Supporting Information

Application of Ru-Catalyzed [5+2] Cycloaddition for the Total Synthesis of (+)-Frondosin A

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Experimental Procedures:

General:

All reactions were run under an atmosphere of nitrogen unless otherwise indicated. Anhydrous solvents were transferred by an oven-dried syringe or cannula. Flasks were flame-dried under vacuum and cooled under a stream of nitrogen or argon. Diisopropylamine, diisopropylethylamine, dimethylsulfoxide, N,N-dimethylformamide, N,N-dimethylacetamide, were distilled from calcium hydride. Acetonitrile, toluene, diethyl ether, benzene, pyridine, and dichloromethane were purified with a Solv-Tek solvent purification system by passing through a column of activated alumina. Tetrahydrofuran (THF) and dimethoxyethane (DME) were distilled from sodium benzophenone ketyl. Acetone was distilled from calcium sulfate, and hexane was distilled from sodium. Methanol was distilled from magnesium methoxide.

Analytical thin layer chromatography (TLC) was carried out using 0.2 mm commercial silica gel plates (DC-Fertigplatten Krieselgel 60 F254). Preparative

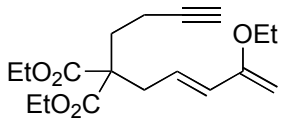
column chromatography employing silica gel was performed according to the method of Still. Solvents for chromatography are listed as volume: volume ratios.

Melting points were determined on a Thomas-Hoover melting point apparatus in open capillaries and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1420 spectrophotometer. Absorbance frequencies are reported in reciprocal centimeters (cm^{-1}). Elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona. High resolution mass spectra (HRMS) were obtained from the Mass Spectrometry Regional Center of the University of California-San Francisco on a Kratos MS-90 mass spectrometer with an ionizing current of 98 A and an ionizing voltage of 79 eV and reported as m/e (relative intensity). Accurate masses are reported for the molecular ion (M+) or a suitable fragment ion. Low resolution CI mass spectral data was obtained using an AX-505H mass spectrometer (JEOL, USA, Inc.).

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded using a Varian UI-500 (500 MHz), Varian XL-400 (400 MHz), Varian Gemini 300 (300 MHz), or Varian Gemini 200 (200 MHz) spectrometer. Chemical shifts are reported in _ units, part per million (ppm) downfield from tetramethylsilane (TMS) or in ppm relative to the singlet at 7.24 ppm for deuterochloroform. Coupling constants are reported in Hertz (Hz). The following abbreviations are used: s, singlet, d, doublet, t, triplet, q, quartet, m, multiplet.

Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded using a Varian UI-500 (125 MHz), Varian XL-400 (100 MHz), Varian Gemini 300 (75 MHz), or Varian Gemini 200 (50 MHz) spectrometer. Chemical shifts are reported in _ units, part per million (ppm) relative to the center line of the triplet at 77.00 ppm for deuterochloroform. ^{13}C NMR spectra were routinely run with broadband decoupling.

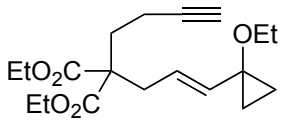
Optical rotation data was obtained with a Jasco DIP-360 digital polarimeter at the sodium D line (589 nm) in the solvent and concentration indicated.



2-But-3-ynyl-2-(4-ethoxy-penta-2,4-dienyl)-malonic acid diethyl ester (16)

To a solution of diphenylphosphinoethane (200 mg, 0.5 mmol) and $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (78 mg, 0.21 mmol) in 5 mL THF was added acetate **15** (330 mg, 1.94 mmol) followed by a solution of the sodium salt of malonate **14** [prepared by addition of malonate **14** (428 mg, 2.01 mmol) to a suspension of NaH (80 mg, 2 mmol) in 10 mL THF. The reaction was stirred at rt under argon balloon for 2.5 h. The reaction was then concentrated *in vacuo* and the product purified by flash chromatography (silica gel, 8:1 petroleum ether:ether) to yield 521 mg **16** (81%) as a clear, light yellow oil.

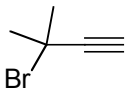
R_f=0.57 (2:1 petroleum ether:ether); IR (thin film, cm^{-1}) 3291, 2981, 1732, 1661, 1585, 1446, 1369, 1183, 1076; ^{1}H NMR (300 MHz, $CDCl_3$): _ 5.87 (m, 1H), 5.11 (m, 1H), 4.16 (m, 4H), 4.03 (s, 1H), 4.00 (s, 1H), 3.74 (q, J=7.1 Hz, 2H), 2.65 (dd, J=9.8, 6.3 Hz, 2H), 2.15 (m, 4H), 1.94 (s, 1H), 1.30 (t, J=7.1 Hz, 3H), 1.23 (t, J=7.1 Hz, 6H) ppm; ^{13}CNMR (75 MHZ, $CDCl_3$): _ 165.9, 152.9, 127.2, 126.0, 118.7, 81.4, 63.9, 58.0, 56.6, 52.2, 31.1, 26.7, 26.5, 9.6, 9.3 ppm; HRMS (EI+) m/z calculated for $C_{18}H_{26}O_5$ $[M]^+$: 322.1780, found 322.1759.



2-But-3-ynyl-2-[3-(1-ethoxy-cyclopropyl)-allyl]-malonic acid diethyl ester (17)

To a solution of diene **16** (200 mg , 0.62 mmol) in 5 mL CH_2Cl_2 under argon was added diethylzinc (650 μL, 1.0 M in hexanes, 0.650 mmol) followed by addition of diiodomethane (192 mg, 1.40 mmol). The reaction was stirred at r.t for 7.25 h. The reaction mixture was poured into 5 mL saturated aqueous NH_4Cl, diluted with 5 mL CH_2Cl_2, and the organic layer washed with 10 mL saturated aqueous $NaHCO_3$ and 10 mL H_2O. The organic layer was dried over $MgSO_4$ and concentrated to yield a light yellow oil. The product was purified by flash chromatography (silica gel, 4:1 petroleum ether:ether) to yield recovered starting material, 75 mg **16** (38%) and 105 mg **17** (50%, 80% BRSM) as a clear, colorless oil.

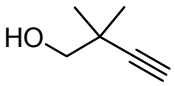
R_f=0.36 (2:1 petroleum ether:ether); IR (thin film, cm^{-1}) 3463, 3289, 2979, 2936, 2907, 1728, 1446, 1391, 1190, 1064, 1020; ^{1}H NMR (300 MHz, $CDCl_3$): _ 5.37 (m, 2H), 4.16 (q, J=7.1 Hz, 4H), 3.42 (q, J=7.1 Hz, 2H), 2.64 (m, 2H), 2.14 (m, 4H), 1.93 (s, 1H), 1.24 (t, J=7.1 Hz, 6H), 1.13 (t, J=7.1 Hz, 3H), 0.94 (m, 2H), 0.61 (m, 2H) ppm; ^{13}CNMR (75 MHZ, $CDCl_3$): _ 170.0, 136.6, 121.0, 70.9, 63.1, 60.1, 57.2, 52.9, 32.1, 26.5, 22.0, 15.2, 14.1, 9.6 ppm; HRMS (EI+) m/z calculated for $C_{17}H_{23}O_5$ $[M - C_2H_5]^+$: 307.1545, found 307.1538.



3-Bromo-3-methyl-but-1-yne

To a flame-dried flask containing 2-methyl-3-butyn-2-ol **24** (21.7 g, 0.258 mol) at 0 °C was added PBr_3 (23 g, 0.085 mol) dropwise over 2 h via syringe pump. The reaction was warmed to rt and stirred an additional 30 min. Distillation of the light green solution with a 10 cm vigreaux column in a 40 °C oil bath (bp 25-30°C/55 mm Hg) yields 13.3 g 3-bromo-3-methyl-but-1-yne (35%, 0.090 mol) as a clear, colorless oil. ^{1}H NMR and IR match the reported data.[1]

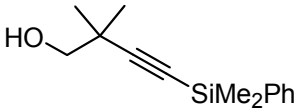
IR (thin film, cm^{-1}) 3298, 2997, 2977, 2928, 1459, 1446, 1368, 1227, 1111; ^1H NMR (300 MHz, $CDCl_3$): _ 2.70 (s, 1H), 2.01 (s, 6H) ppm.



2,2-Dimethyl-but-3-yn-1-ol (25)

To a 1 L flame-dried flask with 100 mL THF was added Al foil (6 g, 0.22 mol) in small 3 cm^2 squares as loose balls. Mercury(II) chloride (300 mg, 1.1 mmol) was added and the flask was purged with N_2 then heated to reflux. After 30 min. a solution of 3-bromo-3-methyl-but-1-yne (32.7 g, 0.22 mol) in 50 mL THF was added dropwise to the suspension over 1 h. The reaction was stirred an additional 1.5 h then pre-dried paraformaldehyde (dried over Ca_2CO_3 & silica gel under vacuum) (6.6 g, 0.22 mol) was added portionwise. The reaction was stirred an additional 18 h, then cooled to rt and concentrated *in vacuo*. The resulting grey/black solid was stirred vigourously with 250 mL 5 M aqueous NaOH until the solid dissolved. Ether, 200 mL and 150 mL THF were added then the organic layer was separated and filtered through a plug of Celite to remove residual Al salts. The combined filtrates were washed with 200 mL saturated aqueous NaCl and dried over $MgSO_4$. The solvent was removed by distillation at atmospheric pressure under N_2 through a 10 cm vigreaux column, oil bath 50-100 °C. Fractional distillation of the residue yields 13.45 g **25** (62%, 0.137 mmol) (bp 115-125°C/760 mm Hg) as a light yellow oil. The volatile product is contaminated with a small quantity of THF ≈10% w/w by ^1H NMR. ^1H NMR and IR match the reported data.[2]

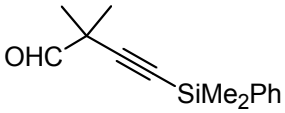
R_f=0.15 (5:1 petroleum ether:ether); IR (thin film, cm^{-1}) 3400, 3303, 2972, 2934, 2875, 1471, 1392, 1363, 1275, 1217, 1152, 1054; ^1H NMR (300 MHz, $CDCl_3$): _ 3.40 (s, 2H), 2.14 (s, 1H), 1.96 (s, 1H), 1.20 (s, 6H) ppm.



4-(Dimethyl-phenyl-silanyl)-2,2-dimethyl-but-3-yn-1-ol

To a 100 mL oven-dried rb flask with alcohol **25** (13.0 g, 0.132 mol) under Ar was added 500 mL THF. The reaction was cooled to -78 °C and *n*-BuLi (174 mL, 1.6 M in hexanes, 0.278 mol) was added dropwise over 15 min. The reaction was stirred 15 min. at -78 °C, then warmed to 0 °C, stirred 30 min., and then recooled to -78 °C. Dimethylphenylsilyl chloride (47.5 g, 0.268 mol) was added dropwise over 15 min. and the resulting white suspension was stirred an additional 15 min. The reaction was allowed to warm to rt and stirred 5.5h. The suspension was poured into 1 L 10 % aqueous HCl and stirred vigorously for 9.5 h. The solution was diluted with 100 mL ether, the organic layer separated, and the aqueous phase washed with 4 x 200 mL ether. The combined organic layers were washed with 500 mL saturated aqueous $NaHCO_3$, 500 mL saturated aqueous NaCl, dried over $MgSO_4$ and concentrated to yield a clear, colorless oil. Purification by flash chromatography (silica gel, 10:1 to 4:1 petroleum ether:ether) yields 24.0 g 4-(dimethyl-phenyl-silanyl)-2,2-dimethyl-but-3-yn-1-ol (78%, 0.132 moll) as a clear, colorless oil.

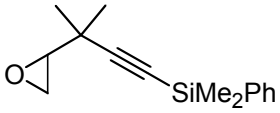
R_f=0.21 (5:1 petroleum ether:ether); IR (thin film, cm^{-1}) 3383, 3070, 2968, 2165, 1428, 1048; ^1H NMR (300 MHz, $CDCl_3$): _ 7.62 (m, 2H), 7.38 (m, 3H), 3.41 (d, J=7.1 Hz, 2H), 1.93 (t, J=7.1 Hz, 1H), 1.25 (s, 6H), 0.40 (s, 6H) ppm; ^{13}CNMR (75 MHZ, $CDCl_3$): _ 137.2, 133.4, 129.2, 127.7, 113.5, 83.5, 71.3, 35.0, 25.2, -0.7 ppm; EA calculated for $C_{14}H_{20}OSi$: C, 72.36; H, 8.67; found: 72.17; H, 8.80; HRMS (EI+) m/z calculated for $C_{14}H_{19}OSi$ $[M - H]^+$: 231.1205, found: 231.1203.



