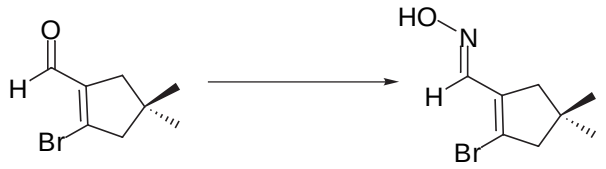
Total Synthesis of the Sesqiterpene (+/-)-Illudin C via an Intramolecular Nitrile Oxide Cycloaddition

*Ronald A. Aungst, Jr., Collin Chan, and Raymond L. Funk**

Department of Chemistry, Pennsylvania State University
University Park, Pennsylvania 16802

7 **8**

2-Bromo-4,4-dimethylcyclopent-1-enecarboxaldehyde (8). To a solution of DMF (513 mL, 6.63 mmol) in CH_2Cl_2 (10 mL) was added $POBr_3$ (1.58 g, 5.52 mmol) at rt. The solution was stirred at rt for 1 h as a white precipitate formed. A solution of silylenol ether **7** (500 mg, 2.21 mmol) in CH_2Cl_2 (2 mL) was added to the mixture and the resultant slurry was stirred 72 h at rt and poured onto ice (5 g). The solution was neutralized with $NaHCO_3$ and extracted with hexane/Et_2O (9 : 1). The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 3 : 97, silica-gel deactivated with 10% triethylamine) gave exclusively one regioisomer as a colorless oil (289 mg, 64%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.11 (s, 6 H), 2.29 (t, J = 2.2 Hz, 2 H), 2.67 (t, J = 2.2 Hz, 2 H), 9.83 (s, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 29.3 (2 C), 37.5, 43.8, 56.8, 139.0, 139.2, 189.2; IR (neat) 1675, 1608 cm^{-1}.



8 **9**

2-Bromo-4,4-dimethylcyclopent-1-enecarboxaldehyde oxime (9). To a solution of aldehyde **8** (325 mg, 1.60 mmol) in EtOH (4 mL) was added a solution of $H_2NOH{\cdot}HCl$ (167 mg, 2.40 mmol) and sodium acetate (197 mg, 2.40 mmol) in EtOH/H_2O (2.70 mL, 1 : 1) dropwise at 0 °C. The mixture was stirred 1.5 h at rt and the EtOH was concentrated off. Brine was added and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated. Purification by silica-gel chromatography (Et_2O-CH_2Cl_2-hexane, 4 : 45 : 51) provided a white solid (285 mg, 82%): ^{1}H NMR (200 MHz, d^6-acetone) δ 1.12 (S, 6 H), 2.32 (td, *J* = 0.7, 2.0 Hz, 2 H), 2.56 (t, *J* = 2.0 Hz, 2 H), 7.93 (s, 1 H), 10.39 (s, 1 H); ^{13}C NMR (50 MHz, d^6-acetone) δ 29.6 (2C), 38.0, 46.4, 55.8, 123.0, 134.4, 145.7; IR (neat) 3286, 1626 cm^{-1}; HRMS (M+H$^+$) calcd for $C_8H_{13}ONBr$ 218.0181, found 218.0198.

