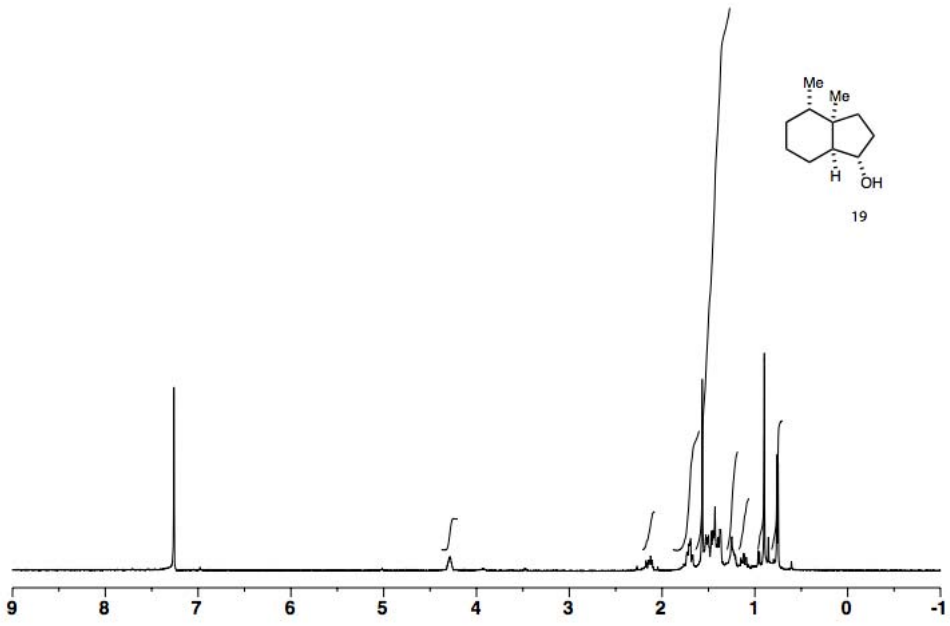
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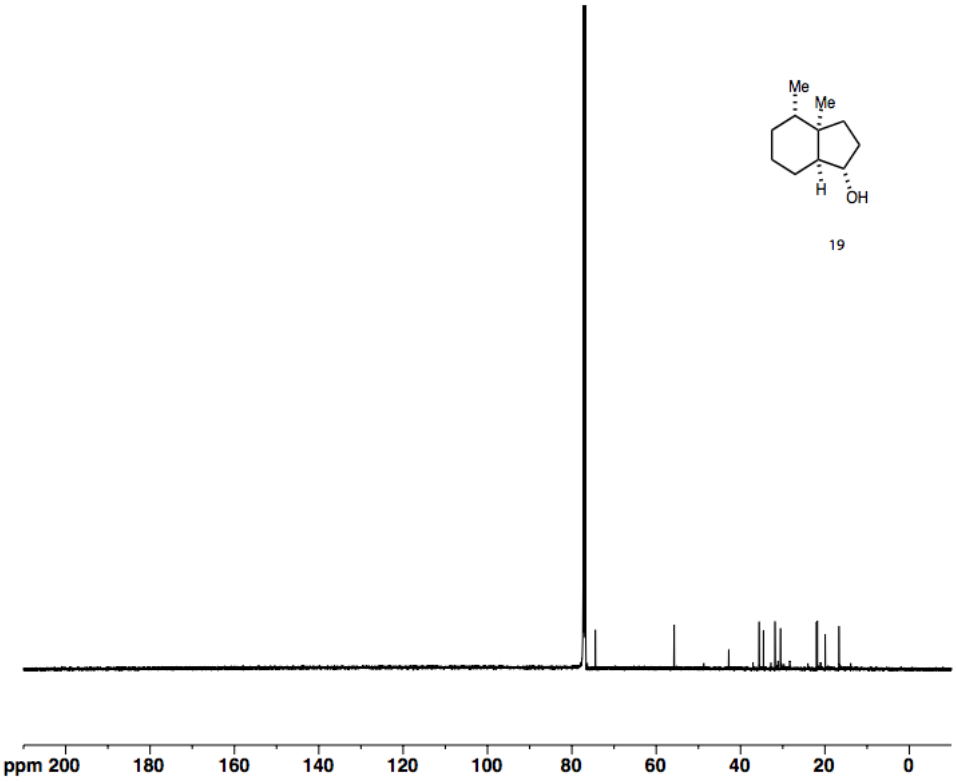
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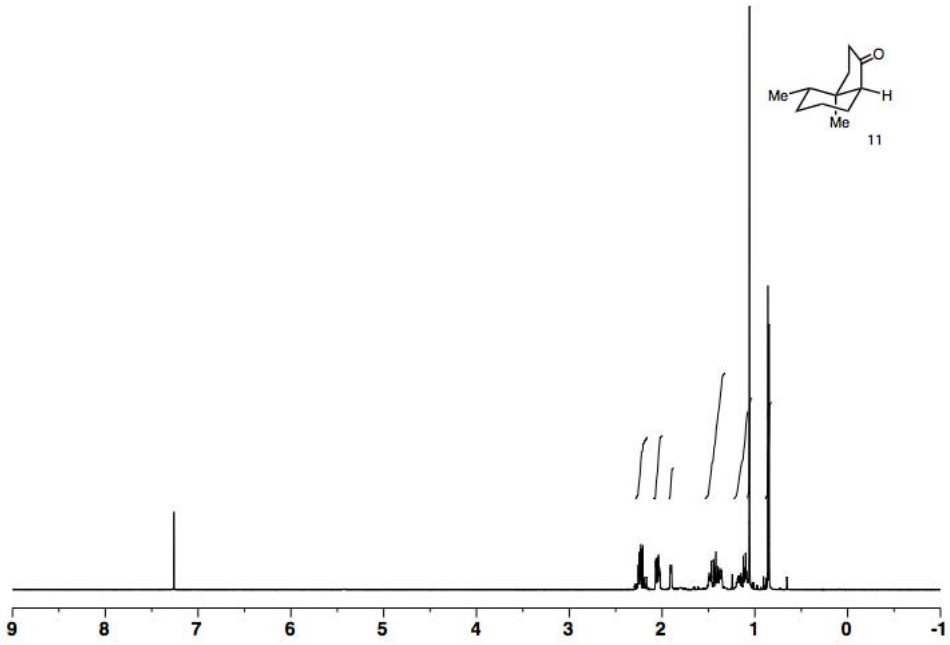
