An Approach to the Total Synthesis of Welwistatin

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**General Methods.** Unless otherwise noted, all reactions were carried out under a nitrogen atmosphere using flame-dried glassware. All moisture sensitive reagents were added via a dry syringe or cannula where possible. Anhydrous tetrahydrofuran (THF), dichloromethane (CH$_2$Cl$_2$), diethyl ether (Et$_2$O), toluene, triethylamine (Et$_3$N), and dimethylformamide (DMF) were obtained from a solvent dispensing system. *N*-Bromosuccinimide (NBS) and Pb(OAc)$_4$ were recrystallized from hot H$_2$O and acetic acid, respectively. All other solvents and reagents were used as obtained from commercial sources without further purification. $^1$H and $^{13}$C NMR spectra were obtained on Bruker 200, 300, or 400 MHz spectrometers. Infrared spectra were obtained using a Perkin-Elmer 1600 FTIR. Chromatographic purification was performed using Sorbent Technologies silica gel 60 (230-400 mesh). Melting points were obtained on a Thomas Hoover melting point apparatus.
4-\((\text{tert}-\text{Butyldimethylsilyloxy})\)-2-(6\(H\)[1,3]dioxin-4-ylmethyl)-5-methyl-5-vinylcyclohexanone (9). To a solution of 4-\((\text{tert}-\text{butyldimethylsilyloxy})\)-3-methyl-3-vinylcyclohexanone (7) (8.21 g, 30.6 mmol) and 6-bromomethyl-4\(H\)-1,3-dioxin (6.57 g, 36.7 mmol) in THF (150 mL) at -78 °C was added LiHMDS (1.0 M in THF, 45.8 mL, 45.8 mmol) dropwise over 10 min. The solution was warmed to rt over 1 h and stirred for 12 h. The mixture was quenched with saturated aqueous NH\(_4\)Cl and extracted with ether. The combined extracts were dried (Na\(_2\)SO\(_4\)) and concentrated. Purification by silica-gel chromatography (CH\(_2\)Cl\(_2\)–hexane, 2 : 1) provided dioxin 9 as a yellow oil (8.42 g, 75%); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 0.12 (s, 3 H), 0.13 (s, 3 H), 0.94 (s, 9 H), 1.06 (s, 3 H), 1.63 (dt, \(J = 1.9, 13.5\) Hz, 1 H), 1.78 (dd, \(J = 9.8, 14.7\) Hz, 1 H), 2.01 (ddd, \(J = 3.6, 5.9, 13.5\) Hz, 1 H), 2.32 (d, \(J = 13.8\) Hz, 1 H), 2.68 (d, \(J = 13.8\) Hz, 1 H), 2.73 (br d, \(J = 14.7\) Hz, 1 H), 2.92 (m, 1 H), 3.67 (m, 1 H), 4.19 (br t, \(J = 2.2\) Hz, 1 H), 4.64 (br t, \(J = 2.2\) Hz, 2 H), 4.96 (d, \(J = 5.3\) Hz, 1 H), 5.02 (d, \(J = 5.3\) Hz, 1 H), 5.03 (d, \(J = 10.9\) Hz, 1 H), 5.04 (d, \(J = 17.8\) Hz, 1 H), 5.62 (dd, \(J = 10.9, 17.8\) Hz, 1 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) -5.0, -4.6, 18.1, 25.7, 25.8, 32.5, 35.6, 40.7, 46.2, 47.6, 63.9, 72.9, 90.4, 98.2, 114.6, 143.4, 152.2, 211.1; IR (neat) 2929, 1711, 1682 cm\(^{-1}\); HRMS (MH\(^+\)) calcd for C\(_{20}\)H\(_{35}\)O\(_4\)Si 367.2305, found 367.2306.
