

## The Formal Total Synthesis of (±) Strychnine via a Cobalt-Mediated [2+2+2]Cycloaddition

Michael J. Eichberg, Rosa L. Dorta, Kai Lamottke, and K. Peter C. Vollhardt

*Department of Chemistry, University of California at Berkeley, and  
the Chemical Sciences Division, Lawrence Berkeley National  
Laboratory, Berkeley, California 94720-1460*

eichberg@socrates.berkeley.edu

### Experimental Section

***N*-Acetyl-1-(1-oxo-(*Z*)-pent-2-en-4-ynyl)indol-3-ethanamine (3):** To a cooled, rapidly stirring suspension of *N*-acetyl tryptamine (900 mg, 4.46 mmol), crushed NaOH (1.8 g, 45 mmol), and Bu<sub>4</sub>NCl (145 mg, 0.523 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 ml) at 0°C was added a solution of acid chloride **2** (1.1 g, 5.9 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 ml) in one portion, followed by water (0.2 ml). The reaction mixture was stirred for 50 min during which time the solution changes color from bright yellow, to orange, to brown-black. The mixture was then poured onto water (60 ml), the layers separated, and the aqueous layer extracted with CH<sub>2</sub>Cl<sub>2</sub> (20 ml). The organic layers were then washed with water and sat. NaCl solution, dried over MgSO<sub>4</sub>, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel with CH<sub>2</sub>Cl<sub>2</sub>-MeOH (20:1) eluant to afford 1.07 g (86%) of **3** as bright yellow solid: mp 110°C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.94 (s, 3H), 2.90 (t, *J* = 6.7 Hz, 2H), 3.48 (d, *J* = 1.6 Hz, 1H), 3.57 (t, *J* = 6.4 Hz, 2H), 5.84 (br s, 1H), 6.25 (dd, *J* = 11.6, 1.6 Hz, 1H), 6.83 (d, *J* = 11.6 Hz, 1H), 7.27 (s, 1H), 7.29 (dt, *J* = 7.6, 1.1 Hz, 1H), 7.35 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.52 (d, *J* = 7.5 Hz, 1H), 8.48 (d, *J* = 8.1 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 23.2, 25.1, 38.7, 79.3, 89.2, 116.8, 118.8, 120.1, 121.3, 121.9, 124.0, 125.4, 130.6, 131.2, 135.8, 162.1, 170.2; IR (KBr) 3360, 3190, 2084, 1664, 750 cm<sup>-1</sup>; MS, *m/z* (relative abundance) 280 (M<sup>+</sup>, 26), 221 (92), 220 (90), 209 (17), 193 (26), 189 (6), 143 (96), 130 (100), 115 (9), 102 (10), 79 (82). Anal. Calcd. for C<sub>17</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>: C 73.02, H 5.84, N 9.96. Found: C 72.84, H 5.75, N 9.99.

**(2-Methoxyethoxy)methyl-(*Z*)-3-iodoprop-2-enoate (5)** To a solution of *Z*-iodopropenoic acid (4.2 g, 21.2 mmol) in DMF (20 ml) was added Na<sub>2</sub>CO<sub>3</sub> (2.63 g, 24.8 mmol), and MEMCl (Aldrich, 3.15 ml, 3.44 g, 27.6 mmol). The mixture was stirred at RT for 50 min, poured onto water (20 ml), and extracted with ether (3 × 20 ml). The combined organic layers were washed with water, satd. NaCl, dried over MgSO<sub>4</sub>, and concentrated in vacuo to yield 5.21 g (86%) of **5** as a yellow oil: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 3.43 (s, 3H), 3.53 (t, *J* = 4.7 Hz, 2H), 3.80 (t, *J* = 4.6 Hz, 2H), 5.40 (s, 2H), 6.90 (d, *J* = 9.0 Hz, 1H), 7.52 (d, *J* = 9.0 Hz, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 59.0, 69.7, 71.3, 89.6, 96.2, 129.4, 163.8; IR (film) 1733, 1596, 1107 cm<sup>-1</sup>; MS, *m/z* (relative abundance) 286 (M<sup>+</sup>, 1), 197 (7), 181 (70), 153 (22), 127 (25), 105 (15), 89 (45), 59 (100), 59 (60). Anal. Calcd. for C<sub>7</sub>H<sub>11</sub>O<sub>4</sub>I: C 29.29, H 3.88. Found: C 29.65, H 3.78.

