Supporting Information

Total Synthesis of (+)-Laurencin: An Asymmetric Alkylation–Ring-Closing Metathesis Approach to Medium Ring Ethers

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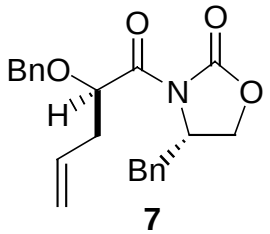
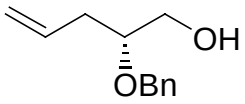
Experimental Section

Materials and Methods: General. Infrared (IR) spectra were obtained using a Perkin-Elmer 283 infrared spectrometer. Proton and carbon nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded on the following instruments: Bruker model WM-250 (^{1}H at 250 MHz), Bruker model Avance 400 (^{1}H at 400 MHz; ^{13}C at 100 MHz), and Bruker model Avance 500 (^{1}H at 500 MHz; ^{13}C at 125 MHz). Optical rotations were determined using a Perkin-Elmer 241 polarimeter. Thin layer chromatography (TLC) was conducted on silica gel F_{254} TLC plates purchased from Scientific Adsorbents, Inc. Flash chromatography was carried out using silica gel (32 to 63μm) purchased from Scientific Adsorbents, Inc. Diethyl ether, tetrahydrafuran (THF), and dichloromethane were dried by being passed through a column of neutral alumina under nitrogen immediately prior to use. Alkylamines and toluene were distilled from calcium hydride immediately prior to use. Dimethyl sulfoxide (DMSO) was distilled under reduced pressure from calcium hydride and stored over 4Å molecular sieves. All air and water sensitive reactions were performed in flasks flame dried under a positive flow of nitrogen and conducted under a nitrogen atmosphere.



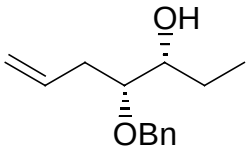
7

(4*S*)-4-Benzyl-3-[(2*R*)-2-benzyloxy-pent-4-enoyl]-oxazolidin-2-one (7). Into a flask fitted with a low-temperature thermometer was added sodium bis(trimethylsilyl)amide (1.0 M in toluene, 124.0 mL, 124.0 mmol). 200 mL of THF was added and the flask was cooled to –78 ºC. (*S*)-(+)-4-benzyl-3-benzyloxyacetyl-2-oxazolidinone **6** (28.00 g, 86.0 mmol) in 100 mL of THF was added via cannula at such a rate so as to maintain the reaction temperature below –60 ºC. After stirring for 30 minutes at –78 ºC, allyl iodide (39.0 mL, 426.5 mmol) was added via syringe. After 10 minutes the reaction was warmed to –45 ºC and stirred at that temperature for 3.5 hours. The reaction was quenched by the addition of saturated NH_4Cl and warmed to room temperature. The THF was removed in vacuo and the remaining solution extracted twice with 50% ethyl acetate/hexanes. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography provided 23.57 g (75%) of acyl oxazolidinone **7**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.16 (m, 10H), 5.92 (ddt, J = 17.8, 10.1, 6.3 Hz, 1H), 5.19-5.08 (m, 3H), 4.60 (m, 1H), 4.55 (AB, J_{AB} = 12.0 Hz, $\Delta\nu_{AB}$ = 46.6 Hz, 2H), 4.15 (d, J = 11.1 Hz, 2H), 3.25 (dd, J = 13.0, 3.8 Hz, 1H), 2.69-2.50 (m, 2H), 2.67 (dd, J = 13.0, 10.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.2, 37.9, 55.0, 66.7, 72.6, 76.7, 118.2, 127.4, 127.8, 128.2, 128.3, 128.9, 129.3, 133.0, 135.0, 137.5, 153.0, 172.2; IR (film) 1775, 1705, 1390, 1210, 1105 cm^{-1}; $[\alpha]^{24}_D$ = +94.4º (*c* 1.79, CH_2Cl_2).



8

(2*R*)-2-Benzyloxy-pent-4-en-1-ol (8). Acyl oxazolidinone **7** (0.555 g, 1.52 mmol) and anhydrous methanol (0.074 mL, 1.83 mmol) in 15 mL of diethyl ether were cooled to 0 ºC. Lithium borohydride (2.0 M in THF, 0.91 mL, 1.82 mmol) was added dropwise via syringe. After stirring 1.5 hours the reaction was quenched by the dropwise addition of 15 mL of 10% NaOH and warmed to room temperature. After 20 minutes the reaction was extracted twice with ethyl acetate, and the combined organic layers were dried over Na_2SO_4. Purification by flash chromatography gave 0.259 g (89%) of primary alcohol **8**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.39-7.23 (m, 5H), 5.81 (ddt, *J* =17.8, 9.6, 7.3 Hz, 1H), 5.18-5.03 (m, 2H), 4.59 (AB, J_{AB} = 12.3 Hz, $\Delta\nu_{AB}$ = 34.2 Hz, 2H), 3.75-3.48 (m, 3H), 2.47-2.23 (m, 2H), 1.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.3, 64.0, 71.5, 79.1, 117.5, 127.7, 128.5, 134.0, 138.2; IR (film) 3700-3100 (br), 2920, 2860, 1090, 910 cm^{-1}; $[\alpha]^{24}_D$ = -14.0º (*c* 0.75, CH_2Cl_2).

