6-exo-Spiro (Alkoxycarbonylamino)methyl Radical Cyclization: Highly Regio- and Stereoselective Synthesis of (-)-Sibirine

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Supporting Information

1-(*t*-Butyldimethylsiloxy)-2-bromo-2-cyclohexene (**9**).

To a solution of 2-bromo-2-cyclohexen-1-ol (2.45 g, 13.8 mmol) in *N,N*-dimethylformamide (12 mL) were added imidazole (1.89 g, 27.8 mmol) and *tert*-butyldimethylsilyl (TBS) chloride (2.15 g, 13.8 mmol). The reaction mixture was stirred at room temperature for 12 h and then aqueous hydrochloric acid (5%, 20 mL) was added. The resulting mixture was extracted with diethyl ether (2 x 30 mL), and the combined organic layers were washed with brine (2 x 50 mL), and dried (Na₂SO₄). The solvent was removed under reduced pressure to give a colorless oil, which was purified by silica gel flash column chromatography using hexanes/ethyl acetate (7/1) as the eluent to give TBS ether **9** as a colorless oil (3.95 g, 98%): *R_f*(hexanes/ethyl acetate, 15/1) 0.50; ¹H NMR (360 MHz, CDCl₃) δ 0.11 (s, 3H), 0.17 (s, 3H), 0.92 (s, 9H), 1.50-1.59 (m, 1H), 1.70-1.85 (m, 3H), 1.95-2.18 (m, 2H), 4.20 (m, 1H, *J* = 4.3 Hz), 6.14 (dd, 1H, *J* = 5.0, 3.6 Hz); ¹³C NMR (90.6 MHz, CDCl₃) δ -4.67 (q), -4.47 (q), 17.19 (t), 18.13 (s), 25.82 (q), 27.78 (t), 33.73 (t), 70.60 (d), 125.81 (s), 131.96 (d); IR (neat) 1643, 1471, 1462, 1438 cm⁻¹. Anal. Calcd for C₁₂H₂₃BrOSi: C, 49.48; H, 7.96. Found: C, 49.45; H, 7.86.

1-(*t*-Butyldimethylsiloxy)-2-[(3'-carbomethoxyamino)propyl]-2-cyclohexene (**11**).

A 100-mL round-bottomed flask was charged with 1-(methoxycarbonyl)amino-2-propene (1.85 g, 16.1 mmol) and 9-BBN (0.5 M in tetrahydrofuran, 48 mL, 24.0 mmol) was added at room temperature. The resulting solution was stirred for 3 h and then bromide **9** (3.86 g, 13.3 mmol) in tetrahydrofuran (10 mL), tetrakis(triphenylphosphine)palladium (463 mg, 0.40 mmol), sodium hydroxide (1.59 g, 39.8 mmol), and water (10 mL) were added successively. The resulting mixture was refluxed for 1.5 h and then cooled to room temperature. To the reaction mixture was added hydrogen peroxide (30% in water, 10 mL). The mixture was stirred for 15 min, and then diluted with diethyl ether (50 mL) and water (40 mL). The aqueous layer was back-extracted with diethyl ether (50 mL). The combined organic layers were washed first with water (80 mL) and then with brine (80 mL), and dried (Na₂SO₄). The solvent was removed under reduced pressure to give a colorless oil, which was purified by silica gel flash column chromatography using hexanes/ethyl acetate (9/1) as the eluent to provide coupling product **11** as a colorless oil (4.03 g, 93%): *R_f* (hexanes/ethyl acetate, 4/1) 0.39; ¹H NMR (360 MHz, CDCl₃) δ 0.08 (s, 6H), 0.89 (s, 9H), 1.40-1.80 (m, 6H), 1.85- 2.20 (m, 4H), 3.17 (br d, 2H), 3.65 (s, 3H), 4.09 (t, 1H, *J* = 5.0 Hz), 4.74 (br s, 1H), 5.49 (br s, 1H); ¹³C NMR (90.6 MHz, CDCl₃) δ -4.72 (q), -4.15 (q), 18.05 (s), 18.81 (t), 25.42 (t), 25.86 (q), 28.06 (t), 30.83 (t), 32.91 (t), 40.88 (t), 51.87 (q), 67.94 (d), 124.49 (d), 136.97 (s), 156.98 (s); IR (neat) 3335, 1709, 1535, 1466, 1252. Anal. Calcd for C₁₇H₃₃NO₃Si: C, 62.34; H, 10.16; N, 4.28. Found: C, 62.21; H, 10.03; N, 4.22.

