Supplementary Information for "A Formal Construction of Fasicularin"

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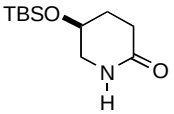
Experimental

General

All reactions were performed under a nitrogen atmosphere in flame-dried glassware. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane and toluene were distilled from calcium hydride. *N,N*-Dimethylformamide was purified by drying over 4Å molecular sieves. Isopropanol was distilled over sodium sulfate. Thin layer chromatography (TLC) was performed on DC-Fertigplatten SIL G-25 UV_{254} pre-coated TLC plates. Gas chromatographic (GC) analyses in a helium carrier gas were performed on a Hewlett-Packard 5890 Series II Plus gas chromatograph equipped with a flame ionization detector. A Chiral Select 1000 (30 m x 0.25 mm ID) fused silica capillary column was used. Melting points were performed using a Mel-Temp II apparatus (Lab devices USA) and are uncorrected. Optical rotations of samples were measured using either a Perkin-Elmer model MC-241 or a Jasco model P1010 polarimeter at 589 nm (sodium 'D' line). Infrared (IR) spectra were obtained using a Perkin-Elmer 1710 FT-IR spectrometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded in deuterochloroform using either a Bruker WH-400, Bruker AV-400, or a Bruker AV-300 spectrometer. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded in deuterochloroform using a Bruker AV-300 spectrometer. Chemical shifts are reported in parts per million (ppm) and are referenced to the centerline of deuterochloroform (d 7.24 ppm ^{1}H NMR; 77.0 ppm ^{13}C NMR). Coupling constants (*J* values) are given in Hertz (Hz). The tin-proton coupling constants (J_{Sn-H}) are reported as an average of the ^{117}Sn and ^{119}Sn values. Low resolution mass spectra (LRMS) and high resolution mass spectra (HRMS) were recorded on either a Kratos-AEI model MS 50 spectrometer (for EI) or a Kratos MS 80 spectrometer (for CI+ or DCI+). Microanalyses were performed by the Microanalytical Laboratory at the University of British Columbia on a Carlo Erba Elemental Analyzer Model 1106 or a Fisions CHN-O Elemental Analyzer Model 1108. Dimethyldioxirane (DMDO) was prepared according to the procedure of Murray.[1] Catalyst **Y** was prepared according to the procedure of Noyori.[2]

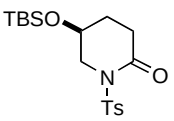
(-)-(5*S*)-5-(*tert*-Butyldimethylsilanyloxy)-piperidin-2-one **(6)**



A mixture of (-)-(5*S*)-5-hydroxy-piperidin-2-one **(5)** (8.45 g, 73.4 mmol, 1.0 eq.), *tert*-butyldimethylsilyl chloride (13.4 g, 88.8 mmol, 1.2 eq.), and imidazole (12.6 g, 186 mmol, 2.5 eq.) was dissolved in *N,N*-dimethylformamide (450 mL) and stirred at rt for 13 h. The solvent was removed *in vacuo* and the crude mixture was purified by column chromatography (1/25 methanol-chloroform) on neutral alumina to afford 15.5 g (92%) of a white solid. m.p. = 50-54 ˚C (hexanes). $[a]_D^{24}$ = -67.3 ± 0.6 (c 0.21, $CHCl_3$). IR (KBr): 3468, 3221, 2958, 1636 cm^{-1}. ^{1}H NMR (400 MHz, $CHCl_3$): d 5.64 (br s, 1H), 4.07 (quin, *J*=4.6 Hz, 1H), 3.37 (ddd, *J*=12, 3.7, 3.7 Hz, 1H), 3.18 (ddd, *J*=12, 3.4, 2.8 Hz, 1H), 2.56 (m, 1H), 2.30 (m, 1H), 1.86 (m,

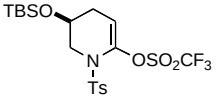
2H), 0.87 (s, 9H), 0.06 (d, *J*=2.4 Hz, 6H). ^{13}C NMR (75 MHz, $CHCl_3$): d 172.0, 64.0, 49.2, 28.8, 27.4, 25.5, 17.9, -5.0. HRMS (DCI+, ammonia/methane): Calcd for $C_{11}H_{24}NO_2Si$ (M^+ + 1): 230.1576. Found 230.1580. Anal. Calcd for $C_{11}H_{23}NO_2Si$: C, 57.60; H, 10.11; N, 6.11. Found: C, 57.31; H, 10.40; N, 6.11

(-)-(5*S*)-5-(*tert*-Butyldimethylsilanyloxy)-1-(toluene-4-sulfonyl)-piperidin-2-one **(7)**



Small scale: To a solution of (S)-5-(*tert*-butyldimethylsilanyloxy)-piperidin-2-one **(6)** (36.7 mg, 0.160 mmol, 1.0 eq.) in THF (4 mL) was added *n*-butyllithium (390 mL, 0.636 mmol, 4.0 eq.) *via* syringe at –78 ˚C. After stirring for 0.5 h, a solution of *p*-toluenesulfonyl chloride (305 mg, 1.6 mmol, 10 eq.) in THF (4 mL) was added *via* cannulation. The mixture was stirred at –78 ˚C for 1.5 h. The reaction was quenched by adding a saturated solution of aqueous ammonium chloride. The mixture was extracted with ethyl acetate and the combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (2/7 ethyl acetate-hexanes) on SiO_2 to afford 45.8 mg (75%) of a white solid.
Large scale: To a solution of (S)-5-(*tert*-butyldimethylsilanyloxy)-piperidin-2-one **(6)** (14.8 g, 64.5 mmol, 1.0 eq.) in THF (1 L) was added *n*-butyllithium (89 mL, 142 mmol, 2.2 eq.) *via* syringe at –78 ˚C. After stirring for 0.5 h, a solution of *p*-toluenesulfonyl chloride (28.6 g, 150 mmol, 2.3 eq.) in THF (1 L) was added *via* cannulation. The mixture was stirred at –78 ˚C for 1.5 h. The reaction was quenched by adding a saturated solution of aqueous ammonium chloride. The mixture was extracted with ethyl acetate and the combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (2/7 ethyl acetate-hexanes) on SiO_2 to afford 18.0 g (73%) of a white solid.
m.p. = 140-142 ˚C (ethyl acetate-hexanes). $[a]_D^{25}$ = -7.3 ± 0.5 (c 0.23, $CHCl_3$). IR (KBr): 2953, 2927, 2884, 2857, 1687, 1354, 1188 cm^{-1}. ^{1}H NMR (400 MHz, $CHCl_3$): d 7.86 (d, *J*=8.4 Hz, 2H), 7.25 (d *J*=7.9 Hz, 2H), 4.26-4.20 (m, 1H), 3.94 (ddd, *J*=12.6, 3.7, 1.5 Hz, 1H), 3.79 (dd, *J*=12.6, 3.0 Hz, 1H), 2.63-2.51 (m, 1H), 2.38 (s, 3H), 2.41-2.31 (m, 1H), 1.93-1.75 (m, 2H), 0.82 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (75 MHz, $CHCl_3$): d 169.6, 144.6, 136.0, 129.2, 128.5, 36.9, 53.3, 29.4, 28.1, 25.5, 21.6, 17.8, -4.9. HRMS (DCI+, ammonia/methane): Calcd for $C_{18}H_{30}NO_4SSi$ (M^+ + 1): 384.1665. Found 384.1663. Anal. Calcd for $C_{18}H_{29}NO_4SSi$: C, 56.36; H, 7.62; N, 3.65. Found: C, 56.11; H, 7.70; N, 3.69.