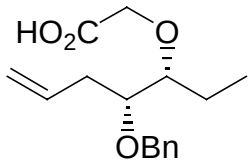


5

(3*R*, 4*R*)-4-Benzyloxy-hept-6-en-3-ol (5). Into a flask equipped with a mechanical stirrer and low-temperature thermometer was added 150 mL of dichloromethane and oxalyl chloride (2.0 M in CH_2Cl_2, 31.6 mL, 63.20 mmol). After cooling to –78 ºC, DMSO (9.00 mL, 126.83 mmol) in 9.0 mL of dichloromethane was added dropwise via addition funnel. After stirring for 10 minutes, alcohol **8** (11.04 g, 57.44 mmol) in 15.0 mL of CH_2Cl_2 was added via addition funnel. After 15 minutes, triethyl amine (40.0 mL, 287.0 mmol) was added dropwise

via addition funnel. The cooling bath was removed and the reaction allowed to warm to room temperature. The reaction mixture was poured into 600 mL of diethyl ether, and the organic layer was washed with water, cold 1M HCl, saturated $NaHCO_3$, water, and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The aldehyde was used immediately without further purification.

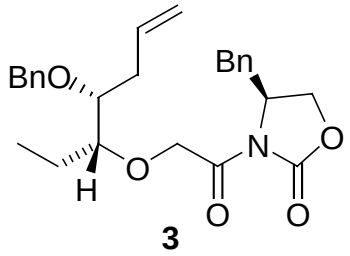
Into a flask equipped with a mechanical stirrer was added anhydrous zinc bromide (14.23 g, 63.19 mmol) and 200 mL of diethyl ether. The reaction was cooled to 0 ºC with vigorous stirring. The crude aldehyde (10.93 g, 57.44 mmol) in 50 mL of diethyl ether was added via cannula. After 5 minutes, ethyl magnesium bromide (1.0M in diethyl ether, 345.0 mL, 345.0 mmol) was added rapidly via cannula. After 1 hour, the reaction was quenched by the careful addition of saturated NH_4Cl. 10% HCl was added until all of the salts had dissolved and the reaction mixture was poured into a separatory funnel. The layers were separated and the aqueous layer extracted with 50% ethyl acetate/hexanes. The combined organic extracts were washed with saturated $NaHCO_3$, brine, and dried over Na_2SO_4. Concentration in vacuo and purification by flash chromatography provided 10.47 g (83%) of secondary alcohol **5**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.38-7.24 (m, 5H), 5.86 (ddt, J = 17.8, 8.7, 7.3 Hz, 1H), 5.18-5.04 (m, 2H), 4.59 (AB, J_{AB} = 11.9 Hz, $\Delta\nu_{AB}$ = 55.2 Hz, 2H), 3.46 (m, 1H), 3.34 (dt, J = 6.2, 5.0 Hz, 1H), 2.53-2.27 (m, 2H), 2.23 (d, J = 5.0 Hz, 1H), 1.64-1.37 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.0, 26.2, 34.8, 72.2, 73.8, 81.2, 117.4, 127.76, 127.83, 128.4, 134.3, 138.2; IR (film) 3630-3160 (br), 2930, 2870, 1060, 905 cm^{-1}; $[\alpha]^{24}_D$ = -32.4º (*c* 5.88, CH_2Cl_2).



9

[(1*R*, 2*R*)-2-Benzyloxy-1-ethyl-pent-4-enyloxy]-acetic acid (9). Sodium hydride (60% dispersion in mineral oil, 0.978 g, 24.46 mmol) was washed twice with hexanes, suspended in 4 mL THF, and cooled to 0 ºC. Alcohol **5** (3.59 g, 16.30 mmol) in 2 mL of THF was added dropwise via syringe, and the reaction allowed to warm to room temperature, where it was allowed to stir for 1 hour. In a second flask, sodium hydride (60% dispersion in mineral oil, 0.978 g, 24.46 mmol) was washed twice with hexanes, suspended in 5 mL THF, and cooled to 0 ºC. Bromoacetic acid (2.49 g, 17.92 mmol) in 3 mL of THF was added via syringe, and the mixture was stirred for 10 minutes. The sodium alkoxide of alcohol **5** was then transferred via cannula into the flask containing the sodium carboxylate of bromoacetic acid. The resultant mixture was allowed to warm to room temperature and stirred for 84 hours. The reaction was quenched by the slow addition of water, extracted twice with diethyl ether, and dried over Na_2SO_4. The aqueous layer was acidified by the addition of 10% H_2SO_4, extracted three times with ethyl acetate, and dried over Na_2SO_4. The diethyl ether extracts were concentrated in vacuo and purified by flash chromatography to give 0.174g (5%) of recovered alcohol **5**. The ethyl acetate extracts were concentrated in vacuo and purified by flash chromatography to provide 3.99 g (88%) of acid **9**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.39-7.22 (m, 5H), 5.83 (m, 1H), 5.17-5.04 (m, 2H), 4.65 (AB, J_{AB} = 10.5 Hz, $\Delta\nu_{AB}$ = 34.2 Hz, 2H), 4.12 (AB, J_{AB} = 17.3 Hz, $\Delta\nu_{AB}$ = 62.4 Hz, 2H), 3.57 (m, 1H), 3.31 (m, 1H), 2.54 (m, 1H), 2.18 (m, 1H), 1.56 (m, 1H), 1.48 (m, 1H), 0.92 (t, J = 7.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.6, 22.9, 33.7,

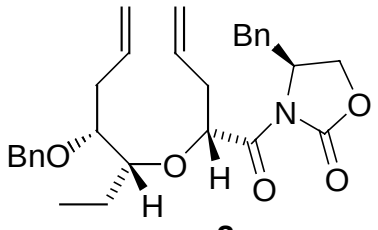
68.2, 72.2, 79.3, 83.4, 118.3, 128.2, 128.3, 128.5, 132.7, 136.6, 172.6; IR (film) 3700-2200 (br), 1735, 1240, 1115, 910 cm^{-1}; $[\alpha]^{24}_D$ = -50.0º (*c* 2.17, CH_2Cl_2).



