Exploiting the Pd- and Ru-Catalyzed Cycloisomerizations: Enantioselective Total Synthesis of (+)-Allocyathin B₂

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Supplementary information

General

All reactions were performed under a nitrogen atmosphere unless otherwise indicated. Some solvents were freshly purified by column before use: acetonitrile, methylene chloride, toluene, benzene, triethylamine, dimethylformamide, tetrahydrofuran and pyridine and diethyl ether. Tetrahydrofuran for Negishi reaction was distilled from sodium benzophenone ketyl. Methanol was distilled from magnesium methoxide. All reagents were used as obtained unless otherwise noted.

Flash Chromatography was performed with EM Science silica gel (0.040-0.063 μm grade). Analytical thin-layer chromatography was performed with 0.2mm coated commercial silica gel plates (E. Merck, DC-Plasrikfolien, kieselgel 60 F₂₅₄). Melting points were obtained on a Thomas-Hoover apparatus in open capillary tubes and are uncorrected.

Proton nuclear magnetic resonance (¹H-NMR) data were acquired at 300 MHz on a Varian GEM-300, 400 MHz on a Varian GEM-400 and at 500 MHz on a Varian GEM-500 spectrometer. Chemical shifts are reported in delta (δ) units, in parts per million (ppm) downfield from tetramethylsilane, or in ppm relative to the singlet at 7.26ppm from chloroform-*d*. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; sept, septet; m, multiplet, br, broad. Carbon-13 nuclear magnetic resonance (¹³C-NMR) data were acquired at 75 MHz on a Varian GEM-300, 100 MHz on a Varian GEM-400 and at 125 MHz on a Varian GEM-500 spectrometer. Chemical shifts are reported in ppm relative to the center line of a triplet at 77.0 ppm for chloroform-*d*.

Infrared (IR) data were recorded as films on sodium chloride plates or a potassium bromide (KBr) pellets on a Perkin-Elmer Paragon 500 FT-IR spectrometers.

Absorbance frequencies are reported in reciprocal centimeters (cm^{-1}). High resolution mass spectral data (HRMS) were obtained from Mass Spectrometry Resource, School of Pharmacy, University of California-San Francisco, on a Kratos MS9 spectrometer at an ionizing current of 98 mA and an ionizing voltage of 70 eV. Elemental analyses (Anal.) were performed by M.-H.-W. Laboratories of Pheonix, AZ. Chiral HPLC analyses were performed on a Spectra Series P-100 chromatograph using the chiral column and heptane:*iso*-propanol mixtures indicated. Optical rotations were measured on a Jasco DIP-1000 digital polarimeter using 5cm cells and the sodium D line (589 nm) at ambient temperature in the solvent and concentration indicated.

(*R*)-2-*tert*-Butoxymethylene-5-methyl-5-(2-propenyl)cyclopentanone (8). To a solution of LDA (67.0 mmol) in 170 mL of DME at $-78\text{ }^{\circ}\text{C}$ was added a solution of enol ether **7** (6.1 g, 33.5 mmol) in 10 mL of DME. After stirring at $0\text{ }^{\circ}\text{C}$ for 15 min, the reaction was charged with *tert*-butanol (22.4 mL, 235 mmol) followed by a solution of trimethyltin chloride (6.67 g, 33.5 mmol) in 10 mL of DME. After stirring at $0\text{ }^{\circ}\text{C}$ for 5 min, the reaction was cooled to $-78\text{ }^{\circ}\text{C}$. Meanwhile, a solution of π -allyl palladium chloride dimer (61.3 mg, 0.168 mmol) and (*S,S*)-ligand (230 mg, 0.335 mmol) in DME (10 mL) was stirred at room temperature for 10 min. The catalyst solution was charged with allyl acetate (4.0 mL, 36.8 mmol) and was then added to the enolate solution at $-78\text{ }^{\circ}\text{C}$. The cooling bath was removed and the reaction was stirred at room temperature overnight. The reaction was diluted with 200 mL of ether and 200 mL of water. The layers were separated and the aqueous phase was extracted with ether ($2 \times 200\text{ mL}$). The

pooled organic extracts were washed with brine (1 × 200 mL), dried (MgSO₄), filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (10% ether/petroleum ether) to give enol ether **8** (6.20 g, 83%) as a colorless liquid. Determination of enantiomeric excess: chiral GC (cyclosil B, isotherm 120 °C) (+) enantiomer t_R = 74.825 min, (-) enantiomer t_R = 74.169 min. $[\alpha]_D^{23.7} = +25.2$ (c 1.0, 23.7 °C, dichloromethane, 95% ee). IR (neat) 2977, 2869, 1708, 1630, 1458, 1371, 1265, 1156, 980, 945 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 7.50 (t, J = 2.5 Hz, 1 H), 5.68-5.76 (m, 1 H), 5.02 (d, J = 14.0 Hz, 2 H), 2.41-2.44 (m, 2 H), 2.13-2.15 (m, 2 H), 1.81-1.87 (m, 1 H), 1.55-1.60 (m, 1 H), 1.34 (s, 9 H), 1.00 (s, 3 H); ¹³C NMR (CDCl₃, 125 MHz) δ 210.9, 149.0, 134.6, 117.6, 115.2, 79.8, 49.5, 41.3, 32.5, 28.3, 22.0, 21.3. Anal. Calc'd for C₁₄H₂₂O₂: C, 75.63; H, 9.97. Found: C, 75.84; H, 10.18.

(R)-5-Isopropyl-2-methyl-2-(2-propenyl)cyclopentanone (9). Methyllithium (100 mL, 1.4 M solution in ether, 140 mmol) was added to a suspension of freshly purified copper(I) iodide (13.3 g, 70 mmol) in 180 mL of ether at -20 °C. The solution was stirred at -20 °C for 30 min at which point it was completely homogeneous. A solution of ketone **8** (6.22 g, 28.0 mmol) in 20 mL of ether was added dropwise. The reaction was allowed to warm to room temperature overnight and was then carefully poured into 200 mL of saturated NH₄Cl. The layers were separated and the aqueous solution was extracted with ether (2 × 200 mL). The ethereal extracts were pooled, washed with brine and NaHCO₃ (1 × 200 mL each), dried (MgSO₄), filtered, and concentrated under reduced pressure. The crude product was purified by column

chromatography (10% ether/petroleum ether) to give **9** (4.30 g, 85%) as a volatile colorless liquid (1:1 mixture of diastereomers). More practically, the volatile isopropyl ketone was concentrated to a minimal volume after purification and used in the next reaction with some residual solvent. IR (neat) 2960, 2872, 1732, 1640, 1457, 1370, 1065, 996, 916 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 5.59-5.68 (m, 1 H), 4.95-5.08 (m, 2 H), 1.43-2.10 (m, 8 H), 0.96 (d, $J = 7.2$ Hz, 3 H), 0.92 (s, 1.5 H), 0.89 (s, 1.5 H), 0.78 (d, $J = 7.2$ Hz, 3 H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 223.3, 223.2, 134.1, 133.6, 118.1, 117.9, 55.8, 54.6, 48.7, 48.4, 42.0, 39.6, 33.2, 32.6, 27.4, 27.1, 22.5, 21.3, 21.1, 21.0, 20.6, 20.4, 18.5, 18.2; HRMS Calc'd for $\text{C}_{12}\text{H}_{20}\text{O}$ [M^+]: 180.1514; Found: 180.1508.

(R)-2-Isopropyl-5-methyl-5-(2-propenyl)cyclopentanone enol triflate (10). To a solution of LDA [prepared from diisopropylamine (3.63 mL, 25.9 mmol) and *n*-butyllithium (1.6 M in hexanes, 16.2 mL, 25.9 mmol) in 100 mL of THF at -78 $^{\circ}\text{C}$ was added a solution of ketone **9** (3.9 g, 21.6 mmol) in 20 mL of THF. The reaction was stirred at 0 $^{\circ}\text{C}$ for 15 min and was then charged with a solution of *N*-phenyltrifluoromethanesulfonimide (10.8 g, 30.3 mmol) in 30 mL of THF. The reaction was stirred at room temperature for 2 h and was then diluted with 100 mL of ether and 100 mL of water. The layers were separated and the aqueous phase was extracted with ether (2×100 mL). The pooled extracts were washed with water and brine (1×150 mL each), dried (MgSO_4), filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (petroleum ether to 5% ether/petroleum ether) to give **10** (6.54 g, 98%) as a colorless liquid. IR (neat) 3080, 2968, 2936, 2875,

1684, 1642, 1409, 1213, 1142, 1027, 843, 610 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 5.68-5.76 (m, 1 H), 5.02-5.07 (m, 2 H), 2.81 (p, $J = 7$ Hz, 1 H), 2.19-2.27 (m, 3 H), 2.08 (q, $J = 8.0$ Hz, 1 H), 1.90-1.95 (m, 1 H), 1.61-1.67 (m, 1 H), 1.12 (s, 3 H), 1.00 (d, $J = 7.0$ Hz, 3 H), 0.99 (d, $J = 7.0$ Hz, 3 H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 144.9, 138.0, 134.2, 118.6, 117.9, 46.3, 43.0, 32.9, 25.7, 24.4, 23.8, 20.5, 20.2; HRMS Calc'd for $\text{C}_{10}\text{H}_{14}\text{F}_3\text{O}_3\text{S}$ $[\text{M}-\text{C}_3\text{H}_5]^+$: 271.0616. Found: 271.0618.

