Collaborative Total Synthesis: Routes to (±)-Hippolachnin A Enabled by Quadricyclane Cycloaddition and Late-Stage C-H Oxidation

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General Information

Owing to the collaborative nature of this project, with experiments taking place in two separate locations, some reagents and instrumentation will differ. Those applying to experiments carried out by Rasik and Brown will be annotated with a "†", while those carried out by McCallum and Wood will be annotated with a "‡".

Unless otherwise noted, all reactions have been carried out with distilled and degassed solvents under an atmosphere of dry N_2 in oven- (135 ºC) or flame-dried glassware with standard vacuum-line techniques. Triethylamine, diisopropylamine, and methanol were dried over calcium hydride and freshly distilled. Dichloromethane and tetrahydrofuran were purified under a positive pressure of dry argon by passage through two columns of activated alumina. Toluene was purified under a positive pressure of dry argon by passage through columns of activated alumina and Q5 (Grubbs apparatus). All work-up and purification procedures were carried out with reagent grade solvents (purchased from Sigma-Aldrich, Fisher, or VWR) in air. Standard column chromatography techniques using ZEOprep 60/40-63 μm or Silicycle SiliaFlash P60 (230-400 mesh) silica gel were used for purification. All melting points were obtained on a Gallenkamp capillary melting point apparatus (model: MPD350.BM2.1) or Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were obtained using a Bruker Alpha ATR-IR or Avatar 360-FT IR E.S.P. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400, Varian 400, Varian 500, Varian 600 or Bruker 600. Chemical shifts (δ) are reported in parts per million (ppm) relative to internal residual solvent peaks from indicated deuterated solvents. Coupling constants (*J*) are reported in Hertz (Hz) and are rounded to the nearest 0.1 Hz. Multiplicities are defined as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, br = broad, app = apparent, par = partial. High Resolution Mass (HRMS) analysis was obtained using Electron Impact Ionization (EI) or Chemical Ionization (CI) and reported as m/z (relative intensity) for the $[M]^+$ or $[M+H]^+$ molecular ion. HRMS data using electro-spray ionization (ESI) were obtained on a ThermoScientific LTQ Orbitrap. GC-MS data was acquired using an Agilent 6890N Gas Chromatograph and 5973 Inert Mass Selective Detector. Microwave reactions were carried out using a Biotage Initiator 60 EXP Microwave system or with CEM Discover SP Microwave system.

Reagents

1,2-Bis(phenylsulfinyl)ethane palladium(II) acetate [abbreviated White's Catalyst] was purchased from Sigma-Aldrich[‡] or Strem[†] and was used as received

Acetic anhydride was purchased from Macron and was distilled over K_2CO_3 immediately before use.

Acetonitrile was purchased from Avantor and was used as received.

(2*S*,2′*S*-(−)-[*N*,*N*′-Bis(2-pyridylmethyl)]-2,2′-bipyrrolidinebis(acetonitrile)iron(II) hexafluoroantimonate (abbreviated (*S*,*S*)-Fe(PDP)) was purchased from Sigma-Aldrich and was used as received.

Boron trifluoride diethyl etherate was purchased from Alfa Aesar and was used as received.

Chloromethylsilane was purchased from Oakwood and used as received.

Copper(II) acetate was purchased from Sigma-Aldrich and was used as received.

(*R*,*R*)-(−)-*N*,*N*′-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediamine [abbreviated Cr(Salen)Cl] was purchased from Sigma-Aldrich and was used as received.

(Diacetoxyiodo)benzene was purchased from Sigma-Aldrich and was used as received.

Diethylfumarate was purchased from Eastman Organic and was distilled before use.

Diisobutylaluminum hydride was purchased from Acros[†] or Sigma-Aldrich[‡] and was used as received.

Diisopropylamine was purchased from Sigma-Aldrich and was distilled over CaH_2.

Dimethylformamide was purchased from Sigma-Aldrich and was stored over molecular sieves.

Dimethyldioxirane (DMDO) was prepared according to the literature [1]

Dioxane was purchased from Sigma-Aldrich and used as received.

2-Ethylpent-2-enoic acid was prepared according to the literature[2]

Ethylene (99.9% purity) was purchased from Praxair and used as received.

Grubbs 1st generation catalyst was purchased from Sigma-Aldrich, was stored and weighed out in a N_2 glovebox,[†] or stored in a desiccator and weighed out under air.[‡]

Hydrogen peroxide (50% aqueous solution) was purchased from Sigma-Aldrich, stored at 0 °C, and used as received.

Iodine was purchased from Macron and was used as received.

Lithium aluminum hydride was purchased from TCI and was used as received.

Lithium bis(trimethylsilyl)amide was purchased from Sigma-Aldirch and was used as received.

Methyl acetate was purchased from Sigma-Aldrich and was used as received.

Methyltriphenylphosphonium bromide was purchased from Sigma-Aldrich, washed with benzene and dried under vacuum over P_2O_5 before use.

Oxalyl Chloride was purchased from Alfa Aesar and was used as received.

Palladium on carbon (5 or 10% $^{w}/_{w}$) was purchased from Sigma-Aldrich[‡] or Strem[†] and used as received.

***p*-benzoquinone** was purchased from Acros and was recrystallized from EtOH[†], or from Sigma-Aldrich[‡] and used as received.

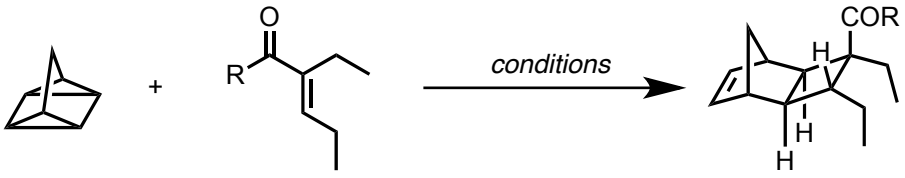
Potassium carbonate was purchased from BDH and was used as received.

Potassium bis(trimethylsilyl)amide was purchased from Sigma-Aldrich and was used as received.
Pyridine was purchased from Macron and was stored over 3Å MS.
Quadricyclane was purchased from Exciton (Dayton, OH)[†], was used as received, or was prepared following the literature procedure[‡3] and was stored at 0 °C under nitrogen. The reagent was stable for months under these conditions according to ^{1}H NMR.
Sodium hydroxide was purchased from Macron and was used as received.
Titanium (IV) chloride was purchased from Sigma-Aldrich as a 1M solution in CH_2Cl_2 and used as received.
Thionyl chloride was purchased from Sigma-Aldrich and used as received.
***tert*-butyl acetate** was purchased from Alfa Aesar and used as received.
***tert*-butyl lithium** was purchased from Sigma-Aldrich and used as received.

Experimental Details

a. Brown Route

■ **Quadricyclane-Alkene Cycloaddition Optimization**

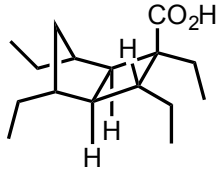


9 **SI-1** **14a,b**

Conventional Heating Reactions: To a 10 mL screw capped test tube was added electron deficient olefin and quadricyclane under N_2. The vial was sealed and heated to the appropriate conditions in an oil bath. Yield and d.r. were determined by analysis of the crude ^{1}H NMR according to internal standard (1,3,5-trimethoxybenzene).

Microwave Reactions: To an oven-dried 0.2-0.5 mL microwave vial (Biotage Code No.: 355458) was added acid chloride and quadricyclane under N_2. The vial was fitted with a cap and septum (Biotage Code No.: 352298), clamped shut and heated to the appropriate conditions in a microwave oven (conditions: 0.2-0.5 mL vial, normal absorption, pre-stirring 0.1 s, fixed hold time on). Yield and d.r. were determined by analysis of the crude ^{1}H NMR according to internal standard (1,3,5-trimethoxybenzene).

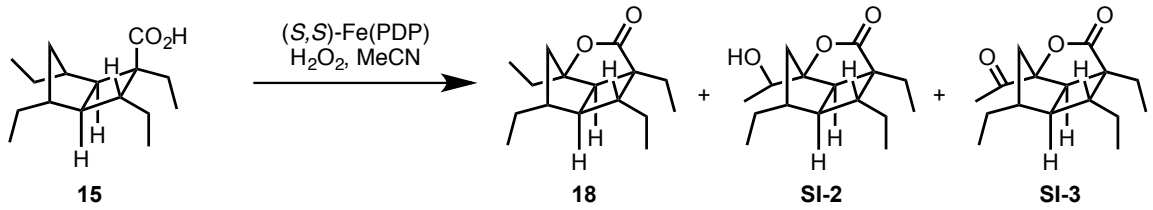
■ **Carboxylic Acid Directed C-H Oxidation**



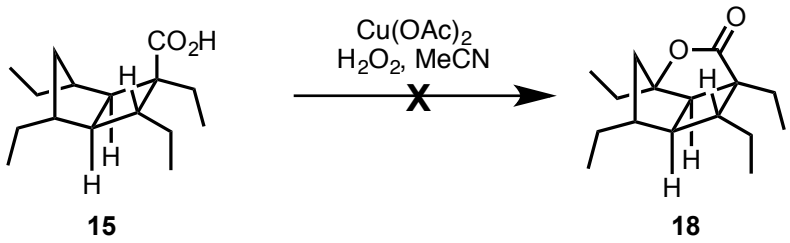
15

Carboxylic acid 15: To a 50 mL oven-dried reducing flask equipped with a stir bar was added acid **14b** (0.124 g, 0.563 mmol, 1 equiv) and ethyl acetate (12 mL). A balloon of ethylene (1 atm) was bubbled through the solution for 30 min. To an oven dried 4 mL black capped vial was added Grubbs 1st generation catalyst (4.6 mg, 0.0056 mmol, 1 mol%) via glovebox. Ethyl acetate (2 x 0.5 mL) was used to transfer the catalyst to the solution of acid and ethyl acetate. The solution immediately became light brown and stirred for 5 h with continued bubbling of ethylene. A second batch of Grubbs 1st generation catalyst (2.3 mg, 0.0028 mmol, 0.5 mol%, total 1.5 mol%) was added using ethyl acetate (2 x 0.5 mL). Stirring and bubbling continued for another 1 h. The ethylene balloon was removed and palladium (5% on activated carbon, eggshell, oxidic, 50% wetted powder, 0.120 mg, 0.056 mmol, 10 mol%) was added and a hydrogen balloon was added. The mixture stirred for 1 h with continued bubbling of hydrogen. After 1 h, the mixture was filtered through Celite and the filter cake was washed with ethyl acetate (3 x

40 mL). The solution was concentrated to yield acid **15** (0.138 g, 0.547 mmol, 97% yield) as a light brown liquid. The color was believed to result from trace Ruthenium impurities. Due to overlapping peaks integrations listed below may not be accurate. **IR (neat):** 3405, 2959, 2931, 2873, 2632, 1693, 1461, 1254, 1213, 1152, 940, 790; **^{1}H NMR (400 MHz, $CDCl_3$):** 2.35 (td, *J* = 9.1, 5.7 Hz, 1H), 2.17 (dt, *J* = 12.7, 6.6 Hz, 1H), 1.96 (t, *J* = 8.0 Hz, 1H), 1.83 (m 3H), 1.77 - 1.54 (m, 4H), 1.46 - 1.23 (m, 3H), 1.16 (m, 2H), 0.95 - 0.79 (m, 12H). **^{13}C NMR (100 MHz, $CDCl_3$):** 182.5, 52.4, 50.1, 48.9, 48.7, 47.1, 45.1, 41.7, 29.2, 28.7, 27.5, 23.3, 13.4, 13.4, 12.2, 10.3. **HRMS (EI):** Calcd for $C_{16}H_{28}O_2$ (M^+): 252.2084, Found: 252.2088.



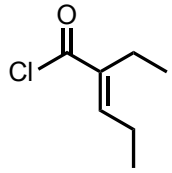
Lactone 18 and oxidation products SI-2 and SI-3: Procedure adapted from literature[4]: To a 6 mL borosilicate vial was added acid **15** (37.0 mg, 1.47 mmol, 1.0 equiv) and acetonitrile (3 mL). While vigorously stirring, two separate solutions of (*S,S*)-Fe(PDP) (137 mg, 0.147 mmol, 10 mol%) in acetonitrile (0.7 mL) and H_2O_2 (0.168 mL, 50% aq, 2.94 mmol, 2.0 equiv) in acetonitrile (6.4 mL) were added simultaneously over 1 h, open to ambient atmosphere, at rt. After the addition, the mixture was concentrated and the residue washed with diethyl ether (2 x 5 mL), filtered, and concentrated to yield the crude reaction mixture (0.326 g). Analysis of the crude reaction mixture by ^{1}H NMR and GC/MS indicated a ratio of (1 : 0.5 : 0.1 : 0.1) of lactone **18** : alcohol (major diastereomer) **SI-2** : alcohol (minor diastereomer) **SI-2** : ketone (see above) **SI-3**. No starting material was observed. Purification by column chromatography (gradient, hexanes -> 50% diethyl ether/hexanes) yielded lactone **18** (0.051 g, 0.203 mmol, 14% yield) as a colorless liquid.



Lactone 18: Procedure adapted from literature[5]: To a 4 mL black screw capped vial was added acid **15** (1 equiv), copper(II) acetate monohydrate (10 mol%), and acetonitrile (0.1 M). To the vigorously stirred solution was added hydrogen peroxide (1 equiv, 50 wt% aqueous solution) in one portion. After 10 min at rt, copper(II) acetate monohydrate (10 mol%) and hydrogen peroxide (1 equiv, 50 wt% aqueous solution) were added in one portion. This process was repeated for a total of 10 additions in the same manner for a

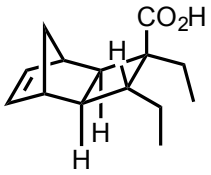
total of 100 mol% copper(II) acetate monohydrate and 10 equiv hydrogen peroxide. After each addition, the mixture was allowed to stir for 10 minutes, for a total of 1h 40 min. After the additions the reaction became a dark forest green. The mixture was diluted with HCl (1 M) and washed with ethyl acetate and the layers separated. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Quantitative recovery of starting material was determined by analysis of the crude ^1H NMR according to internal standard (1,3,5-trimethoxybenzene).

■ Formal Synthesis of Hippolachnin A



10

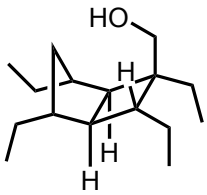
Acid chloride 10: To a flame-dried 100 mL round bottom flask equipped with a stirbar was added 2-ethylpent-2-enoic acid[6] (6.20 g, 48.0 mmol, 1.0 equiv), DMF (2-3 drops, cat.), and dichloromethane (48 mL, 1 M) under an atmosphere of N_2. The solution was cooled to 0 °C and oxalyl chloride (5 mL, 58 mmol, 1.5 equiv) was added down the walls over 5 min. The cooling bath was removed and the solution stirred for 3 h, while slowly warming to rt. The stirbar was removed and the solution was concentrated under reduced pressure. Purification by short-path distillation over potassium carbonate at reduced pressure (~5 mmHg, ~160 °C) afforded acid chloride **10** as an air and moisture sensitive colorless liquid (5.56 g, 37.9 mmol, 79% yield, >20:1 d.r.). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.13 (t, *J* = 7.5 Hz, 1H), 2.67 - 2.13 (m, 4H), 1.27 - 1.06 (m, 3H), 0.99 (m, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 168.9, 154.3, 138.3, 22.7, 21.2, 13.5, 13.0.



14b

Carboxylic acid 14b: To an oven-dried 5 mL microwave vial (Biotage Code No.: 351521) was added acid chloride **10** (0.900 mL, 6.43 mmol, 1 equiv) and quadricyclane **9** (3.00 mL, 32.2 mmol, 5 equiv) under N_2. The vial was fitted with a cap and septum (Biotage Code No.: 352298), clamped shut and heated to 140 °C in a microwave oven (conditions: 2-5 mL vial, normal absorption, pre-stirring 0.1 s, fixed hold time on). After 4 h, the light yellow solution was transferred to a 250 mL round bottom flask (washing with hexanes) and concentrated. A stirbar and NaOH (1M, 50 mL) were added and the mixture stirred vigorously for 24 h at rt. The mixture was diluted with diethyl ether (100 mL) and HCl (1M, 100 mL). The organic layer was separated and the aqueous solution was washed with diethyl ether (2 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to afford a yellow solid. The solid was dissolved in diethyl ether (50 mL) and loosely capped. After the appearance of white crystals the mixture was cooled to -20 °C for 2 d. The resulting yellow liquid was decanted from the white crystals. The crystals were carefully washed with hexanes (2 x 0.5 mL) to yield acid **14b** (0.705 g, 3.20 mmol, 50% yield) as a white solid. The relative stereochemistry was determined by X-ray crystallography (see additional CIF files). **IR (neat):** 2961, 1692, 1462, 1407, 1324, 1252, 1205, 702; **^{1}H NMR (400 MHz, $CDCl_3$):** 5.98 (s, 2H), 3.05 (d, *J* = 2.5 Hz, 1H), 2.64 (d, *J* = 2.6 Hz, 1H), 1.94 (dt, *J* = 10.7, 5.2 Hz, 1H), 1.88 (dq, *J* = 14.5, 7.3 Hz, 1H), 1.78 - 1.67 (m, 2H), 1.66 (d, *J* = 7.5 Hz, 1H), 1.55 - 1.49 (m,

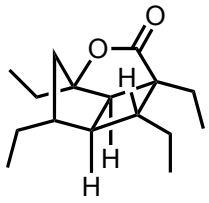
1H), 1.47 (d, *J* = 9.6 Hz, 1H), 1.36 (ddq, *J* = 14.1, 11.1, 7.2 Hz, 1H), 1.24 (dt, *J* = 9.6, 1.6 Hz, 1H), 0.90 (t, *J* = 7.3 Hz, 6H). **^{13}C NMR (100 MHz, $CDCl_3$):** 182.4, 136.0, 135.9, 47.2, 45.0, 44.7, 42.7, 42.4, 41.6, 38.8, 28.6, 22.8, 11.7, 9.7; **HRMS (EI):** Calcd for $C_{14}H_{20}O_2$ (M^+): 220.1438, Found: 220.1455. **m.p.** 118-122 °C.



16

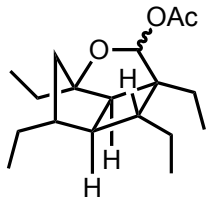
Alcohol 16: To a 50 mL oven-dried flask equipped with a stir bar was added acid **14b** (0.093 g, 0.420 mmol, 1 equiv) and ethyl acetate (8.5 mL). A balloon of ethylene (1 atm) was bubbled through the solution for 30 min. To an oven dried 4 mL black capped vial was added Grubbs 1st generation catalyst (7 mg, 0.0822 mmol, 2 mol%) via N_2 glovebox. Ethyl acetate (2 x 0.5 mL) was used to transfer the catalyst to the solution of acid and ethyl acetate. The solution immediately became light brown and stirred for 5 h with continued bubbling of ethylene. A second batch of Grubbs 1st generation catalyst (3.5 mg, 0.041 mmol, 1 mol%, total 3 mol%) was added using ethyl acetate (2 x 0.5 mL). Stirring and bubbling continued for another 3 h. The ethylene balloon was removed and palladium (5% on activated carbon, eggshell, oxidic, 50% wetted powder, 0.090 mg, 0.042 mmol, 10 mol%) was added and a hydrogen balloon was added. The mixture stirred for 1 h with continued bubbling of hydrogen. After 1 h, the mixture was filtered through Celite and the filter cake was washed with ethyl acetate (3 x 20 mL). The solution was concentrated to yield acid **15**.