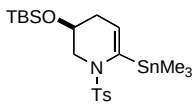
(+)-(5*S*)-Trifluoromethanesulfonic acid 5-(*tert*-butyldimethylsilanyloxy)-1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydropyridin-2-yl ester **(8)**



Small scale: (-)-(5*S*)-5-(*tert*-Butyldimethylsilanyloxy)-1-(toluene-4-sulfonyl)-piperidin-2-one **(7)** (1.01 g, 2.63 mmol, 1.0 eq.) was dissolved in THF (50 mL) and the mixture was cooled to -78 ˚C. Potassium bis(trimethylsilyl)amide (11.6 mL, 5.80 mmol, 2.2 eq.) was added dropwise and the mixture was stirred for 0.75 h. A solution of *N*-(5-chloro-2-pyridyl)triflimide (2.20 g, 5.60 mmol, 2.1 eq.) in THF (50 mL) was added. The reaction mixture was stirred at -78 ˚C for 1.5

h. The resulting red solution was warmed to rt and stirred overnight. A saturated solution of aqueous ammonium chloride was added and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered, and the solvent was evaporated *in vacuo*. Purification by column chromatography (1/20 ethyl acetate-hexanes) on SiO_2 yielded 1.03 g (76%) of a white solid.
Large scale: (-)-(5*S*)-5-(*tert*-Butyldimethylsilanyloxy)-1-(toluene-4-sulfonyl)-piperidin-2-one **(7)** (8.18 g, 21.3 mmol, 1.0 eq.) was dissolved in THF (250 mL) and the mixture was cooled to -78 ˚C. Potassium bis(trimethylsilyl)amide (94 mL, 47 mmol, 2.2 eq.) was added dropwise and the mixture was stirred for 0.75 h. A solution of *N*-(5-chloro-2-pyridyl)triflimide (17.6 g, 44.8 mmol, 2.1 eq.) in THF (250 mL) was added. The reaction mixture was stirred at -78 ˚C for 1.5 h. The resulting red solution was warmed to rt and stirred overnight. A saturated solution of aqueous ammonium chloride was added and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered, and the solvent was evaporated *in vacuo*. Purification by column chromatography (1/20 ethyl acetate-hexanes) on SiO_2 yielded 7.12 g (65%) of a white solid.
m.p.: 87-90 ˚C (hexanes). $[a]_D^{22}$ = +223 ± 1(c 0.48, $CHCl_3$). IR (KBr pellet): 2935, 2862, 1675, 1597, 1422, 1370, 1171, 1120 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): d 7.76 (d, *J*=8.1 Hz, 2H), 7.33 (d, *J*=8.1 Hz, 2H), 5.34 (t, *J*=4.0 Hz, 1H), 3.87 (dd, *J*=13.3, 4.2 Hz, 1H), 3.76-3.66 (m, 1H), 3.11 (dd, *J*=13.3, 10.0 Hz, 1H), 2.43 (s, 3H), 2.45-2.33 (m, 1H), 2.04 (ddd, *J*=18.4, 7.5, 4.0 Hz, 1H), 0.84 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): d 144.9, 138.9, 135.8, 129.9, 127.7, 118.4 (q, *J*=321.2 Hz), 107.4, 62.9, 52.7, 31.9, 25.6, 21.6, 17.9, -4.8, -5.0. HRMS (DCI+, isobutane): Calcd for $C_{19}H_{29}F_3NO_6S_2Si$ (M^++1): 516.1158. Found 516.1156.

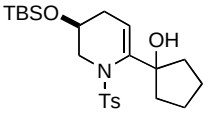
(+)-(3*S*)-3-(*tert*-Butyldimethylsilanyloxy)-1-(toluene-4-sulfonyl)-6-trimethylstannanyl-1,2,3,4-tetrahydropyridine **(9)**



Small scale: THF was degassed for 20 min prior to use by sparging with nitrogen gas. Tris(dibenzylidene)acetone dipalladium(0) (4.5 mg, 0.098 mmol of Pd, 0.1 eq. of Pd) and triphenylarsine (13 mg, 0.042 mmol, 0.4 eq.) were dissolved in THF (2.0 mL) at rt. A solution of (+)-(5*S*)-trifluoromethanesulfonic acid 5-(*tert*-butyldimethylsilanyloxy)-1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydropyridin-2-yl ester **(8)** (48.5 mg, 0.094 mmol, 1.0 eq.) in THF (1.5 mL) was added *via* cannula and the mixture was stirred for 10 min. A solution of hexamethylditin (37 mg, 0.112 mmol, 1.2 eq.) in THF (1.5 mL) was added *via* cannula and the mixture was stirred for 7 h. The solution was poured into brine and extracted with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered, and the solvent was evaporated *in vacuo*. Purification by column chromatography (1/40 ethyl acetate-hexanes) on SiO_2 yielded 35.3 mg (71%) of a white solid.
Large scale: THF was degassed for 20 min prior to use by sparging with nitrogen gas. Tris(dibenzylidene)acetone dipalladium(0) (472 mg, 1.03 mmol of Pd, 0.1 eq. of Pd) and triphenylarsine (1.24 g, 4.05 mmol, 0.40 eq.) were dissolved in THF (200 mL) at rt. A solution of (+)-(5*S*)-trifluoromethanesulfonic acid 5-(*tert*-butyldimethylsilanyloxy)-1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydropyridin-2-yl ester **(8)** (5.20 g, 10.1 mmol, 1.0 eq.) in THF (100 mL) was added *via* cannula and the mixture was stirred for 10 min. A solution of hexamethylditin (4.00

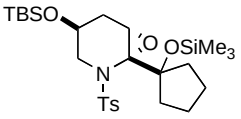
g, 12.2 mmol, 1.2 eq.) in THF (100 mL) was added *via* cannula and the mixture was stirred for 6.5 h. The solution was poured into brine and extracted with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered, and the solvent was evaporated *in vacuo*. Purification by column chromatography (1/40 ethyl acetate-hexanes) on SiO_2 yielded 3.48 g (65%) of a white solid.
m.p.: 80-82 ˚C (water-methanol-ethyl acetate). $[a]_D^{22}$ = +77.8 ± 0.7 (c 0.206, $CHCl_3$). IR (KBr pellet): 2927, 1599, 1348, 1161, 776, 686 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): d 7.62 (d, *J*=8.4 Hz, 2H), 7.27 (d, *J*=7.6 Hz, 2H), 5.13 (dd, *J*=5.0, 2.6 Hz, J_{Sn-H}=21.2 Hz, 1H), 3.68 (ddd, *J*=12.8, 4.0, 1.6 Hz, 1H), 3.24-3.14 (m, 1H), 2.81 (dd, *J*=12.8, 10.4 Hz, 1H), 2.39 (s, 3H), 2.11 (dtd, *J*=17.6, 5.2, 1.6 Hz, 1H), 1.90 (ddd, *J*=17.6, 9.2, 2.8 Hz, 1H), 0.76 (s, 9H), 0.24 (s, J_{Sn-H}=21.2 Hz, 9H), -0.16 (s, 3H), -0.17 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): d 143.4, 140.6, 136.4, 129.7, 127.2, 120.3, 63.2, 50.7, 34.5, 25.7, 21.4, 17.9, -4.9, -5.9. HRMS (DCI+, ammonia and methane): Calcd for $C_{21}H_{38}O_3SiSN^{119}Sn$ (M^+): 531.13714. Found 531.13745.