(*R*)-2-Isopropyl-5-methyl-5-(2-propenyl)-cyclopent-1-enylethynyl-

trimethylsilane (6). To a prestirred solution (10 min) of $\text{Pd}_2\text{dba}_3 \cdot \text{CHCl}_3$ (471 mg, 0.455 mmol) and triphenylphosphine (953 mg, 3.64 mmol) in benzene (20 mL) was added triflate **10** (5.7 g, 18.2 mmol) at room temperature. The catalyst solution was transferred to a solution of copper(I) iodide (173.3 mg, 0.91 mmol), trimethylsilylacetylene (7.74 mL, 54.7 mmol), and *n*-butylamine (4.14 mL, 41.9 mmol) in benzene (30 mL). After being stirred at 50 $^\circ\text{C}$ for 18 h, the reaction was cooled to room temperature and diluted with 50 mL of water. The layers were separated and the organic layer was washed with 50 mL of brine, dried (MgSO_4), filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (5% ether/petroleum ether) to give alkyne **6** (4.18 g, 85%) as a colorless liquid. $[\alpha]_{\text{D}} = +8.72$ (c 1.00, 25.3 $^\circ\text{C}$, dichloromethane). IR (neat) 2960, 2870, 2138, 1250, 842 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 5.71-5.80 (m, 1H), 4.96-5.02 (m, 2 H), 2.90 (sept, $J = 7.0$ Hz, 1 H), 2.14-2.29 (m, 3 H), 2.08 (dd, $J = 13.5, 8$ Hz, 1H), 1.75-1.81 (m, 1 H), 1.46-1.51 (m, 1 H), 1.05 (s, 3 H),

0.99 (d, $J = 7.0$ Hz, 6 H), 0.17 (s, 9 H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 157.4, 136.0, 124.6, 116.6, 101.1, 99.1, 50.0, 44.5, 34.5, 19.1, 15.7, 21.0, 20.7, 0.2; HRMS Calc'd for $\text{C}_{17}\text{H}_{28}\text{Si}$ [M^+]: 260.1960. Found: 260.1958.

(*R*)-2-Isopropyl-5-methyl-5-(propan-1-ol)-cyclopent-1-enylethynyl-

trimethylsilane (11). To a solution of 9-BBN-H (2.06 g, 16.9 mmol) in THF (80 mL) at 0 °C was added a solution of alkyne **6** (3.8 g, 14.0 mmol) in THF (20 mL). The reaction was stirred at room temperature for 3 h. After cooling to 0 °C, the reaction was charged with 7.6 mL of 3 M NaOH followed by the dropwise addition of 30 % hydrogen peroxide (7.6 mL). The reaction was stirred at room temperature for 4 h and was then diluted with 100 mL of brine. The aqueous layer was extracted with ether (3 × 100 mL). The combined extracts were dried (MgSO_4), filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (30% ether/petroleum ether) to give alcohol **11** (3.50 g, 87%) as a colorless liquid. $[\alpha]_{\text{D}} = +9.25^\circ$ (c 1.32, 27.0 °C, dichloromethane). IR (neat) 3334, 2959, 2870, 2137, 1454, 1249, 1058, 857, 842, 759 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 3.60 (t, $J = 6.5$ Hz, 2 H), 2.90 (p, $J = 7$ Hz, 1 H), 2.23-2.32 (m, 2 H), 1.71-1.76 (m, 1 H), 1.40-1.59 (m, 3 H), 1.05 (s, 3 H), 1.00 (d, $J = 2$ Hz, 3 H), 0.98 (d, $J = 2.5$ Hz, 3 H), 0.16 (s, 9 H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 157.3, 124.7, 101.3, 99.0, 63.7, 49.8, 35.8, 34.7, 29.3, 29.2, 28.3, 26.1, 21.0, 20.7, 0.2. HRMS Calc'd for $\text{C}_{17}\text{H}_{30}\text{OSi}$ [M^+]: 278.2066. Found: 278.2062.

(R)-5-(3-Iso-propyl-1-methyl-2-trimethylsilanylethynyl-cyclopent-2-enyl)-pent-2-ynoic acid methyl ester (12). To a stirred solution of $(\text{COCl})_2$ (171.4 mg, 1.35 mmol) in CH_2Cl_2 (8 mL) was added dropwise DMSO (245.7 mg, 3.14 mmol) at -78°C . The mixture was stirred for 5 min before a solution of compound **11** (250.1 mg, 0.9 mmol) in CH_2Cl_2 (4 mL) was added slowly. The mixture was stirred at -78°C for 15 min followed by addition of TEA (381.8 mg, 3.78 mmol). After being stirred for 10 min, the mixture was allowed to warm up to room temperature. The white slurry was treated with water (10 mL) and ether (30 mL). After separation of the layers, the organic phase was washed with water (10 mL), brine (5 mL), dried (MgSO_4), filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography (3% ether in petroleum ether) to afford the corresponding aldehyde as a clear oil (208.6 mg, 84%). ^1H NMR (CDCl_3 , 500 MHz) δ 9.77 (s, 1 H), 2.89 (sept, J = 7.0 Hz, 1 H), 2.24-2.41 (m, 4 H), 1.55-1.80 (m, 4 H), 1.08 (s, 3 H), 1.00 (d, J = 6.5 Hz, 6 H), 0.18 (s, 9 H).

To a stirred solution of PPh_3 (705.4 mg, 2.689 mmol) in CH_2Cl_2 (5 mL) was added CBr_4 (445.7 mg, 1.334 mmol) at 0°C . After being stirred for 3 min, a solution of the aldehyde (185.7 mg, 0.672 mmol) in CH_2Cl_2 (2 mL) was added. The mixture was stirred at 0°C for 10 min and quenched with addition of pentane (30 mL). The suspension was filtered through a pad of celite. The filtrate was concentrated and

purified by column chromatography (100% petroleum ether). The dibromoolefin was obtained as a clear liquid (272.9 mg, 94%).

To a stirred solution of the above dibromoolefin in THF (3 mL) was added *n*-BuLi (2.45 M in hexanes, 0.6 mL, 1.466 mmol) at -78°C . The solution was stirred at this temperature for 40 min and allowed to warm up to room temperature. After being stirred for 1 h, the mixture was cooled again to -78°C and freshly distilled methyl chloroformate (110.7 mg, 1.172 mmol) was added dropwise. After being stirred at -78°C for 1 h, the mixture was warmed up to room temperature and stirred overnight. The mixture was treated with ether (30 mL) and saturated NH_4Cl (10 mL). After separation of the layers, the organic phase was washed with brine (5 mL), dried (MgSO_4), filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography (3% ether in petroleum ether) to afford compound **12** as a clear oil (206.4 mg, 99%), $[\alpha]_{\text{D}} = +9.32^{\circ}$ (*c* 0.90, CH_2Cl_2). IR (neat) 2959, 2870, 2239, 2137, 1719, 1435, 1251, 1075, 843, 754 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 3.73 (s, 3 H), 2.89 (sept, $J = 7.0$ Hz, 1 H), 2.21-2.34 (m, 4 H), 1.54-1.76 (m, 4 H), 1.05 (s, 3 H), 0.99 (d, $J = 2.5$ Hz, 3 H), 0.98 (d, $J = 2.5$ Hz, 3 H), 0.16 (s, 9 H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 158.1, 154.3, 123.5, 100.5, 99.7, 90.7, 72.4, 52.5, 49.8, 37.9, 34.8, 29.3, 29.2, 25.6, 21.0, 20.7, 14.5, 0.2. HRMS Calc'd for $\text{C}_{20}\text{H}_{30}\text{O}_2\text{Si}$ [M^+]: 330.2015. Found: 330.2029.