To a 50 mL oven-dried reducing flask equipped with a stir bar was added acid **15** and tetrahydrofuran (5.50 mL, 0.1 M). The mixture was placed in a 0 °C bath and $LiAlH_4$ (0.104 g, 2.73 mmol, 5 equiv) was added in three equal portions. The flask was fitted with a reflux condenser and septum under N_2. The mixture was allowed to warm to rt and was then heated to 70 °C for 12 h. The mixture was cooled to rt then 0 °C. The reaction was diluted with diethyl ether (5 mL) and quenched with HCl (10 mL) slowly. The mixture was stirred vigorously and warmed to rt. The organic layer was separated and the aqueous solution was washed with diethyl ether (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to afford the crude alcohol. Purification by column chromatography (gradient, hexanes -> 50% diethyl ether/hexanes) yielded alcohol **16** (0.072 g, 0.302 mmol, 72% yield) as a colorless liquid. **IR (neat):** 3444, 2957, 2924, 1644, 1461, 1376, 1026; **^{1}H NMR (400 MHz, $CDCl_3$):** 3.63 (d, *J* = 10.9 Hz, 1H), 3.55 (d, *J* = 10.9 Hz, 1H), 2.10 (dt, *J* = 12.6, 6.4 Hz, 1H), 1.97 - 1.85 (m, 1H), 1.85 - 1.54 (m, 6H), 1.53 - 1.27 (m, 5H), 1.20 (m, 2H), 0.97 - 0.78 (m, 12H). **^{13}C NMR (100 MHz, $CDCl_3$):** 66.8, 51.3, 50.0, 49.4, 47.8, 42.2, 42.1, 42.0, 29.7, 29.1, 24.6, 23.8, 13.6, 13.5, 12.7, 8.3. **HRMS (EI):** Calcd for $C_{16}H_{30}O$ (M^+): 238.2291, Found: 238.2288.



18

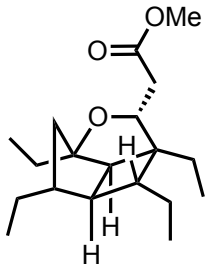
Lactone 18: To a 100 mL flask equipped with a stir bar under ambient air was added alcohol **16** (20.7 mg, 0.087 mmol, 1 equiv), (diacetoxy)iodobenzene (0.031 g, 0.096 mmol, 1.1 equiv), carbon tetrachloride (8.70 mL), and iodine (0.022 g, 0.087 mmol, 1 equiv). The mixture was irradiated with a 300 Watt light bulb approximately 20 cm from the reaction flask and monitored by TLC. After 2 h, (diacetoxy)iodobenzene (0.011 g, 0.034 mmol, total 1.5 equiv) and iodine (0.009 g, 0.035 mmol, total 1.4 equiv) were added. After 30 min, the light was removed, the mixture was cooled to 0 °C and dimethyldioxirane[7] (0.09 M in acetone, 50 mL, 4.5 mmol, ~51 equiv) was added in a single portion. The mixture was loosely capped and allowed to stir for 10 h as the bath slowly warmed. The mixture was diluted with hexanes (20 mL) and water (5 mL). The organic layer was separated and the aqueous solution was washed with hexanes (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to afford crude lactone **18**. Purification by column chromatography (gradient, hexanes -> 50% diethyl ether/hexanes) yielded lactone **18** (16.7 mg, 0.067 mmol, 77% yield) as a colorless liquid. **IR (neat):** 2963, 2925, 2876, 2856, 1756, 1462, 1379, 1215, 1184, 1113, 949, 966, 930; **^{1}H NMR (400 MHz, $CDCl_3$):** 2.70 (d, *J* = 8.3 Hz, 1H), 2.32 (dd, *J* = 13.7, 6.3 Hz, 1H), 2.08 - 1.94 (m, 1H), 1.89 (m, 2H), 1.79 (m, 2H), 1.72 - 1.55 (m, 3H), 1.51 - 1.27 (m, 4H), 1.00 (t, *J* = 7.5 Hz, 3H), 0.89 (t, *J* = 7.3 Hz, 6H), 0.82 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 182.4, 96.1, 51.9, 49.6, 49.4, 47.6, 46.7, 45.1, 31.1, 28.2, 24.8, 21.7, 13.2, 11.6, 9.3; **HRMS (EI):** Calcd for $C_{16}H_{26}O_2$ (M^+): 250.1927, Found: 250.1931.



19

Acetal 19: To an oven-dried 13 x 100 mm test tube under N_2, equipped with a magnetic stir bar and rubber septum, was added lactone **18** (28.1 mg, 0.112 mmol, 1 equiv) and tetrahydrofuran (1.10 mL, 0.1 M). The solution was cooled to -78 °C and diisobutylaluminum hydride (1.10 mL, 1.10 mmol, 10 equiv, 1 M hexane) was added down the walls. The mixture stirred at -78 °C for 5 h. The reaction was quenched with Rochelle's salt (sat. aq. soln., 2 mL) and was allowed to warm to rt. The organic layer was separated and the aqueous solution was washed with diethyl ether (2 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to afford the crude hemiacetal.

To an oven-dried 10 mL screw capped test tube under N_2, equipped with a magnetic stir bar and rubber septa, was added the crude hemiacetal. The test tube was cooled to 0 °C and pyridine (0.60 mL, 0.2 M) and acetic anhydride (0.210 mL, 2.24 mmol, 20 equiv) were added down the walls. The tube was sealed and allowed to stir as the bath slowly warmed to rt. After 14 h, the mixture was cooled to 0 °C, diluted with diethyl ether (2 mL) and quenched, carefully, with $NaHCO_3$ (sat. aq. soln., 2 mL). The mixture was warmed to rt and the organic layer was separated and the aqueous solution was washed with diethyl ether (2 x 5 mL). The combined organic layers were washed with $CuSO_4$ (sat. aq. soln., 2 x 5 mL) dried over Na_2SO_4, filtered, and concentrated to afford acylated hemiacetal **19** (26.9 mg, 0.091 mmol, 81% yield, 4:1 dr). Due to the isolation of a mixture of diastereomers, integrations are only listed below for peaks that are for a single diastereomer. **IR (neat):** 2960, 2930, 2875, 2359, 2341, 1747, 1644, 1462, 1377, 1233, 1035, 948, 899; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.05 (s, 1H, major diastereomer), 5.97 (s, 1H, minor diastereomer), 2.48 (d, *J* = 8.2 Hz, 1H, major diastereomer), 2.43 (d, *J* = 7.6 Hz, 1H, minor diastereomer), 2.34 (dd, *J* = 13.9, 7.2 Hz, 1H, major diastereomer), 2.19 (dt, *J* = 10.6, 5.4 Hz, 1H, major diastereomer), 2.09 (s, 3H, major diastereomer), 2.02 (s, 3H, minor diastereomer), 1.84 (dd, *J* = 14.0, 7.3 Hz, 1H, minor diastereomer), 1.73 (dtd, *J* = 7.3, 4.7, 4.1, 2.5 Hz, 1H, major diastereomer), 1.69 - 1.44 (m), 1.44 - 1.07 (m), 0.95 (t, *J* = 7.5 Hz, 3H, major diastereomer), 0.86 (td, *J* = 7.4, 2.4 Hz). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 170.7, 170.4, 104.2, 101.7, 100.2, 96.7, 52.7, 52.2, 51.7, 51.5, 49.8, 48.8, 48.5, 46.1, 45.8, 45.1, 43.3, 32.3, 31.7, 29.3, 29.0, 24.2, 24.2, 21.7, 21.6, 21.5, 13.1, 13.0, 12.2, 11.5, 11.0, 9.7, 9.0; **HRMS (CI):** Calcd for $C_{18}H_{29}O_3$ ($(M-H)^+$): 293.2111, Found: 293.2113.



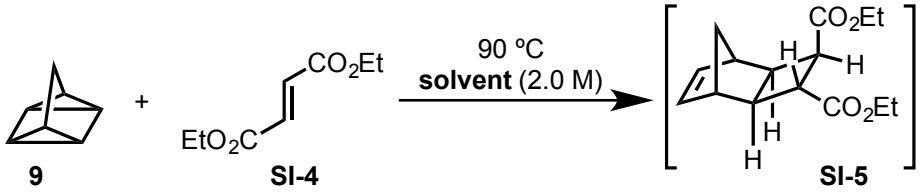
21

Methyl ester 21: To an oven-dried 13 x 100 mm test tube under N_2, equipped with a magnetic stir bar and rubber septum, was added acylated hemiacetal **19** (12.1 mg, 0.041 mmol, 1 equiv), dichloromethane (0.82 mL, 0.05 M), and *tert*-butyl((1-methoxyvinyl)oxy)dimethylsilane (0.014 mL, 0.062 mmol, 1.5 equiv). The mixture was cooled to -78 °C and BF_3•OEt_2 (0.013 mL, 0.103 mmol, 2.5 equiv) was added down the walls. After stirring 1 h at -78 °C, the mixture was quenched with $NaHCO_3$ (sat. aq. soln., 1 mL) and allowed to slowly warm to rt. The organic layer was separated and the aqueous solution was washed with diethyl ether (2 x 8 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to afford the crude ester. Purification by column chromatography (gradient, hexanes -> 50% diethyl ether/hexanes) yielded ester **21** (7.4 mg, 0.024 mmol, 59% yield) as a colorless liquid. Diastereomer was assigned according to the literature[8]. **IR (neat):** 2958, 2875, 1743, 1461, 1435, 1378, 1265, 1161, 1044; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 4.38 (dd, *J* = 10.2, 4.7 Hz, 1H), 3.71

(s, 3H), 2.42 (m, 4H), 1.98 (t, *J* = 7.3 Hz, 1H), 1.89 (dt, *J* = 11.3, 5.6 Hz, 1H), 1.79 (t, *J* = 7.0 Hz, 1H), 1.77 - 1.63 (m, 3H), 1.51 (dd, *J* = 14.0, 7.2 Hz, 1H), 1.44 (m, 1H), 1.36 (m, 2H), 1.31 - 1.22 (m, 1H), 1.13 (dt, *J* = 13.9, 7.3 Hz, 1H), 0.91 (m, 6H), 0.87 - 0.76 (m, 6H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 172.6, 97.0, 86.0, 54.9, 52.1, 51.8, 50.8, 49.2, 46.4, 46.0, 38.7, 34.7, 29.3, 24.5, 22.2, 12.8, 11.9, 11.2, 9.9; **HRMS (CI):** Calcd for $C_{19}H_{33}O_3$ ($H+M^+$): 309.2424, Found: 309.2418.

b. Wood Route

■ **Studies on the [2+2+2] Cycloaddition with Diethyl Fumarate**

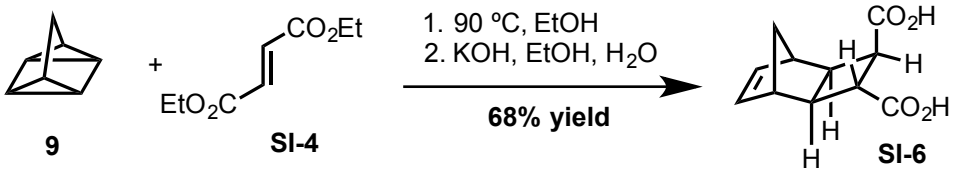


9 **SI-4** **SI-5**

		% Conversion after:[a]	
Entry	**Solvent**	**48 h**	**72 h**
1	toluene	48	63
2	MeCN	64	75
3	$CHCl_3$	63	72
4	EtOH	77	83

[a] determined by ^{1}H NMR in $CDCl_3$

General Procedure for [2+2+2] Cycloaddition with Diethyl Fumarate. A 1.5 dram vial equipped with a stir bar was charged with quadricyclane **9** (0.100 g, 1.08 mmol), freshly distilled diethyl fumarate **SI-4** (0.156 g, 0.904 mmol), and solvent (0.45 mL). The reaction was then sealed and placed in a 90 ºC oil bath. Aliquots were taken at the indicated times, and conversion of alkene to product **SI-5** was monitored by ^{1}H NMR in $CDCl_3$.

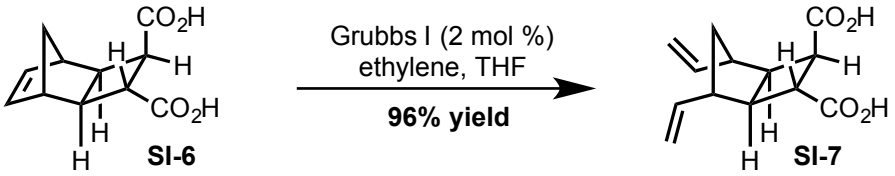


9 **SI-4** **SI-6**

Diacid SI-6. An oven dried 1.5 dram vial equipped with a stir bar was charged with quadricyclane **9** (0.102 mL, 1.08 mmol), freshly distilled diethyl fumarate **SI-4** (0.148 mL, 0.904 mmol), and ethanol (0.45 mL). The reaction was then sealed and placed in a 90 ºC oil bath. After 72 h, the reaction was removed from the oil bath and allowed to cool to room temperature, then additional ethanol (1.4 mL) was added, followed by water (0.36 mL) and potassium hydroxide (0.252 g, 4.50 mmol) to give a brown, opaque reaction mixture. This was stirred vigorously overnight at room temperature, then concentrated *in vacuo*. The resultant slurry was diluted with water until all solids were dissolved, then washed with diethyl ether (1 x 1mL). The remaining aqueous layer was acidified to pH = 1 using 6N HCl, then extracted with diethyl ether (4 x 1 mL). The organic extracts were combined, dried over $MgSO_4$, and concentrated *in vacuo* to give a yellow amorphous solid. Purification via silica gel flash column chromatography (20 to 40 to 50 to 100% ethyl acetate/hexanes) afforded diacid **SI-6** as an off white amorphous solid (0.128 g, 68% yield).

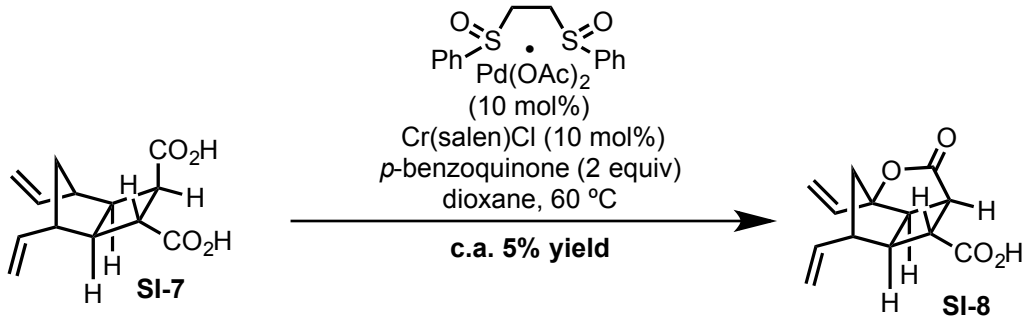
^{1}H NMR (400 MHz, Methanol-d_4) δ 6.03 (s, 2H), 4.98 (bs, 2H), 3.57 (t, J = 8.5 Hz, 1H), 2.94 (s, 1H), 2.83 (s, 1H), 2.81-2.73 (m, 1H), 2.26 (t, J = 8.7 Hz, 1H), 2.08 (t, J = 5.2 Hz, 1H), 1.57 (d, J = 9.6 Hz, 1H), 1.28 (d, J = 11.2 Hz, 1H). **^{13}C NMR (101 MHz,**

Methanol-d_4) δ 177.7, 175.9, 137.1, 136.6, 45.5, 43.3, 41.7, 41.4, 39.9, 39.0, 38.6. **IR (thin film)** cm^{-1} 3057, 2970, 2893, 1691, 1468, 1414, 1287, 1259, 1235, 916, 843, 700, 654. **HRMS (ESI+)** Calcd. for $C_{11}H_{12}O_4Na$. $[M+Na]^+$: 231.0628. Found: 231.0627.



Diene SI-7. An oven dried 100 mL round bottom flask equipped with a stir bar was charged with diacid **SI-6** (0.600 g, 2.88 mmol) and tetrahydrofuran (29 mL) to give a clear, colorless solution, which was flushed with ethylene gas for ~30 sec. To the solution was added Grubbs I (0.047 g, 0.058 mmol), resulting in a clear, purple solution. The reaction vessel was purged with ethylene gas for ~30 sec, then left under a static atmosphere of ethylene via balloon. After 20 h, the reaction was filtered through a plug of celite, eluted with diethyl ether (3 x 20mL), and transferred to a separatory funnel. The organic layer was washed with 1N HCl (1 x 25 mL), and then extracted with 1N NaOH (3 x 25 mL). The combined basic aqueous layers were washed with diethyl ether (4 x 25 mL), then acidified to pH = 1 using 6N HCl. The acidic aqueous layer was then extracted with diethyl ether (3 x 25 mL). The combined organic extracts were washed with water, brine, dried over $MgSO_4$ and concentrated *in vacuo* to furnish diene **SI-7** as a light pink amorphous solid (0.655 g, 96% yield).

^{1}H NMR (400 MHz, Acetone-d_6) δ 10.80 (bs, 2H), 5.89-5.76 (m, 2H), 5.01 (dd, J = 21.5, 17.2 Hz, 2H), 4.89 (dd, J = 10.2, 4.7 Hz, 2H), 3.48 (t, J = 8.7 Hz, 1H), 3.29-3.20 (m, 1H), 2.81-2.73 (m, 2H), 2.73-2.65 (m, 2H), 2.15 (dt, J = 12.3, 5.9 Hz, 1H), 1.48 (m, 1H). **^{13}C NMR (101 MHz, Acetone-d_6)** δ 174.8, 173.1, 142.4, 142.1, 113.9, 113.6, 51.5, 46.7, 46.6, 45.8, 45.1, 42.2, 40.0. **IR (thin film)** cm^{-1} 3078, 2946, 2860, 2627, 1690, 1638, 1415, 1302, 1257, 1210, 907. **HRMS (ESI+)** Calcd. for $C_{13}H_{16}O_4Na$. $[M+Na]^+$: 259.0941. Found: 259.0941.

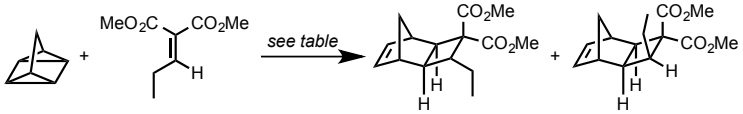


Lactone SI-8. A 1.5 dram vial containing diene **SI-7** and a stir bar was charged with *p*-benzoquinone (45.8 mg, 0.423 mmol), White's catalyst (10.6 mg, 0.021 mmol), and Cr(salen)Cl (13.4 mg, 0.021 mmol). Dioxane (0.641 mL) was added slowly down the

sides of the vial to rinse any stray solids into the reaction mixture. The resultant maroon reaction mixture was sealed and the vial was placed in a 60 ºC heat block. After 48 h, the reaction was diluted with diethyl ether (2.0 mL), washed with sodium meta bisulfite (sat. aq. soln., 1 x 1mL), water (1 x 1mL) and brine (1 x 1mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give a dark red oil. By crude ^{1}H NMR, complete conversion of starting material was observed. This was further purified via flash column chromatography on silica gel using 5 to 10 to 20 to 20% ethyl acetate/hexanes containing 0.5% AcOH. The fractions containing product were concentrated *in vacuo* to give lactone **SI-8** as an orange oil containing inseparable 1,4-dihydroquinone (9.3 mg, 18% yield, 2:1 1,4-dihydroquinone:product).

