

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

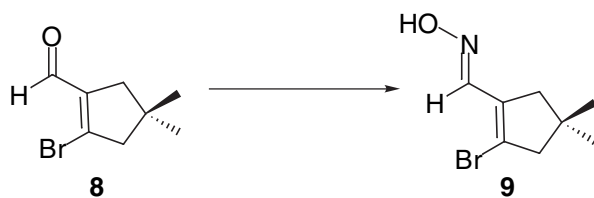
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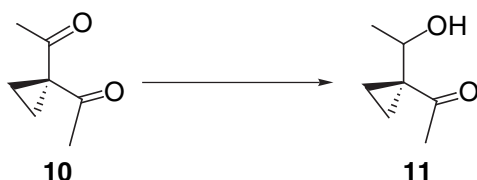
2-Bromo-4,4-dimethylcyclopent-1-enecarboxaldehyde (8).

To a solution of DMF (513 mL, 6.63 mmol) in CH₂Cl₂ (10 mL) was added POBr₃ (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 CH₂Cl₂ (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 NaHCO₃ and extracted with hexane/Et₂O (9 : 1). The combined organic layers were washed with saturated aqueous NaHCO₃, dried (Na₂SO₄) 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%): ¹H NMR (200 MHz, CDCl₃) 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); ¹³C NMR (50 MHz, CDCl₃) δ 29.3 (2 C), 37.5, 43.8, 56.8, 139.0, 139.2, 189.2; IR (neat) 1675, 1608 cm⁻¹.



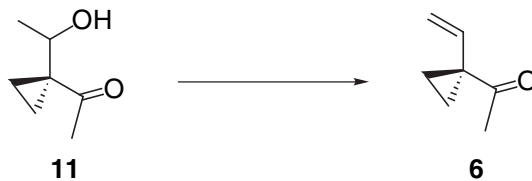
2-Bromo-4,4-dimethylcyclopent-1-enecarboxaldehyde

oxime (9). To a solution of aldehyde **8** (325 mg, 1.60 mmol) in EtOH (4 mL) was added a solution of $\text{H}_2\text{NOH}\cdot\text{HCl}$ (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%): ^1H 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 ($\text{M}+\text{H}^+$) calcd for $\text{C}_8\text{H}_{13}\text{ONBr}$ 218.0181, found 218.0198.

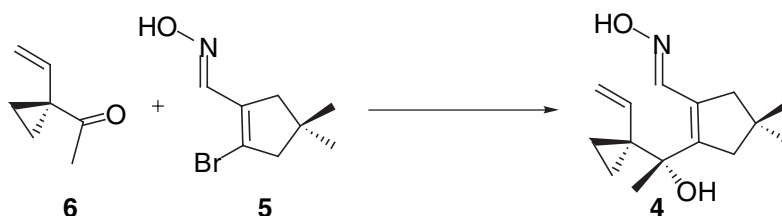


1-[1-(1-Hydroxyethyl)-cyclopropyl]-ethanone(11). Lithium tri(tert-butoxy)aluminumhydride (15.9 mL, 1.0 M in THF, 15.9 mmol) was added dropwise to a solution of dione **10** (2.00 g, 15.9 mmol) in Et_2O (80 mL) at -78 °C. The solution was slowly warmed to rt and stirred overnight. A saturated aqueous 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%): ^1H 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

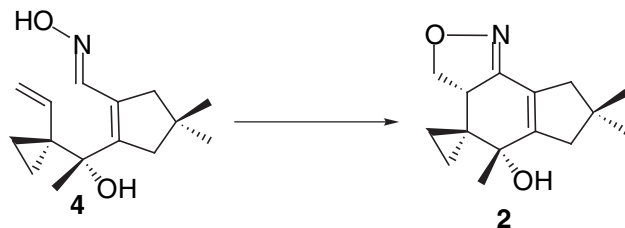
Hz, 1 H), 3.67 (br p, $J = 6.6$ Hz, 1 H); ^{13}C NMR (50 MHz, CDCl_3) δ 11.8, 13.8, 19.8, 24.5, 36.9, 68.8, 209.8; IR (neat) 3440, 1682 cm^{-1} .