**(2-Methoxyethoxy)methyl-(*Z*)-5-(trimethylsilyl)pent-2-en-4-ynoate (6)** To a solution of iodide **5** (16 g, 57.5 mmol) in Et<sub>3</sub>N (200 ml) was added Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (2.02 g, 2.88 mmol) and CuI (1.16 g, 6.10 mmol), and the solution was degassed with argon. Trimethylsilylacetylene (15 ml, 10.42 g, 106 mmol) was then added and the solution stirred for 1 h. The mixture was poured onto satd. NH<sub>4</sub>Cl (400 ml) and extracted with ether (3 × 150 ml). The combined organic layers were washed with satd. NaCl, dried over MgSO<sub>4</sub>, and concentrated in vacuo. The thick oily residue was subjected to flash chromatography on silica with hexanes-ethyl acetate (4:1) as eluant to yield 14.4 g (98%) of **6** as an orange-brown oil: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 0.19 (s, 9H), 3.34 (s, 3H), 3.52 (t, *J* = 4.6 Hz, 1H), 3.78 (t, *J* = 4.7 Hz, 1H), 5.38 (s, 2H), 6.07 (d, *J* = 11.6 Hz, 1H), 6.16 (d, *J* = 11.6 Hz, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ -0.48, 59.0, 69.4, 71.4, 100.6, 109.0, 123.6, 128.8, 163.6; IR (film) 2960, 2149, 1720, 1606, 1251, 1109, 1029, 845 cm<sup>-1</sup>; MS, *m/z* (relative abundance) 197 (M<sup>+</sup> - CH<sub>3</sub>OCH<sub>2</sub>CH<sub>2</sub>, 6), 151 (15), 97 (13), 89 (67), 59 (100). Anal. Calcd. for C<sub>12</sub>H<sub>20</sub>O<sub>4</sub>Si: C 56.22, H 7.86. Found: C 55.58, H 8.07.

**(*Z*)-5-(Trimethylsilyl)pent-2-en-4-ynoyl chloride (2)** A mixture of **6** (1.52 g, 5.91 mmol) and 3N HCl (4 ml) in THF (50 ml) was stirred at room temperature for 3 d. It was then concentrated in vacuo and the residue partitioned between water (50 ml) and CH<sub>2</sub>Cl<sub>2</sub> (20 ml). The water was further extracted with

CH<sub>2</sub>Cl<sub>2</sub> (2 × 20 ml). The combined organic layers were washed with satd. NaCl, dried over MgSO<sub>4</sub>, and concentrated in vacuo to give 1.06 g of the crude acid as a brown oil. The crude acid was dissolved in oxalyl chloride (10 ml) and stirred at RT for 14 h, concentrated in vacuo, and purified by Kugelrohr distillation to yield 917 mg (83% from **6**) of **2** as a clear, slightly yellow oil: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.21 (s, 9H), 6.14 (d, *J* = 10.1 Hz, 1H), 6.37 (d, *J* = 10.1 Hz, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ -0.67, 100.25, 113.6, 125.9, 133.3, 162.0; IR (film) 2963, 1764, 1579, 1252, 957 cm<sup>-1</sup>.