^{1}H NMR (400 MHz, Acetone-d_6) δ 6.66 (s, 8H, *1,4-dihydroquinone*), 6.06 (dd, *J* = 17.3, 10.9 Hz, 1H), 5.87 (ddd, *J* = 17.4, 10.2, 7.6 Hz, 1H), 5.34 (dd, *J* = 17.3, 1.1 Hz, 1H), 5.19-5.16 (m, 1H), 5.14 (m, 1H), 4.99 (d, *J* = 10.7 Hz, 1H), 3.37 (d, *J* = 6.2 Hz, 1H), 3.03-2.92 (m, 2H), 2.87-2.78 (m, 1H), 2.24 (dd, *J* = 13.8, 6.2 Hz, 1H), 1.96 (dd, *J* = 13.8, 11.8 Hz, 1H). **^{13}C NMR (101 MHz, Acetone-d_6)** δ 177.4, 174.1, 151.1 (*1,4-dihydroquinone*), 140.1, 138.7, 116.5 (*1,4-dihydroquinone*), 115.0, 114.5, 95.3, 50.4, 48.7, 47.4, 47.2, 47.2, 41.2. **IR (thin film)** cm^{-1} 3367, 3322, 1732, 1709, 1510, 1466, 1364, 1208, 927, 829, 757, 517. **HRMS (ESI+)** Calcd. for $C_{13}H_{14}O_4Na$ $[M+Na]^+$: 257.0784. Found: 257.0786.

■ Studies on the [2+2+2] Reaction with Alkylidene 11



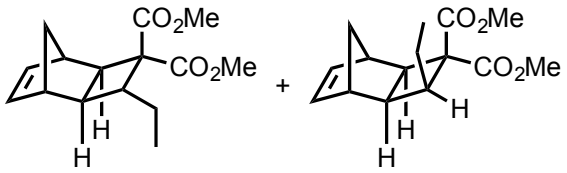
9 **11** **22a** **22b**

Entry[a]	Solvent	Catalyst[b]	Time	dr (22a:22b)[c]	% conversion[c,d]
1	EtOH	--	144 h	9.1:1	52 (37)[h]
2	DCE	--	4 h	2.3:1	11
3	DCE	HCl	4 h	1:1.5	20
4	DCE	$Cu(OTf)_2$	4 h	--	--
5	DCE	$ZnCl_2$	4 h	1.8:1	44
6	DCE	$AlCl_3$	4 h	2.1:1	67
7	DCE	$TiCl_4$	4 h	2.9:1	>95
8[e]	CH_2Cl_2	$TiCl_4$[f]	4 h	3.4:1	>95
9[e]	CH_2Cl_2	$TiCl_4$[f]	1 h	3.7:1	>95 (82)[h]
10[e]	CH_2Cl_2	$TiCl_4$[g]	4 h	4.4:1	73

[a] 90 ºC [b] 10 mol% [c] determined by ^{1}H NMR in $CDCl_3$ [d] conversion of alkylidene to cycloadducts A&B [e] 0 ºC [f] 5 mol% [g] 2 mol% [h] isolated yield

General Procedure for [2+2+2] Cycloaddition with Alkylidene 11. A 1.5 dram vial containing alkylidene **11** and a stir bar was charged with solvent (0.29 mL) followed by quadricyclane (0.065 mL, 0.697 mmol) and catalyst (0.058 mmol). The reaction was then sealed and placed in a 90 ºC heat block. After the indicated time, the reaction was removed from the heat block and allowed to cool to room temperature. An aliquot was dissolved in $CDCl_3$ and the percent conversion was determined via ^{1}H NMR.

■ **Total Synthesis of (±)-Hippolachnin A**

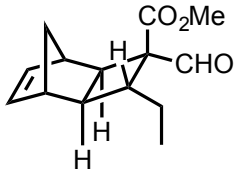


22a **22b**

Cyclobutanes 22a & 22b. A 100 mL round bottom flask equipped with a stir bar was charged with alkylidene **11** (10.0 g, 58.1 mmol), dichloromethane (29.0 mL), and quadricyclane **9** (8.17 mL, 87.0 mmol). The resulting clear, colorless solution was cooled to 0 ºC in an ice/water bath and titanium (IV) tetrachloride (1.0 M in dichloromethane, 2.90 mL, 2.90 mmol) was added dropwise, slowly, over ten minutes to furnish a black/purple solution. After 1 h, diethyl ether (20 mL) was added, followed by NH_4Cl (50% sat. aq. soln., 20 mL), and then the entire heterogeneous mixture was transferred to a separatory funnel containing diethyl ether (20 mL) and NH_4Cl (50% sat. aq. soln., 20 mL). After vigorous shaking, the organic layer became light yellow and the aqueous layer remained colorless. The layers were separated, and the aqueous layer was extracted with diethyl ether (3x 40 mL). The combined organic layers were washed with NH_4Cl (50% sat. aq. soln., 20 mL), water (20 mL), and brine (20 mL), then dried over $MgSO_4$ and concentrated *in vacuo* to give an orange oil. This oil was dissolved in minimal dichloromethane and purified via flash column chromatography on silica gel using 0 to 2% ethyl acetate/hexanes. The product was obtained as a fluffy, off-white solid (12.6 g, 82% yield) as a mixture of diastereomers (**22a**:**22b** = 4.3:1).

The mixture of diastereomers (6.5 g, 24.5 mmol) was then dissolved in minimal, hot Et_2O (5 mL) in a 125 mL Erlenmeyer flask. The resulting supersatured solution was allowed to cool to room temperature, and hexanes (25 mL) was carefully layered on top. This was allowed to stand overnight, uncovered, in a fume hood. The mother liquor was decanted from the resulting clear, colorless, rectangular prismatic crystals, which were subsequently washed with ice cold 5% diethyl ether/hexanes (~10 mL) and determined to be >20:1 d.r. of diastereomer **22a (**0.761 g, 11% yield). This process was repeated on the decanted mother liquor to produce an additional crop of crystals (0.762 g, 11% yield, >20:1 d.r.).

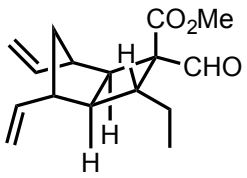
m.p. 72.1-72.6 ºC (Et_2O/hexanes). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 6.03-5.99 (m, 2H), 3.75 (s, 3H), 3.71 (s, 3H), 2.81-2.77 (m, 1H), 2.70-2.69 (m, 1H), 2.62 (dq, *J* = 7.4, 1.2 Hz, 1H), 2.30 (dtd, *J* = 10.7, 5.4, 1.0 Hz, 1H), 1.63 (ddt, *J* = 7.0, 5.5, 1.4 Hz, 1H), 1.58-1.51 (m, 1H), 1.48 (d, *J* = 9.7 Hz, 1H), 1.27-1.13 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.2, 171.1, 136.4, 135.7, 54.4, 52.3, 52.3, 44.7, 42.2, 42.0, 41.4, 40.0, 39.4, 24.2, 11.0. **IR (thin film)** cm^{-1} 3057, 2957, 2899, 2875, 1726, 1457, 1433, 1244, 1208, 1191, 1161, 783, 730, 710, 688. **HRMS (ESI+)** Calcd. for $C_{15}H_{20}O_4Na$. $[M+Na]^+$: 287.1254. Found: 287.1255.



23

Aldehyde 23. A 50 mL round bottom flask equipped with a stir bar was charged with a solution of cyclobutane **22a** (0.872 g, 2.88 mmol) in dichoromethane (5.77 mL, 0.5 M), then cooled to -78 ºC in a dry ice/acetone bath. DIBAL-H (1.0 M in hexanes, 6.05 mL, 6.05 mmol) was added dropwise, slowly, over 5 min. After 40 min, acetone (6.0 mL) was added dropwise to the reaction mixture over 5 min at -78 ºC, followed by diethyl ether (6.0 mL) over 5 min at -78 ºC. The reaction was then removed from the dry ice/acetone bath and water (0.2 mL) was added dropwise with vigorous stirring. After the reaction had warmed to near room temperature, 1N NaOH (aq. soln., 0.2 mL) was added, followed by water (0.2 mL), resulting in an opaque white suspension. $MgSO_4$ was added until a free flowing suspension was obtained. After stirring vigorously for 1 h, the mixture was filtered through a plug of celite, eluted with diethyl ether, and concentrated *in vacuo*. The resultant oil was dissolved in minimal hexanes and purified via flash column chromatography on silica gel (0 to 1 to 2% ethyl acetate/hexanes). Aldehyde **23** was isolated as a clear, colorless oil (0.508 g, 75% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.71 (s, 1H), 6.02 (s, 2H), 3.78 (s, 3H), 2.91 (s, 1H), 2.74 (s, 1H), 2.52 (d, *J* = 7.3 Hz, 1H), 2.35 (dt, *J* = 11.0, 5.9 Hz, 1H), 1.66-1.61 (m, 2H), 1.45 (d, *J* = 9.7 Hz, 1H), 1.38-1.34 (m, 1H), 1.26 (d, *J* = 9.7 Hz, 1H), 0.88 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 198.0, 171.0, 136.4, 135.7, 59.2, 52.4, 44.8, 44.5, 42.1, 41.6, 39.7, 37.7, 23.9, 11.8. **IR (thin film)** cm^{-1} 3057, 2960, 2895, 2875, 1739, 1709, 1459, 1434, 1265, 1219, 1132, 982710, 692. **HRMS (ESI+)** Calcd. for $C_{14}H_{18}O_3Na$. $[M+Na]^+$: 257.1148. Found: 257.1151.

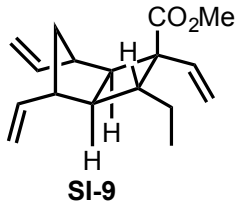


24

Diene 24. A 250 mL round bottom flask equipped with a stir bar was charged with a solution of aldehyde **23** (0.508 g, 2.171 mmol) in dichloromethane (87 mL, 0.025 M). The clear, colorless solution was flushed with a balloon of ethylene with vigorous stirring over 5 min. Grubbs I (0.036 g, 0.043 mmol) was added, giving a clear, bright purple solution, and the reaction was again purged with ethylene for 5 min, then left under a static ethylene atmosphere. Over the next 20 min, the reaction changed color from purple, to pink, to orange, and then finally to brown. After an additional 40 min, the reaction was concentrated *in vacuo* to yield a dark brown oil. This was dissolved in minimal hexanes and purified via flash column chromatography on silica gel (0 to 0.2 to

0.4 to 0.6 to 0.8 to 1.0 to 1.2 to 1.4 to 1.8 to 2.0% ethyl acetate/hexanes). Diene **24** was isolated as an orange oil (0.560 g, 98% yield).

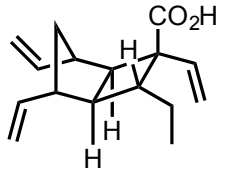
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.80 (s, 1H), 5.77-5.67 (m, 2H), 4.99-4.93 (m, 2H), 4.92-4.87 (m, 2H), 3.72 (s, 3H), 2.94 (t, *J* = 8.6 Hz, 1H), 2.86- 2.78 (m, 1H), 2.65 (dq, *J* = 14.0, 7.3 Hz, 1H), 2.49 (dtd, *J* = 10.8, 6.8, 4.3 Hz, 2H), 2.12 (td, *J* = 8.5, 4.3 Hz, 1H), 2.07 (dt, *J* = 12.4, 6.2 Hz, 1H), 1.55 (tt, *J* = 13.3, 7.3 Hz, 1H), 1.41 (ddd, *J* = 12.7, 11.6, 10.4 Hz, 1H), 1.31 (ddd, *J* = 13.5, 10.2, 7.1 Hz, 1H), 0.83 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 198.6, 170.7, 141.4, 140.5, 114.0, 113.4, 60.1, 52.0, 51.6, 51.0, 47.2, 46.5, 45.7, 42.5, 23.8, 11.8. **IR (thin film)** cm^{-1} 3076, 2955, 2875, 1724, 1639, 1435, 1378, 1260, 1197, 1164, 1051, 993, 911, 791, 735, 646. **HRMS (ESI+)** Calcd. for $C_{16}H_{22}O_3Na$. $[M+Na]^+$: 285.1461. Found: 285.1461.



SI-9

Triene SI-9. A 25 mL round bottom flask equipped with a stir bar was charged with methyltriphenylphosphonium bromide (0.916 g, 2.56 mmol) and tetrahydrofuran (3.0 mL) to give a white, heterogeneous suspension which was cooled to 0 ºC in an ice/water bath. KHMDS (0.5 M in toluene, 4.75 mL, 2.35 mmol) was added, resulting in a bright yellow opaque reaction mixture. After addition of KHMDS was complete, the reaction was warmed to room temperature and stirred vigorously for 30 min, then cooled down to -78 ºC in a dry ice/acetone bath. A solution of diene **24** (0.561 g, 2.14 mmol) in tetrahydrofuran (1.94 mL, 1.1 M) was added dropwise, followed by an additional tetrahydrofuran (2 x 0.5 mL) rinse of the vial containing diene **24**. After stirring for 1.5 h, the reaction was warmed to room temperature and allowed to stir for an additional 2 h, upon which the reaction was quenched with NH_4Cl (50% sat. aq. soln., 15 mL). The resulting layers were separated and the aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give a dark brown oil. The oil was absorbed onto silica gel and purified via flash column chromatography (0 to 0.5 to 1 to 1.5% ethyl acetate/hexanes). Triene **SI-9** was isolated as a brown oil (0.423 g, 76% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.82 (ddd, *J* = 15.9, 9.6, 6.2 Hz, 1H), 5.73 (ddd, *J* = 17.9, 9.5, 7.2 Hz, 1H), 5.26 (dd, *J* = 10.8, 0.7 Hz, 1H), 5.14 (dd, *J* = 17.5, 0.8 Hz, 1H), 4.98-4.85 (m, 4H), 3.65 (s, 3H), 2.69-2.56 (m, 3H), 2.49 (dq, *J* = 6.5, 3.2 Hz, 1H), 2.08 (dt, *J* = 12.5, 6.0 Hz, 1H), 1.99 (td, *J* = 8.2, 3.9 Hz, 1H), 1.53-1.37 (m, 2H), 1.27 (ddd, *J* = 13.4, 9.7, 7.3 Hz, 1H), 0.82 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 174.7, 142.2, 141.4, 137.0, 115.3, 113.4, 112.9, 52.1, 51.3, 51.1, 50.8, 50.3, 47.5, 47.3, 42.9, 24.0, 11.6. **IR (thin film)** cm^{-1} 3079 (w), 2953, 2930, 2873 (w), 1727 (s), 1637 (w), 1433, 1270, 1234, 1207, 992, 909 (s). **HRMS (ESI+)** Calcd. for $C_{17}H_{24}O_2Na$. $[M+Na]^+$: 283.1669. Found: 283.1668.

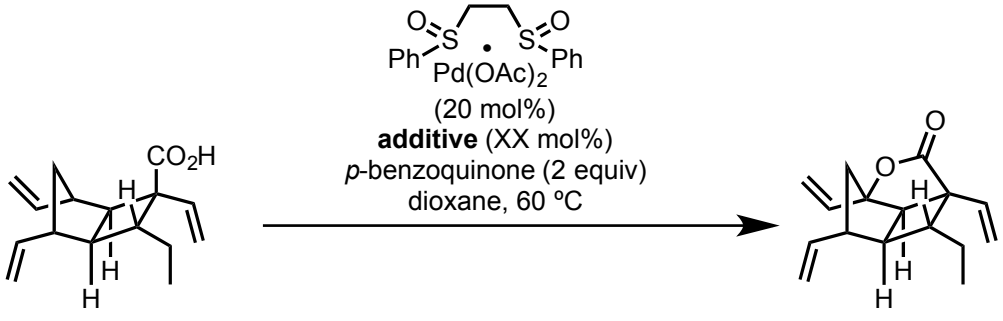


25

Acid 25. A 1.5 dram vial equipped with a stir bar was charged with ester **SI-9** (131 mg, 0.503 mmol), methanol (0.67 mL), water (0.17 mL) and 10 N KOH (0.17 mL). The resulting opaque, bright yellow suspension was sealed and placed in a 60 ºC aluminum heat block for 48 h. After cooling to room temperature, the reaction was washed with diethyl ether (3 x 1mL). The combined diethyl ether washes were extracted with 1N NaOH (3 x 1 mL). The aqueous extracts and preceding aqueous layer were combined, and acidified to pH = 1 with 6N HCl, then extracted with Et_2O (5 x 5mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to furnish acid **25** as a white amorphous solid (116 mg, 94% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.99 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.88 (ddd, *J* = 17.2, 10.3, 6.8 Hz, 1H), 5.74 (ddd, *J* = 17.5, 10.1, 7.9 Hz, 1H), 5.35-5.21 (m, 2H), 5.02-4.85 (m, 4H), 2.80-2.72 (m, 1H), 2.62-2.54 (m, 2H), 2.51-2.47 (m, 1H), 2.11 (dt, *J* = 12.5, 6.2 Hz, 1H), 2.01 (td, *J* = 8.4, 3.8 Hz, 1H), 1.52-1.41 (m, 2H), 1.32-1.24 (m, 1H), 0.82 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 179.6, 142.1, 141.1, 136.3, 116.0, 113.6, 113.0, 51.9, 51.0, 50.7, 50.2, 47.1, 47.1, 42.5, 24.0, 11.6. **IR (thin film)** cm^{-1} 3079, 2956, 2929, 2639 (w), 1696 (s), 1638 (w), 1458, 1407, 1282, 1258, 992, 910(s). **HRMS (ESI-)** Calcd. for $C_{16}H_{21}O_2$. $[M-H]^-$: 245.1536. Found: 245.1543.

■ Studies on the Intramolecular C-H Oxidation

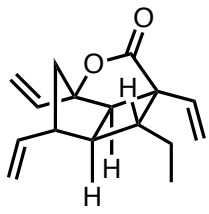


25 **26**

Entry	Additive	Mol%	% yield
1[a]	Cr(salen)Cl	20	40
2	Cr(salen)Cl	20	29
3	DIPEA	50	18
4	Cr(salen)Cl/AcOH	50/20	29
5	water	1000	51

a) old bottle of White catalyst

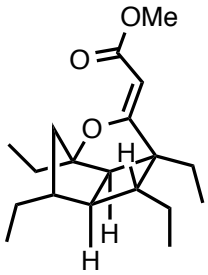
General Procedure for the Intramolecular C-H Oxidation (Entries 1-4). Without precautions to exclude moisture or air, a 1.5 dram vial containing acid **25** (10.0 mg, 0.041 mmol) and a stir bar was charged with additive (see table), *p*-benzoquinone (8.8 mg, 0.081 mmol) and White's catalyst (4.1 mg, 8.12 μmol). The mixture was then dissolved in dioxane (0.41 mL), which was added slowly down the sides of the vial. The vial was then sealed and placed in a 60 ºC aluminum heat block. After 96 h, the reaction was cooled to room temperature and diluted with diethyl ether (2 mL). The reaction mixture was then washed with sodium metabisulfite (sat. aq. soln., 1 x 1mL), sodium thiosulfate (sat. aq. soln., 1 x 1mL), 1N HCl (1 x 1mL) and brine (1 x 1mL). The remaining organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give a dark red oil. This was then purified via flash column chromatography on silica gel (0 to 0.1 to 0.2 to 0.3 to 0.4 to 0.6 to 0.8 to 1.0 to 1.2 to 1.4% ethyl acetate/hexanes). The fractions containing product were combined and concentrated *in vacuo* to furnish lactone **26** as a pale yellow oil.