4-(Dimethyl-phenyl-silanyl)-2,2-dimethyl-but-3-ynal (26)

To a flame-dried 500 mL flask with oxalylchloride (25.2 g, 0.2 mol) in 250 mL CH_2Cl_2 at -78 °C under Ar was added a solution of DMSO (28.4 mL, 31.2 g, 0.40 mol) in 25 mL CH_2Cl_2 via syringe over 5 min. The reaction was stirred 30 min. at -78 °C then a solution of 4-(dimethyl-phenyl-silanyl)- 2,2-dimethyl-but-3-yn-1-ol (23 g, 0.10 mol) in 25 mL CH_2Cl_2 was added via cannula over 10 min. The reaction was stirred 1 h, then NEt_3 (70 mL, 50.8 g, 0.5 mol) was added and the reaction warmed to rt. The reaction was quenched by addition of 250 mL H_2O, diluted with 100 mL CH_2Cl_2 and extracted. The aqueous layer was washed with 2 x 200 mL CH_2Cl_2, the organic layers combined, washed with 200 mL saturated aqueous $NaHCO_3$, 200 mL saturated aqueous NaCl, dried over $MgSO_4$ and concentrated to yield a clear, yellow oil. Purification by flash chromatography (silica gel, 10:1 petroleum ether:ether) yields 17.13 g **26** (91%, 0.074 mol) as a clear, colorless, oil.

R_f=0.78 (5:1 petroleum ether:ether); IR (thin film, cm^{-1}) 2981, 2810, 2707, 2175, 1737, 1429, 1251, 1226, 1117; ^{1}H NMR (300 MHz, $CDCl_3$): _ 9.50 (s, 1H), 7.59 (m, 2H), 7.36 (m, 3H), 1.33 (s, 6H), 0.39 (s, 6H) ppm; ^{13}CNMR (125 MHZ, $CDCl_3$): _ 197.9, 136.8, 133.6, 129.4, 127.9, 107.9, 87.4, 43.6, 22.9, -0.8 ppm; HRMS (EI+) m/z calculated for $C_{14}H_{18}OSi$ $[M]^+$: 230.1127, found: 230.1122.

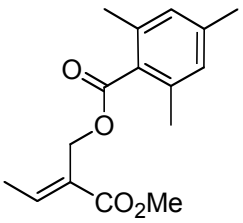


Dimethyl-(3-methyl-3-oxiranyl-but-1-ynyl)-phenyl-silane (22)

To a flame-dried rb flask with aldehyde **26** (0.55 g, 2.4 mmol) under Ar was

added iodochloromethane (846 mg, 4.80 mmol) and 10 mL THF. The solution was cooled to -78 °C and MeLi (3.2 mL, 1.5 M in Et2O, 4.8 mmol) was added over 30 min. via syringe pump. The reaction was stirred 15 min. at -78 °C, then allowed to warm to rt and stirred an additional 45 min. The reaction was quenched with 10 mL saturated aqueous NH_4Cl, diluted with 20 mL Et_2O and extracted. The aqueous layer was extracted with 2 x 10 mL Et_2O. The combined organic layers were washed with 10 mL saturated aqueous $NaHCO_3$, 10 mL saturated aqueous NaCl, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 20:1 petroleum ether:ether) yields 438 mg **22** (75%) as a clear, colorless, oil.

R_f=0.68 (5:1 petroleum ether:ether); IR (thin film, cm^{-1}) 3052, 2972, 2167, 1429, 1249, 1116; ^{1}H NMR (400 MHz, $CDCl_3$): _ 7.61 (m, 2H), 7.37 (m, 3H), 2.88 (dd, J=3.8, 2.6 Hz, 1H), 2.85 (dd, J=5.0, 2.7 Hz, 1H), 2.72 (dd, J=5.0, 3.8 Hz, 1H), 1.30 (s, 3H), 1.29 (s, 3H), 0.37 (s, 6H) ppm; ^{13}CNMR (125 MHZ, $CDCl_3$): _ 137.4(C), 133.6(CH), 129.2(C), 128.0(CH), 111.4(C), 83.4(C), 57.9(CH), 44.9(CH_2), 33.0(C), 26.0(CH_3), 25.2(CH_3) ppm; HRMS (EI+) m/z calculated for $C_{15}H_{19}OSi$ [M - H]$^+$: 243.1205, found: 243.1196.

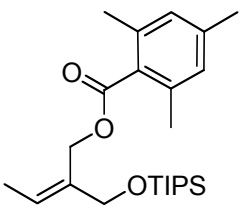


Methyl (*E*)-2-[[(2, 4, 6-tirmethlbenzoyl) oxy] methyl-2-butenoate (29)

To a solution of methyl 3-hydroxy-2-methylenebutyrate **28** (13.61 g, 0.105 mol) in 600 mL THF was added triphenylphosphine (35.26 g, 0.134 mol) and 2,4,6-trimethylbenzoic acid (22.39 g, 0.136 mol). The solution was cooled to -40^{o}C and diisopropyl azodicarboxylate (DIAD) (24.3 mL, 0.117 mol) was added dropwise by

syringe pump over 30 min. The reaction was stirred for 30 min further at -40°C. Then the cooling bath was removed and the reaction was allowed to warm to room temperature, and stirred for an additional 3 h. The reaction was concentrated under reduced pressure to yield an orange oily solid. The flask contents were dissolved in 500 mL ether and extracted with 50 mL water and 2 x 50 mL 1M aqueous NaOH. The combined aqueous layers were washed with 2 x 50 mL ether and the organic layers combined and concentrated under reduced pressure to yield an oily white precipitate. The solid was triturated with 250 mL 5% ether in petroleum ether. The solid triphenylphosphine oxide was collected by vacuum filtration. The filter cake was washed with 120 mL 5% ether in petroleum ether and the combined filtrates concentrated under reduced pressure to yield the crude product. The product was purified by flash chromatography (15% ether in petroleum ether) to yield **29** (23.50 g, 0.085 mol, 81% yield) as a clear oil.

R_f=0.46 (1:1 petroleum ether:ether); IR (thin film, cm^{-1}) 2953, 2923, 1723, 1657, 1612, 1436, 1379, 1339, 1261, 1168, 1145, 1085, 1037; ^{1}H NMR (500 MHz, $CDCl_3$): _ 7.20 (q, J=7.3 Hz, 1H), 6.83 (s, 2H), 5.09 (s, 2H), 3.76 (s, 3H), 2.27 (s, 6H), 2.26 (s, 3H), 2.00 (d, J=7.1 Hz, 3H) ppm; ^{13}CNMR (75 MHZ, $CDCl_3$): _ 169.9, 166.8, 144.9, 139.3, 135.1, 130.7, 128.4, 127.8, 58.0, 51.9, 21.1, 19.7, 14.7 ppm; EA calculated for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30; found: C, 69.38; H, 7.50.



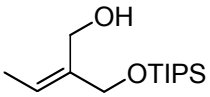
2,4,6-Trimethylbenzoic acid *(E)*-2-triisopropylsilanyloxymethyl-but-2-enyl ester (30)

To a 500 mL flame-dried flask with **29** (16.52 g, 0.059 mol) was added 400 mL CH_2Cl_2 and the solution cooled to -78^oC. DIBAL-H (120 mL, 1.0M in hexanes, 0.12 mol) was added dropwise via syringe pump over 45 min. The reaction was stirred for an additional 2 h at -78^oC, then the cooling bath was removed. The reaction was stirred at room temperature for additional 2 h. Saturated aqueous potassium sodium tartrate (300 mL) was added slowly to quench the reaction. Stirring was continued vigorously for 1 h. The organic layer was separated. The aqueous layer was washed with 2 x 200 mL ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to yield 14.20 g of the crude allylic alcohol as a light yellow oil which was used in the subsequent step without purification. R_f=0.20 (4:1 petroleum ether : ether).

To the crude allylic alcohol was added 400 mL methylene chloride. The solution was cooled to 0^oC. 2, 6-Lutidine (8.5 mL, 0.074 mol) and triisopropylsilyl triflate (17.0 mL, 0.061 mol) were added and the reaction stirred at 0^oC for 15 min. Then the reaction was allowed to warm to room temperature and stirred for an additional 12 h. The reaction was diluted with 500 mL ether and extracted with 3 x 100 mL 1M aqueous HCl, 100 mL saturated aqueous $NaHCO_3$, and 100 mL saturated aqueous NaCl. The organic layer was then dried over $MgSO_4$ and concentrated under reduced pressure to provide the crude product, which was purified by flash chromatography (silica gel, 50:1 petroleum ether : ether) to yield **30** (18.0 g, 0.044 mol, 73% yield) as a clear oil.

R_f=0.84 (4:1 petroleum ether:ether); IR (thin film, cm^{-1}) 2944, 2866, 1728, 1613, 1463, 1381, 1260, 1168, 1075; ^1H NMR (500 MHz, $CDCl_3$): _ 6.87 (s, 2H), 5.89 (q, J=7.0 Hz, 1H), 4.92 (s, 2H), 4.29 (s, 2H), 2.27 (s, 9H), 1.78 (d, J=7.0 Hz, 3H), 1.12-1.01 (m, 21H) ppm; ^{13}CNMR (75 MHZ, $CDCl_3$): _ 170.2, 139.1, 135.1, 133.9,

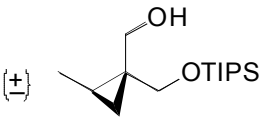
128.3, 125.9, 65.5, 59.8, 21.1, 19.7, 18.0, 17.7, 13.2, 12.0 ppm; EA calculated for $C_{24}H_{40}O_3Si$: C, 71.23; H, 9.96; found: C, 71.01; H, 9.75.



***(E)*-2-triisopropylsilanyloxymethyl-but-2-en-1-ol (31)**

To a solution of **30** (11.69 g, 28.9 mmol) in 260 mL ether at 0°C was added methyl lithium (90 mL, 1.6 M in ether, 144 mmol) dropwise *via* syringe pump over 2 h. The reaction was stirred for additional 2 h at 0°C. Then it was quenched with slow addition of 170 mL saturated aqueous NH_4Cl. The reaction mixture was diluted with 100 mL water and extracted with 2 x 150 mL ether. The organic layers were combined, dried over $MgSO_4$ and concentrated to yield the crude product, which was purified by flash chromatography (silica gel, 25:1 petroleum ether : EtOAc) to yield 6.92 g **31** (93%, 26.8 mmol) as a clear oil.

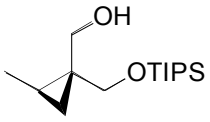
R_f=0.24 (5:1 petroleum ether:ether); IR (thin film, cm^{-1}) 3421, 2944, 2867, 1720, 1464, 1384, 1248, 1186, 1107, 1059, 1013; ^1H NMR (500 MHz, $CDCl_3$): _ 5.55 (q, J=6.8 Hz, 1H), 4.28 (s, 2H), 4.24 (s, 2H), 2.62 (bs, 1H), 1.66 (d, J=6.8 Hz, 3H), 1.16-0.94 (m, 21H) ppm; ^{13}CNMR (75 MHZ, $CDCl_3$): _ 137.4, 123.6, 68.7, 59.8, 17.9, 12.9, 11.8 ppm; HRMS (EI^+) m/z calculated for $C_{11}H_{23}O_2Si$ $[M - C_3H_7]^+$: 215.1467, found 215.1489.



(1,2-*trans*)-2-Methyl-1-hydroxymethyl-1-triisopropylsilanyloxy-cyclopropane [(±)-33]

To a flame-dried 50 mL rb flask under Ar was added Et_2Zn (13.5 mL, 1.0 M in hexanes, 13.5.0 mmol) and 10 mL CH_2Cl_2. The solution was cooled to 0 °C and diiodomethane (7.2 g, 26.9 mmol) in 5 mL CH_2Cl_2 was added over 5 min. The milky white solution was stirred 10 min. allylic alcohol **5.72** (1.75 g, 6.77 mmol) in 5 mL CH_2Cl_2 was added over 5 min. The reaction was stirred 10 min., then the ice bath was removed and the reaction was warmed to rt and stirred 1 h. The reaction was poured into 100 mL saturated aqueous NH_4Cl, diluted with 50 mL CH_2Cl_2 and extracted. The aqueous layer was extracted with 2 x 50 mL CH_2Cl_2. The combined organic layers were washed with 100 mL saturated aqueous NaCl, dried over MgSO4, and concentrated *in vacuo* to yield the crude product. Purification by flash chromatography (silica gel, 20:1 petroleum ether:EtOAc) yields 1.40 g **[(±)-33]** (76%) as a clear, colorless, oil.