3-(tert-Butyldimethylsilyloxy)-5-(6H-[1,3]dioxin-4-ylmethyl)-2-methyl-6-oxo-2-vinyl-cyclohexanecarbonitrile (10). To a solution of diisopropylamine (3.28 mL, 23.4 mmol) in THF (100 mL) at –60 °C was added n-BuLi (2.5 M in hexane, 8.94 mL, 22.4 mmol) dropwise over 10 min. The solution was warmed to –30 °C and stirred for 20 min. The resulting mixture was cooled to –78 °C and ketone 9 (8.20 g, 22.4 mmol) in THF (10 mL) was added dropwise over 15 min. The solution was warmed slowly to –10 °C and stirred for 1 h. The resulting enolate was cooled to -78 °C and p-toluenesulfonyl cyanide (3.68 g, 20.3 mmol) in THF (15 mL) was added in one portion. The solution was warmed to 0 °C over 1.5 h, and then concentrated aqueous NH₄OH was added. After stirring to rt, the mixture was diluted with saturated aqueous NH₄Cl and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 9) provided β-ketonitrile 10 as a yellow oil (6.41 g, 81%); ¹H NMR (400 MHz, CDCl₃) δ 0.07 (s, 3 H), 0.08 (s, 3 H), 0.87 (s, 9 H), 1.27 (s, 3 H), 1.68 (dt, J = 1.9, 14.0 Hz, 1 H), 1.81 (dd, J = 9.7, 14.7 Hz, 1 H), 2.00 (ddd, J = 3.5, 6.1, 14.0 Hz, 1 H), 2.64 (br d, J = 14.7 Hz, 1 H), 2.93 (m, 1 H), 3.70 (m, 1 H), 3.93 (s, 1 H), 4.10 (br t, J = 2.1 Hz, 2 H), 4.63 (br t, J = 2.1 Hz, 1 H), 4.87 (d, J = 5.3 Hz, 1 H), 4.92 (d, J = 5.3 Hz, 1 H), 5.17 (d, J = 11.2 Hz, 1 H), 5.19 (d, J = 17.6 Hz, 1 H), 5.53 (dd, J = 11.2, 17.6 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ -5.2, -4.9, 17.8, 23.3, 25.5, 32.2, 35.0, 40.5, 48.8, 51.1, 63.5, 72.3, 90.2, 98.8, 115.2, 117.7, 137.9, 150.7, 200.7; IR (neat) 2930, 2200, 1726, 1682 cm⁻¹; HRMS (MNa⁺) calcd for C₂₁H₃₃NO₄SiNa 414.2077, found 414.2064.
8-(tert-Butyldimethylsilyloxy)-9-methyl-4,10-dioxo-9-vinylbicyclo[4.3.1]-decane-1-carbonitrile (5). A solution of β-ketonitrile 10 (4.66 g, 11.9 mmol) in toluene (160 mL) was heated in a sealed tube at 165 °C for 45 min. The resulting solution was concentrated to afford the crude enone, which was used immediately without further purification; \(^1\)H NMR (200 MHz, CDCl\(_3\)) δ 0.16 (s, 3 H), 0.18 (s, 3 H), 0.97 (s, 9 H), 1.37 (s, 3 H), 1.89 (dt, \(J = 2.0, 13.8\) Hz, 1 H), 2.02 (ddd, \(J = 3.2, 6.4, 13.8\) Hz, 1 H), 2.41 (dd, \(J = 6.1, 17.9\) Hz, 1 H), 3.19 (dd, \(J = 6.1, 17.9\) Hz, 1 H), 3.38 (heptet, \(J = 6.1\) Hz, 1 H), 3.75 (br t, \(J = 2.5\) Hz, 1 H), 4.08 (s, 1 H), 5.28 (d, \(J = 10.8\) Hz, 1 H), 5.29 (d, \(J = 17.9\) Hz, 1 H), 5.64 (dd, \(J = 10.8, 17.9\) Hz, 1 H), 6.24 (dd, \(J = 2.0, 17.7\) Hz, 1 H), 6.38 (dd, \(J = 9.5, 17.7\) Hz, 1 H). To the crude enone was added a 1 : 1 solution of THF-MeOH (1.30 L) followed by Et\(_3\)N (8.30 mL, 59.5 mmol). The mixture was stirred at rt for 16 h. The resulting solution was concentrated. Purification by silica-gel chromatography (ethyl acetate-hexanes, 1 : 3) afforded bicyclic ketone 5 as a white solid: mp 160 – 162 °C (3.39 g, 79%); \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 0.04 (s, 3 H), 0.05 (s, 3 H), 0.82 (s, 9 H), 1.18 (s, 3 H), 1.94 – 2.08 (m, 2 H), 2.23 (ddd, \(J = 2.7, 5.5, 15.6\) Hz, 1 H), 2.39 (ddd, \(J = 2.7, 13.2, 19.0\) Hz, 1 H), 2.57 (ddd, \(J = 2.5, 5.5, 19.0\) Hz, 1 H), 2.69 (dd, \(J = 7.8, 11.0\) Hz, 1 H), 2.79 (dt, \(J = 2.5, 18.1\) Hz, 1 H), 2.86 – 2.98 (m, 2 H), 4.49 (dd, \(J = 5.5, 11.0\) Hz, 1 H), 5.34 (d, \(J = 17.3\) Hz, 1 H), 5.36 (d, \(J = 10.9\) Hz, 1 H), 5.87 (dd, \(J = 10.9, 17.3\) Hz, 1 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ -4.7, -4.1, 14.5, 17.8, 25.5, 27.6, 35.5, 38.6, 42.8, 44.6, 50.0, 62.1, 66.9, 117.8, 118.9, 137.7, 203.5, 206.5; IR (neat) 2930, 2238, 1723 cm\(^{-1}\); HRMS (MNa\(^+\)) calcd for C\(_{20}\)H\(_{31}\)NO\(_3\)SiNa 384.1971, found 384.1978.