(Z)-(R)-5-(2-Ethynyl-3-isopropyl-1-methyl-cyclopent-2-enyl)-3-methyl-pent-2-en-1-ol (14). To a suspension of freshly purified CuI (800 mg, 4.2 mmol) in THF (15

mL) was added a pre-cooled solution of MeLi (1.6 M, 5.0 mL, 8.0 mmol) dropwise at $-78\text{ }^{\circ}\text{C}$. The suspension was warmed to $-5\text{ }^{\circ}\text{C}$ and stirred for 5 min before being cooled down to $-78\text{ }^{\circ}\text{C}$. To this clear cuperate solution was added a pre-cooled solution of compound **12** (1.26g, 3.82 mmol) in THF (6 mL). The mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 3 h before being quenched with slow addition of MeOH (3 mL) and saturated NH_4Cl solution at $-78\text{ }^{\circ}\text{C}$. The suspension was treated with ether (80 mL). After separation of the layers the organic phase was washed with water (15 mL), brine (10 mL), dried (MgSO_4), filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography (3% ether in petroleum ether) to afford compound **13** as a clear oil (1.229 g, 93%). ^1H NMR (CDCl_3 , 300 MHz) δ 5.61 (m, 1 H), 3.65 (s, 3 H), 2.89 (m, 2 H), 2.31 (t, $J = 7.2\text{ Hz}$, 1 H), 2.11 (m, 1 H), 1.94 (m, 1 H), 1.87 (s, 3 H), 1.57 (m, 2 H), 1.51 (m, 2 H), 1.07 (s, 3 H), 1.01 (s, 3 H), 0.99 (s, 3 H), 0.16 (s, 9 H).

To a solution of ester **13** (1.179g, 3.407 mmol) in THF (15 mL) was added DIBAL-H (1 M in hexane, 13.6 mL, 13.6 mmol) at $-78\text{ }^{\circ}\text{C}$. The mixture was stirred at this temperature for 1 h before being warmed to room temperature and stirred overnight. The reaction was quenched with careful addition of water (20 mL). The suspension was treated with ether (80 mL) and HCl (1 M, 20 mL) to dissolve the solid. After separation of the layers the organic phase was washed with water (10 mL), brine (10 mL), dried (MgSO_4), filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography (20% ether in petroleum ether) to afford the corresponding alcohol as a clear liquid (1.018 g, 94%). IR (neat) 3320, 2959, 2137, 1451, 1248, 1001, 843 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 5.33 (m, 1 H), 4.08 (d, $J = 6.8\text{ Hz}$, 2 H), 2.91 (sept, $J = 7.2\text{ Hz}$, 1 H), 2.28 (m, 2 H), 1.94 (m, 2 H), 1.74 (m, 1 H),

1.71 (s, 3 H), 1.55 (m, 1 H), 1.44 (m, 1 H), 1.37 (m, 1 H), 1.04 (s, 3 H), 0.99 (d, $J = 4.0$ Hz, 3 H), 0.97 (d, $J = 4.0$ Hz, 3 H), 0.15 (s, 9 H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 157.5, 141.8, 124.2, 123.5, 101.1, 99.0, 59.0, 50.2, 39.0, 34.4, 29.5, 29.2, 27.4, 26.5, 23.6, 21.0, 20.7, 0.2.

To a solution of the above alcohol (0.60 g, 1.89 mmol) in THF (6 mL) was added TBAF (1 M in THF, 2.83 mL, 2.83 mmol) at 0 °C. The mixture was stirred at this temperature for 30 min before the addition of brine (20 mL). The suspension was treated with ether (40 mL). After separation of the layers the aqueous phase was extracted with ether (2 $\times$ 10 mL). The combined organic layers were dried (MgSO_4), filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography (20% ether in petroleum ether) to afford compound **14** as a light yellow oil (451.0 mg, 97%). $[\alpha]_{\text{D}} = +13.5^\circ$ (c 6.0, 23.2 °C, CH_2Cl_2); IR (neat) 3311, 2959, 1726, 1452, 1001 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 5.37 (m, 1 H), 4.12 (d, $J = 6.8$ Hz, 2 H), 3.12 (s, 1 H), 2.98 (sept, $J = 7.2$ Hz, 1 H), 2.39 (m, 1 H), 2.32 (m, 1 H), 1.98 (m, 2 H), 1.82 (m, 1 H), 1.74 (s, 3 H), 1.53 (s, br, 2 H), 1.44 (m, 2 H), 1.09 (s, 3 H), 1.04 (d, $J = 4.0$ Hz, 3 H), 1.02 (d, $J = 4.0$ Hz, 3 H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 158.2, 140.8, 123.6, 123.1, 81.9, 79.5, 59.0, 53.8, 50.1, 38.9, 34.4, 29.2, 29.1, 28.8, 27.4, 26.2, 23.6, 21.0, 20.8, 20.7, 14.0; HRMS Calc'd for $\text{C}_{17}\text{H}_{26}\text{O}$ [M^+]: 246.1984. Found: 246.1993.

(S)-4-Hydroxy-4-[(5S,7aR)-3-isopropyl-5,7a-dimethyl-4-methylene-2,4,5,6,7,7a-hexahydro-1H-inden-5-yl]-butyronitrile (18). To a solution of compound **17** (100.0 mg, 0.351 mmol) in methanol (4 mL) was added 10% Pd/C (20.0 mg). The mixture was stirred under hydrogen (1 atm) for 8 h and filtered through a pad of celite. The filtrate was concentrated under reduced pressure and was purified by column chromatography (40% ether in petroleum ether) to afford compound **18** as white crystals (98.7 mg, 98%), mp. 90-91 °C. $[\alpha]_D = +210.3^\circ$ (c 0.82, 24.1 °C, CH₂Cl₂); IR (neat) 3448, 2958, 2360, 1619, 1458, 1068 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 4.96 (d, J = 1.0 Hz, 1 H), 4.75 (d, J = 1.0 Hz, 1 H), 3.65 (m, 1 H), 2.75 (sept, J = 7.0 Hz, 1H), 2.47 (dd, J = 9.0, 5.5 Hz, 1 H), 2.25 (m, 2 H), 1.83-1.71 (m, 3 H), 1.58 (m, 1 H), 1.56-1.46 (m, 2 H), 1.44 (ddd, J = 13.0, 5.0, 5.0 Hz, 1 H), 0.96 (m, 9 H), 0.88 (s, 3 H); ¹³C NMR (CDCl₃, 125 MHz) δ 147.6, 141.4, 139.5, 120.0, 111.2, 70.8, 48.6, 44.9, 39.6, 36.0, 33.4, 28.0, 27.2, 26.5, 23.0, 21.8, 21.3, 18.0, 14.8, HRMS Calc'd for C₁₉H₂₉NO [M⁺]: 287.2249. Found: 287.2244.

(S)-4-Hydroxy-4-[(3S,4R,5S,7aS)-1a-isopropyl-3a,6-dimethyl-7-methylene-octahydro-1-oxa-cyclopropa[c]inden-6-yl]-butyronitrile (19). To a solution of compound **18** (13 mg, 0.0453 mmol) in benzene (0.3 mL) was added VO(acac)₂ (0.6 mg, 0.05 mmol) followed by TBHP (3 M in nonane, 0.018 mL, 0.054 mL) at room temperature. The mixture was stirred at room temperature for 4 h and was treated with saturated Na₂S₂O₅ solution (2 mL) and ether (6 mL). After separation of the layers the

aqueous phase was extracted with ether (5 mL). The combined organic layer was washed with brine (2 mL), dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (50% ether in petroleum ether) to afford compound **19** as colorless oil (11.1 mg, 80%), [α]_D = -12.5° (*c* 1.50, 23.5 °C, CH₂Cl₂); IR (neat) 3491, 2964, 2248, 1643, 1458, 1374, 1067, 914 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 5.11 (s, 1 H), 4.99 (s, 1 H), 4.18 (m, 1 H), 2.53 (m, 1 H), 2.37 (m, 1 H), 1.94 (m, 1 H), 1.87 (sept, *J* = 7.0 Hz, 1 H), 1.82-1.79 (m, 2 H), 1.77-1.66 (m, 2 H), 1.54 (m, 2 H), 1.38 (dt, *J* = 14.0, 4.0 Hz, 1 H), 1.25 (m, 2 H), 1.08 (d, *J* = 7.0 Hz, 3 H), 1.05 (d, *J* = 7.0 Hz, 3 H), 1.03 (s, 3 H), 0.83 (s, 3 H); ¹³C NMR (CDCl₃, 125 MHz) δ 38.1, 113.6, 105.5, 68.0, 63.9 (2), 40.1, 34.8, 25.3 (2), 23.8, 21.7, 21.4, 16.0, 13.8, 12.2, 11.5 (2), 7.7; Anal. Calc'd for C₁₉H₂₉NO₂: C, 75.21; H, 9.63; N, 4.62. Found: C, 75.15; H, 9.55; N, 4.42.