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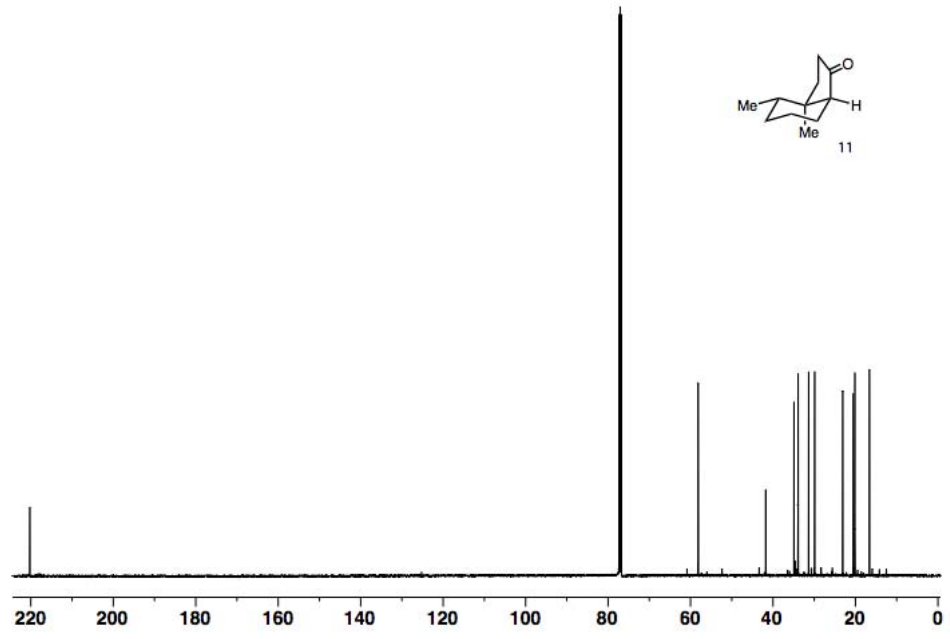
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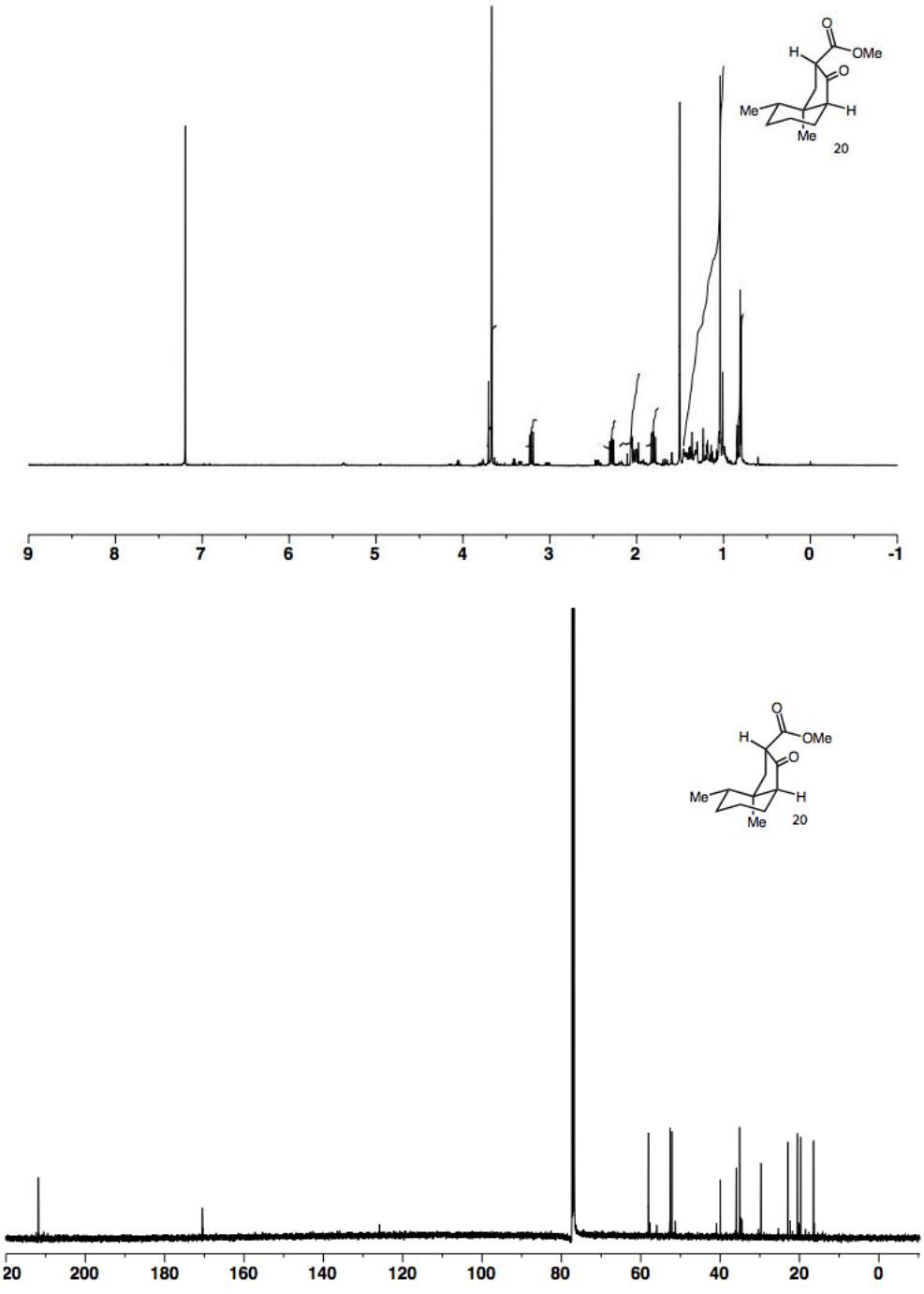
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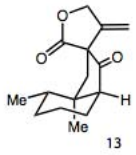