R_f=0.38 (5:1 petroleum ether:ether); IR (thin film, cm^{-1}) 3452, 2944, 2867, 1464, 1108, 1063, 1014; ^1H NMR (500 MHz, $CDCl_3$): _ 3.90 (d, J=11.5 Hz, 1H), 3.77 (d, J=10.0 Hz, 1H), 3.62 (d, J=11.5 Hz, 1H), 3.54 (d, J=9.8 Hz, 1H), 3.11 (bs, 1H), 1.18 (d, J=6.3 Hz, 3H), 1.07 (m, 21H), 0.87 (m, 1H), 0.55 (dd, J=6.6, 4.9 Hz, 1H), 0.18 (t, J=5.2 Hz, 1H) ppm; ^{13}CNMR (125 MHZ, $CDCl_3$): _ 72.8, 66.2, 27.4, 17.9, 16.6, 15.8, 13.8, 11.7 ppm; HRMS (EI+) m/z calculated for $C_{15}H_{31}O_2Si$ $[M - H]^+$: 271.2093, found: 271.2092.

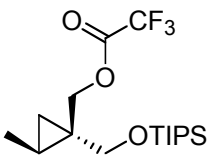


(1*R*, 2*R*)-2-Methyl-1-hydroxymethyl-1-triisopropylsilanyloxy-cyclopropane (33)

To a flame-dried 500 mL flask was added DME (4.4 mL, 42.3 mmol) and 90 mL CH_2Cl_2. The solution was cooled to -30°C and Et_2Zn (43 mL, 1.0 M in

hexanes, freshly prepared from neat Et_2Zn, 43 mmol) was added followed by the addition of diiodomethane (6.8 mL, 84.4 mmol) in 20 mL CH_2Cl_2 over 10 min. The clear solution was stirred for 30 min. Then butylboronic acid *N,N,N′,N′*-tetramethyl-L-tartaric acid diamide ester (7.0 g, 25.9 mmol) in 20 mL CH_2Cl_2 was added over 10 min. After 15 min, allylic alcohol **31** (5.5 g, 21.3 mmol) in 20 mL CH_2Cl_2 was added. The reaction was allowed to warm to room temperature and continued for 1 d. The reaction was later quenched with a solution of 100 mL 1 M aqueous HCl and 100 mL saturated aqueous NH_4Cl. The organic layer was separated. The aqueous layer was extracted with 3 x 100 mL ether. The combined organic layers were washed with 100 mL water, 100 mL saturated aqueous $NaHCO_3$, 100 mL saturated aqueous NaCl, dried over MgSO4, and concentrated under reduced pressure. Purification by flash chromatography (silica gel, 25:1 petroleum ether : EtOAc) yields product **33** (6.0 g, quant. yield) as a clear oil. The enantiomeric excess of the product was determined to be 94.6% ee by conversion into the trifluoroacetate ester and chiral GC, described below.

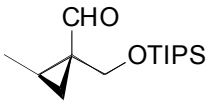
.R_f=0.38 (5:1 petroleum ether:ether); $[\_]_D^{24}$= -27.4^o (c=1.10, CH_2Cl_2). The spectral data matched that of the racemic compound [(±)-33] described above.



(1*R*, 2*R*)-Trifluoro-acetic acid 2-methyl-1-triisopropylsilanyloxymethyl-cyclopropyl methyl ester

Enantiomeric excess of the above product was determined by conversion to the trifluoroacetate ester of alcohol **[(-)-33]**: To a solution of **[(-)-33]** (27.3 mg, 0.1 mmol) in 0.6 mL CH_2Cl_2 under Ar at 0 °C was added pyridine (16 μL, 0.2 mmol)

followed by trifluoroacetic anhydride (28 μL, 42 mg, 0.2 mmol) and the solution stirred 1 h. The reaction was quenched with 5 mL H_2O, diluted with 5 mL ether, the organic layer separated, washed with 5 mL saturated aqueous $CuSO_4$, 5 mL saturated aqueous $NaHCO_3$, 5 mL saturated aqueous NaCl, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography (silica gel, 5% EtOAc:petroleum ether) yields 28.7 mg the trifluoroacetate ester of **[(-)-33]** (78%, 0.78 mmol) as a clear, colorless, oil. Enantiomeric excess was determined to be 94.6% ee by chiral GC (Cyclosil B, 120 °C, 15 mL/min, 50:1 split, minor product (1*S*,2*S*) t_R=47.838 min and major product (1*R*,2*R*) t_R=48.558 min

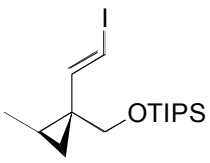


(1*R*, 2*R*)-2-Methyl-1-triisopropylsilanyloxymethyl-cyclopropanecarbaldehyde (34)

To a flame-dried 100 mL flask with oxalylchloride (1.50 mL, 17.1 mmol) in 10 mL CH_2Cl_2 at -78 °C under nitrogen was added a solution of DMSO (2.43 mL, 34.2 mmol) in 10 mL CH_2Cl_2 via syringe over 5 min. The reaction was stirred for 20 min. Then a solution of alcohol **33** (3.10 g, 11.4 mmol) in 10 mL CH_2Cl_2 was added dropwise via cannula over 5 min. The reaction was stirred for 20 min. Then NEt_3 (9.5 mL, 68.4 mmol) was added and the reaction stirred for 1 h at -78°C, then warmed to 0 °C and stirred for an additional hour. The reaction was quenched by the addition of 20 mL H_2O, and then diluted with 20 mL Et_2O. The organic layer was separated. The aqueous layer was washed with 2 x 50 mL Et_2O, the organic layers combined, washed with 50 mL 1M HCl, 50 mL saturated aqueous $NaHCO_3$, 50 mL saturated aqueous NaCl, dried over $MgSO_4$ and concentrated to yield 3.54 g crude aldehyde. Purification

by flash chromatography (silica gel, 100:1 petroleum ether : ether) yields product **34** (3.0 g, 11.1 mmol, 97% yield) as a clear oil.

R_f=0.50 (4:1 petroleum ether:ether); IR (thin film, cm^{-1}) 3440, 2944, 2867, 1700, 1464, 1099, 1067; 1H NMR (500 MHz, $CDCl_3$): _ 9.45 (s, 1H), 4.01 (d, J=10.5 Hz, 1H), 3.87 (d, J=10.5 Hz, 1H), 1.55 (m, 1H), 1.25 (dd, J=8.3, 4.6 Hz, 1H), 1.22 (d, J=6.4 Hz, 3H), 1.18 (dd, J=7.0, 4.6 Hz, 1H), 1.02 (m, 21H) ppm; ^{13}CNMR (125 MHZ, $CDCl_3$): _ 202.7, 62.8, 38.2, 22.0, 19.5, 17.9, 17.6, 13.1, 11.9 ppm; HRMS (EI+) m/z calculated for $C_{15}H_{29}O_2Si$ $[M - H]^+$: 269.1937, found: 269.1935.

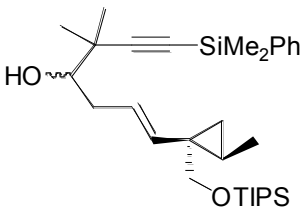


(1*R*, 2*R*)-1-(2-iodo-vinyl)-2-methyl-1-triisopropylsilanyloxymethyl-cyclopropane (23)

To a flame-dried 25 mL round bottom flask was added anhydrous $CrCl_2$ (0.180 g, 1.40 mmol) under N_2 atmosphere. The flask was fitted with an Ar balloon and 1 mL THF was added. The suspension was cooled to 0 °C and a solution of aldehyde **34** (95 mg, 0.35 mmol) in 1 mL THF was added via cannula, followed by the solution of iodoform (0.28 g, 0.70 mmol) in 1 mL THF. The red suspension was stirred 15 min. at 0 °C, then warmed to room temperature and stirred an additional 6 h in the dark. The reaction was quenched with 10 mL water and diluted with 10 mL Et_2O. The layers were separated and the organic layer washed with 10 mL saturated aqueous $Na_2S_2O_3$. The organic layer was then stirred vigorously with 20 mL 1 M NaOH for 2 h to decompose excess iodoform. The organic layer was separated, washed with 10 mL H_2O, 10 mL saturated aqueous NaCl, dried over $MgSO_4$ and concentrated. Purification by flash chromatography (silica gel, petroleum ether)

yields product **23** (0.11 g, 0.28 mmol, 80% yield) as a clear, colorless oil.

R_f=0.90 (5:1 petroleum ether:ether); IR (thin film) 2943, 2891, 1463, 1110, 1067 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): _ 6.50 (d, J=14.4 Hz, 1H), 6.06 (d, J=14.4 Hz, 1H), 3.69 (d, J=10.0 Hz, 1H), 3.57 (d, J=10.0 Hz, 1H), 1.05 (m, 25H), 0.84 (m, 1H), 0.40 (m, 1H) ppm; ^{13}CNMR (100 MHZ, $CDCl_3$): _ 146.3, 74.9, 67.8, 32.6, 18.0, 17.9, 17.2, 16.7, 14.1, 12.0, 11.9 ppm; HRMS (EI+) m/z calculated for $C_{13}H_{24}IOSi$ [M - C_3H_7 (*i*-Pr)]$^+$: 351.0641, found: 351.0643.

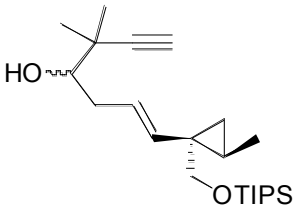


(±)-5,5-Dimethyl-1-(2-methyl-1-triisopropylsilanyloxymethyl-cyclopropyl)-7-trimethylsilanyl-hept-1-en-6-yn-4-ol (35)

To a flame-dried test tube was added vinyliodide **(±)-23** (80.4 mg, 0.205 mmol). The reaction was flushed with Ar and 0.5 mL Et_2O was added. The reaction was cooled with a -78 °C and *t*-BuLi (250 μL, 1.7 M in pentane, 0.42 mmol) was added dropwise and the solution stirred 30 min. A solution of freshly prepared (2-Th)CuCNLi[3] (1.15 mL, 0.175 M in THF, 0.2 mmol) was added and the reaction stirred 1 h. Epoxide **22** (60 mg, 0.247 mmol) was added and the reaction was stirred 1 h at -78 °C, then warmed to rt and stirred 4 h The reaction was quenched by addition of 8 mL 3:1 saturated aqueous NH_4Cl/concentrated aqueous NH_4OH. The reaction was diluted with 10 mL Et_2O and the organic layer extracted. The aqueous layer was washed with 2 x 10 mL Et_2O and the organic layers combined. The combined organic layers were washed with 5 mL H_2O, dried over $MgSO_4$ and concentrated in *vacuo*. Purification by flash chromatography (silica gel, 25:1 petroleum ether:ether) yields 66

mg **35** (51%) as a clear, colorless oil, and a 1:1 mixture of diastereomers.

R_f=0.61 (5:1 petroleum ether:ether); IR (thin film, cm^{-1}) 3331, 2943, 2867, 1466, 1390, 1114, 1070; ^1H NMR (300 MHz, $CDCl_3$): _ 7.60 (m, 2H), 7.43 (m, 3H), 5.58 (m, 2H), 3.66 (m, 2H), 3.31 (m, 1H), 2.53 (m, 0.5H), 2.48 (m, 0.5H), 2.11 (m, 1H), 1.84 (d, J=4.8 Hz, 0.5H), 1.80 (d, J=5.1 Hz, 0.5H), 1.21 (s, 3H), 1.20 (s, 3H), 1.04 (m, 22H), 1.00 (s, 3H), 0.78 (m, 1H), 0.29 (m, 1H), 0.18 (s, 6H) ppm; ^{13}CNMR (125 MHZ, $CDCl_3$): _ 139.8, 136.1, 133.8, 128.3, 127.8, 126.7, 86.1, 85.7, 79.3, 78.8, 78.7, 78.2, 68.5, 37.7, 36.5, 29.9, 28.8, 25.8, 25.7, 25.6, 18.3, 16.7, 16.5, 16.3, 14.2, 12.3, 0.6 ppm; HRMS (EI+) m/z calculated for $C_{31}H_{51}O_2Si_2$ $[M - H]^+$: 511.3428, found: 511.3425.