(*R*)-5-(2-Hydroxyethyl)-2-*iso*-propyl-5-methyl-cyclopent-1-enylethynyl-trimethylsilane (20). To a stirred solution of alkyne **6** (1.06g, 4.08 mmol) in CH₂Cl₂ (6 mL) was added NMO (1.685 g, 14.4 mmol) and OsO₄ (4% in water, 0.305 mL, 0.048 mmol) at room temperature. The mixture was stirred for 8 h and treated with ether (40 mL) and water (10 mL). After separation of the layers the organic phase was concentrated under reduced pressure to give the crude diol.

The crude diol was dissolved in acetone/water (4:1, 6 mL). To this mixture was added NaIO₄ (2.05 g, 9.6 mmol) at room temperature. The suspension was stirred for 1 h

and treated with ether (60 mL) and water (15 mL). After separation of the layers the aqueous phase was extracted with ether (20 mL). The combined organic layers were washed with brine (10 mL), dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue was purified with column chromatography (3% ether in petroleum ether) to furnish the corresponding aldehyde (898.5 mg, 84%) as a clear liquid.

To a solution of the aldehyde in MeOH (2 mL) was added NaBH₄ (134.3 mg, 3.55 mmol) at room temperature. The mixture was stirred for 10 min and concentrated under reduced pressure. The residue was treated with ether (60 mL) and water (10 mL). After separation of the layers the aqueous layer was extracted with ether (3 × 10 mL). The combined organic layers was washed with brine (10 mL), dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue was purified with column chromatography (20% ether in petroleum ether) to furnish the compound **20** (888.1 mg, 94%) as a clear liquid, $[\alpha]_D = +21.0$ (*c* 1.10, 22.7 °C, chloroform). IR (neat) 3333, 2958, 2137, 1454, 1249, 842 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 3.65 (m, 2 H), 2.91 (sept, *J* = 7.2 Hz, 1 H), 2.29 (t, *J* = 7.5 Hz, 2 H), 1.80 (m, 2 H), 1.62 (m, 2 H), 1.08 (s, 3 H), 1.00 (s, 3 H), 0.98 (s, 3 H), 0.17 (s, 9 H); ¹³C NMR (CDCl₃, 100 MHz) δ 157.7, 124.3, 101.0, 99.6, 60.1, 48.9, 42.9, 36.0, 29.2, 29.0, 26.1, 20.8, 20.6, 0.1; HRMS Calc'd for C₁₆H₂₈OSi [M⁺]: 264.1909; Found: 264.1910.

(*R*)-5-(2-Iodoethyl)-2-*iso*-propyl-5-methyl-cyclopent-1-enylethynyl-trimethylsilane (21**).** To a stirred solution of compound **20** (266 mg, 1.0 mmol) in

CH₃CN and ether (3:5, 6.4 mL) was added PPh₃ (340.0 mg, 1.3 mmol), I₂ (355.3 mg, 1.4 mmol), and imidazole (102.1 mg, 1.5 mmol) at 0 °C. The mixture was stirred for 2 h at room temperature and treated with ether (40 mL) and saturated NaHSO₃ solution (20 mL). After separation of the layers the organic phase was dried (MgSO₄), filtered, and concentrated under reduced pressure. The crude material was purified with column chromatography (100% petroleum ether) to give compound **21** (348.3 mg, 93%) as a clear liquid, [α]_D = + 22.3 (*c* 1.30, 23.2 °C, dichloromethane). IR (neat) 2960, 2137, 1458, 1249 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 3.24 (m, 1 H), 3.16 (m, 1 H), 2.89 (sept, *J* = 7.2 Hz, 1 H), 2.28 (m, 2 H), 2.07 (m, 2 H), 1.76 (m, 1 H), 1.54 (m, 1 H), 1.05 (s, 3 H), 1.00 (d, *J* = 2.4 Hz, 3 H), 0.98 (d, *J* = 2.4 Hz, 3 H), 0.18 (s, 9 H); ¹³C NMR (CDCl₃, 100 MHz) δ 157.8, 123.3, 100.5, 99.9, 52.5, 45.5, 34.7, 29.2, 25.4, 20.9, 20.7, 1.5, 0.2; HRMS Calc'd for C₁₉H₂₇ISi [M⁺]: 374.0927; Found: 374.0928.

(*E*)-(R)-5-(2-Ethynyl-3-*iso*-propyl-1-methyl-cyclopent-2-enyl)-pent-2-en-1-ol

(28). To a stirred solution of (COCl)₂ (171.4 mg, 1.35 mmol) in CH₂Cl₂ (8 mL) was added dropwise DMSO (245.7 mg, 3.14 mmol) at –78 °C. The mixture was stirred for 5 min before a solution of compound **11** (250.1 mg, 0.9 mmol) in CH₂Cl₂ (4 mL) was added slowly. The mixture was stirred at –78 °C for 15 min followed by addition of TEA (381.8 mg, 3.78 mmol). After being stirred for 10 min, the mixture was allowed to warm up to room temperature. The white slurry was treated with water (10 mL) and

ether (30 mL). After separation of the layers, the organic phase was washed with water (10 mL), brine (5 mL), dried (MgSO₄), filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography (3% ether in petroleum ether) to afford the corresponding aldehyde as a clear oil (218.6 mg, 88%). ¹H NMR (CDCl₃, 500 MHz) δ 9.77 (s, 1 H), 2.89 (sept, *J* = 7.0 Hz, 1 H), 2.24-2.41 (m, 4 H), 1.55-1.80 (m, 4 H), 1.08 (s, 3 H), 1.00 (d, *J* = 6.5 Hz, 6 H), 0.18 (s, 9 H).

To a solution of the aldehyde (526.0 mg, 1.906 mmol) in benzene (8 mL) was added carboxyethyl methylenetriphenylphosphane (697.1 mg, 2.0 mmol) at room temperature. The mixture was stirred at room temperature overnight and concentrated under reduced pressure. The residue was directly purified by column chromatography (3% ether in petroleum ether) to afford ethyl ester **27** as a clear oil (642.4 mg, 98%). IR (neat) 2960, 2137, 1724, 1654, 1451, 1249, 1179, 843 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 6.99 (dt, *J* = 15.6, 7.5 Hz, 1 H), 5.81 (d, *J* = 15.6 Hz, 1 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 2.93 (sept, *J* = 7.2 Hz, 1H), 2.30 (m, 2 H), 2.15 (m, 2 H), 1.73 (m, 1 H), 1.62 (m, 1 H), 1.53 (m, 2 H), 1.26 (t, *J* = 6.9 Hz, 3 H), 1.08 (s, 3 H), 1.02 (d, *J* = 1.2 Hz, 3 H), 1.00 (d, *J* = 1.2 Hz, 3 H), -0.02 (s, 9 H); ¹³C NMR (CDCl₃, 75 MHz) δ 166.8, 157.4, 150.0, 124.3, 120.8, 100.9, 99.2, 60.0, 49.9, 38.2, 34.8, 29.3, 29.2, 27.9, 25.9, 20.9, 20.7, 14.2, 0.16.

To a solution of ester **27** (735.6 mg, 2.126 mmol) in THF (10 mL) was added DIBAL-H (1 M in hexanes, 8.5 mL, 8.5 mmol) at -78 °C. After being stirred at this temperature for 1 h the mixture was warmed to room temperature for 2 h. The reaction was quenched with addition of 0.5 N HCl (15 mL) and ether (50 mL). The aqueous layer was extracted with ether (2 × 20 mL). The combined organic phases were washed with brine (10 mL), dried (MgSO₄), filtered, and concentrated under reduced pressure. The

residue was purified by column chromatography (20% ether in petroleum ether) to provide the corresponding alcohol (617.5 mg, 96%) as a colorless liquid.