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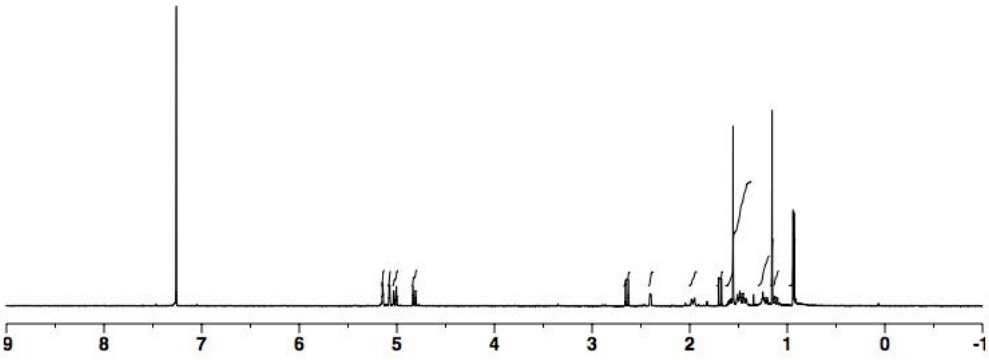
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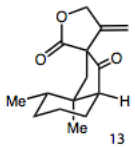
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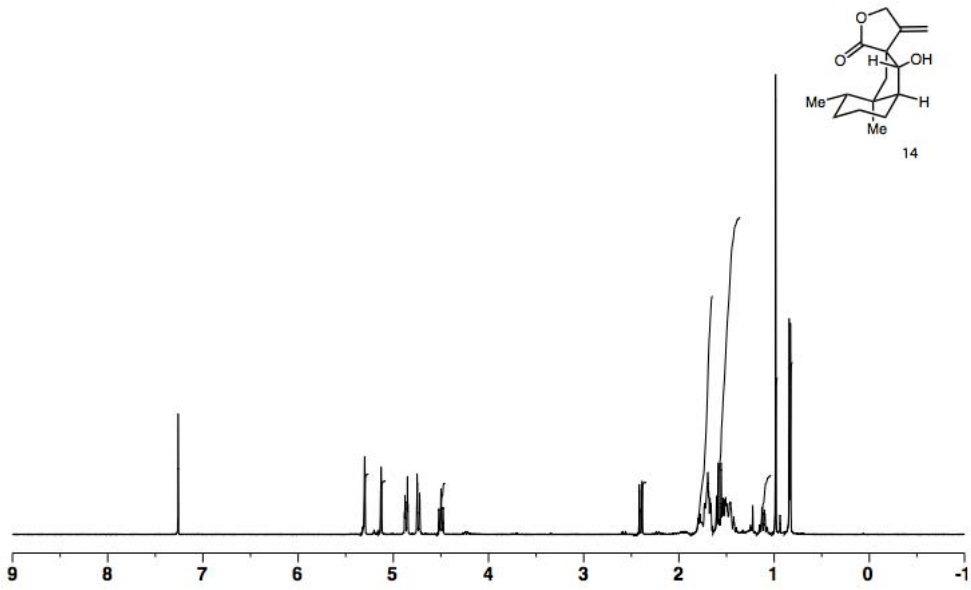
