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Supporting Information

Total Synthesis of the Diterpenoid (+)-Harringtonolide

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Supporting Information

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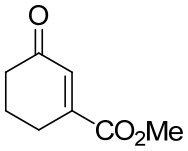
General Information

All reactions involving air or moisture sensitive reagents or intermediates were performed under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Methylene chloride (CH_2Cl_2), diisopropylamine (*i*-Pr_2NH), and triethylamine (Et_3N) were freshly distilled from calcium hydride. Toluene and THF were freshly distilled in the presence of the sodium/benzophenone couple. All reagents were reagent grade and used without purification unless otherwise noted. All extracts were dried over $MgSO_4$ or Na_2SO_4 and concentrated by rotary evaporation below 30 ^oC unless otherwise noted. Proton nuclear magnetic resonance (^1H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were obtained at the indicated field as solutions in $CDCl_3$. Chemical shifts are referenced to the deuterated solvent ($CDCl_3$, δ = 7.27 ppm and 77.0 ppm for ^1H and ^{13}C NMR, respectively) and are reported in parts per million (ppm, δ) relative to tetramethylsilane (TMS, δ = 0.00 ppm). Signal splitting patterns were described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) or broad (br), and coupling constants (J) are reported in Hz. ^1H spectra were recorded on a Brucker Avance 400 Ⅲ spectrometer (400 MHz). ^{13}C NMR spectra were recorded on Brucker Avance 400 Ⅲ spectrometer at 100 MHz. HPLC was recorded on a Waters 600/2996 spectrometer using CHIRALCEL OJ-H, Column No OJHOCE-EAO30. Optical rotations were recorded on a RUDOLPH A21202-T digital polarimeter at ambient temperature. High resolution mass spectra (HRMS) were performed by Analytical Instrument Center at the School of Pharmacy or Department of Chemistry of Lanzhou University on an Electron Spray Injection (ESI) mass spectrometer. Melting point was recorded on a SGW® X-4A melting point apparatus. X-ray diffraction was recorded on a Supernova apparatus.

Experimental Procedures and Characterization Data for (+)-Harringtonolide



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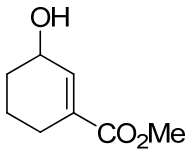
To a 1 L three-necked flask equipped with a stirrer, an ammonia (g) outlet and a cold-finger condenser were added *m*-Anisic acid (70 g, 0.46 mol) and H_2O (90 mL). Ammonia (800 mL) was collected through the condenser containing N_2 (l). Lithium wire (9.6 g, 1.4 mol) was added in small pieces over a period of 30 min and the reaction mixture was stirred vigorously for 4 h. The stirring was stopped and the solution was allowed to warm to room temperature overnight. Then KOH (aq, 1.0 M, 580 mL) was added and stirring was restarted. The solution was heated for 3 h at 60 ^oC and then cooled to about 10 ^oC. Concentrated HCl (72 mL) was added at 0 ^oC until the pH = 2. The aqueous solution was extracted with DCM/^{i}PrOH = 3:1. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was used for the next step without further purification.

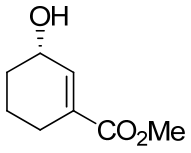
To a solution of the crude product in MeOH (400 mL) was added $SOCl_2$ (44 g, 0.37 mol) at 0 ^oC. The solution was allowed to warm to rt and stirred overnight. The mixture was concentrated under vacuum, diluted with EtOAc, washed with $NaHCO_3$ (aq) and brine sequentially, dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude product was used for the next step without further purification.

To a solution of the crude product in $CHCl_3$ (858 mL) was added DBU (56 g, 0.37 mmol) at 0 ^oC. The solution was stirred at rt for 12 h and then washed with 1.0 M HCl (aq) and brine sequentially. The organic layer was dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc/hexanes = 1:3, R_f = 0.29) to give **9** (35 g, 50% over three steps) as a light yellow oil. **9**: ^1H NMR (400 MHz, $CDCl_3$) δ 6.74 (t, J = 2.0 Hz 1H), 3.83 (s, 3H), 2.61 – 2.57 (m, 2H), 2.47 – 2.44 (m, 2H), 2.10 – 2.03 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 167.0, 148.7, 133.1, 52.6, 37.7, 24.8, 22.1; HRMS (ESI): *m/z* calcd for $C_8H_{11}O_3$ $[M+H]^+$: 155.0703, found: 155.0705.



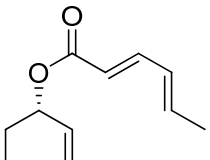
(±)-**8**

To a solution of **9** (28.4 g, 184 mmol) in MeOH (367 mL) was added $NaBH_4$ (6.99 g, 184 mmol) at 0 ^oC. The mixture was stirred for 10 min before it was quenched with NH_4Cl (aq). The aqueous layer was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc/hexanes = 1:3, R_f = 0.22) to giv alcohol (±)-**8** (27.8 g, 98%) as a light yellow oil. (±)-**8**: ^1H NMR (400 MHz, $CDCl_3$) δ 6.88 (d, J = 1.2 Hz, 1H), 4.36 (s, 1H), 3.76 (s, 3H), 2.34 - 2.20 (m, 2H), 1.99 - 1.91 (m, 1H) 1.87 - 1.76 (m, 1H) 1.68 - 1.53 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 139.7, 132.5, 66.0, 51.8, 31.1, 24.2, 19.1; HRMS (ESI): *m/z* calcd for $C_8H_{12}O_3Na$ $[M+Na]^+$: 179.0679, found: 179.0676.



8

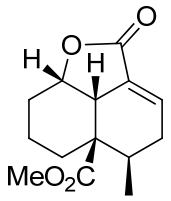
To a solution of **9** (10.2 g, 66.2 mmol) in DCE (200 mL) were added RuCl(*p*-cymene)[(*S*,*S*)-Ts-DPEN] (210 mg, 0.331 mmol), NEt_3 (6.70 g, 66.2 mmol), and HCO_2H (4.88 g, 106 mmol) sequentially at room temperature and the reaction was monitored by TLC. When the reaction was completed, the mixture (organic phase) was washed with $NaHCO_3$ (aq), dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel to give (-)-**8** (10.0 g, 97%, *ee* = 94.0%) as a light brown oil. $[\alpha]_D^{18.2}$ = - 46.1 (*c* 1.28, $CHCl_3$).



7

To a solution of alcohol **8** (30.0 g, 192 mmol) in DCM (550 mL) were added sorbic acid (27.6 g, 246 mmol) and DMAP (23.5 g, 192 mmol). After the solution was cooled to 0 ^oC, DCC (50.7 g,

246 mmol) was added. The solution was allowed to warm to rt and stirred overnight at this temperature. The mixture was filtered using a Buchner funnel and washed with DCM three times. The filtrate was washed with $NaHCO_3$ (aq) and 1.0 M HCl (aq) sequentially. The organic layer was dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc/hexanes = 1:3, R_f = 0.77) to give **7** (47.1 g, 98%) as a light yellow oil. **7**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 - 7.23 (m, 1H), 6.85 - 6.84 (m, 1H), 6.23 - 6.12 (m, 2H), 5.76 (d, J = 15.6 Hz, 1H), 5.49 - 5.46 (m, 1H), 3.75 (s, 3H), 2.40 - 2.22 (m, 2H), 1.98 - 1.90 (m, 1H), 1.86 (d, J = 5.2 Hz, 3H), 1.84 - 1.78 (m, 1H), 1.74 - 1.64 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 166.6, 145.4, 139.6, 136.0, 134.2, 129.7, 118.7, 67.6, 51.8, 27.6, 24.1, 19.0, 18.6; HRMS (ESI): *m/z* calcd for $C_{14}H_{18}O_4Na$ $[M+Na]^+$: 273.1097, found: 273.1095; $[\alpha]_D^{18.9}$ = - 36.6 (*c* 1.61, $CHCl_3$).

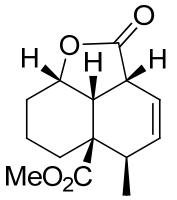


10

A mixture of **7** (57.8 g, 231 mmol) and BHT (5.09 g, 23.1 mmol) was heated at 180 ^{o}C for 24 h, cooled to room temperature, and subjected to purification by flash column chromatography on silica gel (EtOAc/hexanes = 1:3, R_f = 0.32) to give a mixture of **10** and the epimer **10'** (40.0 g). The ^{1}H NMR spectra indicated that the ratio of **10** and **10'** was 2.5:1.

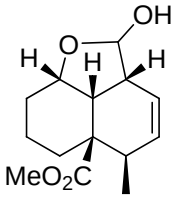
The pure sample of **10** was obtained after **6** was separated in the next step. To a solution of **6** (0.10 g, 0.40 mmol) in $CHCl_3$ was added DBU (0.091 g). After 1 h, the mixture was deluted with EtOAc and washed with 0.1 M HCl (aq). The organic layer was dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc/hexanes = 1:3, R_f = 0.32) to give compound **10** as a light yellow oil (0.095 g, 95%). **10**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (dd, J = 7.2, 3.2 Hz, 1H), 4.94 - 4.88 (m, 1H), 3.74 (s, 3H), 3.40 - 3.38 (m, 1H), 2.62 - 2.54 (m, 1H), 2.27 - 2.20 (m, 1H), 2.19 - 2.11 (m, 2H), 1.79 (d, J = 13.2 Hz, 1H), 1.58 - 1.53 (m, 1H), 1.25 - 1.18 (m, 1H), 1.11 - 0.97 (m, 2H), 0.82 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 169.7, 132.8, 126.7, 76.9, 52.2, 49.6, 37.0, 32.8, 30.6,

30.3, 29.0, 19.3, 17.0; HRMS (ESI): *m/z* calcd for $C_{14}H_{19}O_4$ $[M+H]^+$, 251.1278, found: 251.1275; $[\alpha]_D^{20.2}$ = - 46.1 (*c* 1.02, $CHCl_3$).



6

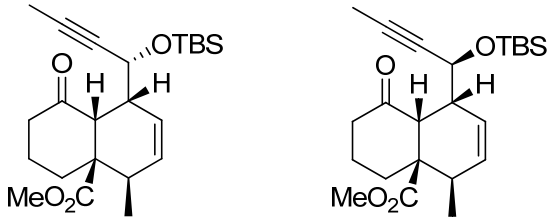
To a solution of freshly distilled diisopropylamine (33.9 mL, 240 mmol) in dry THF (114 mL) was added *n*-BuLi (2.5 M in hexane, 80 mL, 200 mmol) dropwise at - 50 °C. After 20 min, the solution was cooled to - 78 °C and HMPA (55.7 mL, 320 mmol) was added dropwise. After stirring for 10 min, a solution of **10**/**10'** (a mixture, 20 g, 80 mmol, **10**/**10'** = 2.5:1) in dry THF (40 mL) was added dropwise. The reaction mixture was stirred at this temperature for 1 h before AcOH (30 mL) was added as quickly as possible. The mixture was warmed to rt in 0.5 h, diluted with EtOAc (500 mL), and washed with $NaHCO_3$ (aq) until pH = 9 in aqueous. The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc/hexanes = 1:3, R_f = 0.38) to give compound **6** as a light yellow oil (10.2 g, 35 % over two steps). **6**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 - 5.83 (m, 2H), 4.93 (dt, *J* = 6.4, 1.6 Hz, 1H), 3.75 (s, 3H), 3.57 - 3.52 (m, 1H), 3.36 (d, *J* = 10.8 Hz, 1H), 2.24 - 2.18 (m, 1H), 1.95 - 1.89 (m, 1H), 1.81 - 1.71 (m, 1H), 1.70 - 1.60 (m, 1H), 1.59 - 1.51 (m, 3H), 0.80 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 176.6, 131.3, 119.9, 77.8, 52.1, 45.2, 39.1, 37.2, 32.7, 25.9, 22.0, 17.5, 14.3; HRMS (ESI): *m/z* calcd for $C_{14}H_{18}O_4Na$ $[M+Na]^+$, 273.1097, found: 273.1093; $[\alpha]_D^{18.6}$ = - 54.1 (*c* 1.09, $CHCl_3$).



11

To a solution of **6** (5.12 g, 20.5 mmol) in dry THF (100 mL) was added Dibal-H (1.0 M in toluene, 24.6 mL, 24.6 mmol) at - 78 °C. The mixture was gradually warmed to - 40 °C over 3 h and then the reaction was quenched with saturated potassium sodium tartrate at - 78 °C. The mixture was warmed to room temperature and stirred for additional 2 h. The organic layer was

separated and the aqueous layer was extracted with DCM. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc/hexanes = 1:3, R_f = 0.27) to give **11** (5.0 g, 97%) as a colorless oil that contains another unseparated diastereomer in a 1:10 ratio. **11**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 – 5.73 (m, 2H), 5.24 (t, J = 2.8 Hz, 1H), 4.70 – 4.66 (m, 1H), 3.71 (s, 3H), 3.34 – 3.24 (m, 2H), 2.85 (dd, J = 10.0, 2.4 Hz, 1H), 2.27 – 2.21 (m, 1H), 1.88 – 1.64 (m, 2H), 1.63 – 1.55 (m, 3H), 1.50 – 1.40 (m, 1H), 0.84 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 131.4, 124.7, 103.1, 76.9, 51.8, 46.8, 46.4, 37.0, 36.7, 27.7, 23.2, 16.9, 15.5; HRMS (ESI): *m/z* calcd for $C_{14}H_{20}O_4Na$ $[M+Na]^+$, 275.1254, found: 275.1256; $[\alpha]_D^{18.8}$ = – 32.4 (*c* 1.82, $CHCl_3$).

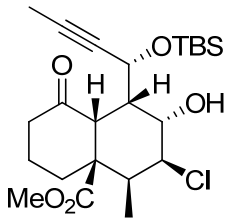


A solution of 1-propynylmagnesium bromide (0.5 M in THF, 114 mL, 57 mmol) was added to **11** (4.99 g, 19.8 mmol) at 0 °C. The mixture was heated at reflux for 36 h. The reaction was quenched with NH_4Cl (aq) at 0 °C and extracted with DCM three times. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum to give the crude product as a yellow foam that required no further purification.

To a solution of the crude product in dry DMF (40 mL) were added imidazole (5.39 g, 79.2 mmol) and TBSCl (5.94 g, 39.6 mmol) at room temperature. After being stirred for 12 h, the mixture was diluted with Et_2O (300 mL), washed with H_2O three times, dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc/hexanes = 1:10, R_f = 0.47) to give a mixture of the product.

To a solution of the above crude product in dry DCM (40 mL) were added DMP (13.0 g, 30.7 mmol) and $NaHCO_3$ (4.99 g, 59.4 mmol) at room temperature. The mixture was stirred for 24 h before quenching with $NaHCO_3$ (aq) and $Na_2S_2O_3$ (aq) at 0 °C. The mixture was extracted with Et_2O. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel to give the

products **14** (2.6 g, 32% over three steps, EtOAc/hexanes = 1:10, R_f = 0.47**)** and **14'** (2.8 g, 35% over three steps, EtOAc/hexanes = 1:10, R_f = 0.36) as light yellow oil. **14**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (d, J = 10.0 Hz, 1H), 5.49 (dt, J = 10.4, 2.4 Hz, 1H), 4.88 (dd, J = 10.8, 2.4 Hz, 1H), 3.71 (s, 3H), 3.34 (d, J = 4.4 Hz, 1H), 2.45 - 2.34 (m, 2H), 2.31 - 2.27 (m, 3H), 2.10 - 2.03 (m, 2H), 1.91 - 1.82 (m, 1H), 1.79 (d, J = 4.4 Hz, 3H), 1.17 (d, J = 7.2 Hz, 3H), 0.86 (s, 9H); 0.12 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.1, 173.3, 131.0, 124.0, 81.2, 80.6, 63.1, 54.7, 51.9, 51.6, 44.2, 42.3, 31.5, 30.9, 25.8, 24.0, 18.0, 14.6, 3.5, - 4.3, - 5.4; HRMS (ESI): *m/z* calcd for $C_{23}H_{36}O_4NaSi$ $[M+Na]^+$, 427.2275, found: 427.2283; $[\alpha]_D^{20.2}$ = - 35.4 (*c* 0.96, $CHCl_3$). **14'**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (d, J = 10.4 Hz, 1H), 5.47 (d, J = 10.4 Hz, 1H), 4.90 (dd, J = 9.6, 2.0 Hz, 1H), 3.70 (s, 3H), 3.42 (d, J = 4.4 Hz, 1H), 2.44 (td, J = 12.8, 6.8 Hz, 1H), 2.36 - 2.24 (m, 4H), 2.11 - 2.05 (m, 2H), 1.90 - 1.75 (m, 1H), 1.79 (d, J = 2.0 Hz, 3H), 1.15 (d, J = 7.2 Hz, 3H), 0.91 (s, 9H); 0.14 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.2, 173.4, 130.6, 124.6, 81.7, 79.2, 63.9, 54.9, 54.3, 52.0, 43.7, 42.0, 31.3, 30.8, 25.9, 23.8, 18.2, 14.7, 3.5, - 4.5, - 5.0; HRMS (ESI): *m/z* calcd for $C_{23}H_{36}O_4NaSi$ $[M+Na]^+$, 427.2275, found: 427.2280; $[\alpha]_D^{19.9}$ = - 104.8 (*c* 1.04, $CHCl_3$).



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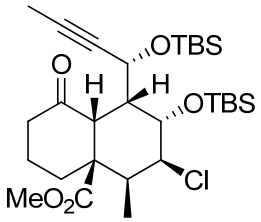
To a solution of **14** (573 mg, 1.42 mmol) in acetone (7.1 mL) was added $(CONCl)_3$ (263 mg, 1.14 mmol) at 0 ^{o}C. After being stirred for 0.5 h, the mixture was quenched with $NaHSO_3$ (aq) and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc/hexanes = 1:8, R_f = 0.56) to give compound **15** (401 mg, 62%) as a colorless foam. **15**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.52 (d, J = 8.0 Hz, 1H), 4.80 (dd, J = 10.8, 2.0 Hz, 1H), 4.26 - 4.23 (m, 1H), 4.05 (t, J = 2.4 Hz, 1H), 4.01 (d, J = 4.4 Hz, 1H), 3.73 (s, 3H), 2.80 (dt, J = 10.8, 4.0 Hz, 1H), 2.51 - 2.44 (m, 1H), 2.36 - 2.30 (m, 1H), 2.22 - 2.16 (m, 1H), 2.10 - 1.95 (m, 3H), 1.84 (d, J = 2.0 Hz, 3H), 1.82 - 1.75 (m, 1H), 1.31 (d, J = 6.8 Hz, 3H), 0.89 (s, 9H), 0.17 (s, 3H), 0.03

(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.8, 174.9, 82.3, 78.9, 71.1, 67.2, 61.7, 52.1, 52.0, 50.7, 42.0, 41.2, 34.9, 34.8, 25.8, 22.1, 18.0, 14.5, 3.6, - 4.2, - 5.3; HRMS (ESI): *m/z* calcd for $C_{23}H_{37}ClO_5NaSi$ $[M+Na]^+$, 479.1991, found: 479.2002; $[\alpha]_D^{20.1}$ = +3.5 (*c* 1.16, $CHCl_3$).



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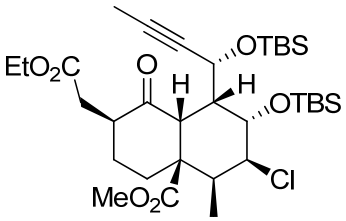
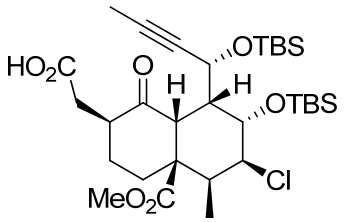
To a solution of **15** (1.69 g, 3.71 mmol) in DCM (19 mL) were added Et_3N (750 mg, 7.42 mmol) and TBSOTf (1.47 g, 5.57 mmol) at 0 ^oC. After the starting material disappeared as monitored by TLC, the mixture was quenched with H_2O and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc/hexanes = 1:10, R_f = 0.65) to give compound **16** (1.5 g, 71%) as a colorless foam. **16**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.43 (dd, *J* = 10.8, 2.0 Hz, 1H), 4.29 (t, *J* = 2.4 Hz, 1H), 3.87 (t, *J* = 2.4 Hz, 1H), 3.69 (s, 3H), 3.40 (d, *J* = 4.8 Hz, 1H), 2.67 (ddd, *J* = 10.4, 4.8, 2.0 Hz, 1H), 2.62 - 2.56 (m, 1H), 2.37 - 2.26 (m, 2H), 2.20 - 2.12 (m, 1H), 1.88 (s, 3H), 1.87 - 1.68 (m, 3H), 1.33 (d, *J* = 7.2 Hz, 3H), 0.87 (s, 9H), 0.86 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H) 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ; 207.7, 175.7, 81.8, 80.7, 72.3, 67.4, 62.9, 51.8, 49.5, 48.3, 43.3, 40.6, 33.9, 33.3, 25.8, 25.7, 18.9, 18.1, 17.9, 14.6, 3.5, - 4.3, - 4.8, - 5.3, - 5.6; HRMS (ESI): *m/z* calcd for $C_{29}H_{51}ClO_5NaSi_2$ $[M+Na]^+$, 593.2856, found: 593.2865; $[\alpha]_D^{20.0}$ = +55.5 (*c* 1.55, $CHCl_3$).



17

To a solution of freshly distilled diisopropylamine (0.66 g, 6.5 mmol) in dry THF (13 mL) was added a solution of *n*-BuLi (2.4 M in hexane, 2.2 mL, 5.2 mmol) dropwise at - 50 ^oC. After 0.5 h, the solution was cooled to - 78 ^oC and then a solution of **16** (1.5 g, 2.6 mmol) in dry THF (13 mL) was added dropwise. After additional 1 h, HMPA (1.4 g, 7.8 mmol) was added dropwise at this

temperature. The resulting solution was stirred for 10 min and $BrCH_2CO_2Et$ (0.65 g, 3.9 mmol) was added dropwise. The mixture was allowed to warm to – 40 °C and stirred for additional 1 h at this temperature. The mixture was quenched with NH_4Cl (aq) at that temperature and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc/hexanes = 1:10, R_f = 0.57) to give compound **17** (0.92 g, 54%) as a colorless oil along with 0.46 g (31%) of recovered starting material. **17**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15 (dd, J = 10.4, 2.0 Hz, 1H), 4.34 (s, 1H), 4.13 – 4.07 (m, 2H), 3.91 (s, 1H), 3.68 (s, 3H), 3.37 (d, J = 5.2 Hz, 1H), 2.88 (brs, 1H), 2.76 – 2.72 (m, 2H), 2.64 (d, J = 16.0 Hz, 1H), 2.43 (dd, J = 16.4, 9.2 Hz, 1H), 2.25 – 2.12 (m, 2H), 1.83 (d, J = 2.0 Hz, 3H), 1.81 – 1.76 (m, 1H), 1.60 (brs, 1H), 1.37 (d, J = 6.4 Hz, 3H), 1.23 (t, J = 7.2 Hz, 3H), 0.90 (s, 9H), 0.83 (s, 9H), 0.20 (s, 3H), 0.14 (s, 3H), 0.10 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.2, 175.3, 172.1, 82.3, 80.5, 72.8, 66.8, 62.8, 60.4, 51.9, 47.9, 46.7, 44.5, 42.3, 36.6, 33.8, 31.5, 26.0, 25.7, 23.3, 18.2, 17.9, 15.0, 14.2, 3.5, – 4.2, – 4.9, – 5.1, – 5.1; HRMS (ESI): *m/z* calcd for $C_{33}H_{57}ClO_7NaSi_2$ $[M+Na]^+$, 679.3224, found: 679.3233; $[\alpha]_D^{20.0}$ = +5.7 (*c* 1.22, $CHCl_3$).

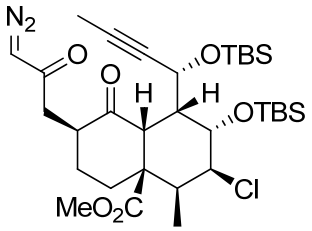


18

To a solution of the crude **17** (0.92 g, 1.4 mmol) in THF/H_2O (4:1, 14 mL) was added LiOH (0.29 g, 7.1 mmol). The mixture was stirred vigorously at 35 °C for 30 h, diluted with DCM, washed with 1.0 M HCl (aq), dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc/hexanes = 1:4, R_f = 0.35) to give compound **18** (0.33 g, 38%) as a colorless solid that contains another unseparated diastereomer in a 1:10 ratio along with 0.36 g (39%) of recovered starting material. **18**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.12 (d, J = 9.6 Hz, 1H), 4.34 (s, 1H), 3.91 (s, 1H), 3.69 (s, 3H), 3.39 (d, J = 5.2 Hz, 1H), 2.88 (brs, 1H), 2.74 – 2.70 (m, 3H), 2.53 – 2.46 (m, 1H), 2.26 – 2.18 (m, 2H), 1.88 – 1.75 (m, 1H), 1.84 (d, J = 1.2 Hz, 3H), 1.62 (brs, 1H), 1.38 (d, J = 5.6 Hz, 3H), 0.90 (s, 9H), 0.83

(s, 9H), 0.20 (s, 3H), 0.15 (s, 3H), 0.10 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.3, 177.6, 175.2, 82.4, 80.4, 72.8, 66.7, 62.8, 51.9, 47.8, 46.8, 44.6, 41.9, 36.3, 33.9, 31.6, 25.9, 25.7, 23.4, 18.2, 18.0, 15.0, 3.5, - 4.2, - 4.9, - 5.1, - 5.2; HRMS (ESI): *m/z* calcd for $C_{31}H_{53}ClO_7NaSi_2$ $[M+Na]^+$, 651.2911, found: 651.2907; $[\alpha]_D^{19.7}$ = +9.0 (*c* 1.22, $CHCl_3$);

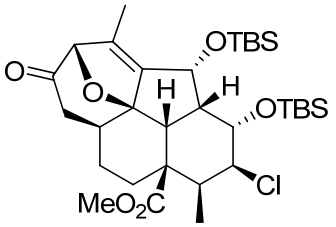
mp = 59 - 61 ^{o}C.



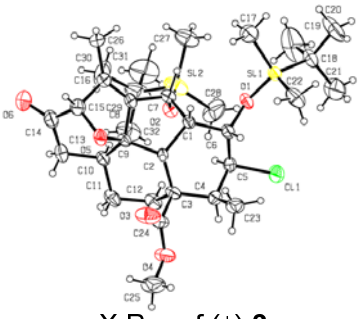
5

Preparation of CH_2N_2: Under continuously shaking, $CH_3N(NO)CONH_2$ (2.6 g, 25 mmol) was added to a mixture of KOH (40% in H_2O, 8.6 mL) and Et_2O (26 mL) at 0 ^{o}C. Decantation of the light yellow solution gave the solution of CH_2N_2 (1.0 M in Et_2O). The solution was dried over dusty KOH and used for the next reaction step.

To a solution of acid **18** (0.32 g, 0.50 mmol) in Et_2O (5.0 mL) were added Et_3N (0.15 g, 1.5 mmol) and $ClCO_2{}^iBu$ (0.14 g, 1.0 mmol) sequentially at 0 °C. After 0.5 h, a freshly prepared solution of CH_2N_2 in Et_2O (1.0 M, 26 mL) was added to the mixture at 0 ^{o}C. The mixture was warmed to room temperature and stirred for 12 h before quenching with silica gel. The mixture was extracted with Et_2O twice. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc/hexanes = 1:4, R_f = 0.46) to give compound **5** (0.25 g, 77%) as a yellow foam that contains another unseparated diastereomer in a 1:10 ratio. **5**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23 (s, 1H), 5.16 (d, *J* = 9.2 Hz, 1H), 4.33 (s, 1H), 3.90 (s, 1H), 3.68 (s, 3H), 3.38 (d, *J* = 5.2 Hz, 1H), 2.94 (brs, 1H), 2.74 - 2.64 (m, 3H), 2.48 - 2.37 (m, 1H), 2.25 - 2.12 (m, 2H), 1.83 (d, *J* = 1.6 Hz, 3H), 1.81 - 1.70 (m, 1H), 1.58 - 1.55 (m, 1H), 1.36 (d, *J* = 6.4 Hz, 3H), 0.89 (s, 9H), 0.82 (s, 9H), 0.20 (s, 3H), 0.14 (s, 3H), 0.10 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.7, 192.8, 175.3, 82.4, 80.4, 72.7, 66.8, 62.8, 54.8, 51.9, 47.9, 46.8, 44.4, 42.9, 42.8, 34.0, 31.4, 25.9, 25.6, 23.3, 18.2, 17.9, 15.0, 3.5, - 4.1, - 4.9, - 5.1, - 5.2; HRMS (ESI): *m/z* calcd for $C_{32}H_{53}ClN_2O_6NaSi_2$ $[M+Na]^+$, 675.3023, found: 675.3016; $[\alpha]_D^{21.2}$ = - 5.5 (*c* 1.09, $CHCl_3$).

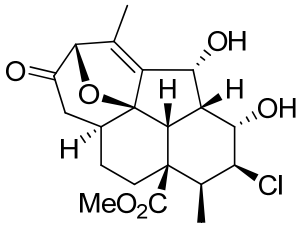


3



X-Ray of (±)-**3**
ccdc: 1457123

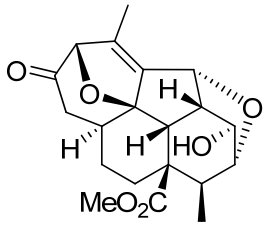
To a suspension of $Rh_2(OAc)_4$ (0.016 g, 0.037 mmol) in refluxing toluene (7.4 mL) was added a solution of diazoketone **5** (0.24 g, 0.37 mmol) in toluene (7.4 mL) over 0.5 h via a syringe pump. After additional 0.5 h, the mixture was cooled to rt and the solvent was removed under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc/hexanes = 1:4, R_f = 0.41) to afford **3** (0.19 g, 81%) as a colorless solid. **3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.76 (d, J = 3.6 Hz, 1H), 4.68 (dd, J = 10.8, 3.6 Hz, 1H), 4.62 (s, 1H), 4.11 - 4.07 (m, 1H), 3.75 (s, 3H), 3.56 (d, J = 11.6 Hz, 1H), 2.89 - 2.83 (m, 1H), 2.66 - 2.45 (m, 4H), 2.11 (td, J = 12.8, 2.8 Hz, 1H), 1.96 (d, J = 11.6 Hz, 1H), 1.79 (s, 3H), 1.64 (brs, 1H), 1.12 - 1.04 (m, 1H), 0.99 (d, J = 7.2 Hz, 3H), 0.93 (s, 9H), 0.89 (s, 9H), 0.17 (s, 3H), 0.15 (s, 3H), 0.14 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.1, 176.2, 149.5, 127.3, 95.2, 93.8, 69.8, 67.8, 63.4, 52.7, 52.4, 50.1, 44.6, 44.3, 39.8, 39.3, 30.7, 27.9, 26.3, 25.7, 18.7, 18.1, 11.3, 11.2, - 4.3, - 4.4, - 4.6, - 4.9; HRMS (ESI): *m/z* calcd for $C_{32}H_{53}ClO_6NaSi_2$ $[M+Na]^+$, 647.2961, found: 647.2953; $[\alpha]_D^{21.3}$ = - 104.6 (*c* 1.08, $CHCl_3$); mp = 52 - 54 °C.



19

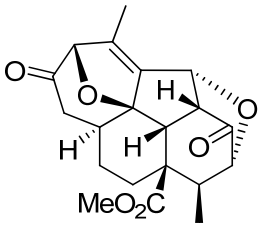
To a solution of **3** (0.17 g, 0.27 mmol) in dry THF (11 mL) was added TBAF (0.42 g, 1.4 mmol) at room temperature. The solution was quenched with H_2O after the starting material disappeared as monitored by TLC. The mixture was extracted with DCM three times. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified

by flash column chromatography on silica gel (EtOAc/hexanes = 1:1, R_f = 0.31) to give compound **19** (91 mg, 85%) as a colorless solid. **19**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90 (dd, J = 3.6, 2.0 Hz, 1H), 4.65 (s, 1H), 4.48 (dd, J = 11.2, 3.6 Hz, 1H), 4.14 (td, J =10.4, 2.8 Hz, 1H), 3.77 (s, 3H), 3.60 (d, J = 12.8 Hz, 1H), 3.18 - 3.12 (m, 1H), 3.00 (d, J = 2.4 Hz, 1H), 2.77 (d, J = 3.2 Hz, 1H), 2.62 (d, J = 2.4 Hz, 1H), 2.60 (d, J = 2.0 Hz, 1H), 2.52 - 2.42 (m, 2H), 2.05 - 2.02 (m, 2H), 1.81 (s, 3H), 1.70 - 1.62 (m, 1H), 1.15 - 1.00 (m, 1H), 0.96 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.9, 175.7, 147.3, 130.2, 95.1, 94.1, 70.4, 67.8, 66.6, 52.6, 50.7, 49.0, 44.6, 43.5, 39.9, 39.1, 30.7, 28.3, 11.3, 10.7; HRMS (ESI): *m/z* calcd for $C_{20}H_{25}ClO_6Na$ $[M+Na]^+$, 419.1232, found: 419.1225; $[\alpha]_D^{21.6}$ = - 192.7 (*c* 1.10, $CHCl_3$); mp = 156 - 158 ^{o}C.