To a solution of the above alcohol (636.8 mg, 2.09 mmol) in THF (5 mL) was added TBAF (1 M in THF, 3.14 mL, 3.14 mmol) at 0 °C. The mixture was stirred for 30 min at this temperature and brine (10 mL) was added. The mixture was extracted with ether (3 × 20 mL), dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (20% ether in petroleum ether) to provide compound **28** (444.0 mg, 92%) as a colorless oil, $[\alpha]_D = +10.5^\circ$ (*c* 0.41, 23.9 °C, CH₂Cl₂). IR (neat) 3310, 2959, 2089, 1454, 1373, 1002, 971 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 5.67 (m, 2 H), 4.08 (d, *J* = 5.0 Hz, 2 H), 3.10 (s, 1 H), 2.96 (sept, *J* = 7.0 Hz, 1 H), 2.31 (m, 2 H), 1.99 (m, 2 H), 1.79 (m, 1 H), 1.60 (m, 1 H), 1.57 (s, 3 H), 1.49 (m, 2 H), 1.09 (s, 3 H), 1.03 (d, *J* = 2.0 Hz, 3 H), 1.00 (d, *J* = 2.0 Hz, 3 H); ¹³C NMR (CDCl₃, 125 MHz) δ 158.3, 134.4, 128.7, 124.1, 82.0, 80.3, 64.2, 50.2, 39.7, 35.1, 29.5, 27.9, 26.3, 21.3, 21.0; HRMS Calc'd for C₁₆H₂₄O [M⁺]: 232.1827 Found: 232.1823.

[(5*R*,7*aS*)-3-Isopropyl-7*a*-methyl-4-methylene-2,4,5,6,7,7*a*-hexahydro-1*H*-inden-5-yl]-acetaldehyde (29**). Employing the similar procedure for the preparation of compound **15**, compound **29** was obtained in 54% yield as a clear liquid. $[\alpha]_D = +178.2^\circ$ (*c* 0.44, 24.1 °C, CH₂Cl₂); IR (neat) 2934, 1726, 1628, 1457, 896 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 9.68 (m, 1 H), 5.01 (d, *J* = 1.8 Hz, 1 H), 4.68 (d, *J* = 2.4 Hz, 1 H), 2.93 (sept, *J* = 7.2 Hz, 1H), 2.81 (m, 1 H), 2.44 (m, 1 H), 2.30 (m, 1 H), 1.98 (m, 1 H), 1.74 (m, 1**

H), 1.54 (m, 5 H), 0.96 (s, 3 H), 0.94 (m, 6 H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 202.8, 145.1, 143.1, 137.2, 111.3, 48.4, 46.2, 39.6, 39.0, 35.7, 28.5, 28.0, 26.4, 23.4, 23.0, 21.6, 21.5; HRMS Calc'd for $\text{C}_{16}\text{H}_{24}\text{O}$ [M^+]: 232.1827 Found: 232.1823.

[(5*S*,7*aS*)-3-Isopropyl-7*a*-methyl-4-methylene-2,4,5,6,7,7*a*-hexahydro-1*H*-inden-5-yl]-acetaldehyde (32**).** To a solution of compound **28** (30.0 mg, 0.129 mmol) in DMF (0.2 mL) was added TBSCl (23.4 mg, 0.155 mmol) and imidazole (21.1 mg, 0.310 mmol) at room temperature. The mixture was stirred overnight and treated with water (10 mL) and ether (15 mL). After separation of the layers the organic phase was washed with water (3×10 mL). The combined organic layers were washed with brine (5 mL), dried (MgSO_4), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (3% ether in petroleum ether) to provide silyl ether **31** (44.1 mg, 99%) as a clear liquid.

To a solution of compound **31** (31.1 mg, 0.0896 mmol) in acetone (0.9 mL) was added $\text{CpRu}(\text{CH}_3\text{CN})_3\text{PF}_6$ (3.9 mg, 0.009 mmol) in one portion at room temperature. The mixture was stirred for 10 h and concentrated under reduced pressure. The crude material was purified by column chromatography (4% ether in petroleum ether) to provide the cyclized enol ether (16.4 mg, 53%) as a clear oil. ^1H NMR (CDCl_3 , 500 MHz) δ 6.20 (dd, $J = 11.5, 1.0$ Hz, 1 H), 5.02 (dd, $J = 12.0, 9.0$ Hz, 1 H), 4.91 (t, $J = 2.0$ Hz, 1 H), 4.68 (t, $J = 2.0$ Hz, 1 H), 2.87 (sept, $J = 7.2$ Hz, 1H), 2.43 (m, 1 H), 2.28 (m, 2

H), 1.70 (m, 2 H), 1.58 (m, 1 H), 1.50 (m, 2 H), 1.41 (m, 1 H), 0.96 (d, $J = 7.0$ Hz, 3 H), 0.94 (d, $J = 6.5$ Hz, 3 H), 0.91 (s, 9 H), 0.14 (s, 6 H).

To a solution of the above compound (13.0 mg, 0.0376 mmol) in CH_2Cl_2 (0.5 mL) and TFA (0.2 mL) was added water (2 drops) at 0 °C. The mixture was stirred at this temperature for 15 min and at room temperature for 10 min. The suspension was treated with ether (10 mL) and saturated NaHCO_3 solution (6 mL). The organic layer was separated and washed with brine (3 mL), dried (MgSO_4), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (3% ether in petroleum ether) to provide compound **32** (7.2 mg, 83%) as a clear liquid. $[\alpha]_{\text{D}} = +128.9^\circ$ (c 0.72, 24.6 °C, CH_2Cl_2); IR (neat) 2927, 1727, 1451 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 9.77 (t, $J = 2.5$ Hz, 1 H), 4.74 (d, $J = 1.5$ Hz, 1 H), 4.70 (d, $J = 1.5$ Hz, 1 H), 2.82 (sept, $J = 7.0$ Hz, 1H), 2.69 (dd, $J = 6.0, 2.0$ Hz, 1 H), 2.46 (m, 1 H), 2.38 (m, 1 H), 2.29 (m, 1 H), 1.75 (m, 2 H), 1.71 (m, 2 H), 1.52 (m, 2 H), 1.45 (m, 1 H), 0.96 (d, $J = 7.0$ Hz, 3 H), 0.94 (d, $J = 6.5$ Hz, 3 H), 0.89 (s, 3 H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 202.8, 145.7, 140.5, 140.3, 108.3, 48.8, 46.6, 40.9, 39.2, 38.7, 31.2, 28.2, 26.4, 23.0, 21.7, 21.6; HRMS Calc'd for $\text{C}_{16}\text{H}_{24}\text{O}$ [M^+]: 232.1827. Found: 232.1823.

(R)-4-Hydroxy-4-[(5S,7aR)-(3-isopropyl-5,7a-dimethyl-4-methylene-2,4,5,6,7,7a-hexahydro-1H-inden-5-yl)]-butyronitrile (42). A suspension of compound

41 (20.1 mg, 0.081 mmol) and 10% Pd/C (8 mg) in EtOAc (2 mL) was subjected to 1 atm of hydrogen at room temperature for 8 h. The mixture was filtered through a pad of celite and concentrated under reduced pressure. The residue was purified by column chromatography (1:2, petroleum ether/diethyl ether) to provide compound **42** as colorless crystals (17.4 mg, 87%). $[\alpha]_D = +180.1$ (c 0.78, 23.2 °C, dichloromethane); IR (neat) 3456, 1618, 1451, 1039 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 4.92 (s, 1 H), 4.76 (s, 1 H), 3.93 (m, 1 H), 2.82 (sept, $J = 7.0$ Hz, 1 H), 2.59 (m, 2 H), 2.33 (m, 2 H), 2.12 (m, 1 H), 1.74 (m, 3 H), 1.60 (m, 3 H), 1.58 (m, 3 H), 1.39 (m, 1 H), 1.01 (s, 3 H), 0.98 (d, $J = 7.0$ Hz, 3 H), 0.95 (d, $J = 7.0$ Hz, 3 H), 0.91 (s, 3 H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 141.7, 134.9, 132.8, 113.1, 101.8, 68.2, 41.8, 37.7, 32.1, 29.4, 23.0, 21.3, 20.4, 19.4, 16.1, 14.6, 14.4, 3.5, 7.7; Anal. Calc'd for $\text{C}_{19}\text{H}_{29}\text{NO}$: C, 79.39; H, 10.17; N, 4.87; Found: C, 79.46; H, 9.96; N, 4.83.