3

(4*S*)-4-Benzyl-3-[2-((1*R*, *2*R)-2-benzyloxy-1-ethyl-pent-4-enyloxy)-acetyl]-oxazolidin-2-one (3). To a solution of carboxylic acid **9** (0.967 g, 3.47 mmol) in 20 mL of diethyl ether was added triethyl amine (0.53 mL, 3.80 mmol) via syringe, and the mixture was cooled to –78 ºC. Pivaloyl chloride (0.43 mL, 3.49 mmol) was added dropwise via syringe. After 5 minutes, the mixture was warmed to 0 ºC, where it was stirred for 1 hour and subsequently recooled to –78 ºC. In a separate flask, (*S*)-(+)-4-benzyl-2-oxazolidinone (0.615 g, 3.47 mmol) was dissolved in 7 mL of THF and cooled to –78 ºC. *n*-Butyl lithium (1.6 M in hexanes, 2.28 mL, 3.65 mmol) was added dropwise via syringe, and the mixture was stirred for 15 minutes. The lithiated oxazolidinone was added via cannula to the mixed anhydride, and the reaction stirred for an additional 10 minutes before being warmed to 0 ºC, where stirring continued for 1 hour. The reaction was quenched by the addition of water and extracted twice with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. Concentration in vacuo and purification by flash chromatography gave 1.16 g (76%) of acyl oxazolidinone **3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.12 (m, 10H), 5.89 (ddt, *J* = 17.4, 7.8, 6.1 Hz, 1H), 5.16-5.03 (m, 2H), 4.81 (AB, J_{AB} = 18.2, $\Delta\nu_{AB}$ = 24.3 Hz, 2H), 4.64 (m, 1H), 4.62 (AB, J_{AB} = 12.1 Hz, $\Delta\nu_{AB}$ = 20.0 Hz, 2H), 4.23-4.12 (m, 2H), 3.58 (m, 1H), 3.49 (m, 1H), 3.26 (dd, *J* = 12.5, 3.5 Hz, 1H), 2.67 (dd, *J* = 12.5, 9.0 Hz, 1H), 2.50 (m, 1H), 2.28 (m, 1H),

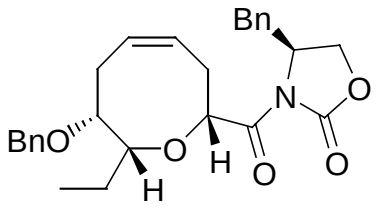
1.62 (m, 1H), 1.57 (m, 1H), 0.98 (t, J = 7.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.1, 23.1, 34.7, 37.6, 54.8, 67.1, 70.7, 72.5, 80.3, 83.4, 117.0, 127.35, 127.44, 127.7, 128.3, 128.9, 129.3, 135.0, 135.1, 138.7, 153.3, 170.4; IR (film) 2940, 1790, 1725, 1400, 1270, 1135 cm^{-1}; $[\alpha]^{24}_D$ = +47.8º (c 1.99, CH_2Cl_2).



2

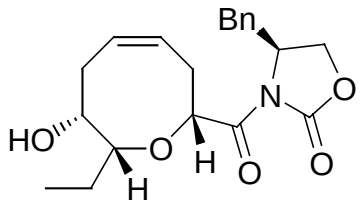
(4*S*)-4-Benzyl-3-[(2*R*)-2-((1*R*, 2*R*)-2-benzyloxy-1-ethyl-pent-4-enyloxy)-pent-4-enoyl]-oxazolidin-2-one (2). Into a flask fitted with a low-temperature thermometer was added sodium bis(trimethylsilyl)amide (0.75 M in toluene/THF, 6.70 mL, 5.03 mmol). 8 mL of THF was added and the flask was cooled to –78 ºC. Acyl oxazolidinone **3** (1.10 g, 2.51 mmol) in 10 mL of THF was added via cannula at such a rate so as to maintain the reaction temperature below –60 ºC. After stirring for 30 minutes at –78 ºC, allyl iodide (1.15 mL, 12.58 mmol) was added via syringe. After 10 minutes the reaction was warmed to –45 ºC and stirred at that temperature for 30 minutes. The reaction was quenched by the addition of saturated NH_4Cl and warmed to room temperature. The solution was extracted twice with 50% ethyl acetate/hexanes. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography provided 0.848 g (71%) of diene **2**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.16 (m, 10H), 5.95-5.81 (m, 2H), 5.29 (dd, J = 7.0, 4.6 Hz, 1H), 5.16-5.01 (m, 4H), 4.66 (m, 1H), 4.53 (AB, J_{AB} = 12.0 Hz, $\Delta\nu_{AB}$ = 36.4 Hz, 2H), 4.18-4.09 (m, 2H), 3.52 (m, 1H), 3.28-3.21 (m, 2H), 2.64 (dd, J = 13.2, 9.5 Hz, 1H), 2.57-2.49 (m, 3H), 2.22 (m, 1H), 1.70 (m, 1H), 1.48 (m, 1H), 0.96 (t , J = 7.4 Hz, 3H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 10.4, 22.8, 34.1, 37.9, 38.0, 55.0, 66.6, 72.4, 76.1, 79.4, 81.7, 116.7, 118.3, 127.4, 127.5, 127.8, 128.2, 128.9, 129. 4, 133.3, 135.0, 135.6, 138.6, 153.1, 172.8; IR (film) 2940, 1785, 1720, 1395, 1220, 1110 cm^{-1}; $[\alpha]^{24}_D$ = +82.5º (*c* 1.25, CH_2Cl_2).