1-(*t*-Butyldimethylsiloxy)-2-{3'-[*N*-(carbomethoxy)-*N*-tri(*n*-butylstannanyl)methyl-amino]}propyl-2-cyclohexene (i**).**

Twenty-two points, plus triple-word-score, plus fifty points for using all my letters. Game's over. I'm

outta here. To a solution of **11** (2.19 g, 6.68 mmol) in *N,N*-dimethylformamide (20 mL) was added sodium hydride (60%, 321 mg, 8.02 mmol) at room temperature. After 15 min, (iodomethyl)tributylstannane (80%, 3.80 g, 7.06 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 12 h, and then diluted with brine (40 mL). The resulting mixture was extracted with diethyl ether (2 x 50 mL) and the combined organic layers were washed with brine (80 mL), and dried (Na₂SO₄). The solvent was removed under reduced pressure to give a colorless oil, which was purified by silica gel flash column chromatography using hexanes (300 mL) then hexanes/ethyl acetate (8/1) as the eluent to provide stannane **i** as a colorless oil (3.69 g, 88%): *R_f* (hexanes/ethyl acetate, 6/1) 0.53; ¹H NMR (360 MHz, CDCl₃) δ 0.09 (s, 6H), 0.78-1.00 (m, 24H), 1.22-

2.15 (m, 22H), 2.80-2.97 (m, 2H), 3.10-3.31 (m, 2H), 3.64 and 3.65 (two sets of singlets, 3H), 4.10 (br s, 1H), 5.49 (br s, 1H); ^{13}C NMR (90.6 MHz, CDCl_3) δ -4.77, -4.16, 9.62, 10.34, 13.66, 18.05, 18.87, 18.93, 25.43, 25.75, 25.87, 26.25, 27.36, 29.00, 29.06, 30.68, 30.80, 32.79, 32.98, 33.97, 50.09, 52.22, 52.49, 67.91, 123.91, 124.00, 139.21, 139.27, 156.18, 156.67; IR (neat) 1692 cm^{-1} . Anal. Calcd for $\text{C}_{30}\text{H}_{61}\text{NO}_3\text{SiSn}$: C, 57.14; H, 9.75; N, 2.22. Found: C, 57.27; H, 9.76; N, 2.29.

1-(*t*-Butyldimethylsiloxy)-2-{3'-[*N*-(Carbomethoxy)-*N*-(phenylselanyl)methylamino]}-propyl-2-cyclohexene (12**) and 1-(*t*-Butyldimethylsiloxy)-2-{3'-[*N*-(carbomethoxy)-*N*-methylamino]}propyl-2-cyclohexene (**ii**).**

To a solution of stannane **i** (884 mg, 1.40 mmol) in tetrahydrofuran (7 mL) at -78°C was added dropwise *n*-butyllithium (1.4 M in hexanes, 1.20 mL, 1.68 mmol). After 10 min at -78°C , diphenyl diselenide (524 mg, 1.68 mmol) in tetrahydrofuran (3 mL) was added dropwise. The reaction mixture was stirred at -78°C for 30 min and then the reaction was quenched with saturated aqueous ammonium chloride (1 mL). The resulting mixture was warmed up to room temperature, and more saturated aqueous ammonium chloride (15 mL) was added and the mixture was extracted with diethyl ether (2 x 30 mL). The combined organic layers were washed with brine (50 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure to give a yellow oil, which was purified by silica gel flash column chromatography using hexanes then hexanes/ethyl acetate (10/1) as the eluent to provide selenide **12** as a colorless oil (337 mg, 49%): R_f (hexanes/ethyl acetate, 6/1) 0.40; ^1H NMR (360 MHz, CDCl_3) δ 0.06, 0.07 and 0.08 (three sets of singlet, 6H), 0.89 and 0.90 (two sets of singlet, 9H), 1.40-2.20 (m, 10H), 3.10-3.65 (m, 6.3H), 4.05 (br d, 1H), 4.72-4.90 (m, 0.7H), 5.45 (br s, 1H), 7.13-7.30 (m, 3H), 7.40-7.62 (m, 2H); IR (neat) 1712, 1578, 1471, 1438, 1402, 1251, 1207 cm^{-1} . Anal. Calcd for $\text{C}_{24}\text{H}_{39}\text{NO}_3\text{SeSi}$: C, 58.04; H, 7.92; N, 2.82. Found: C, 57.75; H, 7.85; N, 2.84.

N-Methyl product **ii** was also isolated as a colorless oil (120 mg, 25%): R_f (hexanes/ethyl acetate, 6/1) 0.31; ^1H NMR (360 MHz, CDCl_3) δ 0.09 (s, 6H), 0.89 (s, 9H), 1.46-2.15 (m, 10H), 2.86 and 2.89 (two sets of singlet, 3H), 3.12-3.30 (m, 2H), 3.67 (s, 3H), 4.10 (br s, 1H), 5.49 (br s, 1H).

Radical Cyclization of Selenide **12**.