8,10-Bis(tert-butyl dimethyl silyloxy)-9-methyl-4-(trimethyl silyloxy)-9-vinyl bicyclo[4.3.1]dec-3-ene-1-carbonitrile (11). To a solution of ketone 5 (1.32 g, 3.65 mmol) in CH$_2$Cl$_2$ (36 mL) at 0 °C was added Et$_3$N (1.53 mL, 10.9 mmol) followed by TMSOTf (1.32 mL, 7.30 mmol). The mixture was stirred at 0 °C for 90 min. The resulting solution was quenched with saturated aqueous NaHCO$_3$ and extracted with CH$_2$Cl$_2$. The combined extracts were dried (Na$_2$SO$_4$) and concentrated to afford the crude silyl enol ether, which was used without further purification; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.04 (s, 3 H), 0.05 (s, 3 H), 0.20 (s, 9 H), 0.83 (s, 9 H), 1.23 (s, 3 H), 1.93 – 2.07 (m 2 H), 2.35 – 2.49 (m, 3 H), 2.82 (dd, $J$ = 8.3, 15.8 Hz, 1 H), 2.92 (m, 1 H), 4.84 (dd, $J$ = 6.2, 10.9 Hz, 1 H), 4.95 (dd, $J$ = 5.6, 8.3 Hz, 1 H), 5.33 (d, $J$ = 17.3 Hz, 1 H), 5.35 (d, $J$ = 10.9 Hz, 1 H), 5.82 (dd, $J$ = 10.9, 17.3 Hz, 1 H). To the crude silyl enol ether in THF (25 mL) at -78 °C was added LiAlH(O-Bu)$_3$ (1.0 M in THF, 5.47 mL, 5.47 mmol) dropwise over 5 min. The resulting mixture was warmed to 0 °C over 1 h and stirred at 0 °C an additional 1 h. The solution was quenched with saturated aqueous NaHCO$_3$ and extracted with ether. The combined extracts were dried (Na$_2$SO$_4$) and concentrated to afford the crude alcohol as a 9 : 1 mixture of diastereomers, which was used without further purification; $^1$H NMR (200 MHz, CDCl$_3$) major diastereomer $\delta$ 0.00 (s, 3 H), 0.02 (s, 3 H), 0.18 (s, 9 H), 0.82 (s, 9 H) 1.48 (s, 3 H), 1.59 (m, 1 H), 2.05 – 2.65 (m, 6 H), 3.89 (br s, 1 H), 4.64 (dd, $J$ = 5.5, 11.6 Hz, 1 H), 4.78 (m, 1 H), 5.27 (d, $J$ = 17.5 Hz, 1 H), 5.29 (d, $J$ = 10.7 Hz, 1 H), 5.77 (dd, $J$ = 10.7, 17.5 Hz, 1 H). To a solution of the crude alcohol in CH$_2$Cl$_2$ (5 mL) was added Et$_3$N (1.53 mL, 10.9 mmol) followed by TBSOTf (1.68 mL, 7.30 mmol). The mixture was stirred at rt for 3 h. The resulting solution was quenched with saturated aqueous NaHCO$_3$ and extracted with CH$_2$Cl$_2$. The
combined extracts were dried (Na$_2$SO$_4$) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexanes, 3 : 97) afforded 11 as a colorless oil (1.48 g, 74% 3 steps); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ -0.03 (s, 3 H), 0.02 (s, 3 H), 0.10 (s, 3 H) 0.19 (s, 9 H), 0.20 (s, 3 H), 0.83 (s, 9 H), 0.95 (s, 9 H), 1.46 (s, 3 H), 1.53 (m, 1 H), 2.03 – 2.18 (m, 3 H), 2.33 (dt, $J$ = 2.8, 16.2 Hz, 1 H), 2.52 (m, 1 H), 2.54 (dd, $J$ = 9.5, 16.2 Hz, 1 H), 3.82 (br s, 1 H), 4.64 (dd, $J$ = 5.5, 11.7 Hz, 1 H), 5.23 (dd, $J$ = 0.9, 17.4 Hz, 1 H), 5.26 (dd, $J$ = 0.9, 17.4 Hz, 1 H), 5.75 (dd, $J$ = 10.8, 17.4 Hz, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ -5.0, -4.7, -4.6, -4.0, 0.3, 17.0, 17.9, 18.0, 25.8, 25.9, 31.3, 33.3, 37.6, 39.1, 46.7, 52.4, 69.9, 79.0, 102.8, 116.5, 122.4, 143.6, 156.6; IR (neat) 2929, 2238, 1664 cm$^{-1}$; HRMS (MNa$^+$) calcd for C$_{29}$H$_{55}$NO$_3$Si$_3$Na 572.3388, found 572.3394.