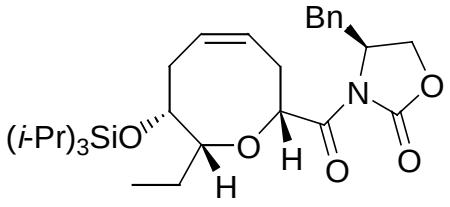
10

(4*S*)-4-Benzyl-3-[(2*R*, 7*R*, 8*R*)-7-benzyloxy-8-ethyl-3,6,7,8-tetrahydro-2*H*-oxocine-2-carbonyl]-oxazolidin-2-one (10). Into a flask equipped with a reflux condenser was added diene **2** (0.819 g, 1.715 mmol) in 350 mL of dichloromethane. Nitrogen was bubbled through the stirring solution for 20 minutes. The solution was heated to reflux and $(Cy_3P)_2Cl_2Ru$=CHPh (0.071 g, 0.0863 mmol) was added in one portion. The reaction was stirred at 40 ºC for 3 hours and cooled to room temperature. The solution was stirred open to air overnight and concentrated in vacuo. Purification by flash chromatography provided 0.726 g (94%) of oxocene **10**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.13 (m, 10H), 5.90 (m, 1H), 5.77 (m, 1H), 4.93 (d, *J* = 8.7 Hz, 1H), 4.68 (m, 1H), 4.56 (AB, J_{AB} = 12.5 Hz, $\Delta\nu_{AB}$ = 101.3 Hz, 2H), 4.27-4.14 (m, 2H), 3.58-3.49 (m, 2H), 3.25 (dd, *J* = 13.2, 3.7 Hz, 1H), 2.82-2.70 (m, 2H), 2.78 (dd, *J* = 13.2, 9.1 Hz, 1H), 2.44 (m, 1H), 2.30 (ddd, *J* = 14.0, 8.2, 1.2 Hz, 1H), 1.77 (m, 1H), 1.53 (m, 1H), 0.77 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.4, 24.9, 29.0, 32.0, 37.7, 55.3, 66.6, 71.1, 79.5, 80.3, 84.5, 127.38, 127.43, 127.8, 128.2, 128.7, 128.9, 129.4, 130.0, 135.0, 138.6, 153.1, 170.7; IR (film) 2980, 2950, 1790, 1725, 1400, 1220, 1080 cm^{-1}; $[\alpha]^{24}_D$ = +67.3º (*c* 1.27, CH_2Cl_2).



11

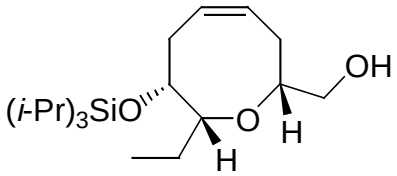
(4*S*)-4-Benzyl-3-[(2*R*, 7*R*, 8*R*)-8-ethyl-7-hydroxy-3,6,7,8-tetrahydro-2*H*-oxocine-2-carbonyl]-oxazolidin-2-one (11). To a solution of benzyl ether **10** (0.218 g, 0.485 mmol) in 8 mL of dichloromethane and 0.8 mL of pH 7 buffer solution, was added DDQ (0.440 g, 1.938 mmol) in one portion. The mixture was allowed to stir for 15 hours and was poured into ethyl acetate and saturated $NaHCO_3$. The layers were separated, and the aqueous layer extracted twice with ethyl acetate. The combined organic layers were dried over Na_2SO_4. Concentration in vacuo and purification by flash chromatography gave 0.145 g (83%) of alcohol **11**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.15 (m, 5H), 5.90-5.78 (m, 2H), 5.03 (dd, *J* = 8.3, 2.5 Hz, 1H), 4.62 (m, 1H), 4.28 (dd, *J* = 8.7, 8.3 Hz, 1H), 4.21 (dd, *J* =8.7, 3.7 Hz, 1H), 3.72 (s, 1H), 3.51 (m, 1H), 3.25 (dd, *J* = 13.2, 4.1 Hz, 1H), 2.78 (dd, *J* = 13.2, 9.1 Hz, 1H), 2.67- 2.54 (m, 2H), 2.44-2.32 (m, 2H), 1.94 (s, 1H), 1.71 (m, 1H), 1.54 (m, 1H), 0.86 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.3, 25.2, 31.9, 33.6, 37.9, 55.1, 66.8, 74.1, 78.7, 83.8, 127.5, 128.1, 129.0, 129.4, 130.3, 134.9, 153.0, 171.1; IR (film) 3740-3160 (br), 2980, 1790, 1720, 1400, 1120, 1080 cm^{-1}; $[\alpha]^{24}_D$ = +84.5º (*c* 0.85, CH_2Cl_2).