In a three-necked, round-bottomed 100-mL flask equipped with an additional funnel and a condenser, selenide **12** (166 mg, 0.334 mmol) was dissolved in 17 mL of degassed dry toluene. A solution of (*n*-Bu)₃SnH (159 mg, 0.501 mmol, 1.5 mol equiv) and AIBN (11 mg, 0.067 mmol, 0.2 mol equiv) in degassed dry toluene was transferred into the addition funnel via a syringe. The reaction flask was immersed into an oil bath and the reaction solution was heated to reflux, to which the (*n*-Bu)₃SnH solution was added over 11 h. As the GC analysis of the reaction mixture indicated still the presence of some selenide **12**, more reagent solution [(*n*-Bu)₃SnH (64 mg, 0.215 mmol) and AIBN (5 mg, 0.030 mmol) in toluene (13 mL)] were added over 2 h through the addition funnel. At the time when the second addition was completed, all starting selenide had been consumed. Upon cooling the reaction mixture to room temperature, the solvent was removed by rotary evaporation. The resulting residue was subjected to purification by silica gel flash column chromatography using 5:1 hexanes/ethyl acetate as the eluting solvent system to provide an inseparable mixture of cyclization products **13** and **14** as a viscous oil (84 mg, 74%). Since the ¹H NMR spectrum of this mixture was highly complex due to the rotational isomers of the carbamate group in each of the three products and peaks extensively overlap beyond analysis, the methoxycarbonyl group of the products were reduced to their corresponding methyl groups. Thus, to the cooled (0 °C) solution of the mixture of **13** and **14** obtained above (21 mg, 0.066 mmol) in dry diethyl ether (3 mL) was added LiAlH₄ (8 mg, 0.20 mmol). The reaction mixture was then slowly warmed up to room temperature and was kept stirring at that temperature for 4 h and the reaction mixture was cooled again in an ice-bath. Excess LiAlH₄ was destroyed with ethyl acetate (0.5 mL). The resulting mixture was washed with, successively, water (3 mL), 15% aqueous NaOH (3 mL), water (3 mL), and brine (3 mL). The organic layer was dried (MgSO₄) and concentrated by rotary evaporation. The oily residue thus obtained was quickly passed through a small silica gel flash column using CHCl₃/Et₃N (20:1) and the purified mixture (12 mg) was analyzed by ¹H-NMR spectroscopy (CDCl₃, 360 MHz) to show that the LiAlH₄ reduction products consisted of those from a mixture of **13** and *cis*- and *trans*-**14** roughly in a, respectively, 2.3 : 0.5 : 1.0 ratio.

2-Bromo-3-phenylthiocyclohex-2-en-1-one (**25**) .

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To a solution of 3-phenylthiocyclohex-2-en-1-one (**15**) (4.20 g, 20.6 mmol) in carbon tetrachloride (50 mL) was added *N*-bromosuccinimide (recrystallized from water, 5.49 g, 30.8 mmol) at 0 °C. The reaction mixture was stirred in the dark for 24 h at room temperature and then saturated aqueous sodium bicarbonate (50 mL) was added. The organic layer was separated and the aqueous layer was back-extracted with dichloromethane (50 mL). The combined organic layers were washed with brine (80 mL) and dried (Na₂SO₄). The solvent was removed under reduced pressure to give a yellow solid which was purified by recrystallization from hexanes/ethyl acetate to give bromide **25** as white prisms (4.70 g, 81%): *R_f* (hexanes/ethyl acetate, 4/1) 0.19; mp: 112-113 °C; ¹H NMR (400 MHz, CDCl₃) δ 1.93-2.00 (m, 2H), 2.21 (t, 2H, *J* = 6.1 Hz), 2.56 (t, 2H, *J* = 6.1 Hz), 7.43-7.58 (m, 5H); ¹³C NMR (100 MHz, CDCl₃) δ 22.42 (t), 32.16 (t), 37.07 (t), 116.73 (s), 129.02 (s), 129.60 (d), 130.36 (d), 135.93 (d), 164.30 (s), 187.64 (s); IR (KBr) 1659, 1546, 1258, 1190 cm⁻¹. Anal. Calcd for C₁₂H₁₁BrOS: C, 50.90; H, 3.92. Found: C, 50.84; H, 3.99.

2-Bromo-3-phenylthiocyclohex-2-en-1-ol (iii).