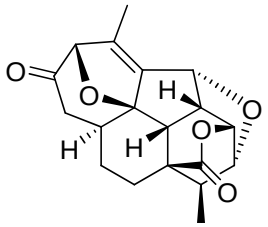
20

To a solution of **19** (76 mg, 0.19 mmol) in dry THF (7.0 mL) was added NaH (60% dispersion in mineral oil, 76 mg, 1.9 mmol) at 0 ^{o}C. The solution was allowed to warm to room temperature over 2 h. After the starting material disappeared, the mixture was quenched with H_2O and extracted with DCM. The combinedorganic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc/hexanes = 1:1, R_f = 0.25) to give compound **20** (49 mg, 71%) as a colorless solid. **20**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90 (d, J = 2.4 Hz, 1H), 4.54 (s, 1H), 4.38 (d, J = 1.2 Hz, 1H), 3.88 (s, 1H), 3.69 (s, 3H), 3.03 (q, J = 9.6 Hz, 2H), 2.91 (dd, J = 18.8, 8.4 Hz, 1H), 2.59 - 2.52 (m, 1H), 2.25 (q, J = 7.6 Hz, 1H), 2.18 (dd, J = 18.8, 3.6 Hz, 1H), 2.10 - 2.02 (m, 1H), 1.91 - 1.86 (m, 1H), 1.89 (s, 3H), 1.84 - 1.70 (m, 2H), 1.59 (brs, 1H), 1.06 (d, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0, 177.6, 147.3, 134.1, 95.7, 94.0, 88.4, 74.9, 72.3, 54.3, 51.9, 46.9, 45.5, 43.3, 42.4, 31.3, 28.9, 26.0, 16.3, 11.5; HRMS (ESI): *m/z* calcd for $C_{20}H_{24}O_6Na$ $[M+Na]^+$, 383.1465, found: 383.1457; $[\alpha]_D^{18.5}$ = - 309.7 (*c* 1.03, $CHCl_3$); mp = 253 - 255 ^{o}C.



21

To a solution of **20** (35 mg, 0.098 mmol) in DCM (4.0 mL) were added $NaHCO_3$ (0.16 g, 1.9 mmol) and DMP (0.21 g, 0.49 mmol). The mixture was stirred for 24 h before quenching with $Na_2S_2O_3$ (aq) and $NaHCO_3$ (aq). The solution was extracted with DCM three times. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc/hexanes = 1:1, R_f = 0.65) to give compound **21** (23 mg, 66%) as a colorless solid along with 9 mg (25%) of recovered starting material. **21**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.77 (d, J = 2.4 Hz, 1H), 4.58 (s, 1H), 3.65 (s, 3H), 3.60 (s, 1H), 3.21 (d, J = 9.6 Hz, 1H), 3.05 (dd, J = 9.2, 2.4 Hz, 1H), 2.96 (dd, J = 18.8, 8.4 Hz, 1H), 2.81 – 2.73 (m, 1H), 2.57 (q, J = 7.6 Hz, 1H), 2.28 (dd, J = 18.4, 3.6 Hz, 1H), 2.15 – 2.06 (m, 1H), 2.00 – 1.91 (m, 2H), 1.89 (s, 3H), 1.86 – 1.82 (m, 1H), 0.98 (d, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.0, 202.5, 175.0, 147.7, 135.8, 95.3, 94.4, 79.8, 72.4, 53.9, 53.3, 51.7, 48.6, 43.1, 42.4, 31.4, 27.5, 25.9, 15.0, 11.7; HRMS (ESI): *m/z* calcd for $C_{20}H_{22}O_6Na$ $[M+Na]^+$, 381.1309, found: 381.1302; $[\alpha]_D^{18.4}$ = – 245.8 (*c* 1.20, $CHCl_3$); mp = 165 – 167 °C.

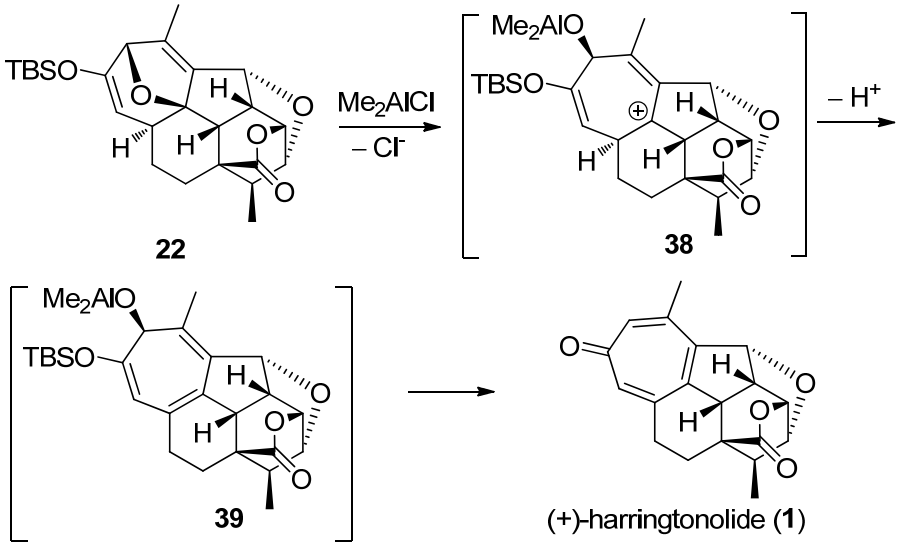


22

To a solution of **21** (23.2 mg, 0.0648 mmol) in MeOH (2.6 mL) was added $NaBH_4$ (10 mg, 0.26 mmol) at 0 °C. After 5 min, K_2CO_3 (45 mg, 0.32 mmol) was added to the mixture. The mixture was warmed to 60 °C and stirred for 20 min before quenching with H_2O. The mixture was extracted with DCM three times. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude product was used for the next reaction without further purification.

To a solution of the above crude product in DCM (2.6 mL) were added $NaHCO_3$ (54 mg, 0.65

mmol) and DMP (0.14 g, 0.32 mmol) at rt. The mixture was stirred until the starting material disappeared as indicated by TLC. The mixture was quenched with $Na_2S_2O_3$ (aq) and $NaHCO_3$ (aq) and extracted with DCM three times. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc/hexanes = 1:1, R_f = 0.44) to give compound **22** (19.1 mg, 90% over three steps) as a colorless foam. **22**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.13 (t, J = 6.0 Hz, 1H), 4.82 (d, J = 4.0 Hz, 1H), 4.50 (s, 1H), 4.07 (d, J = 6.0 Hz, 1H), 3.28 - 3.23 (m, 1H), 2.88 - 2.81 (m, 1H), 2.52 (d, J = 10.0 Hz, 1H), 2.46 - 2.36 (m, 2H), 2.27 - 2.17 (m, 2H), 1.96 - 1.89 (m, 2H), 1.92 (s, 3H), 1.85 - 1.76 (m, 1H), 0.97 (d, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.4, 174.0, 149.0, 142.3, 95.6, 92.8, 78.3, 77.8, 75.1, 47.8, 45.2, 43.7, 42.7, 41.3, 32.7, 26.5, 20.3, 15.0, 12.5; HRMS (ESI): *m/z* calcd for $C_{19}H_{21}O_5$ $[M+H]^+$, 329.1384, found: 329.1390; $[\alpha]_D^{21.2}$ = - 364.2 (*c* 1.85, $CHCl_3$).

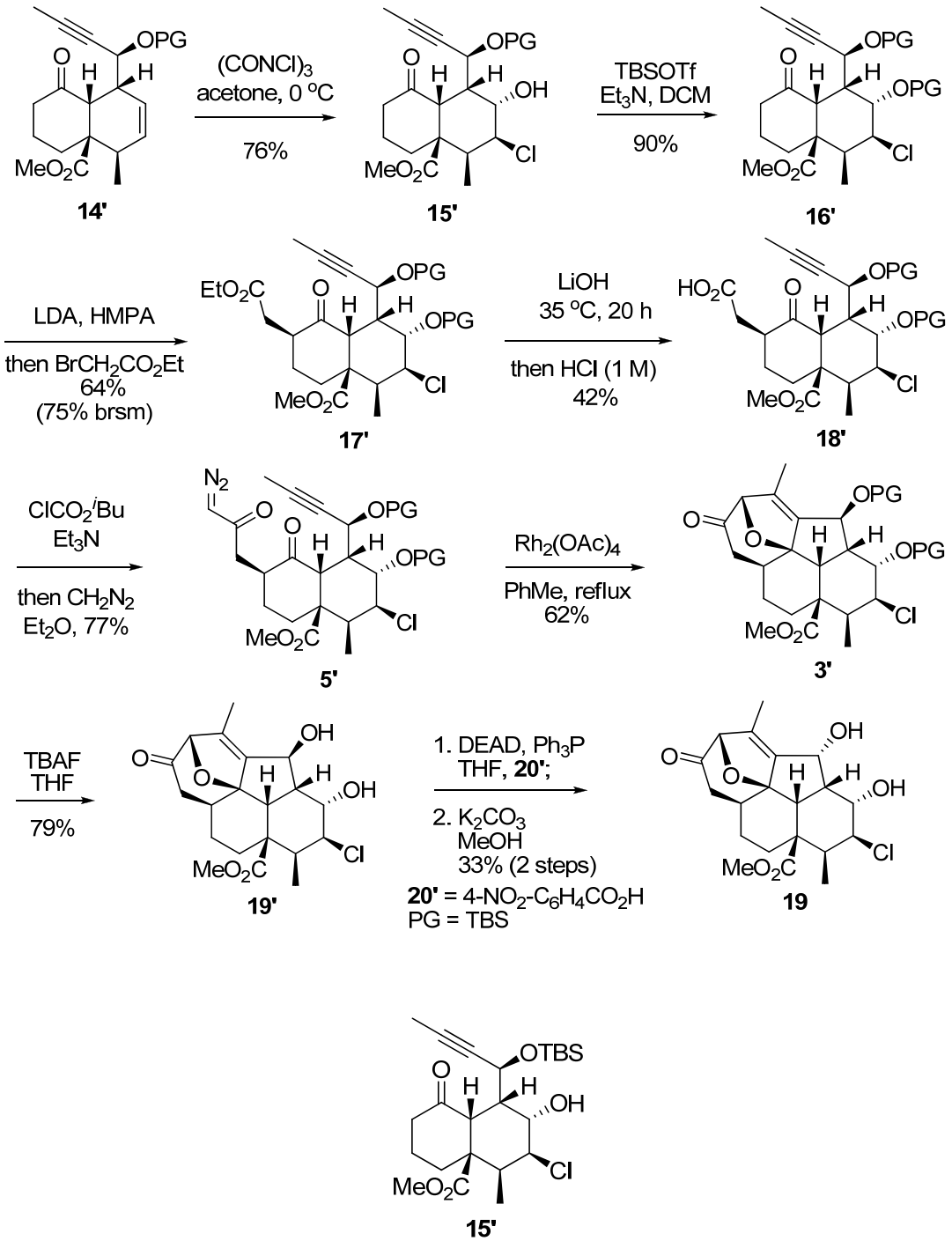


To a solution of **22** (13.4 mg, 0.0409 mmol) in DCM (0.8 mL) were added Et_3N (29 μL, 0.21 mmol) and TBSOTf (38 μL, 0.16 mmol) at room temperature. After the starting material disappeared, the mixture was quenched with H_2O and extracted with DCM. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude product was used for the next reaction without further purification.

To a solution of the above crude product in DCM (3.0 mL) was added Me_2AlCl (0.9 M in heptane, 2.3 mL, 2.1 mmol) at - 78 ^{o}C. The mixture was allowed to warm to 40 ^{o}C. After the starting material disappeared as indicated by TLC, the mixture was cooled to - 78 ^{o}C again and

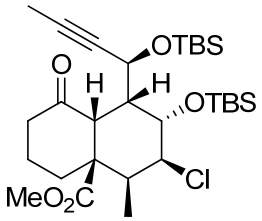
quenched with MeOH added dropwise at the temperature. The mixture was warmed to room temperature, diluted with DCM, treated with NH_4Cl (aq), and extracted with DCM three times. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc/hexanes = 1:1, R_f = 0.15) to give natural product (+)-harringtonolide (**1**, 5.8 mg, 46% over two steps) as a light yellow solid. **1**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (s, 1H), 6.90 (s, 1H), 5.36 (t, J = 2.8 Hz, 1H), 5.21 (t, J = 5.2 Hz, 1H), 3.99 (d, J = 5.6 Hz, 1H), 3.42 - 3.36 (m, 2H), 2.91 - 2.82 (m, 2H), 2.66 - 2.60 (m, 1H), 2.37 (d, J = 0.8 Hz, 3H), 1.76 (q, J = 7.6 Hz, 1H), 1.36 - 1.28 (m, 1H), 0.90 (d, J = 7.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 186.5, 173.5, 145.8, 145.6, 145.0, 143.6, 141.6, 139.3, 86.0, 80.0, 79.7, 49.9, 45.8, 41.8, 40.0, 32.3, 23.9, 22.4, 14.7; HRMS (ESI): *m/z* calcd for $C_{19}H_{19}O_4$ $[M+H]^+$, 311.1278, found: 311.1283; $[\alpha]_D^{17.8}$ = +81.0 (*c* 1.16, $CHCl_3$); mp = 255 - 258 ^oC.

Construction of Oxapentacycle 19 from Compound 14'



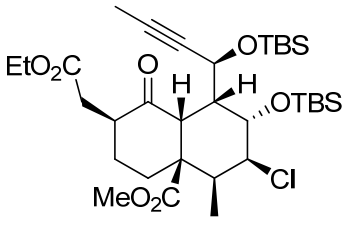
To a solution of **14'** (504 mg, 1.25 mmol) in acetone (5.6 mL) was added $(CONCl)_3$ (0.23 g, 1.0 mol) at 0 °C. After being stirred for 0.5 h, the mixture was quenched with $NaHSO_3$ (aq) and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc/hexanes = 1:8, R_f = 0.53) to give compound **15'** (434 mg, 76%) as a colorless foam that contains another unseparated diastereomer in a 1:16 ratio. **15'**: ^{1}H NMR (400 MHz, $CDCl_3$) δ

5.23 (d, *J* = 7.2 Hz, 1H), 4.85 (dd, *J* = 10.4, 2.4 Hz, 1H), 4.17 - 4.13 (m, 1H), 4.04 (t, *J* = 2.8 Hz, 1H), 4.01 (d, *J* = 4.0 Hz, 1H), 3.74 (s, 3H), 2.70 (dt, *J* = 10.0, 4.0 Hz, 1H), 2.52 - 2.44 (m, 1H), 2.38 - 2.32 (m, 1H), 2.22 - 2.17 (m, 1H), 2.11 - 1.93 (m, 3H), 1.84 (d, *J* = 2.0 Hz, 3H), 1.80 - 1.76 (m, 1H), 1.30 (d, *J* = 7.2 Hz, 3H), 0.91 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.4, 175.1, 82.4, 79.0, 69.4, 67.0, 61.2, 53.0, 52.2, 52.2, 41.8, 40.8, 34.8, 34.5, 25.8, 21.8, 18.2, 14.6, 3.6, - 4.5, - 5.2; HRMS (ESI): *m/z* calcd for $C_{23}H_{37}ClO_5NaSi$ $[M+Na]^+$, 479.1991, found: 479.1997; $[\alpha]_D^{19.8}$ = - 111.1 (*c* 1.26, $CHCl_3$).



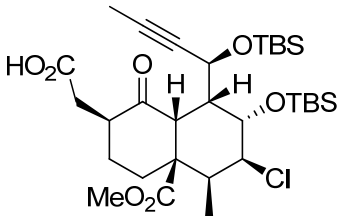
16'

To a solution of **15'** (1.01 g, 2.21 mmol) in DCM (11 mL) were added Et_3N (671 mg, 6.63 mmol) and TBSOTf (1.46 g, 5.53 mmol) at 0 ^{o}C. After being stirred for 3 h, the mixture was quenched with H_2O and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc/hexanes = 1:10, R_f = 0.63) to give compound **16'** (1.1g, 90%) a colorless foam. **16'**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.31 (dd, *J* = 10.0, 2.4 Hz, 1H), 4.30 (dd, *J* = 2.8, 1.6 Hz, 1H), 3.89 (t, *J* = 2.8 Hz, 1H), 3.71 (s, 3H), 3.36 (d, *J* = 4.8 Hz, 1H), 2.70 - 2.61 (m, 2H), 2.43 - 2.31 (m, 2H), 2.24 - 2.15 (m, 1H), 1.87 - 1.80 (m, 2H), 1.82 (d, *J* = 2.0 Hz, 3H), 1.67 (td, *J* = 13.6, 5.2 Hz, 1H), 1.32 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.84 (s, 9H), 0.21 (s, 3H), 0.19 (s, 3H), 0.13 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.8, 176.0, 82.1, 79.4, 70.5, 67.1, 62.9, 51.9, 51.4, 49.3, 43.8, 39.5, 33.1, 32.5, 26.1, 25.7, 18.4, 18.2, 17.9, 14.5, 3.8, - 3.1, - 3.9, - 4.7, - 5.2; HRMS (ESI): *m/z* calcd for $C_{29}H_{51}ClO_5NaSi_2$ $[M+Na]^+$, 593.2856, found: 593.2846; $[\alpha]_D^{19.7}$ = - 25.9 (*c* 1.16, $CHCl_3$).



17'

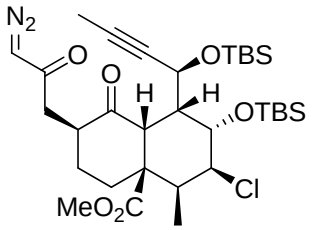
To a solution of freshly distilled diisopropylamine (1.08 g, 10.7 mmol) in dry THF (21 mL) was added a solution of *n*-BuLi (2.5 M in hexane, 3.4 mL, 8.5 mmol) dropwise at – 50 °C. After 0.5 h, the solution was cooled to – 78 °C and then a solution of **16'** (2.4 g, 4.3 mmol) in dry THF (21 mL) was added dropwise. After additional 1 h, HMPA (2.29 g, 12.8 mmol) was added dropwise at the temperature. The resulting solution was stirred for 10 min and $BrCH_2CO_2Et$ (1.06 g, 6.39 mmol) was added dropwise. The mixture was allowed to warm to – 40 °C and stirred for additional 1 h at the temperature. The mixture was quenched with NH_4Cl (aq) at the temperature and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc/hexanes = 1:10, R_f = 0.62) to give compound **17'** (1.80 g, 64%) as a colorless oil along with 0.36 g (15%) of recovered starting material. **17'**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.99 (dd, J = 10.0, 2.0 Hz, 1H), 4.31 (q, J = 1.6 Hz, 1H), 4.13 – 4.08 (m, 2H), 3.91 (t, J = 2.8 Hz, 1H), 3.71 (s, 3H), 3.47 (d, J = 4.8 Hz, 1H), 2.88 – 2.81 (m, 1H), 2.74 – 2.66 (m, 3H), 2.42 (dd, J = 16.0, 9.6 Hz, 1H), 2.21 – 2.11 (m, 1H), 2.09 – 2.03 (m, 1H), 1.92 – 1.87 (m, 1H), 1.85 (d, J = 2.0 Hz, 3H), 1.61 – 1.55 (m, 1H), 1.35 (d, J = 7.2 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H), 0.88 (s, 9H), 0.83 (s, 9H), 0.21 (s, 3H), 0.18 (s, 3H), 0.10 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.3, 175.5, 172.0, 82.5, 79.6, 70.6, 66.5, 62.6, 60.5, 51.9, 49.5, 48.2, 44.0, 42.5, 36.8, 34.2, 31.7, 26.1, 25.6, 23.4, 18.2, 17.9, 14.9, 14.2, 3.8, – 3.1, – 3.8, – 4.8, – 5.1; HRMS (ESI): *m/z* calcd for $C_{33}H_{57}ClO_7NaSi_2$ $[M+Na]^+$, 679.3224, found: 679.3232; $[\alpha]_D^{19.7}$ = – 61.5 (*c* 0.95, $CHCl_3$).



18'

To a solution of the crude **17'** (1.7 g, 2.6 mmol) in THF/H_2O (4:1, 26 mL) was added LiOH (551 mg, 13.1 mmol). After the mixture was stirred vigorously for 20 h at 35 °C, the mixture was diluted with DCM and washed with 1.0 M HCl (aq). The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc/hexanes = 1:4, R_f = 0.21) to give compound **18'** (0.65 g,

42%) as a colorless foam that contains another unseparated diastereomer in a 1:14 ratio. **18'**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.99 – 4.96 (m, 1H), 4.32 (s, 1H), 3.91 (s, 1H), 3.72 (s, 3H), 3.47 (d, J = 5.2 Hz, 1H), 2.86 – 2.84 (m, 1H), 2.80 – 2.69 (m, 3H), 2.46 (dd, J = 16.4, 8.8 Hz, 1H), 2.25 – 2.16 (m, 1H), 2.11 – 2.05 (m, 1H), 1.91 – 1.81 (m, 1H), 1.86 (d, J = 1.6 Hz, 3H), 1.63 – 1.58 (m, 1H), 1.36 (d, J = 7.2 Hz, 3H), 0.89 (s, 9H), 0.83 (s, 9H), 0.21 (s, 3H), 0.18 (s, 3H), 0.10 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.4, 177.5, 175.5, 82.6, 79.5, 70.6, 66.4, 62.6, 52.0, 49.5, 48.1, 44.1, 42.2, 36.4, 34.4, 31.7, 26.1, 25.6, 23.5, 18.2, 17.9, 15.0, 3.8, – 3.1, – 3.8, – 4.9, – 5.1; HRMS (ESI): *m/z* calcd for $C_{31}H_{53}ClO_7NaSi_2$ $[M+Na]^+$, 651.2911, found: 651.2919; $[\alpha]_D^{21.8}$ = – 54.7 (*c* 1.17, $CHCl_3$).

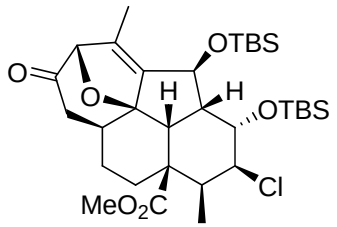


5'

Preparation of CH_2N_2: under continuously shaking, $CH_3N(NO)CONH_2$ (3.4 g, 33 mmol) was added to a mixture of KOH (40% in H_2O, 11.2 mL) and Et_2O (34 mL) at 0 ^{o}C. Decantation of the light yellow solution gave the solution of CH_2N_2 (1.0 M in Et_2O). The solution was dried over dusty KOH and used for the next reaction step.

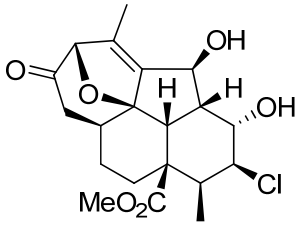
To a solution of acid **18'** (0.41 g, 0.65 mmol) in Et_2O (6.5 mL) were added Et_3N (0.20 g, 2.0 mmol) and $ClCO_2{}^iBu$ (0.18 g, 1.3 mmol) sequentially at 0 ^{o}C. After 0.5 h, a freshly prepared solution of CH_2N_2 (34 mL, 1.0 M in Et_2O) was added to the mixture at 0 ^{o}C. The mixture was warmed to room temperature and stirred for 12 h before quenching with silica gel. The mixture was extracted with Et_2O twice. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc/hexanes = 1:4, R_f = 0.23) to give compound **5'** (0.33 g, 77%) as a yellow oil that contains another unseparated diastereomer in a 1:14 ratio. **5'**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.24 (s, 1H), 4.99 (dd, J = 10.0, 2.0 Hz, 1H), 4.31 (d, J = 1.6 Hz, 1H), 3.90 (t, J = 2.4 Hz, 1H), 3.70 (s, 3H), 3.46 (d, J = 5.2 Hz, 1H), 2.88 (brs, 1H), 2.74 – 2.67 (m, 3H), 2.41 (brs, 1H), 2.18 – 2.12 (m, 1H), 2.10 – 2.04 (m, 1H), 1.91 – 1.81 (m, 1H), 1.85 (d, J = 2.0 Hz, 3H), 1.60 – 1.55 (m, 1H), 1.34

(d, J = 7.2 Hz, 3H), 0.88 (s, 9H), 0.82 (s, 9H), 0.20 (s, 3H), 0.17 (s, 3H), 0.09 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.7, 192.7, 175.5, 82.4, 79.6, 70.6, 66.5, 62.6, 54.7, 51.9, 49.5, 48.1, 44.1, 42.8, 42.8, 34.2, 31.6, 26.1, 25.6, 23.5, 18.2, 17.9, 14.9, 3.8, - 3.1, - 3.8, - 4.8, - 5.2; HRMS (ESI): *m/z* calcd for $C_{32}H_{53}ClN_2O_6NaSi_2$ $[M+Na]^+$, 675.3023, found: 675.3032; $[\alpha]_D^{21.2}$ = - 47.6 (*c* 1.37, $CHCl_3$).



3'

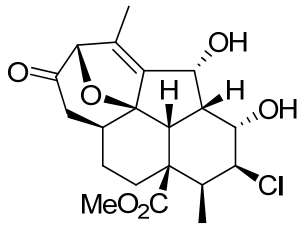
To a suspension of $Rh_2(OAc)_4$ (0.022 g, 0.050 mmol) in refluxing toluene (10 mL) was added a solution of diazoketone **5'** (0.33 g, 0.50 mmol) in toluene (10 mL) over 0.5 h via a syringe pump. After additional 0.5 h, the solution was cooled to rt and the solvent was removed under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc/hexanes = 1:4, R_f = 0.57) to afford compound **3'** (0.20 g, 62%) as a colorless solid. **3'**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.77 (s, 1H), 4.57 (s, 1H), 4.25 (dd, J = 4.8, 1.6 Hz, 1H), 4.19 (d, J = 4.8 Hz, 1H), 3.69 (s, 3H), 3.47 (d, J = 12.0 Hz, 1H), 2.93 (dq, J = 12.0, 2.4 Hz, 1H), 2.83 (dd, J = 18.4, 8.4 Hz, 1H), 2.53 - 2.50 (m, 2H), 2.28 - 2.21 (m, 1H), 2.12 (d, J = 18.8 Hz, 1H), 1.87 - 1.83 (m, 1H), 1.80 (d, J = 1.2 Hz, 3H), 1.73 - 1.67 (m, 1H), 1.51 - 1.42 (m, 1H), 1.08 (d, J = 7.2 Hz, 3H), 0.90 (s, 9H), 0.87 (s, 9H), 0.19 (s, 3H), 0.18 (s, 3H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.8, 175.8, 149.7, 135.1, 96.2, 96.1, 75.0, 68.1, 65.0, 52.6, 52.1, 46.6, 41.3, 38.2, 35.1, 30.9, 28.0, 27.3, 25.7, 25.6, 18.0, 17.9, 14.2, 11.5, - 3.6, - 4.1, - 4.7, - 4.8; HRMS (ESI): *m/z* calcd for $C_{32}H_{53}ClO_6NaSi_2$ $[M+Na]^+$, 647.2961, found: 647.2973; $[\alpha]_D^{22.0}$ = - 213.5 (*c* 1.26, $CHCl_3$); mp = 36 - 37 ^{o}C.



19'

To a solution of **3'** (0.18 g, 0.29 mmol) in dry THF (12 mL) was added TBAF (0.28 g, 0.87

mmol) at room temperature. The solution was quenched with H_2O after the starting material disappeared as indicated by TLC. The mixture was extracted with DCM three times. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc/hexanes = 1:1, R_f = 0.33) to give compound **19'** (92 mg, 79%) as a colorless solid. **19'**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.78 (d, J = 10.8 Hz, 1H), 4.63 (s, 1H), 4.34 (dd, J = 10.8, 3.2 Hz, 1H), 4.19 (t, J =10.0 Hz, 1H), 3.77 (s, 3H), 3.67 (d, J = 13.2 Hz, 1H), 3.63 (s, 1H), 3.10 - 3.01 (m, 1H), 2.76 (s, 1H), 2.64 - 2.52 (m, 2H), 2.45 - 2.39 (m, 1H), 2.15 - 2.11 (m, 1H), 1.87 (d, J = 1.6 Hz, 3H), 1.80 - 1.72 (m, 1H), 1.68 - 1.54 (m, 2H), 1.07 (q, J = 12.8 Hz, 1H), 0.95 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.2, 175.1, 146.7, 127.4, 94.4, 90.9, 70.4, 70.2, 65.2, 52.7, 50.5, 48.3, 43.5, 43.4, 42.1, 38.0, 32.1, 27.8, 10.5, 9.8; HRMS (ESI): *m/z* calcd for $C_{20}H_{25}ClO_6Na$ $[M+Na]^+$, 419.1232, found: 419.1238; $[\alpha]_D^{22.2}$ = - 225.7 (*c* 1.13, $CHCl_3$); mp = 78 - 81 °C.



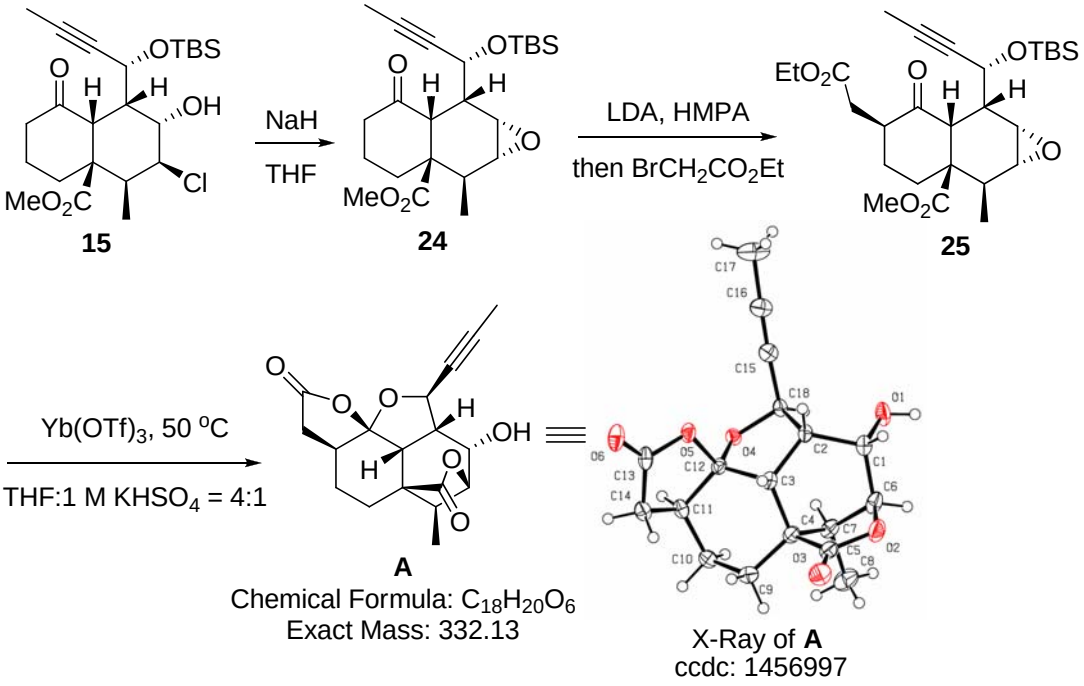
19

To a solution of **19'** (78 mg, 0.20 mmol) in dry THF (4.0 mL) were added Ph_3P (0.16 g, 0.59 mmol), 4-NO_2-$C_6H_4CO_2H$ (99 mg, 0.59 mmol) and DEAD (0.10 g, 0.59 mmol) sequentially at room temperature. The solution was quenched with H_2O after the starting material disappeared as indicated by TLC. The mixture was extracted with DCM three times. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc/hexanes = 1:1, R_f = 0.40) to give a crude product used for the next step.