(+)-(5*S*)-1-[5-(*tert*-Butyldimethylsilanyloxy)-1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydropyridin-2-yl]-cyclopentanol **(10)**



To a solution of (+)-(3*S*)-3-(*tert*-butyldimethylsilanyloxy)-1-(toluene-4-sulfonyl)-6-trimethylstannanyl-1,2,3,4-tetrahydropyridine **(9)** (2.93 g, 5.52 mmol, 1.0 eq.) in diethyl ether (100 mL) was added at -78 ˚C MeLi (7.60 mL, 12.2 mmol, 2.2 eq.) and the mixture was immediately warmed to 0 ˚C. The mixture was stirred at 0 ˚C for 10 min. The mixture was cooled to -78 ˚C and a solution of magnesium bromide (3.48 g, 13.5 mmol, 2.4 eq.) in diethyl ether (100 mL) was added *via* cannulation. The mixture was stirred for 0.5 h and then was cooled to -100 ˚C and a solution of cyclopentanol (1.30 mL, 14.7 mmol, 2.7 eq.) in diethyl ether (50 mL) was added. The reaction mixture was stirred at –100 ˚C for 2 h and then warmed to rt and stirred overnight. The solvent was removed by rotary evaporation. Purification by column chromatography (1/9 ethyl acetate-hexanes) on SiO_2 yielded 2.22 g (89%) of a white solid.
m.p.: 87-88 ˚C (methanol-hexanes). $[a]_D^{23}$ = +218 ± 1 (c 0.16, $CHCl_3$). IR (KBr pellet): 3520, 2951, 1339, 1159 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 7.79 (d, *J*=8.2 Hz, 2H), 7.28 (d, *J*=8.5 Hz, 2H), 5.74 (t, *J*=4.1 Hz, 1H), 4.38 (s, 1H), 3.85 (dd, *J*=13.7, 5.2 Hz, 1H), 3.34-3.25 (m, 1H), 2.77 (dd, *J*=13.7, 10.4 Hz, 1H), 2.41 (s, 3H), 2.32-1.58 (m, 10H), 0.76 (s, 9H), -0.11 (s, 3H), -0.15 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): d 144.1, 143.4, 136.6, 129.8, 127.5, 120.8, 82.7, 62.5, 53.2, 40.8, 38.9, 33.2, 25.6, 23.4, 22.5, 21.5, 17.9, -4.9, -5.0. HRMS (DCI+, isobutane): Calcd for $C_{23}H_{38}NO_4SSi$ (M^+ + 1): 452.2291. Found 452.2271. Anal. Calcd for $C_{23}H_{37}NO_4SSi$: C, 61.16; H, 8.26; N, 3.10. Found: C, 61.23; H, 8.40; N, 3.17.

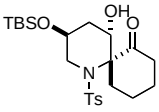
(-)-(1*R*, 4*S*, 7*S*)-4-(*tert*-Butyldimethylsilanyloxy)-2-(toluene-4-sulfonyl)-1-(1-trimethylsilanyloxycyclopentyl)-7-oxa-2-azabicyclo[4.1.0]heptane **(12)**



To (+)-(5*S*)-1-[5-(*tert*-butyldimethylsilanyloxy)-1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydropyridin-2-yl]-cyclopentanol **(10)** (1.08 g, 2.39 mmol, 1.0 eq.) and potassium carbonate (3.40 g, 24.6 mmol, 10 eq.) was added excess dimethyldioxirane solution in acetone until the reaction was

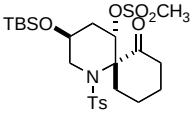
complete by TLC. The mixture was poured into a saturated solution of aqueous ammonium chloride, extracted with dichloromethane, and the combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was dissolved in THF (60 mL) and a solution of freshly distilled TMS-OTf (720 mL, 3.97 mmol, 1.7 eq.) and 2,6-lutidine (720 mL, 6.22 mmol, 2.6 eq.) in THF (60 mL) were added *via* cannula. The mixture was stirred at rt for 15 min. The organic layer was washed sequentially with a saturated solution of aqueous sodium bicarbonate and a saturated solution of aqueous sodium chloride. The organic layer was dried over magnesium sulfate, filtered and evaporated *in vacuo*. Purification by column chromatography (1/15 ethyl acetate-hexanes; 1% triethylamine) on SiO_2 afforded 1.07 g of a white solid (83%).
m.p. = 94-95 ˚C (methanol-hexanes). $[a]_D^{26}$ = -12.3 ± 0.5 (c 0.23, $CHCl_3$). IR (KBr): 2954, 2859, 1353, 1250, 1164, 839 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): d 7.90 (d, *J*=8.3 Hz, 2H), 7.28 (d, *J*=8.3 Hz, 2H), 3.39-3.19 (m, 1H), 3.29 (d, *J*=3.1 Hz, 2H), 2.70 (dd, *J*=13.4, 9.9 Hz, 2H), 2.40 (s, 3H), 2.25 (dd, *J*=15.6, 6.4 Hz, 1H), 2.16-2.00 (m, 1H), 1.97-1.83 (m, 2H), 1.81-1.68 (m, 3H), 1.67-1.53 (m, 3H), 0.75 (s, 9H), 0.16 (s, 9H), -0.20 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): d 143.8, 137.4, 129.6, 128.5, 86.0, 72.4, 63.0, 55.6, 51.1, 40.0, 35.9, 33.0, 25.6, 23.5, 21.8, 21.5, 17.8, 2.0, -5.0. HRMS (DCI+, ammonia/isobutane): Calcd for $C_{26}H_{46}NO_5SSi_2$ (M^++1): 540.2636. Found 540.2644. Anal. Calcd for $C_{26}H_{45}NO_5SSi_2$: C, 57.84; H, 8.40; N, 2.59. Found: C, 57.96; H, 8.51; N, 2.68.

(-)-(3*S*, 5*S*, 6*R*)-3-(*tert*-Butyldimethylsilanyloxy)-5-hydroxy-1-(toluene-4-sulfonyl)-1-azaspiro[5.5]undecan-7-one **(13)**



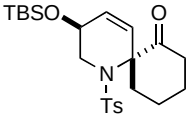
To a solution of epoxide (-)-(1*R*, 4*S*, 7*S*)-4-(*tert*-butyldimethylsilanyloxy)-2-(toluene-4-sulfonyl)-1-(1-trimethylsilanyloxycyclopentyl)-7-oxa-2-azabicyclo[4.1.0]heptane **(12)** (89 mg, 0.17 mmol) in dichloromethane (8.0 mL) was added 180 mL of a 1.0 M solution of titanium tetrachloride (0.18 mmol) at –78 ˚C. The reaction mixture was stirred for 0.5 h at –78 ˚C and then warmed to rt and poured into a saturated solution of sodium chloride. The two layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by evaporation *in vacuo*. Purification by column chromatography (1/3 ethyl acetate-hexanes) on SiO_2 yielded 75 mg (96%) of a white solid.
m.p. = 137-138 ˚C (methanol). $[a]_D^{26}$ = -8.6 ± 0.5 (c 0.25, $CHCl_3$). IR (KBr): 3505, 2941, 2858, 1718, 1329, 1149 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): d 7.83 (d, *J*=8.4 Hz, 2H), 7.30 (d, *J*=8.0 Hz, 2H), 4.13-4.00 (m, 2H), 3.58 (s, 1H), 3.32 (dd, *J*=12.0, 8.0 Hz, 1H), 3.06-2.86 (m, 2H), 2.64-2.53 (m, 1H), 2.52-2.44 (m, 1H), 2.41 (s, 3H), 2.10-1.97 (m, 2H), 1.88-1.54 (m, 5H), 0.81 (s, 9H), -0.04 (s, 3H), -0.06 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): d 209.9, 143.6, 137.6, 129.6, 127.7, 69.9, 69.5, 62.0, 47.7, 40.9, 35.1, 33.7, 26.9, 25.7, 21.5, 20.2, 17.9, -4.9. HRMS (DCI+, ammonia/isobutane): Calcd for $C_{23}H_{38}NO_5SSi$ (M^++1): 468.2240. Found 468.2239. Anal. Calcd for $C_{23}H_{37}NO_5SSi$: C, 59.07; H, 7.97; N, 2.99. Found: C, 59.29; H, 8.09; N, 3.09.