12

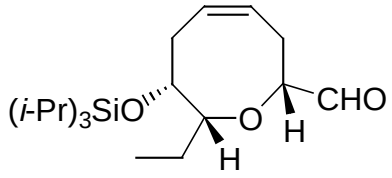
(4*S*)-4-Benzyl-3-[(2*R*, 7*R*, 8*R*)-8-ethyl-7-(tri-*iso*-propylsilanyloxy)-3,6,7,8-tetrahydro-2*H*-oxocine-2-carbonyl]-oxazolidin-2-one (12). A solution of alcohol **11** (0.240

g, 0.668 mmol) in 5 mL of dichloromethane was cooled to 0 ºC. 2,6-lutidine (0.23 mL, 1.975 mmol) was added via syringe followed by the dropwise addition of tri-*iso*-propylsilyl trifluoromethanesulfonate (0.27 mL, 1.005 mmol). The reaction was warmed to room temperature and stirred for 2 hours. The mixture was poured into 30% ethyl acetate/hexanes and washed with 1M HCl, saturated $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography provided 0.345 g (100%) of silyl ether **12**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.17 (m, 5H), 5.87 (m, 1H), 5.75 (m, 1H), 4.88 (d, *J* = 10.2 Hz, 1H), 4.72 (m, 1H), 4.26 (dd, *J* = 9.8, 9.3 Hz, 1H), 4.20 (dd, *J* = 9.3, 3.3 Hz, 1H), 3.96 (m, 1H), 3.43 (m, 1H), 3.27 (dd, *J* = 13.3, 3.0 Hz, 1H), 2.84 (q, *J* = 11.1 Hz, 1H), 2.78 (dd, *J* = 13.3, 9.2 Hz, 1H), 2.71 (m, 1H), 2.27 (dd, *J* = 12.6, 7.6 Hz, 1H), 2.25 (m, 1H), 1.75 (m, 1H), 1.46 (m, 1H), 1.07 (s, 21H), 0.84 (t, *J* = 7.4 Hz, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.8, 12.9, 18.3, 18.4, 25.3, 32.6, 33.8, 37.8, 55.2, 66.7, 75.9, 79.9, 85.6, 127.4, 128.3, 128.9, 129.4, 130.1, 135.0, 153.1, 171.4; IR (film) 2950, 1785, 1720, 1390, 1210, 1085 cm^{-1}; $[\alpha]^{24}_D$ = +67.4º (*c* 1.59, CH_2Cl_2).



[(2*R*, 3*R*, 8*R*)-8-Ethyl-7-(tri-*iso*-propylsilanyloxy)-3,6,7,8-tetrahydro-2*H*-oxocin-2-yl]-methanol. Acyl oxazolidinone **12** (0.345 g, 0.669 mmol) and anhydrous methanol (0.032 mL, 0.790 mmol) in 5 mL of diethyl ether were cooled to 0 ºC. Lithium borohydride (2.0 M in THF, 0.40 mL, 0.800 mmol) was added dropwise via syringe. After stirring 1 hour the reaction was quenched by the dropwise addition of 5 mL of 10% NaOH and warmed to room temperature. After 20 minutes the reaction was extracted with 30% ethyl acetate/hexanes, the

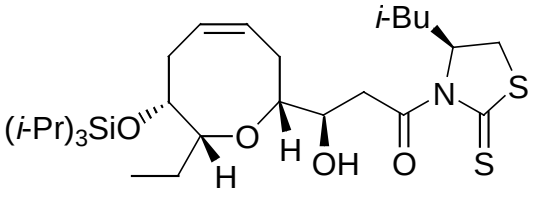
organic layer washed with brine, and the combined aqueous layers extracted with 30% ethyl acetate/hexanes. The combined organic layers were dried over Na_2SO_4. Concentration in vacuo and purification by flash chromatography gave 0.207 g (90%) of the primary alcohol: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (m, 1H), 5.67 (m, 1H), 3.88 (ddd, *J* = 11.2, 5.3, 2.5 Hz, 1H), 3.56-3.48 (m, 2H), 3.42 (m ,1H), 3.35 (m, 1H), 2.73 (q, *J* = 11.4 Hz, 1H), 2.43-2.32 (m, 2H), 2.19 (ddd, *J* = 12.0, 6.2, 5.9 Hz, 1H), 1.90 (ddd, *J* = 13.3, 8.6, 0.9 Hz, 1H), 1.67 (m, 1H), 1.48 (m, 1H), 1.06 (s, 21H), 0.93 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.1, 13.0, 18.3, 18.4, 26.0, 31.1, 33.6, 66.3, 76.0, 81.9, 83.7, 129.0,129.4; IR (film) 3700-3120 (br), 2960, 1470, 1250, 1080, 890 cm^{-1}; $[\alpha]^{24}_D$ = -27.6º (*c* 1.82, CH_2Cl_2).