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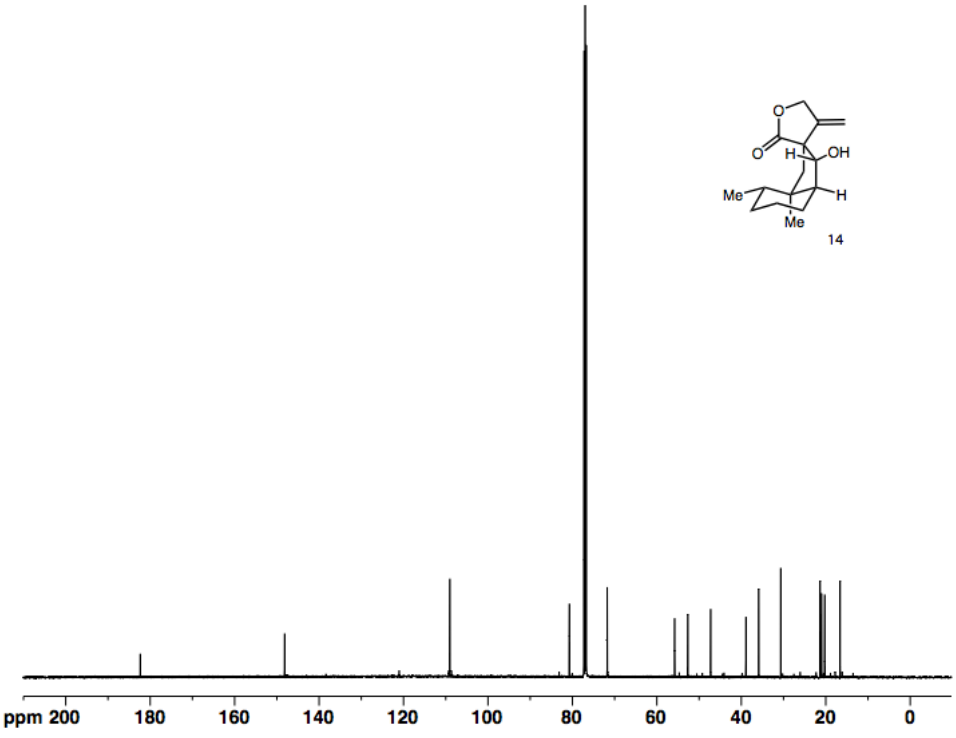
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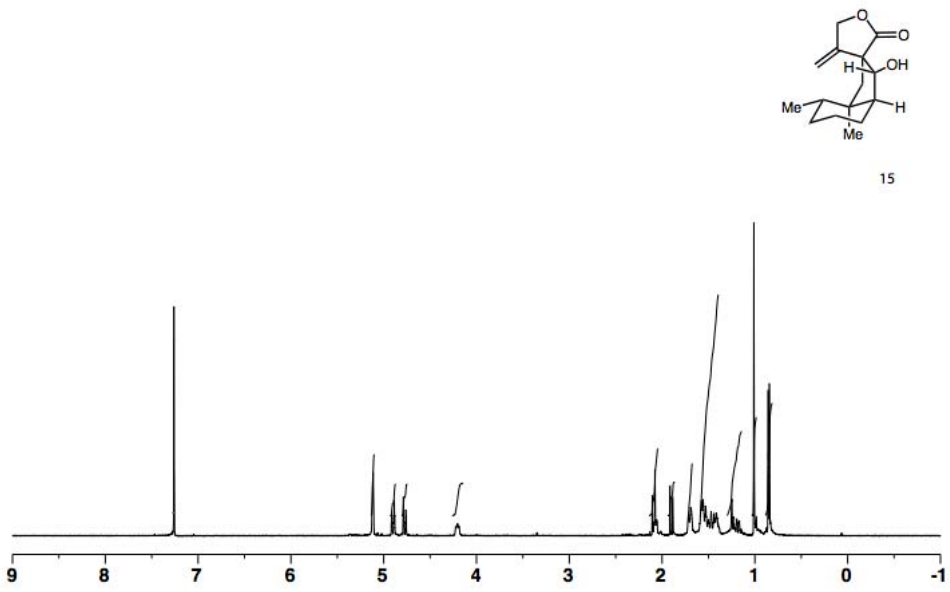
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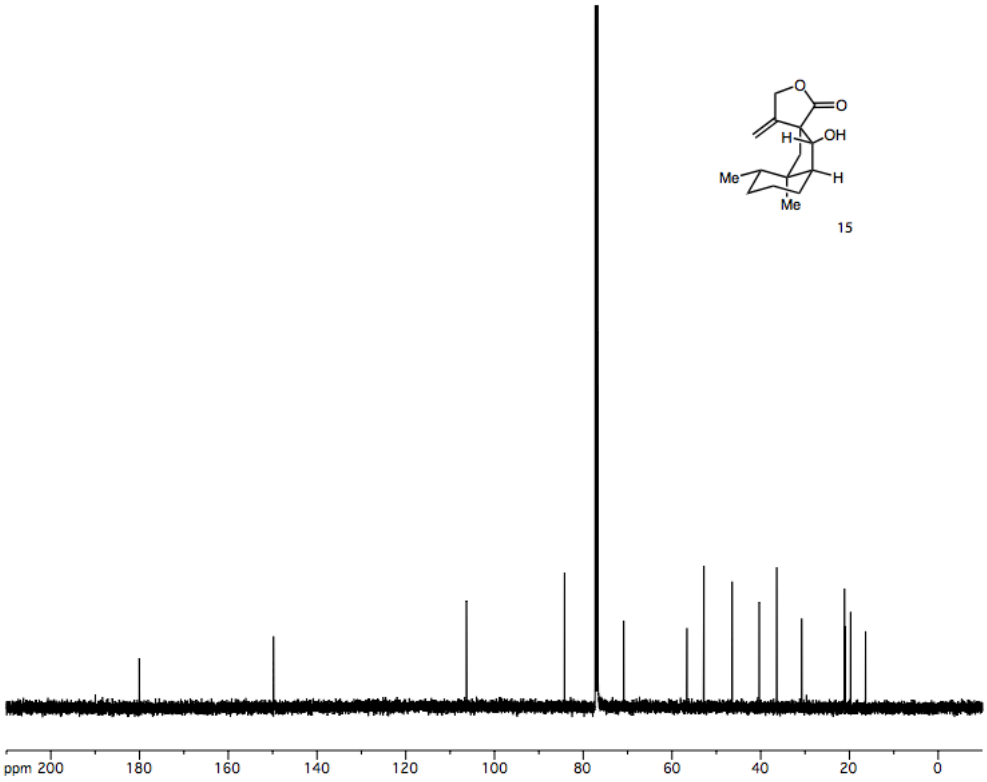