(±)-(η<sup>5</sup>-Cyclopentadienyl)[1,2,3,3a-η<sup>4</sup>]-11b-*exo*-[2-(*N*-acetylamino)ethyl]-11b,12-*exo*-dihydro-1,2-6*H*-pyrido[3,2,1-*jk*]carbazol-6-one]cobalt (**4**) and *Z* and *E* *N*-Acetyl-1-(1-oxo-3-phenylprop-2-enyl)indol-3-ethanamine. A 2L, three-neck flask containing a stirbar was fitted with a fritted-glass gas inlet, a gas outlet routed to an oil bubbler, and a septum. The gas inlet was connected, through a T-joint, to both an argon and an acetylene source, and both of these lines were fitted with oil bubblers by which the rate of gas flow could be monitored. Indole **3** (1 g, 3.57 mmol) was added to the flask and dissolved in THF (750 ml, Fisher reagent grade, used without further purification), and the flask was cooled in an ice/water bath to 0°C. The gas inlet was placed submerged under the surface of the solution, and the solution was degassed with a stream of argon for 30 min. The gas flow was then adjusted such that both argon and acetylene were flowing into the reaction flask at the rate of 4-5 bubbles per second. In a separate flask under argon, CpCo(C<sub>2</sub>H<sub>4</sub>)<sub>2</sub> (650 mg, 3.61 mmol) was dissolved in degassed THF (50 ml) and taken up into a syringe. With the use of a syringe pump, this solution was added over a period of 25 min to the vigorously stirred solution of **3**. After a total of 45 min, gas flow was terminated, and the reaction mixture concentrated in vacuo. The residue was subjected to flash chromatography on silica gel with CH<sub>2</sub>Cl<sub>2</sub>-MeOH (20:1) as eluant to yield 715 mg (46%) of **4** as a red foam: <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>) δ 1.41 (m, 1H), 1.78 (s, 3H), 1.83, (m, 1H), 2.64 (m, 1H), 3.04 (s, 1H), 3.08 (m, 1H), 3.28 (d, *J* = 6.0 Hz, 1H), 4.31 (s, 5H), 5.00 (dd, *J* = 5.7, 4.1 Hz, 1H), 5.15 (br s, 1H), 5.41 (d, *J* = 3.8 Hz, 1H), 6.03 (d, *J* = 9.5 Hz, 1H), 6.55 (d, *J* = 9.4 Hz, 1H), 7.12 (t, *J* = 7.4, 1H), 7.2 3 (d, *J* = 9.2 Hz, 1H), 7.32 (t, *J* = 7.7 Hz, 1H), 8.26 (d, *J* = 7.8 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 23.0, 37.4, 40.6, 52.6, 61.3, 63.2, 65.7, 73.7, 77.9, 81.0, 115.2, 120.5, 122.4, 123.4, 128.1, 137.3, 142.3, 148.6, 163.2, 169.8; IR (KBr) 3443, 1636, 1384 cm<sup>-1</sup>; MS, *m/z* (relative abundance) 430 (M<sup>+</sup>, 72), 342 (100), 277 (54), 250 (18), 220 (15), 191 (19), 169 (13), 143 (10), 130 (8), 124 (14), 59 (7). HRMS Calcd. For C<sub>24</sub>H<sub>23</sub>N<sub>2</sub>O<sub>2</sub>Co: 430.109151. Found: 430.109202.

Elution also gave 281 mg (28 %) of an inseparable mixture of the indolylcinnamides as a (1:3) mixture of *E* and *Z* isomers (by NMR integration), isolated as a yellow foam: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) signals attributable to *E* isomer: δ 1.95 (s, 3H), 2.94 (t, *J* = 6.7 Hz, 2H), 3.62 (dt, *J* = 6.3, 6.6 Hz, 2H), 5.93 (br s, 1H), 7.18 (d, *J* = 15.3 Hz, 1H), 7.26-7.65 (m, 9H), 7.91 (d, *J* = 15.3 Hz, 1H), 8.50 (d, *J* = 8.2 Hz, 1H); signals attributable to *Z* isomer: δ 1.84 (s, 3H), 2.79 (t, *J* = 6.8 Hz, 2H), 3.44 (dt, *J* = 6.3, 6.7 Hz, 2H), 5.26 (br s, 1H), 6.34 (d, *J* = 12.7 Hz, 1H), 6.96 (d, *J* = 12.7 Hz, 1H), 7.26-7.65 (m, 9H), 8.48 (d, *J* = 8.8 Hz, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) signals attributable to *E* isomer: δ 23.3, 25.3, 39.0, 117.0, 117.1, 118.9, 119.6, 122.0, 123.7, 125.3, 128.4, 129.1, 130.6, 130.8, 134.3, 136.3, 146.4, 163.9, 170.3; signals attributable to *Z* isomer: 23.1, 24.9, 38.9, 116.6, 118.7, 119.8, 121.4, 123.0, 123.8, 125.3, 128.5, 128.8, 129.1, 130.8, 134.4, 135.5, 138.9, 165.8, 170.1; IR (film) 3296, 1668, 1652, 1454 cm<sup>-1</sup>; MS, *m/z* (relative abundance) 332 (M<sup>+</sup>, 40), 273 (94), 143 (84), 131 (100), 103 (44), 77 (38).