8,10-Bis-(tert-butyldimethylsilyloxy)-9-methyl-4-oxo-3-phenylselenyl-9-vinylbicyclo[4.3.1]decane-1-carbonitrile (12). To a solution of silyl enol ether 11 (1.48 g, 2.69 mmol) in CH$_2$Cl$_2$ (27 mL) at -78 °C was added phenylselenyl chloride (567 mg, 2.96 mmol) in CH$_2$Cl$_2$ (5 mL) dropwise over 2 min. The mixture was warmed to rt over 30 min. The resulting solution was concentrated to afford the crude $\alpha$-selenyl ketone as a mixture of diastereomers. The mixture of $\alpha$-selenyl ketones was dissolved in CH$_2$Cl$_2$ (40 mL) and Cs$_2$CO$_3$ (2.63 g, 8.08 mmol) was added. The mixture was stirred at rt for 3 h. The resulting solution was filtered and concentrated. Purification by silica-gel chromatography (CH$_2$Cl$_2$-hexane, 2 : 1) afforded the desired $\alpha$-selenyl ketone 12 as a white solid: mp 53 – 55 °C (1.14 g, 67%); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ -0.02 (s, 3 H), -0.01 (s, 3 H), 0.01 (s, 3 H), 0.12 (s, 3 H), 0.82 (s, 9 H), 0.89 (s, 9 H), 1.42 (s, 3 H), 1.45 (m, 1
H), 1.95 – 2.40 (m, 5 H), 2.47 (dd, J = 3.9, 16.0 Hz, 1 H), 3.67 (dd, J = 3.9, 13.6 Hz, 1 H), 3.82 (br s, 1 H), 3.89 (dd, J = 4.7, 11.6 Hz, 1 H), 5.27 (d, J = 17.3 Hz, 1 H), 5.30 (d, 11.0 Hz, 1 H), 5.72 (dd, J = 11.0, 17.3 Hz, 1 H), 7.33 – 7.48 (m, 3 H), 7.57 – 7.64 (m, 2 H); 13C NMR (75 MHz, CDCl₃) δ -5.1, -5.0, -4.7, -3.8, 17.7, 17.9, 18.0, 25.6, 25.7, 29.6, 35.6, 36.9, 40.1, 44.7, 46.6, 49.8, 68.3, 71.7, 117.8, 121.9, 124.7, 129.4, 129.8, 137.5, 141.8, 205.7; IR (neat) 2929, 2238, 1707 cm⁻¹; HRMS (MNa⁺) calcd for C₃₂H₅₁NO₃Si₂SeNa 656.2470, found 656.2473.

3-Bromo-8,10-bis-(tert-butyldimethylsilyloxy)-9-methyl-4-oxo-9-vinylbicyclo-[4.3.1]dec-2-ene-1-carbonitrile (13). To a solution of selenide 12 (633 mg, 1.00 mmol) in CCl₄ (20 mL) at -15 °C was added NBS (623 mg, 3.50 mmol). The mixture was warmed to rt and stirred for 2.5 h. The resulting solution was quenched with 10% aqueous Na₂S₂O₃ and extracted with CH₂Cl₂. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (CH₂Cl₂-hexane, 1 : 1) afforded α-bromoenone 13 as a white solid: mp 122 – 124 °C (439 mg, 79%); ¹H NMR (400 MHz, CDCl₃) δ -0.07 (s, 3 H), -0.01 (s, 3 H), 0.12 (s, 3 H), 0.22 (s, 3 H), 0.81 (s, 9 H), 0.96 (s, 9 H), 1.50 (s, 3 H), 1.57 (m, 1 H), 2.21 (dt, J = 5.6, 13.1 Hz, 1 H), 2.39 (m, 1 H), 2.76 (dd, J = 5.3, 14.9 Hz, 1 H), 2.81 (dd, J = 4.9, 14.9 Hz, 1 H), 3.55 (dd, J = 4.3, 12.2 Hz, 1 H), 4.22 (br s, 1 H), 5.32 (d, J = 10.7 Hz, 1 H), 5.36 (d, J = 17.3 Hz, 1 H), 5.55 (dd, J = 10.7, 17.3 Hz, 1 H), 6.90 (s, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ -5.1, -4.9, -4.7, -4.1, 15.5, 17.9, 18.0, 25.6, 25.7, 30.5, 38.0, 46.7, 47.6, 57.5, 68.6, 72.7, 118.7, 119.4, 126.1, 139.3, 141.6, 194.6; IR (neat) 2929, 2238, 1688 cm⁻¹; HRMS (MNa⁺) calcd for C₂₆H₄₄NO₃Si₂BrNa 576.1941, found 576.1933.