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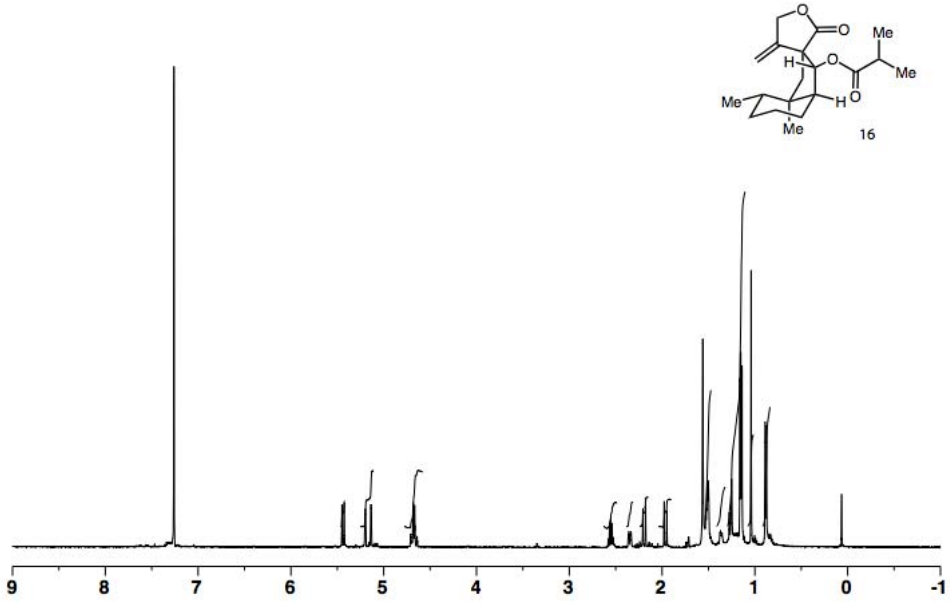
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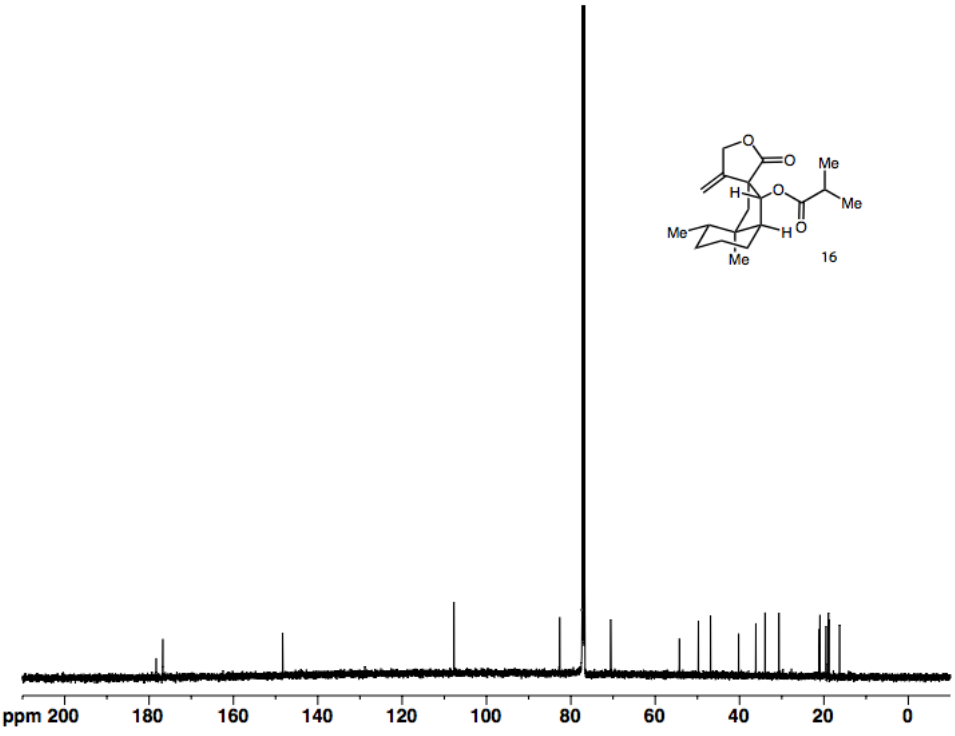