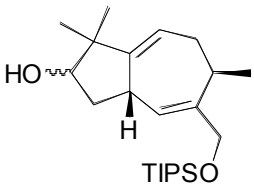


(±)-5,5-dimethyl-1-(2-methyl-1-triisopropylsilanyloxymethyl-cyclopropyl)-hept-1-en-6-yn-4-ol (21)

To a vial with 1,6-eneyne **35** was added 0.2 mL MeOH. K_2CO_3 (44 mg, 0.32 mmol) was added and the reaction stirred 3.5 h The solution was filtered through a medium porosity frit, the filtrate washed with 2 x 2 mL MeOH, and 2 x 2 mL Et_2O. The combined filtrates were combined and concentrated. The residue was purified by flash chromatography (silica gel, 20:1 petroleum ether:ether) to yield 11.4 mg **21** (80%) as a clear, colorless, oil, 1:1 mixture of diastereomers.

R_f=0.41 (5:1 petroleum ether:ether); IR (thin film, cm^{-1}) 2943, 2862, 1466, 1114, 1070, 883, 800; ^1H NMR (500 MHz, $CDCl_3$): _ 5.56 (m, 2H), 3.66 (m, 2H), 3.31 (m, 1H), 2.52 (m, 1H), 2.18 (m, 2H), 1.92 (d, J=4.0 Hz, 0.5H), 1.86 (d, J=4.0 Hz,

0.5H), 1.17 (s, 3H), 1.16 (s, 3H), 1.04 (m, 24H), 0.79 (m , 1H), 0.62 (m, 1H), 0.30 (m, 1H) ppm; ^{13}CNMR (125 MHZ, $CDCl_3$): _ 134.1, 134.0, 127.6, 127.5, 89.0, 84.8, 76.2, 76.1, 70.3, 70.0, 66.8, 66.1, 36.3, 36.2, 26.2, 25.9, 24.9, 24.1, 20.4, 18.8, 18.3, 18.2, 16.1, 16.0, 15.5, 15.4, 12.2 ppm; HRMS (EI+) m/z calculated for $C_{23}H_{42}O_2Si$ $[M]^+$: 378.2954, found: 378.2965.



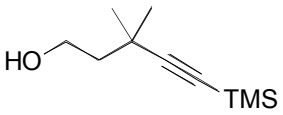
(±)-1,1,6,7-tetramethyl-5-triisopropylsilanyloxymethyl-1,2,3,3a,6,7-hexahydro-azulen-2-ol (20)

To a test-tube with $[CpRu(CH_3CN)_3]PF_6$ (1.9 mg, 0.0044 mmol) was added a solution of 1,6-eneyne **21** (10.6 mg, 0.028 mmol) in 250 μL acetone via cannula. The reaction was stirred at rt 5 h. The crude reaction was purified by flash chromatography (silica gel, 5:1 petroleum ether:ether) to yield 7.0 mg recovered **21** (59%) [R_f=0.41 (5:1 petroleum ether:ether)] and 3.3 mg **20** (43%, 95% BRSM) as a clear, colorless oil and a 3:1 mixture of diastereomers by ^{1}H NMR.

Major Diastereomer:

R_f=0.13 (5:1 petroleum ether:ether); IR (thin film) 3430, 2925, 1463, 1260, 1070 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): _ 5.53 (s, 1H), 5.45 (m, 1H), 4.08 (d, J=12.9 Hz, 1H), 4.00 (d, J=13.2 Hz, 1H), 3.67 (m, 1H), 3.48 (m, 1H), 2.35-2.18 (m, 5H), 1.24 (s, 6H), 1.09 (d, J=5.7 Hz, 3H), 1.03 (m, 21H) ppm. ^{13}CNMR (125 MHZ, $CDCl_3$): _ 134.1, 134.0, 127.6, 127.5, 89.0, 84.8, 76.2, 76.1, 70.3, 70.0, 66.8, 66.1, 36.3, 36.2, 26.2, 25.9, 24.9, 24.1, 20.4, 18.8, 18.3, 18.2, 16.1, 16.0, 15.5, 15.4, 12.2 ppm; HRMS (EI+) m/z calculated for $C_{23}H_{41}O_2Si$ $[M - H]^+$: 377.2876, found: 377.2864.

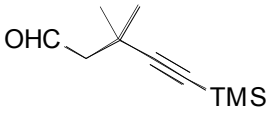
The regiochemistry of product was assigned based upon COSY spectra and coupling constant examination which show coupling with the C-9 proton and the adjacent C-8 methylene. The stereochemistry was not determined, but based upon similar *cis*-substituted cyclopropanes should be the stereochemistry shown.



5-Trimethylsilyl -3,3-dimethyl-4-pentyn-1-ol (42)

In a flame-dried 500 mL round bottom flask were added 3-methylbutyne **41** (8.06 g, 118 mmol) and 100 mL ether. At -20^{o}C, *n*-BuLi (110 mL, 2.19 M solution in hexanes, 237 mmol) was added, followed by tetramethylethylenediamine (TMEDA, 17.7 mL, 118 mmol). The reaction was warmed to room temperature and heated to gentle reflux for 10 h, until a clear orange solution formed. Then it was cooled to -78^{o}C. A solution of ethylene oxide (6 mL, condensed from cylinder, 118 mmol) in 20 mL THF was canulated into the above dianion solution at -78^{o}C over 5 min. The reaction continued at -78^{o}C for 2 h. Then trimethylsilyl chloride (30 mL, 240 mmol) was added dropwise. The reaction was allowed to warm to room temperature and continued for 5 h. The solution was condensed to about 200 mL under reduced pressure. Aqueous HCl (200 mL, 1M, 200 mmol) was added, and the mixture was stirred vigorously for 1 h. The organic layer was collected. The aqueous layer was washed with 2 X 100 mL ether. The combined organic layers were washed with saturated aqueous $NaHCO_3$, NaCl, and dried over $MgSO_4$. Removal of the solvent under reduced pressure, followed by flash chromatography (20% ether in petroleum ether) with silica gel yielded product **42** (11.70 g, 63.6 mmol, 53% yield) as colorless liquid. ^{1}H NMR and IR match the reported data.[4]

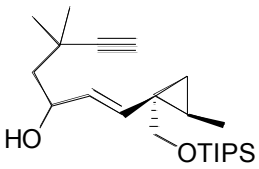
R_f (20% ether in petroleum ether): 0.17; IR (thin film, cm^{-1}) 3345, 2967, 2162, 1451, 1409, 1364, 1251, 1062, 1029; ^1H NMR (300MHz, $CDCl_3$): _ 3.83 (t, J=6.2 Hz,2), 1.68 (t, J=6.2 Hz, 2H), 1.21 (s, 6H), 0.59 (s, 9H).



3,3-Dimethyl-5-trimethylsilanyl-pent-4-ynal (40)

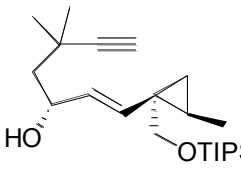
To an oven-dried 100 mL flask with oxalyl chloride (0.37 mL, 98%, 4.22 mmol) in 6 mL dichloromethane at -78°C was added a solution of DMSO (0.60 mL, 8.46 mmol) in 3 mL dichloromethane via syringe over 5 min. The reaction was stirred 20 min at -78°C then a solution of alcohol **42** (0.52 g, 2.82 mmol) in 3 mL dicholoromethane was added dropwise over 2 min. The reaction was stirred 20 min, then triethylamine (2.4 mL, 16.9 mmol) was added and the reaction warmed to room temperature over 60 min. Then it was quenched by the addition of water. Ether (20 mL) was used in the extraction. The aqueous layer was washed with 10 mL ether twice, the organic layer combined, washed with 10 mL 1M HCl, 10 mL saturated aqueous NaCl, dried over MgSO4 and concentrated to yield the crude aldehyde **40**. Flash chromatography (5% ether in petroleum ether) afforded product **40** (0.48 g, 2.63 mmol, 94% yield) as colorless liquid. ^1H NMR, ^{13}C NMR and IR match the reported data.

R_f (20% ether in petroleum ether): 0.75; IR (thin film, cm^{-1}) 2962, 2923, 2852, 2166, 1738, 1410, 1250, 1157, 1115, 1023; ^1H NMR (300MHz, $CDCl_3$): _ 9.87 (t, *J* = 2.9Hz, 1H), 2.36 (d, *J* = 2.9Hz, 2H), 1.27 (s, 6H), 0.12(s, 9H) ppm; ^{13}C NMR (75MHz, $CDCl_3$): _ 203.1, 111.6, 86.0, 55.1, 29.7, 29.5, 0.2 ppm.



(*R*, *R*)-5,5-Dimethyl-1-(2-methyl-1-triisopropylsilanyloxymethyl-cyclopropyl)-hept-1-en-6-yn-3-ol (39)

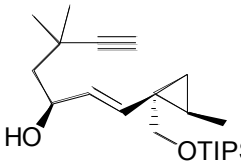
Butyl lithium (1.20 mL, 2.30 M in hexanes, 2.76 mmol) was added to a solution of vinyl iodide **23** (0.85 g, 2.15 mmol) in 15 mL hexanes at 0^{o}C. The resulting solution was stirred at 0^{o}C for 15 min. Then aldehyde **40** (0.45 g, 2.47 mmol) in 5 mL hexanes was added in dropwise. After 2 h, half saturated ammonium chloride aqueous solution (30 mL) was added to quench the reaction. The reaction mixture was extracted with 3 X 30 mL ether. The combined organic layers were washed with saturated NaCl, dried over $MgSO_4$, and concentrated under reduced pressure to yield crude **43** as pale yellow liquid. Compound **43** was then dissolved in 10 mL MeOH with K_2CO_3 (1.50 g, 15 mmol). The solution was stirred vigorously for 2 h at room temperature. Water (30 mL) and ether (30 mL) was added afterwards. The organic layer was separated. The aqueous layer was extracted with ether (3 X 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (5% ether in petroleum ether) yielded product **39** (0.73 g, 1.93 mmol, 90% yield) as a colorless liquid. Further chromatography with silica gel yielded 0.36g **39a** and 0.34g **39b**.



39a

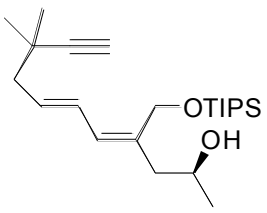
R_f (10% ether in petroleum ether): 0.19; IR (thin film, cm^{-1}) 3447, 3311, 2944, 2868, 2106, 1995, 1660, 1464, 1384, 1249, 1110, 1067, 1007; ^{1}H NMR

(400MHz, $CDCl_3$): _ 5.64(d, *J*=15.7Hz, 1H), 5.53 (dd, *J*=6.6Hz, 15.7Hz, 1H), 4.43(t, *J*=7.3Hz, 1H), 3.65 (q, *J*=5.4Hz, 2H), 2.37(s, 1H), 2.20 (s, 1H), 1.73 (dd, *J*=9.0Hz, 15.4Hz, 1H), 1.53 (dd, *J*=2.9Hz, 14.2Hz, 1H), 1.27 (s, 3H), 1.26 (s, 3H), 0.99-1.03 (m, 25H), 0.80(m, 1H), 0.28 (t, *J*=5.3Hz, 1H) ppm; ^{13}C NMR (100MHz, $CDCl_3$): _ 133.3, 131.0, 91.9, 71.2, 69.6, 67.8, 50.2, 30.7, 29.8, 29.3, 27.9, 18.1, 16.8, 16. 7, 14.0, 12.1 ppm; HRMS (EI^+) m/z calculated for $C_{23}H_{42}O_2Si$ $[M]^+$: 378.2954, found: 378.2949; $[\alpha]_D^{24}$= -40.8 (c=0.75, CH_2Cl_2).