(±)-(η<sup>5</sup>-Cyclopentadienyl)[1,2,3,3a-η<sup>4</sup>]-11b-*exo*-[2-(aminoethyl)]-11b,12-*exo*-dihydro-1,2-6*H*-pyrido[3,2,1-*jk*]carbazol-6-one]cobalt (**7**). Cobalt-complex **4** (2.64 g, 6.1 mmol) was dissolved in a degassed solution of a 30% KOH solution [56.6 g KOH in 200 ml of water-MeOH (1:1)], and heated to reflux under argon for 6 h. The mixture was cooled and extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 × 100 ml). The combined organic layers were washed with water and satd. NaCl and then concentrated in vacuo. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub>, filtered through a pad of celite, and again concentrated in vacuo to yield 2.21 g (93%) of **7** as a red foam: <sup>1</sup>H NMR (400 MHz, C<sub>6</sub>D<sub>6</sub>) δ 0.70 (br s, 2H), 1.01 (m, 1H), 1.48 (m, 1H), 1.96 (m, 2H), 2.82 (s, 1H), 2.86 (d, *J* = 6.0 Hz, 1H), 4.08 (s, 5H), 4.44 (dd, *J* = 5.9, 4.1 Hz, 1H), 4.74 (d, *J* = 4.0 Hz, 1H), 5.86 (d, *J* = 9.4 Hz, 1H), 6.13 (d, *J* = 9.4 Hz, 1H), 7.20 (m, 3H), 8.87 (d, *J* = 7.9 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 29.6, 42.2, 52.9, 61.5, 63.8, 66.0, 73.6, 77.8, 81.0, 115.2, 120.7, 122.3, 123.3, 128.0, 137.7, 142.4, 148.5, 163.3; IR (film); 3045, 1641, 1470 cm<sup>-1</sup>; MS, *m/z* (relative

abundance) 388 ( $M^+$ , 7), 342 (6), 277 (10), 160 (19), 130 (100), 103 (12), 77 (13). HRMS Calcd. for  $C_{22}H_{21}N_2O$ : 388.098586. Found: 388.098630.

(±)-(3aS\*,11bα,13aβ)-1,2,3,9,11b,13a-Hexahydro-9H-pyrido[1,2,3-*lm*]pyrrolo[2,3-*d*]carbazol-9-one (**8**). To a solution of amine **7** (697 mg, 1.78 mmol) in THF (30 ml) and  $CH_3CN$  (12 ml) at 0°C was added a solution of  $Fe(NO_3)_3 \cdot 9H_2O$  (2.29 g, 5.67 mmol) in  $CH_3CN$  (21 ml) and  $H_2O$  (6 ml) at 0°C. After 15 min, the reaction was poured onto 5% HCl (60ml) and washed with  $Et_2O$  (60 ml). The aqueous layer was adjusted to pH 12 with 5N NaOH, and resulting mixture was filtered through a pad of celite, rinsing with  $CH_2Cl_2$ . This filtrate was extracted with  $CH_2Cl_2$  (3 × 30 ml), and the combined organics were washed with water and satd. NaCl, and concentrated in vacuo. This residue was subjected to flash chromatography on silica gel with  $CH_2Cl_2$ -MeOH (15:1) as eluant to yield 360 mg (77 %) of **8** as a brown solid: mp 169°C;  $^1H$  NMR (500 MHz,  $CDCl_3$ ) δ 2.09 (m, 2H), 2.28 (m, 1H), 3.20-3.14 (m, 3H), 3.29 (m, 1H), 3.60 (s, 1H), 4.70 (s, 1H), 5.75 (d,  $J = 10.0$  Hz, 1H), 5.95 (m, 1H), 6.33 (dd,  $J = 10.0, 2.5$  Hz, 1H), 7.08 (td,  $J = 7.5, 1.0$  Hz, 1H), 7.21 (d,  $J = 6.9$  Hz, 1H), 7.25 (td,  $J = 7.7, 1.3$  Hz, 1H), 8.15 (d, 8.0 Hz, 1H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ) δ 37.0, 42.8, 44.6, 52.5, 62.4, 62.5, 115.1, 121.0, 122.8, 124.5, 124.6, 128.3, 132.7, 133.5, 139.0, 140.5, 167.5; IR (KBr) 3310, 1664, 1481, 1400, 754  $cm^{-1}$ ; MS,  $m/z$  (relative abundance) 264 ( $M^+$ , 100), 235 (22), 220 (53), 206 (18), 191 (14). HRMS Calcd. for  $C_{17}H_{16}N_2O$ : 264.126263. Found: 264.126356.