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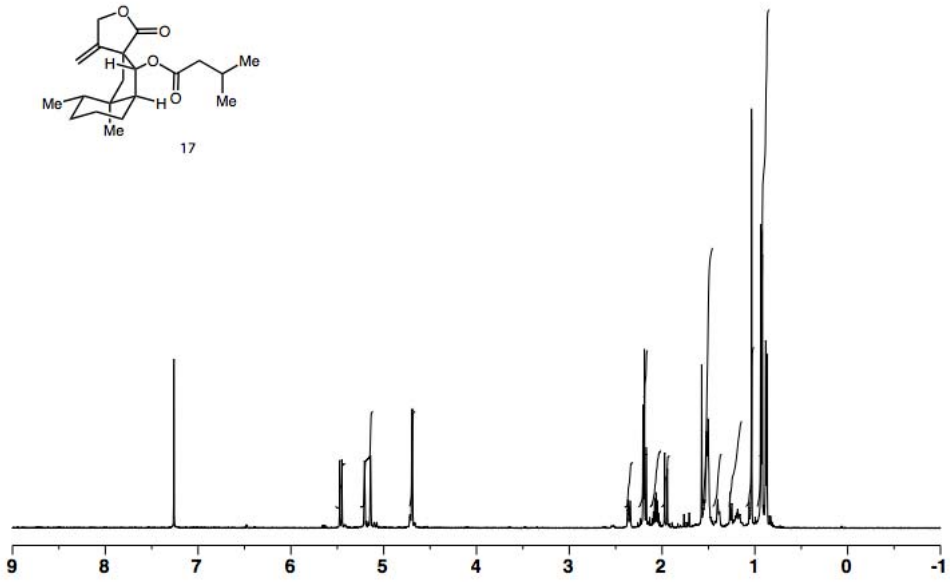
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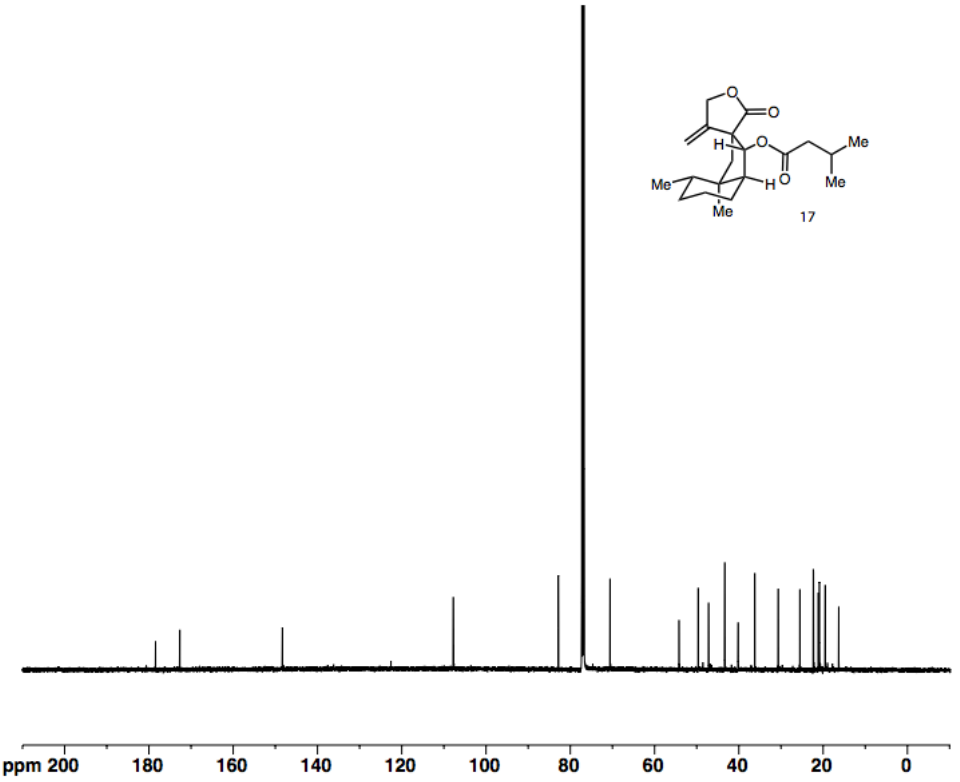
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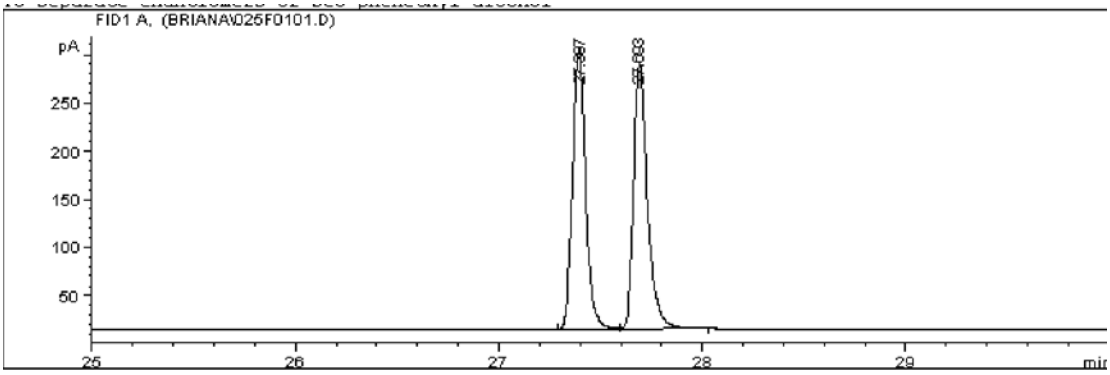
GC Traces