39b

R_f (10% ether in petroleum ether): 0.21; IR (thin film, cm^{-1}) 3432, 3311, 2944, 2867, 2110, 1661, 1464, 1384, 1365, 1248, 1110, 1067, 1013; ^1H NMR (400MHz, $CDCl_3$): _ 5.66 (d, *J*=15.7Hz, 1H), 5.52 (dd, *J*=6.7Hz, 15.7Hz, 1H), 4.44(m, 1H), 3.69 (d, *J*=9.8Hz, 1H), 3.59(d, *J*=9.9Hz, 1H), 2.36 (s, 1H), 2.19 (s, 1H), 1.72 (dd, *J*=8.7Hz, 14.2Hz, 1H), 1.54 (dd, *J*=3.4Hz, 14.2Hz, 1H), 1.26 (s, 3H), 1.25 (s, 3H), 0.99-1.03 (m, 25H), 0.79(m, 1H), 0.30 (t, *J*=4.6Hz, 1H) ppm; ^{13}C NMR (100MHz, $CDCl_3$): _ 133.4, 131.0, 91.8, 71.2, 69.5, 68.0, 50.2, 30.7, 29.7, 29.2, 27.9, 18.1, 16.9, 16.8, 14.0, 12.1 ppm; LRMS (EI^+) m/z calculated for $C_{23}H_{42}O_2Si$ $[M]^+$: 378, found: 378; $[\alpha]_D^{24}$= -26.8 (c=1.56, CH_2Cl_2); EA: calculated for $C_{23}H_{42}O_2Si$ C, 72.95%, H, 11.18%, found C, 73.20%, H, 11.20%.

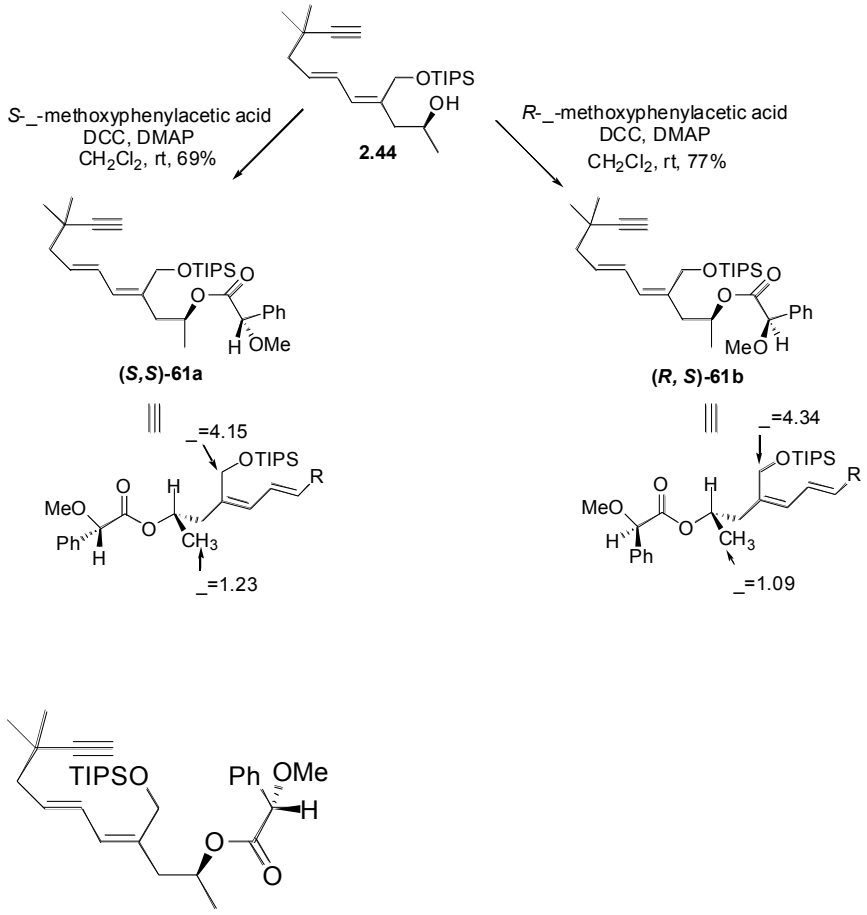


(*S*)-9,9-Dimethyl-4-triisopropylsilanyloxymethyl-undeca-4,6-dien-10-yn-2-ol (44)

To a solution of enyne **39** (15.0 mg, 0.0396 mmol) in 0.1 mL acetone was canulated in a solution of $CpRu(CH_3CN)_3PF_6$ (2.58 mg, 0.00594 mmol) in 0.2 mL acetone under Ar atmosphere at 0^oC. The reaction was allowed to warm to room temperature and continued for 5 h. The solution was filtered through a silica gel pad to remove the catalyst. The filtrate was washed with 5 mL ether. Then the combined organic solution was concentrated under reduced pressure. Flash chromatography (5-10% ether in petroleum ether) yielded dienyne **44** (8.0 mg, 0.022 mmol) as a colorless liquid.

R_f (10% ether in petroleum ether): 0.15; IR (thin film, cm^{-1}) 3438, 3312, 2968, 2945, 2867, 1463, 1384, 1364, 1257 1061, 1013; ^1H NMR (500MHz, $CDCl_3$): _ 6.25 (dd, *J*=14.9, 11.0Hz, 1H), 5.95 (d, *J*=11.0Hz, 1H), 5.77 (dt, J=22.2, 7.6Hz, 1H) 4.40 (d, *J*=11.8Hz, 1H) 4.30 (d, *J*=11.8Hz, 1H) 3.92 (m, 1H), 3.27 (s, 1H) 2.40 (dd, *J*=13.7, 2.7Hz, 1H), 2.11-2.18 (m, 3H), 2.07 (s, 1H), 1.16 (s, 6H), 1.02-1.05 (m, 24H) ppm; ^{13}C NMR (125MHz, $CDCl_3$): _ 135.9, 131.3, 130.0, 128.0, 91.4, 68.2, 67.1, 61.7, 46.4, 31.2, 30.3, 28.8, 28.8, 23.2, 18.0, 12.0 ppm; $[\alpha]_D^{24}$= +6.3 (c=0.63, CH_2Cl_2); HRMS (EI^+) m/z calculated for $C_{23}H_{42}O_2Si$ $[M]^+$: 378.2954, found: 378.2946.

Determination of absolute configuration of compound **44**:[5]

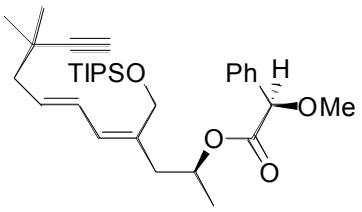


(*S,S*)-Methoxy-phenyl-acetic acid 1, 8, 8-trimethyl-3-triisopropyl silanyloxy methyl-deca-3, 5-dien-9-ynyl ester (61a)

To a solution of the alcohol **44** (7.2 mg, 0.019 mmol) with (*S*)-_-methoxyphenylacetic acid (2.8 mg, 0.017 mmol), *N, N'*-dicyclohexyl carbodiimide (DCC, 3.9 mg, 0.019 mmol) in 0.17 mL methylene chloride was added 4-di(methylamino)pyridine (DMAP, 0.23 mg, 0.0019 mmol) at room temperature. The reaction continued for 12 h. Then the mixture was separated on a small silica gel column (5% ether in petroleum ether) to yield pure ester (6.2 mg, 0.0118 mmol, 69% yield) as colorless liquid.

R_f (20% ether in petroleum ether): 0.67; IR (thin film, cm^{-1}): 3311, 2942, 2867, 1748, 1455, 1384, 1256, 1200, 1177, 1115, 1064; ^1H NMR (400MHz, $CDCl_3$): _ 7.37 (m, 2H) 7.30 (m, 3H), 6.10 (dd, *J* = 14.8, 11.1Hz, 1H), 5.67, (d, *J* = 11.0 Hz,

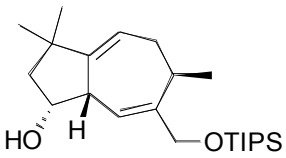
1H), 5.18 (m, 1H), 4.667 (s, 1H), 4.21 (d, *J* = 12.6 Hz, 1H), 4.09 (d, *J* = 12.5 Hz, 1H), 3.37 (s, 3H), 2.38 (dd, *J* = 5.1, 13,9 Hz, 1H) 2.25 (m, 1H), 2.17 (d, *J* = 7.4 Hz), 2.09 (s, 1H), 1.23 (d, J = 6.2 Hz, 3H), 1.174 (s, 3H), 1.168 (s, 3H), 0.98-1.05 (m, 21H) ppm.



(*R,S*)-Methoxy-phenyl-acetic acid 1, 8, 8-trimethyl-3-triisopropyl silanyloxy methyl-deca-3, 5-dien-9-ynyl ester (61b)

To a solution of the alcohol **44** (12 mg, 0.032 mmol) with (*R*)-_-methoxyphenylacetic acid (4.8 mg, 0.029 mmol), *N, N'*-dicyclohexyl carbodiimide (DCC, 6.6 mg, 0.032 mmol) in 0.3 mL methylene chloride was added 4-di(methylamino)pyridine (DMAP, 0.4 mg, 0.0032 mmol) at room temperature. The reaction continued for 12 h. Then the mixture was separated on a small silica gel column (5% ether in petroleum ether) to yield pure ester (11.8 mg, 0.0224 mmol, 77% yield) as a colorless liquid.

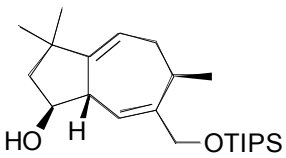
R_f (20% ether in petroleum ether): 0.69; IR (thin film, cm^{-1}): 3310, 2943, 2867, 1748, 1732, 1456, 1384, 1363, 1256, 1200, 1177, 1115, 1065; ^1H NMR (400MHz, $CDCl_3$): _ 7.39 (m, 2H) 7.30 (m, 3H), 6.22 (dd, *J* = 14.8, 11.1Hz, 1H), 5.85, (d, *J* = 11.0 Hz, 1H), 5.71 (m, 1H), 5.22 (m, 1H), 4.66 (s, 1H), 4.39 (d, *J* = 12.6 Hz, 1H), 4.29 (d, *J* = 12.5 Hz, 1H), 3.35 (s, 3H), 2.47 (dd, *J* = 5.1, 13,9 Hz, 1H) 2.32 (m, 1H), 2.18 (d, *J* = 7.4 Hz), 2.09 (s, 1H), 1.17 (s, 6H), 1.09 (d, J = 6.2 Hz, 3H), 0.98-1.06 (m, 21H) ppm.



(1*R*,3a*E*,6*S*,7*E*,8a*R*)-3,3,6-trimethyl-7-((triisopropylsilyloxy)methyl)-1,2,3,5,6,8a-hexahydroazulen-1-ol (38a)

To a solution of 1,6-enyne **39a** (2.95 g, 7.8 mmol) in 150 mL methylene chloride at 0^{o}C was added a solution of $[CpRu(CH_3CN)_3]PF_6$ (0.34 g, 0.78 mmol) in 50 mL methylene chloride The reaction was continued for 3 h. Then the solution was filtered through a silica gel pad to remove the catalyst. The solution was concentrated under reduced pressure. Flash chromatography (5-10% ether in petroleum ether) yielded product **38a** (2.59 g, 6.86 mmol, 88% yield) as a colorless oil.

R_f = 0.17 (10% Et_2O in petroleum ether); IR (thin film, cm^{-1}): 3375, 2945, 2867, 1464, 1383, 1368, 1248, 1064; ^{1}H NMR (500MHz, $CDCl_3$): _ 5.70 (d, *J*=1.5Hz, 1H), 5.50 (dt, *J*=7.0Hz, 3.4Hz, 1H), 4.18 (s, 1H), 4.08 (m, 2H), 3.54 (s, 1H), 2.45 (m, 1H), 2.26 (m, 1H), 2.10 (m, 1H), 1.72 (d, *J*=1.5Hz, 1H) 1.70 (d, *J*=4.0Hz, 1H), 1.18 (s, 3H), 1.15 (d, *J*=3.2Hz, 3H), 1.08 (s, 3H), 1.04 (m, 21H) ppm; ^{13}C NMR (125MHz, $CDCl_3$): _ 149.2, 147.7, 120.1, 119.3, 75.7, 67.7, 66.0, 49.2, 48.3, 41.3, 31.1, 18.2, 17.5, 15.4, 12.1 ppm; HRMS (EI$^+$) m/z calculated for $C_{23}H_{42}O_2Si$ $[M]^+$: 378.2954, found: 378.2954; $[\alpha]_D^{24}$= 29.3° (c=0.820, CH_2Cl_2).