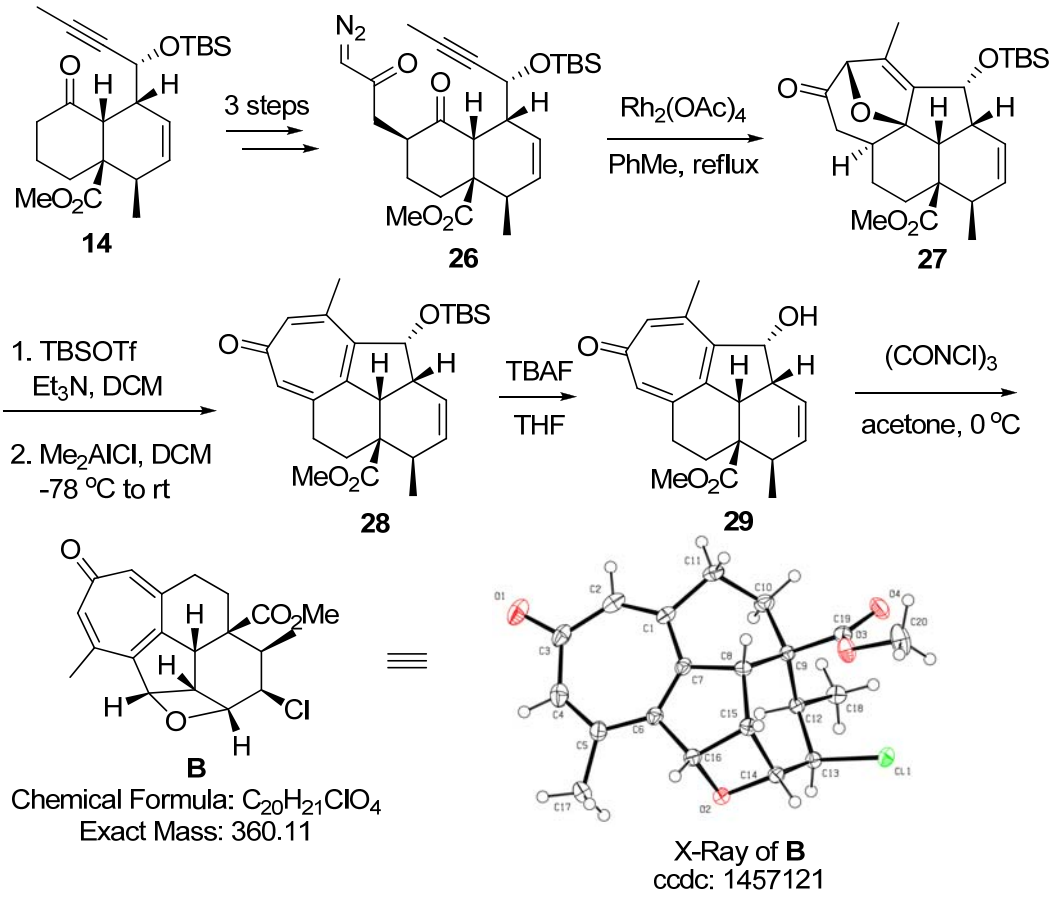
To a solution of the above crude product in MeOH (2.0 mL) was added K_2CO_3 (54 mg, 0.59 mmol). The solution was quenched with H_2O after the starting material disappeared as indicated by TLC. The mixture was extracted with DCM three times. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel to give **19** (25 mg, 33 % over two steps) as a colorless solid.

The ^{1}H NMR and ^{13}C NMR was in agreement with those measured above.

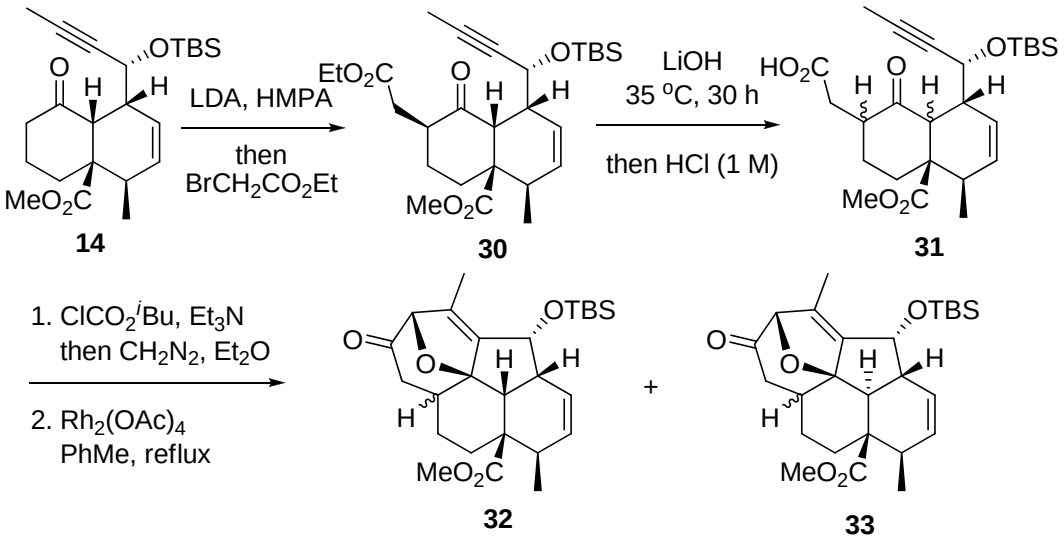
Some Important Intermediates (A−E)

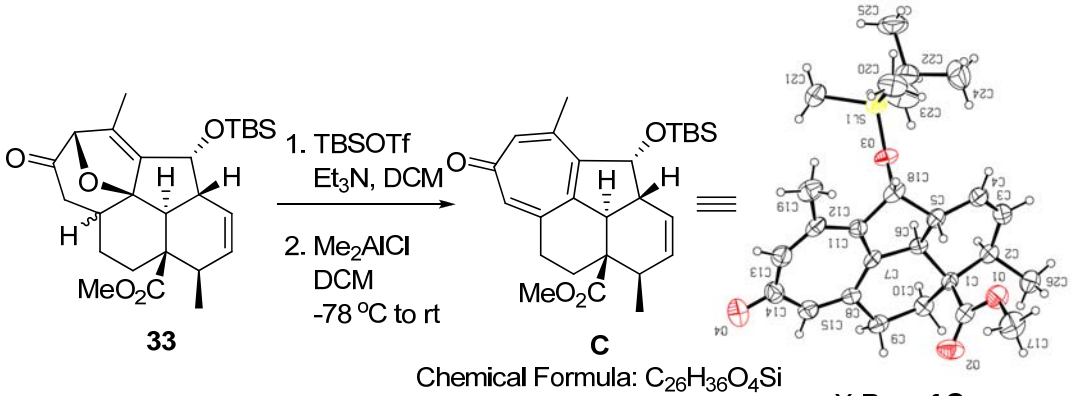


A: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.28 - 5.24 (m, 1H), 4.36 - 4.30 (m, 1H), 4.28 (s, 1H), 3.42 (q, J = 8.4 Hz, 1H), 2.93 - 2.86 (m, 1H), 2.71 - 2.55 (m, 3H), 2.50 - 2.41 (m, 2H), 1.93 - 1.85 (m, 4H), 1.80 - 1.73 (m, 1H), 1.71 - 1.58 (m, 2H), 1.06 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 172.5, 116.7, 85.2, 83.0, 78.8, 72.4, 66.8, 46.9, 45.7, 45.6, 37.1, 34.2, 33.1, 19.3, 19.2, 13.3, 3.9.



B: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (s, 1H), 6.89 (s, 1H), 5.95 (d, J = 5.6 Hz, 1H), 5.20 (dd, J = 7.2, 2.8 Hz, 1H), 3.96 (t, J =2.8 Hz, 1H), 3.90 (d, J = 9.6 Hz, 1H), 3.75 (s, 3H), 3.69 - 3.63 (m, 1H), 2.67 - 2.50 (m, 3H), 2.27 (s, 3H), 1.69 - 1.62 (m, 2H), 1.26 (d, J = 6.8 Hz, 3H).



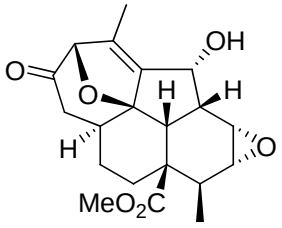


33 **C**

Chemical Formula: $C_{26}H_{36}O_4Si$
Exact Mass: 440.24

X-Ray of **C**
ccdc: 1457120

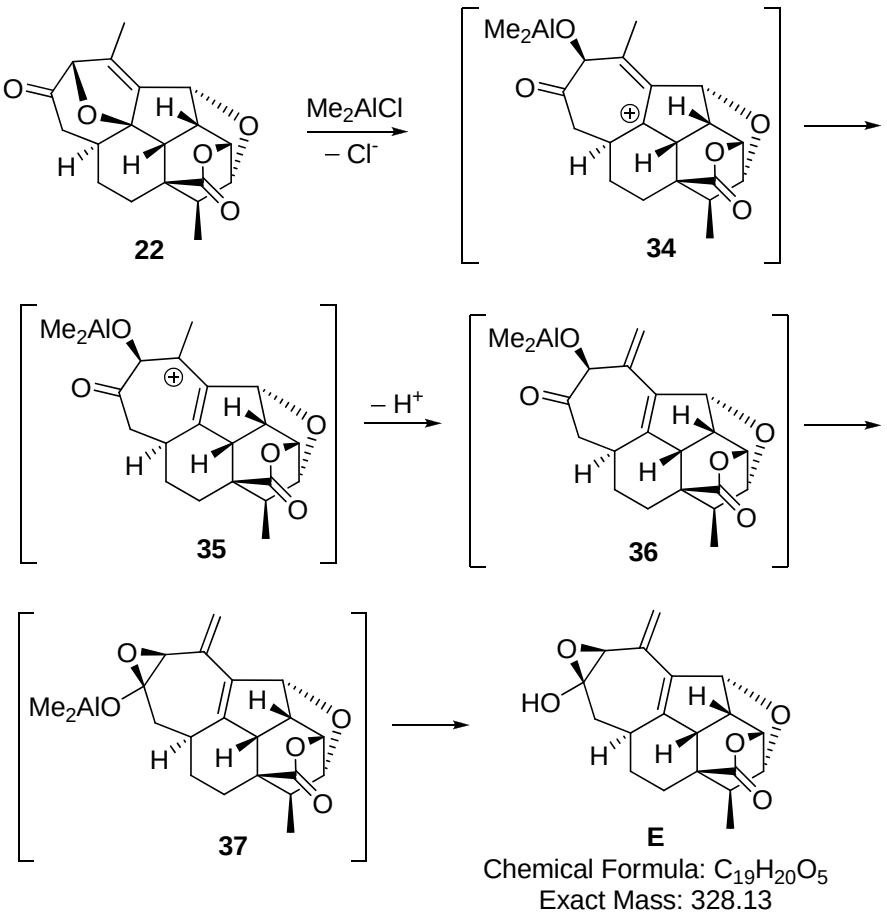
C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (s, 2H), 5.95 (dt, J = 10.0, 2.4 Hz, 1H), 5.51 (dt, J = 10.0, 2.4 Hz, 1H), 5.20 (d, J = 4.4 Hz, 1H), 3.62 (s, 3H), 3.38 (d, J = 10.8 Hz, 1H), 3.23 - 3.19 (m, 1H), 3.00 - 2.81 (m, 2H), 2.65 - 2.60 (m, 1H), 2.44 - 2.42 (m, 1H), 2.35 (s, 3H), 1.54 (td, J = 13.2, 6.0 Hz, 1H), 1.10 (d, J = 7.6 Hz, 3H), 0.82 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.9, 173.0, 148.8, 146.3, 144.7, 144.0, 141.5, 141.2, 134.9, 125.7, 77.2, 52.9, 51.3, 46.6, 45.9, 43.2, 32.1, 30.3, 26.0, 24.1, 18.5, 15.4, - 3.2, - 4.0.



D

Chemical Formula: $C_{20}H_{24}O_6$
Exact Mass: 360.16

D: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90 (s, 1H), 4.72 (s, 1H), 3.77 (s, 3H), 3.38 - 3.37 (m, 1H), 3.29 - 3.23 (m, 2H), 3.20 (t, J = 4.0 Hz, 1H), 2.75 (dd, J = 16.8, 7.2 Hz, 1H), 2.55 - 2.51 (m, 1H), 2.50 - 2.45 (m, 1H), 2.43 - 2.32 (m, 3H), 1.95 (d, J = 13.6 Hz, 1H), 1.86 (s, 3H), 1.61 - 1.44 (m, 1H), 1.19 - 1.08 (m, 1H), 0.87 (d, J = 6.8 Hz, 3H).



E: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.39 (s, 1H), 5.31 (s, 1H), 5.07 (t, J =5.6 Hz, 1H), 4.88 (d, J = 4.4 Hz, 1H), 4.08 (s, 1H), 3.93 (d, J = 5.6 Hz, 1H), 3.24 - 3.16 (m, 2H), 2.61 (dd, J = 14.0, 6.0 Hz, 1H), 2.49 (s, 1H), 2.02 - 1.89 (m, 3H), 1.77 - 1.65 (m, 2H), 1.61 - 1.46 (m, 2H), 0.95 (d, J = 7.6 Hz, 3H); ^{1}H NMR (400 MHz, $CDCl_3/D_2O$) δ 5.38 (s, 1H), 5.31 (s, 1H), 5.07 (t, J =5.6 Hz, 1H), 4.87 (d, J = 4.4 Hz, 1H), 4.07 (s, 1H), 3.93 (d, J = 5.6 Hz, 1H), 3.23 - 3.16 (m, 2H), 2.61 (dd, J = 14.8, 6.0 Hz, 1H), 2.02 - 1.89 (m, 3H), 1.78 - 1.67 (m, 2H), 1.60 (s, 1H), 1.50 (d, J = 10.8 Hz, 1H), 0.94 (d, J = 7.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.7, 145.9, 141.7, 137.8, 118.3, 88.6, 83.5, 79.6, 79.2, 74.8, 49.0, 45.0, 42.9, 40.6, 38.7, 34.5, 28.1, 23.7, 15.0; HRMS (ESI): *m/z* calcd for $C_{19}H_{19}O_4$ $[M-OH]^+$, 311.1278, found: 311.1282.

Comparison of Spectra of Natural and Synthetic Harringtonolide

Comparison of ^{1}H NMR Spectra of Harringtonolide **1** in $CDCl_3$

(a) ^{1}H NMR spectra provided by B. Nay[1]

(b) ^{1}H NMR spectra provided by W. P. Tang[2]

(c) ^{1}H NMR spectra of our synthetic **1**

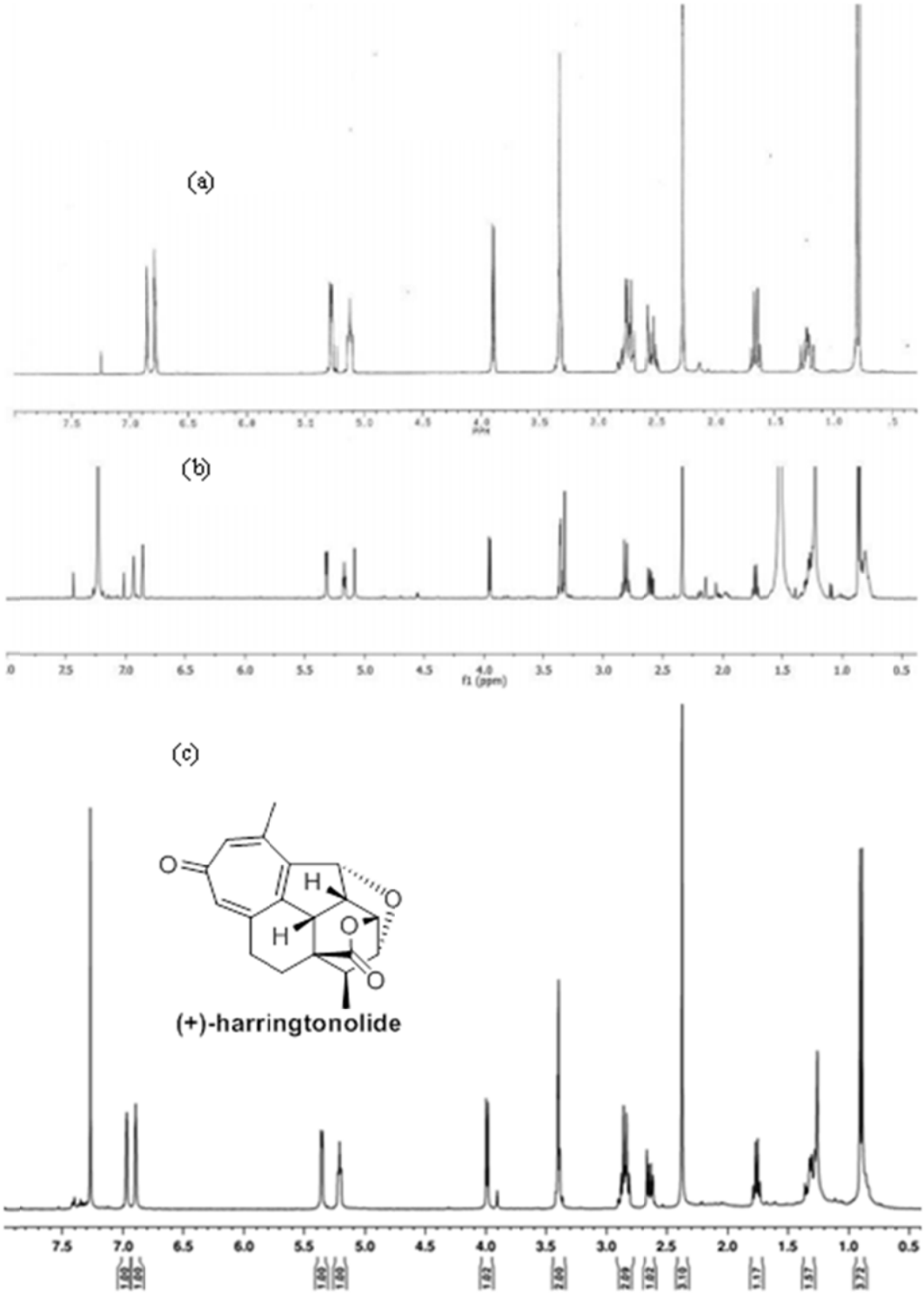


Table S1 ^{1}H NMR Spectroscopic Data of Our Synthetic **1**, Buta's Natural **1**,[3] Sun' Natural **1**,[4] and Tang's Synthetic **1**[2] in $CDCl_3$

δH of our synthetic **1** (400 MHz)	δH of lit. natural **1**[3] (100 MHz)	δH of lit. natural **1**[4] (100 MHz)	δH of Tang's synthetic **1**[2] (500 MHz)
6.97 (s, 1H)	6.98 (s, 1H)	6.95 (d, *J* = 2 Hz, 1H)	6.98 (s, 1H)
6.90 (s, 1H)	6.92 (s, 1H)	6.77 (d, *J* = 2 Hz, 1H)	6.91 (s, 1H)
5.36 (t, *J* = 2.8 Hz, 1H)	5.47 (m, 1H)	5.35 (q, 1H)	5.36 (m, 1H)
5.21 (t, *J* = 5.2 Hz, 1H)	5.32 (m, 1H)	5.19 (m, 1H)	5.22 (dd, *J* = 5.3, 5.3 Hz, 1H)
3.99 (d, *J* = 5.6 Hz, 1H)	4.00 (m, 1H)	3.98 (d, *J* = 6 Hz, 1H)	4.00 (d, *J* = 5.6 Hz, 1H)
3.42 - 3.36 (m, 2H)	3.51 (m, 2H)	3.40 (m, 2H)	3.42 (m, 2H)
2.91 - 2.82 (m, 2H)	2.70 (m, 3H)	2.85 (m, 1H)	2.87 (m, 1H)
2.66 - 2.60 (m, 1H)		2.75 (m, 1H)	2.83 (m, 1H)
		2.65 (m, 1H)	2.64 (dd, *J* = 13.7, 6.5 Hz, 1H)
2.37 (d, *J* = 0.8 Hz, 3H)	2.36 (s, 3H)	2.37 (s, 3H)	2.38 (s, 3H)
1.76 (q, *J* = 7.6 Hz, 1H)	1.75 (q, 1H)	1.74 (q, *J* = 8 Hz, 1H)	1.77 (q, *J* = 7.5 Hz, 1H)
1.36 - 1.28 (m, 1H)	1.25 (m, 1H)	1.32 (m, 1H)	1.31 (m, 1H)
0.90 (d, *J* = 7.6 Hz, 3H)	0.90 (d, 3H)	0.89 (d, *J* = 8 Hz, 3H)	0.91 (d, *J* = 7.6 Hz, 3H)

Table S2. ^{13}C NMR Spectroscopic Data of Our Synthetic **1**, Nay's Natural **1**,[1] Buta's Natural **1**,[3] Sun's Natural **1**,[4] and Tang's Synthetic **1**[2] in $CDCl_3$

δC (I) of our synthetic **1**	δC (II) of lit. natural **1**[1]	δC (III) of lit. natural **1**[3]	δC (IV) of lit. natural **1**[4]	δC of Tang's synthetic **1**[2]
186.5	186.2	186.4	186.9	186.3
173.5	173.3	173.5	173.0	173.3
145.8	145.7	145.9	145.9	145.7
145.6	145.5	145.7	145.2	-
145.0	144.9	145.0	145.0	144.8
143.6	143.4	143.6	143.4	-
141.6	141.3	141.5	141.5	141.5
139.3	139.0	139.1	139.4	139.1
86.0	85.9	85.5	86.0	85.9
80.0	79.8	80.0	79.6	79.9
79.7	79.5	80.0	78.2	79.6
49.9	49.7	49.9	49.7	49.8
45.8	45.6	43.8	45.5	45.7
41.8	41.6	41.7	41.5	41.7
40.0	39.8	40.0	39.7	39.9
32.3	32.1	32.3	31.8	32.2
23.9	23.7	23.8	23.3	23.7
22.4	22.2	22.3	22.0	22.3
14.7	14.6	14.7	14.2	14.6

References:

[1] L. Evanno, A. Jossang, J. Nguyen-Pouplin, D. Delaroche, P. Herson, M. Seuleiman, B. Bodo, B. Nay, *Planta Med*. **2008**, *74*, 870－872.

[2] M. Zhang, N. Liu, W. P. Tang, *J. Am. Chem. Soc*. **2013**, *135*, 12434－12438.

[3] J. G. Buta, J. L. Flippen, W. R. Lusby, *J. Org. Chem.* **1978**, *43*, 1002－1003.

[4] N. J. Sun, Z. Xue, X. T. Liang, L. Huang, *Acta Pharm. Sin*. **1979**, *14*, 39－44.

HPLC Data of (±)-8 and (-)-8

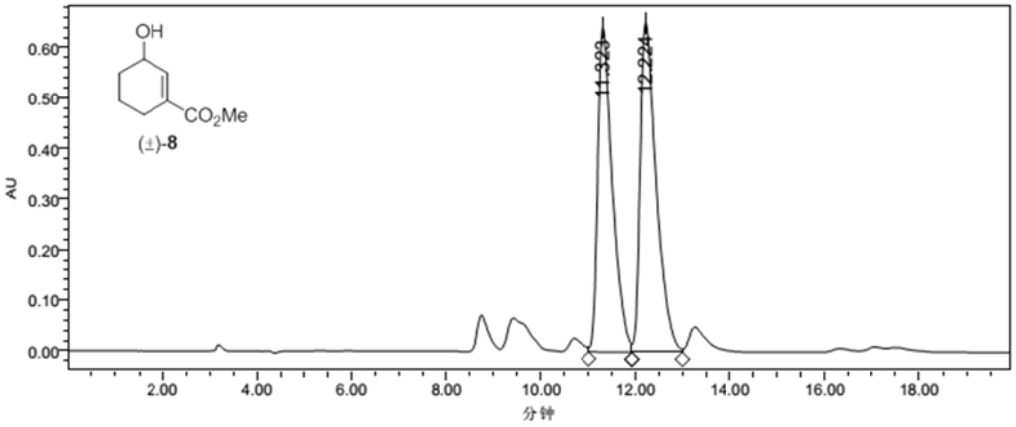
进样综合报告 报告

用户名称: System　　项目名称: a2015

样品信息

样品名称:	zhj-race20151009	采集者:	System
样品类型:	未知	采集时间:	2015-10-8 17:11:05
瓶号:	1	采集方法组:	zhjrace
进样次数:	4	处理日期:	2015-10-8 17:38:33
进样体积:	5.00 ul	处理方法:	zhjrace20151009
运行时间:	60.0 Minutes	通道名称:	Wvln Ch1
样品组名称:		处理通道注释:	PDA 230.0 纳米

自动标尺色谱图



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2	PDA 230.0 纳米	12.224	15283185	52.57	653100

进样综合报告 报告

用户名称: System　　项目名称: a2015

样品信息

样品名称:	zhj-zjf(RuH30g)	采集者:	System
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进样次数:	1	处理日期:	2015-10-21 16:00:08
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运行时间:	60.0 Minutes	通道名称:	Wvln Ch1
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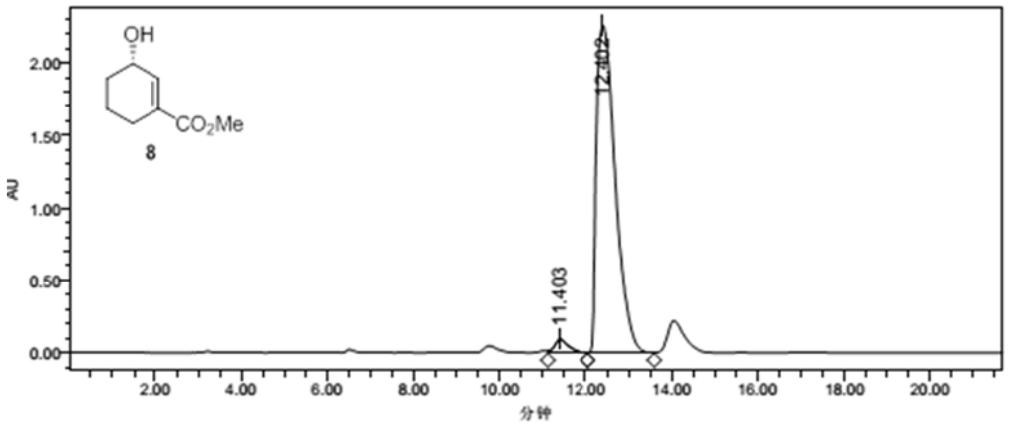

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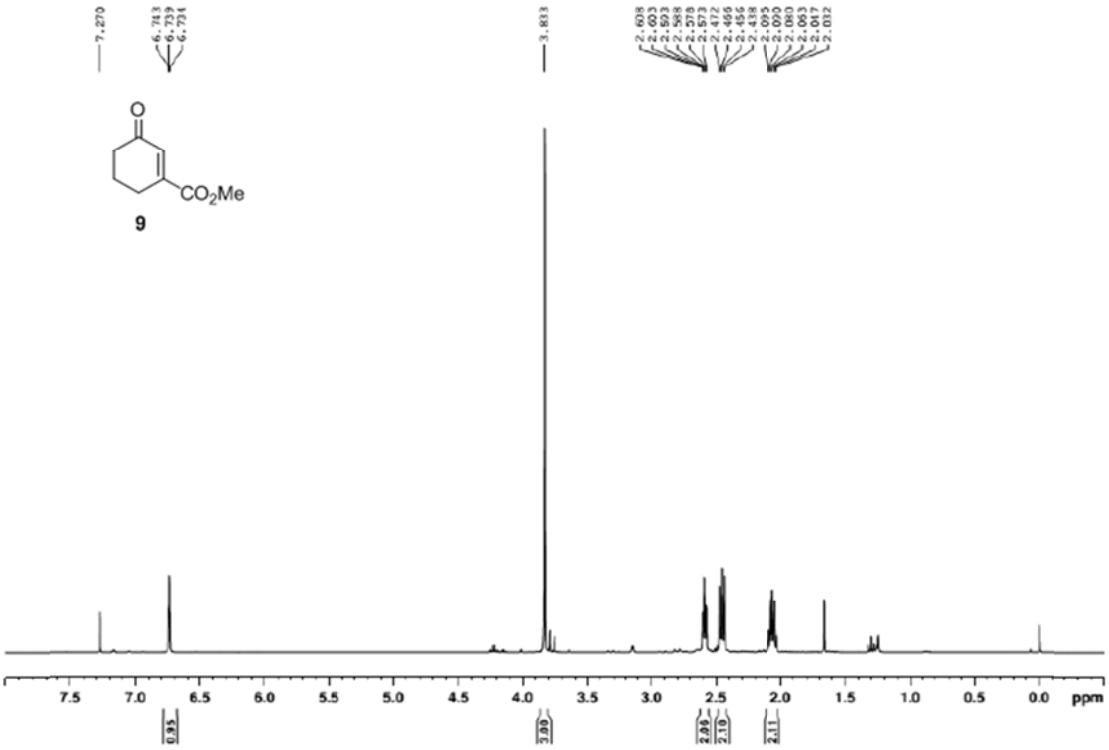
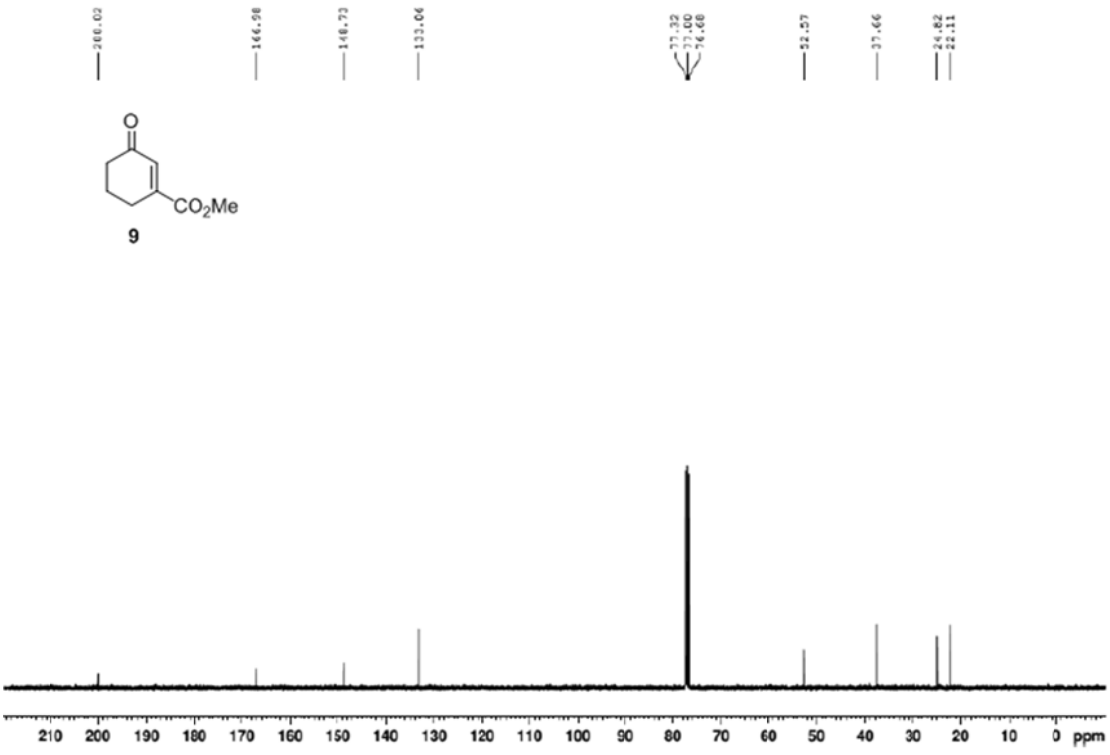
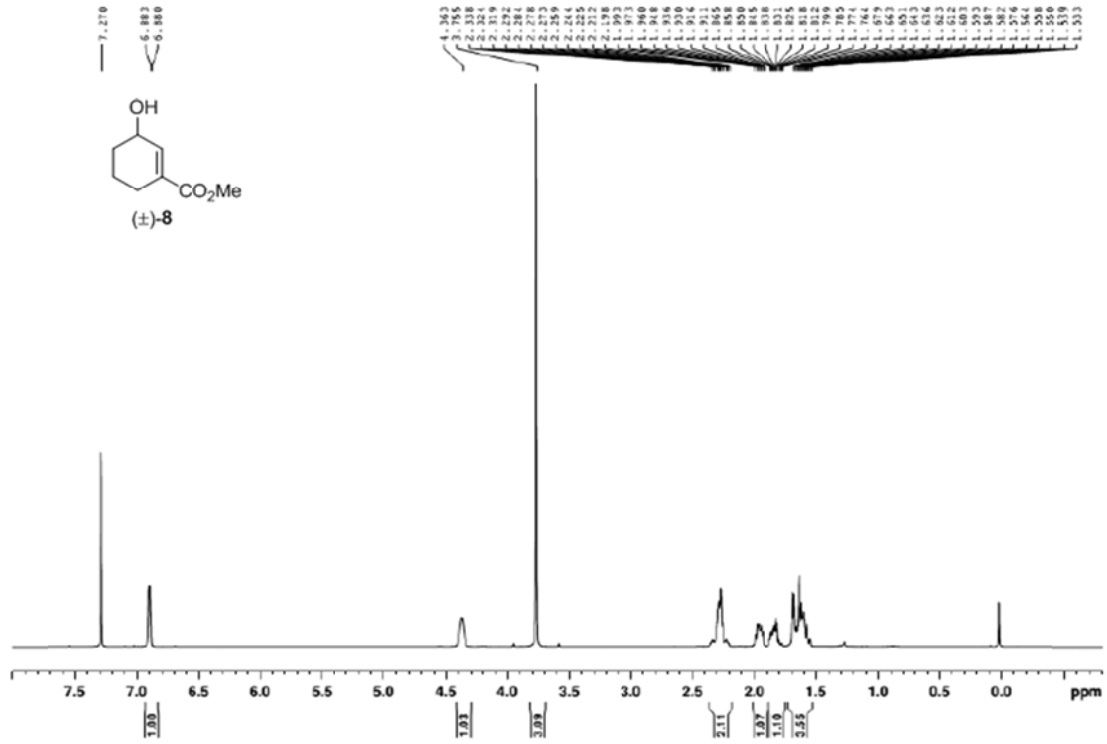
(-)-8