Epoxide 43. To a solution of compound **42** (16.2 mg, 0.065 mmol) and $\text{VO}(\text{acac})_2$ (0.346 mg, 0.0013 mmol) in benzene (0.6 mL) was added TBHP (5.5 M in decane, 0.014 mL, 0.078 mmol) at room temperature. The mixture was stirred for 7 h and diluted with EtOAc (6 mL). The solution was washed with saturated NaHCO_3 (3 mL), brine (1 mL), dried (MgSO_4), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (3% ether in petroleum ether) to provide compound **43** (7.8 mg, 52%) as a white solid. ^1H NMR (CDCl_3 , 400 MHz) δ 3.51 (m, 1 H), 3.36 (d, $J = 4.2$ Hz, 1 H), 2.88 (d, $J = 4.2$ Hz, 1 H), 2.72 (sept, $J = 6.8$ Hz,

1H), 2.51 (m, 2 H), 2.32 (m, 2 H), 2.03 (m, 2 H), 1.68-1.59 (m, 6 H), 1.17 (s, 3 H), 1.01 (d, $J = 8.8$ Hz, 3 H), 0.97 (s, 3 H), 0.93 (d, $J = 9.2$ Hz, 3 H). This compound was not fully characterized due to poor stability.

(E)-(S)-[5-(5-Hydroxy-3-methyl-pent-3-enyl)-2-isopropyl-5-methyl-cyclopent-1-enyl]-propynoic acid *tert*-butyl ester (48c). Following the similar procedure for the preparation of compound **48a**, compound **48c** was obtained as a light yellow oil, $[\alpha]_D = +32.9$ (c 0.52, 24.0 °C, dichloromethane). IR (neat) 3383, 2962, 2194, 1703, 1456, 1370, 1284, 1151 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 5.43 (t, $J = 7.2$ Hz, 1 H), 4.14 (m, 2 H), 2.99 (sept, $J = 6.8$ Hz, 1 H), 2.37 (m, 2 H), 1.99 (m, 1 H), 1.90 (m, 1 H), 1.81 (m, 1 H), 1.69 (s, 3 H), 1.63 (m, 1 H), 1.57 (m, 2 H), 1.51 (s, 9 H), 1.10 (s, 3 H), 1.04 (d, $J = 6.4$ Hz, 3 H), 1.02 (d, $J = 6.4$ Hz, 3 H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 164.2, 153.6, 140.4, 123.0, 122.3, 87.6, 82.8, 80.6, 59.4, 50.3, 38.2, 34.8, 34.8, 29.8, 29.6, 28.0, 26.0, 21.1, 20.8, 16.4; HRMS Calc'd for $\text{C}_{18}\text{H}_{26}\text{O}_3$ [$\text{M}^+ - \text{C}_4\text{H}_8$]: 290.1882; Found: 290.1878.

(E)-(R)-5-(2-Ethynyl-3-isopropyl-1-methyl-cyclopent-2-enyl)-3-methyl-pent-2-en-1-ol *tert*-butyldiphenyl ether (49). To a solution of the compound **21** (110 mg, 0.293 mmol) and anhydrous ZnCl_2 (39.8 mg, 0.293 mmol) in THF (3 mL) was added *t*-BuLi (1.4 M in pentane, 0.627 mL, 0.818 mmol) at -78 °C in 10 min. The mixture was stirred for 5 min at this temperature and warmed to room temperature for 1 h. The yellow solution was transferred through cannular to a mixture of vinyl iodide **22** (100.4 mg, 0.322 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (16.9 mg, 0.146 mmol) at room temperature. The reaction

mixture was stirred overnight before the addition of ether (30 mL) and water (15 mL). After separation of the layers the aqueous layer was extracted with ether (2 × 10 mL). The combined organic layers was washed with brine (10 mL), dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue was purified with column chromatography (3% ether in petroleum ether) to furnish the coupled product as a light yellow liquid which was contaminated with traces of unreacted vinyl iodide. ¹H NMR (CDCl₃, 300 MHz) δ 7.62 (m, 4 H), 7.36 (m, 6 H), 5.27 (t, *J* = 4.2 Hz, 1 H), 4.15 (d, *J* = 6.0 Hz, 2 H), 2.92 (sept, *J* = 7.0 Hz, 1H), 2.27 (m, 2 H), 1.90 (m, 1 H), 1.77 (m, 1 H), 1.44 (m, 1 H), 1.38 (s, 3 H), 1.21-1.06 (m, 3 H), 1.00 (m, 3 H), 0.99 (s, 9 H), 0.98 (m, 6 H), 0.15 (s, 6 H).

To a solution of the above product in MeOH (2 mL) was added K₂CO₃ (80.7 mg, 0.585 mmol) at room temperature. The mixture was stirred for 1 h and treated with water (5 mL) and ether (15 mL). After separation of the layers the aqueous layer was extracted with ether (5 mL). The combined organic layers was dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue was purified with column chromatography (5% ether in petroleum ether) to provide compound **49** (48.9 mg, 68%) as a light yellow liquid, [α]_D = + 3.13 (*c* 1.46, 22.7°C, dichloromethane). IR (neat) 2959, 2137, 1462, 1112 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 7.70 (m, 4 H), 7.40 (m, 6 H), 5.38 (t, *J* = 4.2 Hz, 1 H), 4.21 (d, *J* = 6.0 Hz, 2 H), 3.10 (s, 1 H), 2.97 (sept, *J* = 7.0 Hz, 1H), 2.31 (m, 2 H), 1.95 (m, 2 H), 1.87 (m, 1 H), 1.78 (m, 1 H), 1.59 (m, 1 H), 1.48 (m, 2 H), 1.44 (s, 3 H), 1.09 (s, 3 H), 1.06 (d, *J* = 7.0 Hz, 3 H), 1.05 (s, 9 H), 1.02 (d, *J* = 7.0 Hz, 3 H); ¹³C NMR (CDCl₃, 125 MHz) δ 157.9, 137.9, 135.6, 134.1, 129.4, 127.6, 127.5,

123.6, 123.5, 81.7, 79.7, 61.2, 49.9, 38.3, 34.8, 34.7, 29.2, 26.8, 26.7, 26.0, 21.0, 20.8, 19.2, 16.4; HRMS Calc'd for C₃₃H₄₄OSi [M⁺]: 484.3161; Found: 484.3184.

(E)-(S)-3-[5-(5-Hydroxy-3-methyl-pent-3-enyl)-2-isopropyl-5-methyl-cyclopent-1-enyl]-propynoic acid diethylamide (50). Following the similar for the preparation of compound **51a**, compound **50** was prepared from compound **49** and diethyl carbamoylchloride as a light yellow oil, $[\alpha]_D = +33.1$ (*c* 1.0, 23.0 °C, dichloromethane). IR (neat) 3426, 2191, 1629, 1429, 1283 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 5.41 (t, *J* = 5.5 Hz, 1 H), 4.13 (d, *J* = 7.0 Hz, 2 H), 3.59 (q, *J* = 7.0 Hz, 2 H), 3.43 (q, *J* = 7.0 Hz, 2 H), 3.00 (sept, *J* = 7.0 Hz, 1H), 2.38 (m, 2 H), 1.97 (m, 1 H), 1.89 (m, 1 H), 1.83 (m, 1 H), 1.67 (s, 3 H), 1.62 (m, 1 H), 1.54 (m, 2 H), 1.22 (t, *J* = 7.0 Hz, 2 H), 1.16 (t, *J* = 7.0 Hz, 2 H), 1.11 (s, 3 H), 1.04 (d, *J* = 7.0 Hz, 3 H), 1.03 (d, *J* = 7.0 Hz, 3 H); ¹³C NMR (CDCl₃, 125 MHz) δ 155.5, 147.4, 133.1, 116.1, 115.7, 80.3, 78.5, 52.3, 43.3, 36.5, 32.3, 31.5, 27.8, 27.7, 22.7, 22.6, 19.3, 14.1, 13.9, 9.4, 7.4, 5.9; HRMS Calc'd for C₂₂H₃₅NO₂ [M⁺]: 345.2668; Found: 345.2266.