3-Bromo-8,10-bis-(tert-butyldimethylsilyloxy)-5,5,9-trimethyl-4-oxo-9-vinylbicyclo[4.3.1]dec-2-ene-1-carbonitrile (14). To a solution of enone 13 (300 mg, 0.54 mmol) in THF (5.5 mL) at -78 °C was added LiHMDS (1.0 M in THF, 650 µL, 0.65 mmol) dropwise. The mixture was stirred at -78 °C for 1 h. To the resulting enolate was added MeI (337 µL, 5.41 mmol). The mixture was warmed to rt over 20 min and stirred an additional 1 h at rt. The resulting solution was quenched with saturated aqueous NH₄Cl and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated to afford the crude monomethylated enone which was used without further purification; ¹H NMR (200 MHz, CDCl₃) δ -0.02 (s, 3 H), 0.01 (s, 3 H), 0.08 (s, 3 H), 0.18 (s, 3 H), 0.83 (s, 9 H), 0.94 (s, 9 H), 1.27 (d, J = 7.0 Hz, 3 H), 1.50 (s, 3 H), 1.52 (m, 1 H), 2.02 (m, 1 H), 2.25 (dt, J = 5.6, 13.1 Hz, 1 H), 2.76 (m, 1 H), 3.70 (dd, J = 4.0, 11.9 Hz, 1 H), 4.17 (br s, 1 H), 5.33 (d, J = 10.7 Hz, 1 H), 5.36 (d, J = 17.1 Hz, 1 H), 5.64 (dd, J = 10.7, 17.1 Hz, 1 H), 6.76 (s, 1 H). To the crude monomethyl ketone in THF (5.5 mL) at -78 °C was added LiHMDS (1.0 M in THF, 650 µL, 0.65 mmol) dropwise. The mixture was warmed to -20 °C stirred for 2 h. The resulting enolate was cooled to -78 °C and MeI (337 µL, 5.41 mmol) was added. The mixture was warmed to rt over 20 min and stirred an additional 1 h at rt. The resulting solution was quenched with saturated aqueous NH₄Cl and extracted with ether. The combined extracts were dried (Na₂SO₄) and concentrated. Purification by silica-gel chromatography (CH₂Cl₂-hexane, 1 : 1) afforded the dimethylated enone 14 as a white solid: mp 57 – 59 °C (262 mg, 83%); ¹H NMR (400 MHz, CDCl₃) δ -0.08 (s, 3 H), 0.00 (s, 3 H), 0.15 (s, 3 H), 0.25 (s, 3 H), 0.81 (s, 9 H), 0.96 (s, 9 H), 1.30 (s, 3 H), 1.34 (s, 3 H), 1.48 (s, 3 H), 1.74 (m, 1 H), 2.00 (m, 1 H), 2.09 (ddd, J = 5.6, 12.5, 14.2 Hz, 1 H), 3.39 (dd, J = 4.0, 12.5 Hz, 1 H), 4.54 (br s, 1
H), 5.29 (d, $J = 10.7$ Hz, 1 H), 5.32 (d, $J = 17.3$ Hz, 1 H), 5.54 (dd, $J = 10.7$, 17.3 Hz, 1 H), 6.75 (s, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ -5.0, -4.8, -4.4, -4.1, 15.7, 17.8, 17.9, 25.2, 25.6, 25.7, 26.0, 26.4, 48.0, 48.4, 51.2, 56.8, 68.3, 69.2, 118.5, 120.2, 125.0, 135.7, 141.5, 199.9; IR (neat) 2895, 2233, 1694 cm$^{-1}$; HRMS (MNa$^+$) calcd for C$_{28}$H$_{48}$NO$_3$Si$_2$BrNa 604.2254, found 604.2249.

{1-[8,10-Bis-(tert-butyldimethylsilyloxy)-1-cyano-5,5,9-trimethyl-4-oxo-9-vinylbicyclo[4.3.1]dec-2-en-3-yl]-buta-1,3-dienyl}carbamic acid tert-butyl ester (16). To a solution of bromoenone 14 (262 mg, 0.45 mmol) and stannane 15 ($^6$ (247 mg, 0.54 mmol) in DMSO (4 mL) and THF (1 mL) at rt was added LiCl (95 mg, 2.25 mmol), CuCl (178 mg, 1.80 mmol), and Pd(PPh$_3$)$_4$ (52 mg, 0.045 mmol). The mixture was stirred at rt for 4 h. The resulting solution was quenched with saturated aqueous NaHCO$_3$ and ether. The mixture was filtered through a plug of celite and washed with ether. The organic layer was washed with saturated aqueous NaHCO$_3$, dried (Na$_2$SO$_4$), and concentrated. Purification by silica-gel chromatography (CH$_2$Cl$_2$) afforded enecarbamate 16 as a colorless oil (227 mg, 75%); $^1$H NMR (300 MHz, CDCl$_3$) δ -0.04 (s, 3 H), 0.03 (s, 3 H), 0.17 (s, 3 H), 0.27 (s, 3 H), 0.83 (s, 9 H), 0.96 (s, 9 H), 1.26 (s, 3 H), 1.34 (s, 3 H), 1.47 (s, 9 H), 1.51 (s, 3 H), 1.77 (m, 1 H), 2.01 (m, 1 H), 2.11 (m, 1 H), 3.53 (dd, $J = 4.1$, 12.4 Hz, 1 H), 4.61 (br s, 1 H), 5.07 (d, $J = 10.1$ Hz, 1 H), 5.23 (d, $J = 10.7$ Hz, 1 H), 5.24 (d, $J = 16.7$ Hz, 1 H), 5.32 (d, $J = 17.3$ Hz, 1 H), 5.64 (dd, $J = 10.7$, 17.3 Hz, 1 H), 6.20 (s, 1 H), 6.37 (dt, $J = 10.1$, 16.7 Hz, 1 H), 6.63 (s, 1 H), 6.65 (d, $J = 10.1$ Hz, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ -4.8, -4.7, -4.4, -4.0, 15.8, 17.9, 18.0, 24.6, 25.7, 25.8, 26.2, 26.5, 28.3, 48.2, 48.9, 51.2, 56.0, 68.5, 69.8, 80.5, 82.1, 106.7, 120.2, 125.0, 135.7, 141.5, 199.9; IR (neat) 2895, 2233, 1694 cm$^{-1}$; HRMS (MNa$^+$) calcd for C$_{28}$H$_{48}$NO$_3$Si$_2$BrNa 604.2254, found 604.2249.