To a suspension of enone **25** (2.26 g, 8.0 mmol) in dry methanol (30 mL) at room temperature was added cerium chloride heptahydrate (3.28 g, 8.8 mmol) followed by sodium borohydride (340 mg, 8.8 mmol). Gas evolution and heat generation were observed. The reaction mixture was stirred for another 0.5 h and then aqueous hydrochloric acid (5%, 15 mL) was added followed by water (30 mL). The resulting mixture was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed first with saturated aqueous sodium bicarbonate (100 mL), and then with brine (100 mL), and dried (Na₂SO₄). The solvent was removed under reduced pressure to give a colorless oil, which was purified by silica gel flash column chromatography using hexanes/ethyl acetate (3/1) as the eluent to provide allylic alcohol **iii** as a colorless oil (2.20 g, 96%): *R_f* (hexanes/ethyl acetate, 4/1) 0.21; ¹H NMR (400 MHz, CDCl₃) δ 1.58-1.64 (m, 1H), 1.67-1.82 (m, 1H), 1.83- 2.05 (m, 4H), 2.28 (d, 1H, *J* = 4.0 Hz), 4.34 (m, 1H), 7.33-7.37 (m, 3H), 7.45-7.48 (m, 2H); ¹³C NMR (100.6 MHz, CDCl₃) δ 18.89 (t), 31.62 (t), 32.06 (t), 71.34 (d), 121.68 (s), 128.74 (d), 129.06 (d), 131.03 (s), 134.77 (d), 138.05 (s); IR

(neat) 3407, 1603, 1583, 1475, 1437 cm^{-1} . Anal. Calcd for $\text{C}_{12}\text{H}_{13}\text{BrOS}$: C, 50.54; H, 4.59. Found: C, 50.32; H, 4.70.

1-(*t*-Butyldimethylsiloxy)-2-bromo-3-phenylthio-2-cyclohexene (16).

To a solution of allylic alcohol **iii** (1.96 g, 6.87 mmol) in *N,N*-dimethylformamide (10 mL) were added imidazole (0.94 g, 13.7 mmol) and *tert*-butyldimethylsilyl chloride (1.07 g, 6.87 mmol). The reaction mixture was stirred at room temperature for 12 h and then aqueous hydrochloric acid (5%, 20 mL) was added. The resulting mixture was extracted with diethyl ether (2 x 30 mL), and the combined organic layers were washed with brine (2 x 50 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to give a colorless oil, which was purified by silica gel flash column chromatography using hexanes/ethyl acetate (7/1) as the eluent to provide silyl ether **16** as a colorless oil (2.60 g, 95%): R_f (hexanes/ethyl acetate, 20/1) 0.36; ^1H NMR (400 MHz, CDCl_3) δ 0.12 (s, 3H), 0.19 (s, 3H), 0.92 (s, 9H), 1.50-1.59 (m, 1H), 1.76-2.03 (m, 5H), 4.32-4.34 (m, 1H), 7.31-7.35 (m, 3H), 7.45-7.48 (m, 2H); ^{13}C NMR (100.6 MHz, CDCl_3) δ -4.65 (q), -4.37 (q), 18.16 (s), 18.57 (t), 25.83 (q), 32.11 (t), 33.44 (t), 72.15 (d), 122.26 (s), 128.43 (d), 128.92 (d), 131.53 (s), 134.57 (d), 136.74 (s); IR (neat) 1609, 1469, 1441, 1262, 1249 cm^{-1} . Anal. Calcd for $\text{C}_{18}\text{H}_{27}\text{BrOSSi}$: C, 54.12; H, 6.81. Found: C, 54.09; H, 6.63.

1-(*t*-Butyldimethylsiloxy)-2-(3'-carbomethoxyamino)propyl-3-phenylthio-2-cyclohexene (17).

A 100-mL round-bottomed flask was charged with 1-methoxycarbonylamino-2-propene (1.27 g, 11.0 mmol) and 9-BBN (0.5 M in tetrahydrofuran, 44 mL, 22.0 mmol) at room temperature. The resulting solution was stirred for 3 h and then bromide **16** (3.69 g, 9.24 mmol) in tetrahydrofuran (10 mL), sodium hydroxide (1.32 g, 33.0 mmol), tetrakis(triphenylphosphine)palladium (381 mg, 0.33 mmol),

and water (10 mL) were added successively. The resulting mixture was refluxed for 3 h and then cooled to 0 °C. Hydrogen peroxide (30% in water, 10 mL) was added and the resulting mixture stirred for 15 min at 0 °C. The reaction mixture was then diluted with ethyl acetate (50 mL) and water (40 mL). The aqueous layer was back-extracted with ethyl acetate (50 mL). The combined organic layers were washed first with water (100 mL), and then with brine (100 mL) and dried (Na₂SO₄). The solvent was removed under reduced pressure to give a colorless oil, which was purified by silica gel flash column chromatography using hexanes/ethyl acetate (7/1) as the eluent to provide coupling product **17** as a colorless oil (3.34 g, 83%): *R_f*(hexanes/ethyl acetate, 5/1) 0.30; [α]_D²³ –58.3 (c 1.38, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 0.10 (s, 3H), 0.12 (s, 3H), 0.92 (s, 9H), 1.47-1.82 (m, 6H), 2.00-2.22 (m 2H), 2.36-2.60 (m, 2H), 3.11-3.25 (m, 2H), 3.64 (s, 3H), 4.27 (br t, 1H), 4.82 (br s, 1H), 7.15-7.30 (m, 5H); ¹³C NMR (100.6 MHz, CDCl₃) δ -4.74, -4.15, 18.02, 19.49, 25.82, 28.95, 31.55, 32.53, 40.82, 51.88, 68.66, 126.07, 128.86, 129.14, 129.67, 135.16, 144.21, 156.98; IR (neat) 3346, 1715, 1525, 1250, 1075 cm⁻¹. Anal. Calcd for C₂₃H₃₇NO₃SSi: C, 63.40; H, 8.56; N, 3.21. Found: C, 63.10; H, 8.21; N, 3.17.