26

Lactone 26. A 1.5 dram vial containing acid **25** (10 mg, 0.041 mmol) was equipped with a stir bar. Without precautions to exclude air or moisture, Cr(salen)Cl (5.1 mg, 8.12 μmol) was added, followed by White's catalyst (4.1 mg, 8.12 μmol) and *p*-benzoquinone (8.8 mg, 0.081 mmol). The resulting solid mixture was dissolved in dioxane (0.41 mL), which was added slowly down the sides of the vial. Finally, water (7 μL) was added and the reaction mixture was sealed and placed in a 60 ºC aluminum heat block. After 96 h, the reaction was cooled to room temperature and diluted with diethyl ether (2 mL). The reaction mixture was then washed sodium metabisulfite (sat. aq. soln., 1 x 1mL), sodium thiosulfate (sat. aq. soln., 1 x 1mL), 1N HCl (1 x 1mL) and brine (1 x 1mL). The remaining organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give a dark red oil. This was then purified via flash column chromatography on silica gel (0 to 0.1 to 0.2 to 0.3 to 0.4 to 0.6 to 0.8 to 1.0 to 1.2 to 1.4% ethyl acetate/hexanes). The fractions containing product were combined and concentrated *in vacuo* to furnish lactone **26** as a pale yellow oil (5.1 mg, 51% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.04 (dd, *J* = 17.8, 10.8 Hz, 1H), 5.92 (dd, *J* = 17.2, 10.9 Hz, 1H), 5.76 (ddd, *J* = 17.4, 10.2, 7.5 Hz, 1H), 5.38-5.24 (m, 2H), 5.18-4.94 (m, 4H), 3.20 (d, *J* = 8.6 Hz, 1H), 2.94-2.81 (m, 1H), 2.36 (dd, *J* = 13.8, 6.1 Hz, 1H), 2.16 (ddd, *J* = 10.6, 5.2, 2.9 Hz, 1H), 2.09 (ddd, *J* = 8.9, 6.1, 2.9 Hz, 1H), 1.80 (dd, *J* = 13.8, 11.7 Hz, 1H), 1.62-1.49 (m, 1H), 1.29-1.14 (m, 1H), 0.84 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 179.5, 139.4, 137.4, 132.7, 117.0, 114.8, 114.5, 93.7, 53.2, 51.5, 50.0, 49.7, 47.2, 46.3, 25.1, 10.8. **IR (thin film)** cm^{-1} 3083, 2959, 2928, 1755, 1639, 1459, 1416, 1260, 1226, 1211, 1111, 991, 915, 777, 650, 595. **HRMS (ESI+)** Calcd. for $C_{16}H_{20}O_2Na$. $[M+Na]^+$: 267.1356. Found: 267.1355.



(±)-hippolachnin A (**1**)

Hippolachnin A 1. A 1.5 dram vial containing activated 4Å MS was charged with tetrahydrofuran (2.0 mL) and *t*-BuOAc (0.17 mL). The mixture was swirled vigorously to generate a 0.63 M stock solution of *t*-BuOAc. This was allowed to stand for 20 min under nitrogen prior to use. A freshly dried 1.5 dram vial equipped with a stir bar was charged with tetrahydrofuran (0.5 mL) and cooled to -78 ºC. *Tert*-butyl lithium (1.7 M in pentanes, 77 µL, 0.131 mmol) was added to the cooled tetrahydrofuran to furnish a bright yellow solution. The stock solution of *t*-BuOAc (0.63 M in tetrahydrofuran, 0.2 mL, 0.126 mmol) was then added dropwise to the reaction mixture. After stirring for 15 min at -78 ºC, lactone **21** (5.8 mg, 0.024 mmol) as a solution in tetrahydrofuran (0.4 mL) was added dropwise, slowly, to the reaction mixture, followed by a rinse with tetrahydrofuran (0.1 mL). After stirring at -78 ºC for 2 h, the reaction was removed from the dry ice/acetone bath and placed in a 0 ºC ice/water bath. After 2 h, the reaction was quenched at 0 ºC with 6N HCl (1 mL) and allowed to warm to room temperature with vigorous stirring. The reaction mixture was extracted with diethyl ether (3 x 1mL) and the combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give the crude material as an pale yellow oil (7.8 mg, 96% yield).

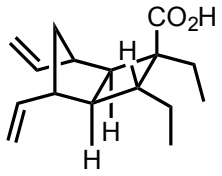
The crude oil was dissolved in tetrahydrofuran (0.76 mL) in a 1.5 dram vial equipped with a stir bar. 10% Pd/C (0.7 mg, 0.666 µmol) was added, and the resulting suspension was stirred vigorously while the reaction was purged with hydrogen gas for 30 sec. The reaction was then placed under static hydrogen via balloon and the vigorous stirring was continued. After 6 h, the reaction was diluted with diethyl ether and filtered through a plug of celite. The eluent was concentrated *in vacuo* to give the crude material as a colorless oil (6.6 mg, 85% yield).

The crude material from the hydrogenation was dissolved in freshly distilled methanol (0.95 mL) in a 1.5 dram vial equipped with a stir bar. Freshly distilled chlorotrimethylsilane (72 µL, 0.568 mmol) was added and the reaction was sealed and placed in a 60 ºC aluminum heat block. After 22 h, the reaction was allowed to cool to room temperature. Sodium carbonate (64.2 mg, 0.606 mmol) was added with vigorous stirring, followed by water (10.9 µL, 0.609 mmol). The resulting suspension was diluted with dichloromethane (2.0 mL) and allowed to stir vigorously for 1 h. The suspension was treated with $MgSO_4$, filtered through a plug of celite, eluted with dichloromethane (5 x 2.0 mL), and concentrated *in vacuo*. The crude reaction mixture was loaded with minimal dichloromethane onto a silica gel column for purification via flash column chromatography (0 to 1 to 2 to 3 to 4 to 5 to 6% ethyl acetate/hexanes). The fractions

containing product were combined and concentrated *in vacuo* to give hippolachnin A **1** as a yellow oil (1.6 mg, 27% yield, 22% over 3 steps). Characterization data matched what was reported in the literature.[8]

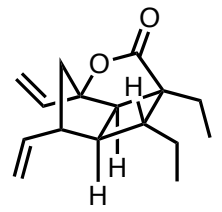
^{1}H NMR (600 MHz, $CDCl_3$) δ 4.56 (s, 1H), 3.66 (s, 3H), 2.59 (d, *J* = 8.1 Hz, 1H), 2.43 (dd, *J* = 13.8, 6.5 Hz, 1H), 2.01-1.95 (m, 1H), 1.87-1.72 (m, 4H), 1.70-1.61 (m, 2H), 1.58 (s, 2H, *water*), 1.53-1.47 (m. 1H), 1.39 (dd, *J* = 13.8, 10.0 Hz, 1H), 1.37-1.26 (m, 3H), 1.25 (s, 3H, *H grease*), 1.02 (t, *J* = 7.4 Hz, 3H), 0.87 (t, *J* = 7.3 Hz, 6H), 0.79 (t, *J* = 7.3 Hz, 3H), 0.07 (s, 2H, *silicone grease*). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 181.2, 167.4, 104.3, 83.6, 56.7, 52.9, 50.5, 49.5, 47.6, 46.4, 45.2, 30.9, 29.8 (*H grease*), 28.4, 24.7, 23.4, 13.1, 11.9, 9.7, 8.7, 1.1 (*silicone grease*). **IR (thin film)** cm^{-1} 2959, 2923, 2874, 2853, 1719, 1692, 1635, 1460, 1434, 1377, 1262, 1214, 1183, 1152, 1139, 1039, 970, 909, 853, 800. **HRMS (ESI+)** Calcd. for $C_{19}H_{30}O_3Na$. $[M+Na]^+$: 329.2087. Found: 329.2089.

c. Collaborative Route



27

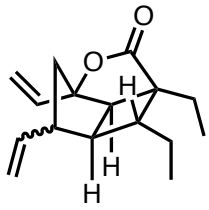
Diene 27. A 25 mL oven dried round bottom flask equipped with a stirbar was charged with acid **14b** (50 mg, 0.228 mmol) as a solution in dichloromethane (9.1 mL). The resulting clear, colorless solution was purged with ethylene gas, then Grubbs I (3.7 mg, 4.56 μmol) was added, furnishing a bright purple, clear reaction mixture. This was purged with ethylene and left under 1 atm of ethylene (balloon). After 7 h, 1N NaOH (10 mL) was added along with diethyl ether (10 mL), and the organic layer was extracted with 1N NaOH (5 x 2 mL). The combined aqueous layers were acidified to a pH of ~1 with 6N HCl, then extracted with diethyl ether (3 x 10 mL). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give **27** as a pink oil (52 mg, 92%). **IR (neat):** cm^{-1} 3077, 2959, 2929, 2874, 1690, 1639, 1458, 1411, 1315, 1248, 1152, 990, 906, 789. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 11.24 (s, 1H), 5.88-5.78 (m, 1H), 5.72- 5.61 (m, 1H), 4.96-4.77 (m, 4H), 2.65 (dq, *J* = 12.8, 6.7 Hz, 1H), 2.38 (ddt, *J* = 13.4, 10.1, 5.0 Hz, 2H), 2.09 (t, *J* = 8.5 Hz, 1H), 2.00 (dt, *J* = 12.4, 6.2 Hz, 1H), 1.96-1.89 (m, 1H), 1.85-1.74 (m, 1H), 1.74-1.64 (m, 1H), 1.62-1.51 (m, 1H), 1.41-1.21 (m, 2H), 0.86 (t, *J* = 7.4 Hz, 3H), 0.78 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 182.3, 142.3, 141.5, 113.1, 112.9, 52.1, 51.3, 49.7, 49.5, 47.0, 47.0, 42.6, 27.4, 23.0, 11.9, 10.2. **HRMS (ESI–):** Calcd. for $C_{16}H_{23}O_2Na$. $[M-H]^-$ 247.1693. Found: 247.1705.



28

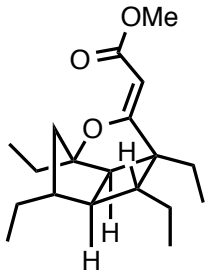
Lactone 28. Without precautions to exclude moisture or air, a 1.5 dram vial containing diene **27** (45 mg, 181 mmol) and a stir bar was charged sequentially with White's catalyst (18 mg, 36 mmol), Cr(salen)Cl (23 mg, 36 mmol), and *p*-benzoquinone (40 mg, 362 mmol). To this mixture was added dioxane (1.8 mL) down the side of the vial, followed by H_2O (33 μL). The reaction was then sealed and placed in a 60 ºC aluminum heat block. After 24 h, the reaction was removed and allowed to cool to room temperature. The crude reaction was diluted with diethyl ether (10 mL) and washed sequentially with sodium metabisulfite (sat. aq. soln., 2 mL), sodium thiosfulate (sat. aq. soln., 2 mL), 1N HCl (2 mL), and brine (2 mL). The organic layer was then dried over $MgSO_4$ and concentrated *in vacuo* to give a maroon slurry, which was adsorbed onto silica gel for purification via flash column chromatography (0 to 1 to 2 to 3 to 4% ethyl acetate/hexanes). The fractions containing lactone **28** were combined and concentrated to

give **28** as a yellow oil (31 mg, 70%). **IR (neat):** 2962, 2929, 1760, 1641, 1460, 1312, 1204, 1182, 1114, 990, 975, 944 **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.87 (dd, *J* = 17.2, 10.9 Hz, 1H), 5.75 (ddd, *J* = 17.5, 10.1, 7.6 Hz, 1H), 5.35 (dd, *J* = 17.1, 1.1 Hz, 1H), 5.15 (dd, *J* = 10.9, 1.1 Hz, 1H), 5.07-4.93 (m, 2H), 2.87 (d, *J* = 8.6 Hz, 1H), 2.82 (m, 1H), 2.32 (dd, *J* = 13.7, 6.1 Hz, 1H), 2.12-2.04 (m, 1H), 1.97 (dt, *J* = 11.4, 3.7 Hz, 1H), 1.81-1.64 (m, 3H), 1.64-1.56 (m, 1H), 1.35-1.25 (m, 1H), 0.86 (t, *J* = 7.2 Hz, 3H), 0.73 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 182.2, 139.6, 137.5, 114.6, 114.3, 93.6, 52.0, 51.1, 50.2, 49.6, 47.6, 46.7, 24.4, 21.4, 11.1, 9.2 **HRMS (ESI+):** Calcd. for $C_{16}H_{22}O_2Na$. $[M+Na]^+$ 269.1512. Found: 269.1515.



SI-10

*In some instances a byproduct, presumed to be **SI-10**, would form resulting in a decreased yield of lactone **28**. However, we found that increasing the amount of Cr(salen)Cl from 20 mol% to 50 mol% in the above reaction deterred the formation of this byproduct to yield lactone **28** in similar yields as above.



(±)-hippolachnin A

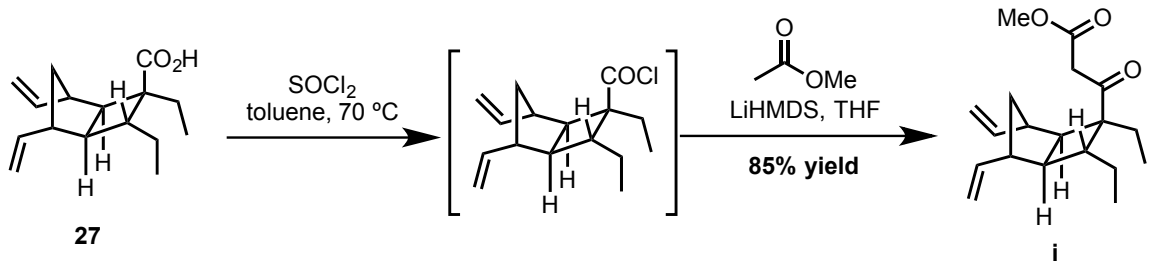
Hippolachnin A (1): An oven dried 10 mL round bottom flask equipped with a stir bar was charged with terahydrofuran (2.8 mL) and cooled to -78 °C. To this solution was added *t*-BuLi (1.3 M in pentanes, 0.65 mL, 0.852 mmol) to give a bright yellow solution. A solution of *t*-BuOAc (96 μL, 0.710 mmol) in tetrahydrofuran (1.3 mL) was added dropwise, slowly, to the yellow solution. The resulting enolate solution was allowed to stir for 30 min at -78 °C, then removed from the bath and allowed to warm to room temperature over an additional 30 min.

An oven dried 25mL round bottom flask equipped with a stir bar was charged with lactone **28** (35.0 mg, 0.142 mmol) as a solution in tetrahydrofuran (0.95 mL) and cooled to -78 °C. To this was added, slowly dropwise over 5 min, the aforementioned enolate solution. The resulting reaction mixture was stirred at -78 °C for 2 h, then placed in a 0 °C bath for an additional 2 h. The reaction was then quenched with 6N HCl (10 mL) at 0 °C with vigorous stirring and allowed to warm to room temperature. The aqueous layer was extracted with diethyl ether (3 x 5 mL). The combined extracts were washed with

brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was loaded with minimal dichloromethane onto a silica gel column for purification via flash column chromatography (0 to 1 to 2% ethyl acetate/hexanes). The fractions containing either olefin isomer of product were combined and concentrated to give a yellow oil (17.8 mg, 36%, 66% brsm). The fractions containing unreacted starting material were concentrated to give **28** (15.9 mg, 45%).

The combined olefin isomers were taken up in tetrahydrofuran (5.2 mL) and transferred to a 10 mL round bottom flask equipped with a stir bar. To this solution was added 10% Pd/C (1.6 mg, 1.55 umol). The resulting black suspension was purged with hydrogen gas, then left under 1 atm of hydrogen via balloon for 3 h. The crude reaction was passed through a plug of celite and eluted with diethyl ether. The combined eluent was concentrated *in vacuo* to give **29** as a clear, colorless oil (15.4 mg, 86%).

Vinylogous carbonate **29** (4.8 mg, 0.014 mmol) was dissolved in dry methanol (0.7 mL) in a 1.5 dram vial containing a stir bar. To this solution was added chlorotrimethylsilane (52 uL, 0.413 mmol). The vial was sealed and placed in a 60 ºC aluminum heat block for 18.5 h, then removed and allowed to cool to rt. With vigorous stirring, Na_2CO_3 (46 mg, 0.440 mmol) was added, followed by H_2O (8 uL), then dichloromethane (2 mL). After 30 min, $MgSO_4$ was added, and the suspension was stirred vigorously for an additional 30 min, then filtered through a plug of celite and eluted with dichloromethane. The combined eluent was concentrated *in vacuo* to give a brown oil. Purification was carried out as previously described (see Experimental Section b.) to give **1** as a yellow oil (2.0 mg, 47%), 15% over 3 steps or 26% based on recovered starting material over 3 steps. Characterization data matched what was reported previously.



β-ketoester (i): Two 1.5 dram vials were each charged with acid **27** (25 mg, 1.0 mmol), toluene (1 mL), and $SOCl_2$ (75 µL, 1.0 mmol). The vials were then sealed and placed in a 70 ºC aluminum heat block. After 5 h, the vials were removed from the heat block and allowed to cool to rt. The contents were combined, concentrated *in vacuo*, stripped with hexanes (3 x 1mL), and further dried on high vacuum. Meanwhile, an oven dried 10 mL round bottom flask equipped with a stir bar was charged with tetrahydrofuran (1.1 mL) and LiHMDS (1.0 M in THF, 2.0 mL, 2.0 mmol) and cooled to -78 ºC. Methyl acetate (0.16 mL, 2.0 mL) was added to the solution at -78 ºC and the resulting reaction mixture was allowed to stir at -78 ºC. After 30 min, the previously generated acid chloride (54 mg, 2.0 mmol) as a solution in tetrahydrofuran (0.8 mL) was added dropwise to the enolate solution, followed by a rinse of tetrahydrofuran (0.1 mL). Allowed to stir as the cold bath evaporated and warmed to rt. After 16 h, the reaction was cooled to 0 ºC and quenched with water (5 mL). The aqueous layer was extracted with diethyl ether (3x

5mL) and the combined extracts were washed with brine (1x 5mL), dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow oil. The oil was loaded with minimal hexanes onto a silica gel column for purification via flash column chromatography (0 to 1 to 2 % ethyl acetate/hexanes). The fractions containing product were combined and concentrated *in vacuo* to give β-ketoester **i** as a yellow oil (52.2 mg, 85%). **IR (neat):** 3077, 2958, 2931, 2874, 1750, 1703, 1639, 1617, 1443, 1297, 1263, 1234, 1150, 994, 874. **^{1}H NMR (400 MHz, $CDCl_3$):** [mixture of keto and enol tautomers; 4.3:1] δ 11.99 (s, 0.2 H), 5.91-5.85 (m, 1H), 5.78-5.64 (m, 1H), 5.12-4.83 (m, 4H), 3.74 (d, J = 4.5 Hz, 1.5H), 3.42 (d, J = 1.3 Hz, 2H), 2.71-2.48 (m, 1H), 2.48-2.33 (m, 1.7H), 2.17 (q, J = 8.9 Hz, 2H), 2.09-1.97 (m, 2H), 1.91 (dd, J = 14.6, 7.4 Hz, 0.8H), 1.82-1.67 (m, 1.2H), 1.67-1.56 (m, 1H), 1.46-1.27 (m, 2H), 0.95-0.76 (m, 6H). **^{13}C NMR (100 MHz, $CDCl_3$):** [mixture of keto and enol tautomers; 4.3:1] δ 205.7, 182.6, 173.2, 168.1, 142.4, 42.1, 142.0, 142.0, 114.2, 113.2, 113.1, 112.7, 89.1, 56.1, 53.0, 52.5, 52.2, 51.4, 51.2, 51.2, 50.7, 48.5, 48.2, 47.6, 47.0, 46.7, 46.6, 45.4, 43.8, 43.1, 28.7, 27.4, 23.4, 23.3, 12.1, 12.0, 10.1, 9.9 **HRMS (ESI+):** Calcd. for $C_{19}H_{28}O_3Na$. $[M+Na]^+$ 327.1931. Found: 327.1936.