NMR Spectra of the Intermediates and (+)-Harringtonolide



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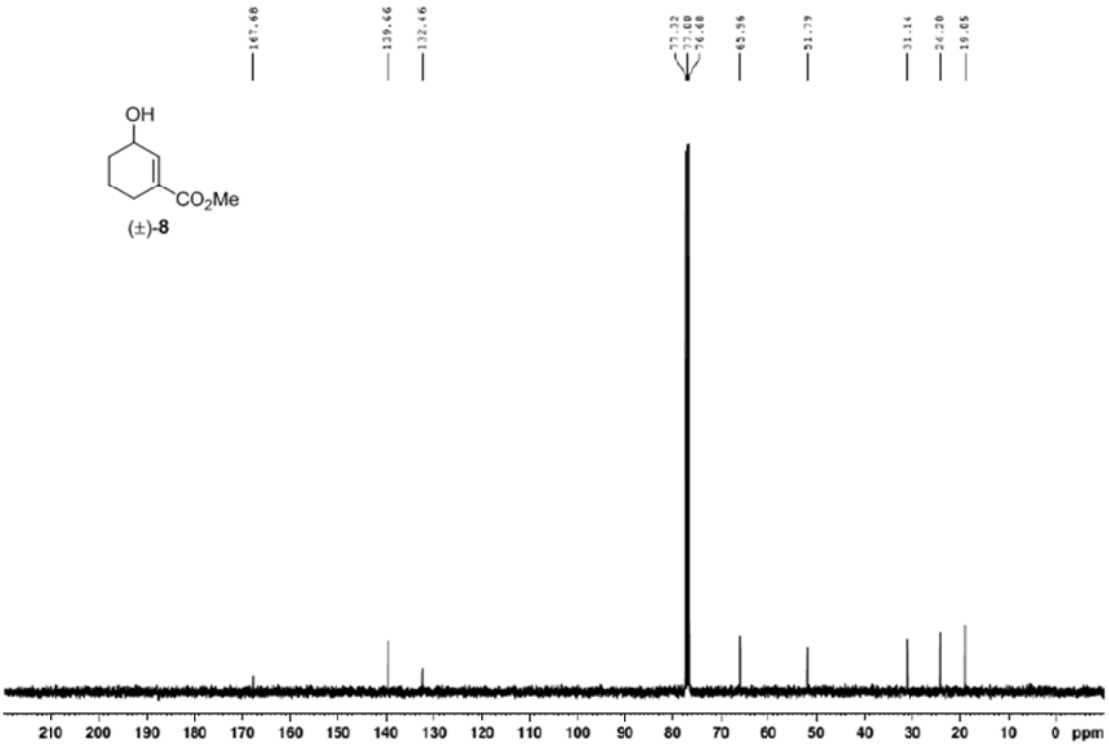
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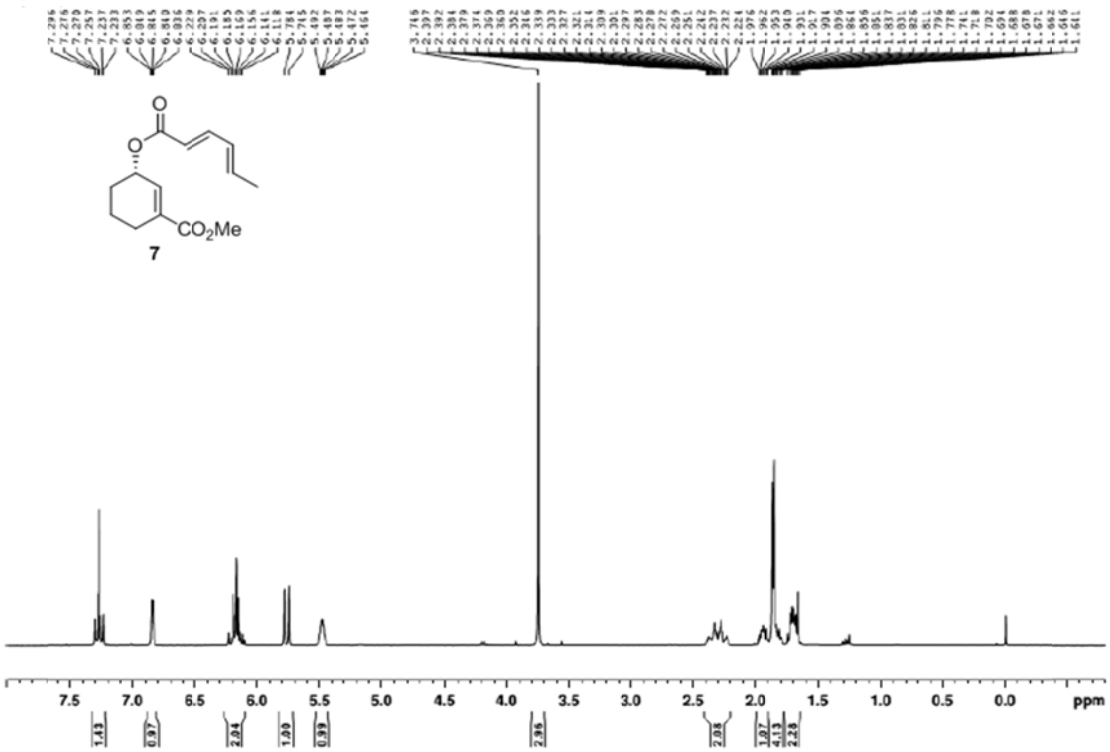
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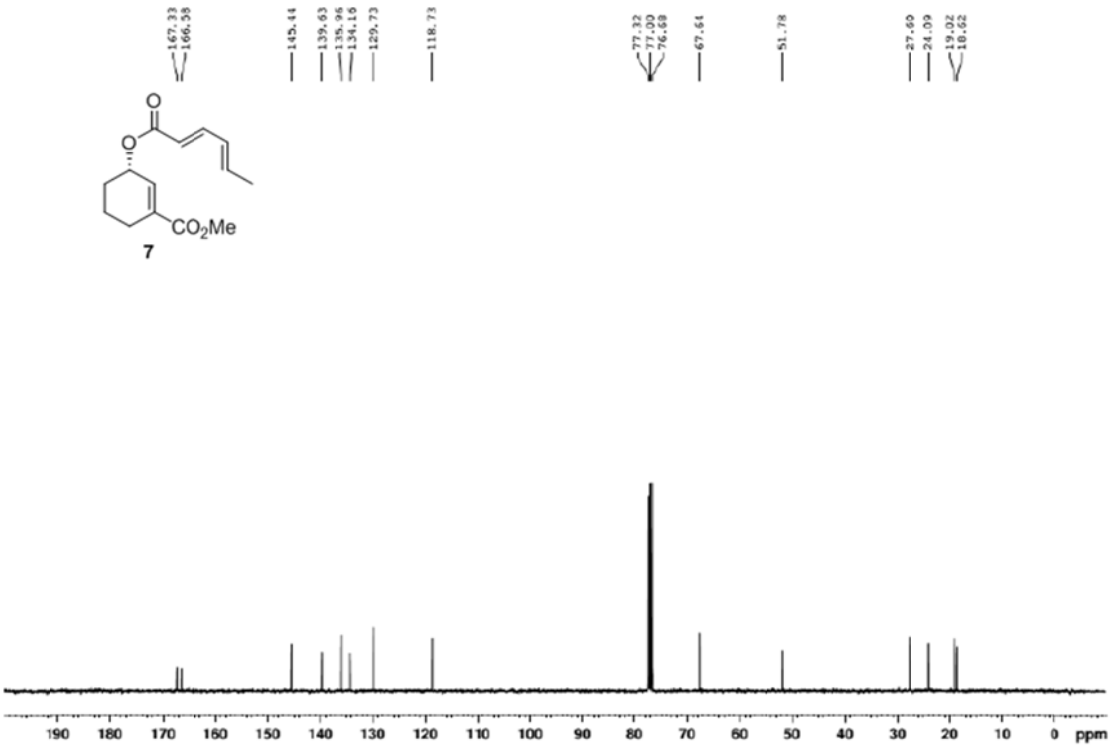
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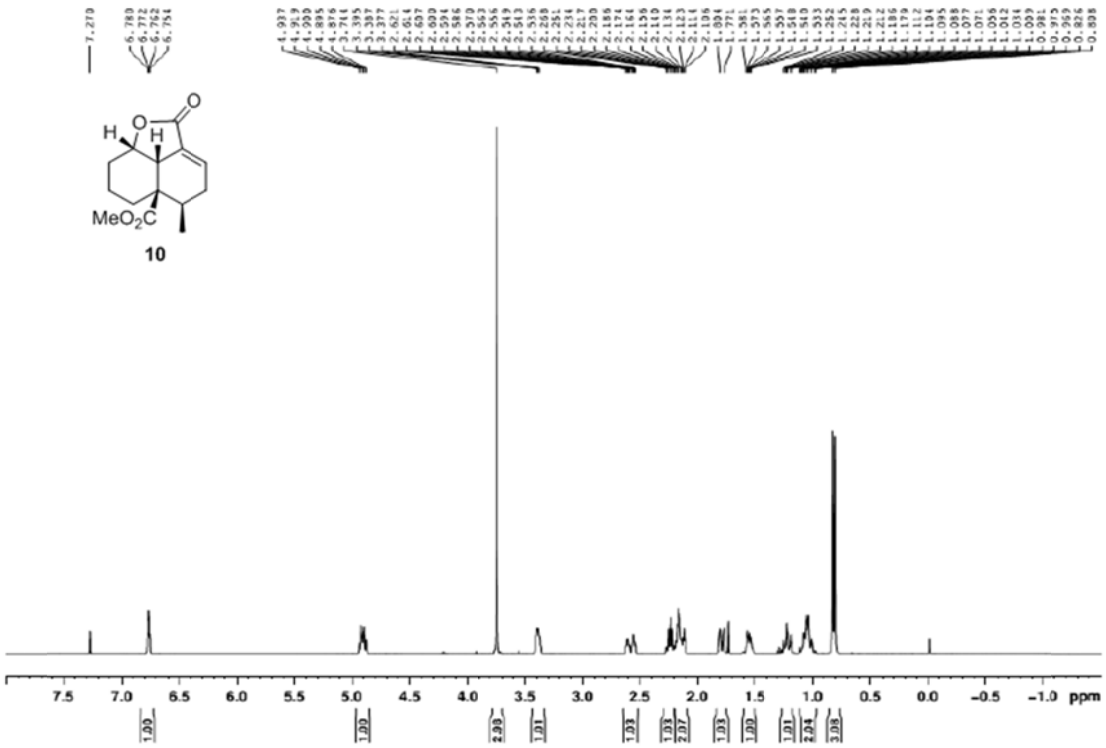
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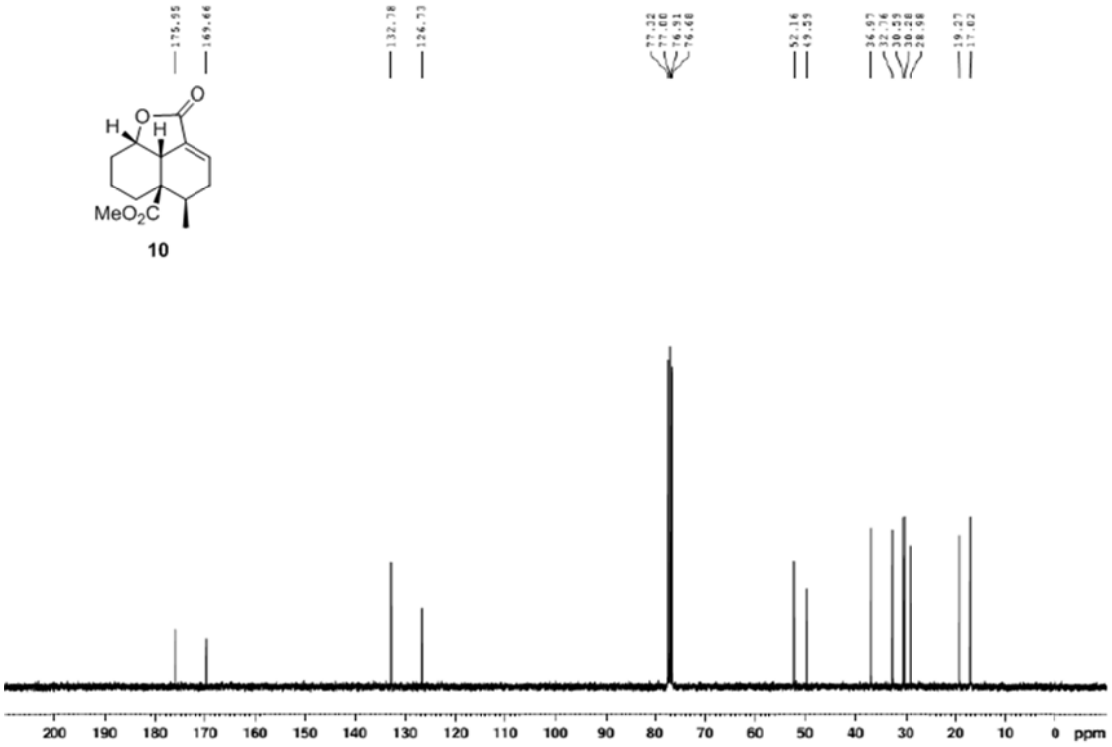
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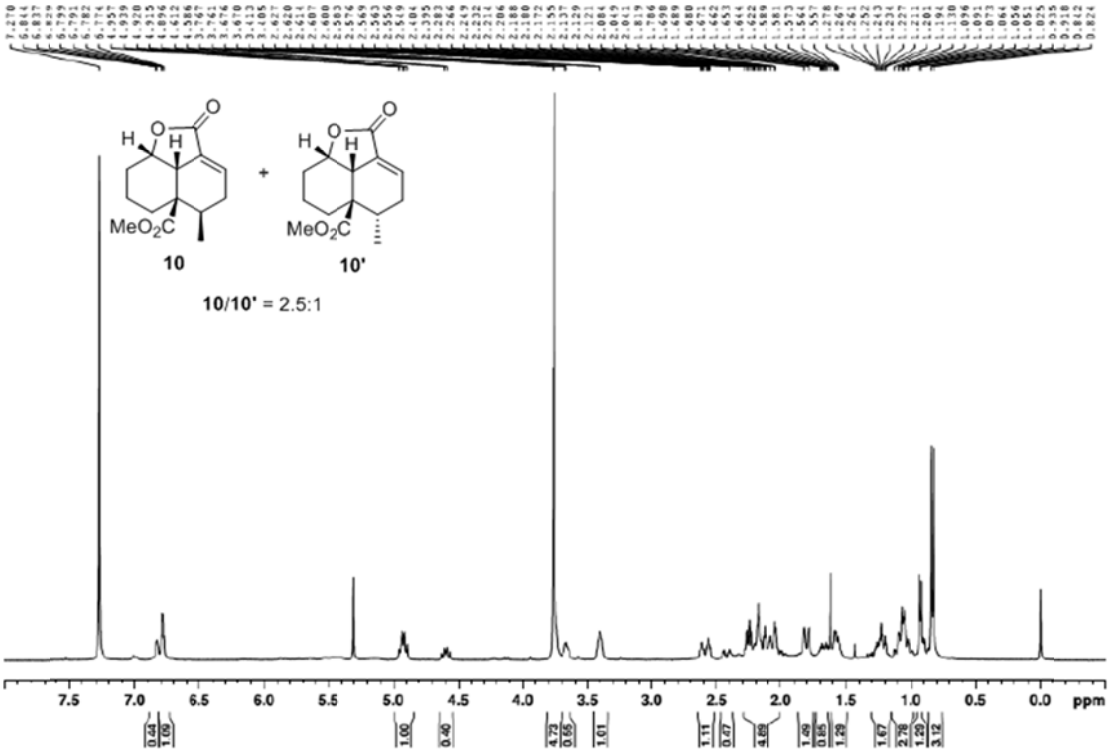