1-(*t*-Butyldimethylsiloxy)-2-(3'-carbomethoxyamino)propyl-3-phenylsulfonyl-2-cyclohexene (18**).**

To a solution of sulfide **17** (103 mg, 0.24 mmol) in dichloromethane (5 mL) at 0 °C was added *m*-chloroperoxybenzoic acid (140 mg, 0.57 mmol) in one portion. The resulting mixture was then taken to room temperature and was stirred for 2.5 h and then aqueous sodium thiosulfate (0.1M, 10 mL) and saturated aqueous sodium bicarbonate (10 mL) were added in succession. The resulting mixture was extracted with ethyl acetate (2 x 20 mL) and the combined organic layers were washed first with saturated aqueous sodium bicarbonate (30 mL), and then with brine (30 mL), and dried (Na₂SO₄). The solvent was removed under reduced pressure to give a colorless oil, which was purified by silica gel flash column chromatography using hexanes/ethyl acetate (2/1) as the eluent to give sulfone **18** as a colorless oil (105 mg, 98%): *R_f*(hexanes/ethyl acetate, 3/1) 0.20; [α]_D²¹ –91.9 (c 0.83, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 0.08 (s, 3H), 0.09 (s, 3H), 0.87 (s, 9H), 1.53-1.82 (m, 6H), 2.00-2.32 (m, 2H), 2.44-2.50 (m, 1H), 2.85-2.95 (m, 1H), 3.13-3.32 (m, 2H), 3.67 and 3.71 (two sets of singlets, 3H), 4.20 (br t, 1H, *J* = 4.4), 4.78 and 5.22 (two sets of broad singlets, 1H), 7.52-7.55 (m, 2H), 7.60-7.63 (m, 1H),

7.84-7.87 (m, 2H); ^{13}C NMR (100.6 MHz, CDCl_3) δ -4.93, -4.25, 17.94, 25.65, 26.91, 27.35, 29.23, 31.32, 40.64, 51.85, 68.63, 127.08, 129.04, 133.07, 135.89, 141.04, 151.32, 157.14; IR (neat) 3388, 1719, 1626, 1525, 1470, 1463, 1446, 1304, 1257 cm^{-1} . Anal. Calcd for $\text{C}_{23}\text{H}_{37}\text{NO}_5\text{SSi}$: C, 59.07; H, 7.97; N, 2.99. Found: C, 58.88; H, 8.02; N, 2.99.

1-(*t*-Butyldimethylsiloxy)-2-{3'-[*N*-(carbomethoxy)-*N*-(hydroxymethyl)amino]}propyl-3-phenylsulfonyl-2-cyclohexene (iv).

To a solution of sulfone **18** (221 mg, 0.47 mmol) in *tert*-butyl alcohol (4 mL) at room temperature was added potassium *tert*-butoxide (112 mg, 0.95 mmol) followed by paraformaldehyde (141 mg, 4.70 mmol equivalents of $\text{H}_2\text{C}=\text{O}$). The resulting yellow suspension was stirred for 1 h at room temperature and then aqueous hydrochloric acid (5%, 10 mL) was added followed by water (10 mL). The resulting mixture was extracted with ethyl acetate (2 x 20 mL) and the combined organic layers were washed first with water (40 mL), and then with brine (40 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure to give a colorless oil, which was purified by silica gel flash column chromatography using hexanes/ethyl acetate (2/1) as the eluent to provide alcohol **iv** as a colorless oil (175 mg, 75%): R_f (hexanes/ethyl acetate, 1/1) 0.23; $[\alpha]_{\text{D}}^{21}$ -80.5 (c 1.04, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 0.08 (s, 3H), 0.09 (s, 3H), 0.87 (s, 9H), 1.53-1.82 (m, 6H), 2.18-2.36 (m, 2H), 2.37-2.48 (m, 1H), 2.92 and 3.10 (two sets of br s, 2H), 3.32-3.52 (m, 2H), 3.72 and 3.76 (two sets of s, 3H), 4.20 (br s, 1H), 4.80 (br s, 2H), 7.52-7.57 (m, 2H), 7.59-7.64 (m, 1H), 7.82-7.87 (m, 2H); ^{13}C NMR (100.6 MHz, CDCl_3) δ -4.77, -4.14, 18.01, 20.36, 24.61, 25.31, 25.77, 26.59, 27.02, 27.54, 27.70, 28.00, 28.42, 31.42, 37.71, 46.20, 52.75, 58.03, 68.29, 75.20, 75.87, 126.86, 127.00, 128.93, 132.88, 135.70, 135.86, 141.27, 150.97, 151.20, 156.05, 156.84; IR (neat) 3466, 1710, 1626 cm^{-1} . Anal. Calcd for $\text{C}_{24}\text{H}_{39}\text{NO}_6\text{SSi}$: C, 57.92; H, 7.90; N, 2.81. Found: C, 57.60; H, 7.91; N, 2.86.