(±)-[1(*Z*),3aS\*,11bα,13aβ]-1-[4-[[1,1-Dimethylethyl]dimethylsilyloxy]-2-iodobut-2-enyl]-1,2,3,11b,13,13a-hexahydro-9H-pyrido[1,2,3-*lm*]pyrrolo[2,3-*d*]carbazol-9-one (**9**) To a suspension of amine **8** (165 mg, 0.625 mmol) and  $Li_2CO_3$  (135 mg, 1.83 mmol) in DMF (20 ml) was added (*Z*)-1-bromo-4-[[*tert*-butyldimethylsilyloxy]-2-iodobut-2-ene (269 mg, 0.688 mmol) in DMF (2 ml) dropwise. The reaction was heated to 40°C for 24 h. The mixture was then poured onto water and extracted with  $Et_2O$  (3 × 15 ml) and the combined organic layers were washed with satd. NaCl, dried over  $MgSO_4$ , and concentrated in vacuo. The residue was subjected to flash chromatography on silica gel with hexanes-ethyl acetate (2:1) as eluant to yield 264 mg (74%) of the vinyl iodide as a yellow solid: mp 80-82°C;  $^1H$  NMR (500 MHz,  $CDCl_3$ ) δ 0.07 (s, 6H), 0.90 (s, 9H), 2.09 (m, 1H), 2.32 (m, 1H), 2.74 (m, 1H), 3.08 (m, 1H), 3.15 (dd,  $J = 19.1, 6.7$  Hz, 1H), 3.19 (m, 1H), 3.29 (s, 1H), 3.60 (d,  $J = 13.9$  Hz, 1H), 3.67 (dd,  $J = 13.8, 1.1$  Hz, 1H), 4.26 (dd,  $J = 5.0, 1.1$  Hz, 2H), 4.58 (s, 1H), 5.93-5.96 (m, 2H), 6.13 (t,  $J = 5.0$  Hz, 1H), 6.37 (dd,  $J = 10.1, 2.2$  Hz, 1H), 7.08 (td,  $J = 7.5, 1.1$  Hz, 1H), 7.24 (td,  $J = 7.4, 1.3$  Hz, 1H), 7.68 (dd,  $J = 7.2, 0.85$  Hz, 1H), 8.12 (d,  $J = 7.6$  Hz, 1H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ) δ -5.2, 18.2, 25.9, 36.9, 41.0, 48.9, 51.2, 63.2, 63.5, 65.3, 67.9, 104.7, 114.6, 120.9, 124.3, 125.1, 125.3, 126.9, 128.1, 133.4, 137.1, 139.2, 140.2, 167.1; IR (KBr) 2926, 1666, 1482, 1403, 1251, 1088, 836  $cm^{-1}$ . Anal. Calcd. for  $C_{27}H_{35}N_2O_2Si$ : C 56.43, H 6.14, N 4.88. Found: C 56.71, H 6.23, N 4.69.