GC Trace of 3 Racemate

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Dilution              :      1.0000

Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
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   2  27.693 VB    0.0664 1296.28491  275.24738 50.09013
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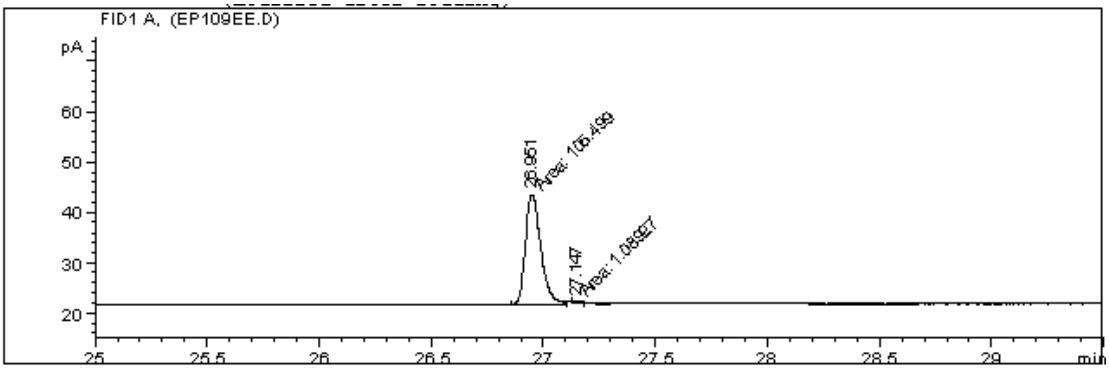
GC Trace of Enantioenriched 3:

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=====================================================================
                        Area Percent Report
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Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
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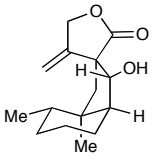
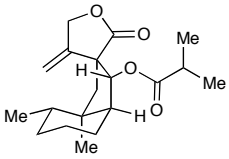
Comparative Analysis of ^{1}H NMR Spectra



Bakkenolide S

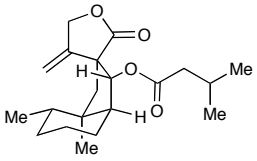
Natural[3]	Synthetic
5.11 (bs)	5.13-5.11 (m, 2H)
4.90 (d, J = 12.8 Hz)	4.90 (ddd, J = 12.8, 2.4, 2.4 Hz, 1H)
4.77 (d, J = 12.8 Hz)	4.80 (ddd, J = 12.8, 1.8, 1.8 Hz, 1H)
4.20 (d, J = 11.2 Hz)	4.21 (dd, J = 10.0, 7.5 Hz, 1H)
2.08 (d, J = 14.0)	2.09 (d, J = 14.4 Hz, 1H)
	2.09-2.05 (m, 1H)
1.90 (d, J = 14.0)	1.90 (d, J = 14.3 Hz, 1H)
	1.72-1.68 (m, 1H)
	1.60-1.40 (m, 4H)
	1.25-1.20 (m, 2H)
1.01 (s)	1.01 (s, 3H)
0.85 (d, 6.4)	0.85 (d, J = 6.7 Hz, 3H)



Bakkenolide I

Natural[3]	Synthetic
5.43 (d, J = 11.6 Hz)	5.44 (d, J = 11.7 Hz, 1H)
5.19 (t, J = 1.8 Hz)	5.20 (dd, J = 2.7, 2.7 Hz, 1H)
5.13 (t, J = 1.8 Hz)	5.14 (dd, J = 3.2, 3.2 Hz, 1H)
4.69 (dt, J = 12.3, 1.8 Hz)	4.69 (ddd, J = 13.0, 1.8, 1.8 Hz, 1H)
4.52 (dt, J = 12.3, 1.8 Hz)	4.66 (ddd, J = 13.0, 2.4, 2.4 Hz, 1H)
2.55 (sept, J = 7.2)	2.58-2.52 (m, 1H)
2.34 (d, J = 11.6 Hz)	2.36-2.33 (m, 1H)
2.19 (d, J = 14.8 Hz)	2.19 (d, J = 14.3 Hz, 1H)
1.96 (d, J = 14.8 Hz)	1.96 (d, J = 14.3, Hz, 1H)
1.56 (m, 4H)	1.53-1.50 (m, 5H)
1.40 (m)	1.38-1.34 (m, 1H)
1.20 (m)	1.22-1.18 (m, 1H)
1.15 (d, J = 7.2 Hz)	1.16 (d, J = 7.0 Hz, 3H)
1.14 (d, J = 7.2 Hz)	1.15 (d, J = 6.9 Hz, 3H)
1.04 (s)	1.04 (s, 3H)
0.89 (d, J = 7.2 Hz)	0.88 (d, J = 6.6 Hz, 3H)