Asymmetric Reduction of 2-Bromo-3-phenylthiocyclohex-2-en-1-one (25)

Under nitrogen, 0.18 mL of 1 M (*R*)-2-methyl-CBS-oxazaborolidine (purchased from Aldrich Chemicals; 0.18 mmol, 0.1 mol equiv) was diluted with 1.5 mL of THF and the solution was cooled in an ice-water bath. Ketone **25** (509 mg, 1.80 mmol) was dissolved in 2.5 mL of THF and 1.5 mL of a 1.0 M solution of BH₃ in THF was diluted with 1 mL of THF. These solutions of ketone **25** and BH₃ were added to the CBS solution simultaneously using syringes over the period of 10 min. The reaction mixture was kept stirring in an ice-water bath for 5 min and then 20 mL of 0.5 M aqueous HCl was added. The resulting mixture was extracted with ethyl acetate (3 x 20 mL) and the combined organic layers were washed first with saturated aqueous NaHCO₃ (30 mL) and then with brine (30 mL) and were dried (MgSO₄). The solvent was removed by rotary evaporation to give a colorless oil which was purified by silica gel flash column chromatography using hexanes/ethyl acetate (3/1) as the eluent to provide 2-bromo-3-phenylthio-2-cyclohexen-1-ol (**26**) as a colorless oil (0.482 g, 94%): [α]_D^{23.5} -96.7 (*c* 0.94, CHCl₃).

(*S*)-*O*-Acetylmandelate Derivative, 27, from Allylic Alcohol 26.

Alcohol (-)-**26** (995 mg, 3.49 mmol), (*S*)-(+)-*O*-acetylmandelic acid (0.815 g, 4.2 mmol), and a catalytic amount of DMAP were dissolved in 40 mL of CH₂Cl₂ and DCC (1.03 g, 4.90 mmol) was added to the solution in portions at room temperature. A white precipitate formed immediately. The reaction mixture was kept stirring for 4 h at room temperature and then was concentrated by rotary evaporation. The resulting residue was purified by silica gel flash column chromatography using hexanes/ethyl acetate (3/1) to afford a 93 : 7 diastereomeric mixture of mandelates **27**. Single recrystallization of this moisture from benzene provided diastereomerically pure (>99 : 1 diastereomeric ratio) mandelate **27** (1.24 g, 77%; 72% overall yield from **25**): mp 98-100 °C; [α]_D²¹ -97.2 (*c* 0.81, CHCl₃); ¹H NMR (400

MHz, CDCl₃) δ 1.58-1.76 (m, 2H), 1.80-1.92 (m, 2H), 2.22 (s, 3H), 5.47 (dd, 1H, $J = 3.9, 3.7$ Hz), 5.90 (s, 1H), 7.33-7.43 (m, 6H), 7.46-7.50 (m, 2H), 7.52-7.56 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 18.6, 20.7, 29.6, 31.5, 74.4, 74.8, 113.3, 127.7, 128.7, 129.11, 129.14, 129.2, 130.3, 133.3, 135.4, 141.9, 168.4, 170.6; IR (KBr) 2944, 1748, 1605, 1440 cm⁻¹. Anal. Calcd for C₂₂H₂₁BrO₄S: C, 57.27; H, 4.59. Found: C, 57.51; H, 4.58.

Removal of the *O*-Acetylmandale Group from **27**.

O-Acetylmandelate **27** (828 mg, 1.79 mmol) was dissolved in 20 mL of THF and to this solution was added dropwise 2M LiBH₄ in THF (9 mL, 18.0 mmol) at room temperature. After stirring at room temperature for 12 h, the reaction mixture was cooled down in an ice-bath for 1 h and the reaction was quenched at that temperature by dropwise addition of saturated aqueous NH₄Cl (10 mL). The mixture was warmed to room temperature and diluted with 50 mL of water and the resulting moisture was extracted with ethyl acetate (3 x 40 mL). The combined organic layers were washed first with saturated aqueous NaHCO₃ (40 mL) and then with brine (40 mL), and dried (MgSO₄). The organic solvent was removed by rotary evaporation and the resulting residue was purified by silica gel flash column chromatography to afford (-)-**26** (496 mg, 97%, 70% overall yield from **25**): [α]_D²³ -110.4 (*c* 1.03, CHCl₃).