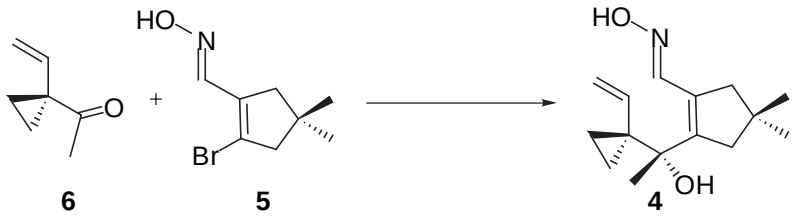
10 **11**

1-[1-(1-Hydroxyethyl)-cyclopropyl]-ethanone(11). Lithium tri(tert-butoxy)alumninohydride (15.9 mL, 1.0 M in THF, 15.9 mmol) was added dropwise to a solution of dione **10** (2.00 g, 15.9 mmol) in Et_2O (80 mL) at –78 °C. The solution was slowly warmed to rt and stirred overnight. A saturated aqueous solution of sodium potassium tartrate was added and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with saturated aqueous sodium potassium tartrate, dried (Na_2SO_4) and concentrated. Purification by silica-gel chromatography (ethyl acetate-benzene, 1 : 4) yielded a colorless oil (1.18 g, 58%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.86 (dd, *J* = 3.1, 5.2 Hz, 2 H), 0.96–1.06 (m, 2 H), 1.04 (d, *J* = 6.6 Hz, 3 H), 2.02 (s, 3 H), 3.36 (br d, *J* = 6.6

Hz, 1 H), 3.67 (br p, J = 6.6 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.8, 13.8, 19.8, 24.5, 36.9, 68.8, 209.8; IR (neat) 3440, 1682 cm^{-1}.

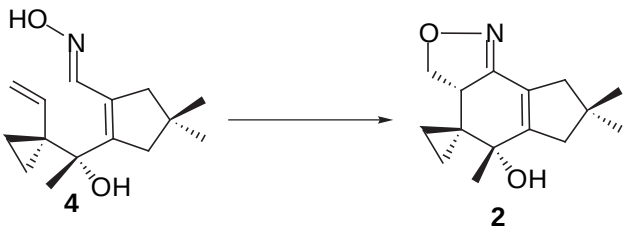
11 **6**

1-(1-Vinyl-cyclopropyl)-ethanone (6). To a solution of ketoalcohol **11** (1.20 g, 9.35 mmol) in benzene (50 mL) was added imidazole (700 mg, 10.28 mmol), triphenylphosphine (2.70 g, 10.28 mmol) and lastly iodine (2.66 g, 10.47 mmol). The solution was stirred 1 h at rt and poured onto a 1 : 1 solution of 10% $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. The aqueous layer was extracted with hexane and the combined organic layers were dried (Na_2SO_4) and concentrated. Purification by silica-gel chromatography (Et_2O–pentane, 2 : 23) afforded a yellow oil (1.81 g, 82%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.07 (ddd, J = 4.1, 6.6, 9.4 Hz, 1 H), 1.22 (ddd, J = 4.3, 6.2, 9.4 Hz, 1 H), 1.44 (ddd, J = 4.1, 6.2, 9.5 Hz, 1 H), 1.60 (ddd, J = 4.3, 6.6, 9.5 Hz, 1 H), 1.81 (d, J = 7.2 Hz, 3 H), 2.08 (s, 3 H), 4.64 (q, J = 7.2 Hz, 1 H). The above iodide (1.63 g, 6.85 mmol) was immediately subjected to elimination by addition of DBU (2.05 mL, 13.7 mmol). The neat mixture was heated to 85 °C at reduced pressure (20 mmHg) as the product was distilled over and trapped at –78 °C to yield a volatile colorless oil (440 mg, 58%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.01 (q, J = 3.5 Hz, 2 H), 1.35 (q, J = 3.5 Hz, 2 H), 2.15 (s, 3 H), 4.99 (dd, J = 1.1, 17.1 Hz, 1 H), 5.07 (dd, J = 1.1, 10.5 Hz, 1 H), 6.46 (dd, J = 10.5, 17.1 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 18.8 (2 C), 27.7, 34.0, 114.6, 136.7, 207.6; IR (neat) 1697, 1639 cm^{-1}.