(-)-(3*S*, 5*S*, 6*R*)-Methanesulfonic acid 3-(*tert*-butyldimethylsilanyloxy)-7-oxo-1-(toluene-4-sulfonyl)-1-azaspiro[5.5]undec-5-yl ester **(14)**



(-)-(3*S*, 5*S*, 6*R*)-3-(*tert*-butyldimethylsilanyloxy)-5-hydroxy-1-(toluene-4-sulfonyl)-1-azaspiro[5.5]undecan-7-one **(13)** (475 mg, 1.01 mmol, 1.0 eq.) and 4-(dimethylamino)pyridine (499 mg, 4.08 mmol, 4.0 eq.) were dissolved in dichloromethane (35 mL). Methanesulfonyl chloride (190 mL, 2.45 mmol, 2.4 eq.) was added *via* syringe. The mixture was stirred at rt for 0.5 h and poured into a saturated solution of sodium chloride. The two layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by evaporation *in vacuo*. Purification by column chromatography (8/5 diethyl ether-petroleum ether) on SiO_2 yielded 527 mg (87%) of a foam. $[a]_D^{25}$ = -19.7 ± 0.7 (c 0.19, $CHCl_3$). IR (KBr): 2955, 2859, 1720, 1338, 1178 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): d 7.85 (d, *J*=8.2 Hz, 2H), 7.31 (d, *J*=7.9 Hz, 2H), 5.14-5.09 (m, 1H), 4.19-4.08 (m, 1H), 3.41 (dd, *J*=14.3, 5.2 Hz, 1H), 3.09 (s, 3H), 3.06 (dd, *J*=14.3, 9.5 Hz, 1H), 3.00-2.88 (m, 1H), 2.70-2.59 (m, 1H), 2.53-2.30 (m, 2H), 2.42 (s, 3H), 2.06-1.95 (m, 1H), 1.87-1.59 (m, 5H), 0.81 (s, 9H), -0.02 (s, 3H), -0.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): d 203.9, 143.7, 137.7, 129.7, 127.5, 69.9, 62.2, 48.0, 40.8, 39.1, 27.6, 25.6, 21.4, 20.6, 17.8, -5.0. HRMS (DCI+, ammonia/isobutane): Calcd for $C_{24}H_{40}NO_7S_2Si$ (M^+ + 1): 546.2015. Found 546.2017.

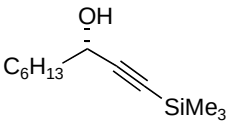
(+)-(3*S*, 6*R*)-3-(*tert*-Butyldimethylsilanyloxy)-1-(toluene-4-sulfonyl)-1-azaspiro[5.5]undec-4-en-7-one **(15)**



(-)-(3*S*, 5*S*, 6*R*)-Methanesulfonic acid 3-(*tert*-butyldimethylsilanyloxy)-7-oxo-1-(toluene-4-sulfonyl)-1-azaspiro[5.5]undec-5-yl ester **(14)** (590 mg, 0.980 mmol, 1.0 eq.) and 1,8-diazabicyclo[5.4.0]undec-7-ene (4.0 mL, 26 mmol, 27 eq.) were dissolved in toluene (40 mL). The mixture was heated to reflux and stirred for 36 h. The mixture was cooled to rt and poured into water. The two layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by evaporation *in vacuo*. Purification by column chromatography (1/5 ethyl acetate-hexanes) on SiO_2 yielded 402 mg (91%) of a clear oil.

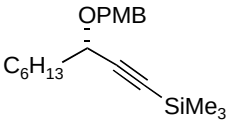
m.p. = 102-103 ˚C (ethyl acetate-hexanes). $[a]_D^{24}$ = +65.4 ± 0.5 (c 0.20, $CHCl_3$). IR (KBr): 2933, 1725, 1597, 1331, 1159 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): d 8.00 (d, *J*=8.3 Hz, 2H), 7.28 (d, *J*=8.1 Hz, 2H), 5.82 (dd, *J*=10.4, 1.8 Hz, 1H), 5.74 (d, *J*=10.5 Hz, 1H), 4.05-3.95 (m, 1H), 3.31 (ddd, *J*=12.2, 6.8, 1.0 Hz, 1H), 2.87 (dd, *J*=12.1, 8.8 Hz, 1H), 2.80-2.59 (m, 2H), 2.51-2.28 (m, 2H), 2.40 (s, 3H), 2.04-1.86 (m, 2H), 1.81-1.61 (m, 2H), 0.75 (s, 9H), -0.13 (s, 3H), -0.15 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): d 205.6, 143.6, 137.2, 132.5, 129.4, 128.3, 126.0, 68.8, 64.7, 46.8, 39.8, 37.0, 25.6, 23.6, 22.3, 21.5, 18.0, -5.1, -5.2. HRMS (CI+, ammonia/isobutane): Calcd for $C_{23}H_{36}NO_4SSi$ (M^+ + 1): 450.2134. Found 450.2131. Anal. Calcd for $C_{23}H_{35}NO_4SSi$: C, 61.33; H, 7.84; N, 3.11. Found: C, 61.47; H, 7.84; N, 3.29.

(-)-(3*S*)-1-Trimethylsilanylnon-1-yn-3-ol **(17)**



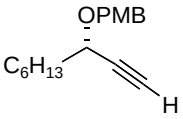
1-Trimethylsilanylnon-1-yn-3-one (1.21 g, 5.75 mmol, 1.0 eq.) was dissolved in isopropanal (55 mL). (h^6-*p*-cymene)[(1S,2S)-N-*p*-toluenesulfonyl 1,2-diphenyletheylenediamine]ruthenium(II) (64.1 mg, 0.107 mmol, 0.019 eq.) was added in one portion and the mixture was stirred for 9.5 h. (h^6-*p*-cymene)[(1S,2S)-N-*p*-toluenesulfonyl 1,2-diphenyletheylenediamine]ruthenium(II) (57.6 mg, 0.0960 mmol, 0.017 eq.) was added in one portion and the mixture was stirred for another 22.5 h. (h^6-*p*-cymene)[(1S,2S)-N-*p*-toluenesulfonyl 1,2-diphenyletheylenediamine]ruthenium(II) (75.4 mg, 0.126 mmol, 0.022 eq.) was added in one portion and the mixture was stirred for another 25 h. (h^6-*p*-cymene)[(1S,2S)-N-*p*-toluenesulfonyl 1,2-diphenyletheylenediamine]ruthenium(II) (57.4 mg, 0.0957 mmol, 0.017 eq.) was added in one portion and the mixture was stirred for another 45.5 h. (h^6-*p*-cymene)[(1S,2S)-N-*p*-toluenesulfonyl 1,2-diphenyletheylenediamine]ruthenium(II) (78.0 mg, 0.130 mmol, 0.023 eq.) was added in one portion and the mixture was stirred for another 55 h. (h^6-*p*-cymene)[(1S,2S)-N-*p*-toluenesulfonyl 1,2-diphenyletheylenediamine]ruthenium(II) (84.1 mg, 0.0140 mmol, 0.024 eq.) was added in one portion and the mixture was stirred for another 48 h. The solvent was removed by evaporation *in vacuo*. Purification by column chromatography (1/12 diethyl ether-pet ether) on SiO_2 gave a 1.15 g (94%) of a pale yellow oil. $[a]_D^{19.9}$ = -0.19 ± 0.01 (c 1.28, $CHCl_3$). IR (NaCl): 3338, 2932, 2860, 2173 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): d 4.31 (dd, *J*=12.2, 6.7 Hz, 1H), 1.95 (d, *J*=5.8 Hz, 1H), 1.73-1.57 (m, 2H), 1.47-1.35 (m, 2H), 1.34-1.20 (m, 6H), 0.85 (t, *J*=6.7 Hz, 3H), 0.13 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): d 107.0, 89.2, 62.9, 62.8, 37.7, 31.7, 28.8, 25.0, 22.5, 14.0, 0.20, -0.17, -0.51. Anal. Calcd for $C_{12}H_{24}OSi$: C, 67.86; H, 11.39. Found: C, 67.56; H, 11.66.