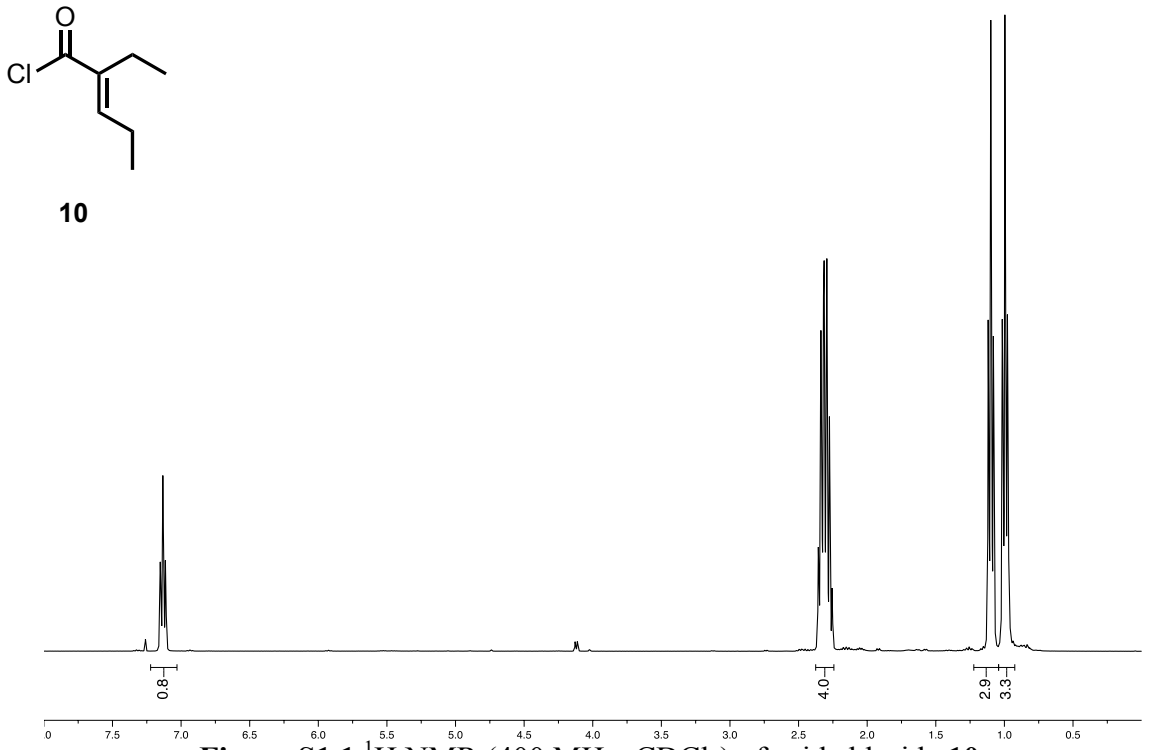


Figure S1.1 ^{1}H NMR (400 MHz, $CDCl_3$) of acid chloride **10**

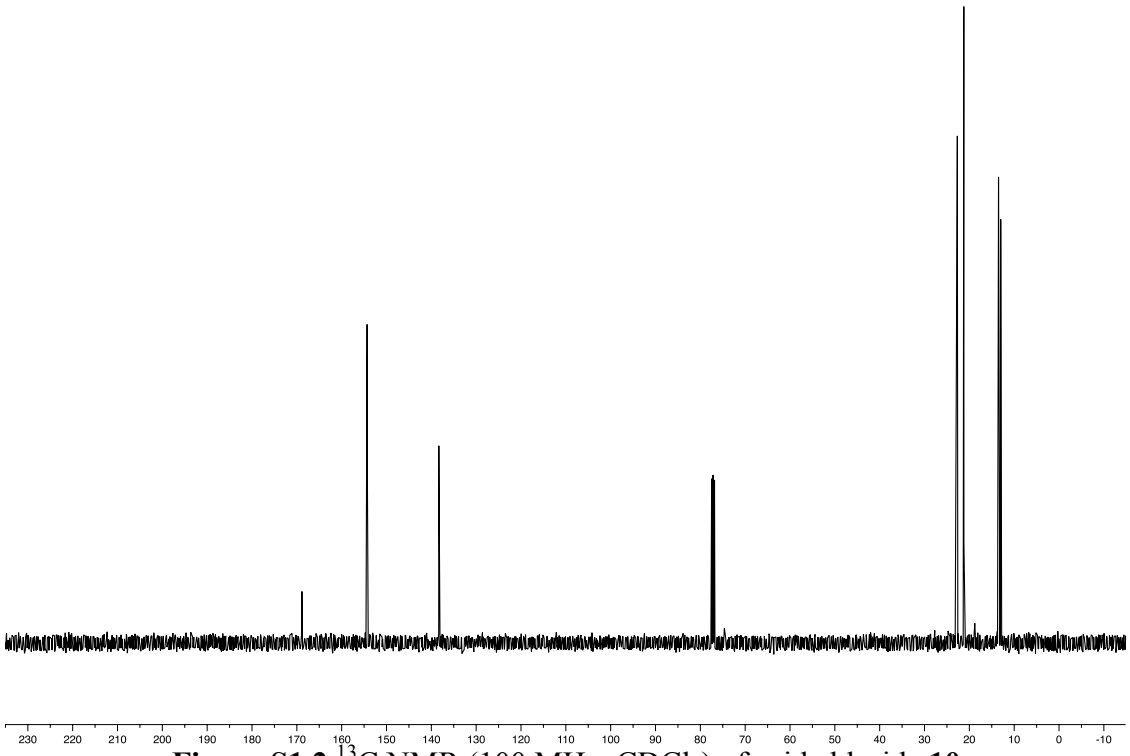
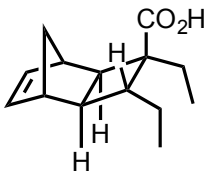


Figure S1.2 ^{13}C NMR (100 MHz, $CDCl_3$) of acid chloride **10**



14b

Figure S2.1 ^{1}H NMR (400 MHz, $CDCl_3$) of acid **14b**

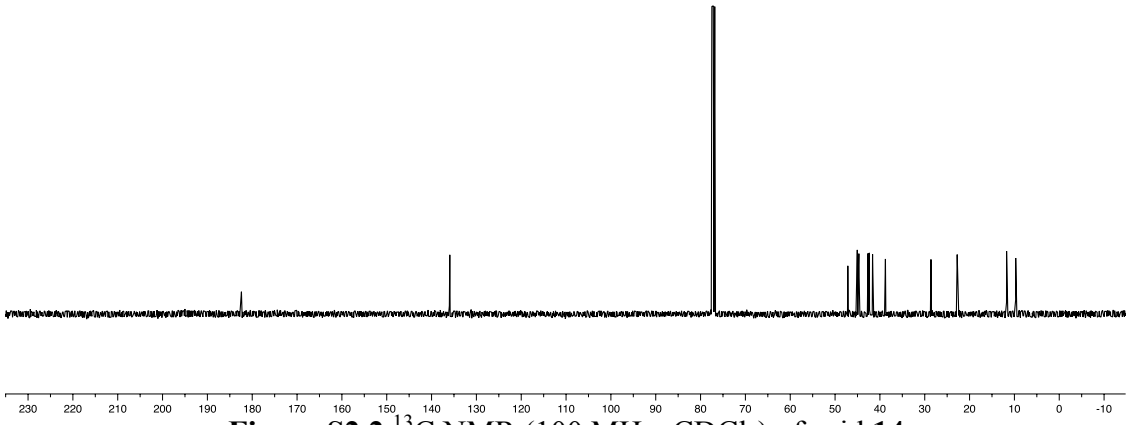
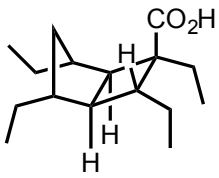


Figure S2.2 ^{13}C NMR (100 MHz, $CDCl_3$) of acid **14**



15

Figure S3.1 ^{1}H NMR (400 MHz, $CDCl_3$) of acid **15**

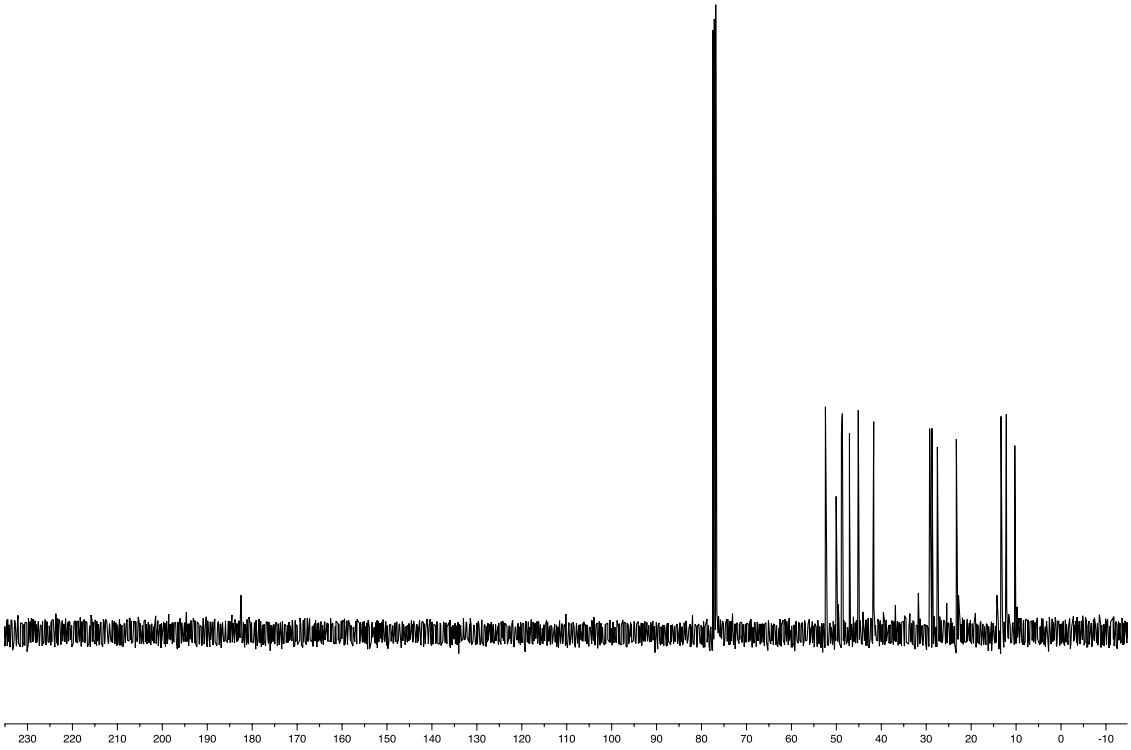
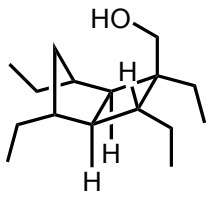


Figure S3.2 ^{13}C NMR (100 MHz, $CDCl_3$) of acid **15**



16

Figure S4.1 ^{1}H NMR (400 MHz, $CDCl_3$) of alcohol **16**

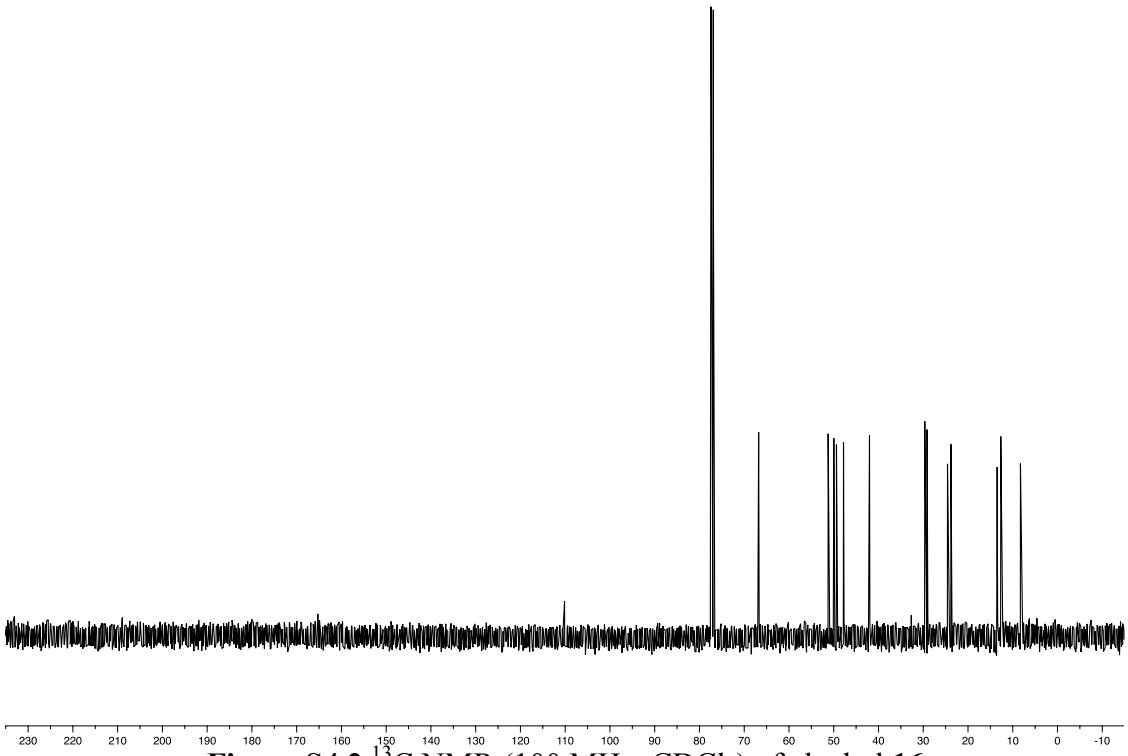
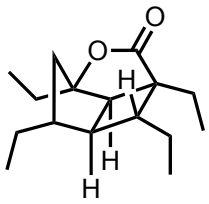


Figure S4.2 ^{13}C NMR (100 MHz, $CDCl_3$) of alcohol **16**



18

Figure S5.1 ^{1}H NMR (400 MHz, $CDCl_3$) of lactone **18**

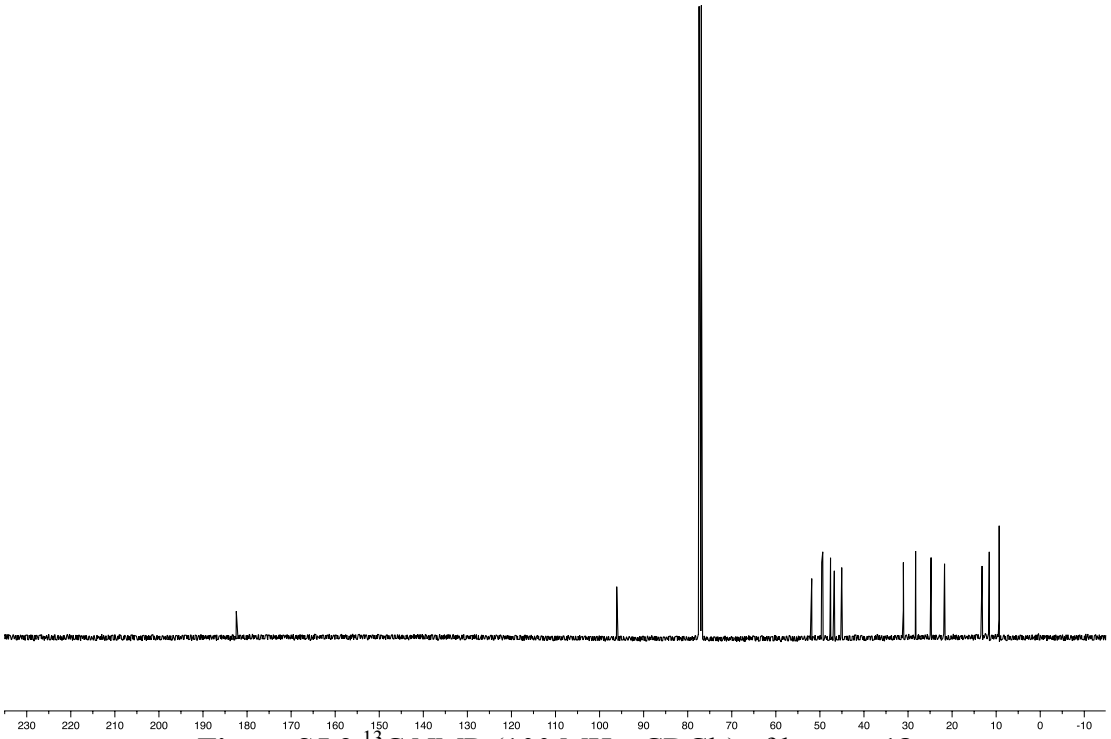
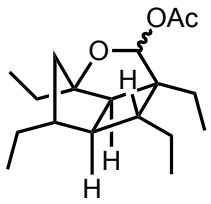