(*S*)-1-(*t*-Butyldimethylsiloxy)-2-{3'-[*N*-(carbomethoxy)-*N*-(phenylselanylmethyl)amino]}-propyl-3-phenylsulfonyl-2-cyclohexene (**19**).

To 5-mL pear-shaped flask was charged with alcohol **iv** (334 mg, 0.67 mmol), *p*-toluenesulfonic acid (10 mg), and benzeneselenol (160 mg, 110 μ L) at room temperature. The reaction mixture was stirred for

2 h at that temperature and then the reaction was quenched with saturated aqueous sodium bicarbonate (20 mL). The resulting mixture was extracted with diethyl ether (2 x 20 mL), and the combined organic layers were washed first with water (30 mL), and then with brine (30 mL), and dried (Na₂SO₄). The solvent was removed under reduced pressure to give a yellow oil, which was purified by silica gel flash column chromatography using hexanes/ethyl acetate (5/1) as the eluent to provide selenide **19** as a colorless oil (303 mg, 71%): *R_f* (hexanes/ethyl acetate, 5/1) 0.22; [α]_D²³ -67.7 (c 1.97, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 0.06 and 0.08 (two sets of singlets, 6H), 0.86 (s, 9H), 1.50-1.80 (m, 6H), 2.20-2.42 (m, 3H), 2.75-2.93 (m, 1H), 3.29 and 3.40 (two sets of broad singlets, 2H), 3.38 and 3.64 (two sets of broad singlets, 3H), 4.16 (br s, 1H), 4.82-4.96 (m, 2H), 7.26-7.29 (m, 3H), 7.49-7.54 (m, 2H), 7.56-7.61 (m, 3H), 7.81-7.84 (m, 2H); ¹³C NMR (100.6 MHz, CDCl₃) δ -4.81, -4.24, 17.96, 25.72, 26.98, 27.40, 27.52, 27.77, 27.85, 31.42, 46.41, 46.53, 46.90, 52.48, 52.85, 68.67, 127.15, 127.62, 127.93, 128.96, 129.08, 133.05, 134.58, 135.64, 135.87, 141.40, 151.05, 151.30, 156.03; IR (neat) 1706, 1625, 1580, 1469, 1439, 1400, 1304, 1255, 1214, 1152 cm⁻¹. Anal. Calcd for C₃₀H₄₃NO₅SSeSi: C, 56.59; H, 6.81; N, 2.20. Found: C, 56.76; H, 6.85; N, 2.27.

(6*R*, 7*S*, 11*S*)-7-(*t*-Butyldimethylsiloxy)-2-carbomethoxy-11-phenylsulfonyl-2-aza-spiro(5.5)-undecane (20).

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A 100-mL three-necked round-bottomed flask was equipped with an addition funnel and a reflux condenser. The flask was charged with selenide **19** (250 mg, 0.39 mmol) and toluene (15 mL). The addition funnel was charged with tributyltin hydride (236 mg, 218 μ L, 0.79 mmol), 2,2'-azobisisobutyronitrile (13 mg), and toluene (45 mL). The system was purged with nitrogen gas for 10 min. It was placed into a preheated oil bath (120 °C) and refluxing started after 5 min. The solution in the dropping funnel was then added slowly to the reaction mixture over 7-h period. The solvent was removed under reduced pressure and the residue thus obtained was purified by silica gel flash column chromatography using first hexanes/ethyl acetate (8/1) and then hexanes/ethyl acetate (4/1) as the eluent to give the cyclized product **20** as a colorless oil (112 mg, 60%): *R_f* (hexanes/ethyl acetate, 5/1) 0.18; [α]_D²¹ -10.3 (c 0.88, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 0.03 (s, 3H), 0.05 (s, 3H), 0.88 (s, 9H),

1.45-2.35 (m, 9H), 2.59 (br t, 1H, $J = 12.0$ Hz), 2.73-2.91 (m, 1H), 3.35-3.40 (m, 1H), 3.50-3.64 (m, 1H), 3.70 (s, 3H), 4.12 and 4.23 (two sets of broad singlets, 2H), 4.36 and 4.51 (two sets of broad doublets, 1H, $J = 12.9$ Hz and 12.2 Hz), 7.56-7.60 (m, 2H), 7.61-7.65 (m, 1H), 7.84-7.86 (m, 2H); ^{13}C NMR (100.6 MHz, CDCl_3) δ -5.05, -4.09, 18.19, 18.98, 20.49, 20.85, 23.15, 25.86, 27.30, 27.82, 29.59, 44.20, 44.56, 46.03, 52.64, 65.69, 68.03, 128.09, 129.11, 133.30, 140.49, 156.15; IR (neat) 1701, 1455, 1415, 1307, 1264, 1192, 1146 cm^{-1} . Anal. Calcd for $\text{C}_{24}\text{H}_{39}\text{NO}_5\text{SSi}$: C, 59.84; H, 8.16; N, 2.91. Found: C, 59.89; H, 7.99; N, 2.88.