(1*S*,3a*E*,6*S*,7*E*,8a*R*)-3,3,6-trimethyl-7-((triisopropylsilyloxy)methyl)-1,2,3,5,6,8a-hexahydroazulen-1-ol (38b)

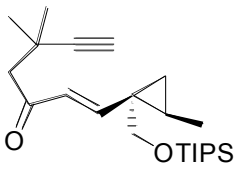
To a solution of **39b** (0.18 g, 0.48 mmol) in 8 mL methylene chloride at 0^{o}C was added a solution of $[CpRu(CH_3CN)_3]PF_6$ (42 mg, 0.096 mmol) in 0.5 mL

methylene chloride. The reaction was allowed to warm to room temperature and continued for 3 h. Then the solution was filtered through a silica gel pad to remove the catalyst. The solution was concentrated under reduced pressure. Flash chromatography (5-10% EtOAc in petroleum ether) yielded product **38b** (0.106 g, 0.29 mmol, 60% yield) as a colorless oil.

R_f (20% EtOAc in petroleum ether): 0.30; IR (thin film, cm^{-1}): 3334, 2944, 2866, 14643, 1383, 13685, 1248, 1067; ^1H NMR (400MHz, $CDCl_3$): _ 5.63(d, *J*=1.9Hz, 1H), 5.28(m, 1H), 3.97(m, 2H), 3.84(m, 1H), 3.19(d *J* = 9.0Hz, 1H), 2.16(m, 2H), 2.04(m, 1H), 1.76(q, *J* = 5.6 Hz, 1H), 1.37(m, 1H), 1.04 (d, *J* = 7.2 Hz, 3H), 1.02 (s, 3H), 0.93-0.98 (m, 21H), 0.88 (s, 3H) ppm; ^{13}C NMR (100MHz, $CDCl_3$): _ 150.2, 144.7, 128.4, 123. 7, 118.3, 67.5, 50.6, 48.6, 40.0, 33.2, 32.7, 30.9, 30.7, 18.1, 18.1, 12.1 ppm; LRMS (EI^+) m/z calculated for $C_{23}H_{42}O_2Si$ $[M]^+$: 378, found: 378; $[\alpha]_D^{24}$= 24.25 (c=0.830, CH_2Cl_2); EA: calculated for $C_{23}H_{42}O_2Si$ C, 72.95%, H, 11.18%, found C, 72.76%, H, 11.38%.

Procedure from the mixtures of **39a** and **39b**:

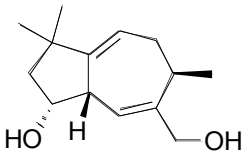
To a solution of 1,6-enyne **39** (dr 1.2/1 = **39a** / **39b**, 13.5 mg, 0.036 mmol) in 0.72 mL methylene chloride at 0^oC was added $[CpRu(CH_3CN)_3]PF_6$ (1.6 mg, 0.0036 mmol) in one portion. The reaction was allowed to warm to room temperature and continued overnight. Then the solution was filtered through a silica gel pad to remove the catalyst and concentrated under reduced pressure. Flash chromatography (5-10% EtOAc in petroleum ether) yielded products **38a** (6.5 mg, 0.017 mmol, 48% yield) and **38b** (5.0 mg, 0.013 mmol, 37% yield).



(*E*)-5,5-dimethyl-1-((1*R*,2*R*)-2-methyl-1-((triisopropylsilyloxy)methyl)cyclopropyl)hept-1-en-6-yn-3-one (46)

Dess-Martin periodinane (0.0702 g, 0.166 mmol) was added to the solution of the alcohol **39** (0.0315 g, 0.0832 mmol) in 0.8 mL dichloromethane at room temperature. The oxidation was stirred for 30 min. After filtration, the solvent was removed under reduced pressure. The compound was purified by flash chromatography (5-10% ether in petroleum ether) to yield product **46** (0.0250 g, 0.066 mmol, 80% yield) as a clear liquid.

R_f (20% ether in petroleum ether): 0.53; IR (thin film, cm^{-1}) 3313, 1944, 2868, 1688, 1654, 1609, 1464, 1385, 1366, 1311, 1247, 1111; ^1H NMR (400MHz, $CDCl_3$): _ 6.78 (d, *J*=16.0Hz, 1H), 6.30 (d, *J*=16.0Hz, 1H), 3.78 (d, *J*=10.1Hz, 1H) 3.70 (d, *J*=10.1Hz, 1H), 2.62 (s, 2H), 2.12 (s,1H), 1.32 (s, 6H), 1.11 (d, *J*=6.3Hz, 3H), 1.03 (m, 21H), 0.84 (m, 2H), 0.61 (dd, *J*=4.6, 6.3Hz, 1H); HRMS (EI^+) calculated for $C_{23}H_{40}O_2Si$ $[M]^+$: 376.2798, found: 376.2786.

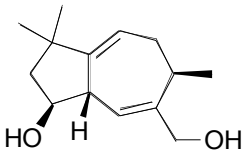


(1*R*,3a*E*,6*S*,7*E*,8a*R*)-7-(hydroxymethyl)-3,3,6-trimethyl-1,2,3,5,6,8a-hexahydroazuln-1-ol (52a)

To a solution of triisopropylsilyl protected **38a** (0.1168 g, 0.31 mmol) in 1 mL THF was added a solution of TBAF trihydrate (0.392 g, 1.24 mmol) with acetic acid (36 _L, 0.62 mmol) dropwise at room temperature. The reaction was allowed to

warm to room temperature and continued for 6 h, then quenched by adding 10 mL ethyl acetate and 10 mL saturated NH_4Cl aqueous solution. The organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography with a small silica gel column (50% EtOAc in petroleum ether) yielded a crude product **52a** (64 mg, 0.288 mmol, 93% yield) as a white semi-solid, which is pure enough to be used in the next reaction.

R_f (60% EtOAc in petroleum ether): 0.28; ^1H NMR (400MHz, $CDCl_3$): _ 5.70 (d, *J*=1.2Hz, 1H), 5.50 (dt, *J*=3.4, 6.6Hz, 1H), 4.20 (dt, *J*=2.1, 4.6Hz, 1H), 3.99 (AB system, *J*=13.6Hz, 2H), 3.53 (d, *J*=8.9Hz, 1H), 2.62 (m, 2H), 2.44 (m, 1H), 2.32 (m, 1H), 2.10(m, 1H), 1.48 (m, 1H), 1.18(s, 3H), , 1.16(d, *J*=7.3Hz, 3H), 1.07 (s, 3H).

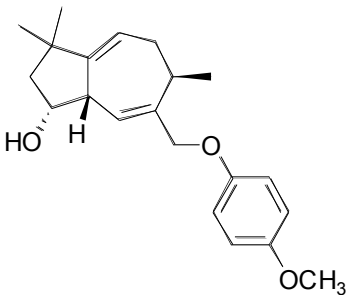


(1*S*,3a*E*,6*S*,7*E*,8a*R*)-7-(hydroxymethyl)-3,3,6-trimethyl-1,2,3,5,6,8a-hexahydroazuln-1-ol (52b)

To a solution of triisopropylsilyl protected **38b** (0.13 g, 0.34 mmol) in 1 mL THF was added a solution of TBAF trihydrate (0.22 g, 0.68 mmol) with acetic acid (20 _L, 0.34 mmol) dropwise at room temperature. The reaction was allowed to warm to room temperature and continued overnight, then quenched by adding 10 mL ethyl acetate and 10 mL saturated NH_4Cl aqueous solution. The organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (50% EtOAc in petroleum ether) with a small silica gel column (50% EtOAc in petroleum ether) yielded a crude product **52b** (75.5 mg, 0.34 mmol, 100%) as a white semi-solid, which is pure enough to be used in the next reaction.

R_f (50% EtOAc in petroleum ether): 0.24; ^1H NMR (400MHz, $CDCl_3$): _

5.72 (s, 1H), 5.40 (m, 1H), 3.99 (m, *3*H), 3.29 (d, *J*=8.7Hz, 1H), 2.31 (m, 2H), 2.13 (m, 1H), 1.88 (q, *J*=5.6Hz, 1H), 1.61 (s, 1H), 1.47, (t, *J* = 10.3Hz, 2H), 1.16 (d, *J* = 7.0 Hz, 3H), 1.12 (s, 3H), 0.98 (s, 3H).

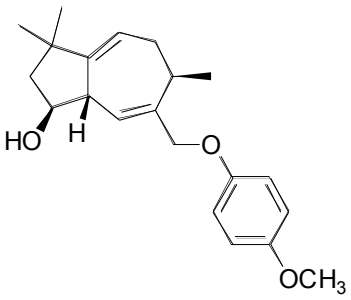


(*1R,3aE,6S,7E,8aR*)-7-((4-methoxyphenoxy)methyl)-3,3,6-trimethyl-1,2,3,5,6,8a-hexahydroazulen-1-ol (53a)

To a solution of **52a** (0.27 g, 1.21 mmol), triphenylphosphine (0.38 g, 1.45 mmol) and *p*-methoxyphenol (0.18 g, 1.45 mmol) in 24 mL THF was added diisopropyl azodicarboxylate (0.30 mL, 1.45 mmol) at 0^{o}C. The reaction was allowed to warm to room temperature and continued overnight. The reaction was quenched by adding 20 mL ethyl acetate and 30 mL saturated NH_4Cl. The organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (10-20% EtOAc in petroleum ether) yielded **53a** (0.33 g, 1.00 mmol, 83% yield) as a colorless liquid.

R_f (17% EtOAc in petroleum ether): 0.22; IR (thin film, cm^{-1}) 3383, 2955, 2834, 1505, 1455, 1372, 1232, 1037; ^{1}H NMR (400MHz, $CDCl_3$): _ 6.81 (m, 4H), 5.83 (s, 1H), 5.53 (dt, *J*=3.2, 6.6Hz, 1H), 4.34 (AB system, *J*=14.6Hz, 2H), 4.20 (dt, *J*=1.9, 3.4Hz, 1H), 3.74 (s, 3H), 3.59 (s, 1H), 2.52 to 2.42 (m, 2H), 2.15 (m, 1H), 1.81 (bs, 1H), 1.69 (t, *J*=1.2Hz, 2H), 1.19 (s, *3*H), 1.18 (s, 3H), 1.08 (s, 3H). ^{13}C NMR (125MHz, $CDCl_3$): _ 153.7, 152.9, 149.3, 143.2, 125.2, 119.2, 115.8, 114.5, 75.0, 73.8, 55.6, 48.7, 48.4, 41.1, 33.4, 32.8, 32.7, 30.9, 17.6; HRMS (EI$^+$) calculated

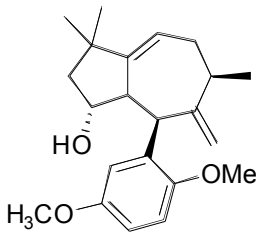
for $C_{21}H_{28}O_3$ $[M]^+$: 328.2038, found: 328.2023; $[\alpha]_D^{24}$= 28.31 (c=0.940, CH_2Cl_2).



(*1S,3aE,6S,7E,8aR*)-7-((4-methoxyphenoxy)methyl)-3,3,6-trimethyl-1,2,3,5,6,8a-hexahydroazulen-1-ol (53b)

To a solution of **52b** (75.5 mg, 0.34 mmol), triphenylphosphine(0.108 g, 0.41 mmol) and *p*-methoxyphenol (51 mg, 0.41 mmol) in 3 mL THF was added diisopropyl azodicarboxylate (0.086 mL, 0.41 mmol) at 0^{o}C. The reaction was continued for 2 h, at which time it was quenched by adding 20 mL ethyl acetate and 30 mL saturated NH_4Cl. The organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (10% EtOAc in petroleum ether) yielded product **53b** (0.086 g, 0.272 mmol, 80% yield) as a colorless liquid.