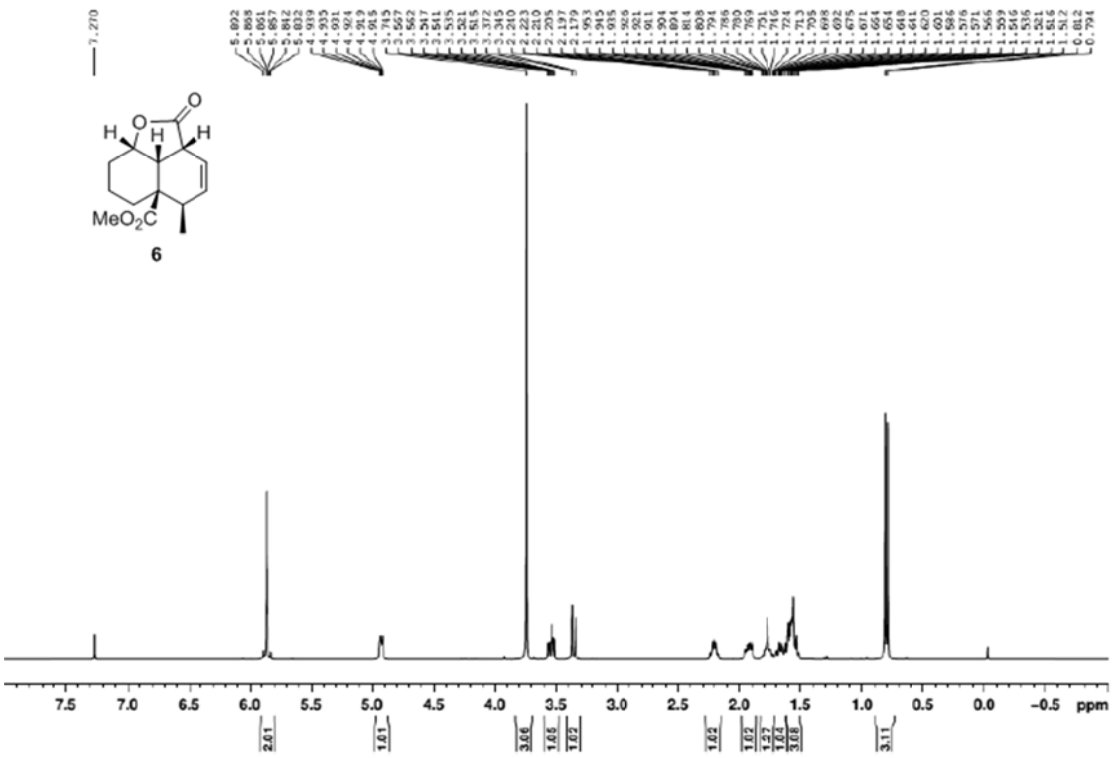
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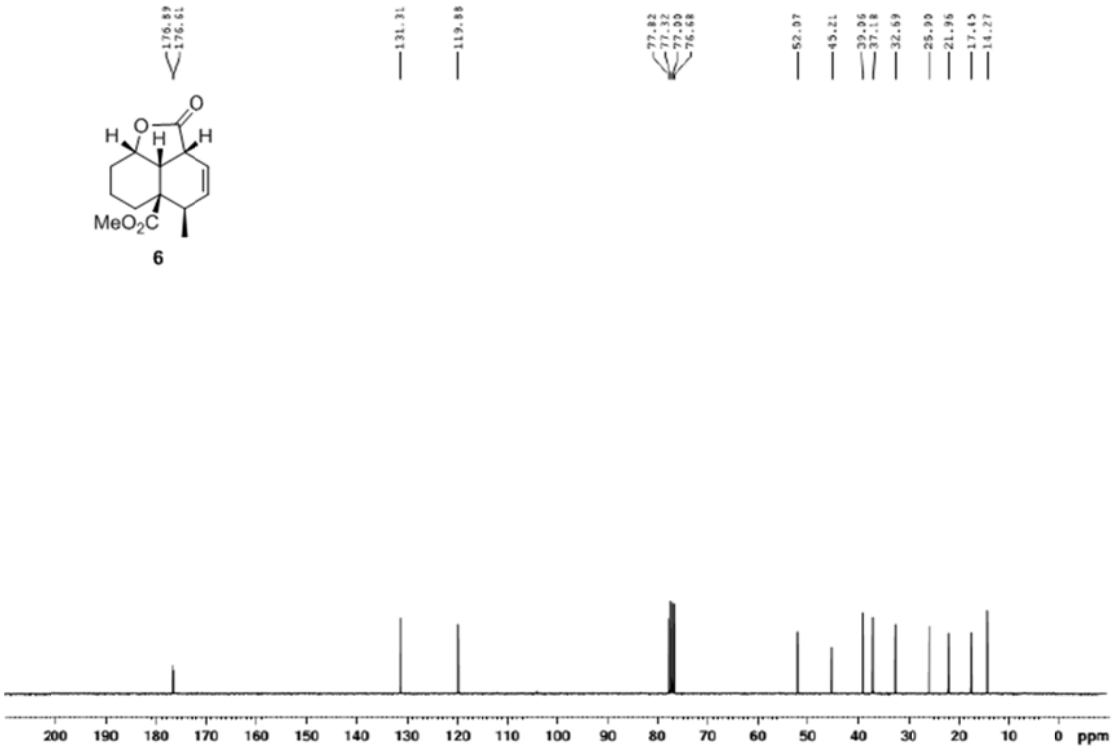
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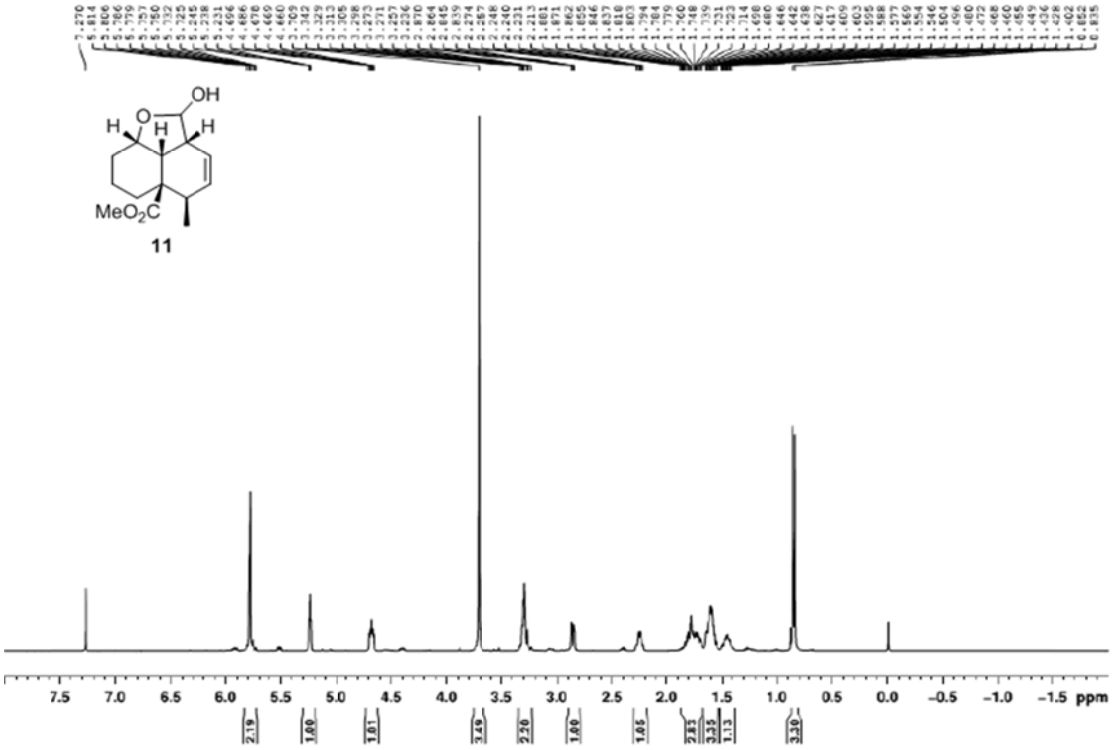
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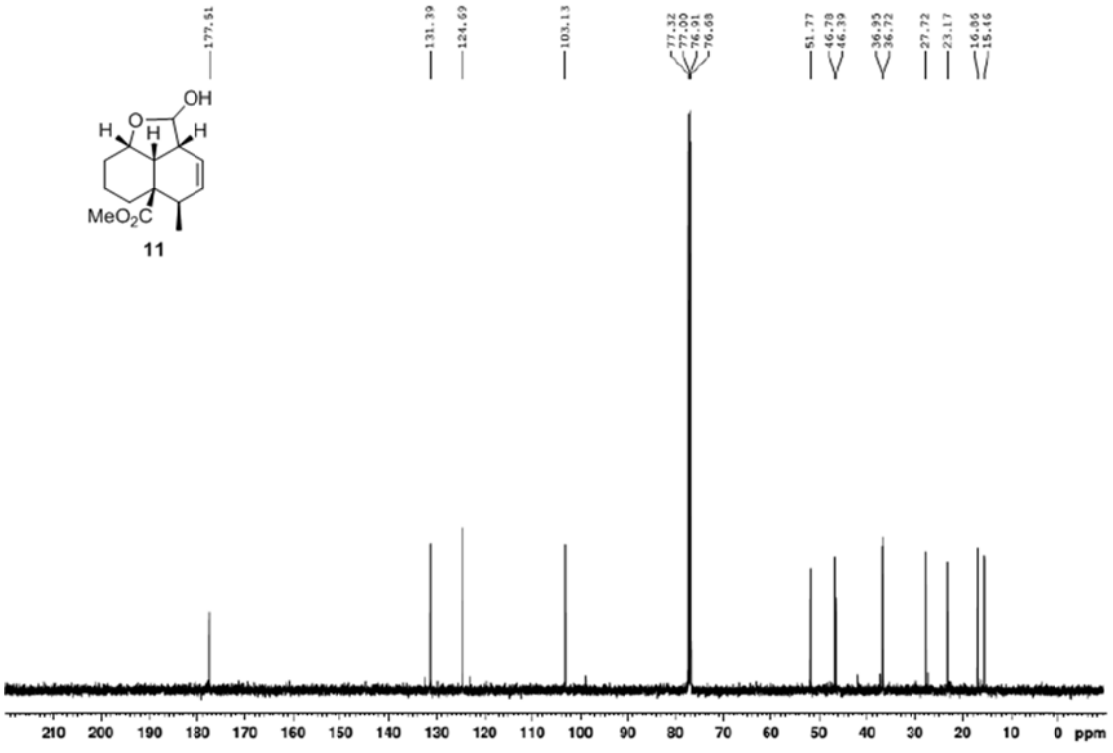
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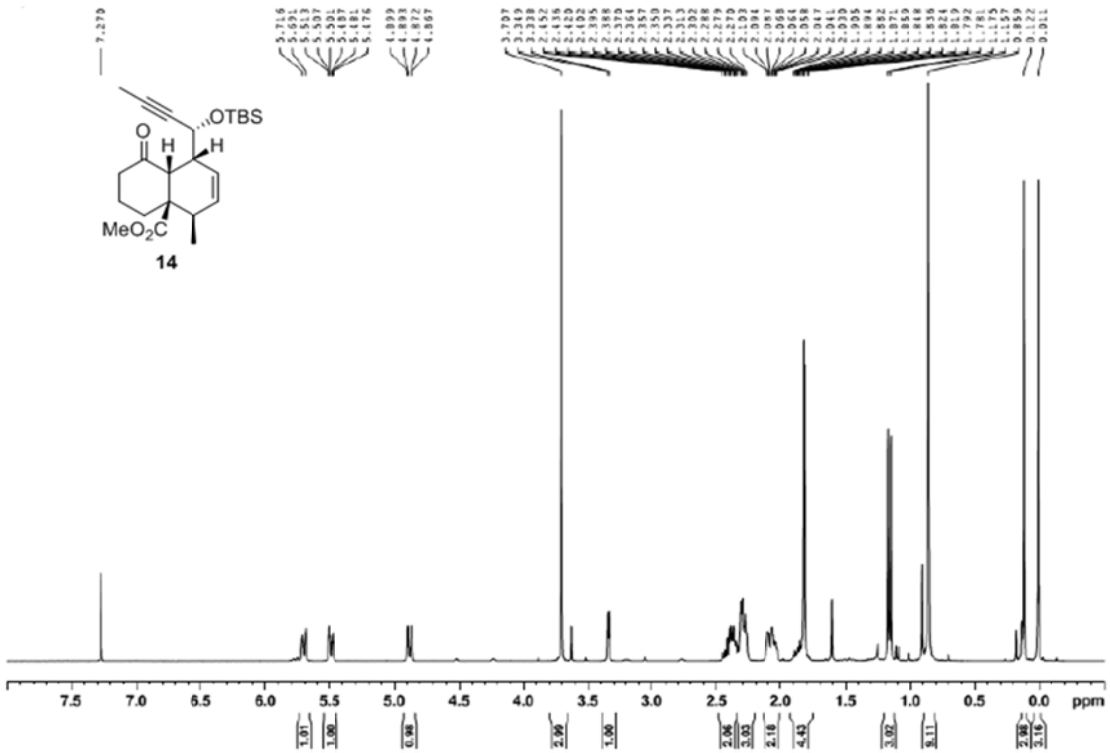
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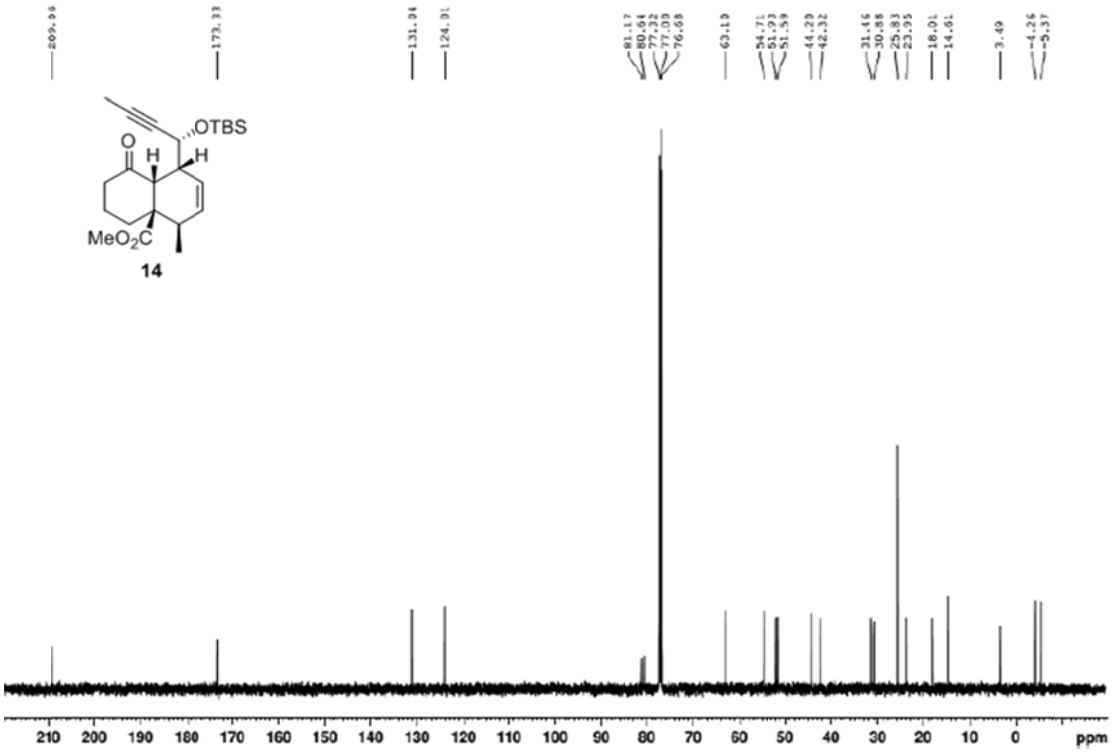
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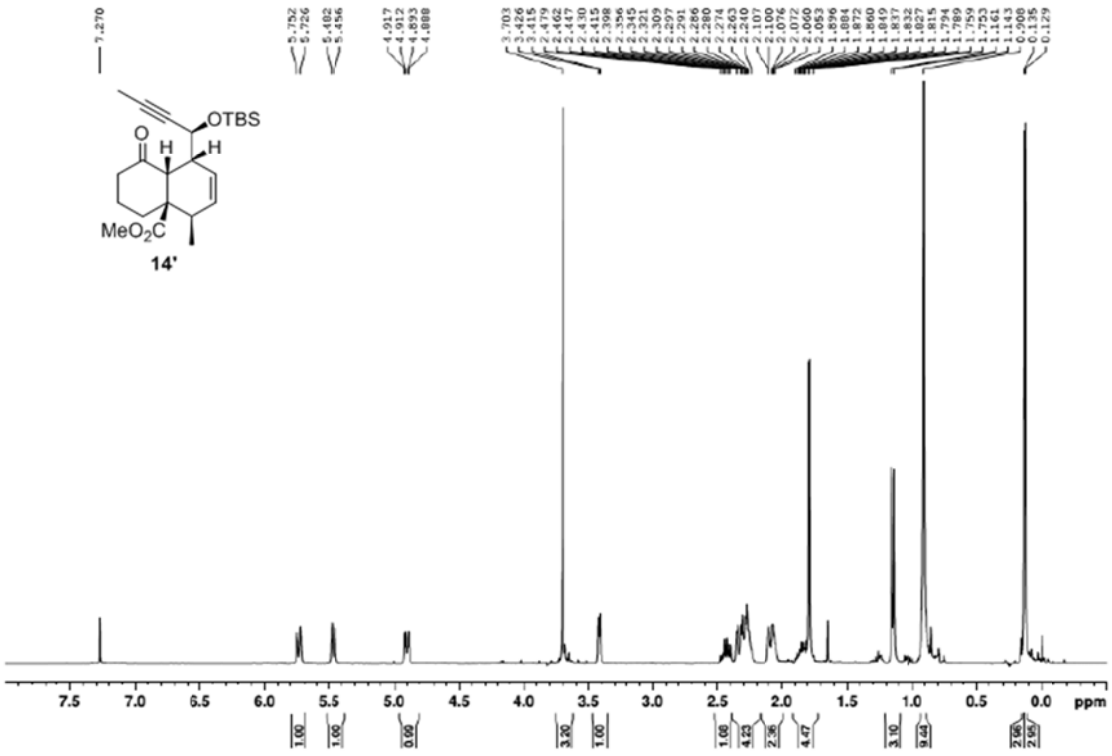
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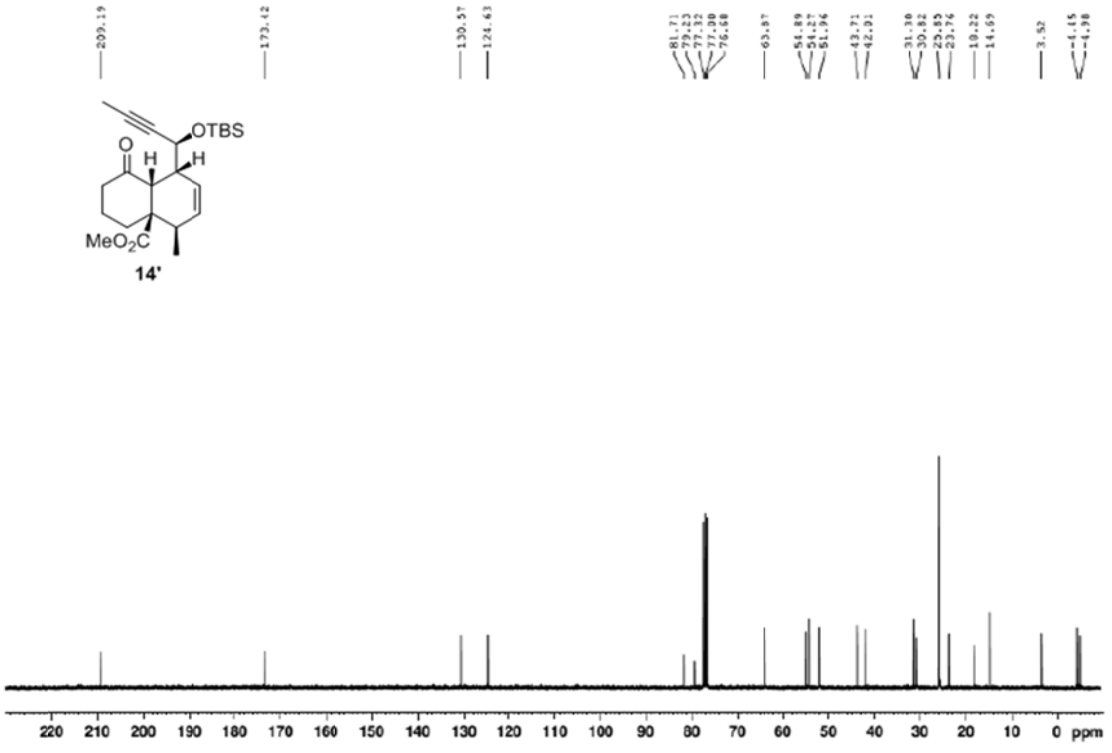
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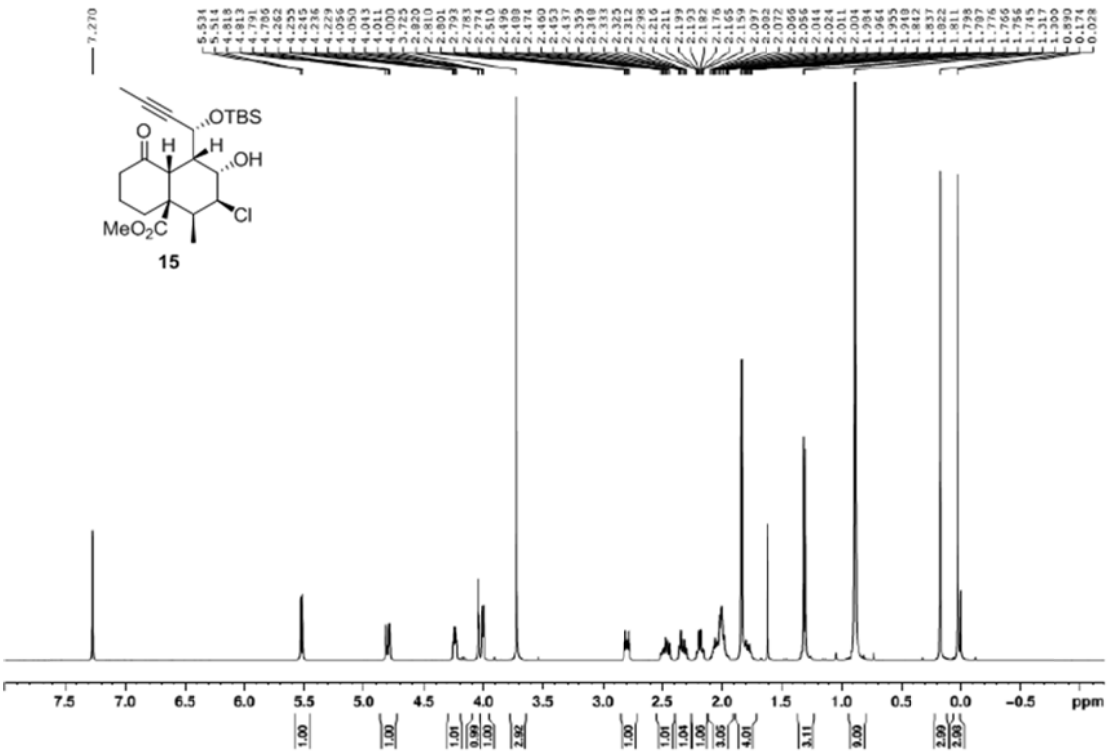
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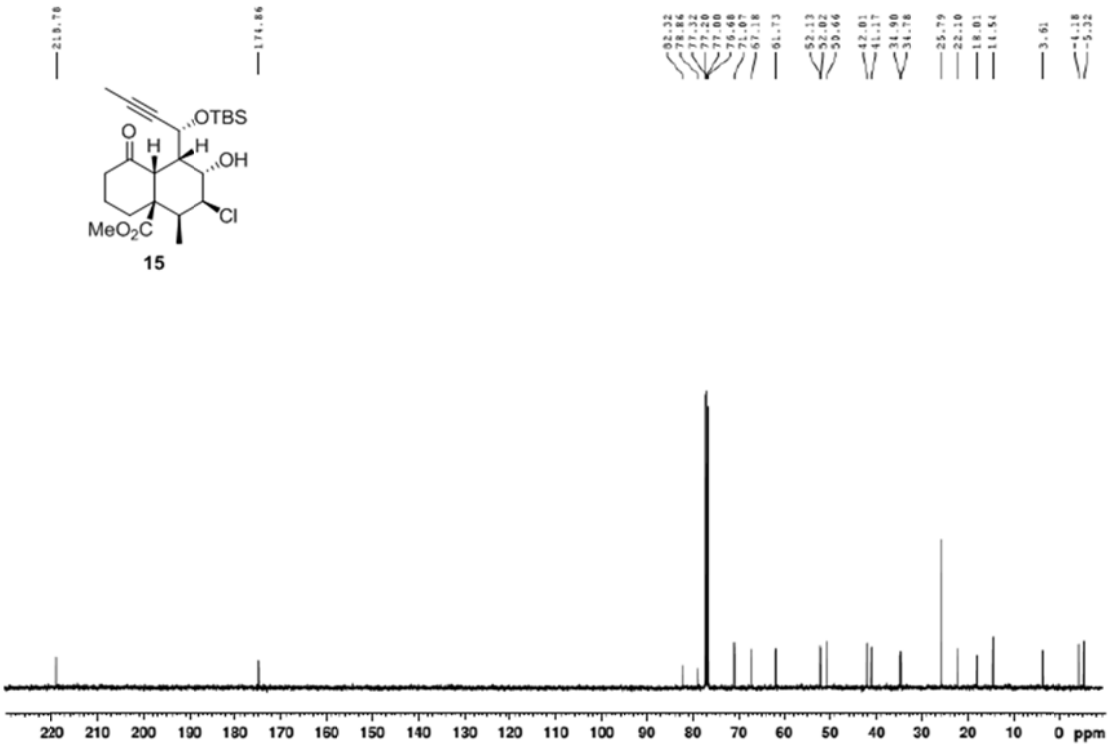
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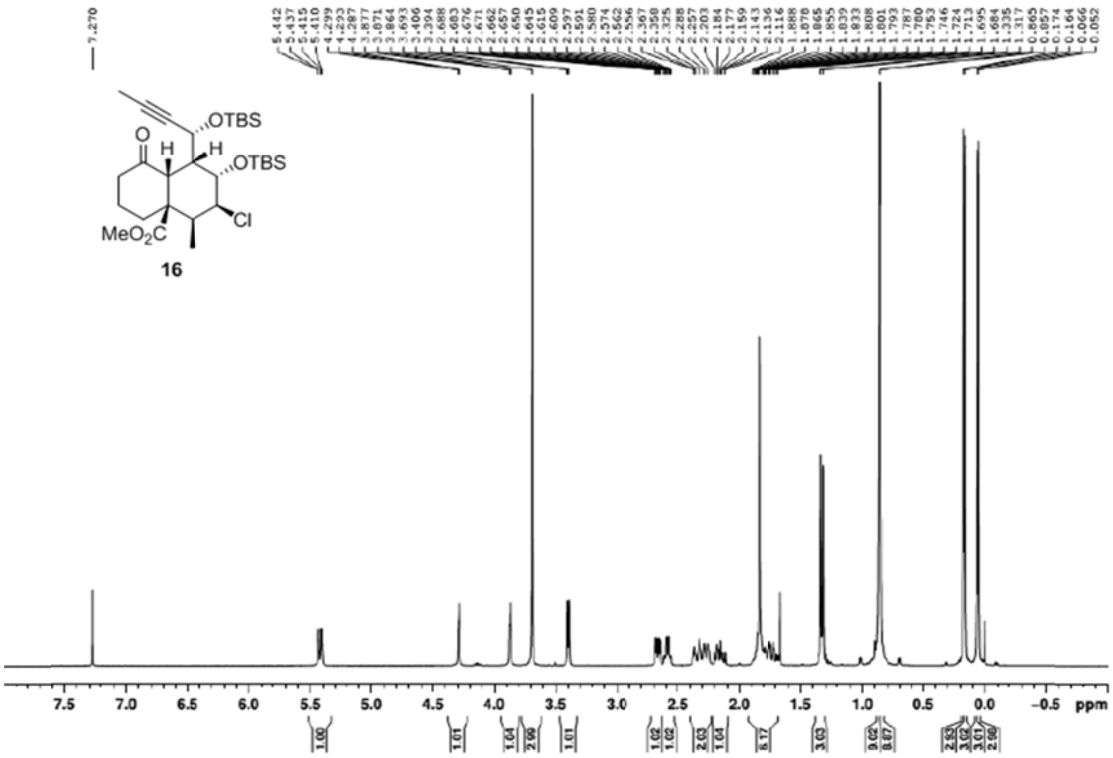
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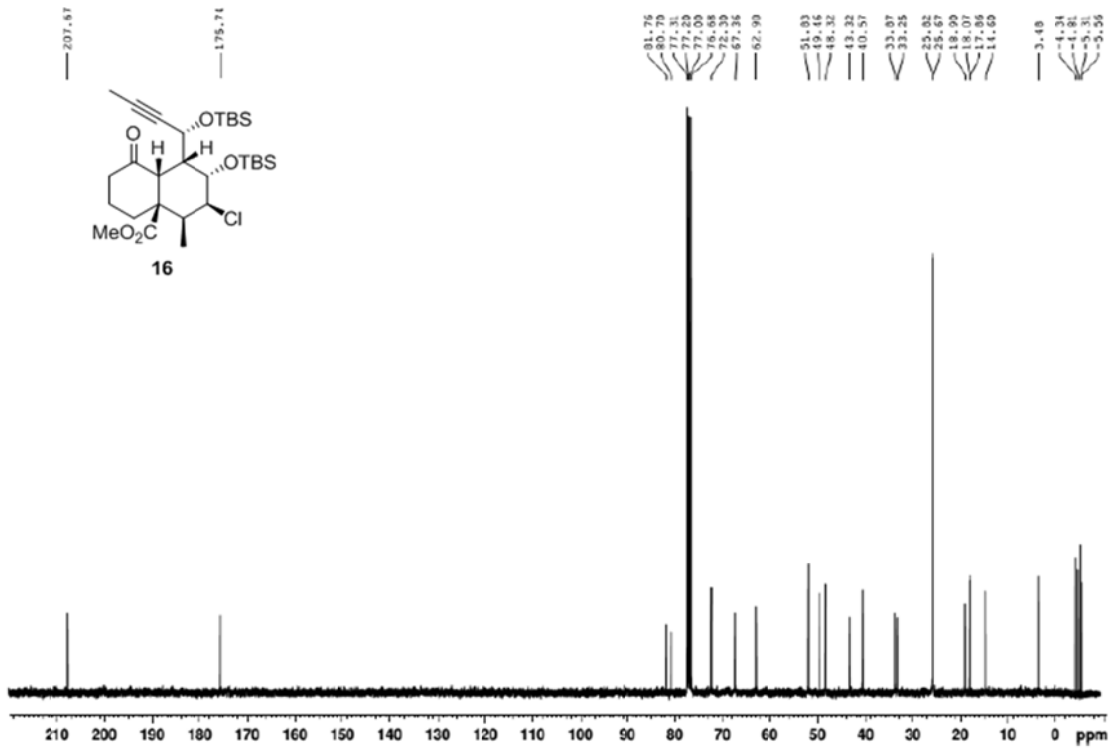
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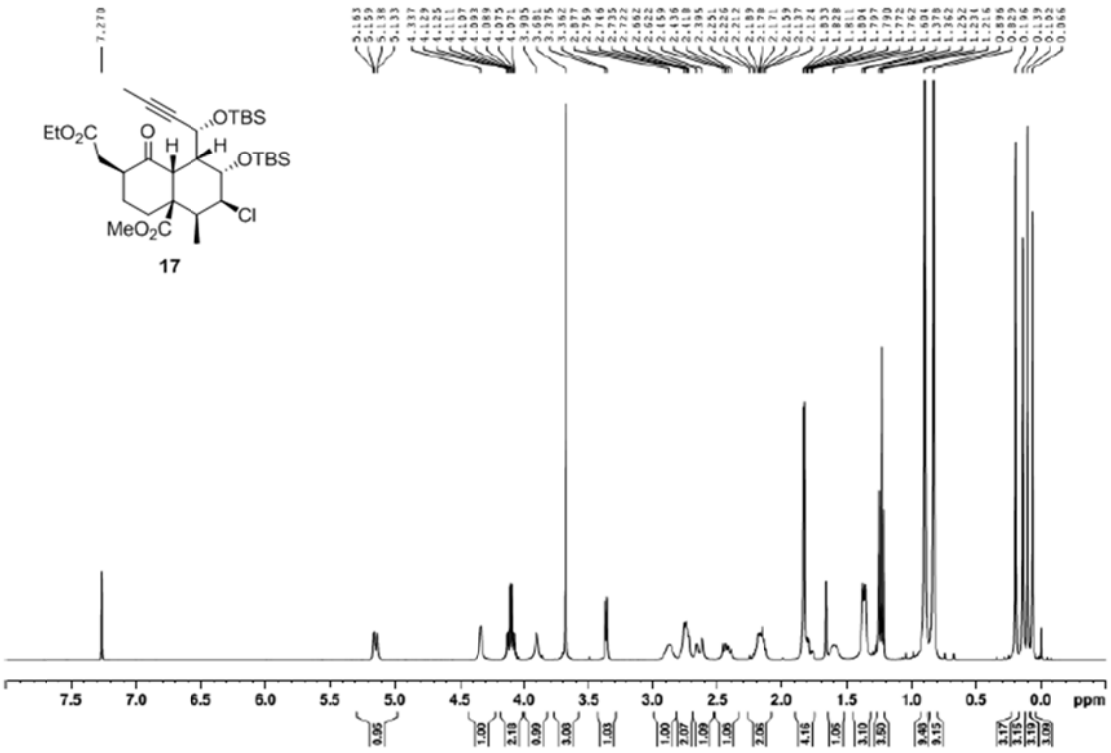
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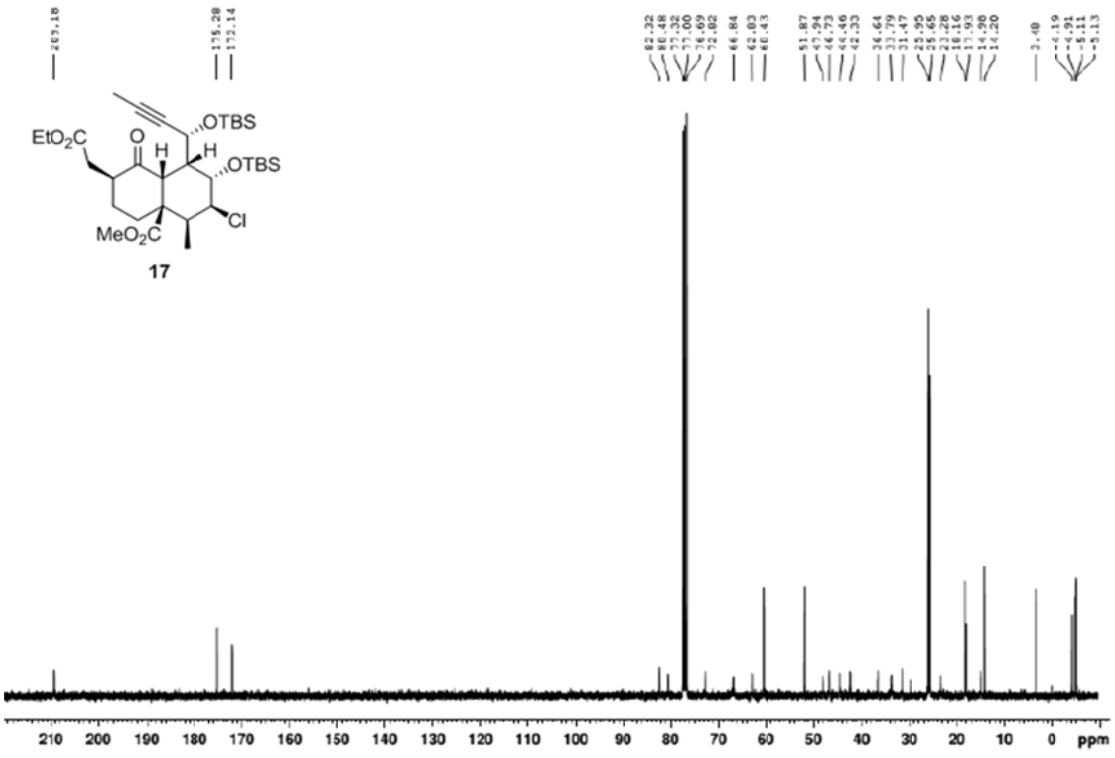
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17
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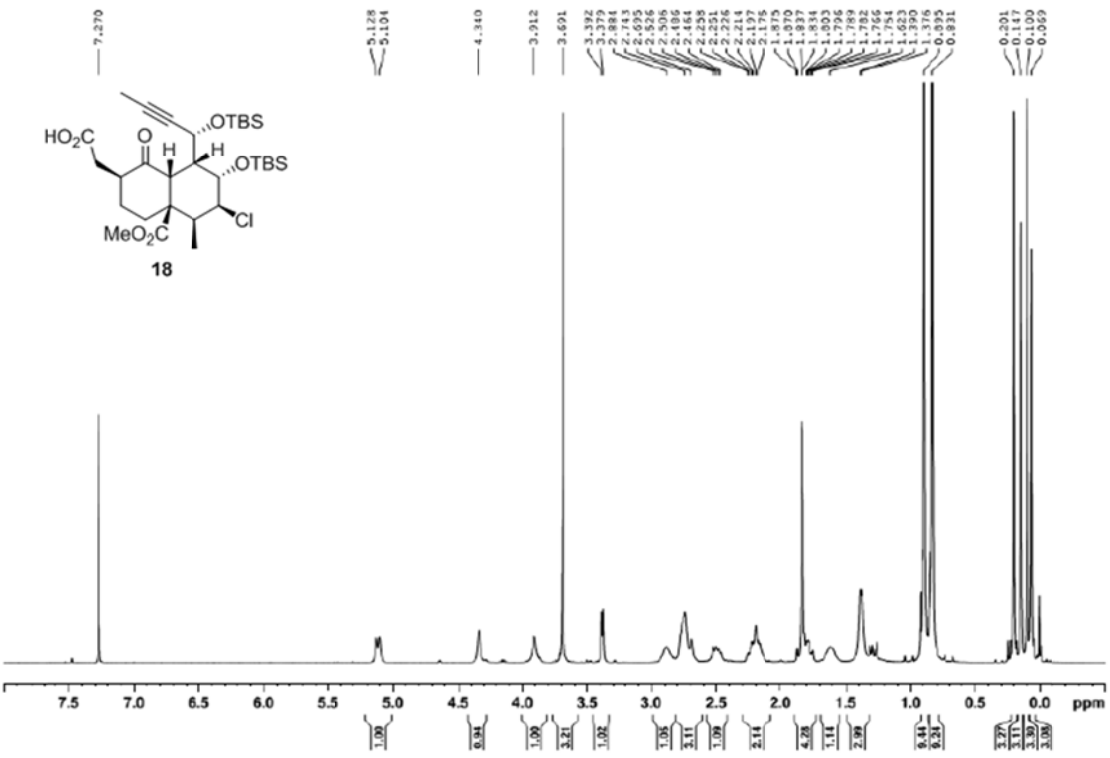
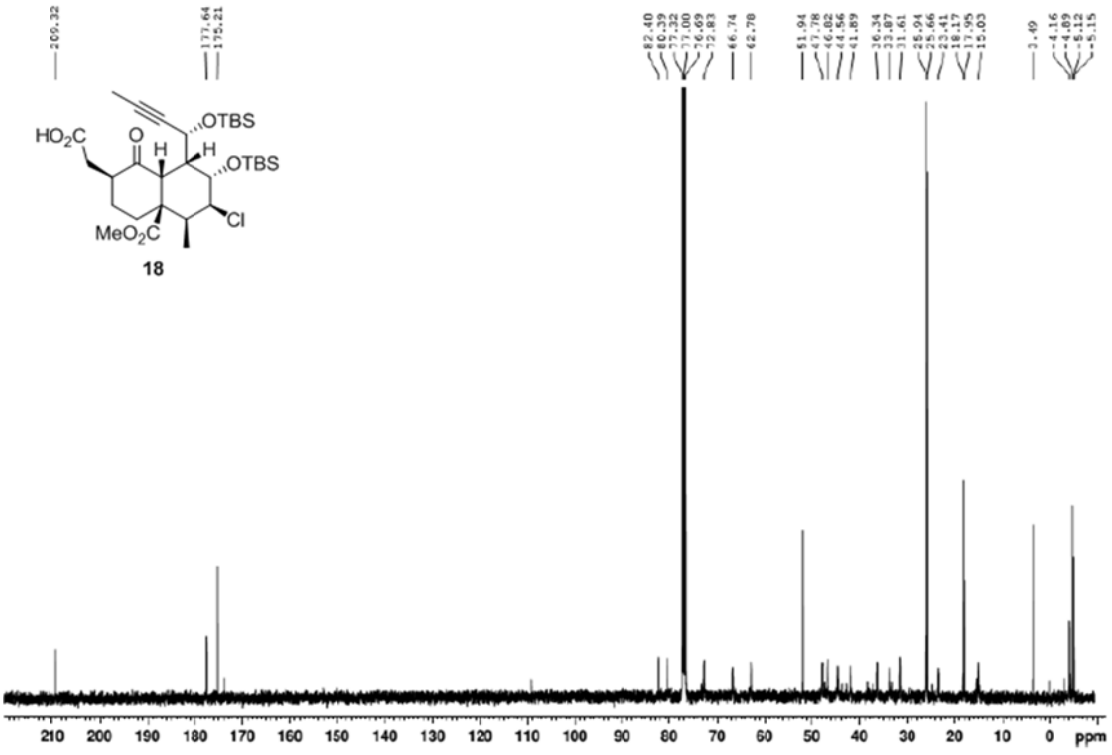
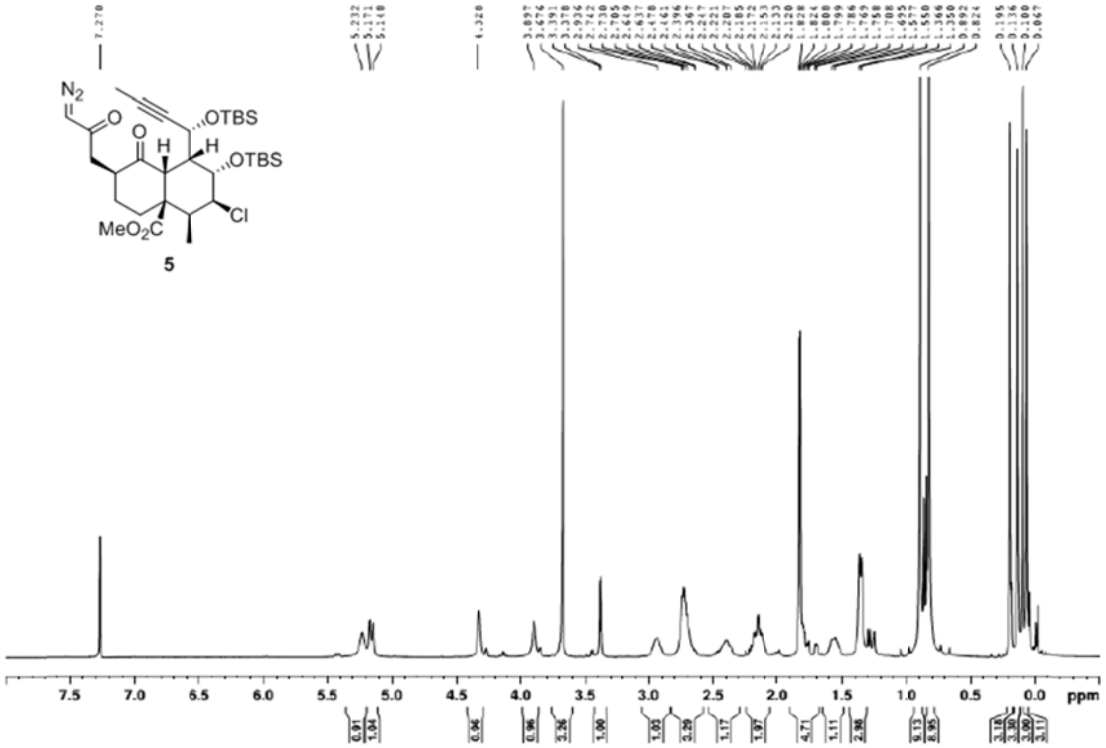
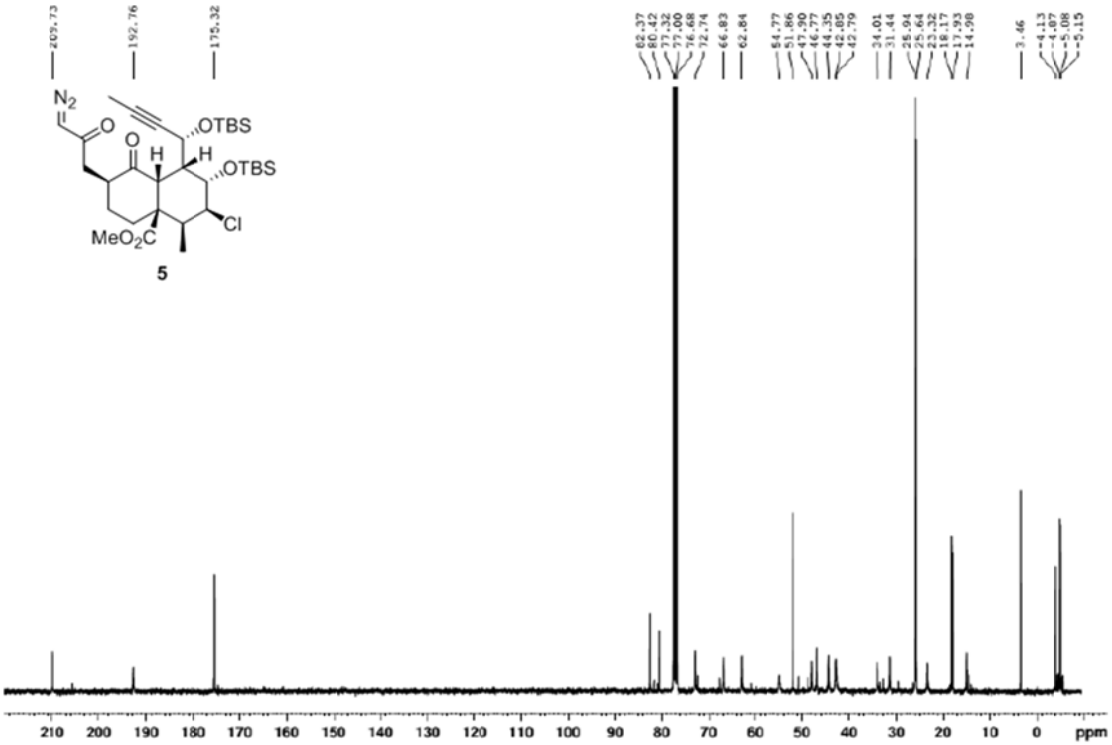
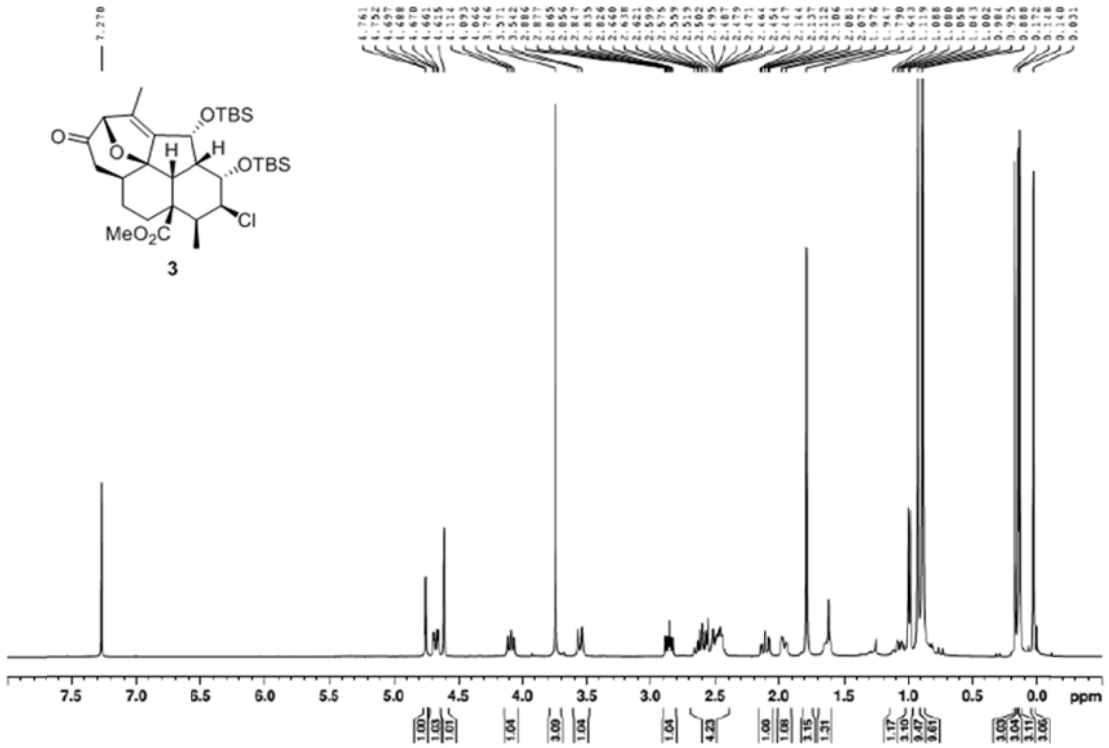
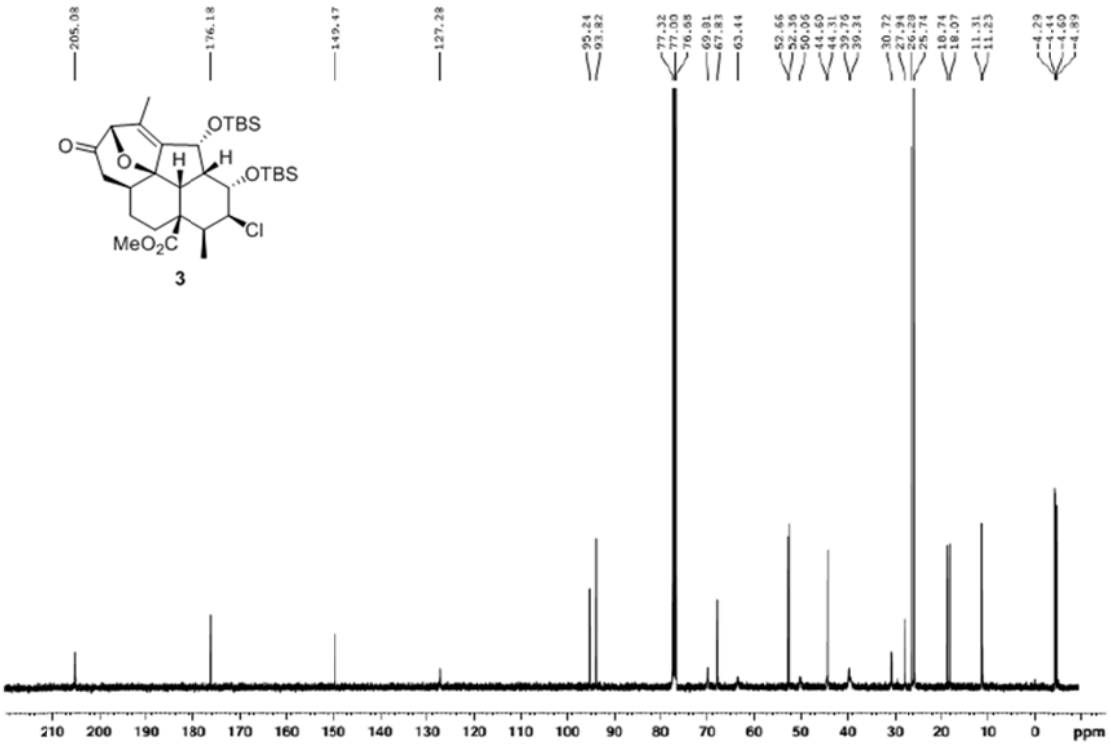