117.6, 118.2, 120.5, 131.7, 134.6, 135.1, 137.2, 137.6, 142.1, 152.6, 206.4; IR (neat) 3389, 2955, 2238, 1713 cm⁻¹; HRMS (MNa⁺) calcd for C₃₇H₆₀N₂O₅Si₂Na 693.4095, found 693.4072.

[12,14-Bis-(tert-butyldimethylsilyloxy)-1-cyano-9,9,13-trimethyl-8-oxo-13-vinyltricyclo[8.3.1.0²⁷]tetradeca-2,4,6-trien-6-yl]carbamic acid tert-butyl ester (17). A solution of enecarbamate 16 (225 mg, 0.34 mmol) in toluene (14 mL) was heated to 110 °C for 3 h. The resulting solution was concentrated to afford the crude cyclohexadiene, which was used without further purification. To the crude cyclohexadiene in dioxane (10 mL) was added DDQ (380 mg, 1.68 mmol). The mixture was heated at 95 °C for 20 h. The resulting solution was quenched with saturated aqueous NaHCO₃ and extracted with ether. The combined extracts were washed with saturated aqueous NaHCO₃, dried (Na₂SO₄), and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 19) afforded the Boc protected aniline 17 as a colorless oil (188 mg, 84%); ¹H NMR (300 MHz, CDCl₃) δ -0.16 (s, 3 H), 0.03 (s, 3 H), 0.12 (s, 3 H), 0.23 (s, 3 H), 0.80 (s, 9 H), 0.99 (s, 9 H), 1.16 (s, 3 H), 1.38 (s, 3 H), 1.48 (s, 9 H), 1.62 (s, 3 H), 1.82 (m, 1 H), 2.07 (m, 1 H), 2.20 (ddd, J = 5.1, 12.4, 14.0 Hz, 1 H), 3.69 (dd, J = 4.1, 12.4 Hz, 1 H), 4.58 (br s, 1 H), 4.74 (dd, J = 10.8, 17.2 Hz, 1 H), 4.97 (dd, J = 1.0, 10.8 Hz, 1 H), 5.15 (dd, J = 1.0, 17.2 Hz, 1 H), 7.40 (t, J = 8.2 Hz, 1 H), 7.69 (dd, J = 1.0, 8.2 Hz, 1 H), 7.84 (s, 1 H), 8.00 (dd, J = 1.0, 8.2 Hz, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ -4.8, -4.7, -4.3, -4.1, 16.3, 17.8, 18.0, 25.2, 25.5, 25.6, 25.7, 25.9, 28.3, 47.6, 49.9, 51.2, 63.0, 68.1, 70.1, 80.7, 116.7, 120.2, 123.8, 127.3, 130.3, 130.9, 131.7, 137.6, 142.7, 153.1, 212.1; IR (neat) 3425, 2931,
2238, 1735, 1664 cm\(^{-1}\); HRMS (MNa\(^+\)) calcd for C\(_{37}\)H\(_{59}\)N\(_2\)O\(_5\)Si\(_2\)Na 691.3939, found 691.3916.