(6*S*, 7*S*)-7-*t*-Butyldimethylsiloxy-2-carbomethoxy-2-aza-spiro(5.5)undecane (v).

To a solution of sulfone **20** (14 mg, 0.029 mmol) in dry tetrahydrofuran (1 mL) was added a tiny piece of sodium (14 mg, 0.58 mmol). The mixture was cooled to -20 $^{\circ}\text{C}$ and dry ethanol (27 mg, 0.58 mmol) was added. The reaction mixture was then warmed up gradually to room temperature and kept stirring for another 2 h at that temperature and then diluted with dichloromethane (5 mL). The resulting solution was washed with aqueous hydrochloric acid (5%, 5 mL) and the aqueous layer was back-extracted with dichloromethane (5 mL). The combined organic layers were washed first with saturated aqueous sodium bicarbonate solution (10 mL), and then with brine (10 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure to give a colorless oil, which was purified by silica gel flash column chromatography using hexanes/ethyl acetate (4/1) as the eluent to provide desulfonylated product **vi** (9.1 mg, 92%): R_f (hexanes/ethyl acetate, 4/1) 0.43; $[\alpha]_{\text{D}}^{22} +58.4$ (c 0.63, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 0.035 (s, 3H), 0.042 (s, 3H), 0.90 (s, 9H), 1.08 (br s, 1H), 1.23-1.75 (m, 11H), 2.92 (br d, 1H, $J = 8.3$ Hz), 3.14 and 3.17 (two sets of singlet, 1H), 3.35-3.54 (m, 2H), 3.68 (s, 3H), 3.74 and 3.85 (two sets of broad doublet, 1H); ^{13}C NMR (100.6 MHz, CDCl_3) δ -4.93, -3.95, 18.15, 20.50, 20.72, 22.55, 25.91, 27.88, 29.57, 29.87, 38.62, 44.88, 51.78, 52.43, 73.80, 156.44; IR (neat) 1707 cm^{-1} . Anal. Calcd for $\text{C}_{18}\text{H}_{35}\text{NO}_3\text{Si}$: C, 63.30; H, 10.33; N, 4.10. Found: C, 63.25; H, 10.28; N, 3.88.

(-)-Sibirine (3).

To a solution of silyl ether **v** (26 mg, 0.077 mmol) in dry tetrahydrofuran (1 mL) at 0 °C was added powdered lithium aluminum hydride (33 mg, 0.77 mmol). The reaction mixture was then taken to room temperature for 1 h. The reaction was then quenched with aqueous hydrochloric acid (5%, 1 mL) and the resulting mixture extracted with diethyl ether (2 mL). The aqueous layer was neutralized with aqueous sodium hydroxide solution (2M, 1.5 mL) and was then back-extracted with ethyl acetate (2 x 2 mL). The combined organic layers were washed with brine (5 mL) and dried (Na₂SO₄). The solvent was removed under reduced pressure to give a colorless oil, which was dissolved in acetonitrile (1 mL). Aqueous hydrofluoric acid (45%, 0.1 mL) was then added at room temperature. After 1.5 h, the reaction mixture was diluted with aqueous hydrochloric acid (5%, 1 mL) and the mixture was extracted with diethyl ether (2 mL). The aqueous layer was neutralized with aqueous sodium hydroxide solution (2 M, 1.5 mL) and was then extracted with ethyl acetate (2 x 2 mL). The combined organic layers were washed with brine (5 mL) and dried (Na₂SO₄). The solvent was removed under reduced pressure to provide sibirine (**3**) as a colorless oil (12 mg, 85%): $[\alpha]_D^{23} -29.7$ (c 0.63, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 0.85-1.01 (m, 2H), 1.16-1.29 (m, 2H), 1.36-1.43 (m, 2H), 1.47-1.56 (m, 2H), 1.68-1.76 (m, 2H), 1.87-1.96 (m, 2H), 2.07-2.22 (m, 2H), 2.24 (s, 3H), 2.61 (d, 1H, *J* = 10.9 Hz), 2.82 (br d, 1H, *J* = 6.9 Hz), 3.61 (dd, 1H, *J* = 11.2, 3.4 Hz), 5.40-6.40 (extremely broadened peak, 1H, OH); ¹³C NMR (100.6 MHz, CDCl₃) δ 20.41, 23.13, 24.44, 27.71, 29.59, 37.16, 37.26, 46.53, 56.45, 69.99, 80.56.