HO2C
O
H
H
OTBS
OTBS
Cl
MeO2C
18
ppm

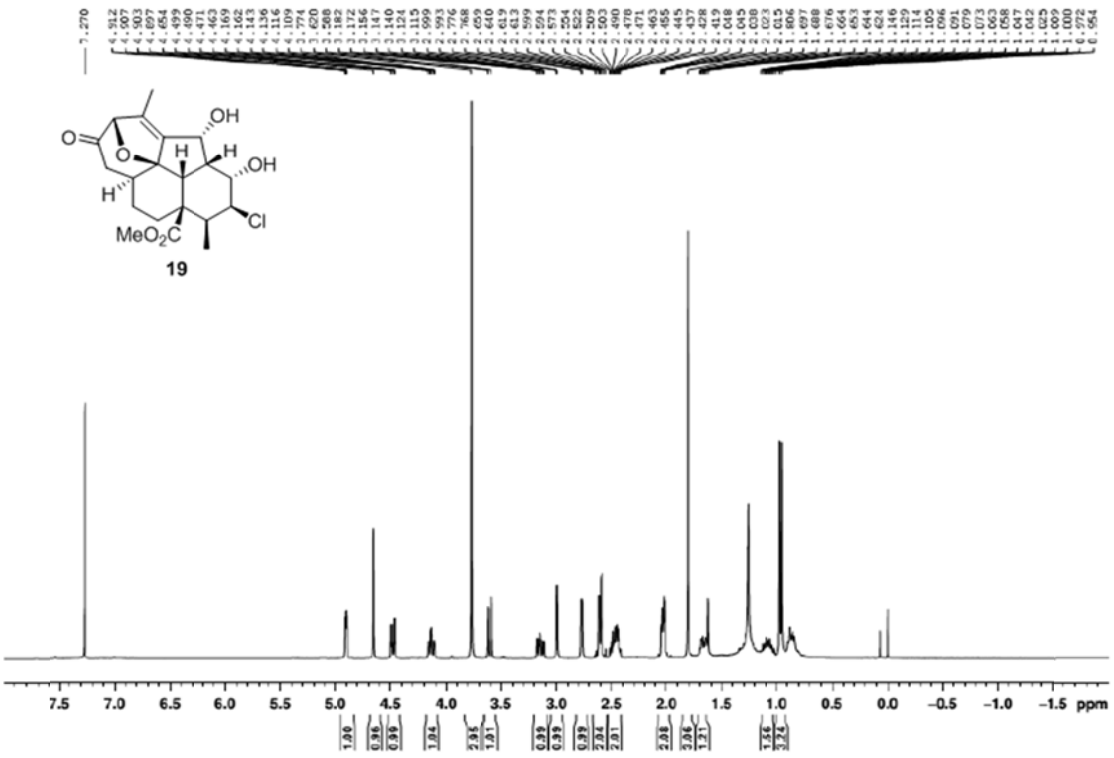

HO2C
O
H
H
OTBS
OTBS
Cl
MeO2C
18
ppm

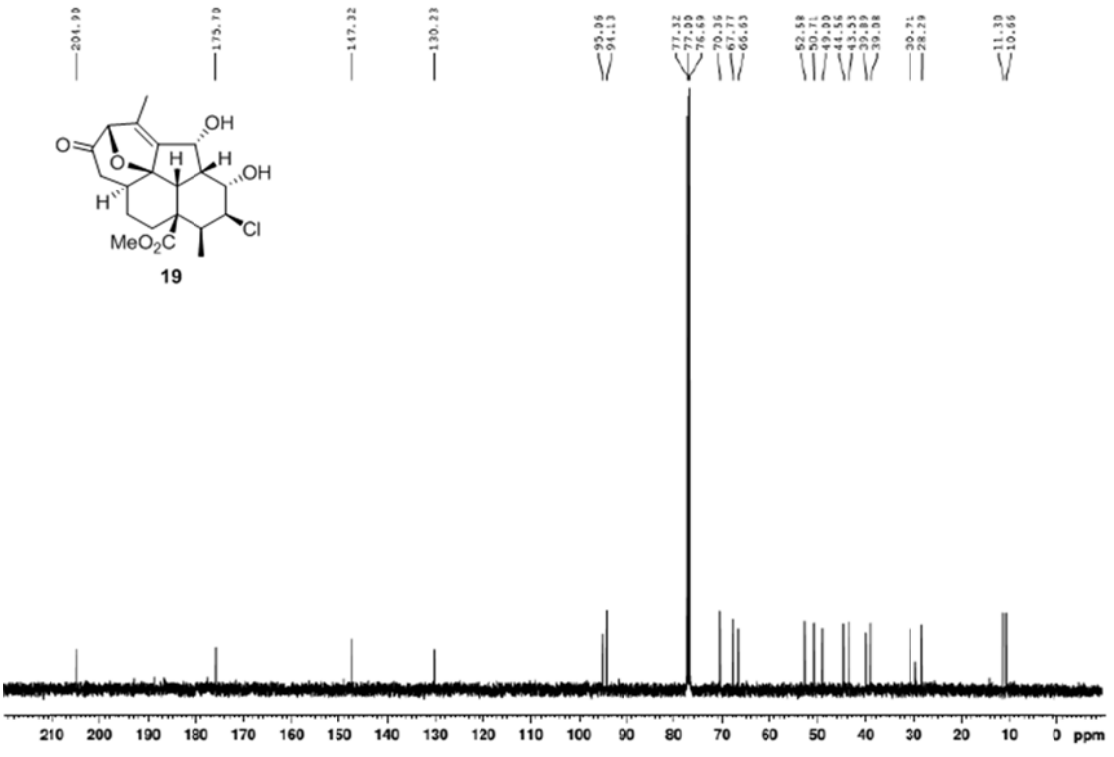

N2
O
OTBS
H
H
OTBS
Cl
MeO2C
5
ppm

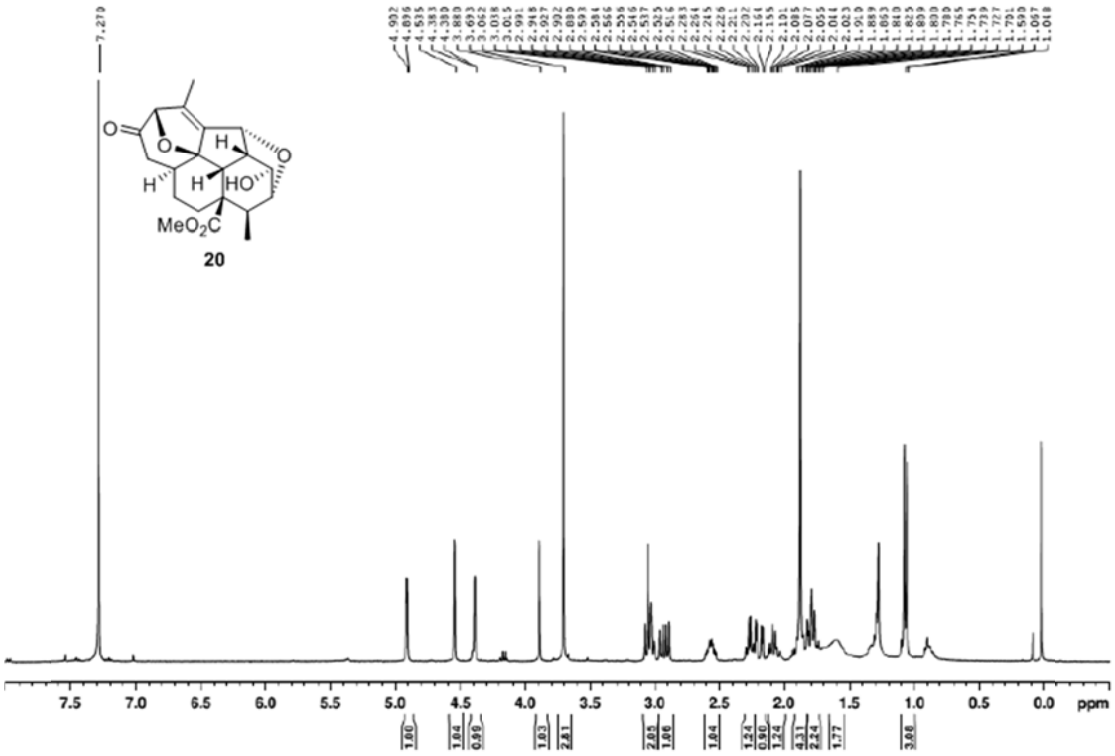

N2
O
OTBS
H
H
OTBS
Cl
MeO2C
5
ppm

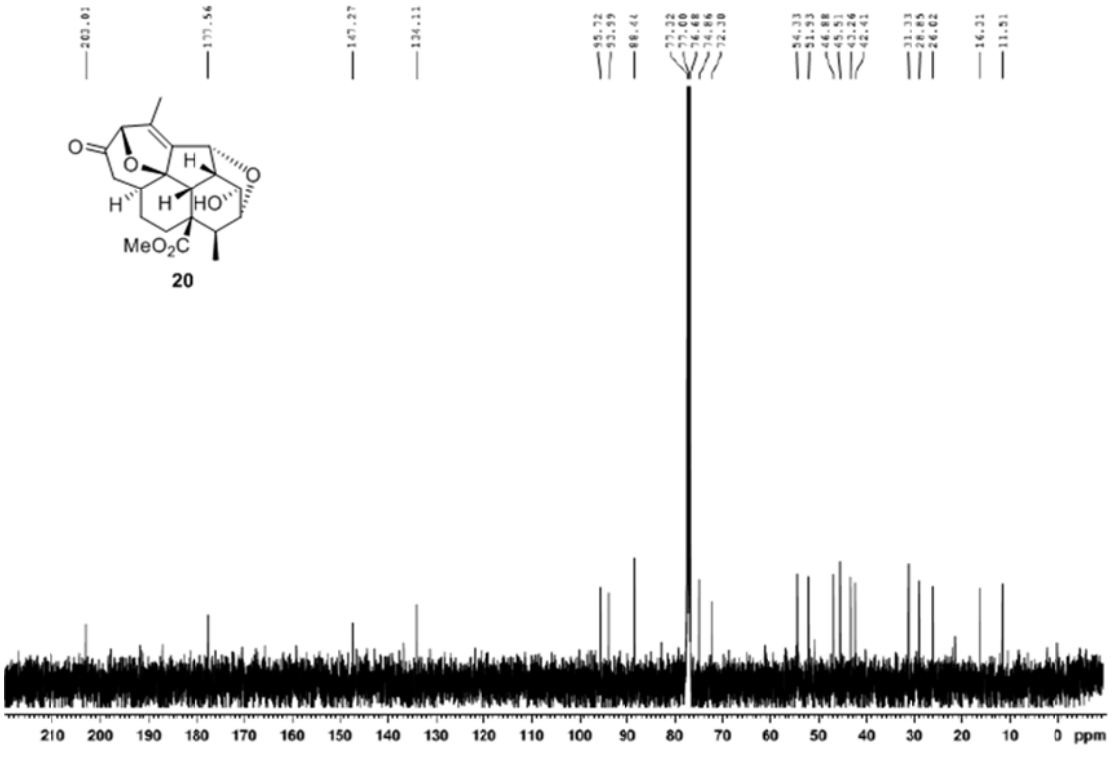

OTBS
OTBS
Cl
MeO2C
3
ppm

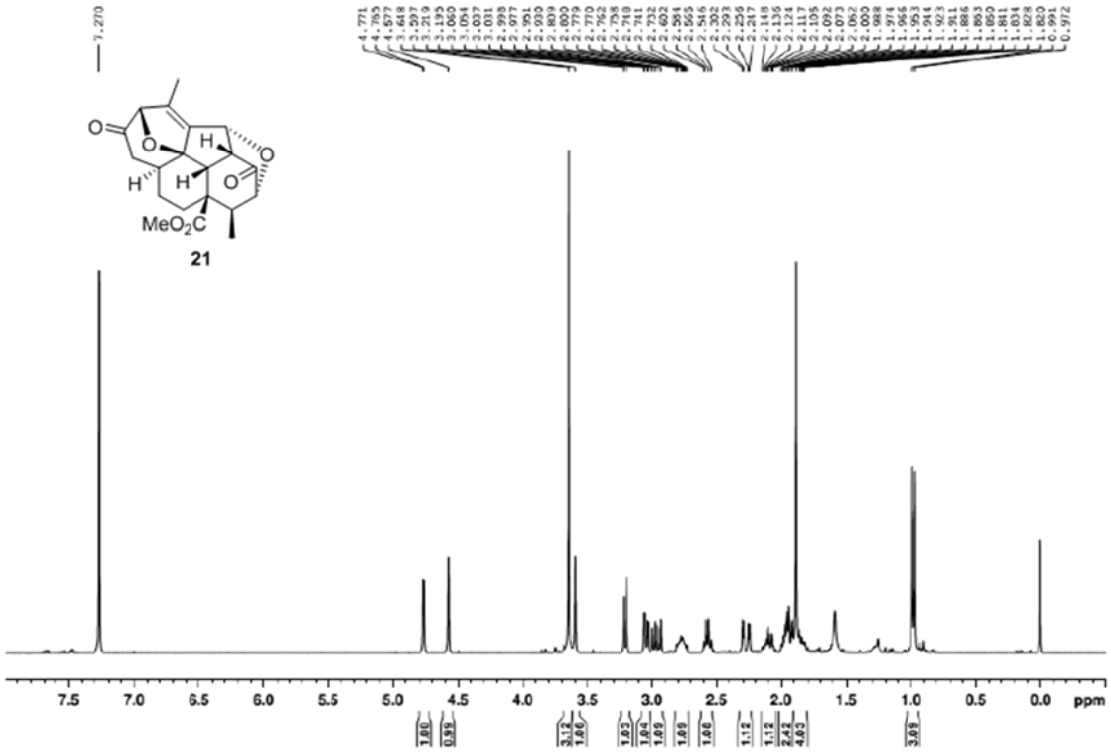

OTBS
OTBS
Cl
MeO2C
3
ppm

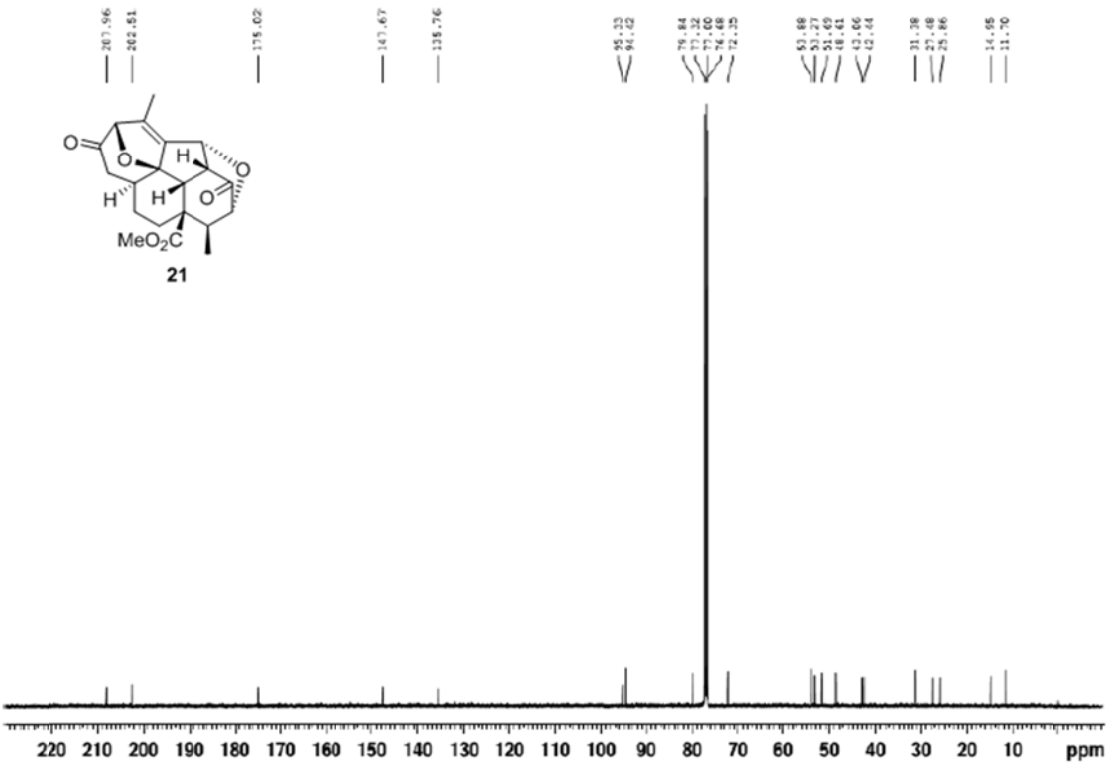

OH
O
H
H
OH
H
Cl
MeO2C
19
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5 −1.0 −1.5 ppm

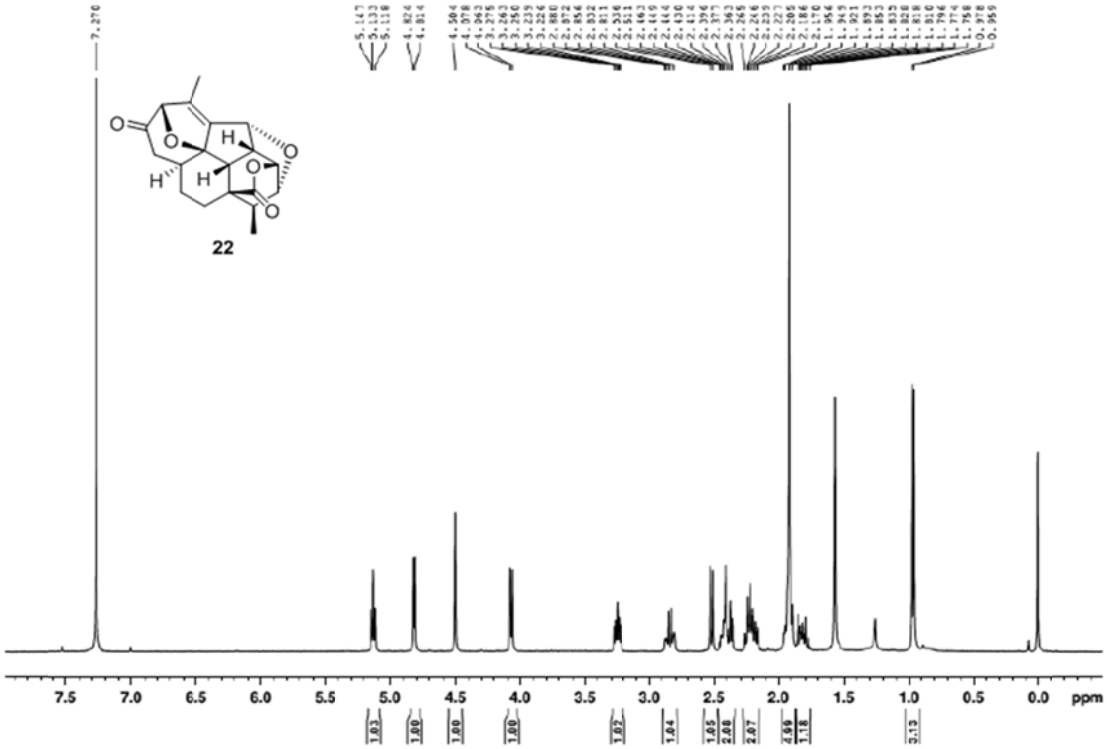

204.99
175.79
147.32
130.23
99.06
94.13
77.32
77.00
76.68
70.36
67.77
66.63
52.58
50.71
49.30
41.56
43.33
39.89
39.38
29.71
28.29
11.39
10.66
OH
O
H
H
OH
H
Cl
MeO2C
19
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

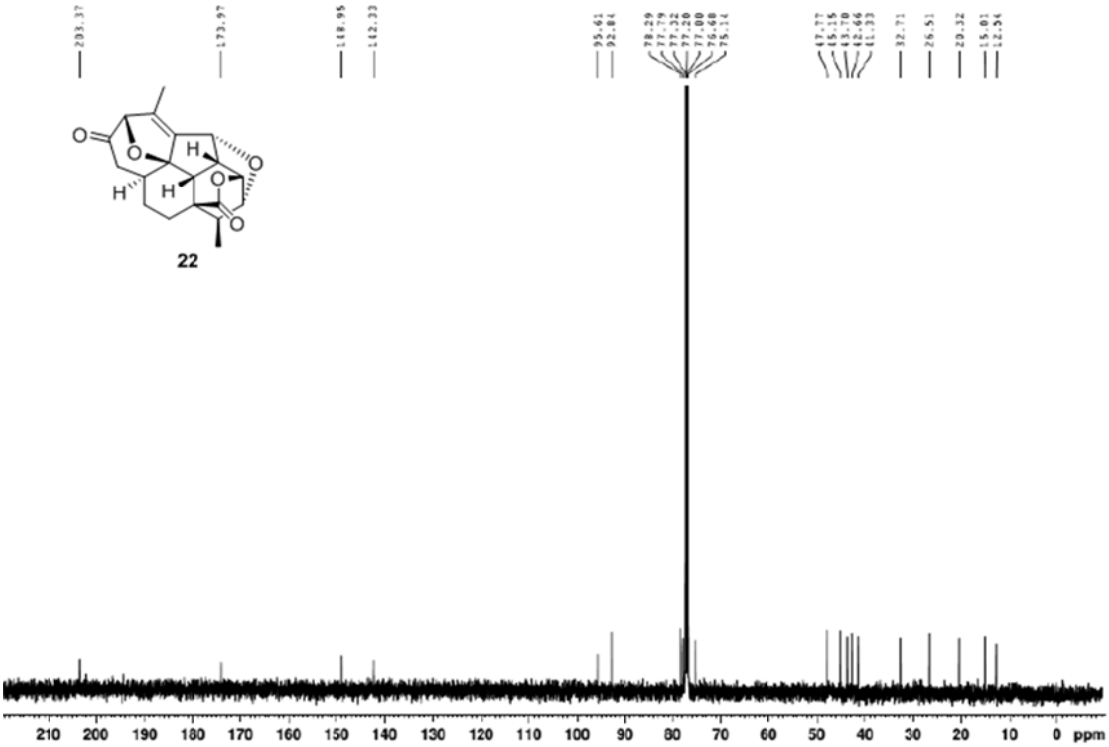

7.279
4.902
4.859
4.535
4.383
4.389
3.880
3.693
3.062
3.018
3.005
2.991
2.945
2.927
2.902
2.889
2.593
2.584
2.566
2.536
2.517
2.503
2.516
2.284
2.283
2.245
2.225
2.211
2.202
2.154
2.155
2.101
2.085
2.077
2.055
2.041
2.023
1.919
1.889
1.865
1.843
1.825
1.839
1.839
1.789
1.765
1.734
1.739
1.727
1.731
1.593
1.067
1.018
O
O
H
O
H
H
HO
MeO2C
20
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
ppm
1.00
1.04
0.89
1.03
2.81
2.05
1.06
1.04
1.24
0.96
1.24
4.31
2.24
1.77
3.08

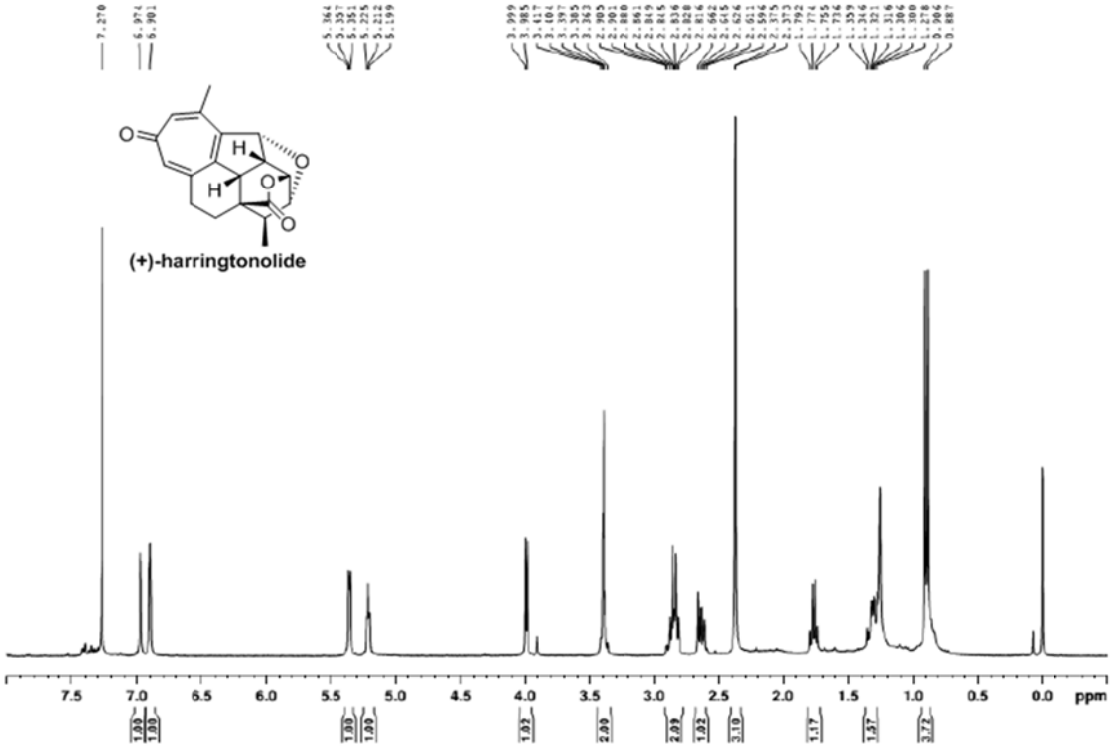

203.01
170.56
147.27
134.11
95.72
93.59
68.44
77.22
77.00
76.48
74.86
72.30
54.33
51.93
46.88
45.51
43.26
42.41
31.33
28.85
26.02
14.31
11.51
O
O
H
O
H
H
HO
MeO2C
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

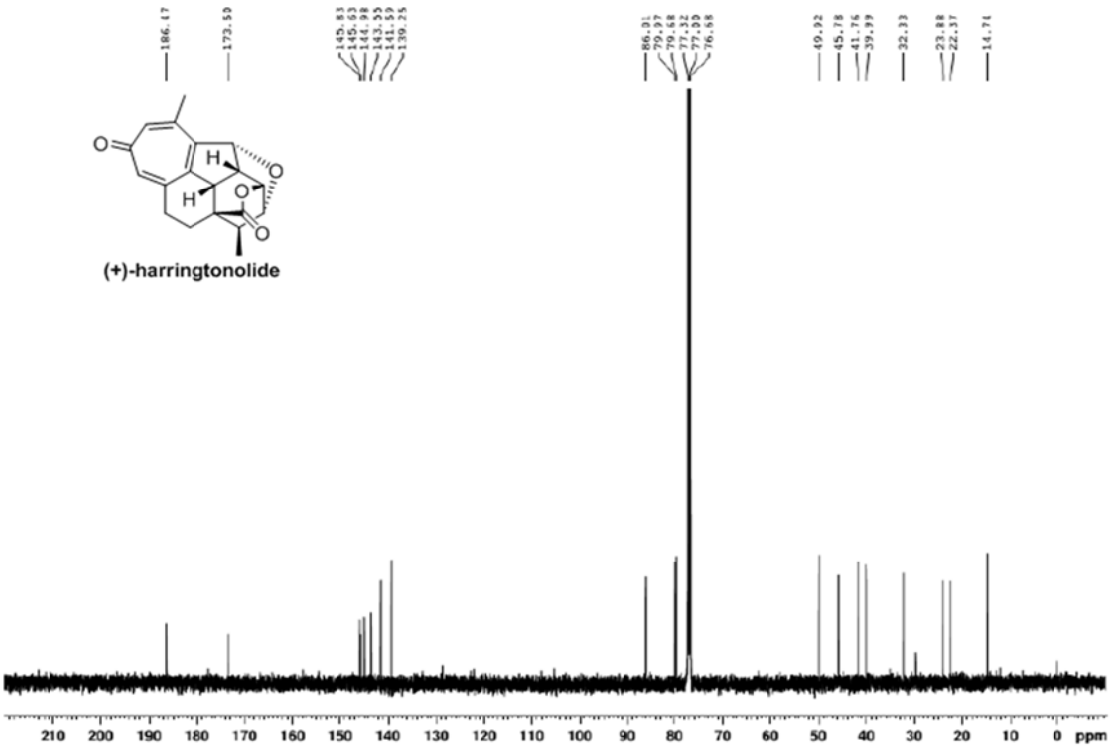

7.270
4.771
4.765
4.577
3.648
3.597
3.219
3.195
3.060
3.054
3.037
3.031
2.998
2.977
2.951
2.930
2.809
2.800
2.779
2.770
2.762
2.758
2.748
2.741
2.732
2.602
2.584
2.565
2.516
2.302
2.293
2.258
2.247
2.148
2.135
2.124
2.117
2.105
2.092
2.073
2.052
2.030
1.988
1.974
1.966
1.953
1.944
1.923
1.911
1.886
1.865
1.850
1.841
1.834
1.828
1.820
0.991
0.972
O
O
H
O
H
H
O
MeO2C
21
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
ppm
1.00
0.98
3.12
1.06
1.03
1.04
1.09
1.09
1.06
1.12
1.12
2.42
4.03
3.09