(E)-(S)-[5-(5-Hydroxy-3-methyl-pent-3-enyl)-2-isopropyl-5-methyl-cyclopent-1-enyl]-propynoic acid methyl ester (51a). To a solution of compound **49** (859.6 mg, 1.775 mmol) in THF (8 mL) was added *n*-BuLi (2.45 M in hexanes, 1.09 mL, 2.66 mmol)

at $-78\text{ }^{\circ}\text{C}$. The mixture was stirred at this temperature for 0.5 h before the addition of methyl chloroformate (335.5 mg, 3.33 mmol). The mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by addition of water (10 mL) and ether (60 mL). The phases were separated and the aqueous layer was extracted with ether ($3 \times 10\text{ mL}$). The combined organic layers were washed with brine (10 mL), dried (MgSO_4), filtered, and concentrated under reduced pressure. The residue was purified with column chromatography (4% ether in petroleum ether) to furnish the ester (952.9 mg, 99%) as a clear liquid. ^1H NMR (CDCl_3 , 300 MHz) δ 7.59 (m, 4 H), 7.30 (m, 6 H), 5.28 (m, 1 H), 4.11 (d, $J = 6.3\text{ Hz}$, 2 H), 3.69 (s, 3 H), 2.92 (sept, $J = 6.3\text{ Hz}$, 1H), 2.29 (t, $J = 7.2\text{ Hz}$, 2 H), 1.82 (m, 1 H), 1.76 (m, 2 H), 1.54 (m, 2 H), 1.52 (m, 1 H), 1.38 (m, 2 H), 1.34 (s, 3 H), 1.02 (s, 3 H), 0.95 (s, 9 H), 0.85 (d, $J = 6.3\text{ Hz}$, 3 H), 0.82 (d, $J = 6.3\text{ Hz}$, 3 H).

To a solution of above compound (952.9 mg, 1.775 mmol) in THF (8 mL) was added TBAF (1 M in THF, 2.13 mmol) at room temperature. The mixture was stirred for 1 h and quenched with addition of brine (10 mL) and ether (60 mL). The phases were separated and the aqueous layer was extracted with ether ($3 \times 10\text{ mL}$). The combined organic layers were washed with brine (10 mL), dried (MgSO_4), filtered, and concentrated under reduced pressure. The residue was purified with column chromatography (30% ether in petroleum ether) to furnish compound **51a** (280.7 mg, 52 %) as a clear liquid, $[\alpha]_{\text{D}} = +18.9$ (c 1.37, $22.5\text{ }^{\circ}\text{C}$, dichloromethane). IR (neat) 3398, 2959, 2201, 1712, 1434, 1272, 1243 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 5.39 (m, 1 H), 4.12 (d, $J = 6.4\text{ Hz}$, 2 H), 3.76 (s, 3 H), 2.97 (sept, $J = 6.4\text{ Hz}$, 1 H), 2.35 (m, 2 H), 1.88 (m, 1 H), 1.82 (m, 2 H), 1.66 (s, 3 H), 1.53 (m, 1 H), 1.51 (t, $J = 8.8\text{ Hz}$, 2 H), 1.09 (s, 3

H), 1.02 (d, $J = 6.4$ Hz, 3 H), 1.01 (d, $J = 6.4$ Hz, 3 H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 165.6, 154.9, 140.3, 123.1, 122.1, 85.9, 83.5, 59.4, 52.5, 50.3, 38.3, 34.9, 34.8, 30.0, 29.7, 26.0, 21.1; HRMS Calc'd for $\text{C}_{19}\text{H}_{28}\text{O}_3$ [M^+]: 304.2038; Found: 304.2040.

(E)-(S)-[5-(5-Hydroxy-3-methyl-pent-3-enyl)-2-isopropyl-5-methyl-cyclopent-1-enyl]-propynoic acid *iso*-propyl ester (51b). Following the similar procedure for the preparation of compound **51a**, compound **51b** was obtained as a light yellow oil, $[\alpha]_{\text{D}} = +14.3$ (c 1.75, 23.1 °C, dichloromethane). IR (neat) 3379, 2961, 2197, 1703, 1454, 1272, 1244, 1103 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 5.42 (t, $J = 7.0$ Hz, 1 H), 5.10 (sept, $J = 6.5$ Hz, 1 H), 4.14 (d, $J = 7.0$ Hz, 2 H), 3.00 (sept, $J = 7.0$ Hz, 1 H), 2.37 (m, 2 H), 1.99 (m, 1 H), 1.90 (m, 1 H), 1.82 (m, 1 H), 1.69 (s, 3 H), 1.63 (m, 1 H), 1.55 (m, 2 H), 1.31 (d, $J = 6.5$ Hz, 6 H), 1.11 (s, 3 H), 1.04 (d, $J = 7.0$ Hz, 3 H), 1.03 (d, $J = 7.0$ Hz, 3 H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 164.8, 154.1, 140.3, 123.0, 122.2, 86.6, 82.5, 69.5, 59.4, 50.3, 38.2, 34.8, 34.8, 29.8, 29.6, 26.0, 21.7, 21.1, 20.8, 16.4; HRMS Calc'd for $\text{C}_{18}\text{H}_{25}\text{O}_3$ [$\text{M}^+ - \text{C}_3\text{H}_7$]: 289.1804; Found: 289.1807.

(E)-[(5S,7aR)-3-Isopropyl-5,7a-dimethyl-5-(2-oxo-ethyl)-1,2,5,6,7,7a-hexahydro-inden-4-ylidene]-acetic acid methyl ester (52a). To a solution of

compound **51a** (296.8 mg, 0.976 mmol) in 2-butanone (9.7 mL) and DMF (71.3 mg, 0.976 mmol) was added CpRu(CH₃CN)₃PF₆ (84.7 mg, 0.195 mmol). The yellow solution was stirred at room temperature for 2 h and concentrated under reduced pressure. The crude material was purified by column chromatography (4% ether in petroleum ether) to give compound **52a** (less polar), **53a** (more polar) and **54a** (most polar). Compound **52a** (100.4 mg, 34%, a clear liquid): $[\alpha]_D = + 373.2$ (c 1.45, 24.2 °C, dichloromethane). IR (neat) 2956, 1718, 1607 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 9.82 (t, $J = 3.5$ Hz, 1 H), 5.59 (s, 1 H), 3.70 (s, 3 H), 3.03 (d, $J = 3.5$ Hz, 2 H), 2.62 (sept, $J = 6.5$ Hz, 1 H), 2.34 (m, 2 H), 1.73 (m, 2 H), 1.67 (m, 2 H), 1.43 (m, 2 H), 1.35 (s, 3 H), 1.00 (d, $J = 6.5$ Hz, 3 H), 0.99 (s, 3 H), 0.98 (d, $J = 6.5$ Hz, 3 H); ¹³C NMR (CDCl₃, 100 MHz) δ 203.0, 166.8, 158.2, 146.6, 141.2, 116.3, 51.5, 50.5, 48.2, 40.5, 39.2, 36.1, 35.0, 28.6, 26.6, 25.2, 24.8, 21.6, 21.4; HRMS Calc'd for C₁₉H₂₈O₃ [M⁺]: 304.2038; Found: 304.2027.

(Z)-[(5S,7aR)-3-Isopropyl-5,7a-dimethyl-5-(2-oxo-ethyl)-1,2,5,6,7,7a-hexahydro-inden-4-ylidene]-acetic acid methyl ester (53a). A clear liquid (83.6 mg, 28%): $[\alpha]_D = + 216.2$ (c 2.30, 22.7 °C, dichloromethane). IR (neat) 2958, 1715, 1626, 1434, 1290, 1194 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 9.92 (t, $J = 3.5$ Hz, 1 H), 5.66 (s, 1 H), 3.64 (s, 3 H), 2.56 (dd, $J = 15.0, 3.5$ Hz, 1 H), 2.52 (dd, $J = 15.0, 3.5$ Hz, 1 H), 2.37 (m, 2 H), 2.42 (m, 2 H), 1.94 (m, 1 H), 1.79 (m, 1 H), 1.72 (m, 2 H), 1.18 (s, 3 H), 1.09 (s, 3 H), 0.90 (d, $J = 9.0$ Hz, 3 H), 0.98 (d, $J = 9.0$ Hz, 3 H); ¹³C NMR (CDCl₃, 100 MHz)

δ 198.3, 162.8, 155.3, 139.6, 131.3, 109.9, 49.2, 47.4, 47.0, 37.5, 34.4, 32.8, 32.4, 25.0, 23.2, 20.5, 19.7, 17.4, 15.3; HRMS Calc'd for $C_{19}H_{28}O_3$ [M^+]: 304.2038; Found: 304.2029.