4

(2*R*, 3*R*, 8*R*)-8-Ethyl-7-(tri-*iso*-propylsilanyloxy)-3,6,7,8-tetrahydro-2*H*-oxocine-2-carbaldehyde (4). Into a flask was added 3 mL of dichloromethane and oxalyl chloride (2.0 M in CH_2Cl_2, 0.12 mL, 0.240 mmol). After cooling to –78 ºC, DMSO (0.035 mL, 0.493 mmol) was added dropwise via syringe. After stirring for 10 minutes, primary alcohol [(2*R*, 3*R*, 8*R*)-8-Ethyl-7-(tri-*iso*-propylsilanyloxy)-3,6,7,8-tetrahydro-2*H*-oxocin-2-yl]-methanol (0.0523 g, 0.153 mmol) in 2 mL of CH_2Cl_2 was added dropwise via syringe. After 20 minutes, triethyl amine (0.11 mL, 0.789 mmol) was added dropwise via syringe. The cooling bath was removed and the reaction allowed to warm to room temperature. The reaction mixture was poured into 25 mL of ethyl acetate, and the organic layer was washed with water, cold 1M HCl, saturated $NaHCO_3$, water, and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Filtration through a short plug of silica gel gave 0.0504 g (97%) of aldehyde **4**: ^{1}H

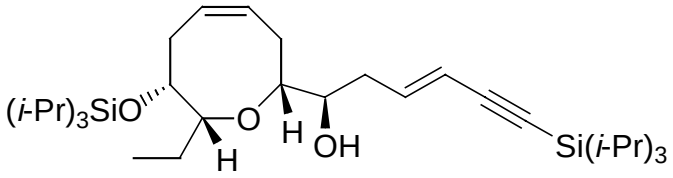
NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 1H), 5.82-5.69 (m, 2H), 3.94 (ddd, *J* = 11.8, 5.6, 3.2 Hz, 1H), 3.54 (dd, *J* = 10.2, 3.2 Hz, 1H), 3.41 (dt, 9.6, 3.2 Hz, 1H), 2.73 (q, *J* = 10.9 Hz, 1H), 2.48-2.33 (m, 2H), 2.25 (dt, *J* = 11.8, 6.4 Hz, 1H), 1.84 (m, 1H), 1.44 (m, 1H), 1.06 (s, 21H), 0.94 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.1, 12.9, 18.27, 18.33, 25.9, 29.8, 33.8, 76.2, 86.1, 86.6, 128.1, 130.2, 203.4.



15

(3*R*)-3-[(2*R*, 7*R*, 8*R*)-8-Ethyl-7-(tri-*iso*-propylsilanyloxy)-3,6,7,8-tetrahydro-2*H*-oxocin-2-yl]-3-hydroxy-1-[(4*S*)-4-(*iso*-butyl)-2-thioxo-thiazolidin-3-yl]-propan-1-one (15). (*S*)-(+)-3-Acetyl-4-(*iso*-butyl)-2-thiazolidinethione (0.407 g, 1.872 mmol) in 8 mL of dichloromethane was cooled to –78 ºC. Titanium tetrachloride (0.18 mL, 1.641 mmol) was added via syringe. After 5 minutes, di-*iso*-propylethylamine (0.29 mL, 1.665 mmol) was added dropwise via syringe. The dark red mixture was allowed to stir for 20 minutes. Aldehyde **4** (0.228 g, 0.669 mmol) in 3 mL of dichloromethane was added via syringe. After 20 minutes, the reaction was quenched by the addition of half saturated NH_4Cl and warmed to room temperature. The mixture was poured into brine and extracted twice with dichloromethane. The combined organic layers were dried over Na_2SO_4. Concentration in vacuo and purification by flash chromatography provided 0.073 g (19.6%) of the minor aldol product **16** and 0.238 g (63.8%) of the major aldol product **15**: ^1H NMR (400 MHz, $CDCl_3$) δ 5.78 (m, 1H), 5.67 (m, 1H), 5.37 (ddd, *J* = 9.2, 3.7, 3.1 Hz, 1H), 4.13 (m, 1H), 3.88 (ddd, *J* = 11.2, 5.6, 2.5 Hz, 1H), 3.55 (dd, *J* = 10.6, 7.2 Hz, 1H), 3.49 (dd, *J* = 18.0, 3.1 Hz, 1H), 3.43 (m, 1H), 3.37 (dd, *J* = 18.0, 9.2, Hz, 1H), 3.24 (dd, *J* = 9.9, 4.4 Hz, 1H), 2.89 (s, 1H), 2.89 (d, *J* = 10.6 Hz, 1H), 2.61

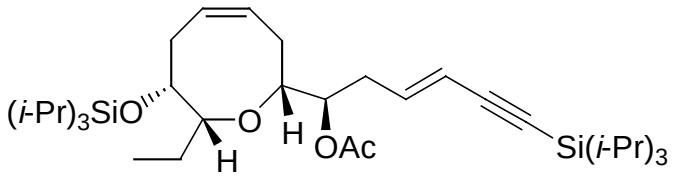
(q, *J* = 10.6 Hz, 1H), 2.54 (m, 1H), 2.21 (m, 1H), 2.07 (dd, *J* = 15.1, 8.6 Hz, 1H), 1.90 (m, 1H), 1.74-1.46 (m, 4H), 1.05 (s, 21H), 0.99 (d, *J* = 6.2 Hz, 3H), 0.97 (d, *J* = 6.2 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.0, 13.1, 18.29, 18.34, 21.3, 23.6, 25.4, 25.7, 30.9, 33.2, 33.5, 39.5, 43.1, 66.2, 70.8, 75.5, 82.7, 83.9, 129.1, 129.5, 172.1, 201.6; IR (film) 3700-3100 (br), 2960, 1700, 1470, 1345, 1275, 1165, 1080 cm^{-1}; $[\alpha]^{24}_D$ = +129.4º (*c* 1.97, CH_2Cl_2).