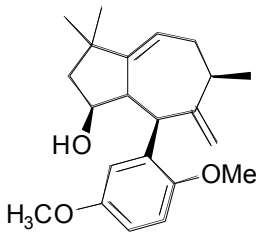
R_f (20% EtOAc in petroleum ether): 0.32; IR (thin film, cm^{-1}) 3383, 2955, 2834, 1505, 1455, 1372, 1232, 1037, 826, 734; ^{1}H NMR (500MHz, $CDCl_3$): _ 6.81 (m, 4H), 5.82 (d, *J* = 1.1Hz, 1H), 5.14 (m, 1H), 4.38 (d, *J* = 11.6Hz, 1H), 4.26 (d, *J* = 11.6Hz, 2H), 3.96 (m, 1H), 3.74 (s, 3H), 3.32 (d, *J* = 7.7 Hz, 1H), 2.40 (m, 1H), 2.30 (m, 1H), 2.16 (m, 1H), 1.86 (q, *J*=5.7Hz, 1H), 1.72 (s, 1H) 1.47 (m, 1H), 1.23 (s, 1H), 1.16 (d, *J* = 7.2Hz, 3H), 1.12 (s, 3H), 0.97 (s, 1H). ^{13}C NMR (125MHz, $CDCl_3$): _ 153.8, 153.1, 150.4, 141.3, 128.1, 118.5, 116.0, 114.6, 76.9, 74.0, 55.8, 48.6, 40.1, 33.3, 33.1, 30.9, 30.5, 38.4; LRMS (EI^+) calculated for $C_{21}H_{28}O_3$ $[M]^+$: 328, found: 328; $[\alpha]_D^{24}$= 24.79 (c=1.0, CH_2Cl_2).



(1*R*,6*S*,8*R*,8a*R*,*E*)-8-(2,5-dimethoxyphenyl)-3,3,6-trimethyl-7-methylene-1,2,3,5,6,7,8,8a-octahydroazulen-1-ol (54a)

A solution of **53a** (0.75 g, 2.28 mmol) in 8 mL diethylaniline was heated to reflux in a sealed tube at 220°C. After 16 h, the reaction was cooled down to room temperature. Then the solvent was removed under reduced pressure at 100°C. The residue was dissolved in 10 mL acetone. K_2CO_3 (0.69 g, 5.0 mmol) and CH_3I (0.62 mL, 10 mmol) were added. The reaction was heated at refluxing temperature for 3 h, and then diluted by addition of 50 mL ether. The organic layer was washed with water, brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (5-10% EtOAc in petroleum ether) yielded product **54a** (0.44 g, 1.28 mmol, 56% yield, 69% brsm) as a pale yellow liquid. Some starting material **53a** (0.144 g, 0.44 mmol) was recovered.

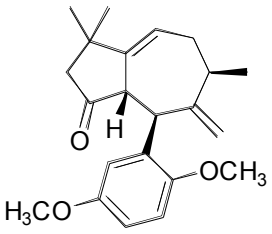
R_f (10% EtOAc in petroleum ether): 0.28; ^{1}H NMR (500MHz, $CDCl_3$): _ 6.85(d, *J*=2.9Hz, 1H), 6.82 (d, *J*=8.9Hz, 1H), 6.73 (dd, *J*=3.1, 8.8Hz, 1H), 5.61 (m, 1H) 4.82 (s, 1H), 4.43 (s, 1H), 4.04 (d, *J*=11.5Hz, 1H), 3.82 (t, *J*=3.7Hz, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 2.89 (d, *J*=11.5Hz, 1H) 2.51 (m, 2H), 1.95 (m, 1H), 1.70-1.56 (m, 4H), 1.22 (s, 2H) 1.17(d, *J*=5.5Hz, 3H) 1.05 (s, 3H). ^{13}C NMR (125MHz, $CDCl_3$): _ 158.1, 153.6, 153.3, 150.9, 132.82, 128.4, 120.0, 116.6, 112.5, 111.2, 109.2, 74.9, 56.6, 55.7, 55.1, 47.1, 42.7, 41.2, 37.1, 33.1, 32.0, 21.8. IR (neat, cm^{-1}) 3563.9, 2953.7, 1494.7, 1463.6, 1280.6, 1226.7, 1049.2; HRMS (EI^+) calculated for $C_{22}H_{30}O_3$ $[M]^+$: 342.2195, found: 342.2210; $[\alpha]_D^{24}$= -52.04 (c=0.31, CH_2Cl_2)



(1*S*,6*S*,8*R*,8a*R*,*E*)-8-(2,5-dimethoxyphenyl)-3,3,6-trimethyl-7-methylene-1,2,3,5,6,7,8,8a-octahydroazulen-1-ol (54b)

A solution of **53b** (24.0 mg, 0.073 mmol) in 1 mL diethylaniline was heated to reflux in a sealed tube at 220°C. After 16 h, the reaction was cooled down to room temperature. Then the solvent was removed under reduced pressure at 100°C. The residue was dissolved in 0.5 mL acetone. K_2CO_3 (15 mg, 0.11 mmol) and CH_3I (15 μL, 0.24 mmol) were added. The reaction was heated to reflux for 3 h. The reaction was diluted by addition of 20 mL ether. The organic layer was washed with water, brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (5-10% EtOAc in petroleum ether) yielded product **54b** (16.0 mg, 0.047 mmol, 64% yield) as a pale yellow liquid. Some starting material **53b** (2.1mg, 0.006 mmol) was recovered.

R_f (20% EtOAc in petroleum ether): 0.50; ^{1}H NMR (500MHz, $CDCl_3$): _ 6.86(m, 2H), 6.75 (m, 1H), 5.63 (m, 1H) 4.82 (s, 1H), 4.48 (s, 1H), 3.81 (q, *J*=7.0Hz, 1H), 3.75 (s, 3H), 3.74 (s, 3H), 3.69 (d, *J* = 10.8 Hz, 1H) 2.91 (t, *J*=7.4Hz, 1H) 2.27 (m, 2H), 2.00 (m, 1H), 1.78 (m, 1H), 1.57 (s, 1H), 1.43-1.48 (m, 2H) 1.23 (s, 2H) 1.14(d, *J*=7.1Hz, 3H) 1.12 (s, 3H). ^{13}C NMR (125MHz, $CDCl_3$): _ 157.4, 155.0, 153.3, 151.6, 132.1, 120.1, 117.1, 113.2, 112.2, 109.2, 76.2, 56.5, 55.8, 55.1, 48.1, 41.3, 40.6, 36.7, 31.0, 29.5, 21.8. IR (neat, cm^{-1}) 3568, 3448, 2956, 1635, 1609, 1589, 1496, 1464, 1417, 1281, 12263, 1177, 1050; LRMS (EI^+) calculated for $C_{22}H_{30}O_3$ $[M]^+$: 342, found: 342; $[\alpha]_D^{24}$= -17.40 (c=0.1, CH_2Cl_2)



(6*R*,8*S*, 8a*R*, *E*)-8-(2,5-dimethoxyphenyl)-3,3,6-trimethyl-7-methylene-2,3,6,7,8,8a-hexahydroazulen-1(5H)-one (37)

From **54a**:

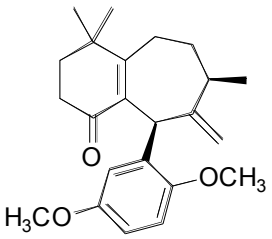
To a solution of **54a** (0.10 g, 0.29 mmol) in 5 mL dichloromethane was added Dess-Martin periodinane (0.25 g, 0.58 mmol) and $NaHCO_3$ (0.24 g, 2.9 mmol) at 0°C. The reaction continued for 1 h at 0°C. Then the mixture was poured into NH_4Cl saturated aqueous solution. The aqueous layer was separated and washed with ether. The organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (5% EtOAc in petroleum ether) yielded product **37** (97.2 mg, 0.285 mmol, 98%) as a pale yellow liquid.

R_f (20% EtOAc in petroleum ether): 0.59; IR (thin film, cm^{-1}) 2958, 2926, 1747, 1589, 1496, 1464, 1415, 1281, 1223, 1179, 1159, 1053, 1029; ^1H NMR (500MHz, $CDCl_3$): _ 6.82 (d, *J*=2.9Hz, 1H), 6.75 (d, *J*=8.8Hz, 1H), 6.70 (dd, *J*=2.9, 8.8Hz, 1H), 5.82 (m, 1H) 4.74 (t, *J*=0.7Hz, 1H), 4,66 (t, *J*=0.7Hz, 1H), 4.19 (d, *J*=6.4Hz, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 3.63 (m, 1H), 2.42 (m, 1H), 2.30-2.05 (m, 4H) 1.22 (s, 3H), 1.21 (s, 3H) 0.82 (d, *J*=7.0Hz, 3H); ^{13}C NMR (125MHz, $CDCl_3$): _ 214.3, 154.5, 152.9, 152.6, 148.8, 132.5, 120.7, 116.5, 112.4, 111.5, 110.6, 56.1, 55.7, 54.8, 54.0, 45.1, 42.1, 38.9, 34.2, 29.9, 28.1, 22.4 ppm; HRMS (EI^+): Calculated for $C_{22}H_{28}O_3$ (M^+), 340.2038, found, 340.2048; $[\alpha]_D^{24}$= +65.58 (c=0.35, CH_2Cl_2)

From **54b**:

YH-XXIV-50

To a solution of **54b** (8.3 mg, 0.024 mmol) in 0.4 mL dichloromethane was added Dess-Martin periodinane (15 mg, 0.038 mmol) and $NaHCO_3$ (20 mg, 0.24 mmol) at 0^oC. The reaction continued for 30 min at 0^oC. Then the mixture was poured into NH_4Cl saturated aqueous solution. The aqueous layer was separated and washed with ether. The organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (5% EtOAc in petroleum ether) yielded product **37** (8.0 mg, 0.023 mmol, 96%) as a pale yellow liquid. IR and ^1H NMR match the data of the product **37** obtained from the oxidation of **54a**



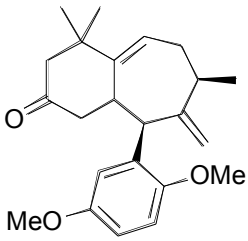
(*7R*, *9S*)-9-(2,5-Dimethoxyphenyl)-4,4,7-trimethyl-8-methylene-2,3,4,5,6,7,8,9-octahydro benzocyclohepten-1-one (36)

To a solution of ketone **37** (0.33 g, 0.97 mmol) in 10 mL methylene chloride at -25^oC was added BF_3 etherate (0.15 mL, 1.22 mmol) followed by $TMSCHN_2$ (0.61 mL, 2 M in ether, 1.22 mmol). The reaction was stirred at this temperature for 8 h. Then a saturated solution of $NaHCO_3$ (20 mL) was injected to quench the reaction. The mixture was extracted with 3 X 20 mL ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to yield crude product as a pale yellow liquid.

The crude product was then dissolved in 10 mL acetonitrile. TBAF trihydrate (0.63 g, 2.0 mmol) was added at room temperature. The reaction was stirred for 4 h. Then it was diluted with 30 mL ethyl acetate and 30 mL water. The mixture was extracted with 2 X 30 mL ethyl acetate, washed with brine, dried over $MgSO_4$,

and concentrated under reduced pressure. Flash chromatography (5-10% ethyl acetate in petroleum ether) yielded the desired product **36** (185 mg, 0.52 mmol, 54% yield) along with ketone **58** (78 mg, 0.22 mmol, 23%) and aldehyde **59** (48 mg, 0.136 mmol, 14%).

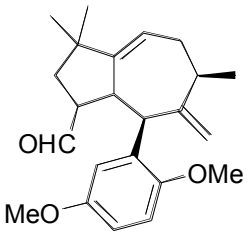
R_f (10% ethyl acetate in petroleum ether): 0.25; IR (thin film, cm^{-1}) 2919, 2850, 1672, 1496, 1458, 1415, 1277, 1218, 1105, 1050; ^1H NMR (500MHz, $CDCl_3$): _ 6.82 (d, *J* = 8.8Hz, 1H), 6.67 (dd, *J* = 3.2, 8.8Hz, 1H), 6.50 (d, *J* = 3.0Hz, 1H), 5.24 (t, *J* = 2.7Hz, 1H), 4.69 (d, *J* = 3.0Hz, 1H), 4.23(m, 1H), 3.82 (s, 3H), 3.68 (s, 3H), 2.83 (m, 1H), 2.32 (m, 4H), 2,19 (m, 1H), 1.91(m, 1H), 1.78 (m, 1H), 1.41 (m, 1H), 1.24 (s, 3H), 1.20 (s, 3H), 1.08 (d, *J* = 6.9Hz, 3H) ppm; ^{13}C NMR (125MHz, $CDCl_3$): _ 197.8, 163.5, 154.7, 153.7, 152.4, 134.5, 132.3, 114.4, 112.9, 111.4, 105.9, 57.2, 55.4, 45.0, 38.1, 37.4, 36.7, 34. 9, 27.2, 26.8, 25.8, 19.3 ppm; HRMS (EI^+) calculated for $C_{23}H_{30}O_3$ $[M]^+$: 354.2195, found: 354.2190; $[\alpha]_D^{24}$= 21.04 (c=0.59, CH_2Cl_2).