To a solution of the vinyl iodide (160 mg, 0.279 mmol) in isopropanol (15 ml) was added 1 ml of a sodium isopropoxide solution (prepared by dissolving 14 mg of Na in 3 ml isopropanol). The solution was stirred at room temperature for 13 h. The mixture was then diluted  $CH_2Cl_2$  (30 ml), washed with water and satd. NaCl, dried over  $MgSO_4$ , and concentrated in vacuo. Filtration through a short plug of silica with hexanes-ethyl acetate (3:2) as eluant gave 144 mg (90%) of **9** as yellow solid: mp 115-117°C;  $^1H$  NMR (500 MHz,  $CDCl_3$ ) δ 0.07 (s, 6H), 0.89 (s, 9H), 2.07 (ddd,  $J = 13.4, 11.2, 6.2$  Hz, 1H), 2.16 (m, 1H), 2.26 (ddd,  $J = 13.2, 9.2, 4.1$  Hz, 1H), 2.39 (ddd,  $J = 12.4, 7.0, 5.5$  Hz, 1H), 2.64 (td,  $J = 11.0, 4.2$  Hz, 1H), 2.87 (dd,  $J = 9.5, 5.1$  Hz, 1H), 3.27 (dt,  $J = 9.4, 6.3$  Hz, 1H), 3.45 (dd,  $J = 13.7, 0.7$  Hz, 1H), 3.59 (dd,  $J = 13.7, 1.3$  Hz, 1H), 4.24 (dd,  $J = 5.0, 1.0$  Hz, 2H), 4.57 (s, 1H), 5.96 (d,  $J = 9.7$  Hz, 1H), 6.01 (m, 1H), 6.09 (t,  $J = 5.0$  Hz, 1H), 6.85 (d,  $J = 9.7$  Hz, 1H), 7.04 (td,  $J = 7.5, 1.0$  Hz, 1H), 7.22 (td,  $J = 7.8, 1.3$  Hz, 1H), 7.82 (dd,  $J = 7.6, 0.9$  Hz, 1H), 8.10 (dd,  $J = 8.0, 0.5$  Hz, 1H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ) δ -5.2, 18.2, 23.4, 25.8, 37.2, 47.0, 51.7, 60.5, 62.5, 63.0, 67.9, 104.8, 114.7, 123.9, 124.9, 126.1, 128.0, 128.1, 131.1, 137.0, 138.2, 138.8, 140.4, 161.5; IR (KBr) 2928, 1656, 1479, 1417, 1109, 837  $cm^{-1}$ ; MS,  $m/z$  (relative abundance) 574 ( $M^+$ , 100), 517 (6), 446 (16), 316 (10), 298 (11), 263 (36), 220 (24), 75 (17). Anal. Calcd. for  $C_{27}H_{35}N_2O_2Si$ : C 56.43, H 6.14, N 4.88. Found: C 56.12, H 6.15, N 4.81.

(±)-(21*E*)- and (21*Z*)-12,13-Didehydro-24-[[1,1-dimethylethyl]dimethylsilyl]-12,24-secostrychnidin-10-one (**10 and 11**) To a refluxing solution of vinyl iodide **9** (40mg, 0.070 mmol) and AIBN (14 mg, 0.85