20

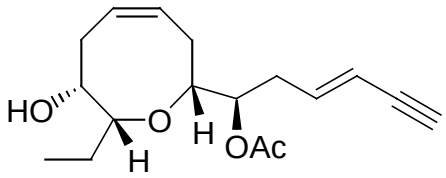
(*E*), (1*R*)-1-[(2*R*, 7*R*, 8*R*)-8-Ethyl-7-(tri-*iso*-propylsilanyloxy)-3,6,7,8-tetrahydro-2-*H*-oxocin-2-yl]-6-(tri-*iso*-propylsilanyl)-hex-3-en-5-yn-1-ol (20). Alcohol **15** (0.182 g, 0.326mmol) in 5 mL of THF was cooled to –78 ºC. Di-*iso*-butylaluminum hydride (1.0 M in hexanes, 0.72 mL, 0.720 mmol) was added dropwise via syringe. After 5 minutes, the reaction was checked by TLC, and an additional amount of (*i*-Bu)$_2$AlH (0.10 mL, 0.10 mmol) was added dropwise via syringe. This process was repeated once more until the reaction was judged complete by TLC. The reaction was quenched by the dropwise addition of 1 mL of methanol. After warming to room temperature, 6 mL of saturated sodium potassium tartrate was added, and the mixture was stirred for 20 minutes. The mixture was poured into brine and extracted twice with ethyl acetate. The combined organic layers were dried over Na_2SO_4. Concentration in vacuo and purification by flash chromatography gave an inseparable mixture of (*S*)-4-(*iso*-butyl)-2-thiazolidinethione and the desired aldehyde. The mixture was carried on the next step.

Phosphonium salt **19** (0.701 g, 1.304 mmol) in 7 mL of THF was cooled to –50 ºC. *n*-Butyl lithium (1.42 M in hexanes, 0.87 mL, 1.235 mmol) was added dropwise via syringe. The bright yellow mixture was stirred for 30 minutes. The aldehyde (0.125 g, 0.326 mmol) in 3 mL of THF was added via syringe. After 10 minutes, the reaction was warmed to 0 ºC, where it was stirred for 1 hour. The reaction was quenched with saturated NH_4Cl and warmed to room temperature. Enough water to dissolve the salts was added, and the mixture was poured into brine and extracted twice with 50% ethyl acetate/hexanes. The combined organic layers were dried over Na_2SO_4. Concentration in vacuo and purification by flash chromatography provided 0.135 g (74%) of enyne **20**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.27 (dt, *J* = 15.5, 6.8 Hz, 1H), 5.82-5.63 (m, 2H), 5.60, (d, *J* = 15.5 Hz, 1H), 3.90 (ddd, *J* = 11.9, 4.1, 2.1 Hz, 1H), 3.52 (m, 1H), 3.43 (ddd, *J* = 8.2, 5.3, 2.1 Hz, 1H), 3.10 (dd, *J* = 10.3, 5.3 Hz, 1H), 2.86 (d, *J* = 4.1 Hz, 1H), 2.71 (q, *J* = 10.3 Hz, 1H), 2.51-2.35 (m, 2H), 2.32-2.17 (m, 2H), 2.02 (dd, *J* = 13.2, 8.2 Hz, 1H), 1.70-1.48 (m, 2H), 1.04 (s, 21H), 1.03 (s, 21H), 0.89 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.9, 11.25, 11.28, 13.1, 18.29, 18.33, 18.6, 25.7, 31.2, 33.5, 37.4, 73.4, 75.4, 83.1, 83.7, 89.4, 105.6, 112.2, 129.0, 129.6, 141.5; IR (film) 3700-3240 (br), 2950, 2140, 1465, 1080, 880 cm^{-1}; $[\alpha]^{24}_D$ = -25.9º (*c* 0.95, CH_2Cl_2).



(*E*), (1*R*)-Acetic acid 1-[(2*R*, 7*R*, 8*R*)-8-Ethyl-7-(tri-*iso*-propylsilanyloxy)-3,6,7,8-tetrahydro-2-*H*-oxocin-2-yl]-6-(tri-*iso*-propylsilanyl)-hex-3-en-5-ynyl ester. Alcohol **20** (0.091 g, 0.162 mmol) was dissolved in 4 mL of dichloromethane. Pyridine (0.39 mL, 4.827 mmol) was added via syringe followed by DMAP (0.002 g, 0.0164 mmol). Acetic anhydride