(-)-(3*S*)-[3-(4-Methoxybenzyloxy)-non-1-ynyl]-trimethylsilane **(18)**



To a solution of (-)-(3*S*)-1-trimethylsilanylnon-1-yn-3-ol **(17)** (353 mg, 1.66 mmol, 1.0 eq.) in dichloromethane (50 mL) was added a solution of *p*-methoxybenzyl trichloroacetimidate (764 mg, 2.70 mmol, 1.6 eq.) in dichloromethane (25 mL) *via* cannula. Pyridium *p*-toluenesulfonate (130 mg, 0.517 mmol, 0.31) was added in one portion and the mixture was stirred at rt for 46 h. The mixture was poured into a saturated solution of aqueous sodium bicarbonate. The two layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by evaporation *in vacuo*. Purification by column chromatography (1/12 diethyl ether-pet ether) on SiO_2 yielded 88.8 mg (25%) of starting material as a pale yellow oil and 405 mg (73%) of a clear oil. $[a]_D^{19.9}$ = -118.07 ± 0.02 (c 2.48, $CHCl_3$). IR (NaCl): 2956, 2859, 2168, 1613, 1515, 1250 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): d 7.27 (d, *J*=8.5 Hz, 2H), 6.86 (d, *J*=8.5 Hz, 2H), 4.70 (d, *J*=11.6 Hz, 1H), 4.43 (d, *J*=11.6 Hz, 1H), 4.02 (t, *J*=6.6 Hz, 1H), 3.79 (s, 3H), 1.78-1.61 (m, 2H), 1.48-1.36 (m, 2H), 1.30-1.21 (m, 6H), 0.86 (t, *J*=6.7 Hz, 3H), 0.19 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): d 159.2, 130.2, 129.6, 113.7, 105.2, 90.3, 70.0, 68.7, 55.1, 35.6, 31.7, 28.9, 25.2, 22.5, 14.0, 0.0. Anal. Calcd for $C_{20}H_{32}O_2Si$: C, 72.23; H, 9.70. Found: C, 72.27; H, 9.94.

(-)-(1*S*)-1-(1-Ethynylheptyloxymethyl)-4-methoxybenzene **(19)**

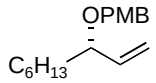


(-)-(3*S*)-[3-(4-Methoxybenzyloxy)-non-1-ynyl]-trimethylsilane **(18)** (405 mg, 1.22 mmol, 1.0 eq.) was dissolved in THF (50 mL). Tetrabutylammonium fluoride (1.40 mL, 1.40 mmol, 1.1 eq.) was added *via* syringe and the mixture was stirred at rt for 15 min. The mixture was poured into water. The two layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by evaporation *in vacuo*. Purification by column chromatography (1/30 diethyl ether-pet ether) on SiO_2 yielded 301 mg (95%) of a clear oil.
$[a]_D^{22.4}$ = -110.22 ± 0.07 (c 0.230, $CHCl_3$). IR (NaCl): 3293, 2931, 2859, 1613, 1515, 1249 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): d , 7.27 (d, *J*=8.5 Hz, 2H), 6.86 (d, *J*=8.5 Hz, 2H), 4.71 (d, *J*=11.3 Hz, 1H), 4.42 (d, *J*=11.3 Hz, 1H), 4.02 (td, *J*=6.6, 2.1 Hz, 1H), 3.78 (s, 3H), 2.43 (d, *J*=2.1 Hz, 1H), 1.80-1.63 (m, 2H), 1.47-1.37 (m, 2H), 1.33-1.21 (m, 6H), 0.85 (t, *J*=6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): d 159.2, 129.9, 129.5, 113.7, 83.1, 73.6, 70.0, 68.0, 55.1, 35.6, 31.7, 28.9, 28.9, 25.1, 22.5, 14.0. Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.29; H, 9.63.

Figure 1. Chiral GC chromatogram of racemic **19**

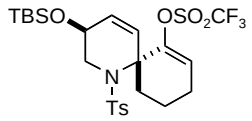
Figure 2. Chiral GC chromatogram of enantioenriched **19**

(-)-(1*S*)-1-Methoxy-4-(1-vinylheptyloxymethyl)-benzene **(20)**



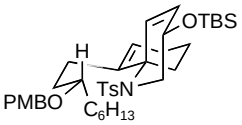
(-)-(1*S*)-1-(1-Ethynylheptyloxymethyl)-4-methoxybenzene **(19)** (229 mg, 0.879 mmol, 1.0 eq.) and Pd-5 wt % on calcium carbonate (209 mg, 0.0982 mmol, 0.11 eq.) were dissolved in ethanol (40 mL) and cooled to -6 ˚C. One atmosphere of hydrogen was introduced and the mixture was stirred at -6 ˚C for 1.75 h. The suspension was filtered through Celite and the solvent was removed by evaporation *in vacuo*. Purification by column chromatography (1/20 ethyl acetate-hexanes) on SiO_2 yielded 214 mg (93%) of a pale yellow oil.
$[a]_D^{22.0}$ = -36.08 ± 0.07 (c 0.203, $CHCl_3$). IR (NaCl): 3076, 2932, 2859, 1615, 1466, 1041, 927 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): d , 7.25 (d, *J*=8.7 Hz, 2H), 6.87 (d, *J*=8.7 Hz, 2H), 5.73 (ddd, *J*=17.1, 10.7, 7.6 Hz, 1H), 5.21 (d, *J*=2.4 Hz, 1H), 5.18 (dd, *J*=10.7, 1.1 Hz, 1H), 4.52 (d, *J*=11.6 Hz, 1H), 4.28 (d, *J*=11.6 Hz, 1H), 3.79 (s, 3H), 3.73-3.66 (m, 1H), 1.69-1.58 (m, 1H), 1.53-1.20 (m, 9H), 0.88 (t, *J*=6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): d 159.0, 139.4, 131.0, 129.2, 116.7, 113.7, 80.2, 69.6, 55.2, 35.5, 31.8, 29.2, 25.3, 22.6, 14.0. HRMS (EI): Calcd for $C_{17}H_{26}O_2$ (M^+): 262.19328. Found 262.19379.