(5R)-[5-(3-Hydroxy-3-methyl-pent-4-enyl)-2-isopropyl-5-methyl-cyclopent-1-enyl]-propynoic acid methyl ester (54a). A light yellow oil (a mixture of two diastereomers, 30%). IR (neat) 3483, 2960, 2201, 1713, 1435, 1274, 1198 cm^{-1} ; 1H NMR ($CDCl_3$, 300 MHz) δ 5.90 (dd, $J = 13.6, 8.4$ Hz, 1 H), 5.20 (d, $J = 13.6$ Hz, 1 H), 5.05 (d, $J = 8.4$ Hz, 1 H), 3.78 (s, 3 H), 2.97 (sept, $J = 6.0$ Hz, 1 H), 2.37 (m, 2 H), 1.79 (m, 2 H), 1.61 (m, 1 H), 1.54 (m, 1 H), 1.44 (m, 2 H), 1.28 (s, 3 H), 1.10 (s, 3 H), 1.04 (d, $J = 4.0$ Hz, 3 H), 1.03 (d, $J = 4.0$ Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.6, 154.8, 145.0, 145.0, 122.0, 122.0, 111.8, 111.7, 85.9, 83.5, 73.1, 73.0, 52.0, 50.0, 37.2, 34.8, 34.7, 33.7, 33.6, 29.8, 29.7, 27.7, 27.5, 26.2, 26.0, 21.1, 20.8; HRMS Calc'd for $C_{19}H_{26}O_7$ [$M^+ - H_2O$]: 286.1933; Found: 286.1940.

(E)-[(5S,7aR)-3-Isopropyl-5,7a-dimethyl-5-(2-oxo-ethyl)-1,2,5,6,7,7a-hexahydro-inden-4-ylidene]-acetic acid *iso*-propyl ester (52b). To a solution of compound **51b** (51.1 mg, 0.154 mmol) in 2-butanone (1.5 mL) and DMF (11.3 mg, 0.154 mmol) was added $CpRu(CH_3CN)_3PF_6$ (13.4 mg, 0.031 mmol). The yellow solution was

stirred at room temperature for 2 h and concentrated under reduced pressure. The crude material was purified by column chromatography (4% ether in petroleum ether) to give compounds **52b** (less polar) and **53b** (more polar). Compound **52b** (18.4 mg, 36%, light yellow oil): $[\alpha]_D = +423.3$ (c 0.91, 23.1 °C, dichloromethane). IR (neat) 1722, 1626, 1452, 1188, 1109 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 9.83 (t, $J = 2.5$ Hz, 1 H), 5.55 (s, 1 H), 4.99 (sept, $J = 6.5$ Hz, 1 H), 3.03 (dd, $J = 16.5, 3.5$ Hz, 1 H), 2.99 (dd, $J = 16.5, 3.5$ Hz, 1 H), 2.85 (sept, $J = 6.5$ Hz, 1H), 2.34 (m, 2 H), 1.74 (m, 1 H), 1.64 (m, 2 H), 1.57 (m, 1 H), 1.48 (dt, $J = 9.0, 3.5$ Hz, 1 H), 1.39 (m, 1 H), 1.35 (s, 3 H), 1.28 (d, $J = 6.5$ Hz, 3 H), 1.26 (d, $J = 6.5$ Hz, 3 H), 0.99 (m, 9 H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 203.2, 166.2, 156.7, 146.3, 141.1, 117.4, 67.8, 50.8, 48.2, 40.4, 39.1, 36.2, 35.1, 28.5, 26.5, 25.3, 24.7, 21.8, 21.7, 21.4; HRMS Calc'd for $\text{C}_{21}\text{H}_{32}\text{O}_3$ $[\text{M}^+]$: 332.2351; Found: 332.2359.

(Z)-[(5S,7aR)-3-Isopropyl-5,7a-dimethyl-5-(2-oxo-ethyl)-1,2,5,6,7,7a-hexahydro-inden-4-ylidene]-acetic acid *iso*-propyl ester (53b**).** Light yellow oil (12.3, 24%): $[\alpha]_D = +196.9$ (c 1.15, 23.8 °C, dichloromethane). IR (neat) 1722, 1626, 1452, 1188, 1109 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 9.93 (t, $J = 3.0$ Hz, 1 H), 5.62 (s, 1 H), 4.96 (sept, $J = 6.5$ Hz, 1 H), 2.55 (dd, $J = 16.0, 3.0$ Hz, 1 H), 2.52 (dd, $J = 16.0, 3.0$ Hz, 1 H), 2.43 (m, 2 H), 2.41 (m, 1 H), 1.95 (dt, $J = 13.5, 4.0$ Hz, 1 H), 1.80 (m, 1 H), 1.74 (m, 1 H), 1.57 (m, 2 H), 1.22 (dd, $J = 6.5, 2.0$ Hz, 6 H), 1.18 (s, 3 H), 1.10 (s, 3 H), 0.92 (dd, $J = 6.5, 2.0$ Hz, 6 H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 202.6, 165.8, 158.6, 143.2, 135.5,

114.8, 67.1, 53.2, 51.4, 41.5, 38.4, 36.8, 36.5, 29.0, 27.2, 24.5, 23.8, 22.0, 21.4, 19.3;
HRMS Calc'd for C₂₁H₃₂O₃ [M⁺]: 332.2351; Found: 332.2359.

(Z)-[(5S,7aR)-3-Iso-propyl-5,7a-dimethyl-5-(2-oxo-ethyl)-1,2,5,6,7,7a-hexahydro-inden-4-ylidene]-acetic acid *tert*-butyl ester (53c). Light yellow oil (12.9 mg, 7%): [α]_D = + 280.4 (*c* 1.80, 24.2 °C, dichloromethane). IR (neat) 2958, 1715, 1626, 1434, 1290, 1194 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 9.93 (t, *J* = 4.0 Hz, 1 H), 5.57 (s, 1 H), 2.54 (dd, *J* = 15.6, 4.0 Hz, 1 H), 2.50 (dd, *J* = 15.6, 4.0 Hz, 1 H), 2.43 (sept, *J* = 6.4 Hz, 1 H), 2.47 (m, 1 H), 1.93 (dt, *J* = 13.2, 4.0 Hz, 1 H), 1.80 (m, 1 H), 1.70 (m, 2 H), 1.58 (m, 2 H), 1.53 (m, 1 H), 1.44 (s, 9 H), 1.17 (s, 3 H), 1.09 (s, 3 H), 0.94 (d, *J* = 6.8 Hz, 3 H), 0.90 (d, *J* = 6.8 Hz, 3 H); ¹³C NMR (CDCl₃, 100 MHz) δ 202.7, 165.0, 158.5, 142.8, 135.2, 115.8, 79.7, 53.3, 51.6, 41.5, 38.1, 36.9, 36.2, 29.0, 28.3, 28.0, 27.2, 24.6, 21.4, 19.4; HRMS Calc'd for C₂₂H₃₄O₃ [M⁺]: 346.2508; Found: 346.2520.

(3S,3aR,5aR)-3-(1-Iso-propyl-3a,5a-dimethyl-8-oxo-2,3,3a,4,5,5a,6,8-octahydro-7-oxa-cyclopenta[*a*]naphthalen-6-yl)-propionitrile (55). To a solution of compound **54** (13.9 mg, 0.045 mmol) in EtOAc (0.4 mL) was added 10% Pd/C (7.0 mg). The suspension was stirred under 1 atm H₂ for 6 h and filtered through a plug of celite. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ether, 1:1) to give compound **55** as white crystals (11.6 mg, 83%), mp. 155-156 °C, [α]_D = + 650.4 (*c* 0.22, 24.8 °C, dichloromethane). IR (neat)

2959, 2252, 1717, 1638, 1250 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 5.75 (s, 1 H), 4.16 (dd, $J = 10.0$ Hz, 3.2 Hz, 1 H), 2.90 (sept, $J = 6.8$ Hz, 1H), 2.68 (m, 2 H), 2.47 (m, 2 H), 1.96 (m, 2 H), 1.80 (dddd, $J = 7.2, 7.2, 2.8, 2.8$ Hz, 1 H), 1.80 (dd, $J = 5.6, 2.4$ Hz, 1 H), 1.72 (m, 2 H), 1.65 (m, 2 H), 1.04 (d, $J = 6.8$ Hz, 3 H), 1.01 (s, 3 H), 0.98 (s, 3 H), 0.97 (d, $J = 6.8$ Hz, 3 H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 164.9, 160.4, 152.3, 134.1, 119.1, 114.0, 83.0, 48.6, 39.1, 39.0, 35.7, 32.6, 29.3, 27.0, 25.3, 23.4, 21.6, 21.4, 17.0, 14.0; HRMS Calc'd for $\text{C}_{20}\text{H}_{27}\text{NO}_2$ [M^+]: 313.2042; Found: 313.2041.