6-Amino-12,14-bis-(tert-butyldimethylsilyloxy)-9,9,13-trimethyl-8-oxo-13-vinyltricyclo[8.3.1.0]tetradeca-2,4,6-triene-1-carbonitrile. To a solution of Boc protected aniline 17 (125 mg, 0.19 mmol) in CH\(_2\)Cl\(_2\) (5 mL) at -50 °C was added TFA (500 µL). The mixture was warmed to rt over 20 min and stirred for 1.5 h. The resulting solution was quenched with saturated aqueous NaHCO\(_3\) and extracted with CH\(_2\)Cl\(_2\). The combined extracts were dried (Na\(_2\)SO\(_4\)) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 3:20) afforded the title aniline as a colorless oil (104 mg, 98%); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) -0.15 (s, 3 H), 0.03 (s, 3 H), 0.13 (s, 3 H), 0.24 (s, 3 H), 0.80 (s, 9 H), 0.99 (s, 9 H), 1.17 (s, 3 H), 1.35 (s, 3 H), 1.61 (s, 3 H), 1.82 (m, 1 H), 2.03 (m, 1 H), 2.18 (ddd, \(J = 5.2, 12.4, 14.0\) Hz, 1 H), 3.80 (dd, \(J = 4.1, 12.4\) Hz, 1 H), 4.60 (br s, 1 H), 4.71 (br s, 2 H), 4.80 (dd, \(J = 10.8, 17.0\) Hz, 1 H), 4.94 (dd, \(J = 1.4, 10.8\) Hz, 1 H), 5.12 (dd, \(J = 1.4, 17.0\) Hz, 1 H), 6.69 (dd, \(J = 1.1, 8.0\) Hz, 1 H), 7.15 (t, \(J = 8.0\) Hz, 1 H), 7.34 (dd, \(J = 1.1, 8.0\) Hz, 1 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) -4.7, -4.6, -4.3, -4.1, 16.3, 17.8, 18.0, 25.5, 25.6, 25.8, 25.9, 26.0, 47.6, 49.8, 51.0, 63.1, 68.3, 70.2, 116.3, 117.9, 120.5, 121.6, 123.0, 131.3, 132.5, 142.8, 147.7, 211.2; IR (neat) 3486, 3383, 2930, 2238, 1776, 1720, 1661 cm\(^{-1}\); HRMS (MH\(^+\)) calcd for C\(_{32}\)H\(_{53}\)N\(_2\)O\(_3\)Si\(_2\) 569.3595, found 569.3541.
N-Acetylindole (19). To a solution of the primary aniline (50.4 mg, 0.089 mmol) in MeOH (2 mL) at rt was added NaOAc (36 mg, 0.44 mmol), HOAc (51 µL, 0.89 mmol), and glyoxylic acid monohydrate (20 mg, 0.22 mmol). The mixture was cooled to -10 °C and NaCNBH$_3$ (11 mg, 0.18 mmol) was added. The reaction mixture was warmed to 0 °C over 1 h. The resulting solution was quenched with saturated aqueous KH$_2$PO$_4$ and extracted with ether. The combined extracts were dried (Na$_2$SO$_4$) and concentrated to afford the crude acid 18 which was used without further purification; $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ -0.15 (s, 3 H), 0.03 (s, 3 H), 0.12 (s, 3 H), 0.24 (s, 3 H), 0.80 (s, 9 H), 0.99 (s, 9 H), 1.16 (s, 3 H), 1.38 (s, 3 H), 1.62 (s, 3 H), 1.83 (m, 1 H), 2.05 (m, 1 H), 2.18 (dt, $J = 5.3$, 12.2 Hz, 1 H), 3.81 (dd, $J = 3.8$, 12.2 Hz, 1 H), 3.96 (br s, 2 H), 4.61 (br s, 1 H), 4.79 (dd, $J = 10.7$, 16.8 Hz, 1 H), 4.95 (d, $J = 10.7$ Hz, 1 H), 5.14 (d, $J = 16.8$ Hz, 1 H), 6.61 (d, $J = 8.2$ Hz, 1 H), 7.27 (t, $J = 8.2$ Hz, 1 H), 7.40 (d, $J = 8.2$ Hz, 1 H), 11.8 (br s, 1 H). To the crude acid was added Et$_3$N (1 mL) followed by Ac$_2$O (1 mL) at rt. The mixture was heated to 130 °C for 30 min. The resulting solution was cooled to rt and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 9) afforded N-acetylindole 19 as a white solid: mp 140 – 143 °C (36.5 mg, 68% 2 steps); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ -0.42 (s, 3 H), -0.19 (s, 3 H), 0.15 (s, 3 H), 0.25 (s, 3 H), 0.72 (s, 9 H), 1.02 (s, 9 H), 1.36 (s, 3 H), 1.62 (s, 3 H), 1.63 (s, 3 H), 1.89 (br dd, $J = 4.0$, 14.2 Hz, 1 H), 2.14 (br d, $J = 6.3$ Hz, 1 H), 2.25 (ddd, $J = 6.3$, 12.6, 14.2 Hz, 1 H), 2.66 (s, 3 H), 3.46 (dd, $J = 4.0$, 12.6 Hz, 1 H), 4.19 (dd, $J = 10.8$, 17.3 Hz, 1 H), 4.80 (br s, 1 H), 4.95 (dd, $J = 0.9$, 10.8 Hz, 1 H), 5.16 (dd, $J = 0.9$, 17.3 Hz, 1 H), 7.32 (s, 1 H), 7.33 (t, $J = 8.0$ Hz, 1 H), 7.64 (dd, $J = 0.9$, 8.0 Hz, 1 H), 8.52 (d, $J = 8.0$ Hz, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ -4.9, -4.7, -4.1, -3.9, 15.2, 17.8, 18.1, 24.3, 25.6, 26.0, 26.9, 29.3, 35.5, 37.0,
49.1, 53.1, 61.0, 68.5, 70.7, 116.0, 116.5, 120.8, 121.9, 124.4, 126.8, 127.1, 127.9, 131.0, 136.3, 144.0, 168.2; IR (neat) 2929, 2226, 1711 cm$^{-1}$; HRMS (MNH$_4^+$) calcd for C$_{35}$H$_{58}$N$_3$O$_3$Si$_2$ 624.4017, found 624.3968.