(+)-(3*S*, 6*R*)-Trifluoromethanesulfonic acid 3-(*tert*-butyldimethylsilanyloxy)-1-(toluene-4-sulfonyl)-1-azaspiro[5.5]undeca-4,7-dien-7-yl ester **(21)**



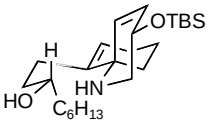
(+)-(3*S*, 6*R*)-3-(*tert*-Butyldimethylsilanyloxy)-1-(toluene-4-sulfonyl)-1-azaspiro[5.5]undec-4-en-7-one **(15)** (29.3 mg, 0.0652 mmol, 1.0 eq.) was dissolved in THF (1.6 mL) and cooled to -78 ˚C. Potassium bis(trimethylsilyl)amide (265 mL, 0.138 mmol, 2.1 eq.) was added *via* syringe and the mixture was stirred at -78 ˚C for 0.75 h. A solution of *N*-(5-chloro-2-pyridyl)triflimide (52.5 mg, 0.147 mmol, 2.3 eq.) in THF (1.6 mL) was added *via* cannula. The reaction mixture was stirred at -78 ˚C for 1 h. The mixture was warmed to rt and poured into a saturated solution of aqueous ammonium chloride. The two layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over magnesium sulfate, filtered, and the solvent was evaporated *in vacuo*. Purification by column chromatography (1/12 ethyl acetate-hexanes; 1% triethylamine) on SiO_2 yielded 36.4 mg (96%) of a clear oil.
$[a]_D^{22.6}$ = +99.6 ± 0.1 (c 0.261, $CHCl_3$). IR (CCl_4): 2931, 2859, 1416, 1337, 1164 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): d 7.83 (d, *J*=8.5 Hz, 2H), 7.28 (d, *J*=7.9 Hz, 2H), 5.91-5.88 (m, 1H), 5.86 (d, *J*=10.1 Hz, 1H), 5.63 (d, *J*=10.1, 2.0 Hz, 1H), 3.96-3.89 (m, 1H), 3.27 (ddd, *J*=12.2, 5.2, 1.2 Hz, 1H), 2.82 (dd, *J*=12.2, 9.5 Hz, 1H), 2.63 (td, *J*=12.8, 3.7 Hz, 1H), 2.48-2.37 (m, 2H), 2.40 (s, 3H), 2.34-2.21 (m, 2H), 1.95-1.85 (m, 1H), 1.81-1.65 (m, 1H), 0.74 (s, 9H), -0.16 (s, 3H), -0.18 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): d 147.2, 144.0, 136.8, 134.4, 129.4, 128.7, 127.9, 120.6, 64.4, 61.8, 47.2, 34.8, 25.6, 24.0, 21.5, 19.5, 18.0, -5.3. Anal. Calcd for $C_{24}H_{34}F_3NO_6S_2Si$: C, 49.55; H, 5.89; N, 2.41. Found: C, 49.89; H, 6.18; N, 2.27.

(+)-(3*S*, 6*R*, 3'*S*)-3-(*tert*-Butyldimethylsilanyloxy)-7-[3'-(4-methoxybenzyloxy)-nonyl]-1-(toluene-4-sulfonyl)-1-azaspiro[5.5]undeca-4,7-diene **(22)**



N,N-Dimethylformamide and water were degassed for 15 min prior to use by sparging with nitrogen gas. To (-)-(1*S*)-1-methoxy-4-(1-vinylheptyloxymethyl)-benzene **(20)** (706 mg, 2.69 mmol, 1.3 eq.) in THF (18 mL) was added 9-borabicyclo[3.3.1]nonane dimer (2.07 g, 8.48 mmol, 4.1 eq.) and the mixture was stirred at rt for 1 h. Water (665 mL, 36.8 mmol, 17.7 eq.) was added via syringe and the mixture was stirred for 1 h. To a round bottom containing dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct (170 mg, 0.208 mmol, 0.10 eq.), triphenylarsine (66.5 mg, 0.217 mmol, 0.10 eq.), potassium bromide (293 mg, 2.46 mmol, 1.2 eq.), and cesium carbonate (1.37 mg, 4.20 mmol, 2.0 eq.) was added a solution of (+)-(3*S*, 6*R*)-trifluoromethanesulfonic acid 3-(*tert*-butyldimethylsilanyloxy)-1-(toluene-4-sulfonyl)-1-azaspiro[5.5]undeca-4,7-dien-7-yl ester **(21)** (1.21 g, 2.08 mmol, 1.0 eq.) in *N,N*-dimethylformamide (18 mL) *via* cannula. To this mixture was added the borane solution via cannula. The resulting dark red solution was stirred at 60 ˚C for 14 h. The mixture was cooled to rt and poured into a solution of diethyl ether. The organic layer was washed sequentially with water and a saturated solution of aqueous sodium chloride. The organic layer was dried over magnesium sulfate, filtered, and the solvent was evaporated *in vacuo*. Purification by column chromatography (1/15 ethyl acetate-hexanes) afforded 1.22 g (84%) of a clear oil.
$[a]_D^{20.5}$ = +100.7 ± 0.1 (c 0.212, $CHCl_3$). IR (CCl_4): 2931, 2859, 1332, 1162 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): d 7.78 (d, *J*=8.5 Hz, 2H), 7.22 (d, *J*=8.5 Hz, 2H), 7.18 (d, *J*=7.9 Hz, 2H), 6.84-6.78 (m, 2H), 5.64-5.56 (m, 2H), 5.53 (dd, *J*=10.2, 1.7 Hz, 1H), 4.42 (dd, *J*=18.3, 11.3 Hz, 2H), 4.11-4.04 (m, 1H), 3.76 (s, 3H), 3.46-3.34 (m, 2H), 2.81 (dd, *J*=11.9, 9.2 Hz, 1H), 2.49-1.96 (m, 6H), 2.36 (s, 3H), 1.91-1.20 (m, 14H), 0.86 (t, *J*=6.7 Hz, 3H), 0.78 (s, 9H), -0.10 (s, 3H), -0.11 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): d 159.0, 143.2, 140.0, 137.8, 134.0, 131.4, 129.4, 129.2, 127.7, 122.8, 113.7, 78.8, 70.2, 65.3, 64.2, 55.2, 48.1, 34.0, 33.3, 32.6, 31.9, 29.6, 26.3, 25.7, 25.5, 24.9, 22.7, 21.4, 20.0, 18.1, 14.1, -4.9, -5.0. LRMS (CI+, ammonia) *m/z* (relative intensity): 696 (M^+ + 1, 8).

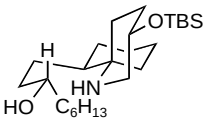
(+)-(3*S*, 6*R*, 3'*S*)-1-[3-(*tert*-Butyldimethylsilanyloxy)-1-azaspiro[5.5]undeca-4,7-dien-7-yl]-nonan-3'-ol **(23)**



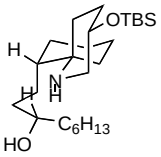
Lithium (12.9 mg, 1.86 mmol, 29 eq.) was washed 3 times with HPLC grade pentane and dissolved in ammonia (10 mL) at -78 ˚C. A solution of (+)-(3*S*, 6*R*, 3'*S*)-3-(*tert*-butyldimethylsilanyloxy)-7-[3-(4-methoxybenzyloxy)-nonyl]-1-(toluene-4-sulfonyl)-1-azaspiro[5.5]undeca-4,7-diene **(22)** (44.4 mg, 0.0638 mmol, 1.0 eq.) in THF (3.0 mL) was added via cannula. The mixture was stirred for 10 min at -78 ˚C and quenched by the dropwise addition of methanol. A saturated solution of aqueous ammonia chloride was added and the mixture was allowed to warmed to rt while open to the atmosphere to allow the ammonia to evaporate. The two layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over magnesium sulfate, filtered, and the solvent was evaporated *in vacuo*.