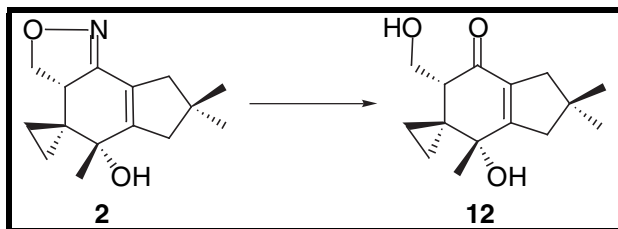
1-(1-Vinyl-cyclopropyl)-ethanone (6). To a solution of ketoalcohol **11** (1.20 g, 9.35 mmol) in benzene (50 mL) was added imidazole (700 mg, 10.28 mmol), triphenylphosphine (2.70 g, 10.28 mmol) and lastly iodine (2.66 g, 10.47 mmol). The solution was stirred 1 h at rt and poured onto a 1 : 1 solution of 10% $\text{Na}_2\text{S}_2\text{O}_3$ 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%): ^1H 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 $^\circ\text{C}$ at reduced pressure (20 mmHg) as the product was distilled over and trapped at -78 $^\circ\text{C}$ to yield a volatile colorless oil (440 mg, 58%): ^1H 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} .



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 $-78\text{ }^{\circ}\text{C}$ was added tert-butyllithium (837 μL , 1.7 M in pentane, 1.42 mmol) dropwise. The resultant yellow solution was stirred at $-78\text{ }^{\circ}\text{C}$ 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%): ^1H 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 ($\text{M}+\text{H}^+$) calcd for $\text{C}_{15}\text{H}_{24}\text{O}_2\text{N}$ 250.1807, found 250.1786.

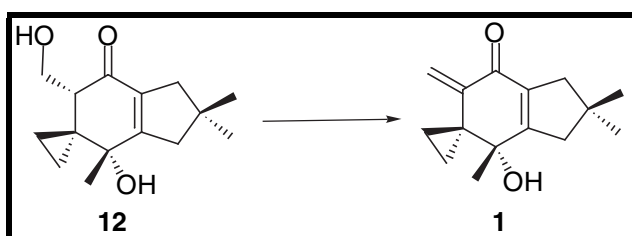


Cycloadduct (2). To a solution of hydroxyoxime **4** (97 mg, 0.39 mmol) in EtOH (4 mL) was added chloramine-T (134 mg, 0.59 mmol) at rt. The mixture was heated to 40 °C for 6 h then concentrated. The residue was dissolved in EtOAc and the organic phase was washed with 1.0 M NaOH (3x) and brine (2x). The organic layer was dried (Na₂SO₄) and concentrated to provide a white solid as a single diastereomer (95 mg, 99%): ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (90 MHz, CDCl₃) 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 C₁₅H₂₂O₂N 248.1651, found 248.1652.



Ketodiol 12. Cycloadduct **2** (92 mg, 0.37 mmol) was dissolved in a MeOH/H₂O (3 mL, 5 : 1) solution. Boric acid (49 mg, 0.79 mmol) and Raney-Ni (20 mg, 50% in H₂O) were added and the mixture was stirred under balloon pressure of hydrogen for 2 h. The solution was poured onto saturated aqueous NaHCO₃ and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with saturated aqueous NaHCO₃, dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ethyl acetate-isopropanol-hexane, 1 : 0.05 : 1) to afford a colorless oil

(68 mg, 73%) : ^1H 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, 1 H), 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;



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%): ^1H NMR (400 MHz, $\text{d}^6\text{-benzene}$) 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, $\text{d}^6\text{-benzene}$) 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} .