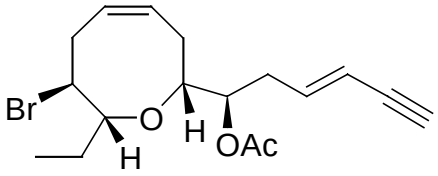
(0.23 mL, 2.438 mmol) was added via syringe, and the mixture was stirred for 14 hours at room temperature. The reaction mixture was poured into 50% ethyl acetate/hexanes and washed with 1M HCl, saturated $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography provided 0.095 g, (97%) of the acetate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (dt, *J* = 15.5, 7.2 Hz, 1H), 5.77-5.62 (m ,2H), 5.57 (d, *J* = 15.5 Hz, 1H), 4.98 (dt, *J* = 8.7, 4.3 Hz, 1H), 3.88 (ddd, *J* = 11.2, 4.7, 2.9 Hz, 1H), 3.32 (dd, *J* = 11.2, 4.7 Hz, 1H), 2.69 (q, *J* = 11.2 Hz, 1H), 2.57 (dddd, *J* = 15.1, 6.2, 2.9, 1.5 Hz, 1H), 2.46-2.30 (m, 2H), 2.18 (m, 1H), 2.06-1.97 (m, 2H), 2.04 (s, 3H), 1.62 (m, 1H), 1.45 (m, 1H), 1.06 (s, 21H), 1.05 (s, 21H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.9, 11.25, 11.28, 13.1, 18.27, 18.33, 18.6, 21.1, 25.7, 29.4, 33.0, 33.6, 74.6, 75.7, 80.3, 84.6, 89.6, 105.5, 112.6, 129.0, 129.7, 140.8, 170.5; IR (film) 2960, 1750, 1470, 1240, 1090, 890 cm^{-1}; $[\alpha]^{24}_D$ = -17.1º (*c* 0.95, CH_2Cl_2).



21

(*E*), (1*R*)-Acetic acid 1-[(2*R*, 7*R*, 8*R*)-8-Ethyl-7-hydroxy-3,6,7,8-tetrahydro-2-*H*-oxocin-2-yl]-6-hex-3-en-5-ynyl ester (21). (*E*), (1*R*)-Acetic acid 1-[(2*R*, 7*R*, 8*R*)-8-Ethyl-7-(tri-*iso*-propylsilanyloxy)-3,6,7,8-tetrahydro-2-*H*-oxocin-2-yl]-6-(tri-*iso*-propylsilanyl)-hex-3-en-5-ynyl ester (0.108 g, 0.178 mmol) in 4 mL of THF was cooled to 0 ºC. Tetrabutylammonium fluoride (1.0 M in THF, 0.41 mL, 0.410 mmol) was added dropwise via syringe. The reaction was stirred for 30 minutes at 0 ºC and subsequently warmed to room temperature, where it was stirred for an additional hour. The mixture was poured into saturated NH_4Cl and extracted three times with dichloromethane. The organic layers were dried over

Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography provided 0.050 g (96%) of alcohol **21**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.13 (dt, *J* = 15.4, 7.7 Hz, 1H), 5.79-5.67 (m, 2H), 5.51 (ddd, *J* = 15.4, 2.3, 1.3 Hz, 1H), 4.96 (dt, *J* = 8.2, 4.6 Hz, 1H), 3.65 (m, 1H), 3.43 (m, 1H), 3.37 (m, 1H), 2.80 (d, *J* = 2.3 Hz, 1H), 2.55-2.25 (m, 5H), 2.11 (ddd, *J* = 14.0, 7.8, 2.3 Hz, 1H), 2.04 (s, 3H), 1.70 (m, 1H), 1.67-1.47 (m, 2H), 0.90 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.5, 21.0, 25.5, 29.8, 33.5, 34.1, 73.6, 74.3, 76.7, 80.5, 81.9, 83.1, 111.5, 128.8, 129.5, 141.2, 170.4; IR (film) 3720-3100 (br), 3300, 2940, 1740, 1375, 1140, 1070 cm^{-1}; $[\alpha]^{24}_D$ = -20.6º (*c* 0.93, CH_2Cl_2).



1

(+)-Laurencin (1). Alcohol **21** (0.0250 g, 0.0855 mmol) and carbon tetrabromide (0.142 g, 0.428 mmol) were dissolved in 3 mL of toluene. Trioctyl phosphine (0.38 mL, 0.852 mmol) was added via syringe. After 15 minutes the reaction vessel was lowered into a 70 ºC oil bath, and the reaction was stirred at that temperature for 3.5 hours. After cooling to room temperature, the mixture was concentrated in vacuo. Purification by flash chromatography provided 0.0175 g (58%) of (+) Laurencin **1**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.14 (dt, *J* = 16.1, 7.3 Hz, 1H), 5.96-5.83 (m, 2H), 5.51 (dd, *J* = 16.1, 1.7 Hz, 1H), 4.98 (dt; *J* = 8.9, 4.5 Hz, 1H), 4.06 (dt, *J* = 9.9, 3.4 Hz, 1H), 3.41 (ddd, *J* = 9.9, 7.4, 2.6 Hz, 1H), 3.37 (dd, *J* = 10.5, 4.5 Hz, 1H), 3.14 (ddd, *J* = 14.2, 8.6, 3.4 Hz, 1H), 2.80 (d, *J* = 1.7 Hz, 1H), 2.52-2.28 (m, 4H), 2.06 (m, 1H), 2.06 (s, 3H), 1.93 (ddq, *J* = 14.5, 7.4, 2.6 Hz, 1H), 1.55 (dqu, *J* = 14.5, 7.4 Hz, 1H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.3, 21.0, 25.8, 29.7, 32.3, 33.8, 56.0, 74.0,

76.7, 81.4, 81.8, 84.6, 111.6, 129.0, 129.2, 141.1, 170.3; IR (film) 3300, 2940, 1745, 1375, 1240, 1075, 965 cm^{-1}; $[\alpha]^{24}_{D}$ = +51.7º (*c* 0.72, $CHCl_3$).