Purification by column chromatography (1/2 diethyl ether-petroleum ether) on SiO_2 yielded 22.4 mg (83%) of a clear oil.
$[a]_D^{19.8}$ = +72.3 ± 0.1 (c 0.213, $CHCl_3$). IR (CCl_4): 3284, 2930, 2858, 1109 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): d 5.67 (d, *J*=10.4 Hz, 1H), 5.60-5.55 (m, 1H), 5.25 (dd, *J*=10.4, 2.1 Hz, 1H), 4.33-4.26 (m, 1H), 3.52-3.42 (m, 1H), 2.99 (ddd, *J*=10.7, 5.8, 1.2 Hz, 1H), 2.66 (dd, *J*=10.7, 9.2 Hz, 1H), 2.14-1.87 (m, 6H), 1.69-1.61 (m, 1H), 1.60-1.49 (m, 1H), 1.47-1.18 (m, 12H), 0.86-0.81 (m, 3H), 0.84 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): d 139.5, 134.0, 131.9, 125.3, 67.2, 65.8, 55.9, 46.3, 37.2, 36.6, 31.8, 31.8, 29.5, 26.0, 25.8, 25.4, 25.1, 22.6, 18.9, 18.0, 14.0, -4.6, -4.7. LRMS (CI+, ammonia) *m/z* (relative intensity): 422 (M^+ + 1, 100), 421 (M^+, 8).

(+)-(3*S*, 6*R*, 7*R*, 3'*S*)-1-[3-(*tert*-Butyldimethylsilanyloxy)-1-azaspiro[5.5]undec-7-yl]-nonan-3'-ol **(24)**



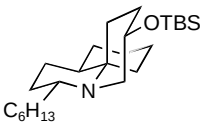
(+)-(3*S*, 6*R*, 3'*S*)-1-[3-(*tert*-Butyldimethylsilanyloxy)-1-aza-spiro[5.5]undeca-4,7-dien-7-yl]-nonan-3'-ol **(23)** (143.9 mg, 0.341 mmol, 1.0 eq.) and Rh-5 wt % on carbon (141 mg, 0.0684 mmol, 0.20 eq.) were dissolved in ethanol (17 mL). The mixture was stirred under 1 atmosphere of hydrogen at rt for 24 h. The mixture was filtered through Celite and the solvent was removed by evaporation *in vacuo*. Purification by gradient column chromatography (1/2 ethyl acetate-hexanes _ ethyl acetate) on SiO_2 afforded 9.6 mg (6.6%) of (-)-(3*S*, 6*R*, 7*S*, 3'*S*)-1-[3-(*tert*-butyldimethylsilanyloxy)-1-azaspiro[5.5]undec-7-yl]-nonan-3'-ol as a clear oil and 99.7 mg (69%) of (+)-(3*S*, 6*R*, 7*R*, 3'*S*)-1-[3-(*tert*-butyldimethylsilanyloxy)-1-azaspiro[5.5]undec-7-yl]-nonan-3'-ol **(24)** as a clear oil.



(-)-(3*S*, 6*R*, 7*S*, 3'*S*)-1-[3-(*tert*-butyldimethylsilanyloxy)-1-azaspiro[5.5]undec-7-yl]-nonan-3'-ol:
$[a]_D^{20.4}$ = -22.37 ± 0.09 (c 0.152, $CHCl_3$). IR (CCl_4): 3628, 3368, 2859 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): d 3.57-3.47 (m, 2H), 2.77 (ddd, *J*=1.2, 4.6, 1.2 Hz, 1H), 2.55 (dd, *J*=12.2, 8.9 Hz, 1H), 2.09-1.99 (m, 1H), 1.82-1.65 (m, 3H), 1.63-1.15 (m, 20 H), 1.06-0.96 (m, 3H), 0.87-0.83 (m, 12H), 0.02 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): d 72.6, 69.3, 52.6, 47.6, 44.3, 37.5, 36.8, 32.5, 31.8, 30.6, 29.7, 29.4, 26.8, 25.9, 25.6, 24.3, 22.6, 21.2, 18.1, 14.1, -4.6. HRMS (EI): Calcd for $C_{25}H_{51}NO_2Si$ (M^+): 425.36891. Found 425.36973.

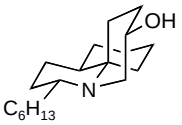
(+)-(3*S*, 6*R*, 7*R*, 3'*S*)-1-[3-(*tert*-butyldimethylsilanyloxy)-1-azaspiro[5.5]undec-7-yl]-nonan-3'-ol **(24)**:
$[a]_D^{20.7}$ = +31.60 ± 0.04 (c 0.201, $CHCl_3$). IR (CCl_4): 3255, 3148, 2929, 2857, 1456, 1361,1110 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): d 3.59-3.44 (m, 2H), 2.80 (ddd, *J*=11.6, 5.5, 4.9 Hz, 1H), 2.69 (dd, *J*=11.6, 10.1 Hz, 1H), 2.28-2.19 (m, 1H), 1.78-1.51 (m, 6H), 1.48-0.82 (m, 32H), 0.02 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): d 70.3, 69.9, 53.3, 48.0, 46.1, 37.6, 35.9, 32.6, 31.8, 29.8, 29.4, 28.3, 25.8, 25.3, 25.1, 24.6, 22.6, 18.1, 14.1, -4.6. HRMS (EI): Calcd for $C_{25}H_{51}NO_2Si$ (M^+): 425.36891. Found 425.36907.

(+)-(1*R*, 4*S*, 7*R*, 10*R*)-4-(*tert*-Butyldimethylsilanyloxy)-7-hexyl-6-azatricyclo[8.4.0.$0^{1,6}$]-tetradecane **(25)**



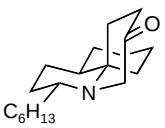
(+)-(3*S*, 6*R*, 7*R*, 3'*S*)-1-[3-(*tert*-Butyldimethylsilanyloxy)-1-azaspiro[5.5]undec-7-yl]-nonan-3'-ol **(24)** (36.7 mg, 0.0862 mmol, 1.0 eq.) and triphenylphosphine (74.6 mg, 0.284 mmol, 3.3 eq.) were dissolved in dichloromethane (2.5 mL) and cooled to 0 ˚C. Carbon tetrabromide (94.3 mg, 0.284 mmol, 3.3 eq.) was added in one portion followed by the addition of triethylamine (40 mL, 0.287 mmol, 3.3 eq.) *via* syringe. The pale yellow solution was allowed to warm to rt and stirred for 5 h. The solvent was removed by evaporation *in vacuo*. Purification by column chromatography (1/4 diethyl ether-petroleum ether; 2% ammonium hydroxide) on SiO_2 afforded 29.6 mg (84%) of a clear oil.
$[a]_D^{20.8}$ = +4.51 ± 0.05 (c 0.265, $CHCl_3$). IR (CCl_4): 2929, 2860, 1464, 1092 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): d 3.95-3.86 (m, 1H), 2.97-2.82 (m, 3H), 2.63 (d, *J*=13.1 Hz, 1H), 1.84-1.47 (m, 1H), 1.40-1.10 (m, 17H), 1.03-0.93 (m, 1H), 0.86 (s, 12H), 0.02 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): d 62.5, 56.6, 53.5, 47.3, 45.9, 34.5, 34.2, 32.6, 31.8, 30.0, 29.9, 29.8, 27.2, 26.2, 25.9, 25.4, 22.8, 22.6, 18.2, 17.5, 14.1, -4.6. HRMS (EI): Calcd for $C_{25}H_{49}NOSi$ (M^+): 407.35834. Found 407.35790.