mmol) in benzene (20 ml) under argon was added Bu<sub>3</sub>SnH (49 mg, 0.17 mmol) in benzene (2 ml). After 1 h, the mixture was concentrated, and the residue dissolved in CH<sub>2</sub>Cl<sub>2</sub>, washed with water and satd. NaHCO<sub>3</sub> solution, dried over MgSO<sub>4</sub>, and concentrated in vacuo. The residue was subjected to flash chromatography on silica with a CH<sub>2</sub>Cl<sub>2</sub>-MeOH (40:1), followed by a 20:1 ratio mixture as eluant to yield 10.5 mg (34%) of the *Z*-isomer **11** as a yellow oil: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 0.06 (s, 6H), 0.89 (s, 9H), 1.43 (d, *J* = 14.0 Hz, 1H), 2.27-2.12 (m, 3H), 2.82 (dt, *J* = 10.5, 6.5 Hz, 1H), 3.03 (m, 2H), 3.09 (dd, *J* = 17.4, 6.6 Hz, 1H), 3.17 (s, 1H), 3.20 (m, 1H), 3.62 (d, *J* = 14.6 Hz, 1H), 3.67 (s, 1H), 4.20 (d, *J* = 6.3 Hz, 2H), 4.23 (s, 1H), 5.58 (t, *J* = 6.3 Hz, 1H), 5.81 (dt, *J* = 5.6, 2.5 Hz, 1H), 7.07 (td, *J* = 7.5, 1.0 Hz, 1H), 7.18 (d, *J* = 7.6 Hz, 1H), 7.22 (td, *J* = 7.7, 1.3 Hz, 1H), 8.14 (d, *J* = 8.03, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ -5.06, 18.3, 25.3, 25.9, 36.9, 39.3, 45.9, 47.0, 52.3, 52.8, 59.3, 63.1, 66.8, 114.6, 119.0, 122.5, 124.0, 127.4, 128.3, 134.6, 136.2, 141.6, 143.6, 168.7; IR (film) 2928, 1676, 1483, 1391, 835 cm<sup>-1</sup>; MS, *m/z* (relative abundance) 448 (M<sup>+</sup>, 2), 446 (5), 391 (3), 317 (26), 316 (100), 303 (10), 220 (6), 144 (7), 75 (9). HRMS Calcd. For C<sub>27</sub>H<sub>36</sub>N<sub>2</sub>O<sub>2</sub>Si: 448.254607. Found: 448.252362

Further elution gave 11.5 mg (37%) of the *E*-isomer **10** as a yellow oil: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 0.06 (s, 6H), 0.89 (s, 9H), 1.44 (d, *J* = 14.2 Hz, 1H), 2.15 (m, 2H), 2.26 (m, 1H), 2.88 (m, 1H), 2.93 (d, *J* = 14.5 Hz, 1H), 3.00 (dt, *J* = 17.4, 2.8 Hz, 1H), 3.10 (dd, *J* = 17.4, 6.7 Hz, 1H), 3.23 (ddd, *J* = 15.6, 7.7, 4.7 Hz, 1H), 3.50 (s, 1H), 3.61 (d, *J* = 14.4 Hz, 1H), 3.72 (s, 1H), 4.31-4.25 (m, 3H), 5.50 (t, *J* = 5.5 Hz, 1H), 5.79 (dt, *J* = 5.4, 2.5 Hz, 1H), 7.07 (td, *J* = 7.5, 1.0 Hz, 1H), 7.19 (d, *J* = 7.5 Hz, 1H), 7.23 (td, *J* = 7.7, 1.2 Hz, 1H), 8.14 (d, *J* = 8.0, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ -5.12, 18.3, 25.4, 25.9, 34.8, 36.8, 45.8, 52.4, 52.7, 53.7, 59.1, 63.1, 66.9, 114.6, 120.4, 122.5, 124.2, 128.2, 128.4, 134.3, 135.3, 141.4, 141.9, 168.4; IR (film) 2929 1674, 1484, 1392, 837 cm<sup>-1</sup>; MS, *m/z* (relative abundance) 448 (M<sup>+</sup>, 4), 317 (27), 316 (100), 303 (21), 220 (11), 207 (9), 144 (10), 73 (14). HRMS Calcd. for C<sub>27</sub>H<sub>36</sub>N<sub>2</sub>O<sub>2</sub>Si: 448.254607. Found: 448.253764.

**Isostrychnine (13)** A solution of silyl ether **10** (20 mg, 0.45 mmol) in 1N HCl (1 ml) and THF (0.5 ml) was stirred at room temperature for 3 h. The mixture was then poured onto satd. NaHCO<sub>3</sub> and extracted with CHCl<sub>3</sub> (3 × 2 ml). The combined organics were dried over MgSO<sub>4</sub> and concentrated in vacuo. The residue was submitted to flash chromatography on silica gel with CH<sub>2</sub>Cl<sub>2</sub>-MeOH (9:1), followed by a 7:1 ratio of this mixture as eluant to yield 14.8 mg (99%) of isostrychnine as white crystals: mp 229-230°C (lit. 226-227°C). The <sup>1</sup>H and <sup>13</sup>C were identical to that of the natural material.