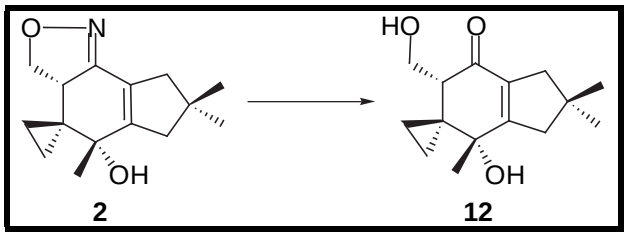
6 5 4

2-[1-Hydroxy-1-(1-vinylcyclopropyl)-ethyl]-4,4-dimethylcyclopent-1-enecarboxaldehyde oxime (4). To a solution of oxime **9** (100 mg, 0.46 mmol) in THF (2.5 mL) at –78 °C was added tert-butyllithium (837 μL, 1.7 M in pentane, 1.42 mmol) dropwise. The resultant yellow solution was stirred at –78 °C for 1.5 h. A solution of ketone **6** (66 mg, 0.60 mmol) in THF (2 mL) was added dropwise over 1 h and the resultant solution was slowly warmed to rt over 1 h. The mixture was poured onto saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated. Purification by silica-gel chromatography (ethyl acetate-*iso*-propanol-hexane, 1 : 0.01 : 4) yielded a white solid (77 mg, 68%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.56 (ddd, *J* = 3.3, 5.0, 8.6 Hz, 1 H), 0.77 (ddd, *J* = 4.4, 5.8, 8.6 Hz, 1 H), 0.84 (ddd, *J* = 4.4, 5.0, 9.7 Hz, 1 H), 0.89 (ddd, *J* = 3.3, 5.8, 9.7 Hz, 1 H), 1.05 (s, 3 H), 1.07 (s, 3 H), 1.15 (s, 3 H), 2.24 (dt, *J* = 1.8, 17.0 Hz, 1 H), 2.36 (dt, *J* = 1.6, 17.0 Hz, 1 H), 2.41 (br s, 2 H), 4.94 (dd, *J* = 1.3, 17.5 Hz, 1 H), 4.96 (dd, *J* = 1.3, 10.3 Hz, 1 H), 6.14 (dd, *J* = 10.3, 17.5 Hz, 1 H), 8.2 (br s, 1 H), 8.83 (s, 1 H); ^{13}C NMR (50 MHz, d^6-acetone) δ 11.1, 12.3, 25.3, 29.6, 32.1, 36.7, 48.4, 51.6, 76.2, 111.5, 130.6, 141.9, 149.7, 150.1; IR (neat) ; HRMS (M+H$^+$) calcd for $C_{15}H_{24}O_2N$ 250.1807, found 250.1786.



4 2

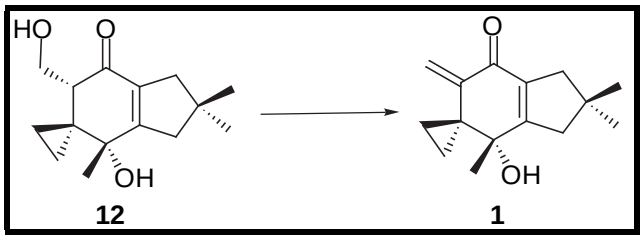
Cycloadduct (2). To a solution of hydroxyoxime **4** (97 mg, 0.39 mmol) in EtOH (4 mL) was added chloramine-T (134 mg, 0.59 mmol) at rt. The mixture was heated to 40 °C for 6 h then concentrated. The residue was dissolved in EtOAc and the organic phase was washed with 1.0 M NaOH (3x) and brine (2x) The organic layer was dried (Na_2SO_4) and concentrated to provide a white solid as a single diastereomer (95 mg, 99%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.18 (ddd, *J* = 4.6, 5.3, 10.1 Hz, 1 H), 0.55 (ddd, *J* = 3.5, 4.9, 10.1 Hz, 1 H), 0.72 (ddd, *J* = 4.6, 4.9, 10.0 Hz, 1 H), 0.77 (ddd, *J* = 3.5, 5.3, 10.0 Hz, 1 H), 1.12 (s, 3 H), 1.15 (s, 3 H), 1.29 (s, 1 H), 1.43 (s, 3 H), 2.31 (dt, *J* = 1.8, 17.8 Hz, 1 H), 2.39 (dt, *J* = 1.8, 12.7 Hz, 1 H), 2.44 (dt, *J* = 1.8, 12.7 Hz, 1 H), 2.54 (dt, *J* = 1.8, 17.8 Hz, 1 H), 3.43 (dd, *J* = 7.9, 13.1 Hz, 1 H), 3.88 (dd, *J* = 10.3, 13.1 Hz, 1 H), 4.29 (dd, *J* = 7.9, 10.3 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 3.0, 5.4, 24.5, 28.2, 29.3, 29.6, 38.4, 45.4, 46.5, 49.8, 68.8, 71.2, 129.1, 155.5, 155.8; IR (neat) 3438, 1630, 1587 cm^{-1}; HRMS ($M+H^+$) calcd for $C_{15}H_{22}O_2N$ 248.1651, found 248.1652.