3. T. S. Wu, M. S. Kao, P. L. Wu, F. W. Lin, L. S. Shi, M. J. Liou, C. Y. Li, *Chem. Pharm. Bull.* **1999**, *47*, 375

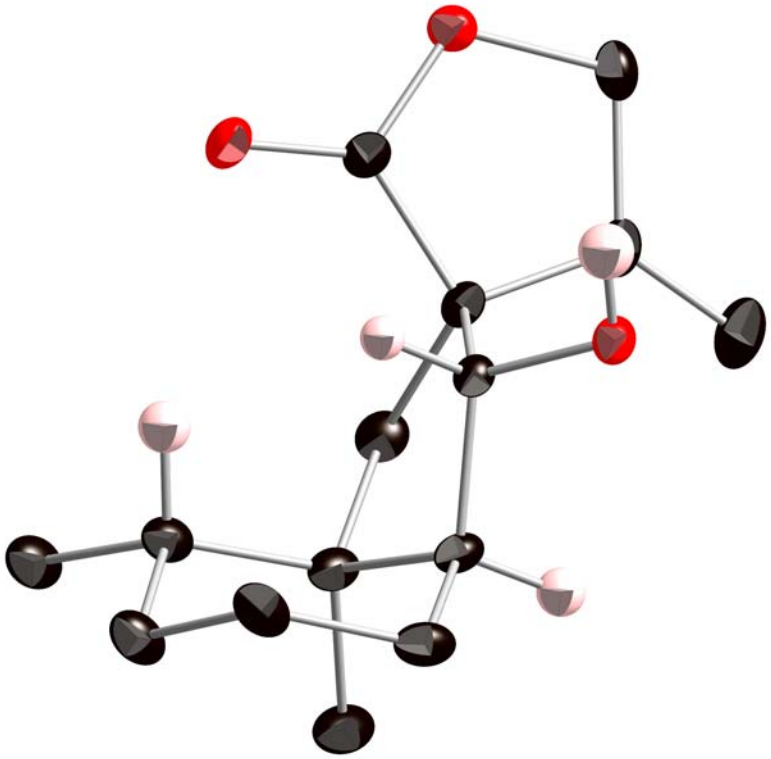


Bakkenolide J

Natural[3]	**Synthetic**
5.47 (d, J = 11.7 Hz)	5.46 (d, J = 11.6 Hz, 1H)
5.21 (t, J = 2.2 Hz)	5.21 (bs, 1H)
5.14 (t, J = 2.2 Hz)	5.14 (bs, 1H)
4.69 (t, J = 2.2 Jz_)	4.73-4.65 (m, 2H)
2.36 (dt, J = 11.7, 4.2 Hz)	2.36 (ddd, J = 3.8, 11.5, 3.8 Hz, 1H)
2.20 (d, J = 7.4 Hz)	2.20 (d, J = 7.39 Hz, 1H)
2.19 (d, J = 14.3 Hz)	2.19 (d, J = 14.4, 1H)
2.07 (m)	2.12-2.01 (m, 1H)
1.96 (d, J = 14.3)	1.96 (d, J = 14.3 Hz, 1H)
1.52 (m, 4H)	1.54-1.48 (m, 4H)
1.40 (m)	1.40-1.38 (m, 1H)
1.15 (m)	1.25-1.14 (m, 2H)
1.04 (s)	1.04 (s, 3H)
0.93 (d, J = 6.7 Hz)	0.93 (d, J = 6.6 Hz, 3H)
0.93 (d, J = 6.7 Hz)	0.93 (d, J = 6.6 Hz, 3H)
0.88 (d, J = 6.6 Hz)	0.88 (d, J = 6.6 Hz, 3H)

X-Ray Crystallography of 14

X-ray diffraction was performed at –120 °C and raw frame data were processed using SAINT. Molecular structure was solved using direct methods and refined by F2 by full-matrix least-squares techniques. The GOF = 1.07 for 166 variables refined to R1 = 0.059 for 3858 reflections with I>2α(I). There was no absorption correction of Flack parameters. Further information is contained in the CCDC file XXX.



X-Ray Crystallography of A

X-ray diffraction was performed at –120 °C and raw frame data were processed using SAINT. Molecular structure was solved using direct methods and refined by F2 by full-matrix least-squares techniques. The GOF = 0.95 for 637 variables refined to R1 = 0.027 for 7845 reflections with I>2α(I). There was no absorption correction of Flack parameters. Further information is contained in the CCDC file 688527.