**Amide (21).** To a solution of nitrile 19 (16 mg, 0.026 mmol) in EtOH-H$_2$O (4 : 1) (265 µL) was added [PtH(PMe$_2$OH)(PMe$_2$O)$_2$H] 20$^{12}$ (4.5 mg, 0.011 mmol). The mixture was heated in a sealed tube at 100 °C for 60 h. The resulting solution was diluted with ether, filtered through a plug of silica-gel, and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 3 : 7) afforded amide 21 as a mixture of N-acetyl rotamers (12.0 mg, 73%); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ -0.52 (s, 3 H), -0.27 (s, 3 H), 0.13 (s, 3 H), 0.15 (s, 3 H), 0.71 (s, 9 H), 0.93 (s, 9 H), 1.43 (s, 3 H), 1.60 (s, 3 H), 1.73 (s, 3 H), 1.88 (m, 1 H), 2.11 – 2.28 (m, 2 H), 2.64 (s, 3 H), 3.37 (br d, $J$ = 12.6 Hz, 1 H), 4.95 (br dd, $J$ = 11.0, 17.4 Hz, 1 H), 5.10 (br d, $J$ = 11.0 Hz, 1 H), 5.22 (br d, $J$ = 17.4 Hz, 1 H), 5.37 (br s, 1 H), 5.96 (br s, 1 H), 6.89 (br s, 1 H), 7.17 – 7.40 (m, 3 H), 8.47 (br d, $J$ = 8.8 Hz, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ -5.0, -4.9, -4.8, -4.4, 14.1, 17.8, 18.3, 24.3, 25.7, 26.1, 27.4, 29.7, 35.8, 36.4, 48.3, 52.4, 67.4, 69.3, 72.3, 115.5, 115.6, 121.7, 124.2, 126.7, 128.9, 131.6, 131.9, 136.5, 147.0, 168.2, 176.7; IR (neat) 3461, 3166, 2927, 1709, 1684 cm$^{-1}$; HRMS (MNa$^+$) calcd for C$_{35}$H$_{56}$N$_2$O$_4$Si$_2$Na 647.3676, found 647.3661.
**Isocyanate (22).** To a solution of amide 21 (8.5 mg, 0.014 mmol) in DMF (0.5 mL) was added Pb(OAc)$_4$ (9.1 mg, 0.020 mmol). The mixture was heated at 90 °C for 15 min. The resulting solution was cooled to rt, diluted with ether, and washed with H$_2$O. The ethereal layer was dried (Na$_2$SO$_4$) and concentrated. Purification by silica-gel chromatography (ethyl acetate-hexane, 1 : 9) afforded isocyanate 22 as a colorless oil (6.6 mg, 78%); $^1$H NMR (300 MHz, CDCl$_3$) δ -0.46 (s, 3 H), -0.21 (s, 3 H), 0.14 (s, 3 H), 0.21 (s, 3 H), 0.71 (s, 9 H), 1.01 (s, 9 H), 1.34 (s, 3 H), 1.50 (s, 3 H), 1.62 (s, 3 H), 1.89 (dd, $J$ = 3.9, 14.0 Hz, 1 H), 2.15 (br d, $J$ = 6.8 Hz, 1 H), 2.23 (ddd, $J$ = 6.8, 12.4, 14.0 Hz, 1 H), 2.65 (s, 3 H), 3.43 (dd, $J$ = 3.9, 12.4 Hz, 1 H), 4.20 (dd, $J$ = 10.9, 17.4 Hz, 1 H), 4.55 (s, 1 H), 4.95 (d, $J$ = 10.9 Hz, 1 H), 5.06 (d, $J$ = 17.4 Hz, 1 H), 7.29 (s, 1 H), 7.33 (t, $J$ = 8.0 Hz, 1 H), 7.51 (d, $J$ = 8.0 Hz, 1 H), 8.50 (d, $J$ = 8.0 Hz, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ -4.9, -4.7, -4.2, -4.0, 13.2, 17.8, 18.1, 24.3, 25.7, 26.0, 27.0, 29.6, 35.5, 36.8, 52.1, 53.9, 69.5, 73.2, 74.0, 115.8, 116.2, 121.5, 122.9, 124.2, 125.9, 126.6, 131.5, 131.8, 136.2, 144.0, 168.2; IR (neat) 2927, 2276, 1713 cm$^{-1}$; HRMS (MH$^+$) calcd for C$_{35}$H$_{55}$N$_2$O$_3$Si$_2$ 623.370, found 623.370.