Figure S5.2 ^{13}C NMR (100 MHz, $CDCl_3$) of lactone **18**



19

Figure S6.1 ^{1}H NMR (400 MHz, $CDCl_3$) of acetal **19**

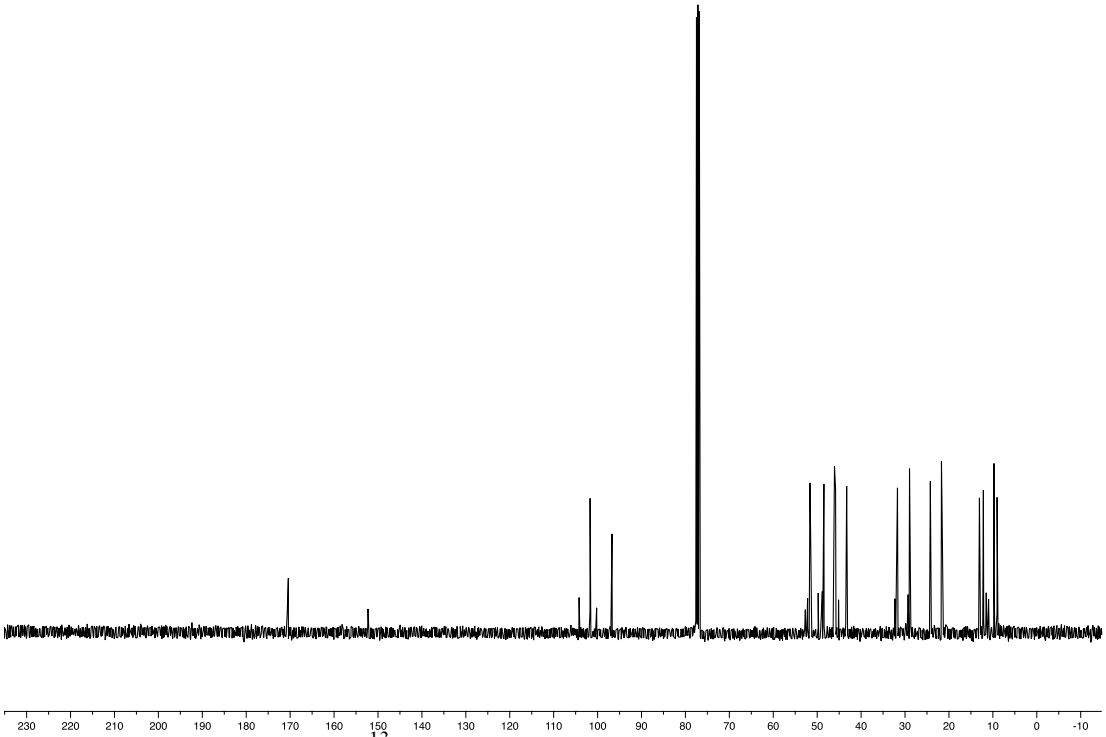
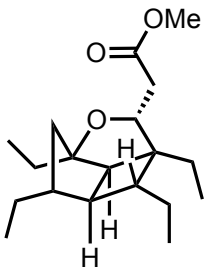


Figure S6.2 ^{13}C NMR (100 MHz, $CDCl_3$) of acetal **19**



21

Figure S7.1 ^{1}H NMR (400 MHz, $CDCl_3$) of ester **21**

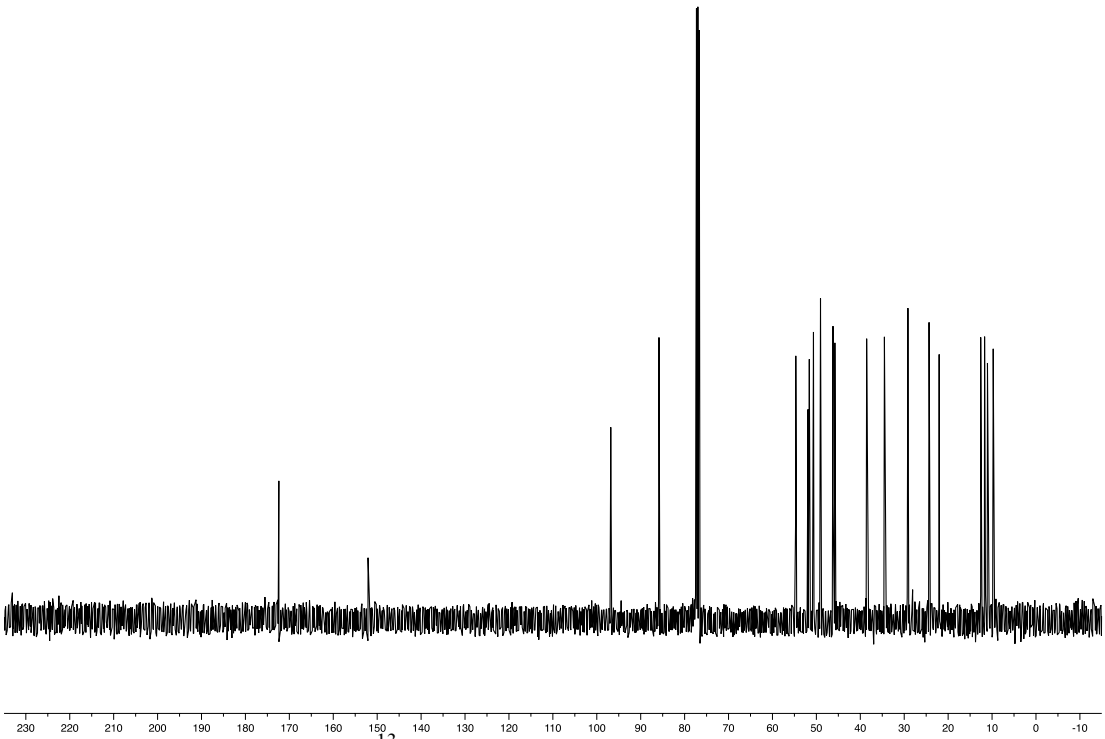


Figure S7.2 ^{13}C NMR (100 MHz, $CDCl_3$) of ester **21**

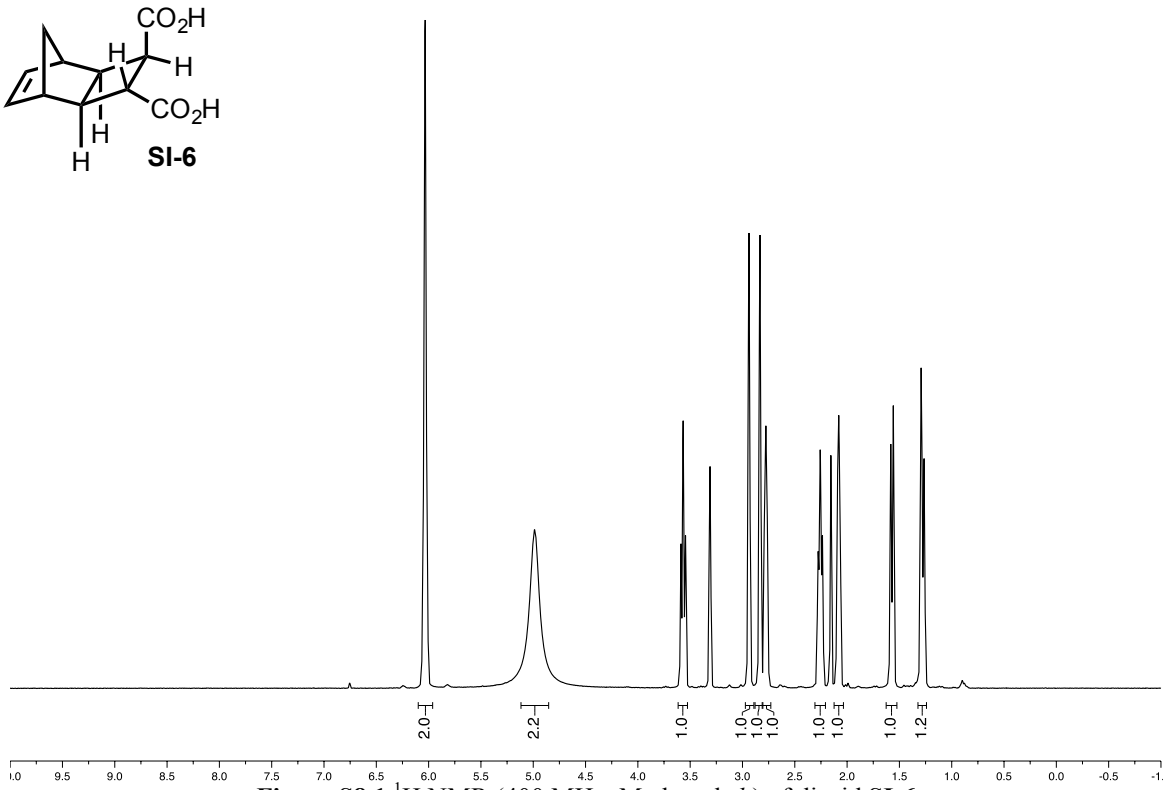


Figure S8.1 ^{1}H NMR (400 MHz, Methanol-d_4) of diacid **SI-6**

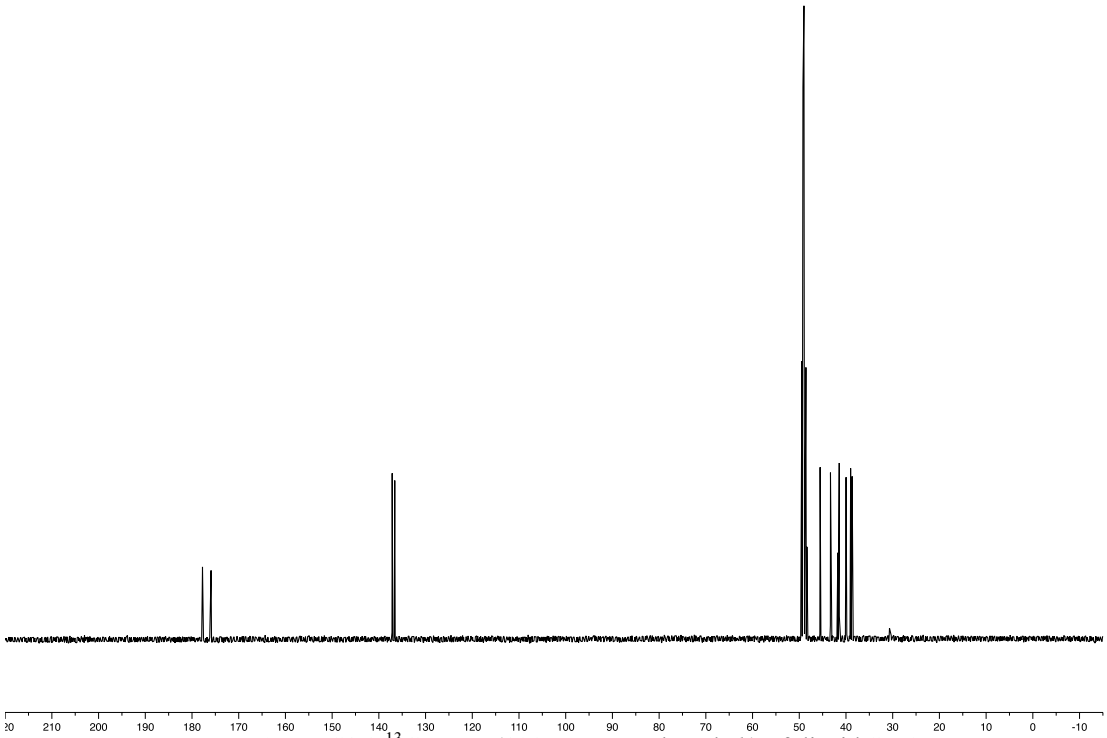
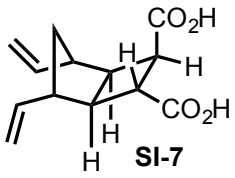


Figure S8.2 ^{13}C NMR (101 MHz, Methanol-d_4) of diacid **SI-6**



SI-7

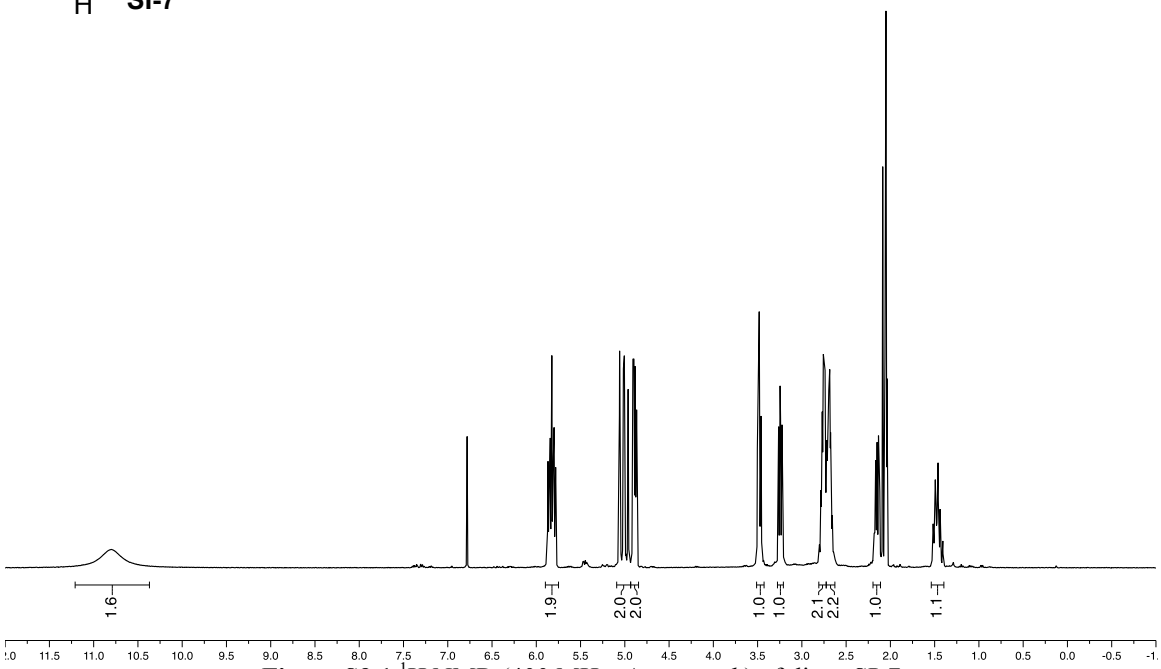


Figure S9.1 ^{1}H NMR (400 MHz, Acetone-d_6) of diene **SI-7**

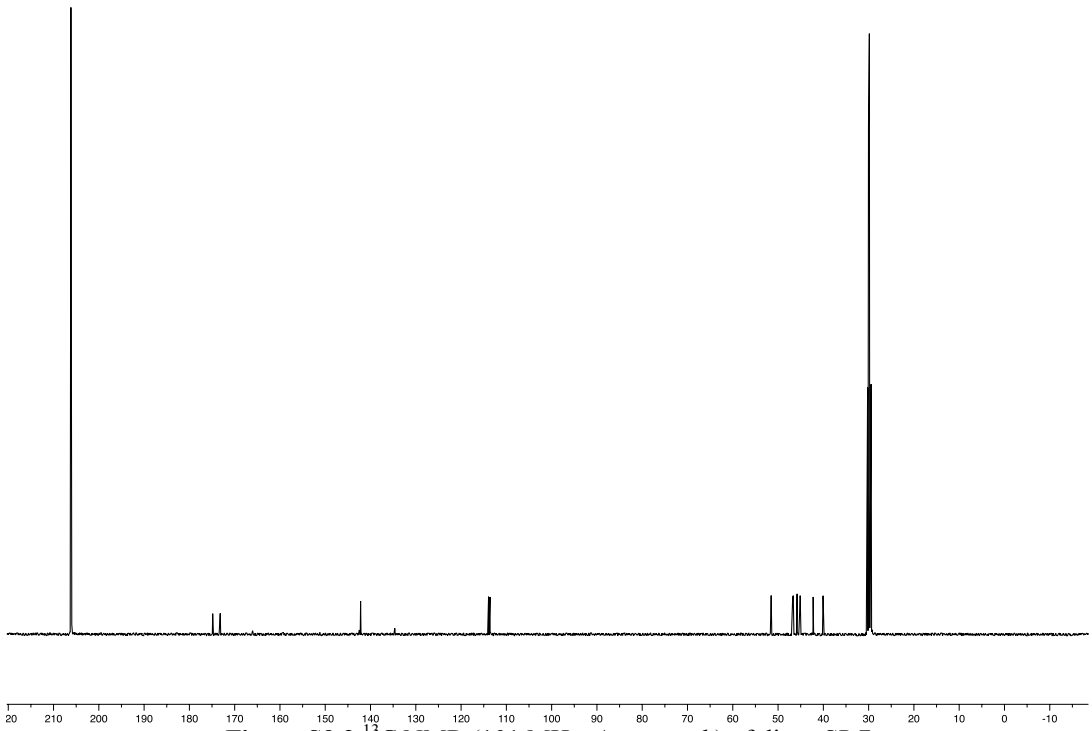
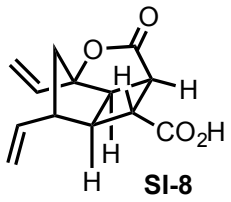