2 **12**

Ketodiol 12. Cycloadduct **2** (92 mg, 0.37 mmol) was dissolved in a MeOH/H_2O (3 mL, 5 : 1) solution. Boric acid (49 mg, 0.79 mmol) and Raney-Ni (20 mg, 50% in H_2O) were added and the mixture was stirred under balloon pressure of hydrogen for 2 h. The solution was poured onto saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4) and concentrated. Purification by silica-gel chromatography (ethyl acetate-isopropanol-hexane, 1 : 0.05 : 1) to afford a colorless oil

(68 mg, 73%) : ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.35 (dt, *J* = 4.5, 9.5 Hz, 1 H), 0.42 (dt, *J* = 4.5, 9.5 Hz, 1 H), 0.74 (dt, *J* = 4.5, 9.7 Hz, 1 H), 0.86 (dt, *J* = 4.5, 9.7 Hz, 1 H), 0.99 (s, 3 H), 1.04 (s, 3 H), 1.11 (s, 3 H), 1.70 (t, *J* = 3.2 Hz, 1 H), 2.34 (t, *J* = 1.6 Hz, 2 H), 2.40 (dt, *J* = 1.6, 18.2 Hz, 1 H), 2.48 (dt, *J* = 1.6, 18.2 Hz, 1H), 3.72 (dd, *J* = 3.2, 10.4 Hz, 1 H), 3.84 (dd, *J* = 3.2, 10.4 Hz, 1 H), 4.53 (br s, 1 H), 5.31 (br s, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 5.7, 13.9, 21.1, 28.1, 29.1, 29.2, 37.7, 43.9, 47.6, 57.3, 63.1, 38.2, 137.4, 167.1, 199.1;



12 **1**

Illudin C (1). To a solution of ketodiol **12** (43 mg, 0.17 mmol) in CH_2Cl_2 (1.7 mL) at –78 °C was added Et_3N (72 mL, 0.52 mmol) and MesCl (16 mL, 0.21 mmol) dropwise. The solution was warmed to 0 °C over 2 h then DBU (51 mL, 0.34 mmol) was added and the mixture was stirred at rt overnight. Saturated aqueous $NaHCO_3$ was added and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated. Purification by silica-gel chromatography (MeOH-$CDCl_3$, 1 : 99) to yield a white solid (29 mg, 73%): ^{1}H NMR (400 MHz, d^6-benzene) δ 0.19 (ddd, *J* = 3.5, 6.6, 9.8 Hz, 1 H), 0.75 (ddd, *J* = 4.9, 6.6, 9.6 Hz, 1 H), 0.79 (dt, *J* = 4.9, 5.1, 9.6 Hz, 1 H), 0.90 (s, 3 H), 0.95 (s, 3 H), 1.17 (s, 3 H), 1.19 (ddd, *J* = 3.5, 5.1, 9.8 Hz, 1 H), 1.75 (s, 1 H), 2.18 (dt, *J* = 2.0, 20.0 Hz, 1 H), 2.47 (dt, *J* = 1.8, 20.0 Hz, 1 H), 2.48 (dt, *J* = 1.8, 16.7 Hz, 1 H), 2.51 (dt, *J* = 2.0, 16.7 Hz, 1 H), 4.86 (d, *J* = 1.6 Hz, 1 H), 6.15 (d, *J* = 1.6 Hz, 1 H); ^{13}C NMR (90 MHz, d^6-benzene) δ 5.2, 13.2, 26.1, 29.3, 29.4, 33.4, 37.5, 44.8, 47.9, 70.1, 135.9, 148.4, 169.2, 169.3, 185.7; IR (neat) 3443, 1657, 1605 cm^{-1}.