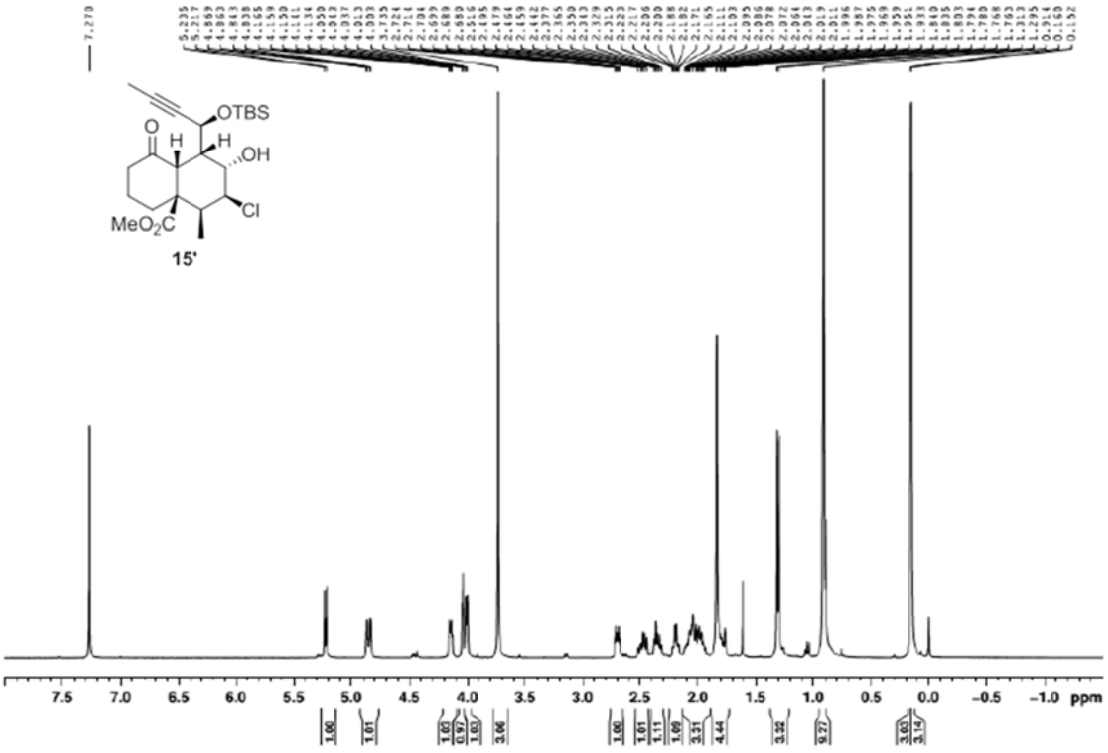

207.96
202.51
175.02
147.67
135.76
95.33
94.42
79.84
77.32
77.00
76.68
72.35
53.88
53.27
51.69
48.61
43.66
42.44
31.38
27.48
25.86
14.95
11.70
O
O
H
O
H
H
O
MeO2C
21
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

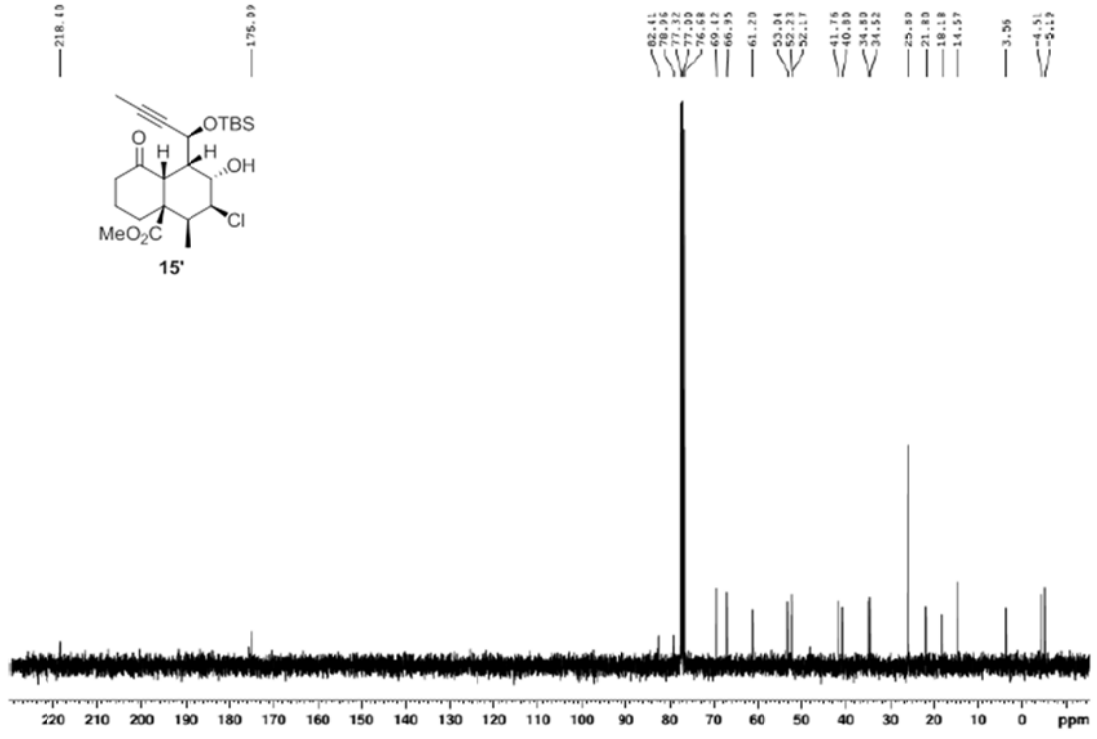

22
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

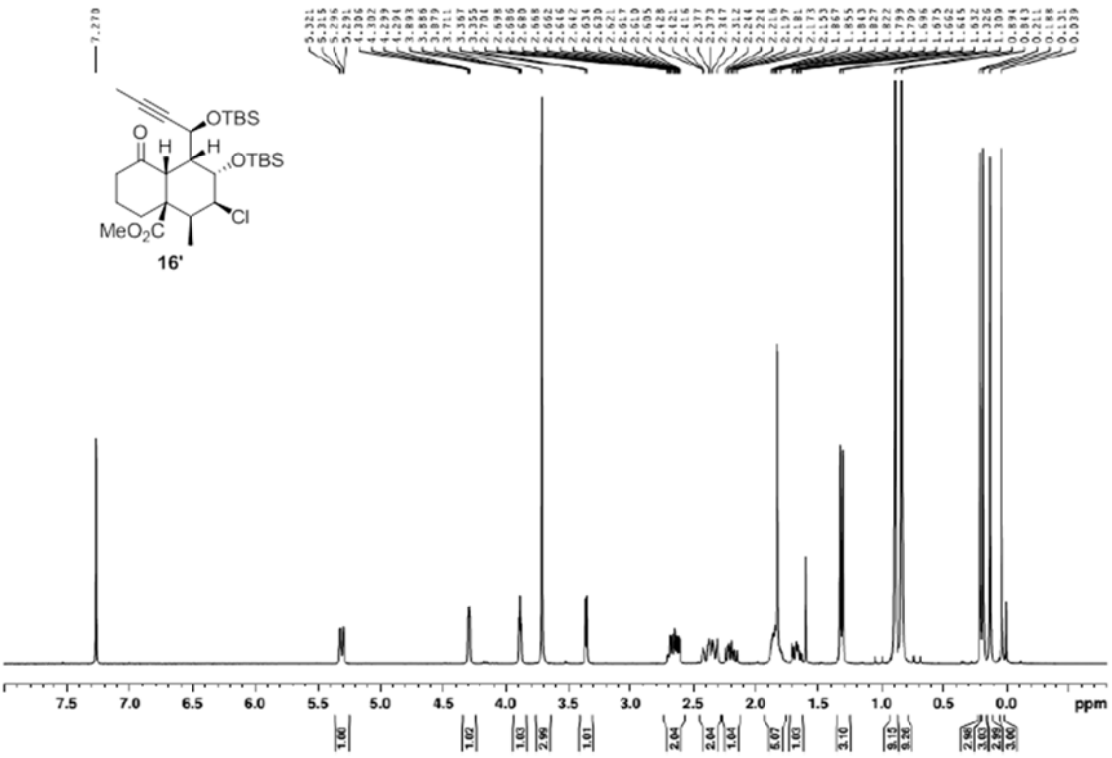

22
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

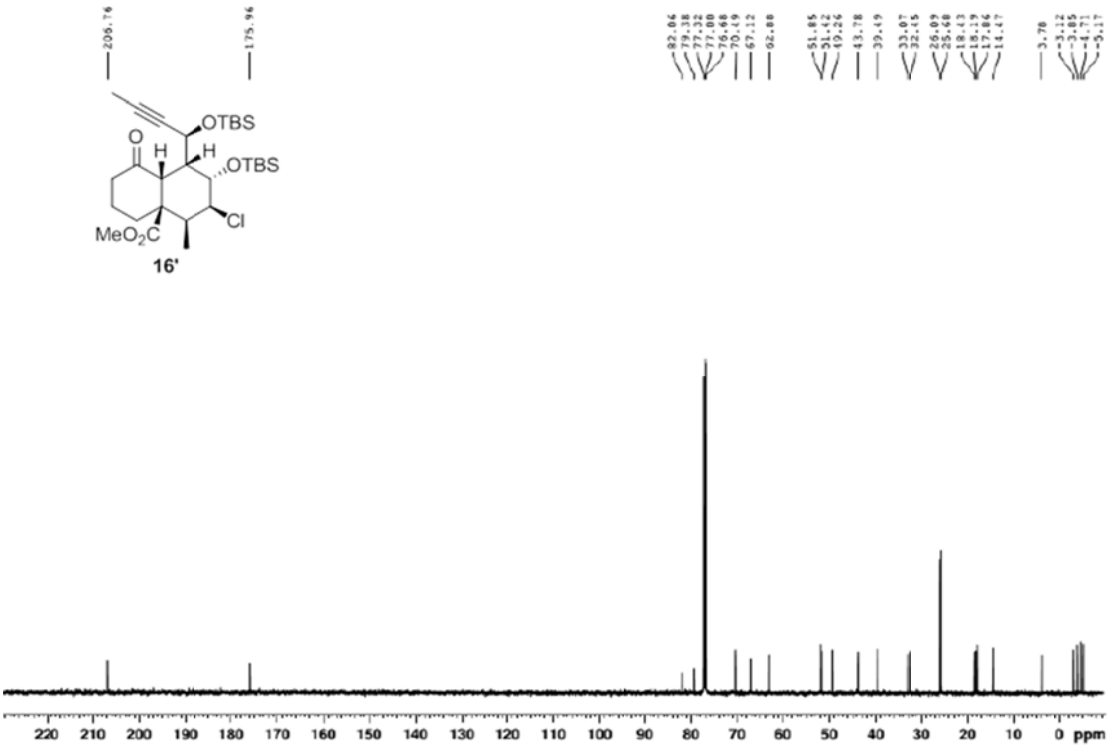

(+)-harringtonolide
ppm

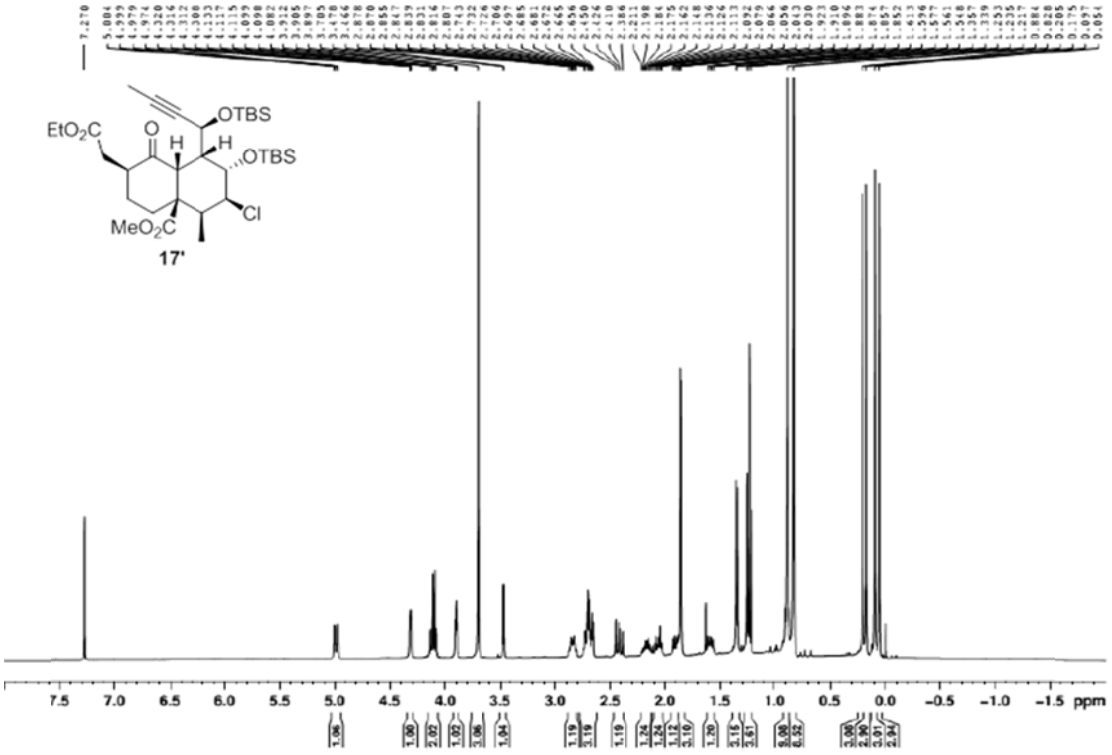

(+)-harringtonolide
ppm

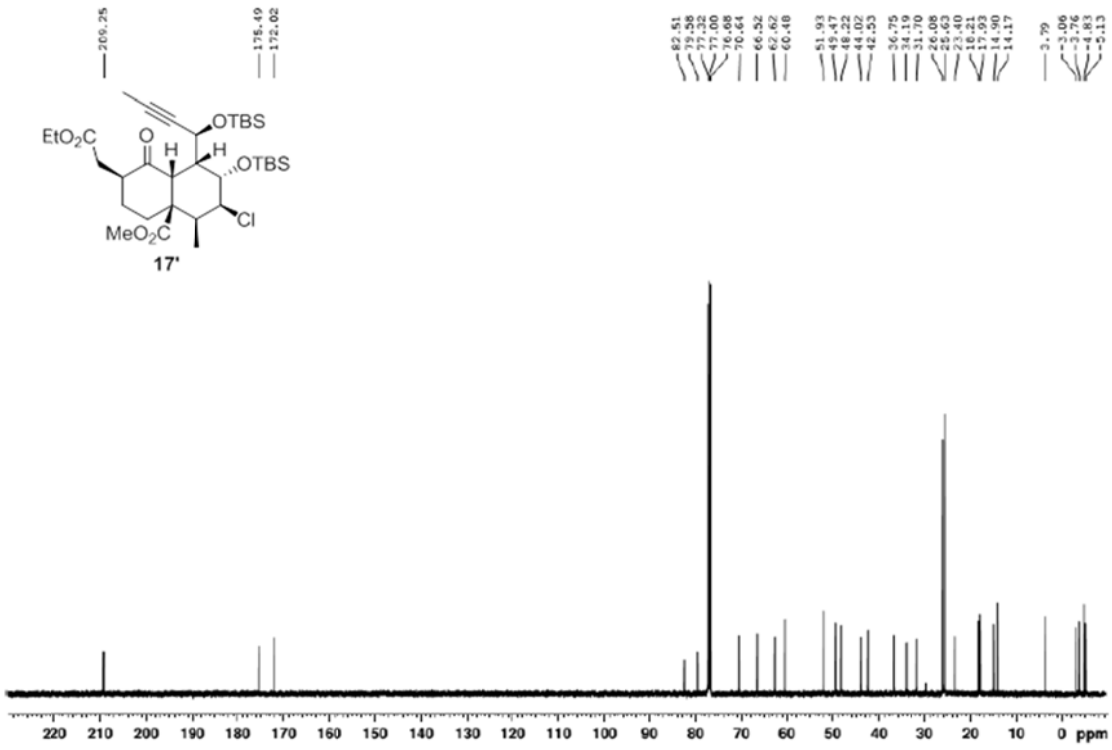

OTBS
H
H
OH
Cl
MeO2C
O
15'
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
−0.5
−1.0
ppm

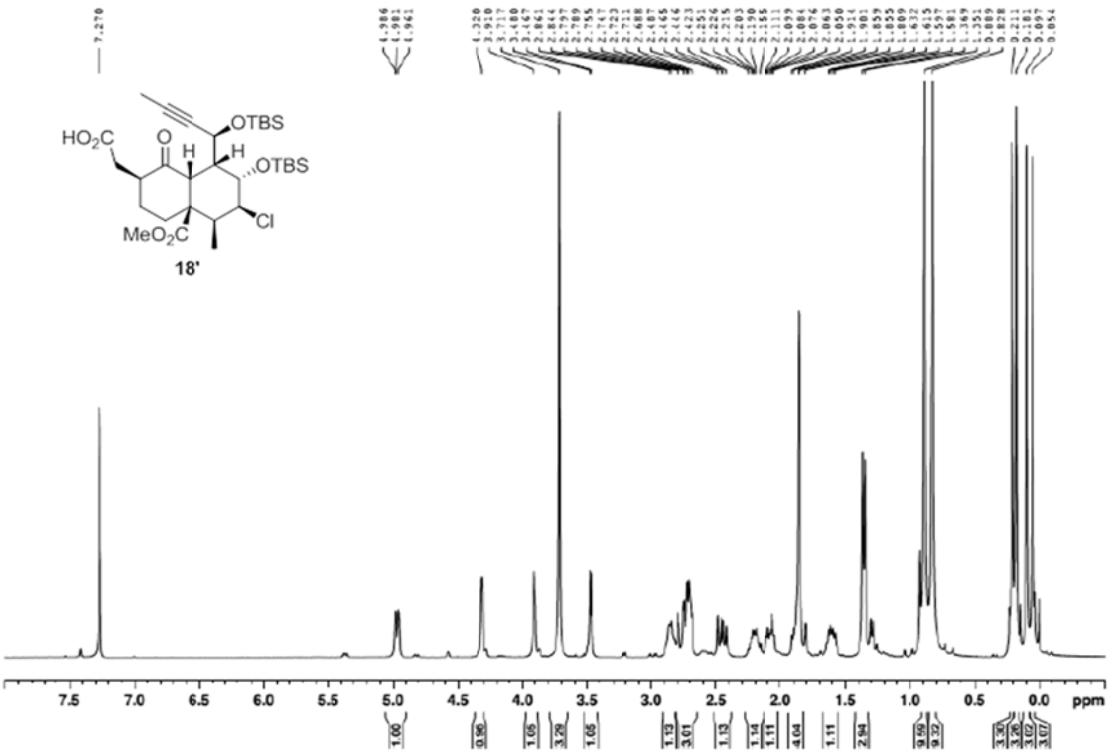

OTBS
H
H
OH
Cl
MeO2C
O
15'
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

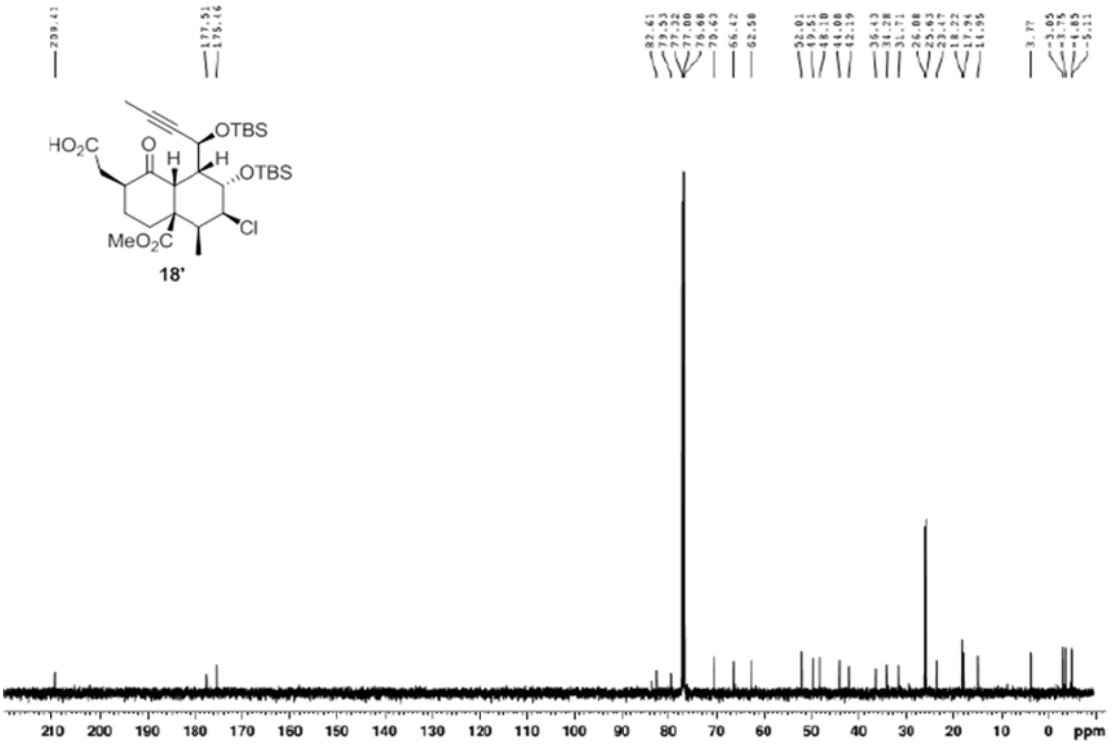

OTBS
OTBS
Cl
MeO2C
16'
ppm

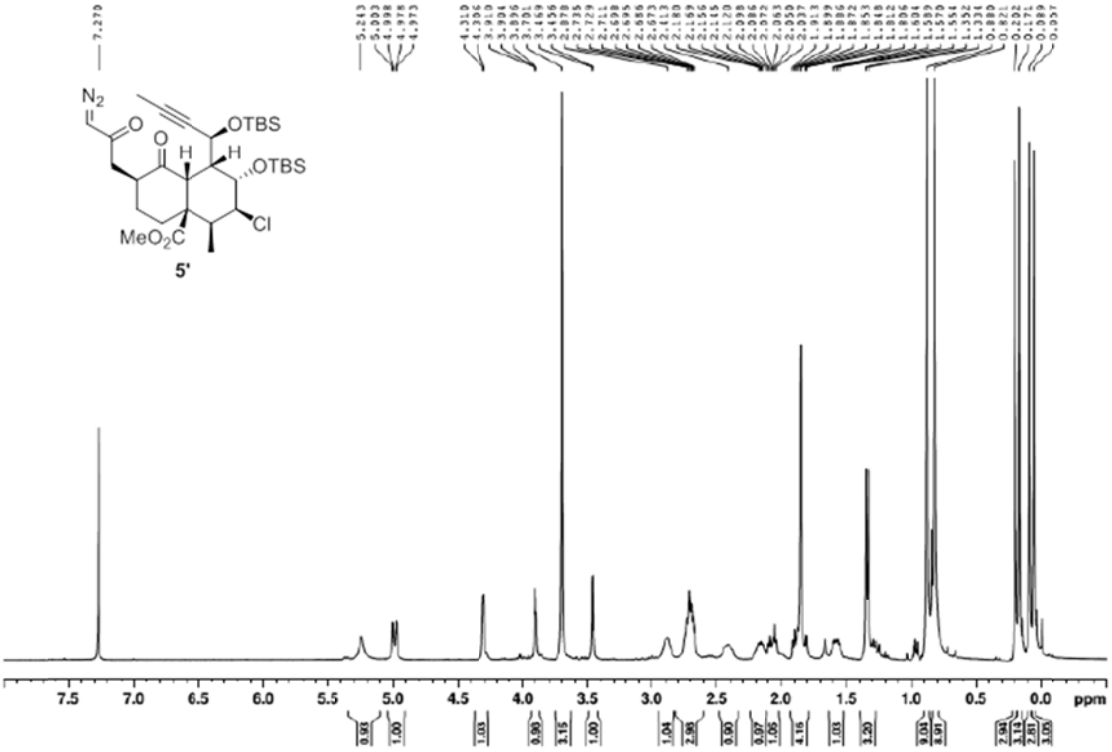

OTBS
OTBS
Cl
MeO2C
16'
ppm

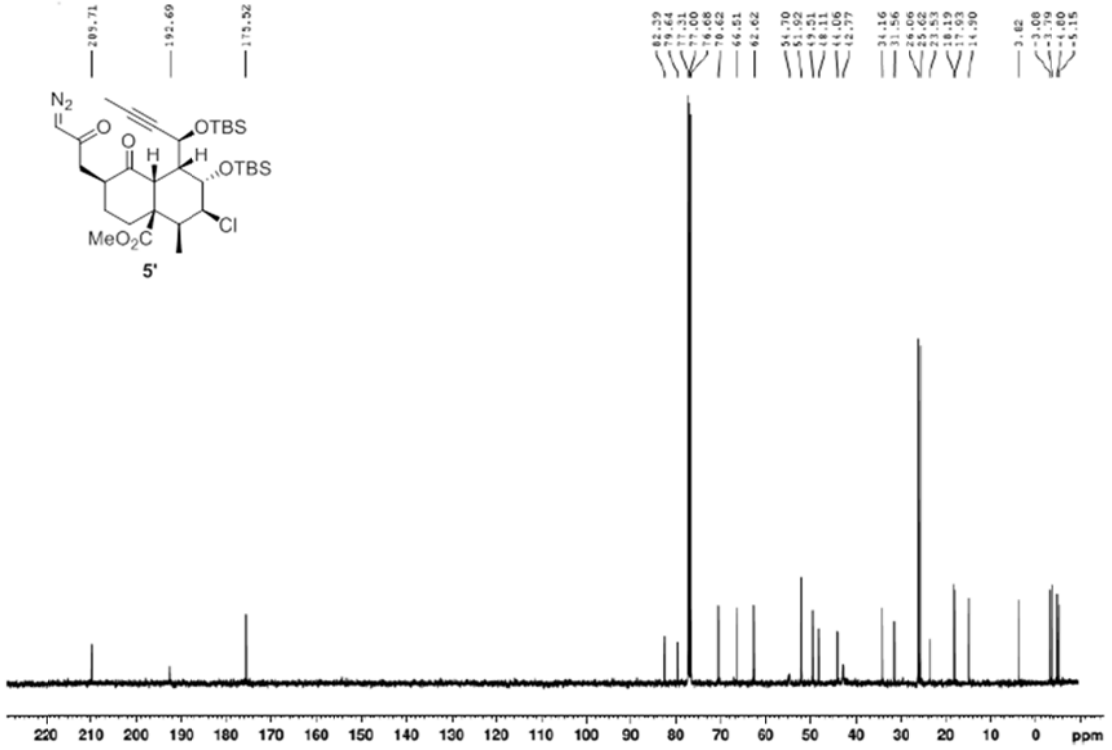

EtO2C
O
H
H
OTBS
OTBS
Cl
MeO2C
17'
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
−0.5
−1.0
−1.5 ppm

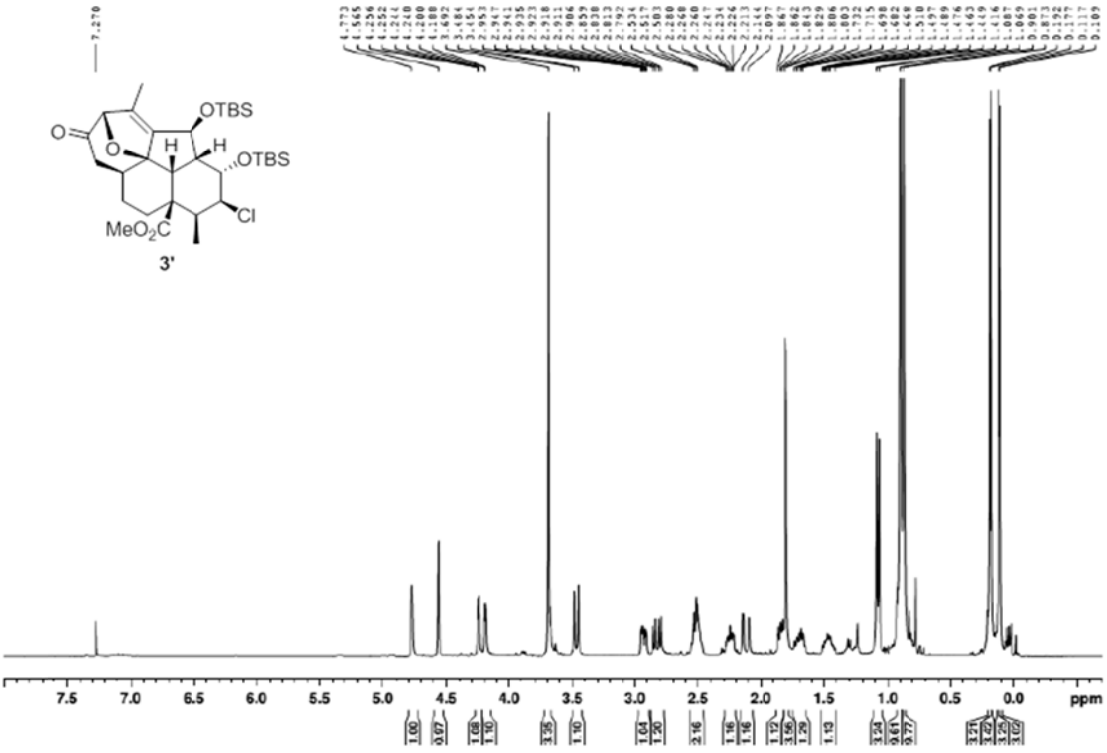

209.25
176.49
172.02
EtO2C
O
H
H
OTBS
OTBS
Cl
MeO2C
17'
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm

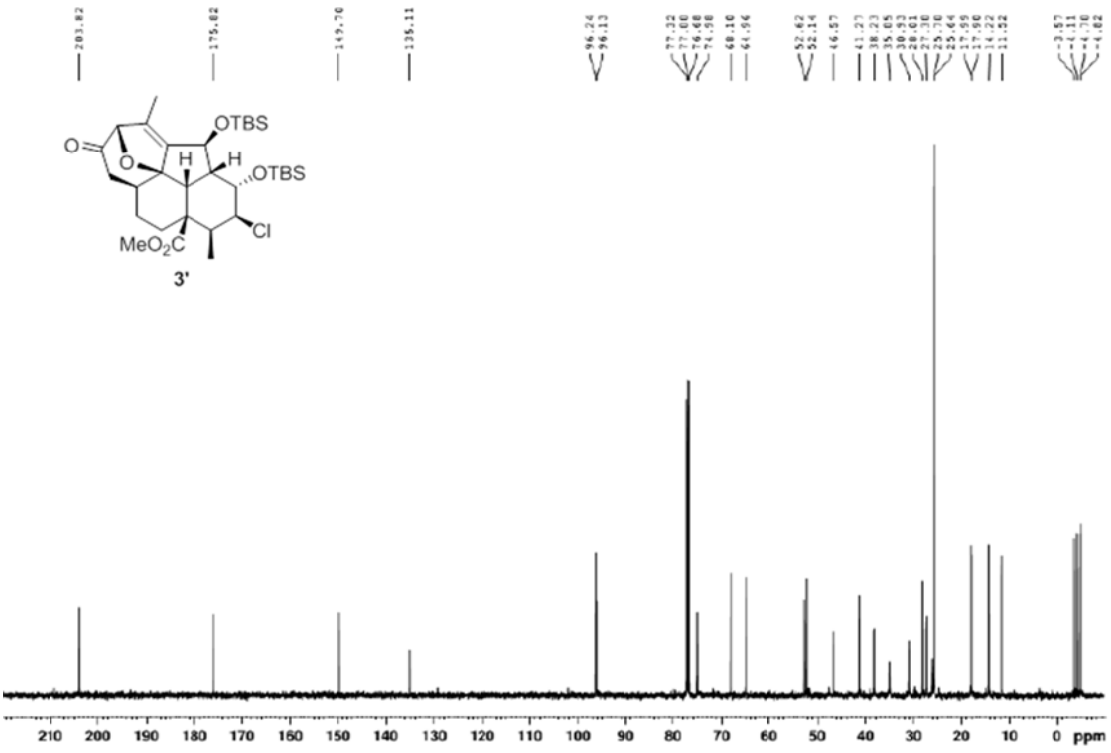

HO2C
O
H
H
OTBS
OTBS
Cl
MeO2C
18'
ppm

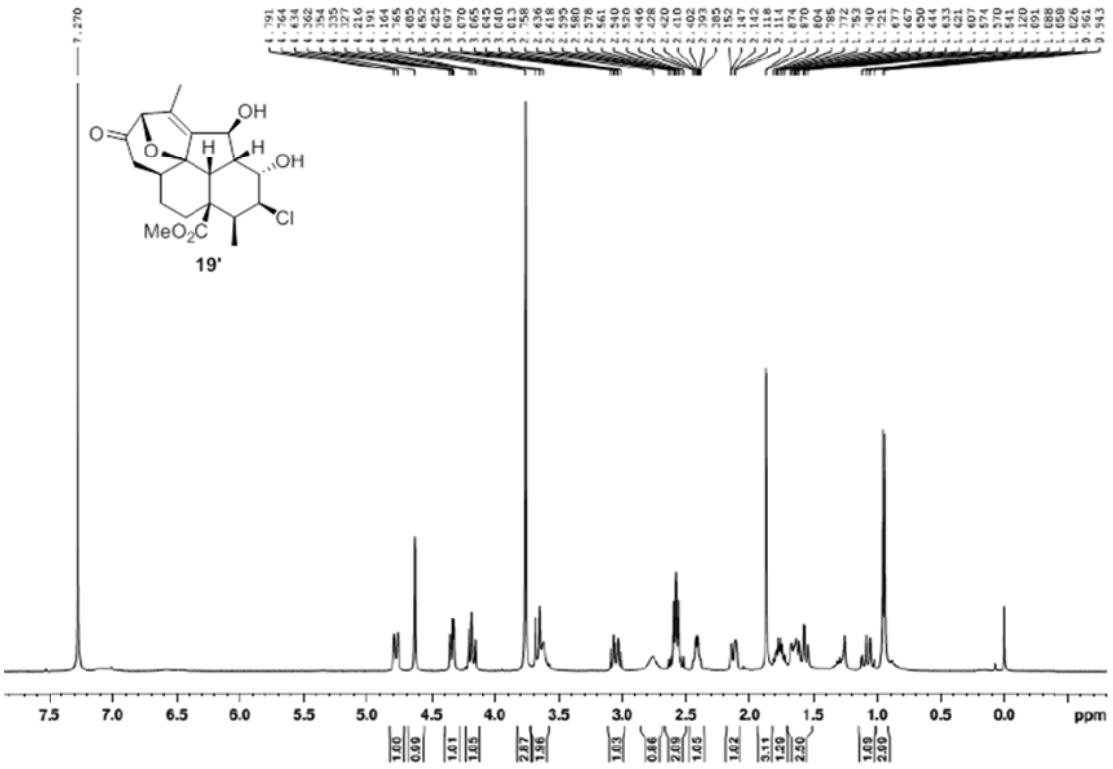

HO2C
O
H
H
OTBS
OTBS
Cl
MeO2C
18'
ppm

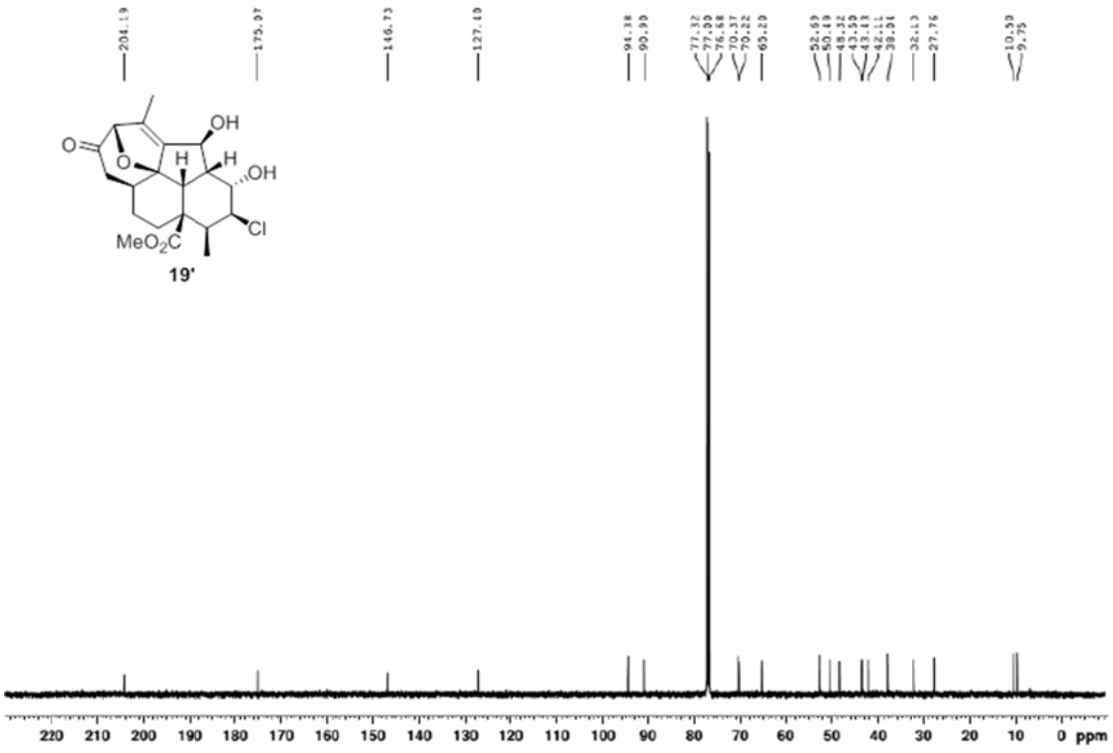

N2
O
OTBS
O
H
H
OTBS
Cl
MeO2C
5'
ppm

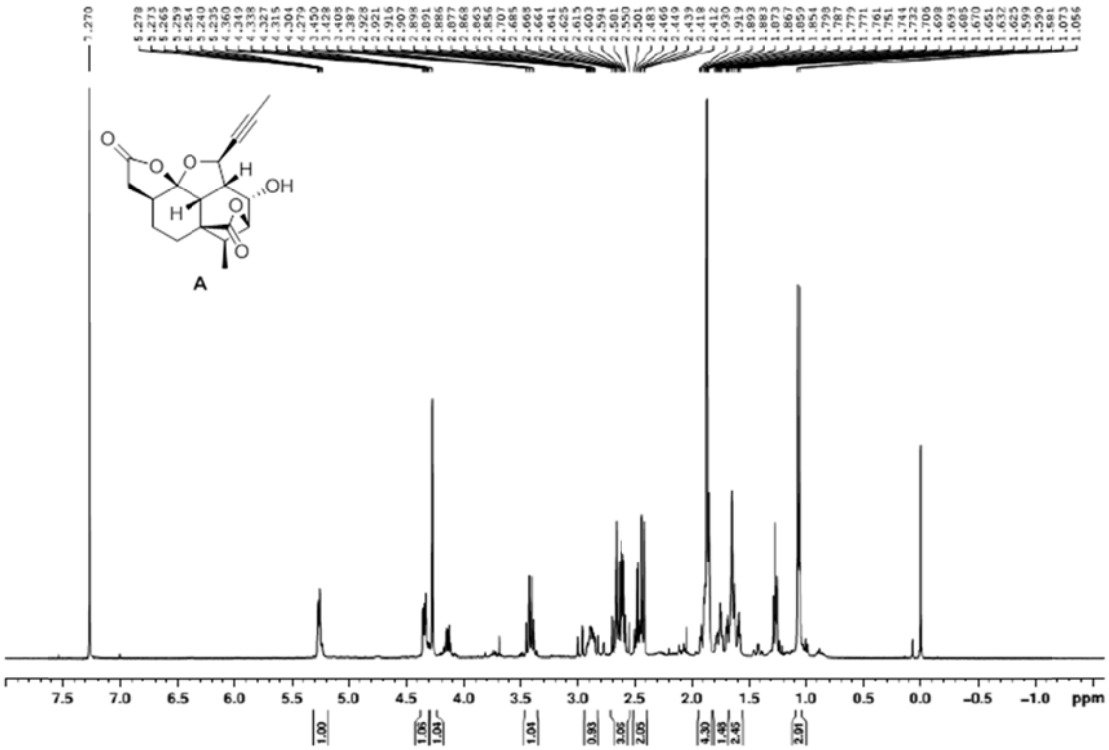

N2
O
OTBS
O
H
H
OTBS
Cl
MeO2C
5'
ppm

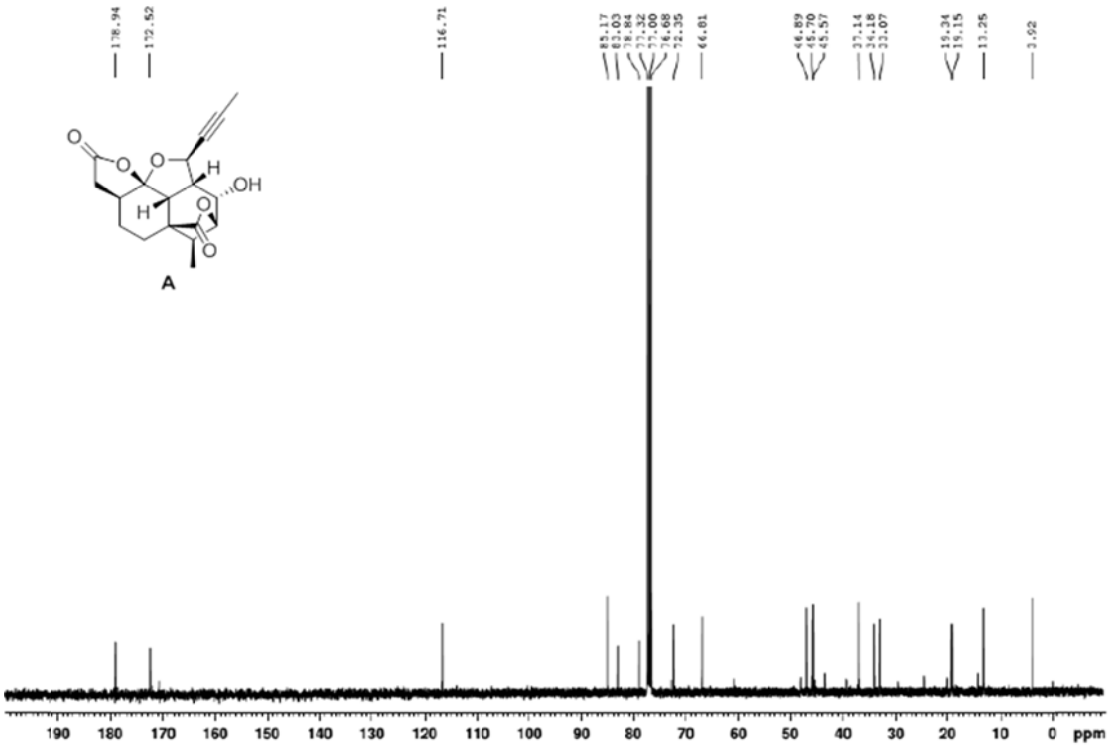

OTBS
OTBS
Cl
MeO2C
3'
ppm

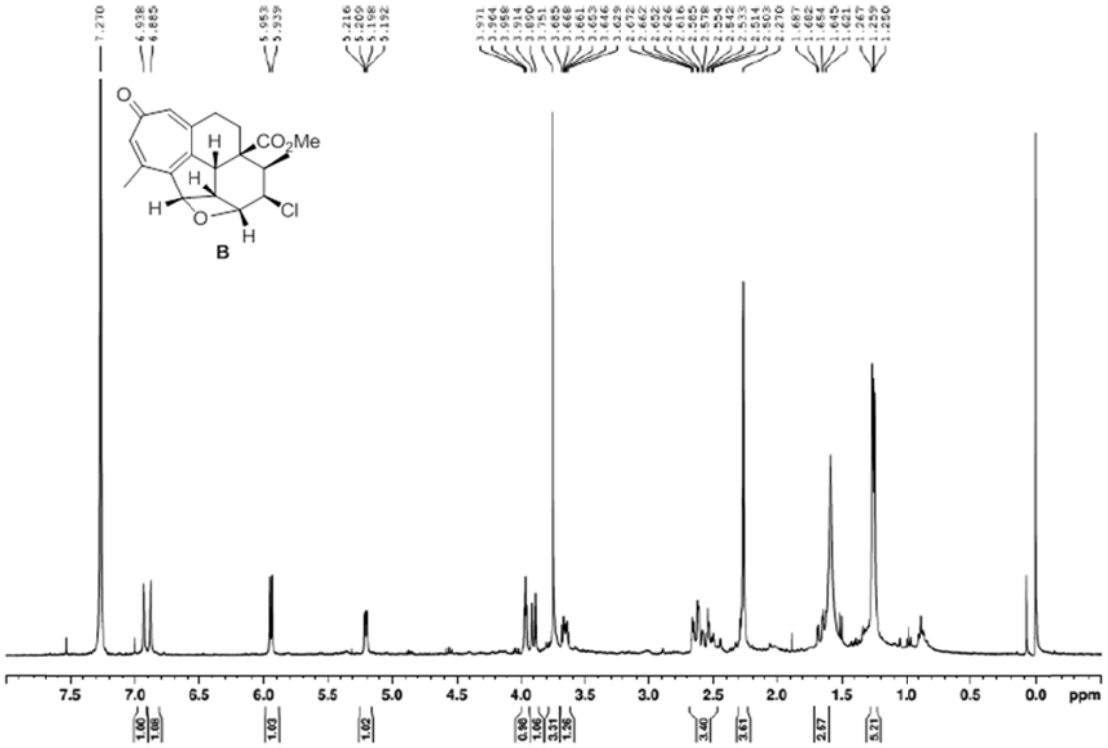

OTBS
OTBS
Cl
MeO2C
3'
ppm

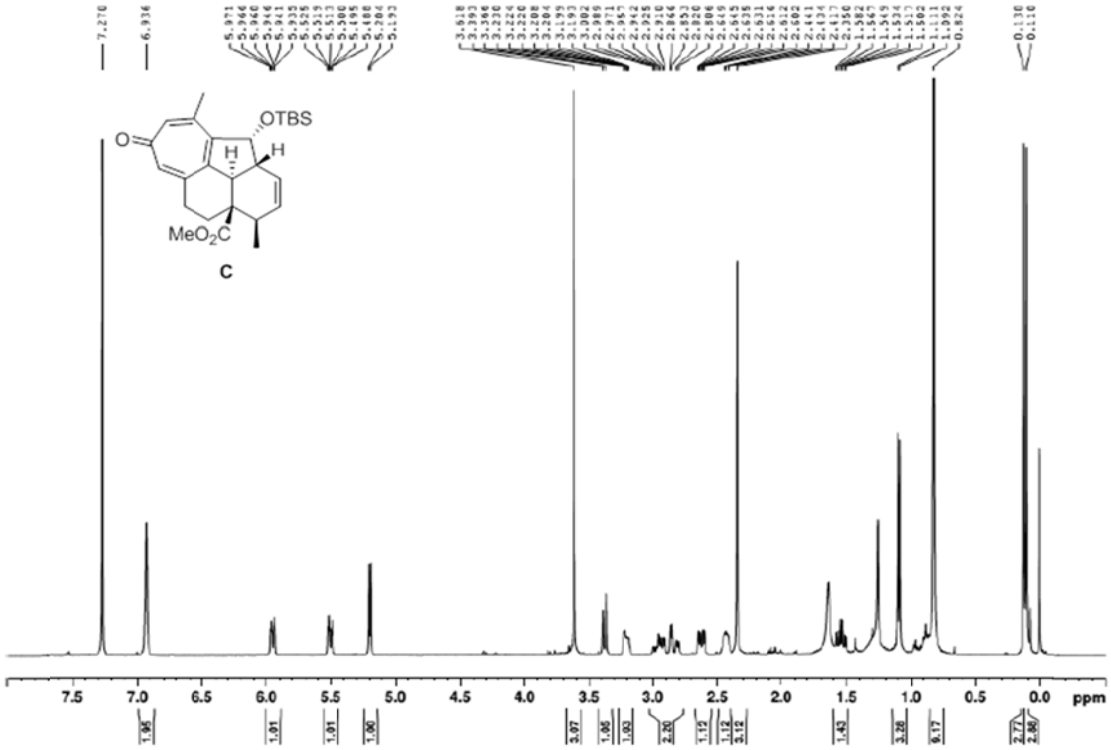

OH
O
H
H
OH
Cl
MeO2C
19'
ppm

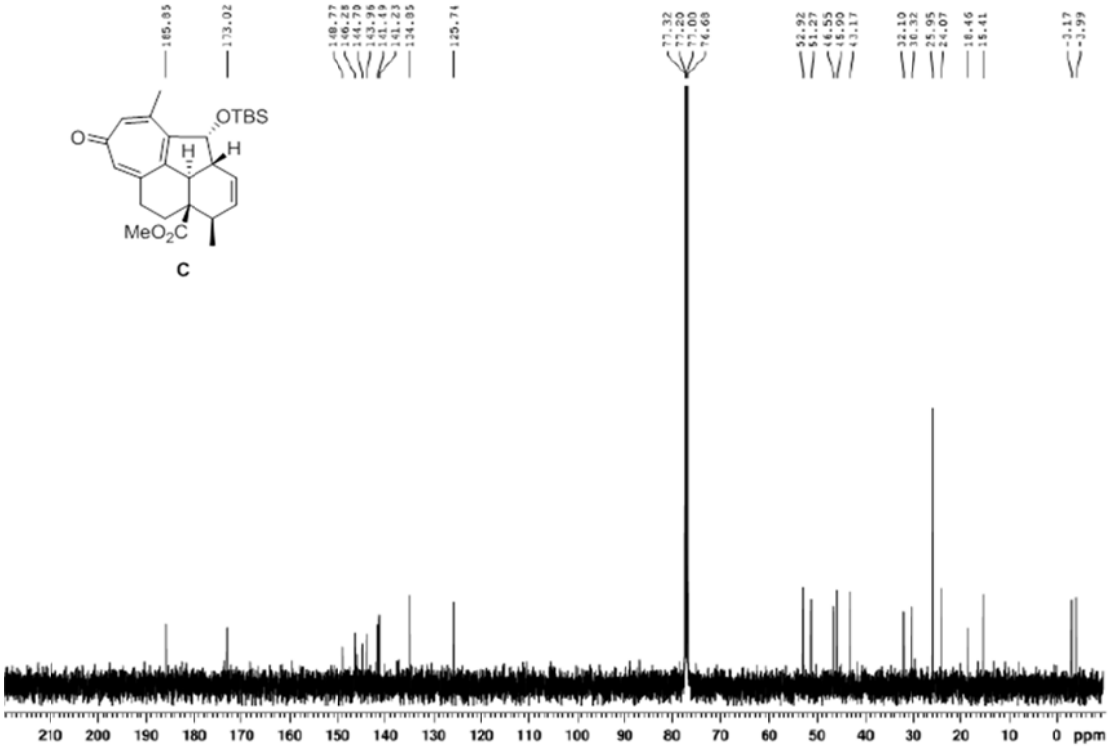

OH
O
H
H
OH
Cl
MeO2C
19'
ppm

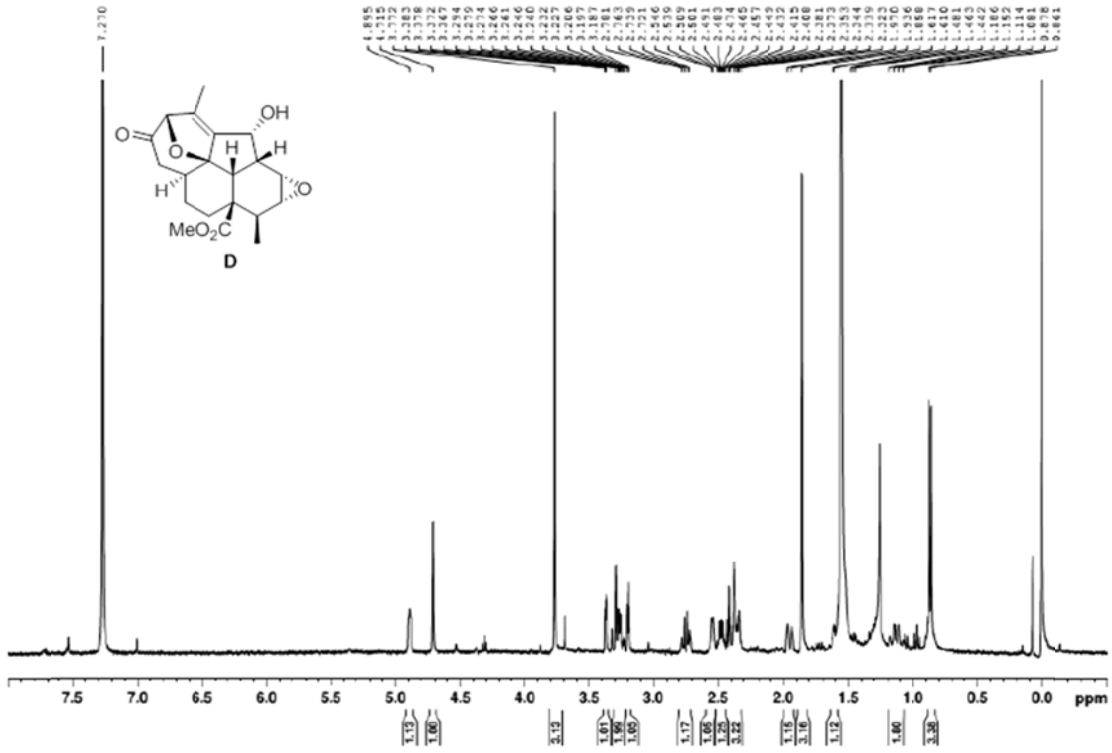

A
ppm

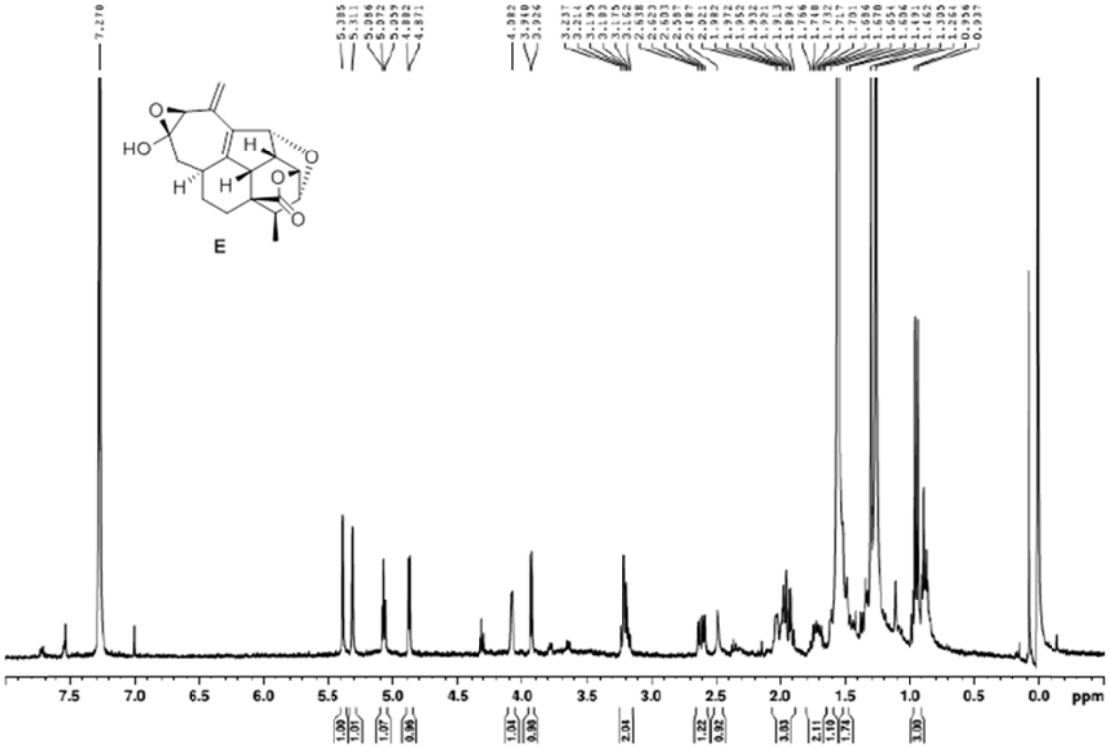

A
ppm

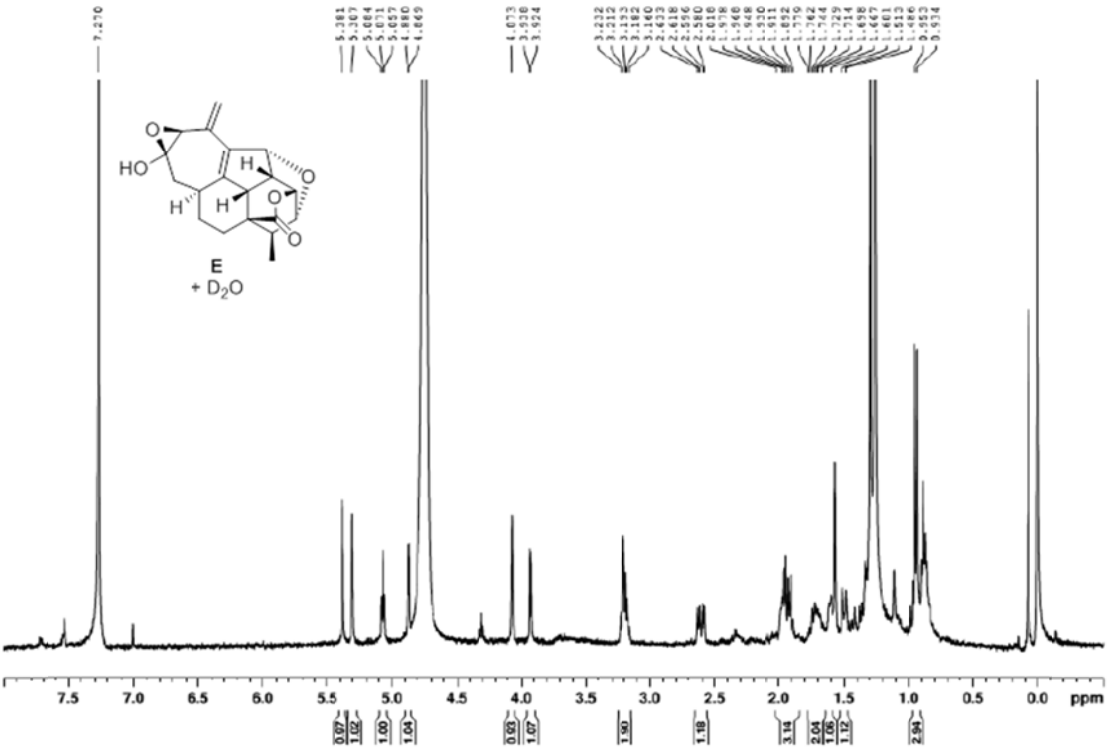

O
H
CO2Me
H
H
O
Cl
H
B
7.270
6.938
6.885
5.953
5.939
5.216
5.209
5.198
5.192
3.971
3.964
3.958
3.954
3.950
3.751
3.685
3.668
3.661
3.653
3.646
3.629
2.672
2.662
2.652
2.626
2.616
2.585
2.578
2.554
2.542
2.533
2.514
2.503
2.270
1.687
1.682
1.654
1.645
1.621
1.267
1.259
1.250
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.00
1.08
1.03
1.02
0.90
1.06
3.31
1.26
3.40
3.61
2.67
5.21

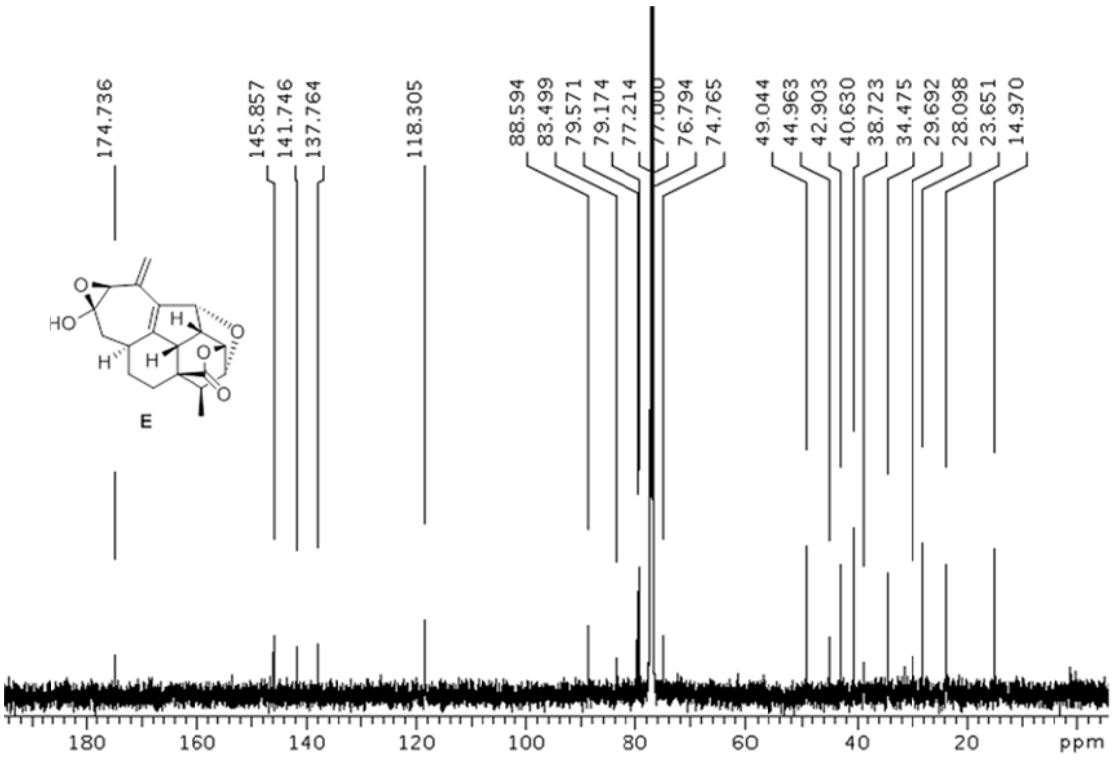

O
OTBS
H
H
MeO2C
C
7.270
6.936
5.971
5.966
5.946
5.941
5.935
5.525
5.513
5.500
5.196
5.188
5.184
5.193
3.618
3.393
3.386
3.230
3.224
3.220
3.206
3.199
3.193
3.002
2.989
2.971
2.957
2.942
2.926
2.916
2.846
2.853
2.820
2.806
2.649
2.635
2.631
2.616
2.612
2.602
2.441
2.434
2.417
2.356
1.582
1.547
1.534
1.517
1.502
1.111
1.092
0.824
0.130
0.110
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
ppm
1.95
1.01
1.01
1.00
3.07
1.06
1.03
2.20
1.19
1.12
3.12
1.43
3.28
9.17
2.77
2.80

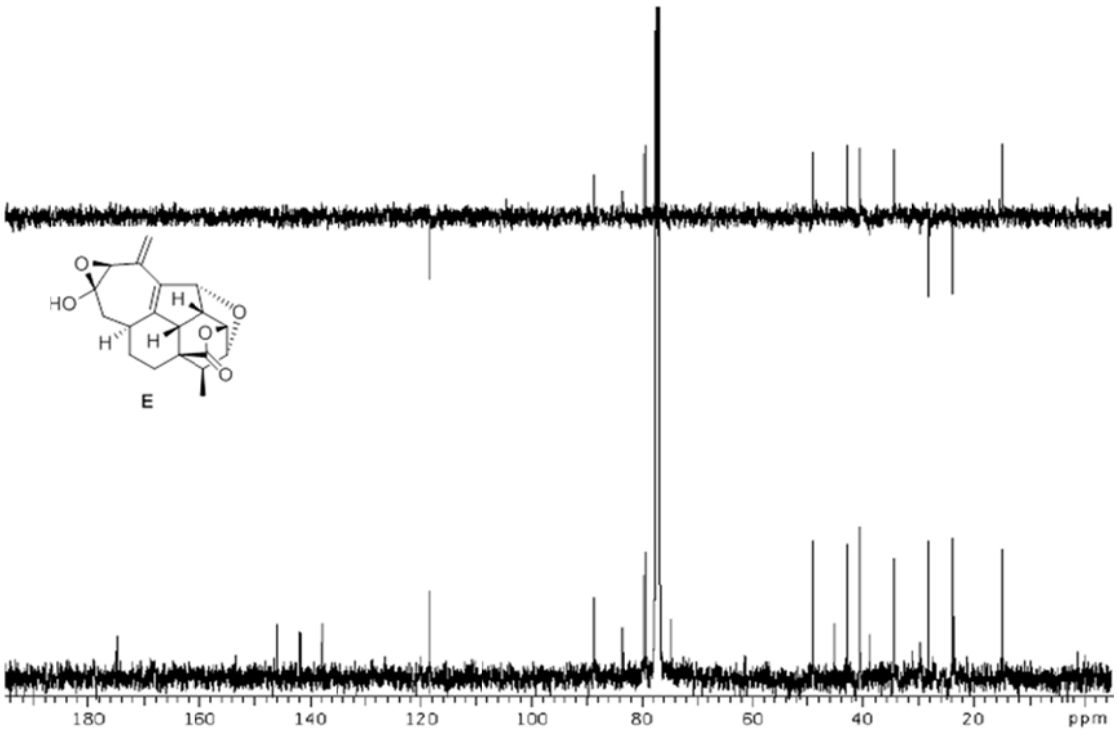

OTBS
O
H
H
MeO2C
C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


OH
O
O
H
H
H
O
MeO2C
D
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 ppm


E


E
+ D2O


174.736
145.857
141.746
137.764
118.305
88.594
83.499
79.571
79.174
77.214
77.000
76.794
74.765
49.044
44.963
42.903
40.630
38.723
34.475
29.692
28.098
23.651
14.970
HO
H
H
O
O
O
E
180
160
140
120
100
80
60
40
20
ppm


HO
H
H
O
O
O
E
180
160
140
120
100
80
60
40
20
ppm