Figure S9.2 ^{13}C NMR (101 MHz, Acetone-d_6) of diene **SI-7**



SI-8

Figure S10.1 ^{1}H NMR (400 MHz, d^{6}-acetone) of lactone **SI-8**

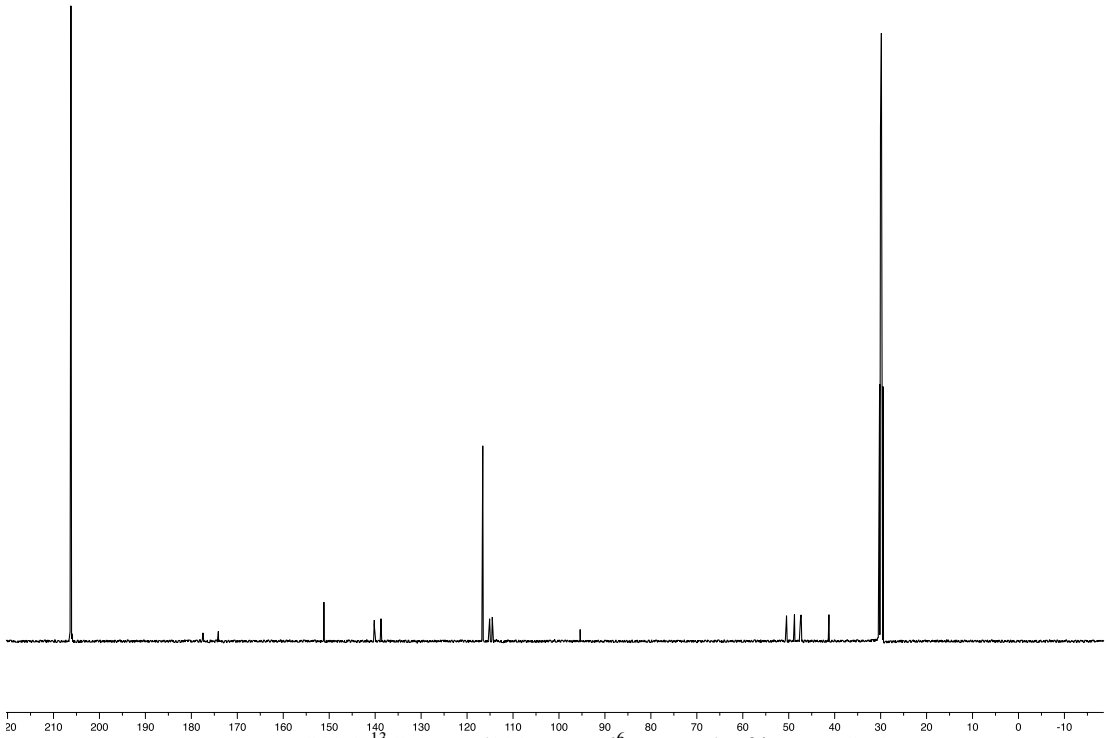


Figure S10.2 ^{13}C NMR (101 MHz, d^{6}-acetone) of lactone **SI-8**

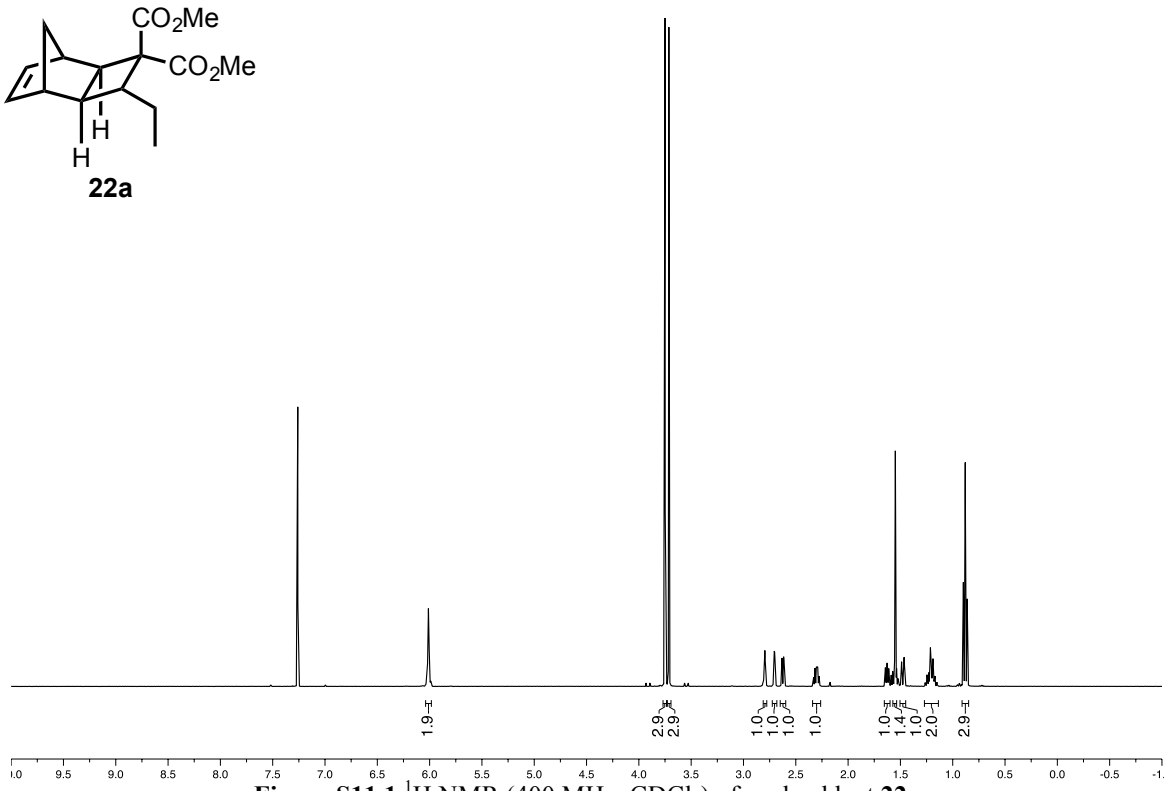


Figure S11.1 ^{1}H NMR (400 MHz, $CDCl_3$) of cycloadduct **22a**

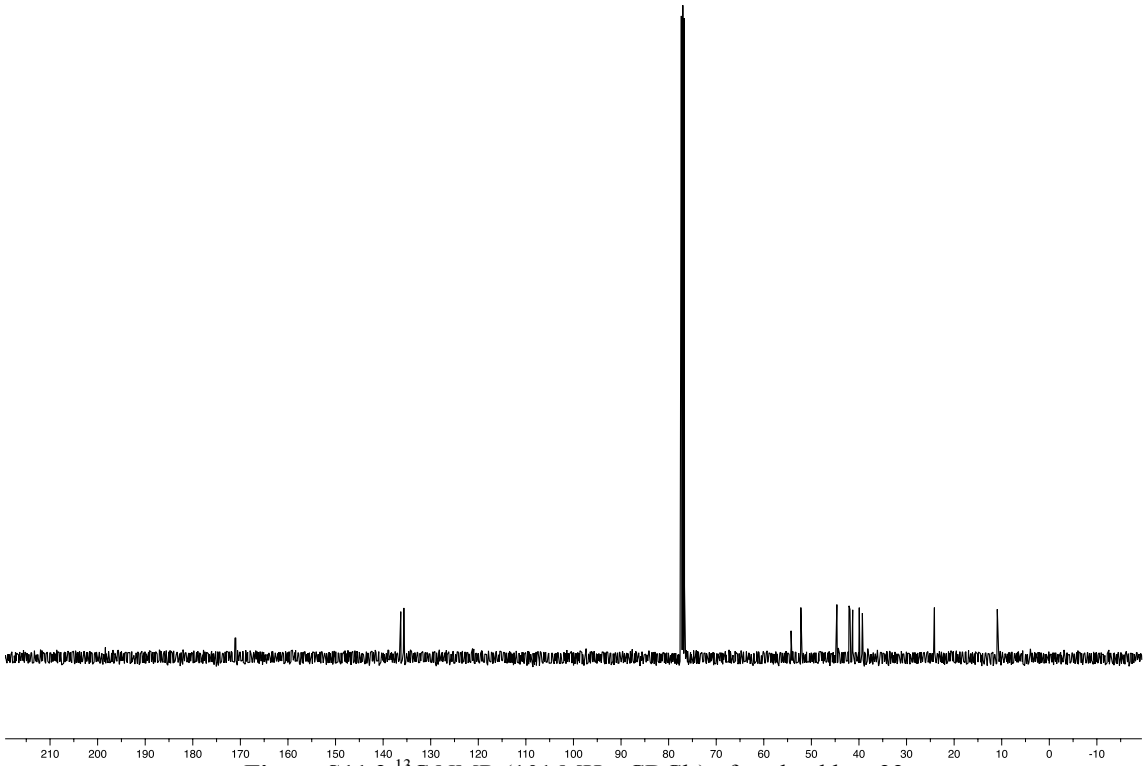
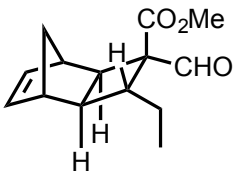


Figure S11.2 ^{13}C NMR (101 MHz, $CDCl_3$) of cycloadduct **22a**



23

Figure S12.1 ^{1}H NMR (400 MHz, $CDCl_3$) of aldehyde **23**

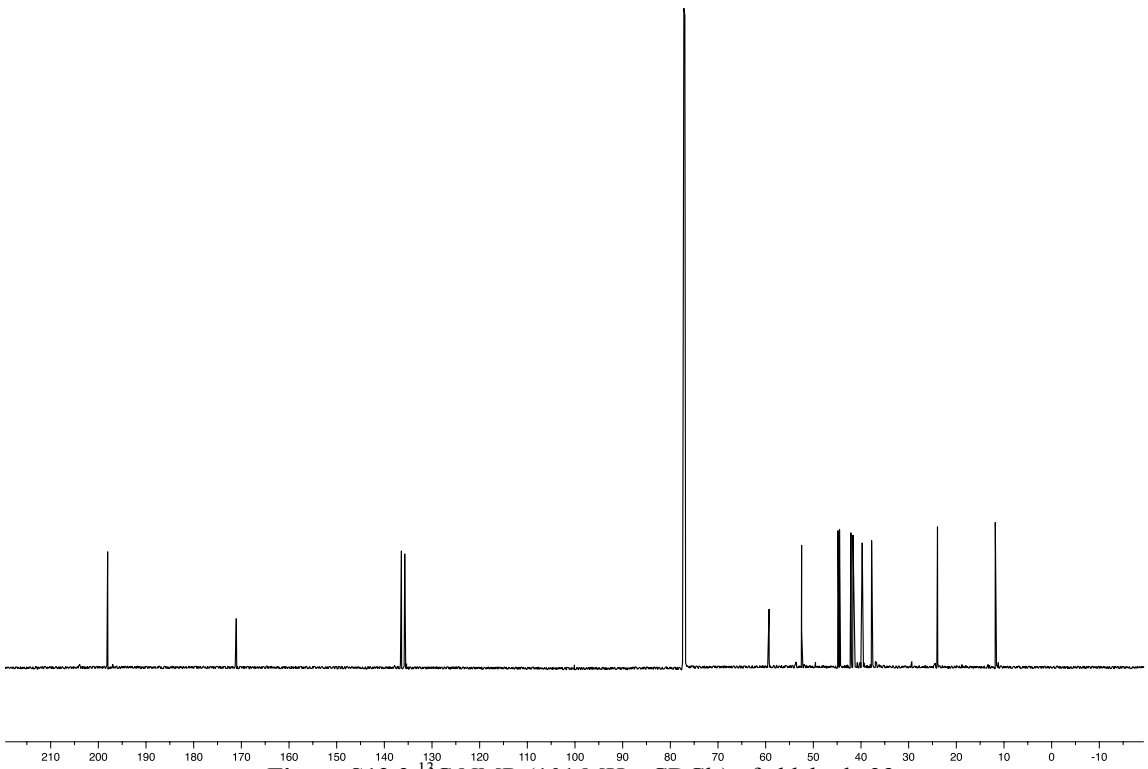
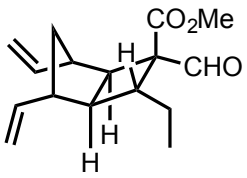


Figure S12.2 ^{13}C NMR (101 MHz, $CDCl_3$) of aldehyde **23**



24

Figure S13.1 ^{1}H NMR (400 MHz, $CDCl_3$) of diene **24**

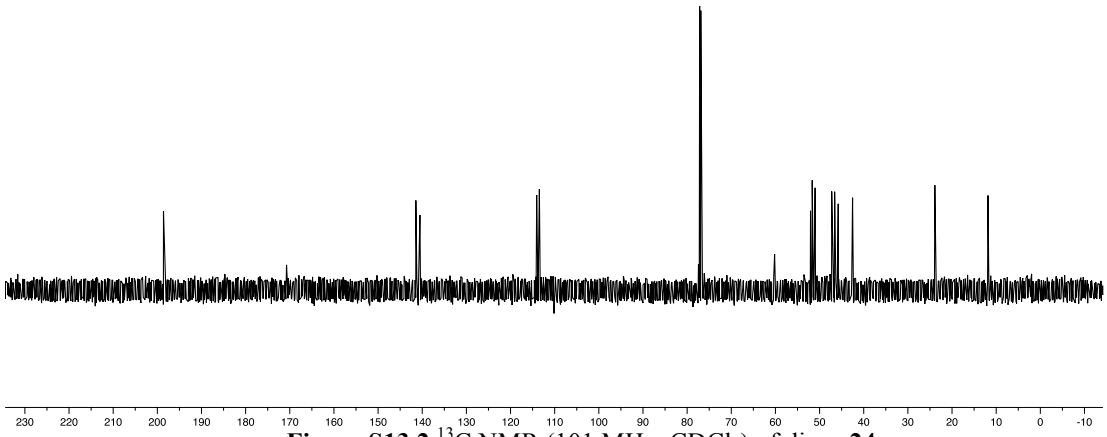
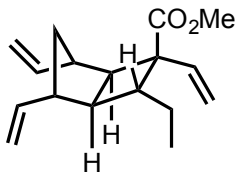


Figure S13.2 ^{13}C NMR (101 MHz, $CDCl_3$) of diene **24**



SI-9

Figure S14.1 ^{1}H NMR (400 MHz, $CDCl_3$) of triene **SI-9**

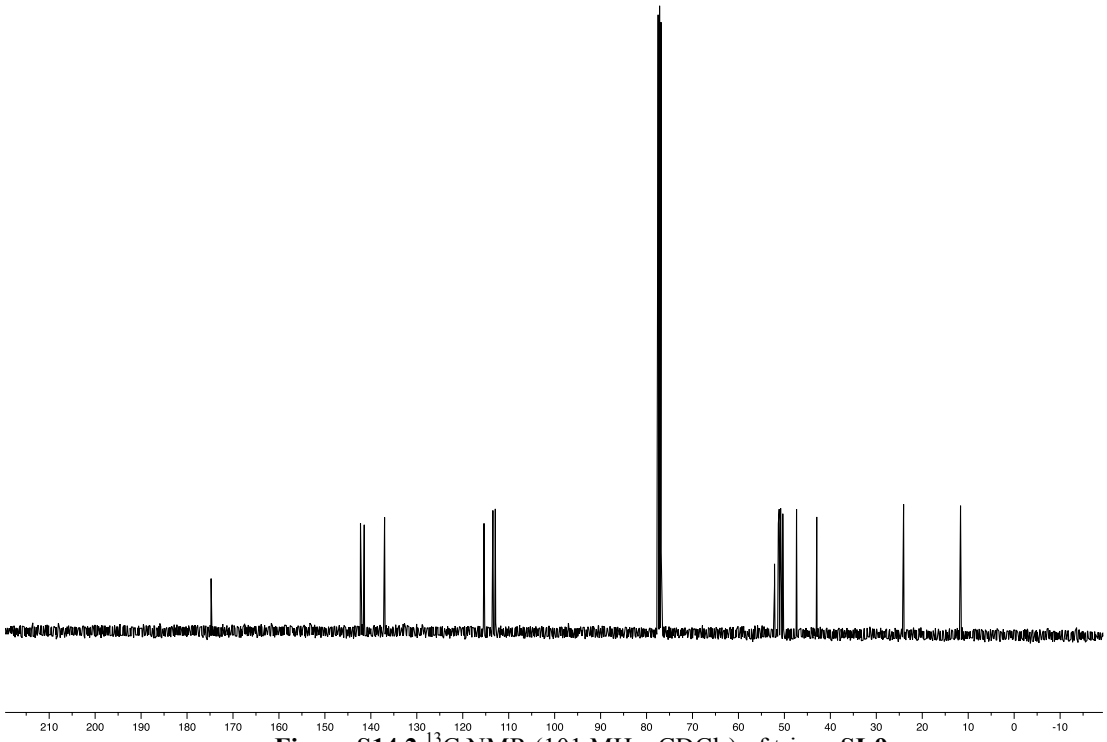
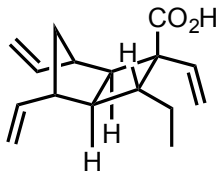


Figure S14.2 ^{13}C NMR (101 MHz, $CDCl_3$) of triene **SI-9**



25

Figure S15.1 ^{1}H NMR (400 MHz, $CDCl_3$) of acid **25**

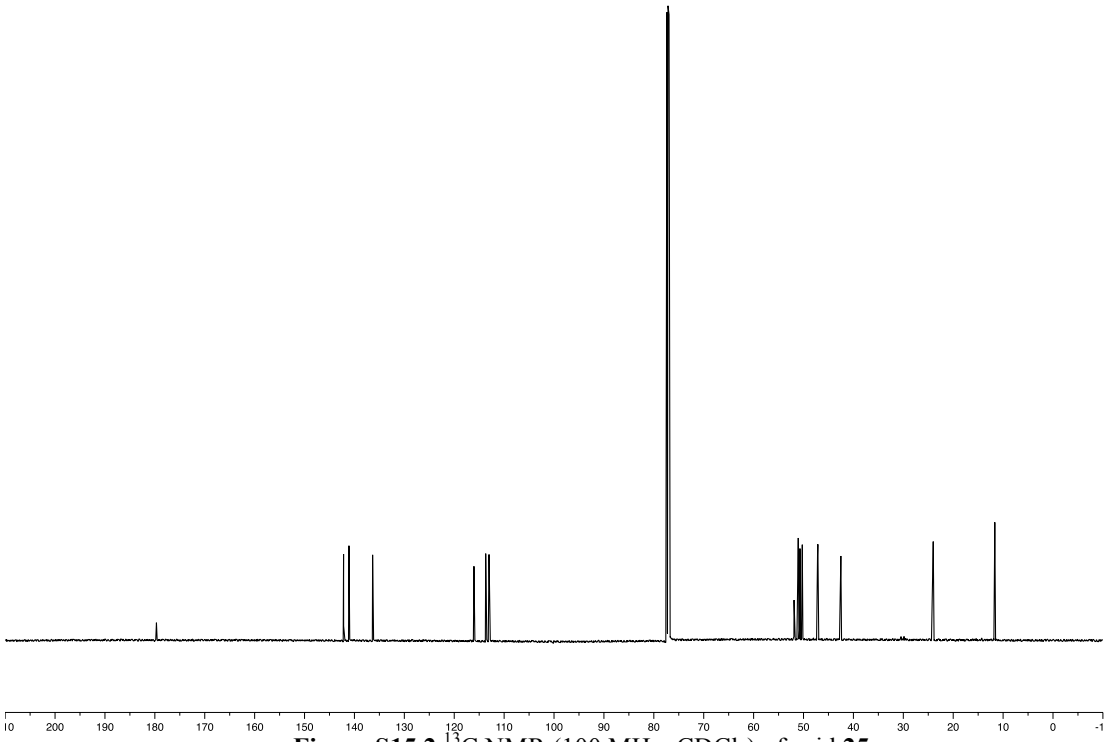


Figure S15.2 ^{13}C NMR (100 MHz, $CDCl_3$) of acid **25**

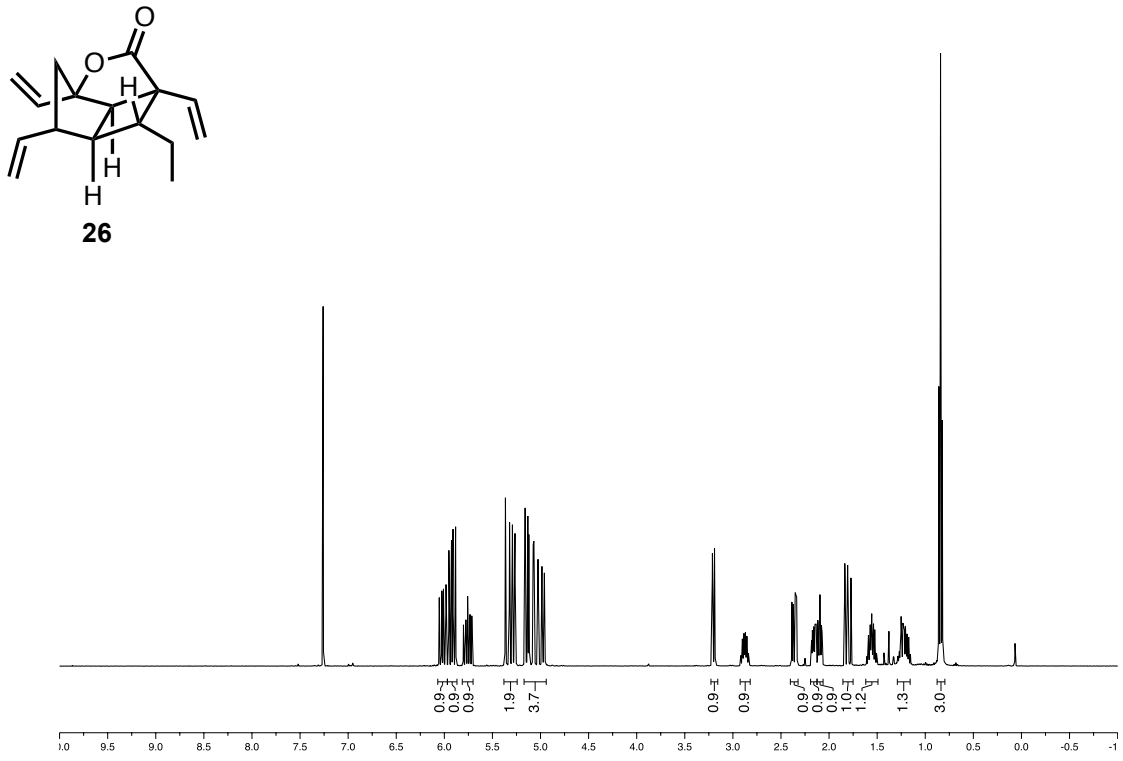


Figure S16.1 ^{1}H NMR (400 MHz, $CDCl_3$) of lactone **26**

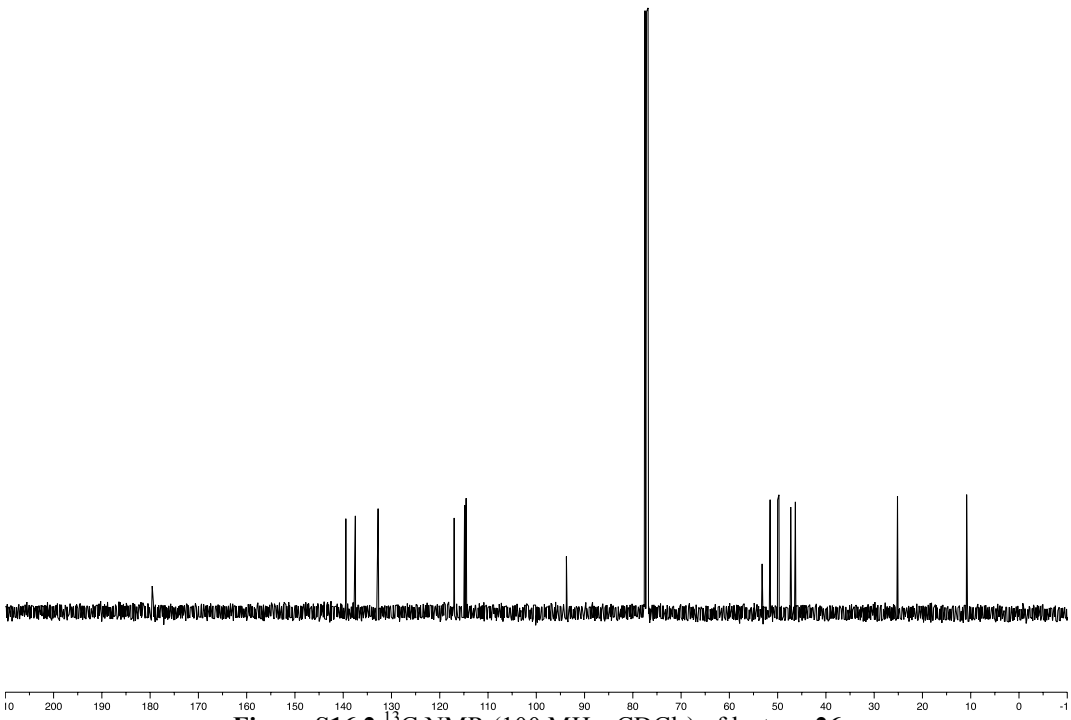
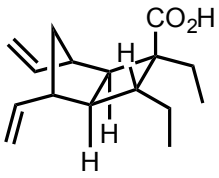