**(±)-(21Z)-8,11,12,13-Tetradehydro-24-[(1,1-dimethylethyl)dimethylsilyl]-12,24-secostrychnidin-10-one (12)** Vinyl iodide **9** (67 mg, 0.12 mmol), Pd(OAc)<sub>2</sub> (8.4 mg, 0.037 mmol), and PPh<sub>3</sub> (18 mg, 0.069 mmol) were dissolved in Et<sub>3</sub>N (5 ml) and the solution was degassed with three freeze-pump-thaw cycles on a vacuum line. The reaction vessel was sealed and heated at 85°C for 5 h. The reaction mixture was then concentrated, the residue dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 ml), washed with H<sub>2</sub>O, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo. Purification by flash chromatography on silica gel using CH<sub>2</sub>Cl<sub>2</sub>-MeOH (30:1) as eluant gave 24 mg (46%) of **13** as a yellow oil, as well as 4.5 mg (15%) of amine **8**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) 0.04 (s, 6H), 0.88 (s, 9H), 1.26 (dd, *J* = 14.0, 3.6 Hz, 1H), 1.96 (dd, *J* = 12.6, 4.5 Hz, 1H), 2.34 (td, *J* = 12.5, 6.6 Hz, 1H), 2.63 (ddd, *J* = 13.9, 3.6, 2.1 Hz, 1H), 3.06 (d, *J* = 15.6 Hz, 1H), 3.13 (dd, *J* = 12.6, 5.8 Hz, 1H), 3.41 (td, *J* = 12.5, 5.7 Hz, 1H), 3.65 (s, 1H), 4.13 (m, 2H), 4.23 (s, 1H), 4.31 (dd, *J* = 13.1, 6.3 Hz, 1H), 5.54 (m, 1H), 6.46 (d, *J* = 9.2 Hz, 1H), 7.25 (m, 1H), 7.26 (d, *J* = 9.2, 1H), 7.38 (td, *J* = 7.8, 1.1 Hz, 1H), 7.41 (d, *J* = 7.3 Hz, 1H), 8.55 (d, *J* = 8.0 Hz, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) -5.18, 18.3, 25.9, 30.9, 34.3, 45.8, 55.5, 56.0, 56.3, 59.6, 61.6, 117.7, 117.9, 119.5, 121.0, 126.5, 128.6, 129.0, 136.4, 138.7, 139.2, 140.6, 153.0, 161.5; IR (film) 1671, 1622, 1585, 1460, 834 cm<sup>-1</sup>; MS *m/z* (relative abundance) 446 (M<sup>+</sup>, 100), 389 (10), 314 (60), 301 (38), 119 (20), 73 (34). Anal. Calcd. for C<sub>27</sub>H<sub>34</sub>N<sub>2</sub>O<sub>2</sub>Si: C 72.61, H 7.68, N 6.28. Found: C 71.31, H 7.67, N 5.94.

**Reduction of 12 to 10:** To a solution of lithium aluminum hydride (10 mg, 0.26 mmol) in Et<sub>2</sub>O (0.5 ml) at 0°C was added a solution of **13** (8.9 mg, 0.016 mmol) in Et<sub>2</sub>O (0.3 ml) and THF (0.3 ml) over 25 min. After 2 h total, MeOH (0.3 ml) was added slowly to the mixture, followed by water (0.6 ml). The mixture was then diluted with CHCl<sub>3</sub>, and the organic layer was washed with H<sub>2</sub>O, dried over Na<sub>2</sub>SO<sub>4</sub>, and

concentrated in vacuo. Flash chromatography on silica gel with CH<sub>2</sub>Cl<sub>2</sub>-MeOH (30:1) as eluant gave 4.8 mg (54%) of **10** as a yellow oil.