(+)-(1*R*, 4*S*, 7*R*, 10*R*)-7-Hexyl-6-azatricyclo[8.4.0.$0^{1,6}$]tetradecan-4-ol **(26)**



(+)-(1*R*, 4*S*, 7*R*, 10*R*)-4-(*tert*-Butyldimethylsilanyloxy)-7-hexyl-6-azatricyclo[8.4.0.$0^{1,6}$]tetradecane **(25)** (40.0 mg, 0.0981 mmol, 1.0 eq.) in THF (5.0 mL) was added *via* cannula to a round bottom containing powdered activated 4 Å molecular sieves (500 mg). Tetrabutylammonium fluoride, pre-treated with 4 Å molecular sieves, (300 mL, 0.300 mmol, 3.1 eq.) was added *via* syringe and the mixture was stirred at rt for 0.5 h. The reaction was filtered and the solvent removed by evaporation *in vacuo*. Purification by gradient column chromatography (diethyl ether _ 19/1 diethyl ether-methanol; 2% ammonium hydroxide) afforded 23.7 mg (82%) of a white solid. m.p. = 69-71 ˚C (ethyl acetate-hexanes). $[a]_D^{20.3}$ = +4.2 ± 0.1 (c 0.259, $CHCl_3$). IR (CCl_4): 3084, 2925, 2860, 1469, 1083 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): d 3.99-3.87 (m, 1H), 3.07 (ddd, *J*=14.4, 4.6, 1.8 Hz, 1H), 2.90-2.80 (m, 2H), 2.57 (d, *J*=13.1 Hz, 1H), 1.95-1.47 (m, 8H), 1.41-0.96 (m, 18H), 0.85 (t, *J*=6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): d 61.8, 56.7, 53.5, 47.1, 45.8, 34.5, 34.0, 32.5, 31.9, 29.9, 29.7, 27.1, 26.1, 25.5, 22.7, 22.6, 17.4,14.1.

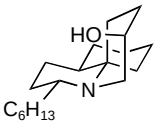
(+)-(1*R*, 7*R*, 10*R*)-7-Hexyl-6-azatricyclo[8.4.0.$0^{1,6}$]tetradecan-4-one **(27)**



A (2.5 mL) dichloromethane solution of (+)-(1*R*, 4*S*, 7*R*, 10*R*)-7-hexyl-6-azatricyclo[8.4.0.$0^{1,6}$]tetradecan-4-ol **(26)** (22.9 mg, 0.0780 mmol, 1.0 eq.) was cannulated to a round bottom containing powdered activated 4 Å molecular sieves (83 mg). Tetrapropylammonium perruthenate (3.1 mg, 0.0088 mmol, 0.11 eq.) was added in one portion. The mixture was cooled to 0 ˚C and 4-methylmorpholine *N*-oxide (12.9 mg, 0.110 mmol, 1.4 eq.) was added in one portion. The mixture was warmed to rt, stirred for 2 h, filtered through Celite, and the solvent was removed

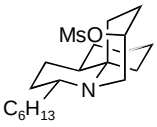
by evaporation *in vacuo*. Purification by column chromatography (1/1 diethyl ether-hexanes) on SiO_2 afforded 18.0 mg (79%) of a clear oil.
$[a]_D^{21.2}$ = +102.6 ± 0.2 (c 0.178, $CHCl_3$). IR (CCl_4): 2931, 2861, 1719 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): d 3.95-3.86 (m, 1H), 2.97-2.82 (m, 3H), 2.63 (d, *J*=13.1 Hz, 1H), 1.84-1.47 (m, 1H), 1.40-1.10 (m, 17H), 1.03-0.93 (m, 1H), 0.86 (s, 12H), 0.02 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): d 213.3, 56.5, 54.8, 53.6, 45.1, 35.8, 34.1, 33.8, 32.2, 31.8, 29.7, 26.8, 25.9, 24.7, 23.2, 22.6, 20.1, 14.0.

(1*R*, 4*R*, 7*R*, 10*R*)-7-Hexyl-6-azatricyclo[8.4.0.$0^{1,6}$]tetradecan-4-ol **(28)**



(+)-(1*R*, 7*R*, 10*R*)-7-Hexyl-6-azatricyclo[8.4.0.$0^{1,6}$]tetradecan-4-one **(27)** (11.2 mg, 0.0384 mmol, 1.0 eq.) was dissolved in THF (1.9 mL) and cooled to -78 ˚C. L-Selectride® (25 mL, 0.0250 mmol, 1.7 eq.) was added via syringe and the mixture was stirred at -78 ˚C for 1 h. 3 N sodium hydroxide (0.48 mL) was added via syringe followed by the addition of 30% hydrogen peroxide (0.42 mL). The mixture was warmed to rt and poured into a saturated solution of aqueous potassium sodium tartrate. The two layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered, and the solvent was evaporated *in vacuo*. Purification by gradient column chromatography (19/1 diethyl ether-methanol to 9/1 diethyl ether-methanol; 1% ammonium hydroxide) on SiO_2 yielded 7.5 mg (67%) of a clear oil. ^1H NMR (400 MHz, $CDCl_3$): d 3.77 (s, 1H), 3.43-3.33 (m, 1H), 3.19 (d, *J*=16.2 Hz, 1H), 3.09 (dd, *J*=16.2, 2.4 Hz, 1H), 2.39 (d, *J*=11.9 Hz, 1H), 2.05 (dt, *J*=13.7, 3.9 Hz, 1H), 1.87 (tt, *J*=14.0, 3.9 Hz, 1H), 1.82-1.54 (m, 5H), 1.45-0.93 (m, 19 H), 0.85 (t, *J*=6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): d 67.4, 57.0, 55.5, 46.6, 45.1, 34.9, 33.8, 32.7, 31.9, 30.3, 30.0, 29.4, 27.7, 27.2, 26.2, 25.2, 22.7, 14.1, 13.0.

(-)-(1*R*, 4*R*, 7*R*, 10*R*)-Methanesulfonic acid 7-hexyl-6-azatricyclo[8.4.0.$0^{1,6}$]tetradec-4-yl ester



To a 0 ˚C cooled solution of (1*R*, 4*R*, 7*R*, 10*R*)-7-hexyl-6-azatricyclo[8.4.0.$0^{1,6}$]tetradecan-4-ol **(28)** (10.2 mg, 0.0348 mmol, 1.0 eq.) in dichloromethane (1.0 mL) was added triethylamine (10 mL, 0.0717 mmol, 2.1 eq.) *via* syringe, 4-dimethylaminopyridine (2.7 mg, 0.022 mmol, 0.64 eq.) in one portion and methanesulfonic chloride (5.0 mL, 0.065 mmol, 1.9 eq.) *via* syringe. The mixture was stirred at 0 ˚C for 3.5 h and then poured into a saturated solution of aqueous sodium bicarbonate. The two layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered, and the solvent was evaporated *in vacuo*. Purification by column chromatography (9/1 ethyl acetate-methanol) on SiO_2 gave 10.8 mg (84%) of a pale yellow oil. $[a]_D^{19.4}$ = -13.0 ± 0.5 (c 0.108, $CHCl_3$). IR (CCl_4): 2931, 2861, 1462, 1342 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): d 4.70 (s, 1H), 3.40 (d, *J*=17.1 Hz, 1H), 3.23 (dd, *J*=16.8, 2.3 Hz, 1H), 3.20-3.12 (m, 1H), 2.97 (s, 3H), 2.32 (d, *J*=12.5 Hz, 1H), 2.10-1.93 (m, 3H), 1.80-1.55 (m, 4H), 1.48-0.95 (m, 19H), 0.85 (t, *J*=6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): d 78.4, 56.6, 54.8, 46.4, 43.7, 38.4, 34.2, 33.7, 32.3, 32.0, 30.0, 29.2, 27.0, 26.1, 25.6, 24.9, 22.7, 14.1, 13.1.

[1] Murray, R.W.; Singh, M. *Org. Synth.* **1996**, *74*, 91
[2] Haack, K.-J.; Hashiguchi S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 285