Figure S16.2 ^{13}C NMR (100 MHz, $CDCl_3$) of lactone **26**



27

Figure S17.1 ^{1}H NMR (400 MHz, $CDCl_3$) of acid **27**

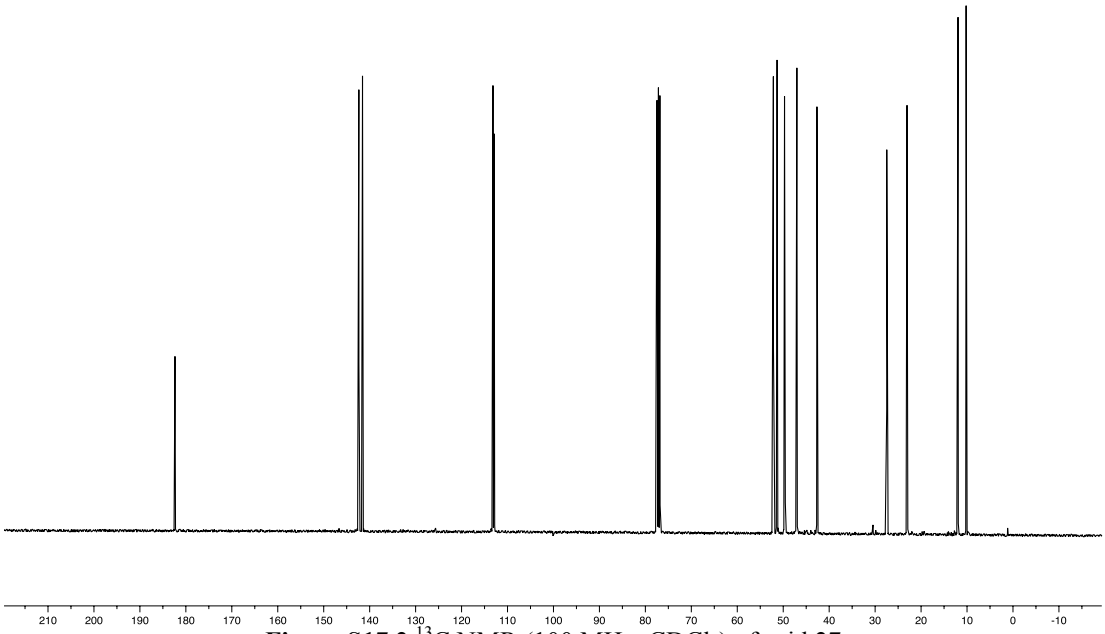
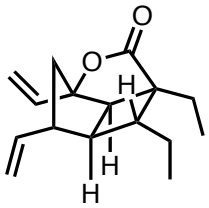


Figure S17.2 ^{13}C NMR (100 MHz, $CDCl_3$) of acid **27**



28

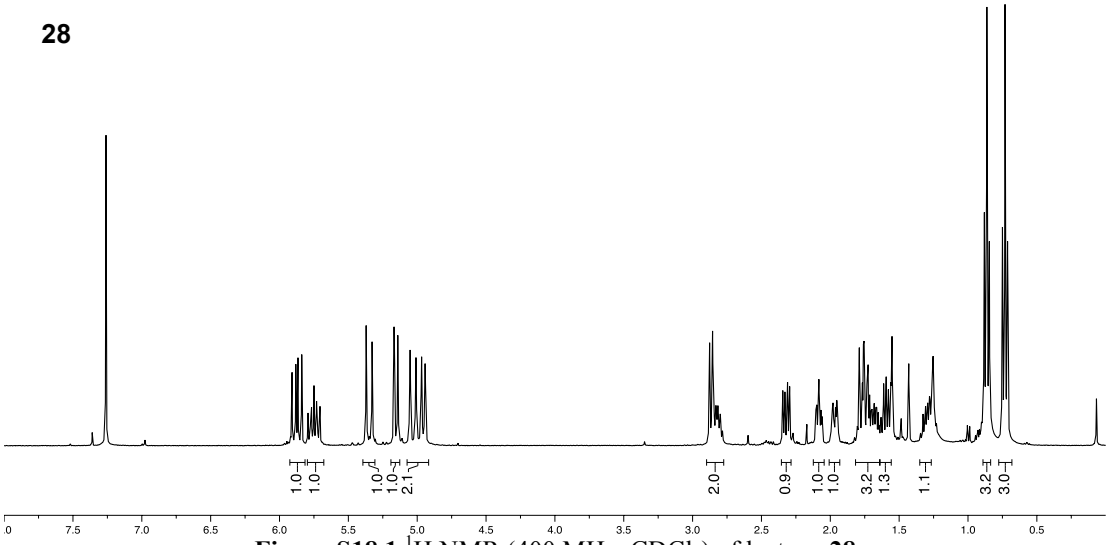


Figure S18.1 ^{1}H NMR (400 MHz, $CDCl_3$) of lactone **28**

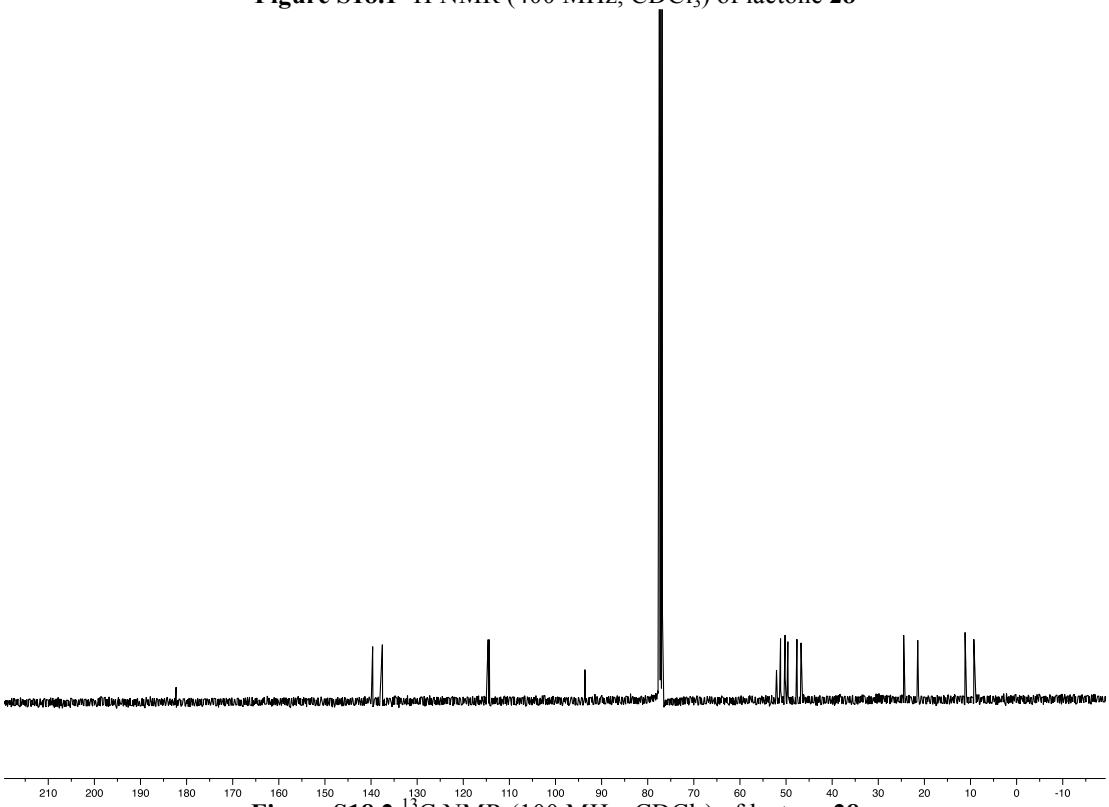
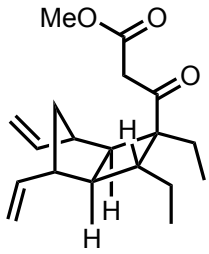


Figure S18.2 ^{13}C NMR (100 MHz, $CDCl_3$) of lactone **28**



i

Figure S19.1 ^{1}H NMR (400 MHz, $CDCl_3$) of beta-ketoester **i**

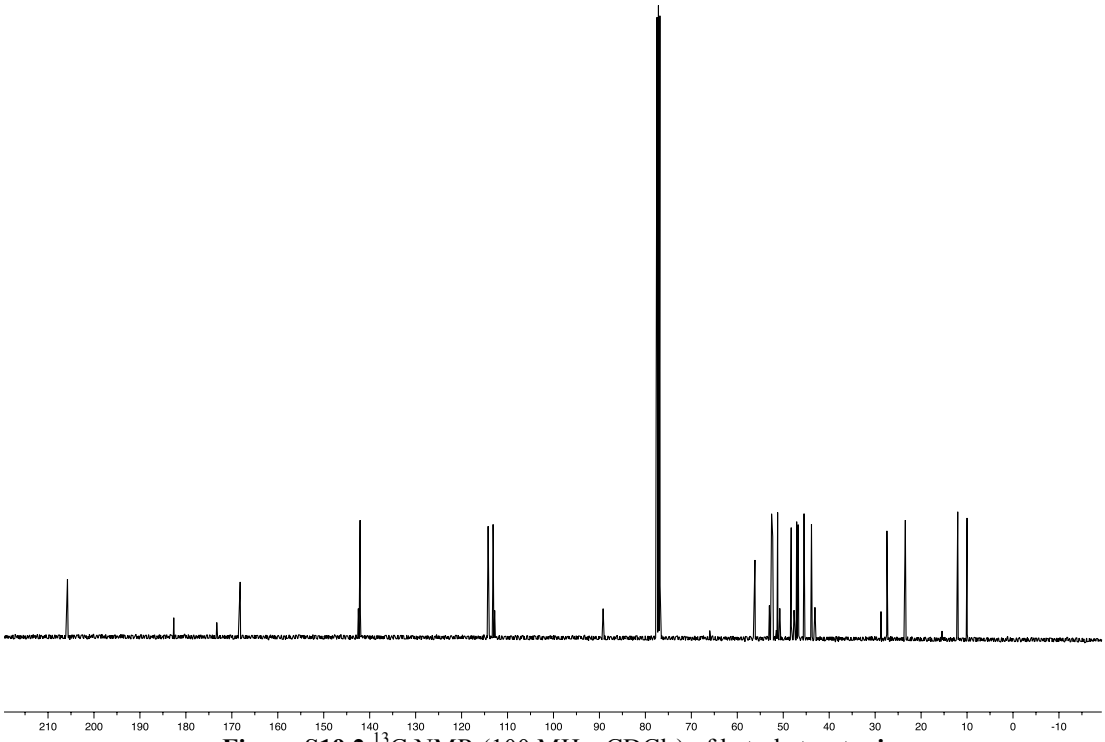


Figure S19.2 ^{13}C NMR (100 MHz, $CDCl_3$) of beta-ketoester **i**

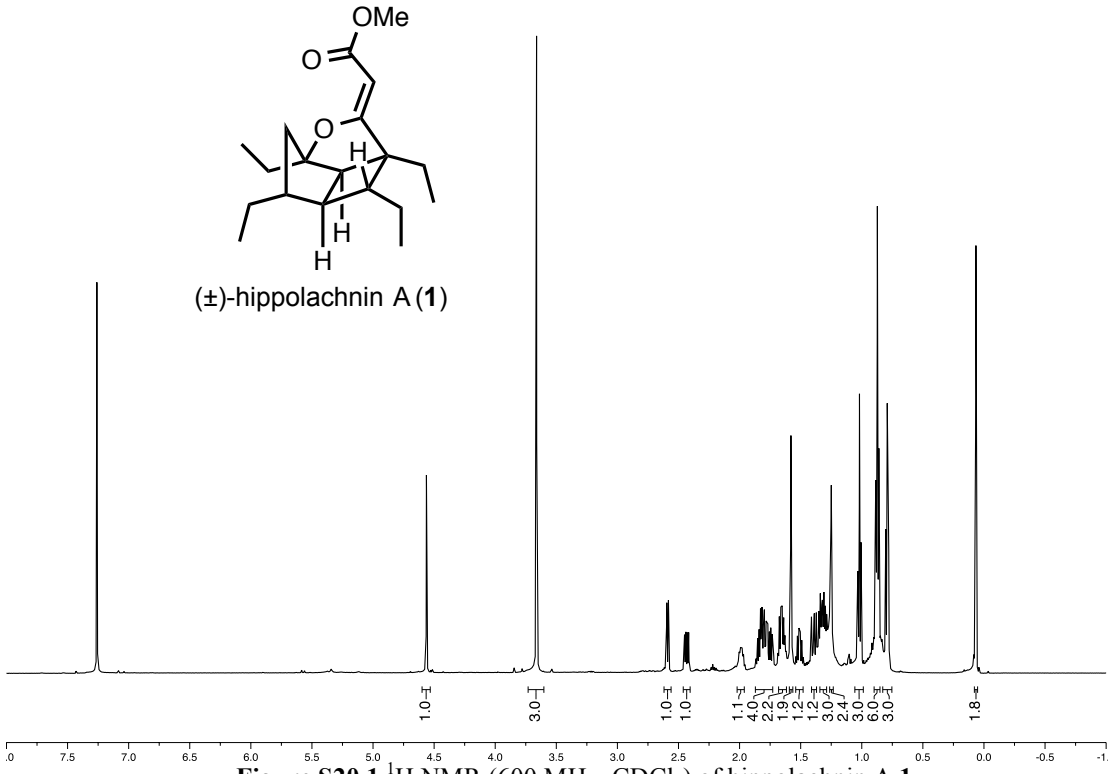


Figure S20.1 ^{1}H NMR (600 MHz, $CDCl_3$) of hippolachnin A **1**

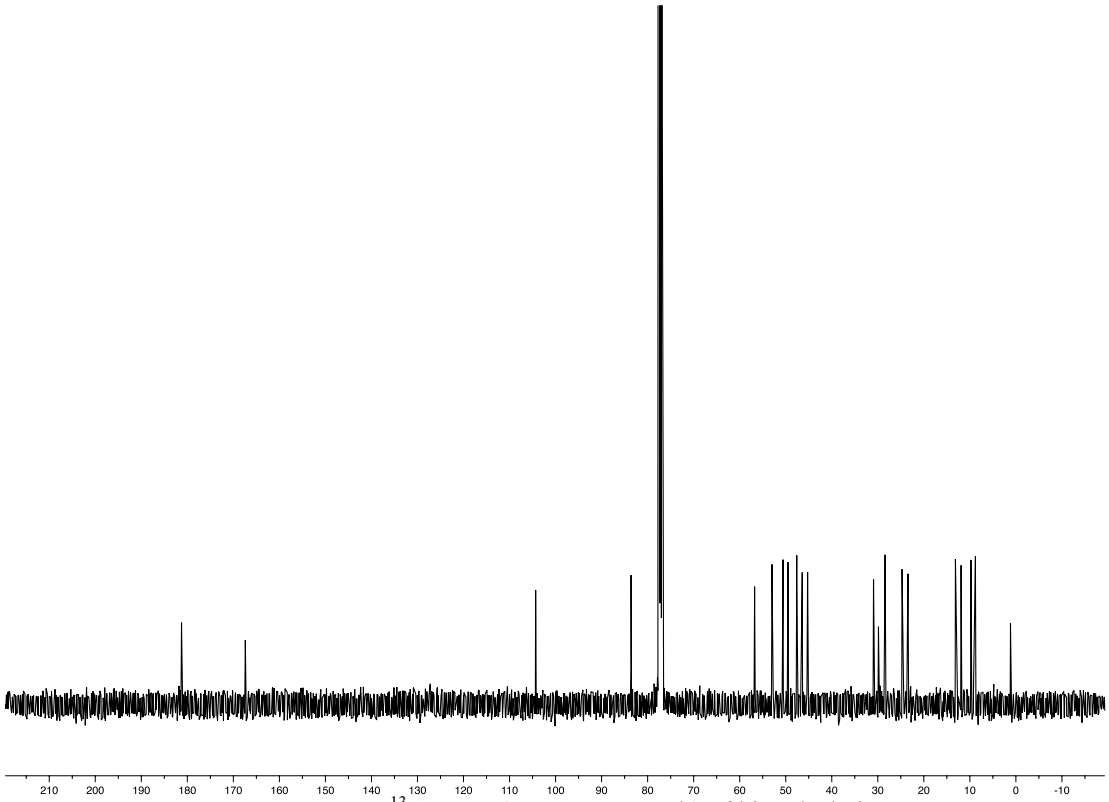


Figure S20.2 ^{13}C NMR (101 MHz, $CDCl_3$) of hippolachnin A **1**

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