(7*R*, 9*S*)-9-(2,5-Dimethoxy-phenyl)-4,4,7-trimethyl-8-methylene-1,3,4,6,7,8,9,9a-octahydro-benzocyclohepten-2-one (58)

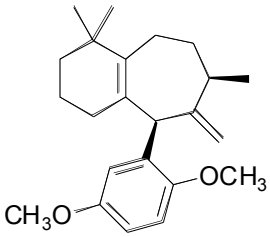
R_f (10% ethyl acetate in petroleum ether): 0.35; IR (thin film, cm^{-1}) 2960, 1714, 1642, 1590, 1496, 1464, 1416, 1281, 1221, 1052; ^1H NMR (500MHz, $CDCl_3$): _ 6.80 (d, *J* = 2.9Hz, 1H), 6.69 (d, *J* = 8.8Hz, 1H), 6.61 (dd, *J* = 2.8, 8.9Hz, 1H), 5.66 (m, 1H), 4.71 (s, 1H), 4.55 (s, 1H), 4.23(d, *J* =10.9 Hz, 1H), 3.69 (s, 3H), 3.65 (s, 3H), 3.17 (m, 1H), 2.91 (m, 1H) 2.83 (m, 1H), 2.76 (m, 1H), 2.40 (m, 1H), 2.32 (m, 1H), 2.01-2.14 (m, 1H), 1.91(m, 1H), 1.09 (s, 3H), 1.06(s, 3H), 1.00 (d, *J* = 8.8Hz, 3H)

ppm; LRMS (EI^+) calculated for $C_{23}H_{30}O_3$ $[M]^+$: 354, found: 354.



(7*R*, 9*S*)-8-(2,5-Dimethoxy-phenyl)-3,3,6-trimethyl-7-methylene-1,2,3,5,6,7,8,8a-octahydro-azulene-1-carbaldehyde (59)

R_f (10% ethyl acetate in petroleum ether): 0.43; IR (thin film, cm^{-1}) 2958, 1723, 1503, 1464, 1280, 1225, 1177, 1049; ^1H NMR (500MHz, $CDCl_3$): _ 9.05 (d, *J*=3.9 Hz, 1H), 6.76 (d, *J*=8.9 Hz, 1H), 6.70 (dd, *J* = 8.8, 2,9Hz, 1H), 6.65 (d, *J*=2.9Hz, 1H), 5.67 (m, 1H), 4.84 (s, 1H), 4.53 (s, 1H), 3.73 (s, 3H), 3.69 (s, 3H), 2.42 (m, 1H), 2.25(m, 2H), 2.03(m, 1H), 1.60 (s, 1H), 1.50 (m, 2H), 1.41(s, 1H), 1.15(d, *J*=6.9Hz, 3H), 1.07 (s, 3H), 1.06(s, 3H) ppm; LRMS (EI^+) calculated for $C_{23}H_{30}O_3$ $[M]^+$: 354, found: 354.

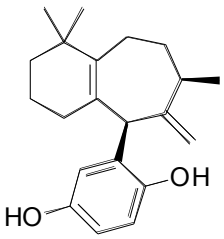


(7*R*, 9*S*)-5-(2,5-Dimethoxy-phenyl)-1,1,7-trimethyl-6-methylene-2,3,4,5,6,7,8,9-octahydro-1H-benzocycloheptene (61)

To a solution of compound **36** (19.2 mg, 0.054 mmol) in $TMSSCH_2CH_2STMS$ (0.10 mL, 0.34 mmol) was added TMSOTf (0.010 mL, 0.054 mmol). The reaction was stirred at room temperature for 24 h. Then the solution was canulated into aqueous $NaHCO_3$ solution. The aqueous layer was extracted with 2 X 20 mL ethyl acetate. The

combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Then 1 mL methanol was added, followed with about 0.5 g Raney Ni, washed with methanol before the addition. This suspension was stirred for 2 h at room temperature. Then the Raney Ni was removed by filtration through a celite pad. The filtrate was concentrated. Flash chromatography (5% ethyl acetate in petroleum ether) yielded product **61** (15.4 mg, 0.045 mmol, 83% yield) as a colorless liquid. 1H NMR matches the reported data.[6]

R_f (10% ethyl acetate in petroleum ether): 0.60; IR (thin film, cm^{-1}): 2925, 2854, 1496, 1464, 1276, 1239, 1220, 1053; ^1H NMR (500MHz, $CDCl_3$): _ 6.83 (d, *J* = 8.7Hz, 1H), 6.76 (dd, *J* = 2.8, 8.6Hz, 1H), 6.71 (d, *J* = 2.9 Hz, 1H), 4.64 (d, *J* = 1.9Hz, 1H), 4.25 (s, 1H), 4.14 (dd, *J* = 1.0, 1.1Hz, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 2.49 (m, 1H), 1.84-2.00 (m, 3H), 1.21-1.64 (m, 7H), 1.10 (d, *J* = 6.9Hz, 3H), 1.07 (s, 3H), 1.04 (s, 3H) ppm; ^{13}C NMR (125MHz, $CDCl_3$): _ 156.4, 154.0, 152.7, 137.6, 132.6, 130.6, 116.4, 114.4, 112.1, 105.1, 56.9, 55.5, 52.8, 39.6, 39.5, 35.5, 35.4, 31.9, 28.2, 28.0, 15.1, 20.1, 19.6 ppm; LRMS (EI^+) calculated for $C_{23}H_{32}O_2$ $[M]^+$: 340.2402, found: 340.2390; $[\alpha]_D^{24}$= 251 (c=0.72, CH_2Cl_2).

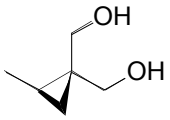


Frondosin A (1)

Solvent (50% water in acetonitrile) was degassed by bubbling with argon for 30 min before use. To compound **58** (4.4 mg, 0.013 mmol) in 0.13 mL solvent at 0°C was added dropwise a solution of cerium (IV) ammonium nitrate (CAN, 14 mg,

0.026 mmol) in 0.13 mL solvent. After 10 min, $NaHCO_3$ (43 mg, 0.52 mmol) was added, followed with $Na_2S_2O_4$ (23 mg, 0.13 mmol). The reaction was stirred vigorously at room temperature for 1 h. The mixture was filtered through silica gel pad and concentrated under argon atmosphere. Separation through achiral HPLC (2% isopropyl alcohol in heptane) yielded frondosin A (2.0 mg, 0.0064 mmol, 49% yield, 89% yield brsm), along with starting material **50** (2.0 mg, 0.0059 mmol, 45%). ^{1}H NMR, IR, and $[\alpha]_D^{20}$ match the reported data.[6]

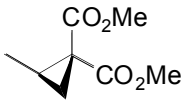
R_f = 0.33 (25% ethyl acetate in petroleum ether); IR (thin film, cm^{-1}) 3384, 2956, 2932, 2871, 1636, 1497, 1452, 1410, 1361, 1279, 1212, 1190, 1147; ^{1}H NMR (400MHz, $CDCl_3$): _ 6.77 (d, *J* = 8.5Hz, 1H), 6.67 (dd, *J* = 2.9, 8.5Hz, 1H), 6.59 (d, *J* = 3.0Hz, 1H), 4.85 (s, 1H), 4.52 (s, 1H), 3.95 (s, 1H), 2.49, (m, 2H), 2.04 (m, 1H), 1.87 (m, 3H), 1.56-1.51 (m, 4H); 1.29 (m, 1H), 1.10 (s, 3H), 1.09 (s, 3H), 1.06 (d, *J* = 7.0Hz, 3H) ppm; HRMS (Maldi-Tof): Calculated for $C_{21}H_{28}O_2$, $[M+H]^+$ 313.2089, found $[M+H]^+$ 313.2081; $[\alpha]_D^{20}$= 37.6° (c=0.20, MeOH), lit. $[\alpha]_D^{20}$ = 31.5° (c = 0.25, MeOH).[6]



(*R*)-(1-Hydroxymethyl-2-methyl-cyclopropyl)-methanol (62)

To a solution of compound **33** (0.15 g, 0.55 mmol) in 3 mL THF under N_2 was added TBAF trihydrate (0.25 g, 0.80 mmol) at room temperature. Reaction continued for 30 min. Then the solution was concentrated under reduced pressure. Flash chromatography (ethyl acetate) over a short silica gel column afforded crude product **62** (0.12 g, quant., with some amount of TIPSOH) as pale yellow liquid, which is good for the next reaction. IR and ^{1}H NMR match the reported data.[7]

R_f (ethyl acetate): 0.37; IR (thin film, cm^{-1}): 3334, 2942, 2866, 1464, 1384, 1249, 1093, 1039, 919, 884, 851, 742; ^1H NMR (500 MHz, $CDCl_3$): _ 3.73 (d, *J* = 11.7Hz, 1H), 3.47 (d, *J* = 11.7 Hz, 1H), 3.43 (d, *J* = 11.4 Hz, 1H), 3.29 (d, *J* = 11.3 Hz, 1H), 1.03 (d, *J* = 6.2 Hz, 3H), 0.68 (m, 1H), 0.44 (m, 1H), -0.03 (m, 1H).



(*R*)-2-Methyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester (63)

To a solution of the above curde diol **62** (0.55 mmol) in 2 mL CCl_4, 2 mL CH_3CN, and 3 mL H_2O, was added $NaIO_4$ (3.5 g, 16.5 mmol) and $RuCl_3$ trihydrate (14.4 mg, 0.055 mmol). Reaction continued for 6 h. Then CH_2Cl_2 (20 mL) and NaCl (25 mL) were added. The organic layer was separated. The aqueous layer was further extracted with CH_2Cl_2 (20 mL) and ethyl acetate (3 X 20 mL). The combined organic layers were concentrated and then diluted with CH_2Cl_2 (40 mL). NaOH solution (1M in water, 40 mL) was used for the basic extraction. The basic aqueous layer was washed with ether (2 X 20 mL). Then it was acidified with 3M HCl until pH was about 3-4. Then NaCl solid was added to saturate the aqueous layer, which was then extracted with ethyl acetate (3 X 30 mL). The combined organic layers was dried over Na_2SO_4 and concentrated under reduced pressure to yield crude acid for the next reaction.

Characterization for the bisacid:

IR (thin film, cm^{-1}): 3400, 3100, 2932, 2872, 2573, 1732, 1715, 1694, 1645, 1634, 1435, 1276, 1216, 1162, 1104, 1056; ^1H NMR (500 MHz); _ 10.94 (bs, 2H), 2.23 (m, 1H), 2.02 (m, 1H), 1.79 (m, 1H), 1.34 (d, *J* = 6.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): _ 176.7, 173.9, 33.3, 30.9, 26.7, 12.6 ppm.

To the above crude bisacid in a mixture of benzene (7 mL) and methanol (1.8 mL) at room temperature was added $TMSCHN_2$ (1.4 mL, 2 M in ether, 2.8 mmol). Reaction continued for overnight. Water (15 mL) was then added. The mixture was stirred for 20 min. Then it was extracted with ether (3 X 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (10% ether in petroleum ether) yielded product **63** (41 mg, 0.24 mmol, 44% yield) as colorless liquid. IR, ^1H NMR, ^{13}C NMR, and $[\alpha]_D^{20}$ match the reported data.[8]

IR (thin film, cm^{-1}) 2956, 2868, 1731, 1438, 1332, 1283, 1214, 1134, 1101, 1058, 1019; ^1H NMR (400MHz, $CDCl_3$): _ 3.72 (s, 3H), 3.67 (s, 3H), 1,89 (m, 1H), 1.39 (m, 1H), 1.31 (m, 1H), 1.06 (d, J = 6.4Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): _ 171.0, 168.6, 52.6, 52.5, 34.2, 23.2, 22.3, 13.6 ppm; LRMS (EI^+): Calculated for $C_8H_{12}O_4$, $[M]^+$ 172, found 172; $[\alpha]_D^{20}$= -46.5° (c=4.0, $CHCl_3$), lit. $[\alpha]_D^{20}$ = -53° (c = 1.15, $CHCl_3$).

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[1] (a) Rank, E.; Brückner, R. *Eur. J. Org. Chem.* **1998**, 1045-1053. (b) Shiner, V.J.; Wilson, W. *J. Am. Chem. Soc.* **1962**, *84*, 2402.
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